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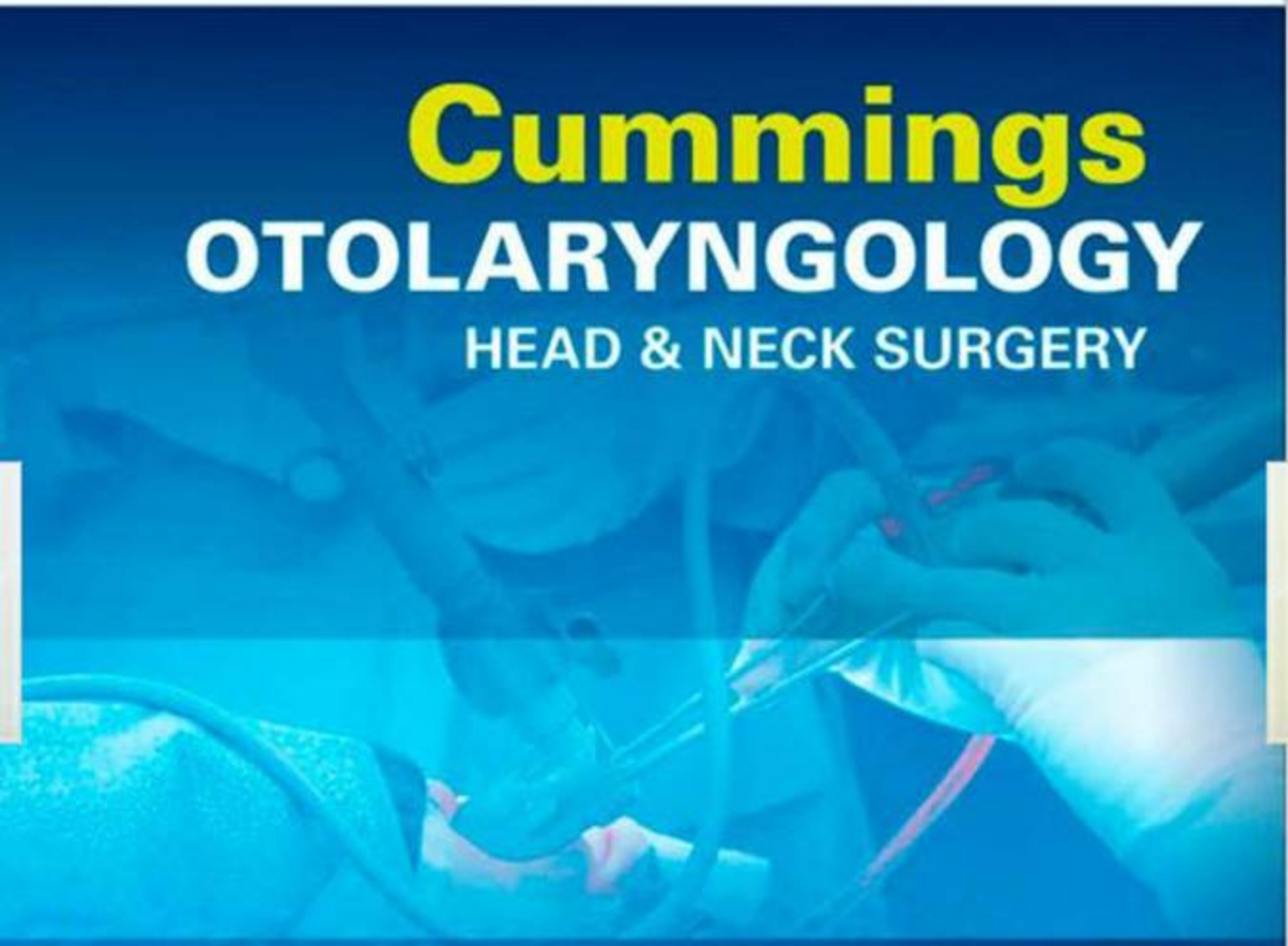

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PAUL W. FLINT
BRUCE H. HAUGHEY
VALERIE J. LUND
JOHN K. NIPARKO
MARK A. RICHARDSON
K. THOMAS ROBBINS
J. REGAN THOMAS

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FIFTH EDITION

Paul W. Flint, M.D.
Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Oregon Health and Science University
Portland, Oregon

Bruce H. Haughey, M.B.Ch.B., F.A.C.S., F.R.A.C.S.
Professor and Director
Head and Neck Surgical Oncology
Department of Otolaryngology–Head and Neck Surgery
Washington University School of Medicine
St. Louis, Missouri

Valerie J. Lund, C.B.E., M.S., F.R.C.S., F.R.C.S.Ed.
Professor of Rhinology
University College London
Honorary Consultant ENT Surgeon
Royal National Throat, Nose, and Ear Hospital
Royal Free Hospital
Moorfields Eye Hospital
London, United Kingdom

John K. Niparko, M.D.
George T. Nager Professor
Department of Otolaryngology–Head and Neck Surgery
Director
Divisions of Otology, Neurotology, Skull Base Surgery, and Audiology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Mark A. Richardson, M.D.
Professor
Department of Otolaryngology–Head and Neck Surgery
Dean
School of Medicine
Oregon Health and Science University
Portland, Oregon

K. Thomas Robbins, M.D.
Director
SimmonsCooper Cancer Institute at Southern Illinois University
Professor
Division of Otolaryngology–Head and Neck Surgery
Southern Illinois University School of Medicine
Springfield, Illinois

J. Regan Thomas, M.D.
Francis L. Lederer Professor and Chairman
Department of Otolaryngology–Head and Neck Surgery
University of Illinois at Chicago
Chicago, Illinois

Illustrator:

Tim Phelps, M.S., F.A.M.I.
Associate Professor and Medical Illustrator
Art as Applied to Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

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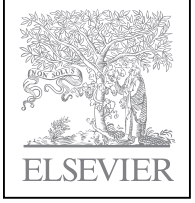

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Contributors

Waleed M. Abuzeid, M.B.B.S.

Resident
Department of Surgery
University of Michigan Health System
Ann Arbor, Michigan

Meredith E. Adams, M.D.

Fellow
Division of Otology and Neurotology
Department of Otolaryngology
University of Michigan Medical Center
Ann Arbor, Michigan

Peter A. Adamson, M.D., F.R.C.S.C., F.A.C.S.

Professor and Head
Division of Facial Plastic and Reconstructive Surgery
Department of Otolaryngology–Head and Neck Surgery
University of Toronto Faculty of Medicine
Staff Surgeon
University Health Network
Toronto General Hospital
Toronto, Ontario, Canada

Antoine Adenis, M.D., Ph.D.

Professor of Medical Oncology
Catholic University
Chief
Department of Gastrointestinal Oncology
Centre Oscar Lambret
Lille, France

Seth Akst, M.D.

Assistant Professor
Department of Anesthesiology and Critical Care Medicine
George Washington University School of Medicine and Health Sciences
Washington, D.C.

Sheri L. Albers, D.O.

Fellow
Pain Management and Spinal Interventional Neuroradiology
University of California, San Diego, School of Medicine
UC San Diego Medical Center
La Jolla, California
VA San Diego Medical Center
San Diego, California

David Albert, M.B.B.S., F.R.C.S.

Honorary Senior Lecturer
University College London Institute of Child Health
Lead Clinician
ENT Department
Great Ormond Street Hospital for Children
London, United Kingdom

Ronda E. Alexander, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Texas Health Science Center at Houston
Houston, Texas

Sue Archbold, M.Phil.

CEO
The Ear Foundation
Nottingham, United Kingdom

William B. Armstrong, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of California, Irvine, School of Medicine
Irvine, California

Moisés A. Arriaga, M.D., F.A.C.S.

Clinical Professor and Director
Division of Otology and Neuro-otology
Department of Otolaryngology and Neurosurgery
Louisiana State University Health Sciences Center School of Medicine at New Orleans
New Orleans, Louisiana
Director
Hearing and Balance Center
Our Lady of the Lake Regional Medical Center
Baton Rouge, Louisiana
Director
Department of Cochlear Implants and Neurotology
Children's Hospital New Orleans
New Orleans, Louisiana

H. Alexander Arts, M.D.

Professor
Department of Otolaryngology and Neurosurgery
University of Michigan Medical School
Ann Arbor, Michigan

Yasmine A. Ashram, M.D., D.A.B.N.M.

Assistant Professor
Department of Physiology
University of Alexandria School of Medicine
Surgical Neurophysiologist
Alexandria University Hospital
Alexandria, Egypt

Jonathan E. Aviv, M.D., F.A.C.S.

Clinical Professor
Department of Otolaryngology
Mount Sinai School of Medicine
Clinical Director
Voice and Swallowing Center
ENT and Allergy Associates
New York, New York

Nafi Aygun, M.D.

Assistant Professor
Department of Radiology
Neuroradiology Division
Johns Hopkins University School of Medicine
Baltimore, Maryland

Douglas D. Backous, M.D., F.A.C.S.

Director
Listen For Life Center
Virginia Mason Medical Center
Seattle, Washington
Department of Otolaryngology–Head and Neck Surgery
Madigan Army Medical Center
Fort Lewis, Washington

Shan R. Baker, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Michigan Medical School
Ann Arbor, Michigan
Chief
Facial Plastic and Reconstructive Surgery
University of Michigan Center for Facial Cosmetic Surgery
Livonia, Michigan

Thomas J. Balkany, M.D., F.A.C.S., F.A.A.P.

Hotchkiss Professor and Chair
Department of Otolaryngology
Professor of Neurological Surgery and Pediatrics
University of Miami Miller School of Medicine
Chief of Service
Division of Otology
Jackson Memorial Hospital
Miami, Florida

Robert W. Baloh, M.D.

Professor
Department of Neurology and Otolaryngology
David Geffen School of Medicine at UCLA
Director
Neuro-otology Program
Department of Neurology
Ronald Reagan UCLA Medical Center
Los Angeles, California

Julie Barkmeier-Kraemer, Ph.D.

Associate Professor
Department of Speech, Language, and Hearing Sciences
University of Arizona College of Medicine
Tucson, Arizona

Fuad M. Baroody, M.D., F.A.C.S.

Professor
Department of Otolaryngology–Head and Neck Surgery
Department of Pediatrics
University of Chicago Pritzker School of Medicine
Chicago, Illinois

Nancy L. Bartlett, M.D.

Professor
Department of Medicine
Division of Oncology
Washington University in St. Louis School of Medicine
Medical Oncologist
Siteman Cancer Center
St. Louis, Missouri

Jonathan Z. Baskin, M.D.

Assistant Professor
Department of Otolaryngology
Case Western Reserve University School of Medicine
Section Chief
Department of Otolaryngology–Head and Neck Surgery
Cleveland VA Medical Center
Attending Physician
Rainbow Babies and Children's Hospital
Cleveland, Ohio

Robert W. Bastian, M.D.

Clinical Professor
Department of Otolaryngology
Loyola University School of Medicine
Chicago, Illinois
Founder and Director
Bastian Voice Institute
Downers Grove, Illinois

Carol A. Bauer, M.D.

Professor of Surgery
Division of Otolaryngology–Head and Neck Surgery
Southern Illinois University School of Medicine
Springfield, Illinois

Michael S. Benninger, M.D.

Professor
Cleveland Clinic Lerner School of Medicine
Case Western Reserve University
Chairman
Head and Neck Institute
The Cleveland Clinic
Cleveland, Ohio

Prabhat K. Bhama, M.D.

Resident and Research Fellow
University of Washington Medical Center
Seattle, Washington

Nasir Islam Bhatti, M.D., F.A.C.S., F.R.C.S.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Andrew Blitzer, M.D., D.D.S.

Professor
Department of Clinical Otolaryngology
Columbia University College of Physicians and Surgeons
Director
New York Center for Voice and Swallowing Disorders
Attending
Department of Otolaryngology
St. Luke's Roosevelt Hospital Center
New York, New York

Simone Boardman, M.B.B.S., F.R.A.C.S.(OHNS)

Great Ormond Street Hospital
London, United Kingdom

Emily F. Boss, M.D.

Assistant Professor
Department of Otolaryngology
Division of Pediatric Otolaryngology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Derald E. Brackmann, M.D.

Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
David Geffen School of Medicine at UCLA
Clinical Professor
Department of Neurological Surgery
University of Southern California Keck School of Medicine
President
House Ear Clinic
Los Angeles, California

Carol R. Bradford, M.D., F.A.C.S.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of Michigan Medical School
Ann Arbor, Michigan

Barton F. Branstetter, IV, M.D.

Associate Professor
Departments of Radiology, Otolaryngology, and Biomedical Informatics
University of Pittsburgh School of Medicine
Director
Head and Neck Imaging
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Edward B. Braun, M.D.

Assistant Professor
Department of Anesthesiology
University of Kansas School of Medicine
University of Kansas Hospital
Kansas City, Kansas

Robert J. S. Briggs, M.B.B.S., F.R.A.C.S.

Clinical Associate Professor
Department of Otolaryngology
The University of Melbourne Faculty of Medicine
Melbourne, Australia

Hilary A. Brodie, M.D., Ph.D.

Professor and Chair
Department of Otolaryngology
University of California, Davis, School of Medicine
UC Davis Medical Center
Sacramento, California

Carolyn J. Brown, Ph.D.

Professor
Department of Communication Sciences and Disorders
Department of Otolaryngology–Head and Neck Surgery
University of Iowa Carver College of Medicine
Iowa City, Iowa

David J. Brown, M.D.

Assistant Professor of Otolaryngology
Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Kevin D. Brown, M.D., Ph.D.

Assistant Professor
Department of Otolaryngology
Weill Cornell Medical College
Assistant Attending Otorhinolaryngologist
NewYork–Presbyterian Hospital
New York, New York

J. Dale Browne, M.D, F.A.C.S.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina

John M. Buatti, M.D.

Professor and Head
Department of Radiation Oncology
University of Iowa Carver College of Medicine
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Luke Buchmann, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Utah School of Medicine
Salt Lake City, Utah

Patrick J. Byrne, M.D.

Associate Professor
Departments of Otolaryngology–Head and Neck Surgery and Dermatology
Johns Hopkins University School of Medicine
Director
Division of Facial Plastic and Reconstructive Surgery
Johns Hopkins Hospital
Baltimore, Maryland

Gabriel G. Galzada, M.D.

Department of Head and Neck Surgical Oncology
Kaiser Permanente
Downey, California

John P. Carey, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Division of Otology, Neurotology, and Skull Base Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Margaretha L. Casselbrant, M.D., Ph.D.

Eberly Professor of Pediatric Otolaryngology
Department of Otolaryngology
University of Pittsburgh School of Medicine
Director
Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Paolo Castelnuovo, M.D.

Professor
University of Insubria
Chairman
Ospedale di Circolo e Fondazione Macchi
Varese, Italy

Steven Chang, M.D.

Resident
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins Medical Institutions
Baltimore, Maryland

Burke E. Chegar, M.D.

Clinical Assistant Professor
Department of Dermatology
Indiana University School of Medicine
Indianapolis, Indiana
Director
Center for Facial Plastic Surgery–Head and Neck Surgery
Fayette Regional Health System
Connersville, Indiana

Amy Chen, M.D., M.P.H.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Emory School of Medicine
Atlanta, Georgia

Eunice Y. Chen, M.D., Ph.D.

Assistant Professor
Dartmouth Medical School
Hanover, New Hampshire
Pediatric Otolaryngologist
Dartmouth Hitchcock Medical Center
Lebanon, New Hampshire

Theodore Chen, M.D.

Department of Head and Neck Surgery
Kaiser Permanente Los Angeles Medical Center
Los Angeles, California

Douglas B. Chepeha, M.D., M.P.H.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of Michigan Medical School
Director
Microvascular Program
A. Alfred Taubman Health Care Center
Ann Arbor, Michigan

Alice Cheuk, M.D.

Resident Physician
Los Angeles County Hospital and USC Medical Center
Los Angeles, California

Neil N. Chheda, M.D.

Assistant Professor
Department of Otolaryngology
Division of Laryngology
University of Florida College of Medicine
Shands at the University of Florida
Gainesville, Florida

Wade Chien, M.D.

Clinical Fellow
Department of Otolaryngology
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Sukgi S. Choi, M.D.

Professor
Departments of Otolaryngology and Pediatrics
George Washington University School of Medicine and Health Sciences
Vice Chief
Department of Pediatric Otolaryngology
Children's National Medical Center
Washington, D.C.

Richard A. Chole, M.D., Ph.D.

Lindburg Professor and Head
Department of Otolaryngology–Head and Neck Surgery
Washington University in St. Louis School of Medicine
Chief of Staff
Department of Otolaryngology
Barnes-Jewish Hospital
St. Louis, Missouri

James M. Christian, D.D.S., M.B.A.

Visiting Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Director
Division of Dentistry and Oral Surgery
Johns Hopkins Hospital
Baltimore, Maryland

Eugene A. Chu, M.D.

Clinical Instructor in Rhinology and Sinus Surgery
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Martin J. Citardi, M.D.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of Texas Medical School at Houston
Chief
Otorhinolaryngology
Memorial Hermann–Texas Medical Center
Houston, Texas

Marc A. Cohen, M.D.

Resident
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania Health System
Philadelphia, Pennsylvania

Savita Collins, M.D.

Physician
Departments of Otolaryngology–Head and Neck Surgery and Audiology
South Bend Clinic
South Bend, Indiana

Nancy A. Collop, M.D.

Professor
Department of Medicine
Division of Pulmonary/Critical Care Medicine
Johns Hopkins University School of Medicine
Medical Director
Sleep Disorders Center
Johns Hopkins Hospital
Baltimore, Maryland

Philippe Contencin, M.D., Ph.D.

Senior Consultant
Department of Otorhinolaryngology
Hôpital Necker
Paris, France

Raymond Cook, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina
WakeMed Health and Hospitals
Raleigh, North Carolina

Jacquelynne Corey, M.D.

Professor of Surgery
Department of Otolaryngology–Head and Neck Surgery
University of Chicago Pritzker School of Medicine
Director
ENT Allergy Program
University of Chicago Medical Center
Chicago, Illinois

Robin T. Cotton, M.D., F.A.C.S., F.R.C.S.C

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Director
Pediatric Otolaryngology–Head and Neck Surgery
Cincinnati Children's Hospital
Cincinnati, Ohio

Marion Everett Couch, M.D., Ph.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of North Carolina at Chapel Hill School of Medicine
Chapel Hill, North Carolina

Mark S. Courey, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
Director
Division of Laryngology
University of California, San Francisco, School of Medicine
Director
UCSF Voice and Swallowing Center
San Francisco, California

Benjamin T. Crane, M.D., Ph.D.

Assistant Professor
Departments of Otolaryngology and Neurobiology
University of Rochester School of Medicine and Dentistry
Department of Otolaryngology
Strong Memorial Hospital
Rochester, New York

Roger L. Crumley, M.D.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of California, Irvine, School of Medicine
Orange, California

Oswaldo Laércio M. Cruz, M.D.

Associate Professor and Chief
Division of Otology-Neurotology
Department of Otolaryngology
Federal University of São Paulo
São Paulo, Brazil

Frank Culicchia, M.D.

Professor and Chair
Department of Neurosurgery
Louisiana State University Health Sciences Center
New Orleans, Louisiana

Charles W. Cummings, M.D.

Distinguished Professor
Johns Hopkins University School of Medicine
Executive Medical Director
Johns Hopkins International
Baltimore, Maryland

Calhoun D. Cunningham, III, M.D.

Assistant Consulting Professor of Surgery
Division of Otorhinolaryngology–Head and Neck Surgery
Duke University School of Medicine
Durham, North Carolina
Associate Physician
Carolina Ear and Hearing Clinic
Raleigh, North Carolina

Greg E. Davis, M.D., M.P.H.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Seattle, Washington

Larry E. Davis, M.D.

Distinguished Professor of Neurology
Research Professor
Departments of Neuroscience and Molecular Genetics and Microbiology
University of New Mexico School of Medicine
Chief
Neurology Service
New Mexico VA Health Care System
Albuquerque, New Mexico

Terry A. Day, M.D.

Professor and Clinical Vice Chair
Department of Otolaryngology–Head and Neck Surgery
Medical University of South Carolina
Charleston, South Carolina

Antonio De la Cruz, M.D.

Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
University of Southern California Keck School of Medicine
Director of Education
House Ear Clinic
Los Angeles, California

Charles C. Della Santina, M.D., Ph.D.

Associate Professor
Departments of Otolaryngology–Head Neck Surgery and Biomedical Engineering
Director
Vestibular NeuroEngineering Laboratory
Division of Otology, Neurotology, and Skull Base Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland

Chadrick Denlinger, M.D.

Assistant Professor
Department of Surgery
Medical University of South Carolina
Charleston, South Carolina

Craig S. Derkay, M.D., F.A.A.P., F.A.C.S.

Professor of Otolaryngology and Pediatrics
Vice Chair
Department of Otolaryngology
Eastern Virginia Medical School
Director of Pediatric Otolaryngology
Children's Hospital of the King's Daughters
Norfolk, Virginia

Rodney C. Diaz, M.D.

Assistant Professor of Otology, Neurotology, and Skull Base Surgery
Department of Otolaryngology–Head and Neck Surgery
University of California, Davis, School of Medicine
Sacramento, California

Robert A. Dobie, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of California, Davis, School of Medicine
Sacramento, California

Suzanne K. Doud Galli, M.D., Ph.D.

Department of Otolaryngology
Inova Fairfax Hospital
Washington, D.C.

Newton O. Duncan, M.D.

Clinical Assistant Professor
Departments of Otorhinolaryngology and Pediatrics
Baylor College of Medicine
Attending Surgeon
Texas Children's Hospital
Houston, Texas

Scott D. Z. Eggers, M.D.

Assistant Professor
Department of Neurology
Mayo Medical School
Ann Arbor, Michigan
Associate
Department of Neurology
Mayo Clinic
Rochester, Minnesota

Avraham Eisbruch, M.D.

Professor
Department of Radiation Oncology
University of Michigan Medical School
Associate Chair of Clinical Research
University of Michigan Health System
Ann Arbor, Michigan

David W. Eisele, M.D., F.A.C.S.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of California, San Francisco, School of Medicine
San Francisco, California

Hussam K. El-Kashlan, M.D.

Associate Professor
Department of Otolaryngology
University of Michigan Medical School
Medical Director
Vestibular Testing Center
University of Michigan Health System
Ann Arbor, Michigan

Ravindhra G. Elluru, M.D., Ph.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Division of Pediatric Otolaryngology
Cincinnati Children's Hospital
Cincinnati, Ohio

Kevin H. Ende, M.D.

Clinical Instructor
Plastic Surgery and Facial Surgery
University of California, San Francisco, School of Medicine
San Francisco, California

Audrey B. Erman, M.D.

Resident
Department of Otolaryngology
University of Michigan Health System
Ann Arbor, Michigan

Samer Fakhri, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of Texas Medical School at Houston
Houston, Texas

Carole Fakhry, M.D., M.P.H.

Resident
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins Hospital
Baltimore, Maryland

Edward H. Farrior, M.D.

Visiting Clinical Associate Professor
Department of Otolaryngology
University of Virginia School of Medicine
Charlottesville, Virginia
Founder and Physician
Farrior Facial Plastic and Cosmetic Surgery Center
Tampa, Florida

Richard T. Farrior, M.D.

Boca Grande, Florida

Russell A. Faust, M.D., Ph.D.

Assistant Professor
Department of Otolaryngology, College of Medicine
Department of Oral Triology, College of Dentistry
The Ohio State University
Staff Attending Physician
Department of Otolaryngology
Nationwide Children's Hospital
Columbus, Ohio

Berrylin J. Ferguson, M.D.

Associate Professor
Department of Otolaryngology
University of Pittsburgh School of Medicine
Director
Division of Sino-Nasal Disorders and Allergy
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Paul W. Flint, M.D.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Oregon Health and Science University
Portland, Oregon

Howard W. Francis, M.D.

Associate Professor
Residency Program Director
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Marvin P. Fried, M.D.

Professor and University Chairman
Albert Einstein College of Medicine
Department of Otorhinolaryngology–Head and Neck Surgery
Montefiore Medical Center
Bronx, New York

David R. Friedland, M.D., Ph.D.

Associate Professor
Department of Otolaryngology and Communication Sciences
Chief
Division of Otology and Neuro-otologic Skull Base Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin

Oren Friedman, M.D.

Assistant Professor
Department of Otolaryngology
Mayo Medical School
Director
Facial Plastic and Reconstructive Surgery
Mayo Clinic
Rochester, Minnesota

John L. Frodel, Jr., M.D., F.A.C.S.

Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
Temple University School of Medicine
Philadelphia, Pennsylvania
Associate
Geisinger Medical Center
Danville, Pennsylvania

Gerry F. Funk, M.D., F.A.C.S.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Iowa Carver College of Medicine
Director
Division of Head and Neck Oncology
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Bruce J. Gantz, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Iowa Carver College of Medicine
Head
Department of Otolaryngology–Head and Neck Surgery
University of Iowa Hospitals and Clinics
Iowa City, Iowa

C. Gaelyn Garrett, M.D.

Professor
Vanderbilt University School of Medicine
Medical Director
Vanderbilt Voice Center
Nashville, Tennessee

Jackie Gartner-Schmidt, Ph.D.

Assistant Professor
Department of Otolaryngology
University of Pittsburgh School of Medicine
Associate Director
University of Pittsburgh Voice Center
UPMC Mercy Hospital
Pittsburgh, Pennsylvania

William Donald Gay, D.D.S.

Hawes Professor of Maxillofacial Prosthetics (retired)
Department of Otolaryngology
Washington University in St. Louis School of Medicine
Attending Dentist
Barnes Hospital
St. Louis, Missouri

Norman N. Ge, M.D., M.S.E.E., F.A.C.S.

Associate Professor
Department of Otolaryngology
University of California, Irvine, School of Medicine
Orange, California
Chief
Department of Head and Neck Surgery
VA Long Beach Healthcare System
Long Beach, California

M. Boyd Gillespie, M.D., M.S.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Medical University of South Carolina
Charleston, South Carolina

Douglas A. Girod, M.D., F.A.C.S.

Professor and Russell E. Bridwell Chair
Department of Otolaryngology–Head and Neck Surgery
Senior Associate Dean for Clinical Affairs
University of Kansas School of Medicine
University of Kansas of Medical Center
Kansas City, Kansas

George S. Goding, Jr., M.D.

Associate Professor
Department of Otolaryngology
University of Minnesota Medical School
Faculty
Department of Otolaryngology
Hennepin County Medical Center
Minneapolis, Minnesota

Andrew N. Goldberg, M.D., F.A.C.S.

Professor
Departments of Otolaryngology–Head and Neck Surgery and Neurological Surgery
University of California, San Francisco, School of Medicine
Director
Rhinology and Sinus Surgery
UCSF Medical Center
San Francisco, California

David Goldenberg, M.D.

Associate Professor
Department of Surgery
Division of Otolaryngology–Head and Neck Surgery
Penn State University College of Medicine
Director
Head and Neck Surgery
Penn State Milton S. Hershey Medical Center
Director
Head and Neck Cancer Program
Penn State Cancer Institute
Hershey, Pennsylvania

Daniel O. Graney, Ph.D.

Professor
Department of Biological Structure
University of Washington School of Medicine
Seattle, Washington

Nazaneen N. Grant, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Georgetown University School of Medicine and Health Sciences
Georgetown University Hospital
Washington, D.C.

Vincent Grégoire, M.D., Ph.D., Hon.F.R.C.R.

Professor of Radiation Oncology
Catholic University of Louvain
Louvain-la-Neuve, Belgium
Head of Clinics
St. Luc University Hospital
Brussels, Belgium

Heike Gries, M.D., Ph.D.

Assistant Professor of Anesthesiology and Pediatrics
Division of Pediatric Anesthesiology
Department of Anesthesiology and Peri-Operative Medicine
Oregon Health and Science University School of Medicine
Portland, Oregon

Samuel P. Gubbels, M.D.

Assistant Professor
Department of Surgery
University of Wisconsin–Madison School of Medicine and Public Health
Madison, Wisconsin

Joel Guss, M.D.

Attending Physician
Department of Head and Neck Surgery
Kaiser Permanente Medical Center
Walnut Creek, California

Patrick Ha, M.D., F.A.C.S.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Physician
Johns Hopkins Head and Neck Surgery at the Greater Baltimore Medical Center
Milton J. Dance, Jr., Head and Neck Center
Baltimore, Maryland

Grant S. Hamilton, III, M.D.

Assistant Professor
University of Iowa Carver College of Medicine
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Ehab Y. Hanna, M.D., F.A.C.S.

Lecturer
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Professor and Vice Chairman
Department of Head and Neck Surgery
Director of Skull Base Surgery
Medical Director of Head and Neck Center
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Lee A. Harker, M.D.

Formerly Deputy Director
Boys Town National Research Hospital
Vice Chair
Department of Otolaryngology and Human Communication
Omaha, Nebraska

Uli Harréus, Dr.Med.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Ludwig-Maximilians University
Grosshadern Clinic
Munich, Germany

Robert V. Harrison, Ph.D.

Professor and Director of Research
Department of Otolaryngology–Head and Neck Surgery
University of Toronto Faculty of Medicine
Senior Scientist
Neuroscience and Mental Health
Hospital for Sick Children
Toronto, Ontario, Canada

Bruce H. Haughey, M.B.Ch.B., F.A.C.S., F.R.A.C.S.

Professor and Director
Head and Neck Surgical Oncology
Department of Otolaryngology–Head and Neck Surgery
Washington University in St. Louis School of Medicine
St. Louis, Missouri

John W. Hellstein, D.D.S.

Clinical Professor of Oral and Maxillofacial Pathology
University of Iowa Carver College of Medicine
Iowa City, Iowa

Kurt Herzer

Marshall Scholar
Department of Social Policy and Social Work
University of Oxford
Oxford, United Kingdom
Woodrow Wilson Fellow
Departments of Public Health Studies and Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Michael S. Hildebrand, Ph.D.

Postdoctoral Fellow
Department of Otolaryngology
University of Iowa Carver College of Medicine
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Frans J. M. Hilgers, M.D., Ph.D.

Professor
Amsterdam Center for Language and Communication (Institute of Phonetic Sciences)
Academic Medical Center
University of Amsterdam
Emeritus Chairman
Department of Head and Neck Oncology and Surgery
The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital
Amsterdam, The Netherlands

Justin D. Hill, M.D.

Physician
Central Oregon Ear, Nose & Throat
Bend, Oregon

Michael L. Hinni, M.D.

Associate Professor and Residency Program Director
Mayo Clinic College of Medicine
Consultant
Department of Otolaryngology–Head and Neck Surgery
Mayo Clinic
Phoenix, Arizona

Henry T. Hoffman, M.D., F.A.C.S.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Iowa Carver College of Medicine
Director
Voice Clinic
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Eric H. Holbrook, M.D., M.S.(Anat.)

Assistant Professor
Department of Otology and Laryngology
Harvard Medical School
Associate Surgeon
Department of Otolaryngology
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Lauren D. Holinger, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Head
Division of Pediatric Otolaryngology
Children's Memorial Hospital
Chicago, Illinois

Allison MacGregor Holzapfel, M.D.

Volunteer Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

David B. Hom, M.D., F.A.C.S.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Director
Facial Plastic and Reconstructive Surgery
University of Cincinnati Medical Center
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

John W. House, M.D.

Clinic Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Southern California Keck School of Medicine
Associate Physician
House Clinic
President
House Ear Institute
Los Angeles, California

Joyce Colton House, M.D.

Chief Resident
Boston Medical Center
Boston, Massachusetts

Timothy E. Hullar, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Washington University in St. Louis School of Medicine
St. Louis, Missouri

Murad Husein, M.D.

Assistant Professor
London Health Sciences Centre
Victoria Hospital
Children's Hospital of Western Ontario
London, Ontario, Canada

Steven Ing, M.D.

Assistant Professor of Medicine
The Ohio State University College of Medicine
Columbus, Ohio

Tim A. Iseli, M.B.B.S., F.R.A.C.S.

Staff Surgeon
Royal Melbourne Hospital
Melbourne, Victoria, Australia

Stacey Ishman, M.D.

Assistant Professor
Department of Pediatrics
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Director
Center for Snoring and Sleep Surgery
Johns Hopkins Hospital
Baltimore, Maryland

Robert K. Jackler, M.D.

Edward C. and Amy H. Sewall Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Associate Dean
Stanford University School of Medicine
Attending Physician
Lucile Packard Children's Hospital at Stanford
Stanford, California

Brian Jameson, D.O.

Clinical Assistant Professor
Temple University School of Medicine
Philadelphia, Pennsylvania
Attending Endocrinologist
Geisinger Wyoming Valley Medical Center
Wilkes-Barre, Pennsylvania

Herman A. Jenkins, M.D.

Professor and Chair
Department of Otolaryngology
University of Colorado, Denver, School of Medicine
University of Colorado Hospital
Aurora, Colorado

Hong-Ryol Jin, M.D., Ph.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
Seoul National University College of Medicine
Seoul, Korea

John K. Joe, M.D.*

Assistant Professor
Department of Surgery
Division of Otolaryngology–Head and Neck Surgery
Yale University School of Medicine
New Haven, Connecticut

Stephanie A. Joe, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Illinois at Chicago College of Medicine
Director
Sinus and Nasal Allergy Center
Codirector
Skull Base Surgery
University of Illinois Hospital
Chicago, Illinois

*Deceased

Gary Johnson, M.D.
Professor
Department of Obstetrics and Gynecology
Director of Gynecologic Oncology
Clerkship Director
Southern Illinois University School of Medicine
Springfield, Illinois

Rhonda Johnson, M.Ed., Ph.D.
Assistant Professor
Department of Psychiatry
Southern Illinois University School of Medicine
Psychologist
SimmonsCooper Cancer Institute
St. John's Hospital
Memorial Medical Center
Springfield, Illinois

Tiffany A. Johnson, Ph.D.
Assistant Professor
Department of Speech-Language-Hearing: Sciences and Disorders
University of Kansas
Lawrence, Kansas

Timothy M. Johnson, M.D.
Professor
Department of Dermatology and Otorhinolaryngology–Head and Neck Surgery
University of Michigan Medical School
Ann Arbor, Michigan

Nick S. Jones, M.D., F.R.C.S., F.R.C.S.(ORC)
Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Nottingham
Queens Medical Centre
University Hospital
Nottingham, United Kingdom

Sheldon S. Kabaker, M.D.
Professor
Department of Otolaryngology
University of California, San Francisco, School of Medicine
San Francisco, California

Lucy H. Karnell, Ph.D.
Research Scientist
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Matthew L. Kashima, M.D., M.P.H.
Assistant Professor
Johns Hopkins University School of Medicine
Chair
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins Bayview Medical Center
Baltimore, Maryland

Robert M. Kellman, M.D.
Professor and Chair
Department of Otolaryngology and Communication Sciences
SUNY Upstate Medical University
Syracuse, New York

Paul E. Kelly, M.D.
Staff Surgeon
Eastern Long Island Hospital
Greenport, New York
Peconic Bay Medical Center
Riverhead, New York

David W. Kennedy, M.D.
Professor of Rhinology
Department of Otolaryngology–Head and Neck Surgery
Vice Dean for Professional Services
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Ayesha N. Khalid, M.D.
Clinical Instructor
Oregon Health and Science University School of Medicine
Portland, Oregon

Merrill S. Kies, M.D.
Professor of Medicine
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Paul R. Kileny, Ph.D.
Professor
Departments of Otolaryngology and Pediatrics
University of Michigan Medical School
Academic Program Director
Audiology and Hearing Rehabilitation
University of Michigan Health System
Ann Arbor, Michigan

David W. Kim, M.D.
Clinical Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Division of Facial Plastic Surgery
University of California, San Francisco, School of Medicine
San Francisco, California

Jason H. Kim, M.D., F.A.C.S.
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of California, Irvine, School of Medicine
Orange, California

Theresa B. Kim, M.D.
Resident
Department of Otolaryngology–Head and Neck Surgery
UCSF Medical Center
San Francisco, California

William J. Kimberling, Ph.D.
Professor of Ophthalmology
Departments Ophthalmology and Visual Sciences and Otolaryngology
University of Iowa Carver College of Medicine
Iowa City, Iowa
Senior Scientist
Boys Town National Research Hospital
Omaha, Nebraska

Jeffrey Koh, M.D., M.B.A.
Professor of Anesthesiology and Pediatrics
Oregon Health and Science University School of Medicine
Chief
Division of Pediatric Anesthesiology and Pain Management
Doernbecher Children's Hospital
Portland, Oregon

Niels Kokot, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Southern California Keck School of Medicine
Los Angeles, California

Peter J. Koltai, M.D., F.A.C.S., F.A.A.P.

Professor of Otolaryngology
Department of Otolaryngology–Head and Neck Surgery
Stanford University School of Medicine
Chief
Division of Pediatric Otolaryngology
Lucile Packard Children's Hospital at Stanford
Stanford, California

Frederick K. Kozak, M.D.

Clinical Professor
University of British Columbia Faculty of Medicine
Head
Division of Pediatric Otolaryngology
Medical/Surgical Director
Cochlea Implant Program
B.C. Children's Hospital
Vancouver, British Columbia, Canada

Paul R. Krakovitz, M.D.

Assistant Professor
Department of Surgery
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Section Head, Pediatric Otolaryngology
Head and Neck Institute
Cleveland Clinic
Cleveland, Ohio

Russell W. H. Kridel, M.D., F.A.C.S.

Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
Division of Facial Plastic and Reconstructive Surgery
University of Texas Medical School at Houston
Houston, Texas

Parvesh Kumar, M.D.

Professor and Chair
Department of Radiation Oncology
University of Southern California Keck School of Medicine
Chair
Department of Radiation Oncology
Los Angeles County Hospital–USC Medical Center
Director
Division of Radiation Oncology
USC Norris Cancer Center Hospital
Los Angeles, California

Melda Kunduk, Ph.D.

Assistant Professor
Department of Communication Sciences and Disorders
Louisiana State University School of Medicine at New Orleans Health Sciences Center
Speech Pathologist
Department of Otolaryngology–Head Neck Surgery
Louisiana State University Health Sciences Center New Orleans, Lourisiana
Our Lady of the Lake Voice Center
Baton Rouge, Louisiana

Ollivier Laccourreye, M.D.

Professor
Department of Otorhinolaryngology–Head and Neck Surgery
Paris Descartes University
Hôpital Européen Georges Pompidou
Paris, France

JoAnne Lacey, M.D.

Assistant Professor
Department of Radiology
Division of Neuroradiology
Washington University in St. Louis School of Medicine
Neuroradiologist
Barnes-Jewish Hospital
St. Louis, Missouri

Stephen Y. Lai, M.D., Ph.D.

Assistant Professor
Department of Head and Neck Surgery
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Devyani Lal, M.D.

Chief Resident
Department of Otolaryngology–Head and Neck Surgery
Loyola University Medical Center
Maywood, Illinois

Anil K. Lalwani, M.D.

Mendik Foundation Professor and Chair
Department of Otolaryngology
New York University School of Medicine
New York, New York

Paul R. Lambert, M.D.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Medical University of South Carolina
Charleston, South Carolina

Amy Anne Lassig, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Minnesota Medical School
Minneapolis, Minnesota

Richard E. Latchaw, M.D.

Professor
Department of Radiology
University of California, Davis, School of Medicine
Director
Neuroradiology Division
Department of Radiology
UC Davis Medical Center
Sacramento, California

Kevin P. Leahy, M.D., Ph.D.

Assistant Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Daniel J. Lee, M.D.

Assistant Professor
Department of Otology and Laryngology
Harvard Medical School
Department of Otolaryngology
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Ken K. Lee, M.D.
Associate Professor
Departments of Dermatology, Surgery, and Otolaryngology
Director
Department of Dermatologic and Laser Surgery
Oregon Health and Science University School of Medicine
Portland, Oregon

Nancy Lee, M.D.
Associate Attending
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Jean-Louis Lefebvre, M.D.
Professor and Chief
Head and Neck Cancer
Center Oscar Lambret
Lille, France

Maureen A. Lefton-Greif, Ph.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Department of Pediatrics
Johns Hopkins University School of Medicine
Speech-Language Pathologist
Johns Hopkins Hospital
Baltimore, Maryland

Donald A. Leopold, M.D., M.S.(Bus.)
Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of Nebraska School of Medicine
Omaha, Nebraska

James S. Lewis, Jr., M.D.
Assistant Professor of Pathology and Immunology
Department of Anatomic and Molecular Pathology
Director, Research Histology and Tissue Microarray Laboratory
Washington University in St. Louis School of Medicine
St. Louis, Missouri

Daqing Li, M.D.
Associate Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Director
Gene and Molecular Therapy Laboratory
Director
Temporal Bone Laboratory
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Timothy S. Lian, M.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Residency Program Director
Louisiana State University Health Sciences Center School of Medicine Shreveport
Shreveport, Louisiana

Greg R. Licameli, M.D., M.H.C.M., F.A.C.S.
Assistant Professor
Department of Otology and Laryngology
Harvard Medical School
Interim Chief
Department of Otolaryngology
Children's Hospital
Boston, Massachusetts

Charles J. Limb, M.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Jeri A. Logemann, Ph.D.
Ralph and Jean Sundin Professor
Department of Communication Sciences and Disorders
Northwestern University
Evanston, Illinois
Professor
Departments of Neurology and Otolaryngology–Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Director
Voice, Speech, and Language Service and Swallowing Center
Northwestern Memorial Hospital
Chicago, Illinois

Thomas Loh, M.B.B.S., F.R.C.S.
Associate Professor
Department of Otolaryngology
National University of Singapore
Senior Consultant
Department of Otolaryngology–Head and Neck Surgery
National University Hospital
Singapore

Brenda L. Lonsbury-Martin, Ph.D.
Professor
Department of Otolaryngology–Head and Neck Surgery
Loma Linda University School of Medicine
Senior Research Scientist
VA Loma Linda Healthcare System
Loma Linda, California

Manuel A. Lopez, M.D.
Chief
Facial Plastic Surgery
Wilford Hall Medical Center
San Antonio, Texas

Rodney P. Lusk, M.D.
Director
Ear, Nose, and Throat Institute
Boys Town National Research Hospital
Omaha, Nebraska

Lawrence R. Lustig, M.D.
Francis A. Sooy, M.D., Chair in Otolaryngology
Chief
Division of Otology and Neurotology
Department of Otolaryngology–Head and Neck Surgery
University of California, San Francisco, School of Medicine
San Francisco, California

Anna Lysakowski, Ph.D.
Professor
Department of Anatomy and Cell Biology
University of Illinois at Chicago College of Medicine
Chicago, Illinois

Carol J. MacArthur, M.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Oregon Health and Science University School of Medicine
Portland, Oregon

Robert H. Maisel, M.D.
Professor
Department of Otolaryngology
University of Minnesota Medical School
Chief of Otolaryngology
Hennepin County Medical Center
Minneapolis, Minnesota

James P. Malone, M.D.
Associate Professor
Division of Otolaryngology
Southern Illinois University School of Medicine
Springfield, Illinois

Ellen M. Mandel, M.D.
Associate Professor
Department of Otolaryngology
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Susan J. Mandel, M.D., M.P.H.
Professor and Associate Chief
Division of Endocrinology, Diabetes and Metabolism
Department of Medicine
University of Pennsylvania Health System
Philadelphia, Pennsylvania

Scott C. Manning, M.D.
Professor
Department of Otolaryngology
University of Washington in St. Louis School of Medicine
Chief
Division of Pediatric Otolaryngology
Seattle Children's Hospital
Seattle, Washington

Lynette Mark, M.D.
Associate Professor
Departments of Anesthesiology and Critical Care Medicine and Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Jeffery C. Markt, D.D.S.
Associate Professor and Director
Department of Otolaryngology–Head and Neck Surgery
Division of Oral Facial Prosthetics/Dental Oncology
University of Nebraska School of Medicine
Omaha, Nebraska

Michael Marsh, M.D.
Physician
Arkansas Center for Ear, Nose, Throat and Allergy
Fort Smith, Arkansas

Glen K. Martin, Ph.D.
Professor
Department of Otolaryngology–Head and Neck Surgery
Loma Linda School of Medicine
Loma Linda, California

Douglas E. Mattox, M.D.
Professor and William Chester Warren, Jr., M.D., Chair
Department of Otolaryngology–Head and Neck Surgery
Emory School of Medicine
Atlanta, Georgia

Thomas V. McCaffrey, M.D., Ph.D.
Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of South Florida College of Medicine
Program Leader and Senior Member
Head and Neck Oncology
H. Lee Moffitt Cancer Center
Tampa, Florida

Timothy M. McCulloch, M.D., F.A.C.S.
Professor
Department of Surgery
University of Wisconsin School of Medicine and Public Health
Chair
Division of Otolaryngology–Head and Neck Surgery
University of Wisconsin Hospitals and Clinics
Madison, Wisconsin

JoAnn McGee, Ph.D.
Scientist
Developmental Auditory Physiology Laboratory
Boys Town National Research Hospital
Omaha, Nebraska

John F. McGuire, M.D.
Attending Physician
Department of Otolaryngology
Fallbrook Hospital
Fallbrook, California

Jonathan McJunkin, M.D.
Resident
Department of Otolaryngology–Head and Neck Surgery
Washington University Medical Center
St. Louis, Missouri

J. Scott McMurray, M.D.
Associate Professor
Departments of Surgery and Pediatrics
University of Wisconsin School of Medicine and Public Health
American Family Children's Hospital
Madison, Wisconsin

Albert L. Merati, M.D.
Associate Professor and Chief
Division of Laryngology
Department of Otolaryngology–Head and Neck Surgery
Department of Speech and Hearing Sciences
University of Washington School of Medicine
Adjunct Associate Professor
Seattle, Washington

Saumil N. Merchant, M.D.
Gudrun Larsen Eliasen and Nels Kristian Eliasen Professor of Otology and Laryngology
Harvard Medical School
Surgeon in Otolaryngology
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Anna H. Messner, M.D.
Professor
Departments of Otolaryngology–Head and Neck Surgery and Pediatrics
Stanford University School of Medicine
Stanford, California
Vice Chair
Department of Otolaryngology–Head and Neck Surgery
Lucile Packard Children's Hospital at Stanford
Palo Alto, California

James Michelson, M.D.

Professor
Department of Orthopedics and Rehabilitation
University of Vermont College of Medicine
Medical Informaticist
Fletcher Allen Health Care
Burlington, Vermont

Henry A. Milczuk, M.D.

Associate Professor of Pediatric Otolaryngology
Oregon Health and Science University School of Medicine
Portland, Oregon

Lloyd B. Minor, M.D.

Andelot Professor and Director
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Steven Ross Mobley, M.D.

Associate Professor
Facial Plastic and Reconstructive Surgery
Department of Otolaryngology
University of Utah School of Medicine
Salt Lake City, Utah

Harlan Muntz, M.D., F.A.C.S., F.A.A.P.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Utah School of Medicine
Director
Department of Pediatric Otolaryngology
Primary Children's Medical Center
Salt Lake City, Utah

Craig S. Murakami, M.D.

Clinical Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Director
Department of Facial Plastic Surgery
Virginia Mason Medical Center
Seattle, Washington

Charles M. Myer, III, M.D.

Professor and Vice Chair
Department of Otolaryngology
University of Cincinnati College of Medicine
Director
Hearing Impaired Clinic
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Robert M. Naclerio, M.D.

Professor and Chief
Department of Otolaryngology–Head and Neck Surgery
University of Chicago Pritzker School of Medicine
Chicago, Illinois

Joseph B. Nadol, Jr., M.D.

Walter Augustus Lecompte Professor and Chair
Department of Otology and Laryngology
Harvard Medical School
Chief
Department of Otolaryngology
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Paul S. Nassif, M.D., F.A.C.S.

Assistant Clinical Professor
Department of Otolaryngology
University of Southern California Keck School of Medicine
Los Angeles, California
Partner
Spalding Drive Cosmetic Surgery and Dermatology
Beverly Hills, California

Julian Nedzelski, M.D.

Professor
Department of Otolaryngology
University of Toronto Faculty of Medicine
Otolaryngologist-in-Chief
Sunnybrook Health Sciences Centre
Toronto, Ontario, Canada

Piero Nicolai, M.D.

Professor
University of Brescia School of Medicine
Chairman
Spedali Civili
Brescia, Italy

David R. Nielsen, M.D.

Executive Vice President and CEO
American Academy of Otolaryngology–Head and Neck Surgery
Alexandria, Virginia

John K. Niparko, M.D.

George T. Nager Professor
Department of Otolaryngology–Head and Neck Surgery
Director
Divisions of Otology, Neurotology, Skull Base Surgery, and Audiology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Susan J. Norton, Ph.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
Adjunct Professor
Department of Speech and Hearing Sciences
University of Washington School of Medicine
Chief
Department of Pediatric Audiology
Seattle Children's Hospital
Seattle, Washington

S. A. Reza Nouraei, M.A.(Cantab.), M.B.B.Chir., M.R.C.S.

Researcher
The Laryngology Research Group
University College London
Academic Specialist Registrar
Charing Cross Hospital
London, United Kingdom

Daniel W. Nuss, M.D., F.A.C.S.

G. D. Lyons Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Louisiana State University Health Sciences Center School of Medicine at New Orleans
New Orleans, Louisiana

Brian Nussenbaum, M.D.

Associate Professor of Otolaryngology
Vice Chair for Clinical Affairs
Patient Safety Officer
Washington University in St. Louis School of Medicine
Attending Surgeon
Barnes-Jewish Hospital
St. Louis, Missouri

Rick M. Odland, M.D., Ph.D.

Associate Professor
Department of Otolaryngology
University of Minnesota Medical School
Staff Surgeon
Departmental of Otolaryngology
Hennepin County Medical Center
Minneapolis, Minnesota

Gerard O'Donoghue, M.Ch., F.R.C.S.

Professor of Otology and Neurotology
University of Nottingham
Codirector
National Biomedical Unit in Hearing
Department of Otolaryngology
Queen's Medical Centre
Nottingham, United Kingdom

Eric R. Oliver, M.D.

Chief Resident
Department of Otolaryngology–Head and Neck Surgery
MUSC University Hospital
Charleston, South Carolina

Bert W. O'Malley, Jr., M.D.

Gabriel Tucker Professor and Chairman
Department of Otorhinolaryngology–Head and Neck Surgery
Professor of Neurosurgery
Abramson Cancer Center
University of Pennsylvania School of Medicine
Codirector
Center for Cranial Base Surgery
Codirector
Head and Neck Cancer Center
University of Pennsylvania Health System
Philadelphia, Pennsylvania

Robert C. O'Reilly, M.D.

Clinical Associate Professor
Department of Otolaryngology and Pediatrics
Jefferson Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania
Pediatric Otology/Neurotology
A. I. duPont Hospital for Children
Wilmington, Delaware

Juan Camilo Ospina, M.D.

Assistant Professor
Javeriana University School of Medicine
Head
Division of Otorhinolaryngology and Maxillofacial Surgery
San Ignacio University Hospital
Director
Division of Otorhinolaryngology
Roosevelt Institute
Bogota, Colombia

Robert H. Ossoff, D.M.D., M.D.

Guy M. Maness Professor of Laryngology and Voice
Department of Otolaryngology–Head and Neck Surgery
Vanderbilt University School of Medicine
Assistant Vice Chancellor for Compliance and Corporate Integrity
Vanderbilt Medical Center
Nashville, Tennessee

Kristen J. Otto, M.D.

Assistant Professor
Department of Otolaryngology and Communicative Sciences
University of Mississippi School of Medicine
Jackson, Mississippi

Mark D. Packer, M.D.

Assistant Clinical Professor
University of Texas Health Science Center at San Antonio School of Medicine
San Antonio Uniformed Services Health Education Consortium
San Antonio, Texas
Staff Neurotologist
Wilford Hall Medical Center
Lackland Air Force Base, Texas

John Pallanch, M.D.

Assistant Professor
Department of Otolaryngology
Mayo School of Graduate Medical Education
Chair
Division of Rhinology
Department of Otorhinolaryngology
Mayo Clinic
Rochester, Minnesota

James N. Palmer, M.D.

Associate Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Director
Division of Rhinology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Stephen S. Park, M.D.

Professor and Vice Chair
Department of Otolaryngology
Director
Division of Facial Plastic Surgery
University of Virginia School of Medicine
Charlottesville, Virginia

Sundip Patel, M.D.

Resident
Department of Otolaryngology–Head Neck Surgery
University of Illinois Hospital
Chicago, Illinois

G. Alexander Patterson, M.D.

Professor
Department of Surgery
Washington University in St. Louis School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Bruce W. Pearson, M.D.
Emeritus Professor
Department of Otolaryngology–Head and Neck Surgery
Mayo Clinic College of Medicine
Jacksonville, Florida

Phillip K. Pellitteri, D.O., F.A.C.S.
Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
Temple University School of Medicine
Philadelphia, Pennsylvania
Chief, Section of Head, Neck, and Endocrine Surgery
Department of Otolaryngology–Head and Neck Surgery
Geisinger Health System
Danville, Pennsylvania

Jonathan A. Perkins, D.O.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Attending Pediatric Otolaryngologist
Seattle Children's Hospital
Seattle, Washington

Stephen W. Perkins, M.D.
Clinical Associate Professor
Department of Otolaryngology
Indiana University School of Medicine
President
Meridian Plastic Surgeons
Meridian Plastic Surgery Center
Indianapolis, Indiana

Colin D. Pero, M.D.
Volunteer Clinical Faculty
University of Texas Southwestern Medical School
Dallas, Texas
Private Practice
Plano, Texas

Shirley S. N. Pignatari, M.D., Ph.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Federal University of São Paulo
Head
Pediatric ENT Division
ENT Center of São Paulo
Professor
Edmundo Uasconcelos Hospital
São Paulo, Brazil

Steven D. Pletcher, M.D.
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of California, San Francisco, School of Medicine
San Francisco, California

Aron Popovtzer, M.D.
Physician
Davidoff Comprehensive Cancer Center
Consultant
Department of Otolaryngology
Rabin Medical Center
Petah-Tikva, Israel

Gregory N. Postma, M.D.
Professor
Department of Otolaryngology
Medical College of Georgia
Director
Center for Voice and Swallowing Disorders
Augusta, Georgia

William P. Potsic, M.D., M.M.M.
Professor
Department Otolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Senior Surgeon
Division of Otolaryngology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Sheri A. Poznanovic, M.D.
Clinical Instructor
University of Colorado School of Medicine
Clinical Staff
The Children's Hospital
Denver, Colorado
Pediatric Otolaryngologist
Colorado Otolaryngology Associates
Colorado Springs, Colorado

Vito C. Quatela, M.D.
Clinical Associate Professor
Department of Otolaryngology
University of Rochester School of Medicine and Dentistry
Quatela Center for Plastic Surgery
Rochester, New York

C. Rose Rabinov, M.D.
Bakersfield, California

Virginia Ramachandran, Au.D
Senior Staff Audiologist
Department of Otolaryngology–Head and Neck Surgery
Division of Audiology
Henry Ford Hospital
Detroit, Michigan

Gregory W. Randolph, M.D., F.A.C.S
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Harvard Medical School
Director
Endocrine Surgery, General Otolaryngology, and General and Thyroid Services
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Christopher H. Rassekh, M.D., F.A.C.S
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Chief
Division of Head and Neck Oncology
West Virginia University School of Medicine
Co-Director, Center for Cranial Base Surgery
Morgantown, West Virginia

Steven D. Rauch, M.D.
Associate Professor
Department of Otology and Laryngology
Harvard Medical School
Coordinator
Medical Student Education
Department of Otolaryngology–Head and Neck Surgery
Massachusetts Eye and Ear Infirmary
Boston, Massachusetts

Lou Reinisch, Ph.D.
Professor of Physics and Head
Department of Physical and Earth Sciences
Jacksonville State University
Jacksonville, Alabama

Mark, A. Richardson, M.D.
Professor
Department of Otolaryngology–Head and Neck Surgery
Dean
School of Medicine
Oregon Health and Science University
Portland, Oregon

Gresham T. Richter, M.D.
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
The University of Arkansas for Medical Sciences College of Medicine
Division of Pediatric Otolaryngology
Vascular Anomalies Center
Arkansas Children's Hospital
Little Rock, Arkansas

James M. Ridgway, M.D.
Fellow
Facial Plastic and Reconstructive Surgery
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Seattle, Washington

K. Thomas Robbins, M.D.
Director
SimmonsCooper Cancer Institute at Southern Illinois University
Professor
Division of Otolaryngology–Head and Neck Surgery
Southern Illinois University School of Medicine
Springfield, Illinois

Frederick C. Roediger, M.D.
Resident
Department of Otolaryngology–Head and Neck Surgery
UCSF Medical Center
San Francisco, California

Jeremy Rogers, M.D.
Chief Resident
Department of Otolaryngology–Head and Neck Surgery
USF Medical Center
Head and Neck Program
H. Lee Moffitt Cancer Center
Tampa, Florida

Ohad Ronen, M.D., F.A.C.S.
Attending Surgeon
Department of Otolaryngology–Head and Neck Surgery
Lady Davis Carmel Medical Center
Haifa, Israel

Richard M. Rosenfeld, M.D., M.P.H.
Professor and Chairman
Department of Otolaryngology
SUNY Downstate School of Medicine
Chairman
Department of Otolaryngology
Long Island College Hospital
Brooklyn, New York

Bruce E. Rotter, D.M.D.
Professor
Oral and Maxillofacial Surgery
Associate Dean for Academic Affairs
Southern Illinois University School of Dental Medicine
Alton, Illinois
Consultant
Oral and Maxillofacial Surgeon
John Cochrane VA Medical Center
St. Louis, Missouri

Jay T. Rubinstein, M.D., Ph.D.
Professor
Departments of Otolaryngology and Bioengineering
University of Washington School of Medicine
Seattle, Washington

Michael J. Ruckenstein, M.D., F.A.C.S., F.R.C.S.C.
Professor
Residency Program Director
Department of Otorhinolaryngology–Head and Neck Surgery
Vice Chair for Education and Academic Affairs
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Zoran Rumboldt, M.D.
Associate Professor
Department of Radiology
Medical University of South Carolina
Charleston, South Carolina

Christina L. Runge-Samuelson, Ph.D.
Associate Professor
Department of Otolaryngology and Communication Sciences
Medical College of Wisconsin
Director
Koss Cochlear Implant Program
Children's Hospital of Wisconsin
Froedtert Hospital
Milwaukee, Wisconsin

Leonard P. Rybak, M.D., Ph.D.
Professor
Department of Surgery
Division of Otolaryngology
Southern Illinois University School of Medicine
Springfield, Illinois

Babak Sadoughi, M.D.
Resident and House Officer
Department of Otorhinolaryngology–Head and Neck Surgery
Montefiore Medical Center
Bronx, New York

John R. Salassa, M.D.
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Mayo Clinic College of Medicine
Jacksonville, Florida

Thomas J. Salinas, D.D.S.
Associate Professor of Dentistry
Department of Dental Specialties
Mayo Clinic
Rochester, Minnesota

Sandeep Samant, M.D., F.R.C.S.
Associate Professor and Chief
Division of Head and Neck Surgery
Department of Otolaryngology–Head and Neck Surgery
University of Tennessee College of Medicine
Director
Multidisciplinary Head and Neck Clinic
University of Tennessee Cancer Institute
Memphis, Tennessee

Robin A. Samlan, M.S., M.B.A.
Doctoral Student
University of Arizona College of Medicine
Tucson, Arizona

Ravi N. Samy, M.D.
Assistant Professor
Department of Otolaryngology
University of Cincinnati College of Medicine
Cincinnati, Ohio

Henry D. Sandel, IV, M.D.
Medical Director
The Sandel Center for Facial Plastic Surgery
Annapolis, Maryland

Guri S. Sandhu, M.B.B.S., F.R.C.S.(ORL-HNS)
Honorary Senior Lecturer
University College London
Consultant Otolaryngologist/Head and Neck Surgeon
Charing Cross Hospital
London, United Kingdom

Isamu Sando, M.D.
Professor Emeritus
Department of Otolaryngology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Cara Sauder, M.A., CCC-SLP
Adjunct Instructor
Division of Otolaryngology–Head and Neck Surgery
University of Utah School of Medicine
Clinical Director
Voice Disorders Clinic
University Hospital
Salt Lake City, Utah

Jeremy A. Scarlett, M.D.
Assistant Professor
Department of Anesthesiology
Medical College of Wisconsin
Milwaukee, Wisconsin

Richard L. Scher, M.D., F.A.C.S.
Associate Professor and Associate Chief
Division of Otolaryngology–Head and Neck Surgery
Duke University School of Medicine
Durham, North Carolina

David A. Schessel, M.D.
Assistant Professor
Department of Otolaryngology
Stony Brook University Medical Center School of Medicine
Stony Brook, New York

Cecelia E. Schmalbach, M.D.
Head and Neck–Microvascular Surgery
Wilford Hall Medical Center
Lackland Air Force Base
San Antonio, Texas

Todd J. Schwedt, M.D.
Assistant Professor of Neurology and Anesthesiology
Washington University in St. Louis School of Medicine
Director
Washington University Headache Center
St. Louis, Missouri

James J. Sciubba, D.M.D., Ph.D.
Professor (Retired)
Otolaryngology, Head and Neck Surgery, Dermatology, Pathology
Johns Hopkins University School of Medicine
Oral Medicine and Oral Pathology
Milton J. Dance, Jr., Head and Neck Center
Baltimore, Maryland

Sunitha Sequeira, M.D.
Resident
Department of Otolaryngology–Head and Neck Surgery
Washington University Medical Center
St. Louis, Missouri

Meena Seshamani, M.D., Ph.D.
Resident
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins Hospital
Baltimore, Maryland

Clough Shelton, M.D.
Professor and Chair
Department of Otolaryngology
Hetzel Presidential Endowed Chair in Otolaryngology
University of Utah School of Medicine
Salt Lake City, Utah

Neil T. Shepard, Ph.D.
Professor of Audiology
Department of Otolaryngology
Mayo Medical School College of Medicine
Rochester, Minnesota

Jonathan A. Ship, D.M.D.*
New York University College of Dentistry
New York, New York

W. Peyton Shirley, M.D.
Assistant Clinical Professor
Department of Otolaryngology
University of Alabama at Birmingham School of Medicine
The Children's Hospital of Alabama
Birmingham, Alabama

*Deceased.

Yelizaveta Shnayder, M.D., F.A.C.S.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Kansas School of Medicine
Kansas City, Kansas

Joseph Shvidler, M.D.

Attending Physician
Department of Otolaryngology
Madigan Army Medical Center
Tacoma, Washington

Kathleen C. Y. Sie, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Director
Childhood Communication Center
Seattle Children's Hospital
Seattle, Washington

Daniel B. Simmen, M.D.

Center for Rhinology and Facial Plastic Surgery, Skull Base Surgery, and Otology
Zurich, Switzerland

Marshall E. Smith, M.D., F.A.C.S., F.A.A.P.

Professor
Division of Otolaryngology–Head and Neck Surgery
University of Utah School of Medicine
Attending Physician and Medical Director
Voice Disorders Clinic
Primary Children's Medical Center
University Hospital
Salt Lake City, Utah

Richard J. H. Smith, M.D.

Professor
Department of Otolaryngology
University of Iowa Carver College of Medicine
Iowa City, Iowa

Robert A. Sofferman, M.D.

Professor and Chief
Department of Otolaryngology–Head and Neck Surgery
University of Vermont School of Medicine
Burlington, Vermont

Marlene Soma, M.B.B.S., F.R.A.C.S.

ENT Clinical Fellow
Great Ormond Street Hospital for Children
London, United Kingdom

Brad A. Stach, Ph.D.

Head
Division of Audiology
Department of Otolaryngology–Head and Neck Surgery
Henry Ford Hospital
Detroit, Michigan

Hinrich Staecker, M.D., Ph.D.

Associate Professor
Otolaryngology–Head and Neck Surgery
University of Kansas School of Medicine
Kansas City, Kansas

Aldo Cassol Stamm, M.D., Ph.D.

Affiliate Professor
Department of Otolaryngology–Head and Neck Surgery
Federal University of São Paulo
Director
ENT Center of São Paulo
Edmundo Vasconcelos Hospital
São Paulo, Brazil

James A. Stankiewicz, M.D.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
Loyola University School of Medicine
Senior Attending Staff Surgeon
Loyola University Medical Center
Maywood, Illinois

Rose Stavinoha, M.D.

Chief Resident
Department of Otolaryngology–Head and Neck Surgery
USF Medical Center
Tampa, Florida

Laura M. Sterni, M.D.

Assistant Professor
Department of Pediatrics
Johns Hopkins University School of Medicine
Director
Johns Hopkins Pediatric Sleep Center
Johns Hopkins Children's Center
Baltimore, Maryland

David L. Steward, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Director of Thyroid/Parathyroid Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

Rose Mary S. Stocks, M.D., Pharm.D.

Professor and Residency Program Director
Department of Otolaryngology–Head and Neck Surgery
University of Tennessee College of Medicine
Memphis, Tennessee

Holger H. Sudhoff, M.D., Ph.D.

Professor
Ruhr University Bochum School of Medicine
Bochum, Germany
Chairman and Medical Director
Department of Otorhinolaryngology–Head and Neck Surgery
Klinikum Bielefeld
Bielefeld, Germany

John B. Sunwoo, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Stanford University School of Medicine
Stanford Cancer Center
Stanford University Hospitals and Clinics
Stanford, California

Neil A. Swanson, M.D.

Professor of Dermatology, Surgery, and Otolaryngology
Chair
Department of Dermatology
Oregon Health and Science University School of Medicine
Portland, Oregon

Veronica C. Swanson, M.D.

Associate Professor
Departments of of Anesthesiology and Pediatrics
Oregon Health and Science University School of Medicine
Director
Pediatric Cardiac Anesthesia
Doernbecher Children's Hospital
Portland, Oregon

Robert A. Swarm, M.D.

Professor
Department of Anesthesiology
Washington University in St. Louis School of Medicine
Director
Barnes-Jewish Hospital–Washington University Pain Management Center
St. Louis, Missouri

Jonathan M. Sykes, M.D., F.A.C.S.

Professor
University of California, Davis, School of Medicine
Director
Facial Plastic Surgery
UC Davis Medical Center
Sacramento, California

Luke Tan, M.B.B.S., F.R.C.S., M.Med.Sci.

Associate Professor (Adjunct)
National University of Singapore
Senior Consultant
Head and Neck Surgeon
Gleneagles Medical Centre
Singapore

M. Eugene Tardy, Jr., M.D., F.A.C.S.

Professor of Clinical Otolaryngology
Division of Facial Plastic and Reconstructive Surgery
Department of Otolaryngology–Head and Neck Surgery
University of Illinois at Chicago College of Medicine
Chicago, Illinois

Sherard A. Tatum, III, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
SUNY Upstate Medical University
Director
Division of Facial Plastic and Reconstructive Surgery
Director
Cleft and Craniofacial Center
University Hospital
Syracuse, New York

S. Mark Taylor, M.D., F.R.C.S.C., F.A.C.S.

Associate Professor
Division of Otolaryngology–Head and Neck Surgery
Head
Section of Head and Neck Surgery
Dalhousie University Faculty of Medicine
Halifax, Nova Scotia, Canada

Natacha Teissier, M.D., Ph.D.

Senior Consultant
Department of Otorhinolaryngology
R. Debre Hospital
Paris, France

Steven A. Telian, M.D.

John L. Kemink Professor of Neurotology
Department of Otolaryngology–Head and Neck Surgery
University of Michigan Medical School
Ann Arbor, Michigan

David J. Terris, M.D.

Porubsky Distinguished Professor and Chairman
Department of Otolaryngology
Medical College of Georgia
Surgical Director
Medical College of Georgia Thyroid Center
Augusta, Georgia

Karen B. Teufert, M.D.

House Ear Institute
Los Angeles, California

J. Regan Thomas, M.D.

Francis L. Lederer Professor and Chairman
Department of Otolaryngology–Head and Neck Surgery
University of Illinois at Chicago
Chicago, Illinois

James N. Thompson, M.D., F.A.C.S.

Clinical Professor
Department of Otolaryngology
University of Texas Southwestern Medical School
Dallas, Texas
President and CEO
Federation of State Medical Boards of the United States

Dean M. Toriumi, M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
Division of Facial Plastic Surgery
University of Illinois at Chicago College of Medicine
Chicago, Illinois

Alejandro I. Torres, B.S.

Department of Biology
Seattle Pacific University
Virginia Mason Medical Center
Seattle, Washington

Joseph B. Travers, Ph.D.

Professor
Section of Oral Biology
Department of Dentistry
Associate Professor
Department of Psychology
The Ohio State University
Columbus, Ohio

Susan P. Travers, Ph.D.

Professor
Section of Oral Biology
Department of Dentistry
Associate Professor
Department of Psychology
The Ohio State University
Columbus, Ohio

Terance T. Tsue, M.D., F.A.C.S.

Associate Dean of Graduate Medical Education
Douglas A. Girod, M.D. Professor of Head and Neck Surgical Oncology
Vice Chair
Department of Otolaryngology–Head and Neck Surgery
University of Kansas School of Medicine
University of Kansas Hospital
Kansas City, Kansas

Ralph P. Tufano, M.D.

Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Director
Thyroid and Parathyroid Surgery
Johns Hopkins Hospital
Baltimore, Maryland

David E. Tunkel, M.D.

Associate Professor of Otolaryngology–Head and Neck Surgery, Pediatrics, and Anesthesia–Critical Care Medicine
Johns Hopkins University School of Medicine
Director
Pediatric Otolaryngology
Johns Hopkins Hospital
Baltimore, Maryland

Michael D. Turner, D.D.S., M.D.

New York University College of Dentistry
New York University School of Medicine
NYU Medical Center
New York, New York

Ravindra Uppaluri, M.D., Ph.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Washington University in St. Louis School of Medicine
St. Louis, Missouri

Michael F. Vaezi, M.D., Ph.D.

Professor of Medicine and Clinical Director
Division of Gastroenterology and Hepatology
Department of Medicine
Vanderbilt University School of Medicine
Director
Clinical Research
Director
Center for Esophageal and Mobility Disorders
Vanderbilt University Medical Center
Nashville, Tennessee

Thierry Van den Abbeele, M.D., Ph.D.

Professor
Department of Otorhinolaryngology
Paris Diderot University
Head
Department of Otorhinolaryngology
R. Debre Hospital
Paris, France

Michiel W. M. van den Brekel, M.D., Ph.D.

Professor
Academic Medical Center
University of Amsterdam
Chair
Department of Head Neck Oncology and Surgery
The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital
Amsterdam, The Netherlands

Mikhail Vaysberg, D.O.

Assistant Professor
Department of Otolaryngology
University of Florida College of Medicine
Gainesville, Florida

David E. Vokes, M.B.Ch.B., F.R.A.C.S.

Consultant Otolaryngologist
Head and Neck Surgeon
Auckland City Hospital
Auckland, New Zealand

P. Ashley Wackym, M.D.

Vice President for Research
Legacy Health System
President
Ear and Skull Base Institute
Portland, Oregon

Tamekia L. Wakefield, M.D.

Clinical Assistant Professor
Department of Otolaryngology
University of Kansas School of Medicine
Pediatric Otolaryngologist
University of Kansas Hospital
Kansas City, Kansas
Children's Mercy Hospital
Kansas City, Missouri

David L. Walner, M.D.

Assistant Professor of Pediatric Otolaryngology
Rush Medical College
Chicago, Illinois
Staff
Lutheran General Children's Hospital
Park Ridge, Illinois

Edward J. Walsh, Ph.D.

Director
Developmental Auditory Physiology Laboratory
Boys Town National Research Hospital
Omaha, Nebraska

Rohan R. Walvekar, M.D.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Louisiana State University Health Sciences Center School of Medicine at New Orleans
New Orleans, Louisiana

Tom D. Wang, M.D.

Professor of Facial Plastic Surgery
Department of Otolaryngology–Head and Neck Surgery
Oregon Health and Science University School of Medicine
Portland, Oregon

Frank M. Warren, III, M.D.

Assistant Professor
Department of Surgery
Division of Otolaryngology–Head and Neck Surgery
University of Utah School of Medicine
Salt Lake City, Utah

Randal S. Weber, M.D.

Professor and Chair
Department of Head and Neck Surgery
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Richard O. Wein, M.D., F.A.C.S.

Assistant Professor
Tufts University School of Medicine
Tufts Medical Center
Boston, Massachusetts

Gregory S. Weinstein, M.D.

Professor and Vice Chair
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Director
Division of Head and Neck Surgery
Department of Otorhinolaryngology–Head and Neck Surgery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Erik Kent Weitzel, M.D.

Adjunct Assistant Professor
F. Edward Hébert School of Medicine
Uniformed Services University of the Health Sciences
Chief
Department of Rhinology
Wilford Hall USAF Medical Center
Lackland Air Force Base, Texas

D. Bradley Welling, M.D., Ph.D., F.A.C.S.

Professor and Chair
Department of Otolaryngology
The Ohio State University College of Medicine
Columbus, Ohio

Richard D. Wemer, M.D.

Clinical Faculty
University of Minnesota
Minneapolis, Minnesota Medical School
Associate Physician
Park Nicolette Hospitals and Clinics
Saint Louis Park, Minnesota

Ralph F. Wetmore, M.D.

Professor
Department of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania School of Medicine
Chief
Division of Otolaryngology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Ernest A. Weymuller, Jr., M.D.

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Washington School of Medicine
Seattle, Washington

Brian J. Wiatrak, M.D.

Clinical Associate Professor of Surgery
University of Alabama at Birmingham School of Medicine
Chief
Pediatric Otolaryngology
Children's Hospital of Alabama
Birmingham, Alabama

Gregory J. Wiet, M.B.S., M.D.

Associate Professor
Departments of Otolaryngology and Biomedical Informatics
The Ohio State University College of Medicine
Department of Otolaryngology
Nationwide Children's Hospital
Columbus, Ohio

Richard H. Wiggins, III, M.D.

Associate Professor
Departments of Radiology, Otolaryngology–Head and Neck Surgery, and Biomedical Informatics
Director
Imaging Informatics
University of Utah School of Medicine
Department of Oncological Sciences–Head and Neck Imaging
Huntsman Cancer Institute
Salt Lake City, Utah

Andrea Willey, M.D.

Assistant Clinical Professor
Department of Dermatology
University of California, Davis, School of Medicine
Physician
Mohs and Reconstructive Surgery and Laser Surgery
Laser and Skin Surgery Center of Northern California
Sacramento, California
Solano Dermatology Associates
Vacaville, California

William N. William, Jr., M.D.

Assistant Professor
Department of Thoracic/Head and Neck Medical Oncology
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Glenn B. Williams, M.D.

Resident
Department of Otolaryngology–Head and Neck Surgery
University of Tennessee College of Medicine
Memphis, Tennessee

Franz J. Wippold, II, M.D., F.A.C.R.

Professor of Radiology
Washington University in St. Louis School of Medicine
Chief of Neuroradiology
Mallinckrodt Institute of Radiology
St. Louis, Missouri
Adjunct Professor
Department of Radiology/Radiologic Sciences
F. Edward Hébert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland
Attending Neuroradiologist
Barnes-Jewish Hospital
St. Louis Children's Hospital
St. Louis, Missouri

Gayle Ellen Woodson, M.D.

Professor and Chair
Division of Otolaryngology
Southern Illinois University School of Medicine
Springfield, Illinois

Audie L. Woolley, M.D.

Associate Clinical Professor of Surgery
Department of Otolaryngology
University of Alabama at Birmingham School of Medicine
Birmingham, Alabama

Christopher T. Wootten, M.D.

Assistant Professor
Department of Otolaryngology–Head Neck Surgery
Vanderbilt University School of Medicine
Division of Pediatric Otolaryngology
Vanderbilt Children's Hospital
Nashville, Tennessee

Peter-John Wormald, M.D., F.R.A.C.S., F.C.S.(SA), F.R.C.S.

Chair
Department of Otolaryngology–Head and Neck Surgery
University of Adelaide and Flinders University
Professor and Head
Department of Otolaryngology–Head and Neck Surgery
Queen Elizabeth Hospital
Adelaide, Australia

Charles D. Yingling, Ph.D., D.A.B.N.M.

Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
Stanford University School of Medicine
Stanford, California
Chief
Surgical Neuromonitoring Services
Sausalito, California

Bevan Yueh, M.D., M.P.H.

Professor and Chair
Department of Otolaryngology–Head and Neck Surgery
University of Minnesota Medical School
Minneapolis, Minnesota

Rex C. Yung, M.D.

Assistant Professor of Medicine and Oncology
Johns Hopkins University School of Medicine
Director
Pulmonary Oncology and Bronchology
Johns Hopkins Hospital
Baltimore, Maryland

Renzo A. Zaldívar, M.D.

Fellow
Ophthalmic Plastic and Reconstructive Surgery
Mayo Clinic
Rochester, Minnesota

George H. Zalzal, M.D.

Professor
Departments of Otolaryngology and Pediatrics
George Washington University School of Medicine and Health Sciences
Chief
Department of Pediatric Otolaryngology
Children's National Medical Center
Washington, D.C.

David S. Zee, M.D.

Professor
Department of Neurology
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Marc S. Zimbler, M.D., F.A.C.S.

Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Albert Einstein College of Medicine
Director
Facial Plastic and Reconstructive Surgery
Department of Otolaryngology–Head and Neck Surgery
Beth Israel Medical Center
New York, New York

S. James Zinreich, M.D.

Professor
Department of Radiology
Division of Neuroradiology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Teresa A. Zwolan, Ph.D.

Associate Professor
Department of Otolaryngology
University of Michigan Medical School
Director
Cochlear Implant Program
University of Michigan Health System
Ann Arbor, Michigan

Preface

The fifth edition of *Cummings Otolaryngology–Head and Neck Surgery* is written in response to the vast expansion of medical knowledge and technological advancements impacting our specialty and presents the most up-to-date information, covering new topics from surgical robotics and image guidance to evidence-based performance measurements. Nonetheless, we have worked hard to keep the fifth edition concise, removing overlapping content to make for easier reading, yet still covering in detail all major developments in the field.

Building on the success of the past four editions, the fifth edition also reflects a technology-driven change in curriculum, featuring access to the Expert Consult website, with text and images from the book as well as online video demonstrating the ACGME Key Indicator Procedures. The video component provides residents with a new opportunity to better understand the critical elements of these core procedures.

As with past editions, the field of otolaryngology–head and neck surgery is represented in all of its diversity. The table of contents has been restructured to reflect the extensive interrelationship of its various components. Every chapter contains Key Points at the start and a "most relevant" Suggested Readings list. A full reference list for each chapter is available online to supplement the overall content. Combined with the online version, the fifth edition remains the definitive resource for our specialty.

In acknowledgement of all those who have contributed to the specialty, the list of authors includes worldwide representation. Adding to excellence at the editorship level, Drs. Valerie Lund and John Niparko have assumed leadership roles, and Dr. Howard Francis has assumed an associate editorship position for the online video content. Through the combined effort of all contributors, our goal is to further the education of those now associated with otolaryngology–head and neck surgery and provide a foundation for continued progress by the generations to follow.

Acknowledgments

For those individuals privileged to serve and train under Dr. Charles Cummings, we recognize him as mentor, colleague and friend, physician and healer; we are grateful for his leadership and everlasting imprint on our mission in academic medicine.

Charlie, thank you. From your student, colleague, and friend,

Paul W. Flint

It has been a distinct honor and pleasure to be part of the editorial and publishing team assembled for this edition of *Cummings Otolaryngology–Head and Neck Surgery*. The authors have been tireless in their efforts and have worked strongly to produce chapters that are truly comprehensive in scope and depth. My sincere thanks goes to each one of them and their families, who inevitably have put up with liberal amounts of "burning the midnight oil." My loyal assistant of 20 years, Debbie Turner, has kept us to our deadlines and liaised with both authors and publishers in a highly organized way, while my office nurses have provided generous amounts of patient care to cover for my time away from the front lines during this textbook's creation. Similarly, the residents and fellows at Washington University in St. Louis have "held the fort" when necessary.

The ability to purvey knowledge starts, and continues, with one's education, for which thanks goes to my parents, the late Thomas and Marjorie Haughey, my teachers, medical professors, Otolaryngology residency mentors in Auckland, New Zealand, and at the University of Iowa, and colleagues in the specialty, from whom I have and will continue to learn.

My family has unswervingly endorsed the time required for this project, so heartfelt love and thanks go to my wife, Helen, as well as to Rachel and Jack, Chris, Will and Rachel, and Gretchen.

Finally, as we enjoy the teaching of this book and its ensuing online components, I try to keep in mind the source of all knowledge and truth: in the words of Proverbs 2 v.6 "…the Lord gives wisdom and from his mouth come knowledge and understanding." My sincere hope is that the readers everywhere will benefit from this textbook, better accomplishing our specialty's common goal of top quality patient care.

Bruce H. Haughey

I would like to thank Paul Flint and his colleagues for inviting me to participate in this prestigious project, the publishers for their exemplary efficiency in its management, and my partner, David Howard, for his constant support and encouragement.

Valerie J. Lund

Otolaryngology is a specialty of immense power. Scholarly work such as this text shows that in the tools of our specialty is the potential to address unmet challenges. I am grateful to Drs. Charles Cummings and Paul Flint, who showed confidence in me in inviting me to join a marvelously collaborative editorial team, and to the many chapter authors who have given their very best efforts in composing this essential resource.

My work is dedicated to those who have provided my guidance. To my parents, my family, my colleagues, and my ever thoughtful patients, you have taught me the importance of dedication to others and that true compassion is shown in action. Through you I've learned that this is not a world of scarcity but one of abundance that is to be shared.

John K. Niparko

The process of learning is truly lifelong. Participating in the creation of this text allows another way for me to continue to become invigorated and inspired by my specialty field. To my invaluable support mechanism, my wife, children, and family: Thank you.

Mark A. Richardson

I am deeply appreciative and honored to again serve as an editor of this important book. I would like to take this opportunity to recognize some individuals who have influenced my career: John Fredricksen; Douglas Bryce; the late Sir Donald Harrison; Robert Byers; Oscar Guillamondegui; Helmuth Goepfert; Robert Jahrsdoerfer; Charles Cummings; and the late Edwin Cocke. Also, I would like to remember and honor my parents, the late Elizabeth and Wycliffe Robbins, for the values they instilled in me. Finally, and

most of all, I cherish the love and support of my wife, Gayle Woodson, and the children, Phil, Nick, Greg, and Sarah, who together provide the caring background for making it all meaningful.

K. Thomas Robbins

It is a great privilege and honor to serve as an editor for this outstanding textbook. Although the knowledge base for our specialty and indeed all of medicine is continually evolving and growing, this contribution serves otolaryngologists and their patients throughout the world with the current expertise required for best ultimate treatment. As an academic department head, I treasure the wealth of information available to my resident physicians in training. As an individual who has centered his career in a subspecialty of Otolaryngology, I am especially proud to help enhance the information available to the reader in the area of Facial Plastic and Reconstructive Surgery.

On a personal note, I want thank and acknowledge the great help and assistance I received from my administrative assistant, Denise McManaman, in editing this textbook. Her tireless work ethic is always admirable and appreciated. Finally, thank you to my wife, Rhonda, and my children, Ryan, Aaron, and Evan, for their enthusiastic and never-wavering support in my professional activities.

J. Regan Thomas

CHAPTER ONE

Genetics and Otolaryngology

William J. Kimberling

Key Points

- Probably more than half of all hearing losses have a genetic basis.
- Genetic hearing loss can be inherited in several different ways: autosomal dominant, autosomal recessive, x-linked, and mitochondrial.
- Identification of specific genes that cause hearing loss has led to a remarkable increase in the understanding of the pathogenic process underlying genetic hearing loss disorders.
- Genetic testing has become a useful tool in diagnosing genetic hearing loss.
- Complex disorders such as tinnitus, vertigo, and susceptibility to otitis media are amenable to genetic study that will identify individuals at risk for developing these common disorders.

Genetics plays a role in just about everything, although the magnitude of that role may be, in a few cases, barely detectable. It is important—and quickly becoming even more so—for the otolaryngologist to understand genetics to carry out his or her medical obligations effectively. There are hundreds of syndromes that affect the head and neck,[1] and people with most of these syndromes come under the care of an ear, nose, and throat (ENT) surgeon at one time or another during their lives. Furthermore, hearing is an important aspect of the otolaryngologist's practice, and more than 50 different genes have been identified that cause nonsyndromic hearing loss (see the Hereditary Hearing Loss home page at http://webh01.ua.ac.be/hhh/). The identification of the basic dysfunction underlying all of these single-gene disorders is the first step to effective prevention and treatment, whether surgical or pharmacologic. An understanding of complex (presumably polygenic) disorders has become an extremely important objective for medical research. Liability for a variety of diseases (e.g., head and neck cancer, otosclerosis, otitis media, dyslexia) is controlled by several genes.[2-5] It is thought that the day is near when knowledge about an individual's genotype will identify those who are at high risk for development of these and other disorders.[6]

The genome revolution has placed mankind at the brink of the development of new and exciting therapies for both rare and common genetic disorders. It has thus become increasingly important for the ENT practitioner to recognize those disorders that have a strong genetic component and to be aware of the new and developing approaches to their treatment.

The Genome

The term *genome* refers to the collection of all of the genes that an organism possesses. It has been estimated that there are between 40,000 and 140,000 genes in the human genome. The genes are assembled into lengthy strands of deoxyribonucleic acid (DNA), which are organized linearly into chromosomes. The chromosomes are made up of the DNA that forms the genes and the intervening DNA as well as chromatin, which is a protein that assists in the maintenance of the structure and regulation of chromosomal expression. The nuclei of most human cells contain 46 chromosomes that are organized as 23 pairs. Except for the mitochondria, all genes that are contained within the human genome lie on one or the other of these chromosomes. The linear order of the genes on the chromosomes allows one to create maps of the human gene order; these maps are generally invariant throughout any given species. It is these maps that allow us to associate specific genes with specific traits through gene mapping.[7,8] Genes are transmitted in groups that correspond with the chromosomes. Aside from cases of the exception known as "crossing over," all of the genes of one chromosome (e.g., the paternal one) are transmitted together to the exclusion of the other one. Crossing over allows one chromosome to become a mosaic of both paternal and maternal genes; the frequency with which crossing over occurs has been studied and forms the basis for one of the two ways of measuring distances between genes. The physical distance between two genes is the number of bases between genes and is measured in megabases or kilobases. The genetic distance between two genes, however, is based on the frequency of observed recombination between them and can only be estimated by the study of informative matings and their offspring. Genetic distance is the result of a biologic phenomenon and is imperfectly correlated with physical distance. The order of genes on a chromosome is constant.

The amount of information stored in the genome is tremendous. In the human genome there are approximately 3×10^9 base pairs of DNA that make up the haploid genome. The largest chromosome, 1, contains about 10% of the total, whereas the smallest autosome, 21, contains about 2.5%. Given that the estimated number of genes is between 20,000 and 30,000, the expected number of genes per megabase is between 20 and 30. The average high-resolution chromosome band is about three megabases in size and would be expected to contain between 60 and 90 genes.

Another way of appreciating the size of the genome is to compare the amount of information in it with that in the typical encyclopedia. The encyclopedia would need to have 200 volumes of 1000 pages each to contain the information found in the human genome. In this analogy, gene size would vary from about a third of a page up to several pages. In actuality, the human genetic encyclopedia is packaged into 23 volumes, and the genes are not as easily demarcated as are chapters in a real encyclopedia. However, the analogy serves well when trying to understand the importance of deciphering the genome. This biologic encyclopedia is in truth a manual for the construction and maintenance

of a human being. By understanding the information contained within the genes, we will come to understand the basics of our own biology.

Unfortunately, the information in the genome is simply not organized into rational groupings. One purpose of the genome project had been to develop an index of the genome that would allow researchers who are trying to connect specific genes with specific disorders to do so efficiently.[9,10] From the perspective of the otolaryngologist, this means first that gene-specific diagnoses are now available for many ENT-related disorders and that ultimately better therapies will emerge as more is learned about the basic nature of hereditary disorders that affect hearing, speech, and the structures of the head and neck.

The genome revolution has placed mankind at the brink of the development of new and exciting therapies for both rare and common genetic disorders.[11] It will thus become increasingly important for the ENT practitioner to recognize those disorders that have a strong genetic component.

DNA Structure and the Genetic Code

Humans store genetic information in DNA, which is a linear polymer made up of four different nucleotides: adenine (A), guanine (G), thymidine (T), and cytosine (C). Nucleotides (also called bases) are linked together by phosphodiester bonds into a single strand. Nucleotides also have the capability of pairing with each other (A with T and G with C) through hydrogen bonds. Two strands of DNA can pair with each other in a complementary fashion (again, A with T and G with C) to form a double helix. The two strands are perfectly complementary; for example, if one strand has an order of ATGGGCCATA, its complement would be TACCCGGTAT. During replication, the two strands separate, and the base sequence of each strand would dictate the construction of a new, complementary strand. In this way, the sequence of the double strands is preserved in the two new identical double strands that are produced.

A single strand has an orientation that reflects the direction of the phosphodiester bond, which is usually referred to as going from the 5′ to the 3′ end; genes are transcribed in this direction. Because there is a double helix, the actual transcription occurs from only one strand, called the *template strand*. The antiparallel strand is referred to as the *coding strand*, because its base sequence corresponds with the sequence of the message; however, uracil is substituted for thymidine in the message.

The sequence of bases is what determines all parts of the gene, and it specifically determines the sequence of amino acids in the protein that results from the process of translation. The nucleotides within the coding region are arranged in groups of three, called *codons*, which determine the precise amino acid sequence. Because there are four bases, there are 64 possible combinations of nucleotides, but there are only 20 amino acids. Thus the code is said to be *degenerate*, because most amino acids are specified by more than one codon. For example, the code for valine can be GTT, GTC, GTA, or GTG. The third nucleotide can vary for most amino acids and is often called the *wobble nucleotide*. A specific codon, ATG, codes for methionine and also indicates the beginning of a coding sequence. There are three stop codons: TAA, TAG, and TGA.

Gene Structure and Expression

The definition of a gene has gone through several stages and is now neither simple nor straightforward. The gene is the basic unit of biologic information that can be transmitted from parents to offspring, and it typically provides information about structural or functional components of the cell. The information transfer occurs not only between parent and daughter cells but also between the nucleus and the cytoplasmic machinery. The transfer of this information is called *inheritance* when it occurs between parent and child. The transfer of information from genome within the nucleus to the cell proper would be referred to as *gene expression*. Gene structure has presumably evolved in a way that facilitates the transfer of genetic information, but the true molecular boundaries that define any specific gene are often poorly recognized.

The basic eukaryotic gene is made up of exons and introns. Exons make up the coding part of the gene; the intron is DNA that is interspersed between the exons. During the process of creating a message, introns are spliced out of the message, thus leaving only the exons to be translated into protein. The gene is thus an interrupted sequence of code that must be further processed into a usable message. Figure 1-1 illustrates how the structure of the gene is related to the process of transcription. During transcription, the whole gene is copied—exons and introns together—into a premessage. The premessage is then processed by excising the introns and joining the exons together to make a series of bases that code for a protein. The sites at which the excisions and rejoining take place are called *splice sites,* and specific sequences of bases are used to signal the cellular machinery to recognize these places. There are specific start and end points for the transcription of the gene as well; within the genes, there are specific signals in the form of three-base sequences (the start and stop codons) that indicate where translation into protein is to begin and end. The gene is thus made up of a coding sequence and punctuation.

In addition to the basic structure of a gene, there are elements that are both 5′ and 3′ of the gene that regulate its expression. These are called *cis-acting elements,* because they are on the same strand of DNA as the gene they regulate. Some of the regulatory elements may be inside one or more introns. In fact, the first few introns of a gene frequently contain such regulatory elements. Although some of the cis-acting elements are close to the actual start of the gene, others may be as much as 50 kilobases in front of (upstream) or in back of (downstream) the genes. Regulatory elements act predominantly by controlling the rate of transcription, and they respond to signals in the nucleoplasm to control the cellular specificity of gene action.

A basic understanding of gene structure is critical to an understanding of how mutations can disrupt gene function. Mutations can change the code, the punctuation, or the elements that regulate the expression of the gene; their detection and analysis are discussed in more detail in subsequent paragraphs.

The Molecular Basis of Patterns of Inheritance

There are three broad categories of genetic disease: chromosomal, monogenic, and complex. Chromosomal disorders are those in which relatively large segments of one or more chromosomes occur in only one copy or in more than the expected two copies. Examples would be Down syndrome (trisomy 21) and Turner's syndrome (missing an X or a Y, depending on your perspective). The term single-gene disorder refers to the large group of disorders that are due to mutations in only one gene. Many hearing loss disorders are known to be the result of mutations in specific genes; almost all single-gene disorders show a specific pattern of inheritance (e.g., dominant, recessive, X-linked). Complex traits are those in which the genetics are not clear. The commonly accepted idea is that complex disorders—like cleft lip and/or palate, reading disability, cancer, and hypertension, to name a few—are the result of the interaction between several genes, the environment, and random factors. The otolaryngologist will encounter each category of genetic disease. Chromosomal disorders are generally severe but will frequently present with hearing and head and neck problems. Single-gene disorders are also severe, but many are not associated with multiple anomalies and/or mental retardation. The bulk of an ENT physician's practice involves individuals with complex disorders, because these are typically more frequent.

Chromosomal Disorders

With some exceptions, chromosomal disorders are generally not heritable. Physical abnormalities associated with chromosomal imbalance are the result of rather extensive duplications or deletions of genetic material and involve multiple genes. The most common chromosomal disorder that involves the autosomes is trisomy 21.[12] Chromosomal disorders can be classified into one of four groups:

1. Aneuploidy: the excess or loss of a whole chromosome.

2. Deletion: the breakage or loss of a piece of a chromosome.

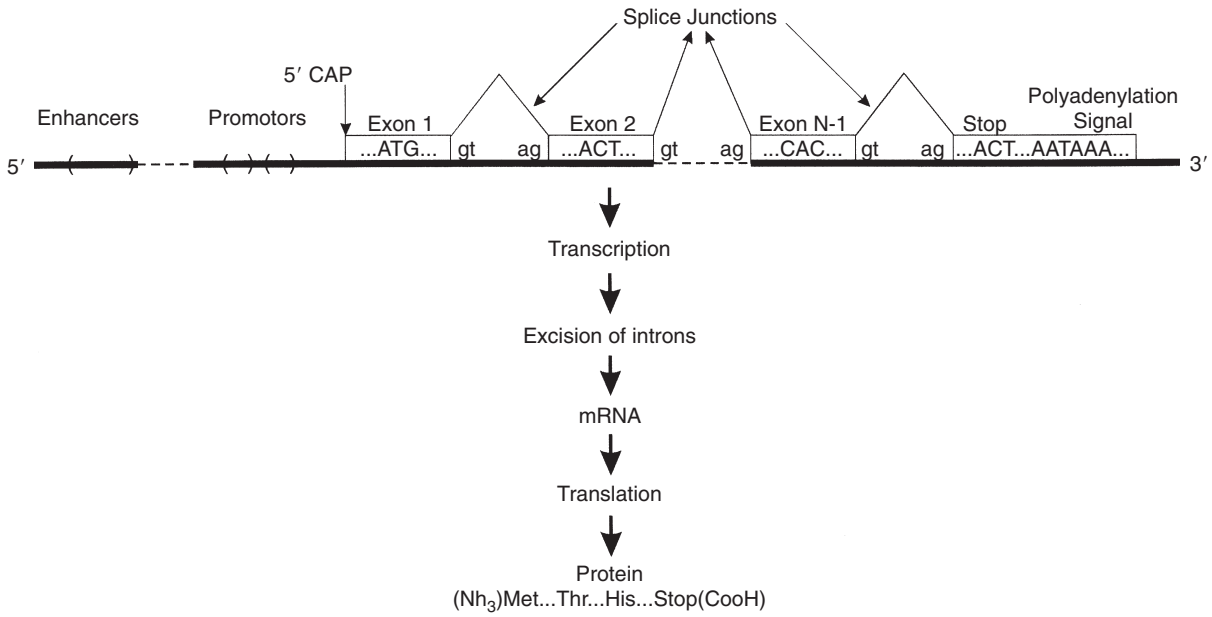

Figure 1-1. Gene structure and transcription. The ultimate primary function of most genes is to produce a protein in a cell at a time at which it is needed. Genes have structures that are adapted to this function. Not only does a gene have syntax that establishes the amino acid sequence of the protein, but it also has punctuation and regulatory sequences that control its expression. The exons make up the coding or information content of the gene; these are interspersed with introns, which are DNA sequences with a function that is only poorly understood. The first step of expression is transcription. The gene is transcribed from the 5′ cap to the end of the polyadenylation signal. This transcript contains both introns and exons, and so the next step is for the introns to be excised. Recognizable splice-site junctions are needed for this to occur normally, and so are other sites that assist in the recognition of the appropriate splice sites. The final mRNA product contains the code that is necessary for the final step of translation, after which a protein is made.

3. Duplication: the insertion of an extra partial copy of a chromosome onto an existing chromosome. This sometimes involves a different chromosome but it is often a tandem duplication that yields a second copy of the same set of genes just adjacent to the original DNA segment.

4. Rearrangement: two breaks of a chromosome or chromosomes and the subsequent refusion of the ends of the chromosome into a different order. When this involves two different chromosomes, it is called a *translocation*; when the same chromosome is involved and the order is reversed, it is called an *inversion*.

A chromosomal abnormality can occur in all or just some of the cells; the latter instance is called *mosaicism*. For example, most malignant cell lines show extensive chromosomal mosaicism, with multiple cell lines present in the tumor. Many females with only one X chromosome (designated as 45,X) are mosaic with a minor cell line that has a normal female constitution, 46,XX. The degree of mosaicism and the distribution in different tissues is believed to determine the severity of some cytogenetic disorders.

Aneuploidies

A trisomy is demonstrated when three copies of a whole chromosome occur in an offspring. This happens because of nondisjunction, which is the movement of a pair of chromosomes to the same pole during cell division; this results in one daughter cell lacking that chromosome and the other daughter cell possessing an extra copy of that chromosome.[13] The three major autosomal trisomies are 21, 18, and 13.

Trisomies 13 and 18 are not compatible with long life, and the average life span of individuals with either of these conditions is less than 1 year. The majority of infants with trisomy 13 are profoundly deaf and have a cleft lip and palate in addition to multiple other congenital anomalies.[14,15] Hearing loss is frequent in trisomy 18 as well.[16] However, hearing and head and neck anomalies are unlikely to be a serious concern because of the limited survival.

Patients with trisomy 21 have ears that are smaller than normal. About 75% have hearing loss, which can be sensorineural, conductive, or mixed.[17] The prognosis of a child with trisomy 21 is generally good, and correction to normal hearing is important for helping such a child achieve maximal abilities.[18]

The common aneuploidies that involve the sex chromosomes include 45,X (Turner's syndrome, phenotypic female) and 47,XXY (Klinefelter's syndrome, phenotypic male). Although profound hearing loss is infrequent, mild to moderate hearing loss is common in 45,X individuals.[19-21] Females with Turner's syndrome are highly susceptible to otitis media, but whether this changes with hormone replacement therapy remains to be investigated.[20,22,23] About 25% of children with Klinefelter's syndrome have a mild sensorineural hearing loss.[24,25] Hearing losses in both Turner's and Klinefelter's syndromes often remain undetected.

Chromosomal Rearrangements

Usually aneuploidies are not heritable; however, rearrangements, translocations, and inversions can be. There is a heritable form of trisomy 21 that involves a translocation between chromosome 21 and another chromosome, usually chromosome 14. This is a so-called centric fusion translocation that results in the loss of both short arms and the fusion of the two long arms of chromosomes 21 and 14. A balanced chromosome complement would be 45 chromosomes. Because of the abnormal way in which the chromosomes need to be paired, this translocation sets the stage for an abnormal separation of chromosomes during meiosis. The result can be a balanced carrier, like the parent (a normal), or a carrier who has three copies of chromosome 21 material. Both translocations and inversions can be heritable and could result in a family that has multiple instances of children with multiple anomalies. The heritable forms can be distinguished by a straightforward cytogenetic evaluation.

Single-Gene Disorders

The terms *dominant* and *recessive* usually refer to the pattern of inheritance of a particular disorder, but, more importantly, they communicate the way in which combinations of two alleles produce a specific (usually abnormal) phenotype. With a dominant inheritance pattern, individuals who carry one copy of the mutant allele (heterozygote) or two copies of the mutant allele (homozygote) are equally affected. With recessive inheritance, a person must be homozygous for the mutant alleles; individuals who are heterozygous are normal. When using these terms to describe a disease, if the disease is called dominant, then normal is recessive, and vice versa. True dominance is probably uncommon. Branchio-oto-renal syndrome (BOR) is described as dominant,[26] but because it is uncommon a true mutant homozygous individual has probably never been born. Most geneticists would expect that patients with the homozygous mutant form of BOR would have a more severe phenotype, one that is possibly even lethal. Similarly, one might expect that patients with many of the recessive nonsyndromic deafness disorders could have a mild manifestation in the heterozygote, possibly contributing to the liability of the development of age-related hearing loss. An example of true dominance occurs with Huntington's disease, in which a homozygous patient who is affected has the same phenotype as heterozygous individuals.[27,28]

Dominant Disorders

Figure 1-2 shows a typical family pedigree of an autosomal dominant disorder. Under full penetrance, each affected individual has an affected parent. Because they are heterozygous, each affected individual has a 50% chance of transmitting the abnormal gene to offspring, each of whom would be similarly affected. The only reasonable instance in which a person could be homozygous and affected would be if both parents were affected. Dominant mutations are recognized through their pattern of inheritance, which typically shows vertical transmission and the involvement of several generations and several sibships.

Affected patients are typically equally distributed between the sexes. However, a few sex-limited and sex-modified dominant disorders do exist.[29]

Dominance occurs with X-linked genes as well. The biochemical basis of the action of dominance is the same, but the pattern of inheritance is distinctly different. Twice as many females as males are expected to be affected. X-linked dominant pedigrees can mimic the characteristics of an autosomal dominant one, but they would not be expected to show male-to-male transmission. When the distinction between autosomal and X-linked dominant is in question, the observation of male-to-male transmission establishes an autosomal position of the gene.

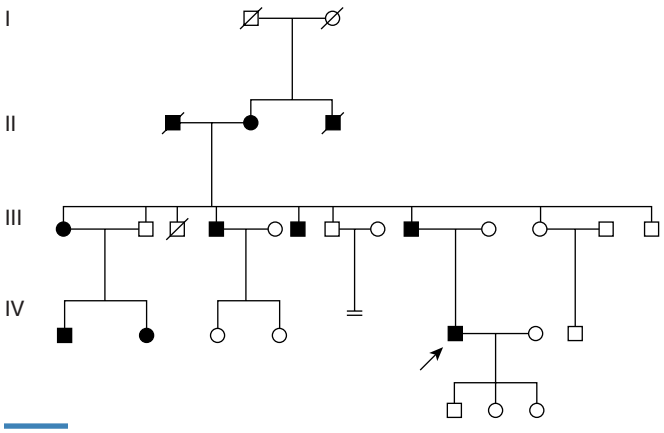

Figure 1-2. Pedigree typical of a dominantly inherited trait; in this case, autosomal dominant congenital deafness. The arrow points to the proband of the family (a proband is the person though whom the family came to your attention). Note that the pattern of transmission in the family covers multiple generations and that both sexes are affected equally. A slash though a circle or square indicates that the person is deceased.

There are three major mechanisms by which dominant genes generally influence phenotype: haploinsufficiency, the dominant-negative effect, and the two-hit effect.[30,31] *Haploinsufficiency* refers to the situation in which the inactivation of one gene reduces the gene product to a point where it is insufficient to maintain some cellular function at its normal level. Genes that contain proteins that regulate metabolic activity or transport are likely candidates for this mechanism. A *dominant-negative effect* occurs when the gene product actively interferes with normal cellular processes; the gene is producing a protein that either has acquired a new function or that competes with the action of the normal protein. The *two-hit effect* refers to the situation (e.g., retinoblastoma) in which one allele is inactive, and the disease results from its homologue being inactivated by second mutation. At the organism level, the inheritance appears to be dominant, but the mechanism of action at the cellular level is recessive. This is an important mechanism for the development of tumors in dominantly inherited cancer syndromes. For example, it is probably the mechanism of the carotid body tumor. The mechanism by which a dominant gene causes pathology is an important consideration in the search for treatments. For those disorders that are caused by insufficient gene products, the addition of a gene (or accompanying products) may be considered a reasonable approach to treatment and is likely to be easier to achieve. A dominant-negative effect, however, requires that the action of the gene and/or its product be stopped; this is a far more difficult task conceptually than is that of product replacement.

Examples of dominantly inherited disorders that are important in otolaryngology include all of the dominantly inherited nonsyndromic hearing losses, Waardenburg syndrome,[31,32] BOR syndrome,[33,34] Treacher-Collins syndrome,[35,36] and many others.[1]

Recessive Disorders

Autosomal recessive disorders result only when a person has two abnormal copies of the same gene. Because the affected person must be homozygous, both unaffected parents are heterozygous and thus carriers. In many families, the heritability of a recessive trait is not obvious. Given today's small family sizes, most individuals with recessive disorders present to the clinician as singleton cases lacking any family history of the same disorder. More than 50% of all cases of Usher's syndrome in the United States represent the only affected individuals in their respective families; most of the rest have a few affected siblings. When normal parents have a child with a recessive disorder, the chance of it occurring in any other children they may have is 25%. Although many of the unaffected relatives may also be normal heterozygotes (e.g., aunts and uncles have a 50% chance of being a carrier; first cousins have a 25% chance), one only infrequently observes recurrence outside of the initial sibship involved. One important clue to recessive inheritance is the presence of consanguinity. Important disorders that are inherited via autosomal recessive routes include nonsyndromic deafness,[37] Pendred syndrome,[38,39] Usher syndrome,[40,41] Alstrom syndrome,[42] and many others.[1]

It is the nature of recessive disorders that the abnormal gene is in a much higher frequency than would be appreciated on the basis of the relative rarity of the disorder. For example, Usher's syndrome type Ib, which is due to a defect of MYO7A,[43] is present in about 1 in 25,000 births; heterozygote frequency is estimated at about 1 in every 80 persons. For every affected person, there are more than 300 heterozygotes; if there are 10,000 patients with type Ib Usher's syndrome in the United States, there should be 3,000,000 carriers. For all rare recessive conditions, most of the gene pool resides with the asymptomatic carriers. In some disorders, the carrier rate is quite high; connexin 26 deafness (caused by a defect of GJB2) is the most common form of deafness in the United States,[44] and carrier rates may be as high as 1 in every 25 persons. Some recessive disorders appear to have a high frequency in certain populations. For example, cystic fibrosis is common among people of European extraction,[45] Tay-Sachs among Ashkenazi Jews,[46] and sickle cell anemia (hemoglobin beta S disease) in individuals of African ancestry.[47,48]

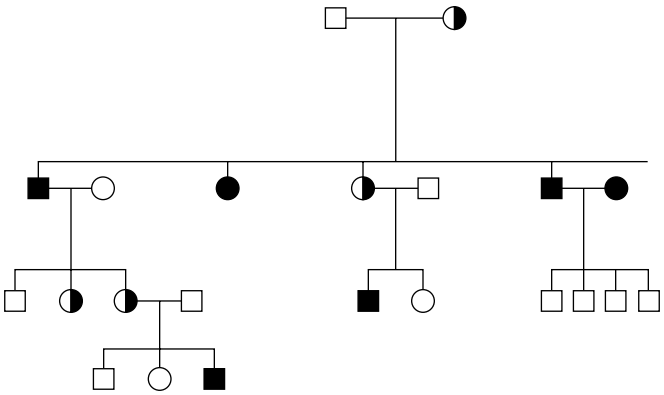

Figure 1-3. X-linked recessive disorders show a very characteristic pattern of inheritance. Females are carriers, and they are usually asymptomatic. They are indicated here by the half-colored circle; the diagnosis of carrier status was done here by inference from the parents having an affected son; however, for many disorders, carrier tests are available.

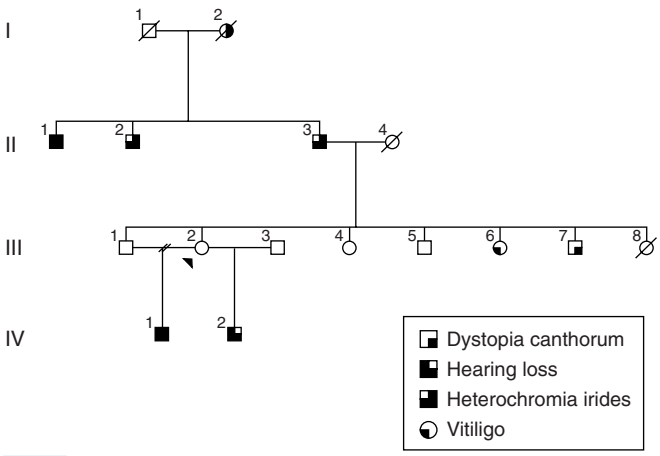

Figure 1-4. This is a pedigree of a family with dominant Waardenburg's syndrome. It shows variable expression and nonpenetrance. Such variability is usual for many dominant hearing-related disorders. Individual III-2 is inferred to be nonpenetrant by virtue of having an affected son.

Sometimes the increase in frequency of certain conditions in certain populations is a result of what is referred to as the *founder effect*. A good example of the founder effect is the very high frequency of Usher's syndrome type IC (due to a defect in the harmonin gene) among the French Acadians of Louisiana.[49] This gene is presumed to have been present in a few individuals who represented a significant part of the small number of immigrants to that region. The French Acadians stayed genetically isolated, and their numbers increased. Because of the chance occurrence of the gene in the founder population, the high frequency has been maintained to this day. Other recessive disorders have a unexpectedly high frequency believed to be caused by certain patterns of selection, such as those that are seen when the heterozygote has a selective advantage over both homozygotes, such as with sickle cell anemia. Selection was important when establishing the high frequency of the hemoglobin beta S allele in Africans. One of the most interesting genetic puzzles now surrounds the reason for the high frequency of connexin 26 deafness alleles. If this is due to a founder effect, then why is there a high frequency of different mutations in Jews, Europeans, and Asians? The high frequency across ethnic lines suggests that the heterozygotes may have (or may have had) a selective advantage over the homozygous normal.

X-linked genes may also harbor recessive mutations. The molecular mechanisms are the same, but the pattern of inheritance is unique and remarkable. Females, who have two X chromosomes, are heterozygotes/carriers. Males, with only one X, are affected; they have only one copy of the abnormal gene, because the Y chromosome carries little in the way of genetic information. The pattern of inheritance is shown in Figure 1-3. Carrier females have a 50% chance of transmitting the abnormal gene, which means that half of a carrier female's sons will be affected and that half of her daughters will be carriers as well. An affected male cannot transmit the gene to his sons, because he would need to transmit a Y to have a son; however, all of his daughters would be carriers, which would mean that 25% of his grandsons could be affected. The two best known X-linked traits are hemophilia[50] and Duchenne's muscular dystrophy.[51] X linkage plays only a minor role in nonsyndromic hearing loss. To otolaryngologists, perhaps the most notable disorders are X-linked deafness with perilymphatic gusher,[9,52] Alport's syndrome,[53,54] and Mohr-Tranebjaerg's syndrome.[55]

Biochemical defects underlying recessive disorders were among the first for human geneticists to understand. Early work in human genetics focused on metabolic defects. Many recessive disorders were found to be due to enzyme deficiencies that interrupted a specific metabolic pathway. Heterozygotes had sufficient enzymes for a typically dosage-tolerant pathway to operate and maintain a normal phenotype. Pathologic results occur either because some product is lacking or because the interruption of the pathway diverts the metabolism to the excessive production of a toxic substance. Some metabolic disorders are treatable by either supplying the missing product or enzyme, or by removing or reducing toxins. Refsum's disease is a metabolic disorder that involves the inability to metabolize phytanic acid, thereby causing a lysosomal storage disorder.[56] The symptoms of Refsum's syndrome can be minimized by a diet that is low in phytanic acid. From the perspective of potential gene therapy, recessive disorders seem ideal, because replacement of the gene—if active—should replace the missing protein. Most recessive disorders are the result of almost total ablation of the gene function, and a reasonably normal phenotype would be expected with only minor restoration of gene function and protein levels.

Penetrance and Expressivity

Penetrance is a frequently misused word; it should refer to a simple "yes" or "no" with regard to the presence of any aspect of the phenotype. A genetic disorder is said to show *reduced penetrance* if some cases fail to show the phenotype (i.e., if the geneticist is unable to make a clinical diagnosis). For example, Figure 1-4 shows a pedigree of a family with Waardenburg's syndrome type I. Waardenburg's syndrome is an autosomal dominant disorder that is characterized by variable hearing loss, pigmentary anomalies (i.e., white forelock, heterochromia irides, vitiligo), and a characteristic broad face with widely spaced inner canthi.[57] Mutations of the PAX3 gene on chromosome 2 are responsible for the majority of cases of this type of Waardenburg's syndrome.[12,58] There is considerable variability in the extent to which the different symptoms appear in different family members. Individual III-7 in Figure 1-4 has dystopia canthorum but no pigmentary anomaly or hearing loss. Still, the gene would be considered to be penetrant, because the diagnosis can be made as a result of the presence of dystopia. On the other hand, individual III-2 shows none of the characteristics expected from having the mutant PAX3 gene, and her genotype can only be inferred by the presence of her two affected children.

The term *expressivity* is used to describe the continuum of the severity of the phenotype. Zero expression is equivalent to nonpenetrance. The expressivity of dominant genes is often quite variable, whereas that of recessive disorder is more consistent, especially within families. Variable expression implies that there is some mechanism by which the severity of the disorder can be modified. These mechanisms may include background genes and/or environmental effects. The investigation of the causes of variable expression could lead to new approaches to therapy.

Pleiotropism is a term used to describe a gene that affects multiple organ systems in an apparently unconnected manner. For example, BOR syndrome can influence renal development as well as hearing.

Oligogenic Disorders

Some disorders are believed to be caused by the interactions among a few genes. Deafness as a result of connexins 26 and 30 is one possible example. The two genes, GJB2 and GJB6, are adjacent to each other on chromosome 13, and deafness has been observed in children with mutations in each of the two genes, each on separate homologues.[11,59,60] This is a digenic effect, and it has also been proposed to occur in certain cases of retinitis pigmentosa.[61,62] In the case of deafness, it is not yet clear whether the effect is truly digenic or whether the deletion in GJB6 interferes with the control of expression of GJB2. It would be expected that many human disorders may have their severity and/or their pleiotropic effects modified by other major genes.

X Linkage

Pedigrees of dominant and recessive X-linked disorders are discussed above and are presented in Figures 1-2 and 1-3. X-linked dominant and recessive traits show more variable expression in females than in males. One reason for this has to do with inactivation of one X chromosome in females, a phenomenon that is also referred to as the Lyon hypothesis. One X from each cell is randomly selected to be inactivated early during development, and all of the daughter cells will have the same X inactivated; this occurs in all cells except germinal line cells. When a female is heterozygous for an X-linked gene, the fraction of cells that have the normal gene inactivated would be expected to vary but to be around 50%. If, by chance, a significant proportion of normal genes are inactivated, a mild phenotype may result; this has been observed in patients with hemophilia and muscular dystrophy. The impact of X inactivation on the few X-linked hearing loss disorders has not been extensively studied. Occasionally, a fully affected female will be observed; many such patients have one or another form of Turner's syndrome, others may have nonrandom X inactivation, and a few may be true homozygotes.

Sporadic Cases

When only one case of a particular disorder occurs in a family, its heritability is not evident; this is an especially frequent event with childhood deafness. The etiology of the sporadic case can be dominant as a result of a new mutation that has not yet had an opportunity to be transmitted and show the typical inheritance pattern. A sporadic case could also be recessive, because most recessive disorders present as sporadic cases. X linkage, if the patient is male, is also a possibility, and so are more complex patterns of inheritance. In the case of childhood hearing loss, obviously there are many nongenetic factors that may be responsible as well. The pattern of inheritance can help with the diagnosis of many ENT-related disorders, but close examination of the clinical phenotype is critical, especially for sporadic cases.

Mitochondrial Disorders

The mitochondria represent the only nonchromosomal DNA that is inherited. Each cell has several hundred copies of usually identical mitochondria. Mitochondria are inherited solely through the maternal line, with the father giving few, if any, mitochondria to his offspring. This makes for a curious pattern of inheritance: all of the children of an affected mother are affected, but there is never transmission through the father (Fig. 1-5). Susceptibility to aminoglycoside-induced hearing loss is the result of a mutation (A1555G) in the 12S rRNA gene of the mitochondrion.[63-65] There are other, more severe disorders that result from mitochondrial mutations. One is the Kearns-Sayre syndrome, in which the hearing loss is extremely variable[66]; this is presumably because not all of the mitochondria carry the causative mutations. A mixed population is called *heteroplasmy*; this is a frequent occurrence in those disorders that may well be lethal if all the mitochondria carried the mutant gene (homoplasmy).

Complex Traits

Common disorders are believed to involve some mix of genetic and environmental causes. The genetics that underlie such traits have been labeled *multifactorial* or *polygenic*. Data indicate that several genes interact to produce a liability for a particular abnormal phenotype. Each gene is presumed to have a small effect. Actually, the number of genes involved remains unknown, and it is possible that some complex disorders could be due to a few major genes that have very reduced penetrances. The idea of using linkage and gene mapping to identify liability genes has become appealing during the last decade, primarily because of the great interest in common disorders and because molecular and gene mapping tools have become quite sophisticated. Some types of neurosensory hearing loss are thought to be inherited in a complex manner. Naturally, age-related hearing loss (presbycusis) is a likely possibility.[67,68] Liability for otitis media has also been hypothesized to be under some genetic control.[69] In the previous section, it was mentioned that liability for aminoglycoside-induced hearing loss is associated with a change in a mitochondrial gene. It would be reasonable to expect that other liabilities for infection (e.g., rubella) may be under genetic control.[70] The discovery of liability genes promises to have a great payoff in terms of the diagnosis of high-risk groups, as well as highlighting new possibilities for treatments that might mimic whatever mechanisms the genes use to confer resistance.

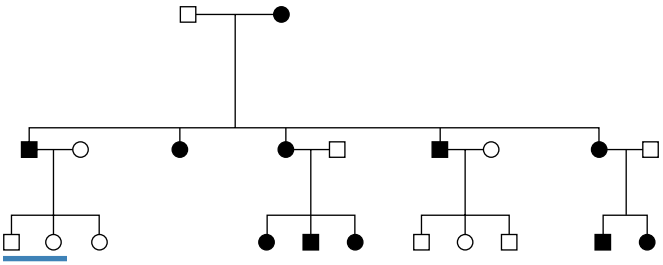

Figure 1-5. Mitochondrial disorders show several generations involved. Transmission is from a mother to all of her children. Males do not transmit the disease to their children. There can be variable expression, which is sometimes due to variable proportions of the mutant-type and wild-type mitochondria.

Genetic Heterogeneity

Genetic heterogeneity refers to the existence of cases with similar phenotypes but with differing causes. Childhood deafness, Usher's syndrome, and retinitis pigmentosa are good examples of this phenomenon. With Usher's syndrome, there are at least five different genes that all cause the severe form of Usher's syndrome type 1.[71] The phenotypes appear to be indistinguishable, and a differential diagnosis can be made only with molecular testing. However, if a man with Usher's syndrome type Ib produces offspring with a woman with Usher's syndrome type Id, all of the children would be expected to have hearing and normal vision, but they would be carriers of both Usher's syndrome types Ib and Id.

Testing Human DNA

DNA and ribonucleic acid (RNA) have two useful properties. One is that of easy replication; DNA generally makes copies of itself. The second is their ability to hybridize; they are sticky. If one starts with a double strand of DNA and heats it sufficiently, the two strands will dissociate (melt) into a mixture of single-stranded nucleic acid chains. If this mixture is cooled, complementary strands will reassociate (hybridize). The replication property is what makes the polymerase chain reaction (PCR) work, and the hybridization property has allowed a variety of DNA and RNA detection systems to be developed.

Polymerase Chain Reaction

PCR is a method of amplifying targeted sequences of DNA.[72] Oligonucleotide primers are constructed that are complementary to the 5′ and 3′ ends of the DNA fragment to be amplified. The size of the fragment is typically only a few hundred bases, but techniques like long PCR may involve several thousand bases. A specific thermostable DNA polymerase is used. The DNA is heated until it melts, and the temperature is then slowly lowered; at the time at which the primers anneal to the test DNA, the PCR is run and the fragment is duplicated. The heating-cooling cycle is then repeated 20 to 30 times; each time, the

DNA fragment between the two primers is duplicated, eventually resulting in several thousand fragments that each have the same length and DNA sequence. PCR is easy to carry out and can be used on minimal samples of DNA; these large quantities of manufactured DNA can then be subjected to a variety of experimental investigations. For example, the DNA can be electrophoresed, stained with ethidium bromide or silver stain, and visualized on a simple agarose or acrylamide gel. The size of the fragment and—more importantly—slight changes in its size can be easily noted. The DNA can be directly used in a sequencing reaction to verify that the sequence of the fragment is as expected. Almost all modern molecular diagnostics start with PCR.

Nucleic Acid Hybridization and Southern Blotting

The early 1980s analysis of genes involved a blotting procedure developed by E. M. Southern that involved hybridizing DNA in a solution (the probe), with the DNA on a stable membrane support, usually filter paper.[73] The probe is labeled with radiolabeled bases (fluorescent tags can be used as well), and the migration of the target DNA can be visualized by autoradiography. Southern hybridization of genomic DNA has limited use in today's molecular genetics laboratories; however, it is still useful for detecting and analyzing large fragments of DNA.

DNA Chips

DNA chips are referred to in two contexts: one when they are used for the analysis of patterns of gene expression,[74] and the other when they are used for the detection of single-base variation in individuals.[10,75] There are several different chip systems, but the basis of the functionality of the chip lies in the ability of antiparallel nucleic acid strands to hybridize.

Oligonucleotides that are typically 8 to 20 bases long and that are each of known sequence are arrayed onto a surface by a photolithographic method. These oligonucleotides can be linked, for example, to a fluorescent detection system. When bathed in a sample, RNA or DNA with homology to the oligonucleotides on the chip can be detected. One use of chips is to analyze changes in the pattern of expression of cells as they change; for example, they have been used to determine which genes are up- and down-regulated during the process of repair after cochlear cells have been damaged by high levels of noise.[76] Chips can help determine which (if any) genes change their pattern of expression in response to different disease processes.

Chips can also be used to detect single-base differences. Many single-base changes are polymorphic (i.e., they have a frequency of heterozygosity of more than 2%); these are called *single-nucleotide polymorphisms,* or *SNPs.* There are thousands of these polymorphisms, and they can be employed effectively for the mapping of complex disorders. Not all single-base changes are clinically neutral; some inactivate or change the gene in which they occur. Chips are an inexpensive and rapid way of detecting single-gene pathologic mutations, and they are likely to become the principal means of diagnosis of many genetic disorders. However, chips cannot be used to detect novel mutations, so the lack of a positive "hit" does not disprove a diagnosis.

Mutation Testing

The detection of pathologic mutations is the essential step toward making a definite molecular diagnosis. Although there are several different strategies to use, the initial evaluation depends on whether one is looking for a known mutation or whether the patient has a novel mutation that has never been seen before. When the mutation is known, molecular techniques that focus on specific base changes can be employed. One method relies on changes in restriction sites. A restriction enzyme is one that recognizes a specific short sequence of bases (usually 4 to 8 bases long) and that cleaves the DNA at that site or nearby. The DNA site that is recognized by a restriction enzyme is usually palindromic, which means that the sequence reads the same in both directions. For example, the restriction enzyme Taq I recognizes the palindromic sequence TCGA and the complementary AGCT, and it cuts the DNA between the T and the C. If there is a change in DNA, it can either disrupt an existing restriction site or create a new one; this can be detected by amplifying the appropriate DNA fragment, cutting it with the restriction enzyme, and running the product on an electrophoresis gel. Fragments with one or more restriction sites will show multiple bands; if a restriction site is added or lost, it can be easily detected by noting the position and number of DNA bands. However, not all DNA changes involve a restriction site. Methods based on the innate annealing capacity of DNA can also be employed. The use of DNA chips in this regard is discussed previously.

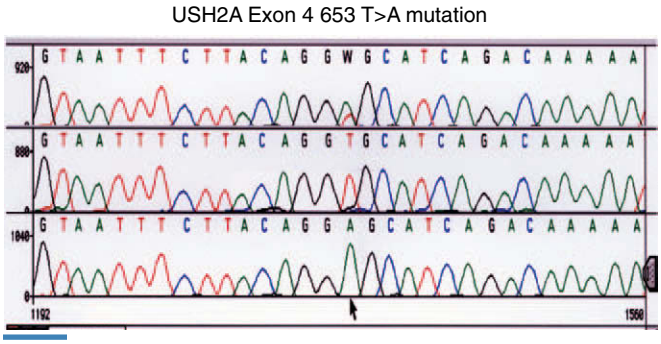

Figure 1-6. Sequencing is currently the best way of determining the genetic constitution of a gene or of part of a gene. This figure shows sequencing that was done to identify the mutation found in a patient with Usher's syndrome type IIa. Each row corresponds to a separate person. The arrow indicates the precise base position at which the mutation was found. The peaks and their colors correspond with each of the four bases in DNA. The control/normal sequence is shown in the middle frame. At position 653 in exon 4, there has been a change in the T (thymine) to an A (adenine). The affected patient in the bottom frame shows only an A at that position, which indicates that he is most likely homozygous for the mutation. His parent is shown in the first frame, and it is evident at that position that both the adenine and thymine bases are being detected by the sequencing reaction; this is typical of a heterozygote.

It is generally thought that screening for known mutations in a gene is a reasonable and less expensive strategy for making a molecular diagnosis. However, if a patient does not show one of the known mutations, this does not rule out the patient as having a pathologic mutation; it could be that the mutation has not yet been observed. In fact, many mutations are extremely rare and occur in only one case or family. Many mutations are limited to a specific family because they have not had time to spread throughout the population. As a result, molecular diagnosis must rely on techniques that can pick up novel mutations. Direct sequencing of a gene is one approach (Fig. 1-6). However, if the gene is large, the sequencing effort can be time consuming and expensive. There are two popular methods that help with screening DNA for mutations: heteroduplex testing and single strand conformation polymorphism (SSCP). In heteroduplex testing, a fragment is amplified, heated, and allowed to anneal with itself.[77,78] If the patient is heterozygous, then the fragment will contain two populations of DNA, one with each of the two DNA variants. When the DNA is heated, it melts. Then, when it cools, it anneals back onto itself. However, three different forms of double-stranded DNA are formed. Two forms are like the original mother strands; the third, however, contains two strands that have mismatched bases—a so-called heteroduplex. This produces a double strand that migrates slightly differently under certain conditions. This can be easily visualized using denaturing high performance liquid chromatography (DHPLC) (Fig. 1-7). After a potential mutation is recognized, the fragment can then be sequenced and the specific base change can be precisely identified. Other methods of mutation detection include allele-specific oligonucleotide hybridization, reverse dot blots, and amplification refractory mutation systems.[79]

Ethical Issues

Genetics has raised a host of ethical issues that had not been of much concern before the 1990s. From the physician's perspective, one issue relates to his or her "duty" to inform patients who are at risk for genetic

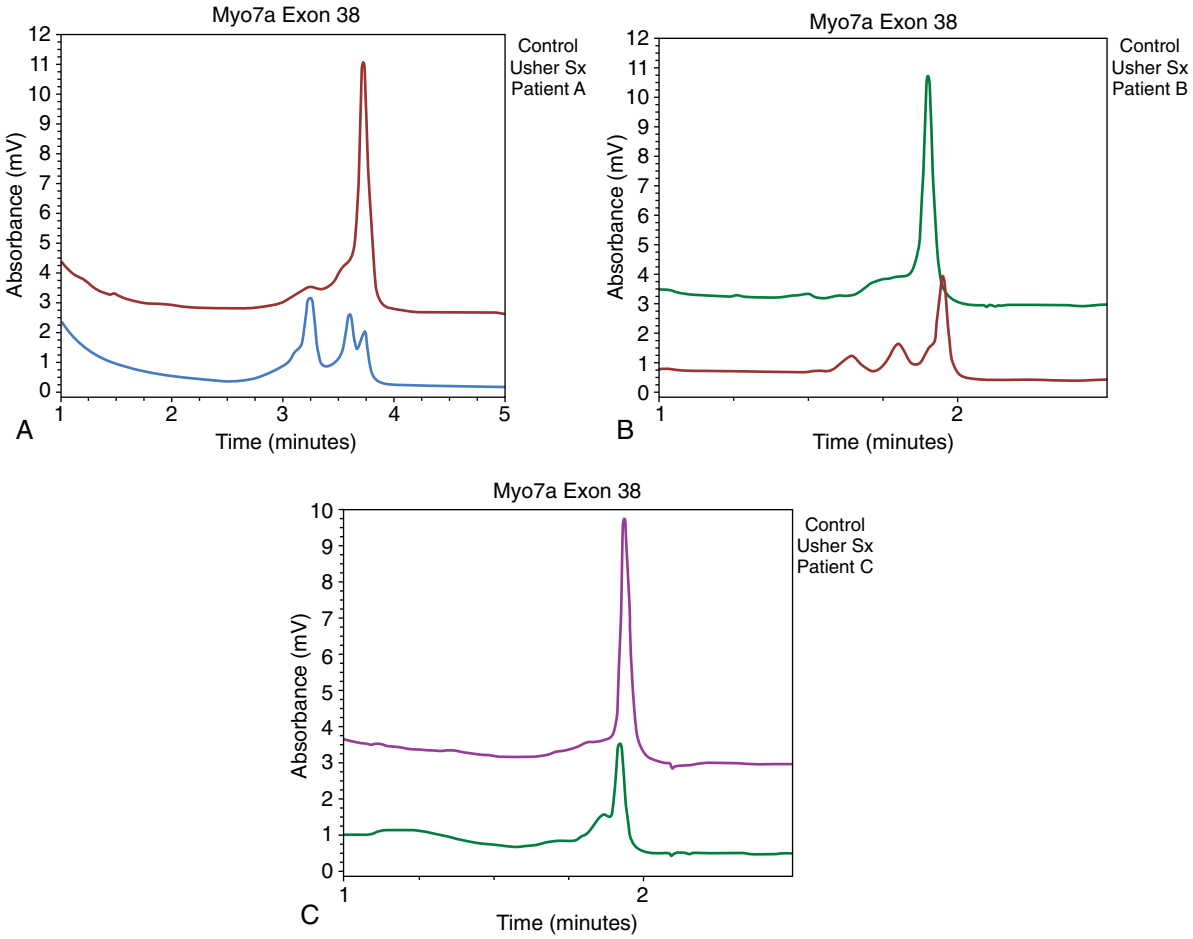

Figure 1-7. Denaturing high-performance liquid chromatography (DHPLC) using a WAVE apparatus is a common method of screening for mutations. This figure shows the results of DHPLC for three different mutations of exon 38 of the Myo7a gene, which causes Usher's syndrome type Ib. A fragment of DNA is amplified by polymerase chain reaction, heated to disassociation, and then cooled. Upon reannealing, four different double-stranded molecules are possible, two of which represent the original fragments. The other two will have double strands that differ slightly (e.g., at only one base) and that cause a slight conformational change that alters their mobility; this is observed as an additional peak or peaks when run out on a column. When a peak is observed, the exact nature of the change must be determined by sequencing.

disorders. If a woman is found to carry breast cancer liability alleles on the BRCA1 gene, is it the physician's responsibility to make sure that this patient communicates the possibility of risk to her female relatives? There is clearly a conflict here between the patient's right to privacy and the responsibility to "do good" by informing women for whom this extra diligence just might be life saving. Any genetic diagnosis carries with it the potential that a person other than the primary patient could be involved. The diagnosis of GJB2 hearing loss identifies siblings, cousins, and other relatives as potential heterozygotes who have an increased risk of having a child with profound deafness. It is not always the case that family members want the information, either. Although the issue is still argued, the general consensus is that the flow of information must come from the patient or an immediate family member, in the case of a minor.

The Utility of Molecular Genetics in Otolaryngology

The main role of molecular genetics in medical science is as a diagnostic tool. At the present time, the emphasis is on disorders that are caused by major genes. DNA testing can be used to definitively establish a diagnosis. This aids in the establishment of a prognosis, the elimination of the need for further expensive (and perhaps invasive) clinical testing, and the provision of information to the family about the likelihood of the disorder in other family members.

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CHAPTER TWO

Fundamentals of Molecular Biology and Gene Therapy

Bert W. O'Malley, Jr.

Daqing Li

Waleed M. Abuzeid

Hinrich Staecker

Key Points

- Gene therapy strategies involve (1) replacing defective genes with functional variants, (2) enhancing the expression of certain key genes, or (3) suppressing genes that contribute to disease.
- Methods of administering gene therapy include (1) direct injection of DNA/RNA, (2) use of specialized nonviral vectors such as nanoparticles, or (3) administration of a viral vector.
- More than 600 clinical trials have demonstrated the effectiveness of gene therapy in the treatment of a wide range of inherited and acquired diseases.
- Gene therapy has shown significant potential within otolaryngology for the treatment of head and neck cancers, to facilitate regrowth of hair cells within otology, and for tissue engineering in reconstructive and plastic surgery.
- Gene therapy continues to evolve with the introduction of new techniques such as RNA interference, which will revolutionize the treatment of disease in the 21st century.

Molecular biology is a relatively young scientific field, arising in the 1970s after the discovery of methods to study and manipulate DNA. The rapid development of these techniques enabled actual clinical application by the 1980s and 1990s. Many diagnostic laboratory tests routinely used in clinical medicine, as well as methods used to develop and mass-produce pharmaceuticals, make use of molecular biology techniques.

The growing field of molecular biology has also led to the development of novel therapeutic strategies for disease. A new understanding of genes and the products of their expression has allowed the emergence of a rising field heralded as "gene therapy." This rapidly expanding field is founded on the ability to introduce genetic material into the body to modulate the expression of genes and to thereby treat disease or alter an ongoing pathologic process.

This chapter reviews basic molecular terminology and introduces the concept of gene and molecular therapy. Emphasis is placed on the rationale, methods, and progress to date for clinical application of these exciting therapies.

Fundamentals of Molecular Biology

The basic premise of molecular biology is to study cell function and regulation at the level of the genome. With this understanding comes insight into human disease because aberrances in cell function or regulation are the basis for most diseases. The following section reviews fundamental terminology and concepts on how information travels from the genetic code to the functional protein level. Included is a brief discussion on cell cycling, which is an important concept in tumor molecular biology.

Gene Expression

The information for conducting all aspects of cellular function is contained within molecules of DNA located in the nucleus. The actual length of a human DNA strand is 1.8 M; however, it is coiled around nuclear proteins called *histones,* which structure the folds and loops of DNA to allow compression into the microscopic size of the cell's nucleus. Each strand of DNA contains thousands of genes, which are specific subunit sequences that are coded for the information required to synthesize a protein. One molecule of double-stranded DNA and its genes make up each of a cell's 46 total chromosomes. Although every cell in the human body contains the same DNA, the expression of individual genes is not the same. Gene expression varies depending on the cell's function. These differences in gene expression result in the multiple cell and tissue phenotypes that constitute the human body as a whole.

The process by which a gene codes for a specific protein begins with transcription, which is the formation of a single-stranded RNA molecule, which complements a single strand of the DNA subunit (Fig. 2-1). This RNA molecule is subsequently modified to become the messenger, which brings the genetic information or directions from the nucleus to the cell's cytoplasm where the actual synthesis of the functional protein occurs. After reaching the cytoplasm, the process of translation begins (see Fig. 2-1). During translation, the message from

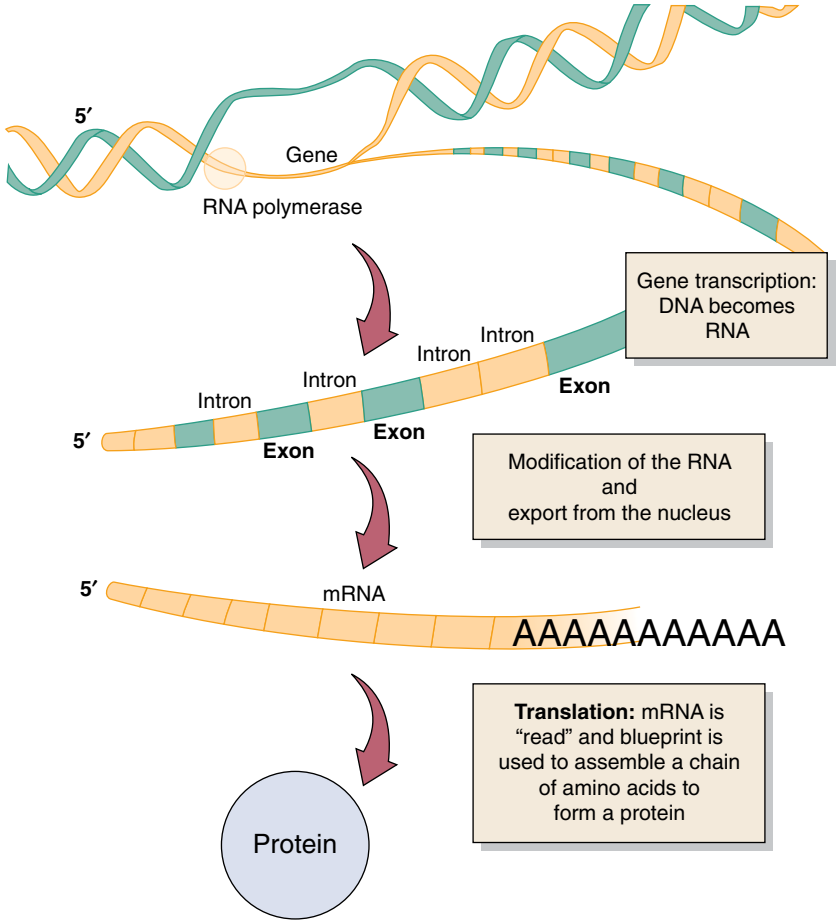

Figure 2-1. The basic steps involved in gene expression. Genes are copied within the nucleus by RNA polymerase, resulting in production of a complementary RNA strand. This is processed to produce mRNA. The mRNA exits the nucleus and undergoes "translation" by ribosomes to form a protein product.

the RNA molecule directs the construction of a protein from its basic subunit, the amino acid. Once a protein is formed, it may require further modification or control steps to enable its designated function. These modifications include the addition of sugars, lipids, or phosphates to the protein backbone. These internal control steps are mediated by existing cytoplasmic enzymes, which, if defective, can also lead to defined diseases. Once a protein is formed within the cell cytoplasm, it can reside in the cell or be released to affect other tissues within the body. Depending on the original genetic program for the protein, it may serve its purpose and be rapidly degraded, or it may enter the circulation or reside in local or distant tissues for an extended period. Although stated simply here, both transcription and translation are complex processes that have many more modification and regulatory steps governed by regulatory genes and their protein products. When these delicate control mechanisms are lost, a disease state or a state of abnormal cell proliferation can ensue, as is exemplified in the development of cancer.

Cell Division

Disorders in cell function can lead either to cell death or proliferation. Abnormal stimulation of cell proliferation is the basis for the development of cancer. For a cell to divide, it must progress through the various phases of growth and reproduction that constitute what is called the *cell cycle* (Fig. 2-2). The principal components of the cell cycle are the replication nuclear DNA and its distribution among the progeny cells (i.e., daughter cells). The first phase of the cell cycle is called G1, and it is here that all the enzymes, nucleic acids, and other factors are produced that will enable DNA replication or "synthesis," which occurs in the S phase. Once the DNA is replicated, a period of cell growth and duplication of cellular proteins and structures occurs in a period called G2. After this cell growth, the actual distribution of the replicated DNA and the physical division of the parent cell into two daughter cells occur in the M phase, which takes approximately 1 hour. After cell division, the cell cycle process can begin again, or the cell may enter a state of rest called G0.

The signal to divide can come from either internal factors or exogenous growth factors, which bind to cell surface receptors and stimulate a cascade of events, which lead to division. Important internal control mechanisms exist at the genetic level, which help regulate cell cycling. The "negative regulatory" genes that code for proteins inhibiting abnormal cell proliferation are called *tumor suppressor genes*. A mutation or loss of a tumor suppressor gene is a basic step in the development of many human cancers. Cell cycling can also be abnormally induced by cellular oncogenes, which naturally exist within cells but are typically kept dormant either by tumor suppressor genes or other regulatory mechanisms. Loss of negative regulation from tumor suppressor genes or amplification or mutation of the actual oncogene has also been associated with cancer formation.

Continued molecular research will provide further understanding of cell cycle regulation and may lead to novel therapies for treating human cancer. A discussion of basic molecular biology techniques, which have provided the means to understand gene expression, regulation, and cell cycling, is found in Chapter 16.

Gene Therapy

The basic principle of gene therapy is that the intrinsic expression of certain genes in body tissues can be modified to treat disease. This may involve replacing a defective gene with a functional version, enhancing

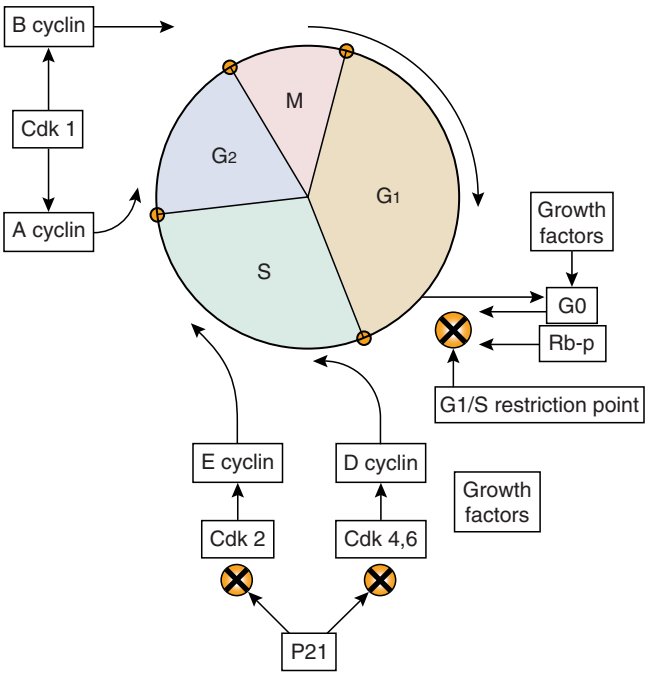

Figure 2-2. Cell cycle. The various phases of the entire cell cycle are depicted, which typically last 10 to 25 hours in animals. Only 1 hour is spent in the M phase. The longest and most variable phase is G1, which can range from 4 to 24 hours. Also depicted are regulation of the cell cycle, many elements of which are targets of gene and molecular therapy.

the baseline expression level of a gene or, contrastingly, suppressing the expression of genes that may contribute to the pathologic process. As the field of gene therapy continues its rapid advancement, it is likely that gene therapy will eventually become a standard clinical regimen available to both internists and surgeons.

Replacing Defective Genes

During the advent of gene therapy, the initial clinical targets were rare inherited diseases such as adenosine deaminase deficiency, which results in a deadly systemic immune deficiency, enzymatic deficiencies resulting in cystic fibrosis and liver disease, or coagulation pathway deficiencies resulting in various types of hemophilia. Gene therapy could be used to introduce a normal gene into the body to compensate for the low or absent function of the patient's mutant gene. For example, a proportion of children born with severe combined immunodeficiency (SCID) have a deficiency in adenosine deaminase (ADA) due to a mutation in the gene encoding this enzyme. Several clinical trials have introduced a functioning ADA gene into the bone marrow of SCID children using a viral vector, effectively reconstituting the patient's immune system.[1] Clinical trials assessing the potential for the treatment of hemophilia B through the transfer of a functioning factor IX gene, and cystic fibrosis via introduction of an intact cystic fibrosis transmembrane conductance regulator (CFTR) gene have also been completed.[2,3] These studies strongly suggest future applicability for gene therapy in the treatment of inherited diseases.

Enhancing Gene Expression

In the past decade, it has become clear that gene therapy may have its most immediate and effective role in treating more common acquired diseases, including various cancers, arthritis, and atherosclerosis.[4,5] In order to tackle these conditions, new approaches have been adopted that focus on increasing the expression of beneficial genes beyond normal levels. For example, in a clinical trial for the treatment of melanoma, tumor-infiltrating lymphocytes (TILs) were purified from a tumor at the time of surgical resection.[6] The TIL cells were then grown in the laboratory, and the gene for tumor necrosis factor (TNF) was introduced into the cells.[7] The genetically engineered cells were subsequently transfused into the patient and preferentially migrated to the site of residual tumor, delivering a therapeutic dose of TNF. As the molecular basis for disease is elucidated, there is likely to be increasing interest in this form of gene therapy.

Suppressing Gene Expression

Most recently, as the molecular pathways that underpin disease—particularly cancers—are unraveled, there has been excitement about the possibility of suppressing key genes known to be involved in the disease process. For example, RET, a proto-oncogene implicated in the pathogenesis of medullary thyroid carcinoma, can be inactivated by inducing expression of a mutant form of the RET gene, resulting in tumor regression.[8] This approach is dependent on the "dominant negative" effect where the mutant gene encodes a protein that retains binding ability to other key proteins that normally interact with the wild-type gene. However, the mutant protein is nonfunctional, creating a competitive inhibition of the wild-type functional variant. Dominant negative therapies are presently being translated to clinical trials in the hope of developing novel treatments, particularly within the field of oncology.

A new technique that may have immense potential for the future of gene therapy is RNA interference (RNAi), a method by which genes can be selectively "silenced." RNAi is a ubiquitous mechanism that is used by the cell to effectively "turn off" specific genes, as described a decade ago in a landmark paper.[9] In this study, injection of double-stranded RNA consisting of both sense and antisense strands into the nematode *Caenorhabditis elegans* profoundly silenced the gene with a sequence complementary to the dsRNA. The potential for RNAi in research and therapeutics was immediately recognized. In effect, any gene, including those involved in cancer, could be silenced and the effect of this loss of function on phenotype could be elucidated. The scientists who discovered RNAi were awarded the Nobel Prize in Medicine in 2006, only 8 years after publication of their initial, landmark paper.

Subsequent studies have partially determined the mechanism for RNAi (Fig. 2-3). In brief, an RNAase enzyme called Dicer cleaves dsRNA to form 21- to 23-nucleotide fragments of RNA. This short-interfering RNA (siRNA) is the actual effector molecule in RNAi.[10-12] The siRNA is integrated into the RNA-induced silencing complex (RISC), after which the sense strand of the duplex is discarded. The antisense siRNA is retained and acts as the "guide strand," directing RISC to mRNA molecules with a complementary sequence.[13] RISC cleaves the targeted mRNA, thereby silencing gene expression by blocking the translation of the mRNA sequence to protein.[10,14]

Considerable progress has been made in applying RNAi to mammalian systems. Transfection of mammalian cells with long dsRNA molecules of more than 30 nucleotides was found to induce a significant host antiviral interferon response that produced a general silencing of untargeted genes and often cell death. This hurdle has recently been overcome by chemically synthesizing 21-nucleotide siRNA molecules and using these to induce efficient, targeted gene silencing in mammalian cells without inducing an interferon response.[11] These siRNAs can be used in subnanomolar concentrations to achieve greater than 90% reduction in mRNA levels, a highly potent gene-silencing effect.[10] Recent animal experiments involving siRNAs have indicated that immune system activation is relatively uncommon, bolstering the safety profile of these novel therapies.

Unfortunately, a persisting problem associated with RNAi techniques are "off-target" effects. This refers to unintended siRNA-mediated silencing of genes that have similar nucleic acid sequences. Even small amounts of sequence homology, as few as seven base pairs, are enough to produce off-target effects. Several computer algorithms have been designed to aid in the selection of siRNAs with minimal off-target effects. It is unclear what effect, if any, off-target effects will have in human trials. In fact, early human trials of RNAi therapies for the treatment of macular degeneration and neurodegenerative diseases have not revealed any significant side effects.[12]

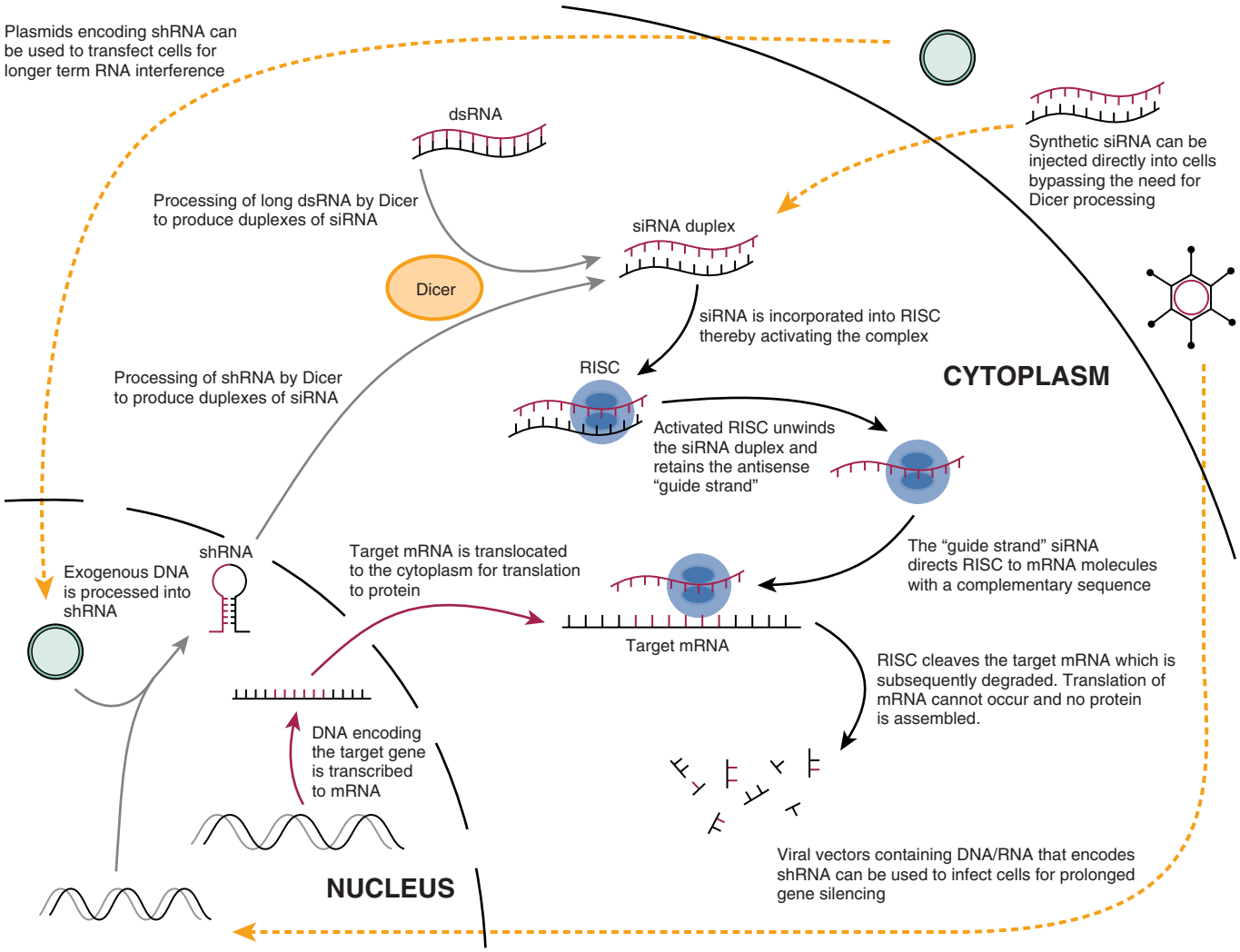

Figure 2-3. Mechanisms of RNA interference. The effector molecule for RNA interference is short-interfering RNA (siRNA). These can be derived endogenously from the production of long double-stranded RNA (dsRNA), which is then processed by Dicer to yield siRNA *(gray arrow)*. Alternatively, synthetic siRNA can be introduced into the cell by direct injection bypassing the need for Dicer *(broken arrows)*. Alternatively, plasmid or viral vectors encoding short-hairpin RNA (shRNA) can be introduced into the cell *(broken arrows)*. The shRNA is then processed by Dicer to yield siRNA *(gray arrows)*. Regardless of the route of production, the siRNA activates RISC, which then "homes in" on the mRNA sequence, which is complementary to that of the antisense siRNA "guide strand" *(black arrows)*. The mRNA is then cleaved and no gene product is produced, effectively "silencing" the gene.

Somatic versus Germ Cell Gene Therapy

Gene therapy has two possible target cell types. The first and presently used targets are the somatic cells, or those cells that constitute the organs and postnatal tissues of the body. The second potential target is the germ cells, or those cells that produce the sperm or ovum and are passed on to a person's offspring. Many different organs and cell types are targets for somatic gene therapy, including bone marrow, liver, tumor cells, muscle, skin, endothelium, thyroid, and others (Fig. 2-4). Genetic manipulation and therapy at these sites does not alter the inherited genetic material and raises few novel ethical or social issues.[15] Genetic manipulation of the sperm or ovum, however, could prevent inherited diseases by altering the genetic constitution of offspring. Although this is an appealing idea on the surface, there are serious technical and safety issues as well as profound ethical concerns involved. Currently, gene therapy is restricted to somatic cells, and genetic manipulation of human germ cells would be prohibited under existing recombinant DNA guidelines.[16]

Permanent versus Temporary Gene Therapy

A common perception is that the goal of gene therapy is to "permanently" modify the expression of the therapeutic gene in the patient. Permanent gene therapy, however, may not be necessary or optimal in a clinical setting. As a general principle, permanent gene therapy could prove more desirable when the methods required for introducing the genetic material into the patient involve significant surgical procedures or substantial risk to the patients such as in the case of organ resection, cellular transplantation, or stereotactic injection under anesthesia. To achieve permanent gene therapy, the expression of the target gene should be either enhanced or blocked indefinitely. The gene must also demonstrate appropriate regulation in response to both normal and pathologic situations, and there should be no detrimental consequences of this gene expression in later life. In considering diseases such as growth hormone deficiency or juvenile diabetes, correction by permanent gene transfer would require precise regulation of the gene products to ensure both short-term efficacy and long-term safety. This tight control and regulation of transferred genetic material is not feasible with present techniques.

For many diseases such as cancer, cystic fibrosis, arthritis, and disorders requiring surgery, "temporary" gene regulation in a patient's tumor, residual tumor, or other target cells could produce a selected beneficial therapy over a limited period of time. For example, the treatment of a tumor or area of residual tumor after surgery may only require

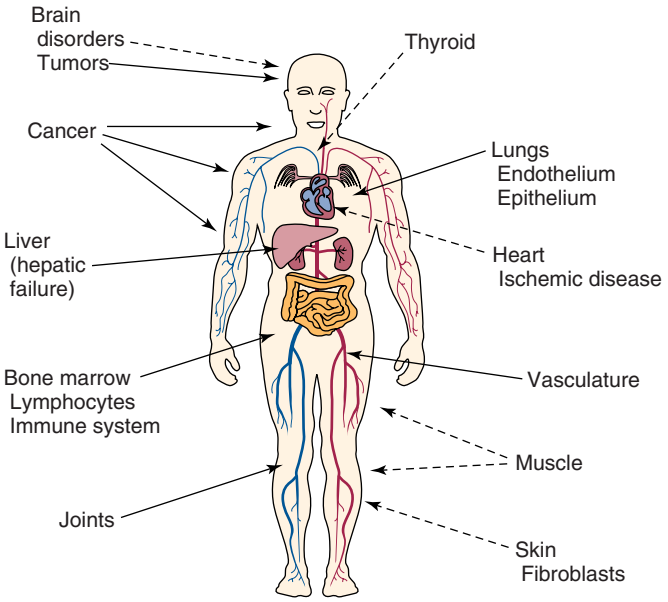

Figure 2-4. Somatic targets for gene therapy. Many different cell types are potential targets for gene therapy. *Solid arrows* represent tissue targets presently under human clinical trial investigation, and *dashed arrows* represent targets under investigation in animal models. Current gene therapy laboratory and clinical investigation explicitly excludes manipulation of germ cells (sperm and ovum), which may pass genes to future generations.

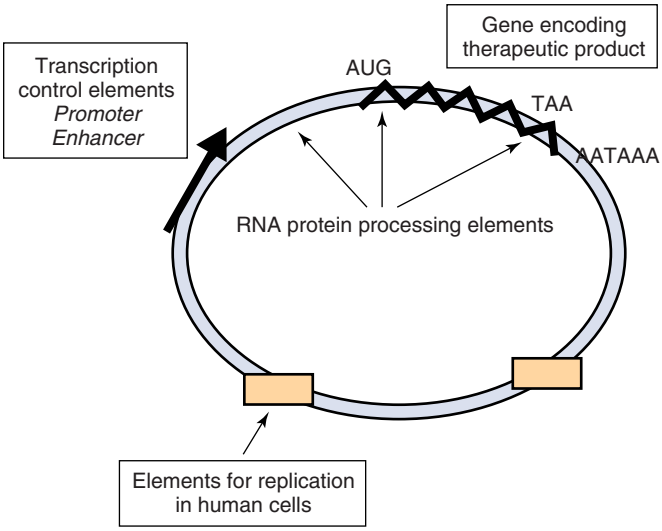

Figure 2-5. Schematic structure of a plasmid DNA vector. Plasmid DNA vectors are circular molecules of DNA encoding a therapeutic gene product. DNA vectors contain special elements required to achieve expression of the gene product at therapeutic levels. Promoter and enhancer regions regulate the transcription of plasmid DNA into RNA, and specific processing elements regulate the translation of RNA into protein. A DNA vector may be complexed with protein, lipids, or synthetic organic compounds that enhance vector uptake or provide cell uptake specificity.

a one-time, limited expression of a gene that either produces a substance directly toxic to the cancer cell or a cytokine or other factor that can initiate an antitumor immune response. Instead of permanent gene therapy, repeat gene transfer over a period of time could also prove effective, as in the case of radiation therapy or possible chemotherapy regimens. With respect to surgical procedures, the use of gene therapy to enhance wound healing or tissue regeneration after an injury might only require gene expression for a period of days or weeks. Another new frontier on the near horizon is minimally invasive or noninvasive routes for gene delivery, such as intramuscular, intravenous, oral, or even aerosol administration. This novel future application could allow the establishment of steady-state gene product levels, which parallels present medical regimens and enables the physician to adjust the dose and schedule of administration to the patient's needs.

Methods of Delivering Gene Therapy

A major focus in the field of gene therapy is the development of vehicles for introducing genetic material into selected target cells. Two general gene therapy delivery methods can be distinguished: (1) direct administration of genetic material, which involves the injection of DNA or RNA into cells in order to modify gene expression, and (2) viral-mediated gene transfer, which involves packaging a therapeutic gene into a defective virus particle and using the natural process of viral infection to introduce the genetic material. The purpose of viral-mediated gene transfer is to exploit the efficient and often complex mechanisms that viruses have evolved to introduce their viral genes into human cells during infections.

The gene that is delivered to a target cell is not itself therapeutic. Rather, it is the product encoded by the gene, which is responsible for the resulting therapeutic effect. The gene product is typically a protein, which has a specific function such as a hormone or cytokine, but could also be a bioactive RNA molecule such as a gene-silencing siRNA that alters the regulation of pathologic processes. Thus, although gene therapy commonly focuses on methods for delivering genes to cells, it is the ability to achieve expression of the gene product at therapeutic levels that ultimately determines the effectiveness and efficacy of therapy.

Direct Injection of Genetic Material

DNA-Mediated Transfer of Therapeutic Genes

The process of DNA-mediated gene transfer is called *transfection*, and the vehicle through which genetic material is transferred into a cell is called a *vector*. Functional DNA vectors are circular molecules of DNA called *plasmids* that contain various additional genetic elements required to achieve expression of the gene product at therapeutic levels (Fig. 2-5). Included in these are the special elements (promoter and enhancer) that direct gene expression and elements that determine the processing and persistence of genetic material within the cell. Plasmid vectors can be used to effectively deliver therapeutic genes to target cells. Plasmids have also been used to prolong the transient, 3- to 7-day gene-silencing effect associated with the transfection of naked siRNAs.

The delivery of DNA vectors into cells is possible via a variety of techniques. One classic method is to simply microinject plasmids directly into the cell nucleus.[17] This technique is both time-consuming and inefficient for achieving large numbers of transfected cells. Although this method is common in the laboratory with in vitro studies, its technical limitations prohibit effective application to living animal models or human subjects. A more efficient process, which also is limited to in vitro application, is the process of electroporation, in which cultured cells are exposed to DNA in the presence of a strong electrical pulse.[18] The electrical pulse creates pores in the cell membrane, which allows electrophoresis of plasmid DNA into the cell.

It is possible to effectively introduce genes into muscle[19] or thyroid[20] simply by injecting DNA into these tissues in vivo, where the process of endocytosis enables cellular uptake. Gene transfer into other organs requires special methods to enhance the uptake of DNA into the specific target cells. A common alternative method is the use of cationic lipids, which encase DNA vectors and fuse with the target cell membrane[21] to enhance intracellular gene uptake. This process has been termed *lipofection*. Another method is to couple the DNA vector to proteins that bind to specific receptors on the target cell leading to uptake of the DNA by receptor-mediated endocytosis.[22,23] A novel approach to DNA vector delivery involves the use of the "gene gun," which uses electrical currents to project microscopic gold beads coated with plasmid DNA into target tissues and organs.[24]

An important point to understand is that DNA-mediated gene transfer typically results in only transient residence of the therapeutic genes in the targeted cell. DNA vectors, which are introduced into cells, are degraded and eliminated from the cell over time. Different cell types eliminate the introduced genetic material at different rates. In muscle, for example, DNA vectors may persist in cells for many months and continue to express gene products.[19] In contrast, DNA vectors injected into the thyroid have a shorter half-life and the gene product is eliminated after 2 days.[20] Vectors introduced into the liver are eliminated with a half-life of approximately 1 to 2 hours and expression is significantly reduced after 6 to 24 hours.[25]

Although permanent incorporation of genes into cells occurs rarely after DNA-mediated gene transfer in cultured cells (less than $1:10^5$ cells), this phenomenon has not been observed in vivo. DNA vectors are therefore considered "safe" because they do not incorporate into the recipient cell's chromosome in vivo and thus should not induce the theoretical risks associated with altering the cell's genome. Moreover, they have not demonstrated significant toxicity to recipient tissues and have not induced any systemic immune response. DNA vectors can thus be delivered repeatedly, which overcomes the potential limitation of transient therapeutic gene expression. The transient nature of gene expression does have an advantage in certain clinical scenarios because the therapeutic gene can be administered by conventional oral, intramuscular, or intravenous routes to provide its beneficial effect over a predictable and extended period. In contrast to conventional medications with short half-lives, DNA-mediated gene therapy could lead to prolonged expression of a gene product at continuous levels, eliminating the need for continuous infusions or enhancing compliance by minimizing the frequency of injections.

Direct Delivery of RNA for Gene Silencing

RNA can also be introduced into cells, opening the door to potential therapeutic implementation of gene silencing. Intravenous administration of siRNA targeting the VEGF gene, for example, has been shown to significantly reduce tumor volume and intratumoral VEGF levels.[26] Unfortunately, the gene-silencing effect of synthetic siRNAs lasts only minutes to a few days before they are degraded. Chemical modification of the RNA can improve stability. The plasma half-life of an unmodified siRNA in a mouse model was 0.03 hour, the half-life of a chemically modified siRNA was 0.8 hour, and the half-life of a lipid-conjugated, modified duplex was 6.5 hours.[27]

Despite the improved stability of modified siRNA, plasma clearance is still rapid and any potential therapeutic benefit will require using chemically modified RNA in combination with some kind of delivery system.[10] Liposomes have been successfully used to deliver siRNA in vivo, and significantly improve both the duration and level of gene suppression compared to nonvector delivery methods. More recently, nanotechnology has been used to design compounds consisting of a cationic polymer that binds the RNA cargo, a neutral "stealth" coating to hide the particle from immune surveillance and a targeting ligand. This type of nanoparticle has been used to selectively target neuroblastoma tumors in nude mice with anti-VEGF receptor siRNA, resulting in a dramatic antitumor effect.[28] Electroporation and "gene gun" techniques have also been used to effectively deliver siRNA in vivo.[10]

The most common method used to date for the delivery of siRNA is termed *hydrodynamic delivery.* This approach involves injecting a large volume of an RNA-containing solution as a rapid intravenous bolus. The hydrostatic pressure generated transiently disrupts the vascular endothelium and achieves siRNA delivery to tissues. To date, hydrodynamic delivery has been successfully used to deliver siRNA to skeletal muscle in rats, dogs, and rhesus macaques.[29] Localized delivery can be achieved by application of a tourniquet to isolate a limb before intravenous injection. The potential for this approach in humans is under investigation and will likely transition to clinical trials soon.[10]

The need for sustained gene silencing has led to the development of novel DNA plasmid expression vectors that direct the synthesis of short RNA over a prolonged period (see Fig. 2-3). The encoded short RNA sequence is transcribed and processed into the effector gene-silencing RNA molecule. One method involves genetically engineering a plasmid to encode a short-hairpin RNA (shRNA). A shRNA molecule consists of a special double-stranded RNA molecule that includes a sharp hairpin turn and is processed in the cell to yield a 21-nucleotide RNA construct capable of gene silencing. Use of DNA plasmid vectors can prolong in vivo mammalian gene silencing for up to several weeks.[12] They are, however, limited by their inability to transfect nondividing cells.[11] This limitation can be overcome, however, through the use of viral vectors to deliver siRNA, which is discussed in the next section.

Viral-Mediated Gene Transfer

The majority of research to date has focused on developing methods for using viruses as vectors. Viral-mediated gene transfer involves the construction of synthetic virus particles that lack pathogenic functions, are incapable of replication, contain a therapeutic gene within the viral genome, and can deliver this gene to cells by the process of infection. Certain viruses have the property of permanently integrating their genes into the chromosomes of the infected cell; therefore select forms of viral-mediated gene transfer can lead to permanent gene therapy. Furthermore, viral-mediated gene transfer has significant advantages over plasmid-based delivery of siRNA to target tissues, in that constructs encoding siRNA can be introduced to both dividing and nondividing cells including neurons, blood, and bone marrow. By altering the type of viral vector used, siRNA expression can be designed to be transient in, for example, cancer therapy or permanent in the case of genetic diseases.

Retroviruses

The original prototypes for viral-mediated gene transfer are retroviral vectors derived from the Moloney murine leukemia virus.[30,31] Retroviral vectors were chosen as vehicles because of several useful properties. First, "defective" virus particles can be constructed that contain therapeutic genes and are capable of infecting cells, but which contain no viral genes and express no pathogenic viral gene products. A general scheme for constructing a defective retroviral particle is illustrated in Figure 2-6. Second, retroviral vectors are capable of permanently integrating the therapeutic genes they carry into the chromosomes of the target cell. Because of this property, retroviral vectors are well suited for treating diseases that require permanent gene expression. Third, modifications can be made in retroviral vectors and in the cell lines producing vectors that result in enhanced safety features.

A major limitation for this strategy is that retroviruses will only integrate into actively dividing cells and the efficiency of retroviral infection is relatively low. It is therefore difficult to generate the large numbers of transduced cells that are required for effective gene expression. This shortcoming has been addressed to some extent with the development of lentiviral vectors, which are related to retroviruses but are capable of inserting into the genome of nondividing cells. Perhaps the most serious problem, however, has been the difficulty in achieving stable, regulated gene expression from retroviral vectors in cells despite the permanent genomic integration. Cells are apparently able to shut off expression from retroviral vectors under certain conditions that have not been clearly defined.

Previous experience in animal models[32,33] and initial experiences in clinical trials suggest that these vectors are, generally, safe. However, there have been serious complications in clinical trials using retroviral vectors to treat X-linked severe combined immunodeficiency. Although gene therapy reconstituted the immune system and produced excellent clinical outcomes in most children, several cases of T-cell leukemia were reported 2.5 to 5 years after therapy.[34] This has been directly attributed to the insertional oncogenesis that can occur when the retroviral vector permanently inserts into the host genome and activates nearby cellular proto-oncogenes. The powerful promoters used to drive expression of the therapeutic gene may also activate nearby genes.[35] Consequently, newer generation retroviral vectors are in development that use weaker promoters to minimize trans-activation of genes. Special "insulator" sequences can also be used to block the transcriptional elements of the vector from interacting with cellular genes. Another option is to include "suicide" genes in the vector that will initiate cell death in overproliferating cells.[36] These methods have shown early promise but have yet to be used in a clinical trial.

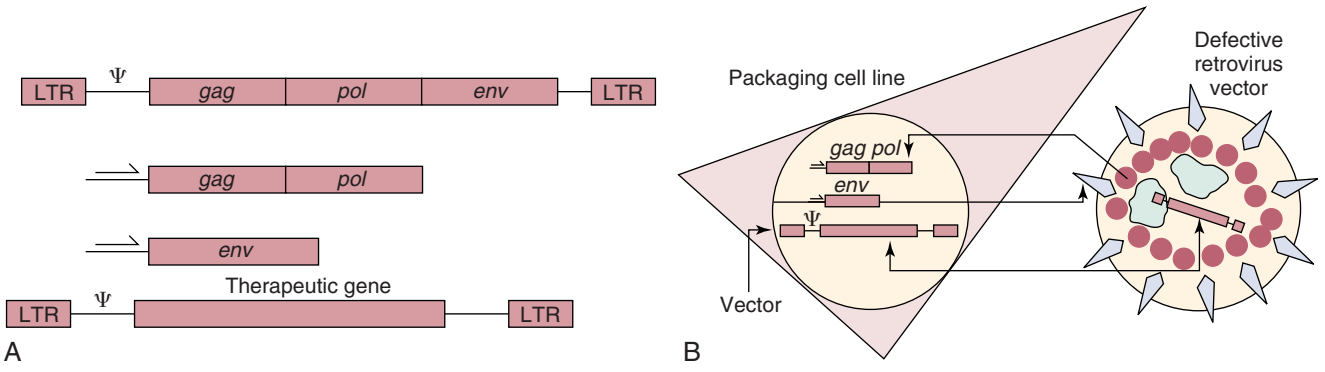

Figure 2-6. Construction of a replication-defective retroviral vector. **A,** The Moloney leukemia virus genome encodes three polyproteins—*gag*, *pol*, and *env*—which together constitute a retroviral particle. The *gag* and *pol* genes encode the inner core of the retrovirus as well as enzymes required for processing the retroviral gene after infection of the target cell. The *env* gene forms the outer envelope of the virus and recognizes a specific receptor on target cells. Defective retroviral vectors are made using several recombinant genes: one that expresses the *gag-pol* polyprotein, one that encodes the *env* protein, and one that contains the therapeutic gene in conjunction with two LTR (promoter and enhancer) sequences and the psi (packaging) sequence. **B,** A packaging cell line expresses *gag*, *pol*, and *env* from the constructs shown in **A**. When a vector containing the therapeutic gene with the LTR and psi sequences is introduced into this cell, a nonpathogenic viral particle will be assembled from the *gag*, *pol*, and *env* proteins that is capable of carrying the therapeutic sequence into cells by the process of infection. *(Reprinted from O'Malley BW Jr, Ledley FD. Somatic gene therapy. Methods for the present and future.* Arch Otolaryngol Head Neck Surg. *1993;119:1100. Copyright 1993, American Medical Association. Used with permission.)*

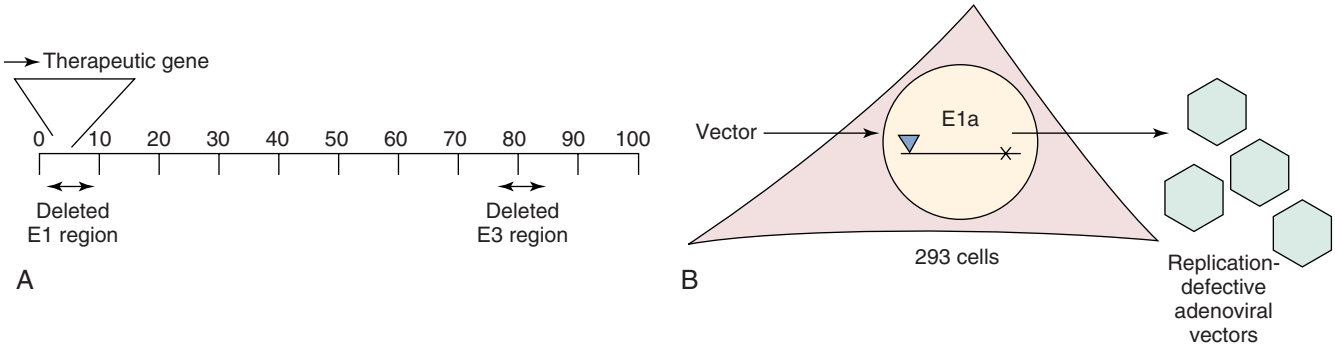

Figure 2-7. Construction of a replication-defective adenoviral vector. **A,** Adenoviral vectors are constructed using a deleted adenoviral genome that lacks the E3 gene as well as the E1 gene that is required for producing a proliferating adenovirus particle. Recombinant genes are inserted into the site of the E1 gene. **B,** Adenoviral particles are produced in the 293 cell line that is able to express E1 and is thus capable of assembling a viral particle containing only the recombinant viral genome with the therapeutic gene. *(Reprinted from O'Malley BW Jr, Ledley FD. Somatic gene therapy. Methods for the present and future.* Arch Otolaryngol Head Neck Surg. *1993;119:1100. Copyright 1993, American Medical Association. Used with permission.)*

Adenoviruses

A recent focus of gene therapy has been the development of adenovirus vectors as powerful and effective vehicles for gene transfer.[37] An overview for the construction of a replication-defective adenoviral vector is shown in Figure 2-7. Adenoviral vectors differ from retroviral vectors in that they remain episomal; that is, they do not integrate their genes into the target cell's chromosome. Compared with retroviral vectors, adenoviral vectors demonstrate the significant advantage of infecting a wide variety of both dividing and nondividing cells in vitro and in vivo with a high level of efficiency.[38-40] Using adenoviral gene transfer, expression of the therapeutic gene is possible for a period of several weeks to months. More recently, adenoviral vectors have been designed to encode and transiently express shRNA, which may be particularly useful in therapeutic strategies against cancers where long-term RNAi is not necessarily desirable.[12]

First-generation adenoviral vectors contained a deletion of portions of their E1a and E3 regions with the former acting as a "master switch" regulating the expression of other viral genes that are critical for viral replication. Consequently, all first-generation adenoviral vectors are replication-deficient. However, despite these modifications, several of the remaining viral genes are still expressed, markedly increasing immunogenicity.[4] This was highlighted during a clinical trial using a first-generation recombinant adenoviral vector that induced a severe systemic inflammatory response that resulted in the death of one patient with partial ornithine transcarbamylase deficiency.[41] The significant limitations imposed by the risk of a severe inflammatory response, as well as the transient gene expression induced by first-generation adenoviral vectors, have been addressed to some extent with further manipulation of the adenovirus genetic backbone. These newer second-generation adenoviruses have E1a, E2a, E3, and E4 region deletions, leaving very few intact viral genes, thereby greatly reducing inflammatory responses. These newer vectors can also remain in the target cell for months.[4,42] The latest generation adenoviral vectors are termed "gutless" and contain no viral genes at all, lowering immunogenicity even further.

The most recent efforts have focused on engineering adenoviral particles to specifically target cell receptors that are highly expressed on the surface of target tissues. This would reduce the risk of a host immune response by increasing the efficiency of gene transfer and reducing the required dose of adenovirus. Multiple studies have demonstrated that this can enhance delivery of therapeutic genes to target cells such as tumors.[43-46] Clinical data are pending and will need to be evaluated in order to determine whether targeted adenoviruses can potentially circumvent the adverse effects associated with untargeted vectors.

Overall, there has been considerable experience with the use of adenovirus vectors in both animal models and over the course of approximately 200 human clinical trials in the United States alone. This research suggests that there is a high margin of safety associated with the use of these vectors.[38-40,47]

Adeno-associated Virus

Recent work has focused on the utility of adeno-associated virus (AAV) in gene therapy. AAV, like retrovirus, permanently integrates into the chromosomes of the target cell but, unlike retrovirus, can stably infect nondividing cells for prolonged periods.[48] Furthermore, AAV vectors integrate in a predictable location within the infected cell and may be safer than retroviral vectors because they do not induce insertional mutagenesis or an innate immune response. Early human trials have used AAV vectors encoding factor IX to boost the levels of the coagulation factor in patients with hemophilia B.[3] These early AAV serotype 2 vectors have the main limitation of only being capable of infecting certain cell types. Newer generation AAV serotype 1 vectors are more than 1000-fold more efficient at infecting a range of cell types.[49] Ligands to cell surface receptors can also be integrated into the capsid of AAV to produce targeted vectors.[4] A disadvantage of AAV is that a wild-type "helper virus" is required to help produce the therapeutic recombinant vector. The "safe" recombinant vector must then be purified from the potentially cytotoxic helper virus before amplification. Further investigation is required to define the role and safety of AAV in clinical application. A summary of viral vector characteristics and gene transfer principles is shown in Table 2-1 and Figures 2-7 and 2-8.

Strategies for Administering Gene Therapy

Two general strategies exist for administering gene therapy (Fig. 2-9). The first and earliest conceived strategy is ex vivo gene therapy, in which tissue from a patient is removed by a surgical biopsy, cells are isolated and grown in culture, genes are inserted into these cells (typically using retroviral vectors), and the cells are then reimplanted in the body by autologous transplantation. The second is in vivo gene therapy, in which DNA or viral vectors (predominantly adenoviral vectors to date) are administered directly to patients.

Ex Vivo Gene Therapy

The initial clinical trials of gene transfer and gene therapy used the ex vivo strategy to deliver genes to lymphocytes, hepatocytes, tumor cells, fibroblasts, or bone marrow stem cells.[50,51] The intent of ex vivo gene therapy is to create a population of cells within the body, which permanently express a therapeutic function. Thus ex vivo strategies for gene therapy commonly make use of retroviral vectors because they integrate into the target cells and theoretically result in permanent therapeutic gene expression.

The initial attraction of ex vivo gene therapy stemmed from the concept that gene transfer could be performed in the laboratory under controlled conditions without exposing the patient directly to a viral or DNA vector. Ex vivo strategies, however, require methods for cellular transplantation to return the genetically manipulated cells back into the patient. Whereas bone marrow transplantation, lymphocyte transfusion, and skin grafting are accepted clinical procedures, there is little precedent for the transplantation of cells into solid organs. At present, this approach continues to be a difficult field of surgical research. Methods have been described for transplanting hepatocytes,[52] thyroid follicular cells,[53] myoblasts,[54] or fibroblasts,[55] although the effectiveness of these methods has not yet been established in clinical practice. In the above models, the number of cells that can be transplanted into the body may limit the amount of the therapeutic gene product that can be expressed by ex vivo methods.[52]

In Vivo Gene Therapy

A major recent focus in gene therapy is the application of in vivo strategies for gene therapy in which genes are administered directly to patients using viral or DNA vectors. Investigations in animal models with retroviral vectors have demonstrated that it is possible to infect dividing cells in the liver, endothelium, lung, or tumors in vivo.[50,51] Studies using adenoviral vectors have demonstrated infection of both

Table 2-1

Viral Vectors Currently Used for Gene Therapy

	Adenovirus	Retrovirus	Lentivirus	Adeno-associated Virus	Herpesvirus
Infectivity	Broad, high efficiency	Dividing cells only, high efficiency	Broad	Nondividing cells, minimal innate immunity	Nondividing, high efficiency
Integration	Episomal	Nonspecific chromosomal	Nonspecific chromosomal	Specific chromosomal	Episomal
Viral titer	High	Low	Low	Low	Low
Max. insert size	Intermediate (~8 kb)	Intermediate (~10 kb)	Intermediate (~10 kb)	Small (~5 kb)	Large (~36 kb)
Risks	Innate immune response	Insertional mutagenesis with secondary malignancy	Insertional mutagenesis with secondary malignancy	Wild-type virus contamination, adaptive immune response	Potential innate and adaptive immune response
Viral production	Helper-free	Helper-free	Helper-free	Helper virus	Helper virus and helper-free vector
No. of U.S. clinical trials	194	>600	6	32	13
Examples of disease applications	CF, colon cancer, ovarian cancer, mesothelioma	ADA-SCID, X-linked SCID, CGD, familial hyperlipidemia	HIV, Mucopolysaccharidosis, AIDS lymphoma	CF, hemophilia B, Canavan disease, AAT deficiency	Brain tumors, colon cancer

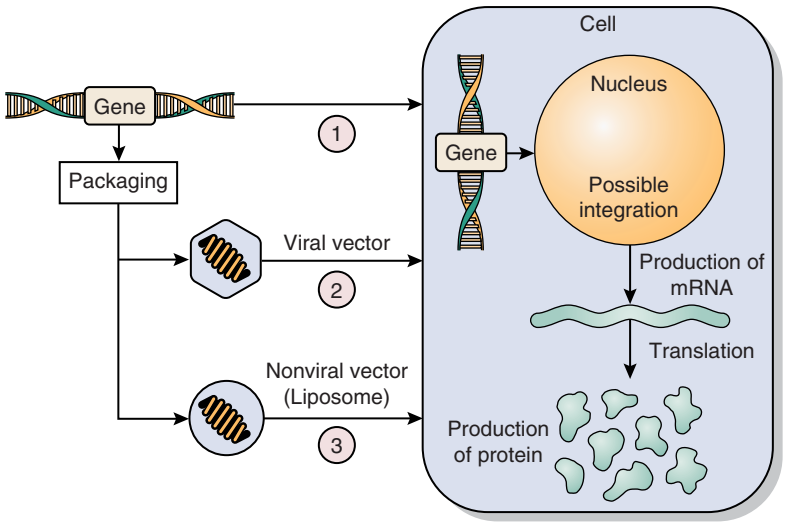

Figure 2-8. Transfer of genes can be achieved through several different delivery mechanisms. Gene transfer was originally described in muscle using naked DNA injected directly into muscle (1). This generally is considered a low-efficiency method of gene transfer but may be very useful for the development of DNA vaccination strategies. Packaging into viral vectors (2) allows for the most efficient gene transfer but is associated with safety concerns. Nonviral vector technology (3) involves coated or condensing the gene construct to allow easy passage into the cell. It is less efficient than viral vector–mediated gene transfer but is considered safer. The final common pathway for all gene delivery is production of a protein resulting in a change in cell phenotype. Alternate gene therapy strategies being developed use inhibitory RNA to decrease the expression of certain genes.

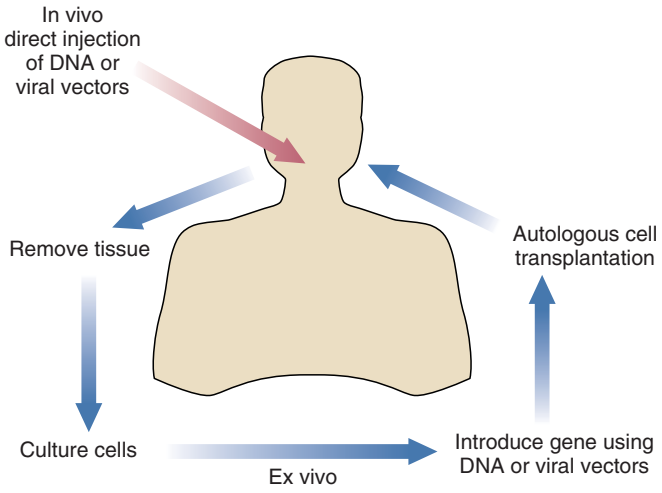

Figure 2-9. Strategies for ex vivo and in vivo gene therapy. In vivo strategies for gene therapy involve the direct administration of DNA or viral vectors to the patient by conventional routes of injection *(red arrow).* Ex vivo strategies involve removing tissue from the patient, growing cells in culture, introducing genes into these cells in the laboratory, and then returning the genetically modified cells to the patient by autologous transplantation *(blue arrows). (Reprinted from O'Malley BW Jr, Ledley FD. Somatic gene therapy. Methods for the present and future.* Arch Otolaryngol Head Neck Surg. *1993;119:1100. Copyright 1993, American Medical Association. Used with permission.)*

dividing and nondividing cells in the pulmonary epithelium,[56] liver,[57] muscle,[58] a variety of tumors,[39,40] and other tissues in vivo. Other studies have demonstrated the feasibility of delivering DNA vectors to organs including muscle,[19] thyroid,[20] liver,[23] and joints[59] in vivo.

Whereas the goal of ex vivo gene therapy is to permanently introduce a recombinant gene into a patient's cells, the primary goal of in vivo strategies can vary depending on the tissue and disease for which the treatment has been designed. In vivo gene therapy can be performed with single treatments for certain tumors,[39,40] administered intermittently in response to acute disease or given long-term to establish steady-state levels of the therapeutic gene product. The in vivo strategy correlates with conventional regimens of medical therapy; however, the gene therapy could provide prolonged or improved effects. Furthermore, the in vivo strategy facilitates the combination of conventional medical treatments or surgical procedures with gene therapy to potentially provide synergistic effects. It is the development of in vivo and relatively noninvasive methods for gene delivery that may allow the widespread application of gene therapy to the routine problems of medicine and surgery.

Therapeutic Levels of Gene Expression

Effective gene therapy requires not only the delivery of genes to the appropriate target cell within the body but the expression of the therapeutic gene product at appropriate levels. It is the ability to achieve adequate gene expression that will determine the efficacy and therapeutic index of gene therapy. There are several ways to achieve appropriate expression of a therapeutic gene product.

Specific genetic elements called *promoters* and *enhancers* that normally control the rate of therapeutic product expression can be incorporated into the gene transfer vehicles. These elements can also control the level of gene expression, restrict it to specific cell types, and provide regulated gene expression in response to endocrine or pharmacologic factors. For example, gene therapy for diabetes will certainly require the incorporation of genetic elements that provide normal regulation of insulin levels by glucose.

Promoter and enhancer elements derived from different genes can be combined to provide an improved effect. In this way, vectors can be designed to produce gene products at high levels from a cell that normally produces only low levels or to constitute expression of a gene product from a cell that does not normally produce that particular gene product. For example, clotting factors or peptide hormones can be expressed from muscle cells after gene transfer using vehicles that incorporate the promoter and enhancer elements from muscle-specific genes such as skeletal actin or myosin. In considering cancer gene therapy, highly efficient viral promoters can be mixed and matched with a variety of gene-delivery vehicles that will result in high levels of expression of therapeutic antitumor genes directly from the targeted cancer cells.

Another important regulatory mechanism resides in the natural actions of a cell, tissue, or organ. As is the case with conventional pharmaceuticals, the basic principles of drug distribution, metabolism, and elimination within the cells and tissues of the body will provide additional means for regulating the level of the gene product.

Why Gene Therapy?

An important universal question asks what advantages gene therapy has over the present accepted medical and surgical treatments that would warrant clinical investigation and application in routine patient care. In response to this basic question are several reasons why gene therapy might become a first-line treatment in clinical practice.

New Therapeutic Approach

With the rapid evolution of molecular biology over the past decade, an increasing number of basic biologic phenomena and pathologic conditions are now understood in terms of the events that take place on a molecular level between genes and their gene products. According to both experimental animal models and early human clinical trials, it is now possible to alter processes such as immunity, growth, development, regeneration, and malignancy on a molecular level using gene transfer. Furthermore, the new field of RNA interference provides a potent method of completely silencing specific genes. This will become an increasingly important area of study as the molecular pathways and the genes that govern these pathways are elucidated. Therapeutic gene transfer provides a novel approach to diseases that are not satisfactorily managed using conventional pharmacologic or surgical intervention. As a general example, using gene therapy to reconstitute deficient functions resulting from failing organs or tissues may provide an alternative to allogeneic transplantation of bone marrow, solid organs, or individual cells.

Site-Specific Gene Expression

Using the techniques and principles of gene transfer, therapeutic products can be released from specific cell types in precise locations within the body. This concept of site-specific gene expression provides a valuable advantage for gene therapy. Therapeutic proteins such as cytokines or growth factors can be expressed in precise locations, rather than administering similar products via a systemic route. The highest concentration of the therapeutic product will therefore be focused at the desired site of action. For example, gene transfer can be used to express products specifically in the epidermal or dermal layers of the skin without affecting underlying connective tissue, nerves, muscles, or vessels. Such spatial specificity will minimize untoward consequences or toxicity in organs or other vital structures outside of the site being treated.

Improved Efficacy and Safety

Gene therapy establishes the expression of normal, human proteins acting in a directed therapeutic fashion within the body. Based on this concept, gene therapy may prove to be more efficacious and safer than the application of proteins purified from microorganisms, animals, or human populations, which carry the attendant risk of transmitting pathogens or inciting allergic reactions. Moreover, gene therapy can be used to achieve regulated, physiologic expression of gene products, which may further improve efficacy. By altering the dose or schedule of gene administration to a patient, it will be possible to optimize the level, effect, and safety of the gene product.

Improved Routes of Administration and Compliance

Most standard medications have short half-lives and need to be administered by frequent oral dosing, injections, or even constant infusions to achieve an optimal therapeutic effect. Gene therapy, however, provides continuous endogenous expression of natural protein products and requires less frequent administration (of the gene), ranging from one time to weekly or monthly treatments, depending on the disease target and gene transfer strategy. As is known to all clinicians, decreasing the frequency of administration improves acceptance and compliance with therapeutic regimens.

Preventive Medicine and a Reduction in Health Care Costs

As molecular and genetic research continues to identify factors that predispose individuals to diseases such as atherosclerosis, cancer, diabetes, infections, or degenerative disorders, the application of gene therapy may allow a physician to alter the expression of these factors in a preventive manner. Of particular importance is the ability to deliver therapy over a long period in clinically asymptomatic or minimally symptomatic patients who have inherited or acquired progressive diseases—a combination of circumstances that is traditionally associated with poor compliance. For example, treating a diabetic patient with gene therapy early in the stages of the disease may prevent morbidity later in life that occurs even with conventional exogenous insulin therapy. Also, combining the advances in molecular diagnostics of cancer may allow replacement of lost or defective critical tumor-suppressor genes in normal or premalignant tissues, thereby preventing the progression of the defective tissue into cancer.

Because gene therapy can establish continuous release of a therapeutic product with one-time treatment or infrequent dosing, its use for prevention is more practical and affordable than conventional therapies. The practice of preventive gene therapy to diminish morbidity and early mortality and the use of more affordable treatment regimens will ultimately reduce the rapidly growing cost of health care.

Applications of Somatic Gene Therapy in Otolaryngology

Gene therapy is relatively new to the field of otolaryngology–head and neck surgery. Its applications are broad and important, and advances in overlapping medical and surgical fields can be applied to the diseases and clinical scenarios common to otolaryngologists.

Inherited Disease

A variety of inherited diseases are associated with head and neck pathology such as sinus disease in cystic fibrosis; hearing loss in Usher's, Alport's, or Pendred's syndrome; and goiter in certain forms of congenital hypothyroidism. In some of these diseases it might be possible to place a normal gene in appropriate cells to carry out the function of the inherited, mutant gene. For example, the first clinical trial of gene therapy for cystic fibrosis involved the introduction of a normal CFTR gene into the nasal mucosa using adenoviral vectors.[60] The intention of this study was to assess expression of the CFTR gene in the respiratory epithelium and to determine any toxic or inflammatory adverse effects. This trial provided a foundation for future studies in which the CFTR gene would be replaced throughout the respiratory tract using viral or DNA vectors.[61]

Head and Neck Oncology

Many of the initial clinical trials of somatic gene therapy are focused on the treatment of cancer. Gene therapy for head and neck oncology patients remains a focal point for this emerging strategy. The original head and neck tumor target was melanoma, but squamous cell carcinoma quickly became the target of choice for human clinical trials. Various approaches for treating cancer by gene therapy have been proposed (Fig. 2-10) and are applicable to common head and neck tumors.

Genetic Modification of Tumor-Infiltrating Lymphocytes

Although the first clinical trial of gene therapy involved only the introduction of marker genes into TIL cells, which infiltrate solid tumors such as melanoma, this trial founded the principle, feasibility, and safety of gene transfer into human patients. The original interest in TIL cells stems from prior studies demonstrating that adoptive transfer of TIL cells coupled with the administration of interleukin-2 (IL-2) could cause significant tumor regression in some patients with malignant melanoma.[62] TIL cells, however, are relatively inefficient in destroying tumors despite their ability to selectively infiltrate tumor sites.

Gene therapy is therefore an ideal strategy to increase the antitumor potential of TIL cells by providing concurrent expression of stimulatory proteins such as cytokines. One clinical trial for cancer patients used autologous cancer cells modified with a gene that produces IL-2,

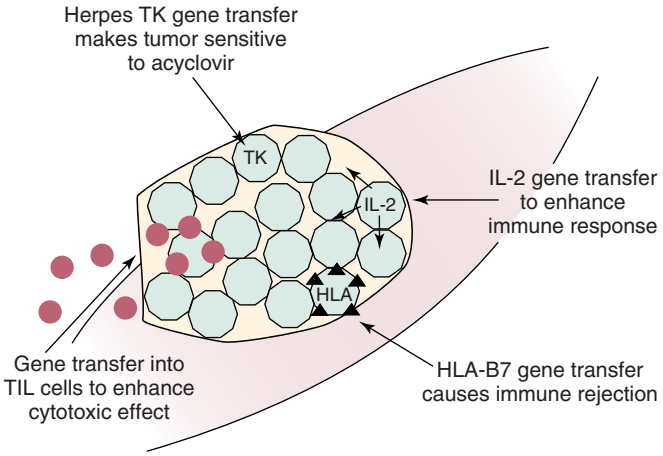

Figure 2-10. Strategies for gene therapy of cancer. Several different strategies have been described for treating cancers by gene therapy. These include expression of cytokines such as interleukin-2 within tumor cells to enhance the immune response against tumor-specific antigens; introduction of a foreign transplantation antigen such as HLA-B7 to induce immune rejection; introduction of cytokines into tumor-infiltrating lymphocytes (TIL cells) to enhance their cytopathic effect; and introducing genes such as herpes TK to make tumor cells sensitive to drugs such as acyclovir or ganciclovir. *(Reprinted from O'Malley BW Jr, Ledley FD. Somatic gene therapy. Methods for the present and future.* Arch Otolaryngol Head Neck Surg *1993;119:1191. Copyright 1993, American Medical Association. Used with permission.)*

a cytokine that increases the immunogenicity of cancer cells and suppresses tumor growth.[63] This strategy involved transfer of the gene for IL-2 directly into a patient's tumor, which resulted in the local formation of tumor-specific cytolytic TIL cells. An excisional biopsy of a draining lymph node allowed harvesting of sensitized TIL cells that were multiplied in culture and then transfused back into the patient. The TIL cells, now sensitized to the specific tumor, could then be infused into the patient and would home in on any cancer tissue or cells to enact a cytolytic response. This protocol focuses on patients with primary or metastatic cancer for which standard therapy has proved ineffective.

Direct In Vivo Stimulation of an Antitumor Immune Response

This method of cancer therapy involves introducing genes for various cytokines directly into tumor cells to increase the natural immune response to tumor-specific antigens. The human body has natural cellular and humoral immune effectors that inhibit or prevent tumor cell growth. Examples of such effectors include major histocompatibility complex (MHC)–restricted cytotoxic T cells, natural killer cells, and lymphokine-activated killer cells. The majority of human malignancies, however, arise in immunocompetent individuals, which implies that tumor cells escape the body's natural immune defenses. Tumors are also known to lack or demonstrate deficiencies in the expression of class I MHC antigens, which prevents recognition and attack by cytotoxic T cells.[64]

In animal models, the transfer of the gene for foreign class I MHC histocompatibility leukocyte antigen (HLA)-B7 into colon carcinoma, melanoma, and sarcoma cell lines has resulted in cytolytic activity from splenic lymphocytes.[65] In this immunologic gene therapy strategy, the gene for HLA-B7 expression is transferred into a cutaneous melanoma lesion of patients who have primary or recurrent tumors or distant metastases that have not responded to conventional therapy.[65] Expression of the HLA-B7 antigen on the melanoma cells is expected to lead to rejection of the primary tumor and metastases by the immune system. B7 gene therapy using nonviral vectors has been approved for a multitumor phase I clinical trial that includes head and neck squamous cell carcinoma.

In a head and neck cancer animal model, the use of adenoviral-mediated delivery of the cytokine IL-2 in combination with a cytotoxic gene has demonstrated synergistic effects on tumor regression.[66] The proposed mechanism is the stimulation of a cytotoxic T-cell immune response magnified by released tumor antigens and cellular debris created by the cytotoxic gene. Recent work has focused on the antitumor cytokine, tumor necrosis factor alpha (TNF-α) which binds to cellular receptors to trigger apoptosis. This apoptotic effect is selective for cancer cells, leaving normal cells unharmed. Despite this inherent selectivity, attempts at systemically administering TNF-α have been unsuccessful due to severe hypotension and shocklike symptoms. TNFerade is a second-generation adenoviral vector with the TNF-α gene inserted downstream of the early growth response 1 promoter, which is induced by ionizing radiation. Thus the activation of transgene expression can be triggered in target tissues through irradiation. In a phase 1 clinical trial, intratumoral injection of TNFerade was shown to have a wide therapeutic window and, coupled with radiation, is capable of inducing complete regression in a range of advanced solid tumors, including melanoma.[67]

Randomized controlled trials investigating immune modulation gene therapy are currently underway and may herald a new approach to the treatment of cancer.

Cytotoxic or Suicide Gene Therapy Strategies

Methods have been described for altering the response of tumor cells to chemotherapeutic agents. One experimental approach involves infecting tumor cells by direct injection with a retrovirus that encodes the thymidine kinase gene from herpesvirus.[68] Because retroviruses infect dividing cells, this virus selectively enters growing tumor cells, causing them to express the herpes thymidine kinase gene and making them susceptible to chemotherapy with ganciclovir or acyclovir. Because these drugs are relatively nontoxic to the immune system, this treatment not only eliminates the fraction of cells that are infected with the virus, but also allows for a more general immune response against tumor-specific antigens.

Based on the low efficiency of retrovirus application in animal model and human application, highly efficient adenovirus vectors have been created, which are capable of transferring the thymidine kinase gene directly to tumor cells.[40] This system has been effective in animal models and received approval from the U.S. Food and Drug Administration for a phase I clinical trial in 1996, which was not completed because of insufficient funding.

Modifying Oncogenes and Tumor Suppressor Genes

The discovery of oncogenes and tumor suppressor genes that are involved in the transformation of normal cells into tumor cells has stimulated new approaches for molecular therapy. Oncogenes are naturally present in cells and have proposed functions involving growth and differentiation until a mutation or over-expression activates them to oncogenic potential. Tumor suppressor genes are also naturally occurring, and their expression prevents unrestrained cell proliferation. A deletion or mutation that results in loss of tumor suppressor gene function will therefore allow uncontrolled cell growth. Mutations in the tumor suppressor genes *p53* and *p16* have been detected in a variety of human tumors and a majority of head and neck cancers.[69] (Refer to Chapter 14 for a discussion of tumor suppressor genes and their relation to head and neck cancer.)

Most gene therapy clinical trials for head and neck cancer have used adenoviruses to restore normal p53 function. This work is based on several studies from the early to mid-1990s illustrating the efficacy and safety of the Ad5CMV-p53 vector in vitro and in vivo for the treatment of head and neck cancer.[70-72] Using nude mouse models, Ad5CMV-p53 induced apoptosis and regression of squamous cell carcinoma without adverse effects. The consistent efficacy of p53 gene transfer in a variety of animal tumor models led to the development of the p53-containing adenoviral vector INGN201 (Advexin). This has since been followed by the approval of Gendicine, a similar adenoviral-based p53 gene therapy agent designed and approved for use in China.

The efficacy of Ad5CMV-p53 based therapy in human trials remains controversial. Several clinical trials have been conducted to date

in patients with ovarian, lung, bladder, esophageal, and breast cancers. Clinical efficacy and safety was demonstrated in several of these studies with improved locoregional control of disease.[73-76] However, other trials have shown no difference in clinical outcome between Ad5CMV-p53 monotherapy and conventional treatments.[77] For example, a recent multicenter p53 gene therapy trial for ovarian cancers was halted due to lack of clinical benefit.[78] In contrast, there is growing evidence from phase I and II trials for a significant benefit of adenovirus-mediated p53 gene therapy in head and neck cancers with improved locoregional disease control and a transient survival advantage.[79,80] Most recently, clinical trials have added gene therapy to conventional treatments in the hope of enhancing clinical response. Preliminary results from phase II and III trials consisting of 135 patients with advanced head and neck squamous cell carcinoma that combined p53 intratumoral gene therapy with radiation demonstrated complete tumor regression in 64% of patients and partial regression in 32%, with self-limiting fever as the only noted adverse effect.[81,82]

In order to improve the overall efficacy of adenoviral-mediated gene therapy in clinical trials, several technical issues will need to be overcome. Methods of ensuring transfer of tumor suppressor genes into a majority of tumor cells will need to be developed. This may involve retargeting viral particles as briefly discussed earlier in this chapter. Furthermore, the expression of the suppressor gene is transient, and the tumor regression in these studies has not been permanent. The development of more advanced viral vectors capable of prolonged gene expression may help circumvent this obstacle. The therapeutic potential for a targeted viral vector with sustained gene expression is considerable, but robust clinical data will be needed before gene therapy can transition from an experimental to a routine treatment.

Conditionally Replicating Adenovirus Therapy

Until recently, all viral vectors used in gene therapy strategies were replication-incompetent. Although the use of replication-incompetent or "nonpathogenic" viruses was based on safety precautions, the strategy does not take advantage of the powerful ability of viruses. That is, viruses have the ability to easily infect target cells, replicate, and release viral particles, thereby killing target cells and spreading to surrounding target cells to continue this process. Continued research and investigation in the fields of molecular biology and the genetics of cancer have led to a greater understanding of the principles of viral replication and the genetics of carcinogenesis. This greater understanding has allowed the development of replication-selective oncolytic viruses for use as novel anticancer therapies.

Conditionally replicating viruses have been engineered to selectively infect and replicate in targeted tumor cells that have inherent genetic defects such as loss of p53 gene expression. Tumor cells that lack p53 expression allow select viral replication that kills the host tumor cell, and then subsequent spread and infection of surrounding tumor cells results in further tumor kill. This modification of classic suicide gene therapy into suicide viral therapy may prove to be a key advance in overcoming limitations of gene transfer efficiency in the presently available replication-incompetent adenoviral vectors.

The first replication-selective viral vector to move from preclinical studies to human cancer clinical trials was the Onyx-015 adenovirus.[83,84] The key alteration that made this adenovirus replication selective was the deletion of the gene that codes for the p53-binding protein, E1B-55kDa. Typically, the adenovirus achieves replication through a process by which the E1B-55kDa protein binds a host cell's p53. The Onyx-015 adenovirus with its deletion of the E1B gene will not express the E1B-55kDa p53-binding protein on infection of a target cell. The lack of E1B-55kDa expression will inhibit viral replication. However, in target cells that lack normal p53 expression, Onyx-015 will maintain its ability to replicate, lyse a target cell, and spread to nearby cells. Because the majority of cancers have a loss of normal p53 function, cancer cells are the ideal target for an E1B-deleted replication-selective adenovirus therapy.

The safety of Onyx-15 for human use has been demonstrated over the course of 15 phase I or II clinical trials involving 258 patients including 99 head and neck cancer cases. Viral replication has been shown to be largely isolated to cancer cells, but this does not appear to translate to a significant clinical benefit when Onyx-015 is used as a monotherapy. Indeed, in two phase II clinical trials for recurrent head and neck cancer, a response rate of only 14% was reported.[85,86] The benefit of Onyx-015 may lie in combination therapy with chemotherapeutic agents such as cisplatin or 5-fluorouracil where significant tumor regression was induced.[87,88] Recent work has also explored the use of conditionally replicating adenoviruses to deliver shRNAs to cancer cells, providing an avenue for the selective silencing of genes involved in carcinogenesis coupled with direct lysis of infected cells.[89]

There are many other evolving strategies for oncolytic viral vector therapy, and it is not the purpose of this chapter to discuss the present state of this novel therapy in detail. However, it is important to mention replication-selective oncolytic viral therapy because it may be thought of as a type of gene-dependent suicide therapy.

Antiangiogenesis

An approach with future potential in cancer gene therapy involves introducing genes that inhibit angiogenesis in the vicinity of a tumor.[90] A decrease or regression of the tumor's important vascular supply by the action of antiangiogenesis factors has been shown to cause significant tumor regression in mouse melanoma models. Continued development and investigation of inhibitors of growth and angiogenesis coupled with the packaging of these factors into vectors for gene transfer in vivo may provide alternative or adjuvant therapies for both benign vascular and malignant tumors of the head and neck.

Plastic and Reconstructive Surgery

Great potential for gene therapy exists in the area of plastic and reconstructive surgery. The principal concept of gene therapy as applied to this field will be the expression of growth-regulating factors to enhance repair or regeneration of damaged tissues and to induce local proliferation to fill surgical defects. By introducing genes into cells within a surgical site, local expression of growth factors can be constituted at levels that maximize the therapeutic response. The use of gene transfer to release growth factors, as opposed to simply injecting suspensions of purified factors, will enable regulated expression of the product over a programmed period with restriction of the product to specific targeted layers of tissue. The combination of this property with the incorporation of proper regulatory elements could minimize associated toxicities or unwanted proliferation of nearby tissues.

Reconstructive Tissue Flaps and Wound Healing

A common problem encountered in the use of local or regional flaps is distal flap necrosis with atrophy or even partial loss.[91] Timely angiogenesis and neovascularization is essential for the survival of these tissues as well as healing of the surgical wound. This process of angiogenesis is stimulated by various growth factors such as basic fibroblast growth factor (bFGF) and heparin binding growth factor.[92] Using gene transfer techniques, a gene encoding an angiogenesis factor could be introduced into cells within a reconstructed tissue, recipient site, or primary wound defect. Subsequent to this gene therapy, an accelerated and magnified vascular response resulting from local expression of angiogenic factors could promote healing with improved tissue survival. The use of gene therapy may prove to be very important in free tissue flaps, where failure often occurs because of inadequate venous efflux leading to vascular engorgement and tissue destruction.

There are multiple other growth factors that influence the process of tissue repair and regeneration. Examples include transforming growth factors (e.g., TGFα, TGFa), insulin-like growth factors (e.g., IGF-I, IGF-II), platelet-derived growth factors (PDGF), nerve growth factors, and others. Indeed, inducing transgene expression of PDGF in a rat incisional wound model increased the mechanical strength of incisions by 75% to 100% for up to 2 weeks post-transfection. Other studies have shown that enhancing expression of epidermal growth factor (EGF) in partial thickness wounds increases re-epithelialization rates and shortened the time to wound closure. Multiple clinical trials are currently underway investigating the use of adenoviral vectors expressing PDGF-β for the enhancement of wound healing.[93]

Different combinations of growth factors can be used to enhance regeneration of vascular tissue, muscle, epithelium, and even nerves.[94]

IGF-1 is especially important in maintaining muscle mass and differentiation and may even be able to promote reinnervation of damaged muscle. Epidermal growth factor, bFGF, and TGFa are potent growth stimulators in dermal layers and may prove advantageous in the management of soft tissue defects caused by trauma or resulting from surgery, a particularly difficult problem for the reconstructive surgeon. For example, the gene for a therapeutic growth factor could be transferred into the surgical defect created by a tongue-jaw-neck resection for oral squamous cell cancer. The local programmed production of healing and growth factors resulting from the direct gene therapy would then stimulate the growth of muscle, fascia, blood vessels, or dermal structures. This growth response would decrease the size of the defect while providing added strength and vascularized tissue to prevent wound dehiscence or extrusion or infection of reconstruction plates. Because of the ability to increase muscle and connective tissue mass and retard atrophy, much smaller flaps could be taken that reduce the overall morbidity and cosmetic defect at the donor site.

Skin Grafting

Skin grafts are an attractive target for somatic gene therapy because of the proven feasibility of cultivating epidermal cells ex vivo and subsequently engrafting these cells successfully in patients. Furthermore, previous studies have established the feasibility of effective gene transfer into skin grafts in animal models.[95] The survival of skin grafts is dependent on adequate nutrition and oxygenation of the graft as well as removal of waste products. Until the blood supply is established, the recipient bed is responsible for the fibrous and plasma exudate through which nutrition is supplied and metabolic wastes are transferred.[96] Gene therapy aimed at increasing vascularization or providing local growth factors for the dermal or epidermal layers (depending on the thickness of the graft) could promote early graft take and lead to overall improved strength. As a protective mechanism, gene transfer of various cytokines, complements, or antimicrobial factors may prove effective in preventing infection. This particular application could prove invaluable in burn patients who require extensive skin grafting and in cases in which grafting is performed over irradiated tissues, ulcers, or prostheses, where survival is typically poor.

Repair and Regeneration of Irradiated Tissue

Morbidity associated with primary or postoperative radiation therapy is common in patients with head and neck cancer. Inflammation, fibrosis, pain, and even wound breakdown with infection are problems encountered in our patients receiving radiation therapy.[97] Despite efforts to narrow the x-ray field and block surrounding structures, there is still substantial damage to superficial and nearby tissues. Growth factors such as ECGF[98] have been shown to enhance viability and vascularity in irradiated soft tissue in animal models. Gene transfer of reparative factors such as ECGF may provide spatially precise and regulated expression of these factors within the field of radiation and may result in reduced toxicity and overall morbidity.

Applications in Laryngology

Treatment outcomes following the surgical repair of the paralyzed larynx are significantly compromised by laryngeal muscle atrophy secondary to denervation. Surgical reinnervation has not consistently improved outcomes. Reversal or prevention of laryngeal muscle atrophy may be possible using gene therapy techniques. In preclinical animal investigations, introduction of human insulin-like growth factor I (hIGF-1) into paralyzed rat laryngeal muscles induced a significant increase in muscle fiber diameter, while also decreasing motor endplate length and increasing the percentage of endplates with nerve contact.[99] In additional studies, hIGF-1 normalized myosin heavy chain composition in denervated rat laryngeal muscles.[100] This novel gene therapy with its combined neurotrophic and myotrophic effects holds potential for optimizing functional outcomes after either acute laryngeal nerve injury or for augmenting surgical reinnervation of the paralyzed larynx.

Applications in Otology/Neurotology

At present, progress with inner ear gene therapy is purely at the experimental stage.[101] Within the auditory system, several vectors have been studied and shown to successfully transfer functional ectopic genes into the mammalian auditory system. Adenoviruses have been shown to transfer functional marker genes such as β-galactosidase (β gal) and green fluorescent protein (GFP), as well as genes that alter the biology of the inner ear such as glial-derived neurotrophic factor (GDNF), to the auditory system.[102-104] Alternate vectors include herpesvirus-derived vectors[105] that have the advantage of being strongly neurotrophic and expressing the transgene for prolonged periods.[106] AAV and liposome packaged plasmids have also been effectively transferred into the cochlea.[107,108] The preservation of hearing in animals treated with infusion of adenoviral vectors into the cochlea and vestibule has recently been demonstrated.[109]

To date several studies have been conducted demonstrating the feasibility and clinical potential of gene therapy for inner ear disease. Adenoviral-mediated delivery of neurotrophin-3, brain derived neurotrophic growth factor and cilial neurotrophic factor have all been shown to promote spiral ganglion cell survival following drug-induced hearing loss in animal models.[110-112] Inner ear tissues can also be protected through the adenoviral delivery of genes for antioxidant enzymes including catalase and superoxide dismutase.[113] These findings could potentially be used to rescue hearing after the administration of ototoxic drugs or to prevent the loss of inner ear hair cells after cochlear implantation.[114]

Gene therapy could have a dramatic benefit in the restoration of hearing loss through the transfer of developmental genes into the inner ear. Studies have already demonstrated that adenoviral delivery of the gene Math1 to the inner ear of guinea pigs results in the production and innervation of hair cells.[115] Transfer of the developmental gene, Atoh1, to the guinea pig inner ear can successfully convert non-sensory cells into functional hair cells with a resulting improvement in hearing on ABR testing following an ototoxic insult.[116] These benchtop studies are laying the foundation for the development of novel therapeutics that may revolutionize the treatment of hearing loss.

For the long-term application of gene therapy for auditory disease to become established, several criteria need to be met. Otologic disease, generally, is not associated with mortality; therefore unlike gene therapy for cancer, vectors need to have low immunogenicity and cytotoxicity. Vectors have to be replication-deficient and nononcogenic, and must express their transgene for prolonged periods. Advances in vector design will make it possible to apply the rapidly growing knowledge of inner ear biology to human disease.

Therapeutic Gene Silencing and the Future of Gene Therapy

The newest frontier in gene therapy involves selectively turning off or "silencing" genes to prevent the development or progression of disease. The therapeutic potential of RNA interference and gene silencing techniques is evidenced by the tremendous number of studies that have been published in the relatively short period of time since the discovery of this molecular therapy technique. Consequently, more than 30 pharmaceutical or biotechnology companies are currently developing RNAi-based therapeutics.[10]

The first condition under evaluation with RNAi technology is age-related macular degeneration (AMD). AMD is caused by the abnormal growth of blood vessels behind the retina. New drugs consisting of modified siRNA targeting either VEGF or its receptor, VEGFR1, have been developed to block retinal angiogenesis. These drugs are administered directly into the eye as a single intravitreal injection and have been shown to stabilize and even improve visual acuity in a dose-dependent fashion with minimal toxicity. Phase II clinical trials are currently underway using various VEGF-targeting RNA interference methods for the treatment of AMD.[10]

Viral RNAs are also potential targets for gene silencing including genes encoding viral entry and replication within cells. Intranasal aerosol delivery of a plasmid-borne siRNA is able to potently inhibit respiratory syncytial virus (RSV) infection in mice, and this approach is currently in phase I clinical trials for human RSV infection.[117] Long-term suppression of HIV replication has been achieved by simultaneously targeting three key genes involved in HIV infection using a lentiviral vector encoding multiple shRNAs.[118] Clinical trials using this approach are underway.

There have been several successful preclinical attempts at using RNAi to induce cancer cell death. RNAi has successfully induced tumor suppression in murine models of pancreatic, ovarian, bladder, breast, liver, melanoma, and cervical cancer.[119,120] Furthermore, RNAi has proven effective in the prevention of tumor metastasis.[119] The targeting of cellular oncogenes that are overexpressed in cancer cells is particularly amenable to RNAi. For example, siRNA-mediated silencing of the tyrosine kinase receptor EphA2 gene, overexpressed in ovarian cancers, induces a 50% reduction of tumor size that can be further improved to a 90% volume reduction when combined with the conventional chemotherapeutic paclitaxel.[12] Oncogenes that arise as a result of chromosomal translocations can also be silenced using RNAi. The Bcr-Abl oncogene, the key mutation in chronic myeloid leukemia, can be silenced using a lentiviral vector expressing anti-Bcr/Abl shRNA. This leads to a down-regulation of Bcr-Abl protein kinase expression and a subsequent suppression of cancer cell proliferation.[121] This gene-silencing approach was also shown to markedly potentiate the action of the kinase-targeted inhibitor drug imatinib.[122]

Cancer cell resistance to chemotherapy is a major factor underlying treatment failure and disease relapse. The multidrug transporter, P-glycoprotein, encoded by the MDR1 gene, is a major system by which cancer cells prevent the intracellular accumulation of chemotherapy drugs. Gene silencing of MDR1 reversed the resistance of pancreatic and gastric cancers to the chemotherapeutic daunorubicin by 89% and 58%, respectively.[120]

The studies outlined above raise the possibility that RNAi can be used to treat cancers in which specific oncogenes have been implicated and may also be used to sensitize cancers to conventional treatment. The translation of RNAi to the clinical realm will require the development of efficient and safe delivery systems, but these agents have the potential to be the most selective, efficient agents ever designed and will likely revolutionize future therapies.

Conclusion

The founding work in molecular biology over the past 40 years has enabled clinical application in the realm of gene therapy. Presently, there are more than 600 completed or ongoing clinical trials, and this pace of progress continues. No longer is gene therapy simply a speculative approach for treating disease in the distant future. While the methods of gene therapy are still evolving, current methods are already sufficiently advanced so as to be used in trials of gene therapy for select diseases and to be incorporated into clinically efficacious pharmaceutical products. Gene therapy has great potential, not only for the treatment of inherited diseases, but also for providing new treatments for complex diseases such as cancer and for the development of novel adjuvants to standard medical or surgical interventions. Gene therapy technologies should have a significant impact on the quality of medicine, while at the same time providing the additional benefit of cost reduction. As the field rapidly advances, increasing opportunities should arise for physicians to apply these technologies in clinical trials and, eventually, clinical practice.

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CHAPTER THREE

Laser Surgery: Basic Principles and Safety Considerations

C. Gaelyn Garrett

Robert H. Ossoff

Lou Reinisch

Key Points

- Laser technology has allowed for enhanced surgical treatment for a wide variety of otolaryngology indications including those in otology, laryngology, bronchoesophagology, and facial plastic surgery.
- Every surgeon should have basic knowledge of laser physics and laser-tissue interactions to minimize unnecessary tissue injury.
- The choice of surgical laser depends on several factors, including the target tissue, available modes of delivery, and desired tissue effects.
- Safe and proper laser use requires an established laser safety protocol at each institution and should include separate credentialing for each laser to be used by an individual surgeon.
- Newer lasers to otolaryngology such as the pulsed dye laser and the pulsed KTP laser have enhanced the ability to perform in-office unsedated treatment for certain laryngeal diseases.

Laser light is the brightest monochromatic (single color) light that exists today. In addition to being a standard tool in the research laboratory, the laser is currently used in communications, surveying, manufacturing, diagnostic medicine, and surgery. Supermarket bar code scanners, lecture pointers, and compact disc players bring laser technology into everyday life. The addition of lasers and the development of new lasers to the surgical armamentarium in otolaryngology offer new and exciting possibilities to improve conventional techniques and to expand the scope of otolaryngology.

This chapter reviews the principles, applications, and safety considerations associated with the use of lasers in the upper aerodigestive tract. The material presented provides a foundation for the otolaryngologist to safely and effectively apply this exciting technology in daily practice.

History of Lasers

Laser is a word derived from the acronym for *l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation. Einstein[1] postulated the theoretical foundation of laser action, stimulated emission of radiation, in 1917. In his classic journal article, "Zur Quantem Theorie der Strahlung" ("The Quantum Theory of Radiation"), he discussed the interaction of atoms, ions, and molecules with electromagnetic radiation. He specifically addressed absorption and spontaneous emission of energy, and proposed a third process of interaction: stimulated emission. Einstein postulated that the spontaneous emission of electromagnetic radiation from an atomic transition has an enhanced rate in the presence of similar electromagnetic radiation. This "negative absorption" is the basis of laser energy. Many attempts were made in the following years to produce stimulated emission of electromagnetic energy, but it was not until 1954 that this was successfully accomplished. In that year, Gordon and others[2] reported their experiences with stimulated emission of radiation in the microwave range of the electromagnetic spectrum. This represented the first *maser* (*m*icrowave *a*mplification by the *s*timulated *e*mission of *r*adiation) and paved the way for the development of the first laser. In 1958, Schawlow and Townes[3] published "Infrared and Optical Masers," in which they discussed stimulated emission in the microwave range of the spectrum and described the desirability and principles of extending stimulated emission techniques to the infrared and optical ranges of the spectrum. Maiman[4] expanded on these theoretical writings and built the first laser in 1960. With synthetic ruby crystals, this laser produced electromagnetic radiation at a wavelength of 0.69 μm in the visible range of the spectrum. Although the laser energy produced by Maiman's ruby laser lasted less than 1 ms, it paved the way for explosive development and widespread application of this technology.

Commercial lasers were being sold for laboratory use within 1 year of being invented. Partially reacting to the recently discovered dangers of x-rays, scientists were concerned about the safety of lasers and how laser light might damage living tissue.

This concern over the safety of laser light prompted much of the early transition of the laser from the scientific laboratory to the medical clinic. In 1962, Zaret and others[5] published one of the first reports of laser light interacting with tissue. They measured the damage caused by lasers on rabbit retina and iris. In 1964, the argon (Ar) and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers were developed.[6] Excited by the ophthalmologists' progress in using the laser as a therapeutic tool, Goldman used his medical laser laboratory to look at the hazards of the laser and to consider the potential uses of the laser in medicine. Two important advances allowed the laser to be useful in

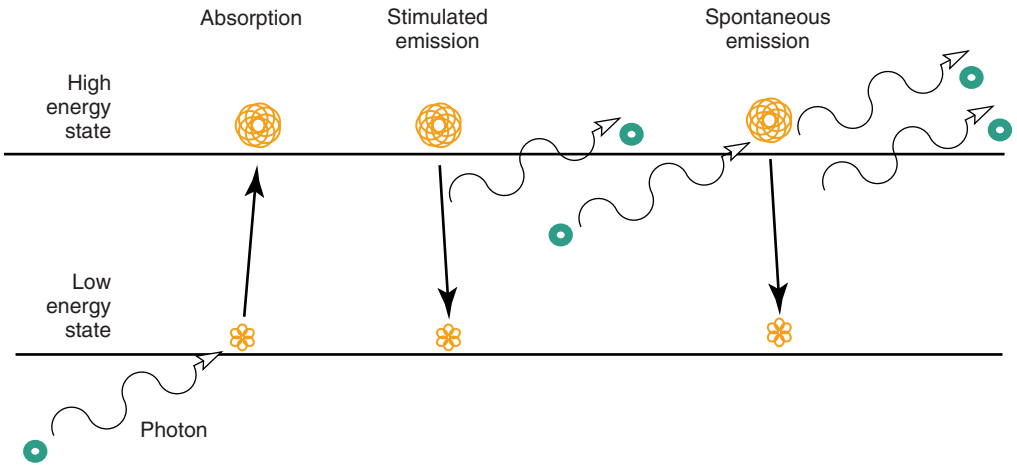

Figure 3-1. The interaction of light (a photon) with an atom. Three processes are shown: the absorption of a photon by an atom in a low-energy state, the spontaneous emission of a photon from an atom in an excited state, and the stimulated emission of a photon by a second photon of the same wavelength from an excited-state atom.

otolaryngology: (1) in 1965, the carbon dioxide (CO_2) laser was developed, and (2) in 1968, Polanyi[7] developed the articulated arm to deliver the infrared radiation from the CO_2 laser to remote targets. He combined his talents with Jako and used the articulated arm and the CO_2 laser in laryngeal surgery. Simpson and Polanyi[8] described the series of experiments and new instrumentation that made this work possible.

A laser is an electro-optical device that emits organized light (rather than the random-pattern light emitted from a light bulb) in a very narrow intense beam by a process of optical feedback and amplification. Because the explanation for this organized light involves stimulated emission, a brief review of quantum physics is necessary.

In the semiclassical picture of the atom, each proton is balanced by an electron that orbits the nucleus of the atom in one of several discrete shells or orbits. Shells correspond to specific energy levels, which are characteristic of each different atom or molecule. The smaller shells, where the electron is closer to the nucleus, have a lower energy level than the larger shells, where the electron is farther from the nucleus. Electrons of a particular atom can only orbit the nucleus at these shells or levels. Radiation of energy does not occur while the electrons remain in any of these shells.

Electrons can change their orbits, thereby changing the energy state of the atom. During excitation, an electron can make the transition from a low-energy level to a higher energy level. Excitation that comes from the electron interacting with light (a photon) is termed *absorption*. The atom always seeks its lowest energy level (i.e., the ground state). Therefore, the electron will spontaneously drop from the high-energy level back to the lowest energy level in a very short time (typically 10^{-8} sec). As the electron spontaneously drops from the higher energy level to the lower energy level, the atom must give up the energy difference. The atom emits the extra energy as a photon of light in a process termed the *spontaneous emission of radiation* (Fig. 3-1).

Einstein postulated that an atom in a high-energy level could be induced to make the transition to a lower energy state even faster than the spontaneous process if it interacted with a photon of the correct energy. This process can be imagined as a photon colliding with an excited atom, resulting in two identical photons (one incident and one produced by the decay) that leave the collision. The two photons have the same frequency and energy and travel in the same direction in the spatial and temporal phase. This process, which Einstein called stimulated emission of radiation, is the underlying principle of laser physics (see Fig. 3-1).

What Is a Laser?

All laser devices have an optical resonating chamber (cavity) with two mirrors. The space between these mirrors is filled with an active medium, such as Ar, Nd:YAG, or CO_2. An external energy source (e.g., an electric current) excites the active medium within the optical cavity. This excitation causes many atoms of the active medium to be raised to a higher energy state. A population inversion occurs when more than half of the atoms in the resonating chamber have reached a particular excited state. Spontaneous emission is taking place in all directions. Light (photons) emitted in the direction of the long axis of the laser is retained within the optical cavity by multiple reflections off the precisely aligned mirrors. One mirror is completely reflective, and the other is partially transmissive (Fig. 3-2). Stimulated emission occurs when a photon interacts with an excited atom in the optical cavity. This yields pairs of identical photons that are of equal wavelength, frequency, and energy and are in phase with each other. This process occurs at an increasing rate with each passage of the photons through the active medium.

The mirrors serve as a positive feedback mechanism for the stimulated emission of radiation by reflecting the photons back and forth. The partially transmissive mirror emits some of the radiant energy as laser light. The radiation leaving the optical cavity through the partially transmissive mirror quickly reaches equilibrium with the pumping mechanism's rate of replenishing the population of high-energy state atoms. (In the preceding discussion, the term *atom* refers to the active material. In reality, the active material can consist of molecules, ions, atoms, semiconductors, or even free electrons in an accelerator. These other systems do not require the bound electron to be excited but may instead use different forms of excitation, including molecular vibrational excitation or the kinetic energy of an accelerated electron.)

The radiant energy emitted from the optical cavity is of the same wavelength (monochromatic), is extremely intense and unidirectional (collimated), and is temporally and spatially coherent. The term *temporal coherence* refers to the waves of light oscillating in phase over a given time; whereas spatial coherence means that the photons are equal and parallel across the wavefront. These properties of monochromaticity, intensity, collimation, and coherence distinguish the organized radiant energy of a laser light source from the disorganized radiant energy of a light bulb or other light source (Fig. 3-3).

After the laser energy exits the optical cavity through the partially transmissive mirror, the radiant energy typically passes through a lens that focuses the laser beam to a very small diameter, or spot size, ranging from 0.1 to 2.0 mm. When necessary, the lens system is constructed to allow the visible helium-neon aiming laser beam and the invisible CO_2 or Nd:YAG laser beam to be focused in a coplanar manner. The optical properties of each focusing lens determine the focal length or distance from the lens to the intended target tissue for focused use.

Control of the Surgical Laser

With most surgical lasers, the physician can control three variables: (1) power (measured in watts), (2) spot size (measured in millimeters), and (3) exposure time (measured in seconds).

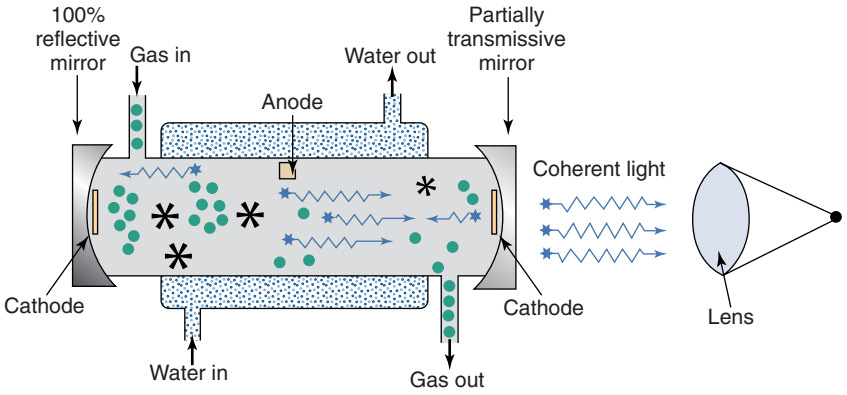

Figure 3-2. The optical resonating chamber of a carbon dioxide laser. The gas molecules are excited by an electric current. The gas is cooled by a water jacket. The two mirrors provide the optical feedback for the amplification. The emitted light is coherent, monochromatic, and collimated. The light can be focused to a small point with an external lens.

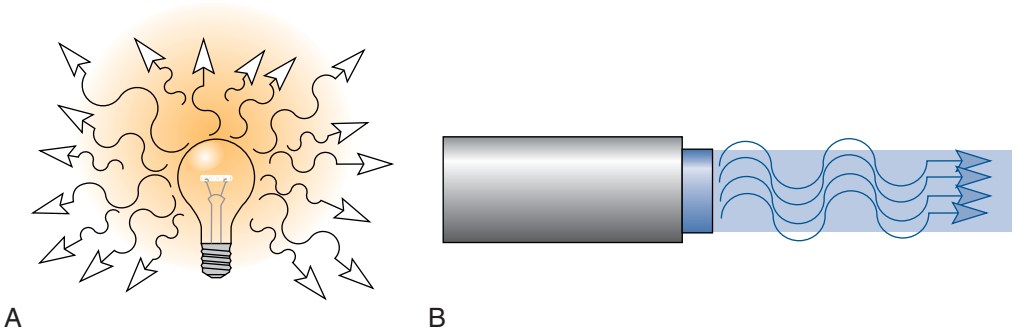

Figure 3-3. A, Light emitted from a conventional lamp. The light travels in all directions, is composed of many wavelengths, and is not coherent. **B,** Light emitted from a laser. The light travels in the same direction, it is a single wavelength, and all of the waves are in phase. The light is coherent.

Power

Of power, spot size, and exposure time, power is the least useful variable and may be kept constant with widely varying effects, depending on the spot size and the duration of exposure. For example, the relationship between power and depth of tissue injury becomes logarithmic when the power and exposure time are kept constant and the spot size is varied.

Irradiance is a more useful measure of the intensity of the beam at the focal spot than power is because it considers the surface area of the focal spot. Specifically, irradiance is expressed (in W/cm^2) as:

$$\text{Irradiance} = \text{Power in the focal spot} / \text{Area of the focal spot}$$

Spot Size

Power and spot size are considered together, and a combination is selected to produce the appropriate irradiance. If the exposure time is kept constant, the relationship between irradiance and depth of injury is linear as the spot size is varied. Irradiance is the most important operating parameter of a surgical laser at a given wavelength. Therefore surgeons should calculate the appropriate irradiance for each procedure to be performed. These calculations allow the surgeon to control, in a predictable manner, the tissue effects when changing from one focal length to another (e.g., from 400 mm for microlaryngeal surgery to 125 mm for handheld surgery). Irradiance varies directly with power and inversely with surface area. This relationship of surface area to beam diameter is important when evaluating the power density because the larger the surface area, the lower the irradiance; conversely, the smaller the surface area, the higher the irradiance. Surface area (A) is expressed as:

$$A = \pi r^2 \text{ or } A = \pi d^2/4$$

where r is the beam radius and d is the beam diameter ($d = 2r$).

Surface area and irradiance vary with the square of the beam diameter. Doubling the beam diameter (e.g., from d to 2d) increases the surface area by 4 and reduces irradiance to one fourth. Halving the beam diameter (e.g., from d to d/2) yields only one fourth of the area and increases irradiance by a factor of 4.

Current CO_2 lasers emit radiant energy with a characteristic beam intensity pattern. This beam pattern ultimately determines the depth of tissue injury and vaporization across the focal spot. Therefore the surgeon should be aware of the characteristic beam pattern of the laser. Transverse electromagnetic mode (TEM) refers to the distribution of energy across the focal spot and determines the shape of the laser's spot. The most fundamental mode is TEM_{00}, which appears circular on cross section. The power density of the beam follows a gaussian distribution. The greatest amount of energy is at the center of the beam and diminishes progressively toward the periphery. TEM_{01} and TEM_{11} are less fundamental modes that have a more complex distribution of energy across their focal spot, causing predictable variations in tissue vaporization depth. Additionally, their beams cannot be focused to as small a spot size as TEM_{00} lasers at the same working distance.[9]

Although simple ray diagrams normally show parallel light focused to a point, the actual situation is a bit more complicated. A lens focuses a gaussian beam to a beam waist of a finite size. This beam waist is the minimum spot diameter (d) and can be expressed as:

$$d \sim 2f\lambda/D$$

where f is the focal length of the lens, λ is the wavelength of light, and D is the diameter of the laser beam incident on the lens (Fig. 3-4).

The beam waist occurs over a range of distances, termed the *depth of focus*, which can be expressed as:

$$\text{Depth of focus} \sim \pi d^2/2\lambda$$

Depth of focus is realized when a camera is focused. With a camera, a range of objects is in focus, which can be set without carefully measuring the distance between the object and the lens. The preceding equations show that a long focal length lens leads to a large beam waist, which also translates as a large depth of focus.

The size of the laser beam on the tissue (spot size) can therefore be varied in two ways:

1. Because the minimum beam diameter of the focal spot increases directly with increasing the focal length of the laser-focusing lens, the surgeon can change the focal length of the lens to obtain a particular beam diameter. As the focal length decreases, a corresponding decrease occurs in the size of the focal spot. Also, the smaller the spot size is for any given power output, the greater the corresponding power density.
2. The surgeon can also vary the spot size by working in or out of focus. The minimum beam diameter and highest power concentration occur at the focal plane, where much of the precise cutting and vaporization is carried out (Fig. 3-5A). As the distance from the focal plane increases, the laser beam diverges or becomes unfocused (see Fig. 3-5B). The cross-sectional area of the spot increases and thus lowers the power density for a given output.

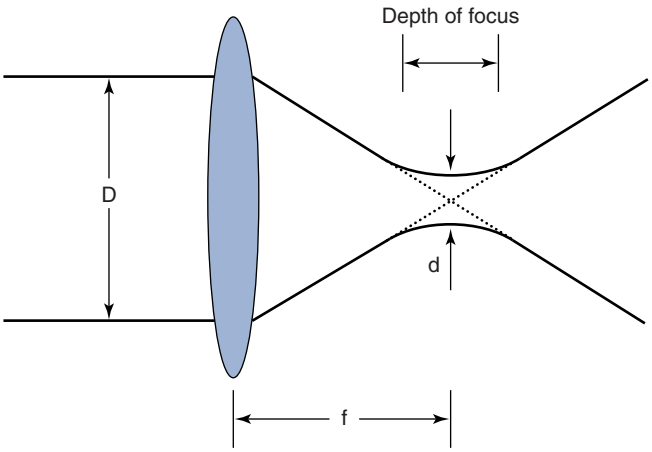

Figure 3-4. The beam waist of parallel light focused by a lens. The focal length of the lens is *f*. The incident beam is transverse electromagnetic mode (TEM_{00}) and has a diameter incident on the lens of 2D. The beam waist has a diameter of 2d.

The size of the focal spot depends on the focal length of the laser lens and whether the surgeon is working in or out of focus.

Figure 3-6 shows these concepts using arbitrary ratios accurate for a current model TEM_{00} CO_2 laser. The laser lens setting (focal length) and working distance (focused/unfocused) combinations determine the size of the focal spot. The height of the various cylinders represents the amount of tissue (depth and width) vaporized after a 1-sec exposure at the three focal lengths.

Exposure Time

The surgeon can vary the amount of energy delivered to the target tissue by varying the exposure time. *Fluence* refers to the amount of time (measured in seconds) that a laser beam irradiates a unit area of tissue at a constant irradiance. Fluence is a measure, then, of the total amount of laser energy per unit area of exposed target tissue and is expressed (J/cm^2) as:

$$\text{Fluence} = \text{Power density} \times \text{Time}$$

Fluence varies directly with the length of the exposure time, which can be varied by working in the pulsed mode (duration, 0.05 to 0.5 sec) or in the continuous mode.

Tissue Effects

When electromagnetic energy (incident radiation) interacts with tissue, the tissue reflects, absorbs, transmits, and scatters portions of the light. The surgical interaction of this radiant energy with tissue is caused only by that portion of light that is absorbed (i.e., the incident radiation minus the sum of the reflected and transmitted portions).

The actual tissue effects produced by the radiant energy of a laser vary with the wavelength of the laser. Each type of laser exhibits dif-

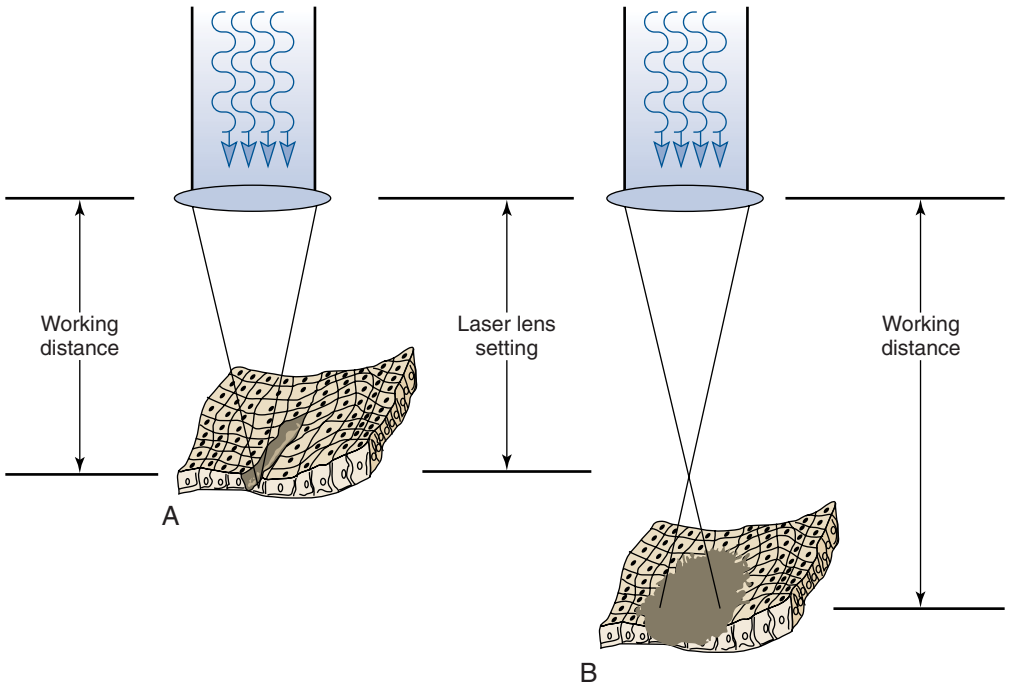

Figure 3-5. A, Laser-tissue interaction when the tissue is the focal distance away from the lens. Note the minimum beam diameter in the focal plane. **B,** Laser-tissue interaction when the tissue is not in the focal plane of the lens. The laser covers a much larger area on the tissue surface.

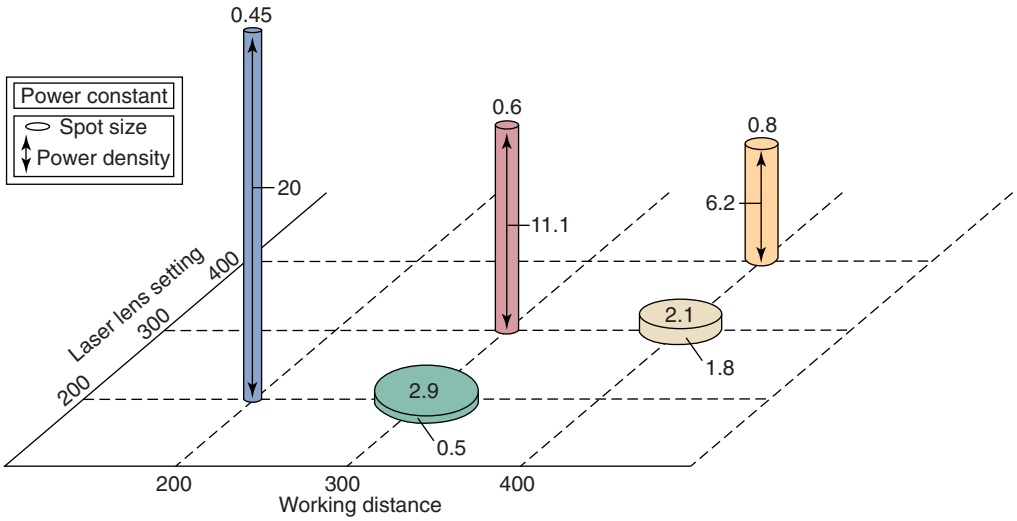

Figure 3-6. Power density versus spot size. The ratios are arbitrary for a current model carbon dioxide laser. The cylinder height represents the amount of tissue vaporized after a 1-second exposure at the three designated focal lengths.

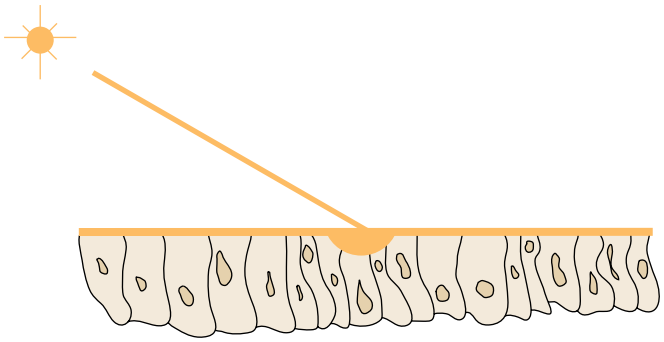

Figure 3-7. Absorption.

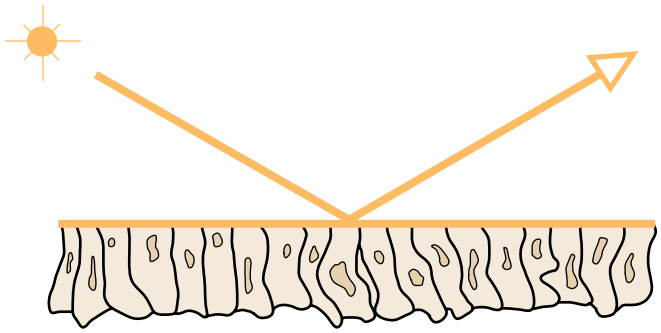

Figure 3-9. Reflection.

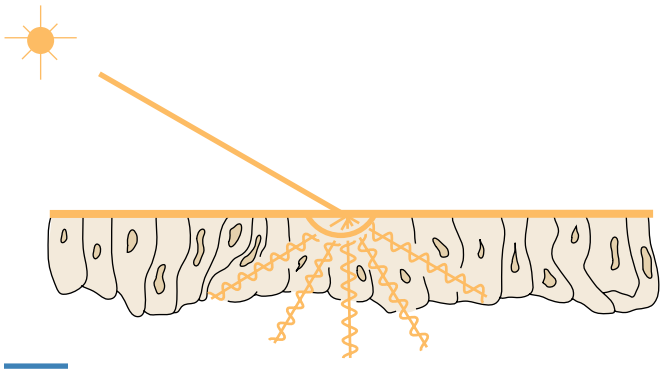

Figure 3-8. Scattering.

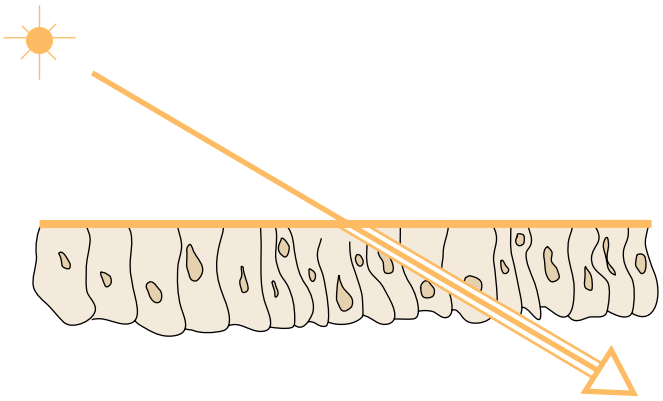

Figure 3-10. Transmission.

ferent characteristic biologic effects on tissue and is therefore useful for different applications. However, certain similarities exist regarding the nature of laser light interaction with biologic tissue. The lasers used in medicine and surgery today can be ultraviolet, meaning the interactions are a complex mixture of heating and photodissociation of chemical bonds. The more commonly used lasers emit light in the visible or the infrared region of the electromagnetic spectrum, and their primary form of interaction with biologic tissue leads to heating. Therefore, if the radiant energy of a laser is to exert its effect on the target tissue, it must be absorbed by the target tissue and be converted to heat (Fig. 3-7). Scattering tends to spread the laser energy over a larger surface area of tissue, but it limits the penetration depth (Fig. 3-8). The shorter the wavelength of light, the more it is scattered by the tissue. If the radiant energy is reflected from or transmitted through the tissue (Figs. 3-7, 3-9, and 3-10), no effect will occur. To select the most appropriate laser system for a particular application, the surgeon should thoroughly understand these characteristics regarding the interaction of laser light with biologic tissue.[10]

The CO_2 laser creates a characteristic wound (Fig. 3-11). When the target absorbs a specific amount of radiant energy to increase its temperature to between 60° C and 65° C, protein denaturation occurs. Blanching of the tissue surface is readily visible, and the deep structural

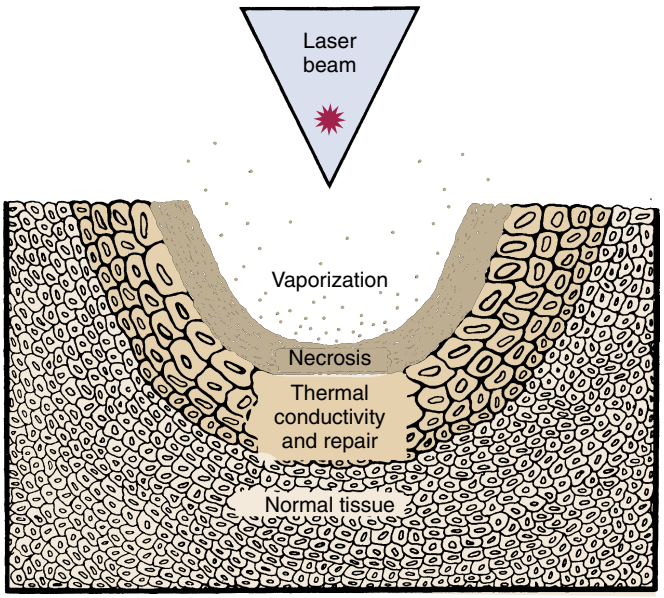

Figure 3-11. The wound created by the carbon dioxide laser, showing the representative zones of injury.

integrity of the tissue is disturbed. When the absorbed laser light heats the tissue to approximately 100° C, vaporization of intracellular water occurs, causing vacuole formation, craters, and tissue shrinkage. Carbonization, disintegration, smoke, and gas generation with destruction of the laser-radiated tissue occurs at several hundred degrees centigrade. In the center of the wound is an area of tissue vaporization, where just a few flakes of carbon debris are noted. Immediately adjacent to this area is a zone of thermal necrosis (about 100 µm wide). Next is an area of thermal conductivity and repair (usually 300 to 500 µm wide). Small vessels, nerves, and lymphatics are sealed in the zone of thermal necrosis. The minimal operative trauma combined with the vascular seal probably account for the absence of postoperative edema characteristic of laser wounds.

Comparison animal studies have been performed on the histologic properties of healing and the tensile strength of the healing wound after laser- and scalpel-produced incisions. Several studies noted impaired wound healing with the CO_2 laser incision when compared with the scalpel-produced incision.[11-15] Other studies of the healing properties of laser-induced incisions concluded that laser incisions have equivalent or better healing results than surgical knife wounds.[16-18] Buell and Schuller[19] compared the rate of tissue repair after CO_2 laser and scalpel incisions on hogs. In this study, the tensile strength of the laser incisions was less than that of similar scalpel incisions during the first 3 weeks after surgery. After this time, the tensile strength of both wounds rapidly increased at a similar rate.

Regardless of which studies accurately depict the effects of the CO_2 laser on wound healing, the incidental, collateral thermal damage is indisputable. To minimize lateral thermal damage from thermal diffusion, the tissue should be ablated with a short laser pulse.

To understand how a pulsed laser reduces thermal diffusion, consider the analogy of filling a large bucket with a hole in the bottom. If a narrow stream of water is used to fill the bucket, the filling process will take a long time and a considerable amount of water will leak out of the hole during the filling process. Instead, if the bucket is filled in one quick dump from an even larger bucket, the water will have little time to leak out of the hole during the filling process.

This analogy can also be used to understand the ablation process. In ablation, the water represents laser energy and the filled bucket represents sufficient energy deposited in the tissue to cause ablation. The hole in the bottom of the bucket represents the thermal diffusion of heat away from the ablation site while the energy is being deposited. A low-intensity, continuous laser beam is similar to the narrow stream of water. The short-pulsed, high-peak power laser is similar to the larger bucket in that it quickly dumps energy into the ablation site.

Laser Types and Applications

Several types of lasers are commonly used in otolaryngology. They include the argon laser, argon tunable dye laser, Nd:YAG laser, KTP laser, pulsed dye laser (PDL), flash lamp pumped dye laser, and CO_2 laser. Other types are in various stages of evaluation for clinical applicability, such as the thulium:YAG laser. The potential clinical applications of these surgical lasers are mainly determined by wavelength and the specific tissue-absorptive characteristics. Therefore the surgeon should consider the properties of each wavelength when choosing a particular laser to achieve the surgical objective with minimal morbidity and maximal efficiency (Table 3-1). Clinical applications are also limited by the available modes of delivery for the various lasers. It is also important to know that the applications listed can, in many cases, be addressed with nonlaser techniques as well or arguably better.

Argon (Ar) Laser

Ar lasers produce blue-green light in the visible range of the electromagnetic spectrum, with primary wavelengths of 0.488 and 0.514 µm. The radiant energy of an Ar laser may be strongly absorbed, scattered, or reflected depending on the specific biologic tissues with which it interacts. Its extinction length (i.e., the thickness of water necessary to absorb 90% of the incident radiation) in pure water is about 80 m. Therefore the radiant energy from an Ar laser is readily transmitted through clear aqueous tissues (e.g., cornea, lens, and vitreous humor) and is absorbed and reflected to varying degrees by tissues white in color (e.g., skin, fat, and bone). Light from an Ar laser is absorbed by hemoglobin and pigmented tissues. A localized thermal reaction occurs within the target tissue, causing protein coagulation. The clinician uses this selective absorption of light from an Ar laser to photocoagulate pigmented lesions, such as port-wine stains, hemangiomas, and telangiectasis. The heat produced destroys the epidermis and upper dermis. Therefore the surgeon should minimize the amount of laser energy delivered to the vascular cutaneous lesion to decrease the tendency of scarring in the overlying skin.

When the beam of the Ar laser is focused on a small focal spot, its power density increases sufficiently to vaporize the target tissue. This characteristic allows otologists to perform stapedotomy in patients with otosclerosis.[20] Bone, being a white tissue, reflects most of the incident radiation from an Ar laser. Therefore to perform an Ar laser stapedotomy, it is necessary to place a drop of blood on the stapes to initiate absorption.

Argon Tunable Dye Laser

The Ar tunable dye laser works on the principle of the Ar laser. The Ar tunable dye laser makes a high-intensity beam that is focused on dye continuously circulating in a second laser optically coupled with the Ar laser. The Ar laser beam energizes the dye, causing it to emit laser energy at a longer wavelength than the pump beam. By varying the type of dye and using a tuning system, different wavelengths can be obtained. The laser energy from this dye laser can be transmitted through flexible fiberoptics and delivered through endoscopic systems or inserted directly into tumors. The major clinical use of this laser is with selective photodynamic therapy (PDT) for malignant tumors after the intravenous injection of the photosensitizer, hematoporphyrin derivative.[21]

After intravenous injection, the hematoporphyrin derivative disseminates to all of the cells of the body, rapidly moving out of normal tissue but remaining longer in neoplastic tissue. After a few days, a differential in concentration exists between the tumor cells and the normal cells. When the tumor is exposed to red light (630 nm), the dye absorbs the light, causing a photochemical reaction. Toxic oxygen radicals such as singlet oxygen are produced within the exposed cells, causing selective tissue destruction and cell death. Because healthy tissues contain less photosensitizer, a much less severe reaction or no reaction occurs. Long-term tumor control has been achieved using PDT for recurrent nasopharyngeal cancer.[22] The overall potential and the place of maximum value of this form of management remain to be established.

Table 3-1

Laser Choices for Various Lesions

Laser	Second-Choice Laser	Anatomic Site	Lesion	Reason
Argon		Ear	Lysis of middle ear adhesions	Optical fiber delivery, hemoglobin absorption
Argon pumped dye laser			Photodynamic therapy	Can tune the laser to maximum absorption of photosensitizer
CO_2		Glottis	Nodules	Microspot, precision; nonlaser better
CO_2, in-office PDL or KTP		Glottis	Polyps	Microspot, precision; nonlaser better
CO_2, in-office PDL or KTP		Glottis	Reinke's edema	Microspot, precision, microflap technique preferred
CO_2		Glottis	T1 midfold squamous cell carcinoma with no anterior commissure involvement	Excisional biopsy
CO_2	KTP	Larynx	Laryngoceles, saccular cysts	Coagulation, hands-off technique
CO_2		Larynx	Laryngomalacia	Aryepiglottic fold division, precision, coagulation
CO_2		Larynx	Stenoses (glottic, posterior, and subglottic)	Radial excision and dilation
CO_2		Lingual tonsils	Recurrent tonsillitis, hypertrophy	Minimal edema with complete vaporization
CO_2		Oral cavity	Carcinoma (verrucous, superficial T1)	Less pain and edema, covers a large area
CO_2		Oral cavity	Premalignant (leukoplakia, erythroplakia)	Vaporization, excision, can cover a large area
CO_2	KTP	Glottis	Bilateral vocal cord paralysis	Laser arytenoidectomy, coagulation
CO_2, in-office PDL or KTP		Larynx	Recurrent respiratory papilloma	Lesion excision/ablation with CO_2 vs. angiolysis with in-office lasers
CO_2	KTP	Larynx	Suprahyoid supraglottic T1 squamous cell carcinoma	Excision with frozen section control
CO_2	KTP	Oral cavity	Tongue T1 and limited T2 cancer	Less pain and edema, precision, coagulation
CO_2	KTP or Argon	Ear	Stapedotomy	Minimal trauma
CO_2	KTP or Nd:YAG	Oral cavity	Lymphangioma	Minimal edema, coagulation
CO_2	KTP or Nd:YAG	Oropharynx	T1 and T2 squamous cell carcinoma	Precision, coagulation, less edema, contact tip with Nd:YAG
CO_2	Nd:YAG	Nose	Turbinate hypertrophy	Coagulation, less scabbing and scarring
CO_2	Nd:YAG	Subglottis	Hemangioma	Defocused beam, shrinkage, coagulation
Flash lamp pumped dye laser			Port-wine stains	Selective photothermolysis
KTP		Nose	Polyps, concha bullosa	Debulking for visualization, coagulation
KTP	CO_2	Larynx	Obstructing squamous cell carcinoma	Debulking airway, staging, coagulation
KTP	CO_2	Oropharynx	Sleep apnea (uvulopalato-pharyngoplasty)	Coagulation
KTP	CO_2	Palatine tonsils	Recurrent tonsillitis, obstructive apnea	Coagulation? Less postoperative pain
KTP	Nd:YAG	Nose	Epistaxis	Fiber delivery, coagulation, hands-off technique
Nd:YAG	KTP	Nose	Hereditary hemorrhagic telangiectasias	Coagulation, hands-off technique
Nd:YAG	KTP or CO_2	Trachea	Obstructing malignant lesions	Debulking, coagulation, fiber delivery

CO_2, carbon dioxide; KTP, potassium-titanyl-phosphate; Nd:YAG, neodymium:yttrium-aluminum-garnet; PDL, pulsed dye laser.

Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) Laser

Nd:YAG lasers produce light with a wavelength of 1.064 µm in the near infrared (invisible) range of the electromagnetic spectrum. Pure water weakly absorbs the radiant energy of the Nd:YAG laser. The extinction length is about 40 mm. Therefore its radiant energy can be transmitted through clear liquids, facilitating its use in the eye or other water-filled cavities (e.g., the urinary bladder). Absorption of light from this laser is slightly color dependent, with increased absorption in darkly pigmented tissues and charred debris. In biologic tissue, strong scattering, both forward and backward, determines the effective extinction length, which is usually 2 to 4 mm. Backward scattering can account for up to 40% of the total amount of scattering. The zone of damage produced by the incident beam of a Nd:YAG laser produces a homogeneous zone of thermal coagulation and necrosis that may extend up to 4 mm deep and lateral from the surface, making precise control impossible.

The primary applications for the Nd:YAG laser in otolaryngology include ablation or palliation of obstructing tracheobronchial lesions, palliation of obstructing esophageal lesions, photocoagulation of vascular lesions of the head and neck, and photocoagulation of lymphatic malformations. The contact Nd:YAG laser is reportedly useful in the removal of malignant tumors in the oral cavity and oropharynx, where it is difficult to maintain a generous safety margin.[23] The Nd:YAG laser has several distinct advantages in the management of obstructing lesions of the tracheobronchial tree. Hemorrhage is the most frequent and dangerous complication associated with laser bronchoscopy, and its control is extremely important. Control of hemorrhage is more secure with this laser because of its deep penetration in tissue.

Nd:YAG laser application through an open, rigid bronchoscope allows for multiple distal suction capabilities simultaneous with laser application and rapid removal of tumor fragments and debris to prevent hypoxemia. Patients for Nd:YAG laser bronchoscopy should be selected after flexible fiberoptic bronchoscopic examination of the tracheobronchial tree and tracheal computed tomography. Patients in whom extrinsic compression of the airway can be shown should be excluded. The radiant energy from the Nd:YAG laser can be transmitted through flexible fiberoptic delivery systems, allowing its use with flexible endoscopes. In the management of patients with obstructing neoplasms of the tracheobronchial tree, it is considered safer to use a rigid ventilating bronchoscope rather than a flexible fiberoptic bronchoscope.[24] During this approach, the laser fiber is passed down the lumen of the rigid bronchoscope with a rod lens telescope and suction catheter. Other advantages of the use of the Nd:YAG laser with a rigid bronchoscope include ventilatory control of the compromised airway, palpation of the tumor-cartilage interface, use of the bronchoscope tip as a "cookie cutter," and use of the bronchoscope tip to compress a bleeding tumor bed for temporary hemostasis. The flexible fiberoptic bronchoscope is often used through the open rigid scope to provide pulmonary toilet and more distal laser application after the major airway is secure.

This laser is an excellent surgical instrument for tissue coagulation. Vaporization and incision also can be performed with the Nd:YAG laser. When this laser is used for these functions, however, precision is lacking and tissue damage is widespread. The major disadvantage of the Nd:YAG laser is its comparatively less predictable depth of tissue penetration. This laser is used primarily to rapidly photocoagulate tumor masses in the upper- and lower-aerodigestive tract at 40- to 50-W, using 0.5- to 1-sec exposures. Whenever possible, the laser beam is applied parallel to the wall of the tracheobronchial tree. The rigid tip of the bronchoscope is used mechanically to separate the devascularized tumor mass from the wall of the tracheobronchial tree.

Otolaryngologists may use the Nd:YAG laser with the CO_2 laser when performing bronchoscopic laser surgery. The effective coagulating properties of the Nd:YAG laser should augment the predictable vaporizing properties of the CO_2 laser when treating patients with obstructive tracheal and proximal endobronchial cancers, especially if an ulcerative or actively bleeding tumor is present.[25]

Carbon Dioxide (CO_2) Laser

CO_2 lasers produce light with a wavelength of 10.6 µm in the infrared (invisible) range of the electromagnetic spectrum. A second, built-in, coaxial helium-neon laser is necessary because its red light indicates the site where the invisible CO_2 laser beam will impact the target tissue. Thus, this laser acts as an aiming beam for the invisible CO_2 laser beam. The radiant energy produced by the CO_2 laser is strongly absorbed by pure, homogeneous water and by all biologic tissues high in water content. The extinction length of this wavelength is about 0.03 mm in water and in soft tissue. Reflection and scattering are negligible. Because absorption of the radiant energy produced by the CO_2 laser is independent of tissue color and because the thermal effects produced by this wavelength on adjacent nontarget tissues are minimal, the CO_2 laser has become extremely versatile in otolaryngology.

Until recently, light from the CO_2 laser could not be transmitted through flexible endoscopes and was limited to transmission from the optical resonating chamber to the target tissue via a series of mirrors through an articulating arm to the target tissue. In this manner, the CO_2 laser can be used free-hand for macroscopic surgery, attached to the operating microscope for microscopic surgery, and adapted to an endoscopic coupler for bronchoscopic surgery. Pattern generators coupled with a micromanipulator on the operating microscope also help with surgical precision of the CO_2 laser in laryngology. More recently, with the emphasis on in-office procedures, the CO_2 laser has been coupled with a new flexible waveguide to allow passage through the working channel of a transnasal endoscope.[26] The Omniguide (OmniGuide, Cambridge, MA) may be adapted to most CO_2 lasers, requires a continuous infusion of helium as a coolant, and has no spot beam. Localization of the beam may be identified by the mucosal disturbance created by the helium jet produced at the end of the fiber. Although application of the Omniguide in head and neck surgery has not been fully explored, use of this technology may ultimately be limited by the cost of the individual nonreusable fibers.

The CO_2 laser is an integral instrument in all aspects of otolaryngology. The numerous types of uses vary from endoscopic resection of malignant laryngeal tumors to the precision of laser stapedotomy, as well as to cosmetic skin treatment, but its most effective use is in laryngology and bronchoesophagology.

For example, surgery for recurrent respiratory papillomatosis (RRP) advanced with the use of the laser. The increased ability to preserve normal laryngeal structures while maintaining the translaryngeal airway more than offsets the initial disappointment associated with the laser's inability to cure the disease. In a published survey in 1995, the CO_2 laser was preferred for the management of RRP by 92% of the respondents.[27] However, surgical treatment of RRP has also been influenced by the introduction of microdébriders to laryngology. A survey published in 2004 indicates that many pediatric otolaryngologists prefer the powered instrumentation over laser technology in treating juvenile RRP.[28] The CO_2 laser, however, remains a popular instrument of choice by many surgeons to treat this unrelenting disease. As in all laser applications, knowledge of laser-tissue interactions will optimize safe and effective surgical outcomes. In pediatric patients, surgery for webs, subglottic stenosis, capillary hemangiomas, and other space-occupying airway lesions has been significantly improved by the precision, preservation of normal tissue, and predictably minimal amount of postoperative edema associated with the judicious use of the CO_2 laser. In adults, surgery for polyps, nodules, leukoplakia, papillomas, cysts, granulomas, and other benign laryngeal conditions can be performed with the laser. Surgeons should be cautioned, however, to be aware of the associated thermal injury that can occur to surrounding normal tissues with use of the laser even at recommended settings. A study by Garrett and Reinisch showed thermal injury beyond the laser ablation crater as much as 285 µm deep into the lamina propria of canine vocal folds.[29] Fibrosis deep into the tissue could affect the vibratory characteristics of the lamina propria.

Management of laryngotracheal stenosis is a difficult problem for the otolaryngologist. Retrospective analysis has determined that stenotic lesions appropriate for endoscopic management have two features in common[8]: (1) All lesions treated with endoscopic techniques must retain intact external cartilaginous support. (2) Lesions appropriate for endoscopic management are usually less than 1 to 2 cm in vertical length, yet favorable results have been reported for lesions up to 3 cm in length when endoscopic incision is combined with prolonged stenting.[30,31]

The addition of the CO_2 laser to endoscopic treatment of bilateral vocal fold immobility due to nerve injury or joint fixation allows the surgeon to perform laser cordotomy, medial arytenoidectomy, or total arytenoidectomy as needed. The precision associated with the CO_2 laser facilitates performance of this operation. Pattern generators are also available that create an incision of desired length, shape, and depth of penetration, aiding in the precision and efficiency of the operating microscope micromanipulator.

The transoral management of squamous cell carcinoma of the larynx using the CO_2 laser is an obvious extension of the application of this surgical instrument. The advantages of precision, increased hemostasis, and decreased intraoperative edema allow the surgeon to perform exquisitely accurate and relatively bloodless endoscopic surgery of the larynx.

Bronchoscopic indications for CO_2 laser surgery include management of recurrent respiratory papillomatosis or granulation tissue within the tracheobronchial tree, excision of selected subglottic or tracheal strictures, excision of bronchial adenomas, and reestablishment of the airway in patients with obstructing tracheal or endobronchial cancers. In the case of obstructing tracheal or endobronchial cancers, palliation or reduction of the patient's symptoms of airway obstruction or hemoptysis is the goal.

Potassium-Titanyl-Phosphate (KTP) Laser

The KTP laser emits light at 532 nm and is therefore comparable with the Ar laser. The scattering and absorption by skin pigments when using the KTP laser are nearly the same as for the Ar laser, yet the KTP laser light is more strongly absorbed by hemoglobin.

The KTP laser has uses in otologic, rhinologic, and laryngologic surgery. It can also be used for tonsillectomy and pigmented dermal lesions. In otology, it has been shown to be effective for initial stapes surgery, as well as for revision stapedectomy.[32] Thedinger has promoted the KTP laser for chronic ear surgery, specifically for removing hyperplastic infected mucosa, disarticulating mobile stapes suprastructure in a complete cholesteatoma removal, and removing previously inserted middle ear implants.[33] Handheld probes also facilitate use of the KTP laser for functional endoscopic sinus surgery and other intranasal applications and for microlaryngeal applications. The optical fiber delivery of the 532-nm laser light can be manipulated through a rigid pediatric bronchoscope as small as 3 mm, facilitating lower tracheal and endobronchial lesion treatment in infants and neonates.[34]

The KTP crystal doubles the frequency (halves the wavelength) of an Nd:YAG laser. Therefore with this laser the output between the 532-nm KTP light and the 1064-nm Nd:YAG light can usually be switched.

Most of the past and current applications of the KTP laser use a continuous-wave mode. Recently, a pulsed mode has been introduced to take advantage of thermal relaxation times of tissue, minimizing collateral thermal damage. The pulsed KTP laser is used for selective photoangiolysis of laryngeal lesions such as papilloma and dysplastic lesions.[35] It can be applied in the office setting through flexible channeled endoscopes.

585-nm Pulsed Dye Laser

The 585-nm pulsed dye laser (PDL) is used mainly as a photoangiolytic laser for laryngeal applications. The targeted chromophore for the PDL is oxyhemoglobin, which has an absorption peak of 571 nm. Consequently, the laser energy is selectively absorbed by intraluminal blood of vascular lesions such as papilloma, vascular polyps, vocal fold ectasias and varices. Numerous surgeons have found this laser useful for in-office unsedated laser laryngoscopy through a flexible channeled laryngoscope that allows passage of the thin laser fiber.[36,37] Unlike CO_2 laser ablation effects, the PDL causes involution of the lesion through disruption of the vascular supply rather than immediate removal of the lesion. Advantages of this laser include the reduced risk of collateral thermal injury compared with the CO_2 laser.

Flash Lamp Pumped Dye Laser

The management of hemangiomas and port-wine stains with lasers has benefited from the application of the flash lamp pumped dye laser. The dye was initially selected for maximum absorption by the oxyhemoglobin at 577 nm. Tan and others showed that at 585 nm, hemoglobin absorption is maximal with minimal scattering and absorption by melanin and other pigments.[38] The light pulse is about 400 µsec long to minimize thermal diffusion in the tissue. Although dark skin types show little or no selective vascular photothermolysis with the flash lamp pumped dye laser, lighter skin types show significant results. At a threshold dose, specific vascular injury is observed without disruption of the adjacent tissue in lightly pigmented skin.

Other Lasers

In an effort to have a more controlled laser effect with less damage to adjacent tissue, several lasers in the near- to mid-infrared region have been investigated, including the erbium:YAG (Er:YAG) and the holmium:YAG (Ho:YAG). The Er:YAG emits at the infrared peak of water absorption at 2.94 µm. The extinction length in water is less than 2 µm. The laser produces very clean incisions with a minimal amount of thermal damage to the adjacent tissue. The negative aspects are that (1) the wavelength is too long to be transmitted through normal optical fibers, giving a distinct advantage to lasers that produce light that can be transmitted through fibers, and (2) more important, the thermal propagation is so short there is practically no tissue coagulation and no hemostasis. The Er:YAG laser is therefore unsuitable for use in highly vascular tissue. It has been used in dental surgery for various indications. In otolaryngology, the Er:YAG laser has been used for stapes surgery and for cutaneous applications, including rhinophyma and resurfacing for wrinkles.[23,26,39]

The Ho:YAG laser operates at 2.1 µm. This wavelength can be effectively transmitted through fibers. The extinction length in water is about 0.4 µm, which suggests that this laser light should interact with tissue in a way very similar to the CO_2 laser. The Ho:YAG has been combined with fiberoptic endoscopy for sinus surgery. The hemostasis is good, and the soft bone ablation is readily controlled. Adjacent thermal damage zones varied from 130 to 220 µm in a study by Stein and others.[8] The laser is as effective in sinus surgery as conventional surgical techniques with less blood loss but increased postoperative edema.[4] The thulium:YAG laser has also been introduced as a possible alternative to the CO_2 laser because it can easily be applied through a flexible endoscope in an office setting. It has a wavelength of 2.013 µm and has water as its main target chromophore. Early clinical reports are encouraging but whether it will replace the CO_2 laser for use in laryngology is uncertain.[40]

Pulse Structure

As mentioned earlier, the surgeon has three parameters to select when using a particular laser. The intensity of the laser is the least useful. The exposure time is important in that it controls the total amount of light incident on the tissue (i.e., the radiant exposure). The pulse structure of the laser light within the given exposure time is also crucial. The pulse structure is a characteristic of the active medium and the cavity configuration. It is often fixed and cannot be changed or modified by the surgeon.

Continuous Wave Lasers

Many lasers operate in a continuous wave mode. In this mode, the laser is always on. The instantaneous intensity and the average laser intensity are essentially the same. A shutter, external to the laser cavity, usually controls the exposure time, allowing the laser to operate independently of the exposure time or the frequency of exposures. This gives the most stable operation. A surgical CO_2 or Nd:YAG laser operates in continuous wave mode at intensities of a few watts to more than 50 W.

Flash Lamp Pulsed Lasers

Certain lasers operate in a pulsed mode. Flash lamp pumped lasers can pulse from about 0.5 msec to several 100 msec. The first ruby laser operated in a pulsed mode. The flash lamp used to pump the ruby crystal had a duration of about 1 msec. The laser output of this first ruby laser clearly was irregular and unstable. When observed with a fast detector and oscilloscope, the output intensity was found not to be a 1-msec long laser pulse but rather a series of irregular spikes. Each spike

is a few microseconds long with several microseconds between the spikes. The stimulated emission in the ruby is so efficient that it quickly depletes the population inversion and the operation stops, after which the flash lamp can reestablish the population inversion and operation can resume. This process repeats until the flash lamp stops. Most of the long-pulsed lasers operate in a spiking mode.

Q-Switched Laser

The spiking of the laser output can be controlled to produce a single very short laser pulse, much shorter than the flash lamp lifetime. One technique to produce the short pulses is Q-switching, in which the laser pumping process (usually a flash lamp) builds up a large population inversion inside the laser cavity. Blocking or removing one of the mirrors prevents the laser from emitting. After a large population inversion has developed, the feedback is restored and a short intense burst of laser light depletes the accumulated population inversion, typically in 10 to 50 nsec. Q-switching can be accomplished by several different methods. The most direct and earliest method is rotating the end mirror so that the light amplification by stimulated emission can occur during the short interval when the mirror is correctly aligned. Waring blender motors were often used as fast, stable motors. However, uncertain timing, lack of reliability, and vibration (and noise) led to many problems, particularly with the alignment. Electro-optic polarization rotators and acousto-optic beam deflectors are now commonly used for Q-switching.

Cavity Dumped Lasers

Cavity dumping produces slightly shorter pulses of light. In this technique, the laser is pumped and allowed to operate between completely reflecting mirrors. The light energy is trapped in the cavity until it reaches a maximum. Then one of the mirrors is "removed" from the cavity and allows all the light to leave the cavity. The laser pulse has a physical length of twice the cavity length. Thus the duration of the laser pulse is $2\lambda/c$, where λ is the length of cavity and c is the speed of light (c is about 3×10^{10} cm/sec or 1 foot/nsec).

Mode-Locked Lasers

Mode locking produces pulses of light as short as a few picoseconds. A Q-switched laser operates in several longitudinal modes (or slightly shifted frequencies). A fast saturable dye brings all these modes into phase. The nanosecond macropulse of light is actually a train of micropulses, each of which is several picoseconds long and repeats at about 100 MHz. These pulses can be further compressed by various techniques. The shortest laser light pulses achieved in the laboratory are less than 4 wave oscillations long (about 6 fsec or 6×10^{-15} sec).

The pulsed laser dramatically changes the interaction of the light with tissue. The intensity of the laser during the pulse is extremely high (approaching 10^9 W). The high intensity and short pulse duration enable the laser light efficiently to ablate tissue before the thermal energy spreads by thermal diffusion. The pulse should be significantly shorter than the thermal diffusion time to prevent thermal diffusion from spreading damage. Typically, a tissue under laser irradiation reaches thermal equilibrium within a few milliseconds. The heat spreads over several micrometers in less than 10 μsec. Also, the transverse mode structure of the laser beam must be preserved in the short pulses to yield the small focal spot size.

Safety Considerations

Education

The laser is a precise but potentially dangerous surgical instrument that must be used with caution. Although distinct advantages are associated with the use of laser surgery in the management of certain benign and malignant diseases of the upper aerodigestive tract, these advantages must be weighed against the risks of complications. Because of these risks, the surgeon must first determine if the laser offers an advantage over conventional surgical techniques. For the surgeon to use good judgment in the selection and use of lasers in practice, prior experience in laser surgery is necessary. Therefore some type of formal laser education program should be a prerequisite to using this technology. Most hospitals now require evidence of participation in a laser use and safety course before granting laser privileges. The surgeon who has not received training in laser surgery as a resident should attend a hands-on training course in laser surgery. Such a course should include laser biophysics, tissue interactions, safety precautions, and supervised hands-on training with laboratory animals. After completing such a course, the surgeon should practice laser surgery on cadaver or animal specimens before progressing to the more simple procedures on patients.

Hospitals that offer laser surgery should appoint a laser safety officer and set up a laser safety committee consisting of the laser safety officer, physicians using the laser, anesthesiologists, operating room nurses, a hospital administrator, and a biomedical engineer. The purpose of this committee is to develop policies and procedures for the safe use of lasers within the hospital. The safety protocols established by this committee will vary with each specialty and use of the laser. In addition, the laser safety committee should (1) make recommendations regarding the appropriate credential-certifying mechanisms required for physicians and nurses to become involved with each laser; (2) develop educational policies for surgeons, anesthesiologists, and nurses working with the laser; (3) accumulate laser patient data in cases where an investigational device was used; and (4) conduct a periodic review of all laser-related complications.

Aside from a few minor eye injuries from a laser beam exposure, most serious accidental injuries related to laser use can be traced to the ignition of surgical drapes and airway tubes.[41] Because the anesthesiologist is also concerned with the airway and because potent oxidizing gases pass through the airway in close approximation to the path of the laser beam, it is necessary to develop a team approach to the anesthetic management of the patient undergoing laser surgery of the upper aerodigestive tract. It is recommended that anesthesiologists involved with laser surgery cases attend a didactic session devoted to this subject. Finally, the operating room staff must be educated with regard to laser surgery. Attendance at an inservice workshop with exposure to clinical laser biophysics and the basic workings of the laser, as well as hands-on orientation, should be the minimal requirement for nurses to participate in laser surgery.

Safety Protocol

Development of an effective laser safety protocol that stresses compliance and meticulous attention to detail by the operating room personnel (laser surgery team) is probably the most important reason this potentially dangerous surgical instrument can be used safely in treating patients with diseases of the upper aerodigestive tract.[7] Such a laser safety protocol is usually general enough to list all the major and most minor precautions necessary when laser surgery is being performed within the specialty of otolaryngology. General considerations concern provisions for protection of the eyes and skin of patients and operating room personnel and for adequate laser plume (smoke) evacuation from the operative field. Additional precautions concern the choice of anesthetic technique, the choice and protection of endotracheal tubes, and the selection of proper instruments, including bronchoscopes.

Eye Protection

Several structures of the eye are at risk. The area of injury usually depends on which structure absorbs the most radiant energy per volume of tissue. Depending on the wavelength, corneal or retinal burns, or both, are possible from acute exposure to the laser beam. The possibility for corneal or lenticular opacities (cataracts) or retinal injury exists after chronic exposure to excessive levels of laser radiation. Retinal effects occur when the laser emission wavelength occurs in the visible and near-infrared range of the electromagnetic spectrum (0.4 to 1.4 μm). When viewed directly or secondary to the reflection from a specular (mirror-like) instrument surface, laser radiation within this wavelength range would be focused to an extremely small spot on the retina, causing serious injury. This occurs because of the focusing effects of the cornea and lens. Laser radiation in the ultraviolet (<0.4 μm) or in the infrared (>1.4 μm) range of the spectrum produces effects primarily at the cornea, although certain wavelengths also may reach the lens.[42]

To reduce the risk of ocular damage during cases involving the laser, certain precautions should be followed. Protecting the eyes of the patient, surgeon, and other operating room personnel must be addressed. The actual protective device will vary according to the wavelength of the laser used. A sign should be placed outside the operating room door warning all persons entering the room to wear protective glasses because the laser is in use. In addition, extra glasses for the specific wavelength in use should be placed on a table immediately outside the room. The doors to the operating room should remain closed during laser use.

Patients undergoing CO_2 laser surgery of the upper aerodigestive tract should have a double layer of saline-moistened eye pads placed over the eyes (Fig. 3-12). All operating room personnel should wear protective eyeglasses with side protectors. Regular eyeglasses or contact lenses protect only the areas covered by the lens and do not provide protection from possible entry of the laser beam from the side. When working with the operating microscope and the CO_2 laser, the surgeon need not wear protective glasses. The optics of the microscope provide the necessary protection (Fig. 3-13). When working with the Nd:YAG laser, all operating room personnel (and the patient) must wear wavelength-specific protective eyeglasses that are usually blue-green. Although the beam direction and point of impact may appear to be confined within the endoscope, inadvertent deflection of the beam may occur because of a faulty contact, a break in the fiber, or accidental disconnection between the fiber and endoscope. Special wavelength-specific filters are available for flexible and rigid bronchoscopes. When these filters are in place, the surgeon need not wear protective eyeglasses.[43]

When working with the Ar, KTP, or dye laser, all personnel in the operating room, including the patient, should again wear wavelength-specific protective eyeglasses that are usually tinted (Fig. 3-14). When undergoing photocoagulation for selected cutaneous vascular lesions of the face, the patient usually wears protective metal eye shields rather than protective eyeglasses. Similar precautions are necessary for the visible and near-infrared wavelength lasers. The major difference is the type of eye protection that is worn.

Skin Protection

The patient's exposed skin and mucous membranes outside the surgical field should be protected by a double layer of saline-saturated surgical towels, surgical sponges, or lap pads. When microlaryngeal laser surgery is being performed, the beam might partially reflect off the proximal rim of the laryngoscope rather than go down it. Thus saline-saturated surgical towels completely drape the patient's face. Only the proximal lumen of the laryngoscope is exposed. Great care must be exercised to keep the wet draping from drying out. It should occasionally be moistened during the procedure. Teeth in the operative field also need to be protected. Saline-saturated Telfa, surgical sponges, or specially constructed metal dental impression trays can be used. Meticulous attention is paid to the protective draping procedures at the beginning of the surgery. The same attention should be paid to the continued protection of the skin and teeth during the surgical procedure.[44]

Smoke Evacuation

Two separate suction setups should be available for all laser cases in the upper aerodigestive tract. One provides for adequate smoke and steam evacuation from the operative field; whereas the second is connected to the surgical suction tip for the aspiration of blood and mucus from the operative wound. When performing laser surgery with a closed anesthetic system, the surgeon should use constant suctioning to remove laser-induced smoke from the operating room. This helps prevent inhalation by the patient, surgeon, and operating room personnel. When the anesthetic system is open or has jet ventilation systems, suctioning should be intermittent to maintain the forced inspiratory oxygen at a safe level. Laryngoscopes, bronchoscopes, operating platforms, mirrors, and anterior commissure and ventricle retractors with built-in smoke-evacuating channels facilitate the evacuation of smoke from the operative field. One report suggested that the smoke created by the interaction of the CO_2 laser with tissue may be mutagenic.[45] Filters in the suction lines should be used to prevent clogging by the black carbonaceous smoke debris created by the laser. Although papillomavirus and other viral particles have been detected in the laser plume, no cases of clinical transmission of diseases are documented.[46,47]

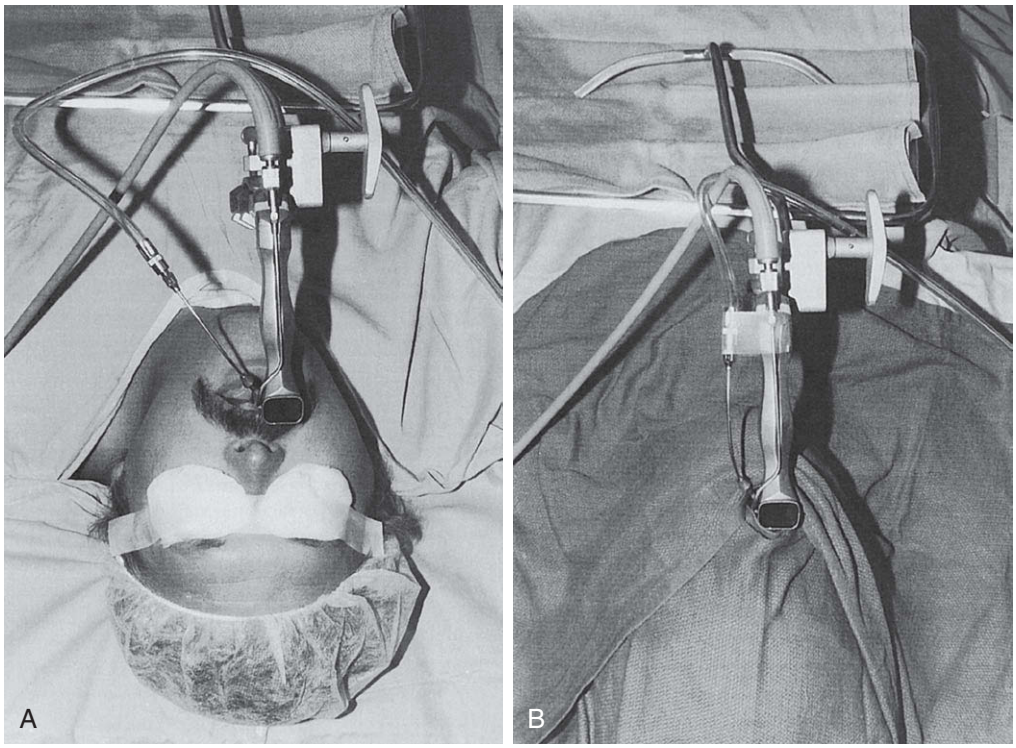

Figure 3-12. Patient undergoing carbon dioxide laser microlaryngoscopy with jet ventilation. **A,** Saline-moistened eye pads are secured with silk tape. The eyes are first taped closed with silk tape to prevent corneal abrasions from the eye pads. **B,** Saline-moistened towels are placed around the patient's head to cover all skin surfaces.

Figure 3-13. Protective eyewear is worn by the assistant surgeon during carbon dioxide laser microlaryngoscopy. The surgeon's eyes are protected by the optics of the operating microscope.

Anesthetic Considerations and Risk of Intraoperative Fire

Optimal anesthetic management of the patient undergoing laser surgery of the upper aerodigestive tract must include attention to the safety of the patient, the requirements of the surgeon, and the hazards of the equipment. Most patients undergoing upper airway laser endoscopy require general anesthesia. Any nonflammable general anesthetic is suitable. Halothane and enflurane are most often used. Because of the risk of fire associated with general endotracheal anesthesia, the inspired concentration of oxygen, a potent oxidizing gas, is critical and both surgeon and anesthesiologist must be aware of the risk involved. Mixtures of helium, nitrogen, or air plus oxygen are commonly used to maintain the forced inspiratory oxygen less than 40% and to ensure that the patient is adequately oxygenated. Nitrous oxide is also a potent oxidizing gas and should not be used in the anesthetic mixture to cut the oxygen concentration. The lowest concentration of oxygen should be used to maintain adequate oxygen saturations for the patient, and continuous dialogue between the surgeon and anesthesiologist is necessary. This is also true when performing laser surgery in the tracheobronchial tree through the rigid, ventilating bronchoscope. Although there is no flammable material in the airway, flash ignition of 100% oxygen may occur. Jet ventilation techniques during laser surgery are effective for selected patients, such as those with subglottic stenosis. Successful use of this ventilation technique requires that the anesthesiologist be experienced in this practice.

One of the most devastating complications of laser surgery of the aerodigestive tract is endotracheal tube ignition and resulting injury to the laryngotracheal mucosa. At present, a nonflammable, universally accepted endotracheal tube for all types of laser surgery of the upper aerodigestive tract does not exist. The traditional polyvinyl endotracheal tube should not be used, either wrapped or unwrapped. It offers the least resistance to penetration by the laser beam of all the endotracheal tubes that have been tested. Its fire-breakdown products are toxic, and tissue destruction associated with combustion of this tube is the most severe when compared with other tubes. Endotracheal tubes for laser surgery that are wavelength specific are now available from several manufacturers and should be used at all times unless jet ventilation techniques are used.

Protection of the endotracheal tube from direct or reflected laser beam irradiation is of primary importance. If the laser beam strikes an

Figure 3-14. Patient undergoing pulsed dye laser treatment for papillomas in the office. Both the patient and surgeon are wearing wavelength-specific protective eyewear. The laser fiber can be seen protruding from the end of the working channel on the video monitor.

unprotected endotracheal tube carrying oxygen, ignition of the tube could result in a catastrophic, intraluminal, blowtorch-type endotracheal tube fire. Protection should also be provided for the cuff of the endotracheal tube, even while using laser-specific tubes. Methylene blue–colored saline should be used to inflate the cuff. Saline-saturated cottonoids are then placed above the cuff in the subglottic larynx to further protect the cuff. These cottonoids require frequent moistening during the procedure. If the cuff deflates from an errant hit by the laser beam, the already saturated cottonoids turn blue to warn the surgeon of impending danger. The tube should then be removed and replaced with a new one. Use of the microlaryngeal operating platform offers further protection against potential danger. Inserted into the subglottic larynx above the level of the packed cottonoids, this unique instrument serves as a backstop to protect the cottonoids, endotracheal tube, and cuff from any direct or reflected laser beam irradiation. A 60-mL bulb syringe and basin of saline should be immediately available to the surgeon. In the event of tube ignition, ventilation must be stopped immediately and the tube withdrawn simultaneously as saline is flushed down the endotracheal tube. The airway must be reestablished immediately and bronchoscopy performed to assess the degree of injury. Intravenous steroids may be delivered and the patient should remain intubated; repeat bronchoscopy should be performed daily until it is established that the airway is stable.

Effectiveness of a Safety Protocol

Strong and Jako[48] and later Snow and others[49] warned of the possible complications associated with laser surgery of the upper aerodigestive tract, including the risks of endotracheal tube fires and tissue damage from reflection of the laser beam. In a survey of laser-related complications by Fried,[10] 49 of 152 otolaryngologists who used the laser reported 81 complications, including 28 incidents of endotracheal tube fires. Healy and others[50] reported a 0.2% complication rate in 4416 cases of CO_2 laser surgery in the upper aerodigestive tract. Ossoff[44] published an extensive view of laser-related complications experienced by 218 past registrants of hands-on laser surgery training courses that he directed. Seven surgeons experienced 8 complications and no endotracheal tube fires. The complication rate was 0.1% in more than 7200 laser surgical procedures. These papers have similar conclusions: (1) certain precautions are necessary when performing laser surgery of the upper aerodigestive tract, and (2) adherence to a rigid safety protocol allows laser surgery of the airway to be performed safely and with an extremely small risk of serious complications.

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CHAPTER FOUR A

Surgical Robotics in Otolaryngology

David J. Terris

Key Points

- Surgical robotics have evolved from rudimentary scope holders to sophisticated and precise telerobotic systems with "wristed" technology and true three-dimensional visualization.
- Experimental robotic surgery investigation has centered on neck and thyroid, skull base, and oropharyngeal applications.
- Clinical robotic applications have so far been restricted to thyroid and oropharyngeal procedures.
- There is a burden with robotic surgery to balance increased time, expense, and technologic challenges with improvements in outcomes or other definable advantages.
- Despite a number of hurdles, it seems likely that the future will bring more indications for robotic assistance, rather than fewer.

History of Robotics

The origins of robotics may be traced to early in the twentieth century, when the Czechoslovakian Capek brothers introduced the concept of automated devices. Joseph Capek wrote the short story "Opilec" in which automats were described, and Karel Capek wrote "Rossum's Universal Robots." This introduction of the term *robot* (deriving from the Czech word *robota*, which means serf or laborer) was part of a fictional depiction of the increasing sophistication of robots, which eventually rose up against their human inventors.[1]

The next seminal spark of the collective imagination of scientists and society alike occurred with Isaac Asimov's collection of short stories in the 1940s.[2] He developed the three laws relating to robot behavior, which were recently popularized in Will Smith's "I, Robot":

1. A robot may not injure a human being or through inaction allow a human to come to harm.

2. A robot must obey orders given it by humans except when doing so conflicts with the first law.

3. A robot must protect its own existence as long as this does not conflict with the first or second law.

Other Hollywood productions stimulating public interest in robotics included the "Star Wars" series, the "Terminator" trilogy, and "Bicentennial Man," starring Robin Williams.

Simultaneous with sensational depictions of the potential for common robotic applications, gradual and stepwise breakthroughs in electronics and computers paved the way for the development and production of the first meaningful robot in 1958, dubbed "the Unimate" by General Motors. Its use in assembly lines to facilitate automobile production in 1961 was the first in what eventually became widespread application of automation in the automobile industry. Honda has been particularly innovative in its development of robotic humanoids, culminating in the ASIMO, which not only can walk but also can negotiate stairs (Fig. 4A-1).

A growing number of other applications for robotics have quickly emerged, including military uses and purposes as far-reaching as exploration of deep sea and space and as mundane as lawn care and use of home appliances. These robots can be characterized in a variety of ways: automated arms, mobile devices, mills, or telerobotic devices. With the advent of these many and varied robots, specific nomenclature has evolved to classify their actions and mechanisms.

Definitions

As the presence of robotics in the operating room becomes more pervasive, a basic knowledge of the language of robotics is desirable. The following terms represent the essential foundation of robotic lexicography[3]:

Robotic surgery—implies the use of a powered device that functions under programmable computerized control and may be used to manipulate instruments and perform surgical tasks.

Active robotics—refers to a robot that is programmed to independently perform a complete task without operator control.

Semiactive robotics—requires the input of an operator to perform defined, powered tasks.

Passive robotics—functions only at the direction of the operator, without independently powered movements (sometimes referred to as a *telemanipulator*).

Telerobotic surgery—refers to a system in which the operator controls a robot from a console containing a virtual three-dimensional visualization framework and from which robotically controlled manipulations are reproduced.

Telepresence—extension of telerobotic surgery to a remote site so that the console from which the operator issues commands is located at a distance from the robot; the robotic surgeon may therefore never have contact with the patient.

Telementoring—when coupling an experienced surgeon with a trainee at a remote location, telepresence provides the technologic framework for distance training or so-called *telementoring*.

History of Medical Robotics

While the earliest applications of robotics were in the automobile industry, the Department of Defense recognized the potential value of remotely controlled robotics, both for the military options they afforded and for the possibility of providing care to wounded soldiers on the battlefield with the surgeon safely out of harm's way. This concept of so-called virtual insertion of the surgeon into the battlefield was championed and funded by the Pentagon's Defense Advanced Research Projects Agency (DARPA). Similarly, the National Aeronautics and Space Administration (NASA) teamed up with the Ames Research Center (Mountain View, CA) and the Stanford Research Institute (Palo Alto, CA) to develop both a head-mounted virtual reality display (Fig. 4A-2A) and a data-glove (see Fig. 4A-2B), by which the user could cause and witness his own interactions within a virtual environment.

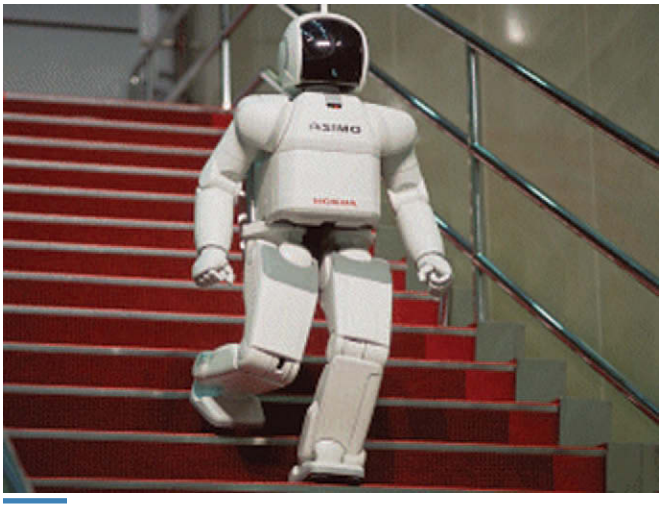

Figure 4A-1. The ASIMO from Honda is a humanoid robot that is capable not only of walking, but of negotiating stairs.

Less sophisticated technology was used to accomplish the first robot-assisted surgical procedure in 1985, a stereotactic brain biopsy.[1] In 1992, the Robodoc (a computer-guided mill used to core the femoral head) was introduced in Europe for use in hip replacement surgery, and later the Acrobot was developed for knee replacement and temporal bone surgery. These have yet to receive U.S. Food and Drug Administration approval for use in the United States, largely because of concerns regarding complication rates.

The growing interest in surgical robotic applications, along with ample funding, spawned a number of market leaders in medical robotics, including the companies Computer Motion, Inc., and Intuitive Surgical, Inc. Computer Motion developed the automated endoscopic system for optimal positioning (AESOP) system (Fig. 4A-3), which was combined with Hermes voice-activation movement technology, and has seen limited adoption in laparoscopic surgical procedures. Computer Motion was also responsible for creating the Zeus telerobotic system (Fig. 4A-4).

Computer Motion was eventually acquired by Intuitive Surgical, the Zeus was retired, and the daVinci system has become the industry standard for surgical robotics. The current leading applications include prostate surgery,[4] cardiothoracic surgery,[5] and advanced gynecologic surgery.[6] More than 50% of radical prostatectomies, for example, are performed using the daVinci system.

The first trans-Atlantic telerobotic surgery received relatively little attention because of the temporal relationship to the 9/11/01 terrorist attacks on the United States. On September 7, 2001, Jacques Marescaux was seated in New York City while he performed a laparoscopic cholecystectomy on a patient who was 3800 miles away in Strasbourg, France. Dubbed the Lindbergh Operation (in tribute to Charles Lindbergh, who was the first to accomplish a trans-Atlantic solo flight), the procedure was a collaboration between Marescaux and Michel Gagner of Mount Sinai Hospital in New York. High-speed fiberoptic connections provided by French Telecom were necessary to minimize the time-lag between surgeon commands and robotic movements, and the response-delay achieved was 155 msec. Even though sensational events like these prompt high expectations, the implementation of robotics into fields such as otolaryngology–head and neck surgery has been a much more gradual and deliberate process.

Robotic Applications in Otolaryngology

A role for this technology in otolaryngology is beginning to emerge, particularly where precision is required or visualization is limited, and there are a number of pioneering contributions. The first otolaryngo-

Figure 4A-2. The combination of a virtual reality headset **(A)** and a data-glove **(B)** allow the user to interact with his virtual environment while witnessing the activity.

logic application of robotics occurred as early as 2002 with several reports from the Terris group at the Medical College of Georgia exploring endoscopic neck procedures.[7-10] The first human application was described by McLeod and Melder[11] with a case report of excision of a vallecular cyst. Hockstein and colleagues further pursued oral and oropharyngeal applications of robotic technology with a stepwise experimental approach.[12,13] Finally, interest in robotic skull base surgery has emerged with the work of Hanna and colleagues.[14]

Experimental Origins

The first use of robotics for otolaryngologic applications was explored in a porcine model of neck surgery that included parotidectomy, submandibular gland resection, and selective neck dissection.[8] This work built on previous promising findings for totally endoscopic neck surgery (also described by Terris and collaborators[15,16]) and provided proof of principle, in that the safety and efficacy of endorobotic neck surgery was demonstrated, and quickly established that advantages in duration of surgery could be easily achieved with the addition of robotic technology.

Figure 4A-3. The AESOP (automated endoscopic system for optimal positioning) combines robotics with voice activation to accomplish precise camera positioning during endoscopic surgery.

The first investigative protocol[8] was represented by a prospective nonrandomized investigation in a porcine model in which four different types of neck surgery were accomplished using the daVinci surgical system (Intuitive Surgical Inc., Sunnyvale, CA) (Fig. 4A-5). This system employs robotics to enable microsurgery in an endoscopic environment. It consists of a surgeon's console with two control handles and a virtual three-dimensional vision projection system, and a patient side cart with three or four robotic arms, three of which manipulate operative instruments and a fourth that controls a video endoscope. The video system contains twin-mounted endoscopes, with projection of one image to one eye of the console and the other image to the other eye (Fig. 4A-6). This therefore produces true three-dimensional images at the tip of the scope. The robotic arms permit utilization of a full range of articulated instruments (Fig. 4A-7) that are used for clamping, cutting, suturing, and tissue manipulation, including electrocautery, forceps, clip appliers, and scissors. These instruments are equipped with EndoWrist technology, which provides up to 7 degrees of freedom (unlike the 4 degrees associated with conventional endoscopic instrumentation), allowing the surgeon's endoscopic movements to closely mimic those of the human wrist. The daVinci tracks the surgeon's hand movements 1300 times each second and relays the data to the instrument tips, reproducing the surgical maneuvers. While the primary surgeon controls the robotic instruments and the camera, an assistant changes and adjusts the instruments.

The procedures performed in this original investigation included one thymectomy, one partial parotidectomy, three submandibular gland resections, and three neck dissections (Fig. 4A-8). There were no complications, and no conversions to open surgery were necessary. Because of the substantial preparation required to ready the robotic system for use, careful documentation of the time that transpired during the establishment of the operative pocket and the time needed to assemble and position the robotic arms was undertaken. Despite a total setup time exceeding 30 minutes, there was still a savings in overall operative duration when comparing robotic submandibular gland resection and neck dissection to historical controls (conventional endoscopic procedures) (Fig. 4A-9).

The natural next model for systematic exploration of feasibility of robotic neck surgery was the fresh cadaver. Terris and colleagues

Figure 4A-4. The Zeus telerobotic system consists of a patient-side cart **(A)** and a console **(B)**. It was the precursor to the daVinci surgical system, which also consists of a console and a patient-side cart. It has been retired, leaving the daVinci as the only commercially available surgical robot in the United States.

Figure 4A-5. With the daVinci surgical system, the surgeon manipulates the robotic instruments of the master console, which is located within several feet of the operating table. *(Reprinted with permission from Haus BM, Kambham N, Le D, et al. Surgical robotic applications in otolaryngology.* Laryngoscope. *2003;113[7]:1139-1144.)*

described a series of 11 endorobotic submandibular gland resections that were accomplished in six fresh cadavers.[9] The port placement was similar to that which had been previously described.[17] A 14-mm incision was created approximately 9 cm lateral to the sternal notch over the clavicular head of the sternocleidomastoid muscle for the camera port, and two 10-mm incisions were created approximately 4 cm to each side of the camera port for 8-mm instrument trocars (Fig. 4A-10). The submandibular gland was accessed by approaching inferiorly in the subplatysmal plane. The facial artery and vein and submandibular duct were ligated using the robotic clip appliers. After the submandibular gland was completely mobilized, the robotic camera was repositioned into one of the 8-mm ports and the specimen was retrieved through the 14-mm trocar incision.

Because prior conventional endoscopic procedures had been accomplished by the same investigators,[17] a noncontemporaneous comparison of outcomes to historical controls was possible and showed a significant reduction in median surgical times, from 65.5 minutes to 48 minutes.

Stimulated by the promising findings in these seminal studies, Hockstein and colleagues likewise embarked on a series of experiments, first in an inanimate model (mannequin[12]) and then in cadaver studies[13] to evaluate the feasibility and potential benefit of robot-assisted oropharyngeal surgery.

In their first publication in 2005, Hockstein and colleagues used a mannequin with the same daVinci device to define the optimal configuration for exposing the oropharynx (McIvor mouthgag combined with the 30-degree three-dimensional endoscope) and relationship of the robot to the operating table and patient (Fig. 4A-11).

In a subsequent study, the same group accomplished several procedures on a single cadaver using a Dingman mouthgag for exposure. These included vocal cord strippings and arytenoidectomies (Fig. 4A-12). These exploratory investigations provided the foundation for subsequent clinical protocols.

Clinical Applications

With McLeod and Melder's[11] report on a patient with a robotically assisted vallecular cyst marsupialization in 2005, and then with the subsequent report by Lobe and colleagues[18] of a successful robotic axillary thyroidectomy later that year, the first human applications of robotic surgery in otolaryngology were realized. A number of other applications of this technology have quickly followed, and with increasing versatility of the robot combined with miniaturization, expansion

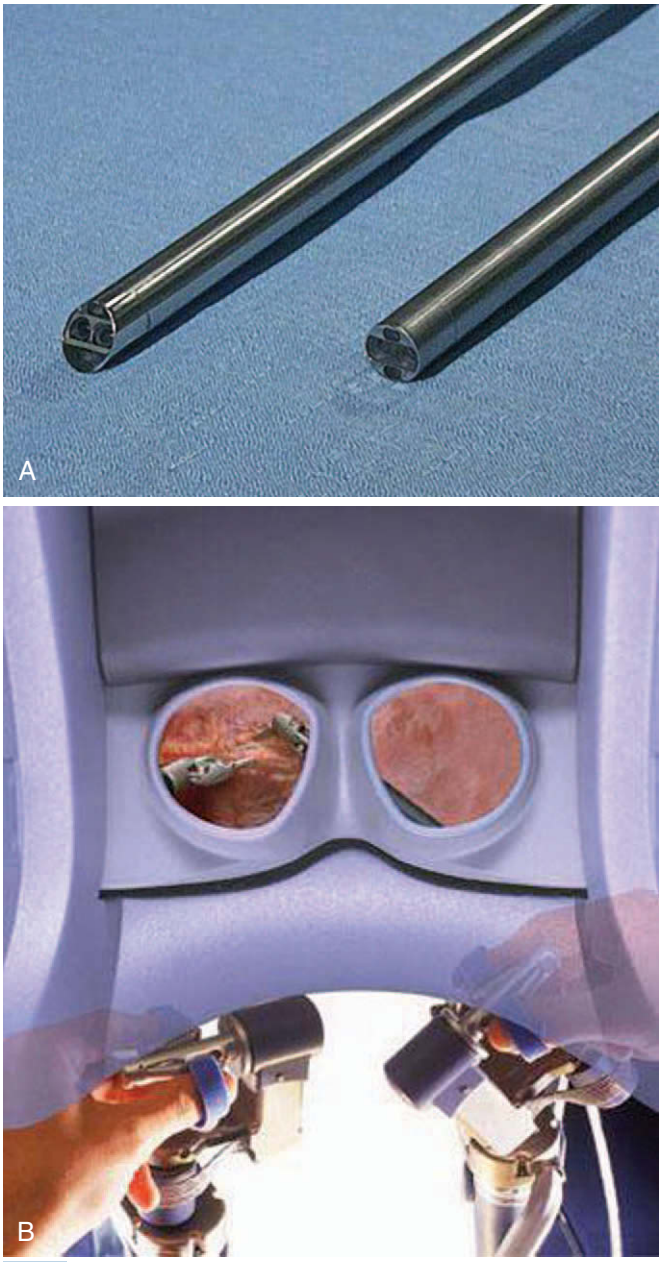

Figure 4A-6. The image obtained with the daVinci system is truly three-dimensional, in that one image of the twin-mounted endoscopes (either 30 degree or 0 degree, depicted in **A**) is projected to one eye on the console, and the other image is projected to the other eye (as seen through the console in **B**).

of the indications for its use seems likely. The only commercially available surgical robot remains the daVinci (Intuitive Surgical, Inc.). A number of challenges are posed by this technology and need to be overcome to justify its use in surgical procedures.[19]

The value-added for thyroidectomy is represented by the ability to work past the clavicle when approaching the thyroid compartment from the axilla. For oropharyngeal surgery, the possibility of working "around corners" provides improved access, particularly to the tongue base. For skull base surgery, the three-dimensional visualization combined with precise manipulation comprise the benefits worthy of additional study.

Robotic Thyroidectomy

A number of Japanese investigators described an axillary approach to the thyroid compartment[20,21] that was coincident with the development

of a central endoscopic-assisted approach.[22,23] The central approach has seen widespread adoption,[24,25] while the axillary technique has remained largely an Asian exercise in patience (3 to 4 hours are required to accomplish a simple lobectomy, and more than 6 hours are needed for a total thyroidectomy). Experimental work done by Terris[26] and Faust[27] spawned the concept of merging the robotic technology with a totally endoscopic thyroid procedure, thereby facilitating access that is necessarily cumbersome because the clavicle impedes direct access to the thyroid compartment. This culminated in the description of an axillary thyroidectomy in a patient in 2005.[18] Even though an improvement in surgical times has not yet been realized (this simple lobectomy lasted 4.5 hours), there were no untoward outcomes and further study seems warranted.

Robotic Skull Base Surgery

Because of the limited exposure and plentiful critical structures demanding skill and precision, there has been intense interest in accomplishing robotic surgery at the skull base. Much of the groundwork was established by Hanna and colleagues in a study of four human cadavers, including bilateral transantral access (Fig. 4A-13) and positioning of the robotic arms, and determination of the advantages related to suturing and reconstruction (Fig. 4A-14).

O'Malley and colleagues[28] took this approach into the human under an IRB-approved protocol in which an infratemporal fossa cyst was removed from a patient. The skull base probably represents the least studied but most fertile surgical site for robotic technology in the head and neck.

Robotic Oropharyngeal Surgery

In an extension of the experimental work done by Hockstein, the surgical robot was eventually paired with the endoscopic oropharyngeal approach pioneered by Steiner[29] and popularized by Grant and others.[30]

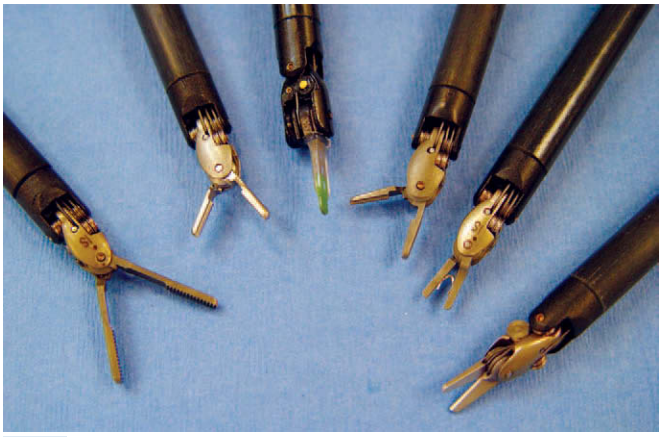

Figure 4A-7. The 8-mm operative ports are used for a variety of robotic instruments designed for clamping, cutting, suturing, and tissue manipulation, including an electrocautery device, forceps, clip appliers, and scissors. *(Reprinted with permission from Haus BM, Kambham N, Le D, et al. Surgical robotic applications in otolaryngology.* Laryngoscope. *2003;113[7]:1139-1144.)*

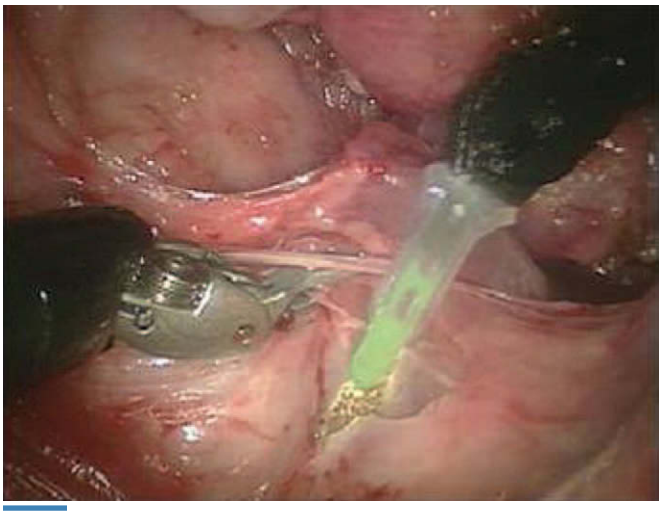

Figure 4A-8. This is a two-dimensional representation of the three-dimensional view of the submandibular gland, which also reflects the multiply articulating EndoWrist device. *(Reprinted with permission from Terris DJ, Haus B. Endoscopic and robotic surgery in the neck: experimental and clinical applications.* Op Tech Otolaryngol Head Neck Surg. *2002;13[3]231-238.)*

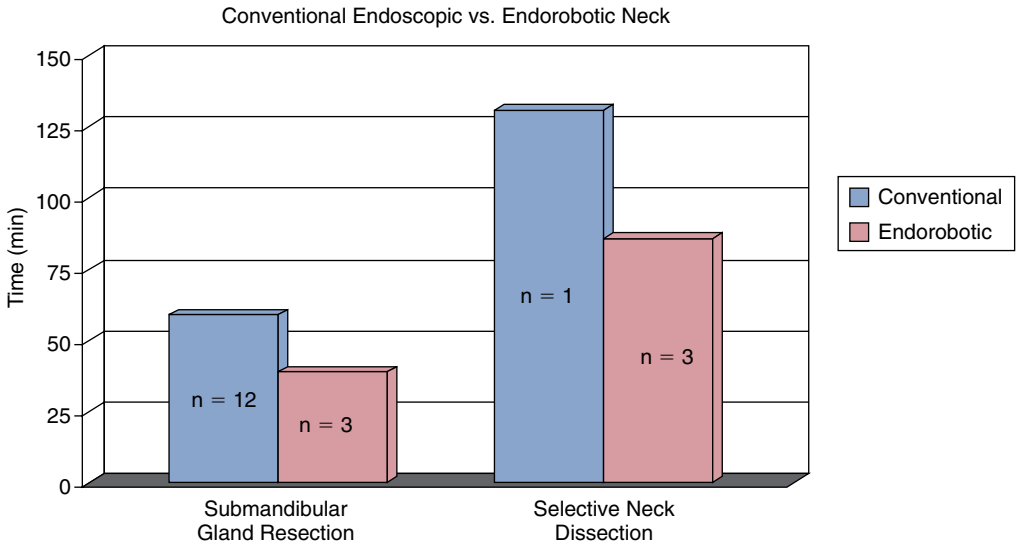

Figure 4A-9. Procedural times for submandibular gland resection and selective neck dissection. The conventional endoscopic surgery times (left column) from prior publications are compared with those from the endorobotic technique (right column). The operative times required for robotic resection were 66.1% and 69.4% of those required for conventional endoscopic submandibular resection and selective neck dissection, respectively. *(Reprinted with permission from Haus BM, Kambham N, Le D, Moll FM, Gourin C, Terris DJ. Surgical robotic applications in otolaryngology.* Laryngoscope. *2003;113[7]:1139-1144.)*

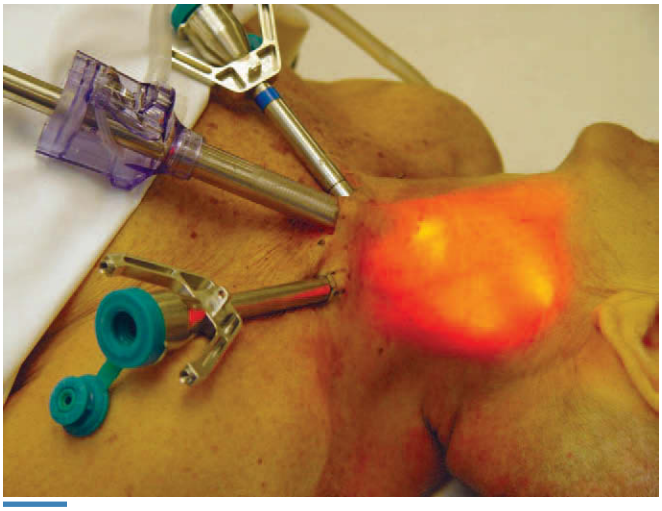

Figure 4A-10. External view of the ideal placement of all three trocars for robotic neck surgery. The central trocar is placed over the clavicular head of the sternocleidomastoid muscle. Two 10-mm incisions are created approximately 4 cm to either side of the camera port and two 8-mm trocars are inserted under direct visualization. *(Reprinted with permission from Terris DJ, Haus BM, Gourin CG, Lilagan PE. Endo-robotic resection of the submandibular gland in a cadaver model.* Head Neck. *2005;27[11]:946-951.)*

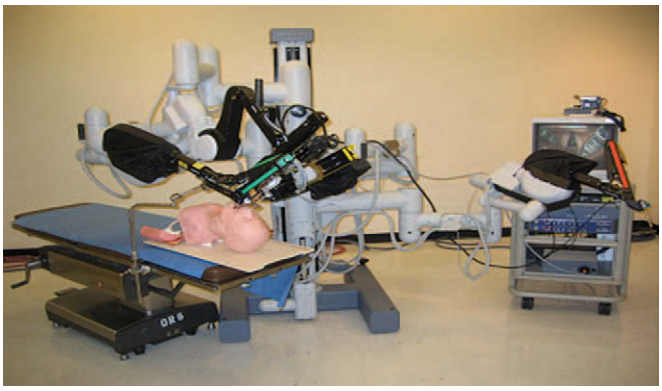

Figure 4A-11. Operating room orientation for robotic-assisted oropharyngeal surgery. The operating table is rotated 30 degrees relative to the base of the robot, allowing for introduction of three robotic arms in an airway mannequin, which is suspended with a McIvor mouthgag. *(Reprinted with permission from Hockstein NG, Nolan JP, O'Malley BW Jr, Woo YJ. Robotic microlaryngeal surgery: a technical feasibility study using the daVinci surgical robot and an airway mannequin.* Laryngoscope. *2005;115[5]:780-785.)*

Figure 4A-12. Photographic representation of the right vocal fold just before resection in a cadaver model. *(Reprinted with permission from Hockstein NG, Nolan JP, O'Malley BW Jr, Woo YJ. Robot-assisted pharyngeal and laryngeal microsurgery: results of robotic cadaver dissections.* Laryngoscope. *2005;115[6]:1003-1008.)*

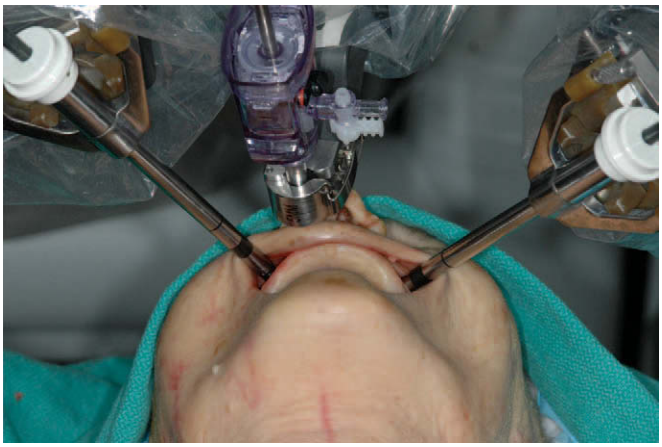

Figure 4A-13. The robotic port placement is depicted. The camera port is placed into the right nasal cavity, and the right and left surgical arm ports are placed through the respective antrostomies. *(Reprinted with permission from Hanna EY, Holsinger C, Demonte F, Kupferman M. Robotic endoscopic surgery of the skull base: a novel surgical approach.* Arch Otolaryngol Head Neck Surg. *2007;133[12]:1209-1214.)*

Three patients with small base of tongue cancers underwent transoral resection with robotic assistance with no apparent complications.[31] It remains too early to assess the oncologic outcomes from these interventions. Introducing robotic technology to accomplish a tonsillectomy has less apparent advantage.[32]

The use of robotic assistance for otolaryngologic applications certainly must still be considered experimental, and findings from each of the robotic groups cited will need to be confirmed at other institutions (or preferably in controlled multicenter trials) before regulatory approval will be granted and more widespread adoption occurs.

Future Directions

The question no longer appears to be "Will robotics find a place in surgery?" Rather, the question appears to be simply "How and in which applications will robotics be used?" Particularly in the field of otolaryngology, head, and neck surgery, inevitable advances in miniaturization and versatility will combine with improvements in visual fidelity to widen the procedural clinical applications. The challenge will be to responsibly pursue these technology-laden procedures in a logical and cautious fashion when they provide meaningful added value and not simply to satisfy the technologic appetite of the surgeon. Nevertheless, one can anticipate a number of additional procedures that may derive benefit from the addition of robotic technology, including precise and technically demanding otologic surgery, delicate voice surgery, and complex resections and reconstructions throughout the upper aerodigestive tract.

Another necessary parallel development will include specific training in robotic surgery. This will manifest in several forms, ranging from the classic weekend primer course for those technologically oriented individuals already adept at advanced endoscopic surgery,

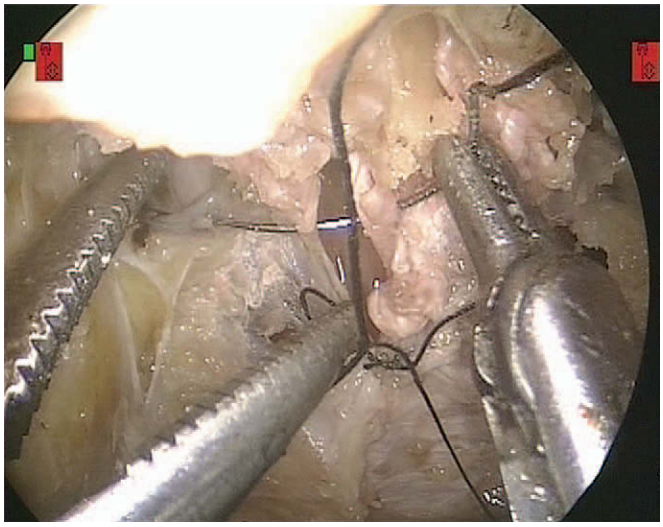

Figure 4A-14. Dural suture placement is made substantially easier with the EndoWrist technology associated with the daVinci surgical system. *(Reprinted with permission from Hanna EY, Holsinger C, Demonte F, Kupferman M. Robotic endoscopic surgery of the skull base: a novel surgical approach.* Arch Otolaryngol Head Neck Surg. *2007;133[12]:1209-1214.)*

all the way to year-long robotic surgery fellowships as we further exploit the electronic and technologic advances that continue to accelerate.

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For complete list of references log onto www.expertconsult.com.

CHAPTER FOUR B

Simulation and Haptics in Otolaryngology Training

Marvin P. Fried

Gregory J. Wiet

Babak Sadoughi

Key Points

- Surgical training must rely on standardized and well-tested methods of instruction.
- Patient risk reduction is an unquestionable priority.
- Simulation provides an ideal environment to train surgeons in realistic conditions without jeopardizing patients.
- Surgical scientific societies support surgical simulators as mandatory training media.
- Scientific validation is a critical factor of simulator development.
- Otolaryngology is a pioneering specialty in the development and implementation of surgical simulators.
- The Endoscopic Sinus Surgery Simulator (ES3) is the most sophisticated simulator available for paranasal sinus surgery.
- Validation studies have demonstrated construct validity of the ES3; further studies are underway to assess the validity of the ES3 to improve actual surgical skills in the operating room.
- A number of temporal bone surgery simulators have been developed around the world; the system designed by The Ohio State University and the Ohio Supercomputer Center, based on volume-rendering, has particularly strong realism and interactivity.
- The Ohio State Temporal Bone Simulator can also easily import imaging data sets and allow a patient-specific surgical rehearsal experience.
- The Ohio State Temporal Bone Simulator is currently being tested as a training tool through a large multi-institutional trial.
- Concurrent curriculum development is an essential part of all simulation training projects.

Surgical skills training must be predicated on standard and well-tested methods of instruction. Besides hands-on operative experience on live patients, resident training currently relies on video tapes and cadaver dissection where available. Some institutions have used cadavers to provide the first surgical experience to residents learning endoscopic sinus surgery. Stankiewicz has long been a proponent of a rigorous curriculum using cadaveric dissection before performing a first sinus surgery procedure, although the utility of such a method has never been demonstrated.[1] More frequently, direct observation of procedures in the operating room is employed, with increased responsibility as residents progress in training, ultimately becoming the major participant by their final year.

In light of the increasing scrutiny on the medical profession, diminishing patient risk is of paramount concern, particularly for surgical procedures. Medical simulator technology provides interim training media wherein proficiency can be achieved before entering the operating room. Indeed, the science of simulation, well past 50 years of implementation in other high-risk professions (e.g., aviation industry, nuclear power plants), has already demonstrated the following capabilities (Brandon Hall Research News, 2005, available at www.brandon-hall.com):

- Providing a safe environment to make mistakes
- Reducing training time, thereby creating the most efficient path for solving a specific problem
- Allowing practice of hazardous procedures, such as shutting down a nuclear reactor or flying in hazardous conditions
- Streamlining the processes that are being taught (e.g., improvements in process are often made when creating simulations)
- Facilitating greater retention
- Transferring expert thinking by "modeling" expert behavior in the learning

High-fidelity virtual reality (VR) simulators have long had an impact on improving the skill level of military and commercial pilots, and they hold similar promise for the medical field. With a validated surgical simulator, proficiency criteria can be attained before permitting the student surgeon to operate upon a patient. Based on the lessons

from aviation training over the past 3 decades, computer-assisted devices have had significant success in augmenting the education and training of surgical residents in a number of fields.[2-5] VR simulation has already played a role in the training of residents for laparoscopic, gastrointestinal, plastic, ophthalmologic, dermatologic, urologic, and some laryngologic procedures.[6-13] The efficacy of VR simulation as a teaching tool is evident, and its superiority to conventional teaching methods is increasingly accepted. Recently, it has been reported that virtual reality training impacts positively not only on resident operating room performance but also potentially on safety.[14]

During the past 15 years, medical simulation technology has gained substantial support. Validation studies have established that surgical skills trained using medical simulation significantly improved trainee performance by decreasing operating times, improving efficiency, and decreasing errors. The medical profession, academics, authoritative organizations (training, testing, licensing and certification bodies) and corporate partners have accepted the importance of simulation within the context of a quantitative assessment environment unique to simulators. The impact on patient safety is *a priori*—that is, make the corrections on a simulator, not on a patient. For instance, the American College of Surgeons is interested in promoting surgical simulators by identifying targets for simulation; researching, writing, and implementing the plan for medical simulation training; and investigating sources of funding.[15] Simulation is expected to soon provide a full range of possible surgical conditions wherein training can occur without placing a patient at risk. Otolaryngology has been a leading field in virtual reality simulation, mainly with efforts in the specific spheres of paranasal sinus surgery and temporal bone surgery simulation.

Endoscopic Sinus Surgery

The impact of sinus disease on quality of life as well as social and work performance is significant.[16,17] In 2004, 31 million Americans, almost 14% of the population, suffered from sinus disease.[18] Every year, sinus disease sufferers account for 12.5 million visits to office-based physicians and 1.1 million hospital outpatient visits per year.[19] The overall direct expenditures attributable to sinusitis in 1996 were estimated at $5.8 billion, of which $1.8 billion (31%) was incurred to treat children 12 years of age or younger.[20] Because of the limitations of large-scale evaluations, these figures likely underestimate true direct costs.[21] The indirect costs of sinusitis are staggering too: the number of total restricted activity days due to sinusitis rose from approximately 50 million per year between 1986 and 1988 to 73 million per year between 1990 and 1992.[18]

In 2004, Lynn-Macrae and colleagues queried a computerized legal database to retrospectively analyze state and federal civil litigation involving injuries resulting from endoscopic sinus surgery (ESS) between 1990 and 2003. They observed that 76% of ESS-related malpractice suits were prompted by alleged negligent technique, with an average verdict award of $751,275.[22]

Surgery is used when medications fail or when complications of the sinus disease ensue. ESS was first introduced in the 1970s and has since been established as the standard of care for operative treatment of the sinuses and nasal cavity.[23-26] ESS involves the introduction of delicate surgical instruments through the nares to perform exacting maneuvers for a wide range of surgical interventions involving the paranasal sinuses and the cranial base. Although the concept of ESS is straightforward, skillfully performing the procedure can be challenging.[27] The relevant anatomy is highly complex and compact, with the added concern of the vicinity of such important structures as the brain, orbital contents, and carotid artery.[1,28] With very little room for error, the surgeon must navigate and manipulate instrumentation using dominant and nondominant hands simultaneously, while coordinating movements indirectly with the aid of a television monitor. Precise hand-eye coordination is an obvious prerequisite. The ESS technique provides the surgeon with excellent visualization, supplemented by an array of instruments that permit access to the depths of the sinuses and to the cranial base. The use of a computer-based image-guidance system (IGS) adds to these capabilities by providing unprecedented navigational support to reach the area of interest while delineating the surrounding anatomy that is not at pathologic risk. The applications of endoscopic procedures have expanded widely as safety and efficacy have been documented.[29-31]

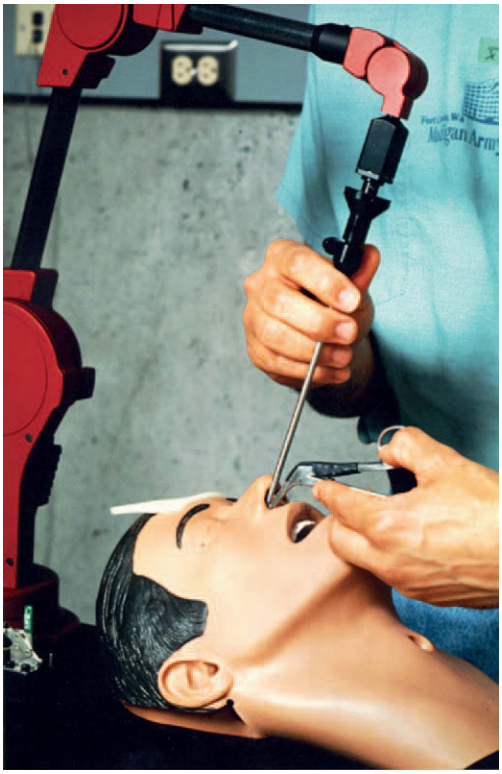

Figure 4B-1. The Madigan/Lockheed Martin Endoscopic Sinus Surgery Simulator (ES3).

However, the potential complications of ESS may be very serious in less than well-trained hands, and simulation may well reduce the complication rates of ESS. While designing a curriculum for ESS, emphasis is therefore placed on the quality and quantity of training that a surgical trainee must have before performing independently.

Endoscopic Sinus Surgery Simulator

The technical acumen required for basic ESS procedures is not achieved, for the most part, until the later half of a resident's training. With the increase in the complexity of microdissection equipment and the growing demand to broaden the indications of ESS,[32] there is a real need to make residents more familiar with the technical skills of ESS at an earlier stage in training. As technology matures, the need for simulators to teach surgery has become apparent.[33] Again otolaryngology took a leadership role in this venture with the conception in 1996 by Department of Defense contractor Lockheed Martin Corporation of the Endoscopic Sinus Surgery Simulator (ES3) (Fig. 4B-1). The system employs virtual anatomy and instruments, visual and haptic (force) feedback, voice commands, phased instruction, and performance monitoring to create a virtual reality environment designed to train otolaryngology residents.[13,34-37] The simulator provides spatial relationships, ability to maneuver in operating space, presentation of sinus anatomy, common surgical instruments, and basic to advanced surgical technologies. The ES3 development team conducted evaluation studies[13,34-37] that have been followed by a series of formal scientific validation studies by multi-institutional academic and corporate consortia.

The ES3 consortium organization, led by the Albert Einstein College of Medicine's Montefiore Medical Center and funded by the Agency for Healthcare Research and Quality, provided a center for curriculum development (Yale University), centers for data collection (New York University Medical Center, New York Eye and Ear

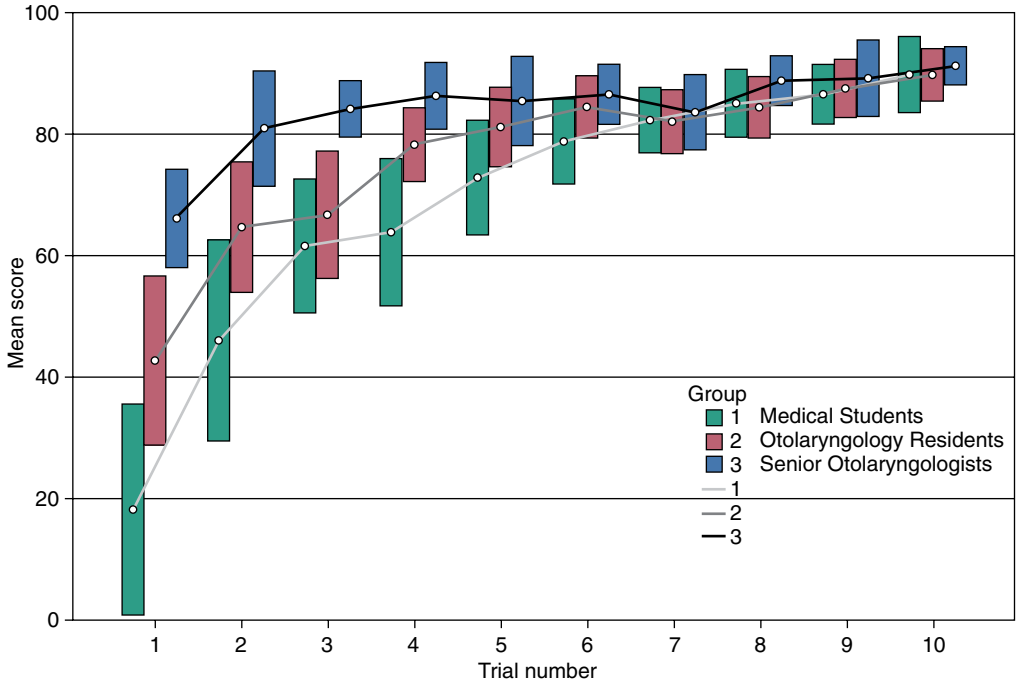

Figure 4B-2. Performance over 10 trials on the ES3 novice level by otolaryngology attendings, residents, and medical students. *(From Fried MP, Sadoughi B, Weghorst SJ, et al. Construct validity of the endoscopic sinus surgery simulator: II. Assessment of discriminant validity and expert benchmarking.* Arch Otolaryngol Head Neck Surg. *2007;133[4]:350-357.)*

Infirmary, Mount Sinai Medical Center), and a center for web database and outcomes reporting (UW-HITLab).

The development team also developed a prototype intelligent multimodal expert surgical assistant for the ES3.[38] The system, which incorporates knowledge of the endoscopic procedure into a structured rule base, interprets the user's multimodal inputs (currently voice and virtual endoscope position) and interacts with the user dynamically. While performing the simulated procedure, the user can query the system about anatomy and the specifics of the procedure, asking the system to identify features or demonstrate maneuvers. In turn the system recognizes the user's actions and can provide vocal and visual feedback, as well as warnings when the user is about to execute a dangerous maneuver. In addition to enhancing simulation for training purposes, the expert surgical assistant can also be used for guidance during actual surgical procedures. This assistance can be particularly helpful for procedures in which situation awareness is diminished due to the complexity of the anatomy or to surgical complications.

One of the initial first validation studies of the ES3 specifically addressed the system's discriminant and concurrent validity, by comparing cumulative performance levels between medical students, otolaryngology residents, and otolaryngology attendings as groups, thereby establishing attending benchmark data against which residents and medical students can be measured. The simulator performance data of 10 medical students were compared with those of 14 otolaryngology residents and 10 attending otolaryngologists. The results (Figs. 4B-2 and 4B-3) clearly demonstrated significant differences in performance among the three groups. Attending otolaryngologists perform the best at all levels, with residents close behind and medical students performing substantially subpar to residents. However, by the end of the curriculum (i.e., trial 10), all groups achieved plateau scores included within a remarkably narrow range. This illustrates the consistency and relatively low variability of performance after simulator training, allowing the instructors to set predefined performance goals tailored to the educational needs of the trainees.[39] A spinoff observation yielded by the study of medical student performance showed that, after a critical period of training had been accomplished, the performance of the trainee did not substantially diminish even after 1 month without simulator training.[40] Hence, the transfer of complex skills facilitated by the ES3 produces long-lasting and memorable performance. This has implications with regard to the use of surgical simulation as a meaningful training tool in an effort to reduce surgical errors and increase patient safety.

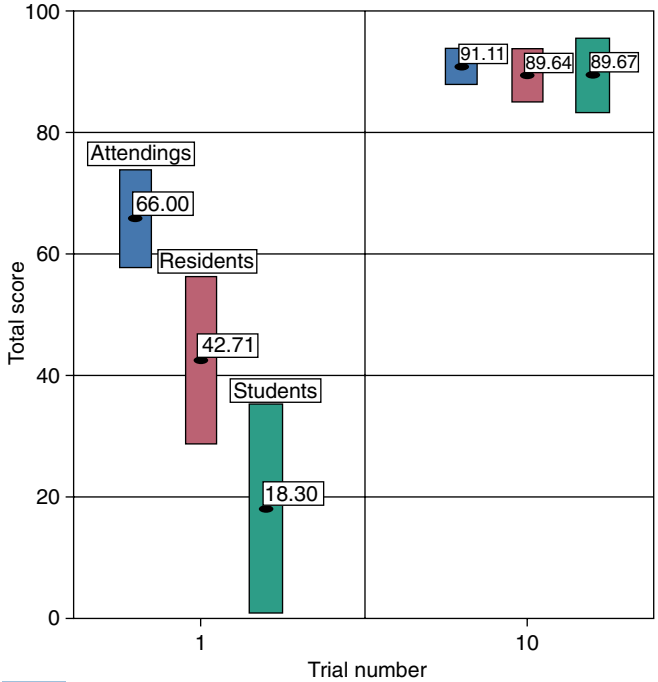

Figure 4B-3. Performance range variability between trials 1 and 10. *(From Fried MP, Sadoughi B, Weghorst SJ, et al. Construct validity of the endoscopic sinus surgery simulator: II. Assessment of discriminant validity and expert benchmarking.* Arch Otolaryngol Head Neck Surg. *2007;133[4]:350-357.)*

Table 4B-1

Pearson Correlation Coefficients between ES3 Hazard and Total Scores and Independent Tests of Visuospatial, Psychomotor, and Perceptual Abilities

	Pict Surface Orientation (PicSOr)	Cube Comparison (CC)	Card Rotation (CR)	MIST-VR Total Score	Regression Model Fit (ES3 trial score, PicSOr, CC, MIST-VR)
ES3 Hazard score	r = .5* (P <.001)	r = .29 (P <.1)	r = .27 (P <.14)	r = .36 (P <.06)	
ES3 Trial score	r = .3 (P <.2)	r = .43* (P <.01)	r = .45* (P <.01)	r = .57* (P <.001)	r = .63* (P <.01)

*Statistically significant correlations.
From Arora H, Uribe J, Ralph W, et al. Assessment of construct validity of the endoscopic sinus surgery simulator. *Arch Otolaryngol Head Neck Surg.* 2005;131:217-221.

A second validation study was designed to correlate the performance of subjects on the ES3 with their performance on other validated tests of innate ability. Indeed, ESS requires two-handed coordination of surgical instruments with an endoscope in three-dimensional space. The technique necessitates complex ambidextrous psychomotor, visuospatial, and perceptual capabilities. This second set of studies aimed to assess whether objective tests of such fundamental abilities might also predict performance on the ES3. Results assessed on 34 medical students and four otolaryngology residents showed conclusively that statistically significant correlations exist between performance on various validated tests and the ES3 (Table 4B-1).[39] This confirmed the robustness and utility of the ES3 and helped develop a multifaceted and enriched learning environment designed to reduce surgical errors and improve patient safety in the operating room.

The third study, focusing on predictive validity ("Virtual Reality to Operating Room," or "VR to OR" protocol), is probably the most significant part of the validation work of the ES3, addressing directly the question of whether training on the simulator improves the performance of otolaryngology residents in actual surgery and reduces their surgical errors. The study required the collection of resident data from 12 different institutions throughout the country. Otolaryngology residents in their junior year were included in either an experimental group (destined to receive conventional sinus surgery training as well as ES3 training) or a control group (receiving only conventional sinus surgery training). One subsequent sinus surgery procedure was used to videotape their first performance in the operating room, which was then reviewed by a masked panel of experts to rate the individual. Preliminary results of this ongoing study are still pending, but a prior similar study on the ES3 with fewer subjects has suggested substantial superiority of surgical performance by residents trained on the simulator compared to that of control residents.[41,42] The VR-to-OR study is expected to further corroborate the hypothesis with increased sample size, statistical power, and refined methodology.

The future of surgical simulation training will rely significantly on the principles learned from flight training: a "mission" will be rehearsed following clearly defined objectives, then performed, and then reviewed and analyzed in order to move toward improved performance and patient safety.

Curriculum Development

A refined state-of-the-art curriculum was developed with assistance from the Yale University School of Medicine Division of Otolaryngology to standardize training on the ES3, regardless of training level. Video information (demonstrating successful as well as erroneous operation of each training level), written background, anatomic information, and other tools were incorporated onto a compact disc. This medium greatly facilitates the trainees' compliance with the protocols and eliminates bias related to the vastly different educational starting points of the subjects.

To better understand the present state of resident training, a survey of the major centers participating in the past ES3 research was conducted. The results showed that residents often did not begin performing endoscopic sinus surgery until their last year of otolaryngologic training and that only half of the institutions that responded gave formal lectures and required a reading list before residents were allowed to perform ESS in the operating room. It was concluded that there clearly was a need to develop curriculum content that would be systematic, comprehensive, and well structured, hypothesizing that such curriculum would improve effectiveness, reduce errors, and improve safety compared to controls.

A new direction of research, based on studies suggesting the use of expert-defined criteria as benchmark levels of performance,[33] has been initiated with funding from the Department of Defense's Telemedicine and Advanced Technology Research Center. This research is expected to confirm the necessity of a paradigm shift in the core concepts of modern specialty training. Surgical residents will be trained on the ES3 until they reach a performance criterion level, objectively predefined by the performance of experienced sinus surgeons on the same simulator tasks. This will ensure that those receiving VR training meet at least the same benchmark criteria on several consecutive training trials. This is in distinction to establishing a specific number of cases as an adequate training criterion. Iterative comparison of videotaped operating room performance to that of control residents (not subject to the proficiency-based training requirement) will aim to objectively evaluate the efficacy of this educational principle.

Other ESS Simulators

The Dextroscope (www.dextroscope.com) is a software application able to create a three-dimensional model based on computerized imaging (computed tomography or magnetic resonance imaging). It allows free volume interaction with a visual model to rehearse surgical procedures. The method was shown to improve understanding of the anatomy for junior residents, but failed to impact their operating room performance.[43] The system paves the way toward patient-specific data analysis for planning, rehearsing, and debriefing of surgical procedures, but lacks haptic feedback and is not designed to emulate the operating room environment.

The Innovation Center for Computer Assisted Surgery (ICCAS) group at the Medical Faculty of the University of Leipzig, Germany, is developing the VR-FESS, in addition to designing a transsphenoidal pituitary surgery simulator. The team also envisions the elaboration of surgical *ontologies* and workflows, that is, formalized descriptions of surgical procedures allowing analysis and detailed evaluation.[44] However, no validation efforts have yet been published by this group.

A second German group has developed the Nasal Endoscopy Simulator, which consists of a graphics workstation, a tracking system for the position of the endoscope and surgical instruments, and a physical model.[45] The virtual model is based on patient-specific imaging data sets, with textures derived from endoscopic images superimposed on the virtual reality environment.[46] The initial prototype was not haptics enabled[47] and a later version was reported to be under development,[48,49] but there has not yet been report of further advancement of this work.

Japan's Surgical Institute for Advanced Industrial Science and Technology developed a Paranasal Sinuses Simulator, comprising a soft dummy with force sensors that deliver counterforce measurements for analysis and computation into a patient risk index. Preliminary studies suggest positive face and construct validity.[50] Despite not being a true virtual reality simulator, the effort is worthy, in that the force applied to instruments is a variable that may be of value for objective skills assessment by any simulator.

Even though the aforementioned undertakings bring unquestionable value to the expansion of virtual reality training for ESS, none has produced a comprehensive surgical training experience comparable to the ES3, which remains the most sophisticated and best evaluated surgical simulator for ESS.

Temporal Bone Surgery

Traditionally, temporal bone surgery has been learned through contemporary media: textbooks and atlases,[51-54] illustrations, CD-ROMS,[55,56] models[57] (www.temporal-bone.com/plastic.htm), and cadaver dissections.[58,59] Although CD-ROMs provide a cost-effective solution through the integration of photographs, illustrations, movies, computer graphics, and tomographic images, the interactivity is limited.

Harada first introduced the concept of exploiting three-dimensional volumetric reconstructions from computed tomography for emulating drilling and exposing the intricate regional anatomy of the temporal bone.[60] In that era, the computational overhead required by volume-rendering algorithms to produce realistic visual display was prohibitive. Subsequently, surface-based approaches were predominantly employed for modeling structure to exploit hardware-accelerated surface rendering techniques that had been developed for the video gaming industry. Similar techniques using reconstructions from histologic sections to derive iso-surfaces (surface-based rendering) have focused on clarifying the spatial relationships of the regional anatomy.[61-64] Stereo presentations of surface-based models acquired from the Visible Human Project (VHP-NLM 2002) were presented for transpetrosal, retrosigmoid, and middle fossa approaches to the cerebellopontine angle.[65] Even though surface-based representations of soft tissues and bone structures have been developed, these systems did not provide haptic feedback to the user and provided only schematic emulation of dissection and surgical technique. As graphics processing hardware (GPU) advanced as a function of the popularity of gaming systems, issues related to poor performance in volume-rendering were resolved. In comparison to surface-based rendering systems, pure volume-rendering systems eliminate the tasks of redrawing surfaces, and interactivity is more realistic. Furthermore, the advent of high-fidelity haptic interfaces has enabled accurate display of the sense of touch. It was these particular steps in graphics processing and haptic development that allowed the possibility of real-time, interactive surgical simulation. Currently, there are several systems in use, each of which has unique features.

First is a system developed at Stanford University in conjunction with Dr. Nikolas Blevins in the Department of Otolaryngology.[66-68] This system uses CT data, a combination of volume- and surface-based rendering for visual display, and a haptic interface consisting of a SensAble Phantom with 3 degrees of freedom haptic feedback and 6 degrees of freedom positional input. The visual interface consists of a computer screen (Fig. 4B-4). A sophisticated haptic model was developed that provides not only force feedback to the user but also sense of vibration that is bit dependent. Bone dust is synthesized using a grid-based approach that requires the user to keep the operative field clean as in real temporal bone surgery. Lastly, sound production relative to bone thickness is provided to further enhance the simulation environment.

Figure 4B-4. The Stanford University simulator demonstrating the visual and haptic user interface.

Figure 4B-5. The Stanford University simulator demonstrating use of the haptic mentoring feature with trainee and expert at linked interfaces.

The developers have used this system to demonstrate construct validity (an element of simulation validation that identifies experts from novices based on their performance in the simulation).[67] Additionally, they have demonstrated a novel approach to trainee interactivity with the system by using "haptic mentoring" (Fig. 4B-5). In this mode, the trainee can "feel" what the instructor is feeling at the same time the instructor is drilling or experience the "feel" when the instructor is off line in a rehearsal mode. Another key component to this system is the ability of the simulation environment to provide automated evaluation and feedback. In this feature, elements such as visibility testing, safe force application, and correct sequence of bone removal are tracked and visual cues are offered to the trainee to either confirm or redirect current activity. It is the automated feedback element of this system that makes it ideal for independent learning of the procedure and is the major advantage of this system. This function provides an environment as if an experienced surgeon were instructing the trainee in elements of technique during the dissection. It offers instant feedback to the trainee, an aspect of training that is critical to skills development.[69]

The system developed at The Ohio State University in conjunction with the Ohio Supercomputer Center demonstrates a strong emphasis on realism and interactivity.[70-73] In comparison to the hybrid renderer used in the Stanford system, the OSU system uses true volume rendering for visual display combined with haptic feedback. The algorithms used to provide the visual display in the OSU system are particularly realistic. Like the Stanford system, a SensAble Phantom device is used for haptic feedback. In contrast to the Stanford system, a stereo-capable display (z800, eMagin) analogous to the microscope is used (Fig. 4B-6). Moreover, the Ohio State System also has the ability to integrate new

Figure 4B-6. The Ohio State University temporal bone dissection simulator demonstrating the stereo visual display, haptic display, and rendering on background monitor. (See www.osc.edu/vtbone for more information.)

data easily. Companion software allows import of raw CT data (DICOM format), three-dimensional segmentation, and conversion of data for immediate use in the simulator. Additionally, an "intelligent tutor" is integrated into the simulation environment that allows trainees to choose and display vital anatomic structures in the context of the surgical environment. Complex time sequence recording capabilities are integrated into the simulator that continuously capture the entire volume while manipulations are performed by the user. This allows highly precise tracking of all visual information, tool position, force development, and navigation data from the user for later analysis. In the simulation environment, various types and sizes of burrs can be selected, zoom adjustments analogous to changing objectives on the microscope can be made, and panning of the microscope is available. Currently, the system provides access to 40 different bones with capability for accessing an unlimited number. It records demographic data, including past temporal bone dissection experience, general computer experience, training year, and additional information from the user for testing purposes. New developments in the system include simulation of fluid flow for irrigation and bleeding (video clip available on website). The system has been tested in a small local trial at The Ohio State University in which novice trainees (fourth year medical students and first and second year residents) were randomized to temporal bone dissection training in a cadaveric laboratory or training on a simulator.[74] Group performance was blindly rated using a validated performance measure for temporal bone dissection.[75] Cadaveric laboratory trainees performed marginally better than those trained in the simulator. The Ohio State University system has been recently upgraded and is currently being tested as a training tool in a large multi-institutional trial using a protocol similar to the local trial.

Lastly, a system for virtual temporal bone surgery was developed at the University of Hamburg-Eppendorf in Germany.[76] This system also uses volume-rendering to display the virtual temporal bone during the act of drilling. It has subsequently been developed into a commercial product, VOXEL-MAN TempoSurg simulator (Spiggle and Theis, Overath, Germany; www.uke.de/voxel-man). This system has been used in a recent validation study.[69] Novice and experienced surgeons' hand movements were videotaped while in the simulator or in the cadaveric laboratory performing temporal bone dissections. The videos were then blindly analyzed by expert raters. Raters were able to distinguish the more experienced surgeons from the novice surgeons while performing cadaveric dissections at a statistically significant level but not when using the simulator. Additionally, hand movements were tracked by electromagnetic marker and analyzed for number of movements, distance traveled, and other parameters. Using this objective hand movement measure of performance, the investigators showed that, overall, study subjects seem to score better in the simulation environment compared to the cadaveric laboratory. The significance of this finding is unclear. Currently, the VOXEL-MAN TempoSurg system is the only commercially available system on the market. Further studies using this system will be needed to demonstrate its efficacy in training and assessment.

Conclusion

Simulation allows teaching surgical technique in a complex but safe environment with no risks for patients. Repetition practice in simulation under criterion-referenced instruction can be achieved until proficiency is reached. There is strong support from the surgical governing and regulating entities to mandate the use of virtual reality simulation in surgical training curricula.

For most surgical simulation environments, it is now possible to import patient-specific data and generate high-fidelity practice environments. As technology achieves greater capabilities, the surgeon will be able to practice the procedure in simulation (preoperative assessment and presurgical planning) and identify critical areas for consideration during the operation. The pathology to be addressed will be detailed and the areas at risk such as critical anatomic structures and pathologic variants will be pre-identified.

Overall, the use of simulation technology for otolaryngologic training and assessment has grown from schematic visualizations that provided limited interactivity to fully featured systems. The task at hand for all involved in the development and application of this technology is to demonstrate improvements in outcomes for trainees and ultimately for patients. This will be a long and arduous course especially because we have few if any gold standards to measure performance and outcomes in this field. This process of validation is key to the eventual widespread acceptance and use of simulation technology in general and in otolaryngology in particular. It does, however, hold the promise of mitigating our learning curve and providing detailed performance measures that are currently unavailable with other technologies.

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CHAPTER FIVE

Outcomes Research

Amy Anne Lassig

Bevan Yueh

Key Points

- Outcomes research or clinical epidemiology is the study of treatment effectiveness or the success of treatment in the nonrandomized, real-world setting. It allows researchers to gain knowledge from observational data.
- Bias and confounding can affect researchers' interpretation of study data, and an accurate assessment of baseline disease status, treatment given, and outcomes of treatment are critical to sound outcomes research.
- Many types of studies are available to evaluate treatment effectiveness and include the randomized trial, observational study, case-control study, case series, and expert opinions. The concept of *evidence-based medicine* uses the level of evidence presented in the aforementioned studies to grade diagnostic and treatment recommendations.
- Outcomes in clinical epidemiology are often difficult to quantify, and thus instruments measuring these outcomes must meet criteria of the *classical test theory* (reliability, validity, responsiveness, and burden) or the *item response theory* to be considered psychometrically valid.
- Many outcomes instruments assess health-related quality of life. These scales are generic or disease-specific, including assessment of head and neck cancer, otologic disease, rhinologic disease, pediatric disease, voice disorders, and sleep disorders.

The time when physicians chose treatment based solely on their personal notions of what was best is past. This era, although chronologically recent, is now conceptually distant. In a health care environment altered by abundant information on the Internet and continual oversight by managed care organizations, patients and insurers are now active participants in selecting treatment. Personal notions ("expert opinion") are replaced by objective evidence. And the physician's sense of what is best is being supplemented by patients' perspectives on outcomes after treatment.

Outcomes research (clinical epidemiology) is the scientific study of treatment effectiveness. The word *effectiveness* is a critical one, because it pertains to the success of treatment in populations found in actual practice in the real world, as opposed to treatment success in the controlled populations of randomized clinical trials in academic settings ("efficacy").[1,2] Success of treatment can be measured using survival, costs, and physiologic measures, but frequently health-related quality of life (QOL) is a primary consideration.

Therefore, to gain scientific insight into these types of outcomes in the observational (nonrandomized) setting, outcomes researchers need to be fluent with methodologic techniques that are borrowed from a variety of disciplines, including epidemiology, biostatistics, economics, management science, and psychometrics. A full description of the techniques in clinical epidemiology[3] is beyond the scope of this chapter. This chapter provides the basic concepts in effectiveness research and a sense of the breadth and capacity of outcomes research and clinical epidemiology.

History

In 1900, Dr. Ernest Codman proposed to study what he termed the "end results" of therapy at the Massachusetts General Hospital.[4] He asked his fellow surgeons to report the success and failure of *each* operation and developed a classification scheme by which failures could be further detailed. Over the next 2 decades, his attempts to introduce systematic study of surgical end results were scorned by the medical establishment, and his prescient efforts to study surgical outcomes gradually faded.

Over the next 50 years, the medical community accepted the randomized clinical trial (RCT) as the dominant method for evaluating treatment.[5] By the 1960s, the authority of the RCT was rarely questioned.[6] However, a landmark 1973 publication by Wennberg and Gittelsohn spurred a sudden re-evaluation of the value of observational (nonrandomized) data. These authors documented significant geographic variation in rates of surgery.[7] Tonsillectomy rates in 13 Vermont regions varied from 13 to 151 per 10,000 persons, even though there was no variation in the prevalence of tonsillitis. Even in cities with similar demographics and similar access to health care (Boston and New Haven, Conn.), rates of surgical procedures varied 10-fold. These findings raised the question of whether the higher rates of surgery represented better care or unnecessary surgery.

Researchers at the Rand Corporation sought to evaluate the appropriateness of surgical procedures. Supplementing relatively sparse data in the literature about treatment effectiveness with expert opinion conferences, these investigators argued that rates of inappropriate surgery were high.[8] However, utilization rates did not correlate with rates of inappropriateness, and therefore did not explain all of the variation in surgical rates.[9,10] To some, this suggested that the practice of medicine was anecdotal and inadequately scientific.[11] In 1988, a seminal editorial by physicians from the Health Care Financing Administration argued that a fundamental change toward study of treatment effectiveness was necessary.[12] These events subsequently led Congress to establish the Agency for Health Care Policy and Research in 1989 (since renamed the Agency for Healthcare Research and Quality, or AHRQ), which was charged with "systematically studying the relationships between health care and its outcomes."

In the past decade, outcomes research and the AHRQ has become integral to understanding treatment effectiveness and establishing health policy. Randomized trials cannot be used to answer all clinical questions, and outcomes research techniques can be used to gain considerable insights from observational data (including data from large administrative databases). With current attention on evidence-based medicine and quality of care, a basic familiarity with outcomes research is more important than ever.

Key Terms and Concepts

The fundamentals of clinical epidemiology are best understood by thinking about an episode of treatment: a patient presents at baseline with an index condition, receives treatment for that condition, and then experiences a response to treatment. Assessment of baseline state, treatment, and outcomes are all subject to bias. We begin with a brief review of bias and confounding.

Bias and Confounding

Bias occurs when "compared components are not sufficiently similar."[3] The compared components may involve any aspect of the study. For example, *selection* bias exists if, in comparing surgical resection to chemoradiation, oncologists avoid treating patients with renal or liver failure. This makes the comparison unfair because, on average, the surgical cohort will accrue more ill patients. *Treatment* bias occurs when comparing, for example, standard stapedotomy with laser stapedotomy, but one procedure is performed by an experienced surgeon, and the other is performed by resident staff.

Similar to bias, *confounding* also has the potential to distort results. However, confounding refers to specific variables. Confounding occurs when a variable thought to cause an outcome is actually not responsible, because of the unseen effects of another variable. Consider the hypothetical (and obviously faulty) case in which an investigator postulates that nicotine-stained teeth cause laryngeal cancer. Despite a strong statistical association, this relationship is not causal, because another variable—cigarette smoking—is responsible. Cigarette smoking is confounding because it is associated with both the outcome (laryngeal cancer) and the supposed baseline state (stained teeth).

Assessment of Baseline

Most physicians are aware of the confounding influences of age, gender, ethnicity, and race. However, accurate baseline assessment also means that investigators should carefully define the disease under study, account for disease severity, and consider other important variables such as comorbidity.

Definition of Disease

It would seem obvious that the first step is to establish diagnostic criteria for the disease under study. Yet this is often incomplete. Inclusion criteria should include all relevant portions of the history, the physical examination, and laboratory and radiographic data. For example, the definition of chronic sinusitis may vary by pattern of disease (e.g., persistent vs. recurrent acute infections), duration of symptoms (3 months vs. 6 months), and diagnostic criteria for sinusitis (clinical examination vs. ultrasound vs. computed tomography vs. sinus taps and cultures). All of these aspects must be delineated to place studies into proper context.

In addition, advances in diagnostic technology may introduce a bias called *stage migration.*[13] In cancer treatment, stage migration occurs when more sensitive technologies (such as CT scans in the past, and positron emission tomography scans now) may "migrate" patients with previously undetectable metastatic disease out of an early stage (improving the survival of that group), and place them into a stage with otherwise advanced disease (improving this group's survival as well).[14,15] The net effect is that there is improvement in stage-specific survival, but no change in overall survival.

Disease Severity

The severity of disease strongly influences response to treatment. This reality is second nature for oncologists, who use tumor-node-metastasis stage to select treatment and interpret survival outcomes. It is intuitively clear that the more severe the disease, the more difficult it will be (on average) to restore function. Yet this concept has not been fully integrated into the study and practice of common otolaryngologic diseases such as sinusitis and hearing loss.

Recent progress has been made in sinusitis. Kennedy identified prognostic factors for successful outcomes in patients with sinusitis and has encouraged the development of staging systems.[16] Several staging systems have been proposed, but most systems rely primarily on radiographic appearance.[17-20] Clinical measures of disease severity (symptoms, findings) are not typically included. Although the Lund-Mackay staging system is reproducible,[21] often radiographic staging systems have correlated poorly with clinical disease.[22-26] As such, the Zinreich method was created as a modification of the Lund-Mackay system, adding assessment of osteomeatal obstruction.[27] Alternatively, the Harvard staging system has been reproducible[21] and may predict response to treatment.[28] Scoring systems have also been developed for specific disorders such as acute fungal rhinosinusitis,[29] and clinical scoring systems based on endoscopic evaluation have likewise been developed.[30] The development and validation of reliable staging systems for other common disorders, as well as the integration of these systems into patient care, is a pressing challenge in otolaryngology.

Comorbidity

Comorbidity refers to the presence of concomitant disease unrelated to the "index disease" (the disease under consideration), which may affect the diagnosis, treatment, and prognosis for the patient.[31-33] Documentation of comorbidity is important, because the failure to identify comorbid conditions such as liver failure may result in inaccurately attributing poor outcomes to the index disease being studied.[34] This baseline variable is most commonly considered in oncology, because most models of comorbidity have been developed to predict survival.[32,35] The Adult Comorbidity Evaluation 27 (ACE-27) is a validated instrument for evaluating comorbidity in cancer patients and has shown the prognostic significance of comorbidity in a cancer population.[36,37] Because of its impact on costs, utilization, and QOL, comorbidity should be incorporated in studies of nononcologic diseases as well.

Assessment of Treatment

Control Groups

Reliance on case series to report results of surgical treatment is time-honored. It is also inadequate for establishing cause and effect relationships. A recent evaluation of endoscopic sinus surgery reports revealed that only 4 of 35 studies used a control group.[38] Without a control group, the investigator cannot establish that the observed effects of treatment were directly related to the treatment itself.[3]

It is also particularly crucial to recognize that the scientific rigor of the study varies with the suitability of the control group. The more fair the comparison, the more rigorous the results. Therefore a randomized cohort study in which subjects are randomly allocated to different treatments is more likely to be free of biased comparisons than observational cohort studies in which treatment decisions are made by an individual, a group of individuals, or a health care system. Within observational cohorts, there are also different levels of rigor. In a recent evaluation of critical pathways in head and neck cancer, a "positive" finding in comparison with a historical control group (a comparison group assembled in the past) was not significant when compared to a concurrent control group.[39]

Assessment of Outcomes

Efficacy

The distinction between efficacy and effectiveness, briefly discussed earlier, illustrates one of the fundamental differences between randomized trials and outcomes research. *Efficacy* refers to whether a health intervention, in a controlled environment, achieves better outcomes than does placebo. Two aspects of this definition need emphasis. First, efficacy is a comparison to placebo. As long as the intervention is better, it is efficacious. Second, controlled environments shelter patients and

physicians from problems in actual clinical settings. For example, randomized efficacy trials of medications provide continuing reminders for patients to use their medications, and nonadherent patients are dropped from further study.

Effectiveness

An efficacious treatment that retains its value under usual clinical circumstances is *effective*. Effective treatment must overcome a number of barriers not encountered in the typical trial setting. For example, disease severity and comorbidity may be worse in the community, in that healthy patients tend to be enrolled in (nononcologic) trials. Patient adherence to treatment may also be imperfect. Consider continuous positive airway pressure (CPAP) treatment for patients with obstructive sleep apnea. Although the CPAP is efficacious in the sleep laboratory, the positive pressure is ineffective if the patients do not wear the masks when they return home.[40] A different challenge is present for surgical treatments, because community physicians learning a new procedure cannot be expected to perform it as effectively as the surgeon investigator who pioneered its development.

Fundamentals of Study Design

A variety of study designs are used to gain insight into treatment effectiveness. Each has advantages and disadvantages. The principal tradeoff is complexity versus rigor, because rigorous evidence demands greater effort. An understanding of the fundamental differences in study design can help interpret the quality of evidence, which has been formalized by the evidence-based medicine (EBM) movement. EBM is the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[41] EBM is discussed in detail elsewhere in this textbook. The following paragraphs summarize the major categories of study designs, with reference to the EBM hierarchy of levels of evidence (Table 5-1).[41,42]

Randomized Trial

Randomized clinical trials (RCTs) represent the highest level of evidence, because the controlled, experimental nature of the RCT allows the investigator to establish a causal relationship between treatment and subsequent outcome. The random distribution of patients also allows unbiased distribution of baseline variables and minimizes the influence of confounding. Although randomized trials have generally been used to address efficacy, modifications can facilitate insight into effectiveness as well. RCTs with well-defined inclusion criteria, double-blinded treatment and assessment, low losses to follow-up, and high statistical power are considered high-quality RCTs and represent level 1 evidence. Lower quality RCTs are rated level 2 evidence.

Observational Study

In observational studies, sometimes called *cohort studies*, patients are identified at baseline *before* treatment (or "exposure" in standard epidemiology cohort studies investigating risk factors for disease), similar to randomized trials. However, these studies accrue patients who receive routine clinical care. Inclusion criteria are substantially less stringent, and treatment is assigned by the provider in the course of clinical care. Maintenance of the cohort is also straightforward, because there is no need to keep patients and providers doubly blinded.

The challenge in cohort studies is to find an appropriate control group. Rigorous prospective and retrospective cohort studies *with a suitable control group* represent high-quality studies and can represent level 2 evidence. To obtain insight into comparisons of treatment effectiveness, these studies need to use sophisticated statistical and epidemiologic methods to overcome the biases discussed in the prior section. Even with these techniques, there is the risk that unmeasured confounding variables will distort the comparison of interest. Poor-quality cohorts without control groups, or inadequate adjustment for confounding variables, are considered level 4 evidence, because they are essentially equivalent to a case series.

Case-Control Study

Case-control studies are typically used by traditional epidemiologists to identify risk factors for the development of disease. In such cases, the disease becomes the "outcome." In contrast to randomized and observational studies, which identify patients before exposure to a treatment (or a pathogen), and then follow patients forward in time to observe the outcome, case-control studies use the opposite temporal direction. This design is particularly valuable when prospective studies are not feasible, either because the disease is too rare or because the time interval between baseline and outcome is prohibitively long.

For example, a prospective study of an association between a proposed carcinogen (e.g., gastroesophageal reflux) and laryngeal cancer would require a tremendous number of patients and decades of observation. However, by identifying patients with and without laryngeal cancer, and comparing relative rates of carcinogen exposure, a case-control study can obtain a relatively quick answer.[43] Because the temporal relationship between exposure and outcome is not directly observed, no causal judgments are possible, however. These studies are considered level 3 evidence.

Case Series and Expert Opinion

Case series are the least sophisticated format. As discussed earlier, no conclusions about causal relationships between treatment and outcome

Table 5-1

Summary of Study Designs

Design	Advantages	Disadvantages	Level of Evidence
Randomized clinical trial (RCT)	Only design to prove causation Unbiased distribution of confounding	Expensive and complex Typically targets efficacy	1, if high-quality RCT 2, if low-quality RCT
Observational (cohort) study	Cheaper than RCT Clear temporal directionality from treatment to outcome	Difficult to find suitable controls Confounding	2, with control group 4, if no control group
Case-control study	Cheaper than cohort study Efficient study of rare diseases or delayed outcomes	Must rely on retrospective data Directionality between exposure and outcome unclear	3
Case series	Cheap and simple	No control group No causal link between treatment and outcome	4
Expert opinion	N/A	N/A	5

Table 5-2

Grade of Recommendation and Level of Evidence

Grade of Recommendation	Level of Evidence
A	1
B	2 or 3
C	4
D	5

can be made because of uncontrolled bias and the absence of any control group. These studies are considered level 4 evidence. If case studies are unavailable, then expert opinion is used to provide level 5 evidence.

Other Study Designs

There are numerous other important study designs in outcomes research, but a detailed discussion of these techniques is beyond the scope of this chapter. The most common approaches include decision analyses,[44,45] cost-identification and cost-effectiveness studies,[46-48] secondary analyses of administrative databases,[49-51] and meta-analyses.[52,53] Critiques of these techniques are referenced for completeness.

Grading of Evidence-Based Medicine Recommendations

EBM uses the levels of evidence described earlier to grade treatment recommendations (Table 5-2).[54] The presence of high-quality RCTs allows treatment recommendations for a particular intervention to be ranked as grade A. If no RCTs are available, but there is level 2 or 3 evidence (observational study with a control group or a case-control study), then the treatment recommendations are ranked as grade B. The presence of only a case series would result in a grade C recommendation. If only expert opinion is available, then the recommendation for the index treatment is considered grade D.

Measurement of Clinical Outcomes

Clinical studies have traditionally used outcomes such as mortality and morbidity, or other "hard" laboratory or physiologic endpoints,[55] such as blood pressure, white cell counts, or radiographs. This practice has persisted despite evidence that interobserver variability of accepted "hard" outcomes such as chest x-ray findings and histologic reports are distressingly high.[56] In addition, clinicians rely on "soft" data, such as pain relief or symptomatic improvement to determine whether patients are responding to treatment. But because it has been difficult to quantify these variables, these outcomes have until recently been largely ignored.

Psychometric Validation

An important contribution of outcomes research has been the development of questionnaires to quantify these "soft" constructs, such as symptoms, satisfaction, and QOL. Under the Classical Test Theory, a rigorous psychometric validation process is typically followed to create these questionnaires (more often termed *scales*, or *instruments*). These scales can then be administered to patients to produce a numeric score. The validation process is introduced herein; a more complete description can be found elsewhere.[57-59] The three major steps in the process are the establishment of *reliability*, *validity*, and *responsiveness*; in addition, increasing consideration is also given to *burden*.

- *Reliability*. A reliable scale reproduces the same result in precise fashion. For example, assuming there is no clinical change, a scale administered today and next week should produce the same result. This is called *test-retest reliability*. Other forms of reliability include *internal consistency* and *interobserver reliability*.[59,60]

- *Validity*. A valid scale measures what it is purported to measure. This concept is initially difficult to appreciate. Because these scales are designed to measure constructs that have not previously been measured, and because the constructs are difficult to define in the first place (what is QOL?), how does one determine what the scales are supposed to measure? The abbreviated answer is that the scales should behave in the hypothesized way. A simple example of an appropriate hypothesis is that a proposed cancer-specific QOL scale should correlate strongly with pain, tumor stage, and disfigurement, but less strongly with age and gender. For more complete discussion, several excellent references are listed.[57-61]

- *Responsiveness*. A responsive scale detects clinically important change.[62] For instance, a scale may distinguish a moderately hearing impaired individual from a deaf individual (the scale is "valid"), but can it detect a different score if the individual's hearing improves mildly after surgery? Alternatively, the minimum improvement in score that represents a clinically important change might be provided.[63,64]

- *Burden*. Burden refers to the time and energy that patients must spend to complete a scale, as well as the resources necessary for observers to score the questionnaire. A scale should not be an excessive encumbrance to a patient, caregiver, or provider using it.

More recently, item response theory (IRT) has been used to create and evaluate self-reported instruments. A full discussion of IRT is beyond the scope of this chapter. In brief, Item Response Theory uses mathematic models to draw conclusions based on the relationships between patient characteristics (latent traits) and patient responses to items on a questionnaire. A critical limitation is that IRT assumes that only one domain is measured by the scale. This may not fit assumptions for multidimensional QOL scales. However, if this assumption is valid, IRT-tested scales have several advantages. IRT allows for the contribution of each test item to be considered individually, thereby allowing the selection of a few test items that most precisely measure a continuum of a characteristic. In other words, because each test item is scaled to a different portion of the characteristic being tested, the number of questions can be reduced.[65-68] Therefore, IRT lends itself easily to adaptive computerized testing, allowing for significantly diminished testing time and reduced test burden.[65] In the future, IRT will likely be the basis to more and more new questionnaires evaluating outcomes, including QOL.

Categories of Outcomes

In informal use, the terms *health status*, *function*, and *quality of life* are frequently used interchangeably. However, these terms have important distinctions in the health services literature. *Health status* describes an individual's physical, emotional, and social capabilities and limitations, and *function* refers to how well an individual is able to perform important roles, tasks, or activities.[58] *QOL* differs because the central focus is on the *value* that individuals place on their health status and function.[58]

Because many aspects of QOL are unrelated to a patient's health status (income level, marital and family happiness), outcomes researchers typically focus on scales that measure only *health-related QOL* (HRQOL). HRQOL scales may be categorized as either *generic* or *disease-specific*. *Generic*, or general, scales are used for QOL assessment in a broad range of patients. The principal advantage of generic measures is that they facilitate comparison of results across different diseases (how does the QOL of a heart transplant patient compare to that of a cancer patient?). *Disease-specific* scales, on the other hand, are designed to assess specific patient populations. Because these scales can focus on a narrower range of topics, they tend to be more responsive to clinical change in the population under study. To benefit from the advantages of each type of scale, rigorous studies often use both a generic and a disease-specific scale to assess outcomes.

In addition to these measures, a number of other outcomes are increasingly popular. These include patient satisfaction, costs and charges,[47,48] health care utilization, and patient preferences (utilities,

willingness to pay).[47,69,70] Descriptions of these methods are referenced for completeness.

Examples of Outcomes Measures

As mentioned earlier, one of the principal contributions of outcomes research has been the development of scales to measure HRQOL and related outcomes. The following paragraphs briefly discuss several validated scales that are relevant to otolaryngology. Unless otherwise indicated, these scales are completed by the patient. The references contain details about validation data, and most also include a listing of sample questions and scoring instructions. The most widely used scales in each category are listed in Table 5-3.

Generic Scales

The best-known and most widely used outcomes instrument in the world is the Medical Outcomes Study Short Form-36, commonly called the *SF-36*.[71] This 36-item scale is designed for adults and surveys general health status. It produces scores in eight health constructs (e.g., vitality, bodily pain, limitations in physical activities), as well as two summary scores on overall physical and mental health status. Normative population scores are available, and the scale has been translated into numerous languages. Reference to instructions, numerous reference publications, and other related information can be found at the SF-36 website (www.sf36.com).

A variety of other popular, generic scales are also available. One health status measure is the Sickness Impact Profile.[72] The Quality of Well Being (QWB[73,74]) and the Health Utilities Index (HUI[75,76]) measure patient preferences, or utilities. The World Health Organization has developed a QOL scale (WHO-QOL[77]) as a measure of generic QOL as well as the International Classification of Functioning (ICF), Disability, and Health to evaluate a patient's functioning and disability.[78] The ICF has been used not only as an instrument itself but also as a standalone reference by which to evaluate other measures of QOL and functioning.[79,80]

Disease-Specific Scales

Head and Neck Cancer

In 2002, the NIH sponsored a conference to achieve consensus on the methods used to measure and report QOL of life assessment in head and neck cancer.[81] There was agreement that an adequate number of scales already exist to measure general QOL in head and neck cancer patients. The three most popular scales at this time are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35[82]), the University of Washington Quality of Life scale (UW-QOL[83-85]), and the Functional Assessment of Cancer Therapy Head and Neck module (FACT-HN[86]). Both the EORTC and FACT instruments offer additional modules that measure general cancer QOL in addition to the head and neck cancer specific modules, but are longer than the 12-item UW-QOL scale.

A clinician-rated scale (i.e., the clinician completes the scale, rather than the patient) that has achieved widespread use is the Performance Status Scale, a three-item instrument that correlates well with many of the aforementioned cancer scales.[87] A number of other excellent, validated patient-completed scales are also available, including the Head and Neck Quality of Life (HNQOL[88]) and the Head & Neck Survey (H&NS[89]), although these scales have not been used as widely. Several validated scales that focus on QOL of patients undergoing radiation are also in use.[90,91]

A few measures focus on symptom inventory and symptom distress directly related to head and neck cancer. These include the Head and Neck Distress Scale (HNDS)[92] and the M.D. Anderson Symptom Inventory, Head and Neck Module.[93]

Table 5-3

Outcomes Measures Relevant to Otolaryngology*

Disease Category		Examples
Generic	Health status Quality of life Utility	SF-36[71] WHO-QOL[77] QWB[73]
Head and neck cancer	General Radiation-specific Clinician-rated	UWQOL,[85] FACT,[86] EORTC,[82] HNQOL[88] QOL-RTI/H&N[90] PSS[87]
Otologic	General Conductive loss Amplification Dizziness Tinnitus Cochlear implants	HHIE[99] HSS[102] APHAB,[103] EAR[162] DHI[113] THI[114] Nimigen,[106] CAMP[107]
Rhinologic	Nasal obstruction Chronic sinusitis Rhinitis	NOSE[124] SNOT-20,[115] CSS,[116] RhinoQOL[123] mRQLQ,[120] ROQ[121]
Pediatric	Tonsillectomy Otitis media Sleep apnea	TAHSI[135] OM-6[131] OSD-6,[133] OSA-18[132]
Other/symptoms	Adult sleep apnea Swallowing Voice Cosmetic	FOSQ,[150] SAQLI[151] MDADI,[158] SWAL-QOL[159] VHI,[139] VOS,[140] VRQOL[146] ROE, BOE[161]

*Refer to text for additional scales.

Several new instruments have been developed as disease-specific measures within the field of head and neck cancer. For example, to assess the impact of cutaneous malignancy on QOL, the Skin Cancer Index has been validated and found to be sensitive and responsive,[94,95] and the Patient Outcomes of Surgery—Head/Neck (POS-Head/Neck) has newly been developed to assess surgical outcomes in cutaneous malignancy.[96] In addition, an instrument has recently been developed to assess QOL after treatment of anterior skull base lesions.[97] A questionnaire has also been developed to evaluate outcomes directly related to the use of voice prostheses after total laryngectomy.[98]

Otologic Disease

The most widely used validated measure to quantify hearing-related QOL is the Hearing Handicap Inventory in the Elderly (HHIE), a 25-item scale with two subscales that measure the emotional and social impact of hearing loss.[99,100] The minimum change in score that corresponds to a clinically important difference has been established.[101] However, the scale does not distinguish between conductive or sensorineural loss. The Hearing Satisfaction Scale (HHS) is specifically designed to measure outcomes after treatment for conductive hearing loss. It therefore addresses side effects or complications of treatment, and is brief (15 items).[102]

Numerous validated measures exist to assess outcomes after hearing amplification. One popular scale is the Abbreviated Profile of Hearing Aid Benefit (APHAB).[103] This 24-item scale measures four aspects of communication ability. Values corresponding to minimally clinically important clinical change have also been established.[104] The Effectiveness of Auditory Rehabilitation (EAR) scale addresses comfort and cosmesis issues associated with hearing aids that are overlooked in many hearing aid scales. There are two brief 10-item modules: the Inner EAR addresses intrinsic issues of hearing loss such as functional, physical, emotional, and social impairment. The Outer EAR covers extrinsic factors such as the comfort, convenience, and cosmetic appearance.[105]

Effects of cochlear implantation on HRQOL have also recently begun to be measured. The Nimegen Cochlear Implant Questionnaire has been used for this purpose,[106] and the University of Washington Clinical Assessment of Musical Perception (CAMP) has been developed to assess perception of music in cochlear implant recipients.[107]

Individuals interested in pursuing research on hearing amplification should also be aware of a number of other validated scales; only a partial listing is referenced here.[108-112] In addition to these scales, there are several excellent, validated scales that assess other aspects of otologic disease including dizziness[113] and tinnitus.[114]

Rhinologic Disease

The ability to assess outcomes in chronic rhinosinusitis has dramatically improved with the development of disease-specific scales. The two most widely used scales are the Sinonasal Outcome Test (SNOT-20[115]) and the Chronic Sinusitis Survey (CSS[116]). The SNOT-20 has 20 items, has been extensively validated, and is a shortened version of the 31 item Rhinosinusitis Outcome Measure.[117] It is responsive to clinical change and has established scores that reflect minimally clinically important differences. The CSS is a shorter scale consisting of two components. The severity-based component has four items, and the duration-based component asks about duration of both symptoms and medication use. In addition to the SNOT and CSS, there are also a number of other excellent validated sinusitis scales.[118,119] Some of these scales focus on rhinitis specifically, including the Mini Rhinoconjunctivitis QOL Questionnaire,[120] the Rhinitis Outcome Questionnaire[121] and the Nocturnal Rhinoconjunctivitis Questionnaire,[122] whereas others focus on rhinosinusitis specifically. The Rhinosinusitis Quality of Life survey (RhinoQOL) has been validated for both acute and chronic sinusitis.[123] Additional new rhinologic scales continue to be developed.

In 2003, the American Academy of Otolaryngology-Head and Neck Surgery Foundation commissioned the National Center for the Promotion of Research in Otolaryngology (NC-PRO) to develop and validate a disease-specific instrument for patients with nasal obstruction for a national outcomes study. The Nasal Obstruction Symptom Evaluation (NOSE) scale is a five-item instrument that is valid, reliable, and responsive.[124]

Pediatric Diseases

An important difference between measuring outcomes in adults and children is that younger children may be unable to complete the scales by themselves. In these cases, the instruments need to be completed by proxy, typically a parent or other caregiver. This difference in perspective should be kept in mind when interpreting the results of pediatric studies. A good generic scale, similar to the SF-36 in adults, is the Child Health Questionnaire (CHQ[125]). This is also a widely used instrument that has been extensively validated and translated into numerous languages. It is a health status measure designed for children 5 years of age and older, and can be completed directly by children 10 and older. Other generic QOL assessments for children include the Pediatric Quality of Life Inventory (PedsQL) and the Child Health and Illness Profile—Child Edition (CHIP-CE).[126,127] The Glasgow Children's Benefit Inventory is a validated measure that evaluates the benefit a child receives from an intervention and is a general measure that was developed with otolaryngologic disease in mind.[128] The Caregiver Impact Questionnaire has been used to evaluate the impact of disease on the child's caregivers.[129,130]

There are a number of excellent, validated disease-specific scales for children. A number of instruments have been developed to assess the impact of otitis media. The most widely used OM-6 is a brief, six-item scale useful for the evaluation of otitis media–related QOL in children.[131] It has been shown to be reliable, valid, and responsive, and has been widely adopted. Two scales are pertinent to children with obstructive sleep disorders, the OSA-18,[132] which has been found to be valid, reliable, and responsive, and the OSD-6.[133,134] A scale has also recently been developed for studying tonsil and adenoid health in children.[135] Voice-related QOL has also been evaluated in children via the Pediatric Voice Outcomes Survey and the Pediatric Voice-Related Quality-of-Life survey (PVQOL).[136-138]

Voice

Several instruments have been developed to assess outcomes in voice.[139,140] The Voice Handicap Index is one of the most widely used instruments and has been well studied. It evaluates the psychosocial impact of dysphonia and has been validated by both Classical Test Theory[108,141] and Item Response Theory.[142] The Voice Symptom Scale (VoiSS),[143,144] the Vocal Performance Questionnaire, and the Voice Related Quality of Life Instrument have all also been well studied and well used.[145,146] These instruments provide independent useful data that complement clinician performed perceptual evaluation.[147,148] In addition, the Singing Voice Handicap Index has been created and found to be valid and reliable for assessing vocal problems specific to singers.[149]

Sleep

Several validated scales are in use to assess HRQOL in adults with obstructive sleep apnea. The most widely used are the 30-item Functional Outcomes of Sleep Questionnaire (FOSQ[150]) and the 50-item Calgary Sleep Apnea Quality of Life Index (SAQLI[151,152]). In addition, the Quebec Sleep Questionnaire (QSQ) was recently validated as an additional OSA instrument.[153] Clinicians interested in a more brief instrument may wish to consider the Symptoms of Nocturnal Obstruction and Respiratory Events (SNORE-25[154]). The eight-item Epworth Sleepiness Scale (ESS) is commonly used to assess the degree of daytime sleepiness,[155] Although perhaps one of the most useful tools available, a recent study found that it was not clinically reproducible,[156] and a number of studies have shown wide variability in correlation between the ESS and objective measures of sleep apnea severity. Because sleepiness and fatigue can be difficult to differentiate on QOL instruments and in clinical practice, recently the Empirical Sleepiness and Fatigue Scales were created (utilizing a number of items from the ESS). These scales were found to have internal consistency and good test-retest reliability and will likely aid in the evaluation of patients with OSA who are more likely to endorse sleepiness variables.[157]

Symptom Scales

Two scales specific to swallowing are available. The M.D. Anderson Dysphagia Inventory (MDADI[158]) is a brief, 20-item scale intended to

measure dysphagia in head and neck cancer patients. The SWAL-QOL is longer (44 items), but validated for use in a more general population.[159] An instrument known as the Quality of Life in Reflux and Dyspepsia (QOLRAD) has also been developed which assesses QOL in patients with laryngopharyngeal reflux.[160] Finally, several instruments have been developed to assess outcomes in facial plastic surgery.[161]

Summary and Future Directions

Outcomes research is the scientific analysis of treatment effectiveness. In the past 2 decades, it has contributed substantially to the national debate on health resource allocation. Outcomes research provides insight into the value of otolaryngology treatments and methods for quantifying important outcomes that were previously too "soft" to measure. Better appreciation for outcomes research will improve the level of evidence about important treatments and operations.

The impact of outcomes research is beginning to extend into deliberations about quality of care as the health care system moves to establish standards for patient safety. The Leapfrog Group, a coalition of the largest public and private organizations that provide health care benefits for its employees, uses its collective purchasing power to ensure that its employees have access to, and more informed choices about, quality health care. Policy makers will increasingly look to outcomes research for insight into how to measure quality and safety, in addition to effectiveness.

It is imperative that clinicians be familiar with these basic principles. Otolaryngologists should participate in local and national outcomes research efforts to improve the evidence supporting successful otolaryngology interventions and to provide informed physician perspective in a health care environment that is increasingly driven by third-party participants.

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CHAPTER SIX

Interpreting Medical Data

Richard M. Rosenfeld

Key Points

- Learning how to interpret medical data will make you a better clinician, researcher, and teacher.
- Interpreting data begins by assessing the investigation that produced it; low-quality, biased data are of limited value, regardless of how appealing the results may seem.
- The presence or absence of a *control group* has a profound influence on data interpretation. An uncontrolled study is purely descriptive and cannot assess effectiveness or efficacy.
- Statistical tests often make assumptions about the underlying data. Unless these assumptions are met, the test is invalid.
- Uncertainty is present in all data, because of the inherent variability in biologic systems and in our ability to assess them in a reproducible fashion. Results should be reported with 95% confidence intervals, which incorporate uncertainty by providing a range of values considered plausible for the population.
- All statistical tests measure error. The *P* value is the likelihood of a type I error (false-positive conclusion), which occurs if a true null hypothesis is mistakenly rejected. Conversely, a type II error (false-negative conclusion) occurs when a real difference is missed, and is related to statistical power and sample size.
- A study has internal validity when the data are analyzed and interpreted properly, but external validity (generalizability) requires that the study sample be representative of the larger population to which it is intended to apply.
- Confidence and common sense are needed to balance statistical significance with clinical importance.
- A single study is rarely definitive. Science is a cumulative process that requires a large body of consistent and reproducible evidence before conclusions can be formed.
- Effective data interpretation facilitates moving from observations to generalizations with predictable degrees of certainty and uncertainty.

In every chapter of this text, whether it relates to clinical medicine or basic science, the authors draw on their own experience and the experience of others to form systematic conclusions. Experience yields data, and interpreting data is the heart and soul of the cumulative process called science. Learning how to interpret medical data will make you a better clinician, researcher, and teacher.

Effective data interpretation is a habit: a combination of knowledge, skill, and desire.[1] By applying the seven habits (Table 6-1) outlined in this chapter, any otolaryngologist—regardless of his or her level of statistical knowledge or lack thereof—can interpret data. The numerous tables that accompany the text are designed as stand-alone reminders, and often contain keywords with definitions endorsed by the International Epidemiological Association.[2]

This chapter also discusses the practice of data interpretation, including specific hypothesis tests, sample size determination, and common statistical deceptions encountered in the otolaryngology literature. You do not have to be a numerical wizard to understand data; all you need are patience, persistence, and a few good habits that will help settle the dust following the clash of statistics with the human mind.

The Seven Habits of Highly Effective Data Users

The seven habits that follow are the key to understanding data.[3] They embody fundamental principles of epidemiology and biostatistics that are developed in a logical and sequential fashion. Table 6-1 gives an overview of the seven habits, as well as the corresponding principles and keywords that comprise them.

Habit 1: Check Quality Before Quantity

Bias is a four-letter word that is easy to ignore but difficult to avoid.[4] Data collected specifically for research (Table 6-2) are likely to be unbiased—they reflect the true value of the attribute being measured. In contrast, data collected during routine clinical care will vary in quality depending on the specific methodology applied.

Experimental studies, such as randomized trials, often yield high-quality data because they are performed under carefully controlled conditions. In *observational* studies, however, the investigator is simply a bystander who records the natural course of health events during clinical care. Although more reflective of "real life" than a contrived experiment, observational studies are more prone to bias. Comparing randomized trials with outcomes studies highlights the difference between experimental and observational research (Table 6-3).

The presence or absence of a *control group* has a profound influence on data interpretation. An uncontrolled study, no matter how elegant, is purely descriptive.[5] Nonetheless, authors of case series often delight in unjustified musings on efficacy, effectiveness, association, and causality. A case series is of greatest value when dealing with uncommon disorders or interventions, or with circumstances in which randomized trials would be unethical or impractical. The best case series include a consecutive sample of subjects, describe the sample fully, include details

Table 6-1

The Seven Habits of Highly Effective Data Users

Habit	Underlying Principles	Keywords
1. Check quality before quantity.	All data are not created equal; fancy statistics cannot salvage biased data from a poorly designed and executed study.	Bias, accuracy, research design, confounding, causality
2. Describe before you analyze.	Special data require special tests; improper analysis of small samples or data with an asymmetric distribution gives deceptive results.	Measurement scale, frequency distribution, descriptive statistics
3. Accept the uncertainty of all data.	All observations have some degree of random error; interpretation requires estimating the associated level of precision or confidence.	Precision, random error, confidence intervals
4. Measure error with the right statistical test.	Uncertainty in observation implies certainty of error; positive results must be qualified by the chance of being wrong; negative results by the chance of having missed a true difference	Statistical test, type I error, *P* value, type II error, power
5. Put clinical importance before statistical significance.	Statistical tests measure error, not importance; an appropriate measure of clinical importance must be checked.	Effect size, statistical significance, clinical importance
6. Seek the sample source.	Results from one data set do not necessarily apply to another; findings can be generalized only for a random and representative sample.	Population, sample, selection criteria, external validity
7. View science as a cumulative process.	A single study is rarely definitive; data must be interpreted relative to past efforts, and by their implications for future efforts.	Research integration, level of evidence, meta-analysis

Table 6-2

Effect of Study Design on Data Interpretation

Aspect of Study Design	Effect on Data Interpretation
How were the data originally collected?	
Specifically for research	Interpretation facilitated by quality data collected according to an a priori protocol
During routine clinical care	Interpretation limited by consistency, accuracy, availability, and completeness of the source records
Is the study experimental or observational?	
Experimental study with conditions under direct control of the investigator	Low potential for systematic error (bias); bias can be reduced further by randomization and masking (blinding)
Observational study without intervention other than to record, classify, analyze	High potential for bias in sample selection, treatment assignment, measurement of exposures, and outcomes
Is there a comparison or control group?	
Comparative or controlled study with two or more groups	Permits analytic statements concerning efficacy, effectiveness, and association
No comparison group present	Permits descriptive statements only, because of improvements from natural history and placebo effect
What is the direction of study inquiry?	
Subjects identified before an outcome or disease; future events recorded	Prospective design measures incidence (new events) and causality (if comparison group included)
Subjects identified after an outcome or disease; past histories examined	Retrospective design measures prevalence (existing events) and causality (if comparison group included)
Subjects identified at a single time point, regardless of outcome or disease	Cross-sectional design measures prevalence (existing events) and association (if comparison group included)

Table 6-3

Comparison of Randomized Controlled Trials and Outcomes Studies

Characteristic	Randomized Controlled Trial	Outcomes Study
Level of investigator control	Experimental	Observational
Treatment allocation	Random assignment	Routine clinical care
Patient selection criteria	Restrictive	Broad
Typical setting	Hospital or university based	Community based
End point definitions	Objective health status	Subjective quality of life
End point assessment	Masked (blinded)	Unmasked
Statistical analysis	Comparison of groups	Multivariate regression
Potential for bias	Low	Very high
Generalizability	Potentially low	Potentially high

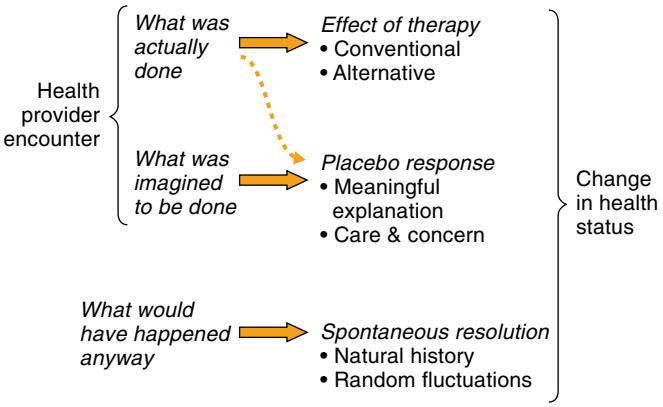

Figure 6-1. Model depicting change in health status after a healing encounter. Dashed arrow shows that a placebo response may occur from symbolic significance of the specific therapy given or from interpersonal aspects of the encounter.

of interventions and adjunctive treatments, account for all participants enrolled (including withdrawals and dropouts), and ensure that follow-up duration is adequate to overcome random disease fluctuations.[6]

Without a control or comparison group, treatment effects cannot be distinguished from other causes of clinical change (Table 6-4). Some of these causes are seen in Figure 6-1, which depicts change in health status after a healing encounter as a complex interaction of three primary factors[7-8]:

1. *What was actually done*. Specific effects of therapy, including medications, surgery, physical manipulations, and alternative or integrative approaches.

2. *What was imagined to be done*. Placebo response, defined as a change in health status resulting from the symbolic significance attributed by the patient (or proxy) to the encounter itself. A placebo response is most likely to occur when the patient receives a meaningful and personalized explanation, feels care and concern expressed by the healer, and achieves control and mastery over the illness (or believes that the healer can control the illness).[9]

3. *What would have happened anyway*. Spontaneous resolution, including natural history, random fluctuations in disease status, and regression to a mean symptom state.

The placebo response differs from the traditional definition of placebo as an inactive medical substance. Whereas a placebo can elicit a placebo response, the latter can occur without the former. A placebo response results from the psychological or symbolic importance attributed by the patient to any nonspecific event in a healing environment. These events include touch, words, gestures, local ambience, and social interactions.[10] Many of these factors are encompassed in the term *caring effects*,[11] which have been central to medical practice in all cultures throughout history. Caring and placebo effects are so important that they have been deliberately used to achieve positive outcomes in clinical practice.[12]

When data from a comparison or control group are available, inferential statistics may be used to test hypotheses and measure associations. Causality may also be assessed when the study has a time span component, either retrospective or prospective (see Table 6-2). Prospective studies measure *incidence* (new events) whereas retrospective studies measure *prevalence* (existing events). Unlike time span studies, cross-sectional inquiries measure association not causality. Examples include surveys, screening programs, and evaluation of diagnostic tests. Experimentally planned interventions are ideal for assessing cause-effect relationships, because observational studies are prone to innate distortions or biases caused by individual judgments and other selective decisions.[13]

Another clue to data quality is study type,[14] but this cannot replace the four questions in Table 6-2. Note the variability in data quality for the study types listed in Table 6-5, particularly the observational designs. Randomization balances baseline prognostic factors (known and unknown) among groups, including severity of illness and the presence of comorbid conditions. Because these factors also influence a clinician's decision to offer treatment, nonrandomized studies are prone to allocation (susceptibility) bias (see Table 6-3) and false-positive results.[15] For example, when the survival of surgically treated cancer patients is compared with the survival of nonsurgical controls (e.g., radiation or chemotherapy), without randomization, the surgical group will generally have a more favorable prognosis independent of therapy, because the customary criteria for operability (special anatomic conditions and no major comorbidity) also predispose to favorable results.

The relationship between data quality and interpretation is illustrated in Table 6-6 using hypothetical studies to determine whether tonsillectomy causes baldness. Note how a case series (examples 1 and

Table 6-4

Explanations Other Than "Efficacy" for Outcomes in Treatment Studies

Explanation	Definition	Solution
Bias	Systematic variation of measurements from their true values; may be intentional or unintentional	Accurate, protocol-driven data collection
Chance	Random variation without apparent relation to other measurements or variables; example: luck	Control or comparison group
Natural history	Course of a disease from onset to resolution; may include relapse, remission, and spontaneous recovery	Control or comparison group
Regression to the mean	Symptom improvement independent of therapy as sick patients return to a mean level after seeking care	Control or comparison group
Placebo effect	Beneficial effect caused by the expectation that the regimen will have an effect; example: power of suggestion	Control or comparison group with placebo
Halo effect	Beneficial effect caused by treatment novelty or by the provider's manner, attention, and caring	Control or comparison group treated similarly
Hawthorne effect	Beneficial effect caused by the participant's knowledge of being evaluated and observed in a study	Control or comparison group treated similarly
Confounding	Distortion of an effect by other prognostic factors or variables for which adjustments have not been made	Randomization or multivariate analysis
Allocation (susceptibility) bias	Beneficial effect caused by allocating subjects with less severe disease or better prognosis to treatment group	Randomization or comorbidity analysis
Ascertainment (detection) bias	Favoring the treatment group during outcome analysis; example: rounding up for treated subjects, down for controls	Masked (blinded) outcome assessment

Table 6-5

Relationship of Study Type to Study Methodology

Study Type	How Were the Data Originally Collected?	Is There a Control or Comparison Group?	What Is the Direction of Study Inquiry?
Experimental Studies			
Basic science study	Research	Yes or no	Prospective or cross-sectional
Clinical trial	Research	Yes or no	Prospective or cross-sectional
Randomized trial	Research	Yes	Prospective
Observational Studies			
Cohort study	Clinical care or research	Yes or no	Prospective
Historical cohort study	Clinical care	Yes	Prospective
Outcomes research	Clinical care or research	Yes or no	Prospective
Case-control study	Clinical care	Yes	Retrospective
Case series	Clinical care	Yes or no	Retrospective or prospective
Survey study	Clinical care or research	Yes or no	Cross-sectional
Diagnostic test study	Clinical care or research	Yes or no	Cross-sectional

2) can have either a prospective or retrospective direction of inquiry depending on how subjects are identified; contrary to common usage, all cases series are not "retrospective reviews." Only the controlled studies (examples 3 through 7) can measure associations, and only the controlled studies with a time span component (examples 4 through 7) can assess causality. The nonrandomized studies (examples 3 through 6), however, require adjustment for potential confounding variables—baseline prognostic factors that may be associated with both tonsillectomy and baldness and therefore influence results. As noted previously, adequate randomization ensures balanced allocation of prognostic factors among groups, thereby avoiding the issue of confounding.

Habit 2: Describe Before You Analyze

Statistical tests often make assumptions about the underlying data. Unless these assumptions are met, the test will be invalid. Describing

Table 6-6

Determining If Tonsillectomy Causes Baldness: Study Design vs. Interpretation

Study Design*	Study Execution	Interpretation
1. Case series, retrospective	A group of bald subjects are questioned as to whether or not they ever had tonsillectomy.	Measures prevalence of tonsillectomy in bald subjects; cannot assess association or causality
2. Case series, prospective	A group of subjects who had or who are about to have tonsillectomy are examined later for baldness.	Measures incidence of baldness after tonsillectomy; cannot assess association or causality
3. Cross-sectional study	A group of subjects are examined for baldness and for presence or absence of tonsils at the same time.	Measures prevalence of baldness and tonsillectomy and their association; cannot assess causality
4. Case-control study	A group of bald subjects and a group of nonbald subjects are questioned about prior tonsillectomy.	Measures prevalence of baldness and association with tonsillectomy; limited ability to assess causality
5. Historical cohort study	A group of subjects who had prior tonsillectomy and a comparison group with intact tonsils are examined later for baldness.	Measures incidence of baldness and association with tonsillectomy; can assess causality when adjusted for confounding variables
6. Cohort study (longitudinal)	A group of nonbald subjects about to have tonsillectomy and a nonbald comparison group with intact tonsils are examined later for baldness.	Measures incidence of baldness and association with tonsillectomy; can assess causality when adjusted for confounding variables
7. Randomized controlled trial	A group of nonbald subjects with intact tonsils are randomly assigned to tonsillectomy or observation and examined later for baldness.	Measures incidence of baldness and association with tonsillectomy; can assess causality despite baseline confounding variables

*Studies are listed in order of increasing ability to establish causal relationship.

Table 6-7

Measurement Scales for Describing and Analyzing Data

Scale	Definition	Examples
Dichotomous	Classification into either of two mutually exclusive categories	Breastfeeding (yes/no), sex (male/female)
Nominal	Classification into unordered qualitative categories	Race, religion, country of origin
Ordinal	Classification into ordered qualitative categories, but with no natural (numerical) distance between their possible values	Hearing loss (none, mild, moderate), patient satisfaction (low, medium, high), age group
Numerical	Measurements with a continuous scale, or a large number of discrete ordered values	Temperature, age in years, hearing level in decibels
Numerical (censored)	Measurements on subjects lost to follow-up, or in whom a specified event has not yet occurred at the end of a study	Survival rate, recurrence rate, or any time-to-event outcome in a prospective study

before you analyze avoids trying to unlock the mysteries of square data with a round key.

Describing data begins by defining the *measurement scale* that best suits the observations. Categorical (qualitative) observations fall into one or more categories and include dichotomous, nominal, and ordinal scales (Table 6-7). Numerical (quantitative) observations are measured on a continuous scale and are further classified by the underlying *frequency distribution* (plot of observed values vs. the frequency of each value). Numerical data with a symmetric (normal) distribution are symmetrically placed around a central crest or trough (bell-shaped curve). Numerical data with an asymmetric distribution are skewed (shifted) to one side of the center, have a sloping "exponential" shape that resembles a forward or backward J, or contain some unusually high or low outlier values.

Depending on the measurement scale, data may be summarized using one or more of the descriptive statistics in Table 6-8. Note that when summarizing numerical data, the descriptive method varies according to the underlying distribution. Numerical data with a symmetric distribution are best summarized with the mean and standard deviation (SD), because 68% of the observations fall within the mean ± 1 SD and 95% fall within the mean ± 2 SD. In contrast, asymmetric numerical data are best summarized with the median, because even a single outlier can strongly influence the mean. If a series of five patients are followed after sinus surgery for 10, 12, 15, 16, and 48 months, the mean duration of follow-up is 20 months, but the median is only 15 months. In this case a single outlier, 48 months, distorts the mean.

Although the mean is appropriate only for numerical data with a symmetric distribution, it is often applied regardless of the underlying

Table 6-8

Descriptive Statistics

Descriptive Measure	Definition	When to Use It
Central Tendency		
Mean	Arithmetic average	Numerical data that are symmetric
Median	Middle observation; half the values are smaller and half are larger	Ordinal data; numerical data with an asymmetric distribution
Mode	Most frequent value	Nominal data; bimodal distribution
Dispersion		
Range	Largest value minus smallest value	Emphasizes extreme values
Standard deviation	Spread of data about their mean	Numerical data that are symmetric
Percentile	Percentage of values that are equal to or below that number	Ordinal data; numerical data with an asymmetric distribution
Interquartile range	Difference between the 25th percentile and 75th percentile	Ordinal data; numerical data with an asymmetric distribution
Outcome		
Survival rate	Proportion of subjects surviving, or with some other outcome, after a time interval (e.g., 1 year, 5 years)	Numerical (censored) data in a prospective study
Odds ratio	Odds of a disease or outcome in subjects with a risk factor divided by odds in controls	Dichotomous data in a retrospective or prospective controlled study
Relative risk	Incidence of a disease or outcome in subjects with a risk factor divided by incidence in controls	Dichotomous data in a prospective controlled study
Rate difference*	Event rate in treatment group minus event rate in control group	Compares success or failure rates in clinical trial groups
Correlation coefficient	Degree to which two variables have a linear relationship	Numerical or ordinal data

*Also called the absolute risk reduction.

symmetry. An easy way to determine whether the mean or median is appropriate for numerical data is to calculate both; if they differ significantly, the median should be used. Another way is to examine the SD; when it is very large (e.g., larger than the mean value with which it is associated), the data often have an asymmetric distribution and should be described by the median and interquartile range. When in doubt, the median should always be used over the mean.[16]

A special form of numerical data is called *censored* (see Table 6-7). Data are censored when three conditions apply: (1) the direction of study inquiry is prospective, (2) the outcome of interest is time-related, and (3) some subjects die, are lost, or have not yet had the outcome of interest when the study ends. Interpreting censored data is called *survival analysis*, because of its use in cancer studies where survival is the outcome of interest. Survival analysis permits full use of censored observations by including them in the analysis up to the time the censoring occurred. If censored observations are instead excluded from analysis (e.g., exclude all patients with less than 3 years of follow-up in a cancer study), the resulting survival rates will be biased and sample size will be unnecessarily reduced.

A *survival curve* starts with 100% of the study sample alive and shows the percentage still surviving at successive times for as long as information is available. The curve may be applied not only to survival as such, but also to the persistence of freedom from a disease or complication or some other end point. For example, one could estimate the 3-year, 5-year, or 10-year rates for cholesteatoma recurrence or the future "survival" of tonsils (e.g., no need for tonsillectomy) in a cohort of children after adenoidectomy alone. Several statistical methods are available for analyzing survival data. The Kaplan-Meier (product-limit) method records events by exact dates and is suitable for small and large samples. Conversely, the life table (actuarial) method records events by time interval (e.g., every month, every year) and is most commonly used for large samples in epidemiologic studies.

The odds ratio, relative risk, and rate difference (see Table 6-7) are useful ways of comparing two groups of dichotomous data.[17] A retrospective (case-control) study of tonsillectomy and baldness might report an *odds ratio* of 1.6, indicating that bald subjects were 1.6 times more likely to have had tonsillectomy than were nonbald controls. In contrast, a prospective study would report results using *relative risk*. A relative risk of 1.6 means that baldness was 1.6 times more likely to develop in tonsillectomy subjects than in nonsurgical controls. Finally, a *rate difference* of 30% in a prospective trial or experiment reflects the increase in baldness caused by tonsillectomy, above and beyond what occurred in controls. No association exists between groups when the rate difference equals zero, or the odds ratio or relative risk equals one (unity).

Two groups of ordinal or numerical data are compared with a *correlation coefficient* (see Table 6-8). A coefficient (r) from 0 to 0.25 indicates little or no relationship, from 0.25 to 0.49 a fair relationship, from 0.50 to 0.74 a moderate to good relationship, and greater than 0.75 a good to excellent relationship. A perfect linear relationship would yield a coefficient of 1.00. When one variable varies directly with the other, the coefficient is positive; a negative coefficient implies an inverse association. Sometimes the correlation coefficient is squared (r^2) to form the *coefficient of determination*, which estimates the percentage of variability in one measure that is predicted by the other.

Habit 3: Accept the Uncertainty of All Data

Uncertainty is present in all data, because of the inherent variability in biologic systems and in our ability to assess them in a reproducible fashion.[18] If hearing in 20 healthy volunteers was measured on five different days, how likely would it be to get the same mean result each time? It is very unlikely, because audiometry has a variable behavioral component that depends on the subject's response to a stimulus and the examiner's perception of that response. Similarly, if hearing was measured in five groups of 20 healthy volunteers each, how likely would it be to get the same mean hearing level in each group? Again unlikely, because of variations between individuals. A range of similar results would be obtained, but rarely the exact same result on repetitive trials.

Uncertainty must be dealt with when interpreting data, unless the results are meant to apply only to the particular group of patients, animals, cell cultures, and DNA strands, in which the observations were initially made. Recognizing this uncertainty, each of the descriptive measures in Table 6-8 is called a *point estimate*, specific to the data that generated it. In medicine, however, one seeks to pass from observations to generalizations, from point estimates to estimates about other populations. When this process occurs with calculated degrees of uncertainty, it is called *inference*.

The following is a brief example of clinical inference. After treating five vertiginous patients with vitamin C, you remark to a colleague that four had excellent relief of their vertigo. She asks, "How confident are you of your results?"

"Quite confident," you reply. "There were five patients, four got better, and that's 80%."

"Maybe I wasn't clear," she interjects, "how confident are you that 80% of vertiginous patients you see in the next few weeks will respond favorably, or that 80% of similar patients in my practice will do well with vitamin C? In other words, can you *infer* anything about the real effect of vitamin C on vertigo from only five patients?"

Hesitatingly you retort, "I'm pretty confident about that number 80%, but maybe I'll have to see a few more patients to be sure."

The real issue, of course, is that a sample of only five patients offers low *precision* (repeatability). How likely is it that the same results would be found if five new patients were studied? Actually, one can state with 95% confidence that four out of five successes in a single trial is consistent with a range of results from 28% to 99% in future trials. This *95% confidence interval* may be calculated manually or with a statistical program; it reveals the range values considered plausible for the population. A point estimate summarizes findings for the sample, but extrapolation to the large population introduces error and uncertainty, which makes a range of plausible values more appropriate.

Precision may be increased (uncertainty may be decreased) by using a more reproducible measure, by increasing the number of observations (sample size), or by decreasing the variability among the observations. The most common method is to increase the sample size, because the variability inherent in the subjects studied can rarely be reduced. Even a huge sample of perhaps 50,000 subjects still has some degree of uncertainty, but the 95% confidence interval will be quite small. Realizing that uncertainty can never completely be avoided, statistics are used to estimate precision. Thus when data are described using the summary measures listed in Table 6-8, a corresponding 95% confidence interval should accompany each point estimate.

Precision differs from accuracy. *Precision* relates to random error and measures repeatability; *accuracy* relates to systematic error (bias) and measures nearness to the truth. A precise otologist may always perform a superb mastoidectomy, but an accurate otologist performs it on the right patient. A precise surgeon cuts on the exact center of the line, but an accurate surgeon first checks the line to be sure it is in the right place. Succinctly put, precision is doing things right and accuracy is doing the right thing. Precise data include a large enough sample of carefully measured observations to yield repeatable estimates; accurate data are measured in an unbiased manner and reflect what is truly purported to be measured. When we interpret data, we must estimate both precision and accuracy.

To summarize habits 1, 2, and 3: "Check quality before quantity" determines whether or not the data are worth interpreting (habit 1). Assuming they are, "describe before you analyze" and summarize the data using appropriate measures of central tendency, dispersion, and outcome for the particular measurement scales involved (habit 2). Next, "accept the uncertainty of all data" as noted in habit 3, and qualify the point estimates in habit 2 with 95% confidence intervals to measure precision. When precision is low (e.g., the confidence interval is wide), proceed with caution. Otherwise, proceed with habits 4, 5, and 6, which deal with errors and inference.

Habit 4: Measure Error with the Right Statistical Test

To err is human—and statistical. When comparing two or more groups of uncertain data, errors in inference are inevitable. If one concludes that the groups are different, they may actually be equivalent. If one concludes that they are the same, a true difference may have been missed. Data interpretation is an exercise in modesty, not pretense—any conclusion we reach may be wrong. The ignorant data analyst ignores the possibility of error; the savvy analyst estimates this possibility by using the right statistical test.[19]

Now that we've stated the problem in English, let's restate it in thoroughly confusing statistical jargon (Table 6-9). We begin with some testable *hypotheses* about the groups we are studying, such as "Gibberish levels in group A differ from those in group B." Rather than keep it simple, we now invert this to form a *null hypothesis*: "Gibberish levels in group A are equal to those in group B." Next we fire up our personal computer, enter the gibberish levels for the subjects in both groups, choose an appropriate statistical test, and wait for the omnipotent *P* value to emerge.

The *P value* gives the probability of making a *type I error*: rejecting a true null hypothesis. In other words, if $P = .10$, there is a 10% chance of being wrong when we declare that group A differs from group B based on the observed data. Alternatively, there is a 10% probability that the difference in gibberish levels is explainable by random error—we cannot be certain that uncertainty is not the cause. In medicine, $P < .05$ is generally considered low enough to safely reject the null hypothesis. Conversely, when $P > .05$, the null hypothesis of equivalent gibberish levels is accepted. Nonetheless, one might be making a *type II error* by accepting a false null hypothesis. Rather than state the probability of a type II error directly, it is stated indirectly by specifying *power* (see Table 6-9).

Moving from principles to practice, two hypothetical studies are presented. The first is an observational, prospective study to determine whether tonsillectomy causes baldness: 20 patients undergoing tonsillectomy and 20 controls are examined 40 years later and the incidence of baldness is compared. The second study will use the same groups, but will determine whether tonsillectomy causes hearing loss. This allows one to explore statistical error from the perspective of a dichotomous outcome (bald vs. nonbald) and a numerical outcome (hearing level in decibels).

Suppose that baldness develops in 80% of tonsillectomy patients (16/20) but in only 50% of controls (10/20). If one infers that, based on these results in 40 specific patients, tonsillectomy predisposes to baldness *in general*, what is the probability of being wrong (type I error)? Because $P = .10$ (Fisher's exact test), there is a 10% chance of type I error, so one is reluctant to associate tonsillectomy with baldness based on this single study. Intuitively, however, a rate difference of 30% seems like a big difference, so what is the chance of being wrong when one concludes it is not significant (type II error)? The probability of a type II error (false-negative result) is actually 48% (same as saying 52% power), which means one may indeed be wrong in accepting the null hypothesis. Therefore, a larger study is needed before any definitive conclusions can be drawn.

Intrigued by the initial findings, one repeats the tonsillectomy study with twice as many patients in each group. Suppose that baldness again develops in 80% of tonsillectomy patients (32/40), but only 50% of controls (20/40). The rate difference is still 30%, but now $P = .01$ (Fisher's exact test). The conclusion is that tonsillectomy is associated with baldness, with only a 1% chance of making a type I error (false-positive result). By increasing the number of subjects studied, the precision is increased to a level where one could move from observation to generalization with a tolerable level of uncertainty.

Returning to the earlier study of 20 tonsillectomy patients and 20 controls, the hearing levels for the groups are 25 ± 9 decibels (dB) and 20 ± 9 dB, respectively (mean value ± SD). What is the chance of being wrong if one infers that post-tonsillectomy patients have hearing levels 5 dB lower than controls? Because $P = .09$ (*t*-test), there is a 9% probability of a type I error. If, however, one concludes there is no true difference between the groups, there is a 58% chance of making a type II error. Thus, there is little to say about the impact of tonsillectomy on hearing based on this study, because power is only 42%. In general, studies with "negative" findings should be interpreted by power, not *P* values.

When making inferences about numerical data, precision may be increased by studying more subjects or subjects with less variability in

Table 6-9

Glossary of Statistical Terms Encountered When Testing Hypotheses

Term	Definition
Central tendency	A supposition, arrived at from observation or reflection, that leads to predictions which can be tested and refuted
Null hypothesis	Results observed in a study, experiment, or test that are no different from what might have occurred due to chance alone
Statistical test	Procedure used to reject or accept a null hypothesis; statistical tests may be parametric, nonparametric (distribution-free), or exact
Type I (alpha) error	Rejecting a true null hypothesis (false-positive error); declaring that a difference exists when in fact it does not
P value	Probability of making a type I error; $P < .05$ indicates a statistically significant result that is unlikely to be caused by chance
Confidence interval	A range of values considered plausible for the population from which the study sample was selected
Type II (beta) error	Accepting a false null hypothesis (false-negative error); declaring that a difference does not exist when in fact it does
Power	Probability that the null hypothesis will be rejected if it is indeed false; mathematically, power is 1.00 minus type II error

their responses. For example, suppose again that there are 20 tonsillectomy patients and 20 controls, but this time the hearing levels are 25 ± 3 dB and 20 ± 3 dB. Although the difference remains 5 dB, the SD is only 3 for this study compared with 9 in the preceding paragraph. For whatever reason, the second subjects had more consistent (less variable) responses. What effect does this reduced variability have on the ability to make inferences? The *P* value is now less than .001 (*t*-test), indicating less than a 1:1000 probability of a type I error if one concludes that the hearing levels truly differ.

All statistical tests measure error. Choosing the right test for a particular situation (Tables 6-10 and 6-11) is determined by (1) whether the observations come from independent or related samples, (2) whether the purpose is to compare groups or to associate an outcome with one or more predictor variables, and (3) the measurement scale of the variables.[20] Despite the myriad of tests available, the principles underlying each remain constant.

Two events are independent if the occurrence of one is in no way predictable from the occurrence of the other. A common example of *independent samples* is two or more parallel (concurrent) groups in a clinical trial or observational study. Conversely, *related samples* include paired organ studies, subjects matched by age and sex, and repeated measures on the same subjects (e.g., before and after treatment). Measurement scales are previously discussed, but the issue of frequency distribution deserves reemphasis. The tests in Tables 6-10 and 6-11 labeled as "parametric" assume an underlying symmetric distribution for data. If the data are sparse, asymmetric, or plagued with outliers, then a "nonparametric" test must be used.

Using the wrong statistical test to estimate error invalidates results. For example, suppose intelligence quotient (IQ) is measured in 20 subjects before and after tonsillectomy, and the mean IQ increases from 125 to 128. For this 3-point increase, $P = .29$ (*t*-test, independent samples) suggests a high probability (29%) of reaching a false-positive conclusion. However, the observations in this example are related before and after IQ tests in the same subjects. What is really of interest is the mean *change* in IQ for each subject (related samples), not how the mean IQ of all subjects before surgery compares with the mean IQ of all subjects postoperatively (independent samples). When the proper statistical test is used (*t*-test, paired samples), $P = .05$ suggests a true association. Related (matched) samples are common in biomedical studies and should never be analyzed as though they were independent.

Habit 5: Put Clinical Importance Before Statistical Significance

Results are *statistically significant* when the probability of a type I error is low enough ($P < .05$) to safely reject the null hypothesis. If the statistical test compared two groups, one concludes that the groups differ. If the statistical test compared three or more groups, one concludes that there are global differences among them. If the statistical test related predictor and outcome variables (regression analysis), one concludes that the predictor variables explain more variation in the outcome than would be expected by chance alone. These generalizations apply to all the statistical tests in Tables 6-9 and 6-10.

The next logical question after "Is there a difference?" (statistical significance) is "How big a difference is there?" (*clinical importance*). Unfortunately, most data interpretation stops with the *P* value, and the second question is never asked. For example, a clinical trial of nonsevere acute otitis media found amoxicillin superior to placebo as initial treatment ($P = .009$).[21] Before we agree with the author's recommendation for routine amoxicillin therapy, let's look more closely at the magnitude of clinical effect. Initial treatment success occurred in 96% of amoxicillin-treated children vs. 92% of controls, yielding a 4% rate difference favoring drug therapy. Alternatively, one must treat 25 subjects (100/4) with amoxicillin to increase the success rate by one subject over what would occur from placebo alone. Is this clinically important? Maybe, or maybe not.

Statistically significant results must be accompanied by a measure of *effect size* that reflects the magnitude of difference between groups.[22] Otherwise, findings with minimal clinical importance may become statistically significant when a large number of subjects are studied. In the above example, the 4% difference in success rates was highly statistically significant because more than 1000 episodes of otitis media contributed to this finding. Large numbers provide high precision (repeatability), which in turn reduces the likelihood of error. The final result is a hypnotically tiny *P* value, which may reflect a clinical difference of trivial importance.

Common measures of effect size when comparing groups include the odds ratio, relative risk, and rate difference (see Table 6-8). For example, in the hypothetical study of tonsillectomy and baldness noted earlier, the rate difference was 30% ($P = .01$), with a 95% confidence interval of 10% to 50%. Therefore, one is 95% confident that tonsil-

Table 6-10

Statistical Tests for Independent Samples

Situation	Parametric Test	Nonparametric Test
Comparing 2 Groups of Data		
Numerical scale	*t*-test	Mann Whitney U,* median test
Numerical (censored) scale	Mantel-Haenszel life table	Wilcoxon, Logrank, Mantel-Cox
Ordinal scale	—	Mann Whitney U,* median test, chi-squared test for trend
Nominal scale	—	Chi-squared, log-likelihood ratio
Dichotomous scale	—	Chi-squared, Fisher's exact test, odds ratio, relative risk
Comparing 3 or More Groups of Data		
Numerical scale	One-way ANOVA	Kruskal-Wallis ANOVA
Ordinal scale	—	Kruskal-Wallis ANOVA, chi-squared test for trend
Dichotomous or nominal scale	—	Chi-squared, log-likelihood ratio
Associating an Outcome with Predictor Variables		
Numerical outcome, 1 predictor	Pearson correlation	Spearman rank correlation
Numerical outcome, 2 or more predictor variables	Multiple linear regression, two-way ANOVA	—
Numerical (censored) outcome	Proportional hazards (Cox) regression	—
Dichotomous outcome	Discriminant analysis	Multiple logistic regression
Nominal or ordinal outcome	Discriminant analysis	Log-linear model

*The Mann Whitney U test is equivalent to the Wilcoxon rank-sum test.
ANOVA, analysis of variance.

Table 6-11

Statistical Tests for Related (Matched, Paired, or Repeated) Samples

Situation	Parametric Test	Nonparametric Test
Comparing 2 Groups of Data		
Dichotomous scale	—	McNemar's test
Ordinal scale	—	Sign test, Wilcoxon signed rank test
Numerical scale	Paired *t*-test	Sign test, Wilcoxon signed rank test
Comparing 3 or More Groups of Data		
Dichotomous scale	—	Cochran Q test, Mantel-Haenszel chi-squared
Ordinal scale	—	Friedman ANOVA
Numerical scale	Repeated measures ANOVA	Friedman ANOVA

ANOVA, analysis of variance.

lectomy increases the rate of baldness between 10% and 50%, with only 1% chance of a type I error (false-positive). Alternatively, results could be expressed in terms of relative risk. For the tonsillectomy study, relative risk is 1.6 (the incidence of baldness was 1.6 times higher after surgery), with a 95% confidence interval of 1.1 to 2.3. Effect size and 95% confidence limits may be calculated manually[23] or with a computer program.

Effect size is measured by the correlation coefficient (r) when an outcome variable is associated with one or more predictor variables in a regression analysis (see Table 6-10). Suppose that a study of thyroid surgery reports that shoe size had a statistically significant association with intraoperative blood loss (multiple linear regression, $P = .04$, $r = .10$). A correlation of only .10 implies little or no relationship (see Habit 2), and an r^2 of .01 means that only 1% of the variance in survival is explainable by shoe size. Who cares if the results are "significant" when the effect size is clinically irrelevant, not to mention nonsensical. Besides, when $P = .04$, there is a 4% chance of being wrong when the null hypothesis is rejected, which may in fact be the case here. A nonsensical result should prompt a search for confounding factors that may not have been included in the regression, such as TMN stage, comorbid conditions, or duration of surgery.

Confidence intervals (CI) are more appropriate measures of clinical importance than P values, because they reflect *both* magnitude and precision.[24] When a study reports "significant" results, the *lower* limit of the 95% CI should be scrutinized; a value of minimal clinical importance suggests low precision (inadequate sample size). When a study reports "nonsignificant" results, the *upper* limit of the 95% CI should be scrutinized; a value indicating a potentially important clinical effect suggests low statistical power (false-negative finding). Confidence intervals are essential for interpreting effect size, which is a critical concept in evidence-based medicine.[25]

Habit 6: Seek the Sample Source

When we interpret medical data, we ultimately seek to make inferences about some target population based on results in a smaller sample (Table 6-12). Rarely is it possible to study every patient, medical record, DNA strand, or fruit fly with the condition of interest. Nor is it necessary—inferential statistics allow one to generalize from the few to the many, provided that the few studied are a *random and representative* sample of the many. However, random and representative samples rarely arise from divine providence. Therefore one must seek the sample source before generalizing the interpretation of the data beyond the confines of the study that produced it.

As an example of sampling, consider a new antibiotic that is touted as superior to an established standard for treating acute otitis media. When you review the data on which this statement is based, you learn that the study end point was bacteriologic efficacy—the ability to sterilize the middle ear after treatment. Furthermore, the only patients included in the study were those whose initial tympanocentesis revealed an organism with in vitro sensitivity to the new antibiotic; patients with no growth or resistant bacteria were excluded. Can you apply these results to your clinical practice? Most likely not, because you probably do not limit your practice to patients with antibiotic-susceptible bacteria. In other words, the sample of patients included in the study is not representative of the target population in your practice.

A statistical test is valid only when the study sample is *random* and *representative*. Unfortunately, these assumptions are frequently violated or overlooked. A random sample is necessary because most statistical tests are based on probability theory—playing the odds. The odds apply only if the deck is not stacked and the dice are not rigged; that is, all members of the target population have an equal chance of being sampled for study. Investigators, however, typically have access to only a small subset of the target population because of geographic or temporal constraints. When they choose an even smaller subset of this *accessible population* to study, the method of choosing (sampling method) affects the ability to make inferences about the original target population.

Of the sampling methods listed in Table 6-13, only a random sample is theoretically suitable for statistical analysis. Nonetheless, a consecutive or systematic sample offers a relatively good approximation, and provides data of sufficient quality for most statistical tests. The worst sampling method occurs when subjects are chosen based on convenience or subjective judgments about eligibility. Applying statistical tests to the resulting convenience (grab) sample is the equivalent of asking a professional card counter to help you win a blackjack game when the deck is stacked and cards are missing—all bets are off because probability theory will not apply. A brute force sample of the entire population is also unsatisfactory, because lost, missing, or incomplete units tend to differ systematically from those that are readily accessible.

Seek the sample source means identifying the sampling method and selection criteria (inclusion and exclusion criteria) that were applied to the target population to obtain the study sample. When the process appears sound, one concludes that the results are generalizable and *externally valid* (see Table 6-12 and Figure 6-2). If the process appears flawed, one cannot interpret or extrapolate the results beyond the confines of the study sample.

Sometimes a study is internally valid but may not be generalizable. Paradise and colleagues[26] concluded that prompt vs. delayed insertion of tubes for persistent otitis media does not affect child development. Although the study was meticulously designed and analyzed (internally valid), the participants had mostly unilateral (63%) or discontinuous (67%) otitis media with effusion; bilateral continuous effusions were uncommon (18%). Moreover, children with syndromes, developmental delays, or other comorbidities were excluded. Whereas no benefits were seen in the healthy children studied, the results are not generalizable to the more typical population of children who receive tubes, many of whom have chronic bilateral effusions with hearing loss and developmental comorbidities.

The impact of sampling on generalizability is particularly important when interpreting a diagnostic test.[27] For instance, suppose an audiologist develops a new test for diagnosing middle ear effusion (MEE). After testing 1000 children, she reports that 90% of children with a positive result did in fact have MEE (positive predictive value of 90%). Yet when you screen unselected kindergarten children for MEE, the positive predictive value of the test is only 50%. Why does this occur? Because the baseline prevalence of MEE is lower in the kindergarten class (10% have MEE) than in the referral-based audiol-

Table 6-12

Glossary of Statistical Terms Related to Sampling and Validity

Term	Definition
Target population	Entire collection of items, subjects, patients, and observations about which one makes inferences; defined by the selection criteria (inclusion and exclusion criteria) for the study
Accessible population	Subset of the target population that is accessible for study, generally because of geographic or temporal considerations
Study sample	Subset of the accessible population that is chosen for study
Sampling method	Process of choosing a sample from a larger population; the method may be random or nonrandom, representative or nonrepresentative
Selection bias	Error caused by systematic differences between a study sample and target population; examples include studies on volunteers and those conducted in clinics or tertiary care settings
Sample size determination	Process of deciding, before a study begins, how many subjects should be studied; based on the incidence or prevalence of the condition under study, anticipated differences between groups, the power that is desired, and the allowable level of type I error
Internal study validity	Degree to which conclusions drawn from a study are valid for the study sample; results from proper study design, unbiased measurements, and sound statistical analysis
External study validity (generalizability)	Degree to which conclusions drawn from a study are valid for a target population (beyond the subjects in the study); results from representative sampling and appropriate selection criteria

Table 6-13

Methods for Sampling a Population

Method	How It Is Performed	Comments
Brute force sample	Includes all units of study (charts, patients, laboratory animals, or journal articles) accessible to the researchers	Time-consuming and unsophisticated; bias-prone because missing units are seldom randomly distributed
Convenience (grab) sample	Units are selected on the basis of accessibility, convenience, or by subjective judgments about eligibility	Assume this method when none is specified; study results cannot be generalized because of selection bias
Consecutive sample	Every unit is included over a specified time interval, or until a specified number is reached	Excellent method when intake period is long enough to adequately represent seasonal and other temporal factors
Systematic sample	Units are selected using some simple, systematic rule, such as first letter of last name, date of birth, or day of week	Less biased than a grab sample, but problems may still occur because of unequal selection probabilities
Random sample	Units are assigned numbers then selected at random until a desired sample size is attained	Best method; bias is minimized because all units have a known (and equal) probability of selection

ogy population in which the test was developed (50% have MEE). Whereas the sensitivity and specificity of the test are unchanged in both situations, the predictive value is related to baseline prevalence (Bayes' theorem). Therefore the ultimate utility of the test depends on the sample to which it will be applied.

Habit 7: View Science as a Cumulative Process

A single study—no matter how elegant or seductive—is rarely definitive. Science is a cumulative process that requires a large body of consistent and reproducible evidence before conclusions can be formed.[28] When interpreting an exciting set of data, the cumulative basis of science is often overshadowed by the seemingly irrefutable evidence at hand. At least until a new study, by different investigators in a different environment, adds a new twist.

Habit 7 is the process of *integration*: reconciling findings with the existing corpus of known similar research. It is the natural consequence of habits 1 through 3 that deal with *description* and habits 4 through 6 that deal with *analysis*. Thus data interpretation can be summarized in three words: describe, analyze, and integrate. This is a sequential process in which each step lays the foundation for subsequent ones, just as occurs for the six habits that underlie them.

Research integration begins by asking "Do the results make sense?" Statistically significant findings that are biologically implausible, or that are inconsistent with other known studies, can often be explained by hidden biases or design flaws that were initially unsuspected (habit 1). Improbable results can become statistically significant through biased data collection, natural history, placebo effects, unidentified confounding variables, or improper statistical analysis. A study with design flaws or improper statistical analysis is said to have low *internal validity* (see Table 6-12), and should be reanalyzed or discarded.

At the next level of integration, the study design that produced the current data is compared with the design of other published studies. The *level of evidence* generally increases as one progresses from uncontrolled observational studies (case reports, case series), to controlled observational studies (cross-sectional, retrospective, prospective), to controlled experiments (randomized trials).[25] Not all randomized trials, however, are of high quality, and reporting standards must be followed to ensure validity.[29] Levels of research evidence are most often applied to studies of therapy or prevention (Table 6-14), but can also be defined for diagnosis and prognosis.[30] Grades of recommendation (Table 6-15) are assigned based on the quality and consistency of supporting research evidence.

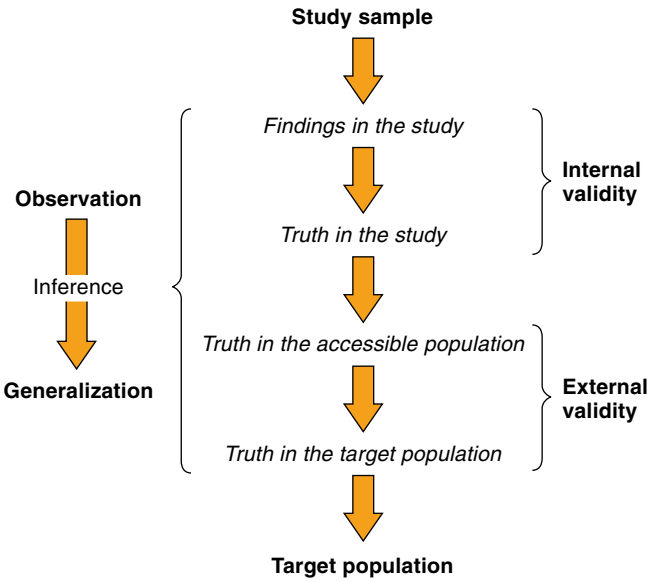

Figure 6-2. Relationship of validity to inference. A properly designed, executed, and analyzed study has internal validity, meaning the findings are valid for the study sample. This alone, however, is inadequate for inference to occur. Another requirement is external validity, which exists when the study sample is representative of an appropriate target population. When a study has internal and external validity, the observations can be generalized.

Bentsianov and Rosenfeld[31] assessed the levels of supporting evidence for therapeutic recommendations in leading otolaryngology journals. Of 1019 articles published in 1999, 72% were clinical research and 36% made therapeutic recommendations. The level of evidence for positive studies was lower than for negative studies, with twice as many negative recommendations supported by randomized trials or controlled studies (analytic research). Similarly, the level of evidence for surgery was lower than for medical therapy, with three times as many medical recommendations supported by analytic research. The authors concluded that a dual evidence standard appears to exist for

Table 6-14

Levels of Research Evidence for Clinical Recommendations

Level	Therapy or Prevention	Diagnosis	Prognosis
1	Randomized controlled trial; systematic review of randomized trials; "all or none" case series	Validating cohort study with good reference standard; CDR tested at one clinical center; SpPins and SpNouts	CDR validated in a single population or in cohort study with greater than 80% follow-up; "all or none" case series
2	Prospective controlled study: cohort study, outcomes research, ecological study	Exploratory cohort study with good reference standard; derivation of CDR; or CDR tested on split-sample or database	Retrospective cohort study or follow-up of untreated controls; derivation or CDR; or CDR tested on split-sample; outcomes research
3	Retrospective controlled study: case-control study	Nonconsecutive study, or without consistently applied reference standards	—
4	Case series and poor-quality cohort and case-control studies	Case-control study, or poor or nonindependent reference standard	Case-series and poor-quality prognostic cohort studies
5	Expert opinion without explicit critical appraisal; or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal; or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal; or based on physiology, bench research, or "first principles"

CD, clinical decision rule (algorithm or scoring system that leads to a prognostic estimation); SpPin, specificity is so high that positive result rules in the diagnosis; SpNout, sensitivity so high that a negative result rules out the diagnosis.
Adapted from Phillips B, Ball C, Sackett D, et al. Levels of evidence and grades of recommendation. Oxford Centre for Evidence Based Medicine. http://www.cebm.net/levels_of_evidence.asp.

Table 6-15

Grades of Recommendation Based on Level of Supporting Evidence

Grade	Level of Supporting Evidence as Defined in Table 6-14
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations* from level 1 studies
C	Level 4 studies or extrapolations* from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

*Extrapolations occur where data are used in a situation that has potentially clinically important differences than the original study situation.
Adapted from Phillips B, Ball C, Sackett D, et al. Levels of evidence and grades of recommendation. Oxford Centre for Evidence Based Medicine. http://www.cebm.net/levels_of_evidence.asp.

negative vs. positive studies and for medical vs. surgical recommendations in the otolaryngology literature.

Quantitative data integration ranges from simple tabular listings to sophisticated health services, including systematic reviews, practice guidelines, decision analyses, and economic analyses.[25] Systematic reviews or *meta-analyses* are an ideal way to synthesize results from a group of logically related randomized trials or, less commonly, observational studies.[32,33] The "bottom line" in a systematic review typically includes a summary measure of effect size (e.g., rate difference), a 95% confidence interval, and a statistical test for heterogeneity among source articles. Graphical comparison of studies using forest and funnel plots helps assess publication trends, small-study bias, and overall combinability and consistency of included studies.[34] Systematic reviews differ greatly from traditional "narrative" review articles (Table 6-16), and are the preferred method for synthesizing research evidence.

Clinical practice guidelines are often the next step in evidence synthesis, using the bottom-line estimates of systematic reviews to develop action statements about appropriate health care in specific clinical circumstances. Guidelines are created through an explicit, evidence-based, multidisciplinary process that links evidence to recommendations and incorporates values and expert consensus.[35] The best guidelines focus on a limited number of specific actions that are likely to improve quality of care, and to not attempt to define comprehensive management of a disease, disorder, or condition. An example is the Adult Sinusitis Guideline from the American Academy of Otolaryngology—Head and Neck Surgery,[36] which focuses on accurate diagnosis, antimicrobial therapy of acute sinusitis, and evaluation and prevention of chronic and recurrent sinusitis.

Popular Statistical Tests Used by Otolaryngologists

Salient features of the most popular tests in otolaryngology journals[37] are listed here. Note that each test is simply an alternative way to measure error (habit 4), not a self-contained method of data interpretation. Tests are chosen using the principles outlined in Tables 6-10 and 6-11, then analyzed with readily available software (which can also help select the best test for a specific data set). Explicit guidelines are available to help authors, editors, and reviewers identify the optimal format for reporting statistical results in medical publications.[38]

t-test

Description

The *t*-test is a classic parametric test for comparing the means of two independent or matched (related) samples of numerical data; also called Student's *t*-test.

Table 6-16

Comparison of Narrative (Traditional) Reviews and Meta-analyses

Characteristic	Narrative Review	Meta-analysis
Research design	Free form	A priori protocol
Literature search	Convenience sample of articles deemed important by author	Systematic sample using explicit and reproducible article selection criteria
Data extraction	Selective data retrieval by one author	Systematic data retrieval by two or more authors to reduce error
Focus	Broad; summarizes a large body of information	Narrow; tests specific hypotheses and focused clinical questions
Emphasis	Narrative; qualitative summary	Numbers; quantitative summary
Validity	Variable; high potential for bias in article selection and interpretation	Good, provided articles are of adequate quality and combinability
Bottom line	Broad recommendations, often based on personal opinion	Estimates of effect size, based on statistical pooling of data
Utility	Provides a quick overview of a subject area	Provides summary estimates for evidence-based medicine
Appeal to readers	Usually very high	Varies depending on focus

Interpretation

A significant *P* value for independent samples implies a low probability that the mean values for the two groups are equal. When the samples are matched, a significant *P* value implies that the mean differences of the paired values are unlikely to be zero. Clinical importance is assessed by examining the magnitude of difference achieved and the associated 95% CI. Because valid results depend on relatively equal variances (standard deviation) within each group, a statistical test is required to verify this assumption (F test).

Precautions

t-tests produce an artificially low *P* value if the groups are small (less than 10 observations) or have an asymmetric distribution (one or more extreme outlying values); instead, a nonparametric test (Mann-Whitney U or Wilcoxon rank sum test) should be used. If, however, each group contains more than 30 observations, the underlying distribution can deviate substantially from normality without invalidating results. *t*-tests should *never* be used to compare more than two groups; analysis of variance (ANOVA) is required.[39] When the outcome of interest is time related (e.g., cancer survival, duration of hospital stay, disease recurrence), survival analysis is more appropriate than a *t*-test.

Analysis of Variance

Description

ANOVA tests if the means of *three or more* independent groups of continuous data differ significantly with regard to a single factor (one-way ANOVA) or two factors (two-way ANOVA). ANOVA also tests whether the effect of one factor on the response variable depends on the level of a second factor (interaction).

Interpretation

A significant *P* value implies a low probability that the mean values for all groups are equal. From a statistical standpoint, we say that the variance *between* groups is larger than the variance *within* each group. Note that ANOVA provides no information on whether *individual* pairs of groups differ significantly; it only tests for an overall global difference. For example, when comparing four groups of data (A, B, C, and D), the finding "$P < .05$, ANOVA" means there is less than a 5% chance that the statement "A = B = C = D" is true; however, it says nothing about AB or CD or DA, and so on. Once the investigators demonstrate a significant global difference ($P < .05$) using ANOVA, they can then use *multiple comparison* procedures (Bonferroni, Tukey, Newman-Keuls, Scheffe, Dunnett) for individual group comparisons.

Precautions

ANOVA will produce an artificially low *P* value if the groups contain small samples (less than 5 observations per group, or 20 in all groups combined) with asymmetric distributions; instead, a nonparametric test (Kruskal-Wallis ANOVA) should be used. A nonparametric test is also preferred if the groups have unequal variance as determined by an F test. Multiple pairwise *t*-tests cannot substitute for ANOVA; the effect is to greatly increase the odds of a false-positive result (type I statistical error).

Contingency Tables

Description

Contingency tables test for an association between two categorical variables by using the chi-square statistic. A modification, called the McNemar test, can be used for two groups of paired data.

Interpretation

A significant *P* value implies a significant association between the two variables, whose categorical values form the rows and columns of the contingency table. However, even a very small *P* value provides no information about the strength of the association (effect size). Therefore effect size can be measured with the odds ratio (2×2 table) or by Pearson's contingency coefficient (tables with more than two rows or columns). The chi-square statistic compares the observed values for each cell (row-column intersection) with the expected values that would occur if chance alone were operating.

Precautions

As with *t*-tests and ANOVA, small samples can produce an artificially small *P* value. If the *expected* frequency for any cell is less than 5, an alternative test must be used (e.g., Fisher's exact test or the log-likelihood ratio). Beware of authors who over-interpret a "significant" chi-square result. As with ANOVA, when $P < .05$, one claims a *global*

association between variables, but one cannot specify which subgroups of rows and columns are or are not associated.

Survival Analysis

Description

Survival analysis estimates the probability of an event (typically, but not necessarily, survival) based on the total period of observation, and tests for associations with other variables of interest. Survival analysis permits maximum use of data from *censored* observations, which occur when a subject is lost to follow-up, or if the study ends before the outcome of interest has occurred.

Interpretation

There are two main ways of analyzing survival data: the life table method divides the time into intervals and calculates survival at each interval; the Kaplan-Meier method calculates survival each time an event occurs. Both methods produce a graph (survival curve) showing the cumulative probability of the event vs. total period of observation. Authors sometimes eliminate the curve and instead give the event rates only for specific time periods (e.g., 1 year, 3 years, 10 years). When two or more survival curves are compared and the *P* value is low, a probable association exists between time to event and the factor used to stratify the curves.

Precautions

When you see a "survival cure," be sure that it has been calculated using survival analysis (life table or Kaplan-Meier), *not* by simply dividing cumulative events at a given time by the total subjects still around at that time. The latter method mistreats censored observations, yielding artificially low estimates. Nor is it desirable to simply exclude from analysis all subjects not meeting some arbitrary cutoff for observation time; resulting rates may be artificially high. Whereas the life table method requires a minimum sample size of 20 uncensored observations, Kaplan-Meier analysis requires only five uncensored observations for valid results.

Multivariate (Regression) Procedures

Description

Examine the *simultaneous* effect of multiple predictor variables (generally three or more) on an outcome of interest. In contrast, *t*-tests, one-way ANOVA, chi-square, and survival analysis examine the *univariate* effect of variables on an outcome one at a time. Different multivariate procedures are used depending on the measurement scale of the outcome variable (see Table 6-10). The most popular regression methods in general medical journals are multiple linear regression, Cox proportional hazards (for survival data), and multiple logistic regression (for a binary or dichotomous outcome).[40]

Interpretation

Multivariate analysis produces a statistical model that predicts outcomes based on combinations of individual variables. The adequacy of the model as a whole is determined by the coefficient of determination (r^2), which indicates how much variability in the response variable is accounted for by the predictors, and its associated *P* value. Each predictor variable also has an associated coefficient, whose magnitude represents the relative effect of the variable on outcome when adjusted for all the other variables in the model. A positive coefficient implies a positive association; a negative coefficient implies a negative association. When the coefficient's *P* value is small, the association is significant. Predictor variables should also be tested for interaction.

Precautions

Biased results may occur if the data set has outliers, or if variables in the model are highly correlated with each other ($r > .90$). Although a model may precisely fit the investigator's data, there is no guarantee that it will predict outcomes for subjects outside the study with equal precision. As with any statistical test: garbage in, garbage out. No degree of multivariate analysis can adjust for confounding variables that were not recorded at the start of the study.

Nonparametric Tests

Description

Test hypotheses *without* requiring that the data have a normal distribution. The nonparametric equivalents of the *t*-test, paired *t*-test, and one-way ANOVA are the Mann-Whitney U, Wilcoxon signed rank, and Kruskal-Wallis tests, respectively (Tables 6-10 and 6-11).

Interpretation

When an author uses a *parametric* test (e.g., *t*-test or ANOVA), the data must be normally distributed or come from a large enough sample (about 30 or more subjects) to relax this requirement of normality. Nonparametric tests avoid this requirement by ranking the data in each group, and then comparing rank sums instead of the actual values of individual observations. Whereas the parametric tests discussed above make inferences about *means*, nonparametric tests make inferences about *medians*. When there is doubt as to whether a nonparametric test is necessary, the *P* value should be calculated both ways—parametric and nonparametric. If the results differ significantly, the nonparametric test is preferred.

Precautions

Very sparse data sets are not suitable for either parametric or nonparametric analysis; more sophisticated *exact* significance tests must be used. Fisher's exact test is a well-known exact procedure for 2×2 contingency tables. Exact tests for other situations require special computer software.[41]

Common Statistical Deceptions

More than a century ago, Benjamin Disraeli noted, "There are three kinds of lies: lies, damn lies and statistics." Although such consummate skepticism is rarely justified, statistics can undoubtedly be misused—either by intent or through ignorance or carelessness—to produce incorrect conclusions (Table 6-17). Confidence and common sense have been advocated as a means to balance statistical significance with clinical importance.[42]

How does statistical misuse slip by editors, peer reviewers, and journal readers? Because of the "dazzle" phenomenon observed by Darrell Huff, author of *How to Lie with Statistics*: "If you can't prove what you want to prove, demonstrate something else and pretend that they are the same thing. In the daze that follows the collision of statistics with the human mind, hardly anybody will notice the difference."[43] Be particularly wary of the following dazzling phenomena:

Surgical Satisfaction Swindle

A surgeon claims a procedure is "highly effective" because 85% of patients were satisfied with results, 85% would have the surgery again, and 85% would recommend the procedure to family or friends. Unfortunately virtually any survey achieves 80% or higher respondent satisfaction for a given question and only a few patients actually express negative views.[44] Satisfaction surveys are particularly prone to positive-response bias because they often relate more to the interpersonal skills of the surgeon and the setting in which treatment was administered than the actual outcomes achieved. Moreover, without a comparison or control group, one cannot distinguish therapeutic effects from natural history or a placebo response.[7]

Survey results are credible only if the investigators use a previously validated instrument or perform their own validation process.[45,46] This process includes assessing (1) test-retest reliability to ensure response stability and consistent item (question) interpretation, (2) internal consistency to determine whether allegedly similar items tap similar content domains, (3) construct validity to verify that items actually measure what they purport to measure, (4) discriminant validity to show that respondents with different levels of satisfaction or disease have measurably different survey scores, and (5) responsiveness to demonstrate that the change in survey scores before and after intervention is able to detect clinically meaningful levels of change within an individual.

Table 6-17

Statistical Deceptions Used in Journal Articles

Deception	Problem	Solution
Standard error is used instead of standard deviation	Range is artificially low, making data look better than they are	Always use standard deviation when summarizing data
Small sample study results are taken at face value	Results are imprecise and would likely vary if study was repeated; uncertainty is ignored	Determine the range of results consistent with data by using a 95% confidence interval
Post hoc *P* values are used for statistical inference	Statistical tests are valid only when hypotheses are formulated before examining the data	Post hoc *P* values must be viewed as hypothesis-generating, not hypothesis-testing
Some results are "significant" but there are a large number of *P* values	"Significant" results may be false-positives because each *P* value has a 5% error rate*	Reduce the number of *P* values through multivariate analysis or analysis of variance
Subgroups are compared until statistically significant results are found	If you torture the data sufficiently, they will eventually confess to something	Subgroup comparisons are valid only when all groups as a whole are significantly different
No significant difference is found between groups in a small sample study	A significant difference may have been missed because of inadequate sample size	Be wary of study results until the authors discuss power and sample size results
Significant *P* values are crafted through improper use of hypothesis tests	Small studies with asymmetrically distributed data require special methods of analysis	Be wary of results unless a nonparametric or exact statistical test was used

*Assuming that .05 is selected as the level of statistical significance.

Standard Error "Switcheroo"

When you see results reported as "mean value ± X," do not assume that X is the standard deviation (SD) unless specifically stated. Sometimes X is actually the standard error (SE), a number that is *always* smaller than SD. Actually, SD and SE are very different; so understanding why many authors report the latter is difficult, unless they are enamored by the smaller value. When describing a set of data, SD is always preferred, because it measures how variable individual observations are within a sample.[47] If the data have a symmetric distribution, the mean ± 2 SD describes about 95% of observations. In contrast, the SE is an inferential, not a descriptive, statistic; it measures how variable the mean is from one sample to another.

Consider a study of 25 patients undergoing rhinoplasty that reports a mean blood loss of 150 ± 30 mL where 30 is the SD. We now know that 95% of subjects had a blood loss of 150 ± 60 mL (assuming the data are normally distributed). To obtain the SE, divide the SD by the square root of the sample size. In this example, the square root is 5, giving an SE five times smaller than the SD: 6 vs. 30. The mean blood loss now is written as 150 ± 6 mL, where 6 is the SE. Obviously this "looks" better than the SD, but what exactly does it mean? It means "based on our results, if we extrapolate to the general population of rhinoplasty patients, we estimate with 95% confidence that the mean blood loss will be 150 ± 12 mL." This statement no longer describes the study data, but makes an inference about some hypothetical population. Unless the authors clearly state that this is their intent, the SD should have been used.

Small Sample Whitewash

Because medical research is costly and time consuming, it is a luxury to study large samples. Fortunately, meaningful conclusions can be derived from small samples by estimating uncertainty (precision) with a 95% confidence interval. Remember—statistics is the art and science of dealing with uncertain data; the smaller the sample, the greater the uncertainty. Beware when authors claim their sample is too small for statistical analysis; that is when they need it most.

For example, while perusing the *Journal of Low Budget Research* an article on an innovative new surgical procedure captures your attention. The authors operate successfully on four of four elephants (100% success rate) and conclude that "testing in humans is indicated based on these superb results." Do you agree? Actually, the range of results (exact 95% binomial CI) consistent with this single experiment on four elephants is 47% to 100%! Knowing that the population success rate (for elephants, at least) may be as low as 47% you may now disagree with the need for human testing. Conversely, if the investigators succeeded in 40 of 40 elephants, the 95% CI would be 93% to 100%—a much greater level of confidence secondary to the 10-fold increase in sample size.

Here is another way to appreciate the value of confidence limits on small samples. Imagine you are about to cross a very flimsy and tenuous appearing bridge. Your reassuring guide states you have nothing to worry about because the first four travelers crossed it successfully. The statistical basis for your persistent trepidation stems from the fact that four of four successes is consistent with up to a 53% failure rate (as noted in the preceding paragraph)—not a very reassuring statistic to stake your life on!

Post Hoc *P* Values

A fundamental assumption underlying all statistical tests is that the hypothesis under study was fully developed before the data were examined in any way. When hypotheses are formulated *post hoc*—after even the briefest glance at the data—the basis for probability statements is invalidated. Unfortunately, there is no way of knowing at which stage of the research process a hypothesis was developed. Therefore, unless the investigators state specifically that the test was planned a priori, one should infer with caution.

As physician-friendly computer programs for statistical analysis continue to proliferate, more physicians are likely to analyze their own data. Unless the probability framework underlying hypothesis tests is understood and appreciated (habits 3 and 4), the risk of post hoc *P* values will increase dramatically as they become easier to produce.

When the primary research purpose is to test an a priori hypothesis, the *P* value will aid in statistical inference. When hypotheses are generated after the study, however, *P* values cannot be used to make inferences. Instead, they become a means of identifying promising associations that might form the new a priori hypotheses in a follow-up investigation.

Multiple *P* Value Phenomenon

When a journal article or data table is chock full of *P* values, realize that some "significant" *P* values ($P < .05$) are likely to occur by chance alone.[48] Consider, for example, that a researcher performs 20 individual hypothesis tests on a group of observations (e.g., calculates 20 *P* values). If the subjects studied do not differ beyond random variation, there is only a 36% chance that *none* of the *P* values will be significant! Furthermore, the chance of there being one, two, or three significant *P* values is 38%, 19%, and 6%, respectively.

What accounts for the multiple *P* value phenomenon? The problem arises because each test is based on a cutoff of $P < .05$ as a measure of significance; the effect of performing multiple tests is to inflate this 5% error level for the study as a whole. The probability of obtaining at least one spurious result is $1-(1-\text{alpha})^n$ where alpha is the level of significance for each individual test (generally .05) and n is the number of tests performed.

Multiple *P* values can arise when pairwise comparisons are made between several groups of data or when numerous hypothesis tests are applied to a single data set. When several groups are compared, ANOVA overcomes the multiple *P* value problem created by repeated *t*-tests. Furthermore, special multiple comparison tests are available with ANOVA that can search for subgroup differences as long as a global difference exists between groups. When a single data set is being studied, multivariate analysis will eliminate the multiple *P* value problem induced by repeated univariate tests (e.g., *t*-test, chi-square).

Selective Analysis of Results

One should check for selective analysis of the results in every study that compares three or more groups of subjects, including animal research. Authors may pluck out a few groups for pairwise comparisons and then pontificate on the "statistically significant" findings they discover. Unfortunately, this violates a basic tenet of statistics—you *cannot* compare subgroups of data *unless* you first check for statistically significant differences between *all* groups considered simultaneously. For categorical data, a chi-square is first calculated for the entire contingency table; if $P < .05$, the authors can then extract subsets of the table for selective analysis *as long as* they adjust for multiple comparisons. For continuous data, ANOVA should be used (not multiple pairwise *t*-tests) as described previously.

Powerless Equalities

Some authors would like to convince you that a new treatment or diagnostic test is *equivalent* to an established standard. In particular, support for the use of a new antibiotic or antihistamine often arises from a randomized trial claiming no significant difference ($P > .05$) from another drug. When interpreting these results, look not at the *P* value but at the statistical *power*; the size of the *P* value is pertinent only when a statistically significant result is given. Power tells the probability that the investigators would have detected a true difference, given that one really existed. The unique issues involved in equivalence (noninferiority) randomized trials have resulted in specific reporting guidelines to aid interpretation.[49]

Understanding Sample Size

A sample size calculation before beginning a study ensures that the planned number of observations will offer a reasonable chance of obtaining a clear answer at the end.[50] This is of paramount importance in animal studies, in which sample size is limited by financial constraints, concerns over animal welfare, and limited laboratory space.[51] For example, a groundbreaking experiment in 10 giraffes is of little value when a sample size of 20 is needed for adequate power or precision. Similarly, why experiment on 200 chinchillas when only 100 are adequate to test a hypothesis? Such considerations are by no means limited to basic science research. Why devote endless hours to abstracting data from 500 patient charts when only 150 observations would suffice?

Calculating sample size is an essential first step in evaluating or planning a research study.[52] Basic requirements for all sample size calculations include (1) estimates of the smallest difference desired to be detected between the groups, (2) level of confidence that any difference detected is not simply due to chance (typically 95% or 99%), and (3) level of confidence that the difference detected will be as small as what was specified earlier (typically 80% or 90%), assuming that such a difference truly exists. In addition, sample size calculations for numerical data require some estimate of the variability (variance) among observations.

Determining the minimally important difference desired to be detected is based solely on clinical judgment. When comparing categorical data, the difference of interest is between proportions (rate difference, see Table 6-8). For example, one may wish to know if success rates for two drugs differ by at least 20% for otitis media, but a difference of perhaps 5% may be important when treating cancer. In contrast, differences in numerical data are expressed as a difference in means. For example, one may wish to know if a potentially ototoxic drug decreases mean hearing by at least 5 dB or if a new surgical technique decreases blood loss by at least 200 mL.

Outcomes measured on a numerical scale require an estimate of variance to calculate sample size. Because variance is defined as the square of the SD, a method is needed to estimate SD to derive variance. If pilot data are available, some estimate of SD may already exist. Alternatively, one can "guess" the SD by realizing that the mean value ± 2 SD typically encompasses 95% of the observations. In other words, the SD of a set of measurements can be approximated as one fourth of the range of that set of measurements. Suppose you are interested in detecting a 200-mL difference in blood loss between two procedures, and based on your clinical experience you expect that about 95% of the time you will see a difference ranging from 100 and 500 mL. Subtracting 100 from 500 and dividing by 4 gives 100 as an estimate of SD. Squaring the SD yields 10,000, which estimates variance.

The remaining elements of a sample size calculation reflect basic principles of statistical error (habit 4). Recognizing that errors are unavoidable (see Table 6-9), one can specify in advance the levels of tolerance and then calculate a sample size that will accomplish this goal. Tolerating a 5% probability of type I error (false-positive) is the same as being 95% certain that any difference detected is not simply due to chance. Tolerating a 20% probability of a type II error (false-negative) is the same as being 80% certain that a true difference of the magnitude already specified (80% statistical power) is not missed.

The size of the sample needed in a given study increases when the difference of interest is small, the variance of the observations is high (applies to numerical data only, not proportions), and the tolerance for error is low. More subjects are also required to determine whether any difference at all exists between groups (two-tailed statistical test) than if one group fares either better or worse than another (one-tailed statistical test). A two-tailed test is considered more conservative and should always be used unless it was determined a priori—before examining the data—that a one-tailed test was appropriate. A one-tailed test requires about half the sample size as a two-tailed test to show significance and produces *P* values about half as small when applied to the data.

The Importance of Principles

My goal throughout this chapter has been to convince you that effective interpretation of medical data involves much more than statistics or numerical formulae. Rather, it is a systematic process of moving from observations to generalizations with predictable degrees of certainty (and uncertainty). Every physician is involved in this process to some extent, whether a solo practitioner in a rural community or a full-time academician in a large university. Moving from observations to generalizations is the foundation for all scientific progress, a foundation that could not exist without a systematic process for interpreting data.

The seven habits listed in Table 6-1 provide a systematic framework for interpreting data, of which statistical tests are only a small

part. Although habit 4—measure error with the right statistical test—generates P values, it is sandwiched between habits 1 through 3 and habits 5 through 7. *P* values are part of the process, but represent neither the beginning nor the end. We begin by verifying that the data are of sufficient quality and precision to merit statistical analysis (habits 1 through 3). We end by seeking clinically significant findings that can be generalized beyond the study and are consistent with prior knowledge and experience (habits 5 through 7). Obsession with *P* values, which has been called the "religion of statistics," may produce medical publications but rarely achieves effective data interpretation.[53,54]

Every clinician need not be a statistician, but all should understand the fundamental principles of data analysis and interpretation. When understood and applied, the habits in Table 6-1 will permit intelligent, synergistic dialogue between clinicians and statisticians. Such dialogue ideally precedes any serious research endeavor, because even the most elegant statistics cannot adjust for biased data or confounders that were never measured.[55] The statistician excels at analyzing data the right way, but the clinician's leadership ensures that the right data are analyzed. Furthermore, clinical importance (habit 5) is best determined by clinicians, not statisticians.

In conclusion, here are some suggestions for putting principles into practice. Dawson and Trapp[20] provide a delightfully palatable overview of research methodology and biostatistics in *Basic & Clinical Biostatistics*. *Making Sense of Data* by Abramson[56] is a useful self-instruction manual on association, causation, odds ratios, and other rates and measures. The essentials of research design and interpretation are discussed admirably by Troidl and colleagues[57] in *Surgical Research* and by Hulley and colleagues[58] in *Designing Clinical Research*. Finally, those ready to enter the brave new world of evidence-based medicine will find a warm welcome in *Users' Guides to the Medical Literature* by Guyatt and Rennie.[25]

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CHAPTER SEVEN

Evidence-Based Performance Measurement

David R. Nielsen

Key Points

- All physicians have a moral and ethical obligation to act professionally as a fiduciary agent for the health of their patients by engaging in quality improvement.
- Physician performance measurement can be used for research, medical error reduction, patient safety, certification, credentialing, or licensing and disciplining. The purpose for which a measure is intended will determine how the measure is created.
- A performance measure is an equation or fraction representing the frequency of an appropriate and recommended intervention. It has a denominator of those who require a recommended intervention, a numerator of those who received the intervention, and defined exclusions or risk adjustments.
- Health services research demonstrating quality gaps and rising health care costs is fueling demand for clinical performance measures.
- Quality can be measured by assessing clinical outcomes, processes of care, capacity and structure, administrative parameters, cost and efficiency, and patient experience.
- Physician measurement should be founded on evidence-based guidelines, relevant and reliable data, and best clinical expertise.
- Physicians should educate themselves about the various perspectives of other stakeholders and their roles in supporting quality care.

Motivation for Physician Performance Measurement

Over the past decade, professional, political, and societal interest in measuring quality in health care has exploded to be the most dominant theme in medicine, integrating clinical care, physician education, research, and health policy. One of the most dramatic changes in the clinical environment is the emphasis on individual physician documentation of quality in daily practice. The striking increase in demand for quality initiatives and measuring the outcomes of health care delivery is motivated by multiple events and conditions. Most prominent among these is the sustained rapid increase in health care costs (at five times the average rate of inflation) and the observation from health services research that, despite spending more per capita than any other nation in the world on health care, the United States lags in many areas of public health and wellness measures.[1-5]

Current economic and market forces incentivize and pay for volume and intensity of service. Yet research shows that higher volume and intensity of health care services do not lead to better aggregated quality of life or public health. Overall, only about half of all Americans receive the recommended health interventions identified by consensus standards of care. And even more striking than the low overall proportion of those receiving recommended care is the wide variation that exists across conditions, races, gender, and financial status.[6-8] Dissatisfaction with the health care system is higher in the United States than in parallel Western nations. Likewise, the percentage of U.S. citizens who did not get health care because of cost constraints is higher than in many other Western nations. There is a huge gap between the consensus recommended appropriate care and the care that is actually delivered for easily identifiable and definable conditions.[3] Large geographic variations in care, unexplainable by patient demographics and characteristics, are easily observable over a broad range of conditions. These geographic variations are far more significant than even the health care disparities seen due to ethnic or health literacy differences in the population.[6-11] Unacceptably high rates of mortality and morbidity related to medical error have been the subject of many reports from federal agencies and independent health services researchers.[2,6,12] And finally, there does not seem to be any correlation between per capita costs of health care and quality of health care delivered on a range of observations and bases.[10]

What Is Quality and Who Defines It?

As quality improvement and physician performance have taken center stage, the question arises as to who will define quality and its measurement. Each stakeholder has a reasonable perspective for viewing quality differently, including the patient and the physician.[1,3] A patient might define quality as the relief of a symptom, the perception of a cure, or an improvement in lifestyle. However, the physician might define quality as the achievement of a particular desired or expected medical or surgical outcome. An employer may see quality as a return on investment for premiums paid, reduced liability for injury, and a workforce that is healthy, productive, and present in the workplace. A health plan purchaser may look at global health outcomes and the need to spread vast resources over large populations with competing

needs. Therefore defining quality and deciding exactly what to measure to determine whether quality is being delivered continues to be debated.

In oversimplified terms, most measures of clinical quality or performance today fall into the following categories:

- Outcomes measures
- Process measures
- Capacity and structure measures
- Administrative measures
- Cost and efficiency measures
- Patient experience or satisfaction measures

Argument continues over choosing what to measure. Purchasers of health care have access to voluminous claims and economic data, making administrative, cost effectiveness, and capacity measures attractive.[13,14] Although many physicians opposed to administrative or efficiency measures clamor for outcomes measures as the only valid assessment of physician performance, in truth, physicians rarely have complete control over all the factors that determine medical outcomes. Additionally, for valid outcome measures, effective risk adjustment needs to occur to reflect differences in the case mix of the patients served; this is often neglected, which results in misleading outcome data. Process measures are easier to define and are more attributable to the practitioner. However, focusing primarily on processes of care can be deceptive when no one takes responsibility for the final outcome. Levels of evidence for different types of interventions can vary greatly, especially when comparing chronic medical care that may involve primarily medication management to acute surgical care for which randomized, double-blind, controlled studies may not exist or even be feasible. Because elements such as availability of support services and tertiary care, patient compliance, comorbidities, ethnic and religious practices, and preferences can all influence the assessment of any medical outcomes, measuring performance attributable to and under the control of the physicians being measured must be a common basic theme if fairness and true patient-centered quality improvement are to be achieved.[13,15]

The purpose for which measures are developed has a powerful influence on how those measures look and what kinds of measures are employed. Among other reasons, performance is measured today for the following overlapping purposes:

- Researching, developing, and improving the effectiveness of an intervention
- Reducing medical error
- Improving patient safety
- Certifying achievement—meeting standards for maintaining board certification or privileges
- Credentialing or accreditation—documenting competence or proficiency for payment or inclusion in a plan, group, or tier
- Licensing and disciplining—identifying, limiting, and punishing poor performance

There is both overlap and synergy between these categories, as well as distinct subcategories further separating these types of measures. The AMA House of Delegates recently addressed criteria and standards for acceptable elements of any pay-for-performance system. As the quality movement matures and value-based purchasing takes different forms, such criteria will become increasingly important to ensure patient-centeredness.

The Process of Building a Coherent System of Performance Measurement

There are three basic principles that must underscore the role of physicians and their organizations in addressing performance and quality improvement.

- First, it is essential that *practicing physicians*, not just methodologists and health policy scientists, actively and formally engage in prioritizing, developing, field testing, and implementing quality initiatives and performance measures.
- Second, demand for quality and its definition and measurement must be aggregated.
- Third, physicians and their organizations must be unified in their response to this demand.

Engaging in Performance Measures Development

As can be seen from even a cursory scan of the practice environment during the first part of the twenty-first century, every stakeholder group is placing powerful impetus behind defining quality improvement and implementing measurement primarily motivated by the desire to improve efficiency in utilization of resources, reduce medical error, advance patient safety, address inequity and maldistribution of health care, and control a national and global crisis of escalating health care costs.[1,14,16] As described in more detail later, failure of physicians to engage and ensure that any definition of quality or program for improvement is truly based on scientific evidence and is relevant and valid to improving patient health outcomes will allow proprietary measurement to focus solely on administration, capacity, and cost. Although these are legitimate concerns, physicians must insist on keeping the focus on improving the patient's health, not on driving profitability for purchasers of health care.[17]

Aggregating Demand for Performance Measurement

With so many organizations involved in quality initiatives and the development of measures, one of the largest concerns that physicians have is trying to "aggregate the demand" for measures—in other words, to make sure that payers, purchasers, licensing and certification processes, and quality improvement organizations are all asking for the same measures, that the measures are based on solid evidence, and that they are focused on similar quality improvement goals. Imagine an environment in which each independent insurance carrier, every major employer who pays premiums for employee health care benefits, government purchasers such as Medicare or state Medicaid contractors, state licensing boards, and specialty certifying boards all developed and required a physician to gather and report data on quality through a separate mechanism and with differing goals and purposes. The administrative quagmire would be a nightmare and virtually impossible to navigate, even for large clinics and groups with sophisticated electronic medical record systems and resources. The ideal situation would be to standardize data points, create a single or simplified set of measures for a given clinical condition or intervention, and establish agreement among stakeholders to accept a unified process of measuring quality.

Unifying the Response to the Demand for Performance Measurement

The medical profession is not homogeneous. Specialists of varying backgrounds, training, and experience may treat similar conditions and bring diverse perspectives to their delivery of health care services. Undesired variation in health care and its outcomes is one of the hallmarks of poor quality.[3,7,12] It is not in the patient's or society's best interest to have varying processes and quality measures for a given clinical condition coming from competing specialties or groups. For example, pediatricians, family physicians, otolaryngologists, emergency physicians, and infectious disease specialists could all develop and implement competing guidelines and performance measures for treating otitis media based on limited perspective and with varying data points and recommendations. This fosters unhealthy competition and turf battles, and

is unlikely to improve quality care. By engaging in multidisciplinary work groups, definitions can be standardized, best evidence can be reviewed and analyzed, scope and purpose of measurement can be agreed upon, learning can take place, and acceptable guidelines and measures can be developed that all physicians who treat otitis media, regardless of specialty perspective, can use to improve their clinical care. Creating evidence-based guidelines and performance measures is labor intensive and costly. By collaborating in a multidisciplinary fashion, waste of resources from competing and parallel development processes can be avoided.

In designing a validated, relevant, and attributable system of measurement, the following process is useful and involves the best combination of rigor and scientific foundation with practical implementation at the physician-patient level.

- Identify and prioritize areas that can be measured and improved
- Develop or identify the best evidence or guidelines for clinical care
- Develop specific performance measures that are physician attributable, implementable, effective, practical, and affordable (See Institute of Medicine domains for quality care: effective, efficient, equitable, timely, safe, patient-centered).[12]
- Use validated, relevant, patient-oriented performance measures in systems and populations for credentialing, licensing, certifying, and documenting competence.[18,19]

Quality-Based or Value-Based Purchasing

Currently there is a sea change in the manner in which physician services are recognized, reported, and remunerated. The traditional system of paying for volume and intensity of care is being replaced by quality-based or value-based purchasing of health care services.[14] In this discussion, the popular term "pay for performance" is not used. *Performance* can apply to any required activity, regardless of whether it leads to better quality or health outcomes. Focus should remain on delivering high-quality patient care, not on some arbitrarily contractually required performance. The term "pay for performance" currently is highly politicized and is not well defined; it routinely means widely different things to different people. It will likely be replaced in a few years with other descriptors, but the underlying concept of recognizing and rewarding excellence (quality-based purchasing) is likely to be a longstanding foundation for future models of paying for health care.

The concept of rewarding excellence is based not only on the desire for improved quality, but also on the premise that poor quality care is more expensive than high quality care.[7,10,20,21] Although certainly debatable, there is evidence to support this contention in specific areas. Intuitively, healthy populations consume fewer health care interventions and cost less than sick ones. So improving public health, encouraging healthier lifestyles, and employing effective preventive medical interventions all make sense. Schematically, many discussions have linked the issue of quality to cost by relegating poor quality medical care into three categories:

- Too little care
- Too much care
- The wrong kind of care

It is clear that if poor quality in medical outcomes is the result of unneeded care, then reducing the overuse of services and improving quality would reduce health care costs. It is also not hard to believe that if the wrong kind of care is replaced by the most effective care, then costs could also be reduced. It is less obvious that correcting the problem of too little care or providing more timely care would also reduce costs. But global statistics from developed nations with better public health, preventive health, and healthy behavior or lifestyle systems that have demonstrably superior public health outcomes (e.g., infant mortality, longevity, chronic disease management) when compared with the United States at a much lower per capita cost are suggestive.[22,23]

As a result of this premise, purchasers of health care are implementing strategies that reward better medical outcomes and improved effectiveness and efficiency of care. The forces behind these strategies include the dramatic increases of health care costs in the United States at a rate more than five times the annual inflation rate, evidence that higher intensity and volume of services do not lead to better outcomes, and the increasing development and acceptance of standards for organizing and implementing quality initiatives.[4]

Medical Professionalism—The Physician-Patient Relationship

At the core of physician performance measurement is the ethical and moral obligation of all physicians to practice according to the highest standards. This is true globally, and the issues and discussions of evidence-based practice, quality improvement, and physician performance measurement are universal. The difference between a "profession" and a "trade" has often been defined by the fiduciary responsibility of the professional to act in the best interest of the public or the receiver of the service, rather than in the personal self-interest of the provider.[17,24,25] In medicine, in addition to legal requirements, virtually every association or physician group has an ethical code or stated commitment to act in the best interest of the patient.[26]

Medical professionalism is defined as a set of values, behaviors, and relationships responsible for public trust in physicians.[25] In the absence of sustained physician leadership in addressing quality, this trust is in serious danger of erosion. Many decry the commercialization of health care over the last century as a repudiation of the tradition of "doing good" in exchange for "making a profit." The ancient tradition of the covenant between the physician and patient has become a contract between physician and intermediary, creating a split loyalty to both the patient and the organization that contracts on behalf of the patient whose motive is cost containment and profit for shareholders.[17] As a result of the observation of this decline, a statement of medical professionalism has recently been developed jointly by The American College of Physicians–American Society of Internal Medicine Foundation, the American Board of Internal Medicine, and the European Federation of Internal Medicine that has been endorsed by many major physician associations in the United States, including the American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS).[27]

The ethical basis of medical care is called into question as a result of the recent well-documented health services research focused on irrefutable data that undesirable variations in physician practice and in clinical outcomes are not explained by patient factors, but are due to failure of medical practitioners and systems of care that do not incorporate the latest and best evidence or practices in health care delivery. This has stirred extensive political, public, and private debate. Because health care delivery in most parts of the Western world is still highly individual, reliance on individual physician judgment remains dominant. Unequivocal data show unwarranted and unexplained variations from recommended care on a regular basis across all disciplines.[3,4,7] Physician judgment is being challenged as population and systems studies suggest that patients are being harmed because best practices are not being observed. Personal physician accountability is an increasing focus.[3,28] Because the practice of medicine is so individualized and often unpredictable, and because a past tradition of unchallenged reliance on physician judgment exists, doctors are vulnerable to the charge that their decisions are not transparent, nor are they accountable for the global results of all they do. By combining the best available evidence for treating a condition with the physician's judgment and patient preferences, more optimal care can be achieved.[4,25,29,30]

Professionalism and the ethical and moral imperative for physicians to put their patients first should be *the* major driving force for physician performance measurement. This needs to be done in conjunction with the creation and application of systems and processes to eliminate the opportunity for error, identify error before it impacts patients, mitigate the effects of error, and thus improve patient safety and outcomes.[20,21] Physicians will need to work in concert with

all elements of health care delivery systems to accomplish this. Employers, governments, and other purchasers, contractors, administrators, and managers of health care have a reciprocal duty to help create the organizational capacity and infrastructure to support physicians in providing optimal care and fulfilling their ethical obligation to the patient. Optimal health care implies both organizational and clinical excellence. In order for a physician to maintain professionalism in our current environment, there must be a shared commitment and collaboration with the patient, fellow professionals, and the institution or system within which health care is provided, but only to the extent that all elements of the system support patients' interests first.[13,15,25,31-33]

Stakeholder Roles in Defining and Implementing Quality Improvement and Measurement Activity

To understand the landscape of physician performance measurement, one must first identify and understand the roles of key stakeholders in the public health care arena, as well as their confluent and sometimes competing perspectives. Current demand for measuring physician performance is driven by patients and public interest groups, as well as by physicians and their associations. In addition to physicians and their patients, many other groups have a legitimate and often powerful stake in measuring outcomes and performance. These stakeholders include physician educators and academic institutions, certifying boards and bodies, agencies whose missions revolve around quality, public and private purchasers of health care services (e.g., federal and state governments, employers, and private insurers), hospitals and health care systems, outpatient clinics and free-standing procedural centers, public interest groups, and many group collaboratives and agencies of all of these. Table 7-1 outlines some of the major stakeholder groups and participants in defining and advancing quality in health care delivery.[31,34]

Interface between Physician Education and Performance Measurement

Historically, practicing physicians have augmented their skills and education by engaging in continuing medical education (CME). There is currently tremendous interest in how medical education processes can be improved to advance quality in health care and institute behaviors early in training and careers that will serve physicians and their patients throughout a professional lifetime.[35,36] The most valued and acceptable form of ongoing postresidency education has been formalized by standards developed and monitored by the Accreditation Council for Continuing Medical Education (ACCME). The ACCME is made up of seven member organizations: the American Board of Medical Specialties, the American Hospital Association, the American Medical Association, the Association for Hospital Medical Education, the Association of American Medical Colleges, the Council of Medical Specialty Societies, and the Federation of State Medical Boards. Examples of the types of organizations that are evaluated and accredited by ACCME include hospitals, universities, medical associations, and proprietary medical education providers.

ACCME assists its accredited providers and shares their goal to ensure that physician education is relevant, valid, and free from bias or commercial influence in order to maintain the focus on professionalism and patient-centered care. The ACCME accomplishes this by establishing and promoting standards for physician education, by accrediting organizations that provide educational activities for physicians, and by monitoring and ensuring compliance. The issues related to quality and physician performance measurement are linked more tightly than ever before to the activities surrounding medical education, the care of patients, and the health policy and political activity related to our economy.

Traditional methods of physician CME have been mostly didactic, with minimal emphasis on other multifaceted activities, interactive media, hands-on learning, and demonstrations. Physicians have also been charged with assessing their own performance, learning, and application of new material. However, until now there has been no effective method to ensure that what is being learned is actually changing physician behavior for the better or improving patient outcomes. In fact, studies have shown that physicians are poor assessors of their own knowledge and competence. Health policy and clinical research have suggested that traditional CME has little impact on improving health outcomes or changing performance. Such research also suggests a significant difference in improving physician practice when active interventions such as reminders, patient-mediated interventions, outreach visits, and audits of performance are used with a focus on measuring outcomes.[37-39]

As a result of this evidence, the ACCME is continually expanding its requirements for accreditation of CME providers to include documentation that what is being learned will actually change behavior and lead to physician implementation and performance improvement. How that is to be measured and reported is an ongoing challenge.

Board Certification and Maintenance of Certification (MOC)

Throughout most of the twentieth century, specialty certifying boards have focused on the mission of being a public trust—ensuring that those qualifying as diplomates of the certification process meet a rigorous standard of education, knowledge, and professional standing. The American Board of Medical Specialties (ABMS) is the oversight body whose member organizations are the individual independent specialty

Table 7-1

Stakeholder Groups*

Stakeholder Group	Examples
Government purchasers and agencies	CMS—Medicare, Medicaid QIOs AHRQ VA DoD
Private purchasers of health care and their collaborations	Health plans and insurance companies Employers Private group and independently rated insurance plans AHIP The Leapfrog Group National Business Group on Health Pacific Business Group on Health
Licensing, certifying, and educational oversight bodies	FSMB and state licensing boards ABMS and professional certifying boards ACGME ACCME AAMC ABMS
Private health quality agencies	NCQA The Joint Commission
Physician societies	National, state, and county medical associations National specialty societies
Academic institutions	Medical schools Residency training programs Allied health training programs
Collaborative organizations of many stakeholder groups	National Quality Forum AQA AMA-PCPI (the Consortium) HQA

*This is not a comprehensive list but shows examples of some of the largest or most influential stakeholders. For more detail, see Table 7-2.

Box 7-1

The Mission of the American Board of Otolaryngology

The mission of the American Board of Otolaryngology (ABOto) is to assure that, at the time of certification and recertification, diplomates certified by the ABOto have met the ABOto's professional standards of training and knowledge in otolaryngology–head and neck surgery.

The American Board of Otolaryngology (www.aboto.org) was founded in 1924 and is the second oldest of the 24 member boards of the ABMS.

For a more complete review of board certification in otolaryngology–head and neck surgery, refer to *Booklet of Information* published by ABOto at www.aboto.org/BOI.htm.

certifying boards representing most of allopathic medicine (including otolaryngology). See Box 7-1. Within the ABMS there are 24 member boards representing the major practice specialty areas. There are also subspecialty certifications sponsored by one or more of the 24 major boards.

Specialty certifying boards have made it clear that they do not define, measure, or certify proficiency, competence, or performance, but rather a high standard of preparation, education, and knowledge. Following an era in the nineteenth and early twentieth centuries in which quackery, charlatanism, and undocumented claims of education and background were common, certifying boards were a major step forward. Having raised the bar significantly and successfully promoted standardized medical education and strong oversight in training and professionalism, the boards had not significantly altered their approach to certification in decades until recently. With the rapid expansion and application of biotechnology, major advances in basic and clinical science, and the identification of new disease processes and management techniques, it has become increasingly apparent that traditional board certification, without any attention to performance in practice, could become irrelevant shortly after a physician becomes certified. With the expanding emphasis on improving the quality of health care over the last decade, the public, purchasers of health care, physicians and even the licensing boards themselves began to question the value of the previous traditional method of board certification alone as evidence of competence or quality in practice. As the quality movement has gained momentum, so has the desire for certifying boards to find a method to enable the ongoing competence of their diplomates and require evidence that they maintain the standard that certification has always implied.

In the 1980s, the first ABMS specialty boards began to issue time-limited certificates. This prohibited a physician who did not recertify from using ABMS "board certification" as a credential beyond a defined period of time. Today, all ABMS board certificates are time-limited and none currently being issued are valid beyond 10 years.

There is a critical distinction between specialty certifying boards and the professional specialty societies that represent physicians. The certifying boards are independent from, and are not governed by or responsible to, physician associations. The missions of the certifying boards are to serve as a public trust, to promote standards of quality, and do not represent physician interests, except those interests that support patients and public health. Furthermore, there are many other certifying bodies outside of the ABMS. There also exists a framework of osteopathic certifying boards—The Bureau of Osteopathic Specialists, an agency of the American Osteopathic Association. Each of 18 osteopathic specialty boards offers certification of a specialty area, including osteopathic ophthalmology and otolaryngology–head and neck surgery (www.do-online.org).

The ABMS has six core competencies (formed in conjunction with the Accreditation Council on Graduate Medical Education, or ACGME) on which all member boards focus to ensure their diplomates possess a high standard of professionalism and training when first certified (Box 7-2). In 2000, in response to the demand for improved quality measures over the certificate holder's lifetime of practice, the ABMS through a vote of its member boards established standard criteria for Maintenance of Certification (MOC) with common elements that each member board would be expected to require of its diplomates (Box 7-3). The four required areas are Part I: professional standing; Part II: evidence of life-long learning and self-assessment; Part III: cognitive expertise; and Part IV: practice performance assessment. Although boards have Part IV processes in place, most are still working to determine how best to demonstrate evidence of practice quality and performance, and all boards are looking for ways to improve this criterion. This provides another strong motivation for physicians to be engaged in quality improvement and performance measurement activity: to qualify for board certification—a longstanding and respected element of a physician's credentials.

Box 7-2

ACGME/ABMS Six Core Competencies

All ABMS member boards are required to ensure that their diplomates qualify in the following competencies:

The six core competencies of all ABMS certifying boards:

1. Patient Care: Provide care that is compassionate, appropriate, and effective for the treatment of health problems and promotes health.
2. Medical Knowledge: Demonstrate knowledge about established and evolving biomedical, clinical, and cognate sciences and their application in patient care.
3. Interpersonal and Communication Skills: Demonstrate skills that result in effective information exchange and teaming with patients, their families, and professional associates (e.g., fostering a therapeutic relationship that is ethically sound, using effective listening skills with nonverbal and verbal communication, working as both a team member and at times as a leader).
4. Professionalism: Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to diverse patient populations.
5. Systems-Based Practice: Demonstrate awareness of and responsibility to larger context and systems of health care. Call on system resources to provide optimal care (e.g., coordinating care across sites or serving as the primary case manager when care involves multiple specialties, professions, or sites).
6. Practice-Based Learning and Improvement: Investigate and evaluate patient care practices, appraise and assimilate scientific evidence, and improve practice of medicine.

ABMS, American Board of Medical Specialties; *ACGME,* Accreditation Council on Graduate Medical Education.

State Medical Boards and Maintenance of Licensure

The legal permission to practice medicine in the United States is granted by state licensure. Each state has its own professional practice act that defines the practice of medicine and establishes a medical board charged with licensing qualified physicians and prescribes the manner in which physicians will be scrutinized to ensure the public will be protected and well served by each licensee. State medical boards and their requirements are fairly standardized and uniform in most respects, and states support each other in weeding out the incompetent and unprofessional.

The Federation of State Medical Boards (FSMB) is a membership organization whose constituents are independent state licensing boards

Box 7-3

Maintenance of Certification Requirements

Whereas the American Board of Medical Specialties (ABMS) guides the Maintenance of Certification (MOC) process, the 24 member boards of the ABMS set the criteria and curriculum for each specialty. All certificates issued by the American Board of Otolaryngology (ABOto) since 2002 are time-limited for 10 years. To maintain ABOto certification, all diplomates with time-limited certificates must participate in MOC, which includes these requirements.

A Four-part Process for Continuous Learning

Part I—Professional Standing

- Possess an unrestricted license in all states in which the diplomate practices
- Maintain hospital or ambulatory surgical center privileges (if diplomate does not have privileges, he or she must attest that the lack of privileges is not due to an adverse action)

Part II—Lifelong Learning and Self-Assessment

- Obtain sufficient CME credits to meet the individual's state CME requirements (15 credits minimum)
- Participate in the ABOto self-assessment program, which includes on-line clinical management modules

Part III—Cognitive Expertise

- Since many otolaryngologists tend to focus on a limited area of practice, the examination consists of two modules:
  - Fundamentals module for all otolaryngologists, which covers material all otolaryngologists should know such as patient safety, antibiotics, anesthetics, and pain management
  - Specialty specific module; diplomates select one module:
    - Allergy
    - General
    - Head and neck
    - Laryngology
    - Otology/audiology
    - Pediatric otolaryngology
    - Plastic and reconstructive
    - Rhinology
    - Sleep medicine and neuro-otology for subcertification in these areas

Part IV—Practice Performance Assessment

- The plan is to initially have participants complete an online chart survey and receive feedback on how their outcomes compare with that of their peers
- Ultimately, the ABOto hopes to obtain outcomes data from other sources

See http://www.aboto.org/BOI.htm for more information.

and their appointed leadership. Traditionally, initial licensure requires the young physician to engage in rigorous examination and scrutiny before being allowed to practice. For a variety of reasons, most state medical boards devote little time and energy in prospectively ensuring continuing competence of licensed physicians thereafter. With the exception of requiring a physician to demonstrate CME credits, there is no method for licensing boards to measure competence or performance other than reviewing complaints or accusations of malfeasance. After initial licensure, according to an FSMB draft report, "In virtually all states, it is possible for a physician to practice medicine for a lifetime without having to demonstrate to the state medical board that he or she has maintained an acceptable level of continuing qualifications or competence." The report goes on to say, "State medical boards recognize that such practices are no longer acceptable … State medical boards have historically functioned in a policing capacity, responding to complaints and devoting their resources to removing from practice the 'bad apples.' In order to meet increased public demands for greater accountability, state medical boards will need to broaden their responsibilities to include facilitating the continued competence of all licensees."[40]

In 2003, the FSMB established a special committee to study the role of independent state medical boards in ensuring the continued competence of licensees and to develop recommendations for implementation. The Special Committee on Maintenance of Licensure (MOL) responded by developing a position statement addressing the responsibility of state medical boards and suggested strategies for implementing programs to achieve that goal.

In 2004, the FSMB House of Delegates adopted a policy recommendation stating that state medical boards have a responsibility to the public to ensure the continuing competence of physicians seeking relicensure. In a subsequent report the following year, the FSMB stated that collaboration with other stakeholders interested in physician performance and competence would be essential and that state licensing boards should set the standards for relicensure and rely on other parties to develop the tools, resources, programs, and processes that would help physicians achieve those standards for ongoing competence. In its next report, released in 2008, FSMB addressed the current environmental trends that will support a climate conducive to state boards' efforts in maintenance of licensure, guidelines for reentry into practice, and ways in which FSMB can assist state boards in implementing standards for MOL.[40]

The Institute of Medicine

As managed care grew exponentially during the 1990s, autonomous physician judgment became less dominant, and medical necessity and utilization were scrutinized more closely, it became apparent that traditional accountability for quality was being shared in new ways. Few organizations have had as powerful an influence on the climate of quality improvement and measuring physician performance as the Institute of Medicine (IOM). Among the many white papers, studies, and reports it has produced, the statements on accountability, "To Err is Human," and "Crossing the Quality Chasm," have continuing impact on galvanizing stakeholders to address quality. One of the most basic standards is the statement including the IOM's six defined characteristics of acceptable care against which all performance must be measured. The IOM states that quality health care must be:

- Safe
- Patient-centered
- Timely
- Efficient
- Effective
- Equitable

An earlier IOM conference report on how accountability for quality and performance should be divided among relevant stakeholders is a landmark concept whose principles are still being used today.[41] The domains of professional accountability, market accountability, and regulatory accountability are identified and their relationships and scope described. This report clearly recognizes that historically, quality and performance have not been major features in health care contracts. A brief summary of the descriptors follows:

1. Professional accountability: "Fiduciary relationships in medicine are an essential part of any quality accountability mechanism, and it will be important to maintain the strength of the professional model in the changing health care system."

2. Market accountability: "[C]onsumers will select options based on perceived value to them and will make new choices based on their information and experience. Market accountability requires choice … and information to inform choice. In health care, however, individuals rarely have the information they need and often do not have choice."

3. Regulatory accountability: Because of a "perception of defects in a market-based health care system … there is a need for a regulatory structure to correct market failures. The use of regulation to impose accountability for quality requires that a regulatory framework, penalties for violations, and effective enforcement mechanisms are all established."

The powerful conclusion drawn a decade ago still holds true today as performance measurement is both imposed upon and shared by physicians: "[T]he medical profession … must be accountable to society for providing leadership in the development of knowledge about effective medical care, in defining high-quality care, and in advocating for and improving the quality of care."[34] More about other stakeholder perspectives is discussed later.

The Anatomy of Performance Measures

If physicians are to retain their traditional leadership role in caring for patients, they and their organizations must take a leadership role in defining and measuring quality and performance in their professional behavior. Specialty societies, representing the content and practice experts, must insist that performance measures be relevant, patient-centered, focused on medical and health outcomes, validated, practical, affordable, and attributable to those whose performance is being measured. Performance measures should be based on the best available evidence, such as high-quality clinical guidelines that systematically inform and assist physicians and their patients in decision making about appropriate care.[30] Developers of performance measures, including medical specialty societies, academicians, methodologists, and systems experts, must have a process in place with agreed-upon standards for reviewing and evaluating clinical evidence and creating guidelines for treating relevant conditions. With this in mind, the American Academy of Otolaryngology–Head and Neck Surgery convenes a Guidelines Development Task Force with representatives from all national otolaryngology societies and ABOto to identify, prioritize, and plan the development of guidelines based on the best clinical evidence to serve as the foundation for performance measures. To ensure rigor in this process, a guidelines development manual has been published with input from multiple disciplines, which is used by each topic-specific task force.[42] Representation from all relevant specialties on each guideline is sought to ensure that guidelines are broadly acceptable and to prevent specialty bias.

A clinical performance measure can be most simply viewed as an equation or fraction representing the frequency of an appropriate and recommended intervention. It contains a denominator—the number of patients for whom a given intervention or recommendation applies; a numerator—the number of patients who actually received the recommended intervention; and exclusions—those patients for whom the recommended care was not given for specific reasons identified and excluded by the measure (Fig. 7-1). Although simple in concept, in reality the development and implementation of a performance measure can be extremely complicated and controversial. The process of translating guidelines into performance measures involves reviewing the action statements inherent or explicitly recommended in the guideline, defining the patient populations to whom the actions do and do not apply, developing a logical scheme for collecting information to measure how often the actions recommended in the guideline are carried out, and creating the tools for physicians to efficiently and accurately collect that information affordably and with little disruption of their clinical activity. In order to achieve high quality, standardization, unity, and collaboration, closely related specialty societies agree to work together within the framework of the AMA's Physician Consortium for Performance Improvement (PCPI, also called the Consortium). This allows multiple societies with common areas of interest to work collegially, coordinate care, create measurement that can easily cross specialty boundaries, and unify physician response to the multifaceted demand for measures.

The Consortium is comprised of more than 100 national medical specialty and state medical societies, as well as methodologic experts and other stakeholders in measures development. They select topics for developing measures that are attributable to physicians, that can be implemented, for which established clinical recommendations (often guidelines) are available, and for which feasible data sources exist. They then recruit multidisciplinary work groups from all of the specialties relevant to a measure set. The Consortium work groups review the levels of evidence provided in clinical practice guidelines that demonstrate potential positive impact on health outcomes and propose feasible measures for inclusion in a physician performance measurement set. The Consortium then assists in developing and assessing tools for collecting the data required for measurement in practice, using either centralized or distributed, paper or electronic methods.

Other Stakeholder Perspectives

Virtually every stakeholder group is heavily involved in quality initiatives and performance measures development. In this section a representative sample of additional major agencies and organizations is briefly introduced. Because of the varying perspectives and backgrounds of these stakeholders, an extensive collection of collaborations and consortia has emerged to promote quality across stakeholder groups, to align incentives and goals, and to combine resources. This has created a dizzying array of potential activity with which physicians might be required to engage. Table 7-2 summarizes some of the related acronyms and terms. A few of them are briefly discussed here.

The Agency for Healthcare Research and Quality (AHRQ) is charged by the federal government to serve as the health services research arm, just as the National Institutes of Health (NIH) serves as the basic and clinical research arm. In addition to fostering research into quality, performance measurement, technology assessment, preventive medical care, delivery systems, and health care costs, AHRQ is a major source of funding for academic and community-based organizations engaged in health services research and implementation activity. AHRQ supports evidence-based clinical practice, develops and tests measures, and promotes the use of measures through dissemination of guidelines and measures. AHRQ also provides support for many of the quality improvement initiatives undertaken by the Centers for Medicare and Medicaid Services (CMS).

The National Committee for Quality Assurance (NCQA) is a private nonprofit quality organization that has been accrediting health plans and developing performance measures since 1990. Their goal is simple—measure, analyze, improve, repeat. Organizations that qualify for the NCQA seal must first pass rigorous review, report annually on a set of measures, and deliver high-quality care and service. The performance measurement set used in NCQA's accreditation process and most frequently reported to purchasers and the public are HEDIS (Health Plan Employer Data and Information Set) measures and CAHPS (Consumer Assessment of Health Providers and Services) surveys of patient experiences of care. CAHPS was developed by AHRQ and has survey instruments that apply not only to patient experiences with health plans but also with individual physicians and clinician group practices.

The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations, or JCAHO) creates standards and measures performance for hospitals, freestanding ambulatory care centers, office-based surgery, long-term care facilities, and others. Its mission is to continuously improve the safety and quality of care provided to the public through the provision of health care accreditation and related services that support performance improvement in health care organizations. Its standards cover structural characteristics and processes of care and include standards that measure the degree to

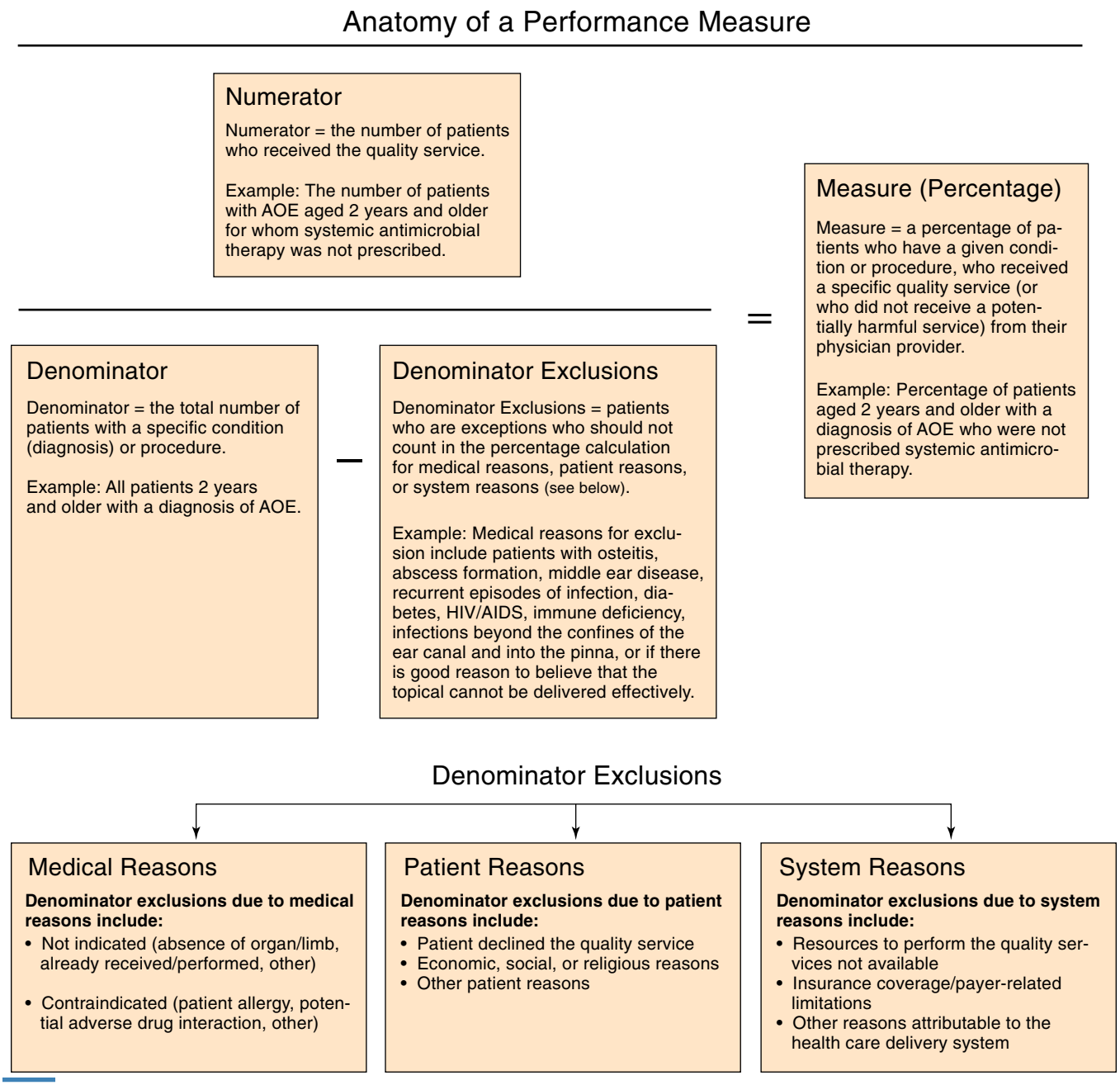

Figure 7-1. Anatomy of a performance measure. Both the schematic and a current example of an existing measure of quality in treating acute otitis externa (AOE) are applied for illustration. One of the measures of improved quality in treating acute otitis externa is the avoidance of unnecessarily administering systemic antibiotics. Compliance with this measure of quality is demonstrated in the formula. *(With permission of the American Academy of Otolaryngology–Head and Neck Surgery Foundation.)*

which facilities conform to guidelines for promoting a set of National Patient Safety Goals.

The Physician Consortium for Performance Improvement (PCPI, or the Consortium) is composed of representatives of more than 100 specialty societies and methodologic experts in measures development. They select topics for performance measures development that are actionable, for which established clinical recommendations are available, and for which feasible data sources exist. They then recruit cross-specialty work groups from all of the specialties relevant to a measures set. The Consortium work groups review the levels of evidence provided in clinical practice guidelines that demonstrate potential positive impact on health outcomes and propose feasible measures for inclusion in a physician performance measurement set. The Consortium then develops and tests tools for collecting the data required for measurement in practices with both paper and electronic records systems.

The organizations that are (and should be) most actively engaged in the development of performance measures are the physicians, usually through their medical specialty societies. Performance measures should be based on high-quality clinical guidelines that systematically develop and assist practitioners and patients in decision making about appropriate care. Each medical specialty society has a process in place for reviewing and evaluating clinical evidence and creating guidelines for treating conditions relevant to that specialty society.

The process of translating guidelines into performance measures involves reviewing the action statements inherent in the guideline, defining the patient populations to whom the actions do and do not apply, developing a logical scheme for collecting information to measure

Table 7-2

Glossary of Terms and Acronyms of Groups Engaged in Defining, Measuring, or Reporting on Quality in Health Care

Acronym or Abbreviation	Title of Group and Description
AAMC	The Association of American Medical Colleges (AAMC) is a nonprofit organization established in 1876. AAMC is the principal administrator of the Medical College Admission Test (MCAT) and is involved in the accreditation of medical schools that grant medical degrees and of teaching hospitals in the United States and Canada.
ABMS	The American Board of Medical Specialties (ABMS) was established in 1933 and is a nonprofit physician-led organization that oversees the certification and ongoing professional development of physician specialists by its 24 medical specialty member boards. ABMS works closely with the member boards to set educational and professional standards for the evaluation and certification of physician specialists.
ABOto	The American Board of Otolaryngology, founded in 1924, is the second oldest of the 24 ABMS member boards. See Boxes 7-1 and 7-3.
ACCME	The Accreditation Council for Continuing Medical Education (ACCME) is the overseeing body for continuing medical education (CME) in the United States. The ACCME sets the standards for the accreditation of all providers of CME activities. The ACCME's seven member organizations are the American Board of Medical Specialties (ABMS), the American Hospital Association (AHA), the American Medical Association (AMA), the Association of American Medical Colleges (AAMC), the Association for Hospital Medical Education (AHME), the Council of Medical Specialty Societies (CMSS), and the Federation of State Medical Boards (FSMB).
ACGME	The Accreditation Council for Graduate Medical Education (ACGME) is the body responsible for the accreditation of postgraduate medical training programs (i.e., internships, residencies, and fellowships—now all called "residencies") for medical doctors in the United States. It is a nonprofit private council that evaluates and accredits medical residency programs. The ACGME oversees the postgraduate education and training for all allopathic and the majority of osteopathic physicians in the United States.
ACS	The American College of Surgeons (ACS) is an educational association of surgeons created in 1913 to improve the quality of care for the surgical patient by setting high standards for surgical education and practice. Members of the ACS are referred to as "Fellows." The letters FACS (Fellow, American College of Surgeons) after a surgeon's name mean that the surgeon's education and training, professional qualifications, surgical competence, and ethical conduct have passed a rigorous evaluation, and have been found to be consistent with the high standards established and demanded by the College.
AHIP	America's Health Insurance Plans (AHIP) is a national political advocacy and trade association with about 1300 member companies that provide health insurance coverage to more than 200 million Americans. AHIP was formed through the merger of Health Insurance Association of America (HIAA) and American Association of Health Plans (AAHP).
AHRQ	The Agency for Healthcare Research and Quality (AHRQ) (formerly known as the Agency for Health Care Policy and Research), is a part of the United States Department of Health and Human Services which supports research designed to improve the outcomes and quality of health care, reduce its costs, address patient safety and medical errors, and broaden access to effective services.
AMA	The American Medical Association (AMA), founded in 1847 and incorporated in 1897, is the largest association of medical doctors and medical students in the United States. The AMA's mission is to promote the art and science of medicine for the betterment of the public health, to advance the interests of physicians and their patients, to promote public health, to lobby for legislation favorable to physicians and patients, and to raise money for medical education. It also publishes the *Journal of the American Medical Association* (JAMA), which has the largest circulation of any weekly medical journal in the world.
AMA PCPI (also known as the Consortium)	The AMA-convened Physician Consortium for Performance Improvement is a physician-led initiative that includes methodologic experts, clinical experts representing more than 100 national medical specialty societies, state medical societies, medical specialty boards, AHRQ, NCQA, the Joint Commission, CMS, and other stakeholders. The Consortium, in conjunction with the stakeholders represented, develops performance measurement sets and clinical quality improvement tools useful for the practicing physician. The Consortium's vision is to fulfill the responsibility of physicians to patient care, public health, and safety by becoming the leading source organization for evidence-based clinical performance measures and outcomes reporting tools for physicians.

Table 7-2

Glossary of Terms and Acronyms of Groups Engaged in Defining, Measuring, or Reporting on Quality in Health Care—cont'd

Acronym or Abbreviation	Title of Group and Description
AQA	Formerly called the Ambulatory Care Quality Alliance, the AQA was formed in 2004 by AHRQ, AHIP, ACP, and AAFP (American Academy of Family Physicians). The AQA is one of two consensus organizations (along with the NQF) that can approve measures for implementation on a national level for CMS (Medicare and Medicaid) programs and other health plans. The AQA is composed primarily of health plans (payers including CMS), employers (purchasers), clinicians—physicians and nonphysicians, consumer groups, and supporting industries.
B2E or BTE	Bridges to Excellence, a not-for-profit coalition-based organization (predominantly purchaser-driven) was created to encourage voluntary participation in quality health care initiatives by recognizing and rewarding health care providers who demonstrate that they deliver safe, timely, effective, efficient, equitable, and patient-centered care.
CAHPS	The Consumer Assessment of Healthcare Providers and Systems is a public-private initiative to develop standardized surveys of patients' experiences with ambulatory and facility-level care, first launched and funded by AHRQ in 1995. Health care organizations, public and private purchasers, consumers, and researchers use CAHPS results from standardized surveys to assess the patient-centeredness of care, compare and report on performance, and improve quality of care. A surgical CAHPS instrument has been developed with support from the ACS with participation from other surgical societies, including otolaryngology.
CMS	The Centers for Medicare and Medicaid Services (CMS), previously known as the Health Care Financing Administration (HCFA), is a federal agency within the United States Department of Health and Human Services (HHS) that administers the Medicare program and works in partnership with state governments to administer Medicaid, the State Children's Health Insurance Program (SCHIP), and health insurance portability standards.
DoD	The United States Department of Defense (DoD) is a major purchaser and provider of health care for its military employees, service men and women, and their beneficiaries. It partners with the VA, CMS, HHS, and other government organizations in quality measurement and reporting initiatives.
DOQ-IT	The Doctor's Office Quality—Information Technology (DOQ-IT) program is a national initiative that promotes the adoption of Electronic Health Record (EHR) systems to improve quality and safety for Medicare beneficiaries in small- and medium-sized physician offices.
EHR (EMR; HIT)	Electronic Health Record (Electronic Medical Record or Health Information Technology)
FSMB	The Federation of State Medical Boards (FSMB) is a not-for-profit organization composed of 70 medical licensing and disciplinary boards of the United States and its territories and serves as an authoritative source of research, policy development, education, and information. The FSMB's primary mission is to improve the quality, safety, and integrity of health care by promoting high standards for physician licensure and practice and assisting state medical boards in protecting the public. The FSMB monitors state and federal legislative initiatives, works collaboratively with state and federal regulatory agencies, and offers legislative assistance to and on behalf of its member medical boards.
HQA	The Hospital Quality Alliance (HQA) works to improve care through information—it is a public and private collaboration to improve the quality of care provided by the nation's hospitals by measuring and publicly reporting on that care. Quality performance information collected from the more than 4000 participating hospitals is reported on *Hospital Compare*, a website tool developed by the CMS.
IHI	The Institute for Healthcare Improvement (IHI) is a not-for-profit organization that aims to lead the improvement of health care throughout the world. Their goals are to improve the lives of patients, the health of communities, and the joy of the health care workforce by focusing on initiatives in safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity.
IOM	The Institute of Medicine (IOM) is one of the four United States National Academies, and is a not-for-profit, nongovernmental American organization chartered in 1970 as a part of the National Academy of Sciences. The IOM reports, such as "To Err Is Human," are often referred to in developing quality improvement initiatives. The IOM domains are effectiveness, efficiency, equity, patient-centeredness, safety, and timeliness.
The Joint Commission	The Joint Commission, until 2007 the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), is a United States–based nonprofit organization formed in 1951 with a mission to maintain and elevate the standards of health care delivery through evaluation and accreditation of health care organizations.

Continued

Table 7-2

Glossary of Terms and Acronyms of Groups Engaged in Defining, Measuring, or Reporting on Quality in Health Care—cont'd

Acronym or Abbreviation	Title of Group and Description
Leapfrog Group	The Leapfrog Group is an employer group formed by a number of major U.S. corporations that strongly encourages the adoption of a number of safer practices in hospitals, including EMR, proper staffing of intensive care units, concentrating highly technical surgical procedures in high-volume centers, and implementation of the NQF Safe Practices.
NBGH	The National Business Group on Health (NBGH) members are primarily Fortune 500 companies and large public sector employers—including the nation's most innovative health care purchasers—who provide health coverage for more than 50 million U.S. workers, retirees, and their families. The NBGH fosters the development of a safe, high-quality health care delivery system and treatments based on scientific evidence of effectiveness.
NCQA	The National Committee for Quality Assurance is a private nonprofit committee creating standards and measures for quality. It was established in 1990 with support from the Robert Wood Johnson Foundation. NCQA accredits and certifies a wide range of health care organizations including health plans and physician organizations. Health plans seeking accreditation by NCQA measure performance often utilizing data from tools such as the Healthcare Effectiveness Data and Information Set (HEDIS) and the CAHPS survey. The NCQA also has a voluntary program to recognize individual physicians who follow evidence-based guidelines and use evidence-based measures and up-to-date information and systems to enhance patient care.
NGC	The National Guidelines Clearinghouse at www.guideline.gov is a public online comprehensive database of evidence-based clinical practice guidelines. NGC is an initiative of the AHRQ and the HHS. The mission of NGC is to provide physicians, nurses, and other health professionals, health care providers, health plans, integrated delivery systems, purchasers and others an accessible mechanism for obtaining objective, detailed information on clinical practice guidelines and to further their dissemination, implementation, and use. NGC was originally created by AHRQ in partnership with the AMA and the American Association of Health Plans (now AHIP).
NSQIP	The ACS National Surgical Quality Improvement Program (ACS NSQIP) is the first nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of hospital surgical care. The program employs a prospective, peer-controlled, validated database to quantify 30-day risk-adjusted surgical outcomes, which allows valid comparison of outcomes among all hospitals in the program. The ACS NSQIP is available to all private sector hospitals that meet the minimum participation requirements, complete a hospital agreement, and pay an annual fee. The goal is the reduction of surgical mortality and morbidity. The VA has a parallel system (VA NSQIP) to compare its results against the ACS NSQIP private sector data.
NQF	The National Quality Forum (NQF) is a voluntary consensus standards-setting organization as defined by the National Technology Transfer and Advancement Act of 1995. The NQF is the other of two consensus organizations (along with the AQA) that can endorse measures on a national level for CMS quality programs and for other health plans. The NQF is a membership organization created to develop a national strategy for health care quality measurement and reporting. The NQF has participation from consumers, purchasers, health plans, hospitals (providers), health professionals (including physicians and non-physicians), accrediting bodies, labor unions, and supporting industries.
NQMC	The National Quality Measures Clearinghouse (NQMC), www.qualitymeasures.ahrq.gov, sponsored by the AHRQ and HHS, is a public repository for evidence-based quality measures and measure sets. The NQMC also provides excellent educational resources for those who want to learn more about quality measures.
ONC	The Office of the National Coordinator for Health Information Technology (ONC) provides counsel to the Secretary of HHS and departmental leadership for the development and nationwide implementation of an interoperable health information technology infrastructure. Use of this infrastructure will improve the quality, safety, and efficiency of health care and the ability of consumers to manage their health information and health care.
PCPI	Physician Consortium for Performance Improvement (see AMA PCPI above).
PBGH	The Pacific Business Group on Health (PBGH), a business coalition of 50 purchasers, seeks to improve the quality and availability of health care while moderating cost. Since 1989, PBGH has played a leading role both nationally and in California in health care quality measurement and system accountability through public reporting.
QASC	Government agencies, physicians, nurses, pharmacists, hospitals, insurers, employers, consumers, accrediting agencies, and others have formed the Quality Alliance Steering Committee (QASC) to better coordinate the promotion of quality measurement, transparency, and improvement in care. Through the efforts of the QASC, Americans will have helpful information on health care available through the Internet.

Table 7-2

Glossary of Terms and Acronyms of Groups Engaged in Defining, Measuring, or Reporting on Quality in Health Care—cont'd

Acronym or Abbreviation	Title of Group and Description
QIO	Quality Improvement Organizations (QIOs) monitor the appropriateness, effectiveness, and quality of care provided to Medicare beneficiaries. They are private contractor extensions of the federal government that work under the auspices of the CMS.
SQA	The Surgical Quality Alliance (SQA), which is convened by the ACS, aims to bring more than 20 surgical specialties and anesthesiology together to coordinate the definition and measurement of surgical quality and respond to federal and private quality-related initiatives. SQA provides a forum to coordinate efforts among specialties to monitor and participate effectively in patient data registries, data aggregation, and the development, validation, and implementation of physician performance measures.
VA	The United States Department of Veterans Affairs (VA) is a government-run military veteran benefit system with Cabinet-level status. It is responsible for administering benefits, including health care, for veterans, their families, and survivors (see also DoD).

how often the actions recommended in the guideline are carried out, and creating the tools for physicians to collect that information as part of their ongoing clinical activities. Some medical specialty societies undertake the translation of guidelines into performance measures themselves, but many choose to work through the AMA's Physician Consortium for Performance Improvement (Fig. 7-2).

The National Quality Forum (NQF) is a voluntary consensus standards organization with a broad membership of providers, payers, and health plans working to create a standardized national set of measures that can be used to evaluate the entire spectrum of care. The NQF endorses national standards for measurement created by other groups and promotes public reporting of health care performance data that provide meaningful information about quality of care. Because of its broad stakeholder makeup, its endorsement facilitates the rapid acceptance and implementation of quality activity. The NQF has endorsed quality measures developed by the AMA's Consortium, which have then been adopted for use by both CMS and private-sector purchasers of health care.

The NQF derives most of its clout in the health care marketplace from a provision in the National Technology Transfer and Advancement Act of 1995 (Public Law 104-113) that requires federal agencies to use technical standards that are developed or adopted by voluntary consensus standards organizations. Because NQF is such an organization, Medicare (CMS), as a federal agency, is required to use NQF-endorsed measures if it intends to engage in quality initiatives in those areas addressed by NQF. Developers of performance measures who want to aggregate demand and have their measures become the national standard will submit them to the NQF's technical review and consensus process, knowing that if the measures are endorsed by NQF they are likely to be broadly adopted in the marketplace.

The AQA alliance (formerly the Ambulatory Care Quality Alliance) was formed in September 2004 by the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), America's Health Insurance Plans (AHIP), and the Agency for Healthcare Research and Quality (AHRQ). These organizations joined together to lead an effort for determining, under the most expedient timeframe, how to most effectively and efficiently improve performance measurement, data aggregation, and reporting in the ambulatory care setting. However, its activity has now expanded to all treatment and care settings. AQA's mission and goals focus on key areas that can help identify quality gaps, control skyrocketing cost trends, reduce confusion over redundant measures, and alleviate administrative burdens for physicians and purchasers.[43-45]

The Hospital Quality Alliance (HQA) is a voluntary alliance led by the Association of American Medical Colleges (AAMC), American Hospital Association (AHA), and the Federation of American Hospitals (FAH). CMS participates in this national effort that encourages hospitals to publicly report quality performance data. The data set is posted on Medicare's Hospital Compare website. The website started with a core set of clinical measures and will be adding additional clinical indicators and patient experience of care data in coming years. The activities of the HQA do not directly affect otolaryngologists because they are focused on measurement at the hospital/facility level; however, the HQA provided the prototype for the AQA, which directly affects all physicians.

The Centers for Medicare and Medicaid Services (CMS, not to be confused with CMSS, the Council of Medical Specialty Societies) is an agency of the federal government responsible for managing the health care services for all qualifying civilian beneficiaries of federal health care. *The Department of Veterans Affairs (VA)* has a similar responsibility for qualifying retired or ex-military personnel, as does the *Department of Defense (DoD)* for active military personnel. These agencies are critical to include in this discussion because they cover the health care of large numbers of people, they have been charged by presidential order to measure and improve the delivery of quality health care, and each is engaged in specific independent and collaborative quality initiatives.[46]

In addition to the alliances and consortia mentioned above, independent private groups of purchasers and administrators of health care have been organizing for years in an attempt to control what they observe to be unsustainable increases in health care costs in the private sector, just as CMS, the VA, and the DoD are working to do the same for government health care beneficiaries. Private collaborations on quality are numerous at local, state, and federal levels. A sampling of examples of the activities of several of these can be seen in a report from AAMC. However, a representative group of prominent and influential corporations and employers would include the *Leapfrog Group, the National Business Group on Health (NBGH),* and the *Pacific Business Group on Health (PBGH).* Because these groups' constituent employer members collectively pay billions of dollars in health care premiums, their concerns carry great weight in the debate about quality and cost.

Standardization and Implementation of Measures

For years, the management of expensive chronic conditions by specialty medical care providers fueled the impetus for measuring performance. Some surgical societies have less experience and often a greater challenge in finding high levels of evidence for surgical interventions. However, a number of activities are under way in many surgical societies and within the specialty of otolaryngology—head and neck surgery that are intended to bring all of the various stakeholders together to agree on standard data fields common to all surgeons, and the quality measures to be used to assess perioperative care and the performance of the health care system and individual physicians within that system. Otolaryn-

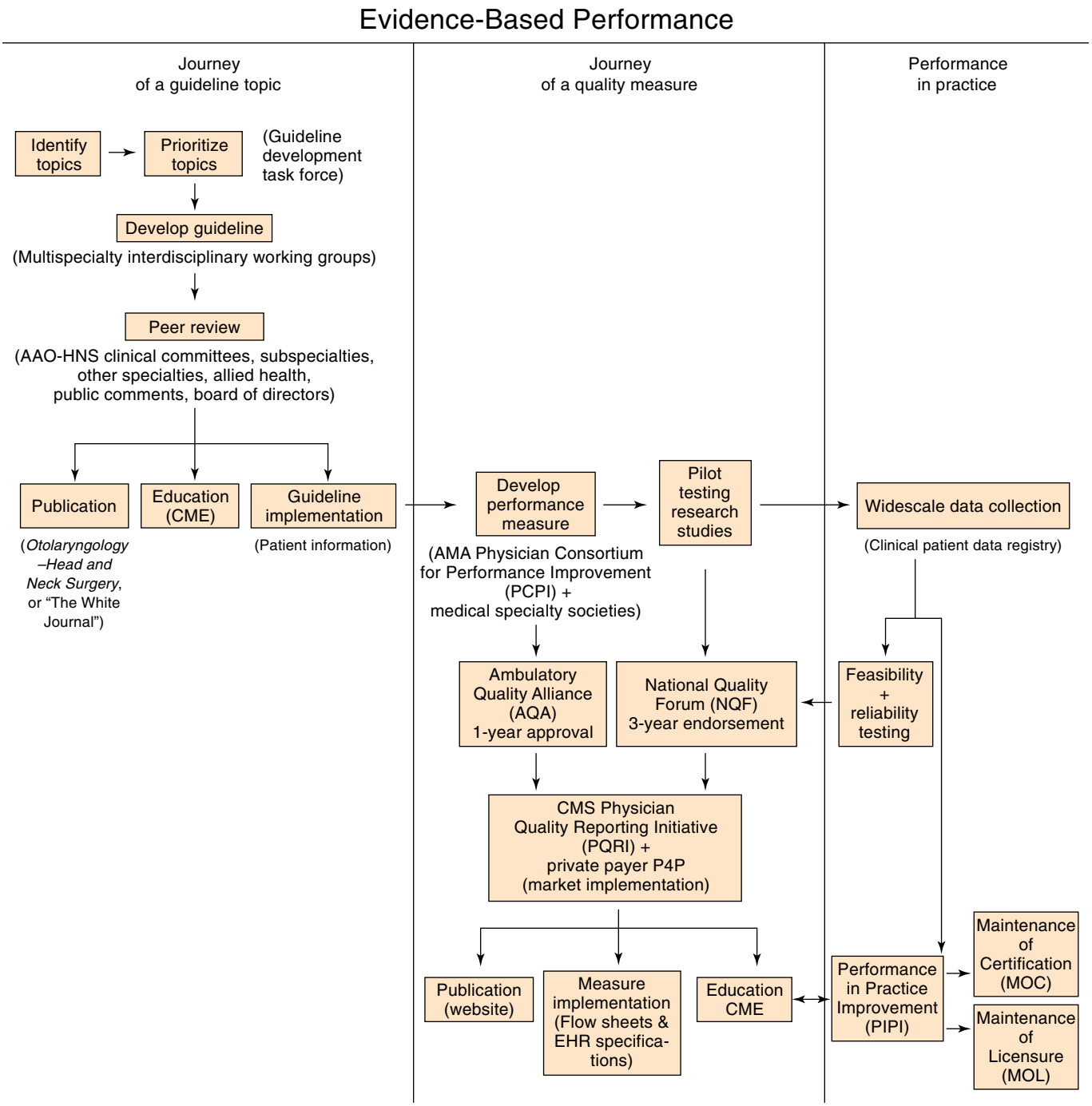

Figure 7-2. Evidence-based performance. This figure outlines the current pathway from topic identification to implementation of quality measures. AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery. *(With permission from the American Academy of Otolaryngology–Head and Neck Surgery Foundation.)*

gologists should be aware of the leadership role that their societies are playing in surgical quality.

As the AQA has gained momentum, many surgical specialty societies have recognized that the distinctive characteristics of acute surgical care and the unique issues related to measurement, data collection, and reporting for surgical care were not adequately addressed through other committees and processes. In response, the American College of Surgeons convenes the surgical specialty societies in an effort to educate surgeons about the issues, to strategize about how to best communicate the message of the unique aspects of surgical care, and to speak with one unified voice on those issues of surgical quality measurement where there is consensus. This activity has led to the formation of the *Surgical Quality Alliance (SQA),* of which the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) is a member. The SQA is staffed by the American College of Surgeons and supported through the staff and volunteer physician time of its member surgical specialty societies.

There are hundreds of existing "guidelines" related to otolaryngology from many sources. They are of variable quality, rigor, and usefulness. Most are consensus statements, with low levels of evidence, weak recommendations, or merely suggested clinical pathways or indicators. Although currently more rigorous processes for increasing the level of evidence for head and neck medical and surgical care are being employed, it is useful to examine the strength of past recommendations,

to identify best evidence, and to strengthen existing evidence where possible.

In 2006 the AAO-HNS convened the specialty's first quality conference entitled Translating Research into Cross-Specialty Measures. A follow-on conference was convened in summer 2007. As a result of the conference, an ongoing rigorous process for identifying, prioritizing, developing, validating, and implementing multidisciplinary evidence-based guidelines has been created and successfully launched. Nine otolaryngology societies and the ABOto form the Guidelines Development Task Force (GDTF), which meets quarterly throughout the year to formulate a pipeline of evidence for quality improvement activity. At this point, the GDTF and prioritized content-specific work groups are producing guidelines rigorous enough for high-quality performance measures developed through the Consortium. In ensuing years a stable of measures for every subspecialty area of otolaryngology will exist, in addition to general surgical and perioperative measures so that every otolaryngologist, regardless of practice type, will be able to comply with demand for measurement with relevant, validated, patient-centered quality activity in his or her practice.[14,17]

Barriers to Implementation of Performance Measurement

The development of performance measures should be founded on the best science. Combining health services research *with type 2 translational research*, that is, the extension of clinical advances from the bedside into populations and systems, should always be about making patients better. The processes should not be taken for granted and not every proposed quality initiative (even those that look good in print) turns out to be implementable or effective when broadly applied. An open, curious, and critical mind is no less necessary in investigating the effectiveness of quality initiatives than in basic science and clinical research. There are significant challenges to be overcome in implementing and benefiting from measuring performance in practice. First, as described, the process of identifying and strengthening the level of evidence for the care being delivered is daunting. *Eminence based medicine*, that is, patient care based on tradition or uncritical opinion, must be replaced by the best available evidence in practice. Residency training programs must engage and educate their residents and fellows in these processes and keep focus on evidence and data, combined with the best clinical expertise and patient preferences.[29,35,36] Educational (CME) processes must be implemented to ensure that physicians are aware of existing guidelines and best practices, rather than relying on the idiosyncrasies and unwarranted variation from undocumented past experience. Electronic medical records, office and hospital systems, imaging centers, laboratories, and other clinical sites must develop, implement, and integrate data collection systems that protect physician and patient privacy while seamlessly importing and exporting relevant data on practice that can be used to improve quality and patient safety and reduce medical error. The cost of such integration of systems can be tens of thousands of dollars in a small office, hundreds of thousands for larger practices, millions for clinics and groups, and close to $100 billion for national integration and standardized implementation. The Office of the National Coordinator (ONC) for health information technology (HIT) has developed a road map for creating synergistic or integrated platforms by 2014. The financial and technical barriers alone will be difficult to overcome. Much work is needed to standardize data fields, coordinate specialty requirements for data entry, integrate existing platforms, and consolidate resources. One of the most significant and difficult barriers is the resistance to change at all levels from organizations, departments, and entrenched practitioners. Even in processes as innocuous as safe medication review and coordination of care, it is difficult to alter a professional lifetime of behavior. And in an environment of cost consciousness and budget neutrality, individual physicians are feeling the pressure of having to personally fund a change in behavior being imposed by outside influences.[47]

The Surgeon's Role in Performance Measurement

Perhaps no other issue will affect physicians' clinical practice, quality of care, professional satisfaction, and economics more in the next decade than performance measurement. Otolaryngologists, their colleagues in related specialties, and their medical societies have embarked on a bold course to ensure that practicing clinicians develop an inventory of evidence-based guidelines that can apply to every practicing otolaryngologist as quickly and efficiently as possible. Every otolaryngologist who is offered an opportunity or required to participate in programs that provide incentives for quality of care should have evidence-based performance measures that are relevant to his or her practice, that are easy to collect and report, and that are shown to have a measurable impact on patient outcomes.

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CHAPTER EIGHT

History, Physical Examination, and the Preoperative Evaluation

Marion Everett Couch

Key Points

- In patients with head trauma, postauricular ecchymosis (or Battle's sign) suggests that a temporal bone fracture may have occurred.
- The pretracheal, paratracheal, precricoid (Delphian), and perithyroidal nodes are contained in level VI, which extends from the hyoid bone to the suprasternal region.
- A Virchow node, often a left supraclavicular node associated with visceral metastasis, is not in the V_B region but is located in level IV.
- When removing cerumen, remember that the canal is well supplied with sensory fibers: CN V3, the auricular branch of CN X, C3, and CN VII. CN X is also the source of referred throat pain to the ear.
- The tympanic membrane is oval, not round, and has a depressed central part called the *umbo*, where the handle of the malleus attaches to the membrane.
- This superior flaccid area is critical to examine carefully because retraction pockets may develop here, which may develop into cholesteatomas.
- In congenital cholesteatomas, often diagnosed in young children, the tympanic membrane is intact and a white mass is seen in the anterior superior quadrant. In contrast, acquired cholesteatomas in adults are often in the posterior superior quadrant and are associated with retraction pockets, chronic otitis media with purulent otorrhea, and tympanic membrane perforations.
- A midline Weber result is referred to as "negative." "Weber right" and "Weber left" refer to the direction to which the sound lateralized.
- To compare air conduction with bone conduction, perform the Rinne test using the 512-Hz tuning fork placed by the ear canal and then on the mastoid process. A "positive test" result is air conduction louder than bone conduction.
- While examining the buccal membranes, note the location of the parotid duct, or Stensen's duct, as it opens near the second upper molar.
- Small yellow spots in the buccal mucosa are sebaceous glands, commonly referred to as *Fordyce spots*, and are not abnormal.
- The hard palate may have a bony outgrowth known as a *torus palatinus.*
- The point wherein numerous small branches of the external and internal carotid arteries meet, or Kiesselbach's plexus, is the most common site for epistaxis.
- Risk factors for a perioperative cardiovascular complication include jugular venous distention, third heart sounds, recent myocardial infarction (MI) (within 6 months), nonsinus heart rhythm, frequent premature ventricular contractions (>5 per minute), age older than 70 years, valvular aortic stenosis, previous vascular or thoracic surgery, and poor overall medical status.
- The term *thyroid storm* refers to a life-threatening exacerbation of hyperthyroidism that results in severe tachycardia, fever, and hypertension.
- Treatment of hyperthyroidism attempts to establish a euthyroid state and to ameliorate systemic symptoms.
- Chvostek's sign (facial nerve hyperactivity elicited by tapping over the common trunk of the nerve as it passes through the parotid gland) and Trousseau's sign (finger and wrist spasm after inflation of a blood pressure cuff for several minutes) are clinically important indicators of latent hypocalcemia.
- Congenital deficiencies of hemostasis affect up to 1% of the population.
- Preoperatively, the platelet count should be greater than 50,000; at levels below 20,000, spontaneous bleeding may occur.
- Severe azotemia secondary to renal failure may lead to platelet dysfunction (uremic platelet syndrome). Dialysis should be performed as necessary.
- Approximately 50% of all postoperative deaths in older adults occur secondary to cardiovascular events, thus severe cardiac disease should be treated before any elective procedure and should be weighed against the benefit of any more urgent procedure.

A physician is privileged when requested to evaluate a person and render an opinion and diagnosis. The importance of obtaining an accurate, detailed patient history cannot be overemphasized because it is the framework upon which the otolaryngologist places all available information. Without this, the evaluation may be incomplete and the diagnosis flawed. Unnecessary testing may ensue, and at a minimum, a delay in symptom management may result. In the worst scenario, a misdiagnosis may occur. Therefore the energy expended in obtaining a complete history is always worthwhile.

Preoperative evaluation of surgical patients is, in its broadest sense, an extension of the diagnostic process. The surgeon should (1) strive to determine the extent of disease, (2) prove the necessity of surgery or clearly demonstrate its benefit to the patient, (3) optimize the choice of surgical procedure, and (4) minimize the risk to the patient by defining concomitant health problems and instituting appropriate therapy or precautionary measures. Integral to each of these goals is an appreciation of the ideal set forth in the Hippocratic Oath—above all else, do no harm. It is the surgeon's responsibility to ensure that an appropriate patient assessment has been completed before entering the surgical suite. Surgical complications can often be avoided by recognizing the physiologic limitations of the patient preoperatively. Documentation of findings, decision making, and discussion between surgeon and patient regarding surgical risks and benefits have become medicolegal imperatives.

Gathering a Patient History

The otolaryngologist should always try to request that previous medical records pertaining to the patient's current problem be sent to the office before the visit. If previous operations have been performed, operative reports can be important sources of information. In addition, pertinent radiographic imaging is helpful to obtain for review. Reports of computed tomography (CT) or magnetic resonance imaging (MRI) scans are valuable but cannot substitute for actual review of the imaging by the otolaryngologist. For head and neck cancer patients, any pathologic slide specimens from past biopsies should be sent to the pathology department for review so that a second opinion may be rendered. This is especially helpful when patients are referred with an unusual pathologic diagnosis. Finally, laboratory values can provide much information and should be carefully reviewed.

The physician should address the patient's chief complaint by determining its duration, intensity, location, frequency, factors that make the problem worse or better, any past therapy, and related symptoms. Whether the complaint is vertigo, pain, sinusitis, hearing loss, allergies, or a neck mass, the approach should entail asking many of the same basic questions followed by more specific ones designed to elucidate the full scope of the problem.

A discussion of the patient's medical history not only leads the otolaryngologist to a better understanding of the patient, but also often reveals pertinent information. For instance, a patient with an otitis externa who also is diabetic requires a high level of concern for malignant otitis externa, which may be reflected in the management plan. If the patient requires surgery, complete knowledge of the patient's medical problems is necessary before the operative procedure.

The surgical history is equally valuable. All the past operations of the head and neck area are important to note, including surgery for past facial trauma, cosmetic facial plastic surgery, otologic surgery, and neoplasm. However, full disclosure of all past operations may be critical. The otolaryngologist needs to know whether a patient scheduled for surgery has had adverse reactions to anesthetic agents or a difficult intubation.

Any known drug allergies and side effects are crucial to note prominently in the medical chart. True allergies should be distinguished from side effects of a medication. In addition, all medications and current dosages should be accurately recorded. Often it is valuable to inquire whether the patient has been compliant with the prescribed medication regimen because the physician needs to know what dose the patient actually is taking.

It is also advantageous to assess for risk factors associated with certain disease states. Tobacco use is important to note. It is helpful to specifically ask about cigarette, cigar, and chewing tobacco consumption—either current or past use. Alcohol consumption also is occasionally difficult to quantitate unless the interviewer asks direct questions regarding frequency, choice of beverage, and duration of use. Recreational drug use should be addressed, as should risk factors for communicable diseases such as the human immunodeficiency virus (HIV) and hepatitis virus. For patients being assessed for hearing loss, major risk factors such as exposure to machinery, loud music, or gunfire should be discussed. Finally, past irradiation (implants, external beam, or by mouth) and dosage (either high or low dose) should be ascertained. A history of accidental radiation exposure also is important to document.

Box 8-1

History

Introduce yourself

Review:
- Questionnaire
- Medical records
- Radiographic imaging
- Laboratory values
- Pathology specimens

Inquire about chief complaints:
- Location
- Duration
- Characteristics
- Medical history
- Surgical history
- Allergies
- Medications

Risk factors:
- Tobacco, alcohol
- Social history
- Family history

Review of systems:
- Respiratory
- Neurologic
- Cardiac
- Endocrine
- Psychiatric
- Gastrointestinal
- Urogenital
- Skin
- Musculoskeletal

The patient's social history should not be overlooked because it may often reveal more occult risk factors for many diseases. For instance, a retired steel worker may have an extensive history of inhaling environmental toxins, whereas a World War II veteran may have noise-induced hearing loss from his or her military service. Family history often is equally revealing, and asking patients questions about their familial history of such conditions as hearing loss, congenital defects, atopy, or cancer may uncover useful information that they had not previously considered.

Finally, a review of systems is part of every comprehensive history. This review includes changes in the patient's respiratory, neurologic, cardiac, endocrine, psychiatric, gastrointestinal, urogenital, cutaneous skin, or musculoskeletal systems. The otolaryngologist often may derive more insight into the patient's problem by inquiring about constitutional changes such as weight loss or gain, fatigue, heat or cold intolerance, rashes, and the like (Box 8-1).

Physical Examination

The otolaryngologist must develop an approach to the head and neck examination that allows the patient to feel comfortable while the phy-

sician performs a complete and comprehensive evaluation. Many of the techniques used by the otolaryngologist, such as fiberoptic nasopharyngolaryngoscopy, may leave a patient feeling alienated if not done correctly. Thus, it is essential to establish a rapport with a patient before proceeding with the examination.

A word of caution is necessary. The head and neck examination should only be done with the examiner wearing gloves and, in some instances, protective eye covering. Universal precautions are mandatory in today's practice of medicine. This has the added benefit of showing the patient that the examiner is concerned about not transmitting any diseases, which builds trust between the patient and physician.

General Appearance

Much information can be obtained by first assessing the general behavior and appearance of the patient. For instance, the patient's affect may suggest possible depression, anxiety, or even alcoholic intoxication. Psychotic behavior in the office may be a result of many factors but may indicate profound hypothyroidism in head and neck cancer patients. Astute observation of the patient's appearance is equally important. Tar-stained fingernails, teeth, or moustache are harbingers for heavy tobacco consumption. Even the gait of patients as they enter or leave the office may reveal information. Neurologic impairments, especially involving the cerebellum, may affect the patient's ability to navigate the room.

Facies

After assessing the patient's overall appearance, the face should be analyzed for facial asymmetry by positioning the head squarely in front of the examiner. For instance, in patients considering facial plastic surgery, a hemifacial microsomia may affect the final outcome, which should be discussed before the operation. In addition, a paretic facial nerve always is a serious finding that can be detected by observing the tone of the underlying facial musculature and overlying facial skin. Facial wrinkles are more prominent when the facial nerve is functioning. For patients recovering from facial nerve paralysis, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Facial Nerve Grading System is a respected standard for reporting gradations of nerve function (Table 8-1).

Table 8-1

AAO-HNS Facial Nerve Grading System

Grade	Facial Movement	
I	Normal	Normal facial function at all times
II	Mild dysfunction	Forehead: moderate-to-good function Eye: complete closure Mouth: slight asymmetry
III	Moderate dysfunction	Forehead: slight-to-moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
IV	Moderately severe dysfunction	Forehead: none Eye: incomplete closure Mouth: asymmetrical with maximum effort
V	Severe dysfunction	Forehead: none Eye: incomplete closure Mouth: slight movement
VI	Total paralysis	No movement

Facial Skeleton

The facial skeleton then should be carefully palpated for bony deformities. This is especially true in patients with recent facial trauma. The periorbital rims may be irregular as a result of fractures involving the zygomatic arches or orbital floor. The dorsum of the nose may be displaced as a result of a comminuted nasal fracture. After evaluation of the facial skeleton, the regions overlying the paranasal sinuses may be firmly palpated or tapped for tenderness, which may be present during an episode of sinusitis.

Evaluation of the temporomandibular joint (TMJ) is convenient to perform at this point in the examination. By having the examiner place three fingers over the TMJ region, which is anterior to the external auditory canal, anteromedial dislocation (caused by the action of the lateral pterygoid muscle) or clicking of the joint can be ascertained. The patient should open and close the jaw to assist in evaluating this synovial joint.

Parotid

Masses in the parotid may be benign or malignant neoplasms of the parotid, cysts, inflammatory masses, or lymph node metastasis from other areas. The tail of the parotid extends to the region lateral and inferior to the angle of the mandible. This is a common site for parotid masses to reside. The parotid-preauricular and retroauricular lymph nodes also should be systematically assessed in every patient. By facing the patient and placing both hands behind the ears before palpating the preauricular nodes, the often-neglected retroauricular nodes will not be missed.

Skin

Skin covering the face and neck should be examined, and suspicious lesions should be noted. The external auricles often receive sun exposure and are at risk for developing the skin malignancies such as basal cell and squamous cell carcinomas. The scalp should be examined for hidden skin lesions, such as melanoma, basal cell carcinoma, or squamous cell carcinoma. All moles should be inspected for irregular borders, heterogeneous color, ulcerations, and satellite lesions.

Neck

The neck, an integral part of the complete otolaryngology examination, is best approached by palpating it while visualizing the underlying structures (Fig. 8-1). The midline structures such as the trachea and larynx can be easily located and then palpated for deviation or crepitus. If there is a thyroid cartilage fracture, tenderness and crepitus may be present. In thick, short necks, the "signet ring" cricoid cartilage is a good landmark to use for orientation. The hyoid bone can be inspected and palpated by gently rocking it back and forth.

Thyroid Gland

Traveling more inferior in the neck, the thyroid gland, which resides below the cricoid cartilage, should be examined by standing behind the patient and placing both hands on the paratracheal area near the cricoid cartilage. Having the patient swallow or drink a sip of water often helps better delineate the thyroid lobes by having the trachea rise and fall. Pressing firmly in one tracheal groove allows the contents of the other side to be more easily distinguished by gentle palpation. Nodules or cystic structures should be carefully noted and evaluated, often by fine-needle aspiration. Adjacent adenopathy also should be carefully assessed.

Adenopathy

After assessing the thyroid gland, palpation of the supraclavicular area—from the paratracheal grooves posteriorly to the sternocleidomastoid muscle to the trapezius muscle—will help detect masses or enlarged lymph nodes, which are worrisome for metastasis from sources such as the abdomen, breast, or lung. Proceeding more superiorly, the area inferior to the angle of the mandible houses the carotid arteries and often has many lymph nodes, either "shoddy" and indistinct or firm. Palpable nodes always should be noted and may need evaluation with either fine-needle aspiration or radiologic imaging when observation is not appropriate. The carotid artery, often mistaken for a prominent node, can be assessed for the presence of bruits. The entire jugulodi-

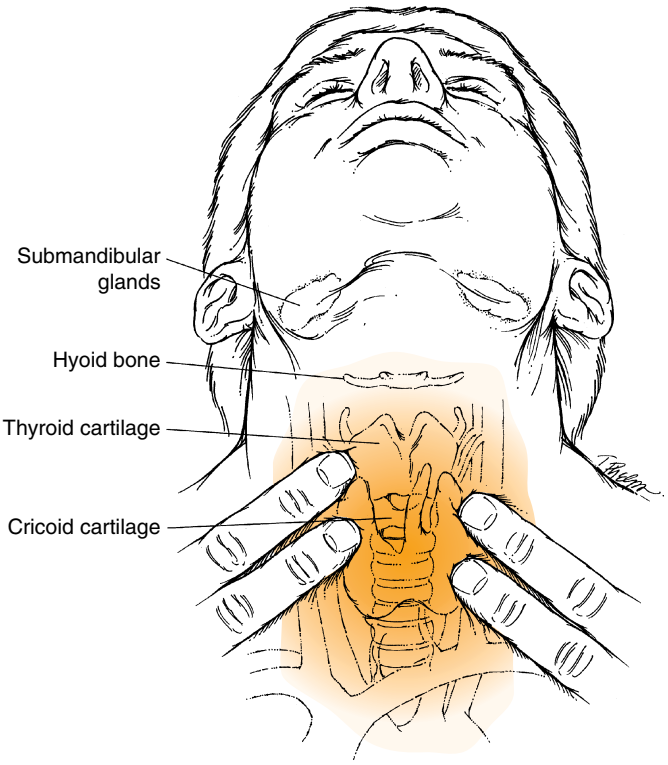

Figure 8-1. Basic anatomy of the anterior neck. Visualize structures while performing neck examination.

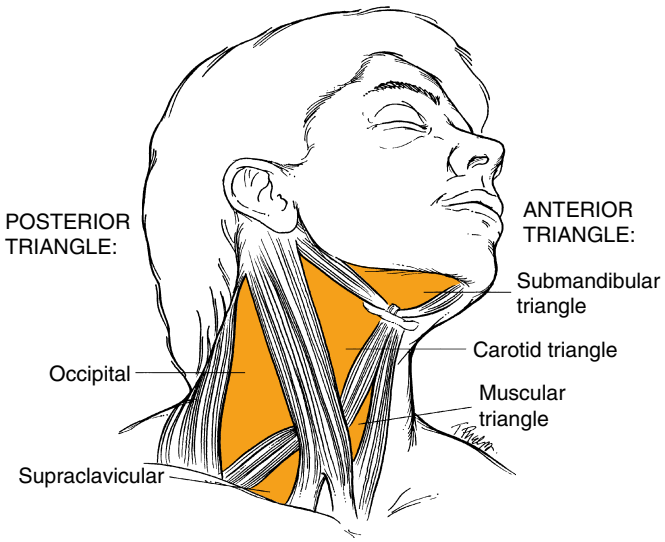

Figure 8-2. Triangles of the neck. The anterior triangle is divided from the posterior triangle by the sternocleidomastoid muscle.

gastric chain of lymph nodes merits careful inspection by outlining the sternocleidomastoid muscle and palpating the soft tissue anterior and posterior to it. The submandibular and submental regions are palpated by determining the outline of the glands and any masses present. It often is difficult to distinguish masses from the normal architecture of the submandibular gland. Therefore, bimanual palpation of this area using a gloved finger in the floor of the mouth is helpful.

Triangles of the Neck

Most physicians find it helpful to define the neck in terms of triangles when communicating the location of physical findings (Fig. 8-2). The sternocleidomastoid muscle divides the neck into a posterior triangle—whose boundaries are the trapezius, clavicle, and sternocleidomastoid muscles—and an anterior triangle—bordered by the sternohyoid, digastric, and sternocleidomastoid muscles. These triangles are further divided into smaller triangles. The posterior triangle houses the supraclavicular and the occipital triangles. The anterior triangle then may be divided into the submandibular, carotid, and muscular triangles.

Lymph Node Regions

Another classification system for neck masses, endorsed by the American Head and Neck Society and the AAO-HNS, uses radiographic landmarks to define six levels to depict the location of adenopathy (Fig. 8-3). Level I is defined by the body of the mandible, anterior belly of the contralateral digastric muscle, and the stylohyoid muscle. Level IA contains the submental nodes, and level IB consists of the submandibular nodes. They are separated by the anterior belly of the digastric muscle.

The upper third of the jugulodigastric chain is level II, whereas the middle and lower third represent levels III and IV, respectively. More specifically, the jugulodigastric lymph nodes from the skull base to the inferior border of the hyoid bone are located in level II. Sublevel IIA nodes are located medial to the plane defined by the spinal accessory nerve and sublevel IIB nodes are lateral to the nerve.

Level III extends from the inferior border of the hyoid bone to the inferior border of the cricoid cartilage, and level IV includes the

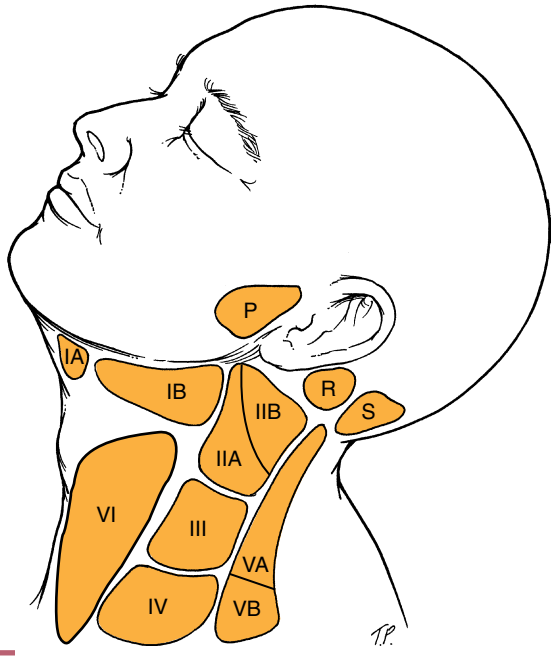

Figure 8-3. Lymph node regions of the neck. See text for details.

lymph nodes located from the inferior border of the cricoid to the superior border of the clavicle. For levels III and IV, the anterior boundary is the lateral border of the sternohyoid muscle and the posterior limit is the lateral border of the sternocleidomastoid muscle.

Level V is the posterior triangle, which includes the spinal accessory and supraclavicular nodes, and encompasses the nodes from the lateral border of the sternocleidomastoid muscle to the anterior border of the trapezium muscle. Sublevel VA (spinal accessory nodes) is separated from sublevel VB (transverse cervical and supraclavicular nodes) by a plane extending from the inferior border of the cricoid cartilage. Of note, the Virchow node is not in the VB region but is located in level IV.

The pretracheal, paratracheal, precricoid (Delphian), and perithyroidal nodes are contained in level VI, which extends from the hyoid bone to the suprasternal region. The lateral borders are the common carotid arteries.

Although not part of this classification system, the parotid-preauricular, retroauricular, and suboccipital regions are commonly designated as the P, R, and S regions.

Ears

Auricles

The postauricular region, which is frequently overlooked, often has many hidden physical findings. For instance, well-healed surgical incisions signify that previous otologic procedures have been performed. In children, the postauricular mastoid area may harbor important clues that mastoiditis with a subperiosteal abscess has developed. Finally, in patients with head trauma, postauricular ecchymosis (or Battle's sign) suggests that a temporal bone fracture may have occurred.

The area anterior to the pinna, at the root of the helix, may have preauricular pits or sinuses, which may become infected. The external auricles also may show abnormalities or congenital malformations, including canal atresia, accessory auricles, microtia, and prominent protruding "bat ears." The outer ears may have edema with weeping, crusting otorrhea, which may signify an infection. Psoriasis of the auricle or external auditory canal with its attendant flaking, dry skin, and edema is another common finding.

Careful examination of the auricles may reveal conditions that require prompt management. For instance, an auricular hematoma—with a hematoma separating the perichondrium from the underlying anterior auricular cartilage—will present as a swollen auricle with distortion of the normal external anatomy. If not surgically drained, a deformed "cauliflower ear" may result. Another important diagnosis is that of carcinoma of the auricle. Because early diagnosis is important, all suspicious lesions or masses should be judiciously biopsied or cultured. A maculopapular rash on the auricle and the external auditory canal in patients with facial nerve paralysis most likely is a result of herpes zoster oticus or Ramsay-Hunt syndrome. Finally, an erythematous painful pinna may represent many diseases, such as perichondritis, relapsing polychondritis, Wegener's granulomatosis, or chronic discoid lupus erythematosus. Metabolic disorders also may have manifestations that affect the auricles. Patients with gout may have tophus on the pinna that exudes a chalky white substance if squeezed. Ochronosis is an inherited disorder of homogentisic acid that will cause the cartilage of the auricles to blacken. These examples of various diseases and syndromes illustrate the importance of routinely examining the auricles.

External Auditory Canal

The outer third (approximately 11 mm) of the auditory canal is cartilaginous. The adnexa of the skin contain many sebaceous and apocrine glands that produce cerumen. Hair follicles also are present. The inner two thirds (approximately 24 mm) of the canal is osseous and has only a thin layer of skin overlying the bone. Cerumen is commonly found accumulating in the canal, often obstructing it. When removing cerumen, remember two points. The canal is well supplied with sensory fibers: first, CN V3, the auricular branch of CN X, C3, and CN VII. Second, the canal curves in an S-shape toward the nose. To visualize the ear canal, gently grasp the pinna and elevate it upward and backward. This will open the external auditory canal and allow atraumatic insertion of the otoscopic speculum. Cerumen impaction may be removed with many techniques, such as careful curetting, gentle suctioning, or irrigation with warm water.

Otitis externa, or "swimmer's ear," is a painful condition with an edematous, often weeping external canal. If severe, the entire canal may be so edematous and inflamed that it closes, making inspection of the tympanic membrane difficult. Gently tugging on the auricle is painful for many patients. The periauricular lymph nodes may be tender and enlarged. If the patient is immunocompromised or diabetic, the canal should be carefully inspected for the presence of granulation tissue at the junction of the cartilaginous and bony junction. This may signify that a malignant otitis externa is present, which, as an osteomyelitis of the temporal bone, requires aggressive management, including prompt intravenous antibiotics.

In older patients, atrophy of the external auditory canal skin is frequently seen and may be associated with psoriasis or eczema of the canal. If patients attempt to soothe an itch with foreign objects such as keys, hair pins, or cotton-tipped swabs, scabs or areas of ecchymosis may be present in the posterior canal wall.

Children are the most likely patients to insert foreign materials into the ear canal. Although most objects lodge lateral to the narrowest part of the canal, the isthmus, some are found in the anterior recess by the tympanic membrane. This makes it especially difficult for the physician to visualize with an otoscope, so patients should turn their head for this area to be viewed. In adults, cotton plugs are commonly lodged and often are impacted against the tympanic membrane. In patients of all ages, insects may find their way into the canal. An operating microscope allows excellent visualization and enables the physician to use both hands to manipulate the instruments needed to remove the object.

Otorrhea is commonly seen in the external auditory canal. The characteristics of the aural discharge may reveal the etiology of the otorrhea. For instance, mucoid drainage is associated with a middle ear chronic suppurative otitis media because only the middle ear has mucus glands. In these patients, a tympanic membrane perforation should be present to allow the mucoid otorrhea to escape. Foul-smelling otorrhea may be caused by chronic suppurative otitis media with a cholesteatoma. Bloody, mucopurulent otorrhea frequently is seen in patients with acute otitis media, trauma, or carcinoma of the ear. Otorrhea with a watery component may signify a cerebrospinal fluid leak or eczema of the canal. Black spores in the otorrhea may be present in a fungal otitis externa caused by *Aspergillus* species. Gentle suctioning is used to thoroughly clean and inspect the canal.

In patients with head trauma, a temporal bone fracture is important to recognize. Bloody otorrhea in conjunction with an external canal laceration or hemotympanum is a very serious finding. Longitudinal fractures often involve the external canal. Because longitudinal fractures may be bilateral, careful inspection of both canals is essential.

Tympanic Membrane

To view the tympanic membrane, the correct otoscope speculum size is used to allow a seal of the ear canal. With pressure from the pneumatic bulb, the tympanic membrane will move back and forth if the middle ear space is well aerated. Perforations and middle ear effusions are common causes for nonmobile tympanic membranes.

The tympanic membrane is oval, not round, and has a depressed central part called the *umbo*, wherein the handle of the malleus attaches to the membrane. The lateral process of the malleus is located in the superior anterior region and is seen as a prominent bony point in atelectatic membranes. Superior to this process is the pars flaccida, wherein the tympanic membrane lacks the radial and circular fibers present in the pars tensa, which is the remainder of the ear drum. This superior flaccid area is critical to examine carefully because retraction pockets may develop here, which may develop into cholesteatomas. In congenital cholesteatomas, often diagnosed in young children, the tympanic membrane is intact, and a white mass is seen in the anterior superior quadrant. Acquired cholesteatomas in adults are different in that they often are in the posterior superior quadrant and are associated with retraction pockets, chronic otitis media with purulent otorrhea, and tympanic membrane perforations.

To assess the middle ear for effusions, use the tympanic membrane as a window that allows a view of the middle ear structures (Fig. 8-4). Effusions may be clear (serous), cloudy with infection present, or bloody. When the patient performs a Valsalva maneuver, actual bubbles may form in the effusion.

Hearing Assessment

Tuning fork tests, usually done with a 512-Hz fork, allow the otolaryngologist to distinguish between sensorineural and conductive hearing loss (Table 8-2). They also may be used to confirm the audiogram, which may give spurious results because of poor-fitting earphones or variations in equipment or personnel. All tests should be conducted in a quiet room without background noise. Furthermore, one should ensure that the external auditory canal is not blocked with cerumen.

The Weber test is performed by placing the vibrating tuning fork in the center of the patient's forehead or at the bridge of the nose. If

the patient has difficulty with these locations, the mandible or front teeth may be used; however, the patient then should tightly clench his or her teeth. The patient then is asked if the sound is louder in one ear or is heard midline. The sound waves should be transmitted equally well to both ears through the skull bone. A unilateral sensorineural hearing loss causes the sound to lateralize to the ear with the better cochlear function. However, a unilateral conductive hearing loss causes the Weber test to lateralize to the side with the conductive loss because the cochlea are intact bilaterally and because bone conduction causes the sound to be better heard in the ear with the conductive loss (because there is less background noise detected through air conduction). Interestingly, a midline Weber result is referred to as "negative." "Weber right" and "Weber left" refer to the direction to which the sound lateralized.

To compare air conduction with bone conduction, perform the Rinne test. The 512-Hz tuning fork is placed by the ear canal and then on the mastoid process. The patient determines whether the sound is louder when the tuning fork is by the canal (air conduction) or on the mastoid bone (bone conduction). A "positive test" result is air conduction louder than bone conduction. A conductive hearing loss will make bone conduction louder than air conduction, and this is called "Rinne negative." When the air and bone conduction are equal, it is called "Rinne equal."

The Schwabach test compares the patient's hearing with the examiner's hearing and uses multiple tuning forks such as the 256-, 512-, 1024-, and 2048-Hz forks. The stem of the vibrating tuning fork is placed on the mastoid process of the patient and then on the mastoid of the physician. This is done, alternating between the two participants, until one can no longer hear the tuning fork. This test assumes that the examiner has normal hearing. If the patient hears the sound as long as the physician, the result is "Schwabach normal." If the patient hears the sound longer than the physician, it is called "Schwabach prolonged." This may indicate a conductive hearing loss for the patient. If the patient hears the sound for less time than the physician, it is called "Schwabach shortened." This is consistent with sensorineural hearing loss for the patient.

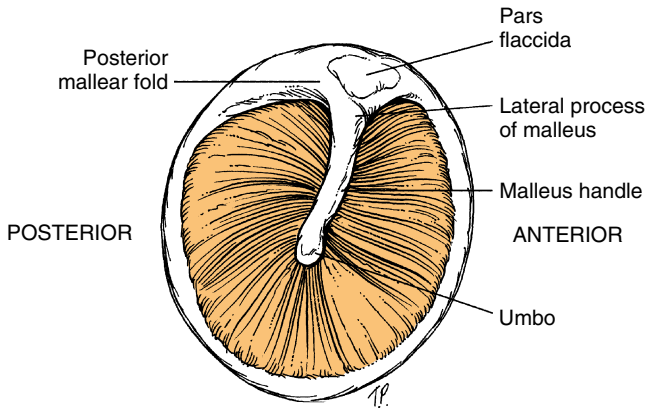

Figure 8-4. The tympanic membrane.

Oral Cavity

The boundaries of the oral cavity extend from the skin-vermillion junction of the lips, hard palate, anterior two thirds of the tongue, buccal membranes, upper- and lower-alveolar ridge, and retromolar trigone to the floor of the mouth. This region may be best seen by having the otolaryngologist use a well-directed headlight and a tongue depressor in each gloved hand. The lips should be carefully inspected. Remember that lip squamous cell carcinoma is more common on the lower lip. The commissures may have fissuring, which is seen in angular stomatitis or cheilosis. When the fissures and cracking are present on the mid-portion of the lips, this may be cheilitis.

The occlusion of the teeth and the general condition of the alveolar ridges, including the gums and teeth, should be noted. The tongue, especially the lateral surfaces where carcinomas are most common, should be inspected for induration or ulcerative lesions. Gently grabbing the anterior tongue with a gauze sponge allows the examiner to move the anterior tongue from side to side. By having the patient lift the tongue toward the hard palate, the floor of mouth and Wharton's ducts (associated with submandibular glands) can be viewed. Pooling of carcinogens in the saliva on the floor of the mouth has been postulated to cause this area to have a high incidence of carcinoma. The examiner should palpate the floor of the mouth using a bimanual approach with one gloved hand in the mouth.

Table 8-2

Tuning Fork Testing

Begin with 512-Hz fork, then include 256- and 1024-Hz forks

Weber

Place tuning fork in center of patient's forehead. Ask patient if sound is louder on one side or is heard midline.

	Weber "Negative"	Weber Right	Weber Left
Patient response	"Sound is midline"	"Sound is louder on right"	"Sound is louder on left"
Interpretation	Bone-conducted sound equal in both ears	Unilateral right conductive hearing loss; unilateral left sensorineural hearing loss	Unilateral left conductive hearing loss; unilateral right sensorineural hearing loss

Rinne

Place tuning fork lateral to ear canal, then place it firmly on mastoid process. Ask patient if sound is louder by canal or on mastoid bone.

	Rinne "Positive"	Rinne "Negative"	Rinne "Equal"
Patient response	"Sound louder when fork by canal"	"Sound louder when fork on mastoid process"	"Sound equal"
Interpretation	Air conduction louder than bone conduction; normal	Bone conduction louder than air conduction; conductive hearing loss	Air and bone conduction equal

The buccal membranes should be inspected for white plaques that may represent oral thrush, which easily scrapes off with a tongue blade, or leukoplakia, which cannot be removed. More worrisome for a precancerous condition is erythroplakia; therefore all red lesions and most white lesions should be judiciously biopsied for cancer or carcinoma in situ. While examining the buccal membranes, one should note the location of the parotid duct, or Stenson's duct, as it opens near the second upper molar. Small yellow spots in the buccal mucosa are sebaceous glands, commonly referred to as *Fordyce spots*, and are not abnormal. Aphthous ulcers, or the common canker sore, are painful white ulcers that can be on any part of the mucosa but are commonly present on the buccal membrane.

The hard palate may have a bony outgrowth known as a *torus palatinus*. These midline bony deformities are benign and should not be biopsied, although growths that are not in the midline should be more carefully evaluated as possible cancerous lesions.

Oropharynx

The oropharynx includes the posterior third of the tongue, anterior and posterior tonsillar pillars, the soft palate, the lateral and posterior pharyngeal wall, the soft palate, and the vallecula (Fig. 8-5). It is best visualized using a head lamp and two tongue depressors. A dental mirror is beneficial in viewing the vallecula and the posterior pharyngeal wall, which often are obscured. Using a gloved finger to examine the base of tongue or tonsil may reveal indurated areas that may be appropriate for biopsy for neoplasm. The patient should be aware of the possibility that gagging may ensue when this is done. In patients with especially strong gag reflexes, a fiberoptic examination may be necessary to fully assess the base of tongue, posterior pharyngeal wall, and vallecula. By carefully passing the flexible fiberoptic endoscope through the anesthetized nose, the interaction of the soft palate and tongue base during swallowing also may be viewed. The uvula should be inspected because a bifid structure may signify a submucosal cleft palate. In addition, an inflamed large uvula may mean the uvula has been traumatized during the night if the patient snores heavily. Small carcinomas or papilloma lesions also may be present, so careful palpation may be indicated.

The size of the tonsils usually is denoted as 1+, 2+, 3+, or 4+ (for "kissing tonsils" that meet in the midline). The tonsils and the base of tongue may contribute to upper-airway obstruction, especially if the soft palate and uvula extend posteriorly. Therefore the oropharyngeal aperture should be carefully assessed in each patient. Tonsillitis, caused by either bacterial or viral sources such as group A streptococci or mononucleosis, often presents with an exudate covering the cryptic tonsils. Tonsilliths are a common cause for a foreign body sensation in the back of the throat. These yellow or white concretions in the tonsillar crypts are not caused by food trapping or infection, but they often cause the patient to have halitosis and may be removed with a cotton-tipped swab.

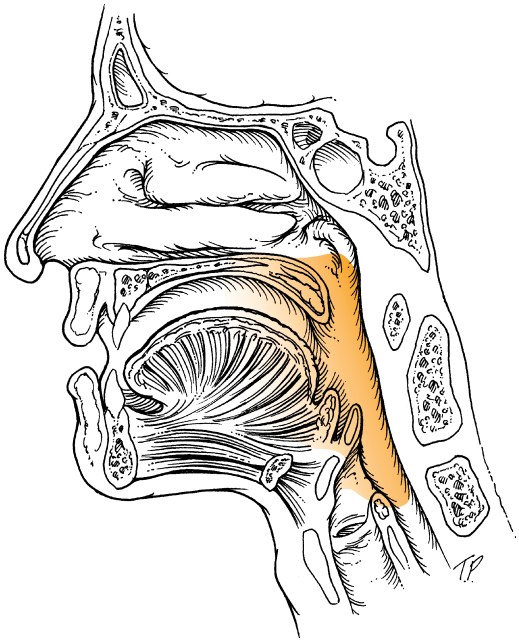

Figure 8-5. The oropharynx, which includes the posterior third of the tongue, soft palate, tonsillar pillars (anterior and posterior), lateral and posterior pharyngeal wall, and vallecula.

Larynx and Hypopharynx

The larynx often is subdivided into the supraglottis, glottis, and subglottis. The supraglottic area includes the epiglottis, the aryepiglottic folds, the false vocal cords, and the ventricles. The glottis comprises the inferior floor of the ventricle, the true vocal folds, and the arytenoids. The subglottis region generally is considered to begin 5 to 10 mm below the free edge of the true vocal fold and to extend to the inferior margin of the cricoid cartilage, although this is somewhat controversial (Fig. 8-6).

The hypopharynx can be challenging to understand. It extends from the superior edge of the hyoid bone to the inferior aspect of the cricoid cartilage by the cricopharyngeus muscle. It connects the oropharynx with the esophagus. This region comprises three areas: the pyriform sinuses, posterior hypopharyngeal wall, and the postcricoid area. This area, rich in lymphatics, may harbor tumors that often are detected only in an advanced stage. Thus early detection of these relatively "silent" carcinomas is important and should not be missed.

The examiner should not only detect anatomic abnormalities but also should observe how the larynx and hypopharynx are functioning to allow the patient to have adequate airway, vocalization, and swallow function. To survey the larynx for lesions and assess the true vocal fold function is not enough. For example, the patient with a normal-appearing larynx may have decreased laryngeal sensation with resultant aspiration and may need further diagnostic and therapeutic evaluation. Therefore important information can be obtained when the physician carefully assesses the anatomic and functional aspects of this complex area.

Correct positioning of patients increases their comfort while maximizing the examiner's view of the larynx. The legs should be uncrossed and placed firmly on the footrest. The back should be straight with the hips planted firmly against the chair. Patients, while leaning slightly forward from the waist, should place their chin upward so that the examiner's light source is sufficiently illuminating the oropharynx. After discussing the examination procedure with the patient, the patient's tongue is pulled forward by the examiner, who uses a gauze sponge between the thumb and index finger. This allows the physician's

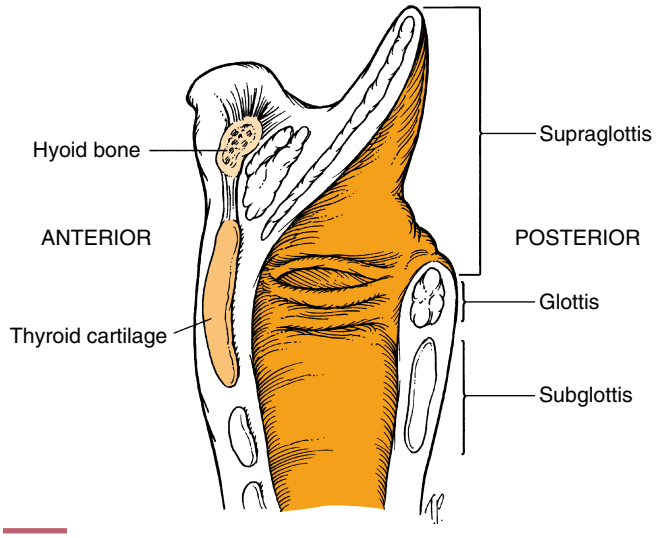

Figure 8-6. The larynx.

Figure 8-7. The laryngeal examination.

long middle finger to retract the patient's upper lip superiorly. A warm dental mirror (to prevent fogging) is placed in the oropharynx and elevates the uvula and soft palate to view the larynx (Fig. 8-7). The patient with a strong gag reflex may benefit from a small spray of local anesthetic to help suppress the reflex.

Some maneuvers allow better visualization of the larynx and its related structures. Panting, quiet breathing, and phonating with a high-pitched E aid in assessing true vocal fold function.

The epiglottis should be crisp and whitish. An erythematous, edematous epiglottis may signify epiglottitis, a serious infection or inflammation that mandates consideration of airway control. The petiole of the epiglottis is a peaked structure on the laryngeal surface of the epiglottis above the anterior commissure of the true vocal folds. It may be confused for a cyst or mass but is a normal prominence. Irregular mucosal lesions may be carcinomas and require further evaluation.

In the posterior glottis, movement of the arytenoids allows determination of true vocal fold mobility. The interarytenoid mucosa may be edematous or erythematous, sometimes representing gastroesophageal reflux laryngitis. The mucosa over the arytenoids may be erythematous as a result of rheumatoid arthritis or as a result of recent intubation trauma. Posterior glottic webs or scars also may be present.

The true vocal folds should have translucent white, crisp borders that meet each other. Edema of the folds that extends for the entire fold length often is caused by Reinke's edema, seen in tobacco users. Actual polypoid degeneration of the vocal cord with obstructing polyps may occasionally be seen in patients and may be a result of tobacco use or hypothyroidism. Ulcerative or exophytic lesions deserve further investigation, usually requiring operative direct laryngoscopy. True vocal fold paralysis and subtle gaps present between the folds during cord adduction should be noted.

During abduction of the cords, the subglottic area may be viewed. A prominent cricoid cartilage, seen inferiorly to the anterior commissure, may be mistaken for a subglottic stenosis. It is difficult to fully inspect the subglottic area in the office setting. Any concerns about subglottic inflammatory swelling, masses, or stenosis should be addressed in an operative setting or through radiographic imaging.

Flexible Endoscopy

Perhaps the best technique to evaluate the function of the larynx uses the flexible fiberoptic nasopharyngolaryngoscope. In conjunction with a strong light source, this allows a more complete evaluation of the structures of the larynx than a mirror examination.

A topical decongestant and anesthetic spray usually is applied to the nares. The patient is asked to gently sniff these nose sprays. Commonly used as topical anesthetics are 1% Pontocaine and 2% lidocaine. Another way to administer anesthesia is to carefully apply a viscous 2% lidocaine solution to the nares with a cotton-tipped applicator. It is important to allow time for these topical agents to anesthetize the nasal mucosa. While the physician is waiting, the scope can be prepared. The focus ring is used to get the brightest possible image. Often a small amount of residue is at the end of the fiberoptic scope. This can be carefully removed using either a pencil eraser or an alcohol swab. If the image is unclear before the scope is put in the nose, the image will be inadequate when the fiberoptic scope has been passed through the nares. Once the best possible focus has been obtained, before passing the scope through the nares, a small amount of water-soluble lubricant should be applied approximately 1 cm from the tip of the scope. This is to prevent breakage of the fiberoptic component of the scope while it is passed through the nose.

The laryngoscope then is gently passed along the floor of the nose and, with the instrument tip held above the epiglottis, the larynx may be viewed. Pooling of secretions in the pyriform sinuses is abnormal and is common in patients with decreased laryngeal sensation, neurologic impairment, or tumors. Saliva freely flowing in and out of the true cords is another indication of decreased laryngeal function. In some patients, having patients inhale and hold their breath often aids in viewing the pyriform sinuses. Asking the patient to cough and swallow and then viewing the residual saliva or phlegm also is helpful. The flexible fiberoptic examination enables the patient to freely phonate, unlike with the mirror examination. The true vocal folds may be assessed by moving the instrument tip into the laryngeal vestibule for closer inspection.

Rigid telescopic examination with 70-, 90-, and 110-degree telescopes is performed in a similar fashion to the mirror examination. It permits photographic documentation of the laryngeal examination. In patients with trismus, this is better tolerated than the mirror examination, and a minimal amount of local anesthetic usually is necessary.

Nose

Anterior rhinoscopy, using a head lamp and nasal speculum, allows assessment of the nasal septum and inferior turbinates. The speculum should be directed laterally to avoid touching the sensitive septum with the metal edges. The point wherein numerous small branches of the external and internal carotid arteries meet, or Kiesselbach's plexus, is the most common site for epistaxis; prominent vessels in this area should be noted. Anterior septal deviations and bony spurs often are evident. The characteristics of the mucosa of the inferior turbinate may range from the boggy, edematous, pale mucosa seen in those with allergic rhinitis to the erythematous, edematous mucosa seen in those with sinusitis.

Nasal endoscopy using rigid endoscopes allows thorough examination of even the most posterior portions of the nasal cavity. After applying a local anesthetic to the nares (either lidocaine or Pontocaine spray or topical 4% cocaine), the rigid 0-degree endoscope may be passed into the nose along the floor of the nasal vault. The septum, inferior turbinate, and eustachian tube orifices in the nasopharynx may be seen this way. Often at this time it is necessary to spray a decongestant to shrink the nasal mucosa. It is helpful to attempt to view the nasal anatomy in both the native state and after the decongestant so that the effect of the decongestant may be seen. After inspecting both sides, the endoscope is placed above the inferior turbinate to view the middle turbinate. Accessory ostia from the maxillary sinus often are present, especially in patients with chronic sinusitis. These openings into the lateral nasal wall often are mistaken for the true maxillary ostium.

Nasopharynx

The nasopharynx extends from the skull base to the soft palate. This is a challenging area to examine, but with the available technology, there are many ways to approach this region. The technique used often

depends on the anatomy of the patient. In the patient with a high posterior soft palate and small tongue base, an otolaryngologist may use a small dental mirror and a head lamp to visualize the nasopharynx. By having the patient sit upright in the chair, the physician may firmly pull the tongue forward while opening the mouth to place the mirror just posterior to the soft palate. In a manner analogous to that used to view the larynx with a mirror, the structures in the nasopharynx are seen when the mirror is oriented upward.

Another method uses a fiberoptic nasopharyngoscope, which allows excellent visualization of this area. After anesthetizing the nares with either topical cocaine (on pledgets) or applying lidocaine spray, many otolaryngologists spray the nares with a decongestant. The flexible fiberoptic scope then is gently passed along the floor of the nostril beneath the inferior turbinate. The eustachian tube orifice, torus tubarius, and fossa of Rosenmüller should be inspected on each side. This may be accomplished by using the hand control to turn the tip of the scope from side to side. The midline also should be inspected for any masses, ulcerations, or bleeding areas. Rigid endoscopes offer good visualization also, although the ability to view both sides of the nasopharynx often means passing the endoscope through each nostril. The endoscopes have various angles (e.g., 70, 90, and 110 degrees).

Arguably, the best view may be obtained using a 90-degree rigid scope in the oropharynx. By advancing the rigid scope through the mouth and by placing the beveled edge posterior to the soft palate, the nasopharynx may be seen in its entirety. Both sides of the nasopharynx may be compared for symmetry using this technique.

Whereas children have adenoid tissue present, adults should not have much adenoid tissue remaining in this area. Thus adenoid tissue should not be a cause of nasal or eustachian tube obstruction in adults. One possible exception is in patients with HIV infections, who may manifest adenoid hypertrophy as part of their disease. Nonetheless, adults with an otitis media, especially unilateral in nature, should have their nasopharynx inspected for possible nasopharyngeal masses. If present, it is important to diagnose nasopharyngeal carcinomas, which are most common lateral to the eustachian tube orifice in the fossa of Rosenmüller. In young male patients, nasopharyngeal angiofibromas are locally aggressive but histologically benign masses that are most commonly present in the posterior choana or nasopharynx. These masses should not be missed. Another malignancy to consider is non-Hodgkin's lymphoma. Cysts in the superior portion of the nasopharynx may represent a benign Tornwaldt cyst or a malignant craniopharyngioma.

Neurologic Examination

Table 8-3 outlines the basics of a neurologic examination appropriate for most head and neck patients. Certainly patients presenting with vertigo or dysequilibrium require a highly specialized neurologic examination, but that is beyond the scope of this chapter. Much valuable clinical information can be obtained with an evaluation of the cranial nerves.

Table 8-3

Neurologic Examination

Cranial Nerves	Tests
I	Sense of smell to several substances Do not use ammonia (common chemical sense caused by CN V stimulation)
II	Visual acuity Visual fields Inspect optic fundi
III	Extraocular movements in six fields of gaze
IV	Pupillary reaction to light
V	Palpate temporal and masseter muscles Patient should clench teeth Test forehead, cheeks, jaw for pain, temperature, and light (cotton) touch Corneal reflex (blinking in response to cotton touching the cornea)
VI	Near reaction to light Ptosis of upper eyelids
VII	Symmetry of face in repose Raise eyebrows, frown, close eyes tightly, smile, puff out cheeks
VIII	Auditory—tuning fork tests for hearing Vestibular—nystagmus on lateral gaze; Hallpike-Dix test; head shaking; caloric testing; Frenzel lenses
IX, X	Hoarseness True vocal cord mobility Gag reflex (CN IX or X) Movement of soft palate and pharynx
XI	Shrug shoulders against examiner's hand (trapezius muscle) Turn head against examiner's hand (sternocleidomastoid muscle)
XII	Stick tongue out Tongue deviates toward side of lesion Tongue atrophy, fasciculations

CN, cranial nerve.

Preoperative Evaluation

The patient presenting with an otolaryngologic disease process that requires surgical management must be evaluated by both general and specialty-specific criteria. Additional testing, prophylactic measures, and behavioral modification before surgery can then be implemented to maximize the surgical outcome. In addition, the patient's prior anesthetic record provides invaluable insight into issues such as airway management and overall tolerance of general, regional, local, or neuroleptic anesthesia. A social history can often be extremely beneficial as well, providing a means of anticipating postoperative needs and circumventing some prolonged admissions. Any significant issues should be raised with the departmental or hospital social worker, preferably before surgery. Last, it is important to elicit a detailed list of current medications and allergies.

In uncomplicated cases, the history and physical examination are followed by routine screening tests. Blood is drawn for a complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and a clotting profile to rule out a wide range of possible occult abnormalities. In patients older than 40 years of age or in those with pertinent past medical histories, chest radiography and electrocardiography (ECG) are performed. Additionally, women of childbearing age should undergo pregnancy testing.

When the need arises, consultation with appropriate specialties should be sought quickly. The consultant should be clearly informed about the nature of the proposed procedure and should be asked to comment specifically on the relative safety of performing the procedure with respect to concomitant disease processes. In cases complicated by many medical problems or those in which the establishment of a safe airway is an issue, close consultation with the anesthesia team is advised to avoid undue delay, cancellation of the procedure, or an undesirable outcome.

It is imperative to have copies of all laboratory results, radiographs, and pertinent tests available for review before surgery. Additional studies should be ordered by the surgeon as deemed necessary.

Consent

Although a detailed discussion of the legal ramifications of informed consent is beyond the scope of this chapter, the ethical ideal deserves consideration. An integral part of the preoperative process is the physician's thorough and candid explanation to the patient of the procedure, its risks, and the probable outcomes. The relationship that develops between the surgeon and patient at this time often does more to prevent litigation if an unfortunate circumstance occurs than any legal document detailing the risks and benefits. The potential risks and outcomes that would sway a patient's decision to undergo the procedure must be discussed with the patient and documented in the chart.

Allergy

The surgeon must guard against anaphylactic reactions in all patients. The crux of this process is to have the patient identify any untoward reactions to medications, foods, or other materials. In most instances, many of the drug "reactions" described by patients do not represent true allergic phenomena. Instead, they are simply drug side effects. Nonetheless, these reactions require thorough documentation and avoidance of the allergens in the perioperative period.

Anaphylaxis results in the release of potent inflammatory agents, vasoactive substances, and proteases, all of which bring about the shock reaction. Urticaria, profound hypotension, tachycardia, bronchoconstriction, and airway-compromising edema of the mucosal surfaces of the upper aerodigestive tract may develop. Even in intubated patients, rapid oxygen desaturation is often a prominent feature. As the reaction progresses, cardiac arrest can ensue despite maximal resuscitative efforts. Given the potential morbidity and mortality of anaphylactic reactions, the otolaryngologist must identify all of a patient's allergens in the preoperative phase.

The incidence of serious adverse reactions to penicillin is about 1%. It is widely believed that there is a 10% to 15% chance that patients who manifest these reactions also react adversely to cephalosporins. Based on my empirical observations, I believe that unless these patients have had a history of significant atopy or penicillin-induced urticaria, mucosal edema, or anaphylaxis, they can be given cephalosporins with relative impunity. Anaphylactic reactions to cephalosporins in true penicillin-allergic patients are probably less than 2%. Moreover, cephalosporins cause their own independent hypersensitivity reactions. The notion of cross-reactivity with penicillin on skin testing seems to stem from data obtained in the 1970s, in which contamination of cephalosporins with penicillin was subsequently proven. Finally, if a serious penicillin allergy is evident, alternative antibiotics such as clindamycin may be substituted for the cephalosporins.

Mucosal absorption of latex protein allergens from the surgeon's gloves can rapidly incite anaphylactic shock in patients who are highly sensitive to latex. About 7% to 10% of health care workers regularly exposed to latex and 28% to 67% of children with spina bifida demonstrate positive skin tests to latex proteins. Preoperatively, if a patient gives a history suspicious for latex allergy, it should be investigated before surgery. If the allergy is documented, perioperative precautions to avoid latex exposure must be instituted.

Similarly, patients with allergic or adverse reactions to soybean or eggs may react to propofol, a ubiquitous induction agent. Protamine and intravenous contrast agents can potentially provoke hypersensitivity responses in patients with known shellfish or other fish allergies. Although rare, some patients have allergic reactions to ester types of local anesthetics such as cocaine, procaine, and tetracaine.

Finally, if the suspicion of allergy or adverse reaction exists, the best course of action is to avoid use of the potential offending agent altogether during surgery. If this is not feasible for some reason, then the surgeon and anesthesiologist should plan on premedicating the patient with systemic steroids, histamine antagonists, and even bronchodilators. The physicians should then be prepared to deal with the potential worst-case scenario of anaphylactic shock.

Systems

Cardiovascular

Cardiovascular complications are the most common cause of perioperative mortality. Specifically, an almost 50% mortality rate is associated with perioperative myocardial infarction. Meticulous review of the cardiovascular system is of utmost importance in determining a patient's surgical candidacy, especially those who will require a general anesthetic. Risk factors for a perioperative cardiovascular complication include jugular venous distention, third heart sounds, recent myocardial infarction (MI) (within 6 months), nonsinus heart rhythm, frequent premature ventricular contractions (>5 per minute), age older than 70 years, valvular aortic stenosis, previous vascular or thoracic surgery, and poor overall medical status. Emergency surgery poses an additional risk for cardiovascular complications. In the head and neck oncology patient population, the high incidence of tobacco and alcohol abuse leads to a relatively high incidence of coronary artery disease, cardiomyopathy, and peripheral vascular disease.

The otolaryngologist should obtain a history of previous MIs, angina, angioplasty or bypass surgery, congestive heart failure (CHF) or dyspnea on exertion, hypertension, general exercise tolerance, paroxysmal nocturnal dyspnea, claudication, stroke or transient ischemic attack, syncope, palpitations or other arrhythmias, as well as known anatomic or auscultative cardiac anomalies. The presence or suspicion of coronary artery disease, heart failure, untreated hypertension, or significant peripheral vascular disease should prompt a specific anesthesiology or cardiology consultation before surgery. This evaluation would include an assessment of the electrocardiogram, as well as possible exercise or chemical stress testing, echocardiography, and cardiac catheterization as indicated. The result of this consultation should determine the surgical and anesthetic risk and should optimize the patient's preoperative cardiovascular status. Furthermore, specific intraoperative and postoperative physiologic (e.g., invasive monitors) and pharmacologic precautionary measures should be delineated, as should the level of postoperative observation.

In general, patients are maintained on their antihypertensive, antianginal, and antiarrhythmic regimens up to the time of surgery. Certain medications such as diuretics and digoxin may be withheld at the discretion of the anesthesiologist or cardiologist. Preoperatively, serum electrolytes and antiarrhythmic levels should be checked and adjusted as necessary. Coagulation studies (prothrombin time [PT]/partial thromboplastin time [PTT]) and platelet quantification are routinely obtained in patients with cardiovascular risk factors because significant bleeding can lead to major perioperative cardiovascular complications. A relatively current chest radiograph is considered essential in this high-risk group.

Preoperatively, the otolaryngologist must be aware of the types of procedures that may have specific cardiovascular ramifications. Patients with prosthetic valves and those with a history of rheumatic fever, endocarditis, congenital heart defects, mitral valve prolapse with regurgitation, or hypertrophic cardiomyopathy should receive prophylactic antibiotics at the time of surgery. Such prophylaxis is especially important during procedures performed on the oral cavity and upper aerodigestive tract. This is also important when dealing with surgical drainage of head and neck infections, in which the risk of hematogenous bacterial seeding is high. For low-risk procedures, intravenous ampicillin—2 g given 30 minutes before surgery, followed by 1 g given 6 hours later—is sufficient prophylaxis. In high-risk procedures, intravenous gentamicin (1.5 mg/kg) and intravenous ampicillin (2 g) are administered 30 minutes before surgery, followed by the same doses of each 8 hours later. Patients with pacemakers or implanted defibrillators and those with mitral valve prolapse without regurgitation do not require endocarditis prophylaxis.

Airway, carotid, and vagus nerve manipulation can induce bradycardia and hypotension. Agents such as lidocaine, epinephrine, and cocaine, which are frequently used in sinonasal surgery, can trigger undesirable cardiovascular events. Injury to the cervical sympathetic chain may precipitate postural hypotension postoperatively. Finally, the surgeon must also be cognizant that a unipolar electrocautery device can reprogram a pacemaker during surgery.

Respiratory

Postoperative pulmonary complications are considered the second most common cause of perioperative mortality. This is not surprising considering the effects of general anesthesia and surgery on pulmonary

performance. Atelectasis and ventilation/perfusion mismatch occur secondary to a number of factors, including the use of anesthetic agents and positive pressure ventilation, as well as supine positioning. Anesthetic agents, barbiturates, and opioids tend to diminish the ventilatory response to hypercarbia and hypoxia. Endotracheal intubation bypasses the warming and humidifying effects of the upper airway, leading to impaired ciliary function, thickened secretions, and subsequent decreased resistance to infection. Furthermore, postoperative pain substantially affects a patient's ability to cough, especially following thoracic or abdominal procedures (e.g., chest myocutaneous flap, gastric pull-up, percutaneous endoscopic gastrostomy, rectus free-flap, iliac crest bone graft). Because of their attenuated respiratory reserve, patients with chronic pulmonary disease are much more likely to suffer postoperative pulmonary complications than are healthy patients. For instance, heavy smokers have a threefold increase in the risk of postoperative pulmonary complications when compared with nonsmokers. Hence it is imperative to identify these patients during the preoperative evaluation.

Specifically, a positive history of asthma, chronic obstructive pulmonary disease, emphysema, tobacco abuse, pneumonia, pulmonary edema, pulmonary fibrosis, or adult respiratory distress syndrome requires heightened attention before surgery. The prior treatment of these lung problems, including the number of hospitalizations and emergency department visits; the use of medications like steroids, antibiotics, and bronchodilators; and the need for intubation or chronic oxygen therapy should be addressed. The otolaryngologist should obtain an estimate of the patient's dyspnea, exercise limitation, cough, hemoptysis, and sputum production. Factors that exacerbate chronic lung disease must be identified. Once again, it is of paramount importance to investigate the tolerance of previous anesthetics in this high-risk group. Coexisting cardiac and renal disease such as CHF and chronic renal failure also impact heavily on pulmonary function. Pulmonary hypertension and cor pulmonale secondary to obstructive sleep apnea, cystic fibrosis, muscular dystrophy, emphysema, or kyphoscoliosis further complicate anesthetic management. Congenital diseases affecting the lungs such as cystic fibrosis and Kartagener's syndrome (rare) present the challenge of perioperative clearance of secretions.

On physical examination, the clinician should be attuned to the patient's body habitus and general appearance. Obesity, kyphoscoliosis, and pregnancy can all predispose to poor ventilation, atelectasis, and hypoxemia. Cachectic patients are more likely to develop postoperative pneumonia. It should be noted that clubbing and cyanosis, although suggestive, are not reliable indicators of chronic pulmonary disease. The patient's respiratory rate is determined, and the presence of accessory muscle use, nasal flaring, diaphoresis, or stridor should be documented. Auscultation that reveals wheezing, rhonchi, diminished breath sounds, crackles, rales, and altered inspiratory/expiratory time ratios should raise the suspicion of pulmonary compromise.

In patients with pulmonary disease, preoperative posteroanterior and lateral chest radiography is mandatory, because findings often direct modification of the anesthetic technique used during surgery. Arterial blood gas (ABG) testing on room air is also indicated. Patients with an arterial oxygen tension less than 60 mm Hg or an arterial carbon dioxide tension greater than 50 mm Hg are more likely to have postoperative pulmonary complications. Serial ABG determinations can also be used to assess the overall efficacy of preoperative medical and respiratory therapy. As with chest radiography, preoperative ABG levels also provide a baseline for postoperative comparison.

Preoperative pulmonary function tests such as spirometry and flow-volume loops are quite helpful. A quantitative measure of ventilatory function can also be used to assess the efficacy of both preoperative and surgical interventions. Spirometry can be used to differentiate restrictive from obstructive lung disease, as well as to predict perioperative morbidity from pulmonary complications. Generally, a forced expiratory volume in 1 second/forced vital capacity ratio of less than 75% is considered abnormal, whereas a ratio of less than 50% carries a significant risk of perioperative pulmonary complications. Preoperative flow-volume loops can distinguish among fixed (e.g., goiter), variable extrathoracic (e.g., unilateral vocal cord paralysis), and variable intrathoracic (e.g., tracheal mass) airway obstructions.

The preoperative management of otolaryngology patients with significant pulmonary disease is vital and should follow the recommendations of a pulmonologist. Smokers are advised to cease smoking for at least a week before surgery. Chest physiotherapy aimed at increasing lung volumes and clearing secretions is instituted. This includes coughing and deep breathing exercises, incentive spirometry, and chest percussion with postural drainage. It is not advisable to operate on a patient with an acute exacerbation of pulmonary disease or with an acute pulmonary infection. Acute infections should be cleared with antibiotics and chest physiotherapy before elective surgery. Prophylactic antibiotics in noninfected patients are not recommended for fear of selecting out resistant organisms. Finally, the medical regimen, including the use of inhaled beta-adrenergic agonists, cromolyn, and steroids (inhaled or systemic), must be optimized. Serum levels of theophylline, if used, should be therapeutic.

Renal

The preoperative identification and evaluation of renal problems is also imperative. Any significant electrolyte abnormalities uncovered during the routine screening of healthy patients should be corrected preoperatively, and surgery should be delayed if additional medical evaluation is warranted. Preexisting renal disease is a major risk factor for the development of acute tubular necrosis both during and after surgery. Renal failure, whether acute or chronic, influences the types, dosages, and intervals of perioperative drugs and anesthetics. An oliguric or anuric condition requires judicious fluid management, especially in patients with cardiorespiratory compromise. Furthermore, chronic renal failure (CRF) is often associated with anemia, platelet dysfunction, and coagulopathy. Electrolyte abnormalities, particularly hyperkalemia, can lead to arrhythmias, especially in the setting of the chronic metabolic acidosis that often accompanies CRF. Hypertension and accelerated atherosclerosis resulting from CRF are risk factors for developing myocardial ischemia intraoperatively. Blunted sympathetic responses may predispose to hypotensive episodes during administration of anesthesia. The otolaryngologist must also be wary of the potential for injury to demineralized bones during patient positioning. An impaired immune system can contribute to poor wound healing and postoperative infection. Finally, because patients with CRF have often received blood transfusions, they are at increased risk of carrying blood-borne pathogens such as hepatitis B and C.

The possible causes of renal disease, including hypertension, diabetes, nephrolithiasis, glomerulonephritis, polycystic disease, lupus, polyarteritis nodosa, Goodpasture's or Wegener's syndrome, trauma, or previous surgical or anesthetic insults, should be elicited. The symptoms of polyuria, polydipsia, fatigue, dyspnea, dysuria, hematuria, oliguria or anuria, and peripheral edema are recorded, as is a complete listing of all medications taken by the patient.

In dialyzed patients, it is important to document the dialysis schedule. A nephrologist should assist with the preoperative evaluation and should optimize the patient's fluid status and electrolytes before surgery. A nephrologist should also be available to help manage these issues postoperatively, especially when major head and neck, skull-base, or neurotologic surgery—which may require large volumes of fluids or blood transfusions intraoperatively—is planned.

Preoperative testing on patients with significant renal disease routinely includes ECG, chest radiography, electrolytes and chemistry panel, CBC, PT/PTT, platelet counts, and bleeding times. In addition to a nephrologic consultation, patients with significant renal disease should also receive a preoperative anesthesiology consultation, and, if indicated, further evaluation by a cardiologist.

A history of benign prostatic hypertrophy or prostate cancer, with or without surgery, may predict a difficult urinary tract catheterization intraoperatively. Finally, elective surgery should not be performed on patients with acute genitourinary tract infections because the potential for urosepsis can be increased by the transient immunosuppression associated with general anesthesia.

Hepatic Disorders

Preoperative evaluation of patients with suspected or clinically evident liver failure should begin with a history detailing hepatotoxic drug

therapy, jaundice, blood transfusion, upper gastrointestinal bleeding, and previous surgery and anesthesia. The physical should include examination for hepatomegaly, splenomegaly, ascites, jaundice, asterixis, and encephalopathy. The list of blood tests is fairly extensive and includes hematocrit, platelet count, bilirubin, electrolytes, creatinine, BUN, serum protein, PT/PTT, serum aminotransferases, alkaline phosphatase, and lactate dehydrogenase. A viral hepatitis screen can be obtained as well. Of note, patients with moderate to severe chronic alcoholic hepatitis may present with relatively normal-appearing liver function tests and coagulation parameters; these patients are at risk for perioperative liver failure.

Cirrhosis and portal hypertension have wide-ranging systemic manifestations. Arterial vasodilation and collateralization leads to decreased peripheral vascular resistance and an increased cardiac output. This hyperdynamic state can occur even in the face of alcoholic cardiomyopathy. The responsiveness of the cardiovascular system to sympathetic discharge and administration of catechols is also reduced, likely secondary to increased serum glucagon levels. Cardiac output can be reduced by the use of propranolol, which has been advocated by some as a treatment for esophageal varices. By decreasing cardiac output, flow through the portal system and the esophageal variceal collaterals is diminished. Additionally, there is likely a selective splanchnic vasoconstriction. Once initiated, beta-blockade cannot be stopped easily because of a significant rebound effect.

Renal sequelae vary with the severity of liver disease from mild sodium retention to acute failure associated with the hepatorenal syndrome. Diuretics given to decrease ascites can often lead to intravascular hypovolemia, azotemia, hyponatremia, and encephalopathy. Fluid management in the perioperative period should be followed closely and dialysis instituted as needed for acute renal failure.

From a hematologic standpoint, patients with cirrhosis often have an increased 2,3-diphosphoglycerate level in their erythrocytes, causing a shift to the right of the oxyhemoglobin dissociation curve. Clinically, this results in a lower oxygen saturation. This situation is further compounded by the frequent finding of anemia. Additionally, significant thrombocytopenia and coagulopathy may be encountered. The preoperative use of appropriate blood products can lead to short-term correction of hematologic abnormalities, but the prognosis in these patients remains poor.

Encephalopathy stems from insufficient hepatic elimination of nitrogenous compounds. Although measurements of BUN and serum ammonia levels are useful, they do not always correlate with the degree of encephalopathy. Treatment includes hemostasis, antibiotics, meticulous fluid management, low-protein diet, and lactulose.

Endocrine Disorders

Thyroid

Symptoms of hyperthyroidism include weight loss, diarrhea, skeletal muscle weakness, warm, moist skin, heat intolerance, and nervousness. Laboratory test results may demonstrate hypercalcemia, thrombocytopenia, and mild anemia. Elderly patients also can present with heart failure, atrial fibrillation, or other dysrhythmias. The term *thyroid storm* refers to a life-threatening exacerbation of hyperthyroidism that results in severe tachycardia and hypertension.

Treatment of hyperthyroidism attempts to establish a euthyroid state and to ameliorate systemic symptoms. Propylthiouracil inhibits both thyroid hormone synthesis and the peripheral conversion of T4 to T3. Complete clinical response may take up to 8 weeks, during which the dosage may need to be tailored to prevent hypothyroidism. Potassium iodide (Lugol's solution), which works by inhibiting iodide organification, can be added to the medical regimen. In patients with sympathetic hyperactivity, beta-blockers have been used effectively. Propranolol has the added benefit of decreasing T4-to-T3 conversion. It should not be used in patients with CHF secondary to poor left ventricular function or bronchospasm because it will exacerbate both of these conditions. Ideally, medical therapy should prepare a mildly thyrotoxic patient for surgery within 7 to 14 days. If the need for emergency surgery arises, intravenous propranolol or esmolol can be administered and titrated to keep the heart rate below 90 bpm. Other medications that can be used include reserpine and guanethidine, which deplete catechol stores, and glucocorticoids, which decrease both thyroid hormone secretion and T4-to-T3 conversion. Radioactive iodine also can be used effectively to obliterate thyroid function but should not be given to women of childbearing years.

The symptoms of hypothyroidism result from inadequate circulating levels of T4 and T3 and include lethargy, cognitive impairment, and cold intolerance. Clinical findings may include bradycardia, hypotension, hypothermia, hypoventilation, and hyponatremia. There is no evidence to suggest that patients with mild to moderate hypothyroidism are at increased risk for anesthetic complications, but all elective surgery patients should be treated with thyroid hormone replacement before surgery. Severe hypothyroidism resulting in myxedema coma is a medical emergency and is associated with a high mortality rate. Intravenous infusion of T3 or T4 and glucocorticoids should be combined with ventilatory support and temperature control as needed.

Parathyroid

The prevalence of primary hyperparathyroidism increases with age. Of patients with primary hyperparathyroidism, 60% to 70% present initially with nephrolithiasis secondary to hypercalcemia, and 90% are found to have benign parathyroid adenomas. Hyperparathyroidism secondary to hyperplasia occurs in association with medullary thyroid cancer and pheochromocytoma in multiple endocrine neoplasia type IIA and, more rarely, with malignancy. In humoral hypercalcemia of malignancy, nonendocrine tumors have been demonstrated to secrete a parathyroid hormone-like protein. Secondary hyperparathyroidism usually results from chronic renal disease. The hypocalcemia and hyperphosphatemia associated with this condition lead to increased parathyroid hormone production and, over time, to parathyroid hyperplasia. Tertiary hyperparathyroidism occurs when the CRF is rapidly corrected as occurs in renal transplantation.

In addition to nephrolithiasis, signs and symptoms of hypercalcemia include polyuria, polydipsia, skeletal muscle weakness, epigastric discomfort, peptic ulceration, and constipation. Radiographs may show significant bone resorption in 10% to 15% of patients. Depression, confusion, and psychosis also may be associated with marked elevations in serum calcium levels.

Immediate treatment of hypercalcemia usually combines sodium diuresis with a loop diuretic and rehydration with normal saline as needed. This becomes urgent once the serum calcium levels rise above 15 g/dL. Several medications can be used to decrease serum calcium levels. Etidronate inhibits abnormal bone resorption. The cytotoxic agent mithramycin inhibits parathyroid hormone–induced osteoclastic activity but is associated with significant side effects, and calcitonin works transiently again by direct inhibition of osteoclast activity. Hemodialysis can also be used in the appropriate patient population.

The most common cause of hypoparathyroidism is iatrogenic. Thyroid and parathyroid surgery occasionally results in the inadvertent removal of all parathyroid tissue. Ablation of parathyroid tissue can also occur after major head and neck surgery and postoperative radiation therapy. Symptoms include tetany, perioral and digital paresthesias, muscle spasm, and seizures. Chvostek's sign (facial nerve hyperactivity elicited by tapping over the common trunk of the nerve as it passes through the parotid gland) and Trousseau's sign (finger and wrist spasm after inflation of a blood pressure cuff for several minutes) are clinically important indicators of latent hypocalcemia. Treatment is with calcium supplementation and vitamin D analogs.

Adrenal

Adrenal gland hyperactivity can result from a pituitary adenoma, a corticotropin hormone (ACTH)-producing nonendocrine tumor, or a primary adrenal neoplasm. Symptoms include truncal obesity, proximal muscle wasting, "moon" facies, and changes in behavior that vary from emotional lability to frank psychosis. Diagnosis is made through the dexamethasone suppression test, and treatment is adrenalectomy or hypophysectomy. It is important to regulate blood pressure and serum glucose levels and to normalize intravascular volume and electrolytes. Primary aldosteronism (Conn's syndrome) results in increased renal tubular exchange of sodium for potassium and hydrogen ions. This

leads to hypokalemia, skeletal muscle weakness, fatigue, and acidosis. The aldosterone antagonist spironolactone should be used if the patient requires diuresis.

Idiopathic primary adrenal insufficiency (Addison's disease) results in both glucocorticoid and mineralocorticoid deficiencies. Symptoms include asthenia, weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, constipation, hypotension, and hyperpigmentation. Hyperpigmentation is caused by overproduction of ACTH and beta-lipotropin, which leads to melanocyte proliferation. Measurement of plasma cortisol levels 30 and 60 minutes after intravenous administration of ACTH (250 mg) aids in diagnosis. Patients with primary adrenal insufficiency demonstrate no response. Glucocorticoid replacement is required on a twice-daily basis and should be increased with stress. Mineralocorticoid therapy can be given once daily. Of note, patients treated for more than 3 weeks with exogenous glucocorticoids for any medical condition should be assumed to have suppression of their adrenal-pituitary axis and should be treated with stress-dose steroids perioperatively.

Pheochromocytoma is a tumor of the adrenal medulla that secretes both epinephrine and norepinephrine. Of these tumors, 5% are inherited in an autosomal dominant fashion as part of a multiple endocrine neoplasia syndrome. Symptoms include hypertension (which is often episodic), headache, palpitations, tremor, and profuse sweating. Preoperative treatment begins with phenoxybenzamine (a long-acting alpha-blocker) or prazosin at least 10 days before surgery. A beta-blocker is added only after the establishment of alpha-blockade to avoid unopposed beta-mediated vasoconstriction. Acute hypertensive crises can be managed with nitroprusside or phentolamine.

Diabetes Mellitus

Diabetes is a disorder of carbohydrate metabolism that results in a wide range of systemic manifestations. It is the most common endocrine abnormality found in surgical patients and can be characterized as either insulin-dependent (type I or juvenile onset) or non–insulin-dependent (type II). Hyperglycemia may result from a variety of etiologies that affect insulin production and function. Management techniques seek to avoid hypoglycemia and maintain high-normal serum glucose levels throughout the perioperative period. These goals are often difficult to maintain, however, because infection, stress, exogenous steroids, and variations in carbohydrate intake can all cause wide fluctuations in serum glucose levels. Close monitoring is mandatory with correction of hyperglycemia, using a sliding scale for insulin dosage or continuous intravenous infusion in more severe cases. Fluid management should focus on maintaining hydration and electrolyte balance.

Hematologic Disorders

A history of easy bruising or excessive bleeding with prior surgery should raise suspicion of a possible hematologic diathesis. A significant number of patients will also present on anticoagulative therapy for coexisting medical conditions. After a careful history, the physician should obtain laboratory studies. PT, PTT, and platelet count are included in the routine preoperative screen. PT evaluates both the extrinsic and the final common pathways. Included in the extrinsic pathway are the vitamin K–dependent factors II, VII, IX, and X, which are inhibited by warfarin. Conversely, heparin inhibits thrombin and factors IXa, Xa, and XIa, elements of the intrinsic clotting pathway. PTT measures the effectiveness of the intrinsic and final common pathways. Relative to the normal population, some patients may demonstrate significant variation in the quantitative levels of certain factors in the absence of clinically relevant clotting abnormalities. Thrombocytopenia or platelet dysfunction can also lead to derangements in coagulation. A standard CBC includes a platelet count, which should be greater than 50,000 to 70,000 before surgery. The ivy bleeding time, a clinical test of platelet function, should be between 3 and 8 minutes. Fibrin split products may also be measured to help determine the diagnosis of disseminated intravascular coagulation.

Congenital

Congenital deficiencies of hemostasis affect up to 1% of the population. The majority of these deficiencies are clinically mild. Two of the more serious deficiencies involve factor VIII, which is a complex of two subunits, factor VIII:C and factor VIII:von Willebrand's factor. Gender-linked recessive transmission of defects in the quantity and quality of factor VIII:C leads to hemophilia A. Because of its short half-life, perioperative management of factor VIII:C requires infusion of cryoprecipitate every 8 hours. The disease that has a milder presentation than hemophilia A is von Willebrand's disease, in which bleeding tends to be mucosal rather than visceral.

This disease is categorized into three subtypes. Types I and II represent quantitative and qualitative deficiencies, respectively. These deficiencies are passed by autosomal dominant transmission. Type I von Willebrand's also is characterized by low levels of factor VIII:C. Type III von Willebrand's disease is much rarer and presents with symptoms similar to those of hemophilia A. Because of the longer half-life of factor VIII:von Willebrand's factor, patients with type II von Willebrand's disease can be transfused with cryoprecipitate up to 24 hours before surgery, with repeat infusions every 24 to 48 hours. Patients with type I von Willebrand's disease require additional transfusion just before surgery to boost factor VIII:C levels and normalize bleeding time.

Patients with hemophilia, von Willebrand's disease, and other less common congenital hemostatic anomalies should be followed perioperatively by a hematologist. Correction of factor deficiencies should be instituted in a timely fashion, and patients should be monitored closely for any evidence of bleeding.

Anticoagulants

Warfarin, heparin, and aspirin have become commonly used medications in the medical arsenal. Conditions such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, and heart valve replacement are routinely treated initially with heparin, followed by warfarin on an outpatient basis. This therapy markedly decreases the incidence of thromboembolic events and, when appropriately monitored, only slightly increases the risk of hemorrhagic complications. Aspirin is widely used both as an analgesic and as prophylaxis for coronary artery disease. Patients taking any of these medications need careful evaluation to assess the severity of the condition necessitating anticoagulation. The benefit of surgery relative to the risk of normalizing coagulation should be clearly established with both the patient and the physician prescribing the anticoagulant.

Warfarin should be stopped at least 3 days before surgery, depending on liver function. Patients who have been determined to be at high risk for thromboembolism should be admitted for heparinization before surgery. The infusion rate can then be adjusted to maintain the PTT in a therapeutic range. Discontinuation of heparin approximately 6 hours before surgery should provide adequate time for reversal of anticoagulation. In emergency situations, warfarin can be reversed with vitamin K in approximately 6 hours and more quickly with the infusion of fresh frozen plasma (FFP). Heparin effects can be reversed with protamine or FFP. Of note, a heparin rebound phenomenon in which anticoagulative effects are reestablished can occur up to 24 hours after the use of protamine. Anticoagulative therapy can be reinstituted soon after surgery if necessary. Most surgeons, however, prefer to wait several days unless contraindicated. The surgeon may often find it helpful to discuss the timing of postoperative therapy with the hematologist before surgery.

Aspirin, an irreversible inhibitor of platelet function, leads to prolonged bleeding time. No strong evidence links aspirin therapy with excessive intraoperative bleeding. However, the theoretical risk that aspirin and other nonsteroidal anti-inflammatory medications present leads most surgeons to request that their patients stop taking these medications up to 2 weeks before surgery to allow the platelet population to turn over.

Liver Failure

Patients with liver failure can present with several hematologic abnormalities. Bleeding from esophageal varices secondary to portal hypertension can lead to anemia. Hypersplenism and alcoholic bone marrow suppression can result in serious thrombocytopenia. An elevated PT may indicate a deficiency in the vitamin K–dependent factors of the

extrinsic clotting pathway, as well as factors I, V, and XI, which are also produced in the liver. Last, as liver failure progresses, excessive fibrinolysis may occur. All of these hematologic sequelae of hepatic failure increase the risk of operative morbidity and mortality. Preoperative management should attempt to correct anemia and thrombocytopenia as indicated and replenish deficient clotting factors with FFP. Fluid management may prove to be a difficult issue.

Another less common cause of PT elevation is the intestinal sterilization syndrome in which intestinal flora, a major source of vitamin K, are eradicated by prolonged doses of antibiotics in patients unable to obtain vitamin K from other sources. Reversal occurs rapidly with vitamin K therapy.

Thrombocytopenia

A decrease in platelet count can occur as a result of a variety of medical conditions, including massive transfusion, liver failure, disseminated intravascular coagulation, aplastic anemia, hematologic malignancy, and idiopathic thrombocytopenic purpura. With the increasing use of chemotherapeutics for a variety of malignancies, the prevalence of iatrogenic thrombocytopenia has risen. Preoperatively, the platelet count should be greater than 50,000; at levels below 20,000, spontaneous bleeding may occur. Additionally, any indication of platelet dysfunction should be evaluated with a bleeding time. Severe azotemia secondary to renal failure may lead to platelet dysfunction (uremic platelet syndrome). Dialysis should be performed as necessary.

Correction of thrombocytopenia with platelet transfusion should preferably come from human leukocyte antigen–matched donors, particularly in patients who have received prior platelet transfusions and may be sensitized. One unit of platelets contains approximately 5.5×10^{11} platelets. One unit per 10 kg of body weight is a good initial dose. The platelets should be infused rapidly just before surgery.

Hemoglobinopathies

Of the more than 300 hemoglobinopathies, sickle cell disease and thalassemia are by far the most common. Approximately 10% of blacks in the United States carry the gene for sickle cell anemia. The heterozygous state imparts no real anesthetic risk. There are significant clinical manifestations to the 1 in 400 blacks who are homozygous for hemoglobin S. The genetic mutation results in the substitution of valine for glutamic acid in the sixth position of the beta-chain of the hemoglobin molecule, leading to alterations in the shape of erythrocytes when the hemoglobin deoxygenates. The propensity for sickling directly relates to the quantity of hemoglobin S. Clinical findings include anemia and chronic hemolysis. Infarction of multiple organ systems can occur secondary to vessel occlusion. Treatment consists of preventive measures. Oxygenation and hydration help maintain tissue perfusion. Transfusion before surgical procedures decreases the concentration of erythrocytes carrying hemoglobin S, thereby lowering the chance of sickling.

Multiple types of thalassemia exist, each caused by genetic mutations in one of the subunits of the hemoglobin molecule. Symptoms vary on the severity of the mutation. Patients with the most severe form, beta-thalassemia major, are transfusion-dependent, which often leads to iron toxicity. Other thalassemias cause only mild hemolytic anemia. If transfusion dependency exists, the patient should be screened carefully for hepatic and cardiac sequelae of iron toxicity.

Neurologic

For medicolegal reasons, it is critical to document all neurologic abnormalities. The surgeon should distinguish peripheral from central lesions, and CT or MRI is often helpful in this regard. Frequently, neurologic consultation is sought in the setting of subtle findings or confusing or paradoxic findings and for evaluation of possible nonotolaryngologic etiologies of certain complaints, such as headache and dysequilibrium. During preoperative patient counseling, the surgeon must be aware of the potential for nerve injury or sacrifice and must communicate the possible sequelae of these actions to the patient.

If the patient has a history of seizures, the surgeon needs to find out the type, pattern, and frequency of the epilepsy, as well as the current anticonvulsant medications in use and their side effects. Phenytoin therapy can lead to poor dentition and anemia, whereas treatment with carbamazepine can cause hepatic dysfunction, hyponatremia, thrombocytopenia, and leukopenia, all of which represent concerns for the surgeon and anesthesiologist. Preoperative CBC, liver function tests, and coagulation studies are thus advised. Anesthetic agents such as enflurane, propofol, and lidocaine have the potential to precipitate convulsant activity, depending on their doses. In general, antiseizure medications must be at therapeutic serum levels and should be continued up to and including the day of surgery.

Symptomatic autonomic dysfunction can contribute to intraoperative hypotension. It may be necessary to augment intravascular volume preoperatively through increasing dietary salt intake, maximizing hydration, and administering fludrocortisone.

Additional considerations must be taken into account in patients with upper motor neuron diseases, such as amyotrophic lateral sclerosis, or lower motor neuron processes affecting cranial nerve nuclei in the brainstem. In either case, the otolaryngologist may be confronted with bulbar symptoms such as dysphagia, dysphonia, and inefficient mastication. As bulbar impairment progresses, the risk of aspiration increases significantly. When respiratory muscles are affected, the patient is likely to have dyspnea, intolerance to lying flat, and an ineffective cough. Coupled with aspiration, these factors put the patient at considerable surgical risk for pulmonary complications. Hence, if surgery is necessary for these patients, preoperative evaluation should include a pulmonary workup (including chest radiography, pulmonary function tests, ABG analysis) and consultation. A video study of swallowing function may also be indicated. Finally, the patient's neurologist should be closely involved in the decision making (i.e., whether to proceed with surgery).

Parkinsonism presents the challenges of excessive salivation and bronchial secretions, gastroesophageal reflux, obstructive and central sleep apnea, and autonomic insufficiency, all of which predispose to difficult airway and blood pressure management in the perioperative period. Dopaminergic medications should be administered up to the time of surgery to avoid the potentially fatal neuroleptic malignant syndrome. Medications such as phenothiazines, metoclopramide, and other antidopaminergics should be avoided. Preoperatively, the patient's pulmonary function and autonomic stability should be investigated.

If clinically indicated, patients with multiple sclerosis should also undergo full pulmonary evaluation preoperatively, because these patients can present with poor respiratory and bulbar function. The presence of contractures can limit patient positioning on the operating table. In addition, before surgery, the patient must be free of infection because pyrexia can exacerbate the conduction block in demyelinated neurons.

Older Patients

Of all surgeries currently performed, 25% to 33% are performed on people older than 65 years of age. This percentage is likely to increase as the population ages. A greater likelihood of comorbid conditions exists with increasing age. In addition, physiologic reserve is often compromised. Preoperative assessment in this population should take these considerations into account and weigh the benefit of the procedure against the often increased risks in this population. Consultation with the anesthesia service facilitates planning for high-risk older patients.

Approximately 50% of all postoperative deaths in older adults occur secondary to cardiovascular events. Severe cardiac disease should be treated before any elective procedure and should be weighed against the benefit of any more urgent procedure. If surgery is required, cardiac precautions should be instituted. Patients with physical evidence or a history of peripheral vascular disease should be evaluated for carotid artery stenosis. If a critical stenosis is identified, carotid endarterectomy should be performed before any elective procedure that requires a general anesthetic. The risk of a cerebrovascular accident should be considered when evaluating patients for more urgent procedures. From a respiratory standpoint, increasing age leads to loss of lung compliance, stiffening of the chest wall, and atrophy of respiratory muscles. In many otolaryngology procedures, the surgeon should consider the risk of intraoperative or postoperative aspiration and postobstructive pulmonary edema. Patients with borderline pulmonary function may not

tolerate even mild respiratory complications. The function of all the organ systems diminishes with age, necessitating a thorough preoperative evaluation to maximize older patient safety.

Conclusion

This chapter provides a brief overview of the importance for the surgeon to gather a patient's history and complete a physical examination and preoperative evaluation. Disturbances in one organ system often have repercussions for other systems, so an interdisciplinary approach involving the otolaryngologist, anesthesiologist, internist, and specialized consultants is often warranted. This chapter emphasizes the physiologic aspects of the evaluation, without intending to overshadow the importance of gaining insight into a patient's psychosocial preparedness, which often requires the help of family members, social workers, psychiatrists, and support groups, as well as a keen sense of intuition on the part of the surgeon. Furthermore, the surgeon's preoperative discussions with the patient provide a means to reinforce the patient's postoperative expectations and coping mechanisms. Finally, the responsibility of ensuring an appropriate preoperative evaluation lies with the surgeon and the expediency of this process should be in keeping with the best interests of the patient.

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CHAPTER NINE

General Considerations of Anesthesia and Management of the Difficult Airway

Lynette Mark

Kurt Herzer

Seth Akst

James Michelson

Key Points

- Preoperative patient evaluation by the anesthesiologist identifies a patient with a potentially difficult airway/intubation.
- Basic anesthetic techniques are undertaken with specific attention to implications of anesthetics in airway management.
- Indications and limitations of airway techniques primarily used by anesthesiologist and emergency physicians are discussed.
- The American Society of Anesthesiology (ASA) Guidelines for Management of the Difficult Airway and the role of the otolaryngology—head and neck (OLHN) surgeon in using these guidelines are reviewed.
- The Johns Hopkins Medical Institutions Departments of Anesthesiology and Critical Care Medicine (ACCM) and OLHN Airway Management Initiative are outlined.
- Mechanisms for communicating patient airway information to other health care providers and patients are discussed.
- Case presentations are focused on the use of the ASA Difficult Airway Algorithm.
- Case presentations are focused on catastrophic events and the role of the OLHN surgeon.

Airway management is the essence of clinical anesthesiology. Complex airway management of the patient with an anticipated difficult airway/intubation or the patient with an unanticipated difficult airway/intubation is a multispecialty process that involves anesthesiologists, surgeons, pulmonologists, critical care physicians, emergency physicians, and nursing/technician staff support.

The OLHN surgeon with expertise in rigid laryngoscopy and bronchoscopy, flexible fiberoptic bronchoscopy, and surgical approaches to the airway is uniquely qualified to take the lead surgical role in a team approach with the anesthesiologist to safely manage difficult airway/intubation patients. The goal of airway management is simple: to provide the most expeditious form of management that has the lowest potential for injury and the greatest potential for control of the airway.[1]

The approach to the patient with a difficult airway varies, depending on whether management is elective or urgent and whether the health care setting is an operating room or a non–operating room environment.

This chapter presents the anesthetic component of complex airway management in a manner that OLHN surgeons can incorporate into their practice. The focus of this chapter is on clinical airway algorithms and the decisions that must be made by the anesthesiologist together with the OLHN surgeon to safely provide anesthesia and airway management for their patient or for a non-OLHN patient seen in joint consultation for airway management. In-depth discussions about the pharmacology and physiology of anesthesiology are beyond the scope of this chapter but can be found in any number of authoritative textbooks of anesthesiology.[2,3]

Difficult Airway/Intubation: A Multispecialty Problem

Complex airway management is a multifaceted problem involving health care providers in a variety of clinical settings. The consequences of failed airway maintenance, endotracheal intubation, or both, can be devastating to the patient, the practitioner, and the health care system. Critical issues include identification of difficult airway/intubation patients, mobilization of physician and support staff, mobilization of airway management equipment, preparation of the patient, implementation of appropriate airway algorithms, documentation of airway management techniques, dissemination of critical airway information to future health care providers, and quality improvement/medicolegal considerations.

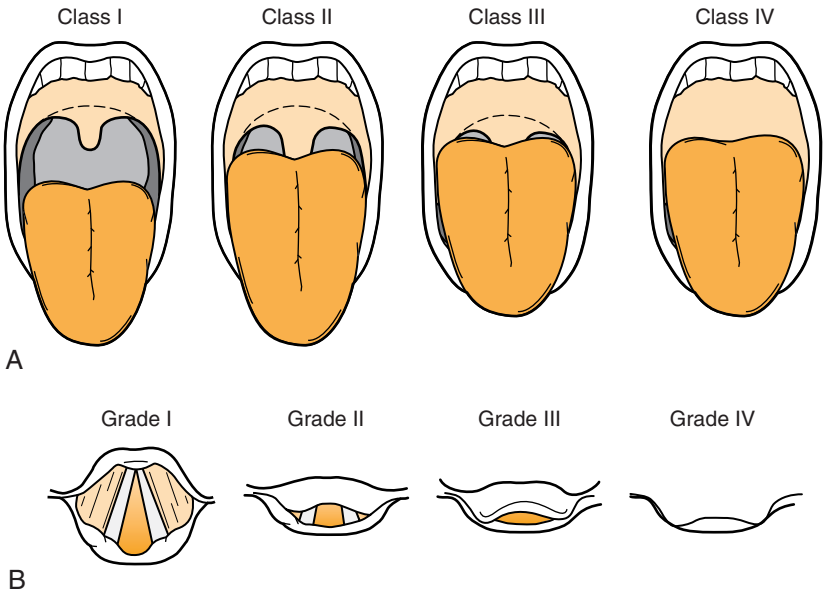

Figure 9-1. Mallampati, Cormach, and Lehand oral **(A)** and laryngoscopic **(B)** views.

Figure 9-2. Anesthesia resident with thick neck, 5′8,″ 95 kg, viewed by colleagues as "anticipated difficult" airway. Mallampati class I oral view. Airway algorithm for elective surgery: mask ventilation easy; direct laryngoscopy times one with MAC No. 4 with full grade I laryngoscopic view.

Figure 9-3. Patient evaluated to have a Mallampati class II airway with a tongue blade and anticipated easy intubation with conventional laryngoscopy. Airway algorithm for elective surgery: mask ventilation easy; unsuccessful direct laryngoscopy with MAC No. 3/4 Miller No. 2/3 times 4; successful asleep oral fiberoptic intubation with No. 7.0 ETT with view of complete glottic opening.

Patient Identification

Controversy regarding predictors and definitions of "difficult" exists in both intraspecialty and interspecialty, dependent and independent of practitioner skill, related to specific techniques, and complicated by changing patient pathophysiology.[4] Some patients may be anticipated to be difficult to intubate on the basis of a history of difficulty intubation or clinical predictors of difficult intubation. The ASA Practice Guidelines for Management of the Difficult Airway[5] reviews some of the historical or physical examination findings possibly suggestive of a difficult intubation. Some of these predictors of anticipated difficulty with conventional direct laryngoscopy (MAC/Miller) include a large overbite, large tongue, narrow mouth opening, or short chin. Various prediction models, such as correlation with Mallampati oral view I to IV to the Cormack and Lehand laryngoscopic view grades I to IV have been proposed, but none offer 100% sensitivity for prediction of a difficult airway (Figs. 9-1 to 9-4).[6] Historically, anesthesiology literature cites an incidence of 1% to 3% for unanticipated difficult airway/intubation in patients undergoing general endotracheal anesthesia.[5-7] The airway management technique used to define "difficult" in this literature was conventional rigid laryngoscopy (Macintosh or Miller blades).

Despite advances in airway management techniques and refinement of difficulty predictors, the cited 1% to 3% incidence of unanticipated difficulty has not changed and is still defined by conventional laryngoscopy.[6-9] In an institution where approximately 25,000 general endotracheal anesthetic procedures are done annually, there are potentially 250 to 750 unanticipated difficult airway/intubations per year. Assuming that a full-time practicing anesthesiologist would encounter one unanticipated difficult airway/intubation per year, then, based on ASA membership (which represents 90% of practicing anesthesiologists), there are potentially 30,000 to 90,000 unanticipated difficult airway/intubations annually in the United States. However, these numbers may underestimate the true incidence, because anesthesiologists may not recall the more common "near misses" as vividly as they recall the smaller number of actual difficult airway/intubations in which the outcome was suboptimal. On a national and international level, the scope of this problem and its impact on patients, practitioners, and the health care system is sufficient to warrant vigorous efforts to identify and implement solutions.

In addition to those patients who have unanticipated difficult airway/intubations on initial presentation, there are cohorts of patients

Figure 9-4. Postoperative evaluation of patient in Figure 9-3. Note that without the tongue blade, the patient has a Mallampati class IV airway and should have been considered to be anticipated difficult intubation with conventional laryngoscopy.

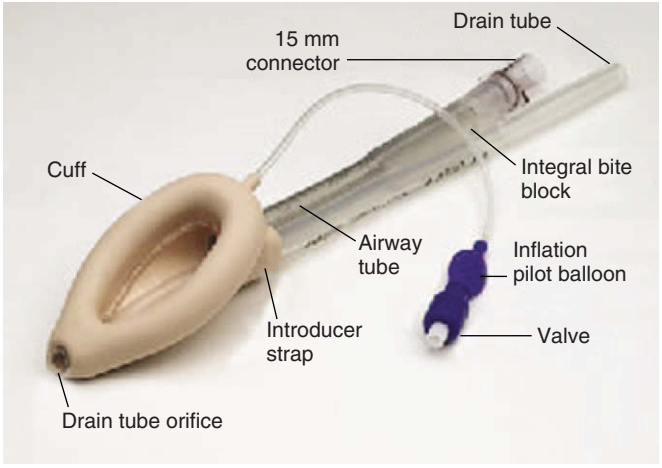

Figure 9-5. Laryngeal mask. *(Courtesy of LMA, North America Inc.)*

who have anticipated complex airway management; these patients can be successfully managed by a variety of innovative and specialty-specific techniques. Some of these techniques (laryngeal mask airway [LMA][10] and Combitube)[11] are readily available (Figs. 9-5 and 9-6), require minimal practitioner education or training, and are inexpensive; other techniques (fiberoptic bronchoscope, surgical airway, specialized rigid laryngoscopes, and fluoroscopic-assisted intubation) are available primarily in specialty centers, may require extensive practitioner skill, and may be relatively expensive. For patients who have undergone head and neck surgery and have visible or hidden implants (e.g., laryngeal stents, thyroplasties), specific considerations for airway management may be unknown to future providers (e.g., thyroplasty patients might require smaller endotracheal tubes than anticipated), thus compromising patient safety and increasing practitioner risk for adverse events.

Successful future management of previously unanticipated difficult airway/intubation patients depends on identification of those patients, and documentation and dissemination of information detailing successful and unsuccessful airway management techniques and primary difficulties encountered. These patients then become anticipated difficult airway/intubations, and the availability of this information promotes quality and safety of care.

Consequences of Difficult Airway Management

The consequences of difficult airway/intubation (with or without an adverse outcome) may be as unsettling as the event itself. The patient may perceive this as a threat to future anesthetic safety or may lack understanding as to the significance of the difficulty. There may be

Figure 9-6. Diagram of usage of a Combitube.

practitioner-perceived threat to professional security. The impact of complex airway management-related events in direct and indirect costs to the health care system is far reaching.

Three studies specifically demonstrated the consequences of difficult airway/intubation management on liability exposure.[12-14] An analysis of approximately 5000 claims filed in the Maryland legal system over a 15-year period in which one or more anesthesiologists were named as defendants revealed that insertion of an endotracheal tube was the sixth most common medical procedure leading to a liability claim. Most of these claims also included other members of the operating room team (e.g., otolaryngologists, general surgeons, nurse anesthetists, orthopedic surgeons, plastic surgeons, cardiac surgeons, dentists, or nurses) as defendants. One claim (in 1994) resulted in a jury award of $5 million.[15] In a 1992 loss analysis study conducted by the Physicians Insurers Association of America (PIAA), files from 43 physician-owned malpractice insurance companies (representing approximately 2000 anesthesiologists nationally) ranked "intubation problems" as the third most prevalent misadventure (behind "tooth injury" and "no medical misadventures"). The average paid indemnity for 175 of 339 files was $196,958.[15] The ASA Committee on Professional Liability closed claims study found that respiratory events were the most common cause of brain damage and death during anesthesia, with difficult intubation being the likeliest category for risk reduction. The median payment for respiratory claims was $200,000.[12]

To put these statistics in perspective, the following must be considered.

1. The number of malpractice claims reported represents only a small fraction (one eighth) of all adverse outcomes, with one malpractice claim filed for every 7.5 patient injuries from difficult airway/intubation events and adverse outcomes.[12]

2. Claims may often be aborted by good physician-patient communication.

3. Claims are often initiated against physicians because of poor communication and inadequate records.[16]

Routine Anesthetic Care of the Patient with the Nondifficult Airway

Before discussing management of the difficult airway, this section will discuss the routine provision of anesthesia to provide a framework for

the discussion that follows. The three main tasks of the anesthesiology team are (1) to keep the patient safe, (2) to keep the patient comfortable, and (3) to provide for good operating conditions during the preoperative, intraoperative, and immediate postoperative periods. The component qualities of an anesthetic are loss of consciousness, amnesia, analgesia, and muscle relaxation/paralysis. Anesthesia can be general, regional, or local; general anesthesia is provided for most head and neck surgeries, thus the need for airway management.

In a routine setting, the patient receives a general anesthetic, and the anesthetic "take-off" follows after a thorough preoperative history and physical. The patient is then brought into the operating room and positioned supine. Standard monitors are placed, as described later in this section. Preoxygenation occurs with 100% inspired oxygen to denitrogenate the patient's functional residual capacity. At that point, anesthesia is induced and the airway is managed appropriately. After intubation or other airway control, invasive monitors or additional intravenous access may be placed, and the surgery is allowed to commence.

Advances in Monitoring

As a previous section made clear, there are serious legal and financial consequences of failed airway management. Fortunately, adverse outcomes related to poor airway management have decreased in frequency with the standardization of anesthetic monitoring. The American Society of Anesthesiology Standards for Basic Anesthetic Monitoring statement was first released in 1986 and further amended in 1998 and 2005.[17] These standards call for continual evaluation of the patient's oxygenation, ventilation, circulation, and temperature during all administered anesthetics. Practically speaking, the standard mandates continuous oxygen analysis of the anesthetic circuit, pulse oximetry, end-tidal capnometry, tidal volume measurement, electrocardiography, and temperature, as well as intermittent (no less frequent than every 5 minutes) measurement of arterial blood pressure and heart rate. In addition, the routine use of the neuromuscular blockade (NMB) monitor (also called the "twitch" monitor) to assess degree of muscle paralysis and return of muscle strength after pharmacological reversal of paralyzing agents significantly contributed to improved patient safety. Compared with earlier eras, this document made the important leap of elevating pulse oximetry and capnometry to standards of care, thus allowing more rapid, accurate recognition of oxygen desaturation and rapid recognition of previously unrecognized esophageal intubation.

The consequences of this change were staggering. Respiratory system adverse events (including airway mishaps) accounted for 36% of claims in the ASA Closed Claims Project data set for the 1970s, but this percentage decreased to 14% of claims in the 1990s after implementation of the routine use of capnometry and pulse oximetry.[18] Claims related to death or brain injury likewise had a similar drop in the percentage that was attributable to respiratory adverse outcomes. Caused in part by continuous pulse oximetry and capnometry, anesthesiology has been a leader in the patient safety movement in the past decade.

Standard Anesthetic Pharmacology

This section provides a brief introduction to the array of drugs used by anesthesiologists to facilitate anesthesia and maintain control of the airway. An in-depth discussion of these agents is not within the scope of this chapter; however, certain features of these drugs that are particularly applicable to airway management are highlighted.

Induction Agents and Volatile Anesthetics

In most adult patients, a peripheral intravenous line is started preoperatively to administer fluid and drugs. Therefore, most adult patients receive an intravenous induction of anesthesia. The most commonly used intravenous induction agents are thiopental, propofol, etomidate, and ketamine. Each of the intravenous induction agents has the advantage of quick onset, producing unconsciousness within 1 to 2 minutes when given in standard induction doses. Of note, thiopental and propofol are both associated with negative inotropic effects and a related drop in blood pressure when used for induction of general anesthesia. Etomidate's effects are considered to be more hemodynamically stable, but this drug has the drawbacks of potential adrenal suppression and myoclonic activity. Thiopental, propofol, and etomidate all produce apnea along with unconsciousness. In contrast to the other three agents, ketamine is notable for not producing apnea with administration. The maintenance of spontaneous ventilation with ketamine is an important consideration in the management of patients with potentially difficult airways and other subsets of patients presenting for surgery. In addition, ketamine has the advantage of being able to be given intramuscularly in patients without intravenous access. The major disadvantages of ketamine include emergence delirium and the sympathomimetic effects of the drug, and thus can cause tachycardia and hypertension, which limit its role in the treatment of patients with cardiovascular disease. Additionally, ketamine produces exaggerated secretions, and an antisialogue such as glycopyrrolate should be coadministered if the airway is not secured immediately after induction.

For most adults, the volatile anesthetic agents (e.g., halothane, isoflurane, sevoflurane, and desflurane) are used for maintenance of anesthesia rather than induction. Their role in induction of anesthesia is limited by slower onset of activity and patient inability to tolerate the scent of the anesthetic gas. However, in pediatric anesthesia, wherein most patients are intolerant of intravenous placement before coming to the operating room, "mask inductions" with volatile agents is common. Sevoflurane is typically the agent used for mask induction because it is considered less noxious than the other agents. All of the volatile agents have the significant advantage of maintaining spontaneous respiration while producing unconsciousness.

Adjuncts to Induction: Sedatives and Opioids

Benzodiazepines are also commonly given in the immediate preoperative period for their anxiolytic and amnestic effects. Midazolam is the most commonly used benzodiazepine, because it has onset of activity in 2 to 4 minutes. In larger doses, benzodiazepines can also be used as induction agents themselves. In sedative doses, the benzodiazepines do not typically produce significant respiratory depression. However, in combination with opioids, the respiratory depression can be synergistic. Furthermore, the response to benzodiazepines can be idiosyncratic, and a sedative dose can produce unconsciousness and apnea in sensitive patients.

Opioids are used intraoperatively to provide analgesia and a balanced anesthetic. When given as part of anesthetic induction, they are useful in blunting the sympathetic response to laryngoscopy and intubation. They also have a role during sedation of patients, because they can produce a sense of well-being, with decreased responsiveness to noxious stimuli. Commonly used opioids are fentanyl, sufentanil, remifentanil, morphine, and hydromorphone. Opioids produce a dose-dependent central respiratory depression with increased $Paco_2$ and diminished respiratory drive. This respiratory depression can often be offset in the awake patient by asking the patient to consciously breathe deeply. However, the combination of opioids with benzodiazepines can result in a patient with central apnea who is unresponsive to instructions to breathe. Both opioids and benzodiazepines can be antagonized at the receptor level by naloxone and flumazenil, respectively.

Lidocaine is sometimes used as adjunct during anesthetic induction, although not in doses large enough to be an induction agent itself. Propofol can cause venous irritation during administration, and pretreatment with lidocaine into the same vein may decrease patient discomfort. In addition, lidocaine does have its own anesthetic effects and may decrease sympathetic response to laryngoscopy and intubation. Doses are kept to 1 to 1.5 mg/kg to avoid potential toxicity of local anesthetics, which are described later.

Paralytic Agents

Paralysis of the patient eases endotracheal intubation by relaxing the jaw and stopping vocal cord motion. Furthermore, paralysis is often necessary for the surgical procedure itself. There are two classes of paralytics, depolarizing agents and nondepolarizing neuromuscular blockers.

The depolarizing agent used in the United States is succinylcholine. Succinylcholine acts at the acetylcholine receptor in the neuromuscular junction, activating the receptor but then occupying it and therefore prolonging the refractory period before the muscle can contract again. The drug eventually diffuses away from the receptor and is

metabolized and deactivated by pseudocholinesterase. Succinylcholine does produce fasciculation of the muscle, which can cause postoperative myalgia. In addition, the original opening of the receptor causes potassium efflux from the muscle, which raises the serum potassium transiently by approximately 0.5 mEq/L. This increase in potassium is exaggerated in patients with up-regulated amounts of acetylcholine receptors, such as after differentiation caused by stroke or other central nervous system injury. In patients with already elevated serum potassium levels, succinylcholine can precipitate ventricular dysrhythmias.

The major advantage of succinylcholine is its very fast onset of action. Paralysis sufficient for endotracheal intubation can be reliably produced within 45 to 60 seconds. Another advantage is its short duration of action, because clinical paralysis usually dissipates within 5 minutes of an intubating dose. It has been thought that this quick return of strength would allow resumption of spontaneous respirations if positive-pressure ventilation were not successful. However, a past study shows that deleterious oxygen desaturation may occur before resumption of spontaneous respirations.[19] In addition, the small percentage of patients who are pseudocholinesterase deficient will have prolonged paralysis after administration of succinylcholine. Vigilant use of the NMB monitor has led to increased diagnosis of patients with atypical cholinesterase activity, which varies with the population but is cited to be 1 : 2800 in the general population in the United States, with a 1 : 1 male/female ratio.[3] Confirmatory blood laboratory diagnosis is made by determining the patient's dibucaine number. Succinylcholine has also been identified as the most common muscle relaxant trigger for malignant hyperthermia (MH).[20] Primary contraindications for the use of succinylcholine include known or suspected MH, increased intracranial pressure, increased intraocular pressure, and elevated potassium. Although not contraindicated in patients with pseudocholinesterase deficiency, administration should be monitored with the NMB monitor to verify full return of strength before extubation.

The other group of paralytics is the nondepolarizing neuromuscular blockers. These drugs work in the neuromuscular junction by preventing the binding of acetylcholine to its receptor and subsequent muscle contraction. There are many different nondepolarizing agents, clinically distinct because of their different times of onset, durations of action, and different routes of metabolism. None of these agents work as quickly as succinylcholine. In the patient in whom there is a contradiction to the use of succinylcholine, the nondepolarizer of choice for rapid sequence intubation is rocuronium, which has an onset of action between 60 and 75 seconds. However, when given in doses sufficient for intubating conditions, the effects of rocuronium persist for 30 to 40 minutes (and cannot be pharmacologically reversed for 20 to 30 minutes), which can be a major problem if the initial attempts to intubate the trachea are unsuccessful. Establishment of mask ventilation is then essential, and although the risk of aspiration is now greater, there are no other options available to the practitioner.

Local Anesthetics

Local anesthetics are discussed here because of their use surgically as an adjunct for analgesia, and because of their use for topical and regional anesthesia of the airway in awake patients. Lidocaine and bupivacaine are the most commonly used local anesthetics for local infiltration or nerve blocks at our institution. The surgeon must be aware of the maximum dose allowable, given the risk of local anesthetic toxicity, manifested first by central nervous depression and seizures, followed by cardiovascular dysrhythmias, and potentially ventricular fibrillation. The maximum dose of lidocaine is 5 mg/kg and up to 7 mg/kg can be given safely if epinephrine is used in the solution to slow uptake through subcutaneous tissues into the central circulation. A 2% lidocaine solution contains 20 mg/mL of lidocaine, so a 70-kg patient should receive no more than 17.5 mL of this solution. The effects of intravenous lidocaine administered during induction are additive to the amount of lidocaine absorbed from local infiltration, topical application, or regional block, so communication between the anesthesiology and surgical teams is crucial to avoid potentially toxic overdoses. The maximum dose of bupivacaine is 2 to 3 mg/kg, with the upper end of the range reflecting the addition of epinephrine to the solution during local infiltration. As a word of caution, toxic effects are seen with much lower doses of local anesthetics administered directly into the circulation, so careful aspiration must be done before injection of these drugs during infiltration or regional blocks. Injection into the carotid artery during extraoral glossopharyngeal block can produce immediate seizures and loss of consciousness.

Cocaine is also used for topicalization of the airway during head and neck surgery. The advantage of cocaine applied to the nasal mucosa is its vasoconstrictive properties in addition to its anesthetic properties. However, the side effects of cocaine include tachycardia and hypertension, which can be particularly deleterious in patients with coronary artery or other cardiovascular disease. The addition of phenylephrine to lidocaine jelly offers similar vasoconstrictive properties with fewer risks than cocaine. In addition, cocaine has significant addictive properties, so its use during surgery must be intensively monitored.

Antihypertensives

Airway management in the last decade has been radically advanced by the increased understanding of the pathophysiology of ischemia and the judicious perioperative use of antihypertensives for patients at increased risk of ischemic events. Intraoperative hypertension and tachycardia can be a direct response to agents used in topicalization of the airway for awake airway management techniques, specifically cocaine, epinephrine in lidocaine mixtures, and phenylephrine in lidocaine mixtures. In the asleep patient, translaryngeal intubation of the trachea stimulates laryngeal and tracheal receptors, resulting in marked increase in the elaboration of sympathomimetic amines. This sympathetic stimulation results in tachycardia and an increase in blood pressure. In normotensive patients, this increase is approximately 20 to 25 mm Hg; it is much greater in hypertensive patients. This increase in blood pressure results from vasoconstriction, owing to unopposed alpha stimulation in hypertensive patients taking β-blocking agents.

The most commonly used antihypertensives for intraoperative control of hypertension and tachycardia related to airway management include the β-blockers esmolol and metoprolol, and the α- and β-blocker labetalol. Most blood pressure and heart rate changes occur about 15 seconds after the start of direct laryngoscopy and become maximal after 30 to 45 seconds. Esmolol is especially effective in blunting these responses because of its almost immediate onset of action, ease in titration, and short action of duration with half-life of 9 minutes. Labetalol is comparable in attenuating hemodynamic effects, but is less immediate in onset of action and has a half-life of 5 hours.

Standard Induction versus Rapid Sequence Induction

After the patient with an expected routine airway is monitored and anesthesia is induced, the next step is appropriate management of the airway.

An important question to ask before this point is whether the patient is at risk for aspiration of gastric contents into the airway, an event that can be potentially catastrophic. The patient's risk of aspiration of gastric contents helps determine whether the patient should be managed with rapid-sequence induction (RSI) and intubation or with a nonrapid sequence of events. The increased risk of aspiration is due to the presence of gastric contents and is the reason anesthesiologists are concerned about the length of time patients have been without food or drink before surgery. The ASA has published guidelines for preoperative fasting that are based on the time required for gastric emptying in healthy patients.[21] As surgeons, your familiarity with these guidelines can prevent the delay or cancellation of elective surgery.

The summary of fasting recommendations is 2 hours for clear liquids, 4 hours for breast milk, and 6 hours for other food or beverage, including infant formula and milk. In patients with delayed gastric emptying, such as diabetic gastroparesis, further fasting may be necessary for reduced risk of aspiration. In addition to adherence to fasting guidelines, pharmacologic agents given preoperatively may reduce risk of aspiration and include clear antacids (30 mL of 0.3 M sodium citrate), anticholinergic agents (atropine or glycopyrrolate), metoclopramide (to stimulate gastric emptying and to increase lower esophageal sphincter tone), and H_2-receptor antagonists (cimetidine or ranitidine) to decrease further secretion of additional acid.

Figure 9-7. Establishing mask ventilation with Anesthesia Attending L. Mark, MD.

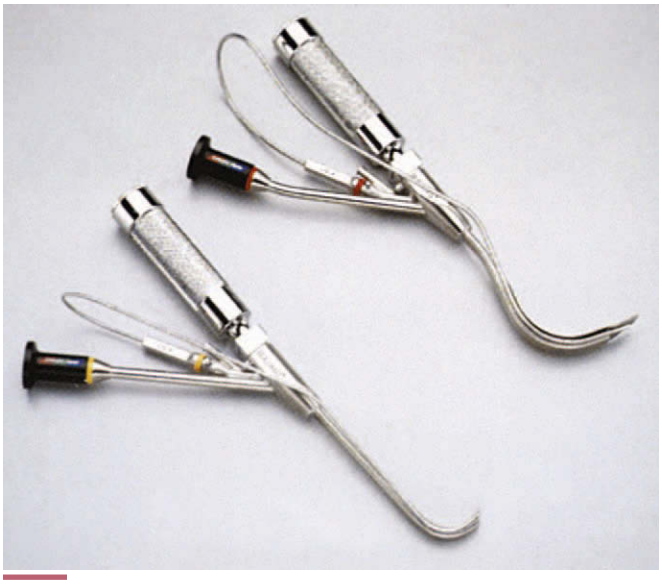

Figure 9-8. Rigid bronchoscopes.

In patients without increased risk of aspiration, a controlled and stepwise approach is taken with induction and intubation. After monitoring and preoxygenation, general anesthesia is induced. Once the patient is unconscious, positive-pressure mask ventilation is performed (Fig. 9-7). Only after successful mask ventilation is established is a paralyzing agent given. This stepwise approach to the airway increases patient safety because, even if intubation cannot be performed successfully, it is known that the patient can be mask ventilated and oxygenated while the paralytic wears off or alternative intubation techniques are readied. The ability to ventilate a patient is more crucial than the ability to intubate a patient, and bag-valve-mask ventilation is a lifesaving skill that every anesthesiologist must master. After successful mask ventilation, the paralytic is given, and intubation is performed after the paralytic takes effect.

RSI and intubation are done for patients with an increased risk of aspiration, such as a patient with a full stomach or a patient with a significant history of gastroesophageal reflux. During an RSI technique, mask ventilation is not done, because it can fill the stomach with air and increase the risk of aspiration even further. Instead, the paralytic agent is given immediately after the induction agent. Cricoid pressure is held throughout, and the patient is not ventilated for the time it takes the paralysis to take effect.

Proper preoxygenation allows most apneic patients to maintain oxygen saturation during this minute. The patient is intubated once paralysis is achieved, usually by means of direct laryngoscopy. After confirmation of proper endotracheal tube placement by end-tidal CO_2 and auscultation of bilateral breath sounds, the endotracheal tube cuff is inflated, and cricoid pressure can be released.

The risk of an RSI is that intubation may not be successful and the ability to mask ventilate the patient has not been previously established. The most dangerous result of failed RSI could be a paralyzed patient who cannot be ventilated or intubated (see Case 8).

Therefore, the stepwise approach to the induction of anesthesia and establishment of mask ventilation before paralysis is the safer and preferred technique for a patient without increased risk of aspiration and without an expected difficult airway. The stepwise approach for a patient with risk for aspiration and with an expected difficult airway requiring general anesthesia is awake versus RSI, with immediate backup in the event of failed intubation.

Difficult Airway/Intubation: Advances in Airway Devices and Techniques

In parallel with organizational responses to difficult airway management, individual practitioners responded with inventions of new airway devices and with innovative combinations of existing techniques. In Table 9-1, a brief review of many of these devices is presented, with identification of primary use by anesthesiology and of OLHN. For a more in-depth discussion of the devices and appropriate techniques, refer to *Airway Management: Principles and Practice*[22] and references identified in Table 9-1.

To appreciate the scope and magnitude of these efforts, consider that in the early 1990s, most anesthesiologists in the United States had the following airway management techniques: awake blind nasal, awake nasal fiberoptic intubation, and awake and asleep conventional laryngoscopy. Select difficult patients would undergo spontaneous ventilation "breathe-down" inductions without paralysis to facilitate optimal conditions for the OLHN surgeon to attempt to secure the patient's airway with either rigid laryngoscopy or bronchoscopy. Complications of this technique included laryngospasm, aspiration, lost airway because of inability to maintain spontaneous ventilation, or difficult positive pressure mask ventilation, and inability to intubate by the OLHN surgeon.

In the early 1990s, OLHN surgeons had the following airway management techniques: awake and asleep surgical airway, awake fiberoptic bronchoscopy, and asleep rigid laryngoscopy and bronchoscopy (Fig. 9-8).

Indisputably, the most significant invention in the recent history of airway management was the LMA (see Fig. 9-5).[10] Although introduced into the United States in the early 1990s as an alternative to elective face mask ventilation (Fig. 9-9) in general anesthetics not requiring intubation, the value of the LMA as a rescue device for the most devastating situation "cannot intubate/cannot ventilate" quickly became realized. In the 1993 ASA Practice Guidelines for Management of the Difficult Airway, the LMA was the airway device that routed the Difficult Airway Algorithm into the significant branch points. In the 2003 amended Guidelines, the LMA was promoted as a first choice device for cannot-ventilate rescue options.[23]

In the past decade, for elective difficult airway management, the "family" of LMAs (Classic, ProSeal, Flexible, and Fastrach) has had a major impact on the decision branches with the Difficult Airway Algorithm. Specifically, many practitioners decide that if they can mask the patient with an LMA, definitive placement of an endotracheal tube (ETT) can be achieved with either fiberoptic bronchoscopy or ETT exchanger assistance. Backup plans, however, must be in place, because these techniques can be difficult and unsuccessful, as described in Case 7.

Table 9-1 briefly presents many of the advances in airway management devices discussed previously and throughout this chapter. References, including links to more comprehensive websites, are provided

Table 9-1

Difficult Airway/Intubation: Advances in Airway Devices

Technique	Visualization	Site	Awake/ Asleep	Contraindictions	OLHN	Anes	Comments	References
Face mask	None	Oral	Both	Full stomach	–	+	Nasal/oral airways to optimize; headstrap to optimize	
Laryngeal mask airway (LMA)	None	Oral	Both	Full stomach	–	+	Variants include intubating LMA, LMA flexible, LMA ProSeal	www.lmana.com; see Fig. 9-5
Blind nasal	None	Nasal	Both	Nasal pathology, coagulation status	–	+		
Digital	None	Oral	Both	Limited jaw opening	–	+		
Lighted stylet	None	Oral, nasal	Both	Nasal or laryngeal pathology, large neck/mass	–	+	Requires transillumination at sternal notch	Interactive Airway IDevice Tutorials: www.anest.ufl.edu
Conventional laryngoscopy	Direct	Oral	Both	Limited jaw opening	–	+	Macintosh/Miller blades	
Endotracheal tube guides (Eschmann, Frova, Arndt, Aintree)	Direct or none	Oral, nasal	Both		+	+	Adjunct to conventional and rigid laryngoscopy intubation with LMA, and extubation techniques	www.cookgroup.com
Rigid laryngoscopy (Hollinger/Dedo)	Direct	Oral	Both	Limited jaw opening	+	–	Hollinger is difficult airway scope	
Rigid bronchoscopy	Direct	Oral	Both	Limited jaw opening	+	–		
Fiberoptic bronchoscopy	Direct	Both	Both	Blood or secretions	–	+		
Rigid fiberoptic laryngoscope (Bullard, Upsher, Wu)	Indirect	Oral	Both	Blood secretions	–	+	Combination of fiberoptic and conventional laryngoscopy	
Retrograde intubation	Indirect	Neck	Both		+	+		
Percutaneous cricothyrotomy	Indirect	Neck	Both	Neck pathology, technique	+	+	OLHN assisted with FOB/direct visualization	www.cookgroup.com
Cricothyrotomy	Direct	Neck	Both	Neck pathology, technique	+	–		
Tracheotomy	Direct	Neck	Both	Neck pathology, technique	+	–		
Transtracheal jet ventilation		Oral, neck	Both	Via angiocath, attachment to rigid laryngoscope, ventilating EET changers	+	+		
Combitube	Indirect	Oral	Both	Limited jaw opening	–	?	AHA guidelines for prehospital management; Interactive frame face with Combitube	See Fig. 9-6

Figure 9-9. Face mask ventilation with head strap.

for additional information. Cases 1 to 10 span 10 years of experiences with difficult airway patients and advancements of airway management techniques.

The Johns Hopkins Departments of Anesthesiology and Critical Care Medicine and Otolaryngology—Head and Neck Surgery Airway Management Initiative and Formation of a Hospital-Wide Airway Service

The following section briefly outlines ongoing efforts of the Departments of ACCM and OLHN Surgery Airway Management Initiative and formation of a hospital-wide Airway Service.

Conceptual Framework

The Johns Hopkins Medical Institutions Departments of ACCM and OLHN Surgery responded to the release of the ASA guidelines by developing an Airway Management Initiative that has evolved over the past 15 years into the present-day Airway Management Service, education program, and hospital-wide difficult airway management response system. For the first 6 years, both departments provided financial support. However, in 1999, the Legal Department issued the following statement regarding the Airway Management Initiative and multidisciplinary Airway Service that resulted in full financial support by The Johns Hopkins Medical Institutions[24]:

> The institution will be well served by supporting a coordinated team approach dealing with patients with difficult airways. Being able to call upon such a team would assist us in preventing claims and would help with management of claims that do arise because of the assurance of excellence of care and good documentation.
>
> We were fortunate enough to have a lawsuit dismissed in which we allegedly did not render appropriate care for a patient with a difficult airway. The dismissal was a direct result of involvement of members of the multidisciplinary airway service team and their review of the case and their expert opinions.
>
> With appropriate funding and education about the multidisciplinary airway service team, we may have been able to avoid an incident that led us to settling a case in which a patient's compromised airway led to an arrest and her death.
>
> Based on even these two examples, it will be prudent for the Hospital to fund the multidisciplinary airway service and to make sure that it remains functional. We would also need to make sure that the medical staff is aware of the existence and expertise of the service.

Multispecialty Service and Joint Clinical Faculty Appointment

To facilitate familiarity between faculty from each department and to support the academic careers of individuals, joint faculty appointments were/are awarded to physicians interested in becoming active members of the Airway Management Service. At any given time, there are two to three members from each department with such appointments. These individuals have the primary responsibility for teaching other faculty, residents, nursing, and support staff within an organized educational program that includes a month-long elective for senior anesthesiology residents. They are the physicians who provide consultation electively and urgently for patients requiring difficult airway management. They are encouraged to be members of Society of Airway Management (SAM) and to participate in the annual meeting.

Preoperative Evaluation and Identification of "Airway Alert"

Approximately 50% of patients seen for surgery are evaluated in our Preoperative Evaluation Center (PEC) several days or weeks before their scheduled procedure by the PEC staff, which consists of an attending anesthesiologist, anesthesiology resident, and nurse practitioner. The PEC anesthesiologist identifies the difficult airway/intubation patient on the basis of prior documented history, physical examination, or specific surgical needs. If consultation with an otolaryngologist or other specialist is needed to facilitate airway management, this is arranged. On the basis of the PEC staff evaluation, the patient is identified as an "Airway Alert" on the Preanesthesia Assessment Form and entered into the hospital's operating room scheduling system (ORSCIS) with "Airway Alert" identified in the free text field associated with the surgical procedure. Whenever possible, an anesthesia attending is identified who will be available for assistance with airway management on the day of surgery and who has experience with the specific condition or airway difficulty the patient has and the recommended technique. However, the designated anesthesiologist and surgeon caring for the patient during the surgical procedure determine the final airway management plan. When appropriate, postoperative intensive care unit beds are requested to facilitate extubation management. The PEC anesthesiologist, and Airway Service members if consulted, discuss with the patient overall concerns and probable airway management plans A, B, and C. Discussions include any potential for the procedure to be aborted if issues arise during airway management that are not appropriately planned for. Written informed consent is obtained, including for elective tracheotomy if considered part of the airway management plans. For select patients, recommendations are made for enrollment into Medic Alert.

Before surgery, the anesthesiologist reviews the Preanesthesia Assessment Form to specifically identify the following information: surgical procedure, airway requirements (e.g., nasal/oral ETT, jaw wired at end of procedure, tracheotomy as part of procedure), patient's yes/no response to the presence of gastroesophageal reflux/hiatal hernia (to assess aspiration risk and potential for awake vs. RSI technique), previous anesthesia experiences/airway difficulties, height and weight, and attempted-standardized airway examination (oral excursion in fingerbreadths [scale of 1 to 4], temporomandibular distance in fingerbreadths [scale of 1 to 4], upper and lower dentition [normal, dentures, caps, decayed], Mallampati I to IV, neck extension/flexion [scale of normal to decreased by 1 to 2]). The final patient interview and examination are conducted, and the anesthesiologist and surgeon (with assistance from Airway Service, as requested) formulate their actual plans A, B, and C.

Formulation of Intraoperative and Postoperative Plans A, B, and C

Members of the Airway Service are familiar with the ASA difficult airway/intubation algorithm and our institutional experience with rigid

laryngoscopy as a primary otolaryngology technique within the ASA algorithm.

The first question the Airway Service asks is, "What is the surgical expectation at the end of the procedure?" Specific answers need to be provided for questions about if and at what stage of the procedure the patient might have a tracheotomy done, if the jaw will be wired closed, whether direct manipulation of the airway will result in edema or significant bleeding, whether positioning could cause airway edema, what will total fluid management entail, and what other considerations might suggest continued intubation at the end of the procedure. For these patients, precise extubation strategies are planned to include the location of extubation (intensive care unit vs. returning to the operating room for extubation) and physicians, staff, and equipment resources that must be available.

Next, the Airway Service explores the concept of "difficult." Although the ASA attempts to distinguish between difficult mask and difficult intubation, when the patient does not have a documented prior airway history and is assessed to be difficult for either mask or intubation, considerations for awake intubation techniques are discussed. Obvious limitations to awake techniques are severe mental status issues (e.g., intoxication, noncooperative, mental retardation), severe respiratory/hemodynamic compromise, and unstable trauma. In our experience, patient refusal of an awake intubation has rarely been an issue, primarily because of the positive approach to awake intubation taken by the anesthesiologist during the discussion with the patient.

The next question that the Airway Service asks is, "Should the intubation be awake, oral, nasal, or surgical?" followed by, "What is the surgical preference for the ETT (cuffed or uncuffed, smaller-than-expected size, right-angle endotracheal (RAE) or nasal RAE tube, reinforced, laser, double lumen, microlaryngeal, or other specialty ETT)?"

Finally, the Airway Service addresses the issue of the patient's surgical attending airway management expertise and comfort with specific airway management techniques. Specifically, if the situation deteriorates and an emergency surgical airway becomes necessary, who will do it: the patient's surgical attending or OLHN member of the Airway Service?

Based on this knowledge, plans A, B, and C are developed by the Airway Service and communicated to the surgeon, patient, and nursing and support staff. Modifications to the plans are made jointly, before the initiation of any airway management.

Operating Room Preparation

In the early years of the Airway Management Initiative, the Airway Service had as resources four designated OLHN operating rooms (in a single operating room suite) and a small work room to house and clean airway equipment. As the Airway Service expanded coverage to non-OLHN patient consultations in multiple operating room suites within the institution, and responded to emergency responses in nonoperating room locations, the need for duplicate central locations, and numerous mobile sites became apparent. In addition, the standard airway equipment in each operating room was expanded and upgraded to facilitate more efficient operating room preparation for both elective and emergency airway management.

Equipment: Standard Anesthesia Equipment and Airway Service Resources

Standard anesthesia equipment in all adult anesthetizing locations includes the following airway management equipment: Eschmann stylet; LMA sizes 3, 4, and 5; conventional laryngoscopes (MAC No. 2, 3, and 4; Miller No. 2 and 3); Sanders jet ventilator; and AMBU bag.

Airway Service resources include a wall poster listing contact numbers for the surgical airway support individuals who are in the hospital daily (elective and on call), the airway equipment specialist support staff contact numbers, and a copy of The Johns Hopkins Adult Airway Management Card. There is specific identification of which services are available and when (24 hours a day, electively, or emergently). The Airway Management Card includes the following information: the contents of the anesthesia fiberoptic cart, the contents of the adult emergency airway cart, information on local anesthesia toxicity, techniques for topical anesthesia, airway blocks, techniques for fiberoptic intubation, information on size issues with the LMA, techniques for changing from LMA to ETT, techniques for changing from a double-lumen ET to a single-lumen ETT, information about size issues with the light wand, lung isolation techniques, techniques for jet ventilation and cricothyrotomy, and information about airway fires, surgical airways, challenging situations, and difficult airway telephone numbers.

Carts: Anesthesia Fiberoptic Cart and Adult Emergency Airway Cart

Two airway carts were created to address specific airway management situations: the Anesthesia Fiberoptic Cart and the Adult Emergency Airway Cart. Both are available with and without a monitor. Both carts include airway alert wristbands and information on how to enroll patients in the in-hospital registry, enter an airway note into the Electronic Patient Record (EPR), and enroll into Medic Alert. The complete contents for each cart are listed on the Adult Airway Management Card.

The Anesthesia Fiberoptic Cart is specifically set up for elective fiberoptic intubations or for fiberoptic verification of double-lumen ETT placement. It has both an LF 1/2 Olympus (3.5/4.0 mm) bronchoscope and adult bronchoscope, Olympus (5.0/6.0 mm) assorted airway management equipment, and topical anesthesia supplies. This cart is specifically designed to be used by anesthesiologists in the operating room.

The Adult Emergency Airway Cart is specifically set up for elective procedures in the operating room in which the following techniques are part of the airway management plan and for which the otolaryngologist has primary involvement: fiberoptic bronchoscopy, rigid laryngoscopy, rigid bronchoscopy, jet ventilation, and surgical airway. Adult Emergency Airway Carts are also located in all intensive care units and the Emergency Department. To note, monitors are included with these carts.

For an emergency in the operating room, our otolaryngologists prefer to use the Adult Emergency Airway Cart without the monitor and organized on a single flat-surface cart without numerous drawers. It has the same equipment as the preceding Adult Emergency Airway Cart, but the critical equipment, rigid laryngoscopes and adult fiberoptic bronchoscope, is already assembled for immediate use.

Staff: Anesthesiologist, Specialty Nursing Staff, Surgical Technologists, and Airway Equipment Specialist

For years, anesthesiologists were taught to believe that all aspects of airway management were the responsibility of the anesthesiologist, without specified assistance from nursing or support staff. At The Johns Hopkins Medical Institutions, it was the practice of otolaryngologists and pulmonologists to schedule patients with complex airway pathology to have a diagnostic fiberoptic bronchoscopy in the operating room, with monitored sedation by an anesthesiologist. It became increasingly apparent that successful management of these patients required a team of four professionals: an anesthesiologist to monitor and provide sedation, a surgeon or pulmonologist to perform the bronchoscopy, a nurse to assist with the bronchoscopy, and an equipment specialist to set up the equipment. We found that if any one of the team members failed to perform these duties, the patient's airway management was compromised. We realized that it was not reasonable to expect that an anesthesiologist (or other physician with airway expertise) working alone could provide all the components of complex airway management in a timely and successful manner. When the OLHN surgeon was not immediately required, the Airway Service provided an additional anesthesiologist to provide patient monitoring and sedation while the airway management was being accomplished by the Airway Service and/or operating room anesthesiologist facile with complex airway management. The goals were successful airway management, patient safety, patient satisfaction, and efficient use of operating room resources.

The Airway Service currently has support staff from the Departments of ACCM, Surgery, and Nursing, including specialty operating room nurses, airway equipment specialists, certified surgical technologists (CST), and critical care technicians. Their primary responsibilities are to assist physicians in difficult airway management, maintain and

upgrade airway equipment, and ensure that the organizational process of a functional airway team is maintained. They are also responsible for the education other operating room staff, specifically as to their roles in airway emergencies.

Operating Room Setup

There are three standard operating room bed positions that we use, depending on the surgeon, anesthesiologist, and procedure to be performed. These are (1) the classic position with the patient's head in alignment with the anesthesiologist; (2) the patient's head rotated 90 degrees from the anesthesiologist; and (3) the patient's head rotated 180 degrees from the anesthesiologist. Decisions regarding positioning are determined by specific operating room equipment issues, the choice of airway algorithm, and the comfort of the anesthesiologist and/or support anesthesia staff (when staff is needed) with having the patient's head rotated away from the classic position and the anesthesia machine. For example, if the clinical algorithm has plan A as conventional laryngoscopy and plan B as rigid laryngoscopy, and if the anesthesia team includes an attending and resident, then an optimal position to facilitate the rigid laryngoscopy setup is with the patient's head/operating room table rotated 90 degrees from the classic position. One member of the anesthesia team has the designated role of monitoring the anesthesia, while the other member is responsible for the airway; the otolaryngologist and nurse are set up to immediately assist, if required.

Advanced Monitoring in the Operating Room and Postoperative Considerations

In efforts to optimize the surgical positioning, as described previously, careful planning of advanced monitoring—specifically arterial and central venous monitoring—must be communicated between the anesthesia and surgery teams. In procedures in which the positioning involves both patient's arms tucked by the sides and the bed rotated 180 degrees from the anesthesiologist, placement of a radial, dorsal pedal, or femoral arterial catheter facilitates more precise management of blood pressure and ability to easily obtain laboratory values as required. Considerations for central venous access include limitations of adequate peripheral venous access (either difficult peripheral venous access or request by surgeon not to access the patient's arms for flap procedures), potential for large blood loss, or patient cardiac issues that suggest monitoring of central venous pressures for optimal management. Communication with the surgical staff facilitates placement of internal/external jugular, subclavian, or femoral venous cannulation. Specific indications for use of pulmonary artery catheters and/or invasive cardiac pacing catheters can be limited by surgical request for femoral venous only and must be carefully considered for relative risk/benefit and issues of difficulty with successful placement from the femoral venous site.

Difficult airway management includes algorithms for difficult extubation management.[25] Specific considerations include when, where, and how to extubate, and the safe disposition of the patient postoperatively. Preoperative discussions between anesthesiologists, surgeons, and patients should always include the extubation strategy. Issues can occur in the event that a relief anesthesia teams takes over the patient's care, but extubation strategies are not clearly communicated by the original team. In an attempt to avoid the potential for adverse airway events, it is our practice to clearly communicate the entire airway management plan to the operating room nursing, recovery, and intensive care unit staff when possible. When a team decision is made to extubate a complex airway patient, techniques to optimize successful extubation include the following: (1) elevation of the head to at least 45 degrees; (2) careful suctioning of the trachea and oropharynx; (3) nebulizations with bronchodilators; (4) suctioning of the stomach and administration of an antiemetic drug; (5) verification of the reversal of muscle relaxants; (6) verification of appropriate respiratory parameters (head lift of 5 seconds, tidal volume approximately 10 mL/kg, negative inspiratory effort of −20 mm Hg, oxygenation of greater than 90%, appropriate level of CO_2); (7) appropriate volume status (nonedematous); (8) hemodynamic stability, and (9) normal laboratory values, if indicated. Considerations for extubation over an Eschmann or ventilating ETT changer, the use of heliox,[26,27] or a "trial extubation" should be clearly communicated to all appropriate physician, nursing, and technician support staff. Emergency airway equipment should be immediately available. The final algorithm for a potentially difficult extubation poses the question, "Who does the emergency tracheotomy?" If the answer is uncertain and the appropriate physicians are not immediately available, it might be prudent to leave the patient intubated and transport to the recovery room or to an intensive care unit.

Extubation Locations

In The Johns Hopkins Medical Institutions, extubations of known difficult airway/intubation patients are done in the recovery room or intensive care units but treated as if they were in the operating room in that the patient's condition must be optimized for a successful extubation, emergency airway equipment must be immediately available and/or set up, a physician who can create a surgical airway must be present, and a physician must be present who can monitor the patient and administer anesthesia or resuscitation medications, if needed. Depending on the complexity of the airway management, some patients are returned to the operating room for extubation and airway management as required.

Nursing Critical Pathway for Difficult Airway/Intubation Patients

Once the care of the patient is transferred to the recovery room or intensive care unit, the patient is entered into a nursing critical pathway, a key element of which is education and Medic Alert enrollment of the patient with a difficult airway/intubation. The pathway prompts nursing personnel to specifically query difficult airway/intubation preoperatively and again on arrival in the recovery room. If difficult airway/intubation is present, the pathway initiates implementation of a specific protocol that includes in-hospital identification, patient-family teaching, enrollment into the in-hospital registry, and a quality improvement system.

In-Hospital Difficult Airway/Intubation Alert Wristbands and Chart Labels

Difficult airway/intubation patient identification also includes a green identification wristband and a patient chart airway alert label. This facilitates transition from a temporary in-hospital registry to the permanent Medic Alert Registry. Similar in appearance to an allergy alert wristband, the green difficult airway/intubation wristband provides continued patient identification and safety during hospitalization. The Joint Committee on Clinical Investigations at The Johns Hopkins Medical Institutions issued a waiver on the need to obtain written informed consent before placing green wristbands on identified patients with a difficult airway/intubation. Health care personnel and patients recognize that the tremendous implications to patient safety outweigh the concern for breach of confidentiality, as already modeled in existing in-hospital allergy alert temporary wristbands and out-of-hospital permanent medical alert bracelets.[28]

Education

The educational component of the Airway Initiative and Airway Service is divided into directed efforts toward family and patient, physicians and health care providers within the institution, administrators of The Johns Hopkins Medical Institutions, and health care providers at large.

Patient and Family

At numerous times during a patient's hospitalization, effective communication with the patient and family is accomplished in preoperative consultation, immediately preoperatively, during the procedure (as requested), immediately postoperatively, and during the postoperative course. Discharge follow-up consists of a letter from the Department of ACCM with an enclosed brochure for enrollment into Medic Alert, as previously discussed with the patient.

Physicians

Physicians at The Johns Hopkins Medical Institutions are invited to participate in the Airway Rotation as appropriate. During this rotation,

in addition to exposure to airway devices identified in the ASA Difficult Airway Guidelines, senior anesthesia residents receive training in the elective use of the OLHN Hollinger and Dedo rigid laryngoscopes. Before elective use in the operating room, the anesthesia resident completes an in-service and mannequin practice under OLHN attending guidance.

Physicians are also invited to attend monthly airway management multidisciplinary case conferences, attend quarterly mandatory risk management seminars in which airway events are highlighted, and participate in monthly equipment workshops and optional cadaver laboratories. Arrangements can be made to observe airway management in the operating room, intensive care units, or emergency department as appropriate.

Institutional Systems Approach

All operating room personnel participate in yearly disaster drills in which difficult airway management is highlighted and protocols are reviewed. The use of simulation has been a component of the educational program for the past 4 years, with acute airway management being the most recent component. Effective education in difficult airway management encompasses much more than simple task training. The high-level components of learning difficult airway management skills include (1) task training (different techniques of airway management), (2) decision making (learning to recognize and react appropriately to an evolving critical situation), and (3) team building (who needs to be present and what their roles are). Classically, this process has taken place in the setting of delivering patient care, under conditions that may not be particularly conducive to education.

Ongoing Education and CME: Workshops, Role of Simulator, and SAM Annual Meeting

Ongoing education includes a series of annual workshops organized by the Airway Service and offered to all members of the medical institution. They include cadaver surgical airway techniques; mannequin rigid laryngoscopy, fiberoptic bronchoscopy, light wands and a variety of other specialty scopes; and mannequin percutaneous cricothyrotomy and jet ventilation. All are case-based to facilitate discussion and are staffed by at least one attending anesthesiologist, otolaryngologist, nursing specialist, and airway equipment specialist.

In recent years, technology has been developed that can realistically simulate a myriad of critical airway scenarios by use of computerized mannequins. Depending on the verisimilitude required, such mannequins can cost between $30,000 and $300,000, with operating costs ranging from negligible to $60,000 per year. Despite the apparent high cost, the use of simulation in airway management education ultimately should be cost-effective with respect to the improved outcomes that would be expected from better-educated clinicians.

The implementation of simulation is occurring in the context of the "competency-based" education movement that is underway in medical education as a whole. The advantages of simulation over the classic methods of patient-based education are fourfold. First, by using simulation, the trainees can get unlimited experience in critical airway situations that are not very common, thereby having an opportunity to practice and improve their skills until a level of proficiency is achieved. Every time an adverse outcome results, the student can review it, learn from it, and hit the reset button to revive the mannequin to try again. Second, the mannequin is programmed to respond to the interventions of the student, whether correct or not. In either case, the student is forced to reassess the situation and make alternative plans. This decision-making process is essential to learn if one is to be capable of managing the difficult airway. The entire process is recorded and compared with instructor-developed objective standards, which permits focused learning. Third, critical airway management is a team game and requires an understanding of the roles of each team member. This is easily simulated using the mannequins while in an environment that is less pressured than if a real critical airway event was taking place. This facilitates better communication between team members, so that everyone has a common understanding of the overall process. Last, the use of simulation ensures that all the clinicians have educational exposure to a set of clinical situations that are standardized with respect to the specific conditions and the specific learning objectives to be achieved. This is not possible in the patient-based educational model.

Individuals interested in participating in a formal continuing medical educational, multidisciplinary, comprehensive, airway course, complete with simulation technology are encouraged to attend the annual SAM Meeting.

Difficult Airway/Intubation: Documentation and Dissemination of Critical Airway Information to Patients

Written documentation of airway events is institution-specific and specialty variable. No standardized, uniform, readily available document exists to precisely record airway events and summarize salient issues.

Issues with Conveying Information Verbally to Difficult Airway/Intubation Patients

When complex airway management patients are discharged, information about critical airway events may be inadvertently not communicated or miscommunicated. Verbal communication of difficult airway information by the provider to the patient is unreliable. Communication may be hindered by patient intubation, sedation, or both. The patient may be expeditiously discharged from the health care facility or discharged by personnel other than the primary health care provider before airway events have been fully communicated. Miscommunication may arise because of the patient's lack of medical knowledge or because of overriding anxiety related to the medical condition. In addition, providers may underrepresent the severity of difficulty, attempting to allay the patient's anxiety or because they themselves fear liability exposure. Written communication of difficult airway/intubation information by the provider to the patient may be a more effective strategy, but the patient may fail to accurately and comprehensively convey this information to future health care providers. Patients may lose the anesthesiologist's letter or memo or fail to give a copy of it to their primary care provider. Then, in an emergency situation, the information will most likely be inaccessible.

When difficult airway/intubation patients re-enter the health care system electively or emergently, they may relate vague verbal histories, deny any difficult airway/intubation history, or be physically unable to communicate.

Issues with Obtaining Information from Previous Medical Records

Attempts to retrieve prior anesthesia records and documentation should be initiated but may be unsuccessful because of time constraints or unavailability. Even when available, written documentation may be incomplete and difficult for other health care providers to decipher. These situations create confusion as to the exact nature of the airway difficulty encountered and airway management used, thus potentially delaying or compromising patient care.

Even when written documentation is complete and adequate, the information is contained in the patient's original medical record. Subsequent elective or emergent retrieval of records by future health care providers, who are separated by geography or time from the original event, may prove to be untimely or impossible.

Electronic Patient Record: Airway Notes and Anesthesiology Consultant Report

Building the electronic patient record (EPR) at Johns Hopkins, we developed and implemented two templates that can be used by the anesthesiologist for either dictating or typing a note on a patient with a difficult airway/intubation. The first template, the Airway Note, is a brief, free-text dictated entry that specifically summarizes airway management. The second, more complete template, the Anesthesiology Consultant Report (ACR), is a one-page to two-page summary that includes airway information in addition to more comprehensive anesthesia concerns.[29]

"Difficult Airway/Intubation" is placed as a "problem" in the patient's PAM (problem, allergy, medication) list in the overview of

the medical record, so that subsequent health care providers will be aware of this specific issue. Because many providers may not read the specific notes on a patient, this PAM alert, similar to an allergy alert, is immediately highlighted whenever the medical record is accessed.

As electronic anesthesia intraoperative records begin to appear in hospitals, it is imperative that they be integrated into the hospital EPR, so that the anesthesiologist only needs to enter relevant difficult airway/intubation information one time. Finally, to close the loop from the surgical side, all surgeons, particularly OLHN surgeons who understand the nuances of difficult airway management, should be encouraged to include in their operative dictation an accurate description of whatever difficult or unanticipated airway events occurred.

Finally, a letter regarding the airway management is sent from the Department of ACCM to the patient, along with a brochure for enrollment into the Medic Alert Foundation.

Case-Based Learning: Case Presentations of Difficult Airway/Intubation Patients

The following cases are available on the book website. Major teaching points for each case are included below.

Case 1: Consultation with the Airway Service for Future Airway Management

- Despite major advances in airway techniques, anesthetic agents, and monitoring, there remain instances when an elective tracheotomy is the airway management technique of choice.

Case 2: Anticipated from Physical Examination: Awake Nasal Intubation

- Patient's upper airway anatomical considerations and presence of a pedunculated lesion in the glottic opening made the first choice of an awake nasal intubation the safest technique.

Case 3: Anticipated from Surgical Procedure: Three Staged Surgeries for Temporomandibular Joint (TMJ) Surgery

- This case illustrates the concept that, for each patient, the airway algorithm used is on the basis of these concepts: full stomach (yes/no), oral or nasal intubation (or neck/surgical), and awake or asleep intubation. In each case, the anesthesia team chose a technique that they had expertise with, that suited the surgical needs, and that was agreed on with the patient.

Case 4: Anticipated Difficult Intubation and Extubation: Trismus versus Fused TMJ

- The diagnosis of trismus presents practitioners with at least two major challenges: (1) distinguishing between masseter muscle spasm/pain and TMJ limited opening, and (2) having multiple airway techniques immediately available, and limited by (1).

Case 5: Anticipated Difficult Intubation: Asleep Oral Intubation

- A multidisciplinary approach to airway management and immediate mobilization to equipment facilitated successful intubation on a patient with a known difficult airway.

Case 6: Unanticipated Difficult Intubation, Difficult Mask Ventilation with LMA, Can Wake Up

- This was a case of difficult mask ventilation in which the LMA proved invaluable as a "bail out" device.

- Until it becomes standard to have anesthesia documentation within electronic medical records, surgeons should be encouraged to briefly document the airway management of their patient in their dictated operative note.

Case 7: Unanticipated Difficult Intubation, Maskable, Cannot Wake Up Because of Long-Acting Paralysis

- In the hands of an experienced practitioner, the Hollinger laryngoscope has a significant role in the management of difficult airway/intubations, as detailed in The ASA Difficult Airway Management Algorithm.[8]

Case 8: Unanticipated Difficult Intubation, Failed RSI, Respiratory Compromise

- Although anesthesiologists assume that most surgeons are facile with surgical airways, this is not always the reality in an emergency situation. Although the introduction of percutaneous cricothyrotomy into anesthesiologists' difficult airway algorithms was thought to address this issue, there are many complications related to its emergency use.

Case 9: Known Difficult Intubation Patient: Consequences of Failed Regional Anesthesia

- The authors strongly advocate for immediate availability of appropriate airway management equipment and support staff for any patient with a difficult airway/intubation receiving regional anesthesia throughout the entire operative period.

Case 10: "Fast Track Evaluation": Preoperative Evaluation and Airway Management of a Patient with Prader-Willi Syndrome

- The optimal evaluation of this patient would have been to be seen by members of the Airway Service before the day of surgery, as had been originally planned by the attending surgeon.

Case-Based Learning: Case Presentations of Catastrophic Events In The Operating Room and the Role of the OLHN Surgeon

The following cases are available electronically. Major teaching points for each case are included below.

Case A: Fire in the Airway

- The best treatment for fire in the airway is prevention.

- In the event of an airway fire, the following steps should be taken:
  1. Stop the flow of O_2 to the ETT.
  2. Remove the ETT.
  3. Flood the field with fluids, if appropriate.
  4. Mask ventilate with 100% O_2.
  5. Reintubate as soon as possible.
  6. Consider positive end-expiratory pressure (PEEP), continued ventilatory support, and high-dose steroids.
  7. Call for immediate consultation with an otolaryngologist to evaluate the extent of the airway burn.

Case B: Postobstructive Pulmonary Edema

- With the relief of the obstruction, either with a surgical airway or oral/nasal ETT, the pulmonary edema becomes evident but can be delayed for some time after the episode of obstruction. Prompt recognition and treatment are essential and include reintubation/surgical airway, oxygenation, PEEP, and diuretics as indicated.

Case C: Rule Out Tension Pneumothorax versus Anaphylactic Reaction

- Rule out latex anaphylaxis has increasingly become the number one differential diagnosis when faced with acute respiratory and cardiovascular compromise that appears anaphylactic in presentation. Many hospitals are latex-safe with the goal of becoming latex-free.

Case D: Rule out MH

- Treatment includes immediate notification to the surgeon, discontinuation of any potential triggering agents, administration of dantrolene, and cardiovascular support of the patient. Temperature increases can be a late sign, and meticulous measurement of temperature and appropriate treatment are critical.

Case E: Rule Out Pheochromocytoma

- Although pheochromocytomas only account for 0.1% of cases of hypertension, when first identified unexpectedly under general anesthesia, the physiologic effects of released catecholamines can be catastrophic and life threatening.[31]

- While this patient does not have known MEA, practitioners must be vigilant in the evaluation of patients in risk populations for MEA, specifically to diagnose pheochromocytoma before the diagnosis is made under general anesthesia.[31]

Conclusion

Difficult airway management, anticipated or unanticipated, is multidisciplinary. Although there is an obvious interactive role for the OLHN surgeon and the anesthesiologist in the "airway" of the ABCs of patient management, successful management depends on joint preoperative evaluation, precise discussions of airway plans, and discussion of immediate plans of action in the event of failed airway management or patient compromise for nonairway issues.

Effective communications, verbal and written, regarding critical airway information is essential to the future safety of patients and facilitates efficient and appropriate future airway management. Practitioners are encouraged to incorporate any/all of the documents presented in this chapter into their practice. Enrollment into Medic Alert should be encouraged for all patients who might benefit from the immediate identification of critical medical information (e.g., difficult airway and anaphylaxis).

Development of an institutional Airway Service can be significant in the delivery of quality patient care. Familiarity with medical, societal, and institutional airway algorithms is a key in the success of an Airway Service.

Finally, all physicians must remain current in basic and advanced resuscitation protocols if they are to actively practice in environments that administer sedation or general anesthesia to patients, because unexpected catastrophic events cannot be predicted and occur when one least expects them or is inadequately prepared to immediately respond to the emergency.

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CHAPTER TEN

Surgical Management of the Difficult Adult Airway

Nasir Islam Bhatti

Key Points

- The difficult airway must be considered as involving at least one of the following: difficult laryngoscopy and difficult mask ventilation (DMV), and/or difficult tracheal intubation.
- It is important to realize that identification of the difficult airway before manipulation is the first step in preparing for optimal patient care and a safe outcome.
- The otolaryngologist with her or his training and expertise in endoscopic techniques, such as rigid and flexible laryngoscopy, bronchoscopy, and the ability to provide open surgical access to the airway, is an essential member of the difficult airway response team (DART).
- Techniques commonly used in management of the difficult airway include awake fiberoptic laryngoscopy, intubation through a laryngeal mask airway (LMA) with or without fiberoptic laryngoscopy, intubation by direct laryngoscopy with an anterior commissure laryngoscope, and the surgical airway.
- Awake fiberoptic intubation should be considered in the obese patient with obstructive sleep apnea (OSA), in conditions resulting in supraglottic obstruction (e.g., edema, supraglottic tumor), and in patients with history of difficult intubation by other techniques.
- Lack of training and experience in fiberoptic bronchoscopy is a common cause of failure in awake fiberoptic intubation.
- Once the "can't intubate, can't ventilate" situation has been identified, immediate consideration should be given to surgical airway access.

Failure to maintain a patent airway may result in catastrophic events for the patient, including brain damage or death. In 1990, more than 85% of all respiratory event–related closed malpractice claims involved an anoxic brain injury or death.[1] Difficulties with intubation and emergent airway issues remain the leading causes of serious intraoperative complications.[2] As many as 30% of deaths attributable to anesthesia involve failure to manage the difficult airway.[3] In any given patient, the risk of anoxic injury or death increases in direct proportion to the degree of difficulty in maintaining a patent airway.[4] Any scientific or clinical description of the difficult airway must include clearly defined terminology. In this chapter, the difficult airway must be considered as involving three distinct but often clinically related scenarios.

The first of these is difficult tracheal intubation. This condition exists when multiple attempts are needed in the presence or absence of tracheal disease. An infinitely difficult intubation means the trachea cannot be intubated under direct vision, despite full paralysis, optimal head and neck positioning, cricoid pressure, forceful anterior elevation of the laryngoscope blade, and attempts by multiple operators with a variety of laryngoscope blades.[4] The incidence of failed endotracheal intubation ranges from 5 to 35 in 10,000 patients.[5,6]

The second difficult airway scenario is the difficult laryngoscopy. Difficult laryngoscopy is described as not being able to visualize any portion of the larynx, vocal folds, or glottic aperture after multiple attempts at conventional laryngoscopy. Many investigators include grades III and IV or grade IV alone, according to the Cormack-Lehane original grading of the rigid laryngoscopic view.[7] For studies of difficult laryngoscopy to be reliable and for the preceding laryngoscopic grading system to be helpful, the reported grades must describe the best view that was obtained, which in turn depends on the best performance of laryngoscopy.[4] The technical components that optimize laryngoscopy include optimal position, complete muscle relaxation, firm forward and upward traction on the laryngoscope, and, if necessary, firm external laryngeal manipulation with cricoid pressure. External laryngeal pressure, for example, may reduce the incidence of grade III view from 9% to 1.3%.[8] Theoretically, if the preceding technical components of laryngoscopy are used and the pitfalls avoided, all laryngoscopists (novice and expert) should have close to the same laryngoscopic view. Difficult laryngoscopy is synonymous with difficult intubation in most patients. A grade II or III laryngoscopic view requiring multiple attempts with different blades, or both, is relatively common, occurring in 100 to 1800 of 10,000 patients.[9] The incidence of a higher grade III laryngoscopic view ranges from 100 to 400 of 10,000 patients.[10,11]

The third difficult airway scenario is difficult mask ventilation (DMV), which is a condition in which it is not possible to provide adequate face mask ventilation as a result of inadequate mask seal, or excessive resistance due to inadequate patency of airway.[4] Langeron and colleagues compiled a list of predictors of difficult mask ventilation based on a survey of anesthesiologists asking them to rate difficulty of face mask ventilation.[12] This difficulty was based on whether it was clinically relevant and could have led to potential problems if mask ventilation had to be maintained for a longer time. Six reasons for DMV were identified: (1) inability of the unassisted anesthesiologist to

Box 10-1

Differences Between 1993 and 2003 ASA Management of the Difficult Airway Algorithms

1. Difficult ventilation is now listed first under assessment of the likelihood and clinical impact of basic management problems. Also, in the same category, difficult tracheostomy was added.
2. To pursue actively opportunities to deliver supplemental oxygen throughout the process of difficult airway management was added.
3. When considering the relative merits and feasibility of basic management choices, awake intubation versus intubation attempts after induction of anesthesia should now be considered first before nonsurgical techniques as the initial approach to intubation.
4. The use of laryngeal mask airway (LMA) is incorporated into the algorithm in awake limb and after induction of general anesthesia limb in both emergency and nonemergency pathways (either as a ventilator device or as a conduit for tracheal intubation).
5. One more intubation attempt was removed.
6. Rigid bronchoscope was added as an option for emergency noninvasive ventilation.

From Hagberg CA, Benumof JL. The American Society of Anesthesiologists management of the difficult airway algorithm and explanation—analysis of the algorithm. In: Hagberg CA, ed. *Benumof's Airway Management*. 2nd ed. Philadelphia: Mosby Elsevier; 2006:236-251.

maintain oxygen saturation to greater than 92% using 100% oxygen and positive-pressure mask ventilation, (2) significant gas flow leak by the face mask, (3) necessity to increase the gas flow to greater than 15 L/min and to use the oxygen flush valve more than twice, (4) no perceptible gas movement, (5) necessity to perform a two-handed mask-ventilation technique, and (6) change of operator required.

The incidence of DMV is difficult to estimate in that there has not been a standard definition used universally by researchers, so each study needs to be carefully read to determine the definition used. Langeron and colleagues reported a 5% incidence of DMV with 1 in 1502 patients being impossible to ventilate with a face mask.[13] A very significant finding from this study is that DMV conferred a fourfold increased risk for difficult intubation and 12-fold increase in the risk for an impossible intubation.

The incidence of the ultimately critical failed airway, the "can't intubate, can't ventilate" situation, can be estimated because it frequently results in anoxic brain injury or death, ranging from 0.01 to 2 of 10,000 patients.[14,15] Although the cause of this dire apneic or obstructive state may be completely or partially related to the patient's disease, there is often an identifiable iatrogenic component. The clinicians caring for the patient in this urgently life-threatening state must be prepared to act swiftly and decisively in order to sustain or recover oxygen saturation and ensure ventilation.

With these definitions in mind, it is important to realize that identification of the difficult airway before manipulation is crucial, and the key step in preparing for optimal patient care and a safe outcome.[16] Selection of airway equipment or devices, techniques, and procedures all pivot on airway evaluation. The literature provides strong evidence that specific strategies and communication of these strategies with the airway team facilitate management of the difficult airway. The American Society of Anesthesiologists' (ASA) algorithm on the management of the difficult airway is an example of such collaborative effort and should act as a foundation for locally developed institution-specific action strategies.[17] Refer to the differences between 1993 and 2003 versions of the ASA algorithm (Box 10-1).

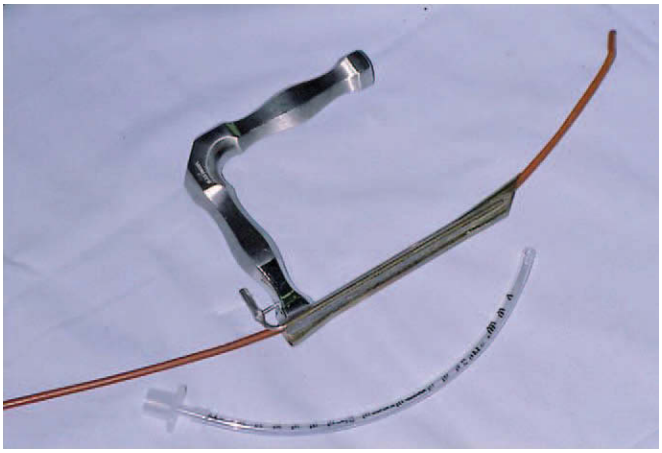

Figure 10-1. Hollinger laryngoscope is the most dependable scope for direct laryngoscopy in management of the difficult airway. Both cuffed and cuffless tubes may be passed through the scope, although size is limited to 5.0 cuffed endotracheal tube. If a larger tube is required, intubation over an Eschmann stylette is possible.

When considering management options for the difficult airway situation, the anesthesiologist and surgeon must give consideration to aborting the planned procedure, waking the patient, and reassessing airway management options before proceeding. When this is not an option, the team must consider alternative techniques for laryngoscopy such as the video-assisted Glidoscope, placement of a laryngeal mask airway (LMA) and intubation by fiberoptic laryngoscopy with or without an Aintree catheter, or direct laryngoscopy with an anterior commissure (Hollinger) laryngoscope and intubation through the laryngoscope.

Use of the LMA in the difficult airway situation has increased as equipment has evolved to facilitate intubation through the LMA. The success of this device led to the introduction of the intubating LMA (LMA Fastrach) into clinical practice.[18,19] Intubation may be accomplished by passing the endotracheal tube (ETT) alone through the LMA (blind technique), or by intubation over a fiberoptic bronchoscope with or without an Aintree catheter placed over the bronchoscope. This technique provides visualization of the intubation and may be combined with videoendoscopy. The addition of the Aintree catheter facilitates intubation after removal of the LMA if this is required to proceed with surgery.

The Hollinger anterior commissure laryngoscope is the otolaryngologist's most useful tool in difficult airway management, and should be considered when all other techniques have failed. This is particularly true for fixed laryngeal and subglottic lesions where a small cuffless ETT may be passed under direct visualization. The Hollinger scope will accommodate a 5.0 or smaller cuffed ETT, although the insufflation port may become lodged in the barrel of the scope. This should be determined before intubation. An Eschmann stylette may also be passed through the laryngoscope and the ETT passed over the stylette, allowing placement of a larger sized ETT (Figs. 10-1).

Awake fiberoptic intubation should always be considered as a viable option, especially in the anticipated difficult airway situation. This technique is discussed in more detail in following sections.

Surgical procedures such as open cricothyroidotomy, tracheostomy, and transtracheal jet ventilation must be considered when faced with the "can't intubate, can't ventilate" situation. The role an otolaryngologist can play in such situations is critical, providing expertise in endoscopic techniques with the ability to provide open surgical access to the airway. The indications, contraindications, technique, and strategies to optimize success with these techniques are discussed herein in detail.

Awake Fiberoptic Nasotracheal Intubation

Awake fiberoptic nasotracheal intubation is now a common technique employed in the management of the difficult airway in both the operating room and intensive care unit settings.

Box 10-2

Indications for Fiberoptic Intubation

I. Difficult intubation
   A. Known or anticipated
   B. Unanticipated failed intubation
II. Compromised airway
   A. Upper airway
   B. Lower airway (tracheal compression)
III. Intubation of the conscious patient preferred
   A. High risk of aspiration
   B. Movement of neck not desirable
   C. Known difficult mask ventilation
   D. Morbid obesity
   E. Self-positioning
IV. High risk of dental damage

From Ovassapian A, Wheeler M. Fiberoptic endoscopy-aided techniques. *Benumof's Management: Principles and Practice*. 1st ed. St Louis: Mosby; 1996:282-319.

Figure 10-2. Cart for anesthesia for the difficult airway demonstrating organization of ancillary items used for fiberoptic intubation.

Historical Perspective

Flexible fiberoptic technology has provided the vehicle for developing and perfecting these intubation techniques. A flexible fiberoptic choledochoscope was first used for nasotracheal intubation on a patient with Stills' disease as early as 1967.[29] Five years later, nasotracheal intubation was successfully carried out in a patient with severe rheumatoid arthritis using a fiberoptic bronchoscope (FOB).[30] Stiles and colleagues subsequently reported the first series of 100 fiberoptic endotracheal intubations.[31] These intubations were performed both orally and nasally, and the authors suggested that with experience, fiberoptic intubation could be performed in less than 1 minute.

Davis and colleagues described the use of FOB for checking the ETT position in relation to carina.[32] Use of FOB in assessing ETT position was shown to be as good as chest radiography in both adults and children.[33,34] Many other uses of FOB technique were also described, especially in critically ill patients, to evaluate the upper and lower airway.[35-38] Several authors cited advantages of the technique, including the ability to perform diagnostic and therapeutic procedures at the bedside without general anesthesia and without interruption of ongoing mechanical ventilation. Another advantage cited was the ability to perform the procedure orally, nasally, or through an in situ ETT or tracheostomy tube. One main disadvantage reported by many authors was the increased airway resistance particularly in pediatric patients because the FOB may occupy a significant portion of the lumen of the tube. FOB was not originally developed for the management of the difficult intubation.[39] However, as technology was advanced and visualization improved, anesthesiologists soon appreciated the value of the FOB in the management of the difficult airway.[40-43] Use of the FOB has been described for airway management in Ludwig's angina,[44] rheumatoid arthritis,[45] trauma,[46] unstable cervical spine,[47] disruptive injuries of the soft tissue of the neck,[48] acromegaly,[49] and Pierre Robin syndrome,[50] among other conditions. Several authors have reported successful use of the FOB in securing the airway in awake patients with increased risk of aspiration.[51-54] As a result, the teaching of fiberoptic airway endoscopy is now an integral part of training for otolaryngology head and neck surgery (OHNS), anesthesiology, and emergency medicine.

Indications

When the airway is compromised or a difficult airway is anticipated, awake fiberoptic intubation (FOI) with or without sedation should be considered (Box 10-2). Awake fiberoptic intubation is an ideal procedure for patients with morbid obesity, supraglottic mass, or edema with the ability to visualize the glottic aperture, risk of aspiration, history of known DMV, patients with limited mandible excursion or trismus, and history of prior difficulty with transoral intubation using other techniques. Contraindications to awake fiberoptic intubation include fixed stenotic lesions at all levels that will not allow passage of an ETT without dilatation, active bleeding obscuring visualization, and acute obstructing supraglottitis, as well as in patients unable to cooperate during the examination. In general, many patients who might be denied general anesthesia or receive a tracheostomy can be safely intubated using the FOB. To intubate patients safely and quickly, certain preparatory steps should be taken.

Bronchoscopy Cart

Proper functioning equipment is essential to a successful outcome. A fully equipped videobronchoscopy cart should be available for use in the intensive care units, emergency department, critical care wards (e.g., otolaryngology patient floor) as well as in the operating room. All equipment and supplies for administration of anesthesia, resuscitation, and monitoring should be available and should be checked following a standard protocol before beginning a nonemergent fiberoptic intubation (Fig. 10-2). For awake intubations, the cart is placed on the left side at the head of the bed while a right-handed operator stands on the right side facing the patient. The light source should be checked for integrity and the necessary supplies are laid out on top of the fiberoptic cart, and suction is connected and at hand. The cart should contain ancillary equipment including nasopharyngeal airway and endotracheal tubes (standard and MLT long tubes), among other items.

Fiberoptic Intubation of the Conscious Patient

The advantages of awake fiberoptic intubation include maintenance of spontaneous ventilation and the ability to position the tip of the ETT precisely beyond the obstruction/compression. It is easiest in the awake near upright patient because the tongue does not fall back in the pharynx, and breathing tends to keep the airway open. In addition, with deep inspiration, the patient can assist the operator in locating the glottis when airway anatomy is distorted. Box 10-3 lists the factors that are crucial for successful completion of an awake fiberoptic intubation. These include training and preparation of the airway team, psychological and pharmacologic preparation of the patient, appropriate monitoring and delivery of oxygen during preparation of the patient and the procedure, expertise of the operator, and a well-functioning bronchoscopy cart.

Preparing the Patient

Psychological Preparation

A successful outcome is more likely to occur with a relaxed and cooperative patient. The preparation starts with an informative, reassuring

Box 10-3

Keys to Successful Awake Fiberoptic Intubation

I. Expert endoscopist
II. Functioning fiberoptic bronchoscope and supplies
III. Preparation of the patient
  A. Psychological preparation: informative, reassuring preoperative visit
  B. Pharmacologic preparation
    1. Premedication
      a. Light or no sedation for calm patients
      b. Heavy sedation for anxious patients
      c. Narcotics when pain is present
      d. Specific drugs for habitual drug users
      e. Anti-sialagogue unless contraindicated
    2. Intravenous sedation
      a. No sedation for patients with severely compromised airway
      b. Conscious sedation for most patients
      c. Heavy sedation for uncooperative patients
    3. Topical anesthesia
      a. Oral intubation: oropharynx, laryngotracheal
      b. Nasal intubation: nasal mucosa, laryngotracheal
      c. Monitoring and oxygen

Modified from Wheeler M, Ovassapian A. Fiberoptic endoscopy–aided techniques. In: Hagberg CA, ed. *Benumof's Airway Management*. 2nd ed. Philadelphia: Mosby Elsevier; 2006:399-438.

preoperative visit with the patient. The process is explained in detail and all the questions are answered. If intubation is going to be performed without any sedation, the reason (which is almost always patient safety) is explained. The patient's active participation is requested, which may include maintaining head position, taking deep breaths, or clearing secretions when requested. When minimal or no sedation is used, the patient should be informed that recall of the procedure is possible.

Pharmacologic

There are three components to the pharmacologic preparation of the patient for awake fiberoptic intubation. These include premedication, limited sedation at the time of intubation, and application of topical anesthesia. The goals of premedication include sedation that augments the psychological preparation and provision of an anti-sialogogue to reduce secretions. Midazolam 1 to 3 mg intramuscularly or 10 to 20 mg by mouth provides adequate sedation in most patients. If the patient's airway or physical condition is compromised, no sedative or opioid should be given before the patient's arrival at a monitored setting where the airway team including an anesthesiologist is in attendance. An anti-sialogogue agent is essential for establishing good topical anesthesia and to optimize conditions for fiberoptic visualization of the glottis.[55] Glycopyrrolate is considered the agent of choice in that it does not cross the blood-brain barrier and causes less tachycardia.

Monitoring

Standard monitoring is applied to all patients undergoing FOB, whether the procedure is performed in the operating room suite, intensive care unit, or any other location. Oxygen is provided by nasal cannula at a flow rate of 3 L/min to all adult patients undergoing FOI unless contraindicated.

Conscious Sedation

When possible, conscious sedation is administered in immediate preparation for intubation. The goal of conscious sedation is to have a calm and cooperative patient who can follow verbal commands and maintain adequate oxygenation and ventilation. Depending on the indication for FOI, an opioid, a sedative, or a combination of both is used. A combination of fentanyl (1.5 μ/kg) and midazolam (30 μ/kg) has been used successfully for these procedures. Remifentanil infusion may also be used for sedation for fiberoptic intubation.[56,57] This approach may not be indicated in the obese patient with obstructive sleep apnea, because it may precipitate an airway crisis. Use of sedation should be discussed with the anesthesiologist before initiating the procedure.

Topical Anesthesia

Instrumentation of the airway without using topical anesthesia is uncomfortable and distressing to an awake patient. Pharmacologic preparation should, therefore, include application of topical anesthesia. Adequate topical anesthesia eliminates pharyngeal, laryngeal, and tracheobronchial reflexes. Presence of excess secretions dilutes the local anesthetic solution, creates a barrier between the drug and the mucosa, and carries the local anesthetic away from the site of action.[58,59] Using an effective antisialogogue is therefore necessary. Furthermore, the absorption rate and amount of topical anesthetic vary according to the site of application, the dose of the drug, and the general condition of the patient.[60-62] The agents are absorbed more rapidly from alveoli than from the tracheobronchial tree. The rate and amount absorbed from the pharynx is even lower. The dosage for topical agents should be halved when applying them to the respiratory mucosa because the plasma levels rise more rapidly than do injections into the tissues.[54]

Nasotracheal Intubation of the Awake Patient

Topical Anesthesia

The more patent nostril is selected and sprayed with 2 mL of oxymetazoline (Afrin). This should be determined in clinic if possible or just before the procedure by direct examination. The cotton-tipped applicators are then soaked in 4% cocaine (4 mL) and gently pasted over the septum and the inferior turbinates. Alternatively, a combination of 4% lidocaine with 1% phenylephrine may be used instead. It is advisable to wait at least 5 minutes, allowing maximal vasoconstriction and topical anesthesia. Using cotton-tipped applicators helps evaluate the patency of the nostril as well as predict the angle of the nasal floor, which slopes downward from front to back. Laryngotracheal anesthesia is achieved by transtracheal injection of 1% lidocaine or by spraying through the FOB during intubation. The oropharynx should also be anesthetized as the gag reflex is stimulated by the nasal route. Using nebulized lidocaine during set-up before the procedure is a useful technique.

Technique

Intubating fiberoptically via the nasal route is easier than the oral approach because the scope is usually pointed straight at the vocal cords as it enters the oropharynx and is generally better tolerated by the patient.[63] Our preferred method is to prepare the nose as described above while setting up the equipment and supplies. The ET tube is placed in warm saline to soften the tube. The cuff is tested by inflation, and to minimize resistance, when deflated the cuff is retracted back so that it is flush with the outer wall of the tube. The nasal passages are first dilated to appropriate diameter with increasingly larger nasal trumpets, which are generously lubricated with lidocaine gel and epinephrine solution (Fig. 10-3). The ET tube is then placed into the nostril, directed downward as it is advanced toward the nasopharynx. If the tube does not make the bend toward the oropharynx, it is pulled back and rotated 90 degrees to the right or left and then reintroduced.

The FOB, which is connected to a videoendoscopy unit, is then passed through the ETT and used to visualize the airway (Fig. 10-4). It is preferable to have the patient's head elevated and if possible to be sitting near upright to minimize airway collapse; the operator faces the patient and video monitor (Fig. 10-5). The video-assisted FOI provides feedback to those assisting with the procedure and facilitates intubation. In 80% to 85% of patients, the epiglottis and vocal folds are seen

Figure 10-3. Nasal trumpet placed for dilatation is lubricated with Xylocaine gel.

Figure 10-4. After placement of the endotracheal tube into the nasal cavity, the fiberoptic bronchoscope is passed through the tube for visualization of the airway.

with minimal or no manipulation of the tip of the scope. In patients who are not breathing spontaneously or are older, the tongue and pharyngeal tissue may fall back and block the exposure of the larynx. A few maneuvers, including extending the head, applying jaw thrust, or gently pulling the tongue forward, help visualize the cords. Once visualized, application of 3-mL aliquots of 2% lidocaine instilled through the scope should be performed at the level of the vocal folds before intubation and time should be allowed for effect. Patience is extremely helpful at this point and continuous communication with the patient, letting him or her know that all is proceeding as planned, helps minimize anxiety. It is also helpful to have multiple syringes with "slip-tip" preloaded with lidocaine, because repeated injections may be necessary until the patient no longer coughs in response to stimulation. The scope is then advanced through the vocal folds. Timing the entry of the scope with the breathing cycle is a useful trick. Once adequate visualization is achieved, the scope is then advanced into the cervical trachea and additional lidocaine in instilled. The scope is then advanced to a level just above the carina and the ET tube is passed over the scope into position. If there is resistance during this maneuver, it is helpful to rotate the ETT 90 degrees clockwise, changing the orientation of the bevel.[64]

Figure 10-5. Optimal setup for fiberoptic intubation includes patient with head elevated to minimize airway collapse, operator facing patient, and entire team observing the procedure on the video monitor.

Avoiding Failure in Fiberoptic Awake Intubation

Causes of Failure

Lack of training and expertise in the use of FOB is the single most common cause of failure in awake fiberoptic intubations. Other causes may be considered under the categories of team factors, patient factors, and equipment issues. These are outlined in Box 10-4.

Pearls to Ensure Successful Awake Fiberoptic Intubation

The training and expertise of the operator and the team is most critical (see Box 10-3 for a list of keys for successful awake intubation). There is no substitute for structured training during residency or fellowship.[65,66] Preparing the team and keeping the communication lines open during the entire process helps ensure successful intubation. Maintaining a fully stocked, easily transportable, and functioning FOB cart at hand is highly desirable as well.

Psychological and pharmacologic preparation of the patient increases likelihood of successful outcome. It is essential to administer an adequate dose of anti-sialogogue, sedative if indicated, and topical anesthesia. The value of proper suctioning before an intubation attempt cannot be overemphasized. The conscious patient can be asked to swallow and cough to clear secretions. In some patients, the tip of the epiglottis may fall against the posterior pharyngeal wall, interfering with the navigation of the scope into the larynx. Application of jaw thrust or gentle but firm pull on the tongue moves the epiglottis away from the posterior pharyngeal wall and corrects the problem.

Advancing the ET tube into the trachea is not possible when the FOB is passed through the Murphy eye of the ET tube rather than the distal opening.[67] Withdrawal of the FOB may be difficult or impossible without damaging the instrument. The scope and the tube should be withdrawn as a unit, the scope disengaged, and the procedure repeated. It is also necessary to use lubrication on the scope to facilitate movement of the tube into and out of the ET tube.[68]

Operative Surgical Airway Options

Historical Perspectives

The role of surgical airway as a lifesaving procedure has been appreciated for thousands of years.[20] Egyptian tablets dating back to 3600 BCE depict surgical tracheostomy.[21] Galen in the second century CE described a tracheostomy using a vertical incision as an emergency measure for airway obstruction.[22] The first detailed description of tracheostomy was published in the sixteenth century by Vesalius, who proposed using the procedure to ventilate the lungs. The Spanish

Box 10-4

Causes of Failure of Fiberoptic Intubation

I. Team factors
   A. Lack of expertise
   B. Poor topical anesthesia
II. Patient factors
   A. Suboptimally prepared patient
   B. Presence of secretions and blood
   C. Decreased space between epiglottis and posterior pharyngeal wall
   D. Distorted airway anatomy
III. Equipment factors
   A. Fogging of the objective and focusing lens
   B. Passage of the fiberoptic bronchoscope through the Murphy eye
   C. Inadequate lubrication of a tightly fitting fiberoptic bronchoscope

Modified from Wheeler M, Ovassapian A. Fiberoptic endoscopy–aided techniques. In: Hagberg CA, ed. *Benumof's Airway Management*. 2nd ed. St Louis: Mosby Elsevier; 2006:399-438.

Inquisition, however, condemned his alleged resuscitation of a Spanish nobleman.[23]

The first recording of a successful tracheostomy in the United States was in 1852. The patient later died of airway stenosis, which remained a common complication of the procedure for decades to follow. A mortality rate of 50% was quoted for tracheostomy in an 1886 paper with many of these deaths attributed to a high incidence of stenosis.[24] A landmark paper by Chevalier Jackson in 1909 described a safe surgical technique and principles that are still applicable.[25] He described many factors that he considered to contribute to a lower mortality rate (3%) at the time. These included optimal securing of the airway before the procedure, the use of local anesthesia instead of sedation, using a specifically designed tube, and meticulous surgical technique and postoperative care. In the same paper, Jackson condemned the technique of high tracheostomy, which was the term used for cricothyrotomy at the time. In a later paper in 1921, Jackson described his series of 200 patients with postcricothyrotomy stenosis in patients referred to him. In addition to the obvious referral bias, the primary indication at the time (inflammatory lesions of the upper airway) might have accounted for high incidence of subglottic stenosis.[26]

After Jackson's criticism, cricothyrotomy continued to be condemned for more than half a century. It was not until Brantigan and Grow published a series of 655 patients undergoing cricothyrotomy for chronic airway management.[27] They described a procedure that was faster, simpler, and less likely to cause bleeding than tracheostomy. The stenosis rate was 0.01% and there were no major complication. Many subsequent studies support their conclusion that cricothyrotomy is a safe and effective surgical procedure and in fact preferable to tracheostomy for emergent airway control.[28]

Cricothyrotomy

Definition

Cricothyrotomy is the establishment of a surgical opening into the airway through the cricothyroid membrane (CTM) and placement of a tube for ventilation.[20] It differs from tracheostomy in the anatomic location of entry into the airway.

Anatomic Considerations

In emergent situations, cricothyrotomy is preferable to tracheostomy because of relative simplicity, speed, and lower perioperative complication rate. The airway at the level of CTM is separated from the skin only by the subcutaneous fat, anterior cervical fascia, and strap muscles laterally. The trachea moves progressively deeper in the neck as it moves caudally. This makes anterior access more difficult. Additionally, the thyroid isthmus overlies the second to fourth tracheal rings, acting as an additional structure to negotiate when performing a tracheostomy.

Box 10-5

Equipment for Emergency Surgical Cricothyrotomy

No. 15 blade
Crile forceps or hemostats
Small endotracheal tube (5.0) or a tracheostomy tube (size 4 cuffed)
Cricoid hook (single curved hook)
Scissors
Tracheal dilator

Cricothyroid Membrane

The CTM stretches between the thyroid cartilage and the cricoid ring and consists of fibroelastic tissue. In an average adult male it is 1 cm high and 2 to 3 cm wide, and located in the midline approximately 1 fingerbreadth below the laryngeal prominence. The vocal folds are approximately 1 cm above the CTM and therefore prone to injury during a cricothyrotomy. The ligament does not calcify with age. It has no overlying muscles, major vessels, or nerves; however, the anterior jugular veins border the membrane laterally and bleeding from these vessels may be substantial.

The right and left cricothyroid arteries are branches of the right and left superior thyroid arteries. In most patients these vessels cross the superior aspect of the CTM to anastomose in the midline.[69] Although at risk for injury during cricothyrotomy, the resulting bleeding is usually self-limiting and easily controlled with gauze packing.

The CTM lies a fingerbreadth below the laryngeal prominence. Its location can also be estimated to be 3 to 4 fingerbreadths above the suprasternal notch with the neck in neutral position, although this may be quite variable depending on body habitus. Identification of the landmarks may be difficult or impossible in the edematous or traumatized neck, and in obese patients.

Surgical Cricothyrotomy

Indications

The primary indication for cricothyrotomy is failure to intubate by oral or nasal means in the presence of an immediate need for definitive airway management and inability to mask-ventilate the patient.

The American Society of Anesthesiologists (ASA) Difficult Airway algorithm recommends a surgical airway as the final endpoint for the unsuccessful arm of the emergency pathway.[70] Despite the introduction of numerous rescue devices for failed airway, the most common errors in the management of the difficult airway result from repeated unsuccessful attempts at intubation in these situations.[71] *Once the "can't intubate, can't ventilate" situation has been identified, immediate consideration should be given to a surgical airway.* Failure to pursue this approach when unable to ventilate will most likely result in delay in achieving airway control, placing the patient at risk for subsequent hypoxic brain injury and/or death. Often the main obstacle is lack of experience or timely recognition of the need to perform this procedure. Adequate training in the laboratory, planning based on an algorithm and availability of equipment, as well as trained personnel, are the keys to successful performance of the procedure. Availability of necessary equipment, preferably packaged as a preassembled kit, prevents wasting crucial minutes gathering supplies in the emergency situation (Box 10-5).

Relative contraindications for cricothyrotomy include age younger than 10 years of age, severe neck trauma with inability to palpate the landmarks, and expanding neck hematoma. Preexisting laryngeal disease with subglottic extension (e.g., malignancy) is another relative

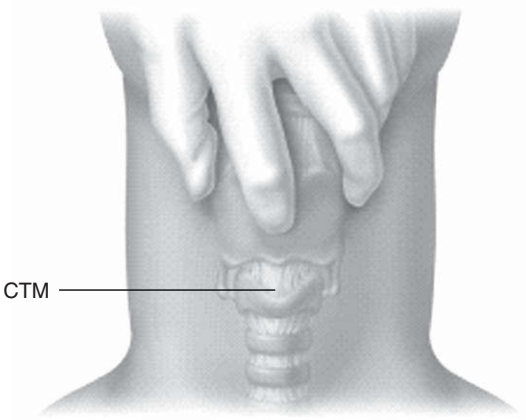

Figure 10-6. With the superior cornu of the larynx firmly immobilized by the thumb and long finger of the nondominant hand, the index finger is free to palpate and locate the cricothyroid membrane (CTM). *(From Walls RM, Murphy MF, Luten RC.* Manual of Emergency Airway Management*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.)*

Figure 10-7. A vertical skin incision is made down to, but not through, the airway. *(From Walls RM, Murphy MF, Luten RC, et al.* Manual of Emergency Airway Management*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.)*

contraindication. A planned urgent awake tracheostomy is preferred in this situation. Emergency or "slash" tracheostomy is a procedure that carries a very high risk of complications (up to 5 times that of elective procedure).[72]

Surgical Procedure

Identification and palpation of the sternal notch, thyroid cartilage (especially the superior thyroid notch), and cricoid cartilage (felt as an indentation below the thyroid cartilage) is the critical first step (Fig. 10-6). Stabilizing the upper airway with the nondominant hand of the operator during the rest of the procedure is the single most important factor determining successful outcome.[73] This technique pins the larynx in the midline, facilitating dissection by maintaining anatomic positioning of the airway.

A midline vertical skin incision over the cricoid cartilage avoids the often engorged anterior jugular veins and minimizes the risk of injury to the carotid arteries and jugular veins (Fig. 10-7). The membrane is palpated through the incision (Fig. 10-8) and entered with a horizontal incision at the lower edge of the cricothyroid space (Fig. 10-9). This incision is then dilated with a hemostat or Kelly clamp placed in the airway and opened horizontally while lifting upward to expose the opening (Fig. 10-10). A cricoid hook may be placed at the

Figure 10-8. The index finger is used to directly palpate and relocate the cricothyroid membrane. *(From Walls RM, Murphy MF, Luten RC.* Manual of Emergency Airway Management*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.)*

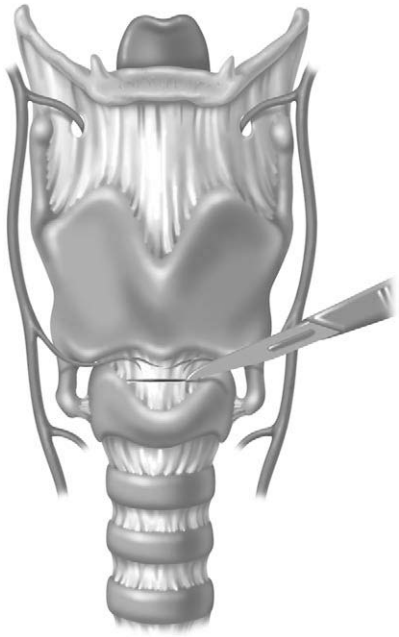

Figure 10-9. A transverse incision is made in the cricothyroid membrane, staying low to attempt to avoid the cricothyroid artery and vein. *(From Hagberg CA, ed.* Benumof's Airway Management*. 2nd ed. Philadelphia: Mosby Elsevier; 2006.)*

inferior edge of the thyroid cartilage (Fig. 10-11) to facilitate elevating and opening the airway. A small (5.0) endotracheal tube or a tracheostomy tube is then placed and secured in position (Fig. 10-12). After stabilizing the patient, the cricothyrotomy should be converted to a formal tracheostomy preferably in the operating room if long-term intubation is anticipated. If early extubation is anticipated, the cricothyrotomy may be used until extubation. See reference 74 for basic technique of cricothyrotomy.

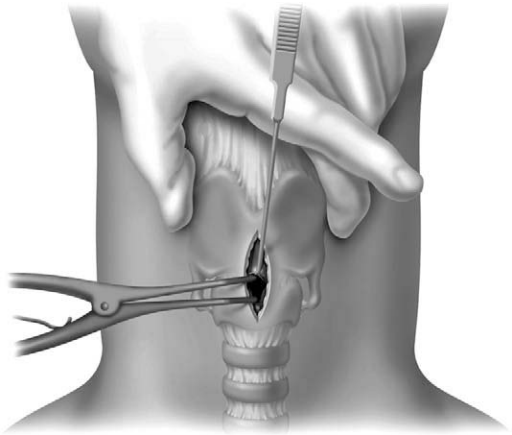

Figure 10-10. The Trousseau dilator is used to enlarge the vertical dimension of the membrane, the aspect providing the most resistance to insertion of the tube. *(From Hagberg CA, ed.* Benumof's Airway Management. *2nd ed. Philadelphia: Mosby Elsevier; 2006.)*

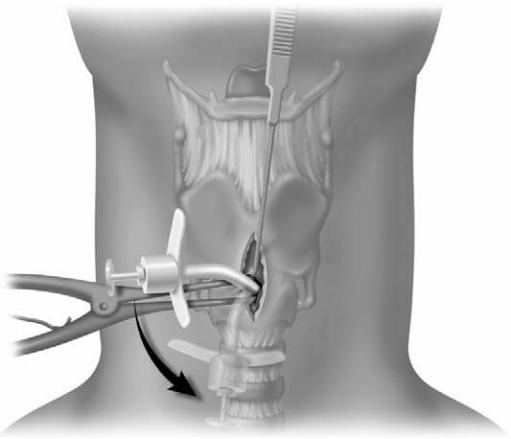

Figure 10-12. The tracheostomy tube is inserted and then the dilator can be rotated counterclockwise 90 degrees. *(From Hagberg C, ed.* Benumof's Airway Management. *2nd ed. Philadelphia: Mosby Elsevier; 2006.)*

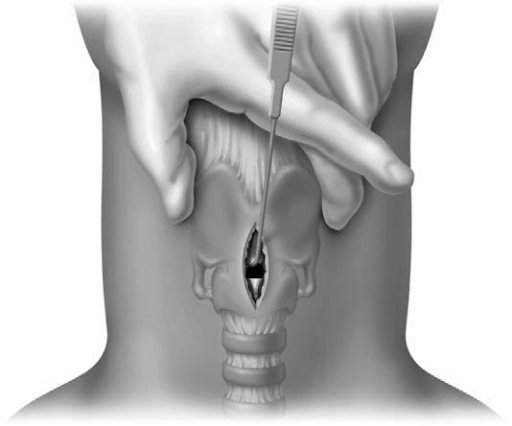

Figure 10-11. The tracheal hook exerts light traction on the inferior aspect of the thyroid cartilage. *(From Hagberg CA, ed.* Benumof's Airway Management. *2nd ed. Philadelphia: Mosby Elsevier; 2006.)*

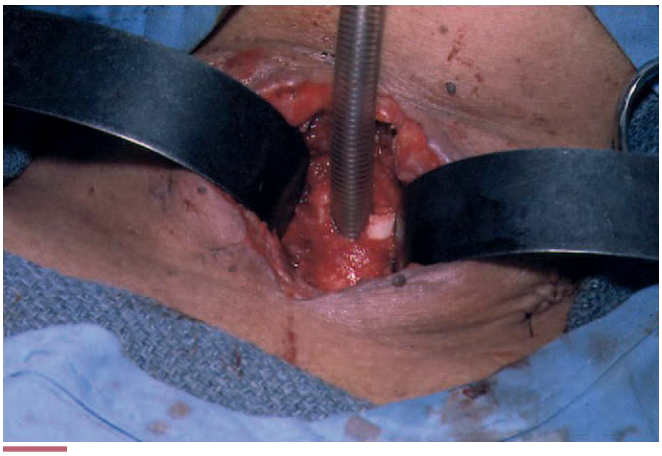

Figure 10-13. Cricoid cartilage shown split in midline following emergency cricothyrotomy. The site was repaired at the time of revision to formal tracheotomy.

Rapid Five-Step Technique

A rapid four-step technique has been described and reported to be simple to learn and faster in obtaining a surgical airway.[75] This technique has many advantages, including (1) the need for less equipment, (2) the need for only one operator without assistance, (3) the positioning is such that the operator stands at the head end of the patient.[76] The authors prefer a slight modification and use a five-step rule.

1. Identify landmarks and stabilize the airway.
2. Make vertical skin incision.
3. Make horizontal incision through the cricothyroid membrane.
4. Insert clamp to spread and elevate the airway.
5. Insert tracheostomy tube or small endotracheal tube.

The incidence of complications reported after cricothyrotomy varies from 6% to 39% depending on whether the procedure was done semielectively or as an emergent procedure. Reported complications include bleeding, trauma, or injury to the laryngeal framework and/or vocal folds (Fig. 10-13), mediastinal emphysema, pneumothorax, false passage with the tube placed in the mediastinum, esophageal laceration, and failure to secure the airway.

Percutaneous Cricothyrotomy

Primarily based on modified Seldinger technique, many commercially available kits and systems can help place a tracheal airway with limited surgical dissection beyond the skin incision. Although deemed simpler than surgical technique by many nonsurgeons, the procedure increases complexity and requires execution of more than five steps to secure an airway. Although no significant differences in performance times between open surgical cricothyrotomy and the percutaneous procedure have been noted in cadaver and dog models, as with the open cricothyrotomy, severe complications are more likely to occur in the emergent situation.[77,78] One of the limitations of percutaneous cricothyrotomy, especially with the commercially available kits, is the relatively small lumen of the cannula.[76]

In general, percutaneous tracheotomy is considered an elective procedure and should not be considered for emergency airway scenarios. More information and links to demonstrate this technique are available in the online version of this textbook.

Transtracheal Needle Ventilation

This technique can be used as a great option to buy time in an emergency. Access to the equipment, including 100% oxygen at 50 psi, a

large-bore needle and cannula (14 G), and a Luer-Lok connector is all that is required. The airway is accessed by puncturing the trachea or the CTM with a small saline-filled syringe attached to the needle-cannula combination. It is advanced through the skin in the midline in a 30-degree caudal direction. Upon confirming entrance into the airway by the presence of bubbles in the saline-filled syringe, the cannula is advanced while withdrawing the needle. The cannula is then connected to the oxygen with the Luer-Lok connector and a manual interrupter switch. The patient can only be oxygenated with this technique for 30 minutes to 2 hours because this type of ventilation is suboptimal.

Complications associated with this procedure are similar to those in cricothyrotomy and include improperly placed catheter and mediastinal emphysema, pneumothorax, hematoma, and kinking of the catheter with inability to adequately oxygenate or ventilate the patient. Similar to percutaneous cricothyrotomy, the author prefers to use this technique in elective or semiurgent situations only.

Conclusion

It is our belief that difficult airway management is an emerging subspecialty within otolaryngology head and neck surgery. The nature of these situations demands a multidisciplinary effort to standardize institutional action plans and strategies for training, and day-to-day management of these patients, capitalizing on the skills provided by experienced anesthesiologists, otolaryngology head and neck surgeons, general surgeons, emergency department physicians, respiratory therapists, and nursing staff.

Acknowledgments

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CHAPTER ELEVEN

Overview of Diagnostic Imaging of the Head and Neck

Nafi Aygun

S. James Zinreich

Key Points

- The choice of imaging modality varies depending on the location and nature of the disease process.
- CT is fast and widely available and can be employed as the first and often the only imaging modality in the majority of the disease processes affecting the neck.
- CT excels in demonstrating bone detail.
- IV contrast administration for CT examinations improves the quantity and quality of information provided.
- Radiation exposure from CT examination is substantial and should be taken into account particularly in young patients who require repeat examinations.
- MRI provides excellent soft tissue contrast and is the modality of choice in most aggressive processes.
- Appropriate use of fat suppression and IV contrast are essential for most MRI examinations of the head and neck.
- The accuracy of PET increases when it is used in conjunction with CT.
- Successful primary staging of most malignant lesions in the neck can be accomplished with CT or MRI and clinical examination.
- PET/CT is superior in identifying distant metastases and postoperative follow-up.
- Image interpretation should always be made in conjunction with clinical information.
- To provide a practical differential diagnosis for neck mass lesions, an approach based on neck spaces that are defined by the cervical fascia is advised.

Diagnostic medical imaging has changed medical and surgical diagnosis in ways never imagined. Every area of clinical medicine has been affected in a profound way. Radiologists are able, through their consultations, to assist the otolaryngologist in a variety of ways, including providing primary diagnosis, confirming a clinical impression, evaluating regional anatomy and extent of disease, assessing response to treatment, and assisting in definitive treatment of patients.

Neuroradiologists are subspecialty trained radiologists who specialize in the imaging of the head and neck, skull base, temporal bone, brain, and spine. They are the primary imaging consultants for otolaryngologists.

This chapter provides an introduction and overview of head and neck imaging for the otolaryngologist. The various available imaging modalities are discussed. Imaging strategies for various regions and clinical questions are reviewed. The basic approach to the radiologist's image acquisition and interpretation are described so that the referring physician will gain a measure of understanding of this field. This is intended to maximize the usefulness of diagnostic imaging in the care of patients.

The scope of head and neck imaging is too broad a topic to be covered in one chapter. The authors provide the clinician with an outline and brief synopsis of the field. Definitive textbooks for each area of head and neck imaging are available.[1-4]

Available Imaging Modalities

Conventional Radiography

Since the discovery of the x-ray, conventional radiography (CR) has been used in imaging the head and neck region. CR in the head and neck imaging has been largely replaced by computed tomography (CT). The traditional projections obtained with CR that are applicable to head and neck imaging are described here.

Views of the Facial Bones and Sinuses

Lateral, Caldwell, Waters, and submentovertex (SMV or base) views are attainable. The lateral view shows the frontal, maxillary, and sphenoid sinus. It is best obtained 5 degrees off the true lateral position to avoid superimposition of the posterior walls of the maxillary sinuses. The Caldwell view displays the frontal sinuses and posterior ethmoid air cells. It is obtained in the posteroanterior (PA) projection with 15 degrees of caudal angulation of the x-ray beam. The Waters view can show the maxillary sinuses, anterior ethmoid air cells, and orbital floors. It is obtained in the PA projection with the neck in 33 degrees of extension. The SMV view can show the sphenoid sinuses and the anterior and posterior walls of the frontal sinuses. It is obtained in the anteroposterior (AP) projection with the head in 90 degrees of extension.

Views of the Neck

AP and lateral views of the neck exposed for soft tissue detail are useful for the evaluation of the overall contour of the soft tissues of the neck. These views are essentially the same projections used in the evaluation of cervical trauma, but they are not exposed for bone detail.

Temporal Bone Views

Several projections are acceptable for visualizing portions of the temporal bone, including the Schüller projection, a lateral view of the mastoid obtained with 30 degrees of cephalocaudad angulation. The Stenvers projection is an oblique projection of the petrous bone obtained with the patient's head slightly flexed and rotated 45 degrees toward the side opposite the one under study. The beam is angulated 14 degrees. The transorbital projection is a frontal projection of the mastoids and petrous bones. Conventional imaging of the temporal bone has largely been replaced by CT scanning.

Computed Tomography

CT was developed for clinical use in the mid-1970s by Hounsfield. CT scanners have evolved over time such that the most advanced scanners now scan in a "helical" fashion, in which the scanner uses a slip-ring technique. This allows the table to move as the scan is performed, resulting in complete volumes of tissue being imaged without skipping tissue between slices. The ratio of the speed at which the table moves to the time it takes for a complete rotation of the CT tube is called the pitch. Multidetector CT allows scanning of multiple slices during one rotation of the CT tube which significantly increases the speed of examination, which in turn makes it possible to obtain much thinner slices in a short time. At present, CT scanners can obtain slices 0.5 mm thick. A neck examination from skull base to the mediastinum can be performed in less than 30 seconds. More importantly, enhanced computer technology permits real-time manipulation of these data, allowing multiplanar and various forms of three-dimensional reconstructions without image degradation. Images can be reconstructed in any desired plane regardless of the plane at which they are acquired.

CT uses a tightly collimated x-ray beam that is differentially absorbed by the various body tissues to generate highly detailed cross-sectional images. The degree of attenuation of the x-ray photons for each voxel (smallest imaging unit) is assigned a numeric readout. These units of attenuation are known as Hounsfield units (HU) and generally range from −1000 HU to +1000 HU. Water is assigned a value of 0 HU. Fat is approximately −80 to −100 HU. Calcium and bone are in the 100 to 400 HU range, and most fluids are in the 0 to 30 HU range.

To create images from the attenuation values, CT uses complex mathematical reconstruction algorithms. Bone disease and bone trauma are best visualized with a bone detail algorithm whereas a soft tissue algorithm is used to evaluate soft tissue structures (Fig. 11-1).

Computed Tomography Image Display

Images from a given reconstruction algorithm can be displayed in various ways to highlight differences in attenuation of different structures. The window width refers to the range of attenuation values in HU that make up the gray scale for a given image. The window level refers to the center HU value for that given window width. A narrow window width of 80 HU and a level of 40 HU is frequently used for brain imaging because it centers the density at the common density of brain tissue, and displays only those densities 40 HU greater than and 40 HU less than the window level. Thus any density greater than 80 HU will be displayed as white, and any density less than 0 will be displayed as black on the gray scale. Any intermediate density will be spread out evenly along the gray scale. For imaging of the soft tissues of the head and neck, a window level of approximately 40 to 70 HU is usually chosen, at a midpoint approximately equal to the density of muscle. The window width frequently is in the 250 to 400 HU range, thus displaying a wider range of densities including calcification, intra-

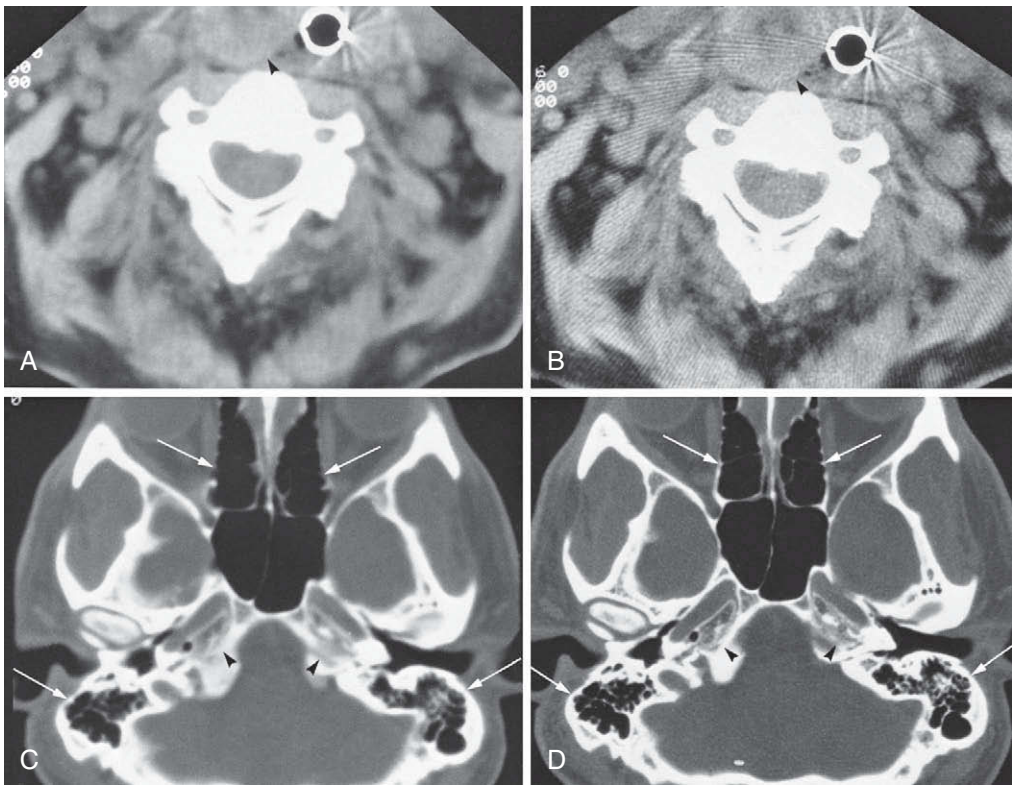


Figure 11-1. Comparison of various computed tomography algorithms and windows. **A,** Soft tissue algorithm and **B,** bone algorithm images of a laryngeal hematoma *(arrowheads)* using soft tissue windows (350 HU width). The bone algorithm image has a grainier appearance, whereas the standard algorithm gives a smoothed image. Soft tissue algorithm **(C)** and bone algorithm **(D)** images of the skull base using bone windows (4000 HU width). Note the improved sharpness of the petrous apex trabeculae *(arrowheads)* and bony walls of the mastoid and ethmoid sinus air cells *(arrows)*.

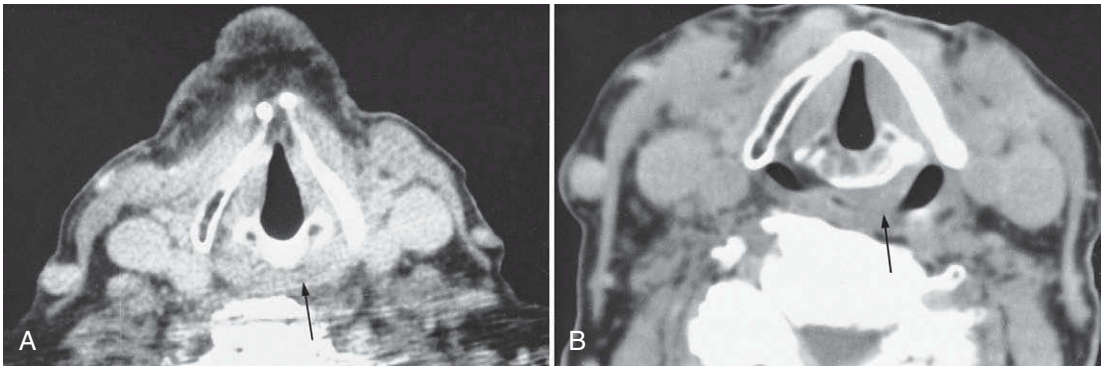


Figure 11-2. Larynx without and with modified Valsalva maneuver. **A,** Axial contrast-enhanced computed tomography (CECT) performed during quiet breathing does not allow discrimination of the retrocricoid carcinoma *(arrow)* because the posterior pharyngeal wall is collapsed against the mass. **B,** Axial CECT in the same patient (a few minutes later) obtained with a modified Valsalva maneuver causes distention of the now air-filled hypopharynx, permitting tumor detection *(arrow)*.

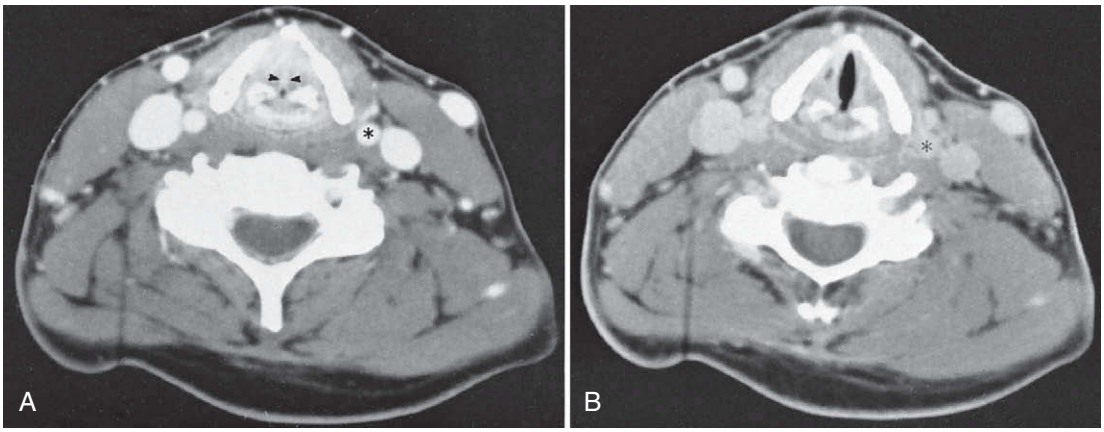


Figure 11-3. Axial contrast-enhancing computed tomography during breath holding and while phonating. **A,** This axial computed tomography, obtained during breath holding, shows the true vocal cords adducting and approximating each other *(arrowheads)*. Note the superb high-contrast density in common carotid artery *(asterisk)* and jugular veins. **B,** Phonating "eeee" causes the vocal cords to partially adduct into the paramedian position. Note that the contrast density has significantly decreased in the common carotid artery *(asterisk)* and the jugular veins in this delayed image, obtained well after contrast infusion had finished.

venous contrast, muscle, and fat to best advantage. For imaging bony structures such as paranasal sinuses and temporal bone, window levels from 0 to 400 HU and a wide window width of 2000 to 4000 HU may be chosen. The reason for a wide bone window width is that a wide range of densities ranging from cortical bone (approximately +1000 HU) down to gas (−1000 HU) need to be displayed on the same image. However, structures of intermediate density between bone and gas occupy a narrow range on the gray scale at this window width and are poorly discriminated (appear washed out) on these settings. The terminology commonly used to describe the previously mentioned windows includes soft tissue windows (window width of 250 to 400 HU) and bone windows (2000 to 4000 HU). It is important to understand that these display windows are completely independent of the mathematical imaging algorithm chosen for creation of the image. In other words, an image created by a soft tissue algorithm can be displayed with soft tissue and bone window widths (see Figs. 11-1A and C). Conversely, the image may be computer reconstructed using a bone algorithm and displayed with either soft tissue or bone window width (see Fig. 11-1B and D). To optimize the imaging of the soft tissue lesion and the adjacent bone, a soft tissue and a bone algorithm may be used, generating images with the appropriate soft tissue and bone windows. (See also Figs. 11-12A and C).

Multiple options for displaying the image (adjusting the window level and width parameters on the imaging console) and recording it permanently on radiographic film or other media are available. Picture archiving and communication systems (PACS) are becoming the norm for image display and storage.

Patient Cooperation

Patient cooperation is necessary to obtain optimal image quality. The patient is instructed not to swallow and to stop breathing or to maintain quiet breathing during each slice acquisition to minimize motion artifact from the adjacent airway and pharyngeal structures. Occasionally, provocative maneuvers such as blowing through a small straw or using a cheek-puffing (modified Valsalva) maneuver to distend the hypopharynx, or phonating to assess vocal cord movement, may be necessary (Figs. 11-2 and 11-3).

Contrast enhancement often is used to opacify blood vessels and to identify regions of abnormal tissue as identified by abnormal enhancement patterns (Fig. 11-4). As it relates to head and neck imaging, contrast is particularly useful in CT scans of the neck and orbits. Contrast often is not needed in evaluation of the temporal bones, although it can be necessary on occasion. CT of the facial bones and paranasal sinuses does not require intravenous contrast for most common applications.

Radiation Exposure

As a brief review, the radiation exposure (dose) that a patient receives is known as the *radiation absorbed dose*. This radiation absorbed dose is a measure of the total radiation energy absorbed by the tissues, and

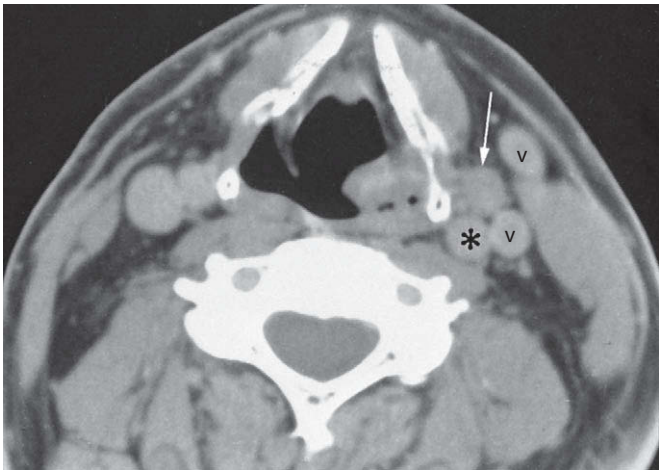


Figure 11-4. Contrast-enhancing computed tomography (CECT) with suboptimal contrast infusion. This axial CECT of a patient with a left piriform sinus tumor was obtained with insufficient contrast infusion, resulting in poor discrimination of the common carotid artery *(asterisk)* and jugular vein (v) from the isodense adjacent metastatic lymph node *(arrow)*. Inadequate contrast infusion also reduces the likelihood of identifying the focal defect in nodal metastasis.

it is expressed in an international system (SI) unit known as the Gray (Gy). One Gy is the amount of radiation needed to deposit the energy of 1 Joule (J) in 1 kg of tissue (1 Gy = 1 J/kg). Formerly, the unit used to express radiation absorbed dose was the rad (1 rad = amount of radiation needed to deposit the energy of 100 ergs in 1 g of tissue). The conversion of rads to Gy is 1 Gy = 100 rad.

Radiation dose equivalent is a more useful term as it considers the "quality factor" (Q) of the radiation involved (radiation dose equivalent = radiation absorbed dose Q). The quality factor considers the varying biologic activity of various types of ionizing radiation. For x-rays, Q = 1. Thus when discussing diagnostic x-rays, the radiation dose equivalent equals the radiation absorbed dose. The SI unit for the radiation dose equivalent is the Sievert (Sv). The former unit was the Roentgen equivalent for man (rem). In summary, 1 Gy = 1 Sv, and 1 Sv = 100 rem.

The radiation dose equivalent depends on the choice of tube voltage and current settings (kVp and mAs), slice thickness, pitch, and gantry cycle time. For a given kVp, the radiation dose equivalent will vary linearly with the mAs. The actual dose will vary slightly among machines. The radiation dose equivalent for a CT examination can be considerably reduced using a low-mAs technique.

The effective dose equivalent was developed as a means of representing the fraction of the total stochastic risk of fatal cancers and chromosomal abnormalities resulting from the irradiation of a particular body part. A system of weighting is used to consider the individual susceptibility of the body's major tissues and organs. A full discussion of this is beyond the scope of this chapter. Suffice to say that, for a given examination, the effective dose to the patient is less than the dose (radiation dose equivalent) received by the area under examination. Table 11-1 lists common radiologic procedures and their effective dose equivalents.

Table 11-1

Estimated Effective Dose Equivalent of Common Examinations

Examination	Effective Dose Equivalent
Chest radiograph	20 mrem
CT, abdomen	1000 mrem
CT, chest	1000 mrem
CT, brain	120 mrem
CT, sinus	70 to 130 mrem

From Nationwide Evaluation of X-Ray Trends (NEXT) 2000 Survey of Computed Tomography. Frankfort, KY: Food and Drug Administration, Center for Devices and Radiological Health; August 2007. CRCPD Publication E-07-2.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imaging modality that uses the response of biologic tissues to an applied and changing magnetic field to generate images. It is not possible to completely describe the principles of MRI in an introductory chapter of all head and neck imaging. A brief summary of MRI follows.

Two types of magnets are used to perform clinical MRI: permanent and superconducting. Permanent magnets do not require continual input of energy to maintain the magnetic field. They are composed of large magnetic metallic elements set up to generate a uniform magnetic field between components. Superconducting magnets are electromagnets usually composed of niobium-titanium wire. They require input of energy to start them, but once they are up to strength, they are maintained in a superconductive state by means of an encasing system of liquid nitrogen and liquid helium shells.

The earth has a magnetic field strength of 0.5 Gauss (G). The tesla (T) is another unit of magnetic strength that is related to G by the equation 1 T = 10,000 G. Clinical MRI units usually operate at magnetic field strengths of between 0.3 and 3.0 T. Small-bore research scanners of strengths up to 9.0 T are in use.

Many MR pulse sequences are available to generate images. The most common pulse sequences in MRI are the spin-echo and gradient echo techniques.

MRI is one of the most active areas of development and research within diagnostic radiology. MRI derives its signal from hydrogen protons, most abundant in tissue fat and water. When placed in a high magnetic field, the spinning protons are aligned in the direction of the magnetic field. Radio frequency pulses are transmitted into the subject to excite the spinning protons, changing their orientation with respect to the magnetic field. As the protons realign with the magnetic field, they lose energy and give off a signal, which is picked up by coils and reconstructed into an image. The quality of MRI depends on a high signal-to-noise ratio, which is used to improve image contrast and spatial resolution. In general, the higher the field strength of the magnet, the higher the signal-to-noise ratio.

A surface coil is a receiving antenna for the radio frequency signal that is emitted from the imaging subject after the initial radio frequency stimulation. The standard head coil is usually adequate for studying head and neck disease above the angle of the mandible. A head coil allows imaging of the adjacent brain and orbits, an advantage when head and neck lesions extend intracranially. Neck coils cover a larger area from the skull base to the clavicles and come in various configurations, for example, volume neck coil and anterior neck coil. Surface coils significantly improve the quality of head and neck imaging by more effectively collecting the signal hence increasing the signal-to-noise ratio but they are able to collect signal from a smaller body part.

Slice thickness on MRI is most commonly 5 mm, with 3-mm sections used for smaller regions of interest. However, a thinner slice has a smaller signal-to-noise ratio. Occasionally, 1- to 2-mm sections may be needed for small structures (e.g., facial nerve), requiring a volume acquisition technique. The number of slices is limited in MRI (as opposed to CT) by the specific sequence used. Covering the entire neck from skull base to superior mediastinum often requires that two separate acquisitions be obtained.

Magnetic Resonance Imaging Artifacts

Motion artifact, chemical shift artifact, susceptibility artifacts from metallic implants (e.g., amalgam, orthodontic implants), and eyelid mascara degrade MRI (Fig. 11-5). Motion artifact becomes more

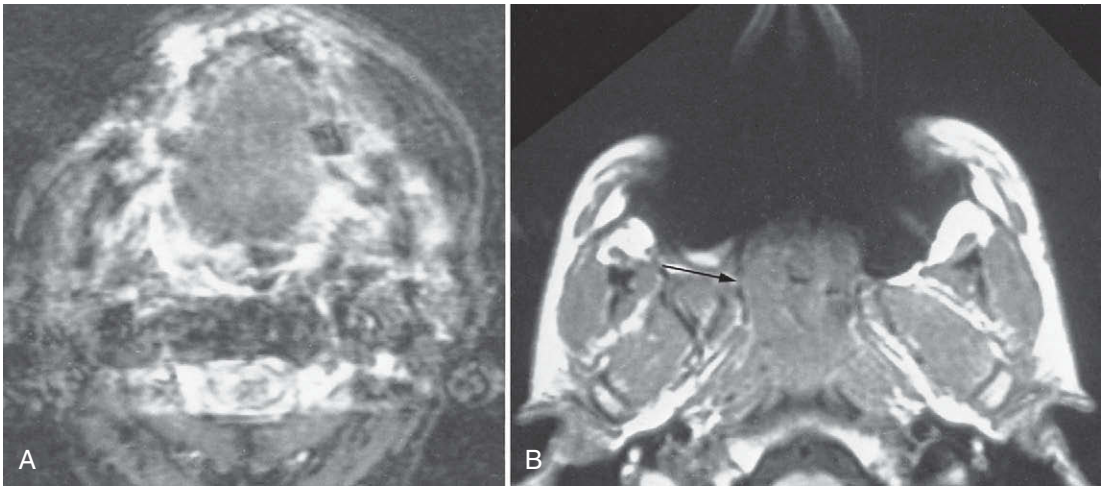


Figure 11-5. Magnetic resonance imaging artifacts. **A,** Motion during axial short T1 inversion recovery sequence caused significant degradation of the image with anatomic distortion and mismapping of the signal intensity. **B,** Metallic dental braces cause artifacts distorting anterior facial structures in this T1-weighted image of a boy with juvenile angiofibroma filling the nasal cavity *(arrow)* and nasopharynx. Anterior maxilla and portion of the nose have been distorted.

prominent with increased field strength, increased length of individual pulse sequences, and the total length of the imaging study. A typical imaging sequence may last from 2 to 8 minutes. To limit motion artifact, sequences fewer than 4 minutes are preferred, and the patient should be instructed not to swallow and to breathe shallowly and quietly.

Chemical shift artifact arises from the differences in resonance frequencies of water and fat protons. The result is an exaggerated interface (spatial misregistration) in areas where fat abuts structures containing predominantly water protons such as the posterior globe or a mass. Chemical shift artifact may produce the appearance of a pseudocapsule around a lesion or cause obscuration of a small-diameter structure such as the optic nerve. Chemical shift artifact may be identified as a bright band on one side of the structure and a black band on the opposite side. This is usually most noticeable on T1-weighted images (T1WIs).

Metallic artifact from dental work varies in severity depending on amount and composition of the metal in the mouth, as well as the pulse sequence and field strength of the MRI scanner. Most dental amalgam causes mild distortion to the local magnetic field, resulting in a mild dropout of signal around the involved teeth. Extensive dental work, metallic implants, and braces may cause more severe distortion of the image, precluding visualization of the maxilla, mandible, and floor of the mouth. Mascara containing metallic compounds can also cause localized signal loss in the anterior orbit and globe.

Magnetic Resonance Imaging Pulse Sequences

Numerous pulse sequences are available on clinical MRI units. The details of the physics of MRI may be found in most radiology and MRI textbooks. Commonly used imaging protocols include T1-weighted, spin (proton) density, T2-weighted, gadolinium-enhanced T1-weighted, fat-suppressed, and gradient echo imaging. Magnetic resonance angiography (MRA) is infrequently obtained (Figs. 11-6 and 11-7). The abbreviations used to identify sequence parameters are repetition time (TR), echo time (TE), and inversion time (TI) and are measured in milliseconds. The following description of pulse sequences is intended to assist the clinician in identifying and understanding the commonly performed sequences and in determining their respective use in the head and neck.

T1-Weighted Images

T1-weighted (short TR) sequences (see Figs. 11-6A and 11-7A) use a short TR (500 to 700 msec) and a short TE (15 to 40 msec). T1-weighted imaging is the fundamental head and neck sequence because it provides excellent soft tissue contrast with a superior display of anatomy, a high signal-to-noise ratio, and a moderate imaging time (4 to 5 min), minimizing motion artifacts. Fat is high signal intensity (bright or white) on T1WIs and provides natural contrast in the head and neck. Air, rapid blood flow, bone, and fluid-filled structures (e.g., vitreous and cerebrospinal fluid [CSF]) are low signal intensity (dark or black) on T1WIs. Muscle is low to intermediate in signal intensity on T1WIs. The inherent high contrast of fat relative to adjacent structures allows excellent delineation of the muscles, globe, blood vessels, and mass lesions that border on fat. The cortical bone is black, and the enclosed bone marrow is bright from fat within the marrow. The aerated paranasal sinuses are black, whereas retained mucous or mass lesions are of low to intermediate signal intensity. Most head and neck mass lesions show a comparable signal to muscles on T1WIs. (To quickly identify a T1WI: fat is white, CSF and vitreous are black, and nasal mucosa is low signal.)

T2-Weighted Images

T2-weighted images (see Fig. 11-6C) use a long TR (2000 to 4000 msec) and a long TE (50 to 90 msec) and are sometimes referred to as long TR/long TE images. Note that spin density and T2WI are acquired simultaneously from a single sequence that produces two sets of images with the same TR but different TEs. For example, spin density = 2000/30 and T2WI = 2000/80. T2WIs are most useful for highlighting pathologic lesions. T2WIs show the vitreous and CSF as high signal intensity (bright) relative to the low to intermediate signal intensity of head and neck fat and muscle. Fat loses signal intensity with increased T2 weighting. Most radiologists use a fast spin-echo (FSE) T2WI for head and neck imaging, which provides a much faster acquisition with improved signal-to-noise. Fat remains bright, however, on FSE images. Most head and neck masses are higher signal intensity on a T2WI compared with their low-to-intermediate signal intensity on T1WI. The combination of the T1WI and T2WI is often useful for characterizing fluid-containing structures, solid components, and hemorrhage. Bone, rapid vascular flow, calcium, hemosiderin, and air-containing sinuses are black. Inflammatory sinus disease and normal airway mucosa appear very bright. (To quickly identify a T2WI: CSF, vitreous, and nasal mucosa are bright. Muscle is low to intermediate in signal.)

Gadolinium Enhancement

Gadolinium-based contrast material is used in conjunction with T1WI sequences (gadolinium shortens the T1) and, with the dose used, it has little effect on T2WI. The advantages of contrast enhancement are increased lesion conspicuity and improved delineation of the margins of a mass relative to the lower signal of muscle, bone, vessel, or globe.[5]

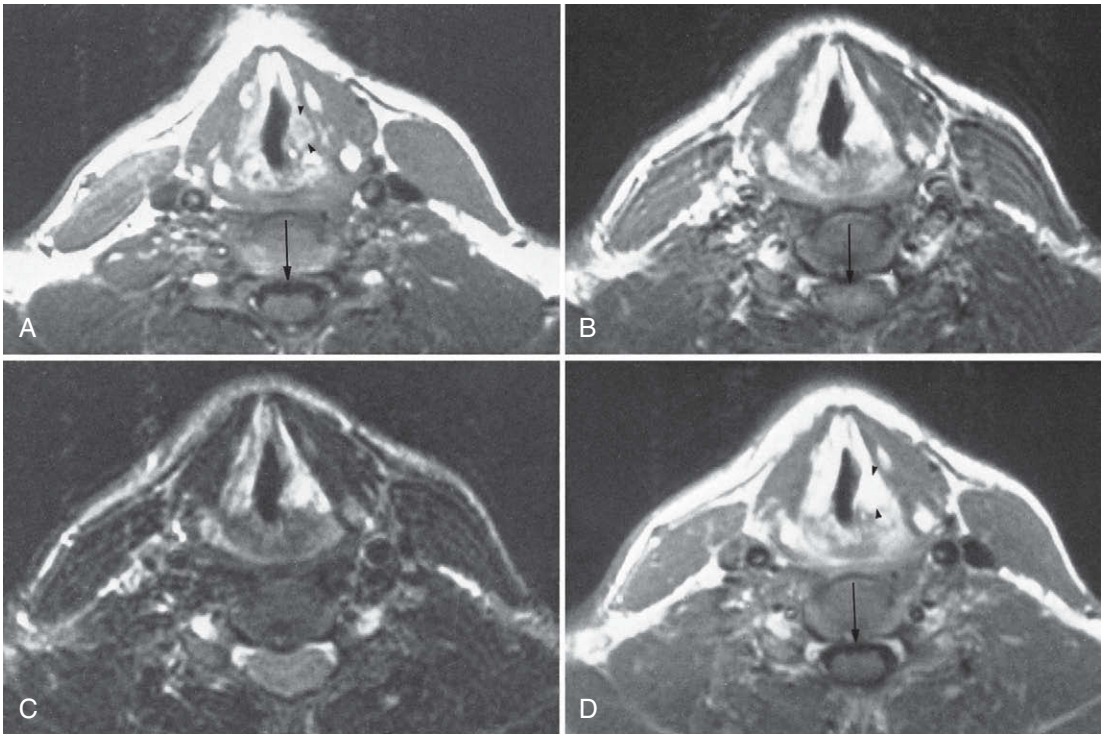


Figure 11-6. Common magnetic resonance imaging pulse sequences without fat suppression. **A,** Axial T1-weighted image (T1WI) of the left glottic tumor *(arrowheads)*, which is intermediate in signal intensity and thickens the true cord. Note that the cerebrospinal fluid (CSF) surrounding the spinal cord *(arrow)* is black, indicating that this is a T1WI. **B,** Spin density-weighted image also reveals high signal intensity (caused by increased water content) of the vocal cord tumor. CSF is now isointense to the spinal cord *(arrow)*, indicating this is a spin density sequence. **C,** T2-weighted image demonstrates a high signal intensity mass clearly demarcated against the dark background of fat and muscle. **D,** Postgadolinium T1WI shows enhancement of the cord tumor *(arrowheads)*. CSF remains black *(arrow)*.

However, gadolinium enhancement (without concomitant fat suppression) has had limited usefulness within the head and neck, as well as in the orbit, because of the large amount of fat present within these regions (see Fig. 11-6D). After gadolinium injection, the signal increases within a lesion, often obscuring the lesion within the adjacent high signal intensity fat.[6] Therefore, for head and neck imaging, gadolinium is optimally used with specific fat suppression techniques that turn fat dark or black. Gadolinium enhances normal structures including nasal and pharyngeal mucosa, lymphoid tissue in Waldeyer's ring, extraocular muscles, and slow-flowing blood in veins, all of which may appear surprisingly bright, especially if combined with fat suppression techniques. (To quickly identify a gadolinium-enhanced T1WI: nasal mucosa is white, fat is white, and CSF and vitreous are black. Also look for Gd-DTPA printed directly on the image or on adhesive study labels.)

Fat Suppression Methods

Several sequences have been developed that suppress fat signal intensity. T2WIs, short TI inversion recovery (STIR), spectral presaturation inversion recovery (SPIR), and chemical shift selective presaturation (fat saturation) are some of the more common clinically available methods of fat suppression. One advantage of fat suppression is reduction or elimination of chemical shift artifacts by removing fat signal from the image while preserving water signal. Additionally, some fat suppression techniques take advantage of gadolinium enhancement by eliminating the surrounding high intensity signal from fat while retaining the high intensity enhancement produced by gadolinium. Most pathologic lesions have increased water content, and gadolinium exerts its paramagnetic effects while in blood vessels and in the increased extracellular fluid of the lesion, but gadolinium does not enhance fat. The fat signal can be manipulated in the following ways:

1. STIR (see Fig. 11-7E) provides reliable fat suppression over large body parts.[7] The inversion time (e.g., TI = 140 msec) is individually "tuned" for each patient to place fat at the null point of signal intensity and thus eliminates fat signal by turning it completely black. STIR images show the mucosa, vitreous, and CSF as very high signal intensity. Most mass lesions in the head and neck have similar high signal intensity on STIR and T2WI. The disadvantages of STIR are image degradation secondary to a decreased signal-to-noise ratio, and increased vulnerability to motion artifacts including the vessel pulsations. Additional disadvantages of STIR, such as increased scan time and fewer slices, are circumvented by the recently available fast sequences. (To quickly identify a STIR image: fat is almost completely black; CSF, vitreous, and mucosa are very bright. A TI is listed with the TR and TE times on the image.)

2. Frequency selective presaturation sequences (see Fig. 11-7B) typically used with a spin-echo technique selectively suppress fat signal. (Note that for the remainder of this chapter, the terms fat suppression and fat saturation are used interchangeably and refer to frequency [chemical shift] selective presaturation techniques). T1-weighted fat saturation sequences take full advantage of gadolinium enhancement. A gadolinium-enhancing lesion within the head and neck retains its high signal intensity and is not obscured, because fat is suppressed to become low to intermediate signal intensity. Enhancing masses within the head and neck and orbit are particularly well imaged with this technique.[8] Frequency selective fat suppression is also complementary for FSE T2WIs (see Figs. 11-7C and D). Fat-saturated T2WIs provide excellent fat suppression, optimizing the high signal from normal structures and lesions that are high in water content contrasted against a black background of fat. The disadvantages of fat saturation sequences are that non–gadolinium-enhancing lesions may be less well discriminated, that these sequences are more susceptible to artifacts, and that nonuniform fat suppression can occur. Also, fewer slices are acquired than with T1WI, unless the TR time is lengthened, which prolongs imaging time. (To quickly identify a gadolinium-enhanced T1WI

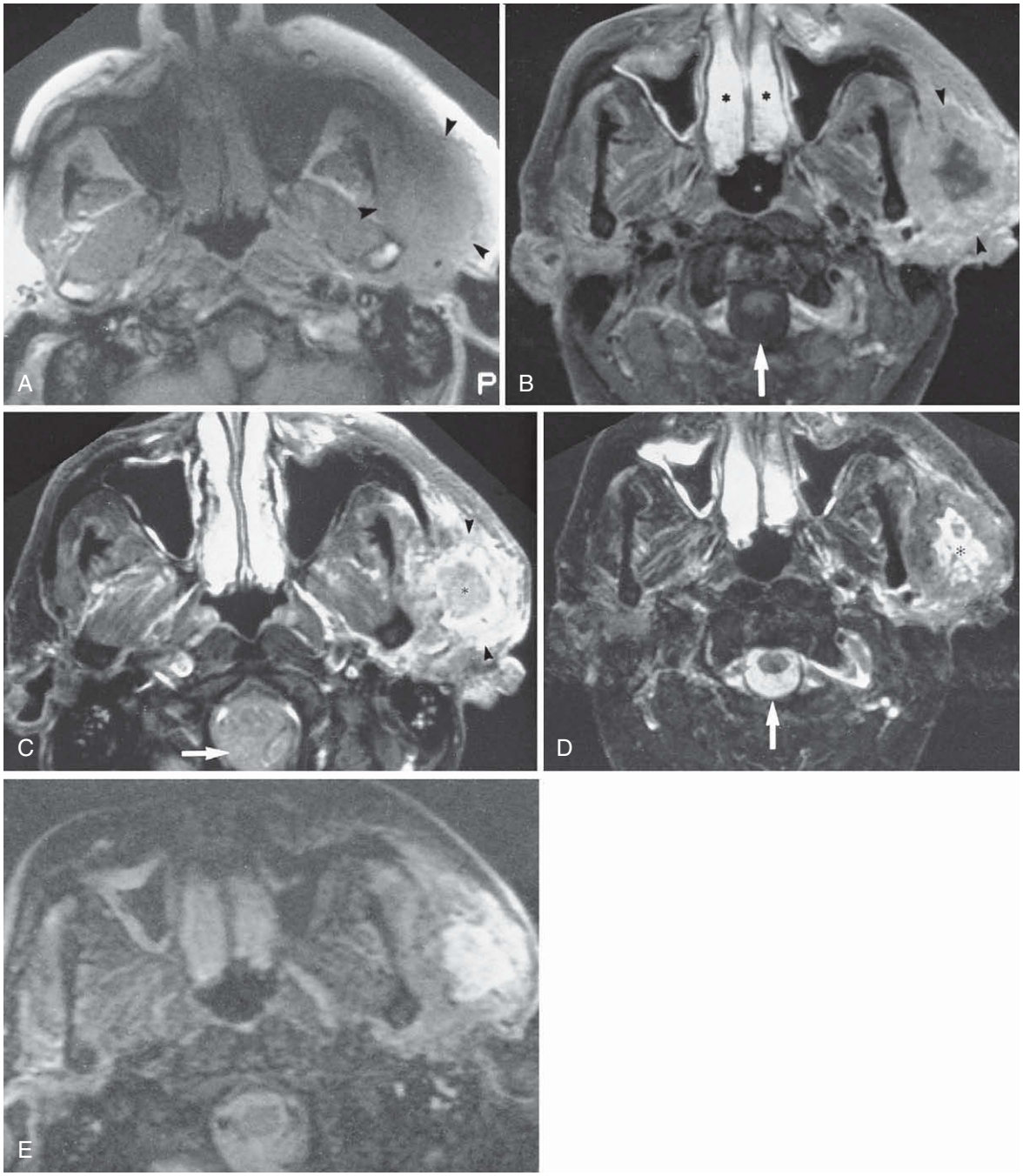


Figure 11-7. Magnetic resonance imaging pulse sequences with fat suppression. **A,** Axial T1-weighted image (T1WI) without contrast in a patient with squamous cell cancer shows a poorly defined mass in the left parotid gland *(arrowheads)*. Suboptimal signal in the image is the result of a signal drop-off at the edge of the anterior neck surface coil. **B,** Axial postgadolinium T1WI with fat saturation has adequate suppression of subcutaneous fat (compared with **A**) and enhancement of the tumor *(arrowheads)*. Center of the mass enhances less and likely is necrotic. Cerebrospinal fluid (CSF) is black *(arrow)*, indicating a T1WI. Note the marked enhancement of the inferior turbinates *(asterisks)* compared with the precontrast T1WI. **C,** Axial postgadolinium spin density image with fat saturation shows a high signal in the mass *(arrowheads)* with a lower-intensity necrotic center *(asterisk)*. Fat signal is suppressed and the image is similar to **B.** CSF is isointense with the spinal cord indicating the use of a spin density sequence. Turbinates are very bright. **D,** Axial T2-weighted image with fat saturation demonstrates nearly ideal fat suppression, almost as good as a short T1 inversion recovery (STIR) sequence. Necrotic or cystic center of the mass *(asterisk)* and CSF *(arrow)* have become very bright. **E,** On this axial STIR image with excellent fat suppression, the margin and center of the mass are bright.

with fat saturation: mucosa and small veins are white, fat is low to intermediate intensity, and CSF and vitreous are black.)

Gradient Echo Techniques

Numerous gradient echo sequences are available that have a variety of applications. Gradient echo scans have a very short TR (30 to 70 msec), a very short TE (5 to 15 msec), and a flip angle of less than 90 degrees. They have a variety of proprietary acronyms, including GRASS, MPGR, SPGR, FLASH, and FISP. Gradient echo sequences take advantage of the phenomenon of flow-related enhancement. That is, any rapidly flowing blood appears extremely bright. These sequences are useful for localizing normal vessels, detecting obstruction of flow in compressed or thrombosed vessels, and showing vascular lesions that have tubular, linear, or tortuous bright signal representing regions of

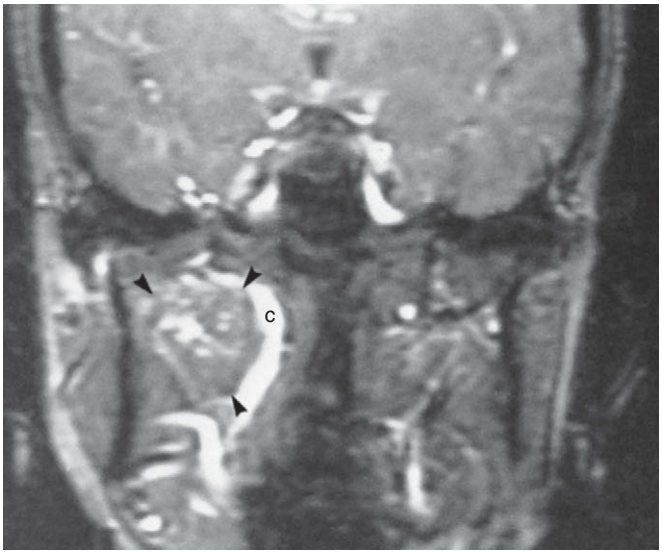


Figure 11-8. Gradient echo sequence in patient with right vagal paraganglioma. Coronal multiplanar gradient echo image demonstrates a mass *(arrowheads)* displacing the internal carotid artery (c) medially. Arterial blood flow is very high in signal intensity in the medially displaced internal carotid artery, as well as within the feeding vessels deep inside mass.

rapid blood flow (Fig. 11-8). Gradient echo sequences may be obtained faster than conventional spin-echo techniques, although their increased susceptibility to motion artifact decreases the benefits of a short scan time. Gradient echo techniques also permit volume, that is, three-dimensional versus two-dimensional acquisition of images, allowing increased spatial resolution and computer workstation reconstruction of any imaging plane at various slice thicknesses. The disadvantage of gradient echo sequences is the increased magnetic susceptibility artifact from bone or air, thus limiting their role near the skull base or paranasal sinuses. (To quickly identify a gradient echo image: arteries and often veins are white; fat, CSF, vitreous, and mucosa may have variable signal intensities depending on the technique used.)

Magnetic Resonance Angiography

MRA is most commonly generated by time-of-flight or phase contrast techniques, which rely on the flowing blood within the vessels as the signal source. Contrast-enhanced MRA uses the enhancement of blood with gadolinium-based contrast as the primary source of signal. MRA can be obtained with two-dimensional and three-dimensional algorithms. At present, MRA provides the most pertinent information in many clinical scenarios but lacks the temporal resolution (ability to image a vessel over time as the contrast material passes through) necessary to evaluate some of the vascular malformations.

Magnetic Resonance Imaging Disadvantages

Several disadvantages of MRI of the head and neck bear consideration. MRI frequently requires 30 to 45 minutes of scanning time, during which time the patient must remain motionless, a process difficult for a sick patient to accomplish. Motion artifacts are more frequently encountered than with CT, although dental artifacts may be less problematic. Although no harmful effects are known to occur during pregnancy, MRI should not be used during the first trimester. Absolute contraindications to MRI include patients with cardiac pacemakers, cochlear implants, and ferromagnetic intracranial aneurysm clips. With the ever-increasing variety of implants with electronic components, one must follow the manufacturer's recommendations as to the safety of MRI. Those patients at risk for metallic orbital foreign bodies should be screened with plain films or CT before MRI. Generally, ocular prostheses and ossicular implants are safe. Unfortunately, MRI is one of the more expensive imaging modalities.

Ultrasound

High-resolution diagnostic ultrasound uses the properties of reflected high-frequency sound waves to produce cross-sectional images, obtainable in almost any plane. The transducer, a high-frequency 5- or 10-MHz probe, scans over the skin surface of the region of interest. Fat has a moderate degree of internal echoes (echogenicity). Skeletal muscle is less echogenic than fat. A solid mass has a variable echogenicity but is usually less echogenic than fat. A cyst has few, if any, internal echoes, a strongly echogenic back wall, and strong through-transmission of sound behind the cyst. Both calcium and bone are strongly echogenic, thus obscuring adjacent structures by an acoustic shadow. Ultrasound has no known harmful effects and no contraindications. High-resolution ultrasound is quick and accurate. Doppler ultrasound provides information on blood vessels and flow patterns. Furthermore, it is relatively inexpensive compared with CT or MRI. Disadvantages include limited field of view, lack of easily identifiable anatomic landmarks, and operator dependence.

Nuclear Medicine

Positron Emission Tomography

As opposed to the imaging modalities already discussed in this chapter, which allow detailed anatomic information, positron emission tomography (PET) imaging provides physiologic and biochemical data. A positron emitting radiopharmaceutical is intravenously injected and its distribution in the body is measured. Positron emitting radiopharmaceuticals can be developed from naturally occurring substances such as 15O water, 11C carbon monoxide, or 13N ammonia, or radioactive analogs of other biologic substances such as 18F fluoro-2-deoxy-2-glucose (FDG). After being emitted from the atom, the positron travels in the tissue for a short distance until it encounters an electron and forms a positronium, which immediately annihilates (converts its mass to energy) forming two 511-keV photons. These annihilation photons travel away from each other at approximately 180 degrees and are picked up by the detectors placed around the patient. Simultaneous detection of these photons relates them to the same annihilation event and allows spatial localization. Annihilation coincidence detection can be accomplished by very expensive dedicated PET scanners, yielding superior spatial resolution and sensitivity. Less costly gamma camera-based hybrid systems allow utilization of PET imaging outside of academic centers.

Attenuation of the photons in tissues they travel through decreases the apparent activity picked up by the detectors. Attenuation correction methods provide improved anatomic detail and better lesion localization but they result in noisier images. The effect of attenuation correction on visual image quality is controversial and, in many centers, the images are generated both with and without attenuation correction. For semiquantitative and quantitative evaluation, however, attenuation correction is necessary.

Depending on the radiopharmaceutical chosen, PET imaging can provide information regarding blood flow, ischemia, deoxyribonucleic acid metabolism, glucose metabolism, protein synthesis, amino acid metabolism, and receptor status. Radiopharmaceutical development requires sophisticated knowledge and equipment which, combined with the very short half-life of most of these substances, limits clinical utility. The relatively long half-life of FDG (110 minutes) accounts for its widespread use. FDG can be delivered to PET imaging facilities through commercial vendors obviating the need for an on-site cyclotron.

Glucose metabolism in growing neoplastic cells is enhanced and accounts for the increased uptake on FDG-PET studies. Molecular studies have revealed that several genetic alterations responsible for tumor development also have direct effects on glycolysis. It has also been shown that increased tumoral FDG uptake is strongly related to the number of viable tumor cells, but not clearly associated with their proliferative rate. The glucose analog 2-deoxy-D-glucose is transported into the cell and metabolized in the glycolytic cycle. After phosphorylation with hexokinase to DG-6-phosphate, the compound is metabolically trapped in the cell. Because of this trapping mechanism, FDG concentration steadily increases in metabolically

active cells, yielding a high contrast between tumor and normal tissue. Bear in mind that increased glucose metabolism is not unique to malignant cells and can be seen in benign tumors, inflammatory or infectious lesions, and even normal tissues. Also, some malignant cells may not have increased glucose metabolism for a variety of reasons.

A typical PET scan is started 30 to 60 minutes after the intravenous administration of approximately 10 mCi of 18F-FDG. A 6- to 12-hour period of fasting is required before injection. Patients are encouraged to drink water before the FDG injection to minimize collection in the urinary system. The patients are told not to speak or chew before PET scanning. Because normal FDG uptake in muscle may mimic tumor, muscle relaxants such as benzodiazepines are used in some centers. Scanning is performed in the supine position at multiple table positions to cover the entire body. Scan time is 30 to 60 minutes.

Qualitative evaluation of FDG-PET images is sufficient for most clinical purposes, but quantitative measurement of FDG concentration is possible. Several approaches of different complexity can be applied for this purpose. Some of these require complex computation, data acquisition, and arterial blood sampling during scanning. The most commonly used method, standardized uptake values (SUV), is simple and confined to the measurement of radioactivity concentrations at a single time point. The activity concentration is normalized to the body weight or body surface area. SUV may allow differentiation of malignant tissue from benign causes of increased uptake and can be used to measure the response to treatment. A downside of SUV calculation in therapy monitoring is that it only allows comparison of two measurements obtained at the same time point after tracer injection.

A major disadvantage of PET is lack of anatomic information, resulting in poor lesion localization. A number of software applications are used to "fuse" PET images with CT or MR images, which are obtained at different time points. Fusion of anatomic and functional images significantly improves lesion localization, but it is still subject to many technical difficulties and errors. Combined PET/CT units permit acquisition of both CT and PET images using a single piece of equipment in the same session without the need to move the patient. Errors in lesion localization are minimized, although they do occur in certain body regions where physiologic or involuntary motion is unavoidable.

Another major limitation of PET is poor spatial resolution. Currently, the maximum spatial resolution of dedicated PET scanners is about 5 to 6 mm. It is substantially inferior for more commonly used hybrid scanners. PET is an evolving technology and improvements in spatial resolution will surely be accomplished. Because of fundamental limitations inherent to the method, however, the maximum achievable spatial resolution is 1 to 2 mm. Therefore PET is incapable of showing microscopic disease.

Radionuclide Imaging

Scintigraphy has several applications in the head and neck. In salivary gland imaging, technetium-99m (99mTc)-pertechnetate imaging may be useful for assessing salivary gland function in autoimmune and inflammatory disease of the salivary glands. If the salivary glands are obstructed, the degree of obstruction, as well as the follow-up of obstruction after treatment, can be assessed. In evaluating neoplasms of the salivary glands, the findings of the 99mTc-pertechnetate scan are almost pathognomonic of Warthin's tumor and oncocytoma. Spatial resolution is limited to approximately 1.5 cm, so accurate localization of the mass within the gland is difficult. Single photon emission computed tomography (SPECT) may be useful in some cases.

Techniques of thyroid imaging and thyroid therapy are described in several textbooks.[9,10] Many centers use I-123 to obtain a thyroid update determination, and 99mTc-pertechnetate is used to obtain whole gland images. It is these images that determine whether thyroid nodules are "hot" or "cold." I-131 is used for therapy of hyperthyroidism and in follow-up to detect and treat residual, recurrent, and metastatic thyroid cancers.

Medullary carcinoma of the thyroid is difficult to visualize, but 99mTc-DmSA has been used. In-111 pentetreotide has been used with some success.

Identification of parathyroid adenomas has been done for several years with a subtraction technique using 99mTc-pertechnetate and Tl-201 (Fig. 11-9). The basis of this test is that thallium is taken up by thyroid tissue and parathyroid tissue. Thyroid tissue is the only tissue that uptakes 99mTc-pertechnetate. Therefore the subtraction of the 99mTc-pertechnetate image from the thallium-201 image should leave only parathyroid tissue. The sensitivity of this technique is believed to be very high for lesions larger than 1 g. Sensitivity decreases for smaller lesions, and the subtraction technique can be hampered by patient motion. 99mTc-sestamibi is now the favored agent in many institutions. A double-phase imaging protocol is employed with improved identification of parathyroid adenomas.

CSF leaks can be detected with In-111 DTPA placed into the subarachnoid space. This technique is described and illustrated in Chapter 44.

Three-Dimensional Reconstruction Techniques

Image data from either CT or MRI can be processed to create three-dimensional reconstructions. The state-of-the-art picture archival and communication systems (PACS) that are now available in most institutions obviate the need for a separate workstation to perform these reconstructions.

CT data are loaded as a stack of contiguous two-dimensional slices that define the scanned volume. Reconstructions are created either by choosing a specific range of densities for display or by manually tracing the outline of the desired structure. Improvements offered by multislice-multirow CT scanners and enhanced computational capacity of imaging workstations have led to a paradigm shift in radiology; volume imaging has replaced axial imaging. CT data from a large body part can be gathered in a very short time as a whole and the obtained "volumetric" data set can be displayed in various planes and as three-dimensional reconstructions.

Magnetic resonance data for image analysis are best acquired using a "volume acquisition" method, in which data are acquired as a complete three-dimensional block rather than as individual slices. Because volume acquisition takes longer, gradient echo techniques are usually required to reduce the imaging time. Once acquired, the data are displayed in any desired plane and, by selecting a range of signal intensities or by tracing specific structures with a cursor, three-dimensional surface models are created.

The utility of three-dimensional reconstruction is best appreciated with craniofacial reconstructions.[11,12] Directly visualizing the three-dimensional relationships of the facial structures aids surgical planning. Instructors find three-dimensional models of the face and orbital structures useful for teaching medical students, residents, and anatomy students. Virtual endoscopy is a computer-generated simulation of endoscopic perspective. The virtual endoscopic images of the trachea, larynx, pharynx, nasal cavity, and paranasal sinuses and ear have demonstrated clinical utility (Fig. 11-10).

At present, the spatial resolution of CT is superior to MRI in the head and neck for displaying bony relationships. However, MRI provides a superior display of transcranial soft tissue structures, such as the entire visual pathway, and has better tissue contrast resolution than CT. Thus CT and MRI will likely have complementary roles in three-dimensional image display.

Applications of CT, MRI, and Ultrasound in the Head and Neck

Each anatomic region requires a different imaging approach to optimize the detection and characterization of the structure or lesion of interest. The following is a description of the indications for using CT, MRI, or ultrasound in specific head and neck regions, plus a general imaging approach relevant to each anatomic region in terms of imaging planes, slice thickness, contrast agents, and pulse sequences. Whenever possible, CT and MRI are performed before biopsy or resection of lesions because the resulting edema may obscure the true margins of a mass.

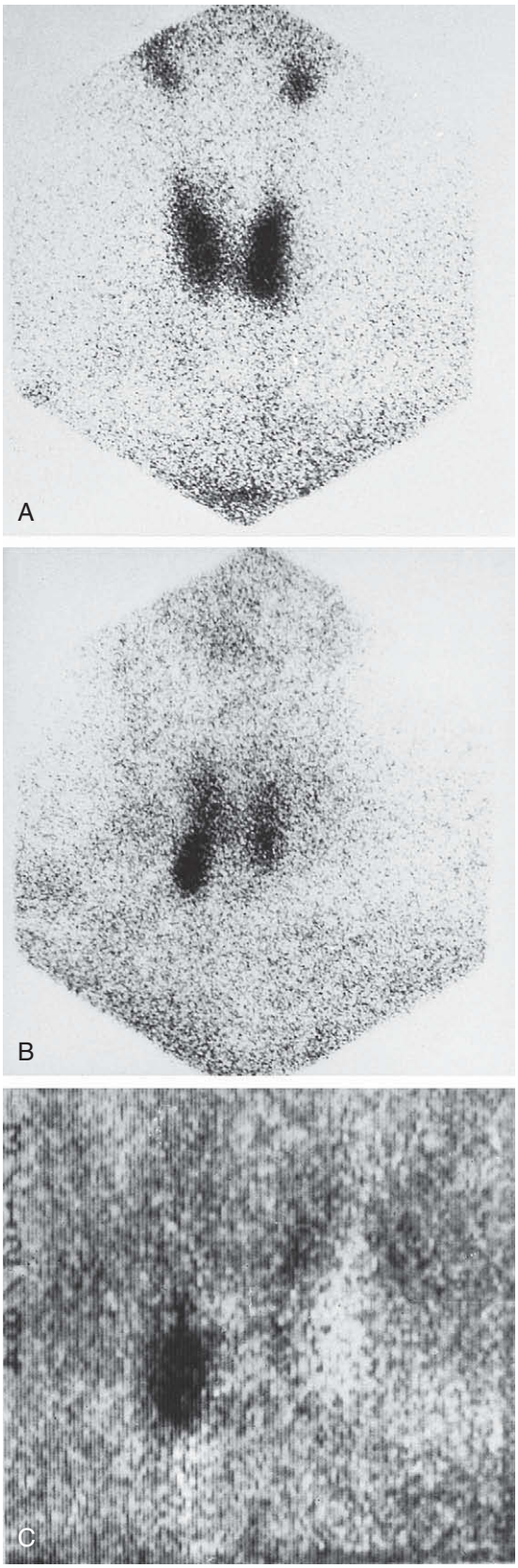


Figure 11-9. **A,** Technetium-99m (99mTc)-pertechnetate scintigraphy in a patient with suspected parathyroid adenoma is essentially normal. **B,** Corresponding T1-201 scintigraphy reveals an apparent area of increased uptake adjacent to the lower pole of the right lobe. **C,** Subtraction of the 99mTc-pertechnetate study from the T1-201 study confirms the presence of a parathyroid adenoma.

Application of Computed Tomography in Head and Neck Region

Multichannel CT scanners revolutionized head and neck imaging. The entire neck can be scanned in less than a minute at a slice thickness of less than 1 mm. These data can then be reconstructed in any plane with a desired slice thickness. This obviated the need for site specific imaging protocols. A typical neck CT using a multidetector scanner employs 1-mm slice thickness and a pitch of approximately 1, with contiguous axial scanning performed from the sella turcica down to the thoracic inlet. Then, typically 3-mm-thick axial, sagittal, and coronal images are reconstructed for view. The use of intravenous contrast is critical for interpretation of the study. Determination of extent of disease and vascular invasion, compression, and discrimination of vessels from nodes and small muscle bundles can be extremely difficult (see Figs. 11-3 and 11-4). Evaluation of the normal mucosa-submucosa interface and mucosal tumors can not be accomplished without contrast enhancement. Optimally, contrast should be present in both arteries and veins during image acquisition. Also, enough contrast should be allowed to diffuse from vessels to the tissue interstitium for tumors to enhance. This is particularly important for high-end multidetector CT scanners, which tend to finish image acquisition before optimal tumor enhancement is achieved, unless a delay between injection of contrast and scanning is employed. To maintain good opacification of vessels after this delay, a biphasic contrast injection scheme is used. The delay time and the rate at which contrast material is injected vary depending on the specifications of the scanner. Contrast is best administered with a mechanical pump infusion although a drip-infusion technique may also be effective. Frequently, image reconstruction using a soft tissue algorithm suffices. If a suspicion of bone erosion or destruction by tumor or inflammation exists, sections of the skull base and mandible need to be reconstructed using a bone algorithm.

Suprahyoid Neck

Suprahyoid neck CT is often performed for simultaneous evaluation of the deep extent of mucosal based tumors and to evaluate associated metastatic disease to the cervical lymph node chains. Because streak artifacts from dental fillings frequently obscure the oropharynx and nasopharynx, it is usually necessary to obtain additional angled sections to assess the pharynx directly posterior to the dental work (Fig. 11-11).

Cervical Lymphadenopathy

Lymph node CT evaluation is concomitantly performed during CT investigation of most suprahyoid and infrahyoid tumors or inflammation. The quality of lymph node assessment depends very much on the success of achieving a high concentration of contrast in the arterial and venous structures of the neck. Otherwise, nodes and vessels may appear remarkably similar.

Salivary Glands

Dental amalgam can cause significant streak artifacts that obscure the parotid or submandibular gland parenchyma. If the dental work is identified on the lateral scout view (scanogram), dental artifacts can usually be avoided if an oblique semiaxial projection is chosen with the scanner gantry angled in a negative direction (between a coronal and an axial plane), thus avoiding the teeth. This plane has the advantage of visualizing both parotid and submandibular glands in the same slice and is parallel to the posterior belly of the digastric muscle.[13] Contrast administration is required for both neoplastic and inflammatory conditions of the salivary glands. Enhancing intraglandular vessels may mimic or obscure small stones, thus a precontrast scan is also advised in cases of suspected sialolithiasis. The CT attenuation of a normal parotid gland is variable depending on the proportion of fat and glandular tissue present, which varies with age. Submandibular glands have a more predictable attenuation that is similar to that of muscle. Any difference in attenuation values of the right and the left submandibular glands should be suspicious for an obstructing lesion such as floor of the mouth cancer.

Sialography and CT-Sialography

Conventional sialography, although rarely needed, remains the best radiographic method for evaluating ductal anatomy in obstructive,

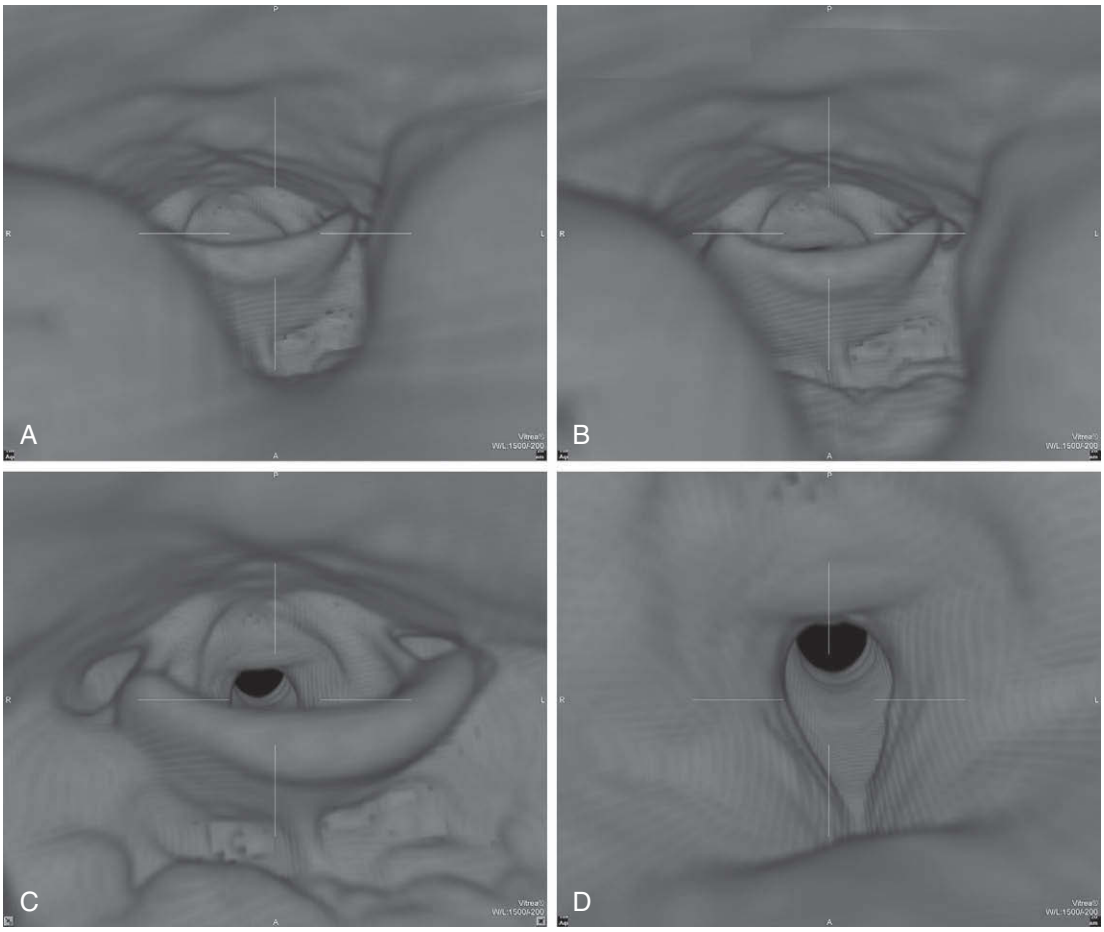


Figure 11-10. Normal virtual laryngoscopy. A real-time navigation in the larynx can be performed with ease using a workstation and special software.

inflammatory, and autoimmune salivary gland diseases. Supplemental CT-sialography may be performed in evaluation of a dense gland that is suspected to harbor a mass in patients who cannot have MRI. CT-sialography may be obtained at the time of intraductal injection of fat-soluble or water-soluble contrast or after a routine sialogram (the gland may be reinjected during the CT with the catheter left in place). The plane of study is the same as that used for NCCT and should be similarly angled to avoid dental filling artifacts. The use of concentrated sialographic contrast material may cause significant streak artifacts if too much contrast collects in dilated ducts, acini, or large pools, all of which can obscure smaller masses in the gland. For optimal CTS, the injection is extended into the acinar phase to maximize parenchymal opacification and thereby silhouette mass lesions within the parenchyma.[14]

Larynx and Infrahyoid Neck

Laryngeal and infrahyoid neck CT is most commonly requested to evaluate squamous cell carcinoma of the larynx or hypopharynx, associated cervical lymph node metastasis, trauma, and inflammation. The fine detail of the larynx and vocal cords requires thinner reconstructions than the routine 3-mm sections. Sections through the vocal cords are optimally reconstructed parallel to the plane of the true vocal cords. Because assessment of vocal cord mobility is important in staging glottic carcinoma, various provocative techniques may facilitate laryngeal imaging in those cases where the vocal cords are obscured on physical examination. Quiet breathing places the cords in a partially abducted position. By having the patient blow through a straw or do a modified Valsalva maneuver (puffing out the cheeks) the hypopharynx and supraglottic larynx can be distended, allowing better separation of the aryepiglottic folds from the hypopharynx, while simultaneously abducting the cords (see Fig. 11-3). The vocal cords can be assessed during phonation ("eeee"), which causes the cords to adduct and move to a paramedian position (see Fig. 11-3). Breath holding will also adduct the vocal cords, close the glottis, and significantly reduce motion artifacts. By scanning the larynx twice, once to adduct and a second time (sections limited to the glottis) to abduct the vocal cords, the radiologist can assess vocal cord motion and identify fixation. Evaluation of laryngeal trauma may not require intravenous contrast. Bone windows are helpful for assessing cartilage fractures or tumor erosion.

Thyroid and Parathyroid Glands

The scanning should extend to the aortic arch to cover potential sites of ectopic thyroid and parathyroid tissue. Although the normal thyroid is hyperdense because of its natural iodine content on NCCT, a CECT is preferred for this study. The normal thyroid enhances intensely on CECT, with most mass lesions of the thyroid appearing less enhanced. The parathyroids are rarely imaged primarily by CT because nuclear medicine and ultrasound techniques are more feasible for localizing parathyroid adenomas.

Paranasal Sinuses

Paranasal sinus CT can be approached in several ways depending on the anticipated disease process. A screening axial sinus NCCT (Fig. 11-12A) is clearly superior to conventional radiographs and provides information on specific sinus involvement by inflammatory processes as well as better delineation of bony sclerosis or destruction. One method is to use 5-mm-thick sections obtained at 10-mm intervals (5-mm gap), which can cover the entire paranasal sinuses with six to eight slices. The technical parameters can be optimized to achieve a low radiation exposure that is similar to radiographs.

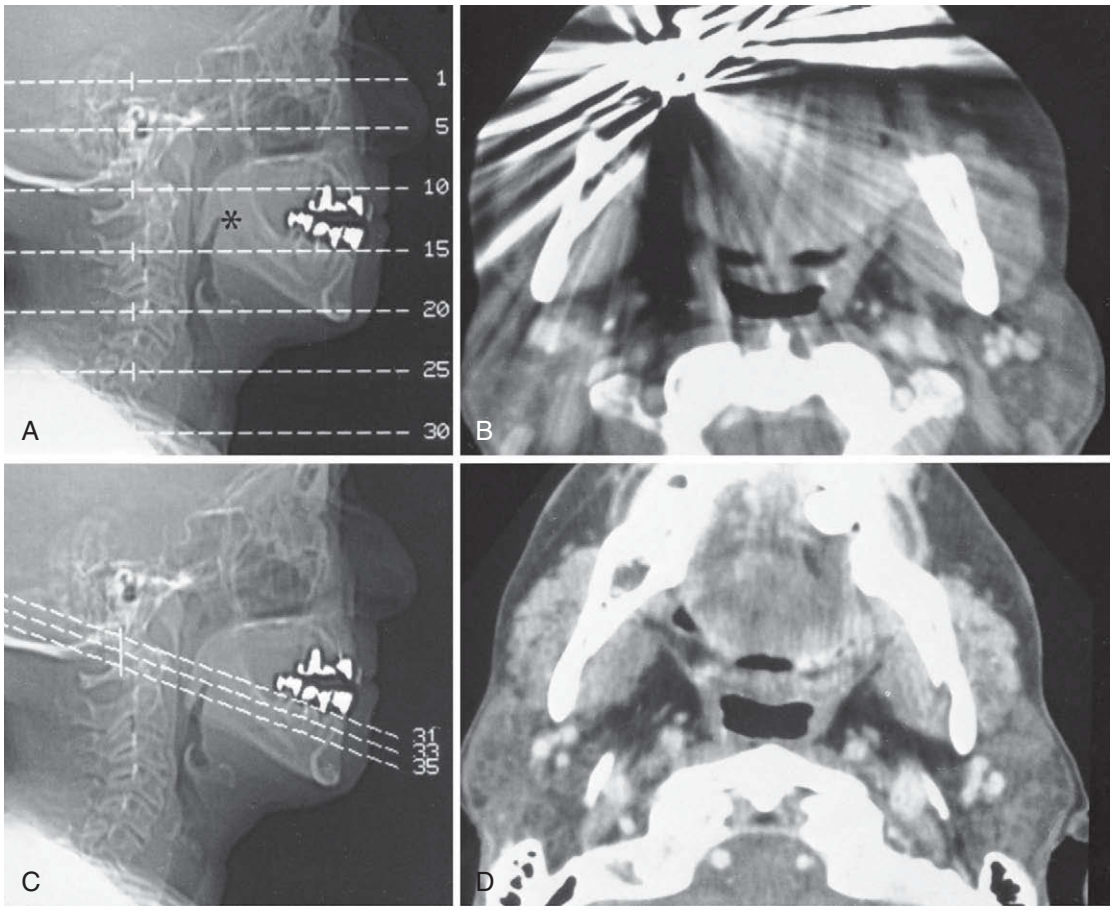


Figure 11-11. Avoiding dental artifacts on computed tomography (CT). **A,** Lateral scout image without angulation of the CT gantry (dashed lines represent selected axial images) in a patient with numerous metallic densities in teeth from dental work. Posterior tongue *(asterisk)* and soft palate lie directly posterior to metal. **B,** Axial contrast-enhanced computed tomography (CECT) at the level of the dental work is not interpretable because of the numerous streak artifacts caused by metallic fillings and crowns. **C,** Scout view depicting additional slices with the CT gantry angled to avoid dental work. **D,** Angled axial CECT at the same level as B shows a significant improvement in image quality of the posterior tongue and oropharynx.

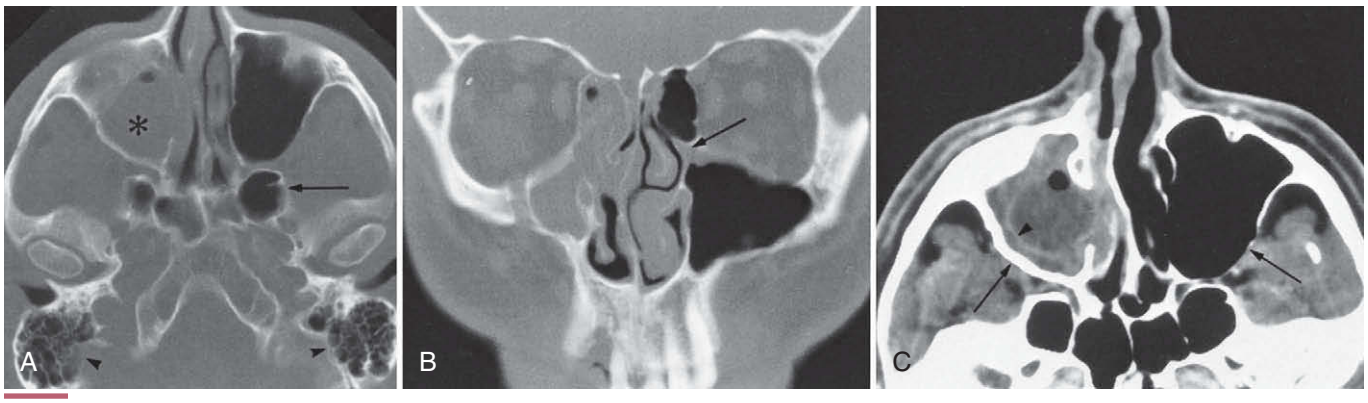


Figure 11-12. Computed tomography in evaluation of sinusitis. **A,** Axial 5-mm sinus screening noncontrast computed tomography (NCCT) using bone algorithm and bone windows in a patient with chronic right maxillary sinusitis. Excellent bony detail is obtained of both maxillary sinuses (posterior wall thickening and sclerosis are present on right) and mastoids. Clear discrimination of soft tissue opacification of the right maxillary sinus *(asterisk)* is achieved compared with the normal air-filled left maxillary sinus. Pneumatized pterygoid process *(arrow)* is an extension of sphenoid sinus pneumatization. **B,** Coronal 3-mm NCCT with bone algorithm and bone windows in the same patient clearly demonstrates mucosal thickening and opacification of the right maxillary and ethmoid sinuses, and left maxillary infundibulum *(arrow)*. Sharp anatomic detail of the bony architecture and the use of coronal plane are essential for preoperative planning before endoscopic sinus surgery. **C,** Axial 3-mm contrast-enhanced computed tomography with soft tissue algorithm and soft tissue windows exaggerates the right maxillary sinus posterior wall thickness *(arrows)*. Thickened mucosa has a thin rim of enhancement along its luminal margin *(arrowhead)*. Combination of bony sclerosis and mucosal thickening is often seen in chronic sinusitis.

When endoscopic sinus surgery is anticipated, NCCT imaging of the sinuses is mandatory for preoperative evaluation of the extent of sinus disease, to detect anatomic variants, and for planning the surgical approach (see Fig. 11-12B). This study is done in the axial plane while the patient is supine with thin sections reconstructed in sagittal and coronal planes. Frequently, only the bone algorithm with its edge enhancement properties is needed for evaluating the detailed anatomy of the ostiomeatal complex. Contrast administration is usually not necessary for routine sinusitis, although when severe nasal polyposis is suspected, contrast may be useful to demonstrate the characteristic "cascading" appearance of the enhancing polyps or to characterize an associated mucocele. A soft tissue algorithm with soft tissue windows may be useful when using CECT for intracranial complications from sinus inflammatory processes. A nasal decongestant may be used to help decrease normal but asymmetrical nasal mucosa congestion (normal nasal mucosal cycle) from a mucosal based mass.

The assessment of sinus tumors requires the most detailed imaging. The intracranial compartment, parapharyngeal, masticator, and buccal spaces should sufficiently be included in the field-of-view as to allow for assessment of tumor extension. At least the lymph node levels I and II should be visualized. For an optimal study, both soft tissue and bone algorithms are used. This differentiates the soft tissue component, as well as evaluating subtle bony destruction (see Figs. 11-12A and C). The coronal plane is best for evaluating the cribriform plate. CECT is used to maximize the enhancement characteristics of the tumor and differentiate it from adjacent soft tissue structures.

Facial Trauma

Facial trauma CT characterizes fractures and facial soft tissue injury very well. Contrast material is not needed. Bone algorithm is mandatory for demonstration of fine bone detail but soft tissue algorithm for assessing orbital and facial soft tissue injury is often very helpful. Three-dimensional surface reconstructions or volume-rendered images are helpful when planning facial restoration and assessing surgical results.

Temporal Bone and Skull Base

High-resolution CT images obtained with a multichannel scanner are now the standard of imaging for the temporal bone. The acquired data set is reconstructed at 0.5-mm slice thickness at any plane desired. Rotationally reformatted images are most helpful in displaying an entire semicircular canal in a single plane to aid in the diagnosis of dehiscent superior semicircular canal. In general, intravenous contrast is not necessary for temporal bone imaging, although vascular tumors or squamous cell carcinoma invading the temporal bone may require the use of intravenous contrast plus supplemental soft tissue algorithms to best image the extracranial and intracranial soft tissue component of the lesion. However, bone algorithm with bone windows is used in all temporal bone imaging.

Application of Magnetic Resonance Imaging in Head and Neck Region

Suprahyoid Neck

MRI is ideally suited for imaging the suprahyoid neck (including nasopharynx, oropharynx, oral cavity, and tongue). The standard head coil which has a high signal efficiency will permit visualization of the suprahyoid neck structures caudally down to approximately the level of the inferior margin of the mandible and floor of mouth. For imaging the oral cavity, floor of mouth, submandibular space, and cervical lymph node chains, a head coil will not suffice. Either an anterior or volume neck coil is needed to visualize the entire neck from the skull base to the thoracic inlet (from dura to pleura). Several pulse sequences and imaging planes using 5-mm thick sections are required to adequately assess the deep and superficial structures of the neck. (Implicit in this discussion of MRI technique for all areas of the head and neck is the fact that a sagittal T1WI is obtained as the initial sequence in all of the authors' studies and is used primarily as a scout view for the proper positioning in other imaging planes, as well as for anatomic information.) A precontrast axial T1WI, and often a coronal T1WI, are required to optimally assess fat planes in the neck. Fat provides an excellent white background from which muscle and fascial planes, bone, sinus, and vascular structures can easily be discriminated. The coronal plane is particularly useful for visualizing the relationships of the suprahyoid neck structures to the skull base and also for delineating the anatomy of the tongue and floor of mouth. A T2WI or STIR, usually obtained in the axial plane, is required to detect structures with a long T2 (e.g., tumors, cysts, lymphadenopathy, edema) that appear brighter than the background muscle and fat. Postgadolinium T1WIs with fat suppression in the axial and coronal plane are frequently helpful to discriminate the enhancing margins of a lesion or to detect perineural spread of tumor. The T2WI may also be combined with fat suppression to optimize the information obtained.

Lymphadenopathy

Before the widespread use of gadolinium and fat suppression techniques, MRI was often less specific than CT in characterizing cervical lymph node metastases because of the lower ability to show heterogeneously enhancing nodes which is a highly accurate sign of nodal metastasis in the setting of squamous cell cancer of the neck. However, improved MRI scanner technology, gadolinium enhancement, and fat suppression sequences have allowed a comparable accuracy. Also, the MRI detection of carotid artery invasion by extracapsular spread of tumor from nodes is often superior to CECT.

An anterior or volume neck coil using 5-mm thick sections with a small 1- to 2-mm interslice gap is necessary to encompass the entire lymph node chain throughout the neck from the skull base to the clavicles within the imaging field of view. The detection of cervical lymphadenopathy with MRI may be accomplished with (in decreasing order of sensitivity) a STIR sequence, a fat suppressed T2WI, a fat-suppressed post gadolinium T1WI, a conventional T2WI, or a precontrast T1WI. Although STIR is the most sensitive sequence, it may be limited by prominent pulsation artifacts from vessels. The significance of a heterogeneously enhancing node on MRI should be analogous to the same finding on CECT and is best demonstrated on post-contrast, fat-suppressed T1WIs.

Salivary Glands

MRI of the parotid gland can be accomplished with a standard head coil using 3- to 5-mm slices, but at the risk of excluding a portion of the submandibular gland that lies at the edge of the usable field of view. A volume neck coil is the better coil for imaging both parotid and submandibular glands within the same field of view, especially if a malignancy is suspected and cervical lymph node metastases are sought lower in the neck. A smaller surface coil may be necessary for evaluation of perineural tumor spread along with facial nerve into the mastoid segment of the facial nerve canal. Depending on the fat content of the parotid gland, a tumor may be better defined on T1W or T2WIs. Fat suppression on postcontrast T1WI allows better depiction of the margins of the tumor which is a critical imaging finding in differentiating malignant from benign masses. More recently, magnets with superior gradient performance allowed MR sialography images. Despite its limitation in spatial resolution compared with conventional sialography, MR sialography eliminated the need for conventional sialography in many clinical scenarios.

Larynx and Infrahyoid Neck

The larynx and infrahyoid neck require either an anterior or a volume neck coil, preferably using no thicker than 3-mm sections for the larynx. The field of view should include the area from the inferior margin of the mandible to the clavicles. Although the larynx can be examined well by both axial CECT and MRI, laryngeal MRI has a higher proportion of suboptimal studies. Laryngeal MRI is more susceptible to motion artifacts than MRI of other regions of the neck because of a combination of swallowing, breathing, and vascular pulsation from the adjacent common carotid arteries. Precontrast axial and coronal T1WIs are essential to assess the paraglottic fat planes. The coronal plane, angled parallel to the airway, is especially useful for determining transglottic tumor spread. Fat saturation postgadolinium

T1WIs in the axial and coronal planes are best for detecting lesion margins, invasion of adjacent cartilage, and associated malignant nodes. T2WI in the axial plane may help detect moderately increased tumor signal and improve detection of high signal cystic or necrotic neck lesions.

Thyroid and Parathyroid Glands

The same techniques and slice thickness as those of the larynx are used for the thyroid and parathyroid glands. The field of view may need lower centering to include the upper mediastinum and ensure complete evaluation of the inferior extent of a thyroid tumor or an ectopic parathyroid gland. Coronal and sagittal views aid understanding of the craniocaudal extent of the lesion relative to the aortic arch, great vessels, and mediastinum. This information is especially useful to the surgeon. Although MRI may detect an unsuspected thyroid or parathyroid lesion during routine neck or cervical spine imaging, MRI is less frequently used for primary evaluation of these lesions because of the cost of the study and susceptibility to motion artifacts. The normal thyroid gland will enhance mildly on both gadolinium-enhanced MRI and CECT. A solid mass in the thyroid or parathyroid is usually low intensity on T1WI and high signal on T2WI, and it may enhance with gadolinium. Cystic lesions are bright on T2WI.

Paranasal Sinuses

Sinus MRI is primarily indicated for evaluating sinus tumors (and occasionally inflammatory disease such as a mucocele) and may be accomplished with a standard head coil, using 3- to 5-mm slices. The principal value of MRI over CT for sinus tumors is the ability of MRI to distinguish between tumor and obstructed sinus secretions and to predict the true extent of the tumor. A precontrast sagittal, axial, or coronal T1WI will provide a good demonstration of the sinuses, nasal cavity, cribriform plate, masticator and parapharyngeal spaces, and orbits. Sinus secretions with low protein content show low T1 and high T2 signal. With increasing protein content the T1 signal increases and T2 signal decreases. Very high concentrations of protein result in low signal on both pulse sequences and may occasionally mimic normally pneumatized sinus. No enhancement of the sinus secretion is seen on postcontrast images except for the mucosa of the sinus whereas tumors often enhance and show intermediate T2 signal allowing differentiation of postobstructive secretions from tumor. Fat saturation T1WI is recommended to better define the sinus tumor margins when the tumor extends directly or by perineural spread beyond the sinus into the anterior cranial fossa, orbit, parapharyngeal space, or pterygopalatine fossa. The sagittal and coronal planes are very helpful for evaluating cribriform plate extension. The coronal and axial planes are best for orbital, cavernous sinus, pterygopalatine fossa, and parapharyngeal space spread.

Temporal Bone

MRI is the imaging standard for the detection of internal auditory canal (IAC), facial nerve canal, and jugular foramen lesions. MRI is useful, in combination with CT, for assessing expansile or destructive lesions of the temporal bone and external auditory canal. A standard head coil is adequate for most temporal bone lesions, but a smaller 5- to 10-cm surface coil may provide improved resolution for certain regions in the expense of coverage. The small size of the temporal bone structures and their respective lesions requires high spatial resolution images, which may be accomplished by using thinner slices of 0.5 to 3.0 mm (preferably without an interslice gap), smaller surface coils (higher signal-to-noise ratio), volume acquisition, or T1WI (higher signal-to-noise ratio). Precontrast T1WI in the sagittal and axial planes is useful for defining anatomy and for detection of high-signal lesions such as fat, methemoglobin, and viscous or proteinaceous cysts. Postgadolinium T1WIs (without or with fat saturation) in the axial and coronal planes are essential for detecting small enhancing lesions and determining the extent of larger lesions. In fact, for routine evaluation of a suspected acoustic schwannoma, only a postgadolinium axial and coronal T1WI study may be required. T2WIs are frequently unnecessary for IAC tumors but may be helpful when brainstem ischemic or demyelinating disease, meningioma, blood products, proteinaceous secretions, or a large destructive tumor is suspected or is being further evaluated after a preliminary temporal bone CT. A facial nerve lesion in the mastoid segment of the facial nerve canal is best evaluated for proximal and distal extension using a surface coil with sagittal and coronal pregadolinium and postgadolinium T1WIs.

Skull Base

MRI may be indicated for primary lesions of the skull base or for intracranial and extracranial lesions that secondarily involve the skull base. A standard head coil using 3- to 5-mm slices images this region well. Pregadolinium sagittal, axial, or coronal T1WI allows for assessment of the fat planes of the suprahyoid neck and detection of high signal intensity blood breakdown products, proteinaceous fluids, or fat within the lesion. Postgadolinium axial and coronal (occasionally sagittal) fat saturation T1WIs are excellent for determining the extent of an enhancing lesion above, below, and within the skull base. T2WI in the axial or coronal plane may be helpful for detecting a high signal lesion. STIR images usually give similar information to T2WIs in the skull base and may not be necessary.

Ultrasound Applications in the Head and Neck

High-resolution ultrasound evaluation of the suprahyoid neck, salivary glands, and infrahyoid neck is limited to the more superficial neck structures because of the impediment to sound transmission caused by the highly reflective facial bones, mandible, mastoid tip, and air within the oral cavity and pharynx. The ultrasound technique, using a high-frequency (e.g., 10 MHz) transducer and multiple imaging planes, is similar for all these regions. A small superficial lesion is best seen with a high-frequency transducer, which has a higher spatial resolution, whereas a deeper lesion requires a lower frequency transducer. Color flow Doppler technique may help differentiate vascular structures from a cystic or solid lesion. Head and neck ultrasound is performed less frequently in North America than in Europe, perhaps because of the common availability of CT in North America and the perception of the greater accuracy of CT.

Metastatic Lymphadenopathy

Ultrasound, combined with fine needle aspiration, may be a very effective tool in evaluating metastatic lymph nodes in head and neck cancer. The upper one third of the internal jugular, retropharyngeal, and tracheoesophageal groove nodes are poorly evaluated, however, because of obscuration by bone or airway structures. Ultrasound may be the best method (possibly better than MRI or CT) for determining the presence of tumor invasion of the carotid by the extracapsular spread from metastatic nodes, but evaluation may not be reliable as the tumor approaches the skull base. Invasion of the carotid artery is characterized by loss of the echogenic fascial plane between the vessel wall and the tumor.

Salivary Glands

Ultrasound has indications for both inflammatory and neoplastic disease. It may detect salivary duct stones as small as 2 mm. An obstructed dilated duct may appear as a tubular cystic structure. An abscess may be detected and drained under ultrasound guidance during the acute stage of sialadenitis. A mass in the superficial parotid gland is easily assessed by ultrasound, but the deep lobe of the parotid gland is obscured by the mandible, styloid process, and mastoid tip. Ultrasound is also very sensitive for a mass in the submandibular gland. Although ultrasound can determine the sharpness of margins of the lesion, an aggressive neoplasm or inflammatory process extending beyond the margins of the gland is better evaluated by MRI or CECT because the deep landmarks are more easily demonstrated with these methods. Well-defined margins usually indicate a benign mass, and infiltrative margins suggest malignancy.

Infrahyoid Neck

Ultrasound using a high-frequency transducer is usually the first imaging modality for evaluating thyroid gland and parathyroid gland masses because it is relatively inexpensive, has no side affects, and is

easily performed. Solid and cystic masses and calcification are easily identified but, like with other imaging modalities, a reliable differentiation of malignant thyroid nodules from benign ones is not possible. Ultrasound is the imaging modality of choice for image-guided biopsies. A parathyroid adenoma is readily evaluated if its location is cranial to the sternum.

FDG-PET Applications in Head And Neck Cancer

PET technology is still evolving as is its exact role in imaging head and neck malignancies. PET-CT is becoming more widely available as the preferred method.

Staging

T-Staging

The detection rate of a primary tumor in the setting of squamous cell carcinoma of the head and neck (SCCHN) with FDG-PET is slightly superior to that with MRI and CT and comparable to that of panendoscopy. For the superficial mucosal lesions, however, the limitations of all imaging modalities including PET are well recognized and panendoscopy remains the best way to evaluate such lesions. PET, because of limited spatial resolution and lack of anatomic detail, is often insufficient for the assessment of submucosal extent of disease and involvement of adjacent structures. MRI and CT remain the modality of choice for this purpose. FDG-PET may identify a primary tumor that is not detected by other diagnostic modalities in the setting of cervical nodal metastasis with unknown primary, although false-positive results are also frequent in this setting.

N-Staging

The sensitivity of FDG-PET in detection of metastatic lymph nodes in the neck is higher than that of CT and MRI. The impact of this increased sensitivity on patient management remains to be seen. A modality that would reliably differentiate N0 from N1 necks is very much needed, but it is unrealistic to expect PET to diagnose microscopic metastasis—even in the future—because of inherent technical limitations of spatial resolution. Currently available data do not justify the routine use of FDG-PET for nodal staging despite its proven superiority.

M-Staging

FDG-PET imaging is suitable for detection of distant disease because of its great sensitivity and ability to examine virtually the entire body in a single study. Synchronous lesions in the upper aerodigestive tract and lungs are also detected with FDG-PET more accurately than other modalities, although false-positive results remain problematic.

Therapy Planning and Monitoring

Radiotherapy fields can be determined on the basis of PET-CT data. Tracer uptake can be quantified and changes in tumor metabolism can be monitored by PET imaging during treatment. Whether these changes can predict response to treatment is an active area of research. Early data suggest that very early FDG-PET study performed days after initiation of treatment may separate responders from nonresponders even before any structural changes have occurred. If this is proved to be true, it may permit modification of treatment very early in the process.

Detection of Residual and Recurrent Disease

Evaluation of the neck after surgery and radiotherapy is limited both clinically and radiologically. PET is definitely superior to anatomic imaging modalities and clinical examination in distinguishing recurrent disease from fibrosis or scar tissue (Fig. 11-13). It is, however, well recognized that false-positive results, because of surgery and radiotherapy-induced inflammation, are common in the first months after therapy. It is generally recommended to defer FDG-PET studies at least 2 months after treatment, which limits the use of this modality in the evaluation of planned neck dissection cases.

Principles of Image Interpretation

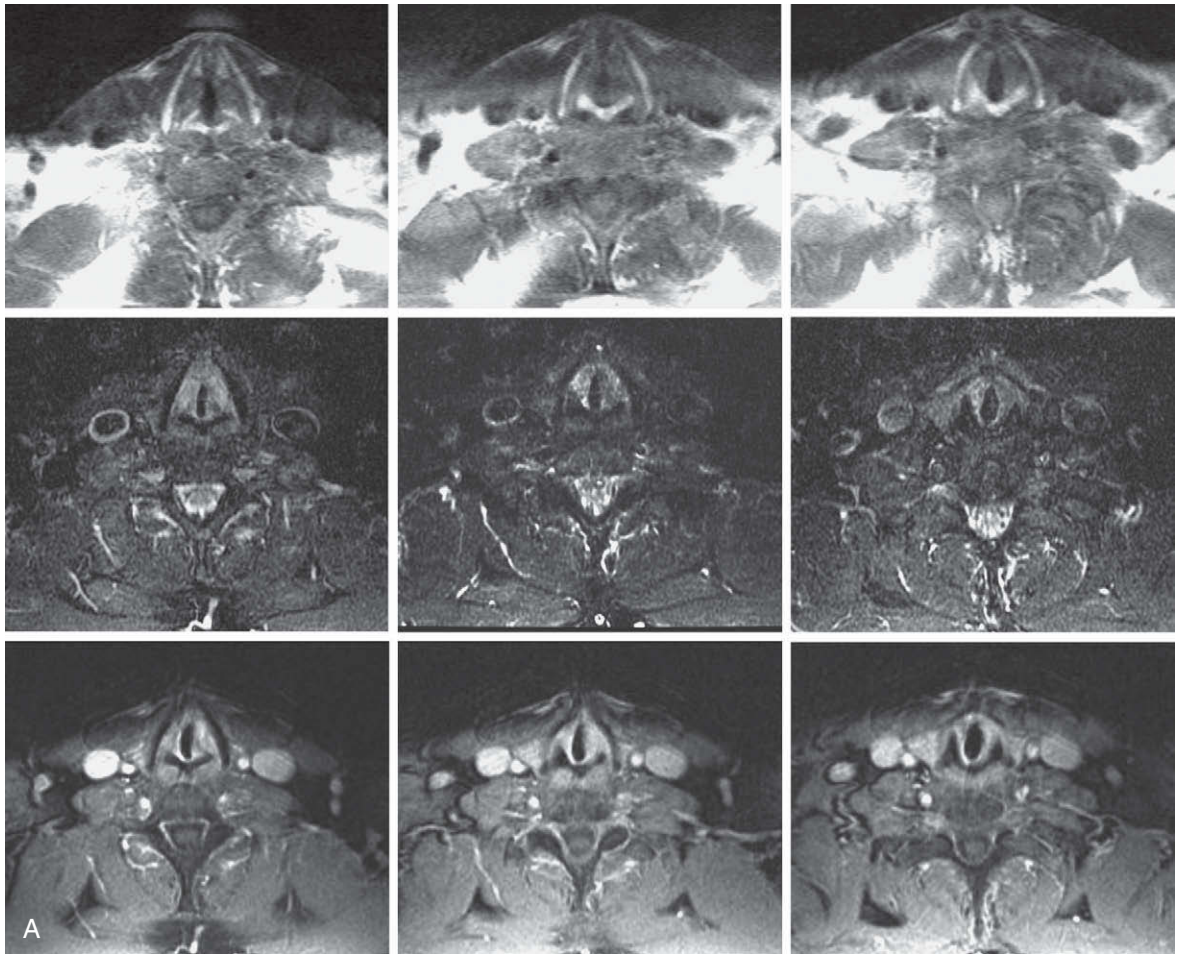
Strategy for Image Interpretation and Differential Diagnosis

This section is included to aid the beginning surgeon or oncologist in developing a basic strategy for image interpretation. Normally, the radiologist chooses and supervises the appropriate imaging study, evaluates and interprets the images, and communicates its significance to the referring physician. However, frequent dialogue between the referring physician and the radiologist will significantly improve interpretation of the imaging study. Accurately interpreting an imaging study of the head and neck requires a systematic method of observation, knowledge of the complex anatomy and pathophysiology, and an understanding of imaging principles. The differential diagnosis of lesions of the head and neck requires a systematic approach as well. One such diagnostic imaging process is summarized here:

1. Obtain clinical data: age, sex, history, physical findings.
2. Survey the films for all abnormalities and summarize these findings.
3. Compartmentalize the lesion.
4. Interpret the chronicity and aggressiveness of the observations: acute or chronic, nonaggressive or aggressive, benign or malignant.
5. Develop a differential diagnosis. Use pathologic categories: congenital, inflammatory, tumor, trauma, vascular. Use clinical and radiographic information to narrow the choices and arrive at the most appropriate diagnosis.

By using such a strategy, it is unlikely that important findings will be missed because all the images have been evaluated. This may be done by looking at all the anatomic spaces on each slice and proceeding sequentially through all the slices. Alternatively, each anatomic space can be evaluated on serial slices, followed by the next anatomic space, and so on. Characterizing a lesion requires specific observations: location, anatomic space of the epicenter, size, definition of margins, extent of spread in each direction, invasion of adjacent compartments, involvement of neurovascular structures, enhancement pattern, cysts, calcification, density, signal intensity, echogenicity, hemorrhage, and lymphadenopathy. Next, summarizing the findings helps to tie them together into a logical pattern. Compartmentalizing a lesion is the last step in the observational process and requires placing the epicenter or site of origin of the lesion in a specific anatomic space, although some lesions may be multicompartmental. The origin of a lesion is limited by the types of tissue that reside in each specific space. An example of such a summary would be, "A 35-year-old male has a cystic, nonenhancing mass in the sublingual space." A frequent cause of misdiagnosis is the failure to make all the observations first. Interpretation and differential diagnosis of the lesion are the final steps.

The interpretation of the significance of a lesion uses both its radiologic and clinical features. For example, the interpretation might use the following descriptions: inflammatory (edema, abscess cavity, fever), nonaggressive (remodeling of bone, slow progression of symptoms), aggressive (destruction of bone, rapid progression), benign neoplastic (well-defined margins, displacement of adjacent structures, nonpainful), malignant (poorly defined margins, invasion and destruction of adjacent structures, pain and neuropathies), or cystic (low-density center with a thin rim of enhancement, fluctuant). The differential diagnosis is narrowed by further refining the interpretation, "A 35-year-old male has an asymptomatic cystic, nonenhancing mass in the sublingual space that appears chronic and nonaggressive." With knowledge of the relevant clinical findings, the proper differential diagnosis, which is specific for each anatomic space, can then be constructed and limited to one (or at least a few) possible pathologic causes. In this example, a ranula would be the most likely consideration.



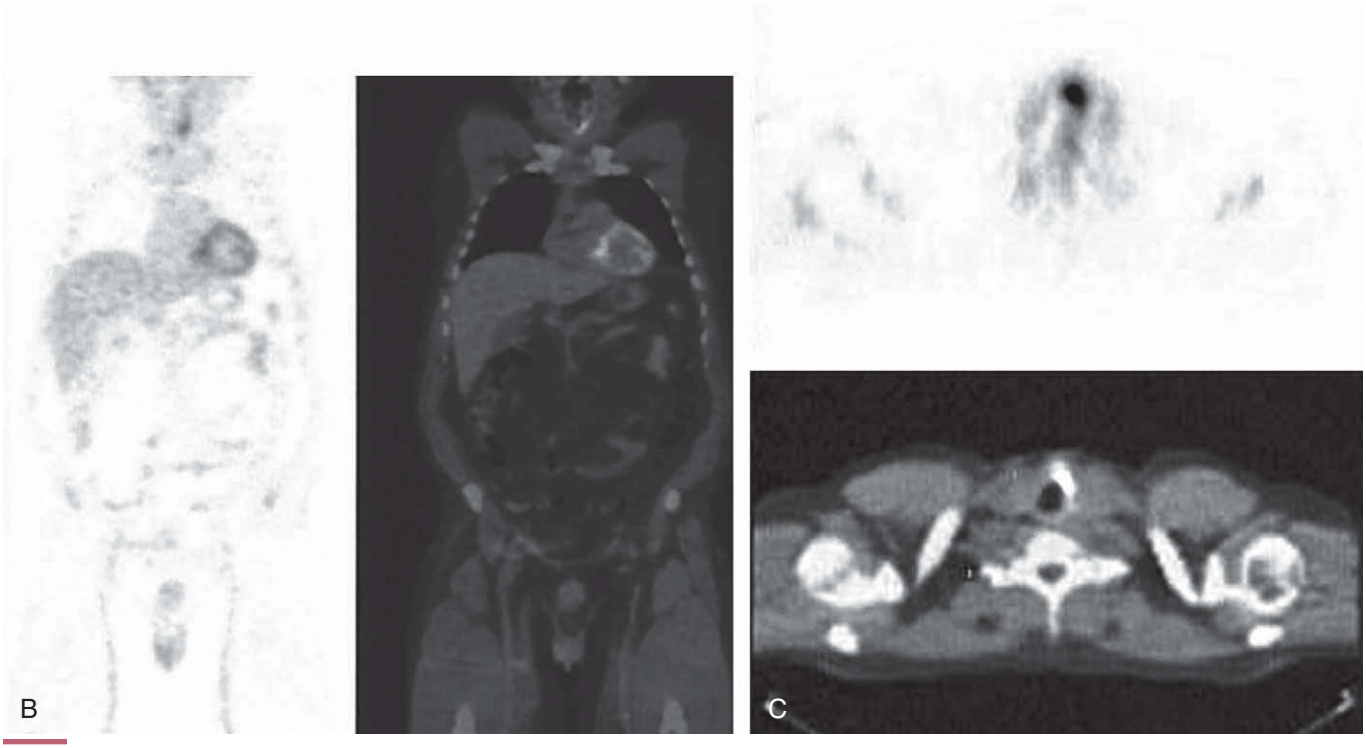


Figure 11-13. Recurrent glottic squamous-cell cancer previously treated with radiotherapy. **A,** T1-weighted, T2-weighted (STIR) and contrast enhanced, fat-saturated T1-weighted MRIs show mild fullness in the left true vocal cord without a discrete mass. It is impossible to differentiate post-therapy changes from the recurrent tumor. **B,** Coronal PET *(left)* and PET-CT *(right)* demonstrate increased metabolic activity in the left glottic and subglottic region. **C,** Axial PET *(above)* and PET-CT *(below)* show uptake anterior to the cricoid, compatible with extra-laryngeal involvement not visualized on the MRI (surgery-pathology proven).

Imaging Anatomy, Site-Specific Lesions, and Pseudotumors of Head and Neck

Spaces of Suprahyoid Neck

With the advent of cross-sectional imaging in radiology, first with CT and later with MRI, the radiologic interpretive approach changed from a pattern based on surgical compartmental anatomy to one dependent on fascial spaces. However, a combination of the two interpretive approaches, for example, parapharyngeal space at the nasopharyngeal level (with the compartmental designation serving as a modifier) may be more helpful in precisely defining a lesion location.

The head and neck region, the anatomic territory that extends from the skull base to the thoracic inlet, is best and most conveniently divided into the suprahyoid and infrahyoid neck with the hyoid bone serving as the divisional point.[15] Figures 11-14 through 11-16 demonstrate normal cross-sectional CT and MRI anatomy of the suprahyoid neck. The suprahyoid neck may be divided into a series of fascial spaces based on the division and layers of the superficial and deep cervical fascia. The superficial cervical fascia surrounds the face and neck, providing a fatty layer on which the skin is able to slide. The underlying deep cervical fascia is separated into three distinct layers: superficial (investing) layer, middle (visceral) layer, and deep (prevertebral) layer.

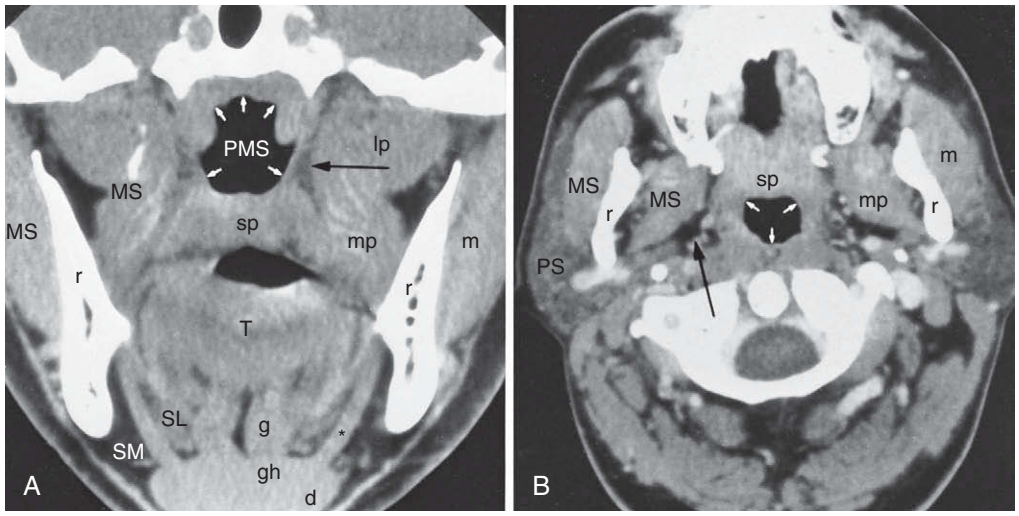


Figure 11-14. The normal computed tomography anatomy of suprahyoid neck. **A,** Coronal contrast-enhanced computed tomography (CECT) and, **B,** axial CECT demonstrate low-fat density of the parapharyngeal space *(arrow)*. Note its central position as a marker space. The following structures can be identified: anterior belly of digastric muscle (d), genioglossus muscle (g), geniohyoid muscle (gh), lateral pterygoid muscle (lp), masseter muscle (m), medial pterygoid muscle (mp), masticator space (MS), mylohyoid muscle *(asterisk)*, nasopharyngeal mucosal space (PMS, small arrows), parotid space (PS), ramus of mandible (r), sublingual space (SL), submandibular space (SM), soft palate (sp), and intrinsic tongue musculature (T).

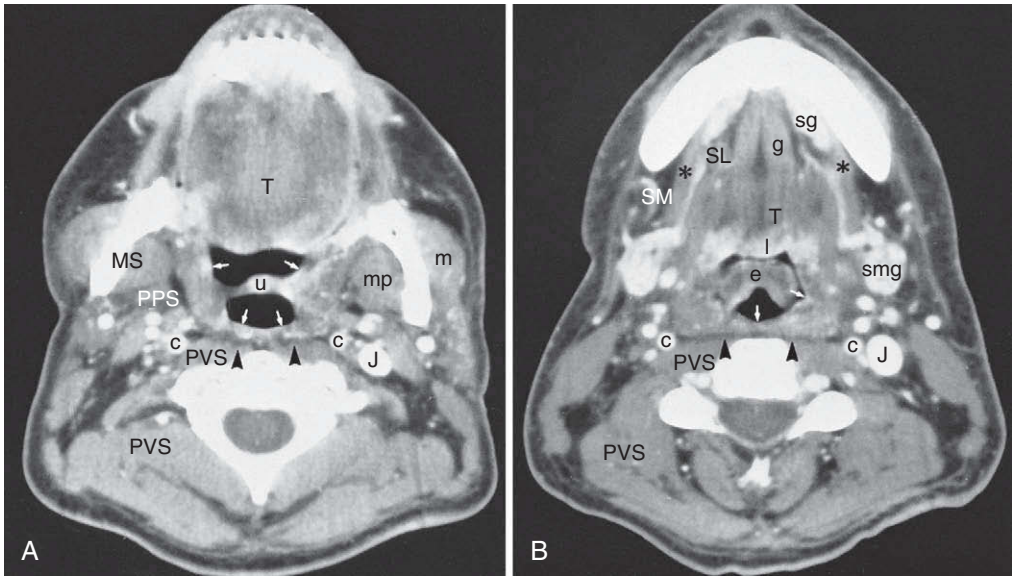


Figure 11-15. The normal computed tomography anatomy of sublingual space, submandibular space, and oral cavity. **A,** Axial contrast-enhanced computed tomography at superior and, **B,** inferior tongue levels, respectively. Note the following structures: internal carotid (c), epiglottis (e), genioglossus muscle (g), jugular vein (J), lingual tonsil (l), masseter muscle (m), medial pterygoid muscle (mp), masticator space (MS), mylohyoid muscle *(asterisk)*, pharyngeal mucosal space of oropharynx (*small arrows)*, prevertebral space (PVS), retropharyngeal space *(arrowheads)*, sublingual space (SL), submandibular space (SM), submandibular gland (smg), intrinsic musculature of tongue (T), and uvula of soft palate (u).

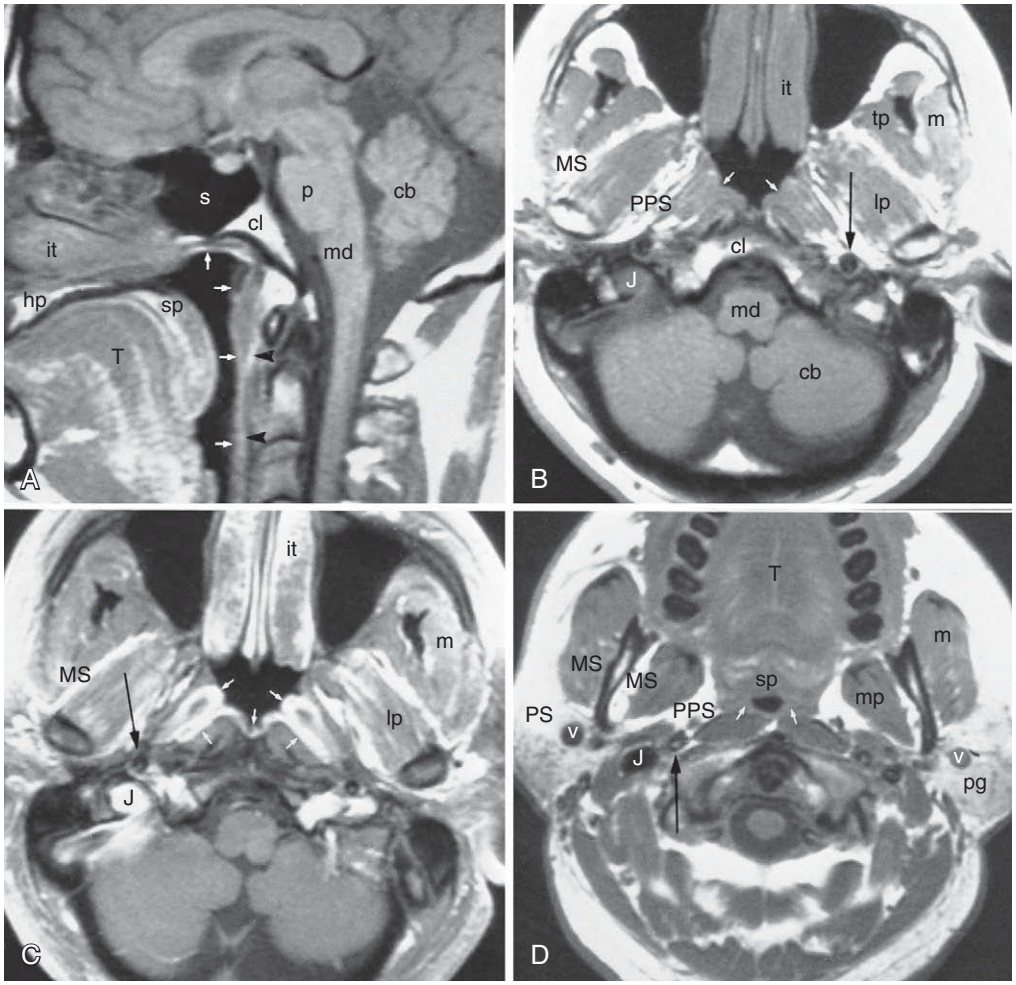


Figure 11-16. The normal magnetic resonance imaging anatomy of suprahyoid neck. **A,** Sagittal midline noncontrast T1-weighted image (T1WI). **B,** Axial noncontrast T1WI at the level of jugular foramen. **C,** Axial postgadolinium T1WI at the same level of **B** demonstrates enhancement of the nasopharyngeal mucosa and jugular veins. **D,** Axial noncontrast T1WI at the level of C2 vertebral body and mid tongue demonstrates high signal intensity of parapharyngeal space fat. The following structures are labeled: cerebellum (cb), clivus (cl), hard palate (hp), internal carotid artery *(arrow)*, inferior turbinates (it), jugular vein (J), lateral pterygoid muscle (lp), masseter muscle (m), medulla (md), masticator space (MS), nasopharyngeal mucosal space (*small arrows*), pons (p), parotid gland (pg), parapharyngeal space (PPS), parotid space (PS), retropharyngeal space *(arrowheads)*, sphenoid sinus (s), soft palate (sp), intrinsic musculature of tongue (T), temporalis muscle (tp), and retromandibular vein (v).

(Space limitations and the complexity of the fascial spaces do not allow for a detailed description or explanation of the deep cervical fascia.) Although not usually visualized on CT or MRI, these fascial layers divide the suprahyoid neck into distinct anatomic and surgically defined spaces:

1. Parapharyngeal space (PPS)
2. Pharyngeal mucosal space (PMS)
3. Parotid space (PS)
4. Carotid space (CS)
5. Masticator space (MS)
6. Retropharyngeal space (RPS)
7. Prevertebral space (PVS)
8. Oral cavity (OC)
9. Sublingual space (SLS)
10. Submandibular space (SMS)

Inflammatory and neoplastic disease, the major pathophysiologic processes of the head and neck territory, tend to grow and spread in the boundaries and confines of these fascial spaces.[16] Nevertheless, this approach based on the use of fascial anatomy allows delineation of specific anatomic spaces, with identification of disease-specific lesions for each of these spaces. As a consequence, a more accurate differential diagnosis and resulting final diagnosis are attained.

Parapharyngeal Space

The crucial anatomic center point to understanding suprahyoid anatomy is the parapharyngeal space (PPS). This fibrofatty fascial space extends from the skull base to the level of the hyoid bone and serves as a marker space around which the remaining fascial spaces are arranged. It contains fat, portions of the third division of cranial nerve V, the internal maxillary artery, the ascending pharyngeal artery, and the venous plexus. In the axial plane, this space has a triangular configuration and demonstrates bilateral symmetry. In the coronal plane, the

PPS has an hourglass shape, thicker at the skull base and hyoid level and thinner in the mid suprahyoid neck.

The PPS is clearly defined and located on both the axial and coronal planes with both CT and MRI.[17] With the former technique, the predominant fat content serves as a low-density marker between the medial muscles of deglutition found in the pharyngeal mucosal space and the muscles of mastication, located more laterally. With MRI, the PPS has bright signal intensity on T1WI (the scanning sequence that best highlights fat and muscle tissue differences). With longer TR times and more T2 weighting, this fatty space becomes less intense in signal.

Because this space is the epicenter around which the other fascial spaces are arranged, it serves as a potential marker or pivotal space. By noting the position and direction of displacement of the PPS, one can determine the epicenter and fascial space origin of a suprahyoid lesion. Because the PPS contains few structures from which lesions arise, most lesions found in this space have spread here secondarily from an adjacent fascial space.[18]

The fascial spaces that are centered about the parapharyngeal space include the pharyngeal mucosal space (PMS), the carotid space (CS), the parotid space (PS), the masticator space (MS), the retropharyngeal space (RPS), and the prevertebral space (PVS). Each space has well-defined anatomic boundaries, contains major structures of importance, and gives rise to pathologic processes that are site selective for that space. For consideration of pathologic processes in each fascial space, it is convenient to use the following outline: congenital, inflammatory, neoplastic (benign and malignant), pseudolesions, and miscellaneous. This approach, using these few disease categories, elicits most of the major lesions to be found in the head and neck and is used in the following discussion of suprahyoid and infrahyoid lesions.

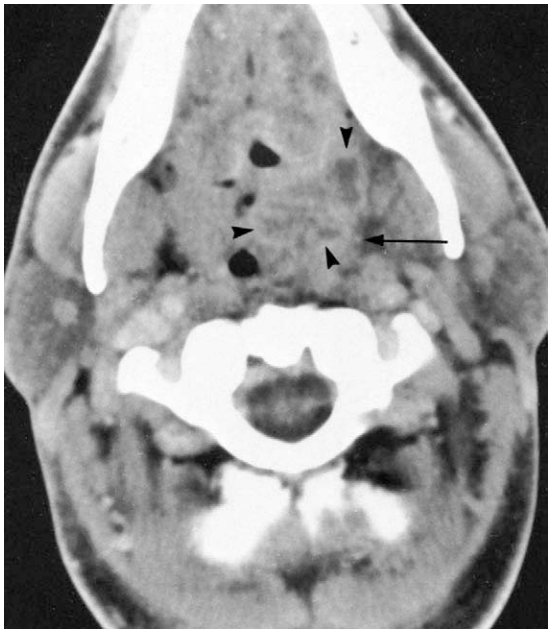


Figure 11-17. Tonsillar abscess. Axial contrast-enhanced computed tomography demonstrates a low-density left tonsillar lesion *(arrowheads)* with thin peripheral rim enhancement. The left tonsil is increased in size. Partially effaced left parapharyngeal space *(arrow)* is lateral in position.

Pharyngeal Mucosal Space

The PMS lies medial to the PPS and anterior to the PVS. It encompasses the mucosal surfaces of the inner boundaries of the nasopharynx and oropharynx and includes lymphoid (adenoidal) tissue, minor salivary glands, portions of the constrictor muscles, and muscles of deglutition. The medial portion of the eustachian tube passes through it. These structures lie medial to or on the airway side of the buccopharyngeal fascia. This fascial structure may be seen on MRI as a band of low signal intensity. On CECT or gadolinium-enhanced MRI studies, the overlying pharyngeal mucosa enhances.

The PMS extends from the skull base to the lower margin of the cricoid cartilage, extending into the upper portion of the infrahyoid neck. It encompasses the nasopharynx, oropharynx, and portions of the hypopharynx. Lesions in this space displace the PPS laterally.

In general, caution is used when interpreting the mucosal surfaces of the pharynx, oral cavity, and larynx. The normal mucosa is high signal on T2WI and STIR and enhances on postgadolinium T1WI (and with CECT). It may be confused with a superficial mucosal based malignancy. Likewise, a small superficial mucosal based tumor may be indistinguishable from the adjacent normal mucosa. The direct clinical examination of the mucosal surfaces is still superior to cross-sectional CT or MR imaging in detecting superficial tumor; however, both CT and MRI excel in detecting submucosal tumor and deep invasion. Mucosal irregularity and slight asymmetry are common, especially near the fossa of Rosenmüller (the lateral pharyngeal recesses of the nasopharynx), and care is taken in ascribing abnormality. Repeat studies with a modified Valsalva maneuver to distend the airway may be helpful. Involvement of the submucosal muscles and adjacent deep structures, such as the PPS, will confirm the presence of a suspected neoplastic mucosal lesion. Lymphoid (adenoidal) tissue is often hypertrophic and prominent, especially in children and young adolescents, and may encroach on the airway. On CT, lymphoid tissue is isodense to muscle. With MRI, it has a similar intensity to muscle on T1WI but has a bright signal on T2WI. It lies superficial to the buccopharyngeal fascia and is relatively homogeneous.

Inflammatory lesions of the PMS include pharyngitis, abscess (especially tonsillar abscess), and postinflammatory retention cysts (Fig. 11-17). Benign mixed salivary tumor is the most common benign neoplasm.

A Thornwaldt cyst is a common congenital lesion of the midline posterior nasopharyngeal mucosa and only rarely becomes secondarily infected. It is very bright on long TR sequences on MRI.

Squamous cell carcinoma (SCC), the most common tumor of the upper aerodigestive tract, originates from the PMS. The majority of lesions arise from squamous epithelium in the region of the lateral pharyngeal recess (Figs. 11-18 and 11-19). Small submucosal lesions may be missed on the clinical examination but may be detected with cross-sectional imaging. Involvement of the adjacent musculofascial spaces confirms the presence of a mucosal lesion. It may become large and lead to extensive invasion and destruction of the neighboring fascial spaces or extend medially to involve the PPS. With CT, SCC demonstrates inhomogeneous lesion enhancement, commonly with extension into adjacent spaces. With MRI, it is of intermediate intensity on T1WI and high intensity on T2WI and enhances after gadolinium infusion.[19] It may cause serous otitis media and mastoid cell opacification because of dysfunction of the eustachian tube from invasion or mass effect. Extension superior to the skull base is common. The foramen lacerum, foramen ovale, carotid canal, jugular foramen, and clivus may be affected. Perineural tumor spread along cranial motor nerve V is common and its presence should be diligently sought, especially if there is unilateral atrophy of the muscles of mastication innervated by the mandibular division of the fifth cranial nerve. Inferiorly, nasopharyngeal SCC may extend to involve the soft palate, tonsillar pillars, and nasal cavity. Asymptomatic cervical adenopathy with involvement of the superior internal jugular and spinal accessory lymph node chains is the presenting mode in more than 50% of patients. Lymph nodes are usually considered positive when larger than 1.5 cm in diameter. An enhancing lymph node rim with necrotic low-density center on CECT indicates neoplastic involvement. On MRI, lymph nodes have bright signal intensity on T2WI. On T1WI, after gadolinium administration, lymph node enhancement may be seen.

The extensive lymphoid tissue in this space is a source for development of non-Hodgkin's lymphoma (Fig. 11-20). Both SCC and lymphoma may have extensive lymph node involvement. The nodes associated with SCC commonly have necrotic centers, whereas those of lymphoma are usually noncavitary and homogeneous. Malignant

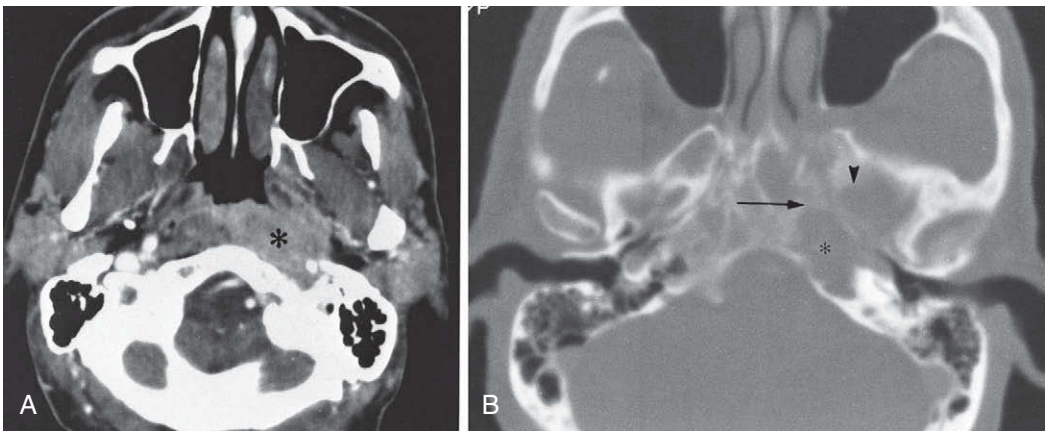


Figure 11-18. Nasopharyngeal carcinoma. **A,** Axial contrast-enhanced computed tomography (CECT) demonstrates enhancing lesion *(asterisk)* involving the pharyngeal mucosa space, retropharyngeal spaces, and prevertebral space. A tumor abuts the skull base. **B,** Axial CECT image with bone settings at the level of the skull base demonstrates a lytic destructive lesion involving the anteromedial left petrous bone *(asterisk)*, medial portion of greater sphenoid wing *(arrowhead)*, and adjacent clivus *(arrow)*.

Figure 11-19. Squamous cell carcinoma of oropharynx. Axial contrast-enhanced computed tomography demonstrates a mixed-density enhancing lesion *(asterisk)* in the right oropharynx. The tumor has extended posterolaterally to surround the carotid vessels *(arrow)*. Enhancing lymph node *(arrowhead)* with low-density necrotic center is noted posterior to the carotid space, lying just beneath the sternocleidomastoid muscle. Enhancement of the adjacent sternocleidomastoid muscle indicates muscle invasion.

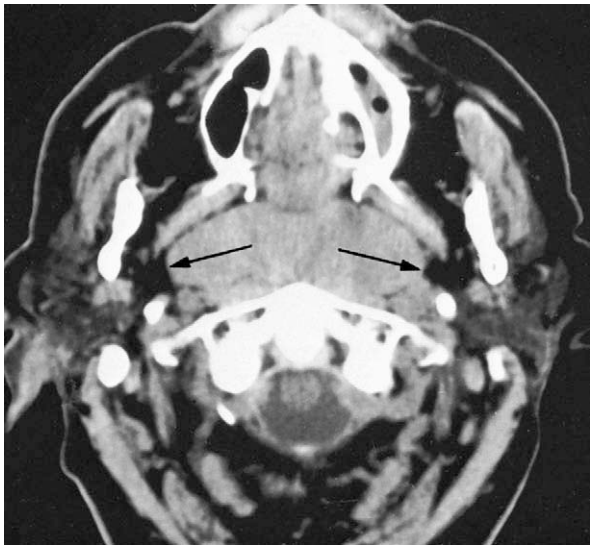


Figure 11-20. Nasopharyngeal lymphoma. Axial non-contrast computed tomography demonstrates a large homogeneous pharyngeal mucosal space with a nasopharyngeal mass lesion, displacing prevertebral and retropharyngeal spaces posteriorly. The lesion bulges into parapharyngeal space bilaterally *(arrows)*.

minor salivary gland tumors also occur in this space. These three malignant lesions are difficult to separate radiologically.

Parotid Space

The PS, the home of the parotid gland and the extracranial portion of the facial nerve, lies lateral to both the PPS and the CS and posterior to the masticator space. It extends superiorly from the level of the mid squamous temporal bone to the angle of the mandible inferiorly. It contains the parotid gland, multiple lymph nodes (within and outside the parotid gland parenchyma), the facial nerve, the retromandibular vein, and branches of the external carotid artery. The parotid gland overlies the posterior portion of the masseter muscle. Its deep retromandibular portion lies posterior to the mandible and lateral to the PPS and the CS. The posterior belly of the digastric muscle separates the PS from the CS.

Because of its high fat content, especially in the adult, the parotid gland parenchyma is frequently low density on CT but may vary and approach muscle density. It is high intensity on T1WI (slightly less than subcutaneous fat) and has decreased intensity on T2WI but often retains its bright T2 signal intensity relative to muscle. The retromandibular vein lies just posterior to the lateral margin of the mandibular ramus. The diagonal course of the facial nerve, paralleling a line drawn from the stylomastoid foramen to a point just lateral to the retromandibular vein, divides the parotid gland into superficial and deep portions. Although this is not a true anatomic division, it is useful for surgical planning. The facial nerve may be seen on some MRI studies. Its course must be considered and determined when removal of deep parotid lobe lesions is planned.

Lesions in the parotid space are usually surrounded by parotid gland tissue and are better defined with MRI than CT.[20] With NCCT, lesions are usually isodense to the normal gland or of increased density. With MRI, lesions are of muscle intensity on T1WI and usually hyperintense to normal parotid gland on T2WI.[17] When small, parotid

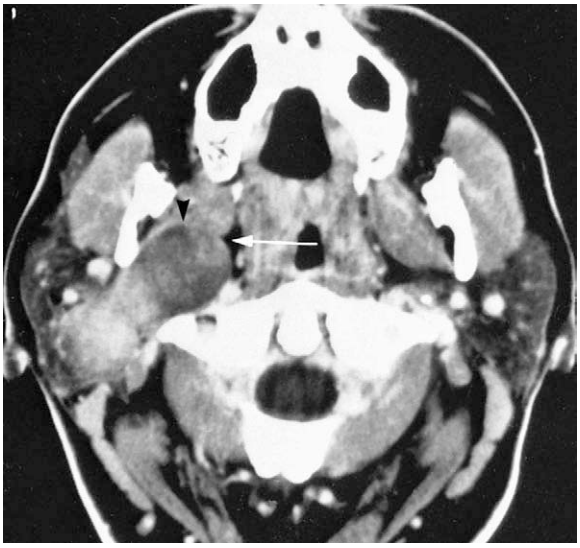


Figure 11-21. Benign pleomorphic adenoma of the right parotid gland. Axial contrast-enhanced computed tomography demonstrates a dumbbell-shaped tumor with enhancement of its superficial portion. Its deep portion is predominantly low density. Parapharyngeal space is displaced medially *(arrow)*. The lateral pterygoid muscle is indented and lies anteriorly *(arrowhead)*. The lesion has displaced the ramus of mandible anteriorly.

lesions tend to be homogeneous. With increase in lesion size, areas of hemorrhage, necrosis, and calcification may develop. If the lesion extends or originates from the deep portion of the gland, it displaces the PPS medially and occasionally anteriorly. Large lesions in the parotid gland proper will cause widening of the stylomandibular notch, the space between the posterior border of the mandible and the styloid process. Comparison with the contralateral side will make subtle widening of this space evident.[21] Deep lobe lesions, if large, may displace the carotid artery posteriorly. Benign lesions as a general rule are well defined. Malignant lesions have indistinct margins and may invade adjacent structures. Lesions in the PPS or CS may extend laterally into the parotid space, mimicking a parotid lesion clinically.

Congenital lesions of the PS include hemangioma, lymphangioma, and first and second branchial cleft cyst, the latter presenting as a cystic-appearing lesion with smooth walls.[22] Enhancing margins of the cyst indicate it is secondarily infected. Inflammatory disease may present as diffuse swelling or as a localized abscess. Infection of the adjacent skull base is best demonstrated with CT. Infection may occur secondary to calculus disease.

Calculi are also best demonstrated by sialography as intraluminal filling defects or by CT because of its tenfold higher sensitivity over plain films for detecting calcified calculi. Sialadenitis, autoimmune disease, and strictures are still best evaluated by conventional sialography, which best demonstrates ductal anatomy. Chronic sialadenitis will cause the affected parotid gland CT density to approach that of muscle. This appears as lower parotid gland signal on T1WI and brighter signal on T2WI than that of the contralateral parotid gland. Autoimmune diseases, such as Sjögren's syndrome, demonstrate bilateral parotid enlargement. Bilateral gland enlargement by benign lymphoepithelial cysts is seen in acquired immunodeficiency syndrome.

Benign pleomorphic adenoma (benign mixed tumor), the most common benign neoplasm of the parotid gland, is well defined and demonstrates variable degrees of contrast enhancement (Fig. 11-21). It is usually ovoid in configuration and may involve either the superficial or deep lobe of the parotid gland or, less commonly, both. Rarely, benign mixed tumors may arise from salivary rest tissue medial to the deep lobe and have a fat border on both their medial and lateral margins. Calcification is occasionally seen within the tumor. The tumor is hypointense on T1WI and hyperintense on T2WI. Both the superficial and deep lobes of the parotid gland may be involved, leading to a dumbbell configuration of the mass and associated widening of the stylomandibular notch.

Malignant lesions include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, and malignant mixed tumor (Fig. 11-22). High-grade malignant lesions have infiltrative borders. MRI is superior to CT for showing lesion margins and extent. Because of the abundant lymph node tissue within the parotid gland, lymph node involvement may be seen with non-Hodgkin's lymphoma, and metastatic involvement may be seen with SCC and malignant melanoma. Basal cell carcinoma of the adjacent ear and cheek may metastasize to the parotid lymph nodes.

Carotid Space

The CS—the space of vessels, nerves, and lymph nodes—lies posterior to the PPS, lateral to the retropharyngeal space, anterolateral to the prevertebral spaces, and medial to the PS and styloid process. The posterior belly of the digastric muscle separates the CS from the parotid space. The CS is formed from portions of all three layers of the deep cervical fascia. The CS extends from the temporal bone and base of the skull superiorly to the mediastinum inferiorly.[23] It contains the common carotid artery, its major divisions, the internal and external carotid artery, the jugular vein, cranial nerves IX to XII, sympathetic plexus, and lymph nodes. The jugular vein lies lateral and posterior to the carotid artery. The vagus nerve lies in the posterior groove between the two vessels. Cranial nerves IX, XI, and XII migrate to the anteromedial portion of the CS lower in the neck. Lesions of the CS displace the PPS anteriorly and, if large, may remodel the styloid process, displacing it anterolaterally.

Infection of the CS occurs most commonly secondary to spread of infection from adjacent fascial spaces. Reactive inflammatory lymph nodes, which are characteristically homogeneous and less than 1 cm in size, may be seen in any portion along the carotid space and be seen with such varied infectious processes as sinusitis, infectious mononucleosis, and tuberculosis. Suppurative lymph nodes may have low-density centers and may not be distinguished from malignant lymph nodes. Clusters or groups of lymph nodes lumped into large masses are not uncommon. Cellulitis causes a loss of normal soft tissue planes. Abscesses are characterized by focal fluid collections with enhancing margins.

On CECT, normal blood vessels demonstrate contrast enhancement. With dynamic CECT, a wash-in phase (early visualization of contrast) may be demonstrated within normal vessels and within the feeding or draining vessels of a mass, which further indicates the vascular etiology of a lesion. On MRI, blood vessels appear as circular or linear areas of flow void, because of flow of fast-moving blood. Turbulent or slow flow may lead to areas of mixed signal intensity. Vessel ectasia, dissection, aneurysm, pseudoaneurysm, and thrombosis may be diagnosed readily with either cross-sectional imaging technique. Assessment of adjacent sectional images will demonstrate a tubular configuration to the lesion. An ectatic carotid artery or an asymmetrically enlarged jugular vein may present clinically as a lateral neck mass, but is readily discernible radiologically. The right jugular vein is usually larger than the left and at times may be several times larger than the left, reflecting its greater venous drainage from the brain. Thrombosis, either arterial or venous in nature, appears as a linear or tubular intraluminal filling defect with or without associated mass effect on CECT because the vasa vasorum of the vessel wall enhances in a ringlike fashion.[24] Subacute thrombosis or vessel wall hemorrhage secondary to dissection or trauma will yield a bright signal on T1WI because of the T1 shortening effects of paramagnetic methemoglobin, a blood breakdown product.

Most mass lesions originating in the CS are of neoplastic origin. Most neurogenic tumors are schwannomas (Fig. 11-23). A schwannoma arises from Schwann cells that form the covering of nerves and most commonly originate from the vagus nerve (less commonly from the sympathetic plexus). A neurofibroma contains mixed neural and Schwann-cell elements and arises from the peripheral nerves. Neurofibromas are rare; when present, they usually are multiple and part of neurofibromatosis. Both tumors are well defined with CT, with either tumor having a low-density component because of fat infiltration. On

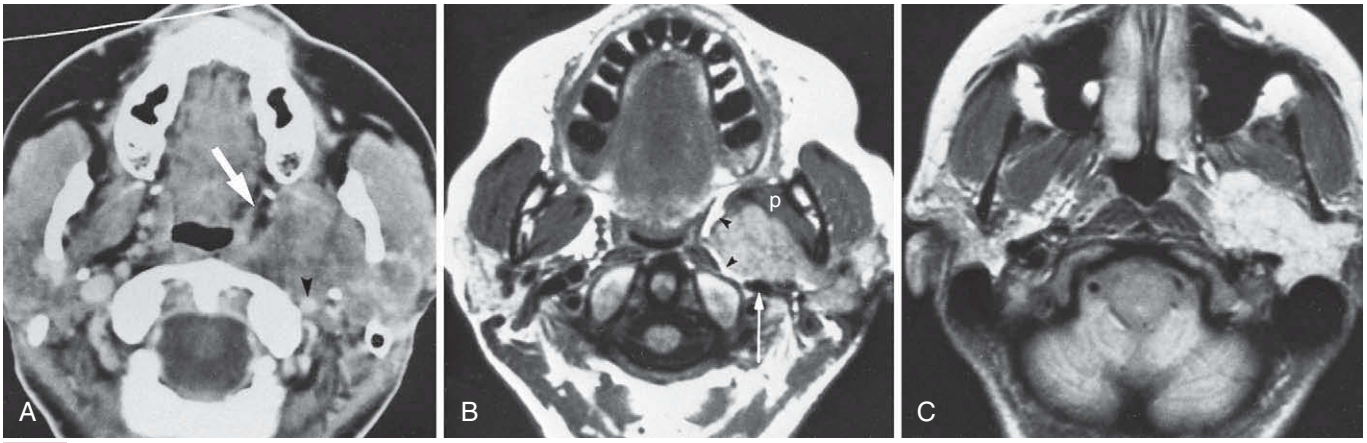


Figure 11-22. Acinic cell tumor of left parotid gland. **A,** Axial contrast-enhanced computed tomography at the level of C1 and C2 demonstrates an inhomogeneous irregular mass lesion involving both the superficial and deep portions of the left parotid gland. Lesion displaces the parapharyngeal space anteriorly and medially *(arrow)*. Stylomandibular distance is increased. Areas of patchy enhancement are noted around the periphery and throughout the lesion. Lesion has displaced the carotid artery posteriorly *(arrowhead)*. **B,** Axial T1-weighted image demonstrates superior contrast resolution of magnetic resonance imaging. Both superficial and deep portions of the lesion are well outlined. The margin of the lesion can be separated from the lateral pterygoid muscle (p), which is displaced anteriorly and laterally. PPS *(arrowheads)*, indicated by its high-intensity fat, is displaced medially. The flow void marks the site of the left carotid artery *(arrow)*. **C,** Axial spin density magnetic resonance imaging image at the level of the skull base demonstrates a well-defined lesion of increased signal intensity. Involvement of both superficial and deep lobes is well delineated.

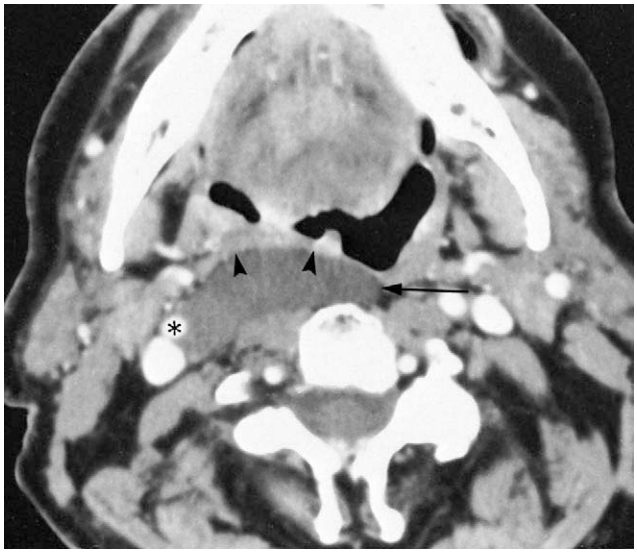


Figure 11-23. Left carotid space and retropharyngeal space ganglioneuroma. Axial contrast-enhanced computed tomography at the level of mid tongue demonstrates a C- or sausage-shaped, well-defined, low-density lesion in the anteromedial portion of the left carotid space. The lesion partially encases the left carotid artery *(asterisk)* and displaces it posterolaterally. It extends medially into the left retropharyngeal space *(arrow)*. Parapharyngeal space has been displaced laterally. Pharyngeal mucosal space *(arrowheads)* lies anterior to the lesion.

CECT, neurofibromas demonstrate variable degrees of enhancement. On MRI, they have a similar appearance. On both CT and MRI, most neural tumors have similar density and intensity characteristics to salivary gland tumors and often may not be differentiated. Neural tumors may have dense enhancement and simulate paragangliomas. On angiography, neuromas characteristically are hypovascular in contrast to paragangliomas, which are hypervascular. Neurogenic lesions arise posterior to the internal carotid artery and thus cause anterior displacement of the latter.

Paragangliomas—lesions developing from neural crest cell derivatives—may arise in the jugular foramen (glomus jugulare), along the course of the vagus nerve (glomus vagale), or at the carotid bifurcation (carotid body tumor) (Figs. 11-24 and 11-25). Paragangliomas are multiple in up to 5% of patients. The lesion is ovoid with smooth margins. Because of its marked hypervascularity, it is densely enhancing on CT. Angiography reveals a very vascular tumor with dense capillary staining. At the skull base, it erodes the jugular spine and causes permeative bone erosion of the jugular foramen in contradistinction to a schwannoma, which causes a smooth expansion with intact cortical margins. A jugular foramen paraganglioma may extend into the temporal bone or infiltrate through the skull base, presenting as a posterior fossa mass. In the midneck, a paraganglioma causes characteristic displacement of the carotid artery anteriorly and the jugular vein posterolaterally. At the carotid bifurcation, a lesion causes splaying of the internal and external carotid arteries. On MRI, it is recognized by its hypervascularity, characterized by multiple areas of signal void and flow-related enhancement from enlarged feeding and draining vessels.[25]

Lymph node involvement in the CS may be seen most commonly with metastases from SCC or as part of a general involvement by non-Hodgkin's lymphoma. Lymph node involvement may be the initial manifestation of squamous cell carcinoma. Extracapsular spread of disease may occur. Complete encasement of the carotid artery (carotid fixation) may indicate inoperability. However, the carotid artery may be sacrificed at operation if the patient successfully tolerates a carotid balloon occlusion test. Metastatic lymph nodes are characteristically inhomogeneous, especially after contrast enhancement.

Masticator Space

The MS, the space of the muscles of mastication and the posterior portion of the mandibular ramus, lies anterior to the PS and is separated from the muscles of deglutition in the pharyngeal mucosal space by the parapharyngeal space. It contains the masseter, temporalis, and medial and lateral pterygoid muscles, motor branch of the third division of cranial nerve V, inferior alveolar nerve, internal maxillary artery and its branches, pterygoid venous plexus, and the ramus and posterior body of the mandible. It includes the temporal fossa (suprazygomatic MS) superiorly, encompasses the zygomatic arch, and extends inferiorly to include the infratemporal fossa and structures on both sides of the mandible. A mass in the MS displaces the PPS posteriorly and medially.

Infection (cellulitis, abscess, osteomyelitis) may involve the mandible or the muscles of mastication. Extension through the skull base or involvement of the suprazygomatic masticator space may occur and

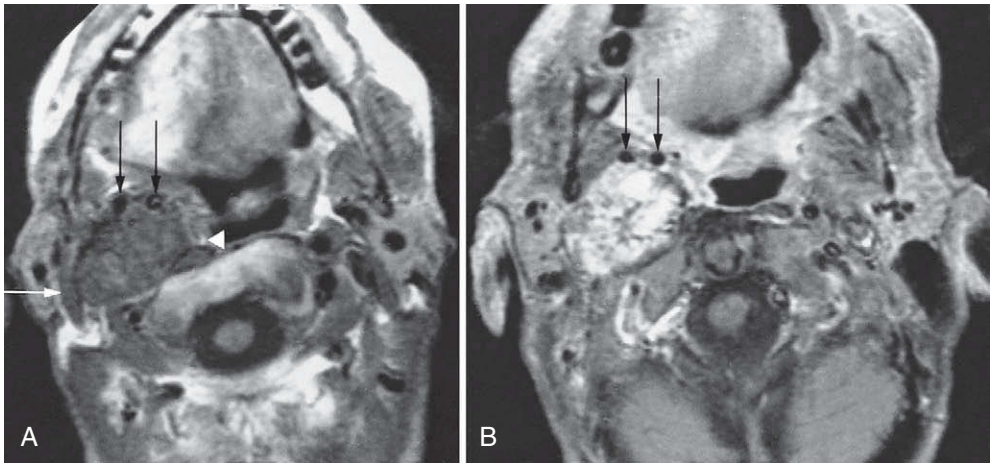


Figure 11-24. Glomus vagale (paraganglioma) of right carotid space. **A,** Axial T1-weighted image (T1WI) at the level of C2 demonstrates a mixed-density, predominantly low-density lesion involving the posterior aspect of the left carotid space. The lesion displaces the posterior belly of the digastric muscle laterally *(white arrow)* and the internal and external carotid arteries anteriorly *(black arrows)*. Parapharyngeal fat is displaced medially *(arrowhead)*. The lesion bulges into the medial aspect of the airway. The small areas of punctate low intensity noted along the margin and in the anterior portion of the lesion represent the tumor vessel flow voids. **B,** Axial T1WI at the same level postgadolinium injection demonstrates dense patchy enhancement of the lesion. Again noted are multiple punctate vascular flow voids within the lesion and around the periphery. Carotid vessels *(arrows)* are noted overlying the anterior lesion margin.

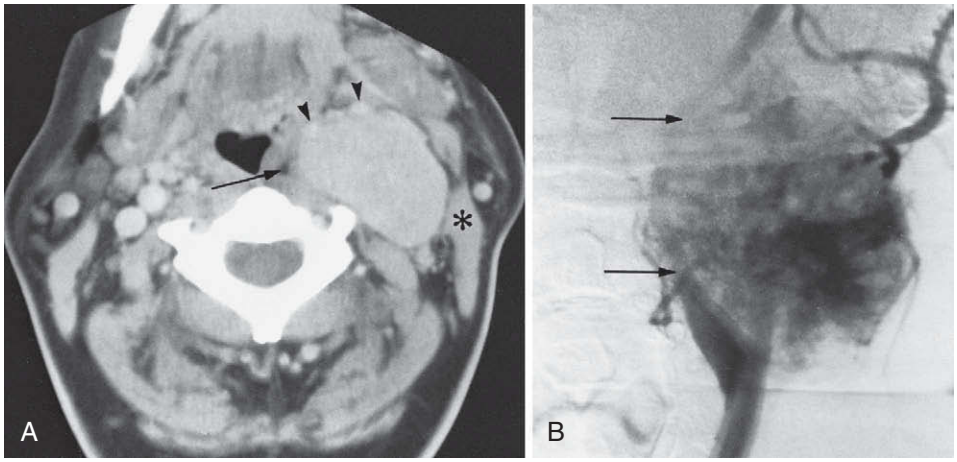


Figure 11-25. Glomus vagale of left carotid space. **A,** Axial contrast-enhanced computed tomography at the level of mid tongue demonstrates a relatively homogeneous, well-defined enhancing lesion in the left carotid space. Carotid vessels lie on the anteromedial margin of the lesion *(arrowhead)*. Parapharyngeal space is displaced medially *(arrow)*. The lesion lies deep to the sternocleidomastoid muscle *(asterisk)*. **B,** Anteroposterior digital subtraction angiogram demonstrates a densely vascular staining tumor displacing the internal carotid artery medially *(arrows)*. Vascularity and dense tumor stain indicate the lesion is paraganglioma.

should be ruled out (Fig. 11-26). Abscesses commonly arise from an odontogenic focus or from poor dentition. The bone changes of osteomyelitis are best demonstrated with CT.

Benign lesions include hemangioma and lymphangioma (Fig. 11-27). Nasopharyngeal angiofibroma, a tumor of young adolescent males, arises in the pterygopalatine fossa and commonly extends into the masticator space (Fig. 11-28). Primary bone neoplasms may arise from the mandible. Chondrosarcoma and osteosarcoma present with chondroid calcification and new bone formation, respectively. The bone lesion is characteristically muscle intense on T1WI and hyperintense with T2WI. Postgadolinium T1WI demonstrates extensive enhancement. An infiltrating mass with mandibular destruction may be indistinguishable from metastatic disease. Non-Hodgkin's lymphoma may present with bone involvement, with a soft tissue mass, or as a lymph node mass. SCC presents as an infiltrating mass and occurs secondary to extension from a neighboring fascial space (Fig. 11-29). Perineural spread of tumor is common in the MS. The fifth nerve should be assessed for thickening and enhancement along its course as it passes from the brainstem to the cavernous sinus, through the foramen ovale, and eventually below the skull base as it passes inferiorly to innervate the individual muscles of mastication (Fig. 11-30). The foramen ovale may be increased in size, and a tumor may be found within the cavernous sinus. Tumor involvement of the inferior alveolar nerve may cause erosion, irregular enlargement, or destruction of the inferior alveolar canal of the mandible.[26]

Pseudotumors may mislead the unwary. An accessory parotid gland overlying the anterior border of the masseter muscle or asymmetric enlargement of the parotid gland may simulate tumor. In both situations the parotid gland variant retains MRI signal characteristics identical to the normal parotid gland. Hypertrophy of the masseter muscle may occur secondary to teeth grinding, mimic a mass lesion, or be bilateral. If the fifth cranial nerve is injured or invaded by a tumor resulting in denervation of the muscles, ipsilateral atrophy of the muscles of mastication and fat infiltration ensue. The normal contralateral muscle group may be incorrectly considered enlarged and misinterpreted as tumor involvement.

Retropharyngeal Space

The RPS, a potential space between the middle and deep layers of the deep cervical fascia, lies posterior to the pharyngeal mucosal space, anterior to the PVS, and medial to the carotid space. It extends from the skull base superiorly to the T3 level of the upper mediastinum inferiorly.[27] The importance of the RPS derives from its potential to serve as a passageway for infection to spread among the head, neck, and mediastinum. Its contents are fat and lymph nodes, the principal nodes being the nodes of Rouvière (the classic lateral retropharyngeal nodes) and the medial retropharyngeal nodes. This nodal group is commonly involved in children, and up to 1 cm in size is considered normal. But a node larger than 5 mm is viewed with suspicion in an adult. A mass lesion in the RPS will displace the PPS anterolaterally. Infection, either pharyngitis or tonsillitis, may give RPS lymph node involvement. Diffuse cellulitis or abscess may occur, the latter usually secondary to infection of the pharyngeal mucosal space or prevertebral space. Infection or mass in the lateral alar portion of the infrahyoid RPS may have a "bow-tie" appearance on axial imaging (Fig. 11-31). SCC may invade the RPS directly or may present solely with lymph node involvement. The pattern is one of inhomogeneous enhancement, commonly with necrotic low-density centers. With non-Hodgkin's lymphoma, lymph nodes are homogeneous and multiple, commonly involving more than one of the fascial spaces.

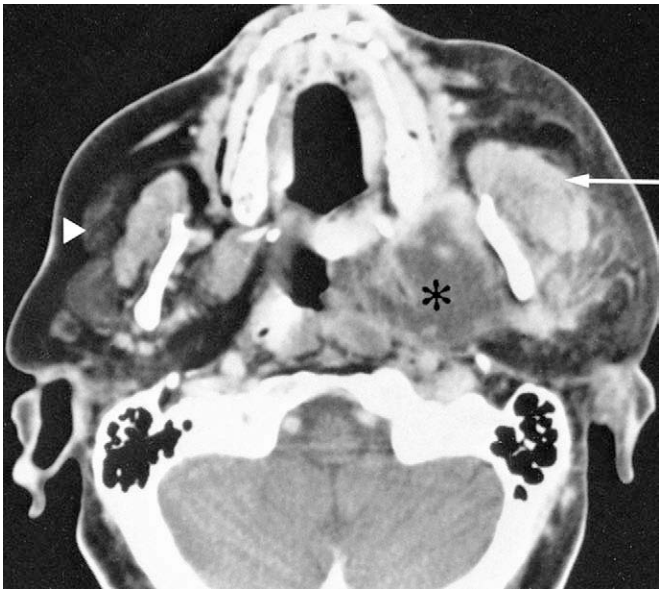


Figure 11-26. Left masticator space abscess. Axial contrast-enhanced computed tomography at the level of the superior alveolar ridge demonstrates a low-density lesion *(asterisk)* in the medial aspect of the left masticator space, involving the left lateral pterygoid muscle. The abscess is surrounded by a rim of irregular enhancement. Edema has infiltrated and obscured the parapharyngeal space. Left masseter muscle *(arrow)* is thickened and edema is present in the soft tissue planes, lateral to the masseter muscle and in the buccal space anteriorly. Note the accessory parotid gland overlying the right masseter muscle *(arrowhead)*.

Prevertebral Space

The PVS, also defined by the deep layers of the deep cervical fascia, is divided into anterior and posterior compartments. The former encompasses the anterior cervical vertebral bodies, extending from one transverse process to another. The posterior compartment surrounds the posterior spinal elements. The PVS contains the prevertebral, scalene, and paraspinal muscles, the brachial plexus, the phrenic nerve, the vertebral body, and the vertebral artery and vein. Similar to the anatomy of the RPS, the PVS extends from the skull base superiorly to the mediastinum inferiorly.

The PVS lies directly posterior to the RPS and posteromedial to the carotid space. An anterior compartment PVS mass causes thickening of the prevertebral muscles and displaces the prevertebral muscles and the PPS anteriorly. A mass in the posterior compartment of the PVS displaces the paraspinous musculature and the posterior cervical space fat laterally, away from the posterior elements of the spine. Infection and malignant disease, the common disease processes of the PVS, usually involve the vertebral body.

Infection, including tuberculosis and bacterial pathogens, characteristically involves the vertebral body, as well as the adjacent intervertebral disc space. Benign processes, although much less common, include chordoma, osteochondroma, aneurysmal bone cyst, giant cell tumor, and plexiform neurofibroma. Malignant disease processes include metastatic disease, leukemia, lymphoma, and direct invasion by SCC. Vertebral body destruction with associated soft tissue mass may be seen. The spinal canal and dural sac may be compromised.

Oral Cavity

The oral cavity, the space of the anterior two thirds of the tongue and the floor of the mouth, lies below the hard palate, medial to the supe-

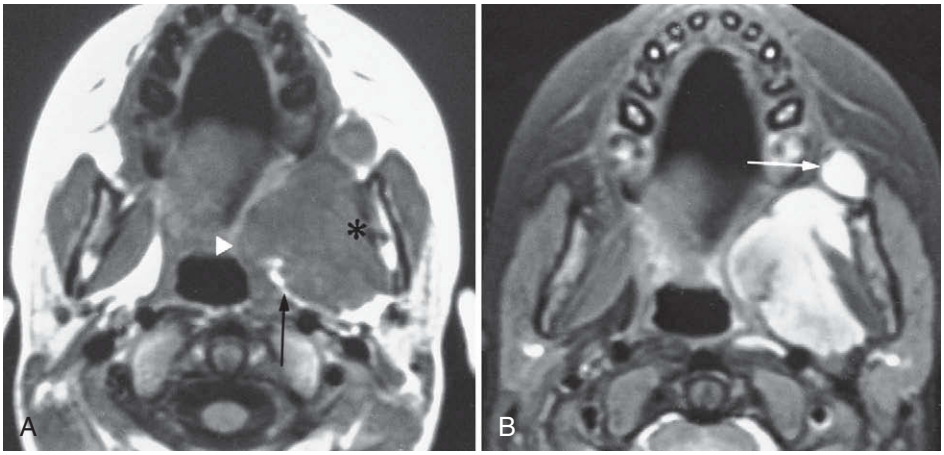


Figure 11-27. Lymphangioma of left masticator space. **A,** Axial T1-weighted image at the level of the base of the tongue and tonsillar region of the oropharynx demonstrates an inhomogeneous low-density soft tissue mass involving the left lateral pterygoid muscle *(asterisk)*. It displaces parapharyngeal space medially and anteriorly *(arrow)*. The mass extends to the anterior medial wall of the left oropharynx *(arrowhead)*. **B,** Axial spin density image with fat suppression demonstrates a lesion with bright signal intensity. The lesion margins are now better defined. The lesion can now be separated from the lateral pterygoid muscle. The lesion abuts the anteromedial wall of oropharynx. Anteriorly, the lesion extends into the buccal space *(arrow)*, anterior to the cortical margin of mandible.

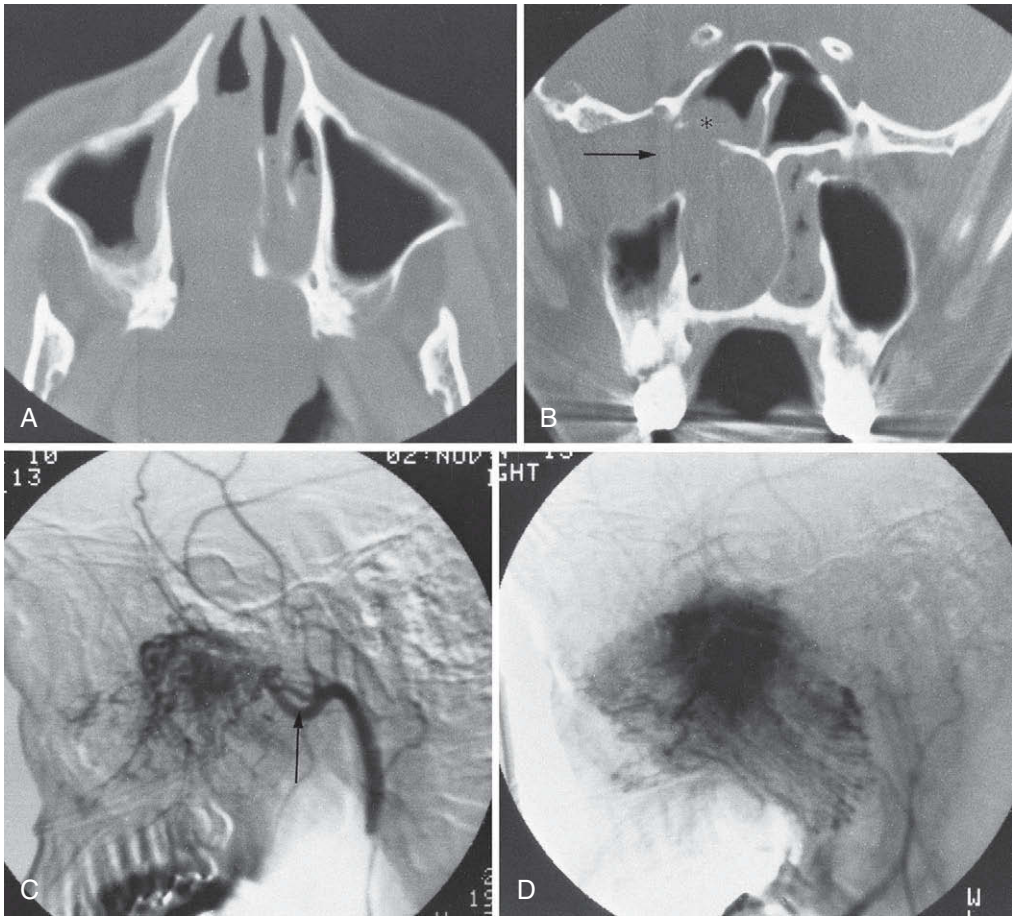


Figure 11-28. Nasopharyngeal angiofibroma. **A,** Axial noncontrast computed tomography (NCCT) demonstrates a homogeneous soft tissue mass enlarging the right nasal aperture. A large component of the tumor projects posteriorly into the nasopharynx and oropharynx. **B,** Coronal NCCT also demonstrates the complete opacification and expansion of the right nasal aperture by a soft tissue mass. The tumor extends into and widens the right infraorbital fissure *(arrow)*. The tumor *(asterisk)*, having destroyed right floor, is present in the sphenoid sinus. **C** and **D,** Lateral subtraction angiograms (early arterial and capillary phase) demonstrate a vascular mass in the nasopharynx and nasal aperture. Internal maxillary artery *(arrow)* gives rise to leash of tumor vessels. Dense tumor stain is noted in the capillary phase.

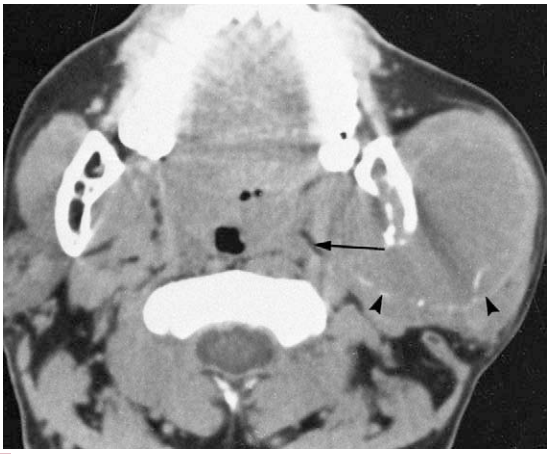


Figure 11-29. Squamous cell carcinoma of mandibular ramus. Axial contrast-enhanced computed tomography at the level of C2 demonstrates a large soft tissue tumor destroying the central portion and medial margin of the left mandibular ramus with an extension of the soft tissue tumor into the masseter and lateral pterygoid muscles. Parapharyngeal space has been displaced medially *(arrow)*. Thin rim of circular enhancement is noted posteriorly and laterally *(arrowheads)*.

rior and inferior alveolar ridge and teeth, anterior to the oropharynx, and superior to the mylohyoid muscle, the muscle stretching between the inferomedial margins of the mandible. The oral cavity is separated from the oropharynx posteriorly by the circumvallate papillae, tonsillar pillars, and soft palate. The oral cavity includes the oral tongue (the anterior two thirds of the tongue), whereas the oropharynx contains the base of the tongue (the posterior one third of the tongue), the soft palate, the tonsils, and the posterior pharyngeal wall.

The oral cavity can be divided into two major spaces, the sublingual space (SLS) and the submandibular space (SMS). The mylohyoid muscle, which constitutes the floor of the mouth, is the boundary marker between these two spaces. Other areas of the oral cavity include the floor of the mouth, oral tongue, hard palate, buccal mucosa, upper alveolar ridge, lower alveolar ridge, retromolar trigone, and lip.

Most masses in the oral cavity and oropharynx are amenable to direct clinical assessment. Mucosal lesions are readily visualized. The purpose of sectional imaging is to evaluate the degree of submucosal involvement. The majority of neoplasms of the oral cavity are readily detected on clinical examination. SCC accounts for approximately 90% of oral cavity and oropharyngeal neoplasms (Figs. 11-32 through 11-34). Cross-sectional imaging has an important role to play in estimation of tumor size, identification of tumor invasion, and assessment of nodal metastasis.

Congenital lesions include lingual thyroid and cystic lesions (epidermoid, dermoid, and teratoid cysts). Most infections of the oral cavity are dental in origin. Dental infections anterior to the second

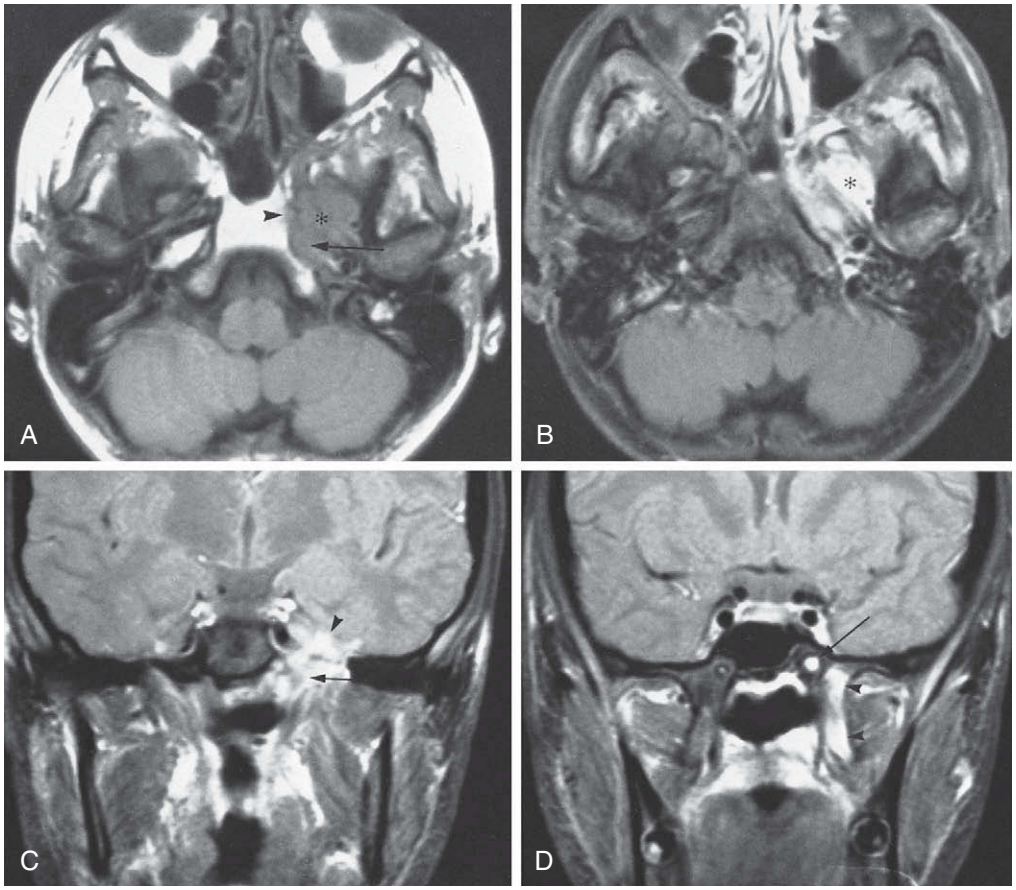


Figure 11-30. Adenoid cystic carcinoma of masticator space invading left skull base. **A,** T1-weighted (T1WI) magnetic resonance image demonstrates a low-density, well-defined lesion *(asterisk)* abutting the lateral border of the clivus and destroying the medial apex of the left petrous temporal bone *(arrow)*. Lateral cortical margin of the clivus has been eroded *(arrowhead)*. **B,** Axial postgadolinium fat-suppressed T1WI demonstrates diffuse patchy enhancement of the left middle fossa lesion *(asterisk)*. On this sequence, the normal high signal intensity of fat has been suppressed. **C,** Coronal postgadolinium fat-suppressed spin density image demonstrates an enhancing tumor *(arrowhead)* below the skull base with the extension through the foramen ovale into the left middle fossa *(arrow)*. **D,** Coronal spin density with fat suppression postgadolinium infusion demonstrates an enhancing tumor in the expanded vidian canal *(arrow)* and pterygoid fossa *(arrowheads)*.

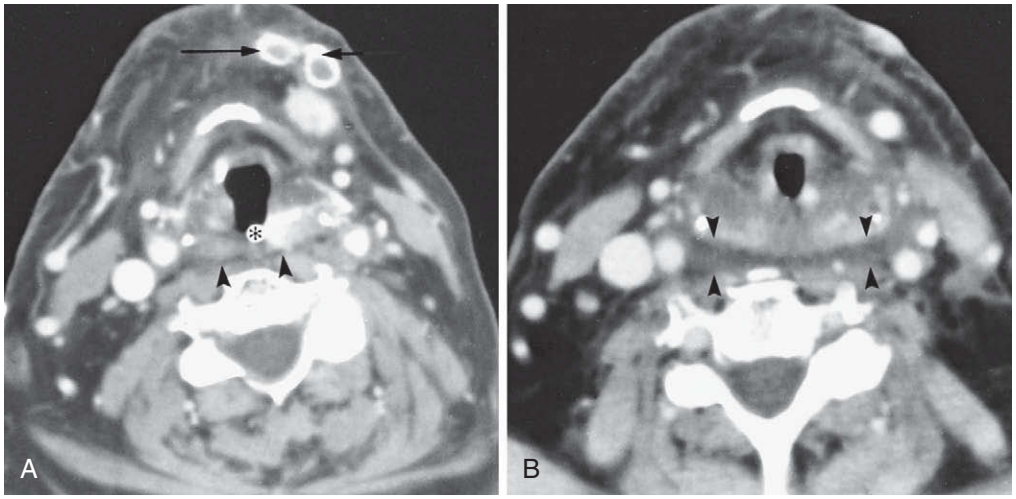


Figure 11-31. Retropharyngeal space (RPS) edema and abscess. **A,** Axial contrast-enhanced computed tomography (CECT) at the level of the superior margin of the hyoid bone demonstrates a nasogastric tube *(asterisk)* in the posterior wall of the oropharyngeal airway and mild thickening of the lateral wall of the larynx. RPS is normal *(arrowhead)*. Two lymph nodes *(arrows)* with rim enhancement lie anterior to the left submandibular gland. **B,** Repeat axial CECT at the same level 6 months later demonstrates a well-defined "bow-tie" appearance of edema in the RPS *(arrowheads)*.

molar tend to involve the sublingual space and lie superior to the mylohyoid muscle. Infections of the posterior molars usually involve the SMS and lie inferior to the mylohyoid muscle. Knowledge of which space is involved is crucial to plan adequate surgical drainage.

Sublingual Space

The SLS is located in the anterior tongue, lateral to the intrinsic muscles of the tongue (genioglossus and geniohyoid) and superior and medial to the mylohyoid muscle. Anteriorly, it extends to the genu of the mandible and, posteriorly, it connects freely with the SMS at the posterior margin of the mylohyoid muscle. It contains the anterior portion of the hyoglossus muscle, the lingual nerve (sensory division of cranial nerve V), the chorda tympani branch of cranial nerve VII, the lingual artery and vein, the deep portion of the submandibular glands and ducts, and the sublingual glands and ducts.

Congenital lesions of the sublingual space include epidermoid, dermoid, lymphangioma, and hemangioma. Lingual thyroid tissue will result if there is failure of normal descent of developing thyroid tissue from the base of the tongue into the lower neck. On CT, the lingual thyroid is midline in the posterior portion of the tongue and demonstrates dense contrast enhancement. Nuclear medicine thyroid scans demonstrate functioning thyroid tissue.

Cellulitis and abscess may occur secondary to dental or mandibular infections or arise as a consequence of calculus disease of either the submandibular or sublingual glands. Abscess is characterized by central areas of low density with or without boundary enhancement (Fig. 11-35). As with parotid gland calculi, CT readily identifies calcified stones and demonstrates bone destruction and sequestra of mandibular osteomyelitis. Ranula, a postinflammatory retention cyst of the sublingual gland, presents as a cystic low-density lesion. As it enlarges, it extends posteriorly and inferiorly into the submandibular space, where it is referred to as a "diving ranula" (Fig. 11-36).

SCC, the most common malignancy of the SLS, may spread from the oropharynx, oral cavity, alveolar ridge, or anterior portion of the tongue. A mass with irregular areas of enhancement, ulceration, central necrosis, and lymph node involvement is characteristic. Normal fat planes may be obscured. Tumor spread across the midline of the tongue, along the lingual or mandibular nerve, or invasion of the cortex or medulla of the mandible is an important finding that alters treatment planning.

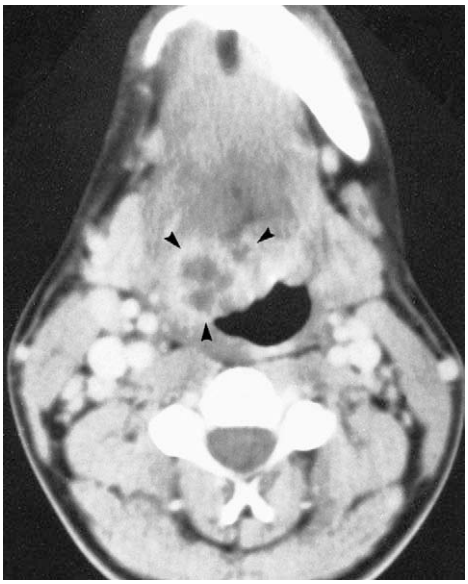


Figure 11-32. Right base of tongue and tonsillar abscess. Axial contrast-enhanced computed tomography of the suprahyoid neck demonstrates an inhomogeneous mixed low-density enhancing mass *(arrowheads)* in the base of the tongue and in the right tonsillar region. Low-density area of the lesion indicates pus within the abscess.

Submandibular Space

The SMS lies inferior and lateral to the SLS. It is located inferior to the mylohyoid bone and superior to the hyoid bone. It contains the anterior belly of the digastric muscle, fat, submandibular and submental lymph nodes, the superficial portion of the submandibular gland, the inferior portion of the hypoglossal nerve, and the facial artery and vein.

Congenital lesions are not uncommon and include second branchial cleft cyst, thyroglossal duct cyst, and cystic hygroma (lymphangioma). Branchial cleft cyst occurs most commonly at the angle of the mandible, posterior to the submandibular gland, anterior to the sternocleidomastoid muscle, and anterolateral to the carotid space (Fig. 11-37). It may have an associated fistula or sinus tract. Thyroglossal duct cysts are midline in location and are found anywhere

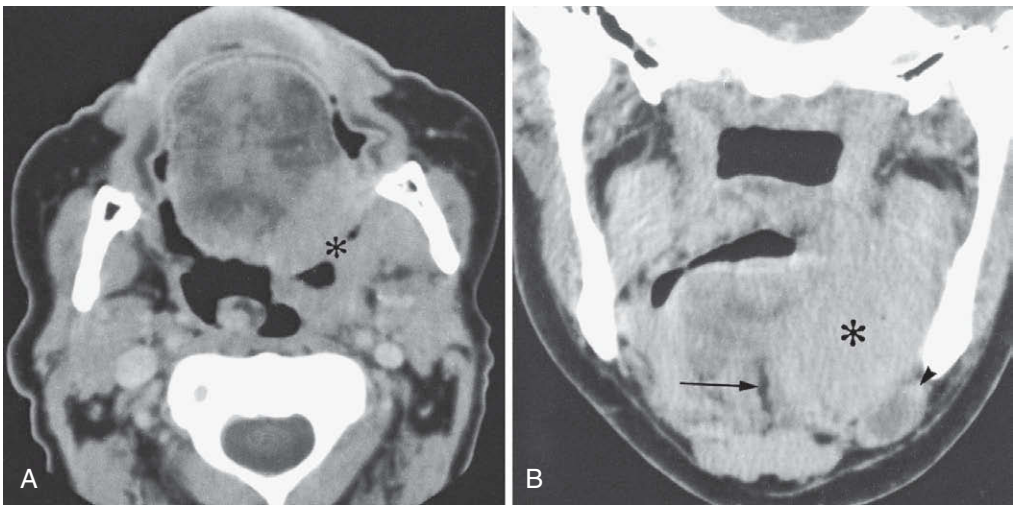


Figure 11-33. Squamous cell carcinoma of the base of tongue and the floor of the mouth. **A,** Axial contrast-enhanced computed tomography (CECT) at the level of the mid tongue demonstrates a homogeneous lesion *(asterisk)*, isodense relative to the muscles of mastication, involving lateral and posterior margins of the left side of tongue, left lateral pterygoid muscle, and tonsillar region of oropharynx. **B,** Coronal CECT demonstrates a homogeneous mass involving the lateral portion of the tongue, extending from the floor of mouth inferiorly to the tonsillar region superiorly *(asterisk)*. Midline septum *(arrow)* of the tongue is displaced laterally. Necrotic lymph node *(arrowhead)* lies inferior to the tongue.

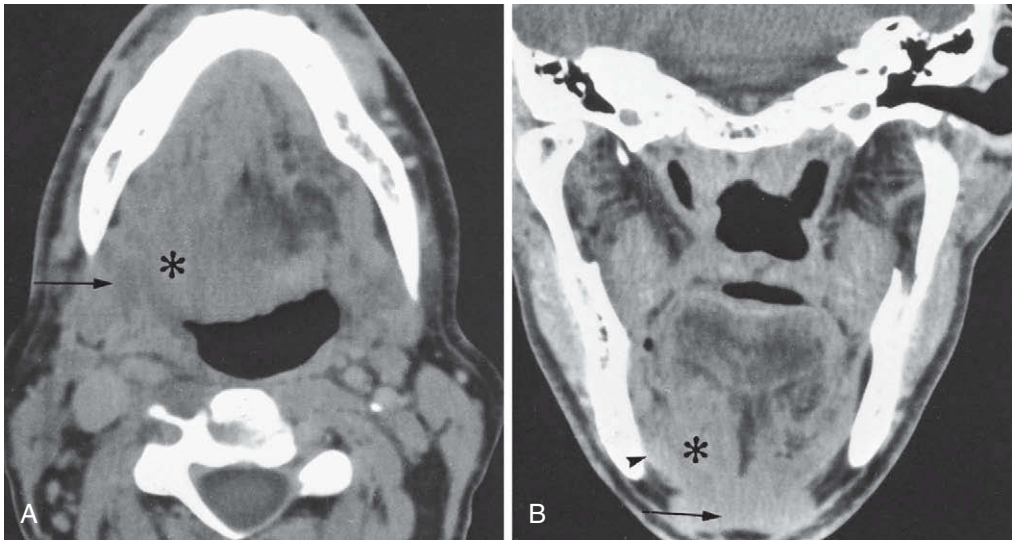


Figure 11-34. Non-Hodgkin's lymphoma of the base of tongue and the floor of the mouth. **A,** Axial contrast-enhanced computed tomography (CECT) at the midlevel of the tongue demonstrates an enlargement of the right side of the tongue by a homogeneous mass lesion *(asterisk)*, isodense to the normal tongue musculature. Submandibular space *(arrow)*, located more laterally, is also involved. **B,** Coronal CECT demonstrates homogeneous involvement of the right inferior lateral base of the tongue *(asterisk)*, mylohyoid muscle *(arrowhead)*, and floor of the mouth. Lesion lies above the anterior belly of digastric muscle *(arrow)*. Homogeneous nature of the lesion favors lymphoma.

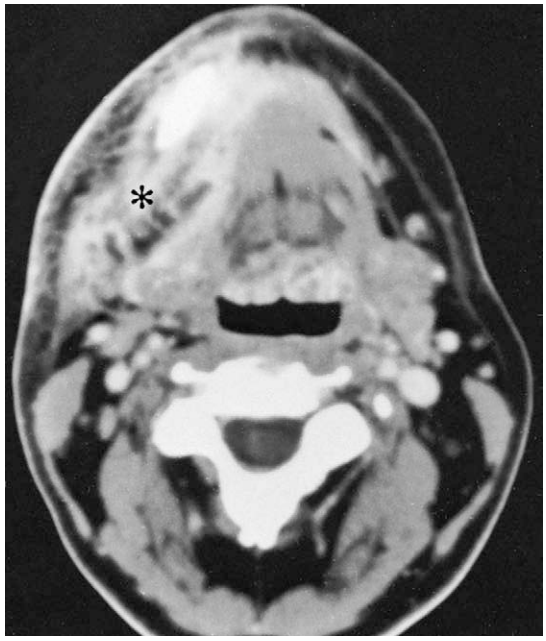


Figure 11-35. Submandibular abscess and cellulitis. Axial contrast-enhanced computed tomography demonstrates a mixed low-density and enhancing lesion *(asterisk)* involving the right submandibular space (SMS). Abscess displaces the midline structures of the tongue to the left. Edema extends laterally from the SMS into overlying soft tissues. Fat is of increased density because of infiltration by edema.

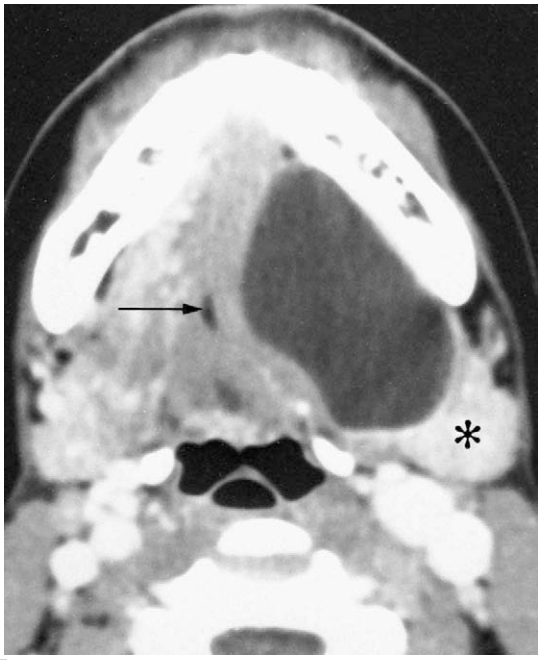


Figure 11-36. Ranula of left lingual and submandibular space. Axial contrast-enhanced computed tomography at the level of the body of the mandible demonstrates a large, low-density lesion with well-defined margins involving both sublingual and submandibular space. Lesion displaces the midline tongue structures *(arrow)* to the right. Submandibular gland is displaced posteriorly and laterally *(asterisk)*.

from the tongue base to the midportion of the thyroid gland. Cystic hygroma, a malformation of lymphatic channels, is a multilocular fluid density lesion that may involve both the SLS and SMS in the adult.

Ranula, a retention cyst of the sublingual gland, commonly extends into and may predominantly involve the SMS. It is unilocular in configuration. Its tail of origin should be carefully searched for in the SLS because this will aid in establishing its origin and diagnosis.

Benign tumors include benign mixed cell tumor, lipoma, dermoid, and epidermoid. Most malignant disease represents secondary submandibular and submental nodal involvement, commonly from SCC of the oral cavity and face. Multiple enlarged lymph node involvement may be seen with non-Hodgkin's lymphoma.

Spaces of Infrahyoid Neck

The infrahyoid neck extends superiorly to the hyoid bone and inferiorly to the clavicles and contains the following spaces:

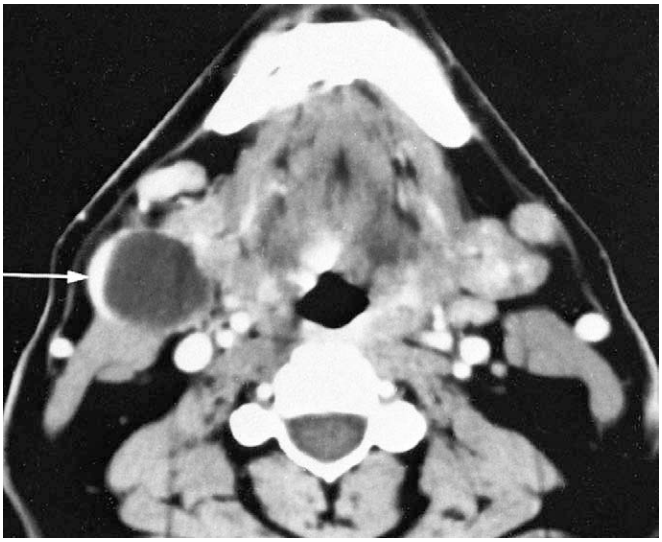


Figure 11-37. Infected branchial cleft cyst. Axial contrast-enhanced computed tomography at the midlevel of the tongue and base of the mandible demonstrates a well-defined, low-density lesion in the lateral portion of the submandibular space lying anterior to the right sternocleidomastoid. A thin rim of peripheral enhancement is noted anteriorly and medially. The lateral wall demonstrates thick enhancement *(arrow)*. Location favors the second branchial cleft cyst. Enhancement of the cyst wall indicates that it is infected.

1. Infrahyoid RPS
2. Infrahyoid PVS
3. Anterior and posterior (lateral) cervical spaces
4. Hypopharyngeal mucosal space (PMS)
5. Visceral space and larynx
6. CS

Normal cross-sectional anatomy of the infrahyoid neck is presented in Figures 11-38 through 11-40. The PPS ends at the hyoid bone and does not continue into the infrahyoid neck. The mucosal, carotid, retropharyngeal, prevertebral, and posterior cervical spaces are all continuous superiorly with the suprahyoid neck and extend inferiorly to the thoracic inlet.[28] These spaces are discussed in more detail in the suprahyoid neck section of this chapter. The posterior cervical space is described in the next section. Lesions may secondarily invade the structures of the infrahyoid neck from the cranial margin (submandibular, parapharyngeal, carotid, retropharyngeal, and oropharyngeal mucosal spaces), posterior margin (prevertebral space and vertebrae), and inferior margin (mediastinum and chest wall).

Infrahyoid Retropharyngeal Space

The infrahyoid RPS, a potential space containing a thin layer of fat and no lymph nodes, is bounded by the middle layer of deep cervical fascia anteriorly, the alar fascia of the carotid sheath laterally, and the deep layer of deep cervical fascia posteriorly.[29] Unlike the suprahyoid RPS, which contains both fat and lymph nodes, the infrahyoid RPS only contains fat. On CT and MRI, the normal infrahyoid RPS is an inconsistently demonstrated fat stripe overlying the anterior margin of the longus colli muscles, nestled between the two carotid sheaths.

The infrahyoid RPS may be involved by processes arising from tissues within this space, but more commonly it is affected by external invasion from the adjacent spaces. Lesions within this space have a characteristic "bow-tie" configuration and lie anterior to the longus colli muscles (Fig. 11-41). Lipomas and lymphangiomas are two low-density congenital lesions arising primarily in, or secondarily extending into, the infrahyoid RPS. Inflammation of this space may arise from pharyngeal mucosal laceration, discitis, or osteomyelitis from the PVS, or from infections tracking in through the posterior cervical space. Gas in this space suggests laceration of the pharynx, larynx, or trachea, pneumomediastinum, or the presence of gas-forming organisms (Fig. 11-42). Edema from inflammation in an adjacent space may track into the RPS and occasionally mimic a true fluid collection or abscess. Neoplasms arising in the hypopharyngeal MS, CS, posterior thyroid gland, and larynx may involve the RPS. Extracapsular spread of internal jugular and spinal accessory metastatic nodes, as well as recurrent visceral space neoplasms, occasionally may invade the RPS. One common pseudomass that indents into this space is a tortuous common or internal carotid artery, usually seen in the middle-aged and elderly populations.

Infrahyoid Prevertebral Space

The infrahyoid PVS continues superiorly into the suprahyoid PVS and inferiorly to the mediastinum. This space is susceptible to the same pathologic processes as the suprahyoid component, which include inflammatory and infectious processes (arthritis, discitis, osteomyelitis), as well as neoplasms arising in the spinal canal, brachial plexus, paraspinous musculature, or vertebral bodies (Fig. 11-43).

Anterior and Posterior Cervical (Lateral Cervical) Spaces

The posterior cervical (lateral cervical) space corresponds to the posterior triangle and is a fibrofatty layer containing the internal jugular, spinal accessory, and transverse cervical lymph node chains, as well as the spinal accessory and phrenic nerves. The posterior cervical space is limited by the sternocleidomastoid muscle and investing layer of deep cervical fascia anterolaterally, the carotid sheath anteriorly, and the prevertebral fascia posteromedially. It extends superiorly from the mastoid process and skull base down to the first rib and clavicles inferiorly.[34] Thus a small portion of the posterior cervical space extends into the suprahyoid neck, with the majority occupying the infrahyoid neck.

A trans-spatial lesion (lymphangioma, plexiform neurofibroma, lipoma, hemangioma) may invade two or more anatomic compartments, without respect for fascial boundaries.[30] Congenital lesions of the posterior cervical space include a second branchial cleft cyst, which tends to lie along the anterior margin of the sternocleidomastoid muscle, and a lymphangioma or cystic hygroma (Fig. 11-44). Both lesions are CSF density on CT, low intensity on T1WI, high intensity on T2WI, and may ring-enhance if secondarily infected. Inflammation may enter this space from cutaneous lesions or from abscessed lymph nodes. Benign neoplasms include neurogenic tumors (plexiform neurofibroma, schwannoma), a lipoma, or a hemangioma. Malignant neoplasms in the posterior cervical space are most commonly metastatic to the spinal accessory or internal jugular lymph nodes, with SCC representing the largest group of both primary and secondary tumors involving this space. Less commonly, sarcomas such as liposarcoma, leiomyosarcoma, or malignant fibrous histiocytoma arise here. Normal structures such as the scalene muscles, poorly opacified vessels on CT, and high-signal, flow-related enhancement in vessels on MRI may be misinterpreted as a pseudomass. Denervation atrophy of the sternocleidomastoid muscle or other neck muscles may occasionally cause an incorrect interpretation of the contralateral (normal-sized) muscles as representing masses.

Hypopharyngeal Mucosal Space

The hypopharyngeal mucosal space forms the walls of the hypopharynx and includes the continuation of the pharyngeal mucosal space below the hyoid bone posteriorly, the piriform sinuses laterally, the aryepiglottic folds and epiglottis anteriorly, and the cricopharyngeus muscle inferiorly. The hypopharyngeal mucosal space, piriform sinuses, and aryepiglottic folds are frequently challenging to evaluate on CECT and MRI because they are relatively thin membranous spaces that are normally collapsed together when the pharynx is relaxed. A modified Valsalva maneuver is usually required to distend the hypopharynx enough to obtain adequate imaging (see Fig. 11-2).

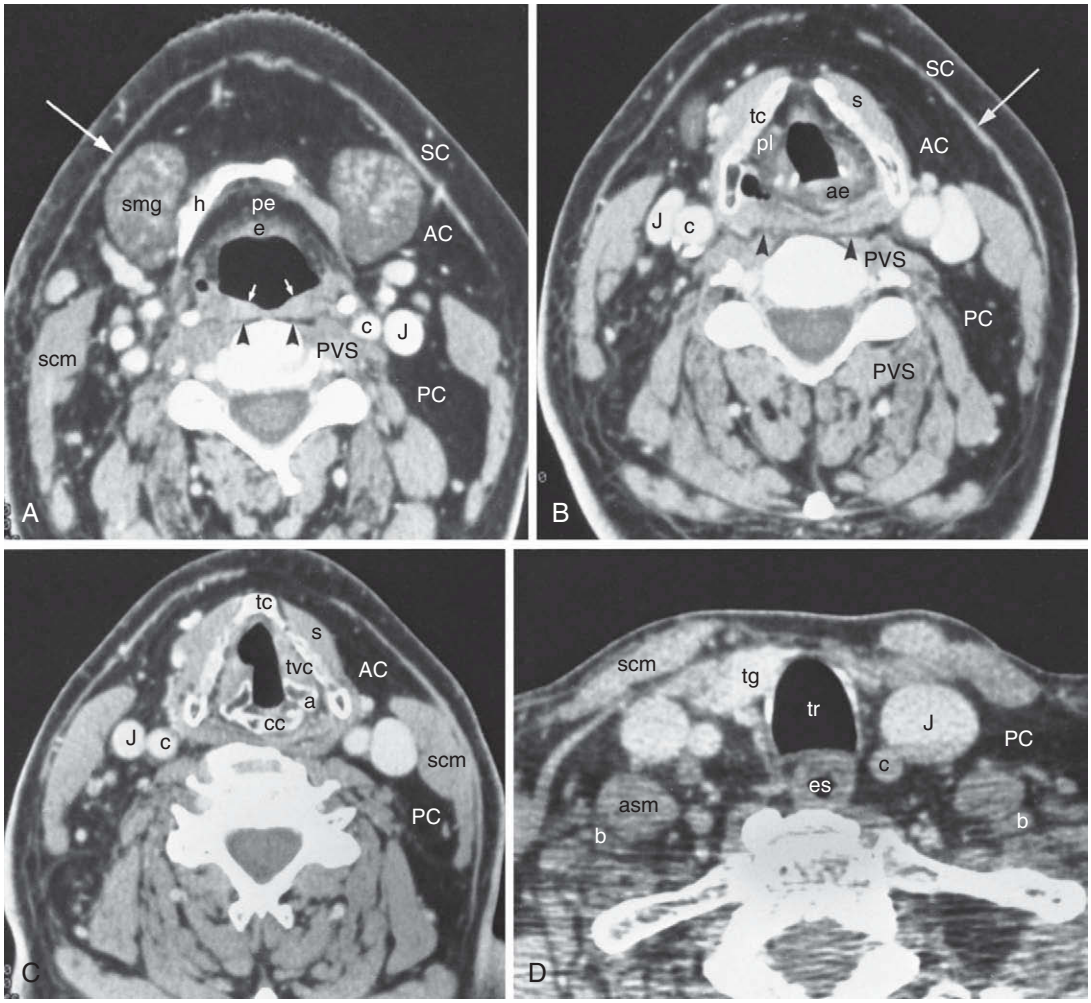


Figure 11-38. Normal axial contrast-enhanced computed tomography (CECT) anatomy of infrahyoid neck. CECT obtained at hyoid bone **(A),** false vocal cord **(B),** true vocal cord **(C),** and thyroid gland levels **(D).** (Streaky densities in the superficial fat of the right neck area in **A** and **B** are from earlier radiation of the right parotid mass.) Note the following structures: arytenoid cartilage (a), anterior cervical space (AC), aryepiglottic fold (ae), anterior scalene muscle (asm), brachial plexus (b), carotid artery (c), cricoid cartilage (cc), epiglottis (e), esophagus (es), hyoid bone (h), jugular vein (J), posterior cervical space (PC), preepiglottic fat (pe), paralaryngeal fat (pl), prevertebral space (PVS), pharyngeal mucosal space *(small arrows),* platysma muscle *(large arrow),* retropharyngeal space *(arrowheads),* strap muscle (s), superficial cervical space (SC), sternocleidomastoid muscle (scm), submandibular gland (smg), thyroid cartilage (tc), thyroid gland (tg), trachea (tr), and true vocal cord (tvc).

As with the suprahyoid pharyngeal mucosal space, caution must be exercised in assigning abnormality to this space, since redundancy of the mucosa and incomplete distention may mimic a tumor. Foreign bodies, inflammation, and SCC are the most common lesions in this space. Inflammation may cause ulceration or swelling of the mucosa, with gas or a ring-enhancing fluid collection suggesting the diagnosis. Reactive lymph nodes are common. The best indicator of hypopharyngeal malignancy is a bulky mass with invasion and destruction of submucosal and deep structures including the retropharyngeal space, aryepiglottic folds, cricoid cartilage and larynx, as well as associated necrotic lymph nodes (Fig. 11-45).

Visceral Space and Larynx

The visceral space, corresponding to the muscular triangle, is confined by the middle layer of deep cervical fascia with the anterior fascial layer splitting around the thyroid gland. The visceral space contains the larynx, trachea, hypopharynx, esophagus, parathyroid glands, thyroid gland, recurrent laryngeal nerve, and tracheoesophageal lymph nodes.[31] The superior margin is the hyoid bone, and the inferior border is the mediastinum. The skeleton of the larynx includes the thyroid, cricoid, arytenoid, cuneiform, and corniculate cartilages. These cartilages may reveal a variable degree of calcification or ossification. These findings progress with the patient's age. Ligaments from the styloglossus and stylohyoid muscles frequently calcify. Knowledge of the normal patterns of calcification is helpful for distinguishing opaque foreign bodies, such as chicken bones, from normal structures on plain films or CT.

Larynx

The hyoid bone supports the laryngeal skeleton and is occasionally fractured in blunt trauma or destroyed by neoplasms. Fractures of the laryngeal skeleton appear on CT as linear lucencies, often with displacement or distortion of the cartilage. A fracture is best appreciated (on bone windows) in well-ossified cartilage, but its identification is more challenging in noncalcified cartilage requiring the use of a narrower window width and careful scrutiny of cartilage configuration. Laryngeal trauma may result in hematomas of the aryepiglottic folds, false cords, true cords, or subglottis, and may potentially compromise the airway (Fig. 11-46). Adjacent subcutaneous emphysema may result from trauma to the laryngopharyngeal mucosa, from a penetrating injury to the neck, or from upward dissection from the chest wall or mediastinum.

Laryngoceles are formed by increased intraglottic pressure (e.g., in horn players and glass blowers) or from obstruction of the laryngeal ventricle and its distal appendix by inflammatory or neoplastic lesions

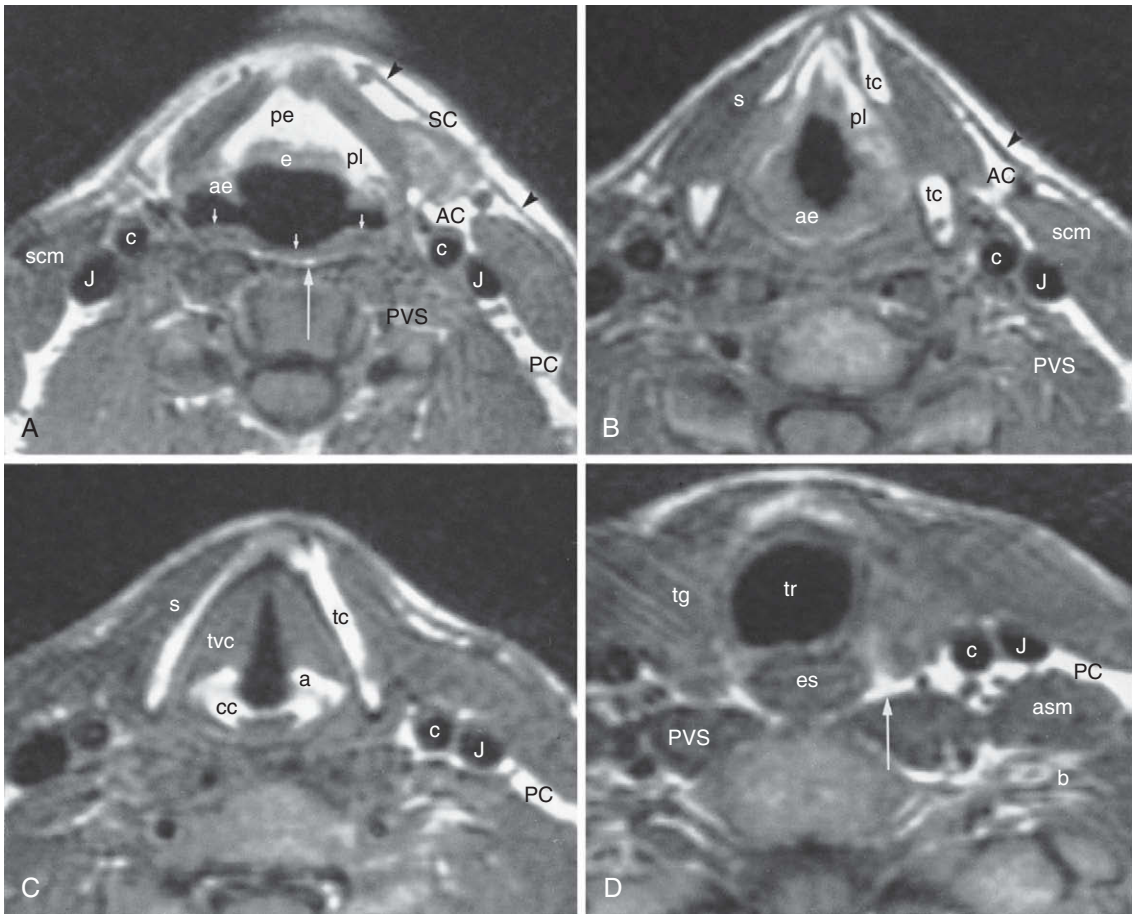


Figure 11-39. Normal axial magnetic resonance anatomy of infrahyoid neck. Noncontrast T1-weighted images obtained at hyoid bone **(A),** false vocal cord **(B),** true vocal cord **(C),** and thyroid gland levels **(D).** The following structures are labeled: arytenoid cartilage (a), anterior cervical space (AC), aryepiglottic fold (ae), anterior scalene muscle (asm), branchial plexus (b), carotid artery (c), cricoid cartilage (cc), epiglottis (e), esophagus (es), jugular vein (J), posterior cervical space (PC), preepiglottic fat (pe), paralaryngeal fat (pl), prevertebral space (PVS), pharyngeal mucosal space *(small arrows),* platysma muscle *(arrowheads)*, retropharyngeal space *(large arrow),* strap muscle (s), superficial cervical space (SC), sternocleidomastoid muscle (scm), thyroid cartilage (tc), thyroid gland (tg), trachea (tr), and true vocal cord (tvc).

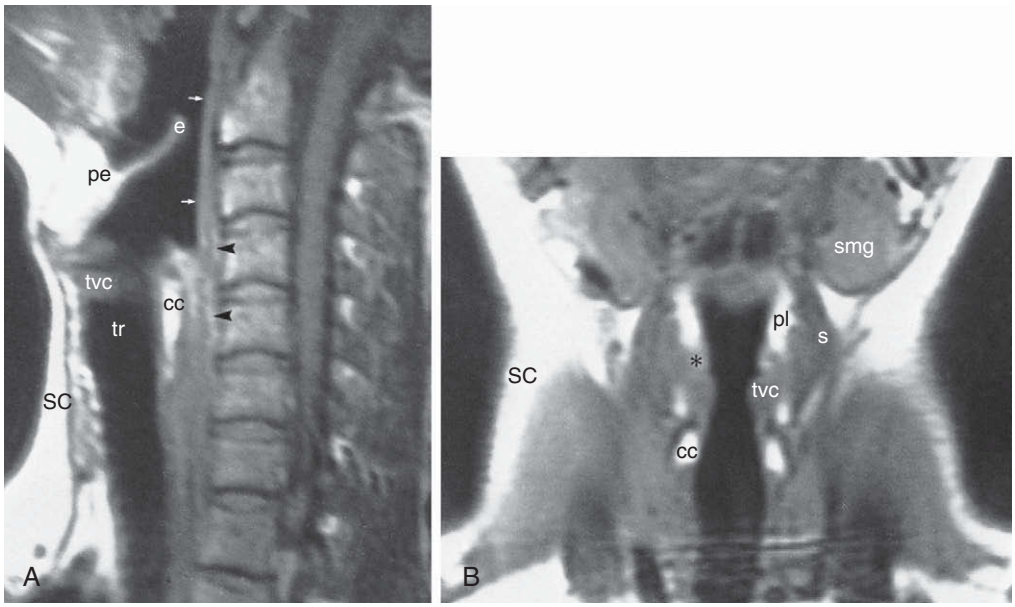


Figure 11-40. Normal sagittal and coronal magnetic resonance of infrahyoid neck. **A,** Sagittal T1-weighted image (T1WI) and, **B,** coronal T1WI obtained through the larynx. Note the following structures: cricoid cartilage (cc), epiglottis (e), false vocal cord *(asterisk)*, pharyngeal mucosal space (*small arrows*), preepiglottic fat (pe), paralaryngeal fat (pl), retropharyngeal space *(arrowheads)*, strap muscle (s), superficial cervical space (SC), submandibular gland (smg), trachea (tr), and true vocal cord (tvc).

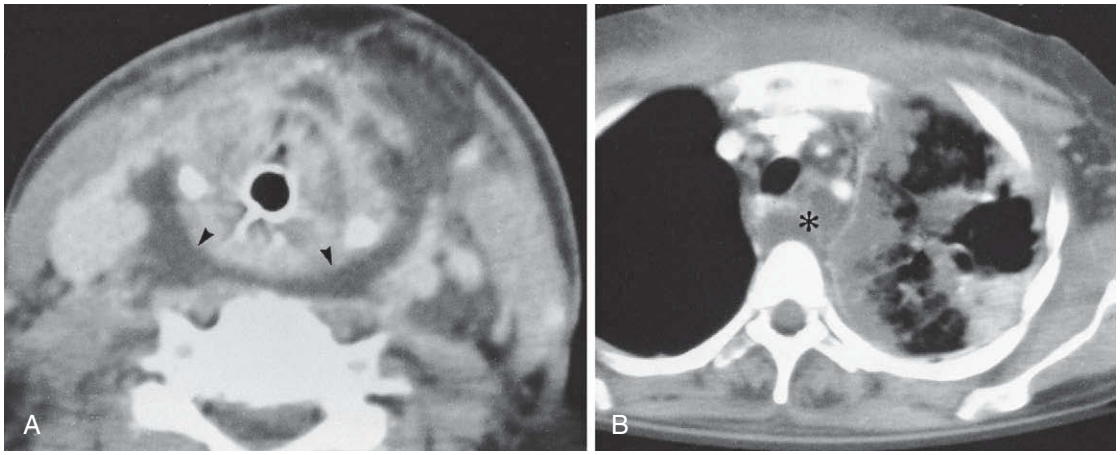


Figure 11-41. Infrahyoid retropharyngeal space and visceral space abscess. **A,** Axial contrast-enhanced computed tomography at the level of the false vocal cords demonstrates a low-density abscess in the retropharyngeal space *(arrowheads)* creating a "bow-tie" configuration. The abscess extends laterally to the left posterior cervical space and anteriorly into the visceral and anterior cervical spaces. **B,** Communication between the retropharyngeal space and mediastinum is well demonstrated by cephalad extension of this mediastinal abscess *(asterisk)* posterior to the trachea.

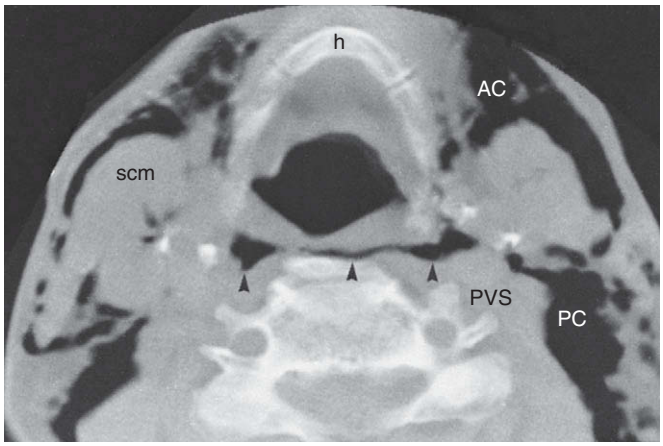


Figure 11-42. Axial non-contrast computed tomography of subcutaneous emphysema highlighting cervical spaces. Gas from a pneumomediastinum has dissected into the anterior cervical space (AC), posterior cervical space (PC), and retropharyngeal space *(arrowheads)*. Note the "bow-tie" pattern of the retropharyngeal space. Other labeled structures include the hyoid bone (h), sternocleidomastoid muscle (scm), and prevertebral space (PVS).

(Fig. 11-47). An internal laryngocele tracks superiorly within the paralaryngeal (paraglottic) fat, is air- or fluid-filled (obstructed laryngocele), and causes variable compromise of the supraglottic larynx. A mixed (external) laryngocele extends further superolaterally, piercing the thyrohyoid membrane, and may present as a neck mass. A mucocele (mucous retention cyst) of the supraglottic laryngeal mucosa may be indistinguishable from an obstructed internal laryngocele. Inflammation of the supraglottic larynx may lead to epiglottitis, thickening the epiglottis and aryepiglottic folds, and compromising the airway (Fig. 11-48).

Apart from routine evaluation of adenopathy from suprahyoid neck and sinus tumors, laryngeal and hypopharyngeal SCC is the most common indication for imaging the infrahyoid neck. Because both CECT and MRI are relatively insensitive to superficial mucosal based lesions, knowledge of the physical examination findings and specific locations of concern is mandatory to facilitate lesion localization and characterization. Findings that help identify SCC of the superficial mucosa of the larynx or pharynx are a mass, mucosal irregularity or asymmetry, and ulceration. Fat planes in the laryngopharynx are critical for determining the extent of deep invasion or inflammation. The fat in the preepiglottic space, epiglottis, and aryepiglottic folds and paralaryngeal fat of the supraglottic larynx are major landmarks that are easily identified on axial CT and MRI. Coronal T1WIs are particularly useful for evaluating the configuration of the airway and for determining the craniocaudal margins of a supraglottic, glottic, infraglottic, or transglottic lesion because the vertically oriented paralaryngeal fat plane terminates inferiorly at the true vocal cords (thyroarytenoid muscle). A lesion becomes transglottic when the fat interface between the thyroarytenoid muscle (true vocal cord) and the paralaryngeal fat (false vocal cord) is eliminated, indicating the tumor has crossed the laryngeal ventricle (Fig. 11-49A). The anterior commissure should be less than 1-mm thick. Greater thickness in this area represents tumor spread from the anterior margin of one cord to another. A diagnosis of vocal cord fixation may be made when the involved cord remains paramedian during quiet breathing or with a modified Valsalva maneuver (see Fig. 11-49B).

Cartilage invasion or destruction by aggressive infections or tumors is an important part of staging, and is often difficult to predict on CECT or MRI when the cartilage is incompletely calcified. If the cartilage has ossified, CECT and MRI are relatively sensitive for detecting cartilage erosion. MRI, using a combination of T1WI, T2WI, and postgadolinium fat saturation T1WI, may be more sensitive than CECT to invasion of the central layer of the thyroid cartilage, especially if the cartilage has ossified and the central fatty marrow has been locally replaced by an invading tumor. The best indicator of cartilage invasion is the presence of a tumor on the external margin of the cartilage in the strap muscles (Fig. 11-50).

Thyroid Gland

The thyroid gland lies within the anterior leaves of the middle layer of deep cervical fascia (within the visceral space), anterior and lateral to the thyroid, cricoid, and upper tracheal cartilages. It consists of the lateral thyroid lobes, isthmus, and pyramidal lobe. Normal iodine content of the thyroid gland makes it higher density than muscle on NCCT. The gland is normally homogeneous with enhancement on both CECT and MRI, but internal inhomogeneity from calcification, goiter, colloid cyst, or a solid mass is occasionally encountered on routine neck imaging. When physical examination, ultrasound, or thyroid scintigraphy raises the suspicion of a thyroid carcinoma or thyroid lymphoma, CECT or MRI may be used for further characterization, especially if it is a low thoracic inlet thyroid or parathyroid mass.

Absence of the thyroid gland at the level of the thyroid cartilage should redirect attention to the tongue for an ectopic lingual thyroid gland (Fig. 11-51). A thyroglossal duct cyst is a remnant of the

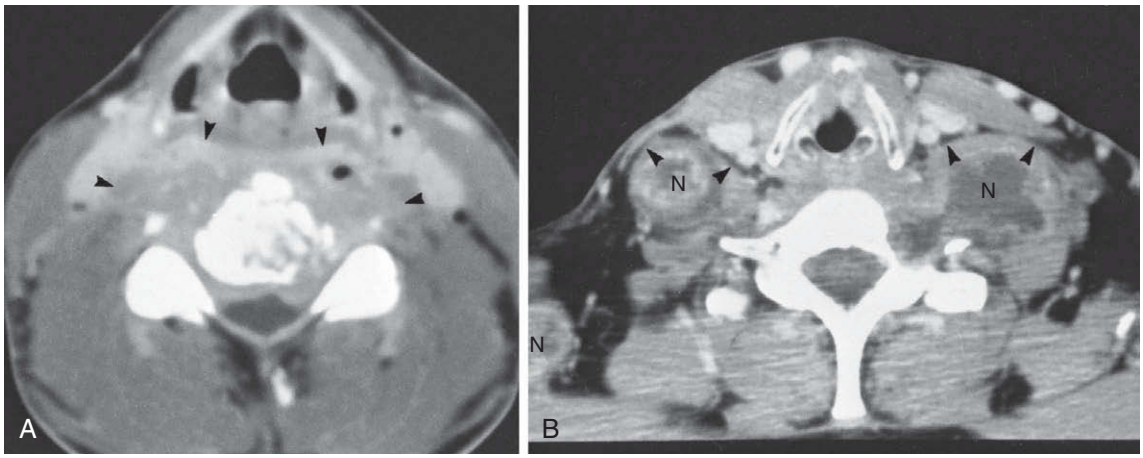


Figure 11-43. Prevertebral space (PVS) lesions. **A,** Axial contrast-enhanced computed tomography (CECT) of the prevertebral abscess extends anteriorly from C5-6 discitis. Anterolateral margins of the abscess *(arrowheads)* displace pharyngeal mucosa and posterior cervical spaces anteriorly. A small amount of gas is present in the abscess on the left. **B,** Axial CECT of bilateral plexiform neurofibromas (N) arising from the brachial plexus in the PVS shows anterior displacement of fat in the posterior cervical spaces *(arrowheads)*.

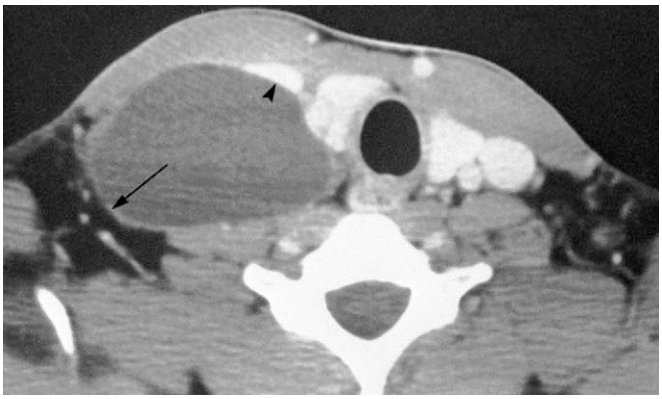


Figure 11-44. Posterior cervical space lymphangioma. Contrast-enhanced computed tomography reveals a homogeneous, bright, low-density mass with sharp margins displacing the posterior cervical space fat *(arrow)* posterolaterally and internal jugular vein *(arrowhead)* anteriorly.

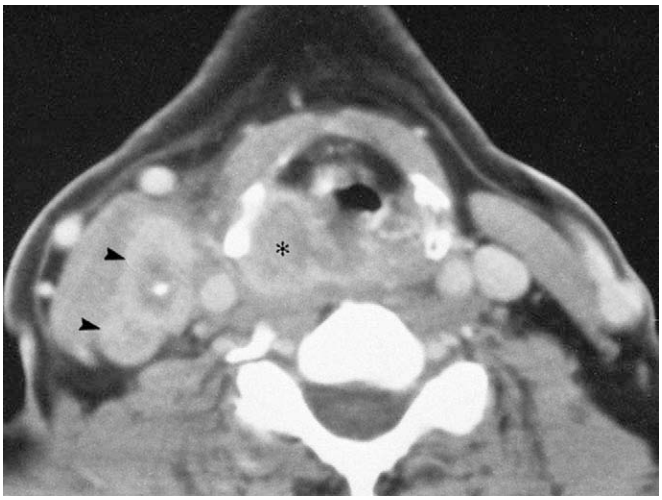


Figure 11-45. Piriform sinus squamous cell carcinomas. Axial contrast-enhanced computed tomography shows a mildly enhancing mass in the right piriform sinus *(asterisk)* displacing the aryepiglottic fold anteromedially. Focal defects in the internal jugular and spinal accessory nodes *(arrowheads)* indicate metastatic tumor spread. Calcification is noted in the internal jugular node.

embryonic thyroglossal duct and may occur anywhere along its migratory path from the foramen cecum in the tongue to the pyramidal lobe, although most occur just inferior to the hyoid bone (Fig. 11-52). Inflammatory thyroiditis may enlarge the thyroid gland. Benign enlargement may also result from colloid cysts and goiters. Thyroid calcification is nonspecific and occurs in goiters, as well as in benign thyroid adenomas. Primary malignancies of the thyroid include papillary, follicular, mixed, and anaplastic carcinomas, as well as non-Hodgkin's lymphoma, all of which may have a similar imaging appearance (Fig. 11-53). Indistinct margins of a thyroid mass, infiltration of adjacent tissues, and necrotic lymph nodes are all indications of thyroid malignancy. Metastasis to the thyroid gland more commonly arises from extracapsular spread of SCC in adjacent nodes than from hematogenous deposits.

Parathyroid Glands

The parathyroid glands are usually four to six in number and underlie the posterior surface of the thyroid gland. Because they are quite small, normal parathyroid glands are frequently not visualized on routine neck imaging. An ectopic parathyroid gland may occur in the mediastinum (Fig. 11-54). A parathyroid adenoma is usually a discrete mass lying deep to the thyroid lobes. Occasionally, an adenoma may be detected on routine CT or MRI as a nodular, enhancing mass that may be dif-

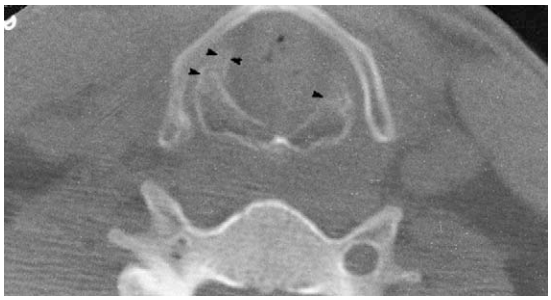


Figure 11-46. Laryngeal trauma. Axial noncontrast computed tomography at the level of cricothyroid articulation shows a laterally displaced cricoid ring *(arrowheads)* fracture and subglottic hematoma obstructing the airway.

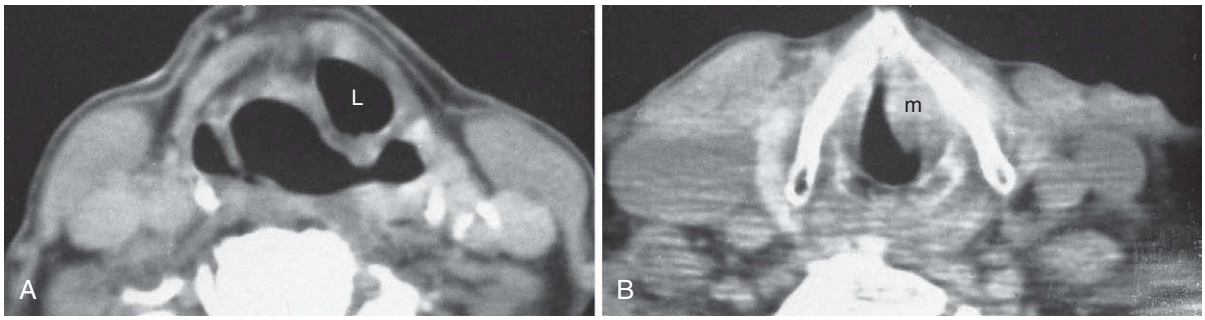


Figure 11-47. Laryngocele. **A,** Axial contrast-enhanced computed tomography (CECT) at the level of the thyrohyoid membrane demonstrates an air-filled internal laryngocele (L) displacing the preepiglottic fat and aryepiglottic fold. Note that the thyrohyoid membrane is separated from the piriform sinus by the aryepiglottic fold. **B,** Axial CECT at the true cord level reveals the cause of the laryngocele—an obstructing transglottic carcinoma (m).

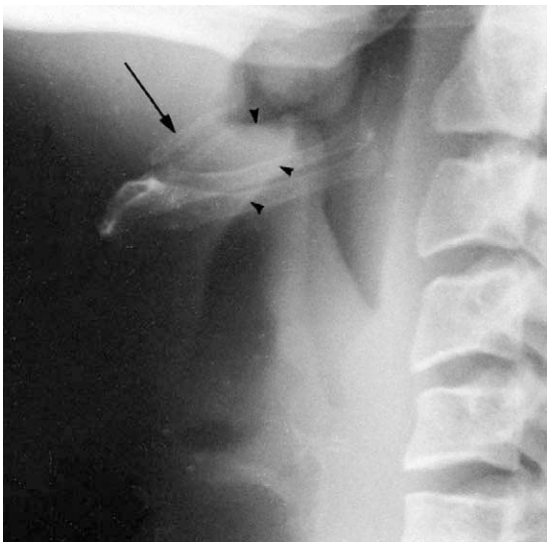


Figure 11-48. Epiglottitis. Lateral plain film of the neck demonstrates the swollen epiglottis *(arrowheads)* and aryepiglottic folds. The lower portion of the stylohyoid ligament *(arrow)* has ossified bilaterally.

ferentiated from lymph nodes by its location posterior to the thyroid gland.

Lymphadenopathy

Lymph Node Anatomy and Classification

The nodes of the superficial triangles of the neck are organized by major lymphatic chains. The traditional classification of lymph nodes of the head and neck includes 10 groups: lateral cervical, anterior cervical, submandibular, submental, sublingual, parotid, facial, mastoid, occipital, and retropharyngeal. The lateral cervical chains are further subdivided into the deep and superficial chains. The deep lateral cervical chain includes the internal jugular, spinal accessory, and transverse cervical (supraclavicular) nodes. The superficial lateral cervical chain consists of the external jugular nodes. The anterior cervical (juxtavisceral) group contains the prelaryngeal (Delphian), pretracheal, prethyroid, and lateral tracheal (tracheoesophageal or paratracheal) nodes.[32] The cervical lymph node chains are found throughout several of the spaces of the neck:

1. Posterior cervical space: spinal accessory, transverse cervical, and internal jugular (posterior to the internal jugular vein) nodes

2. Carotid space: internal jugular nodes (anterior to the internal jugular vein posterior margin)

3. Submandibular space: submandibular and submental nodes

4. Parotid space: parotid nodes

5. Suprahyoid retropharyngeal space: medial and lateral retropharyngeal nodes

6. Visceral space: prelaryngeal, prethyroid, pretracheal, and tracheoesophageal nodes

7. Subcutaneous tissues of the scalp and face: occipital, mastoid, and facial nodes

A condensation of this nomenclature into seven groups with Roman numerals (levels I to VII) has been proposed and is a useful shorthand for node documentation and statistical analysis. Som and others[20] have proposed an imaging-based nodal classification to find a common ground between anatomic imaging criteria and the two most commonly used clinical nodal classifications: the American Joint Committee on Cancer and the American Academy of Otolaryngology-Head and Neck Surgery.

In this classification, level I combines the submandibular and submental lymph nodes. Levels II to IV divide the internal jugular chain roughly into thirds, using landmarks that are easily recognizable on cross-sectional imaging. Level II is the jugulodigastric nodes (upper internal jugular), including the nodes from the skull base down to the bottom of the body of the hyoid bone. Level III is the supraomohyoid internal jugular chain (middle internal jugular), from the bottom of the body of the hyoid bone to the level of the bottom of the cricoid cartilage. Level IV includes the infraomohyoid (low internal jugular), nodes from the level of the bottom of the cricoid to the level of the clavicles. Level V includes the spinal accessory and transverse cervical nodes from the skull base to the clavicles, which lie posterior to the sternocleidomastoid muscle. Level VI includes the upper visceral nodes, which lie between the carotid arteries from the level of the bottom of the hyoid bone to the level of the top of the manubrium. Level VII nodes are located in the superior mediastinum between the carotid arteries, below the level of the manubrium and above the level of the innominate vein.

Subdivisions of the levels I, II, and V are also defined. Level Ia nodes are the submental nodes; they lie medial to the lateral margin of the anterior belly of the digastric muscle. Level Ib nodes lie lateral to the digastric muscle about the submandibular gland. Level IIa nodes are located at the level of, or anterior to, the internal jugular vein. Level II nodes that are posterior to and separate from the internal jugular vein are in Level IIb. Level Va nodes lie above the level of the bottom of the cricoid arch. Level Vb nodes are below the level of the cricoid and above the level of the clavicle. The levels Ib and IIa are divided by an arbitrarily selected imaginary coronal plane that follows the posterior border of the submandibular gland. The posterior margin of the sternocleidomastoid muscle separates the levels II, III, and IV from the level V.

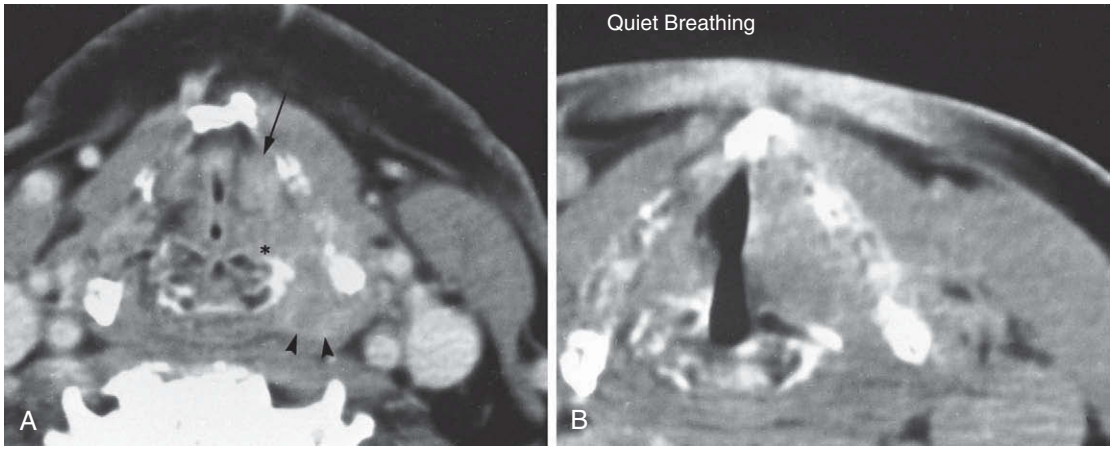


Figure 11-49. Transglottic laryngeal squamous cell carcinoma with vocal cord fixation. **A,** True vocal cords are adducted on an axial contrast-enhanced computed tomography (CECT) obtained during breath holding, with the tumor extending anteriorly and superiorly from the left true cord into adjacent paralaryngeal fat *(arrow)* and posteriorly into the cricoarytenoid joint *(arrowheads)*. Anterior corner of the calcified left arytenoid cartilage *(asterisk)* has been eroded by the tumor. **B,** Repeat axial CECT performed during quiet breathing reveals fixation of the left true cord in midline. Right cord is partially abducted.

Figure 11-50. Transglottic squamous cell carcinoma with cartilage invasion. Axial CECT at the true vocal cord level shows an enhancing mass (m) originating in the left vocal cord, crossing the anterior commissure, and invading the anterior third of the right cord. The tumor has invaded through the anterior thyroid cartilage and displaces the thyroid strap muscles anteriorly *(arrowheads)*.

The retropharyngeal, supraclavicular, and parotid nodes are not included in the level classification. The retropharyngeal nodes lie medial to the internal carotid arteries within 2 cm from the skull base. Supraclavicular nodes lie at the level of, or caudal to, the clavicle and lateral to the carotid arteries. Separation of the supraclavicular nodes from low level IV and level V nodes may be difficult on the transverse images because of the oblique course of the clavicle.

Lymph Nodes: Normal and Pathologic

CECT remains the gold standard for detecting and classifying cervical lymphadenopathy as benign or malignant. The important considerations in radiographic lymph node detection and characterization are location, size, number, clustering, enhancement pattern, calcification, sharpness of margins, and invasion or displacement of adjacent structures. First, the nodes must be detected and localized to a specific nodal chain or level using one of the conventions for labeling node regions discussed previously. Node involvement is described as unilateral or bilateral and in terms of the specific level or chain affected.

Inflammatory (reactive) lymph nodes on CECT tend to be less than 10 mm (rarely larger than 20 mm), have central hilar or mild homogeneous enhancement, and have well-defined margins (Fig. 11-55). Node margins should remain sharp in reactive adenopathy, except in cases with large abscessed nodes that elicit an inflammatory reaction in the adjacent fat, obscuring the node margins (Fig. 11-56). Calcification is a common finding in previously infected or healed nodes and frequently occurs in tuberculosis or bacterial infections. Multiple nodes may be present, but they tend not to cluster. On MRI, these reactive nodes are enlarged and have well-defined margins on all sequences. They are of muscle intensity on T1WI, enhance moderately and homogeneously on postgadolinium fat-suppressed T1WI, and are bright on T2WI and STIR.

The correlation of lymph node size with sensitivity and specificity in predicting malignant metastasis has been performed for different neck regions in patients with head and neck carcinoma, allowing more appropriate size criteria for distinguishing normal from abnormal lymph nodes.[32] Although CT can readily detect lymph node enlargement, it has also proven capable of accurately diagnosing metastases in "normal size" nodes from head and neck primary SCC. The upper range of normal for cervical lymph node size is between 5 and 10 mm, with the jugular digastric node ranging up to 15 mm. The exceptions are the retropharyngeal nodes, which are considered pathologic when larger than 10 mm in children or larger than 5 mm in adults. Generally, cervical nodes larger than 10 to 15 mm are potentially malignant and nodes smaller than this are considered reactive or inflammatory. Nodes larger than 20 mm are frequently malignant. Clinically occult neck disease occurs in 15% to 40% of patients with head and neck SCC. Clinically occult nodes average 12 mm (Fig. 11-57). Studies comparing clinical and CT staging of nodal metastases have shown that physical examination of the neck has an accuracy of 70% to 82% compared with 87% to 93% for CT. In patients with no nodal disease on examination, CT is likely to upstage an N0 neck to N1 in 20% to 46% of cases and upstage clinical staging of the neck between 5% and 67% of cases overall. CT may downstage the clinical neck examination in 3% to 36% of cases.[33,34]

The enhancement pattern on CT is very helpful, but not infallible, in distinguishing inflammatory nodes from metastatic nodes. The presence of a focal defect (central low density) or peripheral enhancement is characteristic of malignancy even in normal-sized nodes. A focal defect in an enlarged node is a strong indication of a necrotic node metastasis, although tuberculosis or an abscessed node may mimic this appearance. Central dense or linear enhancement of the hilum of an enlarged node without ring enhancement is usually a distinguishing

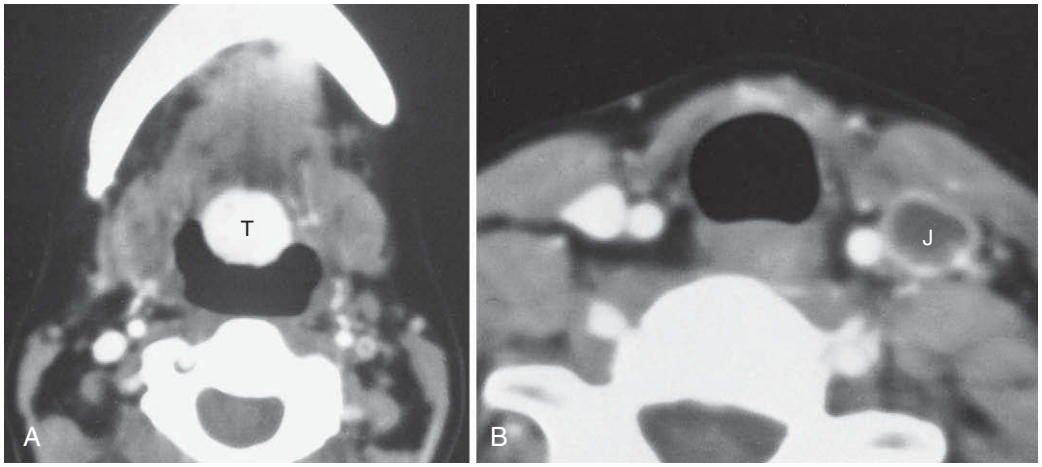


Figure 11-51. Lingual thyroid gland. **A,** Densely enhancing mass of ectopic thyroid tissue (T) bulges posteriorly from the tongue at the level of the foramen cecum on the axial contrast-enhanced computed tomography. **B,** CECT at the upper tracheal level reveals that the thyroid gland is absent from its normal location. Note the pseudotumor of the thrombosed internal jugular vein (J) mimicking ring-enhancing node metastasis.

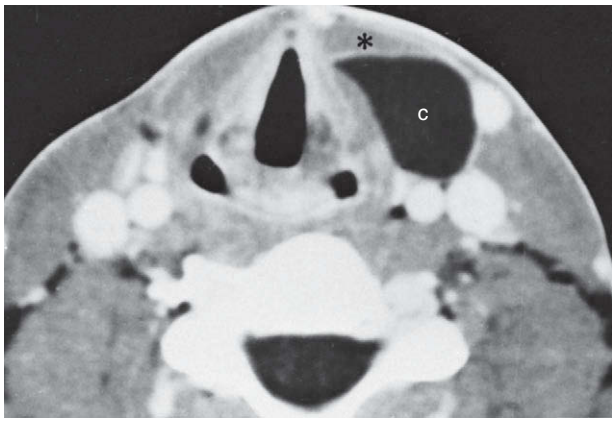


Figure 11-52. Thyroglossal duct cyst. Low-density thyroglossal duct cyst (c) elevates the thyroid strap muscles *(asterisk)* and laterally displaces the sternocleidomastoid muscle in this axial contrast-enhanced computed tomography.

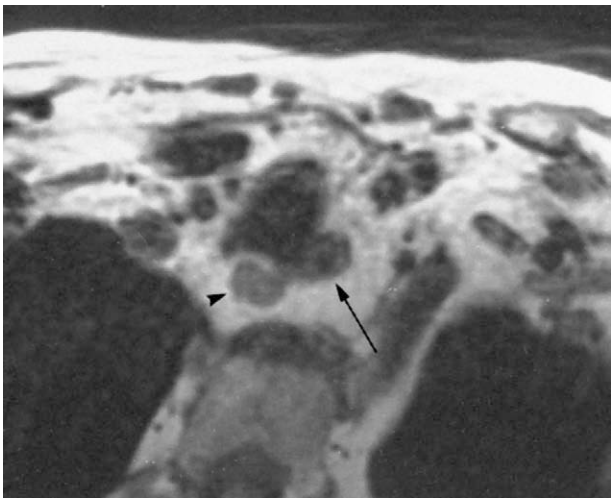


Figure 11-54. Parathyroid adenoma. Retrotracheal ectopic parathyroid adenoma *(arrowhead)* looks similar to the adjacent normal esophagus *(arrow)* on an axial T1-weighted image.

Figure 11-53. Thyroid follicular carcinoma. Axial contrast-enhanced computed tomography just below the cricoid shows a large mass with nodular calcification *(asterisk)* displacing the trachea to the right and distorting the airway. Posteriorly it has invaded the retropharyngeal space *(arrow)*.

sign of a reactive node. Nodes larger than 20 to 40 mm without central necrosis often indicate lymphoma or sarcoidosis (Fig. 11-58). Treated lymphomatous nodes may have dystrophic calcification and, rarely, calcium matrix-forming tumors (osteosarcoma, chondrosarcoma) may have radiodense metastases. When margins of an enlarged node with central necrosis are indistinct, extracapsular penetration of the tumor through the node capsule has likely occurred (Fig. 11-59). This sign may decrease the 5-year survival by 50%. The number of nodes involved is important. Multiple nodes suggest a more widespread inflammatory or neoplastic process. Clustering of multiple nodes—sometimes into a seemingly single, complex mass—suggests malignancy and may be palpable as a single large mass. Round, rather than bean-shaped nodes, clusters of nodes, and indistinct margins suggest malignancy but are less specific than having a size larger than 15 mm, ring enhancement, or focal defect.

MRI of malignant adenopathy has both advantages and limitations compared with CECT. Malignant nodes appear as muscle intensity on T1WI, may show ring enhancement on postgadolinium fat-suppressed T1WI, are very bright on STIR, and are usually bright on T2WI (although necrosis may give both a high and low signal on long TR sequences) (Fig. 11-60). Fat-suppressed long TR sequences

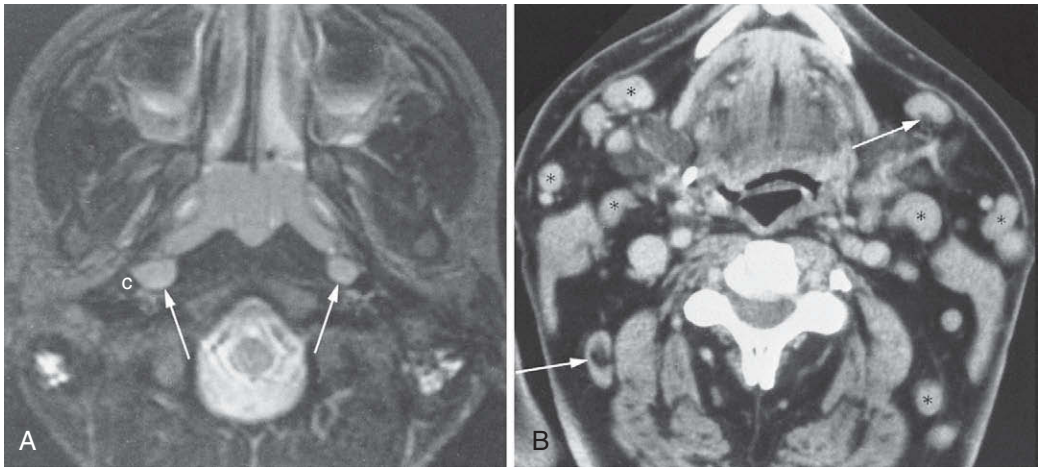


Figure 11-55. Normal lymph node anatomy. **A,** In this 8-year-old child, normal lateral retropharyngeal nodes *(arrows)* lie medial to the internal carotid arteries (c) and demonstrate a moderately high signal on the T2-weighted images. High-signal adenoidal tissue is commonly prominent at this age. **B,** Multiple mildly enlarged nodes *(asterisks)* are present in the submandibular, anterior jugular, internal jugular, and spinal accessory lymphatic chains on this contrast-enhanced computed tomography. Note the eccentric fatty hilum *(arrows)* in two nodes, a potential pitfall in the diagnosis of focal defect in the metastatic node.

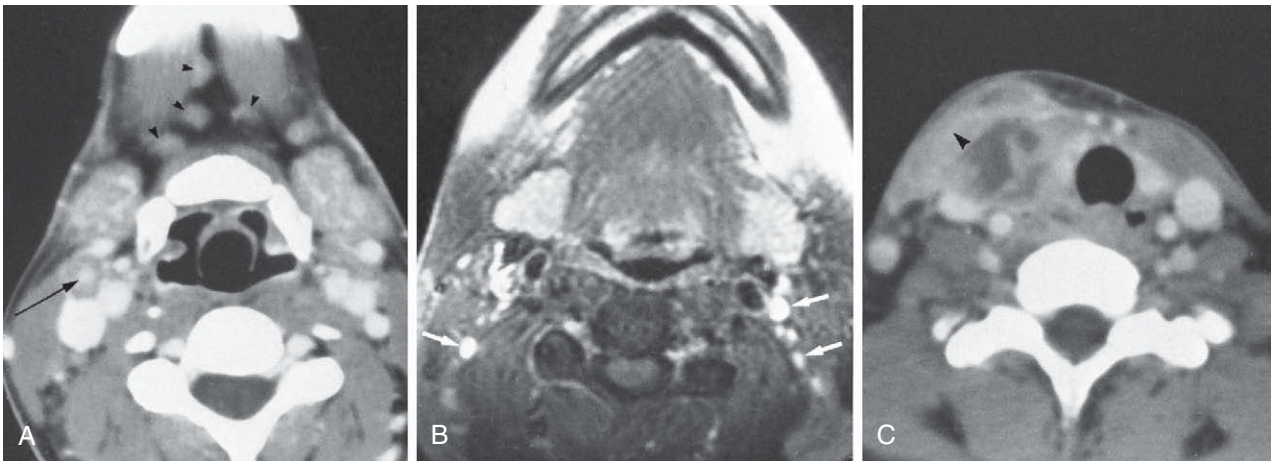


Figure 11-56. Reactive and inflammatory lymph nodes on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging. **A,** Axial CECT of the hyperplastic nodes in a patient with acquired immunodeficiency syndrome-related complex displays multiple submental nodes *(arrowheads)* and an enlarged internal jugular node with central hilar enhancement *(arrow)*. **B,** Small, normal, or reactive lymph nodes *(arrows)* enhance on this fat saturation postgadolinium T1-weighted image. **C,** Axial CECT of a tuberculous nodal mass (scrofula) with peripheral enhancement and invasion of the sternocleidomastoid muscle *(arrowhead)* is difficult to distinguish from the cluster of metastatic nodes.

will diminish background fat signal, further improving detection. The STIR image is superior to CECT in sensitivity for any enlarged lymph node, but is nonspecific for metastases. MRI and CECT rely on the same criteria of size, clustering, margin sharpness, and shape for characterization of abnormal nodes. The specificity of ring enhancement on CECT is the main advantage of CT for diagnosis of metastases. The same finding of ring enhancement on postgadolinium fat-suppressed T1WI likely represents a focal tumor or central necrosis as well. Otherwise, the other MRI sequences described are nonspecific. MRI may better demonstrate invasion of adjacent structures, especially muscles, than does CECT.

Adjacent fat, bone, cartilage, and muscle are commonly compressed or invaded with extracapsular spread. Secondary invasion of adjacent structures and anatomic spaces by aggressive lymph node lesions may develop in the carotid sheath structures, skull base, PVS and vertebrae, and mandible. The superficial nodes may invade adjacent muscle and skin. Internal jugular and spinal accessory nodes may invade the carotid, parapharyngeal fat, prevertebral, and infrahyoid visceral spaces. Parotid nodes may violate the surrounding parotid parenchyma, skin, masticator space, and parapharyngeal space. Suprahyoid retropharyngeal nodes may extend laterally into the CS, posteriorly into the PVS, anteriorly into the mucosal space, and superiorly into the skull base. The tracheoesophageal nodes may involve the common carotid artery and the internal jugular vein in the CS, the recurrent laryngeal nerve, the visceral space structures of the larynx and thyroid, and the mediastinum.

Invasion of the carotid artery carries a poor prognosis, with a local recurrence rate of 46% and a distant metastatic rate of 56% to 68%. For patients with a tumor involving the carotid artery, the 5-year survival rate decreases to 7%, and the mean survival decreases to less than 1 year. Prolonged survival is possible if the involved carotid artery is resected. The best imaging modality among CECT, MRI, or ultrasound for evaluating carotid fixation remains controversial.[35] Surprisingly, criteria for carotid invasion are not well established in the literature. A very high likelihood of carotid invasion exists if the tumor involves 75% or more of the circumference of the carotid whereas invasion is unlikely if the contact of the tumor to the carotid is less than 25% of the circumference of the carotid (see Fig. 3-59). Ultra-

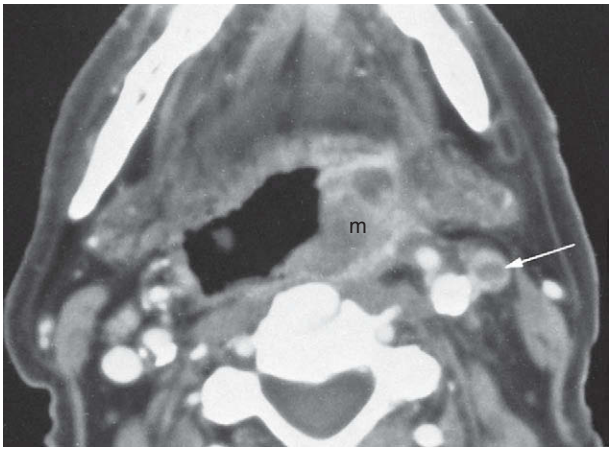


Figure 11-57. Metastatic node on contrast-enhanced computed tomography (CECT). Axial CECT in a patient with a left piriform sinus squamous cell carcinoma (m) and a "normal-sized" 9-mm node *(arrow)* with a focal defect (ring enhancement with "necrotic" center) is diagnostic of metastasis.

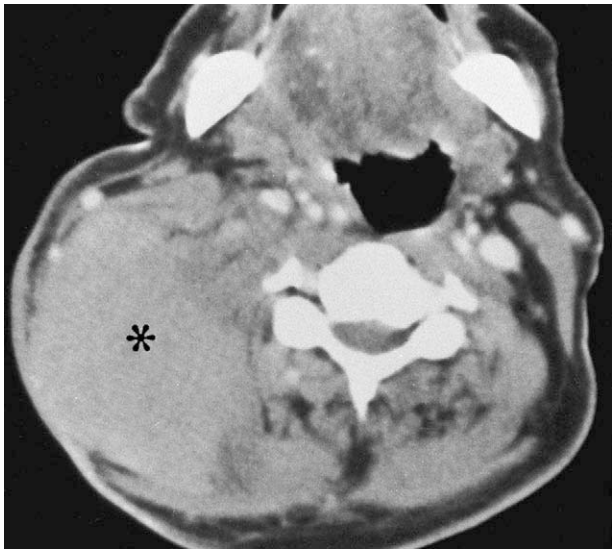


Figure 11-58. Node involvement by non-Hodgkin's lymphoma. Axial contrast-enhanced computed tomography shows a very large, homogeneous spinal accessory node *(asterisk)* invading both the skin and prevertebral space paraspinous musculature. The absence of central necrosis or focal defects in a mass this large is suggestive but not diagnostic of lymphoma.

sonography is a potentially valuable adjunctive technique capable of demonstrating invasion of the carotid artery.

Sinuses and Skull Base

Nose and Paranasal Sinuses

The sinonasal region can be divided into three major regions: the sinuses, the ostiomeatal complex, and the nasal cavity. The paranasal sinuses are mucosal-lined, air-filled cavities that are named after the bones of the face in which they develop. This mucosa is prone to both inflammatory and neoplastic disease. The frontal, maxillary, ethmoid, and sphenoid sinuses all drain through ostia into the nasal cavity. The frontal, maxillary, anterior ethmoid, and middle ethmoid sinuses drain into the semilunar hiatus under the middle turbinate. This area represents the ostiomeatal complex or unit. A small lesion here can cause

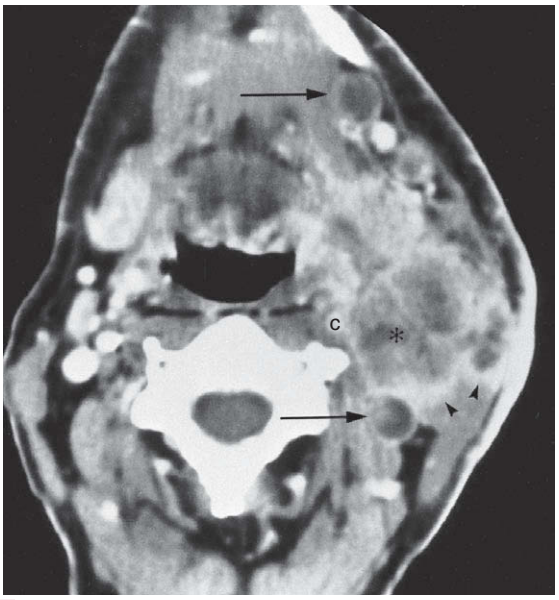


Figure 11-59. Extracapsular spread in multiple nodes in a patient with tonsillar squamous cell carcinoma. Left submandibular and spinal accessory node metastases *(arrows)* have typical ring enhancement and central low density on this axial contrast-enhanced computed tomography. The large cluster of metastatic nodes *(asterisk)* in the left internal jugular chain shows central low-density focal defects. Note the poorly defined infiltrative margins of this mass of nodes characteristic of extracapsular tumor spread. Tumor is invading the sternocleidomastoid muscle *(arrowheads)* posterolaterally and prevertebral space medially. About 40% of the left internal carotid artery (c) circumference is surrounded by tumor, which may still allow surgical preservation of the carotid artery.

obstruction to multiple sinus ostia. The posterior ethmoids and sphenoid sinus drain under the superior turbinate or sphenoethmoidal recess. The nasal cavity extends from the nares anteriorly to the choana posteriorly, and from the hard palate inferiorly to the cribriform plate superiorly. The midline nasal septum, lateral turbinates, and maxillary and ethmoid sinuses form the walls.

The compartments adjacent to the sinuses that are at risk for invasion by aggressive inflammatory or neoplastic processes include the anterior cranial fossa, orbits, cavernous sinus (from the sphenoid sinus), MS, pterygopalatine (pterygomaxillary) fossa, oral cavity, and anterior soft tissues of the face. These compartments are carefully viewed for dural or brain invasion, optic nerve and extraocular muscle compromise, perineural spread into the skull base, or direct extension into the deep compartments of the suprahyoid neck and oral structures. Involvement of any one of these secondary compartments can significantly alter treatment planning and surgical approach.

Paranasal Sinuses

Congenital and developmental anomalies of the sinonasal cavities are sought on all CT examinations. Common anatomic variants include pneumatization or paradoxic curvature of the turbinates, deviated septum, sinus hypoplasia, and Haller air cells (Fig. 11-61). Sinus underdevelopment may range from aplasia to hypoplasia. Pneumatization implies sinus development has occurred. Aeration indicates that the pneumatized portion of the sinus is air-filled. Mucosal thickening or opacification signifies the pneumatized section is filled with soft tissue inflammation or fluid. Either hypoplasia or the reactive new bone formation (chronic inflammation) may cause thickening and sclerosis of the sinus walls.

In general, evaluation of the paranasal sinuses involves assessment of two components: (1) the sinus contents (including the mucosa) and (2) the bony walls. Normal sinus mucosa is very thin and not seen on

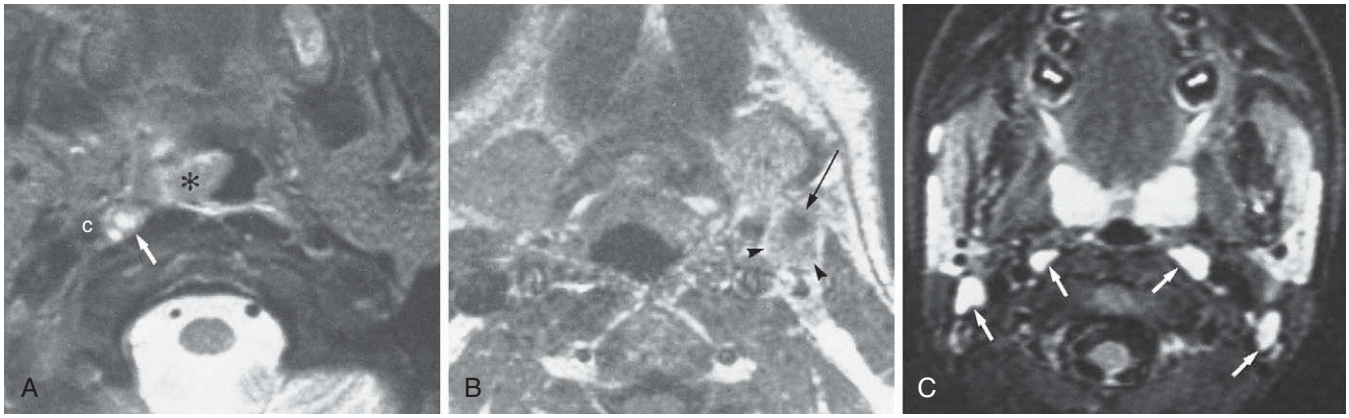


Figure 11-60. Metastatic nodes and focal defects on magnetic resonance imaging. **A,** Axial T2-weighted image at the soft-palate level depicts high-signal intensity at the right tonsillar squamous cell carcinoma *(asterisk)*. A 10-mm metastatic lateral retropharyngeal node of Rouvière with a high-signal intensity central defect *(arrow)* lies medial to the internal carotid artery (c). **B,** Left jugular digastric node *(arrowheads)* with low-signal intensity focal defect *(arrow)* on gadolinium-enhanced T1-weighted image is analogous to focal defect seen with metastases on a contrast-enhanced computed tomography. **C,** Axial short T1 inversion recovery (STIR) image achieves excellent fat suppression of subcutaneous fat. Metastatic neuroblastoma is demonstrated in the bright internal jugular and spinal accessory nodes *(arrows)*. Note the bright appearance of the normal tonsillar and parotid gland tissues on STIR.

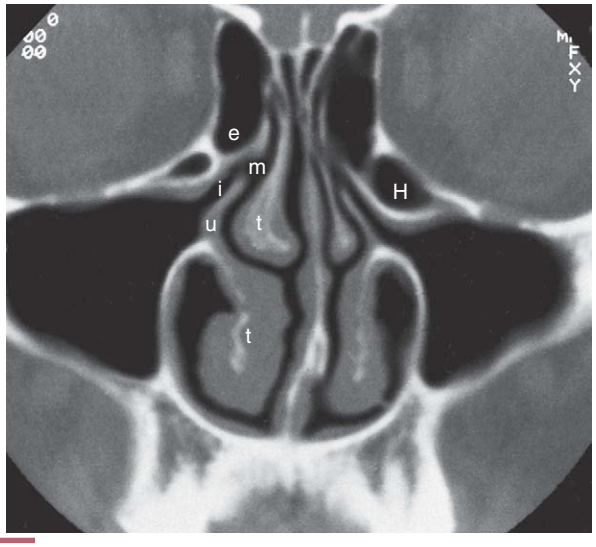


Figure 11-61. Normal ostiomeatal complex. Coronal noncontrast computed tomography demonstrates the ostiomeatal complex to the best advantage. Normal mucociliary drainage is from the maxillary sinus up through the infundibulum (i) and maxillary sinus ostium into the middle meatus (m). Ethmoid bulla (e) and uncinate process (u) form the lateral and medial walls of the infundibulum, respectively. Normal anatomic variant of a Haller air cell (H) underlying the orbit causes a mild narrowing of the left infundibulum. Smaller Haller cell is present on the right. Note the mildly asymmetric mucosa of the turbinates (t), which is part of the normal nasal cycle.

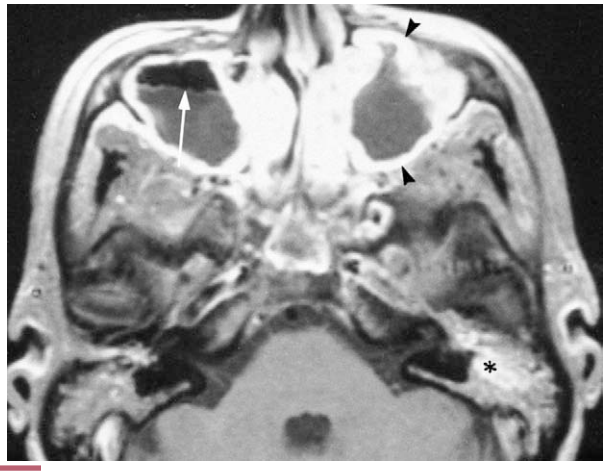


Figure 11-62. Acute and chronic sinusitis. Postgadolinium fat saturation T1-weighted image demonstrates an air-fluid level *(arrow)* in the right maxillary sinus and is diagnostic of acute sinusitis (superimposed on chronic sinusitis). Left maxillary sinus is filled with low-intensity secretions and has a peripheral ring of enhancing inflamed mucosa *(arrowheads)* typical of chronic sinusitis. Mastoid air cells and the left middle ear cavity *(asterisk)*, which normally appear black, are filled with enhancing inflammatory tissue.

CT or MRI, and the bone is normally thin and delicate in the posterior maxillary, ethmoid, and sphenoid sinuses. CT or MRI readily reveals the presence of a normally aerated sinus, mucosal thickening (chronic sinusitis, retention cysts, or polyps), an air-fluid level (acute sinusitis, intubation, and trauma), or complete opacification (mucocele, trauma, and acute or chronic sinusitis) (Fig. 11-62). The normally delicate posterolateral maxillary sinus wall is a much better indicator of bony sclerosis than the anterior wall. The normally thick anterior wall of the maxillary (and frontal) sinus may range from 1 to 3 mm (see Fig. 11-12A and C). Beginning observers frequently forget to assess the bone for important clues such as thickening and sclerosis (chronic sinusitis or hypoplasia), fractures, remodeling (slowly expanding mucocele or neoplasm), or destruction (malignancy or aggressive infection such as mucormycosis).

Deciding which portion of the opacified sinus, sinuses, or nasal cavity contains tumor and which contains obstructed mucous secretions is clinically important with a sinus or nasal tumor. The question is more problematic with NCCT or CECT because tumor and sinus secretions are frequently similar in density, and both the tumor and the mucosa may enhance; however, MRI is usually much more informative (Fig. 11-63). Evaluation of this problem requires a knowledge of signal intensity patterns of tumor versus mucus. Sinonasal tumors tend to be low-to-intermediate signal intensity on T1WI and intermediate signal intensity on T2WI, although minor salivary tumors and adenoid cystic carcinoma may be of high signal intensity.[36] The highly cellular aggres-

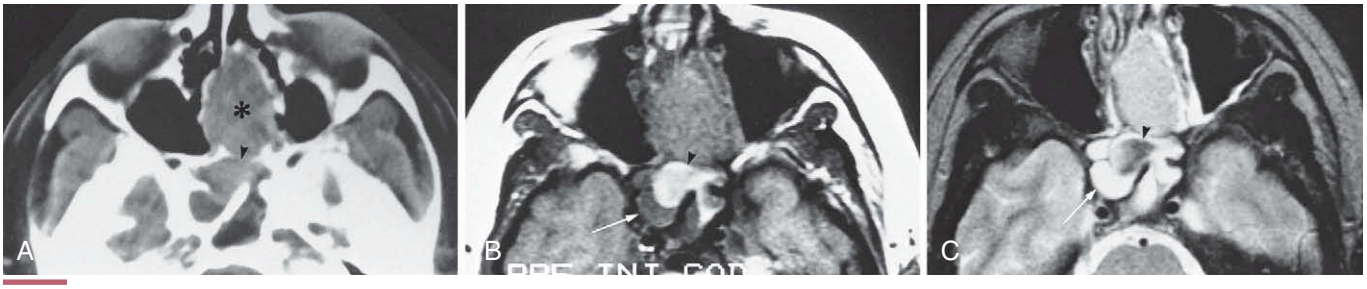


Figure 11-63. Comparison of computed tomography and magnetic resonance imaging for separating sinonasal small cell tumor from sphenoid pyomucocele. **A,** Axial contrast-enhanced computed tomography shows a mildly enhancing mass *(asterisk)* in the left posterior nasal cavity and ethmoids, which appears to extend into the sphenoid sinus. Sphenoid sinus contents actually represent two different viscosities of mucus, with higher density mucus anteriorly *(arrowhead)* correlating with most desiccated or viscous mucus. **B,** Axial noncontrast T1-weighted image demonstrates an intermediate-signal nasal tumor. Anterior, high-signal, viscous mucus *(arrowhead)* in the sphenoid sinus is clearly discriminated from the nasal tumor anteriorly and from the low-signal hydrated mucus *(arrow)* posteriorly. **C,** On axial noncontrast T2-weighted image, the nasal tumor signal is intermediate, similar to the brain. Anterior viscous mucus *(arrowhead)* in the sphenoid sinus has reversed signal to become low intensity, whereas hydrated mucus *(arrow)* posteriorly has now become very bright.

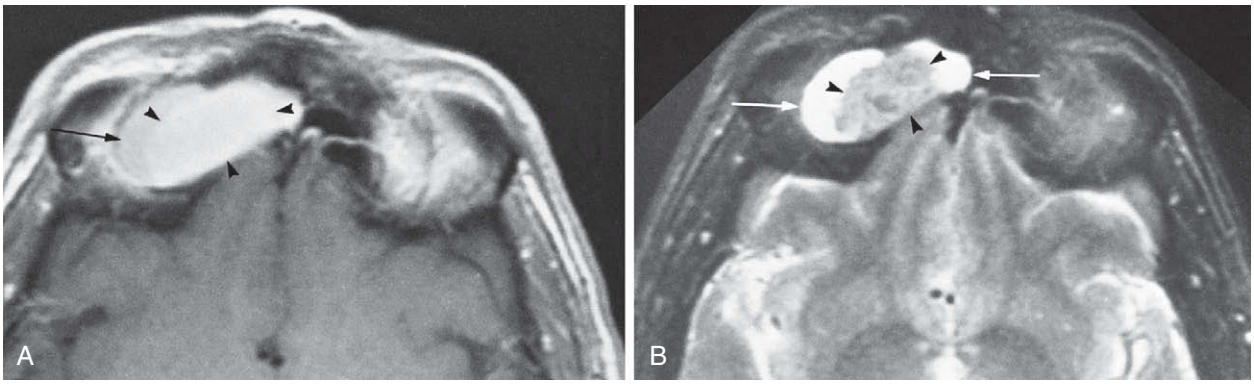


Figure 11-64. Simple mucocele on magnetic resonance imaging. **A,** Frontal mucocele on axial T1-weighted image expands the right frontal sinus and has a very high-signal central viscous or desiccated component *(arrowheads)* and a lower-intensity peripheral concentric ring of less viscous mucus *(arrow)*. **B,** Axial T2-weighted image reversal of signal intensities in concentric rings, with peripheral hydrated mucus *(arrow)* becomes bright and the central viscous mucus *(arrowheads)* loses signal.

sive neoplasms tend to have a lower water content and are less bright on T2WI. Tumors enhance moderately and, more or less, uniformly with gadolinium. Sinus secretions are complex in their patterns. Hydrated, nonviscous mucus is low intensity on T1WI and high intensity on T2WI. Desiccated, viscous mucus tends to be high intensity on T1WI and low-to-intermediate intensity on T2WI. Extremely desiccated mucus may lack signal intensity on T1WI or T2WI, simulating bone or air. Both an obstructed sinus and an expansile mucocele frequently have two or more layers of mucus in a concentric ring pattern with the most desiccated, viscous secretions located centrally. The peripheral mucosa of an obstructed sinus enhances in chronic sinusitis or with a pyomucocele, but does not enhance with a simple mucopyocele. The presence of tumor versus obstructed secretion is best solved by comparing the respective change in signal intensity of each component on the T1WI, T2WI, and post gadolinium T1WI, and is rarely answered by a single sequence. A minimum of a T1WI and a T2WI is required.

Ostiomeatal Complex

The ostiomeatal complex has become an area of active radiologic and pathophysiologic investigation with the development of endoscopic sinus surgery for inflammatory sinus disease. Coronal thin section NCCT is the best means of demonstrating the anatomy of this area (see Fig. 11-61). Pertinent observations include: (1) the individual's sinonasal anatomy and the presence of any anatomic variants (hypoplastic maxillary sinus, concha bullosa, agger nasi air cells, Haller air cells, deviated septum, deviated uncinate process, prominent ethmoid bulla, paradoxic curvature of the middle turbinate); (2) the location of obstructed air cells; (3) the extent of the chronic or acute sinus disease and whether this pattern is consistent with the obstruction of the ostiomeatal complex; and (4) the presence of any earlier surgical alterations (e.g., Caldwell-Luc, internal or external ethmoidectomy, uncinectomy). Ostiomeatal complex obstruction may result from anatomic compression, mucosal inflammation, polyps, benign neoplasms, and SCCA. Mucoceles, indicated by sinus expansion and low-density mucus on CECT, or by concentric rings of variably desiccated mucus in an expanded sinus on MRI, are a complication of chronic sinus obstruction (Fig. 11-64). A mucopyocele only shows peripheral enhancement when it is infected, and is then called a pyomucocele.

Nasal Cavity

The nasal cavity is occasionally the site of symptomatic disease. Anatomic variants include choanal atresia, concha bullosa, paradoxical curvature of the middle turbinate, wide nasal cavity from a hypoplastic maxillary sinus, and septal deviation. The nasal mucosa of the turbinates may be asymmetric in thickness because of the normal nasal cycle or the presence of polyps or inflammation. Obstruction of the ostiomeatal complex and other sinuses may occur with benign (antrochoanal polyp, neural tumors, inverting papilloma) or malignant (SCC, adenocarcinoma, adenoid cystic carcinoma) tumors (Fig. 11-65). If a nasal mass is present, the extent of the mass within the nasal cavity, adjacent sinuses, or orbits, or involvement of the cribriform plate, may be determined by coronal CECT or sagittal and coronal MRI because this may affect the surgical approach and postoperative therapy.

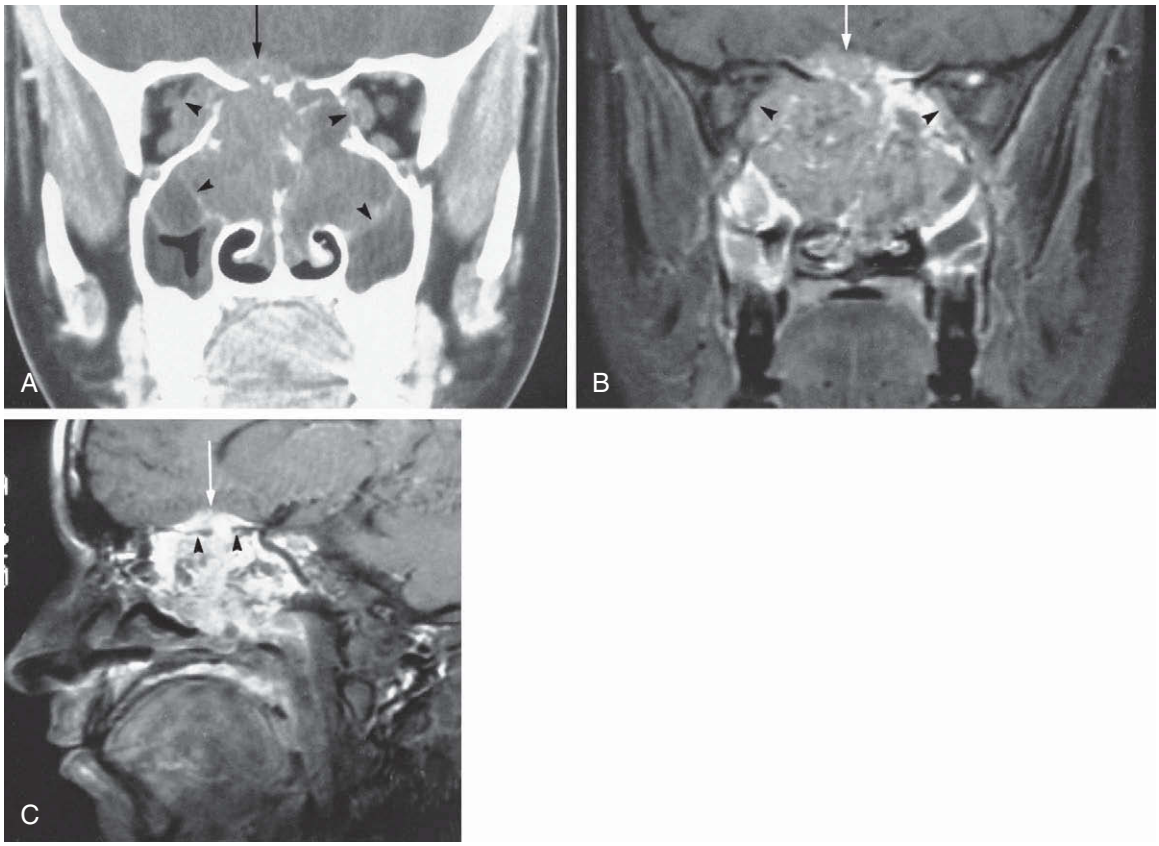


Figure 11-65. Invasive small cell carcinoma of cribriform plate and orbits. **A,** Coronal contrast-enhanced computed tomography shows (more clearly than magnetic resonance imaging) a mass centered in the posterior ethmoid sinuses with bone destruction of the cribriform plate *(arrow)* and medial orbits. The tumor has invaded both orbits and maxillary sinuses *(arrowheads)*. **B,** Anterior cranial fossa extension *(arrow)* through the cribriform plate and orbital invasion *(arrowheads)* are well seen on this coronal fat saturation postgadolinium T1-weighted image. **C,** Sagittal fat saturation postgadolinium T1WI depicts the anterior-posterior dimension of the tumor and extension of enhancing tumor *(arrow)* through the low-intensity cribriform plate and planum sphenoidale *(arrowheads)*.

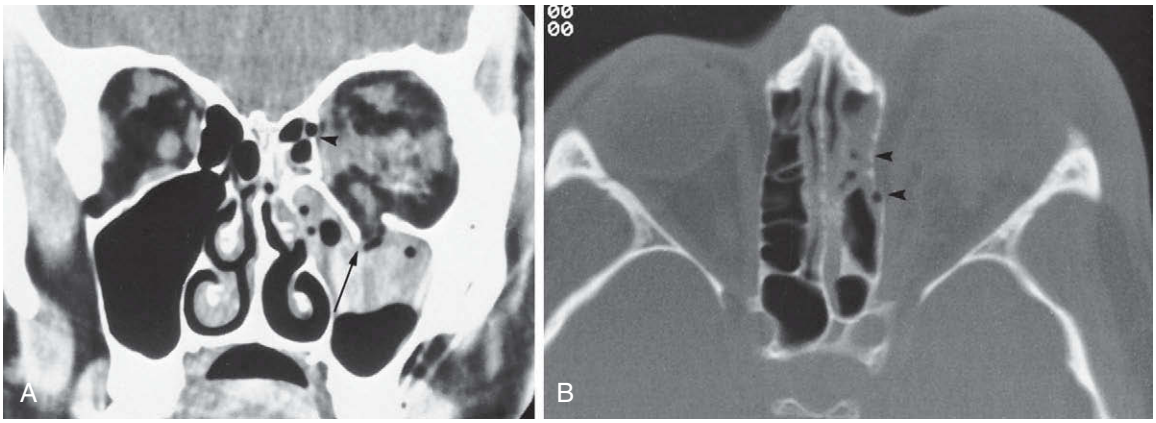


Figure 11-66. Medial and lateral orbital blowout fractures. **A,** Coronal noncontrast computed tomography (NCCT) with soft tissue windows shows an orbital blowout fracture with displacement of the floor *(arrow)*, distortion of the inferior rectus, and herniation of orbital fat through the orbital floor defect. Both intraconal hemorrhage and high-density maxillary sinus hemorrhagic air-fluid level are well demonstrated on these windows. Medial orbital blowout fracture *(arrowhead)* is suspected as well. **B,** Axial NCCT using bone windows shows opacified left anterior ethmoid air cells that help direct the observer to the displaced medial orbital fracture *(arrowheads)*.

Facial Trauma

Facial trauma is briefly included here because of the intimate relationship of the facial bones and sinuses. Thin-section axial and direct coronal NCCT is the ideal method for determining the full extent of facial trauma. One strategy for evaluating the extent of sinus trauma is to visually trace each bony outline on consecutive slices in both imaging planes, looking for fractures, normal fissures and canals, and displacements. However, the quickest way to locate sinus fractures is to search for indirect signs of fracture (Fig. 11-66): an air-fluid level, complete opacification of a sinus with blood, and the presence of gas outside the sinus (pneumocephalus, subcutaneous emphysema, infratemporal fossa, or orbital gas). Identification of the fractures allows determina-

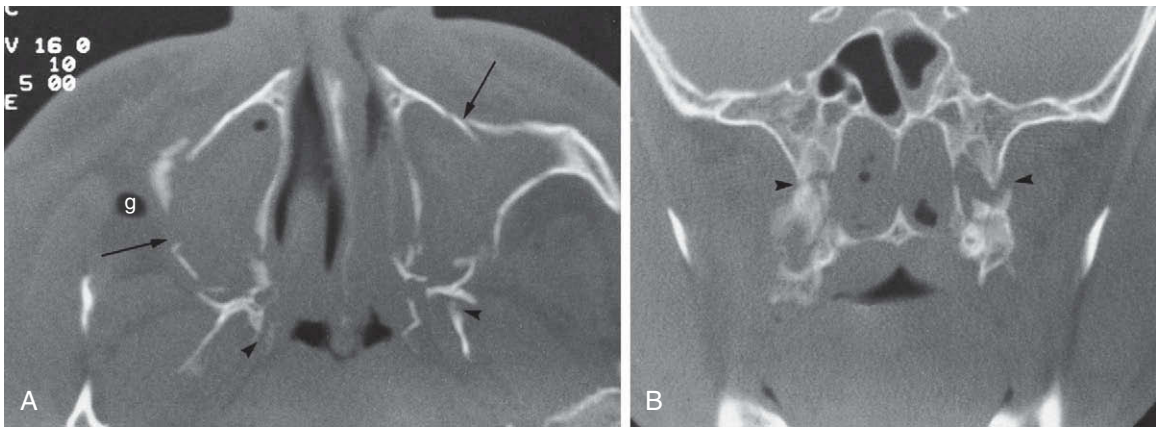


Figure 11-67. Facial fractures. **A,** Bilateral Le Fort type II fractures of the maxillary sinus anterior and posterior walls *(arrows)* and the pterygoid plates *(arrowheads)* appear as discontinuities or lucencies of the bone on this 3-mm axial noncontrast computed tomography (NCCT). Indirect signs of facial fracture are opacified maxillary sinuses, gas (g) in the right buccal fat pad, and premalar facial swelling. **B,** Coronal NCCT clearly demonstrates bilateral pterygoid plate fractures *(arrowheads)*.

tion of fracture classification: nasal, orbital blowout, trimalar or tripod, Le Fort (I, II, III, and complex), or nasoethmoidal complex fracture (Fig. 11-67). Assessment is made of the extent of soft tissue trauma, particularly the orbital soft tissues of the lens, globe, extraocular muscles, and optic nerve. Displaced orbital floor fractures may entrap fat or the extraocular muscles and result in enophthalmos or dysfunction of ocular motility.

Skull Base

Anatomically, the skull base can be divided into the anterior, middle, and posterior fossae. The lesser and greater wings of the sphenoid bone divide the anterior fossa from the middle fossa, while the petrous pyramid and mastoid portions of the temporal bone divide the middle and posterior fossae. The parietal and occipital lobes of the brain do not directly contact the skull base.

The skull base is formed from five bones: frontal, ethmoid, temporal, sphenoid, and occipital. The frontal and temporal bones are paired. Each of these bones can be subdivided into component bones. For example, the occipital bone has basioccipital, condylar, and squamosal portions. The skull base has its longest diameter in the AP plane, extending from the region of the crista galli to the posterior margin of the foramen magnum posteriorly. It is the thinnest in its superior-inferior direction, ranging between 3 and 5 mm in most areas, with the exception of the much thicker petrous temporal bone.

With CT, the skull base may be imaged using the axial or the coronal plane (only a modified coronal plane is possible because of limited gantry tilt). The coronal plane is excellent for delineating the superior inferior extent of a lesion. CT gives excellent visualization of bone detail, especially when bone algorithm techniques are used. In addition to the axial plane, MRI allows imaging both in a true coronal plane and in the sagittal plane, the latter especially useful for the study of midline lesions (e.g., chordoma). MRI also yields improved lesion contrast and conspicuity and more accurate delineation of lesion extent.

Using an anatomic approach, clinicians may classify skull base lesions as anterior, middle, or posterior fossa. They may then develop a unique differential for the medial and lateral portions of each fossa. Lesions may also be categorized as primary, those arising within the skull base itself, and secondary, those extending down from the cranial cavity above (endocranial lesions) or growing up from below (exocranial lesions). Endocranial masses are extracerebral and intracerebral lesions, whereas the exocranial lesions are secondary to extension superiorly from a disease process of the orbit, suprahyoid head and neck, cervical spine, and prevertebral muscles.

The skull base contains multiple foramina that allow the exit of cranial nerves and inflow and outflow of arteries and veins. These foramina also provide an access route for disease processes to spread from the cranial cavity to the infracalvarial structures and vice versa.[16] MRI performed after gadolinium infusion and with the use of fat suppression techniques allows sensitive detection of perineural spread, most readily seen with involvement of the fifth and seventh cranial nerves.[37]

Skull base fractures are readily detected with CT using thin slice sections and reformation techniques. Sinus air-fluid levels, sinus opacification, and clouding of the temporal bones may herald the presence of a fracture. Similarly, sinus opacification and fracture location may indicate the site of a CSF leak.

Inflammatory skull base lesions are now less common. Osteitis is seen as sclerosis of bone margins. Osteomyelitis usually involves all three skull tables and is characterized by irregular serpiginous lytic areas, occasionally with areas of bone sequestration present.

The osseous changes of neoplastic disease may be erosive, infiltrative, expansive, lytic, sclerotic, or of mixed density. Primary skull neoplastic lesions are uncommon. Benign conditions include osteoma, chondroma, giant cell tumor, cholesterol granuloma, and aneurysmal bone cyst (Fig. 11-68). Osteosarcoma, chondrosarcoma, fibrosarcoma, and rarely Ewing's sarcoma and lymphoma, are examples of malignant lesions. Metastatic lesions are more common than primary skull base lesions and frequently have an associated soft tissue component (Fig. 11-69). Osteoblastic metastases are most commonly caused by carcinoma of the prostate or breast; sclerotic changes may be seen occasionally in lymphoma (Fig. 11-70). Lytic lesions are more common than osteoblastic findings and are usually secondary to carcinoma of the lung, breast, kidney, or colon.

Intracerebral neoplastic processes may have associated osseous changes. Cerebral gliomas rarely cause local bone erosion or expansion; however, optic gliomas may cause expansion of the optic canal. Neuromas (nerve sheath tumors) may cause smooth expansion of skull base foramina: internal auditory canal (cranial nerve VIII), jugular foramen (cranial nerves IX, X, and XI), hypoglossal canal (cranial nerve XII), and lateral wall clivus and foramen rotundum (cranial nerve V). Paragangliomas cause irregular erosive changes in the skull base foramina (Fig. 11-71). A meningioma is often heralded by hyperostosis (bone sclerosis), especially common with a lesion of the middle fossa involving either the greater or lesser sphenoid wing. Chordoma, a tumor of notochordal remnants, typically causes destruction of the clivus (basisphenoid and basiocciput) with associated soft tissue mass and calcification.[38,39] Erosion of the sella floor and sella expansion are characteristic of pituitary adenomas.

Temporal Bone

Determination of temporal bone abnormality requires assessment of the external ear, middle ear, mastoid air cells, petrous apex, inner ear,

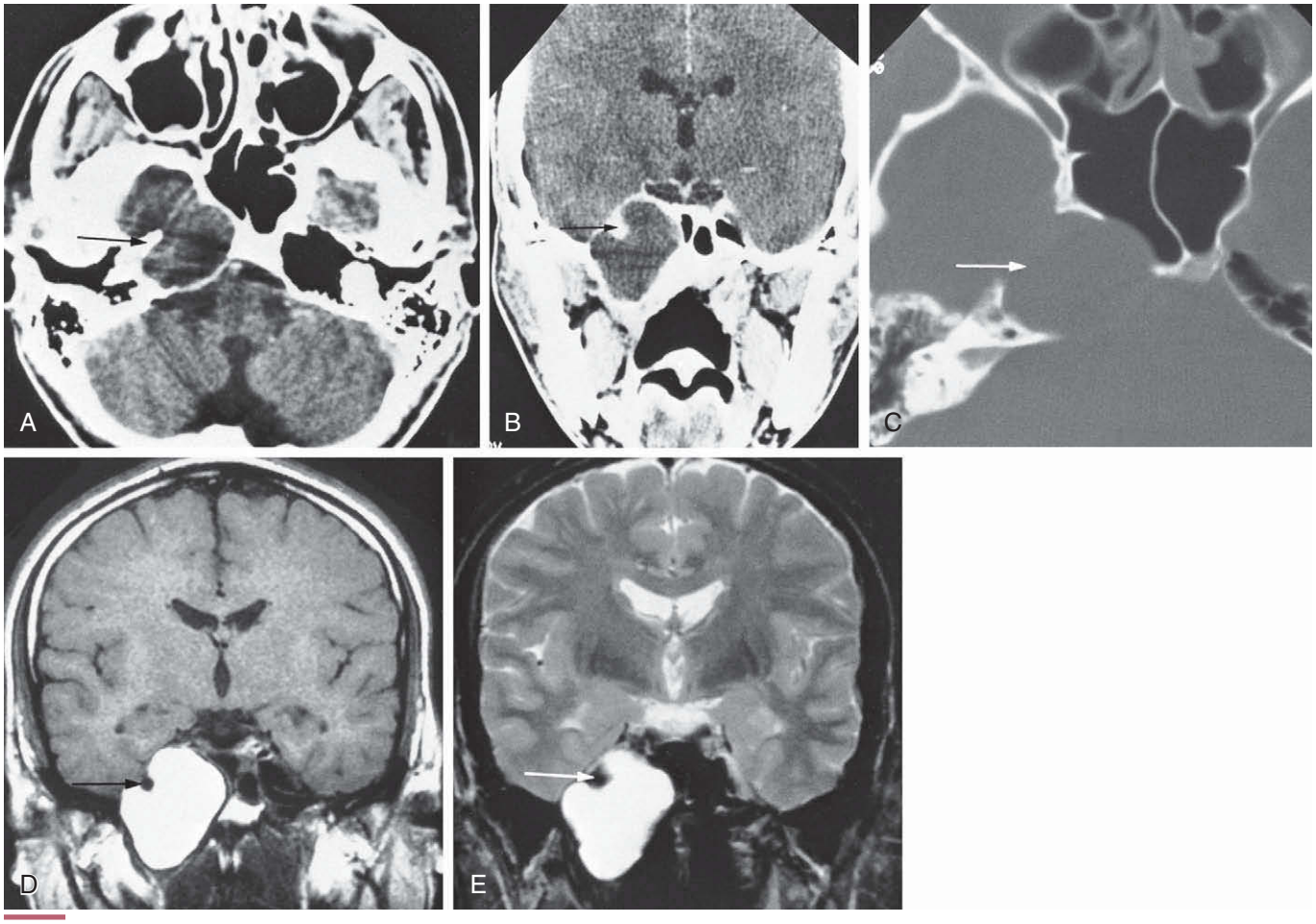


Figure 11-68. Cholesterol granuloma. **A** and **B,** Axial and coronal contrast-enhanced computed tomography (CECT) images demonstrate expansile lesion of the right petrous apex and greater wing of sphenoid. Lesion is homogeneously low density in nature. Displaced right internal carotid artery *(arrows)* lies in the lateral aspect of the lesion. **C,** Axial CECT bone algorithm image using bone windows demonstrates truncation of the anteromedial portion of the right petrous temporal bone *(arrow)* and adjacent posterolateral portion of the sphenoid bone. The lesion bulges into the right sphenoid sinus. **D,** Coronal T1-weighted image and, **E,** T2-weighted image demonstrate a lesion that is high intensity on both sequences, consistent with methemoglobin. Right internal carotid artery is noted in the midlateral portion of the lesion *(arrow)*. The lesion extends above and below the skull base and invaginates into the sphenoid sinus.

IAC, facial nerve canal, and vascular compartment (jugular foramen and carotid canal). The adjacent compartments into which an aggressive temporal bone lesion can spread, or from which a lesion can invade the temporal bone, include cerebellopontine angle (meningioma, acoustic schwannoma), middle cranial fossa (geniculate schwannoma, cholesteatoma), jugular foramen (schwannoma, paraganglioma, glomus tumor), skull base and clivus (chordoma), carotid space (aneurysm, schwannoma), parotid space (adenoid cystic carcinoma), and soft tissues of the external ear and scalp (SCC).

For the external ear and external auditory canal (EAC), the search for abnormality may be accomplished with either high-resolution CT or MRI. Abnormal development (external ear hypoplasia, fibrous or bony EAC atresia), soft tissue opacification (cerumen, EAC cholesteatoma, SCC), bone erosion (EAC cholesteatoma, mucormycosis, squamous cell carcinoma), bone formation (exostoses), or scutum erosion (par flaccida cholesteatoma) can easily be detected and their extent defined by CT. MRI may add additional information on soft tissue involvement below the skull base or on infiltration of the auricle and scalp.

The middle ear is best evaluated with high-resolution CT. Ossicular chain anomalies (fusion, dislocation, prosthesis, stapedial footplate sclerosis), air-fluid level (trauma, acute otitis media), soft tissue opacification (acute or chronic otitis media, cholesteatoma, trauma, chronic endotracheal or nasogastric intubation), and tympanic membrane thickening (otitis media) may all be characterized (Fig. 11-72). The radiographic approach to the mastoid air cells and petrous apex is similar to that of the paranasal sinuses, consisting of the evaluation of the mastoid and petrous apex soft tissue contents and the bony walls. Assessment is made of development or pneumatization of these regions (pneumatization or opacification by soft tissue), the bony septa and walls (hypoplasia or sclerosis from chronic otomastoiditis), the margins of the mastoid or petrous apex (expanded by a primary or secondary cholesteatoma [Fig. 11-73] or a cholesterol granuloma), or bone destruction (SCC, malignant fibrous histiocytoma, glomus tumor). MRI may complement CT for assessment of larger petrous apex or mastoid masses. A normal unpneumatized, fatty (marrow-filled) petrous apex is high signal on T1WI and low signal on T2WI, but a cholesterol granuloma is high signal on T1WI and T2WI from the methemoglobin (see Fig. 11-68). Mucus in an air cell is low intensity on T1WI, is very high intensity on T2WI, and enhances mildly with gadolinium. A primary cholesteatoma is similar to CSF in intensity, appearing low intensity on T1WI and moderately high signal on T2WI, and does not enhance with gadolinium. Postoperative findings encountered on CT and MRI include metallic ossicular prostheses, cochlear implants, and various types of mastoidectomies.

The inner ear structures are best assessed by high-resolution CT with attention to anatomic variants and bone density. A saccular ves-

tibule is one of the more common congenital anomalies. A cochlea with less than 2½ to 2¾ turns represents a Mondini malformation (Fig. 11-74). The basal turn of the cochlea and round window may be identified on both axial and coronal CT images. The horizontal (lateral) semicircular canal cortex may be eroded by a cholesteatoma. The oval window and foot plate of the stapes are thickened in stapedial otosclerosis, and the ring of the otic capsule is demineralized in labyrinthine otosclerosis (otospongiosis). The entire petrous bone may be abnormally low density with dysplasias such as osteogenesis imperfecta or sclerotic in osteopetrosis and Paget's disease. Inflammatory or neoplastic lesions may involve the cochlea and vestibule without obvious bony changes on CT; however, MRI with gadolinium-enhanced T1WI may show an enhancing lesion.

The IAC and facial nerve canals are best evaluated by high-resolution CT for bony detail and by gadolinium-enhanced MRI for the soft tissue abnormality. On CT, the findings might include widening (acoustic schwannoma, surgery) or narrowing (bone dysplasia, hyperostosis from a meningioma) of the IAC. The facial nerve canal may be traced along its entire course in both axial and coronal planes for areas of erosion (facial neuroma, paraganglioma, hemangioma) or abnormal position (anterior location of mastoid segment with EAC atresia). Gadolinium-enhanced MRI is the modality of choice for evaluating the seventh and eighth cranial nerves within the IAC and temporal bone (schwannomas of the facial nerve, of the vestibular nerve, or within the cochlea) or for demonstrating seventh cranial nerve inflammation (Bell's palsy) (Figs. 11-75 and 11-76). Note that the facial nerves may normally enhance mildly and usually symmetrically within the facial nerve canal. Asymmetric enhancement is more likely to be abnormal.

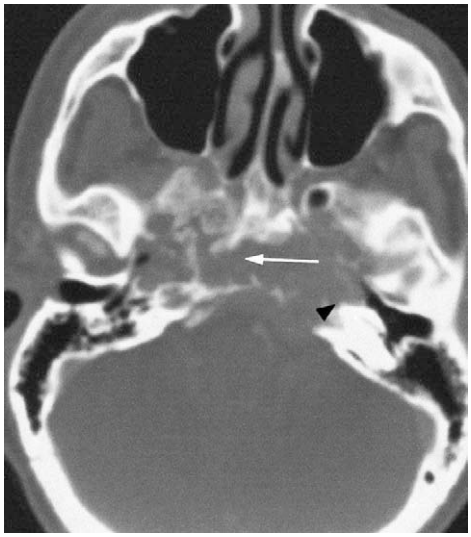


Figure 11-69. Skull base metastasis from adenocarcinoma of the breast. Axial noncontrast computed tomography demonstrates a metastatic tumor infiltrating and destroying a majority of the middle fossa. Clivus *(arrow)* and anteromedial left temporal bone *(arrowhead)* are especially affected.

Postoperative Neck and Face

A preoperative CECT or MRI is extremely helpful for interpreting the postoperative neck, skull base, or face for sites of concern and potential tumor recurrence. Likewise, a baseline CECT or MRI 3 to 6 months after surgery and radiation further improves the ability of imaging to detect posttreatment tumor recurrence. The posterior cervical space is the most frequently altered neck space, and part or all of its contents may be resected for staging and treatment of head and neck carcinoma. Note is made of missing structures.[40] A radical neck dissection (Fig. 11-77A) removes the sternocleidomastoid muscle, internal jugular vein, regional lymph nodes, and most of the fibrofatty tissue that comprises this space. Modified radical, functional, and supraomohyoid neck dissections remove less.

The oral cavity and face also are affected by surgery. Facial trauma is frequently treated by internal fixation with metallic screws and plates. Internal fixation also is performed as part of composite reactions where the mandible is split, or when the mandible is partially resected for invasion by tumor. Metal wires, screws, and plates may cause artifacts obscuring sites of posttraumatic CSF leak or potential tumor recurrence. Sinus and palate tumors may require resection of the maxilla, palate, orbital walls and soft tissue, and cribriform plate. The fat, muscle, or bone contained in free flaps, myocutaneous flaps, and osteocutaneous flaps placed in the surgical cavity further complicates image interpretation (see Fig. 11-77). Laryngeal surgery may remove parts or all of the larynx, often with placement of a tracheostomy. The remaining soft tissues of the collapsed visceral space are difficult to accurately evaluate.

Radiotherapy frequently causes an edematous pattern, characterized on CT by a streaky increase in the density of the subcutaneous, parapharyngeal, and posterior cervical space fat planes (Fig. 11-78A). On MRI it may have an increased signal on T2WI. The mucosal space of the pharynx and larynx may also develop swelling and edema,

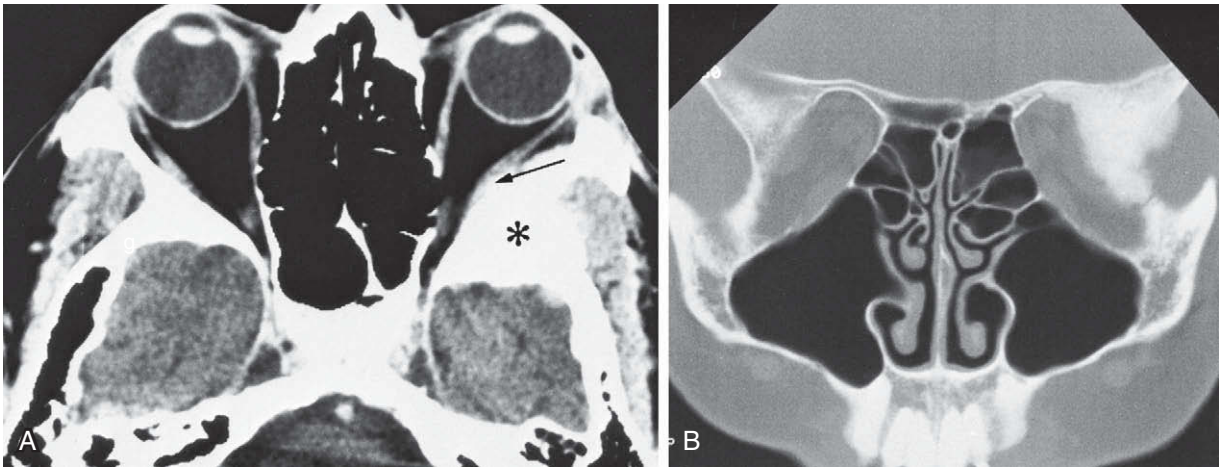


Figure 11-70. Metastatic prostate carcinoma to left orbit. **A,** Axial contrast-enhanced computed tomography (CECT) demonstrates sclerotic metastasis of the posterolateral margin of the left orbit *(asterisk)*. Small soft tissue component *(arrow)* lies deep to the hyperostosis, displacing the lateral rectus muscle medially. **B,** Coronal CECT with bone settings demonstrates a marked sclerotic reaction of the superior lateral portion of the left orbit. Intraorbital volume is decreased.

Figure 11-71. Glomus tumor (paraganglioma) of the right petrous temporal bone. Axial contrast-enhanced computed tomography with bone windows demonstrates an infiltrative destructive lesion of the middle and superior portions of the right petrous temporal bone *(arrow)*. Poorly defined margin of the lesion is characteristic of a glomus tumor. Soft tissue mass *(arrowheads)* is noted in the right cerebellopontine angle cistern and in the inferior portion of the right middle ear cavity *(asterisk)*. Previous right mastoidectomy has been performed.

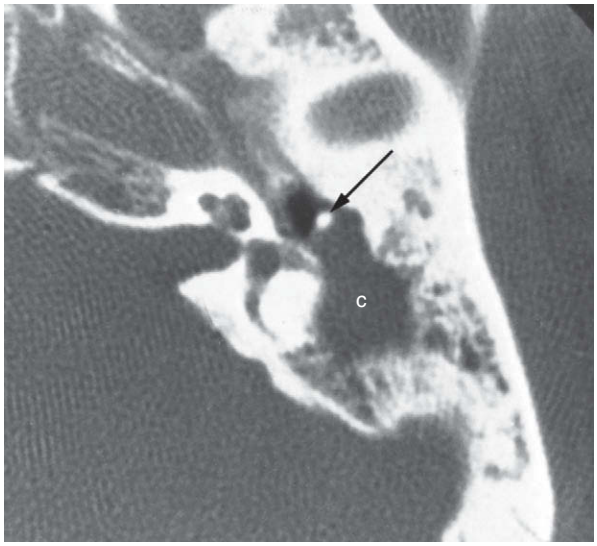


Figure 11-73. Pars flaccida cholesteatoma. Middle ear cholesteatoma (c) expands the mastoid antrum and epitympanic recess on this axial noncontrast computed tomography. The absence of incus and soft tissue abutting the head of malleus *(arrow)* confirm ossicular erosion.

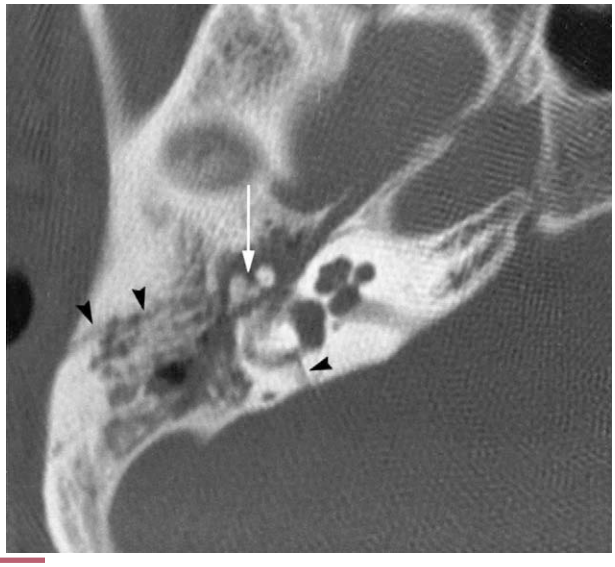


Figure 11-72. Transverse petrous fracture with ossicular dislocation. High-resolution 1.5-mm noncontrast computed tomography using a bone algorithm and bone windows shows a transverse petrous fracture *(arrowheads)* extending through the mastoid bone and semicircular canals. Ossicular dislocation of the head of malleus from its articulation with the fractured body of incus *(arrow)* is seen. Middle ear opacification also confirms presence of temporal bone trauma.

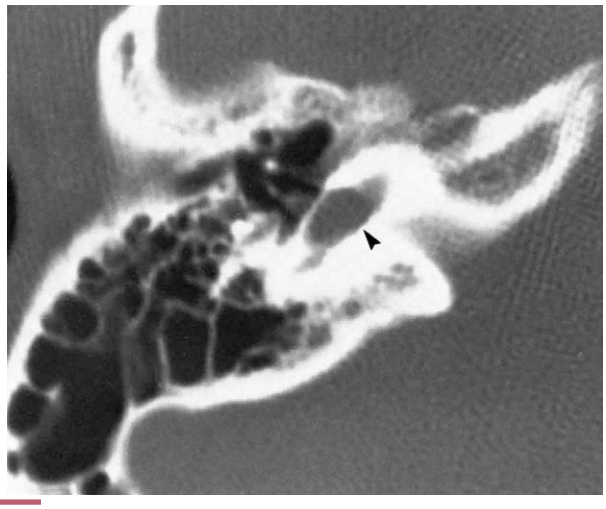


Figure 11-74. Mondini malformation. Saccular combined vestibule and cochlea *(arrowhead)* reveal a severe form of Mondini malformation on this axial noncontrast computed tomography.

appearing as diffuse mucosal thickening and enhancement on CECT, while MRI may show high signal on long TR sequences and on gadolinium-enhanced T1WI (see Fig. 11-78B). Postradiation edema, particularly of the larynx and pharynx, may mimic recurrent neoplasm for as long as 6 months to 7 years after radiotherapy.[41] Finally, treated lymph nodes may decrease in size or totally disappear, leaving a "dirty fat" appearance.

Recurrent tumor spread often produces strands or nodules of soft tissue density within or replacing the normal fat planes. However, CECT has difficulty detecting small (less than 1 cm) or mucosal based tumors, and reliably differentiating between recurrent carcinoma and fibrosis or edema. A new bulky, ring-enhancing mass, local tissue invasion, or further bone destruction is a strong sign of recurrent tumor. MRI is reportedly capable of distinguishing tumor from radiation-induced fibrosis in some cases. Posttreatment fibrosis or scarring is similar to or lower in signal than muscle on all sequences (particularly on T2WI), is usually linear, is not masslike, and may enhance mildly in a linear fashion. MRI is superior to CT (particularly NCCT) in discrimination of recurrent tumor from muscle and vascular structures. In the posttreatment neck, gadolinium-enhanced MRI may have the potential to identify tumor recurrence and allow separation of tumor from fibrosis because recurrent tumor may ring-enhance, a pattern not seen with scar. Finally, PET/CT is better able to differentiate the metabolically active tumor tissue from postoperative changes.

Figure 11-75. Acoustic schwannoma. Axial fat saturation postgadolinium T1-weighted image demonstrates a brightly enhancing right cerebellopontine angle mass with intracanalicular (characteristic of acoustic schwannoma) and extracanalicular components. Note the acute angle that the mass makes with the petrous ridge *(arrow)*.

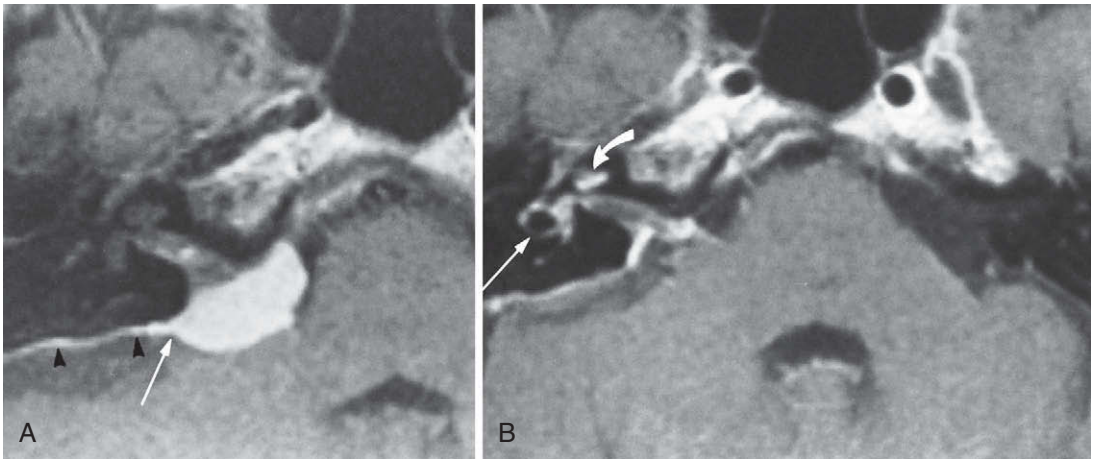


Figure 11-76. Magnetic resonance imaging (MRI) of internal auditory canal (IAC) and facial nerve. **A,** Axial postgadolinium T1-weighted image shows a broad-based brightly enhancing meningioma overlying the IAC. Note its obtuse angle *(arrow)* with the petrous ridge and dural "tail" extending posteriorly *(arrowhead)*, which are characteristic of a meningioma. **B,** In the same patient, postoperative labyrinthitis has developed on this follow-up axial postgadolinium T1-weighted images. Abnormal enhancement of the vestibule, semicircular canals *(straight arrow),* and cochlea *(curved arrow)* are new findings (which can only be observed by gadolinium-enhanced MRI).

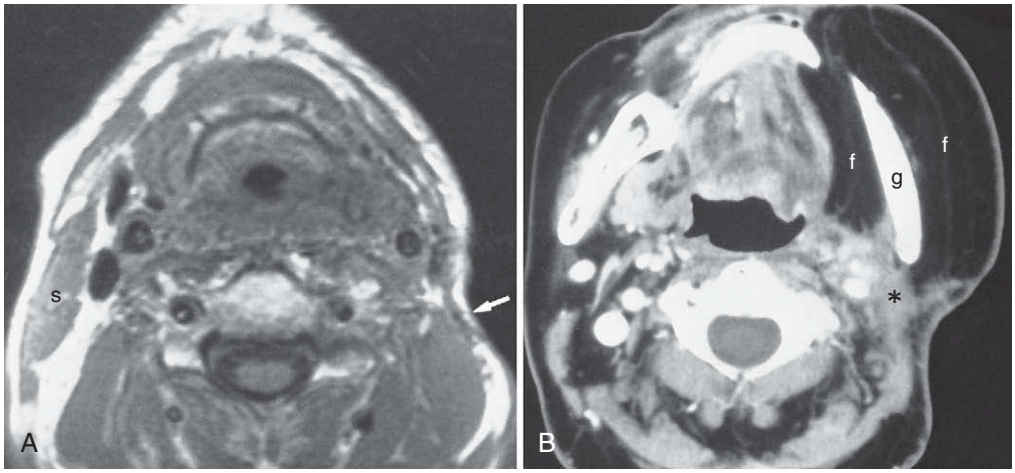


Figure 11-77. Postoperative appearance of neck. **A,** Axial T1-weighted image demonstrates an earlier left neck dissection *(arrow)* with removal of the sternocleidomastoid muscle (s) and posterior cervical space fat. **B,** Patient with an osteocutaneous flap, with thick fat (f) on deep and external margins of the mandibular graft (g), has developed a deep recurrent tumor *(asterisk)* around the carotid sheath.

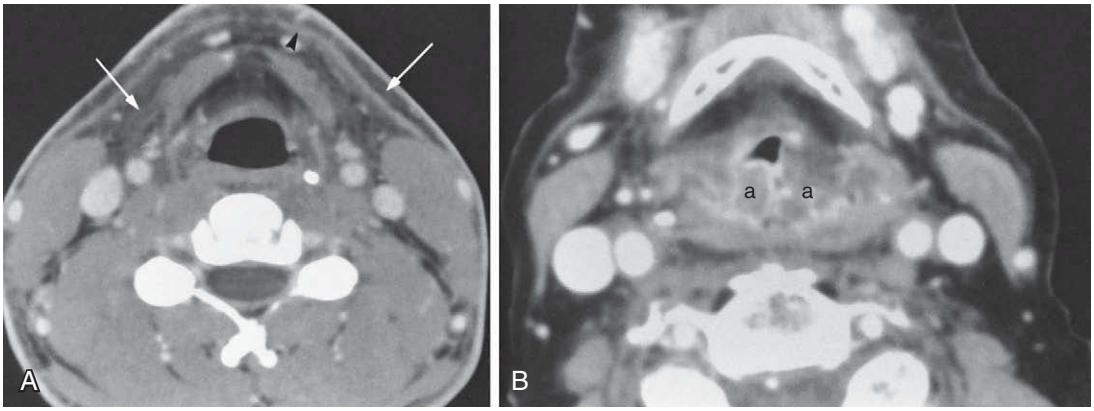


Figure 11-78. Radiation changes in neck. **A,** Axial contrast-enhanced computed tomography (CECT) demonstrates streaky densities in fat throughout the superficial cervical and anterior cervical spaces *(arrows)* and a thickening of the platysma muscle *(arrowhead)*. **B,** Different patient who had radiation therapy for glottic carcinoma has developed a thickening of the epiglottis and aryepiglottic folds (a) on this axial CECT. This finding may persist for many months after therapy.

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For complete list of references log onto www.expertconsult.com.

CHAPTER TWELVE

Odontogenic Infections

James M. Christian

Key Points

- Almost all odontogenic infections are due to mixed bacterial flora, the most common of which are streptococci and oral anaerobes.
- Endodontic therapy or extraction of the tooth, surgical drainage of the abscess, and release of pressure to improve vascularity are all fundamental in management of odontogenic infections.
- The direction of spread of the infection from the tooth apex depends on the path of least resistance of the marrow considering the thickness of the overlying cortical bone and the relationship of the bone's site of perforation to the muscle attachment of the jaws.
- The factor that determines whether the sublingual or submandibular space is involved in spread of an odontogenic infection is the location of the perforation relative to the mylohyoid muscle attachment.
- The hallmark of infection in any or all of the secondary spaces of the mandible (the masticator space) and by extension, the deep neck spaces, is trismus.
- Evaluation and management of the airway is critical to the success of treating severe odontogenic infections.
- A careful history and a thorough physical examination, with the appropriate radiographic images, are paramount in diagnosing and treating patients with odontogenic infections.

Odontogenic infections are among the most frequently encountered infections afflicting humans, the etiology of which is almost always a carious tooth or a tooth suffering from periodontal disease. The vast majority of these infections are minor and acute, and some even drain through the tooth socket , because they are primarily due to chronic periodontal disease. Consequently, there is considerable interest in periodontitis—a chronic inflammatory disease (and by definition a chronic low-grade infection due to a microbial biofilm) of the tooth-supporting structures—as a potential risk factor in the morbidity and mortality of systemic conditions such as cardiovascular disease, diabetes mellitus, and premature birth. Research is ongoing to delve more deeply into these relationships.[1] Refer to the Suggested Readings for more information on periodontal disease. Another topic that frequently arises with reference to odontogenic infection is osteomyelitis, which is an inflammation of the cortical and cancellous bone. It can follow odontogenic infection that is not completely resolved and when appropriate attention is not paid to the jawbone itself on follow-up. Again, refer to the Suggested Readings for more information regarding osteomyelitis.

Odontogenic infections, whether acute or chronic, have been plaguing humanity for millennia, and there are many documented stories, engravings, artifacts, and the like to prove this point.[2] A great deal of pain and suffering continues to be a scourge, especially in populations that neglect dental care, do not have access to dental care, or ignore professional advice on proper oral hygiene. Extraction of the offending tooth usually results in resolution of the infection, even without antibiotics. However, some of these minor tooth-related infections occasionally become more serious and potentially life threatening, especially in immunocompromised patients. The need for more aggressive surgical and medical care is usually necessary then to prevent more disastrous results.

This chapter discusses the more acute odontogenic infections, focusing on diagnosis, clinical and radiographic presentation, microbiology, and treatment and management. Emphasis is on the pathogenesis, especially for the nondental practitioner, to provide a clearer understanding and ensure effective treatment is provided.

Microbiology of Odontogenic Infections

Odontogenic infections are usually caused by normal endogenous flora. The mouth contains many microenvironments, allowing for colonization of many bacterial species. Once this environment is established, which varies with factors such as age, immune status, type of diet, and preferred environment, it can and does change over a lifetime. Table 12-1 lists many of the common "normal" aerobic, facultative, and anaerobic species of bacteria (several fungal species, viruses, and even protozoans can also be found in the "normal oral flora"). In most patients, these normal oral bacteria are the cause of most odontogenic infections. Other organisms can be implicated, however, if there is a compromised host or unusual oral environment, such as that found in chronic osteomyelitis. Facultative streptococci are the most numerous group of organisms in the oral cavity and members of the viridans group are the most abundant; these are classically based on their type of hemolysis on agar. Noticeably absent from these normal organisms are the staphylococci, although they are present in nearly every mouth, but in small numbers. *Staphylococcus aureus*, in particular, is much more common in the nose and throat, and may participate in mixed odontogenic infections. Gram-negative anaerobes comprise much of the rest of the mouth's normal flora, and these organisms can increase in numbers, especially in patients with chronic periodontal disease.[3]

In a recent study describing the microbiology of head and neck infections of odontogenic origin by Rega and colleagues,[4] the most common bacteria isolated were viridans streptococci, *Prevotella*, staphylococci, and *Peptostreptococcus*. This finding has been consistent for many years, even as name changes (especially for *Bacteroides*) have taken place to better reflect more recent genetic information.[5-9]

Based on the results of many studies in the literature and much clinical anecdotal evidence, two important conclusions can be drawn

Table 12-1

Normal Mouth Flora

Aerobic Bacteria	Anaerobic Bacteria
Gram-positive Cocci	
Streptococcus	*Streptococcus* *Peptococcus* *Peptostreptococcus*
Gram-negative Cocci	
Neisseria	*Veillonella*
Gram-positive Bacilli	
Diphtheroids	*Clostridium* *Actinomyces* *Eubacterium* *Lactobacillus*
Gram-negative Bacilli	
Haemophilus *Eikenella*	*Prevotella (Bacteroides)* *Fusobacterium* *Porphyromonas*

Adapted from Peterson LJ. Odontogenic infections. In: Cummings CW, ed. *Otolaryngology Head and Neck Surgery.* Vol 2. 2nd ed. St. Louis: Mosby; 1993:1199.

regarding the microbiology of odontogenic infections: First, almost all odontogenic infections are due to mixed flora. Peterson states that the average number of different organisms is five, but can be as great as 10 or more.[10] Second, between one third and two thirds of these infections are primarily anaerobic,[4,10] which probably has to do with the timing of obtaining the cultures.

The most commonly implicated organisms in mixed infections are viridans streptococci, *Peptococcus, Peptostreptococcus, Eubacterium, Prevotella,* and *Fusobacterium*. Notably absent from this list are the enteric gram-negative cocci and rods, such as group D streptococci, *Escherichia coli, Pseudomonas*, and *Bacteroides fragilis*, among others. This fact has profound implications for treatment when any of these non-normal organisms are cultured from an odontogenic infection.

The anaerobic bacteria seen in odontogenic infections are not usually acknowledged to be pathogenic themselves. The most commonly isolated anaerobe is probably *Prevotella (Bacteroides)*. Entry of bacteria into deeper tissues to cause an infection is probably the result of invasive aerobic bacteria giving access through a necrotic dental pulp. The aerobes then serve as the initiators of the infection, preparing the local environment for anaerobic bacterial invasion and subsequent proliferation. The anaerobes then predominate because the reduction-oxidation potential favors anaerobic growth. The clinical picture is as follows: aerobic or facultative streptococci release exotoxins and lytic enzymes to cause a spreading cellulitis. As the infection progresses, a mixed streptococcal/anaerobic infection ensues. As the hypoxic state increases, the predominance of anaerobic bacteria becomes evident.

Implications of Microbiology for Antibiotic Therapy

For centuries, the primary treatment of odontogenic infections has been surgical, and it will continue to be so in the future. Endodontic therapy or extraction of the tooth, surgical drainage of the abscess, and release of pressure to improve vascularity are all fundamental in the management of these infections.

Antibiotics are a necessary adjunctive therapy in many of these infections to allow for faster and complete resolution. The choice of antibiotic should be based, at least initially, on the susceptibility of the organisms likely to be the cause of the infection. In an *uncomplicated infection,* an empirical choice can be made without the delay of obtaining a specimen for culture and sensitivity testing.

Two microbiologic factors must be kept in mind, however, when making this choice: first, the antibiotic must be effective against *Streptococcus*, because these bacteria are ubiquitous in odontogenic infections; second, the antibiotic should be effective against a wide range of anaerobes, because up to 90% of infections involve some of these bacteria. Fortunately, oral anaerobes are still very susceptible to available antibiotics.[11,12]

The following list summarizes the effectiveness of commonly used antibiotics for odontogenic infections:

- Orally administered drugs
  - Very effective: penicillin, clindamycin, metronidazole (for anaerobes only), amoxicillin/clavulanic acid
  - Effective: erythromycin, cephalexin, tetracycline
  - Less effective: sulfa, quinolones

- Parenterally administered drugs
  - Very effective: penicillin, clindamycin, metronidazole
  - Effective: cefazolin, cefoxitin, carbapenems
  - Not effective: gentamicin, tobramycin, amikacin, cephalosporin (third generation)

The very effective drugs can be used with confidence empirically to treat most odontogenic infections. The effective and less effective drugs are less predictable and should not be used as first-line drugs unless allergy dictates their use or specific culture and sensitivity data are subsequently available. The drugs listed as not effective are not effective against either *Streptococcus* or anaerobes. They should only be used in specific circumstances when indicated by culture results and then in combination with a beta-lactam antibiotic.

In certain infections, other antibiotics may be used. Drugs such as ampicillin, ticarcillin, piperacillin, azlocillin, mezlocillin, moxalactam, third-generation cephalosporins, and chloramphenicol are generally reserved because of their greater toxicity, excess expense, or extended spectra. However, these may be useful in a life-threatening situation, in which case an infectious disease control agency may become involved with the care.

Regarding recommendations for antibiotics, first, it is most useful to use a bactericidal antibiotic rather than a bacteriostatic, if available. The advantages of a bactericidal antibiotic are (1) less reliance on host resistance, (2) killing of the bacteria by the antibiotic itself, (3) faster results, and (4) greater flexibility with dosage intervals.[13] Second, use of the most narrow-spectrum antibiotic first should be considered to allow less opportunity for development of resistant strains. Third, the addition of metronidazole to a beta-lactam antibiotic can add a significant benefit in the treatment of odontogenic infections, especially those considered to be mostly anaerobic. As always, the treating clinician must follow the clinical course of the patient and make the appropriate adjustment in antibiotic therapy as circumstances warrant.[14-17]

Natural History of Odontogenic Infections

The usual cause of an odontogenic infection is necrosis of the pulp of a tooth, which is followed by bacterial invasion through the pulp chamber and into the deeper tissues. Necrosis of the pulp is the result of deep caries in the tooth, to which the pulp responds with an inflammatory response. Vasodilatation and edema cause pressure in the tooth and because the walls of the pulp canal are rigid and cannot expand, severe pain results. If left untreated, blood supply is lost and necrosis results, which then provides a perfect avenue for bacterial invasion into the bone and possibly deeper tissues.

Once the bacteria have invaded the bone, if left unchecked, the infection will spread equally in all directions, but ultimately will seek the path of least resistance until a cortical plate is encountered. During this time, pain continues until the patient seeks treatment, wherein endodontic therapy or extraction results in resolution of the symptoms and the infection.

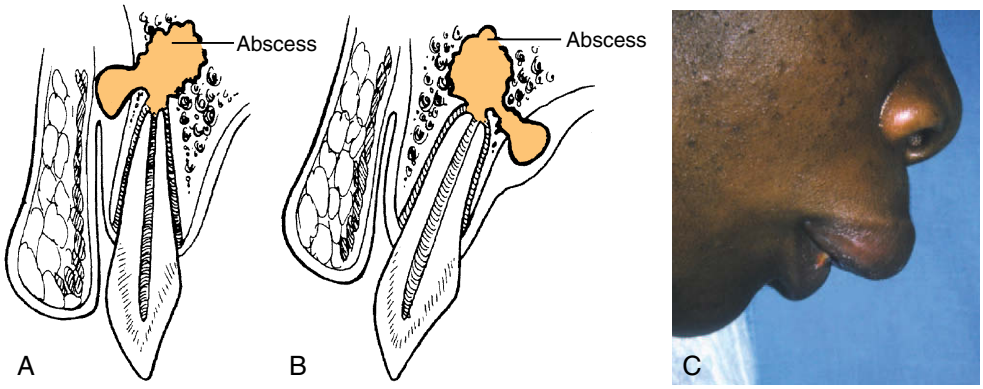

Figure 12-1. When the infection process is allowed to progress, it erodes through the nearest cortical plate. **A,** Tooth apex is near thin labial bone, so infection erodes onto labial side. **B,** Apex is near palatal side and erodes through that side. **C,** Patient with a lip abscess, reflecting **A.**

Direction of Spread of Infection

The direction of spread of the infection from the tooth apex depends on the path of least resistance, considering the thickness of the overlying cortical bone and the relationship of the bone's site of perforation to the muscle attachment of the jaws.

If no treatment is instituted, the infection erodes through the thinnest, nearest cortical plate of bone and into the overlying soft tissues (Fig. 12-1). Fig. 12-1A shows the root apex to be nearest the labial cortex; Fig. 12-1B shows the root apex to be nearest the palatal plate; Fig. 12-1C is a clinical photograph of a patient with a lip swelling, reflecting Fig. 12-1A. Clinical experience reveals that in the maxilla, Fig. 12-1A, is more common in that generally the labial-buccal cortex is thinner. If the root apex is centrally located, the infection erodes through the thinnest bone first, that is, the path of least resistance.

Once the bone has been perforated, local muscle attachments determine the location of the soft tissue abscess (Fig. 12-2). The most common pathway for the abscess is through the labial or buccal bone, occlusal to the muscle attachments, resulting in a vestibular swelling (Fig. 12-3). The vestibular abscess is seen as a fluctuant swelling, literally a "pus pocket," adjacent to the affected tooth or teeth. If no treatment is provided, this pouch of pus usually ruptures and a sinus tract or fistula is established. At this point, the patient's pain is relieved and he or she may believe that all is okay, especially because there are few, if any, systemic symptoms. However, if the tooth continues to be neglected, one of several things can happen. Slowly over time the bone involvement with the abscess can increase with more dissolution, possibly involving adjacent teeth. The patient may develop the classic "gum boil" or parulis, which is the body's attempt at healing the sinus tract with ever-increasing amounts of granulation tissue. Occasionally the tract becomes congested and the pain and swelling may briefly return, until the built-up pressure causes release and relief. This cycle may repeat many times. The one meaningful consequence of continued neglect is development of an osteomyelitis, which may be more severe and more difficult to eradicate. Another unusual possibility is development of an orocutaneous fistula, which is much more common when it occurs in a longstanding mandibular infection (Fig. 12-4).

If the infection perforates the bone above the muscle attachment (see Fig. 12-2, points 2, 4, and 5), fascial space involvement occurs. When this happens, the potential for more severe infection and more significant systemic symptoms becomes greater. A rare occurrence, in my experience, is an odontogenic infection creating a sinusitis, reflected in Fig. 12-2, point 6. The sinus membrane provides a modicum of protection to the spreading infection and allows the body's defenses to "wall off" the abscess, most commonly.

As previously stated, once the infection extends beyond the local muscle attachments, fascial space involvement is possible. Spread of infection along these potential spaces is determined by the presence of loose connective tissue. Fasciae develop in planes covering musculature that is subjected to movement. Surrounding or separating muscles, fascial planes offer an anatomic roadmap for infection to develop from the superficial to deep tissues of the face and neck. It is important to remember that these are potential spaces until separated by pus, blood, or dissection. Other features of these spaces are:

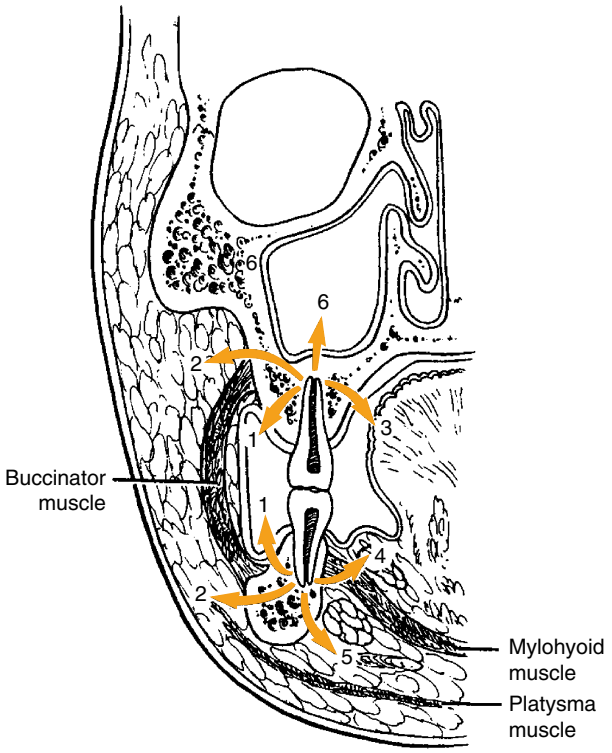

Figure 12-2. As infection erodes through bone, it can express itself in a variety of places, depending on thickness of overlying bone and relationship of muscle attachments to the site of perforation. This illustration notes six possible locations: 1, vestibule; 2, buccal space; 3, palate; 4, sublingual space; 5, submandibular space; and 6, maxillary sinus.

1. Antibiotic availability in pus-filled spaces is limited by poor vascularity.

2. Treatment of a fascial space infection depends on open incision and dependent drainage.

3. Fascial spaces are contiguous and infection can spread readily from one space to another; so it is important to open all primary and

Figure 12-3. Fluctuant swelling in the right maxillary vestibule.

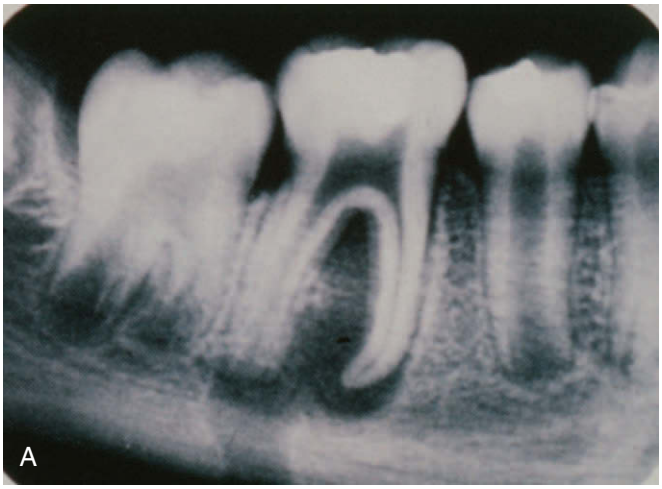

Figure 12-4. **A,** Periapical radiograph of a patient with an abscess on a mandibular molar which shows a tract through the inferior border of the mandible. **B,** Patient with an orocutaneous fistula, which may result from a longstanding infection caused by a molar infection similar to that in **A**. *(From Goldberg MH, Topazian RG. Odontogenic infections and deep fascial space infections of dental origin, Figure 8-2. In: Topazian RG, Goldberg MH, Hupp JR, eds.* Oral and Maxillofacial Infections. *4th ed. Philadelphia: WB Saunders; 2002:162.)*

Figure 12-5. Patient with a canine space abscess. Note the swelling and obliteration of the nasolabial fold. *(From Goldberg MH, Topazian RG. Odontogenic infections and deep fascial space infections of dental origin, Figure 8-9. In: Topazian RG, Goldberg MH, Hupp JR, eds.* Oral and Maxillofacial Infections. *4th ed. Philadelphia: WB Saunders; 2002:169.)*

secondary spaces; once opened, spaces need to have drains and possibly irrigation catheters placed.

4. Involved teeth should be extracted, ideally at the time of incision and drainage to ensure resolution of the infection; once a fascial space infection has occurred, it is prudent to extract the involved teeth rather than rely on endodontic treatment.[18]

It is my opinion that open incision and drainage is the best course of treatment for a fascial space infection, particularly when the mandibular spaces are involved. Although needle aspiration can remove pus, it usually delays recovery because dependent drainage is not accomplished and irrigation of the wound is not possible. Anaerobic bacteria can cause significant tissue destruction and this debris is better cleared with an open wound. Trismus also resolves more quickly and early return to function is a desirable end point. Clearly, clinical judgment and experience play a large role in this treatment decision.

Fascial Space Involvement

Maxillary Spaces

As previously stated, most maxillary tooth infections manifest as vestibular abscesses, more often on the labial-buccal surface, but occasionally on the palatal surface (especially if the palatal root of a maxillary molar is the cause). If the path of infection breaks out above the muscle attachments, then a space infection is possible. The two primary maxillary spaces that may be involved are the canine space and the buccal space.

The canine space becomes infected almost exclusively as a result of apical infection of the root of the maxillary canine tooth. The root must be long enough to ensure that the apex is superior to the insertion of the levator anguli oris muscle. The canine space is located between the anterior surface of the maxilla and the levator labii superioris. When

infected, there is usually swelling lateral to the nose and loss of the ipsilateral nasolabial fold. Drainage is most often accomplished with an intraoral stab incision (Fig. 12-5).

The buccal space becomes involved when the infection of maxillary molar teeth breaks out superior to the attachment of the buccinator muscle. The space itself lies between the buccinator muscle and the skin. All three maxillary molars (uncommon with the third molar) may cause infection in this space; rarely the premolar teeth do. It is an ovoid space, below the zygomatic arch and above the inferior border of the mandible. Infections in this space are dramatic in appearance and may cause trismus, although this is not a consistent finding and may be more of a limitation than actual muscle involvement. The buccal space may also be infected from the mandibular molar teeth, but this involvement is not common. Drainage can be intraoral, but dependent drainage is difficult to obtain. In longer standing buccal space infections, pointing usually occurs and an extraoral incision and drainage is necessary; unfortunately, this usually leaves a noticeable scar after healing (Fig. 12-6).

In addition to these two maxillary space involvements, maxillary odontogenic infections may ascend to cause orbital cellulitis or cavernous sinus thrombosis. These are rare complications in that most patients seek treatment before coming to these extremes. The clinical picture of both of these complications is similar regardless of cause. Early in the course, there is infraorbital edema due to blockage of lymph channels. Progression can then lead to significant swelling and redness of the eyelids, chemosis, and exophthalmos. Once the septum is breached, involvement of the orbital contents includes both vascular and neural components (Fig. 12-7).

Cavernous sinus thrombosis may also occur as a result of the superior spread of an odontogenic infection.[19] Spread to the cavernous sinus is hematogenous and may occur along an anterior or a posterior route (Fig. 12-8), because orbital veins lack valves, permitting blood flow in either direction. This allows contaminated venous drainage into the cavernous sinus. Fortunately this is a rare occurrence and most causes of cavernous sinus thrombosis are nonodontogenic. Signs and symptoms are like those of orbital cellulitis,[20] and are related to the structures in the cavernous sinus.

Mandibular Spaces

Again, most infected mandibular teeth manifest as vestibular abscesses, but these may advance to involve a variety of spaces. Three are designated as primary spaces: submental, sublingual, and submandibular; three are designated as secondary: masseteric, pterygomandibular, and temporal.

The primary spaces are those into which infection spreads directly from the teeth through bone. The submental space lies between the

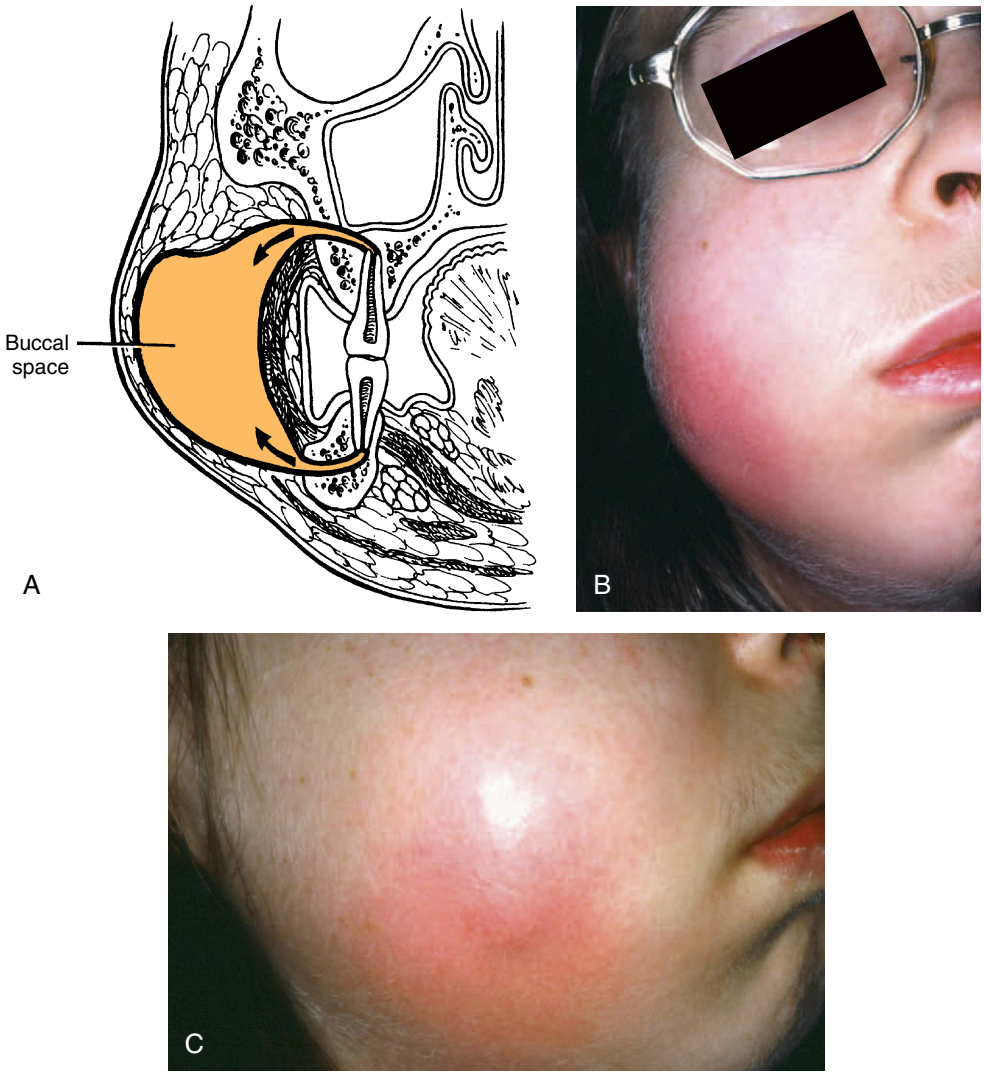

Figure 12-6. **A,** Buccal space lies between the buccinator muscle and the overlying skin and superficial fascia. This potential space may become involved by infection of maxillary and possibly mandibular molars. **B,** Dramatic buccal space infection with skin erythema and "pointing." **C,** Close-up of the "pointing" area.

Figure 12-7. **A,** Patient with multiple space infections and orbital cellulitis, which rapidly progressed to an orbital abscess. **B,** The patient in **A** hours later. Postseptal orbital abscess showing significant edema and chemosis. The globe was nonmobile and red. Urgent incision and drainage was needed.

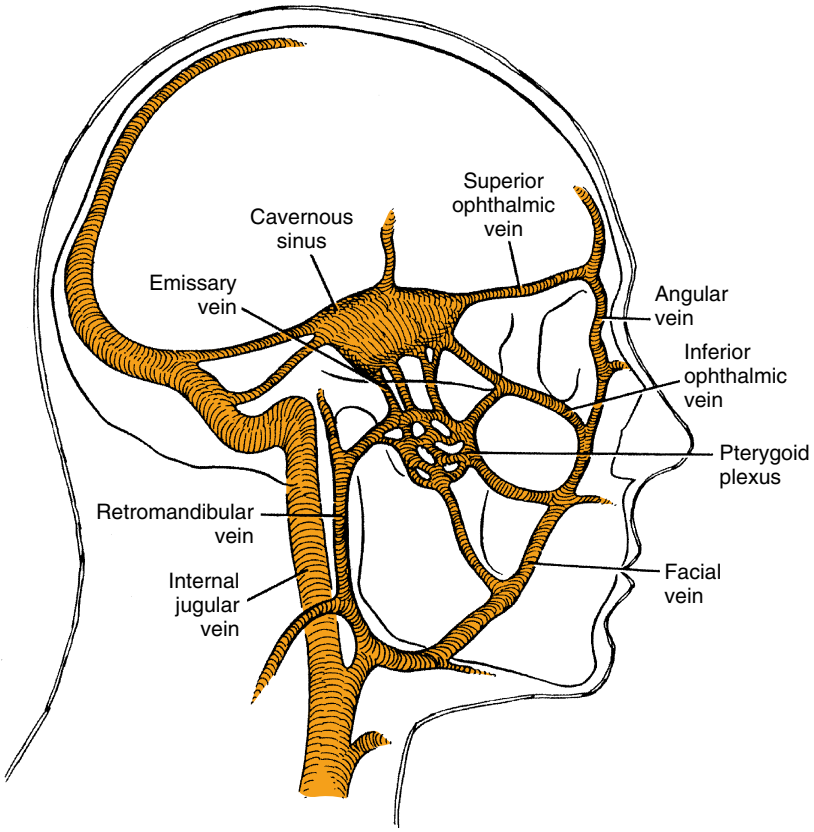

Figure 12-8. Hematogenous spread of infection from jaw to cavernous sinus may occur anteriorly via the inferior or superior ophthalmic vein or posteriorly via the emissary veins to the pterygoid plexus.

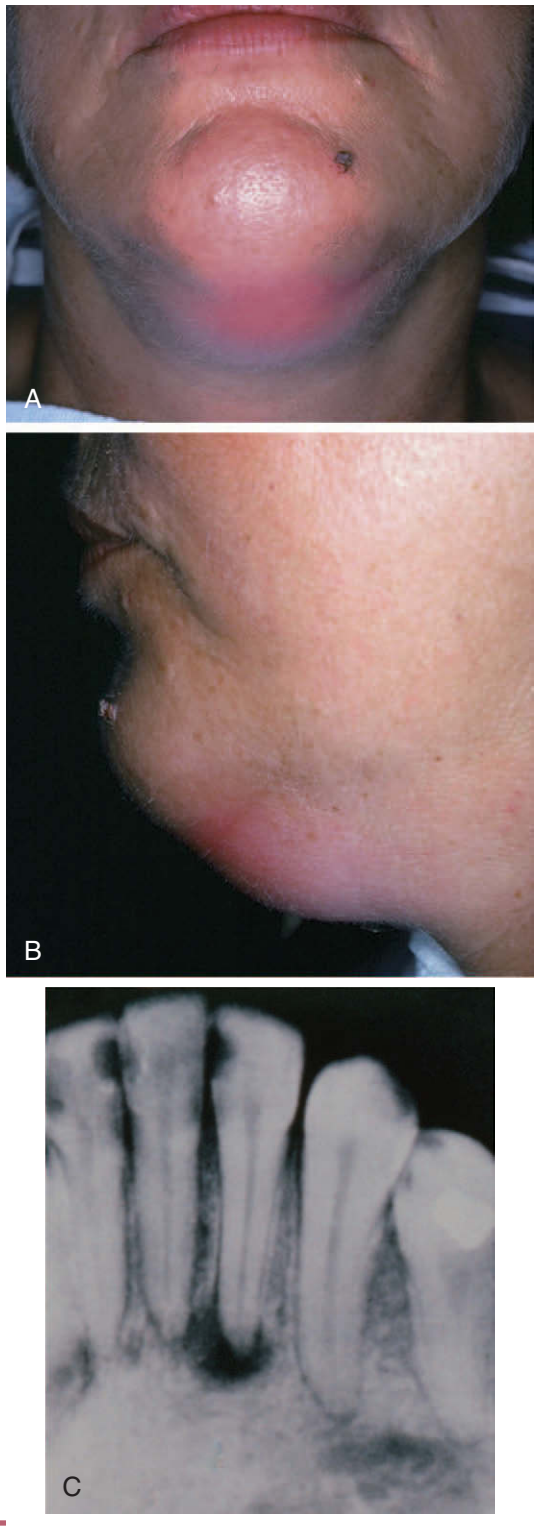

Figure 12-9. **A,** Patient with a submental space infection. **B,** Lateral view. **C,** Periapical radiograph of this patient showing an abscessed mandibular incisor, the result of which is the submental infection.

anterior bellies of the digastric muscles and between the mylohyoid muscle and the skin. This space is involved with infected mandibular incisors, whose roots are long enough to allow erosion apically to the attachment of the mentalis muscle. Isolated submental space infections are not common (Fig. 12-9).

The sublingual and submandibular spaces exit on the medial aspect of the mandible. They are usually involved because of lingual perforation of infection from the mandibular premolars and molars. The factor

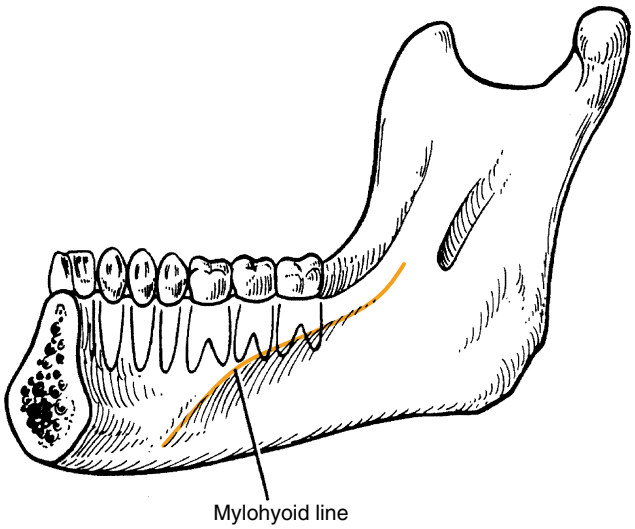

Figure 12-10. The mylohyoid line is the area of attachment of the mylohyoid muscle. Lingual cortical perforation by infection from premolars and first molar causes sublingual space infection, whereas perforation from third molar involves the submandibular space. Second molar may involve either or both spaces.

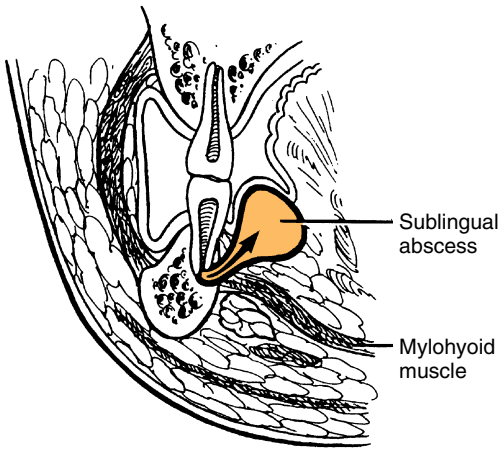

Figure 12-11. Sublingual space, which exists between the oral mucosa and the mylohyoid muscle. It is primarily involved by infection from mandibular premolars and first molar.

that determines whether the sublingual or submandibular space is involved is the location of the perforation relative to the mylohyoid muscle attachment (Fig. 12-10). If the location of the apex of the tooth is superior (premolars, first molar), the sublingual space is involved. Conversely, if the apices are inferior to the mylohyoid (second, third molar), the submandibular space is involved. However, the second molar may be sublingual or both, pending its root apex location.

The sublingual space is between the lingual oral mucosa and the mylohyoid muscle (Fig. 12-11). Its posterior boundary is open, so it communicates freely with the submandibular space and the secondary spaces located more posteriorly and superiorly. Clinically, there is little extraoral swelling, but there can be marked intraoral lingual swelling in the floor of the mouth, and if bilateral, the tongue will be elevated and swallowing becomes very difficult.

The submandibular space lies between the mylohyoid muscle and the skin (Fig. 12-12). Like the sublingual space, it has an open posterior boundary, so it can communicate easily with the secondary spaces as well. When this space becomes infected, the swelling begins at the inferior lateral border of the mandible and extends medially to the digastric area and posteriorly to the hyoid bone (Fig. 12-13). Clinically

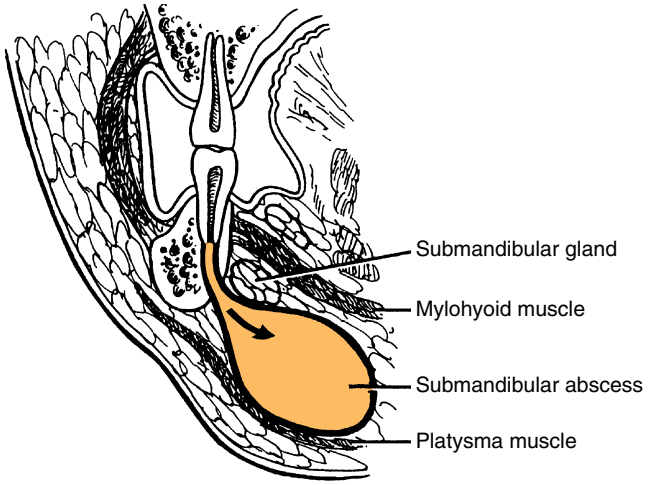

Figure 12-12. Submandibular space, which lies between mylohyoid muscle and the skin and superficial fascia. It is infected primarily by second and third molars.

Figure 12-13. Submandibular space infection, which has produced a large, indurated swelling of the submandibular space. This infection is beginning to "point."

this is a large potential space and the patient is likely to ignore initial swelling; it will not be until the infection has progressed substantially that the patient will seek care.

If all three primary spaces bilaterally become infected, the infection is known as *Ludwig's angina*. Ludwig's angina, described by Wilhelm Friedrich von Ludwig in 1836,[2] was not uncommon in the preantibiotic era and was a significant cause of death. It is characterized, even in the antibiotic era, as a rapid, *bilateral* gangrenous cellulitis of all *three* primary spaces. It can and usually does extend posteriorly to involve the secondary spaces. It causes gross swelling, elevation and displacement of the tongue, and tense brawny induration of the submandibular region superior to the hyoid bone (Fig. 12-14). There is usually minimal or no fluctuance because of the rapidity of the cellulitic process. The patient experiences severe trismus, drooling, inability to swallow, tachypnea, and dyspnea. Impending compromise of the airway produces marked anxiety. If not treated, the cellulitis can progress with alarming speed, producing upper airway obstruction and, ultimately, death. The usual cause is an odontogenic infection from a mandibular molar. Clearly virulent streptococci are involved, but ultimately, it is a mixed picture as usual.[21,22]

The three secondary spaces of the mandible are located posteriorly and superiorly to the tooth-bearing portion of the mandible in the angle-ramus area. They are called *secondary* spaces because they become infected by secondary spread of infection from other anterior spaces: buccal, sublingual, and submandibular. It is also not uncommon to cause infection in these secondary spaces by direct extension of the infection of the tissues surrounding a partially erupted third molar. The hallmark of infection in any or all of these secondary spaces of the mandible is *trismus* caused by muscle irritation and dysfunction due to the infection.

The masseteric space exists between the lateral aspect of the mandible and the masseter muscle (Fig. 12-15). This space is involved from posterior spread of a buccal space infection or from soft tissue infection around the third molar. When involved, the posteroinferior portion of the face swells, especially at the angle of the mandible (Fig. 12-16).

The pterygomandibular space (medial pterygoid space) lies between the medial aspect of the mandible and the medial pterygoid muscle (see Fig. 12-15). This space becomes involved from spread posteriorly of the sublingual and submandibular spaces and from soft tissue infection around the third molar. When this space is involved, there is little or no swelling extraorally, but there is significant trismus, a clue to the diagnosis.

The temporal space is posterior and superior to the masseteric (lateral) and pterygomandibular (medial) spaces (see Fig. 12-15). Bounded laterally by the temporalis fascia and medially by the skull, it is divided into two portions by the temporalis muscle: superficial and deep. Infection in these spaces is more uncommon, unless the infection is overwhelming. Involvement may occur occasionally with extension of a soft tissue infection around a maxillary third molar, in which case the infratemporal portion of this space may first become infected. This area is just the inferior portion of the temporal space and is contiguous with the deep compartment. Swelling is evident over the temporal area, and if the superficial compartment is singularly involved, the swelling can be dramatic.

Collectively, these three secondary spaces are known as the *masticator space*, since they are bounded by the muscles of mastication: masseter, medial pterygoid, and temporalis. These spaces communicate freely with one another, so it is most common to find multiple spaces involved in any one infection. Again, the singular diagnostic symptom of masticator space involvement is trismus (Fig. 12-17).

Cervical (Deep Neck) Spaces

Extension of odontogenic infection beyond the primary and secondary mandibular spaces is not common, again because most patients will have sought care prior to this happening. When it does occur, spread to the cervical or deep neck spaces may have serious, life-threatening sequelae. These sequelae may be the result of local complications, such as upper airway obstruction, or distant problems, such as mediastinitis.

Unfortunately, the deep neck spaces have a variety of names and descriptions, but three are relatively consistent throughout the literature: the lateral pharyngeal space, the retropharyngeal space, and the prevertebral space, or *danger space No. 4*. The layers of deep cervical fascia form and bind these three potential spaces.

The lateral pharyngeal space is classically described as having the shape of an inverted pyramid. The base is the skull base at the sphenoid bone, and the apex is at the hyoid bone. It is located between the medial pterygoid muscle laterally and the superior pharyngeal constrictor medially (Fig. 12-18). Anteriorly the boundary is the pterygomandibular raphe, around which it communicates with the spaces of the mandible. Posteromedially it extends to and is bounded by the prevertebral fascia and communicates freely with the retropharyngeal space. The

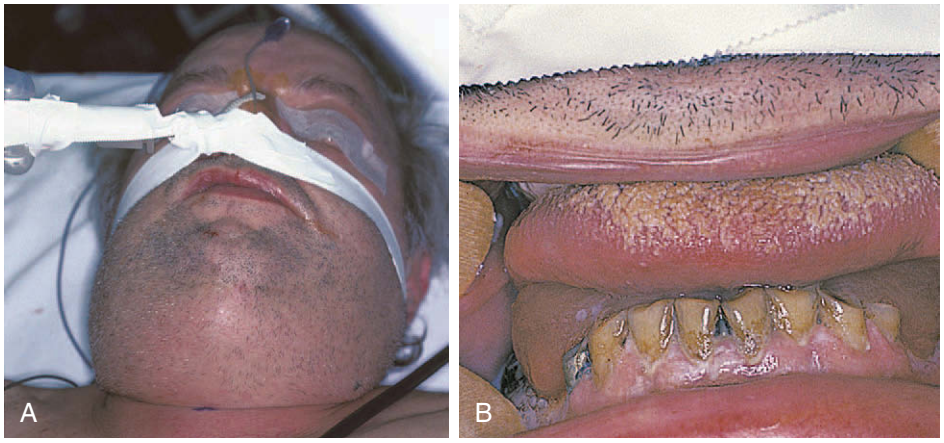

Figure 12-14. A patient with Ludwig's angina. **A,** Note the significant swelling of the bilateral upper neck, involving the bilateral submandibular spaces and the submental space. **B,** The bilateral sublingual spaces are also involved, with resultant obstruction of the oral airway by the tongue.

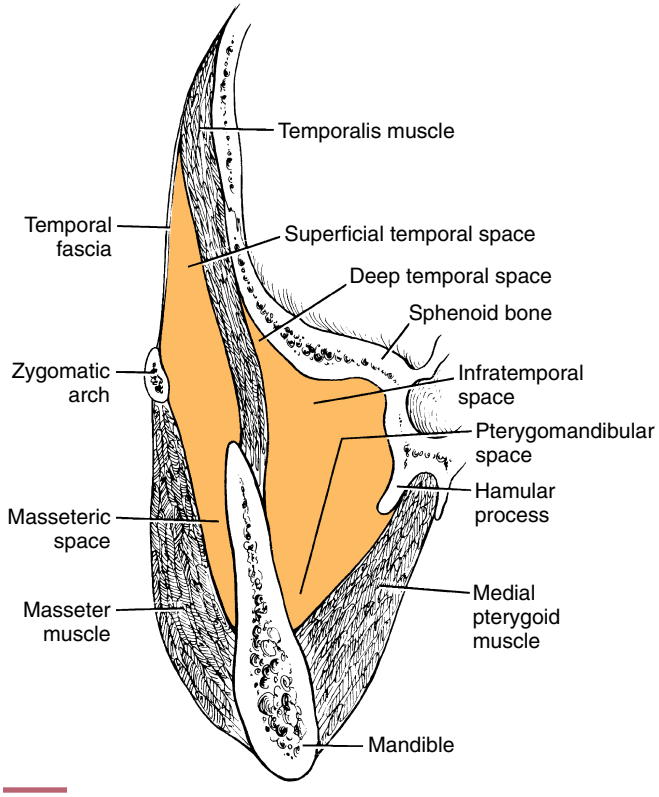

Figure 12-15. Spaces of the ramus of the mandible are bounded by the masseter, medial pterygoid, and temporalis muscles. The temporal space can be subdivided into superficial and deep, superiorly, and infratemporal, inferiorly.

Figure 12-16. Young patient with a masseteric space infection. Note the obliteration of the angle of the mandible.

styloid process and its attached muscles and fascia divide the lateral pharyngeal space into an anterior compartment, which contains muscles, and a posterior compartment, which contains the carotid sheath and cranial nerves.

When the lateral pharyngeal space is involved in an odontogenic infection, there is trismus, because there is extension from the mandibular secondary spaces. If it is severe, it may interfere with accurate diagnosis and treatment. Lateral neck swelling, especially beyond the angle of the mandible, is usually seen, and intraorally, the lateral pharyngeal wall, when visualized, bulges toward the midline. One can differentiate it from a primary peritonsillar abscess primarily because the latter rarely has significant trismus (Fig. 12-19).

Complications result from involvement of the lateral pharyngeal space. First, the odontogenic infection has become severe and may be progressing at a rapid rate. Second, direct effect of the infection on the contents of the space, particularly of the posterior compartment, can include thrombosis of the internal jugular vein, erosion into the carotid artery or its branches, and interference with cranial nerves IX to XII or the sympathetic chain. Third, the infection may progress to the retropharyngeal space.

The retropharyngeal space lies posteromedial to the lateral pharyngeal space. It is bounded anteriorly by the superior pharyngeal muscle and its investing fascia and posteriorly by the alar layer of

prevertebral fascia (see Fig. 12-18). The space begins at the skull base and extends inferiorly to the level of C7 or T1, where the alar and buccopharyngeal layers of fascia fuse (Fig. 12-20), at the level of the posterosuperior mediastinum.

When the infection has extended into the retropharyngeal space, the situation is grave and requires immediate attention. Trismus is severe in essentially all patients at this stage and evaluation of the retropharyngeal space is best performed by evaluation of a lateral radiograph of the neck and a computed tomography (CT) scan, as long as time is not delayed in obtaining one. Average widths of the prevertebral tissues have been well established.[23] The soft tissue shadow should be no more than 7 mm (average: 3.5 mm) at C2 and no more than 20 mm (average: 14 mm) at C6, that is, behind the trachea. The CT scan can be very valuable as well (Fig. 12-21).

Involvement of the retropharyngeal space may also include the prevertebral space, which is a potential space between the two layers of prevertebral fascia, the alar and prevertebral layers. It extends from the skull base inferiorly to the diaphragm. The space is also known as the *danger space No. 4.*[24]

Figure 12-17. Patient with a masticator space infection showing severe trismus.

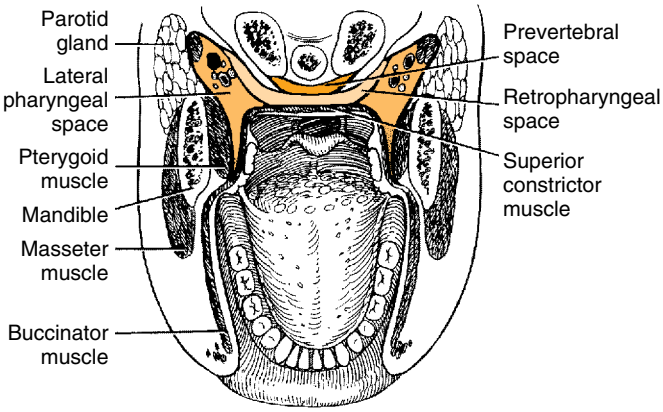

Figure 12-18. Lateral pharyngeal space, located between the medial pterygoid muscle laterally and superior pharyngeal constrictor medially. Retropharyngeal and prevertebral spaces lie between the pharynx and vertebral column. Retropharyngeal space lies between the superior constrictor muscle and alar portion of prevertebral fascia. Prevertebral space lies between the alar and prevertebral layers of prevertebral fascia.

Figure 12-19. **A,** Patient with all of the left masticator spaces and left lateral pharyngeal space infections. **B,** Bulging lateral pharyngeal wall past the midline in this patient; the tongue is retracted inferiorly. **C,** Computed tomography scan showing the lateral pharyngeal space abscess, similar to the patient shown in **A** and **B.** Note the extreme deviation of the airway.

With infection involvement of these deep neck spaces, the patient is seriously ill and is in grave danger of death. Three great potential complications exist: first, the upper airway is in danger of obstruction due to anterior displacement of the posterior pharyngeal wall into the oropharynx (see Fig. 12-21); second, spontaneous rupture of the abscess can result in aspiration, pneumonia, and asphyxiation or this rupture may be caused by attempts at insertion of an endotracheal tube to secure the airway; third, once the infection has gained access to the retropharyngeal spaces, the mediastinum may become infected also (see Fig. 12-20).

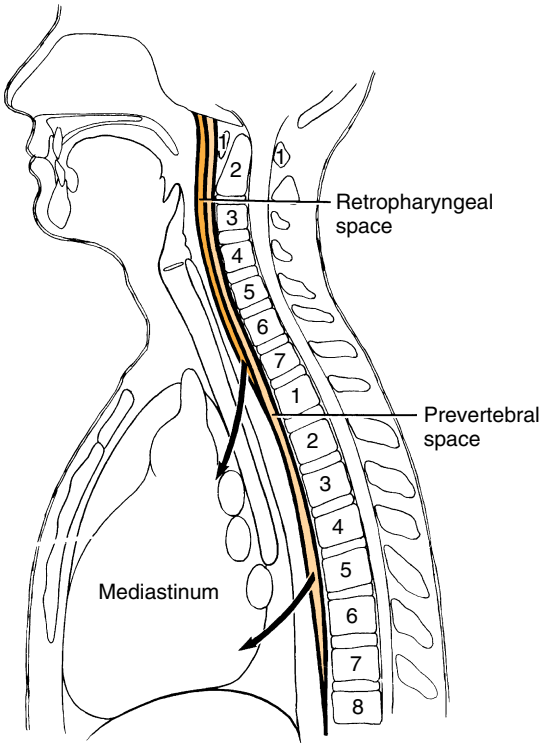

Figure 12-20. Diagram of the fascial spaces of the deep neck. If the retropharyngeal space is involved, the posterosuperior mediastinum may also become infected secondarily. If the prevertebral space is infected, the inferior boundary is the diaphragm, so the entire mediastinum is at risk.

Management of Odontogenic Infections

The principles of treating odontogenic infections are no different from the principles of managing any other infection. These principles are reviewed in the context of treating odontogenic infections that are serious enough to warrant hospitalization. Experience and common sense should dictate that it is better for the patient to be treated in the hospital setting, when a space infection has developed. The initial step, however, in any treatment is the history and physical examination.

History and Physical Examination

A careful history is the essential first step in managing these patients. Focusing on the patient's chief complaint will clue in the practitioner to the origin, extent, and severity of the presenting problem, such as history of tooth pain, presence or absence of fever, use of antibiotics, and any difficulty in opening the mouth or in swallowing. The initial assessment reveals the gravity of the illness, the need for hospitalization, and the possible urgent surgical intervention. Indications of possibly fatal infections are respiratory impairment, difficulty in swallowing, impaired vision and/or eye movement, lethargy, and a decreased level of consciousness. Toxicity is suggested by paleness, tachypnea and tachycardia, fever, shivering, and diaphoresis. Central nervous system impairment includes a decreased level of consciousness, evidence of meningeal irritation such as severe headache, stiff neck, and vomiting, eyelid edema, and ophthalmoplegia. The cardinal signs of inflammation are present to some degree in all patients with an odontogenic infection: rubor, calor, tumor, dolor, and loss of function. Their absence may indicate that the acute phase of infection is past and the infection is spreading to deeper tissues. It may also indicate that antibiotics are effective, but the overall examination of the patient is the key.

Fever is an important finding in a patient with an odontogenic infection, since elevation of the temperature represents systemic involvement by the infection. It is related to the release of endogenous pyrogen, interleukin-1, from inflammatory cells recruited by the body's defense system to fight the infection. Clearly, there are many variables that affect the temperature, but those elevations less than 102° F probably do not harm the patient and may contribute to the defense because elevated temperatures enhance phagocytic activity. Careful consideration should be given to the measurement of the temperature, because oral readings may be erratic; in children, measuring temperature using the external auditory canal is preferable.

Recording the vital signs is an integral part of the examination. In addition to the temperature, the blood pressure, respiratory rate, and

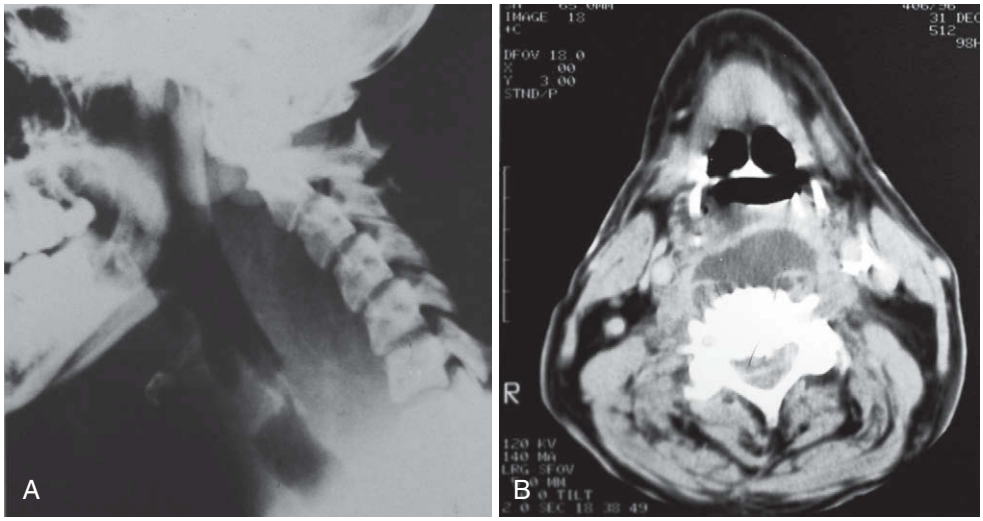

Figure 12-21. **A,** Retropharyngeal space is involved with the soft tissue becoming substantially thicker and width of the oropharyngeal air shadow decreasing. **B,** A retropharyngeal space abscess. Note the widening of the prevertebral region.

pulse can give clues to the extent of the systemic involvement as well. The pulse tends to increase 10 beats per minute for each 1°F of increased temperature, so tachycardia is important to recognize as a vital sign that accompanies fever in an infected patient.

The comprehensive examination should include a regional assessment with inspection, palpation, and percussion as warranted. It is advisable to begin extraorally by examining the skin of the face and neck for swelling, fluctuance, erythema, fistula formation, and crepitus; any lymphadenopathy should be noted. If trismus is present, this is a clue to space involvement and may limit the intraoral examination. Attention can then focus on the teeth and vestibules, noting caries, mobility, swellings, and purulent drainage. The floor of the mouth can be assessed for swelling, as well as the patient's ability to swallow. Ophthalmologic examination should include an assessment of extraocular muscle function and any preseptal or postseptal edema.

Inflammatory swellings in the face of adults represent odontogenic infection until proven otherwise. In children, this is not necessarily the case because there are several more common causes such as gingivostomatitis, sinus infections, and skin infections.

After a thorough history and physical examination, the clinician should proceed with imaging studies. Experience and the evaluation of the physical examination indicate whether plain films, such as a panoramic radiograph, are sufficient for diagnosis and treatment. In general, CT scans are recommended in addition to plain radiography, if fascial space infections have spread to the orbit or neck.[18]

Assessment and Support of Host Defenses

As discussed, odontogenic infections are almost always minor and are easily treated in the office. However, they become serious infections more commonly in patients who have some defense compromise, such as diabetes or immunosuppression. A careful, thoughtful review of the patient's defenses and immune system capabilities should be a routine part of the patient's evaluation.

Patients with moderate or severe odontogenic infections usually have severe pain and dysphagia, which usually results in a poorly hydrated, exhausted patient. Thus the infection itself produces a compromised host. Care must be taken to provide the proper antibiotics, proper analgesics, nutrition, and hydration for patients with these infections, hence the decision to admit the patient.

Airway Establishment

This is one of the most important considerations after admission of the patient. Fascial space involvement that can compromise the airway may be anterior, as in Ludwig's angina, or posterior, as in a deep neck infection. In either case, rapid severe compromise of the airway may occur. The surgeon must be keenly aware of this fact, carefully and frequently evaluating airway status to prevent fatal obstruction, and be prepared to take the patient to the operating room on an urgent or emergent basis.

In the uncomplicated odontogenic infection that involves the spaces of the mandible unilaterally, airway problems are rarely seen. If they are seen, nasal endotracheal intubation is the method of choice for airway establishment, with fiberoptic assistance as needed, especially if the patient has significant trismus. Consideration should be given to leaving the endotracheal tube in place for 2 to 3 days to ensure that acute obstruction does not occur in the time shortly after surgical decompression of the infection. These patients also have some rebound edema associated with the incision and drainage procedure.

In patients with Ludwig's angina, airway embarrassment is the primary cause of death. Once Ludwig's angina is diagnosed, it is imperative that the patient be monitored frequently and carefully for airway problems. These patients cannot lie flat and have difficulty in swallowing. If the decision is made to establish an artificial airway early, intubation with fiberoptic assistance (or blind nasal technique) can be attempted. These procedures should be carried out on awake, unparalyzed patients. Administration of neuromuscular blocking agents is not warranted because their administration may cause airway loss that cannot be regained. These cases require that an experienced anesthesiologist be present. If the decision to establish an artificial airway is delayed or cannot be accomplished, a tracheostomy or a cricothyroidotomy followed by a tracheostomy is the only option. An unhurried approach with a local anesthetic is preferred.[22]

If the infection involving a retropharyngeal space abscess is diagnosed with a radiographically enlarged soft tissue image or CT image, an artificial airway must be seriously considered. If the patient has only mild trismus and the anesthesiologist believes that direct laryngoscopy is possible, an endotracheal tube is preferred. However, if the patient has moderate or severe trismus, a fiberoptically assisted intubation is required. The major concern in this situation is rupturing the abscess while attempting to pass the endotracheal tube into the trachea, even under fiberoptic control. If such a rupture occurs, there is good likelihood of aspiration of pus into the bronchial tree, with all of the attendant sequelae. If there is no surety, even with an experienced anesthesiologist, then a planned tracheostomy (or cricothyroidotomy followed by a tracheostomy) should be carried out.

Identification of Bacteria

Identification of the causative microorganisms in an odontogenic infection is not usually a problem. As indicated earlier, the usual causes are *Streptococcus* and oral anaerobes. Because the data are so consistent among the various reports and the clinical experience of many surgeons, it is unnecessary to perform cultures for uncomplicated odontogenic infections in uncompromised patients. However, it is still appropriate to obtain cultures from patients who have undergone incision and drainage in the hospital setting, including the immunocompromised patients, in whom an unusual pattern of microorganisms may be harbored. Either aspiration with a large-bore needle before the surgical incision and drainage or capturing pus on the actual incision and drainage is sufficient. The specimen should be handled using both aerobic and anaerobic methods to ensure growth of all possible organisms.

Choice of Antibiotic

The drug of choice for odontogenic infections continues to be parenteral penicillin. Even for serious fascial space infections, including Ludwig's angina,[21] penicillin is preferred. Large doses of up to 20 million units daily for intravenous penicillin may be required for serious infections.

In the penicillin-allergic patient, clindamycin is the second drug of choice. It is quite effective against streptococci and anaerobes and has low toxicity. Although clindamycin may cause pseudomembranous colitis, it causes only about one third of the reported cases. (About one third of cases are caused by ampicillin/amoxicillin and one third by the cephalosporins.) The surgeon must be alert to this potential complication and prepared to treat it or to seek consultation. Metronidazole alone or in combination with penicillin is also a useful drug. It has minimal toxicity problems and is effective against anaerobes. Parenteral cephalosporins may be moderately useful. The first-generation cephalosporins have the same effects that penicillin does on the microbial population causing odontogenic infections. The second-generation drug cefoxitin is more active against the anaerobic bacteria but loses some of the antistreptococcal activity of the first-generation drugs. The third-generation cephalosporins are generally effective against anaerobes but also have decreased effectiveness against streptococci. Furthermore, they are expensive and have no clear additional benefit. Thus the second- and third-generation drugs are not highly desirable in most odontogenic infections. Ciprofloxacin and metronidazole in combination may be quite useful in the patient with a severe infection who has had an anaphylactoid reaction to penicillin.

In summary, high doses of parenteral antibiotics with a penicillin-like spectrum are usually effective in treating odontogenic infections. Specific culturing should be done for serious or nonresponsive infections and the results used accordingly.

Surgical Drainage and Decompression

Vestibular Infections

Odontogenic infections that are confined to the oral vestibule can usually be treated in a straightforward manner. These patients complain of mild to moderate pain and some soft tissue swelling, especially if there has not been a sinus tract established. There may be a mild, but

rarely severe, elevation of body temperature, because this is still a local phenomenon.

Treatment is primarily surgical with antibiotic therapy often used as an adjunct. Surgical treatment is extraction of the offending tooth (or endodontic therapy to remove the dental pulp of the tooth) and incision and drainage of the vestibular abscess. A small piece of Penrose drain is inserted to maintain drainage for 1 or 2 additional days. Antibiotic treatment is usually with penicillin. If the patient is allergic to penicillin, either erythromycin or clindamycin can be used effectively as alternatives. Antibiotic administration usually lasts for 7 to 10 days. Such patients can be managed on an outpatient basis. Resolution of the infection is rapid and usually without complications.

Jaw Space Infections

If the infection spreads to one of the fascial spaces surrounding the maxilla or mandible as described earlier, the treatment needs to be more aggressive.

The initial step after obtaining a history and completing a clinical and radiographic examination is to make a decision as to whether hospitalization is necessary. This decision is based on the presence and amount of swelling, the nature of the swelling (soft and doughy, indurated, or fluctuant) and the state of the body's defenses. Infections that appear as chronic abscesses, with or without an orocutaneous fistula present, without a major cellulitis component can be surgically drained in the office setting and the patient observed on an outpatient basis. Similarly, patients with early infections having a soft, doughy swelling and who are not yet dehydrated can be treated as outpatients with antibiotics and tooth extraction.

However, patients who have a moderately elevated temperature with an odontogenic cellulitis that is diffuse and indurated should be managed in the hospital setting. These are the patients who are dehydrated and have a significant amount of pain. Support of the host with hydration, intravenous antibiotics, and analgesics plays an important role in the overall therapy.

Surgical treatment should be considered early. If fluctuance is noted on the physical examination, the patient should be taken to the operating room and incision and drainage procedures performed. Aspiration of pus for aerobic and anaerobic cultures is accomplished first. Drainage of the canine and isolated sublingual spaces is usually performed with a transoral approach. After the incision is made, an exploration is carried out by blunt dissection to break up all loculation of pus, and the Penrose drains are inserted.

The buccal space can be drained transorally or extraorally, depending on the specific patient situation and the preference of the surgeon. Surgery from the mouth side is more difficult, with maintenance of dependent drainage becoming less predictable. Drainage from the cutaneous side is more likely if the infection has progressed to a "pointing area"; unfortunately, this leaves a scar.

The submental space is drained via a horizontal incision, which parallels the inferior border of the symphysis of the mandible (Fig. 12-22). The area between the anterior belly of the digastric muscles is explored posterior to the hyoid bone.

The buccal, submandibular, masseteric, pterygomandibular, and sublingual spaces can all be drained via a horizontal incision parallel and inferior to the angle of the mandible (see Fig. 12-22). An incision from as short as 0.5 cm to as long as 5 cm may be used. If the infection is a tense cellulitis that involves several mandibular spaces, a larger incision is indicated to relieve pressure. After the incision is made, blunt dissection is used to explore the involved spaces. The tip of the hemostat is advanced to hit bone at the inferior border of the mandible. It can then be directed laterally and medially. This medially directed exploration will allow for the medial pterygoid component (pterygomandibular space) to be drained, since it is the most commonly missed space. It can also be directed somewhat anteriorly to drain the submandibular space/sublingual space or a separate incision can be made more anteriorly at the inferior border. The inferior portion to the lateral pharyngeal space just medial to the pterygoid muscle can be explored by this approach as well. In severe infections, anterior (submental), posterior (submandibular), and superior (superficial temporal) incisions may all be required. Penrose drains are inserted to the extent of the dissection to facilitate drainage. Irrigation and suction catheters may be useful in more severe infections,[25] because anaerobic bacteria cause significant tissue damage and this debris needs to be flushed out of the wound. In infections drained by multiple incisions, through-and-through drains should be used, because intraoral incisions can also be of value to ensure thorough treatment.

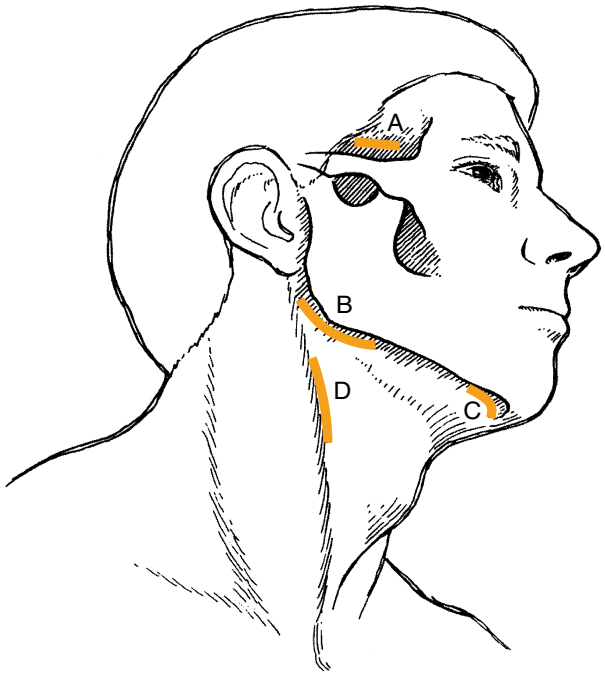

Figure 12-22. Typical incision and drainage sites for various fascial space infections. *A,* Superficial and deep temporal spaces. *B,* Submandibular, masseteric, and pterygomandibular spaces. *C,* Submental space. *D,* Lateral pharyngeal and retropharyngeal spaces.

Resolution of these infections depends on several factors: conditions of host defenses, seriousness of the original infection, appropriateness of antibiotic therapy, and extensiveness of surgical exploration. Of these, a failure to perform adequate surgical drainage is most likely to occur, especially if the patient reaches a plateau and does not continue to progress as expected. It may be necessary to repeat CT scans to identify an additional loculation that was not drained at the initial surgery. In the patient with severe cellulitis, overlying induration may prevent the clinical diagnosis of an abscess formation, especially if the patient was taken to the operating room before any scanning. Again additional surgery may be necessary.[26]

Deep Neck Spaces

Involvement of the deep cervical spaces as a result of odontogenic infection is an uncommon but life-threatening event. A large proportion of these deep neck infections are the result of odontogenic infections that have spread from the primary and secondary spaces of the mandible, because mandibular molars are the likely etiology. When deep cervical involvement does occur, usually beginning in the submandibular space and extending through the pterygomandibular space, the major diagnostic goal is to determine whether the lateral pharyngeal and retropharyngeal spaces are involved. The clinical examination, radiography (using anteroposterior [AP], and lateral soft tissue views of the neck; see Fig. 12-21A), and CT (see Fig. 12-21B) may all be required to make the diagnosis. Lateral and AP neck radiographs and CT scans may reveal the presence of gas in the soft tissue as well as soft tissue swelling. The presence of gas in the tissue in this setting signifies an anaerobic infection and indicates immediate and aggressive surgical therapy, because not only does pus need to be drained, but a continuing necrotizing fasciitis is also a concern.

Initial treatment of a patient suspected of having a deep neck infection requires immediate hospitalization, host support, maintenance of airway, IV antibiotic therapy, and incision and drainage of the involved spaces. Early surgical exploration, even in the absence of palpable fluctuance, is likely to produce more rapid and complete resolution of the infection with minimal mortality. As noted earlier, an artificial airway in these patients must usually be established, earlier rather than later. There must be no hesitation in accomplishing the necessary maneuver, whether it is fiberoptic intubation or tracheostomy. Large doses of parenteral antibiotic therapy must be started immediately as well. Penicillin with metronidazole is the preferred combination; clindamycin is an adequate alternative. If doubt exists concerning the bacterial cause of the infection, gentamicin or a third-generation cephalosporin may be added; in addition, it may be helpful early in the admission to obtain an infectious disease consult, if time permits.

Medical management with antibiotic therapy and host defense support may be used initially without surgery; however, a rapidly progressing infection of the neck should be explored. If gas emphysema, a foul-smelling discharge, or other signs indicating anaerobic infection exist, the indication for surgical intervention increases. If the infection continues to progress rapidly despite aggressive antibiotic therapy, surgical drainage becomes mandatory. If fluctuance is noted, pus should be drained immediately.[27-29]

Drainage of the lateral pharyngeal space is best accomplished by a combined transoral-extraoral approach. An incision is made lateral to the pterygomandibular raphe, and the space is explored by blunt dissection posterior and inferior to the angle of the mandible with a long Kelly hemostat. A skin incision is made over the clamp tip along the anterior border of the sternocleidomastoid muscle (see Fig. 12-22). Loculations of pus are disrupted by blunt dissection with the hemostat and by finger pressure. Through-and-through drains are placed.

The retropharyngeal space can be drained through transoral incision through the posterior pharyngeal mucosa. If this approach is used, a cuffed endotracheal or tracheostomy tube must be in place to prevent any aspiration of pus. An extraoral incision along the anterior border of the sternocleidomastoid muscle will facilitate dependent drainage. The space is explored by blunt dissection between the carotid sheath and pharyngeal constrictor muscle. Deep drains are placed as usual.

When surgical treatment was the only method of therapy (before the antibiotic era), early and aggressive surgery was essential to treat these infections and for survival. However, it is important to realize that, although aggressive antibiotic therapy may reduce the need for extensive surgical exploration in many patients, antibiotics rarely replace the need for surgery completely.

If surgery is emergent or even urgent, attention will not be immediately on the evident malnutrition of the patient. It is important in the postoperative period, then, to focus on correction of any deficiencies in intravascular volume status, electrolyte imbalances, and nutritional compromises. Oral pain, trismus, and swelling can be overcome by the administration of enteral nutrition for several days after the surgical procedure.

Acknowledgment

This chapter is dedicated to the memory of my former attending, teacher, and mentor, Dr. Larry J. Peterson, who I hope would approve of my update from the second edition.

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CHAPTER THIRTEEN

Pharyngitis in Adults

Brian Nussenbaum

Carol R. Bradford

Key Points

- The most common cause (30% to 60%) of pharyngitis in adults is a self-limited viral infection that occurs as part of the common cold. Rhinovirus is the most common etiologic agent.
- Pharyngitis in adults is caused by a bacterial infection in approximately 5% to 10% of patients. This is different than in children, in whom bacterial pharyngitis accounts for 30% to 40% of cases.
- Group A beta hemolytic *Streptococcus pyogenes* (GABHS) is the pathogenic organism responsible for most cases of bacterial pharyngitis in adults.
- Prevention of rheumatic fever is possible if antibiotic therapy is started up to 10 days after the onset of symptoms, but antibiotic treatment does not appear to affect the incidence of acute poststreptococcal glomerulonephritis.
- Other more uncommon bacterial causes of acute pharyngitis include non–group A beta hemolytic streptococcus, *Arcanobacterium haemolyticum,* sexually transmitted organisms (gonorrhea, syphilis, and chlamydia), tuberculosis, tularemia, and diphtheria.
- Influenza continues to be a worldwide problem. Each year, influenza develops in 500 million people globally with approximately 150,000 people requiring hospitalization in the United States alone. In nonpandemic years, 20,000 to 40,000 deaths occur. In pandemic years, this number can reach 100,000 deaths annually. Influenza A rather than type B is responsible for most of the significant morbidity and mortality.
- Sore throat from Epstein-Barr virus is found in 82% of patients with infectious mononucleosis and is the most common complaint. Other symptoms may include abdominal discomfort, headache, stiff neck, and skin rash.
- Treatment for most patients with infectious mononucleosis consists of supportive care, rest, antipyretics, and analgesics. Patients should be advised to avoid contact sports until examination and abdominal ultrasonography confirms resolution of splenomegaly. Antivirals are not beneficial in uncomplicated infections. Antibiotics are indicated only for secondary bacterial infections. Steroids are indicated for complications related to impending upper airway obstruction, severe hemolytic anemia, severe thrombocytopenia, or persistent severe disease.
- *Candida* sp. can affect the oropharynx in the form of pseudomembranous candidiasis (thrush). The most common isolated organism is *Candida albicans* but other organisms (*C. glabrata, C. Tropicalis, C. dubliniensis, C. rugosa*, and *C. krusei*) are now emerging as causative agents, especially in immunocompromised patients and for those who have received previous radiotherapy.

Pharyngitis is defined as inflammation of the pharynx. The anatomic region of the pharynx invariably affected in adults is the oropharynx. The predominant symptom is sore throat, which overall is the third most common chief complaint to physicians in an office-based practice.[1] An infectious-related pharyngitis is just one of the many possible causes of sore throat in adults (Table 13-1). An accurate history and physical examination is critically important for determining the differential diagnosis for each individual patient. For instance, squamous cell carcinoma of the upper aerodigestive tract frequently presents with a history of chronic sore throat. Epiglottitis in adults commonly presents as a severe acute sore throat and odynophagia with a relatively normal oropharyngeal examination. More common conditions such as postnasal drip and laryngopharyngeal reflux can cause an irritative pharyngitis. Occupational[2,3] and environmental[4] exposures can also be associated with an irritative pharyngitis, which has been demonstrated in many different populations, most recently in the firefighters with World Trade Center cough.[5]

Pharyngitis in adults is caused by a bacterial infection in approximately 5% to 10% of patients.[6] This is different than in children, in whom bacterial pharyngitis accounts for 30% to 40% of cases.[6] Approximately 75% of adults presenting with a sore throat are prescribed antibiotics for a presumed bacterial pharyngitis even though this practice will only help a minority of patients.[7] This practice can be attributed to patients' expectations to receive an antibiotic and physicians' beliefs that patients will reconsult if antibiotics are not prescribed and be unsatisfied without a prescription. This inappropriate use of antibiotics has negative consequences for both individual patients and public health.

The focus of this chapter is the appropriate evaluation and management of different microbial causes of pharyngitis in adults. In this chapter, adults are assumed to be older than 15 years.

Bacterial Infection

Group A Beta Hemolytic *Streptococcus pyogenes*

GABHS is the pathogenic organism responsible for most cases of bacterial pharyngitis in adults.[8] Overall, however, GABHS only accounts for approximately 10% of adult cases of pharyngitis.[8] This organism is a gram-positive cocci that grows in chains. Its natural reservoir is the

Table 13-1

Etiologies for Sore Throat in Adults

Microbial-Related Pharyngitis:

Bacterial

Group A-beta hemolytic *Streptococcus pyogenes*
Groups C, G, and F streptococci
Arcanobacterium haemolyticum
Neisseria gonorrhoeae
Treponema pallidum
Chlamydia pneumoniae
Mycoplasma pneumoniae
Mycobacterium tuberculosis
Francisella tularensis
Corynebacterium diphtheriae
Yersinia enterocolitica
Yersinia pestis
Trichomonas vaginalis

Viral

Rhinovirus
Coronavirus
Parainfluenza
Influenza types A and B
Human immunodeficiency virus
Adenovirus
Epstein-Barr virus
Herpes simplex virus types 1 and 2
Cytomegalovirus

Fungal

Candida sp.

Protozoa

Toxoplasma gondii

Other Causes

Abscess (peritonsillar, parapharyngeal, retropharyngeal)
Epiglottitis
Cancer (squamous cell carcinoma, lymphoma)
Autoimmune (Behçet's disease, benign mucous membrane pemphigoid, sarcoidosis)
Laryngopharyngeal reflux
Postnasal drip
Eagle's syndrome
Glossopharyngeal neuralgia
Crohn's disease
Foreign body
Trauma
Medications
Environmental exposures/Air pollution

skin and upper aerodigestive tract mucosa of the nasopharynx and oropharynx. The organism is a pathogen only in humans. Less than 5% of adults are asymptomatic carriers.[9] Spread occurs mostly through aerosolized microdroplets, less commonly by direct contact, and rarely through ingestion of contaminated nonpasteurized milk or food. Infections are more common in the autumn and winter. The pathogenesis of GABHS infections is related to virulence factors intrinsic to the organism (cell wall, hyaluronic acid capsule, M proteins), secreted enzymes (streptolysin O, streptolysin S, DNases, hyaluronidase), secreted exotoxins (exotoxins A, B, and C), and host inflammatory mediators (interleukins 1/6, tissue necrosis factor, prostaglandins, bradykinin, nitric oxide, lysosomal enzymes, free radicals).[1]

The local tissues affected by GABHS pharyngitis include the palatine tonsils, uvula, soft palate, and posterior pharyngeal wall. Symptoms are usually rapid in onset and include severe sore throat, odynophagia, cervical lymphadenopathy, fevers, chills, malaise, headache, mild neck stiffness, and anorexia. Trismus, hoarseness, cough, conjunctivitis, diarrhea, rhinorrhea, and discrete ulcerative lesions are usually not present.[10] The pharynx typically has erythema, edema, and gray-white tonsillar exudates symmetrically involving the affected tissues. Petechiae may be present on the soft palate. The tonsils are commonly swollen, and the breath is characteristically foul. A scarlatiniform rash may be present.

If left untreated, infections are usually self-limited and consist of localized inflammation that resolves after 3 to 7 days. Patients are contagious during the acute illness and for approximately 1 week afterward. Prompt antibiotic treatment reduces the duration of symptoms (if treatment begins within 24 to 48 hours of symptom onset), reduces the period of contagiousness to 24 hours after beginning treatment, and likely decreases the incidence of suppurative complications. Prevention of rheumatic fever is possible if antibiotic therapy is started up to 10 days after the onset of symptoms. Interestingly, antibiotic treatment does not appear to affect the incidence of acute poststreptococcal glomerulonephritis.[8] Other possible manifestations include scarlet fever, toxic shock syndrome, necrotizing fasciitis, and bacteremic spread of infection to distant sites.

GABHS tonsillopharyngitis is difficult to accurately diagnose solely based on symptoms or signs because there is significant overlap with findings that are common to other causes of pharyngitis. In a population of young adults with sore throat, clinical grounds alone overestimated the occurrence of GABHS in 81% of the patients, and overdiagnosis commonly led to unnecessary treatment.[11] This is problematic because antibiotic treatment should be limited only to patients likely to have a GABHS infection.[12] Because of this diagnostic difficulty, scoring systems have been developed for predicting the likelihood of GABHS on clinical grounds alone. Patients can then be divided into high probability groups that should receive empirical antibiotic therapy, intermediate probability groups that should undergo further testing with a rapid antigen test and/or throat culture, and low probability groups that require only symptomatic therapy and appropriate follow-up.[1] Two clinical prediction scoring systems that have been tested and prospectively validated in adult populations are those described by Walsh and colleagues[13] and Centor and colleagues.[14] These scoring systems should not be used in patients who are immunocompromised, have complicated comorbidities, or have a history of rheumatic fever. Clinicians should also consider epidemiologic circumstances. For example, one should avoid using these scoring systems during an epidemic of acute rheumatic fever, in parents with school-aged children, or for adults with occupations that bring them into frequent contact with children.[15]

The Walsh scoring system uses an algorithm based on five items: (1) enlarged or tender cervical lymph nodes, (2) pharyngeal exudates, (3) recent exposure to GABHS, (4) recent cough, and (5) oral temperature greater than 101°F.[13] The Centor scoring system uses history of fever, anterior cervical adenopathy, tonsillar exudates, and absence of cough to generate a simple four-variable additive score.[14] The presence of three or four of the Centor criteria has a positive predictive value of 40% to 60%, whereas the absence of three or four criteria has a negative predictive value of 80%. The Centor criteria have been endorsed by the Centers for Disease Control and Prevention (CDC), the American Academy of Family Physicians (AAFP), and the American College of Physicians (ACP) for use in clinical practice guidelines for treatment of acute pharyngitis in adults.[15] These guidelines state that patients with 0 or 1 Centor criteria should receive no further testing or antibiotic treatment given the unlikely possibility of GABHS infection. For patients with two or more criteria, there are a few appropriate strategies: (1) test patients with two, three, or four criteria with a rapid antigen test and reserve antibiotics for those with a positive test; (2) test patients with two or three criteria with a rapid antigen test and limit antibiotic treatment to those with a positive test or with four criteria; or (3) use no diagnostic tests and limit antibiotic treatment to those with three or four criteria. The authors of these guidelines do not

include throat culture in their algorithm because of poor test-retest reliability, variable results depending on the technique of obtaining and performing the culture, and inability to distinguish acute infection from a carrier state.

After the above recommendations were published, a different viewpoint on the diagnosis and management of GABHS pharyngitis in adults was proposed by the Infectious Diseases Society of America (IDSA).[10,16] In an emergency department practice, the accuracy of the Centor score for predicting a positive GABHS throat culture was 32% to 56%. Based on these data, the IDSA noted that the application of this clinical scoring system alone would result in continued overprescription of antibiotics in adults with non-GABHS pharyngitis.[16] Given this consideration, the IDSA continues to support laboratory confirmation of clinically suspected cases of GABHS pharyngitis in adults. The American Heart Association (AHA) also still recommends laboratory confirmation.[17] In considering the sensitivity (80% to 90%) and specificity (>95%) of the more recently used rapid antigen detection tests, the low incidence of GABHS, and the very low risk of rheumatic fever in the adult population, the IDSA supports the use of rapid antigen tests alone without confirmation by throat culture as an acceptable alternative diagnostic strategy.[10] Even though several variables can affect the results, the IDSA still supports the use of throat culture on a sheep blood agar plate as the gold standard for documentation of the presence of GABHS in the upper respiratory tract and for the confirmation of acute GABHS pharyngitis. The sensitivity of throat culture is 90% to 95%. The use of antistreptococcal antibody titers has no role in the routine diagnosis of GABHS pharyngitis. A major problem in testing of adults with pharyngitis is that clinicians commonly fail to follow any guidelines, which leads to unnecessary treatment in many patients.[18]

Adults with GABHS pharyngitis should be treated with a dose and duration of an antibiotic that is likely to eradicate the organism from the pharynx. Penicillin remains the treatment of choice due to its proven efficacy, narrow spectrum, and low cost. No clinical isolate of GABHS has ever been documented to be resistant to penicillin.[10,15] Amoxicillin appears to be equally effective and is sometimes used as an alternative in children due to its improved taste. The oral course should be for 10 days. Benzathine penicillin can be alternatively used as a single intramuscular injection that provides bactericidal levels for 21 to 28 days. Erythromycin is an acceptable alternative for patients allergic to penicillin, but isolated reports of macrolide resistance (<5% of clinical isolates currently) have been reported in the United States. Clindamycin is an acceptable alternative for patients with both a penicillin allergy and a strain resistant to macrolides. Although studies have shown that cephalosporins, clindamycin, and azithromycin can effectively eradicate GABHS from the pharynx with treatment courses of 5 days or less, the IDSA does not support routine use of these shorter courses due to inadequacies with these studies, the broader spectrum of these antibiotics in comparison to penicillin, and increased cost.[10]

Many explanations for penicillin treatment failure have been proposed: (1) carrier state, (2) lack of compliance, (3) recurrent exposure, (4) in vivo copathogenicity of beta-lactamase-producing normal oral flora, (5) in vivo eradication of normal protective flora, (6) contaminated toothbrushes or orthodontic appliances, and (7) intracellular localization of the bacterium. These explanations are based on observational studies or are laboratory based without clinical confirmation rather than being based on type I or II evidence.[19]

Routine retesting is not recommended for asymptomatic patients after a complete course of treatment for GABHS pharyngitis.[10] This would be indicated only for special circumstances such as patients with a history of rheumatic fever, development of pharyngitis during an outbreak of acute rheumatic fever or poststreptococcal acute glomerulonephritis, or in families with "ping-pong" spread of infection. Patients with persistent symptoms with a repeat rapid antigen or throat culture positive for GABHS may be a carrier in the presence of viral infection, may have copathogens that produce beta-lactamase, may be noncompliant with the antibiotic regimen, or may have acquired a new infection with GABHS from family or community contacts. No tests can distinguish between a carrier in the presence of repeat viral pharyngitis versus bona fide GABHS pharyngitis, and eradication of the GABHS carrier state is rarely possible with penicillin. Clindamycin or amoxicillin-clavulanic acid should be used to treat patients with multiple, repeated, symptomatic episodes of laboratory proven GABHS.[10] Tonsillectomy should be considered when these episodes do not decrease in frequency despite appropriate antimicrobial therapy and no other etiology for the repeated episodes is evident. A randomized clinical trial performed in Finland of tonsillectomy versus observation for adults with documented recurrent episodes of streptococcal pharyngitis showed that tonsillectomy was beneficial for decreasing the number of episodes of further throat infections. The number needed to treat to prevent one recurrence was 5.[20]

Non–Group A Beta Hemolytic Streptococcal Infections

Groups C and G streptococci have been cultured from patients during episodes of acute pharyngitis.[6,8] These organisms are part of the normal upper respiratory tract flora, so differentiating colonization from infection is difficult. These organisms can be cultured in patients with acute pharyngitis with clinical symptoms and examination findings indistinguishable from those of GABHS.[8] Pharyngeal infection with groups C and G streptococci can cause acute glomerulonephritis but has never been shown to cause acute rheumatic fever.[8] Penicillin and clindamycin both provide effective eradication when necessary.

Arcanobacterium haemolyticum

Arcanobacterium haemolyticum is a nonmotile, beta-hemolytic, gram-positive bacillus that causes 0.5% to 2.5% of bacterial pharyngitis cases.[21] This organism also causes deep-seated infections such as pneumonia, meningitis, osteomyelitis, brain abscess, and peritonsillar abscess in both immunocompetent and immunocompromised patients.[22] In these complicated cases, sources from the tonsils, cutaneous wounds, or absence of an identifiable source have all been reported. Phospholipase D and hemolysin are secreted exotoxins believed to play a role in pathogenesis of infections.[23] The mode of transmission appears to be airborne.

A. haemolyticum is not part of the normal upper respiratory bacterial flora.[23] The maximum incidence in patients with acute pharyngitis is 2.5%, which is found in the young adult population 15 to 18 years old.[24] Other reports state that the peak incidence occurs in patients 10 to 30 years old.[23] Infection is rare in other patient populations. The throat symptoms vary from a mild pharyngitis to an exudative tonsillitis to a diphtheria-like illness to septicemia. A rash is present in 25% to 50% of patients and may be urticarial, macular, or maculopapular. The rash usually occurs on the trunk and extremities, with sparing of the palms, soles, and face. The rash can be the predominant presenting symptom, especially in cases with only mild pharyngitis symptoms. Other clinical features include fever (64%) and cervical lymphadenopathy (41%).[24]

Pharyngitis caused by *A. haemolyticum* is easily mistaken for GABHS or viral pharyngitis with an exanthem due to the overlap in symptoms. When suspected, throat culture needs to be performed using 5% human blood agar.[23] Using this culture medium, prominent hemolytic zones are formed within 24 hours by *A. haemolyticum*. Sheep blood agar is usually used for standard throat cultures because it is rapidly hemolyzed by GABHS, but *A. haemolyticum* only forms 0.5-mm colonies with a narrow rim of hemolysis by 48 hours using this culture medium. Because most clinical laboratories discard throat cultures after 48 hours, the diagnosis is commonly missed when using this method.

Oral penicillin was recommended for treatment in the past but bactericidal tests demonstrated increasing tolerance of this organism. Thus first-line antibiotic therapy for *A. haemolyticum* pharyngitis is erythromycin.[23] Interestingly though, many reported cases of deep-seated complicated infections have been successfully treated with high-dose intravenous penicillin alone.[22] Vancomycin, clindamycin, cephalexin, and gentamicin are also effective antimicrobials. *A. haemolyticum* is resistant to oxacillin and trimethoprim-sulfamethoxazole. Antibiotic sensitivity assays are recommended for all positive cultures.

Neisseria gonorrhoeae

Neisseria gonorrhoeae is a sexually transmitted organism that affects the anal-genital region but can also cause gingivitis, stomatitis, glossitis, and pharyngitis.[25] Gonococcal pharyngitis is an uncommon but

Figure 13-1. Traumatic pharyngitis as might be seen in patients presenting with oral manifestations of sexually transmitted diseases. *(Photo courtesy of Richard A. Chole, MD, PhD.)*

well-described manifestation. This infection usually occurs concomitantly with genital infection but rarely occurs as the only site of involvement. Fellatio is the high-risk behavior and thus the incidence of disease is highest in homosexual males and females.[8] Auto inoculation has also been postulated to be a possible mechanism of disease transmission to the oropharynx. In patients with genital gonorrhea, positive oropharyngeal cultures are found in 20% of homosexual males, 10% of females, and 3% of heterosexual males.[26] Combining these groups together, the overall reported incidence of positive oropharyngeal culture in patients with genital gonorrhea is 4% to 11%.[27] Interestingly, however, only 50% of these patients actually have acute pharyngitis symptoms.[26] For asymptomatic patients, evidence suggests that the presence of *N. gonorrhoeae* in the oropharynx may be self-limited.[28] This does not justify withholding treatment, however, because dissemination from the pharynx can still occur. Dissemination most commonly manifests as arthritis, septic joint, or dermatitis.[26]

Symptomatic patients usually present with findings suggestive of tonsillitis. The tonsils are enlarged with a white-yellow exudate arising from the crypts.[25] There may be evidence of oropharyngeal trauma particularly on the soft palate or uvula (Fig. 13-1). Fever (8%) and lymphadenopathy (9%) are uncommon findings. Organisms are found within the cellular debris at the base of crypts.[27] Because of this, it is recommended to obtain Gram stain and culture specimens from deep within the crypts. A typical Gram stain reveals intracellular gram-negative diplococci. This finding should be confirmed by culture on modified Thayer-Martin medium because the pharynx can be colonized by other *Neisseria* species. Sensitivity and specificity of culture has been reported to be 47% and 100% for detection of *N. gonorrhoeae* in the pharynx.[29] The ligase chain reaction, a test based on DNA amplification, has a sensitivity of 95% and specificity of 98% for detecting pharyngeal gonorrhea.[29] This test is not currently approved, however, by the U.S. Food and Drug Administration for use in extragenital testing.

Recommended treatment is with a single dose of intramuscular ceftriaxone.[8,30] Alternative antibiotic regimens include a single intramuscular dose of cefotaxime or a single oral dose of ciprofloxacin or levofloxacin. Combined treatment for *Chlamydia trachomatis* should be given in all cases because this organism is not reliably identified in throat cultures but still coexists in 45% of cases.[30] Treatment for *C. trachomatis* consists of a single oral dose of azithromycin as first choice therapy or, alternatively, a 7-day course of doxycycline.[30]

Treponema pallidum

Treponema pallidum is the spirochete that is the causative agent of syphilis. Primary syphilis can present with manifestations in the oral region in patients with the risk factor of orogenital contact. The most common finding is an ulcer and the most common affected site is the lip followed by the tongue and tonsil.[31] Oral involvement during the primary stage is painless, however, and does not present as pharyngitis. If left untreated, a latent period begins and secondary syphilis subsequently presents up to 6 months later. Secondary syphilis mainly presents with systemic symptoms but oropharyngeal complaints may also be prominent.[31] Symptoms include headache, malaise, low-grade fever, sore throat, rhinorrhea, neck mass, and rash.[32,33] Physical examination of the pharynx reveals oval, red maculopapules, and patches. Initially, these lesions are rich in spirochetes and highly infectious. The tonsils (unilateral or bilateral) may be enlarged and red. Nontender lymphadenopathy can be present in the cervical and other regions. A nonpruritic papular or maculopapular rash involving the palms and soles is characteristic of secondary syphilis.[31,32] Symptoms and signs of secondary syphilis can last for 3 to 12 weeks and disease then enters a latent phase if still left untreated.[31,33] At this point, about one third are cured without any specific treatment, another one third remain latent (no lesions but persistent positive serologic tests), and the remainder progress to the tertiary phase.

Diagnosis during suspected cases of secondary syphilis is made using microscopy or serologic tests.[32] Gram stain cannot detect this bacterium. Spirochetes can be detected by darkfield microscopy but *T. pallidum* cannot be distinguished from *Treponema microdentium*, a commensal in the oral cavity, using this technique.[31] Warthin Starry stain can detect *T. pallidum* in tissue specimens, although detection may not be possible late in the course of disease.[32] Nonspecific (RPR) and specific (FTA-ABS, TPHA) serologic tests are positive and the treponemal-specific tests remain positive even after adequate treatment.

Treatment for primary or secondary syphilis is with a single intramuscular dose of benzathine penicillin G.[30] Alternative therapy is with doxycycline or ceftriaxone but longer courses are required to provide a cure.

Chlamydia pneumoniae

Chlamydia pneumoniae is a gram-negative obligate intracellular organism. It exists in two forms. The elementary body is the infectious metabolically inactive extracellular form and the reticulate body is the noninfectious metabolically active intracellular form. The elemental body gets endocytosed and then changes into the reticulate body, which subsequently forms the characteristic intracytoplasmic inclusions. Approximately 36 hours later, the reticulate body condenses back into the elemental body, which undergoes release by cytolysis or exocytosis at 48 hours. The hallmark of infection is prolonged subclinical infection. The only known reservoir is humans and disease is transmitted through an airborne route.

Chlamydia pneumoniae infection in adults most commonly causes pneumonia and bronchitis.[34] Sore throat and hoarseness are usual complaints among these patients, and these symptoms may be prominent enough to be the presenting complaint. Cases of *C. pneumoniae* that produce pharyngitis without apparent lower respiratory tract involvement are rare.[35] In fact, this organism's role as a causative agent in primary cases of pharyngitis has been questioned. The diagnosis is difficult to confirm because *C. pneumoniae* is not easy to isolate by culture, enzyme immunoassay (EIA) is not sensitive, and polymerase chain reaction (PCR)/DNA amplification kits for reliable detection are still in the developmental stage. Serologic evidence of *C. pneumoniae* infection was found in 8.5% of adults presenting with acute pharyngitis,[36] but follow-up data suggested that the criteria for serologic diagnosis are not specific in that 19% of asymptomatic, healthy, culture, and PCR-negative adults also fulfilled the serologic criteria for acute *C. pneumoniae* infection.[37]

C. pneumoniae is susceptible to tetracyclines, macrolides, and fluoroquinolones but resistant to sulfonamides. Two- to 3-week courses of therapy are needed to eradicate the organism.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is estimated to be responsible for 15% to 20% of cases of community-acquired pneumonia.[38] The greatest proportion of patients with pneumonia caused by *M. pneumoniae* is in the 15- to 19-year-old age group. This organism likely does not cause an isolated pharyngitis. Rather, sore throat, nasal congestion, and coryza accompany the pneumonia. Other symptoms include cough, fever, chills, and malaise. Bullous myringitis is not a common concomitant finding

during episodes of pneumonia. Involvement of other organ systems can occur and be associated with significant morbidity and death. Stevens-Johnson syndrome, hemolytic anemia, disseminated intravascular coagulation, pericarditis, myocarditis, meningitis, transverse myelitis, and Guillain-Barré syndrome have all been described.

Diagnosis of infection from *M. pneumoniae* cannot be made on clinical grounds alone. Chest radiographs usually show bronchopneumonia involving one or more lobes with or without a small pleural effusion. Complete blood count is usually normal, but 50% to 60% of patients have an increase in cold agglutinin titers.[39] This usually occurs after the second week of illness and normalizes 6 weeks later. Isolation by culture is possible but not practical due to the slow and fastidious growth of the organism. A complement-fixation test and enzyme immunoassay are available serologic tests that assist with diagnosis. These tests are limited, however, by the inability to establish an early diagnosis. The complement fixation antibodies do not rise until 2 to 4 weeks after infection and IgM antibodies do not rise until 1 week after infection. Antigen detection techniques and a PCR test are both being developed and tested, possibly providing an accurate method for physicians to make a prompt diagnosis.

Treatment is effective with tetracyclines, macrolides, and quinolones. Beta-lactam antibiotics are not effective.

Mycobacterium tuberculosis

In endemic populations, reactivation of tuberculosis can rarely present in the tonsils with or without concomitant pulmonary involvement.[40,41] All patients with tonsil involvement present with sore throat and most also have cervical lymphadenopathy. The rarity of this finding, however, even in patients with known tuberculosis who complain of sore throat is demonstrated in a study performed by Amin and Dawlatly.[42] These authors studied the tonsil tissue in 14 patients with pulmonary tuberculosis who also complained of sore throat. No granulomas were pathologically demonstrated in any of the specimens. The Armed Forces Institute of Pathology reviewed 22 cases of tonsils with granulomatous inflammation, which represented 0.08% (22 of 26,386 cases) of all tonsil and adenoid cases examined from 1940 to 1999.[43] Only three cases of tonsillar tuberculosis were diagnosed. Other etiologies found in the 21 patients with follow-up included sarcoidosis (n = 7), Hodgkin's disease (n = 2), squamous cell carcinoma (n = 1), toxoplasmosis (n = 1), and idiopathic (n = 7).

When affected by tuberculosis, the oropharyngeal examination reveals hypertrophic tonsils with ulceration and white exudates.[40] The tonsil tissue pathologically reveals caseating granulomas or granulomatous inflammation with organisms frequently seen on Ziehl-Neelsen stain. Mycobacterial culture is also necessary. A purified protein derivative (PPD) skin test will be positive unless the patient is immunosuppressed or has an overwhelming infection. Medical management with antituberculous agents is the recommended therapy. The diagnosis of tonsillar tuberculosis may be difficult to distinguish from sarcoidosis if the Ziehl-Neelsen stain is negative because both diseases are characterized by granulomatous inflammation, pulmonary disease, and lymphadenopathy.[43] It is important in this situation to make a definitive diagnosis rather than treating as a presumed case of sarcoidosis because corticosteroids can be harmful if the patient actually has tuberculosis.

Francisella tularensis

Francisella tularensis is a gram-negative bacillus and is the causative agent of tularemia. Tularemia occurs both sporadically and in epidemics in the United States.[44] There are two subtypes: Jellison type A, which is the more virulent and common biotype in North America, and Jellison type B, which is more common in Europe and Asia.[45] *F. tularensis* is a zoonotic organism that survives in rodents, ticks, raccoons, rabbits, calves, cats, and dogs. Ticks are the primary reservoir. Transmission occurs through blood-sucking arthropods and insects, ingestion of contaminated food or water, or inhalation of dust contaminated by feces of infected arthropods.[44,45] In some cases, the exact source of infection is still unclear even after thorough questioning. Person-to-person transmission is rare and not epidemiologically important.[44]

Luotonen and colleagues studied 127 patients with tularemia manifestations in the head and neck region.[46] This accounted for 11.5% of all patients treated at their institution for tularemia. Disease presented in three forms: glandular, ulceroglandular, and oropharyngeal. The oropharyngeal form accounted for 25% of the head and neck cases. Seventy percent of patients with the oropharyngeal form were older than 15 years. Identified sources of infection in these cases included contaminated hare meat and strawberries. Because the source for this form of tularemia is contaminated food or water, other family members are often infected also.[44]

The oropharyngeal form presents with fevers, chills, malaise, sore throat, and painful neck mass.[45,46] Signs include an acutely ill appearance, fever, pharyngeal erythema, exudative tonsillitis, and tender lymphadenopathy. The lymphadenopathy can suppurate during the course of illness. The clinical presentation can be easily confused with acute infectious mononucleosis, especially because there can be a false-positive Monospot test and atypical lymphocytes can be present on peripheral blood smear.[46] Cases can also easily be confused with GABHS pharyngitis and only discovered after failure of penicillin therapy.

Diagnosis is best determined by serum hemagglutination titers. A fourfold increase in titer or a titer greater than 1:160 at any time is considered sufficient for diagnosis given the clinical suspicion of disease.[44] These titers are usually within diagnostic range by 16 days after disease onset but not before 11 days. A PCR test has recently been described that may allow for earlier diagnosis in highly suspect cases.[47] No other laboratory tests are specific for this disease. Culture is usually not helpful because the organism is fastidious and grows poorly in vitro.

F. tularensis is resistant to beta-lactam antibiotics. Aminoglycosides, macrolides, fluoroquinolones, and tetracyclines are effective choices for antimicrobial therapy. A source from water resources or foods should be sought in order to avoid further cases in the local population.

Corynebacterium diphtheriae

Diphtheria is an example of an infectious disease that has almost been eradicated by the application of microbiologic and public health principles. The worldwide incidence decreased markedly with the administration of diphtheria toxoid shortly after World War II. It is currently a rare disease in the United States with fewer than five cases per year being diagnosed since 1980.[48] This disease has not been fully defeated, however. In 1994, epidemic diphtheria reemerged in the New Independent States (former Soviet Union) causing approximately 50,000 cases and 1800 deaths.[49] Outbreaks can also occur in immunized populations because adults can have serum antitoxin levels below the protective level.[50]

Corynebacterium diphtheriae is a nonmotile, gram-positive pleomorphic bacillus. Toxigenic strains are pathogenic and toxin production is mediated by a bacteriophage. The diphtheria exotoxin inhibits protein synthesis in mammalian cells by inactivating elongation factor 2. Antitoxin neutralizes circulating toxin but is ineffective once cell penetration has occurred.

Transmission occurs through infected secretions from the nose, throat, eyes, or skin lesions. Entry occurs through the mouth or nose and the organism initially remains localized to the mucosal surfaces of the upper respiratory tract. Local inflammation and toxin-mediated tissue necrosis causes formation of a fibrinous, patchy, adherent, gray-black pseudomembrane. The location of pseudomembranes can be nasal, tonsillar, pharyngeal, laryngeal, laryngotracheal, conjunctival, genital, or cutaneous. More than one area can be affected, but the oropharynx is the most commonly involved site. Attempts to remove a pseudomembrane characteristically causes bleeding from the underlying tissue. Sore throat and low-grade fever usually begin 1 to 2 days before development of the pseudomembrane. The severity of local symptoms is variable. Symptoms may be mild and resolve with sloughing of the pseudomembrane in 7 to 10 days. Alternatively, symptoms may be severe and life threatening if disease extends into or primarily involves the larynx, or if the pseudomembrane is aspirated after sloughing. A "bull-neck" appearance caused by marked swelling of cervical lymph nodes and extensive infiltration of the neck soft tissues typically develops in patients. This can cause external compression on the larynx with subsequent airway obstruction.

Toxin effects at distant sites cause myocarditis, neuritis, and acute tubular necrosis. Myocarditis is associated with delayed administration

of antitoxin and typically occurs just as the local disease is improving at 2 weeks after onset. Peripheral neuritis occurs 3 to 7 weeks later, usually affecting motor rather than sensory nerves, and commonly affecting the soft palate and pharyngeal muscles.

Definitive diagnosis is based on isolation of the organism. The pseudomembrane should be cultured and the laboratory should inoculate Loeffler's, tellurite, and blood agar media. Finding GABHS does not rule out the possibility of diphtheria because this organism can be co-cultured in 30% of cases.[51] Smears taken from organisms growing on Loeffler's medium characteristically show club-shaped organisms forming sharp angles with each other. This morphology is reminiscent of a "Chinese character" appearance. Recovered diphtheria should be tested for toxigenicity. This is performed using the guinea pig neutralization test or Elek's test. Elek's test is based on a commercially available antiserum and testing whether a precipitin reaction forms when this antiserum is placed on growing colonies.

Treatment consists of both the antitoxin and antibiotics. Outcome depends on the location and extent of the pseudomembrane, the patient's immunization status, and how quickly the antitoxin is administered. The antitoxin should be given as soon as possible because it can only inactivate toxin that has not already entered cells. The antitoxin is a hyperimmune antiserum of equine origin, so tests for sensitivity to horse serum should be performed before administration. The recommended dose is dependent on location of disease and duration of illness.[52] Antibiotics are needed to eradicate the organism. The recommended antibiotics are penicillin or erythromycin. Alternatively, *C. diphtheriae* is also sensitive to tetracycline, clindamycin, and rifampin. Supportive care is important because most patients have difficulty swallowing and some patients require intubation or tracheostomy to avoid upper airway obstruction. Booster vaccination should be given during the recovery period and serial electrocardiograms should be obtained for early detection of cardiac complications. Disease eradication should be documented by two negative cultures after completing treatment.

The patient's immunization history is important information in determining suspicion of disease because recent immunization or booster injection would make disease highly unlikely. Diphtheria toxoid booster injection is recommended every 10 years in adults. This is especially important for people that travel to epidemic or endemic areas. Immunized patients can still be carriers for the organism since the vaccination is directed solely against the toxin. When carriers are detected, treatment should consist of a course of antibiotics and a toxoid booster injection if none was administered during the previous year.

Yersinia enterocolitica

Yersinia enterocolitica is a motile, gram-negative bacillus that is a well-described cause of enteric infections. Pharyngitis symptoms occur in 20% to 30% of these patients with enteritis and, more recently, *Y. enterocolitica* has been described to cause pharyngitis in the absence of enteritis.[53] During a milk-borne outbreak, 14 of 172 patients with culture-documented *Y. enterocolitica* had pharyngitis without enteritis. All patients were adults with a median age of 38.5 years old. This contrasted with the patients affected by enteritis whose median age was 5 years old. Findings consistent among affected patients included exudative tonsillitis, tender cervical adenopathy, fever, and elevated leukocyte count (mean 16,000/mm^3). All patients demonstrated *Y. enterocolitica* on blood agar or MacConkey's agar from a throat specimen without any other identified organisms and showed a serologic response to the outbreak strain.

Although this organism does not commonly cause pharyngitis, prompt recognition is important because delayed diagnosis can lead to airway obstruction, bacteremia, sepsis, and death.[54] The treating physician should be suspicious in cases of exudative pharyngitis with continued symptoms, positive examination findings, and leukocytosis despite appropriate treatment for the more common causes of bacterial or viral pharyngitis. Throat culture or rapid antigen test for GABHS and serologic tests for infectious mononucleosis are negative. Patients with beta-thalassemia are at particularly high risk for development of *Y. enterocolitica* infection.[55] The organism is sensitive to tetracyclines, aminoglycosides, third generation cephalosporins, and trimethoprim-sulfamethoxazole. Penicillin, ampicillin, and first generation cephalosporins do not effectively treat this organism.

Viral Infection

Common Cold (Rhinovirus, Coronavirus, Parainfluenza Virus)

The most common cause (30% to 60%) of pharyngitis in adults is a self-limited viral infection that occurs as part of the common cold.[6] The average adult gets two to four colds each year, accounting for close to 20% of patients who present with an acute illness to health care providers.[56] Rhinovirus is the most common etiologic agent of the common cold.[8] Coronavirus and parainfluenza virus are less commonly implicated. Before the identification of a novel coronavirus as the cause of severe acute respiratory syndrome (SARS), the only illness that coronaviruses were thought to cause in humans was the common cold.[57] Interestingly, upper respiratory symptoms such as sore throat and rhinorrhea occur in a minority (13% to 25%) of patients with SARS.[57] Rather than showing hyperemia or edema, examination of the oropharynx reveals drying of the mucosa.[58] Lymphadenopathy is also typically absent in SARS.

Rhinovirus is a single-stranded RNA virus in the picornavirus family. More than 100 serotypes of rhinovirus exist. It is transmitted through large particle aerosols that initially affect the ciliated nasal epithelium. The virus does not directly invade the nasal epithelium, but rather causes an acute inflammatory reaction. Inflammatory mediators subsequently cause edema and hyperemia of the nasal mucosa that extends into the pharynx.

Presenting symptoms of the common cold may overlap with those of GABHS pharyngitis, but the sore throat is usually not severe and odynophagia is unusual. Patients usually complain of nasal symptoms (rhinorrhea, nasal stuffiness) that precede the throat symptoms. A nonproductive cough, hoarseness, and low-grade fever may also be present. The nasal mucosa is typically edematous and the oropharynx has mild erythema. Specific virologic diagnosis is unnecessary for most patients because it usually does not affect the management. Computed tomography (CT) scan of the paranasal sinuses cannot reliably distinguish patients with the common cold from those with acute bacterial sinusitis because imaging abnormalities are frequently found in both conditions.[59] The common cold most commonly causes CT scan abnormalities of the maxillary sinuses (87%), followed in frequency by occlusion of the ethmoid infundibulum (77%), abnormalities of the ethmoid sinuses (65%), abnormalities of the sphenoid sinuses (39%), and abnormalities of the frontal sinuses (32%). Imaging findings are usually bilateral. When associated with the common cold, most sinus CT abnormalities either markedly improve or resolve by 2 weeks after onset. Treatment for the common cold is symptomatic and consists of rest, oral hydration, and over-the-counter cold medications for relief of symptoms. Most healthy adults recover within 1 week. Antibiotics are not routinely used and are only indicated for secondary acute bacterial sinusitis, which occurs in 0.5% to 5% of cases.[59]

Influenza Virus

Influenza is a single-stranded RNA virus in the orthomyxovirus family. Three types (A, B, and C) have been identified but only types A and B cause widespread outbreaks.[60] Influenza A viruses are further classified into subtypes based on antigenic differences between the hemagglutinin and neuraminidase surface glycoproteins.[61] Disease is transmitted through an airborne route from respiratory droplets. Virus invades the respiratory epithelium, initially in the tracheobronchial tree but later throughout the whole respiratory tract. The hemagglutinin glycoprotein on the surface of the virus facilitates attachment to respiratory epithelial cells by binding to sialic acid receptors. The neuraminidase glycoprotein facilitates the release of progeny virions by catalyzing the cleavage of glycosidic linkages to sialic acid.

In North America, influenza presents as outbreaks in the late fall or winter. This disease is a worldwide problem, however. Each year, influenza develops in 500 million people globally with approximately 150,000 people requiring hospitalization in the United States alone.[60] This disease is also deadly. The pandemic of 1918 killed 20 million

people. In nonpandemic years, 20,000 to 40,000 deaths occur.[60] In pandemic years, this can reach 100,000 deaths annually. There is a variation in severity of disease based on several factors. Influenza A rather than type B is responsible for most of the significant morbidity and mortality. Very young patients are at higher risk for influenza-related hospitalization. Patients older than 50 years are at higher risk for complications. Patients with underlying comorbidities such as immunosuppression, cardiopulmonary disease, or diabetes are also at higher risk for a complicated disease course. Death is usually caused by a primary viral or secondary bacterial pneumonia. Bacterial organisms that cause pneumonia in these patients are community-acquired pathogens, *Staphylococcus aureus*, and group B *Streptococcus*.[60]

Patients present with abrupt onset of fever, headache, and myalgias. Sore throat, malaise, chills, sweats, nonproductive cough, and rhinorrhea shortly follow. The sore throat can be severe. Examination of the oropharynx typically reveals mild hyperemia and edema without exudates. Lymphadenopathy is an uncommon finding.

In uncomplicated infections, symptoms usually resolve after 3 to 5 days. Supportive therapy is indicated during this time period. Antiviral therapies with M2 ion channel blockers (amantadine) or neuraminidase inhibitors (zanamivir or oseltamivir) are currently available. Amantadine can reduce the duration of symptoms by about 1 day when started within 2 days of the onset of symptoms.[61,62] This medication has limitations, however, including rapid development of drug-resistant viral strains, lack of activity against influenza B, side effects (insomnia, light-headedness, hallucinations, dizziness, headaches, nausea, vomiting), and unproven efficacy for decreasing complications in high-risk populations. The neuraminidase inhibitors are effective against influenza type A and B and decrease symptoms by 1 to 2.5 days when started within 2 days of developing symptoms.[61,63] These drugs have also been shown to reduce complications in high-risk populations.[47] Current treatment recommendations for neuraminidase inhibitors include patients at high risk for complications or with severe disease.[60,61] Treatment should also be considered for patients not at high risk but when disease is diagnosed early.

With the availability of new treatments that need to be started early in the disease course in order to be beneficial, it is now more desirable to make a prompt, accurate diagnosis. The FDA has approved a few rapid diagnostic tests that give results in less than 15 minutes. Compared with throat culture (the gold standard for laboratory diagnosis), the sensitivity and specificity of these tests range from 62% to 73% and 80% to 99%, respectively.[62] Samples should be obtained from the nose rather than from the throat.

The best treatment for disease is prevention with the inactivated influenza vaccine that is prepared yearly based on the anticipated strains likely to appear during the flu season. Vaccination is 70% to 100% effective when the viruses in the vaccine and the viruses in the epidemic have been well matched antigenically.[61] The FDA has recently approved an intranasal vaccine with live attenuated virus as an alternative to the traditional inactivated injected vaccine.[62] This vaccine more accurately mimics natural infection and thus may provide a broader and more durable immunologic response. This vaccine can be used in healthy patients from 5 to 49 years old. Because this vaccine contains live influenza viruses, it should not be used in patients or close contacts of patients with chronic illnesses or immunodeficiency. The CDC recommends routine vaccination for people older than 50 years of age and encourages vaccination of children between 6 and 24 months old.[62] Other populations in whom vaccination is recommended are residents and employees of long-term care facilities, patients with chronic cardiopulmonary disease, patients with metabolic disease or immunosuppression, women in the second or third trimester of pregnancy during influenza season, health care personnel, and providers of home care to high-risk patients.[60] For high-risk patients who did not receive vaccination or who received vaccine in poor-match years, amantadine, zanamivir, or oseltamivir can be effective as prophylaxis against disease.[61,62,64] When used for this indication, medication must be taken daily for the duration of influenza risk in the community. During prolonged courses, the development of drug-resistant strains frequently occurs with amantadine and is a concern with the neuraminidase inhibitors.[65] Long-term use of amantadine is also difficult due to the side effects (listed earlier).

Human Immunodeficiency Virus

Acute human immunodeficiency virus (HIV) type 1 infection causes a mononucleosis-like syndrome in 40% to 90% of patients, which starts days to weeks after exposure.[66] This febrile illness is called acute retroviral syndrome (ARS). Due to the nonspecific signs and symptoms, even patients at risk for HIV are frequently not promptly diagnosed. Thus ARS should be included in the differential diagnosis in any patient with a fever of unknown origin and risk factors for HIV exposure.

The time course from mucosal breach to initial viremia is 4 to 11 days.[66] Symptoms related to ARS are caused by the robust immune response to replicating virus. The most common symptoms and signs include fever (median maximum temperature 38.9°C), lethargy, skin rash, myalgia, headache, pharyngitis, cervical adenopathy, and arthralgia.[67] Pharyngitis occurs in 50% to 70% of patients and usually appears as hypertrophy of the tissues of Waldeyer's ring without exudates. Other oral manifestations that are less commonly observed include ulcers (29%) and candidiasis (17%).[68]

Diagnosis is dependent upon laboratory tests. Complete blood count (CBC) may reveal lymphopenia or thrombocytopenia.[69] Atypical lymphocytes and a decreased CD4 cell count are usually not observed at this time. Because antibodies to HIV appear approximately 4 weeks after infection, enzyme-linked immunoassay (ELISA) and Western blot tests are also negative at this time. A quantitative plasma HIV-1 RNA level, tested by PCR, is necessary to make a timely diagnosis. This level will be greater than 50,000 copies per milliliter.[66,69] The high viral titer associated with ARS is reflective of the initial burst of viremia with wide dissemination of virus and seeding of lymphatic organs. If a quantitative plasma HIV-1 RNA level cannot be obtained, then detection of viral p24 antigen is an alternative test that can be used to make the diagnosis.

The natural history of ARS is resolution of signs and symptoms along with the viremia within 14 days after onset.[69] Disease progression to other HIV manifestations or AIDS ultimately occurs. Although data are limited regarding long-term benefits of early treatment, immediate and sustained therapy with antiretroviral medications may limit the extent of viral dissemination, restrict damage to the immune system, protect antigen-presenting cells, and reduce the chance of disease progression.[66] Patient compliance with sustained treatment is important because inconsistent adherence can cause viral resistance, which can limit future treatment options.

In patients with AIDS, persistent ulcers in the oropharynx can be caused by herpes simplex virus, cytomegalovirus, *Cryptococcus*, histoplasmosis, mycobacterial organisms, and lymphoma.[70] In many cases, however, no identifiable etiology is determined after exhaustive microbiologic, serologic, and pathologic tests. The pathogenesis of these ulcers is unclear but has been postulated to be immunogenic[71] and possibly related to the relative increase of CD8-positive cytotoxic T cells in the local tissues.[70] These ulcers progressively enlarge, have destructive behavior, and are extremely painful. There is a propensity for these ulcers to manifest in the tonsillar fossa, floor of the mouth, and epiglottis.[72] The pain associated with these ulcers causes significant odynophagia that can lead to malnutrition and wasting. Patients with these ulcers typically have advanced immunosuppression with a median CD4 count of 25 cells per cubic millimeter.[71]

Injected[72] and systemic[70] steroids have shown success for treating these AIDS-related ulcers. Friedman and colleagues showed that intralesional injections of triamcinolone acetonide completely healed 51% of the 36 treated ulcers by 4 weeks and 72% by 8 weeks.[72] For the 10 patients without complete clinical resolution, six still had marked symptomatic improvement. In other studies, preliminary data suggested that thalidomide was effective and a multicenter, double-blinded, randomized, placebo-controlled study was subsequently performed.[71] This study revealed complete healing in 55% of the patients in the thalidomide-treated group as opposed to 7% in the placebo-treated group. This was highly statistically significant. The median time to complete healing was 3.5 weeks. Most of the patients in the thalidomide group without a complete response had at least a partial response. Quality of life measures were performed on these patients and showed reduced pain and improved ability to eat.

Adenovirus

Adenovirus is a double-stranded DNA virus in the Adenoviridae family. Although adenovirus is well known as a causative agent of pharyngitis with conjunctivitis (pharyngoconjunctival fever) in children, serotypes 3, 4, 7, and 21 cause outbreaks of febrile respiratory illness in military recruits,[73,74] immunocompromised adults (particularly recipients of hematopoietic stem cell grafts),[75] and rarely in healthy young adult civilians.[76] Military recruits appear to be at particular risk because of crowding and physical stress associated with basic training. Before the availability of vaccines, adenoviral outbreaks occurred frequently in military recruits, affecting up to 10% of recruits and causing as much as 70% of all cases of respiratory disease.[77] This had significant implications on military readiness in that basic training was disrupted by an average of 3 days for each affected recruit.[77] Outbreaks also overwhelmed medical resources and caused significant economic loss. Beginning in 1971, live oral vaccines against serotypes 4 and 7 became available for use in the military and were administered to all male recruits from October to March of each year. This was changed to year-round immunizations in 1984 due to recurring outbreaks in the late spring and early fall. This intervention had a dramatic effect, reducing adenovirus-specific disease rates by 95% to 99%. The manufacturer of this vaccine stopped production in 1995, however, due to the inability to continue "good manufacturing practice" in existing facilities and stores of vaccine against serotypes 4 and 7 were depleted in 1998 and 1999, respectively. Outbreaks have now reemerged as a threat to the health of military recruits.[73,74,77]

In adults, adenovirus causes pharyngitis as part of a febrile respiratory illness. Sore throat is reported in 71% of patients. Adenovirus directly invades the pharyngeal mucosa and has a cytopathic effect. Thus, the sore throat is typically more severe than the common cold. Other associated symptoms include nasal congestion, dry cough, myalgia, headache, nausea, vomiting, and diarrhea. The average oral temperature was 38.9°C in one military outbreak.[77] Examination reveals an exudative pharyngitis that is difficult to distinguish from GABHS pharyngitis. More than half of affected patients received antibiotics at some point during their illness due to concern for a bacterial pharyngitis or respiratory infection.[77]

Adenoviral infection can be confirmed by culture from a throat swab. The culture specimen is grown on various cell lines in vitro and a cytolytic effect is observed. Immunofluorescence using an antiadenovirus monoclonal antibody is performed to confirm the diagnosis. Acute and convalescent serum can also be tested for antibody titers. PCR is a rapid, sensitive test for detecting adenoviral DNA in nasopharyngeal aspirates or serum.[78] In immunocompromised patients, detection of adenoviral DNA in serum precedes the development of severe systemic infections.[75]

Disease is usually self-limited and symptomatic treatment suffices for most cases. The average duration of symptoms is 10 days.[77] Significant morbidity and mortality can occur, however, in immunocompromised patients[75,79] and rarely in previously healthy young adults.[80] Infection can cause pneumonia, secondary bacterial infections, and more rarely meningitis, encephalitis, cystitis, nephritis, colitis, and death. For these severe adenoviral infections, there are no approved antiviral agents or antiviral therapies with proven efficacy. There are case reports and small case series supporting the possible benefits of ribavirin, cidofovir, ganciclovir, leukocyte transfusion, and intravenous immunoglobulin.[79]

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a double-stranded DNA virus in the herpesviridae family. The virus remains ubiquitous in humans by remaining latent in B lymphocytes and intermittently replicating in oropharyngeal epithelial cells to enable transmission through saliva. Blood transfusion is more rarely the mode of transmission. Worldwide, 80% to 90% of adults are seropositive for EBV.[81] Nearly all children in developing countries seroconvert by 6 years old. But in industrialized countries, about 30% of cases occur during adolescence or early adulthood. In this population, 50% of patients seroconvert without development of an overt illness.[81]

EBV is the causative agent of infectious mononucleosis (IM). The initial route of infection occurs through the lymphoid tissues and pharyngeal epithelial cells. There is an initial incubation period of 3 to 7 weeks. A prodrome of malaise, fever, and chills is followed 1 to 2 weeks later by sore throat, fever, anorexia, and lymphadenopathy (especially cervical). Sore throat is found in 82% of patients with IM and is the most common complaint. Other symptoms may include abdominal discomfort, headache, stiff neck, and skin rash.

Figure 13-2. Infectious mononucleosis showing the characteristic exudative tonsillitis with tonsillar hypertrophy. *(Photo courtesy of Richard A. Chole, MD, PhD.)*

Examination of the oropharynx reveals an exudative pharyngitis with erythema and tonsillar hypertrophy (Fig. 13-2). Other findings may include diffuse lymphoid hyperplasia of Waldeyer's ring, petechiae at the hard palate–soft palate junction, and ulcers on the pharyngeal and epiglottic mucosa.[82] Prominent cervical adenopathy is commonly present. Splenomegaly and hepatomegaly are found in 50% and 15% of cases, respectively. Periorbital edema is found in up to 30% of cases.[81]

Infectious mononucleosis causes an absolute lymphocytosis with more than 10% atypical lymphocytes. A vigorous cytotoxic T-cell response to EBV accounts for the lymphocytosis and causes many of the associated symptoms. Finding atypical lymphocytes on a peripheral blood smear may be consistent with a clinical impression of IM but is not specific for this illness. Toxoplasmosis, cytomegalovirus, acute HIV-infection, hepatitis A, tularemia, and rubella can also be associated with this finding. Cytomegalovirus can cause a mononucleosis-like illness but typically the sore throat is much less prominent. Other serologic findings may include neutropenia (50% to 80%), thrombocytopenia (25% to 50%), and asymptomatic elevated transaminases (50% to 80%).[83]

Immunologic studies include the heterophile antibody test and EBV-specific antibody tests.[81] Heterophile antibodies are closely associated with primary EBV infection but they are not produced as an immune-specific response to EBV expressed antigens. Heterophile antibodies form the basis of the currently used Monospot test. Between 70% and 90% of adults with IM have a positive Monospot test, but this is usually detectable for a short time period beginning 2 to 3 weeks after the onset of pharyngitis and fever. EBV-specific antibody studies can accurately diagnose acute IM in Monospot-negative patients when there is still a strong clinical suspicion for this illness. EBV-specific antibodies to viral capsid antigen (VCA) are present at the onset of clinical symptoms as opposed to Epstein-Barr nuclear antigen (EBNA) antibodies that are present only during convalescent IM or with previous exposure.

Although most cases of acute IM have a self-limited course without significant sequelae, there is a wide range of complications that are well described.[83] Secondary bacterial infections, usually GABHS pharyngitis, occur in up to 30% of cases. A progressive upper airway obstructive symptom from lymphoid hyperplasia and severe tonsillitis occur in less than 5% of patients but is one of the most frequent reasons for hospitalization. Hepatitis as manifested by elevated transaminases is a common finding but jaundice occurs in only 5% of cases and ascities or fulminant liver failure occurs more rarely. Severe neurologic complications occur in 1% to 5% of patients and can manifest as

Figure 13-3. Viral pharyngitis with a herpes virus showing reddening of the tonsils. *(Photo courtesy of Richard A. Chole, MD, PhD.)*

meningitis, encephalitis, cranial neuropathies (especially VII), transverse myelitis, and Guillain-Barré syndrome. Other rare complications include spontaneous splenic rupture, hemolytic anemia, myocarditis, and psychosis.

Treatment for most affected patients consists of supportive care, rest, antipyretics, and analgesics. Patients should be advised to avoid contact sports until examination and abdominal ultrasonography confirms resolution of splenomegaly.[81] Antivirals are not beneficial in uncomplicated infections. Antibiotics are indicated only for secondary bacterial infections. Ampicillin or amoxicillin should not be used because these antibiotics cause a maculopapular rash in 95% of patients with IM.[83] Other beta-lactam antibiotics can cause a rash in 40% to 60% of patients with IM, so alternative antibiotics should be used. Steroids are indicated for complications related to impending upper airway obstruction, severe hemolytic anemia, severe thrombocytopenia, or persistent severe disease. Other airway interventions such as placement of a nasopharyngeal tube, endotracheal intubation, or tracheostomy are rarely necessary.

Herpes Simplex Virus

Herpes simplex virus (HSV) is a double-stranded DNA virus in the herpesviridae family. HSV type 1 (HSV-1) and type 2 (HSV-2) are distinguished by antigenicity. HSV-1 is usually associated with disease in the head and neck region, although HSV-2 has also been described to cause disease in this area.[84] Direct contact with oral secretions is the principal mode of HSV-1 transmission. Primary HSV infection has been increasingly recognized as a prevalent cause of acute pharyngitis among college students, where it accounts for approximately 6% of cases.[85] Immunosuppressed patients are also at particular risk.

Primary HSV-1 infection is characterized by pharyngitis with or without gingivostomatitis. Recurrent herpes labialis is a manifestation of reactivation rather than primary infection. The symptoms and physical examination signs are not easily distinguishable from GABHS pharyngitis as reflected by the frequent presumptive treatment with antibiotics.[85] Symptoms include sore throat, fever, malaise, and lymphadenopathy. Findings in the oropharynx include reddening and hypertrophy of the tonsils with an overlying exudates (Fig. 13-3).[82] Enlarged, tender cervical nodes are frequently present. Although the predominant symptoms and findings are associated with pharyngitis, 34% have at least one herpes-like lesion (painful, shallow ulcer) of the oral cavity or oropharynx.[85]

Diagnosis can be obtained by viral culture with confirmation using immunofluorescence. If present, vesicles contain the highest concentration of virus within the first few days of illness. Multinucleated giant cells seen in a Tzanck smear from cells obtained from the base of an ulcer indicate infection with a herpesvirus but further tests need to be performed to identify which virus within that family. Serologic tests for neutralizing antibodies have been described but may not be reliable for diagnosing primary infection.[86]

There is a paucity of data for treatment of primary HSV pharyngeal infections with antivirals. Patients could potentially benefit from effective treatment because 14% require hospitalization and 40% seek further medical attention for their symptoms after the initial evaluation.[85] Extrapolating from the beneficial effects during primary episodes of HSV genital infections, antivirals can potentially decrease symptoms if prescribed early. This needs to be studied in further detail. Unfortunately, there are currently no accurate tests for rapid diagnosis. Until such a test is available, it seems reasonable to consider antiviral therapy until culture results return in high-risk groups with severe pharyngitis symptoms and in patients with suggestive findings who do not present during an influenza outbreak and have no serologic evidence for infectious mononucleosis.[85]

Fungal Infection

Candida sp.

Candida sp. are fungi that can affect the oropharynx in the form of pseudomembranous candidiasis (thrush).[87] The most common isolated organism is *Candida albicans* but other organisms (*C. glabrata*, *C. tropicalis*, *C. dubliniensis*, *C. rugosa*, and *C.* krusei) are emerging as causative agents.[87,88] Because *C. albicans* is a normal commensal of the oral cavity, oropharyngeal candidiasis (OPC) is considered an opportunistic infection and is the most frequent opportunistic infection found in symptomatic HIV-positive patients.[89] In patients receiving radiation for head and neck cancer, *Candida* can be isolated in 73% of patients and cause infection in 27%.[90] Other populations at risk for disease include patients with xerostomia (prior radiation to head and neck area, Sjögren's syndrome, side effects from medications), use of steroid inhalers or broad-spectrum antibiotics, immunosuppression, diabetes mellitus, Cushing's syndrome, terminally ill conditions, and a high carbohydrate diet.[87]

Patients with OPC complain of oral discomfort, burning, altered taste sensation, and dysphagia. White pseudomembranes consisting of desquamated epithelial cells, fibrin, and fungal hyphae can be scraped off to expose the underlying mucosa that appears erythematous. Other areas that can be involved in addition to the oropharynx include the buccal mucosa, hard palate, soft palate, tongue, larynx, hypopharynx, and esophagus. Clinical symptoms and findings are not significantly different if OPC is caused by *C. albicans* or a non-*albicans Candida*. The diagnosis can be confirmed by KOH preparation or positive culture. Cultures can use an oral swab or a swish sample of 10 mL of normal saline instilled in the mouth for 10 seconds and then collected in a sterile container.[88]

Disease manifestations are usually local but rarely can become systemic and cause significant morbidity and mortality. Initial therapy for uncomplicated OPC includes improving oral hygiene and use of topical antifungals.[87] Patients with a refractory or recurrent infection or at high risk for systemic disease should be treated with systemic antifungals. Fluconazole is the predominant medication used to treat OPC because the predominant organism, *C. albicans*, has consistently shown sensitivity to the drug and it is generally well tolerated. With increased use, however, development of resistance to fluconazole has become a growing concern. Resistance is usually correlated to the degree of immunosuppression and the total dose of drug.[91] Itraconazole is an alternative effective antifungal and should be used for fluconazole-resistant strains.[87]

A resistant *C. albicans* infection, a non-*albicans Candida* infection, or a mixed infection should be suspected in patients without a clinical cure after a 14-day course of fluconazole (100 mg/day).[88] Mixed infections can be difficult initially to detect because *C. albicans* can predominate on the initial culture. Several non-*albicans Candida* species have elevated minimal inhibitory concentrations to fluconazole and require increased dosage (as high as 800 mg/day) to achieve a cure.[88,92] Additionally, treatment of mixed OPC infections of *C. albicans* and non-*albicans Candida* often require higher doses or longer courses of fluconazole to eradicate the infection.[93] Some *Candida* species such as *C. krusei* are resistant to fluconazole. Patients should have a repeat culture performed. Use of chromogenic media and antifungal susceptibility testing are helpful in these situations.

Prophylaxis for patients at high risk for relapse of OPC has been considered. Such populations include HIV-infected patients, bone marrow transplant patients, patients with chemotherapy-induced neutropenia, and patients receiving radiation for head and neck cancer. Fluconazole appears to be better than nystatin in this regard.[87] To assess the efficacy of prophylaxis, a randomized controlled trial comparing fluconazole (150 milligrams once weekly) to placebo was performed in a population of HIV-infected patients with an episode of documented OPC that responded to a 7 day course of fluconazole (200 milligrams per day).[89] The end-points of the study were third relapse of OPC, occurrence of an adverse drug reaction, development of resistance, or a total duration in the study of 18 months. This study revealed fewer relapses of OPC in the fluconazole-treated group. Importantly, development of resistant *Candida* was rarely observed and was not significantly different between the groups. Although this study proved that weekly fluconazole effectively decreased OPC relapses, the authors still recommend caution with long-term prophylaxis due to the inherent risk of developing resistance. Because of this concern, it has been suggested by others that antifungal prophylaxis be limited to patients not only at high-risk for relapses of OPC but also at high-risk for invasive fungal infections.[93] The optimal antifungal to be used in these situations is still under investigation.[94-96]

SUGGESTED READINGS

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CHAPTER FOURTEEN

Deep Neck Space Infections

Eric R. Oliver

M. Boyd Gillespie

Key Points

- Methicillin-resistant *Staphylococcus aureus* is an increasingly common cause of deep neck space infections.
- Ultrasound will likely be applied more frequently for the diagnosis and management of deep neck space infections.
- Evaluation and maintenance of the airway are the first steps in management of deep neck space infections.
- Conservative management of deep neck space infections can often be used prior to surgical intervention.

Infections of the deep spaces of the neck often present a true clinical challenge. Although antibiotics have reduced their incidence, deep neck space infections remain a relevant health problem. The complex anatomic organization of the neck makes diagnosis and precise localization of deep infections difficult. Clinical suspicion remains critical in that many deep neck infections are not evident on palpation or visual inspection. Although improved imaging and medical protocols exist, surgical intervention remains a critical component of successful management.

Etiology

Infectious and inflammatory conditions of the upper aerodigestive tract are the primary instigators of deep neck infections. Multiple retrospective studies have revealed dental infections as the most common starting point, followed by oropharyngeal infections.[1-7] Acute bacterial tonsillitis and pharyngitis remain as leading causes in children. Suppuration of lymph nodes after an episode of cervical lymphadenitis may progress to a neck abscess. In the pediatric population, acute rhinosinusitis is a common cause of retropharyngeal lymphadenitis. Oral surgical procedures and endoscopic instrumentation may iatrogenically incite an upper airway infection or traumatize the pharyngoesophageal lumen. Sialadenitis, with or without ductal obstruction, can precipitate infectious spread. A foreign body trapped within the upper aerodigestive tract may initiate infection, while penetrating cervicofacial trauma can both introduce pathogens and serve as a conduit between adjacent spaces. Superficial infections, such as skin cellulitis, may spread along fascial planes. Needle injection associated with intravenous drug use introduces pathogens to the neck in a similar fashion as penetrating trauma. Congenital or acquired lesions such as branchial cleft cysts, thyroglossal duct cysts, or laryngoceles may become infected, with resulting spread. Acute mastoiditis may progress to a Bezold abscess with subsequent spread. Necrotic malignant lymph nodes can form an abscess. Immunocompromised patients must raise the index of suspicion for more virulent or atypical pathogens. Although the etiologic factors are many, a thorough search for the cause often reveals no clear source.

Wherever the starting point, the infection may spread from its portal of entry to other regions of the neck through the lymphatic system, arterial or venous channels, or direct extension between spaces and along fascial planes. The inflammatory process may plateau as a soft tissue phlegmon upon presentation, or culminate in a deep focal abscess, which usually demands surgical intervention.

Microbiology

The microbiology of deep neck space infections most often yields a mixture of aerobic and anaerobic organisms, usually representative of the oropharyngeal flora. Retrospective microbiologic analyses consistently demonstrate polymicrobial isolates.[2,7-11] The commonly cultured organisms, which often reflect the microbiology of odontogenic infections, are *Streptococcus viridans, Staphylococcus epidermidis, Staphylococcus aureus,* group A beta-hemolytic *Streptococcus (Streptococcus pyogenes), Bacteroides, Fusobacterium,* and *Peptostreptococcus* species. Cultures occasionally reveal *Neisseria, Pseudomonas, Escherichia,* and *Haemophilus* species. The proportion of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA)-associated neck space infections is significantly increasing in some regions of the United States, especially in pediatric populations.[12,13] One retrospective review concluded that MRSA is more likely to infect younger patients, but that a medial abscess location was less likely for both MRSA and methicillin-sensitive *S. aureus* infections.[13]

Atypical organisms may also initiate a deep neck infection. Actinomyces are endogenous saprophytic organisms of the oral cavity and tonsil. The most common site of cervicofacial actinomycosis is in the vicinity of the angle of the mandible, and this pathogen may cross fascial planes in its route of spread. A granulomatous reaction with central abscess formation and necrosis with "sulfur granules" is characteristic. Tuberculous and nontuberculous infection of the head and neck most commonly presents with cervical lymphadenopathy. Histopathologically, caseating necrotizing granulomatous inflammation is present. Cat scratch disease, caused by the pleomorphic gram-negative bacillus *Bartonella henselae*, manifests with large, tender cervical lymph nodes. Late lesions may form an abscess. Management of atypical neck space infections often leans toward nonsurgical management, because incision and drainage procedures may result in a chronic wound or fistulous tract.

Anatomy

Accurate diagnosis and application of timely treatment requires an understanding of the complex anatomic organization of the neck spaces. Fascial planes divide the neck into true and potential spaces.

The two main fascial divisions of the neck are the superficial cervical fascia and the deep cervical fascia, which further divides into three layers.

Superficial Cervical Fascia

The superficial cervical fascia, deep to the dermis, envelops the platysma and muscles of facial expression. It incorporates the superficial musculoaponeurotic system and extends from the zygoma to the axillae, clavicles, and deltopectoral region. Deep to the platysma, a potential space separates the superficial and deep cervical fasciae. This space houses adipose tissue, sensory nerves, and blood vessels, such as the anterior and external jugular veins, and facilitates free movement of the skin.

Deep Cervical Fascia

The deep cervical fascia is divided into three layers: the superficial, middle, and deep. The superficial layer of deep cervical fascia, or investing fascia, surrounds the neck. Posteriorly it attaches to the superior nuchal line, the ligamentum nuchae of the cervical vertebrae, and the mastoid process. As it transmits anteriorly, it splits and re-fuses to surround the trapezius and sternocleidomastoid muscles. Anterosuperiorly, this layer attaches to the inferior zygomatic arch. As it proceeds inferiorly, it splits to enclose the parotid gland, forming the parotid fascia superficially, and extends along the temporal bone to the carotid canal deeply. It envelops the muscles of mastication and covers the submandibular gland. This layer also forms the stylomandibular ligament, which separates the parotid from the submandibular gland. Inferiorly the investing fascia attaches to the hyoid, clavicle, acromion, and spine of the scapula, but first splits to encompass the intermediate tendon of the omohyoid and form the suprasternal space. The superficial layer of deep cervical fascia contributes to the lateral aspect of the carotid sheath.

The middle layer of deep cervical fascia, or visceral fascia, is composed of a muscular and visceral division. The muscular division surrounds the strap muscles (sternohyoid, sternothyroid, thyrohyoid, omohyoid). The visceral division surrounds the buccinator, pharyngeal constrictor muscles, larynx, trachea, esophagus, thyroid, and parathyroid glands. The visceral division forms a pretracheal fascia that overlies the trachea. The visceral division also contributes the buccopharyngeal fascia posterior to the esophagus, which separates the esophagus from the deep layer of deep cervical fascia and forms the anterior border of the retropharyngeal space. The buccopharyngeal fascia forms two raphae: (1) one in the posterior midline that adheres to the alar layer of the deep layer, and (2) the pterygomandibular raphe of the lateral pharynx. The middle layer also contributes to the medial aspect of the carotid sheath.

The deep layer of deep cervical fascia, or prevertebral fascia, divides into two layers: the prevertebral and alar layers. The prevertebral layer envelops the paraspinous muscles and cervical vertebrae, lying anterior to the vertebral bodies from the skull base to the coccyx, and attaching laterally to the transverse processes. It covers the scalene muscles and forms the floor of the posterior triangle. As it courses anteromedially, it contributes to the posterior carotid sheath and splits to form the alar layer. The alar layer lies between the prevertebral layer and the buccopharyngeal fascia of the visceral middle layer. The alar fascia separates the retropharyngeal and danger spaces and covers the cervical sympathetic trunk.

The carotid sheath extends from the skull base to the thorax, and is a confluence of each layer of deep fascia. The sheath contains the common carotid artery, internal jugular vein, vagus nerve, and ansa cervicalis.

Neck Spaces

The above fasciae and the structures within the neck form real and potential spaces. Many of these compartments openly communicate with each other, and some spaces are contiguous with distant regions of the body, offering a route of rapid transit for infections. The neck spaces can be organized by their location: the face (buccal, canine, masticator, parotid), suprahyoid neck (peritonsillar, submandibular, sublingual, parapharyngeal), infrahyoid neck (anterior visceral), and along the length of the neck (retropharyngeal, danger, prevertebral, carotid).

Parapharyngeal Space

Also called the *lateral pharyngeal* or *pharyngomaxillary space*, the parapharyngeal space is an inverted pyramid with its superior base at the skull base and its inferior apex at the junction of the posterior belly of the digastric muscle and greater cornu of the hyoid bone. The pterygomandibular raphe and medial pterygoid muscle bound the space anteriorly, while the prevertebral fascia bounds it posteriorly. The superior constrictor, tensor, and levator veli palatini muscles form the medial boundary, and the parotid gland, mandible, and lateral pterygoid muscle bound it laterally.

The styloid process divides the space into two compartments: the prestyloid compartment, which is anterior to the styloid process, and the post-styloid compartment, which is posterior to the process. The prestyloid compartment contains fat, muscle (styloglossus and stylopharyngeus), lymph nodes, deep lobe of the parotid, internal maxillary artery, inferior alveolar, lingual, and auriculotemporal nerves. The post-styloid compartment contains neurovascular structures: carotid artery, internal jugular vein, sympathetic chain, and cranial nerves IX, X, XI, and XII.

The parapharyngeal space provides a central connection for the major deep neck spaces. It connects posteromedially with the retropharyngeal space, inferiorly with the submandibular space, and laterally with the masticator space. The carotid sheath courses through the space into the mediastinum. Lateral extension from the peritonsillar space directly invades the parapharyngeal space.

Submandibular and Sublingual Spaces

These two spaces are best discussed together, because they functionally comprise a single space. The mucosa of the floor of the mouth forms the superior border of the submandibular space, and the digastric muscle and hyoid bone form the inferior. Anteriorly, the mylohyoid muscle and anterior belly of digastric bound the submandibular space, with the posterior belly of the digastric and stylomandibular ligament serving as its posterior borders. The hyoglossus, mylohyoid, styloglossus, genioglossus, and geniohyoid muscles are medial, with the platysma and mandible being lateral.

The mylohyoid muscle divides the submandibular space into a superior sublingual compartment and an inferior submaxillary compartment. This sublingual compartment is also called the *sublingual space,* and contains the sublingual gland and Wharton's duct. The supramylohyoid sublingual space is lateral to the geniohyoid and genioglossus muscles. The sublingual space openly connects to the submaxillary compartment around the free posterior edge of the mylohyoid. The inframylohyoid submaxillary compartment, sometimes itself called the *submandibular space,* connects to its corresponding space contralaterally and contains the submandibular gland and lymph nodes.

The relationship of the mylohyoid to the tooth apices, the mylohyoid line, determines the most likely route of odontogenic infectious spread. The teeth apices anterior to the second molar lie superior to the mylohyoid line and thus involve the sublingual space. Infections of the second and third molars initially involve the submandibular or parapharyngeal space, because their roots extend below the mylohyoid line.

Retropharyngeal Space

The retropharyngeal space, extending from the skull base to the mediastinum at the tracheal bifurcation, refers to the lymph node and connective tissue containing potential space between the middle and deep layers of deep cervical fasciae. The space lies anterior to the alar fascia of the deep layer and posterior to the buccopharyngeal fascia of the middle layer that lines the posterior pharynx and esophagus. The carotid sheath is lateral to the space. It typically becomes involved by direct spread from the parapharyngeal space, or lymphatic spread from the paranasal sinuses or nasopharyngeal region, primarily in children.

Danger Space

The danger space, so named because of the potential for rapid inferior spread of infection to the posterior mediastinum through its loose

areolar tissue, extends from the skull base to the diaphragm. This potential space lies between the retropharyngeal and prevertebral spaces. The deep layer of deep cervical fascia subdivisions bound this space. The alar layer forms its anterior border, and the prevertebral layer forms its posterior border. Laterally, the transverse processes of the vertebrae enclose the danger space. The sympathetic trunk courses through this space. Infectious infiltration from the retropharyngeal, parapharyngeal, or prevertebral spaces are the primary routes to the danger space.

Prevertebral Space

The prevertebral space is enclosed by the prevertebral fascia, vertebral bodies and transverse processes, and extends from the clivus of the skull base to the coccyx. It is a compact potential space that contains dense areolar tissue and lies posterior to the danger space. In addition to the paraspinous, prevertebral, and scalene muscles, it contains the vertebral artery and vein, brachial plexus, and phrenic nerve. The main pathways of spread to the prevertebral space are from infection of the vertebral bodies and penetrating injuries. Tuberculosis of the spine may breach the space and form a Pott's abscess.

Masticator Space

The superficial layer of deep cervical fascia defines the masticator space upon splitting at the inferior border of the mandible to cover the medial pterygoid and masseter muscles. Next, the fascia continues superiorly to cover the inferior tendon of the temporalis muscle and incorporate with the superficial temporalis fascia. It contains the mandible and muscles of mastication (masseter, temporalis, medial pterygoid, lateral pterygoid). The masticator space also contains the third portion of the trigeminal nerve, which enters through the foramen ovale, the internal maxillary artery, and much of the buccal fat pad. This space occupies a position anterolateral to the parapharyngeal space.

The masticator space is also further divided into subspaces: the masseteric space between the masseter muscle and ramus of mandible, the pterygoid space between the pterygoid muscles and ramus, the superficial temporal space between the superficial temporal fascia and temporalis muscle, and the deep temporal space between the deep temporal fascia and temporal bone. Transmission of infection into the masticator space is most commonly from the third mandibular molars.

Peritonsillar Space

The peritonsillar space consists of loose connective tissue between the capsule of the palatine tonsil and the superior constrictor muscle. The anterior and posterior tonsillar pillars contribute to its anterior and posterior borders, respectively. The posterior tongue forms the inferior boundary. Peritonsillar infections may readily spread to the parapharyngeal space.

Parotid Space

The superficial layer of deep cervical fascia forms the parotid space as it splits to surround the parotid gland. However, the fascia, which does not enclose the superomedial aspect of the gland, permits communication with the prestyloid compartment of the parapharyngeal space. The space also contains the facial nerve, external carotid artery, and posterior facial vein. It occupies a position lateral to the parapharyngeal space.

Carotid Space

The carotid, or visceral vascular, space is the potential space within the carotid sheath containing the carotid artery, internal jugular vein, vagus nerve, and sympathetic plexus. Infection from the surrounding parapharyngeal space, penetrating trauma, or intravenous drug use may potentiate spread into this space.

Anterior Visceral Space

The visceral division of the middle layer of deep cervical fascia encloses the anterior visceral space, or pretracheal space, which lies immediately anterior to the trachea. It extends from the thyroid cartilage to the superior mediastinum. It contains the pharynx, esophagus, larynx, trachea, and thyroid gland. Perforation of the anterior esophageal wall by endoscopic instrumentation, foreign bodies, or trauma may introduce infection to this space.

Clinical Evaluation

History

The symptoms of deep neck space infection are determined by both the generalized inflammatory process as well as localizing symptoms at the site of infection. Inflammatory symptoms such as pain, fever, swelling, and redness are common. Symptoms such as dysphagia, odynophagia, drooling, "hot potato" voice, hoarseness, dyspnea, trismus, and ear pain offer further clues about the location of the inflammatory process as well as its potential severity. The onset and duration of symptoms should be elicited. Recent events such as dental work, upper airway surgery or intubation, intravenous drug use, sinusitis, pharyngitis, otitis, or blunt or penetrating soft tissue trauma that preceded worsening symptoms should be identified in order to formulate a differential of likely microorganisms and common pathways of spread.

The past medical history should be reviewed to account for antibiotic allergies and immunodeficiency status. Patients with a history of human immunodeficiency virus, hepatitis, diabetes, collagen vascular diseases, hematologic malignancy, and recent chemotherapy or steroid use are at increased risk of atypical pathogens and rapidly progressive disease.

Physical Examination

A complete head and neck physical examination is required in all patients with a potential deep neck space infection. Palpation of the neck and face may identify localizing tenderness or fluctuance as well as crepitus caused by airway trauma or gas-producing organisms. Otoscopic examination of the ear and nasal passages can rapidly reveal edema, purulence, drainage, and tenderness, as well as ruling out obstructing foreign bodies. Examination of the oral cavity and oropharynx is facilitated by the use of a headlight, which frees up the hands for bimanual examination. Difficulty with mouth opening indicates that inflammation has already spread into the parapharyngeal, pterygoid, or masseteric spaces. An odontogenic source of infection should be considered in the presence of alveolar swelling and decayed, loose, tender, or broken teeth. The floor of the mouth should be assessed for visible edema, which may cause posterior deflection of the oral tongue. Stensen's and Wharton's ducts should be assessed for purulent discharge and palpated for obstructing stones.

Visualization of the oropharynx is necessary to assess for asymmetric lateral or posterior wall swelling, and/or deviation of the uvula. Unilateral pharyngeal wall swelling in the absence of associated inflammatory symptoms such as fever and mucosal erythema should raise the possibility of parapharyngeal tumors, which should not be biopsied or incised without further evaluation. A unilaterally enlarged, irregular, or ulcerated tonsil, especially in the setting of prolonged exposure to tobacco and alcohol, may indicate the presence of tonsillar malignancy.

A complete cranial nerve examination is recommended. Infections of the upper dentition, paranasal sinuses, facial soft tissues, and parotid place the orbits at increased risk due to retrograde flow through the facial and ophthalmic veins. Edematous eyelids must be manually separated in order to assess the underlying globe. Reduced mobility of the globe and/or an absent papillary light reflex indicates orbital inflammation or abscess that requires urgent attention to save the eye.

Awake flexible fiberoptic evaluation of the upper airway is indicated in most cases of suspected deep neck space infections and is mandatory if the patient has hoarseness, dyspnea, stridor, or dysphagia or odynophagia without obvious cause on oropharyngeal examination. Normal pulse oximetry results do not eliminate the need for direct airway evaluation because the oxygen saturation is a poor proxy for airway status and typically does not fall until the airway is completely occluded. The presence of a patent, midline, noninflamed airway should be documented before the patient is transported for radiographic evaluation to prevent an airway emergency while the patient is supine in the radiology suite. Direct evaluation of the airway identifies patients who may be difficult to intubate by standard technique if surgery is required.

Laboratory Evaluation

Blood Tests

An initial complete blood count typically demonstrates leukocytosis in cases of deep neck infection. A lack of a leukocytic response may indicate viral illness, immunodeficiency, or a condition such as a tumor, which can be confused with deep neck infection. Daily measures of the white blood cell count may be helpful in monitoring a patient's response to treatment such as intravenous antibiotics or surgical drainage. Intravenous steroids are often necessary to reduce upper airway inflammation in deep neck infection and should not be withheld out of concern that steroid-related leukocytosis will make it difficult to monitor treatment response. A basic electrolyte panel should also be obtained to assess glucose level, bodily hydration, and renal function in case general anesthesia becomes necessary during treatment.

Imaging Studies

Plain Film Radiography

Radiographic imaging plays a critical role in evaluation of suspected deep neck infections. Plain film technology is inexpensive, rapid, and widely available, and it provides excellent information in select circumstances. In cases of suspected dental origin, plain film radiography or a Panorex of the jaw can help identify dental sources of infection if not already obvious on physical examination. Translucencies at the apex of the dental root are a common finding with dental-related abscess. Lateral neck films are useful for quickly evaluating the upper aerodigestive tract in cases of suspected retropharyngeal abscess or supraglottitis. Presence of an air-fluid level or greater than 5 mm of thickening in a child or greater than 7 mm of thickening in an adult of the prevertebral tissue at C2 indicate retropharyngeal infection until proven otherwise. Thickening of the epiglottis, commonly known as "thumbprint sign," and arytenoids indicate likely supraglottitis with urgent need for direct airway evaluation in a controlled setting with tracheotomy capabilities. Chest radiography is indicated in cases of dyspnea, tachycardia, or cough to rule out aspiration or mediastinitis.

Computed Tomography

Computed tomography (CT) scans of the head and neck are a critical component in the evaluation of deep neck infection because physical examination alone can misidentify the involved space and the number of involved spaces in 70% of cases.[14] CT scans with intravenous contrast provide excellent visualization of most bony and soft tissue structures of the head and neck. The intravenous contrast allows visualization of the great neck vessels and enhancement of areas of inflammation. CT scans are valuable in determining whether the infection is contained within the lymph nodes or has spread beyond into the fascial planes of the head and neck. Although CT is excellent for identifying the presence of deep neck infection, it cannot reliably differentiate between the generalized edema of phlegmon versus purulent abscess because both commonly appear as hypodense collections with peripheral enhancement (Fig. 14-1). The decision to explore the neck therefore should be made on clinical grounds with the expectation that pus will not be found in up to 25% of explorations.[15] Metastatic adenopathy most commonly from a tonsillar primary should be ruled out clinically because this may mimic neck abscess on CT scan, or may contain abscess if secondarily infected (Fig. 14-2).[16,17] The CT scan provides valuable information about which neck spaces require exploration and drainage at the time of surgery. The use of intravenous contrast is contraindicated in most patients with iodine or contrast dye allergy and in patients with compromised renal function. Therefore other imaging modalities are indicated when intravenous contrast cannot be used.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not routinely used for suspected deep neck infections, but it should be considered in select circumstances when it is superior to CT. In addition, MRI scanning is time consuming and less likely to be tolerated by a patient who is in pain or is having trouble swallowing or maintaining an airway while supine. MRI scans may provide additional detail to CT in infections involving the intracranial cavity, parotid, and prevertebral space. Evaluation of the major vessels of the head and neck is occasionally indicated if there is suspicion of suppurative thrombi of major head and neck vessels such as the sigmoid sinus, internal jugular vein, or cavernous sinus, or if infection followed trauma to the neck such as an intravenous needle stick. MR angiography with venous flow-through provides excellent evaluation of thrombi and pseudoaneurysm, but invasive angiographic techniques may be needed for stenting or balloon occlusion in rare cases of infected pseudoaneurysms.

Ultrasonography

Ultrasonography is used extensively in the evaluation of both benign and malignant lesions of the head and neck in Europe, but has been largely limited to the evaluation of thyroid lesions in the United States. It is likely this modality will be used more in the future to evaluate neck infections because portable ultrasounds are becoming more readily

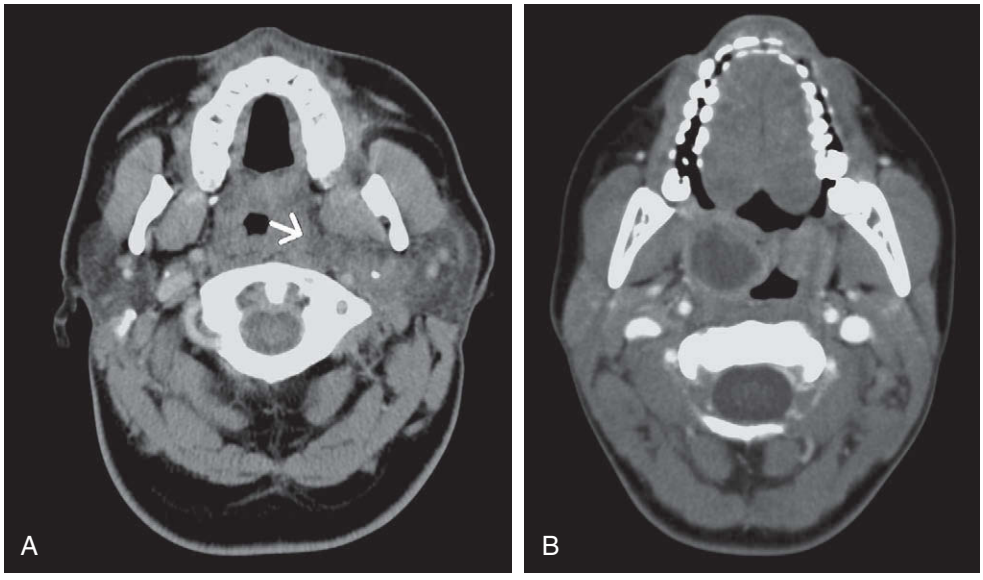

Figure 14-1. Computed tomography scans of deep neck infections may indicate inflammatory phlegmon (*arrow*) without obvious abscess early in the course of deep neck infection **(A)** or a mature infection with abscess formation **(B).**

Figure 14-2. A hypopharynx carcinoma initially diagnosed as a retropharyngeal abscess.

available in emergency departments and outpatient clinics. The noninvasive nature of ultrasound makes it an attractive imaging modality for pediatric patients, and the lack of radiation reduces concerns about potential long-term harm. Most ultrasonography practitioners are adept at using the ultrasound to perform fine-needle aspiration, which may be helpful to obtain culture or provide therapeutic drainage.[18] Ultrasound may be limited in cases of significant neck edema or phlegmon, or when the infection involves spaces beyond the focal range of the technology. Even though the fluid levels of abscesses can be seen by ultrasound if they are large and superficial enough, lack of visualization does not rule out the possibility of abscess due to its limitations on serial evaluation of multiple cross-sectional spaces that are better seen on CT.

Treatment

Medical Management

Airway Management

The initial management of any patient with a known or suspected deep neck infection is securing a safe airway. Loss of airway has traditionally been the major source of mortality from deep neck infection.[19] Airway complications should be anticipated in all cases of deep neck infection and especially infections involving the floor of the mouth, the parapharyngeal space, and the retropharyngeal space. Fiberoptic evaluation of the upper airway at the time of initial evaluation often identifies an evolving airway complication before it occurs. Pulse oximetry monitoring is helpful if interpreted in the proper context, but a normal oximetry should not provide false security in a patient who appears to be in airway distress. Patients with airway compromise should not be transported out of an intensive care suite for prolonged radiographic testing until the airway is secure. Intravenous access should be obtained to allow rapid administration of medications and anesthetic agents when needed. First-line airway therapy includes use of an oxygenated face tent with cool mist humidity, intravenous steroids, and epinephrine nebulizers. If the patient has mild airway symptoms and the examination reveals mild edema with less than 50% obstruction at the glottic or supraglottic level, the patient often responds to medical therapy alone while under direct observation in the emergency suite or intensive care unit.

Urgent airway intervention is necessary if there are greater levels of stridor and dyspnea, usually accompanied by airway obstruction of more than 50%. Effective communication between the consulting otolaryngologist and critical care/anesthesiology personnel is critical. The otolaryngologist needs to convey the results of the initial airway evaluation with the anesthesiologist and be actively involved in intubation planning. In general, an awake fiberoptic intubation can be successfully performed if the airway is visualized to be large enough to allow the passage of the average flexible bronchoscope (5 to 6 mm). Airway preparation with lidocaine nebulizers and lidocaine jelly–lubricated nasal trumpets with or without light sedation allows most adult patients to be intubated comfortably while awake. The patient should be sitting upright, and strong suction should be available to clear airway secretions to improve visualization. A tracheotomy set should be available in the room in case a surgical airway is required. An elective tracheotomy may be considered if extubation is not anticipated within 24 to 48 hours, or if surgical drainage procedures are likely to result in significant or prolonged airway edema. In such situations, elective tracheotomy has been associated with reduced hospital days and reduced costs compared to prolonged intubation.[20] An awake tracheotomy should be planned in cases where minimal or no airway lumen is visualized. Increasing peak airway pressures and frothy airway secretions following successful intubation may indicate the onset of postobstructive pulmonary edema, which typically resolves with positive pressure mechanical ventilation and judicious use of intravenous diuretics.

Fluid Resuscitation

Poor fluid intake is common when neck infection causes significant dysphagia, odynophagia, or trismus. Dehydration is especially common in infections of the peritonsillar and retropharyngeal spaces, and may be the main etiology of sialadenitis-related infections of the parotid space. Signs of fluid deficit include tachycardia, dry and pasty mucous membranes, and decreased skin turgor. Even so, most patients benefit from timely infusion of 1 to 2 L of isotonic intravenous fluids. Providing adequate fluid resuscitation before surgical intervention reduces the severity of anesthesia-related hypotension.

Antibiotic Therapy

Prophylactic antibiotics given before dental, oral, and head and neck procedures may reduce the risk of deep neck infection. Prophylaxis should consist of an oral or intravenous dose of a beta-lactamase–resistant penicillin or clindamycin given within 30 minutes of procedures on nonsterile body cavities, or a first-generation cephalosporin (e.g., cephalexin) or clindamycin for neck incisions in a sterile field. Prophylaxis is mandatory for any patient with a history of heart murmur, rheumatic valve disease, or vascular or joint prosthetic devices.

Deep neck infections require timely treatment with intravenous antibiotics at the time of diagnosis due to the rapidly progressive nature of these infections. Culture is not required before empiric antibiotic therapy because broad-spectrum coverage is usually necessary; most cases involve mixed flora of gram-positive cocci and gram-negative rods with or without anaerobes.[21] Antibiotic coverage may need to be expanded in cases of otologic or sinus infection or nosocomial infections in which *Pseudomonas* is more common, whereas expanded anaerobic coverage is often necessary for fulminate odontogenic infections.

Fluids obtained from aspiration or incision and drainage should be sent for culture due to the increasing rate of resistant organisms in the at-large community. Culture and sensitivity information is especially valuable in the setting of hospital-acquired infections or an immunocompromised host. Due to increasing rates of MRSA in the community, it is likely that more deep neck infection will be caused by this organism in the future. A detailed history and physical examination often identifies patients at risk for atypical infections, which should be confirmed by staining and culturing aspirated fluids or tissue biopsy samples. The choice of antibiotic therapy is typically dictated by the clinical scenario and by culture and sensitivity findings (Table 14-1).

Intravenous antibiotic therapy without surgical intervention may be sufficient therapy in certain circumstances.[22] If a patient is clinically stable and if imaging studies demonstrate inflammation without likely

Table 14-1

First-Line Antibiotic Alternatives for Deep Neck Infection

Community-Acquired Infection (gram-positive cocci; gram-negative rods; anaerobes) Alternatives

- Ampicillin-sulbactam 1.5 to 3 g. IV every 6 hours
- Clindamycin *(if penicillin allergic)* 600 to 900 mg IV every 8 hours

Compromised Patients/Nosocomial Infection (*Pseudomonas*; Methicillin-Resistant *Staphylococcus aureus*)

Pseudomonal and Gram-Negative Alternatives

- Ticarcillin-clavulanate 3 g IV every 6 hours
- Piperacillin-tazobactam 3 g IV every 6 hours
- Imipenem-cilastatin 500 mg IV every 6 hours
- Ciprofloxacin *(if penicillin allergic)* 400 mg IV every 12 hours
- Levofloxacin *(if penicillin allergic)* 750 mg IV every 24 hours

Methicillin-Resistant *Staphylococcus aureus*

- Clindamycin 600 to 900 mg IV every 8 hours, plus vancomycin 1 g IV every 12 hours

Necrotizing Fasciitis (Mixed Gram-Positive and Expanded Anaerobes)

- Ceftriaxone 2 g IV every 8 hours, plus clindamycin 600 to 900 mg IV every 8 hours, plus metronidazole 500 mg IV every 6 hours

Figure 14-3. An infected thyroglossal duct cyst that responded to needle aspiration followed by excision several weeks later.

abscess or an abscess contained within a lymph node, then a 48- to 72-hour trial of empiric intravenous antibiotic therapy is appropriate. A trial of empiric antibiotics is recommended in almost all stable pediatric cases because even sizable collections may respond favorably to intravenous antibiotics and steroids alone.[23] In general, the patient should be given nothing by mouth and closely monitored for changes in clinical status and elevation in white blood cell count. Repeat imaging and/or surgical intervention is necessary in cases that fail to improve or worsen during the observation period. If significant clinical improvement is noted with intravenous antibiotics after 48 to 72 hours, therapy is continued for 24 hours beyond normalization of symptoms followed by a 2-week course of an equivalent oral antibiotic. Patients requiring surgery usually need 48 to 72 hours of intravenous antibiotics postoperatively before being discharged home on oral therapy.

Surgical Management

Surgical drainage is indicated in most cases of deep neck infection. Surgical drainage is necessary under the following circumstances: (1) air-fluid level in the neck or evidence of gas-producing organisms; (2) abscess visualized in the fascial spaces of the head and neck; (3) threatened airway compromise from abscess or phlegmon; (4) failure to respond to 48 to 72 hours of empiric intravenous antibiotic therapy. The main goals of surgical intervention include providing a fluid or tissue sample for tissue staining and culture and sensitivity testing, and providing therapeutic irrigation of the infected body cavity while establishing a stable external drainage pathway to prevent the reaccumulation of abscess.

Needle Aspiration

Needle aspiration without incision often suffices for small abscesses contained within the confines of a lymph node or when an acute infection is caused by suspected congenital cysts or fibrotic pseudocysts (Fig. 14-3). Recurrent infection is common in head and neck cysts; therefore complete surgical excision should be planned after the acute inflammation subsides. For adults, aspiration can be performed at the bedside when the neck mass is palpable and the patient cooperative. Children younger than 12 years of age typically require conscious sedation to prevent errant aspiration. Applying lidocaine ointment to the skin surface for 20 minutes before the aspiration aids in patient comfort. Lidocaine injections often hurt as much as the therapeutic aspiration itself and may obliterate the palpable contours of the mass, making the aspiration more difficult. Slow advancement of a 16- or 18-gauge intravenous catheter on a control syringe while applying negative pressure usually allows localization of the abscess. The needle can be removed from the catheter and the catheter flushed with 1 to 2 mL of sterile saline when the pus is too thick to fully aspirate. Image-guided techniques using ultrasound or CT are being increasingly used when the initial unguided fine-needle aspiration is unsuccessful or the mass is nonpalpable.[24,25] Image guidance also allows placement of small pigtail catheters using Seldinger technique for drainage and flushing.

Transoral Incision and Drainage

The peritonsillar space can be accessed transorally in a cooperative adult without significant trismus. The procedure is often more likely to succeed and be more comfortable to the patient if intravenous fluid rehydration, pain medication, antibiotics, and steroids are administered at least an hour before the procedure. Following application of topical anesthetic spray, 1 to 2 mL of 1% lidocaine with 1:100,000 epinephrine is injected into the mucosa of the lateral soft palate. An initial attempt to drain the space by aspiration is reasonable and helps locate the abscess pocket. If the space cannot be decompressed with aspiration alone, a 1- to 2-cm incision is performed through the mucosa and submucosa along the normal curvature and 1 cm behind the edge of the anterior tonsillar pillar. Gentle vertical spreading of the incision with a hemostat will access the peritonsillar space and allow egress of the abscess. Irrigation with sterile saline using a 20-mL syringe and 18-gauge angiocatheter can easily be performed through the incision. The patient can be discharged home on oral pain medication and antibiotics with outpatient follow-up arranged within 48 to 72 hours. Tonsillectomy at a later date is an option for patients with a history of peritonsillar abscess, recurrent or chronic tonsillitis, or obstructive symptoms from tonsillar hypertrophy. Approximately 16% of adults and 7% of children will experience a recurrent peritonsillar abscess at a later date after an initial episode.[4] Alternatively, acute "quinsy" tonsillectomy at the time of presentation can be considered in cases of recurrent peritonsillar abscess, recurrent acute tonsillitis, or if a general anesthetic is needed due to patient discomfort or poor exposure. Acute

tonsillectomy may be more difficult and bloody than nonacute tonsillectomy due to the surrounding inflammation; therefore the surgeon should have access to adequate lighting, suction, electrocautery, tonsil packs, and suture.

Transoral incision and drainage is also a preferred method of surgery for select deep neck space infections. Odontogenic infections limited to the alveolus may respond to removal of the offending tooth to drain the infected root, although neck incision is necessary when infection has spread beyond the alveolar tissues. A neck incision with dependent drainage of the bilateral floor of the mouth through the mylohyoid muscle is mandatory in cases of Ludwig's angina to reduce the risk of airway obstruction. The buccal space can be accessed via transoral incision of the buccal mucosa with blunt dissection parallel to the facial nerve through the buccinators muscle. The masticator space can be entered by incision of the retromolar trigone with blunt dissection through the masseter. After drainage and irrigation, a ½-inch Penrose drain or gauze wick can be placed through the incision and secured with a silk suture if ongoing drainage is deemed necessary. Otherwise, the wound can be left open to close secondarily or closed loosely with interrupted Vicryl or chromic suture.

The retropharyngeal space is often best entered transorally, especially because many infections in this space originate from the adenoids and are located in the high oropharynx or nasopharynx, which is difficult to access through the neck. After securing the airway and inserting a tonsil gag, transmucosal needle aspiration of the likely site of infection is performed. Once the abscess pocket is identified, the overlying mucosa is incised and blunt dissection used to enter the pocket. Caution should be exercised when dissecting beyond the lateral pharyngeal walls to prevent inadvertent injury to the carotid artery. Drains are typically not placed due to the potential for drain aspiration and potential difficulties with drain removal. If a drain or wick is placed, it can be brought out through the mouth and taped securely to the face. Alternatively, a small ellipse of mucosa and submucosa can be excised at the site of incision to slow the healing process and allow several days of drainage before wound contraction.

Transcervical Incision and Drainage

Transcervical incision and drainage is the traditional surgical approach to deep neck space infection. The location of the incision is dictated by the neck spaces that require exploration. If the skin above a neck abscess has become fluctuant, adequate drainage can often be achieved under local anesthesia with or without sedation via an incision oriented along the relaxed skin tension lines. In general, the deep neck spaces can be accessed by one of three potential incisions that provide both excellent anatomic exposure as well as cosmetic healing. The preauricular parotid incision with neck extension allows access to the parotid and temporal spaces. A horizontal neck incision in a natural skin crease provides access to the masticator, parapharyngeal, pterygoid, submandibular, prevertebral, retropharyngeal, carotid, and lateral neck spaces. The parapharyngeal and pterygoid spaces are entered by retracting the submandibular gland anteriorly while dissecting superior and medial to the posterior belly of the digastric muscle along the medial surface of the mandibular ramus. The prevertebral and retropharyngeal spaces are entered by first identifying the prevertebral fascia by retracting the strap muscles medially and the carotid sheath laterally at a level inferior to the carotid bifurcation. The space can then be bluntly dissected superiorly in the midline to the level of the abscess. The midline horizontal neck incision can be made to access the region of the strap muscles, thyroid, and trachea. A horizontal incision in the lower left neck with dissection to the prevertebral fascia medial to the carotid sheath provides a drainage conduit for the esophagus and upper mediastinum. A horizontal submental incision provides a direct route to the bilateral submandibular spaces and floor of mouth.

After securing the airway by an awake fiberoptic intubation or tracheotomy, the proposed incision site is marked on the neck, injected with 1% lidocaine with 1:100,000 epinephrine, and sterilely prepped and draped. In most cases, the patient should not be paralyzed during the procedure in order to allow monitoring of adjacent cranial nerves. The guiding principle of surgery for deep neck infection is obtaining adequate access and drainage of the infected space while minimizing risk to normal structures. Following incision through the superficial cervical fascia, blunt dissection with a small curved hemostat and Kitner sponge can help separate normal structures while creating a pathway to the infected compartment. Finger dissection of neck tissues should be avoided in patients with a history of transcervical IV drug abuse because broken needles may be left in the neck soft tissue. Access to the deep neck often requires excision of enlarged lymph nodes that block access to the infected space; however, care should be exercised not to overdissect because this may increase the risk to normal nerves and vessels that may be displaced or obscured by inflammation. Once the deep neck space is entered, any fluid or pus should be cultured, followed by irrigation with copious amounts of isothermic normal saline. External drainage is maintained by placement of a ½ to 1-inch Penrose drain, which is brought out through the incision and secured to the neck skin with a suture. The remainder of the incision can be closed loosely with 4.0 nylon sutures.

Selected Complications of Deep Neck Infections

Vascular Complications

Lemierre's Syndrome

Lemierre's syndrome is a rare thrombophlebitis of the internal jugular vein most often caused by the anaerobic, gram-negative bacillus *Fusobacterium necrophorum*.[26] Although this syndrome is rare, awareness is important given the characteristic presentation and potentially fatal outcome if not recognized and treated. The syndrome typically follows a period of pharyngitis before progressing to fever, lethargy, lateral neck tenderness and edema, occasional trismus, and septic emboli most commonly seen as bilateral, nodular infiltrates on chest radiograph or septic arthritis. The bacterium is thought to spread via the tonsillar veins to the internal jugular system where the bacterial endotoxin induces platelet aggregation and septic thrombus formation. Diagnosis is confirmed by neck CT with IV contrast demonstrating a filling defect in the internal jugular system. First-line therapy includes intravenous beta-lactamase–resistant antibiotics with or without heparin anticoagulation. Surgery to excise the jugular vein may be indicated in patients with a worsening clinical course despite appropriate medical therapy or in the event of neck abscess formation.

Cavernous Sinus Thrombosis

Cavernous sinus thrombosis is a life-threatening infection with a mortality rate of 30% to 40% caused by retrograde spread of infection from the upper dentition or paranasal sinuses via the valveless ophthalmic venous system to the cavernous sinus.[27] Symptoms include fever, lethargy, orbital pain, proptosis, reduced extraocular mobility, and dilated pupil with sluggish pupillary light reflex. The diagnosis is best confirmed by magnetic resonance study of the brain with contrast to demonstrate dural enhancement in the region of the cavernous sinus. Treatment includes critical care life support, broad-spectrum intravenous antibiotics, and anticoagulation therapy.

Carotid Artery Pseudoaneurysm or Rupture

Rare cases of carotid artery pseudoaneurysms or rupture have been reported after spread of infection from the retropharyngeal or parapharyngeal spaces to the carotid space.[28] Hallmarks of this complication include a pulsatile neck mass, Horner's syndrome, palsies of cranial nerves IX through XII, expanding hematoma or neck ecchymosis, or bright red blood from the nose or mouth in the setting of a deep neck infection. The complication requires immediate surgical ligation of the carotid artery.

Mediastinitis

Mediastinitis is a relatively rare complication of deep neck infection with a mortality rate of 30% to 40% caused by spread of infection along the retropharyngeal and prevertebral planes of the neck into the upper mediastinum.[29,30] Presentation includes diffuse neck edema, dyspnea, pleuritic pain with deep breathing, tachycardia, hypoxia, and

pleural effusion or mediastinal widening on chest radiograph. Thoracic CT scan with intravenous contrast often reveals the presence of fluid collection, air-fluid levels, or stranding or infiltration of the mediastinal fat. Broad-spectrum intravenous antibiotics are necessary due to a high frequency of multiple pathogens including gram-positive, gram-negative, aerobic, and anaerobic species. If limited to the anterior-superior mediastinum, transcervical drainage via a bilateral cervicotomy with blunt dissection along the prevertebral plane often provides sufficient access for drainage, irrigation, and placement of soft rubber drains. Thoracotomy should be strongly considered in cases that extend beyond the upper mediastinum or that involve more than one mediastinal compartment. In a meta-analysis of 69 patients with mediastinitis from cervical abscess, the mortality rate was 19% among patients who underwent both cervical and thoracic drainage, and 47% among those who underwent cervical drainage alone.[31]

Necrotizing Fasciitis

Necrotizing fasciitis is a severe form of deep neck infection that occurs more often in older age groups (age older than 60 years) and immunocompromised patients, especially patients with poorly controlled diabetes.[32] The origin of the infection is commonly odontogenic and involves mixed aerobic and anaerobic flora. Clinical presentation may consist of a rapidly progressive cellulitis with pitting neck edema and orange-peel appearance from obstructed dermal lymphatics with or without subcutaneous crepitus. Neck CT with intravenous contrast reveals tissue gas in more than 50% of cases, and widespread, nonloculated hypodense areas without peripheral enhancement consistent with liquefaction necrosis. Treatment requires critical care support, management of immunocompromising conditions, broad-spectrum intravenous antibiotics, and surgical exploration. Findings at surgery consistent with necrotizing fasciitis include foul odor, brown, watery fluid collections, and liquefied and grayish fat and muscle that pull apart with minimal finger pressure. Debridement of dead tissue until a bleeding, viable edge or vital nerves or vessels are reached is recommended. The wound is thoroughly irrigated, packed with moist gauze, and left open for a second-look procedure in 48 to 72 hours. Surviving patients may require skin grafting or flap reconstruction once the infection subsides. Adjuvant hyperbaric oxygen therapy can be considered if available.[33] Mortality may be as high as 20% to 30% in treated patients, and is highest in patients with mediastinal extension.[32]

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For complete list of references log onto www.expertconsult.com.

CHAPTER FIFTEEN

Head and Neck Manifestations in the Immunocompromised Host

Theresa B. Kim

Steven D. Pletcher

Andrew N. Goldberg

Key Points

- Immunosuppressed patients are at risk for fungal, bacterial, and viral infections, and have higher rates of certain malignancies, often with a more aggressive clinical course than that seen in immunocompetent individuals.
- Most immune deficiencies are acquired and affect the adaptive immune system, resulting in T and B cell dysfunction.
- Highly active antiretroviral therapy (HAART) has had a profound impact on the disease course of HIV and has led to a decrease in many of the complications associated with the disease.
- There is a striking similarity in the pattern of increased rates of cancer in HIV-positive patients and transplant recipients, suggesting that immune deficiency plays a role in the pathogenesis of cancer.
- Human herpesvirus 8 infection coupled with the host's state of immunosuppression plays a causal role in the development of Kaposi's sarcoma.
- Immunosuppressed organ transplant recipients are at highest risk for nonmelanoma skin cancer and squamous cell carcinoma is twice as likely to develop as basal cell carcinoma.
- Most lymphomas occurring in immunosuppressed patients are non-Hodgkin's lymphoma of the B-cell type, the majority of which are associated with Epstein-Barr virus infection.
- Salivary gland dysfunction marked by decreased salivary flow rates and xerostomia is common in immunosuppressed patients.
- Many patients with HIV develop parotid lesions, the most common of which are benign lymphoepithelial cysts that are effectively treated with HAART in most cases.
- Invasive *Aspergillus* infections such as invasive fungal sinusitis and malignant otitis externa are life-threatening conditions occurring in immunosuppressed patients that require prompt recognition and treatment with surgical debridement and systemic antifungal agents.
- Hearing loss is common in immunosuppressed patients and may result from infectious causes in HIV-positive patients or immunosuppressive drugs in organ transplant recipients.
- Oral candidiasis is the most common oral lesion in HIV-positive patients but must be distinguished from other infectious and neoplastic lesions.

Spectrum of Immunosuppression

Immunosuppression occurs in the setting of genetic, infectious, and other acquired disorders. The cells of the immune system derive from hematopoietic stem cells in the bone marrow, circulate in the blood and lymph, and are present in nearly every tissue.[1] Protection of the host occurs by two mechanisms: innate and adaptive. The innate immune system is widely conserved among many vertebrate species and is the first line of defense. The primary cells involved are neutrophils, eosinophils, basophils, macrophages/monocytes, dendritic cells, and natural killer cells. Adaptive immunity protects the host against pathogens that escape innate immune responses and is a characteristic of higher vertebrates. The cellular components involved in adaptive immunity are T cells and B lymphocytes. Immunodeficiencies can affect any of the components of the innate and adaptive immune systems.

Congenital immunodeficiencies, which are less common than acquired, rarely affect the innate immune system. Severe combined immunodeficiency (SCID) affects both the T and B cells of the adaptive immune system, and children born with this disorder often die of infections in early childhood. Other genetic immunodeficiencies that affect T and B cells include DiGeorge's syndrome, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, and selective immunoglobulin deficiencies in which serum concentrations of one or more immunoglobulin subclasses are reduced. Clinical characteristics of T-cell dysfunction include onset of symptoms in early infancy (4 to 5 months) with recurrent fungal, viral, and mycobacterial organisms and infections with opportunistic infections such as *Pneumocystis*.[2] B-cell deficiencies are marked by recurrent infections with encapsulated organisms such as sinopulmonary infections, otitis

Table 15-1

Causes of Immunosuppression

Genetic

Common variable immunodeficiency (CVID)
DiGeorge's syndrome
Selective immunoglobulin deficiencies
Severe combined immunodeficiency (SCID)
Wiskott-Aldrich syndrome
X-linked agammaglobulinemia (XLA)

Acquired

Human immunodeficiency virus (HIV)
Hematologic malignancies
Myeloproliferative disorders
Diabetes mellitus
Iatrogenic drug-induced immunosuppression
Chemotherapeutic agents
Corticosteroids
Immunosuppressive agents after solid organ and bone marrow transplantation

media and sepsis, and increased incidence of atopy, but no increased susceptibility to fungal or viral infections.[2]

Acquired immunodeficiencies are much more common than genetic immunodeficiencies. Acquired immunodeficiency may result from infection with the human immunodeficiency virus (HIV); hematologic malignancies and myeloproliferative disorders such as multiple myeloma or leukemia; diabetes mellitus; or iatrogenic drug-induced immunosuppression from chemotherapeutic agents, corticosteroids, and other immunosuppressive agents after solid organ and bone marrow transplantation (Table 15-1). Patients with immunosuppression are at higher risk than their immunocompetent counterparts for developing fungal, bacterial, and viral infections, and have higher rates of certain malignancies. Much of this pathology may manifest in the head and neck and thus otolaryngologists should be familiar with the spectrum of disease affecting immunocompromised patients.

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

Biology and Immunology

HIV infects and debilitates lymphocytes and macrophages leading to progressive immune compromise. Progressive decline in immune function in later stages of infection culminates in the acquired immunodeficiency syndrome (AIDS). Anecdotal reports[3] of unusual infections and idiopathic immune deficiency, primarily in homosexual men, began in the early 1980s and rapidly grew into the HIV/AIDS epidemic that has affected the world population. Every day, more than 6800 people become infected with HIV and 5700 people die of AIDS.[4] Worldwide, approximately 33.2 million people are living with HIV infection, with sub-Saharan Africa being the most severely affected region, where AIDS is the leading cause of death. After many years of increase, the global prevalence of HIV has stabilized and in some countries has even decreased.[4] With wider availability of effective treatment, rates of death have also recently begun to decline.

Transmission of HIV occurs through body fluids and tissues. Virus from an infected patient may inoculate the bloodstream of another individual through a breach in skin or mucosa, or via intravenous infusion. Modes of transmission include sexual intercourse, the sharing of needles by intravenous drug users, vertical transmission from mother to child, and, rarely, transfusion of contaminated blood products or accidental exposure in health care workers. More than 50% of new HIV infections in the United States occur in men who have sex with men; infection after heterosexual intercourse and injection drug use lead to 32% and 18% of new infections, respectively.[4]

HIV is a retrovirus in the Lentivirus subfamily, named for the slow progression of disease in affected individuals. These viruses establish chronic infections with a long incubation time and slow progression of disease. Viruses in the Lentivirus family typically infect cells involved in immune modulation; in the case of HIV, that is primarily CD4 T cells and macrophages, resulting in defects in both humoral and cell-mediated immunity. The virus life cycle begins when the virus binds to the CD4 receptor, a surface protein on the helper T subset of T lymphocytes, which is also expressed on macrophages. Fusion of the viral and cell membranes allows entry of the viral core into the cell. The reverse transcriptase enzyme, a protein carried by the virus, allows transcription of RNA into DNA (a reversal of normal transcription), then mediates transcription of the viral RNA genome into viral DNA. Viral integrase, another viral protein, then facilitates incorporation of the viral DNA into the host genome. The viral DNA is transcribed into multiple RNA copies by the host cell. This newly created RNA may be spliced and translated into viral proteins or it may remain intact as a future viral genome. Translation of some viral RNA sequences results in protein precursors or multiple proteins bound together. These precursors undergo proteolytic processing by a viral protease that liberates the functional viral proteins. These proteases are required for viral infectivity. Following replication of the viral genome and proteins, the new viruses bud from the infected cell and proceed to infect new cells. The viral DNA polymerase is error-prone, incorporating one mismatched nucleotide per genome per round of transcription. This, combined with the amount of replication that occurs, establishes a vast pool of genetic diversity.[5,6] The development of vast genetic diversity also gives the virus an advantage in the development of drug resistance and provides a critical barrier to vaccine development.

Diagnosis and Classification

HIV infection is diagnosed when anti-HIV antibodies are detected in the serum by screening enzyme-linked immunosorbent assay (ELISA) and is confirmed with specific antibody detection with Western blot. Persistent antibodies against HIV typically occur within 3 months of infection. The CDC classification system for HIV, last updated in 1993, is based on the clinical manifestations of disease and the patient's CD4 count (Table 15-2).[7] These classifications assist in assessing the level of immune compromise and the corresponding risk for development of opportunistic infection or neoplasm. Three clinical categories have been identified: (A) asymptomatic HIV infection, persistent generalized lymphadenopathy, or acute HIV infection (a mononucleosis-type syndrome); (B) symptomatic conditions such as oral thrush, oral hairy leukoplakia, and fungal sinusitis that are attributed to HIV infection but do not fall into category A or C; (C) AIDS-defining conditions (Table 15-3). Patients may be further stratified according to their CD4 counts: (1) >500 cells/μL; (2) 200 to 499 cells/μL; (3) <200 cells/μL. The lowest accurate CD4 count, not the most recent, is used for classification purposes. AIDS is diagnosed for any patient who develops an AIDS-defining illness (category C) or CD4 less than 200 cells/μL (category 3). The World Health Organization (WHO) classification for HIV infection includes four clinical stages[8]:

1. Asymptomatic HIV infection or persistent generalized lymphadenopathy

2. Moderate unexplained weight loss (<10% of body weight), recurrent respiratory tract infections, herpes zoster, angular cheilitis, recurrent oral ulceration, papular pruritic eruptions, seborrheic dermatitis, or fungal nail infections

3. Unexplained severe weight loss (>10% of body weight), chronic diarrhea or persistent fever for more than 1 month, oral manifestations such as persistent oral candidiasis, oral hairy leukoplakia, or necrotizing gingivitis, pulmonary tuberculosis (current), severe bacterial infections, unexplained anemia, neutropenia, or chronic thrombocytopenia

Table 15-2

Classification System for HIV Infection

CD4 Categories	Clinical Categories (A) Asymptomatic, Acute or Persistent Generalized Lymphadenopathy	(B) Symptomatic	(C) AIDS-Defining Illness
(1) >500 cells/μL	HIV	HIV	AIDS
(2) 200 to 499 cells/μL	HIV	HIV	AIDS
(3) <200 cells/μL	AIDS	AIDS	AIDS

Adapted from CDC 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep.* 1993;41(RR-17):1.

Table 15-3

AIDS-Defining Illnesses

Burkitt's lymphoma, immunoblastic or primary brain
Candidiasis, bronchopulmonary or esophageal
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month)
Cytomegalovirus disease (liver, spleen, and lymph nodes excluded)
Encephalopathy, HIV-related
Herpes simplex, chronic ulcers (>1 month), bronchopulmonary or esophageal
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month)
Kaposi's sarcoma
Mycobacterium avium complex, *Mycobacterium kansasii,* or other species, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site
Non-Hodgkin's lymphoma
Pneumocystis jiroveci pneumonia (formerly *Pneumocystis carinii*)
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome caused by HIV

Adapted from CDC 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep.* 1993;41(RR-17):1.

4. HIV wasting syndrome, *Pneumocystis* pneumonia, recurrent severe bacterial pneumonia, chronic herpes simplex infection for more than 1 month, esophageal candidiasis, extrapulmonary tuberculosis, Kaposi's sarcoma (KS), cytomegalovirus infection, central nervous system (CNS) toxoplasmosis, HIV encephalopathy, extrapulmonary cryptococcosis, chronic cryptosporidiosis or isosporiasis, disseminated mycosis, lymphoma or other solid HIV-associated tumors, invasive cervical carcinoma, or symptomatic HIV-associated nephropathy or cardiomyopathy

Highly Active Antiretroviral Therapy

When left untreated, HIV infection causes gradual debilitation of the immune system over a period of years, resulting in profound immunocompromise and AIDS. Advances in understanding of HIV biology have allowed for the development of medications targeting the reverse transcriptase and protease enzymes critical to the viral life cycle. Current drugs do not eradicate the virus, thus the major goals of treatment are the complete inhibition of HIV replication, reduction in HIV-related morbidity, and prevention of vertical transmission.[9-11] Antiretroviral agents from five classes of drugs are currently available to treat HIV infection. These include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (EIs), and integrase inhibitors.[11] Combinations of three or more of these agents allow for such effective suppression of viral replication that the emergence of drug-resistant variants is delayed, forming the basis of highly active antiretroviral therapy (HAART).[10] The use of HAART is credited for a 45% decline in mortality rates during the late 1990s, although in more recent years, the decline in mortality has been more modest, only 8% between 2000 and 2004.[12]

The U.S. Department of Health and Human Services recommends initiation of HAART for patients with history of an AIDS-defining illness or with CD4 less than 350 cells/μL.[11] The timing of HAART initiation in asymptomatic patients with CD4 greater than 350 cells/μL is not well defined and the decision should be guided by the potential benefits and risks associated with therapy, patient comorbidities, and willingness to adhere to long-term treatment. Drug resistance testing is recommended for all patients with diagnosed HIV, regardless of whether treatment will be initiated. Two types of combination regimens are generally used: NNRTI-based (one NNRTI with two NRTI) and PI-based (one or two PI with two NRTI). The choice of regimen is determined by patient comorbidities (e.g., tuberculosis infection, liver disease, and cardiovascular disease), dosing convenience, potential drug interactions, and results of genotypic drug resistance testing.

Immune Restoration Disease

Recently, infections with opportunistic organisms occurring in HIV-positive patients who initiate antiretroviral therapy have been recognized and are known as immune reconstitution syndrome or immune restoration disease (IRD).[13,14] Diagnostic criteria for IRD include a previous diagnosis of AIDS, concurrent antiretroviral therapy with increasing CD4 cell count, and an exacerbation or atypical presentation of opportunistic infections.[15] The most common pathogens associated with this condition are *Mycobacterium* (tuberculous and nontuberculous), *Cryptococcus*, herpesviruses, and hepatitis B and C viruses.[13] Symptoms may occur as soon as a few days following HAART initiation, although most patients develop symptoms 2 to 8 weeks after beginning HAART.[15] IRD may occur in 10% to 50% of patients initiating HAART, but opportunistic infections are rare, occurring in 5% of patients.[16] It is also seen in 5% of transplant recipients after dose reduction in immunosuppressive medications.[17] IRD is thought to be caused by overly exuberant pathogen-specific immune responses as

patients recover immune function.[13-15,17] IRD-associated mycobacterial infections generally present with fever, lymphadenopathy, and worsening respiratory function.[18] HIV-positive patients not already receiving HAART who present with mycobacterial infections should not be started on HAART until after the infection is controlled.[15] Trials examining the role of steroidal and nonsteroidal anti-inflammatory agents in the treatment of IRD are ongoing.[18]

Occupational Exposure to Human Immunodeficiency Virus Infection

With more than 1.3 million HIV-positive children and adults in the United States[4] and with the high prevalence of otolaryngologic complaints among these patients, most otolaryngologists will treat HIV-positive patients. An understanding of the risks of occupational transmission as well as precautions that may minimize such transmission is essential. There have been 57 documented cases of HIV seroconversion among U.S. health care personnel following occupational exposure, the most recent occurring in 2000.[19] Because of the voluntary nature of the reporting system, there may be underreporting of cases. Exposures that carry a risk for HIV transmission are percutaneous injuries (e.g., needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin with blood, tissue, or body fluids that are potentially infectious. The risk of transmission from fluid other than blood or transmission through nonintact skin is too low to be estimated in prospective studies. Even though cerebrospinal fluid carries a risk of transmission, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered infectious unless they are visibly bloody.[20] Pooled prospective data suggest an average risk of HIV transmission of 0.3% for needlesticks and 0.09% following mucous membrane exposure.[21] Whereas injury from suture needles has been suggested as a possible source of occupational exposure to HIV, such an injury has not been implicated as a source of transmission in prospective studies. Although a lower viral load (<1500 RNA copies/mL) or one that is below the limits of detection probably indicates a lower titer exposure, it does not rule out the possibility of transmission.

Prevention of blood exposure through the use of safe practices, barrier precautions, safe needle devices, and other innovations is the best way to prevent infection with HIV and other blood-borne pathogens.[22] Simple strategies such as using double gloves, eye protection, impermeable gowns, and special techniques for passing sharp objects have all been suggested to minimize exposure risk. Despite such precautions, needlesticks and mucosal exposures will continue. After exposure to blood or other infectious fluids, the following actions should be taken immediately[22]: Wash needlestick areas and cuts with soap and water; flush nose, mouth, or skin with water; irrigate eyes with clean water, saline, or sterile irrigants. To minimize the risk of disease transmission, postexposure prophylaxis (PEP) should be initiated within hours of exposure and should continue for 4 weeks.[20] The number of agents used depends on the type of exposure and risk profile of the source patient (Table 15-4). Treatment may be discontinued if the source patient subsequently tests negative for HIV infection and does not demonstrate any evidence of acute HIV infection. Exposed individuals should be tested for HIV at the time of exposure with follow-up testing at 6 weeks, 12 weeks, and 6 months after exposure.[20] Prevention of HIV transmission following PEP is not complete. There have been at least 20 cases of seroconversion despite the use of PEP,[21] with some of the patients having received multiple drug regimens. Thus careful adherence to universal precautions with avoidance of exposure remains the most prudent way to prevent infection.

Table 15-4

Postexposure Prophylaxis (PEP) Recommendations

	Infection Status of Source		
Exposure Type	**HIV-Positive, Class 1[a]**	**HIV-Positive, Class 2[b]**	**HIV Status Unknown[c]**
Less severe[d]	Basic 2-drug PEP	Expanded ≥ 3 drug PEP	Generally no PEP warranted; consider basic 2-drug PEP for source with HIV risk factors[e]
More severe[f]	Expanded 3-drug PEP		

[a]Asymptomatic HIV infection or known low viral load (<1500 copies/mL).
[b]Symptomatic HIV infection, AIDS, or known high viral load.
[c]For example, deceased source person with no samples available for HIV testing.
[d]For example, solid needle or superficial injury.
[e]If PEP is administered and the source is later determined to be HIV-negative, PEP should be discontinued.
[f]For example, large-bore hollow needle, deep puncture, visible blood on device.
Adapted from CDC Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for Postexposure Prophylaxis. *MMWR Morb Mortal Wkly Rep.* 2005;54(No. RR-9).

Immunosuppression and Malignancy

Patients with immune deficiency are at increased risk for developing malignancy (Table 15-5). The mechanism of oncogenesis is unknown, but the striking similarity between increased malignancies in immunosuppressed transplant recipients and patients with HIV suggests that immune function plays a vital role. In HIV, three types of cancer occur at markedly increased rates during later stages of the disease and are thus considered AIDS-defining malignancies. These include KS, non-Hodgkin's lymphoma (NHL), and invasive cervical cancer. A meta-analysis comparing the incidence of cancer in patients with HIV/AIDS and immunosuppressed transplant recipients demonstrated a striking similarity in the pattern of increased rates of most types of cancer. Both groups had increased rates of AIDS-defining malignancies, Hodgkin's lymphoma, squamous cell carcinoma of the lip, and nonmelanoma skin cancer.[23] Non–AIDS-defining malignancies in patients with HIV also occur later in the disease course, often after the diagnosis of AIDS.[24,25] These findings suggest that immune deficiency plays a role in the pathogenesis of cancer, although the mechanism of oncogenesis is unknown. There is no clear evidence linking immune depression with other types of head and neck cancer.

Kaposi's Sarcoma

Epidemiology and Pathogenesis

KS is an angioproliferative disorder that causes lesions marked by spindle cell proliferation, neoangiogenesis, inflammation, and edema.[26,27] There are four clinical variants with identical histologic features but with distinct epidemiologic patterns: classic KS, endemic KS, immunosuppression—or transplant-related KS, and HIV-associated KS (AIDS-KS).[28-30] The classic form of KS was first described in older men of Eastern European or Mediterranean descent, with lesions typically occurring on the upper and lower extremities.[29] An endemic variety of KS was also recognized in black adults and children in Africa, where it was and continues to be very common.[31] In 1981, Friedman-Kien published a report of KS occurring in otherwise healthy young homosexual men[32] and eventually the association between HIV infection and the development of KS became well established. By 1989, HIV-KS was reported in 15% of all US patients with AIDS.[33] The overall risk of KS in AIDS patients was estimated to be 20,000 times that of the general population and more than 300 times that of other immunosuppressed patients. Since the introduction of effective antiretroviral therapy, there has been a marked decrease in the incidence of AIDS-KS,[34,35] with estimated incidence now being approximately 5%.[36] As solid organ and hematopoietic transplantation became more common, transplant recipients were also found to be at increased risk for developing KS.[37-39] Prevalence reports vary depending on geographic location, ranging from 0.5% in the United States to 5.3% in Saudi Arabia.[40] The risk

Table 15-5

Head and Neck Malignancies Associated with Immunosuppression

Malignancy	Immunosuppressive State	Site(s) of Presentation	Notes
Kaposi's sarcoma*	HIV infection Transplant recipients	Skin, oral mucosa, and lymph nodes HIV—70% occur in head and neck Transplant recipients—lower extremities	More aggressive course compared to immunocompetent Associated with HHV8 Marked decrease since HAART
Lymphoma Non-Hodgkin's lymphoma (NHL)*	HIV infection	⅔ have head and neck involvement	More likely to have advanced disease
Hodgkin's lymphoma (HL)	HIV infection	Nearly universal cervical lymph node involvement	
Posttransplantation lymphoproliferative disorder	Transplant recipients	40% have head and neck involvement	Most are B-cell NHL but HL also occurs
Noncutaneous squamous cell carcinoma (SCC)	HIV infection Transplant recipients	Larynx, lip, oral cavity, oropharynx	Evidence supporting increased incidence is equivocal except for lip SCC (which may be considered cutaneous)
Nonmelanoma skin cancer	HIV infection Transplant recipients	Any site	Much higher risk in OTR, especially for SCC Same risk factors as general population More aggressive course compared to immunocompetent

*AIDS-defining malignancy.
HAART, highly active antiretroviral therapy; HHV8, human herpesvirus 8; OTR, organ transplant recipients.

for KS in organ transplant recipients is highest within the first 2 years after transplant and is increased with HLA mismatches.[41]

During the early AIDS-KS epidemic, a striking relationship was seen between the mode of HIV infection and the risk of developing KS. The risk for acquiring AIDS-KS was reported to be as low as 1% for patients who acquired HIV via blood transfusion, whereas in the population of men who have sex with men (MSM), the risk was 21%.[33] KS was seen in only 2% of AIDS cases in women, with most of them reporting sexual contact with MSM.[31] These epidemiologic disparities led to speculation that an infectious component, possibly sexually transmitted, played a role in AIDS-KS.[33] In 1994, Chang and colleagues identified Kaposi's sarcoma–associated herpesvirus (KSHV), a new herpesvirus, within KS lesions.[42] KSHV is formally designated as human herpesvirus 8 (HHV8) and, along with Epstein-Barr virus (EBV), is a member of the gammaherpesvirus subfamily of herpesviruses.[43,44] HHV8 has been identified in more than 95% of all KS lesions regardless of the epidemiologic subtype.[29,30] The varying prevalence of HHV8 infection worldwide may explain the wide range of KS prevalence in different countries.[45] The mechanism of oncogenesis has not been fully elucidated, in that KSHV is present in both immunosuppressed and immunocompetent individuals.[46] It is believed that HHV8 infection coupled with the host's state of immunosuppression plays a causal role.[29,47,48]

HHV8 infection itself appears to be a worldwide epidemic whose onset may have predated the HIV epidemic.[47,49-51] Despite its widespread prevalence, the modes of transmission of HHV8 are incompletely understood. Some studies suggest that sex between men is an important route of transmission.[49,52,53] In populations with high rates of endemic KS, familial clustering of HHV8 seropositivity was seen.[54] Data suggesting vertical transmission from mother to child have also been reported,[55,56] but do not explain the increased prevalence of HHV8 infection in prepubescent children. Some researchers have concluded there may be a role for child-to-child nonsexual transmission, perhaps via saliva.[56-58]

Presentation and Diagnosis

Compared with the classic and endemic forms of KS, immunosuppression-related KS and AIDS-KS are more aggressive. The clinical course of AIDS-KS ranges from an indolent, slowly progressive disease to a rapidly progressive and fatal course.[28] AIDS-KS is associated with a shortened life expectancy, although most patients die of opportunistic infection or lymphoma and not KS per se.[59] Multiple lesions develop in many patients, who more commonly have lymph node or visceral organ involvement. Frequently involved sites include the skin, oral mucosa, and lymph nodes. AIDS-KS occurs in the head and neck in as many as 70% of cases,[60,61] whereas immunosuppression-related KS tends to occur in the lower extremities.[30] Oral KS occurs in roughly one third of AIDS-KS,[62] whereas in immunosuppression-related KS cutaneous lesions are most common.[63] Cutaneous disease presents as multicentric macular and papular lesions that are nontender and nonblanching. These frequently coalesce and progress to violaceous, nodular lesions (Fig. 15-1). They are usually asymptomatic but may become pruritic and aesthetically displeasing. Mucosal KS commonly occurs in the oral cavity, and oral KS, which is associated with lower CD4 counts than cutaneous disease,[66] may be a first sign of HIV infection.[64,65] Oral KS may resemble cyclosporine-associated gingival hyperplasia in organ transplant recipients but cyclosporine usually causes generalized fibrotic gingival hyperplasia whereas oral KS produces a more localized red-purple enlargement.[67] The most frequently affected sites in oral KS are the hard palate, gingiva, and tongue.[64] Mucosal KS is more likely to be symptomatic than cutaneous disease. Lesions may cause loose teeth and are associated with pain, ulceration, and bleeding.

Depending on its location, visceral KS may be asymptomatic or rapidly fatal. Postmortem studies suggest that more than 25% of AIDS-KS patients have visceral lesions.[30] These most commonly involve the gastrointestinal (GI) tract, liver, spleen, and lungs. GI disease is often asymptomatic, whereas median survival in pulmonary KS without treatment is only a few months.[68] The most common presenting symptoms of pulmonary KS are dyspnea and cough, usually without fever unless concomitant infection is present. It may be difficult to distinguish pulmonary KS from other neoplastic and infectious diseases clinically, thus radiologic studies play an important role in its diagnosis. Computed tomography (CT) of the chest is often sufficient to diagnose pulmonary KS[69] and may identify lymphatic or extrapulmonary involvement.[68]

Otolaryngologists may encounter patients with KS of the larynx associated with symptoms ranging from chronic cough or hoarseness to acute upper airway obstruction.[70-73] If diagnosis and treatment proceed appropriately, acute airway obstruction may be avoided. Local treatment in isolated disease or systemic treatment in multicentric disease is recommended to avoid progression to airway compromise.[71]

Once the diagnosis of KS is suspected, biopsy may be performed for pathologic confirmation. The histopathology of KS is characterized by abnormal proliferation of lymphatics. Lesions may occur in three forms: patch, plaque, and nodule.[74] Nodular lesions are more common in immunosuppression-related and AIDS-KS, and are marked by proliferation of slitlike vascular channels, extravasated erythrocytes, and spindle-cell proliferation (Fig. 15-2). KS lesions may be mimicked by bacillary angiomatosis, which also causes vascular proliferative lesions. The presence of pleomorphic bacilli on Warthin-Starry silver stain helps distinguish bacillary angiomatosis.[75,76] The identification of HHV8 DNA may help distinguish KS from other vascular lesions.[77] If KS is identified in a patient without a known history of HIV infection, an HIV test is warranted.

At the initial evaluation of a KS patient, a complete skin examination and oral cavity examination should be performed. A normal examination in these areas does not ensure the absence of KS because clinically significant visceral lesions may present in the absence of mucocutaneous disease. If unexplained GI or pulmonary symptoms are present, radiologic imaging of the chest and abdomen and GI endoscopy should be performed. The classic appearance of small, submucosal vascular nodules establishes the diagnosis of visceral KS. Endobronchial biopsy may result in significant hemorrhage and is discouraged. The constitutional symptoms of fevers, night sweats, and weight loss should be recorded as well as the immunologic status, including CD4 count and viral load.

Figure 15-1. Nodular Kaposi's sarcoma of the gingiva and palate. Given the ulcerated and fungating appearance, the differential diagnosis includes non-Hodgkin's lymphoma and squamous cell carcinoma. *(Courtesy of Dr. Russel Corio.)*

Treatment

Despite multiple therapeutic options, treatment is palliative and there is no cure. The disease course is variable; many patients achieve remission of KS but succumb to other causes of death. The course is complicated by increased susceptibility for developing opportunistic infections related to immunosuppression. Treatment of KS is determined by the extent and location of disease, as well as the severity of symptoms. Specific indications for treatment of KS include cosmetically disfiguring lesions, symptomatic oral lesions, symptomatic visceral lesions, or pain or edema associated with lymphadenopathy or extensive cutaneous disease. Local therapies may be useful in localized lesions or for cosmesis, but they do not prevent new lesions from developing in untreated areas[78] and recurrence rates are high.[30] Local treatments include alitretinoin topical gel (the only FDA-approved topical treatment for KS), local radiation, intralesional chemotherapy injection, cryotherapy, laser therapy, and surgical excision.

Restoration of immune function when possible should be a primary goal, because lesions often regress with the reversal of immunosuppression. Withdrawal of immunosuppressive agents in transplant recipients may, however, lead to transplant failure in up to half of patients.[29] Some data suggest that using sirolimus instead of

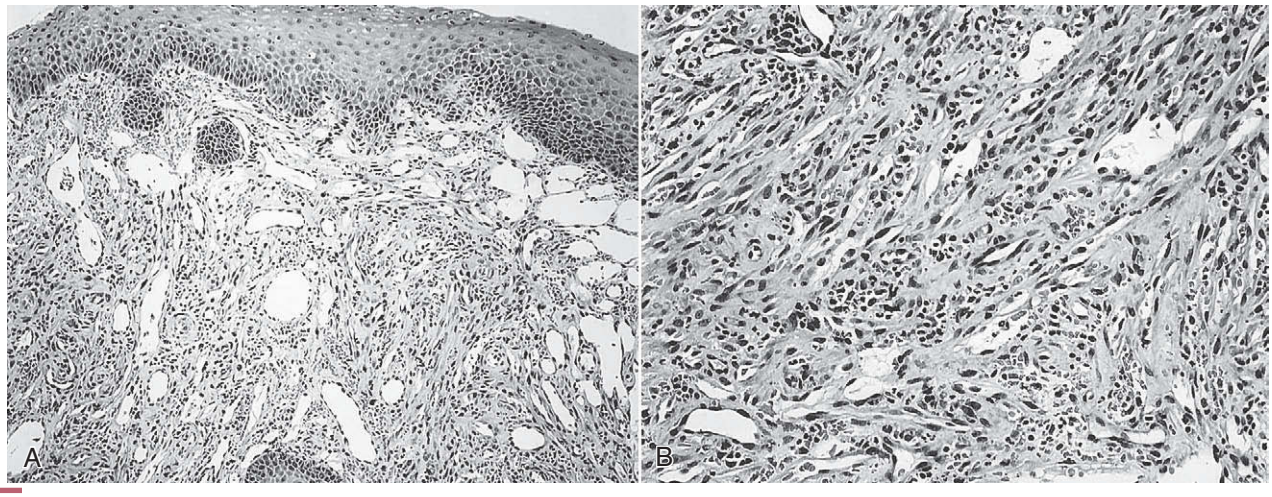

Figure 15-2. Mucosal Kaposi's sarcoma. **A,** Photomicrograph of submucosal Kaposi's sarcoma showing slit-like vascular channels and scattered extravasation of erythrocytes (×100). **B,** Higher-power photomicrograph of the same lesion showing characteristic spindle cell proliferation (×200).

cyclosporine-based immunosuppression regimens may result in regression of immunosuppression-related KS lesions, but further investigation is needed to substantiate these results.[63,79] HAART is now recognized to be a cornerstone of AIDS-KS treatment of all stages.[34,78,80] Antiretrovirals have been shown to decrease KS tumor growth, and active investigation in the use of protease inhibitors for non-AIDS patients with KS is ongoing.[81,82] The AIDS Clinical Trial Group (ACTG) staging system for KS originally took into account tumor burden, immune status as reflected by CD4 count, and the presence of systemic illness to predict likelihood of survival.[83] More recent data have demonstrated that only high tumor burden and systemic illness portend an unfavorable prognosis.[84]

Four agents are currently FDA-approved for systemic treatment of KS. These include liposomal anthracyclines (doxorubicin and daunorubicin), paclitaxel, and interferon-alpha. Other commonly used agents include vinca alkaloids (vincristine and vinblastine) and bleomycin.[34,85] Caution must be exercised when using paclitaxel because serious drug interactions with various components of HAART may occur. Multidrug chemotherapy is associated with increased toxicity, including myelosuppression, and results have been disappointing in widespread disease.[85] HIV-positive patients on chemotherapy are also at increased risk of developing opportunistic infections.[86] As the molecular basis of KS pathogenesis becomes more clearly defined, therapies targeting specific pathways are being developed. These experimental treatments have mostly focused on angiogenesis, HHV8 replication and life cycle, and cytokine regulation.[87] There are ongoing clinical trials investigating antiangiogenic compounds such as imatinib mesylate,[88] matrix metalloproteinase inhibitors,[89] and interleukin-12.[90]

Cutaneous Neoplasms

Immunosuppressed organ transplant recipients and HIV-positive patients have a higher risk of developing skin cancer compared to immunocompetent individuals. Risk factors for the development of skin cancer in immunosuppressed patients are the same as those in the general population, with fair skin, sun exposure, and family history of skin cancer being the principal factors.[91-94] Even though the rate of nonmelanoma skin cancer (NMSC) is increased in both groups, organ transplant recipients have a markedly higher risk than people with HIV/AIDS.[23] The incidence of NMSC in OTR can be as high as 34%.[95,96] In the general population, basal cell carcinoma (BCC) is more common than cutaneous squamous cell carcinoma (SCC), whereas organ transplant recipients develop SCC twice as frequently as BCC.[97] The risk of developing NMSC increases dramatically with longer posttransplant times.[97,98] At 10 years after transplantation, the prevalence of NMSC is 32%.[99] Within the HIV-positive population, BCC is second behind KS as the most common cutaneous malignancy, with a prevalence of 1.8%.[93] CD4 count does not correlate with the incidence or severity of NMSC.[100,101] Both groups have increased rates of lip SCC.[23,24] The evidence linking immunosuppression to increased risk of melanoma is less clear than for NMSC, in that increased rates of detection may reflect greater surveillance in immunosuppressed patients.[92,101]

Compared to NMSC in the general population, NMSC in these patients, particularly SCC, is more often invasive and aggressive, with higher rates of metastasis and recurrence.[92,100-102] Melanoma also has more aggressive features in the setting of immune depression, and shorter disease-free intervals and overall survival have been demonstrated in HIV-positive patients.[103]

Treatment outcomes vary with the type of skin cancer. Although more aggressive types of BCC in HIV-positive patients have been reported,[104-106] standard excisional techniques result in cure rates similar to those in the general population.[100,101] In contrast, cutaneous SCC is associated with higher mortality in immunosuppressed patients, with mortality around 3% in organ transplant recipients[107] and up to 50% in HIV patients who have metastatic SCC.[108] As in the management of Kaposi's sarcoma, reduction of immunosuppression in organ transplant recipients is associated with reduced incidence and improved outcomes for skin cancer.[102] There are no clear guidelines for the management of cutaneous SCC or melanoma in HIV patients, but local excision with early consideration for systemic therapy is generally recommended.[101] Because of the aggressive nature of skin cancers in immunosuppressed patients, early detection with a low threshold for biopsy of suspicious lesions is recommended.

Squamous Cell Carcinoma

Data regarding the incidence of noncutaneous SCC in immunosuppressed patients are controversial. Several studies have reported increased incidence of noncutaneous SCC in organ transplant recipients, with one large series reporting a 0.5% incidence, which was a 20-fold increase over the control population.[109,110] In particular, patients undergoing liver transplantation had an even greater risk.[111,112] There have also been reports of increased head and neck SCC in HIV-positive patients.[24,113] Confounding factors of pretransplantation tobacco and alcohol use, however, may contribute to the increased incidence seen in both groups.[109,112-114] High levels of immunosuppression in organ transplant recipients[109] and lower CD4 count in HIV-positive patients[115] may confer an increased risk. Immunosuppressed patients, however, do appear to experience a more virulent clinical course than the general population. Organ transplant recipients and HIV-positive patients tend to present at an earlier age and with more advanced disease than their immunocompetent counterparts.[109,110,115] As in immunocompetent individuals, the larynx is the most common site of involvement, followed by the oral cavity and oropharynx.[114,116] Tobacco cessation and alcohol abuse counseling, as well as early detection through biopsies of suspicious lesions, are warranted.

Higher susceptibility to infection with HPV in organ transplant recipients and HIV-positive patients may play an important role in the development of noncutaneous head and neck SCC.[24,116] HPV infection has been associated with head and neck SCC, particularly of the tonsil.[117] Organ transplant recipients and patients with HIV/AIDS also have increased incidence of other HPV-related cancers, such as cervical and anogenital cancer.[23] It is thought that immune compromise could lead to increased infection rates and failure to resolve the infections.[118] As more insight is gained into the pathophysiology and clinical behavior of HPV-related cancers, management strategies and the role of prophylactic HPV vaccination in immunosuppressed patients may be better defined.

Treatment of organ transplant recipients and HIV-positive patients with head and neck SCC should follow established guidelines. Even though surgical intervention remains an important option, patients often require combined therapy for advanced disease. The use of chemotherapy in these patients may put them at significant risk for opportunistic infection. Little data exist regarding the tolerance and efficacy of radiation therapy; however, patients with HIV have been shown to tolerate radiation therapy to the head and neck.[119]

Lymphoma

HIV-positive patients and organ transplant recipients are at higher risk for developing non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) than immunocompetent individuals. EBV-associated NHL is the most common type of lymphoma to develop in both groups. NHL comprises a heterogeneous group of tumors, but the overwhelming majority (>95%) are B-cell derived.[78] Lymphomas occurring in immunosuppressed organ transplant recipients are categorized within a disease entity known as posttransplantation lymphoproliferative disorder (PTLD). The WHO classification system divides PTLD into four categories[120,121]:

1. Early lesions (reactive plasmacytic hyperplasia and infectious mononucleosis-like PTLD
2. Polymorphic PTLD (polyclonal and monoclonal)
3. Monomorphic PTLD (B-cell and T-cell lymphomas)
4. HL and HL-like lymphomas

The WHO classification for AIDS-related NHL includes three groups[122]:

1. Lymphomas occurring in immunocompetent patients (Burkitt's, diffuse large B-cell, immunoblastic, and anaplastic)

2. Lymphomas occurring specifically in HIV-positive patients (primary effusion lymphoma and plasmablastic lymphoma)

3. Lymphomas that also occur in other immunodeficiency states (PTLD-like B-cell lymphoma associated with HIV infection)

Most AIDS-related NHL are EBV-associated B-cell lymphomas such as Burkitt's lymphoma, diffuse large B-cell lymphoma, and plasmablastic lymphoma (PBL).[78,85,123,124]

EBV, along with HHV8, is a member of the gammaherpesvirus family. It is estimated that more than 90% of the world adult population is infected.[125] It is found in up to 50% of AIDS-related NHL[126] and nearly 90% of PTLD.[127] EBV alters tumor suppressor p53 gene expression and protein regulation, which is thought to play a role in oncogenesis,[44,85] but given the nearly ubiquitous presence of EBV infection, it may be that the intensity of immune suppression determines the risk of developing NHL.[126] However, immunosuppressed patients have not been found to have increased rates of EBV-associated nasopharyngeal cancer,[128] and a large proportion of AIDS-related NHL have not demonstrated EBV. Thus the role of EBV in NHL oncogenesis remains unclear and is an area of ongoing investigation.

AIDS-Related Non-Hodgkin's Lymphoma

Epidemiology and Presentation

AIDS-related NHL occurs in up to 19% of HIV-positive patients[85] and is the second most common malignancy to develop in HIV-positive patients.[129] Patients are much more likely than their immunocompetent counterparts to present with advanced disease, B symptoms (fever, chills, night sweats, and weight loss), and extranodal disease, including bone marrow involvement.[78,85,129] Seventy percent to 80% of AIDS-related NHL is diagnosed with initial stage III or IV disease, in stark contrast to only 10% to 15% of high-grade NHL in the HIV-negative population.[130-133] Whereas most NHLs develop in the setting of advanced immune suppression, NHL may occur in the setting of relative immune competence and thus cannot be ruled out based on a high CD4 count or low viral load. Burkitt's lymphoma, in particular, has been noted to occur in patients with a relatively high CD4 count.[134,135] Even though the incidence of Kaposi's sarcoma has clearly declined since the advent of HAART, the effect of HAART on AIDS-related NHL has been less significant. Although some studies suggest a trend toward declining incidence, others have found an increased incidence of NHL in the HAART era.[78,136]

As with immunocompetent patients with NHL, AIDS-related NHL most commonly presents in the head and neck, with nearly two thirds of patients with head and neck manifestations.[129] Extranodal disease is twice as common in AIDS-related NHL compared to non-HIV associated NHL.[129,137,138] Extranodal head and neck sites include the oral cavity, sinonasal region, pharynx, nasopharynx, orbit, parotid gland, larynx, mandible, and CNS.[139-145] Other sites of extranodal disease include the GI tract, bone marrow, and liver. Nodal disease predominates in the neck with frequent involvement of the submandibular, jugulodigastric, and supraclavicular regions.[146]

NHL of the head and neck often presents as a growing mass. Constitutional symptoms are frequently present with fever, night sweats, and unintentional weight loss (greater than 10% of body mass) present in 82% of patients.[147] Initial symptoms are dependent upon the location of disease. Sinonasal lymphoma usually presents with nasal obstruction or other nonspecific symptoms consistent with chronic rhinosinusitis.[148] NHL of the oral cavity most commonly affects the gingiva and palate and may manifest as a persistent sore, an enlarging mass, or loose teeth. Hoarseness, respiratory symptoms, and dysphagia may indicate laryngeal or pharyngeal disease. Nasopharyngeal lymphoma may present with nasal obstruction and serous otitis media. Because of the close association with HIV, patients newly diagnosed with NHL should be screened for HIV infection.

PBL is a unique type of diffuse large B-cell lymphoma that typically involves the oral cavity and mandible but has been reported in other regions including the paranasal sinuses, skin, and lymph nodes.[78,149] Although first described as an AIDS-related NHL, there are reports of PBL occurring in HIV-negative patients and OTR.[150-152] The gingiva and hard palate mucosa are most commonly involved and tumors have a propensity for adjacent bone invasion.[153] These lesions must be distinguished from benign gingival enlargements like pyogenic granuloma and peripheral giant cell granuloma.[149] Unlike other NHLs, PBLs are generally HHV8 and EBV-negative,[150] although some series report positivity.[152,154]

Diagnosis

The diagnosis of lymphoma in HIV-positive patients begins with a high index of suspicion. Multiple common manifestations of HIV disease such as peripheral generalized lymphadenopathy and benign oral ulcerations may mimic the findings for patients with lymphoma. The combination of a rapidly enlarging lesion and constitutional symptoms is particularly concerning for NHL. The diagnosis of lymphoma may be made with fine needle aspiration (FNA) biopsy. Even though histologic type may be determined from a cell block following aspiration, this test may not be performed and some pathologists prefer larger tissue specimens for diagnosis and determination of histologic type. Thus open biopsies may be considered. The prognosis and management depend upon the presence of extranodal disease; therefore a thorough investigation of the CNS, mediastinum, and abdomen should be performed with magnetic resonance imaging (MRI), or CT if MRI is not available. Leptomeningeal disease is the most common manifestation of CNS involvement, occurring in up to 10% of patients,[155] and is best evaluated with MRI.[156] A bone scan and bone marrow biopsy may also be useful in the staging process.

Prognosis and Treatment

The International Prognostic Index (IPI), developed in 1993, is a clinical tool used to predict survival in NHL.[157] Factors associated with poor prognosis include age older than 60 years, advanced tumor stage, elevated serum lactate dehydrogenase, poor performance status and more than one extranodal site of disease. It has been validated in patients with AIDS-related lymphoma, in that high-risk IPI scores have been shown to predict poor survival.[130,158,159] One large study demonstrated 3-year survival rates for low, low-intermediate, high-intermediate, and high-risk groups to be 66%, 42%, 35%, and 8% respectively in the HAART era.[160] Recent data suggest that, in the HAART era, the relationship between CD4 count and survival in NHL may be less significant than was previously thought.[158,161] However, other reports show that CD4 count continues to be a predictor of survival.[136,162,163] Before advent of HAART, overall survival in NHL was only 10%.[78] Numerous studies have demonstrated improved survival when combining HAART with standard combination chemotherapy. Up to 92% of patients achieve complete remission[136] and nearly 50% achieve 3-year survival even with high-intermediate risk IPI scores.[130,164]

AIDS-related NHL is typically treated with multiagent chemotherapy in combination with HAART.[165] The therapy must balance the need to eradicate the neoplasm with the risk of further immune suppression. Systemic treatment of NHL may be complicated by marrow suppression, immunosuppression, mucositis, and opportunistic infections, resulting in a high rate of morbidity and mortality.[85] Rituximab, an anti-CD20 antibody, has shown promising results in the treatment of NHL in HIV-negative patients, and clinical trials are ongoing to investigate its use in AIDS-related NHL. Radiotherapy has a role for patients with localized disease or for palliation of symptomatic lesions. NHL confined to the cervical nodes has an improved response to therapy with longer associated survival than extranodal disease involving the paranasal sinuses, mandible, and other extranodal sites.[145] Primary CNS lymphoma has perhaps the poorest prognosis with its tendency to recur and association with profound immune suppression.[133,166] Outcomes for relapsed, aggressive NHL are extremely poor and no effective treatments are available. Whereas the treatment of choice for relapsed NHL in immunocompetent patients is autologous

stem cell transplantation (ASCT), opportunistic infections and toxicity have limited its use in AIDS-related NHL.[165]

Posttransplantation Lymphoproliferative Disorder

PTLD is a complication of solid organ and hematopoietic transplantation marked by EBV-driven abnormal lymphoproliferation. The overall incidence in adults is approximately 2% to 3%,[127] while in children the incidence is close to 8%.[167] It is the second most common malignancy to develop in organ transplant recipients, after cutaneous malignancy.[114] Nearly 40% of patients with PTLD present with findings in the head and neck, especially in Waldeyer's ring and cervical lymph nodes.[168] PTLD involving the head and neck usually presents with mononucleosis-like symptoms and adenotonsillar hypertrophy, and may be associated with upper airway obstruction.[114,168,169] There are also reports of PTLD involving the nasal cavity and paranasal sinuses,[170,171] as well as facial cutaneous manifestations.[140]

Most PTLDs are NHLs of the B-cell type.[114] Incidence varies significantly with the type of organ transplanted, with the highest rates in multiorgan or intestinal transplants and lowest rates in renal transplants.[127] PTLD develops in the setting of severe immunosuppression, which impairs the formation of a cytotoxic T lymphocyte immune response to EBV. The risk of developing PTLD is highest in EBV-naive patients, which may account for the higher incidence in children. It occurs in a bimodal temporal distribution, with most cases occurring within the first 2 years after transplantation and a smaller peak occurring later than 2 years after transplantation.[127]

Treatment should be directed first toward decreasing immunosuppression regimens to allow an adequate T-cell response. Up to 50% of patients respond to immunosuppression reduction.[172,173] Patients who fail to respond to immunosuppression reduction may require systemic therapy such as combination chemotherapy, cytokine therapy, or anti-CD20 therapy (rituximab).[114,127] Surgery is reserved for management of local symptoms, and acute upper airway obstruction caused by tonsillar hypertrophy may require tonsillectomy.[174]

Hodgkin's Lymphoma

Hodgkin's lymphoma can be seen in transplant recipients and patients with HIV. In transplant patients, it is a much less common manifestation of PTLD than NHL, comprising only 1.8% to 3.5% of all PTLDs,[175] but its incidence is still 15-fold greater than that in the general population.[176] Risk factors for the development of HL in transplant recipients include bone marrow transplantation and a history of graft-versus-host disease (GVHD).[175,177] HL-like PTLD is clinically similar to classic HL occurring in the posttransplant setting but is distinguished by its pathologic features such as cell markers and background proliferation.[175,177] HL occurring in the setting of PTLD has a better prognosis than other PTLD lymphomas[176] and should be managed like other PTLD lymphomas with a focus on reduction of immunosuppression and appropriate chemotherapy.[175]

Hodgkin's Lymphoma in Human Immunodeficiency Virus

Although not considered an AIDS-defining malignancy, HL is the most common non–AIDS-defining tumor occurring in patients with HIV.[123,178] The incidence of HL is increased nearly 5- to 15-fold in patients with HIV (HIV-HL) compared to that in HIV-negative patients.[175,179] Data suggest that HIV-HL is more common in homosexual and intravenous drug–using men than in other HIV risk groups.[85,180] Several features distinguish HIV-HL from HL occurring in HIV-negative patients. HIV-HL is more likely to present with advanced disease, extranodal involvement including bone marrow in up to 50%, and B symptoms in 40% (compared to 27% in HIV-negative patients).[178,180,181] In both groups, cervical lymphatic involvement is common; one series demonstrated cervical node involvement in all cases of HIV-HL.[180] Notably, EBV is present in more than 90% of HIV-HL patients compared to less than 50% of non-HIV patients.[123,181] The histology of HIV-HL is also distinct from that of the general population. HIV-positive patients more frequently develop the aggressive mixed cellularity and lymphocyte-depleted subtypes in comparison to the predominance of nodular lymphocytic subtypes in the general population.[179] The most surprising finding in HIV-HL is that its incidence has unexpectedly increased in the HAART era. Patients with moderate immunosuppression (CD4 between 225 and 249 cells/μL) are more than twice as likely to develop HIV-HL than patients with severe immunosuppression (CD4 < 25 cells/μL).[179] It is believed that increased CD4 counts allow for improved survival of Reed Sternberg cells, which are the characteristic pathologic cells seen in HL.[182] Upon diagnosis of HIV-HL, staging evaluation should include CT imaging of the brain, chest, and abdomen, as well as a bone marrow biopsy.[123] Evaluation of the patient's immune status should also be performed with CD4 count and viral load testing.

There have been no randomized controlled trials for treatment of HIV-HL,[183] but the accepted standard of treatment consists of combination chemotherapy and antiretroviral therapy. Patients treated with HAART in combination with chemotherapy have shown improvement in response to therapy, longer disease-free survival, and longer overall survival when compared with patients treated with combination chemotherapy alone.[181,184] Estimated 2-year survival improved from 45% in patients treated with chemotherapy alone to 62% in those treated with combined HAART and chemotherapy.[185] Complete response to therapy and overall survival are much worse than in HIV-negative patients, however. Overall survival rates in HIV-HL patients compared with HIV-negative patients were 68% vs. 92% at 1 year and 41% vs. 77% at 5 years.[181]

Salivary Gland Disease

Parotid Lesions in Human Immunodeficiency Virus

Parotid lesions are common in HIV-positive patients, especially children in whom up to 18% may present with parotid masses.[186-188] These lesions may result from AIDS-related malignancies such as NHL[143,144] or KS[189,190] or from diffuse infiltrative lymphocytosis syndrome (DILS), but the majority of parotid enlargement in HIV-positive patients is the result of a benign process known as benign lymphoepithelial cyst (BLEC). BLEC of the parotid produces persistent, nontender parotid enlargement associated with cervical lymphadenopathy in up to 90% of patients.[191] Inspissated secretions can lead to duct obstruction with resulting sialadenitis and pain.[192] These lesions have varying proportions of cystic and solid components,[193] and even though only unilateral clinical disease may be evident, radiologic evaluation nearly always reveals bilateral changes.[194,195] Histologically, BLEC has cyst walls lined by hyperplastic and metaplastic squamous epithelium, and contains aggregates of lymphoid proliferation.[191] The differential diagnosis of cystic parotid lesions includes Sjögren's syndrome, cystic Warthin's tumor, and branchial cleft cysts. Bilateral cystic Warthin's tumors may be differentiated radiologically from BLEC based on the presence of focal nodularity in Warthin's tumors and the associated lymphadenopathy of BLEC.[195]

Evaluation of HIV-positive patients who present with a parotid mass should begin with thorough history focusing on the time of onset and rate of growth of the mass as well as any symptoms associated with the mass such as pain. Constitutional symptoms such as weight loss, fever, and night sweats should be investigated and if present should alert the physician to the possibility of lymphoma or tuberculosis. Physical examination should focus on the common features of BLEC—the contralateral parotid should be examined for bilateral masses and the neck should be examined for lymphadenopathy. The examiner should look for evidence of malignancy such as induration, pain, fixation, and facial nerve dysfunction.

FNA can be useful in the diagnosis of parotid masses. Unilateral masses, or masses suspicious for malignancy, should undergo FNA. A study of 99 parotid FNAs in HIV-positive patients found 75% to be consistent with BLEC, 14% were infectious/inflammatory, and 6% were neoplastic. Of the neoplastic lesions, all were malignant, with three NHLs, one multiple myeloma, one metastatic adenocarcinoma from the lung, and one direct extension from a cutaneous BCC. In 6% of patients, the FNA was nondiagnostic.[196] FNA of BLEC reveals a heterogeneous lymphoid population, scattered foamy macrophages, and anucleated squamous cells in a proteinaceous background.[191] Germinal centers, myoepithelial islands representing metaplasia of ductal epithelium, and cystic ductal dilatation (Fig. 15-3) differentiate BLEC

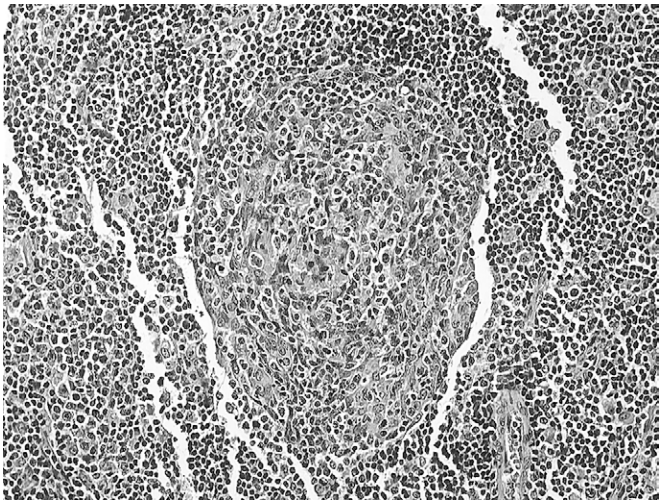

Figure 15-3. Benign lymphoepithelial cyst. Photomicrograph demonstrating squamous metaplasia of the ductal epithelium in human immunodeficiency virus–related cystic lymphoepithelial disease of the parotid gland (×200).

from lymphoma.[197] Aspiration may also be useful for the relief of symptoms in larger cysts, although the lesions may recur. Initial aspirates should be sent for cytologic and microbiologic evaluation.

A variety of treatment options exist for patients with BLEC. Patients not already receiving HAART should be referred for treatment initiation because these lesions may regress with antiviral therapy.[198,199] For minimally symptomatic patients without significant cosmetic deformity, observation alone represents the best option. Low-dose radiation treatment results in a greater than 50% reduction in the size of the lesion. This improvement, however, typically lasts less than 10 months.[200] Some patients are treated with repeated needle aspirations although the repetitive nature of this treatment is suboptimal. Needle aspiration combined with doxycycline or tetracycline sclerotherapy may result in significant size decrease.[201-203] A 1 mg/mL doxycycline solution has been used, injecting 1 to 2 mL through an intravenous catheter following cyst aspiration. Most patients are left with smaller residual fibrotic masses but long-term results of this treatment are unknown.[201,202]

HIV-associated BLEC typically does not require parotidectomy. Parotidectomy may be considered in those rare cases of BLEC that undergo rapid size change, are disfiguring, or have significant pressure symptoms. Other indications for parotidectomy include FNA cytology suggestive of neoplasm or unilateral masses with a significant solid component or features worrisome for malignancy. There have been no reports of malignant transformation of BLEC.[191]

Diffuse Infiltrative Lymphocytosis Syndrome

Parotid gland enlargement associated with sicca symptoms was recognized in HIV-positive patients in the 1980s, and Itescu and colleagues first categorized DILS as a discrete entity in 1990.[204] DILS occurs in the setting of HIV and is marked by salivary gland enlargement with circulating and visceral CD8 lymphocytosis. It is often associated with cervical lymphadenopathy, and up to 60% of patients also report sicca symptoms such as xerostomia and xerophthalmia.[192,205,206] In the pre-HAART era, DILS occurred in approximately 3% to 4% of HIV-positive patients, but in the HAART era its incidence has dropped significantly to less than 1%.[205] It occurs twice as frequently in black patients as in whites.[207,208] Diagnosis is confirmed with minor salivary gland biopsy demonstrating lymphocytic infiltration or with positive gallium Ga67 scintigraphy when biopsy is not possible.[192]

DILS is phenotypically similar to Sjögren's syndrome in terms of salivary gland enlargement, sicca symptoms, and salivary gland histology. However, whereas parotid swelling is universal in DILS, it occurs in less than one third of patients with Sjögren's syndrome.[192] In addition, DILS is characterized by more frequent occurrence of extraglandular lymphocytic infiltration, predominance of CD8 cells in lymphoid aggregates (as opposed to CD4 in Sjögren's syndrome), and the infrequent presence of serum autoantibodies.[192,205] Extraglandular disease in DILS may include lymphocytic interstitial pneumonitis in up to half of patients,[209] but this complication is becoming less common in the HAART era.[205]

Xerostomia in Human Immunodeficiency Virus and Transplant Recipients

HIV-positive patients as well as patients who suffer from chronic graft-versus-host disease (GVHD) are significantly affected by xerostomia. The prevalence of xerostomia is reported to be 2% to 10% in HIV-positive patients.[210] Chronic GVHD may develop in up to 40% to 70% of patients receiving transplants from matched, unrelated donors,[211] and 80% of patients with extensive GVHD complain of xerostomia.[212] In the setting of HIV, some cases are iatrogenically induced by the use of HAART, antidepressants, and other drugs, whereas other cases are caused by chronic mouth breathing secondary to sinonasal disease or adenoidal hypertrophy. Still others are related to DILS as noted earlier. Salivary flow rates are diminished in the setting of HIV infection or GVHD,[210,213,214] which leads to increased incidence of dental caries and impaired deglutition. Salivary substitutes, frequent saline rinses, and sialogogues help alleviate these problems. Dental caries can be prevented with fluoride.

Cervical Lymphadenopathy in Immunosuppressed Patients

The otolaryngologist is often consulted to evaluate cervical adenopathy in immunosuppressed patients. The diagnostic workup of cervical lymphadenopathy starts with a thorough history and physical examination. The clinician should question the patient about risk factors for infectious causes of cervical adenopathy, including contact with cats and dogs and exposure to tuberculosis, and risk factors for head and neck malignancy, including tobacco and alcohol use. An enlarged lymph node is more likely to be pathologic when certain local and constitutional features are found on history and physical examination.

Although constitutional symptoms by themselves are not a specific indicator of infection or malignancy, the presence of such symptoms without a known cause warrants further investigation. Cervical lymphadenopathy caused by lymphoma in immunosuppressed patients is associated with B symptoms in nearly 50% of patients.[78,178,180,215] The distribution, size, and mobility of neck nodes may suggest infectious or malignant etiology. Cervical lymphadenopathy that is greater than 2 cm, unilateral, painful, deep, or asymmetric is suspicious for a pathologic cause, specifically granulomatous disease or lymphoma.[216] Tender adenopathy is more likely to be secondary to bacterial infections, including tuberculosis, whereas nontender, enlarging neck nodes may result from malignancy.[217] A thorough head and neck examination should search for potential primary sites of infection or malignancy.

FNA should be the initial method of pathologic sampling for suspicious nodes. The diagnostic yield of FNA is increased with multiple passes of the needle while suction is applied to the plunger. The presence of a cytopathologist or a technician is beneficial for two reasons: (1) Preparation of the specimen for cytology can be properly and judiciously carried out, and (2) the adequacy of the aspirate for diagnosis can be determined and FNA repeated if necessary. Ultrasound guidance increases the diagnostic yield in lymph nodes that are difficult to palpate. The overall sensitivity and specificity of FNA in HIV-positive cervical adenopathy has not been clearly defined and is likely operator dependent. Sampling errors, improper preparation of cytopathology slides, and misinterpretation of the cytologic features can cause false-negative results. Because lymphoma is always a concern, a cell block should be obtained from the FNA specimen. This allows for further diagnostic evaluation such as flow cytometry to clearly differentiate reactive tissue from lymphoma and determine the class of lymphoma, which may have treatment implications. In patients with lymphoma diagnosed on FNA but without adequate specimen for histologic typing, an open biopsy should be considered. Fresh biopsy

Table 15-6

Differential Diagnosis of Lymphadenopathy in Immunosuppressed Patients

Diffuse infiltrative lymphocytosis syndrome (HIV-positive patients)
Idiopathic
Infectious
Bacterial lymphadenitis or abscess secondary to oropharyngeal infection
Cat-scratch disease
Mycobacterial lymphadenitis: tuberculous and atypical organisms
Pneumocystis lymphadenitis or thyroiditis
Toxoplasma lymphadenitis
Viral lymphadenitis: cytomegalovirus, Epstein-Barr virus
Lymphoepithelial cysts of the parotid gland (HIV-positive patients)
Neoplastic
Lymphoma (includes posttransplantation lymphoproliferative disorder)
Non-Hodgkin's lymphoma
Hodgkin's disease
Metastatic carcinoma
Metastatic Kaposi's sarcoma
Metastatic melanoma
Salivary gland tumors
Thyroid tumors

specimens should be sent directly to the pathologist, who should be informed of the possibility of lymphoma.

Organ transplant recipients are at higher risk for development of cervical involvement, which is seen in 6% of patients, and extrapulmonary tuberculosis, which is seen in 10% to 20%.[218] Head and neck sites of tuberculosis infection in organ transplant recipients include the cervical lymph nodes,[219] larynx,[220,221] and middle ear.[222] Nontuberculous mycobacterial infections also occur in immunocompromised patients and frequently cause pulmonary infections, cervical lymphadenitis, and ulcerative skin lesions, but has also been reported to involve the temporal bone.[223]

Cervical Adenopathy in Human Immunodeficiency Virus

Data regarding the incidence of cervical adenopathy are sparse, but one series demonstrated that of all HIV-positive patients presenting for FNA of an enlarged lymph node, 54% had cervical involvement.[224] Approximately 40% of HIV-positive patients with adenopathy have benign reactive lymphadenopathy.[225-227] and 20% to 30% have tubercular etiology.[226] In this background of hyperplastic adenopathy, however, cases of infectious and neoplastic etiology exist, including *Mycobacterium* tuberculosis, fungal infection, *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), lymphoma, KS, and other processes that also occur in the general population (Table 15-6).[224,225,227] Malignancy may be present in up to 10% of cases. Differentiating among these processes remains challenging, yet critical to the appropriate management of lymphadenopathy in the setting of immunosuppression. The tendencies for multiple pathologic processes to coexist in this population and the poor sensitivity of many clinical findings and tests often make it necessary to perform microbiologic and histologic evaluations of lymph node tissue.

Extrapulmonary tuberculosis is the second most common cause of cervical lymphadenopathy in HIV-positive patients.[224,225,227] Tuberculosis is the leading cause of death in HIV-positive patients and effective treatments are available, thus prompt diagnosis and initiation of therapy are essential. The most common site of extrapulmonary tuberculosis involvement in HIV-positive patients is the lymph nodes,[224] but other head and neck sites that may be involved include the larynx,[220,228,229] oral cavity and lip,[230,231] or the parotid gland.[232]

The patient's immune status, as indicated by the history of opportunistic infection, CD4 count, and viral load, may help narrow the differential diagnosis of cervical adenopathy. Whereas NHL and mycobacterial infection are more likely to be present in the setting of advanced immunosuppression, the CD4 count alone is not sufficient to exclude malignancy or infection.[134,135,179] The purified protein derivative (PPD) or tuberculin skin test may facilitate the diagnosis of mycobacterial lymphadenitis. In the setting of advanced HIV infection and immune compromise, however, the patient may become anergic, resulting in a low sensitivity of the PPD test. The criterion for a positive result in an HIV-infected patient is a skin reaction greater than 5 mm in diameter rather than 10 mm as in the general population.

FNA biopsy should be the initial method of tissue sampling in most cases of suspicious cervical lymphadenopathy in the HIV-infected patient. If possible, a cell block should be created from the sample and the sample should be sent for cytology, flow cytometry, and culture and stains for aerobic and anaerobic bacteria, mycobacteria, and fungi. In the largest series among HIV-positive patients, FNA provided a definitive diagnosis in more than half of patients and directed further clinical investigation in another 30%, while 20% of the initial samples were inadequate for pathologic evaluation.[227] A subsequent study in children corroborated these results, with only 8% of samples being inadequate for diagnosis.[225]

An FNA diagnosis of follicular hyperplasia should be correlated with the clinical picture and should not, by itself, absolve the clinician's suspicion of lymphoma. The decision to perform a diagnostic open biopsy should be driven by a suspicion of malignancy or infection in the setting of a negative or inconclusive FNA.[217,233] Conditions that would favor proceeding with an open biopsy in the setting of an inconclusive finding include nodes greater than 2 cm and growing; onset associated with a low CD4 count; asymmetric, unilateral, or localized lymphadenopathy; constitutional symptoms of unknown origin; mediastinal adenopathy; or hepatosplenomegaly. Open biopsy of suspected metastatic carcinoma should be avoided and, if possible, the diagnosis should made by FNA. When metastatic carcinoma is diagnosed, a thorough examination of the upper aerodigestive tract should be performed under general anesthesia in search of a primary tumor.

Sinonasal Infection

Presentation and Pathogenesis

As in the general population, sinonasal complaints are common a mong immunosuppressed patients. Reports of prevalence among HIV-positive patients range from 10% to 68%, depending on the criteria used.[234-237] Nearly 50% of patients undergoing allogeneic stem cell transplantation (STC) complain of rhinosinusitis, and 12% of solid organ transplant recipients develop acute sinusitis.[238,239] Chronic graft-versus-host disease is a risk factor for sinusitis in hematopoietic transplant recipients.[238,240] The maxillary and ethmoid sinuses are most frequently involved,[234,241,242] and symptoms of acute or chronic sinusitis are similar to those of the general population. These include fever, facial pain or pressure, nasal congestion, and mucopurulent nasal discharge and postnasal drainage. Patients with chronic sinusitis are often relatively asymptomatic, reporting only congestion and nasal discharge. Some patients present initially with pulmonary complaints such as bronchospasm or infection, resulting from postnasal drainage.

Several pathogenic mechanisms have been proposed to account for the high incidence of sinusitis in immunocompromised patients. First, impaired systemic and local immunity due to HIV infection or immunosuppressive therapy leaves the host susceptible to infection.[237] Second, decreased mucociliary clearance times in patients with HIV infection[243,244] and ciliary abnormalities in the nasal mucosa of bone marrow transplant recipients[245] have been noted. Impaired mucociliary function may result in stasis of secretions and increased susceptibility to sinonasal infection, or may reflect damage to the nasal microenvironment from repeated infection resulting in reduced mucociliary clearance. Finally, some data suggest that polyclonal B-cell activation with increased production of immunoglobulin E leads to increased atopy in

HIV-positive patients, manifesting as new or increased allergic symptoms (allergic rhinitis, drug allergies, and asthma).[246] However, attempts to directly correlate sinusitis with atopic disease in HIV-positive patients have been unsuccessful,[235] and a recent study in HIV-positive children did not find increased prevalence of atopy.[247]

The spectrum of bacteria implicated in immunosuppression-associated sinusitis is similar to that seen in the general population. The most common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in acute sinusitis and *Staphylococcus*, *Pseudomonas*, and anaerobes in chronic sinusitis.[248,249] Other unusual nonfungal pathogens cultured from immunocompromised patients include *Legionella pneumophila*,[250] *Acanthamoeba*,[251-253] *Mycobacterium kansasii*, *Pasteurella multocida*,[254] and cytomegalovirus.[255]

The clinical and radiologic characteristics of sinusitis are closely linked to the degree of immunosuppression. Patients with relatively normal immune function (CD4 ≥ 200 cells/μL) should be treated with standard regimens for acute and chronic sinusitis.[248,256] As immune function deteriorates, patients are more susceptible to extensive disease and chronic sinusitis is more likely to develop,[257] thus antibiotic coverage should include *Staphylococcus*, *Pseudomonas*, and anaerobes.[248] One report found that patients with a diagnosis of AIDS had significantly worse CT findings by the Lund Mackay classification system[258] than did patients with HIV.[234] Patients in more advanced stages of immunosuppression as reflected by CD4 less than 200 cells/μL or absolute neutrophil count (ANC) less than 600 cells/μL are at risk for infection with more aggressive disease such as pseudomonal or invasive fungal sinusitis.[259,260]

Fungi such as *Aspergillus* and the Mucorales order (especially *Rhizopus* and *Mucor*) are particularly important pathogens in immunosuppression-related sinusitis because these organisms have the potential to cause invasive and oftentimes fatal disease.

The incidence of invasive fungal sinusitis (IFS) is 1.7% after hematopoietic transplantation,[238] with the highest risk occurring in the immediate posttransplant period.[261,262] It is much more common in hematologic malignancy such as acute myelogenous leukemia (14% incidence) or acute lymphoblastic leukemia (4% incidence) than in HIV/AIDS or solid organ transplantation.[263,264] This difference in susceptibility may be explained by the fact that neutrophils are essential in the immune response to fungal infections.[265,266] Solid organ transplant recipients and patients with HIV/AIDS generally retain neutrophil function, but patients in the later stages of HIV can become neutropenic and typically are at risk for IFS when CD4 counts fall below 50 cells/μL.[267] Regardless of the cause of immunosuppression, the major determinant of risk is the presence and duration of neutropenia (ANC < 600 cells/μL).[263,265] Prophylactic antifungal therapy in patients with hematologic malignancies and hematopoietic and solid organ transplant recipients has not been shown to be effective for the prevention of IFS.[262] *Aspergillus fumigatus* is the most common fungal pathogen in invasive and noninvasive sinusitis for both immunosuppressed and immunocompromised patients.[260] Other fungi that have been isolated include *Candida albicans*,[268] *Rhizopus arrhizus*,[269] *Cryptococcus neoformans*,[270] *Exserohilum*,[271] and *Valsa sordida*,[272] among others.[263]

Invasive fungal sinusitis is a life-threatening condition and early diagnosis and treatment are paramount. Histopathology combined with culture and stains is the most effective diagnostic approach for fungal sinusitis. Unilateral symptoms (facial paresthesias, swelling, pain, or rhinorrhea) with or without fever in a patient with ANC less than 600 cells/μL or CD4 less than 50 cells/μL should alert the clinician to the possibility of IFS. Proptosis along with cranial nerve findings, such as decreased extraocular motions or vision, suggests orbital involvement. Meningismus and mental status changes are late-stage symptoms suggestive of intracranial spread.

Diagnosis

The initial evaluation of an immunosuppressed patient with symptoms of sinusitis should include a thorough head and neck examination as well as nasal endoscopy in order to identify any mucosal or structural abnormalities. Endoscopy-guided cultures should be obtained if discharge from the middle meatus or sphenoethmoid recess is identified. The diagnosis of IFS can pose a challenge, because physical examination findings may be very subtle. The endoscopic findings range from pale, ischemic mucosa to well-circumscribed necrotic plaques. Perforations of the nasal septum and hard palate may be present. Fungal infection may be accompanied by suppuration, causing confusion with bacterial sinusitis.[260]

Radiologic studies often play a key role in diagnosis. Unilateral edema of the sinonasal mucosa with or without bony erosion on seen CT scan (Fig. 15-4) should lead to suspicion of fungal sinusitis or a neoplasm. But even though CT imaging is the study of choice to identify bony erosion, MRI is superior in delineating the intracranial or orbital extent of disease.[261] Changes seen on T1 images are isointense

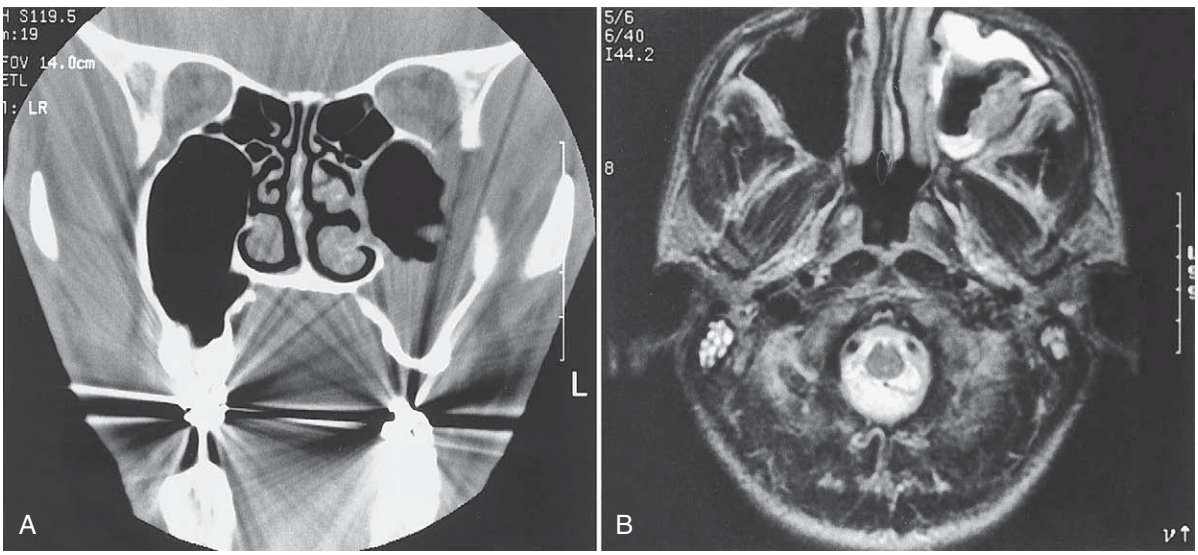

Figure 15-4. Computed tomography and magnetic resonance imaging of *Aspergillus* sinusitis. **A,** Coronal computed tomography of the paranasal sinuses shows left maxillary sinusitis with erosion of the superior lateral bony wall. **B,** T2-weighted axial magnetic resonance imaging of the same case shows thickened left maxillary sinus mucosa with a hyperintense signal consistent with inflammation and a transmural process of the lateral wall with a hypointense signal corresponding to the region of bone destruction in **A**. Differential diagnosis includes invasive fungal disease, lymphoma, and squamous cell carcinoma.

in bacterial and fungal infections, but the T2 images demonstrate low signal intensity for fungal disease and high intensity for bacterial disease. A low threshold for imaging patients with low neutrophil or CD4 counts is advised.

Invasive fungal sinusitis represents a diagnostic and therapeutic emergency and any suspicion should be addressed as soon as possible. Consideration may be made for inferior and/or middle turbinate biopsy[263,273] or diagnostic antral lavage[226] with biopsy and histologic examination. Frozen section of biopsy specimen is often used to accelerate initiation of treatment with antifungal agents. Drainage from the middle meatus and biopsy tissue should be collected and sent for bacterial and fungal culture. There are as yet no uniform guidelines for the diagnosis of IFS, although any suspicious lesions should undergo biopsy with silver staining, histopathology, and culture.

Fungal sinusitis can extend via thrombophlebitic or hematologic spread and thus may enter into the orbit or intracranially without histologic evidence of mucosal invasion.[274] The angiocentric invasion pattern of *Aspergillus* may allow extension of disease into the orbit or intracranially without evidence of bony destruction on imaging study. Thus, in the clinical scenario consistent with fungal sinusitis and fungal elements identified on silver stain or culture, treatment of fungal sinusitis should begin regardless of the histologic confirmation of invasion.

Treatment

The goals of management of sinusitis in immunocompromised patients include swift treatment of bacterial sinusitis and early identification of fungal sinusitis or neoplasm. Initial medical management of acute bacterial sinusitis consists of broad-spectrum antibiotics, decongestants, and saline irrigation. Antibiotics should have good coverage of *Streptococcus*, *Staphylococcus*, and *H. influenzae*; amoxicillin/clavulanate or cefuroxime represent good first-line choices. Antibiotic coverage should also include *Pseudomonas* and anaerobes in patients with moderate immunosuppression or those who do not respond to initial antibiotic treatment.[248] Topical decongestants may enhance sinus drainage and provide symptomatic improvement.[275] Patients should be followed closely, and if fever or local symptoms persist after 10 days of therapy, surgical drainage should be considered. Patients with a rapidly progressive course or toxic presentation should undergo early imaging and aggressive treatment, including parenteral antibiotics and possible surgical intervention. As culture and biopsy results become available, the antibiotic coverage may be narrowed. A total of 4 to 6 weeks of antibiotics should be administered.[256]

Fungal sinusitis should be suspected when fever or other symptoms persist despite aggressive medical treatment. Histopathology combined with culture and stains is the most effective diagnostic approach for fungal sinusitis. Sinusotomy and debridement should be pursued to establish drainage and obtain mucosa and sinus contents for histopathologic and microbiologic evaluation. Surgical intervention is particularly important for patients with a low neutrophil or CD4 count. Endoscopic or external approaches may be used depending on the surgeon's preference. Fresh frozen section should be performed on suspicious mucosal lesions to allow rapid diagnosis and timely intervention.

Invasive fungal sinusitis requires immediate, aggressive treatment. Without treatment, mortality is reported to be 50% to 80% due to intracranial and orbital involvement.[261] Ideal treatment involves three components: systemic antifungal therapy, surgical debridement of infected tissue, and restoration of immune function. In particular, immunosuppression should be reversed because restoration of neutrophil count is required to prolong survival.[263,264] Granulocyte colony-stimulating factor has not been substantiated to be helpful in the treatment of invasive fungal sinusitis. Initiation of HAART should be considered in an attempt to improve the underlying immune status of HIV-positive patients. High-dose, broad-spectrum antifungal medication such as amphotericin B should be administered intravenously in all cases with a clinical picture compatible with IFS, regardless of whether invasion has been demonstrated histologically. Liposomal amphotericin B,[261,276] echinocandins such as caspofungin[277,278] or micafungin,[279] and broad-spectrum triazoles such as posaconazole[280] are alternative medical therapies for patients with poor renal function.

Surgical debridement of involved tissue is important to minimize fungal load, in that medical therapy alone is typically insufficient. The severity of infection and level of immune impairment should be considered when planning surgical intervention. Sinusotomy alone is insufficient; as much as possible, involved tissue should be debrided to bleeding margins.[261] Intraoperative frozen sections may assist in defining the extent of resection by determining the boundaries of invasion.[281] Transfacial approaches may be required in the setting of extensive disease, which may require maxillectomy, orbital exenteration, or craniofacial resection for optimal disease control; however, the chances of survival with intracranial extension are dismal.[282] Aggressive surgery must be considered in the context of the patient's overall condition and prognosis. Postoperative management should continue intravenous antifungals with consideration for antifungal-containing saline irrigation.[280] Careful follow-up and a low threshold for repeated surgical exploration is required. Patients in whom fungal disease appears clinically to have resolved may develop persistent chronic bacterial sinusitis, thus continued follow-up is necessary.[283]

Although more commonly involving the paranasal sinuses, invasive fungal infections of the pharynx and larynx have been described in HIV-positive[284-286] and other immunosuppressed patients.[287-290] Diagnosis and treatment of these invasive infections requires a high degree of suspicion and prompt initiation of medical therapy. In one case, a total laryngectomy was required for disease control.[291]

Immunosuppressed patients with chronic sinusitis are also candidates for surgical intervention. Friedman and colleagues found that endoscopic sinus surgery in HIV-positive patients with chronic sinusitis resulted in symptomatic improvement in 75% of patients, comparable to their results in the general population. This effect was found to be independent of CD4 count and has led the authors to suggest the same treatment algorithm for chronic sinusitis in patients regardless of HIV status.[292] These findings were bolstered by Murphy and colleagues who showed a significant decrease in the symptoms of sinusitis and increased quality of life in HIV-positive patients with chronic sinusitis following endoscopic sinus surgery.[293] Follow-up time in these studies was limited. Because of the devastating nature of invasive fungal sinusitis and the susceptibility of posttransplant patients to opportunistic infections, some authors advocate pretransplant endoscopic sinus surgery in patients who demonstrate evidence of sinusitis.[239,294]

Otologic and Neurotologic Manifestations of Immunosuppression

External and Middle Ear

Malignant Otitis Externa

Although most commonly occurring in older diabetic patients, malignant otitis externa (MOE) also occurs in immunocompromised patients,[295] often in younger and nondiabetic patients with hematologic malignancy or HIV.[296] The susceptibility of the immunocompromised patient to MOE is attributed to a combination of impaired chemotaxis and neutrophil function, and depressed humoral immunity.[297] The pathogenesis of MOE is further facilitated by the breakdown of the local cutaneous barrier in the external auditory canal (EAC) secondary to dermatologic lesions (e.g., eczema, seborrhea) and self-induced trauma caused by pruritus. Otitis externa (OE) may progress to malignant OE if not managed aggressively and in a timely fashion. Spread to the skull base with resulting temporal bone osteomyelitis occurs via the fissures of Santorini and the tympanomastoid suture.[297] Temporal bone osteomyelitis should be suspected when otalgia, swelling, and otorrhea persist despite therapy or when there is onset of facial nerve paralysis or other cranial nerve dysfunction. Unlike in diabetic patients, fungal MOE accounts for a significant portion of infections in patients with immunocompromise secondary to HIV or hematologic malignancy.[298,299] *Aspergillus* species are most common in fungal infections. As in the general population, *Pseudomonas aeruginosa* is the primary etiologic agent in bacterial MOE.

Early diagnosis and management of MOE is essential in that this is a life-threatening condition, especially in patients with low CD4

counts and neutropenia.[297] Otoscopy may reveal granulation tissue at the bony cartilaginous junction of the EAC, although fungal MOE has a propensity to involve the middle ear and mastoid without EAC involvement early in the disease course.[299] EAC debris should be cultured and stained for bacteria, fungi, acid-fast bacilli (AFB), and *Pneumocystis*, although culture results may be negative due to previously administered topical or oral antibiotics. CT may show erosion of the EAC bone or suggest skull base involvement, whereas MRI is more useful for detecting soft tissue changes. Technetium-99 scintigraphy is a very sensitive but relatively nonspecific test for detecting increased osteoblastic activity. In contrast, gallium-67 citrate scintigraphy is more specific for osteomyelitis and some suggest its use to monitor response to therapy.[295,297] Others, however, have noted persistently positive scans in the setting of recurrent disease.[296]

Oral fluoroquinolones have become the treatment of choice in bacterial MOE with cure rates near 90%.[296] However, recent data demonstrate nearly 35% resistance of *P. aeruginosa* to ciprofloxacin, thus ciprofloxacin in combination with the third-generation cephalosporin ceftazidime has been recommended.[295] Management of fungal MOE consists of long-term intravenous antifungals with adequate coverage against *Aspergillus*. Serial gallium-67 bone scans may help monitor the response to therapy.

Middle Ear

Eustachian tube obstruction caused by adenoidal hypertrophy or sinonasal disease is common in HIV-infected children and adults. It is therefore not surprising that otitis media (OM) commonly occurs in the HIV-infected population. Although there is no clear link between immunosuppression and increased incidence of OM,[226] limited data suggest that HIV-positive patients may be more prone to systemic complications related to acute otitis media (AOM).[300,301] Serous otitis media (SOM) and conductive hearing loss (CHL) are more prevalent in adults and older children, whereas AOM more frequently occurs in young children.[300-302] The bacteriology of AOM parallels that in HIV-negative patients, with *S. pneumoniae*, *H. influenzae*, group A *Streptococcus*, and *M. catarrhalis* predominating.[301,303] Therefore initial therapy for acute OM is the same as that for the HIV-negative patient. In the severely immunocompromised child, antibiotic coverage should be expanded to include *S. aureus*, because there may be an increased incidence of this pathogenic organism in HIV-positive children.[304] If OM persists, tympanocentesis should be considered to guide therapy by culture and sensitivity results.

The role of tympanostomy tube placement and adenoidectomy in the management of recurrent OM and persistent SOM is poorly established in HIV-infected patients. As with immunocompetent patients, placement of tympanostomy tubes may result in chronic otorrhea or persistent tympanic membrane perforation. It has not been established that these adverse scenarios are seen more frequently in HIV-positive patients. The severity of hearing loss and morbidity associated with OM should be taken into account when deciding whether to place tympanostomy tubes.

HIV-positive patients who progress to develop chronic otitis media, cholesteatoma, or persistent tympanic membrane perforations should be evaluated for surgical intervention. Advances in the treatment of HIV infection have resulted in HIV-positive patients living longer with relatively less immune compromise. The improved overall prognosis of HIV-positive patients may lead to an increase in chronic ear disease, and HIV patients undergoing elective otologic surgery have not been shown to have adverse events related to their immunosuppression.[305]

Systemic complications of AOM are uncommon in immunocompetent children, and some data suggest that these complications are more likely to occur in the setting of advanced immunocompromise.[301,306] Patients with suppurative OM refractory to antibiotics should undergo early tympanocentesis for culture and special stains, and granulation tissue, polyps, and other masses should be carefully biopsied to rule out neoplasms and atypical infections.

Special Considerations

P. jiroveci (formerly *P. carinii)* and *A. fumigatus* represent organisms that may cause otomastoiditis in immunocompromised patients. Extrapulmonary manifestations of *P. jiroveci* have become more common with the routine use of pentamidine for *P. jiroveci* pneumonia,[307] and otomastoiditis and caused by *P. jiroveci* often occurs in the absence of pulmonary disease.[307-311] The route of transmission of *P. jiroveci* to the temporal bone is not clear, but retrograde spread from the nasopharynx through the eustachian tube and hematogenous spread have been proposed. Patients with *Pneumocystis* otomastoiditis commonly present with unilateral otalgia, otorrhea, hearing loss, and a polypoid mass on otoscopy. CT of the temporal bones reveals bony sclerosis without erosions and opacification of the middle ear and mastoid air spaces. A persistent aural polyp accompanied by signs and symptoms of OM despite otic drops and systemic antibiotics should undergo biopsy for histopathology and special stains. Silver stains should be requested and may reveal *P. jiroveci* organisms surrounded by a foamy granular exudate. *P. jiroveci* otitis externa is resolved with recovery of hearing using oral trimethoprim-sulfamethoxazole.[307,308]

A. fumigatus infection of the ear may present as a chronic OE in relatively immunocompetent patients, but can also cause a rapidly fatal invasive otomastoiditis or malignant OE in patients with poor immune function. Risk factors for invasive aspergillosis of the temporal bone include a low CD4 count, AIDS diagnosis, neutropenia, corticosteroid therapy, antineoplastic therapy, and prolonged antibiotic therapy. Otomastoiditis caused by *A. fumigatus* may start in the middle ear space or extend from the EAC.[299] Invasive disease results in destruction of ossicles, erosion of the facial canal with nerve invasion, and destruction of dural plates with possible extension to the dural sinuses and other intracranial structures.[312] Vertigo indicates labyrinthine invasion by *Aspergillus*, whereas meningismus and mental status changes indicate intracranial extension. Facial nerve weakness indicates bone invasion, which can often be confirmed by the presence of bony erosion on temporal bone CT.

Invasive OE caused by *A. fumigatus* presents with otalgia, otorrhea, and hearing loss. Otoscopy usually reveals white debris or granulation tissue in the EAC, which may be mistaken for cholesteatoma. There should be a high index of suspicion for the presence of invasive *Aspergillus* of the temporal bone in immunocompromised patients with persistent OE or OM and new cranial nerve findings. Otorrhea should be routinely cultured and stained for bacterial and fungal organisms and for *Pneumocystis*. If the tympanic membrane is intact, tympanocentesis should be performed when antibiotic therapy is ineffective. If *Aspergillus* is identified on stain or culture, invasive disease can be implied by the presence of bone erosion on CT. The presence of fungal invasion in a mucosal biopsy from the middle ear is diagnostic for *Aspergillus* otomastoiditis. MRI of the skull base should be performed if extensive mastoid disease or dural plate erosion is present on CT with special attention given to lateral sinus blood flow and other clues of intracranial extension.

OE and OM caused by invasive *A. fumigatus* require prompt surgical and drug therapy.[313] High-dose amphotericin B should be started immediately. As much *Aspergillus*-infected tissue as possible should be removed to slow down extension of disease to vital structures and to facilitate the ameliorating effects of drug therapy and host immunity. In the case of OE caused by invasive *Aspergillus*, infected soft tissue and bone of the EAC should be debrided. Limited disease may be addressed by a transcanal approach, but a transmastoid approach with removal of the canal wall will provide more complete debridement and less risk to the facial nerve. Otomastoiditis should be managed with a radical mastoidectomy if middle ear contents and mastoid air cells are to be removed. The management of the facial nerve in these cases is controversial because invasion of the nerve by *Aspergillus* is not easily proven without biopsy. When the facial nerve is paralyzed and gross evidence of invasion and necrosis is present, the nerve should be resected and grafted when appropriate.

The absence of tissue invasion on histopathology and the absence of bone erosion on CT do not rule out the diagnosis of invasive *Aspergillus* of the temporal bone. The clinician should maintain a high index of suspicion for invasive aspergillosis in severely immunocompromised patients despite the absence of these findings. Therefore the patient with early *Aspergillus* infection may first be treated with topical clotrimazole and frequent cleaning of EAC debris. If symptoms persist or

cranial nerve deficits occur, surgery and amphotericin B should be considered after biopsy specimens are taken and CT studies repeated.

Neuropathies in Human Immunodeficiency Virus

Neurologic disorders are a common manifestation of HIV infection resulting from the neurotropic and immunosuppressive properties of the virus and susceptibility to CNS infections such as CMV, toxoplasmosis, or cryptococcal meningitis. In the pre-HAART era, 30% to 50% of patients in later stages of immunodeficiency developed the AIDS dementia complex, also known as HIV-associated dementia (HAD).[314,315] The prevalence of neurologic complications of AIDS has decreased by nearly half in the HAART era, but 10% to 15% of patients still develop HAD.[316] HAD is a subcortical dementia marked by memory loss, apathy, and difficulty with reading and comprehension in the early stages. Patients gradually progress over months to develop global dementia and often have concomitant motor and sensory neuropathies.[316] It is thought to be caused either by repeated exposure to infected monocytes that cross the blood-brain barrier or by autonomous viral production in the brain, which serves as a reservoir for the virus.[314]

The incidence of peripheral neuropathy, now the most common neurologic manifestation of AIDS, has also decreased dramatically in the HAART era. Symptomatic peripheral neuropathy is present in approximately 30% of patients.[317,318] Cranial nerve involvement is rare, with 2% to 3% incidence cited in older studies wherein the most commonly affected nerves were the facial, trigeminal, optic, and cochleovestibular nerves.[319,320] Peripheral neuropathy associated with HIV infection may affect motor nerves, causing spastic paraparesis, but more commonly affects sensory nerves in a phenomenon known as distal sensory polyneuropathy (DSP).[316] DSP is characterized by symmetric polyneuropathy and axonal degeneration. A similar pattern of neuropathy can selectively affect cranial nerves in the form of a mononeuritis multiplex, resulting in a transient mononeuropathy or progressive sensorimotor polyneuropathy.[321] Although previously noted to occur in patients with lower CD4 counts, in the HAART era, CD4 count does not seem to correlate with rates or severity of symptomatic DSP.[317,318] The pathogenic mechanisms of DSP are not fully understood, but direct neural invasion by HIV is not likely to play an important role.[317] Rather, its pathogenesis is likely multifactorial. One important factor may be the HIV envelope glycoprotein gp120, which is thought to bind to chemokine receptors and induce neuronal injury in the dorsal root ganglion.[316,317] Direct mitochondrial toxicity from antiretroviral NRTI is also thought to contribute to neuropathy in HIV patients.[316-318,322] Finally, necrotizing vasculitis associated with CMV or varicella zoster virus infection may also play a role in axonal degeneration.[322]

HAD must be differentiated from other causes of CNS dysfunction such as CMV encephalitis, progressive multifocal leukoencephalopathy (PML), meningitis, primary CNS lymphoma, and depression.[316] PML is a demyelinating disease of the CNS associated with papovavirus infection. In PML, there is progressive deterioration of mentation and other neurologic functions, including cranial nerve weakness. *Toxoplasma gondii* infection of the brain produces large areas of coagulation necrosis. The resulting mass lesion causes altered levels of consciousness and focal deficits, including cranial nerve dysfunction. Toxoplasmosis is definitively diagnosed by brain biopsy but is usually diagnosed presumptively by the presence of an enhancing lesion on MRI or CT, and a clinical and radiographic response to empiric management with pyrimethamine and either sulfadiazine or clindamycin.

Cranial nerve deficits may result from primary or secondary CNS lymphoma, with the trigeminal and facial nerves most commonly being involved.[323-325] Aseptic meningitis is also associated with cranial neuropathies secondary to increased intracranial pressure and perineural inflammation.[326] Idiopathic facial nerve paralysis has previously been reported to occur at much higher frequencies in HIV-positive patients.[327] However, given the extremely rare occurrence of idiopathic facial nerve paralysis even among HIV-positive patients, these findings have not been substantiated over time. The diagnosis of cranial neuropathies may be complicated by the presence of multiple concurrent pathologic processes of the CNS and peripheral nervous system.

Hearing Loss

Early in the HIV epidemic, several small studies suggested higher levels of idiopathic sensorineural hearing loss (SNHL), primarily affecting the high frequencies in patients with HIV. However, more recent data have not demonstrated an increased incidence of idiopathic hearing loss in the HIV-positive population.[226,328] Antiretroviral treatment does not appear to cause increased rates of hearing loss.[329] Although patients with HIV may not have clinical evidence of auditory dysfunction, many studies have demonstrated delayed wave latencies on auditory brainstem evoked response (ABR) testing.[330-333] These ABR abnormalities occur in patients with symptomatic or asymptomatic HIV infection. The central auditory pathway in the upper brainstem is dysfunctional in earlier stages of HIV infection as indicated by prolonged I-V and III-V intervals, whereas the lower brainstem is affected in advanced HIV infection as indicated by a prolonged I-III interval.[334] These findings were attributed to the central nervous effects of HIV infection.

The labyrinth is not as common a site of HIV-related pathology as is the central auditory system. Few abnormal findings are present on temporal bone histopathology, even on specimens from which viruses have been cultured.[335] However, a recent study demonstrated that patients with HIV had abnormal posturography results compared to normal individuals and that vestibular dysfunction worsens with advanced immunosuppresssion.[336] These findings may reflect the CNS effects of HIV infection.

Opportunistic diseases including CNS toxoplasmosis, tuberculosis meningitis, cryptococcal meningitis, and NHL may also cause SNHL in the AIDS patient. Sudden deafness and vestibular hypofunction in association with acute HIV infection and aseptic meningitis has been demonstrated, possibly as a result of a viral labyrinthitis or cochleovestibular neuropathy.[337]

Cryptococcal Meningitis

Cryptococcal meningitis is an opportunistic infection by the fungus *C. neoformans* and is the AIDS-defining illness in 40% to 60% of patients who are diagnosed with AIDS.[338,339] Since the introduction of HAART, the incidence of opportunistic infections with *C. neoformans* in patients with HIV has decreased dramatically from up to 66 cases per 1000 persons in 1992 to 2 to 7 cases per 1000 persons in 2000. Meningitis is the most common manifestation, occurring in nearly 75% of cases.[338,340] Cryptococcal meningitis is associated with severe immunocompromise and rarely occurs when the CD4 count is greater than 100 cells/μL. Bilateral SNHL occurs in 18% to 30% of patients with cryptococcal meningitis.[341,342] Hearing loss demonstrates sudden onset with slow progression, and is usually reversible with treatment of the underlying disorder.[342] Cryptococcal meningitis in patients with AIDS differs from that occurring in immunocompetent individuals in that AIDS patients develop fewer mass lesions, have higher fungal burdens, and have a poor cerebrospinal fluid (CSF) inflammatory response.[326,343] Cryptococcal meningitis may present with cranial nerve palsies affecting the facial or vestibular nerves due to elevated intracranial pressure.[343,344] Temporal bone histopathology in patients with cryptococcal meningitis demonstrates extensive invasion and destruction of the fibers and spiral ganglion of the cochlear nerve. Relative sparing of cochlear structures and vestibular nerves occurs in most cases, except in fulminant infections.[345-348]

The diagnosis of cryptococcal meningitis may be delayed because of its sometimes indolent course. The most common presentation is headache, fever, malaise and altered mental status over several weeks,[343] but patients with cryptococcal meningitis may only complain of sudden hearing loss.[348] Hearing loss is the most common cranial nerve manifestation followed by abnormal papillary reflexes, extraocular muscle paralysis, facial nerve paralysis, and blurred vision. Intracranial hypertension is thought to be the primary cause of visual and extraocular abnormalities associated with cryptococcal meningitis.[343]

If SNHL resulting from cryptococcal meningitis is misdiagnosed as idiopathic sudden hearing loss or autoimmune inner ear disease, management with corticosteroids places the patient at risk of develop-

ing fulminant life-threatening cryptococcal infection. Sudden and rapidly progressive hearing loss in an immunocompromised HIV-infected patient should therefore include serum cryptococcal antigen and a lumbar puncture before corticosteroid therapy is considered. Elevated CSF cell count is seen in immunocompetent patients, but is often low in patients with HIV.[343] The diagnosis is made by the detection of cryptococcal antigen and by the identification of *C. neoformans* on culture. Visualization of the encapsulated budding yeast using India ink is a quick and easy but less sensitive test. The current standard therapy is at least 2 weeks of amphotericin B (0.7 to 1 mg/kg/day), or liposomal amphotericin B for patients with renal dysfunction.[343] The addition of 5-fluorocytosine has been shown to have additive benefit.[349,350] Patients are treated with fluconazole (200 mg/day) for 6 to 12 months, with consideration for discontinuation after CD4 count is above 100 to 200 cells/μL for at least 6 to 12 months.[343] Persistent intracranial hypertension may require serial lumbar punctures, acetazolamide, or ventricular-peritoneal shunt placement.[351]

As with mycobacteria, *Cryptococcus* infections in HIV-positive patients may be associated with IRD. Cryptococcal infections in IRD may present with lymphadenitis, CNS lesions, or skin or soft tissue lesions, but aseptic meningitis is most commonly reported.[17,18] These infections usually represent reactivation from previously treated infections.[18] Differentiating IRD-related cryptococcal infections from true opportunistic infections is difficult but important, because management differs in these patients. There are no universally accepted guidelines, but tapered doses of prednisone have been proposed.[17] Moreover, HAART-naive patients who present with opportunistic infections may benefit from deferral of HAART initiation until after the initial treatment phase has succeeded.[15,18]

Otosyphilis

Otosyphilis should be suspected in any HIV-infected patient who presents with cochleovestibular complaints. In turn, HIV infection should be suspected in all patients diagnosed with syphilis. An alarming trend of increased rates of syphilis has emerged with the HIV epidemic. After steady declines in the incidence of infection until 2000, the incidence in the United States by 2005 was up to 3 cases per 100,000 people.[352] The primary demographic group affected has been men who have sex with men who account for 65% of cases.[352,353] The reasons for the change include a decrease in safer sex practices and increased illicit drug use.[352] Patients with HIV differ from HIV-negative patients with syphilis in that HIV infection is associated with a higher risk of developing neurosyphilis.[352] The interval between primary infection and otosyphilis appears to be shortened to 2 to 5 years in HIV infection compared to 15 to 30 years in the general population.[354] Even in patients clinically cured of syphilis, viable treponemes have been isolated from perilymph and temporal bone tissue.[355,356] Thus it has been suggested that residual treponemes, which remain dormant in the temporal bone, are reactivated as cell-mediated immunity deteriorates in the setting of HIV. Neurosyphilis can occur at any stage of syphilis infection, thus otosyphilis should be suspected in an HIV-infected patient with cochleovestibular abnormalities and a previous history of treated syphilis because labyrinthine disease may result from reactivation, reinfection, or persistent treponemal infection.

The incidence of hearing loss has been reported to be nearly 20% in patients with latent syphilis and 54% of patients with neurosyphilis.[357] Hearing loss resulting from syphilis is usually bilateral, may be progressive or fluctuate, or may have a sudden onset.[357,358] Tinnitus, aural fullness, and dysequilibrium occasionally occur. The audiometric curve often shows a low-frequency hearing loss in association with diminished speech discrimination scores. Fortunately, the majority of patients either recover hearing or have stable hearing after appropriate treatment.[357,359]

The diagnosis of otosyphilis is based upon history and serologic testing in patients with no other apparent cause for cochleovestibular dysfunction. Traditionally, nontreponemal tests such as Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests have been used for initial screening. In recent years, however, nontreponemal testing using an enzyme immunosorbent assay (EIA) has become the screening test of choice.[360] If positive, confirmatory testing with treponemal-specific tests such as fluorescent treponemal antibody absorption (FTA-ABS) or microhemagglutinin-treponema pallidum (MHA-TP) should be performed. CSF of any patient suspected of neurosyphilis should be examined.[361] Treponemal-specific tests remain positive for life, even after successful eradication of infection. Nontreponemal EIA testing is not helpful in cases of reinfection, and VDRL may be negative in tertiary syphilis. Patients with reactive treponemal tests but nonreactive nontreponemal tests who have clinical findings consistent with otosyphilis should be presumptively treated. Temporal bone CT findings in otosyphilis may be normal, but irregular lucencies in the otic capsule or ossicular chain with a characteristic "moth-eaten" appearance can help confirm the diagnosis.[362]

Treatment of syphilis is the same in HIV-positive and HIV-negative patients. The current CDC recommendation for treatment for otosyphilis is aqueous crystalline penicillin G (18 to 24 million U per day) for 10 to 14 days, followed by benzathine penicillin G (2.4 million U intramuscularly weekly) for up to 3 weeks.[361] Corticosteroids are also often used in otosyphilis, but in HIV-infected patients may be associated with a risk of further immunocompromise, leading to infectious complications. Corticosteroid therapy should be of short duration and be given in close consultation with the patient's primary care provider.

Approach to Sensorineural Hearing Loss in Human Immunodeficiency Virus–Positive Patients

The first priority in the evaluation of SNHL in a patient with HIV infection is to rule out potentially life-threatening disease. A thorough history should include a description of the rate of progression of hearing loss and the presence of dysequilibrium, other neurologic symptoms, headache, fever or neck stiffness. A complete list of all medications with attention to HAART should be obtained and ototoxic drugs discontinued if medically feasible. A complete head and neck and neurologic examination should be performed. An audiometric evaluation should include a pure tone audiogram, stapedial reflex testing, and speech discrimination scores. Electronystagmography is useful in the evaluation of dysequilibrium to assess peripheral function. Laboratory studies, including VDRL, FTA-ABS, serum cryptococcus antigen, antinuclear antibodies, erythrocyte sedimentation rate, and rheumatoid factor titers should be routine in the evaluation of patients with SNHL. If SNHL is accompanied by headache, fever, meningeal signs, or other neurologic abnormalities, head CT or MRI should be followed by lumbar puncture. Patients with advanced immunocompromise and progressive or sudden SNHL should also undergo brain imaging followed by CSF examination. Cryptococcal antigen and fungal, mycobacterial, and bacterial cultures should be performed. CSF should also be examined for cytology, VDRL and cell count, protein, and glucose. MRI of the cerebellopontine angle (CPA) with gadolinium should be considered in patients with asymmetric hearing loss and an otherwise negative workup to rule out acoustic neuromas or other lesions of this region. Auditory brainstem response abnormalities are common in the HIV-infected population, rendering this test insensitive for the detection of cochlear nerve pathology caused by mass lesions in the CPA and internal auditory canal.

Management of hearing loss in the HIV-infected population should focus on the underlying cause (Table 15-7). As mentioned earlier, indiscriminate administration of corticosteroids in the setting of HIV infection is risky. There may be multiple causes of hearing loss during the course of HIV infection. As a result, the clinician should be prepared to repeat the evaluation in search of new causes of SNHL in cases of sudden and rapid deterioration of residual hearing. Finally, auditory rehabilitation with hearing aids has an important role in maintaining the quality of life in an otherwise disabling and isolating disease. Initial experience with cochlear implantation in patients with HIV has demonstrated successful results with no increase in postoperative complications.[363,364]

Hearing Loss in Transplant Recipients

Patients with chronic renal failure are known to have higher rates of sensorineural hearing loss, as demonstrated by both pure tone audiometry and ABR testing.[365,366] Whereas treatment with dialysis has not been shown to improve hearing function, one small study

Table 15-7

Differential Diagnosis of Sensorineural Hearing Loss in HIV Infection

Idiopathic
Infectious/inflammatory
Aseptic meningitis
Central nervous system toxoplasmosis*
Cryptococcal meningitis*
Mycobacterial meningitis*
Otosyphilis
Progressive multifocal leukoencephalopathy*
Subacute encephalitis*
Neoplastic
Hodgkin's lymphoma
Mass lesions of the cerebellopontine angle/internal auditory canal and petrous apex
Non-Hodgkin's lymphoma of the brain and meninges*
Ototoxic medications

*Associated with late HIV infection, including acquired immunodeficiency syndrome.

Table 15-8

Differential Diagnosis of Oral Lesions in HIV Infection

Aphthous ulcers
Bacillary angiomatosis*
Candidiasis
Gingival and periodontal disease
Herpes simplex virus
Histoplasmosis
Human papillomavirus
Kaposi's sarcoma
Leukoplakia
Non-Hodgkin's lymphoma*
Oral hairy leukoplakia
Squamous cell carcinoma*

*May be associated with bone erosion.

demonstrated improvement in ABR findings after renal transplantation.[366] In contrast, patients who undergo liver transplantation have increased rates of SNHL. Nearly 15% of children undergoing liver transplantation were found to have SNHL by audiologic testing.[367,368] Studies in adults suggest that immunosuppression with tacrolimus may be an important factor in the development of posttransplantation hearing loss.[369,370]

Oral Cavity

Oral lesions occur in many patients during the course of HIV infection. The most common oral manifestation is candidiasis, followed by oral hairy leukoplakia.[371] Other common findings include KS, periodontal and gingival infections, aphthous ulcers, herpes simplex stomatitis, and xerostomia (Table 15-8). The risk for developing an HIV-related oral lesion correlates with lower CD4 counts, although some data suggest that this relationship weakens with longer durations of HIV infection (>10 years).[371] The use of HAART has caused a 10% to 50% decrease in HIV-associated oral disease, particularly for oral candidiasis,[372] although in children this beneficial effect is not as significant.[373] Overall, oral complications develop in approximately 20% of HIV-positive patients on HAART.[374] KS and NHL are the most prevalent malignancies occurring in the oral cavity and pharynx. However, as the longevity of AIDS patients increases, so does their risk of developing other malignancies. The clinician should be prepared to handle this increasing challenge (1) by being familiar with the oral lesions that commonly occur in this patient population, (2) by performing biopsies of all lesions that are suspicious or that do not respond to a short course of empiric therapy, and (3) by not assuming that multiple concurrent lesions have the same pathogenesis.

Oral Candidiasis

Candidal infection is the most common oral manifestation of HIV infection. In the era of HAART, the incidence of oral candidiasis has decreased by nearly 50%.[375] Reports of prevalence of oral candidiasis are 10% to 24% for patients not on HAART, and 2% to 10% for those on HAART.[376,377] With CD4 counts less than 200 cells/μL, the prevalence increases to 39% for patients not receiving HAART.[376] It also occurs in up to 20% of organ transplant recipients.[378,379] The most common organism responsible is *Candida albicans*, and up to 80% of all HIV-positive patients have oral colonization with *C. albicans*.[380] Oral candidiasis is strongly related to lower CD4 counts and higher viral loads, and possibly with smoking.[381,382] The development of OC in patients on HAART is predictive for immune and virologic failure.[374,383]

Candidal infection of the oral mucosa can take four forms[384]:

1. Pseudomembranous candidiasis (thrush) presents as a smooth white or cottage cheese–like plaque that can occur on any mucosal surface. It is distinguished from other white lesions of the oropharynx in that the white plaques can be rubbed off; when the plaque is wiped off, an erythematous and bleeding base remains.

2. Erythematous candidiasis is marked by mild or moderately erythematous patches.

3. Angular cheilitis presents as tender and erythematous fissures and ulcers at the oral commissure (Fig. 15-5).

4. Hyperplastic candidiasis, the rarest type, most commonly involves the buccal mucosa to produce raised white plaques that cannot be scraped off.

The differential diagnosis of this lesion includes leukoplakia, carcinoma in situ, and oral hairy leukoplakia. Candidal infection can be diagnosed based on the resolution of these lesions with empiric anticandidal therapy. More definitive diagnosis can be made by a potassium hydroxide preparation or Gram stain of a scraping or by periodic acid–Schiff stain of a biopsy specimen. Candida species have also been reported to cause necrotizing lesions of the epiglottis in immunocompromised patients.[385,386]

Oral candidiasis in patients with CD4 greater than 200 cells/μL is successfully managed with topical antifungals—nystatin suspension 5 mL four times per day, or clotrimazole troches 10 mg five times per day.[387] For patients with CD4 counts less than 200 cells/μL, oral fluconazole or itraconazole is recommended, with ketoconazole as an alternative.[388] Posaconazole has been demonstrated to be effective for oral candidiasis refractory to azoles.[389,390] The use of fluconazole prophylaxis for the prevention of oral candidiasis is not recommended due to the risk of side effects and lack of survival benefit.[391]

Oral Hairy Leukoplakia

Oral hairy leukoplakia is a white lesion with a corrugated and shaggy surface; it most frequently occurs on the lateral surface of the tongue. Oral hairy leukoplakia affects 3% to 10% of HIV-positive patients,[392,393] and may also occur in immunosuppressed transplant recipients.[378,394] It is rare in children, occurring in only 3% to 4% of HIV-positive children.[186] Oral hairy leukoplakia is caused by EBV,[387] and its presence in an otherwise asymptomatic patient is a strong indicator of a diagnosis of HIV infection with moderate to severe immunosuppression. Risk factors for the development of oral hairy leukoplakia include low CD4 count, high viral load, and the presence of oral candidiasis.[393,395,396] The

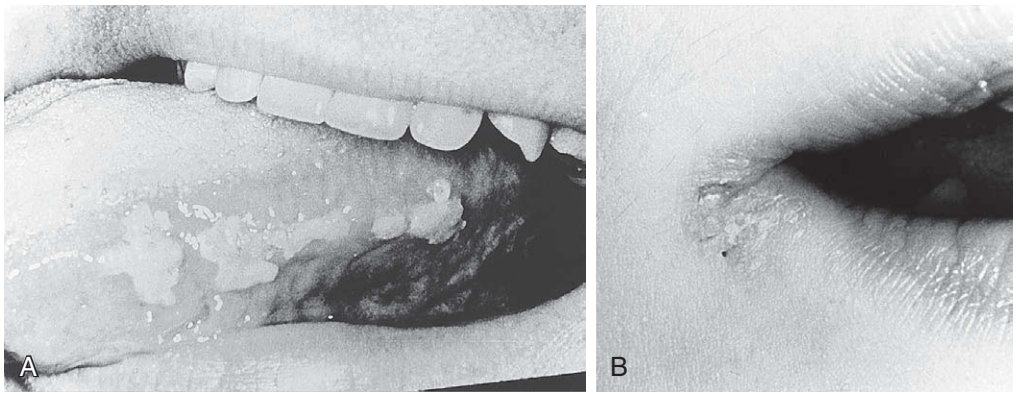

Figure 15-5. Pseudomembranous candidiasis and angular cheilitis. **A,** Pseudomembranous candidiasis of the lateral surface of the tongue. These smooth white plaques are easily scraped from the mucosa, leaving an erythematous and bleeding base. **B,** Angular cheilitis characterized by tender ulcers and fissures of the oral commissure as a result of candidal infection. *(Courtesy of Dr. Steven Ashman.)*

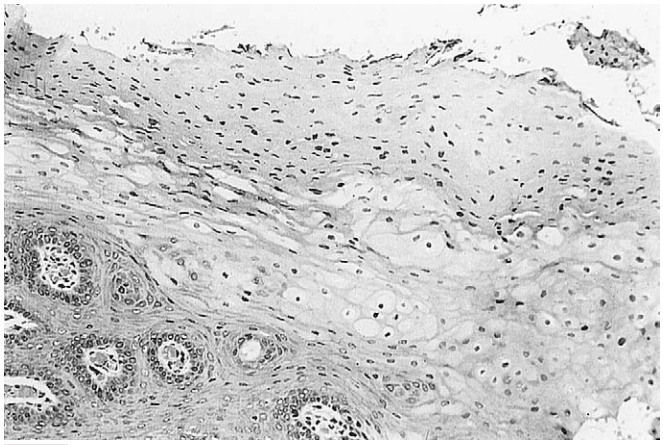

Figure 15-6. Oral hairy leukoplakia. Characteristic hyperparakeratosis is present, as is a layer of "balloon cells" in the upper spinous cell layer. *(Courtesy of Dr. Russel Corio.)*

presence of oral hairy leukoplakia is not as strongly predictive for immune and virologic failure as oral candidiasis.[383]

When an oral lesion persists despite a short course of anticandidal therapy, a biopsy is indicated to rule out a malignant or premalignant lesion. The differential diagnosis of oral hairy leukoplakia includes leukoplakia, carcinoma in situ, hypertrophic candidiasis, and lichen planus. Oral hairy leukoplakia is diagnosed on biopsy by the presence of hyperkeratosis, acanthosis, clear or "balloon" cells in the upper spinous cell layer with minimal inflammation, and the presence of EBV in the basal epithelial cells (Fig. 15-6).[384] Once the diagnosis is made, further management is rarely needed because OHL is often asymptomatic and does not undergo malignant transformation. There are insufficient data to support evidence-based recommendations for treatment. Topical treatments such as podophyllin or retinoin have been investigated, but recurrence is common. One small study found that the addition of acyclovir with podophyllin cream resulted in complete remission at 12 months.[397] The use of systemic antivirals (desciclovir, valacyclovir, acyclovir, ganciclovir, foscarnet, and famciclovir) has been reported, but the body of evidence is too small to determine their efficacy.[387]

Herpes Simplex Virus

Infections of the oral cavity by herpes simplex virus increase in all stages of HIV infection. Seropositivity for HSV approaches 95% in the HIV-positive community, compared to 80% in the general population.[398] The prevalence of HSV lesions has decreased in the HAART era, and recent prevalence is reported at 2% to 3%.[186,399] Herpetic lesions are particularly persistent when the CD4 count is less than 100 cells/μL. Herpes labialis is the most common manifestation of herpes simplex infection of the oral cavity. When this manifestation occurs in the HIV-infected patient, these "fever blisters" are generally larger, more numerous, persist longer, and recur more frequently than in the general population. Intraoral infection by herpes simplex usually affects the keratinized and attached mucosa of the hard palate and gingiva and the dorsum of the tongue. The characteristic appearance is that of small round ulcers without an erythematous halo. Multiple ulcers can produce significant discomfort with mastication and swallowing, threatening nutrition. Herpes simplex virus (HSV) infection in the HIV-infected patient is likely to be prolonged and less localized than in the general population.

Herpes simplex infection is usually diagnosed empirically by the characteristic appearance of lesions and is treated with oral famciclovir, valacyclovir, or acyclovir for 7 days, although severe lesions may require intravenous acyclovir.[398] For lesions that persist after adequate treatment, cell scrapings from the base of the lesion should be cultured for sensitivity testing. The treatment of choice for acyclovir-resistant HSV is intravenous foscarnet. Daily suppressive therapy with oral acyclovir, famciclovir, or valacyclovir should be considered for patients who have frequent or severe recurrences.

Oral Histoplasmosis

Histoplasmosis is a granulomatous fungal disease caused by *Histoplasma capsulatum* and is an AIDS-defining illness.[400] *H. capsulatum* is endemic in areas of North, Central, and South America, Asia, and Africa, but it can be found throughout the world.[401] Nearly 50% to 80% of adults in endemic areas may be infected, with most being asymptomatic.[402] Although immunocompetent patients can develop oral lesions, oral histoplasmosis is strongly associated with HIV infection. In endemic areas, the prevalence of oral histoplasmosis is 3% in HIV-infected patients and less than 0.1% in non–HIV-infected patients,[400,403] thus any patient who presents with oral histoplasmosis should undergo HIV testing. Symptomatic histoplasmosis infection presents as acute pulmonary, chronic pulmonary, or disseminated disease.[403] Mucocutaneous involvement most often occurs in the setting of disseminated histoplasmosis but can occur in isolation.[400] Histoplasmosis affecting the nasal cavity[404] and parotid gland[405] of HIV-positive patients has been reported, and oral histoplasmosis may also occur in immunosuppressed organ transplant recipients.[406] The presence of oral histoplasmosis is associated with CD4 counts less than 50 cells/μL and higher mortality at 6 months than for patients with disseminated histoplasmosis without oral involvement.[407,408]

Patients with oral histoplasmosis present with painful, erythematous patches that progress to raised, granulomatous lesions that may be covered with an adherent pseudomembrane.[400] Associated cervical adenopathy may be present.[409] Diagnosis is established by antigen

testing in body fluids and by biopsy of lesions with histology and culture for *H. capsulatum*.[402] For oral histoplasmosis occurring in the setting of disseminated disease, treatment depends upon the severity of disease.[401] For moderately severe or severe disease, systemic amphotericin B (3 mg/kg/day) for 1 to 2 weeks followed by oral itraconazole (200 mg three times daily for 3 days then 200 mg twice daily for 12 months) is recommended. For mild to moderate disease, oral itraconazole alone may be sufficient. Patients with CD4 counts less than 150 cells/μL or other immunosuppressed patients with recurrent disease should be placed on daily itraconazole prophylaxis.

Gingivitis and Periodontal Disease

Periodontal disease associated with HIV infection is classified into three categories[410]:

1. Linear gingival erythema presents with distinct linear erythema that does not respond to conventional periodontal therapy and is closely related to the presence of oral candidiasis.

2. Necrotizing periodontal disease, which can occur in immunocompetent patients, presents with ulceration of the interdental papilla associated with gingival bleeding and pain (necrotizing ulcerative gingivitis) that may invade the alveolar bone (necrotizing ulcerative periodontitis). Both are also strongly associated with oral candidiasis. Case reports have described extension of this necrotizing process into the maxillary or mandibular bone and is known as necrotizing ulcerative stomatitis.

3. Progression of chronic periodontal disease is enhanced.

With the use of HAART, the prevalence of periodontal disease has dropped from less than 10% to as low as less than 1% in one study.[410] The presence of necrotizing periodontal disease in a patient not known to have HIV infection should prompt serologic testing, because this disease is strongly associated with HIV. Patients with CD4 less than 200 cells/μL are much more likely to develop necrotizing periodontal disease than those with CD4 greater than 200 cells/μL.

The differential diagnosis of a destructive process that involves the soft tissue and bone of the alveolar crests includes lymphoma, SCC, KS, bacillary angiomatosis, fungal infection, and mycobacterial infection. The presence of bone destruction out of proportion with the soft tissue changes is more likely to be caused by bacillary angiomatosis than necrotizing ulcerative periodontitis.[76] Tissue should be sent for histopathologic and microbiologic testing. Periodontal consultation should be requested for appropriate and expeditious management of periodontal disease.

The mainstay of therapy for HIV-related gingivitis and periodontitis includes dental plaque removal and oral rinses with 10% povidone-iodine, with 0.1% to 0.2% chlorhexidine gluconate.[384] Because periodontal disease in HIV-positive patients is closely associated with candidiasis, topical or systemic antifungal treatment should also be employed.[410] If present, necrotic tissue should be debrided and the teeth scaled. If patients fail to respond to initial management, parenteral antibiotic therapy with clindamycin or metronidazole should be instituted.

Aphthous Ulcers

Aphthous ulcers are of three types, all of which affect unattached oral mucosa. Herpetiform ulcers are smaller than 0.2 mm in diameter and are self-limited. Minor aphthous ulcers are well-circumscribed, painful ulcers less than 6 mm in diameter with an erythematous halo. In the HIV-infected patient, ulcers frequently coalesce to form larger lesions lasting about 2 weeks. Major aphthous ulcers (Sutton's disease) are larger than 6 mm in diameter (Fig. 15-7). They are painful, persist for weeks, and threaten nutritional intake. They are difficult to grossly differentiate from malignancy. In the HAART era, the incidence of aphthous ulcers ranges from 1% to 8% in HIV-positive patients.[375,399,411]

Management should focus on ruling out malignancy, providing symptomatic relief, and monitoring nutritional status. The edge of the ulcer should be biopsied and submitted for histopathologic study to rule out lymphoma and SCC. The size, chronicity, and exquisite tenderness of major aphthous ulcers mandate close monitoring of body weight and the provision of liquid nutritional supplements. Initial treatment for minor ulcers with over-the-counter topical protective and analgesic medications is recommended.[412] For major or nonhealing minor lesions, thalidomide (200 mg/day) has been shown to be effective for treatment, but ineffective for prevention of recurrence.[387] Intralesional or systemic steroids have also been found to be effective.[412]

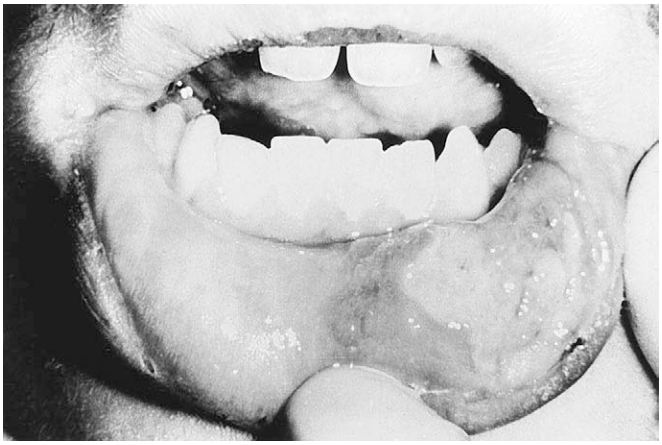

Figure 15-7. Major aphthous ulcer (Sutton's disease) of the lower lip. This lesion is indistinguishable from lymphoma or squamous cell carcinoma and should undergo biopsy. *(Courtesy of Dr. Steven Ashman.)*

Human Papillomavirus

Human papillomavirus (HPV) may cause oral or genital warts, which, like other HIV-associated oral lesions, occur with lower CD4 counts.[413] The incidence of oral warts in HIV-positive patients is 1.6%, and interestingly, the incidence of oral warts increases with lower viral loads.[414] Whether this phenomenon is explained by a mechanism similar to immune reconstitution syndrome is unclear. Oral HPV infection rates have not decreased in the HAART era, and in fact may have increased in white men infected with HIV.[387] Few studies have investigated optimal management of these lesions in the HIV population, but surgery is the most common therapy for symptomatic lesions. Alternative therapies include cidofovir, bleomycin, cimetidine, podophyllin, or intralesional interferon.

Miscellaneous

Although more commonly involving the paranasal sinuses, invasive fungal infections of the pharynx and larynx have been described in HIV-positive[284-286] and other immunosuppressed patients.[287-290] Diagnosis and treatment of these invasive infections requires a high degree of suspicion and prompt initiation of medical therapy. In one case, a total laryngectomy was required for disease control.[291]

Human Immunodeficiency Virus–Associated Facial Lipoatrophy

First described in 1998,[415] lipodystrophy is a term used to refer collectively to the changes in fat distribution that occur in HIV-positive patients. These changes include peripheral lipoatrophy affecting the face and extremities; lipohypertrophy, which may manifest as increased fat deposition in dorsocervical fat pads ("buffalo hump"), increased breast size and abdominal girth, and visceral adipose tissue; and metabolic disturbances such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, type 2 diabetes mellitus, and elevated hepatic transaminases.[416-418] There is not yet consensus regarding the definition and classification of the manifestations of lipodystrophy, which hinders interpretation of the literature.[418] Reports of prevalence vary widely due this lack of standardized case definitions and differences in methodology,[419] but a review of recent literature found that the prevalence of

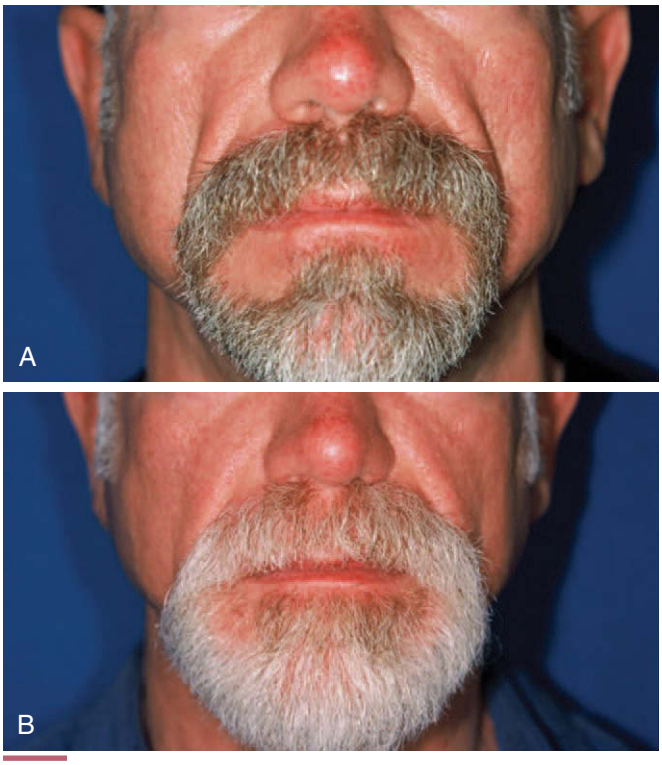

Figure 15-8. Moderately severe facial lipoatrophy, before **(A)** and after **(B)** treatment. *(Courtesy of Dr. Michael Echavez.)*

peripheral lipoatrophy in HIV-positive men and women was 22% to 38%.[420] The cause and mechanism of lipoatrophy remain unknown. Many reports have demonstrated that the use of antiretroviral therapy including NRTIs and protease inhibitors, but not NNRTIs,[418,419,421] is associated with lipoatrophy. These findings have led some to conclude that inhibition of lipid and adipocyte regulatory proteins by antiretrovirals or mitochondrial toxicity from NRTIs is responsible.[418] However, other studies have shown a strong correlation with AIDS diagnosis, CD4 count, and viral load, and not with HAART, suggesting a role for HIV infection itself.[418,422] This discrepancy may be due to different methodologies used in the studies, and it is possible that these various factors may have an impact on some but not others of the different manifestations of lipodystrophy.[416]

Facial lipoatrophy is characterized by fat atrophy in the malar, buccal, melolabial, and temporal regions (Fig. 15-8).[423,424] Patients affected by peripheral lipoatrophy may feel embarrassed or stigmatized by their aesthetic appearance, and studies have shown that these negative effects may lead to decreased adherence to HAART.[418] Objective assessment of the severity of lipoatrophy is difficult, because CT and MRI are both costly and not practical for routine use. Ultrasound has been shown in some studies to be useful,[425,426] but other data suggest that changes detected with ultrasound do not correlate with changes seen on CT.[427] This controversy may reflect difference in methodology used.

Many different treatment strategies have been proposed for facial lipoatrophy, but unfortunately no medical therapies have been shown to be effective. Surgical options include autologous fat grafting,[424,428] hyaluronic acid injection,[429,430] poly-L-lactic acid injection,[431-433] calcium hydroxylapatite injection,[434,435] malar or submalar synthetic implant placement,[436] and other injectable fillers.[437-439] Current FDA-approved treatments for facial lipoatrophy include calcium hydroxylapatite and poly-L-lactic acid. Few comparative studies have been performed and have found no difference in successful outcomes between implant placement and injection with fat or synthetic substances.[440-442] The decision to treat facial lipoatrophy and the method used to correct the cosmetic deformity should be guided by patient and surgeon preference.

Summary

With advances in the treatment of HIV infection and increased success of organ transplantation, patients with immunosuppression live longer, healthier lives. The recognition and management of disease entities occurring in this unique population are important in further reducing morbidity and mortality from head and neck diseases. Even though managing these patients is a challenge for the otolaryngologist, a clear understanding of the basic pathophysiology of conditions affecting the head and neck in immunocompromised patients will allow the otolaryngologist to more effectively evaluate and treat these diseases.

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CHAPTER SIXTEEN

Special Considerations in Managing Geriatric Patients

Meena Seshamani

Matthew L. Kashima

Key Points

- The population is aging, as people are living longer.
- The geriatric population is made up of a significant proportion of otolaryngologic practice.
- Presentation in older adults may be different than in the younger population, and the spectrum of disease may be different.
- Diagnosis, prognosis, and goal of therapy need to be discussed with patient and family.
- Sensory disorders affecting hearing, speech, taste, smell, and balance are common and may significantly affect the quality of life of the geriatric patient.
- Awareness of how otolaryngologic processes affect the geriatric population will allow for better satisfaction for the patients, their families, and the otolaryngologists involved in caring for this population.

The social and economic significance of the graying of America has received a great deal of attention. Numerous articles and editorials document the projected rate of growth of the geriatric population and how it will affect the practice of medicine. Together, geriatricians and other specialists in geriatric medicine and surgery are developing a system of care that keeps older adults healthier, more functional, and more independent at older ages than was previously possible. Otolaryngologists have taken up the challenge of describing and treating problems involving the senescent ear, nose, and throat. Otolaryngologists play a role as communication specialists and are a key resource for helping older adults avoid isolation. The American Society of Geriatric Otolaryngology was formed in 2007 to help the specialty present a unified position in treating geriatric patients with otolaryngologic conditions.

Magnitude

The term *geriatrics* was coined by I. L. Nascher in 1909.[1] Since then, industrialized countries have experienced an exponential increase in life expectancy, from 50 years in 1900 to 78 years in 2005, with a prediction of 85 years by 2050.[2] Coupled with this increased longevity is a historic bump in birth rate during the 2 decades after World War II (i.e., the "baby boom") and a current decline in fertility, leading to an increasing proportion of the population in the older age groups. In 1980, 11.3% of the U.S. population was 65 years of age or older, compared with 12.4% in 2005[3] and a projected 19.6% in 2030.[4] Within the geriatric population, persons 85 years of age and older make up the fastest growing segment, more than doubling from 2 million (1.0% of the population) in 1980 to 5 million (1.7% of the population) in 2005.[3]

The aging of the population in turn affects systems of social support, in that the number of people who work and generate income declines relative to those who do not work. This concept underlies the "old age dependency ratio," which is the number of people aged 65 and older per 100 working people (between 15 and 64 years of age). Currently there are just more than five supporting individuals for every elderly person. By 2050, this number is expected to drop to two.[5]

Disability and disease are more prevalent in older populations. One study of the National Health and Nutritional Examination Survey found that 74.6% of women and 67.4% of men aged 65 and older suffer from chronic diseases such as arthritis, diabetes, coronary artery disease, cerebrovascular accidents, or chronic lower respiratory tract disease.[6] Moreover, older adults are more likely to experience limitations in activities of daily living, with 53% of people aged 85 years and older reporting functional limitations.[7] In turn, chronic disease and functional limitations translate to increased health care utilization and cost. Nearly half of lifetime-per-capita health expenditures occur after age 64 years.[8] From 1980 to 2005, nursing home and home health care expenditures increased 8-fold from $21 billion to $169 billion.[9] The expected growth of the geriatric population therefore portends a significant impact on society's social, economic, medical, and ethical needs and obligations.

Basic Principles of Geriatric Medicine

Irvine defined six basic principles that are useful in the care of older patients.[10] Clinical decisions in this patient group tend to be complex. The fundamentals are:

1. Coexistence of multiple diseases: The unitary disease hypothesis usually does not apply. As people age, they accumulate medical diagnoses, both major and minor. These comorbidities can have an impact on the presentation and response to therapy in older adults. Signs and symptoms are more likely to be the result of several medical problems.

2. Unique spectrum of illness: In addition to many of the diseases seen in their younger counterparts, older adults tend to suffer certain

diseases that occur only in old age. This includes a wide range of degenerative disorders and certain cancers.

3. Unusual presentation of illness: Typical symptoms, such as fever and pain, are often absent, and nonspecific symptoms, such as anorexia or falling, may herald a serious underlying disorder.

4. Proper role of the aging process: Differentiating treatable disease from the natural aging process may be difficult, particularly in the area of degenerative diseases. Most geriatric specialists believe that patients and families have a tendency to overrate the role of aging. As a result, they experience unnecessary suffering and dysfunction. Specific disease processes should be sought and treated whenever possible.

5. Underreporting of health problems: Patients and families often fail to report symptoms commonly relegated to old age.

6. Function-based treatment goals: Improving a patient's quality of life may shift therapeutic goals toward maximizing function and independence, possibly at the expense of potential for cure.

Medical care provided to older adults serves several purposes. Treatment can be directed at specific acute disease processes, and the goal of this therapy can be curative or palliative. Health care can also be directed toward chronic conditions related to the aging process, such as presbycusis. Here treatment can be directed toward reversing these conditions, preventing further disability, or educating patients about their condition. Prevention is also an important function for health care, and otolaryngologists should take advantage of opportunities to educate patients about lifestyle implications on future health.

Access to Medical Care

Consideration of barriers to medical care in older adults can help physicians play a central and effective role in the advocacy of their older patients. For example, a decreased level of strength and confidence may limit the ability of the older adult to visit a physician's office or the hospital, especially in the absence of strong family or community support. Social support systems often function better for acute and more serious problems, leading to the potential neglect of wellness and prevention initiatives. The high cost of modern health care may also create a barrier; the typical older couple has to save $300,000 to pay for health care costs not covered by traditional Medicare plans.[11]

An additional barrier to care is difficulty in obtaining accurate data from this population. Older adults have a relatively high incidence of memory impairment and cognitive dysfunction, which can significantly affect the ability of the practitioner to obtain an accurate history.[12] Even the presence of involved caregivers (e.g., adult children) may not be enough to provide complete historical data.

Diagnostic Testing

Because of the general principles mentioned previously, diagnosis may be the most challenging aspect of medical care in older patients; the focus should be on identifying treatable diseases and symptoms. A good deal of judgment is required to separate specific illness from the adverse (but natural) effects of aging, and it is usually not appropriate to attribute symptoms to aging unless other causes have been ruled out first.

Invasive diagnostic procedures are relatively contraindicated when functional reserve is poor. Fortunately, modern diagnostic techniques, especially in imaging, have limited the need for invasive procedures.

Treatment

Medical Therapy

The proper use of medications is particularly important in the older patient. Indeed, one study showed that the adverse effects of medication were the most common cause of symptoms mistaken for senile dementia.[13] According to Avon and Gurwitz, any symptom in an older patient may be a drug side effect until proven otherwise.[14] It is well known that sensitivity to drugs increases with advancing age, but the reasons for this are not completely clear. There is some evidence that drug metabolism by the liver and clearance by the kidney both decline as one ages, but this does not explain the entire phenomenon. Drug receptors at the cellular level also seem to increase in sensitivity. Drug interactions can be prevented by carefully evaluating existing drug therapy before starting any new medicines; this is especially important in the geriatric population, because most older patients are taking several drugs (both over-the-counter and prescription) at any given time.

Finally, the use of some medications by older adults should be completely avoided because of the known high incidence of side effects. A good example is sympathomimetic decongestants in older men, which frequently cause urinary retention.

Surgical Therapy

The decision to operate is never made lightly, and this is particularly true for older patients. Given the higher rate of chronic disease, preoperative cardiac, renal, and pulmonary clearance is important. Moreover, the physiologic changes that occur with aging affect the body's ability to respond to insults. Aging is associated with globally decreased functional reserve, which may be well-compensated under normal conditions, but not during times of physiologic stress. For example, reduced fibroplasia and decreased ability to remodel collagen can lead wounds in the older adult to heal slower. Up to 60% of older patients hospitalized for major surgical procedures suffer acute delirium or confusion.[7] Data from the Department of Veterans Affairs demonstrates a 6% 30-day mortality for patients aged 70 years and older, and 20% are likely to have at least one complication during their hospital stay. The 30-day mortality rate increases by 10% for every year after age 70. Complications and mortality are also associated with preoperative American Society of Anesthesiologists status, and may be more common after emergency procedures.[15]

End-of-Life Care

An important consideration with the treatment of older patients is the goal of therapy. Whether palliative or curative, the goal must be explicitly discussed with patients and their families to ensure that everyone is in agreement regarding the patient's global state of health.[7] Difficulties can arise when there is a difference in goals between a patient and his or her adult children, or when the patient's or family's expectations are unrealistic.

Issues of end-of-life care are particularly relevant in the current environment of rising health care costs. Even though costs are concentrated in the older age groups, studies have shown that they are particularly concentrated at the end of life, with costs in the last year skyrocketing six times higher than costs in prior years.[16] Indeed, economic studies have shown that inpatient expenditures are related more with proximity to death than with age, whereas long-term care expenditures are more closely related to patient age.[17] As the population ages, decisions on end-of-life care can have far-reaching socioeconomic ramifications.

The Aging Ear

The normal process of aging affects all parts of the ear, but the greatest clinical impact is on cochlear and vestibular function. Presbycusis, which is the loss of hearing that is associated with aging, is the most common type of auditory dysfunction and is thought to be due to a series of insults over time, including age-related degeneration, noise exposure, and diseases of the ear. It is greatly affected by genetic background, diet, and systemic disease. Vestibular symptoms are present in more than half of older adults. Because balance depends on input from the ears, eyes, and peripheral sensory systems, all of which degenerate over time, impaired function in any of these systems contributes to vestibular complaints.

The pinna is commonly involved in actinic disorders, especially basal and squamous cell carcinoma. Sun protection and frequent inspection are important. The external auditory canal suffers a decrease in cerumen production due to degeneration of cerumen glands and a reduction in the total number of glands. This may lead to a drier cerumen that is less protective of the underlying skin and may result

in a higher incidence of impaction and infection. Ceruminosis can be exacerbated by an increase in hair at the external auditory meatus. The skin also undergoes atrophy, which results in itching, fragility, and subsequent self-induced lacerations. The use of topical emollients has been recommended for difficult cases.

Presbycusis

Presbycusis, which is the auditory dysfunction associated with the aging process, is a generic term used to include several forms of hearing degeneration. It has been estimated that of the 27 million Americans with hearing loss (13% of the population), only 10% to 20% are due to noise exposure and most of the remainder is age-related.[18] Presbycusis may have a devastating effect on older individuals by reducing their ability to communicate, thereby jeopardizing autonomy and limiting opportunities of being an active member of society. An impaired ability to communicate can also have wide-ranging health effects, because ineffective communication between a patient and his or her health care provider can lead to missed diagnoses.[7] With the growth of the aged population, presbycusis has become a great challenge to the otologist.

Gacek and Schuknecht initially defined four histopathologic types of presbycusis: (1) sensory, which is characterized by hair cell loss; (2) neural, which is associated with the loss of spiral ganglion cells and axons; (3) metabolic, which is characterized by strial atrophy; and (4) mechanical or conductive.[19] Subsequently, two more categories were added: mixed and indeterminate. The indeterminate category alone may account for 25% of cases.[20] Recent studies indicate that a mixture of pathologic changes may be present most of the time.[21]

Sensory Presbycusis

The audiometric findings in this type of presbycusis include an abrupt, steep, and high-frequency sensorineural loss with slow, symmetric bilateral progression, usually beginning during middle age. Pathologic lesions are limited to the first few millimeters of the basal turn of the cochlea. There is flattening and atrophy of the organ of Corti due to the loss of hair cells and supporting cells. There is also an accumulation of lipofuscin, which is the aging pigment.

Neural Presbycusis

Audiometric findings include gradual hearing loss with a moderate slope toward the high frequencies; however, there is a disproportionately severe decrease in speech discrimination. This difficulty with speech discrimination makes hearing loss refractory to amplification in many cases. Atrophy of the spiral ganglion and nerves of the osseous spiral lamina occur mainly in the basal turn of the cochlea. The organ of Corti is largely intact, as opposed to what is found in sensory presbycusis.

Strial Presbycusis (Metabolic Presbycusis)

The hearing loss associated with strial presbycusis is flat sensory loss beginning during the third through sixth decades and progressing slowly. Speech discrimination is generally good, and no recruitment is present. This condition is often familial, and patients do well with amplification. The characteristic pathologic findings are that atrophy of the stria vascularis is either patchy in the basal and apical turns or diffuse. The organ of Corti and spiral ganglion cells are usually unaffected.

Inner Ear Conductive Presbycusis

Both inner ear conductive presbycusis and atrophy of the spiral ligament cause bilateral symmetric sensorineural loss, with an upward slope toward the high frequency and preserved speech discrimination. No anatomic correlates with conductive sensorineural hearing loss are known, but it is hypothesized that the functional loss is due to stiffness of the basilar membrane, which correlates with its anatomic shape. The histopathologic pattern of atrophy of the spiral ligament includes different degrees of pathologic changes that are progressive through the patient's life; it is most noticeable in the apical turn and least in the basal turn. Cystic degeneration may cause detachment of the organ of Corti from the lateral cochlear wall, thereby resulting in hearing loss.

Proposed Etiologies

The specific causes of presbycusis are speculative at this time, but they are likely a combination of the effects of years of function, of exposure to harmful environmental factors such as noise and chemicals, and of genetically programmed biologic degeneration.

Morphology

It is clear that morphologic changes in human beings (as well as animal models) regularly demonstrate the age-related loss of inner and outer hair cells and supporting cells, primarily from the basal turns of the cochlea. Outer hair cells decrease more than inner hair cells. Age-related loss of eighth nerve fibers has been reported to be as high as 20% in old rats.[22] Age-related changes may occur as high as the superior olivary complex in the brainstem.

Nixon[23] and previously Glorig and Davis[24] showed high-frequency conductive hearing losses attributed to stiffness and laxity of the joints in the aging middle ear. They also proposed the concept of an inner ear conductive hearing loss due to stiffness of the cochlear partition.

Vascular

Circulatory disorders have long been proposed as the cause of hearing loss in aging persons. In the Framingham cohort, coronary artery disease, stroke, intermittent claudication, and hypertension were linked to hearing loss.[25] However, there is insufficient histopathologic evidence of this etiology for confirmation. The relationship between high-frequency sensorineural hearing loss and the degree of cerebral atherosclerosis has been used to support this theory; unfortunately, both may be independent but age-related. Atherosclerotic disease of renal vessels and inner-ear vessels has also been related to age. In 1959, Johnson and Hawkins demonstrated the progressive involution of the human cochlear vasculature from the fetus and newborn through the aged. They noted that, during the first decade of life, the radiating arterioles and outer spiral vessels in the basal coil attain adult size. Devascularization of capillaries and arterioles was subsequently found in the spiral ligament that is associated with aging.[26] They found a similarity between the degeneration of inner ear vessels with analogous changes in the retina due to microangiopathy, and they demonstrated that the plugging of vascular canals by bony tissue is a generalized phenomenon that is related to aging. They believed that the plugging of vascular canals was one of the major causes of presbycusis.[27]

Metabolic

Much like arteriosclerosis, diabetic angiopathy may contribute to presbycusis. In this disorder, disseminated proliferation and hypertrophy of the intimal endothelium of arterials, capillaries, and venules causes significant narrowing of the lumen; there is also the precipitation of lipids and other substances in the vascular wall. In addition, arteriolosclerosis is more common and more extensive in patients with diabetes. Even though recent epidemiologic studies demonstrate a higher incidence of sensorineural hearing loss among diabetic patients than age-matched controls, this effect is mitigated in populations older than 60 years. Additionally, hemoglobin A1C levels did not correlate with hearing loss.[28,29]

Serum cholesterol may also play a role in presbycusis. In Rosen's studies of Finnish patients on long-term controlled diets,[30] the reduction of saturated fat resulted in a significant lowering of serum cholesterol and an improvement in auditory threshold testing. However, the link between serum lipids and hearing loss is not definitive.[25,31]

Noise

Noise is thought to be a common cause of presbycusis. It is clear that a direct correlation exists between noise-induced inner ear damage and the frequency, intensity, and duration of noise exposure. However, some may effectively argue that noise exposure causes hearing loss at any age and is not true presbycusis. Indeed, recent studies on the interaction of noise-induced hearing loss and age-related hearing loss are contradictory and variable, likely secondary to the underlying influence of other intrinsic and environmental variables on both mechanisms.[32-35]

Noise-induced hearing loss may arise from mechanical damage, metabolic exhaustion, or vascular changes. Mechanical damage is seen

in the cochlea that has been exposed to high-intensity or impulse noise of short duration. There may be detachment of the organ of Corti from the basal membrane. Metabolic exhaustion is characterized by changes of intracellular ultrastructure, thereby indicating the depletion of enzymes and metabolites in overstimulated sensory cells. Noise has clearly been shown to cause ischemic changes of the inner ear. Capillaries below the basilar membrane have been noted histologically to undergo spasmodic changes. In addition, edema of endothelial cells impairs blood flow to the spiral ligament and stria vascularis. Sludging and aggregation of erythrocytes with increased blood viscosity secondary to decreased capillary flow also occurs.

Genetic Considerations

Presbycusis has been found to cluster in families, and in fact approximately half of the variability in presbycusis may be attributed to genes.[36,37] The effect of genes is more pronounced for the strial atrophy pattern of hearing loss (flat audiogram) than the sensory phenotype (high-frequency loss).[25] Genes that may play a role include those that protect against oxidative stress, in that this stress plays a significant role in presbycusis. Proposed genes in recent studies include those that code for glutathione peroxidase and superoxide dismutase, two antioxidant enzymes that are active in the cochlea.[38,39] Genes responsible for monogenic deafness may also play a role.

Hearing and Dementias

Recent studies of the cochlea in temporal bones from patients with confirmed Alzheimer's disease showed a lack of degeneration in the cochlea, which is typical of Alzheimer's patients. This finding is distinguished from findings in the peripheral olfactory and visual systems, which show the typical neurofibrillary tangles and neuritic plaques.[40]

Conversely, a possible relationship between central auditory dysfunction was found in the Framingham follow-up study of 1662 subjects. However, that study is weakened by the absence of objective testing in competing message tests.[40]

Treatment

Amplification remains the mainstay of treatment for presbycusis. The correction of other health factors that may impact age-related hearing loss, such as smoking, hypertension, and cholesterol levels, may play a role. Although dietary measures over the long term may be effective in reducing the progression of hearing loss in certain aging patients, further data are necessary before this treatment modality is clinically accepted.

Cochlear implantation may play a role in treating older adults with severe to profound sensorineural deafness. Such a degree of hearing loss is most often due to an underlying pathologic process such as Meniere's disease or otosclerosis in combination with presbycusis; the latter does not produce this degree of hearing impairment on its own. A recent study of 749 adolescent and adult cochlear implant recipients found that age was a clinically insignificant predictor of audiologic outcome from cochlear implantation, compared with duration of profound deafness and residual speech recognition.[41] Quality-of-life scores between elderly and nonelderly cochlear implant recipients are also similar.[42] As discussed previously, comorbid chronic health conditions seen more commonly in older populations will play a role in surgical planning and perioperative management.

Presbystasis

Presbystasis, which is the dysequilibrium of aging, is a group of disorders that affect the mobility of a large number of older persons. Due to the degeneration of the vestibular, proprioceptive, and visual senses, the ability to walk and drive can be reduced to the point of incapacitation; lessening spatial-orientation abilities contribute to this as well. Loss of balance is the most common manifestation of vestibular dysfunction in older adults.

Although attempts have been made to categorize the dysequilibrium of aging as a single specific entity, a large number of vestibular disorders are seen in older patients. These include vascular disease, Meniere's disease, benign positional vertigo, and adaptation deficits. Input from the vestibular, visual, proprioceptive, and other systems can be thought of as providing input into a common central processor that, in turn, controls posture and eye movement. This adaptive control system alters afferent signals from the various receptors at both visual-vestibular interfaces as well as proprioceptive-vestibular interfaces. Control circuits can be affected by disturbances in the general condition of the patient, the availability of the neurotransmitter, and in pathologic disorders.[43] Other feedback loops help control visual tracking and postural adjustment in response to motion. Cognitive controls also exist and contribute primarily in the areas of spatial orientation, the hallucination of motion, and the development of athletic skills.

Disorders of these sensory organ systems have traditionally been treated by otolaryngologists, neurologists, and ophthalmologists, depending on the organ system causing the most obvious dysfunction. However, development of the unifying discipline of neuro-otology has led to an integrated approach to, evaluation of, and care for older persons with dysequilibrium. Otolaryngologists must be aware of other causes of dysequilibrium or dizziness, because a variety of organ systems may contribute to these difficulties, including vestibular, ocular, proprioceptive, musculoskeletal, central processing, cardiovascular, and neuromotor. For example, side effects of psychotropic medications, abnormalities in blood pressure, leg muscle weakness, neuromotor disorders such as Parkinson's disease, and generalized loss of coordination can contribute to feelings of dysequilibrium and dizziness. The failure of one organ system can be overcome with compensation, but with multisystem failure, increasingly severe deficits occur.[7]

Falls are one of the most common concerns relating to imbalance in older adults. Approximately one-third of adults older than age 65 in the community and one-half of adults older than age 80 in institutionalized settings fall each year. One-third of these falls result in injuries that require medical attention or the restriction of activities for at least 1 day, and 10% to 15% of these falls result in fracture. As a result, the medical costs of fall-related injuries totaled $19 billion in 2000, with nearly $9 billion for hip fractures alone.[44] Moreover, falls lead to functional decline, anxiety, depression, and social withdrawal. In particular, one-half of older adults hospitalized for a hip fracture do not return to prior levels of function.[45]

Vestibular Pathology

Age-related degeneration has been noted in hair cells, neurons, and supporting structures of the peripheral vestibular system, as well as more centrally in the vestibular nuclei and cerebellum. Hair cell loss has been found in the semicircular canals, the utricle, and the saccule. This degeneration is most noted in the central area of the cristae, whereas macular degeneration is more diffuse. Degeneration of the saccule may be greater than that of the macula. A decrease in the total number of peripheral vestibular neurons, as well as a decrease in the size of myelinated nerve fibers, has been described in patients who are older than 65 years old. Degenerative changes also occur in otoconia of the human maculae, deformities of the vestibular end organs, and degeneration of the synaptic structures of afferent dendrites.[46] These degenerative changes are considered to be the vestibular equivalent of presbycusis. Unlike presbycusis, however, asymmetric loss of vestibular function can result in incapacitation.

Diagnostic Methods

The use of objective tests to identify the etiologic basis of presbystasis is essential. Vestibular function studies described elsewhere are applicable in older adults as well. Avoidance of a "trash basket" diagnosis of presbystasis and continuing clinical research into etiologic diagnosis are essential. In particular, studies of electronystagmography, platform posturography, and sinusoidal harmonic acceleration in older adults are ongoing.

In cases of presbystasis arising in the peripheral labyrinth, generalized hypofunction is often found. Symmetric maximum slow-phase velocity responses to warm and cool caloric stimulation of less than 10°C per second per irrigation can be empirically used to identify this condition. In cases of peripheral hypofunction, the use of vestibular nerve suppressants may be contraindicated. Such treatment further reduces the already reduced vestibular input, thereby resulting in further incapacitation.

Treatment

Nonvestibular causes of presbystasis need to be identified and treated specifically. Examples include postural hypotension associated with antihypertensive medications, endocrine imbalances, malnutrition, and cardiovascular insufficiency.

Because of the adaptive control feedback mechanism in the complex vestibular system, treatment modalities have been developed to allow for compensation. Vestibular habituation training involves "exercises" based on feedback control initiated by the habituation effect. Mechanisms of adaptation and compensation are stimulated through repeated elicitation of minor degrees of vertigo.

Other goals of vestibular exercise programs include the improvement of visual tracking when the head is stationary, gaze stability during head movement, and visual-vestibular interactions during head movement and general balance. These exercises are designed to incorporate visual and proprioceptive experiences with vestibular cues.

The twin goals of these exercises are the reestablishment of balance and the reduction of the symptoms of dizziness and disorientation. In many cases, consultation and therapy with a physical or occupational therapist trained in vestibular compensation exercises can be extremely helpful.

Another important consideration that must be stressed to the patient is the prevention of falls. Precautions include the use of night lights (especially en route to the bathroom), the removal of throw rugs, the avoidance of stairs, and the use of ambulatory assistance devices when necessary.

The Aging Nose

Nasal structure and physiology are affected directly by the aging process and by a multitude of indirect factors that are commonly seen in older adults. For example, older adults are more likely to suffer from falls, leading to head and face trauma that can affect nasal function and the sense of smell. They are also more likely to suffer from olfactory dysfunction following a viral upper respiratory tract infection.[47] Some medications used commonly by older adults (e.g., lipid-lowering drugs, anti-inflammatories, and antihypertensives) may desiccate the nose and alter smell and taste.[48] Decongestants and antihistamines make secretions thicker and worsen postnasal drip. Blood thinners can precipitate epistaxis. Age-related deficits in nasal function can adversely affect sleep, eating, and breathing, and significantly alter patient quality of life.

Common Symptoms

The most common nasal complaints in older adults are nasal drainage, postnasal drip, sneezing, coughing, olfactory loss, and gustatory rhinitis. Other symptoms, such as nasal obstruction, epistaxis, and sinus pain, have not been shown to significantly increase with age. It is thought that nasal discharge and postnasal drip among older adults may be explained by the loss of autonomic control. Gustatory rhinitis, which is nasal discharge that is stimulated by eating, similarly may be caused by overactivation of the autonomic control of the mucoserous and Bowman's glands initiated by the sight of food or the act of eating.[49]

There is a general increase in nasal resistance with age, despite the lack of subjective symptoms of nasal obstruction. This may be explained by the fact that many older patients believe that some nasal obstruction is normal and hence not worth mentioning. However, older persons often notice that nasal airflow is subjectively less with exertion.[49]

Mucoepithelial Changes

The effect of age on mucociliary transport is modest. Transport rates are not significantly different between young adults and middle-aged adults, or between middle-aged adults and older adults. However, significant differences exist between younger adults and older adults.[50] The reasons for this are yet unclear. Neither age nor smoking has been definitively related to a reduction in ciliated cells. Other unknown factors may influence change in the viscoelastic properties of the nasal mucus and therefore predispose the older adult to nasal crusting.[51]

Olfactory Changes

Smell and taste typically peak in the third to fourth decades of life and decline in the older ages.[48] Many studies have shown that olfactory thresholds for a wide range of odorants progressively decrease with age.[52-54] The process is probably due to a combination of a loss of receptors and neurons, with alterations in neurotransmitters and central pathways.[55] There is a decrease in olfactory epithelium and reciprocal increase in respiratory epithelium with age, with increased degenerative changes and loss of olfactory bulb fibers.[56-58] One mechanism for the change in the number of olfactory receptor neurons is an increase in apoptosis.[59]

Changes in Nasal Appearance and Intranasal Examination

There is a significant increase in the nasolabial angle and a decrease in the height-to-length ratio of the nose with age. This may be due to the lengthening of the upper lip, resorption of premaxillary fat, resorption of the malar and alveolar ridge, and changes in dentition that are caused by the degenerative process of aging. The decreased height-to-length ratio accentuates the drooping of the nose as it ages. Weakening of the lower lateral cartilage and the caudal septum, along with the loss of elasticity in the enveloping skin, contributes to the descent of the aged nose tip.

On intranasal examination, nasal polyps are more common with advancing years.[60] Abnormalities of the nasopharynx are not common in older subjects.

Treatment

As is the case with younger age groups, medical or surgical treatment of rhinologic problems in older adults requires an accurate diagnosis to select appropriate treatment. Humidification is generally helpful, as is the prudent avoidance of medications that desiccate the nose and aggravate mucosal atrophy, such as topical and systemic decongestants. Underlying osteomeatal blockage due to allergies or infection should be addressed; this may involve treatment in a multidisciplinary setting by the pulmonologist, allergist, otolaryngologist, and other specialists. The treatment of associated medical conditions may be helpful. In patients with vasomotor or gustatory rhinitis, anticholinergics such as ipratropium bromide spray may be effective.

Surgical reconstruction is aimed at reconstituting support for the upper lateral cartilage and elevating the drooping nasal tip.[61] The removal of turbinate mucosa should be avoided, especially when excessive dryness is already a factor. Vidian neurectomy may be indicated in select cases.

The Aging Voice and the Upper Aerodigestive Tract

The phonatory organ is composed of the resonator (larynx), the articulators (supraglottic structures), and the compressors (lungs).[62] Age-related changes in any one or all of these structures can have a direct impact on voice quality and general comfort level (Table 16-1). Furthermore, older people are often exposed to a wide array of environmental and medicinal irritants (indirect factors) that compound the problem, particularly in the case of long-term tobacco smoking (Table 16-2). Older patients may also suffer from a host of medical conditions that can affect vocal quality, such as cancer, vocal fold paralysis, Parkinson's disease, amyotrophic lateral sclerosis, benign essential tremor, diabetes, and other endocrine dysfunctions (see Tables 16-1 and 16-2).[63-67] The frequent occurrence of depression with sensorineural hearing loss can lead to a hyperfunctional voice and muscular tension dysphonia. Therefore treatment of geriatric patients with vocal problems must be directed not only at maximizing the efficiency of the aging phonatory organ through appropriate voice therapy or surgery, but also at treatment of the underlying medical, neurologic, or psychiatric disorder.

Histologic Changes

Laryngeal tissues change a good deal before alterations in the voice are detected. Histologic changes seen within the aging larynx appear to occur with approximately equal frequency in both sexes. Histologic examination suggests that the yellowish discoloration seen clinically represents fat degeneration or keratosis of the mucous membrane. Vocal fold atrophy is thought to represent the laryngeal manifestation

Table 16-1

Common Factors with a Direct Effect on Vocal Quality

Factors	Effect on Vocal Quality
Laryngeal muscle atrophy/fibrosis	Effect on glottic gap and vocal fold thickness, resulting in increased air loss and abnormal acoustics
Cricoarytenoid joint changes	
Mucosal atrophy	Increased chance for injury, pain, and guarding, which affect articulation
Salivary gland atrophy	Decreased lubrication, dry mouth, and secondary dental problems
Alveolar bone resorption	Increased chance for injury, pain, and guarding, which affect articulation
Dental/gingival loss	
Temporomandibular joint disease	
Lower respiratory tract changes	Decreased chest elasticity, abdominal tone, and breath support, which result in decreased vital capacity, vocal fatigue, and decreased volume

Table 16-2

Common Factors with an Indirect Effect on Vocal Quality

Factors	Effect on Vocal Quality
Hearing loss	Vocal misuse
Anxiety/depression	
Dehydrants: alcohol, antihistamines, decongestants, diuretics, megadoses of vitamin C, antidepressants, antihypertensives	Reduced lubrication/ altered secretions
Surgery/disease processes: prior intubation, laryngeal surgery or disease, oral/pharyngeal surgery or disease, nasal/sinus surgery or disease, superior/recurrent laryngeal injury, dental/temporomandibular joint surgery or disease, abdominal/thoracic surgery or disease, limb surgery or disease	Changes in phonation, resonance, and articulation; reduced pulmonary support/ altered posture
Mucosal irritants: allergies, smoking, gastroesophageal reflux, pollution	Direct effect on mucous membranes/ altered secretions
Endocrine dysfunction: hypothyroidism, hormonal therapy	Mucosal/soft tissue alterations, vocal fold edema
Abrupt weight change	Multifactorial

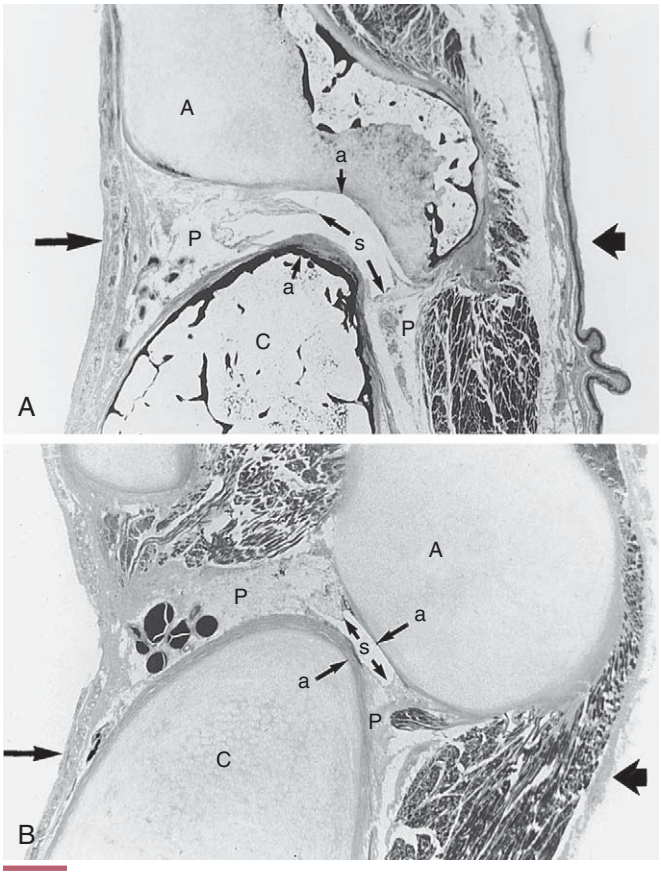

Figure 16-1. **A,** Young cricoarytenoid joint (patient is 29 years old). *A,* Arytenoid; *a,* articular surface; *C,* cricoid; *P,* periarticular soft tissues; *s,* synovium; *fat arrow*, hypopharyngeal epithelium; *thin arrow,* subglottic respiratory epithelium (hematoxylin-eosin; ×3). **B,** Old cricoarytenoid joint (patient is 69 years old). *A,* Arytenoid; *a,* articular surface; *C,* cricoid; *P,* periarticular soft tissues; s, synovium; *fat arrow*, hypopharyngeal epithelium; *thin arrow,* subglottic respiratory epithelium. Note increased calcification and muscle atrophy (hematoxylin-eosin; ×3).

of senescent changes in muscle and mucous membranes. There is general thinning, decreased fiber density, fatty degeneration of the laryngeal muscles, and a decrease in fragmentation of elastic fibers in the submucosa.[68] Studies suggest these changes may be caused by changes in neural input to the muscles.[69] Decreased fiber density is also seen in the laryngeal ligaments and the conus elasticus.

Progressive calcification of the laryngeal cartilages occurs with age.[70] Calcification and ossification begins during the early 20s and is essentially completed by the sixth decade. Small islands of cartilage remain in the central portion of the thyroid cartilage of men; there is preservation of cartilage in the upper portion in women. The cricoid may be almost completely ossified. The arytenoid undergoes ossification of the body and muscular process, with the apex remaining cartilaginous (Fig. 16-1). There seems to be some controversy regarding whether the vocalis process ossifies.[71] This ossification represents the creation of a true haversian system with lamella, osteocytes, and fat marrow. In general, the onset of ossification is later and less extensive in women, and the entire process is quite variable among individuals. Similar age-related changes may occur in the cricoarytenoid joint as well.[72]

Laryngoscopic Appearance

Laryngoscopic characteristics of the aging larynx include a yellowish or dark grayish discoloration of the vocal fold, edema, and vocal fold atrophy. This results in bowing of the vocal fold edges, incomplete glottic closure, and visibility of the ventricle. The prominence of

the contour of the vocal process leads to the typical "arrowhead configuration" of the glottis that is seen so often in the senescent larynx.[73,74]

Acoustic Changes

Dysphonia is present in at least 10% of older adults. Although variable, the senescent voice is typically stereotyped as being tremulous, weak, hoarse, and altered in pitch. Overall, jitter (cycle-to-cycle frequency variation) continues to be significantly greater in the aging population as compared with younger age groups, particularly in men.[75] Aging of the larynx is also associated with a slowing in the opening quotient of the vocal folds, which further adversely affects vocal quality.[76] In men, fundamental frequency levels progressively decrease from 20 to 40 years of age and then increase from 60 through 80 years of age.[77] Vocal fold edema, which is seen in some women, is thought to be due to general endocrine changes that occur after menopause. The latter, along with the lowering of laryngeal position that occurs in women who are more than 60 years old, results in marked lowering of the fundamental frequency and roughness of the voice.[78] The aging woman also tends to read with larger intonation ranges and a greater number of inflections than younger adults.[79] The acoustic characteristics of women's voices show a significant lowering of the frequency of the first formant (f1) with advancing age, which suggests age-related changes in the vocal tract and mentions or positions of speech structures.

Mucosal Changes

The aging process results in significant changes within the mucosa of the oral cavity, salivary glands, teeth, mandible, maxilla, temporomandibular joint, and taste buds. In combination or individually, oral dryness, soft tissue atrophy, decreased mandibular excursion, and temporomandibular joint disease can significantly affect the voice by altering its resonant characteristics.

The epithelium of the mouth becomes atrophic, especially in the prickle cell layer. Parakeratosis and hyperkeratosis may be present, particularly in areas of denture use. Histologically, there is thinning of the tunica propria and blunting of the rete pegs; decreases in capillaries, water content, hyaluronic acid, and collagen content; and an increase in ground substance. In combination with small vessel disease (e.g., arteriosclerosis), these changes make oral tissues more prone to injury, prolonged wound healing, and contribute to the shiny smooth appearance of the senescent oral mucosa.[80] Guarding as a result of oral trauma may adversely affect the voice by modifying the way one articulates and projects speech sounds.

Glandular Changes

Normal physiologic changes that occur in the salivary glands of older adults are the principal cause of dry mouth syndrome, which is one of the most common complaints of this population.[81,82] Secretory rates diminish and salivary viscosity increases in these patients. Submandibular gland parenchymal volume decreases as a result of a reduction in acinar tissue, whereas ducts enlarge. There is also an increase in focal chronic inflammatory changes resulting from hyalinization of the acini and an increase in salivary duct adhesions and obstructions. The end result is a loss of one fourth of the active secretory parenchymal volume and its replacement by connective tissue and fat.[82] Because adequate lubrication is essential for the production of sound in the phonatory apparatus, the presence of dry mouth should be recognized and treated.

Sense of Taste

Many older patients complain of a metallic or salty taste, and decreased levels of sensitivity to sweet, bitter, and sour foods. This loss of taste is multifactorial. Both a reduction in salivation and a reduction in the number of taste buds can occur normally during the aging process.[83] Decreased olfaction, as discussed earlier, as well as systemic medical conditions and various medications can alter patient taste.

Dental/Mandibular Changes

As one ages, there is resorption of mandibular and maxillary alveolar bone and a diminution in regenerative capacity, leading to a loss in the vertical height of the face and a "purse-string" appearance of the mouth. This problem is magnified in edentulous patients, in whom up to 50% of mandibular height may be lost. Histologically, the aging mandible often displays signs of osteoporosis in the form of cortical thinning and loss of its coarse trabeculation patterns. Bone resorption and the diminution of connective tissue around the nerves allow the neurovascular surface to be more easily damaged. Common complaints are paresthesia or pain due to irritation of the mental nerve by ill-fitting dentures, and a burning sensation of the hard palate. As in other areas of the oral cavity, these connective tissue changes contribute to a reduction in the repair capacity after injury.

As far as teeth are concerned, a secondary dentin (calcified dentin) replaces most of the dental pulp. The cementum shows continued deposition and calcification throughout life. Apical migration of gingival tissue leads to a gradual exposure of the tooth root. These processes make individuals prone to periapical infection and periodontal disease.

Any changes in the bony architecture of the maxilla or mandible may adversely affect the voice by affecting the resonance characteristics of speech sounds. The absence of teeth, the use of ill-fitting dentures, oral or dental pain, and paresthesias may further affect certain speech sounds, particularly those involving tongue-to-lip, palate, or teeth apposition. The ability to produce clear plosive (p, t, k, b, d, and g) and fricative (s, z, f, v, sh, ph, and th) sounds may therefore be affected.

The temporomandibular joint may also be affected by the aging process. There is a loss of elasticity and hardening of the articular disc and capsular ligament, a thinning of the articular disc, fibrosis of the articular space, and a flattening of the articular surfaces. Complaints such as joint clicking, dislocation, subluxation, and fracture of the articular head (with subsequent decrease in mouth opening) may indirectly affect the voice, again by altering resonance characteristics and the projection of speech sounds. Speaking with a tight oral aperture narrows resonance of sound within the oral cavity; it may further result in laryngeal elevation, which increases tension in the vocal tract.

Respiratory Changes

The effects of aging on pulmonary function are significant. Age causes changes in the musculature of the lower respiratory tract that affect the function of the chest wall, abdomen, and diaphragm. Pulmonary perfusion, forced expiratory volume, forced vital capacity, elastic recoil, and dynamic pulmonary compliance decrease significantly with age.[84-87] There is a ventilation/perfusion mismatch, an increase in alveolar dead space, an increase in the alveolar-arterial gradient for oxygen delivery, a loss of alveolar surface area, and a change in the pulmonary circulation.[88,89] Body weight commonly increases with age, which increases the demand on the respiratory system. Older men have been found to require more intrasentence breaths, which is thought to be related to decreased vital capacity.[90] All of these changes can result in inadequate breath support and excessively harsh glottal closure to phonate. Over time, this can fatigue the laryngeal apparatus and result in secondary muscular tension dysphonia.

Treatment

For the most part, treatment of presbyphonia is directed at controlling the underlying medical illness and maximizing the efficiency of the phonatory apparatus. This typically involves a multidisciplinary approach involving the expertise of a speech pathologist, otolaryngologist, pulmonologist, neurologist, psychiatrist, oral surgeon, and a generalist. Treatment for gastric acid reflux and attention to proper hydration and other general vocal hygiene measures are important. Maximizing pulmonary efficiency in patients with underlying pulmonary disease is a necessity. General conditioning may be quite helpful in motivated patients. Symptomatic dryness can be addressed with the judicious use of sialogogues, salivary substitutes, and expectorants. Other specific medical illnesses discussed above must be addressed, when present.

Surgery is recommended only after the more conservative measures addressed earlier fail to achieve the results required by the patient. Procedures have been devised in an attempt to adjust vocal pitch as

well as strengthen the voice of patients with flaccid or bowed vocal folds.[91] Isshiki advocates a type 4 thyroplasty for this problem.[92] Others have advocated similar advancement of the anterior commissure to adjust vocal cord tension through an anterior commissure laryngoplasty.[93] Short-term success with these procedures has been achieved, with improvement in loudness and clarity and a decrease in breathiness and air escape. More recently, technologic advancements in injectable fillers hold promise for the treatment of glottic insufficiency; short-term options include hyaluronic acid gels (e.g., Hylaform, Restylane) and collagen-based products (e.g., Cymetra), while calcium hydroxylapatite (e.g., Radiesse) provides more long-term results.[94]

Presbyphagia

Dysphagia is relatively common in older adults, affecting 15% of those in the community and approximately 40% of patients in institutionalized settings.[95] This has contributed to the supposition that swallowing deficits may reflect normal age-related changes. Granieri suggests that the effects of aging on swallowing can be divided into primary, secondary, and tertiary categories.[96]

Primary effects of aging on swallowing include physiologic and structural changes in the oral cavity, pharyngeal, and laryngeal structures. Older adults have a smaller cross-sectional area of masticatory muscles, increased lingual atrophy and fatty infiltration, and diminished strength, mobility, and endurance of these muscles. As a result, swallowing becomes slower with age; the pharyngeal swallow response initiates later, and the swallowing motor response is not as responsive to sensory stimuli.[97-107] Secondary factors include a plethora of general medical and neurologic conditions, such as head and neck cancers and their treatments, neuromotor disorders including stroke and cricopharyngeal spasm, or the general deconditioning associated with illness. Side effects from the use of pharmacologic agents are also more common in older adults. Tertiary aspects involve those changes that can result from social, environmental, and psychologic factors.

Diagnostic Testing

When swallowing disorders are suspected, a complete oropharyngeal and esophageal swallowing evaluation is warranted because of the increased incidence of concomitant problems in both areas. A careful history and physical examination should allow the clinician to distinguish between the two major categories of swallowing impairment: difficulty initiating swallowing and obstruction.[108] Because speech, voice, and swallowing problems are often the first signs of degenerative neurologic or neuromuscular disease, the physical examination should include both head and neck and neurologic evaluations.

Radiographic assessment is considered the gold standard for dysphagia assessment. The modified barium swallow (MBS), which is a videofluoroscopic swallowing study of the head and neck, provides critical physiologic information (i.e., bolus transit from the mouth to the cervical esophagus), swallow transitions, and biomechanics of the swallow that are necessary for treatment. The procedure also provides valuable information about the timing and etiology of aspiration and the effectiveness of rehabilitative strategies. If the study reveals structural or motility disorders of the esophagus, endoscopy and manometric examination are the next diagnostic steps.

Flexible endoscopic evaluation of swallowing is an adjunctive assessment tool to the MBS. Visualization of the pharyngeal-laryngeal mechanism provides symptomatic information about the swallow (i.e., aspiration and pharyngeal residue). This type of endoscopic evaluation is also a valuable biofeedback tool for airway closure maneuvers.

Treatment

Proper treatment of swallowing disorders in older adults requires management by the multidisciplinary team and is contingent on correct diagnosis, considering primary, secondary, and tertiary causes. Treatment may be medical or surgical, but it is more often rehabilitative. Rehabilitative treatment strategies that will improve the safety and efficiency of the swallow are identified during the radiographic procedure and based on the nature of the patient's disorder. Many swallowing rehabilitation techniques require the application of voluntary control to disordered aspects of swallow physiology. These include swallowing therapy strategies, such as the supraglottic swallow or Mendelsohn maneuver, and other oropharyngeal exercises. However, a number of treatment strategies require little patient cognition or cooperation by the older individual, such as postural techniques or changes in diet or food consistency. Recent randomized trials indicate that more research is needed to assess the efficacy of combining these modalities.[109,110] Moreover, little research has looked into sensory-based swallowing therapies such as delivering a sour or cold bolus, given that intraoral stimulation does affect swallowing biomechanics.[111-113] If nonoral feeding is required, reevaluation at regular intervals should be conducted to determine progress in recovery and the optimal time to reinitiate oral intake.

Facial Trauma

Wound healing is affected by aging, in that angiogenesis, epithelialization, and remodeling are all delayed in older patients.[114] Moreover, a decrease in immunologic response can lead to increased susceptibility to wound infection.[115] The facial skeleton undergoes changes with aging; as mentioned above, the most prominent change is resorption of the alveolar bone in the maxilla and mandible. The bone of the facial skeleton becomes brittle, and decreased metabolic activity in the bone makes healing times prolonged. Resorption of bone and its fragility can make placing fixation plates difficult. In particular, the repair of fractures in an edentulous mandible presents a particular challenge, with an atrophic mandible making iatrogenic fractures during repair more likely, and the lack of teeth making the determination of appropriate reduction and occlusion more difficult.[115] Planning for repairing facial fractures in older adults must take these factors into account to ensure the best possible outcome.

Head and Neck Oncology

Etiology

Approximately one fourth of head and neck cancers happen in patients older than age 70.[116] Environmental exposure to carcinogens, most notably tobacco and alcohol, is an important cause of these cancers. The occurrence of cancer in advanced age is probably related to the duration of carcinogen exposure, but also to immune senescence. Immune dysfunction associated with aging is complex and involves several components of the immune system. Wolf suggests that the most important deficit may occur in antigen-specific T-cell cytotoxic function.[117] Autoimmune diseases also are more common with advancing age, and may facilitate tumor progression.

Treatment

Interestingly, although many cancer patients are older than 65 years old, they represent a minority of participants in clinical trials.[118] To encourage the inclusion of older adults in clinical trials, President Clinton in 2000 issued a directive for Medicare to reimburse the costs of routine patient care during clinical trials.[119] However, treatment paradigms are often applied from studies examining younger patients.

As discussed, aging leads to multiorgan functional decline, reduced nutritional status, and psychosocial factors including depression and absence of social support. These factors must be considered with any treatment protocol. In general, older patients tolerate major head and neck cancer surgery well. Morgan and others[120] reviewed 1773 patients undergoing major head and neck operations under general anesthesia. Of the 810 patients between the ages of 65 and 95 years, 3.5% died, and 32% suffered nonlethal complications. By contrast, only 8 of 863 patients between the ages of 35 and 65 years died (0.8%), and the complication rate was 21%. The differences in mortality and complication rates are both significant, but a mortality rate of 3.5% in persons older than 65 years does not seem prohibitive. In a more recent study, McGuirt found that patients who were older than 80 years old had a similar prognosis to that of patients between 65 and 80 years old, but complications were more common with advancing age.[121] Recent studies on reconstructive surgery with free flaps show that the risk of postoperative complications is related to the presence of comorbidities and not age.[122-124] Length of time under anesthesia also correlates with complication rates.[125]

More intensive combination therapies must take into account the presence of comorbidities, age-related frailty, and underlying psychosocial problems. For example, toxic side effects from chemotherapy are more common in older age groups, and older patients—particularly those with poor performance status—may demonstrate reduced compliance and tolerance to radiation therapy.[126]

Thyroid disease is common in the geriatric population, and thyroid cancer behaves more aggressively in older patients. Undifferentiated carcinoma is more common, and recurrence and metastasis occur more frequently in the older adult, even with well-differentiated thyroid cancer. The mainstay of management for well-differentiated thyroid cancer is surgery, but multimodality therapy that includes radioactive iodine is commonly advised in older patients, especially those who have follicular cancer. Bliss and colleagues investigated thyroid surgery in patients who were older than 50 years old. They found no difference in morbidity or mortality when comparing patients 50 to 60 years old with patients 61 to 70 years old and with patients who were older than 70 years old.[127]

Regardless of pathology, before advising a major surgical procedure, careful consideration is given to the patient's motivation as evidenced by his or her current level of function. An active 80-year-old patient with good muscle tone may be a better surgical candidate than a sedentary 65-year-old patient with poor functional residual capacity. A comprehensive preoperative evaluation needs to be completed in all surgical candidates. Current trends in health care are to minimize inpatient care and shorten postoperative admissions. Although this may be feasible for young, healthy adults, the goal of short-stay admissions for older adults may not be realistic; this needs to be taken into account when planning treatments for geriatric patients.[128]

Preoperative teaching is important for all patients and their families, and selected patients may benefit from a 2-week course of nutritional and physical therapy aimed primarily at improving cardiorespiratory function. Patients should understand that they will need to participate in the recovery process, which may last several months; a substantial portion of this time will not be spent in an acute care setting. Patients should understand that recovery may entail a period of rehabilitation at a rehabilitation facility or a subacute care facility; placement in one of these facilities is not to be construed by the patient or his or her family as an adverse event or failure of treatment.

Conclusion

Otolaryngologists and all health care providers are faced with an aging population. Although the spectrum of disease is likely to remain constant for practitioners, the makeup of individual practices may reflect this change in demographics. To prepare for this change, we must continue to expand our knowledge base of the disease processes that affect older adults and our ability to treat this population. Future research will also need to include this group.

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CHAPTER SEVENTEEN

Pain Management in the Head and Neck Patient

Edward B. Braun

Jeremy A. Scarlett

Todd J. Schwedt

Robert A. Swarm

Key Points

- Optimizing control of postoperative pain can reduce postoperative morbidity and cost.
- Development of opioid addiction in the context of acute pain treatment is rare.
- Use of patient-controlled analgesia (PCA) postoperatively can improve pain control and patient satisfaction.
- Preemptive analgesia may reduce the magnitude and duration of postoperative pain, thereby reducing use of postprocedural pain medications.
- Perioperative regional anesthetic techniques may allow for superior postoperative pain control compared with the use of systemic opioids and adjuvant pain medications alone.
- Referencing the World Health Organization analgesic ladder can assist in providing pain relief for patients.
- Use of long-term opioid therapy in patients with chronic noncancer pain can be complicated by the development of tolerance, addiction, and hyperalgesia.
- Use of anticonvulsants, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), or interventional therapies is important in the treatment of chronic pain.
- Headaches affect most people at some point in their life, with a 78% lifetime prevalence of tension-type headache and a 16% lifetime prevalence of migraine. Migraine headache is the most common primary headache type leading to physician visits.
- Abnormalities on examination of a patient presenting with headache should be accompanied by consideration of possible secondary causes.
- Therapy for migraine should consist of both acute and prophylactic interventions consisting of headache trigger avoidance, medications, physical therapy, and biobehavioral therapy.
- Initial treatment of trigeminal neuralgia should center around prophylactic medications such as carbamazepine.

Pain Defined

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Pain can be broadly categorized as either acute or chronic. Acute pain is a predicted response to a noxious mechanical, thermal, or chemical stimulus such as trauma or surgery. It is for an acute period of time and is often responsive to appropriately adjusted analgesics.[2] Pain is defined as "chronic" when it persists for at least 3 to 6 months or lasts longer than the time in which healing would normally occur.[2]

Pain is subjective, and a known pathophysiologic etiology is not necessary for pain to be experienced. Although the most reliable indicator for the presence and severity of pain is the patient's self-report, the decision to administer pain-relieving therapy should not be based exclusively on the patient's ability to communicate. Nonverbal, and especially noncommunicative, patients, must be carefully and repeatedly evaluated for uncontrolled pain.

Measurement of Pain

Evaluation of pain in an accurate and reliable way is a critical component of patient assessment. The visual analog pain scale and verbal numeric scales are frequently used as pain assessment tools. The visual analog pain scale is usually presented as a 10-cm line anchored by the verbal descriptors "no pain" and "worst imaginable pain." Both of these scales have been shown to have high sensitivity in the measurement of pain intensity, a reflection of their ability to detect change.[3]

Inadequate assessment of pain, lending to inadequate provision of pain relief, is a prevalent barrier to pain management in cognitively impaired adults with either acute or chronic pain. For some cognitively impaired adults, scales such as the Faces Pain Scale Revised (FPS-R), Verbal Descriptor Scale (VDS), Numeric Rating Scale (NRS), and Iowa Pain Thermometer (IPT) can be used and have been shown to have low failure rates and high preference evaluations.[4] Evaluation of pain in the severely cognitively impaired patient may be challenging. For the nonverbal patient, observation of behavior is the best approach for pain assessment.[5]

Pain assessment is especially difficult in children with cognitive impairment. The Face, Legs, Activity, Cry, Consolability (FLACC) tool assigns a value of 0 to 2 for each variable, for a total FLACC score of 0 to 10. This tool has been shown to facilitate reliable and valid observational pain assessment in children with cognitive impairment who cannot report their own pain.[6] It uses pediatric nurses' clinical judgment to determine analgesic choice based on their determination of the score.[7] The FLACC pain assessment tool is also appropriate for preverbal children experiencing pain.[7]

Acute Pain Management

Epidemiology

Approximately 72 million surgical procedures are performed in the United States annually, 3.5 million (4.9%) of which are related to the ear-nose-throat (ENT) specialty. Three million (86%) otolaryngologic procedures are performed in an ambulatory setting. The growth of ambulatory surgery has represented one of the most significant recent changes in surgical practice.[8]

Patient Satisfaction

Potential benefits of providing adequate postoperative pain relief include improved patient comfort, increased recovery speed, reduced postoperative morbidity, and shorter hospital stay.[9,10] Poorly controlled postoperative pain increases morbidity and mortality, and decreases quality of life.[11]

Factors contributing to patient satisfaction with postoperative pain management include how seriously the medical staff takes the complaint of pain, the frequency of breakthrough pain episodes, and actual pain intensity. Patient dissatisfaction is increased if a request for analgesics is followed by inadequate pain treatment. There is not a direct correlation between pain intensity and patient satisfaction. For example, patients who have the opportunity for self-administration of analgesics, as with PCA, report a feeling of autonomy and security, and improved satisfaction compared with those treated with as-needed nurse-administered analgesia.[12] Health care provider knowledge regarding dosing and duration of action of opioids also impacts the quality of postoperative pain management.[13] Therefore, patients treated with standardized pain management by an acute pain service are more likely to report being satisfied with their postoperative pain management.[14]

When evaluating the desirability of the outcome of postoperative pain management, patients place similar importance on analgesic efficacy and the type and severity of the side effects experienced. Common side effects of opioid therapy include sedation, respiratory depression, nausea or vomiting, mental confusion or dizziness, mood change, nightmares or hallucinations, and sleep disorders. Additionally, when comparing intravenous (IV) PCA in the hospital to oral opioids in the hospital versus oral opioids at home, the site of delivery, as well as mode of delivery for opioid administration appear to be of less importance to patients than pain relief and side effects. Patient variability is high regarding willingness to trade pain efficacy for different or milder side effects. These factors may assist with selecting pain treatments that match the patient's needs, thereby improving compliance and patient satisfaction, if pain treatment plans are individualized to each patient and clinical setting.[15]

Opioid Addiction versus Tolerance

A barrier to effective management of postoperative pain is the concern that opioid use will result in addiction. Approximately 10% of patients report preoperative or postoperative fear of addiction from postoperative analgesics. Physician or patient fear of opioid addiction in the acute postoperative setting may prevent needed treatment of pain. Tolerance is loss or reduction in the normal response to a drug over time. In contrast, addiction is characterized by behaviors including impaired control over drug use, compulsive use, continued use despite harm, and craving.[16] In the absence of history of addiction, it is rare to develop opioid addiction in the context of acute pain treatment.[17]

Patient-Controlled Analgesia

Parenteral administration of opioid analgesics via IV PCA is commonly used in the immediate postoperative setting. PCA benefits potentially include improved pain control and patient satisfaction, as well as improved nursing satisfaction and efficiency.[18] The degree of pain relief achievable and the amount of analgesic used with PCA, relative to conventional methods of administration (intramuscular, subcutaneous, oral, continuous, IV intermittent), is variable. Patients who are not satisfied with PCA therapy may either fear opioid overdose or addiction.[19,20] It is reasonable to assume that provision of analgesics in a dose and interval tailored to an individual's specific needs would result in good outcomes regardless of the specific technique used. The choice of opioid should be made based on the patient's clinical history and drug availability. Choice of opioid used with PCA does not appear to affect patient satisfaction.[21]

Using PCA opioids to control pain may be complicated by nausea and vomiting, pruritus, respiratory depression, sedation, confusion, urinary retention, and drug-induced ileus. These adverse effects are characteristic of opioid receptor agonists administered by any route or method of delivery. Comparing the incidence of respiratory depression with PCA and conventional opioid analgesia administration is difficult to study. This is in part due to difficulty in defining an incident of respirator depression as well as the low incidence of occurrence with a resulting need for a large number of patients to show a significant difference.[22] It should be noted that after IV administration, morphine slowly crosses the blood-brain barrier, resulting in delayed onset of analgesic and ventilatory depressant effects. This necessitates added caution when morphine is used for PCA, particularly in the setting of renal insufficiency, which prolongs morphine elimination.[23,24]

To use PCA opioid for pain control, choices must be made regarding selection of drug, demand (bolus) dose, time interval (frequency), and whether to use a basal (continuous) setting and the maximum dose allowed. Table 17-1 lists equianalgesic doses of commonly used opioid analgesics. The typical starting dose for IV PCA would be 1 mg morphine or 0.5 mg hydromorphone, with a 10-minute lockout interval between doses, and no basal infusion. Meperidine is not recommended due to risk of central nervous system toxicity from its metabolite normeperidine.[25] A lockout period helps prevent overdosage caused by overzealous demands for more analgesia. The lockout time should be long enough for the previous dose to have an effect. In view of the high intrinsic potency of fentanyl, it may be reasonable to use a longer lockout period. Regular review is needed in every case to ensure that pain relief is safe and adequate.

Basal (continuous) infusion of opioid, in addition to intermittent PCA bolus doses, is rarely indicated for acute pain in opioid-naïve patients. Use of a basal opioid infusion does not decrease the number of patient-activated PCA opioid doses, so the total dose of opioid is increased.[26] Opioid basal infusion increases risk of opioid adverse effects, including respiratory depression. In our practice, we seldom use a basal opioid infusion except when using PCA in patients with chronic pain and opioid tolerance. For example, if a patient on long-term oral opioid therapy for chronic pain requires surgery (and will not be able to take usual oral medication for some period), a basal opioid infusion may be used to administer opioid equivalent to the chronic opioid dose, with supplemental PCA bolus opioid titrated to control acute pain.

Perioperative Considerations for Older Adults

The number of surgical patients older than 65 years of age is increasing, with the fastest growing segment being those older than age 85 years. Due to increased prevalence of comorbidities, older adults have increased risk for postoperative complications and surgical mortality, mainly due to cardiac and pulmonary dysfunction.[27] Primary concerns

Table 17-1

Equianalgesic Doses of Commonly Used Opioid Analgesics

Opioid Analgesic	Parenteral Dose (mg) = 10 mg Morphine (IM/IV)	Oral Equivalent (mg)	Approximate Plasma $T_{1/2}$ Elimination in Hours
Morphine	10	30	2.9 ± 0.5
Codeine	120	200	3
Fentanyl	0.1	N/A	4
Hydrocodone	N/A	30	4.5
Hydromorphone	2	6	2.5
Oxycodone	N/A	30	3
Methadone	10	10 to 20	30 ± 19
Meperidine	100	300	3
Propoxyphene	N/A	400	14

regard perioperative effects on cardiac, pulmonary, cerebral, and cognitive function. Postoperative opioid requirements decrease with increasing age, due to age-related changes in the metabolism and clearance of these analgesics.[28] Effective analgesia promotes early ambulation, shortened hospital stay, and reduced health care costs.[29] Barriers to adequate pain control in older adults include concerns about drug overdose, adverse effects, and addiction. Also, the increased prevalence of abnormal mental status in older adults complicates perioperative care, including pain management, in this group.[30]

Perioperative Considerations for Patients Receiving Chronic Opioid Therapy

Surgical patients may vary greatly in their intraoperative and postoperative opioid requirements. Patients with a history of chronic opioid use often become opioid tolerant, creating a situation where standard treatment dosages and strategies may be ineffective. Patients with a history of chronic opioid consumption should be expected to require more opioid medication postoperatively than opioid naïve patients. Because tolerance develops to opioid adverse effects, opioid tolerant persons may experience fewer side effects, such as nausea, pruritus, and sedation. Despite receiving appropriately titrated, increased doses of opioid for acute pain, patients with a history of chronic opioid use tend to report higher pain scores.[31]

Considerations for NSAID Use for Postoperative Pain

The use of NSAIDs after surgery, such as tonsillectomy, is controversial. NSAIDs play an important role as adjuvant analgesic agents to opioids, and may improve pain control and/or reduce opioid requirements (and thereby reduce opioid adverse effects). Potential complications of NSAID use include postoperative hemorrhage secondary to impairment of platelet function, renal insufficiency, and acute gastric ulceration. Postoperative hemorrhage is a particular concern following tonsillectomy, with an incidence of 1.5% to 5%, with delayed hemorrhage (>24 hours) being more common than primary hemorrhage (<24 hours).[32] A recent study of pediatric patients undergoing tonsillectomy and adenoidectomy revealed no difference in postoperative bleeding rate in patients provided perioperative ibuprofen versus control, concluding that ibuprofen is not contraindicated in this setting and should be used in the control of postoperative pain if it is indicated.[33] Although post-tonsillectomy hemorrhage is a severe complication, if further research supports that NSAID use does not increase the risk of hemorrhage in this setting, more widespread use of NSAIDs would be indicated to improve postoperative pain control.

Preemptive Analgesia

Preemptive analgesia is pain treatment given before tissue injury to prevent establishment of altered central processing of afferent input from sites of injury, and thereby prevent development of pain hypersensitivity. Preemptive analgesia may reduce the magnitude and duration of postoperative pain. Emphasizing the importance of measures to reduce postoperative pain is the observation that patients with high intensity of acute postoperative pain scores demonstrate a higher risk of developing a chronic pain state.[34] Preemptive analgesia can be established with local infiltration of incision sites, peripheral nerve block, or central neuraxial blockade.

Examination of preincisional and postincisional analgesic medication regimens reveals mixed results. Pharmacologic agents, such as NSAIDs, opioids, N-methyl-D-aspartate (NMDA) antagonists, and α_2-receptor antagonists are effective at synergistically decreasing postoperative pain.[35] However, preemptive administration of these pharmacologic agents is not of increased analgesic benefit when compared with postincisional administration.[34] Gabapentin, which has been used extensively in the treatment of neuropathic pain, is a useful adjunct for the management of postoperative pain.[36]

Preemptive administration of peripheral local anesthetics does appear to offer an advantage over postincisional administration. Peripheral afferent neuronal signaling, which occurs during surgery, produces central nervous system excitability. When done before initiating surgery, wound infiltration with bupivacaine, in comparison to saline, has been shown to reduce plasma β-endorphin levels significantly in the first 48 hours postoperatively, indicating blockade of nociceptor input by the local anesthetic. When preincisional local anesthetic is used, lower reported pain scores and decreased self-administered pain medications by patients is also observed.[37] Preincisional infiltration of local anesthetic and general anesthesia for pediatric tonsillectomy reduces post-tonsillectomy pain and provides a more rapid return to activity compared with use of general anesthesia alone.[38]

Perioperative Regional Anesthesia

Perioperative regional anesthetic techniques may allow for superior postoperative pain control compared with the use of systemic opioids and adjuvant pain medications alone, but regional anesthesia is not used widely for otolaryngologic surgery. Regional anesthesia is a potentially important therapy in otolaryngology because it may provide superior pain control, enhanced recovery, and earlier discharge, as in other areas of surgical practice.[39] Examples of head and neck procedures for which regional blocks can be used, perhaps in conjunction with general anesthesia, include myringotomy and tympanostomy

procedures, sinus surgery, facial plastic surgery, thyroidectomy, and parathyroidectomy.[40]

The trigeminal nerve, the fifth cranial nerve, supplies sensory innervation to the face as well as motor function to the muscles of mastication. It originates at the gasserian ganglion, also referred to as the semilunar ganglion, and is composed of three major branches: ophthalmic (V1) and maxillary (V2), sensory nerves, and mandibular (V3). Branches of the trigeminal nerve are potential targets for multiple regional anesthetic techniques.[41]

The ophthalmic division (V1) enters the orbit through the superior orbital fissure and branches into the supraorbital and supratrochlear nerves as well as the nasociliary nerve. The nasociliary branch carries sensory input to the mucous membrane of the nasal cavity as well as the frontal, sphenoidal, and ethmoidal sinuses. Although blockade of the ophthalmic division of the trigeminal nerve can be useful in sinus surgery, its proximity to vascular structures and other nerves requires a high level experience for its performance due to the increased risk of complications.[42]

The maxillary nerve (V2), called the infraorbital nerve once it reaches the infraorbital fossa, emerges from the infraorbital foramen. Branches of the nerve provide sensory innervation to the lower eyelid and upper lip, the teeth and gums, the nasal mucosa, the palate, and roof of the mouth. The infraorbital nerve also combines with the nasociliary branch of V1 to supply the maxillary, ethmoid, and sphenoid sinuses, as well as the nasal mucosa. The infraorbital foramen is located in a line between the pupil and the corner of the mouth just below the infraorbital rim.[42] The foramen can be approached from an intraoral approach and an extraoral approach.[42]

Nerve innervation of the palate is mainly derived from sphenopalatine branches of the maxillary nerve, which are distributed to the roof of the mouth, soft palate, tonsil, and membrane lining of the nasal cavity. The three main divisions of the nerve, the anterior, middle, and posterior branches, supply the gums and glands of the hard palate, the uvula, the tonsils, and the soft palate.[41]

Mandibular (V3) nerve blocks performed before bilateral mandibular osteotomy for oropharyngeal carcinoma surgery decreases both intraoperative and postoperative opioid consumption.[43] A branch of the mandibular nerve, the mental nerve, emerges at the mental foramen and communicates with the facial nerve. It emerges from the mental foramen, providing sensory input from the skin of the chin and mucous membrane of the lower lip. Blockade of the mental nerve is useful for surgery involving the lower lip and skin of the chin.[41]

The auricular branch of the vagus nerve joins the posterior auricular nerve, and innervates the skin of posterior auricula and external acoustic meatus. This nerve gives sensory innervation to the external auditory meatus and inferior portion of the tympanic membrane, making its blockade useful for myringotomy and tympanostomy procedures. The nerve passes through the tympanomastoid fissure, between the temporal bone and mastoid process. Blockade of the nerve can be performed by pulling the tragus forward and injecting local anesthetic posterior to the tragus.[41]

The cervical plexus is formed by the ventral rami of cervical nerves 1 through 4. The lesser occipital, the great auricular, the transverse cervical, and the supraclavicular nerves comprise the branches of the cervical plexus. Superficial cervical plexus block is useful for tympanomastoid surgery, otoplasty, and cochlear implant, or bilateral nerve block can be used for thyroidectomy.[44]

In some instances, cervical epidural anesthesia can be useful for neck surgery, where it has been described as a primary anesthetic technique for thyroidectomy.[45] Cervical epidural anesthesia typically results in blockade of the superficial cervical plexus (C1-C4) and brachial plexus (C5-T2). Hemodynamics and respiratory rate must be closely monitored because hypotension and ventilatory failure can develop. Epidural analgesia and general anesthesia can be combined to minimize postoperative complications and improve postoperative pain control. A meta-analysis of eight trials comparing preemptive versus postincisional continuous epidural regimens in thoracic and abdominal surgeries concluded that epidural analgesia significantly decreased postoperative pain, but no overall improvement in pain relief was observed with preemptive continuous epidural analgesia when compared with epidural infusion initiated postoperatively.[34] Only limited data are available regarding the perioperative use of epidurals in otolaryngology, and the efficacy of epidural analgesia for acute pain control in this setting needs further evaluation.

Chronic Pain

Chronic pain is one of the leading causes of health care consumption and worker disability in the developed world.[46,47] Uncontrolled postoperative pain can negatively impact surgical recovery and may persist beyond wound healing due to induced changes in the central nervous system.[48] It is important not only to treat pain effectively in the postoperative period, but also to be vigilant for the development of chronic pain afterward.[49,50] Chronic pain should be treated with analgesics and other therapies as needed. When chronic pain persists, referral to a pain management specialist may be appropriate.

Pain Definition and Types

Chronic pain may persist indefinitely, especially when the etiology is unknown or definitive treatment is unavailable. Chronic pain may or may not be associated with a long-term medical illness and appropriate therapy may differ depending upon this distinction. Because of its emotional component, chronic pain is often associated with psychological comorbidities, including depression.[51] Whether depression precedes chronic pain or chronic pain precedes depression is controversial and may vary, but the relationship between the two calls for appropriate treatment of both conditions.

Chronic pain is often a source of frustration for many medical professionals because it may be refractory to treatment. Complicating the issue is the concern of opioid addiction or abuse. Seeking drugs for pain relief is not the same as addiction. The American Pain Society defines opioid addiction as "a pattern of compulsive drug use characterized by continued craving for an opioid and the need to use it for effects other than pain relief." Furthermore, this compulsive craving and seeking of a drug often persists despite known negative consequences. However, the taking of opioids for pain relief does not constitute addiction, regardless of the dose or duration of use. Well-established literature suggests that addiction results from the use of opioids for pain relief in very few patients.[52-54]

Responding to reports of inadequate pain control in the 1980s, the World Health Organization (WHO) developed a stepwise approach to treatment of cancer pain. The steps of this analgesic ladder advocate choosing analgesics primarily based upon pain intensity. According to the ladder, a patient with mild pain should be started on acetaminophen, aspirin, or one of the NSAIDs. Someone with moderate pain should receive low potency opioids (e.g., codeine, hydrocodone), whereas those with severe pain receive potent opioids (e.g., morphine, hydromorphone). Adjuvant drugs (e.g., tricyclic antidepressants, anticonvulsants) should be added to the primary analgesics at each step of the ladder as needed.[55]

The WHO approach also provides a five-component framework for administering analgesics. First, oral administration of analgesics is preferred (whenever feasible) because oral administration is effective, inexpensive, and easily adjusted. Second, analgesics should be given on a routine schedule, using immediate-release (IR) formulations and/or sustained-release (SR) preparations, so that pain relief is continuous. Third, the severity of the pain and its responsiveness to medication should dictate which part of the analgesic ladder should be applied. Fourth, analgesics must be appropriately titrated to each patient in order to achieve optimal pain relief. Fifth, one must vigilantly assess the degree of pain relief both before and after implementing a new pain regimen, and carefully monitor for adverse effects.[2,55,56]

The WHO three-step analgesic ladder has been extensively validated in several studies over the past 20 years and found to be extremely effective in cancer pain management.[2,56] In one 10-year prospective study involving more than 2000 patients, 76% of patients reported good pain relief from analgesics prescribed in accordance with the WHO guidelines.[2,56] Furthermore, these patients experienced a low rate of analgesic-associated complications. Another study involving 174 patients showed that oral drug therapy successfully managed pain in 89% of patients. Greater than 80% noted their pain to range

between "none" and "moderate" with implementation of the WHO guidelines.[2,57]

Despite the efficacy of the WHO guidelines for cancer pain in general, some patients continue to have uncontrolled pain even with optimal use of systemic analgesics. When cancer pain is not controlled with systemic analgesics, a fourth step should be considered to extend the WHO ladder to encompass interventional pain therapies, such as intrathecal catheters with indwelling pumps,[58] and techniques of neural blockade. For head and neck cancers this may include such interventions as trigeminal nerve blockade with local anesthetic or radiofrequency ablation. Other interventions include occipital nerve block, glossopharyngeal block, and sphenopalatine block, depending upon the location of pain.[58]

Even though the WHO ladder has been validated in cancer pain, it has no such validation in noncancer settings.[59] Recently, several guidelines have been proposed for the use of opioids in chronic noncancer pain. These guidelines note that opioid therapy may prove beneficial for some patients and that there exists considerable personal and societal costs of chronic noncancer pain.[59,60] In accordance with good medical practice, such guidelines dictate that opioid therapy should be tailored to the individual patient, and many suggest that opioid should only be prescribed after other therapies have failed.[61] Opioid treatment should include thorough patient evaluation, careful formulation, and clear documentation of treatment objectives and plans, and periodic follow-up to assess treatment safety, efficacy, and patient compliance. One should carefully consider psychiatric consultation for patients with comorbid psychiatric disorders or substance abuse consultation when there is a high index of suspicion for substance abuse. Further studies are needed to substantiate guidelines for opioid use in chronic noncancer pain and to provide guidance regarding the key issue of patient selection.[60-64]

Considerable controversy abounds as to whether or not long-term opioid therapy is appropriate in chronic noncancer pain.[62,65] Beyond the concerns of addiction or diversion, there are considerable side effects to long-term opioid use such as hypogonadism, decreased immune function, constipation, tolerance, dependence, and opioid-induced hyperalgesia.[66] Furthermore, one study looking specifically at chronic facial pain found 75% of patients failed to respond to opioid therapy and many who took chronic opioids had functional decline.[67] Because of the adverse effects of opioid therapy over months to years, other treatment modalities such as anticonvulsants, antidepressants, NSAIDs, or interventional therapies may be preferable.[59,61]

First line agents for chronic pain have been in continuous flux over the last few years. Increased scrutiny has been given to the safety of COX-2 selective and nonselective NSAIDs, including removal of the most specific COX-2 selective inhibitors from the market secondary to concerns for increased cardiovascular risk.[68]

Not only NSAIDs but also most analgesics have a ceiling of efficacy and/or safety. One way to minimize toxicity is to combine lower doses of agents from different classes of drugs to obtain an additive or even synergistic effect while staying within the tolerability limits of each agent. An example of this approach is to use acetaminophen with tramadol. Whereas acetaminophen works centrally as a COX inhibitor, tramadol works both as a partial agonist at the opioid receptors as well as a serotonin and norepinephrine reuptake inhibitor. This is a logical combination that takes advantage of the agents' different mechanisms of action and different onset and duration of action. These agents have efficacy not only in the control of acute pain but also subacute and chronic pain. Combination of tramadol and acetaminophen has been effective in the management of many chronic pain states with associated functional improvement for up to 2 years of treatment. In some settings, this combination offers an effective, safer alternative to NSAIDs, because it lacks typical adverse effects associated with NSAIDs.[69-71]

Adjuvant Analgesics

Anticonvulsant Agents

There is strong evidence for anticonvulsant therapy in the management of neuropathic pain.[72] While carbamazepine has been used extensively in the past for chronic neuropathic pain, newer anticonvulsant drugs, specifically gabapentin and pregabalin, have moved to the forefront in the treatment of neuropathic pain, with evidence supporting the efficacy and safety of these newer agents.[51,72]

Anticonvulsants have a variety of mechanisms of action, working both centrally as well as peripherally by inhibiting excitatory transmission via the NMDA receptor, enhancing GABA mediated inhibition, and antagonizing sodium channel activation. These multiple modes of action allow anticonvulsants to treat neuropathic pain from a number of mechanisms. Different mechanisms may account for why some patients respond to a particular agent and not to others. Recent studies suggest that the newer anticonvulsants have similar tolerability and efficacy as antidepressants in the treatment of neuropathic pain.[73]

Currently, gabapentin is the most commonly used drug for neuropathic pain. It is thought to antagonize voltage-gated calcium channels in afferent neurons and also to centrally modulate GABA activity.[74] Several trials have shown its efficacy to approach that of amitriptyline in the treatment of diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).[75-77] A common and well-tolerated dosing strategy starts with one 300-mg tablet nightly, and increasing by one tablet every 3 to 7 days until the dose of 300 mg three times per day is reached. Adjustment is continued in 300-mg increments until the patient experiences either acceptable relief or intolerable adverse effects. Maximal benefit at a total dose of 3600 mg daily has been suggested. Fatigue, sedation, nausea, and loss of coordination are the most common adverse effects, but temporarily suspending the dose escalation may minimize the development of these adverse effects. Total daily dose of 1800 to 3600 mg of gabapentin is usually well tolerated.[78] Extremely sensitive patients, such as older adults, should receive more conservative dosing, whereas those with chronic renal insufficiency require dosing based on creatinine clearance.

Another anticonvulsant increasingly used for pain control is pregabalin (isobutyl-GABA). This agent works by mechanisms very similar to those of gabapentin, but tolerability or lack thereof to one of these medications does not necessarily indicate similar results with the other. No head-to-head comparison of gabapentin and pregabalin has been published, but both have similar efficacy in the treatment of DPN and PHN.[79]

Phenytoin, an older anticonvulsant, also suppresses ectopic neural discharges but does so through inhibition of voltage-gated sodium channels and suppression of the release of glutamate.[80] Phenytoin is considered an acceptable second-line agent in patients with trigeminal neuralgia, but the paucity of evidence in the treatment of other neuropathic conditions, combined with the need for serum monitoring and noted adverse effects, have decreased its use, especially since the introduction of safer anticonvulsants.[76,81,82]

Carbamazepine, which has a similar structure to the older tricyclic antidepressants (TCAs), is mechanistically similar to phenytoin. It has shown efficacy over placebo in treatment of PHN and DPN and has remarkable efficacy in the management of trigeminal neuralgia.[51,80] During the initial period of therapy, adverse effects such as hyponatremia, aplastic anemia, and leukopenia may develop. Baseline hematologic and electrolyte laboratory values should be checked and periodically repeated throughout treatment.[80] Oxcarbazepine, a carbamazepine analogue, may have fewer drug interactions and fewer adverse effects than carbamazepine.[82] Oxcarbazepine, like carbamazepine, has shown efficacy against the induction of mechanical hyperalgesia and allodynia in experimental models[80] and has shown efficacy in the treatment of PHN and DPN.[83]

Lamotrigine, a sodium channel inhibitor, works by inhibiting glutamate release. Studies have shown lamotrigine to be effective in DPN, HIV-related neuropathic pain, and central mediated pain. Caution should be used while adjusting lamotrigine because serious rash may occur and its use has rarely been associated with Stevens-Johnson syndrome.[84]

Anecdotal reports suggest that the antiepileptic drugs zonisamide, valproate, and tiagabine may be useful as single agents for neuropathic pain in selected patients or as additions to first-line agents.[85,86] Caution also should be used with these medications, in that zonisamide, like lamotrigine, has been associated with Stevens-Johnson syndrome, and tiagabine has been associated with new onset of seizures.[87,88] Addition-

Table 17-2

Anticonvulsants Used in the Treatment of Neuropathic Pain

Drug	Mechanism of Action	Pharmacokinetics	Adverse Effect	Monitoring
Carbamazepine	Blocks Na^+ and Ca^{2+} channels; modulates descending inhibition	Metabolism: hepatic Elimination: hepatic	Hepatotoxicity, diplopia, nystagmus, memory loss, drowsiness, nausea, gastrointestinal upset	Complete blood count (CBC), platelets, liver function tests (LFTs), electrolytes, thyroid-stimulating hormone
Gabapentin	Antagonizes voltage-gated Ca^{2+} channels	Elimination: renal No alteration of hepatic metabolism of other medications	Edema, somnolence, dizziness, weight fatigue gain	Serum creatinine
Lamotrigine	Blockade of voltage-gated Na^+ and Ca^{2+} channels	Metabolism: hepatic Elimination: hepatic	Rash (5% to 10%), Stevens-Johnson syndrome, hepatic/renal failure, insomnia, nystagmus	CBC, LFT, serum creatinine
Levetiracetam	Unknown	Elimination: renal No alteration of hepatic metabolism of other medications	Asthenia, behavior changes, fatigue, depression	CBC, serum creatinine
Oxcarbazepine	Blocks Na^+ channel	Metabolism: hepatic Elimination: hepatic and renal	Hyponatremia, rash, sedation, gastrointestinal upset, diplopia	LFTs, electrolytes
Pregabalin	Antagonizes voltage-gated Ca^{2+} channels (at α_2-δ subunit)	Elimination: renal No alteration of hepatic metabolism of other medications	Weight gain, fatigue, edema, somnolence, dizziness	Serum creatinine
Topiramate	Na^+ and Ca^{2+} channel blockade, GABA potentiation, glutamate blockage	Metabolism: hepatic Elimination: renal	Open angle glaucoma, nephrolithiasis (1% to 5%), dizziness, cognitive dysfunction, weight loss, paresthesias	Serum creatinine
Zonisamide (sulfonamide derivative)	Blocks Na^+ and T-type Ca^{2+} channel	Metabolism: hepatic Elimination: hepatic	Stevens-Johnson syndrome, rash, nephrolithiasis (3%), hyperthermia, decreased white blood cells, photosensitivity, weight loss, dizziness, fatigue	CBC, LFTs, serum creatinine

ally, valproate has been rarely associated with fatal hepatotoxicity.[89] The use of potentially toxic drugs may be more easily justified in the control of seizures than in the treatment of neuropathic pain (Table 17-2).

Antidepressants

Antidepressants are commonly used in the treatment of neuropathic pain. These medications work not only by treating depression which facilitates pain signal transmission, but also decrease the reuptake of neurotransmitters (dopamine, norepinephrine, and/or serotonin), thereby potentially inhibiting pain neurotransmission.[81] TCAs, such as amitriptyline, have multiple mechanisms of action and have been used with some success for neuropathic pain. Because of potential TCA adverse effects (anticholinergic effects, effects on cardiac conduction and intraocular pressure, and increased orthostatic hypotension), these drugs must be used with caution. More specific serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine) have efficacy in management of neuropathic pain and may be better tolerated than TCAs, but there are few data comparing efficacy of these newer agents with TCAs. Agents with adrenergic mechanism (or mixed serotonergic and adrenergic) such as TCAs, or duloxetine and venlafaxine, are considered to be more effective analgesics than selective serotonin reuptake inhibitors (fluoxetine, citalopram).[90,91]

Most of the adverse effects associated with TCAs, such as orthostatic hypotension, cardiac conduction disturbances, thrombocytopenia, agranulocytosis, and acute angle-closure glaucoma, are caused by inhibition of H_1-histaminergic receptors.[92] Caution should be exercised in treating patients with comorbid depression because the TCAs are more lethal in overdose than other antidepressants. The secondary amines (e.g., amitriptyline, imipramine) are often preferred over the tertiary amines because they tend to have similar efficacy and fewer side effects.[93] Tricyclics are usually started at low doses and increased slowly over several days until the patient notes either acceptable benefit or unacceptable adverse effects. Comorbid conditions and a high variability in an individual's response makes careful titration necessary. After the daily dosage exceeds 100 mg, serum drug levels should be checked even if no adverse effects have been noticed. Patients with nocturnal pain and insomnia may benefit from taking these medications in the evening. Every patient should be educated to look for common adverse

effects such as somnolence, decreased salivation, hyperphagia, constipation, and urinary retention. Close monitoring and open communication allows better vigilance for adverse effects and appropriate interventions such as concomitant use of sialagogues, stool softeners, or in severe cases discontinuation of the medication.[80] Antidepressants are too often discontinued without a thorough trial, secondary to poor management of adverse effects and/or inadequate dosing.[93,94]

Several different antidepressants have been recommended for severe neuropathic pain. While citalopram and paroxetine have shown superiority to placebo in trials of DPN, most clinicians agree that analgesic efficacy of these agents is suboptimal and generally use other agents.[91,95] Bupropion has some efficacy in the treatment of pain and has the added benefits of decreasing nicotine dependence and generally good tolerability.[96] Newer antidepressants such as venlafaxine inhibit norepinephrine and serotonin reuptake but appear to have less adverse effects than the TCAs. Venlafaxine has been shown to approach the efficacy of the TCA imipramine in treatment of neuropathic pain associated with painful polyneuropathy with fewer side effects.[97] Duloxetine, another serotonin and norepinephrine reuptake inhibitor, has efficacy in treatment of pain caused by DPN as well as fibromyalgia, and has become one of the most commonly used antidepressants for pain control (Table 17-3).[98]

Interventional Techniques

Pain related to head and neck cancer is often challenging to manage due to the erosive nature of the malignancy, the dense sensory innervation of this area, and local anatomic distortions from surgery and/or radiation. Although systemic analgesics control most head and neck cancer pain, neural blockade or other techniques may be necessary for refractory pain.[99,100] Careful assessment of the nature and location of the pain is critical to choosing an appropriate intervention. (See Table 17-4 for a list of blocks of the head and neck and their indications.)

Local anesthetics, such as lidocaine or bupivacaine, block sodium entry into axons, effectively halting the propagation of axonal action potentials. These agents can work both at the central and peripheral levels, but need to be injected close to the neural target. Lidocaine may be used intravenously to treat neuropathic pain, but extreme caution must be used to avoid seizures and cardiac toxicity. Inadvertent intravenous injection of local anesthetic during neural blockade should be avoided with frequent aspiration of needle and vigilant monitoring for signs of cardiac or neurotoxicity. Ropivacaine, a newer local anesthetic, may have less cardiac toxicity than bupivacaine. In addition to their effect at the axon, local anesthetics also prevent axonal sprouting and have effects on G-protein-coupled receptors, as well as on the conductance of other ions beyond sodium that may have important roles in the modulation of pain.[101]

Neurolytic blocks, phenol or alcohol, are sometimes indicated for treatment of incapacitating chronic pain in association with end-stage malignancy.[102] Neurolytic blocks in the head and neck can be done percutaneously or endoscopically.[99] They are rarely applied in the head and neck, due to risk of significant complications related to close proximity of targeted nerves to other critical structures. In addition, if tar-

Table 17-3

Antidepressants Used in the Treatment of Neuropathic Pain

Drug	Mechanism of Action	Pharmacokinetics	Adverse Reactions	Monitoring
Amitriptyline	Tricyclic antidepressant inhibition of serotonin, norepinephrine, and dopamine	Metabolism: hepatic Elimination: hepatic and renal	Urinary retention, xerostomia, orthostasis, blurry vision, weight gain, constipation, sedation	Serum levels may need to be monitored at higher dosing levels or in those at higher risk of altered metabolism such as older adults
Bupropion	Selective reuptake inhibition of dopamine and norepinephrine	Metabolism: hepatic Elimination: hepatic and renal	Seizures, insomnia, anxiety	May consider closely monitoring renal and hepatic function in patients with preexisting impaired function.
Duloxetine	Selective reuptake inhibition of serotonin and norepinephrine	Metabolism: hepatic Elimination: renal and hepatic	Nausea, somnolence, constipation, dry mouth, dizziness, sweating, decreased appetite	
Imipramine	Tricyclic antidepressant inhibition of serotonin, norepinephrine, and dopamine	Metabolism: hepatic Elimination: hepatic and renal	Dry mouth, tachycardia, orthostatic hypotension, weight gain, constipation, urinary retention, blurred vision, sexual dysfunction; most side effects are better tolerated than with amitriptyline	
Nortriptyline	Tricyclic antidepressant inhibition of serotonin, norepinephrine, and dopamine	Metabolism: hepatic Elimination: renal	Anxiety, urinary retention, orthostasis, weight gain, blurry vision, constipation, sedation; most side effects are less pronounced than with amitriptyline	Serum levels may need to be monitored at higher dosing levels
Venlafaxine	Selective reuptake inhibition of serotonin and norepinephrine	Metabolism: hepatic Elimination: renal	Insomnia, sexual dysfunction, sweating, headache, anorexia, hypertension	

Table 17-4

Head and Neck Nerve Blocks and Indications

Trigeminal gasserian ganglion block	Facial cancer pain to the distribution of the V2 and V3 divisions of the trigeminal nerve
Mandibular nerve block	Painful malignancy involving the jaw and anterior two thirds of tongue
Maxillary nerve	Painful tumors of the middle third of face (maxilla, cheek, nasal cavity, and hard palate)
Glossopharyngeal nerve	Localized pain arising from the base of the tongue, soft palate, or nasopharynx.

geted nerves are close to the skin, cutaneous ulceration may complicate neurolytic injections.

Neuroablative lesions in the head and neck must be carried out cautiously to avoid increasing patient morbidity through unintended sensory or motor deficits. A local anesthetic trial is often used to aid in the determination of the extent of sensory or motor deficit and success expected from neurolysis. Peripheral neurolysis in the head and neck may be associated with the delayed development of neuritis or deafferentation pain, as well as the risk of inadvertent trauma to nearby essential structures. Therefore one should only consider these blocks in patients with intractable pain and short life expectancy.[99]

Radiofrequency lesioning techniques, which may provide better control of lesion distribution and greater analgesic efficacy, have largely replaced neurolytic blockade of the gasserian (trigeminal) ganglion.[58] Radiofrequency neurotomy is the destruction of neural tissue by using heat generated by a high-frequency electrical current.[58,103,104] Precisely controlled radiofrequency energy is delivered by a wire probe placed adjacent to the neural tissue to be destroyed. Because radiofrequency lesions are limited in size, the area of tissue damage may be more predictable than with neurolytic injections. When a focused lesion is needed, as is the case in the treatment of trigeminal neuralgia, radiofrequency has clear advantages over neurolytic injection techniques; however, injection techniques using chemical agents continue to be the neurolytic technique of choice when the tissue target is large and diffuse (e.g., celiac plexus).

Radiofrequency has been used for pain control in many clinical settings, including trigeminal ganglion ablation, spinal facet denervation, dorsal root ganglion ablation, and sympathetic chain lesioning at different levels (stellate, thoracic and lumbar sympathetic ganglia). There is extensive experience with radiofrequency for trigeminal neuralgia in patients not responding to appropriate analgesics. Radiofrequency of somatic nerves with cutaneous sensation may result in the delayed generation of neuropathic pain (anesthesia dolorosa) and thus is rarely used except in patients with advanced cancer pain or other terminal illness.[58]

Despite the best efforts of internists, surgeons, and pain specialists, some patients will continue to suffer from uncontrolled pain. For these patients, chronic pain may become a disease itself with a negative impact on mood and function for both the patient and his or her family. In these cases, it is important not to become so focused on the pathology that the individual is forgotten. There is a large body of evidence and growing consensus within the professional community that an appropriate referral to a pain psychologist may help the patient to acquire management skills that aid with symptoms and allow for a more active and meaningful lifestyle.[105]

Headache

Headaches are a nearly universal human experience, affecting most people at some point in their life. There is a 78% lifetime prevalence of tension-type headache and a 16% lifetime prevalence of migraine.[106] Headaches may be secondary, due to an identified underlying abnormality, or primary in nature. Although tension-type headaches are the most common primary headache disorder in the general population, migraine is the most common primary headache type leading to physician visits.[107] Primary headaches may be considered episodic or chronic, terms used in the headache field to refer to the frequency of headaches (tension-type, migraine) or the duration of headaches without remission (cluster, new-daily persistent headache, paroxysmal hemicrania, hemicrania continua).

The initial evaluation of the headache patient requires careful history, physical, and neurologic examinations. During these evaluations, the clinician must search for headache "red flags," findings that increase the suspicion for a secondary headache disorder. Suspicious findings in a headache history include, but are not limited to:

- New onset of headaches
- Preceding trauma
- Positional headaches (initiated by standing, lying down, bending)
- Systemic symptoms (fever, chills, weight loss)
- Systemic illness (immunosuppression, hypercoagulable state, cancer)
- Rapid onset of headache ("thunderclap headache")
- Older age at onset
- Focal neurologic symptoms (not consistent with typical migraine aura)
- Headaches due to transient increases in intracranial pressure (coughing, sneezing, Valsalva)

In addition to usual physical and neurologic examinations, patients with headache should also have examination of the eye, temporomandibular joint, cerebrovasculature (temporal arteries, carotid bruits), cervical paraspinal and trapezius muscles, and sinuses. Abnormalities on examination should not be attributed to a primary headache disorder without careful consideration of possible secondary causes. Figure 17-1 is a flow diagram outlining the basic approach to headache diagnosis.

The presence of worrisome features in the headache history or examination raises the suspicion for a secondary headache disorder, which may be clarified with diagnostic tests. Generally, a patient without historical or examination red flags does not require additional diagnostic testing. When a secondary headache is suspected, however, testing must be individualized but may include blood work (complete blood count, complete metabolic panel, erythrocyte sedimentation rate, thyroid function tests, tests for autoimmune disorders, others), brain imaging (computed tomography, magnetic resonance imaging), angiography (conventional catheter, magnetic resonance, computed tomography), cerebrospinal fluid evaluation (including measurement of opening pressure), and cervical spine imaging, among others.

Migraine

Migraine headaches affect one in six people worldwide[106] and result in significant pain, disability, and reductions in quality of life.[108] Chronic migraine, defined as having migraine headaches on at least 15 days per month, affects 3% to 4% of the population and is considered by the WHO to be one of the most disabling illnesses.[109,110]

Migraine is defined as[111]:

- Moderate to severe pain
- Duration of 4 to 72 hours
- Unilateral or bilateral

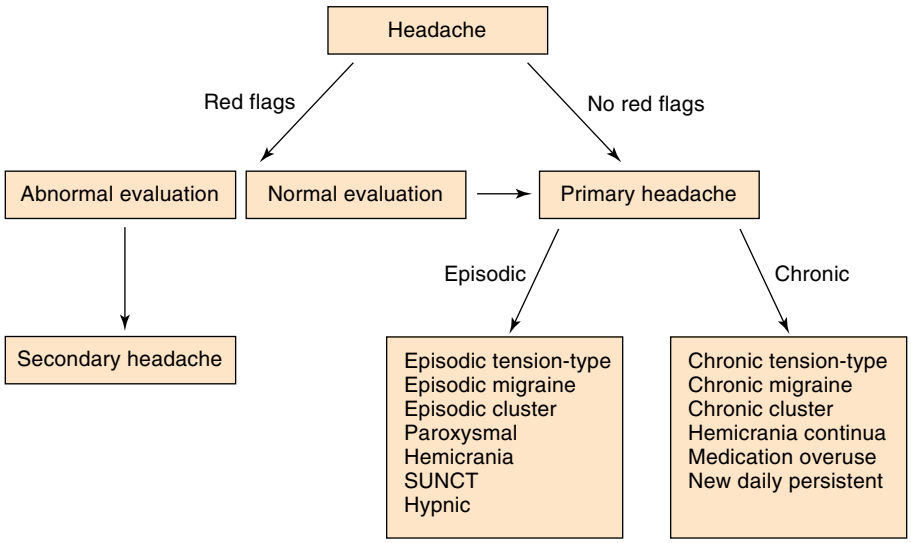

Figure 17-1. Basic approach to headache diagnosis. "Red flags" refers to worrisome features in the headache or medical history, or abnormalities on general physical or neurologic examination. SUNCT, short-lasting *u*nilateral *n*euralgiform headache with *c*onjunctival injection and *t*earing.

- Associated with photophobia/phonophobia and/or nausea/vomiting
- Worsened by routine physical activities
- Throbbing or pulsating in quality

Approximately one-third of patients with migraine have a preceding aura.[112] Migraine aura develops slowly over 5 to 20 minutes and resolves within 60 minutes. This slow progression and timing of resolution helps differentiate symptoms of migraine aura from stroke symptoms. Visual symptoms are the most common and are often positive symptoms (scintillations) followed by negative symptoms (scotoma). Sensory symptoms are second most common and typically consist of paresthesias in the hand of one extremity with ipsilateral progression up the arm and eventually to the lower face. Less common aura symptoms may include numbness, weakness, speech changes, dizziness, gait instability, ataxia, and blindness. However, when confronted with these less common symptoms, suspicion for a secondary headache or an uncommon migraine syndrome (hemiplegic migraine, basilar migraine, retinal migraine) is high.

The treatment of migraine may include acute headache medications as well as prophylactic therapy. All patients should have a method of treating individual headaches. Prophylactic measures may be initiated for multiple indications, including frequent headaches, insufficient response to acute headache medications, prolonged headaches, significant impact on quality of life, significant headache-related disability, and bothersome associated neurologic features (such as may be seen with hemiplegic or basilar migraine).[113]

The acute therapy of migraine is heavily reliant on medications. The triptans are arguably the most effective therapy for acute headache relief in the outpatient setting. There are seven different triptans available that allow for four different methods of administration (oral tablet, orally dissolving tablet, nasal spray, injection). Although there are perhaps subtle differences between the triptans (side effects, elimination half-life, recurrence rate, overall efficacy), they have more similarities than differences.[114] There are limitations to the amount of triptan that can be safely used, and there are multiple contraindications to their use, mostly involving vascular diseases and their risk factors. Other outpatient acute headache therapies include dihydroergotamine mesylate nasal spray (DHE), NSAIDs, antiemetics, and opioid analgesics (opioids should rarely be used for the treatment of migraine headache). Regardless of therapy, it is important to instruct patients to treat early after the onset of migraine. When migraine is allowed to persist and sensitization occurs, therapies for acute onset are much less successful.[115]

Prophylactic therapy for migraine may consist of headache trigger avoidance, daily medication, physical therapy, and biobehavioral therapy. Most medications used for the prophylaxis of migraine are either antidepressants (TCAs), blood pressure medications (beta-blockers, calcium channel blockers), or antiepileptics (topiramate, valproic acid). Other frequently used therapies include riboflavin, magnesium, feverfew, and butterbur. Botulinum toxin injections are increasingly being used, but the exact safety and efficacy is yet to be determined conclusively.[116] Prophylactic therapy is considered successful if there is at least a 50% reduction in headache frequency. Physical therapy, biofeedback, relaxation therapy, and acupuncture may be helpful for the individual migraine patient as well.

Tension-Type Headache

Tension-type headache (TTH) is the most common type of headache and is estimated to affect nearly 80% of all people at some point in their life.[106] The vast majority of patients with TTH do not seek medical care.

TTHs are most commonly bilateral, of a pressure quality, mild to moderate in severity, and not made worse by routine activities.[111] They are not associated with nausea or vomiting, and although there can be mild photophobia or phonophobia (not both), these sensitivities are not as prominent as seen in migraine. TTHs endure from 30 minutes to 7 days. If headaches occur on more than 15 days per month, chronic TTH is diagnosed. TTH may be associated with pericranial tenderness to palpation.

Over-the-counter NSAIDs or acetaminophen is usually adequate for acute TTH therapy. Patients with frequent TTH may require prophylactic measures such as physical therapy, biobehavioral therapy, and daily preventive medications.

Cluster Headache

Cluster headache is one of the trigeminal autonomic cephalgias, a group of headaches also including paroxysmal hemicrania, and *s*hort-lasting *u*nilateral *n*euralgiform headache with *c*onjunctival injection and *t*earing (SUNCT). Cluster headache is 4 times more common in men than women.[117]

Cluster headaches are severe headaches that occur in or around the eye and temporal region.[111] The pain is accompanied by ipsilateral signs of autonomic nervous system activation, which include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, sweating on the head or face, miosis, and ptosis. In contrast to the patient with migraine, cluster patients tend to be restless during an attack, often pacing the floor or displaying other agitated behavior.

Individual headaches last 15 minutes to 2 hours and occur once every other day up to 8 times per day. Individual headaches may occur with circadian periodicity. Cluster headaches tend to occur in periods lasting from weeks to months separated by periods of remission lasting months to years. Cluster periods may begin at the same time of the year for an individual patient. If the cluster period lasts for more than 1 year without remission, a diagnosis of chronic cluster headache is made.

The treatment of cluster headache depends upon acute and prophylactic headache measures as well as attempts to shorten or abort cluster periods. Acute therapies include triptans, DHE, and inhalation of oxygen. Oxygen is effective in the majority of patients and may be considered the optimal therapy given its relative safety.[118] Oxygen is administered at high flow (8 to 10 L/min) by mask. Triptans generally must be given as injections or by nasal spray to achieve benefit from timely therapeutic onset.

Prophylactic options for cluster headache include verapamil, lithium, melatonin, and methysergide. There is a potential role for valproate, topiramate, gabapentin, testosterone, and dopamine agonists. Verapamil is considered the mainstay of prophylactic therapy.[119,120] Electrocardiographic monitoring is required when treating patients with verapamil.[121] In patients who have significant periods of headache remission, prophylactics are initiated when the cluster period begins and then discontinued after the patient has remained in remission for several weeks.

Steroids may be used in an attempt to shorten cluster periods and to provide temporary relief from headaches. Occipital nerve blockade has also shown promise in this regard.[122]

Hemicrania Continua

Hemicrania continua is a strictly unilateral headache that is continuous without pain-free intervals.[111] It is moderate in intensity but with superimposed exacerbations of pain into the severe range. During these exacerbations, there is presence of ipsilateral autonomic activation which may include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, and miosis. It is essential to recognize this headache type since it is completely responsive to indomethacin.

The treatment of hemicrania continua is indomethacin. When this headache type is suspected and in the absence of contraindications to this medication, an indomethacin challenge is performed. This may be done in the clinic via intramuscular injection or as an outpatient using an upward titration of oral indomethacin over several days.[123] In patients who respond, the lowest effective dose is determined and continued with coadministration of gastric mucosal protectants. Attempts to lower the dose or discontinue the medication are made over time.

Medication Overuse Headache

Acute headache medication overuse headache or "rebound headache" refers to daily or near daily headaches that are attributed to the excessive use of acute headache medications. Although the exact definition of overuse varies according to the medication being administered, patients who use medication for acute headache on more than 2 to 3 days per week on average are considered to be at high risk for development of this headache.[111] Patients with frequent and regular use of acute medications are more susceptible to development of rebound headaches. Medication overuse is one of the main factors contributing to the progression from episodic headache patterns to chronic headache patterns (e.g., transformed migraine).[124]

Patients suspected of having medication overuse headache need to be withdrawn from the overused medication. Depending on the specific offending medication this may be done via a slow downward taper, use of long-acting NSAIDs, steroid tapers, or hospitalization for withdrawal of the medication and treatment with intravenous medications.[125,126] The treatment of medication overuse headache can be challenging and often requires a multimodal approach to include prophylactic medications as well as psychological therapy.

Thunderclap Headache

The term *thunderclap headache* refers to headaches that start rapidly and reach severe intensity within seconds. Although a primary form of thunderclap headache exists, there must be a high suspicion for a secondary headache. Because of the potential morbidity and mortality from some of these underlying causes, thunderclap headache should be considered a medical emergency and patients must seek immediate medical attention. Although the possible causes of thunderclap headache are numerous, these include: subarachnoid hemorrhage, reversible cerebral vasoconstriction syndromes, cervical artery dissection, intracranial infection, cerebral venous sinus thrombosis, and spontaneous intracranial hypotension.[127]

Trigeminal Neuralgia

Trigeminal neuralgia, also known as *tic douloureux,* is more commonly seen in women than men (1.5 : 1) between the fifth and seventh decade of life.[128] It manifests as sharp lancinating facial pain that lasts a few seconds up to 2 minutes and occurs multiple times per day. Pain is most commonly located in the second and third divisions of the trigeminal nerve (lower face), but can involve the first division as well (International Classification of Headache). Pain may be triggered by touching certain areas of the face, brushing the teeth, talking, and cold air. Trigeminal neuralgia tends to occur in periods lasting days to months separated by remissions of months to years.

The treatment of trigeminal neuralgia focuses on prophylactic medications. Carbamazepine is considered first line therapy and results in pain relief in greater than three-quarters of patients treated at therapeutic doses.[129] Other medications include: oxcarbazepine, phenytoin, baclofen, clonazepam, valproic acid, gabapentin, and topiramate. If recalcitrant to medical therapy, surgical options for the treatment of trigeminal neuralgia are available.

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CHAPTER EIGHTEEN

Sleep Apnea and Sleep Disorders

Stacey L. Ishman

Tamekia L. Wakefield

Nancy A. Collop

Key Points

- Snoring affects at least 40% of men and 20% of women, and often accompanies sleep-disordered breathing. However, only 2% of women and 4% of men older than 50 years of age have symptomatic obstructive sleep apnea (OSA).
- OSA is defined by five or more respiratory events (apneas, hypopneas, or respiratory effort–related arousals [RERAs]) in association with excessive daytime somnolence, waking with gasping, choking, or breath-holding, or witnessed reports of apneas, loud snoring, or both.
- Negative health effects have been attributed to untreated OSA including increased mortality, an increase in cardiovascular disease, and neurocognitive difficulties. In addition, untreated OSA has been demonstrated to be an independent risk factor for insulin resistance, gastroesophageal reflux disease, motor vehicle accidents, and decreased attention, working memory, and executive function.
- The most common symptoms of OSA include loud snoring, restless sleep, and daytime hypersomnolence. However, polysomnography (PSG) is required for diagnosis and is considered the gold standard for diagnosis of OSA.
- Fiberoptic nasopharyngoscopy is an important tool to identify level of obstruction: nasal, retropalatal, or retrolingual. Most people have multilevel obstruction.
- Uvulopalatopharyngoplasty (UPPP) is the most commonly performed surgical procedure for OSA and is often misused as the first line of surgical therapy for OSA regardless of coexistent patient factors such as obesity, retrognathia, and the existence of other sites of obstruction. As a result, it is often unsuccessful in treating OSA in unselected patients.
- Partial midline glossectomy (PMG), lingualplasty, and radiofrequency tongue base ablation are procedures that have been developed in an attempt to address the retrolingual collapse or narrowing that occurs in OSA.
- Surgical treatment of the hypopharyngeal area is comprised of procedures designed to prevent tongue collapse into the airway during sleep. These include genioglossal advancement (GA) and hyoid myotomy (HM), which are both used to create an enlarged retrolingual airway.
- Thirty-one percent of patients whose OSA was diagnosed in a sleep disorder center were found to have coexistent sleep disorders, with the most common being inadequate sleep hygiene (15%) and periodic limb movement disorder (8%).
- Insomnia is defined as difficulty with sleep initiation, maintenance, consolidation, or quality; it is recurrent and causes daytime dysfunction despite adequate occasion and opportunity for sleep.
- Circadian rhythm sleep disorders occur when personal sleep-wake patterns are misaligned with the societal clock on a persistent or recurrent basis, leading to excessive daytime sleepiness or insomnia and resulting in impaired function.
- Parasomnias are undesirable movements or subjective phenomena that occur during sleep; either while falling asleep, while waking up, or during sleep itself.

Over the past decade, interest in sleep and sleep disorders has increased substantially. The majority of this renewed interest within the otolaryngology community has been focused on the sleep-related breathing disorder OSA. As the waistline of the average American has grown, so too has the incidence of OSA. Population-based studies suggest that 2% of women and 4% of men older than age 50 years have symptomatic OSA.[1] Advances have also been made in the understanding of the pathophysiology of OSA, diagnostic methods, and medical and surgical treatments. The recognition that sleep disorders require a multidisciplinary approach has led to the creation of a new medical discipline—sleep medicine—with teams made up of internists, pulmonologists, otolaryngologists, neurologists, pediatricians, psychiatrists, oral/maxillofacial surgeons, dentists, behavioral psychologists, and nutritionists who work together to take care of patients with sleep disorders. Considerable advances have been made in the diagnosis and management of sleep disorders, and otolaryngologists are at the forefront of this new field, providing a host of both traditional and novel operative techniques to facilitate treatment.

Historical Perspectives

The idea of obesity being intimately associated with daytime somnolence seems to have been first written about by Charles Dickens in *The Posthumous Papers of the Pickwick Club*, originally published in 1837. Dickens gives a vibrantly descriptive picture of Joe, a boy so obese that he has difficulty breathing, sounds as if he is snoring even when awake, and frequently falls asleep while standing. In addition, there is evidence to suggest that some of our most noted leaders and dictators suffered from this problem. The 20th president of the United States, William Howard Taft, had a body mass index of 42 kg/m^2 while in office and was reported to snore, to fall asleep during the day frequently, and to have hypertension.[2] Chouard and colleagues describe several reasons to suspect Napoleon I (1769-1821) had OSA in the last decade of his life: he was obese and retrognathic, his neck was short and thick, he had nasal obstruction, he frequently slept during the day, he complained of declining energy and intellect, and he was quite tired looking and somewhat disheveled.[3] In 1956, Drs. A. G. Bicklemann, C. S. Burwell, and colleagues drew on Dickens' description in their case report titled "Extreme Obesity Associated with Alveolar Hypoventilation: a Pickwickian Syndrome." This frequently cited paper served as the first description of the Pickwickian syndrome in an academic journal.[4] Sleep apnea was first described as a clinical entity in 1965, but it was not until the 1970s that Elio Lugaresi's group provided a complete description of the OSA syndrome with its potential adverse cardiovascular effects.

In the infancy of this new diagnosis, treatment options were limited to tracheostomy or weight loss. This changed in the early 1980s with the introduction of the uvulopalatopharyngoplasty (UPPP) as described by Fujita and colleagues[5] and Simmons and colleagues.[6] It was not long after the introduction of UPPP that it was recognized that although this new surgical intervention was helpful in many cases, it left half of the patients with persistent sleep apnea and could be a painful procedure. It was during this same time period that Colin Sullivan, a young Australian medical researcher, developed nasal continuous positive airway pressure (CPAP), which today remains the first-line treatment of adult OSA.

As treatment for OSA has evolved, so too has therapy aimed at treating snoring. The development of office-based surgical treatments, over-the-counter devices, and pharmacologic interventions has increased considerably in recent years.

Classification of Obstructive Sleep-Related Breathing Disorders

Sleep-related breathing disorders range from partial airway collapse and increased upper airway resistance to episodes of hypopnea or complete airway collapse with sleep apnea (Box 18-1). In addition, a number of indices are used to describe sleep-disordered breathing (Box 18-2).

Snoring

Snoring is sound generated by the vibration of the pharyngeal soft tissues. It is often louder during inspiration than expiration. It affects at least 40% of men and 20% of women and often accompanies sleep-disordered breathing (SDB).[7] However, it can occur in isolation and by definition is not associated with symptoms of excessive daytime sleepiness or insomnia. Snoring, in the absence of OSA, is documented when habitual audible snoring occurs with an apnea hypopnea index (AHI) of less than five events per hour without daytime symptoms. Polysomnography (PSG) is not required for diagnosis, but when performed it reveals an audible microphone signal not associated with arousals, desaturations, airflow limitation, or arrhythmias.[8]

Upper Airway Resistance Syndrome

The term *upper airway resistance syndrome* (UARS) was first used to describe patients who do not meet the criteria for OSA syndrome but who experience excessive daytime somnolence and other debilitating somatic complaints.[9] UARS is characterized by respiratory effort–related arousals (RERAs). A RERA is defined as a sequence of breaths over at least 10 seconds with increasing respiratory effort that terminates with an arousal.[10] A RERA is detected using esophageal pressure manometry, which reveals a pattern of progressively increasing negative esophageal pressure followed by an arousal.[10,11] PSG reveals frequent arousals associated with snoring, abnormally negative intrathoracic pressure, or increased diaphragmatic electromyogram activity.[9] The current International Classification of Sleep Disorders does not consider UARS to be a separate sleep disorder, but recommends that it be

Box 18-1

Respiratory Event Definitions and Types

Respiratory Event	Definition
Apnea	A cessation of airflow for at least 10 seconds
Hypopnea	A reduction in airflow (≥30%) at least 10 seconds with ≥4% oxyhemoglobin desaturation OR a reduction in airflow (≥50%) at least 10 seconds with ≥3% oxyhemoglobin desaturation or an electroencephalogram (EEG) arousal
Respiratory effort-related arousal (RERA)	Sequence of breaths for at least 10 seconds with increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the sequence of breaths does not meet the criteria for an apnea or a hypopnea
Obstructive	Continued thoracoabdominal effort in the setting of partial or complete airflow cessation
Central	The lack of thoracoabdominal effort in the setting of partial or complete airflow cessation
Mixed	A respiratory event with both obstructive and central features. Mixed events generally begin as central events and end with thoracoabdominal effort without airflow

From Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep.* 2005;28:499-521.

Box 18-2

Indices of Sleep-Disordered Breathing

Indices	Definition
Apnea index	Number of apneas per hour of total sleep time
Hypopnea index	Number of hypopneas per hour of total sleep time
Apnea-hypopnea index	Number of apneas and hypopneas per hour of total sleep time
Respiratory effort–related arousals (RERAs) index	Number of RERAs per hour of total sleep time
Respiratory disturbance index (RDI)	Number of apneas, hypopneas, and RERAs per hour of total sleep time
Central apnea index	Number of central apneas per hour of total sleep time
Mixed apnea index	Number of mixed apneas per hour of total sleep time

Box 18-3

Symptoms of Sleep-Disordered Breathing

Restless sleep
Loud snoring
Observed apnea, choking, or gasping episodes
Excessive daytime sleepiness (EDS)
Morning fatigue or irritability
Memory loss
Decreased cognitive function
Depression
Personality or mood changes
Decreased libido and impotence
Morning and nocturnal headaches
Nocturnal sweating
Nocturnal enuresis

included under the definition of OSA because the pathophysiology is similar.[8]

Obstructive Sleep Apnea Syndrome

OSA is defined by five or more respiratory events (apneas, hypopneas, or RERAs) in association with excessive daytime somnolence, waking with gasping, choking, or breath-holding, or witnessed reports of apneas, loud snoring, or both. Each episode of apnea or hypopnea must last a minimum of 10 seconds, is commonly accompanied by reductions in blood oxygen saturation of at least 3% to 4%, and is usually terminated by brief, unconscious arousals from sleep. Snoring between apneas is a frequent complaint of bed partners and is often the symptom that prompts these patients to seek medical attention; although, excessive daytime somnolence is a common presenting complaint. Automobile accidents and increased cardiovascular morbidity and mortality are frequent complications if OSA is left untreated. Many OSA sufferers complain of awakening from sleep with morning headache, sore throat, and fatigue or a feeling of being unrefreshed regardless of the duration of sleep (Box 18-3). OSA is exacerbated by ingestion of alcohol, sedative use, and weight gain.

Pathophysiology

The obstruction that occurs in OSA results from collapse of the pharyngeal airway during sleep. The etiology and mechanism of collapse is multifactorial but is largely due to the interaction of an easily collapsible upper airway with the relaxation of the pharyngeal dilator muscles, which happens during sleep. Obesity, soft tissue hypertrophy, and craniofacial characteristics such as retrognathia add to this propensity for collapse by increasing the extraluminal tissue pressures surrounding the upper airway. However, structural compromise of the airway alone is not always sufficient to produce OSA. Notably, patients without anatomic abnormalities may also have OSA. This may occur because the complex reflex pathways from the central nervous system to the pharynx, which control the action of pharyngeal dilator muscles, may fail to maintain pharyngeal patency. The three major areas of obstruction are the nose, the palate, and the hypopharynx, although obstructive sleep apnea associated with laryngeal obstruction from bilateral laryngeal paralysis, laryngomalacia, and obstructing laryngeal lesions has also been reported.

Fujita classified the patterns of obstruction by anatomic location in the following manner: type I, collapse in the retropalatal region only; type II, collapse in both retropalatal and retrolingual regions; type III, collapse in the retrolingual region only.[12] Subsequent studies have evaluated the prevalence of retropalatal versus retrolingual obstruction in patients with OSA and snoring and found that both retrolingual (77% versus 40%) and retropalatal (100% versus 70%) obstruction are increased in OSA patients, confirmed by PSG, compared with snorers.[13]

Nasal obstruction contributes to increased airway resistance and may worsen OSA, but it is rarely the sole cause. Nasal obstruction may contribute to open-mouth breathing during sleep, which increases upper airway collapsibility and may decrease the efficacy of dilator muscles.[14] Snoring is often a presenting symptom of OSA and can be caused by nasal obstruction. Surgical procedures aimed at improving nasal breathing have demonstrated subjective improvement in snoring following correction of nasal obstruction.[15] Even though isolated treatment of the nasal airway rarely leads to cure of OSA, it may allow for decreased CPAP levels to be used for subsequent treatment.[16] Nasal obstruction can be caused by bony and cartilaginous deformation or from soft tissue changes. Because there are many causes of nasal obstruction, they all warrant investigation when evaluating a patient with OSA.

Obesity is a major risk factor for OSA. The increased fat deposition around the neck and parapharyngeal spaces is postulated to narrow and compress the upper airway and may offset the effects of dilator muscles that maintain airway patency.[17] Obesity is also thought to contribute to OSA through its deleterious effects on metabolism, ventilation, and lung volume, resulting in a mismatch between alveolar ventilation (V) and pulmonary perfusion (Q). Obesity can significantly reduce lung volume, which results in a reduction of functional residual capacity. It has been observed that changes in lung volume significantly reduce pharyngeal upper airway size through the mechanical effect of tracheal and thoracic traction, referred to as "tracheal tug," increasing the risk for airway collapse.[18]

Adenotonsillar hypertrophy is the major cause of obstructive sleep apnea in children. In adults there are multiple structural characteristics associated with OSA. Craniofacial variations that have been associated with OSA include increased distance of the hyoid bone from the mandibular plane, decreased mandibular and maxillary projection, a downward and posterior rotation of mandibular and maxillary growth, increased vertical facial length, increased vertical length of the posterior airway, and increased cervical angulation.[19]

Neuromuscular tone contributes to the patency of the upper airway. During sleep this tone decreases and the airway tends toward collapse. The genioglossus muscle is considered to be the most important muscle in maintaining airway patency in OSA. Elevated genioglossal and tensor palatini muscle activity has been observed in awake OSA patients compared with normal awake subjects who have lower levels of activity. This suggests that even while the patient is awake, airway dilator muscle activity compensates for a more anatomically compromised upper airway in the OSA patient.[17] Studies are ongoing to determine the extent and importance of neuromuscular tone in maintaining airway patency during sleep.

Consequences of Untreated Obstructive Sleep Apnea

A number of negative health effects have been attributed to untreated OSA including increased mortality, an increase in cardiovascular disease, and neurocognitive difficulties. In a retrospective study, He and colleagues found that untreated OSA patients with an apnea index (AI) greater than 20 had a statistically significant increase in mortality compared with patients with an apnea index less than 20.[20] He also found that untreated patients with an AI greater than 20 had a 63% probability of surviving 8 years compared with 96% in those with an AI less than 20.[20] Additionally, untreated OSA is reported to increase the risk of fatal and nonfatal motor vehicle accidents by 2.5-fold.[21] A significant proportion of the mortality and morbidity related to OSA occurs through its effect on the cardiovascular system, including hypertension, coronary heart disease, congestive heart failure, arrhythmias, sudden death, pulmonary hypertension, and stroke. Untreated moderate and severe OSA has been reported to result in a threefold increase in fatal and nonfatal cardiovascular events, when compared with both healthy men without OSA and men with CPAP-treated OSA.[22] Treatment of OSA with CPAP has also been reported to lower blood pressure by 10 mm Hg.[23]

Untreated OSA has been demonstrated to be an independent risk factor for insulin resistance.[24] Recently, it has been suggested that OSA may contribute to the development of diabetes and metabolic syndrome, the term used to describe the commonly occurring conditions of obesity, insulin resistance, hypertension, and dyslipidemia. However,

further research is needed to determine whether there is an independent link between OSA and metabolic abnormalities.

The prevalence of gastroesophageal reflux disease (GERD) in OSA patients is significantly higher than in the general population.[25-27] Even though these disorders commonly occur together, no temporal or causal relationship has ever been demonstrated between the two. This may reflect the fact that they share similar risk factors. Treatment of OSA with CPAP has been demonstrated to decrease the occurrence of GERD.[28]

Aside from the obvious physical effects of OSA, such as excessive daytime sleepiness and impaired mood, neurocognitive deficits have also been associated with OSA. Untreated OSA has been documented to cause problems with attention, working memory, and executive function, all of which are improved with CPAP treatment.[29] Bed partner dissatisfaction is also a common complaint among OSA patients and treatment has been shown to improve the quality of life in both the treated individuals and their bed partners.[30] Thus the benefits of treating OSA are substantial and well documented.

Diagnosis

The most common symptoms of OSA include loud snoring, restless sleep, and daytime hypersomnolence. However, a broad range of signs and symptoms have been reported to occur in OSA (see Box 18-3). Obesity is a common finding in patients with OSA with reports that 70% of adult patients with OSA are obese.[31] Screening, including a detailed sleep history and physical examination, is recommended for all obese patients. The Epworth Sleepiness Scale (ESS) is a widely used tool that assesses daytime sleepiness (Fig. 18-1). OSA may be suspected in patients with an ESS greater than 10.[32] Sleepiness or fatigue may also be precipitated by a number of other medical conditions that should be considered when evaluating patients for possible OSA (Box 18-4). In addition, the presence of additional sleep disorders should be considered.

Due to the increased prevalence of OSA in patients with hypertension, coronary artery disease, congestive heart failure, cerebrovascular accident, and diabetes mellitus, these populations must be carefully screened for the signs and symptoms of OSA.[33] It has also recently been recognized that OSA may be underdiagnosed in women due to a lower index of suspicion among physicians or underreporting of the classic symptoms by female patients. Women with OSA are more likely to report symptoms of insomnia, heart palpitations, and ankle edema.[34]

Although the presence of daytime somnolence and loud snoring are frequently the signs which prompt OSA suffers to seek medical attention, it is the physical examination findings that strengthen the likelihood of the diagnosis. Body mass index calculation, blood pressure measurement, and neck circumference are important general assessment parameters. In addition, body habitus, mandible and maxilla position and size, and facial characteristics should be noted. Assessment of the nose should include evaluation of any external deformity, adequacy of the nasal valve, septal position, turbinate size, nasal mucosa swelling, and the presence or absence of polyps, purulence, and rhinorrhea. In the oral cavity, appraisal of the tongue size and position, elongation of the palate and uvula, tonsil size, modified Mallampati score, dentition, and crowding of oropharynx should follow. In the neck, neck size, hyoid position, and jaw position, including retrognathia, should be evaluated (Box 18-5).

Fiberoptic nasopharyngoscopy is an important technique for evaluation of the airway. This examination can be performed in multiple positions in awake and asleep patients and is an important tool to identify level of obstruction: nasal, retropalatal, or retrolingual (Figs. 18-2 and 18-3). Numerous studies have described the benefits and limitations of the addition of the Müller maneuver to this examination for preoperative prediction of the effectiveness of surgical interventions.[35,36] The Müller maneuver is performed in an awake patient who generates negative pressure by inhaling against a closed glottis with the nose and mouth closed, which triggers airway collapse (Figs. 18-4 and 18-5). Sher and associates performed both seated and supine examinations using the Müller maneuver in OSA patients, selected those with palatal collapse, and found that 73% of patients had at least a 50% reduction in respiratory disturbance index (RDI) after UPPP.[36] Aboussouan found that using the Müller maneuver to guide the decision on UPPP resulted in an AHI reduction by 50% in 78% of patients who had velopalatal collapse, compared with 36% for multilevel obstruction.[35] Thus, even though the Müller maneuver can help guide surgical decision making when the area of collapse is purely retropalatal, it appears to be less useful in patients who have multilevel obstruction.

To better identify the site or sites of obstruction in patients with OSA, drug-induced sleep videoendoscopy has been used to guide more effective surgical intervention. Sleep is induced via pharmacologic means and standard fiberoptic nasopharyngoscopy is performed to evaluate the site of airway collapse. Sleep endoscopy may hold greater

EPWORTH SLEEPINESS SCALE

Please answer the following questions based on this scale:

0. Would never fall asleep
1. Slight chance of dozing
2. Moderate chance of dozing
3. High chance of dozing

Situation	Chance of Dozing
Reading	_____
Watching TV	_____
Sitting in a public place (e.g., theater or meeting place)	_____
Driving a car, stopped at a traffic light	_____
As a passenger in a car for an hour without a break	_____
During quiet time after lunch without alcohol	_____
Lying down to rest when circumstances permit	_____
Total Score:	_____

Epworth Score < 10 = Normal

Figure 18-1. Epworth Sleepiness Scale.

Box 18-4

Medical Conditions That Produce Fatigue

- Severe anemia
- Endocrine dysfunction, including hypothyroidism and Addison's disease
- Chronic fatigue syndrome
- Pulmonary disease, including asthma, emphysema, and pickwickian syndrome
- Cardiovascular disease, including congestive heart failure and left heart failure
- Neoplasms, including disseminated and central nervous system lesions
- Anticancer chemotherapy
- Collagen vascular diseases
- Chronic infections, including mononucleosis, hepatitis, and influenza
- Depression and other psychiatric disorders
- Malnutrition
- Neurologic disorders, including Parkinson's disease and multiple sclerosis
- Medication side effects

Box 18-5

Physical Examination Findings

Nasal Obstruction
Septal deviation
Turbinate hypertrophy
Nasal valve collapse
Adenoid hypertrophy
Nasal tumors or polyps

Oropharyngeal Obstruction
Large soft palate
Palatine tonsillar hypertrophy
Posterior pharyngeal wall banding
Macroglossia
Large mandibular tori
Narrow skeletal arch

Hypopharyngeal Obstruction
Lateral pharyngeal wall collapse
Omega-shaped epiglottis
Hypopharyngeal tumor
Lingual tonsillar hypertrophy
Retrognathia and micrognathia

Laryngeal Obstruction
True vocal cord paralysis
Laryngeal tumor

General Neck Obstruction
Increased neck circumference
Redundant cervical adipose tissue

General Body Habitus
Obesity
Achondroplasia
Chest wall deformity
Marfan's syndrome

Cardiovascular Signs
Arterial hypertension, especially morning hypertension
Peripheral edema

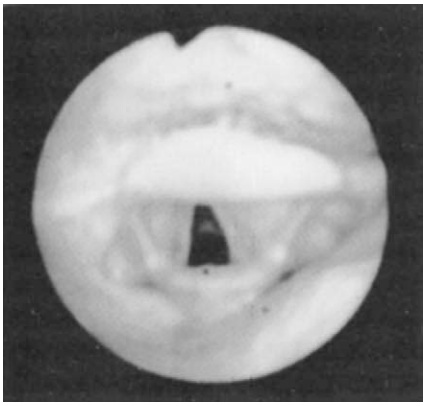

Figure 18-2. Fiberoptic view of the normal hypopharyngeal airway. *(From Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing.* Otolaryngol Clin North Am. *1998;13:983.)*

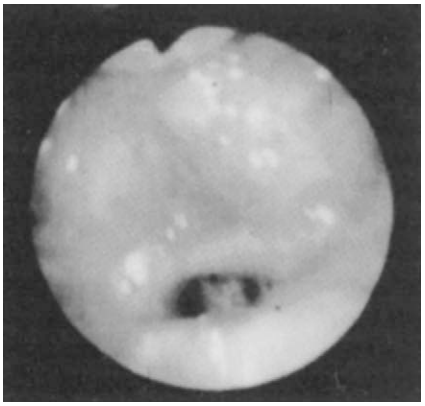

Figure 18-3. Fiberoptic view of base of tongue obstruction. *(From Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing.* Otolaryngol Clin North Am. *1998;13:983.)*

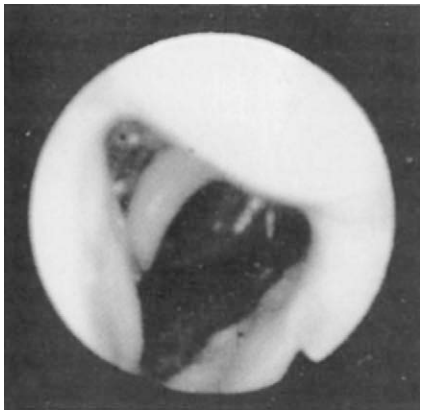

Figure 18-4. Fiberoptic view of the hypopharyngeal airway before the Müller maneuver. *(From Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing.* Otolaryngol Clin North Am. *1998;13:983.)*

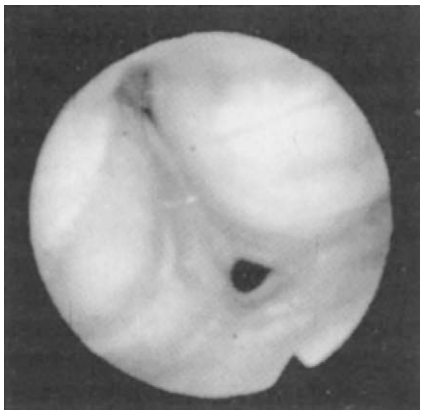

Figure 18-5. Fiberoptic view of hypopharyngeal collapse during the Müller maneuver. *(From Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing.* Otolaryngol Clin North Am. *1998;13:983.)*

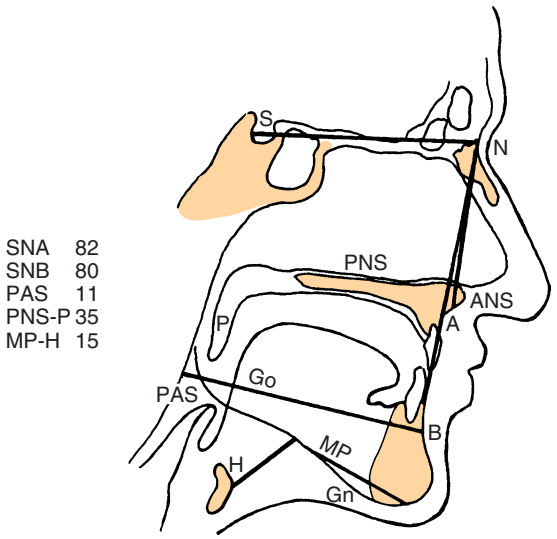

Figure 18-6. Standard cephalometric tracing. S, Sella; N, nasion; A, subnasale; B, supramentale; SNA, maxilla to cranial base; SNB, mandible to cranial base; ANS, anterior nasal spine; PNS, posterior nasal spine; P, tip of uvula; PNS-P, length of the soft palate; PAS, posterior airway space; MP, mandibular plane; H, hyoid; Go, gonion; Gn, gnathion. *(From Riley R, Powell N, Guilleminault C. Obstructive sleep apnea syndrome: a review of 306 consecutively treated surgical patients.* Otolaryngol Head Neck Surg. *1993;108:117.)*

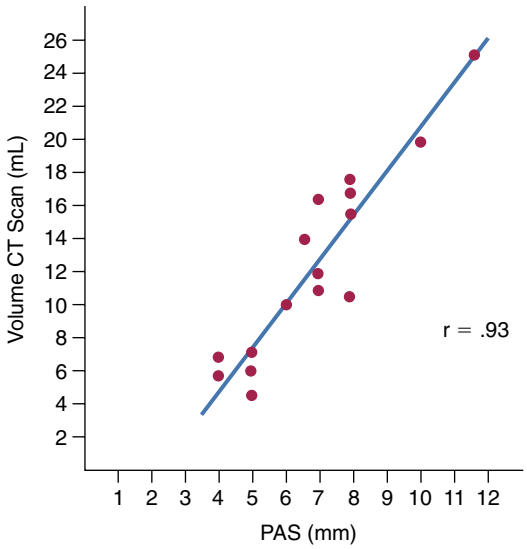

Figure 18-7. Comparison of the hypopharyngeal airway volume by computed tomography scan to posterior airway space (PAS), measured on cephalometric radiographs. *(From Riley R, Powell N. Maxillofacial surgery and obstructive sleep apnea syndrome.* Otolaryngol Clin North Am. *1990;23;809.)*

promise for identifying areas of obstruction because it more closely reflects what occurs in the airway during sleep and may be useful for directing surgical intervention.

A number of radiologic techniques have been used to aid in the identification of the site and severity of upper airway obstruction or collapse in OSA. Because most of the radiologic techniques for evaluation of OSA are performed in awake patients, they provide limited information about obstruction during sleep. The most frequently used imaging modality has been the cephalometric radiograph. The cephalogram is a two dimensional representation of the airway, which is a standardized evaluation system, with broad availability and relatively low cost (Fig. 18-6).[37] These films provide information on both the bony skeleton and the overlying soft tissues. Multiple studies using cephalometry have confirmed that OSA patients have inferior displacement of the hyoid, smaller posterior airway space, and longer soft palates than do non-OSA patients (Fig. 18-7).[38-41] Even so, the differences between OSA and non-OSA patients noted on cephalometry have not been significant enough to allow for the use of lateral cephalograms as a sole diagnostic tool.[42]

Awake computed tomography (CT) provides good anatomic detail of the bone and soft tissue. Like the cephalogram, its has poor sensitivity for diagnosing OSA; however, multiple studies have demonstrated that it is a better modality to illustrate postoperative anatomic changes that correlate with improved PSG parameters.[42]

Magnetic resonance imaging (MRI) provides excellent soft tissue differentiation and does not require radiation exposure. However, it can be hard to tolerate, is expensive, has limited availability, and is noisy, which may preclude asleep evaluations. Like CT and cephalometry, MRI has not been useful in distinguishing OSA from non-OSA patients.[43]

Lastly, fluoroscopy has been used as a dynamic airway examination to directly evaluate the sites of obstruction. Somnoflouroscopy, studies done while asleep, have been shown to improve uvulopalatopharyngoplasty success rates when the site of initial obstruction is identified (67% versus 42%); however, these studies are time intensive and expose the patients to increased radiation, which limits their utility.[44]

Nocturnal PSG is the gold standard for diagnosis of OSA. A full night diagnostic study is considered to be the most accurate instrument for measuring the presence and severity of OSA. The parameters monitored during PSG include electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, airflow, thoracoabdominal effort, and oximetry (Box 18-6). The information obtained from the study is analyzed by a trained polysomnogram technologist and interpreted by a sleep physician. Classification of disordered breathing events recorded during PSG have been standardized to guide practice (Figs. 18-8 through 18-10).[33]

Box 18-6

Polysomnography Monitors

- Electroencephalogram C3 or C4, O1 or O2, F1
- Electro-oculogram
- Nasal and oral airflow monitors: thermistors, nasal pressure transducers, or inductance plethysmography
- Submental electromyogram
- Anterior tibial electromyogram
- Body position monitors
- Chest respiratory effort monitor
- Abdominal respiratory effort monitor
- Electrocardiogram
- Pulse oximetry
- Tracheal microphone
- Optional:
  - End-tidal carbon dioxide monitor
  - Esophageal pressure monitor
  - Nasal continuous positive airway pressure and bilevel positive airway pressure

Treatment

To provide effective treatment for OSA, careful consideration of the individual patient, available medical and surgical therapies, and inherent risks and complications of those interventions must be taken into account. The deleterious effects of untreated OSA on cardiovascular and neurocognitive health are well documented; however, the treating physician should have knowledge of all available interventions, the

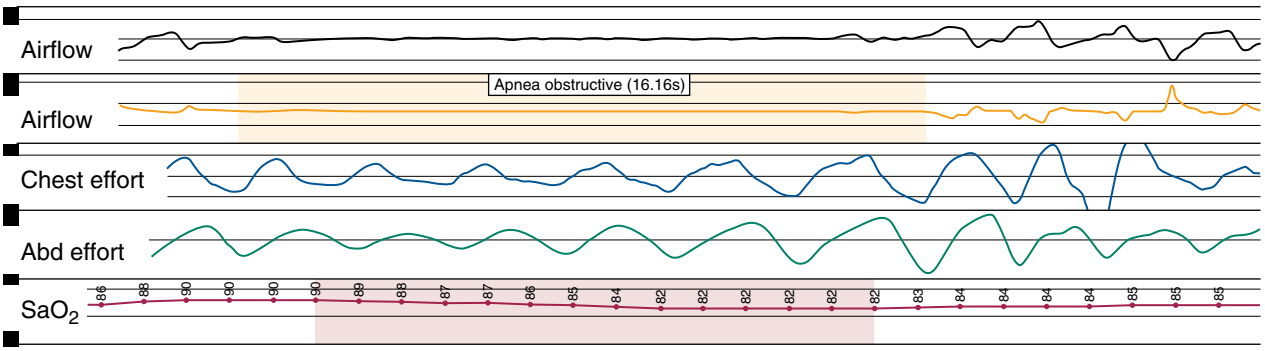

Figure 18-8. Polysomnographic tracing of an obstructive apnea.

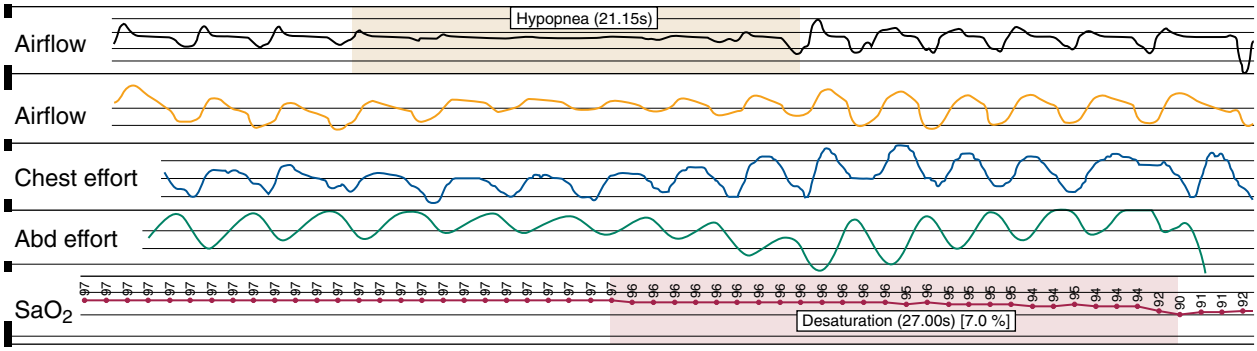

Figure 18-9. Polysomnographic tracing of a hypopnea.

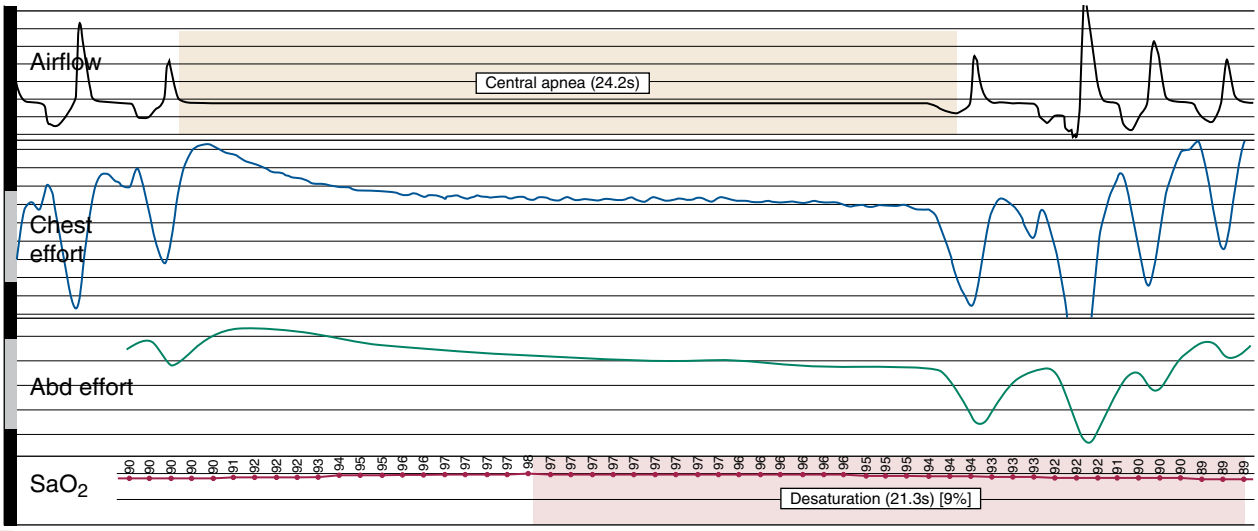

Figure 18-10. Polysomnographic tracing of a central apnea.

success rates, risks of complications, and need for further surgery when outlining a treatment plan.

Medical Treatment

Treatment is generally approached in a stepwise manner and begins with conservative medical measures. Weight loss should be recommended for all overweight patients with OSA. However, sustained weight reduction is difficult and patients often regain the lost weight. Therefore other interventions are often also recommended. Consultation with a bariatric surgeon can be considered when treating patients who are morbidly obese. Recent evidence reveals that surgically induced weight loss significantly improves obesity-related OSA and parameters of sleep quality,[45] and this improvement can occur as early as 1 month after surgery.[46]

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for moderate to severe OSA. Studies have demonstrated CPAP effectiveness in reducing the apnea-hypopnea index and in subjectively improving sleep quality; however, patient adherence remains a significant obstacle.[11,47,48] CPAP acts as a pneumatic splint and prevents upper airway collapse by providing constant positive intraluminal pressure during inspiration and expiration. Numerous effects of CPAP treatment have been described, chief among these being the reduction in AHI, improvement in objective and subjective sleepiness, improvement in overall quality of life, reduction in

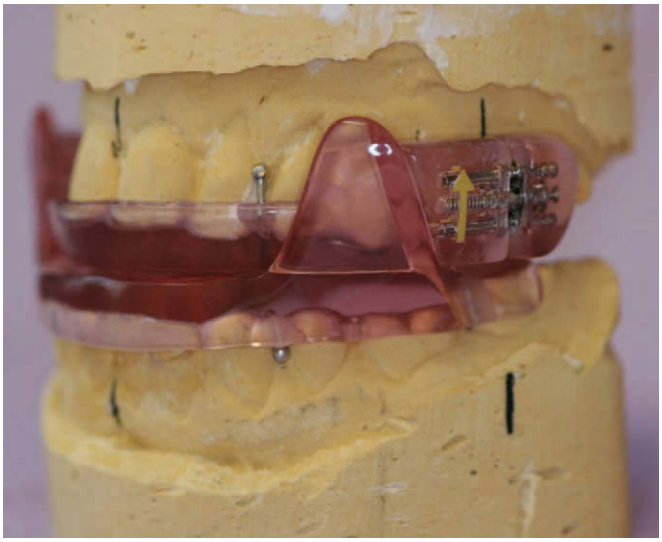

Figure 18-11. Mandibular advancement appliance for mild to moderate sleep apnea.

risk of cardiovascular events, and reduction of the risk of motor vehicle accidents.[20,49,50] Recently, there has also been interest surrounding the beneficial effects of CPAP to cardiovascular health due to decreased inflammation as measured by a decrease in the inflammatory markers C-reactive protein and interleukin-6, improved endothelial function, and reduced diurnal sympathetic activity.[51-53] Bilevel positive airway pressure (BiPAP) and autoadjusting positive airway pressure (APAP) were developed to improve pressure titration and treat patients with neuromuscular disorders and ventilatory disease. BiPAP delivers a separately adjustable lower expiratory positive airway pressure and higher inspiratory positive airway pressure. Although BiPAP has not been shown to improve adherence in an unselected patient population, a change in the method of delivery of positive airway pressure may significantly improve adherence in individual patients.[54] APAP devices autotitrate positive airway pressure to select an effective level of CPAP, which prevents upper airway collapse. The pressure changes in response to variations in airflow magnitude, airflow limitation, snoring, or airway impedance.[55-57]

Oral appliances have been used with success in patients with mild, moderate, and some severe OSA (Fig. 18-11), increasing the posterior oropharyngeal airway. Ferguson and colleagues conducted a crossover study comparing oral appliance therapy and nasal-CPAP therapy and concluded that oral appliances are effective in some patients with mild to moderate OSA (AHI 14-50) and are associated with greater satisfaction than CPAP.[58] Adherence rates of oral appliance therapy have been reported to be as high as 77%.[59] The most often reported complications from oral appliance therapy are tooth and jaw muscle pain, difficulty chewing in the morning, and excessive salivation. Although oral appliance therapy is cost effective and has higher rates of patient adherence, CPAP has proven to be more effective in reducing AHI.[60] Therefore this intervention should be recommended cautiously as first-line therapy for moderate OSA, but may serve as an effective treatment option for patients with mild, symptomatic OSA.

Pharmacologic therapy has been proposed as a treatment alternative in patients intolerant of CPAP; however, there is currently insufficient evidence to recommend the use of drug therapy as primary therapy for the treatment of OSA.[61] The many proposed mechanisms by which drugs may reduce the severity of OSA include increasing upper airway dilator muscle tone, increasing ventilatory drive, and increasing cholinergic tone during sleep versus reducing the proportion of REM sleep, reducing airway resistance, and reducing surface tension in the upper airway.[61]

Medications have been investigated as treatment for OSA. Fluticasone has shown some success in treating OSA patients with coexistent rhinitis. Kiely and colleagues reported that the AHI was lower in 24 patients given intranasal fluticasone compared with those given placebo (23.3 versus 30.3).[62] Brouillette and coworkers gave children with OSA and adenotonsillar hypertrophy a 6-week course of intranasal fluticasone and reported a decreased frequency of mixed and obstructive apneas and hypopneas.[63] Given these demonstrated benefits, treatment with intranasal fluticasone warrants further investigation. Leukotriene receptor antagonist montelukast has also shown promise by reducing the adenoid size and respiratory-related sleep disturbances in children with mild OSA.[64] However, no adult studies have been published and further study is necessary to corroborate this early evidence.

Lastly, modafinil is a central stimulant of postsynaptic alpha$_1$-adrenergic receptors, which acts by promoting alertness. It is currently used for treatment of narcolepsy and idiopathic hypersomnia. Recently, modafinil was used successfully to alleviate residual sleepiness in patients with OSA who were regular users of CPAP but still experienced excessive daytime sleepiness.[65] However, modafinil should not be used in the absence of definitive treatment of underlying OSA.

The use of nasal dilator strips and topical decongestants has been advocated in patients who have OSA and severe nasal obstruction. McLean and colleagues found that treating nasal obstruction with 0.4 mL oxymetazoline 0.05% and nasal dilator strips reduced mouth breathing during sleep and obstructive sleep apnea severity, but did not effectively alleviate obstructive sleep apnea.[66] However, nasal dilator strips have been shown to significantly reduce snoring, mouth breathing, and sleepiness in patients who do not have OSA.[67]

Box 18-7

Surgical Indications for Treatment

- AHI > 5 and < 14 with excessive daytime sleepiness
- AHI > 15
- Oxyhemoglobin desaturation < 90%
- Upper airway resistance syndrome, preferably with objective improvement of neurocognitive dysfunction and medical therapy
- Significant cardiac arrhythmias associated with obstructions
- Unsuccessful or refused medical therapy and desire for surgery
- Medically stable enough to undergo recommended procedures

Surgical Treatment

Factors important in making the decision to treat OSA with a surgical procedure include the patient's wishes, CPAP tolerance, severity of symptoms, severity of disease, patient comorbidities, and site and severity of upper airway collapse (Box 18-7). As mentioned previously, OSA patients are frequently overweight, hypertensive, and have other cardiac risk factors. These patients must be cautiously screened with a comprehensive medical examination before considering surgery for treatment of OSA.

The surgical planning for patients with OSA should include a discussion between the anesthesia team and the surgeon regarding plans for airway management. A stepwise algorithm that is frequently used includes using an oropharyngeal airway to prevent airway obstruction by the tongue, refraining from using paralyzing agents until the patient can be easily mask-ventilated, and preparing alternative methods of ventilation in case of unsuccessful intubation. Also the surgeon should have a frank discussion with the patient about the possibility of tracheotomy. A preoperative evaluation by the primary doctor or the anesthesia team is critical and includes evaluation for latent cardiovascular disease.

Patients with OSA are usually managed using a staged stepwise surgical protocol. The site of obstruction must be determined in each patient to determine the type and extent of surgical intervention. Generally, patients with isolated palatal obstruction undergo palatal surgery and those with obstruction at the base of the tongue undergo procedures aimed at treating this area. Endoscopic examination is performed

Box 18-8

Surgical Treatment Options

Nasal Surgery
Nasal septoplasty
Inferior turbinate reduction
Adenoidectomy
Nasal tumor or polyp resection
Nasal valve reconstruction

Palatal Surgery
Palatal radiofrequency
Pillar implants
Injection snoreplasty
Tonsillectomy
Uvulopalatopharyngoplasty/Z-palatoplasty
Transpalatal advancement pharyngoplasty

Hypopharyngeal Surgery
Lingual tonsillectomy
Partial midline glossectomy
Tongue base radiofrequency
Mandibular osteotomy and genioglossal advancement
Hyoid myotomy and suspension
Tongue suspension suture
Maxillomandibular osteotomy and advancement

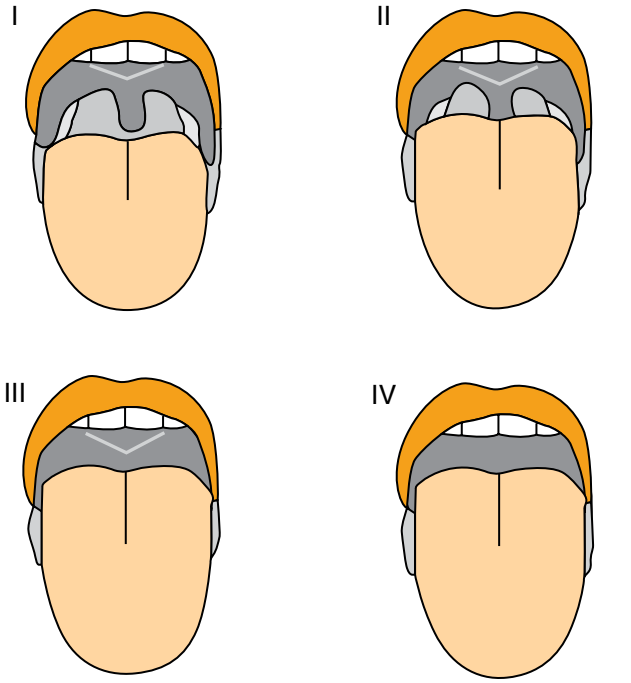

Figure 18-12. Modified Mallampati palate position. **I,** The entire uvula can be seen with the tongue at rest. **II,** A partial view of the uvula is seen. **III,** Only the soft and hard palate can be seen. **IV,** Only the hard palate can be seen.

to determine the site of obstruction. Most patients are symptomatic because both the palatal and base of tongue areas are obstructed. Before therapy is initiated, patients should be counseled regarding the possible need for multiple surgical procedures to achieve a symptomatic cure. Sleep endoscopy may be the optimal method of airway evaluation in these cases (Box 18-8). Patients with laryngeal obstruction should be treated appropriately to alleviate the obstruction and be considered for tracheostomy if improvement is not achieved surgically or with CPAP.

Critical to this decision process is the identification of the site or sites of obstruction. Several endoscopic studies have evaluated the prevalence of retropalatal and retroglossal obstruction in patients with OSA. In 2000, Steinhart and colleagues evaluated 117 OSA patients and found that 100% had retropalatal obstruction and 77% had retroglossal obstruction, thus illustrating that a majority of patients have a combination of the two.[13] In 2005, den Herder and colleagues evaluated 127 patients who underwent a similar evaluation and found that 88% of patients had retropalatal obstruction while 49% had retroglossal obstruction. In this study, 51% exclusively had palatal obstruction whereas only 12% solely had obstruction at the base of tongue.[68]

Nasal Surgery

Nasal obstruction has been associated with poor sleep quality, snoring and OSA.[69-71] Septoplasty, turbinate reduction, nasal valve surgery, and sinus surgery are procedures that have been used to treat nasal obstruction associated with OSA, and the selection of a nasal procedure is based on pathology. However, even though nasal procedures are unlikely to significantly improve OSA when used alone,[16] improving nasal patency may help restore physiologic breathing and may allow for the use of nasal CPAP in patients previously unable to tolerate it. Consideration should be made to address nasal obstruction as an initial step in OSA management so as to facilitate better CPAP adherence.

Palatal Surgery

In 1981, Fujita and colleagues described the first palatal procedure for OSA treatment, the UPPP.[5] UPPP with tonsillectomy was developed to eliminate palatal obstruction by resection of redundant palatal and pharyngeal tissue. It is the most commonly performed surgical procedure for OSA and is often misused as the first line surgical therapy for OSA regardless of coexistent patient factors such as obesity, retrognathia, and the existence of other sites of obstruction.[72] As a result, it is often unsuccessful in treating OSA in unselected patients. The site of pharyngeal collapse has a marked effect on the probability of the success of UPPP. In a meta-analysis of 37 published reports of results from UPPP, success rates were at best 50% and were related to severity of OSA.[73] Success in this case was defined as a respiratory disturbance index (RDI) of less than 20 or an AHI at 10 or less, along with at least a 50% improvement in the RDI.[73] Using a staging system based on palate position, tonsil size, and body mass index (BMI), Friedman and colleagues demonstrated the value of staging OSA patients for the prediction of success for UPPP.[74] In this staging system, palate position (based on the modified Mallampati staging), tonsil size, and BMI are used to stratify patients (Fig. 18-12). Stage I patients have an 80% success rate, stage II patients have a 40% success rate, and stage III patients have only an 8% success rate (Table 18-1). These results demonstrate that clinical staging clearly improves the overall success rate and is critical to identify which patients are unlikely to benefit from UPPP. Complications associated with UPPP include temporary nasal reflux in 12% to 15% of patients, postoperative bleeding in 1% to 5%, infection in 2%, and rare altered speech.[75]

To improve on the traditional UPPP procedure, other techniques have been suggested to address retropalatal obstruction. Woodson and coworkers introduced the transpalatal advancement pharyngoplasty, which aims to decrease retropalatal obstruction by altering the bony hard palate and the soft tissue attachments of the posterior maxilla.[76] With this procedure, a 1-cm portion of the hard palate is removed and the soft palate is then advanced and secured medially and laterally in the tensor aponeurosis, which enlarges the retropalatal region. Woodson and colleagues have reported success with this procedure when used in patients who have persistent retropalatal obstruction after UPPP and in patients with OSA who have small tonsils without the characteristic long, thick, soft palate (Fig. 18-13).[76] Another procedure, the Z-palatoplasty, was introduced by Friedman for use as a primary or revision palatal procedure in selected patients (Fig. 18-14).[77,78]

To reduce the resultant pain, cost, and morbidity of UPPP, less invasive office techniques have been developed. The palatal implant was

Table 18-1

Preoperative Versus Postoperative Data Obtained During Polysomnography in UPPP Only and UPPP with Radiofrequency of the Base of Tongue

		Stage I	Stage II	Stage III
Apnea Index				
UPPP only	Preoperative	5.4 ± 14.2	16.0 ± 26.9	8.7 ± 14.5
	Postoperative	0.3 ± 1.3*	2.7 ± 5.4*	12.4 ± 24.8
UPPP +	Preoperative	—	11.5 ± 15.5	9.3 ± 18.2
TBRF	Postoperative	—	2.7 ± 7.8*	3.2 ± 7.4*†
Apnea-Hypopnea Index				
UPPP only	Preoperative	24.0 ± 12.8	47.2 ± 31.3	34.9 ± 22.4
	Postoperative	6.7 ± 4.7*	34.2 ± 29.9*	39.1 ± 22.7
UPPP +	Preoperative	—	47.9 ± 26.6	41.7 ± 21.8
TBRF	Postoperative	—	19.5 ± 16.4*†	28.5 ± 21.9*†
Minimum Spo_2 (mm Hg)				
UPPP only	Preoperative	85.9 ± 12.5	80.0 ± 15.0	85.7 ± 8.8
	Postoperative	93.1 ± 1.9*	85.3 ± 8.2*	82.8 ± 12.9
UPPP +	Preoperative	—	82.1 ± 9.7	79.9 ± 14.3†
TBRF	Postoperative	—	87.5 ± 6.7*	83.8 ± 14.8*

*Significantly different from preoperative value.
†Significantly different from UPPP only.
Spo_2, arterial oxygen saturation; TBRF, radiofrequency base of tongue reduction; UPPP, uvulopalatopharyngoplasty.
From Friedman M, Ibrahim H, Joseph NJ. Staging of obstructive sleep apnea/hypopnea syndrome: a guide to appropriate treatment. *Laryngoscope.* 2004;114:454.

designed to reduce soft palate airway collapse and obstruction through placement of three woven implants, which stiffen the palate. The porosity of the implants also encourages the formation of a fibrotic capsule, which connects the three implants and further stiffens the palate. Nordgard and colleagues reported a significant reduction in AHI, daytime somnolence, and snoring using palatal implants in patients with mild to moderate OSA as long as body mass index was maintained.[79] The most common complication of this procedure is partial implant extrusion. Potential advantages include the fact that it can be done in a single office visit, has minimal morbidity, and has been noted to significantly reduce snoring. Due to its low morbidity, the palatal implant procedure is commonly used to treat snoring and may be useful in patients with mild OSA.

Tongue Base Procedures

Partial midline glossectomy (PMG), lingualplasty, and radiofrequency tongue base ablation have been developed to address the retrolingual collapse or narrowing that occurs in OSA. Lingual tonsillectomy may also be helpful in patients with lingual tonsillar hypertrophy. PMG creates a larger retrolingual airway by removal of a midline rectangular strip of the posterior half of the tongue. In selected patients, lingual tonsillectomy, reduction of the aryepiglottic folds, and partial epiglottectomy are also performed.[80] With lingualplasty, additional tongue tissue is removed posteriorly and laterally to that portion excised in PMG. Woodson and colleagues report that lingualplasty resulted in a 79% response rate in patients who had previously failed UPPP.[81] Because of the significant degree of tongue swelling that often occurs after these procedures, they are often performed in combination with a tracheotomy for airway protection.

Radiofrequency tongue base ablation (RFA) decreases upper airway collapse by producing a volumetric reduction in tongue base tissue via the generation of scar tissue. An insulated probe that delivers radiofrequency energy at 465 KHz is introduced into several areas of the tongue base and produces coagulation necrosis and healing by scar. The procedure is often performed in an outpatient setting under local anesthesia and may require multiple treatments to achieve desired results.[82] A review of 11 series showed success rates from 20% to 83% with multiple RFA applications and concluded that this procedure is not adequate as a sole treatment method, especially in light of the fact that most patients require multiple sessions.[83]

Hypopharyngeal Procedures

Surgical treatment of the hypopharyngeal area is comprised of procedures designed to prevent tongue collapse into the airway during sleep. Genioglossal advancement (GA) and hyoid myotomy (HM) both create an enlarged retrolingual airway. In GA, the genial tubercle of the mandible, which is the anterior attachment of the genioglossus muscle, is mobilized by means of limited osteotomy (Fig. 18-15). The segment is then advanced and fixed into place at the inferior aspect of the osteotomy. In four case series, GA performed as a solo procedure has been shown to have success rates from 39% to 78% in patients with severe OSA (mean preoperative RDI 53 to 59).[83] HM requires that the hyoid be mobilized via inferior myotomy and fixed anteriorly and inferiorly by attachment to the thyroid cartilage (Fig. 18-16). Success rates for HM performed with UPPP range from 52% to 78% in three series with patients with mean BMIs less than 30.[83] However, in one series with a patient mean BMI of 34.1, the success rate was only 17% (5 of 29).[84] These procedures result in an enlarged retrolingual airway by fixing the major dilators of the pharyngeal airway forward without changing dental occlusion. Complications associated with GA and HM include permanent numbness in 6%, infection in 2% to 5%, need for a root canal in 4%, and seroma in 2%. In addition, there is a less than 1% risk of mandibular fracture, aspiration, and death.[85]

The Repose tongue suspension procedure fixes the tongue forward, thereby preventing collapse into the airway. Via an intraoral incision made in the frenulum, a titanium screw is placed at the lingual cortex of the geniotubercle of the mandible, and a permanent suture is passed through the paramedian tongue musculature along the length of the tongue, through the tongue base, and then back through the length of the tongue musculature. It is then anchored to the screw, pulling the tongue base anteriorly.[86] When performed with UPPP, reported success

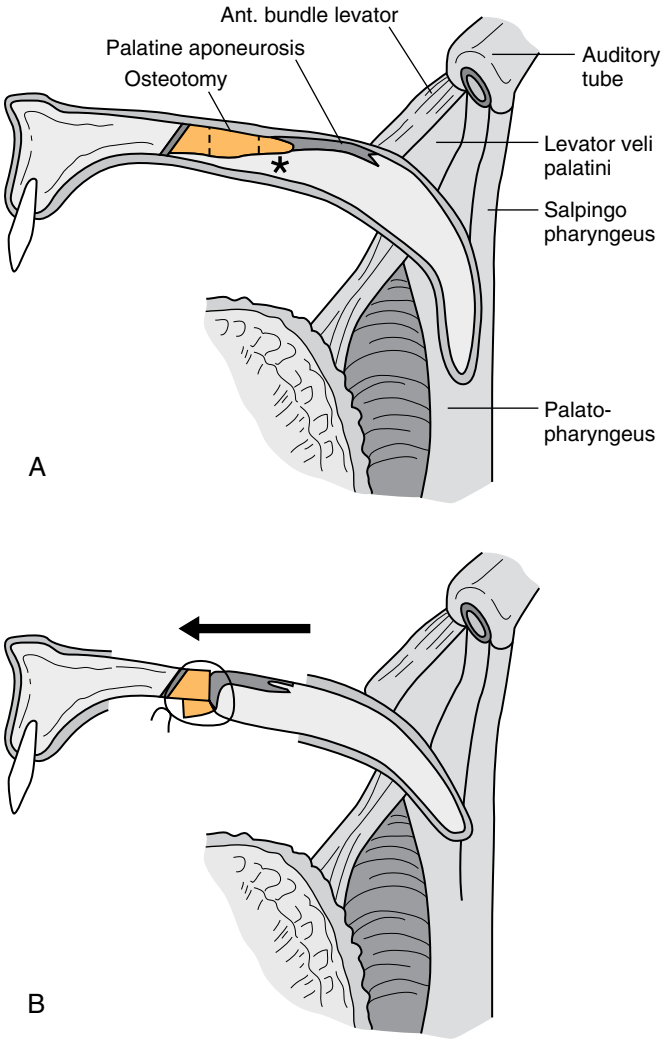

Figure 18-13. Midsagittal depiction of palate showing palatal advancement. **A,** Drill holes are placed from the oral cavity to the nose and are anterior (Ant) to bone removal (*orange*). A strong rim of bone supports the sutures. The anterior extent of the middle flap is placed in the thinner palatal mucosa. Mucosa is thicker posteriorly (*asterisk*). **B,** After osteotomy, sutures are placed through the drill holes, and the bone fragment with attached tendon and ligaments is advanced. *(From Woodson BT. Transpalatal advancement pharyngoplasty.* Oper Tech Otolaryngol. *2007;18;11.)*

rates range from 20% to 57%[83] although one study demonstrated a 3-year surgical success of up to 78% for patients with severe OSA who refused nasal continuous positive airway pressure.[87]

Maxillomandibular advancement (MMA) increases the retropalatal and retrolingual airway (Fig. 18-17). The maxilla and mandible are advanced by means of Le Fort I maxillary and sagittal-split mandibular osteotomies. This procedure is usually performed after other surgical intervention has been unsuccessful. Potential complications include malocclusion, relapse, nerve paresthesia, nonunion or malunion, temporomandibular joint problems, infection, bleeding, and the need for subsequent dental work. The success rate of this procedure approaches 90%.[88]

Tracheotomy

Tracheotomy represents the traditional gold standard of surgical management of OSA. It relieves OSA by completely bypassing the portion of the airway that most commonly collapses during sleep. However, the associated psychosocial problems, perceived inconvenience, and morbidity rarely make tracheotomy a desirable surgical option. It should be considered in patients who have failed all other OSA treatments, patients who have life-threatening OSA and are unable to tolerate

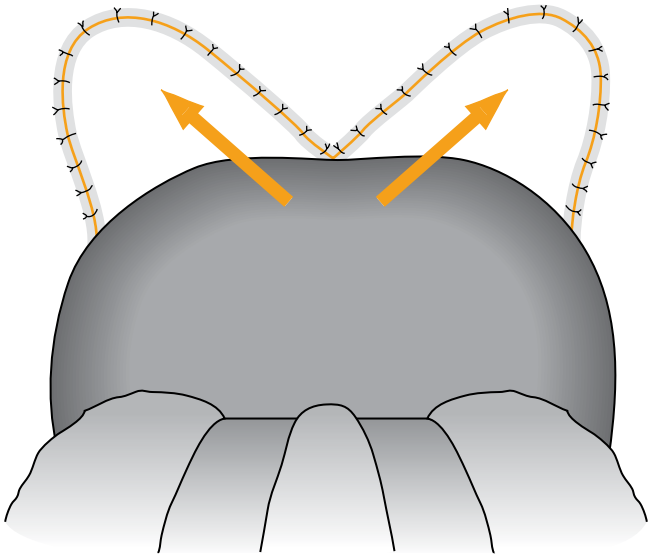

Figure 18-14. Z-palatoplasty. Note the anterolateral direction of pull *(arrows)* on the soft palate that widens the retropharyngeal space. *(From Friedman M, Schalch P. Z-palatoplasty.* Oper Techn Otolaryngol. *2007;18:2.)*

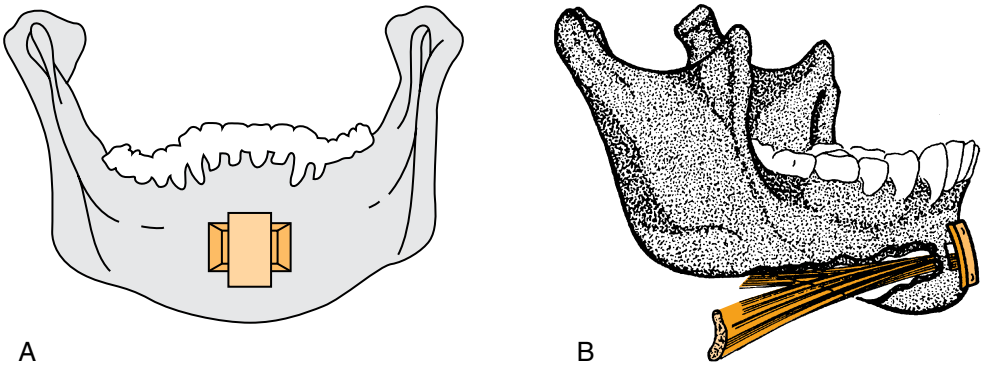

Figure 18-15. The genioglossal advancement procedure: rectangular geniotubercle osteotomy modification. **A,** Anterior view. The rectangular geniotubercle osteotomy modification offers excellent tension on the genioglossus muscle with a minimal fracture risk, and it is technically reliable. The geniotubercle fragment is rotated enough to allow bony overlap. A single inferior placed miniscrew is used to fix the fragment. **B,** Lateral view. *(From Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing.* Otolaryngol Clin North Am. *1998;13:983.)*

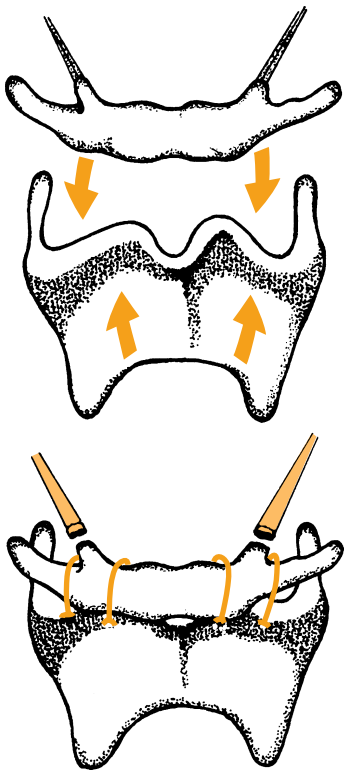

Figure 18-16. The modified hyoid myotomy and suspension procedure. *(From Riley R, Powell N, Guilleminault C. Obstructive sleep apnea and the hyoid: a revised surgical procedure.* Otolaryngol Head Neck Surg. *1994;111:717.)*

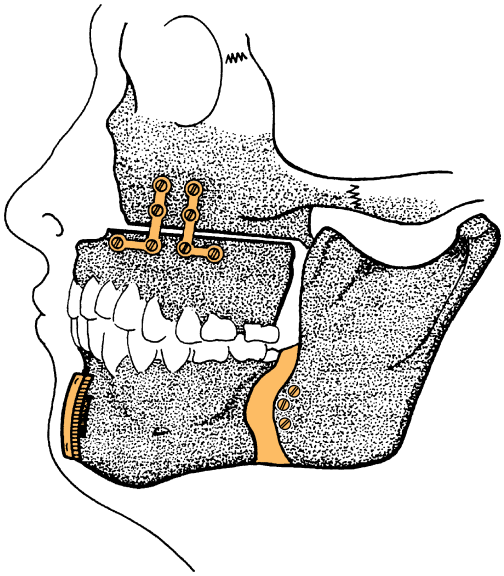

Figure 18-17. The maxillomandibular advancement procedure, lateral view. Le Fort I maxillary osteotomy with rigid plate fixation and a bilateral sagittal split mandibular osteotomy with bicortical screw fixation. The advancement is at least 10 mm. A previous genioglossal advancement is shown. *(From Powell NB, Riley RW, Guilleminault C: The hypopharynx: upper airway reconstruction in obstructive sleep apnea syndrome. In: Fairbanks DNF, Fujita A, eds.* Snoring and Obstructive Sleep Apnea. *2nd ed. New York: Raven Press; 1994:205).*

CPAP, or are neurodevelopmentally impaired.[89] It may also be the best option for patients who are morbidly obese or as an interim measure for patients undergoing base of tongue surgery.

Postoperative Management

With the trend toward multisite surgical treatment of OSA, there may be an increased chance of postoperative airway obstruction due to resultant edema in multiple sites in the upper airway. In addition, postanesthesia sedation along with altered respiration secondary to narcotic pain medications can be additive in patients with an already compromised airway.

In a retrospective review of 135 patients who underwent surgery for OSA, Esclamado and colleagues identified complications in 13% of patients: 14 airway issues such as failed intubation and airway obstruction after extubation (1 of which resulted in death), 3 patients with hemorrhage, and 1 patient with arrhythmia.[90] Patients with intubation problems were more likely to be heavier, whereas the patients with extubation complications had been given significantly more narcotic pain medications during the procedure. Risk of a perioperative complication was unrelated to age, preoperative symptoms, concurrent medical problems, or the performance of simultaneous septoplasty or tonsillectomy. In 1990, Fairbanks did a national survey of 72 sites carrying out UPPP and found that over 9 years there were 16 deaths, with 46 cases of nasopharyngeal stenosis and 42 cases of palatal incompetence. Additional complications reported include hemorrhage and wound dehiscence.[75]

Because of the recognized temporary increased risk of airway compromise after surgery, patient care algorithms have been developed to minimize patient morbidity and mortality.[90,91] Hospitalization is recommended for most patients who undergo airway surgery and admission to the intensive care unit should be considered in multilevel surgery.[92] A prospective evaluation of patients with severe OSA showed that nasal CPAP used for the first postoperative night was effective in keeping oxygen saturations above 90% even though the mean preoperative oxygen saturation level was 51.5%.[93] Based on these findings, it is recommended that patients with severe OSA use CPAP for the first 2 weeks after surgery. In addition, it is recommended that a postoperative polysomnogram be carried out in 3 to 4 months to evaluate the response to surgery.

Sleep Disorders

Otolaryngologists generally focus their attention on the diagnosis and treatment of obstructive sleep apnea (OSA), and little consideration is given to the presence of additional sleep disorders in patients suspected to have OSA. A 2005 study retrospectively reviewed 643 consecutive patients diagnosed with OSA in a sleep disorder center and found that 31% had coexistent sleep disorders.[94] In this population, 19 different sleep disorders were concomitantly diagnosed in patients with OSA, with the most common being inadequate sleep hygiene (15%) and periodic limb movement disorder (8%) (Table 18-2). Therefore, screening for the presence of concurrent sleep disorders is important both at the time of OSA diagnosis and in patients with persistent disease after medical or surgical treatment.

Classification of Sleep Disorders

The second edition of the *International Classification of Sleep Disorders* (ICSD-2) changed the classification of sleep disorders from a dichotomized system of intrinsic and extrinsic sleep disorders to a categoric system with six main disease groupings and two sections of miscellaneous conditions (Box 18-9).[8] These disease categories include insomnia, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders, isolated symptoms/apparently normal variants/unresolved issues, and other sleep disorders. OSA, the sleep disorder most commonly treated by otolaryngologists, is covered in the sleep-related breathing disorders category.

Sleep is divided into rapid eye movement (REM) and non–rapid eye movement (NREM) stages. About 80% of the night is spent in NREM, which is divided into three stages characterized by specific electroencephalographic patterns. Stage N1, previously stage 1, is a

Table 18-2

Prevalence of Concomitant Sleep Disorders in Patients with Obstructive Sleep Apnea

Disorder	Number	Prevalence Among Other Disorders (%)	Prevalence Among Total Cohort (%)
Inadequate sleep hygiene	93	41.7	14.5
Periodic limb movement disorder	52	23.3	8.1
Narcolepsy	16	7.2	2.5
Primary (idiopathic) insomnia	14	6.3	2.2
Central alveolar hypoventilation	9	4.0	1.4
Shift work disorder	5	2.2	0.8
Psychophysiological insomnia	5	2.2	0.8
Bruxism	5	2.2	0.8
Idiopathic hypersomnia	4	1.8	0.6
Sleepwalking	3	1.3	0.5
Sleep talking	3	1.3	0.5
Environmental sleep disorder	3	1.3	0.5
Hypnotic dependent sleep disorder	3	1.3	0.5
Delayed sleep phase syndrome	3	1.3	0.5
Toxin dependent sleep disorder	1	0.1	0.2
Sleep terrors	1	0.4	0.2
Nightmares	1	0.4	0.2
Enuresis	1	0.4	0.2
Confusional arousals	1	0.4	0.2

From Scharf SM, Tubman A, Smale P. Prevalence of concomitant sleep disorders in patients with obstructive sleep apnea. *Sleep Breath.* 2005;9:50.

Box 18-9

Classification of Sleep Disorders

Insomnia
Sleep-related breathing disorders
Hypersomnias of central origin
Circadian rhythm sleep disorders
Parasomnias
Sleep-related movement disorders
Isolated symptoms, apparently normal
Variants and unresolved issues
Other sleep disorders

transition stage between sleep and wake in which a mixed voltage pattern emerges with 3 to 7 cycles per second (cps) waves. People may feel that they are awake in this stage. Stage N2, previously stage 2, is identified by the presence of spindles and K complexes and may be the first true sleep stage. Stage N3, previously stage 3 and 4, is also referred to as *slow-wave sleep* and is distinguished by delta waves, which are high-amplitude (up to 2 cps) and make up at least 20% of a 30-second scoring period (also known as an epoch). Stage R, REM, is characterized by rapid eye movements and low-frequency mixed amplitude waves. REM usually alternates with NREM periods in 90-minute cycles with REM periods increasing in length as the night goes on.

Insomnia

Insomnia is defined as recurrent difficulty with sleep initiation, maintenance, consolidation, or quality; insomnia causes daytime dysfunction that exists despite adequate occasion and opportunity for sleep.[95] This may include sleep that is nonrestorative or of poor quality. Using this definition, the NIH State-of-the-Science Conference estimated that insomnia occurs in 10% of adults.[96] Children also suffer from insomnia, which has been reported to occur in 20% to 30% of infants, toddlers, and preschoolers[97] and in 12% to 30% of adolescents.[98] In children, caregivers may report that a child has difficulty with sleep initiation, reluctance to go to bed, or an inability to sleep independently. Daytime symptoms must include at least one of the following: fatigue or malaise, cognitive impairment (attention, concentration, or memory), social/vocational difficulty or poor school performance, mood impairment or irritability, daytime sleepiness, reduced motivation or energy, tendency to be accident-prone in addition to physical symptoms such as headache, muscle tension, or gastrointestinal symptoms, or concerns about sleep itself. There are a number of different subtypes of insomnia (Box 18-10).[8]

Box 18-10

Insomnia Disorders

Adjustment insomnia (acute insomnia)
Psychophysiologic insomnia
Paradoxical insomnia
Idiopathic insomnia
Insomnia due to mental disorder
Inadequate sleep hygiene
Behavioral insomnia of childhood
Insomnia due to drug or substance
Insomnia due to medical condition
Insomnia not due to substance or known physiologic condition, unspecified (nonorganic insomnia)
Physiologic (organic) insomnia, unspecified

Box 18-11

Sleep-Related Breathing Disorders

Central Sleep Apnea Syndromes
Primary central sleep apnea
Central sleep apnea due to Cheyne Stokes breathing pattern
Central sleep apnea due to high-altitude periodic breathing
Central sleep apnea due to medical condition not Cheyne Stokes
Central sleep apnea due to drug or substance
Primary sleep apnea of infancy

Obstructive Sleep Apnea Syndromes
Obstructive sleep apnea, adult
Obstructive sleep apnea, pediatric

Sleep Related Hypoventilation/Hypoxemic Syndromes
Sleep-related nonobstructive alveolar hypoventilation, idiopathic
Congenital central alveolar hypoventilation syndrome
Sleep-related hypoventilation/hypoxemia due to medical condition
Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
Sleep-related hypoventilation/hypoxemia due to lower airway obstruction
Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders

Other Sleep-Related Breathing Disorders
Sleep apnea/sleep-related breathing disorder, unspecified

Psychophysiological insomnia is associated with anxiety about sleep and difficulty falling asleep in planned situations. Often, learned behaviors prevent the onset of sleep in these patients. It may occur in up to 2% of the general population.[8] Paradoxical insomnia, though less common, is also associated with daytime dysfunction but it may be far less than would be expected given the patient's complaints. Patients with paradoxical insomnia may report little or no sleep, but there is often a mismatch between perceived sleep time and time recorded by sleep study or actigraphy. Idiopathic insomnia often begins during infancy or childhood, is lifelong, and has no other identifiable cause. Behavioral insomnia of childhood, on the other hand, is related to specific, identifiable limit-setting issues or sleep-onset behavioral patterns that prevent children from falling asleep. These are often associated with caregiver behaviors or patterns and may manifest as requirements for special rituals or extended processes to fall asleep.[99]

Inadequate sleep hygiene is diagnosed when insomnia persists for at least 1 month and includes at least one of the following: improper sleep scheduling including frequent daytime naps; variable bedtime or wake time or excessive amount of time in bed; the routine use of narcotics, caffeine, or alcohol, especially before bed; participation in mentally or physically stimulating activities close to bedtime; frequent use of the bed for other activities such as television watching or reading; or failure to maintain a comfortable sleep setting (including temperature, lighting, and bedding).[8] While sleep hygiene is not often the primary cause of insomnia, it may complicate adequate treatment unless addressed.[100] In addition, inadequate sleep hygiene is often present in conjunction with other sleep disorders and may be diagnosed as a secondary sleep disorder.

Insomnia in very young children is often related to a mismatch between caregiver expectations and childhood development.[99] Behavioral insomnia of childhood should be considered in younger children. Often insomnia in the pediatric population is treated with appropriate sleep hygiene, strict limit-setting, and/or behavioral therapy. In addition, common-sense methods such as decreasing fluids before bed and timing stimulant medications, such as those used for attention deficit–hyperactivity disorder, should be instituted before considering pharmacologic intervention. The occurrence of the delayed sleep phase circadian rhythm disorder (defined later) should also be evaluated in older children and adolescents. In addition, special populations such as those with autism or Asperger's syndrome have been shown to have an increased incidence of insomnia.[101]

Sleep-Related Breathing Disorders

Conditions included in this section are distinguished by disordered breathing during sleep, whether of an obstructive or central nature. This section includes central and obstructive sleep apnea syndromes along with disorders related to hypoventilation or hypoxemia (Box 18-11).

Central sleep apnea is characterized by an absence in respiratory effort, resulting in an absence of airflow. Central hypopneas, which are categorized with central apneas, are characterized by a reduction in respiratory effort, resulting in a reduction of airflow due to nervous system or cardiopulmonary dysfunction, such as chronic obstructive pulmonary disease or congestive heart failure.[102] Patients with central sleep apnea often present with symptoms similar to OSA patients such as excessive daytime sleepiness, snoring, witnessed apneas, and waking up with shortness of breath. Similar to OSA, central sleep apnea in adults is defined by greater than five apneas per hour, although they are differentiated by being central in nature.[8] Infants often outgrow central sleep apnea as they age.[103]

Sleep-related hypoventilation/hypoxemic syndromes are subcategorized as congenital, idiopathic, or due to medical conditions such as parenchymal pulmonary disease, vascular disease, and neuromuscular or chest wall disorders. Hypoventilation is a physiologic condition characterized by hypercapnea with arterial carbon dioxide (CO_2) tension greater than 45 mm Hg in an arterial blood gas measurement.[8] This elevation is precipitated by an imbalance between the elimination and production of CO_2 and is chronic in nature (i.e., not precipitated by an acute event within the past month). Ventilation is usually adequate while patients are awake, but hypoventilation occurs with the shallow breathing and decreased tidal volumes of sleep.[104]

Hypersomnias of Central Origin

These disorders are central hypersomnias not due to circadian rhythm disorders, sleep-related breathing disorders, or other causes of disturbed nocturnal sleep. They are primarily characterized by excessive daytime sleepiness after the previously mentioned sleep disorders have been ruled out. This section includes narcolepsy, recurrent hypersomnia, and idiopathic hypersomnia (Box 18-12).

Daytime sleepiness is characterized by difficulty staying awake or alert, resulting in inadvertent sleepiness or sleep during the day. Sleepiness is most commonly measured by the multiple sleep latency test (MSLT) after a documented night without significant sleep-disordered breathing. The ESS may also be used to screen for sleepiness in this

Box 18-12

Hypersomnias of Central Origin Not Due to Circadian Rhythm Sleep Disorder, Sleep-Related Breathing Disorder, or Other Causes of Disturbed Nocturnal Sleep

Narcolepsy with cataplexy
Narcolepsy without cataplexy
Narcolepsy due to medical condition
Narcolepsy, unspecified
Recurrent hypersomnia
Klein-Levin syndrome
Menstrual-related hypersomnia
Idiopathic hypersomnia with long sleep time
Idiopathic hypersomnia without long sleep time
Behaviorally included insufficient sleep syndrome
Hypersomnia due to medical condition
Hypersomnia due to drug or substance
Hypersomnia not due to substance or known physiologic condition (nonorganic hypersomnia, NOS)
Physiologic (organic) hypersomnia, unspecified

Box 18-13

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorder, delayed sleep phase type
Circadian rhythm sleep disorder, advanced sleep phase type
Circadian rhythm sleep disorder, irregular sleep-wake type
Circadian rhythm sleep disorder, free-running type
Circadian rhythm sleep disorder, jet lag type
Circadian rhythm sleep disorder, shift work type
Circadian rhythm sleep disorder due to medical condition
Other circadian rhythm sleep disorder (circadian rhythm disorder, NOS)
Other circadian rhythm sleep disorder due to drug or substance

population.[105] The MSLT is a test of the tendency to fall asleep in darkened, quiet situations during the day. It is the primary test for daytime sleepiness and is only considered valid if there has been at least 6 hours of polysomnographically characterized sleep before initiation and 2 hours between the nap opportunities. The time to sleep onset and the occurrence of sleep onset REM periods (SOREMPs) is recorded for four or five naps during the day.[106]

Narcolepsy is strongly suspected with two or more SOREMPs and an average nap sleep onset of less than 8 minutes. Characteristic features include sleep paralysis, the inability to move upon awakening in 25%, hypnagogic hallucinations, the sensation of dreaming while awake in 30%, and cataplexy, a sudden and transient loss of muscle tone in response to strong emotions in 70%.[107] Narcolepsy is subdivided into those patients with cataplexy and those without cataplexy. In addition, a cerebrospinal fluid hypocretin-1 level less than 110 pg/mL is highly specific for narcolepsy with cataplexy.[108] Narcolepsy rarely occurs before 4 years of age and only 6% of patients present younger than 10 years of age.[109] Onset primarily occurs from 15 to 30 years of age and has equal prevalence among men and women.

Idiopathic hypersomnia is characterized by severe excessive daytime sleepiness with either normal sleep time (6 to 10 hours) or prolonged sleep time (greater than 10 hours) and great difficulty with awakening either from nocturnal sleep or naps. It also results in an average nap sleep onset of less than 8 minutes on MSLT but with fewer than two SOREMPs (often none), and the REM-intrusion features of narcolepsy are absent. This disorder usually has an onset earlier than 25 years of age and is insidious in nature.[110]

Circadian Rhythm Sleep Disorders

The body's internal clock is located in the suprachiasmatic nucleus. This endogenous system, along with external light and social cues, keeps people regulated on a 24-hour clock. Circadian rhythm sleep disorders occur when personal sleep-wake patterns are misaligned with the societal clock on a persistent or recurrent basis, thus leading to excessive daytime sleepiness or insomnia and resulting in impaired function. There are a number of disorders within this category, but the underlying dysfunction in all of them is that people are unable to sleep when they want or need to sleep (Box 18-13).

The most common of the circadian rhythm disorders is the delayed sleep phase type. It is especially common among adolescents and young adults.[111] In this disorder, sleep onset is delayed, usually more than 2 hours, and often is later than desired. Sleep duration and quality are usually normal, but the natural wake-up time is delayed and if allowed to sleep according to their desired sleep schedule, these patients will have difficulty falling asleep at a conventional sleep time and wake up late after an appropriate sleep duration.

The advanced sleep phase type is also common, but is more frequently seen in older adults.[112] These patients have difficulty staying awake as late as they would like and commonly wake up earlier than desired. They may be less likely to seek medical attention as fewer social problems result from early morning awakening. These patients also have normal sleep duration and quality for age, but their natural sleep-onset time is shifted earlier in time than desired.

The shift work type of circadian rhythm disorder may affect up to 32% of nighttime shift workers and 26% of rotating shift workers.[113] It has been estimated that 18% of the US population may be engaged in shift work that falls at least partially outside the daytime hours of 6 AM to 6 PM.[114] It is characterized by insomnia or excessive daytime sleepiness that is associated with a work schedule that overlaps the normal sleep time and persists for at least 1 month.[8] This tends to remit if sleep onset returns to a more traditional sleep time.

Lastly, the jet lag type of circadian rhythm disorder is a temporary condition associated with travel across at least two time zones, causing insomnia or excessive daytime sleepiness. Its onset is usually 1 to 2 days after travel and resolution depends on the number of time zones crossed and the direction of travel, in that eastward travel or phase advancement is harder to adjust to than westward travel.[115]

Parasomnias

Parasomnias are undesirable movements or subjective phenomena that occur during sleep; while falling asleep, while waking up, or during sleep itself. These phenomena include autonomic nervous system activation and abnormal movements, dreams, emotions, or behaviors.[8] As a group, parasomnias tend to appear early in childhood and often have a steady and gradual transformation with resolution of symptoms that suggests that the etiology may be maturational. Spontaneous remission with age is common, and there are usually no obvious clinical abnormalities while awake. Few pathophysiologic abnormalities have been identified to explain parasomnias. They are categorized as disorders of arousal (during NREM), REM sleep-related parasomnias, and other parasomnias (Box 18-14).

Sleep terrors, sleepwalking, and confusional arousals are disorders of arousal that usually occur in the first third of the night, predominate in childhood, and commonly decrease in frequency with age.[116] Most of these can be treated with reassurance or improved sleep hygiene. Pharmacologic intervention is rarely necessary.

REM-related parasomnias include REM sleep behavior disorder, isolated recurrent sleep paralysis, and nightmare disorder. REM sleep behavior disorder (RBD) results from a persistence of muscle tone during REM and resulting injurious movements while acting out dreams during REM. It is often associated with, and may precede the onset of, neurologic disorders such as Parkinson's disease and Lewy body dementia.[117] PSG is indicated because patients with OSA may have arousals during REM that mimic RBD.[118] Nightmare disorder is characterized by recurrent episodes of awakenings from sleep with

Box 18-14

Parasomnias

Disorders of Arousal (from NREM Sleep)
Confusional arousals
Sleepwalking
Sleep terrors

Parasomnias Usually Associated with REM Sleep
REM sleep behavior disorder (including parasomnia overlap disorder and status dissociatus)
Recurrent isolated sleep paralysis
Nightmare disorder

Other Parasomnias
Sleep-related dissociative disorders
Sleep enuresis
Sleep-related groaning (catathrenia)
Exploding head syndrome
Sleep-related hallucinations
Sleep-related eating disorder
Parasomnia, unspecified
Parasomnia due to drug or substance
Parasomnia due to medical condition

Box 18-15

Parasomnias Associated with Obstructive Sleep Apnea

OSA-induced arousals from REM sleep
OSA-induced arousals in NREM sleep
OSA-induced cerebral anoxic attacks or nocturnal seizures
REM rebound from CPAP use leading to:
- Confusional arousals
- Sleepwalking
- Sleep terrors

CPAP, continuous positive airway pressure; NREM, non–rapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement.

recall of intensely disturbing dreams, usually accompanied by dysphoric emotions such as fear, anxiety, or anger and with full alertness on awakening and immediate and clear recall.[8] It is common in both childhood and adulthood, and may be especially associated with acute stress events or posttraumatic stress disorder. Treatment may include reassurance, cognitive-behavioral therapy, or pharmacologic intervention.[119]

Several parasomnias have been specifically associated with OSA or OSA treatment (Box 18-15). These include OSA-induced arousals from REM sleep that mimic RBD with the occurrence of complex or violent behaviors upon arousal that are dream-related. The second type occurs after an arousal in NREM sleep with similar complex or violent behaviors that can easily be confused with the disorders of arousal or a seizure. OSA-induced arousals in NREM can also lead to sleep-related eating disorder, which itself can lead to worsening clinical OSA. Another associated parasomnia is the OSA-induced cerebral anoxic attack or nocturnal seizure that can also manifest with parasomnia-type complex or violent behavior. Lastly, the use of nasal CPAP for OSA may result in a significant increase in REM (or REM rebound), leading to confusional arousals, sleepwalking, or sleep terrors.[8] Except when RBD is suspected, PSG is rarely necessary in these patients unless comorbid sleep apnea is suspected. However, in patients with sleep-related violent behaviors, excessive daytime sleepiness, frequent events, unusual age of onset, or unusual clinical features, PSG may be indicated.[116]

Box 18-16

Sleep-Related Movement Disorders

Restless leg syndrome
Periodic limb movement disorder
Sleep-related leg cramps
Sleep-related bruxism
Sleep-related rhythmic movement disorder
Sleep-related movement disorder, unspecified
Sleep-related movement disorder due to drug or substance
Sleep-related movement disorder due to medical condition

Box 18-17

Isolated Symptoms, Apparently Normal Variants, and Unresolved Issues

Long sleeper
Short sleeper
Snoring
Sleep talking
Sleep starts (hypnic jerks)
Benign sleep myoclonus of infancy
Hypnagogic foot tremor and alternating leg muscle activation during sleep
Propriospinal myoclonus at sleep onset
Excessive fragmentary myoclonus

Sleep-Related Movement Disorders

SRMDs are characterized by repetitive movements that occur during sleep and lead to sleep disruption (Box 18-16). The most common of these are restless leg syndrome (RLS) and periodic limb movement disorder (PLMD).[120,121] RLS is defined as an uncomfortable sensation in the legs causing an urge to move them. This discomfort is worsened by inactivity, occurs more commonly in the evening or night, and usually is relieved by movement. In children, diagnosis may be aided by a family history of RLS or polysomnographic documentation of greater than five periodic limb movements per hour.[122] Current research investigating the pathophysiology of RLS has implicated low iron levels and the nigrostriatal dopaminergic system. For this reason, evaluation should include ferritin and transferrin saturation levels. Iron deficiency should be treated for ferritin levels below 18 g/L or a transferrin saturation percentage below 16%.[123]

PLMD is characterized by repetitive stereotypical leg movements that occur while sleeping and result in sleep disturbance or daytime fatigue.[124] Unlike RLS, in which daytime symptoms occur, these patients are usually unaware of the leg movements or the sleep disturbance. The prevalence of PLMD is estimated to be between 4% and 11% of people aged 15 to 100 years, and has been shown to increase with age.[121] Because these disorders also have been related to changes in the nigrostriatal dopaminergic system, it is hypothesized that the onset of PLMD may signal a decline in dopaminergic function.[121] A limited number of studies have shown some reduction in PLMD with clonazepam (mechanism unknown) and dopamine agonist therapy.[125-128]

Isolated Symptoms, Apparently Normal Variants, and Unresolved Issues

Conditions highlighted in this group are generally thought to occur on a continuum between normal and abnormal sleep (Box 18-17).[8] This

includes long sleepers, who generally sleep longer than 10 hours a day, and short sleepers, who usually sleep 5 hours a day or less; sleep time definitions for pediatric patients are adjusted for age. A number of conditions associated with myoclonus or jerks during sleep are also included in this section, as is snoring.

Snoring is diagnosed when the audible noise of snoring is recorded by an observer and there are no complaints of excessive daytime sleepiness (EDS), insomnia, or sleep disruption. Results from a 2005 National Sleep Foundation poll found that 59% of 1500 adults reported that they snore.[129] The 1993 Wisconsin Sleep Cohort Study reported that snoring occurs in 28% of adult women and 44% of adult men.[31] The prevalence of habitual snoring in pediatric populations has been reported to be lower at 7% to 13% in children aged 4 years and younger[130] and 10% in middle and high school students.[98] Whereas treatment for snoring has classically been focused on alleviating social concerns, recent data suggest that patients with habitual snoring alone have lower neurocognitive outcomes (including lowered attention, memory, and intelligence scores) and increased behavioral hyperactivity than their nonsnoring counterparts.[131-134]

Conclusion

While the majority of patients referred to otolaryngologists will have sleep-disordered breathing, a significant cohort may also suffer from other sleep disorders including inadequate sleep hygiene, insomnia, circadian rhythm disorders, and limb movement disorders. Diagnosis of concurrent sleep disorders will allow us to more effectively treat patients with EDS and may be especially important in evaluating patients with persistent disease after medical or surgical treatment.

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CHAPTER NINETEEN

Aesthetic Facial Analysis

Marc S. Zimbler

Key Points

- After completing the chapter, the reader should have a comprehensive understanding of facial landmarks and aesthetic analysis.
- Both soft tissue and skeletal landmarks should be clearly identified as should a relationship to cephalometric analysis.
- The concepts of facial proportions as well as subunit principles should be clearly understood.
- The works of Powell and Humphreys are rudimentary to topographic facial relationships as well as formulated angles.
- Digital photography and standardized patient photo documentation are reviewed.

Throughout history, mankind has tried to define beauty. Poets, philosophers, and artists have pondered its elusive quality while attempting to quantify that which is evident to all of us. As surgeons, however, we are required to have a more scientific approach to beauty to formulate operative plans with successful surgical outcomes. Common reference points are essential in communicating with colleagues and medical record keeping. Furthermore, we must be able to accurately define specific characteristics that deviate from the norm so that we may identify congenital anomalies and facial deformities.

As early as ancient Egypt, aesthetic facial proportions have been idealized in art. However, it was not until the era of Greek philosophy that the study of beauty became a formal discipline. To Plato and Aristotle, beauty meant symmetry, harmony, and geometry. In the fifth century BC, the Greek sculptor Polyclitus defined perfect beauty as the mutual harmony of all parts, such that nothing could be added or subtracted. Such harmonic proportions were held to be beautiful in themselves, independent of any observer.

These ideas were later revisited by the Renaissance artists, who began to define ideal proportions for the human form. This example is nowhere more evident than in the drawings of Leonardo da Vinci and his Vitruvian man (Fig. 19-1). It was da Vinci, who, through the study of anatomy, formulated ideal facial proportions and divided the profile into equal thirds (Fig. 19-2). Leonardo's scientific accuracy rivaled that of Vesalius, whereas his artistic beauty remains unchallenged. Another Renaissance artist inspired by the Vitruvian notion of perfect proportions was the German printmaker Albrecht Durer. Durer used his own finger as a unit of measurement to construct a proportional system for the entire body, and in 1528 he published a four-book treatise on human proportions. Durer divided the facial profile into four equal parts and recognized that the length of the nose equals that of the ear.

The artistic canons set forth in antiquity and during the Renaissance dominated Western art for centuries. In the twentieth century, anthropometrist Leslie Farkas and colleagues[1] challenged the classic canons by measuring the facial proportions of 200 women, including 50 models. His results concluded that some of the canons are nothing more than artistic idealizations. Nevertheless, although social and cultural factors influence every generation's concept of beauty, the aesthetic canons have withstood the test of time. Currently, the parameters established in the facial plastic surgery literature are based predominately on the works of Powell and Humphreys, who in 1984 crystallized this topic into a single text, *Proportions of the Aesthetic Face*.[2]

Anatomic Landmarks and Reference Points

Facial analysis is dependent on both soft tissue and skeletal anatomic landmarks. Soft tissue reference points are shown in Figure 19-3 and listed in Box 19-1. Skeletal reference points are defined by cephalometric analysis and are shown in Figure 19-4 and listed in Box 19-2.

The Frankfort horizontal plane (Fig. 19-5) is the standard reference point for patient positioning in photographs and cephalometric radiographs. The Frankfort plane is defined as a line drawn from the superior aspect of the external auditory canal to the inferior border of the infraorbital rim while the patient's gaze is parallel to the floor. A soft tissue definition for the inferior aspect of the infraorbital rim is the point of transition between lower eyelid and cheek skin.

Facial Proportions

The initial assessment of the face evaluates symmetry. Symmetry is rarely perfect when comparing halves through a midsagittal plane (Fig. 19-6); nevertheless, midline points should lie on the axis line. Facial width is evaluated by dividing the face into equal fifths (Fig. 19-7). The width of one eye should equal one fifth of the total facial width, as well as the intercanthal distance or nasal base width.

Facial height is commonly assessed by one of two methods. The first method divides the face into equal thirds (Fig. 19-8) as described by da Vinci. Measurements are made in the midline from the trichion to the glabella, from the glabella to the subnasale, and from the subnasale to the menton. The second method excludes the upper third of the face because of common variability regarding hairline position. Measurements are made from the nasion (as opposed to the glabella) to the subnasale and from the subnasale to the menton (Fig. 19-9). With this method the midface represents 43% of the height, with the lower face representing 57%.

Subunit Analysis

The face is divided into aesthetic units (Fig. 19-10) that are further divided into subunits. The major units that are classically defined for facial analysis include the forehead, eyes, nose, lips, chin, ears, and neck. The units and subunits are based on skin thickness, color, texture, and underlying structural contour. Precise planning of surgical incisions

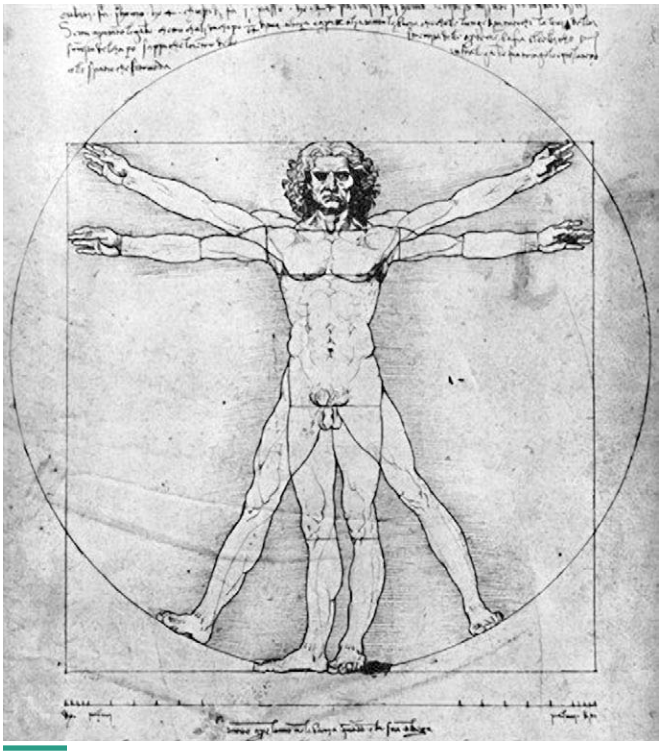

Figure 19-1. Leonardo da Vinci. The proportions of the body according to Vitruvius, ca. 1490. Pen and ink with touches of wash, over stylus 34.4 × 24.5 cm. *(Courtesy of the Galleria dell' Accademia, inv.228, Venice.)*

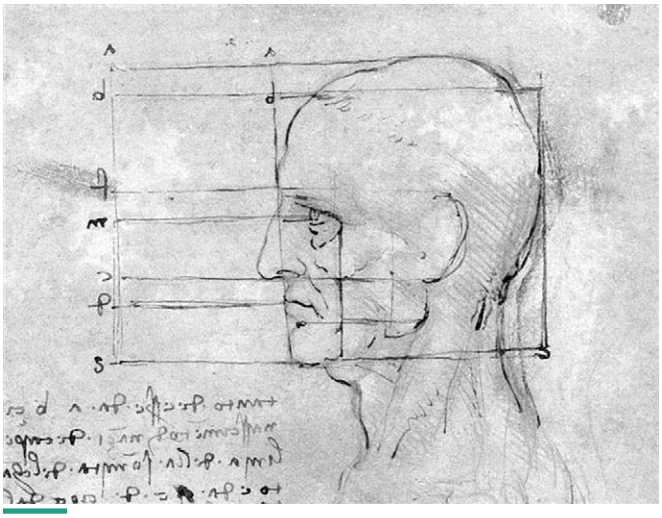

Figure 19-2. Leonardo da Vinci. The proportions of the head, ca.1490. Pen and ink over black chalk, 28.0 × 22.2 cm. *(Courtesy of the Galleria dell' Academia, inv.236v, Venice.)*

and reconstructions require analysis of the entire unit or subunit. Incisions parallel to relaxed skin tension lines (Fig. 19-11) and within unit or subunit borders result in the most favorable scars.

Forehead

The boundaries of the forehead are from the hairline to the glabella and make up the upper third of the face. The contour anatomy of the forehead is most aesthetically pleasing with a gentle convexity on profile. The nasofrontal angle (Fig. 19-12) is created by a line tangent to the glabella through the nasion and intersecting with a line tangent to the nasal dorsum. The range of aesthetic measurements for this angle is from 115 to 135 degrees.

Box 19-1

Soft Tissue Anatomic Landmarks

Trichion (Tr): Anterior hairline in the midline
Glabella (G): Most prominent point of the forehead on profile
Nasion (N): The deepest depression at the root of the nose; typically corresponds to the nasofrontal suture
Radix: Root of the nose, a region and not a point; part of an unbroken curve that begins at the superior orbital ridge and continues along the lateral nasal wall
Rhinion (R): Soft tissue correlate of the osseocartilaginous junction on the nasal dorsum
Sellion: Osseocartilaginous junction on the nasal dorsum
Supratip: Point cephalic to the tip
Tip (T): Ideally, the most anterior projection of the nose on profile
Subnasale (Sn): Junction of columella and upper lip
Labrale superius (Ls): Vermilion border of upper lip
Stomion (S): Central portion of interlabial gap
Stomion superius: Lowest point of upper lip vermilion
Stomion inferius: Highest point of lower lip vermilion
Labrale inferius (Li): Vermilion border of lower lip
Mentolabial sulcus (Si): Most posterior point between lower lip and chin
Pogonion (Pg): Most anterior midline soft tissue point of chin
Menton (Me): Most inferior soft tissue point on chin
Cervical point (C): The innermost point between the submental area and the neck

Box 19-2

Cephalometric Reference Points

(S) Sella: The midpoint of the hypophysial fossa
(Or) Orbitale: The most inferior point on the infraorbital rim
(P) Porion: The most superior point on the external auditory meatus
(Cd) Condylion: The most superior point on the head of the mandibular condyle
(Ar) Articulate: The point of intersection of the posterior margin of the ascending mandibular ramus and the outer margin of the cranial base
(ANS) Anterior nasal spine
(PNS) Posterior nasal spine
(A) Point A, subspinale: The deepest point in the concavity of the premaxilla
(Pr) Prosthion: The lowest most anterior point on the alveolar portion of the premaxilla
(Id) Infradentale: The highest most anterior point on the alveolar portion of the mandible
(B) Point B, supramentale: The most posterior point in the outer contour of the mandibular alveolar process
(Pg) Pogonion: Most anterior point on the bony chin in the midline
(Gn) Gnathion: A point between the most anterior (Pg) and inferior (Me) point on the chin
(Me) Menton: The lowest point on the mandible
(Go) Gonion: The midpoint at the angle of the mandible

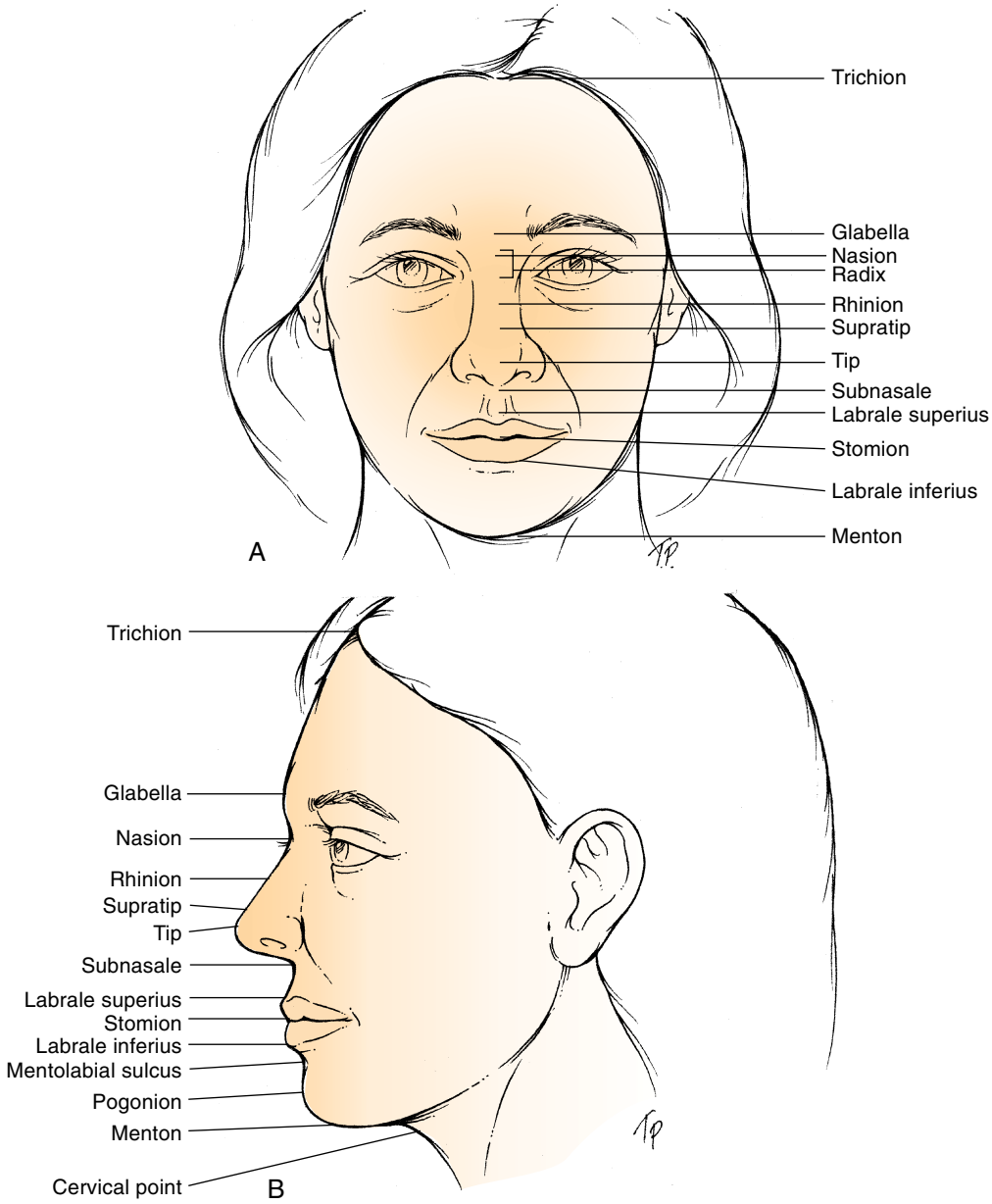

Figure 19-3. Frontal view **(A)** and lateral view **(B)** of soft tissue reference points.

The ideal eyebrow shape follows a smooth and gently curving arc. The brow should begin medially with a slight clublike configuration and gradually taper toward its lateral end. Lateral position for a female is well above the supraorbital rim, whereas for a male it is at or close to the rim. The medial edge of the eyebrow lies on a perpendicular line that passes through the lateral-most portion of the nasal ala and approximately 10 mm above the medial canthus (Fig. 19-13). In women, the highest point of the eyebrow arc is at a line drawn tangentially from the lateral limbus. However, this ideal eyebrow position can vary with fashion trends, and the highest point may actually lie anywhere from the lateral limbus to the lateral canthus. Sheen[3] describes the eyebrow arc as most pleasing when it extends as an unbroken line from the brow down to the lateral nasal tip (Fig. 19-14).

Eyes

The boundaries of the orbits are in the lower third of the upper face and the upper third of the midface. The width of one eye from medial to lateral canthus should equal one fifth of the facial width. The intercanthal distance should equal the width of one eye. Normal intercanthal distances for women and men are 25.5 to 37.5 mm and 26.5 to 38.7 mm, respectively. In general, the eye should be almond shaped with the lateral canthus slightly more superior than the medial canthus. The average palpebral opening is 10 to 12 mm in height and 28 to 30 mm in width. The upper lid crease is the line created by the insertion of the levator aponeurosis and orbital septum into the orbicularis oculi and dermis. The location of the crease averages approximately 11 mm from the lash line but can vary between 7 and 15 mm. The upper eyelid normally covers a small portion of the iris but not the pupil. The lower eyelid is within 1 to 2 mm of the iris on neutral gaze, with the sclera not being visible below the iris margin.

Nose

The boundaries of the nose are within the middle third of the face. On the lateral view, the nasal starting point begins at the nasion, which ideally corresponds to the same level as the upper eyelid's superior palpebral fold (see Fig. 19-3) and ends at the subnasale. Because the nose is the central and most prominent aesthetic unit of the face, it is always analyzed in relationship to other facial structures, most importantly the chin, lips, and eyebrows. The topographic subunits of the nose (Fig. 19-15) have been described by Burget[4] and are essential when

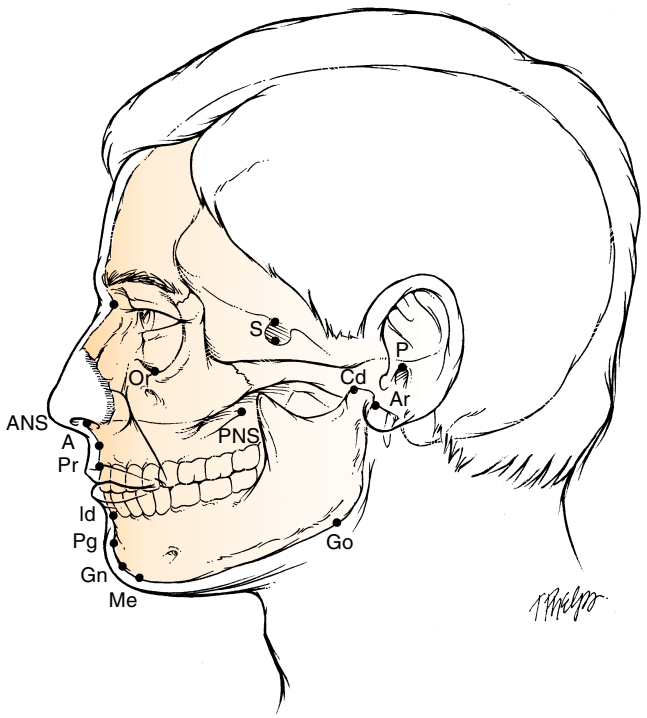

Figure 19-4. Cephalometric reference points. See Box 19-2 for definitions of all abbreviations.

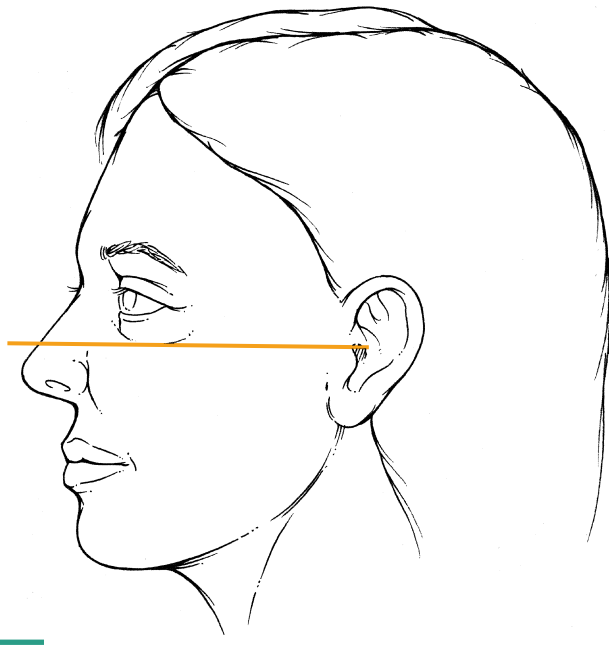

Figure 19-5. Frankfort horizontal plane. A line is drawn from the superior aspect of the external auditory canal to the most inferior aspect of the infraorbital rim.

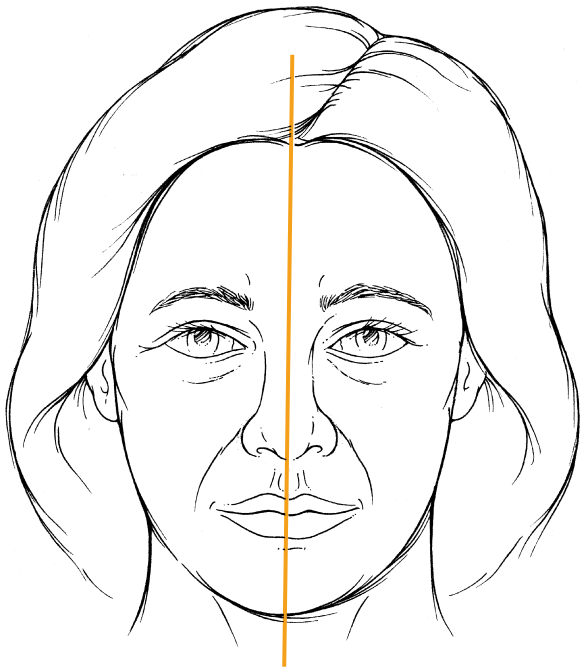

Figure 19-6. Facial symmetry through midsagittal plane.

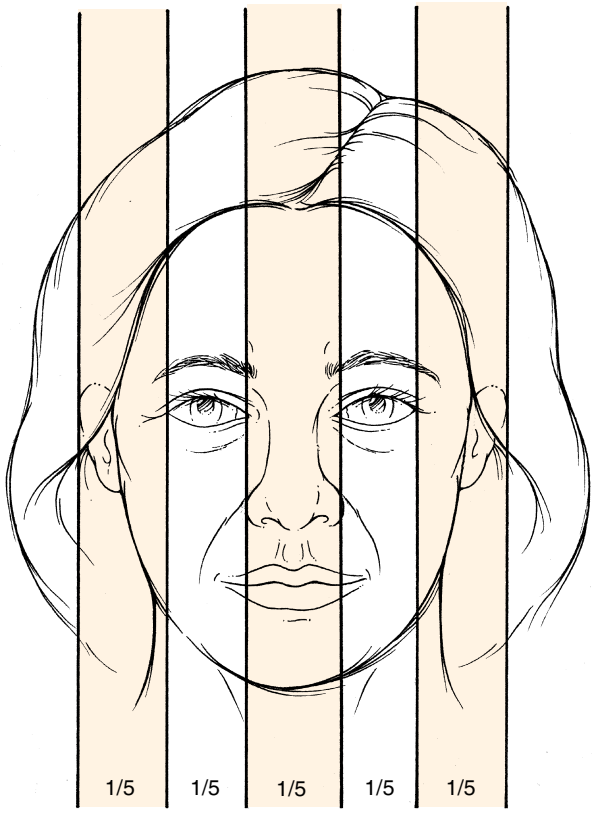

Figure 19-7. Facial width. The facial width is divided into equal fifths.

planning reconstructive procedures. The borders of nasal subunits allow for scar camouflage when incisions lie along subunit margins.

Nasofacial Relationships

Powell and Humphreys[2] formulated relationships between the nose and face. They include the nasofrontal angle, nasolabial angle, nasofacial angle, and nasomental angle. The nasofrontal angle (see Fig. 19-12) is described in the forehead section of this chapter. The nasolabial angle defines the angular inclination of the columella as it meets the upper lip. The angle is formed between the intersection of a line tangent to the labrale superius and subnasale and a line tangent to the subnasale and the most anterior point of the columella (Fig. 19-16). This angle should measure 95 to 110 degrees in women and 90 to 95 degrees in men. The nasofacial angle is the incline of the nasal dorsum in relation to the facial plane (Fig. 19-17). It represents the angle formed from a vertical line tangent from the glabella through the pogonion intersect-

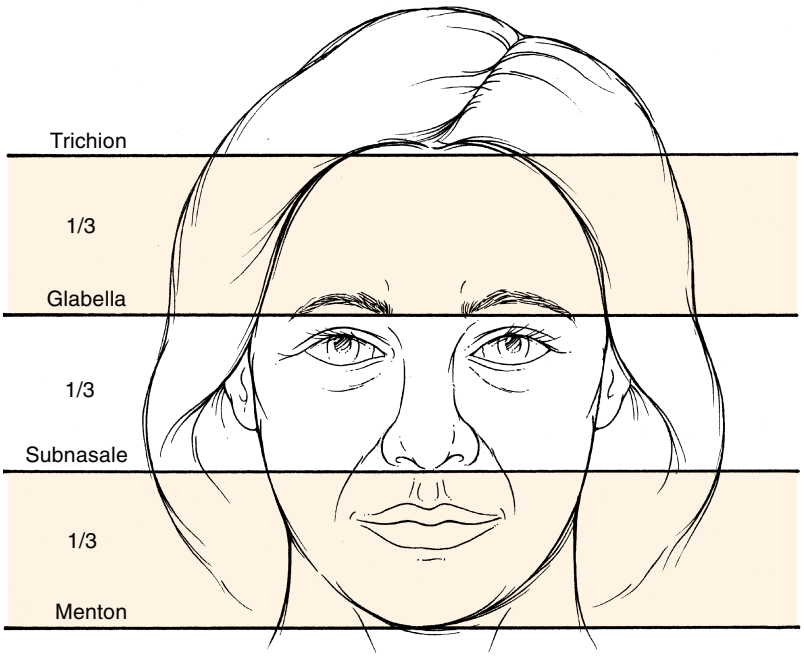

Figure 19-8. Facial height. The facial height is divided into equal thirds. From trichion to glabella, from glabella to subnasale, and from subnasale to menton.

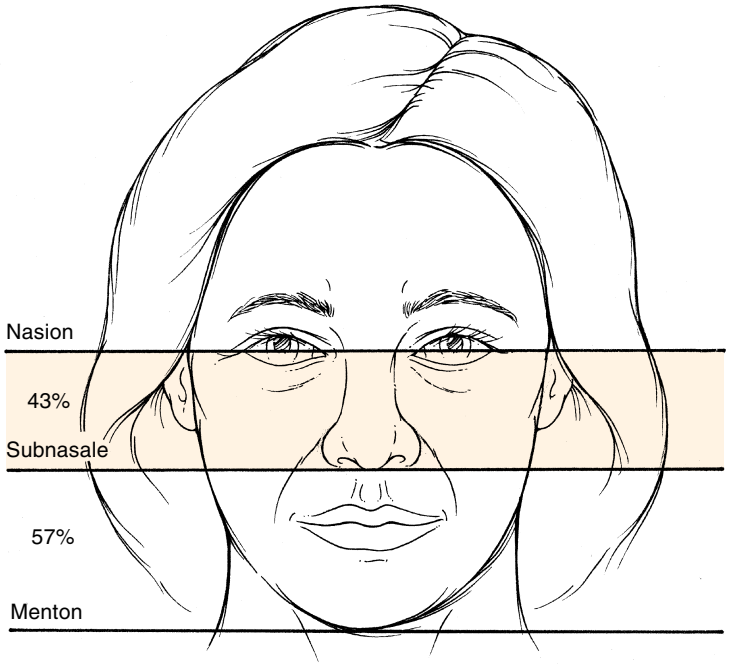

Figure 19-9. Middle and lower facial height. Division of height is unequal and measured from the nasion to subnasale and from the subnasale to the menton.

ing a line from the nasion through the nasal tip. This angle ideally measures 36 degrees but can vary from 30 to 40 degrees. The nasomental angle describes the angle between a tangent line from the nasion to the nasal tip intersecting with a line from the tip to the pogonion (Fig. 19-18). The range of this angle is from 120 to 132 degrees, and it can clearly be obscured if the chin or lip position is in facial disharmony.

Nasal Rotation and Projection

Nasal rotation and projection are essential measurements in determining nasal aesthetics. Tip rotation generally occurs along an arc produced by a radius based at the external auditory canal (Fig. 19-19). Rotation increases along the upper portion of the arc and decreases along the lower portion. Several methods have been used to analyze tip projection and, in turn, have defined nasal length. Simons[5] measures tip projection in relation to the length of the upper lip (Fig. 19-20). Nasal projection is approximately equal to the length of the upper lip, giving a ratio of 1:1. Goode's[2] method uses a vertical line drawn from the nasion to the alar groove, a perpendicular line from the alar groove to the nasal tip, and a line from the tip back to the nasion (Fig. 19-21). The ratio comparing the length of the perpendicular line (alar groove to tip) with that of the nasal length (nasion to tip) should be 0.55 to 0.60. When

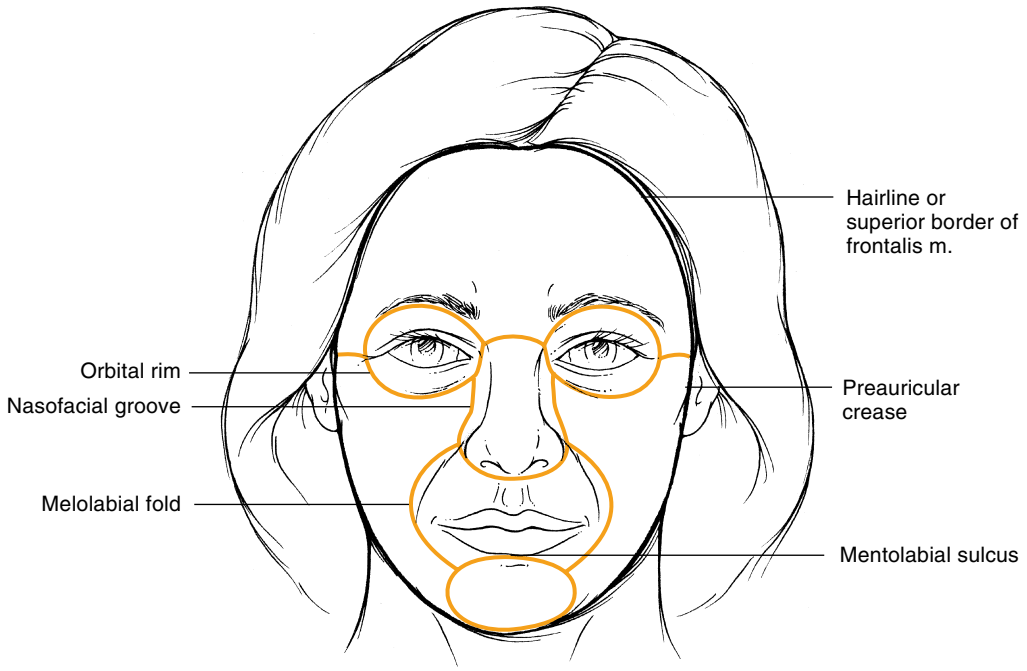

Figure 19-10. Aesthetic units of the face.

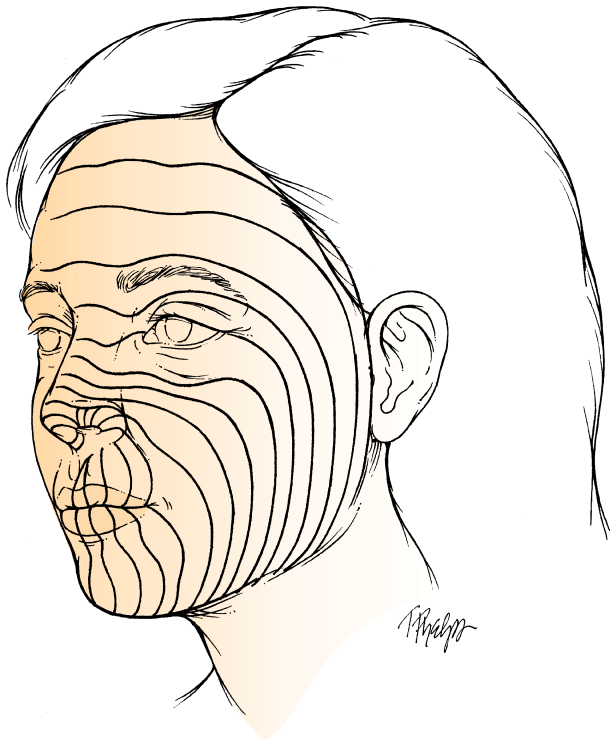

Figure 19-11. Relaxed skin tension lines of the face.

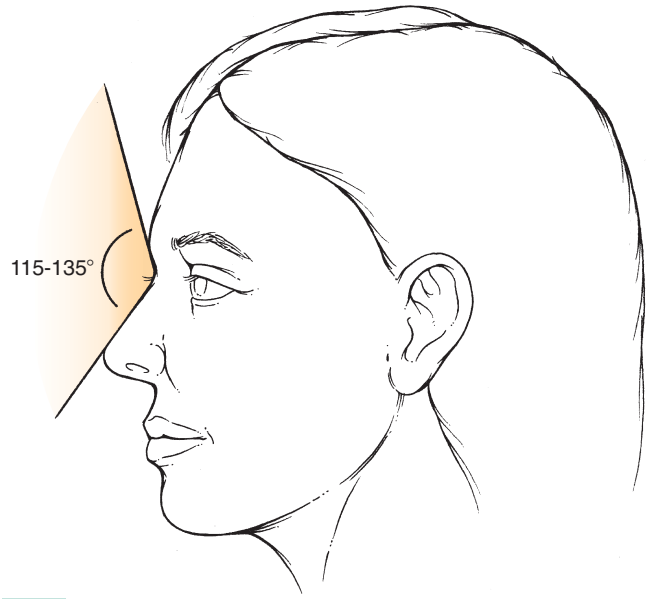

Figure 19-12. Nasofrontal angle (115 to 135 degrees).

these ratios are observed, the nasofacial angle is approximately 36 degrees. Crumley and Lanser[6] use a similar method and use a 3-4-5 triangle, where the hypotenuse is the nasal length and the projection is the smallest arm of the triangle.

Alar-Columellar Complex

On lateral view, the ala-to-tip lobular complex ratio is considered optimal at 1:1 (Fig. 19-22); columella shown at 3 to 5 mm is considered acceptable. From the basal view, the nose should be triangular and divided into three equivalent units (Fig. 19-23).

Lips

The boundaries of the lips are contained within the lower one third of the face. The upper lip is measured from the subnasale to the stomion superius, whereas the lower lip and chin are measured from the stomion inferius to the menton (Fig. 19-24). The subunits of the lip are well defined (Fig. 19-25), whereas the height of the upper lip to the lower lip should have a ratio of approximately 1:2. Horizontal lip position can be determined by two separate methods. The first constructs a line from the subnasale through the labrale inferius to the pogonion (Fig. 19-26). A perpendicular line through the anterior-most point of each lip defines its horizontal position. The upper and lower lip should lie 3.5 and 2.2 mm anterior to this line, respectively. The second method uses the nasomental angle to determine horizontal lip position. The lips should fall just behind this line at a

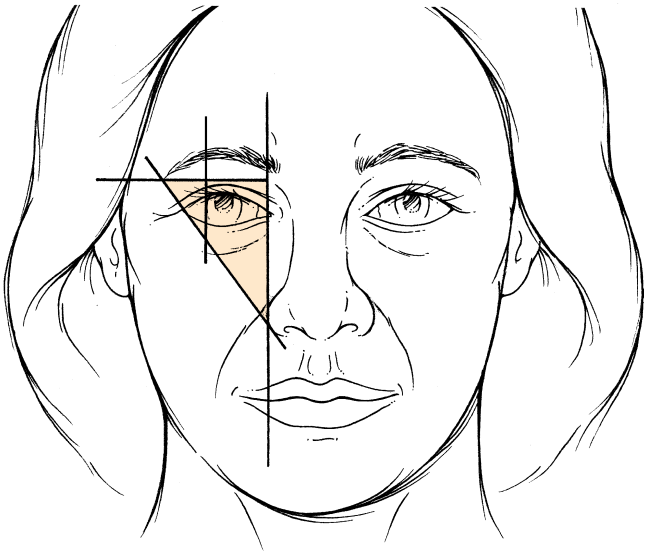

Figure 19-13. Ideal eyebrow position. Medial brow head lies along horizontal tangent with medial canthus and nasal ala. The highest point of brow arch is located above the lateral limbus.

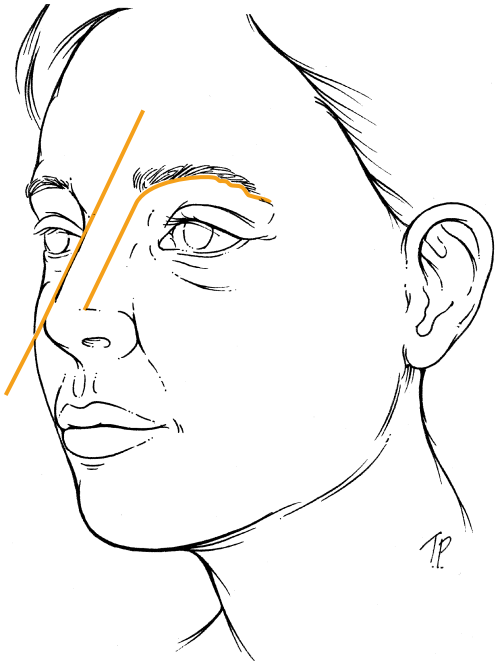

Figure 19-14. Unbroken aesthetic line forms eyebrow to nasal tip.

distance of 4 mm for the upper lip and 2 mm for the lower lip (see Fig. 19-18).

Chin

The boundaries of the chin lie in the lower one third of the face and can be measured from the mentolabial crease to the menton. The chin is a pivotal facial unit when analyzing the nose or neck. Most rhinoplasty analysis begins with proper chin position in relation to nasal projection and facial harmony. Gonzalez-Ulloa[7] described the ideal chin position by a tangential line through the nasion to pogonion, which is almost perpendicular to the Frankfort horizontal plane (Fig. 19-27). An alternative method for analyzing chin position is described in the lip section (See Fig. 19-26), where the mentolabial sulcus lies approximately 4 mm behind this line.

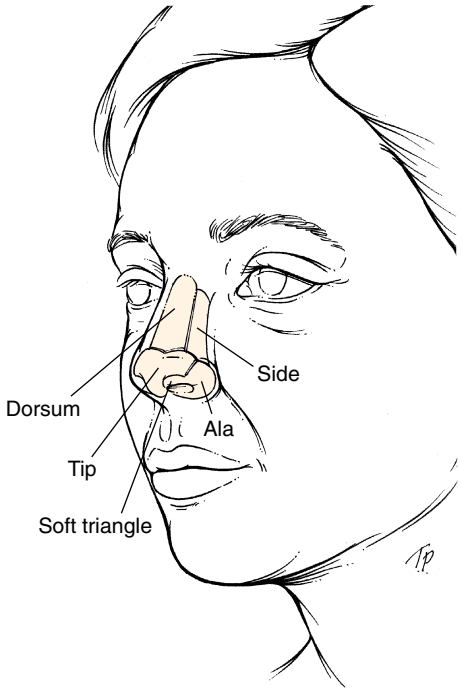

Figure 19-15. Nasal aesthetic subunits adapted from Burget's description.

Neck

The ideal neck has a well-defined mandible from the pogonion to the angle with an acute mentocervical angle. This angle is produced by drawing a line from the glabella to the pogonion and intersecting with a line tangent from the menton to the cervical point (Fig. 19-28). The cervical point is defined as the innermost point between the submentum and neck. It is also important to evaluate chin position when analyzing the neck, because an obtuse mentocervical angle may cause the perception of poor chin projection.

Ears

The width of the ear is approximately one half its length. The ear length should approximate the length of the nose measured from the nasion to the subnasale. The superior aspect of the ear lies at the level of the eyebrow, whereas its inferior aspect is at the level of the nasal ala. The long axis of the ear is parallel to the long axis of the nasal dorsum (Fig. 19-29) and is noted to have a posterior rotation of approximately 15 degrees from the vertical plane. The ear protrudes from the skull at an angle of approximately 20 to 30 degrees, which usually translates into a measurement of 15 to 25 mm from the helix to the mastoid skin.

Skin and Rhytids

When analyzing the face, evaluation of the skin deserves special attention. Skin texture, thickness, elasticity, and solar damage are all critical factors contributing to one's overall facial appearance. In 1988, Fitzpatrick[8] established skin type classification (Box 19-3), and in 1994, Glogau[9] categorized photoaged skin (Box 19-4). Most importantly, however, in the examination of the skin is the analysis of facial rhytids. Wrinkles or rhytids originate from a wide variety of sources that can include chronologic aging, photoaging or solar damage, and skin folding secondary to loss of underlying skeletal or soft tissue support. Hyperdynamic facial lines (Fig. 19-30) are specific wrinkles that are caused by long-term facial muscle animation. Examples of these include horizontal forehead creases, crow's feet, and glabellar lines. Each line is caused by repeated underlying muscle contraction. Hyperdynamic lines should be distinguished from other facial lines such as the melolabial fold, mentolabial sulcus, and the fine crisscross wrinkling found on the cheek and under the eyelids.

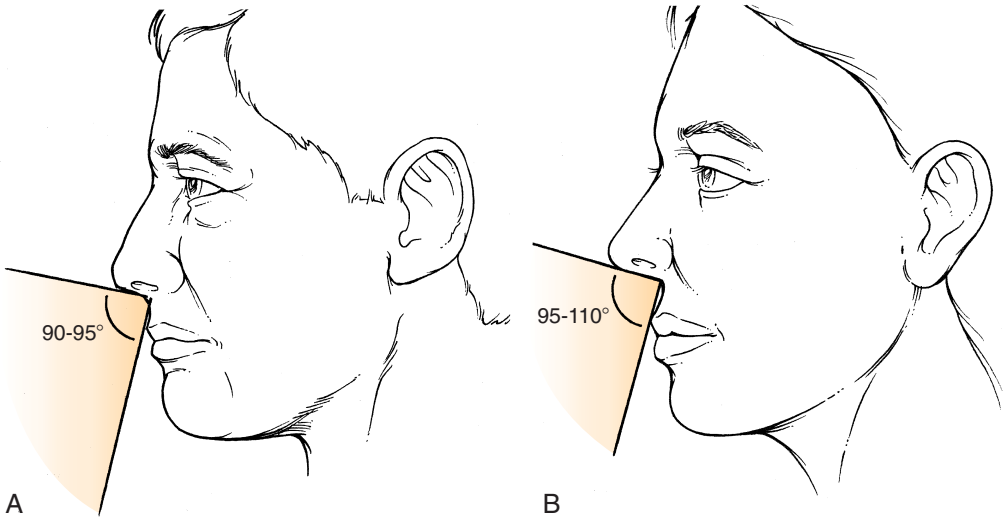

Figure 19-16. Nasolabial angle. Male **(A)**, 90 to 95 degrees; female **(B)**, 95 to 110 degrees.

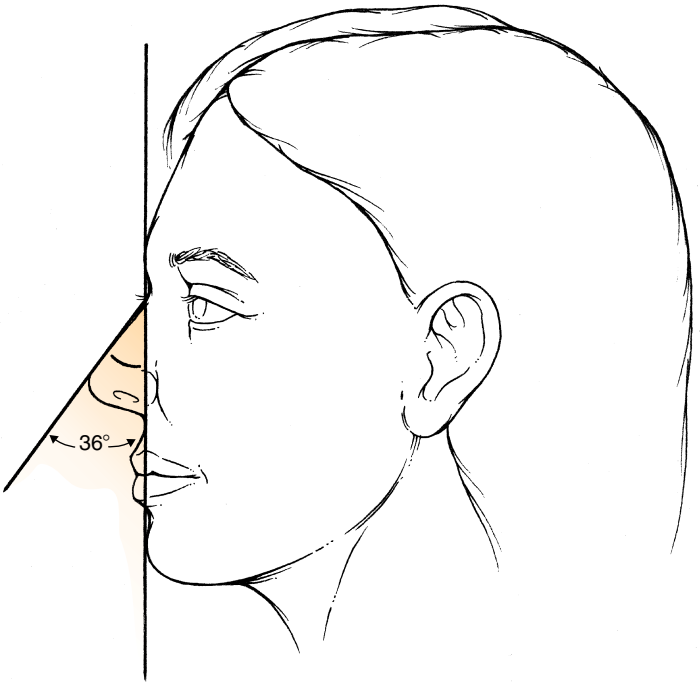

Figure 19-17. Nasofacial angle (30 to 40 degrees).

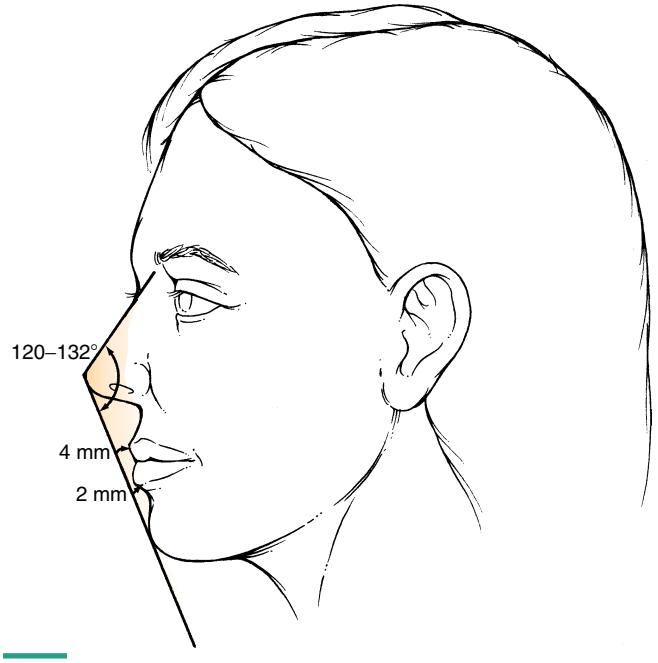

Figure 19-18. Nasomental angle (120 to 132 degrees). The lips should fall just behind this line at a distance of 4 mm for the upper lip and 2 mm for the lower lip.

Box 19-3

Fitzpatrick Classification of Sun-Reactive Skin Type

Skin Type	Skin Color	Characteristics
I	White	Always burns, never tans
II	White	Usually burns, tans with difficulty
III	White	Sometimes burns, sometimes tans
IV	White	Rarely burns, tans with ease
V	Brown	Very rarely burns, tans very easily
VI	Black	Never burns, always tans

Box 19-4

Glogau Photoaging Classification

Type I: No keratoses, few wrinkles, age 20 to 30, rarely wears makeup

Type II: Early lentigenes, wrinkles on animation, age 30 to 40, sometimes wears makeup

Type III: Advanced photoaging, wrinkles present at rest, age 50 to 60, always wears makeup

Type IV: Severe photoaging, severe wrinkling, age 60 to 70, makeup has minimal benefit

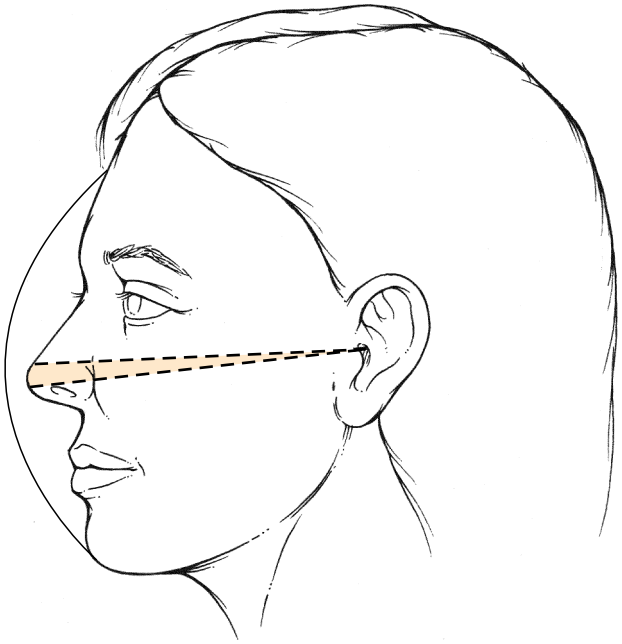

Figure 19-19. Tip rotation generally occurs along an arc produced by a radius based at the external auditory canal.

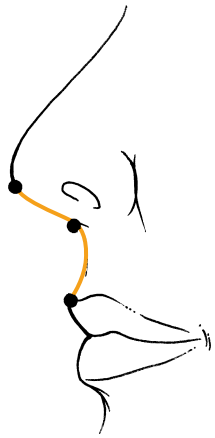

Figure 19-20. Simons' nasal projection is approximately equal to the length of the upper lip with a ratio of 1:1.

Computer Imaging and Digital Photography

Technologic advances in digital photography and computer graphics have revolutionized the way many surgeons obtain and process patient photographs. The immediate availability of photographs for review and the ability to generate computer-modified images provide an easy and effective means of preoperative analysis. Routine office consultations typically include "patient imaging," which has become a vital tool toward preoperative education. It provides the surgeon an opportunity to strengthen communication with the patient regarding realistic expectations of surgical outcome. Added benefits of computer imaging also include photoarchiving and its use as an instructional tool for residents and fellows. Over the past few years, this technology has evolved from being costly, cumbersome, and slow to one that is highly efficient, user-friendly, and reasonably priced.

The essential components for a computer imaging system include a computer, an image capture device or camera, and imaging software. Computer specifications are dependent on the demands and expectations of the surgeon. Additional components that are highly recommended include a CD burner for archiving and storage, a graphics board, digital drawing tablet, and a high-resolution color printer.

As with 35-mm photography, the clarity of digital photography is dependent on the sophistication of the camera and its lens. The resolution of digital cameras is described in pixels, and it currently ranges up to 12.0 megapixels. However, a camera containing 3.0 megapixels is sufficiently suited for the demands of most medical photography. A 3.0-megapixel image printed on 4- × 6-inch glossy photo paper is nearly indistinguishable from a conventional photograph. For

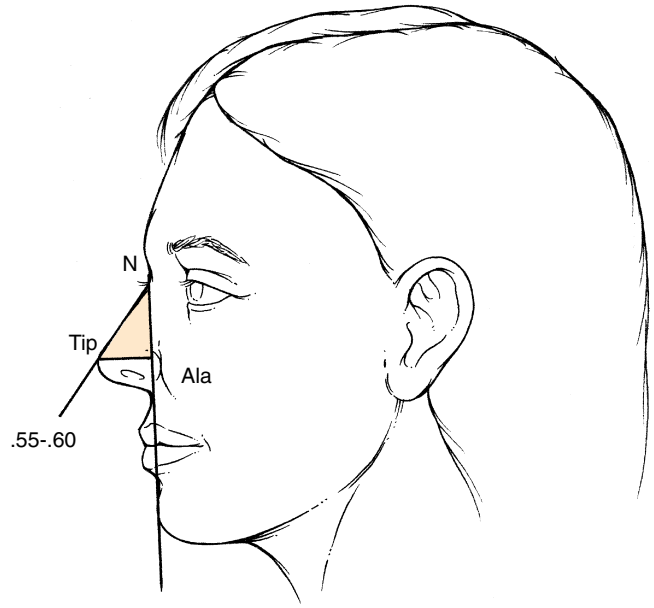

Figure 19-21. Goode's method of tip projection.

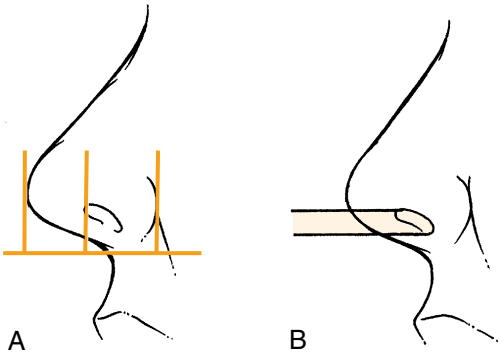

Figure 19-22. Nasal ala. **A,** Ala-to-tip lobular ratio should be 1:1. **B,** Columella is shown between 3 and 5 mm.

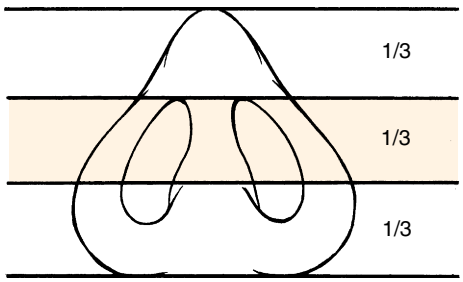

Figure 19-23. Nasal base divided into equal thirds.

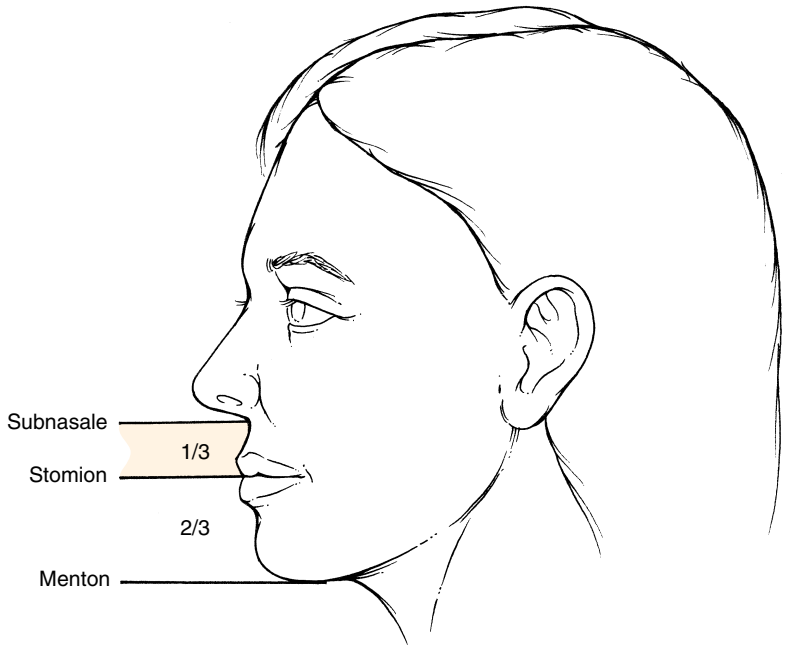

Figure 19-24. Lip ratio and lower facial third.

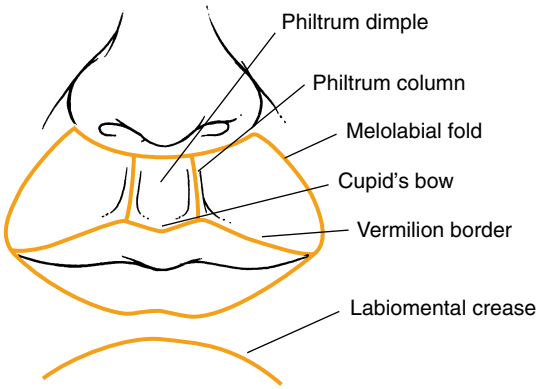

Figure 19-25. Lip aesthetic subunits.

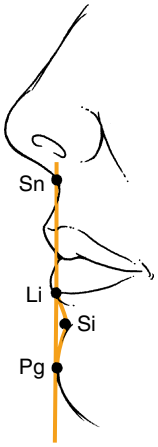

Figure 19-26. Horizontal lip position. Mentolabial sulcus (Si) should lie 4 mm posterior to a vertical line dropped from the subnasale (Sn) through the labrale inferius (Li) and extending to the pogonion (Pg).

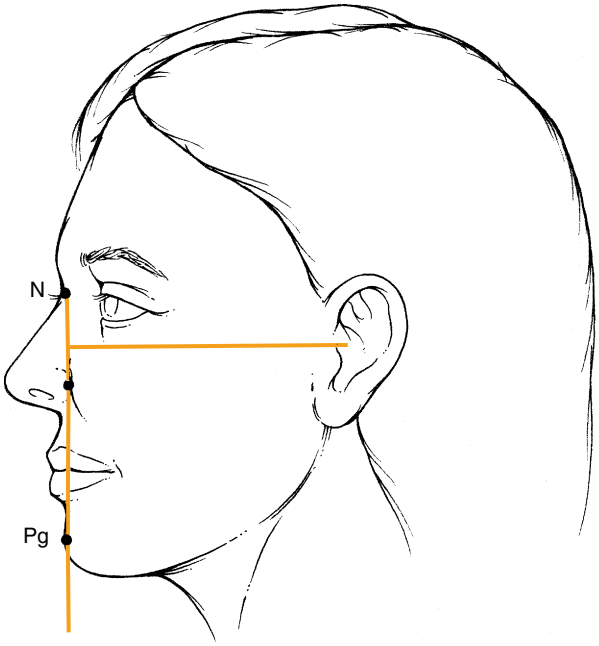

Figure 19-27. The zero meridian of Gonzalez-Ulloa. Ideal chin position is on a vertical line from the nasion (N) to the pogonion (Pg), which is perpendicular to the Frankfort horizontal.

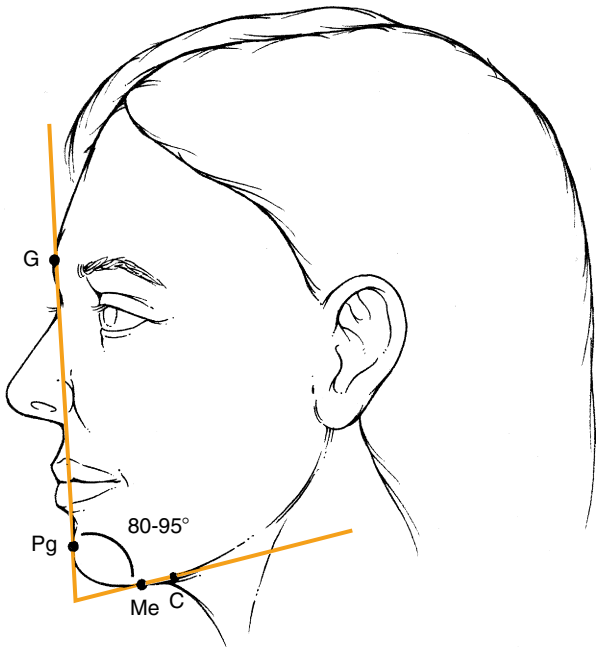

Figure 19-28. Mentocervical angle (80 to 95 degrees). C, cervical point; G, glabella; Me, menton; Pg, pogonion.

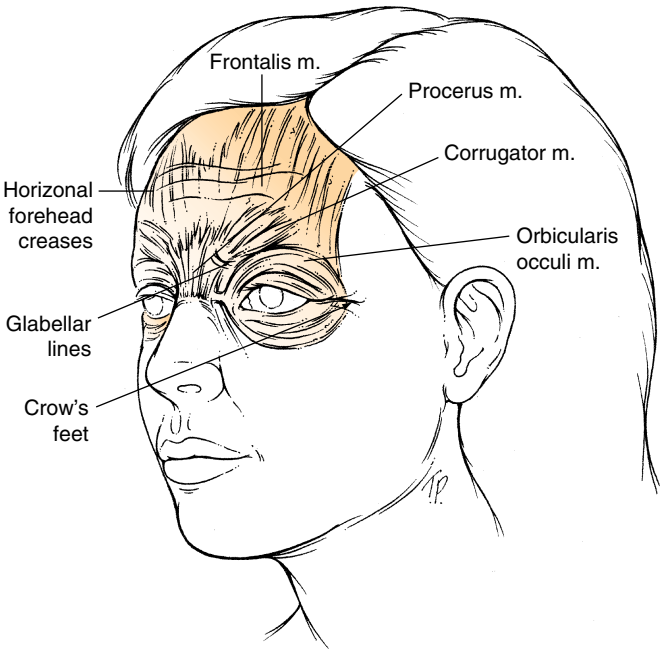

Figure 19-30. Hyperdynamic facial lines caused by repeated underlying muscle contraction.

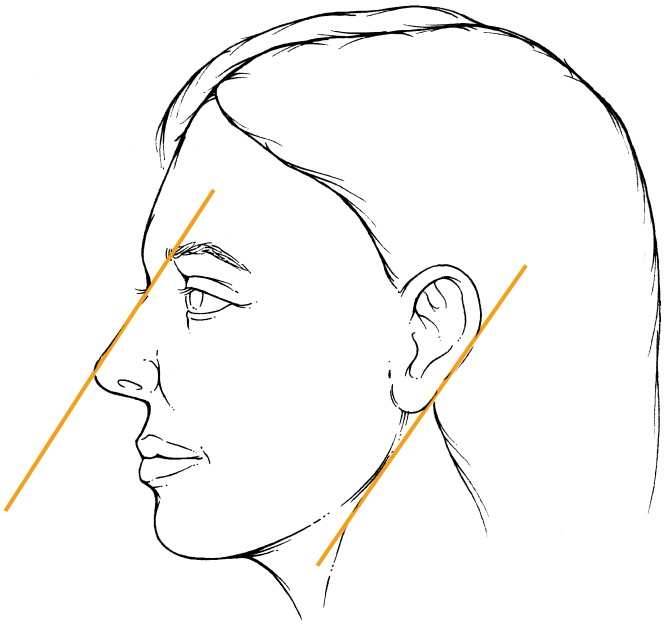

Figure 19-29. Long axis of the ear parallels the long axis of the nasal dorsum.

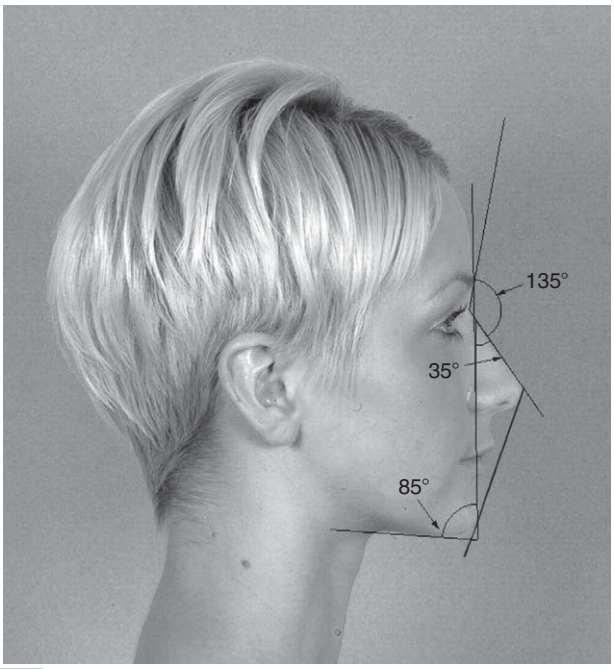

Figure 19-31. Facial angle analysis, including nasofrontal angle, nasofacial angle, and mentocervical angle. *(Courtesy of Canfield Clinical Systems.)*

a more professional look with 35-mm like quality and control, a true single lens reflex (SLR) with higher mega pixels is preferred. The additional capabilities include interchangeable lenses and through-the-lens (TTL) metering. The price for advanced digital SLR cameras has dropped dramatically over the past several years, and a 6.0-megapixel camera can be purchased, with lens included, for around $700. Lighting, background, and patient positioning are similar to conventional photography, and shoe mount external flashes are suggested for improved results with minimal shadow.

Once the photographic images are downloaded onto the computer, a variety of image or graphics software may be used to open and alter images. The Mirror Suite (Image Management Plus Simulation) (Canfield Scientific, Inc., Fairfield, NJ) is sophisticated but user-friendly high-end software designed for medical professionals. Image files from the camera once downloaded are automatically tethered into the Mirror Software and saved into patients' charts. The ease and speed of image alteration lies at the heart of this sophisticated software, making patient consultations streamlined and informative. Furthermore, this advanced software has the ability to measure and analyze facial angles for assistance in preoperative analysis and planning (Fig.

Figure 19-32. Preoperative *(left)* and postcomputer imaging *(right)* of combined rhinoplasty and chin augmentation. *(Courtesy of Canfield Clinical Systems.)*

For list of references log onto www.expertconsult.com.

19-31). The cost of such commercially available systems, complete with computer, camera, and software, is several thousands of dollars. More basic systems, however, may be pieced together by a physician to maintain a more modest price.

Computer imaging and its ability to generate altered images for patient education can be particularly helpful during the preoperative rhinoplasty consultation. Computer-generated changes are compared with preoperative images and reviewed with the patient. The surgeon must be conservative with computer-generated changes and avoid overzealous alterations. In this manner, realistic expectations are nurtured, and a common outcome concept can be reached between surgeon and patient. Computer imaging can be particularly helpful to demonstrate to the rhinoplasty patient with microgenia the added benefit of chin augmentation (Fig. 19-32). The computer-generated images assist patients in visualizing the overall improvement in facial harmony.

CHAPTER TWENTY

Recognition and Treatment of Skin Lesions

Andrea Willey

Neil A. Swanson

Ken K. Lee

Key Points

- Recognition and treatment of benign and malignant skin lesions is an important aspect of otolaryngology–head and neck surgery.
- The skin is limited in the number of ways it can respond to stimuli; thus many neoplasms appear similar and features that differentiate them may be subtle.
- Skin biopsy is essential for the definitive diagnosis of many cutaneous neoplasms.
- The proper use of biopsy techniques to establish a histologic diagnosis is critical, because the ability to establish a definitive diagnosis depends directly on the clinical specimen obtained for histopathologic evaluation.
- A wide variety of therapeutic options exist for benign, premalignant, and cancerous skin lesions, the selection of which relies upon the accurate clinical and histologic diagnosis and the technique best suited to the individual lesion.
- Cutaneous neoplasms may be associated with internal malignancies and genetic syndromes that may warrant further evaluation and management from other medical specialties.

Recognition and treatment of skin lesions is an important aspect of otolaryngology–head and neck surgery. Many of the diseases that an otolaryngologist–head and neck surgeon sees can involve the skin. Whether they are a patient's chief complaint or are noted on a routine examination, skin lesions need to be recognized so that proper diagnosis and management are instituted. This chapter provides the otolaryngologist–head and neck surgeon with practical knowledge of benign and malignant cutaneous neoplasms, including epidermal tumors, cystic lesions, vascular tumors, and fibroadnexal tumors. Preferred therapeutic options are reviewed and diagnostic methods commonly used by dermatologists and cutaneous surgeons are presented that can easily be applied by the otolaryngologist–head and neck surgeon. Biopsy techniques used to establish a histologic diagnoses are stressed because the pathologist's ability to establish a definitive diagnosis depends directly on the clinical specimen obtained for histopathologic evaluation. An in-depth discussion of all cutaneous tumors is beyond the scope of this chapter. Recognition and treatment of common neoplasms of the skin are discussed. The management of cutaneous carcinomas and melanoma are discussed in another chapter.

Epidermal Neoplasms

Epithelial neoplasms of the skin can range from entirely benign to highly malignant tumors. Epidermal tumors are so common that few people go through life without acquiring at least one. A great assortment of epidermal tumors under a wide variety of names have been described; the more common and important ones are discussed in this chapter.

The following important factors relevant to epidermal tumors should be noted. First, the epidermis in the healthy person is a relatively thin structure and is the outermost layer of the skin. Hyperproliferation of epidermal cells results in tumors that usually appear superficially and are often associated with scale, ulceration, or changes in skin texture. Dermal tumors and tumors of the cutaneous appendages (adnexal tumors) are usually deeper and therefore more nodular in appearance. Recognizing these differences is one general way of differentiating between the two tumor groups. The second important factor is that there are three types of lesions that occur within epidermal tumors: benign, precancerous, and cancerous. The precise nature of precancerous lesions has been debated widely, but the term persists in the literature; it refers to a group of epidermal lesions of which a small percentage can become malignant. Third, because the epidermis is limited in the number of ways it can respond to stimuli, the clinical presentations of many tumors will be similar and may be subtle, with little outward change in appearance. Even the most experienced dermatologist must rely on a skin biopsy for the definitive diagnosis of epidermal tumors. Finally, many epidermal neoplasms may be associated with internal malignancies or genetic syndromes that warrant further evaluation and management from other subspecialties.

Seborrheic Keratoses

Seborrheic keratoses are common lesions, usually appearing around the fourth decade of life.[1] They can be single or multiple and can occur anywhere on the body, with the exception of the palms and soles. Clinically, they are sharply demarcated and slightly raised, appearing as if they were stuck on the skin's surface (Fig. 20-1). Many have a verrucous surface with a soft, friable consistency; however, others may have a smooth surface. Characteristically, all seborrheic keratoses show keratotic plugs on careful surface inspection. Their color is usually brownish to brown-black, although color can vary from flesh color to

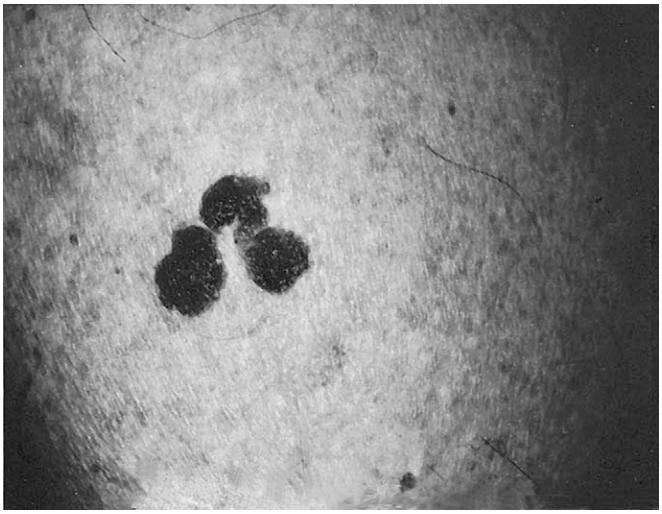

Figure 20-1. Seborrheic keratoses.

deep black. The color within the individual lesion is usually uniform. Lesions can measure from a few millimeters to several centimeters. When subjected to trauma, they can become irritated, thereby causing an inflammatory base and occasional bleeding. Occasionally, seborrheic keratoses are pedunculate, especially on the neck.

The etiology of seborrheic keratoses is unknown, although they may be dominantly inherited. They are benign with no malignant potential, although the appearance of hundreds in rapid "showers" may be a sign of internal malignancy; this is the much-debated Leser-Trélat sign.[2] The most common tumor seen with this association is colonic adenocarcinoma. In the head and neck, the most common mistaken diagnosis is melanoma; therefore the pathologist sometimes receives a widely excised seborrheic keratosis that has been mistaken for melanoma. If the diagnosis is in doubt, a biopsy before definitive treatment should be performed.

Treatment of these lesions varies. Because these lesions are so superficial, they often can be excised flush with the skin, using any of the shaving techniques described later. These lesions also are amenable to light liquid nitrogen freezing, which creates a subepidermal blister and allows for removal of the keratosis with the blister. Because these are truly benign lesions, the best treatment is often no treatment, unless the lesions are cosmetically disfiguring.

Dermatosis Papulosa Nigra

Dermatosis papulosa nigra is a condition found in approximately 35% of black adults; its onset often occurs during adolescence. The lesions are located predominantly on the face, especially in the malar region, but they may also occur infrequently on the neck and upper trunk. They consist of small (1 to 3 mm), smooth, pigmented, stuck-on appearing, hyperkeratotic papules. Although they have the histologic appearance of a fibroma, many clinicians consider these papules to be a variant of seborrheic keratoses. The treatment of dermatosis papulosa nigra is difficult because of pigmentary problems that occur with the treatment of black skin. Options that have been tried include fine-needle electrosurgery followed by use of a small curette, shave excision, light freezing with liquid nitrogen, and dermabrasion. If the lesions are few, we prefer the first two methods. Cryosurgery can produce spotted hypopigmentation in blacks and should be avoided unless other treatment modalities are not available. Dermabrasion can be of two types: using either a 2-mm wheel or a small cone or pear diamond fraise, the lesions can be removed singly, very quickly, and easily. Dermabrasion can also result in mottled pigmentation after healing, which usually will fade with time. If the lesions are multiple and confluent, total regional dermabrasion may be the treatment of choice for the best cosmetic blend. Judicious use of ablative and pigment-specific lasers can be used to treat these lesions focally; however, meticulous technique is required to avoid pigmentary changes common to this patient population.[3]

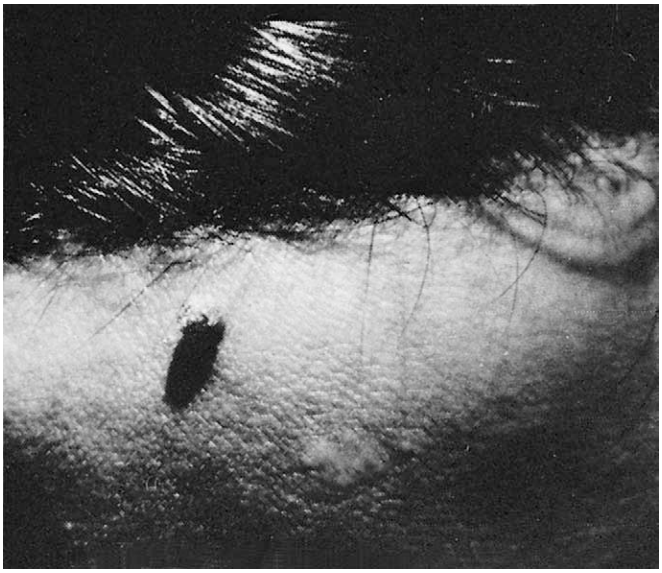

Figure 20-2. Filiform warts.

Warts (Verruca Vulgaris)

Warts are common lesions caused by the human papillomavirus (HPV), which is a deoxyribonucleic acid (DNA) virus. Warts are traditionally classified by clinical appearance and location: verruca vulgaris (or common wart), deep hyperkeratotic palmar-plantar; superficial mosaic-type palmar-plantar; verruca plana; epidermodysplasia verruciform; and condyloma acuminatum. Classification may also be based on the genotype of papilloma virus. Hundreds of DNA genotypes have been identified, each with a distinct type-specific antigen, some of which correlate with various benign and malignant conditions.[4] The most common facial warts include common warts (including filiform) and flat warts which are most commonly associated with the antigenic serotypes HPV-2 and HPV-3. Clinically, these lesions are hyperkeratotic. The filiform wart is often a pedunculate lesion occurring in isolation on the cheek, nasal tip or columella, or eyelid (Fig. 20-2). Common warts can occur anywhere on the face. Flat warts usually occur in younger patients or on the legs of women who regularly use a razor for shaving; they are small (1 to 2 mm), flat-topped, hyperkeratotic lesions, which can coalesce (Fig. 20-3).

Because the virus survives within cells at the base of the hyperplastic epithelium and within the adjacent normal-appearing skin, eradication of warts can be difficult and recurrences are common. Most common treatments involve destruction of the infected tissue. The filiform wart can be anesthetized at its base and excised with scissors, with the base being lightly curetted and fulgurated under low current; this approach affords the best chance for cure. Filiform warts often are too verrucous and hyperkeratotic to be effectively treated with cryosurgery. Common warts that are thinner can be treated effectively with liquid nitrogen cryotherapy, although several treatments are usually needed. Flat warts present a difficult problem. At times, they can be effectively treated with liquid nitrogen. Perhaps the best method is to individually scrape each small wart off of the skin with a small curette, treating, when possible, all of the flat warts in an area at one time. In young children who do not tolerate surgical therapy well, one may use topical tretinoin at a concentration sufficient to produce erythema and irritation in an attempt to stimulate the body's own immunity against the wart virus. In healthy children, avoiding treatment is often best, because the vast majority of warts spontaneously involute once the patient's immune system recognizes the virus.[5]

Related to the poxvirus family is a group of viruses known as the molluscum contagiosum virus family (EM-2). An infection with one of these viruses appears clinically as a variable number of small, discrete, waxy, skin-colored, dome-shaped papillomas, 2 to 4 mm in diameter, with umbilicated centers (Fig. 20-4). Like all viral lesions, they ultimately will involute spontaneously. Histologically, they have a classic

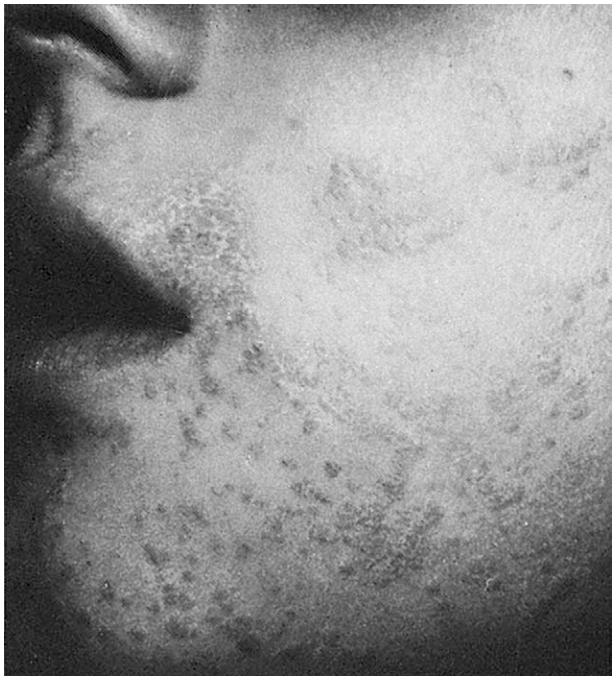

Figure 20-3. Flat warts.

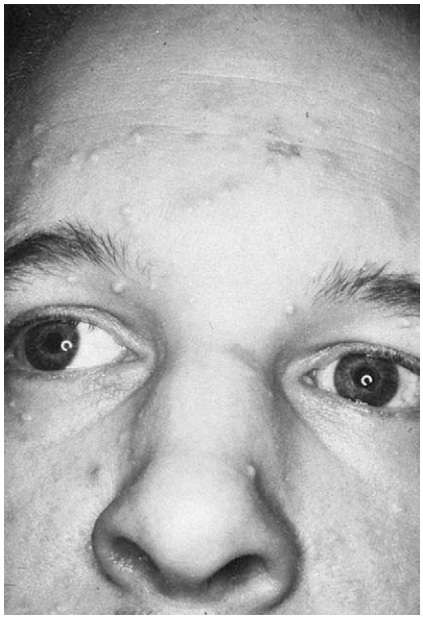

Figure 20-4. Molluscum contagiosum.

appearance of cytoplasmic inclusion bodies, which are the so-called molluscum bodies. The best treatment is usually superficial cryotherapy or curettage, as is the case with common warts. Topical therapies, including imiquimod cream, liquid podophyllin, cantharidin, and more recently, injectable candidal antigens, have been successfully used for the treatment of warts and mollusca.

Actinic Keratoses

Actinic keratoses, also called *solar keratoses,* are precancerous lesions.[6] Studies indicate that squamous cell carcinoma will develop in one or more lesions in 5% to 20% of persons with solar keratoses.[7-10] They are seen on sun-exposed areas of the skin, usually in persons after the fourth decade of life. They are seen most commonly in fair-skinned individuals who get sunburned frequently. Clinically, these lesions are usually erythematous with adherent scale and show little or no infiltration (i.e., they are very superficial) (Fig. 20-5A). Often, the patient can feel the rough, adherent scale before the lesion is clinically visible. Solar keratoses can also be flesh colored or pigmented. They often do not have a sharp demarcation from surrounding skin and can spread peripherally. Occasionally these lesions develop marked hyperkeratosis, giving a clinical appearance of a cutaneous horn. On the vermillion lip, actinic keratoses are known as *solar* or *actinic cheilitis.*

Actinic keratoses lesions are best removed and not watched. The most commonly used method for removing discrete lesions is cryosurgery. Shave excision can also be performed, but it would lead to extensive scarring in areas with numerous lesions. In persons with severe sun damage to the face or with diffuse actinic keratoses, regional treatment with topical 5-fluorouracil, imiquimod, or retinoid creams are effective therapies for an entire region of the body such as the arms, hands, scalp, or face.[11,12] Because proper use results in severe irritation, sound patient understanding and education, and physician reassurance are necessary to ensure adequate compliance. Photodynamic therapy, laser resurfacing, dermabrasion, and chemical peels are also effective field therapies.[13-16]

Basal Cell Carcinoma

Basal cell carcinoma is the most common malignancy in humans,[17,18] accounting for 75% to 80% of new cancers in the United States each year. Depending on the study cited, approximately 86% of lesions occur initially in the head and neck, with 25% of all primary lesions occurring on the nose. Approximately 96% of recurrences are in the head and neck, with 38% being on the nose. Emmett reported that 75.5% of previously untreated basal cell carcinoma found in Australia occurred in the head and neck, 8.4% on the chest and back, and 16% on the arms and legs.[19] When looking at recurrent tumors, 91% occurred on the head and neck, 7.5% on the chest and back, and 1.5% on the arms and legs. Similarly, the primary tumor of metastatic basal cell carcinomas is usually found on the head and neck. However, metastasis of basal cell carcinoma is rare, with reports estimating rates of 0.0028% to 0.1%.[20-22] In this discussion, we outline the epidemiology and clinical and histologic variations of basal cell carcinoma. Management of head and neck basal cell and squamous cell carcinomas are addressed in Chapter 82.

Basal cell carcinoma, which is more common in men than in women, is seen most frequently in individuals between 40 and 60 years of age. With the aging of the sunbathing generation, however, basal cell carcinomas are occurring with increasing frequency in younger people. Scandinavians and people of Celtic extraction (particularly Irish), who frequently have Fitzpatrick skin type I or type II (sunburn easily), appear to be more prone to basal cell carcinoma than those with more darkly pigmented skin. Although uncommon in blacks, predilection for occurrence on the head and neck is the same as in whites.[23] Exposure to sunlight—primarily to the rays in the ultraviolet B spectrum—is the primary risk factor for basal cell carcinoma; this has been shown experimentally and reproduced clinically. The tumor is more common as one approaches the equator and at high altitudes. Basal cell carcinomas occur most commonly on the head and neck areas, with the nasal tip and the nasal ala being the most common; the cheeks and the forehead are the next most common. The left side of the body is more common than on the right, perhaps because of selective sun exposure in individuals whose occupation preferentially exposes the left side (i.e., driving).

Although sun exposure is the primary etiologic agent of basal cell carcinoma, other risk factors include genetics, occupation,[24] immunosuppression, ionizing radiation, and the presence of scars. Farmers, sailors, and fishermen, because of their heavy occupationally actinic exposure, have a higher than average incidence of skin cancer. The most common genetic syndromes include nevoid basal cell carcinoma syndrome and xeroderma pigmentosum.[25] The former is an autosomal dominant condition in which basal cell carcinomas arise on any area of the body, with the predilection being toward sun-exposed sites, beginning at an early age and continuing throughout life. These patients also have skeletal abnormalities, including bifid ribs, jaw cysts, frontal

Figure 20-5. **A,** Actinic keratoses. **B,** Keratoacanthoma. **C,** Noduloulcerative basal cell carcinoma. **D,** Nodular basal cell carcinoma. **E,** Pigmented basal cell carcinoma. **F,** Morpheaform basal cell carcinoma.

bossing, and calcified falx cerebri. Xeroderma pigmentosum is an autosomal recessive disease caused by a defect in DNA repair that leads to the development of basal cell carcinoma and other cutaneous malignancies in response to sun exposure and other carcinogens in childhood and early adulthood.

Immunosuppression (iatrogenic or associated with leukemias or lymphomas) has been shown to increase the incidence and aggressiveness of basal cell carcinomas. Chemical carcinogens—notably arsenic—play a tumorigenic role. Arsenic usually comes from well water that has been contaminated with arsenic, but patients with asthma, hay fever, or psoriasis may ingest arsenic in medicinal Fowler's solution. Arsenic-induced basal cell carcinomas tend to be primarily on the trunk and are accompanied by keratoses of the palms and soles, pigmentary changes, and nail changes (Mees' lines). Exposure to ionizing radiation is also an important etiologic factor; tumors can arise in areas of radiation damage, often many years after superficial radiotherapy for acne or tinea capitis, or as a depilatory at an early age. Basal cell carcinoma can arise within a scar or area of trauma. The injury may act as a cofactor, adding to the effect of already existing risk factors, such as sunlight and genetic susceptibility. Smallpox vaccinations and burn scars have been associated with basal cell carcinoma.

To the trained and observant eye, the clinical recognition of basal cell carcinoma is not difficult. Typically, lesions are nodular with a smooth, raised, translucent or "pearly" border with prominent telangiectasia (see Fig. 20-5D).[26] In addition, they may ulcerate and form a crust (see Fig. 20-5C). A typical history involves a pimple-like lesion that bleeds and does not heal. Pruritus is a common early symptom. Basal cell carcinoma may be pigmented (see Fig. 20-5E) yet maintain the clinical features of pearly, translucent borders and telangiectasia. Superficial multicentric basal cell carcinomas are flat and pink with differing, intercommunicating extensions of tumor that may be either scaly or with raised borders.

Other forms of basal cell carcinoma are clinically more subtle, histologically more aggressive, and more difficult to treat. Approximately 20% of primary basal cell carcinomas demonstrate infiltrative growth patterns with significant subclinical disease and high rates of recurrence.[27-29] Importantly, many primary tumors demonstrate histologic heterogeneity with subclinical extension.[30] Morpheaform basal cell carcinomas (see Fig. 20-5F) present as yellowish plaques, which develop telangiectasia, may ulcerate, and may have a sclerotic or scarlike appearance. The margins are often indistinct. Histologically, this tumor extends subclinical, finger-like projections intradermally, which make complete excision difficult. This tumor has a scarlike, stromal matrix that gives it a fibrous, sclerotic appearance and nature.

Recurrent basal cell carcinomas (Fig. 20-6A) present with varying clinical appearance, depending on the type of initial treatment. It may appear at the edge of a skin graft, within a scar created by electrosurgery, under a scar created by cryosurgery, or as a nodule developing within a suture line. Recurrent basal cell carcinomas are often nodular and accompanied by a morpheaform or sclerotic histologic picture in the deeper portions of the tumor. This picture may represent an aggressive histologic de-differentiation of the tumor, a factor that may partially account for its clinically aggressive behavior and resistance to treatment. The majority of recurrent basal cell carcinomas demonstrate infiltrative patterns in the original tumor; aggressive behavior may be predicted by careful evaluation of histologic features.[31]

Figure 20-6. **A,** Recurrent basal cell carcinoma. **B,** Chondrodermatitis nodularis helicis. **C,** Squamous cell carcinoma. **D,** Pigmented squamous cell carcinoma. **E,** Superficial spreading melanoma. **F,** Irregular border of superficial spreading carcinoma.

The typical basal cell carcinoma that occurs in the head and neck of the middle-aged or older fair-skinned person is not difficult to diagnose. One must be aware, however, that this tumor has a variety of clinical appearances, can appear in young people, and can occur in areas other than the head and neck. Any suspicious, nonhealing, pruritic, scaly lesion—especially one that occurs in a sun-exposed area of the fair-skinned individual—should be investigated with a biopsy. Biopsy techniques for basal cell carcinoma are simple. It has been well documented that implantation metastases from basal cell carcinoma do not occur, because the tumor needs a stroma to provide an environment in which to grow. The most appropriate technique is a medium-depth shave biopsy. The depth of the biopsy ideally should be mid-dermis; this depth gives a dermal collagen network that is amenable to any form of therapy. If a morpheaform basal cell carcinoma is suspected, the biopsy specimen often must extend deeper, perhaps through a punch or incisional biopsy. In cases of recurrent or superficial multicentric lesions or large clinical lesions, biopsy specimens should be obtained from multiple sites to assess the true clinical nature and size of the tumor. Biopsies of recurrent deep nodular lesions should be performed in an appropriate fashion to ensure an adequately deep specimen from the dermal nodule; this maneuver can be accomplished by means of an incisional biopsy or a deep-punch biopsy. As a rule of thumb, if the biopsy does not confirm the clinical opinion of basal cell carcinoma and the lesion remains suspicious, an additional biopsy of the lesion is indicated.

Chondrodermatitis nodularis helicis (see Fig. 20-6B) is an inflammatory disease of underlying helical cartilage that can mimic and be mistaken for basal cell carcinoma. The condition usually results from chronic trauma on the most protuberant portion of the ear. Surgery is the treatment of choice.

Squamous Cell Carcinoma

Squamous cell carcinoma is the second most common skin cancer and accounts for 10% to 20% of all cutaneous malignancies. Because of their tendency to recur and metastasize, squamous cell carcinomas carry the highest mortality of nonmelanoma skin cancers and account for the majority of deaths due to skin cancer in adults older than 85 years.[32] The development of squamous cell carcinoma is multifactorial and involves both environmental and genetic factors. Risk factors for the development of squamous cell carcinoma include fair skin; chronic cumulative sun exposure; history of previous skin cancer; age older than 50 years; smoking; chronic inflammatory, infectious, or scarring skin lesions; chemical carcinogens; PUVA; HPV infection; and various genodermatoses. Similar to basal cell carcinomas, the most important factor is ultraviolet radiation. Fair-skinned individuals with longstanding chronic sun exposure, especially those close to the equator and at high altitudes, are at greatest risk. Men are affected two to three times more than women, and multiple cutaneous carcinomas are common.

Whereas the majority of squamous cell carcinomas may be cured if diagnosed and treated early, some behave aggressively with high rates of metastasis. Risk factors associated with high rates of recurrence and metastasis include chronically sun exposed skin, scarred areas in non–sun-exposed skin, tumors greater than 2.0 cm in diameter, recurrent tumors, chronic immunosuppression, poor histologic differentiation, depth of invasion, and perineural involvement.[33,34] The true risk of

recurrence or metastasis for each variable is unknown; however, associations are clearly established. Clinically, squamous cell carcinomas can be separated into actinically induced and those that arise de novo on non–sun-exposed skin. The former are the more common and are associated with a low incidence of metastasis (<1% in most series). Some studies suggest that de novo lesions have a higher metastatic potential; approximately 2% to 6%. The mucosal variant of the squamous cell carcinoma, seen clinically as carcinoma of the lip, has a metastatic potential of up to 13.7%; therefore these distinctions are important in prognosis.[35] The worst prognostic indicator is perineural invasion, which has been shown to metastasize in 47.3% of cases.

Squamous cell carcinoma may present clinically in several ways.[36] Thick, scaling, hyperkeratotic plaques may present on the exposed surface of the body, in particular the ear, lip, or nose (see Fig. 20-6C). Lesions may change slowly over a period of time. If the crust is removed, the base is often ulcerated and has a rolled margin. Lesions may also present as a persistent ulcer, particularly in an old scar, or as a superficial multifocal change in generally sun-damaged skin. The latter is often the most difficult lesion to diagnose, requiring several biopsies at different points. Occasionally, a squamous cell carcinoma will become a vegetative nodular lesion; this lesion often has a cystic feel and can ulcerate and progressively enlarge. Often these exophytic lesions have not invaded deeply. They all have a tendency to ulcerate and become more erosive in appearance than a basal cell carcinoma. As with basal cell carcinoma, they can become pigmented (see Fig. 20-6D) and often appear similar clinically to keratoacanthomas, especially when the latter are in the growth phase. However, these lesions usually grow more slowly than keratoacanthomas, thereby allowing for distinction on clinical as well as histologic grounds. When this occurs, biopsy is always indicated. The treatment of cutaneous squamous cell carcinoma is discussed in depth in another chapter.

Bowen's disease refers to an intraepithelial squamous cell carcinoma or carcinoma in situ. Clinically it presents as a well-demarcated, erythematous, scaling thin plaque that may be easily misdiagnosed as psoriasis, eczema, or tinea. Bowen's disease on sun-exposed skin behaves less aggressively than non–sun-exposed such as the genitalia; if left unrecognized and untreated, it may progress to invasion. Bowen's disease associated with arsenic exposure may be associated with internal malignancies. In the absence of arsenic exposure, however, this association is not well supported.

Keratoacanthoma is a rapidly growing tumor that presents as an exophytic dome-shaped nodule with central keratin on sun-damaged skin (see Fig. 20-5B). The categorization of keratoacanthoma has been controversial, but it is now thought to be a variant of squamous cell carcinoma. There are some unique features that distinguish it clinically from the common type of squamous cell carcinoma. Keratoacanthomas are characterized by a rapid proliferative phase followed by plateau, then involution. Not all keratoacanthomas, however, involute, and predicting which ones will is difficult. The involution phase can sometimes take up to 1 year. Two rare clinical forms of keratoacanthomas deserve mention. The giant keratoacanthoma can reach 5 cm or more and can cause the destruction of underlying tissues. Eruptive keratoacanthomas often present as many hundreds of characteristic papules that measure 2 to 3 mm in diameter. Metastatic keratoacanthomas have been reported, however, and may represent typical squamous cell carcinoma. Keratoacanthomas can be difficult to treat. Surgical excision is the treatment of choice for most keratoacanthomas, with Mohs micrographic surgery reserved for facial lesions. Because of the involution potential of keratoacanthomas, cytotoxic agents can be used to induce involution. We favor methotrexate at a dose of 12.5 to 25 mg/mL, with approximately 0.5 to 1 mL injected into the lesion at 3- to 4-week intervals. Although complete involution may not occur, it may allow for easier surgical management by reducing the size of the tumor.

Melanocytic Neoplasms

The melanocyte is the pigment-producing cell of the epidermis. However, many tumors of this cell line, which is embryologically from the neural crest, occur in the dermis either by migration or because crest cells fail to reach the epidermis during embryogenesis. The most common of these tumors are nevocellular nevi and melanoma. A wide spectrum of melanocytic nevi and pigmented skin lesions exist, many of which appear similar and can be confused with melanoma.[37] This section discusses the clinical manifestations of nevocellular nevi and other melanocytic neoplasms. The presentation, behavior, and treatment of melanoma are discussed elsewhere.

Nevocellular Nevus

Nevocellular nevi, commonly known as moles, are common benign skin neoplasms that appear shortly after birth to late in life. Acquired nevocellular nevi are classified according to their location and stage of development within the skin.

Junctional Nevus

Junctional nevi are tan to brownish macules (flat lesions) of uniform color and smooth border (Fig. 20-7B). Dots of black pigment may be present, but, unlike with melanoma, the normal skin markings are preserved. Lesions vary from a few millimeters to a centimeter or more in diameter. The melanocytes or nevus cells are located at the junction of the epidermis and the dermis (dermoepidermal junction). The lesion can occur anywhere on the body and is the nevus most commonly mistaken for melanoma. When in doubt, one should perform a biopsy of the lesion. Junctional nevi occur anytime after birth and are the common moles found in children before puberty. Their importance lies in their ability to develop into malignant melanoma, although this rarely occurs before puberty. Most junctional nevi remain benign throughout life and can evolve over time into either compound or intradermal nevi. Treatment of these nevi is often dictated by suspicion of melanoma or cosmetic reasons, and usually includes a shave in noncosmetic areas or a fusiform excision with closure in cosmetically important areas. Melanocytes are cold sensitive, and strictly junctional nevi can be removed with deep cryotherapy.

Intradermal Nevus

Intradermal nevi are common mature moles of adults, occurring anywhere on the body but rarely on the palms and soles. It is most common on the scalp or face in adults, varying in size from a few millimeters to several centimeters. It may be flat and smooth or raised and warty, pigmented or nonpigmented, sessile or pedunculate (see Fig. 20-7C). It often contains coarse hairs, reflecting the depth within the dermis of the nevus cells. It is benign and rarely becomes malignant. By definition, all of the nevus cells occur within the dermis. This mole is best treated by shave excision when it is pedunculate and hairless. When it is on the head or neck and contains hair, it is necessary to excise this mole using either the punch excision technique or routine excision to remove the complete depth of the hair follicles within the nevus.

Compound Nevus

Compound nevi, which are a combination of junctional and intradermal elements, are found most commonly in adults. They are brown to black moles, usually less than 1 cm in diameter. A brown macular ring is frequently around the periphery of the lesion. It can contain hair and is often clinically indistinguishable from an intradermal nevus. Although the compound nevus, like any mole, can develop into a malignant melanoma, it usually remains benign and matures into an intradermal nevus. Treatment usually consists of shave or excision and closure. As with intradermal nevi, the choice of treatment depends on location and on the presence or absence of hair.

Blue Nevus

Blue nevi present as dark blue or black hairless flat or raised lesions that are usually less than 0.5 cm in diameter, indurated, and palpable. The overlying epidermis is remarkably smooth and the outline regular (see Fig. 20-7D). Blue nevi most commonly occur on the head and neck, the dorsa of the hands and feet, and the buttocks. They are more common in women than men and usually undergo very little change after their initial presentation. The treatment of these lesions is excision or observation. The excision must be deep, because the pigment often extends deep into the subcutaneous fat, thereby resulting in the deep blue color of the lesion. Malignant transformation of blue nevi is rare;

Figure 20-7. **A,** Lentigo maligna melanoma. **B,** Junctional nevus. **C,** Intradermal nevus. **D,** Blue nevus. **E,** Halo nevus. **F,** Nevus sebaceus.

however, tumors demonstrate highly aggressive behavior, thus these lesions must be carefully evaluated histologically.[38,39]

Halo Nevus

The halo nevus is a phenomenon usually associated with a junctional nevus in children or adolescents. Most commonly found on the back, it is often a benign-looking brown papular lesion in the center of a well-circumscribed pale white circle of depigmented skin (see Fig. 20-7E). This appearance reflects the body's rejection of the nevus cells, because an inflammatory response ensues in which the melanocytes of the nevus and those of the immediately surrounding epidermis are destroyed.[40] Often, when left alone, these nevi disappear.

Spitz Nevus

Spitz nevus is also known as a *juvenile melanoma* or a *compound melanocytoma*. These rapidly growing pigmented lesions occur principally in children, although they can occur in adults. They are usually less than 1 cm in size and are pink or red, or occasionally brown or black. A Spitz nevus may be soft or hard, but is usually dome-shaped and can be either sessile or pedunculated. It can occur anywhere on the body and is often difficult to diagnose clinically. Its main importance is its histologic resemblance to melanoma, with even experienced pathologists having difficulty distinguishing between the two.[41] Very few of these nevi, however, progress to malignancy. Treatment of a Spitz nevus is the same as that for an intradermal or compound nevus.

Congenital Nevi

Congenital nevi are malformations of neuroectoderm comprised of melanocytes, affecting 1% to 6% of the population. There is great heterogeneity in their appearance, size, and location. Lesions may be light brown to black, are variously shaped, usually have sharp borders, are flat to mammillated on the surface, and often contain hair. When large or in conspicuous locations such as the face, they may be associated with significant psychosocial impact on affected individuals and their families.

Congenital nevi are usually present at birth; however, in some lesions pigmentation may occur gradually over the first few years of life. In addition to being aesthetically disfiguring, congenital nevi may be associated with a risk of melanoma, neurocutaneous melanocytosis, or malignant tumor, such as rhabdomyosarcoma, among others. Whether this malignant potential is due to the increased number of melanocytes or to some inherited premalignant tendency in the cells themselves is not clear. Congenital nevi are classified according to size with those less than 1.5 cm being small, 1.5 to 20 cm being medium, greater than 20 cm being large, and greater than 50 cm being giant. The precise risk for development of melanoma associated with congenital nevi is difficult to establish; however, risk clearly correlates with size, with the greatest risk being associated with giant congenital nevi. The risk of cutaneous or extracutaneous melanoma associated with small congenital nevi is estimated at 0% to 4.9% and generally occurs at or after puberty. The risk is 4.5% to 10% in large congenital nevi and usually occurs before puberty in this group.[42,43] Histologic evaluation of changes within congenital nevi should be evaluated by a dermatopathologist experienced in the evaluation of pigmented lesions. Individuals with large congenital nevi are also at risk for development of neurocutaneous melanosis in which proliferation of leptomeningeal melanocytes may be associated with neurologic disease, structural malformations, and malignant degeneration. Giant axial lesions and those

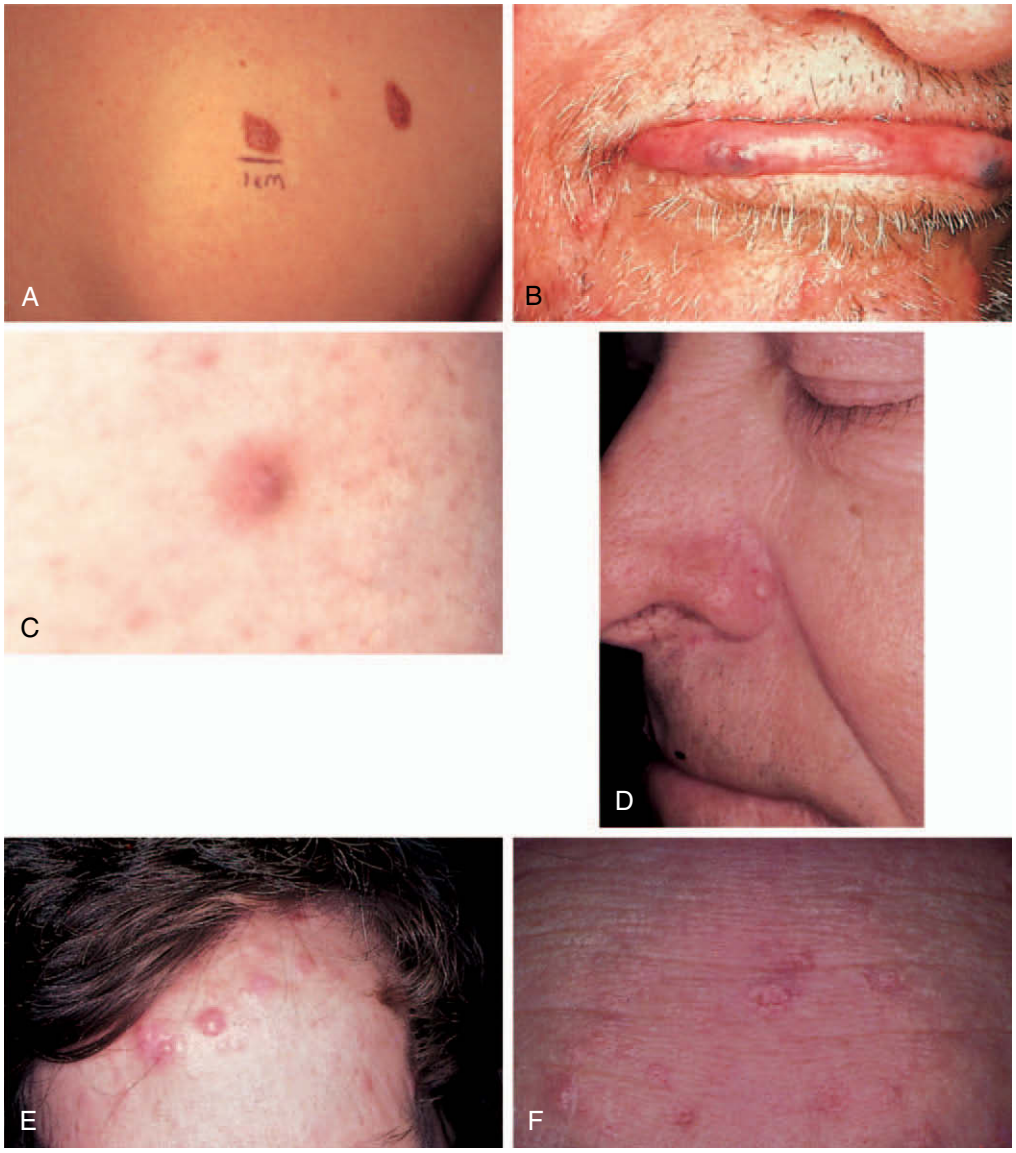

Figure 20-8. **A,** Dysplastic nevus. **B,** Venous lakes. **C,** Dermatofibroma. **D,** Fibrous papule. **E,** Cylindroma. **F,** Sebaceous hyperplasia.

with greater than 20 satellite lesions are at greatest risk.[44] The prognosis for patients with symptomatic neurologic disease is poor. Approximately half of patients with neurocutaneous melanosis develop central nervous system melanoma.[45]

The management of congenital nevi should be individualized based upon nevus size, thickness, location, risk for development of melanoma and other associated conditions, psychological impact, and effects of therapy on the patient and family. Treatment options include surgical excision, dermabrasion, chemical peels, laser therapy, and observation. The timing and choice of therapy should take into consideration the medical, cosmetic, and psychological factors.[46,47]

Dysplastic Nevus

Dysplastic nevus syndrome, described by Clark and colleagues, is also known as the B-K mole syndrome.[48] It consists of the association of familial malignant melanoma, which often occurs in multiple lesions, with "dysplastic nevi" in both the melanoma patient and many of his or her relatives. Dysplastic nevi are usually larger than ordinary melanocytic nevi, ranging from 5 to 15 mm; they present with an irregular border and a haphazard mixture of colors: tan, brown, black, and pink. Centrally, there is often a small, palpable component (Fig. 20-8A). Dysplastic nevi are located on either exposed or nonexposed skin and form throughout adult life, unlike typical nevi that form in earlier years and tend to fade in later years. The idea that a dysplastic nevus may transform itself into a malignant melanoma remains controversial.[49]

Solar Lentigo

Solar lentigo, also known as *actinic lentigo*, are keratinocytic pigmented macules that commonly present on the sun-exposed skin of the head and neck.[50] They commonly occur as multiple lesions and have been referred to as *lentigo senilis.* The lesions rarely occur before the fifth decade of life, they slowly increase in size and number, and they form in more than 90% of whites who are older than 70 years old, most commonly on the dorsa of the hands and on the face. They are not infiltrative, and they possess a uniform dark brown color and an irregular outline. Varying in size from minute to greater than 2 cm, they may coalesce to form larger lesions. Malignant degeneration does not occur. These lesions may resemble seborrheic keratoses in clinical appearance, and both conditions are referred to in lay terms as "liver spots." Solar lentigo, however, are less hyperkeratotic than seborrheic keratoses and have no areas of follicular prominence. It is important to distinguish solar lentigo from melanoma in situ, which may also present as dark brown macules on sun-damaged skin of the head and neck. Solar lentigo can be easily treated with pigment-specific lasers, intense pulsed light devices, cryotherapy, topical retinoids, or chemical peels such as trichloroacetic acid.

Nevus Sebaceus

Nevus sebaceus of Jadassohn is a common benign congenital lesion that presents as a pebbly, flesh-colored, hairless, well-demarcated lesion of the scalp (see Fig. 20-7F) and other areas of the head and neck. The size varies from 0.5 cm to several centimeters. Off the scalp, the lesion can be linear, closely resembling a linear epidermal nevus. Histologically, these tumors evolve in three discrete stages of growth. In the first few months of life, the sebaceous glands in the lesion are well developed. Thereafter, through childhood, the sebaceous glands are underdeveloped and therefore greatly reduced in size and number; in this phase, the diagnosis may be missed. At puberty, the lesions assume a diagnostic appearance, which is histologically characterized by the presence of large numbers of mature or nearly mature sebaceous glands and by papillomatous hyperplasia of the epidermis. During puberty, various benign and malignant epidermal and adenexal tumors develop in nevus sebaceous. Ten percent to 30% of lesions develop neoplasms during adulthood, usually between the fourth and seventh decades. The most common benign neoplasms include trichoblastoma and syringocystadenoma papilliferum. Of primary importance is the occurrence of basal cell carcinoma in 5% to 7% of sebaceous nevi; numerous other malignant neoplasms have been reported, including squamous cell carcinoma, sebaceous carcinoma, ductal carcinoma, and leiomyosarcoma.[51-55] Treatment of nevus sebaceus is complete surgical excision. Complete excision before puberty as a preventive measure had been previously advocated; however, more recently this recommendation has been called into question due to the low incidence of malignant lesions and the ability to identify such changes clinically.[56,57] Others have proposed observation with excision of selected lesions, however many prefer excision for aesthetic reasons.[58]

Cysts

Cutaneous cysts may be located either intradermally or within subcutaneous tissue. These generally spherical growths contain a cavity that may be filled with fluid or contain cellular products or debris. A true cyst has an epithelial lining, whereas a pseudocyst lacks such an organized epithelium. Cysts are generally classified according to the pattern of differentiation they exhibit on histologic examination; many are difficult to differentiate clinically. As a rule, malignant degeneration is rare for all of the cysts described here.

Epidermoid Cysts

Epidermoid cysts are true cysts. Their lining resembles that of the normal epidermis. This lining produces fully matured, keratinized cellular debris, which fills the cavity of the cyst. Epidermoid cysts are thought to originate from the follicular infundibulum of hair shafts and may arise either spontaneously or as a result of inflammation or trauma to the area. Injection of surface epidermal material to deeper dermal or subcutaneous layers as a result of penetrating trauma or the use of needles has also been postulated. These cysts are rarely found before puberty, but they have been found in all age groups after this period. If these cysts appear before puberty or in large numbers, they may be an indication of Gardner's syndrome, which is an autosomal dominant condition that predisposes the patient to intestinal cancer. Although malignant degeneration is uncommon, epidermoid cysts can present a cosmetic problem, and, if they rupture or become infected, they may cause severe pain and scarring. Although some of these lesions occasionally respond to intracystic injections of triamcinolone, surgical excision is the most effective treatment. It is necessary to carefully dissect and remove the entire cyst wall, because retained segments may lead to recurrent growth of the cyst.

Pilar Cysts

Pilar cysts, which are also known as *trichilemmal cysts* or *wens*, are also true cysts; they are clinically indistinguishable from epidermal cysts. The tendency to form such cysts appears to be inherited as an autosomal dominant trait. The lining of the cyst differentiates in a manner analogous to that of the outer root sheath of the hair follicle; this fact allows for its differentiation from epidermal cysts. Most pilar cysts occur on the scalp, and they are uncommon before puberty. Multiple cysts are often present. If a pilar cyst ruptures or becomes infected, considerable pain and scarring may result. As with epidermal cysts, the best treatment is complete surgical excision. Proliferating pilar tumors are uncommon tumors thought to originate from pilar cysts and have the potential for malignant transformation. Although these lesions are uncommon, they may be associated with significant morbidity and mortality and must be excised completely.[59,60]

Dermoid Cysts

Dermoid cysts are rare tumors that are frequently present at birth. They may measure up to 4 cm in diameter, although they are generally less than 2 cm. They may occur anywhere, but they are most common on the face, particularly in the area of the lateral eyebrow, the orbit, and the nose. Dermoid cysts appear to result from the inclusion of embryonic epidermis within embryonal fusion planes. Histologically, these cysts are lined by an epithelium that resembles normal epidermis. They can be differentiated from epidermal cysts by their attachment to adnexal structures, which include hair, sebaceous glands, eccrine glands, and apocrine glands.[61] Treatment is by surgical excision. If a dermoid cyst is located over the nasal root, however, care must be taken, because this tumor may be confused with a nasal glioma.[62]

Steatocystoma Multiplex

Steatocystoma multiplex, an uncommon condition, is often familial, demonstrating an autosomal dominant mode of inheritance. Although lesions can be discovered at any age, they most commonly occur shortly after puberty. The condition presents as multiple 1- to 2-cm cysts, generally located intradermally. They are most commonly found on the anterior chest, but they are also found on the face, forehead, ears, eyelids, and scalp. When punctured, these lesions exude a yellowish, oily fluid and, occasionally, hairs. On histologic examination, these cysts contain a highly corrugated wall of epithelial cells. Embedded within the wall are multiple sebaceous gland lobules, which may be partially responsible for the contents of the cyst. The mode of keratinization of the epithelial lining appears to resemble that of the outer root sheath, and indeed invaginations are often present within the cyst wall that appear similar to hair follicles. Infection with pain and subsequent scarring is a major problem associated with this condition. Treatment is disappointing because of the large number of lesions present, although individual lesions can easily be excised. On the face, cosmetically acceptable improvement has been reported with excision, CO_2 laser, dermabrasion, and oral retinoids.[63-66]

Milia

Milia are small (usually 1 to 2 mm) cysts that differ histologically from epidermal cysts only in their small size. Clinically, they are whitish, smooth globules, most commonly seen on the face. They may arise spontaneously, but they are also frequently present as a result of trauma such as dermabrasion or burns or as a result of bullous diseases. When they arise after trauma or disease as a result of the occlusion of the pilosebaceous unit, they represent a retention cyst. Treatment is the same whether milia arise spontaneously or secondarily and is necessary only for cosmetic reasons; the lesion can easily be shelled out with a hypodermic needle or a comedo extractor. Because they may occasionally number in the hundreds, this treatment can be a considerably tedious chore.[67]

Mucous Cysts

Mucous cysts are pseudocysts, because no true lining is present; they are also called *mucous retention cysts* or *mucoceles*. These lesions are usually located on the mucous surface of the lower lip and are asymptomatic. They are generally less than 1 cm in diameter and, if superficial, may appear slightly bluish and translucent. They appear to be the result of traumatic rupture of the ducts of minor salivary glands. With leakage of the contents into the tissue, an inflammatory process ensues, with the resultant formation of granulation tissues surrounding the cystic space. Mucous cysts may resolve spontaneously or can otherwise be treated by the intralesional injection of low-dose triamcinolone (2.5 mg/mL), excision, or marsupialization.[68]

Vascular Neoplasms

Cutaneous neoplasms of vascular origin are common and have a variety of presentations. They may be true proliferative tumors, or they may be ectatic vascular malformations present in the dermis or subcutaneous tissue. Differentiation may be toward blood vessels, lymph vessels, or both. These lesions may be congenital or arise later in life. Most vascular anomalies are benign. However, they may cause serious psychological or physical problems (because of impingement on important anatomic structures), and, importantly, they may be markers of more serious underlying diseases or syndromes. Vascular anomalies are generally classified as tumors and malformations.[69-71] Vascular tumors are characterized by abnormal endothelial proliferation and include infantile hemangioma, kaposiform hemangioendothelioma, tufted angioma, and pyogenic granuloma. Vascular malformations include lesions with anomalous vessels without an increase in cellular turnover and are further classified according to the predominant vessel type (capillary, venous, arteriovenous, lymphatic). These lesions present at birth and are present throughout life.

Infantile Hemangiomas

Infantile hemangiomas are the most common benign soft tissue tumor of childhood, occurring in approximately 10% of children. The incidence is greater in females than males and is increased in premature infants. Infantile hemangiomas are uniquely characterized by rapid proliferation during the first months of life followed by slow involution over several years. While most are of little significance, some have the potential for serious complication. The pathogenesis is not known, although positive staining for GLUT-1 (erythrocyte-type glucose transporter protein), which is normally expressed in endothelial cells of placenta, has suggested origination or transplantation from placental cells, although this has not been proven.[72]

Historically the term hemangioma has been used to describe a variety of vascular anomalies, which led to much diagnostic confusion. The recent identification of specific immunohistochemical markers that distinguish infantile hemangiomas from other vascular malformations has allowed for classification based on biologic markers. The term infantile hemangioma is used exclusively to describe lesions with this distinct presentation and clinical behavior; older terms such as *cavernous hemangioma* and *strawberry angioma* have been abandoned.[73]

Hemangiomas most often occur on the head and neck, although any area may be affected. When first noted at or shortly after birth, they are generally macular pink or bluish lesions. During the first year of life, hemangiomas exhibit a rapid growth phase, and the lesions become raised, dome-shaped to polypoid, and bright red to deep purple. After the first year of life, they enter a quiescent phase that is followed by a period of spontaneous involution. Hemangiomas may be superficial, deep, or mixed, and thus may vary in appearance significantly depending on the location, size, depth, and stage of development. Superficial hemangiomas develop into bright red noncompressible, partially blanching plaques. Deep lesions become partially compressible dermal nodules with a blue hue, often with overlying telangiectasia. Mixed lesions occur in 25% to 30% of lesions. In addition, there is great variation in the degree and rate of growth and involution of hemangiomas. In general, rapid proliferation occurs in the first 6 months, slow growth in the second 6 months, and involution occurs at a rate of 10% per year, with the majority of lesions completely involuted by the age of 10 years. Following involution the affected skin may not appear normal and may have residual telangiectasia, atrophy, scarring, and fibrofatty masses.

Although most hemangiomas are small and innocuous, a minority may present serious medical and psychological complications and may be associated with structural anomalies and neurocutaneous syndromes. The visible presence of hemangiomas and concerns for permanent disfigurement can lead to significant psychosocial stress that can be life altering for the child and family. Nasal tip lesions may distort the nasal anatomy and lead to significant deformity. Hemangiomas in the periorbital area may obstruct the visual axis or compress the orbit, leading to amblyopia and permanent visual loss. Lesions on the oral mucosa and perineum have a propensity for ulceration and bleeding during the rapid growth phase. Hemangiomas in the "beard area" may be associated with airway compromise. A small number of hemangiomas involve a large area of segmental distribution within developmental subunits. Segmental hemangiomas may have associated structural abnormalities with a high risk of serious complications. PHACES syndrome is a constellation of structural anomalies, including *p*osterior fossa malformation, *h*emangioma, *a*rterial anomalies, *c*oarctation of the aorta, *e*ye abnormalities, and *s*ternal defects that are associated with segmental hemangiomas.[74,75]

The heterogeneity of presentation of infantile hemangiomas and the potential risk of serious complications introduces complexity to the management of these lesions.[76] The majority of hemangiomas involute spontaneously with little consequence, thus treatment is primarily that of "active nonintervention," which involves close observation during the proliferative phase and familial education and support. Treatment with pulsed dye lasers may be helpful for ulcerated lesions, but has been less useful for deeper lesions. Recent advances in laser therapy using combinations of visible and near infrared wavelengths, however, may have additional benefits for the treatment of hemangiomas. Lesions that threaten to impinge upon important anatomic structures, especially the eye or the respiratory tract, require treatment with systemic corticosteroids. Recalcitrant, life-threatening hemangiomas that are resistant to steroid therapy may require interferon-α 2a or 2b or vincristine chemotherapy, which may have significant adverse side effects. Surgical excision with purse-string closure has been demonstrated to be a valuable intervention for many lesions, particularly those on the face, at all stages of hemangioma development.[77]

Cherry Angiomas

Cherry angiomas are also called *senile angiomas* or *De Morgan's spots.* They may occur anywhere on the body but are most commonly found on the trunk and usually appear during young adulthood. They are generally 1- to 3-mm, bright-red, slightly raised, dome-shaped lesions. The lesions consist of multiple dilated capillaries found in the upper dermis. Cherry hemangiomas are benign and unrelated to systemic or congenital disease. Treatment is not necessary but may be desired for cosmetic reasons; these angiomas respond to both superficial electrodesiccation and laser surgery.

Pyogenic Granuloma

Pyogenic granuloma are common acquired vascular lesions of the skin and mucous membranes. They are most common in children and young adults, or during pregnancy, but may occur at all ages. The pathogenesis is unknown. Pyogenic granuloma most commonly occur at sites of trauma on the distal extremities and the face, and occasionally gingival mucosa, but may present on any part of the body. Histologically, the appearance is that of a polypoid, lobulated mass of newly formed capillary blood vessels surrounded by an edematous stroma.[78] Clinically, pyogenic granuloma present as dark red pedunculated nodules often with a surrounding collarette of scale at the base. Pyogenic granuloma are prone to ulceration and bleeding, which often brings the patient to medical attention. Because of their rapid and exuberant growth, these lesions are sometimes mistaken for a malignancy. The differential diagnosis includes malignant melanoma, Kaposi's sarcoma, metastatic carcinoma, bacillary angiomatosis, and angiolymphoid hyperplasia with eosinophilia. Occasionally, the lesion spontaneously resolves. Lesions associated with pregnancy frequently involute after delivery; most often, however, the lesion must be treated surgically. This treatment is easily accomplished by surgical excision or curettage with electrodesiccation.

Salmon Patch

The salmon patch nevus is the most common vascular malformation of infancy, occurring in 30% to 40% of newborns. Salmon patch nevi are thought to represent persistent fetal circulation and present as pink macular patches on the posterior neck, scalp, glabella, forehead, and upper eyelids. When located on the nape of the neck, it is referred to as a "stork bite"; when present on the eyelid or glabella, it is referred to as an "angel's kiss." Eyelid lesions generally resolve within the first year of life, and the glabellar lesions also spontaneously involute but

take somewhat longer. The nuchal lesions may persist into adult life, although some spontaneously fade.

Port Wine Stain

Port wine stain, or *nevus flammeus,* is a congenital vascular malformation that presents in approximately 0.3% of newborns. Port wine stains show no tendency to fade and, in fact, generally darken and thicken with age, becoming deeply violaceous and nodular during adult life. These lesions are often unilateral and may follow a trigeminal distribution on the face. Extensive areas of facial skin, oral mucosa, and conjunctival membranes are often involved, although any area may be affected. Although port wine stains are usually limited to the skin, their psychosocial impact may be great. Lesions present initially as pink or pale red patches that, with time, progress through deepening shades of red to take on a deeply violaceous hue. With increasing age, the ectatic vessels become progressively more dilated and may become nodular and protuberant. Their prominent location on the face may have a significant psychosocial impact on developing children. Large nodular lesions may also tend to bleed and become crusted. The treatment of choice is the flashlamp-pumped pulsed dye laser. With repeated treatment sessions, significant fading can occur, although only a small percentage of these nevi resolve completely.

Port wine stains may indicate more serious underlying disease associated with several congenital syndromes.[71] Sturge-Weber syndrome (leptomeningeal nevus flammeus) is a port wine stain located along the distribution of the trigeminal nerve and angiomas within the meninges, with progressive calcification in these areas. Abnormalities associated with this condition include intractable seizures, developmental delay, and ocular abnormalities such as glaucoma. Increased incidence of Sturge-Weber syndrome is associated with involvement in the distribution of the three branches of the trigeminal nerve, bilateral involvement, and upper and lower eyelid involvement. Klippel-Trénaunay-Parkes-Weber syndrome (osteohypertrophic nevus flammeus) is characterized by hypertrophy of the soft tissues and bones of the lower extremity accompanied by a venous varicosity and an overlying port wine stain.

Telangiectasia

Telangiectasia are permanent vascular dilations caused by a variety of processes that affect blood vessel endothelium and its supporting structures. They may be congenital or acquired and may be of only cosmetic concern; however, they can be associated with internal disease or genetic syndromes. Clinically telangiectasias are easily recognized and blanch readily with diascopy.

Spider Angioma

Spider angioma, or *nevus araneus*, is a common type of telangiectasia often presenting on the face, upper body, and distal extremities. Spider angiomas may occur on mucous membranes, in which case the differentiation from hereditary hemorrhagic telangiectasia must be made. Clinically, lesions appear as a central, raised, small body that may be pulsatile with multiple legs fanning out from the center. They may be associated with liver disease, pregnancy, and estrogen therapy; however, spider angiomas are often idiopathic, presenting in 15% of healthy children and adults. Treatment is by obliteration of the central feeding arterial, which can be accomplished with electrocautery or photocoagulation.

Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome)

Hereditary hemorrhagic telangiectasia is a dominantly inherited condition that affects blood vessels throughout the body.[79] It is characterized by ectatic vessels of the skin, mucous membranes, and viscera. Often the presenting symptom is spontaneous epistaxis, which may begin during early childhood but more likely appears at puberty or during adult life. Telangiectasia generally begin around and after puberty. The superficial telangiectasia assumes three morphologic forms; the most common lesions are punctate, but they may also be linear or spider-like. The mucous membranes are almost always involved, with lesions occurring on the lips, oral and nasal mucous membranes, nasopharynx, and throughout the gastrointestinal tract. The lesions may ulcerate and frequently bleed. The condition is associated with pulmonary, cerebral, and hepatic arteriovenous malformations. Bleeding may occur from any of the vascular lesions throughout the body and may be fatal. The diagnosis is generally made when the combination of frequent hemorrhagic episodes, vascular ectasias, and a family history is recognized. Genetic testing is available for prenatal diagnosis. Importantly, because catastrophic hemorrhage can occur in children with clinically silent disease, screening imaging for cerebral and pulmonary arteriomalformations is indicated in children who have a family history. Treatment is aimed at control of specific hemorrhages and of anemia, if it arises. Individual cutaneous lesions may be treated by electrocauterization and photocoagulation.

Venous Lake

Venous lakes present as deep blue, cutaneous nodules that occur most frequently on the face, lips, and ears of elderly patients (see Fig. 20-8B). Sometimes called *senile angiomas,* they are composed of dilated thick- and thin-walled, otherwise normal-appearing vessels. The lesions may thrombose and involute, but frequently they persist. They are of no significance other than a cosmetic nuisance and may be treated with vascular-specific lasers.

Fibroadnexal Tumors

Fibroadnexal tumors are derived from components of the deeper layers of the skin. They generally show differentiation toward the specific cell or tissue of origination and may be derived from any of the neurogenous, fibrillar, glandular, or pilar components of the dermis, as well as the subcutaneous tissue.

Acrochordon

Acrochordon (skin tag, fibroepithelial papilloma) are extremely common lesions, occurring most often during middle to late life. They are flesh-colored, pedunculate tumors that are generally up to about 2 mm in diameter. They are soft and most commonly occur in flexural regions such as the axillae, the sides of the neck, inframammary areas, and the upper eyelids. The lesions are composed of mostly loose fibrous tissue (similar to that of the superficial dermis), and they are covered by a thin epidermis. No adnexal structures are present. The lesions are easily removed by simple sharp-scissors excision or light electrodesiccation.[79]

Keloids and Hypertrophic Scars

Keloids and hypertrophic scars are uncontrolled proliferative responses to trauma by the fibrous tissue of the dermis.[80] Hypertrophic scar is a thickened scar that does not extend beyond the margins of the original injury, whereas a keloid is an exuberant growth extending beyond the borders of the initial scar. Keloids are most commonly seen in blacks. The epithelium overlying the tumor is frequently thinned and shiny, and the tumor may be tender and pruritic. The areas of predilection for keloids include the sternal area, the shoulders, and the upper back; they are also frequently seen on the earlobes after ear piercing and on the face. These tumors may be flat or extremely protuberant, dome shaped, or bosselated. They are most common in the second and third decades of life, becoming less common with age. Histologically, they present with distinctive keloidal collagen. Hypertrophic scars usually occur on sites of increased skin movement and tension; there is no racial predilection. Treatment of keloid and hypertrophic scars is challenging. Excision of these tumors generally has resulted in regrowth. Some success has resulted from radiation therapy, pressure, cryotherapy, injection of high-potency corticosteroids, interferon and fluorouracil, topical silicone dressings, and pulsed-dye laser treatment. Simple surgical excision is usually followed by recurrence unless adjunct therapies are used.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is an uncommon soft tissue sarcoma of low to intermediate malignancy with low metastatic risk, however with aggressive local behavior and high recurrence rates. All ages may be affected. It usually presents a pink to reddish protuberant

mass on the trunk or extremities; however, approximately 15% occur on the head and neck. Metastasis occurs in 1% to 4% of lesions, although approximately 10% demonstrate a high grade of malignancy with high risk of metastasis. Ninety percent of DFSP demonstrate translocation of chromosomes 17 and 22, in which the platelet-derived growth factor (PDGFB) gene is fused with the collagen 1 alpha gene, leading to upregulation of PDGFB expression in the tumor. Histologically DFSP are characterized by monomorphous spindle cells arranged in a storiform pattern. Less common variants include the Bednar tumor (laden with melanin) and myxoid variants. Small lesions may clinically and histologically resemble benign fibrous histiocytomas (dermatofibroma). Positive staining with CD34 differentiates these two entities. Some tumors demonstrate fascicles of spindle-shaped tumor cells with atypia, high cellularity, and an increased mitotic rate; clinically these tumors exhibit a more aggressive course with a greater probability of recurrence and metastasis.

Complete surgical resection of the tumor is the treatment of choice. Lower recurrence rates have been demonstrated by Mohs micrographic surgery with microscopic margin control, providing a distinct advantage over wide local excision.[81] Head and neck lesions tend to have high recurrence rates, and may particularly benefit from the use of Mohs surgery techniques. Some success has been demonstrated with pretreatment of advanced and metastatic DFSP with imatinib mesylate, a selective inhibitor of PDGFB kinases, before Mohs surgery, suggesting it may have a primary role in the treatment of DFSP in future.[82]

Atypical Fibroxanthoma

Atypical fibroxanthoma is a low-grade malignant spindle-cell tumor that most commonly occurs on the sun-exposed areas of the elderly. They are believed to be of fibrohistiocytic origin and to be a superficial variant of a malignant fibrous histiocytoma.[83] The lesion is a pink to translucent nodule, generally 1 to 2 cm in diameter. Ulceration is not uncommon. Clinically these tumors may be mistaken for several different types of malignancies, including basal cell carcinomas, squamous cell carcinomas, and melanomas. The risk of metastasis is low, although local and distant metastases have been reported. Histologically, these lesions have a bizarre appearance, with large and atypical epithelioid and spindle cells, and multinucleate giant cells. Surgical excision is the treatment of choice. Accumulating data suggest lower recurrence rates with Mohs micrographic surgery.

Neurofibromas

Neurofibromas are soft, dome-shaped, flesh-colored lesions that may be located anywhere on the body; they may vary greatly in size, from quite small to large pedunculate lesions. Neurofibromas are derived from the Schwann cells of cutaneous nerves.[84] On histologic examination, they present as nonencapsulated, loose, spindeloid tumors. Solitary lesions may be easily excised. These tumors may be indicative of the genetic neurofibromatosis syndrome, which may be associated with severe neurologic problems as well as a risk of malignant degeneration of the tumor. When a neurofibroma is found, a careful search for other manifestations, which include café-au-lait spots and axillary freckling as well as a family history, should be carried out to rule out the syndrome.

Angiofibroma

Angiofibroma (adenoma sebaceum) is present as part of the genetic syndrome tuberous sclerosis. The autosomal dominant syndrome has variable expressivity; the finding of even one angiofibroma requires genetic counseling, because the patient may pass on a much more severe form of the disease to offspring.[85] Angiofibromas present as small dome-shaped papules, 2 to 3 mm in diameter, that are flesh colored or reddish brown. They are most commonly present on the sides of the nose and the medial cheeks. The original name is a misnomer, because, on histologic examination, no sebaceous components are noted. The tumors are composed mostly of fibrous tissue and have an angioid component. Laser therapy with a 532-nm KTP laser has been shown to be effective treatment with long remission periods, although new lesions develop with time.

Fibrous Papule

The fibrous papule is a common lesion, generally occurring on the nose—especially the alae—in older persons (see Fig. 20-8D). However, it can also be seen on the medial cheeks. These lesions present as small, 0.5-cm, dome-shaped, flesh-colored papules. Although they are rather common, some confusion persists regarding their origin and histologic nature.[86] They have been regarded as perifollicular fibromas, involuting melanocytic nevi, angiofibromas, or simply the result of trauma, such as folliculitis or excoriating pimples. Histologically, the lesion presents as a papule that is composed of numerous spindle-shaped and stellate cells, with occasional multinucleate cells present. Once the lesions have grown, they are generally quite stable and may be present for years; they may be treated by excision or curettage and electrodesiccation. They are of no significance unless related to tuberous sclerosis.

Trichoepithelioma

A trichoepithelioma is an uncommon entity that most often presents as small rounded nodules on the cheeks, eyelids, and nose. It appears to be dominantly inherited; however, pedigrees indicate a greater preponderance of affected females. The lesions are skin-colored to slightly pink and gradually increase, with time, in both number and size. A few telangiectatic vessels may be present, and there may be a slightly translucent quality to the lesions, which may lead to confusion with basal cell carcinoma; however, the lesions rarely ulcerate. If ulceration does occur, basal cell carcinoma should be considered. The histologic appearance of these lesions also closely resembles basal cell carcinoma, and distinguishing between the two is often difficult.[87] There are basophilic cells similar to those seen in basal cell carcinoma. The cells are arranged in masses, which may have fully keratinized centers. Occasionally the presence of a solitary lesion makes differentiation from basal cell carcinoma somewhat more difficult, and, unless definite differentiation toward hairlike structures is present, the tumor should be treated as a carcinoma. When multiple lesions are present, treatment is difficult because of the large number of tumors. Some success has been obtained with dermabrasion or laser resurfacing of the entire affected area.

Cylindroma

Cylindromas are slow-growing appendageal tumors derived from follicular epithelium. They may assume apocrine phenotype and usually present as solitary pink to red dermal nodules on the head, neck, and scalp. They present predominantly in older women with a 9:1 female-to-male ratio. The presence of multiple cylindromas is associated with the Brooke-Spiegler syndrome,[88] in which an autosomal dominantly inherited mutation in the CYLD tumor suppressor gene leads to the development of multiple cylindromas, trichoepitheliomas, and spiradenomas primarily located on the head and neck.[89,90] Multiple cylindromas may literally cover the scalp, resulting in a syndrome called "turban tumors" (see Fig. 20-8E). Individual tumors can reach 2 to 3 cm in diameter. Histologically, these tumors are composed of nests of darkly staining epithelial cells surrounded by a narrow band of hyaline material. The solitary lesion must be differentiated from basal cell carcinoma. Surgical excision is the only treatment. When large areas of the scalp are involved, this may be quite difficult and may require grafting. Although usually benign, cylindromas may undergo malignant transformation with subsequent local invasion and metastatic disease.

Hidrocystoma

A hidrocystoma may be either eccrine or apocrine in origin.[91] In either case, the tumor usually presents as a solitary lesion and is most frequently seen on the face, especially around the eyelids. The lesion consists of translucent nodules with a firm, cystic consistency. The eccrine hidrocystoma is generally from 1 to 3 mm in diameter, whereas the apocrine hidrocystoma may attain a diameter of 1 cm. Both may have a bluish hue. The two types are distinguishable by histologic criteria. Microscopic examination reveals differing cellular detail and secretion patterns for the two types. In either case, treatment is excision.

Syringoma

Syringomas are benign tumors that originate from the eccrine sweat gland duct; they appear more often in women than in men.[92] Syringo-

mas are most commonly located on the face, with the lower eyelids being the most common site. They generally occur in adolescence or early adulthood and may be eruptive or occur in crops. They present as small 1- to 5-mm papules that are usually flesh colored but may be slightly translucent or yellowish. They may resemble trichoepitheliomas, but their location and histology help differentiate them. Histologically, these tumors appear as small nests of cystic ductal structures or as solid epithelial strands, many of which may have a characteristic tail-like projection. They are not associated with underlying abnormality. They do not tend to involute, however, and may present a cosmetic problem when located on the face. They can be treated with a pulsed ablative laser (CO_2 or erbium) or with light electrocoagulation using a fine epilating needle.

Sebaceous Hyperplasia

Sebaceous hyperplasia occurs mainly on the face, particularly the forehead, and represents benign enlargement of the normal sebaceous gland (see Fig. 20-8F). It is frequently called *senile sebaceous hyperplasia*, because it is usually seen in older persons.[93] One or hundreds of lesions may be present. They may be from 2 to 5 mm in diameter, and there is usually a central umbilication. These lesions are soft and yellowish and must be differentiated from basal cell carcinoma. Histologically, they present as hyperplastic sebaceous lobules that are otherwise normal in appearance. They are only a cosmetic problem; solitary lesions can be easily treated with a shave excision, electrodesiccation and curettage, or cryosurgery. When the lesions are numerous, surgical excision is not warranted. Therapy with systemic 13-cis retinoic acid has also been described.

Xanthelasma

Xanthelasmas present on or close to the eyelids as soft, yellowish, irregular papules. They usually appear in middle age and can affect either sex, and they are not often associated with xanthomas elsewhere on the body. Frequently, they are an isolated finding and do not always signify elevated serum triglyceride levels, although each patient should be examined for the existence of such a systemic problem.[94] Histologically, these lesions present as an accumulation of xanthoma cells, which are lipid-laden histiocytes. Treatment is the application of 50% to 65% trichloroacetic acid, light cautery, or excision.

Lipoma

Lipomas are single or multiple benign tumors composed of adipose tissue. They are soft and may be lobulated or rounded and cystic in nature, and they are generally freely movable. Except in rare syndromes, lipomas are nontender. They generally occur on the trunk, but they may also occur on the neck or any other part of the body. Histologically, they present as proliferations of normal-appearing fat cells that may be surrounded by a thin connective-tissue capsule. Single lesions present only cosmetic problems, and they are generally easily excised. Despite attaining sizes of more than 1 inch in diameter, they may often be expressed through a small, 4-mm punch hole.[95]

Treatment Methods and Biopsy Techniques

Excisional Surgery

The shave biopsy is one of the most commonly performed procedures for cutaneous lesions.[96,97] It is a rapid means of removing tissue either as part of therapy or to establish diagnoses. A shave can be performed using various techniques, with the depth of the shave depending on the angle of the blade as it enters the skin. Usually a No. 15 or No. 10 Bard-Parker blade is used. One should remember that the sharpest point of the No. 15 blade is the rounded tip, whereas the No. 10 has its sharpest edge along the belly of the blade. The shave should be performed using the sharpest portion of the blade. One of the sharpest blades is the Gillette Blue Blade; it is excellent for shaving lesions. A blade breaker or hemostat can break the Blue Blade into any size or shape desired. The blade can then be held between the thumb and forefinger and flexed, thereby allowing for the performance of a superficial shave in which the blade sculpts along the contour of the surface being excised (e.g., the ala of the nose or the helix of the ear). Hemostasis can then be achieved with aluminum chloride. Monsel's solution (ferric subsulfate) should be avoided on the face or cosmetic areas because of the ability of macrophages to phagocytose the iron, thereby causing a tattoo.

The punch, a fixed-diameter surgical knife, is an extremely valuable tool to a dermatologist for excision or biopsy. It comes in various sizes, from 2 mm to 1 cm, with 0.5-mm increments. Punches can be purchased as disposable instruments (Baker) or as permanent, sterilizable instruments. The most common sizes used for biopsy are 3 mm and 4 mm; however, a 2-mm punch can provide a cosmetically elegant biopsy of sufficient size for the pathologist. Whenever possible, the 4-mm punch should be used. All punch-biopsy incisions should be closed. Some tricks help with the use of a punch. By putting tension on the skin perpendicular to the anticipated line of closure (skin tension lines), one can cause the circular punch to leave an oval or ellipse for easier closure. The incision is usually closed with sutures or the recently introduced single-shot staple. A valuable trick is to use a punch to excise intradermal nevi. By selecting a punch that just fits around the nevus, one can easily excise it to the depth necessary to remove the entire lesion. Another trick, which can be used when nevi occur in areas of neutral skin tension or where skin tension lines are not obvious (e.g., the chin), is to use the punch to help determine the best lines of closure. If the surgeon uses a punch excision with no tension placed on the skin, the resulting circle will usually form itself into an oval along lines of facial expression and help in the determination of skin closure lines. Often the skin closure lines can occur at an angle that is perpendicular to what one might expect.

The wedge excision or biopsy, which is a variation of the fusiform excision (ellipse), can be used to remove lesions cosmetically or to perform biopsies. As a biopsy technique, it is either incisional or excisional. Whenever possible—especially when dealing with pigmented lesions—the excisional biopsy is preferred to give the pathologist the best chance for an accurate diagnosis. When the wedge procedure is performed as an incisional biopsy of a large, nodular lesion, the narrowest possible wedge (greater than the classic 3:1 length-to-width ratio) is made at the edge of the lesion so that one end of the wedge is through normal skin; then one side of normal skin is available through which to pass suture. This is an especially important advantage if the other side of the wedge is within friable tissue.

Scissors excision is a valuable method of cosmetically removing benign skin tumors. In the experienced hand, scissors can be used to produce an often-elegant cosmetic result very quickly. Scissors are best used on raised, pedunculate skin lesions in which the pedicle can be easily and rapidly cut with scissors. Our preference is to use fine-tipped, curved Iris or Gradle scissors. Tricks similar to those used for the shave biopsy apply to scissors excisions. Raising a bleb of anesthesia under a pedunculate lesion allows for better access to the base. Scissors are an excellent tool around the eyelids. Often a small chalazion clamp can be placed around a lesion, thereby permitting easy excision with fine scissors. Filiform or pedunculate lesions on the eyelids can be lifted with fine forceps and then cut with curved scissors. This procedure produces a small ellipse upon release of the eyelid skin, which either heals by itself or with the placement of one small stitch. Scissors can also be used for biopsies of oral mucosa. Again, a chalazion clamp can be placed on the lip, or a stitch can be placed around the area of the biopsy. One can then pull up on the stitch, thus creating a tent of tissue that can be scissors excised at the base to obtain a biopsy specimen.

A curet is a valuable tool to the skin surgeon. One should have a variety of sizes of curets available; larger curets are used to debulk or remove larger tumors, and smaller curets are used to do the same for small tumors or to help track small extensions of cutaneous tumors, such as basal cell carcinoma. A curet is held like a pencil, with the ring or small finger placed on the skin to anchor and stabilize the hand. Normal skin has a "gritty" feel with the curet, whereas abnormal skin or tumor often feels mushy or soft. One way to remove multiple molluscum contagiosum lesions on the face, for example, is to individually curet each small lesion (a small curet is used). If anesthesia is required, one can use either the usual local anesthetic or one of the refrigerant anesthetics, which both induces some anesthesia in the skin and hardens the lesion; hardening allows the lesion to be easily flicked off with a curet. A curet is often used in conjunction with electrosurgery.

Electrosurgery

Electrosurgery is a useful way to remove small benign lesions, to assist the curet with the removal of malignant lesions, and to assist the surgeon with the obtaining of hemostasis. Most electrosurgery performed in the office requires nothing more than a hyfrecator-like unit. This versatile instrument is easy to use because the patient does not need to be grounded, and the electrodesiccation or fulguration is at a more superficial depth than the electrocoagulation or cutting seen when a patient is grounded. Most of these electrosurgical units have two current settings. The low current is best for light electrodesiccation of benign lesions. One can also purchase a fine steel tip or place a 30-gauge needle on the standard tip; this tip can then be threaded down adnexal structures to treat benign adnexal tumors or to coagulate arterial vessels that are feeding vascular lesions. The high current setting, which is a more destructive mode, is used to burn tumor and surrounding tissue, such as during electrodesiccation or fulguration of basal cell carcinomas. Bipolar units, with the patient grounded, can be used to help sculpt lesions, such as in the case of a rhinophymatous nose.

Cryosurgery

Cryosurgical removal is the treatment of choice for many lesions. Systems vary from elaborate cryospray and cryoprobe units to something as simple as a Styrofoam cup containing liquid nitrogen to be applied with a cotton-tipped applicator. The superficial use of cryosurgery destroys tumor tissue, often with excellent cosmetic results. Hypopigmentation and other sequelae can develop, however, which make the use of cryosurgery in darker skin more difficult.

Chemical or Abrasive Surgery

Many superficial cutaneous lesions of the head and neck can be removed with the application of a chemical or with the use of abrasion. The chemicals most commonly used as peeling agents are trichloroacetic acid and phenol. The concentration of trichloroacetic acid used varies from 35% to 70%. Phenol is usually used as a concentrated solution (88%) or mixed as Baker's solution. These chemicals can be used to peel benign pigmented or melanotic lesions, with good success. The most common form of abrasion is spot dermabrasion. Our favorite tool is the Bell hand engine with the diamond fraise or wire brush. The fraise can be purchased in varying sizes and shapes; small, 2-mm wheel, cone, or cylindric fraises are excellent tools for removing multiple small epithelial tumors.

Laser Surgery

The use of lasers in surgery and medicine has rapidly advanced in recent decades and continues to play an important role in the treatment of many cutaneous neoplasms on the head and neck. Innovations in optical technology have allowed for improved therapeutic efficacy and safety and the ability to treat patients with an increasing number of medical and aesthetic indications. Advances in visible and near infrared lasers and broadband light sources, including the development of longer pulse durations, broader spectrums, and combined wavelengths, continue to improve the treatment of numerous benign vascular and pigmented lesions. Far infrared lasers including CO_2 and erbium:YAG lasers remain a useful tool for the safe and effective treatment of numerous benign epidermal lesions, and can be the treatment of choice for some premalignant epidermal lesions, including actinic keratoses and actinic chelitis.[98,99] They may have a role in the treatment of some in situ carcinomas, although they may be less suitable without the evaluation of tissue margins. The basic principles of laser surgery are discussed in detail in Chapter 3; specific use of lasers used to treat vascular lesions is discussed in Chapter 201.

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CHAPTER TWENTY-ONE

Scar Revision and Camouflage

J. Regan Thomas

Steven Ross Mobley

Key Points

- The ideal scar is narrow, flat with surrounding skin, parallel to the relaxed skin tension lines (RSTLs), or camouflaged within natural anatomic lines.
- Available scar revision techniques include excision, irregularization (including Z-plasty, W-plasty, and geometric broken line closure (GBLC), and dermabrasion.
- Adjunctive techniques include steroid injection, silicone sheeting, and cosmetics.

The head and neck is a prominent part of the human body and can frequently be injured as a result of trauma, burns, or surgery. With superficial injuries, most facial wounds will heal with little to no scar formation. However, once the reticular dermis has been violated, some amount of residual scarring is destined to occur. Several factors that are beyond the surgeon's control can affect the final appearance of the scar, including the mechanism of injury, position of the wound, health status of the patient, the patient's skin type, and the tendency to form robust scars. Factors that are under the surgeon's control include proper realignment of wound edges, conservative débridement of injured tissues, meticulous handling of tissues during primary repair, and aesthetically favorable alignment of scars whenever possible.

After complete maturation and healing, an ideal scar should be flat and level with the surrounding skin, a good color match with the surrounding skin, narrow, parallel to the RSTLs (Fig. 21-1) or on the border of aesthetic facial subunits, and without straight, unbroken lines that can be easily followed with the eye (Fig. 21-2).[1] Scars with aesthetically unfavorable characteristics include those that are wide or misaligned with relaxed skin tension lines or aesthetic subunits, and those that are thickened, hypertrophied, or keloid (Fig. 21-3).[1] The facial plastic surgeon has many options to improve, but not eliminate, these aesthetically unfavorable scars. Successful application of various treatments requires an understanding of which techniques are best indicated when performing scar revision or treating hypertrophic and keloid scars.

Successful scar revision begins with a precise analysis of both the scar and the patient's expectations. Patients often have the false perception that plastic surgery can make an existing scar invisible. The surgeon should educate the patient on the true realistic goal of surgery, which is to modify the scar to a point of maximized camouflage within the natural shadows, lines, and borders that exist within the head and neck.

Indications for Revision

The surgeon should first begin with a detailed analysis of the scar. Experience has shown that many scars that are narrow, well positioned along aesthetic subunit borders, or in parallel with RSTLs will continue to mature, improve, and become less noticeable over a period of 12 to 36 months.[2]

More commonly, patients will have scars that are amenable to improved surgical camouflage. Indications for scar revision include scars that are (1) widened, (2) perpendicular to RSTLs, (3) webbed, (4) pin-cushioned, (5) long and linear and misaligned with RSTLs, (6) hypertrophied, (7) interrupting an aesthetic unit of the face, (8) adjacent to, but not lying within, a favorable site, or (9) causing distortion of facial features or anatomic function. Many of these scars should be considered for revision after the first 60 to 90 days of scar maturation has occurred. In fact, early revision with realignment of the scar may allow it to mature more rapidly.

Numerous techniques are available when planning scar revision. This chapter organizes the techniques into the following categories:

1. Excision
2. Expansion with excision
3. Irregularization
4. Dermabrasion
5. Steroids
6. Silicone sheeting
7. Adjunctive

Excision

A cardinal principle of surgery is that the best treatment of any complication is primary prevention. For scar revision, this translates into the use of proper technique when closing any wound primarily. When presented with wounds that were not closed properly, re-excision with meticulous closure may be all that is needed. Re-excision should be done by use of fusiform shape with 30-degree angled ends positioned within RSTLs when possible (Figs. 21-4 and 21-5). A slight vertical bevel outward from the original scar will prepare the wound edges for proper everted closure. Routine undermining of 1 to 2 cm around the periphery of the wound allows reapproximation of the skin edges with minimal tension. The use of buried subcutaneous sutures further decreases wound edge tension. Final eversion of the wound edges is achieved with properly placed monofilament interrupted sutures. Vertical mattress sutures can also prove helpful when wound edge eversion needs to be maximized.

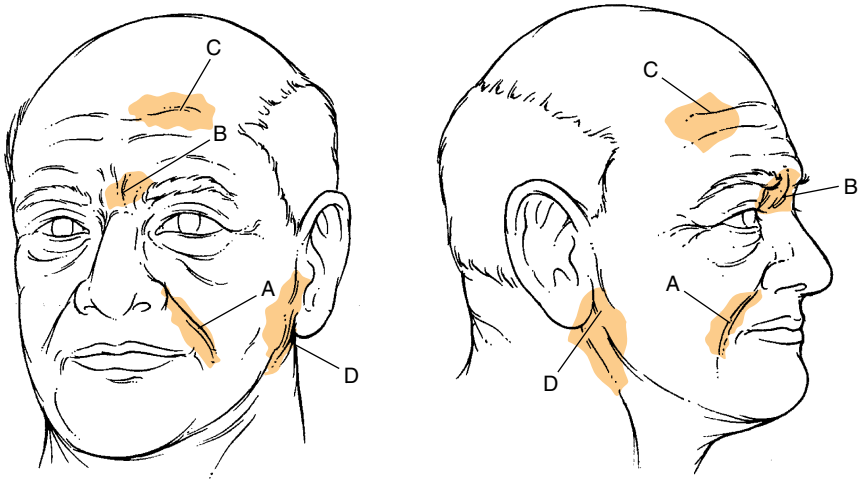

Figure 21-1. Relaxed skin tension lines and creases can aid in scar camouflage. **A,** Nasolabial. **B,** Glabellar furrows. **C,** Horizontal forehead rhytids. **D,** Subunit junctions (ear and cheek). *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

Figure 21-2. A 4-cm-long incision placed in alignment with relaxed skin tension lines and closed with multilayered closure and vertical mattress sutures.

Figure 21-3. Scar on right cheek with unfavorable characteristics: depressed and not in alignment with relaxed skin tension lines.

Expansion with Excision

Serial Excision

Wide scars, birthmarks, and skin grafts with poor match to surrounding tissues can all be candidates for serial excisions. In some ways, this is a variant of tissue expansion in that scarred skin is excised and adjacent normal skin brought into the defect area. Like tissue expansion, this technique relies on the skin's biologic creep (ability to stretch over time) and is limited by the given amount of stretch attainable during each excision. Typically, older patients and those with increased skin laxity will require fewer excisions than younger patients with increased skin tone. As with all techniques of scar revision, the patient must be well informed as to the proposed number of excisions and must understand that serial excision can require months to years to complete.

Tissue Expansion

When treating larger scars, the best camouflage is afforded when abundant amounts of similar-appearing tissue can be brought into the repair. Tissue expansion can be a powerful tool to help create excess amounts of surrounding tissue. Tissue expanders are available in a variety of shapes and sizes. Studies on the gain of surface area afforded by the three most commonly shaped expanders have determined that rectangular expanders provide the greatest expansion at 38%, crescent-shaped expanders provide 32%, and round expanders provide only 25%.[3] As a general rule, the base of an expander should be approximately 2.5 to 3 times as large as the area to be reconstructed.[4]

The effects of tissue expansion on skin have been debated. Is new skin actually produced or is the existing skin simply thinned and stretched? The currently accepted understanding regarding tissue layer expansion is that (1) the epidermis is thickened, (2) melanin production increases, (3) mitotic activity increases, (4) dermis thins (30% to 50%), (5) collagen synthesis is enhanced, (6) hair follicle number remains unchanged, (7) hair density decreases, (8) muscle thins and can atrophy, and (9) blood vessels proliferate.[5] Interestingly, epidermal changes and increased melanin production seen during expansion resolve a few months after surgery.

Implantation of the expanders must take into account the neurovascular supply and final positioning of the skin to be transferred. A second pocket is created for the injection port, which should be several centimeters away from the expansion device and in an area that is easily accessed. Expander systems with external injection ports may be needed in select patients. A 23-gauge or smaller needle is used to inject the expander. Expansion can proceed until the skin blanches or the patient complains of discomfort. Intervals between injections can be from 4 to 14 days, ideally two to three times per week. By properly selecting the correct expander device and understanding the principles of tissue expansion, reconstruction of larger and more complex scars can be successfully achieved.

A critical point of understanding for the clinician is the temporary psychological toll that is placed on the patient undergoing expansion. Tissue expanders can cause impressive disfigurement of the head and neck, which naturally results in significant emotional stress to the patient (Fig. 21-6A). Repeated acknowledgment and affirmation of the patient's uneasy feelings regarding the appearance of the expanders help support the patient throughout the expansion process. It is helpful to remind the patient that the disfigurement is temporary and that the

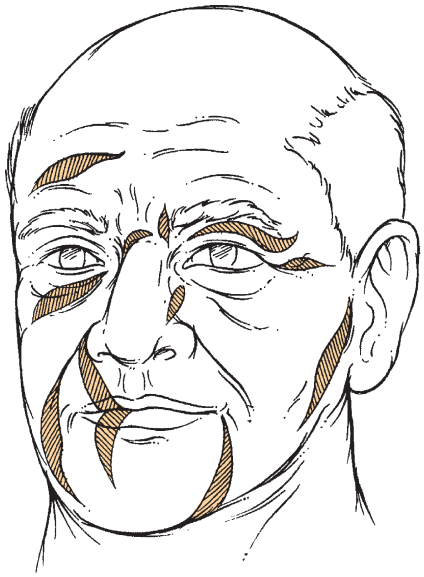

Figure 21-4. Examples of proper placement of fusiform incisions with 30-degree angled ends aligned with relaxed skin tension lines and aesthetic unit boundaries. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

Figure 21-5. A, Design of fusiform closure of Mohs defect. Note the design of a longer scar in parallel with relaxed skin tension lines to achieve 30-degree angles. **B,** Same patient 1 month postoperatively.

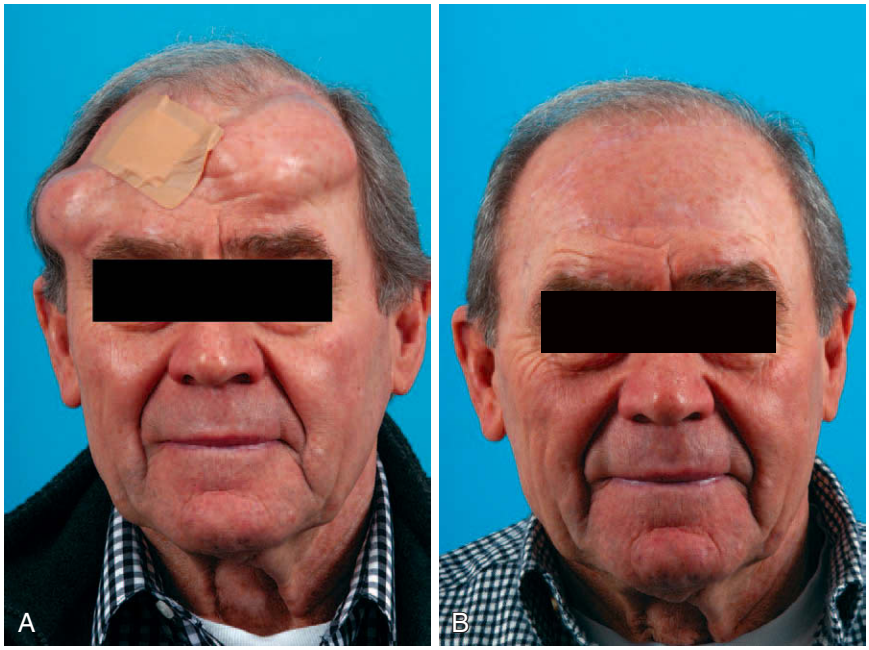

Figure 21-6. Patient midway **(A)** through process of bilateral forehead tissue expansion to close a Mohs defect in the forehead, and after **(B)**.

final reconstruction will warrant the time spent dealing with the expansion devices (see Fig. 21-6B).

Irregularization

The human eye is more likely to perceive scars that are long, linear, and not in alignment with RSTLs and aesthetic subunits. To best camouflage these types of scars, the three most common techniques are Z-plasty, W-plasty, and geometric broken line closure (GBLC). All three of these techniques convert linear scars to irregularized zigzagged scars that are less noticeable to the casual observer. When irregularization alone is needed, GBLC and W-plasty are the treatments of choice. However, when both irregularization and lengthening of the scar are needed, a Z-plasty technique is the technique of choice.

Z-plasty

The Z-plasty is one of the oldest and simplest techniques for scar irregularization. A "classic" Z-plasty involves the transposition of equilateral 60-degree triangles (Fig. 21-7). When these triangular flaps are transposed and closed, the original direction of the scar is rotated, and the scar is lengthened by 75%. When lesser amounts of lengthening are required, a 30-degree or 45-degree Z-plasty can be used that will lengthen the scar by 25% and 50%, respectively. Longer scars may benefit from multiple Z-plasties. This can be particularly helpful when correcting scar contractures along anatomic concavities. Consecutive Z-plasties allow for the redistribution of forces more evenly along the entire length of the scar and help camouflage the scar into the surrounding RSTLs (Fig. 21-8). Another common indication for multiple Z-plasties is when wounds or skin flaps have healed with a "pin-cushioned" appearance. Placing several small Zs around the perimeter of the wound allows interdigitation of flap with surrounding skin (Fig. 21-9). The resultant interdigitated skin edge provides excellent camouflage, especially if it is later treated with light dermabrasion.

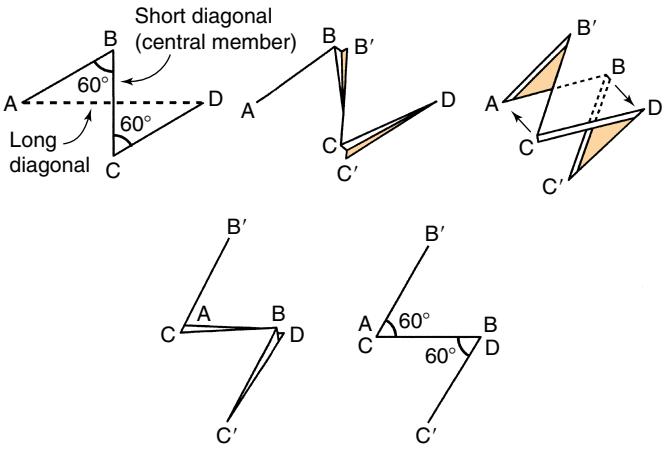

Figure 21-7. Classic equilateral triangle 60-degree Z-plasty. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

W-plasty

The most common application of W-plasty is when several Ws are used in series in a technique originally described by Borge as "running W-plasty." This is a useful irregularization technique that often uses shorter limbs compared with Z-plasty and does not create lengthening of the scar.

The technique begins with the marking out of a series of consecutive triangles (Ws) along the wound or scar edge. The arms should be between 5 and 7 mm in length, and one arm of the triangle should be drawn in parallel to the RSTL (Fig. 21-10). After excision of the triangles, superficial undermining of adjacent tissues is performed, and the triangular shaped flaps are then imbricated. Care should be taken to preserve the subcutaneous scar tissue, because this can provide a stable bed for new scar healing. These wounds are also amenable to postoperative dermabrasion to further camouflage the wound.

Geometric Broken Line Closure

GBLC is an excellent technique of scar revision that creates an "irregularly irregular" scar without affecting its length. The geometry of the resultant scar is less predictable by the casual observer's eye and frequently goes unnoticed. This technique is particularly well suited to scars that traverse broad flat surfaces such as the cheek, malar, and forehead regions (Fig. 21-11).

The design of a GBLC is a series of random, irregular, geometric shapes cut from one side of a wound and interdigitated with the mirror image of this pattern on the opposite side (Fig. 21-12). As in running W-plasty, the length of the geometric shapes is between 5 and 7 mm. Principles of undermining and leaving deeper scar tissue in the bed of the wound are similar to those previously described. Two-layered closure is performed, and the suture line is often reinforced with adhesive medical strips. The patient is typically seen back in 1 week for suture removal, with repeat taping of the wound edges for the next 2 weeks.

Dermabrasion

Dermabrasion is a method of controlled superficial skin ablation useful for smoothing out surface contour irregularities and softening the appearance of suture lines after primary closure or irregularization. We routinely use dermabrasion as a preplanned adjunctive procedure to any irregularization scar revision procedure. Dermabrasion is best per-

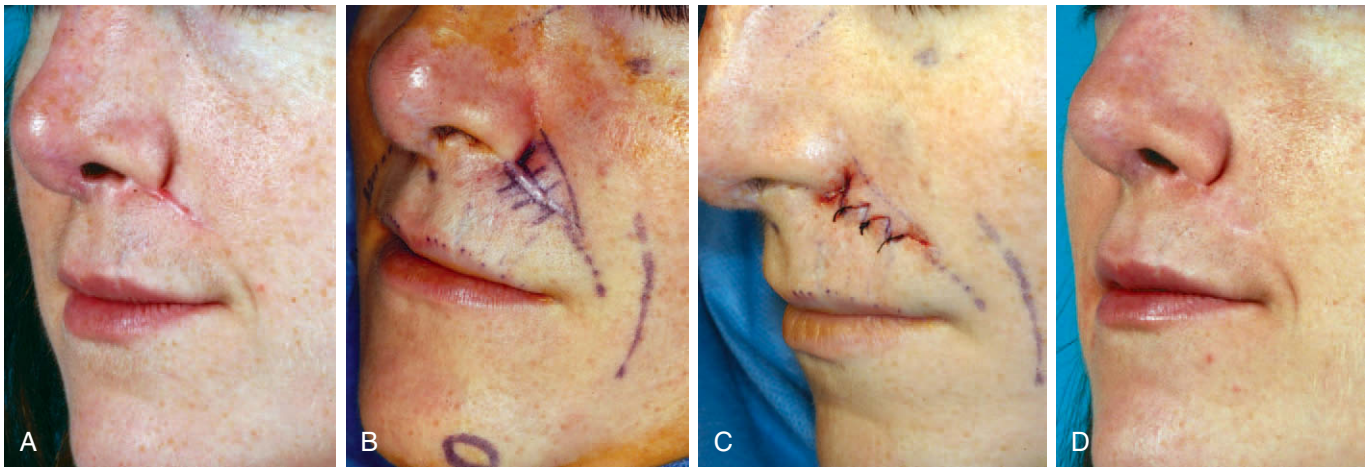

Figure 21-8. A, Preoperative appearance of scar on upper lip region. **B,** Operative plan for multiple Z-plasty technique. **C,** Appearance after transposition of Z-plasty. **D,** Postoperative appearance.

formed at the 6- to 8-week interval. There is evidence to suggest that rewounding during fibrillogenesis (i.e., 4 to 8 weeks after injury) may promote reaccumulation of hyaluronic acid in the wound matrix, thereby stimulating more epidermal cells to migrate and proliferate in the wound, improving the final appearance of the scar.[6]

The best candidates for dermabrasion are those with lighter complexions, because the risk of postabrasion dyspigmentation is lowest in these individuals. It is prudent to avoid dermabrasion in patients with human immunodeficiency virus or hepatitis because of the risks to health care personnel from airborne pathogens. The use of 13 cis-retinoic acid and its effect on healing after dermabrasion has been debated in the literature. Conflicting reports exist, and until the controversy is resolved, prudence would suggest waiting 6 to 12 months before performing dermabrasion on anyone with a prior history of 13 cis-retinoic acid use.[7,8] Patients with a history of herpetic infection should be placed prophylactically on antiviral therapy. Others have advocated placing all patients on prophylactic antivirals.[6]

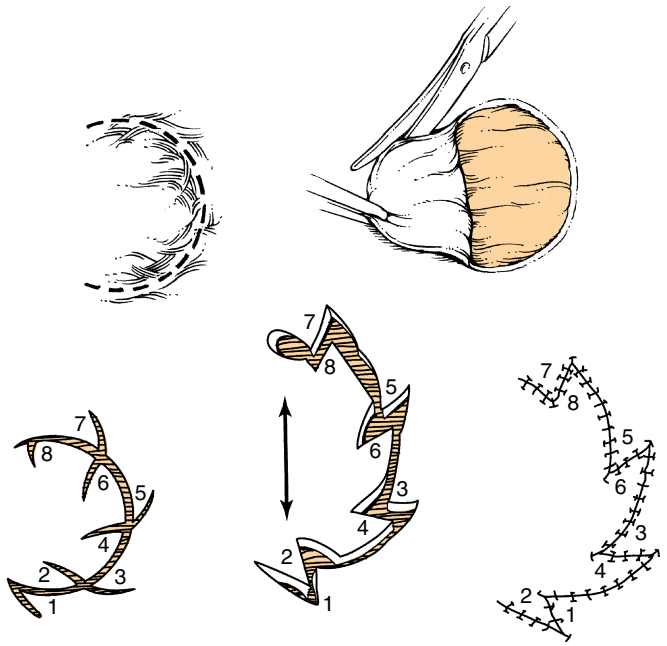

Figure 21-9. Multiple small Z-plasties to improve the appearance of circumferential or pin-cushioned scars. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

Diamond fraise bits are preferred, because they are easier to control and remove the skin less aggressively than wire brush fraises. The handpiece is generally held 90 degrees to the direction of wheel rotation and is advanced at right angles to the direction of wheel rotation (Fig. 21-13). Preparation of the area to be dermabraded can be accomplished with local anesthesia both for nerve block and infiltration. Infiltration not only provides anesthesia but can also cause distention of the skin, which aids in the technique. Preferably, local anesthetic without epinephrine is used to allow for more clear visualization of capillary bleeding that is seen with dermabrasion. As one enters the superficial papillary dermis, small capillary loops are identified as pinpoint bleeding. As the papillary dermis is penetrated more deeply, small parallel strands of white-colored collagen can be appreciated. Once this is seen, dermabrasion is taken to the appropriate depth. Preservation of the reticular dermis with its adnexal structures allows for the proliferation of undamaged epidermal cells across the abraded surface. The periphery of the treated area should be feathered with fine diamond fraises to allow for a smooth transition between treated and untreated areas.

Immediately after treatment, an occlusive dressing such as polyethylene oxide hydrogel (Vigilon) is applied. This is left in place for 48 hours, and then the patient is instructed to keep the area moist at all times with bacitracin for the next 7 to 10 days. After that, the patient can use a thick moisturizing lotion such as Eucerin. Re-epithelialization is usually accomplished after 5 to 7 days, but post-treatment erythema can often take 2 to 3 months before resolution (Fig. 21-14). This should be clearly communicated to the patient before the procedure. Women are usually less bothered by this, because they can begin to cover the area with make-up once re-epithelialization is complete.

Steroids

Intralesional corticosteroids can be an effective adjunct in the treatment of healing wounds, hypertrophic scars, and keloids. Steroid injections

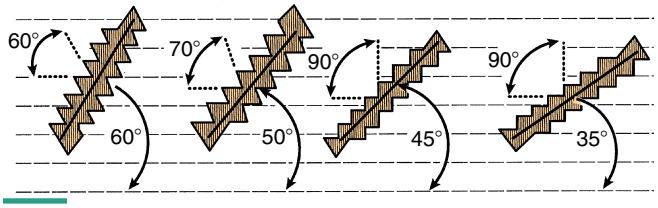

Figure 21-10. Running W-plasty with one area of triangle aligned in parallel with relaxed skin tension lines (RSTL). As scar inclination decreases, the degree of the angles should be increased to keep one arm of the triangle aligned with RSTL. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

Figure 21-11. **A,** Moderate-sized Mohs defect in the left cheek. **B,** Design of geometric broken line closure that is in parallel with relaxed skin tension lines. **C,** Several months postoperatively.

into areas of scar revision can be useful when persistent tissue edema detracts from the wound's appearance. Small doses of triamcinolone (10 mg/mL) injected into the dermis or the dermis subcutaneous junction can provide the surgeon with an ability to "sculpt" an otherwise normally healing wound and hasten the resolution of edema. For example, intralesional steroids can help lessen the "pin-cushion" edema seen frequently in local flap reconstruction techniques such as bilobed flap repair (Fig. 21-15). Steroids can cause hypopigmentation and telangiectasias when injected in higher concentrations into the dermis. One should avoid the injection of steroids into the subcutaneous fat, because this can lead to deformity from fat atrophy. Judicious use and conservative clinical judgment are usually all that is needed to prevent these untoward events.

Topical steroids can also be used when one is trying to diminish minor wound erythema that can be a normal part of the healing process. This has an application in younger patients and those with more sebaceous skin who are prone to erythematous wounds. Also, after dermabrasion of other resurfacing procedures, short-term low-dose topical steroids can be applied after re-epithelialization is complete.

Silicone Sheeting

The topical application of silicone gel sheets to the surface of keloids has been shown to be beneficial to the improvement of scars. Ohmori[9] studied the effects of silicone sheeting on 46 patients with 48 keloids in all areas of the body. By use of a study-defined grading scale, he reported excellent and good results in 60% of patients and fair to poor results in 40%. Katz[10] investigated the use of silicone sheeting for both

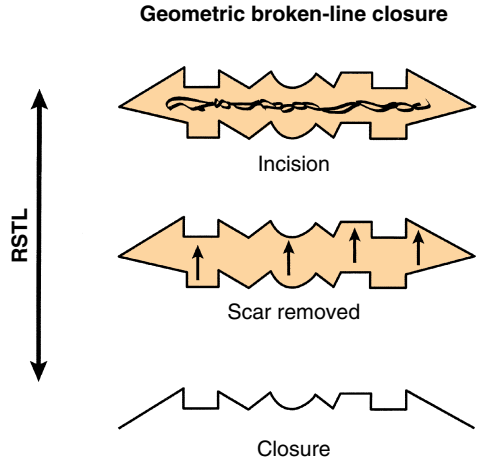

Figure 21-12. Geometric broken line closure irregularizes the scar to a less predictable pattern, further increasing camouflage. Note parts of geometric shapes in parallel with relaxed skin tension lines. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

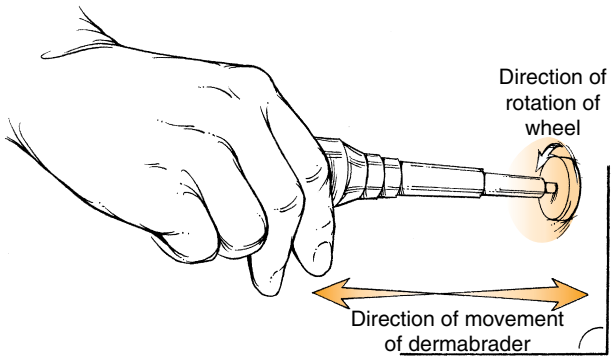

Figure 21-13. Dermabrader moved at right angles to direction of wheel rotation. *(Adapted from Thomas JR, Holt GR.* Facial Scars, Incisions, Revision & Camouflage. *St. Louis: Mosby; 1989.)*

Figure 21-14. **A,** Patient 6 weeks after full-thickness skin graft to nasal tip. **B,** Same patient 1 month after dermabrasion of entire nasal aesthetic unit.

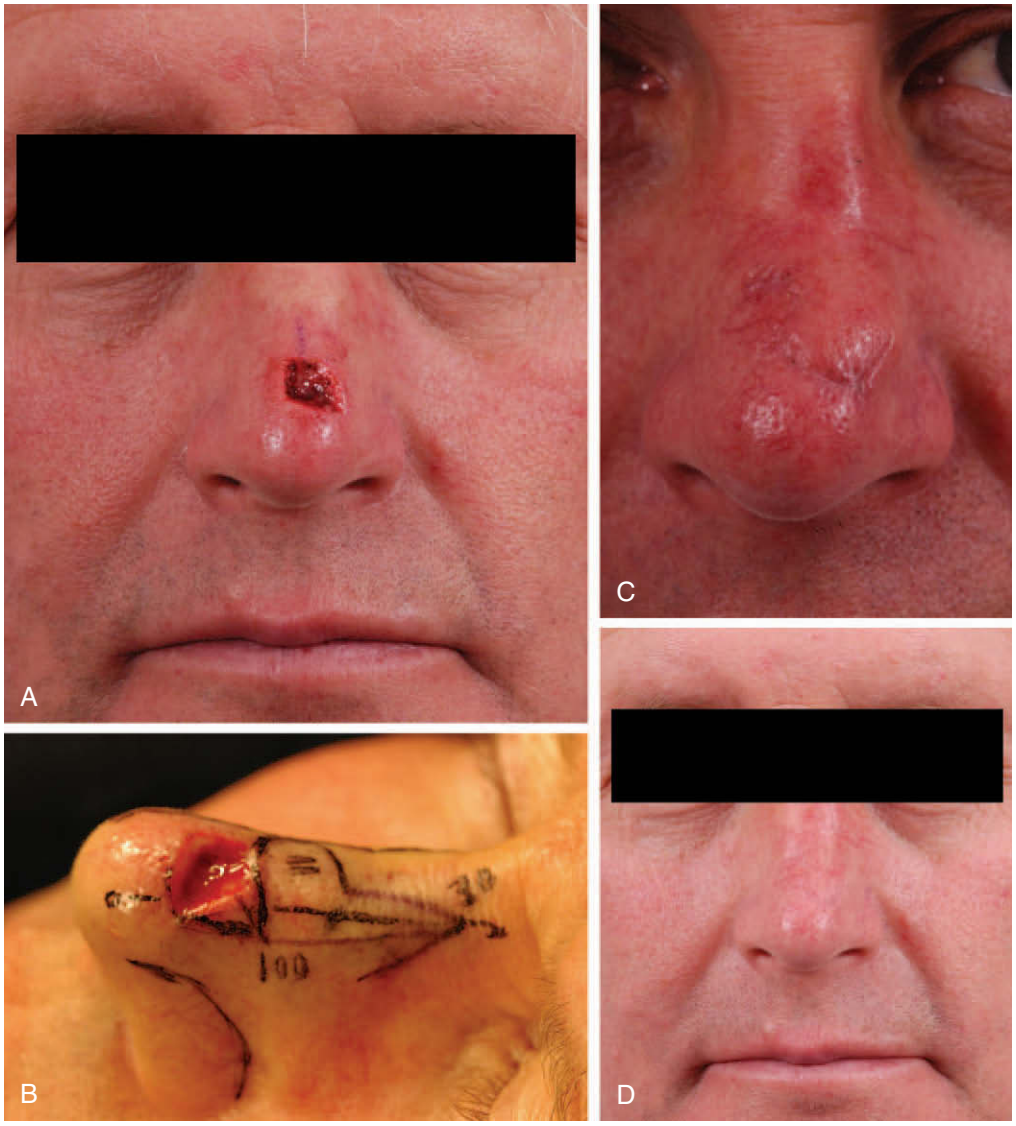

Figure 21-15. **A,** Patient with Mohs defect of nasal tip. **B,** Intraoperative photo demonstrating design of flap; note the design of the second lobe to lie within aesthetic subunits of the nose. **C,** Three weeks postoperatively with typical "pin-cushion" edema seen with bilobed flaps. **D,** Three months postoperatively. Patient has received three subcutaneous injections of 10 mg/mL triamcinolone delivered 2 weeks apart.

keloids and hypertrophic scars. Fifty-six percent of keloids demonstrated measurable improvement. Zero of five patients with a history of hypertrophic scarring had recurrence of their hypertrophied scars after excision and postoperative silicone sheeting. Typically, patients are encouraged to wear the silicone for a minimum of 8 to 12 hours per day and to use it for 6 to 12 months. The use of topical silicone sheets should be considered in any scar that is not ideal secondary to being slightly raised or possessing hyperpigmentation.

The biophysical properties of silicone sheeting have been studied, but still the mechanism by which silicone sheeting may improve scar healing is not well characterized.[11,12] Changes in pressure, temperature, and oxygen tension have all been studied and found to be negligible. Silicone sheeting has been shown to increase scar hydration by reducing evaporation by more than 50%. This is postulated to cause a decrease in capillary activity and perhaps collagen deposition. It can be stated with reasonable confidence that silicone sheeting seems to have a favorable effect on wound healing and exposes the patient to little or no morbidity from the treatment.

Adjunctive Procedures

Cosmetics and Hairstyling

Although not routinely thought of as part of the medical management of scar revision, cosmetics and hairstyling can play an important role in these patients. Surgeons who routinely perform scar revision are encouraged to seek out aesthetic professionals in their area that have interest in helping with the care of these patients. The physician's familiarity with these adjunctive professional services is often met with great pleasure by the patient who is eager to look normal and regain confidence in his or her appearance.

For complete list of references log onto www.expertconsult.com.

CHAPTER TWENTY-TWO

Facial Trauma: Soft Tissue Lacerations and Burns

Justin D. Hill

Grant S. Hamilton, III

Key Points

- Examination and repair of facial soft tissue trauma must be systematic and thorough.
- Treatment of traumatic injuries is often a process of restoring facial appearance and function rather than a single procedure.
- A high index of suspicion and careful examination are required to rule out potentially occult injuries to the facial nerve, parotid duct, canalicular system and underlying maxillofacial skeleton.
- Identification and repair of facial nerve and parotid duct injuries should be done as soon as possible.
- Adequate anesthesia is essential for optimal repair and may be established through direct infiltration, topical application, or regional blocks.
- Pediatric patients may require sedation but often respond favorably to a graduated approach, a calm demeanor, and gentle technique.
- Eversion of wound edges is critical to the favorable appearance of a scar and is best accomplished with appropriately placed vertical mattress sutures.
- Microvascular replantation of well-preserved tissue avulsions and amputations of the nose, ears, lips, and scalp is a proven option for severe injuries to these unique structures.
- Salivary fistulas and sialoceles resulting from parenchymal injuries often respond to conservative therapy. Surgical repair of ductal injuries is the preferred method of treatment.
- Favorable outcomes in facial burns depend on aggressive wound care followed by early excision and grafting.
- Rapid rewarming is the most important component of frostbite injury treatment.

Traumatic injuries to the soft tissues of the head and neck are a common problem encountered by otolaryngologists. Whether these patients present acutely or after a delay, it is important to follow specific principles and a systematic approach to assessment and repair. An optimal outcome requires a combination of technical expertise and an ability to gain the confidence of patients and families affected physically and psychologically by traumatic injuries. The ultimate goal of treatment should be a repair that is acceptable to both the patient and the physician and that most closely approximates preinjury appearance and function. For some patients, repair of their injuries is a single event; for others, it is a process, requiring patience, forethought, and excellent rapport. Facial trauma often occurs in the setting of other, potentially more serious injuries and is therefore prone to benign neglect, requiring vigilance on the part of the treating physician to ensure that every patient is treated appropriately.

Etiology

The most common causes of traumatic injuries to the face include motor vehicle accidents, interpersonal violence, activities of daily life, sports-related injuries, work-related injuries, and bites, both human and animal.[1,2] Although generalized facial trauma, including bony trauma to the maxillofacial skeleton, is more common in men than women at approximately a 2:1 ratio, soft tissue facial trauma appears to have no distinct sex predilection and occurs in a wide range of ages, although the majority of injuries occur during the first 3 decades of life.[3] Motor vehicle accidents are a common cause of facial injuries, affecting approximately 50% of survivors. The use of seatbelts alone, or in combination with airbags, has been shown to reduce the frequency and severity of facial injuries; however, airbags alone have not demonstrated the same benefit.[4]

Approach to Traumatic Injuries

History

Every clinical encounter begins with an accurate and thorough history followed by a detailed physical examination. The approach to patients with facial trauma is no different. However, because these patients often have a wide range of concomitant injuries, access to the patient for a history and physical examination may be limited on initial presentation. Multiply injured patients require systematic evaluation according to Advanced Trauma Life Support (ATLS) protocol. Patients with severe or life-threatening injuries to the chest, abdomen, or extremities present a unique challenge. A cursory head and neck examination by first responders and even other physicians may reveal seemingly uncompli-

cated facial injuries, which when evaluated carefully demonstrate significant structural or functional compromise such as a facial nerve or parotid duct injury, lid laceration with exposed cornea, retained foreign bodies, or canalicular injury. Every possible attempt to gain an accurate history and perform a complete examination should be made before opportunities for optimal repair are missed.

An often neglected component of the history is premorbid appearance and function. It should not be taken for granted that a patient with facial weakness on examination had normal facial nerve function before the injury. Details like this must be obtained to prevent unnecessary workup and treatment. If possible, it is helpful to have a photo of the patient from friends or family when significant disfigurement occurs. Even a driver's license photograph may be helpful. Although a photograph may not change overall management, it does provide a frame of reference for patient and family expectations of repair and gives the surgeon an opportunity to better see the patient as a person rather than as another injured face.

The social context in which injuries take place is as important as the physical context. Injuries from interpersonal violence make up a large component of facial trauma. Assault and abuse victims may not volunteer the mechanism or the assailant without confidence that the health care system will protect them from immediate and future harm. Depending on their age and development, children may not be able to volunteer details of abuse, requiring a thorough history from parents or caregivers and witnesses in an effort to identify discrepancies. More than 50% of victims of child abuse demonstrate injuries to the face, although injuries to the face alone are not sufficient to suspect abuse.[5] Abuse should be suspected when the described mechanism does not fit the injury pattern or when the child displays signs of abuse elsewhere.

A detailed history of the mechanism is crucial. The traumatic event should be reconstructed as accurately as possible, including time, location, involved parties, degree of contamination (e.g., dog bite or clean laceration from a sharp object). In motor vehicle injuries, pertinent components include speed of impact, the victim's use of a seatbelt or helmet, deployment of airbags, whether the victim was ejected from the vehicle, the presence of broken glass, chemicals, or fire at the scene, and the involvement of drugs or alcohol. In injuries resulting from tripping or falls, it is important to ascertain the height of the drop, the nature of the landing area, and whether the patient struck any objects. The level of consciousness during and after the injury should always be determined. In cases of assault, the type of weapon, information about the assailant, and any prior history of assault should be determined.

Assurance of tetanus prophylaxis is imperative. Tetanus-prone wounds are typically deep lacerations, avulsions, or puncture wounds contaminated with soil, feces, saliva, or mineral debris. If the immunization status is unknown or if the patient has not completed the series of tetanus immunizations, tetanus immunoglobulin (TIG) and vaccine (tetanus toxoid) should be administered. All other patients who have completed a primary immunization series should receive toxoid unless they have had a booster or completed the series within the last 5 years.[6]

Physical Examination

Many soft tissue injuries to the face occur in the setting of underlying trauma to the maxillofacial skeleton, and a thorough examination must be performed with this in mind. Although the focus of this chapter is on injury to the soft tissues, an adequate evaluation of facial trauma includes an assessment to rule out fractures. A systematic approach is essential to prevent errors, both in diagnosis and management. Every practitioner caring for a trauma patient is obligated to follow ATLS protocol regardless of that caregiver's role in treatment.[7] An orderly approach using the ABCDE mnemonic with primary and secondary surveys assures that the most threatening conditions are dealt with first and that nothing is missed. A seemingly innocuous forehead laceration in the emergency department triaged quickly to the "facial trauma service" may mask occult intracranial or cervical spine injury depending on the mechanism—something that could be missed by simply focusing on fixing the laceration rather than treating the patient. Vigilance must be exercised in patients transferred from other institutions, and experienced surgeons recognize that an assessment from a transferring provider may not be an adequate substitute for their own careful examination.

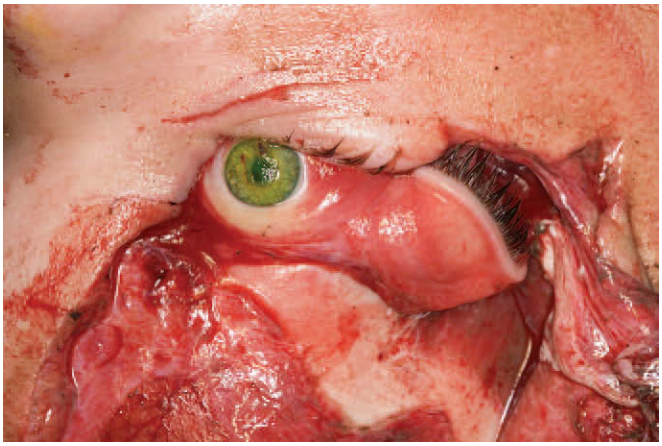

Figure 22-1. Complex laceration involving the eyelids resulting in exposure of the globe. This wound demands immediate attention to prevent corneal exposure and ocular injury.

The examination begins with careful investigation of problems with airway, breathing, and circulation—immediate or impending. Airway compromise is rarely associated with superficial soft tissue trauma alone; however, severe hemorrhage with collection of blood in the upper airway can rapidly compromise airway, breathing, and circulation, particularly in a combative or obtunded patient.[8] The airway is secured by controlling hemorrhage with direct pressure or identification and ligation of the injured vessel. This must be performed with caution, however, to avoid injuring other important structures such as the facial nerve or parotid duct in attempts to quickly stop hemorrhage by clamping a bleeding vessel in the wound bed. Another injury requiring immediate intervention is that of corneal exposure from eyelid laceration or avulsion. Immediate corneal protection prevents potentially devastating ocular injury (Fig. 22-1).

A general assessment of surface anatomy includes assessing the scalp and facial features in repose to evaluate for asymmetries that suggest underlying skeletal or neurologic injury. The remainder of the examination is conducted systematically. The exact order of the examination is unimportant, but the same sequence should be used every time to ensure a comprehensive assessment of injuries. Facial bones are palpated for deformities, step-offs, and mobility including the entire skull, orbit, zygoma, maxilla, palate, and mandible. Computed tomography (CT) scans and plain films are not an adequate substitute for this examination. Whereas most traumatic soft tissue injuries to the face are often obvious on initial inspection, certain areas require careful examination to rule out more significant injuries. Otoscopy often demonstrates a blood-filled canal in patients with facial lacerations who are transported supine. After removal of blood and debris, closer inspection may reveal lacerations in the ear canal in the setting of a skull base fracture even in the absence of hemotympanum. A thorough examination of the eyes and periorbital areas includes the medial canthus, fornix, conjunctiva, cornea, and orbital rims. A careful examination of these areas is even more crucial in an obtunded patient who cannot volunteer symptoms of visual loss, ocular or conjunctival foreign body, or diplopia. When there are lacerations of the upper or lower eyelids in the medial canthal region, one must rule out disruption of the lacrimal apparatus. The long-term sequela of canalicular disruption with subsequent blockage of a tear drainage pathway into the nose is epiphora and is not present on initial examination. A positive fluorescein instillation test (Jones test) effectively rules this out, although probing the lacrimal punctum and ducts with lacrimal probes while examining the wound before repair is safe, reliable, and relatively straightforward. Every patient should have visual fields tested, and motility and acuity assessed and documented. Patients with any periorbital or ocular trauma should also be evaluated by an ophthalmologist for a full examination, including a dilated retinal examination.

All examination findings, both positive and negative, should be documented, including the time at which the findings were noted. Simple omissions in the medical record can lead to significant difficulties in ongoing diagnosis and management in addition to unnecessary medicolegal liability.

Anesthesia

Complete assessment of wounds is often only possible after establishing adequate anesthesia. Additional patient discomfort during wound exploration and repair is unnecessary and creates an adverse environment for a technically successful repair. Comfortable working conditions for both the patient and the physician can generally be established with local anesthetics through topical application, infiltration, or nerve blocks of the trigeminal distribution. Lidocaine, with or without epinephrine in concentrations from 0.5% to 2%, is a commonly used agent for infiltration or regional block. Lidocaine is well tolerated by nearly all patients with minimal side effects and a safe dosing range.[9] Widely quoted maximum doses for local anesthetics actually have little basis in human studies or evidence-based medicine and are largely extrapolated from animal data and case reports of toxicity.[10] These theoretical guidelines suggest that toxicity from lidocaine, in the form of central nervous system disturbances (e.g., seizures or cardiac dysrhythmias), will develop with doses greater than 5 mg/kg of patient body weight or 7 mg/kg if epinephrine is added. Toxicity, however, is probably multifactorial, taking into account fluid status, age, site of injection, medical comorbidities, and other injuries.[11] Even so, in the multiply injured patient requiring repair at separate sites by more than one practitioner, the aggregate dose of local anesthetic should be tracked and documented by all parties involved to avoid toxicity. In children, doses may be inadvertently high because of the patient's smaller body mass.

Lidocaine alone has a modest vasodilatory effect on capillaries and can impair hemostasis during closure. The addition of epinephrine in a dilution of 1:100,000 to 200,000 encourages hemostasis and mitigates systemic absorption but requires caution in certain circumstances. Dense infiltration of macerated wound edges or long, tenuous flaps of avulsed skin with epinephrine may compromise otherwise salvageable tissue and should be avoided. The need for local infiltration can be markedly reduced or obviated by a well-performed regional block. Physicians involved in the treatment of soft tissue trauma should become facile with their use. Near-total anesthesia of the face for soft tissue work can be accomplished by selective blocks of the infraorbital, supraorbital/supratrochlear, zygomaticotemporal, zygomaticofacial, dorsal nasal, great auricular, and mental nerves.[12] Appropriate use of these blocks decreases the overall dose of local anesthetic required and the pain associated with the injection of local agents. They are also helpful when infiltration of wound edges would distort important landmarks such as the vermillion border. Significantly, in a cooperative patient, establishment of good regional anesthesia may eliminate the need to perform a repair under general anesthesia in the operating room. Longer acting local agents such as bupivacaine may also be used for direct injection into the wound edge, or, more appropriately, for a long-acting block in select cases. Bupivacaine does have a narrower therapeutic window than lidocaine with potential for cardiotoxicity.[13] Ropivacaine is another well-established long-acting local agent with a better dose-dependent toxicity profile than bupivacaine; however, higher cost may be a barrier to its use at many institutions.

The four chief causes of pain associated with injection are the temperature of the injectate, the acidity of the solution, the speed of injection, and the size of the needle. These factors are all easily addressed to minimize the discomfort of the patient. Warming the local agent to body temperature decreases the pain of injection.[14] Similarly, buffering 1% lidocaine with 8.4% sodium bicarbonate solution in a ratio of 9:1 brings the pH of the solution up from 4 to a value around neutral. The only real tradeoff with buffering is the resultant diminished duration of effect, which can be as short as 30 minutes.[9] Injecting slowly with small needles, 27 or preferably 30 gauge, also decreases pain. It is much easier to inject with a small needle when a small syringe is also used because there is a smaller discrepancy between the diameter of the syringe and the diameter of the needle. A calm, comforting demeanor, combined with appropriate technique, enables the surgeon to provide the patient with adequate anesthesia without any additional pain or anxiety. With children, it is best to take a graduated approach. Frequently, by the time the consultant is seeing the patient, the initial psychological trauma has abated and the child is fairly calm. One could first talk to the child about something other than the injury. Also, the clinician should explain everything he or she is going to do in advance. The patient's anxiety only increases when awaiting a "surprise attack." Next, the clinician should "examine" part of the patient's body that was uninjured. This nonpainful touching can set the precedent that not everything is going to hurt. Next, the wound is gently examined. Gentle irrigation with warm saline is rarely painful and allows the wound to be cleaned and thoroughly examined. At this point, careful infiltration of local anesthesia with a small-bore needle is almost always possible. Most patients fall asleep during the wound closure. However, for some pediatric patients, the idea of the needle trumps all efforts to alleviate anxiety. Rather than restraining a child to anesthetize a wound through injection, the clinician should choose topical anesthesia or conscious sedation.

Topical anesthesia first gained popularity in the form of a solution of 0.5% tetracaine, 1:2000 adrenaline, and 11.8% cocaine, known as TAC anesthesia, after comparable efficacy and safety were demonstrated relative to injection with lidocaine.[15-17] Based on the potential systemic toxicity and security concerns of the cocaine component of TAC, a variation on this technique, known as LAT (4% lidocaine, 1:2000 adrenaline, and 1% tetracaine), has been shown to be equally effective. It is also one-tenth the cost of TAC—a significant savings.[18] Even though LAT and TAC have become agents of choice for anesthetizing simple lacerations in children and select adults, their role in more complex wounds has yet to be defined. In an uncomplicated laceration, it is relatively easy to uniformly administer a topical agent to all areas of the wound bed.[19] Typically, an anesthetic solution is applied by saturated cotton tips or sponges and replaced every few minutes until anesthesia is obtained. This usually takes about 10 minutes. However, large, irregular wounds filled with clot or debris that would impair administration and require débridement are not candidates for this method. TAC should also be avoided near mucous membranes because of reports of systemic toxicity associated with high mucosal uptake of cocaine. It is important that adult patients understand that there is a possibility of testing positive for cocaine after TAC administration.[20]

Some children require sedation in addition to adequate local anesthesia. Conscious sedation or procedural sedation of children is a safe and effective way to diminish the potentially significant psychological distress associated with repair of soft tissue injuries.[21] Administering sedation to children requires training, experience, skill, and appropriate institutional resources. In the emergency setting, this is best administered by trained nursing staff under the direction of a physician or other provider certified to perform procedural sedation in children. This allows the surgeon to focus on the patient's injuries without the added responsibility of drug administration and monitoring. Despite its benefits, sedation does add to emergency department length of stay and cost of treatment, warranting judicious use when the child may tolerate repair with local anesthetic alone. This should not be used as an excuse, however, for withholding sedation for seemingly uncomplicated lacerations in children who are clearly distressed by the prospect of local anesthesia. Several agents have been demonstrated to be effective, including midazolam, ketamine, and fentanyl; these are often used in combination. The most common adverse effects are hypoxia and vomiting, which are usually minor and self-limited or resolve with minimal intervention.[22]

Cleaning

Carefully irrigating and cleaning wounds and surrounding skin is important not only for decreasing risk of infection but also to improve visualization of wound characteristics in preparation for repair. In the multiply injured, obtunded, or sedated patient, meticulous cleaning is even more important. It is not an uncommon scenario to encounter an unconscious patient in the trauma bay, positioned supine with an endotracheal tube and bite-block in the mouth, a nasogastric tube taped in place, a cervical collar around the neck, and dry, crusted blood, dirt,

or debris concealing soft tissue injuries. With so many impediments to a thorough examination, cleaning the entire head and neck is critical to avoid missing injuries. This includes hair-bearing scalp and facial hair where many soft tissue injuries are easily hidden. Hair may need to be shaved or trimmed to adequately clean, assess, and repair injuries. Eyebrows may be trimmed conservatively or shaved if necessary, although it may take 6 months for them to fully regrow.[23]

In most cases, simple antimicrobial cleansers such as chlorhexidine are adequate. Saline alone does little to remove bloody crusts. Warm saline is slightly better. Warm saline with dilute peroxide is better still, although studies showing fibroblast and keratinocyte inhibition in vitro with peroxide and povidone-iodine have led to many authors voicing caution regarding their liberal use in open wounds.[24] For most wounds, warm saline under moderate pressure will be adequate for irrigating debris and foreign material. Retained foreign bodies left unrecognized can develop into a significant problem and are a well-known cause of medicolegal action related to repair of traumatic injuries. Fortunately, the limited depth of soft tissue in the face relative to other areas of the body allows for most foreign material to be identified in the course of routine wound exploration.

Imaging is helpful in certain circumstances. Glass is a common foreign body associated with motor vehicle trauma and is easily detected with plain films. However, the utility of these studies is limited to wounds deeper than the immediate subcutaneous fat.[25] Contrary to commonly held assumptions, a negative CT scan does not rule out a retained foreign body. The radiodensity of substances such as wood, plastic, and vegetative material are so low that imaging frequently misses them. Wood, however, is often visible on magnetic resonance imaging (MRI). There is an increasing body of literature in support of the use of ultrasound to detect the presence of radiolucent foreign bodies.[26] Most foreign bodies in the head and neck, however, are discovered in the course of a detailed history, careful examination, and meticulous wound exploration. Loupe or microscope-assisted magnification is often helpful.[27]

Embedded debris in a wound bed may require gentle scrubbing for complete removal. This must be balanced against the potential for additional disruption of tissue. However, traumatic tattooing can easily occur when pigmented debris left in the wound bed is subsequently covered by epithelium as the wound heals.

This is most noticeable when debris is left embedded in dermis that has been denuded of epithelium. Judicious use of solvents such as acetone may even be necessary to help remove petroleum-based products. Time spent removing debris likely to cause permanent pigmentation will benefit both patient and physician in that delayed treatment of traumatic tattooing is difficult and often has disappointing results (Fig. 22-2).

Figure 22-2. This patient presented approximately 1 week after a blast injury. Traumatic tattoos are evident. Targeted surgical débridement of each lesion was unsuccessful and the patient subsequently underwent successful laser removal of most of the pigment.

Infection Control

There are no convincing data on the role of routine antibiotic administration for soft tissue injuries. Wounds treated within 8 hours and those created surgically are generally considered "clean," indicating a presumed safety of primary closure. It is also generally accepted that in highly vascular areas such as the face, this margin of safety may be extended to 24 hours. Few data exist, however, regarding precise cutoff points to determine which wounds are too contaminated to safely close.[28] The general principle of increasing bacterial counts as a function of time should be kept in mind. Even in wounds without a significant amount of exogenous bacteria, normal skin flora such as staphylococci and streptococci and mixed flora in wounds involving mucosa will proliferate. Heavily contaminated, partially devitalized, extensive, or deep wounds with oral contamination may benefit from at least a single dose of broad-spectrum antibiotics. Even animal bite injuries of the face may be adequately treated without routine antibiotic prophylaxis.[29] Human bites are notoriously contaminated with various aerobic and anaerobic bacteria and recent studies support the use of antibiotic prophylaxis with broad-spectrum agents.[30]

Repair

Throughout the assessment and repair of injuries, clear communication with the patient and any attendant friends or family is essential. Informed, written consent should be obtained before repair. It is also important to help the patient set reasonable expectations for the outcome, keeping in mind that for more severely injured patients, treatment of their injuries will likely constitute a process rather than a single event. Allowing patients to see their injuries either with a mirror or photograph, although potentially distressing, often aids in this endeavor. Ideally, photodocumentation should be performed throughout the encounter, obtaining images of the wound at presentation, after prepping, and again after repair. Photographs are a key component of the medical record for both medical and legal reasons but also for patient education. Patients who are not able or willing to gain an assessment of their wounds before repair will have an opportunity to better understand the extent of their injury by reviewing the photographs at a later time.

Depending on the nature of the wound, a great deal of the surgeon's work can easily be degraded by poor wound care from other health care providers, family, and patients. It is important to educate all parties involved regarding the appropriate wound care regimen. Abrasions, for example, depend as much on ongoing wound care for optimal healing as they do on initial cleaning and débridement. Close follow-up in the acute phase is therefore often necessary, especially in multiply injured patients in whom wound care can sometimes suffer at the expense of efforts to treat more severe injuries.

The first step to performing a technically successful repair is preparation of the work environment. Excellent lighting, comfortable positioning for both the patient and physician, appropriate instruments for soft tissue work in the face, available support staff, and adequate anesthesia are all essential. The absence of any of these elements compromises the primary focus of the surgeon. If necessary, the patient may be transferred to an appropriate venue for repair such as the operating room or minor procedure room. Facial soft tissue work demands instrumentation such as fine tooth forceps, small needle holders, skin hooks, tissue scissors, suture scissors, and a scalpel handle with replaceable No. 15 and 11 blades (Fig. 22-3).

Loupe magnification is also often helpful in improving the precision of repair.

A variety of suture materials and tissue adhesives are available for closure, the choice of which depends upon characteristics of the wound, the patient, and the surgeon. Deep suturing is usually performed with interrupted, inverted, absorbable sutures, although permanent sutures may be used sparingly when deep closure is subject to ongoing forces of tension or muscle contraction. Commonly used absorbable sutures for deep closure include polyglactin 910 (Vicryl), polyglecaprone 25 (Monocryl), polydioxanone (PDS II), polytrimethylene carbonate (Maxon), Polysorb, and Caprosyn.

Epithelial closure is commonly performed with permanent monofilament sutures such as 6-0 or 7-0 nylon or polypropylene (Prolene).

Figure 22-3. A basic set of fine instruments for facial soft tissue repair, including needle drivers, forceps, scissors, and skin hooks.

Absorbable suture with minimal tissue reactivity, such as fast absorbing gut, is also useful, especially in children or patients in whom suture removal may be difficult.[31] A child who requires sedation for repair is unlikely to tolerate removal of permanent sutures. Similarly, adult patients who are unwilling, unable, or unlikely to follow up for suture removal are better served with absorbable sutures than permanent sutures left in too long or removed by inexperienced hands.

Tissue adhesives now have a proven role in wound closure with acceptable results compared to suture techniques in simple lacerations.[32] Even though caution is appropriate in entirely sealing off a heavily contaminated wound such as a human or animal bite, there is no evidence that routine lacerations appropriately cleaned and irrigated have increased rates of infection with tissue adhesive than with suture. They can even be combined with fast absorbing gut on skin, preventing premature suture removal. There are limitations, however. Octyl cyanoacrylate combined with a subcutaneous 4-0 Vicryl closure has approximately the same tensile strength of percutaneous 5-0 nylon suture and cannot be relied upon to close a wound on tension without some widening of the scar.[33] For tissue adhesives to be used effectively, epithelial edges must sit in good approximation before application to prevent glue from entering the wound, resulting in a wider scar or even wound breakdown.[34] Eversion of the wound edges is more difficult with adhesives.

Eversion is critical to the favorable appearance of the final result. Because scars contract as they heal, a laceration that is flat when reapproximated will become inverted. An inverted scar, unless coincidentally located in a wrinkle, will create an obvious shadow and be easily noticed. The best technique for everting the edges of a wound is to use vertical mattress sutures. Properly placed, these sutures elevate the incision just enough to counteract scar contracture. The distal pass of the needle should be placed perpendicular to the surface of the skin and should be placed one half the chord-length of the needle from the incision. The chord-length is the distance from the tip of the needle to the swage. The proximal pass of the needle should only include enough of the epidermis to align the edges and reapproximate them. It is a common technical error to place the distal pass too close to the laceration and the proximal pass too far away. This has several negative effects. First, there is very little skin supporting the suture and, as the wound swells, the tension causes the suture to act as a seton, creating suture tracks. The second is that the epidermal edges will not be in apposition, which results in a gap that granulates and reepithelializes, creating a red, shiny scar (Fig. 22-4).

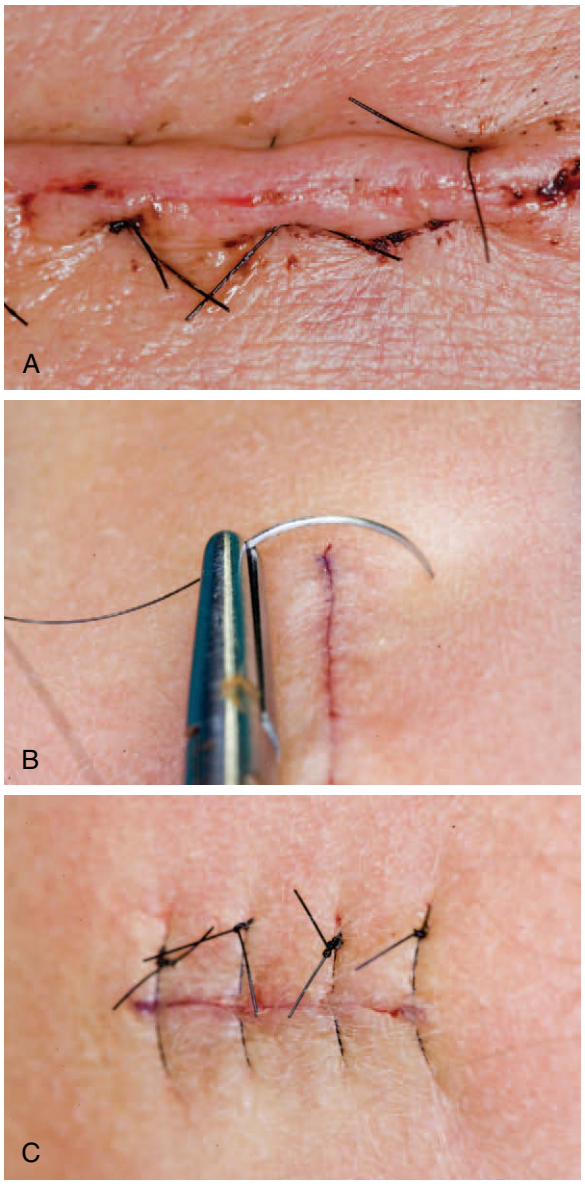

Figure 22-4. **A,** Improperly placed vertical-mattress sutures will cause separation of the wound edge and suture-track marks. This happens when the far bite is too close to the wound and the near bite is too far. **B,** Properly placed vertical-mattress sutures have the far bite bisecting the chord-length of the needle and enter the skin at a 90-degree angle. **C,** This results in an everted wound with good approximation of the edges and lots of skin supporting the sutures.

Types of Injuries

Abrasions

Abrasions are defined as a superficial soft tissue wound caused by contact with a hard, irregular surface, resulting in skin loss not extending to the subcutaneous layer. In the multiply injured patient, these wounds are often neglected and can ultimately result in significant color and contour irregularities. Even with appropriate initial treatment consisting of meticulous cleaning, débriding devitalized tissue, dirt, or debris, these wounds require ongoing care for optimal healing. Once clean, a moist environment conducive to reepithelialization can be achieved with a variety of media including antibiotic ointment, hydrogel, or hydrocolloid dressings.[35] Because these wounds tend to weep and collect fibrinous debris, especially in the setting of increased interstitial fluid, ongoing gentle cleaning is essential. This allows a maximum degree of epithelialization with a minimum degree of fibrosis and scar. Pigmentation abnormalities are nearly universal; however, significant changes are usually temporary and based partially on the depth of injury. Abrasions deep to the papillary dermis cause a greater degree of scarring than more superficial injuries. As with any other scar, protection from sun exposure decreases the likelihood of postinflammatory hyperpigmentation.

Lacerations

Although the technical aspects of treating lacerations demand varied approaches to repair based on the complexity of the wound, some principles and techniques are nearly universal. The goals of treating any laceration should be the same as those for closure of a surgical incision: appropriate reapproximation of deep tissue, reapproximation of dermis with a tension-free closure, precise apposition of epidermal edges, and an everted skin closure.

The excellent blood supply in the face allows for conservative débridement; however, obviously devitalized tissue and significantly irregular wound edges must be excised. When an experienced surgeon recognizes that a wound edge will result in a wide, irregular scar likely needing later revision, that wound may be approached with conservative, beveled excision to optimize closure. This is especially true in areas of soft tissue laxity or in lacerations along relaxed skin tension lines. Judicious undermining in subcutaneous or subfascial planes may be performed to decrease tension. This should be performed with proper attention to how redistributing tension may affect surrounding structures. For example, a periorbital laceration excessively undermined toward rather than away from the eye may result in excessive lid tension with eventual distortion of the palpebral fissure.

Lacerations occurring as a result of a severe contusion are caused by a ripping, rather than cutting of the tissues. Force is transmitted through the skin and soft tissues to the underlying bony prominences of the facial skeleton resulting in a full-thickness crush injury, splitting open the skin, and often, the underlying soft tissue as well. In these cases, the laceration is frequently centered in a periphery of crush injury and diffuse soft tissue hematoma. Closure of these lacerations where the surrounding tissue is partially compromised is best accomplished with the least amount of suture material capable of achieving adequate closure. Such lacerations commonly result in depressed, widened scars requiring later revision for optimal cosmesis. Stellate lacerations often occur in this setting. Small stellate lacerations can be excised in an elliptical fashion, converting the injury to a simple laceration that may then be closed primarily within a relaxed skin-tension line. Larger stellate lacerations should be closed under as little tension as possible, recognizing that there may need to be a balance between optimal tension and optimal approximation. Although the characteristics of some complex lacerations may appear to lend themselves to additional manipulation and rearrangement with local flaps, such endeavors in a contaminated wound bed with extensively injured tissue are rarely indicated. Patients or family members should be counseled regarding the anticipated outcome and potential for improvement with scar revision in the future. This strategy allows for appropriate initial management with the creation of a clean, safe wound without exhausting future resources for local reconstruction or scar revision.

Lacerations rarely divide the skin at a 90-degree angle to the surface. Nearly all are tangential to some degree and consideration should be given to converting a thin, beveled flap to a square edge while undermining the opposing side, such that deep and superficial sutures can be placed with equal eversion of skin edges. A good general rule is that any laceration with an angle too tangential to successfully evert both skin edges with simple sutures should be revised. This problem becomes more apparent in cases of a partial avulsion where a U-shaped flap is elevated. If such a flap is sutured to the surrounding tissues without appropriate eversion of the excessively beveled component, a pincushion or trapdoor deformity often ensues with a bulky, raised appearance to the flap skin. However, it should be noted that, even under ideal circumstances, lymphedema and scar contracture of a U-shaped laceration will also contribute to a pincushioned flap. Steroid injections in the postoperative period may make these contour irregularities less noticeable.

Soft Tissue Avulsions

Many partial avulsions with an apparently well-preserved pedicle can be treated as a complex laceration followed by close observation (Fig. 22-5). Any resultant wounds from ischemia, venous congestion, or suture-line dehiscence may be treated as a secondary rather than primary defect. There is no evidence that various interventions such as topical nitroglycerin paste, anticoagulants, or vasodilatory agents improve the outcome of partially devitalized or ischemic avulsion injuries and soft tissue flaps. Medicinal leeches may have a role in alleviating venous congestion in avulsion injuries with an intact arterial supply.[36]

Partial avulsions with devitalized tissue and complete avulsions with full-thickness tissue loss represent some of the greatest challenges in managing facial trauma. Full-thickness loss of soft tissue in an area amenable to wide undermining may be suitable for primary closure if surrounding structures are not distorted in the process. Otherwise, resultant wounds may be managed with débridement and local wound care, allowing healing by secondary intention if no critical structures are exposed and a wound bed suitable for developing granulation tissue is observed. Depending on location, this process can be aided with negative pressure wound therapy by placement of a wound VAC (vacuum-assisted closure) device. Application of subatmospheric pressure to a wound has been shown to decrease bacterial counts and aid in the formation of granulation tissue and increase the rate of wound contraction.[37] Sequential management with conversion of a larger, contaminated wound to a smaller, clean wound followed by undermining or local flap closure may circumvent the need for more extensive reconstruction upon presentation. In areas such as the forehead or non–hair-bearing scalp, such wounds may even be left to heal by secondary intention with results superior to split-thickness skin grafting or local flap reconstruction. In general, there are few areas in the face where split-thickness skin grafting is indicated as the optimal technique for final reconstruction. Usually surrounding or even distant tissue is available for an aesthetically superior repair.

Perhaps the greatest dilemma comes from avulsion of specific structures with distinct anatomic features such as the nose, ears, lips, eyelids, and scalp where the avulsed portion appears relatively clean and viable. Small, composite segments from the ear or nose may be sutured in place as a graft. Depending on the nature of the defect, this strategy adds little to no additional morbidity and preserves future reconstructive options if necessary. In this situation, there is little adjunctive care, outside of routine suture line care, that has been demonstrated to be beneficial. Patients are typically appreciative of the effort made to salvage a particular structure and no additional reconstructive efforts have been compromised.[38]

When an avulsed segment appears viable and has identifiable vessels suitable for microvascular anastomosis, free-flap replantation of the avulsed segment under a microscope or 4.5× loupe magnification may be possible. The level of technical difficulty involved with such an endeavor obviously requires some degree of experience in microvascular surgical technique. Microvascular replantation of all or portions of distinct structures such as the nose, ear, lip and scalp have all been described with varying degrees of success.[39-42] Most replants are at least partially successful, allowing the reconstruction of a portion of the defect with original tissue. This has been demonstrated to be particularly beneficial in the nose where preservation of even the mucosal layer alone allows for a simpler treatment plan for further reconstruction. Perioperative management usually includes anticoagulation with heparin and/or aspirin. In many cases when the venous anastomosis fails or when no suitable veins can be found for anastomosis, leech therapy has been reported to alleviate venous congestion.[43] Hyperbaric oxygen therapy (HBO) has also been described as an adjunctive measure for improving the viability of hypoxic replanted tissue. No controlled trials have been performed in humans but animal studies demonstrate a clear benefit to HBO, and a failing flap is an accepted indication for initiating treatment.[44] Even in experienced hands, both patient and physician should be prepared for flap failure and ongoing wound management.

Special Considerations in Repair of Specific Structures

Lacrimal Apparatus and Eyelids

Injuries to the eyelids and lacrimal apparatus require exceptional attention to detail in evaluation and treatment in order to obtain the best possible functional and aesthetic outcome. First, a thorough examina-

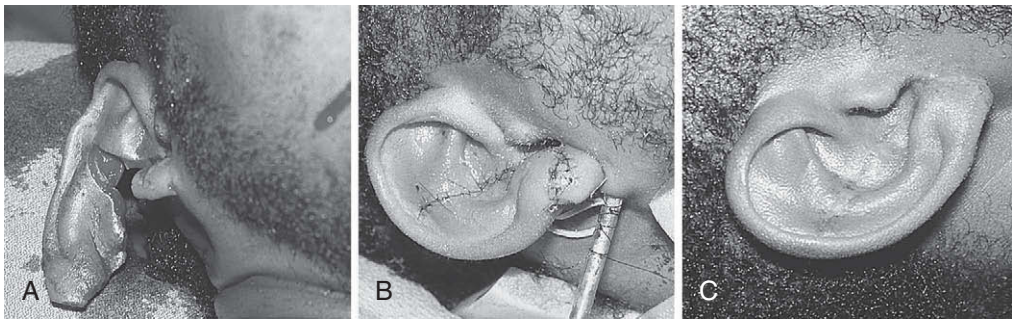

Figure 22-5. **A,** Knife injury resulting in a complex auricular avulsion. The vascularity is preserved by a small superior pedicle. **B,** After three-layer closure. **C,** Follow-up at 6 months showing normal auricular contour.

tion includes evaluation by an ophthalmologist to rule out injury to the globe. After assessment and treatment of the globe, repair of the lids may be performed with special attention to key structures. Lacerations of eyelid skin penetrating no deeper than the preseptal fat may be closed with 6-0 or 7-0 monofilament sutures, which should be removed in 5 days. The use of tissue adhesives for closure of blepharoplasty incisions has been described and may be an acceptable alternative in experienced hands.[45] Full-thickness lacerations of the lids, especially those involving the margin, must be closed in layers. In such injuries to the upper lid, involvement of the tarsal plate, orbicularis muscle, levator muscles (levator palpebrae superioris and Müller's muscle) and conjunctiva should be identified. The pretarsal component of the orbicularis muscle is crucial to the blink reflex and failure to adequately repair a levator injury will likely result in ptosis. If the margin is involved, this landmark is aligned first by approximating the edges of the gray line and lash margin with a 5-0 absorbable suture. The tarsal plate is incorporated into this suture to improve the strength of closure. The conjunctival component may be closed loosely with buried 5-0 or 6-0 absorbable suture such as chromic gut if the material is not likely to abrade the cornea. Alternatively, leave the conjunctiva open if the edges sit in relatively close approximation. With the wound edges properly aligned, close the muscular or tarsal layer with 5-0 absorbable suture, followed by skin closure as described previously. The temptation to débride troublesome orbital fat herniating into the wound should be tempered by the fact that lacrimal glands can closely mimic fat and inadvertent overresection of orbital fat may result in an asymmetric hollowed-out appearance.

Traumatic loss of a lid segment with resultant tissue deficit is rare. When this does occur, however, corneal protection and ophthalmologic consultation to rule out other globe injuries are primary concerns. Up to one fourth of the lid may be lost before primary closure is likely to result in entropion.[46] A lateral canthotomy and cantholysis may add some laxity to the lateral segment, facilitating primary closure without undue tension. This can be extended onto the face to become a cheek rotation advancement flap if necessary. Additional techniques of lid reconstruction (e.g., lid transposition) or cartilage, skin, or mucosal grafts generally require advanced training and skill.[47]

Injuries in the medial canthal region should be evaluated for injury to the lacrimal system and traumatic telecanthus from disruption of the canthal tendon. Normal intercanthal distances are approximately 30 to 35 mm. After underlying bony injury has been ruled out, lacerations of the medial canthal tendon are repaired with permanent suture such as 5-0 polypropylene. Canalicular injuries are best assessed with lacrimal probes, which in cases of canalicular transection are visible in the wound bed when advanced through the punctum (Fig. 22-6). Irrigation of the ducts may also be performed but is less reliable in ruling out an injury. All lacerations of the canalicular system are repaired over silicone stents to prevent stenosis. The introducer is first advanced and the stent attached through the punctum and into the wound bed. The distal segment is located and the stent advanced through the lacrimal sac and into the nose. These steps are repeated for the other limb of the system even if uninjured because it allows the free ends of the stents to be tied together and left in the nose. Repair under a microscope or

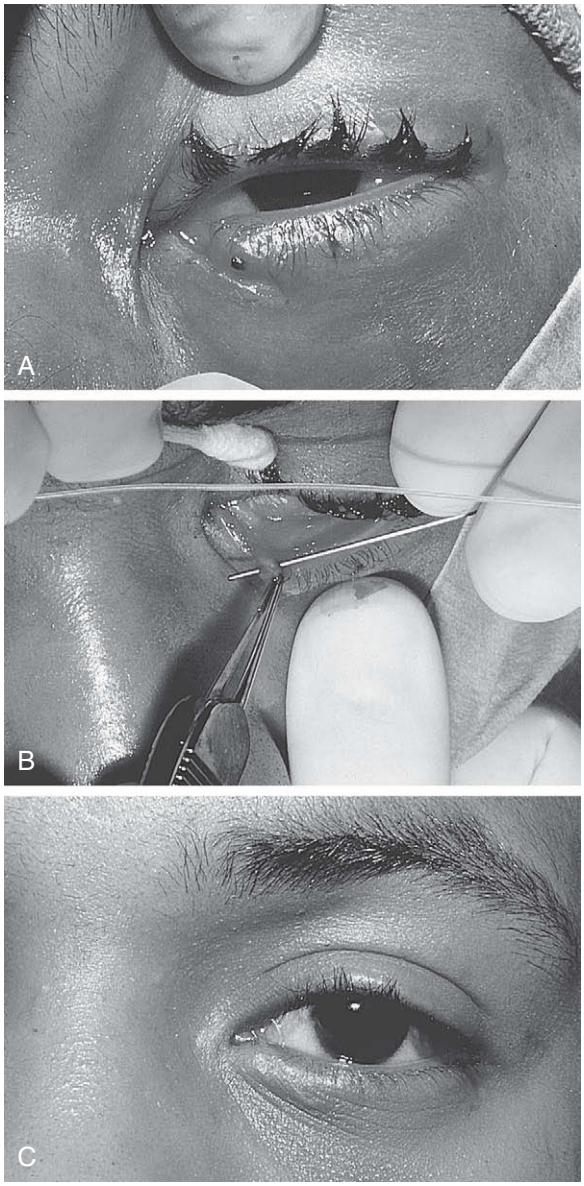

Figure 22-6. **A,** Laceration of the medial lid, suspicious for lacrimal duct injury. **B,** Confirmation of duct injury with lacrimal probe; the duct is repaired over a lacrimal stent with fine monofilament suture. **C,** No epiphora present at 6 months postoperatively; note the stent, visible medially, coursing into both puncta.

loupe magnification allows the placement of 7-0 or 8-0 absorbable sutures to reapproximate the edges of the canaliculus. Excessive effort should not be directed at placing sutures exactly through the lumen of the canaliculus because the low-pressure lacrimal system does not require a water-tight seal when closed over a stent.[48] Stents are usually left in place for several weeks. After removal, the clinician assesses the patency of the system with a Jones test.

Facial Nerve

Facial nerve function should be routinely evaluated and documented early in the course of assessing and treating patients with facial trauma. In every case, this is done before wound exploration, anesthetic application, and repair, because each intervention has the potential for additional nerve compromise. Delayed identification of a deficit can result in significant confusion regarding the mechanism of injury or location of the damaged segment. This is especially true when multiple possible sites of injury exist, as is the case with skull base fractures, cheek lacerations, or severe mastoid trauma. Injury to any of these areas should significantly raise the index of suspicion for damage to the facial nerve in patients otherwise unable to cooperate with a neurologic examination. Penetrating injuries or lacerations to the facial soft tissues between the tragus and a line drawn vertically through the lateral canthus must be carefully examined to rule out facial nerve injury unless a convincingly normal examination has been obtained. Injuries medial to the lateral canthus are unlikely to result in significant deficits. Transections to the main trunk or major branches should ideally be repaired as soon as the injury is recognized.[49] Distal segments will maintain excitability and may be identified with a nerve stimulator for up to 72 hours. Proximal segments not identified in the wound bed can be located by retrograde dissection of adjacent, intact branches, or by parotid dissection or even transmastoid approaches if necessary.

In the rare but devastating case of a missing segment of nerve, a cable graft from the great auricular or sural nerve can be performed. Primary anastomosis or interposition graft neurorrhaphy is performed under the microscope or with loupe magnification using 9-0 or 10-0 monofilament suture. Alternative methods of nerve repair have been described including sutureless techniques with fibrin glue and CO_2 laser welding in both end-to-end anastomosis and interposition grafting. Proponents of fibrin glue neurorrhaphy cite ease of repair and favorable outcomes on a par with microsuture techniques as advantages.[50] CO_2 laser-assisted techniques with a protein solder such as bovine albumin have shown results similar to microsuture and fibrin glue techniques in a rat model.[51] However, epineurial repair with fine monofilament suture remains the gold standard, particularly for extratemporal injuries, and is probably a more accessible technique to the majority of surgeons treating traumatic nerve injuries.[52] Routine facial paralysis precautions, including vigilant eye care, must be emphasized to patients and caregivers even after a technically successful nerve repair. Patients should be counseled regarding the usual return of function, occurring over the course of months rather than days or weeks. When the injury is proximal, it is important to explain the limitations of repair and the implications of synkinesis.

Lips

The function of the lips in articulation of speech and maintaining oral competence depends largely upon an intact oral sphincter. Deep lacerations and avulsions involving the lips can cause significant disruption of the orbicularis oris muscle, which must be addressed in the repair. Complex, full-thickness lacerations should be closed by approximating mucosal, muscular, and cutaneous layers individually (Fig. 22-7). In lacerations involving the vermilion border, the surgeon first places a key-stitch to accurately align the vermilion-cutaneous junction of the opposing wound edges. Depending on the degree of injury to the surrounding skin, defining this landmark can be difficult and may be aided with magnification. In some cases, the white roll can be a more visibly defined marker just below the vermilion border. Avulsions of the lower lip are more common and are usually more forgiving than full-thickness tissue loss in the upper lip. Loss of up to one third of the lower lip may be managed with primary closure without significant distortion or resultant microstomia, whereas similar defects in the upper lip would cause significant deformity.[53] As with other areas of the face, many avulsion injuries of the lip should be ultimately treated with local flap reconstruction not suited to acute repair. Large-segment avulsions with a salvageable amputated segment may be replanted with microvascular reconstruction.[41] Unlike the ear or nose, replantation without micro-

Figure 22-7. A, Complex full-thickness laceration of upper and lower lips with extension to nose and chin; repair focuses on precise anatomic reapproximation of all layers. **B,** Follow-up at 1 year showing appropriate alignment at vermilion border of both lips.

vascular anastomosis is unlikely to be even partially successful and should be avoided.

Ears

The prominent position of the ears over a firm underlying bony surface leaves them particularly susceptible to lacerations, avulsions, and blunt trauma (see Fig. 22-4). The unique and intricate detail of the ear's cartilaginous skeleton is virtually irreplaceable, making it a fairly unforgiving structure with regard to revision of an unacceptable scar. Full-thickness lacerations require accurate reapproximation of the cartilage to maintain the original orientation, although the cartilage itself does not necessarily need to be sutured. Perichondrial sutures and skin sutures are usually sufficient to close simple and complex lacerations involving cartilage. Occasionally, anchoring sutures through cartilage must be placed sparingly to bring wound edges together while maintaining the original shape and prominence. In older patients, the cartilage is more brittle and it is difficult to place sutures solely in the cartilage that do not pull through.

Traumatic loss of auricular tissue can be problematic. Small segments of denuded cartilage can be reliably covered with split or full-thickness skin grafts, as long as perichondrium is still present. Small or moderately sized complex or composite defects that cannot be closed without distorting the ear, especially those involving the helical rim, can be dealt with in a staged manner. Various techniques for composite grafting and local flap reconstruction have been described and are performed in a delayed manner after adequate cleaning, débridement, and local wound care.[54]

Larger segments of composite defects require a different set of treatment options. A robust vascular supply frequently allows partially avulsed auricular segments to survive, even large segments on a relatively small pedicle. In the case of near-total avulsion injuries it is therefore reasonable to replant the avulsed portion, leaving the pedicle intact. Management may then proceed as described earlier for other avulsions. There is some debate, however, regarding the management of total and near-total avulsion injuries as it relates to the cartilaginous framework of the ear. Some authors advocate deepithelialization of the avulsed segment followed by burial in a postauricular subcutaneous pocket (Fig. 22-8), while others believe that the final result of a reconstructed auricle is more reliable with an autograft than with banked cartilage, which often resorbs to some degree and is ultimately distorted.[55] A variation of the "pocket principle" described by Baudet involves deepithelialization of only the posterior aspect of the avulsed segment followed by fenestration of the exposed cartilage at 1-cm intervals.[56] The anterior skin edge of the avulsed segment may then be sutured to a modest postauricular scalp flap elevated over the mastoid to provide a vascular supply. The flap should be divided several weeks later and a skin graft applied posteriorly on the auricle. Advocates of this technique cite preservation of the original cartilaginous framework and overlying skin with reliable results.[57] A temporoparietal fascia flap followed by split-thickness skin grafting also serves to salvage an amputated auricle in an acute setting. In experienced hands, microvascular replantation of an avulsed segment generally yields the best final outcome, even in cases of venous insufficiency or inability to perform a venous anastomosis. Leech therapy and anticoagulation protocols are acceptable adjuncts in these cases and often have favorable results.[43]

Auricular hematomas typically present as a sports-related injury, particularly in wrestlers. Simultaneous application of blunt and shearing forces to the pinna results in disruption of perichondrial attachments to the underlying cartilage with subsequent accumulation of blood in the subperichondrial space. The separation of cartilage from its blood supply will lead to resorption or necrosis if left untreated, leaving potentially severe scarring and a "cauliflower deformity." Prompt needle aspiration or incision and drainage followed by application of a splint or bolster is the treatment of choice. No difference has been shown between various methods of treatment such as casting or bolstering.[58] A recent publication, however, describes the successful use of mattress sutures in 18 ears with only one recurrence.[59] Whatever the method, the splinting must be secure to ensure complete obliteration of the subperichondrial space. Recurrent hematoma or seroma that fails to respond to seemingly appropriate evacuation and bolstering can also be treated with wider incision and drainage followed by packing with thin iodoform gauze until healing of the pocket by secondary intention has occurred. If this method is used, it is usually possible to place the incision just under the helical rim so that the final scar is less noticeable. Keep in mind that, for many athletes, especially wrestlers, a misshapen ear is a desirable outcome. It is not unusual for the patient to remove bolsters, sutures, or packing after going home, thwarting every effort to treat the hematoma.

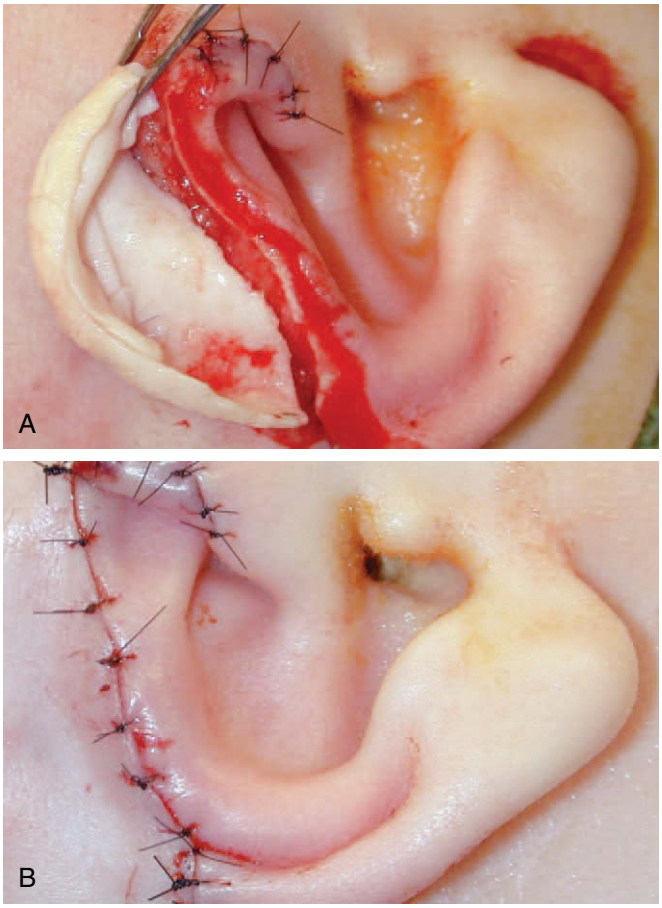

Figure 22-8. **A,** Dog-bite injury resulting in composite defect of superior auricle. Devitalized skin has been removed, revealing well-preserved cartilaginous framework suitable for reconstruction. **B,** Avulsed cartilage anatomically aligned with intact inferior framework and banked in a postauricular scalp pocket.

Antibiotic therapy with a fluoroquinolone is prudent for injuries involving cartilage. In the ear, the rationale for fluoroquinolone use is related to the presence of *Pseudomonas aeruginosa* and the excellent skin and soft tissue penetration with oral administration rather than some distinct cartilage-protecting characteristic of the drug. Contaminated wounds may benefit from at least a single dose of levofloxacin or ciprofloxacin, although there is no evidence for a full treatment course in an uninfected wound.

Nose

The prominent position of the nose on the face makes nasal trauma especially noticeable. The additional functional component of nasal airway compromise, both acutely and as an adverse long-term outcome, poses a significant challenge as well. As with any three-dimensional structure with an internal and external lining, all layers of the nose must be repaired in complex lacerations and avulsions. Although these injuries may look confusing at first, the best course of action is to simply put the pieces back together again. A thorough understanding of nasal anatomy is a prerequisite, however.

Significant underlying nasal injuries such as a septal hematoma or nasal fracture should be ruled out or identified and treated before soft tissue work. In complex, full-thickness, or marginal lacerations, the nasal mucosa and vestibular skin are closed first, with close attention given to the resultant position of the free edge of the alar rim. If this closure distorts the position of the rim, a deep anchoring suture is placed close to the margin first to prevent an irregular step-off or notching (Fig. 22-9). Vertical mattress sutures ensure enough eversion to minimize the risk of alar notching. Undue effort to perform a watertight internal closure is rarely necessary because simple approximation of internal wound edges usually heals with proper wound care. Judicious placement of deep sutures through perichondrium or cartilage should be used to reestablish the cartilaginous framework of the nose. Deep lacerations through the soft triangle and columella almost always involve the lower lateral cartilage, and repair with fine, clear monofilament suture helps prevent distortion of the tip and vestibule resulting

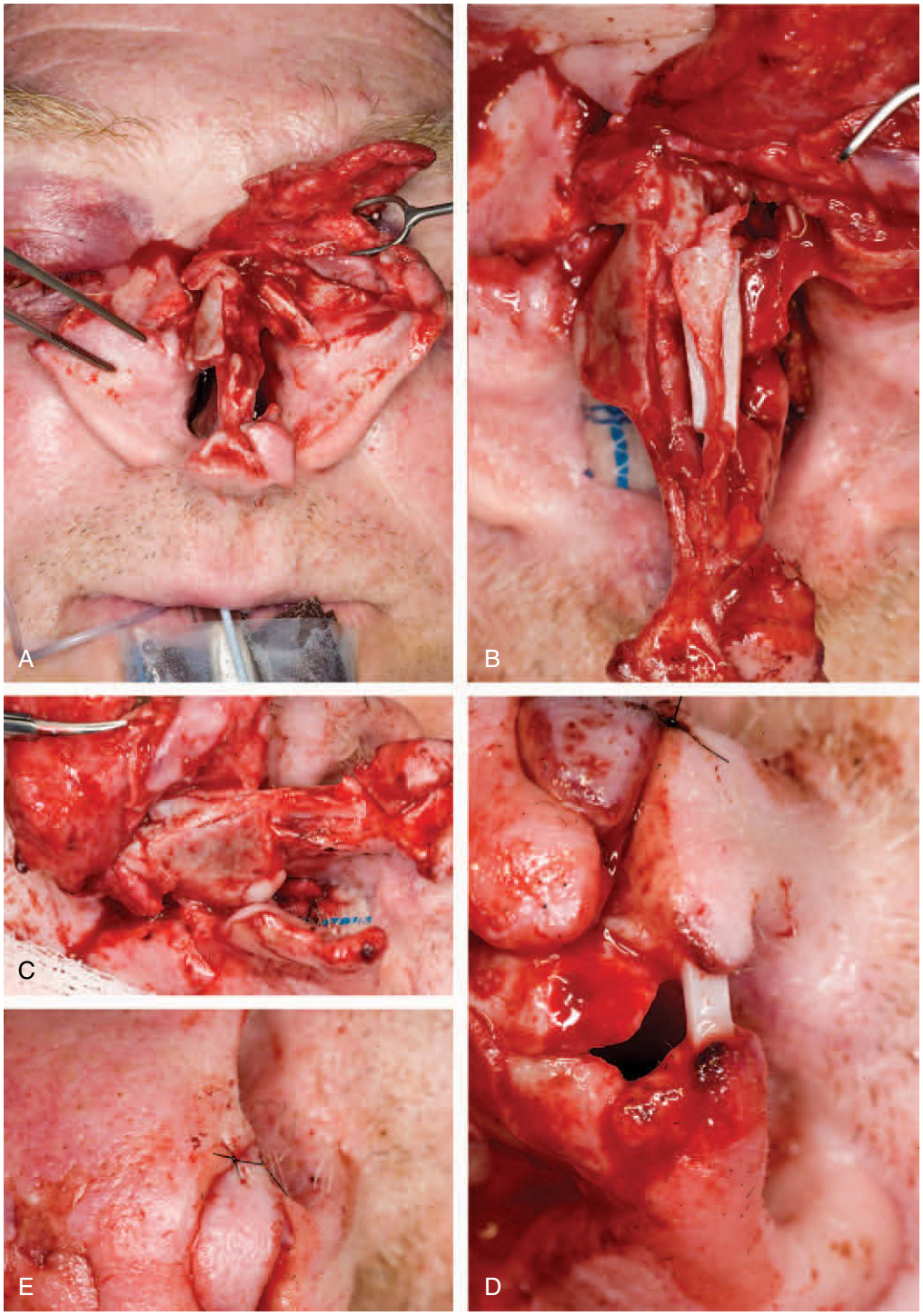

Figure 22-9. **A,** This man was injured when his single-engine airplane crashed. He sustained complex lacerations to the soft-tissue and cartilage. **B,** His dorsal septum was also fractured, necessitating spreader graft placement for reinforcement. **C,** Systematic reapproximation of the upper lateral cartilages provides structure for the internal nasal valve. **D,** An alar rim graft was also placed to make alar notching less likely. **E,** Vertical-mattress sutures along the alar margin also help prevent notching.

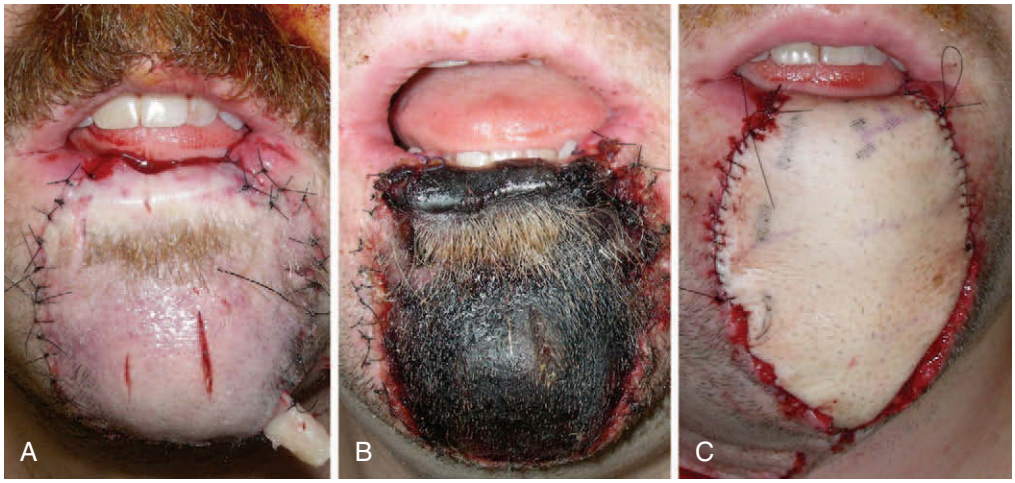

Figure 22-10. A, A replanted lower lip and chin that had a tenuous blood supply. **B,** Several days later, the replanted tissue was necrotic. **C,** Reconstruction was ultimately completed with a forearm free-flap.

from contracture and scarring. The clinician should have a low threshold for removing and revising any sutures that seem to distort the tip, ala, or columella.

Composite defects should be managed according to size and severity. Small defects may be successfully repaired with careful mobilization and reapproximation of all layers. An avulsed segment may be replanted as a composite graft, although with increasing size, the likelihood of graft survival decreases. As initial interventions, these techniques may fail and often result in the need for scar revision; however, they may also provide an adequate result and do not immediately exhaust any other reconstructive options. Local or regional flap reconstruction is rarely indicated in the acute setting. In the nose, even apparently minor defects are often best managed with local or regional flaps combined with cartilage or mucosal grafts. These repairs require careful counseling, planning, and execution and are best postponed until after the acute injury has healed. Healing by secondary intention is remarkably well tolerated on the dorsum and in concavities. These defects may not need further revision.

Large-segment, composite avulsions or amputations are best managed with microvascular replantation if possible.[40] If no suitable vessels for anastomosis can be identified, the patient may still benefit from simple replantation and aggressive wound care with the potential for preservation of at least some of the original structure (Fig. 22-10).

Salivary Gland Trauma

Salivary gland trauma is uncommon and is often more significant with regard to implications for adjacent structures than for any injury to the submandibular or parotid glands themselves. Submandibular gland trauma may be accompanied by injury to the marginal mandibular branch of the facial nerve or the facial artery. Parotid gland injury may also present with facial nerve injury, parotid duct injury, or damage to the carotid sheath. Penetrating injuries to the parotid region must be managed carefully to rule out more serious injuries to these structures. Workup of salivary gland injuries requires an appropriate degree of suspicion and a carefully executed physical examination, whereas radiographic studies play a lesser role. Sialography can be useful in assessing the integrity of the parotid duct, although in most centers this is an infrequently performed examination, potentially limiting the reliability of the results. Cannulating the duct for dye injection can be the most technically challenging part of the study and, if necessary, the surgeon should offer assistance with this. The utility of sialography is limited in cases in which the wound can be easily explored but may be useful in the rare circumstance of deep penetrating trauma or puncture wounds with an intact facial nerve. Adequately exploring a narrow but deeply penetrating injury with potential for parotid duct injury can be difficult and may subject branches of the facial nerve to unnecessary trauma. Sialography may help rule out a ductal injury in such a circumstance. Imaging of the salivary glands with CT or MRI is rarely helpful in the acute setting, whereas other studies such as CT angiography, MR angiography, or Doppler ultrasound may be beneficial in instances of penetrating salivary gland trauma to rule out vascular injuries. Sialoendoscopy is an emerging technique that, in the future, may play a greater role in the exploration of parotid duct injuries.[60] Fig. 22-11 is an overview of the management of parotid injuries.

Parotid Duct

Whereas facial nerve injuries are often detected on a basic head and neck examination, parotid duct injuries are less evident and require a high index of suspicion. They should be considered in any deep laceration or penetrating injury of the cheek. If the possibility of an injury is being considered, then detecting a transection of the duct is relatively straightforward. Like injuries to the lacrimal system, integrity of the parotid duct is assessed by cannulating the papilla intraorally, while searching both visually and with palpation in the wound bed for the probe. Lacrimal probes work well in this setting but should never be forced into the duct because they may cause additional trauma. Alternatively, an angiocatheter may advance into the duct without additional trauma. The papilla of Stensen's duct has a reliable position in the buccal mucosa, opposite the second upper molar. Clear saliva from the papilla does not necessarily rule out injury to the duct proximally. Conversely, a lack of saliva from the papilla, especially in a multiply injured, sedated, or obtunded patient, is not a reliable sign of injury. The parotid gland does not normally produce saliva at a basal rate, rather it acts as an on-demand source of saliva in response to parasympathetic stimulation. The duct exits the parotid gland at approximately the level of the tragus where the parotid abuts the masseter muscle. It then travels in a line toward the upper lip over the belly of the masseter, curling medially to enter the oral cavity as it crosses the anterior border of the muscle. The buccal branch of the facial nerve typically lies inferolaterally to the duct or crosses over it.[61] Because of the close proximity of these two structures, ductal injuries are frequently accompanied by transection of the buccal branch. Loss of upper lip elevation and saliva pooling in the wound are hallmarks of this type of injury. A missed diagnosis and subsequent repair of overlying soft tissues results in significant inflammation within the wound, leading to dehiscence, abscess formation, or parotitis. One should suspect an unrecognized injury with any increasing pain, erythema, or edema after an otherwise uncomplicated soft tissue repair. Identification of the duct at this point is more difficult because the surrounding inflammation and friable tissue complicate efforts to identify the proximal portion of the duct and any exposed facial nerve branches.[62]

Although different techniques for repair have been described, in most injuries where both ends of the severed duct can be identified and mobilized, primary anastomosis over a stent is the preferred method

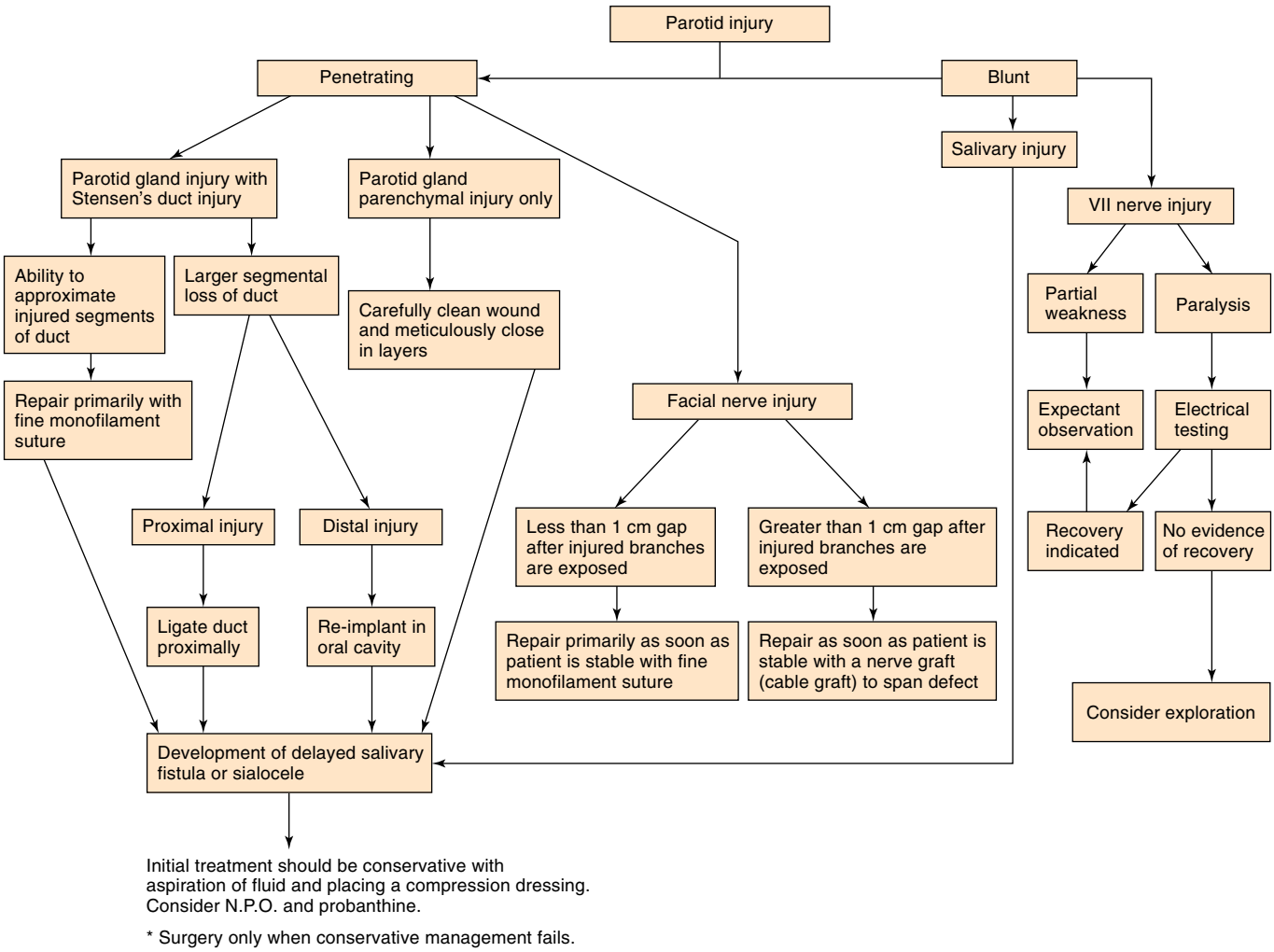

Figure 22-11. Algorithm for the management of parotid injuries.

(Fig. 22-12).[63] If necessary, the papilla is dilated with lacrimal dilators and the duct is probed through the mouth. A readily available and reliable stent can be easily fashioned from a 20- or 22-gauge Silastic catheter, which can be cut to length and advanced into the duct transorally. The catheter is identified in the wound and advanced into the proximal segment of the duct. This segment may also need to be dilated to accommodate the catheter. When both lacerated ends of the duct are safely positioned on the catheter, anastomosis under an operating microscope or loupe magnification is done with 7-0 or 8-0 monofilament suture. The catheter is sewn to the buccal mucosa adjacent to Stensen's duct and left in place for 2 to 3 weeks.

Microsurgical instruments including microvascular clamps for duct positioning encourage precise repair, reducing the risk of postoperative sialocele, fistula, or stricture.[64] The use of vein grafts has been described for cases of duct loss, precluding a tension-free approximation of the proximal and distal segments.[65] In cases of severe buccal trauma with an intact proximal duct and no identifiable distal duct or papilla, sialodochoplasty with rerouting of the duct proximally can be performed.[63] In this case, widely opening the duct with a longitudinal incision and a filleted inset into the surrounding buccal mucosa are essential to prevent stenosis. Even when initial rerouting is technically successful, ongoing patency is frequently difficult to maintain. Another option is to tie off the duct completely, although this is less than ideal. This invariably results in parotitis manifest as swelling and pain, which usually resolves with fibrosis and atrophy of the gland. Occasionally, it also results in infectious parotitis requiring treatment with antibiotics, although the final outcome is usually the same.

Parenchymal injuries of the major salivary glands with intact nerves and ducts still require thorough examination, cleaning, and débridement, followed by a layered, tension-free closure. Sialocele and fistula are less likely in this instance than in cases of ductal injury but are still possible, warranting placement of a gentle pressure dressing after repair to mitigate salivary leak into the wound.

Sialocele and Salivary Fistula

Posttraumatic salivary fistulas and sialoceles, although rare, can cause significant morbidity and discomfort related to impaired wound healing, infection, and irregular scarring. However, most cases resolve with conservative therapy.[66,67] Much of the available data on treatment of salivary fistulas and sialoceles come from series of postparotidectomy patients; however, the applicability of treatment options to the traumatic patient has also been demonstrated in a number of reports. An overlooked parotid duct injury usually first manifests as swelling, mimicking soft tissue edema, glandular swelling, or hematoma. If the missed diagnosis is identified early, before significant granulation tissue, inflammation, or fibrosis develops, the wound may be safely reopened and explored while the possibility of a successful anastomosis exists. Some authors recommend sialography to identify ductal injuries at this stage.[63] Injection of dilute methylene blue into the parotid duct transorally is another technique for assessing ductal integrity in the setting of a fistula.[68] Blue exudate from the fistula tract confirms the diagnosis, but tissue staining may complicate subsequent exploration and repair. Sialoendoscopy may be beneficial in these cases and may facilitate identification of the site of duct injury.

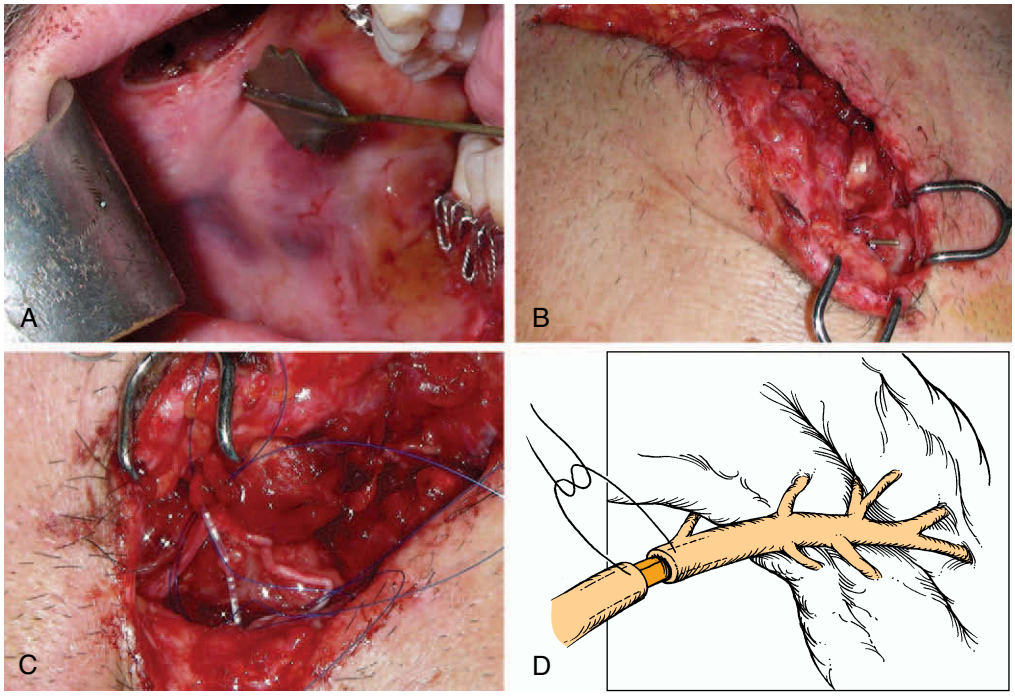

Figure 22-12. **A,** Lacrimal probe advanced intraorally into parotid duct to confirm suspected involvement of the duct associated with a through-and-through laceration of the right cheek. **B,** Tip of lacrimal probe visible in wound. **C,** Silastic stent is visible between the skin hooks, traversing the cut ends of the duct. Fine monofilament sutures have been placed and are positioned to bring the duct together over the stent. **D,** Demonstration of intraluminal placement of fine suture for repair over a stent. *(**D** from Olson NR. Traumatic lesions of the salivary glands.* Otolaryngol Clin North Am. *1977;10:345.)*

Sialoceles may be managed initially with needle aspiration and compression, which can be repeated if necessary.[63] Broad-spectrum antibiotic coverage is indicated because of the significant risk of infection in a contaminated wound bed. Aspirated fluid may be sent for amylase levels to confirm a salivary source. Parenchymal injuries respond best to this conservative treatment and do so in a shorter time period than ductal injuries.[69] Those tend to require longer periods of conservative treatment or are refractory. Anticholinergic pharmacotherapy in the form of propantheline, scopolamine, or glycopyrrolate may be added, diminishing saliva production and, perhaps, the risk of recurrence. Tricyclic antidepressants exhibit the side effect of cholinergic blockade and may also be helpful in diminishing salivary flow. No convincing evidence exists to indicate a clear benefit to adding these agents; however, they are well tolerated by most patients for a short period of time and have been included in case reports and small series as a component of conservative treatment regimens.[70]

Increasing numbers of reports describing the use of botulinum toxin in the treatment of sialoceles and salivary fistulas have emerged in the last several years with favorable outcomes, although no large series or controlled trials currently exist to support a clear benefit.[71] The limited data that exist support use of botulinum toxin A as an adjunct to conservative therapy by way of direct injection into the parenchyma of the involved gland. Ultrasound guidance may aid in the precision of injections, limiting side effects such as masticator or facial weakness, which may occur if injections are placed too far anteriorly.[72]

Other strategies advocated for conservative management include elimination of oral intake and parenteral nutrition, if necessary, in combination with needle aspiration and pressure dressings.[66] Although this strategy has been employed successfully in cases of known ductal injuries, surgical repair, if possible, is the preferred method of treatment.

Conservative management of delayed or chronic salivary fistula or sialocele may require exceptional patience and persistence; however, these measures are often more appealing when one considers the available alternatives. Parotidectomy alone would presumably remove the source of the problem and provide a definitive cure. However, the difficulty of such a procedure with the concomitant risk to the facial nerve in an inflamed surgical bed must be considered against the presumed benefit of resolution. Tympanic neurectomy has also been described although reports of efficacy in treating chronic parotitis demonstrate variable results.[73] Low-dose radiotherapy has been discussed by authors in the past although currently is more of a theoretical "last resort" option given the risks associated with irradiating nonmalignant tissue.

The previous discussion primarily centers on the parotid gland. Submandibular injuries are rare and are usually associated with penetrating trauma. Although these injuries are also reported to respond to the conservative measures described, surgical removal of the gland is accompanied by far less risk than parotidectomy.[74] Accordingly, some authors have advocated surgical excision as the preferred initial intervention.

Burns

Classification

Burns result in cellular damage due to heat, cold, chemical exposure, electrical current, and ionizing radiation. The depth of injury depends on the intensity and duration of the exposure, although electrical burns can have irregular patterns of damage. Broadly categorized as partial thickness or full thickness injuries, burns can be further classified as first-, second-, third-, or fourth-degree injuries based on depth.

First-degree burns are characterized by damage no deeper than the epidermis, resulting in pain and erythema but little or no permanent injury. The injured epidermis typically regenerates in a matter of days with no significant scarring. Second-degree or deep partial-thickness burns extend into the dermis to some extent and are accompanied by pain, erythema, and blistering. Early after initial exposure, second-degree burns may appear to be limited to the epidermis, demonstrating only erythema and pain. The true depth of injury may only become apparent as blistering occurs and the amount of pain increases, often becoming severe. Adnexal structures are generally preserved and serve as a source of epithelial regeneration. This occurs spontaneously,

Figure 22-13. Second- and third-degree burns. Note the gray, leather-like appearance of the third-degree burns in contrast to the erythema of the second-degree burns elsewhere.

resulting in healing with little scarring over the course of a few weeks depending on the depth of dermal injury.

Third-degree or full-thickness burns involve all of the epidermis and dermis, destroying adnexal structures, blood vessels, and nerve endings. The skin often appears leathery and gray, in contrast to the erythema and blistering of partial thickness injuries often seen around the periphery of a third-degree injury (Fig. 22-13). Because of the deep damage to nerve endings, the skin is insensate. Pain is usually due to accompanying partial thickness injuries, and pricking the affected skin with a needle typically does not elicit pain or bleeding. Full-thickness burns extending to the hypodermis form a dense eschar, which ultimately requires débridement because no source of epithelial regeneration is left. These injuries are conceptually similar to soft tissue avulsion injuries in that they result in a full-thickness tissue deficit which, when left to heal secondarily, results in significant hypertrophic scarring. Fourth-degree burns penetrate to deeper structures such as muscles, tendons, ligaments, and bone, resulting in composite defects that typically require débridement, wound care, and subsequent reconstruction.

Assessment and Treatment

Although the head and neck compose only 10% of total body surface area, severe third-degree burns in these areas can be life-threatening. Depending on the mechanism, initial evaluation mandates an appropriate degree of suspicion for a concomitant inhalation injury. Patients with both cutaneous and inhalation burn injuries, especially those with facial burns, are more likely to need airway intervention than those with inhalation injuries alone.[75] An upper airway examination includes flexible endoscopy of all nasal, oral, pharyngeal, and laryngeal mucosal surfaces to establish the immediately visible extent of injury. Airway intervention is generally subject to the same principles that apply in any traumatically injured patient, recognizing that it may take several hours for the full extent of mucosal injury, swelling, and resultant mechanical obstruction to occur. When there are burns on the anterior neck, orotracheal or nasotracheal intubation is preferable to an early tracheotomy due to adverse effects on healing and the potential for pulmonary sepsis from an infected burn eschar.[76]

The general approach to a burn patient follows an orderly progression from initial assessment, stabilization, and resuscitation to definitive measures for healing and reconstruction.[77] Major fluid shifts, with the potential for significant hemodynamic instability, should be treated according to the amount of total body surface area affected. This can be estimated using the Parkland formula or other protocols for fluid resuscitation. Pain control, tetanus prophylaxis, nutritional support, vigilant wound care, and close monitoring are all performed in the acute phase. Systemic antibiotics have a role in treatment only on an episodic basis such as at initial presentation, eschar excision, and skin graft placement.[78] Routine, ongoing administration of systemic antibiotics for prophylaxis alone should be avoided to reduce the risk of selecting for resistant organisms. A burn eschar at significant risk for superinfection has exceptionally poor blood supply, decreasing the likelihood that any significant amount of systemically delivered antibiotic will actually penetrate the wound bed. Instead, topical antibiotic wound preparations such as silver sulfadiazine, mafenide acetate, and bacitracin are all administered to burn wounds and eschars in the acute phase to prevent infection and promote healing.[78] Biobrane is a bilaminar temporary skin substitute and has been shown to decrease pain.[79]

The best functional and aesthetic outcomes in facial burns occur with early reepithelialization (within 14 days), whether spontaneous or by eschar excision and skin grafting. Because of this, it has become standard care in most burn centers to determine early which burns will heal well with ongoing wound care and which will require débridement and reconstruction.[80] After 7 to 14 days of wound care, including gentle mechanical débridement of grossly necrotic or infected tissue and topical antibiotics, burn wounds should be assessed for improvement and likelihood of spontaneous epithelial coverage.[80] In the face, this is facilitated by robust blood supply and high density of epithelial appendages. Beyond 7 to 14 days, secondary healing is associated with a higher degree of contracture, hypertrophic scarring, and poor appearance. Wounds that have not reepithelialized or that were obviously third degree at initial presentation are appropriate for tangential excision and reconstruction. Eschars should be excised tangentially down to healthy, bleeding tissue rather than to some predetermined depth to ensure preservation of as much viable tissue as possible. Delaying grafting for 48 to 72 hours after excision allows time for the recipient wound bed to display adequate vascularity for graft take, following a "no bridges burned" policy of reconstruction.

Operative intervention for wound closure and reconstruction should be based on optimizing function first and appearance second. Some structures, such as the eyelids, perioral region, and nasal aperture, have particularly critical roles in that they provide corneal protection, oral competence, and airway patency. Skin grafting and other reconstructive efforts should also be based on the principle of aesthetic units.[81] Replacing facial units as a whole and placing scar lines along the borders of adjacent units or parallel to relaxed skin tension lines diminishes the visual impact of flaps and grafts with distinctly different characteristics from surrounding skin. Postoperative care is equally important in optimizing aesthetic and functional outcome. Physical therapy can help avoid contracture; placement of pressure garments, silicone sheeting, and splints may diminish the likelihood of hypertrophic scarring.[82]

Skin grafting remains the mainstay of reconstruction for deep partial-thickness and full-thickness burns. Although full-thickness skin grafts often provide the best match for texture and color, size limitations often preclude their use. Common sites for full-thickness skin graft harvest include the upper eyelids, supraclavicular fossae, preauricular and postauricular skin, and nasolabial folds. If the initial defect is too large for full-thickness grafting, donor sites can be saved for secondary procedures aimed at scar revision or contracture release.

Split-thickness grafts are the most commonly employed technique of burn coverage because of the simplicity of the technique and the wide availability of donor sites. Secondary contraction is inevitable but is inversely proportional to the amount of dermis included with harvest. Grafts from 0.018 to 0.035 inch in thickness may be reliably used to cover large defects, depending upon the recipient bed. Even with extensive facial burns, split-thickness grafts applied to this area should never be meshed. Bolstering grafts to the face is usually impractical, necessitating vigilant wound care and regular rolling of the graft to express fluid from the undersurface until graft take.

Other reconstructive options, including regional flaps and free tissue transfer, are often best used as secondary, staged procedures.[83] However, wounds demanding immediate coverage with a large volume of well-vascularized tissue, such as deep full-thickness burns extending to underlying bone or critical structures, may warrant flap reconstruction acutely. Tissue expansion of adjacent or distant donor sites can increase the surface area of regional flaps or distant full thickness skin grafts and is best used as a secondary technique after initial treatment with split-thickness grafting. In this way, an open burn wound at risk

for infection and contracture is first converted to a safe, epithelialized surface that is then replaced with tissue more similar to surrounding skin.

Special Considerations

Eyelids

Eyelid injuries have special priority in treatment because of their role in corneal protection. Many severe periorbital burns do not actually involve the globe, and corneal exposure occurs as a secondary event after resolution of edema, eschar formation, and wound contraction. The globe may actually be protected acutely by significant periorbital edema; however, early eschar excision and grafting should be performed as soon as swelling subsides. Reconstruction of the anterior lamella with skin grafts is frequently complicated by graft contracture and late cicatricial ectropion. Split-thickness grafts are theoretically well suited to replicate the thin, pliable skin of the upper lid, although some authors advocate using full-thickness grafts from the contralateral lid because they contract less than split-thickness grafts.[84] Full-thickness grafts match the lower lid characteristics best and reduce the risk of ectropion.

Nasal and Auricular Cartilage

Burns of the nose and ears are common because of their location and prominence. Before the routine use of topical antimicrobials, nasal and auricular cartilage were at high risk for severe progressive chondritis.[85] With proper wound care currently, the need for radical débridement or excision is relatively rare. However, suppurative chondritis of the ear may still develop despite adequate wound care. This requires incision and drainage to save cartilage not otherwise injured. Conservative débridement and eschar excision followed by split-thickness grafting may be performed if a suitable wound bed develops over the underlying cartilage. Exposed cartilage must be excised or covered with a flap. Otherwise, nasal or auricular reconstruction as previously described may be performed on a secondary basis with local, regional, or free flaps.[86]

Lips and Oral Commissure

Thermal injuries of the lips and perioral region can cause severe functional impairment by limiting oral competence, hygiene, speech, eating, and airway access. These injuries also often pose significant challenges in accomplishing an aesthetically pleasing reconstruction. Microstomia is a common complication, both in patients in whom reepithelialization occurs spontaneously and in patients who undergo reconstruction secondarily. Consequently, most authors recommend initial conservative treatment with wound care and pressure application, waiting to intervene surgically until scars are fully mature.[82] Furthermore, fitting the patient with an oral appliance designed to splint the commissure or labial margin keeps the tissue under constant tension and may help prevent microstomia. Multiple types of devices exist and no single protocol has been established; however, this approach has gained acceptance for improving outcomes. Patients should be fitted with a device approximately 3 weeks after injury and should continue to wear it for 4 to 6 months.[87]

Isolated oral commissure burns are a unique class of burns and are seen almost exclusively in young children who have bitten an electrical cord. Because of the irregular depth of penetration of the electrical current, the initial appearance of the injury is an unreliable indicator of severity. The extent of tissue injury and necrosis often takes up to 48 hours to become evident. Therefore excision and reconstruction for most oral commissure burns is generally not recommended; rather, conservative treatment with wound care and limited débridement are standard of care.[88] Topical antibiotics should be applied until the wound spontaneously reepithelializes or until the eschar clearly demarcates itself from surrounding tissue and begins to come off. Early experiences with oral commissure eschars demonstrated a 25% rate of significant hemorrhage from labial artery exposure at the time of eschar breakdown and separation; more recent series have not reported this complication.[89]

The priority in the treatment of oral commissure burns should be prevention of microstomia. Severe burns involving the oral commissure, lips, and adjacent facial structures with early, obvious development of microstomia and associated difficulties with oral competence often benefit from early excision and reconstruction, similar to other facial burns. Oral commissure burns not associated with electrical injury and clearly superficial in nature will generally respond well to local wound care with or without splinting. The difficulties in management, therefore, primarily involve deep partial-thickness, localized full-thickness, and electrical burns. In such cases, satisfactory results have consistently been obtained with conservative management as described above, often combined with application of a splint device, which typically applies a stretching force in the horizontal direction. Whereas one series managed patients successfully without splinting, others were able to show a benefit and some authors recommend regular use of a splint during the maturation of scars.[88,89]

Frostbite

The nose, cheeks and ears are commonly exposed to cold and are frequent sites for frostbite. Despite the rich blood supply to the face, cold exposure results in peripheral vasoconstriction as blood is shunted to the core. A relative hypothermia develops in exposed areas, which is tolerated by local tissue until the skin temperature drops toward freezing. As tissue freezes, ice crystals form in the interstitium, drawing water out of cells and resulting in cell death. Cells are also killed directly by intracellular freezing and indirectly by ischemia from vascular stasis. A significant component of tissue damage in the form of progressive dermal ischemia continues after the initial temperature insult and appears to be related to inflammatory mediators such as prostaglandins, thromboxanes, bradykinin, and histamine, rather than the coagulation cascade alone.[90]

The initial examination of frozen tissue before rewarming yields little diagnostic information about the degree of injury. Even after rewarming, many seemingly superficial injuries demonstrating a margin of erythema around a numb, white central plaque may go on to show more ominous signs of deep involvement with hemorrhagic blisters or a hard, black eschar in the ensuing 2 to 3 weeks. Favorable findings include return of pinprick sensation, normal skin color, and blisters that fill with clear, not milky fluid.[91]

The single greatest factor in improving outcomes is rapid rewarming of the affected tissue as soon as possible. Avoid partial rewarming or slow rewarming through exposure to a warm ambient temperature. Immerse or continuously bathe the affected area in a solution of warm water with a mild antibacterial agent. The water temperature should be maintained at 40°C to 42°C (104°F to 108°F). Rapid rewarming continues for 15 to 30 minutes until thawing is complete. As tissue thaws it becomes redder or purple in color and more pliable in texture, indicating the end of vasoconstriction. Avoid mechanical manipulation of the tissue or any immediate débridement, except in cases of clear blisters, and apply aloe vera every 6 hours. Aloe vera is an antithromboxane agent and has been shown to reduce ischemia when used alone or in combination with pentoxifylline.[92] Rewarming can be painful and often requires narcotic analgesia. Tetanus prophylaxis is also indicated and many authors recommend prophylactic treatment with systemic antibiotics such as penicillin. Post-thaw care aimed at diminishing the severity of progressive dermal ischemia should include ibuprofen 400 mg orally every 12 hours, ongoing application of aloe vera every 6 hours, and daily hydrotherapy at 40°C for 30 to 45 minutes until wounds appear stable. Other adjunctive measures include treatment with rheologic agents such as dextran, vasodilators such as reserpine, thrombolytic agents, and anticoagulants. These strategies have a theoretical benefit, but there is no convincing evidence for routine use.[93]

Surgical treatment is primarily a reconstructive endeavor. In the absence of an uncontrolled subeschar infection, early débridement is rarely necessary. An uninfected injury typically mummifies over the course of several weeks, and elective débridement with immediate or staged reconstruction may be performed when the demarcation between normal and devitalized tissue is clear.

Conclusion

Traumatic facial injuries have a broad scope of etiologies. Necessarily, their treatment also comprises a wide variety of treatment strategies. As

a rule, an aggressive examination is usually coupled with conservative management. Initial treatment should emphasize reapproximating lacerations or creating an environment conducive to reepithelialization. Scar revision or reconstruction with flaps is usually best postponed until a time when the full extent of the injury can be appreciated.

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CHAPTER TWENTY-THREE

Maxillofacial Trauma

Robert M. Kellman

Key Points

- Proper repair of craniomaxillofacial fractures requires accurate diagnosis and a plan for repair. Diagnosis requires a good physical examination and high-resolution computed tomography (CT) scanning, with evaluation of at least axial and coronal scans.
- Associated injuries must be recognized and addressed.
- The mandible is often evaluated using panoramic tomography, but CT scans pick up missed fractures and better demonstrate condylar head malpositions.
- Fractures must be classified: frontal, skull base, naso-orbital-ethmoid, orbital wall, zygomatic, maxillary, and mandible.
- Familiarity with the Le Fort classification is mandatory.
- Familiarity with surgical access is important. Attempts are made to minimize violation of the facial skin; for example, the upper third is often accessed via a coronal incision and the mandible is approached transmucosally whenever possible.
- The middle third bones are accessed from above via a coronal incision, centrally through orbital incisions, and from below transorally via sublabial transmucosal approaches to whatever extent is possible, minimizing use of transcutaneous approaches.
- Endoscopic approaches help minimize surgical access.
- Repair requires understanding of biomechanical principles: The upper third requires repair for cosmesis and separation of the cranial vault from the nose and sinuses. Naso-orbital-ethmoid fractures require repositioning of the medial canthal tendons. The middle third is supported by vertical and horizontal buttresses. Repair of these buttress areas restores facial dimension and functional support.
- The mandible sustains large forces during mastication, and repair must overcome tension forces in function. Proper restoration of occlusion is key to reduction of tooth-bearing bones.
- Panfacial fractures are most difficult and require a comprehensive plan for repair.
- Rigid fixation allows for anatomic repair and early restoration of function, but requires precise repositioning and adherence to technical principles.

The term *maxillofacial trauma* is generally used to refer to the injuries of the facial skeleton, and the management of these injuries is sometimes thought of as "facial orthopedics." (*Craniomaxillofacial trauma* might be a better term because the anterior wall and floor of the anterior cranial fossa are included in these injuries.) As in this text, soft tissue injuries are often discussed separately. However, accurate repositioning of fractured skeletal fragments has major implications for facial aesthetics and soft tissue redraping as well as a significant impact on critical functions such as vision and mastication. Positioning of incisions and the extent of various surgical exposures can influence the final appearance of the face and the function of facial structures such as the eyelids, lips, and nose. Therefore the proper management of maxillofacial trauma requires a comprehensive approach. These injuries should be addressed by practitioners who are familiar with the various ramifications of skull base, orbital, facial, sinus, dentoalveolar, and airway injuries and, most importantly, by those willing to collaborate when necessary with other specialists who may have overlapping areas of expertise. For example, combined facial and anterior skull base injuries are frequently best approached jointly by the neurosurgeon and the craniomaxillofacial surgeon rather than by the use of separate, independent, and even staged management. Even though this chapter only scratches the surface of many complex and controversial aspects of craniomaxillofacial trauma management, it always assumes a comprehensive approach to these often complex and challenging injuries.

The management of facial injuries has evolved significantly during the past 2 decades. Evaluation of craniomaxillofacial injuries has changed significantly with the advent of computed tomography (CT), which has improved dramatically during this interval. Modern CT scanners are exceptionally fast and offer high enough resolution to allow dependable and accurate reconstruction in multiple planes and in three-dimensional imaging. These advances have added greatly to the surgeon's preoperative understanding of the nature of the injuries.

Borrowing from the revolutionary techniques of congenital craniofacial surgery pioneered by Paul Tessier, wider exposures have been possible, while visible scars have been minimized. Wider access has led to better understanding of common fracture patterns and their management, and, as might be expected, taking advantage of the experience gained from extended access approaches, surgeons are now trying to perform the same complex surgeries using less invasive techniques.[1] Recently, these have been improved by taking advantage of the additional visualization made possibly by endoscopy.[2-10]

Bone repair techniques have evolved as well from the frequent use of interosseous wire repairs and Adams suspension wiring[11] to the common use of rigid fixation with plates and screws. Many early mandibular fixations used large plates with large-diameter screws,[12-15] and these repairs have progressed more recently to the frequent use of smaller ("miniplating") techniques as advocated by Michelet and colleagues,[16] Champy and associates,[17-19] and more recently, Ellis.[20] Micro-

plates and even absorbable plates have been advocated for the repair of mid and upper facial as well as cranial fractures and osteotomies. Progress in understanding the biomechanical principles involved in facial fracture repair has resulted in more dependable repairs, both from the standpoint of the technology and in its application. Although not yet widely available, advanced intraoperative imaging techniques allow for more dependable and accurate restoration of the complex three-dimensional facial skeletal architecture.[21,22]

Advances in implant technology, particularly the wide use of titanium mesh, plates, and screws have led to better biocompatibility.[23] Porous polyethylene implants so far seem to be well tolerated in the orbit, and such implants along with hydroxyapatite cements have provided a wider variety of options for craniofacial reconstruction. Finally, secondary (late) repair of unsatisfactory results has progressed as well, providing more options for the unfortunate patient with a poor outcome due to either an untreated injury or a suboptimal initial repair. This chapter focuses primarily on management, including evaluation and primary repair, with mention of complications and the treatment of unsatisfactory late outcomes.

Anatomy, Physiology, and Pathophysiology

General

While form and function are the underpinnings of facial anatomy, and generally speaking form is important for function, the facial architecture is also critically important aesthetically. Knowledge of facial skeletal anatomy is necessary for understanding the mechanisms and patterns of facial injuries as well as the approaches to their repair. Anatomic depictions are available in many anatomy texts and atlases; the focus herein is on aspects relevant to injury and repair.

The face can be arbitrarily divided into sections, each including bony anatomic structures and associated visceral and soft tissue entities. From superior to inferior, the frontal bones are generally considered the upper third of the face. The maxillae, zygomas, and orbits comprise the middle third, or midface, which may include the nose. Or, the nose and nasoethmoid complex may be separately considered as the central face. The mandible is generally considered the lower third, although the vertical (posterior) portions of the mandible extend superiorly to the skull base, which is well above the lower third.

Upper Third

The frontal bone forms the contour of the forehead. Displaced fractures can create various deformities, the most common of which is a central forehead depression (Fig. 23-1). The frontal bone forms the junction between the cranium and the face, and it relates to several visceral structures, the most critical of which is the brain. The typically paired frontal sinuses, when present (approximately 85% of the time), are housed completely within the frontal bones (Fig. 23-2). Frontal bone fractures may involve only the anterior sinus walls, in which case the fractures are significant only for sinus function and cosmesis; or they may involve the posterior wall of the sinus or extend beyond the sinus, in which case they are true skull fractures and become neurosurgical concerns as well. The supraorbital rims and roofs are also part of the frontal bones, which are therefore also related to the orbits, and fractures can thus affect orbital and ocular functions. Inferiorly in the midline, the glabella portion of the frontal bone relates to the superior extent of the nasal bones. This thick glabellar bone protects the underlying frontal outflow tracts and the cribriform plates, which house the branches of the olfactory nerves. The supraorbital and supratrochlear nerves pass through notches or foramina in the supraorbital rims and can be injured from trauma or, more commonly, from surgical manipulation.

Middle Third

The middle third includes the zygomas, orbits, and maxillae, as well as the nose, which together with the anterior medial orbits form the central face. The anterior projection of the zygomas, the malar eminence, or "cheekbone prominences," are important determinants of facial projection and contour. The posterolateral projections, the zygomatic arches, abut the temporal bones posteriorly and provide the attachments for the masseter muscles superiorly. The superior and

Figure 23-1. Lateral view of a patient with a depressed central frontal fracture.

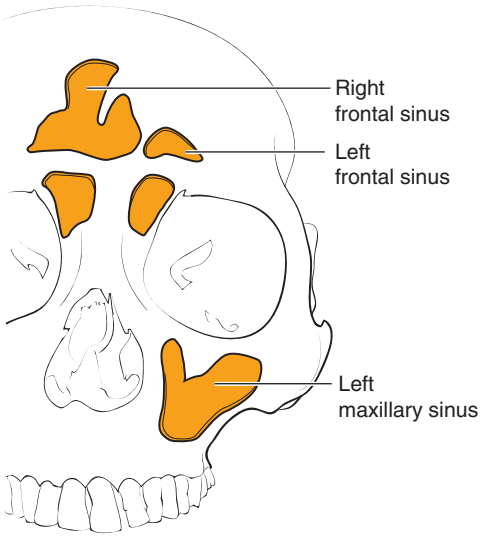

Figure 23-2. Front view of the craniofacial skeleton demonstrating the presence of the frontal sinuses within the frontal bone. *(Redrawn from Grant JCP.* Grant's Atlas of Anatomy. *Baltimore: Williams & Wilkins; 1972, with permission.)*

medial projections of the zygoma contribute to the lateral and inferior orbital rims and the inferolateral orbital walls. Displacement of this portion of the zygoma can significantly alter the position of the globe in the orbit. The inferomedial extension of the zygoma extends from the inferior orbital rim and broadly contacts the maxilla, forming the important lateral buttress of the midface (Fig. 23-3). While the superior, medial, and inferior orbital rims extend anterior to the globe, the lateral rim, which is comprised primarily of the zygoma, is situated near the equator of the globe (Fig. 23-4).[24] Therefore minor changes in the position of the zygoma can have a significant impact on the anteroposterior position of the globe. Enophthalmos is a common complication of inadequately repaired or unrepaired zygomatic fractures.

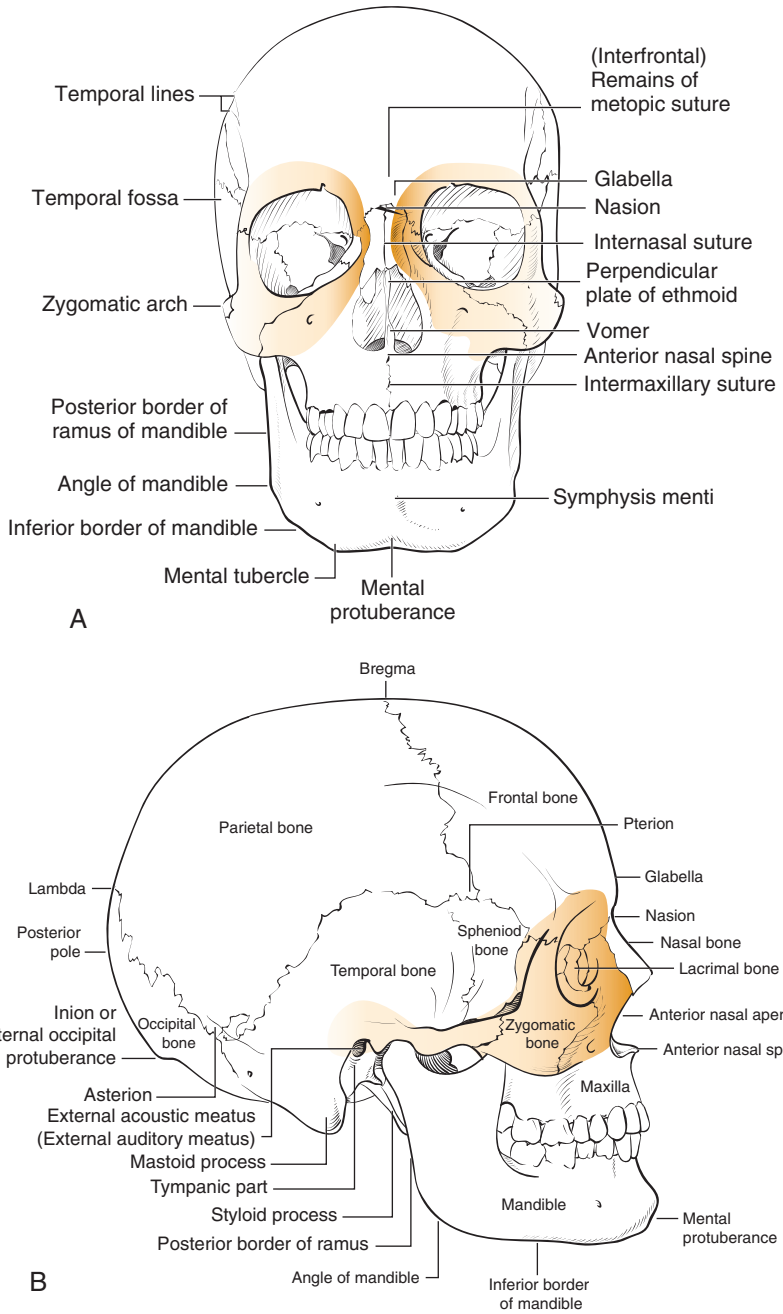

Figure 23-3. Frontal **(A)** and lateral **(B)** view of the craniofacial skeleton demonstrating the broad attachment of the zygomatic bone to the maxilla extending from the infraorbital rim inferolaterally. *(Redrawn from Grant JCP.* Grant's Atlas of Anatomy. *Baltimore: Williams & Wilkins; 1972, with permission.)*

The maxillae extend from the zygomas laterally to the nasal bones medially, forming the medial portions of the infraorbital rims and anterior orbital floors and support for the nasal bones. They also form the piriform apertures and house the nasolacrimal ducts. The maxillary dentition is important for mastication, and proper repositioning of the maxilla after trauma is critical to the recreation of a functional occlusion between the maxillary and mandibular teeth. Superomedially, the anterior lacrimal crest is formed by the maxillary bone. Fractures of this area often lead to malpositions of the medial canthal ligaments, which can result in telecanthus, an unsightly cosmetic deformity.

The maxilla also contains the infraorbital nerve, the terminal branch of V2, which provides sensation to the medial cheek, lateral nose, upper lip, and upper gingiva and teeth (Fig. 23-5). Fractures can compromise this nerve, and care must be taken to both preserve it and, if necessary, decompress it when repairing these fractures. The maxillae also house the maxillary sinuses, which drain into the middle meatus of the nose, lateral to the middle turbinates. Injury to the outflow tracts is uncommon, but preexisting obstruction may contribute to infection.

The nasal bones form the bony nasal projection and support the upper lateral cartilages, which form the internal nasal valves. Because of their prominent position in the middle of the face, the nasal bones are the most frequently fractured bones in the human body. Restoration of nasal function is important for breathing and olfaction, which also may have a significant impact on taste. The nasal bones are also cosmetically important, and suboptimal restoration of nasal contour is usually quite apparent. The nasal bones are supported by the frontal processes of the maxillae, which are anterior projections of the maxillae superomedially. Failure to identify fractures in this area can lead to unsatisfactory results of nasal fracture reductions.

The orbits are complex bony structures with structural contributions from multiple facial and skull bones. In addition to the frontal, zygomatic and maxillary contributions discussed earlier, the lacrimal

bone sits behind the maxillary bone medially (Fig. 23-6). The maxillary bone and the lacrimal bone together form the lacrimal fossa, which houses the lacrimal sac. The strong anterior (maxillary bone) and posterior (lacrimal bone) lacrimal crests provide the sites of attachment of the components of the medial canthal ligaments. Note that the medial canthal ligaments have three components, an anterior, a posterior, and a superior attachment (Fig. 23-7). The thin lamina papyracea of the ethmoid bone completes the medial orbital wall. The palatine bone makes a small contribution posteroinferiorly. The posterior lateral orbit is provided by the greater wing of the sphenoid and the solid optic canal bone is contributed by the lesser wing of the sphenoid. The optic canal sits posteromedially behind the medial wall where it is generally protected from all but the severest injury. The optic foramen is actually directed toward the lateral orbital rim rather than directly anteroposterior. The important "orbital apex" includes the area lateral to the optic canal through which cranial nerves III, IV, V, and VI pass to enter the orbit, which is considered part of the superior orbital fissure. When pressure from an injury (or tumor, abscess, hematoma) causes dysfunction in these nerves, it is called *superior orbital fissure syndrome,* which requires urgent surgical intervention.[25,26]

Familiarity with the complex shape of the orbital walls is important for repair. The position of the globe is determined by the orbital shape and contents. The best way to prevent globe malpositions is to restore the natural shape of the orbit and ensure that orbital fat that has escaped through fractures is returned to the orbit. While the orbital floor is gently concave inferolaterally, it tends to be more convex medially and becomes significantly convex posteriorly behind the equator of the globe (see Fig. 23-6). Familiarity with this anatomy increases the likelihood of proper repair after injury.

It is also important to understand the proper terminology associated with injuries. The term *blowout fracture* implies that the orbital rims have remained intact, while one or more walls of the orbit, typically the floor, though the medial wall are also commonly affected or have fractured. It also has implications for the mechanism of injury: a force transmitted by a blunt impact through the globe to the surrounding walls. Floor fractures can damage the infraorbital nerve, which runs through the floor of the orbit.

Midfacial structures are paired and the central bones are joined in the midline. The nasal bones and maxillae are joined vertically, and the palate forms the inferior horizontal bridge between the two maxillae. The upper horizontal bridge is formed by the anterior cranial base. There are horizontal connections across the nasal bones, but these are not straight across, because the nasal bones are situated on a line superior to the infraorbital rims, and posteriorly across the sphenoid. The relationships between the various bones are important not only when considering normal anatomy and its reconstitution, but also for understanding how facial architecture distributes biomechanical forces, which is important for the repair of fractured structures.

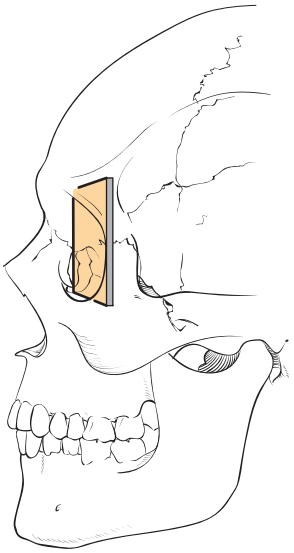

Figure 23-4. Schematic representation of axis of the globe extending from the lateral orbital wall to the lacrimal bone. The entire lateral wall is behind the axis of the globe, whereas only a portion of the floor is so situated. *(Redrawn from Pearl RM. Treatment of enophthalmos.* Clin Plast Surg. *1992;19:99.)*

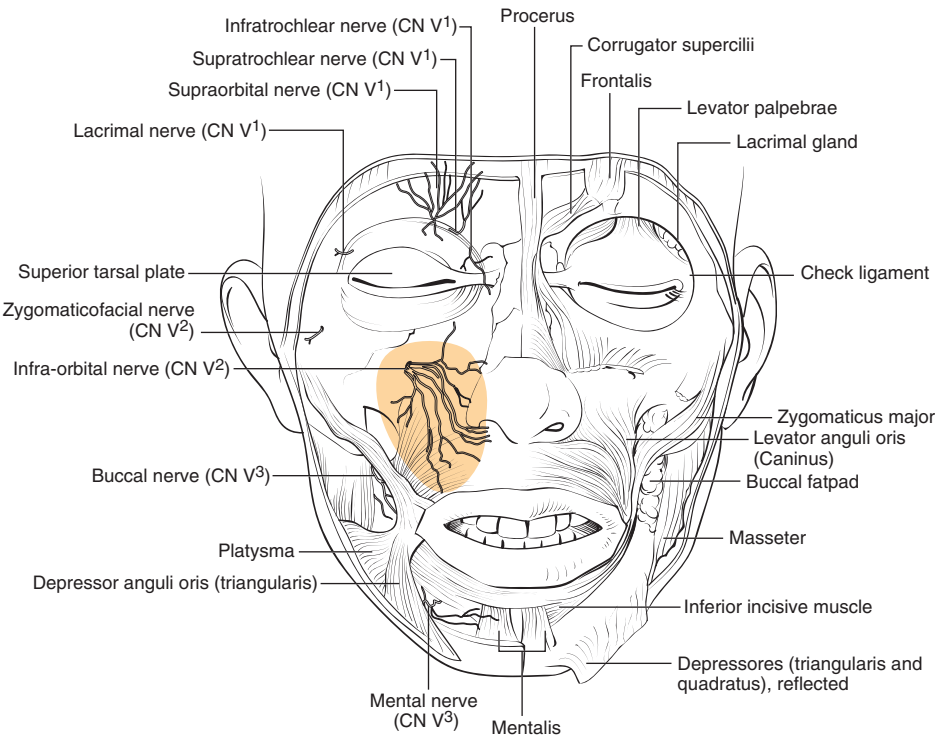

Figure 23-5. Front view of the partially dissected face. The infraorbital nerve is seen exiting the infraorbital foramen. *(Redrawn from Grant JCP.* Grant's Atlas of Anatomy. *Baltimore: Williams & Wilkins; 1972, with permission.)*

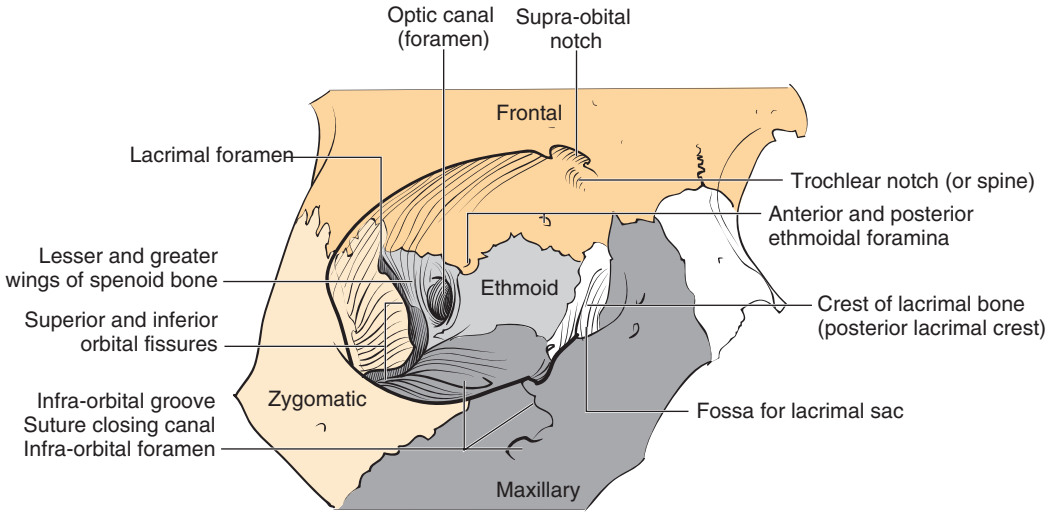

Figure 23-6. Bony orbital anatomy demonstrating the contributions of multiple bones. *(Redrawn with permission from Zide BM, Jelks GW.* Surgical Anatomy of the Orbit. *New York: Raven Press; 1985.)*

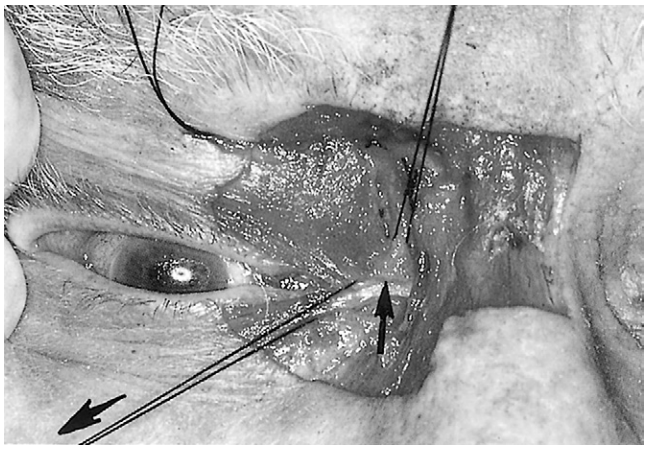

Figure 23-7. A cut-away view of the medial canthal complex. In this view, a suture near the nose is around the superior component and the suture pulling laterally is around the anterior component, which has been severed. The posterior component is running behind the anterior component and is fixing the medial structures to the posterior lacrimal crest. *(Redrawn with permission from Zide BM, Jelks GW.* Surgical Anatomy of the Orbit. *New York: Raven Press; 1985.)*

Table 23-1

"Survival Protection" Anatomic Structures

Facial Crumple Zone	Area Protected
Medial orbital wall	Optic nerve, globe
Orbital floor	Globe
Maxillary sinus	Globe, middle cranial fossa
Ethmoid sinus	Globe, optic nerve, anterior cranial fossa, middle cranial fossa
Frontal sinus	Anterior cranial fossa
Sphenoid sinus	Carotid arteries, cavernous sinuses
Face as a whole	Cranial cavity
Condylar necks of mandible	Middle cranial fossae

The concept of the "central face" comes into play only in the presence of injury and refers to injury in which the trauma to the solid nasal root is transmitted posteriorly resulting in a telescoping injury. This has variously been called *naso-orbital fractures, fracture of the ethmoids,*[27] *nasoethmoid complex (NEC) fractures,* and more recently *naso-orbital-ethmoid (NOE) fractures.* It is an important fracture clinically, but it takes on even greater significance when used as a paradigm for the understanding of how facial fractures occur and how the face is designed to provide maximum protection for structures important for the survival of the human organism.

The nose is important for airway, smell, and cosmesis, but it is less critical to human survival than vision or cerebral function. The solid glabellar and nasal root bones not only protect the underlying cribriform plate, but also take the first impact to the central face. Because the nasal bones and frontal processes of the maxillae are backed up by the thin laminae papyracea of the ethmoid bones, these latter provide little support and crumple, thereby allowing the nasal bones to "telescope" posteriorly while dissipating the shockwave into the ethmoid sinuses. The optic nerves are suspended in cushioning orbital fat anterior to the optic foramen and more posteriorly are protected by the thick bone of the lesser sphenoid wings once they enter the bony canal. Thus the medial orbits form a "crumple zone" to protect the globes and optic nerves in most central facial traumas.

This same concept can be applied to other aspects of facial skeletal anatomy. The globes tend to be protected in direct blunt trauma by the thin bones of both the orbital floors and medial walls. The globes are relatively round and suspended in fat so that most blunt traumas are transmitted to the thin orbital floors and medial walls, accounting for why "blowout fractures" are much more common than globe ruptures.[27a] Similarly, the face itself functions as a "shock absorber" for the cranial cavity, so that the frequency and severity of brain injury can be limited. Finally, this theory provides an explanation for the presence of the paranasal sinuses that offers a survival advantage: that is, the sinuses serve as a crumple zone for the face,[27a] allowing the energy to be dissipated before it reaches the eyes and brain. Thus the entire facial architecture has evolved by design to provide survival protection for critical organs (Table 23-1).

Lower Third

The mandible is generally considered the lower third of the facial structure. It contains the mandibular dentition, which interfaces with

the maxillary dentition for mastication. Unlike the middle third, which is fixed to the skull, the mandible is mobile and swings, hinged to the skull base in two, bilaterally symmetric attachments. The hinges occur at the temporomandibular joints (TMJs), which are true arthrodial joints that both swing and slide. The conformation of the mandible, a somewhat horseshoe-shaped bone hinged in two places to the same solid entity, the skull, makes it well designed to absorb impact forces rather than transmit them to the solid middle fossa floor, and therefore multiple mandible fractures due to a single impact force are not uncommon. (Mandibular trauma causing injury to the skull base can occur, and the condylar head of the mandible has even rarely traversed the glenoid fossa, which houses the articular cartilage of the joint and entered the middle fossa, but such injuries remain rare.)[28] The condylar head of the mandible is housed within the TMJ and is connected to the vertical ramus by the relatively thin and weak condylar neck. This weak area of the bone seems to give easily when a contralateral impact is applied, and fractures of this neck area are generally called *subcondylar fractures*, indicating that they occur below the TMJ. A central impact to the mentum does not uncommonly result in bilateral subcondylar fractures. The condylar neck extends inferiorly into the vertical ramus, which is also relatively thin compared to the tooth-bearing body and symphyseal regions of the bone. However, fractures of the vertical ramus (other than extensions of subcondylar fractures) are relatively uncommon, presumably due to the protective effects of the muscular sling provided by the muscles of mastication, all of which attach to aspects of the vertical rami. The powerful masseter muscle attaches broadly to the inferolateral surface of the ramus, whereas the pterygoids attach to the medial surface. The temporalis attaches to the coronoid process, a superior extension of the anterior ramus. The angle region of the mandible occurs at the posterior extent of the tooth-bearing region and is a common area for fracture. Fractures here extend from the thick, tooth-bearing area in the third molar region posteroinferiorly into the much thinner bone of the ramus. The presence of the third molar tends to thin the bone superiorly, and tension of the muscle sling may also splint the area, creating a natural break point. Fractures in this region are particularly difficult to stabilize, and repairs have traditionally resulted in the highest rates of complications (see later). As might be predicted, the mandible is thickest in the tooth-bearing areas. The anterior portion from canine to canine is referred to as the *symphyseal region* or *symphysis* (sometimes arbitrarily divided into symphysis in the midline and parasymphyseal regions on either side of the midline). From canine to the angle of the body of the mandible contains the two premolar (bicuspid) and three molar teeth. Another unique aspect of mandibular anatomy is the presence of the inferior alveolar nerve. A branch of the third division of the trigeminal nerve, the inferior alveolar nerve enters the mandible at the lingula and travels beneath the tooth roots that it supplies, exiting the mental foramen as the mental nerve, generally in the region of the first bicuspid tooth. It is important to keep in mind when repairing mandibular fractures that the mental foramen does not generally represent the most inferior position of the nerve, and this must be considered when placing hardware on the mandible in the body region behind the mental foramen.

A common classification scheme for mandible fractures uses the terms *favorable* and *unfavorable*.[29] However, this scheme has no impact on management and is not addressed here. It is also important to be familiar with the changes that take place in the mandible with age and tooth loss. When people lose teeth, the normal stresses on the bone are significantly altered, and bone remodeling tends to result in atrophy of the alveolar portion of the bone. The tooth-bearing portions of the mandible atrophy from the top down, bringing the inferior alveolar nerve closer and closer to the oral surface; in extreme cases, it can even rest on top of the bone. In addition, atherosclerosis of the inferior alveolar artery occurs, limiting the blood supply to the thin atrophic bone.[30] This has significant implications for repair of these fractures.

Fractures of alveolar segments, tooth fractures, and tooth avulsions are beyond the scope of this chapter.

A knowledge of basic dental anatomy and familiarity with normal and common abnormal occlusal relationships is important for anyone treating fractures in the tooth-bearing facial bones. The normal adult complement of teeth is 32, with eight in each quadrant of the maxilla and mandible. Common numbering in adults in the United States is from 1 to 32, starting from the right maxillary third molar (number 1) counting toward the left with the left maxillary third molar being number 16, the left mandibular third molar being number 17, and ending with the right mandibular third molar being number 32. The dental surfaces contain cusps for chewing and grooves between these cusps, and in multicusp teeth these are identified by their positions as mesial (toward the incisors), distal (toward the posterior mandible or maxilla), buccal (toward the cheek), and lingual (toward the tongue). Occlusion is complex and has many aspects, but a normal molar relationship has been defined by Angle as the "mesiobuccal cusp of the maxillary first molar sitting within the mesiobuccal groove of the mandibular first molar."[31] This is Angle's class I. When the maxillary molar is more anterior (chin generally relatively retruded), it is class II, and when the maxillary molar is more posterior (chin relatively prognathic), it is Angle's class III. The maxillary arch should be wider than the mandibular, and when the maxillary buccal cusps fall lingual to the mandibular buccal cusps, there is a crossbite on that side. Similarly, anteriorly, the maxillary teeth should extend anterior to the mandibular teeth, which is defined as a normal overjet. The maxillary incisors should overlap the mandibular incisors vertically, which is defined as a normal overbite (Fig. 23-8).[32]

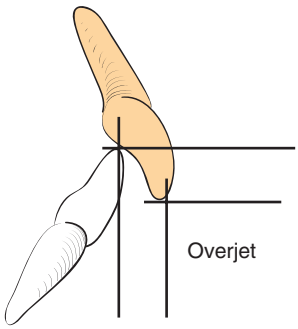

Figure 23-8. Overbite is the vertical overlap of the maxillary incisors over the mandibular incisors. Overjet indicates the horizontal extension anteriorly of the maxillary incisors forward of the mandibular incisors. *(Redrawn from Bailey BJ.* Head & Neck Surgery—Otolaryngology. *2nd ed. Philadelphia: Lippincott-Raven; 1998.)*

Evaluation and Diagnosis

Physical Examination

While the CT scan has become the workhorse of maxillofacial trauma diagnosis, there are still important aspects of facial injuries that are best assessed by performing a good physical examination. The importance of this sometimes lost art must be emphasized.

First and foremost, the initial assessment must address the ABCs and any other potentially life-threatening injuries. Facial trauma may be associated with primary airway injuries to the larynx or trachea, or the airway may be secondarily obstructed by swelling of the oral cavity and/or pharynx or by blood. Establishing a safe airway may require intubation or tracheotomy, and the status of the cervical spine must always be considered. When bleeding is not severe, use of a fiberoptic endoscope may allow intubation without manipulation (extension) of the neck. Other options include use of the lighted stylet and retrograde intubation, or temporary airway stabilization using the laryngeal mask airway. When necessary, a cricothyroidotomy may be performed, although if possible, a tracheotomy is preferred.

Most severe bleeding is from the nose and sinuses and can be managed by tamponade with packing. However, laceration of the internal carotid artery in the skull base may require immediate angiography and balloon occlusion above and below the tear, although these injuries

are rarely compatible with survival. Of course, neurologic injuries should be evaluated by the neurosurgeons, because these may be life threatening as well.

Although the injury may not be not be life threatening, visual status should be evaluated as soon as possible, because progressive loss of vision usually indicates increasing intraorbital pressure or optic nerve injury, and early intervention is needed to salvage vision.

The quality of the physical examination of the facial structures varies depending on the amount of time that has transpired since the injury, the amount of swelling that has developed, the presence of hematoma, and the presence of treatment-related devices such as packing, tubes, and cervical collars. The general facial appearance should be assessed first, looking for penetrating injuries and lacerations as well as the possibility of foreign bodies. Facial nerve function should be evaluated in each division, and the possibility of cerebrospinal fluid (CSF) leakage, otorrhea, and/or rhinorrhea, should be considered if there is any fluid discharge. If the patient can cooperate, a thorough evaluation of cranial nerve function should be performed. When lacerations are present, sterile examination of the wound may yield information about the status of the underlying bone. In particularly severe injuries, for example, brain herniation through the wound, this should be deferred to surgery.

Upper Third

In the upper third of the face, the forehead is evaluated for sensation and motor function. In some cases, fractures may be visible as depressions (see Fig. 23-1) or palpable as step-offs, although typically these fractures are more readily seen on CT scans.

Middle Third

As noted earlier, the middle third of the face houses numerous structures. Of these structures, the eyes are the most important functionally. Vision should be assessed as soon as possible, because progressive visual loss demands emergency management. A light shined in the eye will evaluate pupillary response, even in the unresponsive patient. Failure of the pupil to respond can indicate injury to the afferent system (optic nerve) or efferent system (third cranial nerve and/or ciliary ganglion), or it could indicate a more serious intracranial condition. This must be immediately evaluated by both the neurosurgeon and the ophthalmologist. A CT scan is imperative to assess the nature and extent of injuries. Other significant but less serious dysfunctions include gaze limitation with or without diplopia. Forced duction testing is performed by anesthetizing the conjunctiva and then manually manipulating the globe in all directions with forceps. An applantation tonometer can also be used to determine whether there is an increase in pressure when the patient looks in the direction of gaze limitation (an increase in pressure of 4 mm Hg or more is indicative of entrapment).[33] The position of the globe should be assessed both in its anteroposterior position (enophthalmos vs. proptosis) and its vertical position. The Hertel exophthalmometer is a good tool for measuring globe position when the lateral orbital rims are not displaced. Otherwise, devices that measure relative to the external auditory canal should be used (e.g., Naugle device).[34] Enophthalmos may also be identified clinically, either by recognizing the more posterior position of the globe or sometimes by the deepening of the upper lid crease and elongation of the upper lid. Schubert recommends measuring the anteroposterior distance from the globe to the upper brow with the patient in the supine position, because the distance increases in the presence of enophthalmos.[35] Chemosis and subconjunctival hemorrhage as well as periorbital ecchymosis are telltale signs of orbital injury. Although not universally accepted, regardless of the findings, if a periorbital fracture is identified, I believe that ophthalmologic evaluation should be performed before repair, because subtle injuries such as retinal tears may be a contraindication for surgery.

Zygomatic malposition may be visible or palpable, although if there is a large amount of swelling present, it may be obscured. The same is true of nasal fractures. The nasal septum must be visualized, because septal hematomas must be drained before they result in necrosis of the septal cartilage. A careful nasal examination may also reveal trauma to the upper lateral cartilage with resultant loss of nasal valve support. Cheek and lateral nasal numbness (V2 injury) may be the only indication of the zygomatic fracture and should alert the clinician to obtain a CT scan.

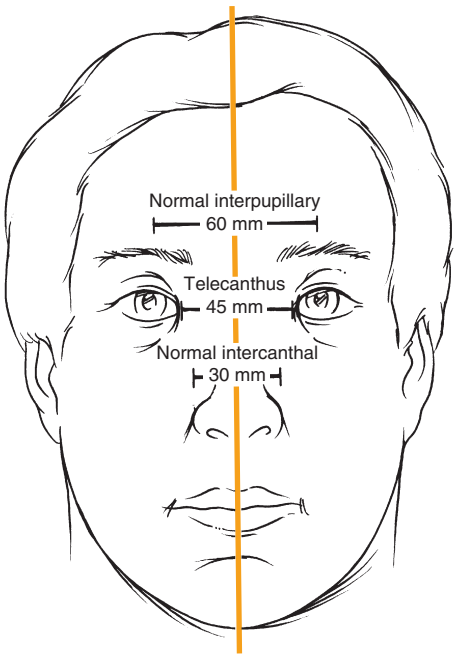

Figure 23-9. Metric relationship of normal and abnormal intercanthal distances to interpupillary distance in traumatic telecanthus. *(Redrawn from Holt JE, Holt GR.* Ocular and Orbital Trauma. *Washington, DC: American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc., 1983.)*

Telescoping fractures of the nasal, lacrimal, and ethmoid bones (so-called NEC or NOE fractures) require careful evaluation of the medial canthal relationships, and even with close study, they can still be missed. When the canthal ligament is fully avulsed (which is uncommon) or when the bone to which it attaches is completely detached (more common), the medial canthal ligament gets slowly pulled away from its natural position. It tends to displace laterally, anteriorly, and inferiorly, although the displacement may take place gradually and be missed during the acute phase. Careful assessment includes measurement of the horizontal palpebral widths and the intercanthal distance, as well as the distance between the nasal dorsal midline and each medial canthus. The two sides should be equal, and the intercanthal distance should be approximately equal to each horizontal palpebral width, both of which should be equal. It has also been described as one-half the interpupillary distance (Fig. 23-9).[36] A loss of nasal dorsal height and development of epicanthal folds are other telltale signs. Finally, direct traction on the medial canthi should be performed to test the firmness of the attachment. A bimanual examination performed with an instrument in the nose and a finger over the medial canthal area as advocated by Paskert and Manson[37] may also be attempted. Evaluation of the lacrimal collecting system is generally reserved for surgery.

Displaced or mobile fractures of the maxillae are generally assessed at the level of the dentition. A change in the patient's preinjury occlusion is indicative of a fracture in one or more of the tooth-bearing bones. Of course, evaluation starts at the teeth themselves, which if displaced will alter the occlusion. Excluding loose teeth, the teeth are carefully evaluated for mobility of the alveolar segments to which they are attached. Motion of an entire midfacial segment indicates midfacial fracture, most of which occurs at the maxillary level, even when more superior fractures are present. Pure craniofacial separation at the Le Fort III level in the absence of lower midfacial (maxillary) fractures is an extremely rare occurrence. More important than identifying the level of a midfacial fracture on clinical examination is finding evidence of its presence, which indicates the need for repair as well as careful study of the CT scan to identify all levels involved. Generally, if the teeth and

alveoli are intact, grasping the maxilla at or above the incisors and gently rocking back and forth will identify motion relative to either the nasal root or the skull above it. Note that the absence of motion does not assure that the bones are not fractured, because impacted segments may not be mobile. The presence of an anterior open bite is also suspicious, even though subcondylar mandible fractures may produce the same finding. Examination of the palate may also reveal evidence of fracture, and it is not uncommon to find mucosal tears along the paths of palatal fractures.

Lower Third

The mandible should be evaluated for sensitive areas, mucosal tears along the gingiva, and mobility of fragments. Foreshortening of a vertical ramus, deviation to that side, premature contact of the molars, and an anterior open bite may all be indications of a subcondylar fracture. Bilateral subcondylar fractures may show only the anterior open bite and bilateral premature molar contact when they are present. It is important to assess sensation in the mental nerve distribution, because postoperative numbness is not uncommon, and unless it is documented preoperatively, it would be difficult to determine whether it was due to the injury or the surgery. The patient's teeth should be assessed for fractures and other injuries such as intrusions, subluxations, and avulsions. Unless the facial plastic/head and neck surgeon is comfortable managing these, a dental consultation should be obtained.

Radiographic Evaluation

With some exceptions, the CT scan has replaced other forms of radiographic imaging for the assessment of craniomaxillofacial injuries. With the high availability of modern high-speed, high-resolution CT scanners, most maxillofacial trauma surgeons have abandoned plain radiographic imaging of middle and upper third facial bones, even as a screening tool. The numerous overlapping shadows make it easy to miss fractures that would be found on a CT scan, and the presence of a fracture would necessitate a CT scan. The exception here is for simple nasal fractures (*simple* meaning without evidence of involvement of other facial bones) that are routinely assessed using plain radiographic study (although even these may be unnecessary, in that they have little impact on management). Another exception is the use of the 6-foot AP Caldwell view for creation of a template for use in creating an osteoplastic frontal sinus bone flap.

In general, the plane of the CT (axial vs. coronal) does make a difference in how effectively selected fractures are visualized.[38,39] In a series of studies, fractures were created in fresh cadaveric heads, and these were scanned using various protocols. Dissections were then carried out to correlate the CT findings and to determine which planes of orientation yielded not only the best primary CT data but also the best three-dimensional reconstructions. It was found that axial orientation was best for visualizing most frontal fractures as well as NOE fractures and the zygomatic arches and vertical orbital walls. Coronal orientation was better for the orbital roofs and floors and the pterygoid plates. In general, as would be predicted, vertical structures were better seen on axial scans and horizontal structures were better seen on coronal scans. It was also found that scans performed at a resolution of less than 1.5 mm should not be used to make three-dimensional reconstructions, because the "fill-in" algorithms used by the computer programs created too many misrepresentations. In general, three-dimensional reconstructions create an overview picture that may help the surgeon visualize the overall facial architecture; however, they contain potential inaccuracies that are not present in directly obtained scans.

Upper Third

For frontal fractures, a high-resolution axial CT gives good information about the anterior and posterior walls (Fig. 23-10). However, in the presence of posterior wall fractures, it is impossible to determine the significance of soft tissue density inside the sinuses. When the posterior wall is displaced (regardless of the degree of displacement), and there is soft tissue density within the sinus, I recommend that the inside of the sinus be visualized (either directly or endoscopically). (We have had more than one experience in which placement of an endoscope in a sinus with minimal displacement of the posterior wall and no CSF leakage revealed brain tissue herniating into the sinus.) Displaced anterior wall fractures that require repair are commonly found on CT, even when there is no clinical evidence of cosmetic deformity. Fractures extending into the floor of the anterior fossa are best evaluated with a high-resolution CT scan.

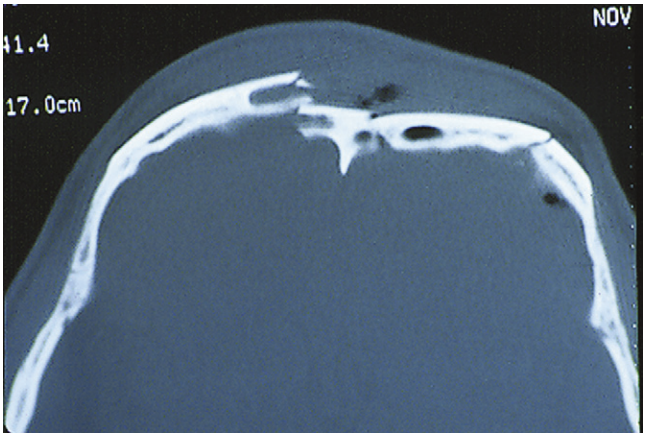

Figure 23-10. Axial computed tomography scan demonstrates markedly displaced anterior and posterior walls of the frontal sinus.

Middle Third

Simple orbital floor blowout fractures are best assessed via coronal CT scanning. However, if there is suggestion of extension into the medial wall, an axial scan (or a high-quality reconstruction from a 1.0 or 1.5 mm coronal) should be obtained as well (Fig. 23-11). In addition, for accurate orbital assessment, Schubert[35] has recommended creating a parasagittal reconstruction in the plane of the optic nerve (which actually traverses the orbit from posteromedial to anterolateral, so it is not in a true sagittal plane).

Accurate assessment of orbital wall displacement allows the surgeon to anticipate the amount of enophthalmos that is likely to result if the fractures are not repaired.[40-42] This not only helps determine the extent of orbital repair that will be necessary but also whether repair is required at all. CT evaluation of the optic canal and orbital apex take on critical significance in the presence of cranial neuropathies related to these areas. Visual loss due to trauma necessitates immediate analysis of orbital CT scans when possible, because a reversible injury causing constriction of the orbital apex may be identified.[25,26]

Whereas zygomatic fractures can be visualized on plain films, accurate assessment of displacement is best analyzed on CT scans. The status of the arch can be evaluated on plain films (so-called bucket-handle views). Although this may be adequate for simple zygomatic arch fractures (without involvement of the malar portion of the zygoma), most zygomatic fractures involve complex three-dimensional alterations in position as well as involvement of the lateral and inferior orbital walls and are best assessed with CT scans. The axial CT demonstrates shifts in the position of the zygomatic arch that may be otherwise missed in high-impact trauma in the anteroposterior direction. Careful comparison with the contralateral arch is important, as is a familiarity with the normal shape of the zygomatic arch, which is more flattened anteriorly and does not therefore represent a true convex arch.

Displacement of maxillary fractures is typically well demonstrated on axial scans. These scans also show fractures through the pterygoid plates, which help define the presence of Le Fort type fractures. However, the horizontal components of these fractures are best displayed on coronal scans (and as might be expected on three-dimensional reconstructions from the coronal scans).[43]

Lower Third

For the mandible, unlike the middle and upper thirds of the face, most surgeons prefer plain radiographs, or more commonly panoramic tomography, and often both are the imaging techniques of choice.

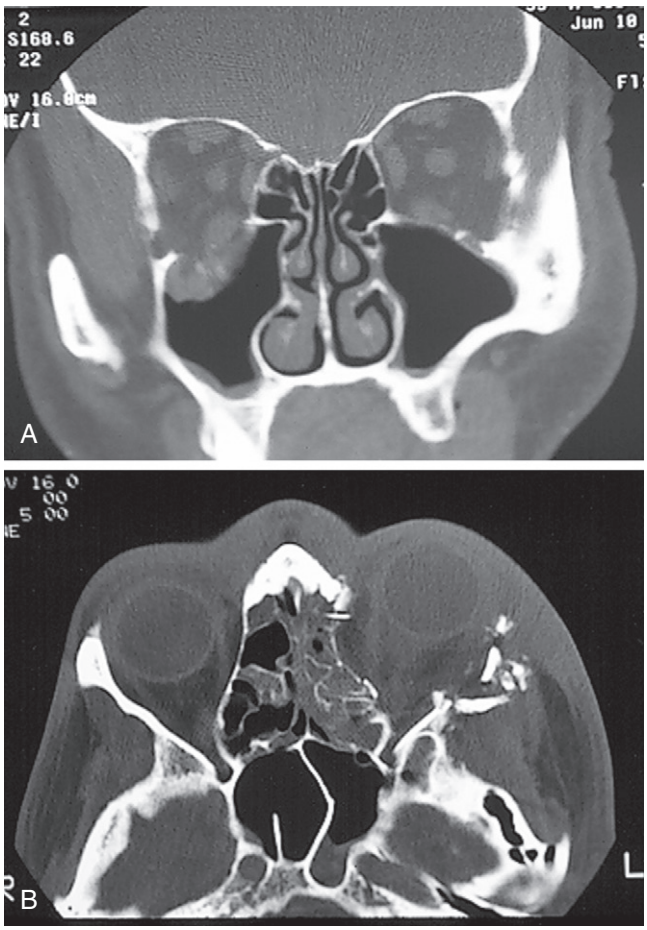

Figure 23-11. A, A coronal scan clearly demonstrating a complete blowout fracture of the right orbital floor. **B,** An axial scan demonstrating a medial orbital blowout fracture.

Several studies[44,45] have found radiographic films to be better than CT scans, although 3-mm slice resolution was used in these studies. Wilson and colleagues,[46] suggested that the addition of axial CT in 39 patients with mandible fractures revealed two parasymphyseal fractures and 15 cases of comminution or displacement that had been missed on panoramic tomography. However, the CT also missed posterior mandibular fractures, so that both were required to maximize information. However, 3- to 5-mm slice resolution was used, and this might account for the poor sensitivity of the CT scans in their series. In a subsequent study using high-resolution helical CT (1-mm slice resolution), the sensitivity for the CT scans was 100% while that for panoramic tomography was 86% (seven fractures missed in 6 of 12 patients).[47] Considering the cost disparity between panoramic tomography and CT scanning, it is unclear whether the standard of care for mandibular evaluation will change. Lee has suggested that coronal CT scanning with three-dimensional reconstruction is the procedure of choice for assessing the position of the proximal fragment in subcondylar fractures of the mandible.[6] Furthermore, he recommends a postoperative scan to assure that the reduction is accurate after endoscopic repair. This is certainly a more expensive approach than the Towne's view radiographic study, which is typically used to view the position of the condylar fragment. Additional experience will ultimately determine the most appropriate studies.

Classification Schema

Numerous classification systems have been developed and reported for the various fractures that occur in the facial skeleton. Such systems are useful for communication between physicians and are valuable for documentation purposes, particularly statistical analyses, but they should also be useful for treatment planning. However, many classification schemes fail to meet one or more of these criteria. A brief summary of some of the more widely used systems is given.

Upper Face

In the frontal area, classification schemes have focused on the involvement of the frontal sinuses, and these systems have been treatment oriented. The most useful classification, which predicts the likelihood of disruption of the frontal sinus drainage passages, was presented by Stanley and Becker.[48] They separated frontal sinus fractures into linear horizontal and linear vertical and comminuted anterior and posterior walls, with and without NEC or supraorbital rim fractures. Of interest was the finding that whenever an NEC or a supraorbital rim fracture occurred in combination with comminuted fractures of either the anterior or posterior frontal sinus walls, a ductal injury was predicted. This scheme has been modified by Gonty and colleagues,[49] but interestingly, in the commentary on this paper written by Stanley,[50] he suggests that even his own classification system is not all that useful clinically. Numerous other classification systems have been suggested, but they offer little to the planning of the treatment approach.

There are also classification schema designed to predict the incidence of CSF rhinorrhea after anterior skull base trauma. The most useful of these, which is also somewhat intuitively predictable, was reported by Sakas and colleagues,[51] who found that the more centrally located the fracture in the skull base and the more severe the fracture, the greater the likelihood of CSF leakage.

Middle Third

Numerous classification systems have been created for addressing the multiple fractures that occur in this area. Although not always applicable, the most important system is that developed more than 100 years ago by Rene Le Fort.[52] It was developed artificially by analyzing the facial fracture patterns that were seen in cadavers that were traumatized by being dropped from a height. The Le Fort I fracture, or horizontal maxillary fracture, occurs above the level of the maxillary dentition, separating the alveoli and teeth from the remaining craniofacial skeleton. It crosses the nasal septum, and posteriorly it completes the fractures through the posterior maxillary walls and pterygoid plates. The Le Fort II fracture, or pyramidal fracture, starts on one side at the zygomaticomaxillary buttress, crosses the face in a superomedial direction, fracturing the inferior orbital rim and orbital floor, traverses the medial orbit, crosses the midline at the nasal root or through the nasal bones, and then travels inferolaterally across the contralateral side of the facial skeleton, creating a pyramidal shaped inferior facial segment that is separated from the remaining craniofacial skeleton. Like the Le Fort I, it fractures the nasal septum, the posterior maxillary walls, and the pterygoid plates. The Le Fort III fracture, or complete craniofacial separation, occurs at the level of the skull base, separating the zygomas from the temporal bones and frontal bones, crossing the lateral orbits and medial orbits, and reaching the midline at the nasofrontal junction, also violating the nasal septum and pterygoid plates (Fig. 23-12). Even though many fractures seen clinically do not fit precisely into this classification scheme, it has stood the test of time, and it does prove useful for communication and treatment planning. In order to use it for documentation purposes, it is helpful to more specifically describe the nature of the particular fractures in each case. For example, the pure Le Fort III fracture is probably a rare occurrence, yet many surgeons will describe an injury by the most severe level encountered and then describe the additional components.

Numerous classification schemes have been used to describe NOE fractures. The system that is probably the most useful for treatment planning is that described by Markowitz and colleagues (Fig. 23-13).[53] In this scheme, a type I fracture occurs when a large central fragment containing the medial canthal ligament is freed from the surrounding bone. It is repaired by rigidly fixing this central fragment in place. In a type II fracture, there is significant comminution, but the fragment containing the medial canthal ligament is still repairable. However, transnasal fixation of this fragment and/or the tendon is still necessary. In type III injuries, the tendon is either detached or attached to an unusable fragment. It must be freed and directly repaired with transnasal fixation. This description shows how a useful classifica-

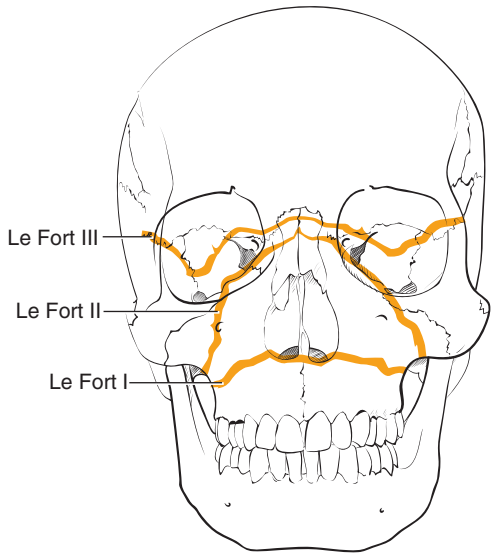

Figure 23-12. Le Fort I fracture is a horizontal fracture that separates the bone containing the maxillary dentition from the remainder of the craniofacial skeleton. The Le Fort II fracture is a "parametal" fracture, which extends across the maxilla through the infraorbital rim and orbital floor up through the medial orbital wall and across the nasal root area and then across similarly the other side. The Le Fort III fracture is the true craniofacial separation, which includes fractures of the zygomatic arches and frontozygomatic areas, then crosses the lateral inferior and medial orbits, and is completed across the nasal root. Note that all Le Fort fractures cross the nasal septum and pterygoid plates.

tion not only describes the injury but also helps in the planning of the repair.

Lower Third

Mandibular fractures are for the most part classified by the anatomic region in which they occur and by their severity. Severity typically includes simple, comminuted, or avulsive (bone loss). The mandible is also categorized as dentulous, edentulous, or atrophic edentulous. Historically, a common classification has separated so-called favorable from unfavorable fractures. In fact, these descriptions are no longer considered helpful in determining the treatment plan, and they certainly offer no documentation or communication advantages. They are thus of historical significance only.

Management

General

Once the injuries have been identified, a management plan should be developed. As noted earlier, appropriate consultations should be made, and, when necessary, the consultants should be included in the process so that the management plan is comprehensive. A piecemeal approach increases the likelihood of a less than ideal outcome and should therefore be avoided.

It is generally accepted that because most maxillofacial injuries are considered contaminated due to communication with the nose, sinuses, and/or oral cavity, antibiotic treatment should be initiated at the time the patient initially presents. A prospective study by Chole and Yee demonstrated some benefit of this approach.[54] Typically, antibiotics that cover oral organisms such as penicillins, cephalosporins, or clindamycin are selected. It is unclear how long they should be continued, but they are generally administered until at least 24 hours after surgery, although they are sometimes given for longer periods.

An issue that has generated strong opinions is that of the timing of surgery. Early reviews of mandible fractures suggested that delay in treatment increased the likelihood of infection.[55] However, since the advent of routine prophylactic antibiotic therapy, this does not seem to be true. Many surgeons have suggested that surgery should be delayed until swelling resolves so that facial asymmetries can be better assessed. However, because fractures are assessed using CT scans, this is probably not a relevant concern either, particularly because extensive soft tissue exposures recreate the soft tissue swelling anyway. More recent and cogent arguments have suggested that re-insulting the soft tissues after the acute inflammatory phase has resolved may result in a less pliable and resilient soft tissue envelope and less satisfactory healing and outcomes, although this remains more theoretical than proven. Certainly, logic seems to suggest that early intervention to restore the hard and soft tissues to their normal anatomic positions would be beneficial. However, it is not uncommon for other considerations to intervene, particularly in severe trauma in which the stabilization of the

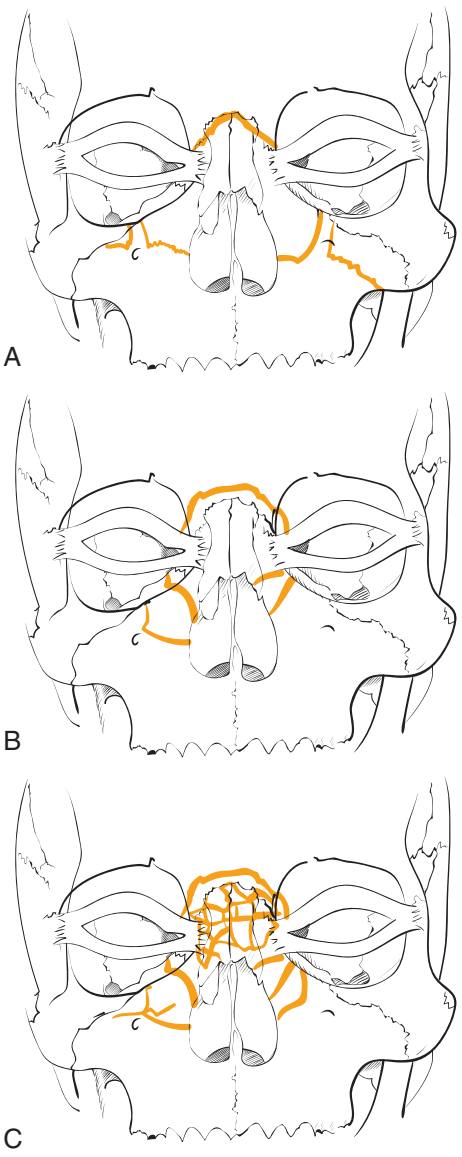

Figure 23-13. Naso-orbital ethmoid fractures have been classified as type I, type II, and type III by Markowitz and colleagues.[53] The type I fractures **(A)** include a solid central segment to which the medial canthus is attached. Type II injuries **(B)** are more comminuted than type I but still leave a central segment to which the medial canthus is intact. In type III injuries **(C)**, the bone is shattered and there is no solid bone to which the medial canthal tendon is attached. *(Redrawn from Markowitz BL, Manson PN, Sargent L, et al. Management of the medial canthal tendon in nasoethmoid orbital fractures: the importance of the central fragment in classification and treatment.* Plast Reconstr Surg. *1991;87:843.)*

patient with life-threatening injuries takes priority. Thus the level of urgency remains an individual decision.

Surgical Access

The frequent use of extended access approaches[56,57] has led to a better understanding of fracture patterns and the complexities of reduction and fixation. Combined with the use of rigid fixation techniques and the liberal use of bone grafts,[58] repair of the facial skeleton has become more dependable, and the need for postsurgical maxillomandibular fixation (MMF) and tracheotomy has been minimized.[59] However, there are also disadvantages to these wide exposures, and facial asymmetries may be seen in the presence of excellent skeletal reduction. These have been attributed to problems with soft tissue healing and redraping, leading surgeons to look for more limited access approaches that will still allow for correct bony repositioning.[60]

There is also an additional challenge in craniomaxillofacial surgery, which is the inability to make incisions directly over most fractures, because unacceptable scars and facial nerve injuries would result. Incisions are carefully planned to take advantage of sites that are either well hidden, transmucosal, or in which the scar can be adequately camouflaged. Frequently, however, this requires extensive undermining and elevation as well as significant intraoperative retraction, all of which can lead to soft tissue changes that result in a less than ideal outcome. These issues must be carefully considered when planning surgery, keeping in mind that it is sometimes wiser to extend an incision than to damage the soft tissues with overzealous retraction.

Upper Third

The workhorse of frontal and supraorbital rim exposure is the coronal incision. (Generally speaking, this incision is less obtrusive even in the bald or balding man than the bilateral brow, so-called butterfly or gullwing incision. The exception might be a unilateral brow incision in the patient with bushy eyebrows, or in the presence of a significant laceration.) In the patient with hair, irregularizing the incision with a running W or a wavy line[61] prevents the scar from parting the hair, making the scar virtually unnoticeable. However, a straight incision seems to be less visible on the bald scalp (Fig. 23-14).

Shaving the hair is not required, although creating a hairless strip makes it easier to keep hair out of the wound during surgery and wound closure (Some neurosurgeons favor a complete shave when an intracranial injury is present.) When full exposure of the zygomas is required, the incision typically begins in the preauricular crease and extends superiorly above the auricle and over the top of the head to the contralateral auricle. The incision may curve anteriorly over the central scalp to shorten the skin flap, which allows the flap to flip more easily. When zygomatic exposure is not needed, the incision starts above the auricle. When a long pericranial flap is needed (for anterior fossa repair and/or frontal sinus obliteration), the incision should not violate the pericranium. The skin can then be elevated posteriorly over the pericranium, which is then incised more posteriorly and elevated with the anterior skin flap, thus creating a long, anteriorly based pericranial flap for later use (Fig. 23-15).

As the flap is elevated anteriorly, care must be used to avoid injury to the temporal (frontalis) branches of the facial nerve. This can be accomplished by either elevating directly against the temporalis fascia or incising the superficial layer of the deep temporal fascia at the temporal line of fusion so that elevation can be continued beneath this layer. If this is done, it is critical that the fascia be resuspended at the time of closure to prevent desuspension of the midfacial soft tissues. The supraorbital and supratrochlear nerves are encountered as the flap is elevated to the supraorbital rims. When the supraorbital nerve passes through a notch, it is easily elevated inferiorly with the flap, although care must be used to avoid injuring it. When the nerve passes through a true foramen, the inferior lip of the foramen must be fractured (using an osteotome, curet, or other bone-biting instrument) to allow the nerve to move inferiorly with the flap. Orbital fat may herniate around the nerve. Elevation of the superior orbital periosteum from the orbital roof requires elevating first in a superior direction once over the rim, because there is typically an overhang of 3 to 7 mm. (Failure to recognize this may result in elevation directly into the orbital tissues.) The periosteum tends to be adherent at the nasofrontal suture, and sharp elevation may be needed here. Elevation to this level provides wide access to the upper third of the face. Elevation of this flap can also be continued inferiorly in the midline for exposure of the nasal bones, medial orbital walls, and frontal processes of the maxillas; elevation laterally provides exposure of the zygomatic arches and most of the zygomatic bones and lateral orbital walls.

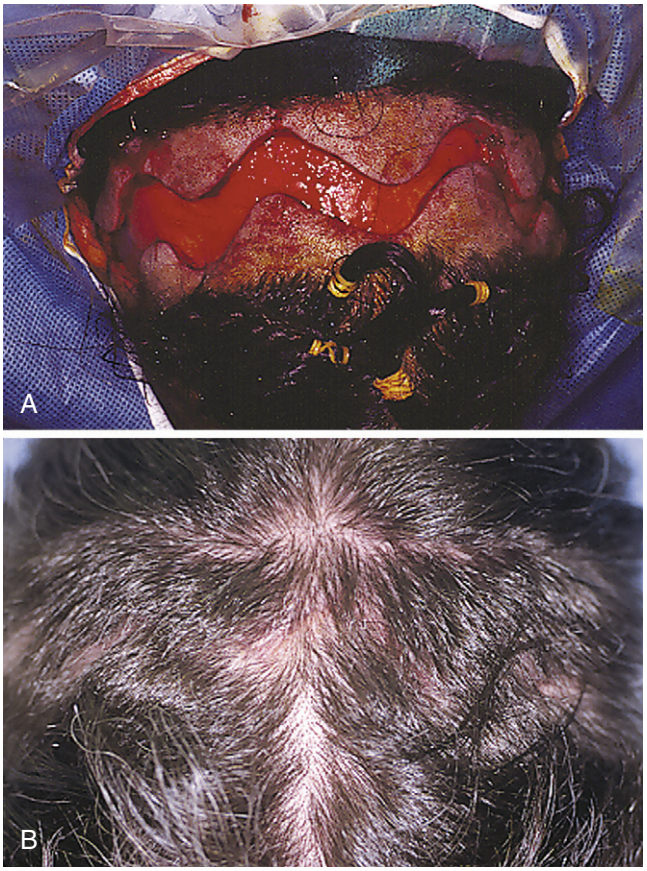

Figure 23-14. A, A coronal incision broken up by irregularization. **B,** Even when the hair is relatively short, the irregularization of the incision allows it be well hidden beneath the hair.

Middle Third

There are numerous options available to the surgeon for approaching the middle third of the facial skeleton, and the surgeon should select incisions based on the access needed to properly repair a particular injury, the ability to camouflage scars, and the surgeon's experience. Zygomatic fractures are generally repaired at more than one site, often necessitating more than one surgical exposure. As noted earlier, the zygomatic arches are well exposed via the coronal incision. A simple arch fracture, however, may be accessed via a Gillies' incision, which is made within the temporal hairline and elevated beneath the temporalis fascia (over the temporalis muscle, because the fascia inserts on the arch, while the muscle passes beneath the arch), allowing an instrument to be passed with assurance beneath the arch for elevation. Or it may be similarly approached using a transmucosal incision in the gingivobuccal sulcus intraorally. The frontozygomatic area (lateral orbital rim) may be accessed in several ways, and the facial plastic surgeon must select the most appropriate incision for the individual situation. The lateral upper lid incision (sometimes described as the "upper lid blepharoplasty incision") is commonly used (Fig. 23-16), because it tends to hide well in the upper lid crease, and it is replacing the lateral brow incision, which, though still considered acceptable by many, not infrequently leaves a noticeable scar. The lateral rim can also be reached through a lower lid conjunctival incision, when the incision is extended laterally

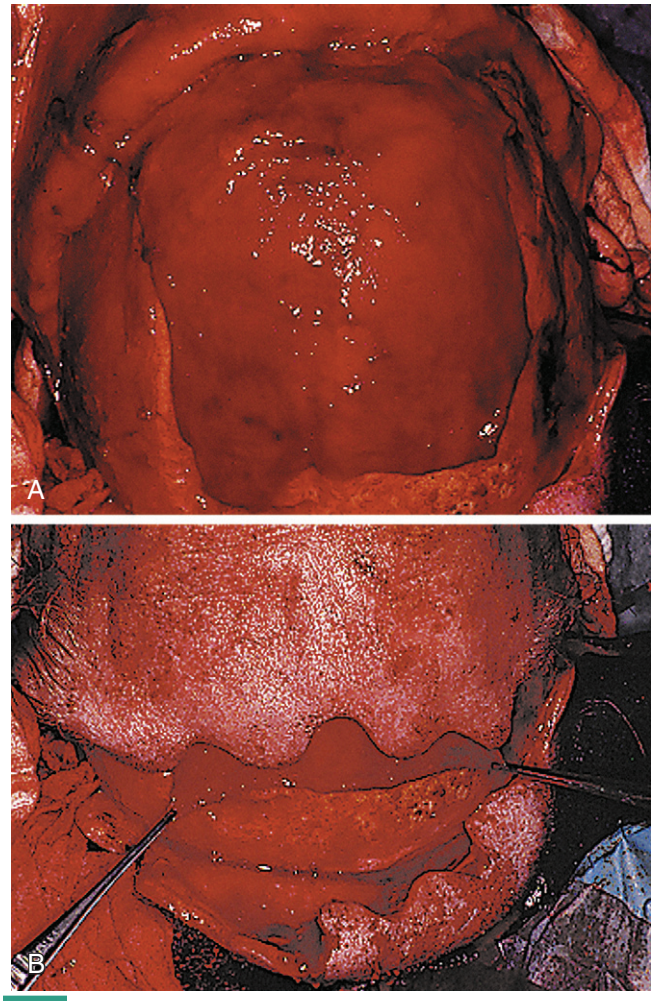

Figure 23-15. **A,** Note that the pericranium is cut posterior to the skin by elevating the posterior skin flap over the pericranium and then incising the pericranium more posteriorly. **B,** Demonstrates the longer pericranial flap made possible by this approach.

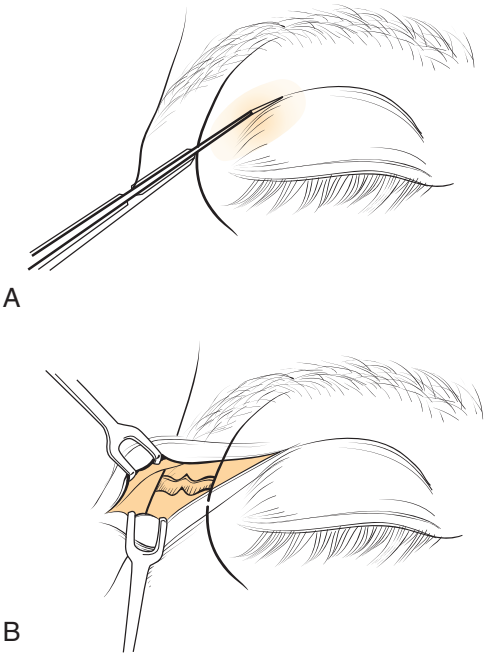

Figure 23-16. The upper lid blepharoplasty incision provides excellent access to the lateral orbital rim and lateral orbit. *(Redrawn from Bailey BJ, Calhoun KH.* Atlas of Head & Neck Surgery—Otolaryngology, *Philadelphia: Lippincott Williams & Wilkins; 2001.)*

Figure 23-17. Photograph demonstrates the fixation of a "Frost stitch." The suture is placed through the lower lid and then pulled under gentle tension over the forehead with the upper lid closed. A Steri-Strip is placed over the suture. The suture is folded back, a second Steri-Strip is placed, and then the suture is folded back upward and a third Steri-Strip is placed. This holds the lower lid under tension.

and a canthotomy is performed. However, an unacceptable amount of retraction may sometimes be required using this approach. The orbital floor, on the other hand, is well exposed via the transconjunctival incision through the lower lid. This can be performed using either a preseptal or a postseptal approach, and each has its advantages and disadvantages. Whichever approach is used, care must be taken to avoid injury to the orbital septum, because scarring in this layer tends to lead to postoperative lower lid malpositions. Extending these incisions to include a lateral canthotomy and skin incision allows wider exposure, particularly for placement of large grafts and for exposure of the medial and lateral orbits. The orbital floor can also be explored via transcutaneous incisions through the lower lid, including the subciliary and the lower lid crease incisions. The infraorbital incision has for the most part been abandoned due to limited access and excessive, prolonged lower lid swelling (except when there is already a significant laceration present). The medial orbit can be explored via a coronal incision, a transconjunctival incision (transcaruncular or retrocaruncular) or a cutaneous incision similar to an external ethmoidectomy approach. Note that whenever a lower lid incision is used, it is wise to place a Frost stitch at the end of the procedure and leave it in place for 24 to 48 hours. It is placed through the lower lid and taped to the forehead; it stretches the lower lid and may decrease the likelihood of lower lid malposition (Fig. 23-17).

The lower portion of the middle third, that is, the anterior maxillary walls, including the piriform apertures, the frontal processes, and the zygomaticomaxillary junction are best approached transorally by incising the mucosa of the gingivobuccal sulcus. Care must be taken to avoid elevating bone fragments in the flap and to avoid injury to the infraorbital nerves. This incision allows elevation superiorly to the infraorbital rims. Additional exposure can be obtained by using the midfacial degloving approach, although this does add the risk of nasal stenosis, in that the mucosa of the nasal vestibule is incised circumferentially in this approach. Palatal exposure is generally obtained through lacerations that occur along fracture lines. A U-shaped palatal flap can also be elevated for wide palatal exposure.

Lower Third (Mandible)

The mandible can be exposed either transmucosally or transcutaneously. Early concerns that intraoral exposures would lead to higher

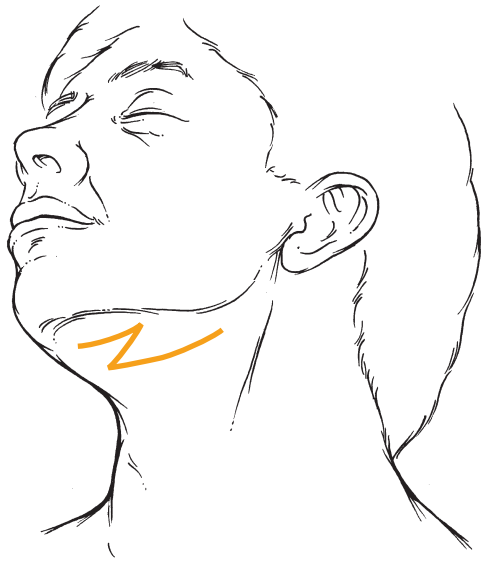

Figure 23-18. The mid body is difficult to reach through an external incision. The direction of the submental incision is different than the direction of the submandibular incision. Sometimes greater length can be obtained by combining these two incisions in a Z-plasty fashion.

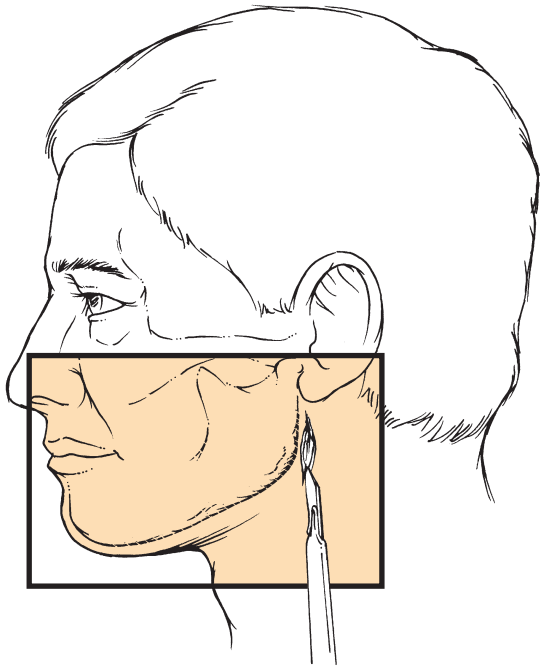

Figure 23-19. Vertical incision just posterior to the mandible through skin and subcutaneous tissue to the depth of the platysma muscle. *(Redrawn from Ellis E III, Zide MF.* Surgical Approaches to the Facial Skeleton. *Philadelphia: Lippincott Williams & Wilkins; 1994:143.)*

infection rates have not proved true in large experiences.[62] Virtually all areas of the mandible can be reached via transoral incisions. The symphyseal region is easily exposed using an incision that is placed 5 to 10 mm below the gingival margin, thereby leaving enough free mucosa for easy wound closure. Body fractures can be similarly exposed. Care must be used to avoid injury to the mental nerve as it exits the mandible and enters the soft tissues to supply sensation to the overlying skin. The angle region is best exposed using an incision that begins at the inferior portion of the anterior ramus of the mandible. This is extended over the oblique line and carried below the gingival margin of the posterior molars. Finally, the vertical ramus and subcondylar regions are exposed using the vertical portion of this last incision and extending it superiorly. Exposure of the subcondylar region is enhanced with the aid of endoscopes.[5-7]

Extraoral incisions add the risk of a visible scar as well as the possibility of injury to the mandibular ramus of the facial nerve. On the other hand, for anterior body fractures, the risk of injury to the mental nerve may be decreased. The symphysis is best approached using a submental incision. The posterior body, angle, and even the subcondylar regions are best approached using a submandibular incision. To aid bone exposure and minimize retraction, the incision may be made one fingerbreadth or less below the mandible and elevated inferiorly superficial to the platysma. The platysma is incised two fingerbreadths below the mandible to minimize the risk to the facial nerve (Fig. 23-18). The anterior body is more difficult to reach transcutaneously, because the relaxed skin tension lines cross the mandible and risk injury to the facial nerve. This area is probably best approached by combining a submental incision with an anterior submandibular incision and connecting them via a Z to minimize the scar. The ramus and subcondylar regions can be approached via the submandibular incision and elevating between the masseter muscle and the bone. Alternatively, a retromandibular incision may be used as advocated by Ellis (Fig. 23-19).[63] A preauricular incision may be used, but this may increase the risk of injuring the main trunk of the facial nerve, and if a preauricular approach is used, a facial nerve dissection should be considered for protection of the facial nerve.

Bone Healing

A cursory introduction to bone healing is included here from the standpoint of the interaction between repair techniques and the way that bone tends to heal. In general, like other injured tissue, bone tends to heal. The process begins almost immediately after injury with the development of a fracture hematoma. Subsequent ingrowth of vessels brings fibroblasts and other progenitor cells. There is a differentiation to chondroblasts, and these lay down fibrocartilage and chondroid matrix, which lead to early stabilization and provide the substrate for the development of osteoid. With differentiation into osteoblasts, osteoid is deposited, resulting in callus formation. It is helpful to think of callus as nature's fixation device, in that callus is deposited until motion ceases at the site of the fracture. Once motion ceases, delicate osteons, each with their own delicate vessels, can grow across the fracture, resulting in the bridging of the fracture by new bone and thus full stabilization and healing.[23,64] Once the fracture is bridged by bone, the bone form can then be remodeled to match its function according to Wolff's law, which says that bone remodels according to the forces acting on it. This results in a re-creation of proper form to match function. This process tends to be very effective for long bone healing.

Unfortunately for the craniomaxillofacial surgeon, Wolff's law fails to account for two key needs of the facial skeleton: aesthetics and dental function. Thus, allowing facial bones to heal on their own tends to result in both significant cosmetic deformities and compromised masticatory function, which can also have significant implications for nutrition. Even though the tooth-containing bones will indeed remodel in response to the forces that act on them, they will not remodel to re-create a proper and functional occlusal relationship between the maxillary and mandibular dentition. It is therefore critical that these fractures be managed in a way that will guide the healing process to re-create both satisfactory form and proper function.

There are two aspects to consider in performing these repairs. One is as noted the proper realignment of the bones to re-create aesthetic form and occlusal function. The other is methodologic and refers to the type of fixation accomplished, rigid fixation, which is designed to maximize the amount of stability created at the time of repair to minimize callus formation, infection, and any shifting in the surgical positioning. Rigid fixation refers to the use of devices (typically plates and screws) that fix the positions of the bones firmly enough to prevent motion of the fragments, even in the presence of functional loading. When properly accomplished, this type of fixation minimizes the development of callus (which may be cosmetically deforming), minimizes

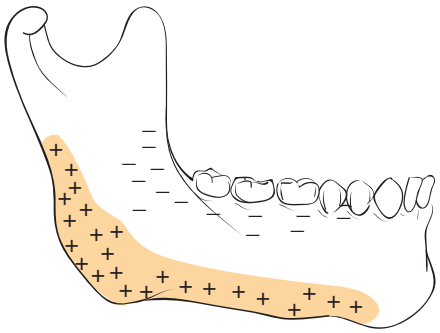

Figure 23-20. Oversimplified depiction of the tension and compression areas created in the mandibular body when force is directed along the anterior mandible by placement of a bolus between the anterior dentition of the mandible and maxilla.

infection, and allows for immediate function, thereby avoiding the need for MMF.

Bone healing via the differentiation cascade described earlier has been referred to as *indirect* or *secondary* bone healing to distinguish it from *direct* or *primary* bone healing, which only occurs when there is no motion across the fracture line.[23] It appears that the bridging of a bony gap by bone can only occur in the absence of motion across that gap. The more motion that is present, the greater the amount of callus needed to stabilize the fragments so that healing by bone can eventually occur. Conversely, the more stable a repair and thus the less motion, the less callus that will form and the greater the likelihood that bone will directly bridge the fracture and heal the injury. It follows that when callus is unable to stabilize a fracture, bone will never form; the fracture remains bridged by fibrous tissue, thus forming a fibrous union, alternatively known as a *nonunion, fibrous nonunion,* or *pseudoarthrosis* (see Complications). To accomplish a stable repair, it is necessary to understand the biomechanics of the facial skeleton, and even more important, it is critical to use this understanding when applying fixation. Otherwise, motion tends to occur when the repair is loaded in function, and complications are then more likely to occur.

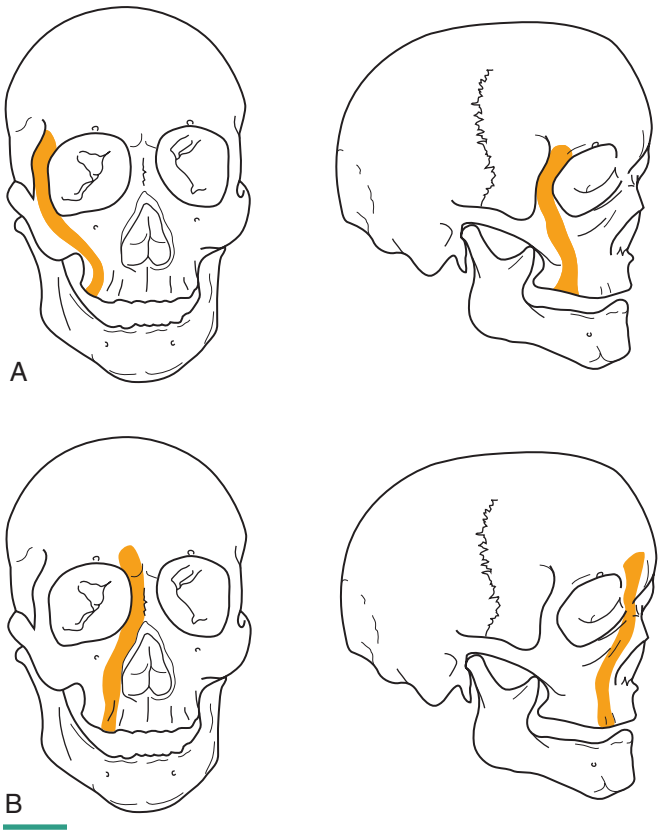

Figure 23-21. A, The lateral vertical buttress of the midface extends from the frontal bone along the frontozygomatic area down across the strong bone of the zygomaticomaxillary area. **B,** The medial vertical buttress extends from the frontal bone across the frontonasal region and down across the nasomaxillary junction encompassing the thick bone of the piriform aperture.

Biomechanics of the Facial Skeleton

The forces acting on the facial bones are complex and not yet fully elaborated.[65] However, the current level of understanding provides enough information to guide rigid repair techniques that can result in a high success rate. On the other hand, disregarding these principles will likely result in higher than acceptable complication rates.

As discussed, the facial form is designed to support its function and to serve as a buffer to protect more critical organs from traumatic injury. Areas that support function must have strength along the paths of force. In the midface, these have been variously called *pillars* and *buttresses*, and these areas support the facial architecture during the powerful acts of biting and chewing.[65-67] It is particularly important to reestablish these buttresses when they have been fractured. Furthermore, these buttresses are separated by areas of weakness, which seem to facilitate their acting as "crumple zones." The mandible provides support to the dentition during biting and chewing. Because this bone swings from the cranium, forces generated when a bolus of food is compressed between the teeth result in a fulcrum effect that generates tension and compression zones in various areas (Fig. 23-20). These must be considered when repairing fractures, because the repairs must overcome both the forces exerted by muscular contraction and the forces created by particular functions such as chewing.

Upper Third

In the upper third, the anterior wall of the frontal sinus is thin, in that it merely provides cover to the sinus itself, and there are no significant forces acting on this area. This can be considered when planning the repair. As long as the bones are held in position, a satisfactory outcome should result. The supraorbital rims, on the other hand, and the frontal bones lateral and superior to the frontal sinuses are thicker, providing protection for the orbital contents and the anterior fossa contents, respectively. It requires more force to fracture these bones, and they are therefore more likely to be impacted and difficult to reduce. Still, there are no significant functional forces acting on these bones.

Middle Third

The middle third is more complex. The so-called pillars or buttresses accept the high forces of mastication without fracturing. These "vertical" buttresses have been described as lateral and medial on each side, as well as posterior (Fig. 23-21). The lateral buttress passes from the molar regions superiorly along the zygomaticomaxillary suture, through the solid malar eminence, then up along the lateral orbital rim and the frontozygomatic suture into the frontal bone. The medial buttress passes from the canine region superiorly along the solid bone that borders the piriform aperture, then superiorly along the solid frontal process of the maxilla into the frontal bone. As Rudderman and Mullen[65] point out, the goal of repair is to reconstruct "load paths," so that the bone can once again support the loads for which it was designed. In the middle third, this requires reestablishment of these four vertical buttresses, which support the impact forces of mastication. There is an additional posterior vertical buttress that transmits forces via the pterygoid plates to the skull base, but little attention is paid to this buttress because there is no access to repair it.

The horizontal buttresses of the midface serve as the connectors across the vertical buttresses. These occur at the palate, incompletely across the central face from malar eminence to malar eminence along the infraorbital rims (incomplete because this horizontal strut is incomplete across the piriform aperture), and across the frontal bar. These buttresses are primarily important to the facial surgeon for reestablishing the correct facial architecture. There is also the third dimension

from anterior to posterior, and the only reconstructible buttress in this direction passes from the temporal root of the zygomatic arch anteriorly to the malar eminence on each side.

The zygoma forms an important attachment for the powerful masseter muscle. To support the function of this muscle, the bone needs to be solidly attached; yet in order to crumple, it also has to be able to give in response to a traumatic force. The multiple attachments of the so-called zygomatic "tripod" make this possible. Whether it is considered a tripod or quadrapod matters little; what is important is the nature of its attachments. The malar eminence is quite solid, but its attachments to the surrounding bone are less so. The zygomatic arch is quite thin, as is the inferior orbital rim. The lateral orbital rim is quite solid, and it is not uncommon for zygomatic fractures to be hinged from this attachment. The attachment to the remainder of the maxilla is broad (and continuous with the inferior orbital rim, thereby allowing the tripod nomenclature to make sense). Whereas the bone is relatively solid vertically to support the forces of mastication, it is actually thin bone that gives easily to a more horizontally or obliquely directed force. Repair requires stabilization of the zygoma in three dimensions. Traditional repairs focused on the most solid fixation point, and it was not uncommon for zygomatic fractures to be repaired with a single wire at the frontozygomatic fracture. The validity of this repair was called into question years ago,[68] and more recent data have suggested that multiple fixation points are required to maintain the three-dimensional position of the zygoma against the strong masseteric pull.[69] More recent repair techniques have focused on the zygomaticomaxillary buttress, because this is usually the mobile area, rather than on fixing the hinge point, which tends to be the frontozygomatic area.

The bony orbit serves as a support for the orbital contents. Thus for the orbit the only biomechanical concerns are the reconstitution of the orbital shape for proper positioning of the orbital contents. This assures proper globe position, which is necessary both cosmetically and functionally. The orbital reconstruction must be strong enough to support the orbital contents.

The central facial area includes the attachments for the medial eyelids and the projection of the nose. The medial eyelids are attached by the medial canthal ligaments to the solid lacrimal crests. When these are disrupted, the tendons are pulled laterally (as well as anteriorly and inferiorly), and the horizontal length of the eyelids is shortened. This needs to be reconstructed adequately to withstand the constant lateral tension of the lids. Otherwise, an unsightly appearance is likely, and poor function of the lacrimal collecting system may result as well. Reconstitution of the nasal bones is important both for nasal function and cosmesis.

Lower Third

As noted earlier, while the dental portions of the mandible occupy the lower third, the vertical rami of the mandible are included in this discussion as well. The normal adult mandible is a strong, solid bone that contains the mandibular dentition. Numerous muscles attach to the mandible, and forces are developed across the bone when these muscles contract, even in the absence of mastication. (This is important, in that forces continue to act across the mandible when a patient is in MMF.) The mandible supports the tongue and the hyoid, structures important for swallowing and airway function. However, the most significant forces across the mandible are developed during mastication, and the forces acting on a given area of the mandible vary depending upon the location of a food bolus between the teeth.

Early explanations of mandibular biomechanics assumed a simple beam with forces along the top of the beam always creating tension zones superiorly (toward the alveolar surface) and compression zones inferiorly. This concept was introduced in Europe almost simultaneously by Spiessl[14] in Switzerland and by Champy and colleagues[17,19] in France. Interestingly, however, these two maxillofacial surgeons developed two entirely different repair techniques to overcome these forces, and two competing schools of thought developed as a result. Those who followed Spiessl and the Arbeitsgemeinschaft fur Osteosynthesefragen (AO) used compression plating techniques to repair most mandible fractures, and those who followed Champy used so-called

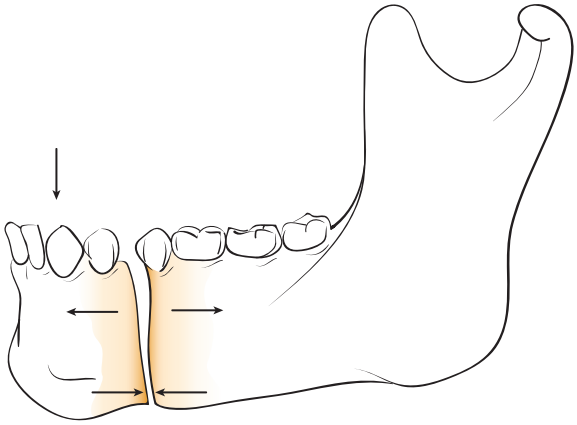

Figure 23-22. When force is applied anteriorly along the dental surface, the posterior portion of the mandible was held in place by the mandibular musculature. This results in a compressive force being generated along the inferior border while the superior border is distracted (an area of tension). *(Redrawn from Kellman RM, Marentette LJ.* Atlas of Craniomaxillofacial Fixation. *New York: Raven Press; 1995.)*

miniplating techniques. Today, it has become apparent that there is room for both of these concepts, and it is more important to understand the biomechanics of fracture repair and to select a particular technique that has the highest likelihood of success in a given situation.

In the simple beam model, a fracture of the mandibular body is distracted superiorly (the tension zone) and compressed inferiorly (compression zone) when a force is applied to the dental surfaces anteriorly (e.g., chewing a bolus between the incisors) (Fig. 23-22). In this situation, controlling the tension zone results in a maintenance of reduction. Furthermore, when a force is applied by chewing anteriorly with the tension zone controlled, the compressive force in function is distributed across the length of the fracture. Once this is clearly understood, a variety of repair options become available to the head and neck surgeon. However, certain limitations created by the unique aspects of mandibular anatomy must first be overcome. These are the presence of tooth roots within the bone and the presence of the inferior alveolar nerve within the bone. Because it is important to preserve these structures uninjured, certain areas of the mandibular bone become unavailable for the placement of fixation appliances. Both Champy and Spiessl came to the same conclusions regarding the need to control the tension zones without injuring vital structures, but they solved the problem of avoiding the teeth and nerves in different ways. Champy chose to control the tension zone with small ("mini") plates positioned carefully between the tooth roots and the inferior alveolar nerve using screws that pass through only one bony cortex, thereby minimizing the risk to the teeth and nerve in case the placement is imperfect. Spiessl shunned the use of these small plates with monocortical screws and instead used a well-placed arch bar across the dentition to control the tension zone and a larger compression plate using bicortical screws placed below the inferior alveolar nerve to maximize the amount of stabilization. The larger, compressive fixation was believed to be necessary in that it was being placed in a position that was actually biomechanically disadvantageous. However, using this approach, it is absolutely critical that the tension zone be controlled first; otherwise, the compression plate on the inferior mandible will distract the alveolar portion of the fracture. Ultimately, as it became clear that both of these techniques had high success rates, the battle between the schools of thought dissolved, and it is now clear that as long as biomechanical principles are properly followed, high success rates should be expected.[70]

Unfortunately, not all aspects of mandibular function follow this simple beam model. There are also irregularities of the mandibular bone that make some areas potentially more unstable than others. There appears to be greater potential for torque and rotational motion in the symphyseal region, so that when using miniplates, two are

required to obtain a stable fixation in this area. A single miniplate appears to be adequate along the mandibular body, as long as the patient does not chew on the side of the fracture during the healing period. The angle region presents some particular problems, and it is the region in which the highest number of complications has always been noted.[71,72] The angle region has thick bone superiorly and thin bone posteroinferiorly. There is often a tooth in the thick superior bone, and its presence may weaken the bone, but extracting this tooth (which may be unavoidable in some cases) tends to weaken the area even more. Furthermore, there is no dentition behind the fracture, so an arch bar lends no support to the repair. The complexity of forces acting on this area adds another challenge. It was first noted by Kroon and coworkers[73] that depending upon where a bolus of food was placed along the mandibular dentition, the location of the compression zones and tension zones at the angle actually varied so much that the inferior area could change from compression to tension and vice versa. (Rudderman and Mullen[65] confirmed this finding for other areas of the mandible as well.) The repair of the angle area remains controversial, but most authors agree that, although more difficult, time consuming, and demanding to apply, the larger, longer, mandibular reconstruction plates[71,74] offer the most dependable repairs and the highest overall success rates. On the other hand, the desire to use easier and simpler techniques has resulted in a pushing of the envelope, and Potter and Ellis have recently advocated the use of a single 1.3-mm miniplate placed intraorally along the oblique line of the mandible as adequate fixation for mandibular angle fractures.[75] A more recent report by Fox and Kellman[76] suggests that when using miniplating techniques to repair mandibular angle fractures, two miniplates are best (and they should probably be 2 mm), as has been previously suggested by Levy and colleagues,[72] as well as by Kroon and colleagues.[73] In a recent prospective study, Siddiqui and associates found no significant difference in complications when using one or two miniplates to repair mandibular angle fractures.[77]

Another important aspect of mandibular biomechanics is the role that the vertical ramus plays in establishing facial relationships. When the midface is shattered, the vertical rami of the mandible become the only determinant of the correct facial height. Therefore, it is critical that these buttresses of facial height be reestablished before attempting to reposition the crushed midfacial bones.

Fracture Repair

The key to fracture repair is an understanding of the biomechanical principles described, along with the various aspects of evaluation and access outlined earlier. Applying all of these principles should allow the surgeon to analyze the injuries, plan the repair, and execute it. The following description addresses some of the controversies and sequencing issues that the surgeon faces in managing these patients.

Most repairs are performed using titanium plates and screws, although a variety of absorbable plates and screws are used as well. These are generally polyester polymers containing polylactic acid (PLA), polyglycolic acid (PGA), or a variety of mixtures of these and a few other polymers. They degrade primarily via hydrolytic scission, and their byproducts are for the most part well tolerated by the human body. However, there is no contraindication to the use of stainless steel wires when needed, and repairs using such wires have stood the test of time.

Occlusion

In any maxillofacial trauma that involves tooth-bearing segments, it is essential that the proper occlusal relationship be reestablished. This is important for the restoration of normal masticatory function. The occlusal relationship between the maxillary and mandibular dentition also determines the relationship between the bones of the lower central face. Direct alignment of bone fragments virtually always takes second place to alignment of the occlusion. This is particularly true when the middle third of the face is collapsed, because the mandibular height is used to reestablish facial height, and the occlusion is a key component of the relationship between the mandible and the maxilla.

Occlusion is best reestablished using arch bars, which are pliable metal bands with hooks for wires or rubber bands that are wired directly to the teeth. The most common arch bar in the United States is the Errich arch bar. Other options include Ivy Loops, although these only stabilize a few teeth rather than the entire dental arch. They also do not provide tension banding across the mandibular dental arch. A variety of other options are available as well. A recent innovation has been the use of screws for MMF. Even though these can be placed quickly and easily, there are several disadvantages, the most common of which is the frequent penetration of tooth roots when placing them (Fig. 23-23).[78] All arch bars tend to pull the dentition lingually, but the more inferior and buccal positioning of the screws when screw-MMF is used tends to increase this tendency.

Figure 23-23. Orthopantomographic x-ray film of a mandible. Arch bars replace the IMF screws. Note the presence of multiple holes in mandibular tooth roots created by the placement of the IMF screws. *(Courtesy of Dr. Michael Ehrenfeld, Munich, Germany.)*

Once arch bars have been placed, they can be used to hold the patient in MMF. This is done by placing wires or rubber bands between the hooks on the upper arch bar and those on the lower arch bar. After rigid fixation of all facial fractures is completed, the MMF can be released, but the arch bars should be kept in place in case training elastics are needed during the healing period. MMF does not correct a malocclusion that is the result of rigid fixation of fragments in suboptimal positions; only replating the fragments corrects such malpositions. MMF may also be needed for management of unfixed fractures, such as subcondylar fractures of the mandible.

Upper Third

A number of algorithms have been published regarding the management of frontal, particularly frontal sinus, fractures. While each has its merits, they tend to be somewhat complicated. Instead, a more simplified approach is presented here. The key issues in frontal sinus trauma relate to two fundamental questions: (1) Is exploration necessary? (2) Is obliteration necessary? The answers require the use of surgical judgment, but certain guidelines are logical.

Keep in mind the purposes of the bone being repaired. The anterior wall needs to be repaired for cosmetic reasons. The posterior wall needs to be managed to protect the anterior cranial fossa. The sinus outflow tracts must function to drain the sinuses, or the sinuses must be obliterated; otherwise chronic infection will result. Thus pure anterior wall fractures that do not extend into the nasofrontal ducts are repaired for cosmetic purposes only. These should be explored if they are significantly depressed, because even in the absence of acute deformity, they are likely to lead to deformities when the swelling resolves. The smallest plates available are generally used, and absorbable plates may work well in this area as well, because there are little or no force demands on the repair. Comminuted fragments may be pieced together and "lagged" with single screws to a plate that bridges the defect, or small fragments can be pieced together with small plates and/or wires. Use of the endoscope may allow repair of selected anterior wall fractures with minimal incisions. These techniques are currently in their infancy, and they are likely to become more prevalent as new instruments are developed to simplify the procedures. When the ducts are involved but the posterior wall is intact, judgment allows more than one option. Frontal sinus obliteration is always acceptable, but it is also reasonable to allow the sinus to function to see what happens. If the sinus becomes

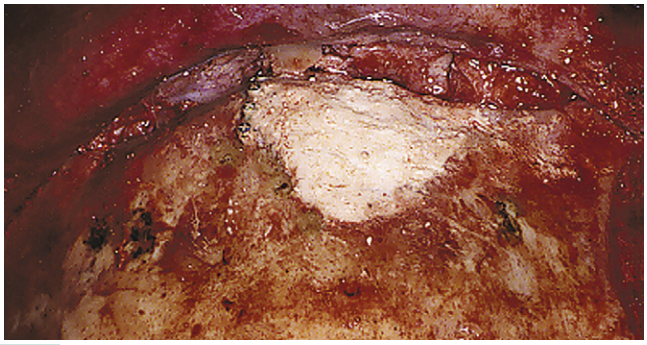

Figure 23-24. The anterior frontal sinus wall was unilaterally severely comminuted in this patient. The sinus was therefore obliterated using hydroxyapatite cement, which was simultaneously used to create a satisfactory contour.

obstructed and acute or chronic sinusitis develops, the sinus can be opened endoscopically, or obliteration can be carried out at a later date.[79] In the absence of posterior wall injury, nothing should be lost by this approach (as long as appropriate follow-up of the patient is assured).

The presence of posterior wall injury complicates the questions. A nondisplaced posterior wall fracture that does not demand exploration for ductal injury or for anterior wall displacement can be observed. However, if the posterior wall is displaced, it is difficult to determine the status of the dura and underlying brain. In the absence of apparent ductal injury, it is still wise to consider trephination and transcutaneous endoscopy, because unexpected herniation of brain into the sinus has been observed using this approach. (The dictum about a wall width of displacement has little meaning in this regard.) In the absence of posterior wall displacement and with no soft tissue abnormalities associated with such a nondisplaced fracture, it is unclear that obliteration is mandatory, even in the presence of ductal injuries. Careful follow-up including interval CT scans will demonstrate whether or not aeration of the sinus ensues. If chronic obstruction persists, then obliteration should be carried out. The choice of obliteration technique includes several options, and most seem to work. Fat has certainly withstood the test of time, as has bone and even leaving the sinus empty (after careful obstruction of the ducts with fascia) to allow for osteoneogenesis.[80-84] Numerous complications have been encountered using hydroxyapatite cements,[85,86] but in one series using it in combination with live pericranial flaps, no complications were seen.[87] The cements do offer the unique advantage of contourability, so they can be used to repair the frontal contour in the presence of severe comminution and/or bone loss of the anterior wall (Fig. 23-24).

Finally, the option of obliteration via cranialization, that is, the complete removal of the posterior sinus walls, is reserved for cases in which the posterior walls are severely comminuted. Donald and Bernstein[88,89] use this technique extensively whenever the posterior wall of the frontal sinus is involved in trauma. On the other hand, Schulz[90] believes that obliteration of the frontal sinuses is never necessary. If the sinus is to be obliterated anyway, it seems logical that the additional layer of the posterior wall adds another barrier between the contaminated nasal cavity and the anterior fossa and should be reconstructed and preserved if possible.

CSF Rhinorrhea

In the presence of severe trauma with fractures of the anterior fossa, CSF rhinorrhea is not rare and may occur via the frontal sinuses, or through the cribriform plate, ethmoid sinuses, and/or sphenoid sinuses. Large defects should be repaired at the time of facial fracture repair. Small defects should be identified endoscopically and can usually be repaired using this approach. Careful examination of defects is important, because a transient leak may have stopped as a result of herniated brain, and late complications such as meningitis or death may occur if these are left untreated.[91]

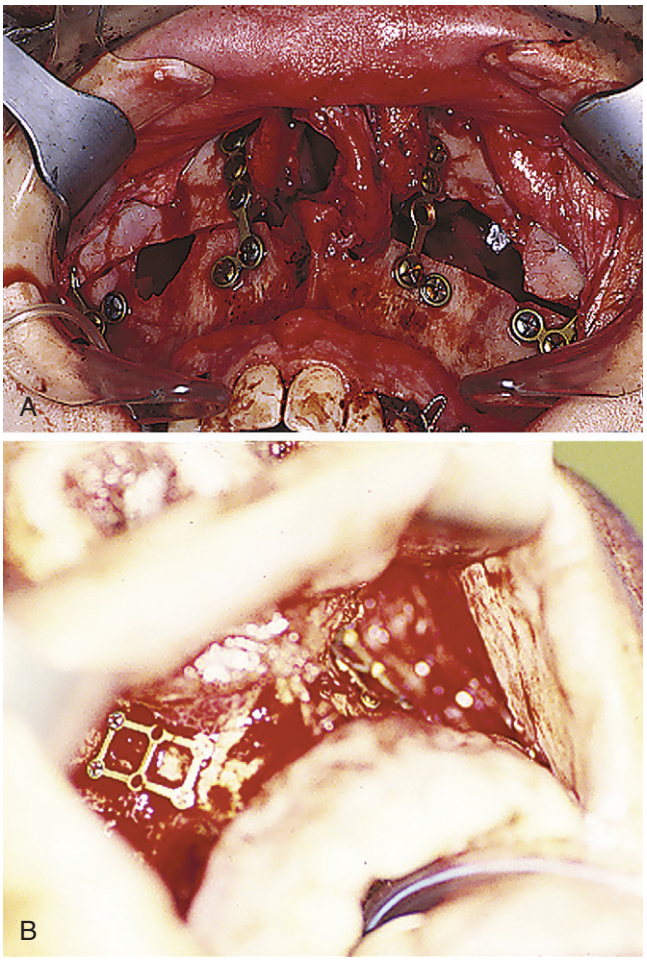

Figure 23-25. A, This is an example of a planned Le Fort I osteotomy repaired using L and J plates. **B,** An alternative repair using 1-mm box plates. The geometric shape of these plates adds additional strength to the repair.

Skull Base Disruption

In the presence of severe disruption of the anterior skull base, brain injury and CSF rhinorrhea are common. The best way to address these injuries is in collaboration with the neurosurgeons. The presence of brain injuries often lead to delays in management of the facial fractures and may actually increase the risk of meningitis. There is good evidence that the longer a CSF leak persists, the greater the risk of meningitis.[51,92] Therefore, earlier intervention may decrease the risk of such complications. The use of the transglabellar subcranial approach may allow for earlier intervention, in that it allows more direct access to the anterior fossa floor without the need for significant retraction of the frontal lobes.[93-96] It also allows direct visualization of the cribriform area without disarticulating it completely, so that many anterior fossa floor injuries may be repaired without completely sacrificing olfaction. The anterior fossa may be segregated from the nasal and sinus cavities, and the facial fractures may be repaired earlier, hopefully leading to better outcomes in these severely injured patients.[93]

Middle Third

Fractures that involve tooth-bearing segments are first stabilized at the level of the occlusion. Horizontal fractures above the occlusal level (Le Fort I) are repaired by reestablishing the four vertical buttresses, two medial and two lateral. Most surgeons repair these fractures using 1.5- to 2-mm L and J plates (Fig. 23-25), although other combinations and sizes may be used. It is important to ensure that two screws are placed on either side of each fracture plated, although more can be placed as long as tooth roots are not violated. The key is to fix these in the direc-

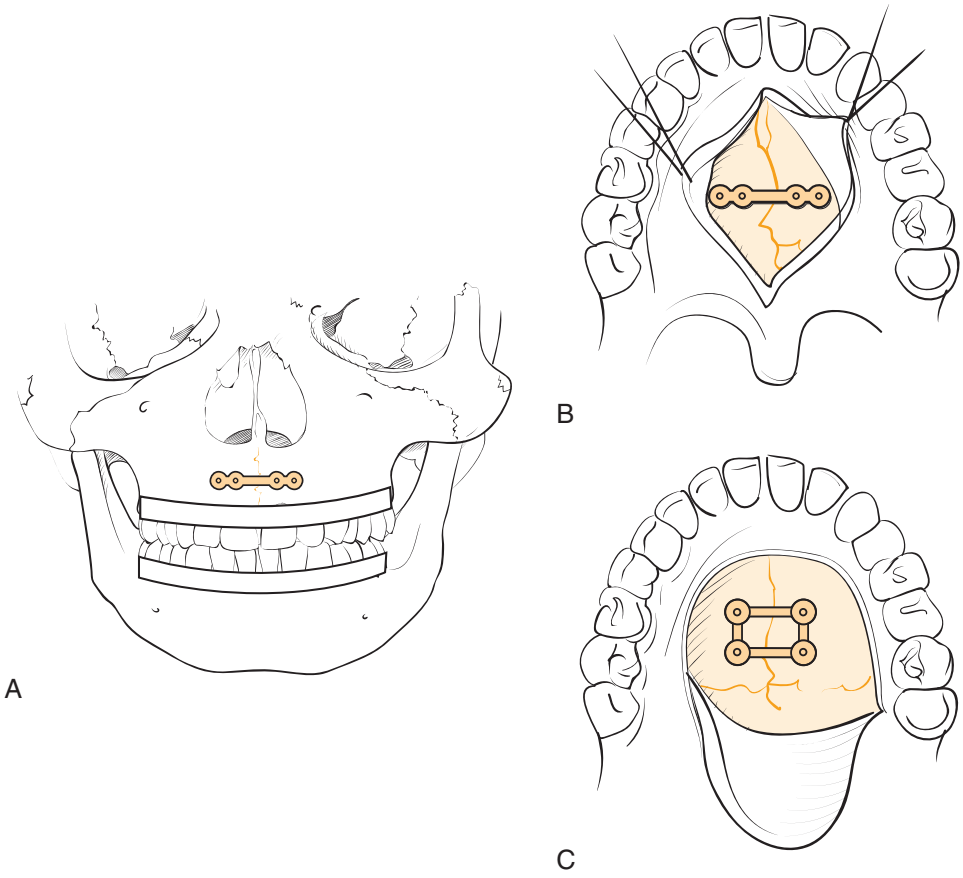

Figure 23-26. **A,** This demonstrates the repair of a split palate by the placement of a plate across the fracture in the anterior maxilla. **B,** This demonstrates direct placement of a plate along the palatal fracture. **C,** Similar to **B,** this demonstrates the use of a box plate to lend greater stability to the palatal fracture repair. *(Redrawn from Bailey BJ, Calhoun KH.* Atlas of Head & Neck Surgery—Otolaryngology. *Philadelphia: Lippincott William & Wilkins; 2001.)*

tion of the forces of mastication, so that chewing will not be likely to disrupt the repair.[65]

When the palate is fractured, it is important to ensure that the teeth have not rotated around the palatal fracture, which would result in lingual or buccal version of the teeth and a significant malposition of the bone fragments. In cases of severe disruption, particularly when alveolar segments are fractured and/or the mandible is similarly disrupted, a palatal splint may be needed to stabilize the dentition in the proper position. The palate may be repaired directly with a plate, or it may be stabilized along the premaxillary area if the occlusal stabilization is adequate to prevent rotation (Fig. 23-26).

Maxillary fractures at the Le Fort II level are similarly stabilized using 1.5- to 2-mm plates, again ensuring that at least two screws are placed on either side of each fracture plated (Fig. 23-27). A plate may be placed along the infraorbital rim to stabilize the upper portion of these fractures. Otherwise, when accessed, the nasal root should be rigidly fixated using very small plates (Fig. 23-28). It is critically important to be certain that the midface is not impacted and rotated superiorly before fixing the bones in place. Although MMF is applied first, it is actually possible to pull the patient into what appears to be good occlusion even though the midface is impacted; the mandibular teeth are pulled by the MMF toward the superiorly rotated maxilla, pulling the mandibular condyles out of the glenoid fossae. A patient may even remain in what appears to be good MMF for a full 6 weeks or longer, and when the MMF is released, the mandible returns to its neutral position revealing a significant anterior open bite. It is therefore important to recognize this at the time of surgery, so that the midface can be properly rotated downward into the correct position. If it is severely impacted, the Rowe midfacial disimpacters may be required to mobilize the midface and bring it down into its proper

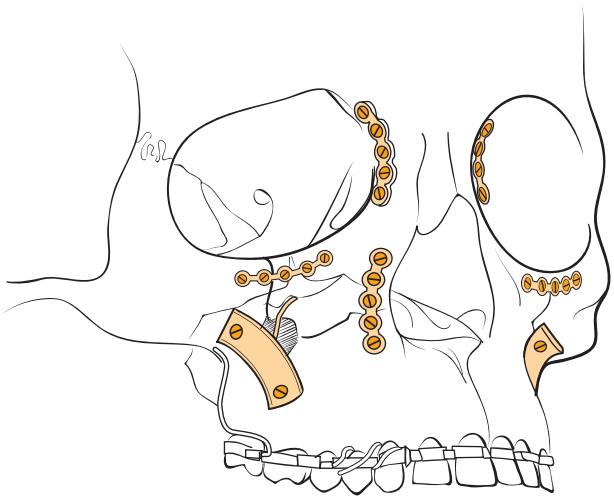

Figure 23-27. Diagrammatic representation of rigid fixation of Le Fort I and II level fractures with miniplates. Note that the right maxillary defect is repaired with a bone graft. The bone graft is lagged to the bone on either end so that the bone graft itself functions as the rigid fixation device. *(Redrawn from Kellman RM, Marentette LJ.* Atlas of Craniomaxillofacial Fixation. *New York: Raven Press; 1995.)*

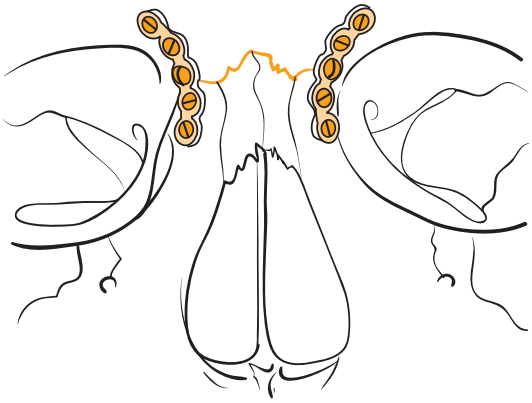

Figure 23-28. Diagrammatic representation of repair of the nasal frontal region with small plates and screws. *(Redrawn from Kellman RM, Marentette LJ.* Atlas of Craniomaxillofacial Fixation. *New York: Raven Press; 1995.)*

position. For many years, surgeons were more concerned about the possibility of facial elongation due to MMF pulling on unfixed maxillary fractures than they were about midfacial rotation and foreshortening. Therefore, the mainstay of treatment was Adams suspension wiring, in which the upper arch bar was wired to the zygomatic arches (or frontal bones when the zygomas were fractured) to prevent facial elongation; such treatment probably aggravated midfacial rotation and led to foreshortening and anterior open bite formation in many patients. With the advent of extended access approaches and routine exposure and fixation of midfacial fractures, this problem was recognized and is now carefully avoided. Similarly, with the availability of rigid fixation techniques, the use of halos for external fixation of midfacial fractures has become extremely uncommon. Nonetheless, familiarity with such techniques is of value in understanding the variety of surgical options.

Whereas the areas between the buttresses are not particularly important for structural support, the buttresses themselves are. Therefore, when bone is deficient along these buttresses, it should be replaced. A defect less than 5 mm in a single buttress can probably be safely bridged with a plate. Otherwise, defects should be bridged using bone grafts from another site. Split calvarium is a common source of bone graft material. It can be stabilized under a plate, or it may be used as a biologic plate and fixed to the bone at each end using lag screws (see Fig. 23-27).

The amount of stabilization (and therefore the amount of surgical exposure) required for fixation of zygomatic fractures may vary depending on the amount of instability and comminution of the fractures. Manson[97] has suggested that the severity of the injury is determined by the amount of energy transmitted to the bone at the time of injury. This is implied by the injury, so it is the severity that is actually analyzed in planning the repair. However, for minimally displaced fractures, the zygoma tends to hinge at the frontozygomatic area and repair may require only percutaneous reduction, and it may pop into place and stay, or it may need only a sublabial exposure and fixation along the zygomaticomaxillary area. When greater force causes the injury, there tends to be comminution at the zygomaticomaxillary area, making this an inadequate point of reference for reduction. A lower lid exposure allows alignment of the infraorbital rim, as well as later exploration of the orbital floor if needed. Access to the lateral orbit is also particularly helpful, in that alignment of the zygoma with the greater wing of the sphenoid in the lateral orbit tends to be a dependable landmark for proper bony reduction. With more severe impacts, marked comminution may make it more difficult to be assured that the zygoma has been properly repositioned. A coronal incision allows full exposure of the entirety of the zygomatic arches. When the contralateral zygoma is intact, it serves as a good frame of reference. Otherwise, even wide exposure may not ensure accurate repositioning of the zygoma. Intraoperative radiography can be useful in this regard. The arch position can be checked using fluoroscopy.[21] However, while not commonly available, intraoperative CT scanning certainly provides the most accurate assessment of bone position. Otherwise, a postoperative scan may indicate the need for revision surgery. Finally, it is important to keep in mind that although most orbital floor defects can be evaluated on preoperative CT scans, a potential orbital floor defect may not be visible. This occurs when the zygoma is severely impacted into the orbital space. After disimpaction of the zygoma, a previously absent orbital floor defect that requires repair may be present. Failure to look for this may result in unanticipated enophthalmos postoperatively. An endoscope placed into the maxillary sinus provides a minimally invasive way to assess the orbital floor in this situation. It is also important to repair the orbital rims before addressing the orbital walls, because the rim position will affect the globe position and the overall shape of the orbit.

The orbit itself needs to be restored as best as possible to its preinjury shape. This requires a familiarity with the normal orbital contours. A skull in the operating room may be helpful in this regard, and some surgeons even place a skull into a clear sterile bag and bend orbital wall implants on it. It is important to recognize the convexity on the orbital floor medially behind the equator of the globe. Failure to reconstitute this will create a tendency toward enophthalmos. It is also important to fill in significant defects in the medial wall for the same reason. Any trapped orbital tissues must be released into their normal positions in the orbit, and forced duction testing should be performed before and after all maneuvers in the orbit. The orbital wall contours can be reconstructed with autologous materials or with alloplastic materials, and each option has its particular advantages and disadvantages. Split calvarial bone is readily available, but it is very rigid and cannot be bent to shape.[98] Molding requires cutting the bone and plating pieces together in different shapes. Split rib is more pliable and can be bent to shape, but it undergoes greater resorption. For small defects, nasal septal cartilage or bone and front face of maxillary bone have been used successfully. After release of the inferior rectus, a crack in the orbital floor can be covered with fascia or gelatin film. Titanium is easily moldable, but there is concern about the growth of fibrous tissue into holes in the material, although there are no actual reports of this being a problem. Porous polyethylene has become popular in the last few years for the repair of orbital floor defects, and it is replacing previously used materials that had variable extrusion rates. Most surgeons place orbital implants directly via transconjunctival and transcutaneous lid incisions, although recently the successful placement of these implants via the maxillary sinus using endoscopic assistance has been reported.[4,99] Enophthalmos generally needs to be slightly overcorrected to compensate for the swelling that develops during the surgical procedure itself. Hypophthalmos (inferior eye position), on the other hand, should not be overcorrected, because overcorrection in this direction is more likely to persist.

Naso-orbital ethmoid fractures (NOE, NEC) are among the most difficult to repair. Simple fractures in which the medial canthal ligaments remain attached to a significant, solid piece of central bone (type I) are repaired by stabilizing the solid piece of bone to the surrounding skeleton with plates. This must be properly positioned and fixed, or it will slowly lateralize, resulting in a significant deformity over time. Repair of the more severe type II and III injuries is a bit more controversial, and some argue for maintenance of any ligamentous attachments to bone, while others recommend focusing on the ligaments themselves.[93-96] With the ligaments exposed (generally via a coronal incision), a permanent suture or wire is passed through the ligament and the suture is passed through the area of the posterior lacrimal crest (which may or may not be present), behind the nasal bones, through the nasal septum, out the same area on the contralateral side (using extreme caution to avoid injury to the contralateral globe), where it may be fixed either to the contralateral frontal bone (around a screw, through a plate hole, or through a hole in the supraorbital rim) or to the contralateral medial canthal ligament. A broad retractor (a sterilized teaspoon may be used) should cover and protect the contralateral globe during passing of wires or sutures from one side to the other. If this latter approach is done, tightening the wire fixes both medial canthal ligaments together. If the suture is fixed to the frontal bone, the same

procedure must be repeated for the contralateral medial canthal ligament (assuming it is also damaged) (Fig. 23-29).

Great care must be used to ensure proper positioning and fixation of the canthal ligament. When identification of the medial canthal ligament is difficult, a hemostat may be placed in the caruncle and pushed medially. When examining the area from the deep surface, the ligament should be approximately in the area of the bulge created by the hemostat (Fig. 23-30). (Obviously, great care must be used to avoid corneal injury when using this technique). If the ligament is not fixed medially, it will slowly lateralize over time, resulting in unsightly telecanthus, malposition of the caruncle, horizontal shortening of the lids, and potential lacrimal dysfunction. It is also important to make certain that the full nasal dorsal height is reestablished, and bone grafts should be used if necessary. Failure to do so tends to exaggerate any appearance of telecanthus and increases the likelihood of developing epicanthal folds. Some surgeons advocate the placement of percutaneous supporting plates against the overlying nasal skin to recreate the natural concavity in this area. It is unclear whether these are necessary. Even though these are passed transnasally, these are not the same as the old percutaneous repairs of NOE fractures, which should not be used to repair these fractures, because they are, for the most part, ineffective.

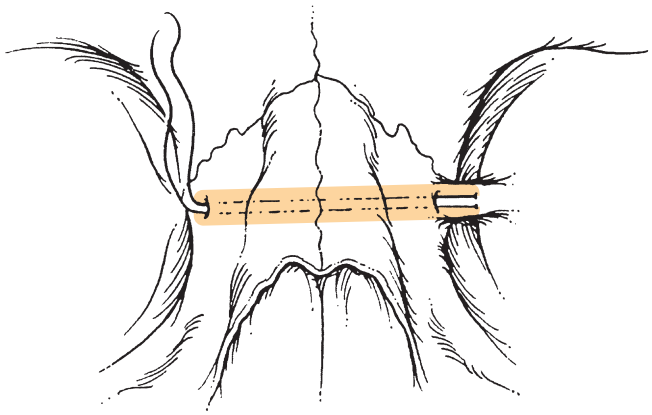

Figure 23-29. A diagrammatic representation of a suture passing through the left medial canthal ligament and then through the lacrimal bone behind the nasal root. It is then fixed to the contralateral frontal bone. This allows appropriate tension to be placed on the medial canthal ligament for proper repositioning. *(Redrawn from Bailey BJ, Calhoun KH.* Atlas of Head & Neck Surgery—Otolaryngology. *Philadelphia: Lippincott William & Wilkins; 2001.)*

Lower Third

The basic principles of mandibular fracture repair are discussed in the Biomechanics of the Facial Skeleton section. The repair of particular fractures is discussed more specifically here. In the dentate mandible, the first priority is the reestablishment of the proper occlusal relationship of the teeth. As noted, a good arch bar not only aids in this effort but also provides a good tension band across the alveolar portion of the fracture. Sometimes a badly displaced fracture makes arch bar application more difficult. In this situation, an intraoral incision that exposes the fracture will allow preliminary reduction of the fracture and aid in the proper positioning of the arch bar. If placement of the arch bar is begun at the fracture site and successive wires are placed alternately on either side of the fracture, a tight tension band can be well applied that will hold the fracture in reasonable approximation. (Some surgeons repair simple mandible fractures without the aid of arch bar fixation of the occlusion, but this approach is not currently recommended.) The proper occlusal relationship between the maxillary and mandibular dentition should then be determined, and wires are generally used to hold the patient in MMF while the fracture is repaired.

There are a variety of treatment options for most fractures, and a familiarity with the basic principles of fracture repair allows the surgeon to select a preferred method for any given fracture. First, a familiarity with load-sharing and load-bearing repairs helps determine what options are available for the repair of a particular mandible fracture. A load-sharing repair depends on the integrity of the underlying bone, and the fixation appliance is positioned so as to ensure that the forces in function are borne by the bone itself. Thus, as discussed above, a small plate across the tension zone will ensure that the solid bone is pushed together in function so that it shares the load with the fixation appliance. Miniplate fixation, compression plate fixation, and lag screw fixation all represent load-sharing repairs and require adequate bone contact to succeed. On the other hand, when the bone is inadequate to share the load with the fixation appliance, as is seen when bone is too thin and atrophic, fractures are significantly comminuted, or there is bone loss, the repair has to bear the load across the repaired area, and thus a load-bearing repair is needed. This requires a repair that is strong enough to bear the load that is applied to the particular area in function, and thus a fairly long and strong plate is required. Until recently, 2.7-mm plates and screws were used for most load-bearing mandibular repairs; however, a strong 2.4-mm titanium mandibular reconstruction

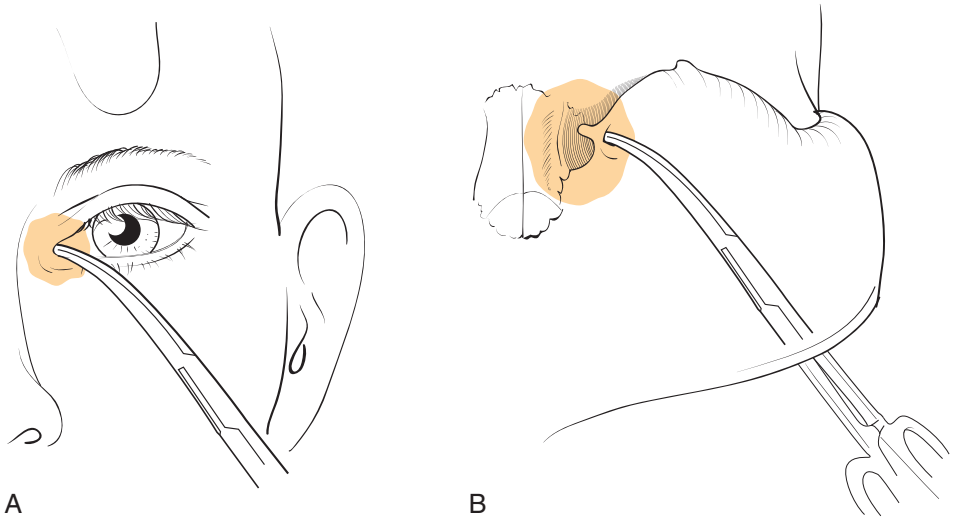

Figure 23-30. A, This demonstrates the placement of a Crile clamp into the area of the caruncle just lateral to the medial canthus. **B,** With the clamp in position pushing medially, the coronal flap is flipped downward. The area where the Crile clamp is indenting the soft tissues is the area in which the medial canthal ligament can generally be identified and grasped. *(**A,** Redrawn from Bailey BJ, Calhoun KH.* Atlas of Head & Neck Surgery—Otolaryngology. *Philadelphia: Lippincott William & Wilkins; 2001.)*

plate appears to be adequate in most instances. To successfully accomplish a load-bearing repair in the mandible, a minimum of three and preferably four solidly held bicortical screws should be placed in the bone on each side of the weak (defective) area.[100] It should also be apparent, therefore, that a load-bearing type of reconstruction plate can be used as a fallback technique for any fracture, because, if it is strong enough to support a defect, it should be strong enough to repair any fracture. This is consistent with the finding noted above that a mandibular reconstruction plate (MRP) provides the most dependable repair of mandibular angle fractures.[71,74]

If the MRP can be used as a fallback technique for any fracture, then why it is not recommended for all fractures? The answer is technical. Because the plate is larger and because it requires multiple bicortical screws over a long distance, it is more difficult to place. It is a stronger plate, which makes it harder to bend; it is longer, which requires more surgical exposure; and the screws have to be bicortical, which means they have to be placed along the inferior border of the mandible, which often requires external incisions, particularly in the more posterior portions of the mandible. Furthermore, improper placement of a bicortical screw results in complications.

When using a reconstruction plate, the option of a design that locks the head of the screw to the plate should be considered. Various devices have been developed, including those in which the screw heads were threaded and expandable, and after placement, an insert screw was placed that expanded the screw head so that it was "fixed" to the plate. More recent designs employ a threaded screw head that tightens (locks) directly into the plate. A particular advantage of such designs is that they may allow for imperfect bending of the plate without disturbing the fracture reduction, because the screw stops when the head is fully engaged in the plate hole rather than continuing to tighten and pull the bone to the less than ideally bent plate. However, the use of this type of plate should not be considered a substitute for proper bending.

External fixation is also an option, although it is less stable than a rigidly placed reconstruction plate. This technique requires externally placed pins, which leaves scars around the pin sites and increases the risk of infection. Like an MRP, the more fixation points placed, the greater the stability obtained.

Whenever there is an oblique fracture, that is, when the bone splits obliquely so that the two fragments overlap rather than abut each other, lag screw fixation is recommended with or without plate fixation. Lag screws are placed so that the first cortex functions as a washer; when the screw is tightened, the two cortices are compressed together. This is accomplished most easily by overdrilling the first cortex, rather than requiring special screws with unthreaded portions. At least two screws are required to prevent rotation around the first one, and three provide a more secure fixation.

In the symphyseal region, when a load-sharing repair can be done, there are a number of options available to the maxillofacial surgeon. Because the bone is curved, there is a solid cortex on either side of the fracture that is accessible to screws. Therefore, lag screw fixation can be applied. When this is performed, it is recommended that two screws be used, and although it is not critical, it is probably better if the head of each screw comes in from the opposite side of the fracture (Fig. 23-31). It is also possible to use two miniplates, with a minimum of two screws on each side of the fracture through each miniplate. It is recommended that 2-mm screws be used. Once a good tension band arch bar (or miniplate) has been applied, a bicortical compression plate along the inferior border of the mandible is also an option.

In the body region, a single miniplate is generally believed to be adequate, as long as the patient does not chew on the side of the fracture during the healing period. A tension band arch bar (or miniplate) can also be combined with a bicortical compression plate along the inferior border.

The angle region is more complex, and, as expected, the choice of repair technique is more controversial. The use of a tension band plate and a compression plate, while once advocated by proponents of AO technique,[14,15] is no longer recommended.[71] In fact, current AO philosophy recommends using either a miniplate technique or a reconstruction plate (load-bearing repair). However, the best miniplate approach remains controversial as well. Champy and associates[18,19] recommend a single 2-mm miniplate placed along the oblique line of the angle region. The patient is then instructed not to chew on that side for 6 weeks. Kroon and coworkers[73] on the other hand performed studies that demonstrated the changing location of the tension zone and therefore recommended using two miniplates at the angle. Levy and colleagues[72] reviewed their experience using a single miniplate at the angle and compared the results with those in patients who had two miniplates placed at the angle. There was a significant difference in the outcomes, with the two miniplate group experiencing a 3.1% infection rate, compared with a 26.3% infection rate when a single miniplate was used. Fox and Kellman[76] reported an infection rate of 2.9% in 72 patients using two four-hole 2-mm miniplates to repair angle fractures. Potter and Ellis, on the other hand, reported a low major complication rate using a single 1.3-mm miniplate along the oblique line.[75] However, major complications were arbitrarily defined as requiring a return to the operating room, so that some complete failures did not count as major complications because they were managed in the office. As noted earlier, Siddiqui and colleagues saw no significant difference when one or two miniplates were used.[97] However, the numbers were small. Thirty-six had one miniplate and 26 had two miniplates, and although there were many minor complications, there were no failures reported in either group, making it difficult to draw any definite conclusions. Finally, Niederdelmann and colleagues[101] advocated a lag screw technique for mandibular angle fractures, but this is a difficult technique, and it should not be attempted unless the surgeon has extensive experience with these techniques.

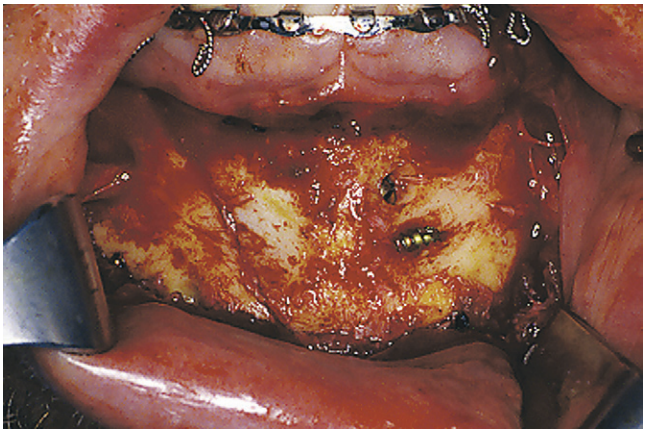

Figure 23-31. An example of an anterior mandibular fracture repair using two lag screws.

The amount of fixation required for mandibular ramus fractures is less clear, but it is probably wise to consider two 2-mm miniplates for such fractures.

The management of subcondylar fractures remains the most controversial, and many surgeons treat almost all of these with MMF, whereas some advocate routine open reduction for these fractures. It is interesting that the so-called closed reduction has been so well accepted for so many years, because it is really closed treatment and not reduction at all. MMF is used to train the mandible to return to its preinjury occlusion, and, combined with physiotherapy, a satisfactory outcome is typical. However, if radiographs are obtained at the completion of a period of closed reduction, the position of the condylar fragment is not likely to be altered. Even so, patients usually do reasonably well. If this approach is selected, it is recommended that the MMF be released after 10 to 14 days, so that physiotherapy can be initiated early. Some surgeons are recommending no MMF, treating the patient instead with immediate physiotherapy. If the patient develops a malocclusion, the surgeon has the option of replacing the MMF (usually using training elastics) or of reconsidering open reduction. On the other hand, it is not clear that patients do much better when a true open reduction is accomplished, and this fact, combined with the traditionally significant risk of facial nerve injury (which is indeed a major complication), has led to the acceptance of closed treatment. Most surgeons have accepted

the classic indications for open reduction reported by Zide and Kent in 1983,[102] including (1) condylar displacement into the middle fossa, (2) inability to obtain reduction, (3) lateral extracapsular displacement of the condyle, and (4) invasion by a foreign body. The relative indications they offered are more frequent, including (1) bilateral condylar fractures in an edentulous mandible when no splint is available, (2) condylar fractures when splinting is not recommended, (3) bilateral condylar fractures along with comminuted midface fractures, and (4) bilateral condylar fractures associated with gnathologic problems. In truth, recent prospective studies have suggested that patients actually do better after open reduction than closed treatment.[103-106] The key issue is whether or not the unacceptable complication of facial nerve paralysis can be lowered to an acceptable level to justify routine open reduction of these fractures. In recent years, the introduction of endoscope-assisted transoral repair of these fractures seems to be changing the paradigm somewhat.[5-9,107] Unfortunately, while the overall success rate is high and the complication rate exceedingly low, the endoscopic repair of subcondylar fractures remains a challenging technique with a steep learning curve, and it requires specialized instrumentation to facilitate its performance.[5] However, as greater experience is obtained, it is not unlikely that it will become a more commonplace technique, and more subcondylar fractures will likely be opened, reduced, and rigidly fixed.

Even though the focus has been on open reduction, there is still a place for closed reduction of mandible fractures as well. Closed reduction refers to the use of MMF as the sole treatment for selected mandible fractures. Generally speaking, closed reduction using 4 to 6 weeks of MMF is reserved for fractures within the line of dentition that are nondisplaced. The teeth have to be adequate to support a solid arch bar, and the patient has to be willing to cooperate with the period of MMF. The patient must also be carefully observed for any signs of movement of the fragments, and if the bone is shifting or if signs of infection appear, then open reduction should be considered.

The issue of teeth in the line of mandibular fractures has evolved significantly over the last several decades. Before the routine use of antibiotics, the presence of a tooth in the fracture line was associated with a high incidence of infection and even osteomyelitis.[108] Dental extraction would minimize these complications, although they still were not rare. More recent reviews have still noted a higher incidence of infection when a fracture occurs through or around a tooth, but extraction no longer decreases the already lower infection rate. Thus there does not appear to be an indication to extract an otherwise healthy tooth, as long as it is not interfering with the reduction. On the other hand, an abscessed or infected tooth in the line of fracture should be extracted. Note that in the region of the angle, the third molar contributes significantly to the cross-sectional area of the bone, and extracting it tends to destabilize the fracture and its repair.[71] Iizuka and Lindqvist[71] found that a higher complication rate resulted when these teeth were extracted at the time of repair of angle fractures. They therefore recommend that the angle fracture be stabilized before the extraction using a load-bearing repair, following which the tooth may be extracted.

Edentulous Mandible

The edentulous mandible presents two particular problems. One is the absence of teeth, which are important to the proper re-establishment of the occlusal relationship, which is in turn critical to proper masticatory function. The other consideration is the amount of mandibular atrophy that is typically seen in edentulous mandibles.

The occlusion is important both for function and for proper repositioning of the bone fragments. Therefore, if there is a denture available, it should be used as a splint to assure proper realignment of the bones. In addition, functional repositioning is important even in the absence of teeth, because improper positioning may make prosthetic rehabilitation more difficult or even impossible, and even when a prosthesis can be constructed, the stress on the TMJ may lead to additional problems for the patient.

Mandibular atrophy is an even bigger problem, in that it has traditionally led to unacceptably high complication rates. A common misconception is that because the mandible is small, only a small plate is required to repair it. In fact, the forces on the mandible continue to be large and the small amount of bone available means that there is limited bone-to-bone contact for healing, and the thin bone does not provide enough support to adequately share the load with small fixation plates. Thus, the atrophic mandible is a contraindication to a load-sharing repair. To minimize the complication rate, a load-bearing repair must be used, and this requires long, strong plates with multiple fixation points using bicortical screws. Because this approach has been used, the success rate for bone healing in these difficult fractures has risen dramatically.[109]

Panfacial Fractures

When broken down into individual parts, each of the fractures described is reparable. However, when all or most of the facial skeleton is fractured, it is much more difficult to re-create the correct three-dimensional shape and to properly reposition the fractured fragments. Logic dictates that reconstruction should be performed from the known to the unknown, which might also be stated as working from the stable to the unstable. In fact, with the exception of the occlusion, which should be established first to whatever extent is possible, the reconstruction actually develops from the periphery toward the center. Using this approach, the typically more solid cranial areas are first repaired so that they can help form the template for repositioning the zygomas. The facial height is reestablished by completing the reconstruction of the mandible, so that the mandibular teeth can serve as the template for the repositioning of the maxillary dental arches. Tooth loss and bone comminution may mandate the use of prosthetic splints, and there should be no hesitation to have these made. In panfacial fractures, open reduction of subcondylar fractures, particularly bilateral subcondylar fractures, becomes an essential component of the repair, because the mandibular ramus height is a critical guide to the overall facial height. The lower maxilla can then be stabilized to the repositioned zygomas above and the mandibular dentition below. Once the maxillae have been repositioned and reconstructed, attention can be turned to the central face, that is, the nose and nasal-ethmoid complex region (NOE fractures). Finally, after the facial architecture has been reestablished, the orbital walls are reconstituted. If this has been performed successfully, a postoperative CT scan should confirm a reasonably normal facial skeletal architecture.

Complications

The most common complication is failure to obtain an ideal reduction. When this involves tooth-bearing bones, a malocclusion results. If it is minimal and can be resolved with occlusal grinding, reoperation may be unnecessary, but this is up to the discretion of the surgeon and the patient. If the malocclusion is more significant, then reoperation is indicated. When a closed reduction technique has been used, a malocclusion may be corrected by adjusting the MMF. However, if rigid fixation has been applied, then only removing the plates and repositioning them will repair a malposition. When the bone heals in the incorrect position, a malunion results. The term *malunion* implies that healing has in fact occurred (as opposed to nonunion). In other areas of the face, malunions usually lead to facial asymmetries. In the orbit, globe malpositions may result, the most common of which is enophthalmos. When the orbital floor has been inadequately reconstituted, it is not uncommon to see hypophthalmos as well. These deformities generally mandate reexploration and placement of additional graft material. Failure to adequately repair NOE fractures will lead to telecanthus; however, this may not be recognizable initially, and the deformity may become apparent later when repair is more difficult.

Nonunion is a more serious complication. It is not common in the mid and upper face, but it is not rare in the mandible. It is usually associated with motion at the fracture site, although it may be associated with an infected tooth. When fracture fragments are mobile, the motion interferes with bone healing and seems to predispose to the development of infection. Once infection develops, failure to stabilize the fracture and treat the infection may lead to osteomyelitis. This results in bone loss and typically results in an infected nonunion. As a result of bone loss, even if the infection resolves, the defect will likely heal with fibrous tissue rather than bone. This also occurs when an

injury results in bone loss. There is a race between bone growth and fibrous ingrowth. If the fibrous tissue wins, the bond that forms between the bone fragments is not solid, and therefore motion persists between the fragments. This has been called a *pseudarthrosis* because the movement of the bones around the fibrous union acts as a false joint. It has been variously also called a *nonunion*, implying that the bone has not healed across the area, or a *fibrous nonunion*. If the bone is stabilized across a fibrous nonunion either using prolonged MMF or a rigid fixation device, the bone may still bridge the gap and heal. In the presence of osteitis, it is important to débride any devitalized bone in addition to treating the infection with antibiotics.

Multiple soft tissue complications occur as well. The most common is scar. However, a significant problem after extended open access approaches is a droop of the midfacial soft tissues. This can be prevented by proper resuspension of the soft tissues before wound closure. Lower lid malpositions such as ectropion or entropion may result when lower lid incisions are used. Care should be used to avoid injury to the orbital septum as well as excessive retraction during the bony repair. A Frost stitch left in place for 1 to 2 days postoperatively may decrease the occurrence of this problem. It is also recommended that the lower lid be massaged by the patient multiple times daily beginning after the first week postoperatively to help break up any developing scar contracture. Suture fixation of the nasal alae subcutaneously may prevent alar base widening after use of the midface degloving approach. Also, as noted earlier, irregularization of the coronal incision allows it to hide more gracefully within the hair.

Related structures may be injured as well, typically as a result of the trauma, although these can occur as a result of the surgery as well. Most feared are brain and ocular injuries. Great care must be exercised when exploring the orbit. Surgical injury to branches of the trigeminal nerve is not uncommon. The supraorbital and supratrochlear nerves are at risk when elevating the coronal flap inferiorly over the supraorbital rims. The infraorbital nerves are at risk when exposing the maxilla via the sublabial approach and via the lower lid approach. Finally, the mental nerve is vulnerable during mandibular exposure and its predecessor, the inferior alveolar nerve, is particularly vulnerable during drilling and screw placement in the mandibular body and angle regions. The facial nerve is at risk during multiple facial exposures, and great care should be exercised to avoid injuring this important structure. The lacrimal collecting system may be injured from the trauma, but it can also be injured during surgery. If its continuity is in question, cannulation of the canaliculi and stenting are recommended. Injury to the extraocular muscles and their nerves can result in diplopia, even in the absence of entrapment.

Finally, the issue of secondary, revision, or delayed fracture repair represents an entire field of advanced maxillofacial trauma management. It relies heavily on the techniques of craniofacial surgery and orthognathic surgery. As in primary repair, the most critical part is careful assessment via clinical evaluation and CT scanning, followed by careful planning of these complex and difficult procedures. Sometimes prefabricated prostheses may be created to assist in the reconstruction. Even with extensive planning and precise execution, the limitations of the soft tissue envelope may preclude obtaining an ideal result.

Future Directions and New Horizons

It is impossible to predict exactly how the problems discussed herein will be managed in the future. However, some of the new technologies currently being used can provide some insight into the directions that developments are going. The recent introduction of endoscopes into facial trauma management has already altered the way some surgeons manage mandible and orbital fractures,[4-8,99] and some are already adapting these techniques to more complex fractures, such as zygomatic fractures[3] and frontal fractures, and even a variety of maxillofacial osteotomies.[110] The development of better CT-based planning and navigational technology may well result in the more frequent use of percutaneous techniques for the repositioning of facial bones.

Constantly improving distraction technology not only allows for better correction of congenital deformities but also allows for repair of secondary traumatic defects as well as primary reconstruction of traumatically induced defects.

Advances in understanding of biomechanical principles will allow for continued refinement of fixation appliances and their placement. Improvements in resorbable technology may lead to the routine use of such materials in the repair of many if not all facial fractures. Currently, one of the intrinsic problems with resorbables is that they break down faster when the stresses acting on them are greater. This makes them less useful for fractures in high stress-bearing areas. Hopefully, such problems will be overcome with new materials.

Finally, bone replacement materials and glues are currently under intense study. Combined with proteins that modulate bone healing, it may become possible not only to repair bones more effectively, but the technology of reconstruction and guided healing may allow for controlled repair and reshaping of the facial skeleton.

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CHAPTER TWENTY-FOUR

Reconstruction of Facial Defects

Shan R. Baker

Key Points

- Local flap may be classified by method of movement: pivotal, advancement, or hinged.
- Most flaps are moved by a combination of pivoting and advancement.
- Pivotal flaps move toward the defect they are designed to repair by rotating the base of the flap around a pivotal point.
- Pivotal flaps may be categorized as rotation, transposition, or interpolated.
- Advancement flaps move toward the defect they are designed to repair by stretching or recoiling the tissue of the flap.
- Advancement flaps may be categorized as unipedicle, bipedicle, V-Y, and Y-V.
- Small cutaneous defects of the nose are best repaired with adjacent nasal skin in the form of a local flap.
- Cutaneous defects of the nose too large to repair with a local flap are best resurfaced with a full-thickness skin graft for shallow defects and an interpolated paramedian forehead flap or interpolated melolabial flap for deeper defects.
- Full-thickness nasal defects require replacement of internal lining, structural support in the form of cartilage or bone grafts, and external cover in the form of an interpolated cheek or forehead flap.
- Defects of the lip less than one half the lip width can usually be repaired by primary wound closure or by using local flaps confined to the aesthetic regions of the lips.
- Reconstruction of full-thickness defects from one half to two thirds the width of the lip often requires full-thickness flaps from the opposite lip or from the cheek.
- Full-thickness defects greater than two thirds the width of the lip are best reconstructed by using regional flaps or vascularized microsurgical flaps.

Skin cancer is the most common cancer of humans, and most skin cancers occur on the face. The incidence of squamous cell carcinoma, basal cell carcinoma, and melanoma is increasing, perhaps because of the depletion of the ozone layer or other environmental factors not yet determined. Most cutaneous malignancies are managed surgically, leaving skin defects that require reconstruction. Skin cancers, birth defects, and injuries as a result of trauma and burns require that surgeons be skilled in the repair of facial defects. This chapter addresses the management of many types of facial defects, primarily those resulting from ablation of cutaneous malignancies. However, the principles of local flap design and tissue movement can be readily applied to the reconstruction of all forms of facial defects.

Most facial defects result from ablation of cutaneous malignancies, and most cases can be repaired by primary wound closure or with a local cutaneous or musculocutaneous flap. Because the topic of facial reconstruction is extremely broad and complex, this chapter discusses only local flaps and grafts in the repair of facial cutaneous defects with the occasional appropriate reference to the repair of skeletal deficiencies. Other publications better address the use of regional flaps in facial reconstruction.[1-3]

The face can be divided into aesthetic facial units, which include the forehead, cheeks, eyelids, nose, lips, auricles, and sometimes the scalp. Reconstruction of some of these areas of the face is discussed elsewhere in this textbook. A multitude of different flaps and grafts can be used to repair a given facial defect; thus several techniques for repair of a given aesthetic facial unit are discussed. The algorithm in Fig. 24-1 displays an approach for analyzing and developing a management plan for surface defects of the face and neck. The selection of a specific flap depends on the location and size of the defect and the intrinsic properties of the flap. Larger defects of the face and neck may be difficult to resurface with local flaps without considerable impairment in form or function. In such circumstances, the surgeon should select a regional flap or skin graft that might be aesthetically less pleasing but will provide a functional repair. These decisions are determined by clinical judgment. The greater the experience of the surgeon, the better will be the clinical judgment.

Classification of Local Flaps

Several methods are used to classify cutaneous flaps[4,5]: (1) by arrangement of their blood supply (e.g., random vs. arterial); (2) by configuration (e.g., rhomboid, bilobe); (3) by location (e.g., local, regional, distant); and (4) by the method of transferring the flap. Local cutaneous flaps are designed immediately adjacent to or near the location of the defect. When classified by method of transfer (Box 24-1), local flaps are divided into pivotal, advancement, and hinged categories. A fourth method of tissue movement is microsurgical, although this method does not apply to local flaps. In reality, most local flaps are moved through a combination of pivoting and advancement. For example, most pivotal flaps are aided in tissue movement by using the intrinsic elasticity of the flap through stretching (advancement). Thus surgeons often speak of combined mechanisms of tissue movement, such as advancement rotation flap. For classification purposes, however, the

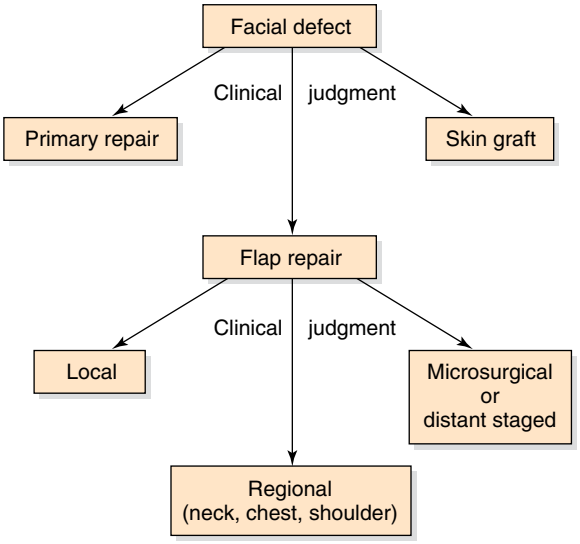

Figure 24-1. Skin defect repair.

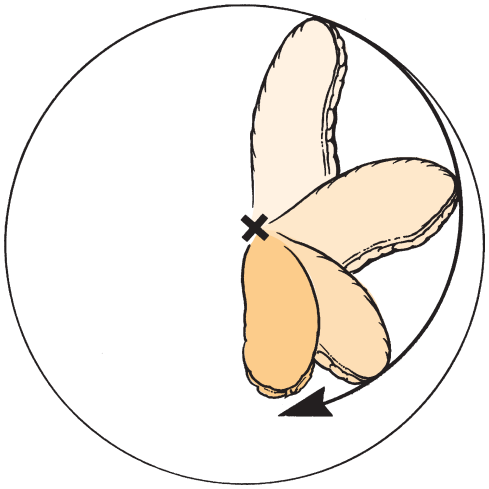

Figure 24-2. The effective length of a pivotal flap moving through an arc of 180 degrees is reduced 40%. *(Adapted from Gorney M. Tissue dynamics and surgical geometry. In: Kernakian DA, Vistnes LM, eds.* Basic Concepts of Reconstructive Surgery. *Boston: Little, Brown; 1977.)*

Box 24-1

Local Flaps Classified by Tissue Movement

Pivotal flaps
- Rotation
- Transposition
- Interpolated

Advancement flaps
- Unipedicle
- Bipedicle
- V-Y
- Hinged flap

major mechanism of tissue transfer should dictate the term given to describe a particular flap, unless both mechanisms are of approximately equal importance, in which case the terms describing both mechanisms should be used.

Pivotal Flaps

The three types of pivotal flaps are rotation, transposition, and interpolated (see Box 24-1). All pivotal flaps are moved toward the defect by rotating the base of the flap around a pivotal point. Except with island axial flaps, which have been skeletonized to the level of the nutrient vessels, the greater the degree of pivot, the shorter the effective length of the flap (Fig. 24-2). This is because the pivotal point is fixed in position and the base of the flap is restricted when pivoting around this point because of the development of a standing cutaneous deformity (dog ear). A pivotal flap should be designed to account for this reduction in effective length which may be as much as 40% with flaps that are pivoted through an arc of 180 degrees.

Rotation Flaps

Rotation flaps are pivotal flaps that have a curvilinear configuration. They are designed immediately adjacent to the defect and are best used to close triangular defects (Fig. 24-3). Rotation flaps are usually random in their vascularity but, depending on the position of the base of the flap, may be axial. Because a rotation flap has a broad base, its vascularity tends to be reliable. When possible, the flap should be designed to be inferiorly based, which promotes lymphatic drainage and reduces flap edema. Rotation flaps are useful in repairing medial cheek defects located near the nasofacial sulcus or nasal sidewall. The curvilinear border of the flap can often be positioned along the infraorbital rim, which represents

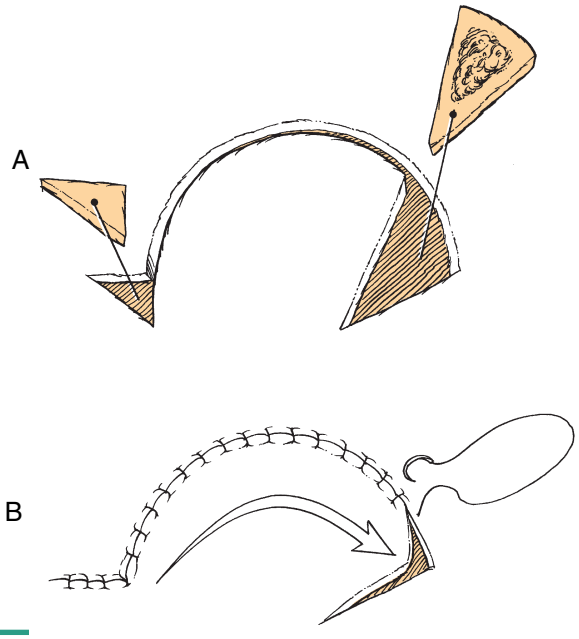

Figure 24-3. A, Rotation flaps are pivotal flaps with curvilinear configuration. Removal of a Burow's triangle can facilitate repair of the donor site. **B,** Standing cutaneous deformity will form at the base of the flap. Triangle-shaped defects use a portion of this redundant tissue. *(From Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

an important border of aesthetic units (eyelid and cheek). Positioning the incision for the flap along this border enhances scar camouflage.

Large rotation flaps are particularly useful for reconstruction of sizable posterior cheek and upper neck defects. Large medial, inferiorly based rotation flaps are a flexible means of transferring large amounts of tissue from the remaining cheek and upper cervical regions. Incisions for the flap are placed in a preauricular crease and can extend for some distance along the anterior border of the trapezius muscle to facilitate rotation of upper cervical skin toward the area of the posterior cheek. A Z-plasty at the base of the flap facilitates closure of the secondary defect. Chin reconstruction can often be readily accomplished with rotation flaps, occasionally using two flaps to optimize the use of the

aesthetic border of the submental crease to camouflage incisions. Smaller rotation flaps can also be used for repair of defects located in the glabellar area. Because rotation flaps are less dependent on tissue elasticity for movement than most local flaps, they are particularly useful for scalp defects because scalp skin is quite inelastic. In addition, curvilinear configuration of rotation flaps adapts well to the spherical shaped cranium. Thus scalp defects in general are best reconstructed with one or more rotation flaps. A rotation scalp flap must be quite large relative to the size of the defect, with the width of the pedicle being twice the width of the defect.[6]

Rotation flaps have relatively few disadvantages. The defect itself should be somewhat triangular or should be modified by removal of additional tissue to create a triangular defect. The configuration of the flap creates a right angle at the distal tip, and the surgeon should take care in positioning the tip so that it is not subjected to excessive wound tension and vascular compromise. As with all pivotal flaps, a rotation flap develops a standing cutaneous deformity at the base that may not be easily removed without compromising the vascularity of the flap. Thus a second-stage removal of the deformity may be necessary.

Transposition Flaps

In contrast to rotation flaps, transposition flaps have a linear axis (Fig. 24-4). Both are pivotal flaps moving around a pivotal point. A transposition flap can be designed similar to a rotation flap so that a border of the flap is also a border of the defect. However, it may also be designed with borders that are removed from the defect, with only the base of the flap contiguous with the defect. The ability to construct a flap at some distance from the defect with an axis that is independent of the linear axis of the defect is one of the greatest advantages of transposition flaps. This advantage enables the surgeon to recruit skin at variable distances from the defect, selecting areas of greater skin elasticity or redundancy. In addition, the ability to select variable sites for harvesting a flap ensures that the donor site scar by its location and orientation will best be camouflaged.

Transposition is the most common method of moving local flaps into skin defects of the head and neck. Transposition flaps, elevated in a multitude of sizes, shapes, and orientation, are usually of random blood supply but may occasionally be axial or compound. A transposition flap is a reconstructive option for small- to medium-sized defects in most configurations or locations, thus making it the most useful local flap in head and neck reconstruction. Although it is recommended that the length of random cutaneous transposition flaps not exceed three times their width, this ratio is not very applicable to such flaps designed on the face and scalp. More important than this ratio are the location and the specific orientation of a transposition flap. The abundant vascularity of the skin of the face and scalp often enables the development of flaps that exceed the 3:1 ratio. An example is the inferiorly or superiorly based melolabial transposition flap, in which its linear axis is directly above and parallel to the linear axis of the angular artery. Although the flap is rarely elevated as a true axial flap incorporating the angular artery, many small peripheral branches of the artery are probably included in the base of the melolabial flap, accounting for its dependability even when designed as a lengthy flap.

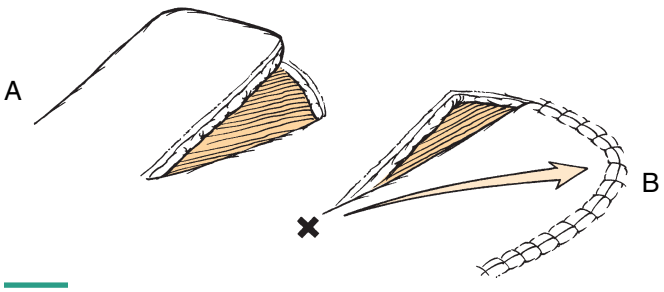

Figure 24-4. **A,** Transposition flaps have a linear configuration. **B,** The flap turns about a pivotal point at the base. *(**A,** Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

Interpolated Flaps

The interpolated flap is a pivotal flap that has a linear configuration, but it differs from transposition flaps in that its base is located at some distance from the defect (Fig. 24-5). Thus the pedicle must pass over or under intervening tissue. If the pedicle passes over intervening tissue, the flap should subsequently be detached in a second surgical procedure. This is perhaps the greatest disadvantage of these flaps. On occasion, the pedicle can be de-epithelialized or reduced to subcutaneous tissue only and brought under the intervening skin as an island flap to allow a single-stage reconstruction.

Common interpolated flaps used in the repair of facial defects are the vertically oriented midforehead flaps, which include median and perimedian flaps.[7] These flaps are highly effective in reconstruction of the midface because of their excellent vascularity and because their skin color and texture superbly match the skin of the nose. The high success rate, reliability, and popularity are primarily the result of a dependable axial blood supply. Based on the supratrochlear artery and its anastomoses to surrounding vessels, midforehead flaps are axial flaps with excellent vascularity that can be transferred without delay. The excellent vascularity allows for the incorporation of cartilage or tissue grafts,

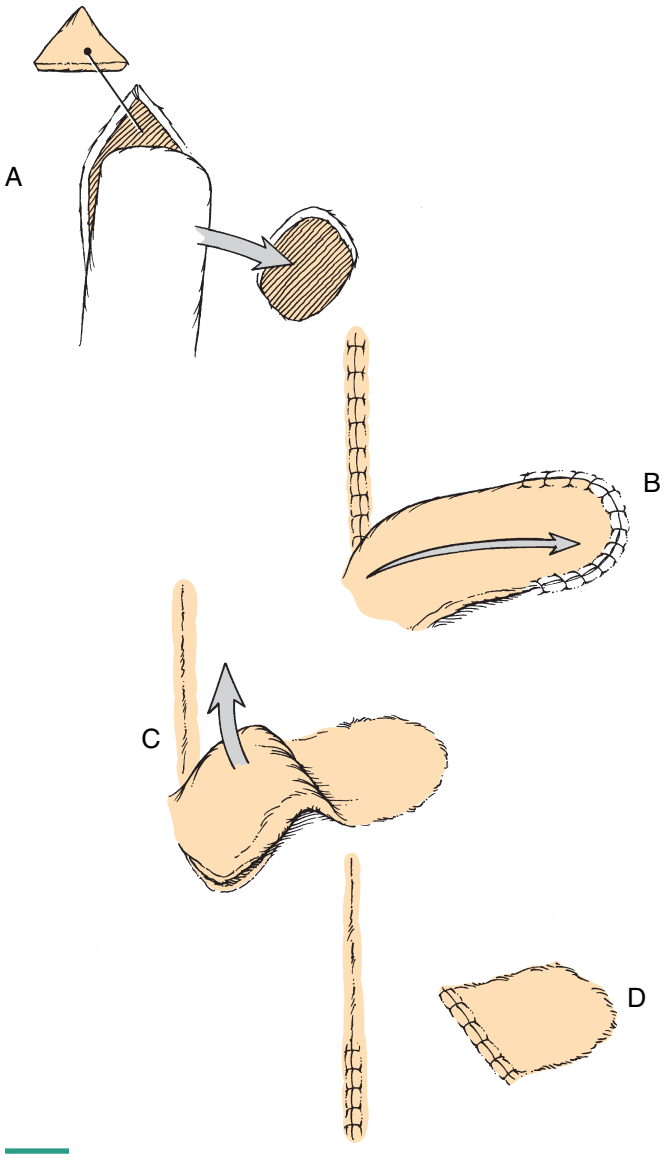

Figure 24-5. Interpolated flaps are pivotal and have a linear configuration. **A** and **B,** Flap pedicle passes over intervening tissue. **C** and **D,** Flap requires pedicle division and inset during second surgical procedure.

which can then act as support structures or lining tissue for nasal reconstruction. Careful removal of muscle and subcutaneous fat from the distal portion of a midforehead flap makes it thin, pliable, and easily contoured to fit any defect of the midface. The frontalis muscle and fascia are included with the distal flap when more stiffness and bulk are required to fit defects of greater depth.

The close proximity of forehead skin to the midface provides a source of skin with excellent color and texture match to the central face. Modern use of the midforehead flap has been expanded beyond nasal reconstruction to include any soft tissue defect of the midface that the flap can be designed to reach.[8] Defects of the medial canthal region, upper and lower eyelids, medial cheek, melolabial region, and upper lip can be repaired with midforehead flaps. These flaps can also be used in combination with other flaps for the reconstruction of complex facial defects; for example, a midforehead flap can be combined with a scalping flap for total nasal reconstruction.

Advancement Flaps

Advancement flaps have a linear configuration and are moved into a defect by being stretched forward. These flaps depend on the elasticity of the tissue of the flap (primary movement) and tissue adjacent to the defect (secondary movement) to achieve wound closure. Tissue transfer is achieved by moving the flap and its pedicle in a single vector. Advancement flaps can be categorized as single or unipedicle, bipedicle, Y-V, or V-Y. Bipedicle advancement flaps are used primarily for repair of large defects of the scalp; the flap is designed adjacent to the defect and advanced into the defect perpendicular to the linear axis of the flap. This leaves a secondary defect, which usually should be covered with a split-thickness skin graft. As a consequence, bipedicle flaps are rarely used for reconstruction of the face and neck.

Unipedicle Advancement Flap

A unipedicle advancement flap is created by parallel incisions that allow the tissue to "slide" in a single vector toward a defect (Fig. 24-6). The movement is in one direction, and the flap advances directly over the defect. As a consequence, the flap should be developed adjacent to the defect, and one border of the defect becomes a border of the flap. Repair with an advancement flap involves primary and secondary tissue movement. In primary movement, the incised flap is pushed or pulled forward by stretching the skin. Secondary movement of surrounding skin and soft tissue immediately adjacent to the defect occurs in a direction opposite the movement of the advancing edge of the flap. This secondary movement may help in repair by providing less wound closure tension, or it may be detrimental, displacing nearby facial structures.

Complete undermining of the advancement flap, as well as of the skin and soft tissue around the pedicle, is important to enhance tissue movement. Standing cutaneous deformities are created with all advancement flaps and may require excision. Excision of standing cutaneous deformities (Burow's triangles) may also facilitate movement of the flap. Unlike the pivotal flap, in which a single standing cutaneous deformity develops at the base, deformities develop on both sides of the base of advancement flaps. However, they may be excised anywhere along the length of the flap and not necessarily adjacent to the base. Selection of the best location for excising tissue is based on where it can be placed within relaxed skin tension lines or long aesthetic borders. Bilateral Z-plasties performed at the base of the flap often eliminate or reduce the need for excision of standing cutaneous deformities. Occasionally, if the flap is sufficiently long, standing cutaneous deformities can be subdivided into multiple smaller puckers of tissue that need not be excised but merely can be "sewn out" by sequentially suturing the wound lengths in one half. On the face, pedicle advancement flaps work especially well in the forehead (particularly in the vicinity of the eyebrow), helical rim, upper and lower lips, and medial cheek. Mucosal advancement flaps are also useful for vermilion reconstruction. Bilateral advancement of unipedicle flaps is commonly used to close large defects, resulting in H- or T-shaped repairs, depending on the configuration of the defect (Fig. 24-7). Repair in this manner is often referred to as an H-plasty or T-plasty. In both cases, advancement flaps are designed on opposite sides of a defect and advanced toward each other, each responsible for reconstructing a portion of the defect. In such cases, standing cutaneous deformities are often excised partly in the area of the defect and partly along the linear axis of the two flaps. The two flaps harvested from either side of the defect do not necessarily have to be of the same length. The length of each flap is determined primarily by the elasticity and redundancy of the donor resource.

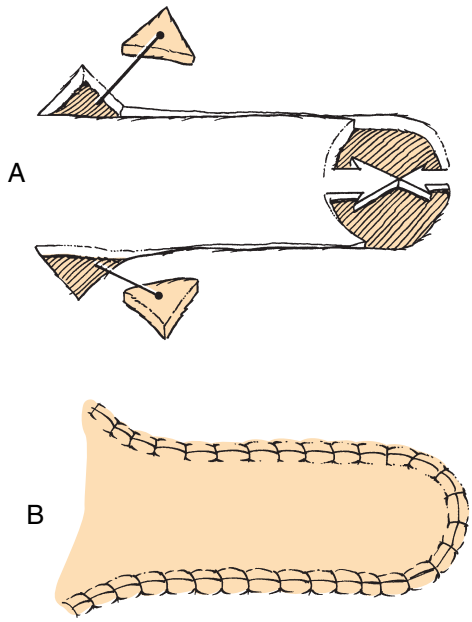

Figure 24-6. A, Unipedicle advancement flap is created by parallel incisions, which allow flap tissue to slide in a single vector *(large arrow)* toward the defect. Secondary movement of surrounding skin immediately adjacent to the defect occurs in a direction *(small arrow)* opposite the direction of flap movement. **B,** Configuration of wound following flap transfer. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

A special type of unipedicle advancement flap is the island advancement flap. A segment of skin is isolated as an island while protecting the subcutaneous tissue and blood supply. The geometric shape of the cutaneous island may vary but is frequently triangular. As the flap advances toward the recipient site, the donor area is closed in a simple V-Y manner. This flap is particularly useful in the repair of medium-sized defects of the medial cheek near the alar base.

V-Y Advancement Flap

The V-Y advancement flap is unique in that the V-shaped flap is not stretched toward the recipient site but advances by recoil or by being pushed rather than pulled toward the defect. Thus the flap is allowed to move into the recipient site without any wound closure tension. The secondary triangular donor defect is then repaired by advancing the two edges of the remaining donor site wound toward each other. In so doing, the wound closure suture line assumes a Y configuration, with the common limb of the Y representing the suture line resulting from closure of the secondary defect.

V-Y advancement is useful when a structure or region requires lengthening or release from a contracted state. The technique is particularly effective in lengthening the columella in the repair of cleft lip nasal deformities in which a portion or all of the columella is underdeveloped (Fig. 24-8). A V-Y advancement flap is elevated, recruiting skin from the midportion of the lip between the philtral ridges. The length of the columella is augmented by advancing the flap upward into the base of the columella. The secondary donor defect is approximated by closing the remaining lip skin together in the midline. V-Y advancement is also helpful in releasing contracted scars that distort adjacent structures, such as the eyelid or vermilion. An example is the correction of an ectropion of the vermilion caused by scarring (Fig.

24-9). The segment of distorted vermilion is incorporated into the V-shaped flap and advanced toward the lip to restore the natural topography of the vermilion-cutaneous junction. The skin edges on both sides of the secondary defect are then advanced toward each other and sutured. The suture line becomes the vertical or common limb of the Y configuration.

Y-V Advancement Flaps

Y-V advancement flaps differ from V-Y advancement flaps in that a Y-shaped incision is made initially. In contrast to the V-Y design in which the V-shaped flap recoils or is pushed toward the area for supplementation, in the Y-V design, the flap is pulled or stretched toward the area for supplementation. The flap augments the area of the common limb of the Y while reducing the triangular area. Y-V advancement flaps are indicated in circumstances in which the surgeon wants to decrease the redundancy of an area by moving tissue away from the site. Occasionally, relocating a free margin of a facial structure using a Y-V flap can be useful to improve symmetry.

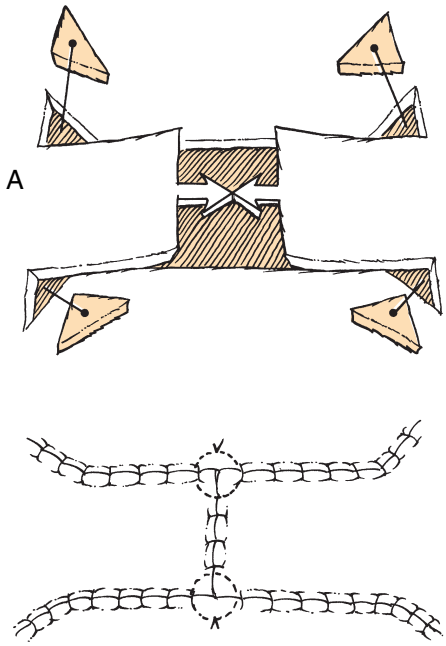

Figure 24-7. **A,** Bilateral advancement flaps. Excision of Burow's triangles facilitates movement of flaps toward each other *(arrows)*. **B,** Configuration of wound following transfer of flaps. Circular corner suture used at opposing corners of flaps.

Hinge Flaps

Cutaneous hinge flaps, sometimes referred to as trap door, turn-in, or turn-down flaps, have a unique method of tissue movement. These flaps can be designed in a linear or curvilinear shape with the pedicle based on one border of the defect. The flap is dissected in the subcutaneous tissue plane and turned over onto the defect like a page in a book. The epithelial surface of the flap is turned downward to provide internal lining for a facial defect that requires external and internal lining surfaces. The exposed subcutaneous surface of the hinge flap is covered by a second flap. Thus hinge flaps are always used with another flap or graft that provides the external coverage of the defect. The vascular supply of hinge flaps is derived from the soft tissue border of the defect that it is designed to repair. As a consequence, such flaps have limited and often restricted vascularity. Survival of hinge flaps can be improved if they are used when the wound margin of the defect is well healed rather than freshly created. Because the pedicle of the hinge flap is along a border of the defect, the flap should be elevated in such a way that, as flap dissection proceeds toward the base of the flap, the plane of dissection becomes deeper; thus the base is thicker than the distal portion of the flap. This technique enhances the vascularity of the flap by increasing the likelihood of including more nutrient vessels within the pedicle.

Hinge flaps are commonly used for repair of full-thickness nasal defects in which the remaining adjacent nasal skin is sufficient to develop a hinge flap for internal nasal lining. Hinge flaps can also be used to close mature sinofacial and salivary fistulas anywhere in the upper aerodigestive tract. Hinge flaps consisting of subcutaneous tissue, and sometimes muscle without overlying skin, can be used to fill in contour deficits.[9] Hinged flaps consisting of nasal mucosa (with or without attached septal cartilage) are frequently used for internal lining in the repair of full-thickness nasal defects. These mucosal flaps are axial and do not require a thick base to ensure adequate vascularity.

Defects of the Nose

Skin cancer most frequently occurs on the nose; thus reconstructive surgeons should be familiar with several methods for repairing nasal defects using local flaps. Burget and Menick[10] have elevated the success of reconstructive rhinoplasty by emphasizing the importance of replacing deficient nasal tissue with similar tissue. For example, defects of the internal nasal lining are replaced with hinged or bipedicle advancement mucosal flaps harvested from the remaining nasal lining. Missing cartilage or fibrofatty tissue giving contour to the nose is replaced with septal or conchal cartilage, positioned and sculpted to replicate the missing skeletal support as closely as possible. Thinning and contouring the cartilage grafts should be emphasized so that they replicate the exact topography of the contralateral cartilage if present, or the form that can be expected in an ideally shaped nose. Burget and Menick[10] also emphasized the aesthetic advantages of isolating nasal defects as a separate entity from any extension of the defect onto the cheek or lip, repairing each aesthetic unit with independent flaps. This

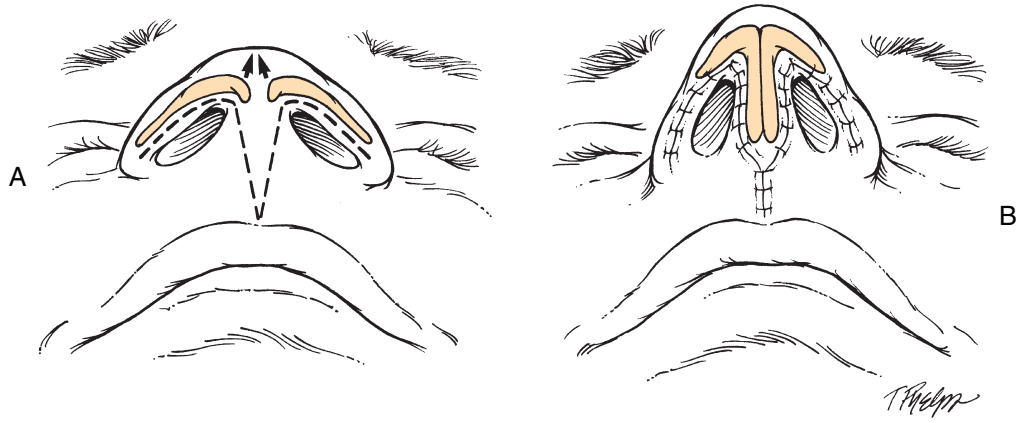

Figure 24-8. **A,** V-Y advancement flap recruits skin from midline of upper lip. **B,** Flap is advanced into columella to enhance columellar length.

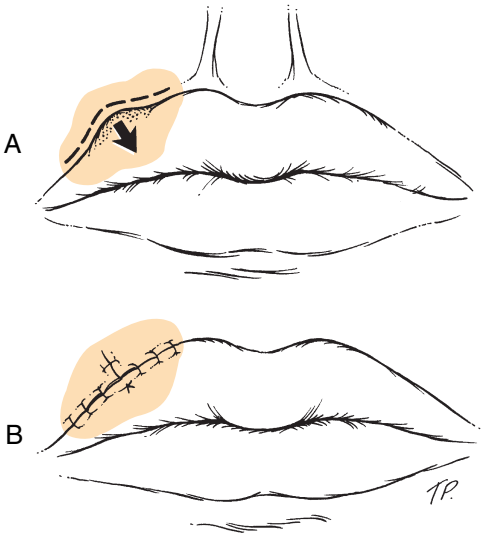

Figure 24-9. **A,** V-Y advancement flap designed at superior border of vermilion ectropion. **B,** Advancing V-shaped flap corrects ectropion. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

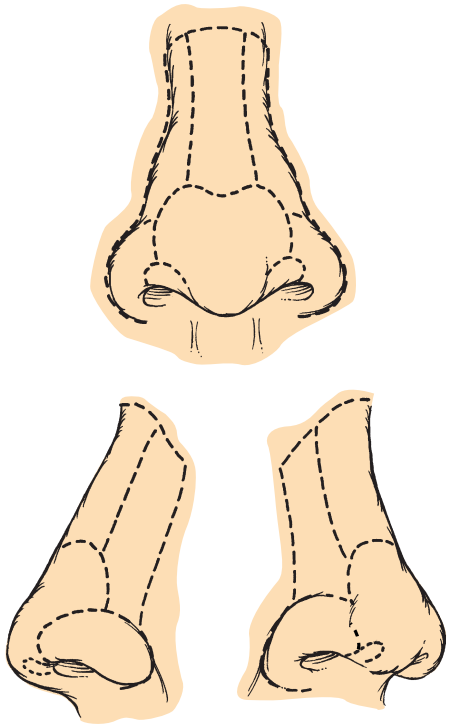

Figure 24-10. Nasal topographic aesthetic units. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

maintains scars in borders between major aesthetic regions and prevents distortion or obliteration of these borders while maximizing scar camouflage. Within the nasal aesthetic region, units can be identified, including the dorsum, nasal sidewalls, facets, alae, tip, and columella (Fig. 24-10). When a surface defect involves greater than 50% of the surface area of the unit, resurfacing of the entire unit with a flap usually provides a better aesthetic result by hiding scars along borders of the units.[10]

The nasal ala is a common site of nasal defects resulting from removal of skin cancers. If not repaired properly, distortion of the alar margin and partial collapse of the external nasal valve occur with compromise of the airway. Too often in the past, the alar facial sulcus and nasal alar crease have been violated by transposition flaps harvested from the medial cheek to repair alar defects. When this occurs, a completely natural-appearing border between the cheek and the ala and nasal sidewall is extremely difficult to restore. For this reason, the author prefers to use interpolated flaps from the cheek, the pedicle of which crosses over, but not through, the alar facial sulcus. The pedicle may consist of skin or subcutaneous tissue only, and is detached from the cheek 3 weeks after the initial transfer to the nose.[11] This interval allows the surgeon to aggressively defat and sculpt the distal flap at the time of flap transfer and again at the time of pedicle detachment and flap inset. On detachment of the flap, the patient has a completely natural-appearing alar facial sulcus and nasal alar crease (provided the defect does not extend into the crease) because no incisions or dissections have been made in these regions. Usually, resurfacing of the entire ala is preferred, removing any remaining skin. Full-thickness defects are reconstructed by restoring the internal nasal lining deficit with a vascularized vestibular skin or mucosal flap. Full-thickness defects of the ala with a vertical height of 1.5 cm or less can use a bipedicle mucosal flap for internal lining (Fig. 24-11). The flap is created by making an extended intercartilaginous incision from the nasal dome to the lateral floor of the vestibule. The vestibular skin is mobilized inferiorly, and the inferior edge is sutured to the inferior border of the nasal vestibular skin defect. If the vestibular skin defect extends to the alar rim, then the inferior aspect of the flap used is sutured to the edge of the cutaneous flap used to provide external coverage of the defect. The flap is attached to overlying cartilage grafts placed to provide structural support by horizontal mattress sutures placed through the cartilage and bipedicle flap. The donor site for the flap is repaired with a thin full-thickness skin graft harvested from the standing cutaneous deformity removed when closing the donor site of the interpolated cheek flap.

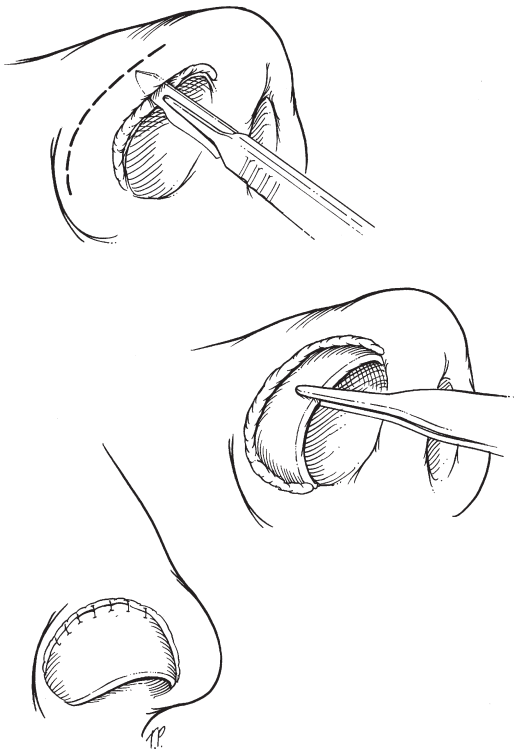

Figure 24-11. For full-thickness defects of the ala with a vertical height of 1.5 cm or less, one can use a bipedicle mucosal advancement flap for internal lining. The donor site is closed with a thin full-thickness skin graft. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

After reconstruction of the internal nasal lining defect with a bipedicle mucosal flap, the next step is to completely replace all missing nasal cartilage with free cartilage grafts harvested from the nasal septum or, preferably, from the auricle. If the inferior edge of the lateral crura has been removed, the missing cartilage should be replaced with a free cartilage graft, and additional grafts should be placed along the alar margin inferior to the position of the original lateral crus. This prevents notching or superior contraction of the alar rim. Likewise, when the fibrofatty tissue of the lateral portion of the alar lobule is missing, it should be replaced with free cartilage grafts because this tissue, although not rigid, provides structural support and contour to the lobule. If the surgeon depends strictly on a skin flap to replace the fibrofatty tissue in the alar lobule, less structural support is provided and scar contracture causes an unnatural appearance, usually with some notching of the alar rim and partial collapse of the external nasal valve.

Once the structural support for the alar lobule has been secured, a cheek flap is planed to resurface the lobule and cover the restored skeletal support. A template is fashioned to exactly represent the size and shape of the surface defect. This template is used to design a superiorly based melolabial interpolated flap. The flap should be designed so that the medial border falls in the melolabial sulcus. The flap is elevated in a subcutaneous tissue plane and may be lifted on a skin and subcutaneous fat pedicle or based on a subcutaneous tissue pedicle only. A subcutaneous tissue pedicle is preferred in most cases because the flap can transpose more easily and reduces the amount of skin to be removed from the upper melolabial fold, thus maintaining better facial symmetry. The flap donor site is closed primarily by undermining the skin of the cheek. The standing cutaneous deformity that occurs with advancement of the cheek skin medially is excised, and a portion is used as a full-thickness skin graft to cover the donor site of the intranasal mucosal flap. The interpolated flap is transposed over the alar facial sulcus, and the distal two thirds of the flap is thinned appropriately so that the flap will drape over the cartilage grafts in a manner that replicates the contour of the alar lobule and alar nasal crease. This may require thinning of the flap to the level of the dermis in the area along the alar rim to restore the delicate topography of the rim. When the defect involves the alar rim and internal nasal vestibular skin, the inferior border of the flap is sutured to the inferior border of the bipedicle mucosal flap used to replace the missing internal nasal lining. The proximal third of the interpolated flap is left with an ample amount of subcutaneous tissue to enhance flap vascularity. At the time of pedicle detachment, the proximal portion of the flap to be inset is defatted and contoured.

The main advantage of the melolabial interpolated flap is that it does not violate the aesthetically important alar facial sulcus. It also minimizes distortion of the melolabial fold because the skin removed from the cheek is located at the inferior aspect of the fold where greater skin redundancy is present. Using a subcutaneous tissue pedicle, only a small amount of skin from the upper melolabial fold is discarded as a result of a small-standing cutaneous deformity forming in that area during closure of the donor site.

When tissue defects extend into the alar facial sulcus, the task of restoring this area of complex topography to its natural appearance (i.e., symmetrical to its counterpart) is difficult. When confronted with this problem, the surgeon often prefers to reconstruct the medial cheek and alar facial sulcus component of the defect with an advancement cheek flap and reconstruct the alar lobule with a separate cheek or forehead interpolated flap (Fig. 24-12). This allows each flap to reconstruct the independent aesthetic regions of the nose and cheek, and it places the junction of the borders of the two flaps along the restored alar facial sulcus. When such defects are reconstructed with a single transposition cheek flap, partial or complete obliteration of the alar facial sulcus occurs, and it should be restored through additional operations. This usually involves multiple surgical procedures and only limited success.

Surface defects of the nasal tip, columella, sidewalls, and dorsum that cannot be repaired with a local nasal cutaneous flap or skin graft are best repaired with paramedian forehead flaps, although partial loss of the columella may be repaired with a single or bilateral superiorly based melolabial interpolated flap. If the defect involves more than 50% of the surface area of an aesthetic unit, the remaining skin should be removed and the entire aesthetic unit of the nose resurfaced. As with reconstruction of the ala, all missing cartilage should be replaced. Auricular cartilage is an excellent source for replacing missing lower lateral cartilage, whereas septal cartilage is most useful for replacing upper lateral cartilage. Full-thickness defects require unilateral or bilateral septal mucosal flaps for repair of the internal lining (Fig. 24-13). Burget and Menick[10] showed that the entire mucosal lining of the nasal septum can be mobilized as a hinge flap based anteriorly on the caudal septum and nourished by the septal branch of the labial artery. This hinge flap is turned laterally across the nasal passage to provide lining to the lateral nasal wall. When greater lining deficits (e.g., the entire length of the sidewall) are present, a second septal mucosal flap from the contralateral side is developed. In contrast to the ipsilateral flap, the contralateral flap is hinged on the dorsal septum and is nourished by the anterior ethmoid artery (see Fig. 24-13). Thus the lining for a heminasal defect is supplied inferiorly by an ipsilateral hinge septal mucosal flap based on the superior labial artery and superiorly by a contralateral septal mucosal hinge flap based on the anterior ethmoid artery. A permanent septal fistula remains. Although crusting can occur for several months, the large septal fistula is rarely symptomatic. The ipsilateral mucosal flap crosses the nasal passage in such a way that it blocks the airway, and should be detached from the caudal septum to restore a patent nasal passage. This maneuver is accomplished using local anesthesia 3 weeks after initial transfer. The excellent vascular supply of these mucosal flaps provides a well-vascularized recipient site to support free cartilage grafts of all sizes. The grafts are sandwiched between the mucosal flap internally and the interpolated forehead or cheek flap externally and thus have a dual source of vascularization.

In repair of full-thickness central nasal defects of the tip or dorsum, a composite turnout flap consisting of septal cartilage with attached mucosa on either side is developed. Its base is centered in the region of the nasal spine and upper lip and contains both septal branches of the superior labial arteries. A flap of appropriate dimensions is outlined and incised with a right-angle knife or scissors. Such flaps may include bone and extend from the nasal floor inferiorly to the level of the medial canthi cephalically and posteriorly to include portions of the perpendicular plate. To allow rotation, the septal mucoperichondrial leaves are separated from the septal cartilage near the nasal spine and a triangular-shaped piece of septal cartilage at the level of the inferior septal angle is removed (Fig. 24-14). This maneuver permits the flap to rotate up and out to reach the tip and dorsum. The flap is designed overly wide and long to create an excess of mucosa and cartilage. As the flap pivots into position, its distal end passes over the exposed remnant of the nasal bones or missing dorsal septum and locks into position. The extra lining is peeled downward as bilateral hinge flaps, which extend laterally to line the dorsal nasal vaults and tip. Cartilage grafts are placed on top of these flaps to restore missing dome cartilage in the case of central tip defects or to restore nasal bridge in the case of dorsal defects. A paramedian forehead flap provides the external surface cover to complete the reconstruction (Fig. 24-15).

Paramedian forehead flaps are the preferred local flap for resurfacing most large nasal defects. The flap can be dissected under local or general anesthesia. The base of the pedicle is placed in the glabellar region centered over the supratrochlear artery on the same side as most of the nasal defect. The origin of the supratrochlear artery is consistently found to be 1.7 to 2.2 cm lateral to the midline and corresponds usually to a vertical tangent of the medial aspect of the brow. The vessel exits the orbit by piercing the orbital septum and passing under the orbicularis oculi muscle and over the corrugator superciliary muscle. At the level of the eyebrow, the artery passes through orbicularis and frontalis muscle and continues upward in a vertical direction in a subcutaneous tissue plane. The pedicle of the flap may be as narrow as 1.2 cm. A narrow pedicle provides greater effective length with less standing cutaneous deformity than a broader pedicle (Fig. 24-16). An exact template of the defect is used to design the paramedian forehead flap, which is centered over the vertical axis of the supratrochlear artery. If adequate length necessitates extending the flap into hair-bearing scalp, turning the flap obliquely along the hairline will prevent transfer of hair-bearing skin to the nose. The flap is elevated in a plane just superficial to the periosteum of the frontal bone. To avoid injury to the arterial pedicle,

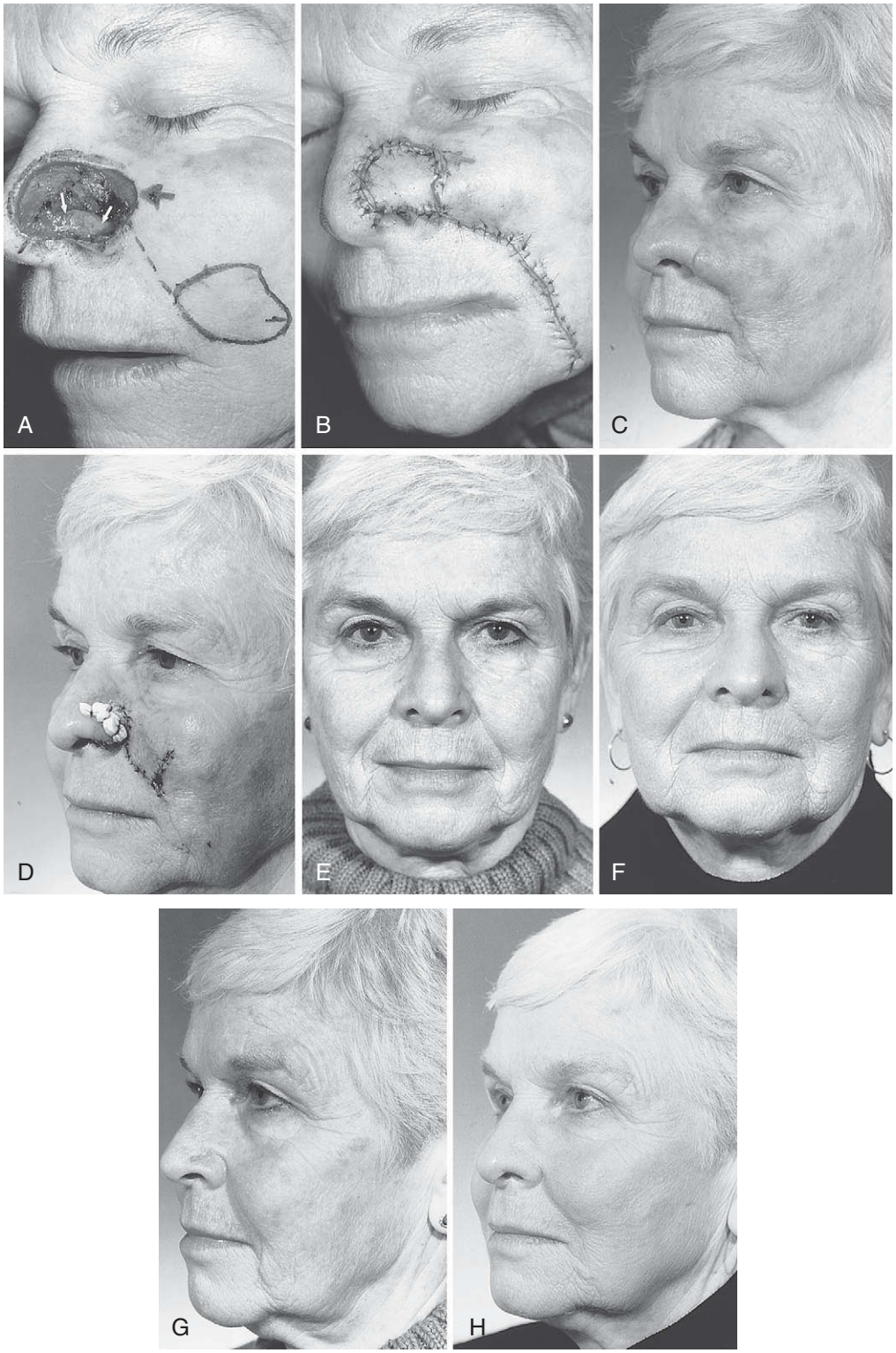

Figure 24-12. **A,** A skin and soft tissue defect extends from alar lobule into medial cheek. The cheek advancement flap is designed to repair cheek defect. Separate subcutaneous tissue pedicle transposition flap is designed to resurface the alar lobule after placement of auricular cartilage graft *(small arrows)* along the missing alar margin. **B,** Two flaps are in position. **C** and **D,** Three weeks after transfer of transposition flap, the pedicle is separated and the distal flap is sculptured to reconstitute the alar nasal crease. The standing cutaneous deformity from the cheek advancement flap is removed in the melolabial sulcus. Preoperative **(E)** and 1 year postoperative **(F)** views. Harvesting the transposition cheek flap from jowl area reduces asymmetric fullness of the melolabial folds. Preoperative view **(G)** and 1-year postoperative **(H)** view. The reconstituted alar crease simulates original crease by aggressively debulking flap.

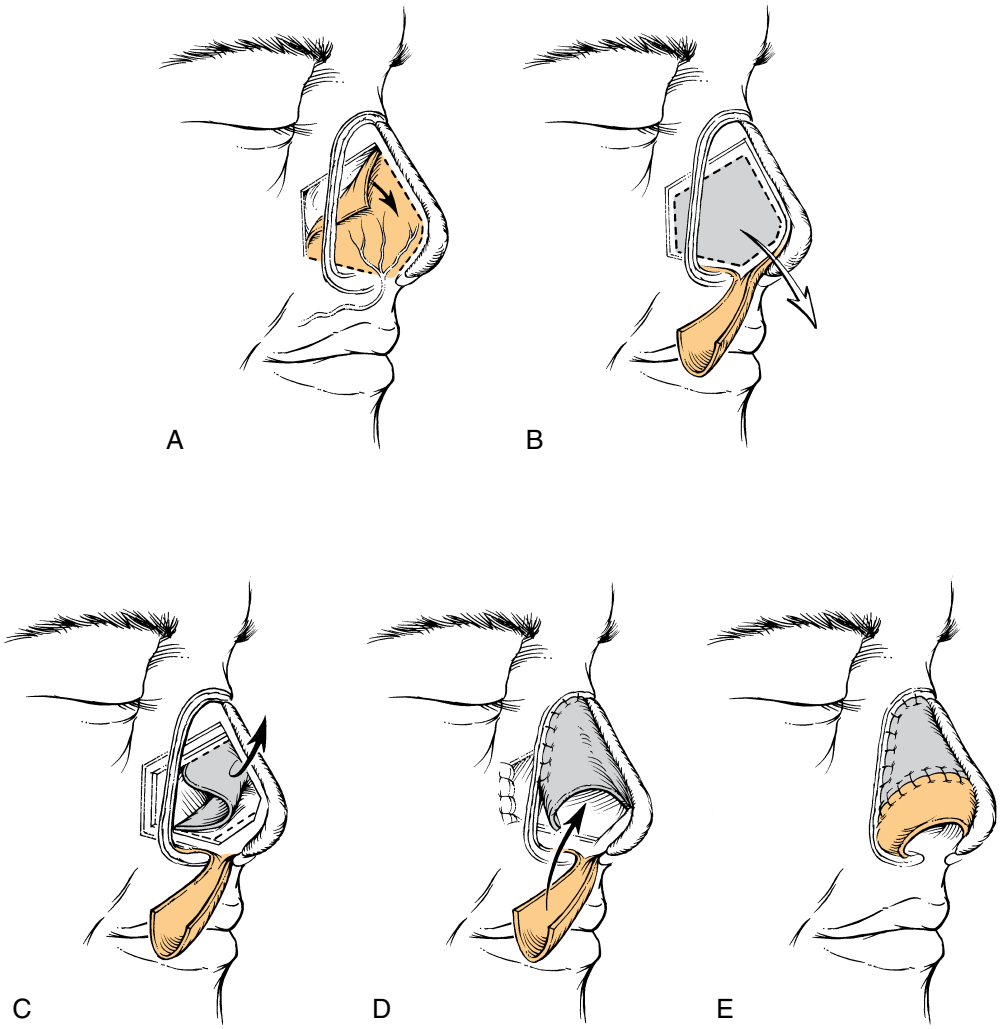

Figure 24-13. **A** and **B,** Ipsilateral hinged flap can be used to restore internal lining of full-thickness nasal sidewall defects with a vertical height of 2.5 cm or less. In such instances, exposed septal cartilage can be left in situ and will heal by second intention. **C, D,** and **E**, For defects greater than 2.5 cm in vertical height, a second contralateral septal mucosal hinged flap is required to supplement ipsilateral flap. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

blunt dissection near the brow separates the corrugator muscles from the flap and facilitates mobility. If necessary, incisions can be extended below the brow to enhance the length of the flap. Adequate flap mobilization usually requires complete sectioning of the corrugator supercilliary muscle to achieve free movement of the flap. Before inset, the flap is sculptured and contoured to fit the depth, breadth, and height of the defect by removal of all or some of the muscle and subcutaneous tissues from the distal portion of the flap. When necessary, all but 1 mm of the fat beneath the dermis can be removed. It may be necessary to resect a portion of the dermis along the edge of the flap so that the thickness of the skin flap matches the adjacent nasal skin. Only the distal three-fourths of the flap required for reconstruction is sculptured; the proximal one-fourth is left thick and is debulked at the time of pedicle detachment 3 weeks later. Donor site closure is accomplished by undermining the forehead skin in the subfascial plane from the anterior border of one temporalis muscle to the other. Several parallel vertical fasciotomies 2 to 3 cm apart may be necessary to achieve primary closure of the wound. Any portion of the donor site that cannot be closed primarily should be left to heal by second intention, keeping the open wound moist at all times. Healing by second intention usually results in an acceptable scar but may take several weeks for complete healing. When necessary, the scar can be revised later. Three weeks after the initial flap transfer, the pedicle is divided under local anesthesia. The dorsal skin above the defect is undermined for approximately 1 cm. The portion of the transposed skin flap that was not thinned at the time of flap transfer is now thinned appropriately. For skin-only nasal defects that extend to the rhinion, the flap should be aggressively thinned to the level of the dermis to reduplicate the thin skin that is normally found in this area. Deep layer closure is not necessary because closure should not be under any tension. The base of the pedicle is returned to the donor site in such a way as to create the normal intereyebrow distance (see Fig. 24-16). Care should be taken to maintain the muscular component of the proximal pedicle that is returned so that a depression between the eyebrows does not occur. Any excess pedicle should be discarded rather than returned to the forehead above the level of the eyebrows.

Defects of the Lip

The lips play a key role in deglutition, formation of speech, and facial expression. Reconstruction offers a unique challenge to the surgeon. Few other sites require such attention to precise details of form and function. Over the past several years, emphasis has been placed on reconstructing the aesthetic units of the lip. For the upper lip, these are the filtrum and the two lateral segments. This principle can be applied in repairing smaller-sized defects of the lip and frequently obviates the need to borrow tissue from the cheek.

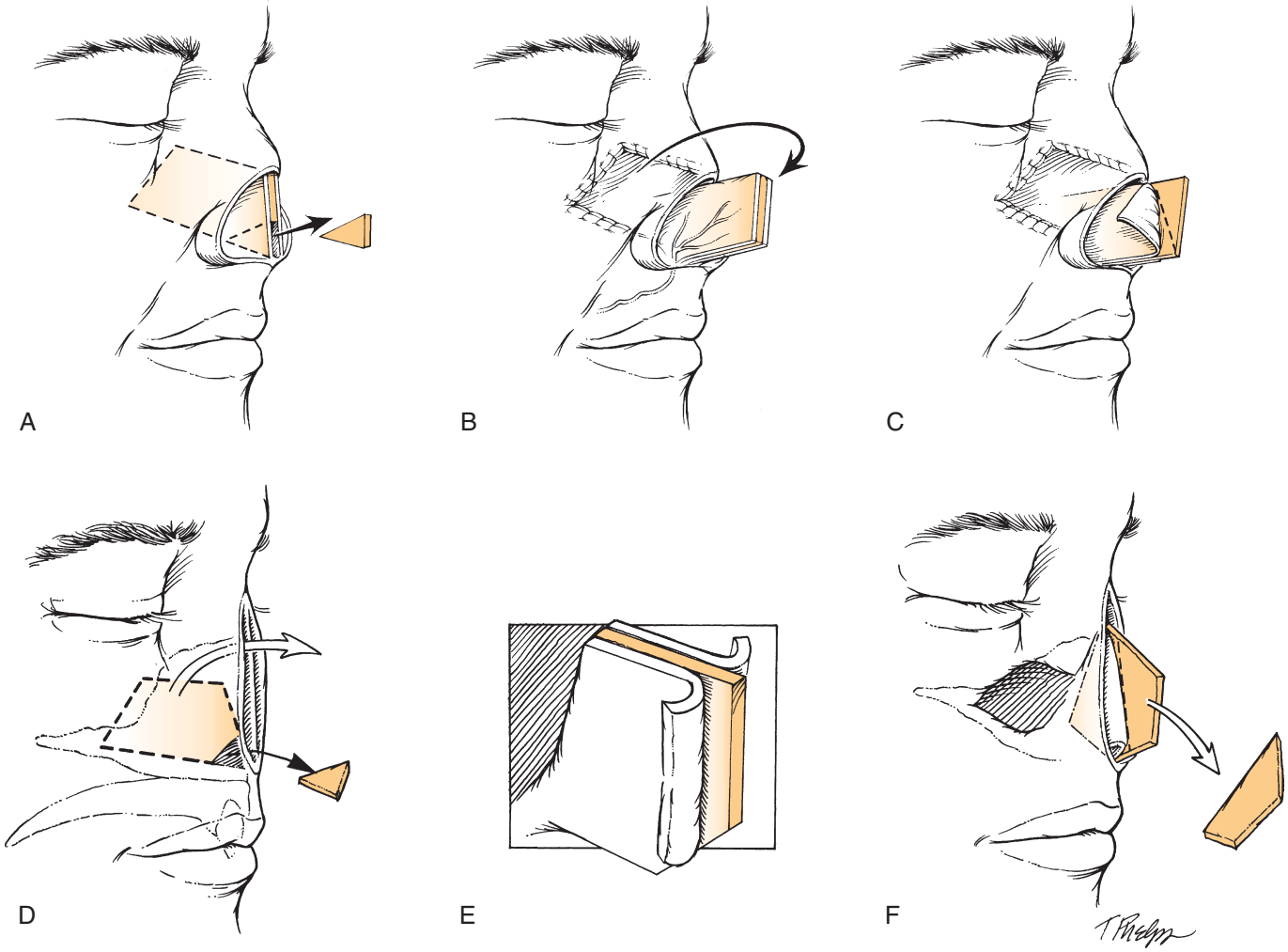

Figure 24-14. **A** through **C,** A composite pivotal septal flap is used to replace structure and internal lining for full-thickness central defects of the tip and dorsum. **D** through **F,** A similarly constructed composite flap can be used to reconstruct internal lining and skeletal support for the nasal dorsum. *(Adapted from Baker SR, Swanson N:* Local Flaps in Facial Reconstruction, *St. Louis, Mosby, 1995.)*

Surgical procedures used to reconstruct the lip after tumor ablation may be classified as[12]: (1) those that use remaining lip tissue, (2) those that borrow tissue from the opposite lip, (3) those that use adjacent cheek tissue, and (4) those that use distant flaps. The first two categories enable the reconstruction to remain within the aesthetic region of the lips and, when possible, are the preferred method of surgical management. The algorithms displayed in Figs. 24-17 and 24-18 provide a helpful approach to reconstruction of the lip for defects that are full thickness or that represent loss of skin and muscle.[12] This approach categorizes the size of lip defects into those less than one half the width of the lip, those between one half and two thirds of the lip, and those greater than two thirds of the lip width. The edges of the defect immediately retract, so the defect size is measured before excising the lesion. Defects less than one half the lip width can usually be managed by primary wound closure or by using smaller local flaps confined to an aesthetic unit of the lip (Fig. 24-19). In the lower lip, a wedge excision should not be carried below the mental line unless necessary for tumor removal. A W-plasty at the mental line allows for rectangular excision. Lateral advancement flaps may be required when the defect base is broad. The W-shaped configuration maximizes the conservation of tissue and prevents an unsightly pointed chin, which occurs when the incision is extended below the mental crease. Primary closure should be in four layers: mucosa, muscle, deep dermal, and skin. Care is taken to perform a precise approximation of the "white line" at the vermilion border on either side of the defect.

Primary wound closure of defects near the midline of the upper lip can be facilitated by excising a crescent of cheek skin in the perialar region to increase flap advancement. This method is similar to that described by Webster.[13] Perialar skin excision allows advancement of the remaining lip segments medially and lessens wound closure tension after primary wound repair.

Reconstruction of defects from one half to two thirds of the lip usually requires lip augmentation. Closure can be most readily achieved by a full-thickness pedicle flap from the opposite lip (lip switch flap) or from the adjacent cheek. The Karapandzic flap[14] may also be effective in closing medium-sized defects of the lip and, in some instances, may provide better functional results than other denervated flaps. This technique consists of circumoral incisions through the skin and subcutaneous tissue, encompassing the remaining portions of the upper and lower lips.[1] The orbicularis oris is mobilized and remains pedicled bilaterally on the superior and inferior labial arteries. Adequate mobilization enables primary closure of the defect by rotating portions of the remaining lip tissue into the defect. The advantage of the Karapandzic flap is that it restores a continuous circle of functioning orbicularis muscle to maintain oral competence. However, because no new tissue is recruited to aid in the reconstruction of the lip, microstomia may be a problem. Also, the circumoral incisions can be unsightly. Patients 60 years of age or older often develop laxity of the oral stoma following a Karapandzic flap and do not require commissuroplasties to correct the microstomia.

Local flaps are preferable to regional flaps for closing defects of less than two thirds of the lip width because of the close skin color, the similar texture, and the availability of mucous membrane for internal lining. Defects located away from the commissure are best closed with an Abbé flap consisting of a full-thickness flap from the opposite lip pedicled on the vermilion border and containing the labial artery.[15] Estlander[16] devised an operation for closure of a lower lip defect near the commissure of the mouth. Since the original description of the Abbé and Estlander flaps, the operations have been modified to accommodate surgical defects located anywhere in the upper or lower lip.

The Abbé and Estlander flaps should be constructed so that the height of the flap equals the height of the defect. The width of the flap should be approximately one-half that of the defect to be reconstructed; however, when the entire philtrum is missing, the width of the flap should equal that of the philtrum. This will restore the total aesthetic unit, which is preferable cosmetically and functionally. The pedicle should be made narrow to facilitate transposition and should be positioned near the center line of the recipient site. The secondary defect should be closed in four layers with accurate approximation of the vermilion border.

The pedicle of the Abbé flap crosses the oral stoma and can be severed in 2 to 3 weeks. During the interval between transfer of the flap and the division of the pedicle, the patient is maintained on a liquid or soft diet that does not require excessive chewing. It is essential to ensure precise approximation of the vermilion border at the time of pedicle severance.

The superiorly based Estlander flap may be modified from its original description so that the flap lies within the melolabial sulcus (Fig. 24-20).[17] This provides better scar camouflage of the donor site and, at the same time, allows easy pivot of the flap into the lower lip defect. The Estlander flap causes oral commissure distortion, or microstomia, which can be corrected with a secondary commissuroplasty when desired.

Defects greater than two thirds the width of the lip and some smaller lateral defects are best reconstructed by using adjacent cheek flaps in the form of advancement or transposition flaps. Massive or total lip defects are best reconstructed by using regional or distant flaps or vascularized microsurgical flaps. Large defects of the upper lip can be reconstructed by transferring bilateral crescent-shaped perialar cheek tissue downward and medially (Bruns flaps). If wound closure tension is excessive, an Abbé flap can be added in the midline.[17]

Similarly, midline lower lip defects can be closed by full-thickness advancement flaps as described by Bernard,[18] Webster[13] or Gilles. These techniques may require excision of additional triangles in the melolabial sulcus to allow advancement of the cheek flaps. Triangular excision should follow the lines of the sulcus and should include only skin and subcutaneous tissues. The underlying muscle is mobilized to form a new commissure. The mucous membrane is separated from the muscle

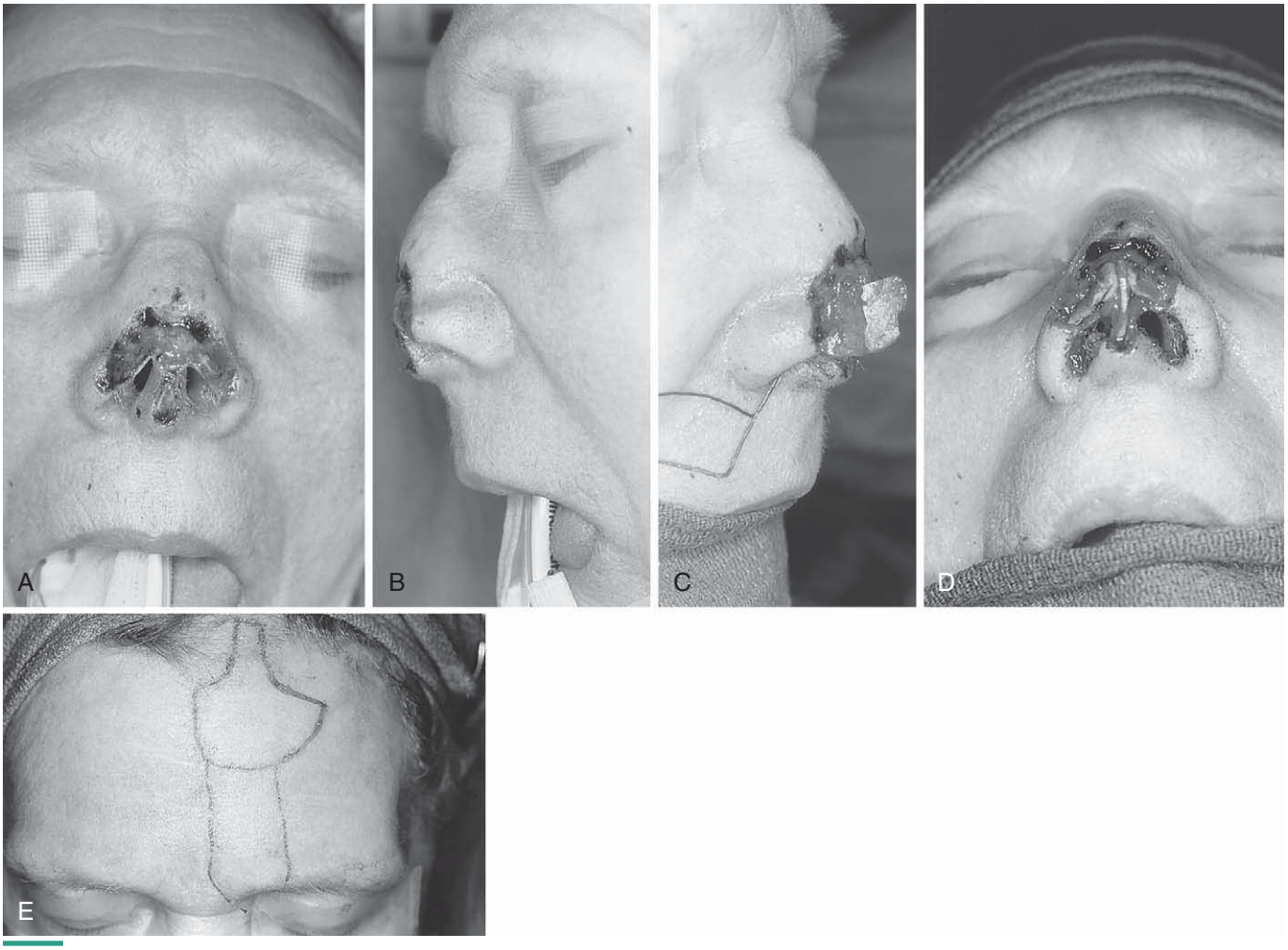

Figure 24-15. **A** and **B,** Full-thickness defect of the nasal tip and columella. Medial and intermediate crurae of lower lateral cartilages are absent. **C,** Composite pivotal septal flap turned outward to provide structure and mucosa for reconstruction. Bilateral hinged septal mucosal flaps have been turned downward to provide internal lining to the missing nasal tip. **D,** Septal cartilage from the composite flap replaces medial crurae whereas auricular cartilage grafts replace dome cartilage bilaterally. **E,** Paramedian forehead flap is designed to resurface the nasal tip and columella.

Continued

Figure 24-15, cont'd. Preoperative **(F)** and 1-year postoperative **(G)** profiles show enhanced tip projection after reconstruction. Preoperative **(H)** and 1-year postoperative **(I)** views show restored tip definition and shape.

and advanced outward to provide a vermilion border. Incisions are made in the gingival buccal sulcus as far posterior as the last molar tooth, if necessary, to allow proper approximation of the remaining lip segments without excessive wound closure tension.

Melolabial transposition flaps consisting of skin and subcutaneous tissue or full-thickness flaps consisting of skin, subcutaneous tissue, and mucosa can be useful in reconstructing lip defects as large as three fourths of the width of the lip.[19] Large skin-only defects of the lateral lip are repaired nicely with melolabial flaps; however, in keeping with the principles of maintaining borders between aesthetic regions, some surgeons prefer to repair defects that extend from the lip onto the cheek with two separate flaps (Fig. 24-21). A large rotation flap from the remaining lip segment is useful for repairing skin-only defects of the upper lip that extend into the cheek. The cheek component of the defect is then repaired by a separate transposition or advancement cheek flap. This places nearly all the scars in the melolabial sulcus while maintaining the integrity of the border between the lip and cheek aesthetic regions.

Adjacent cheek tissue may not be applicable or sufficient for reconstruction of near-total defects of the lip. In such cases, regional flaps can be used for reconstruction. Excisions of the lower lip, chin, and anterior section of the mandible for carcinoma often require such flaps for reconstruction.

The temporal forehead flap designed as a bipedicle advancement or unipedicle interpolation flap can be used for total upper lip reconstruction, but the unsightly secondary deformity precludes its common use. The flap may be lined with a full-thickness skin or mucosal graft. In males, hair-bearing scalp can be incorporated to provide hair growth for scar camouflage.

Several regional flaps are used for repair of large defects of the upper and lower lip. Other publications describe the use of regional flaps in lip reconstruction.[2]

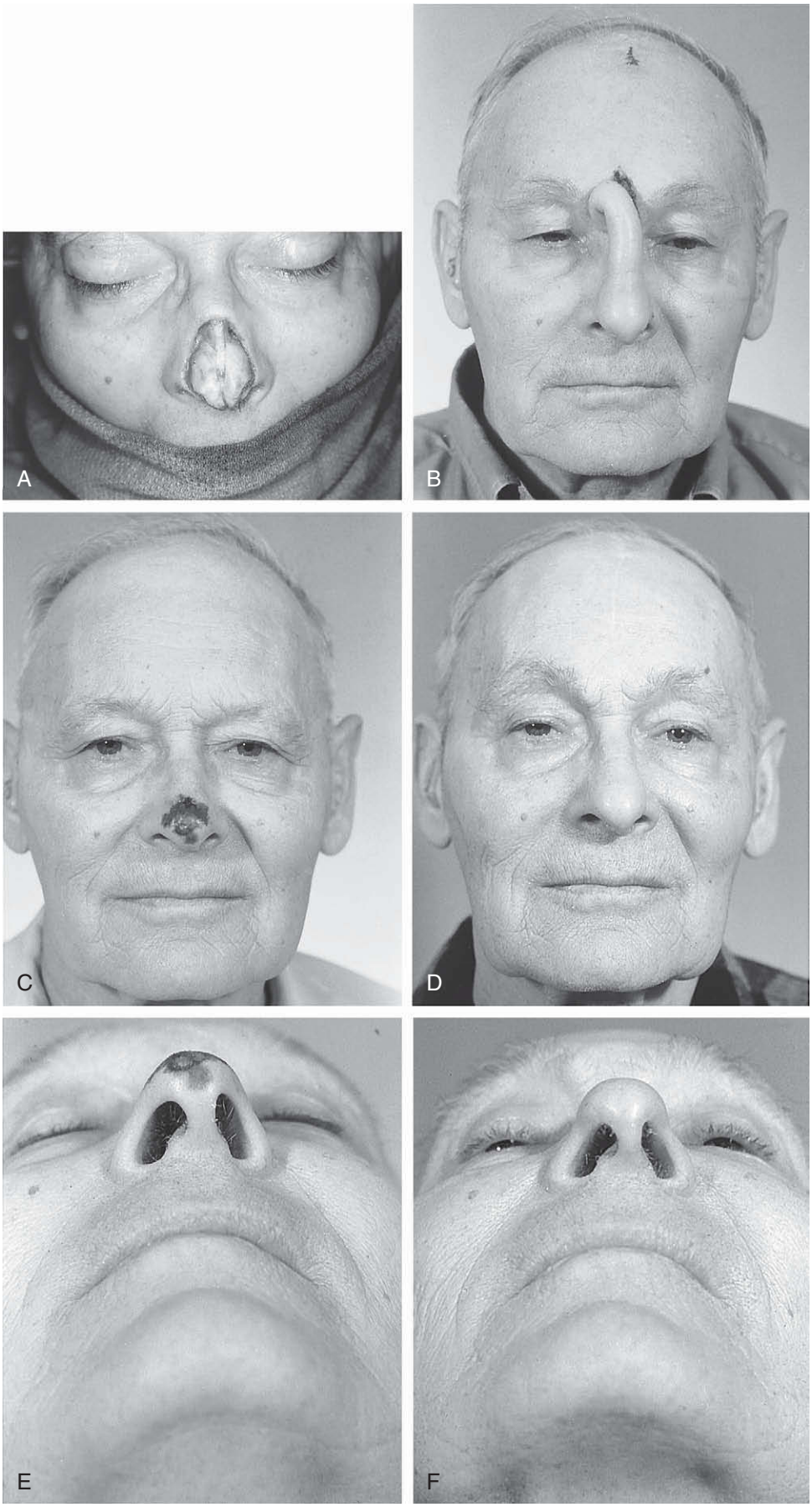

Figure 24-16. **A,** Cutaneous defect of nasal tip following removal of melanoma. **B,** Paramedian forehead flap used to resurface skin defect of the nasal tip and dorsum. A narrow pedicle enhances effective flap length. **C** and **D,** Preoperative and 2-year postoperative views. Note symmetry of medial brows after detachment of the pedicle. **E** and **F,** Preoperative and 2-year postoperative views.

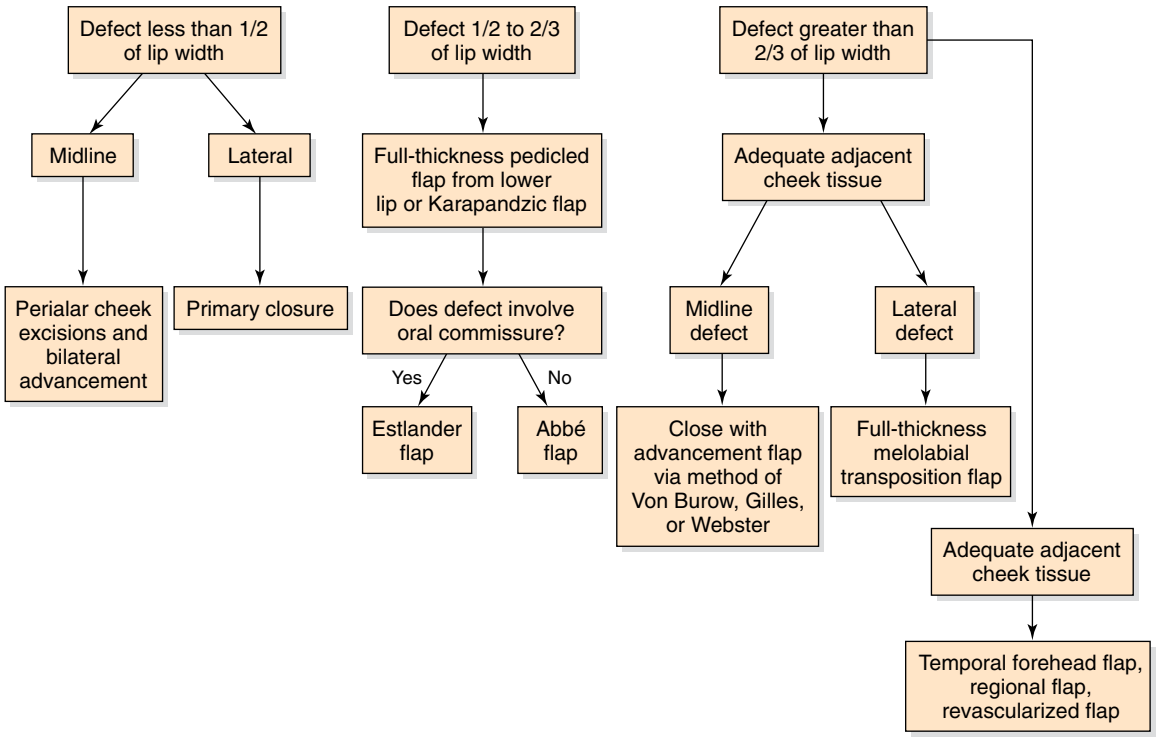

Figure 24-17. Correction of upper lip defects.

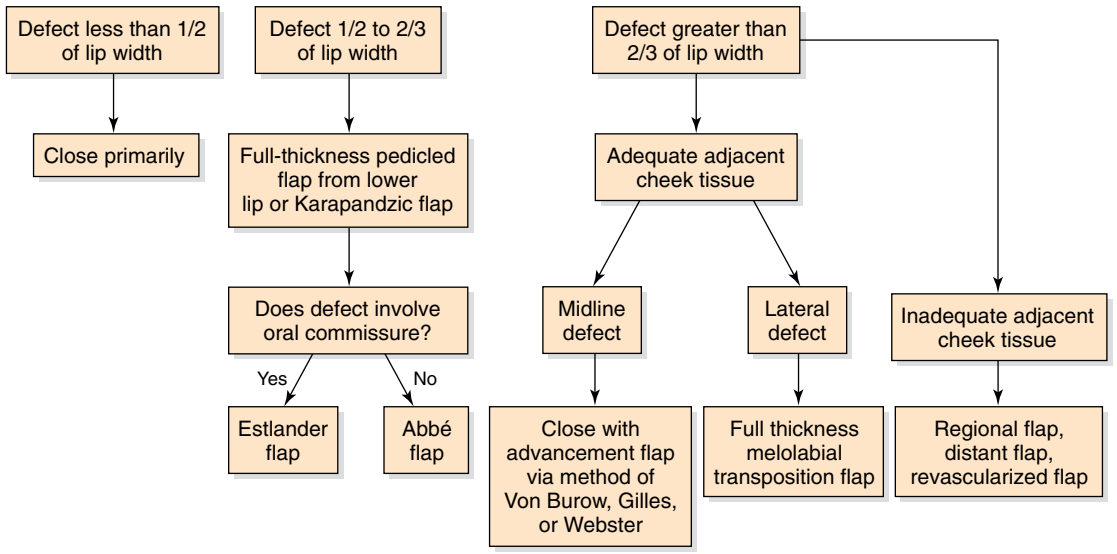

Figure 24-18. Correction of lower lip defects.

Reconstruction of Cheek Defects

Relative to the nose and lip, repair of cheek defects is less complex and is usually best accomplished with transposition or advancement flaps. Rhombus-shaped and other transposition flaps are very versatile and can be used anywhere in the cheek for small- to medium-sized defects. Particular attention should be placed in designing flaps for repair of defects near the lips or eyelids. For rhombus-shaped flaps, the orientation should be designed so that the area of greatest wound closure tension is away from these structures so as not to cause distortion. Rhombus-shaped flaps are a type of transposition advancement flap. This flap is useful when the defect has a shape of a rhombus with angles approximating 120 and 60 degrees. Success of the flap depends on adjacent areas of redundant skin. These areas should lie adjacent to the 120-degree angle of the rhombus. The flap is designed by extending a line of the rhombus straight out from the point of the 120-degree angle. The length of this line should equal the length of the side of the rhombus. At the end of this line, a second line is extended parallel to the side of the defect and is of the same length. The flap is dissected in the subcutaneous tissue plane and requires wide undermining of the entire area of the flap and defect. The flap is transposed and sutured into position. The donor site is closed primarily and represents the area of greatest wound closure tension. Usually a standing cutaneous deformity should be excised to complete the repair.

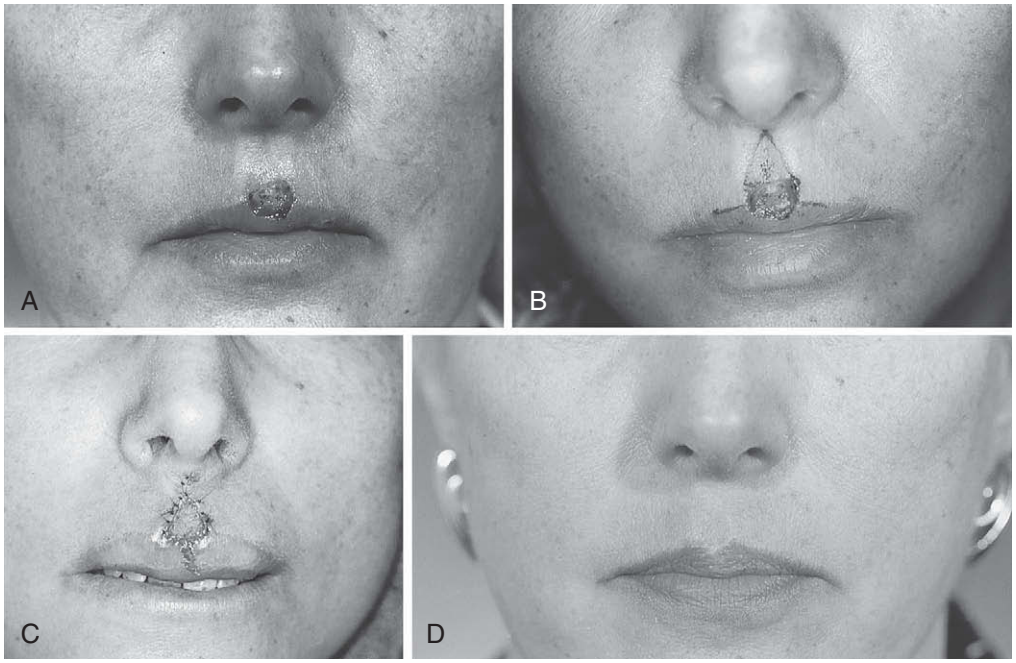

Figure 24-19. **A,** A small skin defect confined to the philtral aesthetic unit. **B,** A V-Y musculocutaneous island pedicle flap is designed within the unit. **C,** Flap advancement. **D,** The 7-month postoperative view.

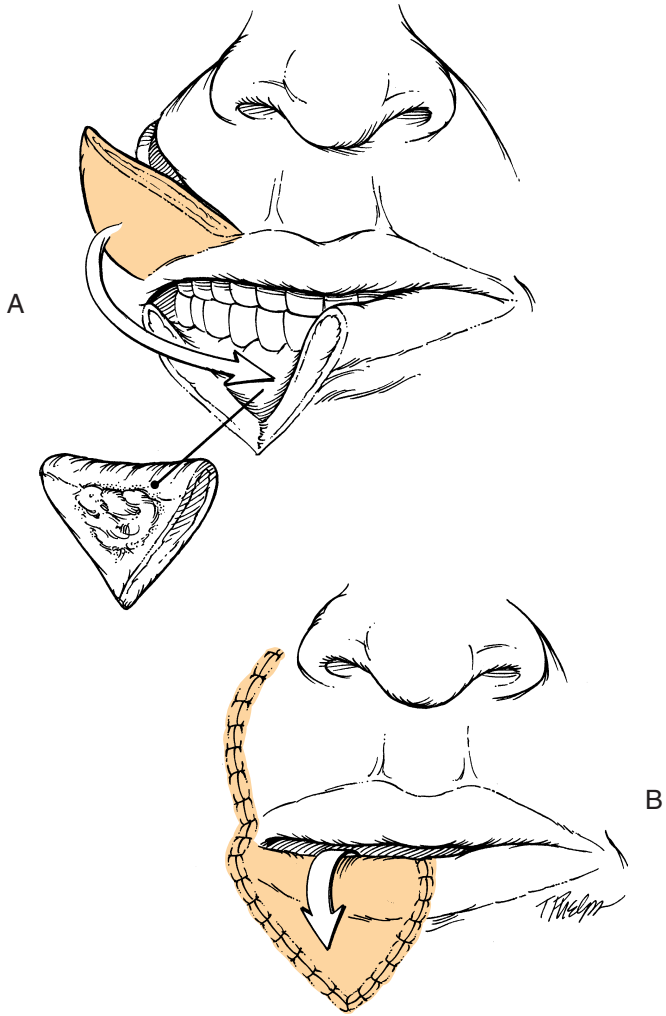

Figure 24-20. **A** and **B,** Superiorly based Estlander flap is designed so the resulting donor site scar lies within or parallel to melolabial sulcus. Mucosal advancement assists in correcting discrepancies in vermilion vertical height of flap and recipient site. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

A bilobed flap represents a double transposition flap that has a single pivotal point and is useful in repairing larger cheek defects (Fig. 24-22). The axis of the two lobes is dependent on where the resource of tissue is located and, as such, may be separated by a few degrees up to 180 degrees. The greater the separation, the greater the standing cutaneous deformity between the two lobes. Large bilobed flaps are useful for the repair of central and lateral cheek defects recruiting tissue from the remaining preauricular and infra-auricular areas. Depending on the location of the defect, the first lobe may be designed as much as 20% smaller than the defect. It may be made even smaller when a great deal of advancement of the defect margins is possible or desirable. The second lobe that is used to repair the donor site of the first lobe is usually constructed 20% smaller than the first lobe. In general, the major advantage of a bilobed flap is the ability to recruit redundant tissue from two independent areas to assist in the repair of the defect. The major disadvantage of the flap is the extensive undermining that is required and the extensive linear scar that is created. When the incision lines do not fall within relaxed skin tension lines, the scars may not be favorable. Bilobed flaps for repair of cheek defects should be based inferiorly, and the standing cutaneous deformities should be excised in such a way that the resulting scars are parallel to or lie within natural skin creases.

Rotation flaps are useful for repairing medial cheek defects in the vicinity of the border between the nasal sidewall and the cheek. The curvilinear border of the flap can often be positioned along the infraorbital rim, which represents an important aesthetic boundary.

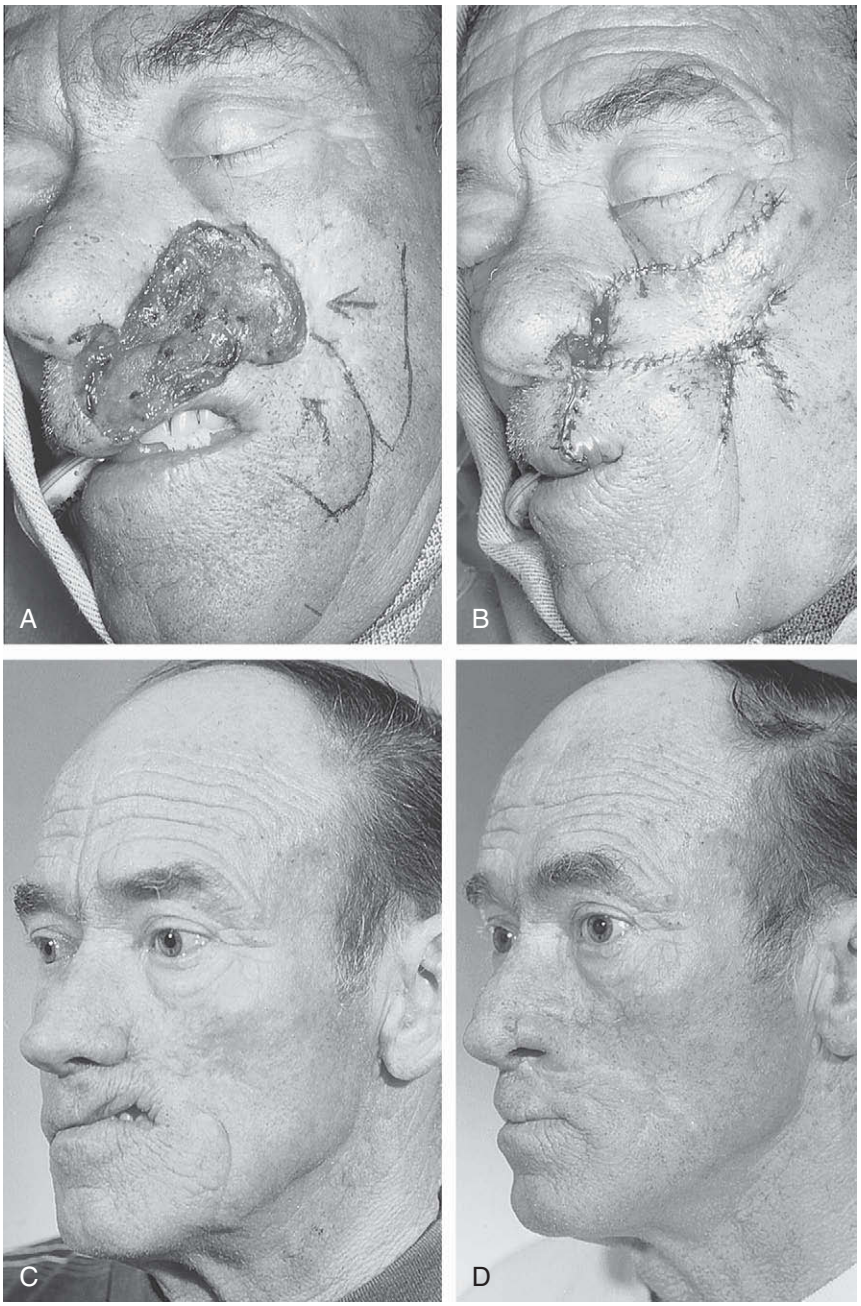

Figure 24-21. **A** and **B,** Extensive skin defect of upper lip and cheek. A full-thickness loss of the alar lobule is present. Repair of cheek and lip defects are planned with flaps harvested from separate aesthetic regions of the face (lip and cheek). Repair of the alar defect is delayed. Preoperative **(C)** and 1-year postoperative views **(D).** The alar lobule was reconstructed with a hinged septal mucosal flap, auricular cartilage graft, and paramedian forehead flap.

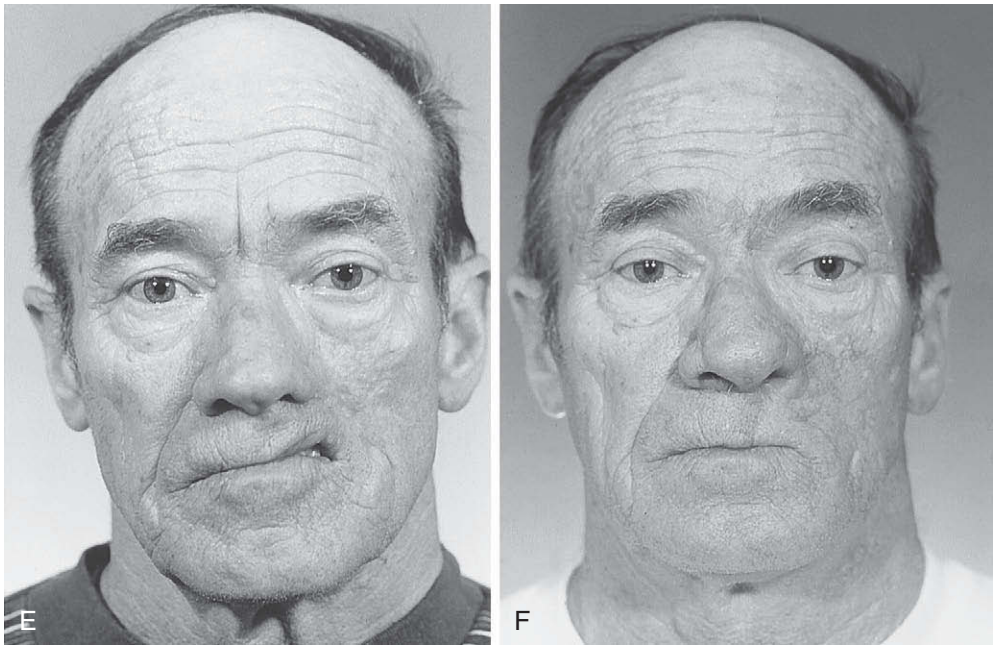

Figure 24-21, cont'd. Preoperative **(E)** and 1-year postoperative views **(F).**

By positioning the incision for the flap along this border, the surgeon can enhance scar camouflage. When possible, the margin of the rotation flap should extend above the level of the lateral canthus to reduce the risk of lower lid retraction (Fig. 24-23). It may also be helpful to suspend the flap to the periosteum of the lateral orbital rim. Despite these precautions, lower lid retraction is not an uncommon sequela when a rotation flap is used to repair large medial cheek defects in elderly patients, who frequently have lax lower eyelids. Large rotation flaps are particularly useful for the reconstruction of sizable defects of the posterior cheek and upper neck. Large inferiorly based rotation flaps provide a flexible means for transfer of large amounts of skin from the remaining cheek and upper cervical skin.[4] Incisions for the flap are placed in a preauricular crease and can extend to the level of the clavicle or below along the anterior border of the trapezius muscle to facilitate rotation of the upper cervical skin toward the posterior cheek area. To enhance the vascularity to such flaps, it is advantageous to dissect the flap beneath the superficial musculoaponeurotic system in the cheek and beneath the platysmal muscle in the neck. A sub-superficial musculoaponeurotic system dissection in the face allows the placement of a great deal of tension on the flap without compromise of the skin vascularity. However, care should be taken to not injure the mandibular branch of the facial nerve (Fig. 24-24).

Advancement flaps are dependent on the elasticity of the skin for successful repair. Many cheek defects can be closed or greatly reduced in size by simply advancing the defect margins and closing as much of the defect as possible orienting the wound closure parallel to relaxed skin tension lines. Advancement flaps can be designed so that the incisions fall within natural skin creases of the cheek. To follow this principle, incisions used to form the borders of the flap usually should diverge slightly, rather than remaining completely parallel. It is usually necessary to remove bilateral standing cutaneous deformities near the base of the flap. This should be accomplished in such a way that the resulting scar lies within relaxed skin tension lines. As an alternative, two bilateral Z-plasties at the base of the flap reduce or eliminate the standing cutaneous deformities. Advancement flaps work well for medial and central cheek defects.

V-Y advancement flaps are particularly useful for repair of small- and medium-sized skin defects of the medial cheek near the alar facial sulcus. This technique is useful for younger patients in whom there is a lack of redundant facial skin and in patients who have considerable subcutaneous facial fat ("chipmunk cheeks") (Fig. 24-25). The flap is designed in a triangular configuration with the surface area of the flap 1.5 to 2 times the surface area of the defect. The skin of the flap is isolated as an island on a subcutaneous tissue pedicle by incising through skin around the perimeter of the flap. The subcutaneous tissue pedicle is then dissected, flaring away from the margins of the flap. Incisions should be made through the fat down to the level of the facial musculature. This deep dissection provides the mobility of the flap, enabling it to be advanced 2 to 3 cm. This mobility is enhanced by undermining the proximal and distal fourth of the flap just deep to the skin. The peripheral margins of the donor and recipient sites should also be undermined for 2 cm in the subcutaneous tissue plane to provide for secondary tissue movement and easy closure of the donor site. The flap is advanced and sutured in the recipient site first, followed by layered closure of the donor site.

A disadvantage of the V-Y subcutaneous tissue advancement flap is that not all of the incisions used to harvest the flap fall within relaxed skin tension lines. However, when appropriately selected, the flap has many advantages. A major advantage is the limited dissection required compared with other techniques. Thus there is minimal dead space with a concomitant reduced risk of the development of hematoma and seroma. Another major advantage is that no standing cutaneous deformity develops; therefore no tissue is discarded. The flap is harvested from the jowl area, where facial skin is most redundant and, as a consequence, there is minimal or no deformity of the melolabial fold and sulcus.

Most skin defects of the cheek can be repaired with primary closure, transposition, or rotation flaps. Transposition flaps tend to be very useful and are usually harvested from adjacent cheek skin, but they can be developed in the upper neck to resurface larger defects in the lower cheek. Melolabial transposition flaps are best designed as a superiorly based flap (Fig. 24-26). This design allows the recruitment of redundant skin in the lower medial face for construction of the flap. Such flaps can be used for small- to moderate-sized defects of the upper, middle, and lower medial aspect of the cheek. Positioning the base of the flap near the alar facial sulcus enhances the vascularity of the flap by including the numerous perforating vessels that extend into the subcutaneous tissue from the facial artery. Superiorly based transposition flaps are excellent for repairing defects of the medial and lateral aspect of the cheek. The flap is designed so that the medial border of the flap lies in the melolabial sulcus whenever possible. The width of

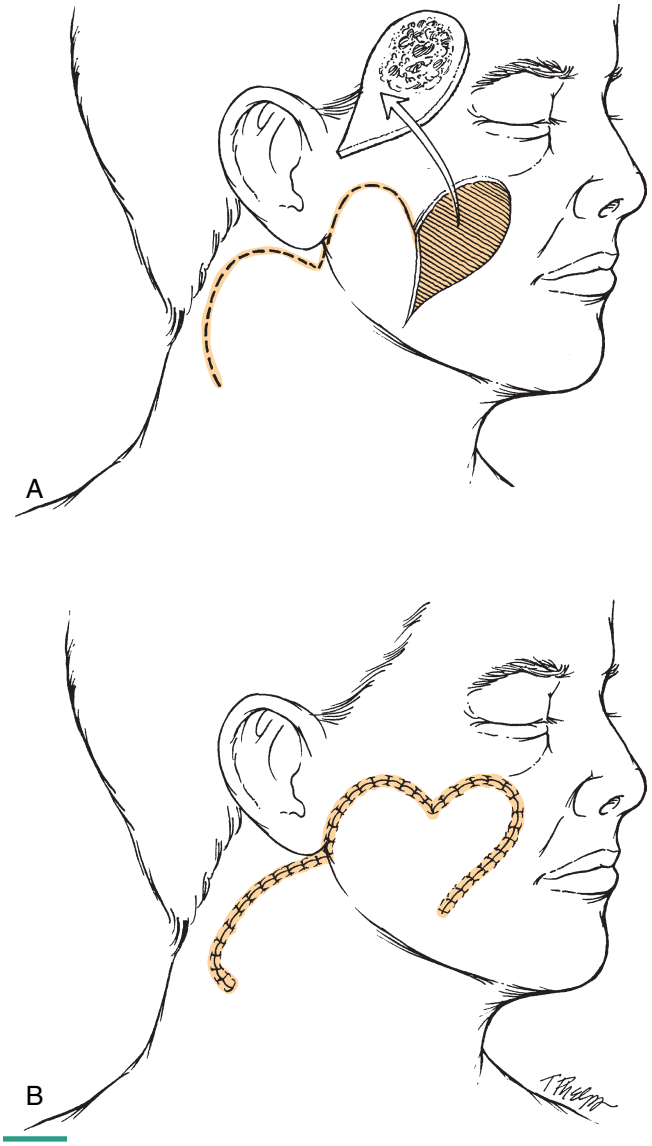

Figure 24-22. Bilobed flaps represent a double transposition flap with a single pivotal point. **A,** Bilobed cheek flap designed to repair large cutaneous cheek defects. **B,** Flap transferred. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

the flap is dependent on the size of the defect and the quantity of donor site resource. The larger the flap or the greater the arc of pivot, the larger the standing cutaneous deformity. Excision of standing cutaneous deformities of the cheek can be accomplished at the time of flap transfer or delayed for a second stage; however, some excision of the standing cutaneous deformity is nearly always necessary because it will not completely absorb by itself.

Forehead Defects

Reconstruction of defects of the forehead should accomplish the following goals[20]: (1) preservation of frontalis muscle function, (2) preservation of sensation of the forehead skin, and (3) placement of scars within aesthetic borders or the horizontal furrows of the forehead. The forehead aesthetic region is defined by junctional lines with the frontal scalp superiorly, the temporal scalp and temple laterally, and the eyebrows and glabella inferiorly. The forehead can be divided into aesthetic units, which include median, paramedian, and lateral temple.[20] The median is in the midline of the forehead. The paramedian extends from midline to a vertical axis above the pupil, and the lateral temple extends from the paramedian border to the temporal hairline laterally. Siegle[20] noted that when planning repair of forehead defects, aesthetic goals include the following: (1) maintenance of eyebrow symmetry, (2) maintenance of natural-appearing temporal and frontal hairlines, (3) the hiding of scars, when possible, along hairlines or eyebrows, (4) the creation of transverse instead of vertical scars whenever possible (except in the midline forehead), and (5) the avoidance of diagonal scars.

Primary wound repair of defects of forehead skin are often possible in older persons and in those with sun-damaged skin. Deep horizontal furrows may provide extra skin for reconstruction. When primary closure is not possible, the use of single or multiple local flaps is preferred over skin grafts because of the poor aesthetic result from the use of skin grafts. When a local flap is not possible, healing by second intention is often less deforming than a skin graft. For midline forehead defects, healing by second intention often produces a very acceptable aesthetic result, particularly when the defect is located in the superior aspect of the forehead. Should the scar not be acceptable, a later scar revision usually provides an excellent result.

Defects of the central third of the forehead can be repaired in a vertical axis with a predictably pleasant aesthetic result. This is probably caused by the natural dehiscence or attenuation of the frontalis muscle in this portion of the forehead. Larger midline defects closed in a vertical orientation can result in large standing cutaneous deformities, which may be excised with use of a W-plasty within glabellar creases (Fig. 24-27). An M-plasty superiorly may also be necessary to eliminate a standing cutaneous deformity at the hairline. M-plasty and W-plasty techniques reduce the overall vertical length of the closure scar. This

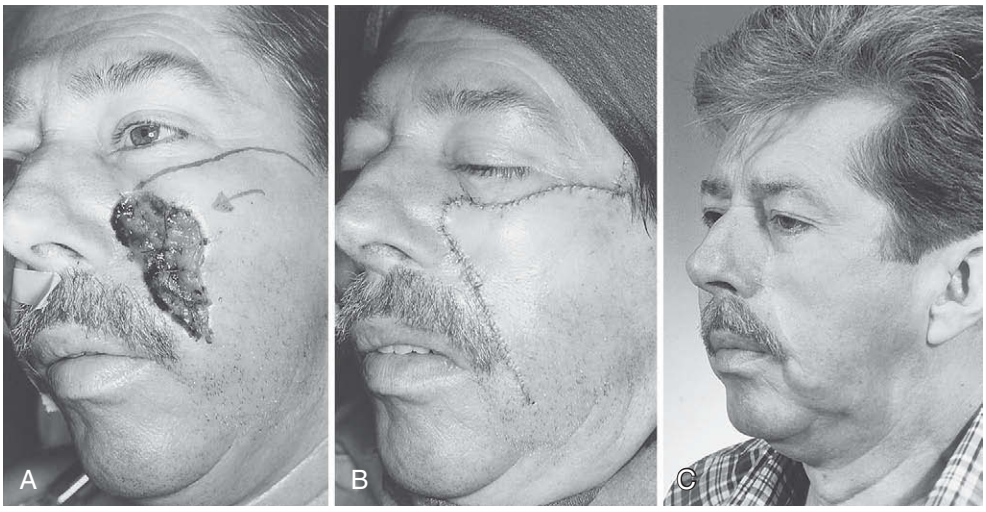

Figure 24-23. **A,** A rotation flap designed to repair medial cheek defect. **B,** The flap in position. The border of the flap extends above the level of the lateral canthus. **C,** The 7-year postoperative view.

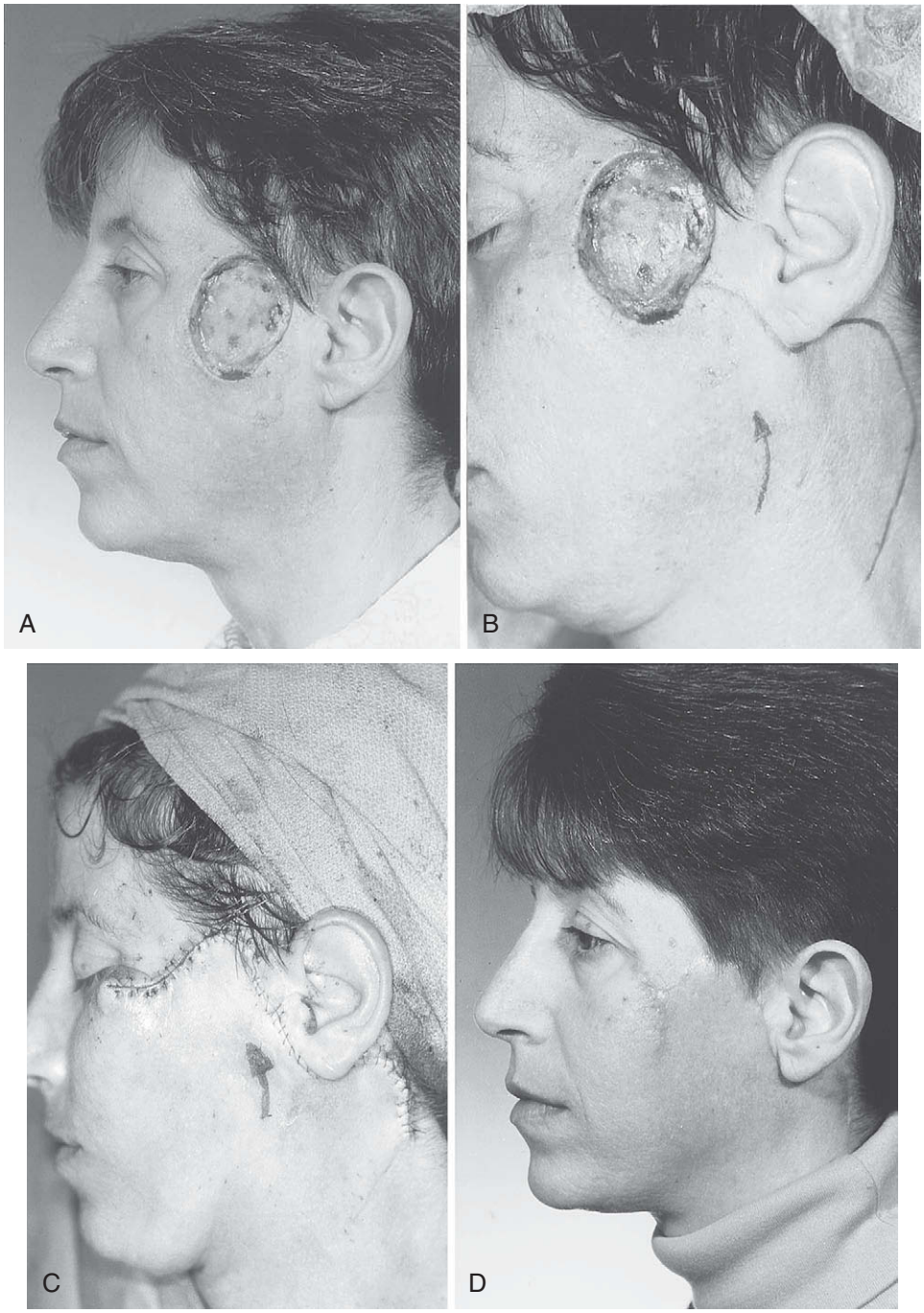

Figure 24-24. **A,** A large cheek defect in a 40-year-old female smoker. No redundant cheek skin is available because of the patient's age. **B,** A bilobed cheek and neck flap designed for repair. **C,** The flap is transferred. The flap was dissected beneath the superficial musculoaponeurotic system, which allowed great wound closure tension without compromise of skin vascularity. **D,** The 3-month postoperative view.

type of repair allows extensive undermining in the subfascial plane to facilitate closure without compromise of motor or sensory function of the forehead.

In general, vertical-oriented primary repairs, rotation flaps, and transposition flaps are to be avoided in the repair of paramedian forehead defects because they often result in vertical scars.[20] Vertical scars in the lateral two thirds of the forehead on either side are usually wide and quite noticeable. Such scars should be avoided whenever possible and revised with a running W-plasty closure when present. Median and paramedian forehead defects can be reconstructed with unilateral or bilateral advancement flaps, keeping most of the resulting scars oriented horizontally.

The lateral forehead represents a transition in topography from the convexity of the median and paramedian forehead to a flat lateral forehead, which continues into a slightly concave temple. The slightly concave nature of the temple makes this region of the forehead particularly good for healing by second intention. The enhanced elasticity of lateral forehead skin compared with more centrally located skin allows more reconstructive options. Primary wound closure is also often feasible with orientation of the repair parallel to the forehead skin creases, which become curvilinear as they arc downward toward the cheek. These lines are excellent locations for placement of incisions. The location of the temporal hairline and the brow dictate the orientation and size of advancement, rotation, and transposition flaps in this

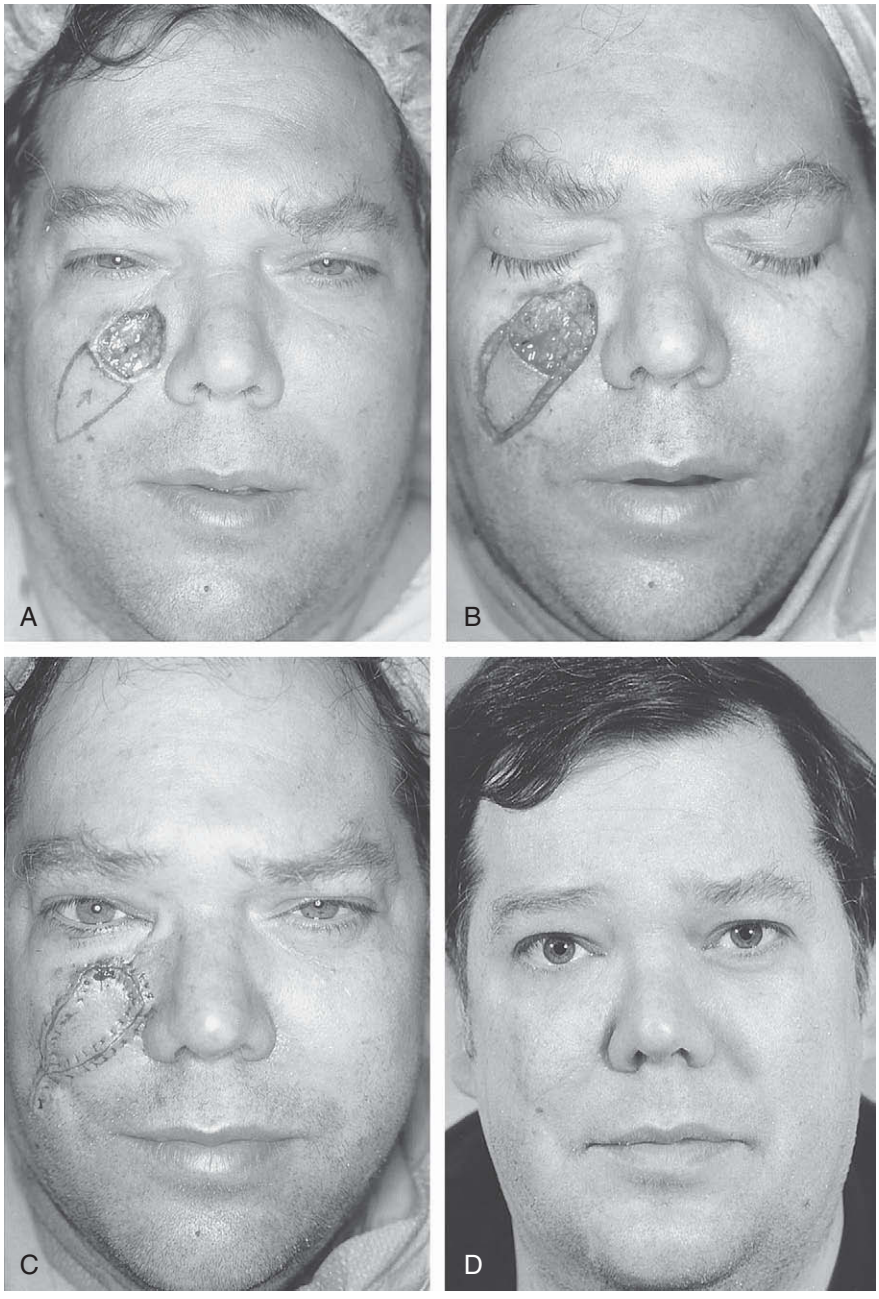

Figure 24-25. **A,** V-Y advancement flap designed to repair medial cheek defect. **B,** The flap is based on a subcutaneous tissue pedicle. **C,** The flap is positioned in the recipient site. **D,** The 5-month postoperative view.

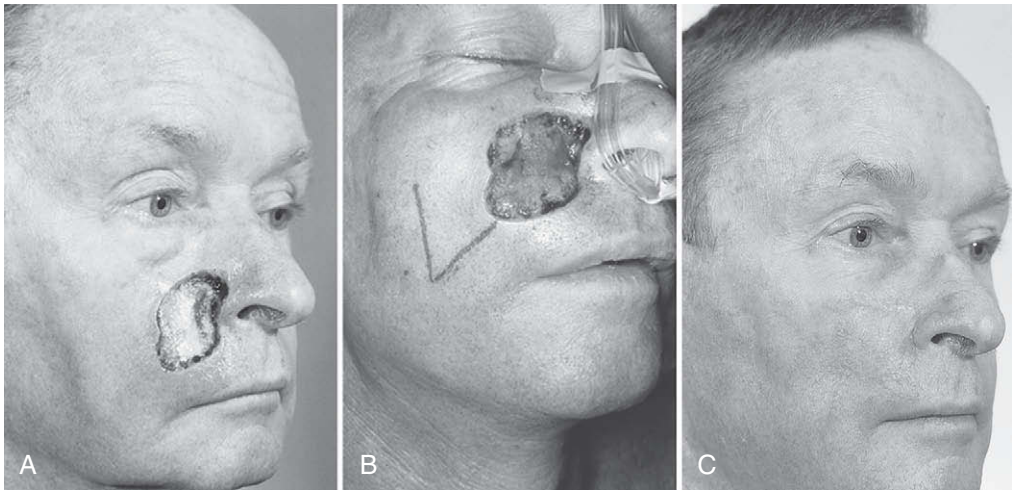

Figure 24-26. **A,** A large medial cheek defect. **B,** A superiorly based transposition flap designed for repair. **C,** The 2-month postoperative view.

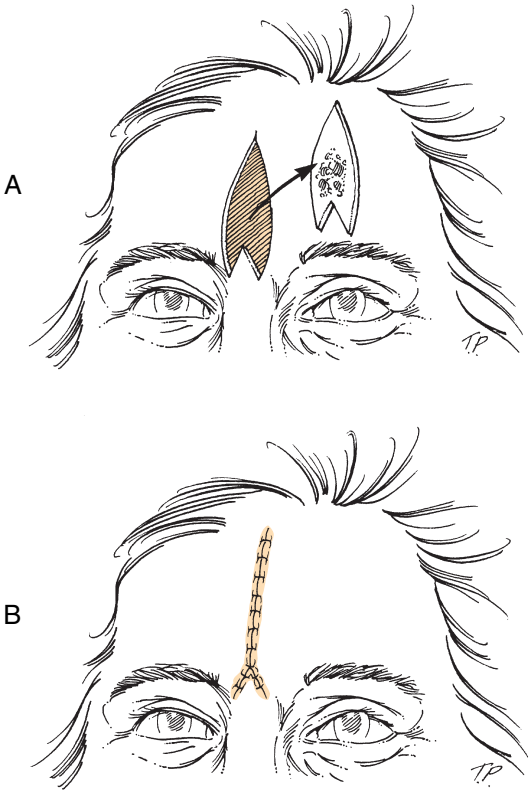

Figure 24-27. Closure of large midline forehead defects is often facilitated by W-plasties inferior or M-plasties superior to the border of the defect. **A,** W-shaped cutaneous defect created by excising the skin tumor. **B,** Wound is closed. The W-shaped excision limits the vertical length of the scar. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

area. The surgeon should take particular care in the lateral forehead area when dissecting such flaps because of the vulnerability of the frontal branch of the facial nerve. Advancement and advancement rotation flaps are perhaps most useful for repair of lateral forehead defects (Fig. 24-28). Usually bilateral advancement flaps are preferred over single flaps, with the greatest advancement achieved from the more elastic laterally based flaps.

A variation of advancement flaps for repair of medium-sized defects of both the lateral and paramedian forehead is the O-T or A-T repair. This method consists of extending horizontal incisions along both sides of the defect within relaxed skin tension lines or along the border of the brow or temporal hairline. The two flaps are dissected in the subcutaneous tissue plane and advanced toward the triangular or circular defect (Fig. 24-29). Standing cutaneous deformities are resected when necessary from within the brow or are eliminated by the rule of halving the wound closure. If necessary, the standing cutaneous deformity that results from the pivotal portion of the flap movement can be removed by enlarging the defect itself. The final wound closure takes the configuration of a T-shaped repair. Thus circular defects closed in this manner are referred to as an O-T repair and triangular defects (A-shaped) are referred to as an A-T repair. These techniques camouflage scars, except for those along the central vertical wound closure line.

Rotation flaps are very useful in reconstructing medium and large lateral forehead defects. A unilateral rotation flap, based inferiorly and laterally and designed so that its curvilinear incision follows the margin of the temporal hairline, is an excellent method of reconstructing lateral forehead defects that are close to the hairline. The curvilinear incision can be designed to incorporate hair-bearing scalp to bring hair into the reconstructed area if some of the temporal tuff has been lost.[20] The standing cutaneous deformity that inevitably forms with such a flap can be removed inferiorly in the crow's feet to camouflage the scar.

The most effective technique for reconstruction of the forehead usually involves one or more advancement flaps. Despite the relative inelasticity of forehead skin, the use of advancement flaps is preferred

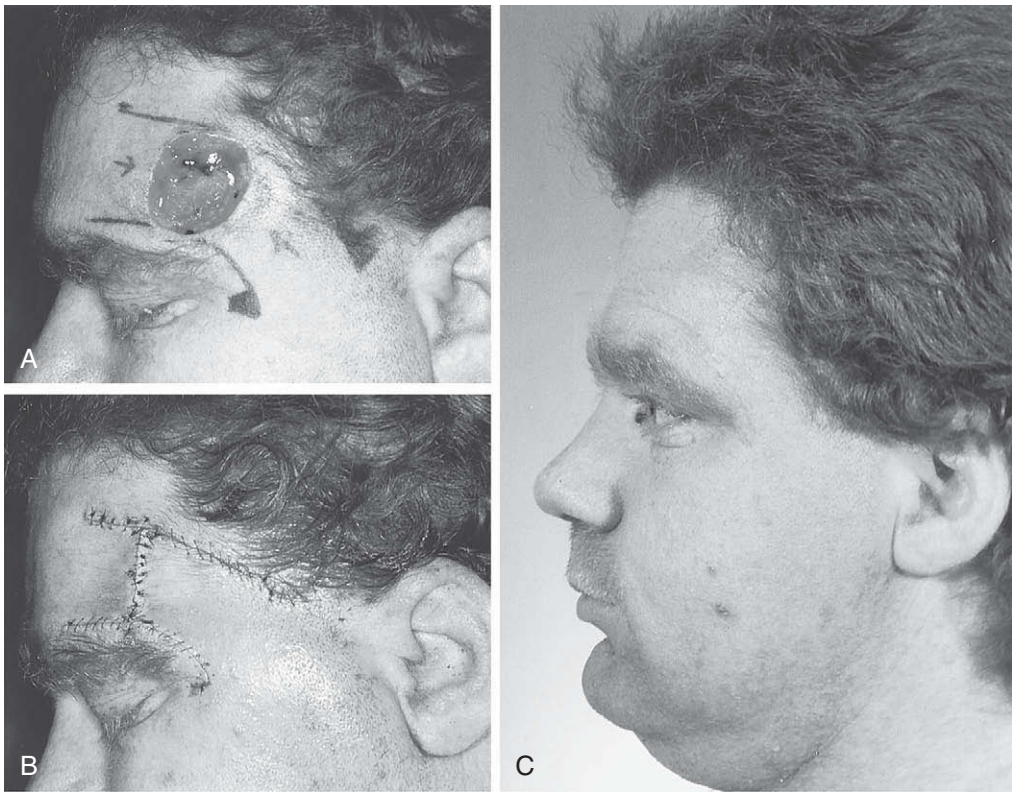

Figure 24-28. A, The medially based advancement and laterally based advancement rotation flap designed to repair lateral forehead defect. **B,** The flaps advanced. A standing cutaneous deformity of the laterally based flap is removed in periocular rhytid. **C,** The 6-month postoperative view.

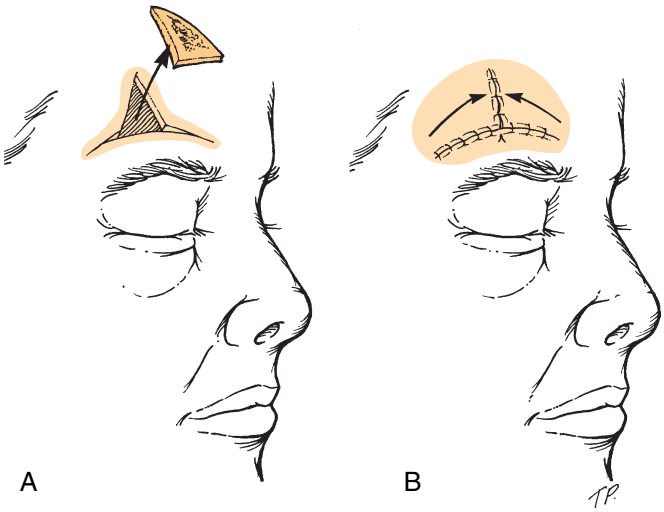

Figure 24-29. A T-shaped repair of a lateral forehead defect. **A,** The skin tumor is excised with a triangular-shaped excision. **B,** The wound is closed in a T configuration. *(Adapted from Baker SR, Swanson N.* Local Flaps in Facial Reconstruction. *St. Louis: Mosby; 1995.)*

because they produce the most favorable cosmetic result. However, the surgeon should be aware that many skin defects of the forehead can be successfully managed by allowing the wound to heal by secondary intention. This often gives a cosmetic result that is comparable with that of flap repair when the appropriate forehead site is selected. An ideal location for healing by secondary intention is high on the forehead well away from the brow, in the central or lateral third of the forehead.

Tissue expansion enables the surgeon to reconstruct sizable forehead defects, which in the past could be repaired only with skin grafts. Controlled, prolonged tissue expansion can be used to reconstruct very large forehead defects by expansion of the remaining forehead skin over 6 to 12 weeks. Reconstruction is achieved by direct advancement of the expanded skin or used in combination with other scalp, cheek, or temple skin flaps. The disadvantages of tissue expansion include the fact that it is a two-staged procedure and considerable deformity of the forehead is present during the expansion process. These disadvantages are far outweighed by the excellent results that can be achieved with tissue expansion in the repair of very large defects of the forehead.[21]

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CHAPTER TWENTY-FIVE

Nasal Reconstruction

Norman N. Ge

C. Rose Rabinov

Roger L. Crumley

Key Points

- The nose is a three-layered structure composed of a skin and fibrofatty covering, a bony and cartilaginous framework, and an inner lining of vestibular skin and nasal mucosa. Nasal defects may involve any combination of these three layers and each component should be reconstructed.
- The external nasal envelope is divided into topographic subunits: tip, dorsum, sidewalls, alar lobules, soft triangles, and columella. When a defect involves greater than 50% of a subunit, replacement of the entire subunit should be considered.
- Options for repairing external defects include healing by secondary intention, primary closure, skin grafting, adjacent flap coverage, and regional flap coverage. Secondary intention is a good choice for superficial wounds on concave surfaces.
- Good donor sites for skin grafts are the preauricular, postauricular, nasolabial, supraclavicular, and upper eyelid areas. Due to the sebaceous nature of the lower third of the nose, a skin graft in this region may heal with a contrasting flattened and shiny appearance.
- Advantages of local flaps over skin grafts are better contour, color, and texture match as well as less scar contracture. Local flaps are useful for defects of about 2 cm or less.
- Nasal defects larger than 2 cm can be repaired with melolabial or forehead interpolation flaps. The second stage of pedicle division and inset is usually performed 3 weeks later.
- Autogenous cartilage and bone are the best choices for repairing defects of the nasal skeletal framework. However, alloplastic materials, including silicone rubber, expanded polytetrafluoroethylene, and polyamide mesh, have been used with success for restoration of tip, alar, and septal defects.
- Composite grafts composed of skin and cartilage are useful for alar and columellar reconstruction. These grafts may be harvested from the helical rim, helical root, or conchal bowl for one-stage repair.
- Split-thickness calvarial bone is the graft of choice for bony framework reconstruction, as it has a low rate of resorption. Rigid fixation of bone grafts to the frontal bone or maxilla is important for re-establishment of a stable skeletal structure.
- The internal nasal lining should be reconstructed when defects are full thickness. Without replacement of the lining, contracture and fibrosis may result in stenosis and airway obstruction.
- Options for internal nasal lining repair include advancement of bipedicled mucosal flaps, skin grafts, turbinate mucosal grafts, and septal hinge flaps.

Reconstruction of nasal defects is a common procedure for facial plastic surgeons. Such defects may result from trauma, tumor resection, prior aesthetic rhinoplasty, or congenital deformities. When planning for reconstruction of distorted or missing tissues of the nose, the surgeon should consider both form and function. Systematic evaluation of nasal defects involves perception of the nose as a three-layered structure: (1) a cover of skin and subcutaneous fibrofatty tissue, (2) an underlying bony and cartilaginous framework, and (3) a soft tissue lining of vestibular skin and nasal mucosa. Defects may involve any combination of these layers. The choice of tissue for reconstruction is generally determined by which elements are missing. The primary reconstructive goal is that each component be restored as closely as possible to its original anatomic state for optimal functional and aesthetic outcome.[1]

The outermost to innermost layer is evaluated in terms of options for restoration. Although each layer is discussed separately, defects usually involve multiple levels, and a combination of reconstructive procedures may be required. Regional nasal characteristics and involvement of adjacent structures require further specific consideration.

External Covering Layer

The nose has been described as being composed of concave and convex surfaces separated by ridges and valleys.[2] These surfaces, known as aesthetic or topographic subunits, include the tip, the dorsum, the paired side walls, alar lobules, soft triangles, and the columella. When a defect involves greater than 50% of a subunit, replacement of the entire subunit is often better than replacement of only a part. Placement of scars along contour lines re-creates normal highlights and landmarks. Although this may require some healthy tissue to be discarded, the outcome is often improved.

Just as the contour of the nasal surface varies, nasal skin texture and thickness also demonstrate regional variation. Skin over the upper

Figure 25-1. A 65-year-old woman with basal cell carcinoma of the supra-tip skin. **A,** The defect immediately after Mohs' resection. **B,** One month after primary closure with increased nasal labile angle and improved breathing.

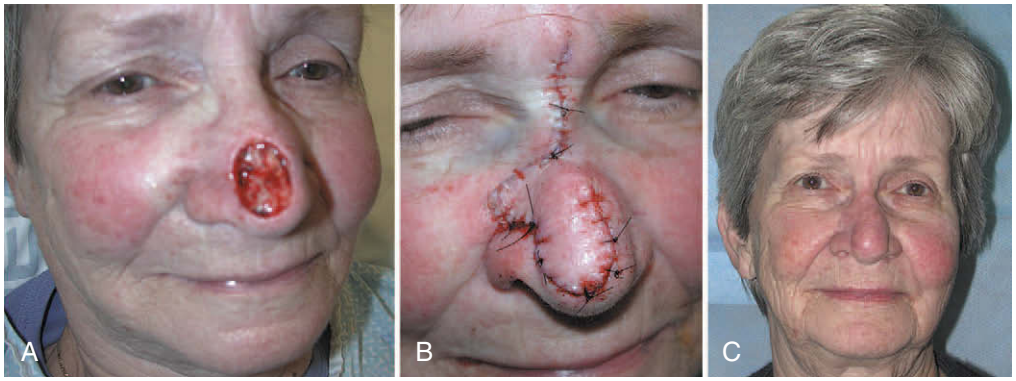

Figure 25-2. A 67-year-old woman with basal cell carcinoma of the right nasal tip and dorsum. **A,** The defect immediately after Mohs' resection. **B,** Bilobed reconstruction. **C,** Three months after the reconstruction. The patient does not wish to have further procedures.

half of the nose is thin and nonsebaceous, whereas the skin over the tip and alar lobules is thicker and contains sebaceous glands. Caudally, over the alar margins and columella, the skin again becomes thin and shiny. Nasal skin mobility also varies. Skin over the upper half of the nose is freely movable; whereas that over the caudal half is firmly adherent to underlying cartilage and fibrofatty tissues. These tissue differences should be considered when reconstruction is planned.

Options for repairing defects involving skin alone include healing by secondary intention, primary closure, skin grafting, and local and regional flap coverage. The choice of method is best guided by evaluation of location and depth of the wound. Healing of superficial wounds by secondary intention on concave surfaces may result in a satisfactory aesthetic outcome. For example, this method is a good choice for wounds of the medial canthal region where advancement of local tissue may distort the eyelids. However, when wounds on convex surfaces heal by secondary intention, the result is often a flattened or depressed scar. Similarly, primary closure may be used for a small defect of the mobile skin over the nasal dorsum, whereas closure of a similar defect over the tip region may result in alar retraction or asymmetry. However, in patients with tip ptosis, primary closure of a symmetrical supratip defect can improve functional as well as aesthetic results of the nose (Fig. 25-1).

Full-thickness skin grafts (FTSGs) are useful in the reconstruction of superficial defects involving convex surfaces of the nose. This is especially true in the areas of the tip and alar lobules where tissue mobility is limited for the creation of local flaps. Donor sites for FTSGs include the preauricular, postauricular, nasolabial, supraclavicular, and upper eyelid skin, each providing good color match and an easily hidden donor site. Tissue from the nasolabial crease results in the most satisfactory aesthetic reconstruction because it matches most closely the thickness, color, and texture of nasal skin.[3,4] When the defect is deeper than the thickness of an FTSG, it can granulate for 7 to 14 days before the granulation tissue surface is scraped and a delayed skin graft is placed.

Because of the sebaceous nature of the lower third of the nose, an FTSG may heal with a contrasting flattened, shiny appearance.[5] Thus the best results are obtained when FTSGs are used to repair superficial defects in areas of the nose where the skin is naturally thin and nonsebaceous. In addition, when placing an FTSG for reconstruction, it is often best to excise sufficient normal tissue to allow replacement of an entire nasal subunit to minimize a patched appearance. Dermabrasion of the area 3 months after grafting further improves texture match between the graft and its recipient site.[6]

Local flaps provide several advantages over skin grafts in nasal reconstruction. Contour, color, and texture match are usually superior to FTSG, and there is usually less scar contracture, contributing to a more reliable aesthetic and functional result. Survival is greater with local flaps than with grafts because of the abundant vascular supply of the dermal and subdermal plexus. Choice among the many flaps available depends on the area of the nose to be reconstructed and the secondary deformity that will result. Simple transposition and bilobed flaps are common choices for coverage of soft-tissue defects of the dorsum or lateral walls. Using Zitelli's modifications of the original design, the bilobed flap is the most useful of the nasal cutaneous flaps.[7] This flap is most useful in the lower half of the nose where the skin from the nasal dorsum and the cheek can be recruited to close the defect of the second lobe (Fig. 25-2). Glabellar flaps are used for the more superior areas[8]; whereas the dorsonasal or Rieger flap is useful for single-

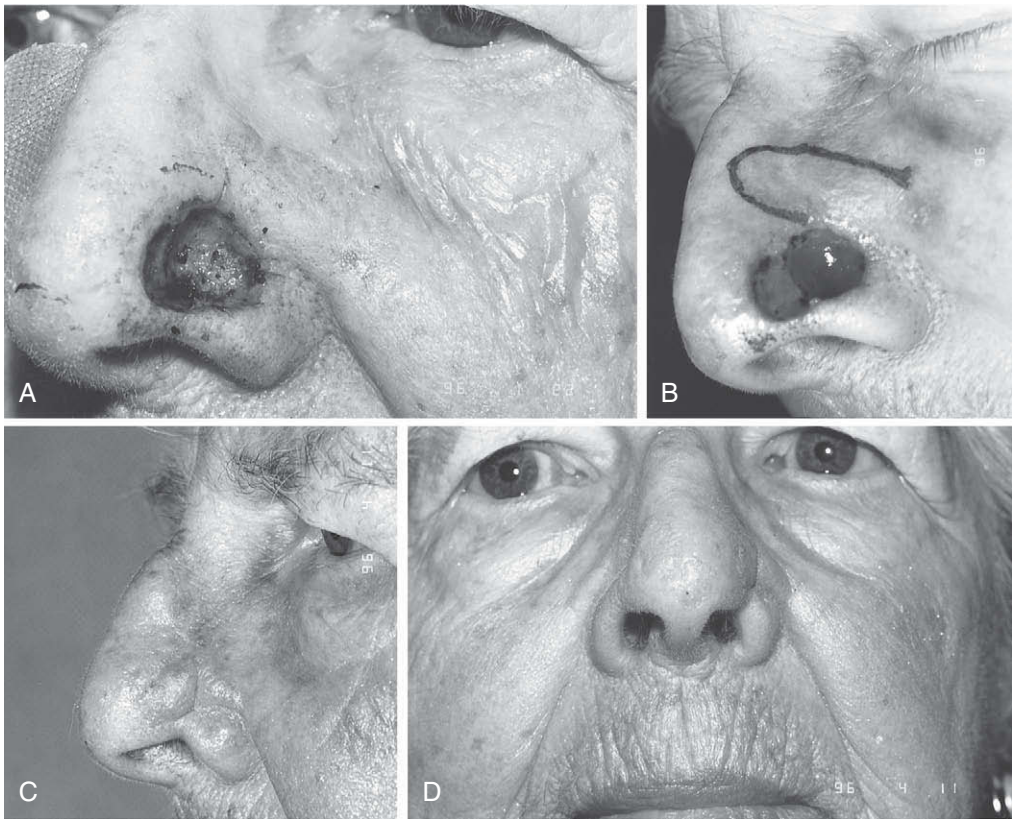

Figure 25-3. An 87-year-old woman with basal cell carcinoma of the left lower aspect of the nose. **A,** The defect immediately after Mohs' resection. **B,** Several days later, granulation tissue is seen and the adjacent transposition flap marked. **C** and **D**, The postoperative result at 3 months. The patient refused further revision.

stage repair of the more caudal regions.[9] A retroauricular flap is an excellent technique for difficult nasal reconstruction in young patients. Transferring retroauricular tissue on a temporal pedicle was first described by Washio.[10] Flaps should be designed so that incisions are hidden within relaxed skin tension lines and along borders of natural aesthetic units as much as possible. Wide undermining of the nasal skin and, in some cases, reduction of a dorsal hump are necessary for closure without tension. These local flaps are useful for defects of about 2 cm or less in diameter (Fig. 25-3).[11]

With larger and deeper defects of the nasal dorsum, lateral wall, and alar regions, it is often necessary to use tissue from areas adjacent to the nose for reconstruction. The melolabial flap is probably the most widely used flap for this purpose. Composed of skin and subcutaneous fat, this flap is harvested from lateral to the melolabial sulcus. Its abundant blood supply, based on perforating branches of the facial artery, results in the creation of a highly reliable flap.

Since the earliest descriptions of the melolabial flap, many variations have been reported.[12] Based superiorly, the flap may be used for defects of the lower two thirds of the nose (Fig. 25-4). With full-thickness defects, the distal portion of the flap may be turned on itself to provide internal lining coverage. When based inferiorly, the melolabial flap is appropriate for reconstruction of the upper lip, floor of nose, and columella (Fig. 25-5). Larger defects can be reconstructed using bilateral melolabial flaps or a combination of local flaps with cheek advancement.

The melolabial flap may also be used as an island flap.[13] In this procedure, a circumferential skin incision is made to create a flap the size of the defect. After wide undermining of the skin, a vascular pedicle of subcutaneous tissue is made, extending from the skin island superiorly toward the infraorbital rim. The flap is then tunneled beneath the skin bridge and rotated into the defect with its subcutaneous pedicle intact. This permits one-stage reconstruction, usually without effacement of the nasofacial or alar-facial creases. The usual design of the melolabial flap requires two stages to complete, with the second procedure being a revision of the pedicle. Tacking sutures from the flap dermis to the underlying periosteum[8] or temporary external mattress sutures may be used to recreate the nasofacial convexity.

The most common complications of local flaps include necrosis or "pincushioning."[14] Distortion of adjacent anatomic structures can also be a problem if flaps are not designed carefully. Necrosis with partial or complete flap loss may be caused by arterial ischemia or venous congestion. Technical problems that can contribute to complications include inadequate hemostasis, excessive tension at closure, and damage to the blood supply by excessive thinning or narrowing of the vascular pedicle.[14] In addition, patients who smoke, who have received prior irradiation to the area, or who are diabetic are at increased risk for flap necrosis.

Pincushioning occurs when persistent edema of the flap results in elevation above the surrounding skin after healing. This problem occurs most frequently when C-shaped flaps are designed with the pedicle located superiorly. Causes of this inadequate lymphatic drainage include scar tissue on the dependent edges of the flap and a thick scar layer on the deep surface of the flap, which is sometimes caused by an unrecognized hematoma.[14] Management options for trap-door deformities include the injection of corticosteroids into the scar tissue, Z-plasties in the parts of the scar running perpendicular to relaxed skin tension lines, and thinning of the flap with excision of the deep surface scar tissue. Although the deformity usually contributes to an unsatisfactory aesthetic result, this same process may in some instances create a favorable mounding of the flap, which helps mimic a preexisting convex contour.[2]

The most widely described method for reconstruction of nasal skin defects greater than 2.5 cm in diameter is the use of a forehead flap. Historically, this flap was designed to be centered in the midline of the forehead, based on one or both supratrochlear vessels. Since the description by Kazanjian in 1946,[15] many variations have been

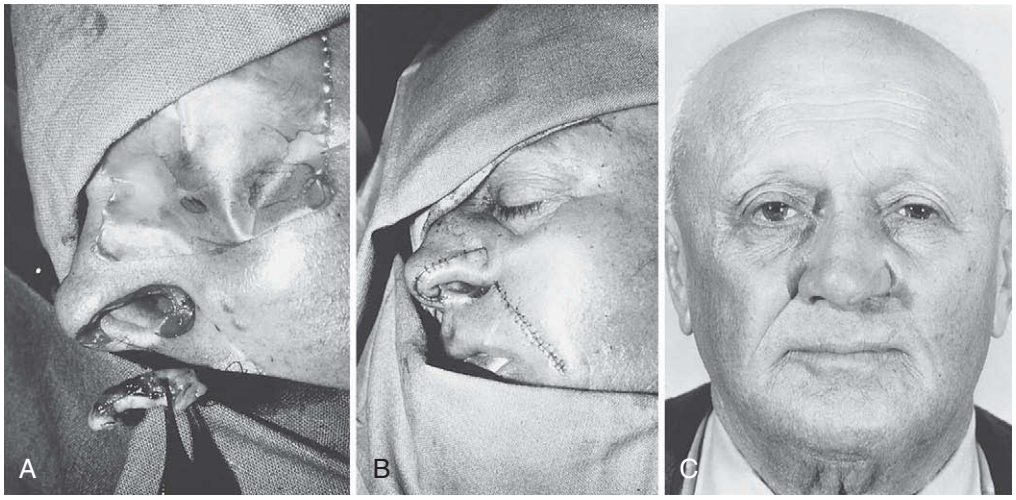

Figure 25-4. A 65-year-old man with carcinoma of left nasal ala. **A,** At time of resection. **B,** A superiorly based nasolabial flap was used to reconstruct the nasal ala. **C,** Postoperatively (not revised), a deformity of the upper melolabial crease amenable to defatting or Z-plasty can be seen.

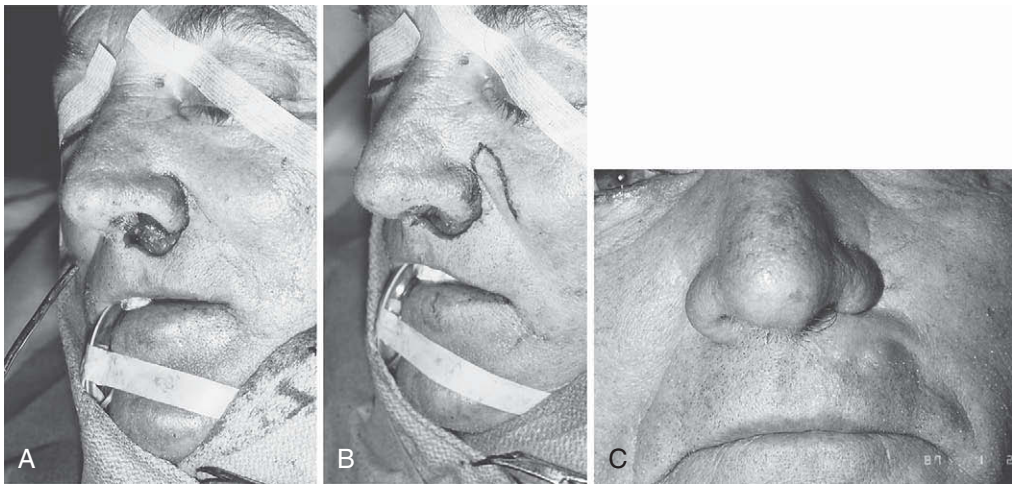

Figure 25-5. A 74-year-old man with squamous cell carcinoma of upper lip and floor of nasal vestibule. **A,** After cancer excision. **B,** The inferiorly based nasolabial fold is marked. **C,** The postoperative result at 5 months. The patient subsequently underwent Z-plasty to restore the melolabial crease.

proposed, including paramedian, oblique, sickle, up and down, and seagull flaps.[16] The paramedian design is used most frequently.

Forehead skin provides tissue of excellent color and texture match for nasal reconstruction. A flap width of 3.5 cm or less allows primary closure of the donor site while providing enough tissue for total resurfacing of the nose. The use of tissue expanders to increase the amount of tissue available, assist in donor site closure, and increase vascularity has been reported,[16-18] although it is generally not necessary.[19] The paramedian flap design provides adequate tissue and allows for ease of transposition by minimizing the width at the base. In addition, the axial blood supply makes this flap extremely reliable.

Nasal reconstruction using a forehead flap is a multistage procedure, and patients should be fully aware of the time commitment. The initial flap design is based on an exact template of the defect. Once the size is determined, the required flap length is measured and marked. Parallel skin incisions are then made with the base of the pedicle positioned over one supratrochlear artery. A Doppler device ensures that the artery is located centrally within the pedicle. The flap is elevated in a subgaleal plane. The distal half may be thinned as the vessels run superficial to the frontalis muscle superior to the eyebrows.[20] Once the base has been narrowed as much as possible without jeopardizing the blood supply, the flap is rotated and set into the defect. The donor site is closed primarily after wide undermining of the forehead. The pedicle is divided 3 weeks later, and the base of the flap returned. Staged revisions involving thinning or dermabrasion of the reconstructed area are completed 3 to 6 months later.

The forehead flap is versatile when used for nasal reconstruction, and it can be combined with cheek advancement, cervical rotation, or Karapandzic type flaps for larger defects that extend laterally or involve the upper lip. In cases of total or near-total nasal loss, the forehead flap is combined with cartilage or bone grafting for restoration of a stable structure (Fig. 25-6).

Framework

When nasal defects extend more deeply to include skeletal supporting structures, functional issues become more important. Strength and stability of the bony cartilaginous framework are of primary consideration. Without adequate support, contracture of the overlying soft tissue envelope may occur, resulting in an abnormal contour and possible airway stenosis. A solid skeletal structure is essential to achieve satisfactory aesthetic and functional results.

Grafting material for skeletal reconstruction should ideally be compatible with the host tissues, easily shaped, and resistant to infection, resorption, and extrusion. Replacement of missing tissue with

Figure 25-6. A 58-year-old woman with basal cell carcinoma of the nose. **A,** The defect immediately after Mohs' resection. **B,** Immediate postoperative picture, defect repaired with midline forehead flap. **C,** One month postoperative result. **D,** One month postoperative result, lateral view.

similar tissue is usually the best option for accurate reproduction of the rigid nasal dorsum and strong but flexible tip-alar complex. Autogenous cartilage and bone are the natural choices for this purpose. When these tissues are unavailable, alternative materials should be substituted. Some surgeons advocate using alloplastic implants when autogenous bone or cartilage is unavailable, although such scenarios are infrequent.

Solid medical grade silicone rubber, polytetrafluoroethylene carbon, and polyamide mesh are among the alloplastic (synthetic) materials that have been used for restoration of tip, alar, and septal defects and for saddle deformities.[21-23] Expanded polytetrafluoroethylene (ePTFE) has been used in rhinoplasty since the mid-1970s when it attracted much attention as an alloplast.[24] Calcium phosphate cement paste seems to be a suitable material for augmentation rhinoplasty. Calcium phosphate cement consisting of alpha-tricalcium phosphate, dicalcium phosphate dibasic, and tetracalcium phosphate monoxide has been used for bone replacement and augmentation because of its good biocompatibility and osteoconductivity.[25] Porous high-density polyethylene implants for cleft lip nasal reconstruction are well tolerated and achieve good aesthetic results. Porous high-density polyethylene implants lend stability through fibrovascular ingrowth, with integration of the implants to the surrounding tissue.[26,27]

AlloDerm has been used in secondary rhinoplasty to cover the osseocartilaginous framework of the nose in an attempt to cover osseocartilaginous irregularities, to eliminate the adhesions between nasal bones and overlying skin, and to create a smooth nasal dorsum.[28]

Advantages of these materials include their ready availability and lack of donor site morbidity. Current alloplasts, however, lack the composition and stability necessary for permanent structural support and are better used as onlay grafts for contour deficiencies. Further disadvantages include a high extrusion rate, foreign body reaction, and susceptibility to infection.[29] These disadvantages relegate alloplastics to a secondary role at this time.

Homograft tissues may also be used for nasal skeletal reconstruction. Biologic implants (e.g., irradiated cartilage,[30] demineralized bone) have been used for support in total nasal reconstruction and in cases of severe saddle deformity. As with alloplasts, these materials are easily obtained and readily sculptured. They are, however, associated with a low rate of infection and extrusion. The main disadvantages of homografts are a high rate of resorption, occasional warping, and a tendency to become mobile over time.[31]

Autogenous cartilage and bone are the most appropriate and useful materials for reconstruction of the nasal framework. Cartilage may be used alone or in a composite graft of skin and cartilage depending on the need.[32,33] Composite grafts have been used to open stenosis of the nasal airway, to repair alar retraction after rhinoplasty, and to perform columellar and alar reconstruction after tissue loss (Fig. 25-7). Revision rhinoplasty is a challenge in reconstructive rhinoplasty, both in the techniques of repair and the choice of implant material for augmentation grafting. Auricular cartilage is the best in revision rhinoplasty, because of its superior long-term survival characteristics, its ready availability in the head and neck region, its resistance to infection and resorption, and its bendability and flexibility when implanted in the nose.[34]

Composite grafting is a relatively simple, one-stage procedure. Grafts may be harvested from the conchal bowl, helical rim, or root of the helix with minimal donor site deformity. Survival of free

Figure 25-7. **A,** The composite graft reconstructive technique in an older woman with small squamous cell cancer of left nasal ala. **B,** The donor defect is closed at the superior portion of the auricle. **C,** The immediate postoperative result. **D,** The healed defect at 1 year.

composite grafts is unpredictable and depends on nutrients from the recipient bed until ingrowth of new blood vessels occurs. Viability of the graft depends on the successful transfer of fluids and nutrients from serum imbibition in the recipient site immediately after placement. Inosculation occurs during the next 24 hours, and vascular ingrowth occurs in 3 to 5 days. The successful survival of the graft depends on a recipient site with good blood supply, meticulous hemostasis, and careful immobilization of the graft. In addition, graft size is critical in survival. Grafts larger than 2 cm in diameter are prone to fail.

Autogenous cartilage may also be used as a free graft without attached soft tissue. The most common donor sites include the nasal septum, auricular concha, and costal cartilage. Cartilage grafts have been used for multiple purposes, including increased tip support, rebuilding of missing or weakened alar cartilages, and dorsal augmentation (Fig. 25-8).[35] In addition, autogenous cartilage is especially useful in managing nasal valve collapse when used as battens or spreader grafts.[36]

Reconstruction of the bony nasal framework is commonly required in major facial trauma. When severe comminution or loss of bone occurs, grafting is necessary to re-create the projection and shape of the nasal dorsum and base. Although the lower turbinate bone,[37] the iliac crest, and rib have been used, calvarial bone is currently the donor site of choice[38] because of the easy access and low morbidity of the donor site and the decreased graft resorption noted with this membranous bone.[39] Harvest is most often done from the parietal region, using outer cortical bone contoured to reconstruct the nasal dorsum or used as an L-shaped strut when dorsal and columellar support are needed (Fig. 25-9).[40] Such a reconstruction is often combined with cartilaginous grafts for alar reconstruction and a forehead flap for external coverage.

Proper fixation of bone grafts is imperative for reestablishment of a stable skeletal structure. In addition, rigid fixation results in less resorption of the graft.[41] Dorsal grafts are cantilevered to the nasal process of the frontal bone, whereas lateral grafts are fixed to the maxilla (see Fig. 25-9). Miniplates or lag screws are usually used for this purpose.[13,42] Repair of nasal skeletal defects in this manner yields satisfactory functional and cosmetic results. The main disadvantage of using autologous bone grafts is their rigidity, which distorts the natural flexibility of the distal segment of the nose.

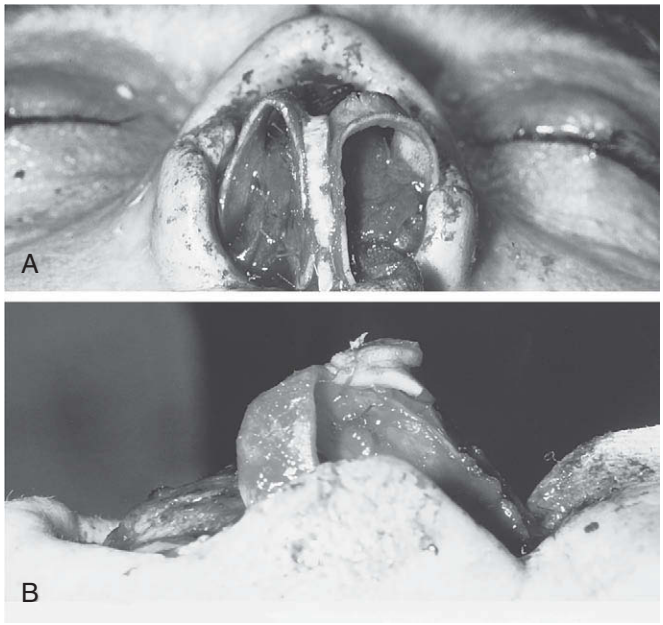

Figure 25-8. **A,** A patient after subtotal lower nasal resection. Tip reconstruction with a columellar strut, conchal cartilage graft, and lower lateral cartilage reconstruction from additional pieces of auricle cartilage was tailored to restore contour of alar cartilage. **B,** The additional onlay graft for improved tip contour was sutured before forehead flap placement.

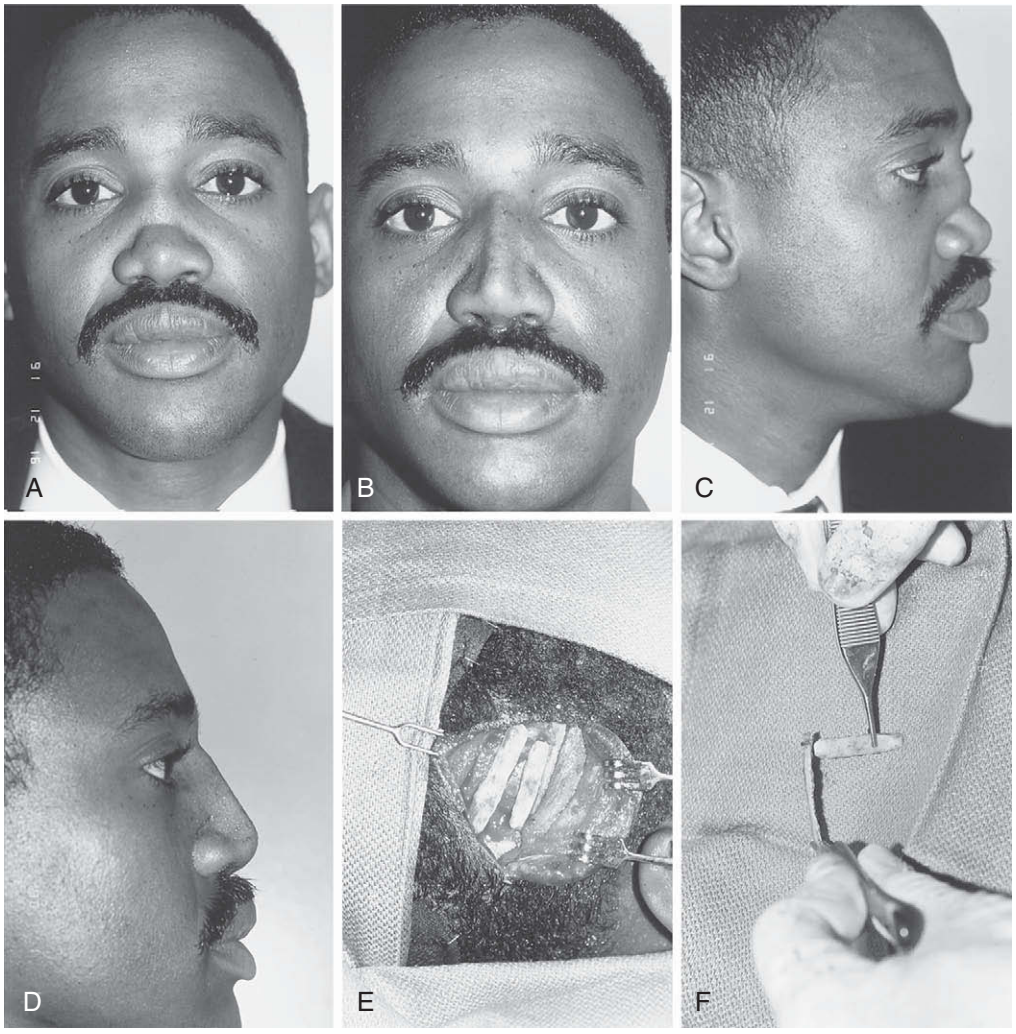

Figure 25-9. **A,** A 27-year-old man with total nasal collapse caused by large septal perforation. **B,** The patient is seen after an L-shaped double calvarial bone graft. Lag screw fixation through the dorsal skin was used for approximately 6 weeks postoperatively. **C,** Preoperative right lateral view. **D,** Postoperative right lateral view. **E,** The harvesting of two bone grafts forms an L-shaped bone graft. **F,** The L-shaped bone graft is secured and ready for implantation. Fixation was with one microplate, lag screw dorsally, and wire to anterior nasal spine.

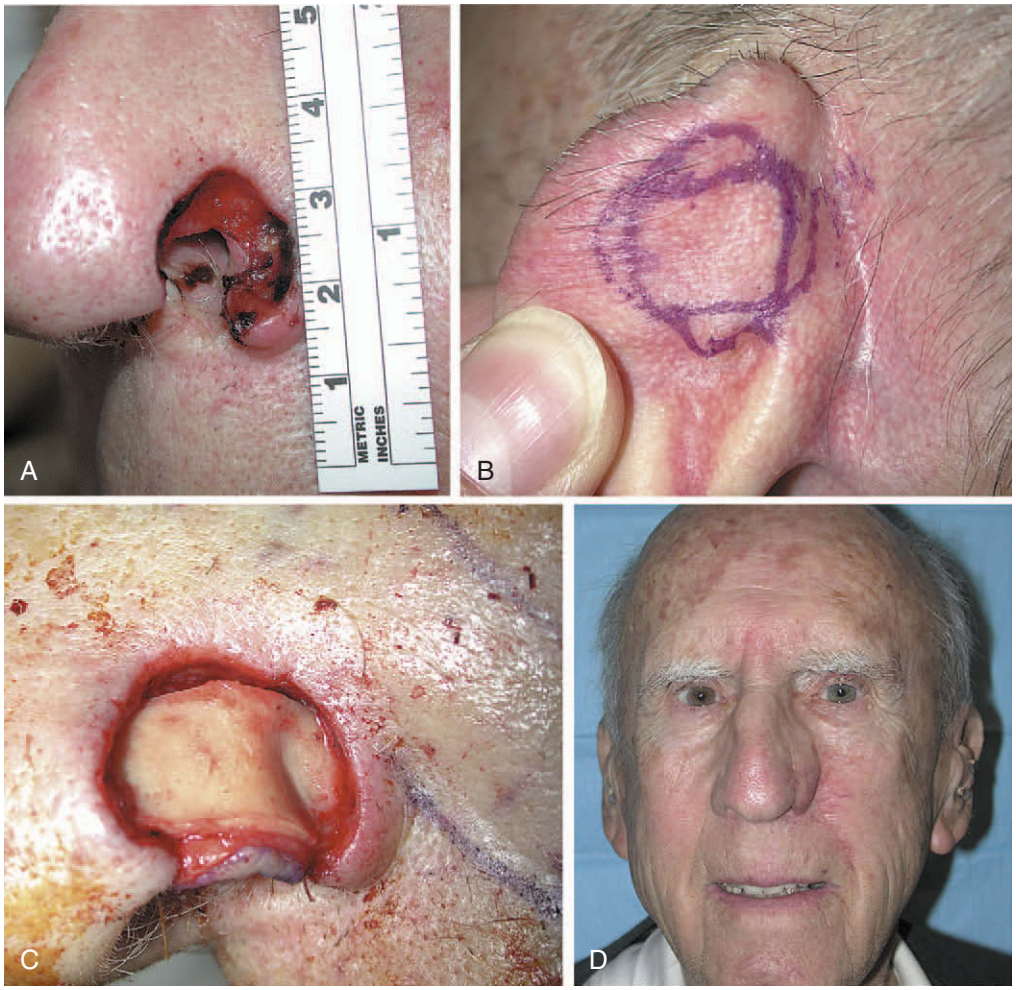

Figure 25-10. An 82-year-old man with basal cell cancer of left ala. **A,** The defect immediately after Mohs' resection. A melolabial flap is designed to reconstruct the external layer. **B** and **C,** The cartilage and posterior auricle skin at the antihelical fold was used to reconstruct the intermediate layer and internal lining. **D,** One month after the initial reconstruction, thinning of the flap is planned.

Surgical management of the nasal dorsum has traditionally been relegated to either augmentation or reduction followed by osteotomy. Reconstructive rhinoplasty demands attention to re-create a natural profile line, which may require dorsal reduction in some areas and augmentation in others. Appropriate surgical techniques are required to narrow the nasal dorsum, while maintaining dorsal height.[43] Power-assisted bone removal is a useful tool in a second-stage reconstructive rhinoplasty requiring reduction of bony irregularities. Using osteotome may injure the newly reconstructed bony structure. Powered instrumentation may allow the performance of a surgical maneuver more efficiently and accurately.[44,45] Endoscopic-powered rhinoplasty provides an excellent approach to the bony dorsum. It allows sculpting to be completed under direct vision, permitting precise contouring and easy visualization.[42]

Internal Lining

The vestibular lining should be reconstructed when nasal defects involve full-thickness loss. Resurfacing of the internal lining is the most difficult of the three layers. Without replacement of the lining, contraction and fibrosis may result in stenosis and inadequate nasal airway. The restoration of this thin, vascular lining is best accomplished using similar tissue.

When a defect is limited to the alar margin, adjacent nasal lining may be advanced caudally as a bipedicle flap. Any remaining alar cartilage is also advanced toward the rim margin to maintain structural support. A hinge flap of septal cartilage with its contralateral mucosa attached is then used to repair the defect at the donor site.[6] When more extensive tissue loss occurs or when the existing vestibular lining is severely scarred, this method of repair is usually impossible. The intranasal portion of a total nasal defect can be successfully reconstructed with a fascial forearm flap with a turbinate or mucosal graft, which allows for a thin mucosalized lining to achieve an excellent functional outcome.[46] Other options include skin grafting of the undersurface of the covering flap, a turn-over flap to provide lining, and placement of a second local flap or composite ear cartilage graft that can provide good functional and aesthetic results when combined with overlying skin flaps in reconstruction of partial nasal defects (Fig. 25-10).[47] Although these methods usually provide adequate internal coverage, postoperative shrinkage of a skin graft or unnatural bulkiness of a flap may cause nasal obstruction.

An ipsilateral septal mucoperichondrial flap hinged on the caudal border of the cartilaginous septum can provide adequate mucosa to reline the entire interior of the ala and nasal dome. The septal mucoperichondrial hinge flap should be designed as large as possible. Two horizontal incisions start 1 cm posterior to the caudal margin of the septal cartilage and extend 1 to 2 cm posterior to the bony cartilaginous junction where a vertical incision connects these two horizontal incisions. The dorsal horizontal incision is placed 0.5 to 1.0 cm below the roof of the middle vault. The inferior horizontal incision is placed along the junction of the nasal crest and the floor of the nose. The septal mucoperichondrial flap is dissected in the subperichondrial plane. The exposed septal cartilage and bone is left to heal

Figure 25-11. A 62-year-old man with squamous cell carcinoma of left ala. **A,** The defect after resection with clear margin. **B,** Ipsilateral septal mucoperichondrial hinge flap reflected out of nasal passage. **C,** Septal cartilage graft replaces missing upper lateral cartilage. Auricular cartilage graft replaces missing lower lateral cartilage while serving as alar batten graft. **D,** Postoperative result at 3 months after thinning of the flap.

by secondary intention. The septal mucoperichondrial hinge flap is supported by a framework of septal and auricular cartilage grafts. The cartilage grafts should be protected from exposure to the nasal passage. The mucoperichondrial flap will obstruct the nasal passage until it is detached from the septum in 2 to 3 weeks after the initial reconstruction (Fig. 25-11).

Summary

The evaluation of nasal defects is best carried out systematically. The three-layered approach to this assessment allows surgery to be planned based on precise information regarding the amount and type of tissue requirements. Reconstructive procedures may then be selected and tailored to the specific defect and patient.

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CHAPTER TWENTY-SIX

Hair Restoration: Medical and Surgical Techniques

Kevin H. Ende

Sheldon S. Kabaker

Key Points

- The vast majority of hair loss problems facing the facial plastic surgeon are due to hereditary male pattern baldness.
- Hair density must decrease by 50% before alopecia becomes noticeable.
- The hair cycle has three stages: anagen, catagen, and telogen.
- Ninety percent of hair is in the anagen phase.
- 5-Alpha reductase activity is associated with the inhibition of hair growth and is responsible for the metabolism of testosterone into dihydrotestosterone (DHT). Finasteride inhibits this conversion to DHT.
- Norwood's modification has become the standard system of baldness classification used by hair restoration surgeons.
- Follicular unit transplantation is the gold standard in surgical hair restoration.
- Follicular units are naturally occurring groups of one to four terminal hairs. All of the support structures, including sebaceous glands, subcutaneous fat, and a circumferential band of collagen around the follicle, are left intact.
- Follicular unit hair transplantation has replaced the traditional procedures such as plug grafts, scalp reductions, and rotational flaps.
- The senior author continues to advocate one routine aesthetic scalp flap procedure. It is an advancement flap operation for hairline lowering in patients, mostly female, with high hairlines. An anterior hairline advancement with excision of forehead skin is performed via an irregularly irregular trichophytic incision made perpendicular to the hair follicles. Scalp expansion is used in patients with minimal scalp laxity or for more than 3 cm of hairline advancement.

Throughout history, powerful cultural symbolism has been associated with hair—both its length and its loss. An individual's hair plays an important role in his or her overall appearance. Framing the face, hair helps to draw the observer to the focus of the face: the eyes. Hair also conveys nonverbal clues about an individual's age and personality. Long, luxuriant hair is associated with youthfulness and physical attractiveness. Balding, thinning, and graying hair signifies maturity and advanced age.

As a result, hair restoration has long been considered an integral part of facial rejuvenation. Scalp hair loss—alopecia—can dramatically affect an individual. In fact, alopecia has been associated with significant changes in self-image, psychological well-being, and even success in a career.[1] Hair loss draws attention to the forehead, the scalp, and the shape of the head and distracts the viewer from the central face and eyes. Hair loss can be a source of tremendous patient concern and anxiety. Subsequently, individuals invest considerable time and money in seeking treatment.

Neither gender escapes the difficulties associated with hair loss. In women, greater distress may be associated with even minimal hair loss, because alopecia in women is a less common and accepted problem.[1] Although alopecia is the result of several different processes, the most common cause remains androgenetic alopecia (AGA). In men, AGA is characterized by the classic hereditary male-pattern baldness. In women, it manifests as a diffuse thinning with an intact anterior hairline, although occasionally a male-pattern type of hair loss can occur. AGA affects more than half of the male population and up to 40% of women older than 70 years.[2,3]

Aging and hair loss are dynamic processes. Therefore the goal of treatment should be to create and maintain an appearance that remains natural over time. In recent years there has been an explosive growth in techniques for the management of alopecia. New advances in both medical and surgical treatments have been developed and modified to achieve more natural appearing and undetectable hair restoration. Current medical therapies provide powerful treatment options that arrest hair loss and, in some patients, provide hair regrowth. Advanced surgical techniques such as follicular-unit hair transplantation have replaced the traditional procedures such as plug grafts, scalp reductions, and rotational flaps to become the state of the art in terms of inconspicuous hair restoration. This chapter provides an overview of the pathophysiology, the evaluation, and the current medical and surgical management of hair loss.

Pathophysiology

The average scalp has approximately 100,000 to 150,000 hairs.[4] Hair density must decrease by 50% before alopecia becomes noticeable. Each hair contains both a matrix that is located below the dermis and a visible hair shaft (Fig. 26-1). The matrix lies beneath the dermis in the subcutaneous fat at the base of the hair follicle and contains rapidly dividing cells that migrate superiorly into the zone of keratinization. In this zone, cells undergo a process of dehydration and chemical change that

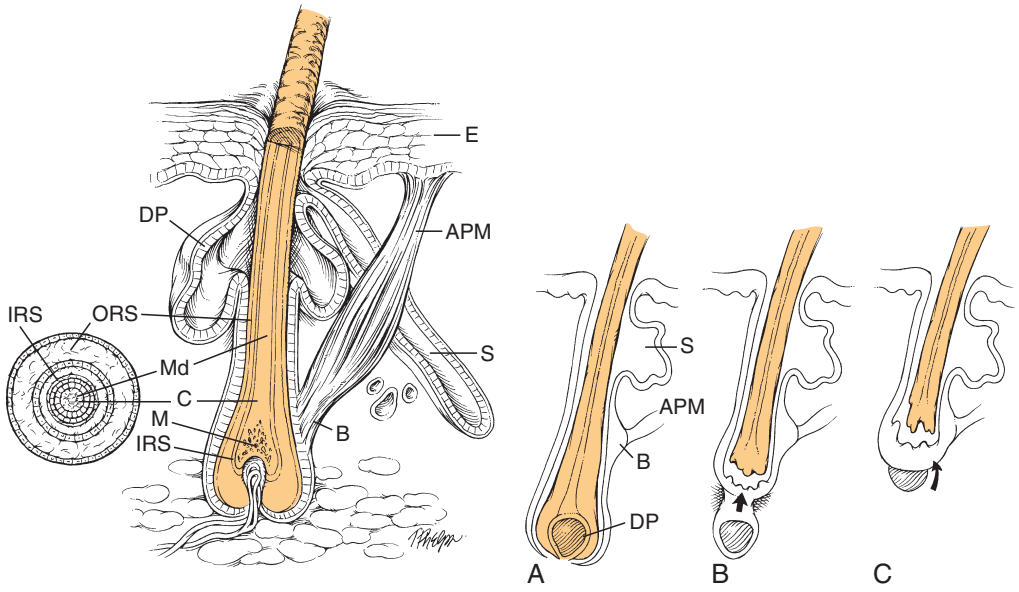

Figure 26-1. Anatomy of the hair follicle and the different phases of the hair cycle. **A,** Anagen. **B,** Catagen. **C,** Telogen. Labeled structures include the arrector pili muscle (APM), bulge (B), cortex (C), dermal papilla (DP), epidermis (E), inner root sheath (IRS), matrix (M), medulla (Md), outer root sheath (ORS), and sebaceous gland (S). (**A,** *Adapted from Bennett RG. Anatomy and physiology of the skin. In: Papel ID, ed.* Facial Plastic and Reconstructive Surgery. *2nd ed. Papel, NY: Thieme, 2002:11.* **B** *and* **C,** *Modified from Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis.* Cell *1990;61:1329, as reprinted in Stough DB, Haber RS, eds.* Hair Replacement: Surgical and Medical. *St Louis: Mosby, 1996:222.)*

results in the formation of the hair shaft, which is a dense mass of dead keratinized cells. As more cells are added to the base of the follicle, the shaft is displaced superiorly, and the hair shaft grows to become visible at the surface.

The formation of hair is a cyclical but asynchronous process that has periods of growth, involution, rest, and shedding.[5] The majority of hair follicles in the scalp (approximately 90%) are in the growth, or *anagen* phase. This growth phase lasts approximately 3 to 10 years and is longer in women than in men. In the next stage, the *catagen* phase, proliferation ceases and involution occurs secondary to apoptosis. Less than 1% of the hair follicles are in the catagen phase, which lasts for less than 2 weeks. The remaining 5% to 13% of hair follicles are in the resting, or *telogen* phase. This stage last approximately 3 to 4 months during which there is no active hair growth.[1] Alternatively, proteolytic enzymes may be induced during the telogen phase, which causes the hair shaft to be shed during a recently described *exogen* phase.[5a] Fifty to 100 hairs may enter the exogen phase each day from the normal telogen phase, and up to 400 may shed during a telogen effluvium (described later). The cycle begins again with the anagen phase and results in new hair growth from the area of shedding or displaces the previous hair shaft. Androgens play an essential role in regulating hair growth. At puberty, androgens increase the size of the follicles in the beard, chest, and extremities while decreasing the size of the follicles in the temporal region, thereby reshaping the anterior hairline.[6]

Androgenetic Alopecia

There are various causes of hair loss. AGA, or male-pattern baldness, is the most common cause in both genders (Table 26-1). AGA eventually affects 60% to 80% of white men and can begin in puberty. Approximately 20% of men note some hair loss at puberty, and the number increases sequentially with each decade. For example, by 30 years of age, 30% of white men have noted baldness, and, by 50 years of age, approximately 50% to 60% demonstrate alopecia.[3] In women, the onset is typically later, with 40% of women 70 years old or older demonstrating alopecia.[2]

The incidence of AGA varies among ethnic groups. In the black population, the incidence is approximately one-fourth that of white men.[7] Japanese men have a similar incidence of AGA as black men during the earlier years, but the incidence increases to one-third that of whites as age advances.[8] In Chinese men, AGA is rare before age 40 years.[3] In all groups of patients, the incidence and severity of AGA increase with age.

The development of AGA depends on several factors. In a study of identical twins, Hamilton showed that the extent and development

Table 26-1

Various Etiologies of Alopecia

Diffuse Hair Loss	Focal Hair Loss
Nonscarring	Nonscarring
Androgenetic alopecia	Androgenetic alopecia
Alopecia areata	Alopecia areata
Anagen effluvium	Trichotillomania
Congenital hypotrichosis or atrichia	Traction alopecia
Hair shaft abnormalities	Hair shaft abnormalities
Syphilis	Tinea capitis
Telogen effluvium	Syphilis
Thyroid disorders	Scarring
Postpartum	Lacerations
Postmenopause	Postsurgical
Drug-induced	Burns
Iron deficiency	Radiation
Malnutrition	Neoplasms
Physiologic stress	Discoid lupus erythematosus
Psychological stress	Sarcoidosis
	Dermatomyositis
	Lichen planopilaris
	Scleroderma variant morphea
	Temporal arteritis
	Bacterial folliculitis
	Herpetic infections

of AGA depended on the interaction of three factors: androgens, genetic predisposition, and age.[3] The interaction of several genes (polygenic) and certain environmental factors influence the expression of hair loss.[9,10] It is most important to note that androgens play a critical role in the development of hair loss. No expression of baldness due to AGA occurs in the absence of circulating androgens.

Hair follicles on the scalp are genetically predisposed to be either sensitive or resistant to androgenic factors that inhibit hair growth. Autograft studies have demonstrated this genetic predisposition. For example, hair follicles from the occipital scalp that are immune to androgens were transplanted to the bald frontal scalp and continued to grow. These findings established and continue to advance the concept of donor dominance and are the basis for successful hair graft transplantation.[11]

Various androgens variably affect different regions of hair growth. Testosterone influences axillary and pubic hair growth, whereas DHT affects beard growth and scalp hair, specifically the development of AGA.[12] In addition, a hair's sensitivity to androgens may change over time, accounting for the effect of age, puberty, and possibly environment.

Extensive hair loss in men is not necessarily a reflection of an overall increase in testosterone. Two enzymes play critical roles in AGA (Fig. 26-2). The 5-alpha reductase enzyme is responsible for the metabolism of testosterone into DHT, which is the androgen that is most directly associated with the inhibition of hair growth and AGA. The cytochrome P-450 aromatase enzyme also has an important role in the hormonal pathway. Aromatase metabolizes testosterone into estradiol and androstenedione into estrone.[13] A decrease in aromatase consequently increases the amount of testosterone that will be metabolized into DHT via the 5-alpha reductase pathway. Therefore AGA is mediated by increased 5-alpha reductase activity and by the lack of aromatase enzyme in specific regions of the scalp, thereby resulting in higher levels of DHT.

The end result of this androgen-mediated process in the development of AGA is the miniaturization of susceptible hair follicles. The follicles become progressively smaller in size and have shorter periods of growth so that coarse terminal hairs progress through a thinner, more lightly pigmented intermediate phase before they are replaced by fine vellus hairs (Fig. 26-3).[14] In women, this process may advance beyond the stage of vellus hairs to produce a bald scalp that is completely free of hair.

Although androgenetic alopecia is the most common cause of hair loss, a variety of other etiologies should be considered in the patient's evaluation (see Table 26-1). Alopecia manifests as either a focal or diffuse process and can be associated with or without scarring. Scarring can directly injure the hair follicle and lead to focal alopecia. Scarring alopecia is typically seen in patients with traumatic injuries such as lacerations, burns, radiation, and unfavorable sequelae of facelifting and endoscopic browlifting, as well as with selective connective tissue diseases, including discoid lupus erythematosus, lichen planopilaris, dermatomyositis, and sarcoidosis.[15] If only the hair shaft is damaged, alopecia is temporary, because the underlying follicular apparatus continues to grow new hair. If the follicle, including the matrix, is com-

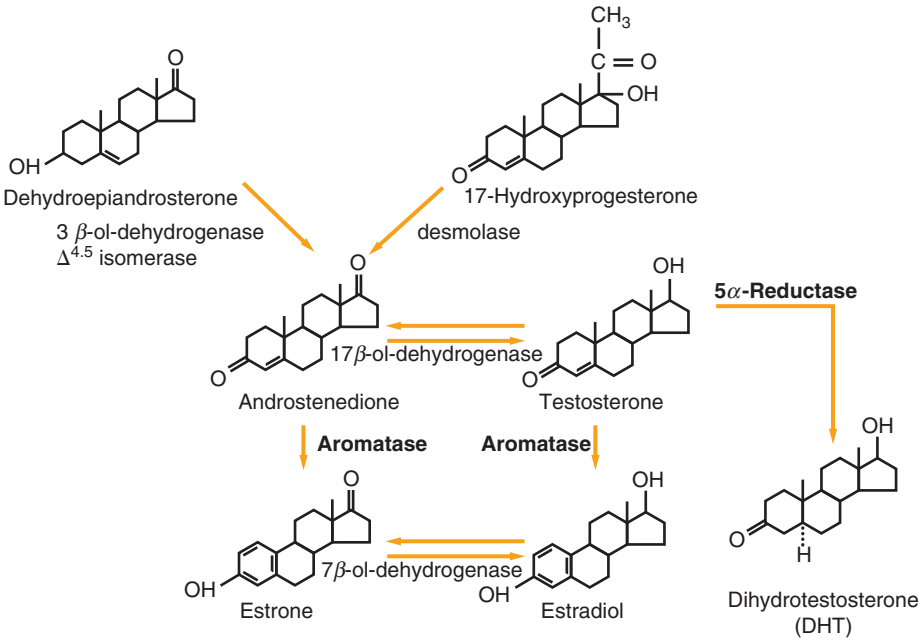

Figure 26-2. The androgen metabolic pathway within the skin. Both 5-alpha reductase and aromatase have significant roles in androgenetic alopecia. *(From Stough DB, Haber RS, eds.* Pathophysiology of Androgenic Alopecia. *St Louis: Mosby, 1996:11.)*

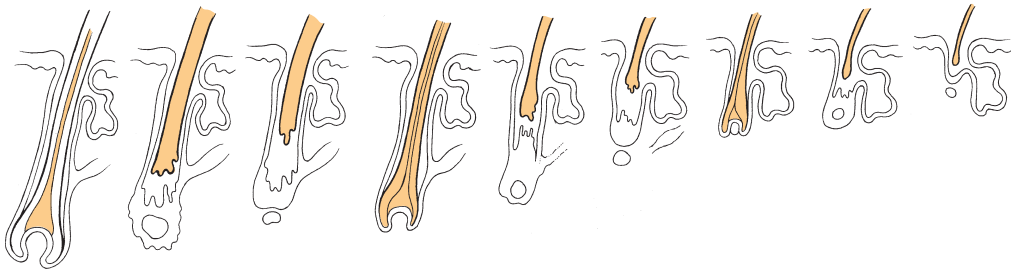

Figure 26-3. Miniaturization of the hair follicle in androgenetic alopecia. Hair grows for shorter periods of time, becoming smaller, finer, and lighter as it approaches the vellus stage. *(From Stough DB, Haber RS, eds.* Pathophysiology of Androgenic Alopecia. *St Louis: Mosby, 1996:9.)*

pletely destroyed, the loss of hair is likely permanent. Traumatic, nonscarring alopecia may also occur as a result of externally applied traction with certain hairstyles (e.g., cornrows, hair weaves).

Infectious etiologies should be considered in cases of focal alopecia. *Staphylococcus aureus, Streptococcus*, and syphilis are associated with folliculitis and furuncles, which can result in scarring and permanent alopecia. Tinea capitis is a fungal infection that results in focal, nonscarring alopecia and is diagnosed with a Wood light or a potassium hydroxide preparation of a hair sample.[15]

Diffuse, nonscarring alopecia is often associated with telogen effluvium in which diffuse hair shedding occurs as hairs precipitously shift from the growth phase to the resting and exogen phases. Telogen effluvium is a physiologic response to a variety of stressors including hormonal or systemic conditions and a broad range of medications. Hypothyroidism, hyperthyroidism, postpartum, and postmenopause are frequently seen as manifesting with diffuse alopecia.[16] Categories of drugs that may result in temporary hair loss include chemotherapy agents, anticoagulants, anticonvulsants, thyroid replacement, beta-blockers, tricyclic antidepressants, and oral contraceptives.[16] Patients with malnutrition, specifically with deficiencies in protein and essential minerals such as zinc and iron, may have poor hair growth and develop alopecia. Finally, patients undergoing severe physiologic (e.g., with acute and chronic systemic illness) or significant psychological stress (i.e., trichotillomania) can suffer from temporary hair loss.[16]

Focal or diffuse alopecia can also result from alopecia areata. Alopecia areata is an autoimmune disease that affects almost 2% of the population and typically manifests as small round patches of hair loss without evidence of scarring.[6,17] The hair loss ranges in severity from small areas of alopecia that spontaneously regrow to persistent, extensive patches. The extent of loss can include the complete loss of all scalp hair (alopecia totalis) or all hair on the body (alopecia universalis).[6] Inflammation may play a role by stimulating cytokines and growth factors, which retard hair growth.[5]

Patient Evaluation

When evaluating a patient with hair loss, a detailed history and physical examination are mandatory for the proper diagnosis and treatment of the underlying etiology. Focused questioning should center on the hair loss onset, progression, location, and other associated conditions that affect the skin, joints, and thyroid gland. Past medical history and medications need to be reviewed. Family history can also play an important role in predicting the probable progressive pattern of future hair loss in androgenetic alopecia.

For the majority of women with AGA, extensive hormonal evaluation is not necessary. Testing total testosterone, dehydroepiandrosterone, and prolactin levels is warranted if any of the following conditions associated with androgen excess are present: hirsutism, severe cystic acne, irregular menses, infertility, virilization, or galactorrhea. Measuring thyroid-stimulating hormone levels may be helpful if thyroid abnormalities are suspected. A complete blood count and iron studies should also be considered for a woman who has heavy or long-lasting menses.[6]

Examination of the scalp skin should include evaluating the pattern of hair loss as well as any skin lesions that are indicative of infection or malignancy. Hamilton[3] published the first useful classification of AGA in 1951; Norwood and Shiell's[18] modification has become the standard system of classification used by hair restoration surgeons. This complete classification system includes seven categories (Fig. 26-4). The anterior hairline is altered with bitemporal recession occurring first, followed by balding of the vertex. As a more uniform frontal recession progresses posteriorly, the entire frontoparietal region eventually bears only inconspicuous vellus hair. The inferior occipital and temporal scalp are spared, resulting in the classic hair fringe.

Female baldness patterns can be similar to those seen in men, but the genetic transmission is less clear. The Norwood classification system can be used, but female alopecia more often consists of a diffuse thinning in an oval area on top of the scalp. In 1977, Ludwig classified AGA in females into three stages (Fig. 26-5).[19] In grade I, only perceptible thinning of the hair occurs at the vertex, while a thin band of more dense hair from 1 to 3 cm in width is retained at the hairline. More advanced stages correlate with an increase in hair loss on the vertex and a progressive thinning of the anterior hairline.

Patient Counseling

The initial consultation of a patient with hair loss must foster open communication and trust. Often these patients suffer from an altered body image and insecurity about their physical appearance. The patient must understand that the goal is not necessarily to restore his or her previous head of hair but rather to remove the appearance of baldness by recreating hairlines and improving hair density (Fig. 26-6).

Hair restoration surgery is a calculated risk. Although family history and age at the time of presentation may give the surgeon some feel for the possible course of hair loss, these factors are by no means always predictive. In cases of AGA, it should be impressed upon the patient that the natural progression of alopecia is usually relentless and often unpredictable. Ideally, management should allow for changes in the hair pattern with an ever-increasing bald area and a decreasing supply of permanent hair as the patient ages. As a result, the physician should evaluate the patients' subjective expectations and provide realistic options and outcomes. As with any facial plastic surgical procedure, photodocumentation of physical findings, specifically the hair loss pattern, needs to be done in a consistent manner.

Medical Management

Before considering a surgical approach to a patient's alopecia, any treatable etiologic factors should be eliminated. Endocrinopathies associated with hair loss should be appropriately managed. Scalp infections need to be properly diagnosed and treated. Autoimmune conditions such as alopecia areata, lichen planopilaris, and lupus erythematosus can benefit from corticosteroid therapy delivered either topically, orally, or intralesionally.

Numerous topical and oral treatments for androgenetic hair loss claim hair regrowth. Only two therapies, topical minoxidil (Rogaine) and oral finasteride (Propecia), have been clinically proven to be effective for preventing further hair loss and promoting future growth. Both drugs affect the hair growth cycle via different mechanisms of action and result in an increase in existing hairs' length and diameter.

Minoxidil

Topical minoxidil is a piperidinopyrimidine derivative vasodilator that possesses trichogenic properties. Topical minoxidil is available in two strengths (2% and 5%) and is applied topically to the scalp twice daily. Minoxidil is safe for both men and women for the treatment of androgenetic hair loss. Originally used as an oral antihypertensive medication, minoxidil acts as a potassium-channel agonist, thereby resulting in a reduction in cytoplasmic-free calcium. The relevance of this unique cellular mechanism to hair growth is unclear. Various theories have postulated that hair growth is due to several mechanisms at the cellular level: (1) decreased activity of epidermal growth factor; (2) increased angiogenesis as a result of the up-regulated expression of vascular endothelial growth factor; and (3) increased activation of prostaglandin endoperoxide synthase-1.[18,20,21]

In several clinical trials, applying topical minoxidil (2%) twice daily resulted in dense hair regrowth on the vertex scalp in less than 5% of patients, while 25% to 30% of patients demonstrated moderate hair regrowth over one year.[22-24] In patients for whom significant hair regrowth did not occur, minoxidil did appear to stop or significantly slow the progression of AGA.[25] The results in women with AGA have been similar to those seen in men. Unfortunately, maintenance of the regrowth is dependent on continued use of minoxidil. When the treatment is discontinued, the hair gained is lost, and the hair that should have been shed during the treatment period will follow within 3 to 4 months. For those who continue its use, a peak effect is reached at approximately 1 year, with a subsequent slow decline in regrowth.[26,27]

Adverse reactions associated with topical minoxidil are primarily limited to irritant dermatitis or folliculitis (3% to 5%), which is now probably less with newer formulations such as the foam vehicle. Allergic contact dermatitis occurs in less than 1% of patients.[23] Modifying treatment to include a lower concentration and less frequent application may alleviate these reactions. Increased hair growth (hypertricho-

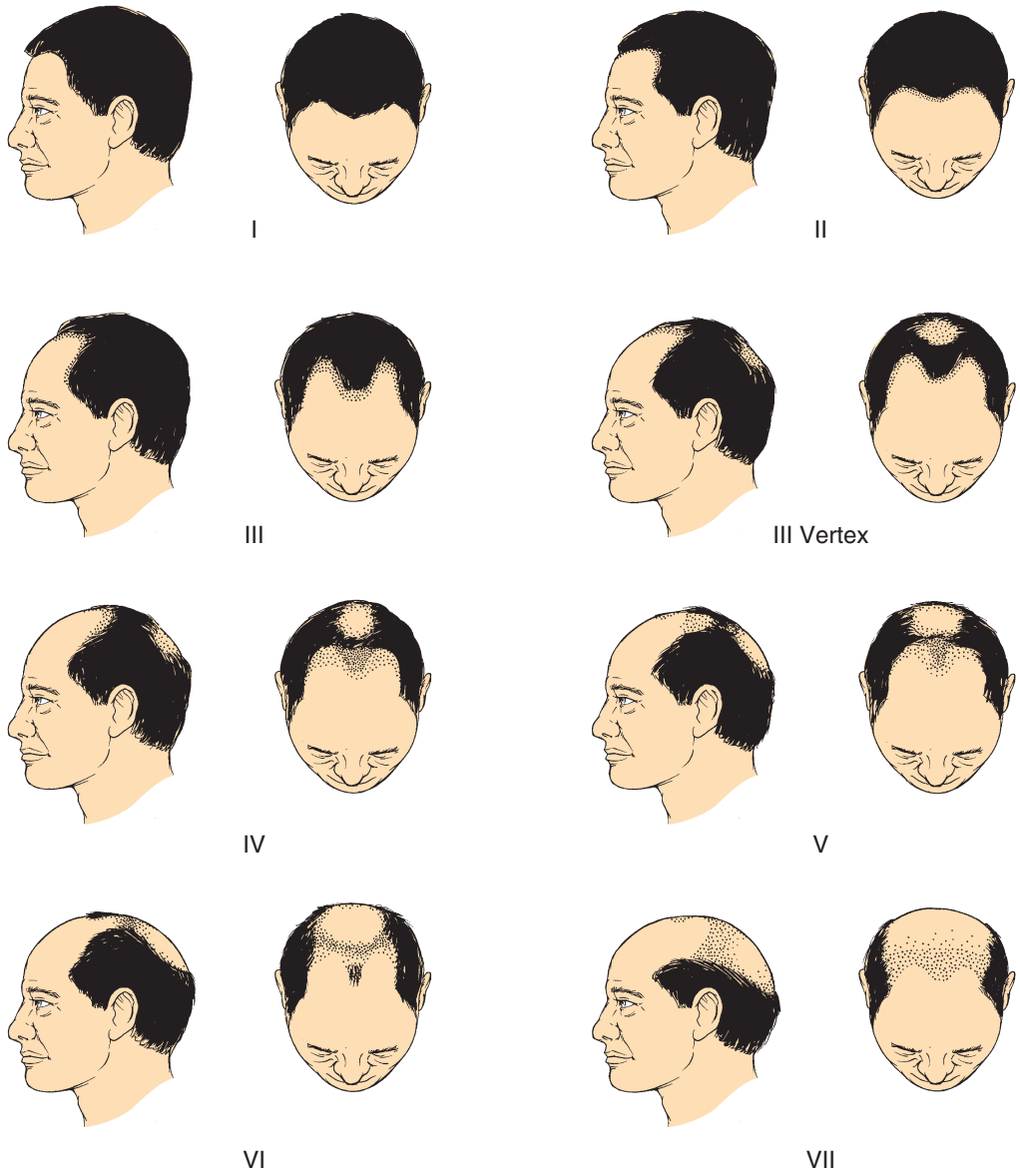

Figure 26-4. Norwood classification of the most common types of male-pattern baldness. *(Adapted from Norwood OT. Male pattern baldness: classification and incidence.* South Med J. *1975;68:1359. Courtesy of Charles C Thomas, Publisher, Ltd., Springfield, Illinois.)*

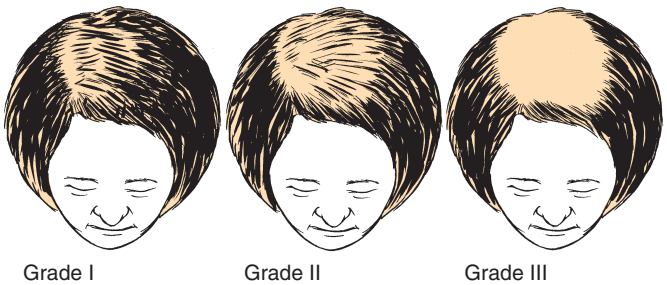

Figure 26-5. Ludwig classification of female-pattern baldness. *(Adapted from Montagna W, Parakkal PF.* The Structure and Function of the Skin. *3rd ed. New York: Academic Press, 1974.)*

sis) outside of the area of application (e.g., eyebrows, face, ears, arms, beard) has been reported, and is more common in women. The reason is unclear, but its occurrence is possibly the result of the inadvertent transfer of the topical solution.[14,28] Patient compliance had also been an issue with the original topical minoxidil given twice-daily application, but some practitioners now suggest once-daily therapy.

Finasteride

Finasteride (Propecia) is a type 2 5-alpha reductase inhibitor that results in the suppression of circulating DHT, the hormone that directly affects AGA. Finasteride has no affinity for the androgen receptor and therefore does not interfere with the actions or effects of testosterone. Treatment with finasteride has been shown to increase hair weight, promote conversion of hairs into the anagen phase, and can reverse hair miniaturization. Dutasteride (Avodart), which inhibits DHT at two receptor sites, has been used off-label by some practitioners for a theoretical pharmacologic advantage.

In studies of young males with mild to moderate hair loss, 1 mg of finasteride maintained or increased 48% to 65% of their hair counts, primarily on the vertex and anterior midscalp. After 24 months, the

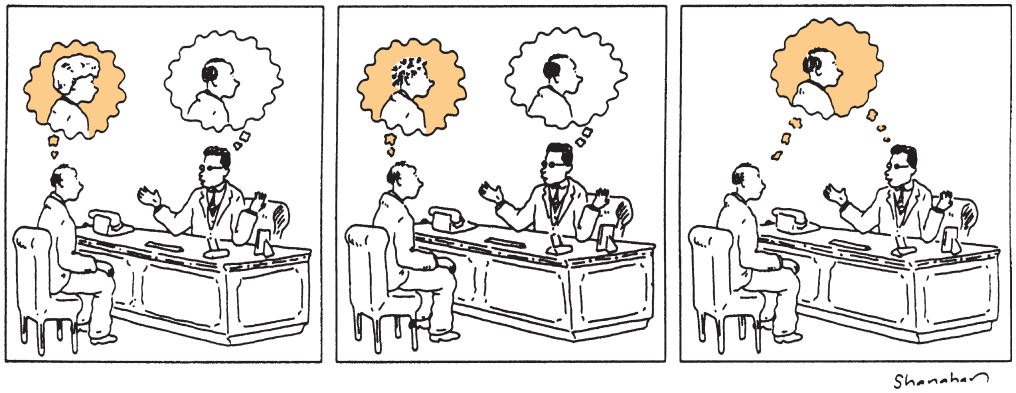

Figure 26-6. The initial consultation must foster the open discussion of realistic and obtainable goals. *(From Quinlan P.* The consultation. *In: Stough DB, Haber RS, eds.* Hair Replacement: Surgical and Medical. *St. Louis: Mosby; 1996:29, Fig. 1-17.*

number of patients that responded increased to 66% to 80%.[29-31] A 5-year controlled clinical trial demonstrated that 65% of men taking finasteride maintained or improved their hair count, whereas men taking placebo continued to lose hair. In addition, a review of standardized clinical photographs showed 90% of men on finasteride were rated as having no further visible hair loss as compared with baseline versus 25% of patients on placebo.[32] As is the case with minoxidil, patients need to be on continued therapy to preserve the renewed hair growth. Recent studies have noted a possible synergistic response with the combination therapy of minoxidil and finasteride.[33,34]

Finasteride is limited to male patients because of its potential teratogenic effects during pregnancy. There are unpublished favorable reports of postmenopausal females with hair loss being treated off label with finasteride. Men 50 years old should obtain a baseline PSA at 4 months after the initiation of therapy, and yearly thereafter. The possibility of sexual side effects is listed in the package insert as an FDA warning. However, the senior author has not had a single patient with negative sexual side effects in the past 4 years after explaining the FDA warning, and relaying anecdotal reports of a handful of patients who claimed to have sexual enhancement with finasteride. A slight elevation in testosterone due to the lack of conversion to DHT might explain this phenomenon. The placebo effect in men seeking hair loss therapy, so sensitive about their hair, is perhaps more powerful than in other therapies.

Treatment with finasteride is also used to complement hair transplantation. Non-transplanted, preexisting hair in balding areas remains susceptible to androgens. The androgenetic process of miniaturization and eventual hair loss will continue in these areas unless blocked. Treatment with finasteride may also prevent the halo effect, which is characterized by a progressive zone of baldness around the transplanted area. A randomized trial showed statistically significant improvements in the superior/frontal view, and hair counts for patients treated with finasteride until 1 year after transplantation.[35]

Surgical Management

Surgical options for alopecia have ranged from individual follicular-unit hair graft transplantation to scalp reductions and axial flap transfers. The goals of surgery are to create a natural-appearing hairline, increase scalp coverage, and to camouflage scars if present. A multifactorial based (age, rate of loss, pattern, family history) estimation of future hair loss needs to be considered during the surgical planning. In addition, the patient must be informed that usually two to four grafting sessions may be required to recreate a substantial anterior hairline and an increase in hair density. Although the patient may be satisfied by the results of a single extensive transplant session, we stress that it is unlikely for hair restoration to be completed with the first operation.

Follicular-Unit Hair Transplantation

Hair transplantation with hair grafts (based on the follicular unit) has been modified over the last two decades to become the established method of choice for hair restoration. Earlier grafting techniques depended on harvesting 15- to 20-hair, 4-mm round punch grafts, which evolved into 3- to 6-hair minigrafts, single-hair micrografts, and currently follicular unit grafts. The principal problems with the larger grafts have been related to the unnatural creation of a "doll's-hair" or "toothbrush" appearance that is the result of circumferential contracture and compression of the hair follicles during wound healing (Fig. 26-7).

Figure 26-7. The classic "doll's hair" appearance results from circumferential contracture and compression of the hair follicle after placement of 4-mm punch grafts.

Micrografts were primarily reserved for the transition zones (e.g., the anterior hairline), because these individual hairs blend naturally. Micrografts are too small to provide substantial density in more posterior areas. Nonetheless, micrografts have evolved into the concept of follicular-unit grafts. Follicular units are naturally occurring groups of one to four terminal hairs.[36] All of the support structures, including sebaceous glands, subcutaneous fat, and a circumferential band of collagen around the follicle, are left intact. The final result is a more natural look as compared with minigrafts and micrografts, which consist of multiple, partial, or complete follicular units along with intervening skin (Fig. 26-8). The ideal candidates for transplantation have minimal contrast between hair color and skin color (e.g., blond hair in whites), have an adequate donor area, and are old enough that future hair loss is more likely to be predictable.

Preoperative Evaluation

During the preoperative evaluation, specific attention should be given to planning the anterior hairline. The lowest point of the midfrontal hairline, called the *trichion*, frames the face. In terms of dividing the face into proportional vertical thirds, the distance between the trichion

and the glabella should equal the distance between the glabella and the subnasale (Fig. 26-9). However, in patients with significant hair loss and regression, the newly created hairline should be placed higher for a more aesthetically acceptable appearance. The hairline design should have some degree of frontotemporal recession while augmenting a dense frontal forelock. The natural hairline does not abruptly start on the forehead; instead, a 0.5- to 1-cm "feathering" transition zone exists and needs to be recreated using fine, single-hair, follicular-unit grafts. The balding vertex should be addressed thoughtfully given that hair loss will progress in this region in a circumferential manner. Follicular-unit grafts may provide some coverage, but they may be insufficient in number to adequately cover all balding areas during the patient's lifetime.

The recipient regions can be marked out on the scalp in a grid pattern of 1-cm^2 squares (Fig. 26-10). By creating a grid pattern over the recipient sites, the surgeon is able to ensure a uniform distribution of hair grafts during their placement. In addition, the estimated number of grafts needed is calculated by multiplying the measured recipient area by the goal in graft density, approximately 20 to 40 units per square centimeter. The ability to create the illusion of density at lower than normal mathematical density varies based on the surgeon's attention to hair angulation, caliber, spacing, color, and curl.[37] An

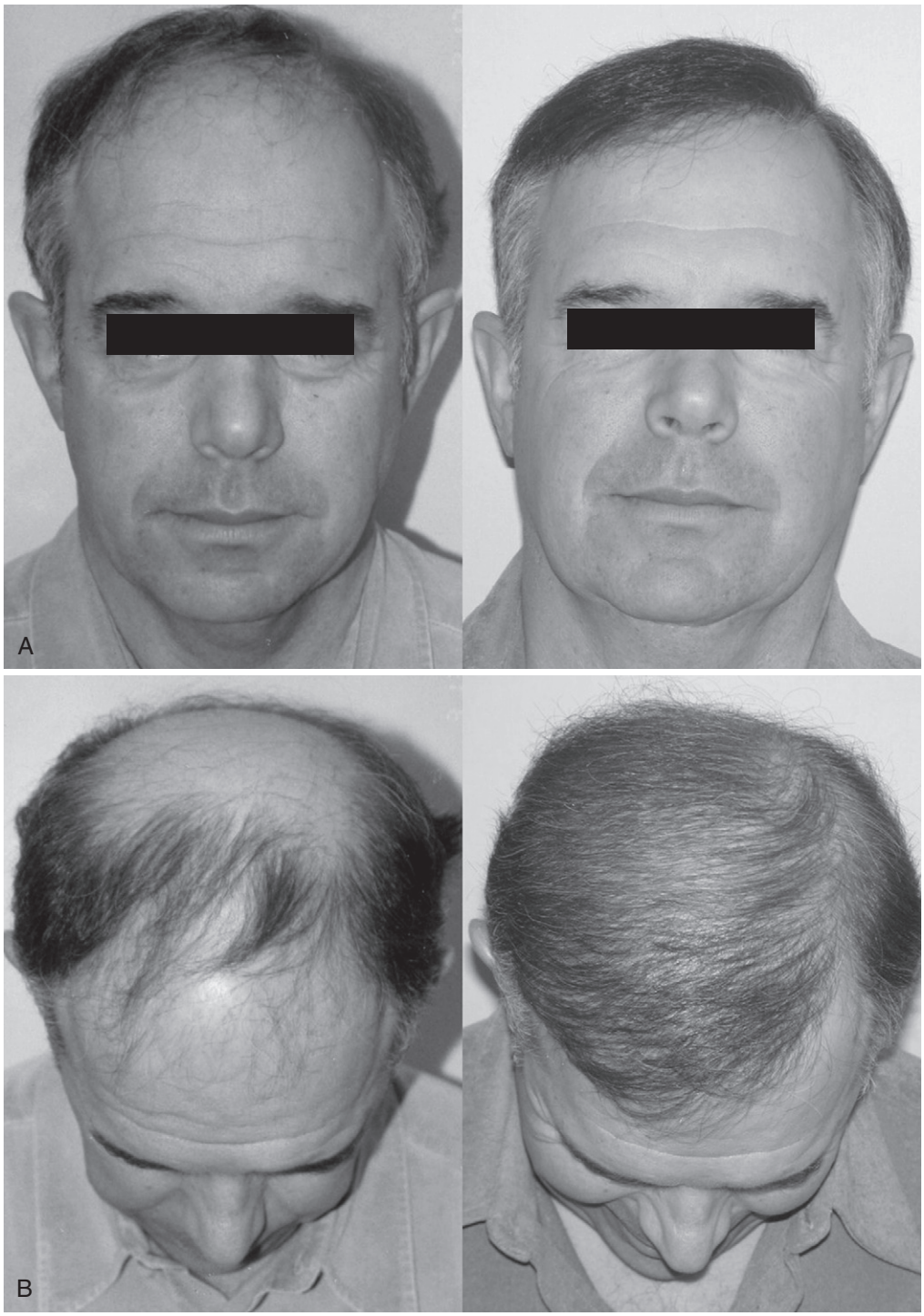

Figure 26-8. **A** and **B,** Preoperative *(left)* and postoperative *(right)* photographs after three sessions of follicular-unit hair transplantation using approximately 1500 grafts per session.

Continued

Figure 26-8, cont'd. Preoperative **(C)** and postoperative **(D)** photographs after two sessions, totaling 4100 grafts. **E** and **F,** Preoperative and postoperative views of patient in views **C** and **D**.

Figure 26-8, cont'd. Preoperative **(G)** and postoperative **(H)** photographs after two sessions, totaling 3000 grafts.

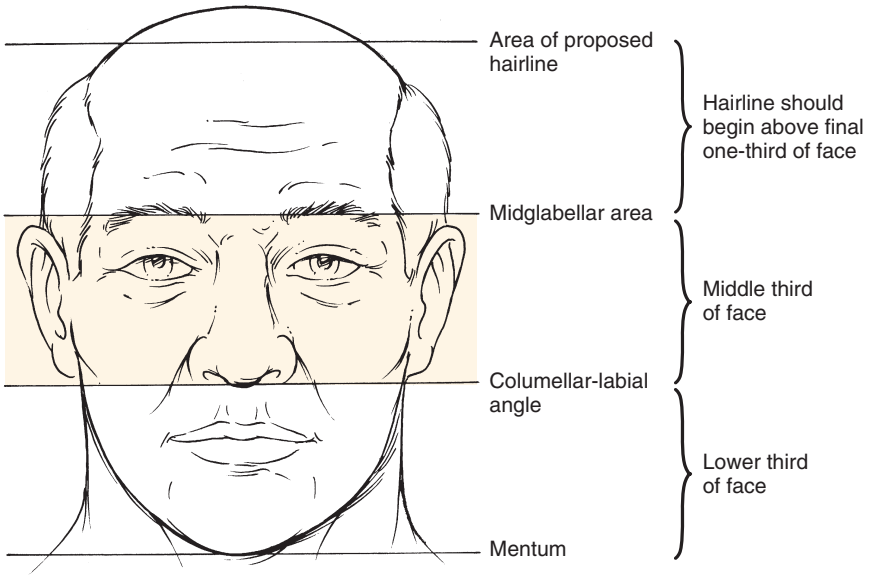

Figure 26-9. The anterior hairline, or trichion, should generally begin 6 to 8 cm above the glabella, in accordance with the rule of thirds of facial analysis. Its exact placement may need to be higher to create a more aesthetically acceptable appearance in the setting of significant hair loss and regression. *(Adapted from Stough DB, Haber RS, eds.* Hair Replacement: Surgical and Medical. *St Louis, Mosby, 1996:170.)*

assessment of the donor reserves should also be completed during the preoperative evaluation. The donor hairs are harvested within the predicted fringe margin of the scalp. The fringe margin extends between each temporoparietal region across the midoccipital scalp at the inion, which is the most prominent point on the posterior skull. The hair follicles within the hair fringe are relatively resistant to the effects of DHT and tend to persist, even in extensively bald individuals.

Specifically, the scalp in the donor region needs to be evaluated in terms of donor hair density and laxity. The number of follicular units in the midoccipital portion of the donor area of a typical white male is 100 follicular units per square centimeter.[38] In terms of estimating donor site hair density, approximately 100 units per square centimeter can be used as a rough guide, and accounts for follicles in the telogen phase.[39]

A donor strip of scalp is generally 0.6 to 1.5 cm wide by 8 to 30 cm long and marked off in 1-cm intervals (Fig. 26-11). If a prior session was performed, the scar is often included in the subsequent donor strip. If there has been a prior donor harvest, the follicles will be spaced

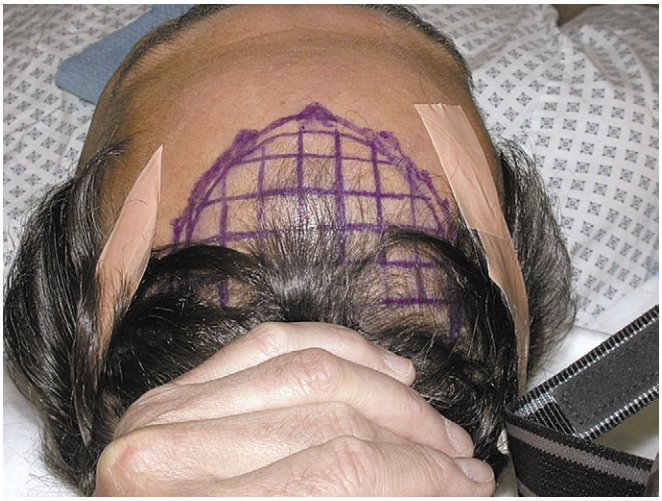

Figure 26-10. The recipient sites are marked out on the scalp in a grid pattern of 1 cm^2.

Figure 26-11. The donor strip is marked off within the hair fringe, where the hair follicles are relatively resistant to the effects of dihydrotestosterone.

Figure 26-12. The dissection of the donor strip is carried out within the subcutaneous fat layer, below the hair follicles.

further apart, thus resulting in a decrease in hair density. Furthermore, the less laxity the scalp has, the more likely that the closure will be more difficult and that it may lead to a widened scar. In such cases, a donor strip of less width and greater length should be taken. It has been observed, however, that very lax scalps eventually develop wide donor scars despite tension-free closures. Tight scalps, if they can be closed readily, often yield thinner long-term scars.

Operative Procedure

After the appropriate donor site is located, the surrounding hair is kept away from the surgical field using either tape or elastic bands. The donor area is trimmed with a mustache trimmer, leaving a few millimeters of hair growth to assist in the fashioning and placement of the grafts (see Fig. 26-11).

The procedure is performed with the patient in a sitting position in a standard comfortable dental chair. After cleansing the scalp with an antiseptic solution, the donor and recipient areas are anesthetized with 10 to 20 mL of 1% lidocaine with 1:100,000 epinephrine. Forty milligrams of triamcinolone are added to 10 mL of the local anesthesia for the infiltration of the recipient site. This infiltration has been shown to minimize postoperative swelling and telogen effluvium (or "shock loss"), which is the temporary hair loss that results from local trauma during surgical manipulation. Preoperative oral sedatives, inhaled nitrous oxide, or intravenous sedation may be used to decrease the discomfort associated with initial local anesthesia infiltration. Twenty to 150 mL of diluted lidocaine solution (approximately 0.1% with epinephrine 1:1,000,000) is infiltrated using a 3-inch 22-gauge needle inserted into the subcutaneous layer of the donor strip. This tumescent infiltration assists with tissue dissection and minimizes bleeding.

The donor strip is harvested with a No. 10 scalpel blade in a single strip. Care is taken to cut parallel to the hair shafts to preserve intact hair follicles. Because of inadvertent injury to hair follicles, the use of a multibladed (usually four to seven blades) knife to create strips of narrower widths has largely been abandoned. The single strip of scalp is excised at a level just below the hair follicles within the subcutaneous fat layer (Fig. 26-12). Bleeding vessels are occasionally coagulated or sutured if needed, particularly if the occipital vessels are transected. Although the occipital nerve is within proximity and can be drawn into scar tissue from a previous harvest, transection is uncommon during primary transplantation. The incision is closed in a running fashion using 3.0 Prolene suture placed at half the depth of the surrounding hair follicles. De-epithelialization of the inferior edge prior to closure can allow for hair growth through the scar. Undermining or deep closure may be performed if a skin closure cannot be readily achieved such as in tight scalps or repeated harvests.

The team approach becomes extremely important for the remainder of the procedure, and the participation of highly trained and skilled hair transplant technicians cannot be overly emphasized. The donor strip is passed off the field to the hair technicians for further sectioning. Usually one technician is used per 700 grafts. Using 10 × power binocular magnification or surgical loupes, the strip is dissected into individual vertical slivers of one follicular-unit thickness using countertraction and a No. 10 scalpel blade (Fig. 26-13A). The dissection is made carefully in a line parallel to the follicle. Under magnification, these slivers of follicular units are dissected transversely into individual grafts that contain one to four hairs, depending on the natural follicular-unit makeup (see Fig. 26-13B). During their dissection and throughout the transplant procedure, the grafts must be kept moist on Telfa pads in saline-filled Petri dishes.

The graft recipient sites or incisions are made with specific attention given to the surrounding natural hair growth in terms of proper hair direction and angulation from the scalp. In general, acute anterior angulation of frontal hairs is designed. If there are residual hairs, we try to mimic their angulation. If there is a balding cowlick, one can recreate it or graft all of the hair anteriorly, assuming all native hairs will be lost later. Most hair anterior to the vertex point grows forward, while temporoparietal hair grows downward. Occipital hair posterior to the vertex grows downward with an angulation changing at the whorl. We

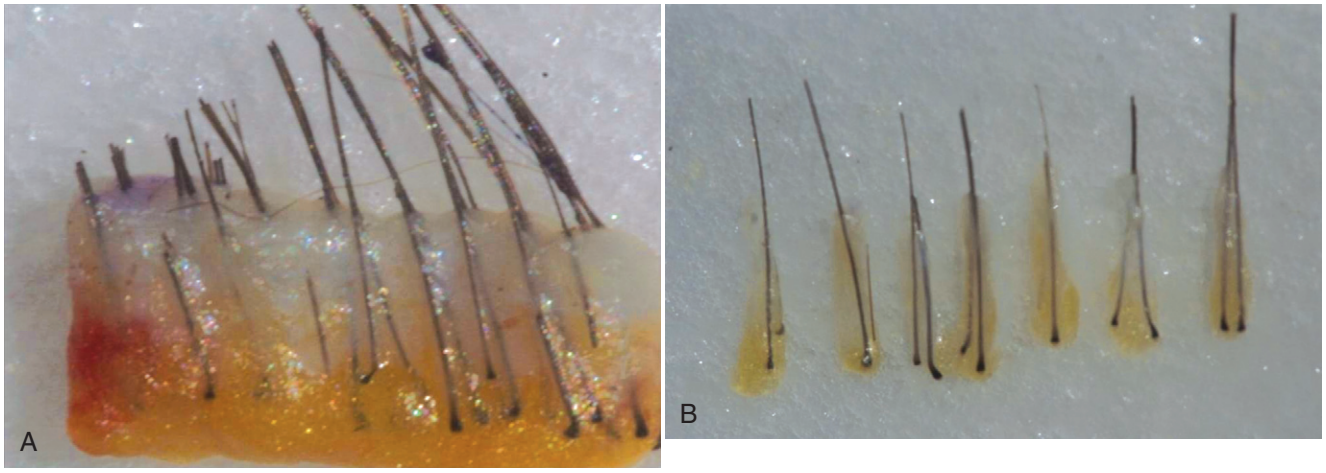

Figure 26-13. **A,** Under 10× magnification, the donor strip is carefully cut into slivers of follicular units. **B,** These are dissected into individual follicular-unit grafts that contain one to three hairs.

Figure 26-14. The incisions at the recipient sites are made with 1.3- or 1.5-mm Minde blades in the same direction and angulation from the scalp as the surrounding hairs.

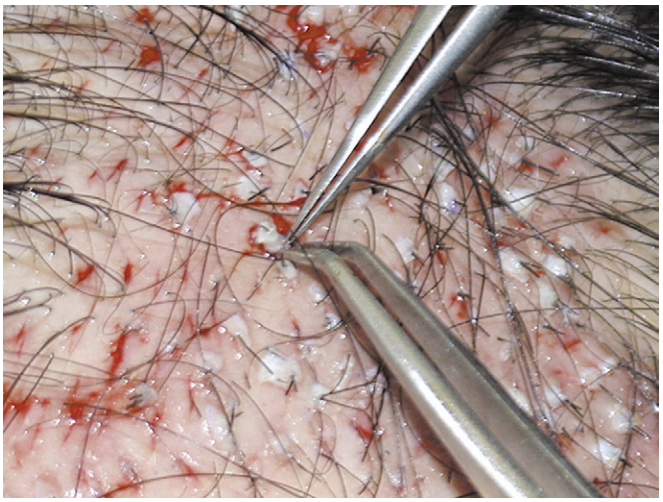

Figure 26-15. Using fine-pointed forceps, the grafts are individually placed within the recipient slits, with attention given to proper orientation and angulation. One set of forceps is used to open the slit, while a second set is used to place the graft into the opening.

rarely perform significant grafting of the downward growing hairs unless the patient is older and has only crown baldness.

The location of the hairline must be designed to anticipate future hair loss so that it continues to look natural for years to come.[40] The hairline should begin at a minimum of 6 to 8 cm cephalad to the glabella in young men (see Fig. 26-9). Incisional slits are made with 0.6 to 1.5 mm Minde (minimal depth) knives (Medical Sterile Products, Rincon, P.R.), Sharpoint blades (Surgical Specialties Corporation, Reading, PA), one of various other types of needles and miniature blades, including the NoKor needle (Becton Dickinson & Co, Rutherford, NJ) (Fig. 26-14), or standard hollow point 18-,19-, and 20-gauge needles (our current preference). The smaller incisions are primarily placed at the anterior hairline and in the "feathering" transition zone to allow for the placement of smaller grafts.[40] More slits per unit area are made within a 5-cm circle starting 1 cm posterior to the feathering zone for larger grafts that provide additional hair density and can be combed posteriorly as future hair loss arises. Slits should be large enough to accommodate 2-, 3-, and 4-unit hair grafts in this area. A similar "feathering" transition zone can also be created posteriorly toward the vertex. If the patient prefers to part his or her hair, a greater numbers of grafts should be placed on the part side to provide greater density in this exposed area. We usually prefer to create a symmetrical distribution of the lateral frontal grafts. The depth of the slit incisions should be made to accommodate most of the graft's length.

The actual placement of the grafts requires meticulous manipulation as they are placed into the individual slits. Using fine-pointed forceps, the grafts are individually placed within the recipient slits, with attention given to proper orientation and angulation. One set of forceps is used to open the slit, while a second set places the graft into the opening (Fig. 26-15). A one-forceps technique is also commonly used. Emphasis is placed on keeping the grafts moist and placing the grafts as atraumatically as possible by grasping them by the surrounding fat so that the hair follicle is not injured. An alternative technique is to place a graft immediately after creating a slit; this is called the "stick and place" technique. Before the placement of the grafts, the recipient areas can be reinjected with small amounts of 2% lidocaine with epinephrine 1:25,000 to enhance anesthesia and vasoconstriction. No more than 0.5 mL is injected via a 30-gauge needle at any one time. A typical session consists of 600 to 2800 grafts placed, but graft sessions of 3600 or more are currently being performed in a few practices.

At the completion of the procedure, the scalp and the recipient sites are cleansed with 1.5% hydrogen peroxide or saline spray to remove crusted blood. Antibiotic ointment is applied to the closed donor incision, and no surgical dressing is applied. Postoperative care

includes oral antibiotics for 3 days, pain medication, and frequent light spraying of the scalp with saline (approximately every hour while awake for 24 to 48 hours postoperatively). The patient is allowed a light shower and shampoo after 72 hours.

The patient can expect crusting at the grafted sites and occasional scalp and forehead edema after the operation. Nonetheless, the patient can often return to normal daily activities within 1 day while wearing a loose-fitting cap or by styling existing hair to cover the expected crusting. Although minigrafts had a high incidence of popping out from recipient sites, follicular unit grafts are placed into size-matched tiny slits and rarely fall out after a few hours postoperatively. Grafts can be readily pulled out until day 6, and crusting seems to extend the at-risk period.[41] Although crusting can help hold grafts in place in the immediate postoperative period, usual care during the first 2 postoperative weeks is to remove crusting by moistening the scalp with a saline spray bottle and frequent showering. After 10 to 14 days, the donor site suture is removed, and most patients should have no visible signs of the procedure.

Follicular-Unit Extraction

In the past 4 years, there has been an increasing interest in harvesting follicular-unit grafts individually so as not to have a linear scar in the donor site as occurs in standard strip harvesting. The technique seems similar to the old punch graft technique in that a small sharp punch (usually 0.8 to 1 mm in diameter) is used on a trimmed donor site to cut around a follicular unit. Done under loupe magnification or with an operating microscope, the cut goes through the dermis and just barely into the subcutaneous fat. The encircled follicular unit is then grasped with a fine forceps and teased out with a small dissecting needle. The follicular unit is extracted, trying not to damage it or the surrounding follicles. Transplanting to the recipient area is directed into premade slits or by a "stick and place" method. Follicular-unit extraction (FUE) has recently evolved into a useful technique for body hair (mainly the beard, chest, back, and extremities) transplantation to the scalp. Curiously, chest hair has been shown to grow on average to triple its length after transplantation to the scalp.[42] This recipient site dominance is due to the increased time spent in the anagen phase. This phenomenon somewhat contradicts the original theory of donor dominance discussed previously in this chapter. At present, some surgeons are doing this particularly tedious and costly technique on only those patients who are salvage cases, those that think in the future they might want to shave their heads, or who are fearful of having any scars. Whether or not this technique becomes frequently performed will depend on leaders in the field developing efficiency and economy in its use.

Complications

Complications from follicular-unit transplantation are uncommon. Poor results can be due to inappropriate design and technique. A hairline placed too low is often done in accordance with a patient's requests; this result should be avoided with careful preoperative evaluation and consultation. In addition, telogen effluvium (temporary hair loss, "shock loss") may occur in both donor and recipient regions as a result of the surgical manipulation of the adjacent hairs. The patient must be informed of this possibility before undergoing the procedure, and he or she needs to be reassured that hair regrowth is expected in approximately 3 months, along with the growth of the transplanted hairs. Epidermal cysts and ingrown hairs are the most common complication from 6 to 14 weeks post transplant; these require unroofing with a needle tip. Temporary or permanent hypoesthesia is possible, primarily in the regions that are cephalad to the harvested donor strip. Scarring is usually minimal. However, with repeated harvests some donor site scars—primarily in the lateral occipital regions—may widen with time. Graft survival may decrease slightly during subsequent sessions as a result of scarring and altered vascularity at the recipient sites. Revision of the unsatisfactory results of older grafting techniques can be performed; however the fine points are beyond the scope of this chapter.

Eyebrow, Eyelash, and Mustache Transplantation

Single hair transplantation has been demonstrated for the eyebrow, eyelash, and mustache (Fig. 26-16). Eyebrow tattooing or penciling for those with eyebrow deficiencies often results in an unsatisfactory appearance. Some will seek surgical correction with growing hairs.

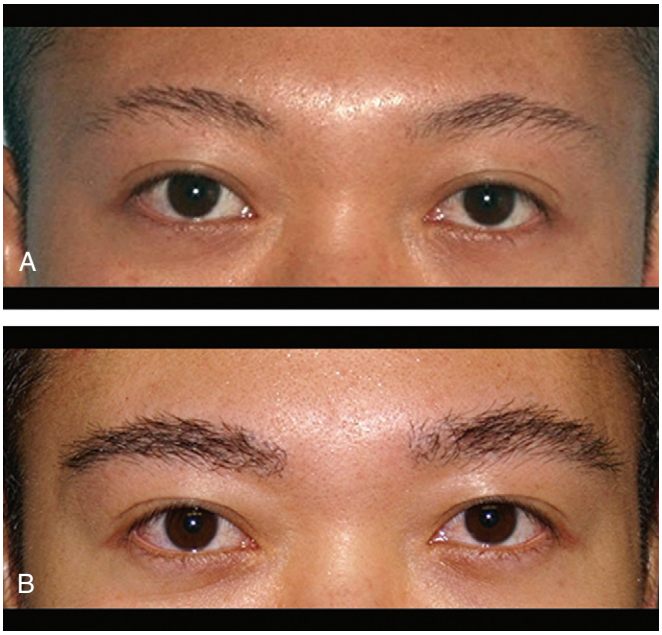

Figure 26-16. Preoperative **(A)** and postoperative **(B)** photographs after eyebrow transplantation with single hair grafts.

Although the hair pattern of the eyebrow is variable, single hair grafts are most often oriented in a vertical direction medially, and transitioned to a horizontal direction laterally. Inferior eyebrow hair is usually oriented superiorly whereas superior hair is most often oriented in an inferior direction. No matter what the direction, hair grafts should be placed with an extremely acute angle to the plane of the forehead, with the curl of the hair placed toward the skin. Trimming is necessary to maintain a natural length. Hair dye may also become necessary, if the patient regularly dyes the scalp hair. Grafts of the patient's original hair color can often be obtained from the lower occipital scalp. In reconstructive eyebrow surgery, pedicle flaps and full thickness strip grafts are considered obsolete.

Mustache transplantation has the unique ability to camouflage scars of the upper lip, especially of the prolabium in male patients years after cleft lip repair. Hair orientation should be angled acutely with the skin, angled down medially, and trended slightly laterally as one moves away from the philtrum.[43] Several different eyelash implantation techniques with single hairs have been described.[43]

In all facial hair transplants, the donor hair should be taken from areas of the donor scalp that most closely resemble the texture and curl of the hairs in the recipient areas. In some cases such a match may not be possible.

Scalp Reductions

In the past, scalp reductions were used extensively to minimize or eliminate areas of alopecia by excising bald portions of the scalp after subgaleal undermining. The amount of scalp excision was proportional to its inherent elasticity. Numerous shapes of excisions have been used to excise the balding areas of scalp. These designs include an ellipse, a Y, a crescent, and a horseshoe. They are individualized on the basis of the patient's pattern of hair loss (Fig. 26-17).

Additional bald scalp excision can be achieved with the use of tissue expanders or scalp extenders. The expander or extender is placed in the subgaleal plane approximately 6 to 8 weeks before the scalp reduction. In scalp or forehead expansion, serial injections of saline via the percutaneous port results in a progressive increase in scalp surface area or excess forehead skin laxity. Scalp extension depends on the inherent elastic recoil of the implanted extender device to give tissue creep to adjacent areas of hair-bearing scalp (Fig. 26-18C).

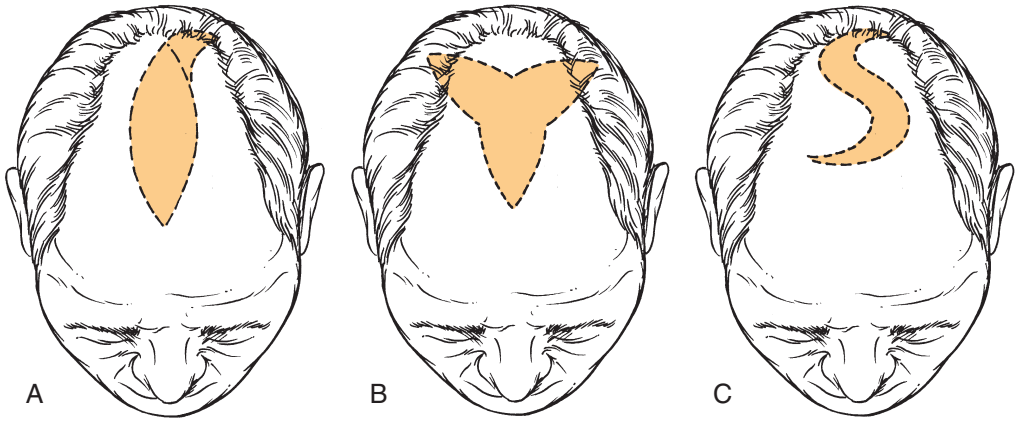

Figure 26-17. Three commonly used patterns for scalp reduction. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

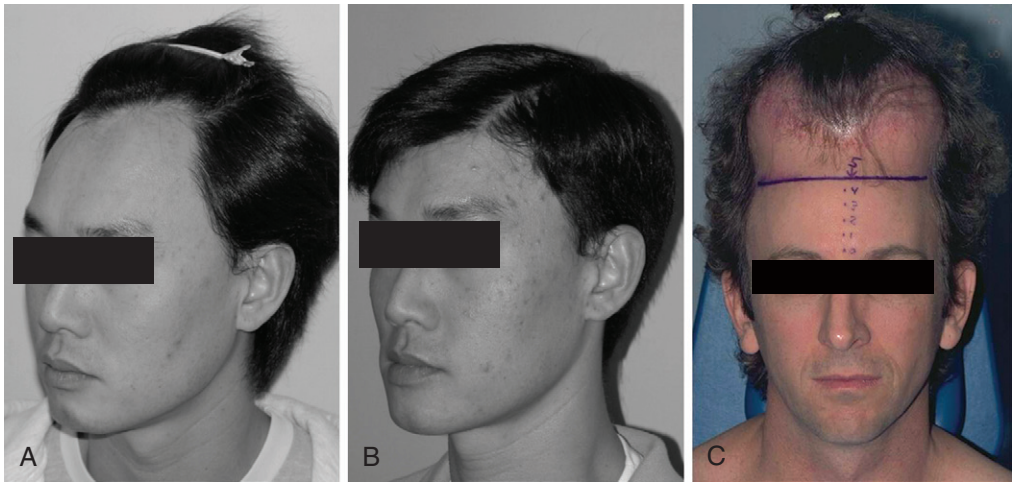

Figure 26-18. Preoperative **(A)** and postoperative **(B)** photographs of a patient with a high hairline who underwent an anterior hairline advancement after scalp expansion with a tissue expander. **C,** Preoperative photograph with 700 mL of tissue expansion over 10 weeks, now just prior to hairline advancement.

While scalp reductions are now rarely performed, forehead feminization or hairline lowering is becoming more commonplace in our practice. This is similar to a scalp reduction; however, it is done to achieve a forehead reduction. Females or even males with a high hairline or prominent forehead, or transgender individuals who desire forehead feminization, can elect to undergo this anterior hairline advancement with excision of forehead skin. The advancement can be performed in conjunction with a browlift procedure that also addresses the corrugator and procerus muscle groups. An irregularly irregular trichophytic incision made perpendicular to the hair follicles facilitates hair growth through the resulting scar, and precise wound closure ensures inconspicuous healing. Preliminary scalp expansion as described above may be needed in patients with minimal scalp laxity and in those who need more than 3 cm of advancement (see Fig. 26-18).

Complications

Although effective for the removal of areas of baldness, reductions have created their own unique set of problems: misdirected hair, severely decreased hair density, stretchback, elevated hairlines, detectable scars, and, most notably, the posterior vertical "slot" defect (Fig. 26-19).

Perhaps the most noticeable of these complications is related to the misdirected hair from repetitive scalp reductions. Normally, temporoparietal hair points directly down toward the ears and exits the scalp at an acute angle; midscalp hair grows in a frontal direction and with greater angulation from the scalp. When both superior aspects of the fringe are brought together in the midline with scalp reduction, the hair direction becomes noticeably divergent in this region, which creates a distorted appearance.

The vertical or "slot" defect is created in the posterior occiput by closing an elliptically resected area into an elongated scar. This unfavorable scar can be corrected by excising the scar and using a series of three anteriorly based rotational flaps as described by Frechet.[44] Using these flaps, hair direction is reoriented so that hair grows inferiorly, thereby covering the incisions (Fig. 26-20). Scalp reduction for male pattern baldness is considered by many to be conceptually flawed and is rarely performed.

Flap Procedures

Large delayed temporoparietal-occipital (TPO) pedicle flaps are unique and involved procedures that can create complete hairlines 4 centimeters in width and of great density in a short period of time (Fig. 26-21). Originally described by Juri and popularized by Kabaker,[45,46] the TPO pedicle flap essentially recreates the anterior hairline with hair-bearing scalp from the TPO hair fringe, which is resistant to androgenetic alopecia.[47] Although it does achieve its primary goal, the TPO flap is an exacting procedure that requires three staged surgeries in addition to a highly motivated patient with frontal baldness, stable crown coverage, and good hair density and laxity in the donor region.

The pedicle of the axial TPO flap is centered over the posterior branch of the superficial temporal artery, which usually runs superiorly through the midportion of the sideburn and curves posteriorly. Because of the large flap length-to-width (7:1) ratio and the random blood

supply at the distal portion of the flap, Juri[45] described two delay procedures for vascular preconditioning of the flap. The average flap was 28 cm in length and 4 cm in width. The first delay procedure is the creation of a bipedicle flap with posterior circulation that is provided by the perforating branches of the occipital artery. One week later, the posterior bridge of scalp is transected and stapled closed in a brief second procedure. The need for delaying these large flaps has been challenged, and the operation has been performed with only one or no delay. In addition, tissue expansion can be performed before flap transfer as originally described by the senior author.[46,48]

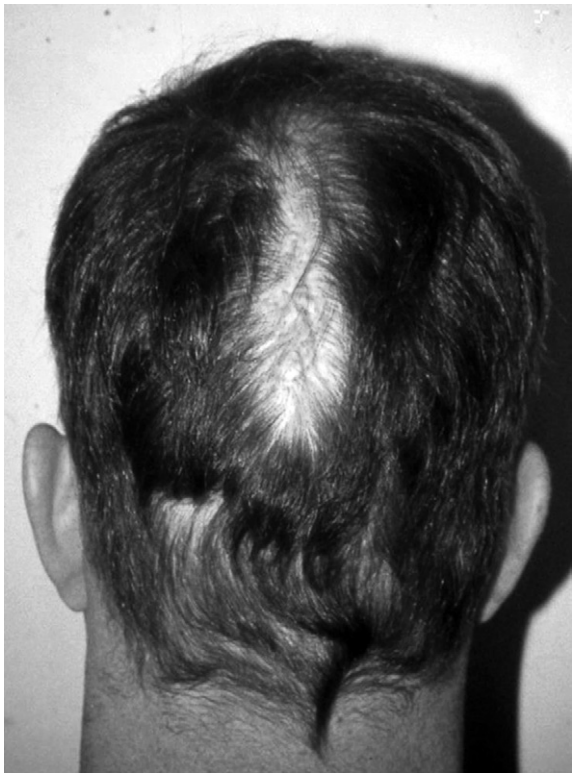

Figure 26-19. The posterior vertical "slot" defect after serial scalp reductions. Note the misdirected hair.

The third stage involves the actual flap transfer and is performed 1 week after the second delay (Fig. 26-22). The flap is elevated in the subgaleal plane. An irregular hairline incision, as described by Fleming and Mayer, is beveled posteriorly at about a 45-degree angle to the scalp.[49] Extensive undermining of the scalp, neck, and postauricular region is necessary to facilitate a two-layered closure with minimal tension. The leading edge of the flap is de-epithelialized before being sutured to the forehead after the overlapped bald skin is excised. A dog-ear inevitably forms at the proximal side of new hairline and is dealt with 6 weeks later.[45,49] A second TPO flap can be performed months after the initial flap transfer for additional posterior coverage. However, closure problems as a result of subsequent decreased scalp laxity become more of a concern. Prior tissue expansion of the temporal and parietal scalp can allow for wider flaps (up to 6 cm) and minimal tension in the donor closure.[47,49]

Complications

Complications associated with the TPO flap include postoperative swelling and ecchymosis; a persistent dog-ear deformity at the proximal side of the flap, with a blunted temporofrontal angle; widened temporal scars; and occasional necrosis of the distal end of the flap.

Of further concern is the aesthetic result in terms of progressive alopecia and misdirected hair growth. After a successful flap procedure, further hair loss can result in an unnaturally dense anterior hair zone with an extensively bald vertex. This undesirable effect can be camouflaged by combing the hair straight back or with a hairpiece system. Nonetheless, the results are generally not consistent with the current philosophy of inconspicuous hair restoration. Consequently, given its complexity, long learning curve, and possible complications, the TPO flap has regretfully been abandoned as routine correction for male pattern baldness.

It is of note that bilateral nondelayed flaps from the temporal-parietal (TP flaps) scalp have also been used to recreate the anterior hairline.[50] These flaps are mentioned only to be avoided given their

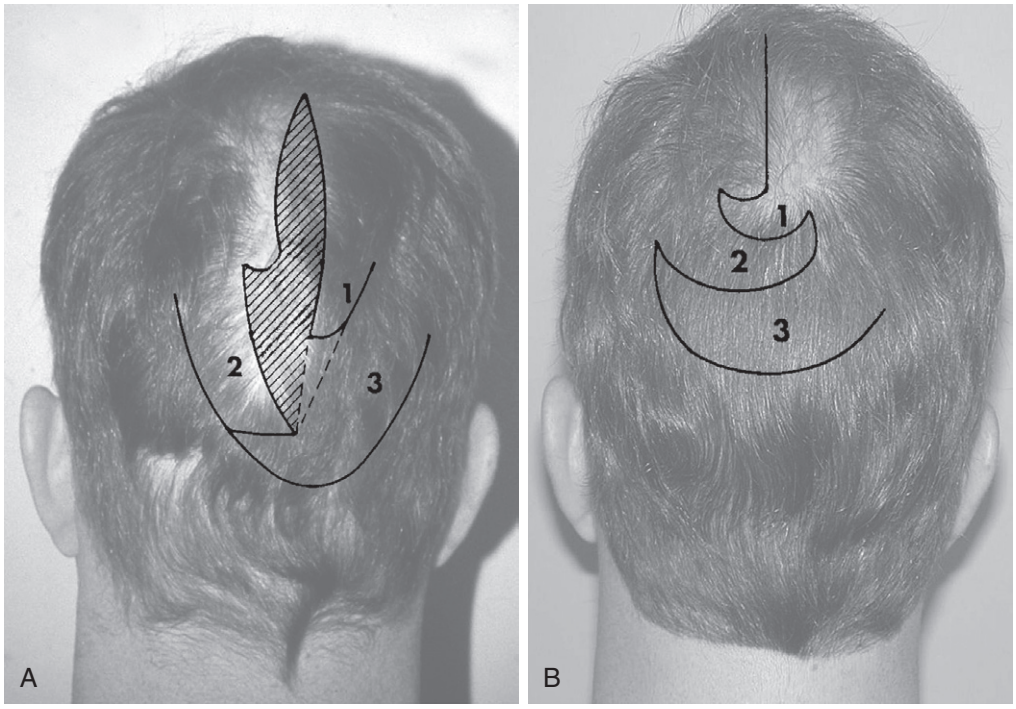

Figure 26-20. **A,** The Frechet triple flap repair for the correction of the vertical "slot" defect. **B,** The postoperative result.

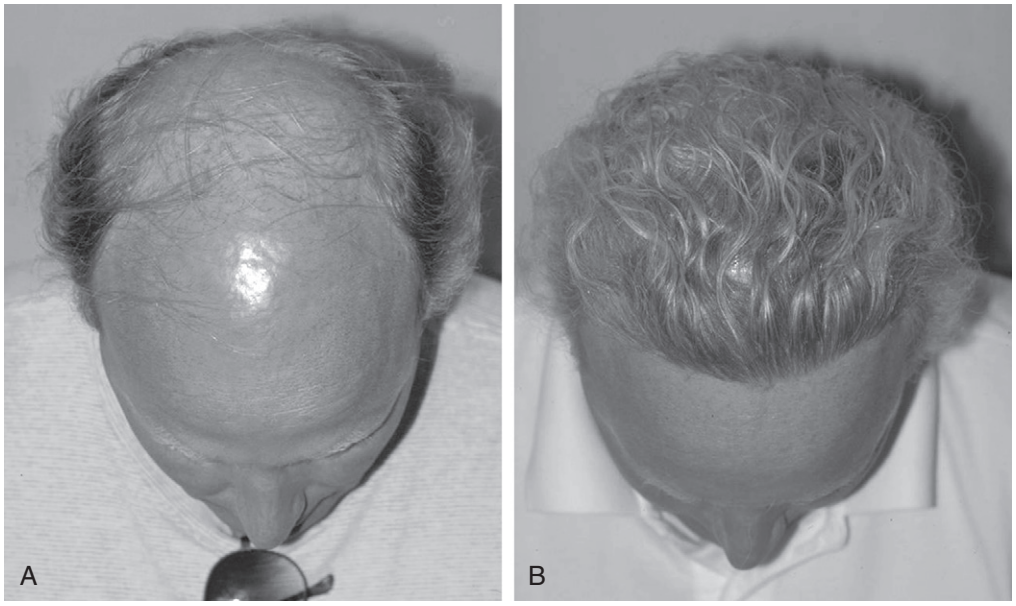

Figure 26-21. Preoperative **(A)** and postoperative **(B)** photographs after a temporoparietal-occipital (or Juri) flap.

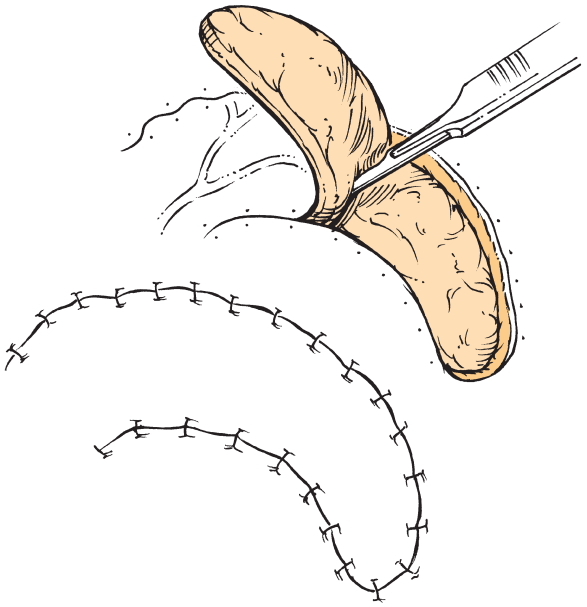

Figure 26-22. The temporoparietal-occipital or Juri flap. (© 2008 by Johns Hopkins University, Art as Applied to Medicine.)

more numerous problems with misdirected hair and hairline asymmetry when compared with the wider, long, delayed TPO flaps.

Reconstructive Procedures

All of the principles and techniques described in this chapter also can apply to alopecia resulting from prior surgical procedures, trauma, and radiation. Again, the surgeon must be attentive preoperatively to proper positioning of the hairline and the surrounding hair direction to achieve the most aesthetically pleasing results. Limited scarring alopecia may be treated as an excisional scar revision with undermining at the subgaleal level or with local rotational or advancement flaps. More extensive areas of alopecia may require serial scalp reductions, often after tissue expansion. Whenever possible, we advocate the consideration of tissue expansion for reconstructive scalp surgery.

Follicular-unit hair transplantation is used as a separate modality or in conjunction with other procedures to further enhance coverage and camouflage scalp scarring. Specifically, follicular-unit hair transplantation has been successfully implemented in cases of unfavorable scarring and hair loss after procedures such as rhytidectomy, browlift, or craniotomy.[51] For example, altered hairlines with stepoff deformities in the temporal and occipital areas can occur in rhytidectomies with poorly designed incisions or after skin necrosis. These cases can be successfully corrected with follicular-unit hair grafting (Fig. 26-23). Alternative procedures may be required in cases of more extensive scalp loss, such as after scalp avulsion with loss of viable tissue or significant scalp resection for malignancy. If the underlying pericranium is intact, a split-thickness skin graft may be used. This approach is preferred in cases that involve high rates of cancer recurrence, given the fact that the thin graft will allow for enhanced monitoring. For larger scalp defects, a superficial temporoparietal fascia flap, a trapezius myocutaneous rotational flap, or a latissimus dorsi muscle or radial forearm microvascular free flap can provide well-vascularized tissue for proper soft tissue coverage.[52]

Nonsurgical Hair Restoration

Modern artificial hair systems or additions can augment surgical hair restoration or serve as a substitute. Although these options are often associated with negative images, current designs in hair systems can provide a natural appearance and remain virtually undetectable. Devices include hair weaves, partial hairpieces, and complete wigs. The fibers used consist of human hair, synthetic fibers, or combinations of both. Custom designs are generally integrated with the patient's own hair or hairline to create a natural appearance while the patient remains comfortable. Improved fixation techniques involving either the scalp or the surrounding hair can accommodate a wide variety of lifestyles.

Alternatives and Future Treatment Options

Various new avenues are being explored in surgical hair restoration. Synthetic hair grafts were originally introduced in Japan by Yamada and Fukuta in 1972,[53] and they remain an accepted alternative treatment for alopecia in many countries. The synthetic hair consists of polyethylene terephthalate, which is the same material used in the suture fiber Prolene (Ethicon, Johnson & Johnson, Somerville, NJ) with a thin coating of amorphous silver added for its antibacterial properties.[53] Disadvantages include the constant risk of infection and progressive scarring as a result of a chronic foreign body reaction. In addition, the hair fibers have an unnatural appearance on close inspection, and monthly follow-up visits and frequent graft replacements are necessary.[54] Given that no independent clinical studies have shown that

Figure 26-23. Alopecia after rhytidectomy. **A,** Notice the loss of the temporal tuft of hair, the altered occipital hairline, and the visible scars. **B,** Patient's appearance 6 months after two sessions (520 grafts and 400 grafts, respectively) of follicular-unit hair transplantations. **C,** Close-up showing hair growth in the temporal region.

synthetic grafting is safe, the Food and Drug Administration has never approved its use, and it is outlawed in the United States.

Research has also focused on follicle regeneration and its possible implications in the field of hair transplantation. Studies have demonstrated that horizontal sectioning of a hair follicle across its perifollicular sheath will result in two portions that will continue to grow.[55] One follicular-unit hair graft could possibly be fashioned into two or more viable grafts, thereby dramatically increasing the number of available donor grafts. Although autografting is the most popular form of hair transplantation, allogeneic hair transplantation from a bone marrow donor to his recipient has been reported.[56] Follicular stem cell research is currently in phase II studies. Adult hair follicles contain multipotent stem cells, which have shown the ability in vitro to yield hair growth. Ultimately, this exciting area of tissue engineering may overcome current limitations of individual donor hair supply.[43]

Summary

Although an extensive list of causes of alopecia exists for both men and women, the most common type remains AGA. Advances in medical therapy (e.g., finasteride) have been relatively successful for selectively targeting the underlying processes of hair loss. For patients who require significant hair coverage, follicular-unit hair transplantation has become the gold standard surgical method for providing a patient with a natural-appearing hairline and the illusion of a full head of hair. Other surgical options (e.g., scalp reductions, large flaps) should be avoided if possible, but remain in the surgeon's armamentarium for select patients and situations. Future advances are focused on hair restoration at the cellular level in terms of maximizing both remaining follicles and aesthetic results. Overall, the treatment of alopecia should be viewed as having an integral role in appearance enhancement and facial rejuvenation as well as in improving a patient's self-image and quality of life.

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CHAPTER TWENTY-SEVEN

Management of Aging Skin

Stephen W. Perkins

Henry D. Sandel, IV

Key Points

- Combined resurfacing modalities tailored to skin type and location are more effective than single modality alone.
- The ideal patient for skin resurfacing is the thin-skinned woman with fair complexion and fine rhytids.
- Impairment of liver and/or kidney function could slow the excretion of phenol, increasing the likelihood of cardiac complications.
- All patients should receive appropriate antiviral therapy to prevent and treat possible herpetic outbreaks before resurfacing.
- Retinoic acid increases the depth of chemical peels by decreasing the thickness of the stratum corneum.
- Fitzpatrick type III or greater should consider the use of 4% to 8% hydroquinone gel before and after resurfacing to prevent hyperpigmentation.
- Superficial peels extend to the papillary dermis, medium depth peels extend to the upper reticular dermis, and deep peels extend to the midreticular dermis.
- Indications for medium depth peel are moderate photoaging, actinic keratosis, pigmentary dyschromia, mild acne scarring, and blending of other modalities.
- Pigmentary changes are the most common complication of chemical peels.
- CO_2 laser is particularly good for treating perioral vertical furrows, periocular crow's feet, glabellar rhytids, diffuse acne scarring, and aging spots.
- Nonablative resurfacing usually require multiple treatments to obtain a desired effect.
- Multiple superficial peels do not equate to single moderate or deep peels.

Aging skin is one of the primary characteristics of the aging face that must be addressed as a part of comprehensive facial rejuvenation. Proper skin care regimens can be started at an early age in order to decrease the amount of photoaging, dyschromias, and superficial scarring that a person accumulates over time. Even though these preventive measures are becoming more commonplace, there are still many patients who seek treatment of their aging skin in order to "reverse" this process. This chapter focuses mainly on the resurfacing techniques available to treat advanced skin damage. Chemical peels and laser ablative techniques have been proven to produce substantial results in a consistent manner. We will also discuss emerging trends including nonablative laser therapy and fractionated ablative laser therapy. Other topics including dermabrasion and medical skin care regimens will also be addressed. Each of these techniques alone can produce predictable results in selective patients. However, it has been our experience that combined modalities tailored to skin type and location can be most effective.[1]

Histologic Changes of Aging Skin

The first scholarly report on phenol chemical peels was written by Brown and others.[2] Brown described the histologic changes that were induced including laminated collagen in the epidermis, with fibrous strands consistently paralleling the newly formed epidermis. Later, Kligman and colleagues[3] studied the skin taken from Baker and Gordon's facelift patients who had chemical peels 1½ to 20 years earlier. First, they described histologic changes of nonpeeled skin. These aging skin changes were typical of actinic exposure with a loss of orderly differentiation in the epidermis and degeneration of the elastic network, along with some mottled pigmentation and lymphocytic infiltration. There was a decrease in collagen amounts as well as disordered degeneration of the dermal fibers, a flattening of the dermal-epidermal junction, and multiple actinic keratoses with atypia. The number of melanocytes was increased in this actinic skin, but they were unevenly distributed and contained variable amounts of melanin.

The skin of patients who had undergone a previous chemical peel showed a new band of dermis 2 to 3 mm thick just beneath the epidermis and lying on top of the old elastotic dermis. The epidermis had returned to orderly cellular differentiation without irregularities or microscopic actinic keratoses. Although there was an abundance of melanocytes present containing some fine, evenly distributed melanin granules, there appeared to be impaired melanin synthesis with a generalized bleaching effect, or hypopigmentation. Lentigines were not seen. Furthermore, the epidermal-dermal matrix was composed of thin, compact, parallel collagen bundles arranged horizontally in contrast to the usual wavy pattern. Elastotic fibers had actually regenerated, forming a network of fibers paralleling the new collagen. Finally, the lymphocytic infiltration was diminished compared with that of untreated skin. Kligman and colleagues[3] believed that the dermal reconstruction lasted about 20 years based on their study. They further concluded that chemical peel reduced the development of new neoplasms. The laying down of a band of new connective tissue can adequately account for the effacement of the wrinkles seen clinically. The skin is smoother, fuller, and tighter. Stegman[4] and Litton and colleagues[5,6] showed the chemical peel solution penetrating deeper in the dermis of actinically damaged

skin than nonactinically damaged skin. Hayes and Stambaugh[7] demonstrated that during the first 2 to 5 days of a chemical peel there is epidermal necrosis, edema, and homogenization with the lymphocytic infiltration all the way into the reticular dermis.[8] At 2 weeks, new collagen formation had begun. Stegman,[4] Alt,[9] and Brody and Alt[10] have illustrated that there is deeper penetration of phenol with occlusion than with nonocclusion. According to Beeson and McCollough,[11] this is apparently true but not necessarily desired.

Litton and others[6] agreed with Kligman and colleagues[3] that the rate of appearance with precancerous and early cancerous lesions of photoaged skin was decreased after a phenol chemical peel.

Brodland and Roenigk[12] showed that trichloroacetic acid (TCA) destroys the epidermis and upper dermis and further showed that the new epidermis migrated from the cutaneous adnexa beneath the destroyed tissue. This is similar to phenol peel. Histologically, the atypical clones of keratinocytes are removed and replaced by normal epidermal cells.

Patient Evaluation, Classification, and Selection

The process or technique of chemical peels (and other resurfacing modalities) is relatively easy to learn. However, it takes a great deal of experience with many different types of patients to learn the wide variation in skin types and how these respond to peel solutions.[13] It also takes a great deal of experience to predict the way in which each area of the face will respond to light or deep resurfacing in an individual patient, and how one can influence the method of application used. Careful selection of the appropriate patients for resurfacing is the first and most important consideration. According to McCollough and Hillman,[14] "The ideal patient is a thin-skinned female with fair complexion and fine rhytids."

Fitzpatrick[15] described types of actinically damaged skin ranging from type I to type VI (Table 27-1). Brody[16] stated that Fitzpatrick types I through III patients are suitable for a chemical peel. He describes the ideal patient as a light-complected person of Celtic or Northern European descent with skin types I or II.[17]

The Glogau classification system[18] was created in 1994 and provides an objective assessment of the degree of photoaging, categorizing the patient's skin damage into mild, moderate, advanced, or severe (groups I through IV) (Table 27-2). Patients in category I are often young with minimal photoaging and are best managed with a superficial peel in conjunction with a good medical skin care program. Patients in category II or III are candidates for medium-depth peels in addition to long-term medical therapy as with retinoids or alpha-hydroxy acids. Category IV photoaging patients are best treated with medium or deep chemical peels, ablative lasers, or dermabrasion, in conjunction with long-term medical skin care regimens.

There are several aesthetic and therapeutic indications for chemical peels and resurfacing (Table 27-3).

Today's facial plastic surgeon must be aware of the aesthetic and therapeutic indications of facial resurfacing to effectively rejuvenate aging skin. Additionally, treating a patient based on his or her Fitzpatrick skin type and Glogau aging characteristics is essential to select the best type and depth of facial resurfacing.

Contraindications

There are a few relative contraindications to chemical peels in addition to some absolute contraindications (Table 27-4). In the past, a history of herpes simplex virus was a contraindication to chemical peel.[19] With the advent of antiviral drugs, however, acyclovir (Zovirax) or valacyclovir (Valtrex) can be effectively used as preventive or therapeutic intervention. Telangiectasias are relative contraindications in that they become more apparent after chemical peels or laser resurfacing. Confirmed malignant lesions should not be treated with chemical peels unless they are very superficial basal cell carcinomas. Nevoid or nevus lesions may become darker or actually stimulated to grow, and port-wine stains, hemangiomas, and neurofibromatoses are not effectively treated with chemical peels. Contraindications include the presence of hepatorenal disease or cardiac disease (for phenol peels), unless approved by an appropriate specialist. True documented allergies to an agent are obvious contraindications, and dressings should be latex free in sensitive patients. Patients who are unstable psychologically should not be treated with any resurfacing modality, particularly because the postoperative care may require intense patient involvement, education, and understanding.

Chemical Peels

Patient Selection and Education

Patients requesting rejuvenation of aging skin via chemical peels must have a realistic understanding of potential outcomes, limitations, and

Table 27-1

Fitzpatrick Sun-Reactive Skin Types I to VI

Type I	Fair-skinned, blue or hazel eyes, blond or red hair Always burns, never tans
Type II	Fair-skinned; blond, red, or brown hair Usually burns, tans less than average
Type III	Fair-skinned, largest group of U.S. citizens Sometimes burns mildly, tans about average
Type IV	Still considered white-skinned Rarely burns, tans more than average and with ease
Type V	Intermediate-colored skin; that is, Asian, Latin, Indian Brown skin
Type VI	Black-skinned persons Never burns

Table 27-2

Glogau Classification of Photoaging Groups

Group I Mild	Group II Moderate	Group III Advanced	Group IV Severe
Little wrinkling or scarring	Early wrinkling; mild scarring	Persistent wrinkling or moderate acne scarring	Wrinkling: photoaging, gravitational, and dynamic
No keratoses	Sallow color with early actinic keratoses	Discoloration with telangiectasias and actinic keratoses	Actinic keratoses with or without skin cancer or acne scars
Typical age, 28 to 35 years old	Typical age, 35 to 50 years old	Typical age, 50 to 65 years old	Typical age, 60 to 75 years old

Table 27-3

Indications for Facial Resurfacing

Aesthetic Indications
Fine facial rhytids
Atrophic changes in skin caused by excessive sun exposure
Spotty or splotchy hyperpigmentation
Multiple actinic and solar keratoses
Superficial acne scarring
Melasma
Excessively wrinkled skin
After blepharoplasty or facelift
Therapeutic Indications
Multiple actinic, seborrheic, and solar pigmented keratoses
Superficial basal cell carcinomas
Lentigo maligna lentigines
Melasma (discoloration of skin caused by pregnancy)

Data from McCollough EG, Hillman RA Jr. Symposium on the aging face. *Otolaryngol Clin North Am*. 1980;13:353; Farber GA, Collins PS, Scott MW. Update on chemical peel. *J Dermatol Surg Oncol*. 1984;10:559; and Litton C, Sachowicz EH, Trinidad GP. Present day status of the chemical face peel. *Aesthetic Plast Surg*. 1986;10:1.

Table 27-4

Brody's Relative and Absolute Contraindications to Chemical Peels

Relative Contraindications
Darker skin type (Fitzpatrick IV, V, and VI)
Keloid formation by history
History of herpes infections
Cardiac abnormalities
History of previous facial irradiation
Marked quantity of vellus hair present
Unrealistic patient expectations
Physical inability to perform quality postoperative care
Telangiectasias
Anticipation of inadequate photo protection because of job, vocation, or recreation
Absolute Contraindications
Significant hepatorenal disease
HIV-positive patient
Significant immunosuppression (i.e., hypogammaglobulinemia)
Emotional instability or mental illness
Ehlers-Danlos syndrome
Scleroderma or collagen vascular diseases
Recent isotretinoin (Accutane) treatment (within 6 to 12 months before)

postoperative care. The preoperative consultation should include a discussion of the patient's expectations and motivation to participate in postoperative care. The patient must have a clear understanding of the postoperative discomfort, appearance, and care that will follow. He or she must understand that preexisting large pores will remain unchanged, and that telangiectasias may appear to be more prominent. Informed consent about the risks and benefits is essential. At the end of the consultation, high-quality photographic documentation is obtained and should be standardized using reproducible measures. Acne scarring is notoriously underdemonstrated or overdemonstrated, depending on the lighting or flash used; therefore the clinician should adjust the setup to accurately reflect the patient's true skin appearance. This is the only objective way that the surgeon can later determine whether he or she is achieving satisfactory results. Standard preoperative workup and medical clearance is obtained, depending on the patient's preexisting health status. If a phenol chemical peel is to be used, special attention must be given to cardiac, liver, and kidney function in the preoperative medical workup. Any impairment of liver or kidney function could slow the excretion of phenol, potentially increasing the bloodstream concentration and leading to cardiac irregularities or even death.

Prepeel Preparations

Before any resurfacing procedure, considerations must be taken to optimize the patient's final aesthetic outcome. The preoperative consultation is used to assure that the patient is adequately prepared for the day of the chemical peel. Considerations such as a positive history of herpetic outbreaks should warrant appropriate prophylaxis. In patients with no preceding history of fever blisters who are undergoing a medium or deep peel, we have found that Valtrex is an appropriate prophylaxis at 500 mg by mouth twice a day, starting the day before the peel and continuing through the 10th to 14th day. For patients with a known history of herpetic outbreaks, we have found that prophylaxis with acyclovir at 800 mg by mouth four times per day over the same period, until reepithelialization is complete, is more effective at preventing outbreaks.

To achieve optimal results, patients must adhere to a skin care regimen in both the preoperative and postoperative periods. Patients undergoing medium or deep chemical peels are best pretreated with tretinoin (Retin A or Renova) on a nightly basis starting 2 to 4 weeks before the peel. The use of retinoic acid before chemical peels, dermabrasion, or laser resurfacing speeds epidermal healing and enhances the effects of the procedure. Retinoic acid also increases the depth of a chemical peel by decreasing the thickness of the stratum corneum. Its use is restricted during the postoperative period until reepithelialization is complete and maturization of the skin has occurred. This takes approximately 3 months.

In darker-skinned individuals, Fitzpatrick type III or greater, the use of 4% to 8% hydroquinone gel in the preoperative and postoperative periods may reduce the incidence of hyperpigmentation. It is also necessary to use hydroquinone when peeling for the treatment of pigmentary dyschromia (i.e., melasma) in patients of any skin type. Hydroquinone blocks the enzyme tyrosinase from developing melanin precursors for the production of new pigment in the epidermis during the healing phase.

All patients undergoing medium to deep facial resurfacing procedures must minimize sun exposure in the postoperative period. This is even more important in patients taking estrogens and those with preexisting pigmentary disturbances. Wearing sunblock with a sun protection factor (SPF) of 30 or greater is recommended during the first 9 to 12 months after a peel.

Chemical Peel Agents

Superficial Peels

Depending on the surgical goal, the appropriate agent is selected for each individual patient. Histologically, superficial peels extend down into the level of the stratum granulosum and papillary dermis. Such depth is good for treating mild photoaging (Glogau I and II), melasma, comedonal acne, and postinflammatory erythema. Multiple peels are usually required for a maximal result, ranging from six to eight peels on a weekly basis or every other week. A nice "refreshing of the skin" is achieved; however, multiple superficial peels do not equate to the results of a medium or deep chemical peel.

Several chemical agents fall into the superficial peel category. These agents include low concentrations of glycolic acid; 10% to 20% TCA; Jessner's solution (resorcinol, 14 g; salicylic acid, 14 g; lactic acid, 14 mL; ethanol, 100 mL); tretinoin; 5-fluorouracil (5-FU); and salicylic

acid, a beta-hydroxy acid. The depth of the peel achieved with each of the above agents varies depending on the concentration of agent used, the duration of the application, and the number of times the agent is applied. During application, there may be a mild stinging followed by a level I frosting, defined as the appearance of erythema and streaky whitening on the surface.[18] Regular washing with a mild cleanser and the use of routine moisturizers and sunscreens is all that is needed after the procedure. Superficial peels usually cause mild erythema and desquamation, with a healing time varying from 1 to 4 days, depending on the strength of the chemical agent.

Medium-Depth Chemical Peels

A medium-depth peel is one in which the injury extends through the epidermis to the upper reticular dermis. In the past, 50% TCA was the standard medium-depth peeling agent, but it has been abandoned with time because of a high rate of complications including pigmentary changes and scarring. Currently, a combination of agents or modalities is used for medium-depth resurfacing. The most common agents include a combination of 35% TCA with Jessner's solution, 70% glycolic acid, or carbon dioxide (CO_2) laser. Phenol 88% by itself will give a medium-depth peel. The senior author prefers to use phenol 88% for chemical exfoliation of the lower eyelid. It produces more consistent results than CO_2 laser resurfacing without the temporary lower eyelid-tightening effect. Current indications for medium-depth chemical peels include moderate photoaging (Glogau II), actinic keratoses, pigmentary dyschromia, mild acne scarring, and blending of other resurfacing modalities (i.e., deep peels or lasers).

Monheit has demonstrated the use of Jessner's solution before the application of TCA as a synergistic combination.[19a] Jessner's solution effectively destroys the epidermal barrier by breaking up individual keratinocytes, allowing deeper and more even penetration of the 35% TCA. This technique is useful for the improvement of mild to moderate photoaging. There is minimal risk of pigmentary or textural complications, and this combination softens fine rhytids and freshens sallow, atrophic skin. Collagen remodeling and thickening occur over a 3- to 4-month period, with continued improvement in rhytid effacement and texture quality of aging skin. Deep furrows, however, are not eliminated with this medium-depth combination alone. The Jessner's solution plus 35% TCA combination has been as effective as topical 5-FU chemotherapy in removing grossly visible and clinically undetectable actinic keratoses, with less morbidity and the positive effect of antiaging. This combination of agents is also used to blend resurfacing procedures with the surrounding skin. For example, patients who have undergone dermabrasion, CO_2 laser resurfacing, or deep chemical peels in an isolated region (e.g., perioral or periorbital) may develop a sharp line of demarcation or hypopigmentation when compared with nontreated skin. In these instances, use of Jessner's solution plus 35% TCA on the surrounding nontreated skin helps blend the treated area into its surroundings.

Technique: Medium-Depth Chemical Peels

The medium-depth Jessner's plus 35% TCA peel is performed with the patient under intravenous sedation as necessary as an isolated procedure. The burning sensation is typically short-lived, therefore short-acting drugs are sufficient. Five to 15 mg of diazepam plus 1 to 2 mg of hydromorphone hydrochloride (Dilaudid) is typically sufficient. Nonsteroidal anti-inflammatory drugs or aspirin can also be given within the first 24 hours to relieve pain and inflammation. A fan to cool the patient is also helpful.

The skin must first be cleansed of all residual oils, debris, and excess stratum corneum before the application of any peels (Fig. 27-1). The patient's face is vigorously scrubbed with acetone using 2- × 2-cm gauze pads folded on a hemostat. Thorough degreasing is necessary for even penetration of the peeling solution. Uneven or splotchy peels are typically caused by residual oils on the stratum corneum from inadequate degreasing.

Once adequate preparation and cleansing of the skin has been completed, the Jessner's solution is evenly applied with cotton pads or gauze. On application, a faint frosting appears within 1 minute within a background of mild erythema. The frosting is much less obvious than that seen when using TCA, and this portion of the peel is not uncomfortable for the patient.

Figure 27-1. Chemical peel equipment tray.

Figure 27-2. Medium-depth 35% trichloroacetic acid chemical peel; treatment of perioral area.

After the Jessner's solution has dried, 35% TCA is evenly applied using cotton pads or swabs. The amount of TCA delivered to the skin surface is dependent on the number of applications, the degree of saturation (volume of solution), the amount of pressure applied to the skin, and contact time with the peel solution. Larger areas, including the forehead, bilateral cheeks, nose, and chin, are treated first with cotton pad applicators. Then, using cotton swabs, the perioral area and eyelids are treated, coming within 1 to 2 mm of the lower eyelid margin. An assistant should always be on standby with sterile eye wash for irrigation in case the surgeon inadvertently spills any peel solution into the eye. The white frost should appear within 30 seconds to 2 minutes after application of the TCA peel (Figs. 27-2 and 27-3). Before retreating an area, however, one should wait at least 3 to 4 minutes to ensure that the frosting has reached its peak before determining asymmetry. Additional applications can then be added with caution, because the depth of peel and potential complications are proportional to the volume of chemical applied.

The white frosting seen after a peel indicates the process of keratocoagulation, the completion of the chemical reaction. A level II or III frosting is a sufficient end point of a medium-depth peel. Level II frosting is defined as a white coat frosting with a background of erythema. Level III frosting is a solid white enamel frosting with no background of erythema, indicative of penetration into the reticular dermis. Such level III peeling should be limited to areas of thicker skin and heavy actinic damage. Sensitive areas such as thin eyelid skin and

bony prominences (which have a high propensity for scarring) should be limited to a level II frosting.[18]

An immediate burning sensation is felt with the application of the TCA peel, but this begins to dissipate with the onset of frosting and is typically resolved by the time of discharge. Cool saline compresses offer symptomatic relief for a peeled area and are used over the entire face after completion of a peel. On completion of the peel, a brawny, dusky erythema progresses over the first 12 hours. Mild to moderate edema soon follows and can be severe over the thin eyelid skin and forehead regions. As the edema begins to resolve, dark crusts appear that peel off during the subsequent 5 to 7 days to reveal a new, erythematous epithelium. The redness soon fades to a pink color that resembles a sunburn and can typically be camouflaged with makeup by the 10th day after the peel. A formal makeover with a makeup artist within the aesthetics department is a valuable experience for the patient once he or she has reepithelialized on day 10. The patient can begin using sunscreens as tolerated. He or she should wait at least 3 months before resuming regular aesthetic skin care services such as superficial chemical peels or microdermabrasion. Cleansing facials can begin as early as 4 to 6 weeks after the peel. Repeat medium-depth chemical peel should not be performed for at least 1 year. Several studies have demonstrated microscopic improvement of collagen thickness progressing over a 6- to 13-month period (Fig. 27-4).

The medium-depth peel is a widely accepted resurfacing modality that has a broad range of applications for the management of aging skin. If the measures and precautions described here are followed, an excellent safety profile will be maintained.

Figure 27-3. Medium-depth 35% trichloroacetic acid chemical peel; treatment of eyelid area.

Deep Chemical Peels

Resurfacing techniques that penetrate or wound the midreticular dermis are classified as deep chemical peels. Patients with Glogau group III or IV photodamage may require deep chemical peeling. The classic chemical compound is the Baker's solution that consists of the following[20]:

- Phenol 88%, 3 mL
- Septisol, 8 drops
- Croton oil, 3 drops
- Distilled water, 2 mL

This depth can also be achieved with a 50% or greater TCA peel; however, the high risk of scarring and pigmentation problems have resulted in a trend away from these concentrations.

Phenol itself is carbolic acid (C_6H_5OH), an aromatic benzene-ring hydrocarbon formed from coal tar.[6,14,21] At concentrations greater than 80%, carbolic acid is a keratocoagulant precipitating the surface protein, thus preventing further penetration of the peel solution. Phenol produces an extremely rapid denaturization and irreversible coagulation.[5] Further penetration of the phenol is prevented when the keratin protein binds to the phenol, creating large molecules that cannot penetrate further. McCollough and Hillman[14] state that if the concentration of phenol is less than 50%, it becomes keratolytic, interrupting sulfur bridges in the keratin layer, and can then produce deeper penetration and more destruction than desired. Therefore, as one decreases the

Figure 27-4. **A,** Pretreatment medium-depth chemical peel. **B,** Posttreatment medium-depth chemical peel.

concentration of phenol, the depth and therefore wounding of tissue becomes more severe.

The croton oil included in the formula is composed of glycerides of several acids and can be very irritating to the skin. Because of its inflammatory characteristics, it induces more collagen formation.[6,14] Recent studies have demonstrated that croton oil is the key ingredient, creating the significant depth of wounding.[22] Some surgeons vary the depth of Baker's solution peeling by using one, two, or three drops of croton oil. Soap in the solution acts as a surfactant, reducing surface tension and enhancing the penetration of the waxes and cholesterol esters of phenol. Septisol (hexachlorophene and alcohol) is a partial astringent that helps remove the stratum corneum and plays the role of a surfactant. The addition of distilled water produces the desired concentration of phenol between 50% and 60%. The mixture of ingredients is freshly prepared and must be stirred vigorously before application because of its poor miscibility.

The two main variations in deep chemical peeling with Baker's phenol solution are occluded and nonoccluded. Occlusion of the peeling solution with tape increases its penetration, creating injury to the midreticular dermis. Classically, this technique has been used for deeply lined, "weather-beaten" faces, but it should only be used by the experienced surgeon due to the higher risk of complications such as delayed healing, prolonged erythema, and late hypopigmentation. The unoccluded technique as modified by McCollough and Langsdon[23] involves more cleansing of the skin and the application of more peel solution. This enhances the efficacy of the solution without penetrating as deeply as in the occluded peel. Both methods are reliable resurfacing tools for the rejuvenation of advanced to severe photoaged skin.

Patient selection is crucial with deep chemical peeling. These patients must be informed and willing to undergo a greater degree of morbidity and the higher potential for textural changes and pigmentary disturbances. They must accept the possibility that they will always need to wear makeup and use protective sunscreen.

Phenol itself is cardiotoxic and undergoes both hepatic and renal elimination. Standard preoperative workup must include a complete blood cell count; liver function tests; serum urea nitrogen, creatinine, and electrolyte determinations; and a baseline electrocardiogram. Any patient who has a history of cardiac arrhythmias or is taking medications that are potentially arrhythmia precipitating may not be a good candidate for Baker's phenol peeling. Additionally, patients with poor renal or hepatic function are poor candidates.

Technique: Deep Chemical Peels

Patient preparation and education before a deep chemical peel procedure is important. Preoperative prescriptions should be given at the time of scheduling. Preoperative antibiotics such as cephalexin (Keflex) (500 mg twice daily) are started 24 hours before the procedure and continued for 1 week. Patients are offered a sedative to help them sleep the night before the procedure. Patients are given 5 mg of diazepam (Valium) by mouth 1 to 2 hours before the peel. All makeup, including mascara, eyeliner, eye shadow, and lipstick, is to be removed before arrival at the surgery facility. The face is washed twice with Septisol and rinsed thoroughly after each washing. pHisoHex or pHisoDerm should not be used because they leave a residue on the skin[23] that may interfere with the penetration of the phenol. Brody and Alt[10] believe in treating the skin with retinoic acids (Retin A) immediately before the peel to stimulate skin healing and to remove more of the stratum corneum. This, however, only pertains to a medium-depth chemical peel and should not be used before a Baker's solution chemical peel.

A deep Baker's peel is a time-consuming procedure that must be performed in a properly suited facility. The patient is given a preoperative sedative (diazepam), antinausea medication (promethazine), and a prokinetic agent (metoclopramide; e.g., Reglan). An intravenous line is introduced and approximately 500 to 1000 mL of Ringer's lactate solution is administered. The patient is then moved to the operative or procedure room where full cardiovascular monitoring is commenced, including checks of blood pressure and oxygen saturation. The patient is given a narcotic medication to offset the burning sensation, typically 1 or 2 mg of Dilaudid. Additional midazolam (Versed), usually 1 to 2 mg, is given for sedation and as an amnestic agent at this time. Sensory nerve blocks are then administered with injections of bupivacaine (Marcaine) 0.05% with 1:200,000 epinephrine solution. The regional blocks include the supraorbital, infraorbital, incisive foramen, and mental nerves, as well as infiltration of the lower eyelids and preauricular area. This spares the patient the typical 4 to 6 hours of postoperative burning discomfort. An additional liter of saline is given over the course of the procedure.

The face is divided into six aesthetic subunits including the forehead, perioral region, bilateral cheeks, nose, and periorbital region. First, thorough scrubbing with acetone soaked 2 × 2-inch gauze is applied to each region. Baker's solution is then applied with a cotton-tipped applicator to each region with feathering performed at the periphery of the peeled area, especially in the regions of the hairline, jawline, and overlap of regions by 5 mm. There is a minimum of 15 minutes between the treatment of each cosmetic area, totaling 60 to 90 minutes for the entire procedure. This allows for the renal clearance of phenol from the circulatory system. Death from arrhythmia has been reported when phenol was applied to the full face in a short period of time. Frosting occurs rapidly, therefore less solution is used compared with TCA peels. The solution should be applied in the direction of relaxed skin tension lines. A prominent white frost should be obtained immediately on application of the solution in each area, which rapidly changes to a zone of intense erythema extending 1 to 2 cm beyond the area treated with solution. It is therefore important to peel across this band of erythema when peeling the next region to avoid skipping areas.

When peeling the perioral area, one must apply the phenol solution with a slanted-cut wooden applicator so that the solution reaches the bottom of each individual rhytid. The lip is then stretched to spread out the rhytids while the solution is applied with a very wet cotton-tipped applicator. One needs to obtain a white frost that is carried 2 to 3 mm across the vermilion border. When treating the lower eyelid, it is important to use a semidry applicator rolled once across the skin. The lower eyelids need to be treated to within 1 to 2 mm of the ciliary margin. On the upper eyelid, one must be judicious about treating below the supratarsal fold, and most surgeons do not breach this boundary.

Application of the peeling agent creates an immediate burning sensation that lasts for 15 to 20 seconds and then resolves. After 20 minutes, the pain returns and lasts from 6 to 8 hours; then it typically resolves. The combination of Marcaine nerve blocks and narcotics usually makes the procedure very well tolerated by the patient.

Phenol Toxicity

Phenol is essentially toxic to all cells. It is absorbed through the skin into the bloodstream, and therefore must be excreted rapidly. The cardiac, hepatic, and renal systems are all affected by toxic doses of phenol (between 8 and 15 g for adults). Systemic toxicity is first suggested by central nervous system (CNS) stimulation, including tremors, hyperreflexia, and hypertension. After this, CNS depression occurs with respiratory failure, hypotension, and cardiac arrhythmias ensuing rapidly. Cardiac signs of toxicity develop in the following order: (1) tachycardia, (2) premature ventricular contractions, then (3) atrial fibrillation.[24] In Gross' study,[24] the average time from application of phenol to the onset of arrhythmias was 17.5 minutes, and most patients had 50% of the face covered at one time. Therefore, to prevent such toxicity, volume loading with intravenous fluids before, during, and after phenol peeling enhances excretion in patients with normal liver and renal function. Many authors, including Botta and colleagues,[25] recommend maintaining a fluid load to force diuresis with 20 mg of furosemide given 10 minutes before the application of phenol. Controversies exist over the use of plasma expanders (i.e., colloids). Therefore phenol should be avoided in patients with renal disease because they may not excrete it rapidly enough to avoid direct cardiac toxicity. Waiting as long as 20 to 30 minutes between treatment of each area and not peeling more than 50% of the face at one time minimizes the risk of phenol toxicity in most patients. Postoperative cardiac monitoring is necessary for a minimum of 30 minutes after the procedure, and personnel trained in advanced cardiac life support must be immediately available in the recovery unit.

Postoperative Care Routine

Postoperative care includes administration of an analgesic such as oxycodone (Percocet) or hydrocodone and acetaminophen (Lortab). Patients should minimize activity and rest until the next morning's office visit. Cool compresses can be applied in addition to Aquaphor ointment or petroleum jelly. The patient will need assistance and is not allowed to drive or take care of himself or herself the day of the peel. A postoperative instruction booklet is given to the patient that discusses the expectations of marked edema, moderate temperature elevation to 99°F to 100°F, occasional nausea, and moderate discomfort. The morning after surgery, the patient is instructed to wash or rinse the face without soap using tepid tap water five or six times per day, followed by the application of Aquaphor in an "icing on cake" fashion. Alternately, Eucerin cream or bacitracin ointment can be applied; however antibiotic sensitivity may develop with time. The patient is given 10 mg of dexamethasone (Decadron) IV intraoperatively and methylprednisolone (Medrol Dose Pack) postoperatively to reduce swelling. The patient is encouraged to take 1000 to 2000 mg/day of vitamin C as well as a multivitamin and to continue the antibiotic prophylaxis for 4 to 5 days postoperatively.

The patient is asked to return to the office on the third postoperative day to assure the physician that the wound is being cleaned as instructed. At this time the physician has the opportunity to intervene early if the wound has been neglected or if superficial infection has become a problem, such as with *Pseudomonas*, which can create a deeper injury. The patient often requires further education regarding the importance of his or her involvement in removing the desquamating skin and crust. The patient is then again evaluated in 3 to 4 days to observe the amount of wound healing and residual crusting. After 7 to 10 days, the patient can begin to apply makeup if epithelialization is complete. A makeup artist should be available and camouflage techniques should be provided to instruct the patient how to cover the pink/red areas. Generally, a mint green base is used before the foundation is applied to neutralize the red areas. Additionally, a brand name hypoallergenic moisturizer is recommended for use once or twice daily.

The use of sunscreens and sun avoidance is critically important. Sunscreen with an SPF of 30 or greater is advised. The patient is not allowed any direct sun exposure for 6 weeks and is told to minimize sun exposure for up to 6 months.

To reduce the possibility of hyperpigmentation, estrogens should be withheld 4 weeks before the peel and for at least 6 to 8 weeks postoperatively. As the erythema is fading, pigmentation abnormalities are possible, and estrogen may increase the risk of this abnormality.

At our facility, nonfluorinated hydrocortisone (Hytone cream 2.5%) is recommended for 2 or 3 weeks after reepithelialization to decrease the erythema and the hypersensitivity that is common. The patient often complains of intense pruritus during the early recovery period, and Pramosone 2.5% steroid cream (pramoxine hydrochloride and hydrocortisone) with an antipruritic agent can be helpful. During the day, the patient may benefit from a nonsedating antihistamine such as desloratadine (Clarinex) or fexofenadine (Allegra), and may require hydroxyzine (Atarax) or diphenhydramine (Benadryl) at night to decrease the sensation of itching. Hypnotics such as temazepam (Restoril) or zolpidem tartrate (Ambien) may be necessary for sleep.

Although some surgeons begin the administration of retinoic acid (Retin A) as soon as epithelialization has occurred, we prefer to wait at least 3 months after the peel before giving the patient Retin A, and we then use it only if the patient desires it.

The patient returns for an office visit at 2 weeks and again 6 weeks later for evaluation of the early development of splotchy hyperpigmentation. Collins[26] recommends the use of hydroquinone gel almost routinely for 2 to 4 months as a prophylactic regimen against this condition, especially in darker-skinned persons, Fitzpatrick type III or greater. If splotchy pigmentation develops, a combination of Retin A, hydroquinone (Eldoquin Forte), and triamcinolone (Aristocort) may provide improvement. The patient is seen again at the 3-month, 6-month, and 1-year periods postoperatively. Photographs are taken at each session (Fig. 27-5).

Chemical Peel Complications

It is important to recognize the expected sequelae that accompany healing with chemical peels, as opposed to true complications. The following represent sequelae of chemical face peeling:

1. Pigmentary changes
   a. Hyperpigmentation
   b. Hypopigmentation
   c. Depigmentation (rarely, and in isolated areas)

Figure 27-5. **A,** Pretreatment, Baker's chemical peel. **B,** Posttreatment, Baker's chemical peel.

2. Persistence of rhytids
3. Prolonged erythema
4. Persistent texture change of skin
5. Hypertrophic subepidermal healing
6. Milia
7. Skin pore prominence
8. Increased prominence of telangiectasias
9. Darkening and growth of preexisting nevi

Pigmentation changes are by far the most common phenomenon seen with chemical peels, and these predominantly occur as hypopigmentation. These areas are most obvious in transition zones between peeled and nonpeeled areas, which can be minimized with the feathering technique described earlier. Splotchy pigmentation can either be hypopigmentation or hyperpigmentation and is increased with exposure to sun or the use of systemic estrogens. This sequela is most commonly seen during the first 3 months of healing. Brody[16] notes that pigmentary changes rarely occur in Fitzpatrick type I and II patients, but in type III and IV patients there are frequently prominent lines of demarcation. In type V and VI patients, hyperpigmentation usually develops that may resolve over 18 to 24 months; however, most surgeons will not peel this population (Asian, Latin, or Indian) because of the risk of irregular coloration postoperatively. Retin A 0.1% and Eldoquin Forte 4% mixed with Aristocort 0.1% should be applied at the onset of early hyperpigmentation and continued for 2 to 3 months after the peel.

Persistent rhytids or wrinkles are relatively common after peeling, especially if they were prominent before the peel. McCollough and Brody believe that waiting 3 to 6 months is appropriate before repeating a chemical peel. We often touch up rhytids of the vermilion border and perioral area with dermabrasion between 3 and 6 months. Repeeling rhytids before the 2-month mark can result in severe hypopigmentation and subepithelial hypertrophic scarring. Prolonged erythema should be expected with early repeeling.

Complications of chemical peels include, but are not limited to, the following:

1. Skin infection
   a. Herpes simplex virus
   b. *Pseudomonas* organisms
   c. *Staphylococcus*/*Streptococcus* organisms
   d. *Candida* organisms
2. Lower eyelid ectropion
3. Cardiac arrhythmias
4. Renal failure
5. Laryngeal edema[27]
6. Toxic shock syndrome[28]
7. Facial scarring
8. Poor patient-physician relationship

Infections are uncommon, but herpetic breakouts can almost be expected if appropriate antiviral prophylaxis is not given (e.g., Valtrex 500 mg orally twice daily or Zovirax 800 mg orally four times daily starting 2 to 3 days before the peel). For patients with a strong history of herpetic outbreaks, at least 2 weeks of antiviral therapy should be administered after the peel. For patients who do undergo a herpetic outbreak despite prophylaxis, we have found that Zovirax dosed at 4 g/day is most expedient at clearing the infection. Superficial infection with *Pseudomonas, Staphylococcus,* or *Streptococcus* is rare and can usually be attributed to poor postoperative wound care. Candida infections can occur, which delays epithelialization. These should be treated with topical nystatin cream. Prolonged use of ointments after chemical peel may promote folliculitis and acne, especially in patients with a prior history. These conditions may become secondarily infected with *Staphylococcus* or *Streptococcus* species and should be treated with the appropriate oral antibiotic, in addition to topical clindamycin phosphate (Cleocin T) gel.

In summary, chemical peels are an effective and extremely satisfactory procedure with which every facial plastic surgeon should be familiar. Careful patient selection and education are crucial to both the patient's final result and his or her satisfaction. Learning the chemical peel technique is only a small part of the overall process; postoperative care and close patient follow-up are equally as important. Understanding these principles and knowing how to treat the sequelae or complications of chemical peels allows the surgeon and patient to achieve a satisfactory result in facial skin rejuvenation, in addition to establishing a positive long-term relationship.

Dermabrasion

Facial dermabrasion is an effective technique in skilled hands. It dates back to 1905, when Kronmayer[29] used rotating burrs for removal of various skin lesions, and was modernized in the late 1940s by Kurtin[30] with the development of the wire brush technique. Although discussed here for the management of aging skin, dermabrasion is most commonly used for the treatment of facial scars induced by acne, trauma, varicella, or surgery, in addition to removal of superficial skin lesions. However, dermabrasion is a time-tested technique for the removal of wrinkles, especially in the difficult-to-treat perioral and vermillion regions.

Dermabrasion is a mechanical method using abrasive surfaces to remove the epidermis and create a wound in the papillary or reticular dermis. This subsequently causes the stimulation of type I and III collagen and formation of a fresh new layer of skin. An excellent cosmetic improvement is seen, and the collagen continues to thicken over a 12- to 18-month period, further enhancing a youthful appearance. Sun-damaged cells, superficial scars, and premalignant lesions are removed and replaced with the epithelialization process, enhancing the final aesthetic outcome.

Patient Selection and Consultation

Facial scars and skin lesions can be improved but not entirely eliminated by dermabrasion techniques. The treatment of rhytids and photodamage may improve only by 50% to 80%, especially in the perioral region. Similarly, bad acne scars are expected to improve by only 30% to 40% or less. This point must be stressed during the initial patient consultation for both patient and physician satisfaction. The patient must accept a 10- to 14-day healing time with a relatively intense postoperative wound care regimen. The patient should be educated on the amount of anticipated drainage, swelling, discomfort, and bruising in addition to a period of prolonged erythema lasing up to 8 to 12 weeks. The risks and benefits should be covered during the consultation period with a witnessed informed consent form signed. Preoperative and postoperative photographs are very important for documentation, although acne scarring may be difficult to photograph without proper lighting techniques.

Careful patient selection is important to the final outcome of dermabrasion resurfacing. Patients with a history of prior skin resurfacing tend to have a less dramatic result with dermabrasion and are at a slightly higher risk of hypopigmentation and complications. A minimum of 12 months is recommended before a second dermabrasion procedure to allow for maximal improvement of scars and completion of the healing process. Scars or wrinkles on the neck should not be treated with dermabrasion due to the high risk of hypertrophic scarring and depigmentation caused by a significant decrease in adnexal structures and a much thinner dermis.

Patients with a history of acne should be under complete medical control before any dermabrasion resurfacing techniques. The use of

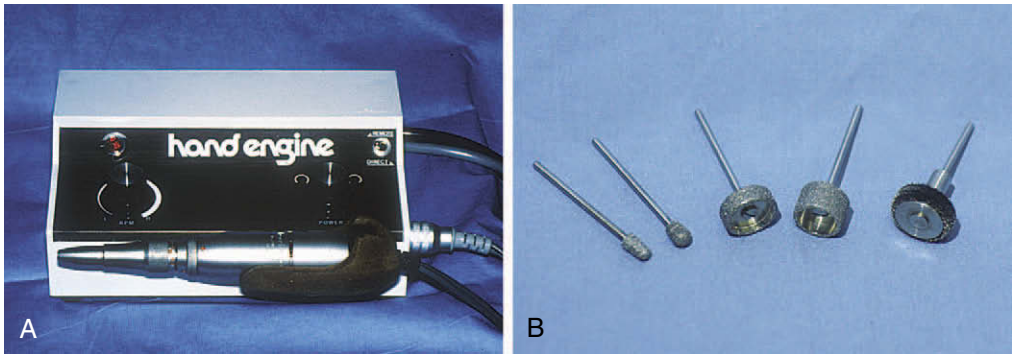

Figure 27-6. **A,** Electrical dermabrasion machine. **B,** Various tips for use with electrical dermabrasion machine handpiece.

isotretinoin (Accutane) within a 6-month period is a contraindication to dermabrasion due to the increased risk of scarring because this medicine decreases the number of pilosebaceous units required for adequate healing.[31-33] Some dermatologists recommend waiting a full year after the end of Accutane administration before facial resurfacing. Dermabrasion is also contraindicated in patients with deficient healing capacities, collagen vascular disorders, and a personal history of keloids.

Equipment

Equipment for dermabrasion techniques varies from handheld manual units, to sterile sandpaper, to high-speed machines. Modern electrical dermabrasion machines are compact and easy to use, and they generate rotational speeds up to 33,000 rpm. The handpiece accepts various tips that allow site- and lesion-specific treatment for the patient (Fig. 27-6). Additionally, the rotation of direction is reversible, making the approach to anatomic sites safer and enabling access for either a right- or left-handed surgeon.

Dermabrasion is performed with either a wire brush, diamond fraise, or serrated wheel placed into the handpiece unit. The wire brush attachment is a wheel with rigid stainless steel wires protruding from its circumference. The wire brush is very efficient at tissue removal, often achieving the desired depth with only one pass. It therefore has a narrow margin of error and is preferred by more experienced surgeons. The microlacerations created by the wire brush are believed to improve the final result of the procedure because the papillary or outer reticular dermis is wounded and subsequent collagen formation stimulated. The skin surface must be frozen when using the wire brush to achieve efficient abrasion and to maintain the surface topography. This technique also decreases the risk of gouging the skin, and free margins of the lip must also be approached with care because it is easy to catch the margin and create an intraoral tear.

The diamond fraise attachment consists of wheels or cones studded with diamond chips of various degrees of coarseness. The coarser the unit, the deeper the skin penetration achieved, and the finer diamond fraises are used more as a "polishing" or blending tool. The diamond fraise is the safest and easiest dermabrasion unit to use, but is also the slowest. The use of the diamond wheel/burr also requires little or no cryogen spray, which is unique among the dermabrasion attachments.

Technique

Dermabrasion at our facility can be performed with the patient under intravenous sedation, or with "twilight anesthesia" as an isolated procedure. The patient receives 10 to 20 mg of Valium orally before the procedure. Cardiovascular monitoring is used, and the patient is administered 3 mg of Versed and 1 mg of Dilaudid before regional blocks. The local blocks are performed with bupivacaine 0.25% and epinephrine 1/200,000 and include the supraorbital, infraorbital, and mental foramen for full-face dermabrasion. This technique, in conjunction with the use of refrigerant spray (Frigiderm), allows for a pain-free experience for most patients.

The face or region of concern is treated in 1- or 2-square inch segments. These areas are blocked off by a 4 × 4-inch gauze pad before

Figure 27-7. Proper technique for use of dermabrasion handpiece.

application of the refrigerant spray, which prevents inhalation or ocular injury. Once the skin has been chilled, a 10- to 12-second period of dermabrasion is allowable until further freezing is required. Overzealous use of the refrigerant spray should be avoided, however, because tissue damage and focal skin necrosis is possible. The dermabrasion handpiece should be held firmly and pulled only in a plane perpendicular to the plane of rotation (Fig. 27-7). One should avoid rotary or back-and-forth motions because this may increase the risk of gouging the skin and causing deeper injury. Use of the wire brush requires minimal pressure because the steel wires cause numerous microlacerations, whereas the diamond fraise requires significantly more pressure. Adequate depth of treatment is determined by observing the skin surface. Stripping off the epidermis reveals a slightly gray papillary dermis. In the midpapillary dermis, multiple small punctate bleeding points are seen and represent the dermal capillary loops. The border between the papillary and reticular dermis is marked by a slightly yellow color signifying the sebaceous gland lobules. As the midreticular dermis is approached, larger but fewer bleeding points appear and the surface becomes coarser. Care must be taken when proceeding deeper than this level because the risk of scarring significantly increases.

It is best to begin the dermabrasion process centrally near the nose and work outward toward the cheeks (begin in the dependent areas to avoid pooling of blood in the upcoming region). In the perioral areas, special care must be given to holding the lip taut and keeping the direction of rotation away from the mouth to avoid significant laceration (Fig. 27-8). One must always stay parallel to the skin's surface when performing dermabrasion. Dermabrasion should also be carried out in facial units and carried to, but not across, the jawline, hairline, and orbital rims. Untreated areas are then peeled with the appropriate chemical agent such as Jessner's solution plus 35% TCA or phenol 88% to the lower eyelids. This allows for better blending of pigmentation and avoids discrete areas of hypopigmentation. One should never der-

mabrade the neck due to the high risk of scarring and pigmentation difficulties.

Postoperative Care

The regional nerve blocks given during the onset of the dermabrasion procedure typically last for 6 to 8 hours, and a narcotic script is provided to control delayed pain. Wet gauze is applied to the dermabraded regions immediately after the procedure for about 5 minutes, and after this most bleeding has usually subsided. Xeroform gauze is applied topically to all areas of dermabrasion, not a silicon-based (Silon) mask. The Xeroform dressing is allowed to dry overnight before moisturization and lubrication are begun. Using tepid water or saline-soaked gauze, the clinician cleanses the sites of dermabrasion of all serum and crusting all the way down to the visible gauze fibers, and a fresh coat of Aquaphor or bacitracin is applied topically four to six times daily. Alternatively, if Silon was applied, it would be removed on the third postoperative day, at which point lubrication would begin. The administration of a Medrol Dose Pack is usually started on the day of the procedure, and the patient continues to take antibiotic and antiviral prescriptions started on preoperative day 1. When epithelialization begins, the Xeroform gauze starts to separate and can be trimmed progressively. Complete reepithelialization has occurred by the seventh to the 10th day, and a session with a makeup artist is provided for the patient to teach him or her more about camouflage techniques. Strict adherence to sun avoidance or the use of sunscreen with an SPF of 30 or greater is discussed with the patient because serious pigmentation problems can be caused by early sun exposure. Patients with prolonged erythema are given Hytone cream 2.5% topically twice a day. Patients with signs of hyperpigmentation or known melasma are given topical hydroquinone 4% or 8% to be applied nightly. Most patients can return to work by day 7 to day 10 postoperatively with a light covering of makeup; however, such cosmetics should be avoided before complete reepithelialization because contact dermatitis and further infection may follow (Fig. 27-9).

Figure 27-8. Proper technique for performing dermabrasion in the perioral area.

Complications

Acne outbreaks are a common complication of dermabrasion, especially in patients with a previous history. The breakouts can be minimized with the preoperative use of tetracycline in high-risk patients. Active breakouts respond to tetracycline plus topical Cleocin T gel. Other common complications include milia formation at the site of dermabrasion. This can be avoided or treated with the use of tretinoin therapy. The use of a sloughing pad or sponge (Buf-Puf) to lightly abrade the surface of these lesions is helpful. Deep pore cleansing facials and extractions are also helpful and can be performed by an aesthetician. Prolonged erythema beyond 4 weeks should be treated with a topical steroid such as Hytone cream 2.5% to avoid pigmentary problems or scarring. Subepithelial hyperplasia should be injected with triamcinolone steroid (Kenalog-10) to avoid potential scarring. Another uncommon complication is postoperative infection. The most common microorganisms include *Staphylococcus aureus,* herpes simplex virus, and *Candida* species.[34] The prompt use of the appropriate antibiotic, antiviral, or antifungal agent should be sufficient for treatment, and often poor cleansing is the culprit for infection. Additionally, some hypopigmentation is seen quite often after dermabrasion.[35]

Dermabrasion is therefore a longstanding, reliable method for rejuvenation of aging skin with predictable and reproducible results. The equipment is inexpensive and simple to operate; however, technique is very important to obtain the best results. Recent studies have shown that dermabraded skin in the perioral region has identical cosmetic results when compared with results with CO_2 laser but heals in half of the time with less postoperative erythema and morbidity.[36,37] Additionally, dermabrasion for lip rhytids tends to be more effective and predictable as a single treatment compared with use of CO_2 laser or chemical peel. Therefore an understanding of and an ability to perform dermabrasion techniques should be in the armamentarium of all facial plastic surgeons because it serves as an excellent and diverse tool for facial resurfacing.

Laser Resurfacing

Laser skin resurfacing has become more popular over the past several years and is an important modality in rejuvenation of the aging face. Many surgeons have turned to laser resurfacing instead of dermabrasion to ameliorate the higher risk of infection with bloodborne pathogens when performing dermabrasion. The primary lasers used for facial resurfacing are the pulsed carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG) lasers. The practice of combining these lasers is also gaining popularity.[38] Laser resurfacing can also be combined with the use of chemical peels or dermabrasion when clinically indicated. Additionally, laser skin resurfacing is commonly combined with other surgical procedures such as endoscopic browlifts, facelifts, and transconjunctival blepharoplasty. The physician should become aware of the unique properties of these resurfacing lasers to best treat his or her patients' aging skin needs.

Figure 27-9. **A,** Perioral dermabrasion: preoperative view. **B,** Perioral dermabrasion: postoperative view.

Figure 27-10. Pulsed CO_2 laser.

CO_2 Laser

Energy of the pulsed CO_2 laser is produced in the 10,600-nm spectrum. Approximate tissue ablation of the CO_2 laser depends on the amount of energy (fluence) that is delivered and is typically between 50 µm and 300 µm, although depths have been reported up to 1500 µm. There is a characteristic pattern of thermal necrosis and thermal conduction damage between 30 µm and 50 µm away from the zone of ablation. The pulsed CO_2 laser is considered to be the gold standard in laser resurfacing, improving considerably the past 20 years.[38a] It is particularly good for treating mild to moderate rhytids in the perioral area, periocular crow's feet, glabellar rhytids, and diffuse actinic damage, aging spots, and dyschromias. Although excellent results have been seen with full ablative resurfacing, new techniques in fractional ablation have shown remarkable results with less risk of hypopigmentation, prolonged erythema, or social downtime.

There is a variety of pulsed CO_2 lasers available (Fig. 27-10). The laser energy is delivered through a flexible waveguide handpiece to the targeted area in a geometric pattern that varies in size and is easily adjustable. The UltraPulse Encore CO_2 laser (Lumenis, Inc. [Formerly Coherent], Santa Clara, Calif.) has a randomization pattern feature (cool scan) that prevents the "postage-stamped" mark on the patient's skin. The operator selects the energy density and power in millijoules that determines the depth of tissue ablation. The microprocessor calculates the peak power in watts based on the settings and the spot size delivered. Standard settings for a patient undergoing initial full-face resurfacing for moderate aging and photodamage ranges from 80 to 90 mJ and a density of 4 or 5, with the largest rectangular spot size at our facility (ranging from 46 to 60 W). A second pass over regions with more photoaging is typically set at 20 mJ less than the first pass and at a density setting of 4. The deeper passes are used to treat the base of the furrow, using the principle of dermal remodeling with subsequent collagen thickening. The edges of the wound are also blended with that of nondamaged skin, giving a more uniform appearance after healing (Fig. 27-11). Depending on the depth of treatment required, the clinician can pass superficially to the upper papillary dermis, to the upper reticular dermis, or to the deepest recommended midreticular level. Care must be given when treating the thin eyelid skin, and most operators recommend only one pass in this region.

Figure 27-11. Example of blending of wound edges with that of nondamaged skin during CO_2 laser treatment.

In the past few years, more advanced delivery methods for the CO_2 laser have become popular. Fractionated devices such as the ActiveFX and DeepFX (UltraPulse Encore CO_2) and Fraxel Re:pair CO_2 (Solta Medical, Inc., Hayward, Calif.) are showing excellent clinical results similar to the traditional complete ablative CO_2 laser devices. Fractional technology allows for only a small fraction of the skin surface to be treated using a pattern of microscopic pulsed laser columns. The untreated skin can then promote improved healing times and reduced risks of hypopigmentation and prolonged erythema. Some authors have shown good results even in patients of Fitzpatrick skin types 4 and 5 without postinflammatory hyperpigmentation.[38b] The pulsed CO_2 laser column can penetrate deeper into the dermis than the traditional methods, allowing for improved collagen remodeling.[38c]

Fractionated CO_2 laser devices use a scanner to apply a fractional pattern of laser columns onto the skin. Adjustments are easily made in regards to the energy density, density of treated to untreated skin, and time between pulses. This affects the depth of treatment into the dermis and the total percentage of ablation and allows for improved thermal dissipation. Fractional deep ablation can also be combined with superficial complete ablation during the same treatment. This combination allows for the complete removal of superficial keratosis and dyschromias while the fractionated columns stimulate collagen production and improve the appearance of fine lines and wrinkles.

Er:YAG Laser

The technique of facial resurfacing using the Er:YAG laser is similar to that of the CO_2 laser, except there is no coagulative necrosis with less tissue interaction. Therefore, one can overlap pulses by 10%, which must be avoided when using the CO_2 laser secondary to thermal damage. Due to less tissue damage, the classic skin color changes involved in CO_2 laser surgery are not seen, however, a useful depth indicator when using the Er:YAG laser is pinpoint bleeding, which occurs at the level of the papillary dermis. This high-powered laser transforms the superficial skin into particulate matter, therefore a smoke evacuator and laser that masks filter 0.1-µm particles is recommended in addition to laser eyewear. Some authors recommend the combined use of the CO_2 laser with the Er:YAG laser for optimum postoperative healing. The first pass is performed using the CO_2 laser for primary resurfacing. The Er:YAG laser is then used to clean up the zone of thermal necrosis created by the CO_2 laser, which would otherwise turn into persistent erythema. The favorably heated deeper dermis remains, and the fibroblasts have been stimulated to secrete neocollagen.[39] Usually two to three passes are required, using the Er:YAG laser with this technique. The study by Utley and colleagues[40] showed that one pass with the Er:YAG laser penetrated 20 µm whereas one pass with the CO_2 laser penetrated 62.5 µm.

Figure 27-12. **A,** Postlaser occlusive (Silon) dressing, frontal view. **B,** Postlaser occlusive (Silon) dressing, lateral view.

Figure 27-13. **A,** CO_2 laser resurfacing, preoperative view. **B,** CO_2 laser resurfacing, postoperative view.

Postoperative Laser Care

A postlaser occlusive dressing (silicone-based Silon) is used for the first 3 to 4 days. The use of an occlusive dressing is less painful for the patient, prevents crusting seen with the exudative phase, and promotes moist reepithelialization (Fig. 27-12). Once this dressing is removed on postoperative day 4, the patient is instructed on wound care. This regimen includes cleansing the entire face (or resurfaced region) using saline and 4 × 4-inch gauze four to five times daily down to pink-healing skin, followed by a generous layer of Aquaphor. If required, dilute acetic acid soaks are used for increased removal of serum exudates. Additionally, appropriate antibacterial agents (e.g., bacitracin ointment) or antifungal agents are used if clinically indicated and are typically a sign of inadequate cleansing. Once reepithelialization has occurred, by day 7 to 10, a makeup session with an aesthetician or makeup artist should be offered to teach important camouflage techniques during the period of postoperative erythema. A good waterproof sunscreen with an SPF of 30 or greater is recommended for a minimum of 6 to 12 months postoperatively to minimize discoloration issues and to maximize healing (Figs. 27-13 and 27-14).

Figure 27-14. **A,** CO_2 laser resurfacing, preoperative view. **B,** CO_2 laser resurfacing, postoperative view.

Postoperative laser complications are the same as discussed in terms of chemical peel procedures, and therefore frequent and meticulous postoperative visits and patient evaluation cannot be overemphasized. Additionally, "hot spots" often seen with CO_2 laser treatment will benefit from hydrocolloid (DuoDerm) occlusive dressings during the early healing periods. These should be changed every 24 to 72 hours until reepithelialization has occurred.

In general, facial resurfacing using the CO_2 laser requires a longer "downtime" of 7 to 10 days with prolonged erythema up to 3 to 4 months compared with the Er:YAG laser, which tends to involve a healing time of 4 to 5 days with short-lived erythema. However, the CO_2 laser produces a true skin-tightening result with improved elasticity, rhytid removal, and long-term results compared to the Er:YAG laser.[40] Although the pulsed CO_2 laser and Er:YAG laser are the most popular ablative resurfacing lasers currently available, technology is rapidly advancing, and one must stay current with such advances to be competitive. Additionally, nonablative resurfacing lasers and technologies are gaining more popularity and may surpass conventional laser use due to the minimal downtime and postlaser care required for the patient. However, to date, none of these lasers is able to treat significant rhytids and photoaging, even with a series of four to six treatments.

Aesthetician's Role in the Management of Aging Skin

The role of the aesthetician in facial rejuvenation and skin care is rapidly expanding. The aesthetician has numerous options and skills available that do not require sedation or direct physician supervision to improve skin quality. Such interventions include:

- Nonablative resurfacing
- Microdermabrasion
- Superficial chemical peels
- Medical skin care regimens

Nonablative Facial Resurfacing

As technology improves, new devices are being introduced to the marketplace at a stunning pace as options for nonablative facial rejuvenation. Nonablative laser resurfacing refers to the techniques that avoid damage to the epidermis while treating the dermis to produce the desired resurfacing effect. Ablative resurfacing (previously discussed) requires destruction of the epidermis, thus requiring a substantial period of healing and regrowth. This presents patients with long "downtimes," necessitating extensive skin care before reepithelialization. Erythema and edema can persist for several weeks depending on the depth of resurfacing involved. Nonablative lasers, intense pulsed light, and fractionated lasers are shown in Table 27-5.[41]

Radiofrequency energy has also found a role in promoting new collagen formation in the dermis while reducing epidermal damage. The effect is to induce thermal damage of the dermis by elevating temperatures to 65°C to 75°C, thereby causing collagen to denature. The resultant healing process is thought to create skin contracture and neocollagen growth.

Each laser discussed has its unique characteristic that is marketed for skin rejuvenation. No one technique has been shown to be superior, and there is a wide variety of treatment settings, methods, and outcome measures. Although none has been shown to be as predictable or effective as the ablative techniques, they can all be used as alternatives for patients who are unwilling to accept long, intensive recovery times required for resurfacing. Typically, multiple treatments are required for improved rhytid removal and skin texture quality, usually over a 4- to 12-week interval. Advantages of the nonablative techniques include avoiding the potential complications of deeper peels and lasers such as hypopigmentation, prolonged erythema, and hypertrophic scarring. The disadvantages of these new technologies are mostly in the long-term results. Many investigators feel that the nonablative devices show modest improvement in wrinkles, at best, which is likely a result of collagen homogenization. This clinical improvement requires 3 to 6 months to appreciate, and such results are often short-lived.[42] With further clinical trials and improving technology, however, these less invasive alternatives to facial rejuvenation may predominate in the future.

Microdermabrasion

Microdermabrasion is a popular noninvasive technique performed by aestheticians for facial rejuvenation. The term for this procedure is actually a misnomer because the controlled injury created by this process is actually to the epidermis. Microdermabrasion uses the abrasive action of small particle microcrystals (i.e., aluminum oxide, sodium

Table 27-5

Types of Lasers Used for Nonablative Facial Resurfacing

Laser Type (wavelength)	Target Molecule	Depth of Penetration	Properties
Pulsed-dye (585-595 nm)	Oxyhemoglobin	Dermal vasculature	Collagen remodeling, dyschromias
KTP (532 nm)	Oxyhemoglobin	Dermal vasculature	Collagen remodeling, dyschromias
Q-Switched Nd:YAG (1060 nm)	Water	Papillary and reticular dermis	Collagen remodeling and selective thermal injury
1320-nm Nd:YAG	Water	Papillary dermis	Epidermal protection by cryogen cooling
Er: Glass (1540 nm)	Water	0.4 to 2 mm	Low melanin absorption
1450-nm Diode		500 µm	Epidermal cooling by cryogen spray
Intense pulsed light (500-1200 nm)	Various	Papillary and reticular dermis	Noncoherent light, treats lentigines, telangiectasia, tattoos
Fractional photolysis (1500 nm)	Water	400 to 700 µm	Microscopic grids of injury

From Kim KH, Geronemus RG. Nonablative laser and light therapies for skin rejuvenation. *Arch Facial Plast Surg.* 2004;6:398-409.

chloride, or sodium bicarbonate) to wound the epidermis, coupled with suction to remove any skin debris. An inflammatory response is stimulated within the epidermis and results in the formation of a new stratum corneum within 3 to 5 days. Some authors believe that repeated microdermabrasion treatments not only increase the thickness of the outer epidermis after a 6-week period, but also may even stimulate fibroblasts and new collagen deposition in the superficial papillary dermis.[43]

Typically, a series of treatments are required to achieve the desired resurfacing results (6 to 10 treatments), followed by a maintenance program every 4 to 6 weeks. The patient's skin surface will feel smoother, with a firmer texture reported. Microdermabrasion is best used for epidermal conditions including fine rhytids, dyschromia, superficial scarring (e.g., acne), and actinic keratosis. Microdermabrasion techniques are best complemented with a daily medical skin care program. As the process histologically removes the stratum corneum, the penetration of the topical medications is enhanced, yielding a more desired outcome. Patient satisfaction is typically good after a full series of microdermabrasion treatments because there is minimal discomfort with little recovery or downtime.

Contraindications to microdermabrasion treatments are relative but should include open herpetic lesions, bleeding disorders, active inflammatory rosacea, open wounds or sores, vascular lesions, warty growths, or sunburned skin. Although active acne regions can be covered individually with small tape, widespread active acne should be viewed as a contraindication.

After each microdermabrasion session, the patient should expect several hours of increased pinkness or redness and sensitivity to the skin (occasionally days with deeper treatments). With the stratum corneum disrupted, the skin requires more moisturization and sun protection. A sunblock with zinc oxide, titanium oxide, or an SPF of 30 or greater is recommended for the first week after each treatment. Patients note increased skin tightness for the first 12 to 24 hours, with a corresponding decrease in fine wrinkles. Some peeling of the skin may be noted 48 to 96 hours after a treatment session; this can be reduced or avoided with the use of a strong moisturizer. Makeup can be reapplied within minutes of a treatment, and medical skin care programs can be resumed within 48 hours.

Superficial Chemical Peels

Although medium and deep chemical peels require a physician's expertise and patient sedation, lighter chemical peels can be performed by the aesthetician as an excellent skin maintenance program. These treatments are often combined with other techniques such as microdermabrasion for improved efficacy. The following are common superficial peels used routinely for skin rejuvenation and maintenance:

- Glycolic acid 20% to 70%
- TCA peels 10% to 30%
- Resorcinol 20% to 30%
- Jessner's solution
- Alpha-hydroxy acid
- Retinoic acid
- Enzymatic peels

Superficial peels effectively slough the outer epidermis (stratum corneum), improving skin texture by producing a thicker epidermal layer. Additionally, superficial skin lesions and dyschromias are treated by these peels. Precautions to avoid sun exposure should be taken for at least 72 hours after a peel, and patients with sensitive skin should avoid hydroxy acid and retinoid products for 24 to 48 hours after the procedure.

Medical Skin Care Regimens

"Antiaging" and "wrinkle cream" products have flooded the market over the past few years, often accompanied by false promises regarding potential facial rejuvenation outcomes. The majority of these products are not approved by the U.S. Food and Drug Administration nor are they supported with clinical prospective trials. It is therefore imperative that clinicians recommend medical skin care maintenance programs that are both safe and effective.

Retinoids are derivatives of vitamin A and are most commonly prescribed as tretinoin. Tretinoin has been proven effective through numerous double-blind studies for treating mild to moderate photodamaged skin. Available tretinoin products include Renova, Retin A, MicroRetin A, and Avita. Daily application of these topical creams has been shown to improve fine wrinkling, surface roughness, hyperpigmentation, and sallowness[44] over a 6- to 12-month period. Tazarotene cream, a tretinoin receptor derivative, has been shown to improve fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, pore size,

irregular depigmentation, tactile roughness, and coarse rhytids in a 12-month multicenter randomized trial.[45] Tretinoin induces type I procollagen formation, thickens the epidermis, reduces melanin content, increases glycosaminoglycans and stimulates angiogenesis, giving a "rosy" appearance to the skin. Histologically, tretinoin-treated skin is more stable due to increased anchoring fibrils and decreased activity of collagenase enzyme. Tretinoin can also reduce UV-induced collagen destruction and therefore helps prevent photodamage.[46] Adverse effects include mild to moderate dryness, skin irritation, peeling, and photosensitivity, therefore protection from sun exposure is important.

Alpha-hydroxy acids have long been used in skin care products and have a proven level of safety as adjunctive therapy in photodamaged skin, melasma, hyperpigmentation, acne, and rosacea. Although their exact mechanism of action is unknown, alpha-hydroxy acids function by thinning the stratum corneum, promoting epidermolysis, dispersing basal layer melanin, and increasing collagen synthesis within the dermis.[47] Alpha-hydroxy acids are often used in combination with retinoids and other antioxidants for maximum clinical benefit.

Beta-hydroxy acids contain salicylic acid and have similar properties to alpha-hydroxy acids. Beta-hydroxy acids are also anti-inflammatory in nature and are often less irritating than their alpha counterparts.

N6-furfuryladenine (Kinerase, ICN Pharmaceuticals, Costa Mesa, Calif.) is a plant growth factor that is good for patients with very sensitive skin who cannot tolerate retinoids and alpha-hydroxy acids. In a large 6-month uncontrolled study, use of N6-furfuryladenine led to a significant reduction in skin roughness (63%) and to smaller reductions in hyperpigmentation (32%) and fine wrinkles (17%).[45] Further double-blind studies are warranted.

Numerous "antiaging" creams and products are being investigated at present. Considerable interest has been given to the antioxidants such as vitamins C and E applied topically to protect or reverse photoaging. Initial results of high-dose vitamin C proved to be a pro-oxidant causing oxidative DNA damage; however, the use of vitamin C esters has been promising in terms of effectively reducing photodamage. Further investigation and trials are warranted in the realm of topical antiinflammatory, antioxidant, cytokine, and growth factor creams to prove their long-term clinical efficacy and safety records.

Summary

The management of aging skin is a very important topic in today's society for which facial plastic surgeons play a predominant role. It is imperative to remain current with the latest technologies because the patient's expectations and knowledge base are rapidly increasing in the Internet age. One should maintain a diverse repertoire of options in his or her armamentarium for the management of aging skin, where patient selection and education will ultimately provide the best clinical outcome and patient satisfaction.

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CHAPTER TWENTY-EIGHT

Rhytidectomy

Shan R. Baker

Key Points

- The superficial musculoaponeurotic system, or SMAS, represents a fascial extension of the platysma that arises superiorly from the fascia over the zygomatic arch and is continuous in the inferior cheek with the platysma. Posteriorly, the SMAS fuses with the fascia overlying the sternocleidomastoid muscle, but it is a distinct layer superficial to the parotid fascia. Anterosuperiorly, the SMAS invests the facial mimetic muscles of the mid-face.
- There are four tissue dissection planes used to perform rhytidectomy: subcutaneous, sub-SMAS, supra-SMAS, and subperiosteal.
- The subcutaneous facelift with plication of the SMAS is the most common surgical approach used.
- SMAS-rhytidectomy may take the form of elevating an SMAS flap limited to the area overlying the parotid gland, or the SMAS flap may be extended anterior to the parotid gland. The SMAS flap is suspended posterosuperiorly.
- Supra-SMAS rhytidectomy, referred to as extended SMAS rhytidectomy, takes the form of a lengthy anterior dissection of the mid-face just superficial to the SMAS.
- Deep plane rhytidectomy combines a sub-SMAS dissection of the lower face with an extended supra-SMAS dissection of the mid-face.
- The subperiosteal, deep plane and extended supra-SMAS rhytidectomies lift the mid-face soft tissues.
- Regardless of the surgical approach used to perform a rhytidectomy, similar goals are (1) to preserve motor and sensory innervation of the face; (2) to reduce cervical fat if excessive; (3) to tighten the SMAS and platysma; and (4) to redrape and trim excessive cervical and facial skin.
- Submentoplasty is required in the majority of patients requesting rhytidectomy.
- Hematoma is the most common complication of rhytidectomy.

Historical Perspective

In 1907, Miller[1] published the first medical book on the subject of cosmetic surgery. Thus was born the surgical field of aesthetic surgery. Around this same time, perhaps as early as 1901, the first rhytidectomy was performed and took the primitive form of excising skin and repairing the wound without undermining the facial skin. Early facelift techniques were probably developed by German surgeons, but by 1906, American surgeons were beginning to adopt and improve the techniques of facelifting. By 1926, surgeons were using coronal incisions for forehead lifting and were developing methods of dealing with the double chin. By the 1930s, facelift surgery had attained a level of sophistication that inspired no major innovations until after World War II, when the development of antibiotics and improved anesthesia provided safer elective surgery. Before World War II, aesthetic surgery was looked on by organized medicine with disfavor, believing that it was not warranted because of associated risks. By 1960, this attitude had changed somewhat. The greater affluence of the middle class and changing attitudes helped spawn a renewed interest in rhytidectomy. However, it was not until the 1970s that significant innovations in facelifting were introduced. This was initiated by the work of Skoog,[2] who reported dissecting beneath the superficial fascia of the face. Before 1974, rhytidectomy had consisted of a simple subcutaneous dissection of facial and cervical skin with or without suture suspension of the underlying superficial fascia. Skoog demonstrated that an advancement flap dissected beneath the superficial fascia, later to be named the superficial musculoaponeurotic system (SMAS), while leaving the overlying skin attached, could improve the jaw line better than a subcutaneous dissection of the skin. Skoog's discovery that enhanced results were possible from dissecting deeper than the conventional subcutaneous tissue plane ushered in a renaissance for rhytidectomy, and today surgeons are in the midst of this renaissance. Skoog's report created considerable interest in the superficial facial fascia and led to the 1976 report by Mitz and Peyronie.[3] This and subsequent studies showed that the SMAS is a fibromuscular fascial extension of the platysmal muscle that arises superiorly from the fascia over the zygomatic arch and is continuous in the inferior cheek with the platysma. Throughout this chapter, when the term *SMAS* is referred to, the reader should understand that this structure consists of a fibrous layer of connective tissue in the mid-face but has more consistency in the inferior cheek, where it consists of the platysmal muscle. This is particularly true over the tail of the parotid gland and anterior to the gland. The distribution of the facial nerve is deep to the SMAS (Fig. 28-1).[3] Presumably, the function of the SMAS is to transmit to the facial skin the activity of the facial mimetic musculature.

Surgeons familiar with the subcutaneous facelift began incising the SMAS superficial to the parotid gland and creating a rotation advancement SMAS flap. Other surgeons made incisions through the SMAS anterior to the parotid gland and dissected beneath the platysma, creating a musculocutaneous advancement flap, which was suspended posterosuperiorly to the fascia of the parotid gland. Some excised a strip of SMAS and reapproximated it rather than dissecting beneath it. Although the SMAS flap dramatically improved the jowl, it did not

improve the melolabial fold of the mid-face. The mid-face can be defined as that portion of the cheek that encompasses the area between the lower eyelid and the level of the oral commissure.

Yousif and others investigated the anatomy of the melolabial fold and found that the fold resulted from descent of the anterior cheek fat and overlying attached skin.[4] With aging, the cheek fat of the mid-face descends inferomedially (Fig. 28-2). This tissue migration has the effect of enhancing the melolabial fold and deepening the melolabial crease. At the same time, the orbicularis muscle of the lower eyelid stretches and descends inferolaterally. This movement causes the margin of the lower eyelid to move below the inferior limbus, which, in turn, produces scleral show. The junction between the cheek and lower eyelid descends below the orbital rim, causing skeletonization of the inferior bony orbital rim and, in some patients, the development of a nasojugal groove. On the basis of the anatomic changes of the lower eyelid and mid-face that occur from aging, it eventually became evident that rejuvenation of the mid-face required elevation and fixation of the mid-facial soft tissues and correction of the redundant orbicularis muscle of the lower eyelid by excision or repositioning of the muscle superomedially.

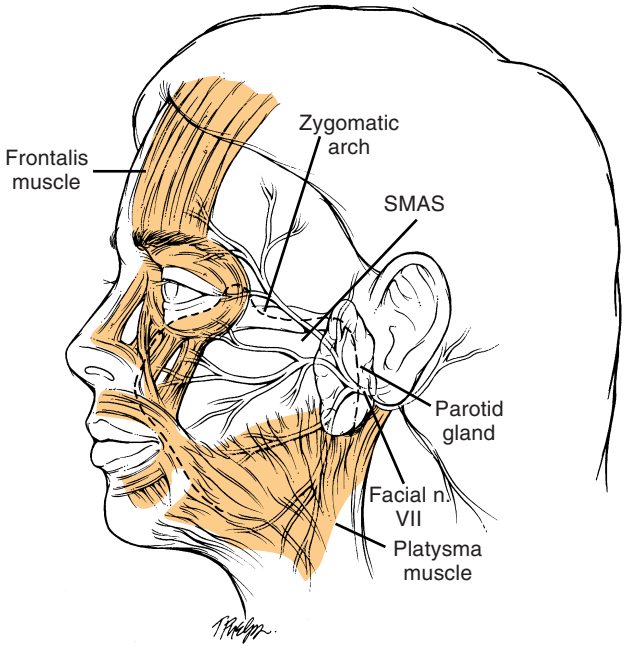

Figure 28-1. The superficial musculoaponeurotic system (SMAS) is a fibromuscular fascial extension of the platysmal muscle that arises superiorly from the fascia over the zygomatic arch and is continuous in the inferior cheek with the platysmal muscle. The facial nerve lies deep to the SMAS and innervates the mimetic muscles of the forehead and mid-face from the ventral aspect of the muscles.

The SMAS is essentially a fascial extension of the platysmal muscle beneath the cheek fat of the mid-face.[4-7] Traction placed on the SMAS is not transmitted to the melolabial fold and as a consequence does not ameliorate the fold. This is because the SMAS is effectively anchored by the bony origins of the mimetic muscles it envelops, especially the zygomatic major muscle in the region of the body of the zygoma. This point of fixation prevents the upward lateral displacement of a sub-SMAS rhytidectomy flap and the flattening of the melolabial fold. This finding led to the realization that a sub-SMAS dissection must release the investments of the SMAS to the zygomatic musculature to move the SMAS and the overlying cheek fat upward, thereby improving the melolabial fold and the appearance of the mid-face.[8] The deep-plane rhytidectomy perfected by Hamra extended a sub-SMAS dissection of the inferior cheek superiorly, cutting through the SMAS peripherally, and releasing it from its investment of the zygomatic muscles, so that the SMAS and the overlying skin and subcutaneous tissues could be advanced upward.[9] This release was accomplished by transitioning from a sub-SMAS plane in the inferior cheek to a supra-SMAS plane in the superior medial cheek (Fig. 28-3). The dissection extended medially beyond the melolabial fold, totally releasing all SMAS attachments to the dermis of the upper lip and creating a thick musculocutaneous flap composed of skin, subcutaneous fat of the cheek, and the platysma. Hamra subsequently modified the deep plane rhytidectomy by including the orbicularis oculi in the rhytidectomy flap and termed it a *composite rhytidectomy*.[10] Owsley[11] showed that by dissecting medially from the malar eminence to the lateral upper lip just superficial to the SMAS in the plane immediately above the orbicularis oculi, zygomaticus, and levator muscles, the cheek fat could be suspended superiorly, restoring a youthful appearance to the mid-face and effacing the melolabial fold. He showed that a sub-SMAS dissection was not at all necessary to improve the mid-face. Owsley's approach is often referred to as an *extended supra-SMAS rhytidectomy*.

From the preceding discussion, it is apparent that advancement of the cheek fat superolaterally is necessary to improve the mid-face,

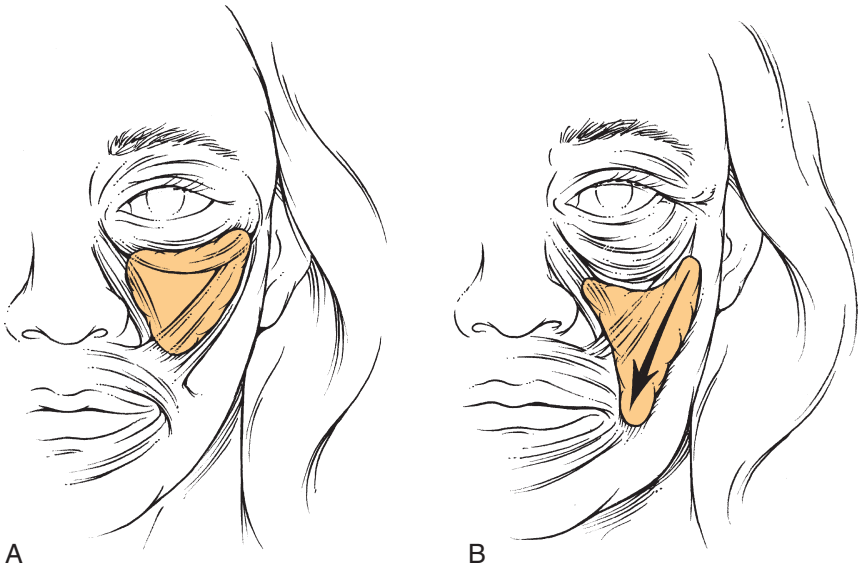

Figure 28-2. A, Aging causes inferomedial descent of the cheek fat, which increases the melolabial fold and deepens the melolabial crease. **B,** The orbicularis muscle of the lower eyelid stretches and descends inferolaterally, causing lower lid retraction and scleral show.

whereas a sub-SMAS dissection with mobilization of a composite flap of platysma and overlying skin is beneficial for correcting the jowl. Dissection beneath the SMAS of the inferior cheek is readily accomplished with blunt dissection once the SMAS has been incised. However, shifting the dissection to a more superficial plane as one extends superiorly from beneath the platysma of the lower cheek to a plane superficial to the SMAS superior and anterior to the zygomatic major muscle in the superomedial cheek is tedious and must be performed sharply. By necessity, the surgeon must make a transition from one surgical plane to another and risk injury to the zygomatic branch of the facial nerve. In addition, to mobilize the ptotic cheek fat upward in the mid-face, a lengthy anterior dissection over the convexity of the zygoma is necessary. The convexity often prevents direct visualization of the dissection.

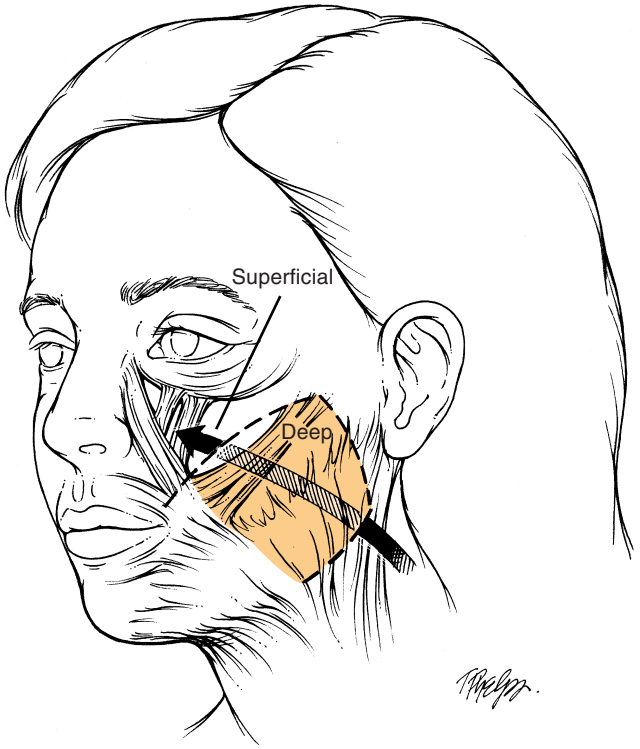

Figure 28-3. The deep-plane rhytidectomy described by Hamra[19] extended a sub-superficial musculoaponeurotic system (sub-SMAS) dissection of the inferior cheek superiorly, cutting through the SMAS peripherally, thus releasing the SMAS from investments to the zygomatic muscles, so that the SMAS and overlying skin and cheek fat could be mobilized upward. This release was accompanied by transitioning from a deep (sub-SMAS) plane in the inferior cheek to a superficial (supra-SMAS) plane in the superior medial cheek.

The knowledge gained from the clinical and anatomic studies performed in the mid and late 1970s enabled continued refinement of sub-SMAS and extended supra-SMAS dissection techniques, culminating in the early 1990s. Emerging in parallel with these surgical approaches was the development of a different concept for rejuvenating the mid-face accomplished by a subperiosteal dissection. In 1980, Tessier[12] demonstrated that undermining the periosteum of the superior and lateral orbital rim allowed elevation of the soft tissues of the forehead and eyebrows, with improved results compared with previous techniques for forehead lifting. In 1988, Psillakis and others[13] reported on a subperiosteal rhytidectomy technique that involved detachment of all periosteum from the bony orbital rims, upper maxilla, zygoma, and nose. After this detachment, the soft tissues of the forehead, lateral canthus, mid-face including the melolabial folds, and to some degree the jowls were lifted to reestablish a more youthful relationship with the underlying facial skeleton. Because of troubling temporary forehead paralysis from trauma to the temporal branch of the facial nerve (6.7%), the authors advocated restricting subperiosteal dissection of the zygomatic arch to the anterior third to reduce the risk of injury. Ramirez and others[14] modified the subperiosteal facelift described by Psillakis, permitting significant improvement in the safety and clinical results. They released the periosteum from the entire zygomatic arch by dissecting deep to the temporalis fascia. The temporalis fascia was then used as a lifting and anchoring element of the entire cheek and perioral soft tissues (Fig. 28-4). The surgical approach by Ramirez and others showed improved mid-face suspension by. complete subperiosteal undermining of the mid-facial bones. The suspension seemed to have the same influence on the melolabial fold as the deep-plane facelift, that is, elevation of the ptotic cheek fat to a more youthful position with effacement of the fold.

The subperiosteal approach had the advantage of rejuvenating the mid-face without placing unnatural tension on the skin in the temporal area. This tension is necessary when using an extended supra-SMAS or deep-plane rhytidectomy to pull the cheek fat with the overlying

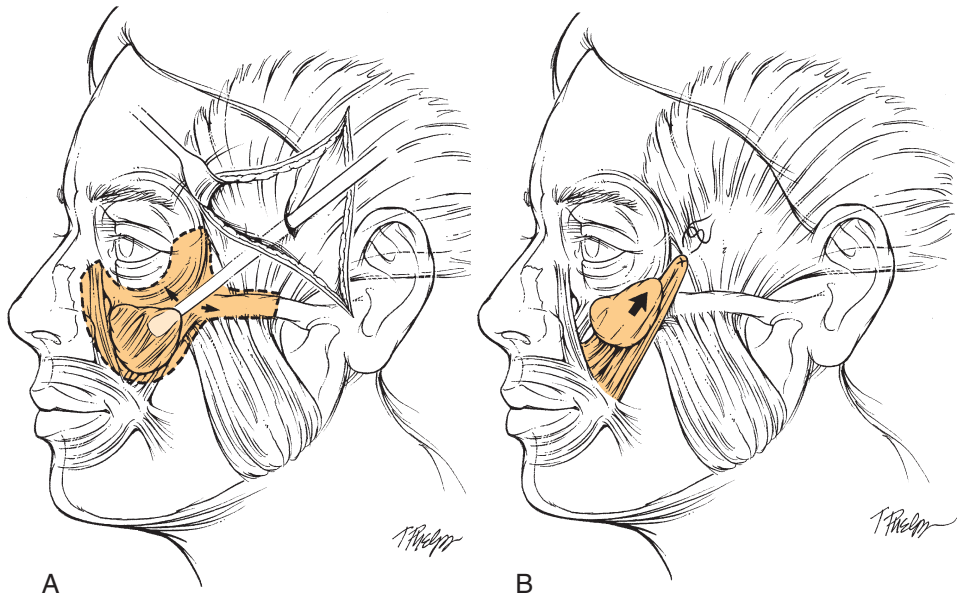

Figure 28-4. **A,** Subperiosteal mid-facelift accomplished through transtemporal approach. Periosteum is released from the maxilla and zygoma and all or portions of the zygomatic arch. **B,** Periosteum of zygoma suspended to temporalis fascia to lift soft tissues of mid-face.

skin upward. In contrast, the subperiosteal approach placed traction on the periosteum to maintain repositioning of the mid-face tissues. It also did not require a long cheek flap extending anteriorly beyond the convexity of the zygoma as called for by the deep-plane and extended supra-SMAS facelifts. The extensive release of the periosteum away from the zygoma and maxilla allowed better elevation of the upper lip and corner of the mouth by moving the origin of the zygomatic musculature to a higher position on the zygoma. This effectively "shortens" the zygomatic musculature, which lifts the oral commissure upward, producing a more pleasant shape to the mouth. This maneuver cannot be accomplished with sub-SMAS or extended supra-SMAS dissections. Finally, in individuals with early facial aging, the subperiosteal approach through endoscopic techniques offered a method of lifting the face without skin excisions and the resulting preauricular scar.

The subperiosteal facelift described by Ramirez and others[14] is technically difficult, because it requires a temporal approach, which is considerably removed from the body of the zygoma and the anterior maxilla where the mid-face soft tissues are attached. As with the deep-plane rhytidectomy, visibility anterior to the convexity of the zygoma is limited, and it may be necessary to perform some dissection blindly. Because the temporal approach by itself presents difficulties with detachment of the periosteum from the maxilla, surgeons turned to other approaches. The most popular of these was transorbital access to the mid-face achieved by performing a lower lid blepharoplasty incision. The periosteum was released from the maxilla and zygoma, and the soft tissues of the mid-face were suspended either to a periosteal cuff at the inferior bony orbital rim or to the temporalis fascia in the anteroinferior aspect of the temporal fossa.[15-18] A major drawback of the transorbital route was not infrequent problems of lower lid retraction or even ectropion. This complication occurs from trauma to the orbicularis oculi and subsequent scar contracture. Some surgeons recommended concomitant lateral canthoplasty or at the very least canthopexy to reduce this risk. Other surgeons avoided this risk altogether by combining a transtemporal and transoral approach and not performing any dissection of the mid-face through the lower eyelid. The transtemporal approach was used to elevate the periosteum from the zygomatic arch and the superior aspect of the zygoma. The transoral approach was used to free the periosteum from the maxilla and inferior aspects of the zygoma. This combined approach had the advantage of allowing the surgeon direct access for performing a subperiosteal dissection of the entire mid-face under direct vision without the need of an endoscope. It also avoided the risk of lower eyelid retraction or ectropion.

Whether superior movement of the mid-face soft tissues is accomplished by a subperiosteal or by an extended supra-SMAS dissection, the goal is to produce a dramatic lifting of mid-face tissues. Proponents of the extended supra-SMAS approach argue that the periosteum does not stretch with age and thus a subperiosteal approach repositions the origin of the zygomatic musculature to a more superior and abnormal position. This may have the effect of giving an excessive horizontal width to the mid-face. Considerably more postoperative facial edema is associated with this approach compared with the transfacial supra-SMAS dissection. Another disadvantage of a subperiosteal dissection is that most approaches call for elevation of the periosteum from the anterior portion of the zygomatic arch, placing the temporal branch of the facial nerve at risk.

Proponents of the subperiosteal approach point to the safety of keeping all of the soft tissue, including the facial nerve, above the plane of dissection. There is less risk of injury to the zygomatic and buccal branches of the facial nerve with the subperiosteal approach compared with the deep-plane or extended supra-SMAS facelift. There is no disruption of the blood supply to the skin of the mid-face, because the plane of dissection is beneath all of the major blood supply to the face. There is no need for a lengthy skin flap lifted from the preauricular area or for a blind dissection of soft tissues of the mid-face. Although not part of the discussion in this chapter, it has become apparent that the aging changes in the lower periocular area are maximally rejuvenated when mid-facelifting is performed in conjunction with orbicularis oculi repositioning to a more superior and medial position.[10] Repositioning of the ptotic orbicularis muscle is most easily accomplished by performing a subperiosteal mid-facelift. Transfacial supra-SMAS mid-facelifts do not reposition this muscle. Table 28-1 summarizes the advantages and disadvantages of the various approaches to lifting the mid-face.

Surgical Approaches

Although there are a multitude of variations in performing a rhytidectomy of the lower face and upper neck, they may be divided into four categories according to the tissue planes used for dissection. These include subcutaneous, sub-SMAS, supra-SMAS, and subperiosteal (Table 28-2).

Subcutaneous Rhytidectomy

All approaches except the endoscopic facelift without preauricular or postauricular incisions call for some subcutaneous tissue dissection of the facial skin. The postauricular skin flap is always elevated in the subcutaneous tissue plane. Likewise, the preauricular skin must be dissected in a similar plane for variable distances before incisions can be made through the SMAS. Typically, the skin of the upper neck is also elevated in the subcutaneous tissue plane or immediately superficial to the platysmal muscle (preplatysmal). Dissection may continue forward in the neck to the midline. The extent of anterior dissection in the subcutaneous tissue plane of the face depends on the surgeon's preference and may be influenced by the degree of facial skin laxity. In the past, there have been controversies concerning the benefits of long-flap versus short-flap rhytidectomies. A benefit of dissecting to the lateral bony orbital rim in the temple is that it releases the skin from the underlying orbicularis oculi. This helps to improve the crow's feet and also assists with redistribution of the vertically advanced preauricular skin flap. Once a skin flap has been elevated, the exposed SMAS can

Table 28-1

Dissection Planes of Mid-Facelifting

	Advantages	Disadvantages
Subperiosteal	1. Does not require preauricular incision/skin flap 2. Does not impair vascular supply of facial skin 3. Avoids risk to zygomatic branch of nerve VII 4. Lifts orbicularis oculi of lower eyelid 5. Some lifting of oral commissure	1. Increases horizontal width of face 2. Risk to temporal and buccal branches of nerve VII and infraorbital nerve 3. Greater postoperative edema
Supra-SMAS	1. Does not reposition zygomatic musculature 2. Avoids risk to temporal and buccal branches of nerve VII 3. Less postoperative edema	1. Long preauricular cutaneous flap 2. Reduces skin vascularity of face 3. Risk to zygomatic branch of nerve VII 4. Does not lift orbicularis oculi

Table 28-2

Surgical Approaches to Mid-Facelifting

Surgical Approach	Plane of Dissection	Advantages	Disadvantages
Transfacial	Supra-SMAS	1. Avoids risk to temporal and buccal branches of nerve VII 2. Less postoperative edema	1. Preauricular incision and long skin flap 2. Requires some blind dissection 3. Does not lift orbicularis oculi
Transtemporal	Subperiosteal	1. No preauricular incision 2. Concomitant lateral brow lift	1. Risk to temporal and buccal branches of VII nerve 2. Requires endoscope 3. Poor access to periosteal dissection of maxilla
Transorbital	Subperiosteal or supraperiosteal	1. Direct access for dissection and suspension of mid-face 2. More vertical vector for suspension of mid-face soft tissues	1. Risk to buccal branch of nerve VII 2. Risk to infraorbital nerve 3. Risk of lower lid retraction/ectropion
Transoral	Subperiosteal	1. Direct access for dissection of mid-face 2. Ease in elevating periosteum of maxilla	1. Risk to buccal branch of nerve VII 2. Does not provide access for suspension of mid-face tissues 3. Greater risk of infection 4. Risk to infraorbital nerve
Combined	Subperiosteal; usually transoral combined with transtemporal or transorbital	1. Direct visualization of entire dissection 2. Ease of suspension of mid-face tissues	1. More postoperative edema 2. Greater risk of infection if transoral route used

be plicated by folding it on itself using sutures to suspend it to the periparotid fascia. The subcutaneous facelift with plication of the SMAS is still the most common surgical approach used by plastic surgeons, composing 23% of facelift procedures performed.[19] It is probably the safest approach from the standpoint of risk of facial nerve injury but has the disadvantages compared with other techniques of shorter long-term improvement of the jowl and no correction of the mid-face.

SMAS Rhytidectomy

The sub-SMAS dissection of the lower face is another common surgical approach performed by approximately 20% of facelift surgeons.[19] This may take the form of elevating an SMAS flap limited to the area over the parotid gland (25% of surgeons) or extending the SMAS flap anterior to the parotid gland. The SMAS flap is then suspended posterosuperiorly. Neither approach lifts the mid-face, but both markedly improve the jowl. When an SMAS flap is dissected from the parotid fascia, it is frequently referred to as an *SMAS rhytidectomy.* Dissecting beneath the SMAS anterior to the parotid gland and then transitioning to a supra-SMAS plane and dissecting all of the cheek fat with attached overlying skin away from the zygomatic musculature as described by Hamra is known as a *deep-plane rhytidectomy* (see Fig. 28-3).[19] Later, Hamra added to this dissection a supraperiosteal dissection of the superior aspect of the mid-face through a lower eyelid incision. This biplane dissection was termed a composite rhytidectomy by Hamra.[10] Nine percent of facelift surgeons perform a deep plane or composite rhytidectomy.[19]

A variation of the sub-SMAS dissection is a strip SMAS-ectomy described by Baker.[20] This technique consists of excising a strip of SMAS along a line that extends from the angle of the mandible to the lateral malar eminence. Usually, a 2- to 4-cm wide strip of SMAS is excised, depending on laxity. Much of this excision is anterior to the parotid gland. No anterior dissection beneath the SMAS is performed. The SMAS is reapproximated, advancing the mobile SMAS and platysma posterosuperiorly to the junction of the SMAS fixed to the periparotid fascia. Approximately 20% of facelift surgeons use the technique of SMAS-ectomy.[19] It has the advantage of simplicity but does not address the mid-face.

Supra-SMAS Rhytidectomy

The term *supra-SMAS* usually refers to dissection just superficial to the SMAS in the mid-face. All subcutaneous tissue dissections in the preauricular area are also supra-SMAS. However, remaining just superficial to the SMAS as the limits of the dissection are extended anteriorly beyond the parotid gland toward the mid-face requires a deeper dissection than is required for a standard subcutaneous facelift. Because the SMAS invests the mimetic muscles of the mid-face, a supra-SMAS dissection requires a forward dissection immediately superficial to these muscles. This results in a thick cutaneous flap consisting of the cheek fat and the overlying attached facial skin. The dissection is usually carried to the upper lip to release all of the dermal attachments of the SMAS to the melolabial crease. This extreme anterior dissection is commonly referred to as an extended SMAS rhytidectomy or an extended supra-SMAS rhytidectomy. The cutaneous flap is then suspended under considerable tension posterosuperiorly to the fascia overlying the zygoma and parotid gland. The primary purpose of the extended supra-SMAS rhytidectomy is to displace superiorly the cheek fat of the mid-face. This corrects the ptotic cheek fat that occurs in the mid-face with aging and softens the melolabial fold.

The main disadvantage of the extended supra-SMAS rhytidectomy is the long preauricular skin flap resulting from a lengthy anterior dissection. This creates a potentially large dead space where hematomas can collect. A dissection beyond the convexity of the zygoma may require some blind dissection or at least impair the exposure available to the surgeon. In addition, remaining above the SMAS throughout the dissection does not provide as much improvement of the jowl compared with developing a SMAS flap of the inferior cheek. Approximately 20% of facelift surgeons perform the extended supra-SMAS rhytidectomy.[19] The advantage of the deep-plane facelift compared with the supra-SMAS lift is that the inferior cheek is dissected in a sub-SMAS plane, creating an advancement flap, whereas the mid-face is dissected in a supra-SMAS plane. The sub-SMAS

dissection in the lower face provides long-term correction of the jowl.[21]

Subperiosteal Rhytidectomy

Subperiosteal rhytidectomy refers to the lifting of the cheek tissues by dissecting in the subperiosteal plane over the maxilla and zygoma. The procedure usually includes an endoscopic subperiosteal forehead lift as well. All of the soft tissues of the mid-face are lifted, including the elevators of the lip, the zygomatic major and minor, and often the orbicularis oculi. The fundamental difference between the subperiosteal mid-facelift and the transfacial supra-SMAS facelift is the superior displacement of these muscles (see Fig. 28-4). The extended supra-SMAS and deep-plane rhytidectomy only elevate the cheek fat and skin and not the muscles of the mid-face. Subperiosteal mid-facelifts do not significantly correct the jowl and have no influence on the upper neck. Another disadvantage of a subperiosteal mid-facelift is the tendency to increase the horizontal width of the face by displacing the origin of the zygomatic major muscle to a more superior and lateral position. However, in most patients this has the pleasing effect of enhancing the malar eminence.

There are four surgical approaches used to perform subperiosteal mid-facelifting: transtemporal usually using an endoscope, transorbital through a lower eyelid or transconjunctival incision, transoral through an upper gingival buccal incision, and combined using two or more of the previously listed approaches. Regardless of the approach, it is necessary to release the periosteum from the lateral and inferior bony orbital rim and from the entire zygoma and maxilla.

The temporal approach is accomplished through an incision behind the hairline in the temple. An endoscope is frequently used to perform a dissection beneath the temporoparietal fascia of the anterior lateral scalp. Transition is then made to a subperiosteal plane as dissection continues inferiorly over the zygoma and zygomatic arch. Subperiosteal dissection also proceeds medially in the mid-face, releasing the soft tissues from their attachment to the maxilla. This necessitates limited dissection onto the upper portion of the masseter muscle. A disadvantage of the transtemporal approach is the difficulty releasing the periosteum from the medial maxilla because of insufficient exposure even when an endoscope is used.

The transorbital route has the advantage of direct access to the mid-face with less need for the use of an endoscope. Through this approach, the subperiosteal dissection is accomplished under direct vision, and the mid-face soft tissues are suspended either to the superior orbital rim or to the anteroinferior temporalis fascia (Fig. 28-5). Some surgeons perform a supraperiosteal dissection of the mid-face through a lower eyelid incision. A disadvantage of the transorbital approach is temporary distortion of the lateral canthal area from bunching of redundant soft tissue. Another disadvantage is the risk of lower eyelid retraction or ectropion.

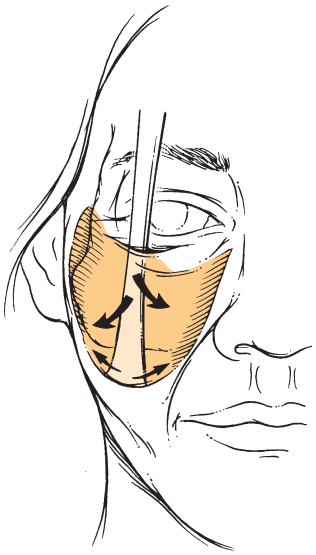

Figure 28-5. Transorbital approach to subperiosteal mid-facelift. The subperiosteal dissection is accomplished under direct vision, and the mid-face soft tissues are suspended to the superior orbital rim or the anteroinferior temporalis fascia.

The transoral approach is not often used by itself but is combined with transorbital or transtemporal incisions to create a combined surgical approach.[22,23] This enables the periosteum to be easily stripped from the inferior aspects of the maxilla and zygoma from the oral access. The remaining periosteum is then elevated from the superior aspect of the zygoma and from the anterior zygomatic arch through an orbital or temporal access. The advantage of this combined approach is ease of dissection and direct visualization without the need for an endoscope. The main disadvantage is the potential risk of wound infection because of exposure of the dissection to bacteria in the oral cavity. Table 28-2 summarizes the surgical approaches to the mid-face and the advantages and disadvantages of each. Only 2% of facelift surgeons generally perform subperiosteal facelifting, and of those, approximately half use an endoscope.[19]

Surgical Technique

Regardless of the surgical approach used to perform a rhytidectomy, the goals are the same. These include (1) preserve motor and sensory innervation of the face; (2) modify cervical fat if excessive; (3) tighten the SMAS and platysma; and (4) redrape cervical and facial skin and trim excess. This chapter has discussed many of the approaches used to achieve these goals and listed many of the advantages and disadvantages of each surgical approach. This section will address more technical aspects of facelifting.

Incisions

Factors that influence the configuration of the facelift incision include gender, hairline, hairstyle, a history of previous facelift surgery, and the redundancy of facial and cervical skin. In the temporal area, the classic incision is one that extends above the auricle into the hair, curving upward and forward to end 1 or 2 cm above the level of the eyebrow. More than half of facelift surgeons also add to this incision a horizontal incision beneath the temporal tuff of hair to facilitate removal of vertically elevated facial skin without raising the temporal hairline to an abnormal height.[19] This horizontal incision is often referred to as a sideburn incision and facilitates removal of a great deal of excess facial skin. Only 13% of facelift surgeons use a prehairline incision in the temple.[19] The disadvantage of creating a permanent and often noticeable scar anterior to the temporal hair tuft prevents most surgeons from using this incision. The preauricular incision follows the curve of the root of the helical crus to the level of the tragus (Fig. 28-6). The incision may then continue posterior to the tragus or in the pretragal crease to the inferior aspect of the earlobe. A retrotragal incision is preferred by 57% of facelift surgeons.[19] The advantages of the retrotragal incision are that this portion of the incision is hidden behind the posterior border of the tragus. It should only be used in women. In men, this technique will result in the tragus being covered with hair-bearing skin. Disadvantages of the retrotragal incision include obliteration of the pretragal crease and scar contraction that can pull the tragus forward, causing an unnatural visibility of the external auditory canal. These problems can be prevented to some degree by thinning the portion of skin flap that will lie immediately anterior to the tragus and trimming the flap so that there is a slight redundancy of skin of the flap covering the tragus. This latter technique ensures that wound closure tension will not occur in this area.

The incision around the earlobe is designed so the lobe is detached from the skin flap, with a 2-mm cuff of facial skin at its base. This ensures the preservation of the sulcus between the lobe and the facial skin and reduces the risk of developing satyr ears.

In women, the retroauricular incision is designed 2 to 3 mm anterior to the postauricular sulcus on the medial surface of the auricle. Placement here allows for the possibility of some posterior migration of the retroauricular scar, so that the scar will remain hidden by the auricle. The posterior scalp incision extends from the retroauricular incision across the postauricular sulcus at the level of the tragus or

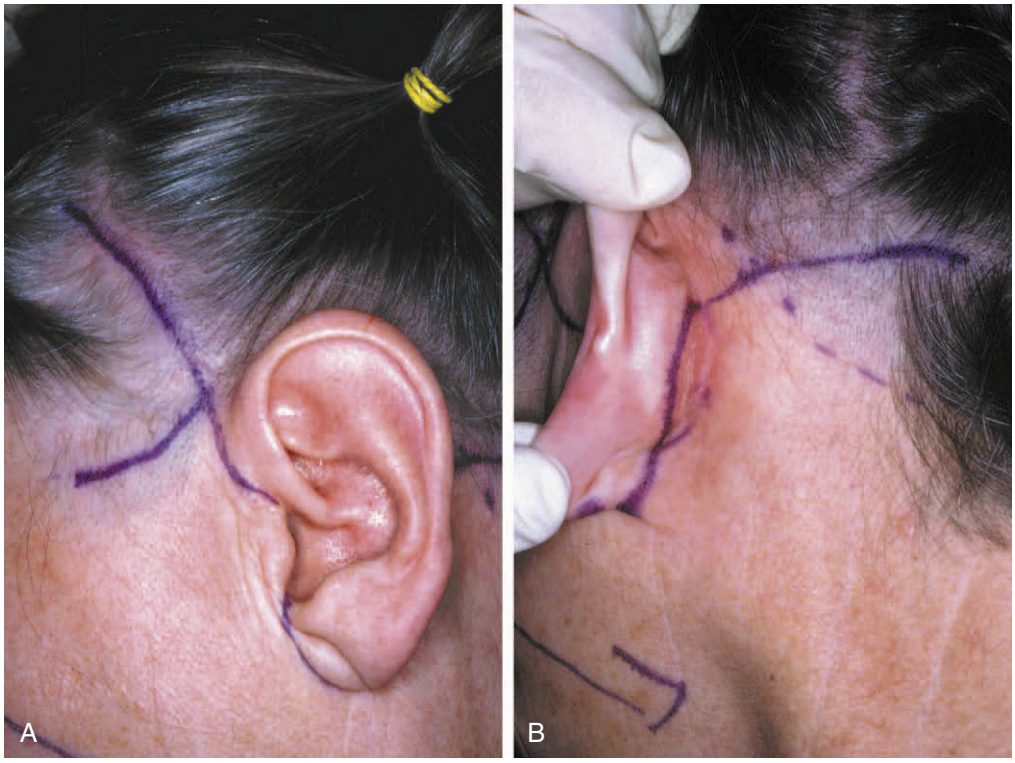

Figure 28-6. Female facelift incision. **A,** The incision begins in the hair above the auricle. A horizontal incision beneath the temporal tuft of hair is usually performed. The preauricular incision follows the curve of the root of the helical crus and then continues posterior to the tragus. **B,** The retroauricular incision is 2 mm anterior to the postauricular sulcus. At the level where the helix meets the hairline (*dotted line*) the incision crosses the postauricular skin to the scalp. The scalp incision curves slightly inferiorly.

where the helix meets the hairline. This straight line from the auricle to the hair-bearing scalp can be modified by making a small superiorly based triangular flap in the mastoid area. This dart of skin helps prevent straight-line scar contracture and subsequent development of a hypertrophic scar. The scalp incision should be directed into the hair, curving slightly inferiorly and parallel to the postauricular hairline. The incision should not be made along the inferior border of the postauricular hairline except under unusual circumstances because of the visibility of the resulting scar. The retroauricular incision may be limited only to a short vertical incision behind the ear in younger patients with only mild elastosis. In such patients, neck dissection may not be necessary and so the skin does not need to be elevated from the postauricular area.

In men, facelift incisions are modified from that described for women. The temple incision remains unchanged, but the sideburn incision is usually not necessary, because the temporal hair tuft is continuous with the facial hair (Fig. 28-7). Retrotragal incisions are not used. The preauricular incision should be curvilinear following the root of the helical crus and then transition into the pretragal crease. The retroauricular incision is also occasionally modified by placing the mastoid incision more inferior than is done in women. This design is used when there is a great deal of cervical skin laxity that will require excision. The more inferiorly located incision reduces the height of the hair-bearing flap behind the ear and the need for shaving in the superior postauricular sulcus.

Submentoplasty

Ellenbogen and Karlin[24] have established five visual criteria that the eye translates as a youthful profile of the neck: (1) distinct inferior mandibular border from mentum to angle with no jowl overhang, (2) slight subhyoid depression at the apex of the cervicomental angle (this depression on profile gives the impression of a thin and long neck), (3) visible thyroid cartilage convexity, (4) distinct visible anterior border of the sternocleidomastoid muscle in its entire length from mastoid to sternum, and (5) cervicomental angle between 105 and 120 degrees. This translates into a 90-degree angle between the axis of the sternocleidomastoid muscle and a line drawn tangent to the submentum in an anteroposterior orientation (Fig. 28-8).[24] An inferiorly positioned hyoid, excessive submental fat, laxity of the platysma (anterior bands), and microgenia can all contribute to blunting of the cervicomental angle.

Anterior bands that develop near the mid-line of the neck with age are the result of elastosis and sagging of the platysmal muscles. When banding is mild, they can be eradicated by developing a platysmal flap posteriorly near the angle of the mandible and advancing this flap posterosuperiorly over the parotid gland. Another less effective method is to suture-suspend the lateral border of the muscle below the angle of the mandible to the fascia of the mastoid and sternocleidomastoid muscle. In the past, surgeons advocated partial or complete horizontal division of the platysmal muscle 5 or more centimeters below the mandible to achieve a greater posterior advancement of the muscle flap and better topographic delineation between the neck and the lower jaw. This practice has been abandoned because of unnatural contours and deformities that develop in the neck as a result of this technique.

When managing platysmal bands, the most effective method, with greatest longevity of results, is to correct the deformity anteriorly where it is located. This is accomplished by performing a submentoplasty. A submentoplasty is indicated if the patient has excessive fatty deposits in the submental area, marked elastosis of neck skin, or platysmal banding. The author performs a submentoplasty with or without posterior neck dissection in a manner described by Hamra.[14] A submentoplasty is required in most patients having rhytidectomy and typically is the first stage of a rhytidectomy. A 2.5-cm incision is made just anterior to the submental crease (Fig. 28-9). A flap consisting of skin and all of the fat superficial to the platysmal muscle is elevated in a preplatysmal plane. This dissection extends to the level of the superior aspect of the thyroid cartilage and laterally for 6 cm on either side of midline. In the paramedian position, the platysmal muscles are bluntly undermined in a vertical direction from the mandible to the level of the thyroid cartilage and then cross-clamped and incised. The muscle between the two incisions is resected. The amount of muscle resected

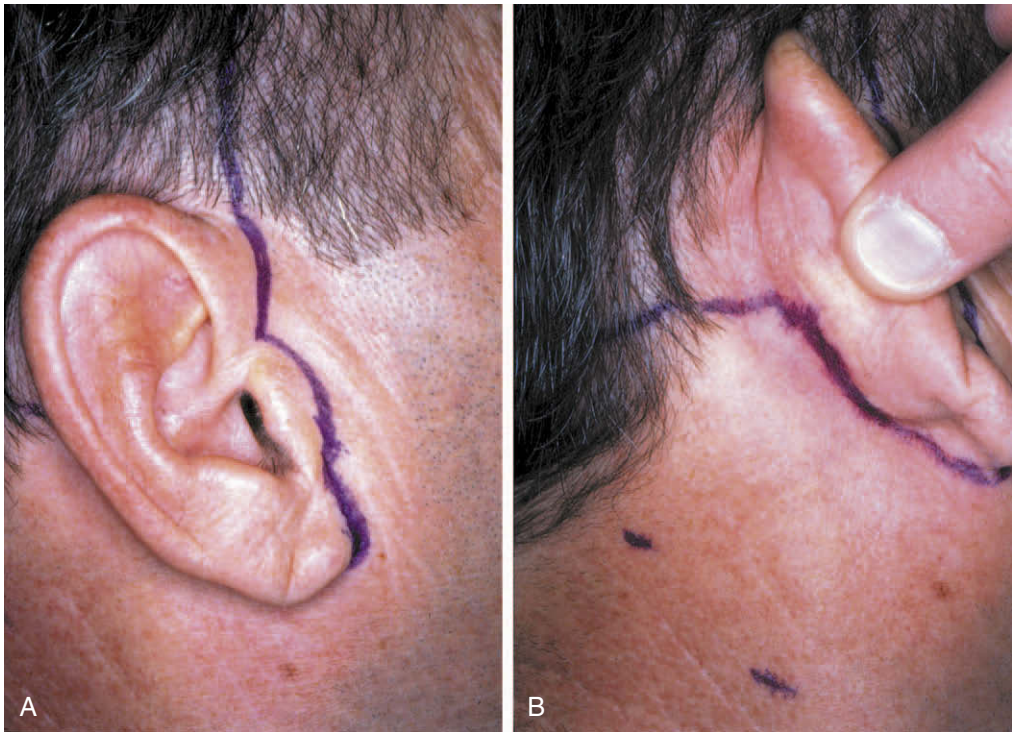

Figure 28-7. **A,** The male facelift incision begins in the hair-bearing scalp above the ear and follows the curve of the root of the helical crus. It then transitions into a pretragal crease. **B,** The retroauricular incision is positioned in the depths of the postauricular sulcus.

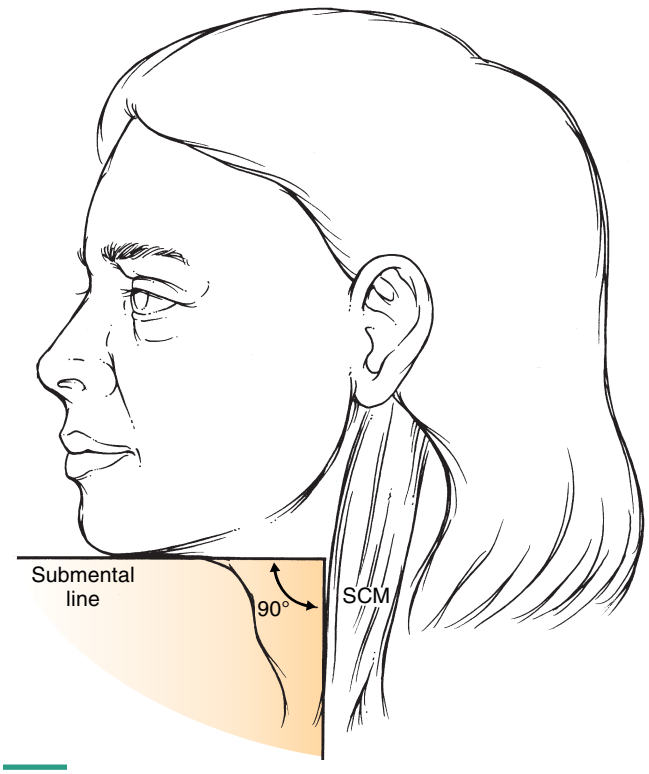

Figure 28-8. The youthful neckline has a cervicomental angle of 105 to 120 degrees. This translates into a 90-degree angle between the axis of the sternocleidomastoid muscle (SCM) and the submental line.

depends on redundancy. Sufficient muscle should be removed so that when the borders of the two platysmal muscles are brought together, a tautness is created. Before suturing the muscles together, any excess subplatysmal fat is resected under direct vision. The incised borders of the platysmal muscles are then approximated with interrupted sutures, burying the knot beneath the muscles. Any excess fat elevated with the submental skin is removed with scissors under direct vision (Fig. 28-10). Other surgeons prefer to use suction-assisted liposculpturing to modify the submental fat instead of direct excision with scissors. Sixty percent of facelift surgeons perform direct excision of submental fat, whereas only 27% perform suction-assisted lipectomy.[19] Perhaps the reason for the popularity of direct excision is that a greater amount of subcutaneous fat can be removed with greater ease and accuracy by direct excision compared with the use of a suction cannula. Because the skin of the neck is attached to the platysmal muscle, wide undermining of the skin in the submental area is necessary to prevent bunching of the submental skin when the platysma is advanced medially. This is the greatest disadvantage of a submentoplasty, as described.

Some surgeons prefer to perform a horizontal incision of the platysma extending laterally from its anterior border for variable distances at the level of the thyroid cartilage. The two platysmal muscles are then sutured together in the midline without excision of muscle tissue. The horizontal incision is believed by some to create a more acute cervicomental angle. Transecting the muscle and midline suturing is performed by 40% of surgeons, whereas 21% perform vertical incision and resection of the platysmal redundancy and midline suturing.[19]

The advantage of resecting redundant platysmal muscle is the elimination of the excess muscle and subplatysmal fat rather than attempting to imbricate the redundancy. By resecting muscle and advancing the platysma medially toward the midline, the surgeon is addressing the deformity at its origin and is advancing tissue in the same direction as the gravitational forces on the neck. In contrast, posterior suspension of the platysma near the angle of the mandible is removed from the area of deformity and moves tissue against gravitational pull. Posterior suspension of the cervical platysma is frequently prone to early recurrence of banding.

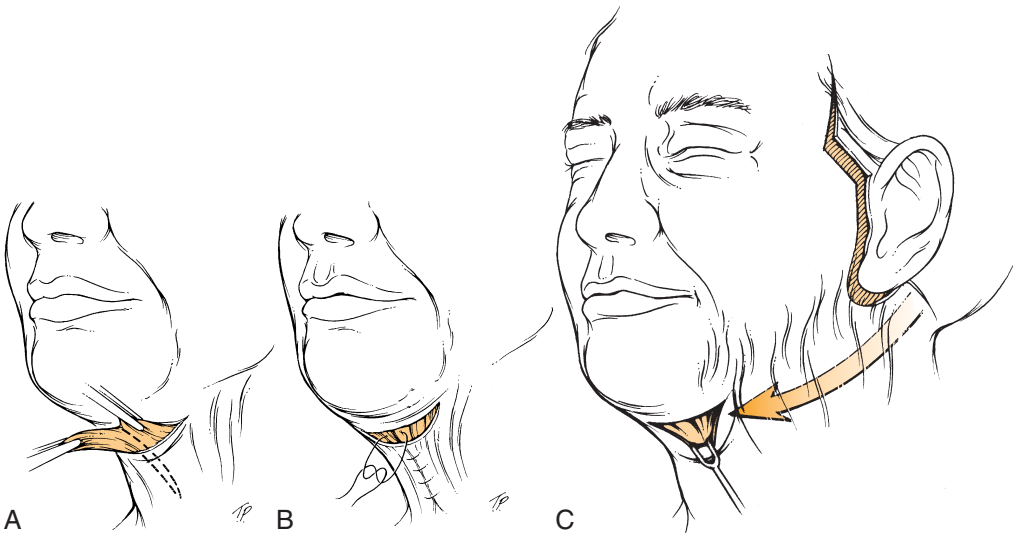

Figure 28-9. **A,** The skin and fat of the submental area are widely undermined in the preplatysmal plane. Redundant platysmal muscle is resected in a vertical orientation. **B,** The skin flap is thinned of excessive fat, and the borders of the platysmal muscles are approximated. **C,** Depending on cervical skin laxity, it may be necessary to connect the submental dissection with a posterior dissection, so that the entire upper cervical skin is freed from the platysma.

Even with the direct approach of correcting banding by performing a surgical excision of muscle redundancy, the anterior neck is the weak link of facelifting. Relaxation of skin and platysma occurs here first before other areas of the face and neck. Mild recurrent banding and skin laxity of the submentum may be observed as soon as 6 months after facelifting. This may be related to the increased tissue creep observed in the SMAS located in the neck compared with the SMAS in the cheek.[17] Patients should be counseled that anterior neck laxity and melolabial folds are the two regions of the face that are most difficult to completely correct with rhytidectomy.

Mid-Facelift

The author performs a subperiosteal mid-facelift using a combined transtemporal and transoral approach. This is accomplished before dissecting SMAS flaps. A bilateral subperiosteal mid-face dissection is accomplished under direct vision with a headlight and tissue retractor. A 2-cm upper gingival buccal incision is made, and with the use of a periosteal elevator, a complete detachment of the periosteum from the face of the maxilla is accomplished including release from the piriform aperture, nasal sidewall, the entire infraorbital bony rim, and zygomatic eminence (Fig. 28-11). Care is taken to observe and preserve the infraorbital nerve. From the zygoma, the dissection is carried inferiorly over the anterior masseter for 2 cm, releasing the soft tissue from its attachment to the anterior tendinous aspect of the muscle. This maneuver detaches the masseteric cutaneous ligaments, allowing upward advancement of the platysma in the region of the jowl.[11] Subperiosteal dissection of the superior aspect of the zygoma is accomplished through a temporal scalp incision. Dissection in the temple begins in the subgaleal plane proceeding forward and downward toward the zygoma (Fig. 28-12). Two centimeters above the zygomatic arch an incision is made through the temporalis fascia, and dissection continues just superficial to the temporal fat pad to the level of the medial aspect of the zygomatic arch. An incision is then made through the periosteum along the superior border of the arch, and the periosteum is raised off of the arch. Dissection of the subperiosteal plane continues anteriorly to connect with the dissection plane created from the transoral approach. The periosteum is also elevated off the frontal process of the zygoma to free the periosteum from the entire lateral orbital bony rim. Once all of the soft tissue of the mid-face has been freed from its bony attachment to the maxilla and zygoma, the tissue is suspended with sutures placed between the periosteum over the malar eminence and the temporalis fascia (Fig. 28-13). This suspension is placed under considerable tension. Marked upward movement of the soft tissues is noted, often resulting in exposure of the upper incisors (Fig. 28-14). Suspension of the mid-face soft tissues is always performed before suspension of the SMAS flap. Subperiosteal mid-facelifts reposition the ptotic cheek fat to a more youthful position. They also lift the orbicularis muscle of the lower eyelid and restore the relationship between the lower eyelid and the cheek observed in youthful faces (Fig. 28-15).

Skin Flap Elevation

The extent of skin undermining varies with each patient and the surgical approach used (Fig. 28-16). When a sub-SMAS dissection is performed, the facial skin may be left attached to the underlying SMAS or may be separated from the portion of the SMAS dissected as a flap. Leaving the skin attached to the SMAS helps to preserve the integrity of this structure and facilitates an easier sub-SMAS dissection. It also provides more substance for suture suspension of the SMAS flap. The depth of dissection varies in each region of the face. The posterior scalp is elevated below the hair follicles transitioning to a more superficial subcutaneous tissue plane under the postauricular skin. Over the sternocleidomastoid muscle, the dissection must be very superficial, remaining above the fascia of the muscle to avoid injury to the greater auricular nerve. Anterior to the sternocleidomastoid muscle, the neck skin is dissected either in the subcutaneous tissue plane or immediately superficial to the platysma. The preplatysmal plane is preferred by the author, because it enables the surgeon to accurately remove excessive fat from the cervical skin flap.

In the temple, the dissection may be in the subgaleal plane or below the hair follicles in the deep subcutaneous tissue plane. The subcutaneous plane of dissection is preferred to the subgaleal approach because greater lifting is possible of the skin lateral to the eye. If the subcutaneous plane is used, the dissection should transition to a more superficial level under the temple skin anterior to the hairline.

Over the parotid gland in the preauricular area, dissection is accomplished in the subcutaneous tissue plane. The anterior extent of the dissection varies with the surgical approach used. The author extends the dissection forward to a line extending from the lateral canthus to the angle of the mandible (Fig. 28-17). The dissection does not extend beyond this line so as to leave the facial skin attached to the underlying SMAS. In individuals with marked laxity of the cervical skin or who require liposculpturing, a posterior neck dissection in the relatively avascular preplatysmal plane is carried forward from the upper sternocleidomastoid muscle to the mid-line. Lifting the cervical fat with the skin enables the surgeon to remove fat from the flap selectively and evenly under direct vision with scissors or a liposculpturing cannula.

Figure 28-10. Preoperative, and 18 months postoperative views after rhytidectomy, subperiosteal mid-facelift, and submentoplasty as described in text.

Figure 28-10, cont'd.

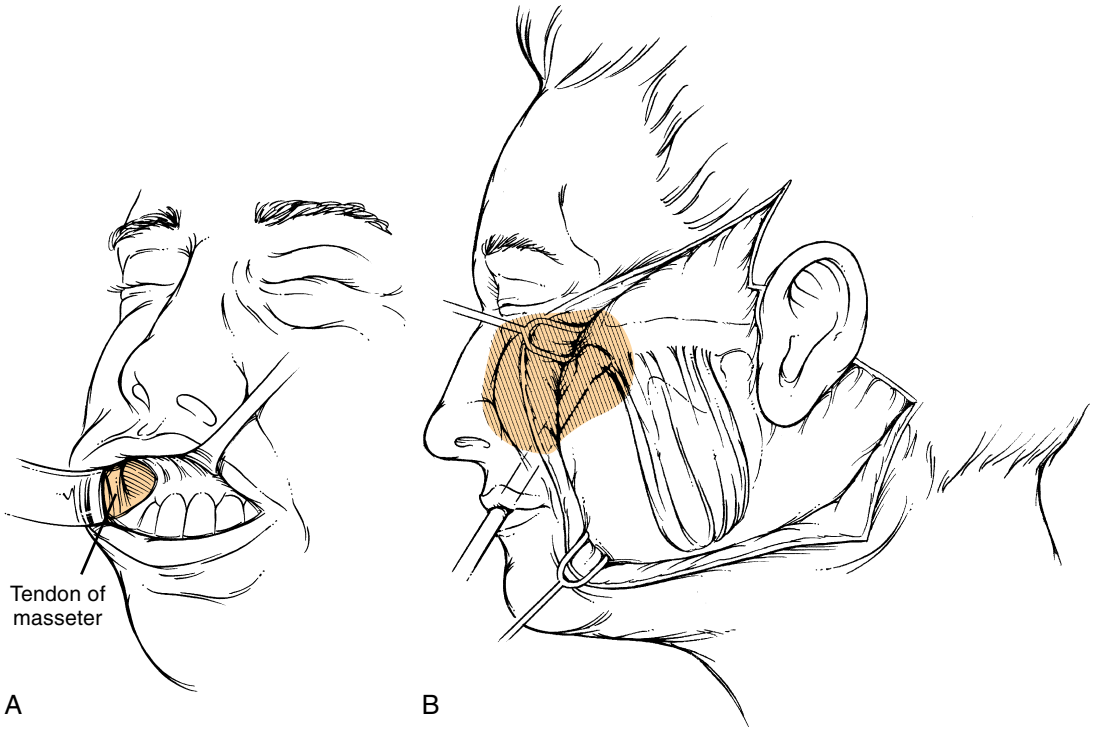

Figure 28-11. **A,** Through an upper gingival buccal incision, the periosteum is elevated from the face of the maxilla and lower portion of the zygoma. **B,** From the zygoma, the subperiosteal dissection is carried inferiorly over the anterior masseter tendon. *(Courtesy of Archives of Otolaryngology. Hamra ST. The deep-plane rhytidectomy.* Plast Reconstr Surg. *1990;86:53.)*

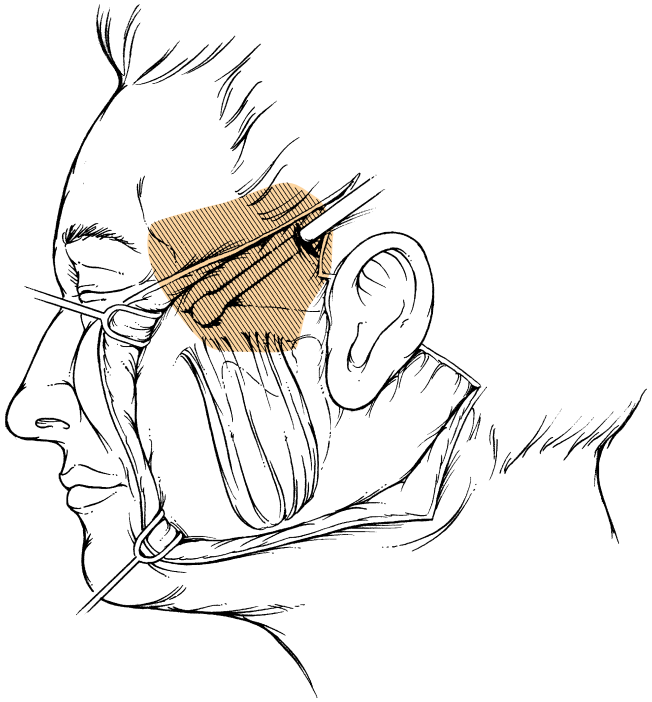

Figure 28-12. Subperiosteal dissection of the superior aspect of the zygoma is accomplished from above through a temporal incision.

Figure 28-13. The mid-face soft tissues are suspended with sutures placed between the periosteum of the zygoma and the temporalis fascia.

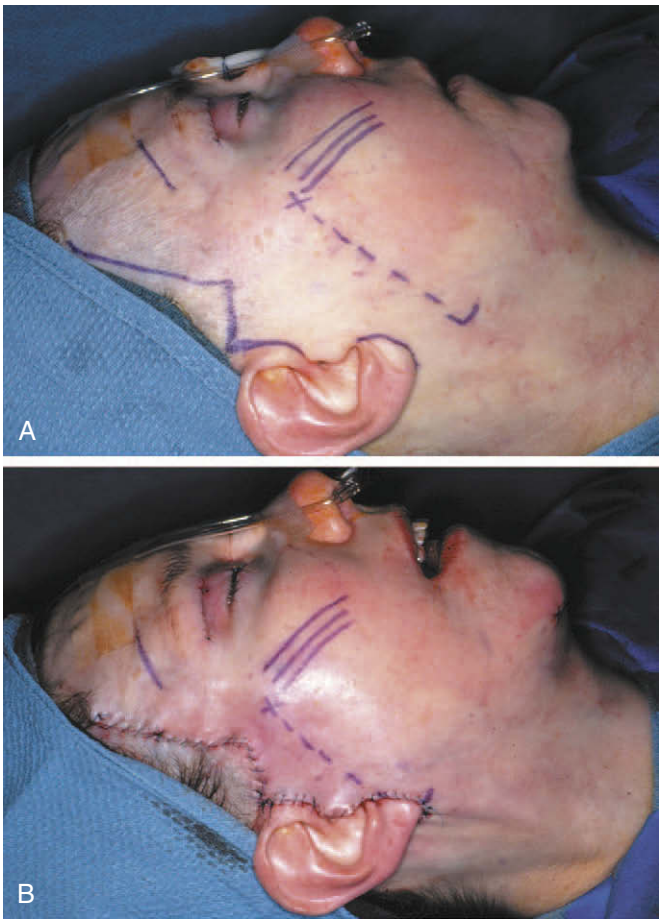

Figure 28-14. **A,** Before suspension of the mid-face. **B,** After subperiosteal dissection of the mid-face and suspension to the temporalis fascia. Note the marked upward movement of the mid-facial soft tissues, with exposure of upper incisors.

After the posterior neck dissection is completed, an incision is made through the SMAS from the malar eminence to the angle of the mandible (Fig. 28-18). The upper third of the incision is undermined 2 cm to allow a cuff of SMAS for suturing. The lower two thirds of the incision is undermined in the subplatysmal plane. The dissection is carried forward beneath the jowl, remaining above the inferior border of the mandible and deep to the platysma. This is accomplished with ease, primarily by blunt dissection, because the SMAS-platysma is separated in this region from the masseter muscle and buccal fat by a layer of loose areolar tissue between the platysma and the masseter fascia (Fig. 28-19). The dissection must remain superficial to the masseteric fascia, because branches of the facial nerve lie deep to the fascia. Before advancement of the SMAS, the cervical skin flap is liposculptured by removing excessive subcutaneous fat from the cervical skin flap (Fig. 28-20). The SMAS flap is suspended posterosuperiorly after suspension of the mid-face if a subperiosteal mid-facelift has been performed. Sutures are placed through the ventral aspect of the elevated platysma of the inferior cheek and secured to the posterior incised border of the SMAS. This causes marked posterosuperior advancement of the SMAS flap, the advance border of which overlaps the parotid gland and is secured to the preauricular parotid fascia with a second series of suspension sutures (Fig. 28-21). The SMAS flap is often advanced to within 2 cm of the earlobe and, on occasion, may require excision and discarding of redundant SMAS and platysmal muscle. The advancement produces a short skin flap in this area.

Skin Trimming

On completion of skin undermining and suspension of the SMAS and the mid-face (if mid-facelifting has been performed), final hemostasis is performed. There has been recent interest in the use of fibrin sealants in facelifting to reduce postoperative bleeding. Applications of these substances assist with hemostasis and cause rapid adherence of the skin flap to the underlying platysma and SMAS. Their use may also enable the surgeon to trim a greater amount of facial skin without increasing wound closure tension. Disadvantages of fibrin sealants are cost of the

Figure 28-15. Preoperative **(A, C, E)** and 1-year postoperative **(B, D, F)** views after upper and lower blepharoplasty and rhytidectomy with subperiosteal mid-facelift. The patient had a left direct brow lift and dermabrasion of the perioral area. Preoperative views show ptosis of the mid-face with skeletonization of the inferior bony orbital rim. The junction between the cheek and lower eyelid appears displaced inferiorly. Postoperative views show elevation of the cheek fat of the mid-face and a youthful repositioning of eyelid and cheek tissues. The vertical height of the lower eyelid (i.e., from lid margin to lid-cheek junction) has been shortened as a result of mid-facelifting.

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Figure 28-15, cont'd.

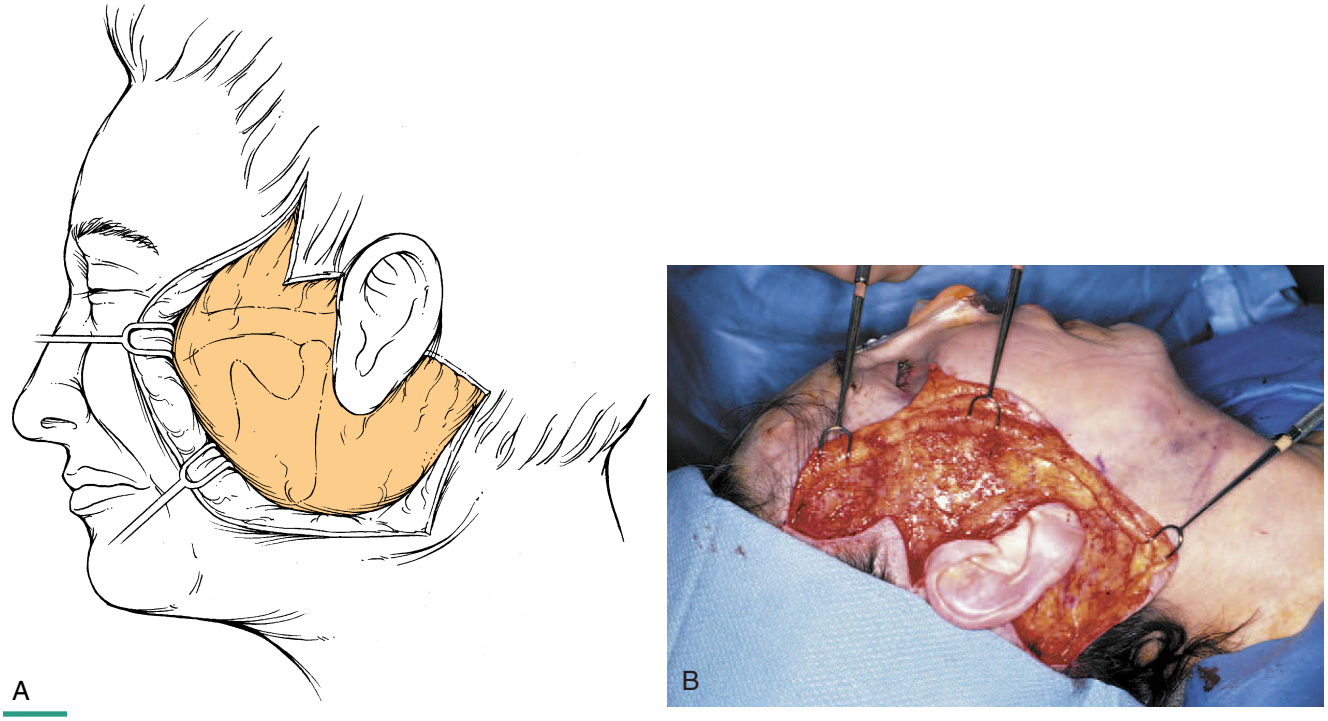

Figure 28-16. Typical extent of skin undermining in subcutaneous tissue plane. Dissection in this plane extends from the auricle to 2 cm anterior to a line drawn from the malar eminence to the angle of mandible.

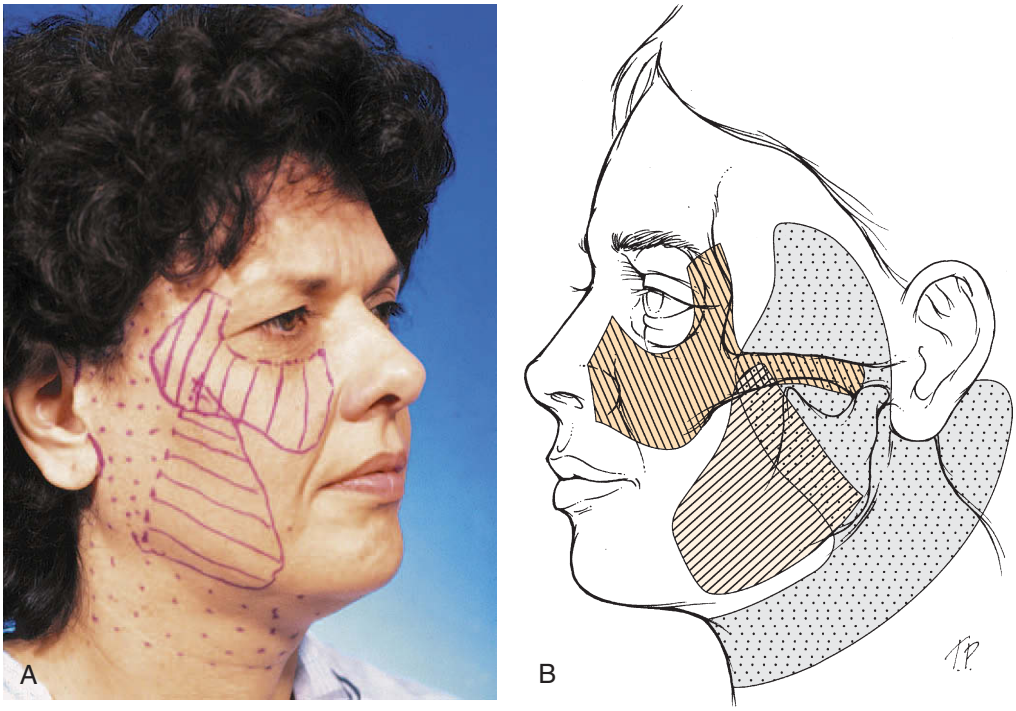

Figure 28-17. **A,** Topographic display of the limits of dissection planes used by the author. Stippled area represents subcutaneous or preplatysmal dissection. Vertical lines represent subperiosteal dissection. Horizontal lines represent sub-superficial musculoaponeurotic system (sub-SMAS) dissection. **B,** Diagram showing limits of subperiosteal and sub-SMAS dissection.

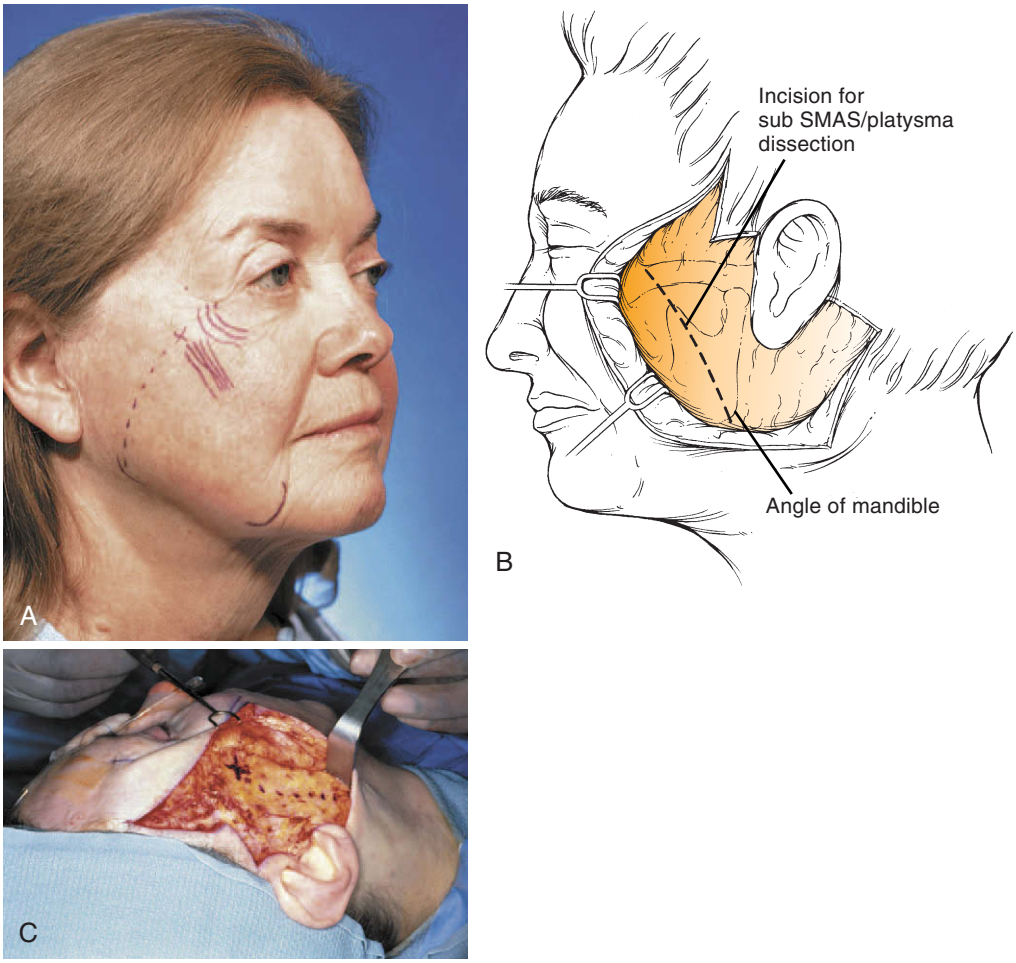

Figure 28-18. **A** and **B,** Dotted line indicates incision line through superficial musculoaponeurotic system (SMAS). **C,** Intraoperative view of SMAS incision. *(Courtesy of Archives of Otolaryngology. Hamra ST. The deep-plane rhytidectomy.* Plast Reconstr Surg. *1990;86:53.)*

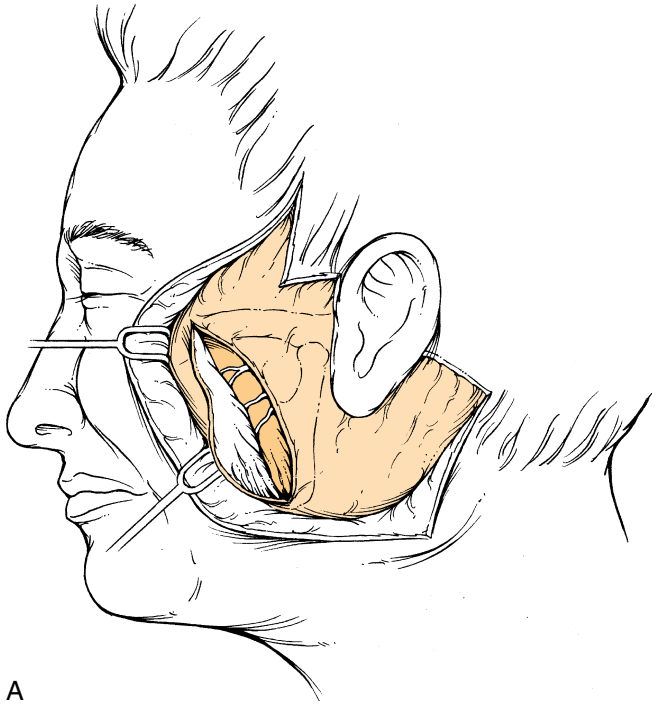

Figure 28-19. **A,** Subplatysmal dissection is carried forward beneath the jowl, remaining above the inferior border of the mandible. **B,** The dissection plane is in the avascular loose areolar tissue plane between the platysma and the mesenteric fascia.

material and problems with seroma formation if the sealant is not applied evenly, carefully, and rapidly. The use of fibrin sealants in an elective surgical procedure raises an ethical consideration, because the material is derived from pooled blood products. Fibrinogen, thrombin, and factor VIII, all present in fibrin sealants, are isolated from human plasma. Therefore, there is a theoretical risk of transmission of hepatitis B and C viruses, human immunodeficiency virus, and human T-cell leukemia/lymphoma virus type I or II from human blood products.[25]

Skin trimming is accomplished in two steps. The first is placement of two key tension sutures, one immediately above the auricle in the scalp and the other midway along the horizontal segment of the posterior scalp incision. This is accomplished by placing the skin flap under traction while it is overlapping the auricle. The flap is split to the point where the flap meets the temporal scalp incision at the level of the superior auricular sulcus, and one of the two key tension sutures is placed. Traction is then placed on the postauricular skin flap, and the flap is split to the point where it meets the posterior scalp incision (Fig. 28-22). The second tension suture is placed at this point. Traction on the skin flap and securing the position of the flap with the key sutures determines the degree of lifting. Use of SMAS flaps as described earlier in this chapter assists with the posterosuperior advancement of the skin flap and reduces the need for as much tension on the key sutures for the same degree of skin advancement compared with not using such techniques (Fig. 28-23).[26]

The temporal scalp flap is trimmed so there is no wound closure tension. To prevent upward migration of the temporal tuft of hair, a horizontal sideburn incision beneath the tuft is usually performed to facilitate excision of vertical lifted skin excess (see Fig. 28-23). The preauricular skin is then trimmed so there is no wound closure tension. When trimming the skin beneath the earlobe, it is important to leave a slight degree of redundancy of the skin flap so it will lift the lobe upward slightly. This will ensure that as the scar contracts in this area and drifts inferiorly, the earlobe will not be pulled down, resulting in loss of the sulcus between the lobe and cheek skin. This technique eliminates the risk of developing a satyr's ear deformity. The postauricular skin flap is pivoted slightly anteriorly on the earlobe as necessary to realign the postauricular hairline. The postauricular flap is then trimmed conservatively to minimize wound closure tension. It is especially important to have no wound closure tension in the area of the superior apex of the mastoid skin incision because of the thin skin in this area. Hypertrophic scars occur most commonly at this point.

Drains may be inserted through separate incisions in the postauricular scalp and tunneled to the area of the neck dissection where they are positioned in the dependent portion of the wound. Wound closure is accomplished by approximating the subcutaneous tissues of the scalp incisions with absorbable suture and staples for the skin. The skin incisions anterior and posterior to the ear do not usually require subcutaneous sutures. A simple running cutaneous suture is all that is required. A compression dressing of the surgeon's choice is then used.

The patient is seen the day after surgery. Dressings and drains (if used) are removed. Careful examination of the skin flap is performed to evaluate skin vascularity. All areas are inspected for the presence of a hematoma. A light compression dressing is reapplied, and the patient is asked to return the next day for a second examination. On the second postoperative day, all dressings are removed, and the patient is allowed to shower and shampoo the hair. The patient is seen on the fifth postoperative day for suture removal and the seventh postoperative day for removal of scalp staples. If all wounds are healing well, patients return 2 and 4 weeks after surgery for examination of their wounds. Photographs are performed 3 months postoperatively. By this time, most of the facial edema from mid-facelifting has subsided (Fig. 28-24).

Complications

All surgical procedures are associated with potential complications. The goal is to minimize the frequency and severity of complications. Modern techniques such as sub-SMAS rhytidectomies and mid-facelifting are associated with certain complications rarely observed with subcutaneous rhytidectomies.

Hematoma

The most common perioperative complication of rhytidectomy is hematoma, which occurs in 1% to 10% of patients and may be a major or minor collection of blood beneath the skin flap. Major and expanding hematomas usually occur within 24 hours of surgery and are heralded by increasing facial edema, bruising, and pain. Hypertension predisposes to this risk, and hematomas occur more frequently in men. Other factors related to hematoma are recent ingestion of aspirin, nonsteroidal anti-inflammatory drugs, high doses of vitamin E, and certain herbal health supplements. Major hematomas require immediate wound exploration, evacuation of blood, and control of hemorrhaging. If not detected and treated within a few hours, there is risk of skin flap necrosis and subsequent scarring of the periauricular skin (Fig. 28-25). Minor hematomas of 2 to 10 mL of blood may not be detected until the first dressing change. These occur most frequently in the infra-auricular and postauricular region of the neck and can be evacuated in the office. Inserting a sterile slender suction device through the postauricular incision line enables complete evacuation of the blood. A compression dressing is applied to the neck, and the area is examined again in 24 hours. Typically, a small residual collection of blood is

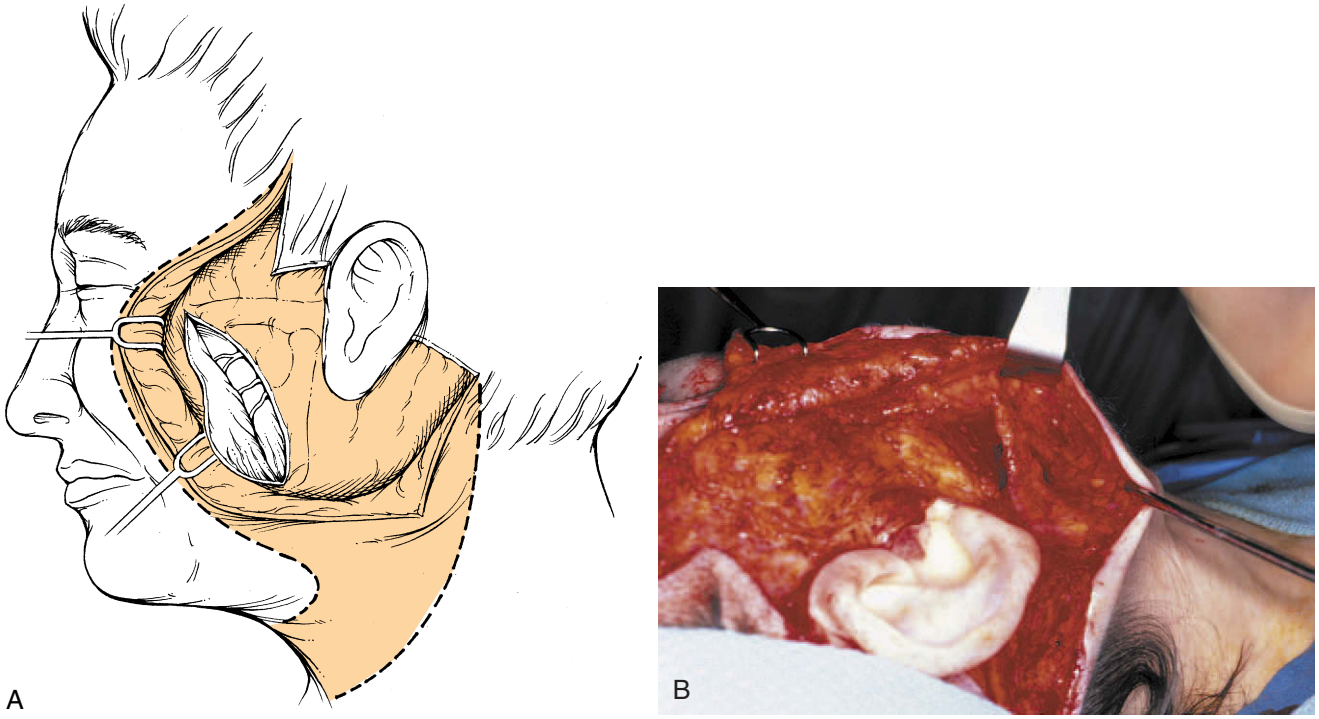

Figure 28-20. **A** and **B,** After dissection and before suspension of the superficial musculoaponeurotic system flap. The cervical skin flap is trimmed of any excessive subcutaneous fat. This may be accomplished with scissors or with a liposculpture cannula. **B,** Intraoperative view showing separate dissection planes for the cervical skin flap and the platysma.

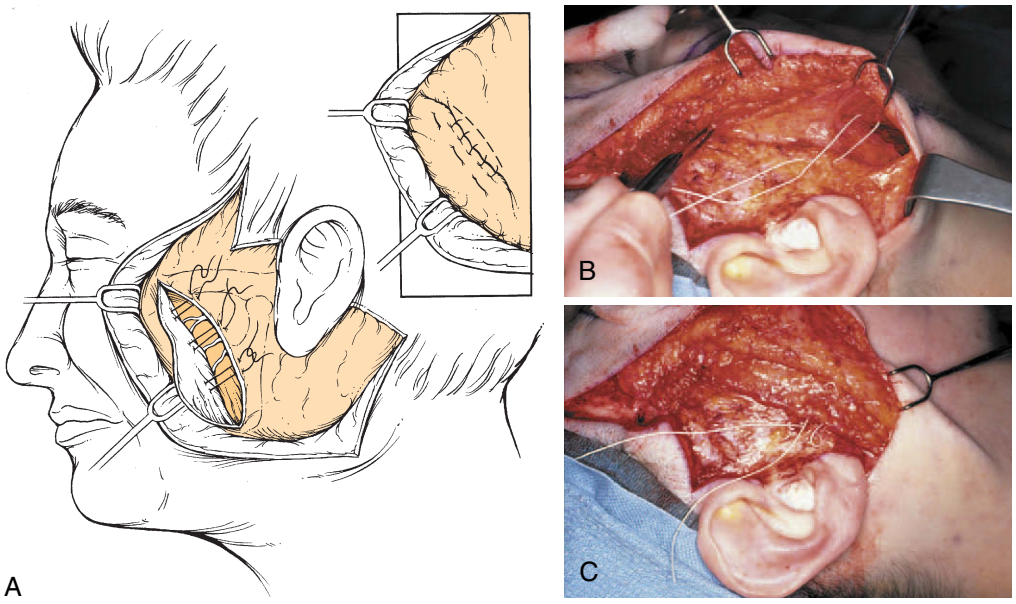

Figure 28-21. **A** and **B,** Sutures are placed through the ventral aspect of the elevated platysma of the inferior cheek and secured to the posterior incised border of the superficial musculoaponeurotic system (SMAS). **C,** The advanced border of the SMAS flap overlaps the parotid and is secured to the fascia with a second series of suspension sutures. *(Courtesy of Archives of Otolaryngology. Hamra ST. The deep-plane rhytidectomy.* Plast Reconstr Surg. *1990;86:53.)*

present and can be removed by percutaneous aspiration with a syringe attached to an 18-gauge needle. Seromas beneath the facial or cervical skin are usually apparent 5 to 7 days postoperatively and can similarly be treated with percutaneous aspiration.

Skin Flap Necrosis

Skin flap necrosis is associated with untreated major hematomas. It may also occur from ischemia related to the use of tobacco, certain systemic medical conditions, injury to the subdermal plexus during flap dissection, or closing the facelift incisions under excessive wound closure tension. Use of tobacco products increases the risk of flap necrosis by a factor of 12. To see any benefit of cessation of tobacco use, the patient must stop all tobacco products (including nicotine skin patches) for a minimum of 2 weeks before and after surgery.

Conservative treatment of a skin slough is recommended (Fig. 28-26). Typically, epithelialization of the affected area will occur. If

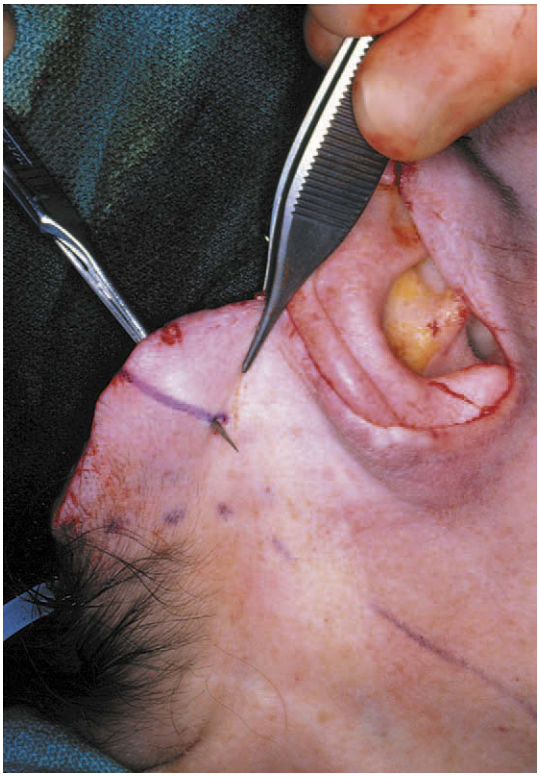

Figure 28-22. Dart incision is made through posterior skin flap to place key scalp suspension suture.

flap necrosis is full thickness, subsequent healing may result in a hypertrophic scar. Partial thickness necrosis may heal with little or no visible sign of scarring or with a hypopigmented scar, depending on the depth of tissue necrosis (Fig. 28-27).

Nerve Injury

When performing a rhytidectomy, the most common nerve injury is to the greater auricular sensory nerve and occurs in 1% to 7% of rhytidectomies. Damage to this nerve results in loss of sensation over the inferior half of the ear. Injury to the nerve can be prevented by a superficial dissection of the skin over the sternocleidomastoid muscle. The neck skin is firmly adherent to the muscle below the earlobe, and hydrodissection by injecting local anesthetic beneath the skin along the vertical axis of the muscle helps facilitate dissection of the skin flap. If the nerve is inadvertently injured, it should be repaired with 10-0 nylon perineural sutures placed under magnification. Like the greater auricular nerve, the lesser occipital nerve and the spinal accessory nerve may be injured during elevation of the postauricular skin flap. These nerves are positioned considerably deeper than the greater auricular nerve, and injury to these structures is rare.

Injuries of motor nerves during rhytidectomy may result in complete paralysis of a facial nerve branch or mild paresis. The incidence of motor nerve injury ranges from 0.3% to 2.6%.[27] The most commonly affected nerves are the temporal and marginal mandibular branches of the facial nerve. The temporal branch is particularly prone to injury when combining forehead and facelifting (Fig. 28-28). Above the zygomatic arch, the nerve travels in the temporoparietal fascia. To avoid injury when dissecting in the temple and lateral orbital areas, the plane of dissection for the lateral portion of the forehead lift is in the subgaleal plane below the temporoparietal fascia. The facelift dissection anterior to the hairline in the temple is in the superficial subcutaneous

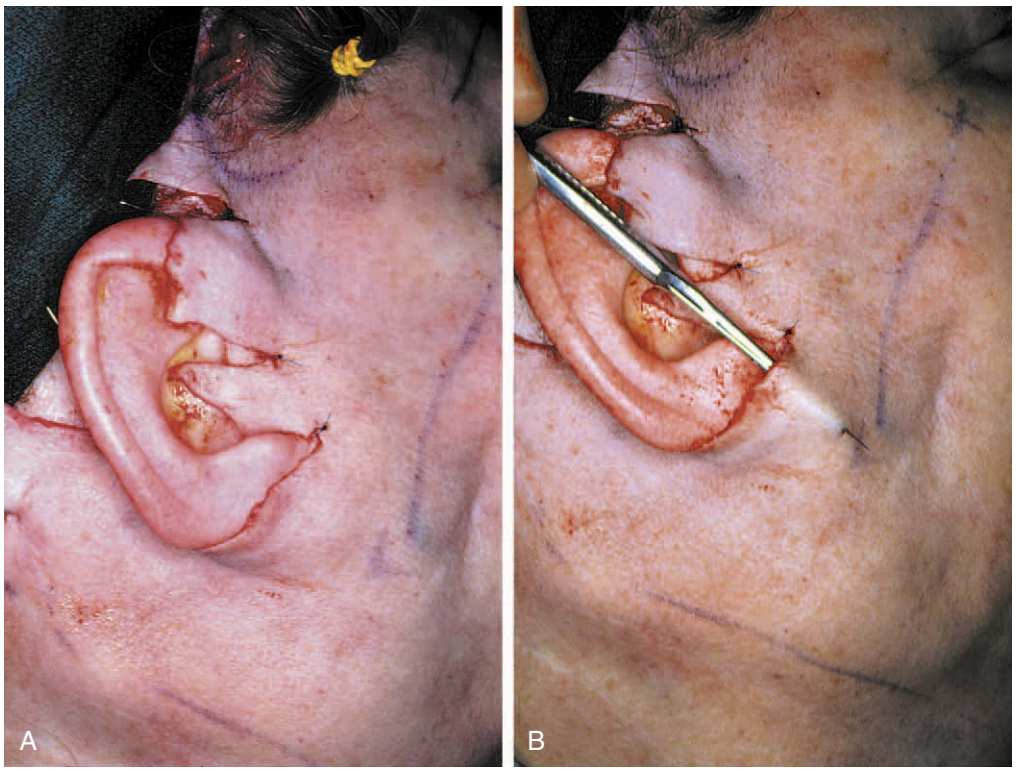

Figure 28-23. **A,** Key suspension sutures have been placed superior and posterior to the auricle. Dart incisions are made through the preauricular flap immediately above and below the level of the tragus, and sutures are placed. **B** and **C,** Dart incision is made to liberate earlobe. **D,** Skin flap is trimmed so that there is minimal wound closure tension. Sideburn incision has been made to spare excision of temporal hair tuft.

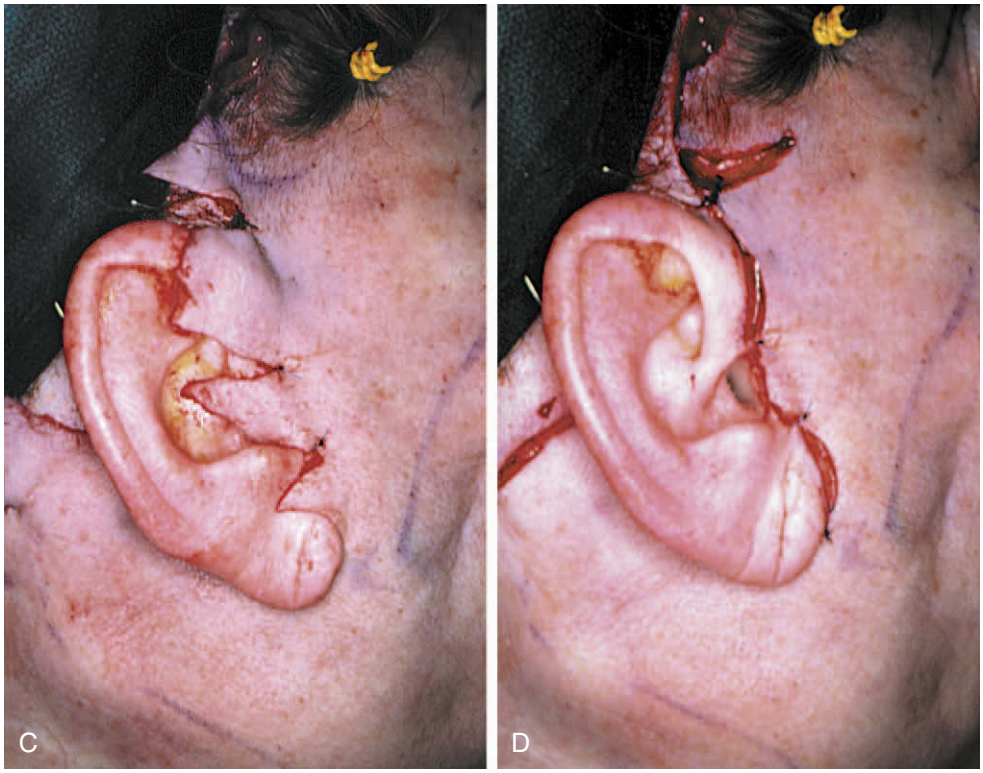

Figure 28-23, cont'd.

Figure 28-24. Preoperative **(A, C, E)** and 6-months postoperative **(B, D, F)** views of patient undergoing endoscopic forehead lift, lower lid blepharoplasty, and rhytidectomy with subperiosteal mid-facelift.

Continued

Figure 28-24, cont'd.

Figure 28-25. Periauricular scarring subsequent to skin necrosis resulting from hematoma that was not detected until 2 days after surgery.

tissue plane. Therefore, there are two planes of dissection overlapping in the lateral orbital and temporal region.

Dissection beneath the lateral border of the platysma below the angle of the mandible is at risk for causing injury to the marginal mandibular nerve, because the nerve is located immediately beneath the muscle in this region (Fig. 28-29). Surgeons who develop a posterior platysmal flap in the superior aspect of the neck to correct platysmal laxity must take care to remain just ventral to the muscle during dissection.

The buccal branch of the facial nerve may be injured when performing mid-facelifting (Fig. 28-30). This is most likely to occur with subperiosteal dissection rather than supra-SMAS dissection of the midface. Release of the periosteum from the inferior border of the zygoma necessitates dissection over the masseter muscle tendon in the vicinity of the buccal nerve.

Mid-facelifting also increases the risks of injury to the zygomatic branch of the facial nerve. The zygomaticofacial and infraorbital sensory nerves are also at risk for injury during mid-facelifting (see discussion on mid-facelifting). Fortunately, injury to motor nerves during rhytidectomy does not usually lead to permanent paresis in most cases. When injury does occur, in most cases it probably represents neuropraxia from traction, heat injury from electrocautery, or needle injury.

Scars

Hypertrophic scars occasionally occur in the retroauricular incision. This is most often observed in that portion of the incision extending from the postauricular sulcus to the scalp. The skin is thin in this, the apex of the mastoid skin, and even moderate wound closure tension may precipitate scar thickening. Fortunately, if scar hypertrophy occurs, it usually responds rapidly to serial intralesional injections of triamcinolone in a concentration of 10 mg/mL. Hypertrophic scars occurring in the preauricular and temple incisions are exceedingly rare. Wound closure tension and subsequent scar contracture of the incisions around the earlobe may produce a variety of deformities, including displacement of the earlobe, obliteration of the sulcus between earlobe and cheek, and downward traction causing a satyr ear. These problems are best avoided by carefully trimming the skin flap beneath the earlobe, so there remains a slight redundancy of flap skin. This redundancy of skin provides a safety against scar contracture and subsequent down-

Figure 28-26. **A,** Postauricular skin slough after rhytidectomy. **B,** Conservative treatment led to healing with modest scar formation.

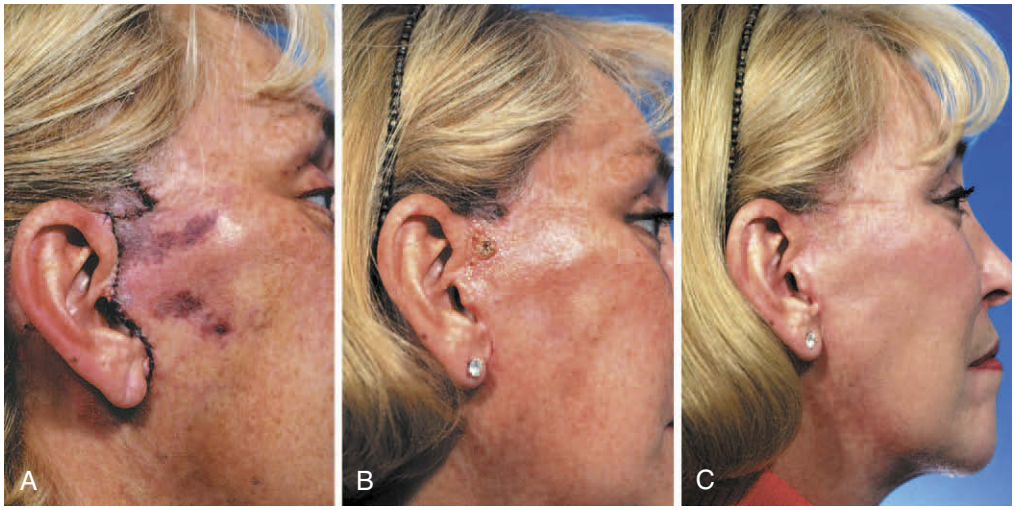

Figure 28-27. Partial-thickness necrosis of skin after rhytidectomy. Conservative treatment led to complete healing without hypertrophic scars or hypopigmentation. **A,** Two days postoperative. **B,** Three weeks postoperative. **C,** Six weeks postoperative.

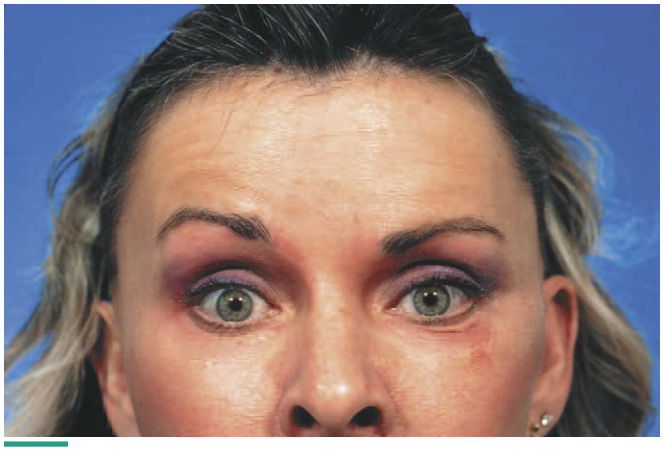

Figure 28-28. Paralysis of left temporal branch of facial nerve after endoscopic forehead lift and mid-facelifting.

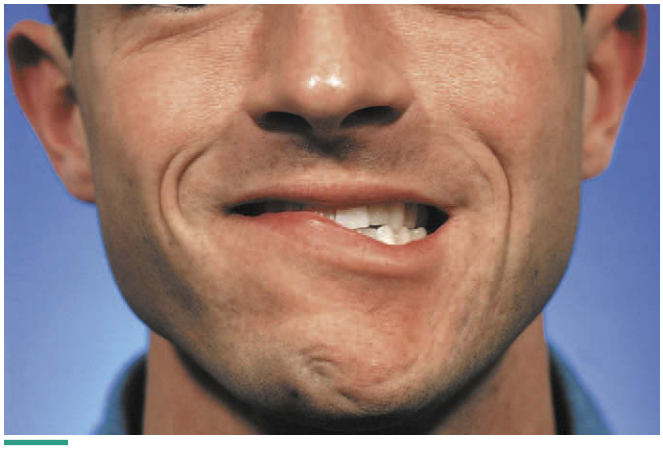

Figure 28-29. Paralysis of right mandibular branch of facial nerve.

ward migration of the earlobe. Mild traction deformities of the earlobe can be corrected as soon as 6 months after facelift by direct excision of the scar, creating a rounded lobule, and closing the triangular-shaped defect primarily. This in essence represents a V-Y advancement of the earlobe. For more severe deformities, repair should be delayed for 1 year from the time of the facelift and requires wide undermining of the inferior periauricular cheek skin, so that the area of the excised scar can be moved behind the ear and closed in the postauricular sulcus by advancement of the infra-auricular skin.

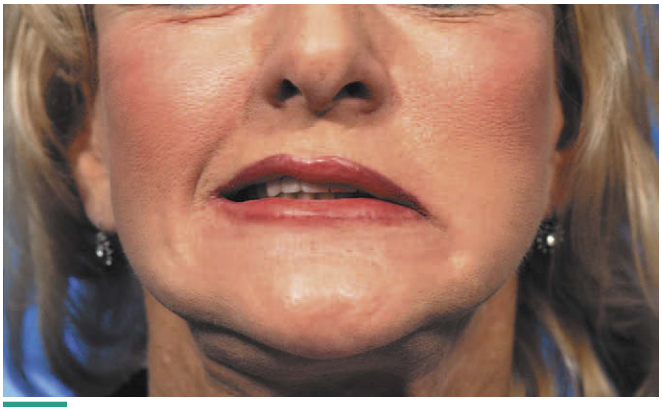

Figure 28-30. Paralysis of left buccal branch of facial nerve after rhytidectomy.

Hair Loss

Hair loss is more common adjacent to temple incisions than postauricular scalp incisions. This may occur even when the dissection is performed well below the level of the hair follicles and is known as *telogen effluvium.* In such circumstances, hair regrowth will occur within 6 months. Electrocautery in the vicinity of the hair follicles and excessive wound closure tension may cause permanent hair loss. This may require excision of the scalp devoid of hair. Micrografting of the area of alopecia is an alternative.

Distortion of the natural hairline may occur if the postauricular flap is not pivoted anteriorly sufficiently to realign the hairline. Stair stepping of the postauricular hairline is more difficult to prevent when there is marked advancement of the cervical skin during rhytidectomy. The temporal hair tuft may be elevated to an unnatural height when trimming the facial flap in the temple (Fig. 28-31). This deformity can be completely prevented by the use of a horizontal sideburn incision beneath the tuft to facilitate trimming of the vertically lifted facial skin.

Parotid Injury

Injury to the parotid gland parenchyma is likely to occur more frequently than in the past because of the popularity of SMAS flaps and

Figure 28-31. Unnatural appearance of temporal hair tuft from excessive elevation after rhytidectomy.

sub-SMAS dissections. Injury can occur either to the parenchyma or the ductal system and may result in a parotid pseudocyst or fistula formation.[28] Salivary collections beneath the facelift flap may delay the healing process by preventing the facial skin from adhering to the underlying tissue. This may prevent sealing of the injured glandular parenchyma and may eventually lead to the development of a pseudocyst. When dissecting beneath the SMAS over the parotid gland, it is important to recognize that parotid tissue has a gray or pink color and should not be confused with the more yellow fat that may be in the vicinity. If parotid gland parenchyma is inadvertently injured, it should be cauterized in an attempt to seal any ductules that have been violated.[7] After SMAS dissection is completed, a secure closure of the SMAS over the area of parotid injury is performed. If a pseudocyst develops, then serial percutaneous aspirations can be performed. Large pseudocysts greater than 3 cm and persistent salivary fistulas should be treated with closed suction drainage.

Pigmentary Changes

Darker complexioned individuals may have postinflammatory hyperpigmentation of scars or of the skin flap. This may persist for many months but eventually fades. Sun exposure during the first few months postoperatively may accentuate this problem. Hypopigmentation of skin adjacent to facelift incisions may occur if there is excessive skin tension on the wound closure. Skin necrosis and electrocautery of the dermis may also cause hypopigmentation. The severest postoperative pigmentary skin changes are observed in areas that have suffered partial or full-thickness skin necrosis. Facial skin telangiectasias are frequently increased in the skin undermined during dissection of the facelift flap. Patients prone to this problem should be advised of the possibility of accentuating telangiectasias.

Contour Deformities

Nodules and skin puckering can result from organization of localized hematomas not aspirated postoperatively. Most of these deformities will resolve with time, but resolution is hastened by use of warm compresses, massage, and subcutaneous injections of triamcinolone. A more diffuse but permanent depression or irregularity may result from suction-assisted liposculpturing. If severe, contour irregularities may require autogenous fat grafting. A major contour deformity can occur in the submentum if excessive subcutaneous fat or subplatysmal fat is removed. This is particularly accentuated if the platysmal muscles are not sutured together in the midline. In such instances, a hollow depression occurs above the hyoid in the midline of the upper neck and is referred as a *cobra deformity.*

Depression

Short-term situational depression occurs in approximately half of women undergoing rhytidectomy.[29] This develops within the first month postoperatively and is related to the distorted unnatural appearance of the face from edema and bruising. Patients should be given emotional support by reassuring them that depression is common after surgery and that they will improve as facial architecture returns to normal. Occasionally, a short course of antidepressant medication may be indicated.

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For complete list of references log onto www.expertconsult.com.

CHAPTER TWENTY-NINE

Rejuvenation of the Aging Brow and Forehead

Paul S. Nassif

Key Points

- Precise incisional markings are not necessary.
- Use high-volume, low-concentration local anesthetic.
- Avoid excess cautery, scalp excision, subcutaneous sutures, and rigid fixation of the scalp.
- Periosteal release is a given, but temporal orbicularis release is essential.
- Bony fixation is usually not necessary in most cases if an extensive release is performed.
- Avoid excess glabellar muscle manipulation.
- Deep temporal fixation only (with absorbable sutures) is all that is needed to maintain brow height.
- Overcorrect brow height.
- Botox is a excellent adjunct in the preoperative or postoperative period.
- Be aware of but do not fear neurologic deficit. Permanent motor damage is rare. Sensory deficit is common and usually temporary.
- Postoperative dressings can increase periorbital swelling and ecchymosis.
- Be careful when adding blepharoplasty.

Proportions of the Aesthetic Brow and Forehead

The forehead, from the eyebrows to the hairline, makes up the upper third of the face. The aesthetically favored forehead produces a gentle convexity on profile. Other shapes include sloping, flat, and protruding. The eyebrows generally follow a smooth, gently curving arc that extends from the lateral eyebrow around the nasion and down the lateral nasal sidewall (Fig. 29-1A). In women, the eyebrow should lie slightly above the supraorbital rim and follow a gently curving arc (Fig. 29-2). The eyebrow begins at a line drawn from the alar-facial groove through the medial canthus and ends at a line drawn from the alar-facial groove through the lateral canthus.[1] In women, the highest point of the eyebrow arc is at a line drawn tangential to the lateral limbus. The medial and lateral ends of the eyebrow should lie in a horizontal line. The medial end should have a clublike configuration that gradually tapers laterally. In men, the brow usually lies at the level of the supraorbital rim (see Fig. 29-1B).

The Aging Brow and Forehead

Although different regions of the face age at variable rates and are influenced primarily by genetic factors, the upper third of the face ages in its own unique fashion (Fig. 29-3).[2] As skin elasticity declines, the forehead, temple, and glabellar skin descend. The brow, especially in its temporal aspect, descends to or below the supraorbital rim with the effects of gravity causing temporal hooding. If brow ptosis is severe, a visual deficit may develop in the superior and temporal quadrant. The supratarsal crease disappears by overhanging ptotic upper eyelid skin. Crow's feet (rhytids at the lateral canthus) appear secondary to gravity and repeated contraction of the orbicularis oculi muscle. Deep forehead creases appear due to the repetitive actions of the primary brow elevator, the frontalis muscle, in an effort to elevate the heavy, ptotic brow. Vertical, oblique, and horizontal rhytids appear in the glabella and nasion from contractions of the brow depressors—the corrugator, procerus, and depressor supercilii muscles.

Patient Selection

Psychological Considerations

As with any facial plastic surgery procedure, careful patient selection is paramount. Realistic expectations and proper motivations of the patient are extremely important in achieving a successful outcome, a satisfied patient, and a pleased facial plastic surgeon. If the surgeon despite a visually pleasing surgical result does not perform proper patient screening, patient dissatisfaction may be encountered. Educating patients about the different surgical procedures and goals requires excellent physician-patient communication and guidance. Computer imaging of the proposed brow elevation may enhance the communication of surgical goals because few patients are aware that brow ptosis is responsible for their orbital changes. Often, patients think and are told that droopy eyelid skin in the presence of a ptotic brow is the cause of their "saddened" look. If upper blepharoplasty is performed in this situation, the eyebrow-lid margin is potentially narrowed, obliterating adequate delineation of the supratarsal anatomy by sacrificing excessive upper eyelid skin.[3] Following the education process, candidates for aging brow surgery must give informed consent after discussing possible adverse outcomes, complications, and risks of the selected surgical procedure.

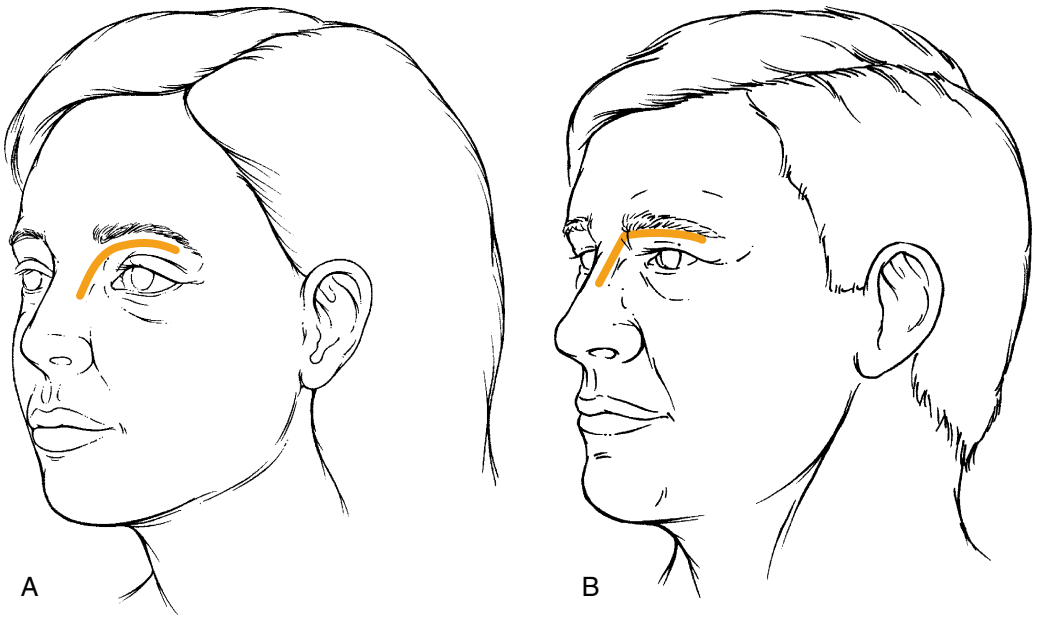

Figure 29-1. **A**, Smooth, gently curving line extending from eyebrow to nose. **B**, Sharp angle between eyebrow and nose. *(Adapted from Nassif PS, Kokoska MS. Aesthetic facial analysis.* Facial Plast Surg Clin North Am *1999;7:1. © 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

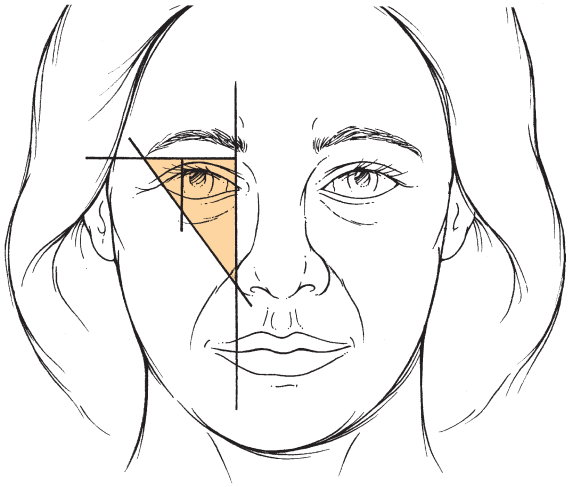

Figure 29-2. The ideal eyebrow. *(Adapted from Becker FF, Johnson CM Jr. Surgical treatment of the upper third of the aging face. In: Cummings CW, Frederickson JM, Harker LA, et al, eds.* Otolaryngology–Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:661, with permission.)*

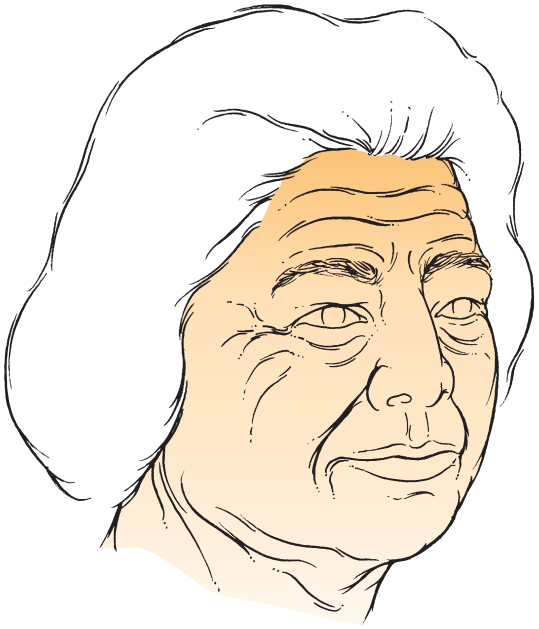

Figure 29-3. Characteristics of the aging brow, temple, eyelids, and face. Although environmental influences may worsen or hasten aging changes, each person's genetic disposition plays the predominant role in the aging process. *(Adapted from Tardy ME, Alex J, Hendrick D. Rejuvenation of the aging brow and forehead. In: Putterman AM, Warren LA, ed.* Cosmetic Oculoplastic Surgery: Eyelid, Forehead, and Facial Techniques. *3rd ed. Philadelphia: WB Saunders; 1999:269; with permission.)*

Anatomic Considerations

Analysis of the upper third of the face, from the eyebrows to the hairline, should begin with the assessment of interpersonal factors that may significantly affect the patient's interpretation of successful surgical intervention and, as such, must be carefully examined. Age, gender, race, body habitus, and personality are the main interpersonal components that must be considered when assessing the eyebrow complex.[4]

When determining which brow-lifting procedure should be used, specific anatomic criteria should be evaluated when examining the patient. The patient should be examined in a sitting position and in facial repose. Manually elevating the brow reveals the favorable effect of brow elevation. Individuals with ptotic eyebrows often involuntarily attempt to elevate the brow with frontalis muscle contraction. To eliminate "pseudoelevation" of the brow, patients close their eyes and then slowly open them after allowing the frontalis muscle to relax. The true position of the eyebrow can then be evaluated in repose by the surgeon. Additionally, the eyebrow position can be examined with the patient's eyes closed. The following are anatomic and physiologic factors to evaluate when considering a patient for aging forehead rejuvenative surgery:

- Location of frontal and temporal hairline
- Quality of hair: alopecia, thinning, or abundant
- Forehead height relative to facial proportions

- Severity of forehead, temporal, and lateral canthal (crow's feet) rhytids
- Eyebrow aesthetics: shape, symmetry, quality, texture, position, and mobility
- Presence of prominent supraorbital ridge or hollow orbit
- Degree of dermatochalasis: excess skin, tone, lateral canthal hooding, and presence of medial fat pad
- Previous eyelid or eyebrow surgery and scars
- Presence of lagophthalmos (inability to close the upper eyelid completely)
- Scalp mobility
- Lateral canthus position
- Skin elasticity and texture
- History of ocular disease
- Previous LASIK surgery or dry eyes

Surgical Goals

The goals associated with rejuvenation surgery of the brow and upper third of the face include the following[5]:

- Elevation of ptotic eyebrows
- Reduction of lateral hooding and redundant upper eyelid skin
- Elevation of lateral canthus (if needed)
- Reduction of glabellar and corrugator rhytids
- Reduction of transverse forehead rhytids
- Reduction of lateral canthal "crow's feet" rhytids
- Correction of eyebrow asymmetry

In general, the selected brow elevation procedure should be performed before upper blepharoplasty so that the facial plastic surgeon can judge the precise amount of upper eyelid skin to be removed. This helps prevent excessive elevation of the brow-lid complex with the potential for causing lagophthalmos. In some cases, the need for upper blepharoplasty may be eliminated after brow-lifting procedures.

Overall, selection of the specific brow procedure will be determined by integrating the psychological and anatomic considerations together with the proposed surgical goals.

Surgical Techniques

Traditional methods of forehead and brow rejuvenation, such as coronal, pretrichal, and direct brow lifts have provided facial plastic surgeons with effective brow elevation for many years. In the past decade, the endoscopic forehead and brow lift has rapidly become accepted as part of the surgical armamentarium and is frequently the technique of choice.[6-8] The indications and contraindications for each forehead and brow-lifting procedure are described in Table 29-1.[5]

Coronal Forehead Lift

For total forehead and brow elevation with excellent longevity, the coronal lift should be considered. The coronal incision is posterior to the frontal and temporal hairline, generally following the shape of the hairline, and extends from the superior helical of one ear to the other ear. The subgaleal plane is used for the dissection. Redundant and excess skin and galea is excised and the wound is closed in layers. Typically 4-0 absorbable sutures are used in the galeal layer and the skin is closed with skin staples. All aspects of the aging forehead and brow, including rhytids and ptosis, are effectively treated with this approach.

Pretrichal Forehead Lift

In patients with an elongated forehead and high hairline, the pretrichal forehead lift may be used. The pretrichal incision created in an irregularized pattern is located at the junction of the cephalic aspect of the forehead and hairline or is placed just within the hairline to further camouflage the scar. A beveled incision is used to allow hair follicle growth through the scar, adding additional camouflage. The temporal component of the incision is connected to the pretrichal incision and is posterior to the temporal hairline similar to a coronal lift. Excess skin and galea are resected from the anterior flap. Closure is beveled to accommodate the hair follicle growth through the scar. The galeal and dermal layers are closed with 4-0 absorbable suture and the skin is closed with 6-0 minimally reactive suture, which is removed in 1 week.

The advantage of the pretrichal incision is that the forehead is not elevated and the frontal hairline is preserved. The pretrichal forehead lift treats all aspects of the aging forehead and brow.

Midforehead Lift

The midforehead lift is performed rarely. The typical patient must have prominent forehead creases because the incision and ultimate scar is placed in an elongated, central transverse rhytid that crosses the midline. The subcutaneous plane is used for the dissection.

Midforehead Brow Lift

The midforehead brow lift is similar to the midforehead lift except that the forehead incisions are bilateral and do not cross the midline nor do they interconnect. Forehead and glabellar rhytids are not treated with this brow-lifting procedure. The procedure may be unilateral as in cases of hemifacial paralysis with brow ptosis on one side.

Direct Brow Lift

In certain situations, the direct brow lift may be used. The incision follows the eyebrow and is placed within and parallel to the uppermost hair follicles of the brow. Even in the best of meticulous closures, the fine scar may be visible. This procedure may also be useful in the facial paralysis patient.

Browpexy

Following the standard blepharoplasty excision of skin and orbicularis muscle, the dissection is extended superiorly toward the brow in the submuscular postorbicularis plane.[9] Dissection should extend approximately 1 to 1.5 cm above the superior orbital rim (Fig. 29-4A). One to three 4-0 permanent sutures are passed transcutaneously from the lower edge of the brow hairs into the previously dissected subbrow space approximately 1 cm apart (see Fig. 29-4B). This transcutaneous introduction of the sutures allows the surgeon to mark the position of the brow hairs while working underneath the dissected flap.

Each suture is then passed through periosteum approximately 1 to 1.5 cm above the supraorbital rim (see Fig. 29-4C). At this stage of the procedure, the height and curvature of the brow can be adjusted according to the patient's gender. Placing the more central suture slightly higher allows the characteristic arch of the female brow to be restored or preserved.

The sutures are then passed again into the subbrow muscular tissue at the level of the original, transcutaneously passed marking suture (see Fig. 29-4D). It is important to engage into firm muscular-subcutaneous tissue with each suture and avoid suturing into superficial subbrow tissue to avoid dimpling of the skin.

The original transcutaneous suture ends are then pulled through the skin under the flap. The surgeon ties the suture in a loop over a 4-0 silk knot, releasing the suture if adjustment is necessary (see Fig. 29-4E). Care is taken to avoid overtightening the suture once adequate placement is achieved, which may immobilize the brow. The upper lid blepharoplasty incision may then be closed.

Table 29-1

Indications and Contraindications for Individual Forehead and Brow-Lifting Procedures

Procedure	Indications and Advantages	Contraindications and Disadvantages
Coronal forehead lift	Treats all aspects of aging forehead and brow	Limited use in men Elevates hairline Vertically lengthens upper third of face Elongated scar Possible prolonged hypesthesia of scalp Less fine-tuning of brow position
Pretrichal forehead lift	High hairline No vertical forehead lengthening Preserves hairline Treats all aspects of aging forehead and brow	Possible visible (exposed) scar Possible prolonged hypesthesia of scalp
Midforehead lift	Prominent horizontal forehead creases Preserves hairline Improved fine-tuning of brow position Corrects brow asymmetry	Possible visible (exposed) scar Avoid in oily, thick skin
Midforehead brow lift	Prominent horizontal forehead creases Improved fine-tuning of brow position Corrects brow asymmetry	Possible visible (exposed) scar Treats brows only Avoid in oily, thick skin
Direct brow lift	Accurate brow elevation Preserves forehead/scalp sensation Patients with abundant or thick brow hair preferred Immediate scar camouflage (with hair) Corrects brow asymmetry	Possible visible (exposed) scar Treats brows only
Temporal lift	Ideal and immediate scar camouflage (with hair) Improves lateral hooding	Not useful for midforehead glabellar creases No effect on medial aspect of brow
Browpexy	Performed through upper blepharoplasty incision Indicated for mild brow ptosis	Possible prolonged eyelid edema Possible brow asymmetry Possible unsatisfactory results
Endoscopic brow lift	Less invasive with small incisions Excellent scar camouflage High hairline No vertical forehead lengthening Preserves hairline Treats most aspects of aging forehead and brow	Less fine-tuning of brow position Possible depressions in soft tissue of scalp due to screw fixation

Adapted from Tardy ME, Thomas JR, Brown R, eds. *Facial Aesthetic Surgery.* 1st ed. St Louis: Mosby; 1995:163.

Endoscopic Brow Lift

Endoscopic brow-lifting techniques have been progressively refined through experience and improvements in equipment.[6-8] In general, the temporal dissection and temporal fixation have been standardized; however, different options for forehead dissection are available. Subperiosteal dissection with release (elevation, incision, and spread) of periosteum or subgaleal dissection and release of brow depressor musculature to the supraorbital rim are both effective techniques used in endoscopic brow lifts.[10] Methods of bony fixation remain a controversial topic in that there are numerous methods. Some of these methods include absorbable and nonabsorbable screws,[6] bone tunnels with sutures, fixation to soft tissue using absorbable attachment devices such as Endotine (Coapt Systems, Inc., Palo Alto, California) and fibrin glue.[11,12] For the majority of my brow lifts, I advocate deep temporal fixation only without any bone fixation.[13] In patients with asymmetric brows, ptotic medial brows, heavy brows, or a severely ptotic brow, I use bone fixation either with the Endotine device or the Bioplate resorbable push-in tac (Bioplate, Inc., Los Angeles, California).

The technique that achieves excellent brow elevation is release of the periosteum from one inferolateral orbit to the other and release of the brow depressor musculature (corrugator, procerus, depressor supercilii, and supraorbital orbicularis oculi) (Fig. 29-5).[10,14,15] Following the brow lift, all depressor vector forces should be eliminated to promote the maintenance of the newly elevated brow position because periosteal reattachment to bone takes approximately 6 to 12 weeks.[16]

Temporal Lift

In patients with adequate medial brow position and ptotic lateral brow and lateral canthal hooding, an endoscopic temporal (temple) lift may be performed. A temporal lift is performed with the same principles and technique as the endoscopic brow lift (surgical technique is described in subsequent paragraphs) except that the medial border of

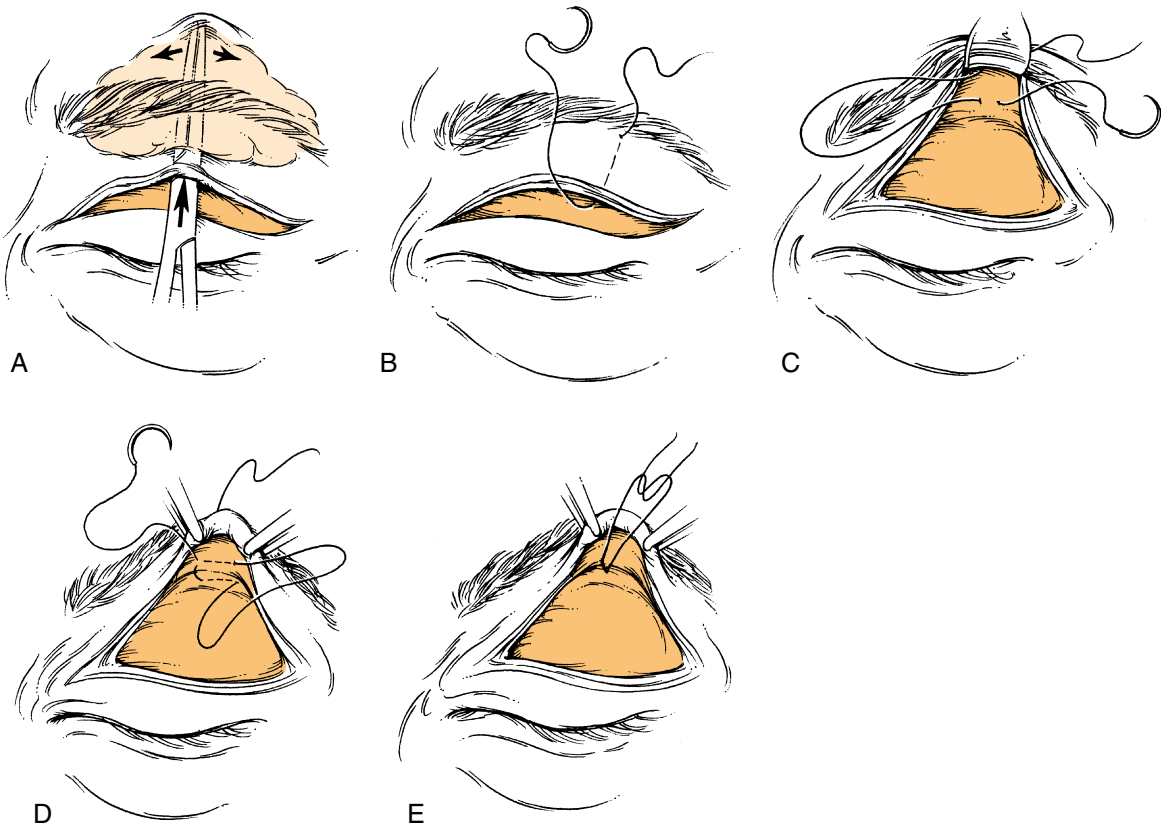

Figure 29-4. Frontal illustration of browpexy. **A**, A skin-muscle eyelid crease approach is used to expose the subbrow fat pad. The plane of dissection is in the submuscular postorbicularis fascia. **B**, A 4-0 polypropylene suture is passed transcutaneously from the lower edge of the brow hairs into the previously dissected subbrow space. **C**, The suture is sewn through the subbrow tissue and through the periosteum above the orbital rim. **D**, The suture is then passed again into the subbrow muscular tissue at the level of the original, transcutaneously passed marking suture. The transcutaneous suture is removed. **E**, The suture is tied in a loop over a 4-0 silk knot, releasing the suture if adjustment is necessary. Care is taken to avoid overtightening the suture once adequate placement is achieved, which may immobilize the brow. *(Adapted from Bowman CB, Tanenbaum M, McCord CD. Internal brow lift: browplasty and browpexy. In: Putterman AM, Warren LA, eds.* Cosmetic Oculoplastic Surgery: Eyelid, Forehead, and Facial Techniques. *3rd ed. Philadelphia: WB Saunders; 1999:117, 119-120, with permission.)*

the periosteal and brow depressor musculature release is the supraorbital neurovascular complex. The supraorbital orbicularis oculi muscle is the only brow depressor treated. The medial brow and glabellar region is not dissected, resulting in elevation of the lateral two thirds of the brow-lateral canthal complex.

Treatment of the Depressor Muscles with Botulinum Toxin

Botulinum toxin may be used synergistically with the surgical brow depressor musculature release in an effort to weaken the inferior vector forces and promote the maintenance of the newly elevated brow. Botulinum toxin is used to block the depressor function of the corrugator, procerus, depressor supercilii, and lateral supraorbital orbicularis oculi muscles.[17] Two weeks before surgery, patients are injected with botulinum toxin. The corrugator, procerus, and depressor supercilii muscles (medial brow depressors) are typically injected with a total of 20 units of botulinum toxin and the lateral supraorbital orbicularis oculi muscles (lateral brow depressor) are injected with about 4 units of botulinum toxin on each side (Fig. 29-6). No botulinum toxin is injected into the frontalis muscle because it acts as the only brow elevator.

Surgical Technique

Following photo documentation of the patient's forehead and brows, the patient is brought into the operating suite. In most situations, an anesthesiologist administers general anesthesia with a laryngeal mask.

Incisions

The incisions are then marked: one midline and two temporal (two paramedian incisions are made if bone fixation is to be performed). The anteroposterior midline incision is approximately 2 cm posterior to the hairline and is 1 cm in length, just large enough to allow the introduction of periosteal elevators into the subperiosteal space. The temporal incisions are 3 cm in length and are approximately 2 cm posterior to the hairline. The key to obtaining a natural-looking brow is to create a temporal incision parallel to the tail of the brow with its medial extent at the temporal conjoint fascia (Fig. 29-7). The temporal incision orientation helps elevate the lateral half of the brow in a superolateral vector.

Local Anesthesia

The local anesthesia consists of 15 mL of 1% lidocaine with 1 : 100,000 epinephrine injected into the corrugator, procerus, and depressor supercilii muscles, the proposed incision sites, and for supraorbital and supratrochlear nerve blocks. The rest of the central forehead, parietal scalp, and the temporal region are infiltrated with approximately 50 to 60 mL of a solution consisting of 500 mL of normal saline mixed with 0.5 mL of 1 : 1000 epinephrine, 5 mL of sodium bicarbonate, and 25 mL of 2% lidocaine without epinephrine. The high volume of the solution acts as a vascular tourniquet and is primarily used in the temporal region. The patient is prepped and draped in the usual sterile fashion. Approximately 15 minutes is allowed for anesthesia and hemostasis to take place.

Frontal and Parietal Bones Dissection

The midline vertical incision is made and extended through the periosteum. Without the use of the endoscope, a periosteal elevator is used to create a subperiosteal pocket posteriorly over the parietal forehead

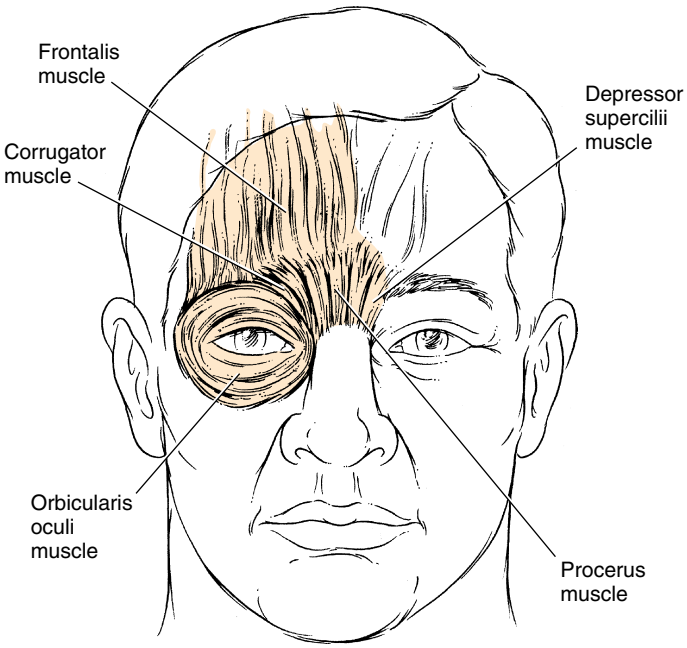

Figure 29-5. Frontal illustration of brow muscles. *(Adapted from Keller GS, Hutcherson R. Endoscopy-assisted small-incision forehead and brow lift. In: Putterman AM, Warren LA, eds.* Cosmetic Oculoplastic Surgery: Eyelid, Forehead, and Facial Techniques. *3rd ed. Philadelphia: WB Saunders; 1999:315, with permission.)*

Figure 29-6. Supraorbital orbicularis oculi Botox injection sites (X). Two injections totaling 4 units. *(Adapted from Zimbler MS, Nassif PS. Adjunctive applications for botulinum toxin in facial aesthetic surgery.* Facial Plast Surg Clin North Am. *2003;11:477-482, with permission.)*

and anteriorly over the central forehead to approximately 1 cm above the brow, with care taken not to injure the supraorbital and supratrochlear neurovascular bundles.

Temporal Dissection and Release of the Periosteum and Lateral Supraorbital Orbicularis Oculi Muscle

The temporal incisions are made and extended to the deep temporal fascia (Fig. 29-8). A blunt elevator dissects over the deep temporal fascia inferiorly until a branch of the zygomaticotemporal vein called the *sentinel vein* is encountered (Fig. 29-9). This is the inferior limit of the dissection without the use of the endoscope. A facelift scissors is used to connect the temporal incision to the central forehead incision by

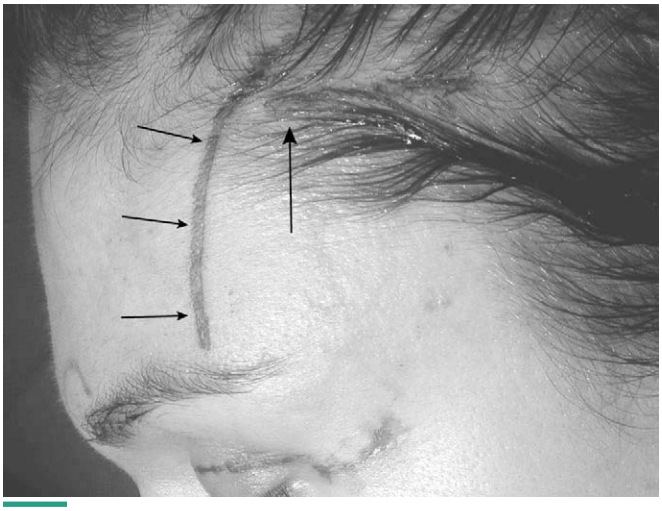

Figure 29-7. Marking of the temporal incision *(large arrow)* parallel to the tail of the brow with its medial extent at the temporal conjoint fascia *(small arrows).*

Figure 29-8. The temporal incision is taken down to the deep temporal fascia *(arrow).*

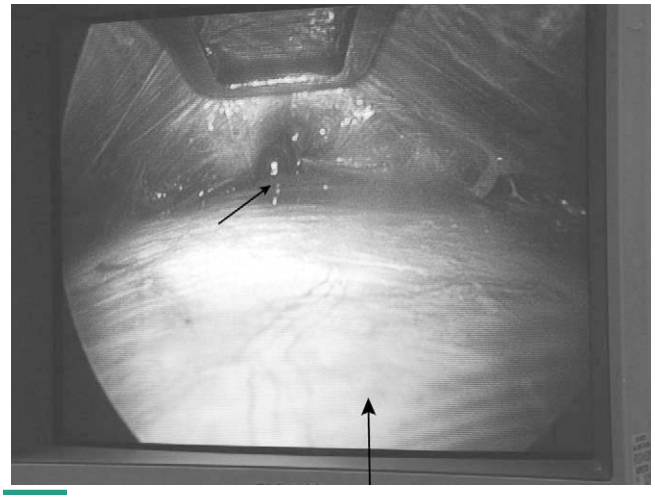

Figure 29-9. Endoscopic photograph of dissection over the deep temporalis fascia *(large arrow)* exposing the sentinel vein *(small arrow).*

Figure 29-10. To prevent elevation of the lateral canthus, the surgeon or the assistant places a finger in the interior aspect of the lateral rim at the lateral canthus.

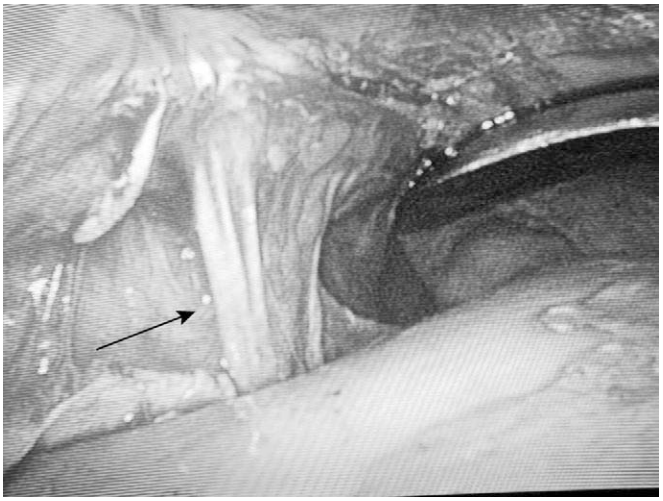

Figure 29-11. After periosteal and brow depressor muscle release, the supraorbital neurovascular complex *(arrow)* is visualized without obstruction from overlying muscle fibers.

severing the temporal conjoint fascia (fusion of the galea and the temporoparietal fascia). The conjoint fascia is released with a periosteal elevator in an inferior direction to the level of the supraorbital rim. Near the supraorbital rim, a thickening of periosteum termed the *conjoint tendon* is incised sharply or bluntly. Adequate release of the conjoint tendon at the lateral supraorbital rim is an essential factor of the periosteal release.

The endoscope is placed into the temporal dissection along with the elevator to visualize the sentinel vein. This vein is a reliable marker for the frontal branch of the facial nerve, which lies superficial to the dissection on the undersurface of the temporoparietal fascia.[18,19] If possible, the sentinel vein is preserved and the dissection is performed medial and inferior to the vein. If the vein is cauterized, the bipolar forceps are placed at the base of the sentinel vein to help prevent a thermal neuropraxic injury to the frontal branch of the facial nerve. Lateral and slightly inferior to the sentinel vein, the zygomaticotemporal sensory nerve is encountered and is usually considered the lateral border of the dissection.

Continuing dissection in a medial diagonal direction toward the malar eminence over the superficial temporal fat pad, the periosteum is penetrated just inferomedial to the lateral canthus over the frontal process of the zygoma and malar eminence. To prevent elevation of the lateral canthus, an assistant places a finger in the interior aspect of the lateral rim at the lateral canthus (Fig. 29-10). If the surgical plan calls for lateral canthal angle elevation, the lateral canthus is released. The periosteal release (elevation, incision, and spreading) begins inferior to the lateral canthus onto the medial malar eminence and extends medially to the supraorbital neurovascular complex; care is taken not to injure the nerve. Following the periosteal release, the lateral supraorbital orbicularis oculi muscle is meticulously released from the inferomedial orbit to the supraorbital nerve, exposing the yellow brow fat. This same procedure is performed on the contralateral temporal region.

Release of the Brow Depressor Muscles

For the temporal lift, this portion of the procedure is eliminated. The endoscope remains placed through the temporal incision and the periosteal elevator is placed through the central incision. The dissection is carried to the central supraorbital region and radix of the nose, releasing the periosteum and avoiding injury to the supraorbital and supratrochlear nerves. Thorough corrugator, procerus, and depressor supercilii myotomies are performed. To ensure that complete myotomies have been performed, each nerve of the supratrochlear and supraorbital neurovascular complexes (Fig. 29-11) should be easily visualized without obstruction from overlying muscle fibers. Finally, harvested deep temporalis fascia placed at the myotomy site of the corrugator muscles may prevent reanastomosis of muscle fibers.

Brow Elevation and Fixation

In men and in patients with a moderate amount of bleeding, a drain is placed for approximately 24 hours. If a complete release of all periosteum and brow depressor musculature is performed, the entire brow complex will elevate to an unnaturally high position without any tension (Figs. 29-12 and 29-13). Brow fixation is achieved by securing the superficial temporal fascia medially to the deep temporal fascia in a superolateral vector with two 2-0 PDS horizontal mattress sutures while the brow is lifted laterally and overcorrected. If bone fixation is indicated, two paramedian 2-cm vertical incisions are made parallel to the lateral two thirds of the brow. The absorbable Endotine device is inserted into a predrilled hole in the cranium. The periosteum/galea complex is lifted posterior to (over) the device. When the desired height is achieved, the tissue is "pushed firmly down" onto the hooks of the device, thus fixating the brow to its new height. The current Endotine absorbs in approximately 9 months. Occasionally, patients may palpate the device or complain of sensitivity in the surrounding region. The manufacturer is currently working on a new generation of Endotine that will be absorbed in 6 to 8 months.

For the Biotac screw (Bioplate, Inc., Los Angeles), a 2-0 PDS is used to grasp the galea and periosteum at the anterior aspect of the paramedian incision. The Biotac push-in screw is placed in the bone in the posterior aspect of the paramedian incisions following manually drilling of a 2-mm hole. Following placement of the screw, the nonneedle end of the suture is passed through the loop attached to the screw head and then the loop is pulled through the hole in the screw with the accompanying suture. The brow is pulled in a posterior direction to the desired brow height, the suture is tied down, thus fixating the brow. The overcorrected brow gradually drops to its final position after 3 weeks. The incisions are closed with surgical staples.

Postoperative Care Principles

Incisions are dressed with antibiotic ointment without a head dressing. Patients may experience headaches and minimal pain initially. Shampooing with gentle cleaning of the hair occurs at 48 hours, when the hair may be blow-dried on a cool setting. For 4 days, the patients are instructed to maintain a semi-upright position when sleeping or resting. The staples are removed at 7 days. Full activities may resume in 3 weeks.

Results (Before and After Photos)

See Figs. 29-14 through 29-17.

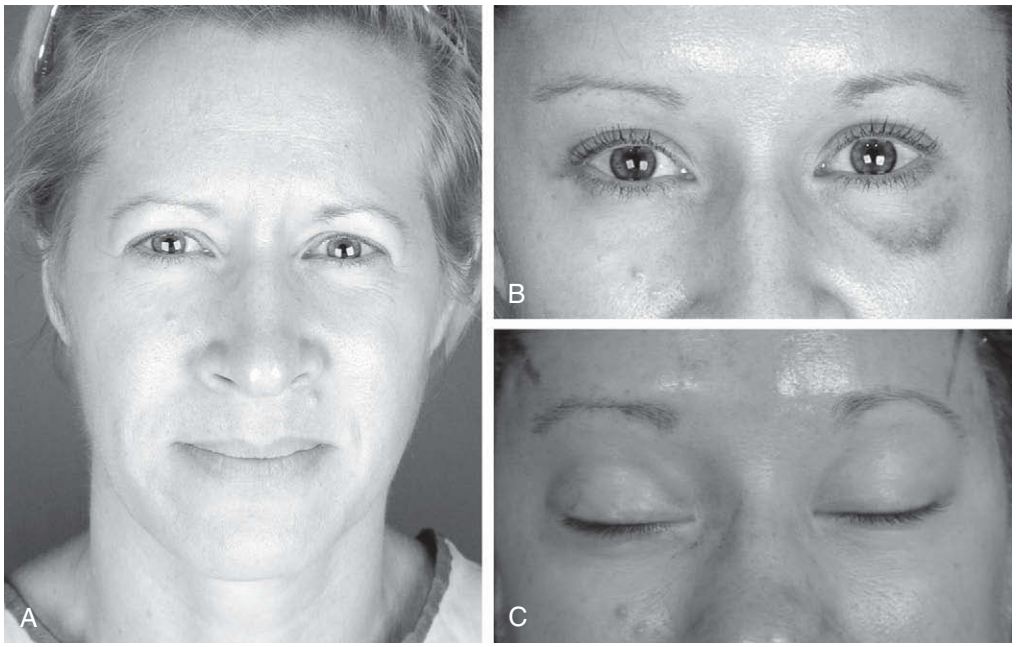

Figure 29-12. Patient before (**A**) and 1 week after (**B**) endoscopic brow lift with deep temporal fixation only. **C**, Intraoperative photograph of the patient's elevated brow complex to an unnaturally high position after a complete release of all periosteum and brow depressor musculature before fixation.

Figure 29-13. Intraoperative photograph of a patient's elevated left brow complex after a unilateral complete release of all periosteum and brow depressor musculature before fixation. Q-tips are positioned at the inferior border of the supraorbital rim.

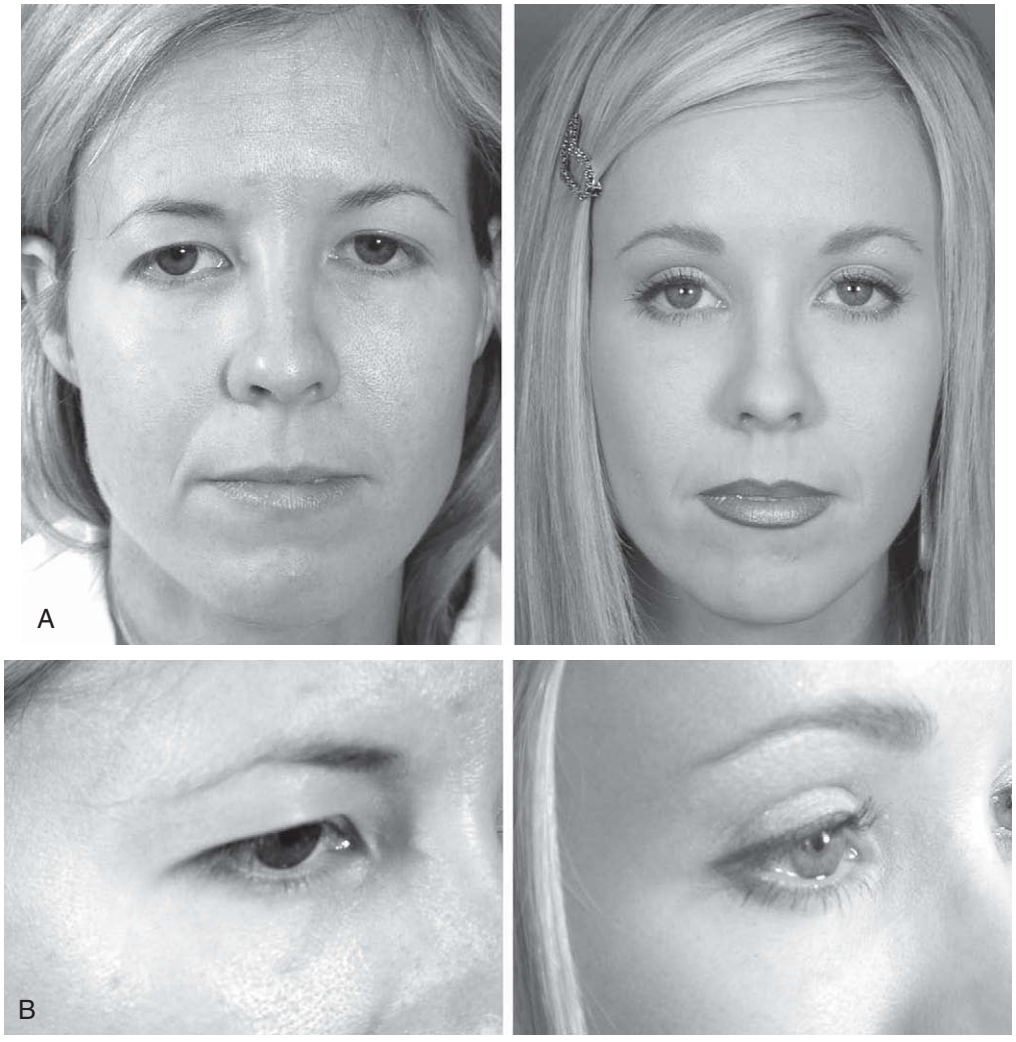

Figure 29-14. A 32-year-old woman with severe brow ptosis and blepharochalasis. **A**, Frontal before and after views. **B**, Right oblique before and after views. Before *(left)* and 1 year postoperatively *(right)* following deep temporal fixation-only endoscopic brow lift and bilateral upper blepharoplasty. The oblique view documents significant improvement in the temporal hooding, lateral canthal, and eyelid regions.

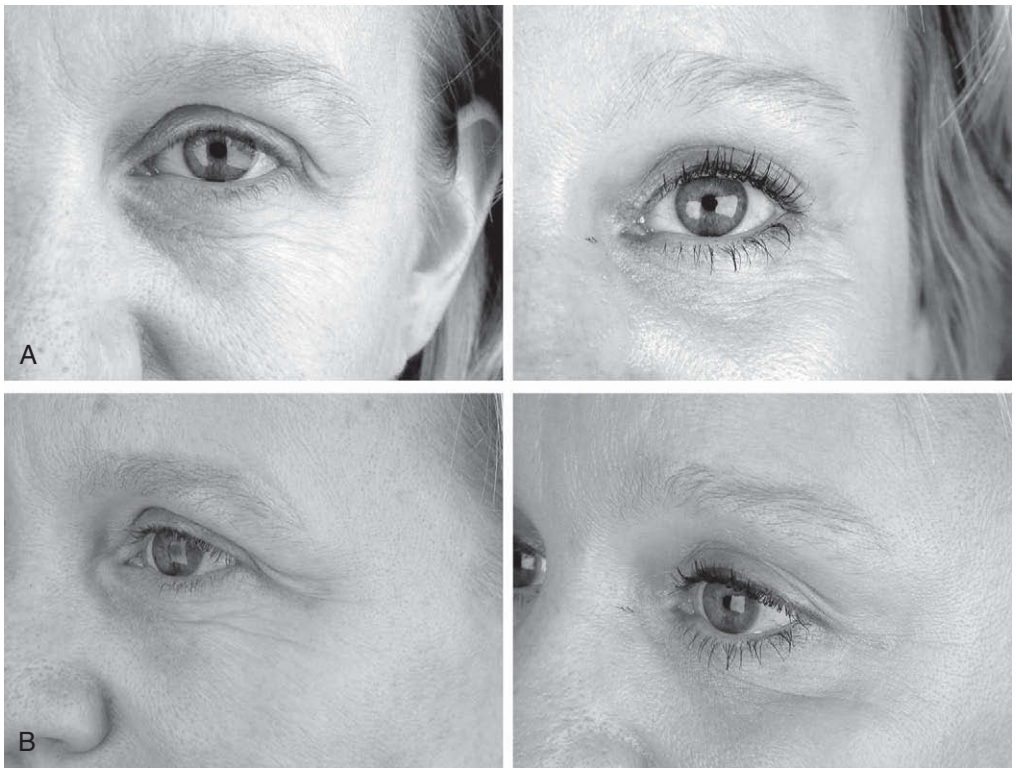

Figure 29-15. Before and after frontal views **(A)** and left oblique before and after views **(B)** of a middle-aged patient with brow ptosis and fat herniation of the lower eyelids. Before *(left)* and 20 months postoperatively *(right)* following deep temporal fixation-only endoscopic brow lift and bilateral lower fat repositioning blepharoplasty. Notice the orbital region is rejuvenated with the natural shape of the eyebrow kept intact.

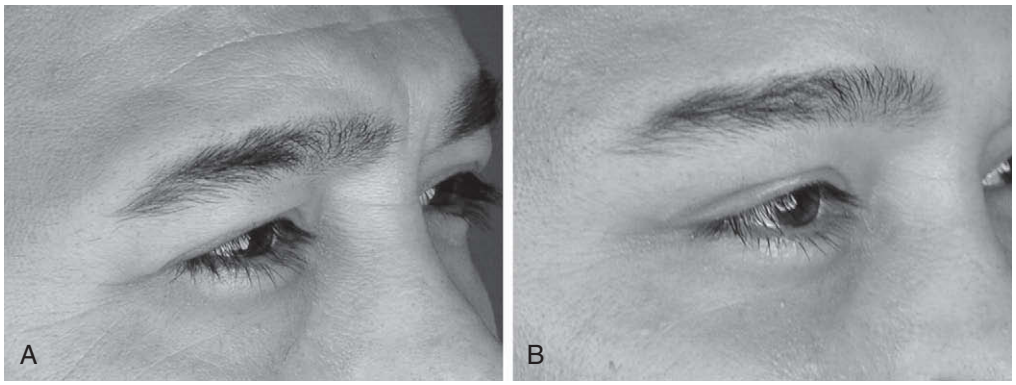

Figure 29-16. Right oblique view of before **(A)** and after **(B)** of a 43-year-old man after an upper blepharoplasty 4 years earlier now complaining of a "tired look." The brow, especially in the temporal region, descends below the supraorbital rim, causing temporal hooding, and the supratarsal crease is covered by overhanging ptotic upper eyelid skin. Following a deep temporal fixation-only brow lift, the patient's brow ptosis is moderately improved.

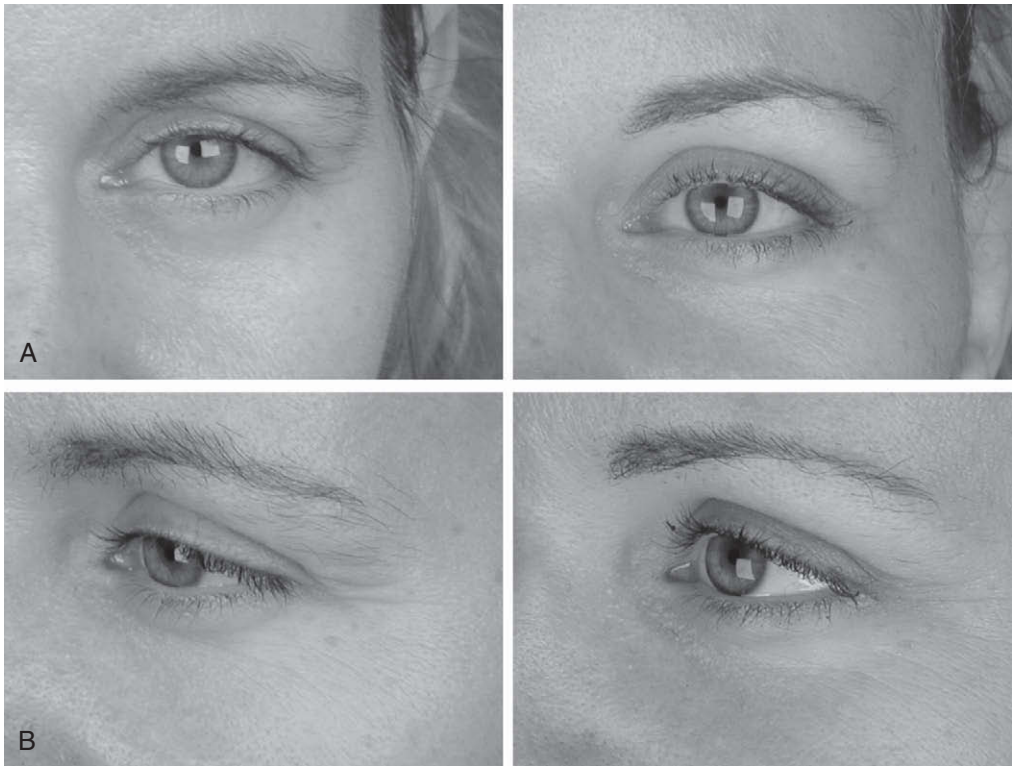

Figure 29-17. Frontal before and after views **(A)** and left oblique before and after views **(B)** of a 41-year-old patient with brow ptosis and fat herniation of the lower eyelids. Following deep temporal fixation only endoscopic brow lift and bilateral lower transconjunctival blepharoplasty, notice the significant medial brow elevation.

Complications

Few complications result from brow lifting. It has been our experience that fewer complications occur with the endoscopic brow lift than with the coronal lift. Hematoma, seroma, hypesthesia, tingling, pruritus, "bandlike" forehead sensation, temporary frontal branch of the facial nerve paresis, temporary or permanent alopecia, infection, stitch abscess, brow asymmetry, relapse of brow ptosis, paramedian incision depressions with screw fixation, and hypertrophic scars have been reported.[5,13]

SUGGESTED READINGS

Bowman CB, Tanenbaum M, McCord CD. Internal brow lift: browplasty and browpexy. In: Putterman AM, Warren LA, eds. *Cosmetic Oculoplastic Surgery: Eyelid, Forehead, and Facial Techniques*. 3rd ed. Philadelphia: WB Saunders; 1999.

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Tardy ME, Thomas JR, Brown R. *Facial Aesthetic Surgery*. 1st ed. St Louis: Mosby; 1995.

For complete list of references log onto www.expertconsult.com.

CHAPTER THIRTY

Blepharoplasty

Oren Friedman

Renzo A. Zaldívar

Tom D. Wang

Key Points

- A thorough understanding of the anatomy is of utmost importance, both for evaluation and treatment of the aging periorbital area.
- Evaluation of a patient before blepharoplasty should include careful assessment of the eyelid position to exclude eyelid and brow ptosis.
- Approximately 20 mm of eyelid skin should remain between the eyelid margin and the start of the brow. Less than this may risk postoperative lagophthalmos.
- When performing ptosis surgery repair, care must be taken to identify the levator aponeurosis to avoid suturing the septum or Müller's muscle, which may cause eyelid irregularities.
- Conservative excision of skin during lower eyelid blepharoplasty is preferred to avoid postoperative complications.

The eyes are often said to be the window to a person's soul. When considering facial plastic surgery, this statement holds true. The eyes play a central role in human communication. They are capable of expressing emotions such as anger, sadness, happiness, surprise, disappointment, hatred, and love. However, it is not the globe itself, nor the color of the iris that is responsible for expressing these emotions. Rather, it is the dynamics of the periorbital region that allows us to convey our feelings through our eyes: alterations in the shape of the palpebral fissure, positioning of the brows, furrowing in the glabella, and redundancy and fullness in the lids.

The aging process affects the skin and underlying tissues by both intrinsic and extrinsic factors. Intrinsic aging refers to the effects of time on the skin. Over the course of one's lifetime, the epidermis and subcutaneous fat layers thin and there is effacement of the dermal-epidermal junction. There are fewer Langerhans cells and melanocytes, and the morphology of the keratinocytes changes. There is a progressive loss of organization of elastic fibers and collagen (elastosis), and a weakening of underlying muscles. Extrinsic factors such as gravity, smoking, and sun exposure may result in keratinocytic dysplasia and accumulation of solar elastosis. Taken together, the intrinsic and extrinsic aging processes create pigmentary changes, rhytids, and texture irregularities of the skin (Fig. 30-1).[1,2]

On a macroscopic level, aging results in brow ptosis, lateral brow hooding, crow's feet, fine and deep rhytids, and loss of elasticity. Even though the effects of aging are normal, ubiquitous, and acceptable to many individuals, others find such changes to be an area of concern. In the periorbital region, the effects of aging may cause an individual to unintentionally convey external expressions of boredom, fatigue, and sadness, even though these are not the emotion being felt (Fig. 30-2). Because the eyes convey emotions, aging of the upper third of the face is almost always more visible and of greater impact than aging of the lower face and neck. To fully address the periorbital region surgically, it is first essential to understand its anatomy and aesthetic ideals.[3]

Anatomy

Orbital Anatomy

The orbits are pyramidal bony structures composed of seven different bones: the frontal, maxillary, sphenoid, zygomatic, ethmoid, palatine, and lacrimal. Each orbit is 30 cm^2 in volume, and lies 25 mm from the other. The entrance of the orbit is 40 mm in height and 35 mm in width, and the widest part of the orbit lies 1 cm posterior to the anterior orbital margin. The orbital periosteum, the periorbita, is firmly adherent to the bone, especially at the suture lines between the seven constituent bones of the orbit. The lacrimal gland fossa, located in the anterior-superior-lateral aspect of the orbit, houses the lacrimal gland. The supraorbital nerve and artery are transmitted through a true foramen in 25% of cases and through a notch in most cases. The frontal sinus lies superior to the orbits, and the ethmoid sinuses lie medial to the orbits.

The lateral orbital wall is formed by the greater wing of the sphenoid and zygoma and is 47 mm long. The lateral orbital tubercle (Whitnall's tubercle) is 10 mm below the zygomaticofrontal suture and 4 mm behind the anterior lateral orbital rim. The lateral canthal tendon, Whitnall's ligament, and Lockwood's ligament attach here. The medial orbital walls are 45 mm long. The medial wall is composed of the frontal process of the maxilla, the lacrimal bone, the lamina papyracea (ethmoid bone), and the lesser wing of the sphenoid bone. The anterior lacrimal crest forms the attachment for the medial canthal tendon. The lacrimal fossa and sac lie between the anterior and posterior lacrimal crests. The anterior and posterior ethmoid foramina transmit the anterior and posterior ethmoid arteries and demarcate the level of the cribriform plate and floor of the cranial fossa. The average distance from the anterior lacrimal crest to the anterior ethmoid foramen is 24 mm, to the posterior ethmoid foramen is 36 mm, and to the optic foramen is 42 mm.[4]

The orbital floor is formed by the zygomatic bone, the orbital plate of the maxilla, and the orbital process of the palatine bone. The

orbital floor ends at the inferior orbital fissure posteriorly, which transmits the sphenopalatine ganglion, and the maxillary division of the trigeminal nerve. The infraorbital neurovascular bundle travels through the infraorbital groove, canal, and foramen. The infraorbital foramen lies 8 mm inferior to the inferior orbital rim.[4]

The optic foramen, within the lesser wing of the sphenoid, transmits the optic nerve, ophthalmic artery, and sympathetic fibers to the orbit. The superior orbital fissure is bounded by the greater and lesser wings of the sphenoid. The annulus of Zinn is a fibrous ring surrounding the optic foramen and superior orbital fissure. The superior orbital fissure transmits cranial nerve IV, ophthalmic and mandibular divisions of cranial nerve V, cranial nerve VI, the nasociliary nerve, the superior and inferior ophthalmic veins, the lacrimal nerve, and the frontal nerve.[4]

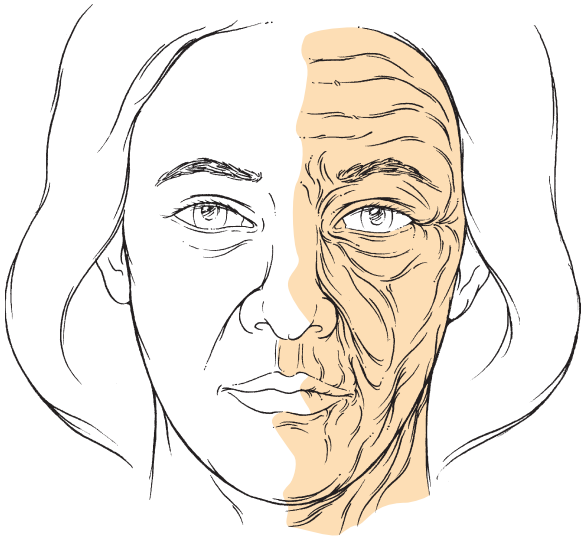

Figure 30-1. The aging face.

Eyebrow Anatomy

Sensory Innervation

Sensation of the brow and anterior scalp region is provided by the ophthalmic division of the trigeminal nerve. The ophthalmic division divides into the lacrimal nerve, which provides sensation to the skin and conjunctiva of the upper eyelid, and the frontal nerve, which further divides into the supraorbital and supratrochlear nerves. The supratrochlear innervates the conjunctiva, upper eyelids, and inferomedial aspect of the forehead, whereas the supraorbital nerve innervates the upper lid skin, forehead, and anterior scalp. The supratrochlear nerve lies 1.5 to 1.7 cm from the midline, and the supraorbital nerve lies 1 cm lateral to the supratrochlear nerve (Fig. 30-3).[5]

Motor Innervation

The temporal, or frontal, division of the facial nerve supplies the muscles of the forehead and the orbicularis oculi muscle. This division of the facial nerve courses from the parotid gland, anterior to the superficial temporal artery, toward its final destination, where it pierces the undersurface of the frontalis muscle 1.5 cm above the lateral canthus. The frontal branch of the facial nerve lies deep to the superficial musculoaponeurotic system fascia (SMAS) and its continuation in the temporal region, the temporoparietal fascia (Fig. 30-4). The course of the nerve may be approximated by a line drawn from a point 0.5 cm anterior to the tragus to a point 1.5 cm lateral to the lateral brow. The danger zone for the temporal branch of the facial nerve has been further described and is shown in Fig. 30-5. The nerve enters the orbicularis oculi muscle and frontalis muscle along the deep surface of the muscles. As the nerve crosses over the zygomatic arch, it lies between the periosteum of the zygoma and the SMAS. Dissection in the region of the zygomatic arch requires caution to avoid injury to the nerve and should be carried out either subcutaneously or subperiosteally.[4,5]

Fascial Layers of the Forehead and Temporal Region

The scalp consists of five layers: the skin, subcutaneous tissue, galea aponeurosis, loose areolar tissue, and periosteum. The galea is a tendinous, inelastic sheet of tissue that connects the frontalis muscle of the forehead with the occipitalis muscle. The frontalis muscle originates from the galea and inserts into the forehead skin. At the superior orbital rim, the galea becomes tightly adherent to the periosteum. Laterally, the galea continues as the temporoparietal fascia, which lies in the

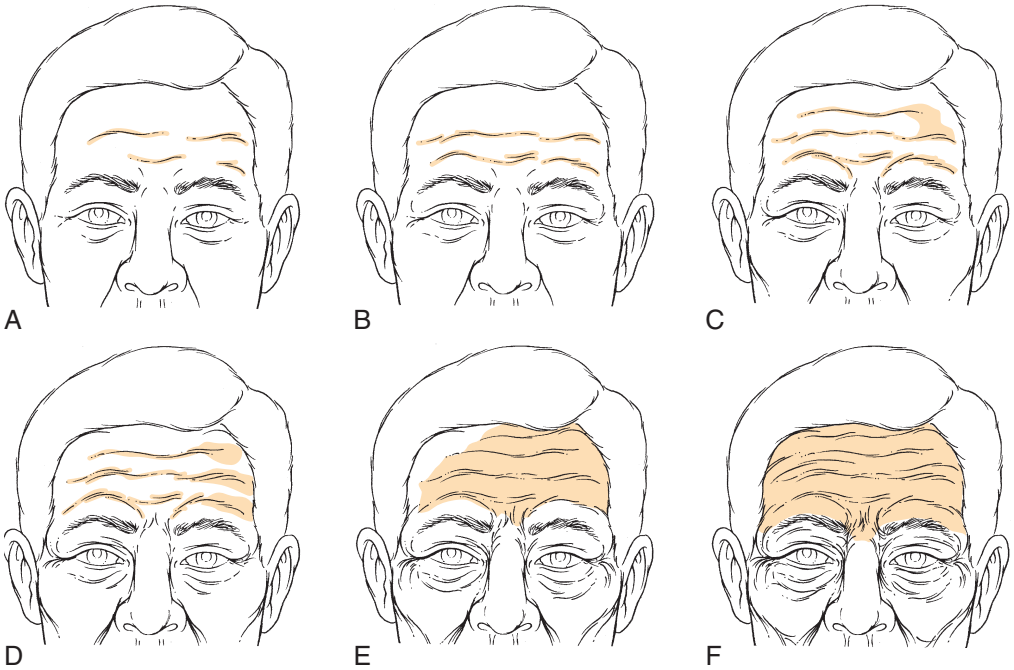

Figure 30-2. Changes in the upper third of the face and the effects of aging on facial expression.

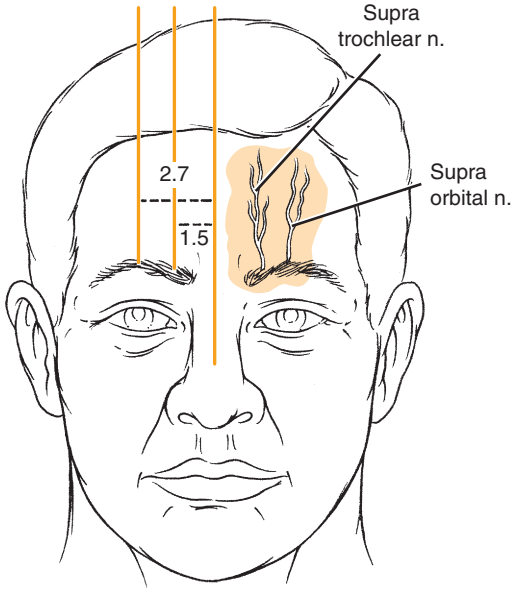

Figure 30-3. Sensory nerves of forehead.

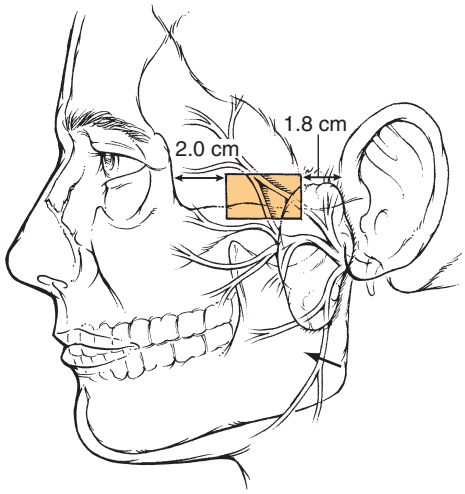

Figure 30-5. The danger zone for the temporal branch of the facial nerve, defined as the region overlying the zygomatic arch between 1.8 cm anterior to the helical root and 2 cm posterior to the anterior end of the arch. *(From Weinberger MS, Becker DG, Toriumi DM. Rhytidectomy. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:650.)*

Figure 30-4. Temporal branch of facial nerve deep to the superficial musculoaponeurotic system fascia and temporoparietal fascia. *(From Weinberger MS, Becker DG, Toriumi DM. Rhytidectomy. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:650.)*

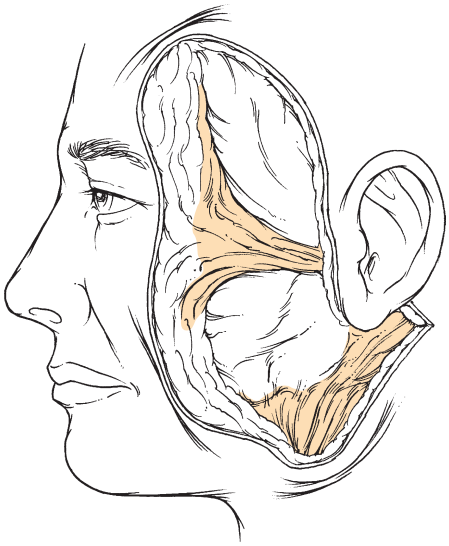

Figure 30-6. The superficial musculoaponeurotic system and the temporoparietal fascia is one continuous layer. *(From Weinberger MS, Becker DG, Toriumi DM. Rhytidectomy. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:649.)*

immediate subcutaneous plane in the temporal region. The temporoparietal fascia is continuous with the SMAS layer of the face and the platysmal layer of the neck (Fig. 30-6). Deep to the temporoparietal fascia lies the deep temporal fascia, which envelops the temporalis muscle. The temporal fascia is contiguous with the calvarial periosteum at the temporal line of the skull, the conjoint tendon. The temporal fat pad, just superior to the zygomatic arch, is ensheathed by the temporal fascia inferior to the level of the supraorbital ridge. At that point, the temporal fascia splits to become the intermediate temporal fascia and the deep temporal fascia, with the fat pad between them. The intermediate fascia layer attaches to the superior aspect of the zygoma laterally, whereas the deep layer attaches medially.[4,5]

Musculature

There are four muscles in the eyebrow: frontalis, procerus, corrugator supercilii, and orbicularis oculi (Fig. 30-7). The frontalis is a paired subcutaneous muscle that inserts into the skin of the eyebrow. It is the continuation of the galea aponeurotica from the coronal suture downward, and inserts in the dermis at the level of the supraorbital ridge. Laterally, the frontalis terminates at the conjoined tendon. The frontalis muscle has no bony insertions, and its only action is brow elevation. Horizontal forehead rhytids correspond to the long-term effects of frontalis activation. Inferonasally, the frontalis muscle extends to form the procerus muscle. The procerus originates on the caudal aspect of the nasal bones and cephalic margins of the upper lateral cartilages, and inserts onto the medial belly of the frontalis muscle and the dermis between the eyebrows. The action of the procerus muscle produces

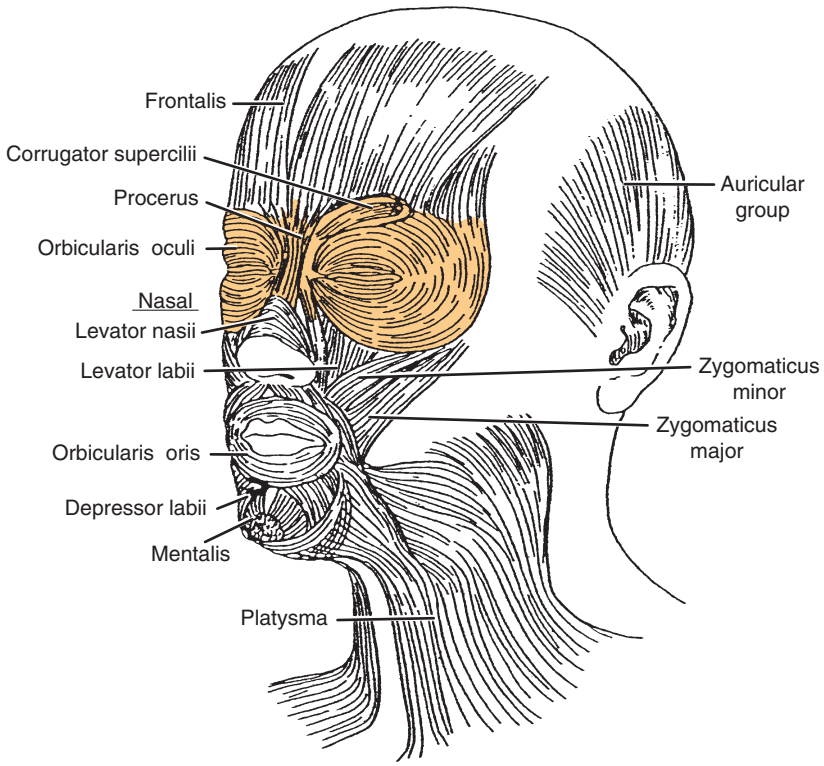

Figure 30-7. Eyebrow muscles include the frontalis procerus, corrugator supercilii, and orbicularis oculi. *(From Graney DO, Baker SR. Anatomy. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:404.)*

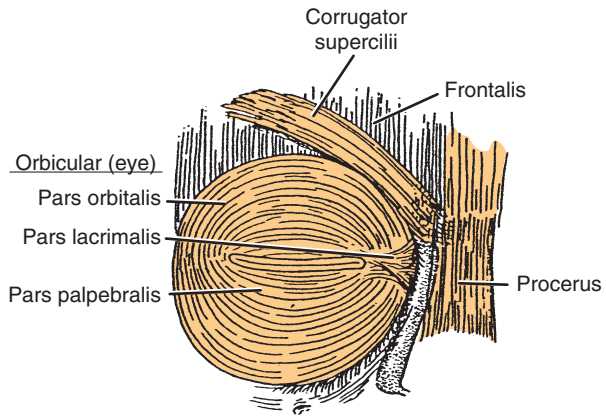

Figure 30-8. Corrugator supercilii contraction causes vertical glabellar rhytids and procerus contraction causes horizontal glabellar rhytids. *(From Graney DO, Baker SR. Anatomy. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:404.)*

inferior brow displacement and is responsible for horizontal glabellar wrinkles (Fig. 30-8).

The corrugator muscle originates from the nasal process of the frontal bone, near the superomedial orbital rim, and inserts into the dermis at the middle third of the eyebrow after blending with the frontalis and orbicularis muscles. Its action produces inferior and medial forehead and brow movement, and results in vertical glabellar wrinkle.[4,5]

Blood Supply

The internal and external carotid artery systems supply the blood to the forehead. The internal carotid artery, via the ophthalmic artery, branches to form the frontal, supraorbital, and supratrochlear arteries. The external carotid artery system supplies the largest area of the scalp via the superficial temporal artery. Thus there is a rich anastomotic complex of vessels providing adequate nutrients to the forehead, allowing for safety in aesthetic surgery of the forehead and scalp.

Eyelid Anatomy

The eyelids are the protective covering over the eyes. They consist of an anterior and posterior lamella. At the level of the tarsal plates, the upper and lower eyelids consist of the same basic components: The anterior lamella consists of skin and orbicularis oculi muscle; the posterior lamella consists of tarsus and conjunctiva. The two lamellae are separated by finely interdigitating eyelid retractors. The anterior and posterior lamellae have separate blood supplies that are important to recognize when approaching eyelid reconstruction (Fig. 30-9).[4]

Surface Anatomy of the Eyelids

The normal horizontal palpebral fissure is 28 to 30 mm and the normal vertical palpebral fissure is 9 to 10 mm. The intercanthal distance, the distance between the medial canthi of the two eyes, is approximately 25 to 30 mm. The upper eyelid margin normally rests at a point midway between the superior corneal limbus and the pupil, whereas the lower eyelid margin typically abuts the inferior corneal limbus. The apex of the upper eyelid is located midway between the medial pupillary margin and the medial corneal limbus. The nadir of the lower eyelid is at the lateral corneal limbus.[6]

The upper lid crease is the line formed by the insertion of the levator aponeurosis and orbital septum into the orbicularis oculi muscle and skin. In women, the lid crease is 10 to 12 mm above the lid margin, whereas in men it is 7 to 8 mm above the lid margin. The lateral canthal angle is more acute and 2 mm higher than the rounded and lower medial canthal angle (Fig. 30-10).[4,6]

A number of anatomic differences exist between the Asian and Occidental eyelids. In the Asian eyelid, the orbital septum and levator aponeurosis attach to the skin further inferiorly, anterior to the tarsus. As a result, orbital fat prolapses anteriorly, thereby preventing the formation of a prominent upper eyelid crease and creating a fullness of the upper eyelid.[4,5]

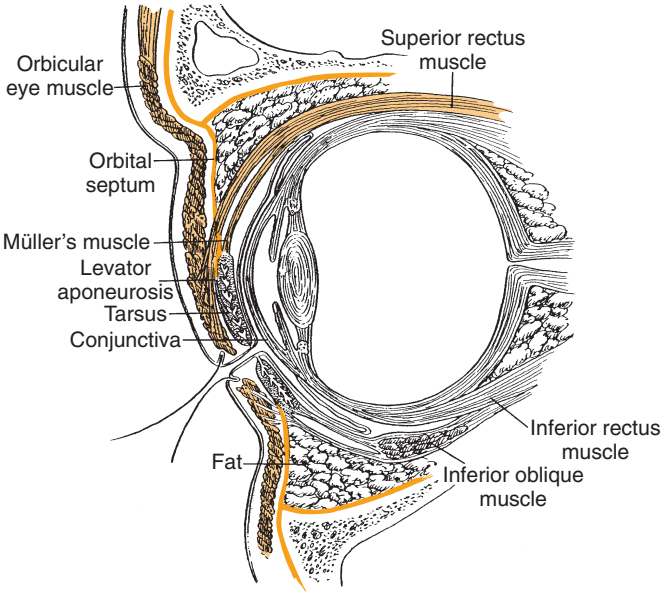

Figure 30-9. The cross section of the orbit and eyelid. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:680.)*

Figure 30-10. The lid crease is 10 to 12 mm above the lid margin in women and 7 to 8 mm above the lid margin in men. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:678.)*

The Anterior Lamella

The skin of the eyelids is the thinnest skin of the body with almost no reticular dermis, and it is highly vascular. These factors allow the eyelid skin to heal rapidly and with minimal scar. As it approaches the orbital rim and the hair-bearing areas of the periorbital region, the skin of the eyelids thickens rapidly. The changes in skin thickness are important to consider when planning incisions in periorbital surgery (see Fig. 30-9).[4-6]

The orbicularis oculi muscle is a subcutaneous muscle that serves as the sphincter of the eyelid. It is innervated by the temporal and zygomatic branches of the facial nerve. In addition to its function in eye closure, the orbicularis oculi muscle is essential for the proper functioning of the lacrimal pump apparatus, which propels tears into the puncta, canaliculi, and lacrimal sac. Failure of the pump mechanism, as may result with facial nerve paralysis, may result in epiphora.[4-6]

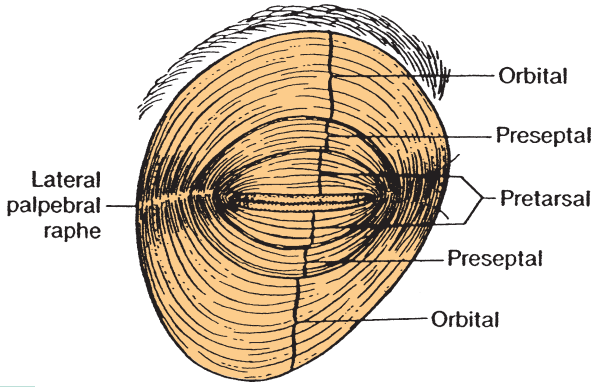

Figure 30-11. The sphincter mechanism of the eyelids depends on the three divisions of the orbicularis oculi muscle. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:679.)*

The orbicularis oculi muscle is divided into three segments: the pretarsal, preseptal, and orbital segments (Fig. 30-11). Even though they all act to close the eye, each segment plays a unique role. Blinking is an involuntary action that depends on contraction of the pretarsal orbicularis. Winking is a voluntary action dependent upon the orbital orbicularis. The preseptal fibers contribute to both the involuntary and voluntary functions of the eyelids.[4-6]

The origin of the pretarsal orbicularis arises from two heads, one of which inserts into the posterior lacrimal crest, and the other inserts into the anterior lacrimal crest and into the anterior limb of the medial canthal tendon. The preseptal orbicularis also has two heads at its origin: the deep portion attaches to the lacrimal sac, and the superficial segment attaches to the anterior limb of the medial canthal tendon. The orbital orbicularis originates at the anterior limb of the medial canthal ligament and interdigitates with the frontalis, corrugator, and procerus muscles. Laterally, the three orbicularis segments fuse to form the inferior and superior crura of the lateral canthal tendon, which insert into Whitnall's tubercle. The lateral attachments of the lateral canthal tendon to Whitnall's tubercle are responsible for eyelid and globe apposition.[4-6]

The Orbital Septum

The orbital septum, which lies just deep to the orbicularis oculi muscle, forms the anterior border of the orbit and confines the orbital fat (see Fig. 30-9). It is a fibrous sheath formed at the orbital rims at the arcus marginalis and is an extension of the orbital periosteum. In white upper lids, the septum fuses with the levator aponeurosis approximately 3 mm above the superior tarsal border. In Asian upper lids, the septum fuses with the levator aponeurosis further inferiorly, below the superior tarsal border, thereby allowing orbital fat to lie anterior to the tarsal plate, preventing the attachment of the levator to the skin, and preventing the formation of an upper eyelid crease. In the lower lids, the septum fuses with the underlying orbital retractor (capsulopalpebral fascia), 5 mm below the inferior tarsal border. The orbital septum acts as a barrier to the spread of infection and neoplasms between the preseptal space and the orbital space.[4]

The Orbital Fat Pads

All of the eyelid fat pads lie deep to the orbital septum. The upper eyelid contains two fat pads medially and centrally, and the lacrimal gland laterally (Fig. 30-12). The lacrimal gland should be avoided during eyelid surgery to prevent postoperative dryness; it can be identified by its pink rather than yellow color and its firm rather than soft texture.[4,6]

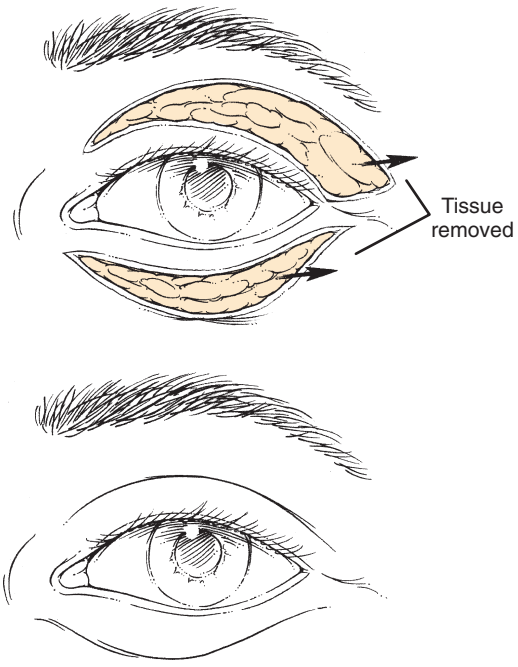

Figure 30-12. Fat pads of the upper and lower eyelids.

The lower eyelid contains three fat pads: medial, central, and lateral. The medial and central fat pads are separated by the inferior oblique muscle, which should be identified during lower eyelid surgery to help prevent its disruption. Disruption of this muscle may result in postoperative diplopia (see Fig. 30-12).[4,6]

Upper Eyelid Retractors

Deep to the fat pads are the eyelid retractors. In the upper lid, the levator palpebrae superioris (the levator muscle) is the major retractor, and it originates from the lesser wing of the sphenoid bone at the orbital apex (see Fig. 30-9). The levator is innervated by the oculomotor nerve (cranial nerve III). The horizontal posterior segment of the levator consists of muscle fibers, which extend anteriorly along the orbital roof for 36 mm until it reaches Whitnall's ligament. At Whitnall's ligament, the levator changes its course by approximately 90 degrees and becomes an aponeurosis that travels vertically for a length of 14 to 20 mm until its insertion into the upper third of the tarsal plate. Some fibers of the levator aponeurosis fuse with the orbital septum approximately 2 to 5 mm above the superior tarsal border, and then together insert into the skin to create the upper eyelid crease. In addition to its inferior attachments to the septum, tarsal plate, and skin, the levator aponeurosis attaches medially to the medial canthal tendon, and laterally to the lateral canthal tendon.[4]

Müller's muscle, or the superior tarsal muscle, arises from the undersurface of the levator aponeurosis just below Whitnall's ligament, and courses inferiorly 10 to 12 mm to attach to the superior tarsal plate (see Fig. 30-9). Müller's muscle is innervated by sympathetic nerve fibers, and its action produces 2 to 3 mm of eyelid retraction. Müller's muscle is adherent to the levator aponeurosis anteriorly and is loosely adherent to the conjunctiva on its posterior surface.[4]

Lower Eyelid Retractors

The capsulopalpebral fascia and inferior tarsal muscle comprise the lower eyelid retractors. The capsulopalpebral fascia originates from the fascia of the inferior rectus muscle and inserts on the inferior tarsal border. This fascia does not move independently, but rather mimics the movement of the inferior rectus muscle from which it originates. The inferior tarsal muscle arises from the undersurface of the capsulopalpebral fascia and the two are tightly adherent to each other and to the lower lid conjunctiva. The inferior tarsal muscle is sympathetically innervated.[4,6]

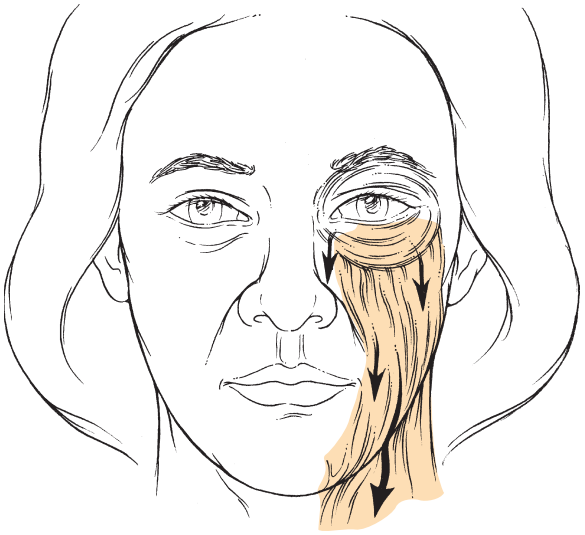

Figure 30-13. Descent of the midface with aging.

The Tarsus

The tarsal plates are dense fibrous connective tissue that form the skeleton of the eyelids (see Fig. 30-9). Each plate is 25 to 30 mm in horizontal dimension. The upper eyelid tarsal plate is 10 to 12 mm in vertical height while the lower eyelid tarsal plate is 3 to 5 mm in vertical height.[4]

The Conjunctiva

The conjunctiva is the innermost surface of the eyelid, which is in contact with the globe (see Fig. 30-9). It is composed of nonkeratinized stratified squamous epithelium with goblet cells that produce the mucous layer of the tear film. The bulbar conjunctiva is the portion of the conjunctiva that lines the globe, whereas the palpebral conjunctiva lines the eyelid. These two segments meet at the conjunctival fornix, at the base of the upper and lower eyelids. Dispersed throughout the conjunctiva are numerous additional glands that produce the aqueous layer of the tear film. The lacrimal gland secretes additional lacrimation in response to stimuli such as ocular irritant and emotional triggers.[4]

Midface Anatomy

With aging, the malar prominences descend inferomedially to deepen the nasolabial crease and expose the inferior and lateral orbital rims to a greater degree. In addition to the underlying bony malar eminence, the malar prominence is formed by a variety of soft tissue components. The orbicularis oculi muscle extends beyond the eyelids to lie over the malar eminence. In youth, the orbicularis maintains a sling around the orbital rim, but with the loss of orbicularis tone associated with aging, descent of the malar soft tissue complex prevails (Fig. 30-13). Both the superficial and deep surfaces of the malar orbicularis oculi muscle are associated with a fat pad. Superficial to the orbicularis is the subcutaneous malar fat pad. Deep to the orbicularis lies the suborbicularis oculi fat, also known as the *SOOF*. The SOOF layer of fat is in close contact with the periosteum of the inferior orbital rim as well as with the insertions of the zygomaticus muscles. The zygomaticus major and minor muscles are innervated by the zygomatic and buccal branches of the facial nerve and enter the muscle on its deep surface.[7]

Aesthetic Considerations and Ideals in the Periorbital Area

In an attempt to rejuvenate the periorbital area in the most natural and aesthetically pleasing way, consideration must be given to all of the elements that constitute this region. If the ravages of aging have caused upper face and midface changes, the surgeon must recognize that correcting the ocular problems alone will not give the patient a harmonious cosmetic result. Rather, the upper face contribution to the aging peri-

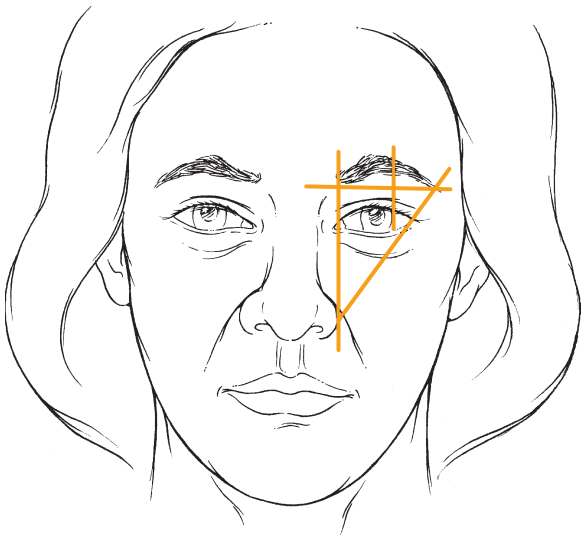

Figure 30-14. Ideal brow position. The classical description places the peak of the brow at the lateral limbus, while more recent trends of beauty place the peak at the lateral canthus.

orbital area as well as the midface contribution to the aging periorbital area must be considered. Brow position, glabellar rhytids, dermatochalasia, eyelid ptosis, pseudoherniation of fat, lateral crow's feet, inferior malar displacement, ptotic lacrimal gland, and eyelid laxity should all be taken into account when addressing the periorbital complex.[8,9]

Brow Position

Management of brow malposition necessitates an understanding of the ideal brow position. Evaluation of the patient should include an examination in front of a mirror in both animation and repose. The patient's eyes should be closed for 10 to 20 seconds to allow for full relaxation of the forehead musculature. Upon eye opening, the true position of the brow is noted with minimal contribution to the brow position from the forehead muscles. The ideal brow anatomy in the male differs from that in the female. The classic brow position in women describes the medial brow as having its medial origin at the level of a vertical line drawn to the nasal alar-facial junction. The lateral extent of the brow should reach a point on a line drawn from the nasal alar-facial junction through the lateral canthus of the eye. The medial and lateral ends should lie on the same horizontal plane (Fig. 30-14). The medial end should have a clubhead appearance and the lateral end should gradually taper to a point. The brow should arch superiorly, well above the supraorbital rim, with the highest point classically described as lying at the lateral limbus, and more recently described as lying at the lateral canthus. In men, there should be less of an arch to the brow position and more of a horizontal contour along the supraorbital ridge. The distance between the midpupillary line and the inferior brow border should be approximately 2.5 cm. The distance from the superior border of the brow to the anterior hairline should be 5 cm.[5,10]

The upper one third of the face elongates with aging as a result of the hairline moving upward and the brow drifting downward (Fig. 30-15). In addition to brow ptosis, the aging brow may reveal dynamic wrinkles or even wrinkles at rest. These furrows in the glabella and forehead are caused by the repeated pull on the skin by the facial mimetic muscles. The distance between the two eyebrows should be the same as the distance between the alar-facial junctions on the two sides of the nose.

Brow ptosis not only gives the face a tired, crowded, angry, and unattractive appearance, it may also accentuate upper eyelid skin redundancy. As the brow descends below the supraorbital rim, it pushes additional skin over the upper eyelid, worsening the cosmetic appearance of the eyelids and aggravating the functional deficits in the peripheral visual fields. Upper eyelid blepharoplasty alone will not correct the patient's problem and may even worsen the degree of brow ptosis by

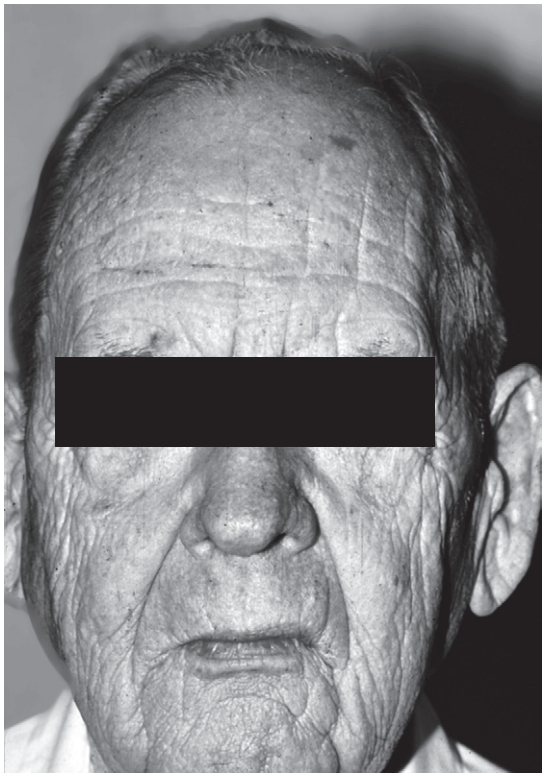

Figure 30-15. Elongation of the upper third of the face with associated wrinkles at rest and ptotic brows.

fixing the brow in an inferior position. Therefore attention to the repositioning of the brow is essential and should be done before blepharoplasty.[11]

Eyelid Aesthetics

Several reproducible themes have been noted in the analysis of beautiful eyes and eyelids. The palpebral fissure should be almond shaped and symmetrical between the two sides. The highest point of the upper eyelid is at the medial limbus, and the lowest point of the lower eyelid is at the lateral limbus. Sharp canthal angles should exist, especially at the lateral canthus. The lateral canthus should lie 2 to 4 mm superior to the medial canthus. The horizontal dimension of the palpebral fissure is 25 to 30 mm, whereas its vertical dimension is approximately 10 mm. Vertical palpebral asymmetry may indicate the presence of true ptosis of the eyelid, which would necessitate ptosis repair. The upper eyelid orbicularis muscle should be smooth and flat, and the upper eyelid crease should be crisp. The upper lid crease should lie between 8 and 12 mm from the lid margin in the white patient. A more inferior position of the upper lid crease gives a heavy and tired appearance to the eye. Excessive lid folds, tissue prolapsing over the upper eyelid crease, should be minimal to avoid the aged and tired look (Fig. 30-16). The upper lid margin should cover 1 to 2 mm of the superior limbus, while the lower lid margin should lie at the inferior limbus or 1 mm below the inferior limbus. Note should be made of excessive skin, muscle, and orbital fat. The pinch test helps determine the degree of excess lid skin that is present. The snap test helps determine the degree of lower lid laxity and is useful in preoperative planning (Fig. 30-17). The lower eyelid is distracted from the globe, and an audible snap should be heard if the eyelid is not significantly lax. Additionally, a ptotic lacrimal gland must be recognized for potential correction at surgery. Excessive lateral skin hooding may require skin excision beyond the lateral orbital rim, and prolonged wound healing would be expected in this area of greater skin thickness—a point that must be relayed to the patient before surgical intervention.[12,13]

The lower eyelid should closely appose the globe without drooping of the lid away from the globe (ectropion) or in toward the globe

Figure 30-16. Prolapsing tissue over the upper eyelid crease, resulting in a tired and aged look, may be the result of skin, soft tissue, hypertrophied orbicularis muscle, and fat herniation. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:678.)*

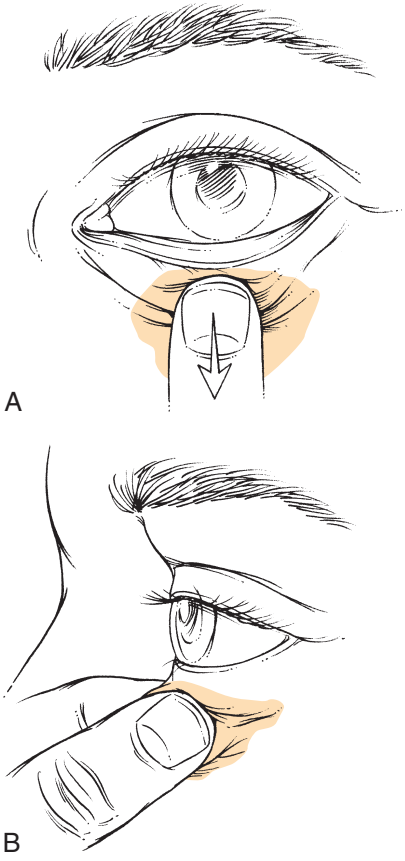

Figure 30-17. A, The snap test helps determine the degree of lid laxity. It is performed by pulling the lid away from the surface of the globe and observing its ability to snap back. A normal lid will return to its position immediately. **B,** Pinching the lower eyelid helps determine excess skin.

(entropion). Excessive lower eyelid laxity should be recognized with the snap test, and when present, a lid shortening/tightening procedure should be performed in conjunction with blepharoplasty. Exophthalmos and enophthalmos should be recognized—neither is favorable—and each may represent an underlying disorder. Visual acuity should be evaluated, as should the presence of a Bell's phenomenon. Absence of the Bell's phenomenon places the patient at increased risk for the development of postoperative corneal abrasions if temporary or permanent lagophthalmos occurs after surgery. If the patient exhibits signs of a dry eye, the Schirmer test should be performed, and caution should be used in deciding on surgical intervention.[13,14]

Upper Eyelid Ptosis

The ptotic eyelid is often masked by dermatochalasis, so preoperative attention should be given to identifying and classifying upper eyelid ptosis. Blepharoplasty alone of the ptotic lid may lead to an unfavorable cosmetic result and need for additional surgery. The most common cause for eyelid ptosis is secondary to acquired involutional changes, although the patient should also be assessed for myogenic, neurogenic, and mechanical causes, as well as pseudoptosis.

Evaluation

The degree of ptosis can be quantified by the margin-reflex-distance (MRD). This is the distance between the central corneal light reflex and the upper lid margin, usually around 3 to 4.5 mm. Asymmetry between lids is not uncommon and is usually reflected in the MRD. Normally, the upper lid margin should rest about 1 mm below the tangent of the superior limbus. The muscle light should be held between the examiner's eyes (coaxial to the examiner's observation axis), the examiner's eyes should be level with those of the patient. The light should not be too bright or else the patient may squint and give an artificially low measurement. The highest point in the upper lid is just medial to midline (near medial limbus) and has a greater curvature than the lower lid margin, whose lowest point is near or at the midline. In addition to the MRD, the central interpalpebral distance, which is another measure of comparison between lids, should also be recorded. Normally 8 to 10 mm, the central interpalpebral distance is the distance from the upper lid margin at its highest and the lower lid margin at its highest. A patient with ptosis of the upper lid and retraction of the lower lid may also have "normal" palpebral fissure measure.

The levator function is helpful in distinguishing the potential etiologies of the ptosis as well as in surgical planning. It is assessed by measuring the excursion of the upper lid margin in extreme downgaze to extreme upgaze. The brow should be fixated by the examiner to prevent recruitment of the frontalis. Normal function is usually greater than 12 mm. Levator shortening procedures potentially have a good prognosis with normal function. If the levator excursion is less than 5 mm, as is often seen in congenital ptosis, another surgical approach (e.g., frontalis sling) may be required.

An important landmark to document preoperatively is the position of the upper eyelid crease. Its position depends on sex and race (as described earlier). A high lid crease may suggest disinsertion of the levator aponeurosis, the anatomic etiology for acquired ptosis. As the levator moves posteriorly, the preaponeurotic fat overlying it likewise moves further into the orbit. This may decrease the upper eyelid fold and result in the appearance of a deep superior sulcus.

Additionally, one should assess the orbicularis function and extraocular movements to help identify possible myopathic causes for the ptosis. Orbicularis strength can be assessed by asking the patient to maximally close the eyelids and resist opening by the examiner. If normal, a patient should be able to nearly resist the examiners efforts in opening the fissures. The presence of lagophthalmos may also indicate slightly weakened orbicularis function. This is important to document and discuss with the patient because it may be exacerbated following ptosis surgery. Decreased extraocular movements can be seen in cases of chronic external ophthalmoplegia and adult onset muscular dystrophy. A decreased Bell's phenomenon can also be seen in patients with a myopathy and may make patients more susceptible to ocular exposure after ptosis correction.

Finally, patients should be questioned about dry eye symptoms and tear secretion should be evaluated, because dry eye may be exacerbated after ptosis surgery. Schirmer test paper is used to estimate tear secretion (Fig. 30-18). If the wet paper measures less than 5 mm after 5 minutes with the use of topical anesthetic, there is a possibility of further complications. A punctal plug inserted postoperatively allows

Figure 30-18. The Schirmer test paper is placed in the conjunctival fornices and evaluated after 5 minutes. Repeated measurements of less than 5 mm of wetting, with anesthesia, can be highly suggestive of aqueous tear deficiency.

for an increased reservoir of natural tears; however, the patient must be counseled that dry eye symptoms may worsen.

Midface Aesthetic Ideals

A prominent cheek bone and malar eminence conveys a youthful appearance. As time advances, the tone of the orbicularis oculi muscle is weakened and the sling that helped maintain the soft tissue fullness in the malar eminence can no longer support the underlying structures. The inferior and lateral orbital rims should be padded with malar fat and SOOF. Descent of the subcutaneous malar fat pads, as well as the suborbicularis oculi fat, results in a flattened malar eminence and prominent orbital rims, which are aesthetically unpleasant (see Fig. 30-13). In cases of ptotic midfacial structures and exposure of the orbital rim, the juxtaposition of prolapsed orbital fat and the fallen SOOF results in a double contour. Restoring the fallen SOOF to its more youthful position with a midface lift eliminates the double contour.[7]

Preoperative Planning

As in all patients who present for cosmetic surgery, stable mental health and healthy motivations for the surgery should be determined. It is essential to establish in the patient realistic expectations for the surgical procedure. A complete history and physical examination is essential to elicit any signs or symptoms of visual field defects, dry eye symptoms, seasonal allergic symptoms, or thyroid dysfunction. Past medical history and past surgical history must expose any prior issues relating to the periorbital region and any systemic disease that may preclude the use of general or local anesthetic. A history of connective tissue disorders, collagen vascular disorders, Graves' disease, or prior facial nerve paralysis should be determined. The medication history should not only include traditional allopathic preparations, but also herbal and homeopathic preparations. Use of eyeglasses, contact lenses, eye medications, and a family history of glaucoma should be elicited.

Before planning surgery, information for informed consent must be given to the patient in completely understandable terms and in a thorough manner. All of the risks of surgery should be explained fully. The patient should be cautioned about medications that may cause an increased risk of bruising and bleeding. The expected postoperative course and ultimate results should be described to the patient in order to prevent any misconceptions or disappointments on the part of the patient.

Preoperative and postoperative photography should be obtained. The patient's head should be in the Frankfurt horizontal plane, and the hair should be pulled back to show the entire forehead and hairline. Standard views for the periorbital area include anteroposterior full face portrait with the patient in repose and while smiling, anteroposterior full face portrait with the patient raising the eyebrows to accentuate the forehead rhytids and to demonstrate normal facial nerve function, anteroposterior full face portrait with the patient squinting to accentuate vertical and horizontal glabellar rhytids, and bilateral lateral profile

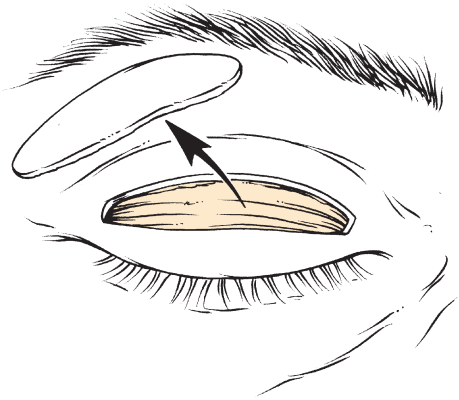

Figure 30-19. Upper eyelid skin incision is marked. The inferior portion of the lid incision is made approximately 8 mm above the lid margin. A skin muscle flap has been excised. *(Redrawn with permission from Mayo Clinic.)*

full face portrait. In addition, close-up photographs of the forehead, eyes, and glabellar region are useful to fully show the fine and deep forehead and glabellar rhytids.

Surgical Techniques

Once the appropriate candidate has been selected, the surgeon has a number of options to consider regarding surgical technique. The type of anesthetic, incision locations, dissection planes, management of forehead muscles, and need for skin excision should all be addressed. Regardless of the technique used, it is essential that the browlift be performed before the blepharoplasty, because upward repositioning of the brow reduces the amount of upper eyelid skin excess, resulting in a decrease in the amount of skin to be excised with the blepharoplasty. Failure to adhere to this principle may result in the development of postoperative lagophthalmos.

Blepharoplasty and Ptosis Repair

Upper Eyelid

Success in blepharoplasty requires that the surgeon understand the aesthetic relationships between the eyelids, eyebrows, forehead, orbit, and midface. These aesthetic ideals are discussed earlier in the chapter and may be reviewed. Once the individual patient's good medical health, psychological motivations, and expectations regarding the surgery are understood to be reasonable, the surgery may proceed. Typically, blepharoplasty is performed as outpatient surgery under either local or general anesthesia.[12]

If performed in conjunction with a browlift, the blepharoplasty incision markings are placed after the browlift is complete and all incisions have been closed. Marking the eyelids is the single most important step in blepharoplasty, and as such, great care must be taken to ensure precision (Fig. 30-19). If there is no eyelid ptosis, the initial lid marking is made at the natural skin crease or 1 mm above the natural crease. Making the incision 1 mm above the natural crease allows for wound contracture to bring the ultimate lid scar into the proper position at the natural crease. Generally, the lid crease is at the same level bilaterally, but if not, the incisions may be designed to create lid symmetry with the use of a caliper. The medial end of the incision descends approximately 1 to 2 mm from the central vertical height and is carried to the punctum of the medial canthus but not beyond the punctum. Incisions medial to the punctum and beyond the nasal orbital depression may cause irreversible webbing. The lateral extent of the incision curves upward slightly, within a natural crease in the sulcus between the orbital rim and the eyelid. The lateral extent is determined by the degree and location of lateral hooding, and may even extend beyond the lateral orbital rim. The patient must be told preoperatively that the skin incision lateral to the lateral orbital rim will take longer to heal because the skin thickens beyond the lateral orbital rim. To determine

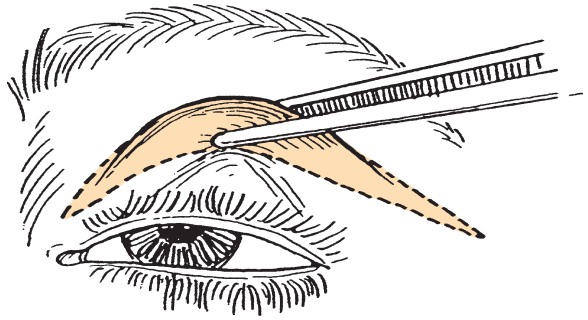

Figure 30-20. The pinch test helps determine the amount of lid skin to be excised. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:687.)*

the amount of redundant skin to excise, the pinch test is performed (Fig. 30-20). One blade of a Graefe forceps grasps the skin at the previously marked lid crease, and the other blade grasps the skin at a point superiorly, which just smooths out the skin of the eyelid until slight eversion of the lid occurs. This technique helps prevent postoperative lagophthalmos. Leaving approximately 20 mm of eyelid skin may also help prevent postoperative lagophthalmos. The superior extent of the eyelid skin can be identified by palpating the abrupt transition from the thin upper eyelid skin to the thicker eyebrow skin. The inferior extent of the brow cilia should be avoided as an endpoint because the patient may have epilated and therefore altered the apparent end of the inferior brow.[6] Both the medial and lateral ends of the upper lid fusiform excision should form a 30-degree angle.[12,14]

If the patient has eyelid ptosis, the lid crease is likely to be higher on the more affected side and therefore a new lid crease may need to be created. The new lid crease is placed according to sex and race as described previously.

Once the markings are complete, local infiltrative anesthesia is injected in the immediate subcutaneous plane. If ptosis surgery is also being performed, care should be taken to ensure that the minimum amount of local anesthesia is used so as to not affect the underlying levator. Usually 1 to 2 mL of local anesthesia is all that is needed. After adequate time is given for the anesthetic to take effect, the skin incisions are made with a fresh blade of the surgeon's choice, and the skin is taken as a single layer or as a two-layer skin-orbicularis unit (see Fig. 30-20). If skin only is excised, a determination is subsequently made regarding the amount of orbicularis oculi muscle to excise. Resection of a strip of orbicularis along the inferior length of the skin excision helps recreate a distinct upper eyelid skin crease. A variable amount of orbicularis oculi muscle should be resected, depending on the degree of muscle hypertrophy.

Resection of orbicularis exposes the orbital septum and allows visualization of the orbital fat through the septum. Two different techniques may be used to address the pseudoherniation of fat. Bovie cautery of the orbital septum contracts the septum and reduces the degree of fat pseudoherniation as has been described for lower lid blepharoplasty.[15] Alternatively, opening the orbital septum and removing fat from the medial and central compartments may be achieved (Fig. 30-21). Clamping the fat that will be removed, followed by cauterization of the fat in the clamp, helps prevent postoperative hematomas. Anterior traction should not be placed on the clamp to prevent avulsion, bleeding, and excessive resection. Only fat that protrudes into the wound with gentle globe pressure should be clamped and excised to avoid overaggressive removal of orbital fat and a hollowed postoperative look. However, care should be used to help avoid the common error in upper eyelid blepharoplasty of failing to remove enough of the medial orbital fat. Laterally, the lacrimal gland may come into view and should be recognized to avoid its injury. The lacrimal gland is more pink, vascular, and firm than is the fat.

If only blepharoplasty is performed, after excellent hemostasis is achieved, wound closure proceeds with a single layer closure of the skin with a 6-0 fast-absorbing gut suture.[12,14] However if ptosis surgery is also going to be performed, then the lower edge of the incision is grasped with a Castroviejo forceps (0.3 or 0.5) and the pretarsal orbicularis is dissected medially and laterally to expose the surface of the tarsal plate (see Fig. 30-21). Next, this strip of orbicularis can be removed to further debulk the lid fold and expose the underlying layers to help identify the levator aponeurosis. An important landmark for identifying the levator aponeurosis is the preaponeurotic fat pad. It lies posterior to the orbital septum and is anterior to the levator. A cotton tip applicator can be used for gentle dissection and may help prevent inadvertent damage to the underlying levator. Once identified, the orbital septum should be opened medially and laterally because leaving the orbital septum attached may result in postoperative lid lag or lagophthalmos. A Desmarres retractor can be used to retract the fat, exposing the underlying levator aponeurosis. To ensure that one has correctly identified the levator, the patient can be asked to look up while grasping the levator. If identified appropriately, a force is transmitted via the forceps. A double-armed 6-0 silk suture can be used as a cardinal suture by passing it in a horizontal mattress fashion through the tarsal plate approximately 5 mm from the lash line. This tarsal bite should be approximately half thickness, because a full-thickness bite may lead to postoperative keratopathy. The sutures are then passed through the cut edge of the aponeurosis and tied in a slip knot. The position of the lid may then be assessed and additional horizontal mattress sutures may be placed medially or laterally to adjust the lid contour. Initially, a slight overcorrection may be desired to allow for postoperative descent that may occur from the stimulation of Müller's muscle by the local anesthesia. Once the desired height and contour are achieved, the sutures may be tied down and the skin closed as described previously.[6,13,20]

Lower Eyelid Blepharoplasty

Transconjunctival

The transconjunctival blepharoplasty has become increasingly popular over the past few years due to the hidden incision, the maintenance of the orbicularis support structure for the lower eyelid, and a reduced rate of postoperative ectropion. Proper patient selection is required for the successful use of this technique in blepharoplasty. Patients with pseudoherniation of fat and little need for skin excision are good candidates for this procedure. In addition, patients who heal with hypertrophic scars, and patients who will not accept an external incision are good candidates. The presence of a mild to moderate amount of excess skin in the lower eyelid does not preclude the transconjunctival approach, in that a pinch excision of skin and lid resurfacing techniques may be used to address the lower lid skin changes.[13]

After local anesthetic is injected and adequate time is allowed for the vasoconstriction to take effect, the lower eyelid conjunctival surface is exposed. Either a preseptal or postseptal approach may be used, depending on the surgeon's preference (Fig. 30-22). A 4-0 silk suture is placed through the eyelid margin for traction. The traction suture, together with a Desmarres retractor, helps evert the lower eyelid. The preseptal approach involves a transconjunctival incision made at the inferior margin of the tarsal plate. A plane is developed just deep to the orbicularis muscle in the avascular plane between the orbicularis muscle and orbital septum, down to the level of the orbital rim, without exposing the orbital rim. A 4-0 silk suture is then passed through the conjunctival edge to provide traction and corneal protection. The orbital septum is then in clear view and may be entered with the Bovie cautery.

Alternatively, the postseptal approach may be used; this entails a single incision placed 4 mm below the inferior tarsal margin, directly through the conjunctiva and lower eyelid retractors, to expose orbital fat from the posterior aspect. The orbital septum is maintained completely intact in this technique. Traction sutures of 4-0 silk or nylon are placed on either side of the transconjunctival incision to allow for blunt and sharp dissection throughout the lower eyelid retractors to the orbital fat. Identification of the inferior oblique muscle, which separates the medial from the middle fat pads, should be performed in both the preseptal and postseptal methods to avoid injury to this structure. The

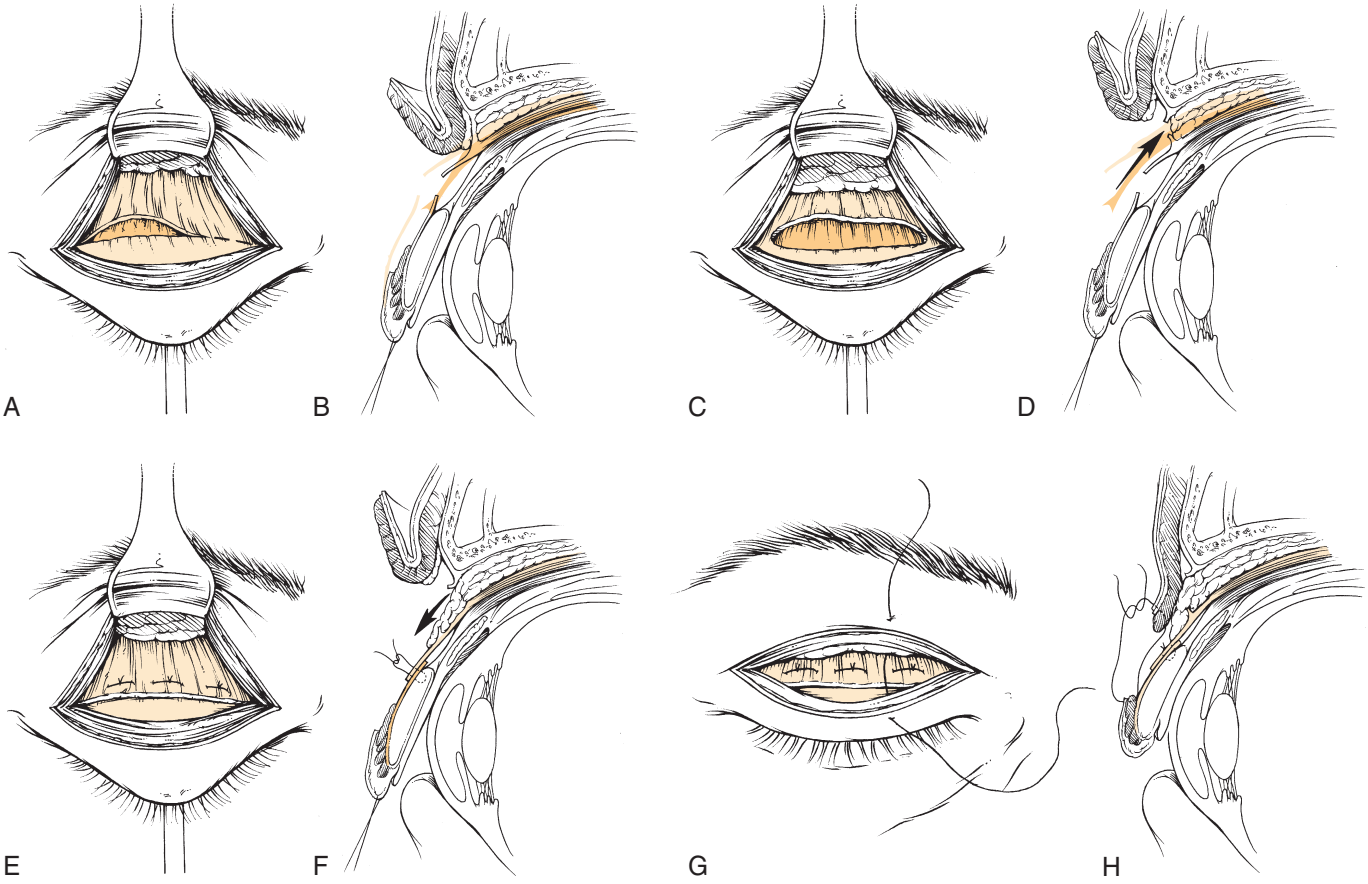

Figure 30-21. **A** and **B,** A silk traction suture has been placed through the gray line. The orbital septum has been opened and a portion of the levator aponeurosis has been released from its tarsal insertion. Müller's muscle is partially visible deep to the levator. **C** and **D,** A Desmarres retractor has been placed and the preaponeurotic fat is visible. **E** and **F,** A double-armed mattress suture is placed through the tarsus and levator. One to three mattress sutures may be required to achieve a natural appearing contour. **G** and **H,** The lid crease can be reformed with interrupted sutures through the skin and orbicularis. The skin is then closed in a running fashion. *(Redrawn with permission from Mayo Clinic.)*

fat is excised as described for the upper eyelid blepharoplasty, using a clamp and Bovie cautery. The lower eyelid fat pads communicate directly with the deeper orbital fat, so excessive traction on the fat should be avoided to help prevent orbital hemorrhage. The incisions may be left open to heal spontaneously, or loosely applied fast absorbing sutures may be used. If redundant skin is present, it may be excised with the scalpel, and the incision closed with 6-0 fast-absorbing gut sutures (Fig. 30-23).

Subciliary Approach

The subciliary approach is most useful for those patients with large amounts of excess skin. A subciliary incision is made 2 mm below the lash line, extending from 1 mm lateral to the inferior punctum to 10-mm lateral to the lateral canthus. The incision extends through the skin and orbicularis muscle along the entire length of the incision (Fig. 30-24). A skin-muscle flap is elevated to the orbital rim, exposing the orbital septum in its entirety. The skin-muscle flap is extended over the rim so that the muscle is separated from the arcus marginalis to allow for proper skin redraping (Fig. 30-25). The orbital septum is then approached either with Bovie cauterization of the intact orbital septum or by excising the bulging orbital fat. After hemostasis is achieved in the fat compartment, a variable amount of skin and muscle is excised as needed (Fig. 30-26). Closure of the incisions is accomplished in two layers. Laterally, the orbicularis fibers are reattached with a 5-0 PDS suture to help prevent tension on the lateral-most aspect of the incisions. This allows the skin edges of the incision to approximate one another closely. Finally, the skin layer is closed with 6-0 fast-absorbing gut suture.[13,14]

Lid Shortening Procedure

If preoperative evaluation determines that the lower eyelid is excessively lax by the snap test, a lid shortening procedure is indicated to prevent postoperative ectropion. We prefer to perform a lateral tarsal strip procedure with reattachment of the tarsus to the superior and inner aspect of the lateral orbital rim. This step is performed before closure of the lower eyelid blepharoplasty incision.

Complications

Orbital hemorrhage is a complication seen most commonly following lower eyelid blepharoplasty. The presence of orbital hemorrhage is first noted by the patient due to increasing edema, ecchymosis, and severe pain. If vision remains intact, the patient simply has swelling and slight pain, and the bleeding has stopped, then ophthalmology consultation for funduscopic examination and close observation should be done. Occasionally, steroids may be used in combination with mannitol to help reduce the swelling; however, there are no prospective studies showing an advantage to this protocol. If there are signs of optic neuropathy, including severe pain and vision loss, immediate lateral canthotomy with cantholysis, mannitol, and intravenous steroids are instituted. If no resolution ensues, orbital decompression is advised. Failure to address this complication within 90 minutes of onset may result in permanent blindness.[16,17]

Lagophthalmos, the failure of complete eye closure, is a common finding following upper lid blepharoplasty and ptosis repair. It is frequently seen in the immediate postoperative period due to orbicularis paresis and possibly levator spasm. Over the next few weeks postoperatively, periorbital edema may cause persistence of the lagophthalmos.

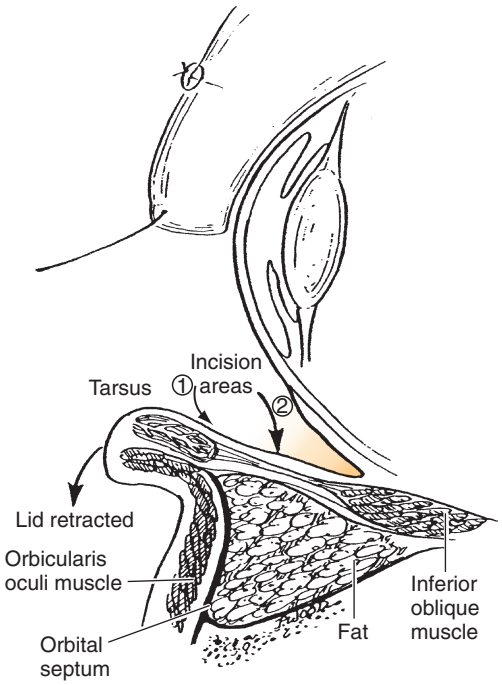

Figure 30-22. Preseptal (1) and postseptal (2) transconjunctival approaches to blepharoplasty. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:693.)*

Figure 30-23. Resection of skin is achieved, as needed, after fat removal. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:694.)*

Such patients should be managed with eye care precautions to prevent corneal exposure complications, including lubrication with ointment at night and artificial tears throughout the day. Additionally, a humidification chamber and taping the eyelids closed may be useful. If lagophthalmos persists beyond 6 to 8 postoperative weeks, an excess of upper eyelid skin may have been removed at the time of surgery. This would require surgical intervention for correction, including the use of a skin graft to replace the missing skin.[16,17]

Eyelid malposition is one of the most common complications following blepharoplasty, and may range in severity from scleral show to frank lower eyelid eversion. Ectropion and lower eyelid retraction may result from two causes, both of which are common and easy to prevent. Overaggressive skin resection may lead to ectropion because contraction of the shortened lower eyelid anterior lamella may progress to ectropion with wound healing. The second cause of ectropion is a failure to recognize and address excessive lower lid laxity in an effective manner. At the time of blepharoplasty, a lid shortening procedure should be done in cases of excessive lower lid laxity. Failure to perform a lid tightening procedure will result in wound contracture causing lower lid ectropion. Ectropion can usually be corrected by addressing the cause of the problem with either a tarsal strip for excessive laxity or with lysis of cicatricial adhesions that are causing persistence of ectropion.[13,14,16,17]

Entropion results from excessive shortening of the posterior lamella of the eyelid and the resultant effects of long-term scar contracture. It is corrected by lysis of cicatricial adhesions and the placement of a hard palate mucosal graft to help prevent recurrent cicatrix and entropion.

Epiphora, in the absence of preoperative dry eye syndrome, is typically the result of a dysfunctional lacrimal collecting system. Causes of a dysfunctional lacrimal apparatus include punctal eversion due to wound contracture or edema, impairment of the lacrimal pump system due to atony, edema, or injury to the orbicularis oculi muscle, or

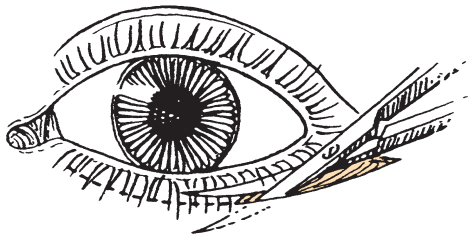

Figure 30-24. The lower eyelid incision may be made with a scissor or with a knife. Care is taken to avoid cutting the eyelashes. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:688.)*

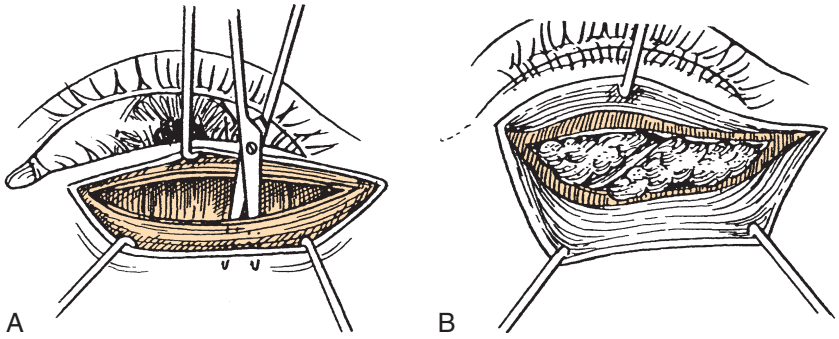

Figure 30-25. A, The skin and muscle flap is dissected bluntly and sharply. **B,** Access is gained to the septum and fat compartments for subsequent fat removal or cauterization of septum. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:689.)*

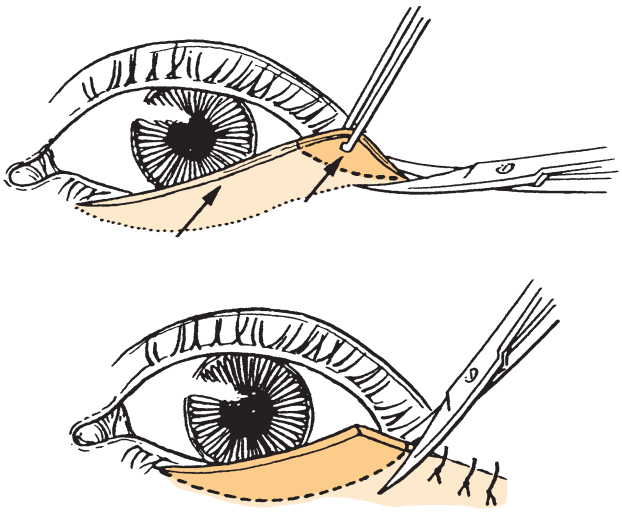

Figure 30-26. The flap is repositioned and excess skin and muscle is excised. Care is taken to excise slightly more muscle than skin to ensure there is no bunching of tissue at the incision line. *(From Colton JJ, Beekhuis GJ. Blepharoplasty. In: Cummings C, Fredrickson J, Harker L, Krause C, Richardson M, Schuller D, eds.* Otolaryngology Head and Neck Surgery. *3rd ed. St. Louis: Mosby; 1998:689.)*

outflow obstruction due to a lacerated canaliculus at the time of incision. If laceration has occurred, placement of a Silastic stent is recommended. Persistent eversion of the lid may be corrected with cauterization or excision of the conjunctival surface below the canaliculus to cause inversion of the lid, punctum, and canaliculus.[13,14,16,17]

Excess skin that remains following blepharoplasty, that is, failure to remove adequate skin at the time of blepharoplasty, is an easy complication to correct. Once the swelling has completely subsided after 4 to 6 weeks postoperatively, additional skin may be excised in the office under local anesthesia.

Asymmetry in the early postoperative period may be the result of asymmetric soft tissue edema. If asymmetry persists after the swelling has completely resolved, then using the caliper and excising the appropriate amount of skin and fat will help reestablish symmetry to the lids.[13,14,16,17]

Skin discoloration that persists after the incisions are well healed may be treated with topical retin A, hydroquinones, chemical peels, laser resurfacing, or dermabrasion. Milia may occur along incision lines and may be treated by unroofing with a scalpel or 18-gauge needle. Skin incisions extending medial to the punctum of the lids not only increase the risk of lacrimal apparatus injury but also increase the risk of web formation in the epicanthal region. Webs may be corrected with Z-plasty.

Adjunctive Procedures

Skin Resurfacing

Facial resurfacing procedures may be used safely in conjunction with surgery to the periorbital area. They produce their effects by ablating skin to variable depths, allowing for collagen regeneration and skin tightening. Different agents and techniques produce varying degrees of penetration and results. Even though resurfacing cannot replace surgery for the treatment of deep hyperfunctioning rhytids, laser, chemical peels, and dermabrasion may be used to treat fine wrinkling, acne scarring, telangiectasias, and photodamaged skin. Care should be exercised when resurfacing skin that has been undermined in the immediate subcutaneous plane for fear of devascularizing the tissue, resulting in flap necrosis. The resurfacing should be feathered into the hairline and eyebrows to avoid evident lines of demarcation. Birth control pills should be stopped 2 months before facial resurfacing to prevent pigment changes. Accutane (isotretinoin) should not have been used in the year preceding skin resurfacing to avoid the increased risks of hypertrophic scarring associated with isotretinoin use. An antiviral agent is prescribed by many physicians for use during the periprocedure period as prophylaxis against herpetic reactivation. Preoperative tretinoin is thought by many to accelerate wound healing.[18]

Milia, 1- to 2-mm pustules originating from the skin adnexa, are frequent following resurfacing procedures. They often resolve without treatment, but if they persist they may be unroofed with a scalpel or 18-gauge needle. Failure to treat the milia may result in permanent scar formation. Pigmentary changes are expected following resurfacing procedures; however, they should resolve by 4 to 6 weeks. If the erythema associated with the resurfacing procedure seems to be excessive, topical steroids may be applied to reduce the erythema. Prolonged discoloration occurs most commonly in patients with Fitzpatrick IV-VI skin types, and may be the result of sun exposure in the period following resurfacing. Persistent hyperpigmentation may require bleaching with hydroquinone or retinoic acid, whereas hypopigmentation may require serial excision and punch graft replacement of the discolored skin. There are no data at present to suggest that pretreatment with any topical agent will help prevent post-resurfacing pigment changes.[18]

Injectable Filler

Whereas the ideal implantable or injectable material has not yet been developed, collagen, silicone, fat, and polytetrafluoroethylene have been used extensively as filler material for facial rhytids. Injectable fillers provide a relatively easy and noninvasive approach to rhytids in difficult-to-get-to facial locations. Augmenting the soft tissues in these areas may eliminate the shadowing caused by the rhytids, thereby making the rhytid less visible. Forehead rhytids are less amenable to these techniques, whereas glabellar rhytids are well treated by these techniques. Each of the different injectable and implantable materials has its own safety and utilization profile.

Botox

Botulinum exotoxin A (Botox), produced by the bacteria *Clostridium botulinum*, is useful in reducing facial wrinkles associated with facial muscle contractions. Botox is safe, easy to administer, and reversible with time, making it a very attractive cosmetic adjunct in the treatment of the periorbital region. It reversibly blocks the release of acetylcholine from the presynaptic neuromuscular junction, thereby temporarily paralyzing the affected muscle. The effects of Botox are observed 2 to 3 days after injection, with maximal weakness occurring 1 to 2 weeks after injection. The effects last for 3 to 6 months. Botox is useful for the treatment of glabellar frown lines, crow's feet, horizontal forehead rhytids, smile lines, horizontal neck lines, and unilateral facial paralysis to reduce the asymmetry between the normal and paralyzed side. Botox may also be used as a browlift procedure. Injection into the orbicularis oculi muscle inferior to the lateral brow allows for unopposed frontalis muscle action, which produces brow elevation. Similarly, frontalis injection along the medial aspect of the brow allows for unopposed orbicularis muscle activity, producing a slight ptosis of the medial brow and a relative elevation of the lateral brow. Complications from Botox use include ptosis and lagophthalmos with inadvertent injection of deeper muscles. Additionally, erythema and bruising may occur.[19]

SUGGESTED READINGS

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For complete list of references log onto www.expertconsult.com.

CHAPTER THIRTY-ONE

Liposuction

Edward H. Farrior

Stephen S. Park

Key Points

- Liposuction is most effective on fat deposits that are congenital in nature and unresponsive to weight loss.
- Preoperative assessment and identification of contributing factors to an oblique cervical mental angle is imperative in avoiding dissatisfied patients. These include the retrognathic chin, a low anterior hyoid bone, skin laxity, and platysmal dehiscence. These factors do not respond to liposuction.
- The surgeon must concentrate at the periphery of the liposuction site to avoid repeated passes in the immediate submental area and the creation of a cobra neck deformity.
- The margin must be feathered with a smaller canula to soften the transition from the treated to the nontreated areas.
- In facial liposuction the vacuum must be released when withdrawing and repositioning the cannula to avoid the creation of grooves or furrows over the posterior face and parotid area.
- A criss-crossed pattern of passes helps create a smoother, more natural reduction of adiposity. This should be the technique in the face and neck.

Having long been a part of cosmetic surgery, lipocontouring has continued to progress with the ever-changing technology of cosmetic surgery. Initially, lipocontouring was accomplished with the direct excision of fat through an open surgical approach; it now includes suction lipectomy, small cannula lipectomy, and, most recently, liposhaving and ultrasonic assisted liposuction. The goal of these procedures is to change the contour of the face or neck through the removal of localized fat deposits.

Suction lipectomy is an effective means of recontouring the face that has been popularized and refined over the past 30 years.[1-5] As with all cosmetic surgery, understanding the anatomy, physiology, and changes that result from the aging process is imperative. On the basis of these changes, a logical approach to the integration of suction-assisted lipocontouring into the practice of facial plastic and reconstructive surgery is possible (Fig. 31-1).

The distribution of body fat is a consequence of genetics and is influenced by hormones, diet, exercise, medications, and patient age. It has become apparent through tissue culture studies that, after a critical mass within an adipocyte has been reached, hyperplasia can occur.[6] Although the mechanism of adipocyte hyperplasia has not yet been determined, the consensus remains that any significant change in fat deposition occurs through the enlargement rather than the addition of cells.[7] Diet-resistant localized fat deposits, which are ideal for lipocontouring, may represent localized adipocyte hyperplasia. Liposuction reduces the number of adipocytes regardless of their size and therefore should yield a lasting result, unless excessive weight gain occurs. The liposuctioned regions of hypertrophy should respond to weight gain in a fashion that is similar to adipocytes in other regions of the body and, therefore, should be resistant to significant contour changes that are out of proportion with overall weight fluctuation.

Liposuction involves the application of negative pressure through a hollow cannula with a 3- to 6-mm lumen in the subcutaneous plane. Fat is then avulsed as atraumatically as possible. Because of the loose intercellular connections, fat cells are more easily aspirated than tissues with greater structural integrity (e.g., muscle, vessels, nerves). The standard suction cannula has no cutting surface; therefore structures with more integrity are protected.

Liposhaving has recently been advocated as an alternative to liposuction. In this technique, a soft tissue shaver is used with minimal suction to gently shave adipocytes.[2] The safety of this technique is of concern, and further investigation is under way. With liposuction and liposhaving, preserving important structures and maintaining bridges of uninterrupted tissue between the deep and superficial layers in an effort to maintain a healthier skin flap are the principles to be followed. Ultrasonic liposuction adds the mechanical agitation of the cannula to assist in the dissection and release of adipocytes and is usually done in conjunction with tumescent infiltration.[8] Recently the use of ultrasonography has been used both internally and externally to assist with liposuction. The ultrasonic energy is transferred into mechanical vibrations that cause the microcavities in the adipocytes to implode, thereby resulting in the liquefaction of the fat.[9] Multiple studies have shown potential complications with the use of subcutaneous ultrasonic energy resulting from heat generated at the cutaneous incision site and the more distal subdermal sites.[8-10] To date there are no controlled studies that demonstrate any added benefit from ultrasonic-assisted liposuction in the face and neck as compared with the standard technique.

Patient Selection

One of the greatest challenges with facial plastic surgery is the art of proper patient selection, and lipocontouring is no exception. Patient selection begins with an informal interview to get a sense of the patient's motivation, expectation, and cooperation. The patient's motivation for pursuing a cosmetic procedure should be investigated. Some patients

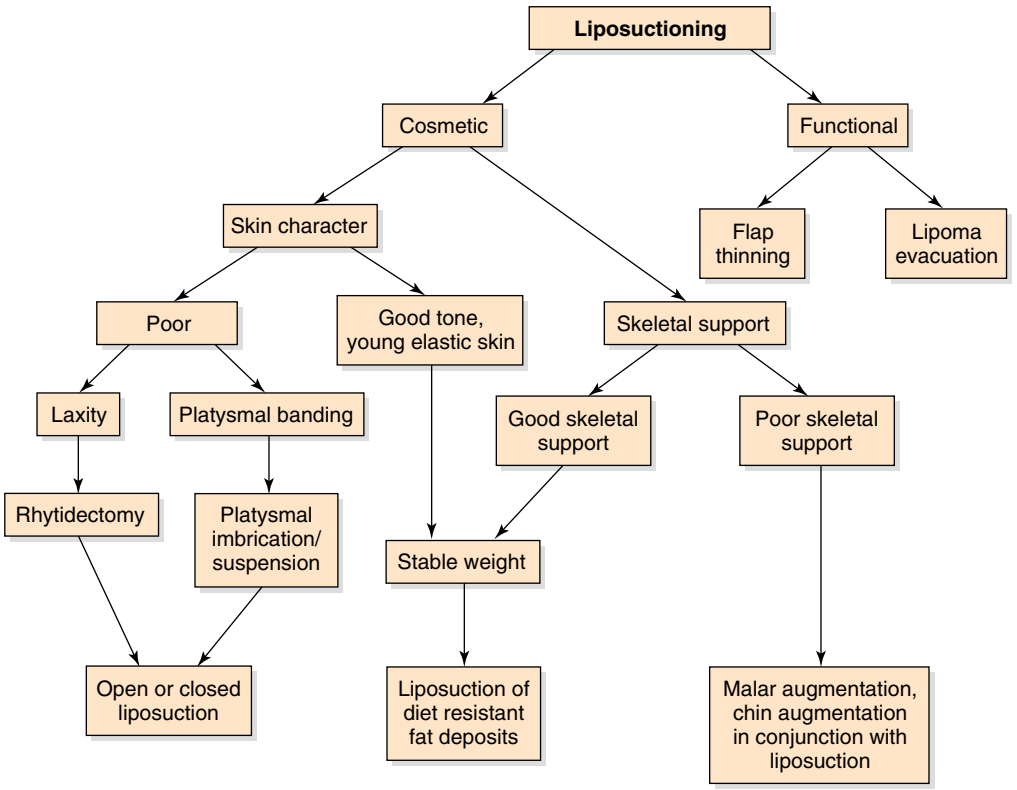

Figure 31-1. The integration of liposuctioning into facial plastic and reconstructive surgery.

expect a change in external appearance to have a significant impact on their personal or professional lives (e.g., to get a promotion at work, to dissuade a spouse's infidelity); these patients are bound to be disappointed. A patient's expectations should be precise and realistic. Lipocontouring allows for the removal of a particular area of subcutaneous fullness; although it will not have a direct impact on other areas, the change in contour may create the illusion of affecting surrounding areas and thereby influence the overall balance of the face. For example, a submental lipectomy may appear to enhance chin projection (Fig. 31-2), shorten the vertical height of the face, and create a wider and more cherubic-appearing face. Likewise, facial and jaw lipocontouring may create a more angular facial contour (Fig. 31-3) but will not increase malar projection and could create a wasted appearance. The patient's expectations should be communicated preoperatively. Computer imaging can aid in communication, but it can also be misleading if not used prudently. Cooperation is imperative during the postoperative phase. A patient who cannot avoid the sun or continue with a pressure dressing postoperatively is a poor candidate for lipocontouring and should be dissuaded from pursuing surgery.

The ideal patient is not particularly overweight and has a localized fullness that is the result of an isolated pocket of subcutaneous adipose tissue refractory to weight loss. A patient who reports a familial pattern or who has had a double chin since childhood is a good candidate. The submental, melolabial, submandibular, and buccal areas lend themselves well to lipocontouring. Younger patients tend to have greater skin elasticity, which contracts better on the new subcutaneous contour; these candidates are ideal for isolated lipocontouring. Conversely, the loss of skin elasticity and turgor in older patients will necessitate a skin-tightening procedure (see Fig. 31-17). Obese patients have excess adipose tissue in multiple layers and do not respond well to lipocontouring. Moreover, this procedure is not intended to replace general weight control.

Common Pitfalls

Patient evaluation may yield common pitfalls that lead to untoward effects:

1. Significant ptosis of facial skin may appear accentuated after lipocontouring, thereby creating a more aged appearance; these problems are best addressed with a formal face lift.[9]

2. Lipocontouring depends on the skin's ability to contract and adhere to the new subcutaneous bed, and several factors may interfere with this intrinsic property of the skin (e.g., age, radiation, scarring, actinic injury, smoking).

3. Skeletal insufficiency may reduce structural definition and give the illusion of excess fullness of a certain area (e.g., the retrusive chin and low hyoid bone causing the blunted cervicomental angle); ancillary chin implantation or genioplasty may significantly improve the aesthetic contour (Fig. 31-4).

4. Muscular problems (e.g., platysmal lift, platysmal plication, imbrication) may be present.

5. Ptotic submandibular glands and hypertrophy of parotid glands can mimic areas of excess adipose collection and should be appreciated and not traumatized.

Instrumentation

The instrumentation for lipocontouring the face and neck remains uncomplicated: a vacuum generator with the capability of reaching 1 atmosphere of negative pressure, a disposable canister to function as a trap for the aspirated fat, sterile tubing, and relatively few liposuction cannulas. The cannulas are available from multiple manufacturers. Some surgeons prefer the round over the spatulated tip, and some prefer the cannulas in which the distal 1.5 to 2 cm is slightly angulated. Angulation of the distal portion allows the positioning of the aspiration port (on the deep surface away from the skin) to be determined on palpation. Cannulas that are 3 to 6 mm are most useful for liposuction. For liposuction. a soft tissue shaver is used (Fig. 31-5), such as the endoscopic soft tissue shaver or the cartilage shaver used in joint surgery. Cannula size varies from 2.9 to 4.8 mm for liposhaving.

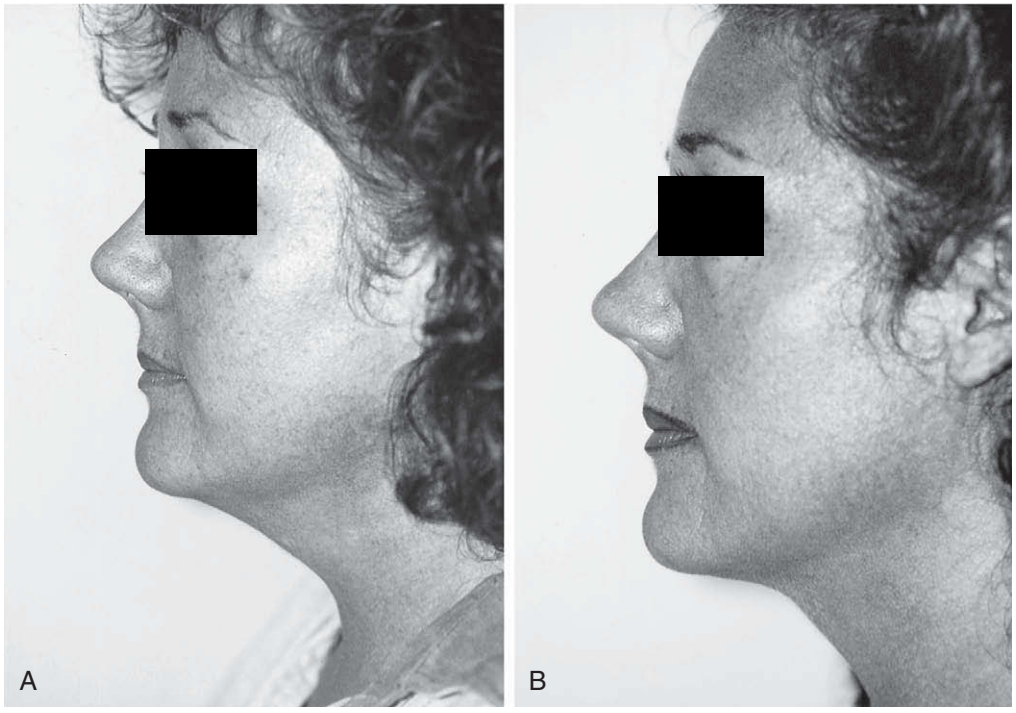

Figure 31-2. Preoperative **(A)** and postoperative **(B)** photographs show the illusion of enhanced chin projection after submental and submandibular liposuction, as well as the enhancement of the mandibular margin with improvement of the cervicomental angle.

Figure 31-3. Preoperative **(A)** and postoperative **(B)** photographs show elimination of the double chin and augmentation of the facial skeleton status after jowl, submental, and submandibular liposuction.

Figure 31-4. Preoperative **(A)** and postoperative **(B)** photographs show chin augmentation in conjunction with cervical liposuction.

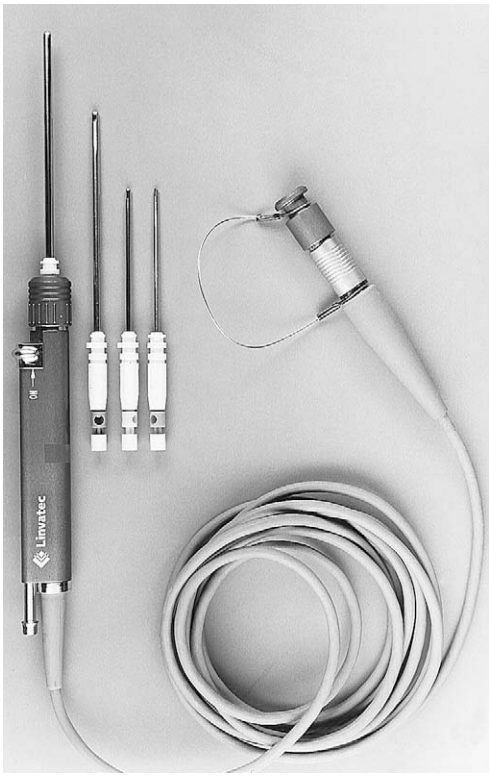

Figure 31-5. Soft tissue shavers and cannulas of various sizes.

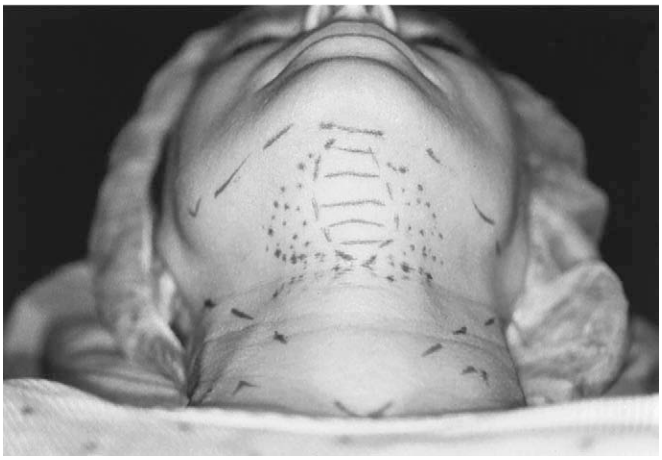

Figure 31-6. Preoperative marking of anatomic structures, including the margin of the mandible, the sternocleidomastoid muscle, and the hyoid bone, with stippling of lateral feathered regions and a vertical line through prominent submental fat pad.

Technique

Patient Preparation

Preoperatively, the patient is given routine instructions, such as to take nothing by mouth after midnight, to avoid any medications that alter platelet function, and to avoid the consumption of alcohol. Patients are instructed to wash their face and hair with an antiseptic soap and to remove all makeup and hair-care products. Prescriptions for antibiotics and pain medicine are given to the patient preoperatively to fill before the surgical procedure. When the patient arrives for surgery, an intravenous line is started and preoperative antibiotics are administered. The patient is marked in the upright position, with the areas to be suctioned circumscribed and the zones of feathering indicated (Fig. 31-6). Anatomic landmarks (e.g., the angle of the mandible, the anterior border of the sternocleidomastoid muscle, the hyoid bone and thyroid notch) may also be marked (see Fig. 31-6). After marking has been completed, the patient is taken to the operative suite, where sedation and infiltration are carried out before preparing and draping the patient. This approach allows additional time for vasoconstriction to occur before surgery.

Anesthesia

Cosmetic procedures (by themselves or in conjunction with other such procedures) are performed under intravenous sedation and infiltration anesthesia. Sedation is administered by an anesthetist with close monitoring of the patient, allowing for the virtually painless infiltration and nerve block. Submental and submandibular sculpturing are done with a block of the cervical plexus and mental nerve and with direct infiltration. Facial and melolabial contouring is accomplished with mental and infraorbital nerve block with infiltration. Block and infiltration are achieved using 0.5% lidocaine with 1:200,000 epinephrine. Long-acting agents are unnecessary for these patients.

Adequate sedation is paramount but generally needs to be heavy only during nerve block and infiltration of the local anesthetic. Midazolam, fentanyl, and propofol are short-acting agents and combine sedation with analgesia and amnesia. When necessary, these procedures are performed under general anesthesia. In this case, infiltration without nerve block is sufficient to obtain vasoconstriction and improve hemostasis.

Surgery

The location of incisions depends on the site to be contoured, and marking and infiltration are done accordingly. Incisions are limited to 5 to 10 mm and are made within relaxed skin tension lines. The submental region is usually done first, then the jaw and posterior cervical areas, followed by the region of the melolabial fold, as indicated. Flaps are then elevated, starting with a small cannula and graduating to the cannula size to be used for the lipectomy. A 5-mm cannula is usually used in the submandibular, submental, and jowl areas, and a 3-mm cannula is used for the melolabial fold.

A nonaspirative cannula is used to make multiple interconnecting tunnels throughout the region to be aspirated. During the nonaspirative phase of flap elevation, it is important to follow the same technique that would be followed when aspirating. The aspiration port should be kept on the deep surface. The skin incision is stabilized with countertraction using a skin hook, and the correct plane is identified with scissors (Fig. 31-7). Graduating cannula sizes are used to develop the tunneling after the cannula is in the correct plane (Fig. 31-8). The free hand is used to palpate the cannula tip and determine the depth of dissection (Fig. 31-9). Dissection is carried out in a spoke-like fashion from the incision; multiple distal pseudopods from each spoke are used to ensure that lateral aspiration with feathering is executed thoroughly (Fig. 31-10). Additionally, nonaspiration tunneling is performed beyond the margins of the area to be aspirated to allow for complete redraping. The surgeon should concentrate on distal aspiration, because each repetitive motion (Fig. 31-11) of the cannula crosses over the proximal adipose tissue in the region adjacent to the original insertion, possibly resulting in a hollowed appearance at that point. Hollowing and inconsistent flap elevation can also be avoided by palpating the cannula tip and preserving some fat on the undersurface of the flap.

After complete nonaspiration elevation has been accomplished, the suction is applied at one atmosphere of negative pressure, and multiple passes are re-executed. The assessment of evacuated fat may require the release of the vacuum so that any fat in the cannula and tube may be drawn into the canister; this approach may be necessary when the volume removed is small. Aspiration from the postauricular incision includes the jowl, posterior cervical, and submandibular regions (Fig. 31-12).

Cross-hatching occurs with the submandibular portions aspirated from the submental incision. In aspiration of the jowl, it is imperative to release suction when withdrawing the cannula over the posterior facial soft tissue and masseter because this area may not require aspiration, and a groove may be created in the posterior face. The margins can be tapered with a smaller cannula or with fewer passes. Liposuction of the melolabial fold or, more appropriately, of the superior border of the fold is performed with a small cannula through an incision in the nasal vestibule (Fig. 31-13).

Submental lipectomy should extend inferiorly to the level of the thyroid cartilage, posteriorly to the anterior border of the sternocleidomastoid muscle (with feathering over the muscle), and superiorly to the margin of the mandible. Lipectomy directed from the postauricular incision can extend anteriorly to the submandibular area to the anterior border of the platysma muscle and superiorly to the margin of the mandible. In the jowl, the specific deposit is aspirated, and feathering should be extended to the oral commissure and inferiorly to the margin of the mandible.

With liposhaving (Fig. 31-14), flap elevation is done in a similar fashion. The cannula is inserted with the blade inactive. After the blade is activated, extreme care should be taken at the incision to avoid damage to the skin margins. The cannula is passed in a more delicate fashion and at a slower rate than it is with liposuction, because shaving—rather than avulsion—is occurring. Minimal amounts of suction are applied, and the cannula must remain in motion when the blade is active, because it will shave progressively deeper, thereby jeopardizing other structures.

Lipocontouring can augment other cosmetic procedures. In conjunction with cervicofacial rhytidectomy, the cannula can be used to elevate the flap while sculpturing the fatty tissue. We prefer to perform open liposuction for sculpturing after flap elevation; this approach frequently requires the extension of liposuction tunnels beyond the

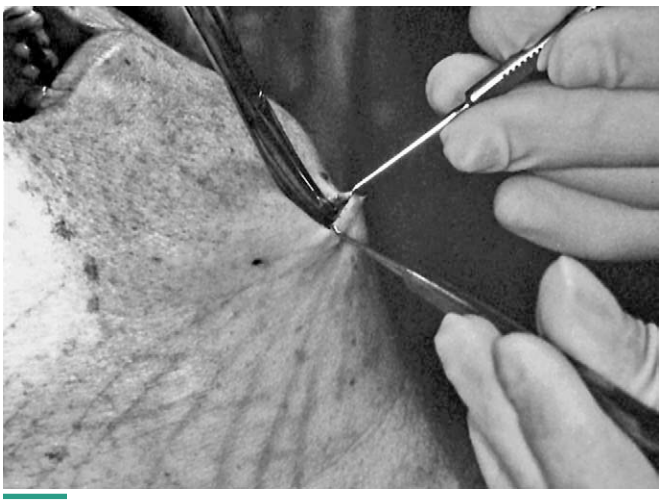

Figure 31-7. Identification of the plane of dissection using Metzenbaum scissors.

Figure 31-8. Use of the suction cannula to develop subcutaneous tunnels while stabilizing the skin with a skin hook.

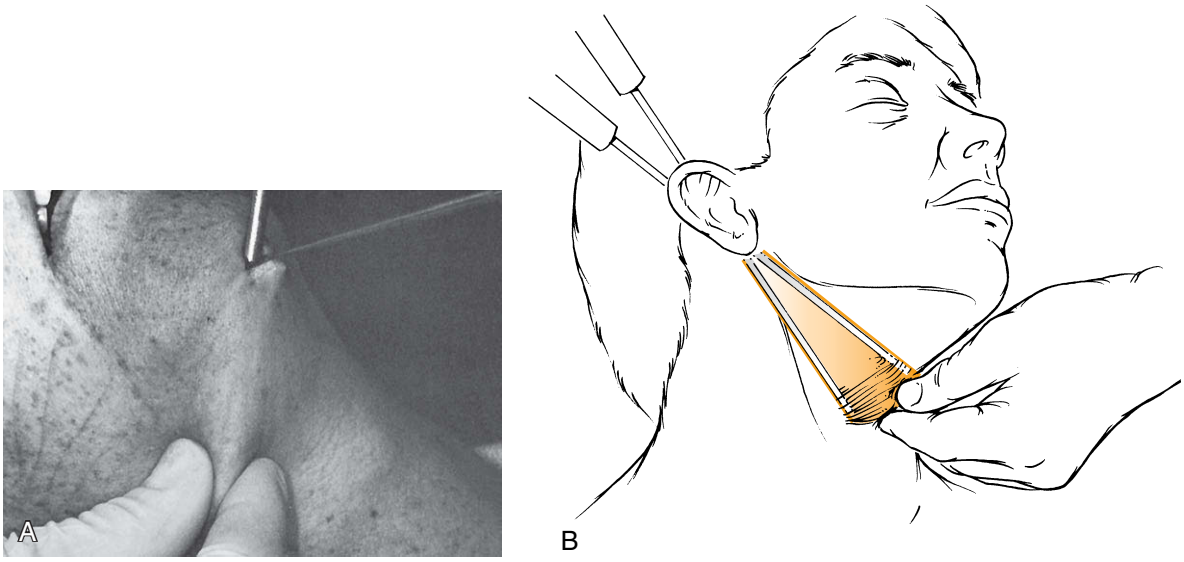

Figure 31-9. Photographic **(A)** and diagrammatic **(B)** representations of the transcutaneous palpation of the distal cannula to ensure the depth of dissection and the location of the distal cannula lumen. *(B, © 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

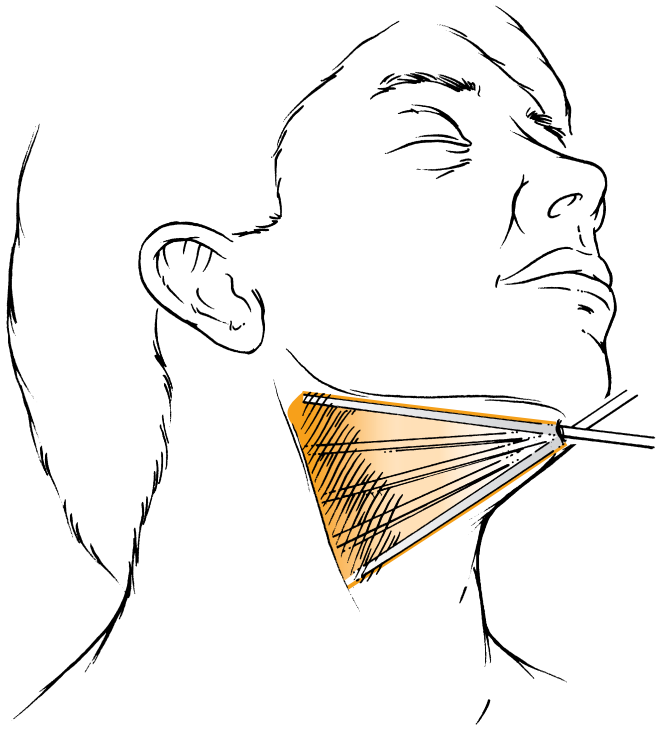

Figure 31-10. Distal feathering to ensure smooth transition to non-aspirated sites. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

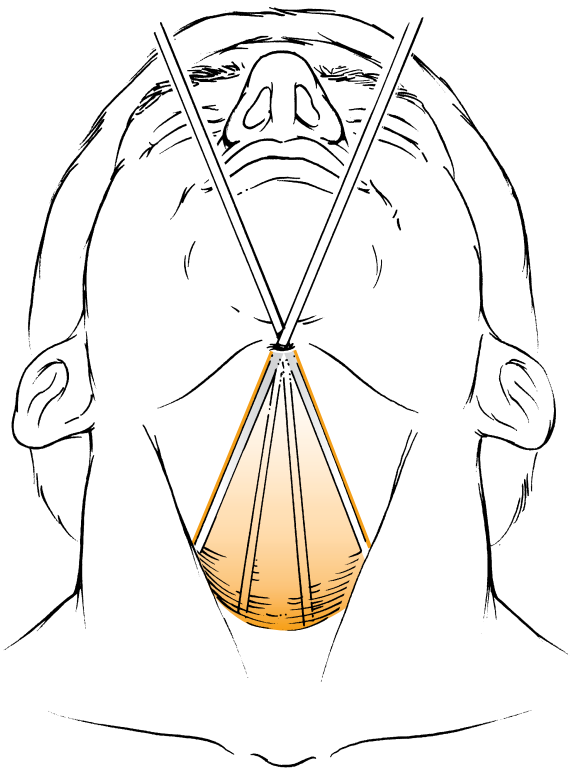

Figure 31-11. Multiple distal tunneling to ensure smooth transition in all regions and to avoid overreduction of the immediate submental adiposity. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

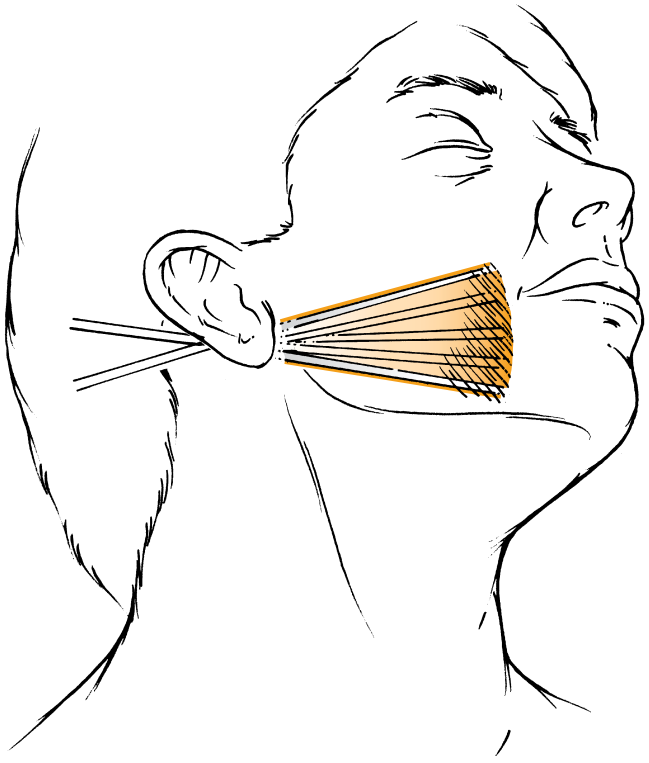

Figure 31-12. Suction lipectomy of the jowl, posterior cervical, and submandibular regions, which can be approached through the postauricular incision. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

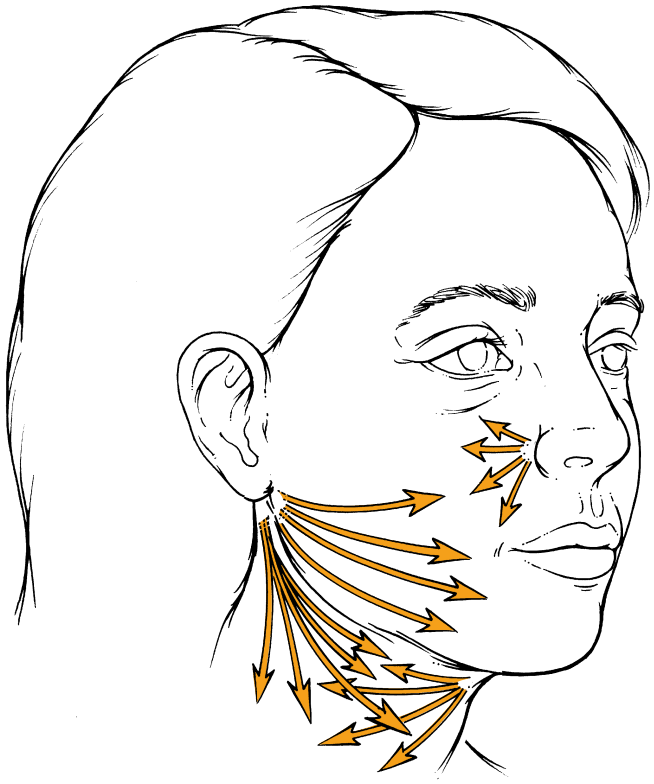

Figure 31-13. Sites that can be approached through the submental, postauricular, and vestibular incisions. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

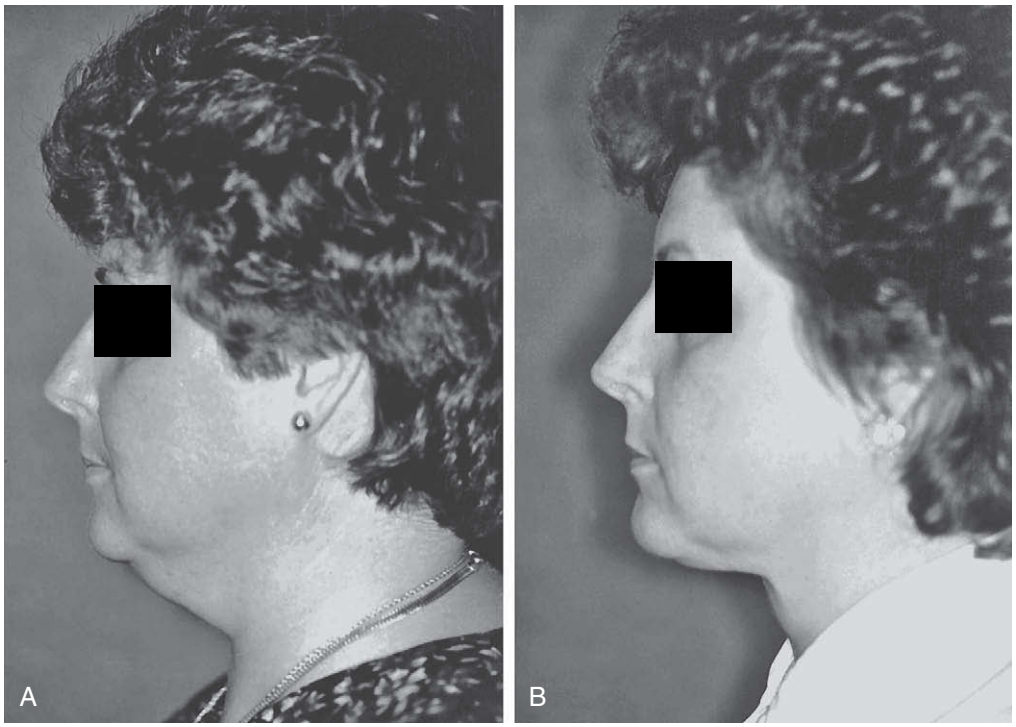

Figure 31-14. Preoperative **(A)** and postoperative **(B)** photographs show a patient who has undergone submental liposhaving with the illusion of enhanced chin projection caused by augmentation of the cervicomental angle.

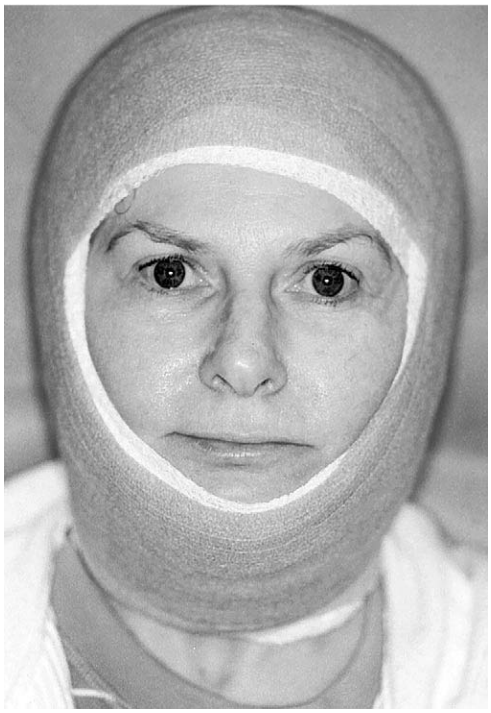

Figure 31-15. Immediate postsurgical dressing.

Figure 31-16. A light dressing can be applied by the patient after the immediate postsurgical dressing is removed.

limits of skin flap elevation. Open liposuction with cervicofacial rhytidectomy allows the surgeon to completely cross-hatch each area, thereby reducing the risk of banding. Additionally, uniform flap thickness can be ensured at the time of sharp elevation, thereby reducing the risk of dimpling of the skin. By combining lipocontouring with mentoplasty, the surgeon need only extend the submental incision to about 3 cm to allow for the placement of the implant. All wounds are closed in a layered fashion.

Dressing

Postoperatively, all patients require a pressure dressing circumferentially around the head and neck. Antibiotic ointment is first applied to the incision and then covered with a nonadhesive dressing. Fluffs are then placed over the region that has been aspirated, and a rolled cotton gauze is used to hold these fluffs in place. Coban R (3M; St Paul, Minn) dressing is applied using light but continuous pressure (Fig. 31-15). The dressing is left undisturbed for 2 to 3 days and then removed. After this, an elastic dressing is used at night and when indoors, and is changed by the patient as needed (Fig. 31-16). Antibiotics are used in all elective surgeries; drains are not routinely used. Liposuction is usually not painful, but the circumferential dressing can be uncomfortable and produces anxiety in some patients. For this reason, mild analgesics are helpful. Elevation of the head and the continuous use of ice packs minimize swelling.

Recovery Phase

Diligent patient education about the recovery phase can be very comforting for all involved. Some degree of bruising and facial edema is to be expected and may last for a week; the elevated skin may be numb for 3 to 9 weeks. As the facial skin scars and adheres to the new underlying contour, patients often note some firmness and tightness that diminishes over the subsequent months. Pain is usually minimal and sufficiently relieved with acetaminophen. When larger volumes of fat are removed, shallow dimpling and wrinkling from excess skin can occur as the skin adheres; diligent massage and patience will lead to a smoother final contour. Exercise is avoided for 3 weeks after surgery and should be resumed gradually, beginning with aerobic activities and progressing to more strenuous exercise.

Complications

Complications from lipocontouring are uncommon but may be dramatic. The most frequent complication is hematoma or seroma, which is evacuated by needle aspiration, and then a pressure dressing is reapplied. If a hematoma accumulates acutely, there should be a low threshold for drainage and exploration in the operating room. Infections or cellulitis usually arise from a preexisting hematoma and should be managed aggressively to reduce the risk of skin flap necrosis or scarring. Pigment changes can follow an undiagnosed hematoma and result from a breakdown in hemoglobin products. Contour irregularities and asymmetries may manifest after all swelling has subsided and are more likely to occur as residual fullness on the right neck area because most surgeons are right-handed, which makes the left side of the neck more accessible to them than the right side. If significant, this complication is best repaired with minor touch-up procedures using the handheld syringe technique, but not before six months have passed since the original operation to allow the full skin flap to soften as much as possible. For subtle areas, small quantities of corticosteroids can be injected to induce fat atrophy. This approach should be used conservatively, because its effects continue for many months and are not reversible. Minor depressions can be remedied with autologous fat injection, but the longevity of the procedure is unknown. Motor or sensorineural injuries are rare but more serious, and they usually appear as transient neuropraxias. Cardiovascular instability is associated with total body liposuction and results from massive fluid shifts; this complication does not occur from lipectomy in the head and neck areas. Pulmonary fat embolism can theoretically occur during any surgical procedure but has not been reported after liposuction alone.

Summary

Lipocontouring is a necessary adjunct to a facial plastic and reconstructive practice. Multiple tools are available and should be judged individually. Patient selection and education are paramount to achieving satisfaction. The judicious use of liposuction in conjunction with other cosmetic procedures will enhance the results and the satisfaction of both the patient and the surgeon (Fig. 31-17).

Figure 31-17. Preoperative oblique **(left)** and 18 months postoperative oblique **(right)** views when adiposity and laxity need to be addressed with cervical facial liposuction and a face lift.

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For complete list of references log onto www.expertconsult.com.

CHAPTER THIRTY-TWO

Mentoplasty and Facial Implants

Jonathan M. Sykes

John L. Frodel, Jr.

Key Points

- The chin should be evaluated in three dimensions: horizontal (anteroposterior; AP), vertical, and transverse.
- The chin should be evaluated as it relates to other important adjacent structures, such as the lips, teeth, and nose.
- Analysis of the chin should include a careful history and detailed physical examination. When appropriate, a cephalometric radiograph should be performed.
- Chin augmentation with an alloplast should be performed with an extended anatomic implant. The implant should be fixated by using a subperiosteal lateral pocket.
- Reapproximation of the mentalis muscle should be performed to prevent or minimize mentalis muscle dyskinesis.
- Bony genioplasty should be used in patients with vertical chin discrepancies or transverse asymmetries.
- Bony genioplasty is performed intraorally with preservation of both mental nerves.
- A reciprocating saw is used to perform horizontal osteotomy of the mentum. After the prescribed movement of the chin, fixation is achieved with a pre-bent titanium plate and screws.

Mentoplasty

The chin prominence is not present in any four-legged mammal.[1] During evolution, with the adoption of an upright posture and with verticalization of the face; the chin became an important facial feature. The events contributing to the evolutionary development of the chin in humans are open to speculation; however, the importance of the chin in the overall appearance of the face cannot be overstated.

In general, when patients inquire about improving their facial appearance, they rarely ask about surgical correction of the chin. More commonly, requests focus on seemingly more obvious problems, such as reduction of a large nose or correction of sagging skin of the neck and jowls. However, recognition, evaluation, and treatment of chin abnormalities often has a great impact on facial appearance. It is clear that all attractive faces have an underlying balance and structural symmetry to their facial skeletons.[2] Proper balance of the facial skeleton requires harmony and proportion of all bones of the face in all three planes of space. The chin should therefore be evaluated as it relates to important adjacent structures, such as the lips, teeth, and nose.[3] Appropriate treatment of aesthetic deformities of the chin contributes to facial harmony and often improves the appearance of the mouth, the lips, and the nose. It is for these reasons that every face should be carefully studied to determine why the chin appears unattractive. This enables the surgeon to correct the deformity and improve facial proportion.

Surgical correction of aesthetic deformities of the chin can be performed by either chin augmentation with an implant or by osteotomy and advancement (or reduction) of the bony mentum. Augmentation using alloplastic implants can camouflage a horizontal (AP) bony deficiency.[4] However, this technique is not effective in correcting vertical (superoinferior) or transverse deformities of the lower face and chin. Horizontal bony osteotomy of the chin (osseous genioplasty) is a simple and versatile procedure. This technique allows horizontal advancement or reduction of the chin, vertical lengthening or shortening of the chin, and correction of transverse deformities of the chin. The procedure chosen to correct the specific aesthetic problem is based on the type and extent of the deformity (Table 32-1).[3] If carefully evaluated and planned, aesthetic correction of chin deformities can provide significant improvement in the overall balance and proportion of the face.

Patient Evaluation

To precisely correct any chin deformity, careful preoperative analysis of the deformity is essential.[3,5] Specifically, the chin should be evaluated as it relates to other skeletal and soft tissue structures, including the lips, teeth, nose, and soft tissues of the neck. A detailed history of past trauma, orthodontic treatment, or prior oral surgery is essential. This is important because many patients with dental malocclusion and underlying facial skeletal abnormalities are treated with orthodontics. This method of dental compensation may correct the malocclusion, but it fails to improve the underlying skeletal deformity. It is therefore important to discuss prior therapy, including orthodontics, with the patient.

Physical examination should include inspection and palpation of the chin, lips, nose, and teeth. The entire face should be observed at rest and during animation to evaluate the mentalis soft tissue mound and its support. With aging, patients may develop ptosis of the soft tissue pad of the chin. In patients with open bite deformities and lip incompetence, hyperactivity of the mentalis muscles ("mentalis strain") can occur (Fig. 32-1). For this reason, the dental occlusion should be carefully examined to determine whether orthodontics or orthognathic surgery is needed.

The evaluation of all patients for possible chin surgery should include consistent and reproducible clinical photographs in three views:

Table 32-1

Mentoplasty Procedures

Horizontal (Anteroposterior)	Deformity Vertical	Transverse	Procedure
D	N or sl D	N	Chin implant or genioplasty
D	E	N	Genioplasty (advancement with possible ostectomy if significant vertical excess)
D	D	N	Bony advancement (with down-grafting for chin lengthening)
N	N	Asymmetric	Bony osteotomy (with resection of down-grafting)
E	N	N	Bony osteotomy (with setback)
E	E	N	Bony osteotomy (with ostectomy)

D, deficient; E, excessive; N, normal; sl, slight.
Modified from Sykes J, Frodel JL. Genioplasty. *Op Tech Otolaryngol.* 1995;6:319.

Figure 32-1. Anteroposterior **(A)** and lateral **(B)** photograph of a patient with posterior vertical maxillary access and an open bite deformity. Note the mentalis strain caused by the patient trying to close her lips at rest.

AP (frontal), lateral (profile), and oblique. These photographs allow analysis of the contour and projection of the chin as it relates to the lips, nose, labiomental groove, and soft tissues of the neck. If the physical evaluation and clinical photographs show a minor deformity requiring augmentation with an alloplast, radiographs of the chin are usually not necessary. However, if the deformity is more complex, (e.g., vertical chin excess with horizontal deficiency or transverse bony asymmetry), radiographic analysis is essential.

Radiographic evaluation of the chin routinely includes a panoramic radiograph (Panorex) and cephalometric radiographs in the AP and lateral views. The panoramic radiograph shows the cortical outline of the mandible and the vertical mandibular height (Fig. 32-2). The Panorex also delineates the position of the tooth roots and of the infe-

Figure 32-2. Panoramic radiograph.

rior alveolar canals and mental foramina. It is important to know the exact position of the mental foramen and canal preoperatively so intraoperative damage to the mental nerve can be prevented. The inferior alveolar nerve, a branch of the third division of the fifth (trigeminal) cranial nerve, travels through the mandibular canal and exits the mental foramen as mental nerve. The mental nerve supplies sensation to the skin and mucous membranes of the lower lip and chin. The mandibular canal is often located 2 to 3 mm below the level of the mental foramen.[1] Bony osteotomies should therefore be performed at least 5 mm below the mental foramen to avoid injury to the neurovascular bundle.

If bony genioplasty is considered, AP and lateral cephalometric radiographs should be performed (Fig. 32-3). AP views allow detection and evaluation of transverse skeletal asymmetries of the chin. Transverse asymmetries are common in patients with Goldenhar's syndrome or hemifacial microsomia, but they are also commonly seen in nonsyndromic patients considering aesthetic surgery. When transverse bony or soft tissue asymmetries are overlooked preoperatively in a patient with microgenia, augmentation with an alloplastic chin implant can accentuate the deformity.[3]

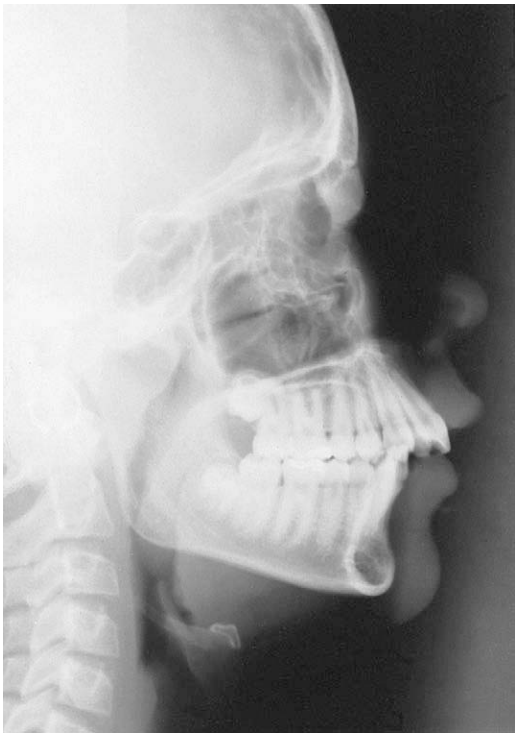

Figure 32-3. Lateral cephalometric radiograph showing the bony and soft tissue outline of a patient with a class II malocclusion and mild open bite deformity.

Lateral cephalometric radiographs allow detailed analysis of both the soft tissues and the facial skeleton. The cephalogram should be obtained at a standard distance with the head positioned so that the Frankfort horizontal line is parallel to the floor.[6] From this standardized lateral radiograph, a series of soft tissue and skeletal points can be identified. This allows various analyses of the chin as described by Ricketts,[7] Steiner,[8] Burstone,[9] Gonzalez-Ulloa and Stevens,[10] and others. Ricketts' analysis (Fig. 32-4) uses a tangent connecting the soft tissue pogonion (most projecting point) of the chin with the most projecting point of the nasal tip.[7] In this system, the upper lip should lie about 4 mm behind the line, whereas the lower lip is ideally located 2 mm behind the line. While the Ricketts analysis correctly evaluates the lower face in profile, it places great importance on the projection of the nasal tip. The Steiner analysis uses the columellar inflection point(s) to identify the correct position for the chin point.[8] This method places importance on the lip position. The Holdaway "H" angle (Fig. 32-5) relates the position of the soft tissue pogonion with important skeletal points on the mid and lower face. No single analysis is ideal, but each method attempts to determine the "ideal" positions for the soft tissues and skeleton of the chin because these structures relate to the remainder of the face.

An accurate chin analysis using the lateral cephalogram involves dropping a vertical line from the Frankfort horizontal (porion-infraorbitale) through the soft tissue subnasale.[11] With ideal horizontal chin projection, the soft tissue pogonion should lie approximately 4 mm behind this line (Fig. 32-6). The most frequently used evaluation of the chin drops a perpendicular line from the vermilion border of the lower lip and compares the AP position of this line with the soft tissue pogonion (the anterior-most projecting chin point) (Fig. 32-7). A general guideline for aesthetic chin position in this method is for the pogonion in a male patient to be positioned at the level of this vertical line and for the pogonion in a female patient to be just posterior to the line. If the position of the soft tissue pogonion is anterior to the proposed line, horizontal macrogenia is diagnosed, whereas microgenia is present if the chin is positioned posterior to the ideal line. Although this method is effective for AP deformities (microgenia or macrogenia), it does not account for vertical or transverse discrepancies. Because many surgeons primarily use this evaluation method, vertical or transverse chin problems are often overlooked.

Analysis of vertical facial heights is also essential in determining the appropriate heights of the lower facial third and the chin. Various methods for evaluating vertical facial heights have been used. The simplest technique involves division of the face into three equal thirds: the upper third, from the frontal hairline to the glabella; the middle third, from the glabella to the soft tissue subnasale; and the lower third, from the subnasale to the menton (the lowest point of the chin). Because frontal hairline can vary significantly, an alternate method described by Powell and Humphreys[12] more accurately analyzes the vertical heights of the lower two thirds of the face. This method describes the middle third as the distance from the nasion to the

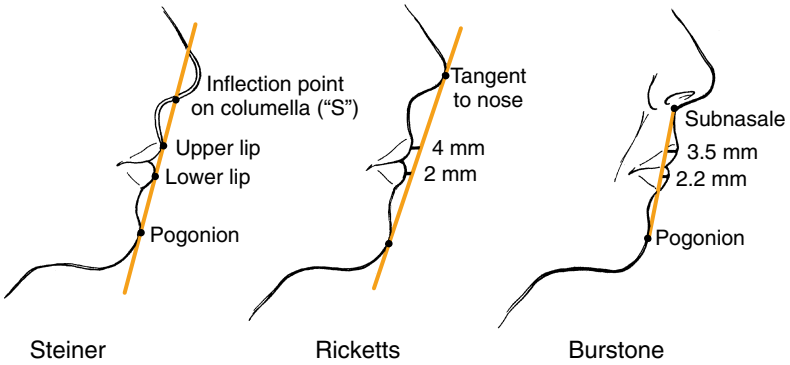

Figure 32-4. Steiner, Ricketts, and Burstone analysis of the ideal relationship of the chin as it relates to the lips and other lower facial structures.

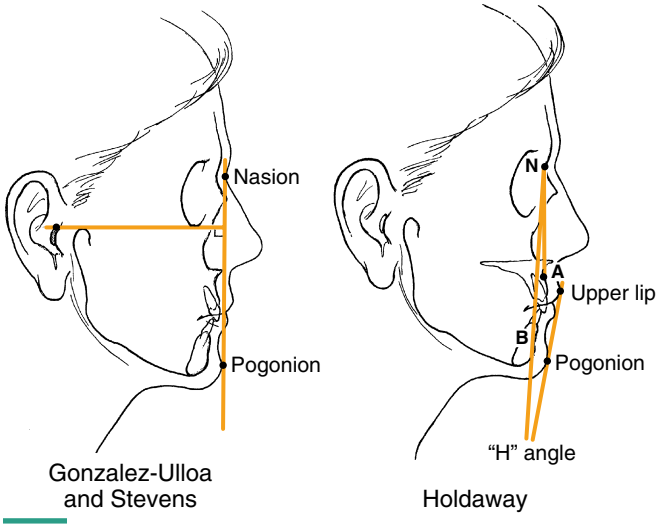

Figure 32-5. The Gonzalez-Ulloa and Stevens and the Holdaway analyses of the chin and lower third of the face.

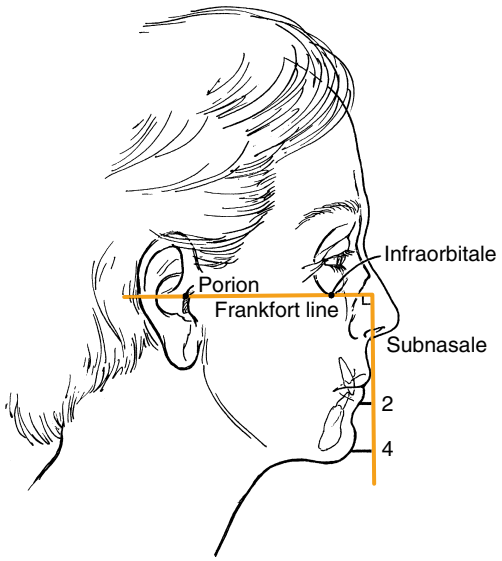

Figure 32-6. Horizontal relationships of the chin and upper and lower lips as they relate to the nasal perpendicular line.

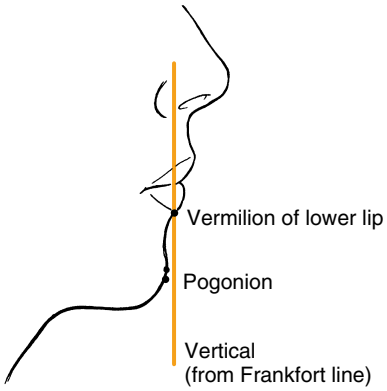

Figure 32-7. The relationship of the chin position to a perpendicular passing through the vermilion border of the lower lip.

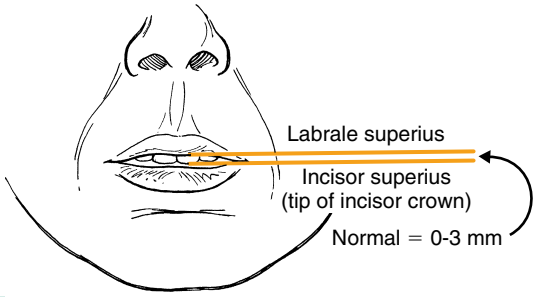

Figure 32-8. Schematic diagram of incisor show of the maxillary teeth. A normal relationship would be 0 to 3 mm of central incisor visible.

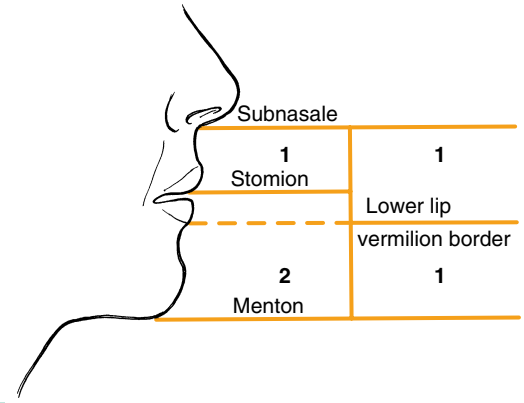

Figure 32-9. Vertical relationships of the lower third of the face.

subnasale and the lower third as the distance from the subnasale to the menton. The middle third distance in this analysis ideally represents 43% of the total height of the lower two thirds of the face, that is:

$$\frac{\text{Nasion} - \text{Subnasale}}{\text{Nasion} - \text{Menton}} = 0.43$$

whereas the lower third distance should approximate 57% of the total vertical height.

Other analyses of the vertical dimensions of the face have been described. One method includes inspection of the face in repose, when the maxillary incisor teeth should show 0 to 3 mm (Fig. 32-8). If more than 3 mm of the maxillary incisors are visible at rest, excessive facial length (usually in the midface) is sometimes present. Additional analysis of the lower face includes subdividing the lower third of the face. Two methods exist for subdivision of lower facial heights. The first includes a vertical third from subnasale to upper lip stomion and two thirds from upper lip stomion to the menton (Fig. 32-9). The second method divides the lower third into two equal parts, from the subnasale to the vermilion border of the lower lip and from the lower lip vermilion border to the menton. All of these analyses relate the height of the chin and lower face to the total facial height. In complex chin deformities, a vertical discrepancy as well as a horizontal deficiency or excess may often be present.

Another parameter that should be assessed is symmetry in the sagittal plane. Transverse asymmetries of the chin exist in many patients with congenital anomalies (Goldenhar's syndrome, hemifacial microsomia) or in patients who have had significant skeletal facial trauma. However, many patients with only aesthetic concerns have minor but definite transverse asymmetries of the chin. In patients with asymmetry of the facial midline, chin augmentation with an implant may correct the horizontal deficiency but accentuate the skeletal asymmetry. AP cephalometric radiographs allow a comparison of the bony midline

of the chin with the dental midlines of the maxilla and the mandible. If the skeletal and soft tissue midline of the chin are not aligned with the dental midlines and with the upper facial skeletal midline (e.g., nasion), an asymmetric bony genioplasty or chin implant can be performed.

Each of the systems of analysis relates the soft tissue pogonion with other facial structures. No single method provides comprehensive evaluation of the chin, but each allows a reference for assessing the bony and soft tissues of the chin and lower face. Using a variety of methods, appropriate evaluation of chin deformities can be achieved.

Chin Deformities

Deformities of the chin and lower face may be related to either bony abnormalities or to soft tissue malposition. The chin should be analyzed in all three planes of space: horizontal (AP), vertical (superoinferior), and transverse. The horizontal and vertical dimensions can each be deficient, normal, or excessive. Simple deformities such as mild horizontal chin deficiency (microgenia) are easily corrected using either an implant or bony advancement. More complex deformities, such as in a patient with horizontal deficiency and vertical excess, usually require horizontal osteotomy for adequate correction.[13]

Soft tissue deformities of the chin and submental region also exist. Ptosis of the soft tissues of the chin often accompanies other signs of facial aging. This condition, commonly called *witch's chin* or *senile chin deformity*, is caused by a weakening of the muscular attachments of the mentalis and depressor labii inferioris muscles. In this deformity, the soft tissue pad of the chin falls below the mandibular line, and a deep horizontal crease develops in the submental region. Descent of the soft tissue chin pad is accentuated with smiling (Fig. 32-10A-C). This deformity can be inadvertently created or worsened surgically if the mentalis muscles are not reapproximated while inserting a chin implant (see Fig. 32-10D).

Procedure Selection

The selection of the best procedure to correct a given deformity of the chin should be based on the type and extent of the deformity (Table 32-2). Augmentation of the chin with an alloplastic implant is a simple and effective method of correcting a horizontal chin deficiency. This technique is limited by the availability of various sizes and shapes of alloplastic implants. An infinite number of shapes and sizes of implants may be required. However, most implants are manufactured in only three or four sizes and one or two shapes. Additionally, chin augmentation with implants is less effective in patients with significant vertical discrepancies (vertical excess or deficiency). Placement of an implant in such a patient may exacerbate the vertical excess and make the chin appear longer. For these reasons, implant augmentation is an effective method of camouflage for minor chin deformities, but may not be satisfactory for complex deformities.

Osteotomy of the bony mentum (osseous genioplasty) is a versatile and reliable procedure for correcting a variety of skeletal chin deformities. First described by Hofer in 1942,[14] this technique involves horizontal osteotomy and down-fracture of the chin, with repositioning and fixation of the distal segment. Osseous genioplasty allows advancement or retrusion in the AP direction, as well as lengthening or shortening in the vertical direction.[15-17] Additionally, the genioplasty procedure provides an approach for correction of transverse asymmetries of the chin. Although customized chin implants can be made to correct chin asymmetries, preformed implants are usually symmetric.

Correction of soft tissue ptosis has been described by Peterson[18] and other authors. The technique involves the removal of an ellipse of submental skin, creation of a flap of chin soft tissue, and advancement and plication of the soft tissue flap inferiorly. This technique tightens the soft tissue pad and obliterates the horizontal submental crease. However, the soft tissue pogonion is effectively moved posteriorly, and some form of simultaneous augmentation (implant or bony advancement) is usually required.

Surgical Technique

Chin Implant

To ensure precise midline placement of the chin implant, the midline of the chin, lower lip, and neck (thyroid cartilage) are marked externally before the infiltration of local anesthesia. A mental nerve block is then performed using Xylocaine 1% with epinephrine 1:100,000. Additional infiltration of anesthesia into the submental region, the gingivolabial sulcus, and the central portion of the lower lip and chin is performed to ensure adequate anesthesia and vasoconstriction.

Either an intraoral or external (submental) incision and approach can be used to place a chin implant. If an extraoral approach is used, an incision (approximately 2 to 3 cm) is made in the submental crease and carried through the dermis and subcutaneous fat (Fig. 32-11). The mentalis muscles are then divided to enter a dissection plane just super-

Table 32-2

Facial Implant Characteristics

Material	Trade Name	Tissue Interface	Advantages	Disadvantages	Complications	Common Sites for Use
Polydimethyl-siloxane	Silastic (silicone rubber) (Dow Corning, Midland, Mich)	Fibrous capsule	Can be carved and removed	Bone resorption, exposure	Malposition, extrusion, infection	Chin, malar, nasal
Fibrillated ePTFE	Gore-Tex (ePTFE, Gore Tex, WL Gore, Flagstaff, Ariz)	Limited tissue ingrowth	Sheets or tubular (lips)	Palpable	Malposition, extrusion, infection	Lips, nose
High-density polyethylene	MEDPOR (Porex Surgical, Newnan, Ga)	Fibrovascular ingrowth	Versatile, resistant to infection	Difficult to remove	Malposition, extrusion	Malar, orbit, chin, nasal
Hydroxyapatite/ carbonated apatite	Bone Source (Stryker Leibinger, Flint, Mich) and Norion CRS (Synthes-Stratec, Paoli, Penn)	Osseointegration	Paste consistency can be molded	Exposure or infection	Exposure, infection (i.e., frontal sinus)	Craniofacial, forehead

Figure 32-10. **A, B,** and **C,** Anteroposterior lateral and smiling lateral preoperative views of a patient with senile ptosis of the chin. Note the deepened submental crease when smiling. **D,** Postoperative lateral view after deep plane face lift and soft tissue correction of the ptotic mentalis pad.

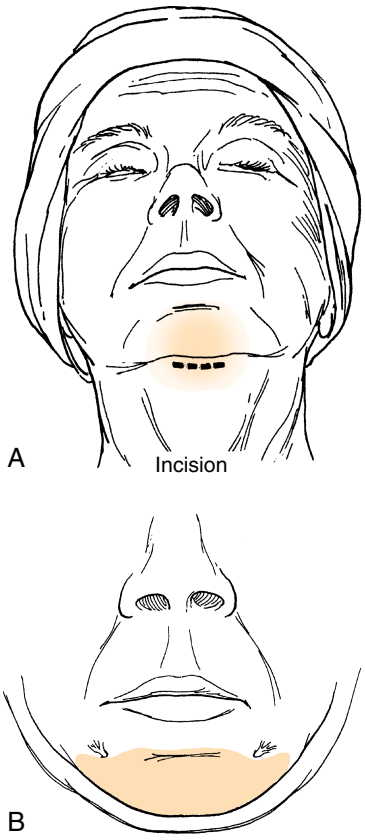

Figure 32-11. **A,** Horizontal submental incision in the crease for placement of a chin implant. **B,** Schematic diagram indicating the extent of dissection (stippled area) for placement of a chin implant.

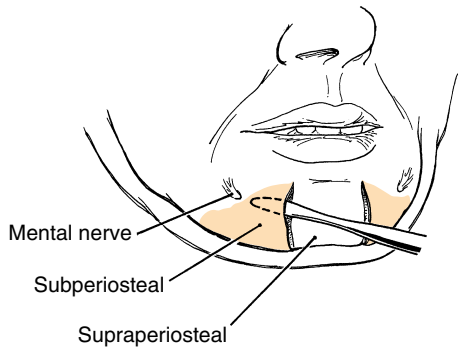

Figure 32-12. Dissection planes for placement of a chin implant with the central dissection being supraperiosteal and the lateral pockets in the subperiosteal plane.

ficial to the periosteum of the anterior face of the mandible. The chin implant can be placed in either the subperiosteal or the supraperiosteal plane. The advantage of placing an implant beneath the periosteum is improved fixation of the implant. However, subperiosteal placement has been shown to result in some erosion of the anterior mandible. For these reasons, most surgeons advocate dissection in the supraperiosteal plane centrally, with subperiosteal placement laterally (Fig. 32-12). This theoretically minimizes mandibular erosion while maximally fixing the implant.

Many sizes, shapes, and types of implants have been used for chin augmentation. In general, the two shapes of implants are the central "button" implant and the extended "anatomic" implant. Longer tapered implants have the advantages of being able to be placed in the

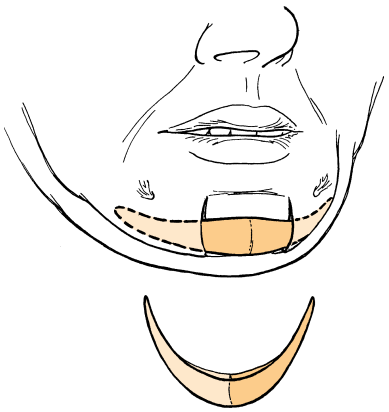

Figure 32-13. Lateral subperiosteal placement of an extended alloplastic chin implant.

subperiosteal plane laterally, and they allow for lateral mandibular augmentation (Fig. 32-13). Most importantly, extended implants have the advantage of not being as apparent if 1 to 2 mm of displacement occurs. Smaller, central implants are more obvious if slight postoperative displacement of the implant occurs.

During the lateral subperiosteal dissection, the mental nerves should be identified and preserved. The implant should be placed along the inferior border of the mandible. If the implant extends laterally beyond the mental foramina, it should be positioned below the exit of the mental nerve (see Fig. 32-13). After placement of the implant, the mentalis muscles should be reapproximated and the soft tissue resuspended meticulously. If the mentalis muscle is not carefully realigned, postoperative ptosis of the soft tissues of the chin may occur. Closure of the mentalis muscle is performed with No. 4-0 braided absorbable suture. The subcutaneous tissues and dermis are reapproximated with No. 5-0 chromic suture, followed by skin closure with interrupted No. 6-0 monofilament nonabsorbable suture. A secure chin strap dressing is placed for 3 days to ensure immobility of the implant. Perioperative antibiotics are used for 48 hours.

If an intraoral approach is used, the gingivolabial incision can be either horizontal or vertical. In either case, dissection through the mentalis muscles again occurs with placement of the implant in a supraperiosteal plane centrally and a subperiosteal pocket laterally. Closure is accomplished in two layers with the muscle closure achieving soft tissue resuspension. A chin strap dressing is used for 3 days to secure the position of the implant.

Osseous Genioplasty

Horizontal bony osteotomy of the chin (osseous genioplasty) is a versatile procedure that can be performed under general anesthesia or intravenous sedation with mentalis nerve block. If general anesthesia is used, nasotracheal intubation is preferred; however, if rhinoplasty is to be performed with the genioplasty, orotracheal intubation should be used.

A gingivolabial incision is made from one canine tooth to the other (Figs. 32-14 and 32-15). The incision is made on the labial side of the gingivolabial sulcus to allow an adequate mucoperiosteal soft tissue cuff for wound closure. Dissection is then carried through the soft tissues and mandibular periosteum. Subperiosteal dissection is performed laterally with identification and preservation of both mental nerves (Figs. 32-16 and 32-17). A small inferior segment of soft tissue is preserved over the central segment (bony mentum) of the mandible to provide vascular supply to the distal segment after osteotomy.[19]

After the lateral subperiosteal dissection is completed, the proposed osteotomy is carefully measured and marked (Figs 32-18 and 32-19). The bony midline is vertically inscribed with a side-cutting burr (Fig. 32-20) to allow the proximal and distal segments to be precisely aligned after osteotomy and repositioning. The osteotomy site is then

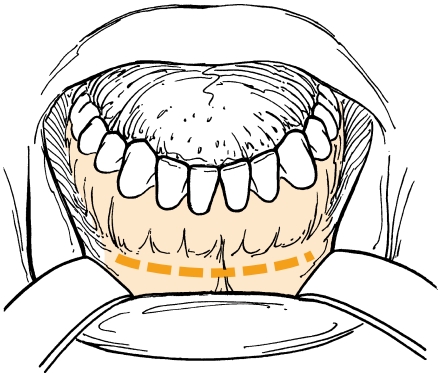

Figure 32-14. Schematic diagram of a horizontal gingivolabial incision for bony genioplasty.

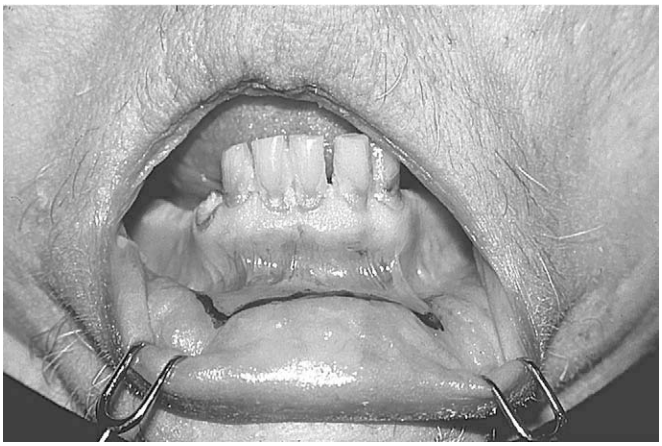

Figure 32-15. Marking on cadaver illustrating the gingivolabial incision not in the crease to facilitate later closure.

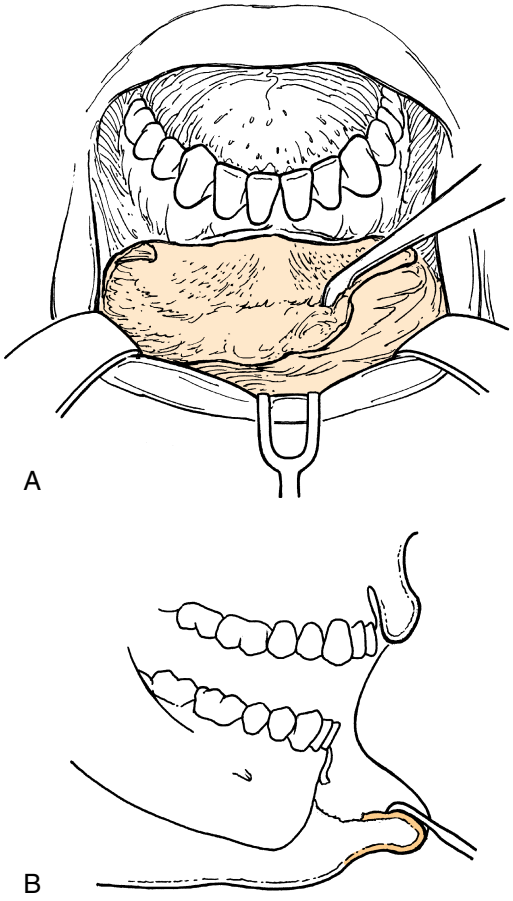

Figure 32-16. Anterior **(A)** and lateral **(B)** schematic illustrations of the subperiosteal plane of dissection for genioplasty. Note the mental nerves are isolated, identified, and preserved and an inferior cuff of central soft tissue is maintained on the distal segment of the chin to increase vascularity.

measured and marked with calipers to ensure a symmetric osteotomy. The horizontal osteotomy should be placed below the level of the tooth roots to prevent dental injury.

During the preoperative assessment, a decision is made on the three-dimensional movement of the chin that is required. This treatment plan will affect the orientation of the osteotomy as well as the actual movement after the osteotomy. If only AP advancement is needed, the osteotomy is made with a horizontal orientation. If vertical movement (shortening) is needed in addition, the osteotomy is made in a more oblique orientation. An oblique osteotomy allows some vertical shortening because the distal segment is advanced. If the chin length is excessive and significant shortening is planned, two oblique osteotomies are made and the intervening bone is removed.

After the osteotomy is marked, the bone cut is created with a reciprocating saw blade in a lateral-to-medial direction (Fig. 32-21). The lateral extent of the osteotomy should be made at least 5 mm below the mental foramen to avoid injuring the mental nerve. Gentle digital pressure is used to down-fracture the bony segment. A small amount of soft tissue must usually be separated from the posterior aspect of the distal segment to facilitate movement.

Repositioning of the distal segment is performed according to the preoperative treatment plan. If vertical lengthening is required, grafts are placed using autogenous bone or allogenic bone (Fig. 32-22). If vertical shortening is planned, a second parallel osteotomy is made above the first, or the intervening bone is burred away (Fig. 32-23).

Figure 32-17. The cadaver dissection of the subperiosteal plane of dissection for genioplasty.

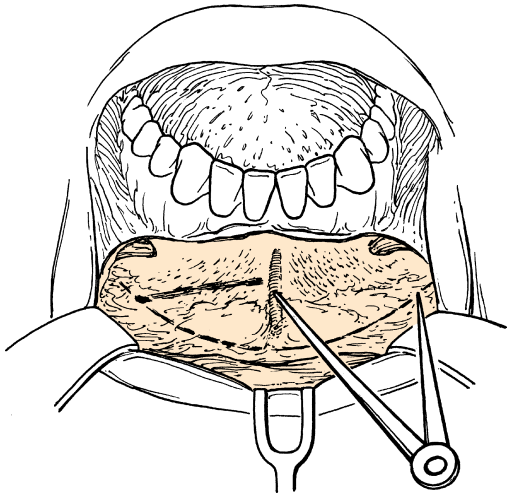

Figure 32-18. Schematic illustration indicating measurement of the osteotomy site from the middle line to ensure symmetry.

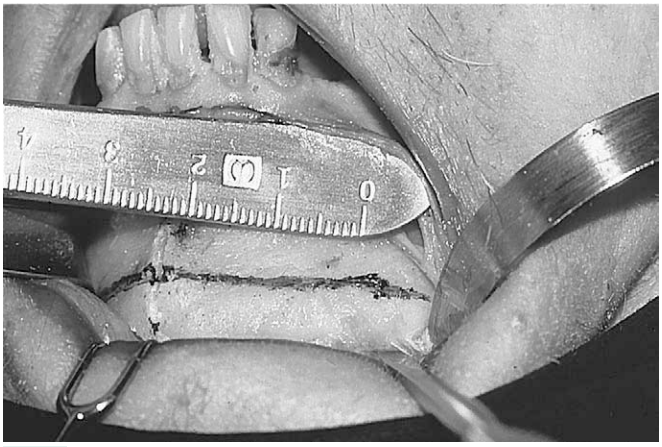

Figure 32-19. The cadaver dissection indicating measurement of the osteotomy site from the middle line to ensure symmetry.

Figure 32-20. Inscription of the bony midline with a sidecutting burr to facilitate later accurate approximation after osteotomy.

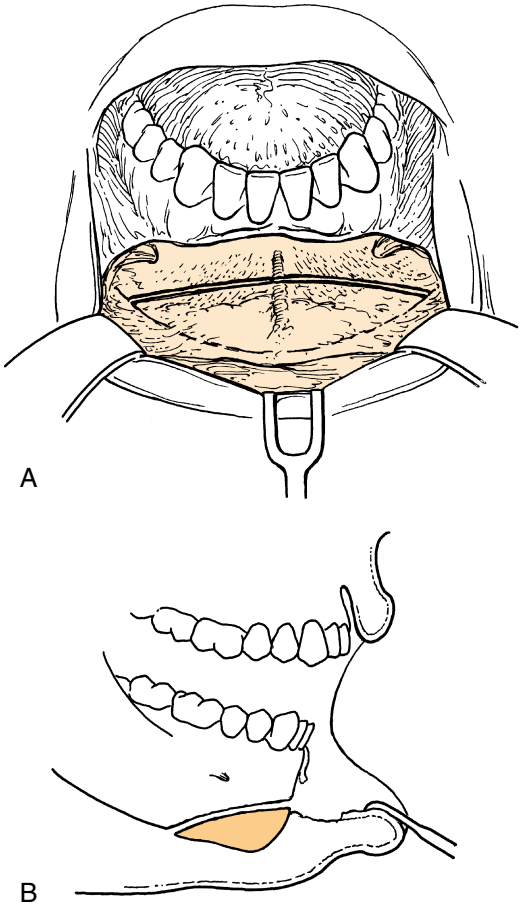

Figure 32-21. Anterioposterior **(A)** and lateral **(B)** schematic illustrations showing the horizontal mandibular osteotomy of the mentum well below the mental foramina.

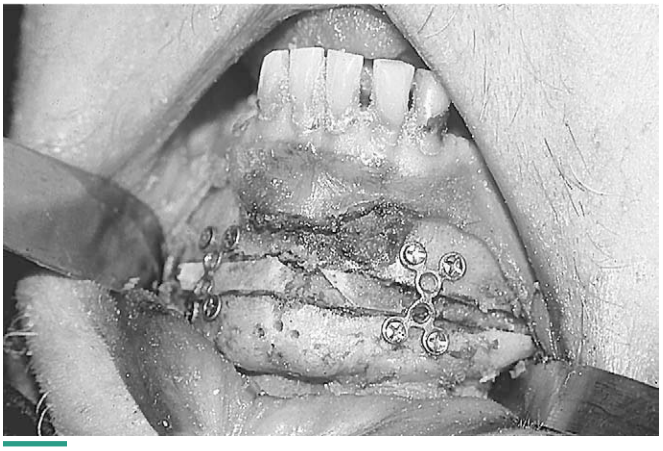

Figure 32-22. Vertical lengthening of the chin by inserting bone grafts into the down-grafted osteotomy site.

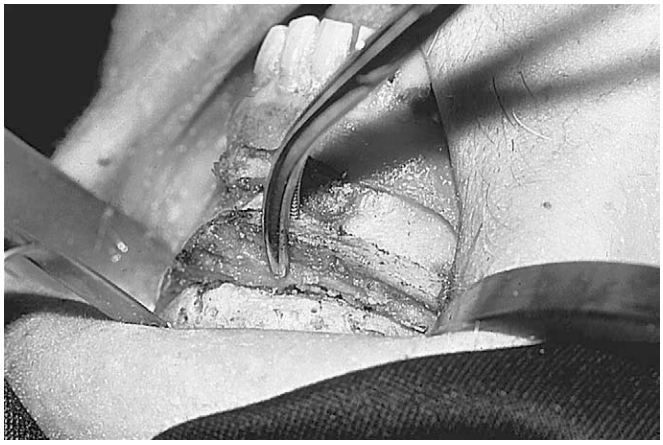

Figure 32-23. Bony ostectomy for shortening of the chin with removal of a segment of bone from the ostectomy site.

Figure 32-25. Intraoperative photograph of the preformed rigid genioplasty plate. Note that two small wires are used in this patient to ensure stability of the bony movement.

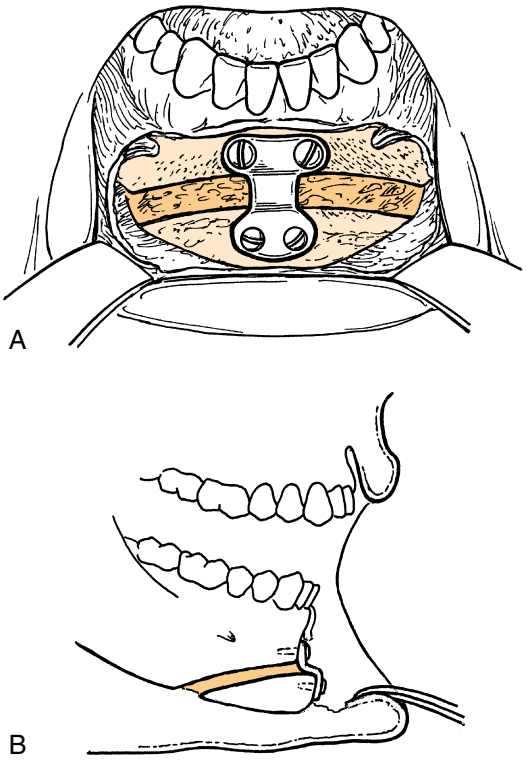

Figure 32-24. Anterior **(A)** and lateral **(B)** views of horizontal bony advancement of the chin with fixation with a pre-bent genioplasty plate. If bony contact is good, a single plate can be used.

After the segment is repositioned, it is fixed in position using adaptation plates, positional screws, or interosseous wires (Figs. 32-24 and 32-25). Adaptation plates can be preshaped and provide excellent fixation. The soft tissues of the chin and lips are then replaced, and the new contour is assessed.

The wound is closed in two layers with care taken to resuspend the soft tissues of the chin. Interrupted No. 3-0 catgut is used for the mentalis muscle, and a running locking stitch of No. 3-0 chromic catgut is used for the mucosa. A pressure chinstrap dressing is applied for 5 days, and the patient should eat a soft diet for 2 weeks.

Clinical Examples

Case 1

A 22-year-old woman presents for rhinoplasty. She has had orthodontic treatment to correct a class II malocclusion. She desires chin augmentation but refuses bony genioplasty. At the time of rhinoplasty, chin augmentation is accomplished using an extended anatomic implant (Fig. 32-26).

Case 2

A 42-year-old woman with a nasal deformity and significant micrognenia undergoes advancement genioplasty and open rhinoplasty (Fig. 32-27).

Case 3

A 25-year-old woman with class III malocclusion, bilateral cross-bite, chin asymmetry, and temporomandibular dysfunction undergoes Le Fort I maxillary osteotomy with advancement, bilateral sagittal split ramus osteotomy of the mandible with setback and rotation, and asymmetric advancement genioplasty (Fig. 32-28).

Complications

Complications after mentoplasty are uncommon. Chin implants can become malpositioned and occasionally are bothersome to patients with a thin overlying soft tissue pad. Infections are infrequent with either the intraoral or the submental approach. There have been reports of anterior mandible resorption with subperiosteal implant placement, occasionally causing secondary chin deformities.[20]

Complications after genioplasty include mental nerve injury and malunion or no union of the bony segments. Nerve damage is extremely uncommon with careful dissection. Malunion of the bone segments can occur, but the excellent vascularity and the lack of direction force on the osteotomy site make this an infrequent problem.

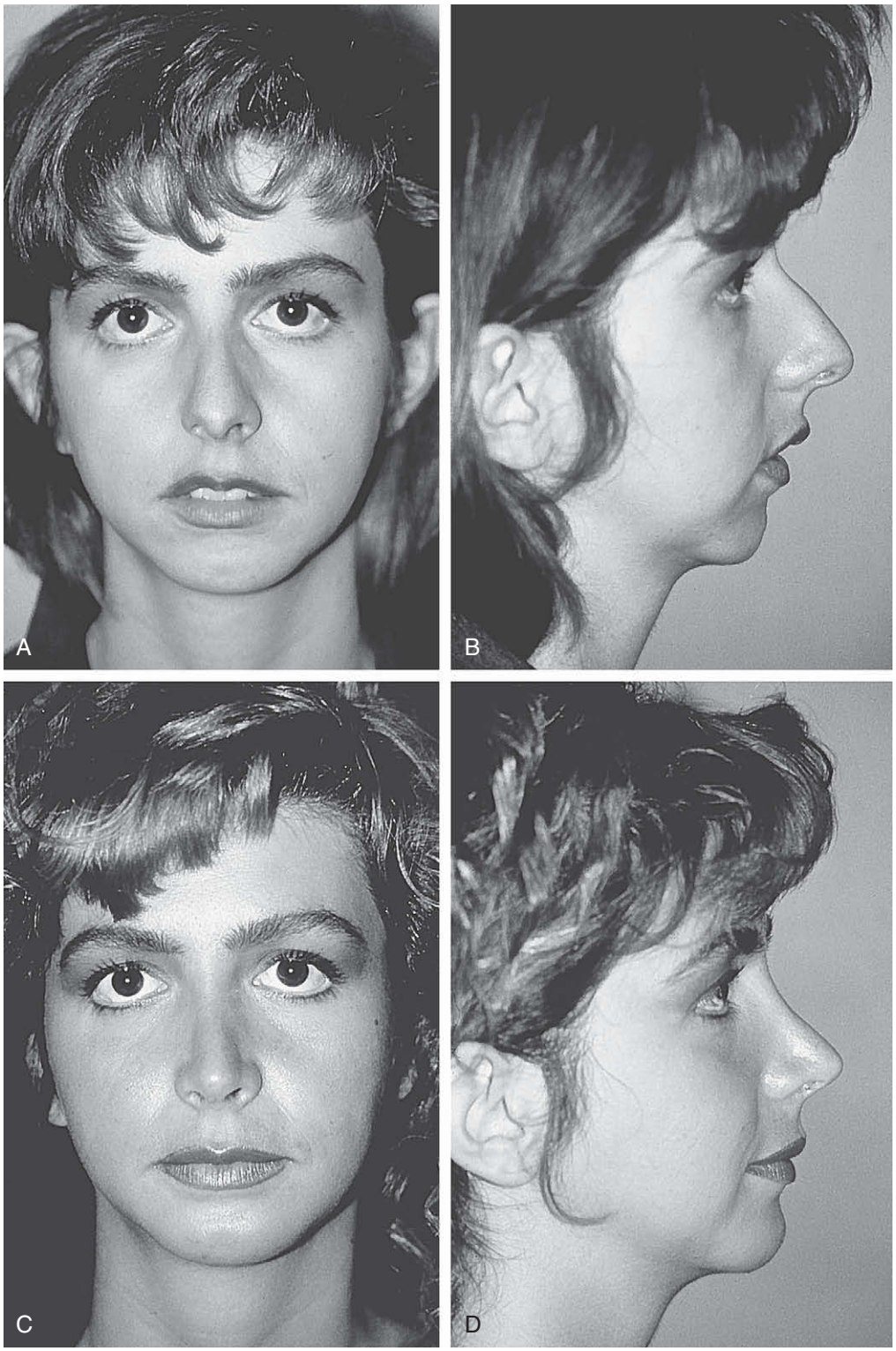

Figure 32-26. **A** and **B,** Preoperative anteroposterior and lateral views of a patient for rhinoplasty and chin augmentation. **C** and **D,** Six-month postoperative photograph of a patient after open rhinoplasty and chin augmentation with alloplastic implant.

Figure 32-27. **A** through **C,** Preoperative anteroposterior, lateral, and oblique views of a patient for rhinoplasty and sliding advancement genioplasty. **D** through **F**, Six-month postoperative views of the patient after open rhinoplasty and advancement genioplasty.

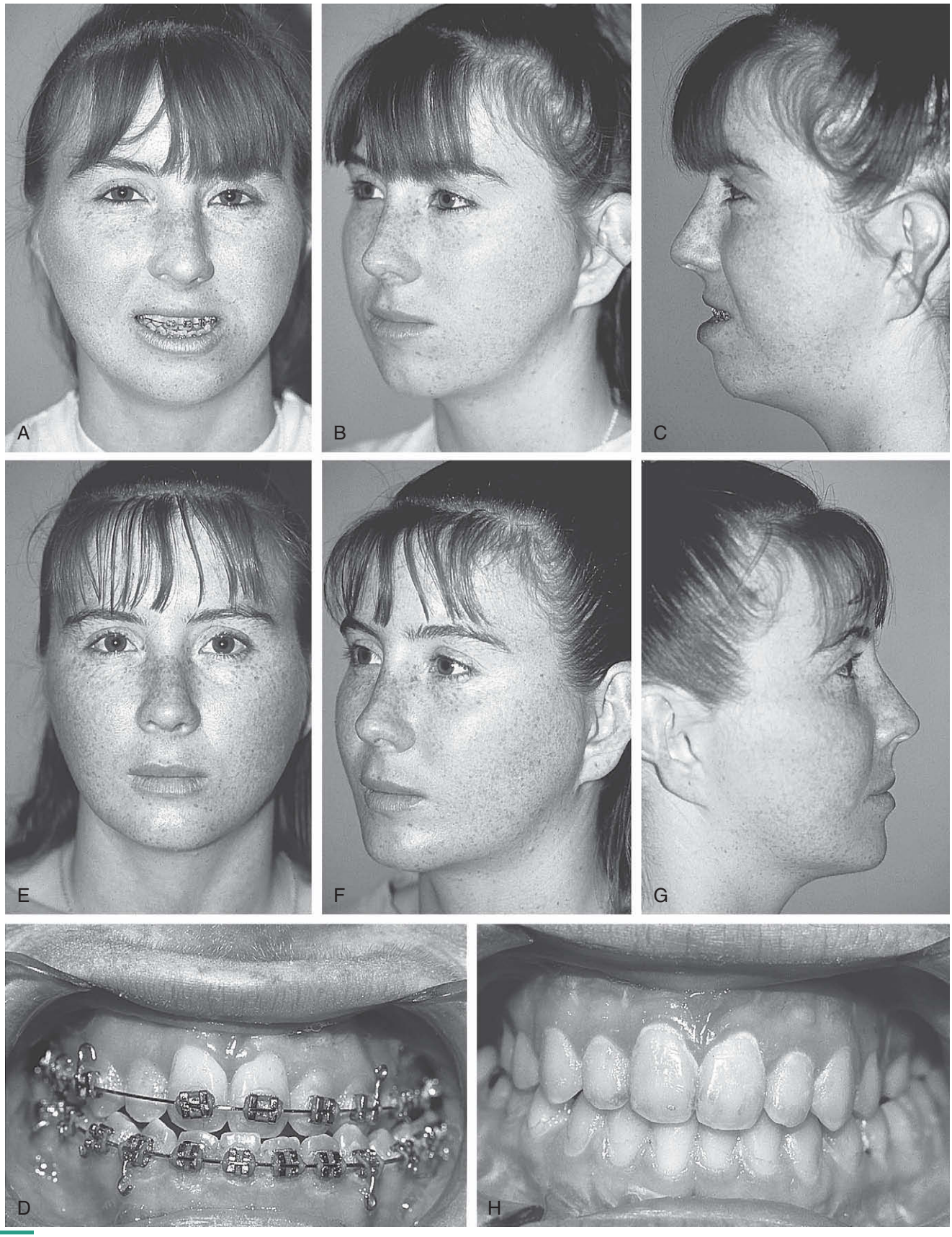

Figure 32-28. **A** through **D,** Preoperative anteroposterior (AP), oblique, lateral, and occlusal views of a patient with significant congenital asymmetry, class III malocclusion, bilateral crossbite, and microgenia. **E** through **H,** One-year postoperative AP, oblique, lateral, and occlusal views of the patient after Le Fort I maxillary osteotomy with advancement bilateral sagittal split, ramus osteotomy of the mandible with setback and rotation, and advancement genioplasty with rotation of the chin point.

Summary

Aesthetic surgery of the chin is extremely rewarding when performed in a carefully selected patient. Chin augmentation with alloplasts is a simple and effective means to correct mild to moderate horizontal microgenia. Horizontal osteotomy of the bony mentum (osseous genioplasty) is a more flexible and versatile procedure that can correct chin deformities in all three planes of space. When properly planned and executed, either procedure provides an important adjunct for the facial plastic surgeon.

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CHAPTER THIRTY-THREE

Otoplasty

Peter A. Adamson

Suzanne K. Doud Galli

Theodore Chen

Key Points

- Protruding ears is one of the most common congenital deformities of the head and neck, occurring in 5% of whites.
- It is inherited in an autosomal dominant fashion with variable penetrance.
- Normal auriculocephalic angle ranges between 25 and 35 degrees; normal pinna position is 15 to 20 mm from the helical rim to the scalp.
- Most common underlying abnormalities are an insufficient antihelical furl and/or a misshapen conchal bowl with a high conchal wall.
- Cartilage-cutting otoplasty techniques may result in less frequent loss of correction but carry an increased risk of developing cartilage irregularities.
- Cartilage-sparing otoplasty techniques may result in more frequent loss of correction but reduce the incidence of cartilage irregularities.
- Performing otoplasty in a stepwise, graduated approach, correcting the specific deformity in a given patient, has proved very successful long term.

Although protruding ears are considered a sign of good fortune by some Asians, in most other cultures, they are associated with feelings of anxiety, social discomfort, and even abnormal behavior.[1] They are frequently a source of teasing or social ridicule, especially for young children.

Today there are techniques that allow for correction of this deformity with minimal pain and disruption of lifestyle. Achieving success as an otoplasty surgeon requires an appreciation of facial aesthetics, intimate knowledge of ear anatomy, a firm understanding of the rationale for the surgical technique employed, and meticulous attention to technical detail (Fig. 33-1).

History

Otoplasty has a long history. The Indian method of auricular reconstruction was described as early as the 7th century in the writings of Sushruta.[2] Sushruta's writings were some of the earliest on the topic of Ayurveda (Indian medicine), and many of modern plastic surgery's roots stem directly from these ancient Indian teachings. In 1597, Tagliacozzi[3] published "De Curtorum Chirurgia," which described techniques of auricular and other reconstruction and became known as the Italian method. However, in the early 1800s the Prussian surgeon Johann Friedrich Dieffenbach described the first technique for treating prominent ears. His techniques were published in the treatise "Die Operative Chirurgie," an extraordinary two-volume work that encompassed all types of reconstructive and general surgical methods.[4] He specified setting back the pinna by suturing the auricular cartilage to the mastoid periosteum once the postauricular skin had been excised.

A few years later, Ely described his treatment of protruding ears with an anterior approach involving a fusiform excision of skin and cartilage.[5] Monks redefined this approach and treated children with a skin-only excision in the postauricular sulcus and adults with an excision of skin with cartilage.[6]

In the early 1900s, Morestin[7] devised a method of excising the conchal cartilage at the medial wall to break the "spring" of the cartilage; this served to medialize the antihelix and decrease the projection of the concha. In 1910, Luckett[8] reported on his method of reestablishing the antihelix with an excision of cartilage and plication of the edges. In 1937, Davis and Kitlowski[9] reported on their technique, which combined cartilage excision, incision, and shaving; these, in addition to postauricular skin removal and sutures through the cartilage, were used to create a new antihelix. Becker[10] sought to avoid unnatural cartilaginous ridging with incisions through the cartilage and reported on his technique in 1949. In 1955, Converse[11] created a new antihelix with two parallel incisions along with suturing; he used a wire brush to round off the edges. In 1958, Gibson and Davis[12] reported that making relaxing incisions in the cartilage resulted in a bending on the opposite side. In 1959, Farrior[13] recorded his excision of cartilage wedges to break the cartilage spring before stabilizing the antihelix with a suture. In 1963, Stenstrom[14] reported his findings that scoring the cartilage anteriorly facilitated the posterior plication; this method was particularly applicable to strong, stiff cartilage. In 1967, Kaye[15] reported on his technique, which involved anterior scoring and posterior plication with removal of a vertical ellipse of the conchal cartilage (Fig. 33-2).

Surgery for the treatment of protruding ears has since evolved. More modern techniques center on less invasive therapies and recognize the underlying anatomic defects. This is evident, in particular, with the Mustarde method of reestablishing the antihelical relief and the Furnas conchal setback method. Mustarde[16] published his method in 1963 and described using suture plication at three points without incision of the cartilage. The Furnas[17] technique was published in 1968 and intro-

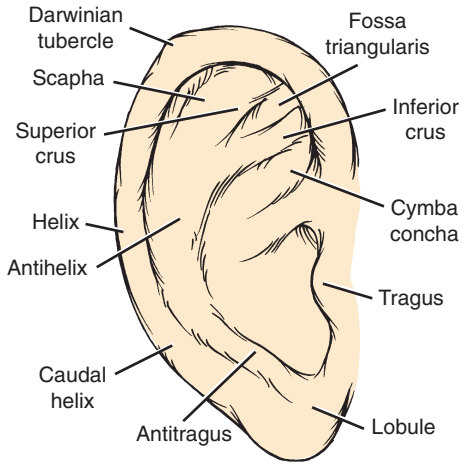

Figure 33-1. Anatomic landmarks of the normal ear. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: J. B. Lippincott; 1991: 709.)*

duced correction of conchal excess by suturing the concha to the mastoid (Fig. 33-3).

Incidence

The incidence of microtia is 1 in 20,000; however, protruding ears are much more prevalent and may be the most common congenital deformity of the head and neck.[18] In the white population, the incidence is 5%,[18] with the unfurled helix being the most common abnormality.[17] The hypertrophic protruding conchal bowl is the second most common deformity and is often present with the deformity of the antihelix.

Etiology

Genetic predisposition plays a role in this development; this is clearly seen in families with auricular deformities in both the parents and the children. In one study, 59% of otoplasty patients had a positive family history,[19] and it has been shown that the inheritance is autosomal dominant with variable penetrance.[20]

Anatomy and Embryology

The pinna is an appendage that is composed of fibroelastic cartilage covered in very thin skin. On the anterior aspect the skin attaches to the perichondrium, whereas posteriorly there is a thin layer of areolar connective tissue underlying the skin. The auricular cartilage is an extension of the cartilage of the external auditory canal; it is invested

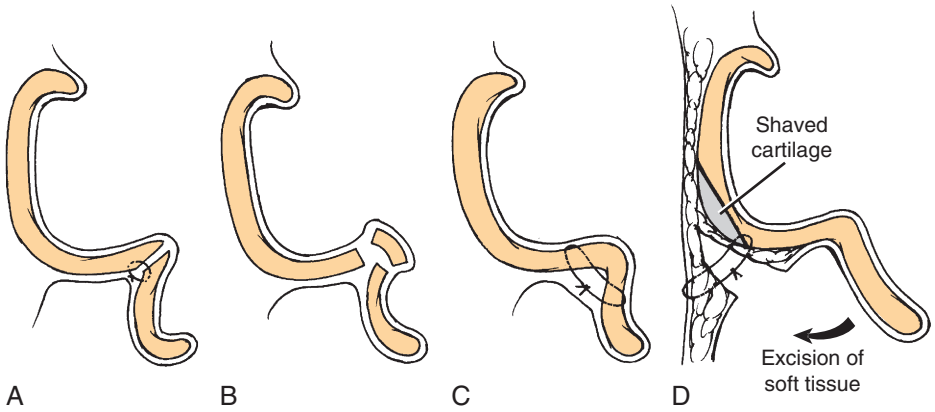

Figure 33-2. Historical techniques in otoplasty. **A,** Cartilage incision to recreate antihelical fold. **B,** Parallel cartilage incisions. **C,** Mustarde suture technique. **D,** Conchal cartilage shaving with excision of postauricular soft tissues. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: J. B. Lippincott; 1991:721.)*

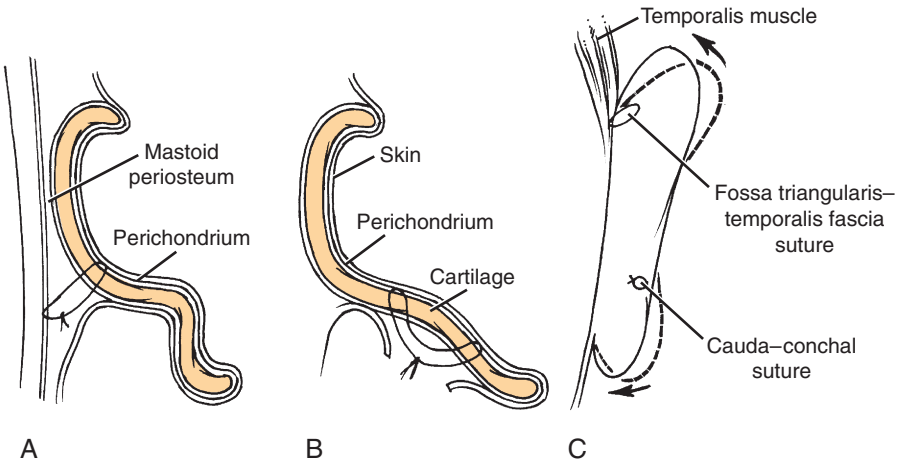

Figure 33-3. Suture techniques in otoplasty. **A,** Concha-mastoid sutures. **B,** Scapha-conchal sutures. **C,** Effects of fossa triangularis–temporalis fascia and cauda-conchal sutures. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: J. B. Lippincott; 1991:721.)*

in perichondrium and secured to the head by several ligaments and muscles. An anterior ligament stabilizes the tragus and helical root at the zygomatic process, and a posterior ligament stabilizes the concha to the mastoid. The "bowl" of the ear consists of three component concavities: the cavum concha inferiorly and the cymba concha and fossa triangularis superiorly. The pinna is defined by the series of folds and prominences on its anterior surface, with the major landmarks being the lobule, the helix and the antihelix, the tragus and the antitragus, the triangular fossa, the scapha, and the helical crus. Sensory innervation is through cranial nerves V (the auriculotemporal nerve), VII (the facial nerve), X (Arnold's nerve), as well as C2 and C3 (the cervical plexus). The main blood supply comes from the external carotid artery via the posterior auricular and the superficial temporal arteries with additional contributions from the occipital artery. The lobule, which lies caudal to the cartilaginous structure, is made up of soft fibrofatty tissue and typically can protrude slightly. A cartilaginous protuberance at the helix is called "Darwin's tubercle" and is the vestigial remnant that corresponds with the tip of an animal's ear.[21]

The otic placode is the first hint of a future ear and is present during the third week of intrauterine growth. The auricle emanates from the mesoderm of the first and second branchial arches; its growth occurs through the development of the six hillocks of His at week 6.[22] The following six structures evolve from these hillocks: (1) the tragus, (2) the helical crus, (3) the helix, (4) the antihelix, (5) the antitragus, and (6) the lobule. By week 12, the hillocks have fused. When these fuse inappropriately, a preauricular sinus tract can result.

Cartilage formation begins at week 7. The concha derives from the ectoderm of the first branchial groove. The upper portion forms the cymba concha, the middle portion forms the cavum concha, and the lowest portion forms the intertragal incisura. Malformation of the conchal bowl contributes to excessive protrusion of the pinna from the head. Additionally, the helical margin may develop separately from a skinfold caudal to hillocks 4 and 5,[23] which then develops rapidly during weeks 8 through 12. Finally, the helix furls during the sixth month. The antihelix furls during weeks 12 through 16; it is the failure of it to do so that results in a protruding scapha.

Normally the pinna is positioned about 15 to 20 mm from the helical rim to the scalp. From the frontal view, the rim is posterior to the antihelix laterally by about 2 to 5 mm. The auriculocephalic angle is 30 degrees in the cosmetic ideal, with the normal range being between 25 and 35 degrees. Ears that exceed 40 to 45 degrees are typically considered abnormal.[24]

In patients with protruding ears, the most common underlying anatomic abnormalities are either an insufficiency in the furl at the antihelix or a misshapen conchal bowl with a high conchal wall. There is often a combination of the two abnormalities, and there can be inappropriate folding of the elastic cartilage at the helix and antihelix to varying degrees. Otoplastic techniques are employed to reestablish the normal anatomic landmarks and/or to adjust the angulation of the pinna in relation to the head at the conchal cartilage. From an embryologic point of view, understanding that there are distinct anatomic bases for the protruding ear leads to choosing the appropriate technique or combination of techniques necessary for repair.

By the time a person is 3 years old, 85% of auricular growth is complete,[25,26] and the cartilaginous growth is almost complete by age 5 years.[27] The average vertical dimension is 5 cm in infants, whereas in adults it is 6 cm.[24] Because of these growth characteristics, surgical intervention can be accomplished at the age of 5 or 6 years without hindering additional growth; this is also the time that other children start to note such abnormalities in others, and, in the social milieu of school, teasing may begin.

Cartilage-Cutting versus Cartilage-Sparing Techniques

The ultimate goal of otoplasty is to achieve a permanent aesthetic result by introducing normal anatomy and normal anatomic position into the deformed auricle. Cartilage-cutting techniques derive from the observation that the cartilage will bend away from the cut side. Physical modification of the cartilage includes techniques that involve cutting the cartilage in either partial- or full-thickness processes, either on the anterior or posterior side. Cartilage can be excised partially to adjust the framework, or it can be sculpted by scoring or abrading the surface. These types of techniques are often appropriate for cartilage that is stiff and thick; however, there is a risk of developing irregularities at the surface or sharp edges, especially over the long term. Additionally, excisions can result in a diminished pinna, and any of these techniques may cause scarring.

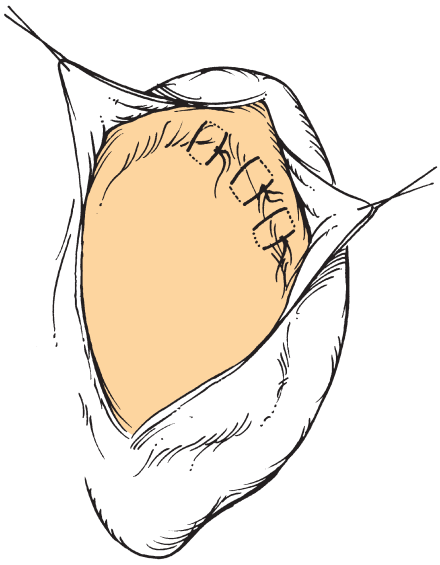

Figure 33-4. Scapha-concha sutures. One to three Mustarde sutures are positioned. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: J. B. Lippincott; 1991:723.)*

The cartilage-sparing techniques involve suturing to maintain the position and contour of the newly shaped pinna. The final result can be readjusted easily, and there is minimal cartilage damage or scarring. Bilateral symmetry can be established by adjusting the sutures after comparing the two sides. Mustarde[16] advised the use of permanent sutures to resculpt the antihelical relief. Multiple horizontal mattress sutures of permanent suturing material were organized posteriorly along the antihelical fold. Furnas[17] also used horizontal mattress sutures, but he used them to anchor the conchal bowl to the mastoid periosteum to relieve mastoid cupping. Since the descriptions of these techniques, many modifications and combinations have been tried and established (Fig. 33-4).

Graduated-Approach Otoplasty

With a graduated approach, auricular deformities are addressed in a stepwise and logical process that entails carefully assessing the deformity and correcting each of its aspects precisely.[25,26]

Local anesthesia is infiltrated before excising a fusiform section of skin from the postauricular sulcus. The precise amount is determined by manipulating the ear to the desired position and identifying the redundant skin. The excision is eccentric and positioned over the posterior aspect of the pinna so that the resultant scar lies in the sulcus. A superiorly placed releasing incision facilitates suture placement. In continuity with the skin excision, variable amounts of soft tissue can be removed from the postauricular sulcus to treat conchal protrusion. Three Furnas-type horizontal mattress sutures secure the concha to the mastoid periosteum. These sutures are placed at the fossa triangularis, the cavum concha, and the cymba concha to address the superior conchal bowl, the inferior conchal bowl, and the mid bowl, respectively. Additional shave excisions at the ponticulus, triangular, and conchal eminences are reserved for very deep conchal bowls.

The conchal-mastoid sutures are placed without excessive overcorrection in the middle third of the ear to prevent the telephone ear

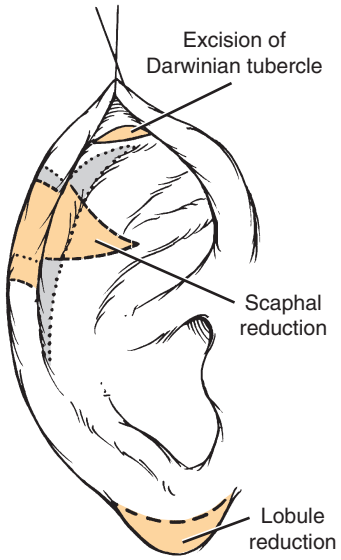

Figure 33-5. Otoplasty refinement. Wedge resection (*yellow*), fusiform scaphal excision with block helix resection (*dotted line*), lobe reduction, and helical trimming may be performed as necessary. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: J. B. Lippincott; 1991: 724.)*

deformity. Additionally, by pulling superiorly and posteriorly on the bowl, stenosis of the external auditory canal is avoided.

After the conchal bowl has been repositioned, the antihelix is treated with one to three Mustarde-type horizontal mattress sutures. These sutures are placed after simulating the desired furl manually, and then they are tied in order. The sutures require a 4 to 6 mm bite through the cartilage and anterior perichondrium. Rasping or scoring on the anterior surface may be required for particularly stiff cartilage.

When these therapies are complete, the skin is closed with dissolvable sutures. These are placed in an interrupted and inverted fashion to allow egress of blood. Bolsters of cotton soaked in mineral oil and hydrogen peroxide are molded against the ear, and a mastoid-type dressing is secured. Scaphal reduction, helical refinement, and lobe reduction are carried out as required (Fig. 33-5).

Other Otoplasty Techniques

Caouette-Laberge[28] reported on a scoring technique that was in use in Quebec, Canada, for more than 30 years. The auricle was approached posteriorly. Then, through a transcartilage incision at the cauda helicis, the antihelical cartilage was exposed, cut, and scored; this served to eliminate the intrinsic memory of the cartilage. With dissolvable sutures, the antihelix was then recreated. Nordzell[29] reported on his scoring technique, which was in use in Sweden for more than 30 years. With an anterior approach, the cartilage was accessed and incised. Abrasion of the cartilage allowed the antihelix to be recreated easily as it folded backward naturally; then absorbable sutures were used to anchor the medial edge of the incised cartilage over the lateral edge. Spira[30] reported on his 30-year experience in otoplasty in Houston, Texas. He depended on a revised Mustarde technique. His four-step technique included anterior otobrasion, posterior suture placement at the antihelix and at the concha and, finally, anterior suture placement at the root of the helix, with a hatch suture to prevent telephone ear. Bauer and colleagues[31] also reported on a combined otoplastic technique to address conchal hypertrophy. The conchal deformity was addressed first through an anterior excision of skin and cartilage. A greater width of cartilage was excised to facilitate skin closure; then the deformity was addressed from the posterior aspect with a "squid-shaped" section of skin removed and sutures used to effect the conchal setback.

Erol[32] described an approach through an anteriorly based skin flap through which the conchal cartilage was incised and freed. After excising the necessary amount, the cartilage was scored. Suturing of the cartilage was arranged posteriorly. He reported that this approach was suited to all modern methods of otoplasty and contributed greatly to the protection of the shape of the cartilage and the avoidance of scarring (e.g., posterior keloids). Horlock and colleagues[33] described the addition of a posterior fascial flap to protect the sutures from extruding; this flap can be applied to both Furnas- and Mustarde-type sutures.

Fritsch[34] described a technique of incisionless otoplasty in which the correction of the auricular protuberance was effected with precise placement of percutaneous retention sutures. In this method, incisions were avoided as suture material was placed subcutaneously to reshape the cartilage; the knots were buried. De la Torre and colleagues[35] described the use of temporary Kaye sutures to make precise adjustments to the antihelix. Three silk sutures were placed percutaneously from the posterior aspect of the auricle; these were left untied until all three were in place, and then secured to recreate the antihelical fold. They served as a guide for permanent nylon suture placement and were especially useful for bilateral correction and assurance of symmetry. After the permanent sutures were placed, the temporary silk sutures were removed.

Epstein and colleagues[36] reported on the use of electrocautery to weaken and sculpt the cartilage. From the posterior approach, an ellipse of skin was excised. Electrocautery was then used to create a partial-thickness Y-shaped trough. Horizontal mattress sutures were placed next, through the cartilage, to recreate the antihelical fold. Azuara[37] described his method of otoplasty with multiple transfixion incisions. The initial incision was from the posterior aspect of the auricle, preserving as much of the underlying connective tissue and perichondrium as possible. The dissection was subperichondrial anteriorly after an initial transfixion incision had been made. Transfixion incisions were then made in a multidirectional but precise manner; they were to be in the newly formed antihelix. These incisions served as relaxing incisions that allowed the cartilage to be rolled into a new antihelix. Permanent sutures were used to secure the new antihelix.

Raunig[38] described a technique where an antihelix was created by abrading the anterior surface of the antihelical cartilage. A skin incision about 10 mm in length was made in the scapha above the superior crus. A subperichondrial tunnel was dissected over the anterior aspect of the concha down to the antitragus. A diamond-coated file was then introduced into the tunnel and used to abrade the anterior cartilaginous surface. Abrasion of the cartilage continued until a suitable curvature of the antihelix was achieved and the ear concha assumed its new shape without any sign of tension. The helical margin was then fixed to the mastoid skin with adhesive tape for approximately six weeks in order to maintain the desired antihelical shape.

Octyl-2-cyanoacrylate is a tissue adhesive that has been used for neonatal otoplasty.[39] The antihelical fold can be recreated as the ear is secured to the mastoid with a drop of this glue; the skin and adhesive slough in a week or two. This simple procedure may relieve the child from further surgical intervention. Finally, endoscopy has been proposed as a method to avoid certain incisions and potential unnecessary scarring during otoplasty. In a report by Graham and Gault,[40] an incision was made in the temporal scalp with an anterior stab incision at the hairline. An optical pocket was formed, and, through the second incision, the cartilage was abraded. Sutures were placed posteriorly through small stab incisions and under endoscopic vision. Sutures maintained the new antihelix and were secured to the mastoid fascia.

Complications

Complications can be classified as early or late. The main early complications are hematoma, pain, infection, perichondritis, and cartilage necrosis. Late complications include problems with sutures, keloids and hypertrophic scars, hypoesthesia, cold susceptibility, and, of course, unsatisfactory results.

Early hematoma is a significant complication that, if left untreated, may progress to infection and cartilage necrosis, or even to the cauliflower ear deformity. Causes of hematoma formation are improper tissue dissection, inadequate hemostasis, and inadequate pressure dress-

ings. The incidence is about 3%, with potentially higher rates seen with cartilage-cutting techniques.[41,42] If a hematoma develops, pain is often the presenting symptom. The collection should be drained immediately under sterile conditions, and any active bleeding should be controlled with electrocautery. The incision should be closed either over a drain or with interrupted sutures to allow egress of any additional blood. The ear should be dressed again with a conforming dressing, and the patient should receive a broad-spectrum antibiotic.

Pain is often equated with hematoma presentation or infection; other causes are dressing problems such as a bent ear, or even pressure necrosis. For the most part, pain should be minimal after otoplasty. If pain is progressive, dressing removal is mandated.

The risk of infection is minimized with sterile technique, intraoperative antibiotics, antibiotic wound irrigation before closure, and antibiotic ointment applied to the suture line. If an infection develops, treatment is by evacuation of any collection and antibiotic use. The typical pathogens are *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa;* these are seen as either acute or chronic infections (e.g., an infected suture, granuloma).[41,42]

Perichondritis may follow any infection or hematoma. It requires treatment under sterile conditions with the débridement of necrotic tissue and the administration of intravenous antibiotics. Cartilage necrosis may result also from infection or hematoma. Additionally, improper surgical technique, cautery use, or even dressing placement may cause cartilage necrosis.

Late suture complications can occur with many types of suture material. Chromic catgut can cause a localized skin reaction and inflammation. Certain sutures (e.g., braided as compared to monofilament) are more reactive and have the potential to initiate a foreign-body granuloma; if this happens, the granuloma and suture material should be removed. Removal can be postponed for several months postoperatively and thus diminish the potential for a negative impact on the cosmetic result. Another suture complication is loss of correction with the suture techniques. In these techniques, overcorrection is recommended to account for the expected loss of correction, which can be up to 40%.[25] This type of complication is minimized by placing an appropriate number of sutures and employing cartilage-weakening modalities for stiffer cartilage.

Hypertrophic scarring or keloid formation may develop, especially after a postauricular incision.[43] Patients at risk are younger patients and those with more pigmented skin, particularly blacks with a history of keloid formation. Preventive modalities include avoiding overaggressive skin resection and ensuring an absolutely tension-free closure.

Injury to the greater auricular nerve may lead to hypoesthesia after otoplasty. Although a nuisance, it is of minimal significance clinically; sensory function often returns within weeks to months postoperatively. Disruption of the auricular blood supply may lead to recurrent frostbite and a higher susceptibility to cold temperatures after otoplasty.[44]

Perhaps the most difficult complication is patient dissatisfaction. Preoperative discussion requires dialogue to establish realistic expectations. Patients need to be advised that improvement—not perfection—is the goal. Small asymmetries (i.e., up to 2 or 3 mm when comparing one side with the other) are accepted to be within the norm of the human condition. It is our experience that overcorrection is better tolerated as compared with undercorrection; the patient will require reassurance postoperatively if expectations have not been met. If the deformity can be corrected surgically, then revision can be undertaken when appropriate. Continued reassurance may be needed when correction is not possible.

Several postoperative scenarios have been observed in otoplasty patients. One of the most common is loss of correction. This problem may imply a technical deficiency, because it is more often seen in the suture techniques and usually during the first 3 months postoperatively.[45] It may imply that the sutures were not placed properly or that not enough sutures were placed. Alternatively, failure may occur if the cartilage is too stiff or insufficient conchal setback was obtained. In approximately half of the cases in which there has been a loss of correction, there is a history of associated trauma to the ear.[25]

The telephone ear deformity occurs when there has been overaggressive conchal setback or postauricular skin excision in the central portion of the ear. Other conchal deformities include buckling of the concha or impingement on the external canal. Conchal hypertrophy may limit conchal setback if not addressed surgically either by excision or suture methods. In addition, there is a risk of overcorrection resulting in a "stuck down" look if the conchal bowl is overresected and the antihelix excessively furled.

In the case of the overcorrected antihelix, the ear may appear "stuck down" if excess conchal wall height has not been addressed. Additionally, the helix may appear hidden as the antihelix is more laterally positioned. A vertical post deformity in the scapha may result with overcorrection as well; this refers to an unnatural vertical fold in the scapha and buckling of the helix if sutures are placed incorrectly. Finally, undercorrection and asymmetry are potential complications that may cause dissatisfaction; both may obligate surgical revision.

Summary

Protruding ears are a common congenital condition that cause significant emotional discomfort for many individuals. Numerous techniques—from simple to complex—have been described over the years to correct this deformity. Cartilage-cutting incisions may result in less frequent loss of correction but increased cartilage irregularities in the long term. Cartilage-sparing suture techniques primarily leave the cartilage intact, thereby reducing the incidence of these irregularities. Our experience of using the soft tissue conchal bowl setback and horizontal mattress antihelical fold suture technique in a graduated approach has proved very successful (Figs. 33-6 and 33-7). Cartilage scoring is

Figure 33-6. This 10-year-old girl had a minimal soft tissue bowl excision for conchal setback and minimal modified Mustarde sutures to recreate the antihelical fold to set back the superior pole. **A,** AP preoperative view (*left*) and results 1 year later (*right*). **B,** Lateral preoperative view (*left*) and results 1 year later (*right*).

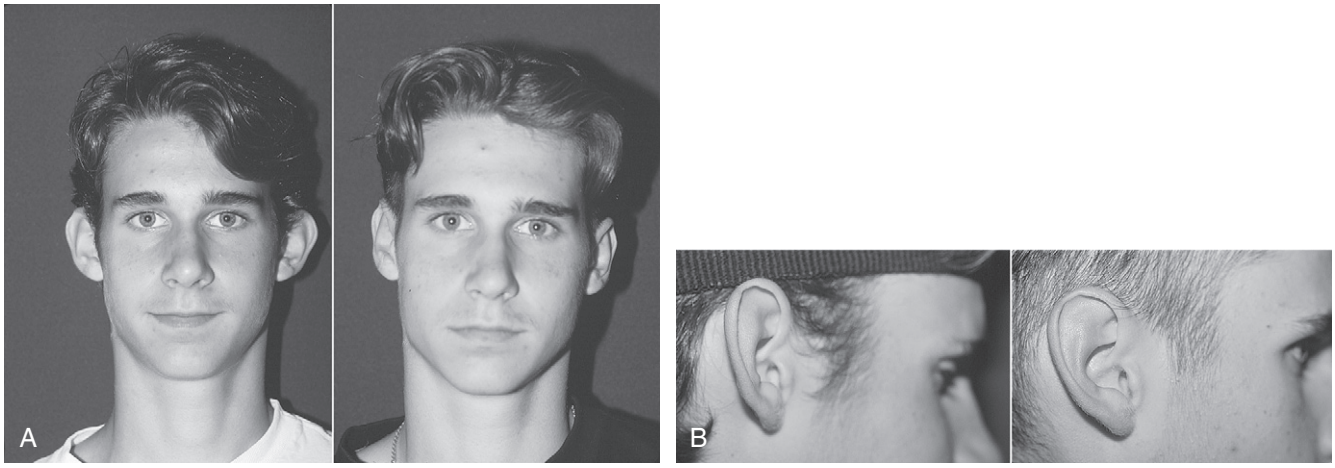

Figure 33-7. This 15-year-old young man had a moderate soft tissue bowl excision for conchal setback and minimal modified Mustarde sutures to recreate his antihelical fold and superior pole protrusion. **A,** AP preoperative view (*left*) and results 2 years later (*right*). **B,** Lateral preoperative view (*left*) and results 2 years later (*right*).

reserved for thicker cartilage that may be more refractory to suture-only techniques. Complications are not common and are usually minor. Creating a natural ear brings harmony to the face and requires an appreciation of the finer aspects of ear anatomy and attention to surgical detail; the surgeon who is so committed is rewarded with a high degree of patient satisfaction.

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CHAPTER THIRTY-FOUR

The Nasal Septum

Russell W. H. Kridel

Paul E. Kelly

Allison MacGregor Holzapfel

Key Points

- Examination of the patient should be performed before and after decongestion to fully evaluate the contributing factors to nasal obstruction.
- The internal nasal valve is the narrowest portion of the nasal cavity and, therefore, any compromise of the components of the valve creates symptoms of nasal obstruction.
- The external valve is a laterally based space boxed by the piriform aperture, the upper lateral cartilage (ULC) and lower lateral cartilage (LLC) attachments, and the caudal septum.
- The nasal cycle is an alternating one, with the total resistance in the nose remaining constant. In patients with a fixed septal deviation and intermittent nasal obstruction, the interplay of the nasal cycle becomes evident; the sensation of obstruction frequently mirrors the congestion phase.
- The bony conchal and mucosal hypertrophy is considered compensatory and can be found in the patient with a septum that is significantly deviated away from the enlarged turbinate.
- Physiologic models of airflow have shown that 50% of inspired air passes along the nasal floor.
- Even more so than with the full-transfixion incision, tip support is significantly weakened with an open dissection technique.
- Dissecting within a subperichondrial plane ensures little bleeding and a hardier flap with less likelihood of perforation.
- Before advancing posterior to the bony-cartilaginous junction, elevation of the mucoperiosteum along the nasal floor is frequently necessary to address any maxillary crest deviation or to address the septum that has shifted off the crest and is found to be obstructing the inferior airway.
- Any tear in the membrane is repaired with 5-0 plain suture, and, if bilateral membrane rents are noted, not only should they be repaired, but an interposition graft of crushed cartilage should also be placed. This interposition graft will significantly decrease the chance of permanent perforation.
- To prevent cribriform plate injury, the superior bony septum is never manipulated without first performing a superior septal incision or cut.
- To decrease the potential for loss of dorsal or tip support, the surgeon preserves at least a 1-cm dorsal and 1-cm caudal septal segment, which has been termed the *L-strut*[1] and is inclusive of the nasal spine.
- One of the more frequently seen septal deviations occurs when the quadrilateral cartilage has shifted laterally off the crest or there is deviation of the crest itself; this leads to nasal floor obstruction.
- After reskeletonization, the entire septal flap from anterior to posterior is mattressed with a continuous 5-0 plain stitch; a curved needle (instead of the popular straight Keith needle) should be used for this purpose.
- Employing methods of repositioning and fixation of the caudal septum often make it unnecessary to aggressively trim or excise the caudal end. After the septum along the floor and the crest are straightened, the caudal margin can be replaced to the midline nasal spine, secured, and sandwiched within a pocket created between the medial crural footplates—a technique named the *tongue-in-groove maneuver.*
- Approximately 20% to 30%[2-5] of patients who undergo septoplasty find that their symptoms are not corrected adequately.
- Observing the side wall motion during restful breathing and during forced inspiration allows the surgeon to evaluate for external valve contributions to nasal obstructive complaints.
- Use of a tight pack or gauzelike materials is still done by some, but we disagree with this practice because of the tendency of packing to adhere to the mucosa, cause pain, and create bleeding when removed.
- Internal nasal splints are generally only used in septal perforation surgery or when the septal membrane is excoriated or perforated and then we use soft, thin Silastic sheeting. Splints increase the degree of rhinorrhea. Hard, thick nasal splints with airway tunnels hurt patients going in and coming out and often get clogged.

The nasal septum serves many functions, including separation of the nasal airway into two distinct chambers, support of the nasal dorsum, and maintenance of the shape of the columella and tip. Traumatic deviation or developmental abnormalities of the nasal septum can lead to significant nasal airway obstruction and cosmetic deformity. Poor airflow can lead to impaired olfaction, impaired humidification and filtering of the passing air, and reduced oxygen inflow. Anatomic septal deviation can also lead to chronic sinus disease and can sometimes be reflected as an external nasal deformity. The septoplasty operation has evolved from simple cartilage manipulation to today's more complex procedures, which are often combined with surgery on the turbinates and valves. Septoplasty corrects structural deformities of the nasal septum to relieve nasal obstruction. When septoplasty is combined with rhinoplasty, the procedure may help straighten the deviated nose and provide cartilage grafts. Septoplasty is also performed in patients with a history of severe epistaxis caused by septal varices that develop from anterior cartilage deviation and the secondary interruption of lamellar airflow with resultant drying and irritation of the mucosa.

Anatomy and Embryology of the Nose

Development of the nasal airway begins during the fourth week of gestation. Collections of neural crest cells undergo proliferation and form the nasal placodes.[6,7] On the fetal face, adjacent cells proliferate and give rise to the medial and lateral nasal processes. The frontal and maxillary processes fuse to give origin to the lateral two thirds of the upper lip, the superior alveolar ridges, and the palatal shelves. The medial nasal processes join the maxillary processes to form the philtrum and columella; they also fuse with the frontal prominence to form the frontonasal process, which eventually encompasses the nasal bones, the frontal bones, the cartilaginous nose, the ethmoid bones, the central incisors, and the hard palate. With the growth of the medial and lateral nasal processes, two nasal pits form that invaginate until only the nasobuccal membrane remains. This membrane eventually ruptures by the 10th week, thereby allowing communication between the nose and the nasopharynx.[6,8]

The nasal septum develops as a downgrowth from the merged medial nasal processes and the nasofrontal process, thus defining the right and left nasal cavities. The nasal septum and the palatine processes begin to fuse anteriorly during the ninth week, and fusion is completed posteriorly by the 12th week.[6,8]

During the late embryonic period, the epithelium invaginates on each side of the nasal septum, thereby forming diverticula that are known as the *vomeronasal organs*. A vomeronasal cartilage develops ventral to each diverticulum. Shortly before birth, the vomeronasal organs begin to regress and usually disappear completely; the vomeronasal cartilages are usually the only adult remnants. These narrow strips of cartilage are located between the inferior edge of the cartilage of the nasal septum and the vomer.[8] They are often found in conjunction with a septal spur, and they can be used as cartilage grafting material when other sources are absent or exhausted (Fig. 34-1).

The cartilaginous framework of the nose develops from three paired mesenchymal condensations in both the medial and lateral nasal swellings. Part of this cartilage begins to ossify, thereby forming the membranous bone encasing the vomer and perpendicular cartilaginous plates. The perpendicular plate of the ethmoid and the nasal bones do not completely ossify until puberty.[6] Injury to the nose in the young child or teenager may not elicit a true fracture, but it may instead create growth changes in this transitioning tissue, which may ultimately result in a deviated posterior bony septum or even the formation of a spur.

The nasal septum has functional and aesthetic significance. The septum is the main support structure of the external nose.[9] It divides the nose into two cavities, regulates airflow through the nose, and supports the mucosal lining of the nasal cavities.[9] Where once the lining was afforded greater significance, now both the mucosa and the cartilage are recognized as codependent and necessary.

The bony components of the septum include the nasal crest of the palatine bone, the nasal crest of the maxilla and premaxilla, the vomer, the perpendicular plate of the ethmoid, the nasal crest of the frontal bone, and the spine of the paired nasal bones. The anterior septum is composed of the quadrilateral cartilage, with its caudal-most projection extending beyond the nasal spine. Because of the complicated embryologic development of the septum, any one of a number of arrangements of the bone and cartilage contributions may be encountered during surgery (Fig. 34-2).

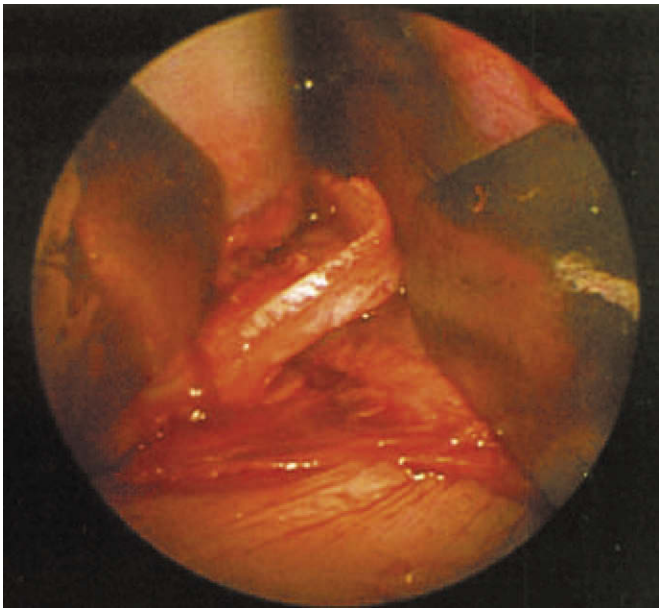

Figure 34-1. Intraoperative photo showing a septal spur with cartilage and bone overlap beginning at the bony-cartilaginous junction of the septum and going posteriorly. This cartilage strip can be used for grafting material if no other source of autologous cartilage is available.

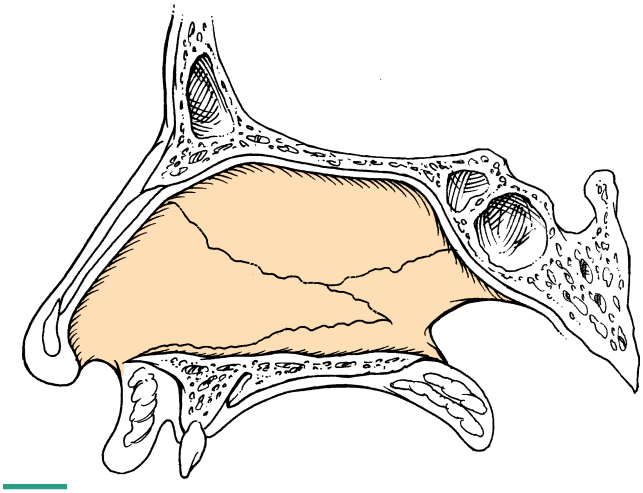

Figure 34-2. This lateral schematic depicts one of many configurations of the bony and cartilaginous posterior of the septum that vary substantially from patient to patient. What is fairly consistent, however, is the posterior triangular segment of cartilaginous septum, which often overlaps the bony septum.

Turbinates

The lateral nasal wall is composed of the laminae papyracea of the lacrimal bone, portions of the ethmoid bone, and the inferior and middle nasal conchae or turbinates. The turbinate bones develop from a cartilage ossification center during the fifth intrauterine month. The inferior, middle, and superior turbinates are composed of a thin bone for structural support and covered by an adherent mucoperiosteum. Stratified squamous epithelium is found on the anterior tip of the inferior turbinate, whereas pseudostratified ciliated columnar respira-

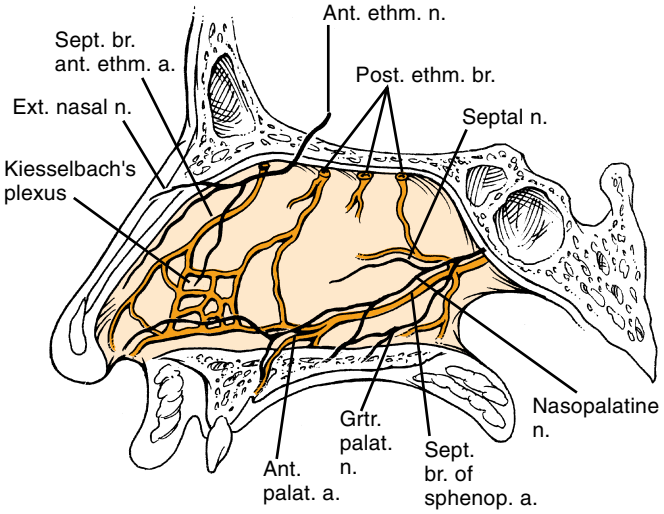

Figure 34-3. Depiction of the blood and neural supply to the nasal septum.

tory epithelium covers all other surfaces. The continually beating ciliated mucosa provides constant motion to the mucous blanket within the nose; this blanket acts as a cleaning and filtering system for the upper respiratory tract and also helps to maintain the moisture content within the nose. The turbinates maximize the effective intranasal surface area and rapidly humidify and warm the inspired air.[10]

Blood Supply and Innervation

Blood supply and innervation of the nasal septum are delivered within the mucoperiosteal and mucoperichondrial linings. The arterial blood supply originates from the ophthalmic branch of the internal carotid artery and the maxillary and facial branches of the external carotid artery. Blood to the upper nasal septum is supplied by anastomoses of the anterior and posterior ethmoid arteries, which originate from the ophthalmic branch. The external carotid artery contributes via a major branch of the sphenopalatine artery that perfuses the posterior and inferior septum. The columella and caudal septum receive blood supply from the septal branch of the superior labial artery. The septal mucosa itself contains complex arteriovenous anastomoses and venous sinusoids that can become engorged or constricted via neural or extrinsic pathways.

A variably located incisive artery and its associated neural fibers are found at the superior border of the vomer. This neurovascular bundle may be encountered when trimming a badly deviated maxillary crest or when elevating periosteum when a nasal floor approach is needed. Control of bleeding from this site may be obtained by infiltrating the incisive foramen from below, "plugging" the site from above, or carefully using suction Bovie cautery. After resection or trimming of the maxillary crest or work on the nasal spine, patients may complain of numbness or pain of the central incisors or of the mucosa of the hard palate just posterior to the incisors. This lack of sensation or complaint of pain is generally a short-lived phenomenon (Fig. 34-3).

Innervation of the nasal mucosa includes both autonomic and sensory components. The autonomic nervous system regulates the degree of vascular tone, turbinate congestion, and nasal secretions present in the nose at any given time. Presynaptic parasympathetic fibers travel along the facial nerve and continue as the greater superficial petrosal nerve at the geniculate ganglion. These fibers then join the deep petrosal nerve to form the vidian nerve. Within the vidian nerve, the fibers travel to the sphenopalatine ganglion and synapse with the postganglionic neurons before innervating the nasal mucosa. Postsynaptic sympathetic fibers pass through the sphenopalatine ganglion and terminate in the nasal mucosa. The first and second divisions of the trigeminal nerve supply sensory innervation to the nasal mucosa. Trigeminal nerve fibers also pass through the sphenopalatine ganglion and transmit sensations of pain, temperature, and touch.

Figure 34-4. **A,** Deviated nose before septoplasty. **B,** The significant correction of the deviated nose with septoplasty alone makes it incumbent on surgeons to always straighten the deviated septum before any lateral or medial osteotomies.

Nasal Obstruction

Thorough examination and visual inspection of the patient who complains of nasal airway obstruction are essential for diagnosis and treatment planning. Visual assessment of the external appearance of the nose is of utmost importance. This examination initially focuses on the size, shape, symmetry, and straightness of the nose; one should document the size of nostril openings, the thickness of the alae, and the width of the columella. Columellar widening may be seen with caudal septal cartilage deviation, splaying of the medial crura, or excess soft tissue. Septoplasty will correct airflow only if air can get into the nose. A previously fractured nose can hold the dorsal septum off the midline, and no septoplasty alone can correct this problem (Fig. 34-4). Such situations require sharply freeing up the septum from the upper lateral cartilages and performing medial osteotomies and a septoplasty with release of the septum from the maxillary crest for correction. Deformity of the nasal vault can narrow the diameter of the nasal passage. The patient with a crooked or C-shaped nose often has a severely deviated septum as well. Before examining the nose internally, one must observe the patient's nose during normal and exaggerated nasal breathing, watching the side walls for evidence of internal or external collapse (Fig. 34-5). Care must be taken when assessing the chronic sniffer or "nasal neurotic," however, who will show collapse as a result of an overly aggressive inspiratory force being generated, regardless of the competency of the valve. Surgery for the chronic sniffer will generally lead to poor outcomes despite adequate anatomic support and deflection

Figure 34-5. **A,** Patient breathing through the nose at rest. **B,** Collapse of the nasal side wall inclusive of nasal valve with forced inspiration.

correction, and it will often include frequent postoperative phone calls and second opinions obtained with regard to his or her problem, which is still perceived as uncorrected.

Anterior rhinoscopy allows for visualization of the septum, the turbinates, and the nasal valve—the most narrow area of the airway bordered by the septum, the upper lateral cartilage, and the anterior aspect of the inferior turbinate. Examination of the patient should be performed before and after decongestion to fully evaluate the contributing factors to nasal obstruction and to allow for a complete nasal examination. A large swollen turbinate can often obscure a posterior nasal spur. There should be no surprises at the time of surgery as a result of inadequate preoperative problem recognition. Nasal endoscopy with a rigid endoscope of the sinonasal region can be carried out to fully evaluate intranasal structures and assess for polyps, masses, and adenoidal size. The 4-mm 30-degree endoscope provides an excellent view.

External evaluation of the patient's nose should include performance of the Cottle maneuver, in which lateral distraction of the nasal valve is performed (Fig. 34-6). This maneuver may improve the sensation of nasal obstruction in cases of external nasal valve collapse or anterior septal deviation. A positive Cottle maneuver may suggest nasal valve compromise,[11] but it is not always a reliable indicator, with many false-positive results seen. Lateralizing the upper lateral cartilage (ULC) and then assessing for improvement in the obstruction sensation may provide a more accurate assessment of the nasal valve. Lateralizing the upper lateral cartilage (ULC) with a cotton-tipped applicator or the use of a cerumen curette or similar instrument increases the internal nasal valve angle and, in those with a narrow angle, will provide improvement in airflow. The surgeon must also evaluate the nasal tip to determine whether the tip ptosis is contributing to decreased airflow (Fig. 34-7).

Deviated Nasal Septum

Deviation of the nasal septum is a common cause of unilateral nasal airway obstruction and may follow nasal and midfacial trauma. Trauma during birth, including forceps placement or passage through a narrow pelvic canal, can cause injury that may lead to early septal deviation or

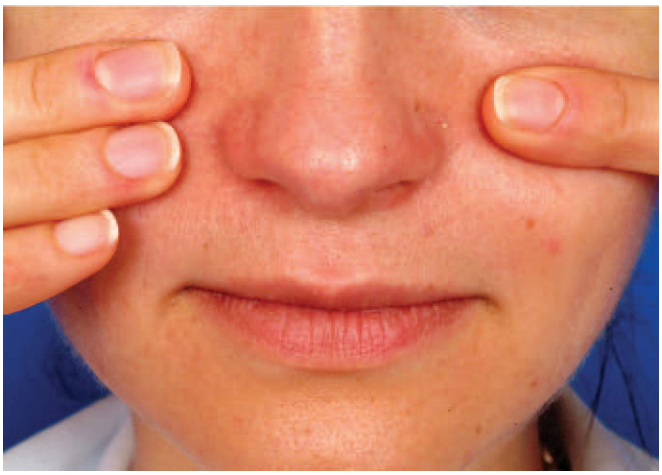

Figure 34-6. Cottle maneuver assessing for nasal valve component to nasal obstruction.

to deviation that is not evident until the more active growth phase of puberty. Minor trauma sustained early in life can be easily overlooked and frequently causes microfractures of the septal cartilage; healing of these microfractures leads to bending of the cartilage away from the side of injury. When this occurs early in life, it may lead to asymmetric growth of the entire nasal structure as a result of chondrocyte growth interruption. Patients with unilateral septal deviation most often complain of nasal obstruction on the contralateral side, a phenomenon called *paradoxic nasal obstruction.*[12] Patients are confused when the physician explains that the nasal passage through which the patient feels airflow moves most freely is actually the smaller of the two sides. Decongesting the nose and then testing airflow through each nostril separately or showing the patient an endoscopic photograph of each passage can help the patient accept the explanation and understand the true problem.

Figure 34-7. Patient with tip ptosis. Note the acute nasolabial angle.

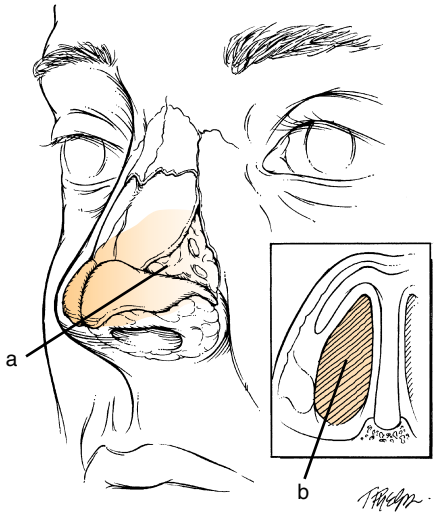

Figure 34-8. Schematic depicting (a) the external nasal valve area and angle and (b) internal nasal valve.

Nasal Valve Angle and Nasal Valve Area

The internal nasal valve, as described before, is the narrowest portion of the nasal cavity and, therefore, any compromise of the components of the valve creates symptoms of nasal obstruction. The angle is bound medially by the septum and laterally by the inferior edge of the upper lateral cartilages and the anterior aspect of the inferior turbinate; this junction forms a trapezoidal configuration (Fig. 34-8). This angle widens and narrows with nasal muscular contraction and relaxation on inspiration and expiration. The nasal valve is normally 10 to 15 degrees in white patients and wider in nonwhite and Asian patients.[13,14] Deformities of the adjacent nasal septum or loss of anatomic support structures can predispose the valve to collapse or narrowing, thereby causing nasal airway obstruction. The upper lateral cartilage at its junction with the septum may be thickened, twisted, or concave as a result of weakness or trauma or even absent if there was prior surgery. Webs of scarred mucosa may form between the septal mucosa and the lateral nasal wall or turbinates and may narrow the valve through scar contracture (Fig. 34-9). Adhesions that result in valve narrowing can create a fixed obstruction with a false-negative Cottle maneuver.

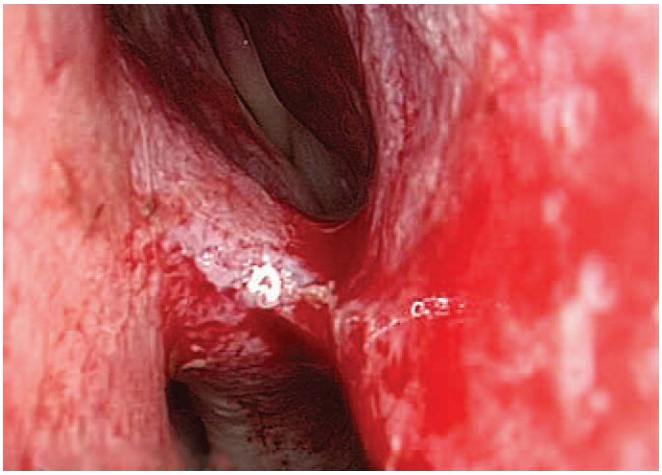

Figure 34-9. Intraoperative photo showing scar band from the septum to the lateral nasal side wall.

The external valve is a laterally based space boxed by the piriform aperture, the ULC and LLC attachments, and the caudal septum. Obstruction as a result of external valve compromise may be a postrhinoplasty phenomenon, a result of the aging process,[15] or a result of caudal septal dislocation or trauma.

Nasal Physiology (Resistance and Airflow)

On inspiration, the airstream funnels through the vestibule of the nose, squeezes through the narrow valve, and disperses in the nasal cavity. Cadaver studies indicate that flow through the nasal valve of an adult at rest is accelerated to a linear velocity of 16 m/sec. As the airstream leaves the valve and enters the nasal cavity, its velocity decelerates by a factor of four; this deceleration promotes disruption of the air by allowing it to mix in the nasal cavity.[16] This is essential for the effective conditioning of inspiratory air and may aid in the ability to smell. Conditioning consists of humidification, the removal of antigenic particles, and warming.

Resistance to airflow refers to forces that impede the flow of air through a conduit. Nasal resistance is evaluated by simultaneously measuring nasal airflow and the resultant pressure gradient in the nasopharynx. Ohm's formula integrates these measurements to calculate nasal resistance in centimeters of H_2O/L/sec (or Pascals/cc/sec).

The single most important variable in nasal airflow is the diameter of the nasal passage. Dimensions and shape of the airway lumen and airflow velocity determine the magnitude of resistance to airflow. Resistance varies inversely and exponentially with lumen cross-sectional area and, because the nasal valve has the smallest lumen dimension, nasal valve resistance is very sensitive to structural or vascular displacements. In healthy noses, resistance to airflow is reduced by a third after topical decongestion, and resistance of the decongested nose is reduced by two thirds with wide alar retraction.[17]

Nasal resistance is modified and controlled physiologically by the erectile tissues of the nasal mucosa. The parasympathetic system controls the congestion and increased nasal secretions by vasodilation of the sinusoids and capillaries in the mucosa, whereas the sympathetic system provides a steady vasoconstrictor tone. Nasal obstruction can be felt not only as an actual decrease in the nasal diameter but also as a feeling of obstruction even when no anatomic obstruction exists. Eliciting a medical history is clearly important, because certain medicines (e.g., exogenous hormones, oral contraceptives) can alter the neural input to the mucosa and result in mucosal hypertrophy and nasal obstruction. Turbulent airflow creates a perception of increased

resistance and prevents proper clearance of air volume. In patients with severe nasal septal deviation or with septal perforations, airflow is turbulent. The nose interprets turbulent flow as low flow and thus creates a sensation of stuffiness for the patient.

The Nasal Cycle and Paradoxic Nasal Obstruction

The nasal cycle was first observed in 1927 by Heetderks,[18] who described alternating turgescence of the inferior turbinates in 80% of a normal population. The turbinates in one fossa filled up while the opposite turbinates decongested. This cycle, which is controlled by the autonomic nervous system as described earlier, had a mean duration of 2½ hours. He further observed and documented that the turbinates in the dependent nasal fossa filled when the patient was in the lateral decubitus position. Some postulate that this alternating positional obstruction has the purpose of causing a person to turn from one side to the other while sleeping. The nasal cycle is an alternating one, with the total resistance in the nose remaining constant. In patients with a fixed septal deviation and intermittent nasal obstruction, the interplay of the nasal cycle becomes evident; the sensation of obstruction frequently mirrors the congestion phase.

Some patients with a severely deviated septum learn to subconsciously eliminate the increased resistance sensation of the obstructed side. The opposite or normal side has a variable resistance as a result of the continued fluctuations of the nasal cycle. Nasal obstruction will be perceived on the open side during the turgescent phase; this phenomenon is known as paradoxic nasal obstruction.[12,19] Knowledge of this phenomenon is essential to avoid misinterpretation of the significance of unilateral enlargement of one inferior turbinate, which is often present in normal noses. Surgical correction must address the deviated septum, but it must also address the etiology of the patient's subjective complaint of increased resistance on the side on which clinical evaluation shows a more open nasal passage.

The dynamic portions of the nose (including the nostrils, vestibules, and lumen) can be narrowed due to the Venturi effect (see Fig. 34-5). Identification of collapsible nasal structures is important and should be addressed during preoperative review. Surgery can then be planned to widen the angle between the upper lateral cartilages and the septum with spreader grafts or to stiffen the nasal side wall with batten or umbrella graft placement.

Septal versus Turbinate Obstruction

Hypertrophy of the nasal turbinate can be classified as either mucosal or bony. Etiologies for mucosal turbinate hypertrophy include both allergic and nonallergic (vasomotor) rhinitis. The hypertrophy is generally seen bilaterally, and the sense of obstruction is relieved with topical decongestants. Surgery usually makes little difference in these patients unless mucosal redundancy is such that the nasal airway is persistently obstructed. Primary treatment would include antihistamine and decongestant use as well as topical steroid management. Surgery may be reserved for those who still complain of nasal obstruction.

Patients who smoke or who are exposed to chronic nasal irritants will frequently complain of nasal obstruction and chronic nasal drainage. Medical treatment for these patients is usually ineffective. However, these patients should not be considered primary surgical candidates until they have stopped smoking or have taken measures to avoid nasal irritants.

When mucosal decongestion does not elicit intranasal airway changes or symptomatic improvement, bony turbinate hypertrophy, along with deviation to the septum and nasal valve compromise, should be considered. This obstruction is generally constant. One theory of bony turbinate hypertrophy is that it is based on a lack of structural resistance created by the midline nasal septum during development. The bony conchal and mucosal hypertrophy is considered compensatory and can be found in the patient with a septum that is significantly deviated away from the enlarged turbinate.[10] The turbinate mucosa and underlying bone enlarge into the more open nasal passage in pursuit of normalizing nasal airway resistance.[10] Correction of the deviated septum and trimming of the enlarged turbinate are performed together to relieve obstructive complaints. Straightening only the septum without modifying the hypertrophic turbinate will result in obstruction as a result of the large turbinate on the side on which obstruction was not perceived before.

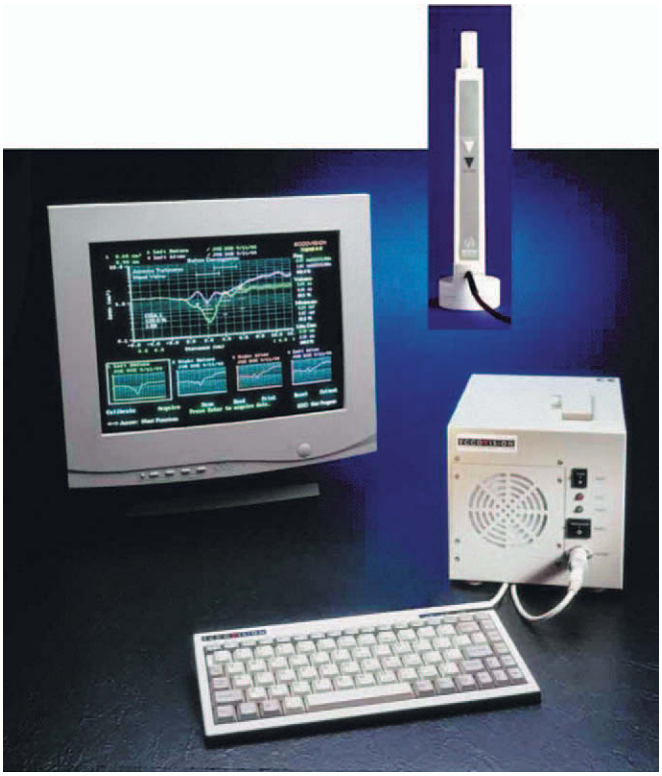

Figure 34-10. The Acoustic Rhinometer used to assess for intranasal cross-sectional area. *(Photo provided courtesy of Hood Laboratories.)*

Turbinate size—along with maxillary crest and septal floor deviations—can impair overall flow patterns. Physiologic models of airflow have shown that 50% of inspired air passes along the nasal floor.[20] Addressing each problem improves overall flow and decreases the obstructive sensation. Although the longevity of turbinate therapy varies,[10,21] conservative turbinate surgery is a useful adjunct to include with septal surgery.

Measurement of Obstruction

The ability to objectively assess for nasal obstruction allows for appropriate treatment planning, provides a tool for outcomes analysis, and creates documentation for insurance justification or medicolegal reasons.[22] It is astonishing for most surgeons to note the varied subjective preoperative and postoperative patient complaints, which sometimes do not correlate with physical findings and objective measurements. A minor correction in some patients can elicit great improvement in the sensation of nasal obstruction and, conversely, a large structural improvement in septal anatomy may not be appreciated at all.

Acoustic rhinometry, which is an easy test for patients to tolerate and for staff to perform, provides a minimally invasive, convenient, accurate, and expeditious method of measuring dimensions of the nasal airway.[17,23-25] Acoustic rhinometry was initially used in 1977 for area measurements of the lower airway (e.g., trachea, bronchi) and was subsequently expanded to assess nasal geometry.[26] The equipment delivers sound waves to the nasal cavity and then measures their reflection (Fig. 34-10); the resulting wave is called a *rhinogram*. The nasal valve causes the first dip in the rhinogram, and the second is caused by the anterior tips of the inferior and middle turbinates (Fig. 34-11). Topical vasoconstriction is applied to differentiate anatomic from physiologic causes of obstruction. With the acoustic rhinometer, the minimal cross-sectional area of the nose and the nasal airway resistance can be calculated. Acoustic rhinometric assessment of the valve can be used to determine whether valve surgery may be helpful for the correction of the patient's complaint of nasal airway obstruction. During the

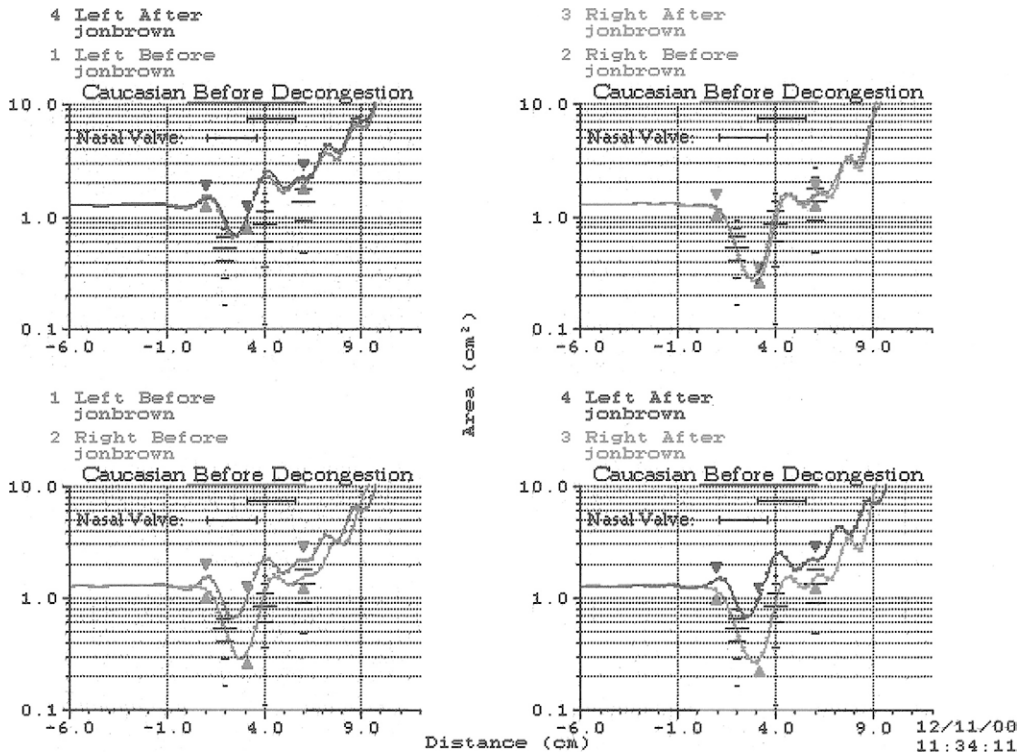

Figure 34-11. Rhinogram generated by the Acoustic Rhinometer.

assessment and treatment of nasal obstruction, which is a highly subjective sensation, it is possible to determine whether this obstructive sensation is caused by structural or dynamic nasal components. Objective postoperative improvement in nasal function can be documented by the appearance of the rhinogram. Disadvantages of this tool include the variability associated with the nostril opening and the fit of the acoustic measurement tip used for echo calculation. Furthermore, the acoustic rhinometer overlooks the contribution that narrow nostrils, a wide columella, a caudal septal deflection, or tip ptosis makes to the sensation of nasal obstruction.

Airflow rhinometry, a second assessment tool, is a dynamic test of resistance to nasal airflow both before and after vasoconstriction.[25] Reproducible data can be obtained to evaluate anatomic abnormalities and document surgical or medical management outcomes.[17] Although rhinometry is very sensitive, there does exist some margin of error that is based in test administration. Rhinometry provides a numeric value that indicates how hard it is to breathe through the nose. Breathing resistance of the combined cavities of the adult nose at rest greater than 3 cm H_2O/L/sec indicates obstruction.[17] Decongestion of the nasal cavities and alar retraction enable the physician to determine the sites of mucovascular and structural components of resistance. Airflow resistance created by the adenoidal pad can also be measured in children. A complete test requires at least 20 to 30 minutes. Standard rhinometer measurements also fail to assess for nostril opening or to take into account the effect of tip ptosis on airflow.

Septoplasty Technique and Evolution

Patient complaints of airway obstruction that are consistent with intranasal physical findings often lead to septoplasty and turbinate surgery. However, some patients with huge septal deviations present with few if any complaints, and some patients with minor deviations complain the most. Treatment must be individualized. Review of the history of septoplasty provides better understanding of the terminology handed down to the younger generation of nasal surgeons and serves as a reminder of ground covered and abandoned. The techniques we use in modern surgical procedures have evolved from those that originally were less than optimal or that had unscheduled outcomes. It is interesting to note that the goal of septal surgery is the same as it was 100 years ago, but now the process has changed; the nasal surgeon still strives to maximize the symptomatic improvement of nasal obstructive complaints and minimize the risks involved in such a pursuit.[27]

Technique Evolution

The closed septal redisplacement methods described and advocated by Adams[28] and Asch[29] in the late 1800s relied on blunt force and attempts to disrupt cartilage attachments and inherent properties. Freer[30] goes so far as to suggest that the technique involves the "temptation to use violence to overcome the resiliency of the septum." Asch was careful to advocate this method only for correction of the cartilaginous deviations and never for correction of vomer or ethmoidal bone crookedness. Asch lent his name to the forceps specifically designed to accomplish the closed reduction of this cartilaginous segment.

Although not thoroughly disappointing to all patients, Asch's technique provided little long-term improvement for the complaint of nasal obstruction and only seemed to mobilize cartilaginous deformities by failing to specifically address the factors responsible for them. Asch certainly had good intentions and even describes the crushing and disruptive techniques and tools that he used in attempts to disrupt the intrinsic forces. However, correction of patient complaints was ultimately short lived.[29] Asch's technique, which was widely abandoned around the turn of the century, perhaps provided a base from which the closed bony nasal reduction procedure takes root. Few today will even attempt septal redisplacement after injury and certainly not consider it as a primary corrective maneuver for the complaint of nasal obstruction, simply because of lack of efficacy.

Krieg[31] described a technique of mucosal resection in which the deflected cartilaginous segment, along with overlying mucosa, was removed in its entirety; this left a large perforation and caused other complications that surely outweighed any temporary benefits. Follow-up notes for patients who had undergone the mucosal removal procedure may have included descriptions of crusting, bleeding, and worsened nasal obstructive complaints. The increased obstructive complaints may have even provided insight for nasal researchers during this timeframe and may have led to baseline research of nasal flow principles and, ultimately, the description of laminar and turbulent airflow dynamics as discussed by Proetz[32] and further refined by Fomon and colleagues.[33]

Krieg would ultimately suggest mucosal preservation and removal of only the deflected cartilaginous segment, which probably gave rise to the more prevalent submucous resection procedure still practiced by some today. Freer[30] gives credit to American researcher and surgeon E. F. Ingals in 1882 for the description of mucosal flap elevation and removal of a triangular portion of the quadrilateral cartilage. This was the so-called window resection. Krieg[31] described resection of the entire deflected cartilage segment and used a slightly different mucosal incision. Boenninghaus[34] suggested that resection be continued more posteriorly into the vomer and perpendicular plate of the ethmoid, if necessary, for definitive airway straightening.

Overall, little emphasis was placed on the potential structural support that the septum afforded. In fact, many, including Freer[30] and Fomon and colleagues,[33] felt that the overlying mucosa was the only physiologically important structure within. Saddling of the nose was blamed not on cartilage resection but rather on the cicatricial forces of healing.

Septoplasty Today

As nasal anatomic nuances and physiologic properties have become better understood, surgical correction for the problem of nasal obstruction has also evolved. The role of the septum as a determinant of nasal shape and contour has been recognized.[35]

Correction of Cartilaginous and Bony Septal Obstruction

Techniques used today are still geared toward septal resection, but more emphasis has been placed on preservation, realignment, or a combination of the two. Indeed, the term *septoplasty* takes its meaning from the Greek term that means "to reshape or mold the septum." Most standard procedures today recognize mucosal preservation as a primary goal and make use of a submucous cartilaginous and bony approach.

Anesthesia and Analgesia

The operator must use topical and local vasoconstrictive anesthetic for not only the analgesic qualities but also, more importantly, for the vasoconstrictive effects. A dry operative field allows the surgeon to carefully dissect the lining away from the deviated cartilage or bony septum so that resection or reshaping can take place. The most popular topical solutions are 4% cocaine or 2% Pontocaine mixed with 1% ephedrine or 1% Neo-Synephrine. Before placement of these topical agents into the nose, preoperative treatment by the anesthesia team with fentanyl and versed acts as a stabilizer for cardiac and smooth muscle. These agents counter the potential increase in heart rate or blood pressure that is sometimes seen. With the use of 2 to 4 mL of 4% cocaine solution or 1 mL of the 2% Pontocaine solution on cotton pledgets, toxicity is rare. If local and intravenous sedation make up the chosen anesthetic path, the chance of toxicity may be more, because this option relies more heavily on the local analgesic properties of the topical and local medicines. Systemic toxicity from these topical solutions is marked by constriction of the pupils, hypotension, vomiting, and cardiac or respiratory arrest. The ability to assess for toxicity depends on the plane of anesthesia and requires close surveillance. Administration of 100% oxygen—along with use of a ventilator for respiratory support and the administration of vasopressive and/or cardiotropic medicines—may be required while these agents are naturally metabolized by the patient's body. The older or pediatric patient is best served by minimizing doses. For the patient with cardiac issues or for cardiac hypersensitivities seen in patients with a past or present history of drug abuse, local injection for anesthetic effects and oxymetazoline (Afrin) for vasoconstrictive purposes may be more appropriate. Our injectable anesthetic of choice for the otherwise healthy individual is 1% Xylocaine with 1:100,000 epinephrine used with a maximum suggested dose of 4 to 7 mg/kg, depending on the epinephrine content.

The local injection is performed with either a 27- or 30-gauge needle and has a second useful purpose in that it will further ease identification of the correct dissection plane as a result of its hydrodissective qualities. The injection is started at the caudal end of the septum, and secondary injections are performed more posteriorly until the mucosa is well blanched or maximum volume based on patient weight is met. The contralateral membrane should also be injected, and so should the area of the nasal floor around the maxillary crest. After the injection is performed, waiting at least 10 minutes ensures maximum vasoconstriction.

Incisions and Plane of Dissection for Septoplasty

The Killian incision,[36] which was described and published in the early 1900s, is one that is created approximately 1 to 2 cm posterior to the caudal septal margin within the respiratory epithelium. Some surgeons were taught this incision and still find it very useful when septal deviation is only found in the middle to posterior third of the nasal cavity. Its greatest downfall, however, is in its relative inaccessibility to the caudal septal edge and the higher potential for membrane tearing as a result of its location within the delicate respiratory lining.[37]

By contrast, the hemitransfixion or transfixion incision made at the caudal border of the septum allows access to the deviated caudal septum and any posterior deflections. The incision is created within the squamous epithelium of the vestibule and hence has less of a tendency to tear under stressors. Although the hemitransfixion incision is ideal in most scenarios, conversion to a full transfixion incision is easily accomplished by incising completely through to the opposite membrane (Fig. 34-12). Some may still approach the septum through an open rhinoplasty approach using marginal and transcolumellar incisions. In the open approach to the septum, the medial crura are separated, and the caudal septum is then identified. Even more so than with the full-transfixion incision, tip support is significantly weakened with this open dissection technique, and so the authors reserve this approach for those undergoing an open approach to septal perforation repair or in complex cases when using an external approach to rhinoplasty. Even then, tip support should be reconstituted to prevent future tip ptosis at the completion of the procedure.[38]

The hemitransfixion incision decreases tip support to a minimal degree, and, for this reason as well as for the access it affords to the caudal septum, the hemitransfixion incision is used almost solely in our practice. It is created by first identifying the caudal end of the septum itself. Inserting the nasal speculum into the nose and gently retracting the slightly opened speculum clearly reveals the caudal septal edge. The No. 15 blade is then used to incise mucosa down to and through the perichondrium. Identification of the proper plane is now of utmost importance. Dissecting within a subperichondrial plane ensures little bleeding and a hardier flap with less likelihood of perforation. "Scraping" the cartilage at the incision site to denude any hint of perichondrium before initiation of the elevation process helps to ensure the proper plane.

The Cottle elevator, with its two dissecting faces—one shaped like a sharpened spade and the other more flat and dull—is still used to raise the envelope under direct vision. The sharper spade-like end is used first to begin the dissection in the submucoperichondrial plane. After the dissection is started, the flat and dull end efficiently elevates the envelope in an atraumatic fashion. The surgeon should elevate the envelope with a wide front to ensure the best visibility and decrease the risk of mucosal tearing. Some surgeons prefer the Freer elevator with its straighter dissecting face, but caution is suggested because of the increased ease of perforation through the membrane (Fig. 34-13). Advantages of the Cottle elevator over the Freer are because of its two dissecting faces.

Addressing the Deflected Cartilaginous and Bony Septum Proper: Basic Technique

Having created the incision and begun the elevation of the mucoperichondrium, longer specula are used as the dissection proceeds posteriorly. Before advancing posterior to the bony-cartilaginous junction, elevation of the mucoperiosteum along the nasal floor is frequently necessary to address any maxillary crest deviation or to address the septum that has shifted off the crest and is found to be obstructing the inferior airway. Identifying the piriform rim, scraping along the bone to ensure that one is under the periosteum, and then elevating the mucoperiosteum along the nasal floor accomplishes the floor dissection. By elevating above the crest or deviated floor segment and then elevating below the segment, the surgeon creates two pockets or tunnels.

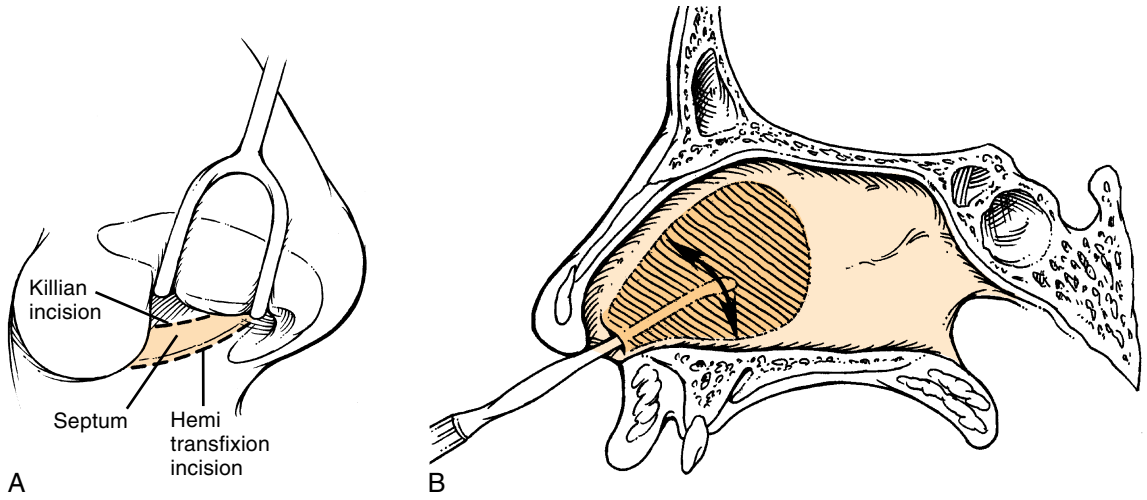

Figure 34-12. **A,** Schematic showing the Killian incision and the hemitransfixion incision. Note the incision placements relative to the caudal end of the septum. **B,** The Cottle elevator is inserted in a subperichondrial pocket and the flap is elevated.

Figure 34-13. The Cottle and Freer elevators. Note the two faces of the Cottle instrument, one spadelike and the other more blunt. The spade end is used to initiate the separation of the microperichondrium and the cartilage; once the flap is raised anteriorly, the blunt end is used to elevate posteriorly.

Incising the nasal floor deflection or connecting the two tunnels directly helps to avoid mucosal tears during the envelope elevation phase of the procedure. The dissection may be eased with the use of the sharper spade end of the Cottle elevator. The surgeon will find the transition from mucoperichondrium to mucoperiosteum to be a difficult dissection, and tearing the mucoperichondrium may be unavoidable. Any tear in the membrane is repaired with 5-0 plain suture, and, if bilateral membrane rents are noted, not only should they be repaired, but also an interposition graft of crushed cartilage should be placed. This interposition graft significantly decreases the chance of permanent perforation.

The dissection continues past the bony-cartilaginous junction to gain access to any posterior bony deflection or spur. At this time, the Cottle elevator may be used to separate the bony and cartilage septal segments, which is helpful if a posterior septal bony deflection is a primary issue. Separation at the juncture allows bilateral posterior septal membrane elevation. A septal spur or a projection of either cartilage, bone, or a combination of both is frequently seen at the bony-cartilaginous junction. Bilateral membrane elevation followed by septal incision using a Becker septal scissor above and below any deviated septal segment or spur allows increased mobility of the deflected segment. The nasal speculum can then be used here to push the crooked incised segment medially or laterally and, in so doing, the mucoperichondrial flaps can be more easily elevated, thereby giving reasonable assurance that membrane perforation will be minimal. It is in the area of a spur that the risk of membrane fenestration is greatest. The risk is increased because of the difficulty of membrane release and the frequently thinned overlying membrane. We avoid the Jansen-Middleton forceps for cartilage removal, preferring instead the wide-mouthed Watson-Williams forceps, which have less risk of cutting the cartilage that may be required for nasal grafting later in the procedure. To prevent cribriform plate injury, the superior bony septum is never manipulated without first performing a superior septal incision or cut. Even then, any posterior septal removal is done within one rotational plane.

Having addressed the posterior septum, the surgeon turns his or her attention to the cartilaginous septum, including the caudal end and the floor segment. To decrease the potential for loss of dorsal or tip support, the surgeon preserves at least a 1-cm dorsal and 1-cm caudal septal segment, which has been termed the *L-strut*[1] and is inclusive of the nasal spine. Preservation of the L-strut is perhaps the base upon which most surgeons work (Fig. 34-14). Resection of a large central septal segment can be done safely, if required, to address central septal deflections or if grafting materials are needed for rhinoplasty. After the membrane is elevated from at least one side, the sharper beveled edge of the Cottle elevator can be used to incise the cartilage. The incision is started at the bony-cartilaginous junction by gently penetrating the cartilage with the Cottle elevator. The incision is carried forward and deflected inferiorly, thus preserving the 1-cm dorsal and caudal support segment. Contralateral septal membrane is elevated with the freeing of the inferiormost aspect of the septum from the maxillary crest trough with gentle blunt dissection. If the floor is deviated, creating an incision on the deviated segment and then using the two-tunnel approach as described above for the floor deviation proper provides another method for membrane elevation. Removal of the freed segment with a nonbiting forceps completes the resection. A No. 15 blade can be used for the cartilage incision but may result in contralateral membrane injury if one penetrates the contralateral perichondrium. The Ballenger swivel knife is an older septoplasty instrument that is

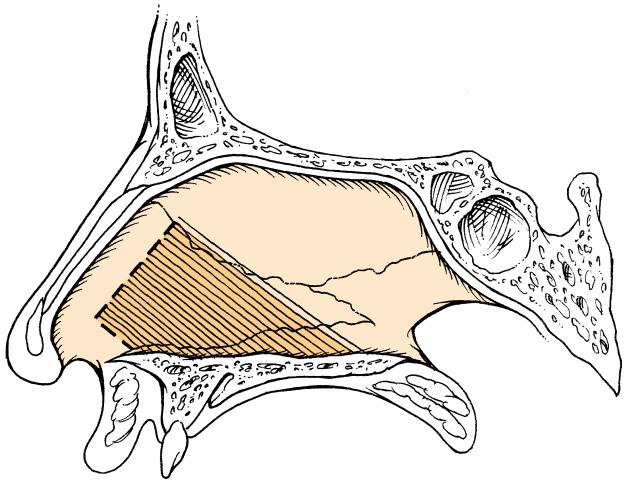

Figure 34-14. Schematic showing the 1-cm caudal and dorsal segment that should be left intact so as to provide tip and dorsal nasal support (L-strut).

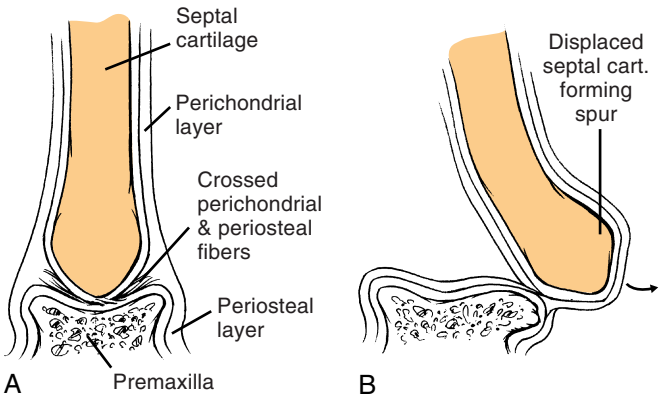

Figure 34-15. **A,** Schematic showing the relationship of the trough of the maxillary crest and the inferior aspect of the septum. **B,** Schematic showing the inferior aspect of the septum shifted from a crest, which is also deviated and needs to be reduced.

sometimes used, but it has a propensity to tear membrane and overresect septal cartilage.

One of the more frequently seen septal deviations occurs when the quadrilateral cartilage has shifted laterally off the crest or there is deviation of the crest itself; this leads to nasal floor obstruction. Explanation for this occurrence may be found in the patient's history of early trauma with crest fracture or may simply be due to cartilage growth and a shallow groove of the maxillary crest (Fig. 34-15). Correction of this problem requires bilateral membrane elevation, with extension of the membrane elevation along the nasal floor. The Cottle or the No. 15 blade can then be used to excise the deviated cartilaginous component, and a 4-mm unguarded osteotome is used for any bony contribution. The nasal spine is preserved in almost all scenarios. After the inferior floor segment has been excised, a superiorly based swinging door is created (Fig. 34-16). The now-mobile septal segment is then relocated to the maxillary crest groove, and the anterior-most aspect is secured to the periosteum of the maxillary crest or spine with 5-0 long-lasting absorbable suture. This maneuver should be used as a primary step for straightening the extremely bowed septal segment, especially when the external nose is also deviated. If the obstructing maxillary crest segment is limited to one side, the deviation is tangentially shaved with a 2-mm osteotome placed parallel to the crest; this allows for improvement of the nasal airway without any loss of otherwise normal crest support.

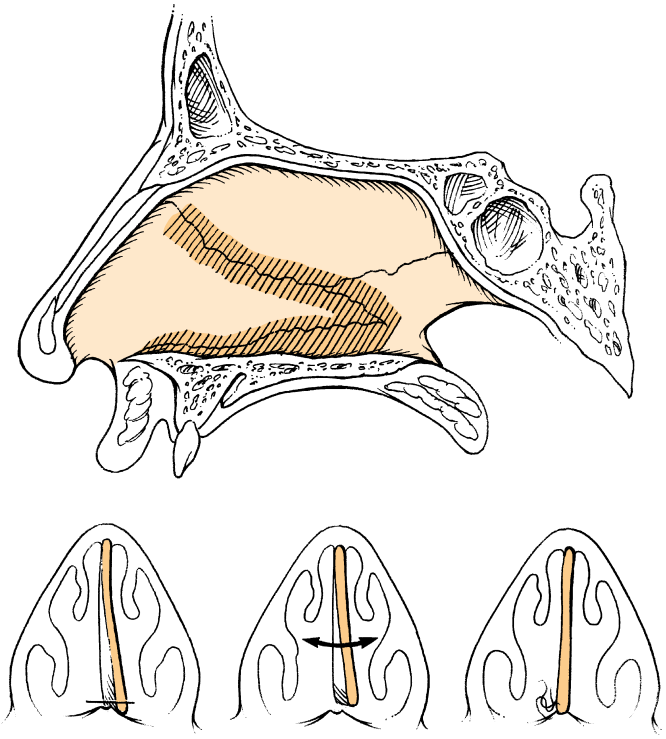

Figure 34-16. A deviated septum that is off to the side of the maxillary crest must be separated from the bony perpendicular plate; the inferior cartilaginous portion must be trimmed so it can be slid back onto the crest by swinging it back to the midline, basing its attachment superiorly. Once back into the midline, the caudal end is sutured to the periosteum of the maxillary crest to maintain its position. If a caudal deviation is also present, a tongue-in-groove maneuver may also be necessary by placing and sewing the caudal end of the septum in between the medial crura.

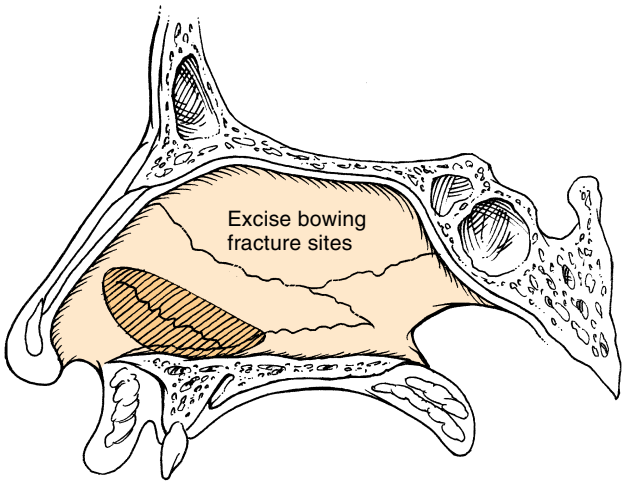

Figure 34-17. Schematic demonstrating wedge excision of septal fracture or deviation.

Bowing in the high anterior septum that is not adequately corrected by freeing the segment from the crest attachments can be addressed in a number of different ways. In any area in which the cartilage is thick (e.g., near the dorsum at the bony-cartilaginous junction), tangentially shaving cartilage with the No. 15 blade may provide improvement without structural change. Other options may be to crosshatch or score the deviated segment or to excise a full-thickness cartilage wedge (i.e., as is done with a septal fracture) (Fig. 34-17).

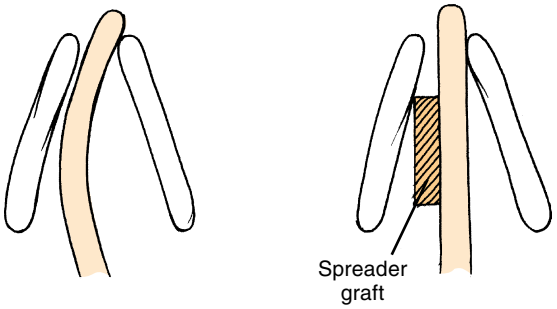

Figure 34-18. Schematic showing unilateral spreader graft placement for septal straightening.

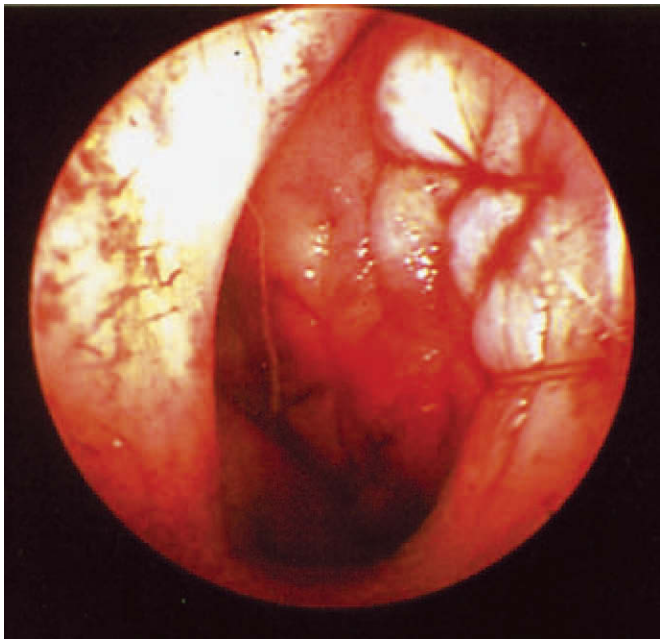

Figure 34-19. Quilting mattress sutures of the septal flaps prevent hematomas and bleeding and obviate the need for internal splints.

Finally, a straight cartilage graft can be placed along the dorsal deviation between the septum and the upper lateral cartilage to combat bowing of the high anterior septum. The graft, which is fashioned from harvested septal cartilage, is sewn in place with 5-0 polydioxanone in a horizontal mattress fashion. This is easily accomplished through an external rhinoplasty approach; however, a closed approach may also be used (Fig. 34-18).

Having addressed the deviated cartilage, septal spur, and deviated maxillary crest, the cartilage that is not to be used for another purpose (e.g., grafting in rhinoplasty) is crushed and placed back into the membrane pocket for reskeletonization of the flaps. Postoperatively, septal flaps without interposed cartilage adhere to one another without supporting structure; these weakened flaps are susceptible to injury and potential perforation, especially if there are contiguous membrane fenestrations. Placing crushed cartilage back into the envelope serves as a barrier for perforation development, prevents motion of the membrane with inspiration or expiration, and allows easier reentry if another procedure is required. After reskeletonization, the entire septal flap from anterior to posterior is mattressed with a continuous 5-0 plain stitch; a curved needle (instead of the popular straight Keith needle) should be used for this purpose (Fig. 34-19). Using a curved needle during the mattressing procedure decreases the potential for lateral nasal wall or turbinate injury, thereby decreasing formation of intranasal synechiae. The mattress suture secures the cartilage replacement grafts in place, recoapts the elevated mucoperichondrial membrane, and

Figure 34-20. A nonhealing fissure of the skin of the apical nostril can be caused by rubbing sutures against the skin while tying intranasal knots.

Figure 34-21. Photo showing the widened columella created by caudal septal deviation, which additionally pushes the medial crura into the airway.

prevents hematoma.[39,40] To prevent future perforations, any identified fenestrations in the septal lining—even unilateral fenestrations over the segment—are closed with 5-0 plain suture at the time of septoplasty. Rents in the membrane are most likely to occur in proximity to a septal spur or a severely deviated septal segment due to the difficulty of dissecting or due to thinned mucous membrane over the segment. Sometimes, as indicated above, the spur is so large and the membrane is so thin that a perforation is unavoidable. The key is to prevent contiguous bilateral mucous membrane fenestrations, close them if they occur, and always interpose a crushed cartilage graft for added support.

The hemitransfixion incision is also closed with 5-0 plain stitch. Care is exercised when tying the individually interrupted sutures so that suture cutting of the alar facet does not occur at the alar rim apex. When the stitch is pulled cephalad during tying, it can easily cut the alae, thereby leading to long-term deformity or fissuring in this area (Fig. 34-20). This alar deformity is extremely difficult to correct and rarely heals because of chronic bacterial colonization.

Septoplasty and the Caudal Septum

Employing methods of repositioning and fixation of the caudal septum rarely make it necessary to aggressively trim or excise this segment (Fig. 34-21).[41] The deviated inferior edge of the septum (which has shifted from the crest) and the truly dislocated caudal margin are first addressed by bilateral mucoperichondrial elevation. After the septum along the floor and the crest are straightened as described above and the swinging door created, the length of the septum is evaluated. If the septum is long, a conservative trim is warranted. Otherwise, the caudal margin can be replaced to the midline nasal spine, secured, and sandwiched within a pocket created between the medial crural footplates. A colu-

mellar-septal mattress suture of 4-0 chromic is passed transcutaneously and holds the caudal septal margin and medial crura in place. This maneuver, which was first described by Rethi[42] in 1934 and later by Fred[43] in 1950, was repopularized and named the tongue-in-groove maneuver by Kridel and colleagues[44] in 1999; it provides a midline fixation technique and helps to make caudal septal trimming less necessary (Fig. 34-22). If the caudal septum is significantly gnarled (which contributes to a hanging columellar appearance) or extremely deviated, it can be trimmed or excised. If the caudal septum is removed or significantly trimmed, it must be replaced with a septal reconstruction graft.[27] Tip ptosis occurs when the caudal septum is overresected as a result of interference with two of the four recognized tip-support mechanisms described by Janeke and Wright.[45]

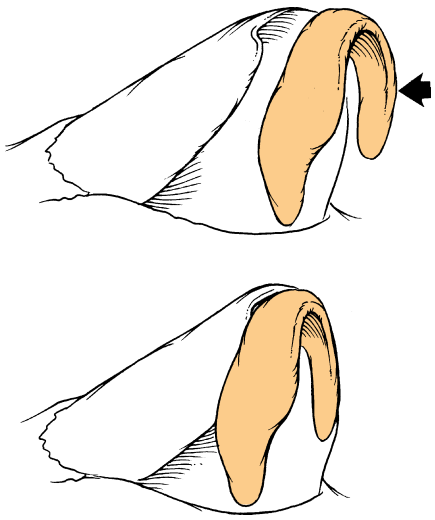

Figure 34-22. Schematic showing the tongue-in-groove technique marked by interposition of the caudal septum between the feet of the medial crura.

Septoplasty with Caudal Absence and Tip Collapse: Septal Reconstruction

Overaggressive resection of the caudal septum is still performed. Tip ptosis, retraction of the lower aspect of the columella, and widening of the alar base are characteristic findings of aggressive caudal septal trimming. Although there certainly are indications for caudal septal trimming, we limit this practice to only those cases in which the septum is so crooked it cannot be straightened or so long that it pushes the columella down and can be palpated between the medial crura (Fig. 34-23). Refer to the article by Kridel and Lunde[27] for further description and explanation of the caudal septal replacement procedure.

Septoplasty Combinations: The Rule and Not the Exception

Approximately 20% to 30%[2-5] of patients who undergo septoplasty find that their symptoms are not corrected adequately. A subset of these patients may undergo reoperation in an attempt for definitive correction. Partial explanation for the requirement for reoperation may be found in the inherent memory that cartilage possesses or in the requirement to end septal correction surgery when support of the nose is at risk for compromise. In the patient with a severely deviated septum, preoperative discussion should focus on the improvement of nasal obstructive complaints and not perfection. The failure rate may also suggest that we, as nasal surgeons, are not looking actively enough for other contributors to this subjective complaint. Obstruction as a result of internal valve compromise is most often an issue in the patient with a narrow middle third of the nose as seen, for example, in the patient with the typical tension septum.[46] Such a patient has an increased nasal dorsal height or hump that narrows to the nasal bridge and a tethered appearance to the upper lip (Fig. 34-24). Others with valve compromise may have high septal bowing into this area, inferior turbinate hypertrophy, or a paradoxic inferior conchal curve. The patient may also have had a rhinoplasty, in which case the upper lateral cartilages were either not reattached to the septum or the ULCs were mobilized from their attachments beneath the nasal bones, with subsequent inferior ULC displacement. This inferior displacement or replacement at a lower level creates an "inverted V" sign externally and a narrowed valve angle intranasally (Fig. 34-25). Identification of the patient with internal nasal valve collapse should be done before surgery so that the procedure can include enlarging this angle.

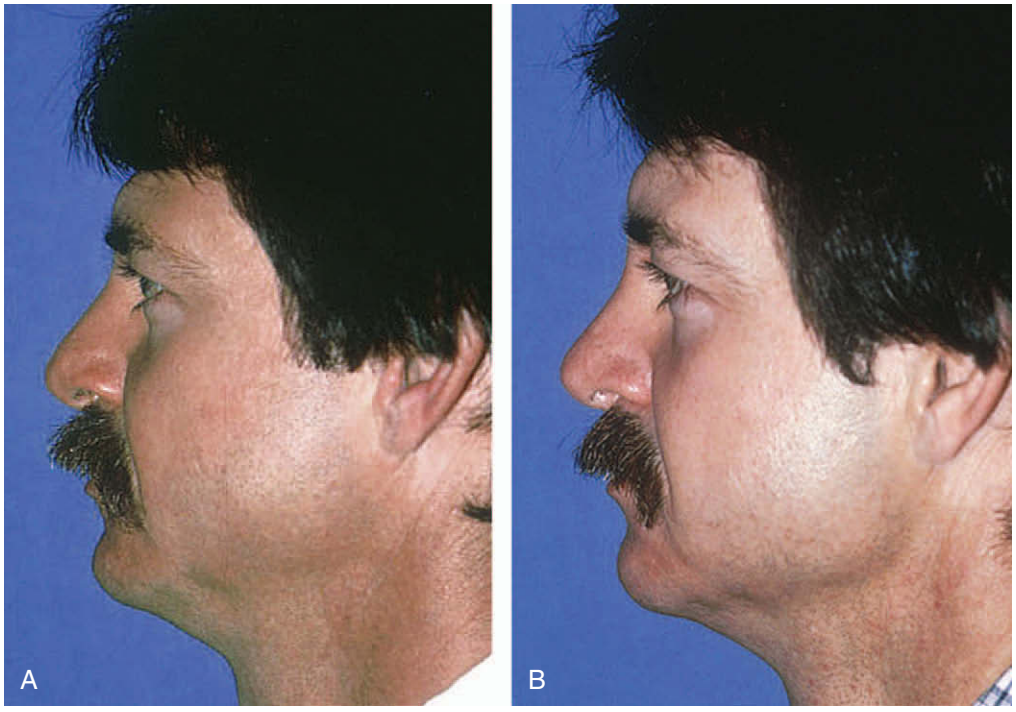

Figure 34-23. **A,** Patient with loss of projection and tip ptosis second to overaggressive resection of the caudal septum. **B,** Patient after caudal septal replacement.

Figure 34-24. Photograph of the typical patient with a tension septum. In such a patient, the cartilaginous dorsum projects above the dome tip cartilages, tents up the soft tissue of the nose, narrows the middle third of the nose, and causes a tethered appearance to the upper lip.

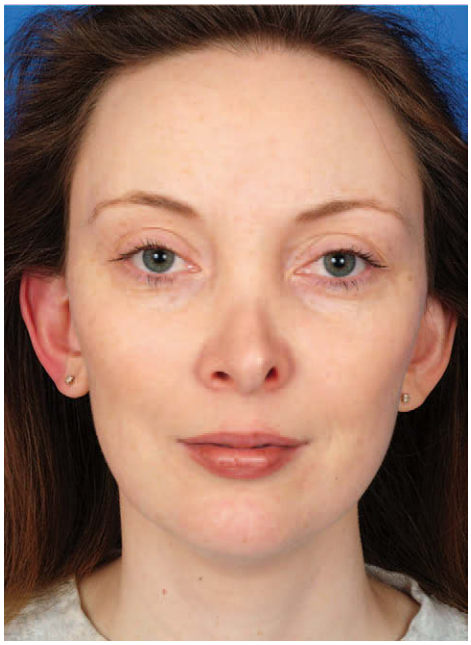

Figure 34-25. Photograph of a post-rhinoplasty patient with an "inverted V" sign seen secondarily to descent of the upper lateral cartilages or improper replacement after rhinoplasty.

The external valve plays a large role in airflow regulation. External collapse occurs as a result of previous nasal surgery in which the LLCs were overresected or morselized to the point of losing their supportive function or as a result of the natural aging process, in which the scroll between the ULC and LLC begins to unfurl. Preservation of an adequate strip of intact LLC ensures that the external nasal valve area retains adequate support.[47] The amount of in situ cartilage that should remain depends on the nature of the cartilage, the thickness of the patient's skin, and the tip dynamics (e.g., projection, rotation).

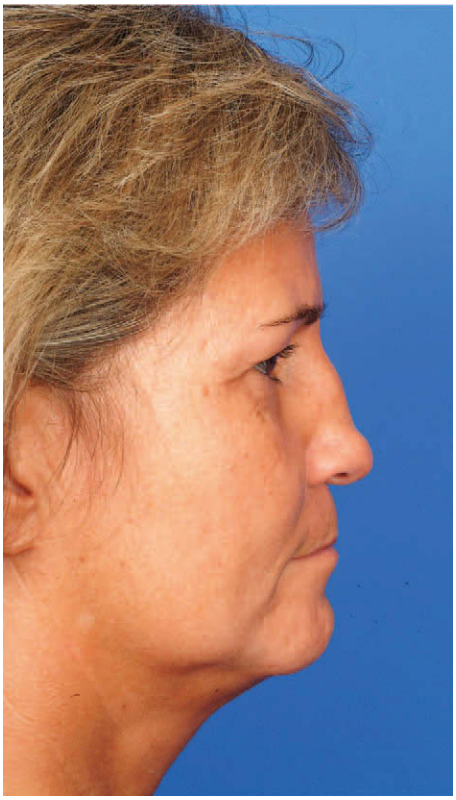

Figure 34-26. Photograph of a patient with a large central septal perforation and secondary nasal saddling.

Discussion of past surgical history with the patient is important. Observing the side wall motion during restful breathing and during forced inspiration allows the surgeon to evaluate for external valve contributions to nasal obstructive complaints. Although a Cottle maneuver may be helpful in those patients with a history of previous surgery, a false-negative Cottle maneuver is possible if scar banding from the septum to the lateral nasal wall is present. False-positive results with the Cottle maneuver are also likely, and so lateral displacement of the ULC is a better predictor of whether valve surgery would be warranted.

Septoplasty with Correction of the Nasal Valve

If valve grafting is required, preoperative planning should allocate cartilage harvest for this purpose. The harvested septal cartilage can easily be fashioned into spreader grafts for stenting of the internal nasal valve angle or batten grafts for bolstering the valve area (i.e., an external nasal valve). Discussion of repair of the nasal valve externally and endonasally is covered elsewhere in this text.

Septoplasty with Septal Perforation Repair

Septal perforation has been a recognized potential complication of septoplasty and should always be included in preoperative disclosure discussions of surgical procedure risks. Prevention of septal perforation begins with techniques that include immediate intraoperative closure of any fenestrations, meticulous membrane elevation within the appropriate subperichondrial plane, and reskeletonizing the septal membrane pocket with crushed septal cartilage. A perforation creates changes in the airflow pattern; this change from laminar to turbulent flow results in the crusting of naturally produced mucous. Nasal mucosa drying, bleeding at the perforation edge, and a whistling noise with nasal breathing are sure to follow. Long-term sequelae in patients with untreated perforations as a result of a loss of septal support can include saddling of the nose[48] and tip ptosis (Fig. 34-26). Ignored and untreated

perforations can ultimately produce chronic low-grade infection with resulting osteitis of the bony septum or of the nasal floor or side walls.

Almost all current literature supports septal perforation closure with intranasal flaps and connective tissue interposition grafts. Our preference is a procedure that is performed through an external rhinoplasty approach with nasal floor advancement flaps and an interposition graft of temporalis fascia or acellular human dermis.[38,49]

Septoplasty and the Crooked Nose

In the nose with a deviated dorsum, the septum is frequently responsible for the crooked appearance. Septoplasty should include bilateral release of the ULCs from their attachments to the dorsal septum, which is done by elevating the septal membrane from the septum up into the area of the internal valve and followed by the careful insertion of the No. 15 blade into the pocket and releasing the ULCs from their dorsal attachments. This maneuver will oftentimes release intrinsic cartilage forces and both improve nasal airway patency and accomplish dorsal straightening. Occasionally a single spreader graft (as indicated earlier) can be inserted at the point of greatest septal bowing to act as a straightening crutch. The spreader is attached as described. Ultimately, reattachment of the ULC to the dorsal septum at the completion of the rhinoplasty procedure is imperative to prevent additional nasal valve angle compromise.

Septoplasty Adjuncts

Some surgeons use an endoscope during mucoperichondrial elevation for better visualization[50,51]; the increased vision in a dry operative field may help prevent mucosal tearing when deviations are acute.

The CO_2 laser has been used to selectively excise septal spurs; however, this is not our preferred method. Mucoperichondrium and the cartilaginous spur are completely excised, with the laser taking no more than 2 to 3 mm of vertical height to permit mucosal healing and closure; the opposite mucoperichondrium is left intact.[52] The laser has found other uses in the nose, ranging from ablation of intranasal papilloma[53] to turbinate reduction procedures.[54]

Postoperative Care

At the conclusion of septal surgery, a light nasal pack is placed to safeguard against large clot accumulation and to quiet light bleeding when turbinate surgery or osteotomies were included in the procedure. We have found that less bleeding translates to less nausea and, in turn, to a lessened incidence of postoperative vomiting; vomiting worsens the bleeding and increases the postoperative swelling. Use of a tight pack or gauze-like materials is still done by some, but we disagree with this practice because of the tendency of packing to adhere to the mucosa, cause pain, and create bleeding when removed. If neither osteotomy nor turbinate surgery was performed, the quilting stitch of 5-0 plain suture is adequate for preventing the formation of a septal hematoma. In our practice, a single- or double-folded nonstick cotton pad impregnated with gentamicin cream is inserted before extubation and is removed on the day after surgery (Fig. 34-27).[55] The use of cream rather than petroleum-based ointment may decrease the initiation of petroleum cysts during this early healing phase.[56-59] The use of sutures laden with antibiotic ointment product is also discouraged.

After the nasal packs are removed, a three-times-a-day regimen of saltwater flushing of the nose is initiated. Twenty-four hours after the procedure, when incisions are closed and sealed, the patient is instructed to start the instillation of antibiotic ointment in each vestibule. Gentle suctioning on postoperative days 5 through 7 and continued local care for at least 2 to 3 weeks allows for adequate healing. Gentle nasal blowing is permitted after the third week, and strenuous exercise is discouraged for a total of 5 weeks.

Internal nasal splints are generally only used in septal perforation surgery or when the septal membrane is excoriated or perforated. Splints increase the degree of rhinorrhea, can be uncomfortable, and, if coapting sutures are too tight, can actually lead to perforation of the membrane themselves. When required, we advocate the use of soft, transparent Silastic splints that are 0.02-inch thick and hand-sized from Silastic sheets; these splints are not uncomfortable. Hard, thick nasal splints with airway tunnels hurt patients going in and coming out and often get clogged.

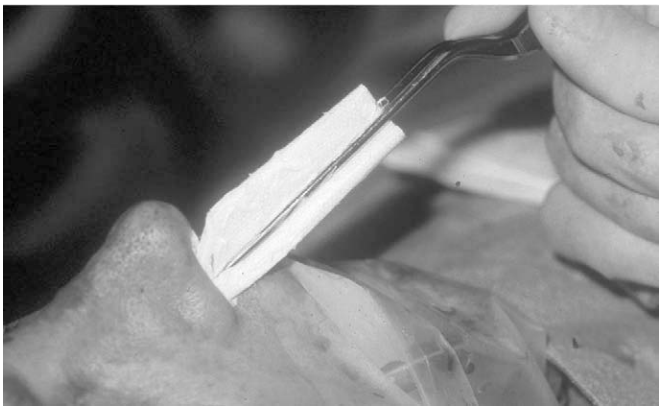

Figure 34-27. A soft Telfa pack coated in antibiotic cream is inserted into the nose at the completion of the nasal operation to prevent clots.

Complications of Septoplasty

The most common septoplasty complication is persistence in the subjective complaint of nasal obstruction.[3,4] A septal hematoma may be seen when either a quilting stitch is not used or nasal packing is not placed. Septal perforations resulting from unrepaired contiguous septal mucoperichondrial fenestrations or failure to reskeletonize the mucoperichondrial envelope at the completion of the septal resection maneuver are possible. Nasal shape changes (e.g., tip ptosis, dorsal nasal saddling) may result from overresection of the caudal septum or the loss of dorsal nasal support. Mild postoperative oozing is common and not necessarily a complication during the early phase but rather something to be expected. Some patients may experience significant bleeding postoperatively; this is usually seen in those who also underwent inferior turbinate resection.

Conclusion

Nasal obstruction is a subjective sensation that is unique to each individual and that variably correlates with anatomic pathology. The structural support that the septum affords must be preserved and is the reason that surgeons have moved from aggressive resection to preservation. The importance of an intact L-strut, an adequately supported nasal valve, and relief of obstruction is recognized. A good septoplasty with attention to all of these areas is a prerequisite for not only a functional nose, but a straight nose as well.[60]

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CHAPTER THIRTY-FIVE

Nasal Fractures

Burke E. Chegar

Sherard A. Tatum, III

Key Points

- Nasal fractures tend to occur along the thinner bone below the intercanthal line.
- Septal fractures are commonly found in injuries where the nasal pyramid is deviated by at least one-half the nasal width.
- Nasal fractures from lateral trauma typically are less severe in nature and have a better prognosis than those from frontal force injuries.
- Plain film radiographs have a high false-positive rate and should not replace history and physical examination findings in the diagnosis of a fracture.
- Ideal timing for closed nasal reduction is between two and ten days after injury.
- Unsuccessful closed reduction is often due to inadequate treatment of a concurrent septal fracture.
- Extensive nasal injuries from high velocity trauma require open reduction, fixation, and bone/cartilage grafts to restore nasal form and airway patency.
- Avoidance of overaggressive treatment of pediatric nasal fractures is important to prevent damage to the nasal septal growth centers responsible for midface development.
- Septal hematomas are more commonly seen in pediatric nasal trauma. Untreated hematoma may lead to infection, septal destruction, and long-term nasal deformity and airway obstruction.

The prominence and delicate structure of the nose make it vulnerable to a broad spectrum of injury, which accounts for why it is the most frequently fractured facial bone.[1-11] Sports, falls, and assaults are the usual mechanisms responsible for the majority of nasal fractures, with alcohol consumption being an important contributing factor in many cases.[7,8,12-19] Males are affected approximately twice as often as females in both the adult and pediatric populations, with a peak incidence occurring during the second and third decades of life.[8,12,13,15,17,20,21] Deformity, swelling, epistaxis, and periorbital ecchymosis are signs that are suggestive of nasal fracture, whereas bony crepitus and nasal segment mobility are diagnostic.

Although these injuries often do not appear to be severe, the mistake of undertreating nasal trauma can lead to significant long-term problems. External deformity, nasal obstruction, septal perforation and other complications (e.g., chronic sinusitis) will persist and sometimes worsen months or years after the original insult. Injuries in children may also lead to devastating growth retardation of the nose and midface. Thoughtful assessment and proper management of nasal injuries can reduce the risk of these sequelae, thereby reducing the need for delayed corrective septorhinoplasty.

Anatomy

The bony vault is a pyramid-shaped structure that is composed of paired nasal bones centrally and the frontal processes of the maxilla laterally. Ossification of these bones via intramembranous bone formation starts at the end of the third trimester and continues for years after birth.[22] Superiorly the thickness of the nasal bones is greater above the level of the intercanthal line as they taper upward toward the nasofrontal suture. Below the intercanthal line, the thinner nasal bone projects anteriorly to join with the upper lateral cartilages at an externally defined midline point known as the rhinion (Fig. 35-1). On the inner surface of the nose, the perpendicular plate of the ethmoid fuses in the midline with the nasal bones to provide additional support to the nasal pyramid; this construct creates a tent-like structure, with the ethmoid plate representing a pole and the nasal bones representing the side walls of the tent. This interrelationship helps explain the susceptibility of the septum to injury by the transmitted forces from the external nose to the perpendicular plate of the ethmoid (Fig. 35-2).

The midportion of the nose is composed of the upper lateral cartilages and the dorsal segment of the quadrangular cartilage. Made up of hyaline cartilage, these structures are fused as a single unit, with only the lower third separated by fibrous tissue.[23] The cephalic ends of the upper lateral cartilages are overlapped by the nasal bones by as much as 11 mm and secured with a solid fibrous union referred to as the *keystone area* (Fig. 35-3).[24] Laterally the upper lateral cartilages do not articulate with the bony pyramid; rather, they are attached to the frontal process of the maxilla by a fibrous aponeurosis in which the sesamoid cartilages can be found. Therefore, the preservation of the attachments of the upper lateral cartilages with the nasal bone and the septum is crucial to prevent destabilization.

The lower third of the nose is formed primarily by the alar cartilages in addition to the accessory cartilages and fibrous fatty connective tissue that define the nostrils laterally. The alar cartilages are bilobed structures composed of medial and lateral crura with an intervening middle segment (intermediate crus) that has an important role in the definition of the nasal tip. These cartilages are interconnected as a single unit by transverse, fibrous connective tissue called the *interdomal ligament*.[25] Structural support is mainly provided by the scrolled, overlapped upper portion of the lateral crus with the lower border of the upper lateral cartilage and the medial crural attachment with the caudal

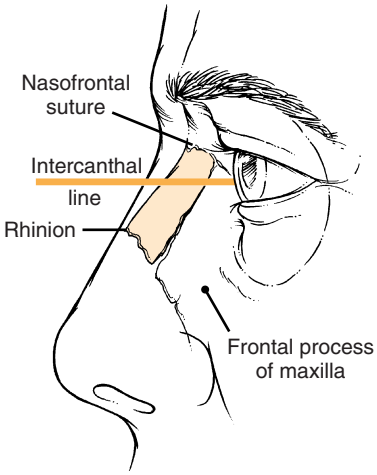

Figure 35-1. The intercanthal line demarcates the transition point between thicker nasal bone superiorly and thinner bone inferiorly. Most nasal fractures occur below this level.

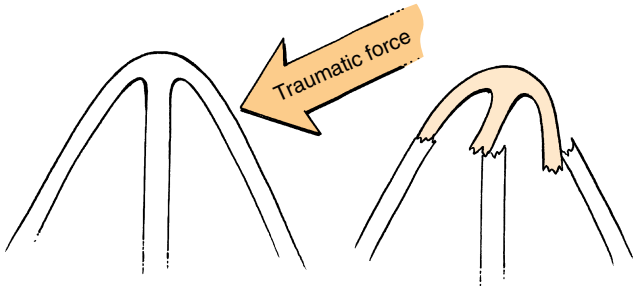

Figure 35-2. Transmitted forces from a lateral nasal bone impact resulting in fracture of the perpendicular plate of the ethmoid.

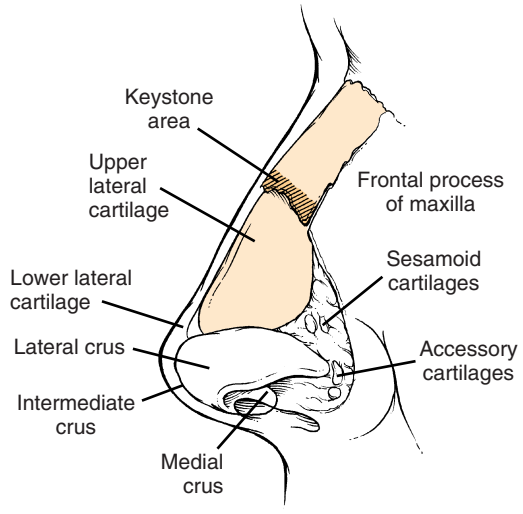

Figure 35-3. The strong fibrous connection between the nasal bones and the upper lateral cartilages (keystone area) provides stability to the middle third of the nose.

septum. The dermocartilaginous ligament, which originates from the superficial fascia of the superior nose, inserts into the intermediate crus and caudal septum to provide additional tip support.[26]

The septum is a key element of the structure of the entire nose. The posterior bony septum is made up of the perpendicular plate of the ethmoid superiorly and the wedge-shaped vomer inferiorly. Smaller

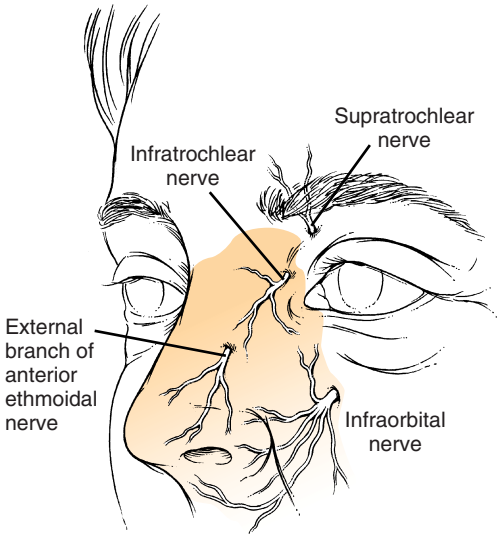

Figure 35-4. Sensory innervation of the external nose.

contributions from the nasal crests of the palatine bones and the maxilla underlie the vomer and terminate anteriorly at the nasal spine. Extending anteriorly toward the nasal spine, the superior edges of the vomer and nasal crest of the maxilla form a bony groove in which a thickened inferior portion of the quadrangular cartilage lies. This articulation represents the basal foundation upon which all of the overlying nasal structures rest. Mobility of the cartilage within the groove helps prevent septal fractures by allowing for slight lateral rotation during compression of the septum.[25] A thickened osteocartilaginous buttress along the septoethmoid junction is the main strut for the bony and cartilaginous dorsum, whereas a thick caudal septum provides the majority of the nasal tip support.

The sensory innervation of the nose is supplied by the first two divisions of the trigeminal nerve. The supratrochlear, infratrochlear, and external branches of the anterior ethmoid nerves (V_1) provide sensation to the upper, dorsal, and nasal tip surfaces, whereas the infraorbital nerve (V_2) supplies sensation to the side walls (Fig. 35-4). Internally along the lateral nasal wall, the anterior and posterior ethmoidal nerves provide sensation to the upper portions of the nasal cavity. The sphenopalatine ganglion (V_2), which originates at the end of the middle turbinate, provides innervation throughout the posterior nasal cavity. Branches from anterior and posterior ethmoid nerves and the sphenopalatine (nasopalatine) nerve cross over superiorly and posteriorly to provide sensation to the majority of the septum.

A rich plexus between both the internal and external carotid arteries provides the blood supply to the nose. The ophthalmic artery branch of the internal carotid supplies blood to both the internal nose via the anterior and posterior ethmoid vessels and to the outer nose from the dorsal nasal artery and the external nasal artery. The external carotid artery provides the primary vasculature to the outer nose via the infraorbital (branch of internal maxillary artery), superior labial, and angular arteries (branches of the facial artery). In addition, the external carotid supplies blood to the internal nasal cavity via the sphenopalatine artery, which emanates just posterior to the middle turbinate. Venous drainage follows along the arterial vessels and empties through either the facial vein and pterygoid plexus into the internal jugular vein or through the ophthalmic vein into the cavernous sinus.

Pathophysiology

Understanding the process by which nasal fractures occur and how injuries to key areas of support can alter appearance and function are essential to appropriate treatment. Variables such as force, impact direction, nature of the striking object, patient's age, and other host factors will influence the pattern of injury to both the bony and cartilaginous components of the nose. Younger adults often suffer the dislocation of major segments, whereas older individuals tend to have more commi-

nution of brittle, osteopenic nasal bones.[27] Children, on the other hand, have more cartilaginous injuries and greenstick fractures due to a greater proportion of nasal cartilage and the incomplete ossification of nasal bones.[9]

A combination of the projection of the nose and its relatively fragile supporting structures as compared with other facial bones make it particularly susceptible to fracture. The thinner nasal bone below the intercanthal line, which projects more prominently from the face, is fractured much more easily than the thicker bone of the nasal root above the line. Lateral forces may produce an ipsilateral depressed fracture or may outfracture the opposite nasal bone, thereby resulting in significant deviation of the entire nose. Although lateral forces are a more frequent cause of nasal injuries,[3] deviated fractures can occur from either frontal or laterally directed impacts as well.[28]

The cartilaginous portions of the external nose are able to absorb a greater amount of force without fracture as compared with the bony components, but they are still susceptible to injury given their greater exposure. Avulsion and dislocation of the upper lateral cartilage from the nasal bone and septum will result in a hollowed-out appearance of the midportion of the nose.[24] This injury may also tear the external nasal artery as it exits between the nasal bone and upper lateral cartilage, thereby causing a dorsal hematoma.[29] In cases of severe frontal trauma, reduction of nasal projection and increased nasal tip rotation are indicative of fracture and telescoping of the cartilaginous portions of the anterior nose and caudal septum.[30]

Septal injury is one of the most crucial elements of nasal deformity and dysfunction. The thinnest portions of the septum that tend to fracture most readily are located around the superior septal angle, the central-dorsal area of the quadrangular cartilage, and the posterior portion of the perpendicular ethmoid plate. Cadaver studies done both by Harrison[28] and Murray and coworkers[18] found that either frontal or lateral forces produced a consistent C-shaped fracture through the cartilaginous septum and perpendicular plate. Failure to reduce these septal fractures has been shown to be responsible for many cases of decreased nasal projection and lateral deviation found after unsuccessful attempts at closed reduction.[18] Transmitted impact forces from the nasal bones and upper lateral cartilages can also result in septal dislocation off the maxillary crest, thus further destabilizing overlying structures and aggravating airway obstruction. Incomplete fracture of the septal cartilage was hypothesized by Fry[30A] to cause the release of "interlocked stress" within the cartilage, which leads to further deformity.

Associated Injuries

Injury to the structures that surround the nose often occurs in cases of high-velocity impacts, such as those sustained in motor vehicle accidents. Epiphora from disruption of the nasolacrimal drainage system occurs with 0.2% of nasal fractures.[31] Severe injuries with fracture of both the lacrimal bones and the ethmoidal complex are associated with depressed nasal fractures from frontally directed forces.[27] Widening of the intercanthal distance caused by the detachment of the medial canthal tendons is a classic appearance of these fractures, and these are better known as nasal-orbital-ethmoid complex fractures. Hard palate instability and open bite deformity are signs of Le Fort's fracture, whereas unilateral malar deformity and facial asymmetry suggest a zygomaticomaxillary complex fracture. Significant trauma to the upper portions of the facial skeleton may be associated with frontal sinus fracture, cribriform plate fracture, and dural tears leading to pneumocephalus and cerebrospinal fluid rhinorrhea.[32]

Classification

Due to the variations in individual anatomy and trauma etiology, there are several different types of nasal injuries that may be encountered. Fractures of the bony pyramid may be described as unilateral, bilateral, comminuted, depressed, open-book (splayed), impacted (telescoped), and greenstick (Fig. 35-5). Septal damage should also be documented for fractures that have caused deviation or dislocation off the maxillary crest. The extension of fractures to involve surrounding structures such as the maxilla, lacrimal bone, ethmoid complex, or frontal sinus should be included in the description as well.

Although there have been many attempts to apply an all-encompassing classification scheme to nasal fractures, the wide variety of injuries has precluded the acceptance of a single system that has practical application. Anatomic descriptions of nasal injuries often focus on the fracture pattern of the nasal bones but do not include cartilaginous components[4] or do not describe the involvement of surrounding structures.[28] Murray and Maran[8] attempted to narrow down fractures of the nasal bones and septum to seven anatomic groupings using data collected from cadaver experiments. Although their publication is popularized for highlighting the importance of septal management to the overall success of reduction, the classification has not been widely accepted because of its complexity.

The other broad method of categorization is based on the direction of the impact force. Lateral-type injuries, which are more common, tend to have less severe damage and a better prognosis than the frontal types.[27,33] Stranc and Robertson[33] developed a classification system using these two main groups, with further breakdown of the frontal type into three different planes that are determined by the depth of injury from the nasal tip (planes 1 through 3) (Fig. 35-6). Each successive plane is associated with a higher likelihood of residual deformity after reduction. Plane 1 injury includes damage to the anterior nasal

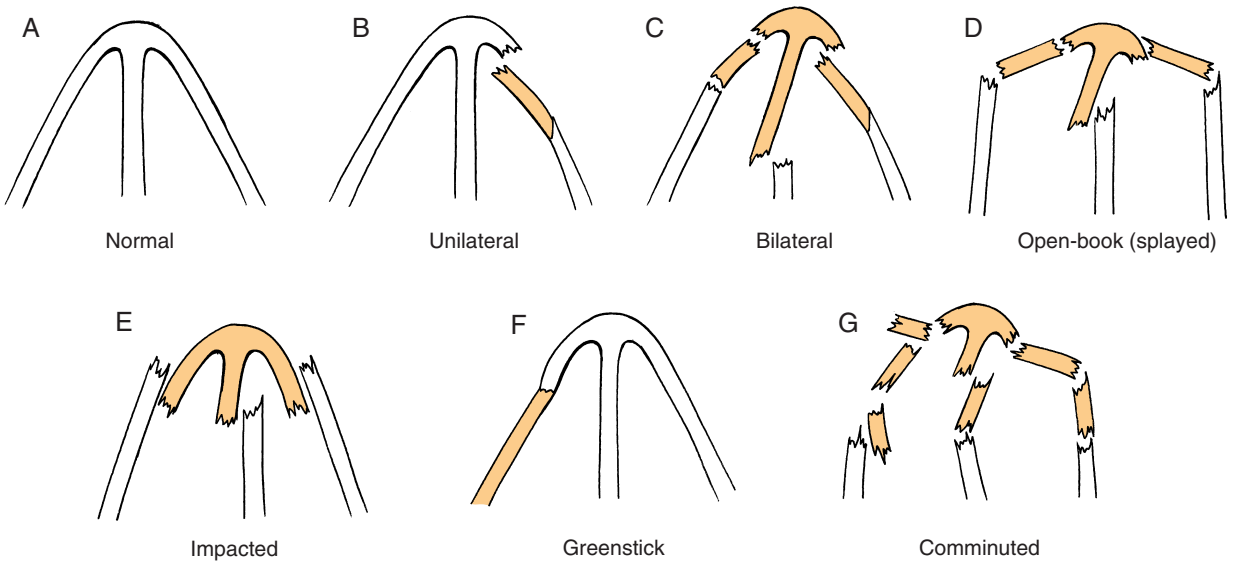

Figure 35-5. Examples of nasal fracture patterns.

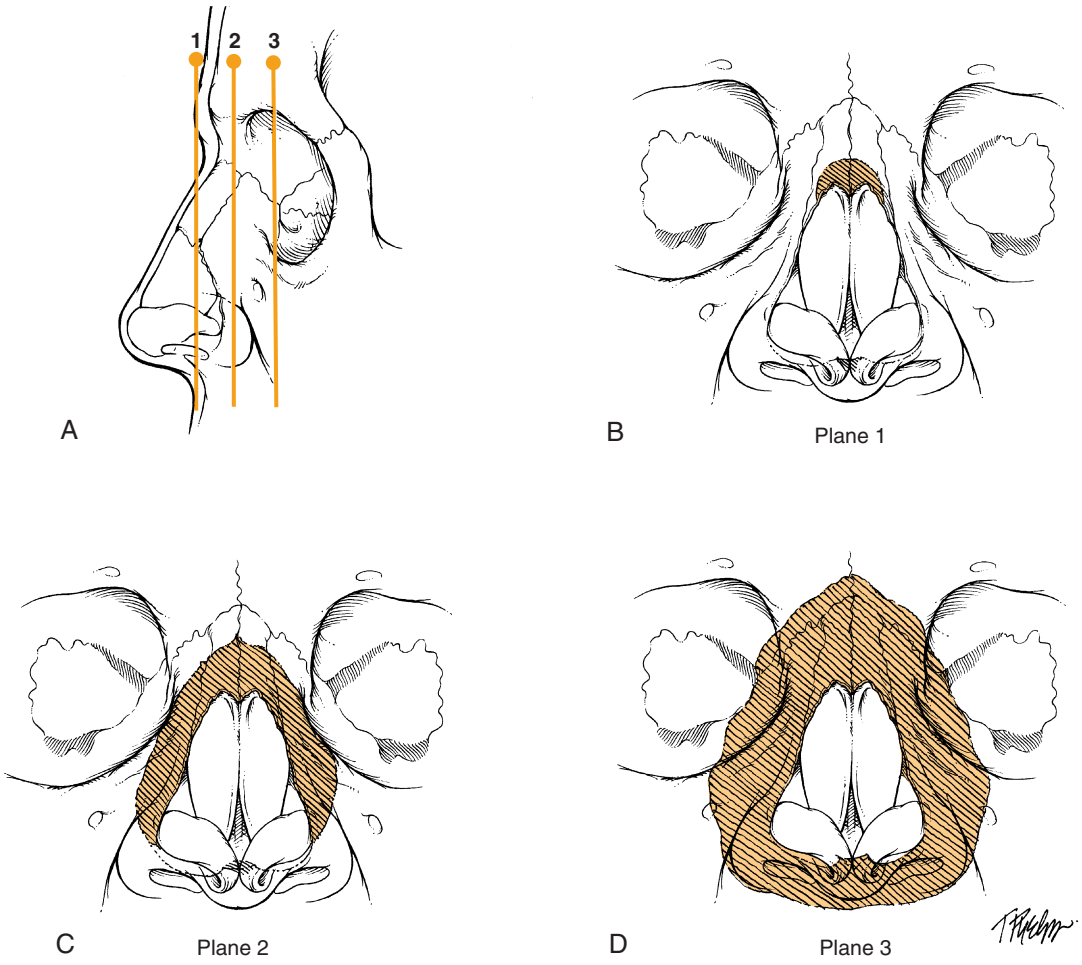

Figure 35-6. Stranc and Robertson classification of frontal impact injury. **A,** Lateral view of planes 1, 2, and 3. **B,** Plane 1 injury. **C,** Plane 2 injury. **D,** Plane 3 injury. *(From Stranc MF, Robertson GA. A classification of injuries of the nasal skeleton.* Ann Plast Surg. *1979;2:468.)*

spine, the anterior septum, or the lower ends of the nasal bones. Dislocation and telescoping of the upper lateral cartilages and septum may be found with a plane 1 injury. Plane 2 injury results in more extensive damage to the nasal bones and ascending maxillary process but does not involve the orbital rims. The septum has a significant amount of deviation and may lack stability to support the nasal dorsum. Plane 3 injury results in nasal-orbital-ethmoid complex disruption. Patients with this injury are usually found to have other midface and cranial base fractures; the nasal bones and septum are severely comminuted and overlapped. Surgery for plane 3 injuries often is unable to fully restore the preexisting nasal appearance and function, particularly if the orbital-ethmoid complex components of the injury are not recognized and treated properly. These conclusions were supported in a study by Daw and Lewis[3] that showed a significantly higher incidence of residual anatomic and functional defects in frontal injuries as compared with lateral injuries.

Diagnostic Assessment

History

A detailed account of the events surrounding nasal trauma is helpful in determining the type and severity of injuries that may be present. In cases of motor vehicle accidents, information about the speed, direction of impact, and the presence of restraining devices should be obtained. Young children who are located in the front passenger seat are at risk for head and cervical injuries related to airbag deployment, even in incidences of low-speed collisions. Patients who present after an assault should be questioned about the nature of the striking object and the direction of the blows. It is important to note that up to 30% to 60% of women with facial trauma as a result of assault are victims of domestic violence.[34,35]

In addition to changes in appearance, the patient history should be evaluated for functional changes in nasal breathing and smell as well as bleeding and watery drainage with a sweet/salty taste (possible cerebrospinal fluid [CSF] leak). Although loss of smell should be documented, poor nasal airflow as a result of edema is almost always present at the initial interview and therefore sense of smell should be reassessed after swelling has diminished. Persistent anosmia or hyposmia may occur in as many as 5% of individuals who suffer head injury with or without nasal trauma and has been observed to resolve spontaneously in only a third of cases.[36]

A review of a patient's medical history includes any prior nasal injury, deformity, surgery, dyspnea, allergies, or sinus disease. Individuals who have had prior rhinoplasty are more susceptible to nasal fracture, even after complete healing.[37] Old photographs or detailed descriptions of previous nasal deformities should be assessed for significant changes; up to 40% of normal individuals without a history of nasal trauma have evidence of significant malformation.[7] A complete review of systems should also screen for associated trauma (e.g., ophthalmic or cervical spine injuries).

Physical Examination

The diagnosis of nasal fracture is made primarily by physical examination. Although the presence of deviation and asymmetry may clearly indicate acute traumatic deformity, more subtle findings can easily be missed without a high index of suspicion. The presence of epistaxis, nasal swelling, and periorbital ecchymosis are signs that are suggestive of significant nasal trauma and warrant a thorough internal and exter-

nal examination. A complete assessment should always be performed using a routine, stepwise approach so that no details are missed. Multiple-view photographs obtained with the patient's head positioned in the Frankfort horizontal plane are recommended to accurately document injuries for future comparison after treatment as well as for medical-legal purposes.

An external examination begins with observation of the nasal shape and contour from multiple perspectives with the patient sitting up, if possible, in a well-lit room. Deviation of the nasal pyramid, medial collapse of the nasal bones or upper lateral cartilages, and broadening of the nasal dorsum can best be appreciated from the frontal perspective. Lateral inspection may reveal a dorsal hump or collapse of the nasal profile. Significant loss of the nasal length is indicative of telescoping of the bony or cartilaginous fragments and is usually accompanied by an increased nasolabial angle that normally falls between 90 degrees for males and 110 degrees for females. Inferiorly, deviation of the columella with narrowing of the external nasal valve will occur with fracture and displacement of the caudal septum or anterior nasal spine. Collapse of the nostril can also indicate disruption of the supporting attachment of the alar cartilage to the upper lateral cartilage. If open wounds are present, gentle probing for stepoffs or mobile pieces of bone or cartilage can provide a better appreciation of the underlying damage. The mobility of the nasal bones is assessed by grasping the dorsum between two fingers and firmly rocking the pyramid back and forth. Reexamination of the patient 2 or 3 days later in the office will allow for a better appreciation of these deformities after swelling has decreased. In the meantime, cold packs around the nose will expedite the reduction of edema and give an extra measure of pain control for the patient.

Before the evaluation of internal structures, all necessary equipment and medications for the examination should be ready at the bedside, including materials to control epistaxis. Using a headlight and a nasal speculum, clotted blood is removed with a Frazier suction to visualize all mucosal surfaces for evidence of mucosal tears, hematoma, and active bleeding. The use of topical decongestants will aid visualization and help control bloody oozing. The septum is carefully evaluated for any abnormal soft-tissue swelling that is indicative of a hematoma. Bimanual palpation of the septum with cotton-tipped applicators helps differentiate hematoma, which tends to be more compressible than tissue edema. Areas of increased mobility are suggestive of septal fracture. The use of a 0- or 30-degree 4-mm rod telescope is particularly helpful to assess for posterior septal abnormalities and localization of occult bleeding sources. Although fracture and dislocation of the nasal septum is a common occurrence with nasal trauma, up to 50% of normal individuals without a history of significant nasal injury have a deviated nasal septum.[6]

If the patient can be examined while heavily sedated, a more complete assessment of the condition of the supporting nasal structures is possible. The Brown-Gruss provocation maneuvers break down the analysis of the infrastructure of the nose into upper, middle, and lower segments by applying digital pressure over each of the compartments.[38] Lower vault compression (Brown-Gruss III) may show hyperrotation of the nasal tip with disruption of the septal angle or inward collapse if the supporting caudal septum is severely fragmented. Middle vault compression (Brown-Gruss II) will produce a saddle deformity when the central portion of the septum has been damaged. Upper vault compression (Brown-Gruss I) will cause collapse of the upper third of the nose in cases with severe comminution of the nasal bones and frontal processes of the maxilla. Complex fractures with two or more involved vaults will show more extensive collapse or even complete disappearance of the nose in cases in which severe trauma has affected all three vaults.

Radiography

Despite clear evidence that plain films do not have a role in the management of nasal fractures, these studies are frequently obtained to evaluate individuals after nasal trauma. An investigation by de Lacey and others[39] found that plain films had a 66% false-positive reading as a result of the misinterpretation of normal suture lines or developmental thinning of the nasal bones. It is also difficult to distinguish old fractures from new ones on plain films, because only 15% of nasal bone fractures heal by ossification.[40] These studies are further limited by their inability to detect cartilaginous injuries, which are more prevalent in pediatric cases. Logan and colleagues[16] found that, out of 100 consecutive patients presenting with nasal trauma who had undergone nasal radiography, in no case did the plain film alter management. The diagnosis and proper treatment of the majority of nasal injuries should be successfully achieved with the use of the history and physical findings alone.

However, in cases involving more severe trauma and in which there is physical evidence of other facial fractures, computed tomography should be employed to assess the extent of bony injury. Thin cut coronal and axial views are most appropriate for the evaluation of midfacial, orbital, and frontal sinus fractures. For extensive injuries involving the nasal-orbital-ethmoidal complex, a combination of both two- and three-dimensional computed tomography is recommended for the localization of fractures and the spatial orientation of displaced fragments.[41]

Management

Acute Intervention

Practitioners who are called upon to treat individuals who have been appropriately stabilized before consultation must still follow the protocol set forth by the American College of Surgeons Advanced Trauma Life Support course. Therefore it is mandatory that every new evaluation begins with an assessment of the ABCs (airway, breathing, and circulation) before the initiation of a problem-focused history and examination. This is especially critical for cases in which narcotics and sedatives may be ordered by the consultant for pain management or bedside procedures. A patient with a tenuous airway or poor hemodynamic reserve may unexpectedly experience decompensation if signs such as increasing heart rate, tachypnea, or changing mental status are not appreciated. All treating physicians must be trained and ready to provide acute resuscitation, if necessary.

Epistaxis from nasal trauma may range from minor mucosal oozing to life-threatening, large-vessel hemorrhage. Treatment of bleeding that is not responsive to topical vasoconstriction should first be localized. Anterior sources may be cauterized with silver nitrate or sealed with topical materials such as thrombin combined with gelatin foam, FloSeal, fibrin glue, or other procoagulant substances. Formal anterior packing with an inflatable tampon or ribbon gauze is placed if more conservative measures fail. For cases in which skull base fractures may exist, caution should be used with pack placement to avoid an iatrogenic, intracranial injury. Bleeding from branches of the sphenopalatine or ethmoid vessels requires anterior-posterior packing followed by several days of close respiratory monitoring. Alternatively, initial treatment with surgical methods, such as direct endoscopic cauterization or vessel ligation, have been shown to offer better hemostasis, less patient discomfort, and less cost than management with packing.[42] Angiography with embolization can also be considered.

Timing of Reduction

Appropriate timing is essential to obtaining the best realignment possible. The development of fibrous connective tissue within the fracture line becomes the limiting factor for successful reduction starting at around 10 days to 2 weeks after injury. Ideally, manipulation should be performed before this point, with some preference before 10 days[43]; however, some authors have suggested that attempts to reduce nasal fractures can be done as far out as 3 weeks.[29] A short delay period is also recommended during the first 2 to 3 days to allow for diminution of swelling so that the nasal bone position may be best appreciated. Treatment before this delay is reasonable if the patient presents within an hour or two after injury, before edema has obscured the underlying structure.

Open versus Closed Reduction

The most appropriate treatment for a nasal injury is the least invasive one that will fully correct the deformity without long-term complications or relapse. Nondisplaced fractures that do not result in any defects are best managed with observation alone. Closed nasal reduction is best

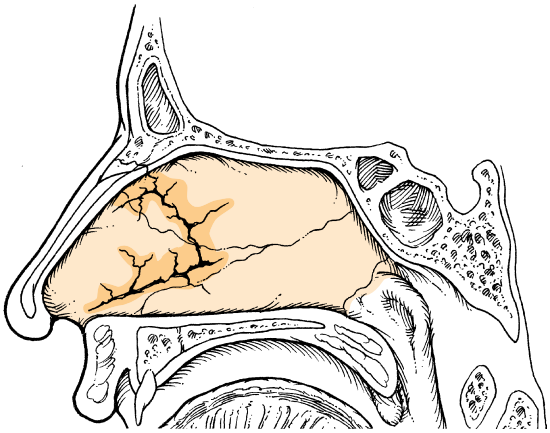

Figure 35-7. A C-shaped septal fracture is commonly found with nasal fractures deviated by at least half the width of the nasal bridge.

for simple injuries such as an isolated, unilateral nasal bone fracture with medial displacement. For more severe trauma (e.g., a bilateral, depressed fracture with septal and cartilaginous involvement), an open approach with reduction, fixation, and possible grafting is the best means of producing a satisfactory outcome. The optimal treatment for the large number of cases that fall between simple and severe injuries is not so clear.

Many of the studies that have supported closed nasal reduction as the primary modality of treatment use patient opinion to gauge results. A study by Crowther and O'Donoghue[2] found that 85% of a group of 85 patients treated with closed reduction were satisfied with appearance, and only 9% later requested septorhinoplasty. These results were similar to those of a prospective study published by Illum,[6] who found that, out of a total of 88 patients, 91% were satisfied at 3 months, 87% were satisfied at three years, and only 3% were interested in secondary corrective treatment. Although in the latter study 35% of patients had evidence of nasal deformity found during a follow-up examination by the physician, this was not a significant difference from a control group of 80 normal patients. Crowther and Illum both concluded that closed nasal reduction alone is adequate treatment for most nasal fractures and that only a limited number of delayed open septorhinoplasty procedures are necessary.

However, the success rates of studies that were reported in terms of physician observations have been quite different. A summary of 13 different publications that analyzed the outcomes of closed reduction found that, overall, 79% of patients were satisfied with their appearance versus only 37% of surgeons who thought the reduction was successful.[44] Although there is no clear explanation for this disparity, it has been the reason for many surgeons to look for better results in their management of nasal fractures.

One of the most important reasons for the failure of closed nasal reduction is concurrent nasal septal fracture. Murray and Maran[8] prospectively evaluated 756 consecutive nasal trauma patients and found a 30% to 40% incidence of residual deformity in patients treated with manipulation on the basis of an examiner's score, regardless of the etiology, timing of manipulation, surgeon's skill, type of anesthetic, or method of postoperative fixation. The authors indicated that such a uniformly high failure rate was most likely the result of poor understanding of fracture pathophysiology, so a cadaver study was designed to analyze patterns of nasal injury.[18] The results showed a consistent C-shaped septal fracture (Fig. 35-7) for cases in which the external nose was deviated by at least half of the nasal bridge width; this pattern was identical to one that was found by Harrison[28] in an earlier published cadaver experiment. Murray and Harrison both hypothesized that the interlocking of the septal fracture was responsible for creating tension that caused nasal bone displacement. In the same article by Murray and coworkers,[18] a prospective analysis of 160 patients showed that resection of the septum along the C-shaped fracture combined with closed nasal reduction resulted in significantly better appearance as compared with manipulation alone. Murray and colleagues concluded that septoplasty plus closed nasal reduction is the treatment of choice in cases of deviation of at least half the bridge width and that, for less severe injuries, manipulation alone is sufficient.

The use of open surgical reduction has also been advocated for many commonly encountered nasal fractures.[9,45] Although it is argued that the superior exposure afforded by these procedures produces better long-term results,[45] there has not been much evidence to support these conclusions. Other surgeons have shown possible benefits of using a stepwise protocol of advancing from closed nasal reduction to progressively more invasive open surgical techniques until adequate nasal form and patency are achieved.[44] The disadvantages of using open reduction for the majority of nasal fractures are the higher treatment costs and the increased risk of surgical complications. Ideally open surgical reduction should be limited to those cases in which it would yield significantly better results than more conservative measures to justify the drawbacks. Verwoerd's[29] outline of what he considered to be the indications for open reduction includes the following: (1) bilateral fractures with dislocation of the nasal dorsum and significant septal pathologic changes; (2) bilateral fractures with major dislocation with or without significant septal pathologic states; (3) infracture of the nasal dorsum; and (4) fractures of the cartilaginous pyramid without mobilization of the bony nasal dorsum and with or without dislocation of the upper lateral cartilages. Although using an algorithm to determine the need for operative intervention is convenient (Fig. 35-8), it should not replace clinical judgment on an individualized basis.

Anesthesia for Closed Reduction

Proper pain management has become a critical topic since the publication of the 2000-2001 standards manual by the Joint Commission on Accreditation of Healthcare Organizations.[46] As a result, practitioners are subject to greater expectations to ensure that procedures will not cause undue discomfort to their patients. This expectation may have the effect of increasing the demand for general anesthesia during the performance of nasal reductions. However, this degree of pain control may not always be feasible as a result of medical risk factors, scheduling conflicts, or operating room availability. Therefore, the surgeon must consider alternative anesthetic options so that he or she provides the most appropriate pain control without sacrificing timely management.

A well-administered local nasal block provides excellent anesthesia for the majority of reductions that require both septal and nasal bone manipulation. Studies have shown that the frequency of successful nasal reduction is similar regardless of the use of either general or local anesthesia.[21,47,48] The most common method of performing a nasal block is through a combination of topical and injected anesthetic. Cotton pledgets soaked with either 4% cocaine or 0.05% oxymetazoline combined with 4% topical lidocaine are placed strategically throughout the nasal cavity to cover branches of the anterior and posterior ethmoid, sphenopalatine, and nasopalatine nerves. After 5 to 10 minutes, the pledgets are removed, and 1% lidocaine with 1:100,000 epinephrine is injected along the septum, lateral walls, and floor of the nasal cavity. The external nasal branch is blocked via an intercartilaginous injection of the dorsum from the rhinion to the supratip region. Through the vestibule, the needle tip is passed into the facial soft tissue to a point just below the midportion of the orbital rim to anesthetize the infraorbital nerve. Branches from the nasopalatine nerve are then blocked with an injection at the base of the columella and nasal tip just inside of the nasal sill. After infiltration of the contralateral side in a similar fashion, the topical-soaked pledgets are replaced posteriorly along the deep internal nasal branches for 5 minutes to allow for maximal anesthesia.

The process of placing a nasal block is often more painful than the reduction itself; several strategies and alternatives may help reduce this discomfort. Buffering the lidocaine with 7.5% sodium bicarbonate solution in a 1:5 dilution by volume (e.g., 2 mL sodium bicarbonate and 10 mL lidocaine) significantly reduces the burning sensation associated with the acidity of the anesthetic preparation.[49] Infiltration should be done slowly, using a thin needle (27 gauge or less) within the dermal-subdermal or mucosal-submucosal plane to lessen pain from soft tissue dissection by the local anesthetic.[50] Patients may have less

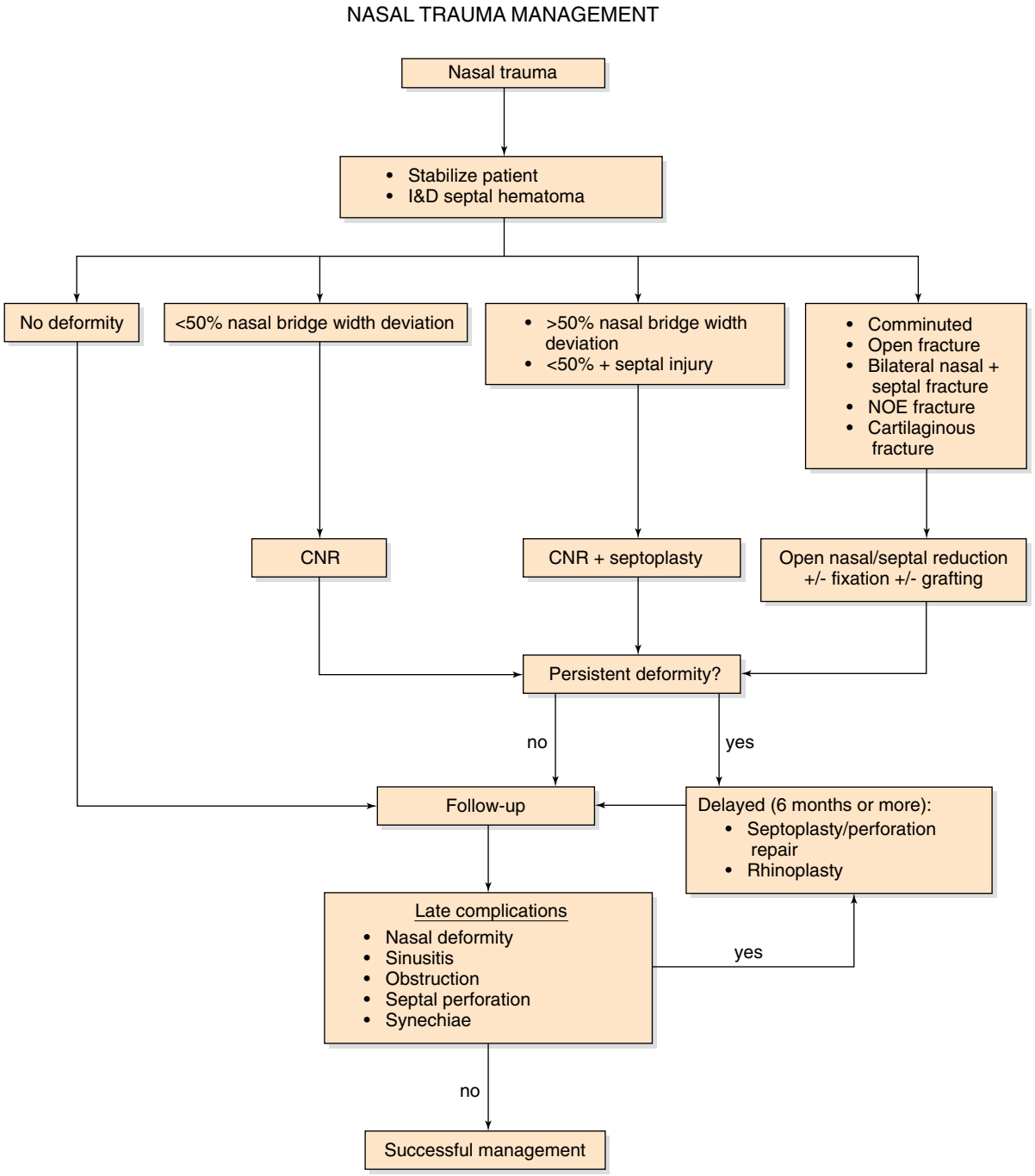

Figure 35-8. Algorithm for the management of nasal trauma. CNR, closed nasal reduction; I&D, incision and drainage; NOE, naso-orbitoethmoidal.

discomfort with percutaneous injection of the infraorbital, infratrochlear, and external nasal nerves as compared with the intranasal approach.[20] There is also evidence that the use of EMLA cream applied over the nose an hour before reduction, in combination with intranasal topical anesthetics, provides similar nasal anesthesia for reduction with significantly less discomfort than needle infiltration.[51,52]

Attempts by the practitioner to administer a nasal block to those who are unable to tolerate the injections will often result in insufficient pain control, poor intranasal visualization, and an inadequate reduction. Therefore, intravenous sedation is recommended for most children and any patient who is unable to cooperate with nasal manipulation. If the appropriate monitoring equipment and trained staff are available for conscious sedation, anxious individuals may be successfully managed in the office setting using anxiolytics and/or narcotics before the application of the nasal block. Patients who require deep sedation and those with complicated medical issues should be treated in the operating suite in the presence of an anesthesiologist to assist with hemodynamic and airway management. When using deep sedation, topical decongestion alone is usually adequate before reduction to improve visualization and control mucosal bleeding. Intermittent mask ventilation is used to manage the apneic patient, but a laryngeal mask airway or orotracheal intubation should be used for individuals with potentially difficult airways.

Technique

Closed Reduction

For cases of mild nasal bone deviation in which the fragment ends are still in close contact, finger manipulation alone may be adequate to achieve normal appearance. The nasal bones are grasped between two

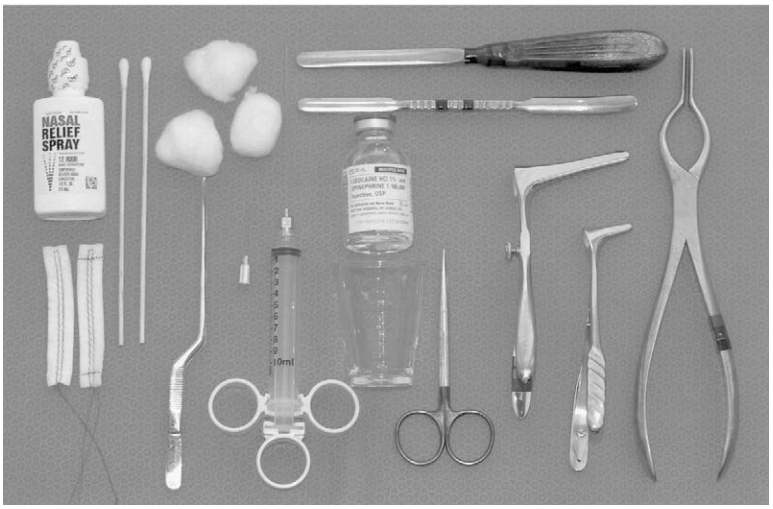

Figure 35-9. Equipment and medications commonly used for closed nasal reduction. Boies (*top right*) and Joker elevators (*below Boies*) provide good control and tactile feel during nasal bone manipulation. Asch forceps (*far right*) are used to disimpact and reduce septal fractures.

fingers, and gentle pressure is applied laterally in the opposite direction of the deviation. Although this technique is simplified, it does not provide the surgeon with much control and often will fail for cases in which there is significant fragment overlap or impaction. Inadvertent overcorrection may result in additional fractures of the nasal bones or septum, thereby producing even worse deformity or destabilization.

The use of a blunt elevator is recommended for most closed reductions, especially for cases in which there is significant medial collapse. Several different instruments, such as a Boies or Joker elevator (Fig. 35-9), can provide the surgeon with good tactile feedback and control of segment positioning. Before manipulation, the proper depth of insertion is determined by placing the instrument against the skin surface of the lateral nose, with the distal tip at the intercanthal line. The surgeon marks the position of the elevator at the alar rim and inserts it into the nasal cavity approximately 1 cm less than the measured depth. With only the tip of the instrument contacting the medial side of the nasal bone, the elevator is lifted anteriorly and laterally until the depressed segment is in proper position. The hand not holding the instrument can be used to pinch the nasal bones to mold the segments and prevent unnatural widening of the bridge. In the presence of a contralateral outfracture, the thumb places medial pressure on the opposite nasal bone so that both sides of the nasal pyramid are repositioned in a simultaneous, coordinated movement (Fig. 35-10).

For cases in which the fractured segments are overlapping, grasping instruments are often helpful for the achievement of a successful reduction. Walsham forceps are used to manipulate the nasal bones with greater versatility but lack the fine tactile input of an elevator. With one arm of the forceps inserted into the nasal cavity and the other against the skin surface, the displaced bone is grasped firmly but without crushing intervening tissue; the segment can then be disimpacted before it is repositioned into its proper anatomic location. Excessive torquing of the fragments should be avoided to prevent additional fracture. Grasping instruments usually are traumatic to the nasal mucosa and commonly provoke bleeding during reduction.

Because of its role as the central support of the entire nasal complex, the septum is one of the most important structures to properly realign after a traumatic injury. Reduction of the septum before the nasal bone manipulation will release tension that is often responsible for relapse of an external nasal deformity.[38] Closed reduction of the septum is often more challenging than nasal bone reduction due to the complexity of the forces exerted by surrounding structures and the frequent occurrence of preexisting deformities. The best results are usually obtained with the use of Asch forceps. Each arm of the instrument is inserted on either side of the septum and positioned superiorly just underneath the dorsum (Fig. 35-11). Using an upward and outward force perpendicular to the plane of the dorsum, the surgeon

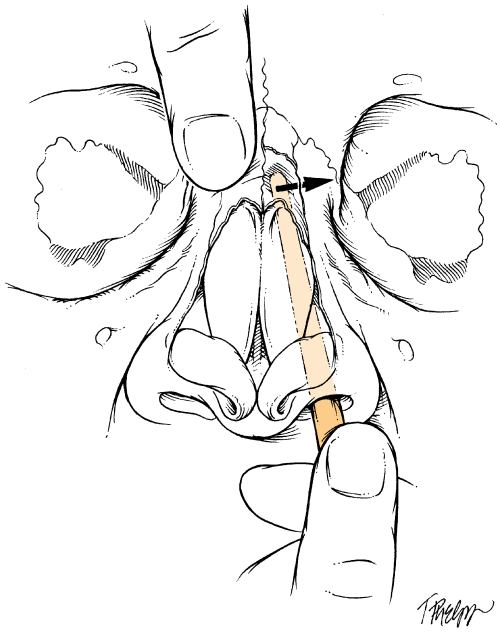

Figure 35-10. Closed nasal reduction. After marking the distance of the intercanthal line on the elevator with a thumb, the tip of the instrument is used to reduce the medialized fragment. The opposite thumb may simultaneously reduce a contralateral outfractured nasal bone.

lifts the septum out of overlap and then uses the arms to push the ends back into realignment.

The correction of cartilaginous injuries with closed reduction techniques is difficult and often unsuccessful. For upper lateral cartilage avulsion with medial displacement, reduction may be possible if it is performed soon after injury and followed by 10 to 14 days of internal packing to maintain the union of the keystone area. If treatment is attempted beyond 2 weeks, an open approach through an intercartilaginous incision with the removal of fibrous adhesions between the nasal bone and superior upper lateral cartilage is necessary before reduction and stenting.[24] For patients with poor results, delayed cartilage grafting may be offered to restore the external nasal contour after the injury has completely healed.[53,54]

Persistent deviation of the external nasal complex after an attempt at reduction is usually the result of inadequate understanding of the

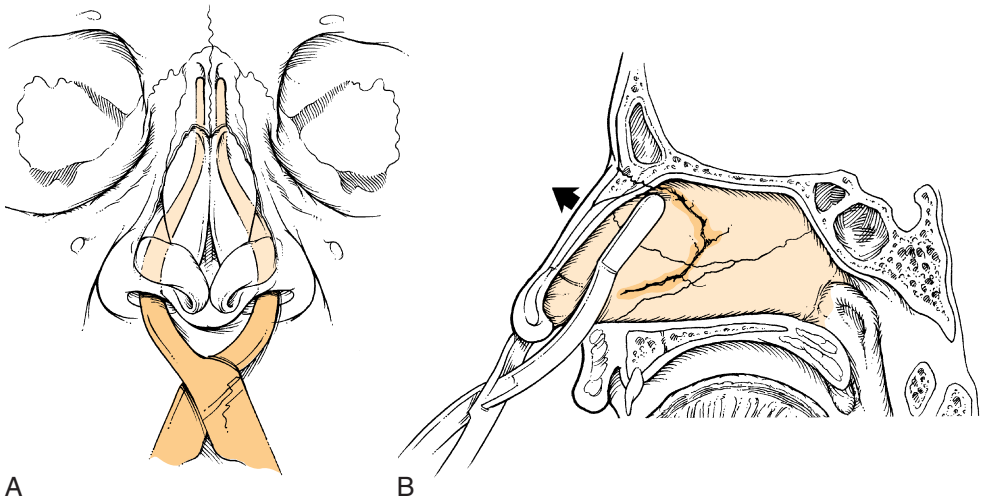

Figure 35-11. Closed septal reduction using Asch forceps.

injury or poor timing. The most common reason for a failed reduction that is performed within the first week to 10 days is an unreduced septal fracture.[10] For injuries that are more than 2 weeks old, fibrous tissue formation and early osseous remodeling are the causes of inadequate realignment. Osteotomy refracture to lyse these adhesions can be considered if reduction is desired acutely. If persistent deviation occurs after an appropriately timed reduction of a minor external deformity and a septal injury has been ruled out, an incomplete nasal bone fracture (greenstick) is likely. Conversion of the greenstick fracture to a complete fracture with an osteotome is necessary if internal stenting is unable to maintain the appropriate position. For the remaining cases of inadequate reduction, the surgeon should consider an unrecognized injury to the nasal cartilages or midfacial bones. Severe injuries that affect underlying support to the nasal pyramid will require open reduction and rigid fixation with or without bone grafting.

Care after Reduction

In an attempt to prevent collapse of the postreduction framework, intranasal packing may be placed under the mobile fracture segments to provide greater internal support.[4,9,15] Additionally, intranasal synechiae formation may be reduced or prevented. Several different materials may be used for this task, including tampon sponges (e.g., Merocel), folded Telfa sheets, or ribbon gauze. The packs are coated in antibiotic ointment and placed superiorly within the nasal cavity to support the fracture without causing overdisplacement of the fragments. The material is removed after 3 to 5 days but can be left in as long as a week for cases of severe instability. Patients are placed on oral antibiotics during this period to prevent rhinitis and sinusitis. Other potential complications from pack placement include pain, epistaxis, and septal perforation[55]; these factors should be considered on an individual basis before nasal packing is used. Although Illum and coworkers[7] found that internal packing was associated with a trend toward decreased nasal obstruction and better cosmetic appearance, there was not a statistically significant improvement for the entire group to justify its use in all patients. Some authors have advocated nasal packing only in cases of severe fracture instability,[43] whereas others do not use it at all.[21,52,56]

The role of septal splints after nasal fractures has also been somewhat unclear. Splints have been advocated to provide additional support after septal reduction, prevention of hematoma, and intranasal adhesions,[4,9,27] but there has been little evidence to support routine use in nasal fractures. The most likely benefit from their use is in cases with extensive mucosal injury and comminuted septal fractures that do not maintain alignment. Splints are custom-trimmed silicone sheets or manufactured products in various sizes and shapes with magnets or tubed nasal lumens (Doyle splints). The splint is coated with antibiotic ointment, inserted along each side of the septum, and secured with a loose anterior septal suture. Further reinforcement using packing material on the lateral surface of the splints should place even pressure on the septum. Splints are removed after 1 week but may be kept in place for longer periods in cases of greater instability. The potential complications from splints include increased pain,[57] obstruction, septal perforation, and toxic shock syndrome.[58,59]

External nasal splinting is routinely performed at the conclusion of reduction.[4,9,27,43] The skin is cleansed thoroughly with an alcohol or skin-preparation swab before the application of skin adhesive (e.g., Mastisol). After the surface is dry, a paper tape dressing (e.g., layered Steri-Strips) is applied to cover the nasal skin; the tape is generally thought to help prevent excessive swelling over the dorsum, resist hematoma formation, and protect the skin from potentially irritating splint adhesives.[60] One of several different types of splinting material (e.g., plaster of Paris, Denver Splint, Thermoplast, Aquaplast) is custom molded to the surface of the nose, with care taken to not displace underlying bony fragments. The splint is left in place for seven to 10 days and kept dry to maintain adhesion. Illum's[7] prospective trial that evaluated the efficacy of fixation found that patients treated with an external plaster cast had significantly better appearance than those who received adhesive tapes alone. This was in contrast with the results published by Houghton and colleagues,[56] who found no benefit to the use of external splinting. Despite conflicting evidence, the use of external nasal splinting is recommended, considering that it is usually well tolerated by the patient and provides a useful reminder to avoid potentially traumatizing activities.

The postreduction instructions should outline restrictions and proper care to optimize nasal healing. Avoidance of activities that may result in further nasal trauma should be prescribed for 6 to 8 weeks, depending on the degree of injury. Athletes or other individuals who are unable to refrain from contact sports can wear face masks that are specially designed to protect the nose during competition. Regular nasal saline sprays or irrigations are recommended to remove blood, reduce crusting, and help prevent adhesion formation. Antibacterial ointment should be applied to skin wounds, and oral antibiotics should be taken for 1 week by individuals with intranasal packing, septal splints, or extensive mucosal injuries. Refraining from nose blowing is also advised, especially in cases of concurrent sinus fracture that could potentially lead to air dissection into the orbit, the cranial cavity, or facial soft tissues.

Open Reduction

Repair of acquired nasal deformities by open reduction can represent two different types of surgical management. The first, which will be discussed in this chapter, is the immediate repair of displaced nasal fractures using wide surgical exposure, reduction, fixation, and reconstruction of severely damaged structures. The second is a delayed

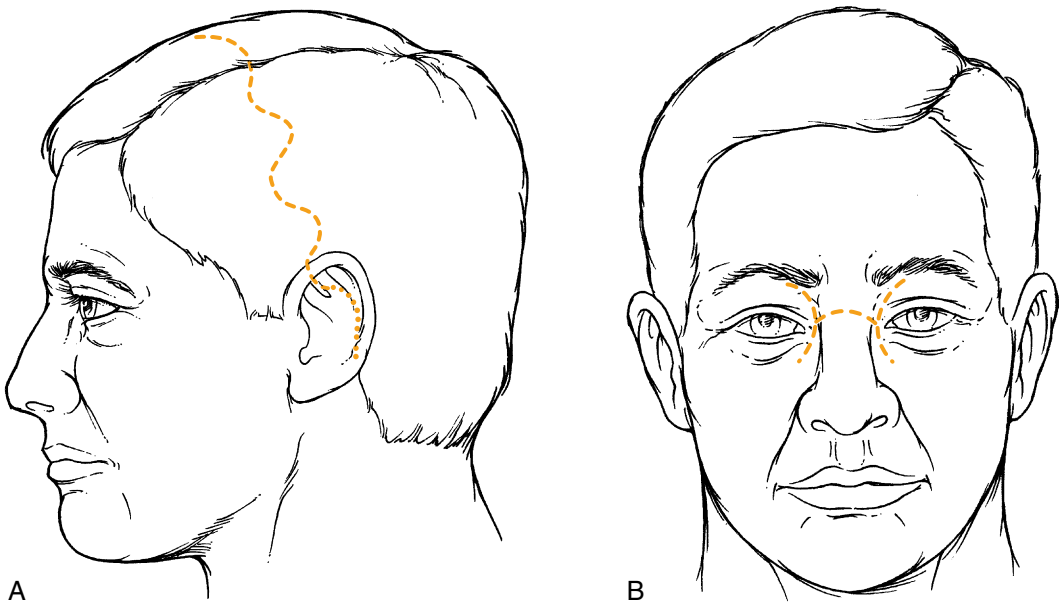

Figure 35-12. Two examples of surgical approaches that are used for open nasal reconstruction. **A,** Bicoronal incision. **B,** "Open sky" incision.

correction (usually 6 months or more) of persistent nasal deformities using the standard techniques of rhinoplasty (e.g., osteotomy, dorsal rasping, cartilage graft augmentation). Although the postponement of surgery in this situation is to allow for fracture healing and stabilization, the use of these procedures during the immediate postinjury phase has been recommended as an alternative to closed nasal reduction alone.[44] Further discussion of this technique may be found in the chapters that cover rhinoplasty.

The most appropriate approach necessary to reconstruct a nasal deformity is dictated by the location of the injury and the type of reconstruction that is anticipated. For injuries of the upper third of the nose, an "open sky" incision through the nasofrontal crease provides direct access to comminuted nasal and ethmoid complex fractures, whereas a lateral rhinotomy can be used for unilateral nasal deformities; these incisions tend to leave a fairly visible scar. Preexisting lacerations in these areas can be extended within skin creases to allow for sufficient exposure. A bicoronal scalp flap is an excellent utility incision that can expose the superior nasal complex as well as other upper facial skeletal injuries (e.g., zygomatic arch and frontal sinus fractures) without creating conspicuous scarring (Fig. 35-12). This approach is also employed for cases in which calvarial bone may be necessary for defect reconstruction; the midfacial degloving incision can be used to expose the nasal bones as well. Lower nasal pyramid injuries can be accessed with a standard open rhinoplasty approach via bilateral marginal and transcolumellar incisions. Decortication is carried out superiorly to visualize the nasal cartilages and the caudal septum; this exposure may be inadequate if reduction and fixation of nasal bone fractures is required, and it also should not be used if there are dorsal and alar lacerations that may have disrupted the superiorly based blood supply that is vital to the columellar flap.[11]

After the fracture line has been adequately exposed and realigned, fixation is performed using one of several different methods to stabilize the reduction. Small-gauge wires (26 or greater) passed through predrilled holes can secure fracture segments to stable areas of the maxilla or frontal bone. Renner[9] recommended that slow-absorbing sutures be used instead of wire to avoid palpable sharp edges underneath the skin surface. Titanium microplates are also less likely to be palpable through skin, and they provide the additional benefit of more versatile fragment positioning as compared with wiring techniques. The potential complications of using any metal fixation materials include bone erosion, skin breakdown, infection, migration, and localized pain. Rigid fixation techniques also preclude future rhinoplasty unless the hardware is first removed. Some of these problems may be avoidable with the use of bioabsorbable plates, but their efficacy in nasal reconstruction is yet to be established.

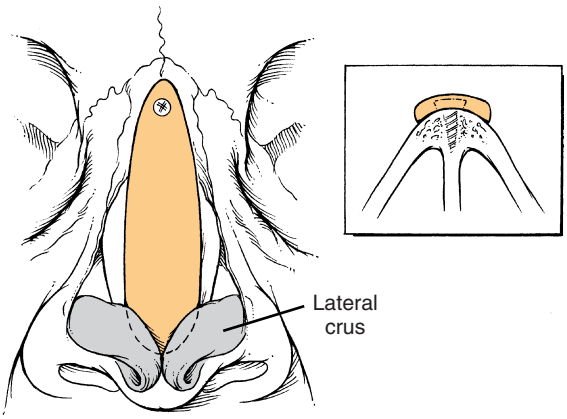

Figure 35-13. A cantilever bone graft secured proximally to an unfractured nasal bone with a lag screw. The distal tip of the graft is tucked under the cephalic ends of the lateral crus.

For more severe injuries that have poor underlying structural support or a significant loss of dorsal bone or cartilage, reconstruction using a cantilever graft is indicated. Although fracture segments should be conserved as much as possible, small fragments that do not contribute to the structure of the nasal complex should be removed to avoid their serving as a nidus for infection. The defect is then reconstructed with a graft that extends from the nasion to just beneath the cephalic border of the alar cartilages (Fig. 35-13). Autologous cranial bone, rib bone or cartilage, or homograft bone or cartilage are commonly used. Lag screw fixation to stable bone proximally is usually successful, but graft mobility has been reported in a portion of cases during long-term follow-up.[61] Increased stability may be possible by anchoring the graft with a plate secured from the distal undersurface to the anterior nasal spine.[38]

Septal injuries that cannot be realigned with closed reduction should also be addressed with open techniques. Fracture lines are exposed with a hemitransfixion incision, or they can be more widely visualized with an open rhinoplasty approach. The edges of overlapping segments are placed under traction; then, if necessary, they are conservatively trimmed until end-to-end reduction is possible. In cases of anterior septal dislocation, a small strip of cartilage is removed inferiorly

so that the quadrangular cartilage can be replaced within the maxillary crest. Fry[62] suggested that scoring of the concave surface of a deformed cartilage surface may also help straighten the septum by releasing interlocked stress. If severe trauma has completely destroyed the integrity of the anterior septum, graft reconstruction is necessary to restore tip support and prevent columella retraction, saddle deformity, and internal nasal valve collapse. Posterior septal bone and split calvarium have been recommended as donor sources for reconstruction.[63] Replacing the anterior septum with bone, however, may impart undesirable rigidity to the anterior aspect of the nose. The authors prefer replacing the damaged anterior septum with a cartilaginous graft such as auricular or costal cartilage.

Alternative Reduction Methods

The use of external compression plating is another method that has been used to treat severely comminuted nasal fractures. With this technique, padded lead plates are placed externally on either side of the nose and secured with transnasal wiring. Intranasal splints can be placed superiorly under the nasal dorsum to help prevent internal collapse, but results are commonly still poor. This procedure has largely been replaced with internal fixation and reconstruction and is not recommended as a primary treatment.

There have been attempts to find other minimally invasive methods of nasal realignment as alternatives to open reduction. Burm and Oh[64] described an intranasal approach through an intercartilaginous incision to reduce a depressed nasal bone fracture. After mucoperiosteal tunnel dissection under the displaced segment, a wire is placed distally beneath the unfractured nasal root and over the distal lower lateral cartilage to keep the fragment elevated (Fig. 35-14A). The wire is trimmed, and a small piece is left exposed in the nasal cavity to allow for retrieval after 10 to 14 days. A success rate of 85% was reported in a group of 27 patients treated with this method, although there was no control group in the study.

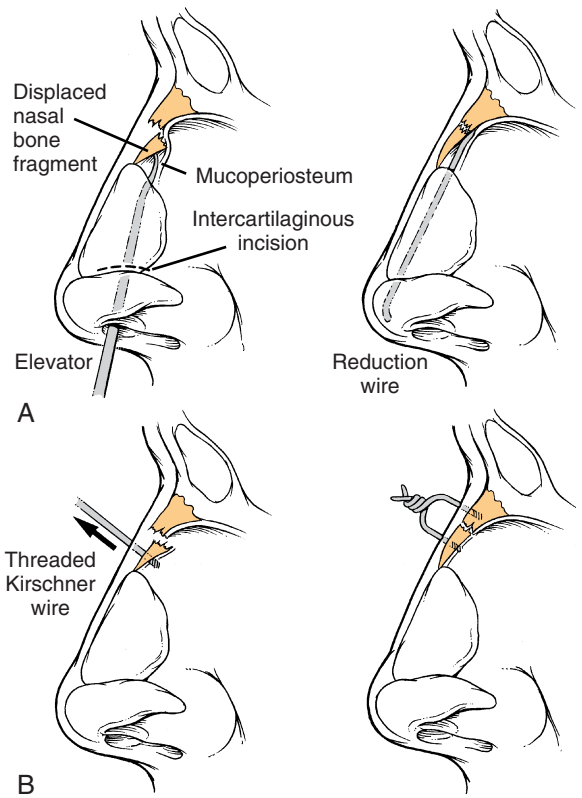

Figure 35-14. Alternative nasal reduction methods. **A,** After a mucoperiosteal tunnel is developed underneath the nasal bone, a temporary wire is placed under the reduced fragment. **B,** Percutaneous Kirschner wires secure the mobile fragment to stable bone after reduction.

Won Kim and coworkers[65] proposed another technique for unfavorable fractures that involved the use of percutaneous wire fixation. With the use of fluoroscopic imaging, a threaded Kirschner wire is secured perpendicularly through the midpoint of the bony fragment. The segment is then aligned, and the wire is secured to a second wire that has been placed into stable bone to maintain reduction (see Fig. 35-14B). After 2 weeks, a repeat x-ray study is obtained, and the Kirschner wires are removed. Satisfactory results were noted in all cases, although only eight patients were treated in this study, and no control group was used for comparison.

Pediatric Nasal Fractures

Nasal fractures in children are quite different than those in adults and often prove to be more challenging to diagnose and manage. Anatomically, the child's nose is more malleable because it has a greater cartilaginous composition and has less frontal projection. Traumatic forces are therefore easily spread to surrounding structures, which accounts for the higher incidence of concurrent facial fractures.[66] The softer, more flexible nose is prone to greenstick fractures, which are difficult to palpate as compared with the more obvious stepoff deformities seen in adults. Palpation is also complicated by the presence of facial edema that quickly masks subtle deformities. Plain film studies are even less reliable in children given the incomplete ossification of nasal bones; therefore, the possibility of nasal fracture should be carefully considered in any case of pediatric facial or anterior cranial trauma. The most common alerting signs are asymmetry, epistaxis, edema, periorbital ecchymosis, skin lacerations, and nasal bone crepitus.[67]

One of the most important factors related to nasal trauma during early life is the risk of damage to the growth centers that are responsible for normal nasal and facial development. Normal growth of the child's nose is mainly dependent on the septal cartilage. Animal studies have shown that removal of the septum during early life results in stunted nasal proportions, midfacial hypoplasia, relative mandibular prognathism, and malocclusion.[68] The greatest amount of septal growth in children occurs in two different stages.[69] The first stage is from birth to 5 years of age for both boys and girls; the second stage is from ages 10 to 14 years for boys and ages 8 to 12 for girls. Closed reduction of displaced fractures is generally considered safe in young children, but any elective open surgical correction should be postponed if at all possible until after these critical growth phases are complete.

If a displaced nasal fracture requires treatment, closed reduction should be carried out as soon as swelling no longer inhibits the assessment of underlying structures. Because of faster rates of bone healing, realignment in children should ideally be performed within four days of injury for best results.[70] General anesthesia is almost always necessary for these cases. The correction of nasal and septal deformities is performed using an appropriately sized blunt instrument that will not excessively traumatize the nasal airway. Synechia formation and/or stenosis are more common in the smaller pediatric nasal cavity. The use of postreduction nasal splints and packing usually increases discomfort without significantly improving outcomes and therefore is not recommended; an exception may be considered for infants less than 6 months old who are obligate nasal breathers. Goode and Spooner[67] suggested the use of intranasal silicone rubber tubing to stent the nasal passages in these children for a period of 4 to 5 days after manipulation until nasal edema subsides.

Although most deviated nasal fractures in children are successfully treated with conservative measures, there is an important role for open surgical reduction for the most severe trauma cases. Comminuted nasal and septal injuries that cannot be corrected with closed reduction are likely to produce long-term complications with poor nasal breathing and cosmetic malformation.[71] Several authors have published evidence supporting the use of rhinoplasty in children with such injuries, citing that surgical correction can improve appearance and function without compromising nasal-facial development.[71-76] This lack of growth disturbance may be due to the fact that the procedures did not damage the overlying mucoperichondrium, which has been shown to regenerate septal cartilage in young mammals after partial submucosal resection.[77,78] Therefore, open surgical correction may be performed in cases of severe deformity, with the goal being realignment and reconstruction

using as little dissection and tissue resection as possible. If total loss of the septum has occurred by trauma or infection, acute reconstruction with bone or cartilage grafts is necessary to reduce long-term complications.[19] Schrader and Jahnke[79] reported successful reconstruction using tragal cartilage and recommended it over posterior septal bone to avoid further risk of damage to important growth centers. For children who have septal destruction due to infection, immediate graft implantation has not been associated with a significant incidence of graft loss and is therefore recommended shortly after incision and drainage.[63,79]

Complications

Septal hematoma is one of the most severe early complications of nasal trauma. Blood collection under the perichondrium separates the vascular supply from the underlying cartilage, and this results in necrosis within 3 days.[80] Immediate treatment is necessary to prevent long-term problems such as saddle deformity, perforation, columellar retraction, and nasal base widening. For children who are more likely to develop hematoma because of increased shear trauma to the softer nasal tissues, septal destruction can lead to devastating nasal and midfacial growth abnormalities.[19] Incision and evacuation of the collection is performed, and several small openings are left to allow for dependent drainage. Splints or transseptal dissolving sutures are placed to obliterate the potential space and prevent re-collection. If the hematoma is not treated, bacterial seeding of the collection will result in abscess formation 6 to 7 days after trauma.[81] Contiguous spread of the septal infection can then lead to further complications, such as osteomyelitis, orbital and intracranial abscesses, meningitis, and cavernous sinus thrombosis.[82,83]

CSF leakage is also a common complication of severe nasal, nasal-orbital-ethmoid complex, and frontal sinus fractures. CSF rhinorrhea is confirmed with β2-transferrin levels, and the location of the fistula is usually best identified with high-resolution computed tomography scanning.[84] Most CSF leaks will spontaneously resolve with bedrest, head elevation, and possible lumbar CSF drainage. Persistent fistulas that do not resolve after 1 week of conservative treatment should be repaired surgically to prevent intracranial infection and pneumocephalus.

The potential for ophthalmologic complications from associated injuries should be closely scrutinized in all cases of nasal injury. Surrounding orbital wall fractures may result in fat or muscle herniation, retrobulbar hematoma, or penetrating globe injury. If the patient is unconscious, forced duction testing is necessary to rule out entrapment. Unrecognized or untreated displaced orbital floor fractures may result in late-onset enophthalmos after swelling has subsided. Ophthalmology consultation is recommended to assist with the evaluation and management of orbital injuries.

There are several delayed nasal complications that are often seen after a fracture. Worsening septal deviation, spurs, internal nasal valve collapse, and synechiae can all cause nasal airflow obstruction with growth. Blockage of mucociliary clearance can lead to a higher incidence of acute and chronic sinus infections. Illum and colleagues[7] found that a significant increase in saddle deformity and dorsal humps occurred in patients who were reexamined 3 years after their injuries; some of these problems may be worse in children who have more profound deformations after injury during the critical developmental phases of the nose. Regeneration of destroyed or missing cartilage may also result in overgrowth of the septum, thereby leading to a late onset of internal and external deformity.[74] Patients with significant nasal injuries should be followed up for at least a year or more to evaluate for these complications.

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For complete list of references log onto www.expertconsult.com.

CHAPTER THIRTY-SIX

Rhinoplasty

M. Eugene Tardy, Jr.

J. Regan Thomas

Key Points

- Best results in rhinoplasty are achieved by conservative techniques maintaining natural and normal-appearing outcomes.
- Most successful outcomes are achieved through primarily tissue reorientation and augmentation rather than aggressive resection or reduction techniques.
- The quality and thickness of the skin is an essential part of preoperative planning.
- A critical surgical assessment factor is evaluation of the inherent strength and support of the nasal tip anatomy.
- Standard and uniform color photography recorded before and serially after surgery is as important to the rhinoplasty surgeon as are radiographs to the orthopedic surgeon or electrocardiograms to the cardiologist.
- No "routine" tip procedure is used; rather the incisions, the approach, and the tip technique are based on the patient's individual anatomy.
- The underlapping attachment of the upper lateral cartilages to the undersurface of the nasal bones should be preserved.
- A strong, high bone-cartilage dorsal profile is typically a superior aesthetic goal.
- Narrow, sharp osteotomies provide for less trauma to soft tissue during surgery and less swelling and ecchymosis postoperatively.
- The patient should be instructed that subtle postoperative changes continue for many months following surgery.

Surgical Philosophy

Technical advances in rhinoplasty techniques inexorably develop as the virtues of new operative procedures are proved by the creation of favorable long-term outcomes. The common philosophy surrounding rhinoplasty, however, remains constant: the operation is best achieved by conservative techniques based on (1) the exact anatomy encountered and (2) refinement techniques planned to achieve natural and normal-appearing outcomes (see Key Indicator Video on website). Radical departures from time-proven techniques should only be considered when significantly variant anatomic features are encountered.

Aesthetic and reconstructive rhinoplasty, universally acknowledged as the most elegant but most difficult of all plastic surgical procedures, has reached the 100th anniversary of its modern development. Although certain refinements in technique gained progressive acceptance during the first three fourths of the 20th century, the fundamental operation remained primarily a tissue reduction procedure, characterized by various degrees of excision (often rather profound) of the fundamental nasal anatomic components.

In the past 20 years, a striking revolution has occurred in the fine points of analysis and technique, guided by surgeons devoted to tissue reorientation and augmentation rather than resection, individualization of technique rather than a lock-step approach, and atraumatic tissue dissection in proper nasal cleavage planes. A more thorough understanding of and respect for the long-term surgical outcome now dominates and guides the selection of the surgical technique because surgeons are no longer content with satisfactory short-term results at the expense of risking future visual and functional misadventures. Thus all modifications to nasal structures should factor in the dynamic effects each maneuver exerts upon the immediate overall nasal appearance, in the nasal airway, and the anticipated control of the vagaries of healing nasal tissues. Clearly, the surgically altered nose continues to be modified by the healing process and certain inexorable aging phenomena during the lifetime of the patient. Thus it is seldom possible to designate a "final result" after nasal surgery.

The philosophy, approaches, and graduated techniques presented in this chapter seek to document and validate the long-term virtues of accurate detailed analysis and planning, atraumatic and conservative surgical techniques devoted to tissue repositioning and reorientation, and methods of exercising the highest control over the healing process.

Preoperative Patient Assessment

Anatomic Evaluation

The final result of any rhinoplasty procedure is the consequence of the individual patient's anatomy (Fig. 36-1) as much as the surgeon's skill. No two noses are ever quite alike; it follows then that no single, standard procedure suffices to reconstruct every nose pleasingly. The ability to diagnose the possibilities and limitations inherent in each patient is an absolute prerequisite to achieving outstanding results. Sometimes patients with minimal deformities (a small hump; a minimally bulbous tip; a slightly overwide nose) are the best candidates for near-perfect surgical results (Fig. 36-2). Because the initial problem is minimal, however, this group of patients often expects and even demands perfection. More dramatic surgical results are possible in patients who demonstrate significant departures from an aesthetic ideal (a large hump; an elongated, drooping nose; a twisted nose); these patients might tolerate possible minor imperfections that result because the overall improvement is dramatic (Fig. 36-3). It is the fundamental responsibil-

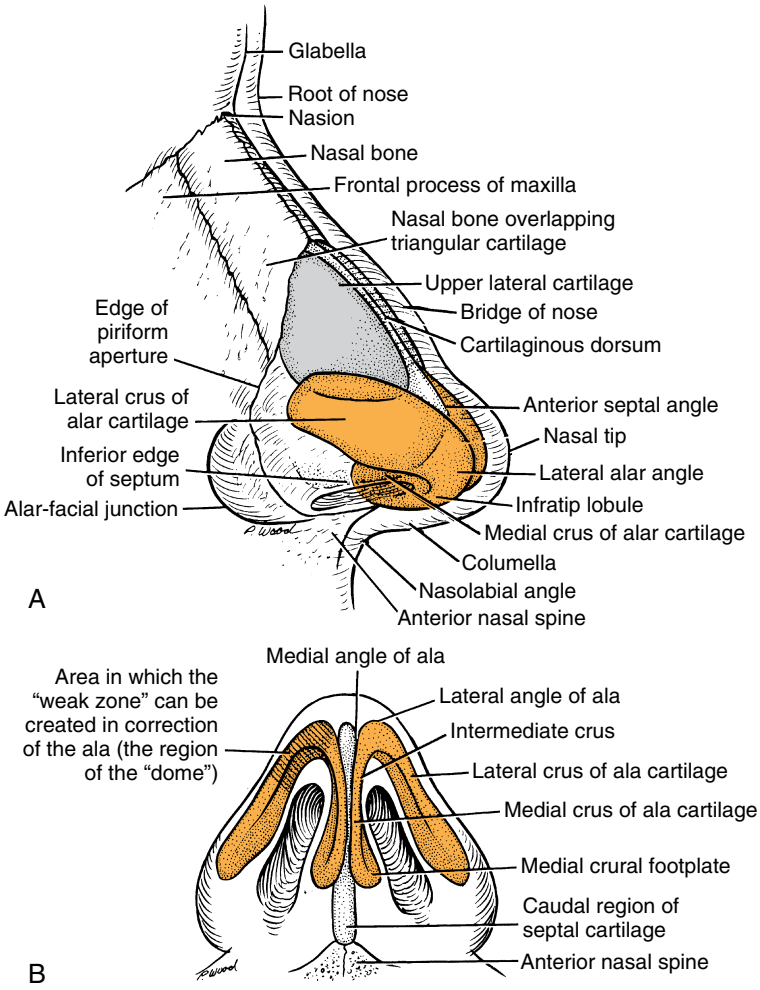

Figure 36-1. Practical nasal surgical anatomy. **A,** Lateral view. **B,** Base view.

Figure 36-2. Ideal candidate for rhinoplasty surgery. **A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

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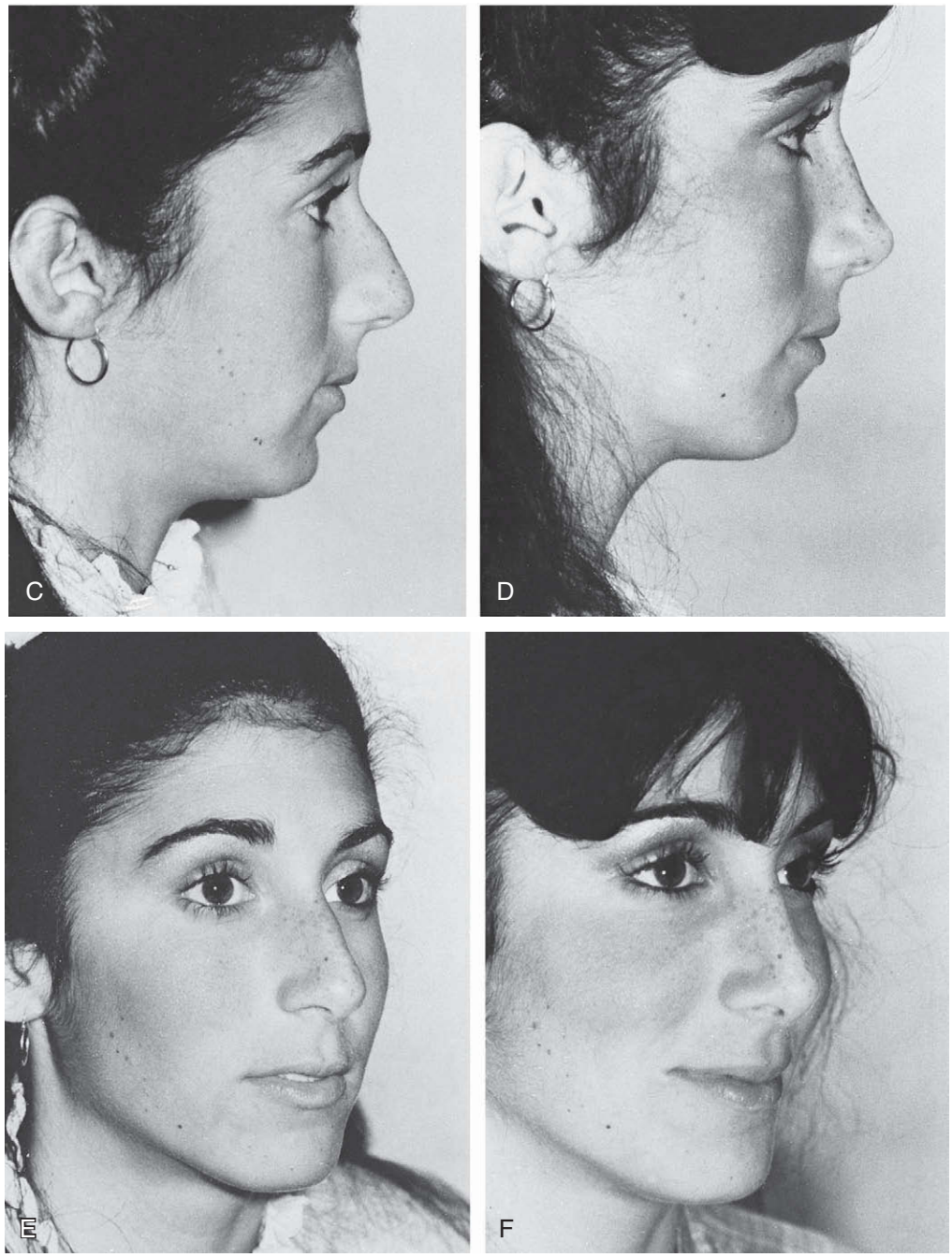

Figure 36-2, cont'd.

Figure 36-3. Reconstruction of twisted nose, demonstrating major surgical changes. **A** and **B,** Frontal views. **C** and **D,** Lateral views.

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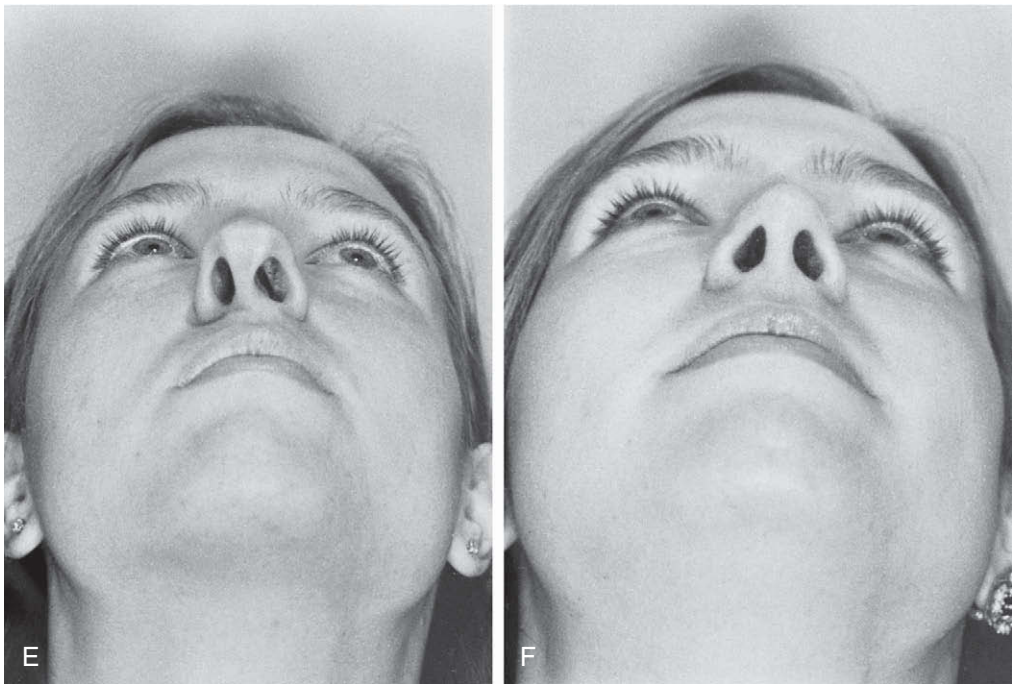

Figure 36-3, cont'd. **E** and **F,** Base views.

Figure 36-4. Revision repair of patient referred with typical soft tissue "pollybeak" deformity. Supratip scar carefully excised with restoration of appropriate tip-supratip relationship. Cartilage-only graft covers dorsum to smooth and improve contour of nasal skeleton. **A,** Preoperative view. **B,** Postoperative view.

ity of the surgeon to balance the wishes and desires of the patient with what is realistically possible given the anatomic limitations (or possibilities) inherent in each individual nose.

The quality of the skin is an essential indicator of the surgical outcome and plays a significant role in preoperative planning. Extremely thick skin, rich in sebaceous glands and subcutaneous tissue, is the least ideal skin type for achieving desirable refinement and definition. Care should be taken not to overreduce the bony-cartilaginous skeleton in thick-skinned patients in a futile attempt to produce a much smaller nose. Failure of thick skin to contract favorably in this situation may lead to excess soft tissue scar, an amorphous nasal appearance, and even the dreaded soft tissue "pollybeak" (Fig. 36-4). When properly supported by the retention or creation of a vigorous supportive skeletal structure, elegant outcomes can be produced in thick-skinned patients with sufficient passage of time.

Extremely thin skin, often pale, freckled, and nearly translucent, should also be recognized and respected for its inherent limitations. Although ideal for achieving critical definition, thin skin with sparse subcutaneous tissue provides almost no cushion to cover even the most minute of skeletal irregularities or contour imperfections, and therefore demands near-perfect surgery to achieve the desired natural result. Occasionally, patients with this anatomic condition demonstrate an

undesirable progressive skin retraction and unattractive shrinkage over several years, rendering the nose unnatural and angular.

The ideal skin type falls somewhere between these two extremes, being neither too thick and oily nor too thin and delicate. It possesses enough subcutaneous tissue to provide a satisfactory cushion over the nasal skeleton but still allows critical definition to become apparent in a relatively short time after surgery. Evaluation of skin type is made by inspection and palpation—rolling the skin over the nasal skeleton and gently pinching it between the examining fingers.

A critical factor in assessing the candidate for rhinoplasty is the inherent strength and support of the nasal tip, referred to as the tip recoil. Finger depression of the tip toward the upper lid provides a quick and reliable test of the ability of the mobile tip's structures to spring back into position (Fig. 36-5). The tip that possesses weak, somewhat flail alar cartilages does not tolerate an extensive sacrifice of tissue well and may require the addition of supportive struts to improve its long-term stable support. These weak tips often are accompanied by thin alar side walls and thin skin (see Fig. 36-31C). If the recoil is instantaneous and vigorous, and the tip cartilages resist the deforming influence of the finger, more definitive tip surgery can usually be performed without fear of substantial loss. The size, shape, attitude, and resilience of the alar cartilages can be estimated by palpation or ballottement of the lateral crus between two fingers surrounding its cephalic and caudal margins. During this assessment, the surgeon makes the all-important decision about whether to enhance, reduce, or carefully preserve the tip projection that exists preoperatively. Any asymmetry of the alar cartilages must be carefully noted for later correction.

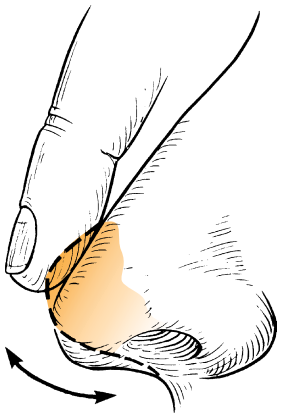

Figure 36-5. Forceful depression of nasal tip structures, with assessment of tip recoil, guides surgeon to a better understanding of strength and integrity of tip-support mechanisms. This information is vital in selecting proper tip sculpture technique.

A gratifying amount of diagnostic information can be gained by palpating the internal vestibules of the nose with the thumb and forefinger surrounding the columella. Otherwise, undetected twists and angulations of the nasal septum, which may significantly influence the final functional and aesthetic appearance, may not be discovered. The width and length of the columella and the medial crura it contains are determined. Short medial crura will probably require supportive cartilaginous struts to support and minimally lengthen the columella and aid in rotation, if desirable; extremely flaring or overlong medial crura invite reduction in width and length as well as retropositioning. Information about the potential of the tip to undergo desirable cephalic rotation is gained by the exploring fingers, which determine whether the tip-lip complex is tethered by muscle and its inadequate length. It is also important to determine whether the central skeletal component of the nose (the quadrangular cartilage) is overlong and might interfere with satisfactory tip rotation (Fig. 36-6). The size and position of the nasal spine and its related caudal septal angle must also be evaluated.

An experienced surgeon can accomplish these visual and palpatory diagnostic exercises with precision and facility, often while eliciting further history from the patient. Detecting the minute but critical structural distinguishing characteristics of each individual's nasal anatomy is the first and most important step toward a splendid surgical result.

Careful examination of the nasal fossae before and after shrinkage of the mucosa and turbinates is an essential component of the initial examination. Supplemental anterior and posterior rhinoscopy with the fiberoptic rhinoscope expands diagnostic information beyond that furnished by the nasal speculum alone. An overt, symptomatic deviation of the nasal septum is easily diagnosed; the deflected ethmoid plate,

Figure 36-6. A, A young patient demonstrating classic prolongation of caudal aspect of quadrangular cartilage, leading to webbed, indistinct nasolabial angle, overprojecting tip, and nasal proportion disharmony. **B,** Reduction of overlong caudal quadrangular cartilage with profile reduction combined with augmentation of deep nasofrontal angle with onlay cartilage graft. Note improvement in lip contour and overall nasal and facial proportion and balance.

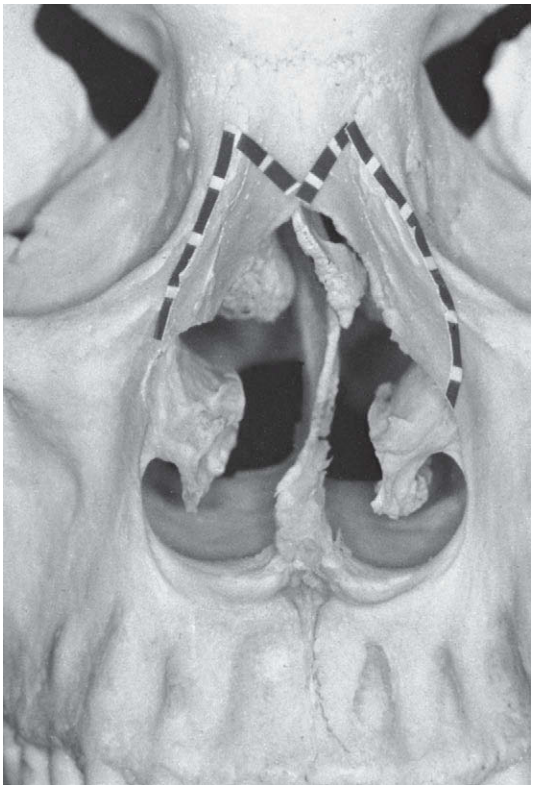

Figure 36-7. Typical deviated ethmoid perpendicular plate. Narrowing the nasal bony side walls without initially correcting septal deviation inevitably leads to creation of nasal obstruction, even if none existed preoperatively.

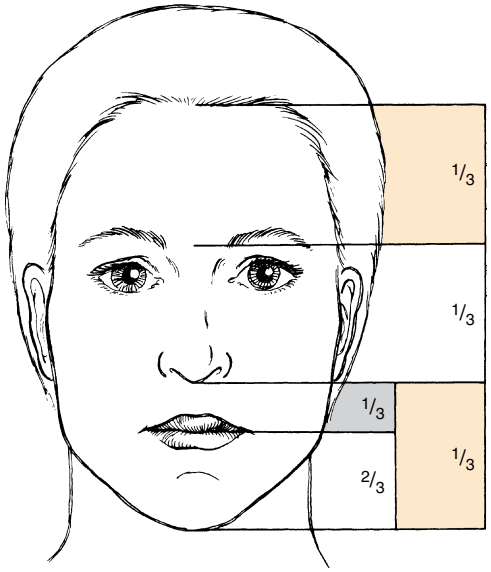

Figure 36-8. Relatively ideal proportions of the human face on frontal view.

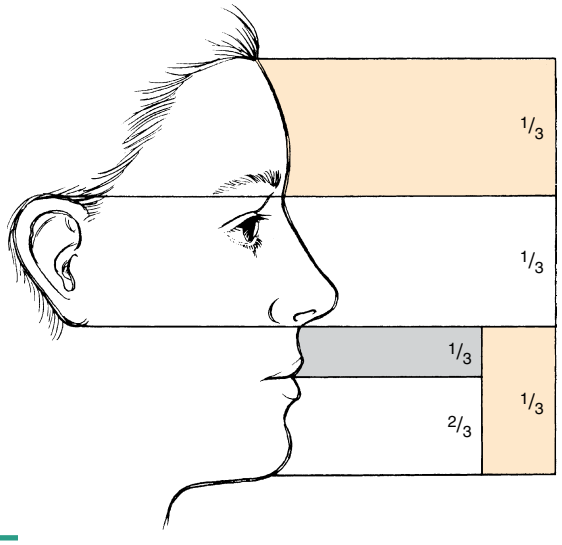

Figure 36-9. Ideal proportions, lateral view.

which may appear innocent but can be responsible for airway blockade after infraction of the bony side walls during an osteotomy (Fig. 36-7), may be easily overlooked by casual inspection. Internal examination confirms the condition of the internal nasal valves and their associated upper lateral cartilages and discovers whether the turbinates require repair or relocation to improve overall nasal function. If a septal perforation exists, its size and location may significantly influence the planned extent of the surgical procedure, particularly if substantial hump removal is planned.

Finally, the position and inclination of the nasofrontal and nasolabial angles, the shape and size of the alae, the overall width of the middle and upper thirds of the nose, and the relationship of the nose to the remainder of the facial features and landmarks are evaluated (Fig. 36-8). In particular, facial asymmetries (which are present more often than not) and the relationship of the chin projection to the nose should be documented (Fig. 36-9), particularly for patients who are unaware of the existence of such abnormalities. The routine use of a three-way mirror, facial photographs, and even computer imaging catalyze this vitally important communication process between the expectant patient and the cautious surgeon. This is the time, reinforced by later discussions, to make the patient aware of any and all limitations that the existent variant anatomy imposes on the desired surgical outcome. Realistic expectations and thoroughly informed consent are the keystones on which the most important surgical outcome—a happy patient—is achieved.

Photography and Imaging

Standard and uniform color photography of a rhinoplasty patient, recorded before and serially after the surgical event, are as important to the rhinoplasty surgeon as radiographs are to bone specialists and electrocardiograms are to cardiologists. They are important guides to operative planning and execution, definitive records for evaluation by the surgeon and patient, invaluable teaching tools, and vital medicolegal records. Reliable methods of making standardized, consistently uniform photographs are described in Fig. 36-10. A rhinoplasty surgeon should either become expert in personally securing uniform and standard photographs or should arrange uncompromisingly for their provision by a medical photographer or knowledgeable assistant. Modern digital photography has multiple advantages including ease of storage and retrieval.

Computer imaging has proved to be a useful communication tool in the consultative, preoperative period. Realistic and surgically attainable images must be presented to the patient to avoid misleading or spurious expectations. We emphasize that the computerized images represent a "realistic goal" of surgery and not a guaranteed outcome.

Laboratory Evaluation

The extent of indicated laboratory evaluations performed in the preoperative period depends on the needs of the individual patient. Whether the surgeon obtains an automated biochemical survey (SMA-12), a

Figure 36-10. Ideal photographic views of rhinoplasty should include, at minimum, frontal **(A)**, lateral (**B**), oblique **(C)**, and basal **(D)**. Smiling view is often helpful (Left oblique and lateral not shown). In special cases, close-up views may provide additional documentation.

complete blood count, a urinalysis, a bleeding and coagulation survey (routinely consisting of a complete blood count, platelet count, bleeding and clotting time, and partial thromboplastin time), or a combination thereof will depend on the patient's history and individual needs. This information is augmented by a thorough history of any personal or familial bleeding disorder. Of particular importance is any history of recent ingestion of aspirin or aspirin-containing drugs or herbal and alternative medicines, which must be stopped at least 2 weeks before the scheduled surgery. Many of these nonstandard drugs can lead to untoward bleeding during or following nasal surgery and thus are to be avoided.

Routine sinus radiographs are requested only if nasal and sinus disease is suspected; radiographs of the nasal skeleton usually provide little useful information that cannot be better obtained from minute inspection and palpation. When nasal implants or foreign bodies are suspected, computed tomography (CT) scans can be invaluable in pinpointing their position, composition, and extent.

Anesthesia and Analgesia

Successful rhinoplasty depends on a careful preoperative analysis, an exacting operative technique, and favorable postoperative healing.

Each surgical step in the correction of the nose is interrelated and interdependent with the other steps; the success of each step depends in no small measure on the preceding ones. Because the administration of infiltrations anesthesia is the initial surgical step in rhinoplasty, a well-planned and well-executed technique that avoids tissue distortion is necessary for a successfully controlled procedure (Fig. 36-11).

Improper administration of anesthesia results in an uncomfortable, agitated patient and a bloody operative field, which at best hinders surgery. Correct anesthetic administration commonly results in a com-

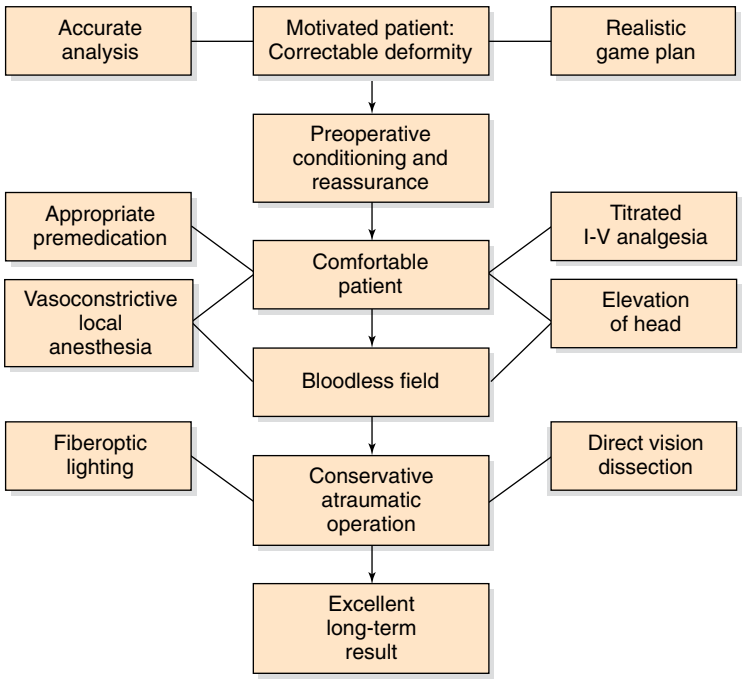

Figure 36-11. The components of a successful rhinoplasty.

fortable, relaxed patient and a relatively bloodless operative field, permitting precise anatomic dissection.

Just as there are a multitude of rhinoplasty techniques, so are there various approaches to nasal anesthesia. Experience suggests that a combination of monitored intravenous analgesia with local topical and infiltration anesthesia works well for rhinoplasty. General endotracheal anesthesia can be safely used for routine nasal surgery and may be chosen according to the preference of the patient and surgeon.

Surgical Planes

To achieve the goals of local anesthesia fully, it is important to appreciate, identify, and correctly use the surgical planes of the nose. The importance of anatomic tissue planes is stressed throughout surgical training because dissection within these favorable planes facilitates surgery with minimal bleeding and postoperative scarring.

Within the nose, four distinct dissection planes can be identified. An extraperiosteal plane exists lateral and medial to the ascending process of the maxilla along the intended course of the lateral osteotomies. Infiltration of the local anesthetic on both sides of the ascending process aids remarkably in eliminating or reducing bleeding after a lateral osteotomy (Fig. 36-12). A second plane exists in the submucoperichondrial and submucoperiosteal spaces flanking the nasal septum. Infiltration of the local anesthetic into this plane results in a hydraulic dissection of the septal flap, facilitating elevation and preservation of flap integrity (Fig. 36-13). Of greatest importance is the surgical plane occupying the immediate supraperichondrial and supraperiosteal regions over the lower and upper cartilages and nasal bones that exist just below the subcutaneous tissue layer (Fig. 36-14). It is entered in all rhinoplasty operations. Infiltrating and operating in this plane produces a virtually bloodless field for delicate precision surgery. The fourth relatively avascular and favorable dissection plane exists in the submucoperichondrial space flanking the septal cartilage on either side.

A paucity of vascular and neural structures exists in these planes; anesthetic infiltration into these planes misses the vessels and nerves that lie more superficial in the subcutaneous tissue and dermis. When the anesthetic is injected into the proper planes, it diffuses more readily and requires only small amounts (usually 3.5 to 5 mL) to obtain the desired anesthetic and vasoconstrictive effects. If the infiltration is placed in the subcutaneous tissue or epithelium overlying these planes, larger quantities are needed to obtain these effects, and there is a ten-

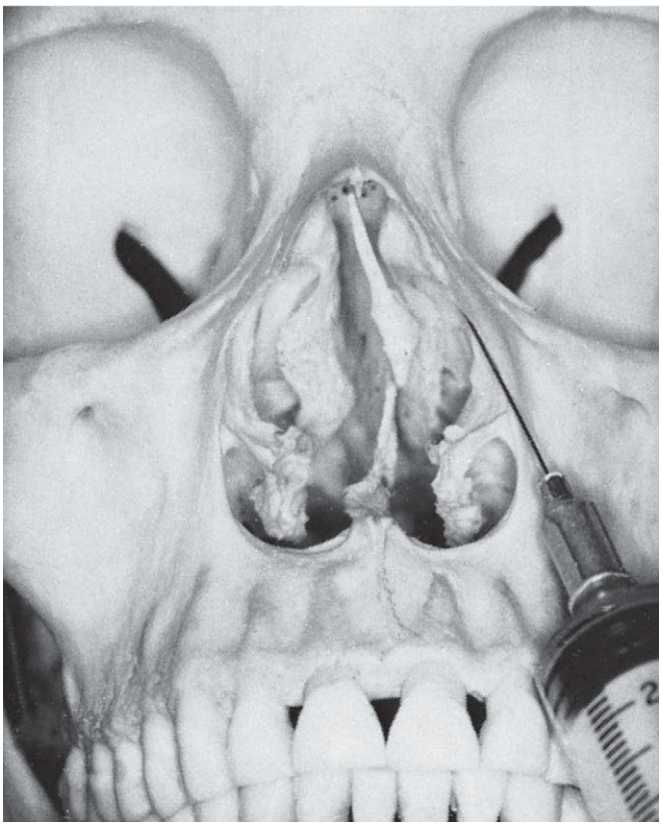

Figure 36-12. Anesthetic infiltration of internal (medial) aspects of ascending process of maxilla as well as lateral surface creates vasoconstricted pathway for progression of lateral osteotomy, thereby reducing or eliminating bleeding and edema.

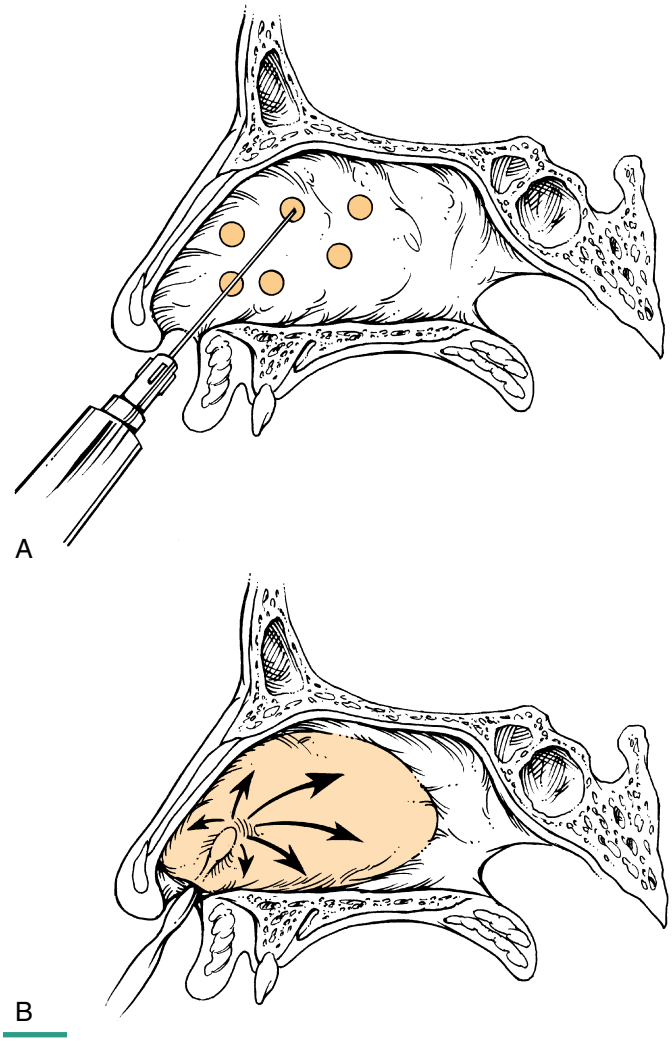

Figure 36-13. **A,** Anesthetic infiltration of submucoperichondrial plane results in "hydraulic dissection" of mucoperichondrial flap. **B,** Facile elevation of mucoperichondrial septal flap is more easily accomplished when proper anesthetic infiltration is carried out. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

dency to distort and "balloon" the nose, creating a distortion that leads to inaccurate judgment. By identifying and using the proper dissection planes, only small amounts of anesthetic are needed to achieve maximal anesthesia and vasoconstriction with consequent minimal nasal distortion.

Preoperative Medication and Intravenous Analgesia

Local infiltration anesthesia is administered after the patient has been sedated with preoperative medication and intravenous analgesia. It is important that the patient not receive many different families of drugs before or during surgery. Combinations of drugs, particularly when they are intermingled with intravenous medications given during surgery, are often unpredictable in their individual and combined effectiveness. Any drug reaction that can arise from the use of multiple families of pharmacologic agents is confusing to treat and may be impossible to counteract intelligently.

Close cooperation between the surgeon and the anesthesiologist is important at this time as well as throughout the operation. Each is responsible for the patient's safety and well-being, and each catalyzes the operative process by a healthy respect for the other's responsibilities.

For increased comfort, the patient is maintained in the reverse Trendelenburg position with the head elevated. This enhances vasoconstriction and facilitates venous and lymphatic drainage.

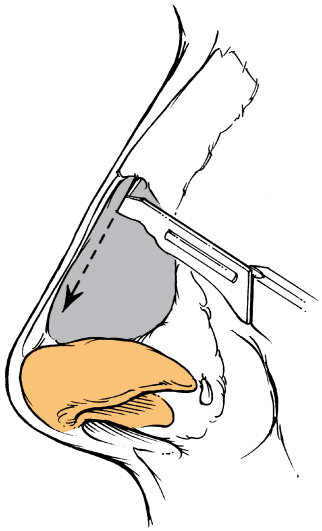

Figure 36-14. Increments of cartilaginous dorsum are shaved away with a sharp knife under direct vision until a satisfactory tip-supratip relationship is established. Except in unusual circumstances, underlying mucoperichondrium bridging upper lateral cartilages to quadrangular cartilage is always preserved. The hump can alternatively be reduced by resecting cartilage and bony elements en bloc manner. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Infiltration Anesthesia

For infiltration anesthesia, 1% lidocaine with a 1:100,000 dilution of epinephrine is preferred. The weaker solution is used in older patients or in those with any question of cardiovascular or peripheral vascular disease. Both concentrations of epinephrine produce profound vasoconstriction if incisions are delayed for 10 to 15 minutes after the final injection. The concentration of 1% lidocaine is sufficient to produce excellent anesthesia and has an effective duration of 1.5 to 2 hours.

Except in unusual cases, a total of 5 to 10 mL of the solution, sparingly injected into the proper surgical planes, is sufficient to produce profound vasoconstriction and complete nasal anesthesia with no significant tissue distortion. No effort is made to block specific nerves. If septal reconstruction is required, an additional 3 to 5 mL of the anesthetic is injected into the septal submucoperichondrial and submucoperiosteal planes to aid in the hydraulic dissection of the septal flap.

The infiltration of the local anesthetic is initiated by retracting the ala cephalically with the thumb and forefinger, exposing the caudal edge of the upper lateral cartilage (specula or retractors are unnecessary and redundant at this point). A long 27-gauge needle is placed parallel to the long axis of the exposed upper lateral cartilage, and with a quick stabbing motion the needle penetrates the epithelium, usually with minimal sensation to the patient (Fig. 36-15A).

The needle is advanced along the lateral wall of the dorsum, hugging the perichondrium of the upper lateral cartilages and the periosteum of the nasal bones, thus remaining in the proper plane. Identification of this plane is enhanced by lifting the soft tissues overlying the nasal dorsum with thumb and forefinger.

A minimal quantity of anesthetic solution, usually less than 0.5 mL, is deposited into this plane as the needle is withdrawn to but not beyond the point of initial penetration (see Fig. 36-15B). If the nose becomes distorted during this maneuver, the needle is not in the proper plane, and the infiltration stops until the plane is located. With alternate slight rotation of the needle laterally and medially over the dorsum (see Fig. 36-15C and D), the procedure is repeated until the anesthetic is deposited in the proper plane over the area to be dissected. The procedure is repeated on the opposite side. With this method, only two injection penetrations are sufficient to anesthetize the nasal dorsum.

Anesthesia of the base of the nose and columella is accomplished next. The needle penetrates the skin at the junction of the floor of the

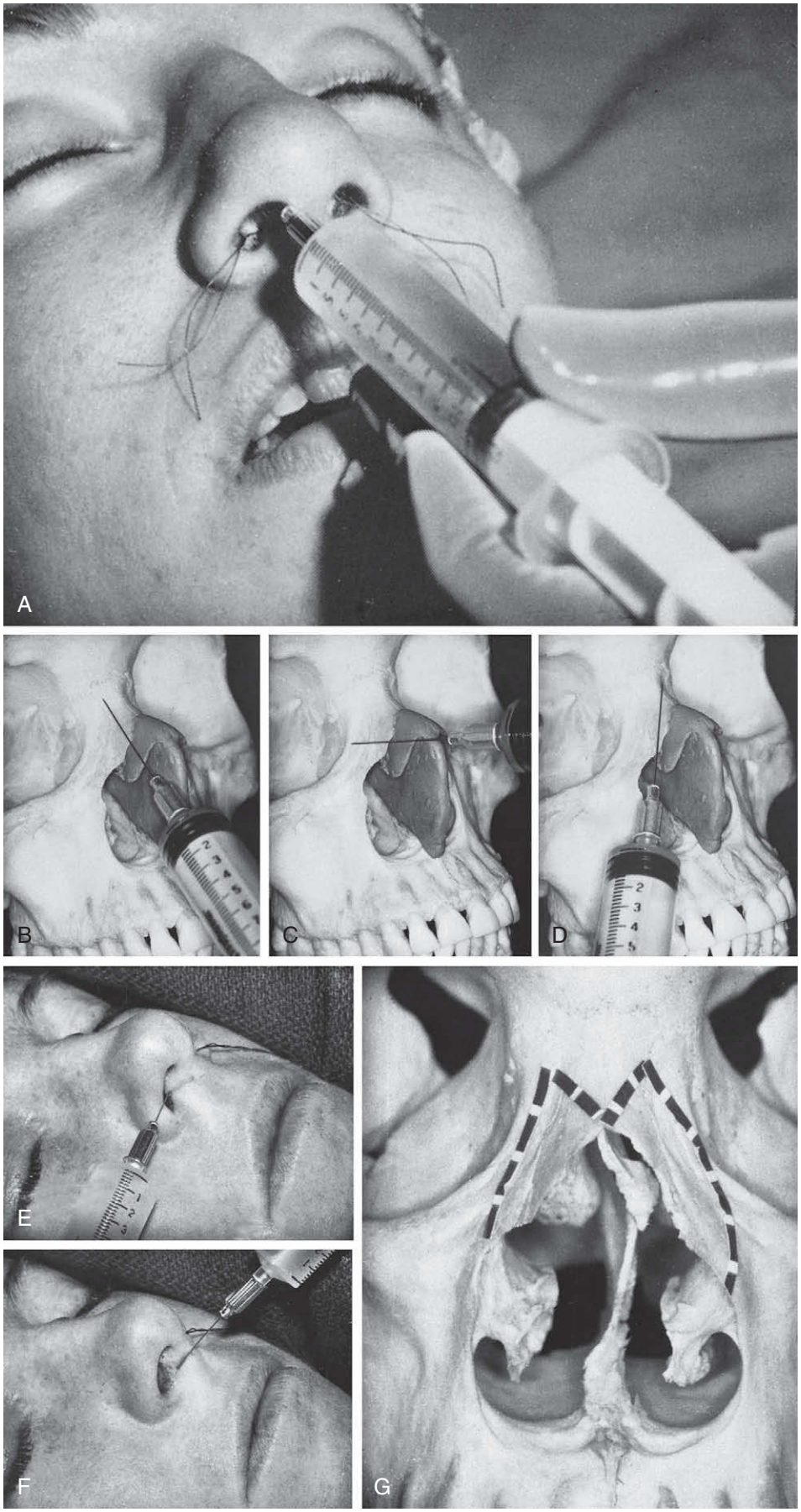

Figure 36-15. **A,** Initial advancement of needle in proper plane over bony and cartilaginous vaults, with infiltration in plane between nasal skeleton and subcutaneous tissues. **B,** Infiltration of lateral wall of nose, intimate to nasal skeleton. **C** and **D,** Rotation of needle within soft tissues to effect further anesthesia of lateral and dorsal nasal tissues. **E** and **F,** Infiltration of nasal base and floor with one-needle penetration. **G,** Intended pathway of low lateral osteotomies. Infiltration of local anesthetic should surround this pathway medial and lateral to ascending process.

right nostril and columella and is advanced to a point just beyond the left alar facial junction (see Fig. 36-15E). Infiltration occurs as the needle is withdrawn to the columella. Without removal, the needle is rotated and advanced into the columella. Again, a small amount of anesthetic is deposited as the needle is withdrawn. Sparing the patient an additional needle prick, the needle is rotated into the right nasal base, which is anesthetized in a similar fashion (see Fig. 36-15F).

The technique of nasal tip anesthetic infiltration depends on the type of planned nasal tip incision. If a transcartilaginous incision is intended, the vestibular skin on the undersurface of the lower lateral cartilage is exposed and everted by pressure above the nostril. The solution is deposited along the course of the proposed incision in the natural plane beneath the perichondrium. Surgical elevation and preservation of an intact vestibular skin flap is thereby facilitated. If delivery of the alar cartilage is contemplated, the anesthetic is infiltrated in the soft tissue along the extent of the planned incision at the caudal margin of the cartilage. If an open approach is contemplated, additional infiltration occurs in the interdomal region, the infratip lobule, and the columella.

The anesthetic can then be deposited along the course of the lateral osteotomies (see Fig. 36-15A and B) or, if desired, this can be deferred until later in the operation. This delay adds a safety measure to the procedure by allowing the patient to metabolize the initial lidocaine and epinephrine before adding any additional solution. The margin of the piriform aperture just above the leading anterior edge of the inferior turbinate is brought into sharp relief by surrounding it with the blades of a small nasal speculum. The needle is inserted at this site, and a small amount of medication is injected. The needle is advanced lateral to and then medial to the ascending process of the maxilla along the intended path of the lateral osteotomies (see Fig. 36-15G), and as the needle is withdrawn, solution is deposited. Thus the path of the lateral osteotomies is surrounded by local vasoconstrictive anesthesia, a valuable adjunct to bloodless osteotomies and patient comfort. Postoperative ecchymosis is reduced to a minimum or eliminated by the latter maneuver combined with a gentle operative procedure.

When septal reconstruction is planned, anesthesia of the already anesthetized (with cocaine) septum is accomplished. Unlike the preceding steps, infiltration of a generous amount of solution into the proper septal plane is preferred. This quantity results in hydraulic dissection of the mucoperichondrium and mucoperiosteum from the cartilaginous and bony septum (see Fig. 36-13). It allows for an avascular flap elevation and may help to dissect synechiae from areas of old fractures.

With nasal shrinkage intense at this point, the cottonoids are removed temporarily. The needle is inserted with the bevel down into the mucous membrane on the side of intended mucoperichondrial flap elevation. The needle is advanced to the plane between the quadrangular cartilage and the perichondrium, and with anesthetic infiltration hydraulic elevation is created. This is repeated at several other sites along the mucous membrane. The needle is then inserted beneath the mucoperiosteum overlying the bony septum on both sides, and the anesthetic is infiltrated there. Small amounts of solution are also deposited on both sides of the base of the septum at the maxillary crest–quadrangular cartilage junction. After completion of the septal anesthesia, the cottonoids are reinserted. If surgery is deliberately delayed 10 to 15 minutes, vasconstriction will reach its maximal effectiveness and bleeding will be minimized.

Surgical Landmarks

Although not strictly necessary, it can be helpful to the new as well as the experienced surgeon to indicate on the external skin surface the anatomic surgical landmarks with a marking pen. These external manifestations of the nose skeleton and framework may ordinarily be judged within tolerances of 1 to 2 mm, allowing the development of critical, measured judgments about planned excisions, augmentations, and reorientation of nasal structures (Fig. 36-16). It may be helpful (particularly in a teaching environment) to mark the margins of the alar cartilages and their precise tip-defining points, as well as the preplanned amount of cephalic reduction required for refinement and definition. The caudal margins of the nasal bones and maxillary ascending processes are indicated, and the estimated extent of the bony-cartilaginous hump removal and the planned osteotomy pathways can be indicated by dotted lines. A plus (+) mark on contour depressions serves to remind the surgeon of the need for intended augmentation because small depressions may later be obscured by anesthetic infiltration and surgical edema. Skin markings are general guidelines to the intended surgical maneuvers, but they may be useful in guiding the thought processes by which precise surgery is executed.

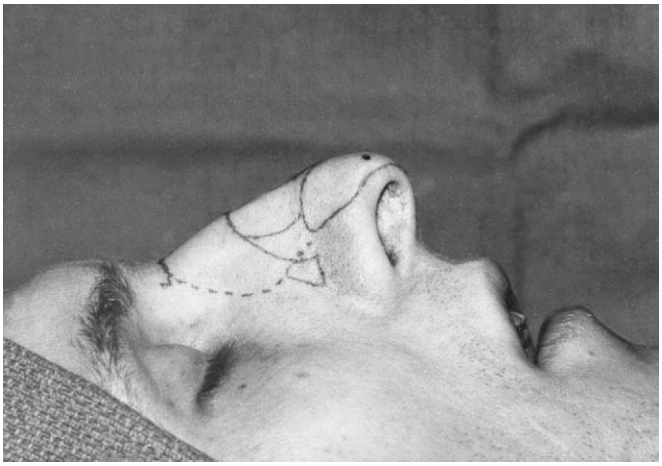

Figure 36-16. Skeletal landmarks and boundaries depicted on nasal soft tissues. Tip-defining point is indicated by black dot.

Surgical Refinement of the Nasal Tip

Because it is mobile and animate, the nasal tip is approached as a rather distinctive and separate portion of the rhinoplasty operation. It is helpful, although not mandatory, to operate on the nasal tip first, because it is usually technically more efficient to align and reconstruct the remainder of the nose to dimensions dictated, to a substantial degree, by the projection, size, and attitude of the tip.

The objective of tip surgery is to construct a defined, stable, properly projecting nasal tip, which is roughly triangular on the base view and blends harmoniously with the remainder of the nasal anatomy. Cephalic rotation of the tip during rhinoplasty is usually desirable. In the past, strong emphasis was placed on tissue excision and more radical division of the tip cartilages and supporting structures. Gradually, surgeons have come to realize that improved long-term results occur when the supporting structures of the tip are preserved and more conservative reconstructive techniques of tip sculpture are used.

The surgical anatomy of the nasal tip is extraordinarily varied, a fact that makes tip sculpture difficult but also exciting and challenging. Fig. 36-1 shows this pertinent surgical anatomy and the terms applied to it.

Tip sculpture cannot be successfully undertaken, let alone mastered, until the major and minor tip-support mechanisms are appreciated, respected, and preserved (or, when indicated, reconstructed). Loss of tip support and projection in the postoperative healing period is one of the most common surgical errors in rhinoplasty. This "tip ptosis" is usually the inevitable result of the sacrifice of tip supports (Fig. 36-17).

The major tip support mechanisms consist of (1) the size, shape, and resiliency of the medial and lateral crura; (2) the wrap-around attachment of the medial crural footplates to the caudal end of the quadrangular cartilage; and (3) the soft tissue attachment of the caudal margin of the upper lateral cartilage to the cephalic margin of the alar cartilage (Fig. 36-18). If any or all of these major tip supports are compromised in any fashion during the operation, compensatory reestablishment of major tip support should be considered.

The minor tip-support mechanisms (see Fig. 36-18), which in certain anatomic configurations may assume major support importance, include (1) the dorsal cartilaginous septum; (2) the interdomal ligaments; (3) the membranous septum; (4) the nasal spine; (5) the surrounding skin and soft tissues; and (6) the alar side walls.

Figure 36-17. **A,** The preoperative view of a patient desiring rhinoplasty. **B,** The patient 6 months after surgery performed elsewhere, demonstrating tip ptosis and loss of tip projection caused by excessive sacrifice of tip-support mechanisms.

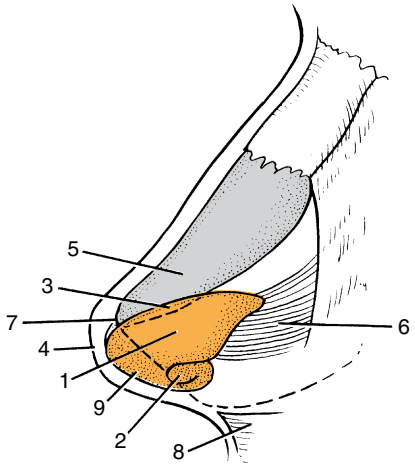

Figure 36-18. Major tip support: 1, Alar cartilage size and shape; 2, medial crural footplate attachment to caudal quadrangular cartilage; 3, upper lateral cartilage attachment to alar cartilage. Minor tip support: 4, Interdomal soft tissue; 5, cartilaginous dorsum; 6, soft tissue-sesamoid complex attaching lateral crus to piriform wall; 7, alar cartilage attachment to skin and soft tissue; 8, nasal spine; 9, membranous septum.

In every rhinoplasty operation the procedure inevitably results in either preservation of the existing tip projection, reduction of projection, or, frequently, enhancement of tip projection. Anatomic situations in which each of these outcomes is desirable and intended are regularly encountered in a diverse rhinoplasty practice. Preservation of the projection already existent is the desirable surgical goal, if, as is true in the majority of rhinoplasty patients, preoperative projection of the tip is satisfactory. Certain patients require an increase in the projection of the tip relative to the intended new profile line. A predictable variety of reliable operative methods exist for creating or augmenting tip projection; they are discussed later in this chapter. Finally, in a limited but clearly definable group of patients with overprojecting tips, a calculated intentional reduction of excessive tip projection is desirable.

Successfully achieving these diverse surgical results requires an understanding of and a healthy respect for the major and minor tip-support mechanisms, seasoned by the recognition of the intraoperative surgical tip dynamic principles that interact in every tip operation. It clearly follows, then, that the appropriate tip incisions and approaches should be planned to preserve as many tip supports as possible. Alar cartilage sculpturing should similarly respect this principle by conserving the volume and integrity of the lateral crus and avoiding, in all but the most extreme anatomic situations, radical excision and sacrifice of tip cartilage.

To understand healing dynamics clearly and to assess and compare results accurately, surgeons should differentiate between incisions, approaches, and techniques. Incisions are simply methods of gaining access to the underlying supportive structures of the nose and by themselves have little importance. Approaches to the nasal tip provide important exposure to the skeletal structures and consist of procedures either to deliver the tip cartilages or to avoid complete delivery. Sculpturing techniques, then, are defined as surgical modifications: excision, reconstruction, or reorientation of the alar cartilages calculated to result in significant changes in the definition, size, orientation, and projection of the nasal tip. The principal incisions, approaches, and techniques used in nasal tip surgery are listed in Fig. 36-19 and Table 36-1. Because of the complexity of anatomic configurations encountered in nasal tip surgery, further modifications are frequently used to ensure further stable refinements.

In assessing the need for tip remodeling, the surgeon must determine whether the tip requires (1) a reduction in the volume of the alar cartilages; (2) a change in the attitude and orientation of the alar cartilages; (3) a change in the projection of the tip; (4) a cephalic rotation with a consequent increase in the columellar inclination (nasolabial angle); (5) a narrowing of the domal angles; (6) a narrowing of the interdomal distance (Box 36-1). Once these factors are accurately assessed, the most favorable incisions, the approach, and the tip-sculpture technique can be chosen (Fig. 36-20).

Ideally, conservative reduction of the volume of the cephalic margin of the lateral crus, preserving the majority of the crus while maintaining a complete (uninterrupted) strip of alar cartilage, is pre-

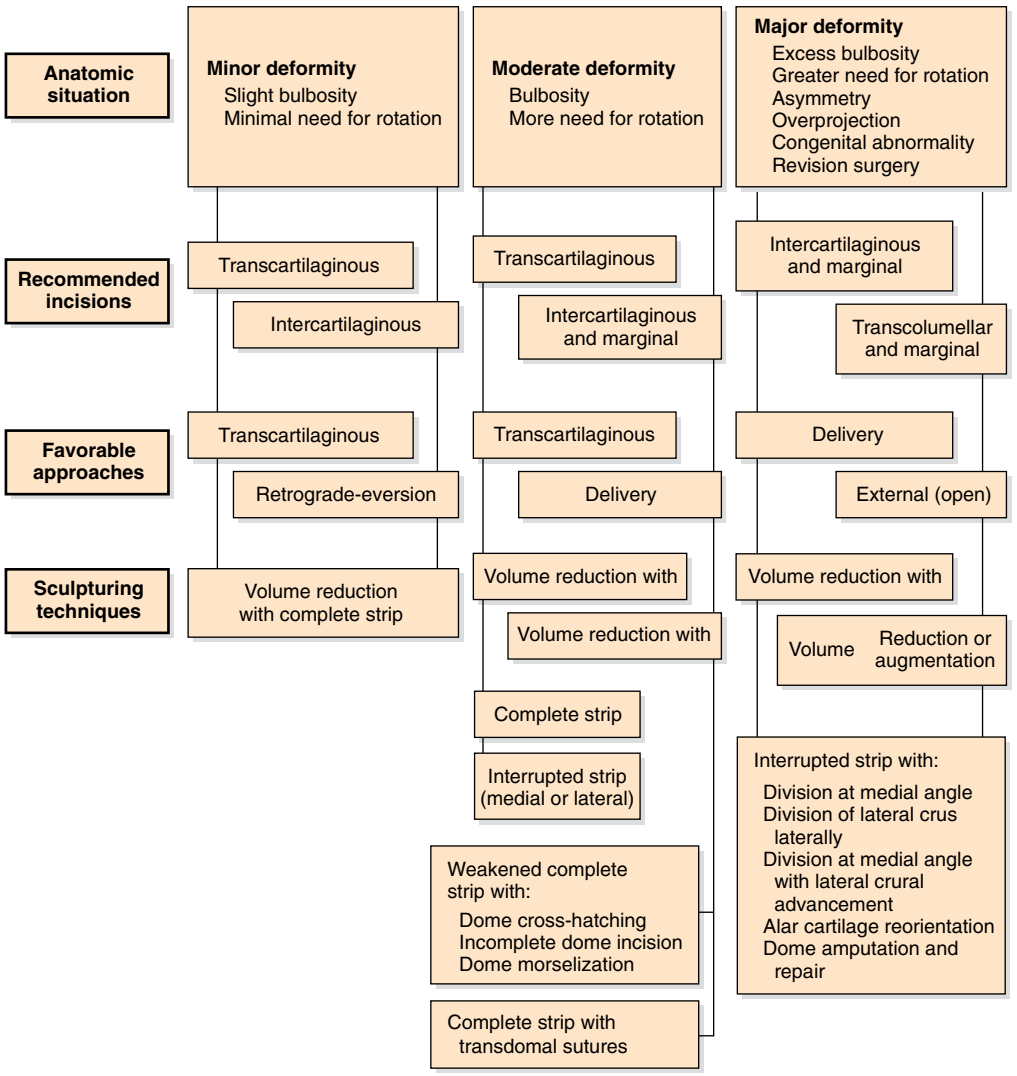

Figure 36-19. Operative algorithm useful in selecting the incisions, approaches, and techniques used in nasal tip surgery. In every case, the patient's anatomy dictates the selection. As the anatomic deformity worsens or becomes more abnormal, a graduated approach is taken in a stepwise fashion to correct the deformity.

Table 36-1

Classification of Surgical Terms

Incisions	Transcartilaginous Intercartilaginous Marginal
Approaches	Delivery Nondelivery Cartilage splitting Retrograde External (open)
Techniques	Volume reduction with: Complete strip Weakened complete strip Interrupted strip

Box 36-1

Possible Indications for Open Approach

Severely twisted nose
Asymmetrical alar cartilages
Transdomal suturing
Tip graft suturing
Augmentation rhinoplasty
Cleft lip or nose complex deformities
Large septal perforation repair
Excision of nasal tumors
Severe tip overprojection/underprojection
Difficult revision rhinoplasty
Infantile nostrils
Teaching

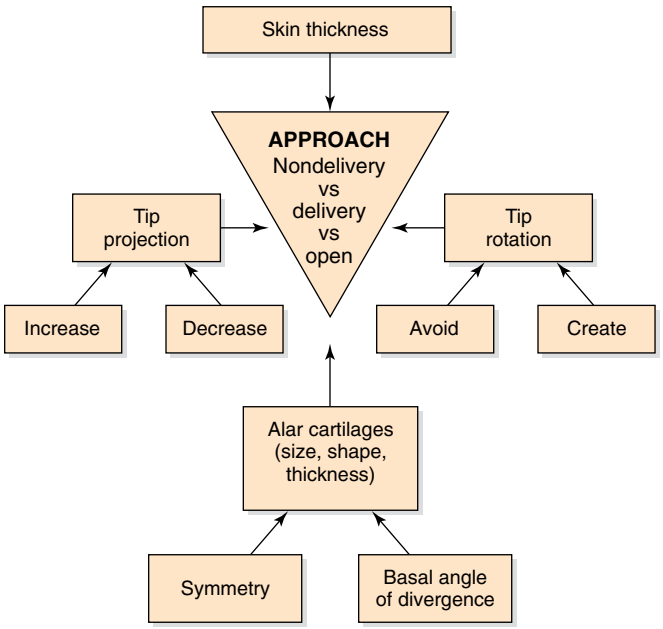

Figure 36-20. Considerations in tip surgery.

Figure 36-21. Preservation of complete strip of alar cartilage after volume reduction is desirable. At least 6 to 10 mm of uninterrupted lateral crus in vertical dimension should be preserved to ensure long-term support and natural contouring. Only in special variant circumstances is the dome divided and subsequently resutured to restore continuity to the crus. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

ferred (Fig. 36-21). This procedure is satisfactory and appropriately safe when minimal conservational tip refinement and rotation are required. As the tip deformity increases in size and complexity, more aggressive techniques are required. A philosophy of a graduated incremental anatomic approach to tip surgery is recommended. This implies that no routine tip procedure is ever used; instead the appropriate incisions, approach, and tip-sculpting technique are selected based entirely on an analysis of the varying anatomy encountered. When possible, a complete strip operation is done, reserving more risky interrupted strip techniques for anatomic situations in which more profound refinement changes and significant rotation are desirable.

Nondelivery Approaches

When the anatomic situation requires conservative or minimal tip refinement and rotation, a nondelivery (cartilage-splitting or retrograde-eversion) approach is preferred (Fig. 36-22). The majority of the lateral crus is left intact as a complete strip, with resection of only a few millimeters of the medial-cephalic portion of the lateral crus to effect refinement. This operation is useful in many patients because it tends to mimic nature; it disturbs very little of the normal anatomy of the tip, and therefore consistently heals predictably, with symmetry and minimal scarring (Figs. 36-23 and 36-24).

Delivery Approaches

As the tip anatomy becomes more abnormal or asymmetric, more complex surgical techniques are gradually used. In these patients, a delivery approach is recommended, allowing visual presentation of the alar cartilages as bipedicle chondrocutaneous flaps for further analysis and reconstruction (Fig. 36-25). Alternatively, an open or external approach may be used. Under direct vision, surgical modifications of varying designs can then be executed symmetrically. Greater volume reduction of the medial portion of the lateral crus is usually necessary, still maintaining a complete strip at least 7 to 9 mm wide (Figs. 36-26 and 36-27). If judged necessary, further refinement in the tip may be safely achieved with single domal, transdomal, and interdomal sutures of 4-0 PDS (polydioxane) or clear nylon sutures (Fig. 36-28). We rely heavily on the reorientation capabilities of suture techniques in tip cartilages because suture techniques provide advantageous long-term narrowing refinement of the tip, as well as an additional benefit of increased support and projection. In patients with extremely thin skin, delicate alar side walls, and bulbous cartilage, predictable narrowing refinement can be achieved by transdomal suturing of the complete strips with horizontal mattress sutures (Figs. 36-29 and 36-30). Narrowing refinement is accomplished, vital tip supports are preserved, and symmetric healing is facilitated (Fig. 36-31). Delivery approaches are indicated almost exclusively when significant defatting or scar resection is required.

In cases of more severe tip deformities, and particularly when marked tip asymmetries, variant deformities, and overprojection exist, the surgeon must consider interrupted strip techniques for maximal results (Figs. 36-32 and 36-33). Here the residual complete strip, after volume reduction of varying degrees, is divided somewhere along its course (usually at or near the angle), excessive portions of the lateral and occasionally the medial crus are removed, and the cartilages are reconstructed so that their cut ends abut or overlap. Inherent dangers (asymmetric healing and scarring) exist whenever the complete strip is interrupted, and some tip support is almost always sacrificed, which may be compensated for by placement of a shoring cartilage strut in the columellar compartment. Interrupted strip techniques tend to foster cephalic tip rotation but are a decided liability if rotation of the tip is contraindicated. Tip rotation can be further accentuated by shortening of the caudal septum and placement of cartilage plumping grafts to efface the nasolabial angle further. When possible, the edges of the interrupted strips are reconstituted with fine suture.

Open Approach

In patients with cleft lip and nose deformities, severely asymmetric tips, and some markedly overprojecting tips with eccentric anatomy, an open (external) approach to the tip may be helpful (Fig. 36-34; see Box 36-1), particularly when the variant anatomy is not clear preoperatively. Although more operative edema and scarring result from this approach, the advantages of precise direct-vision diagnosis, bimanual surgery, and extraordinary exposure render this approach useful in selected patients (Fig. 36-35).

In the open approach, the soft tissues of the nose are elevated off the underlying cartilaginous and bony skeleton to reveal the exact anatomy responsible for the nasal shape. Reduction and augmentation procedures, particularly when adding cartilage grafts to the tip and dorsum, can be effected precisely with suture control. Because both sides of the nose are viewed simultaneously, surgical symmetry can be easily achieved. When markedly variant tip anatomy exists, or when

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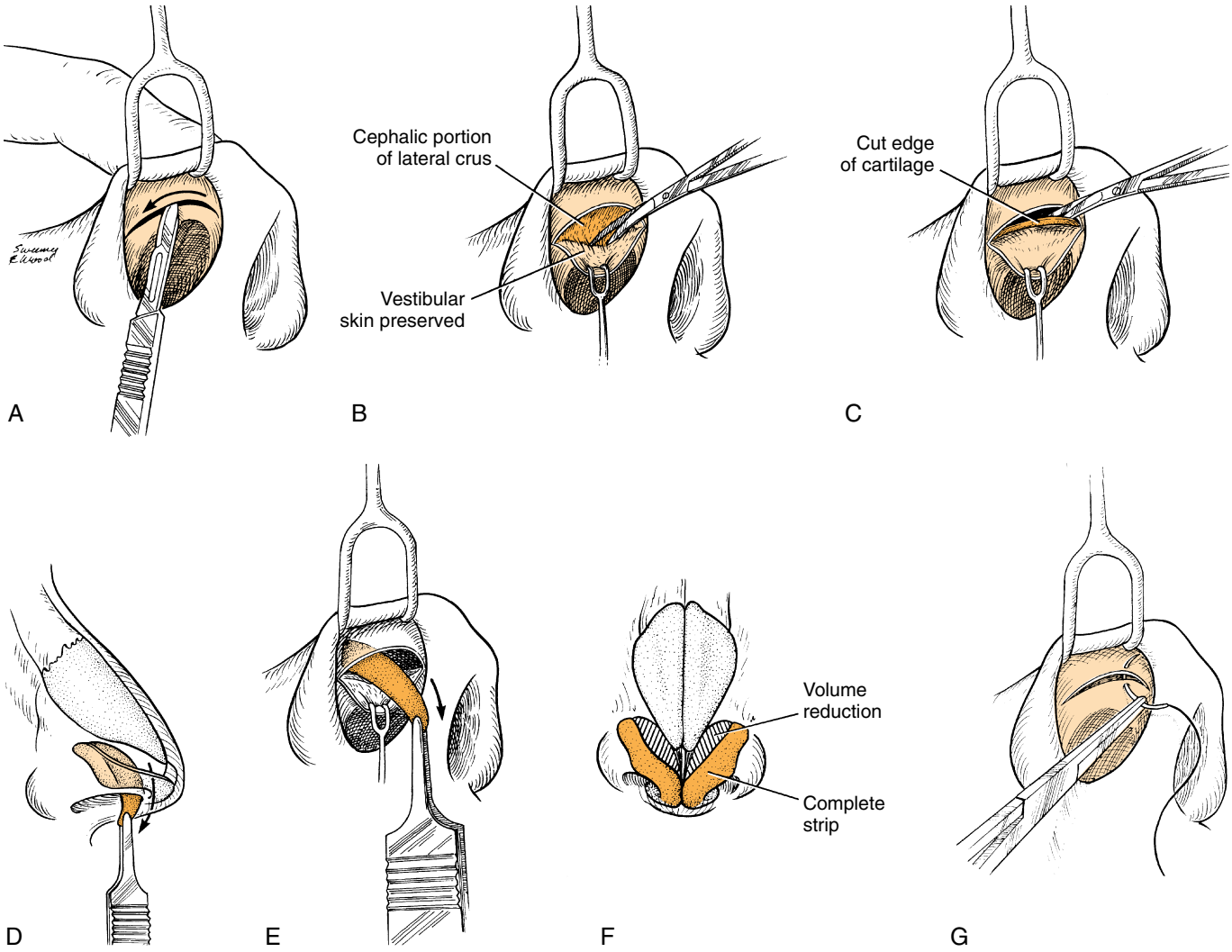

Figure 36-22. Cartilage-splitting (transcartilaginous) nondelivery approach with preservation of a generous, complete strip used on patients demonstrating satisfactory preoperative projection and minimal interdomal distance who require only minimal tip-cartilage modeling. **A,** Single incision through vestibular skin only, made several millimeters cephalic to caudal margin of lower lateral cartilage. **B,** With scissors, vestibular skin is dissected free from a portion of the lower lateral cartilage to be removed. **C,** Mobilization of the cartilage to be excised for volume reduction of lateral crus; a portion of the dome and medial crus are included when indicated. **D,** Medial detachment of the lateral cartilage from the dome area. **E,** Volume reduction of the lower lateral cartilage completed with lateral detachment; a complete strip of intact residual alar cartilage remains. **F,** Final intended result: symmetric volume reduction and refinement of alar cartilages. A generous intact complete strip remains. **G,** Transcartilaginous incision repair with 5-0 chromic catgut.

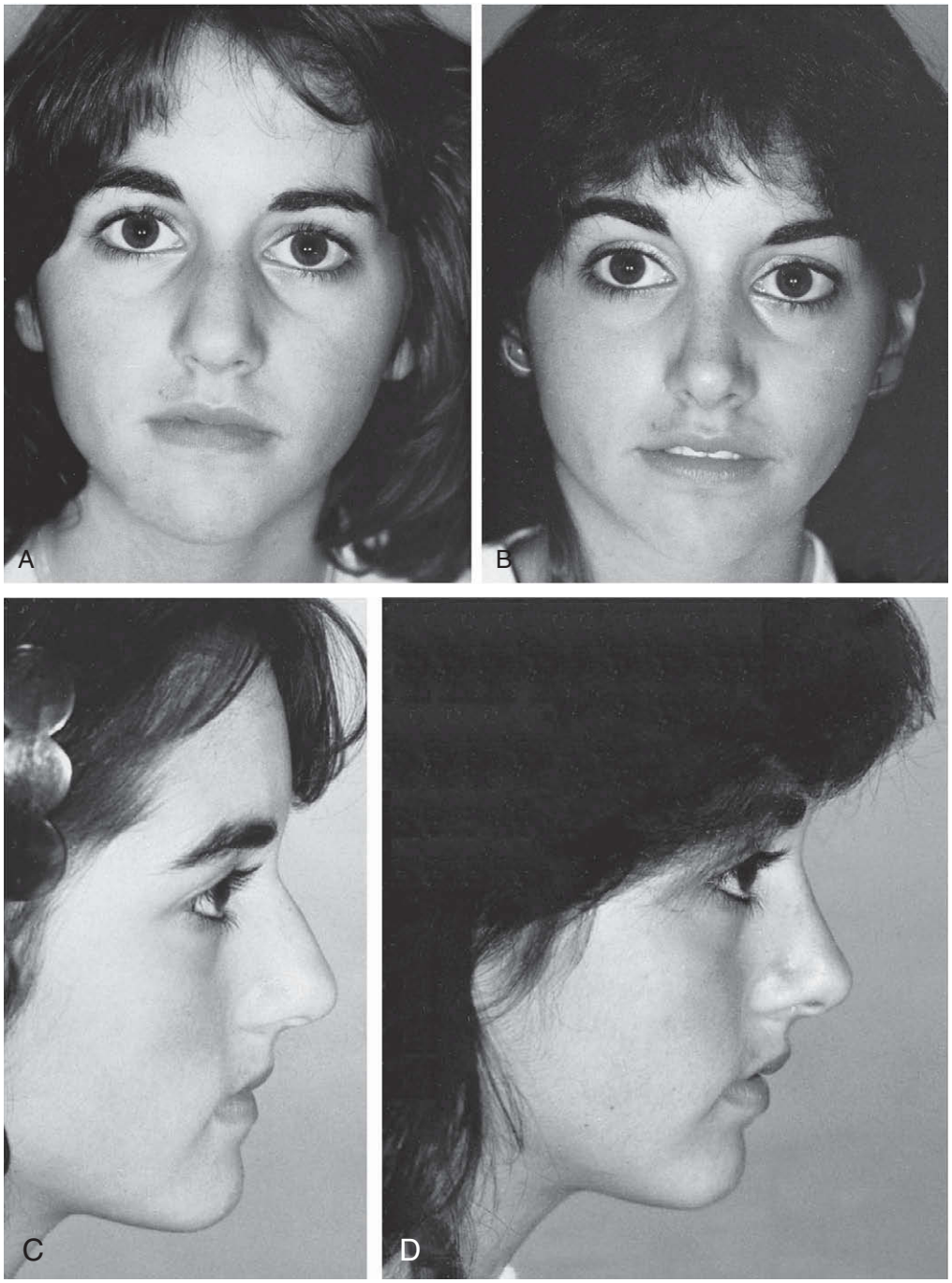

Figure 36-23. One-year surgical result using a transcartilaginous approach with volume reduction, complete strip technique**. A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

Figure 36-23, cont'd.

Figure 36-24. One-year surgical result using transcartilaginous approach with volume reduction, complete strip technique. Addition of chin augmentation enhances the rhinoplasty result. **A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

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Figure 36-24, cont'd.

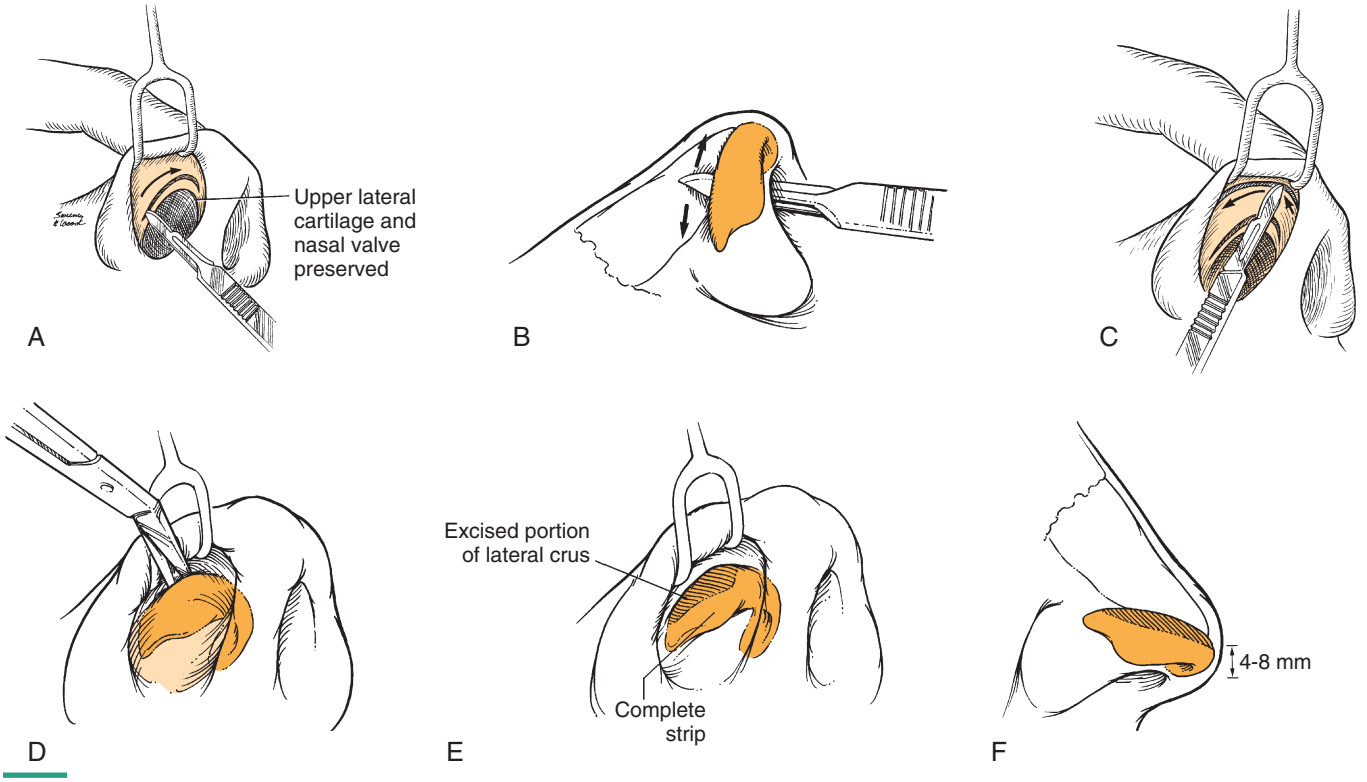

Figure 36-25. Delivery approach to surgery of alar cartilages using intercartilaginous and marginal incisions. Alar cartilages are delivered as individual bipedicle chondrocutaneous flaps for inspection and sculpturing. **A,** Intercartilaginous incision created along and above the projecting rim of the upper lateral cartilage. **B,** Knife elevates skin and soft tissue from the cartilaginous pyramid and septal angle, dissecting in the immediate supraperichondrial plane. **C,** Curved incision created in the vestibular skin precisely at the caudal margin of lower lateral cartilage. **D,** Lateral crus and dome dissected free in preparation of delivery through the nostril for sculpturing refinement. **E,** Cartilage remodeling, conservative excision of a portion of the cephalic margin lateral crus. **F,** Maximal extent of cartilage excision necessary to preserve a strong, intact, complete strip (4-8 mm).

Figure 36-26. Surgical result obtained in patient judged ideal for delivery approach with volume reduction, complete strip technique. **A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

Continued

Figure 36-26, cont'd.

Figure 36-27. Surgical result using delivery approach with volume reduction, complete strip technique. Generous defatting of tip carried out. Note value of chin augmentation to overall facial balance. **A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

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Figure 36-27, cont'd.

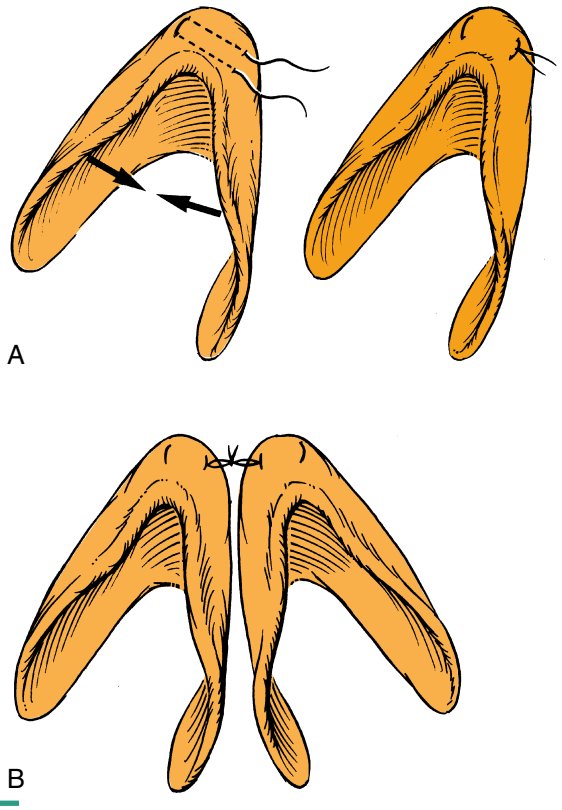

Figure 36-28. To enhance tip refinement further while maintaining tip support, the complete strip can be narrowed at the dome with either single-dome sutures **(A)** or by employing a horizontal mattress suture to narrow the interdomal distance **(B).** *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

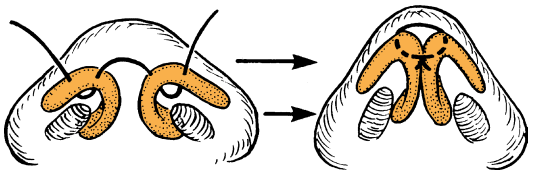

Figure 36-29. Narrowing refinement of nasal tip in patients with delicate cartilages and thin skin can be effectively accomplished with one or more 4-0 clear nylon transdomal sutures. Suture passes through both medial and lateral crus on either side and is "test-tightened" before final securing to ensure proper suture placement and symmetric narrowing. A modest increase in projection and significant refinement of the trapezoidal tip can be realized, if desired, with transdermal suture narrowing.

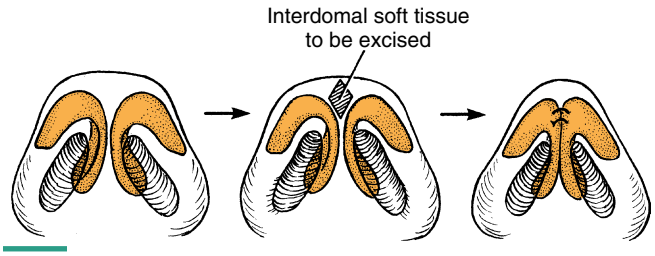

Figure 36-30. Interdomal suturing of medial crura for modest narrowing.

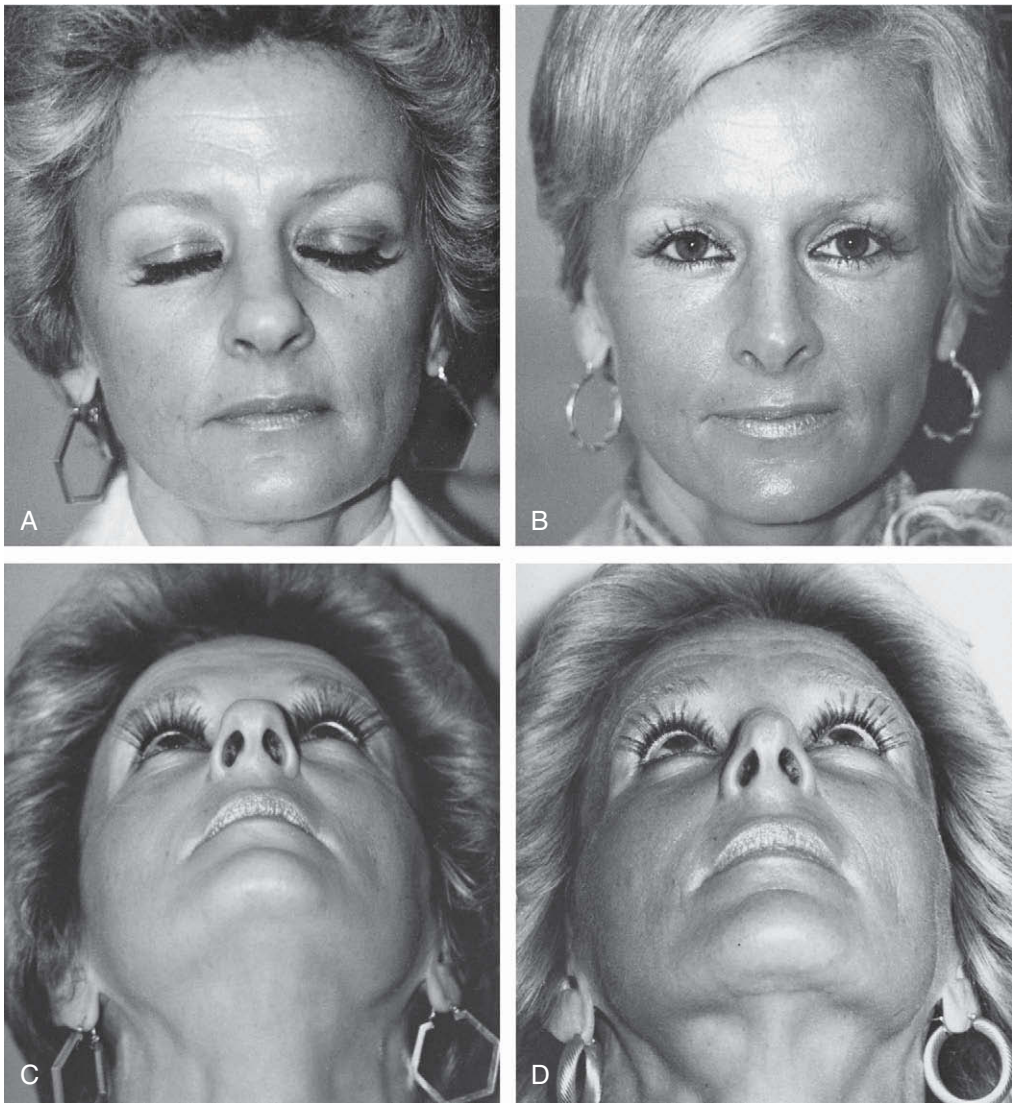

Figure 36-31. Two-year surgical result in patient suitable for transdomal suture narrowing of nasal tip. Minimal volume reduction carried out, maintaining generous complete strip. Note permanent change from trapezoidal tip to more desirable triangular configuration. **A** and **C,** Preoperative views. **B** and **D,** Postoperative views.

Figure 36-32. Significant narrowing refinement obtained through the use of volume reduction, interrupted-strip technique with suture reconstitution of interrupted strip. Thick skin and subcutaneous tissue allows vertical interruption of complete strip at the angle between the medial and lateral crus. **A** and **C,** Preoperative views. **B** and **D,** Postoperative views.

Figure 36-33. Interrupted-strip technique chosen for patient with bulky cartilages, thick skin, and a need for modest tip rotation. **A** and **C,** Preoperative views**. B** and **D,** Postoperative views.

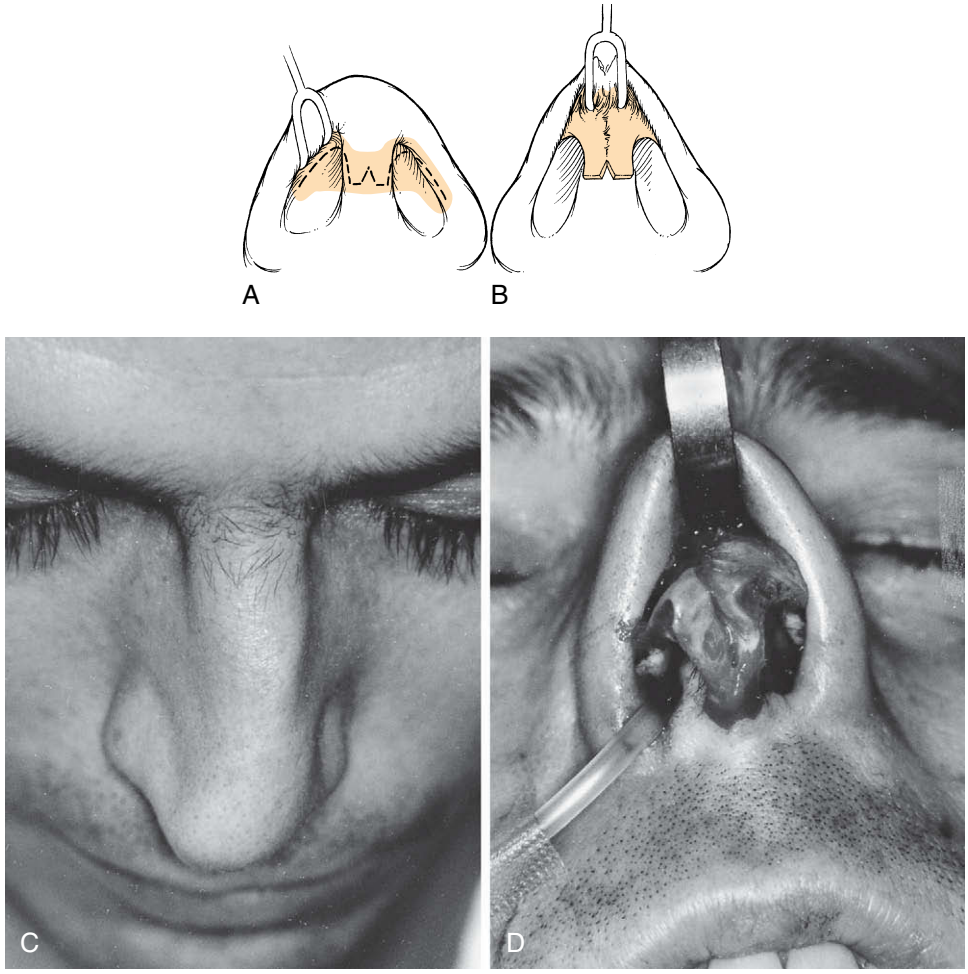

Figure 36-34. **A,** Incision used for open (external) approach to nasal tip. **B,** Exposure of nasal tip anatomy through open approach. **C,** Dorsal view of nose characterized by asymmetric nasal tip, demonstrating convex left lateral crus and concave right lateral crus. **D,** View, through open approach, of asymmetric, twisted, and unequal lateral cartilages.

Figure 36-35. Refinement of nasal tip combined with cartilage graft augmentation of collapsed nose through open approach; result after 3 years. **A, C,** and **E,** Preoperative views. **B, D,** and **F,** Postoperative views.

Figure 36-35, cont'd.

extensive middle vault reconstruction is necessary, the open approach facilitates favorable reconstruction.

Tip Projection

A final critical decision in undertaking nasal tip surgery involves the need for preservation, enhancement, or reduction of existing tip projection. Because most patients undergoing a rhinoplasty demonstrate satisfactory projection, it becomes the surgeon's responsibility to ensure that the major and minor tip supports are left largely intact (or reconstructed) to prevent an eventual loss of projection. Complete strip techniques are therefore recommended whenever feasible, avoiding the complete transfixion incision, which destroys the vital support provided by the medial crural overlap of the caudal septum (Fig. 36-36). If additional projection is required, it can be achieved in a variety of ways. Autogenous cartilage struts positioned below or between the medial crura (Figs. 36-37 and 36-38) are effective in establishing permanent support and projection. Plumping grafts of cartilage fragments, introduced into the base of the columella through a low lateral columellar incision (Fig. 36-39), provide an additional platform for the tip projection resulting from the strut. Cartilage struts should be shaped with a gentle curve to match the anatomy of the curved columella, at times aiding in the creation of a distinct "double break," but should never extend to the apex of the tip skin lest a visible tent-pole appearance develop. If the medial crural footplates diverge in a widely splayed fashion, further tip projection can be gained by resecting excessive intercrural soft tissue and suturing the medial crura together. Height and contour can be added to the tip with autogenous cartilage grafts from the nasal septum or auricular cartilage (Fig. 36-40). Because these grafts lie immediately subcutaneously, intimately subjacent to the skin, great care must be taken in their position-

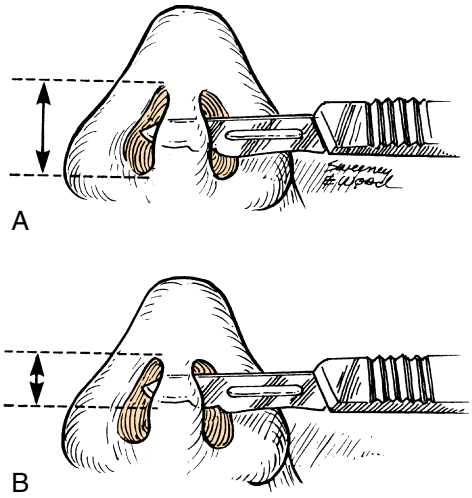

Figure 36-36. Partial-transfixion incisions are always preferable to complete-transfixion incisions, although not always feasible. Preserving medial crural footplate attachment to caudal septum maintains one vital tip-support mechanism. **A,** Complete-transfixion incision, which sacrifices medial crural footplate attachment to the septum. **B,** Partial-transfixion incision, which preserves medial crural footplate attachment to the septum.

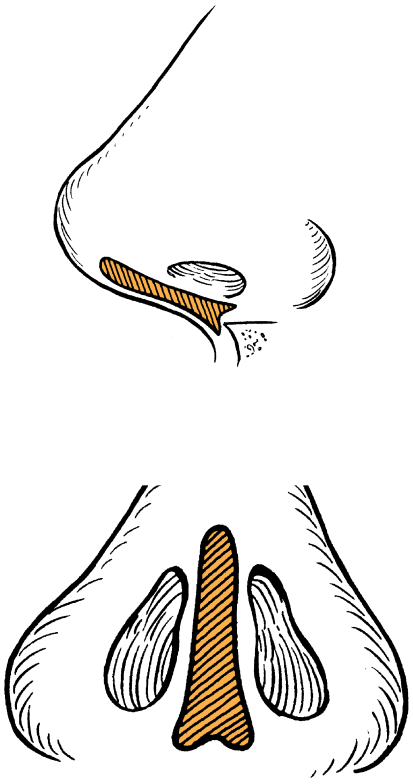

Figure 36-37. Position of cartilaginous strut between the medial crura, creating supportive influence on nasal tip support and projection.

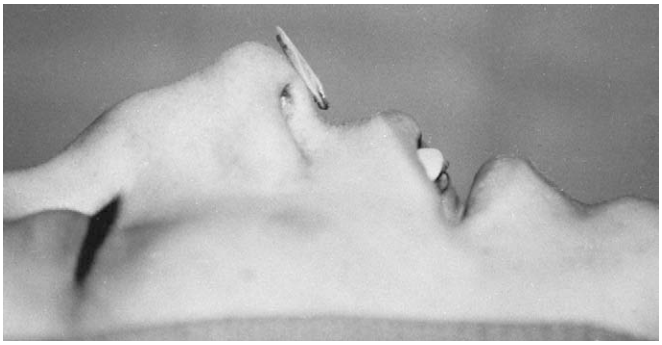

Figure 36-38. Autogenous cartilaginous strut, fashioned from nasal septum, about to be placed in precise columellar pocket.

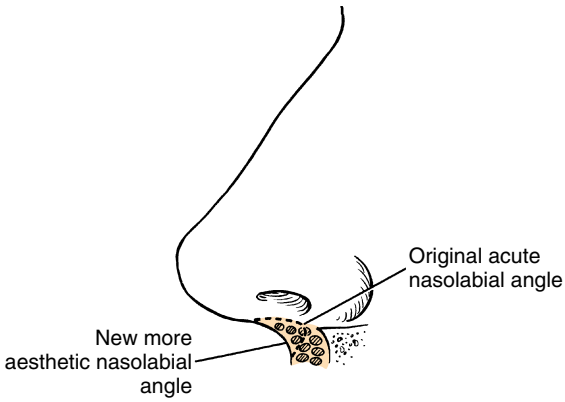

Figure 36-39. Plumping grafts of autogenous cartilage, effective in lending support to an otherwise weak tip and in effacing an acute or retracted nasolabial angle.

ing. An exacting "pocket preparation" becomes a basic prerequisite for their use; that is, a pocket is fashioned into which the graft fits as precisely as a hand in a glove. Carved in a triangular, trapezoidal, or shield-like shape, tip grafts may accentuate favorable tip-defining points and highlights and can succeed in giving a more normal appearance to tips with congenital or postsurgical inadequacies (Fig. 36-41). For modest tip projection and symmetry improvement, cartilage tip grafts can be effectively placed, through limited marginal incisions, and precisely fashioned in the infratip lobule. When more major tip projection and contouring is in order, tip grafts are best suture-fixated to the intermediate crura.

Cephalic rotation of the tip can increase projection by advancing the lateral crura medially and suturing them to lie above the cut ends of the medial crura. Transdomal sutures properly positioned between two complete alar cartilage strips can result in additional projection of the tip.

It should be appreciated, then, that nasal tip surgery is a compromise in which the surgeon gives away something to achieve a narrower, more defined, and stable tip component of the nose. Years of experience are required to understand and master tip surgery techniques thoroughly. Along with this invaluable insight, emphasis should always be placed on conserving tip anatomic structures and avoiding both radical excision and sacrifice of tip tissue. Compulsive long-term follow-up and evaluation of patients both by frequent examination and by review of standardized, uniform photographs facilitates the development of expertise in nasal tip surgical refinement.

Surgery of the Cartilaginous Vault

The dorsal surface of the quadrangular cartilage and its related upper lateral cartilages comprise the cartilaginous vault. Ordinarily, a new relationship should be established between the tip and the profile line. Reduction of the supratip area to a level that allows the leading edge of the tip to exist 1 to 2 mm above the cartilaginous profile is the usual aesthetic goal. Making this new relationship permanent requires that tip projection, whether preexistent or the consequence of tip surgery, be stable and lasting. Tip surgery, then, is usually performed at the outset of the operation, unless a significant overgrowth of the dorsal septum has created an anatomic variant in which this normally minor

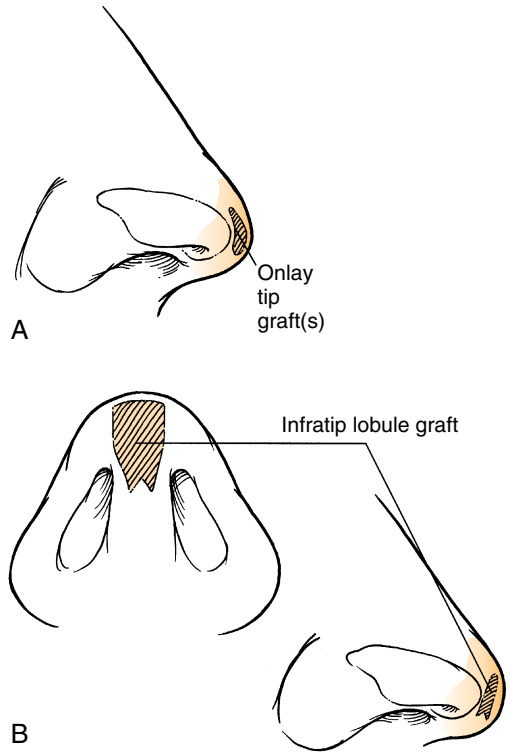

Figure 36-40. **A,** Onlay tip cartilage grafts, frequently used to enhance tip projection and contour nasal tip. **B,** Cartilage grafts, precisely positioned in infratip lobule area, enhance tip projection and aid in contouring tip anatomy. The size, shape, and length of the tip can be altered to achieve a variety of favorable aesthetic contours. Grafts can be sutured in place for greater stability when using either the open or the delivery approach.

tip-support mechanism is giving greater support thrust to the tip projection "tension nose." In this latter circumstance, reduction alignment of the supratip area to eliminate this spurious support precedes tip surgery, thereby allowing more accurate evaluation of the true magnitude of normal tip-support mechanisms.

Aesthetics are best served when reduction in both the cartilaginous and bony vaults results in a relatively strong, high, and straight-line profile in men (Fig. 36-42), with the leading edge of the tip just slightly higher in women (Fig. 36-43). In the latter circumstance, a gentle slope of about 2 to 3 mm should exist between the tip-defining point and the lower extent of the cartilaginous profile. (In the final analysis, however, the "ideal" profile consists of what makes each patient content and happy.) In planning a profile alignment, the two stable reference points are the nasofrontal angle (located ideally at the level of the upper eyelid) and the tip-defining point. Reversal of the usual tip-supratip relationship (in which the supratip cartilaginous dorsum lies variably higher than the tip) is required to achieve this aesthetic ideal.

It can be appreciated, then, that the degree and angulation of hump removal depend on a variety of factors, some of which are under the control of the surgeon and some of which are not. These factors include skin thickness, the amount of bony hump relative to cartilaginous hump, the relative width of the nose, the inclination of the nasal tip, and, equally important, the patient's wishes regarding the desired nasal profile. In the final analysis, it is the surgeon's ability to visualize the final appearance of the nose after approximately 12 to 18 months of healing that allows exact and precise profile alignment.

Because the thickness of the overlying skin differs from that of soft tissues (thinner overlying the rhinion and thicker in the supratip area), it follows that a straight-line removal of both cartilaginous and bony hump may result in overreduction and an unsatisfactory final profile. To accommodate this tissue thickness differential, an initial controlled incremental reduction of the cartilaginous dorsum under direct vision is preferred.

Access to the nasal skeleton is gained by elevation of the soft tissues over the cartilaginous vault by knife dissection in the precise tissue plane that is intimate to the perichondrium enveloping the upper lateral

Figure 36-41. Revision rhinoplasty patient whose appearance is enhanced and normalized with addition of nasal tip grafts as well as onlay cartilage grafts augmenting overreduced nasal dorsum. **A,** Preoperative view. **B,** Postoperative view.

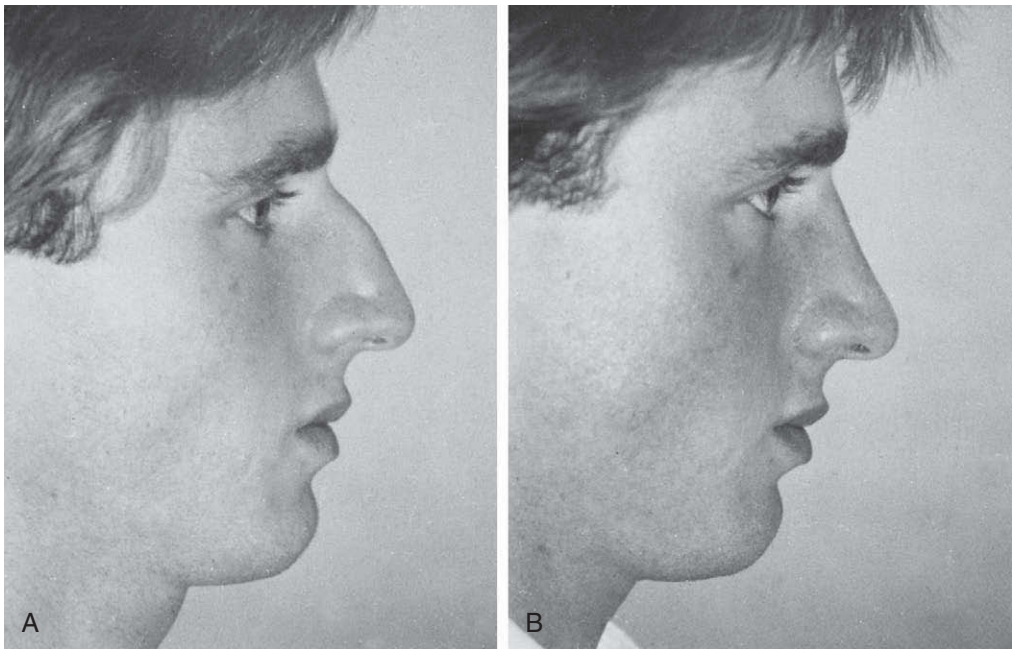

Figure 36-42. **A,** Unsatisfactory male nasal profile aligned to normalize nasal proportions and improve overall facial balance and aesthetics. **B,** Straight nasal profile with strong, high dorsum provides a highly desirable appearance.

Figure 36-43. Desirable female profile remains strong with a high dorsum, but generally is enhanced when nasal tip projection leads supratip profile by 2 to 3 mm. In addition, slightly more open nasolabial profile is desirable, accompanied by subtle columellar "double-break" configuration.

cartilages and the cartilaginous dorsum (Fig. 36-44). Respecting and using this tissue plane prevents unnecessary trauma to the more superficially located blood vessels and sensory nerves, resulting in significantly less bleeding and a reduction in the healing scar. Access to the bony vault is continued by elevation of the periosteum over the nasal bones with the Joseph elevator (see Fig. 36-44B), thereby exposing the entire bony-cartilaginous skeleton of the nose for inspection and direct-vision surgery. Excellent exposure can be gained during these technical maneuvers simply by carrying the medial extent of the transcartilaginous or intercartilaginous incision 4 to 6 mm around the anterior septal angle—the partial transfixion incision. The vital support relationship of the medial crural attachment to the caudal margin of the septum is thereby preserved by avoiding the more traditional complete transfixion incision.

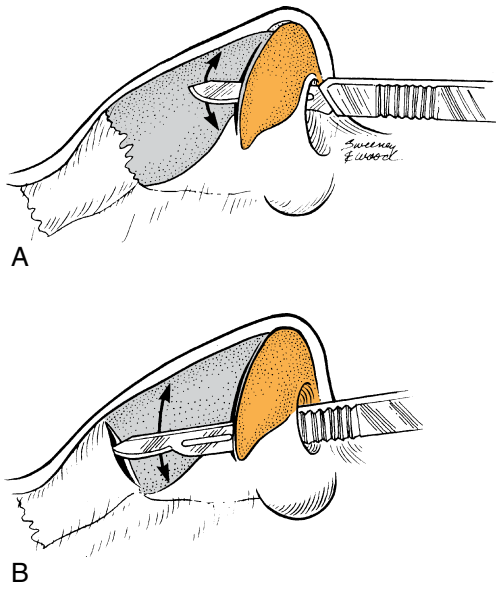

Figure 36-44. **A,** Sharp knife elevation of soft tissues over cartilaginous dorsum should be accomplished in the favorable tissue plane intimate to the cartilaginous pyramid to reduce scarring and bleeding. **B,** Elevation of the periosteum with a knife initially followed by a Joseph periosteal elevator finalizes décollement of nasal soft tissues. Inclusion of periosteum in skin flap creates additional thickness of the covering skin mantle, cushioning and camouflaging any possible irregularities in bony healing.

With the Converse retractor in place, excellent exposure of the nasal dorsum is achieved, visualized best with intense fiberoptic headlamp. The stage is thus set for incremental cartilaginous profile alignment. A knife is positioned at the osseocartilaginous junction and drawn lightly down to the anterior septal angle to allow any remaining soft tissue fibers to fall laterally, exposing the blue-white underlying cartilage clearly. Under direct vision, with the knife blade at precise right angles to the cartilaginous dorsum (quadrangular cartilage and upper lateral cartilages combined), the cartilaginous dorsum components are shaved away smoothly (see Fig. 36-14). How thick a strip (1 to 3 mm) depends on the amount of supratip reduction required to establish the new satisfactory tip-supratip relationship. After each increment is removed, the profile is inspected and palpated to ensure smoothness and a properly developing relationship to the tip. It may be helpful to depress the tip toward the lip from time to time to determine the precise degree of cartilaginous reduction. Failure to reduce this supratip in relation to the ultimate tip projection is a common error, leading to a displeasing tip-supratip relationship, or worse, a cartilaginous pollybeak deformity requiring revision surgery (Fig. 36-45).

In the typical rhinoplasty procedure, the upper lateral cartilages are involved in surgical reduction only as a consequence of their intimate attachment as the wings of the quadrangular cartilage. As this reduction progresses, the underlying bridge of mucoperichondrium stabilizing the upper laterals to the septum may be exposed. This vital portion of the nasal lining contributes significantly to the internal nasal valve and is best left undisturbed and undivided. By gently teasing the mucoperichondrium away from the cartilages, further cartilaginous reduction can be accomplished, if necessary, without jeopardizing the mucoperichondrium to be preserved. Occasionally, the caudal margin

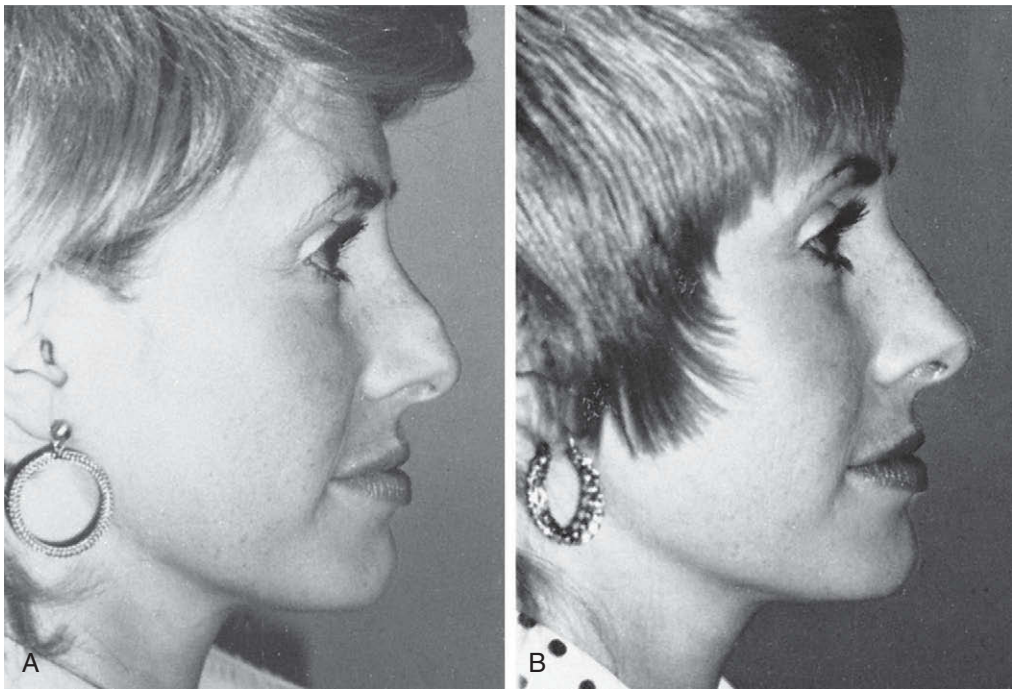

Figure 36-45. Postoperative stigma of cartilaginous "pollybeak" deformity results from inaccurate alignment or inadequate reduction of the cartilaginous pyramid. **A,** Preoperative view. **B,** Postoperative view.

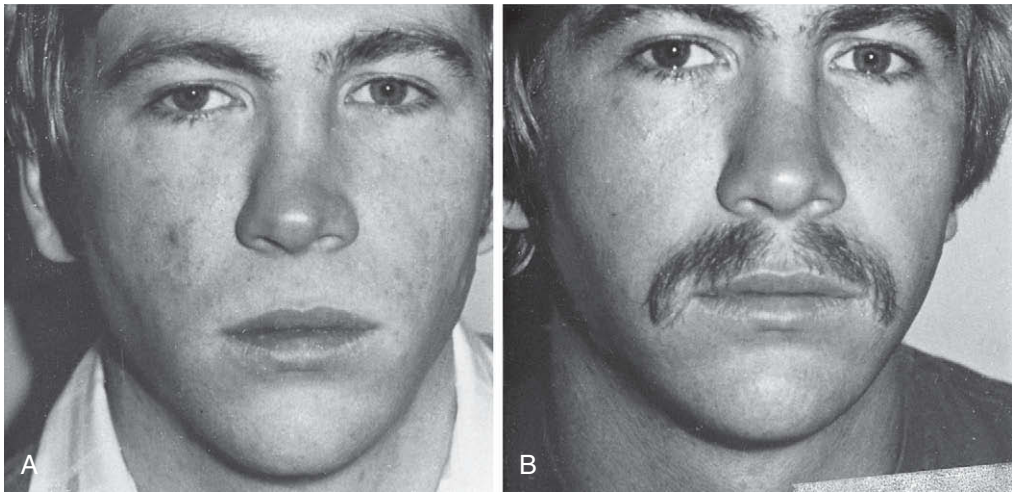

Figure 36-46. **A,** Traumatic or iatrogenic avulsion of upper lateral cartilage from undersurface of nasal bones constitutes serious aesthetic and often functional deficiencies. Once airway integrity is ensured, appearance improvement is best accomplished with thin cartilage autografts **(B).**

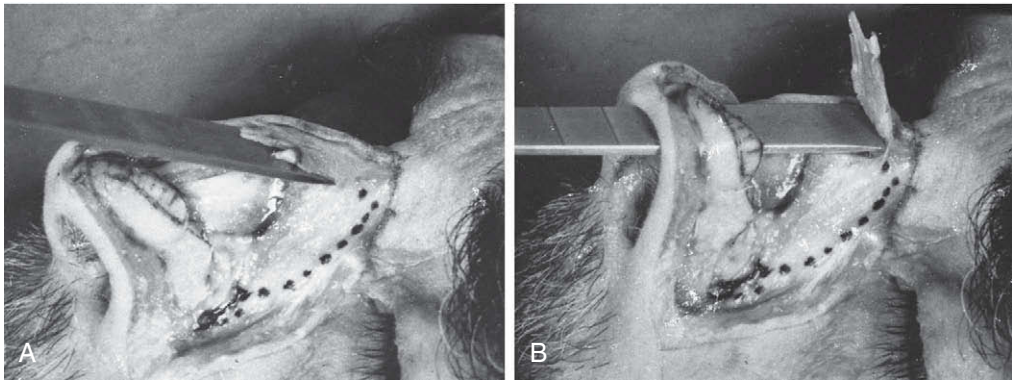

Figure 36-47. **A,** Rubin osteotome seated at the osseocartilaginous junction (caudal end of the bony hump) in preparation for bony profile alignment. **B,** Bony hump removed symmetrically. Precision in alignment is significantly aided by vertical fin on handle of Rubin osteotome, which prevents misalignment or unwanted rotation during cephalic progression of the instrument.

of the upper lateral cartilage, in its anatomic relationship to the cephalic margin of the alar cartilage, demonstrates a scroll-like appearance. If this redundancy of cartilage contributes to excessive thickness in the middle third of the nose on frontal and oblique views, it can be resected. Except in the abnormally long, drooping nose, the length of the upper lateral cartilages plays a small role in overall nasal length and ordinarily requires no significant shortening. Of vital importance, however, is the underlapping attachment of the upper lateral cartilages to the undersurface of the nasal bones. If this critical supportive relationship is avulsed by surgical or nonsurgical trauma, repair is extremely difficult, a typical depressed-contour deformity results, and the ipsilateral airway may be compromised. Repair is often best effected by an onlay cartilage autograft (Fig. 36-46).

Alignment of the cartilaginous profile initially generates several significant advantages. The tip-supratip relationship is established with precision, undesirable overreduction or underreduction is easily prevented, and the exact amount of bony hump to be removed or reduced is clearly apparent.

Surgery of the Bony Vault

Bony Profile Reduction

With the tip-supratip relationship satisfactorily established, the exact degree of bony hump excess is readily apparent (see Fig. 36-38). If minimal bone requires removal to establish the predetermined desired profile, the sharp tungsten-carbide down-cutting rasp facilitates a rapid and minimally traumatic reduction. Even less trauma is created from initial hump removal by the small Rubin osteotome, sharpened to razor edge; a sharpening stone is kept on the operating table setup, allowing the critical edge on each osteotome to be honed just before its use.

As previously described, only enough periosteum to allow removal of the bony hump is elevated over the bony dorsum. Preserving the periosteum and soft tissue attachment overlying the nasal bones and maxillary ascending processes laterally reduces trauma and bleeding and, more importantly, stabilizes the mobile bony side walls after all infractures are complete.

The Rubin osteotome is seated at the caudal end of the bony hump and aligned and positioned to effect removal of only that amount of bone desired to leave a high, strong profile line (Fig. 36-47). Conservatism is most important here because any further bony refinement can be further accomplished with the rasp. Progressive taps with the sound-deadened mallet force the sharp osteotome precisely through the thick nasal bones as guided by the surgeon. The vertical fin located on the handle of the Rubin osteotome serves admirably to allow exact surgical control in aligning the instrument.

The detached bony fragment is then removed and inspected for asymmetries, which can provide the surgeon with clues about the need for further selective bony reduction. If irregularities of the bone persist, several methods may be useful for achieving absolute smoothness. If one cut edge of nasal bone requires further reduction, it can be lowered by shaving with the sharp, thin osteotome, trimmed under direct vision

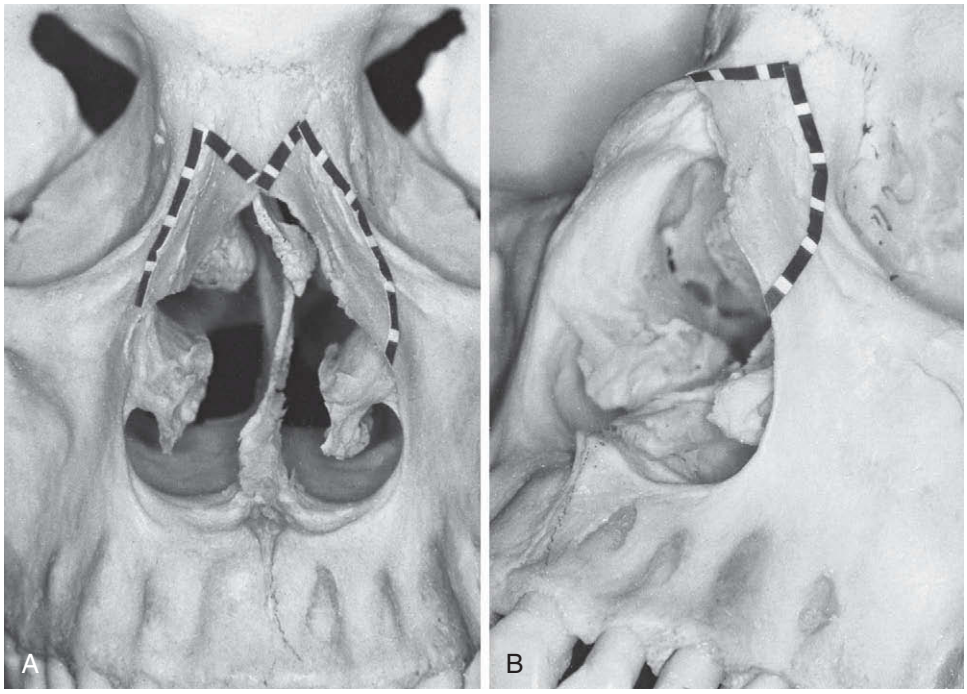

Figure 36-48. **A,** Medial-oblique osteotomy is helpful, particularly in patients with heavy or previously fractured nasal bones, in creating significant and atraumatic narrowing and straightening of bony pyramid. Osteotomy pathway is directed 15 to 20 degrees away from midline; at its most cephalic extent it establishes bony weakness, which dictates the exact point of bony infraction from lateral osteotomies in majority of operations. **B,** Site and direction of medial-oblique and low lateral osteotomy.

with the strong double-action Becker scissors, or smoothed with the down-cutting rasp.

Before final finishing and smoothing of the bony dorsum are carried out with the rasp, it is useful to inspect the relative height of the upper lateral cartilages, trimming them under direct vision to lie at the same level or just below the level of the cartilaginous dorsum. This step is considered to be important at this stage of the procedure because upper laterals that remain too high above the cartilaginous dorsum can be caught in the teeth of the rasp, risking avulsion or displacement—a difficult complication to repair.

The nasal profile must then be critically assessed by the surgeon. The final profile must not only be aesthetically pleasing but absolutely smooth and free of irregularities. Otherwise, displeasing contour irregularities can develop months and even several years later, particularly in the relatively thin-skinned patient. Several techniques are helpful in assessing profile smoothness before completing the bony profile alignment with a finishing rasp. Palpation of the dorsum through the skin with a wet finger reveals irregularities not otherwise detectable with routine palpation. Tensing the skin over the dorsum during palpation facilitates evaluation. During internal visualization of the bony-cartilaginous dorsum, palpating the dorsum with the noncutting edge of the No. 15 Bard-Parker knife blade often allows discovery of minute irregularities that are frequently inapparent to the most critical eye. If redundant soft tissue exists beneath the skin either medially or laterally, it can be conservatively excised at this point.

Final finishing of the bony dorsum is effected with the delicate tungsten-carbide rasp, an instrument that retains its extreme sharpness for long periods without significant detectable dulling. The down-cutting rasp is preferred, preventing trauma to the soft tissues in the nasofrontal area. The rasp should be pulled firmly and obliquely down the bony dorsum, cutting bone with each stroke and eliminating excessive, overly traumatic to-and-from motions. All the products of rasping (bone fragments and "sawdust") must be removed by suction to prevent later irregularities.

If overaggressive hump removal occurs as the result of a misdirected osteotome, several remedies are available. The excised bony hump can be replaced after reduction in size and removal of all attached mucosa. Splinted in place, this bone graft can be used to reconstruct an overreduced dorsum satisfactorily. More delicate realignment of the dorsum's irregularities (bony or cartilaginous) can be satisfactorily reconstructed with autogenous cartilage grafts from the septum, alar cartilage remnants, or auricular cartilage autografts. Reconstruction with alloplastic implants is not always recommended because autogenous tissues are always preferable in the nose.

Narrowing the Nose: Osteotomies

Profile alignment in the typical reduction rhinoplasty inevitably results in an excessive plateau-like width of the nasal dorsum, which requires narrowing of the bony vault for a normal, natural appearance when the patient is viewed from the front. To accomplish this narrowing, the lateral bony side walls (consisting of the nasal bones and the maxillary ascending processes) should be mobilized and moved medially. The upper lateral cartilages are also moved medially because of their stable attachment to the undersurface of the nasal bones.

The stage is set for precision narrowing by medial-oblique osteotomies. A 2- to 3-mm delicate, sharp microosteotome is seated at the superior extent of the bony hump removal on either side of the bony septum and advanced cephalically and obliquely at an angle of 15 to 20 degrees outward (Fig. 36-48). Little trauma results from these medial-oblique osteotomies, which create a predetermined weakness or dehiscence at which the ultimate back-fracture occurs from the lateral osteotomies. This represents a safety factor in the osteotomy procedure, preventing the ever-present possibility of eccentric or asymmetric surgical fractures developing when only lateral osteotomies are performed. In addition, bony narrowing occurs without necessitating strong pressure to be exerted on the nasal bones to accomplish infraction, a traditional but unnecessarily traumatic maneuver.

Lateral osteotomies are reserved for last in a rhinoplasty because they may be more traumatic than the steps previously accomplished. Additional tip refinement, septal reconstruction, or alar base reduction surgery—if indicated—is completed before the lateral osteotomies are initiated.

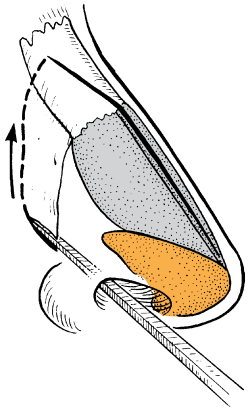

Figure 36-49. Low lateral osteotomy is initiated at the piriform aperture at or just above attachment of the inferior concha to the ascending process of maxilla. No incision is required for 2- or 3-mm osteotome.

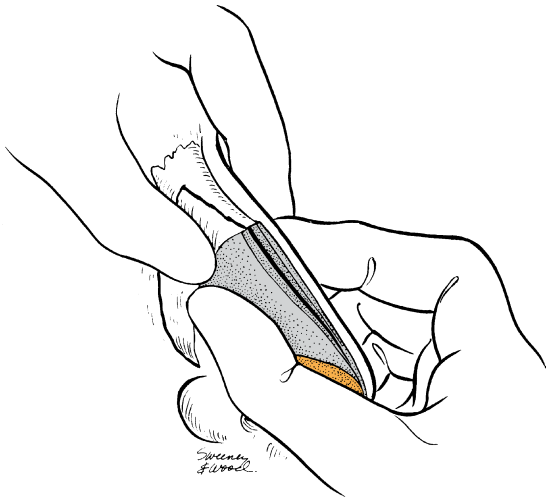

Figure 36-50. After intersection of the low lateral osteotomy with the cephalic extent of the medial-oblique osteotomy, infraction and narrowing of the bony pyramid is ordinarily accomplished easily with gentle medial finger pressure. In young patients, complete fractures with total mobilization of the bony pyramid is desirable. Less mobilization and even so-called greenstick fractures may be acceptable in older adult patients. Gentle pressure held over the lateral osteotomy site until final splint application is effective in reducing edema and potential ecchymosis.

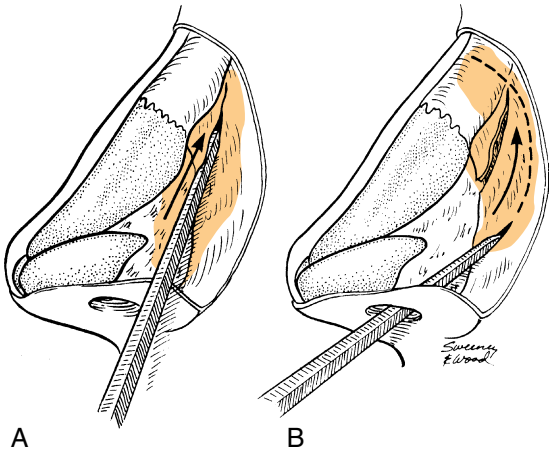

Figure 36-51. A, Intermediate higher lateral osteotomies may be required in patients with extreme asymmetry of bony side walls; only by their use can complete and adequate mobilization be satisfactorily accomplished. **B,** The intermediate osteotomies must always be carried out before lower lateral osteotomies are completed.

Trauma can be significantly reduced in lateral osteotomies if 2- or 3-mm microosteotomes are used to accomplish a controlled fracture of the bony side walls. No need exists for elevation of the periosteum along the pathway of the lateral fractures because the small osteotomes require little space for their cephalic progression. Appropriately, the intact periosteum stabilizes and internally splints the complete fractures, facilitating stable and precise healing. The low-curved lateral osteotomy is initiated by pressing the sharp osteotome through the vestibule skin to encounter the margin of the piriform aperture at or just above the inferior turbinate (Fig. 36-49). This preserves the bony side wall along the floor of the nose (where narrowing would achieve no favorable aesthetic improvement), but might compromise the lower nasal airway without purpose. The pathway of the osteotomy then progresses toward the face of the maxilla, curving next up along the nasomaxillary junction to encounter the previously created small medial-oblique osteotomy. A complete, controlled, and atraumatic fracture of the bony side wall is thus created, allowing infraction without excessively traumatic pressure (Fig. 36-50). Immediate finger pressure is applied bilaterally over the lateral osteotomy sites to forestall further any extravasation of blood into the soft tissues. In reality, little or no bleeding occurs during microosteotomies because the soft tissues embracing the bony side walls remain essentially undamaged.

After infraction, the dorsum is again palpated and inspected for any irregularities; if they exist, they are corrected under direct vision. The upper lateral cartilages are viewed to ensure that their relationship to the height of the septum is appropriate.

The fracture line of the lateral osteotomy should be as low as possible to allow a large lateral wall for infraction and to prevent the palpable step deformity that results when osteotomies are positioned too high on the nasal side wall (nearer the dorsum). The bones should ideally be freely mobile but splinted by the undisturbed periosteum and soft tissues that remain attached to the bony fragments.

When the nasal bony side walls are twisted, asymmetric, or markedly irregular, further osteotomies may be required higher on the ascending process to achieve correction (Figs. 36-51 and 36-52).

Postsurgical Considerations

The care of a patient after rhinoplasty is directed toward patient comfort, reduction of swelling and edema, patency of the nasal airway, and splint compression with stabilization of the nose.

A detailed list of instructions is supplied for the patient or accompanying family member; the important aspects of these "do's" and "don'ts" are emphasized. Prevention of trauma to the nose is clearly the most important consideration. Oral decongestant therapy is helpful, but the value of corticosteroids and antibiotics in a routine rhinoplasty is conjectural.

The external splint is removed by the surgeon or surgical nurse 5 to 7 days after surgery. An important consideration should be the gentle removal of the tape and splint by bluntly dissecting the nasal skin from the overlying splint with a dull instrument, without disturbing or tenting up the healing skin. Failure to follow this policy can lead to disturbance of the newly forming subcutaneous fibroblastic layer over the nasal dorsum with additional unwanted scarring and even abrupt hematoma. After cleansing of the skin with an adhesive solvent, frontal and lateral photographs are taken immediately to document the early postoperative surgical result (these early photographs can assume vital medicolegal importance if the patient's surgical result is compromised by trauma in the immediate future). Thereafter it is to the surgeon's educational advantage and in the patient's best interest to arrange for visits at 1, 3, 6, 9, 12, 18, and 24 months after the operation. After that, yearly visits are helpful to review the subtle changes in

Figure 36-52. Typical twisted pyramid in which double osteotomies may be helpful. **A,** Preoperative view. **B,** Postoperative view.

nasal appearance that inevitably occur. Observing these changes, favorable as well as unfavorable, allows the surgeon to refine his or her technique both to anticipate and to control these long-term healing characteristics.

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CHAPTER THIRTY-SEVEN

Special Rhinoplasty Techniques

Richard T. Farrior

Edward H. Farrior

Raymond Cook

Key Points

- The external approach for rhinoplasty should be considered in the severely twisted or previously operated nose.
- Nasofrontal angle modifications can help shorten or lengthen the nasal dorsum.
- Batten grafts can help correct both internal and external nasal valve collapse.
- Spreader grafts help correct internal nasal valve collapse.
- The septum must be straightened in order to correct a severely twisted nasal deformity.
- The saddle nose deformity is best augmented with autogenous material such as septal cartilage, auricular cartilage, rib, or calvarial bone.
- In general, the noncaucasian nose has thick skin, weak cartilage, a flat broad dorsum and an underprojected, poorly defined tip with a wide alar base.
- In the unilateral cleft nasal deformity, the nasal tip and columella are deviated toward the noncleft side, the nasal floor is widened, and the cleft nostril is wider than that of the noncleft side. The nasal tip is poorly defined and bifid. The alar base is displaced laterally, posteriorly, and inferiorly in relation to the noncleft side.
- In the bilateral cleft nasal deformity, the columella is short and deviated to the less involved side. The nasal tip is poorly defined and bifid. The alar base is displaced laterally, posteriorly, and inferiorly in relation to the noncleft side.
- Reconstruction of the cleft lip nasal deformity is based on improving the symmetry of the nasal tip and base and improving the nasal airway.

Aesthetic and reconstructive rhinoplasty is considered to be the most challenging and difficult of all facial plastic procedures. Every rhinoplasty is unique and presents the surgeon with a diversity of challenges for which he or she must have a variety of specialized techniques to address each patient's anatomic and functional deformities. This chapter addresses some of the less common nasal deformities and the surgical techniques that can be used to correct them. These deformities require the inclusion of all aspects of combined septorhinoplasty, with frequent extension and modification of several techniques.[1,2] These cases are particularly challenging in regard to improving the airway and gaining maximum improvement in appearance. A form of combined septorhinoplasty to correct both the external and the internal nasal deformities in one stage is virtually essential.[1-4] This chapter focuses on modifications of the septum, nasofrontal angle, and nasal tip while detailing the principles and techniques needed to correct the twisted nose, the saddle nose, the noncaucasian nose, and the cleft-lip nose.

Analysis

A thorough examination that uses not only observation but also detailed palpation of the nose is essential in determining preoperatively which anatomic components are actually involved in the nasal deformity. Experience is a great factor in being able to do this at the time of the office examination. Careful examination should be coordinated with appropriate photographs, radiograph films, and facial analysis. The preoperative findings strongly influence the selection of the most appropriate surgical approach and exposure techniques.

Coordination of the preoperative analysis with the findings at the operative table can be accomplished through either the standard intranasal rhinoplasty approaches or the external rhinoplasty approach. The authors use both the standard rhinoplasty approaches and the external approach. The external approach is particularly useful in the twisted nose, the nose requiring implant materials, and the cleft-lip nose.[2,5-7]

Incisions and Soft Tissue Elevation

The authors generally use intranasal incisions for a deviated nose but will frequently use the open or external rhinoplasty technique when there are severe asymmetries, deviations, and tissue deficiencies.[2,5-7] Some of the indications for use of the external rhinoplasty are as follows: (1) a nasal deformity that is difficult to precisely analyze; (2) one in which there is severe asymmetry of the lateral bony walls and the lower lateral cartilages; (3) when tissue deficiencies exist so that it is necessary to precisely place and suture implants in position[8]; (4) congenital anomalies such as the cleft-lip nose or other deformities in which profound asymmetries exist; (5) an extremely wide bony and cartilaginous dorsum, whether or not a hump is removed; and (6) for teaching purposes. The external approach involves a transverse midcolumella incision in a gull-wing curve rather than one with sharp angle. The authors use the gull-wing incision as opposed to the inverted gull-wing incision to create a

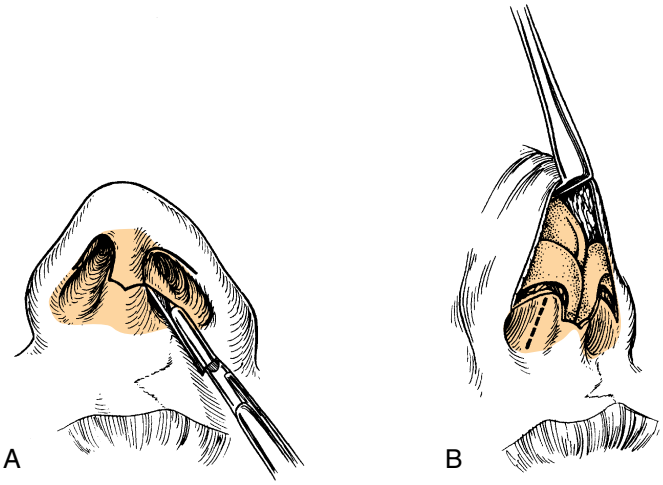

Figure 37-1. The external (open) approach. **A,** A gull-wing incision is made, crossing the columella just above the flare of the feet of the medial crura and then extending upward along the caudal edge of the medial crura and into marginal incisions laterally with the surgical knife. The skin is further elevated with the Stevens tenotomy scissors. **B,** Excellent exposure can be obtained to the root of the nose, which assists in evaluating asymmetry of the dorsum. The caudal septum and anterior nasal spine can be approached through the external approach, or a separate hemitransfixion incision may be made as shown by the dashed line.

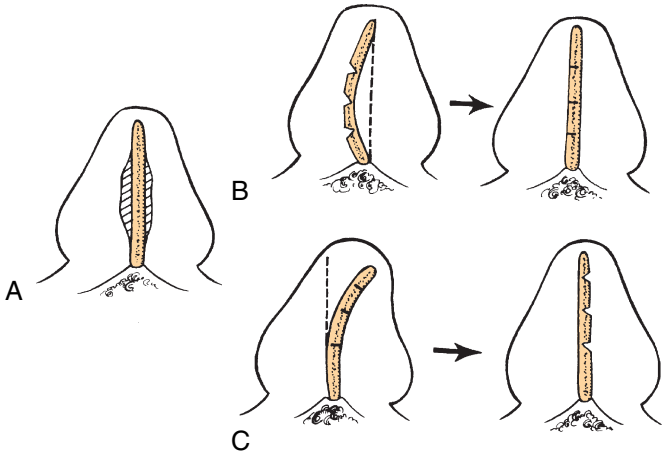

Figure 37-2. Correcting septal curvature. **A,** Vertical shave to reduce septal thickening. The shave may also be used to reduce bowing. **B,** Removal of cartilage wedges to straighten the septum in the midline. **C,** Scoring to allow the cartilage to open and return to the midline.

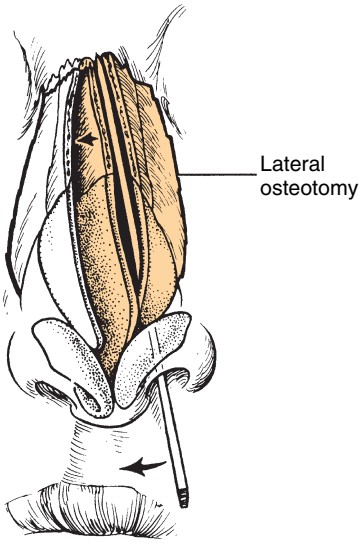

Figure 37-3. Correction of central component deviation. For deviations of the entire root of the nose or the remaining central component of the nose, it is necessary to establish a firm fulcrum with the osteotome to fracture this central portion toward the midline. This difficult maneuver requires a complete medial osteotomy paralleling the septum as close as possible, as opposed to the fading medial osteotomy.

single point rather than two points at the distal end of this diffuse random pattern flap. The incision is then extended upward along the caudal edge of the medial crus and laterally along the caudal margin of the lateral crus as an alar cartilage margin incision (Fig. 37-1). The elevation is initiated with sharp knife dissection, with the columella skin being elevated before the elevation is extended laterally over the lateral crura of the lower lateral cartilages. The external incision crossing the columella leaves a barely perceptible scar and offers excellent visualization by means of the "degloving" of the nose.

Septal and Columella Modifications

It is impossible to discuss correction of the difficult nasal deformity without addressing surgery of the involved septum. The specific techniques required are determined by the amount of cartilage that remains and how angulated or dislocated it is. The septum must be considered as an ideal donor site for cartilage and bone implants. When adequate material is available, it is an excellent implant for the nasal dorsum, a columella strut, a shield implant to the tip, a filler for depressions in the area of the upper lateral cartilages, and for creating spreader and batten grafts. Once the incisions are made, elevation of the mucoperichondrial flaps is frequently difficult because of fibrosis through fracture sites and overlapping or lamination of the cartilage itself. In the previously operated nose, a practical approach involves beginning the elevation of the mucoperichondrium beneath the dorsum, because this area is often previously undisturbed. The elevation then proceeds downward toward the previous operative site, where cartilage and bone may have been removed.

For the severely deviated or previously operated nose, it is usually necessary to elevate the mucoperichondrium on both sides of the septal cartilage, although it is preferable whenever possible to leave it attached on one side as the bone and cartilaginous angulations are corrected. Freeing fibrous contractions and septal angulations is essential in allowing the septal framework to straighten. The extent to which cartilage and bone must be removed or repositioned is dictated by the particular deformity encountered and the direction of the angulations. Generally, scoring or removal of thin strips of cartilage along the existing angulations is required to achieve straightening (Fig. 37-2). Release of all tension vectors allows a buckled septum to straighten. Determination of the final position of the septum may not be possible until osteotomies have been performed, particularly if the nasal bones and upper lateral cartilages are severely deviated from the midline. A final determination of what more, if anything, needs to be done to the septum, therefore, must sometimes await the completion of medial and lateral osteotomies, when the entire nose is positioned in the midline (Fig. 37-3) regarding deviations of the central bony complex).

Transseptal coaptation sutures, which bring the two mucoperichondrial flaps together and pass between angulations or cartilage pedicles to prevent overlap, are great aids in this surgery (Fig. 37-4). Polyethylene splints have been used for a number of years to stabilize the septum in the early postoperative period and to prevent the development of synechiae, particularly when turbinate surgery has been performed. Two through-and-through sutures are always placed through the polyethylene splints. The sutures are placed so that one arm of the suture goes between cartilage pedicles or beneath the septal cartilage for support. The second arm of the suture goes back through

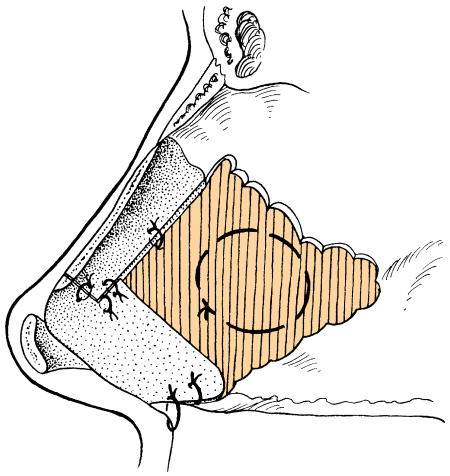

Figure 37-4. Coaptation sutures. Further modifications of the septal reconstruction in which it has been necessary to remove a significant amount of cartilage and bone. Coaptation sutures may be either single sutures through and through the mucoperichondrium or a continuous suture passed back and forth through and through and tied to the original free end.

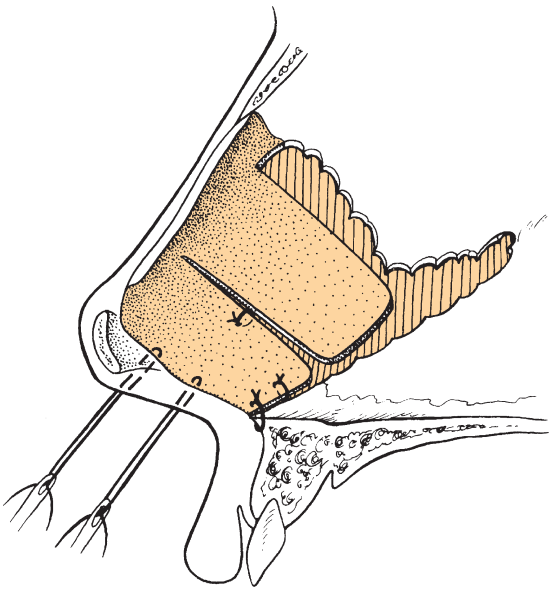

Figure 37-6. Stabilization of the caudal septum with draw sutures through the center of the columella, reestablishing the septocolumellar relationship. At the end of the procedure, the draw sutures may be removed or may be tied loosely against the columellar skin.

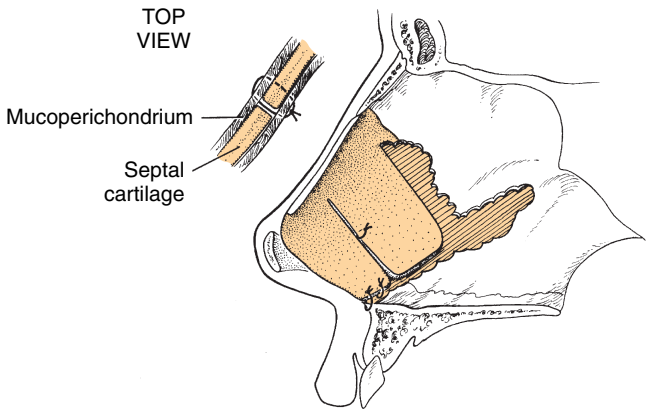

Figure 37-5. Repositioning and suturing of the caudal septum. The dislocated septum is repositioned on the anterior spine and maxillary crest. Reconstruction is augmented by scoring or cross-hatching and proper placement of sutures such that one suture is passed submucosally around the anterior spine. The next fixation suture is passed through one mucoperichondrial flap, between the bone of the anterior spine and the septal cartilage and out through the mucoperichondrium on the other side, and then back through flap, septum, and flap to complete the loop. The other sutures are passed between the mucoperichondrial flaps and between the cartilage pedicles to prevent dislocation.

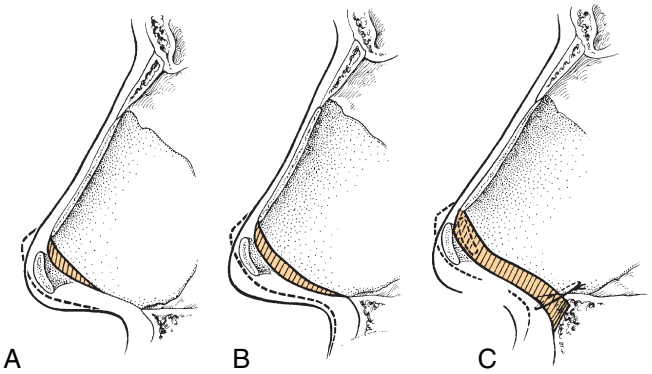

Figure 37-7. Modifications for shortening the nose. **A,** Ideal limited shortening and elevation of the tip involving only the outer one third to one half of the caudal septum and limited transfixion incision. **B,** Shortening of the entire caudal septum with slight angulation extending to the spine. **C,** Shortening of the entire caudal inferior nose with a deepening of the nasolabial angle. The obtuse nasolabial angle is corrected. A right-angle wedge of bone is removed from the anterior spine, and a suture is passed from the cartilage to the base of the membranous columella, reinforcing the angulation and eliminating the dead space.

the mucoperichondrium and cartilage. One may splint the septum further at a major angulation with a straight portion of thin perpendicular plate of the ethmoid.

Caudal Repositioning

When it is necessary to reposition the caudal portion of the septum, it is usually necessary to free the mucoperichondrium on both sides to release all extrinsic tension on the cartilage. The septal cartilage is then detached from the underlying anterior nasal spine and maxillary crest. Intrinsic tension of the septum is relieved by scoring, cross-hatching, and wedging. Once this caudal pedicle is freed of the tension vectors, it may be maintained in the midline by sutures that go around the anterior spine or through a burr hole in the spine (Fig. 37-5). To further prevent dislocation, an additional suture may be passed through the two mucoperichondrial flaps and between the bone of the spine and the cartilage. The cartilage pedicle is attached directly to the spine for alignment, and the two mucoperichondrial flaps when sutured together add further stability. When necessary, the caudal edge of the septum may be held in proper relation to the columella with interrupted sutures or direct through-and-through septocolumellar sutures (Fig. 37-6).

Shortening the Caudal Septum

For the deformed nose with a drooping tip and columella retraction, the entire septocolumellar complex must be critically evaluated. In correcting the drooping tip, the lower lateral cartilages must be rotated cephalically, and strong tip support is needed. Both the caudal septum and the soft tissue may need modification to achieve this (Fig. 37-7).

Frequently, there is an associated columella retraction, resulting in an acute nasolabial angle. Correction of the retraction requires straightening the caudal septum and placement of a columellar strut or a plumping graft (Fig. 37-8). Some limited resection of the caudal edge of the septum may be necessary to remove a portion of deformed septum that is dislocated off the anterior spine and projecting into one nostril. When the caudal edge of the septal cartilage is severely dislocated, it often creates distortion and retraction of the columella, even though adequate cartilage is present. Straightening and repositioning of the caudal septum within the columella sometimes corrects the retraction (Fig. 37-9). Rarely is it necessary to shorten the upper lateral cartilages, although reduction of the scroll along their caudal border may be necessary to reduce excessive width in that area.

Making the Final Septal Assessment

It is not until all septal reconstructive surgery and the osteotomies are completed that the final analysis of the position of the septum can be made. This position is particularly critical at the junction of the bony and cartilaginous portions of the nose, both internally and externally. At this point, the surgeon can determine whether adequate dorsal support has been maintained. If there is any tendency for the cartilaginous dorsum to sink inward, a draw suture can be passed through the skin to pick up either the septum alone or the upper lateral cartilages and the septum along the dorsum (Fig. 37-10). The suture is passed upward through the skin and held in position while all coapting and supporting sutures are placed and packing is completed. The draw suture can then be removed. In extreme cases, the draw suture can be passed through a thin external splint and tied over a bolus to remain in place for a week until the splint is removed.

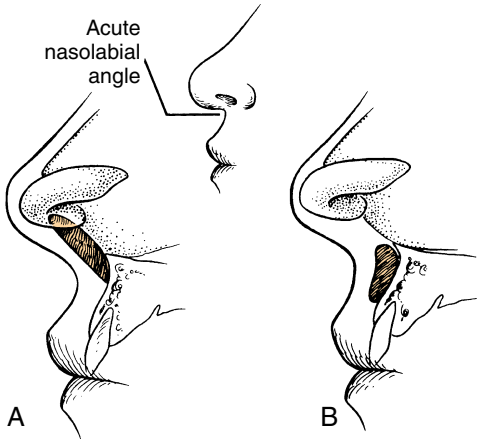

Figure 37-8. Correction of acute septolabial angle. **A,** The columella strut adds columellar fullness. **B,** When the columella strut is not required, a simple plumping graft serves as a filler and gives support to the feet of the medial crura. An implant may be necessary over the face of the maxilla and beneath the anterior spine to create fullness of the lip portion.

The Septocolumellar Complex

The columella and caudal septum must often be addressed in rhinoplasty. There may be columellar retraction caused by retraction of the caudal septum or there may be other abnormalities of the septum and columella that distract from the appearance of the nose. Ptotic lower lateral cartilages with a convex caudal margin can cause increased columellar show. This may be exacerbated by a prominent caudal margin of the septum and/or an excessive membranous septum.

These deformities can be addressed by trimming or sculpturing the medial crura and caudal septum as demonstrated in Fig. 37-11. Other structures that may contribute to the perceived or actual abnormalities of the caudal septum and columella include either ptosis of the lateral crus of the lower lateral cartilage, causing what appears to be a retracted columella, or retraction of the ala, resulting in excessive columella show (Fig. 37-12). These abnormalities must be corrected when addressing the lower lateral cartilages, either through reduction or augmentation (Fig. 37-13). Repositioning of the anterior maxillary spine, division of the depressor nasi musculi, sectioning of the frenulum, and defatting or augmentation of the nasolabial angle may also be necessary when addressing the caudal septum and columella.[9]

Nasofrontal Angle Modifications

Subtle modifications in the nasofrontal angle can significantly enhance a patient's nasal and facial profile. In patients with a shallow nasofrontal angle, the nose often appears to have excessive length. In this type of patient a 2-mm osteotome can be inserted through a stab incision in the midline over the nasal bones (Fig. 37-14). The nasal bones can be scored or weakened on either side with transverse osteotomies, thereby controlling the cephalic fracture site. This will allow the surgeon to control the site of the nasofrontal angle when the bony hump is removed. After removal, the angle may be smoothed or further deepened by the use of the rasp or rongeur.

In patients with a deep nasofrontal angle, the nose often appears to be short and often overprojected. In these patients, the nasofrontal angle can be augmented with autogenous cartilage, bone, or any of the

Figure 37-9. Correction of columella retraction. **A,** Marked columella retraction and drooping tip (preoperative). **B,** After septal reconstruction with tip rotation and columella filling.

alloplastic materials mentioned earlier. Autogenous cartilage is the material of choice secondary to their low rate of absorption and nonreactivity. A precise pocket should be made that does not allow movement of the graft. The graft can be further stabilized by placing transcutaneous sutures through the graft and tying them over a bolster.

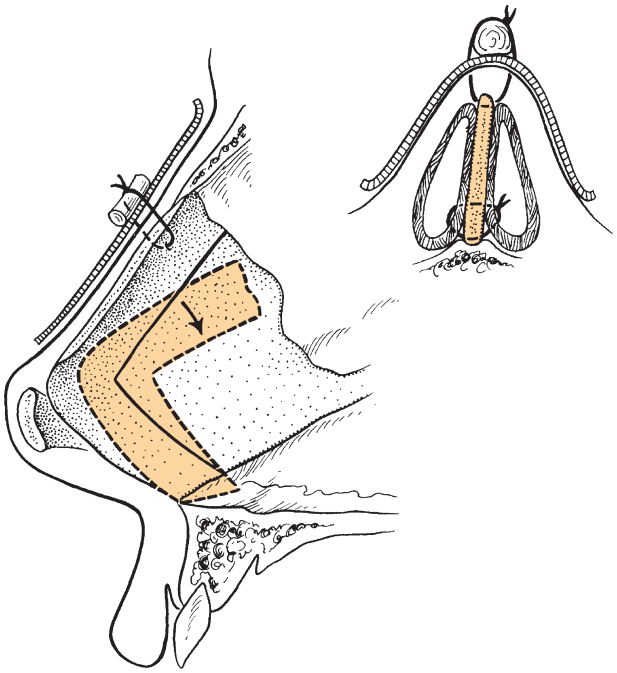

Figure 37-10. Dorsal draw suture. If there is loss of support either from injury or surgery at the junction of the septal cartilage with the nasal bones and perpendicular plate of the ethmoid, the remaining caudal septum tilts downward *(arrow).* A draw suture may be passed through the skin of the dorsum of the nose and then used to pick up either the septum alone or the septum with the upper lateral cartilages. The draw suture is then passed through a soft thin metal nasal splint and tied over a bolus. Dorsal draw sutures may be used simply to maintain the position and support while all intranasal surgery is completed and the nose is packed. The sutures are then removed. When necessary, the sutures may remain in position for one week and are removed with the splint.

Tip and Alar Asymmetries

Tip Grafts

This section considers correction of severe asymmetries and deficiencies of the nasal tip that occur in the traumatized or congenitally deformed nose. For these noses, wide exposure of the lower lateral cartilages is absolutely essential and may be achieved either through delivery of the cartilages or by the external approach.

When there are severe asymmetries of the lower lateral cartilages, management usually requires modification of the more normal cartilage

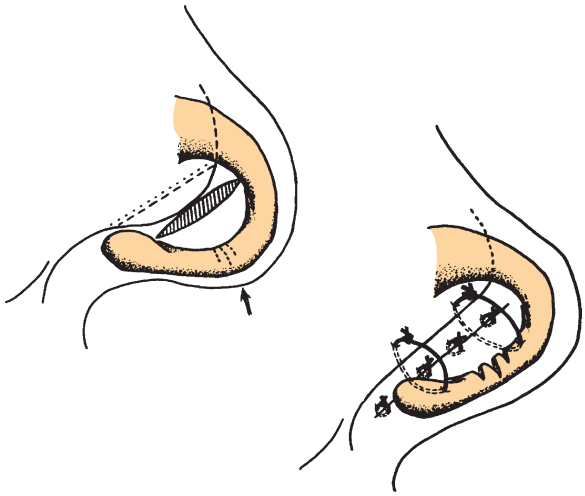

Figure 37-11. The septocolumella complex. Apart from abnormalities of the lateral ala and its relation to the columella, this complex involves at least the caudal septum, the membranous septum, and the curvature and strength of the medial crura. The exaggerated convex caudal edge of the medial crura, as occurs in the hanging columella, may be partially sectioned to allow the crura to straighten with suturing. The caudal cartilaginous septum and membranous septum may require partial resection. The septocolumella complex is reestablished with sutures, including through-and-through septocolumella sutures. The medial crura may be approached retrograde through the transfixion incision and with subcutaneous elevation of the skin or directly by the external approach.

Figure 37-12. Cephalad retraction of the alar margin. **A,** Postoperative complications: the all-too-frequent supratip swelling or pollybeak deformity and cephalic retraction of the lateral alar margin. **B,** Correction is accomplished by reducing the cartilaginous nasal septum and removing supratip fibrous tissue, further sculpturing the lower lateral cartilages, freeing the lateral crus, and inserting a cartilage implant retrograde along the alar margin. (See also Fig. 37-13.)

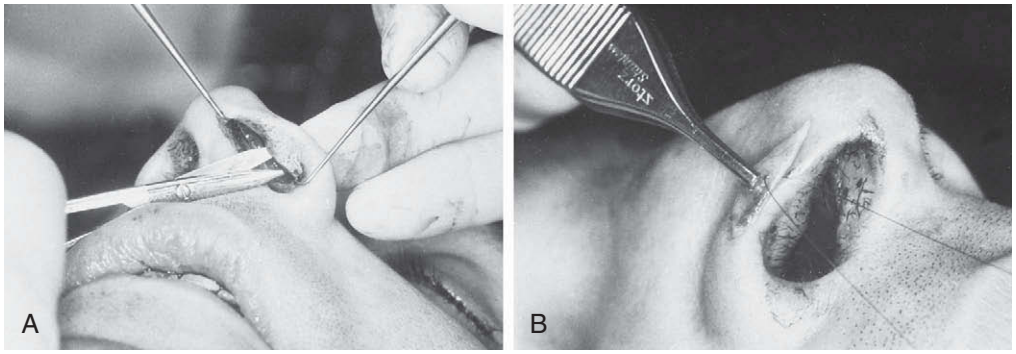

Figure 37-13. Retrograde alar margin implant. **A,** Creation of the retrograde pocket through the alar cartilage margin incision down to the rim. **B,** The sculptured cartilage implant is brought into the pocket with draw sutures and held in position with transalar sutures tied over a thin polyethylene film.

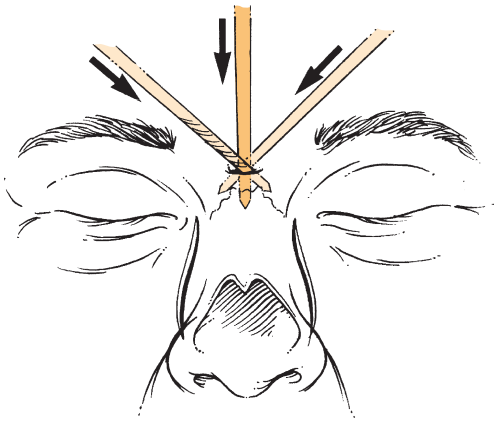

Figure 37-14. The nasofrontal angle is reduced by placing a 2-mm osteotome through a stab incision and creating a deeper angulation by joining the two lateral osteotome cuts at right angles.

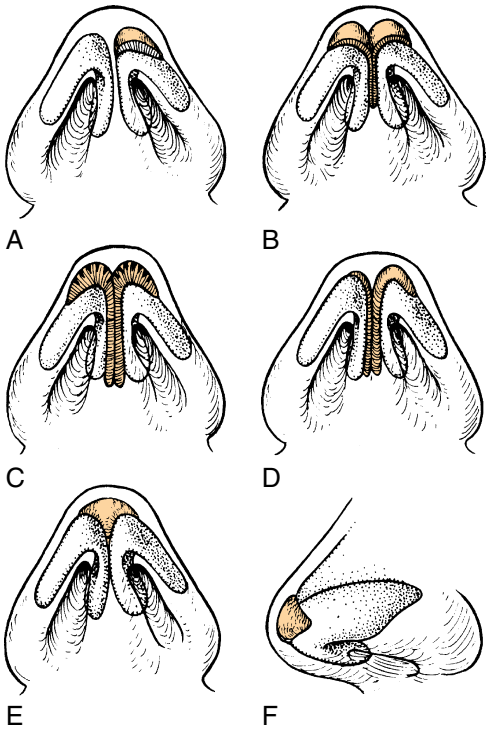

Figure 37-15. Revisional surgery with implants for nasal tip. **A,** A simple onlay implant, which may be sutured in position to the cartilage or held in position by a draw suture through the external skin. **B,** Implant to the tip and columella, most commonly using auricular cartilage. **C,** Contouring of the implant by scoring. **D,** Asymmetric implant. **E** and **F,** Tip button with stabilization between the medial crura.

and the more abnormal side if one is to achieve a symmetric tip. The cephalic portion of the lower lateral cartilage is an excellent implant to be used in the nasal tip to overlie angulations, to fill small depressions, or for splinting cartilage by direct suturing. When more sturdy cartilage is necessary, sculptured or laminated septal or auricular cartilage is useful (Fig. 37-15). In the tip, these implants may be combined and sutured directly to a columella strut or to the domes of the lower lateral cartilages. If there is marked distortion with associated soft tissue contracture, it may be necessary to free the lateral crus of the lower lateral cartilage on the involved side of both dorsal and vestibular skin and then advance the lateral crus into the nasal tip between the two skin layers as in the technique used in the cleft-lip nose repair (Fig. 37-16).

The septum is an ideal source of grafts to be placed in the nasal tip. Such an implant has the effect of stabilizing the medial crura and domes in proper relationship and giving some increased tip projection. This technique is useful in both the severely traumatized tip and the previously operated nose, in which all too often too much tissue has been removed from the lower lateral cartilages. A nasal tip graft or shield graft should be sutured directly to the lower lateral cartilages. This may be accomplished readily through intranasal incisions (alar cartilage margin incisions) or can be placed with greater ease and less chance of dislodgment through an external rhinoplasty (Fig. 37-17). Migration of the shields has been the major problem with their use, and direct suturing prevents this displacement. By removal of a wedge from the inferior border of the shield, two points are created along the inferior border, assisting in stabilization to prevent movement.

Alar Batten Grafts

The nasal airway immediately beneath the upper lateral cartilages is of particular importance functionally. This valve area requires special consideration when there is inward collapse of the upper or lower lateral cartilages at the level of the limen vestibuli. Here it may be necessary to place cartilage implants from the auricle or the septum, shaped into an outward convexity to create a flying buttress effect. The cephalic portion of the lower lateral cartilages with its vestibular skin may be rotated into a supratip defect. Often both skin and cartilage are required, and the natural curvature of the concha of the auricle with its thin anterior skin is an ideal composite graft to use in the valve area. The graft overrides the septal cartilage, and the auricular skin of the graft is sutured to the nasal mucosa (Fig. 37-18). This composite graft is a source of support and lining for the constricted valve area.

Suture Techniques

Suture contouring of the nasal tip is a reversible and nondestructive technique that allows recontouring and repositioning of the nasal tip

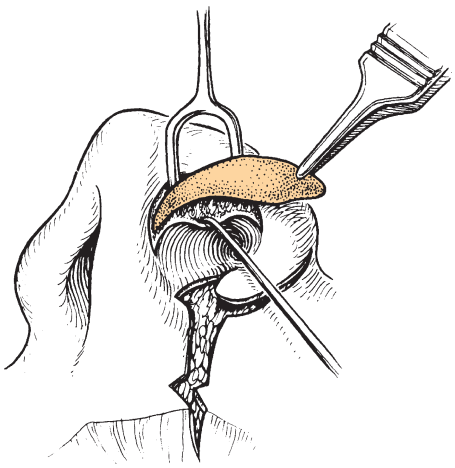

Figure 37-16. Freeing of the alar cartilage for the cleft-lip nose or certain asymmetries of the lower lateral cartilage. The lower lateral cartilage is freed of both surface and vestibular skin, allowing the cartilage to be rotated medially to project the tip of the nose. The cartilage is then sandwiched between the two skin surfaces in the new position and held with transalar sutures tied over a flat plastic film on the external surface. This technique is used for unilateral and bilateral nasal deformities and can be accomplished by either the intranasal or the external approach. Boluses on both surfaces are to be avoided.

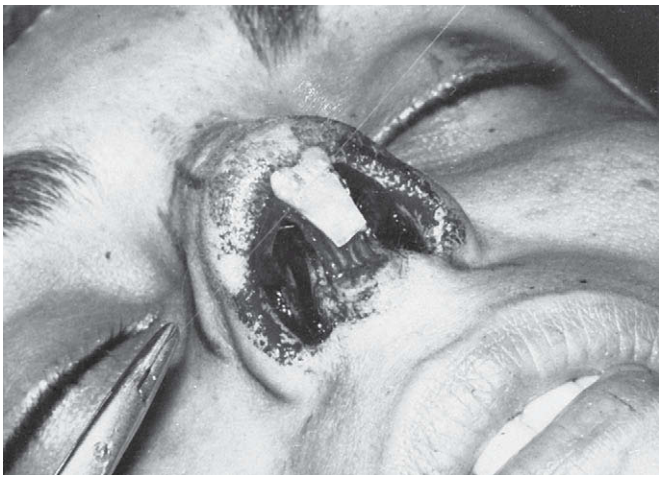

Figure 37-17. The external rhinoplasty allows the shield to be sutured into position. *(Courtesy of Dr. Calvin Johnson, New Orleans, LA.)*

without structural disruption. Suture contouring is performed from "the ground up."[10,11] Multiple suture techniques allow contouring of the lower lateral cartilages. The lateral crural spanning suture, the transdomal suture, and the interdomal sutures are suture techniques that the authors commonly use to allow precise changes to be performed in a reversible manner.

Transposition Techniques

Transposition of the lateral crura may be used in patients with extreme concavities of the lateral crura, which cause dimpling of the lateral nasal lobule and ala with narrowing of the nasal valve. After dome division has been performed, the lateral crura are completely freed from all attachments. The free segment of the concave lateral crura can then be flipped and sutured to the medial crus and vestibular skin. The previously concave lateral crura now presents a convex surface to the external nose, thus correcting the dimpling and collapse.

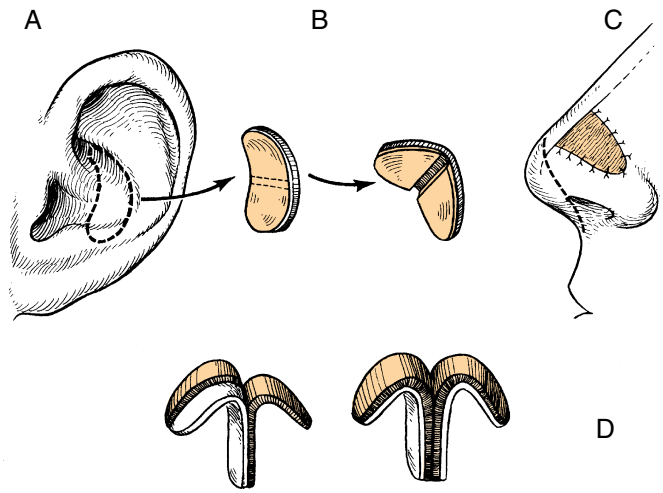

Figure 37-18. **A,** Auricular cartilage may be used as a composite graft, with its attached thin anterior skin being used to open the valve areas when there is marked loss of support and intranasal contracture. The skin is excised from the central portion of the graft, which rides over the septum like a saddle, and the skin is inserted into the mucosal opening. To avoid excessive thickness in the dorsum, it may be necessary to excise a strip of cartilage along the dorsum of the septum. The skin edges are precisely sutured to the nasal mucosa. **B,** Position of spreader graft. **C,** Spreader graft being sutured in position. **D,** Batten sutured into position.

The Twisted Nose

Surgical management of the twisted nose remains one of the most difficult challenges in facial plastic surgery. The patient and surgeon should have realistic expectations to the degree of correction that can be obtained without compromising nasal support and function. To correct the twisted nose, the surgeon must determine the specific deformities that are present. A thorough nasal examination including external and internal inspection with palpation must be performed. The structural support, symmetry, and deviation of the nasal bones, the upper lateral cartilages, and the lower lateral cartilages need to be evaluated during the external examination (Fig. 37-19). The internal examination allows inspection and palpation of the septum and nasal spine. It is important to determine the position of the septum and the nasal spine relative to the midline.

The twisted nose is best managed by the external approach. If the patient's primary deformity is in the bony pyramid, then the closed approach will suffice. It should be noted that the twisted nose is often associated with an asymmetric face. This feature should be pointed out to the patient preoperatively, because complete straightening of the nose on such a patient is often undesirable.

Septal Reconstruction

It cannot be overemphasized that if the septum is not straightened aggressively, a less than ideal result is usually obtained. To release the septum, the surgeon may need to elevate bilateral mucoperiosteal flaps from the floor of the nose to beneath the upper lateral cartilages (ULCs). The ULCs should be freed from the dorsal septum to allow them to be reoriented to the midline. Subluxation of the caudal septum often contributes to the twisted nose deformity. The subluxation diminishes tip support and can cause asymmetries of the alar cartilages. To correct the subluxation, the caudal septum must be freed from the nasal spine and either the septum or the nasal spine trimmed. The caudal septum is then sutured to the nasal spine in the midline. Various septal modifications are discussed elsewhere and are not repeated here.

Osteotomies

Before performing osteotomies to realign the nasal vault, the surgeon must determine exactly how much, if any, hump reduction should be

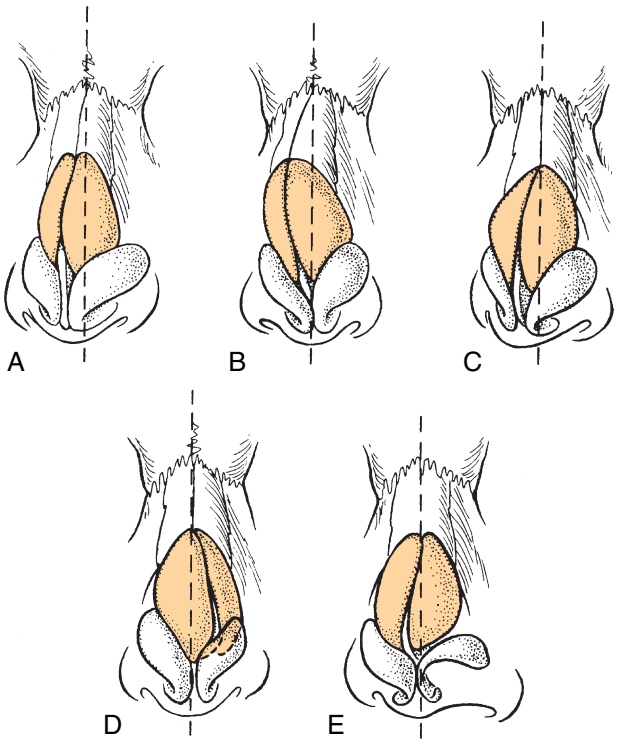

Figure 37-19. A variety of nasal deformities, including the anatomic components involved. Each anatomic component of the deviated or twisted nose influences the remaining components, particularly those immediately adjacent, just as each step of the surgery influences the other steps. **A,** Deviation of the entire nose, including the nasal bones up to the radix. **B,** Twisted nose with the tip and caudal septum returning to the midline. The nasal bones are deviated from the midline up to the radix. The greatest convexity or concavity of the bony and cartilaginous vaults is frequently at their junction. **C,** Deviation of the cartilaginous components of the nose, including the septum, with caudal dislocation off the anterior spine. **D,** Deviation of the dorsal septum and septal angle, with the remainder of the nose in the midline. This creates distortion of the lower lateral cartilage, with actual or simulated asymmetry. **E,** Deviation of the dorsal septum and septal angle with the distortion of the entire tip of the nose and medial crura.

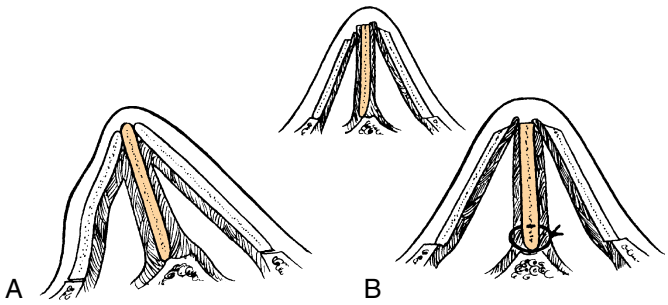

Figure 37-20. **A,** Asymmetric lateral vaults, both osseous and cartilaginous, in the deviated nose. An asymmetric hump removal is used to even the lateral vaults. **B,** The corrected relationship with combined septal reconstruction. Occasionally, grafts may be placed over the short side rather than reducing the long side. Insert shows deformity, which may occur with the long lateral vault remaining longer than the short after hump removal if this asymmetry is not considered.

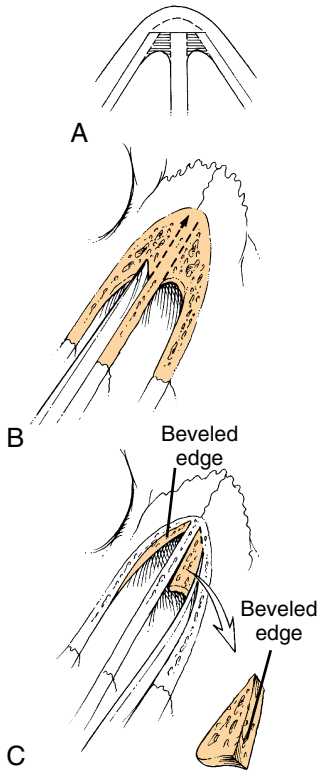

Figure 37-21. **A,** When performing medial osteotomies, it is important to undercut the thick portion of the bone between the dorsum and the lateral bony vault of the nose. **B,** The osteotome is placed vertical in the plane of the nasal septum. The osteotomy is carried slightly higher than the hump removal. **C,** A second cut is made at a beveled angle to undercut the nasal bones. This opens the root of the nose to a higher level, assisting in a more superior back or transverse fracture and prevents the "rocker" phenomenon that leads to widening of the nose in the postoperative period.

carried out. Often in the traumatized nose, a "relative" hump is created by loss of support and flattening in the cartilaginous portion of the dorsum. In these patients, initial attention should be devoted to increasing the cartilaginous projection with combined septal surgery and nasal tip surgery.[12] If the dorsal hump is to be removed, then the deviation of the bony vault must be taken into consideration. In the externally deviated nose, there is usually asymmetry of the lateral vaults, both bony and cartilaginous. This may be corrected with an asymmetric hump removal, with more bone and cartilage being removed on the longer or concave side (Fig. 37-20). In some patients, it is desirable to section the mucosa and the bone or cartilage during hump removal. This is particularly true when a large hump has been removed; the redundant mucosa beneath the dorsum can herniate upward beneath the skin and result in an undesirable dorsal fullness.

The medial osteotomies are performed first.[2,12,13] If there is to be an intermediate osteotomy halfway between the medial and lateral osteotomies, it is done second. The lateral osteotomy is performed last. If there is a thick plate of bone just at the upper edge of the now-open roof, it may act as a fulcrum over which the nasal bones rock outward at the nasion as the lower border is moved medially. This wedge of bone is removed with an osteotome, with an incision being made in the plane of the septum and then in the plane of the nasal bones (Fig. 37-21).[12,13] After this, the medial osteotomies are extended to the radix, either in a plane paralleling the nasal septum or curving laterally toward the position of the upper end of the lateral osteotomy. Extending the bone incision to the radix is considered the complete osteotomy and is often essential in a twisted nose, particularly if the deviation extends up to the radix (Fig. 37-22). When this is required, the osteotome is reinserted into the medial osteotomy after completion of the medial and lateral osteotomies and carried into the firm bone of the radix, where a strong fulcrum for the osteotome is developed. The osteotome is used to fracture the nasal bone and perpendicular plate of the ethmoid

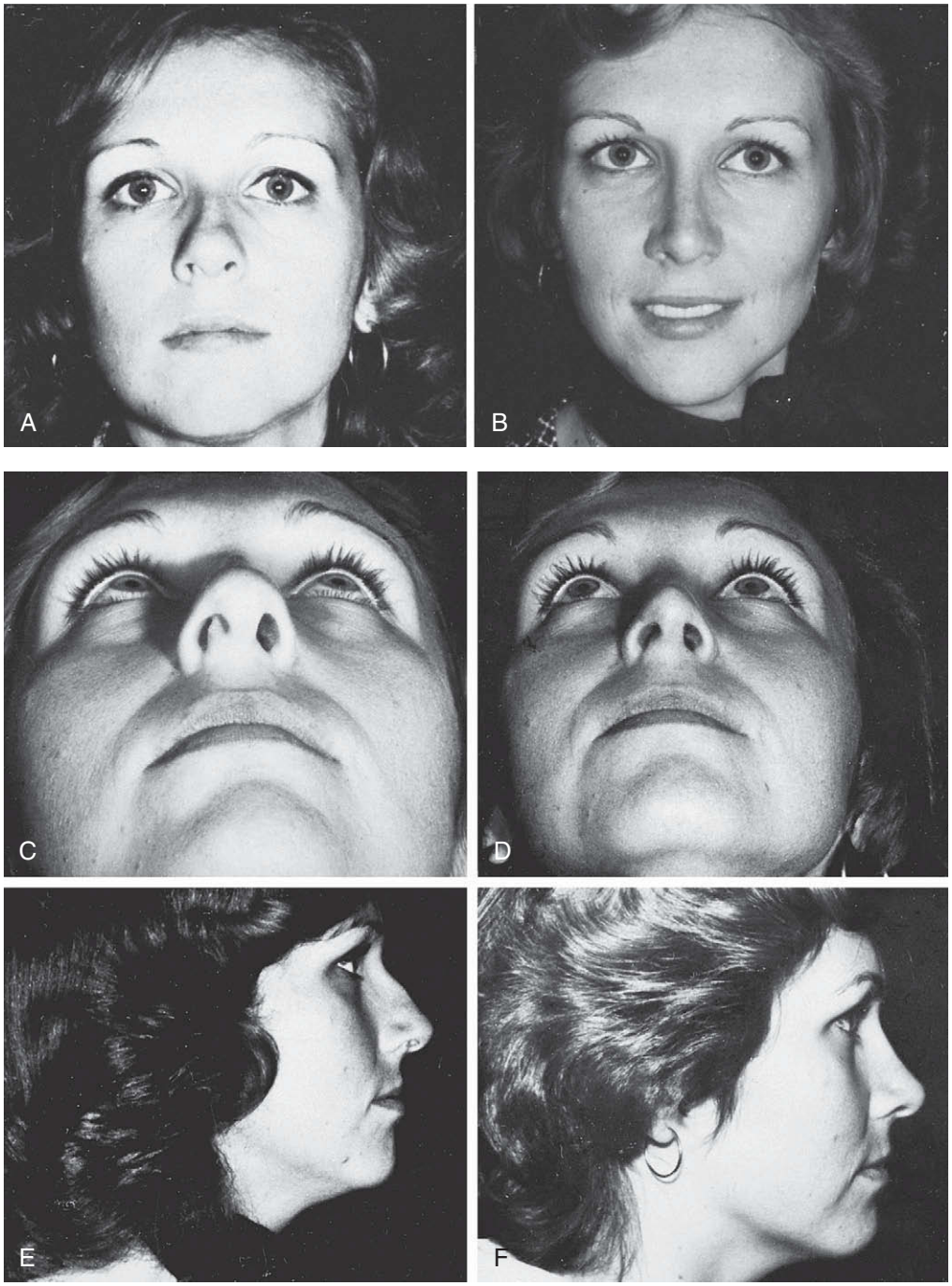

Figure 37-22. Fading medial and curved lateral osteotomies in a twisted nose with a narrow nasal root. **A,** The narrow nasal root with deviation only in the inferior portion of the nasal bones. Dislocation of the caudal edge of the septum is also apparent in this anterior view. Fading or curved medial osteotomies combined with the slightly higher curved lateral osteotomy are advocated in such a case. **B,** Postoperative result where there was no need to fracture the narrow medial portion of the nasal bones. **C** and **D,** The same patient with the obvious caudal dislocation of the septum and some long-term distortion of the flare of the medial crus on the right side. The nose was adequately straightened, the tip projection maintained, and the caudal septum held in position. There is persistent flaring of the distorted foot of the medial crus. **E,** The profile also demonstrates the caudal dislocation of the septum into the right nostril, the need for conservative hump removal, tip projection, and a small chin implant. **F,** Postoperative result.

toward the midline. This is not an outfracturing maneuver but rather a fracturing of the central portion of the superior nasal complex to include the midline root of the nasal bones and perpendicular plate of the ethmoid (see Fig. 37-3).

In the wide flat nose in which it is not necessary to change the profile line, the flat roof of the bony vault and of the upper lateral cartilages must be narrowed. The intermediate osteotomy is useful in narrowing such a nose (Fig. 37-23). The intermediate osteotomy is carried out through the intercartilaginous incision above the upper lateral cartilages.

In the deviated nose, the lateral osteotomy follows the curvature of the nasofacial groove—that is, against the face of the maxilla—and with rotation of the osteotome, it curves upward to join the medial osteotomy. Provided the medial osteotomy has been done first as recommended, back fracture and bony spicules are rare.[12,14] High osteotomies—that is, away from the maxillary face—are satisfactory for some

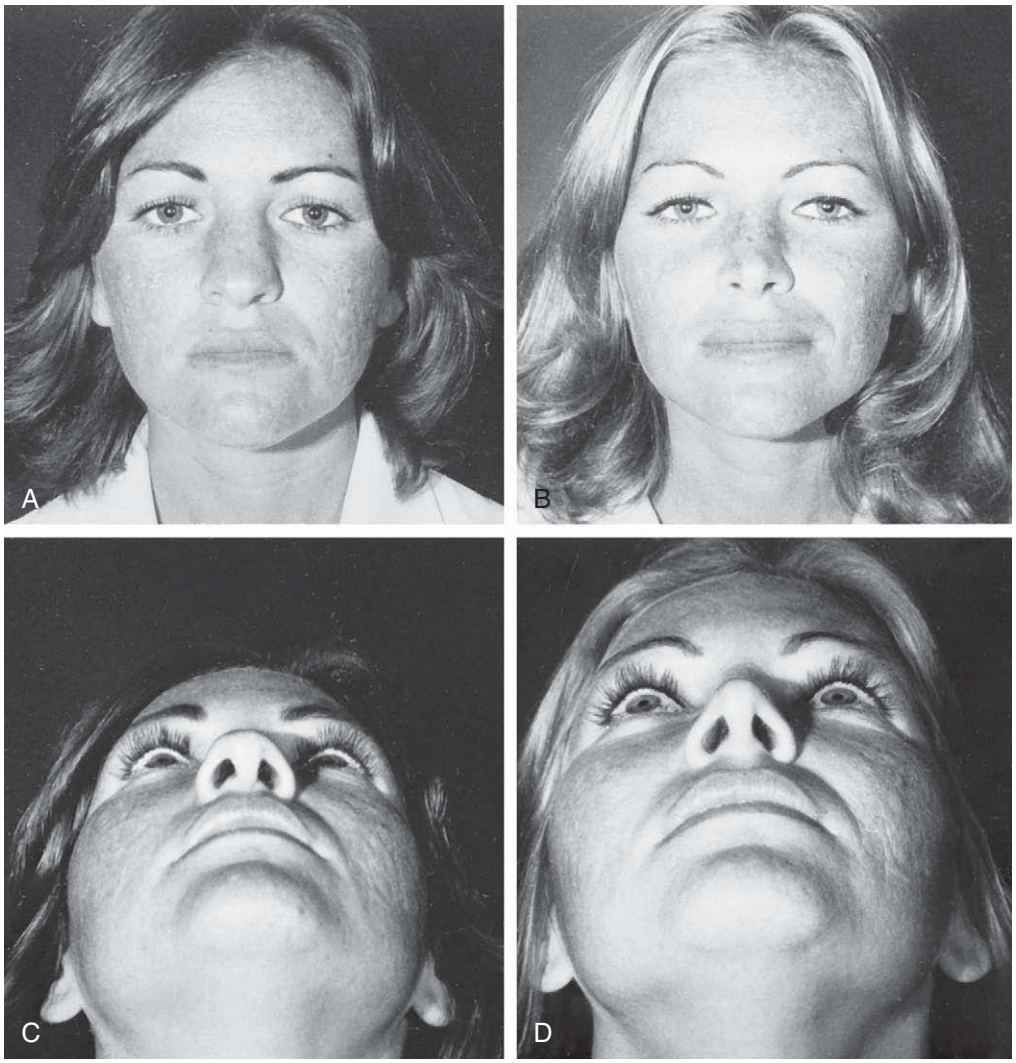

Figure 37-23. Complete and intermediate osteotomies. **A,** This case demonstrates the flattened, wide nose with outward splaying of the nasal bones, and only minimal change in the profile is required. This patient would require narrowing of the nose, which is accomplished in many cases by the use of an intermediate osteotomy placed halfway between the complete medial and low lateral osteotomies. **B,** Results of this surgery combined with an autogenous cartilage columella implant. The cartilaginous dorsum has been narrowed without changing the profile. **C** and **D,** Basal views of the same patient before and after narrowing with tip sculpturing and increases in tip projection and columella support.

cosmetic rhinoplasties, but with deviated external noses, low complete osteotomies are advised. These require the creation of a transverse fracture that joins the medial and lateral osteotomies at their cephalic ends.

Debate exists as to the benefits of elevating the periosteum overlying the osteotomy to preserve it or simply performing the osteotomy through the periosteum. The authors are firm believers in the subperiosteal approach. This is an avascular plane, and with minimal elevation laterally, a periosteal blanket is preserved to drape over the osteotomy site. Without the periosteal elevation, the edge of the osteotome will lacerate the periosteum and perhaps traumatize the subcutaneous tissue as well. The lateral osteotomy may be performed through a horizontal intranasal incision at the piriform rim, an intraoral incision, or at the alar attachment if this has been done as for the Weir procedure or for the cleft-lip nose. For the cases under discussion, in which there is often already a great deal of intranasal scarring resulting from mucosal trauma or extensive earlier surgery, the authors prefer to approach through the buccal sulcus, avoiding additional intranasal incisions and possible circumferential scarring. In revision surgery when there is prominence of the previous osteotomy site, multiple osteotomies or fragmentation over this site seems to produce a more acceptable result than simply rasping the area or repeating the single osteotomy.

Spreader Grafts

Once the ULCs have been freed from the septum, the degree of dorsal deviation can be determined. If there is a minor degree of dorsal deviation, the osteotomies may realign the nose to the midline, and the ULCs only need to be sutured to the septum. If there is a significant dorsal septal deviation, as seen in the C-shaped deformity, then an onlay graft can be placed on the concave side to camouflage the deformity. Another method to help efface the concavity of the septal deformity is by inserting a spreader graft. The spreader graft is carved from septal cartilage and is placed above the intact intranasal mucosa between the septum and ULC (Fig. 37-24). The graft will fill the concavity of the C-shaped deformity and preserve the cross-sectional area of the nasal valve. These grafts will also correct the depression seen from ULC collapse. If the dorsum is reduced more than 3 mm, the confluent width of the cartilaginous dorsum is dramatically compromised, and spreader grafts should be considered to avoid a narrowed dorsum and inverted V deformity.

Saddle Nose Deformity

The saddle nose deformity is seen in patients secondary to loss of support of the nasal framework with subsequent collapse. This deformity can be iatrogenic secondary to overzealous reduction on the nasal

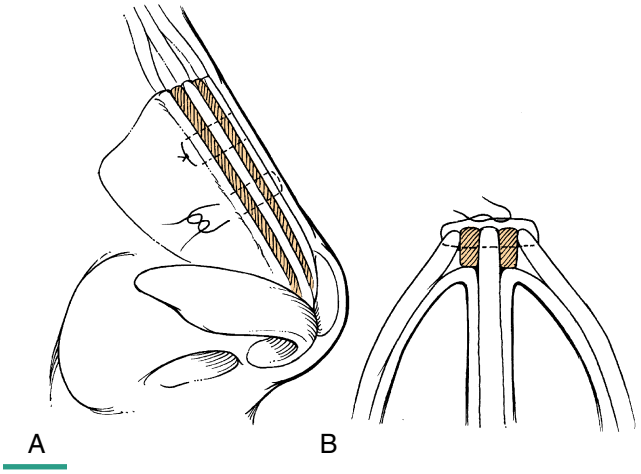

Figure 37-24. **A,** Bilateral spreader grafts being sutured in position. **B,** Spreader grafts in position, extramucosal.

dorsum or can be traumatic or congenital in origin. This loss of support may involve the bony or cartilaginous dorsum. It is often associated with columellar retraction and internal and external deformities. A critical analysis must be made regarding which nasal components are involved in the particular deformity. By analyzing which nasal components are involved, a reconstructive plan can be developed preoperatively.

Augmentation

Once the reconstructive plan has been developed, the surgeon must decide what type of implant material will be used for augmentation. Many different implants have been used in the nose, including autogenous tissue (cartilage, bone, fascia, and dermis), homologous material (irradiated cartilage, lyophilized cartilage, bone, and acellular dermis), and alloplastic material (Gore-Tex, Supramid, Proplast, Mersilene, and Silastic). Heterograft materials such as bovine cartilage and bone are used less frequently because of resorption.

The authors prefer using autogenous materials in the nose.[15-22] Septal cartilage is preferred, but auricular and rib cartilage are also useful. If the bony pyramid needs augmentation, then autogenous iliac crest, calvarial bone, or rib can be used. Temporalis fascia and dermis are easily harvested and can be used to fill, contour, and soften certain nasal defects. Alloderm is processed from human dermis and can be used for augmentation in the same way as fascia or dermis. Homologous materials have been used with success,[23] but in general are less desirable because of long-term unpredictability with resorption and buckling.[24,25]

Surgeons are still awaiting the development of the ideal alloplastic implant. Today's implants still have increased risk of rejection, inflammation, and extrusion. Vicryl, Gore-Tex, Mersilene, Proplast, and Supramid are mesh materials that become partially incorporated into surrounding tissues and provide a thin layer of scar over the irregular dorsum. Silastic implants have been used successfully on the dorsum of the nose but have a higher extrusion rate and artificial feel in the lower third of the nose.

At this time Gore-Tex is our preferred alloplast for dorsal augmentation. The tolerance of Gore-Tex as an implant material has been well documented.[11,26,27] In addition, minimal amounts of fibrous ingrowth lead to stability of the implant but do not restrict its removal when necessary. The reinforced sheets of 4 to 7 mm are much easier to sculpt for augmentation. With these implants and the sheeting, it is important to taper the edge to ensure smooth transition to the surrounding soft tissue. This can be done through sharp beveling with a scalpel or by crushing the margins with a hemostat or needle holder. For the saddle nose deformity in which extensive septal surgery and osteotomies are required, it is sometimes best to stage the procedure, with the implants being placed at a second operation. Extensive septal reconstruction may be essential in completely straightening the nose and in increasing the vertical height, thereby making the required size of the implant smaller (Fig. 37-25). In the saddle nose, the anterior valve is frequently circular rather than oval or piriform, and the septal reconstruction should be combined with intranasal Z-plasties to release the scar contractures and open the anterior valve areas.

One of the difficulties of rhinoplasty, and especially of revision rhinoplasty, is ensuring a smooth contour over the nasal dorsum. This can be especially difficult in thin-skinned patients when implants are used. Where there are skin irregularities and scarring or cicatricial adhesions to the underlying framework, it is necessary to prevent recurrence once elevated. Sculpted laminated autogenous cartilage implants of any sort may leave irregular edges or an irregular surface. One way of softening these edges and other irregularities involves draping a piece of temporalis fascia over the entire bony and cartilaginous nasal framework. The temporalis fascia graft can be placed through either an intercartilaginous incision or an open rhinoplasty approach. The graft is secured in position with draw sutures, which are then tied over a soft plastic bolus at the level of the nasal frontal angle at each corner and with direct suturing inferiorly, laterally, and at the dorsum. Precise, direct suturing can be accomplished through the open rhinoplasty approach. Temporalis fascia has been shown not to resorb significantly in vivo,[28] and donor site morbidity is minimal. This fascial graft technique is an important part of the surgical armamentarium, particularly for revision rhinoplasty, dorsal irregularities, scars, and overlying implants (Fig. 37-26). Gore-Tex 0.4-mm cardiovascular sheeting or Alloderm can be used in place of fascia with little risk of reaction or extrusions (see Figs. 37-26D and E).

Indications

Mild saddle nose deformities are seen in patients with increased supratip depression. The nose appears wide and, if a dorsal hump is present, it is accentuated by the supratip depression. This deformity can be corrected by augmenting the supratip with crushed cartilage or fascia. The implant should be placed in the smallest pocket possible to promote stability. The implant should be carved and beveled to reduce any irregularities and to soften its edges.

The more severe saddle nose deformities have columellar retraction secondary to loss of quadrangular cartilage and a prolapsed dorsum. The cartilaginous and bony pyramid may be broadened and flattened, requiring multiple osteotomies. The dorsal implant should be carefully shaped with particular attention paid to preparing the recipient site and corresponding surface of the implant, so that the implant will fit snugly against roughened nasal bones. The undersurface of the implant should be concave to fit the curvature of the dorsum of the nose. A three-dimensional concept must be kept in mind when shaping the graft. The dorsal aspect of the graft should be nearly straight and extend the full length of the nose (Fig. 37-27). Grafts may be layered to increase the magnitude of augmentation. Bone grafts should be fixed to the nasal bones with a Kirschner wire or a miniplate. An external nasal splint should be applied for several days.

Dynamic Adjustable Rotational Tip Graft

Dynamic adjustable rotational tip (DART) grafts are extended dorsal spreader grafts that extend beyond the caudal septum the desired length of derotation.[8] The DART is particularly useful in the overrotated nose when the inferior displacement of the entire tip complex is necessary and placement of a tip graft would exacerbate columellar show.[8] The DART reestablishes the spring tension of the nasal tip. This helps establish a reliable nasal tip complex position and improves nasal valve collapse. Through an open approach, extended dorsal spreader grafts are typically sutured to a columellar strut and the medial crura of the lower lateral cartilage (Fig. 37-28). The extended spreader grafts can be slid along the anterior-posterior axis of the quadrangular cartilage. This allows the tip complex to be repositioned until the desired tip rotation and projection have been created. Once the desired tip position and tension have been created, the extended spreader grafts are sutured to the quadrangular cartilage. This extended graft helps derotate the tip and strengthen the dorsal septum and anterior septal angle.

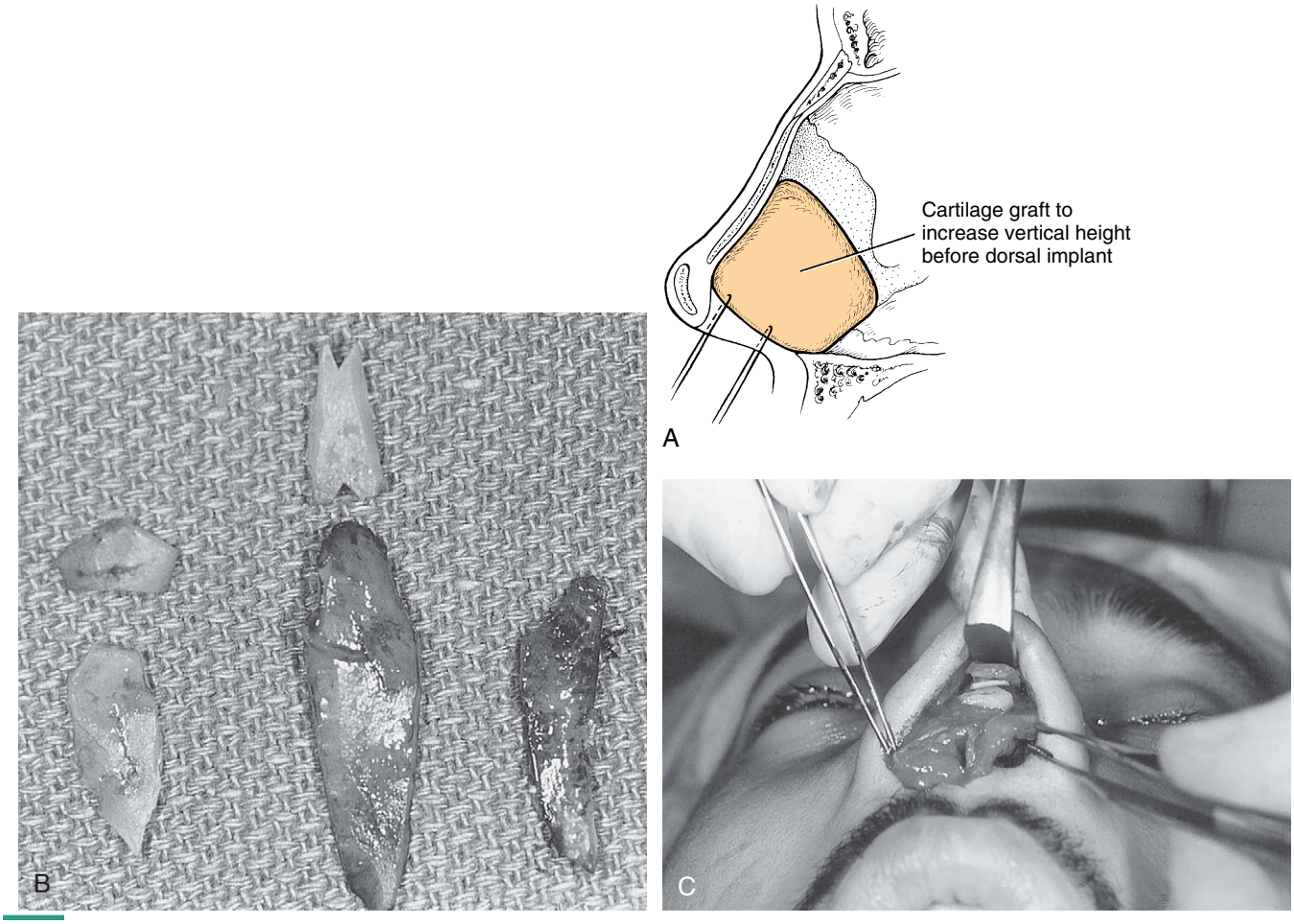

Figure 37-25. **A,** The septum and the saddle nose deformity. Straightened septal cartilage can be reinserted as a large columella strut to increase the vertical height of the nose and provide support for the dorsal implant. **B,** Cartilage implants taken from the nasal septum. **C,** Laminated cartilage implants to be sutured in position by the open approach. Irregularities may be smoothed out by a blanket of temporalis fascia or Gore-Tex sheeting. (See also Fig. 37-26.)

The Noncaucasian Nose

Aesthetic surgery of the noncaucasian nose requires a detailed preoperative analysis to identify the structural deformities present. Once the deformities have been identified, the appropriate surgical modifications can be undertaken. The generalities that follow pertain mostly to the African-American nose, although the Asian and several other ethnic noses have similar characteristics. In general, the noncaucasian nose has thick skin, weak cartilages, a flat broad dorsum, and an underprojected poorly defined tip with a wide alar base (see Fig. 37-30A). The thick sebaceous inelastic skin limits the degree of nasal tip sculpting that can be appreciated. The adipose tissue in the tip can be removed, and postoperative subdermal injections of Kenalog can help decrease supratip edema and scar formation.

The external approach allows the surgeon excellent visualization and the ability to precisely place grafts. The transcolumellar incision in the noncaucasian nose should be placed slightly lower than in the caucasian nose, because the augmentation of the noncaucasian nose advances the columellar skin cephalically.[11] If the incision is placed at the midcolumellar level, it may be advanced into the region of the infratip lobule.

If septal cartilage is available, it should be harvested for possible use as a columellar strut, tip grafts, and possibly a dorsal only graft. The columellar strut graft is sutured to the medial crura to help maintain projection. A tip graft is shaped and used to provide tip definition and to help stabilize the weak lower lateral cartilages. The tip graft may have to be layered to provide length to the nose and to prevent overrotation of the tip.

One of the most consistent findings in the noncaucasian nose is the acute nasolabial angle.[25] The underdeveloped anterior nasal spine contributes to the acute nasolabial angle. Plumping grafts of solid or crushed cartilage or bone can be placed into the premaxillary area to correct the acute nasolabial angle. A columellar strut may also be used to fill this area and provide tip support.

Dorsal Augmentation

The flat and broad appearance of the noncaucasian nose is generally related to the low dorsum. The nasal bones are usually short, and even though the bony pyramid looks wide, it is rare that osteotomies are required to narrow them. Dorsal augmentations give the illusion of narrowing the bony pyramid. The types of grafts available and the techniques for augmentation of the dorsum are described earlier in the section on saddle nose deformities. The same decision process and techniques are applicable for augmentation of the noncaucasian nose.

Nasal Base Sculpting

The thick, wide-based, flaring ala can be modified by reduction and thinning of the ala. There are numerous modifications of the Weir procedure, which involve the excision of triangles, wedges, or crescents from the alar base on either side. These are done to narrow the nasal base and are usually combined with procedures to increase tip projection through added columella support and lengthening. The technique used most often for the extremely wide nose combines narrowing the nasal base and reducing the length of the ala.

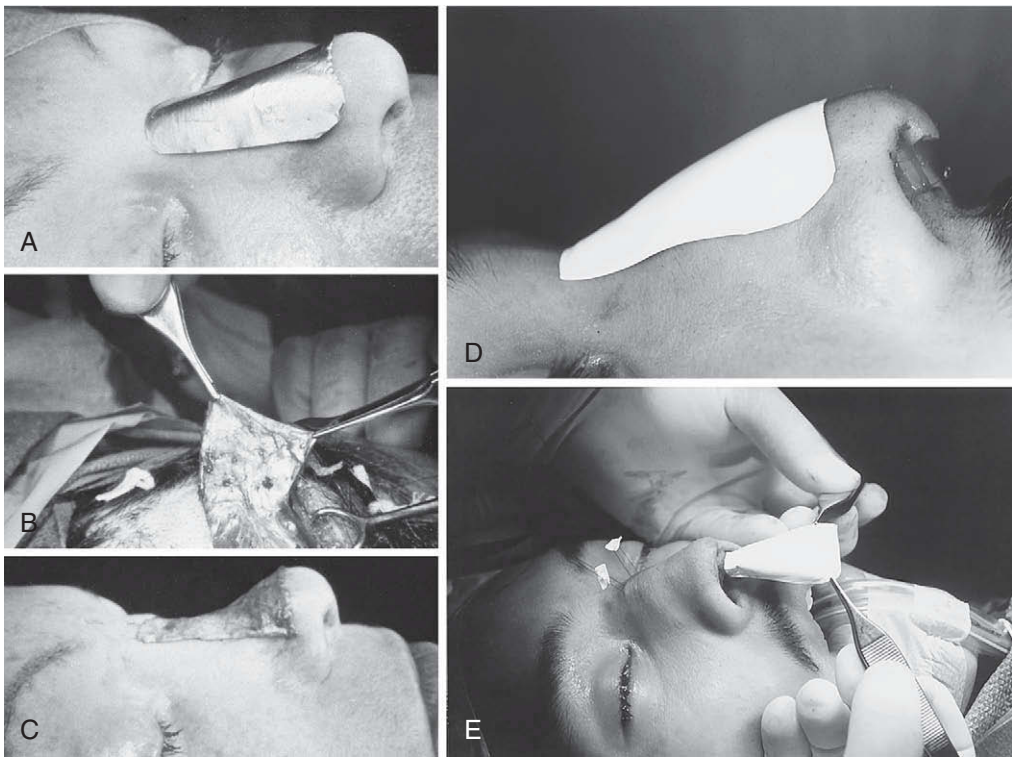

Figure 37-26. In addressing the nose with thin skin and bony cartilaginous irregularities, such as laminated implants, a temporalis fascia graft may be useful. **A,** The template fashioned to the size of the graft to be taken. **B,** Harvesting the temporalis fascia graft through a vertical incision through a shaved portion of the temporal scalp. **C,** Fascial graft draped over the nasal dorsum before insertion into the subcutaneous pocket over the nasal dorsum. **D,** Cardiovascular Gore-Tex sheeting placed as a blanket over the dorsum to smooth out any irregularities. **E,** As with temporalis fascia, Gore-Tex sheeting is carried into position with draw sutures. Inferiorly, the thin sheeting may be precisely sutured into position, especially with the open approach.

Reduction of the ala should be performed in a conservative and symmetric manner. In general, the alar width should equal the distance between the medial canthi. From a lateral view, 2 to 3 mm of columellar show should be visible below the ala. In the noncaucasian nose, the ala have a more caudal insertion into the face, creating a disproportional bulbous alar lobule. This results in alar hooding and an inadequate amount of columellar show.

The planned approach and site of incisions used for reduction of the nasal base is dictated by the patient's needs. The ala and nostrils can be reduced individually or in combination, depending on the need to reduce alar flare and nostril size. In general, the noncaucasian nose would need alar reduction with medial repositioning of the ala. An incision is made from the base of the sill and carried out 1 to 2 mm above the alar-facial crease (Fig. 37-29). The alar flap can be advanced medially, and a conservative amount of the ala can be excised. To avoid visible scaring, the cut edges should be carefully reapproximated. A 5-0 chromic suture should be used to reapproximate the alar rim, and one or two subcutaneous 5-0 Vicryl sutures should be placed to reapproximate the alar-facial junction incision. A few 6-0 nylon sutures are used to reapproximate the skin edges (Fig. 37-30).

Alar Soft Tissue Sculpturing

Reduction of the nasal base may be combined with surgery for the thick inferior border of the ala, which requires excision and thinning (Fig. 37-31). Further sculpturing may be required to arch the ala to correct alar hooding. In sculpturing or thinning the ala or nostril margin, one should make the excision slightly toward the nostril side. This not only makes the scar less visible but also creates a more natural roll to the border. The procedure is usually combined with a columella strut or other procedure to create greater columella "show" relative to the alar margin. Other techniques may be used to create greater columella prominence, such as the use of a composite auricular graft or skin and cartilage transposition flaps from the cephalic border of the lower lateral cartilages.

The Cleft-Lip Nose

The cleft-lip nasal deformity requires special attention to the asymmetric and retrodisplaced lower lateral cartilage in the unilateral cleft and to the depressed tip with a relatively short columella in the bilateral cleft. Associated with the deformity is hypoplasia of the maxilla on the cleft side or bilaterally, with midfacial hypoplasia resulting from the lack of mesodermal penetration (Fig. 37-32).

The unilateral cleft-lip nasal deformity is asymmetric and complex, and one drawing cannot bring out all three-dimensional aspects of the deformity. Major characteristics include the retrodisplacement of the lower lateral cartilage on the involved side, with an S-shaped deformity of the cartilage and soft tissue. There is thickening of the ala laterally, and the alar base is laterally and inferiorly displaced, with a loss of the alar-facial angle. Classically, the caudal end of the septum is dislocated toward the normal side, along with the anterior nasal spine and columella base. Internally, there is often a large posterior spur extending into the cleft side. The maxilla is underdeveloped on the involved side because of the lack of mesodermal development and penetration. The dome of the lower lateral cartilage on the cleft side is depressed, resulting in a lack of tip projection on that side. There is usually an excessively wide nasal floor on the cleft side, although stenosis may occur after childhood surgical repair of the lip and nasal floor.

The bilateral cleft-lip nasal deformity is much more complex than the unilateral deformity, and the surgical challenges are compounded. There is frequently underdevelopment of the entire premaxilla and prolabium, with a short caudal septum and a short columella. Furthermore, in the secondary deformity, there is flattening of the ala with little tip angulation or projection and bilateral widening of the nasal floor and flattening of the alar-facial angle.

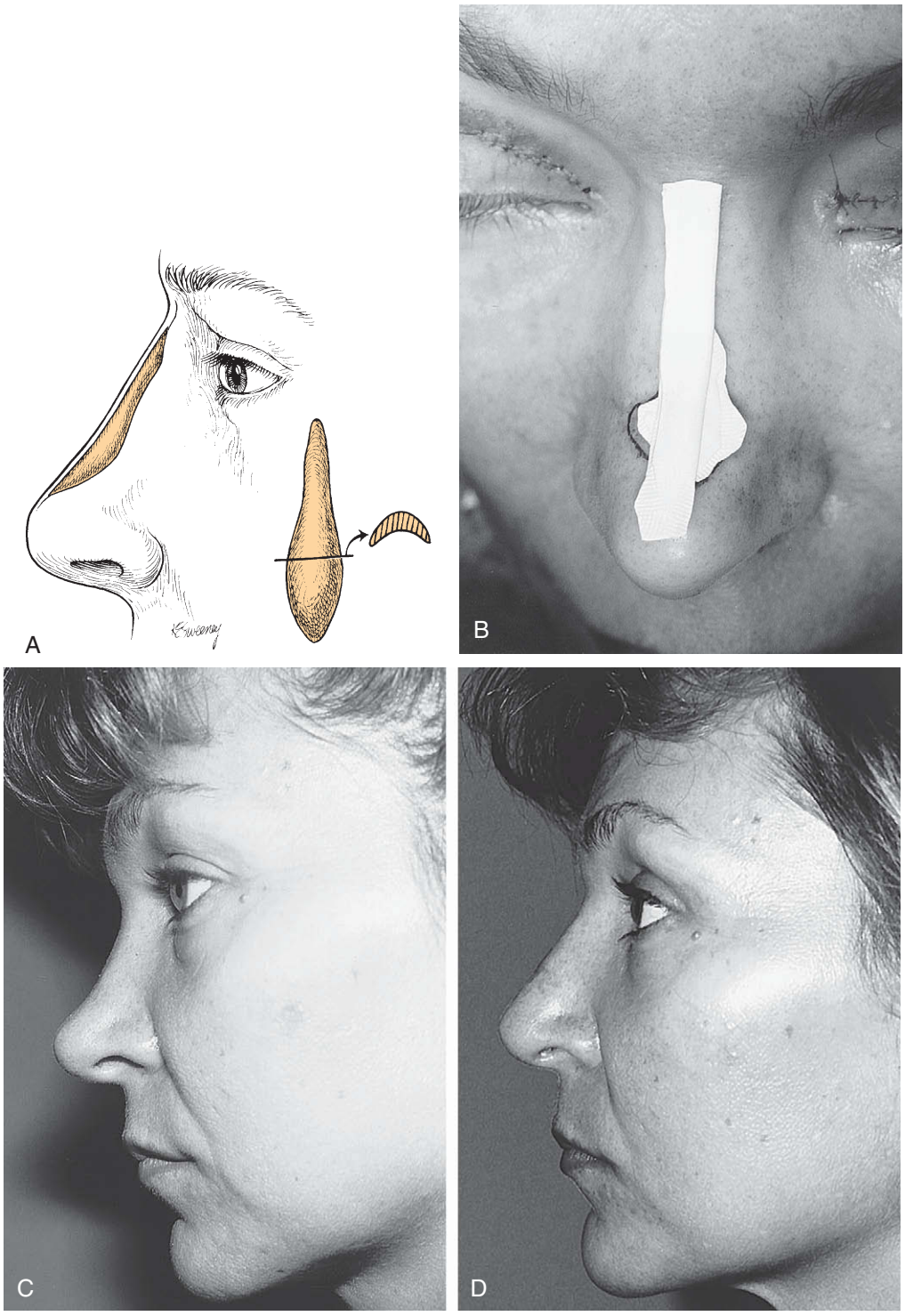

Figure 37-27. **A,** Dorsal implants should be precisely contoured in three dimensions and preferably should extend the entire length of the nasal dorsum. Autogenous material is used, and when nasal tissue or auricular cartilage is not sufficient, cancellous bone from the hip is used. Iliac bone grafts have now largely been replaced by calvarial bone grafts. If iliac bone is used, more cortex is allowed to remain on the cancellous bone. **B,** Laminated Gore-Tex sheet for dorsal augmentation with tapering of the Gore-Tex margin by crushing the edge of the Gore-Tex with the hemostat and separate soft tissue patch. **C,** Preoperative view of mild saddle nose deformity and soft tissue irregularity of the cartilaginous dorsum. **D,** Postoperative view with dorsal augmentation and soft tissue filler of the left cartilaginous nasal dorsum.

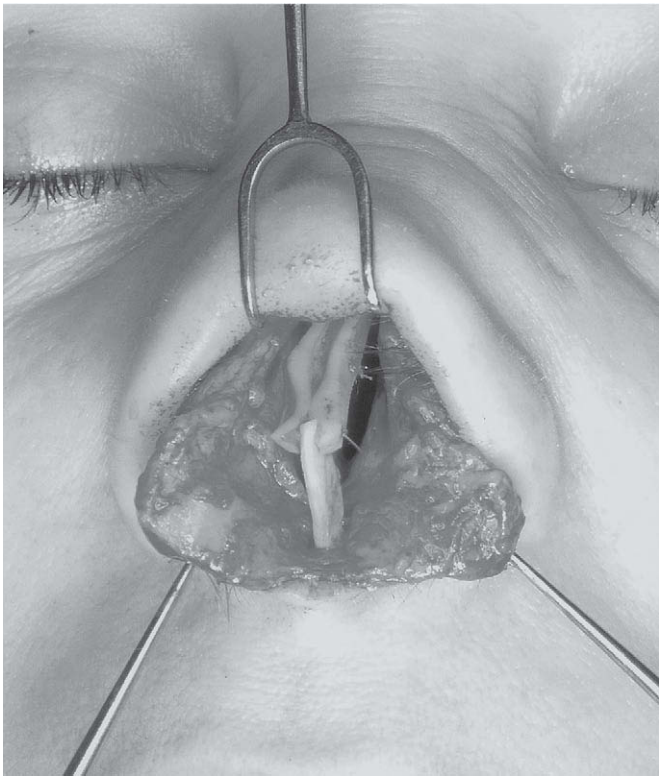

Figure 37-28. The dynamic adjustable rotational tip (DART) graft consists of a columellar strut sutured to the nasal spine and to extended spreader grafts. The extended spreader grafts are sutured between the upper lateral cartilages and the quadrangular cartilage to improve rotation and projection.

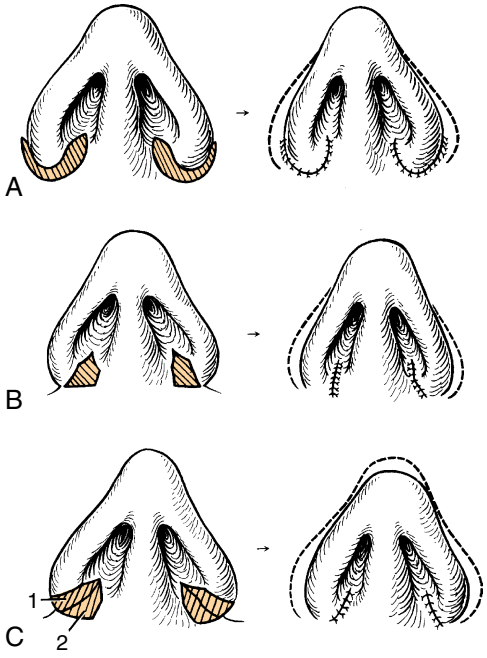

Figure 37-29. Management of the nasal base. **A,** The authors' technique done predominantly to narrow the nasal base. The superior incision, which is the inside of a curve, is lengthened by curving to meet the outer incision in the floor of the nose and laterally. This equalizes the two sides of the excision for closure. The authors use subcuticular sutures and fine skin sutures. **B,** Narrowing the nasal base by excising a wedge from the floor of the nose. **C,** A commonly performed procedure that narrows the base and reduces the height of the alae.

Although soft tissue repair can be readily accomplished at the time of initial lip repair or as revisional surgery, reconstruction will be inadequate if the asymmetry of cartilage and bone is not addressed. The authors most often use the external approach for both the unilateral and the bilateral cleft-lip nasal deformities.[29,30] In the unilateral cleft-lip nasal deformity, the lateral crus of the lower lateral cartilage on the cleft side is dissected free of both surface and vestibular skin, and the cartilage is advanced medially to match the normal side (Fig. 37-33). The position is maintained with sutures to the opposite dome to project the tip on the cleft side, along with sutures through the vestibular skin, cartilage, and surface skin (see Fig. 37-33). These 5-0 nylon transalar sutures are tied over a thin flat plastic bolus on the surface skin side only. With the open rhinoplasty it is possible, under direct vision, to stabilize the involved lateral crus further by suturing it directly to the upper lateral cartilage or septum (Fig. 37-34). This is particularly important when the cleft side is caudally displaced, resulting in a hooding deformity of the columella.

In the unilateral cleft-lip deformity, particular attention must be paid to the dislocation of the caudal septum toward the normal side and the posterior nasal septal spur on the cleft side. All septorhinoplasty techniques may be necessary in correcting the cleft-lip nasal deformity, and onlay grafts are frequently necessary beneath the alar base on the cleft side (Figs. 37-35 and 37-36). In the bilateral cleft-lip deformity, the cartilages can be precisely sculptured bilaterally and dissected free of both skin surfaces to allow medial recruitment and suturing to project the tip (Fig. 37-37).

Grafts are combined with high Le Fort I osteotomies to advance the maxilla in severe deformities associated with both unilateral and bilateral cleft lips.[31,32] Both maxillary and mandibular osteotomies may be required. There is some choice between suspension and intermaxillary wiring and miniplate fixation.[31,33] Occlusion must be precise and is combined with interdental splinting and fixation. Bone grafts are placed between the advanced maxilla and the pterygoid plates, over the face of the maxilla, and about the piriform rim (Figs. 37-38 and 37-39).

For the bilateral cleft-lip deformity, a variety of columella-lengthening procedures have been developed. Selection depends on the severity of the deformity and what previous surgery has been performed. The most commonly used procedures for lengthening the skin of the columella are the forked flap of Millard (Fig. 37-40)[34] and the advancement flap from the floor of the nose of Brauer and Cronin (Fig. 37-41).[35] Both of these procedures provide augmentation of the columella and, when combined with techniques to project the domes of the lower lateral cartilages, result in a marked improvement in the patient's appearance.

When stenosis of the nasal airway is present, the preceding techniques can be used for managing the lower lateral cartilage and septal and alar deformities, but the alar attachment must be displaced laterally to open the airway. The floor is widened with a V to Y advancement flap. The ala is then advanced laterally by excising a crescent of skin just lateral to the site of alar attachment (Fig. 37-42).

Summary

This chapter emphasizes the great variety of nasal and nasal septal deformities that can occur and the many surgical techniques that may be required to correct them. The combined internal and external deformities, dislocations, and twists require combined internal and external surgical correction. To achieve adequate correction, the surgeon's armamentarium must include the full spectrum of advanced and sophisticated techniques for septal reconstruction and corrective rhinoplasty.

The stigma of the cleft lip is often accentuated by a residual nasal deformity. As soft tissue techniques improve, it is often the nasal deformity that draws attention to the lip. Because of the distortions created by a lack of mesodermal penetration, there will frequently be persistent nasal deformities no matter how well the lip and nasal

Text continued on page 566

Figure 37-30. Noncaucasian rhinoplasty, including placement of a columellar strut; shield graft; Weir excisions; and medial, intermediate, and lateral osteotomies. **A,** Preoperative frontal. **B,** Preoperative lateral. **C,** Preoperative basal. **D,** Postoperative frontal. **E,** Postoperative lateral. **F,** Postoperative basal.

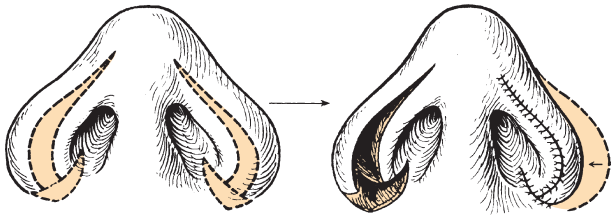

Figure 37-31. Combined reduction and thinning of the alae. For noses with excessive thickening of the ala, a wedge of skin is removed extending toward the tip. This incision should be slightly internal or toward the nasal side of the vestibule to create a more desirable roll and hide the incision.

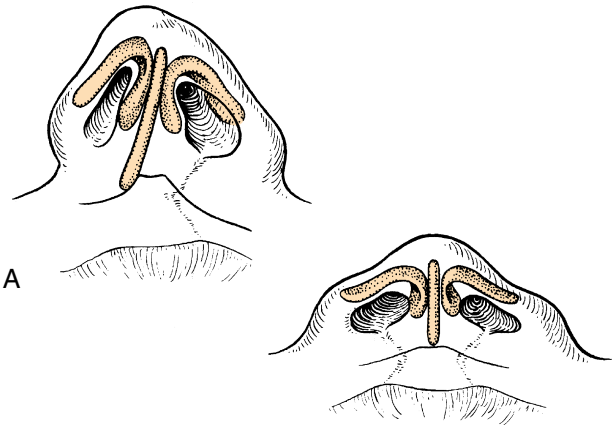

Figure 37-32. Cleft-tip nasal deformities. **A,** Unilateral cleft-lip deformity. **B,** Bilateral cleft-lip deformity.

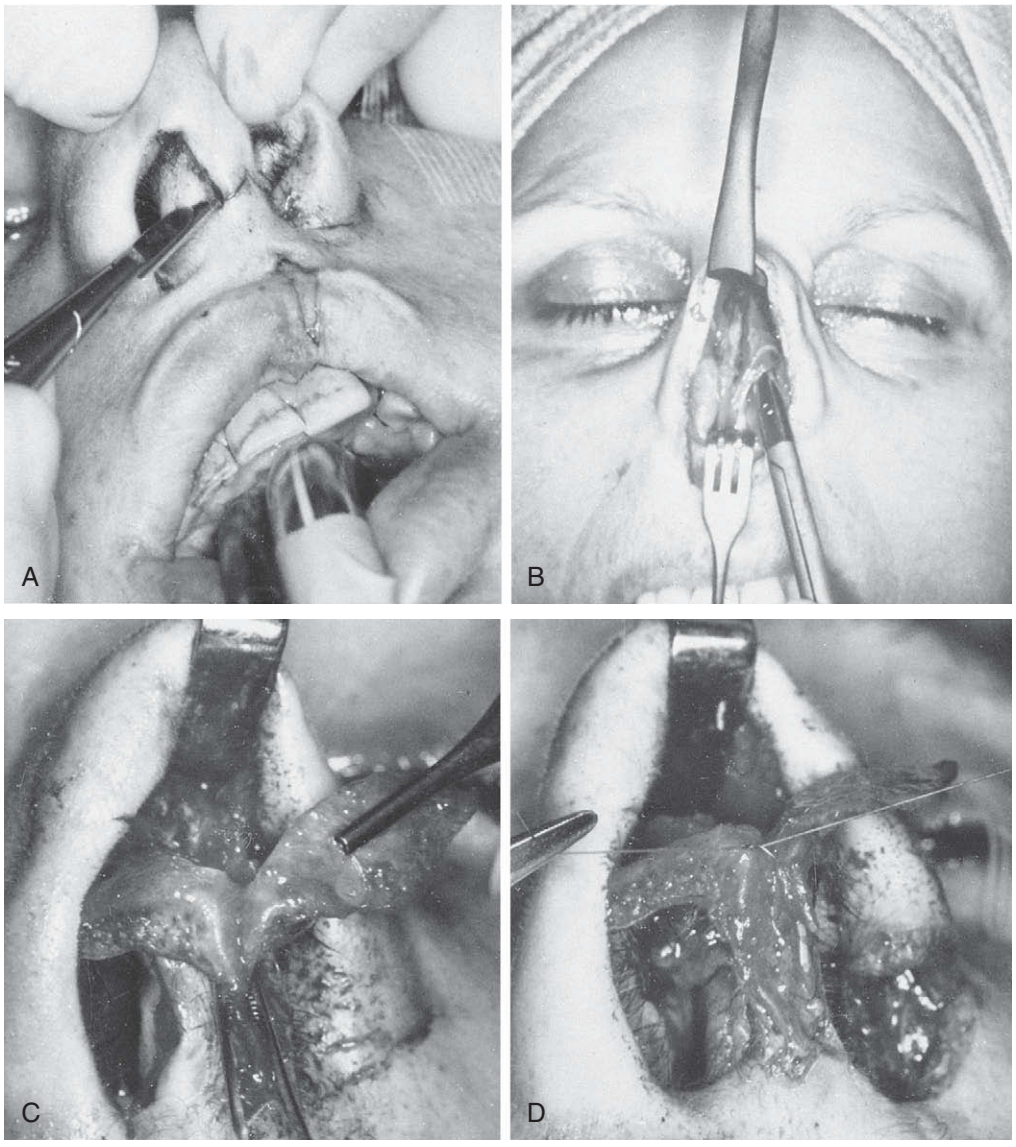

Figure 37-33. External rhinoplasty approach for cleft-lip nasal deformities. **A,** The inverted gull-wing incision is made below the base of the medial crura. **B,** The lower lateral cartilages are dissected free of the overlying dorsal skin and underlying vestibular skin. The two lateral crura are trimmed and shaped until they are symmetric. In this case the upper lateral cartilages have been sutured under direct vision to the septum along the dorsum. **C,** Complete exposure of the lower lateral cartilage on the cleft side, freeing it of both surface and vestibular skin, allows precise repositioning and sandwiching between the two skin surfaces. **D,** The two medial crura are sutured together, recruiting the lateral crus on the cleft side to project the tip on the unilateral cleft side or on both sides in the bilateral cleft deformity.

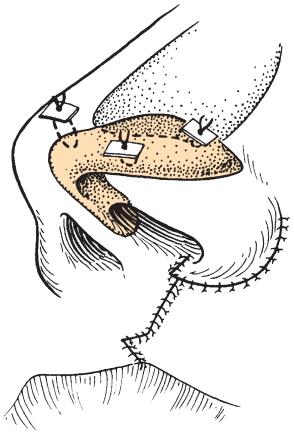

Figure 37-34. Suturing the medial crura together in the dome, sometimes with slight overcorrection for the retrodisplaced cartilage on the cleft side. Lower lateral cartilage overlaps inferior edge of upper lateral cartilage.

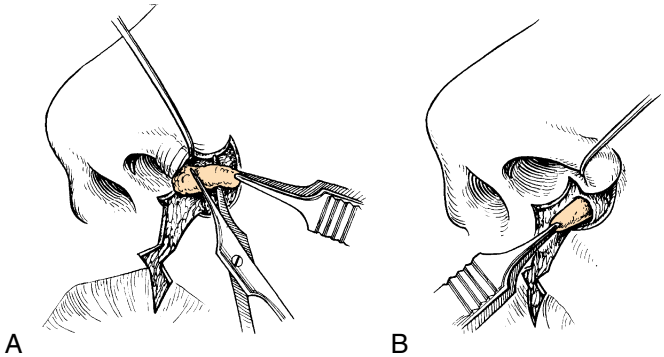

Figure 37-35. Lateral alar thinning and placement of maxillary implants. **A,** Any excessive fibrous tissue at the alar attachment is removed subcutaneously between the vestibular skin and external skin surfaces. **B,** Through the alar incision, implant material of cartilage or bone, usually obtained from the nose, is placed over the face of the maxilla beneath the lip scar and the alar base.

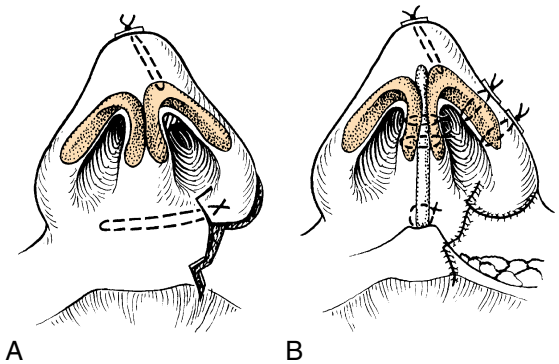

Figure 37-36. Repositioning and suturing of the lower lateral cartilage. **A,** The alar cartilage is repositioned in a slight overcorrection. A subcutaneous suture should be used to reinforce the repositioning of the alar base in a symmetric position. **B,** A composite of the complete operation shows the septal reconstruction, correction of the distorted alar cartilage, and correction of the laterally displaced alar base. Bone and cartilage grafts are placed subperiosteally over the face of the maxilla. Fixation sutures are tied over flat, plastic boluses externally.

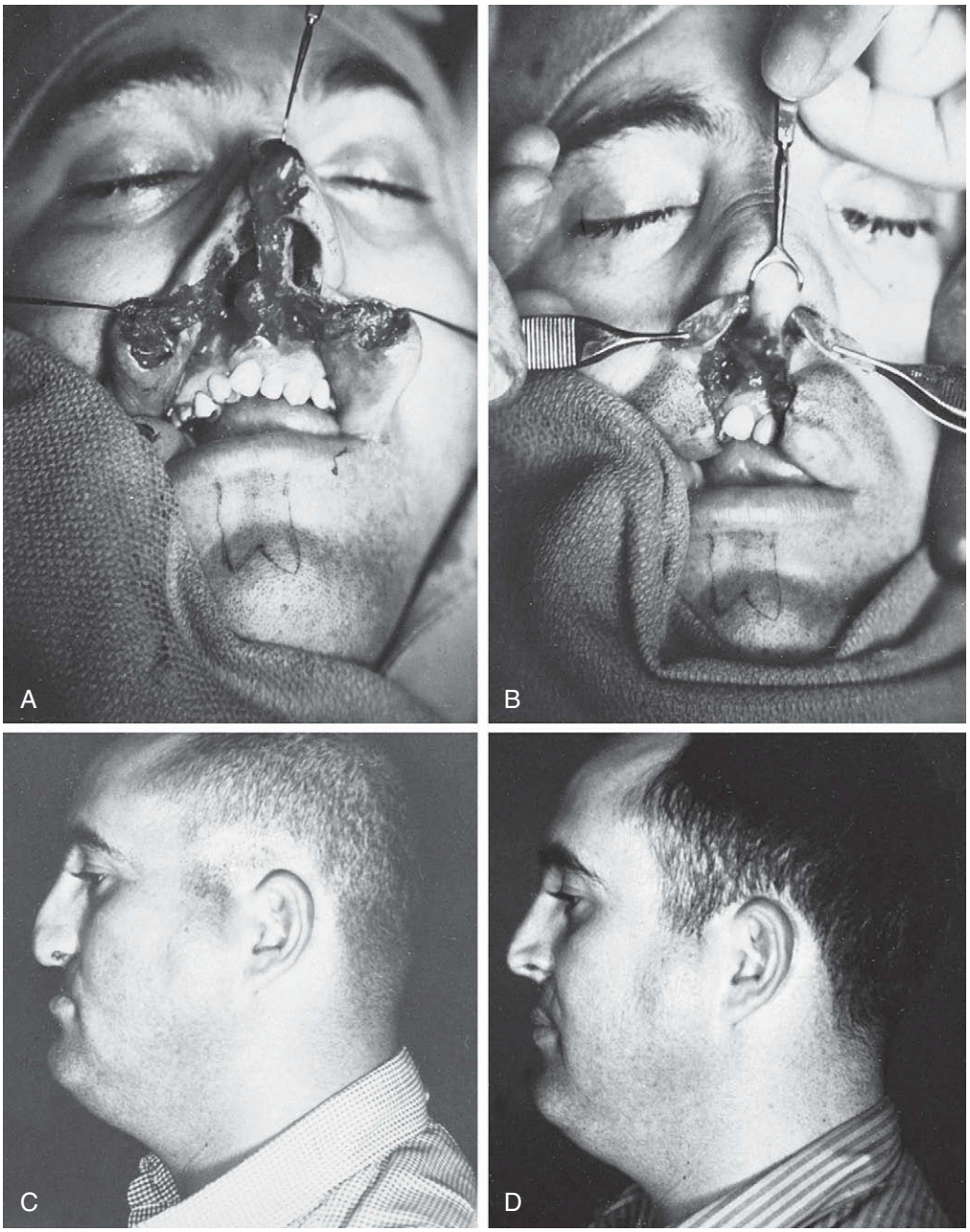

Figure 37-37. Bilateral cleft-lip procedure with Abbé flap to upper lip. **A,** An external approach by use of a transfixion incision. This differs from the external approach more recently popularized, in which the exposure is external to the medial crura rather than internal to the medial crura in the membranous septum. The synchronous lip repair is done with an asymmetric Abbé flap because of the stenosis on the right side. **B,** The lower lateral cartilages are presented bilaterally through the standard alar cartilage margin incisions and dissected free of both surface and vestibular skin so that they may be advanced into the tip, sutured together, and fixed between the surface and vestibular skin. **C,** Preoperative profile, demonstrating the disparity between the lips and between maxilla and mandible and illustrating the fact that the prolabium had been removed. **D,** Postoperative appearance. Autogenous cartilage implants have been placed in the columella, and bone and cartilage from the nose have been placed over the face of the maxilla.

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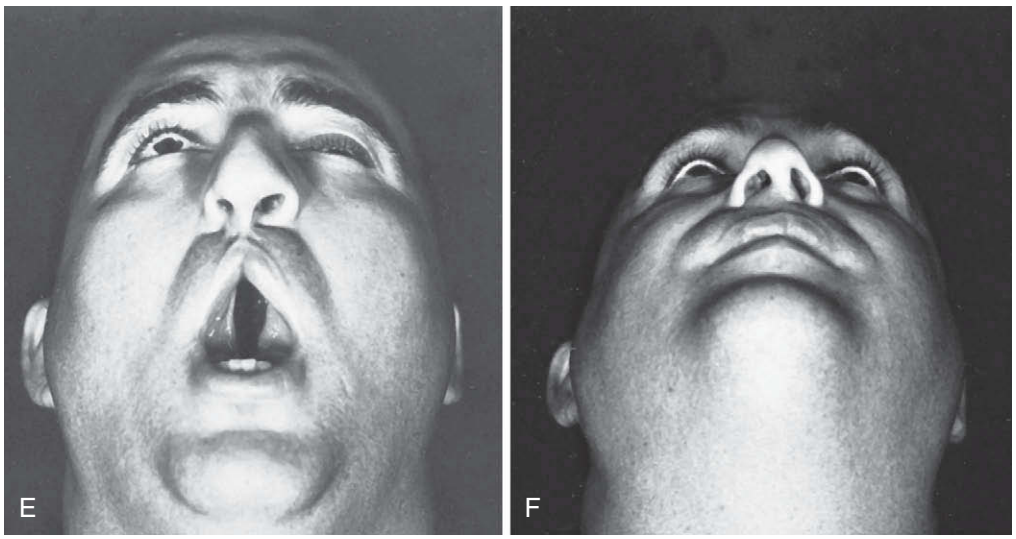

Figure 37-37, cont'd. **E,** Basal view showing the absence of a prolabium and the stenosis of the right nasal vestibule. The palate has never been repaired. **F,** Postoperative view showing the tip projection, columella lengthening, and asymmetric Abbé flap. The flap was later defatted in the floor of the right nostril.

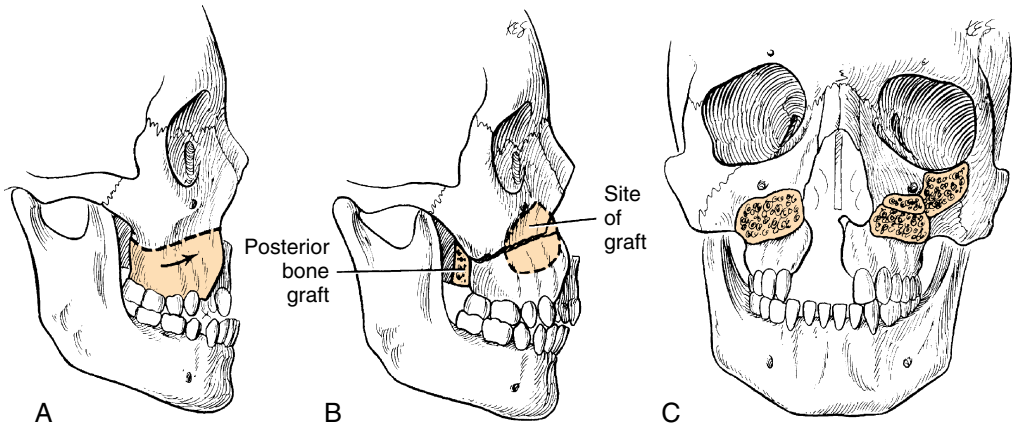

Figure 37-38. Le Fort I maxillary osteotomies to correct underdevelopment of the maxilla. **A,** When the deformity includes severe malocclusion, onlay grafts alone are not adequate, and a Le Fort I osteotomy should be performed. **B,** Bone grafts are placed posteriorly between the maxilla and the pterygoid bones. **C,** Onlay grafts over the face of the maxilla may be required as well. Maxillary repositioning must be coordinated with an orthodontist; there must be preoperative planning and placement of an intradental splint.

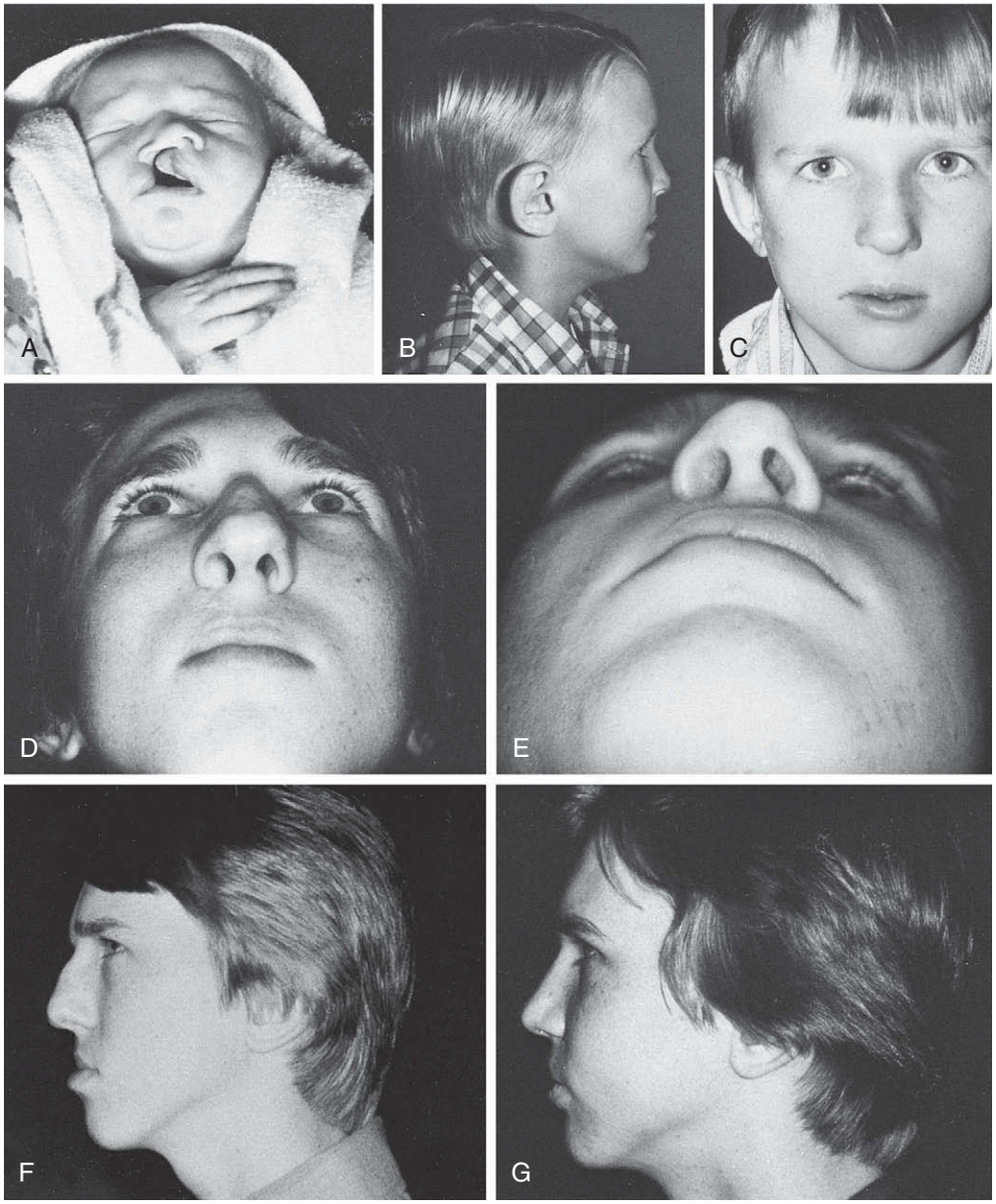

Figure 37-39. Unilateral cleft lip nasal and palatal deformities treated with maxillary osteotomies. The senior author performed the original repair of the unilateral cleft lip and palate. The preoperative photograph **(A)** demonstrates the severity of the deformity and emphasizes the lack of mesodermal penetration in the right maxilla. **B** and **C,** Early postoperative results after lip and palate repair that reveal interval profile with satisfactory nasal appearance and maxillary and mandibular relationships. **D** and **E,** A later result showing the changes that have occurred in the nasal base with correction of the caudal septal dislocation. **F** and **G,** Preoperative and postoperative appearances after a Le Fort I osteotomy and autogenous bone implants along with a revision rhinoplasty at 18 years of age.

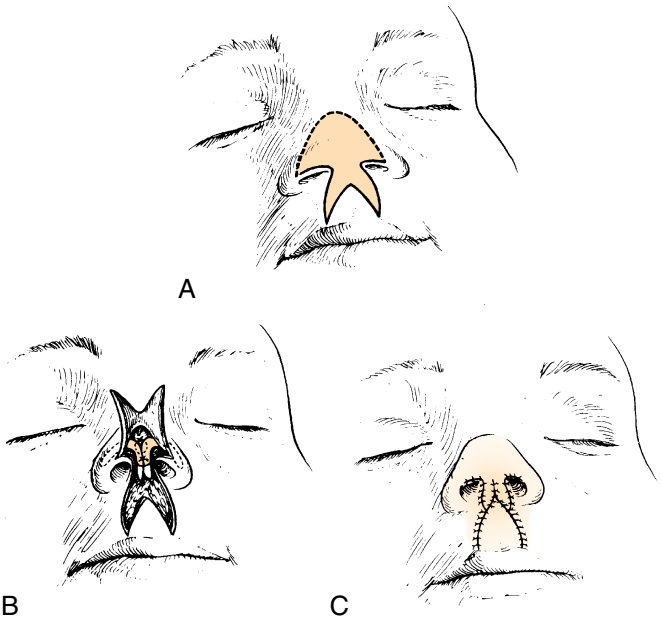

Figure 37-40. Millard's forked-flap technique for lengthening the columella. **A,** Each flap should be carefully designed for proper length and width. Modifications may be necessary, depending on the degree and location of the lip scarring. **B,** Millard's technique should be combined with an external rhinoplasty approach to increase nasal tip projection. **C,** The lip flaps are advanced upward to augment the columella.

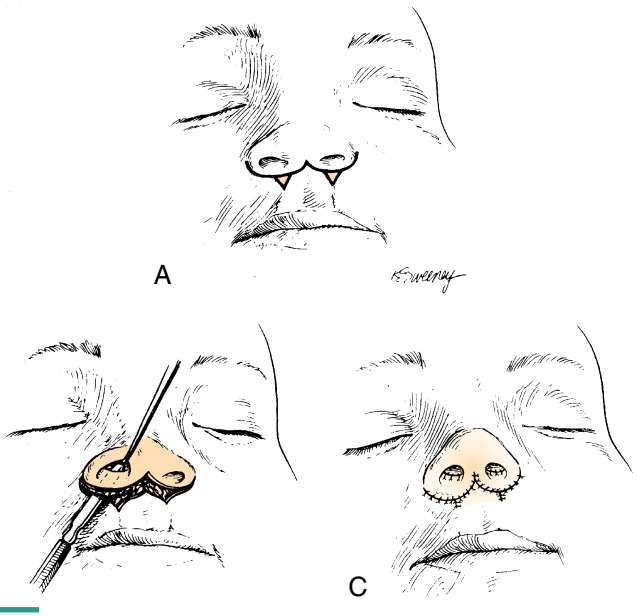

Figure 37-41. The Cronin technique for lengthening the columella. **A,** Incisions are made beneath the nasal sills bilaterally. **B,** The nasal sills are dissected free bilaterally and advanced medially to elongate the columella. The Burow triangles may be excised in the bilateral cleft-lip scars. A columella strut should be sutured into position to maintain the tip projection. **C,** The incisions are closed, advancing the nasal sill tissue upward to augment the columella.

abnormalities are repaired at the time of primary repair. The cleft-lip nasal deformity presents unique surgical problems, which may be difficult to correct.

The patient with a severe nasal deformity should not leave the surgeon's care breathing less well than he or she did before the operation. These patients with complicated nasal deformities deserve the surgeon's critical attention to function and appearance during the planning of surgical correction. In most cases, the aesthetic appearance is markedly improved, even when a major reorganization of the nasal framework is required.

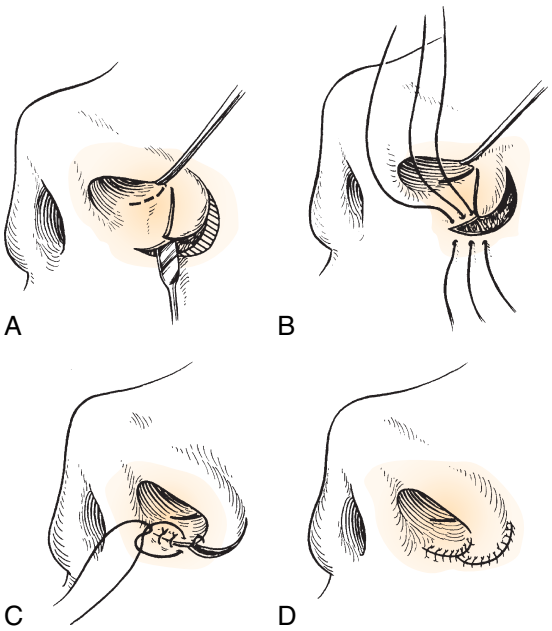

Figure 37-42. Correction of nostril stenosis by increasing the width of the nasal floor. **A,** A laterally based V incision is made across the nasal sill, and a crescent of skin is excised laterally. **B,** The alar base is advanced laterally. **C,** The nasal sill is closed, advancing the alar base as a V to Y. **D,** The alar-facial incision is closed.

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CHAPTER THIRTY-EIGHT

Noncaucasian Rhinoplasty

Stephen S. Park

Hong-Ryul Jin

Key Points

- Cultural variances impact communication, expectations, and aesthetic standards.
- The noncaucasian nose has key anatomic distinctions from the Western nose that must be borne in mind.
- Nasal tip skin is typically thick and sebaceous, while the lower lateral cartilages and septum are paradoxically small, weak, and deficient.
- The nasal bones are broad and flat.
- The low radix and underprojected nasal tip are common features.
- Augmentation to the tip and dorsum remain the workhorse maneuvers.
- Implants should not leave pressure on the overlying skin.
- Alar base surgery should be performed only judiciously.

The primary objective in a noncaucasian rhinoplasty is fundamentally the same as with all rhinoplasty patients. Specifically, the goal is to create a nose that allows facial harmony and balance to radiate from a person's expression. It is not to sculpt a nose that draws attention to it or attempts to define an individual's beauty. There are certain aesthetic truisms that are ubiquitous in different ethnic cultures, such as symmetry and youth. The nose, on the other hand, has many unique cultural nuances that characterize an ethnic beauty. Understanding these specific nasal features along with the cultural nuances and social framework surrounding the patient are all paramount to a successful noncaucasian rhinoplasty. Transplanting an elegant and sculpted occidental nose onto an Asian face will rarely appear natural or aesthetic.

Common features of ethnic noses are lack of definition, broad and amorphous tips, and a flat nasal root. As such, the goal is often to create improved elegance to the nose through sharper lines, tip defining points, and clear shadows. Dorsal augmentation, tip refinement, and narrowing of the pyramid are typical goals in the noncaucasian nose. Beyond these generalities, however, are subtleties that can be understood only through continuous exposure to these types of patients. There are unique considerations with skin characteristics, degree of soft tissue contracture, integrity of lower lateral cartilages, and modifications of normal aesthetic subunits.

The ethnic patient also presents with idiosyncrasies in communication, expectations, and emotional responses to surgical outcomes. The language barrier may leave more ambiguity in terms of patient wishes and can be difficult to overcome through a translator. Moreover, vocabulary and superlatives often mislead the dialogue. Expectations and the manner in which patients respond to surgical outcomes vary among cultures. For example, Koreans tend to be overt or melodramatic in their postoperative reaction. Japanese, on the other hand, are characteristically more reserved and introverted; they are less likely to share openly their disappointment, although those sentiments may be prevalent.

Anatomic Considerations

Although there are individual variations, most noncaucasian noses are anatomically characterized by thicker skin with abundant subcutaneous fibrofatty tissue, a weaker cartilaginous framework, short nasal bones, underdeveloped anterior nasal spine, low nasal sill, smaller quadrilateral septal cartilage, and inferior turbinate hypertrophy (Fig. 38-1). The associated cutaneous findings include a wide and underprojected dorsum, a low radix and nasion, a nasal tip that is bulbous, lacking definition, underprojected, and either ptotic or overrotated (short nose), with a short columella and an alar base that is wide and flaring (Table 38-1).[1-4] The thicker skin can be an important differentiating feature because it allows for great acceptance of nasal implants, including alloplastic, and camouflages augmentation grafts in a more natural fashion. It also obscures minor changes performed on the cartilaginous framework, necessitating overcorrection as a rule.

In addition to the thicker tip skin, the lower lateral cartilages are weak and pliable, making the creation of tip definition a challenging task. Cephalic trim and dome binding sutures are often inadequate; reinforcing struts and projecting cap grafts tend to be more effective. The short columella merits some consideration when placing a transcolumellar incision for an external approach. Because the tip often requires some projection, one should place the transverse incision lightly lower, allowing it to rise with increased tip projection. Intranasally, most noncaucasian noses are characterized by a straight septum with widely patent internal nasal valves, large inferior turbinates, and a low bony nasal sill. The size of the quadrilateral septal cartilage is typically smaller and thinner, ironically leading to a dearth of desirable donor material in a setting where augmentation is often needed. Consequently, one of the primary sources of augmentation material in Asia remains alloplastic materials.[5]

The short and wide nasal bones make traditional osteotomies more challenging as the bone cuts easily drift into the ascending process of the maxilla.[6-7] They also predispose to the inverted V deformity

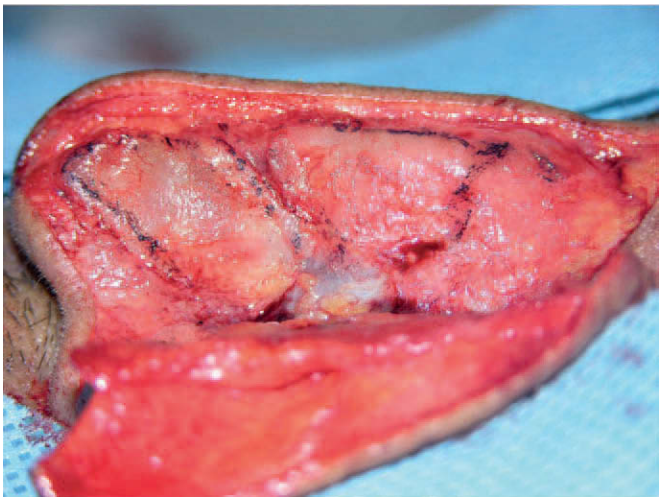

Figure 38-1. The anatomy of a typical noncaucasian nose. Note the weak cartilages, short nasal bones, and thick skin.

Table 38-1

Characteristics of the Asian Nose

Site	Unique Characteristic
Radix	Low and inferior; short nasal bones
Dorsum	Underprojected, short
Tip	Bulbous, poor definition, underprojected, weak lower lateral cartilages
Ala	Thick, flared; with short columella
Skin	Thick
Septum	Straight, lesser quantity, thinner; small anterior nasal spine
Inferior turbinate	Hypertrophied

during the rare hump reduction. Fortunately, the wide internal valve and thick overlying skin make clinical nasal obstruction from this etiology a rare entity in noncaucasians.[8] The flat nasal bones and nasal root extend inferiorly onto the cartilaginous dorsum. Therefore most patients require augmentation to the dorsum as well as the radix area.

Aesthetic Considerations

Cultural definitions of beauty vary widely and it is not the desire of all noncaucasians to acquire Occidental features, nor do the aesthetic norms of Western beauties transition to all ethnic faces. An attractive Asian nose, for example, has a slightly lower nasion, which is somewhat below the upper eyelash line. Textbook normative data of the radix and nasion describe the supratarsal crease for the caucasian face as the ideal landmark, best matching their angular topography. Asians have a flatter contour and the high radix would appear unnatural.[9] Because the dorsum is often flat and wide, it occasionally also requires lateral osteotomies to narrow the bony aperture in addition to the dorsal augmentation. In regard to tip aesthetics, projection, rotation, and volume are the three most important factors to consider. These three factors influence one another in creating an ideal tip shape. The angulated tip with clear tip defining points is not the ideal appearance for most noncaucasians. A more rounded and lobular tip is preferred as it best blends with the cherubic facial shape and cheekbones. It is common for a retruded premaxilla to coexist with the small nose, creating a retrusive columella and an acute nasolabial angle. A plumping graft to efface the nasolabial angle can improve balance and create the illusion of tip rotation. A wide alar base with flaring of the alar lobules can be found in African-Americans and descendants of Southeast Asians (Filipinos, Malaysians). Northeast Asians (Japan, Korea) tend not to have the same degree of alar flaring.

Augmentation Rhinoplasty

Concept

Dorsal augmentation is a common task in the noncaucasian nose. Although the dorsum appears wide, lateral osteotomies are only rarely needed because the midline augmentation creates the illusion of narrowing. For many years in Asia, the alloplastic, L-shaped silicone strut was inserted to augment the dorsum and lengthen the short nose.[10] The tension on the tip occasionally proved too much for even their thicker skin, and cover breakdown with subsequent implant extrusion were unfortunate sequelae. More recently, many surgeons use alloplastic materials for the dorsal upper two-thirds and autologous tissue to the tip region (e.g., tip or cap grafts, columellar struts, and caudal extension grafts).[11-13]

The surgical approach for augmentation rhinoplasty is largely influenced by the need for tip work. When only dorsal access is needed, an endonasal route is usually used, either through an intercartilaginous approach or via an extended septoplasty incision. When tip manipulation is required, the external approach can offer excellent control. This is particularly true when the tip is in need of projection and lengthening as well.[14]

Choice of Augmentation Material

There are numerous factors to consider before deciding which augmentation material to use, the amount of augmentation needed, the availability of septal and conchal cartilages, skin thickness, and certainly the patient's preferences.[11,12,15] The potential disadvantages of alloplastic implants are widely recognized, but the severity and likelihood of occurrence remains controversial. The risk of rejection and extrusion of alloplastic implants is of paramount concern, but contemporary porous materials, particularly when used under thicker, ethnic skin, may reduce that risk. Thorough patient education and informed consent is imperative during this preoperative consultation. Common alloplastic implants include Medpor (porous high-density polyethylene; Porex Inc., Newnan, GA), expanded polytetrafluoroethylene (ePTFE), and silicone (Fig. 38-2).

Autogenous tissue remains the gold standard but can have limitations and potentially significant comorbidities. Limited availability is a first concern in noncaucasian noses. Even in primary surgery, the volume of available septum is limited and conchal cartilage is generally less predictable in terms of resorption. Costal cartilage has an unlimited supply but is associated with greater morbidity and investment. Long-term warping of the rib graft is the primary complication and is best avoided by carefully carving out the central core of the graft.

Patients in need of only a limited degree of dorsal augmentation are usually excellent candidates for autologous implants with septal or conchal cartilages. One must carefully inspect and palpate the septum to verify the presence of adequate cartilage. With revision rhinoplasties, the volume of native septal cartilage cannot be counted on and alternative sources should be planned. It is usually necessary to stack multiple layers of cartilage on one another, including ear cartilage. One should suture-secure the pieces of cartilage together, and carefully bevel all edges (Fig. 38-3A and B). Rib cartilage affords adequate volume to augment major deficiency of the dorsum as well as the rigidity needed to lengthen the nose through a caudal extension graft or strong L strut (see Fig. 38-3C).

Technical Considerations to Dorsal Augmentation

Harvesting autogenous cartilage grafts is often performed first. Septal cartilage harvest is readily performed and one must ensure an adequate dorsal and caudal strut (10 mm) and avoid disruption of the keystone area. Conchal cartilage is harvested through either an anterior or pos-

terior approach. The skin and cartilage incisions are staggered such that a small rim of cartilage supports the closure of the skin. One preserves the root of the helix between the cavum concha and cymba concha, thus maintaining the shape of the auricle. Frequently, multiple layers of the septal and conchal cartilage are stacked and sutured together in order to obtain a desirable height. Particular attention must be made to carving of the edges of the grafts to ensure a smooth transition from the dorsum to the sidewall and at the nasion to avoid a step deformity there. The grafts can be fixed temporarily with two 25-G needles while incisions are closed (Fig. 38-4).

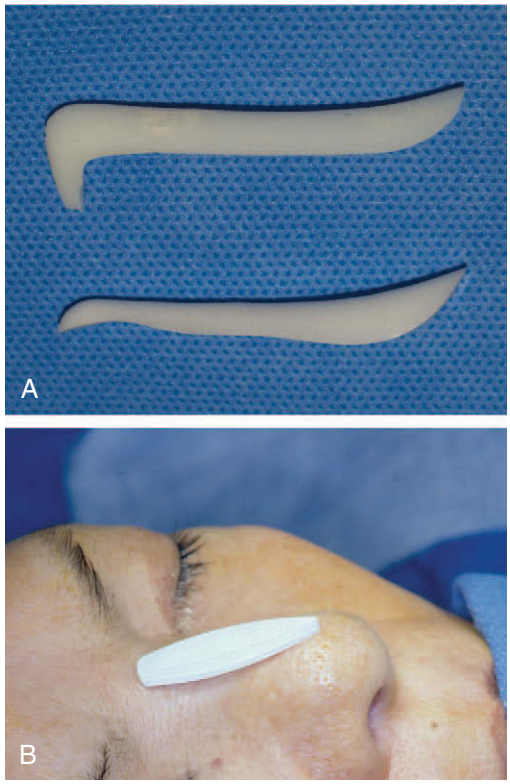

Figure 38-2. Alloplastic implants. **A,** L-shaped and straight silicone implants. **B,** e-PTFE implants in a reinforced, prefabricated form.

Rib cartilage is harvested from the sixth to eighth rib through a 3- to 4-cm skin incision. The incision is performed at the inframammary crease in women to camouflage the incision scar (Fig. 38-5). The rectus muscle is not incised horizontally, but split vertically and retracted, thus reducing the postoperative pain. It is imperative to carve the precise central core of the rib cartilage to avoid untoward warping. Immersion of the cartilage in warm saline for 30 minutes can confirm an accurate shape.[16] A strip of perichondrium from the rib is saved for future use to camouflage graft borders, especially under the nasion or nasal tip.

Before the injection, it is helpful to mark the pocket for implantation (Fig. 38-6). This can guide the surgeon as the pocket is created, reducing the risk of creating an excessively large or asymmetric pocket, which may predispose to displacement. Regardless of the approach (external vs endonasal), the dissection begins in the precise midline, on the supraperichondrial plane over the anterior septal angle of the dorsal septum. The nasal bone periosteum is sharply incised and elevated up to the new radix height. Careful and symmetric dissection over the dorsum prevents malpositioning of the implant. For isolated radix grafts, the inferior opening into the pocket is made slightly tight to reduce the risk of implant migration inferiorly. A single large rib can function well for major dorsal restoration (Fig. 38-7).

Alloplastic implants can be trimmed and sculpted to fit best the needs of the individual augmentation. It is best to minimize direct handling of the synthetic implant and to irrigate copiously with an antibiotic solution before and after implant insertion. Avoiding undue tension on the implant is critical as it may lead to greater risk of skin breakdown and extrusion, especially along the tip. A combination of alloplast and autogenous implants can be effective.

Hump Reduction

Concept

The Middle Eastern patient is the most common group of noncaucasians who request dorsal hump reduction. While the technical proce-

Figure 38-3. Autogenous cartilage grafts for augmentation. **A** and **B,** Stacked cartilage. **C,** Articulated costal cartilage.

Figure 38-4. Temporary fixation of the dorsal graft with two 25-G needles.

Figure 38-5. When harvesting rib cartilage in women patients, the incision is placed along the inframammary crease to camouflage the incision scar.

dure is not dissimilar to that for the Occidental patient, the greatest attention should be paid to the preoperative counseling in terms of expectations and degree of change. This is especially germane to the male patient in whom the strong dorsum has cultural implications. Men from the Middle East may present with large dorsums that would be regarded as excessive in most cultures but are considered a masculine status symbol in Middle Eastern countries. Removing the hump, and certainly scooping the dorsum, may have tremendous untoward implications. The second important consideration in any hump reduction is the accurate diagnosis of the anatomic etiology. Is the hump made of bone, cartilage, or both? Does the hump appear worse due to its relative position (e.g., low radix, small chin)? Asian and African-American

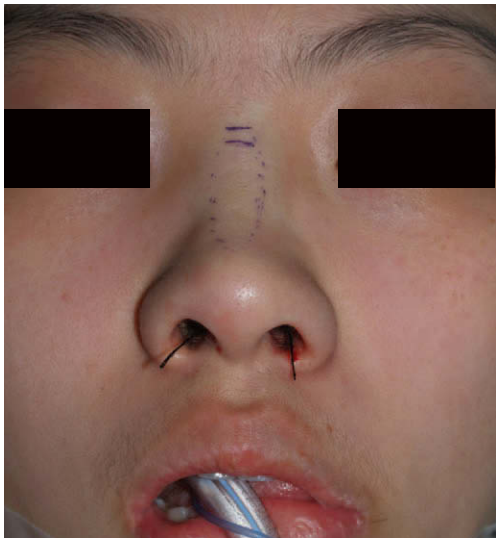

Figure 38-6. Before injection of local anesthetics, the cephalic edge of the implant with presumed graft pocket is marked on the nasal dorsum.

patients occasionally require a selective dorsal hump reduction to create a natural dorsum that is harmonious with the tip and radix. Many times, a simultaneous dorsal reduction and augmentation is warranted to achieve this goal. Most Asian noses differ from their Western counterparts in that the size of the nasal hump is not large and is frequently associated with a relatively low radix with underprojection or underrotation of the nasal tip.[8] Therefore correcting a hump in noncaucasians has distinct differences in concept and techniques that stem from unique anatomy and aesthetic guidelines. First, the relative hump size must be balanced with the additional need for augmentation of certain areas of the dorsum; the augmentation may entirely obviate the need for dorsal reduction. This procedure is technically more challenging than resecting a larger hump (Fig. 38-8). Because the nasal bones are short, spreader grafts or a camouflage graft is often necessary after resection of a moderate size hump to prevent middle vault collapse and the inverted V deformity. The native dorsum has a natural width that functions as a physiologic spreader graft. The hump reduction redefines a new dorsum that does not have the same width as the original one, thus giving rise to the need for spreader grafts.

Technique

An endonasal approach is often used when the hump reduction is mild and limited to the bony upper third alone, in distinction to the dorsal hump, which involves the cartilaginous middle vault as well. The latter is more common and often requires prophylactic spreader grafts to avoid the potential "hourglass" deformity or inverted V. This maneuver can be easier to secure through the external route.

For the endonasal approach, a unilateral or bilateral intercartilaginous incision combined with partial transfixion or hemitransfixion incision is used. Regardless of the approach, the anterior septal angle and the entire nasal dorsum are accessed in the subperichondrial plane. The pocket should be uniform and symmetric. A mild bony reduction is often performed with just rasping and offers the most control. It is important to keep in mind the planned tip projection as it affects the dorsal modification. When the cartilaginous dorsum is being reduced as well, it is usually trimmed with a blade before working on the bony portion. A No. 15 or 11 blade is held at the bony-cartilaginous junction of the dorsum in the horizontal plane and advanced caudally in the plane of reduction to excise the cartilaginous portion of the hump that transects the upper laterals and the cartilaginous septum, leaving it attached to the nasal bones (Fig. 38-9A). If an aggressive reduction is planned, the intranasal mucosa within the internal nasal valve should be elevated off the overlying upper lateral cartilage (ULC) and dorsal septum, thus preserving its integrity. This aids in giving support to the

Figure 38-7. Preoperative and postoperative photographs of a female patient who had augmentation rhinoplasty using autogenous rib cartilage. **A** and **B,** Frontal view. **C** and **D,** Oblique view.

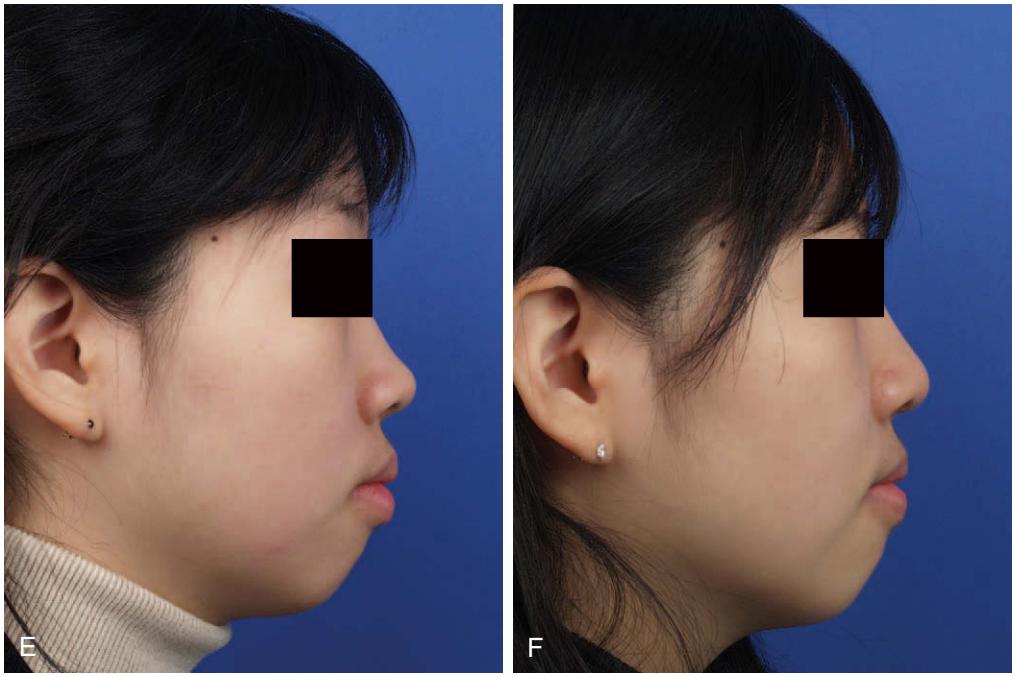

Figure 38-7, cont'd. **E** and **F,** Lateral view.

internal valve after the ULC has been disarticulated off its attachments to the septum.

A 10-mm Rubin osteotome is then inserted under the cartilaginous segment and the bony dorsum is reduced in the desired plane, removing the entire osseocartilaginous hump en bloc (see Fig. 38-9B). Judicious rasping and cartilage trimming is performed with careful and repeated palpation of the dorsum. Completion medial or lateral osteotomy is performed either endonasally or percutaneously to close the resultant open roof deformity. Spreader grafts with autogenous septum are suture-secured between the dorsal septum and ULC in order to maintain middle vault width. Dorsal onlay grafts are used to achieve the desired height of the dorsum or to camouflage any remaining irregularities. Tip surgery is usually reserved for the end of the procedure to achieve a harmonious dorsum.

Correction of a Deviated Nose

Concept

Correction of a deviated nose remains one of the most challenging problems that rhinoplasty surgeons encounter.[17,18] The difficulty is linked to the complex nature of the underlying anatomic deformity, challenging preoperative diagnosis, presumed symmetry in healing and contracture, and the unforgiving nature of the frontal view. Despite the various surgical philosophies and techniques, the basics of surgical strategy do not change and begin with release of deforming forces, structural realignment through reconstruction of the key skeletal support, and correction of functional problems. These strategies should be individualized to address the wide anatomic variations between patients. The strategies include many critical techniques, among which there are four key maneuvers to be effective: (1) septum straightening, (2) complete osteotomies, including intermediate osteotomies, (3) long and wide spreader grafts for cartilaginous dorsal deviation, and (4) strategic camouflage. Twisted dorsums in the underprojected nose (e.g., many noncaucasian noses), often require a large dorsal augmentation to camouflage the twisted dorsum simultaneously. In this setting, it is often not necessary to correct subtle deviations from midline.

Technique

Twisted noses limited to the upper third are corrected with osteotomies. Intrinsic deformity and asymmetry often require an intermediate osteotomy, and they should be applied liberally. Two additional areas that hinder the realignment of the nasal bones include the deviated bony septum that is impeding the complete medialization of the nasal bone, and the deviated frontal beak. For this, one may need to mobilize the bony septum intranasally and perform a *percutaneous osteotomy* in the midline nasion, allowing full mobilization of this superior bony segment.

When the middle vault is twisted, it is usually best addressed from the dorsal approach, that is, the external route. The anatomic culprit may be dorsal septum, intrinsic deformities of the ULCs, displaced attachments between the two, or asymmetric scar contracture. It may be challenging to diagnosis this preoperatively and some anatomic variants are only discovered after the nose is degloved. Thus it is important to be prepared to modify surgical plans intraoperatively. The general approach for correcting the twisted septum involves a progressive destabilization of the deviated cartilages, reestablishing a straight framework, followed by fixation. Selective elevation of the mucoperichondrium and release of the ULC from the concave surface reduce some of the binding forces and allow the septum to straighten, especially along the anterior septal angle. Partial thickness, relaxing incisions on the concave side, and rigid stenting with bony septum or cartilage, can be effective as a next step (Fig. 38-10). A significant deformity may require a complete extracorporeal explantation and reimplanting a straight segment.

Camouflage grafts should not be underestimated, and can be extremely useful as adjunct steps to smooth the topography across the middle vault. Discs of crushed or lightly bruised cartilage can be secured over areas of indentation and quickly correct any residual concavity.

Tip Surgery

Concept

Many noncaucasians have a poorly projected tip that is somewhat amorphous with little definition. The weak lower lateral cartilages, deficient caudal septum, and relatively thick skin all contribute to this phenomenon. The primary aim for tip surgery in this group is projection, rotation, and definition, but not to the extent done in caucasian noses. The overly sculpted and angulated tip will not match the aesthetic ideals of the noncaucasian face.

Figure 38-8. Preoperative and postoperative photographs of a female patient who had hump resection, dorsal augmentation, and tip surgery. **A** and **B,** Frontal view. **C** and **D,** Oblique view.

Figure 38-8, cont'd. **E** and **F,** Lateral view.

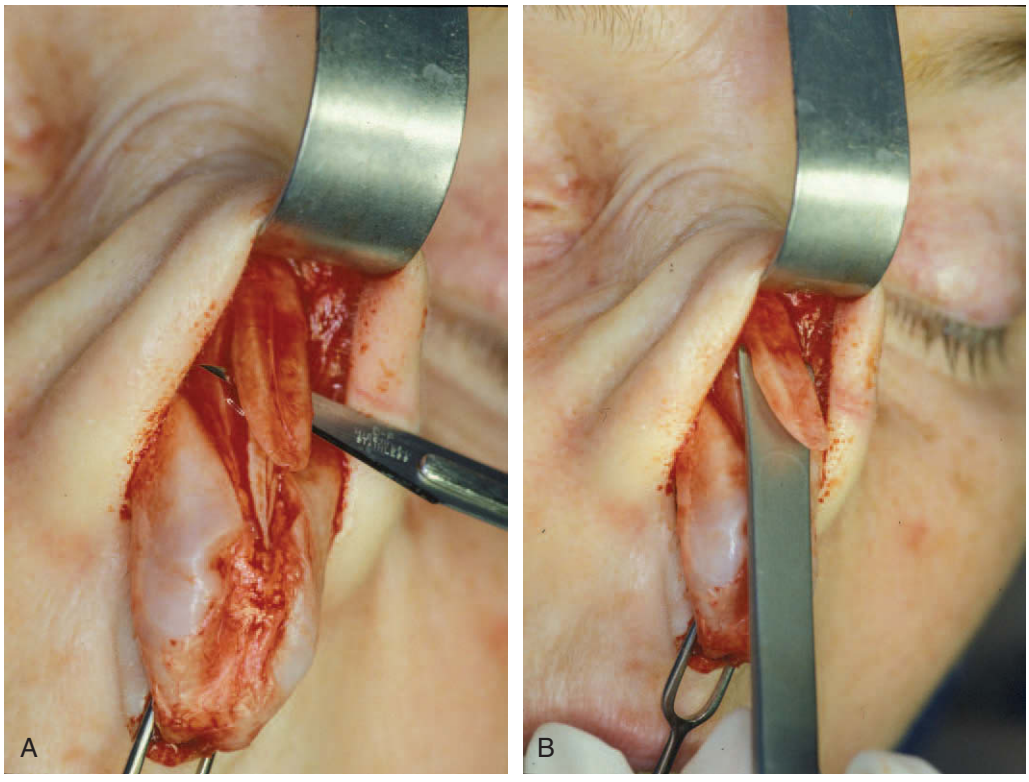

Figure 38-9. Hump resection. **A,** Cartilaginous resection with a #11 blade. **B,** Bone resection with an osteotome.

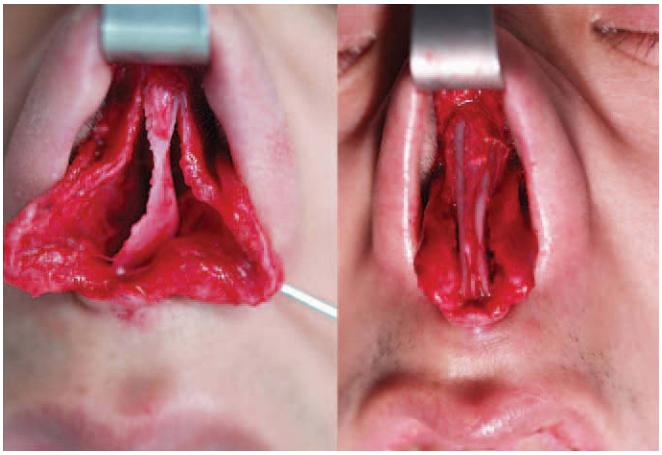

Figure 38-10. Correction of a deviated cartilaginous septum by bilateral spreader grafts. Before *(left)* and after spreader grafts *(right).*

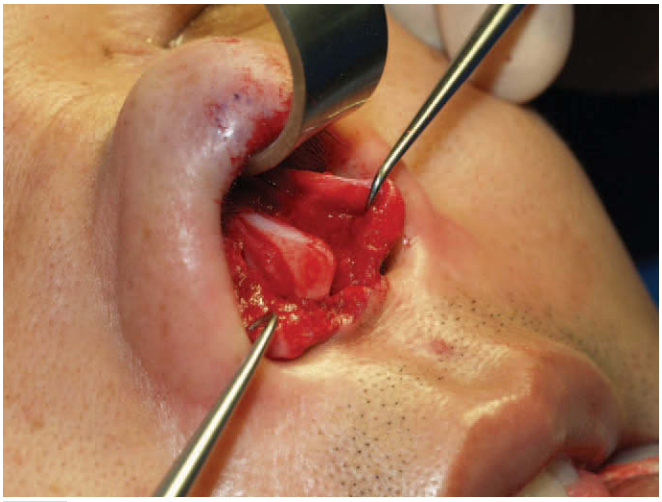

Figure 38-11. Caudal extension graft for tip control.

In years past, the tip was augmented in conjunction with the dorsum with a strong L-shaped silicone implant. Long-term complications with implant extrusion or skin breakdown have led to a change in practice, using a separate alloplast for the dorsum and strictly autogenous material for the tip.[11-13] Despite these advances, there are inherent limitations to the amount of change one can impart to the tip and the surgeon should be realistic in planning. Structural grafting that minimizes tissue sacrifice and that is based on firm septal support is the basis for achieving a desirable projection and rotation of the tip. Overaccentuation of tip projection with resultant cephalic rotation creates the illusion of a short nose, a common pitfall for many rhinoplasties done in Asian patients.

Technique

Cap or shield grafts carved from septal cartilage represent the workhorse for tip-plasty in noncaucasians, providing projection and improved definition. This technique is used only with great caution in the Occidental population because of their thin skin and the continued contracture that ensues, occasionally leading to deformities at the tip. The thicker cover is more forgiving and this complication is exceedingly rare in this ethnic group. The tip grafts should be based on a firm platform, frequently including a strong columellar strut or caudal extension graft. Caudal extension grafts can also provide a firm foundation upon which the lower lateral cartilages can be repositioned, altering projection, rotation, and nasal length (Figs. 38-11 and 38-12).

Tip grafts can be inserted endonasally through a marginal incision and sit in a precise pocket. Bilateral incisions will facilitate a symmetric pocket in the midline. The marginal incision allows immediate access to the dome of the nasal tip, allowing for an endonasal insertion of a tip graft. Larger grafts that require precise suture-securing can be inserted through a wider marginal incision with extension along the medial crura or through an external approach (Fig. 38-13). The soft tissue envelope is dissected, exposing the lower lateral cartilage and the dome, enabling various tip sutures. Shield grafts provide augmentation to the infratip lobule as well and can be inserted either endonasally or externally (Fig. 38-14).

A long shield graft is effective in increasing tip projection and augmenting the infratip lobule segment. However, if the cartilage is thin and under pressure, the superior part of graft may rotate cephalically, making the nose look short. This can be prevented by a buttress graft behind the shield graft or by putting the cap graft in a position that offsets the rotation while achieving the projection.

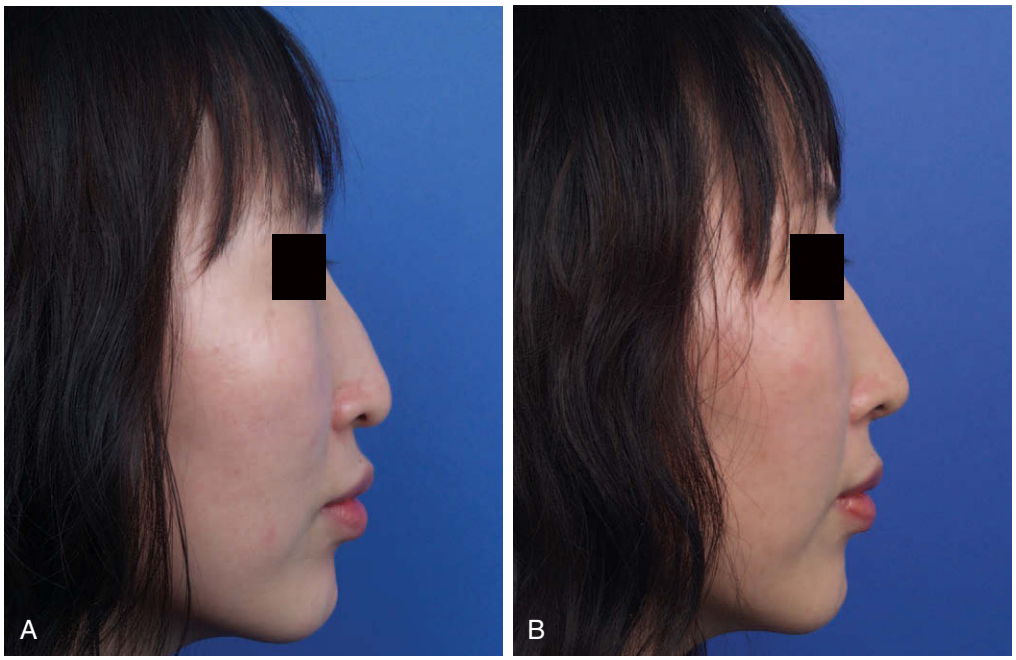

Figure 38-12. **A,** Lateral view of a patient with tip ptosis. **B,** Correction with a caudal extension graft.

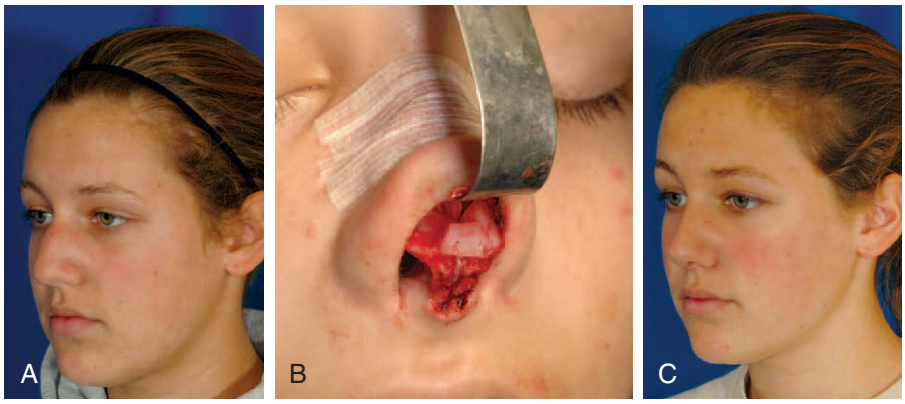

Figure 38-13. Cap graft. **A,** Preoperative view. **B,** Intraoperative cap graft suture secured. **C,** One year postoperative.

Figure 38-14. Shield graft providing tip projection, definition, and nasal length.

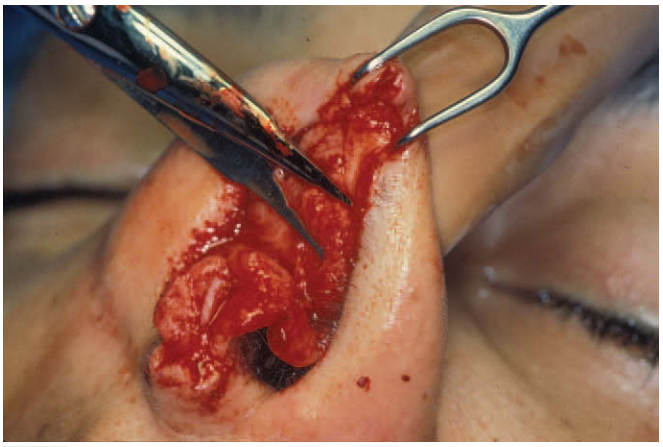

Figure 38-15. Thinning of nasal subcutaneous musculoaponeurotic system and subcutaneous fat from the soft tissue envelope.

Reshaping the existing lower lateral cartilages is a common maneuver in the caucasian nose but much less effective with ethnic noses. The limited quantity and integrity of cartilage diminish the applicability of suture techniques such as dome binding sutures and lateral crural steal techniques. In select cases, however, they can complement tip grafts. Cephalic trim has little if any role in the noncaucasian.

Thinning the robust subcutaneous tissues along the tip lobule can be effective but remains controversial (Fig. 38-15). This cannot serve as the primary means of narrowing the tip, but may permit more distinct features of tip grafts to create definition. The disruption of the nasal SMAS (subcutaneous musculoaponeurotic system) will create extensive scarring and make any revision dissection extremely tedious. One may also argue that the excised tissue will be replaced with scar and that the graft borders will be blunted.

Alar Base Modification

Alar base aberrancies can be viewed as one of two problems: (1) flaring of the alar lobules and (2) excessive width of the alar/facial junction. Both are common findings in the noncaucasian nose, especially in African-American and Southeast Asian patients, including Malaysians and Filipinos. Interestingly, it is uncommon in Northeast Asians such as Koreans and Japanese. Modification of the alar base is generally indicated in only the most severe circumstances in that overcorrection and an unnatural frontal view is not an uncommon occurrence. Only a modest narrowing of the alar base should be performed to preserve the ethnic identity, and tip projection often improves that balance. In addition to the wide alar base, some individuals have an extremely thick alar lobule on base view. Only rarely does one actually thin the lobule via direct excision of subcutaneous tissues.

The precise methodology is case-specific and an anatomic distinction is made between the alar lobule flaring, wide alar base, and excessive subcutaneous thickness. Modifications of the Weir procedure allow for custom design flaps at the alar base. Flaring is reduced with crescent excisions along the alar-facial junction. Direct narrowing of the base is accomplished with a wedge excision within the nasal sill. Thinning is performed with a direct approach at the alar margin. Recognize that the degree of alar flaring will be reduced once tip projection is enhanced.

The crescent excision along the alar-facial junction should extend superiorly, into the supra-alar crease, in order to avoid the pinched appearance at the alar rim, as seen on frontal view after overresection. The incision can be made 1 to 2 mm above the alar-facial crease to preserve the natural sulcus and allow skin edge eversion (Fig. 38-16). A layered closure is critical to promote favorable scars.

Narrowing of the alar base is accomplished by a nostril sill excision or sliding alar flap (Fig. 38-17). A vertical, wedge-shaped excision of the nostril sill measuring 2 to 4 mm in center width followed by layered closure reduces the alar base width. A combined sill and alar wedge excision narrows the alar base while reducing the alar flare. A small flap

of tissue is preserved medially at the base of the columella so as not to change the shape of the nostril radically.

Postoperative Care

Postoperative care for the noncaucasian patient is similar to that for their Western counterparts except with regard to skin care. The soft tissue envelope has a limited ability to contract and does not shrink on the framework as it does on caucasian patients. For this reason, it is not uncommon to use long-term rhinoplasty bandages during the recovery period. One can even teach the patient to dress his or her own nose at night in an effort to maintain tip definition. Subcutaneous steroid injection with triamcinolone is a common practice in this group. One should be conservative because the effects are permanent and continue for several weeks after injection; small aliquots of steroids injected in the bulbous areas of the nasal tip can be effective.

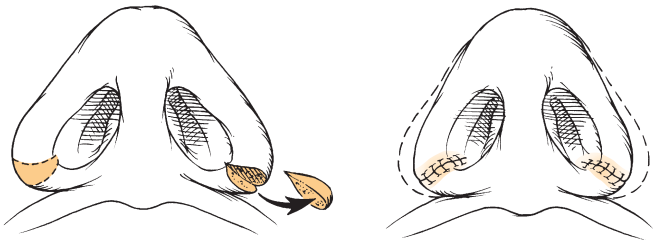

Figure 38-16. A wedge excision of the ala to reduce flaring. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

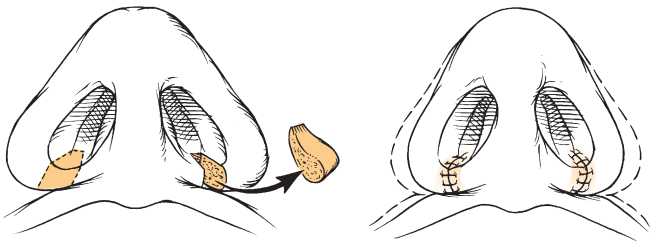

Figure 38-17. A nostril sill excision to narrow the alar base. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Complications

Alloplastic implants can present with infection many months or even years after surgery (Fig. 38-18).[5,19,20] Even though an aggressive antibiotic therapy is nearly always initiated, most often the implant needs to be removed.[10,21] Immediate replacement with autogenous tissue can be performed but carries obvious risk and anxiety. A delayed reimplantation may be more prudent, even if delayed for only a couple of weeks. A prolonged interval may lead to soft tissue contracture along the internal lining as well. Implant extrusion is a distinct problem from infection and can occur from implants exuding pressure under thin skin. It also requires complete removal and replacement with autogenous material.[22] On rare occasions, the offending portion that has become exposed can be trimmed and covered with adjacent soft tissue. Injectable silicone can cause a foreign body reaction presenting as a dorsal cyst, even 20 years after the surgery (Fig. 38-19).

Autogenous dorsal implants are subject to complications: (1) mobility and asymmetry, (2) resorption, and (3) warping. Implants can be inserted off midline or they may drift during the healing process. This can be minimized by suture fixation of the graft to the nasal framework. Resorption is more common with auricular cartilage or when the material has been extensively crushed. Warping of costal cartilage is a terminal complication in that the graft will require replacement; selective trimming or watchful waiting will not be beneficial (Fig. 38-20).

Conclusion

The noncaucasian rhinoplasty introduces several unique considerations that create a more challenging and thoughtful practice. Differences in

Figure 38-18. Infection and breakdown after e-PTFE augmentation of the dorsum. **A,** Pus is coming out of the nostril margin. **B,** The dorsal skin has broken down with the implant extruding.

Figure 38-19. **A,** Dorsal cyst forming many years after injectable silicone. **B,** Intraoperative view of cyst.

anatomy, culture, aesthetic definitions, and expectations all contribute to making this a unique topic. The workhorse in the noncaucasian nose is dorsal augmentation, tip definition, and refinement to the alar base. Harmony and balance remain the cornerstones for rhinoplasty. Autogenous and selective alloplastic implants to the dorsum are accepted

Figure 38-20. A warped costal cartilage graft 9 months postoperatively.

standards. Tip grafting rather than cartilage destruction is the preferred method for creating elegance and definition. Understanding these differences and mastering the techniques unique to the ethnic nose will lead to a successful outcome.

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CHAPTER THIRTY-NINE

Revision Rhinoplasty

David W. Kim

Manuel A. Lopez

Dean M. Toriumi

Key Points

- The understanding of revision rhinoplasty requires understanding the complications of primary rhinoplasty.
- Minor errors in technique or errors of omission result in problems that tend to be straightforward to correct.
- Failure to restabilize weakened structures of the nose or excessive reduction or excision during primary surgery may lead to deformities that require replacing support and strength to the nose during revision surgery.
- Severe problems due to gross errors of judgment are the most challenging cases and may require extensive reorientation and restructuring.
- Following reduction of the nasal infrastructure, a thick, stiff skin–soft tissue envelope (SSTE) may not drape smoothly and may instead result in additional swelling, scarring, or a soft tissue pollybeak.
- A thin or damaged SSTE reveals even small irregularities of the underlying bone and cartilage.
- A pollybeak may result from inadequate reduction of the cartilaginous dorsum, soft tissue fullness caused by poor draping of a thick skin envelope, or decreased nasal tip projection due to loss of support.
- The pinched middle vault may result from failure to restabilize an open cartilaginous dorsal roof; correction requires middle vault reconstruction with spreader grafts.
- The overly narrowed nasal tip, bossae, alar pinching, or lateral nasal wall collapse may result from overly aggressive tip reduction procedures. Correction may require camouflage grafts or reconstructing the lower lateral cartilages.
- The ptotic tip must be corrected by increasing tip support and projection through advancement of the medial and intermediate crura relative to a long native septum, columellar strut, extended columellar strut, or caudal extension graft.

Many consider rhinoplasty to be the most difficult facial plastic operation. The anatomy is intricate, three dimensional, and highly variable. Airway function depends on multiple factors, which are modulated with every surgical maneuver. Postoperative scar contracture and healing may alter surgical structural modifications over the lifetime of the patient. For these reasons, primary rhinoplasty frequently results in a suboptimal outcome. Moreover, the recent information explosion of the Internet has led to a patient population that has become increasingly knowledgeable and discriminating. Not surprisingly, it is estimated that 8% to 15% of primary rhinoplasty patients eventually undergo revision surgery.[1]

Secondary rhinoplasty poses additional challenges because the surgeon must restore nasal cosmesis and function beginning from a compromised baseline. The study of secondary rhinoplasty is the study of the complications of rhinoplasty. It is therefore critical that the surgeon undertake the process with as much information about the condition of the nose as possible.

Although many aspects of the preoperative analysis and surgical technique are similar to those used in primary rhinoplasty, these methods must be focused toward the problems and deformities most commonly found in secondary rhinoplasty. The ability to correct these problems is limited by the integrity of the existing and often compromised structures, the availability of grafting material, and the severity of the individual deformities. In many situations, the techniques themselves must be dramatically altered to restore structure to a nose that has been significantly destabilized. Frequently, secondary rhinoplasty becomes an operation of reconstruction more than of simple refinement.

Patient Interview

It is imperative that the surgeon obtain as much information as possible concerning the problems that led to the patient's visit. A patient seeking secondary rhinoplasty surgery may be more knowledgeable, demanding, or distraught than a primary rhinoplasty patient. Because these patients have endured a period of disappointment regarding the appearance or function of their noses, they may have invested considerable energy and effort in considering revision surgery. The patients must understand that the greater the degree of baseline damage, the more limited will be the possibilities for improvement. Therefore, it is critical that the surgeon instill realistic outcome expectations in these patients. Surgery should not be performed unless common expectations are reached between patient and surgeon.

During the initial consultation, old operative notes and rhinoplasty diagrams can provide useful information. However, they may be incomplete or erroneous regarding grafting material, implants, and septal cartilage status. Preoperative and postoperative photographs may help in determining the nature and time course of the given problems. Photographs can also reveal which problems resulted from surgery and

which problems predated the primary surgery. These original images are valuable because many patients may have had variant nasal anatomy that created a predisposition to a specific postoperative complication or deformity. The physician should list and prioritize patient complaints and gauge how reasonable and achievable these requests are. Functional airway problems that result from anatomic disturbances are surgically correctable. Intermittent obstruction is more likely attributable to mucosal inflammatory problems and should not represent the main impetus for surgery. Cosmetic problems should be discussed in detail with the aid of photographs and computer imaging. Each aesthetic complaint should be discussed with regard to possible etiology and prospects for repair.

Photography

Preoperative and postoperative photographic documentation is essential. Full-face frontal, oblique, lateral images, and close-up base views should be standard. Images should be obtained with dual flash sources angled 45 degrees toward the patient. An additional frontal view taken with a single flash placed in front of and above the patient allows for shadowing and highlighting of the dorsal line. Close-up views should be taken to document any irregularities or damage to the skin. A blue screen or wall is ideal to establish contrast between the patient and background. Standard 35-mm or digital photography are both viable options. At this point, slides produced from a high-quality 35-mm camera provide better resolution and color than even the most advanced digital cameras. Eventually, digital photography may match or surpass traditional methods.

Physical Examination

Cosmetic nasal analysis begins with a global assessment of the nasal deformities. Often one or two problem areas are immediately noticeable to the physician. These may include an asymmetric tip, dorsal irregularities, or a narrowed base. It is important to prioritize these deformities during surgery because surgery on each subunit of the nose affects the appearance of the others. The surgeon must modify a given structure based on the status of adjacent structures. Knowing that one aspect of the nose is particularly problematic allows the surgeon to focus on it and modify the rest of the nose around those corrections. For instance, in a patient with an overly foreshortened nose, the surgeon may first choose to correct nasal length and tip projection by resetting the medial crura onto a caudal extension graft. The dorsal height may then be modified in relation to the newly restored tip position.

Analysis should continue with a systematic assessment of each view of the nose. Whereas analysis of the patient is done in the office setting, high-quality preoperative photographs allow for more detailed study at a later time. On the frontal view, symmetry and width should be assessed in each of the vertical thirds of the nose. If the brow-tip aesthetic lines are irregular or asymmetric, the anatomic cause of the problem should be noted. Middle vault collapse may be visible as pinching in the middle third of the nose or as an inverted V deformity. Indications of previously overresected lower lateral cartilages (LLCs) include supra-alar pinching and alar retraction (revealed as excessive nostril show). Common tip deformities in the previously operated nose include the pinched tip, bossae, and asymmetric tip.

The base view provides information about the shape and size of the columella, alar base, nostrils, and lobule. Excessively narrowed or asymmetric nostrils, malposition of alar insertion, and the presence of visible scars are signs of complications from alar base reduction. Other stigmata of previous surgery on the base view include alar pinching, tip irregularities, alar notching, and persistent caudal septal deviation.

On the lateral view, the dorsum is assessed for smoothness, vertical position of the nasal starting point, convexity or concavity, and presence of a supratip break. An overreacted dorsum can lead to a scooped appearance in the presence of a projecting tip. A pollybeak deformity may be present as the result of relative supratip excess (soft tissue or cartilaginous) or a deficiency in tip projection. In the lower third, the overall projection and rotation of the nasal tip must be assessed. Using Goode's method, nasal tip projection, as defined from the alar crease to the tip defining point, should be just over one-half (0.55) the length of the nose.[2,3] The ideal length should be based on a nasal starting point near the superior palpebral fold and a tip-defining point determined by the ideal degree of tip rotation. One measure of rotation is the nasolabial angle, which in men should be between 90 and 95 degrees and in women between 95 and 105 degrees. In cases of relative tissue excess or deficiency at the premaxilla, this angle may not reflect the degree of rotation at the tip and infratip lobule. A common secondary deformity occurs after excessive caudal septal resection and cephalic trim of the LLCs. In such cases, the nose is foreshortened, the nasolabial angle overly obtuse, and the ala retracted. In other cases in which the nasal base was previously destabilized, the tip may become ptotic, resulting in a long nose with an acute nasolabial angle. Both lateral views should be compared because unequal amounts of cartilage reduction may have been performed.[3]

The surgeon must note the thickness and sebaceous quality of the nasal SSTE. Particularly in thick-skinned individuals, previous reduction of the underlying skeletal framework may cause significant scarring in the dead space. This can cause the SSTE to be exceptionally thick and inelastic. Further structural reduction should be avoided in these patients so that subsequent additional scar formation can be prevented. In such cases, one should augment areas of relative deficiency in the underlying structural framework to project form into the thick soft tissue envelope. An advantage of such a thick SSTE is that irregularities of the underlying nasal skeleton and grafts are camouflaged.

The SSTE may have been overly thinned, damaged, or devascularized during prior surgery. The presence of acquired cutaneous telangiectasias, purple or blue discoloration of the nasal skin with cold temperature, and visible irregularities are signs of such a condition. In these patients, the dissection of the SSTE of the underlying structural framework must be precise, because extensive soft tissue elevation will increase the risk of ischemia and wound breakdown. Although patients with thin skin may not have injury to the SSTE, it is important to remember that there is added risk of contour irregularities becoming visible or palpable. Care must therefore be taken to ensure that all existing bony and cartilaginous structures, grafts, and implants are precisely positioned and smoothly contoured. The benefit of thin skin is that leaving a small amount of dead space will have a greater tendency to contract over time and allow for greater degrees of reduction.[4]

It is crucial to assess each patient's nasal airflow, which should be undertaken before and after decongestion of the nasal mucosa. The surgeon must note the external stigmata of an obstructed nose or one that is prone to develop postoperative problems. These characteristics include a thin SSTE, a narrow or collapsed middle vault, short nasal bones, supra-alar pinching, a prominent supra-alar crease, narrow nostrils, and thin lateral nasal walls. Intranasal examination may reveal a narrow internal valve angle, dynamic lateral wall collapse, septal deviation, inferior turbinate hypertrophy, mucosal synechiae, or shortage of lining from prior excision. Assessment of dynamic function should be performed by observing the lateral wall of the nose with inhalation. Obvious collapse indicates lateral wall weakness. Significant improvement of breathing by supporting the lateral wall with a small instrument may predict airway improvement with placement of a supporting graft to the lateral wall. All of these factors must be considered in formulating a surgical plan, which will restore or preserve a functional airway.

Palpation of the nose is important to determine the shape, position, and strength of the nasal structure. Dorsal irregularities may not be visible beneath a thick SSTE and may require digital palpation to be detected. An attempt should be made to trace the LLCs to assess position and stability. The resistance and recoil of the nasal tip to digital pressure will provide information of tip support. Finally, palpation of the caudal nasal septum will help determine the position and integrity of the caudal septal strut.[5]

Computer Imaging

Computer image modification programs are commercially available and are becoming increasingly popular for consultation of cosmetic patients. In secondary rhinoplasty, these programs are valuable because the patient might have unrealistic goals for surgery or might not understand the limitations to the correction of certain deformities. The limitations of surgery due to soft tissue considerations, grafting materials, or exist-

ing structural damage can be visually demonstrated to the patient to facilitate a mutual understanding between patient and surgeon. The physician should create an image that can be realistically achieved so that the patient can be focused toward a defined and reasonable goal. Computer imaging that leads to unrealistic expectations will inevitably lead to an unhappy patient. It is therefore prudent that the surgeon performs the computer imaging, and does so in a fashion that portrays an outcome within his or her level of skill and experience.

General Considerations

Patients who seek revision rhinoplasty may come with any number of functional and cosmetic complaints. Small asymmetries, malposition, and irregularities can occur as the result of minor errors of technique. These problems are generally straightforward and easily corrected. Significant asymmetries, functional obstruction, and gross deformities are more likely to result from errors of judgment. In such cases, the primary surgeon may have been overly aggressive in excisional or reductive maneuvers or failed to resupport destabilized structures. These problems might not become apparent for years and might therefore escape the awareness of the original surgeon. The goal of analysis in secondary rhinoplasty is not only for the diagnosis of these problems, but also to determine the limitations and strategies for treatment.

There are several categories of complications, each of which result from different types of surgical errors. Identification, diagnosis, and correction of these problems depend on a thorough understanding of surgical pitfalls and postoperative processes. The various groups of complications are listed in Table 39-1.

A common type of problem encountered is one of subtle asymmetry or malposition of existing structures, grafts, or implants caused by minor errors in technique. In thin-skinned patients, suboptimal graft placement or unequal excision of cartilage can lead to slight cosmetic imperfections. In some cases, skeletal modifications can lead to subtle abnormalities of the nasal pyramid. Imprecise closure of the columellar incision can result in a visible scar. These complications are typically minor and relatively easy to correct. An exception to this is the case of migrating or traumatized alloplastic implants that become infected. Although such problems can be remedied by removing the implant, if left untreated, the infection can become serious and lead to permanent damage to the nose. Even after an appropriate and technically sound operation, the forces of scar contracture, mechanical trauma, and edema can result in an imperfect outcome.

Errors of omission will result in variable degrees of postoperative problems depending on the severity and nature of the original problem. This type of error, often committed by an inexperienced or overly conservative surgeon, will be evident in photographs before the original operation. Common examples include a persistent caudal septal deviation, a twisted nose, an asymmetric middle vault, and various tip deformities. As the structures are left relatively undisturbed, these problems are readily corrected with application of the proper techniques.

A third type of error involves failure to reconstruct destabilized structures. Many maneuvers in primary rhinoplasty require disassembling structures of the nose. If left unsupported, these destabilized areas become more susceptible to the forces of scar contracture, gravity, and facial mimetic function. The most common problems of this type include failure to stabilize the nasal tip at the base after compromising tip support mechanisms, failure to resupport the upper lateral cartilages (ULCs) onto the dorsal nasal septum after cartilaginous hump removal, and failure to support the lateral nasal wall in patients with a lateral wall deficiency. Correction of such problems usually requires structural grafting techniques to restore strength to the nasal framework.

A more problematic type of error is one of excessive reduction and excision. Excessive caudal septal resection, lateral crural cephalic trim, dorsal hump reduction, alar cartilage division, and alar base reduction can result in an assortment of cosmetic and functional problems. The type and severity of deformity partially depends on the quality of the SSTE. Many of these problems are challenging to repair because there is a deficiency of tissue that can be difficult to replace. This is particularly true when a portion of the internal lining of the nose has been excised.

The final category of surgical error represents those deformities stemming from gross errors of judgment. Whereas the problems outlined earlier can result from the poor execution of a reasonable surgical strategy, this last class of deformity usually results from a fundamentally flawed plan. These problems can be catastrophic and may not be pos-

Table 39-1

Examples of Surgical Errors with Resulting Deformity

Class of Surgical Error	Common Examples	Resulting Deformities
Minor error of technique	Asymmetric skeletal modification (e.g., osteotomies, dome sutures)	Asymmetric nasal skeletal
	Malpositioned graft	Palpable or visible graft
	Malpositioned implant	Palpable or visible implant (possible infection)
Error of omission	Poor closure of columellar incision	Columellar scar
	Various	Persistent primary deformity (e.g., bulbous tip, cartilaginous pollybeak)
Failure to restabilize	Failure to stabilize nasal base	Tip ptosis and underprojection
	Failure to stabilize middle vault	Pinched middle third, collapse of upper lateral cartilage, inverted V, internal valve obstruction
	Failure to stabilize lateral wall	Supra-alar and alar pinching, dynamic external valve obstruction
Excessive excision	Caudal septum	Short nose, wide nasolabial angle, retracted columella
	Cephalic trim of lower lateral cartilage	Lateral wall weakness, supra-alar and alar pinching, alar retraction
	Dorsal hump reduction	Scooped dorsum, saddle deformity, bony open roof, middle vault collapse
	Alar cartilage division	Palpable or visible graft
	Alar base reduction	Overly narrow alar base, narrow slitlike nostrils
Gross error of judgment	Various	Possible severe deformity (collapse from removal of lateral crura, extruded implant from placement of alloplast in nasal tip, skin necrosis from excessive debulking to tip skin)

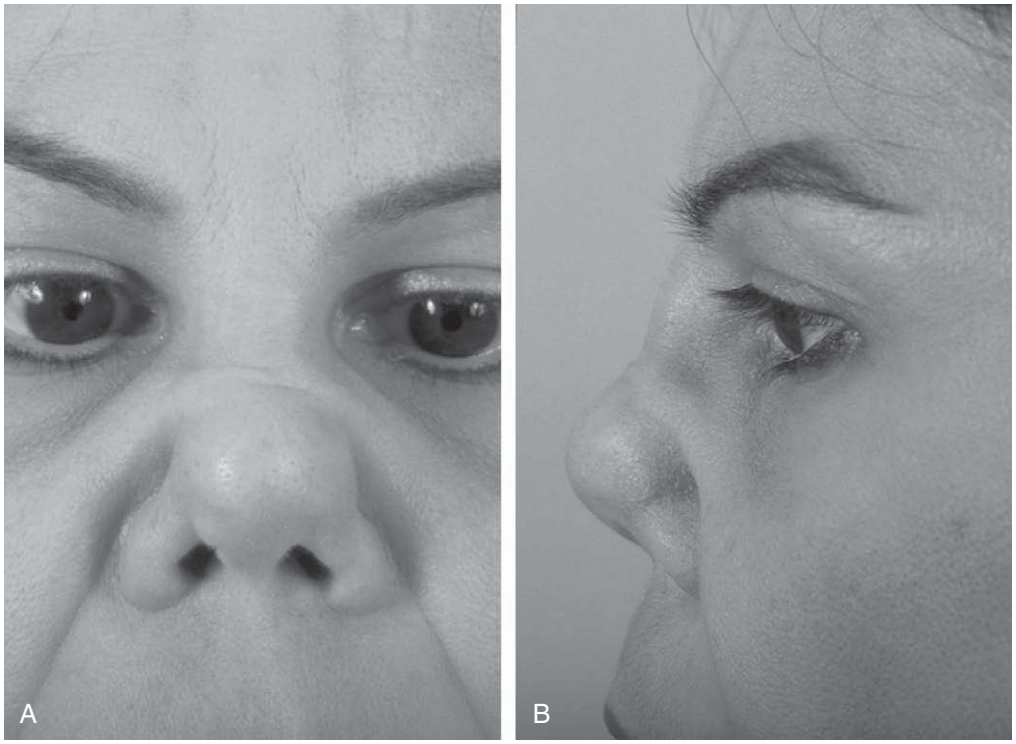

Figure 39-1. Patient with a severe deformity resulting from excessive excision of the lower lateral cartilages and septum. Chronic inflammation from an alloplastic implant has resulted in necrosis of the internal lining and severe contracture of the skin–soft tissue envelope. **A,** Frontal view. **B,** Lateral view.

sible to correct. These mistakes may stem from faulty analysis, disregard for basic principles of rhinoplasty, or use of improper techniques for a given problem. The inexperienced but aggressive surgeon is most likely to commit such an error. These problems are varied and typically cause an unnatural appearance. In some cases, they can result in serious cosmetic and functional deformity. Some of the most difficult cases involve situations in which large areas of soft tissue have been excised or violated (Fig. 39-1).

Grafting Material

Inspection of potential sources of autogenous grafting material will aid in surgical planning. Palpation of various areas of the nasal septum can help determine the amount of remaining cartilage. At minimum, a 1.5-cm dorsal-septal strut must remain for support of the nasal bridge and tip.

In cases in which there is a lack of available septal cartilage, it may be necessary to harvest cartilage from one or both ears. The cartilage can be harvested via an anterior or posterior approach. After a review of a significant number of anterior approach harvests, it was thought that the anterior approach had increased morbidity compared with the posterior approach. Occasionally, the scar and change in shape of the ear were noticed by patients when the anterior approach was used with the posterior approach to make the ear look normal. The procedure for a posterior approach harvest of auricular cartilage begins with a vertical skin incision approximately 1 cm in front of the postauricular sulcus on the posterior conchal bowl. The skin and perichondrium are then elevated from the posterior concha. Care should be taken to leave the peripheral vertical component of the concha intact so that no change in shape of the ear occurs. The harvested segment may extend toward the canal meatus, but the eminentia corresponding to the root of the helix should not be excised. The resulting piece is usually kidney-shaped and varies from 2 to 4 cm in its largest dimension. The skin flaps should be judiciously cauterized to prevent thermal injury. Closure with a few subcutaneous 5.0 resorbable sutures followed by a running 5.0 fast-absorbing gut suture should be placed. A bolster in the anterior conchal bowl can be fashioned from a dental roll and sutured through the ear with a 3.0 nylon suture.[2]

When ear cartilage is insufficient or when exceptionally strong grafting material is needed, costal cartilage may be harvested. Typically, the cartilage from the fifth or sixth rib is taken. A 3- to 5-cm incision is made over the medial aspect of the rib. For female patients, the incision may be placed just above the inframammary crease in order to be hidden from view. The muscle fibers are separated at a point of natural dehiscence to access the rib surface. Bipolar cautery is used judiciously to reduce the amount of postoperative discomfort. Subperichondrial dissection around the rib is performed with an elevator. It is important to maintain a subperichondrial dissection plane on the deep surface of the rib to avoid injury to the pleura. The perichondrium may be harvested from the superficial aspect of the rib for later use as soft tissue onlay material in the nose. Under direct visualization, the graft is freed from the surrounding perichondrium and the desired segment sharply excised. A malleable retractor may be placed deep to the rib to protect the pleura. A needle can be inserted into areas of the rib in which it is unclear whether bone or cartilage is present. Closure should be performed in a layered fashion after hemostasis is achieved. Once the graft is harvested, any sharp edges of remnant costal bone or cartilage should be rongeured smooth to prevent postoperative pain or pneumothorax.

When carving costal cartilage, it is crucial that the surgeon obtain the grafts from the center of a relatively straight segment of rib cartilage. The cartilaginous matrix is circumferentially oriented much like the cross section of a tree trunk. An oblique longitudinal cut will result in asymmetric forces of contracture and warping toward the periphery of the graft. A graft obtained through symmetric trimming from the periphery toward the center of the rib will result in a graft with equal circumferential forces of contracture and thus a decreased chance of warping (Fig. 39-2).[6]

Although the harvest of rib cartilage requires a chest incision and poses a risk of pneumothorax and increased postoperative pain, there are significant advantages to this method. First, a segment of rib cartilage supplies far more material than either septal or auricular sources. And second, costal cartilage is far stronger biomechanically than either of the other traditional sources. For this reason, the authors have significantly increased their use of costal cartilage in the past several years.

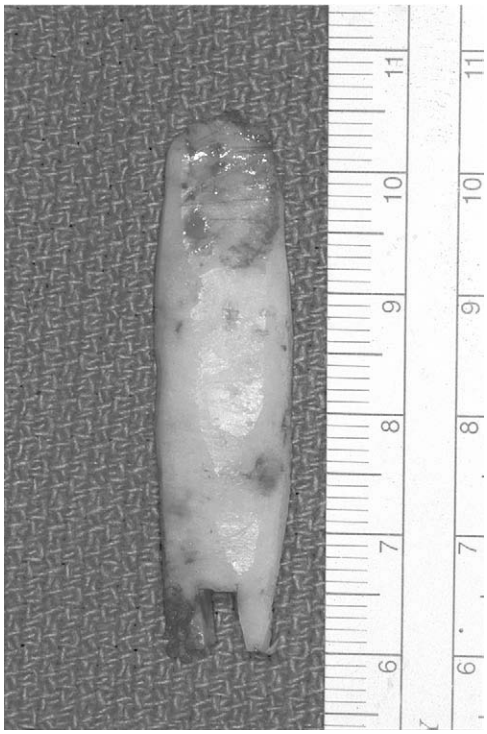

Figure 39-2. Rib graft carved from central portion of the costal cartilage.

Analysis and Treatment of Specific Deformities

The common problems requiring revision surgery are outlined. For any given deformity, the thickness of the SSTE will influence one's ability to assess the underlying structure of the nose. In some cases, it is nearly impossible to determine the structural deficiencies beneath the SSTE. In these situations, the surgeon must be prepared for any number of structural problems that may be encountered intraoperatively. Endonasal approaches are ideal in secondary rhinoplasty operations for patients in which subtle deformities or errors of omission need to be addressed. However, the wider exposure and access afforded by the external rhinoplasty approach is needed to thoroughly correct the deformities encountered in most of these cases.

Dorsal Profile

Dorsal Irregularity

Most commonly, this problem arises after contour irregularities are created along the bony and/or cartilaginous dorsum. Osseous hump reduction and osteotomies can lead to palpable or visible edges of bone. In the bony vault, these deformities must be smoothed or camouflaged to prevent an undesirable aesthetic outcome. An open roof deformity can follow bony hump removal with osteotomies that inadequately medialize the nasal bones. In the middle third of the nose, the dorsal aspect of the ULC, septal cartilage, and spreader grafts (if present) must be stabilized in a horizontal and coplanar orientation. If not, an irregularity due to asymmetric collapse or migration of the ULC relative to the dorsal septum may become evident. These problems tend to occur over many years and can be detected by close inspection and palpation of the nasal dorsum.

Treatment requires smoothing or camouflaging any irregularities and restabilizing the middle vault structures. Persistent osseous deformities can be addressed through remobilizing the nasal bones through previous osteotomy lines. Often digital manipulation is sufficient to reposition the bones into a symmetric midline position. Alternatively, an osteotome can be used to perform the osteotomies. The leading edge of the instrument will tend to follow the path of the previous osseous cuts. Therefore if the prior osteotomies were poorly placed, extra caution should be exercised to redirect the revision osteotomies in a proper orientation. Subtle bony deformities can be addressed with rasping. In cases in which the cartilaginous dorsum is slightly overreduced, onlay grafting can be used to correct irregularities. Small irregularities can be excised to restore a smooth contour.

Low Dorsum/Saddle Deformity

More dramatic dorsal abnormalities can result from the creation of improper height at the upper or middle third. An inexperienced surgeon may fail to recognize that dorsal alignment can be balanced by elevating a low radix to match the height of the rest of the dorsum rather than by lowering a relative convexity at the middle vault to the level of a low radix. The projection and rotation of the tip are also critical in determining ideal dorsal height. If reduction of the dorsum leaves the tip projected significantly beyond the height of the bridge, the nose may appear scooped with an illusion of overrotation on the lateral view. Conversely, if tip projection falls short of the dorsal line, a pollybeak deformity will result. If overly aggressive dorsal reduction of the middle vault results in inadequate dorsal septal support, a saddle nose deformity may occur.

In general, a low dorsum causes less shadowing along the lateral wall of the nose and creates an illusion of increased width on the frontal view. At the upper third of the nose, this can create an appearance of pseudohypertelorism. The washed-out frontal view makes the brow-tip aesthetic lines indistinct and the general appearance of the upper two-thirds amorphous. The ideal lateral profile should be straight or slightly concave at the rhinion for women and straight to slightly convex for men. The overall height of the bridge should be determined by the projection of the tip, which should equal just over one half the nasal length.

Restoring proper bridge height usually calls for onlay material. In severe saddle deformities, costal cartilage might be necessary (Fig. 39-3). The onlay graft should be fashioned into a canoe shape with the cephalic edge placed into a precise pocket over the upper dorsum. The cephalic edge should terminate roughly at the level of the desired nasal starting point. The caudal edge should terminate in the supratip area; ideally, the domes will project above the graft at its caudal aspect, providing a smooth transition from the dorsum to the tip. All edges of the graft must be tapered to minimize visibility of the graft through the SSTE.

Nasal Starting Point/Radix

A large or improperly placed radix graft or an inadequate hump reduction can result in excessive dorsal height. A radix graft that is positioned too cephalically will elevate and blunt the nasofrontal angle, creating the illusion of a longer nose. If placed too caudally, the graft can appear as an unnatural, high dorsal hump. On analysis, the nasal starting point should be at or just below the level of the superior palpebral fissure. The nasofrontal angle should be roughly 120 degrees (although this may vary depending on the plane of the forehead). The degree of radix projection should be harmonious with the rest of the nasal dorsum and tip projection. Byrd[7] proposes that ideal radix proportion measured from the junction of the nasal bone to the orbit be one-third of overall nasal length. Repositioning or replacing an existing radix graft can restore the correct nasal starting point and nasofrontal angle. Such a graft is often created from crushed or bruised cartilage obtained from the nasal septum or from the auricle. Preserving some perichondrium on an auricular cartilage graft helps preserve some form to the segment after morselization and aids in camouflage of the graft. Because these grafts are placed into tight subperiosteal pockets to prevent their migration, it is critical to limit elevation of the dorsal periosteum of the bony vault within a narrow space.

Pollybeak

Pollybeak deformity refers to an abnormality in which the supratip projects beyond the tip. This causes a rounded appearance to the tip with a lack of definition and an absence of a supratip break and a columellar-lobular break. Although the deformity creates the appearance of supratip fullness, the problem can be caused by one of several

Figure 39-3. Patient with previous excessive dorsal reduction. The obvious saddle deformity on the lateral view **(A)** translates into an illusion of increased width on the frontal view **(B)**.

processes. One possibility is the failure to reduce an overly elevated middle vault and supratip dorsum. In a primary tension nose deformity, the anterior septal angle represents the most projecting point of the nose with the tip structures "hanging" from this point. Therefore the dorsum at the level of the anterior septal angle must be reduced or the tip brought out beyond this point to establish a proper tip-supratip relationship. Failure to establish this relationship is an error of omission leading to postoperative pollybeak. Paradoxically, a second cause of pollybeak is the excessive excision of dorsal septal cartilage. Particularly in patients with thick inelastic skin, the SSTE cannot redrape into the area of skeletal reduction. The tissue void fills with scar and fibrosis, resulting in a soft tissue pollybeak. Lastly, pollybeak can result if tip support is compromised and not reconstituted and if the resultant tip ptosis leads to deprojection at the tip with an appearance of supratip fullness (Fig. 39-4).[8]

These three types of pollybeak deformity require individualized methods of treatment. Correction of the untreated tension nose requires completing the dorsal cartilage reduction and ensuring the presence of a stable nasal base to maintain tip position relative to the dorsum. Correction of the soft tissue pollybeak requires projecting the tip into the thick SSTE beyond the level of the supratip and dorsum. The pollybeak caused by tip ptosis mandates reestablishing tip support and returning the tip into its appropriate projection. A variety of methods exist to stabilize the nasal base and restore tip position (see subsequent sections). Because these strategies are quite different from each other, it is crucial to understand the etiology of the problem before surgery. Palpation is critical to differentiate between soft tissue fullness and cartilaginous excess. An acute nasolabial angle and a weak tip with little recoil will indicate the presence of tip ptosis caused by a loss of tip support.

Middle Vault

The middle vault poses one of the most difficult challenges in rhinoplasty. Separation of the ULCs from the septum requires suture restabilization to restore the structural relationship, which may include using spreader grafts. Failure to do this can result in inferomedial collapse of the ULCs, pinching of the middle vault, and internal valve airflow obstruction. Patients with thin skin and short nasal bones are at highest risk for middle vault collapse after separation of the ULCs from the dorsal septum. In severe cases, collapse can result in a visible and palpable inverted V deformity. Restoring symmetry to a crooked middle vault is extremely difficult and requires precise placement of spreader grafts stabilized between the dorsal septum and ULCs. Small irregularities or asymmetries may become apparent on frontal view, secondary to linear shadowing on the nasal side walls. These discrepancies often do not become evident until months or years after surgery.

To identify and diagnose these deformities, the revision rhinoplasty surgeon must perform meticulous examination and analysis of the middle vault. On frontal view, the symmetry and width of the nose should be visualized and palpated. The dimensions of the brow-tip aesthetic line should follow a slight hourglass contour with slight narrowing of the middle vault in relation to the nasal tip. This curve should be subtle. Exaggeration of the curvature may indicate middle vault pinching or excessive width at the bony vault or tip. Asymmetry at the middle vault is best determined by visualizing and palpating from above the head of the patient. Small areas of irregularity may be appreciated in this manner. Intranasal inspection of the internal valve area should be performed with a speculum and light source. The internal angle between the septum and the ULC should be at least 15 degrees. Inspection with the patient inspiring may reveal dynamic collapse of the ULCs. This dynamic examination is very important because it can reveal functional problems that otherwise would be missed (Fig. 39-5).[4,9,10]

In almost all cases, the middle vault width and stability are restored through the placement of spreader grafts. As in primary rhinoplasty, these rectangular grafts are suture-stabilized between the dorsal septum and the ULCs. However, in revision cases, a greater degree of collapse or asymmetry may be present. The surgeon must therefore be prepared to spend more time meticulously reconstructing the middle vault in secondary rhinoplasty. In severe cases, the ULCs may be collapsed into the nasal airway. In these situations, it is critical that the ULCs are grasped and pulled into the proper dorsal position in alignment with the dorsal margin of the septum before placement of spreader grafts.

The dimensions of spreader grafts will vary depending on the length of the nasal bones and the specific deformity noted, but they

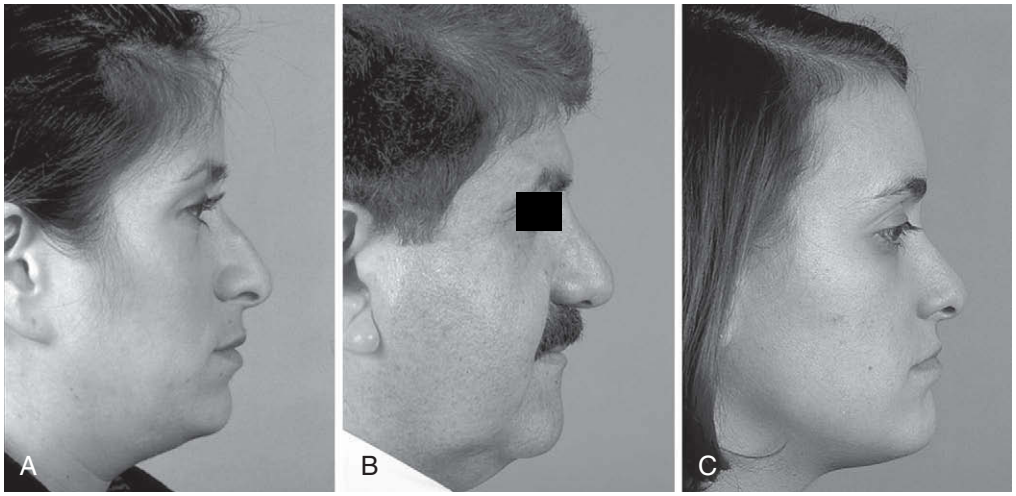

Figure 39-4. Three types of pollybeak deformity. **A,** Relative supratip prominence caused by inadequate elevation of radix and projection of the tip. **B,** Soft tissue pollybeak caused by inability of thick, inelastic skin–soft tissue envelope to drape over reduced underlying nasal structures. **C,** Relative supratip fullness caused by postoperative loss of tip projection due to inadequate stabilization.

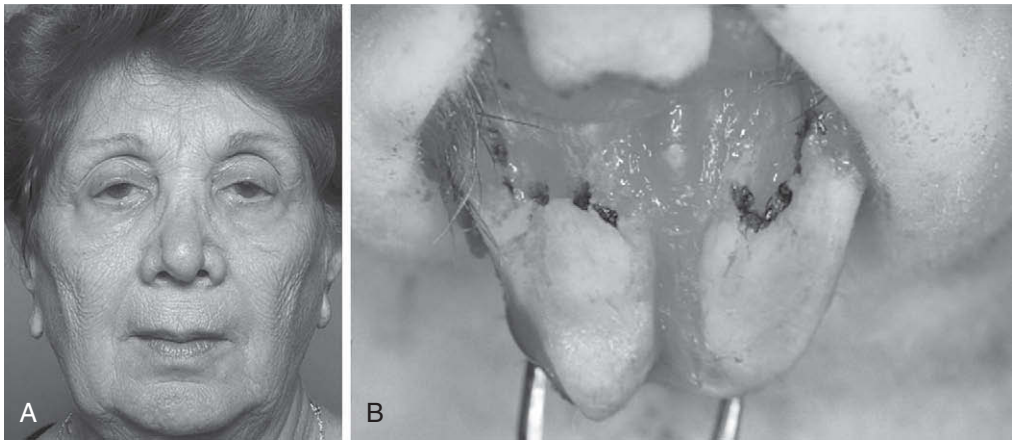

Figure 39-5. A, Patient with supra-alar pinching characteristic of poor lateral wall support. **B,** Excessive cephalic trim is a common cause of lateral wall weakness.

range from 6 to 12 mm in length, 3 to 5 mm in height, and 2 to 4 mm in thickness. The grafts can be placed via an external or endonasal approach. When the external approach is used, the ULCs are usually dissected from the septum. Mucoperichondrial flaps are elevated from the junction of the ULC and septum to prevent injury to the mucosal lining. The spreader grafts are stabilized with two or three 5.0 resorbable mattress sutures that are placed through the ULC, spreaders, and septum. The caudal ULC should be pulled caudally during the suture stabilization to avoid buckling of the ULCs. The dorsal profile of the spreader grafts, ULC, and septum should be coplanar and smooth. Further trimming of the grafts may be needed to ensure an even dorsal surface.

To place spreader grafts via an endonasal approach, a mucoperichondrial incision is made high on the septum just caudal to the junction of the ULC and septum. A tight subperichondrial pocket is made with a thin dissecting instrument such as a Freer elevator. Snug placement of a spreader graft into this tunnel will cantilever the ULC away from the dorsal septum. Suture fixation is not necessary because the tight pocket will maintain the grafts in the proper position. The increased bulk between the septum and the ULC increases the width of the middle vault and angulation of the internal nasal valve.

Lateral Nasal Wall

Some of the most common deformities of the secondary rhinoplasty patient are related to weak, unsupported lateral nasal walls. There are five common causes for lateral nasal wall weakness. Aggressive cephalic trim of the lower lateral crura and division or resection of the alar cartilages are two potential causes. The other three common causes are failure to correct preexisting lateral wall weakness and supra-alar pinching, failure to support the alar margin in patients with inherently weak cartilage, and cephalic positioning of the lateral crura.

Supra-alar and External Valve Collapse

Exaggeration of the supralobular crease can represent an inherent deficiency or internal recurvature of the lateral crura and inadequate support of the lateral wall of the nose. This deformity can also develop as the result of scar contracture on the tissue void caused by previous excision of lower lateral crura. Aggressive cephalic trim and interruption of the lateral crus will decrease support of the lateral wall and contribute to eventual collapse, which is best detected on frontal and oblique views. Inspiration can lead to further dynamic collapse of the weakened external valve. Intranasal inspection may reveal fixed or dynamic inspiratory medialization of the alar lobule. Improvement of breathing achieved by supporting the lateral wall with a narrow instrument such as a cotton tip applicator or cerumen loop confirms the diagnosis.

The degree of collapse may vary in severity and will require appropriately sized alar batten grafts for correction (Fig. 39-6).[11,12] These grafts are curved cartilaginous supports placed into the area of maximal lateral wall weakness. Through the external approach, the grafts are placed into tight pockets that overlap and extend lateral to the lateral

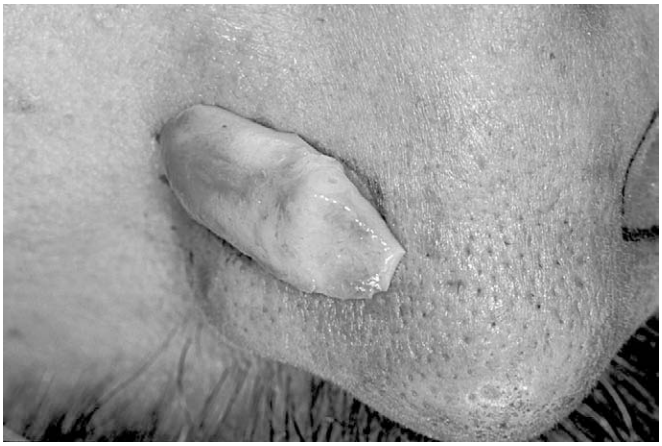

Figure 39-6. Alar batten grafts carved from auricular cartilage. These grafts are inserted into pockets lateral to the lateral crura.

crura. The curvature of the graft should be oriented to lateralize the supra-alar area with the concave surface medial. The cartilage graft is usually placed caudal to the lateral crura, depending on the area of maximal pinching. In severe cases, the grafts may need to extend all the way to the piriform aperture to add support. In cases in which internal recurvature of the native lateral crura impinges on the airway, the lateral crura may need to be sutured to the alar batten grafts for lateral stabilization. Internal vestibular stents may be placed in the postoperative period to prevent postoperative medialization of the lateral wall. These stents may be constructed with pliable plastic stents and may be maintained in the nasal vestibules while the patient sleeps for weeks to months, depending on the severity of the initial problem.[8,13,14]

Alar Pinching and Retraction

Excisional techniques on the lateral crura may cause weakness and contracture at the alar margin. Cephalic retraction may result in alar-columellar disharmony with excessive columellar show (unless the columella itself is also retracted). The retracted alar margin can be notched at the apex in cases in which the internal vestibular skin has become scarred from a poorly healed incision. On lateral view, there should ideally be 2 to 4 mm of columellar show. A distance exceeding this range suggests the presence of either a retracted ala or a hanging columella. An imaginary line through the long axis of the nostril on the lateral view serves as a marker to help in differentiating these possibilities. Normally, the top and bottom of the nostril should be equidistant to this line. If the distance from the top of the nostril to this line significantly exceeds the distance from the bottom of the nostril to the line, alar retraction is present. The converse is true for a hanging columella. This comparison can be applied in cases of decreased columellar show to differentiate between a hooded ala and a retracted columella (Fig. 39-7).[15] Alar retraction on frontal view creates excessively visible nostrils. Normally, the infratip lobule and the alar margins create the shape of a gently curving gull in flight. With retracted ala, the wings of the gull are overly arched in comparison to the body (Fig. 39-8).

Contracture from previous reduction of the LLC may also be evident on the base view as alar pinching. Particularly in cases in which the LLCs are weak or cephalically positioned, excisional techniques can lead to destabilization of an inherently weak alar margin. This pinching can also occur if the tip cartilages have been previously narrowed excessively using vertical dome division, lateral crural flap, or excessive tightening of dome sutures. Excessive narrowing of the nasal base can create an illusion of relative tip width. Nostrils that are thin and slitlike are more prone to collapse with inspiration. Cephalically positioned LLCs can be detected before surgery by palpation of the tip and supratip areas. When curved and prominent, this anatomic variation will manifest as a parenthesis deformity on the frontal view, in which the tip is seemingly enclosed between two curved parentheses (corresponding to the caudal borders of the alar cartilages). If the SSTE is thick and the cartilages flat, however, this variation could go undetected until surgery.

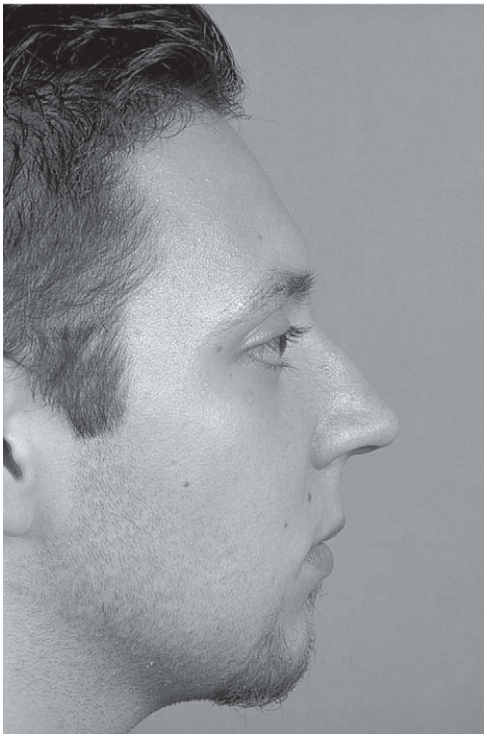

Figure 39-7. Lateral view of a patient with lack of nostril show caused by a retracted columella.

Figure 39-8. Lateral view of a patient with a retracted ala and excessive nostril show.

Placement of alar rim grafts can restore support and create a more triangular nasal base. These grafts are long, narrow cartilaginous grafts that are placed into precise pockets along the alar rim just caudal to the marginal incision. They measure 2 to 3 mm in thickness and width and 5 to 8 mm in length. Softer material, such as cartilage harvested from the ear or from cephalic trim of the LLC, is preferable. The medial aspect of these grafts can be gently bruised to aid in camouflage. They can be stabilized to the surrounding soft tissue or to the lateral aspect of a shield graft with 6.0 PDS (Polydioxanone, Ethicon, Somerville, NJ) suture. These grafts improve the concave or "knock-kneed" appearance of the alar rim on base view and create a more triangular appearance to the basal view. Severe cases of alar retraction may require the use of composite grafts of ear cartilage and skin placed into the marginal incisions to reposition the alar margins in a more caudal position (Fig. 39-9).

Nasal Tip

Some of the most noticeable deformities in secondary rhinoplasty occur in the nasal tip. The challenge lies in modulating tip position and shape and then maintaining the modifications against the forces of scar contracture. Tip deformities in secondary rhinoplasty patients come in all forms and can result from any of the classes of surgical errors described earlier. The external rhinoplasty approach in the revision of the nasal tip allows for an unparalleled ability to correct asymmetries.

Irregularities and Bossae

Asymmetry of the tip can result from problems of unequal excision, suture modification, or grafting. Subtle discrepancies may not become

Figure 39-9. Patient with severe alar retraction from previous aggressive cephalic trim. Preoperative **(A, C, E,** and **G)** and postoperative **(B, D, F,** and **H)** frontal, lateral, oblique, and basal views. Note the excessive columellar show on lateral and oblique views and the prominence of the nostrils and infratip lobule on the frontal view. Correction required placement of alar rim grafts and internal composite grafts to the vestibular alar margin.

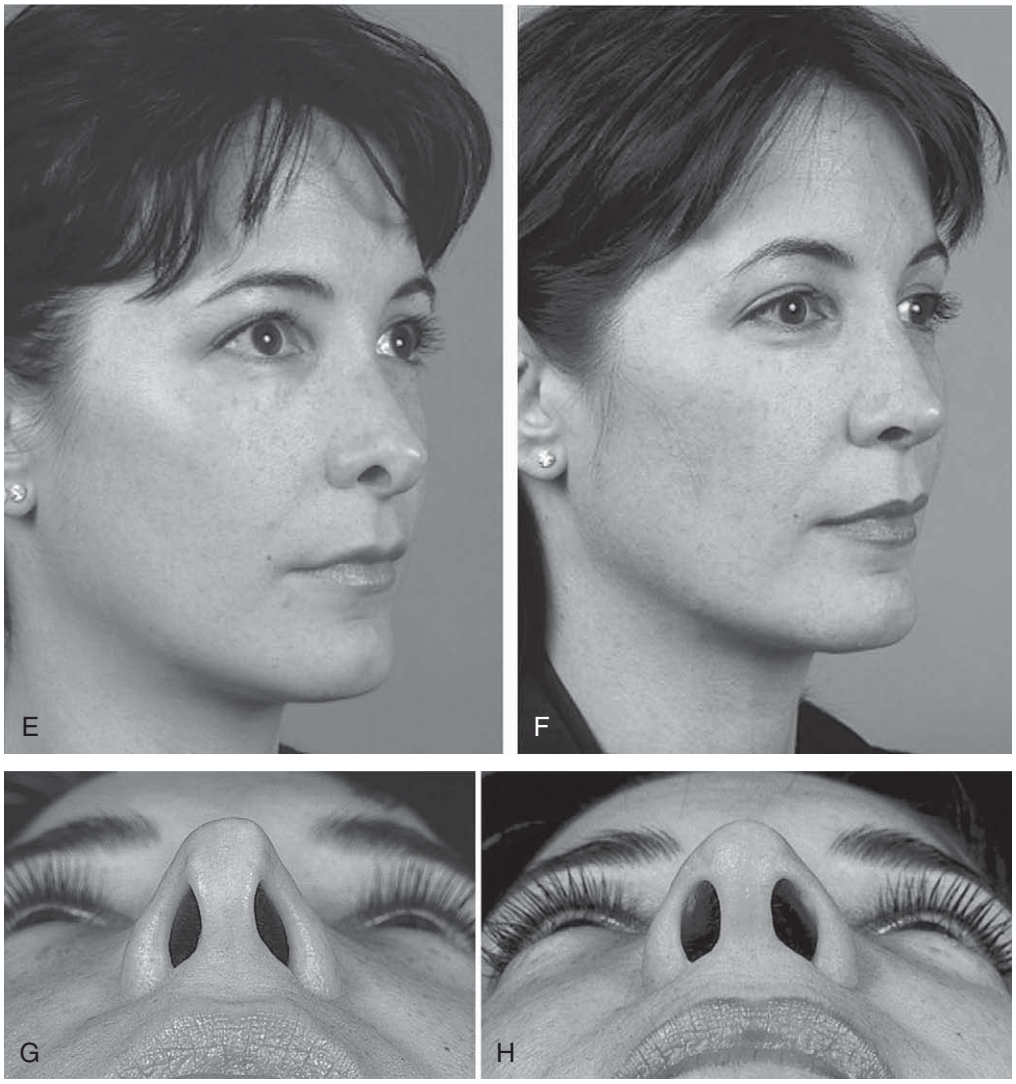

Figure 39-9, cont'd.

evident for several months until the edema resolves. Bossae may form as the result of knuckling or angulation of the LLC and tip grafts as the SSTE contracts (Fig. 39-10). Patients with thin skin and strong cartilage are particularly susceptible to this problem. These palpable and visible irregularities can result from the buckling of weakened or reduced alar cartilage under contractile SSTE forces or may result simply from insufficiently contoured edges of cartilage or grafts under thin skin. Usually, the patient is acutely aware of such abnormalities. Conservative cartilage trimming, revising suture modification of the domal cartilage, and onlay camouflaging cartilage grafts may correct such problems.[3,5,12] In cases of severe structural compromise, the entire tip structure must be reconstructed (see subsequent sections).

Persistently Wide or Bulbous Tip

A persistently wide tip after primary rhinoplasty might be due to the failure of the surgeon to account for a thick, inelastic SSTE when modifying the dome region. In these cases, performing dome-binding sutures alone may improve shape of the alar cartilages, but this change will not necessarily transmit through the thick SSTE. Failure to project the tip into the skin envelope and effectively stretch it to conform to the underlying tip shape will lead to this problem. Study of the overall projection and rotation of the tip, the nasolabial angle, and the nasal length should be performed to determine how best to project the tip and restore optimal tip shape. A shield-shaped tip graft can be sutured to the intermediate and medial crura to provide the desired augmentation to the infratip lobule and tip (Fig. 39-11). Although the nasal base remains unchanged, the leading edge of the shield graft may project beyond the domes by as much as 8 mm. A buttress or cap graft can be placed cephalad to the leading edge of the graft to support the graft and to camouflage the transition to the supratip. Lateral crural grafts are placed on the existing lateral crura and sutured to the lateral edge of the shield graft when the tip graft projects more than 3 mm above the existing domes. These also provide additional support and camouflage to the shield graft. Lateral crural grafts also bolster lateral alar support in cases in which the native lateral crura have been weakened or removed (Fig. 39-12).

Another common error of omission leading to a persistently wide tip is the failure to straighten convex lateral crura. Domal narrowing will not result in a defined triangular tip appearance if the lateral walls are curving outward. Unless the curvature is straightened with a suture technique or lateral crural struts, persistent tip width will be present. These problems can be detected via the base view of the nose. When using lateral crural struts, strong segments of cartilage are required to overcome the curvature of the existing alar cartilage. After separating the vestibular skin from the undersurface of the lateral crura, the grafts are sutured to the undersurface of the curved cartilages. The caudal attachment of the lateral crus and skin should remain intact to prevent caudal migration of the graft. The graft should extend from just lateral to the domes beyond the lateral aspect of the lateral crura. The lateral

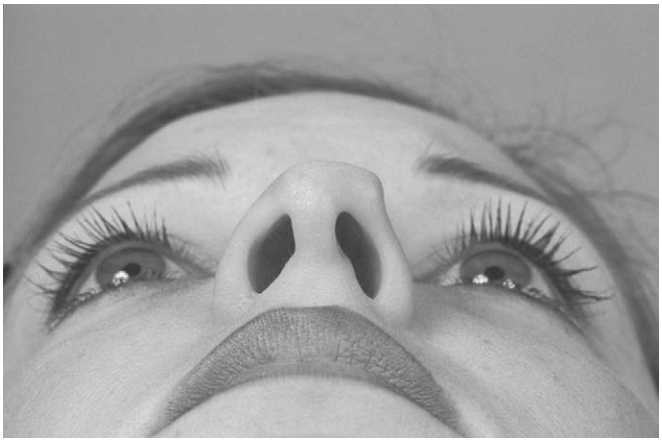

Figure 39-10. Patient with nasal tip bossae.

Figure 39-11. Tip graft used to increase projection in a thick-skinned patient.

crural strut graft can be stabilized with two or three 5.0 clear nylon sutures.

Overrotated (Short Nose)

A short nose deformity is frequently due to overresection of the caudal septum and excessive cephalic trim of the lateral crura. The length of the caudal septum can be determined by palpation. Aggressive excision of the caudal margin of the nasal septum can also result in loss of tip support, which can then cause loss of tip projection. In some patients, the tip can be blunted due to severe compromise of the tip cartilages. Some of these patients may appear to have a short nose as well.

Correction of this deformity may require rebuilding the tripod structure with a shield graft and lateral crural grafts on the existing tip structure (Fig. 39-13). This situation is distinct from the short nose caused by prior septal truncation, which may require lengthening the foreshortened septum with a caudal extension graft (Fig. 39-14). Decreasing nasal tip projection will also help create the illusion of counterrotation of the nasal tip.

Pinched Tip

The pinched nasal tip results from excessive narrowing of the domes from excisional techniques, dome division, or excessive tightening of domal sutures. The narrowness of the tip can be further complicated by lateral wall collapse and alar pinching. This unnatural appearance is a sure sign of prior surgery. The normal width of the tip is created by the inherent curvature of the individual domes as well as the normal divergence of the interdomal angle. This divergence creates a natural infratip lobule width, which should be evident both from the base view as well as the frontal view. The lobule should be wider for men than

Figure 39-12. Lateral crural grafts bolster weakened native lateral crura.

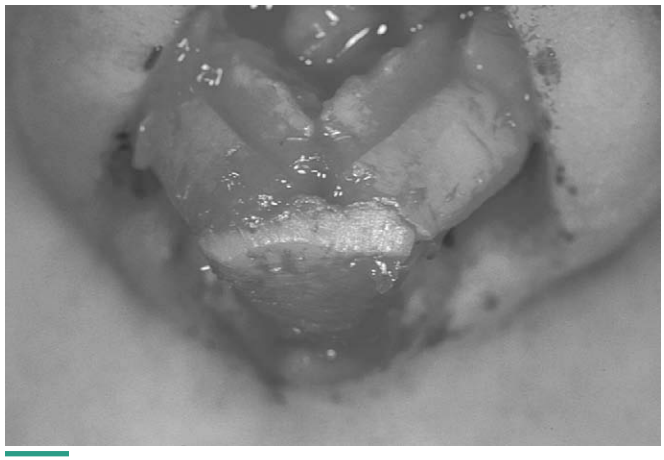

Figure 39-13. Nasal tip reconstruction is often necessary when the previously operated alar cartilages are unable to support the tip.

for women. Restoring a natural tip appearance may require reconstruction of the tip with a shield graft (Fig. 39-15).[3]

Ptotic Tip

Maintaining tip position after rhinoplasty depends on restoring any tip support mechanisms that are weak or have been surgically violated. Separating the LLCs from the ULCs, freeing the medial crura from the caudal septum, and excising or weakening the LLCs are common maneuvers in primary rhinoplasty that compromise major tip support mechanisms. Stabilizing the tip tripod framework at the nasal base can help prevent postoperative loss of tip projection and subsequent elongation of the nose. Methods of base stabilization include suture stabilization of the medial crura onto a long caudal septum, caudal extension graft, columellar strut, or an extended columellar strut.[4]

The medial crura can be sutured to the caudal septum in patients with a relatively long midline caudal septum. This technique is helpful

Figure 39-14. Short nose deformity resultant from excessive caudal septal truncation.

Figure 39-15. Patient with previous reduction rhinoplasty. Preoperative **(A, C,** and **E)** and postoperative **(B, D,** and **F)** frontal, lateral, and basal views. **G** and **H,** overly narrowed, cephalically displaced lower lateral crura. Excessive caudal septal trim, cephalic trim, and dome narrowing has created a short nose with alar retraction and pinching and an overly narrow tip. Treatment required a caudal extension graft, alar batten grafts, alar rim grafts, and tip reconstruction with a shield graft.

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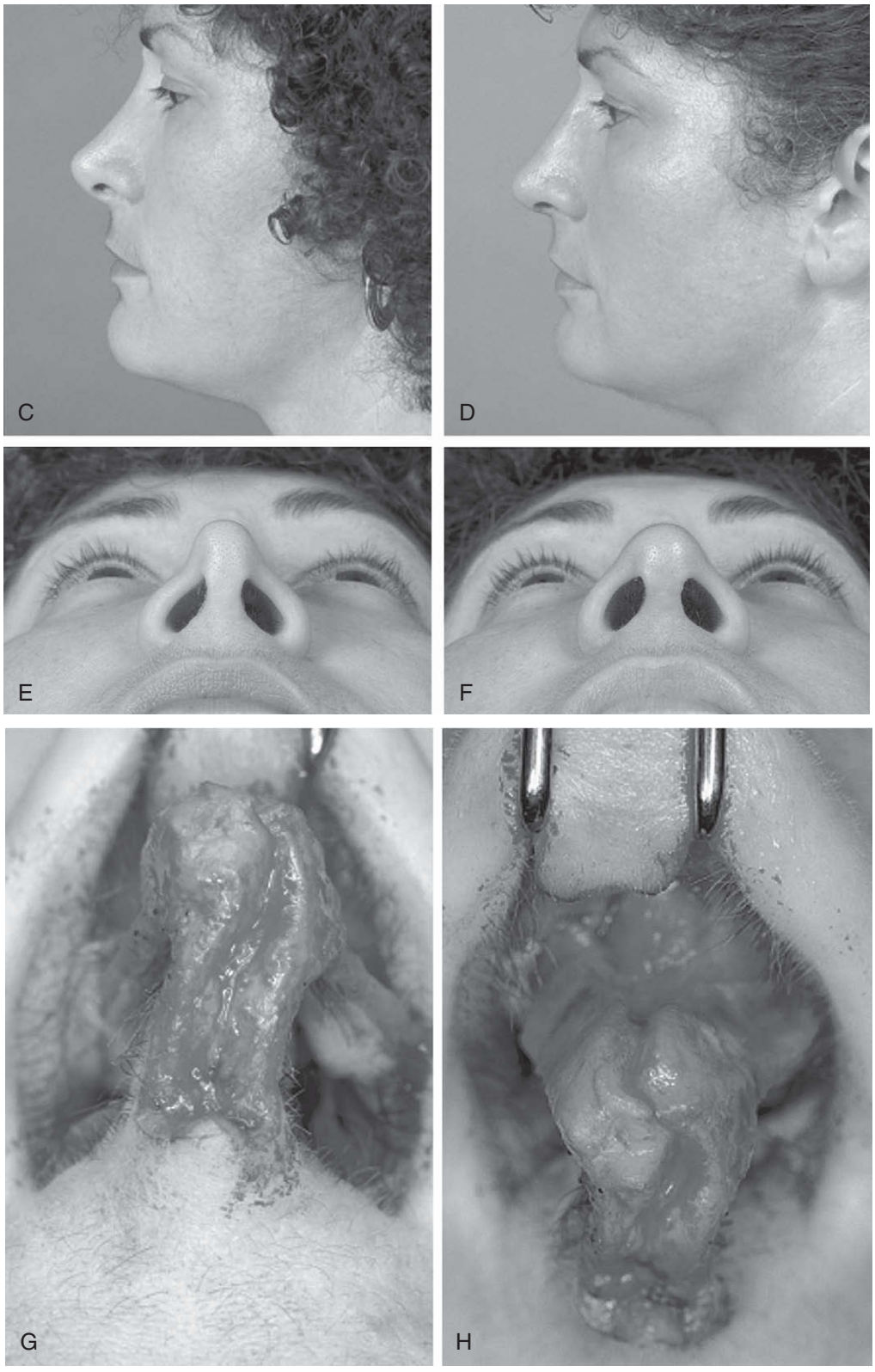

Figure 39-9, cont'd.

in patients with a hanging columella, tension nose deformity, or overprojected tip, and may require trimming of the caudal septum. The medial crura are separated and dissected free of the caudal septum. Bilateral mucoperichondrial flaps are raised and the medial crura are fixated with horizontal mattress sutures in a tongue-and-groove manner. An initial fixation suture can be placed full thickness through the medial crura, caudal septum, and vestibular skin of the membranous septum with 5.0 chromic catgut on a straight septal needle. Once the desired positioning is achieved, a 5.0 PDS suture is used to reinforce the fixation between the inner surface of the medial crura and the septum.

The caudal extension graft provides support to the base for patients with inadequate tip support. Patients with a relative caudal septal deficiency may present with columellar retraction and an underprojected, overrotated tip. This technique is often used in secondary rhinoplasty after previous excessive shortening of the septum. The graft should overlap the existing caudal septum and be suture-stabilized with at least two horizontal mattress sutures. The caudal aspect of the graft should be in the midline so that the medial crura can be stabilized in a midline position. Both the caudal septal stabilization technique and the caudal extension graft allow for changes in projection, rotation, nasolabial angle, and columellar show by variably positioning the medial crura onto the septum or the caudal extension graft. The latter technique has the potential for a greater degree of tip alteration because the shape and orientation of the effective caudal septal margin can be altered. These techniques rely on the stability of the septum to stabilize the tip. Therefore, the caudal septum itself must be structurally intact and securely attached to the nasal spine and maxillary crest to ensure durable stabilization.

The columellar strut is a reliable technique that may be used to stabilize the nasal base. This technique is useful in cases in which major tip alterations are not needed. The strut should be rectangular and can vary from 5 to 12 mm in length, 3 to 6 mm in width, and 1 to 3 mm in thickness. The strut is placed in a pocket between the medial crura and sutured to the medial crura in a horizontal mattress fashion (Fig. 39-16). Because the strut does not extend to the nasal spine, it cannot push the tip beyond its existing projection. Thus, although the floating columellar strut does provide some support to the medial crura, such struts may not be adequate for patients with a deficient nasal base.

Figure 39-16. Sutured in place columellar strut.

Because a columellar strut extends closer to the nasal spine, a theoretical increase in tip support is gained. The strut, however, must be strong enough to withstand the downward tension of the tip, particularly if it is designed to push the tip beyond its current projection. This is the concept of the extended columellar strut. This technique aims to create a significant increase in projection in patients with a major deficiency of tip support. Ethnic patients and patients with congenital nasal deformities often exhibit this scenario. Other anatomic findings indicative of a patient with a deficient nasal base include a ptotic or underprojected nasal tip and an acute nasolabial angle. The extended columellar strut is typically harvested from costal cartilage to impart sufficient strength to the nasal base and tip. The strut is suture-fixated to the periosteum of the nasal spine. A notch in the undersurface of the strut can be made to articulate with the spine and prevent migration from the midline. Alternatively, the extended strut can be incorporated with a separate premaxillary graft in a tongue-and-groove manner. This may be necessary in patients with an exceptional degree of premaxillary deficiency. As in the other techniques, the medial crura are sutured to the extended columellar strut to achieve the desired projection.

The method used is dependent on the patient's skin thickness, length of caudal septum, alar-columellar relationship, and desire to lengthen or shorten the nose. Failure to take such measures can lead to gradual loss of tip support, a hanging infratip lobule, an overly acute nasolabial angle, and an underprojected, long nose. In addition to the obvious appearance on lateral view, poor tip support and poor recoil on palpation confirm the diagnosis. By using one of the base-stabilizing techniques, the tip position and support can be restored.

Nasal Septum

Caudal Septum Deviation

Persistence of a caudal septal deviation is one of the most common causes of a significant postoperative deviated tip. Left uncorrected, such a deformity will cause nasal obstruction as well as an obvious cosmetic problem. Intranasal examination should focus on the shape of the caudal septal margin. It may be tilted, C-shaped, fractured, or dislocated from the nasal spine. The nasal spine itself and the posterior septal angle must be examined for position and symmetry. The remainder of the septum must also be thoroughly visualized to check for persistent bony spurs or cartilaginous deviation obstructing the airway. The strength and caudal-cephalic position of the caudal margin must be assessed to determine the ideal method of correction. A severely weakened or retracted septum may require reconstruction with a large caudal extension graft. A strong, severely deviated caudal septum may need to be removed and replaced with a straight segment of cartilage.

Caudal Septal Excision (Short Nose)

Excessive caudal septal excision can result in rotation of the tip and a shortened nose. Thus the entire tip tripod is cephalically rotated, which opens the nasolabial angle and can lead to a retracted columella. Careful analysis of the nasal base, tip projection and rotation, and palpation of the caudal margin of the septum are critical. The internal vestibular lining should be inspected for previous resection because redundancy of skin and mucosa would ensue following septal truncation.

Correction requires restoring septal length with a caudal extension graft and fixating the tip cartilages onto the new caudal margin of the septum. Minor deformities can be addressed with plumping grafts at the premaxilla for posterior caudal septal deficiency or columellar onlay grafts. If there is a shortage of vestibular lining, an assessment must be made to determine whether the compromised SSTE will tolerate expansion with such grafts. If not, a skin graft or composite graft must be considered.

Alar Base

One of the most difficult rhinoplasty complications to correct is the overly narrowed alar base. Alar base reduction should be performed conservatively with the aim of achieving 60% to 70% of an idealized reduction at the time of primary surgery. Unfortunately, excessive or

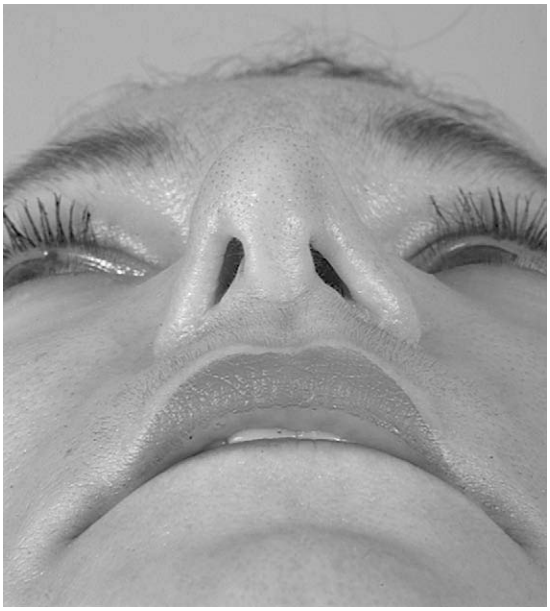

Figure 39-17. Patient with previous overly aggressive alar base reduction. Obvious cosmetic deformity associated with significant airway obstruction. Repair required placement of auricular composite grafts to widen the nostril sills.

asymmetric reduction is a common error made during rhinoplasty. On frontal or base view, the alar insertion should approximate the intercanthal width, and a slight amount of alar flare is desirable, particularly in men. Ethnic variations allow for a greater degree of interalar width and alar flare, especially in patients of African and Asian descent. Poorly placed incisions or uneven closure are also common problems associated with base reduction. Nostril size and shape must be noted on base view. Meticulous measurements should be made of the width of the columellar pedestal, the width of the nasal sill, and the distance of the outer aspect of the alar insertion to the midline. Repositioning the alar base is a three-dimensional process. Horizontal repositioning of the ala can result in asymmetric or undesirable migration of the alar insertion, which can lead to deformity. Comparison of the nose to preoperative photos can help determine which portion of the alar base was previously removed. A significant reduction in the width of the nostril floor and the interalar distance suggests resection primarily of the sill. Reduction of alar flare suggests resection of the lateral alar sidewall. Reduction of both flare and interalar width suggests excision at the junction of the sill and alar sidewall, possibly through the use of a sliding alar flap. This analysis helps determine the shape and size of the tissue needed to replace the previous excision.[13]

Composite grafts harvested from the cymba concha work well to correct such deformities. These grafts can be interposed into incisions placed at the areas of maximal narrowing. A common deformity after overreduction is the overly narrowed or absent nasal sill (Fig. 39-17). In these cases, a composite graft is placed into an incision at the nostril floor, resulting in widening of the sill and the interalar distance. Transposition flaps using a superiorly pedicled cheek flap should be avoided because they tend to cause more distortion, vertical alar malposition, and an unsightly scar.

Skin–Soft Tissue Envelope

When the skin has been significantly damaged, the rhinoplasty surgeon must be exceedingly cautious in manipulating or undermining the SSTE. If there is any doubt regarding the integrity of the SSTE, surgery should be delayed to allow full recovery. Blue discoloration or cutaneous telangiectasias signify damage and added risk for skin complications. In catastrophic cases in which the soft tissue envelope has already been severely compromised, the surgeon should consider staged preliminary repair of the SSTE with skin grafts or local or regional flaps before any structural nasal surgery.

Conclusion

Secondary rhinoplasty can pose some of the most difficult challenges in facial plastic surgery. Many of the tools of analysis are the same as for primary rhinoplasty. However, these methods must be focused toward the problems and deformities most commonly found in secondary rhinoplasty. The ability to correct these problems is limited by the integrity of the existing structures, the availability of grafting material, and the severity of the individual deformities. In many cases, secondary rhinoplasty becomes an operation of reconstruction more than one of simple refinement. Thus, the goal of analysis in secondary rhinoplasty is not only for the diagnosis of these problems, but also to determine the limitations and strategies for treatment.

The examples cited in this chapter represent only a fraction of the multitude of potential problems the surgeon might encounter. In some cases, the cause of the problem may not become clear until surgery. In the face of compromised nasal structures, scarred soft tissue, and a lack of autogenous grafting material, the revision surgeon must be prepared for the worst of scenarios. Even more than in primary rhinoplasty, this requires meticulous attention to detail in preoperative analysis. Thoughtful planning based on this analysis as well as a thorough understanding of the problems often encountered in revision rhinoplasty will maximize the chance of a favorable outcome.

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CHAPTER FORTY

Immunology of the Upper Airway and Pathophysiology and Treatment of Allergic Rhinitis

Fuad M. Baroody

Robert M. Naclerio

Key Points

- The immune system protects the organism from infectious microbes and avoids responses that produce damage to host tissues.
- The immune system is divided into the innate and adaptive systems. The adaptive immune system recognizes different specific antigens, adapts to changing environments, and provides immunologic memory.
- The innate immune system includes all aspects of the host defense mechanisms, such as barrier mechanisms (epithelium, mucus layer, mucociliary transport) and soluble bioactive molecules (complement proteins, defensins, cytokines, mediators, and enzymes).
- Cell-mediated immune responses are orchestrated by T cells and their cytokines and mount appropriate reactions to offending antigens.
- Allergic rhinitis is an example of a type I, IgE-dependent, mast cell–mediated immune reaction, whereby the release of mast cell or basophil mediators creates responses to sensitizing allergens.
- Allergic rhinitis is a common disease that, although benign, leads to significant impairment of quality of life and a large health care expenditure.
- The pathophysiology of allergic rhinitis revolves around mast cell release of inflammatory mediators followed by a chronic inflammatory response, in which the eosinophil plays a predominant role and which leads to hyperresponsiveness of the nasal mucosa to subsequent stimulation.
- H_1 antihistamines are effective agents for the treatment of allergic rhinitis but often do not completely control the bothersome symptom of nasal congestion.
- Leukotriene receptor antagonists are also effective in controlling the symptoms of allergic rhinitis, and their efficacy parallels that of antihistamines.
- Intranasal steroids are potent anti-inflammatory agents that control allergic nasal inflammation and are superior in efficacy to antihistamines and leukotriene receptor antagonists in controlling symptoms of the disease and improving quality of life.
- Immunotherapy is effective in the treatment of refractory allergic rhinitis and can be administered subcutaneously or by the sublingual route.
- Immunotherapy is the only allergic rhinitis therapy that has been shown to alter the natural course of the disease.

The importance of the immune system in health and disease has long been recognized. Not only does the immune system—with its diverse collection of pathogenic mechanisms—protect the organism from infectious microbes; it also avoids responses that produce damage to host tissues. This basic property of the immune system relies on detecting structural features of the pathogens that are distinct from those of host cells.

The immune system is divided into the innate and adaptive systems. The following features of the adaptive immune system distinguish it from the innate system: specificity of antigen recognition, diversity of the antigen receptor repertoire, rapid clonal expansion, adaptiveness to the changing environment, and immunologic memory. The innate immune system recognizes foreign invaders immediately via pattern recognition receptors, whereas the adaptive immune system takes time to mount a response. Evidence also suggests that activation of the innate immune system triggers the direction of the adaptive immune responses, illustrating the relationship between the two systems.

Innate Immunity and Adaptive Immunity

Broadly defined, the innate immune system consists of all aspects of the host defense mechanisms that are encoded in the germline genes of

the host. These include barrier mechanisms, such as epithelial cell layers that express tight cell-cell contact, the secreted mucus layer that overlays the epithelium, and the epithelial cilia that sweep away this mucus layer. The innate response also includes soluble proteins and small bioactive molecules that either are constitutively present in biologic fluids (such as the complement proteins and defensins)[1,2] or are released from activated cells (including cytokines, chemokines, lipid mediators of inflammation, and bioactive amines and enzymes). Activated phagocytes (including neutrophils, monocytes, and macrophages) are also part of the innate immune system.

Mucosal surfaces of the upper airway are less resistant than the skin and are thus more common portals for offending pathogens. The innate immune system reduces that vulnerability through the presence of various physical and biochemical factors. A good example is the enzyme lysozyme, which is distributed widely in secretions and can split the cell walls of most bacteria. If an offending organism penetrates this first line of defense, bone marrow–derived phagocytic cells attempt to engulf and destroy it. Lastly, the innate immune system includes cell-surface receptors that bind molecular patterns expressed on the surfaces of invading microbes.

Unlike the innate mechanisms of defense, the adaptive immune system manifests exquisite specificity for its target antigens. Adaptive responses are based primarily on the antigen-specific receptors expressed on the surfaces of T and B lymphocytes. These antigen-specific receptors of the adaptive immune response are assembled by somatic rearrangement of germline gene elements to form intact T-cell receptor (TCR) and B-cell antigen receptor genes. The assembly of antigen receptors from a collection of a few hundred germline-encoded gene elements permits the formation of millions of different antigen receptors, each with a potentially unique specificity for a different antigen.

Because the recognition molecules used by the innate system are expressed broadly on a large number of cells, this system is poised to act rapidly after an invading pathogen is encountered. The second set of responses constitutes the adaptive immune response. Because the adaptive system is composed of small numbers of cells with specificity for any individual pathogen, the responding cells must proliferate after encountering the pathogen to attain sufficient numbers to mount an effective response against the microbe. Thus the adaptive response generally expresses itself temporally after the innate response in host defense. A key feature of the adaptive system is that it produces long-lived cells that persist in an apparently dormant state but that can re-express effector functions rapidly after repeated encounter with an antigen. This feature provides the adaptive response with immune memory, permitting it to contribute to a more effective host response against specific pathogens when they are encountered a second time. This chapter first discusses the innate immune system and its components, followed by the different cells and effector responses of the adaptive immune system.

Innate Immune System

Innate immune effectors are critical for effective host defense. In addition to local defenses at mucosal surfaces, such as mucus and mucociliary transport, the effectors of innate immunity include Toll-like receptors (TLRs), antimicrobial peptides, phagocytic cells, natural killer (NK) cells, and complement.

Toll-Like Receptors

An important advance in our understanding of innate immunity to microbial pathogens was the identification of a human homolog of the *Drosophila* Toll receptor. Mammalian TLR family members are transmembrane proteins containing repeated leucine-rich motifs in their extracellular portions. Mammalian TLR proteins contain a cytoplasmic portion that is homologous to the interleukin-1 (IL-1) receptor, and can therefore trigger intracellular signaling pathways. TLRs are pattern recognition receptors that recognize pathogen-associated molecular patterns present on a variety of bacteria, viruses, and fungi. The activation of TLRs induces expression of costimulatory molecules and the release of cytokines that instruct the adaptive immune response. Finally, TLRs directly activate host defense mechanisms that directly combat the foreign invader or contribute to tissue injury.[3]

Expression and Distribution of Toll-Like Receptors

TLRs were initially found to be expressed in all lymphoid tissue but are most highly expressed in peripheral blood leukocytes. Expression of TLR messenger RNA (mRNA) has been found in monocytes, B cells, T cells, and dendritic cells.[4,5] The expression of TLRs on cells of the monocyte-macrophage lineage is consistent with the role of TLRs in modulating inflammatory responses via cytokine release. Some TLRs are located intracellularly, like TLR9.

Activators of the Different Toll-Like Receptors

Lipopolysaccharides (LPSs) of gram-negative bacteria generate responses mediated via the TLR4 receptor.[6,7] Microbial lipoproteins and lipopeptides have been shown to activate cells in a TLR2-dependent manner.[8] Lipoproteins have been found extensively in both gram-positive and gram-negative bacteria as well as spirochetes. Mammalian TLR9 mediates the immune response to a specific pattern in bacterial DNA, an unmethylated cytidine-phosphate-guanosine (CpG) dinucleotide with appropriate flanking regions. These CpG-DNA sequences are 20-fold more common in microbial than in mammalian DNA; thus, mammalian TLR9 is more likely to be activated by bacterial DNA than by mammalian DNA. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition.[9] Mammalian TLR5 has been shown to mediate the response to flagellin, a component of bacterial flagella.[10] Mammalian TLR3 mediates the response to double-stranded RNA, a molecular pattern expressed by many viruses during infection.[11] Activation of TLR3 induces interferons IFN-α and IFN-β, cytokines important for antiviral responses. Finally, single-stranded RNA binds to TLR7 and TLR8.[12]

Toll-Like Receptors and the Adaptive Immune Response

Critical proinflammatory and immunomodulatory cytokines, such as IL-1, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor-α (TNF-α) have been shown to be induced after activation of TLRs by microbial ligands.[3] Activation of TLRs on dendritic cells triggers their maturation, leading to cell surface changes that enhance antigen presentation, thus promoting the ability of these cells to present antigen to T cells and generate type 1 helper T cell (TH1) responses critical for cell-mediated immunity. Therefore, activation of TLRs as part of the innate response can influence and modulate the adaptive T-cell response and modify the shaping of the TH1/TH2 balance.[13]

Toll-Like Receptors and the Host

Like the *Drosophila* Toll receptor, mammalian TLRs have been shown to play a prominent role in directly activating host defense mechanisms. For example, activation of TLR2 by microbial lipoproteins induces activation of the inducible nitric oxide synthase promoter that leads to the production of nitric oxide, a known antimicrobial agent.[8] In *Drosophila*, activation of Toll leads to the nuclear factor κB (NF-κB)–dependent induction of a variety of antimicrobial peptides.[14] In a similar fashion, it has been shown that LPS induces β-defensin-2 in tracheobronchial epithelium, suggesting similar pathways in humans.[15] The activation of TLRs can also be detrimental, causing tissue injury. The administration of LPS to mice can result in shock, a feature that depends on TLR4,[6] and microbial lipoproteins induce features of apoptosis via TLR2.[16] Thus, microbial lipoproteins have the ability to induce both TLR-dependent activation of host defense and tissue pathology. This might be one way for the immune system to activate host defenses and then down-regulate the response to avoid causing tissue injury.

Antimicrobial Peptides

The function of antimicrobial peptides (AMPs) is essential to the mammalian immune response. They participate primarily in the innate immune system and are used as a first-line immune defense by many organisms, including plants, bacteria, insects, and vertebrates. AMPs directly kill a broad spectrum of microbes, including gram-positive and gram-negative bacteria, fungi, and certain viruses. In addition, these peptides interact with the host itself, triggering events that complement their role as antibiotics. AMPs can be divided into several categories on the basis of their structures, but most of them maintain certain common structural features, such as a cationic charge and the ability to interact

with bacterial membranes through hydrophobic amino acids. Two major families of AMPs have been characterized in mammals—defensins and cathelicidins.

Cathelicidins

Most cathelicidins undergo extracellular proteolytic cleavage that releases their C-terminal peptide containing the antimicrobial activity. The only known human cathelicidin, hCAP-18 (human cationic antimicrobial peptide, 18 kDa), was initially identified in granules of human neutrophils.[17] Its free C-terminal peptide is called LL-37 and has a broad spectrum of antimicrobial activity in vitro against *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Listeria monocytogenes*, and *Staphylococcus aureus*.[18] LL-37, a chemoattractant for mast cells[19] and human neutrophils, monocytes, and T cells,[20] induces degranulation and histamine release in mast cells.[21] Thus, this AMP has the potential to participate in the innate immune response both by killing bacteria and by recruiting a cellular immune response and promoting tissue inflammation.

Defensins

Defensins are a broadly dispersed family of gene-encoded antimicrobials that exhibit antimicrobial activity against bacteria, fungi, and enveloped viruses.[22,23] Defensins are classified into three distinct families: the α-defensins, the β-defensins, and the θ-defensins.

α-Defensins

The α-defensins are 29 to 35 amino acids in length. Human neutrophils express a number of distinct defensins.[24] To date, six α-defensins have been identified. Of these, four are known as α-defensins 1, 2, 3, and 4 (also referred to as human neutrophil peptides HNP-1 through -4). The other two α-defensins, known as human defensins 5 and 6 (HD-5, HD-6), are abundantly expressed in Paneth cells of the small intestinal crypts,[25,26] in epithelial cells of the female urogenital tract,[27] and in nasal and bronchial epithelial cells.[28] HNP-1 through HNP-4 are localized in azurophilic granules of neutrophils and contribute to the oxygen-independent killing of phagocytosed microorganisms. Furthermore, HNP-1 through HNP-3 can either increase the expression of TNF-α and IL-1 in human monocytes that have been activated by *S. aureus* or reduce the expression of vascular cellular adhesion molecule-1 (VCAM-1) in human umbilical vein endothelial cells activated by TNF-α.[29]

β-Defensins

In human beings, four types of β-defensins have been identified thus far; they are referred to as human β-defensins (HBDs) 1 through 4. They have a broad spectrum of antimicrobial activity, bind to CCR6, and are chemotactic for immature dendritic cells and memory T cells.[30] Human β-defensin 2 can also promote histamine release and prostaglandin (PG) D_2 production in mast cells, suggesting a role in allergic reactions.[31,32] Thus, the defensins, like the cathelicidins, can contribute to the immune response by both killing bacteria and influencing the cellular innate and adaptive immune response.

θ-Defensins

θ-defensins have been isolated from rhesus monkey neutrophils, but no data about the presence of these molecules in different tissues are currently available.

Tissue Distribution of Antimicrobial Peptides

All of the β-defensins are present in the respiratory system. These are expressed at various levels in the epithelia of the trachea and lung as well as in the serous cells of the submucosal glands.[33-35] Cathelicidins are also present in the conducting airway epithelium, pulmonary epithelium, and submucosal glands.[36] Investigations have also documented the presence of these peptides in the nose and paranasal sinuses in health and diseases including rhinitis, chronic rhinosinusitis, and nasal polyposis.[37-41]

Self and Nonself

The essence of specific immunity is the ability to discriminate between self and nonself. This ability allows the immune system to attack and destroy potentially harmful microorganisms without simultaneously destroying the person infected by these agents, a process also known as self-tolerance. Failure of self-tolerance underlies the broad class of autoimmune diseases. This crucial function is mediated by the molecules determined by the human leukocyte antigen (HLA) complex. Initial study of the HLA system focused on the role of these antigens in determining the success of organ and tissue transplantation. The HLA complex and its homologs in other species were thus termed the major histocompatibility complex (MHC). In humans, the MHC occupies about 4000 kDa of DNA on the short arm of chromosome 6 and contains many genes that encode molecules for various functions. Among these molecules, a group of glycoproteins belonging to the immunoglobulin (Ig) supergene family are present on the cell surface and play a major role in allowing the immune system to distinguish between self and nonself. These are MHC class I molecules (HLA-A, -B, and -C) and class II molecules (HLA-DR, -DQ, and -DP).

MHC class I molecules are present on the surface of most nucleated somatic cells. They are responsible for presenting endogenous antigens to cytotoxic T cells, allowing the recognition and elimination of virus-infected cells and cells containing autoantibodies. A class I molecule and an antigenic (e.g., viral) peptide are recognized as a complex by the TCR. When cytotoxic T-lymphocyte precursors recognize the combination of a particular foreign peptide and a particular class I molecule on a sensitizing cell, they proliferate and differentiate to become mature cytotoxic T lymphocytes ($CD8^+$). These mature lymphocytes recognize and kill only target cells that bear the same class I molecule and the same viral peptide as were present on the sensitizing cells. Cytotoxic T-lymphocyte killing is peptide specific (lymphocytes will not lyse a target cell bearing the same class I molecule infected with a different virus). Cytotoxic T-lymphocyte killing is also class I restricted (lymphocytes will not lyse a cell bearing a different class I molecule infected with the same virus).

In contrast to class I molecules, MHC class II molecules are expressed primarily on immunocompetent antigen-presenting cells (APCs), including macrophages, monocytes, dendritic cells, and B lymphocytes. Class II molecules can be up-regulated by IFN-γ, permitting these cells to present antigens to $CD4^+$ cells at sites of inflammation. Class II molecules allow binding of peptides of 10 to 25 amino acids, and the bound peptide and the class II molecule constitute the ligand for the receptor on a $CD4^+$ T lymphocyte (helper T cell). Thus, just as class I molecules restrict the recognition of peptides by $CD8^+$ T cells, class II molecules restrict the recognition of peptides by $CD4^+$ T cells. Therefore, class II molecules are necessary for the presentation of exogenous antigen to helper T cells.

Adaptive Immunity: Cells of the Immune System and Their Responses

The human immune system consists of dispersed organs (spleen, thymus, lymph nodes) and of cells capable of moving from the bone marrow to the blood and the lymphatic system. An intact immune response includes many subsets of leukocytes that can be discriminated morphologically through the use of conventional histologic stains and, more accurately, by surface phenotype as defined by monoclonal antibody binding to registered differentiation antigens. These differentiation antigens are assigned cluster of differentiation (CD) numbers; updates are issued by the International Workshop on Human Leukocyte Differentiation Antigens (published at http://www.hcdm.org/Home/tabid/36/Default.aspx).

The pluripotent stem cells, which are derived from the yolk sac and ultimately reside in the bone marrow, are the progenitor cells from which all cells of the immune system are derived (Fig. 40-1). These pluripotent stem cells give rise to lymphoid and myeloid stem cells. Lymphoid stem cells differentiate further into the three major populations: T cells, B cells, and NK cells. T cells are defined by their cell surface expression of the TCR, a transmembrane heterodimeric protein that binds processed antigen displayed by APCs. B cells are phenotypically defined by their expression of the B-cell receptor for antigen, membrane-bound immunoglobulin. NK cells are defined morphologically as large granular lymphocytes. They are distinguished by their lack

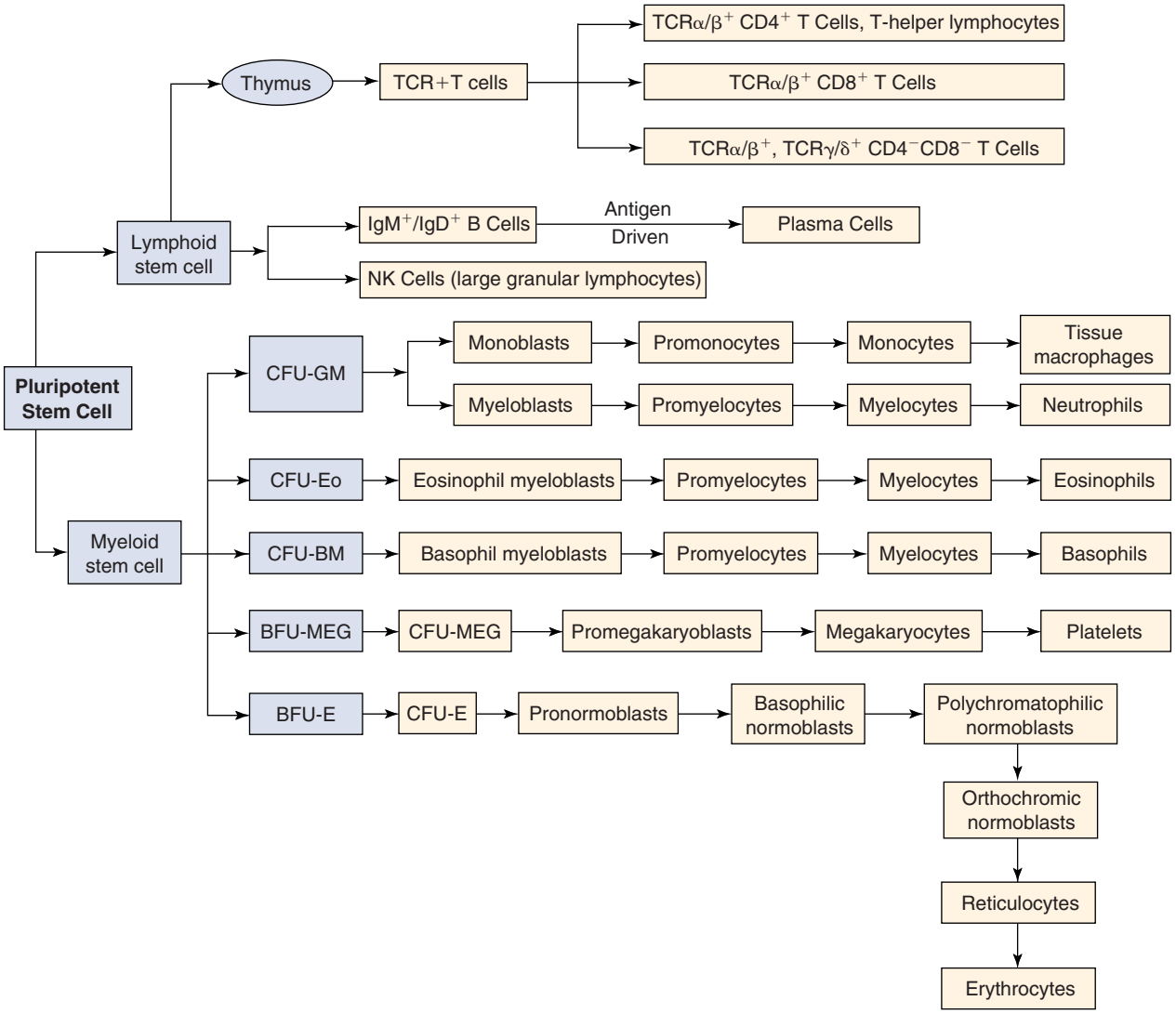

Figure 40-1. The development of the various cells that are important in the immune response from their pluripotent stem cell origin to their final stages of maturation. BFU, burst-forming unit; BM, basophil mast cell; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; GM, granulocyte-monophage; Ig, immunoglobulin; MEG, megakaryocyte; NK, natural killer; TCR, T-cell receptor.

of either TCR or surface immunoglobulin. They recognize their virus-infected or tumor cell targets through the use of a complex collection of activating and inhibitory cell surface receptors.[42] Lymphocytes represent about 25% of leukocytes in the peripheral blood. The relative contribution of each subtype to this percentage is as follows: T lymphocytes, 80%; B lymphocytes, 10%; NK large granular lymphocytes, 10%.

Myeloid stem cells give rise to different forms of granulocytes, megakaryocytes and erythrocytes. Cells of the granulocyte lineage that play prominent immune roles include neutrophils, monocytes, eosinophils, basophils, and mast cells. Differentiation of the myeloid stem cell occurs in the bone marrow, as does the development of B lymphocytes and NK lymphocytes. In contrast, T-cell progenitors leave the bone marrow and migrate to the thymus, where they differentiate into mature T lymphocytes.

Differentiation of lymphoid and myeloid stem cells depends on their interaction through their surface receptors with soluble ligands (cytokines) or surface ligands (cell interaction molecules). Therefore, proliferation and differentiation along one of the myeloid or lymphoid lineages are controlled (1) through the spatially and temporally regulated exposure of these stem cells to different ligands or factors and (2) through the differential expression of receptors on the stem cells. Cytokines have pleiotropic effects on the development of lymphoid and myeloid cells, affecting both growth and maintenance of pluripotent stem cells and their development and differentiation to specific lineages. Stromal cells within the bone marrow and thymus also regulate cell growth and differentiation by releasing cytokines, such as IL-4, IL-6, IL-7, IL-11, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[43] They also participate in cell-cell interactions with progenitors through engagement of cell surface molecules that provide additional regulatory stimuli and participate in the development of the intercellular matrix (e.g., collagen, fibronectin).[43,44]

T Cells

T-Cell Development

Lymphoid stem cells leave the bone marrow and reach the thymus gland via the bloodstream. At this stage of development, these cells lack surface antigens that make up the TCR complex and do not express the CD4 or CD8 coreceptor (double-negative). These precursors begin recombination of TCR gene segments, of which there are four: α, β, γ, and δ. Recombination begins at the δ, γ, and β loci, and if expression of the γδTCR is successful, commitment to the γδ T-cell lineage results.[45] γδ T cells remain double-negative and leave the thymus, populating lymphoid tissue and epithelia. A portion of the γδ T cells are generated in the thymus, with a major fraction generated in an extra

thymic compartment.[46] Alternatively, successful αβ loci recombination results in βTCR expression, which pairs with the surrogate α receptor and forms the pre-TCR. The pre-TCR provides ligand-independent signals enabling commitment to the αβ T-cell lineage and CD4/CD8 coexpression (double-positive). Assembly of the pre-TCR is followed by recombination at the α loci, which, if successful, generates the αβTCR. Ligand-dependent selection follows and is determined by double-positive cells binding peptide-loaded MHC molecules on thymic cortical epithelia. Double-positive cells that bind MHC with sufficient affinity are selected to survive (positive selection), whereas those that do not are eliminated by apoptosis. The interaction between the TCR and MHC molecules is restricted by the specificity of the TCR and the T-cell coreceptor: CD4 restricts interaction to class II MHC and CD8 to class I MHC. Surviving double-positive cells then lose the CD4 or CD8 coreceptor not involved in MHC recognition. These single-positive cells traffic to the thymic medulla, and those that react too strongly with self-antigens presented by medullary epithelia and bone marrow–derived APCs are deleted by apoptosis (negative selection). These processes of positive and negative selection promote viable T cells capable of recognizing and responding to peptide antigen in MHC while checking those that have autoreactivity. This is a rigorous selection, with approximately only 2% of the double-positive cells surviving. Approximately 90% to 95% of circulating T cells use the αβ TCR and are divided into two major subpopulations, $CD4^+$ helper T cells and $CD8^+$ cells.

T-Cell Priming

When T cells recognize their specific peptide/MHC ligand on APCs, TCR signals result in adhesion molecule changes that strengthen and prolong APC contact. During this interaction, a second costimulatory signal is provided by CD28 on T cells binding B7 molecules on APCs and facilitates activation and proliferation of naïve T cells. After costimulation, activated T cells produce IL-2, leading to T-cell proliferation and differentiation. Once primed, naïve T cells differentiate into effector cells that perform antigen-specific functions without the need for costimulation.[47]

Effector T Cells

In the blood and secondary lymphoid organs, 60% to 70% of T cells are $CD4^+$, and 30% to 40% are $CD8^+$. The best understood function of $CD8^+$ cells is that of cytotoxic effectors (cytotoxic T lymphocytes [CTLs]). Their function as suppressors of the immune response is more controversial, and the mechanism of this activity is not very well understood; in some instances, it is thought to be mediated by the production of nonspecific inhibitory cytokines. Although both $CD4^+$ and $CD8^+$ lymphocytes can act as cytotoxic effectors, the $CD8^+$ population has a higher frequency of cytotoxic effectors than the $CD4^+$ population. $CD8^+$ cells show a major cytotoxic activity against cells infected with intracellular microbes and against tumor cells and are the pillars of the cell-mediated immune response. $CD8^+$ effector T-cell function is distinguished by antigen-specific cytotoxicity restricted by MHC class I. On priming, $CD8^+$ T cells produce cytotoxic proteins, including perforin and granzymes, and secrete them at the point of contact with the target cell, resulting in specific killing without bystander cell damage. Perforin is a membrane-disrupting protein that facilitates the ability of granzymes to induce apoptosis in the target cell. Another mechanism for the induction of cytotoxicity, which is thought to play a key role in many inflammatory processes, involves the secretion of cytolytic cytokines by $CD8^+$ cells (e.g., TNF). The perforin-dependent pathway of cytotoxicity is largely responsible for cell-mediated clearance of infectious viruses (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus-1, and influenza A and B, measles, mumps, respiratory syncytial, rubella, and vaccinia viruses) and certain intracellular bacterial infections, and for the rejection of allogeneic tissue grafts and tumors.

Another pathway for cytotoxic cell function involves the cell surface molecule Fas, which is a member of the TNF receptor–nerve growth factor receptor–CD40 superfamily and mediates apoptosis.[48] Binding of the cell surface Fas molecule on a target cell to the Fas ligand on the cytotoxic effector leads to apoptosis of the target cell. Fas-mediated cytotoxicity is thought to play a role in the negative selection process in T-cell development; however, the role of this pathway for cytolysis in various infectious diseases has not been defined.

Generally designated helper cells, $CD4^+$ cells work to activate both humoral immune responses (B-cell help) and cellular responses (delayed-type hypersensitivity responses). After recognizing antigens presented by MHC class II molecules, $CD4^+$ cells become activated to secrete IL-2, partly in response to monocyte-derived IL-1 and partly in response to autocrine stimulation by IL-2 as part of a positive feedback loop (Fig. 40-2). Activated $CD4^+$ cells interact with other $CD4^+$ or $CD8^+$ cells by secreting IL-2, and with B cells by secreting B-cell growth and differentiation factors (IL-2, IL-4, IL-6). Thus, $CD4^+$ cells augment immune responses by stimulating B cells sensitized by antigen, and by stimulating $CD8^+$ cells sensitized by binding of antigen in the context of MHC class I molecules. $CD4^+$ T-cell priming, unlike $CD8^+$ T-cell priming, results in the differentiation of various subsets distinguished by the production of particular cytokines and effector functions. The activities of these $CD4^+$ cells are largely mediated via the secretion of these cytokines, which are small protein hormones that control the growth and differentiation of cells in the microenvironment. Classically, $CD4^+$ effectors were viewed in the context of the TH1/TH2 paradigm, but other subsets have emerged, including IL-17–producing T cells (TH17) and T cells with regulatory functions (regulatory T cells [Tregs]).[49]

TH2 cells produce cytokines, such as IL-4, IL-5, and IL-13, and specialize in facilitating B-cell antibody responses. They drive B-cell proliferation by IL-4 and contact-dependent CD40:CD40 ligand binding, increasing humoral defenses against extracellular pathogens. Moreover, IL-4 and IL-5 enable IgE production and eosinophilic inflammation, both of which are important for the clearance of helminthic disease and the allergic response. TH2 differentiation is initiated by weak TCR signals coupled with IL-4 receptor signaling and signal transducer and activator of transcription (STAT) 6 activation. This results in up-regulation of GATA-3 transcription factor, the master regulator of TH2 differentiation. GATA-3 enhances TH2 cytokine production and inhibits TH1 developmental pathways.

TH1 cells specialize in macrophage activation by IFN-γ production and contact-dependent stimulation through the use of a variety of cell surface costimulatory ligands, thus playing a major role in intracellular pathogen clearance and delayed-type hypersensitivity (DTH). TH1 differentiation is directed by interferons generated by the innate response to infection, which ultimately leads to up-regulation of T-bet, the master regulator of TH1 differentiation. T-bet directs IFN-γ production and IL-12 receptor expression. The presence of IL-12 results in activation of signal transducer and activator of transcription (STAT) 4, further enhancing IFN-γ production and TH1 effector formation. IFN-γ is an essential contributor to the generation of chronic inflammatory responses characterized by mononuclear cellular infiltration and activated macrophages. In addition to orchestrating the immune response by secreting various cytokines and contributing to CTL activities, the characteristic inflammatory reaction induced by $CD4^+$ T lymphocytes is DTH. DTH is elicited by challenge with antigen in immune, sensitized persons. The typical example is the cutaneous reaction to challenge with the purified protein derivative (PPD) of *Mycobacterium tuberculosis* in previously infected or vaccinated persons. Clinically, DTH is manifested by local erythema and induration 24 to 48 hours after challenge. Microscopically, the lesion shows perivascular accumulations of leukocytes (initially neutrophils, later lymphocytes and activated macrophages), edema, and fibrin deposition. Chronic DTH reactions result in the formation of granulomas (nodular collections of macrophages and lymphocytes) and possibly fibrosis as a result of the cytokines produced by macrophages, which stimulate fibroblast proliferation and collagen synthesis.

TH17 cells are a subset of T cells that fills an essential gap in our understanding of inflammatory processes, because it was unclear how TH1 cells actually mediate inflammation in the tissues by the expression of IFN-γ. TH17 cells secret IL-17 (or IL-17A), IL-17F, IL-6, TNF-α, and IL-22. Neutralization of IL-17, but not genetic deletion of TH1 cells, resolves tissue pathology in autoimmune models.[50] IL-17

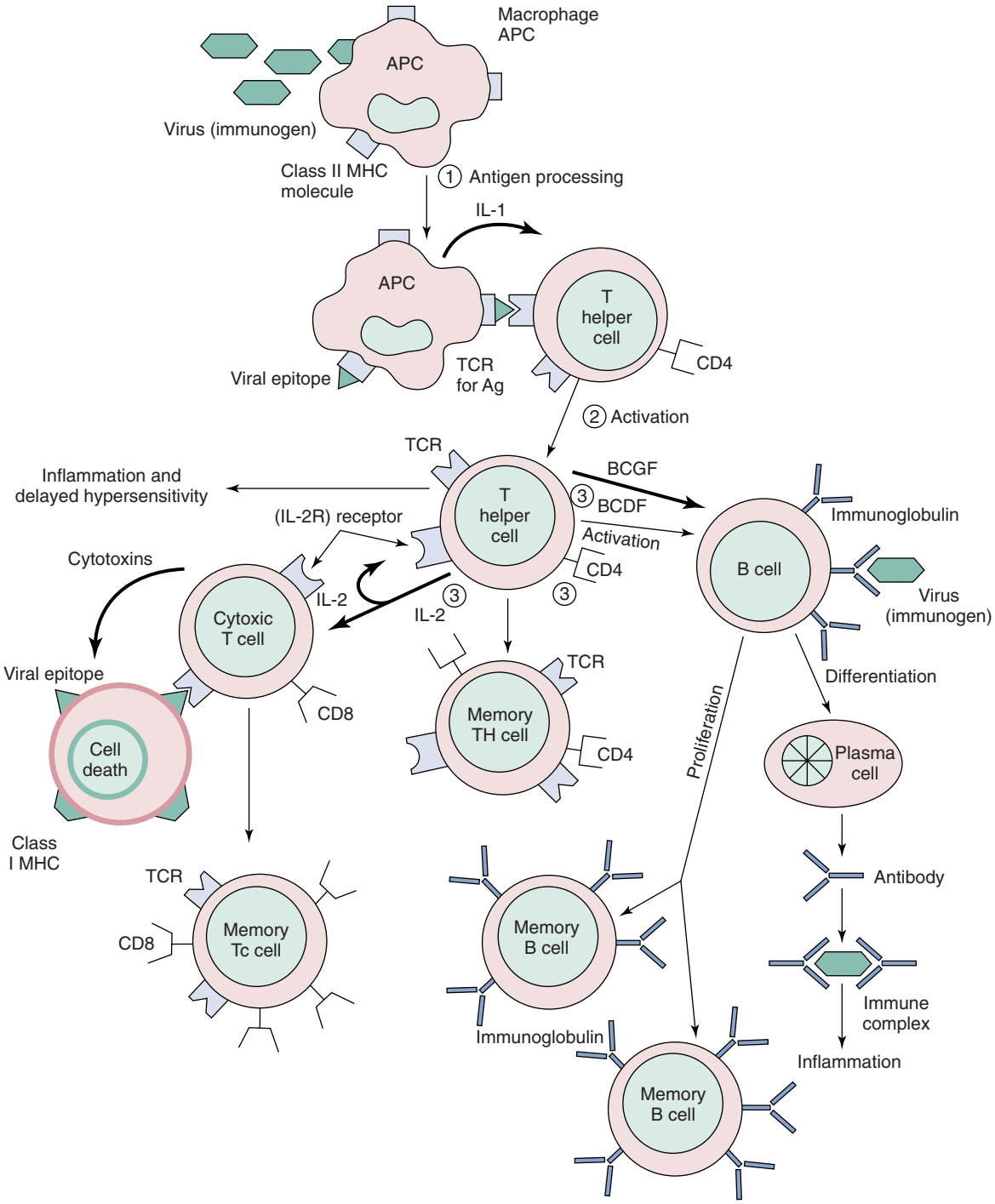

Figure 40-2. Summary of the cell-mediated immune response showing the events that follow exposure to an immunogen and the role of the helper T (TH) cell in orchestrating these events. Ag, antigen; APC, antigen-processing cell; BCDF, B-cell differentiation factor; BCGF, B-cell growth factor; IL, interleukin; MHC, major histocompatibility complex; Tc cell, cytotoxic T cell; TCR, T-cell receptor. *(From Stites DP, Terr AI, eds.* Basic and Clinical Immunology. *7th ed. Norwalk, CT: Appleton & Lange; 1991.)*

is a potent inflammatory cytokine involved in the recruitment and proliferation of neutrophils. It is also known to induce proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, as well as chemokines CXCL1, 2, and 8, which together are hallmarks of acute inflammatory processes.[51] The chemokines mobilize neutrophil recruitment, which is a characteristic feature of TH17-mediated inflammation. Anti–IL-17 reduces joint destruction in experimental arthritis,[52] and decreases neutrophil infiltration in an experimental asthma model while increasing eosinophil infiltration.[53,54] Exogenously administered IL-17 reduces pulmonary eosinophil recruitment and bronchial hyperreactivity, suggesting a regulatory role for this interleukin.[55] Thus, the TH17-directed neutrophil infiltration is inversely linked to the TH2-mediated eosinophil direction, much like the inverse relationships between TH1 and TH2 cells. In the upper airways, IL-17 has been found in nasal polyps and, interestingly, is expressed in polyps from patients in South China, which have a neutrophil-predominant infiltration, in contrast to polyps from patients from Belgium, which express IL-5 and have an eosinophil-predominant infiltration.[56]

$CD4^+$ T cells can also differentiate into cells characterized by the ability to suppress T-cell responses and prevent autoimmunity, or

regulatory T cells (Tregs).[57] Natural Tregs (nTregs) develop in the thymus and constitutively express the high-affinity IL-2 receptor (CD25) in accordance with their high dependency on IL-2 for survival. The transcription factor forkhead box P3 (Foxp3) is also stably expressed by natural Tregs and is required for their suppressive function. Natural Tregs account for 1% to 10% of the $CD4^+$ T-cell population in healthy adult humans, and most investigators identify them from the expression of the preceding factors as $CD4^+CD25^+Foxp3^+$ cells. The importance of these cells is underscored by the description of patients carrying rare loss-of-function mutations in the Foxp3 gene, in whom a range of autoimmune and inflammatory disorders develops, referred to as immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). This syndrome includes type 1 diabetes, autoimmune thyroiditis, eczema, bleeding abnormalities, and chronic wasting. These individuals also demonstrate an increased susceptibility to infection and an elevated incidence of allergic-type symptoms.[58] Other Treg populations may develop extrathymically from naïve $CD4^+$ T cells under the influence of transforming growth factor-β (TGF-β) and are referred to as induced Tregs or TGF-β–producing type 3 helper T cells. These cells are $Foxp3^+$ and are functionally indistinguishable from natural Tregs. Treg type 1 cells do not express Foxp3, but they do produce high amounts of the inhibitory cytokine IL-10 and develop outside the thymus under the control of IL-10–conditioned dendritic cells.

Approximately 5% to 10% of T cells in the peripheral circulation, lymph nodes, and spleen are $CD4^-CD8^-$. Some of these cells use αβ TCRs and others use γδ TCRs. Double-negative cells do not recognize antigen in the context of MHC class I or II. Some of these cells recognize antigen in the class I–related protein CD1 that is adapted to presentation of glycolipid components of mycobacteria and other microbes.[59] A subset of double-negative γδ T cells recognizes the MHC class I–related chain (MIC).[60] Both $CD4^+$ and $CD8^+$ T cells differentiate into functionally distinct subsets after exposure to antigen. This process is best described for the transition of $CD4^+$ T cells from naïve to effector populations.[61] Resting naïve $CD4^+$ T cells (designated helper T [TH] cells) release almost no cytokines. Early after stimulation by antigen and APC, the TH cells begin to produce IL-2 and are designated TH0. As the TH cells continue to respond to the activating signal, they progress toward polar extremes of differentiation designated TH1 and TH2, depending on the nature of the cytokines present at the site of activation.[62] IL-12 produced by macrophages or NK cells induces differentiation toward TH1, and IL-4 produced by $NK1.1^+$ T cells or mast cells induces differentiation toward TH2. TH1 cells produce IL-2, IFN-γ, and lymphotoxin, whereas TH2 cells produce IL-4, IL-5, IL-9, IL-10, IL-13, and GM-CSF. In most immune responses, TH cells show a combination of TH1 and TH2 features; however, after prolonged immunization, the response can become dominantly TH1-like or TH2-like. Generally, TH1 cells support cell-mediated immune responses and play a critical role in the defense against intracellular pathogens, such as viruses, mycobacteria, and listeria, whereas TH2 cells are critical in the responses induced by extracellular pathogens—antigens such as parasites, bacteria, and allergens. Progress with immunization to different types of adjuvants demonstrates the feasibility of reprogramming allergic TH2-type responses in atopic patients to nonallergic TH1-type responses, thereby potentially altering the course of allergic disease.[63]

B Cells

B-Cell Development

B cells constitute approximately 10% of peripheral blood leukocytes. They develop in the bone marrow from hematopoietic stem cells but achieve maturity in peripheral lymphoid organs. Early progenitors committed to the B-cell lineage (pro-B cells) begin recombination at the Ig heavy-chain loci.[64] Successful recombination leads to expression of μ heavy chain, distinguishing them from pre-B cells. With the surrogate light chain and the Igα/β signaling machinery, an Ig-like heterodimer is expressed on the surface (pre–B-cell receptor [pre-BCR]). Pre-BCR signals a halt to μ heavy-chain recombination, and Igκ or Igλ light-chain recombination begins. The surrogate light chain is replaced by successfully formed κ or λ light chain, and the BCR is expressed as surface IgM distinguishing the immature B cell.

B-Cell Responses

B cells provide humoral immunity against extracellular pathogens through the production of antibodies that neutralize pathogens and toxins, facilitate opsonization, and activate complement. Primary infection or vaccination results in prolonged production of high-affinity specific antibodies, the basis of adaptive humoral immunity. On the other hand, IgM antibodies are produced in the absence of infection, are of lower affinity, play a role in first-line defense against bacterial infection, and assist in clearance of endogenous cellular debris. Naïve follicular B cells reside in the follicles of secondary lymphoid tissues. Antigen arrives into these lymphoid organs through circulation of soluble molecules or immune complexes or via transportation by dendritic cells.[65] The B cells, via BCR, process the antigens in the context of MHC class II and then migrate to the T-B cell interface, the border between the T-cell zone and B-cell follicle, where they encounter primed TH cells of cognate specificity. This generates signals from T cell–derived cytokines and binding between CD40 ligand (CD40L) (on T cells) and CD40 (on B cells) that sustain B-cell activation and promote Ig class switching. Signaling through CD40 and its interaction with CD40 ligand on T cells is essential for the induction of isotype switching. The effector T-cell cytokines are as follows: IL-1 and IL-2 promote B-cell activation and growth,[66,67] IL-10 causes switching to IgG1 and IgG3, IL-4 and IL-13 cause switching to IgE, and TGF-β causes switching to IgA. IFN-γ, or some other undefined product of TH1 cells, appears to induce switching to IgG2. Activated B cells either migrate into the follicle and, with continued T-cell help, initiate the germinal center reaction or migrate to the marginal zone and differentiate into short-lived plasma cells. These latter cells secrete antibody for 2 to 3 weeks, providing a rapid, but transient, source of effector molecules. The B cells in the germinal center undergo specificity diversification through somatic hypermutation, and high-affinity variants are selected by survival advantage, a process termed affinity maturation. Thus within the germinal centers, sequential cycles of proliferation, BCR diversification, and selection amplify high-affinity variants of the original activated B cell. The cells that then exit the germinal center reaction give rise to the memory compartment, consisting of affinity-matured memory B cells and long-lived plasma cells. When memory cells re-encounter antigen, they divide rapidly and expand their numbers or differentiate into antibody-secreting plasma cells. These long-lived plasma cells are terminally differentiated B cells incapable of further division that home to the bone marrow and secrete high-affinity class-switched antibody. These B cell responses are orchestrated with the help of T cells and their cytokines and are termed T cell–dependent B-cell responses.

Natural Killer Cells (Large Granular Lymphocytes) and Natural Killer Cell Cytotoxicity

Large granular lymphocytes, the third major subtype of lymphocytes, are referred to as natural killer cells. NK cells are distinct from T cells or B cells and can manufacture and release various cytokines, including IFN-γ, TNF-α, and GM-CSF. They are present in the peripheral circulation and in the spleen, lungs, and liver.[68,69] They are not found in lymph nodes and do not recirculate through the thoracic duct lymph. These cells are usually larger than typical lymphocytes and display less nuclear material and more cytoplasm. They possess electron-dense, peroxidase-negative granules and a well-developed Golgi apparatus. NK cells lack rearranged immunoglobulin and TCR genes and therefore do not express surface immunoglobulin or the TCR complex. They express a unique pattern of surface molecules not usually expressed on other lymphocytes, including CD16 (FcγRIII), a receptor for the Fc portion of immunoglobulin, and CD56, an adhesion molecule that is also expressed on neural cells.[70-73] In addition, they express CD2, which is also expressed on T cells.[71]

The ability of $CD4^+$ and $CD8^+$ T cells to recognize only peptides presented by self MHC molecules is termed MHC restriction, and cytolytic activity mediated by these cells is known as MHC-restricted cytotoxicity. In contrast to these two cell types, NK cells are capable of

cytotoxic activity that is not restricted to recognition of target cells that display MHC molecules. This process is termed unrestricted toxicity. NK cells can mediate antibody-dependent cellular cytotoxicity (ADCC) by activation through their IgG Fc receptors and the subsequent production of cytokines such as IFN-γ, which can affect the proliferation and differentiation of other cell types. They also produce cytotoxicity by mechanisms similar to those of CTLs, including perforin-mediated destruction of cells, receptor-induced apoptosis, and release of cytokines such as TNF-α. NK cells have no antigen-specific receptors. Their cytotoxic activity is inhibited by encounter with self MHC molecules through inhibitory receptors on the surface of NK cells that recognize class I. They thus kill self cells that have down-regulated class I molecule expression. This factor is important in host defense, because several viruses have developed mechanisms to down-regulate class I expression in infected cells as a strategy to avoid $CD8^+$ cell killing. NK cells have prominent antitumor effects and are potent killers of virally infected cells.[74]

Monocytes and Macrophages

Monocytes and macrophages arise from colony-forming unit–granulocyte-macrophage (CFU-GM) progenitors, which differentiate into monoblasts, promonocytes, and monocytes. Monocytes account for about 10% of circulating leukocytes. Several cytokines—including stem cell factor (SCF), IL-3, IL-6, IL-11, and GM-CSF—promote the development of myeloid-lineage cells from $CD34^+$ stem cells, predominantly in the early stages of differentiation. The macrophage colony-stimulating factor (M-CSF) acts at the later stages of development and induces maturation of macrophages.[75] Mature monocytes leave the bone marrow and circulate in the bloodstream until they enter tissues, where they develop into macrophages. These cells include Langerhans cells in the epidermis, Kupffer cells in the liver, microglial cells in the central nervous system, and the broad class of dendritic cells that are present in most tissues of the body and are concentrated in the secondary lymphoid tissues. All of these cells express both class I and class II MHC molecules that are used to permit recognition of processed antigen by the TCR on T cells. Dendritic cells appear to be the most potent APCs, but macrophages, Langerhans cells, and Kupffer cells are also prominent APCs.

Like neutrophils, monocytes and macrophages are also highly phagocytic for microbes and particles that have been marked for clearance by binding immunoglobulin, complement, or both. Phagocytosis is facilitated by opsonization, which coats foreign material with antibodies. After phagocytosis, an intracellular vacuole forms around the foreign material and lysosomal enzymes released into the vacuole destroy the foreign invader. These cells appear to be mobilized shortly after neutrophils and they persist for long periods at sites of chronic inflammation and infection. They use production of nitric oxide as a major mechanism for killing microbial pathogens and produce large amounts of cytokines, such as IL-12 and INF-γ, giving them a regulatory role in adaptive immune responses.[76]

Neutrophils

Neutrophils arise from colony-forming unit–granulocyte-macrophage progenitor cells that give rise to myeloblasts, which differentiate into promyelocytes, myelocytes, and finally, mature neutrophils. After maturation in the bone marrow, neutrophils circulate in the peripheral blood, where they account for 60% to 65% of leukocytes. As for monocytes, SCF, IL-3, IL-6, IL-11, and GM-CSF promote the growth and development of neutrophil precursors. Other cytokines that exhibit more specific effects on neutrophils include granulocyte colony-stimulating factor (G-CSF), which induces maturation of neutrophil precursors into neutrophils.[77] IL-4 also enhances neutrophil differentiation induced by granulocyte CSF. Neutrophils produce large quantities of oxygen species that are cytotoxic to bacterial pathogens and enzymes that appear to participate in tissue remodeling and repair after injury. They accumulate in large quantities at sites of bacterial infection and tissue injury and possess prominent phagocytic capabilities that permit them to sequester microbes and particulate antigens internally, where they can be destroyed and degraded. Thus, neutrophils play a major role in the clearance of microbial pathogens and repair of tissue injury.[78] Neutrophils have also been recognized to produce substantial amounts of the cytokines TNF and IL-12 as well as certain chemokines; this finding supports an additional immunoregulatory role for these cells.

Eosinophils

Eosinophils are derived from colony-forming unit–eosinophil (CFU-Eo), a progenitor that differentiates into an eosinophilic myeloblast, promyelocyte, myelocyte, and finally a mature eosinophil. Eosinophils constitute 2% to 5% of circulating leukocytes in normal individuals and are readily recognized from their prominent cytoplasmic granules, which contain toxic molecules and enzymes that are particularly active against helminths and other parasites.[79] GM-CSF and IL-3 promote eosinophil growth and differentiation.[80] The production of eosinophils from the bone marrow and their survival in peripheral tissues are enhanced by the cytokine IL-5, which maintains their viability through inhibition of apoptosis.[81]

Eosinophils are prominent cells in most allergic responses.[82] Eosinophils possess several surface markers and receptors involved in differentiation, recruitment into tissues, activation, and synthesis and release of their multiple mediators. Receptors for immunoglobulins include those for IgG, IgE, and IgA. Eosinophils have receptors for complement components, including C1q (CR1), C3b/C4b (CR1), iC3b (CR3), C3a, and C5a. Both C3a and C5a are eosinophil chemoattractants that stimulate production of oxygen radicals by eosinophils. Eosinophils potentially express several receptors for chemokines. CCR1 is a receptor for macrophage inflammatory protein-1α (MIP-1α), monocyte chemotactic protein-3 (MCP-3), and the chemokine regulated on activation, normal T cell expressed and secreted (RANTES); CCR3 is a receptor for eotaxin, eotaxin-2, eotaxin-3, monocyte chemotactic protein-3, and RANTES.[83] Mature eosinophils, like their immature precursors, express functional heterodimeric receptors for the three cytokines—GM-CSF, IL-3, and IL-5—that promote eosinophilopoiesis and stimulate the functioning of mature eosinophils.

The eosinophil's cationic granule proteins include major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). Another prominent protein of the eosinophil is the Charcot-Leyden crystal (CLC) protein, which constitutes an estimated 7% to 10% of total cellular protein, possesses lysophospholipase activity, and forms the distinctive hexagonal bipyramidal crystals that are the hallmark of eosinophil-associated inflammation. MBP is a potent cytotoxin and helminth toxin in vitro. It can kill bacteria and many types of normal and neoplastic mammalian cells, stimulate histamine release from basophils and mast cells, activate neutrophils and platelets, and augment superoxide generation by alveolar macrophages. It can also induce bronchoconstriction and transient airway hyperreactivity when instilled into the monkey trachea.[79] ECP, like MBP, has marked toxicity for helminth parasites, blood hemoflagellates, bacteria, and mammalian cells and tissues and has been shown in several studies to produce respiratory epithelial damage similar to that seen in severe asthma. As with MBP and ECP, EPO is highly cationic and exerts some cytotoxic effects on parasites and mammalian cells in the absence of hydrogen peroxide. However, EPO is highly effective in combination with hydrogen peroxide and a halide cofactor (iodide, bromide, or chloride), from which EPO catalyzes the production of the toxic hypohalous acid. In the presence of these compounds, EPO is highly toxic to various unicellular, multicellular, and other targets, including viruses, mycoplasma, bacteria, fungi, and parasites. EDN is a poor cationic toxin, with only limited toxicity for helminths and mammalian cells, but it induces significant neurologic damage when injected intrathecally or intracerebrally into experimental rabbits or guinea pigs. In allergic conditions, eosinophils may play a dual role. They can suppress the local tissue response to inflammatory mediators involved in IgE-mediated hypersensitivity reactions by inactivating histamine, platelet-activating factor, and heparin. On the other hand, eosinophils can augment destruction through the toxic effects of the products they release upon degranulation. The balance between these two seemingly contradictory functions of eosinophils in IgE-mediated reactions is still under investigation.

Basophils and Mast Cells

Basophils mature from a progenitor colony-forming unit–basophil mast cell (CFU-BM) into basophilic myeloblasts, promyelocytes, myelocytes, and then mature basophils. Mast cells are thought to develop from the same progenitor, but less is known about their specific stages of development. IL-3 and SCF have the most consistent effects on human basophil and mast cell growth and differentiation. These cytokines act synergistically to induce basophil and mast cell development from $CD34^+$ progenitor cells.[84] SCF induces functional maturation of human mast cells. Nerve growth factor and GM-CSF[85] affect basophil growth, and IL-5 enhances basophil differentiation.[86] Basophils and mast cells are morphologically similar and both exhibit cell surface expression of high-affinity receptors for IgE (FcεRI), making them key initiators of immediate hypersensitivity responses and the host response to helminthic parasites; these cells release histamine and other preformed mediators from their granules and produce important quantities of lipid mediators that stimulate tissue inflammation, edema, and smooth muscle contraction. Studies have shown that in addition to this role, mast cells play prominent roles in the host response to bacterial infections.[87]

Platelets and Erythrocytes

Platelets and erythrocytes are derived from stem cell progenitors, which differentiate into burst-forming units–megakaryocytes (BFU-MEG) in the case of platelets and into burst-forming units–erythroid (BFU-E) in the case of erythrocytes. Burst-forming units–megakaryocytes then differentiate into colony-forming units–megakaryocytes (CFU-MEG), promegakaryoblasts, megakaryocytes, and platelets. IL-1, IL-3, GM-CSF, IL-6, and IL-11 affect the growth and differentiation of platelets.[88-90] The erythrocyte precursors burst-forming units–erythroid differentiate into colony-forming units–erythroid (CFU-E), pronormoblasts, basophilic normoblasts, polychromatophilic normoblasts, orthochromic normoblasts, reticulocytes, and erythrocytes. Cytokines important in the various stages of erythrocyte differentiation and development include GM-CSF, SCF, IL-9, and erythropoietin.[91]

Lymphoid Organs

The primary lymphoid organs, sites where lymphocytes differentiate and mature from stem cells into effector cells, include the thymus and bone marrow. The secondary lymphoid organs are sites where mature lymphocytes reside and immune responses are generated. They are divided into the systemic immune system (spleen and lymph nodes) and the mucosal immune system (tonsils, Peyer's patches, scattered lymphoid follicles, intraepithelial lymphocytes, and the lamina propria of mucosal tissues). The primary role of the secondary lymphoid organs is to facilitate interactions between antigen-specific T and B cells and antigen-charged antigen-presenting cells. The spleen protects the body from antigens in the bloodstream, whereas lymph nodes respond to antigens delivered through lymphatics draining the skin and deeper tissues. The secondary lymphoid organs, specifically lymph nodes and the mucosal immune system, are of particular interest to otolaryngologists.

Lymph Nodes

Lymph nodes occur as chains or groups. Blood vessels enter and leave them through the hilus, and lymph nodes also receive afferent lymphatic vessels from the structures that they drain. The lymphatic vessels carry APCs and foreign antigens that are subsequently transported into the substance of the lymph node. Lymph nodes are divided into two major regions, the cortex and the medulla.

The cortex contains numerous primary and secondary lymphoid follicles in which B cells predominate. Primary follicles, consisting of a mantle zone without germinal centers, contain resting B cells expressing surface IgM or IgD and CD23. In addition to an outer mantle zone, secondary follicles contain inner germinal centers, which form in response to antigen stimulation. Immunoglobulin class switching, affinity maturation through somatic mutation, and development of memory B cells occur within germinal centers. $CD4^+$ T cells are also found in these centers and play a key role in the B-cell responses through interactions between CD40 (expressed on the B cell) and the ligand for CD40 (present on activated $CD4^+$cells). The paracortical region of the lymph node cortex surrounds the lymphoid follicles and contains mostly T cells (both $CD4^+$ and $CD8^+$) and some macrophages, dendritic cells, and B cells (accessory cells). The accessory cells present peptide antigens in association with MHC molecules to the TCR on T cells, resulting in their activation.

The medulla, the region at the center of the lymph node, is divided into medullary cords surrounded by medullary sinuses that drain into the hilus. Medullary cords contain B cells, T cells, macrophages, and many plasma cells. These cells are joined by B and T cells that migrate from the cortex to the medulla. Efferent lymphatic vessels leave the hilus carrying antibodies and mature B and T cells that migrate to other tissues and act as memory cells during subsequent immune exposure. The lymphatic system eventually drains into the thoracic duct and into the circulation, therefore allowing lymphocytes to circulate throughout the body.

Mucosal Immune System

Mucosal surfaces and skin encounter the environment and possess an immune system capable of responding to pathogens and foreign antigens. The mucosal immune system is composed of the organized mucosal immune system (including tonsils, Peyer's patches, and isolated lymphoid follicles) and the diffuse mucosal immune system (including intraepithelial lymphocytes and lamina propria).

Tonsils

Three lymphoid structures surround the entrance to the throat: the adenoids, the palatine tonsils, and the lingual tonsils. These structures reach full development in childhood and begin to involute around puberty. The palatine tonsils are surrounded by a poorly organized capsule, except at the pharyngeal surface, which is covered with stratified squamous epithelium. Trabeculae extend from the capsule and divide the tonsils into lobules. Blood vessels and nerves enter through the capsule and extend within the trabeculae. The tonsillar surface is covered by pits, which open into crypts that branch down within the tissue of the tonsil, maximizing the surface area exposed to the pharynx. Each lobule contains numerous lymphoid follicles with germinal centers that contain predominantly B cells.[92] The lymphoid tissue that surrounds the follicles contains T cells, macrophages, dendritic cells, and B cells. These structures are strategically located at sites of entry of airborne particles through the nose (adenoids) and at sites of food particle entry (tonsils). The structures filter unwanted organisms and antigens and function as a mucosal immune barrier.

Peyer's Patches and Lymphoid Follicles

Peyer's patches are aggregates of lymphoid follicles within the mucosa of the jejunum and ileum, with most in the terminal ileum. The full development of this component of the mucosal immune system, including the formation of follicles containing germinal centers, occurs several weeks after birth; their number increases until puberty and then decreases. Lymphoid follicles, another component of the mucosal immune system with structures similar to follicles of a Peyer's patch, are scattered throughout the mucosa of the gastrointestinal, respiratory, and genitourinary tracts. These lymphoid organs facilitate antigen presentation from the intestinal lumen to T and B cells.

Intraepithelial Lymphocytes and Lamina Propria

Intraepithelial lymphocytes are found at the basal surface of the epithelium and are interdigitated with epithelial cells. Most are T cells ($CD8^+$ or $CD4^-CD8^-$), and although most express the TCRαβ, some express the TCRγδ. The function of intraepithelial lymphocytes is not understood, but studies have shown their capacity to generate cytotoxic activity.[93,94] The lamina propria, located beneath the epithelium, is populated by various groups of cells. One of the key functions of this tissue is the secretion of IgA antibody from the many IgA plasma cells into the lumen.[95] The lamina propria also contains many $CD4^+$ and $CD8^+$ T lymphocytes in a ratio of about 2:1 and other effector cells, including IgG B cells, macrophages, dendritic cells, eosinophils, mast cells, and neutrophils.

Antigen Presentation

Follicular dendritic cells, specialized APCs in the B-cell areas of lymph nodes and the spleen, are important in the generation and maintenance of memory B cells, which they achieve by trapping antigen-antibody complexes. Peripheral tissue dendritic cells engulf and process antigen, leave the tissues, then go home to T-cell areas in draining lymph nodes or the spleen. In the lymph nodes, these APCs can directly present processed antigens to resting T cells to induce the latter's proliferation and differentiation. Monocytes-macrophages exist as monocytes in blood and as macrophages (a more differentiated form) in various tissues, such as the lungs, liver, and brain. In addition to phagocytic and cytotoxic functions, these cells have receptors for various cytokines (IL-4, IFN-γ), which can regulate their function. Activated macrophages are also a major source of several cytokines (IFN, IL-1, TNF), complement proteins, and prostaglandins.[96] All APCs have MHC class II surface molecules.

Foreign or self proteins undergo hydrolytic cleavage within the APCs and become oligopeptides, which are then loaded onto antigen-binding grooves of MHC molecules before expression at the cell surface (Fig. 40-3). Class I molecules usually bind peptides that are 8 to 10 amino acids long and are derived from proteins synthesized intracellularly (e.g., tumor antigens and viruses), whereas class II molecules bind peptides that are 14 to 22 amino acids long and are derived from proteins synthesized extracellularly (e.g., nonreplicating vaccines and extracellular bacteria). Lipids and lipid derivatives are processed much like extracellular proteins in endosomes, combined with CD1 (an MHC-like molecule) and presented to double-negative T cells frequently bearing γδ receptors.

In addition to the mechanism of presentation of oligopeptide antigens to lymphocytes via MHC molecules, T cells can recognize haptens, which are covalently or noncovalently complexed with peptides residing in the MHC-binding groove. Another exception is the presentation of super antigens, which are about 30-kDa proteins produced by a broad spectrum of microbes ranging from retroviruses to bacteria. These antigens do not undergo processing to oligopeptides but bind intact to MHC class II molecules and the TCR outside the antigen-binding grooves. They can activate more T cells than conventional peptide antigens.

Humoral Immune Response

T Cell–Dependent and T Cell–Independent B-Cell Responses

Humoral immunity consists of responses that are T cell–dependent (TD) and T cell–independent. Follicular B cells present MHC-restricted protein antigens and receive T-cell help that promotes immunoglobulin class switching, affinity maturation, and memory differentiation as discussed previously. These antigen responses are referred to as T cell–dependent. T cell–independent B-cell responses occur with large antigens that have repeating antigenic determinants, such as carbohydrates, which constitute the capsule and cell wall components of bacteria and cannot be presented in MHC class II molecules. This B-cell response represents a major protective role against bacterial pathogens such as *Streptococcus pneumoniae*. These pathogens bridge immunoglobulins on the B-cell surface, causing activation and the subsequent secretion of antibodies, primarily of the IgM class. Antibodies to *S. pneumoniae* mediate the opsonization of bacteria by binding to the bacterial cell surface, thereby targeting them for destruction by Fc receptor–bearing macrophages. Young children and the elderly, who generally show poor response to T cell–independent antigens, are at increased risk for these bacterial infections. Protective immunity against *Haemophilus influenzae* and meningococcal infections is also mediated by T cell–independent B-cell responses.

Antibody-Dependent Cellular Cytotoxicity

ADCC can lead to the destruction of invading foreign organisms (bacteria and helminths), virus-infected cells, or tumor cells. In the process of destruction of invading organisms, ADCC involves the targeting of effector cells to these organisms by antibodies. The antibody's variable regions provide specificity for the organism, whereas the antibody's constant region focuses effector cells to the site via various Fc receptors. In ADCC directed against altered self cells, the process involves the reaction of antibodies with cell surface receptors producing antibody-coated target cells for reaction with NK cells that secondarily destroy these altered self cells. The process occurs via binding of the antibody to FcγRIII receptor (CD16) on NK cells.

Immunoglobulins

The antibodies (immunoglobulins) secreted by activated B cells are glycoproteins composed of polypeptide (82%-96%) and carbohydrate (4%-18%). Immunoglobulin molecules are composed of two identical 50-kDa heavy chains and two identical 25-kDa κ or λ light chains (Fig. 40-4). The amino terminal portions of the heavy and light chains vary in amino acid sequence from one antibody molecule to another. These variable portions are designated V_H and V_κ or V_λ, respectively. The juxtaposition of one V_H segment and one V_κ or V_λ segment creates the antigen-binding portion of the immunoglobulin molecule, and each immunoglobulin molecule has two identical antigen-binding sites. The carboxyl terminal portions of the heavy and light chains are constant in each subclass of antibody. The heavy-chain constant regions pair to form the Fc domain of the molecule that is responsible for most of the effector functions of the immunoglobulin molecule, including binding to Fc receptors and activating complement.

The isotype of a heavy or light chain is defined by the constant region antigenic determinants, which in turn are defined by the par-

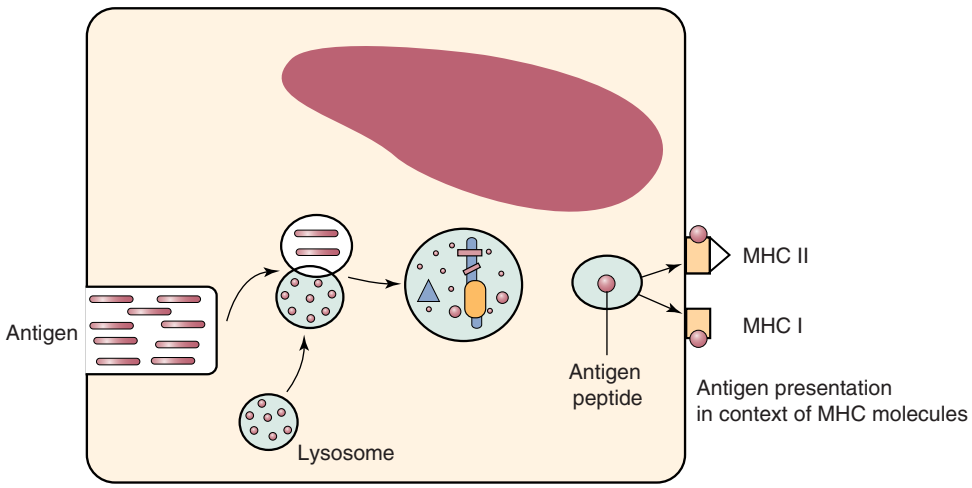

Figure 40-3. Antigen processing and presentation. Antigen undergoes hydrolytic cleavage within antigen-presenting cells, and the resultant oligopeptides are loaded on antigen-binding grooves of major histocompatibility complex (MHC) molecules and expressed at the cell surface.

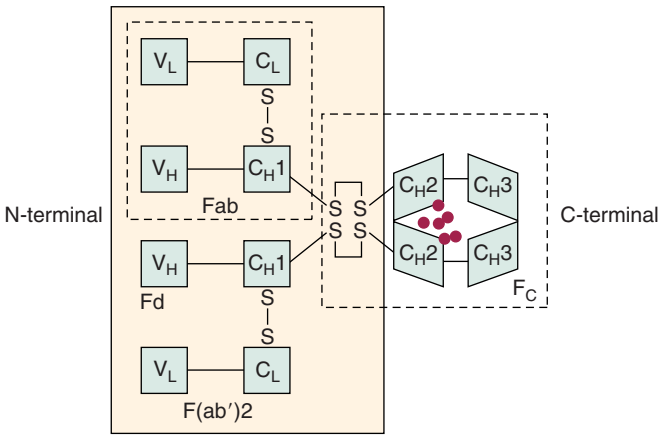

Figure 40-4. Immunoglobulin structure. Human immunoglobulin G1 is a representative example of immunoglobulin structure. C, constant regions; H, heavy chains; L, light chains; V, variable regions. *Red circles* represent carbohydrate residues between the C_H2 domains. *(From Wright A, Shin SU, Morrison SL. Genetically engineered antibodies: progress and prospects.* Crit Rev Immunol. *1992;12:125. Copyright CRC Press.)*

ticular constant region gene of that isotype. All isotypes are present in a healthy person. Because there are nine known separate heavy-chain constant region genes, nine heavy-chain isotypes define the class and subclass of the antibody molecule. These are designated g1, g2, g3, g4, m, a1, a2, d, and e, and the corresponding immunoglobulin isotypes (class or subclass) are IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. Monomers consist of a single immunoglobulin molecule (e.g., IgG), whereas polymers have multiple basic units (e.g., IgM has five basic units, and dimeric IgA has two units). The polymerization of these immunoglobulins is facilitated by the presence of a small glycopeptide with an unusually high content of aspartic acid, known as the J chain.

Immunoglobulin G

IgG constitutes approximately 75% of the total serum immunoglobulins and consists of four subclasses (IgG1, IgG2, IgG3, IgG4). It is a monomer with a molecular weight of 150,000 Da. IgG1, IgG3, and, to a lesser extent, IgG2 can bind and fix complement. Specific Fc receptors for IgG are present on monocytes, macrophages, and neutrophils. IgG is usually bound to the Fc receptor before binding with antigen. IgG functions as an opsonin that facilitates phagocytosis. The Fc receptors for IgG include FcγRI on monocytes and macrophages, FcγRII on most hematopoietic cells except erythrocytes, and FcγRIII on NK cells, eosinophils, neutrophils, and macrophages. In general, the IgG antibody response to soluble protein antigens involves the IgG1 and IgG3 subclasses, whereas polysaccharide antigens elicit primarily IgG2 antibodies. IgG is the immunoglobulin primarily involved in secondary or recall immune responses and is the only immunoglobulin that can cross the placenta and protect the neonate. IgG can fix complement, leading to neutralization, opsonization, bacteriolysis, agglutination, and hemolysis.

Immunoglobulin M

IgM constitutes approximately 10% of serum immunoglobulins. It normally exists as a pentamer of five IgM subunits linked by disulfide bonds and J chains with a molecular weight of 900,000 Da. It is the major immunoglobulin (along with IgD) expressed on the surface of B cells. Membrane IgM functions as the earliest antigen receptor on B cells. Antigen binding results in B-cell activation and differentiation, leading to pentameric IgM secretion. IgM predominates in the early humoral response, and levels then decline rapidly; the IgM is replaced by IgG of the same specificity. IgM is the most efficient complement-fixing antibody, a feature that, as with IgG, increases its array of biologic activities.

Immunoglobulin A

IgA constitutes 15% of the total serum immunoglobulins and exists in both monomeric and polymeric forms (the IgA dimer is a single J chain joined to two IgA monomeric subunits). Each immunoglobulin molecule has a molecular weight of 160,000 Da. Humans produce more IgA than any other immunoglobulin class, and the major role of this immunoglobulin is mucosal immunity. Monomeric IgA is synthesized by plasma cells located in the interstitial spaces of exocrine glands. These monomers combine with the J chain, which is also synthesized by IgA plasma cells, to form IgA2-J dimers. These dimers are too large to cross the tight junctions of the exocrine gland epithelium. They are transported across the epithelium by an active secretory component–dependent mechanism.[97] During transport, IgA dimer covalently links to the secretory component by a disulfide bond. The newly formed complex of IgA dimer and secretory component, referred to as secretory IgA, is subsequently released into exocrine secretions by exocytosis. Secretory IgA appears to be derived from locally produced IgA, not intravascular IgA.[98]

IgA is the predominant immunoglobulin in external secretions and provides the primary defense mechanism against local mucosal infections. The main function of IgA is to neutralize foreign substances and prevent their systemic access.

Immunoglobulin E

IgE accounts for only 0.004% of the total serum immunoglobulins and normally exists as a monomer with a molecular weight of 200,000 Da. High-affinity IgE-specific Fc receptors exist on mast cells and basophils, whereas low-affinity IgE receptors exist on neutrophils, eosinophils, macrophages, and platelets. Cross-bridging of IgE molecules on the surface of mast cells and basophils by antigen triggers release of mediators from mast cells and basophils, a hallmark of allergic reactions. In addition to mediating immediate hypersensitivity reactions, IgE can mediate antibody-mediated cellular cytotoxicity.

Immunoglobulin D

IgD constitutes 0.2% of the total serum immunoglobulins and exists as a monomer with a molecular weight of 180,000 Da. The primary function of IgD appears to be that of a membrane-bound antigen receptor on the B-cell surface.

Complement System

The complement system is an important effector of both the innate and adaptive immune responses. It consists of more than 25 plasma and cell surface proteins that are sequentially activated and can interact with one another other, with antibodies, and with cell membranes. These interactions mediate functions such as immune adherence, phagocytosis, chemotaxis, and cytolysis. Complement system proteins constitute about 15% of the globulin fraction of plasma and circulate as inactive molecules. Complement activation centers on cleavage of C3, which can be achieved by classic, alternative, or lectin pathways (Fig. 40-5).

The classic pathway comprises C1, C4, and C2. C1, in turn, consists of C1q, C1r, and C1s. Antigen-antibody complexes (containing IgG1, IgG2, IgG3, or IgM) provide the activating signal for the classic pathway of complement activation. Sequential activation of complement components C1, C4, and C2 produces the C3 convertase enzyme that then cleaves C3 into C3a and C3b. At this point, the classic and alternative pathways merge. The alternative pathway is activated in the absence of specific antigen-antibody complexes by microbial structures that neutralize inhibitors of spontaneous complement activation. In this pathway, C3 interacts with factors B and D to generate the alternative pathway C3 convertase, which also cleaves C3 to C3a and C3b. The third pathway of complement activation, the lectin pathway, is triggered by microbial cell wall components containing mannans.[99] The interaction of mannan-containing microbes with plasma mannan-binding lectin (MBL) activates the zymogenic plasma proteases MBL–associated serine proteases 1 and 2 (MASP-1, MASP-2). These form a protease analogous to the activated C1 of the classic pathway that then goes on to

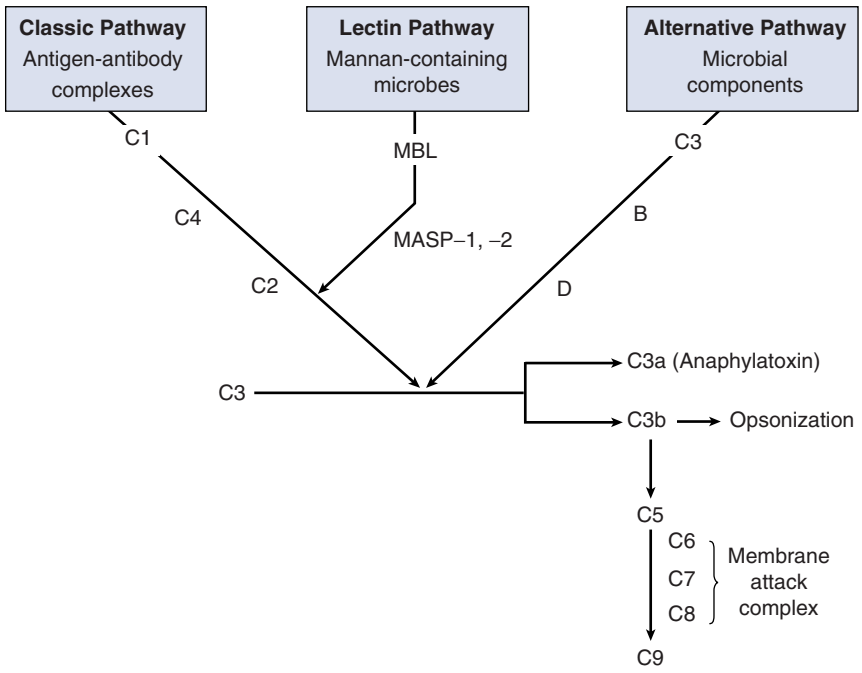

Figure 40-5. The three pathways of the complement system. Please refer to the text for a description of the functions of the complement system. B, factor B; D, factor D; MASP, MBL-associated serine proteases; MBL, mannan-binding lectin.

activate C4, C2, and the remainder of the pathway leading to C3 convertase.

Cleavage of C3 results in the release of the small C3a fragment—a potent anaphylatoxin that induces mast cell degranulation, creates edema, and recruits phagocytic cells—and the larger C3b fragment, which covalently attaches to the activating antigen, marking it for destruction. C3b serves both as a site for attack of the complement membrane attack complex (MAC), a self-assembling pore-forming complex of the plasma proteins C5, C6, C7, C8, and C9 that kills targets by osmotic lysis, and as an opsonin, enhancing phagocytosis by its binding to complement receptors on the surfaces of neutrophils and macrophages.[100] The effector mechanism of complement is potent and recruits intense local inflammation; its importance is underscored by the phenotypes of inherited deficiencies of individual components. For example, deficiencies of components of the membrane attack complex lead to increased susceptibility to *Neisseria* infections, deficiency of C3 results in life-threatening susceptibility to pyogenic infections, often fatal during childhood, deficiency of C4 or C2 causes a lupus-like immune complex disease, and deficiency of the serum inhibitor of C1 leads to episodic mast cell–independent episodes of angioedema.

Cytokines

Cytokines are a diverse group of small, secreted protein mediators that mediate interactions among different effector cells. Each cytokine may have multiple activities on different cell types, and several cytokines often have related functions. They can also have synergistic or antagonistic activities and can inhibit or induce the synthesis of other cytokines. Cytokines can be divided into several groups: the interleukins, the interferons, tumor necrosis factor and related molecules, TGFs, and hematopoietic growth factors. Each of these different cytokines, their principal cell sources, and their main effects in humans are summarized in Table 40-1.

Chemokines

The chemokines are a superfamily of low-molecular-weight, secreted, heparin-binding molecules that serve as potent chemoattractants for cells of the immune system. More than 50 chemokines are currently recognized, and they are characterized by the presence of three or four conserved cysteine residues. They can be divided into four families on the basis of the positioning of the N-terminal cysteine residues. The CXC family is characterized by the separation of the first two cysteines by a variable amino acid. In the CC family, the cysteine residues are adjacent to each other. The majority of these chemokines are contained in these two families. Chemokines of the C family lack the first and third cysteines, containing a single cysteine residue in the conserved position. Members of the CX3C family have the two N-terminal cysteine residues separated by three variable amino acids. The C and CX3C families are small, with one or fewer members per family. Table 40-2 lists the new systematic names of these chemokines as well as their common names and their target cells.

Immunopathology

The two major effector arms of the adaptive immune response are humoral and cellular. In the defense against infections, antibodies are operative against bacteria or bacterial products; cell-mediated immunity operates primarily against viral, fungal, and mycotic infections. With few exceptions, antibody-mediated immune mechanisms work best when directed to extracellular infections, whereas cell-mediated immunity is effective against intracellular infections. The killing effects of immune reactions are extremely efficient and, when specifically directed, can eliminate organisms quickly. However, these same immune mechanisms may cause host-tissue destruction and therefore lead to disease states. In some situations, this destructive effect of immune reactions is termed allergy or hypersensitivity and is considered an immunopathologic reaction.

These reactions are divided into four types. *Type I,* mast cell–mediated reactions, use the release of mast cell or basophil mediators to create responses to sensitizing allergens and can be IgE-dependent (anaphylaxis) or IgE-independent (sensitivity to iodide contrast media). *Type II,* cytotoxic, antibody-mediated reactions (IgG-, IgM-mediated), involve the binding of IgG and IgM antibodies to antigens on the surface of target cells (e.g., erythrocytes, neutrophils, platelets, and epithelial cells of glandular or mucosal surfaces) or to antigens on tissues such as basement membranes. This interaction between IgG and IgM antibodies and cell surface antigens leads to destruction of these cells by opsonization, complement activation, or cell lysis and ADCC. These mechanisms can damage self antigens in various tissues. One clinical example is known as penicillin-induced autoimmune hemolytic anemia.

Table 40-1

Cytokines

Cytokine	Cell Sources	Predominant Effects
The Interleukins		
IL-1α, IL-1β Functionally equivalent isoforms	Macrophages, neutrophils, epithelial and endothelial cells	Fever, local inflammation, T-cell and macrophage activation; principal mediator(s) of septic shock
IL-2	Activated T cells	T-cell proliferation
IL-3	$CD4^+$ T cells, thymic epithelial cells, mast cells	Synergistic action in early hematopoiesis; activates and promotes recruitment of basophils in late allergic reactions
IL-4	TH2 cells, mast cells, basophils, NK T cells	Differentiation and growth of TH2 subset, B-cell activation, isotype switch to IgE and IgG1, suppression of TH1 cells, growth factor for mast cells
IL-5	Activated TH2 cells and mast cells, NK cells, eosinophils	Eosinophil survival, differentiation, and chemotaxis
IL-6	T cells, mononuclear phagocytes, vascular endothelial cells, fibroblasts	T- and B-cell growth and differentiation, acute phase protein production, fever
IL-7	Stromal cells in bone marrow and thymus, B cells, monocytes, macrophages	Growth of pre-B cells and pre-T cells
IL-8, CXC chemokine	Activated mononuclear phagocytes, fibroblasts, and endothelial cells	Neutrophil chemoattractant; promotes neutrophil inflammatory responses
IL-9	TH2 cells	Stimulation of growth and differentiation of hematopoietic cells and mast cells
IL-10	Activated monocytes, macrophages, and TH2 cells	Important in innate and adaptive immunity; has immunosuppressive or immunostimulatory effects on various cell types
IL-11	Bone marrow stromal cells and osteoblasts	Synergistic action with IL-3 and IL-4 in hematopoiesis; stimulates fibroblasts to promote collagen deposition
IL-12	Mainly activated macrophages; some production by neutrophils, dendritic cells, monocytes, and B cells	Activates NK cells; induces TH1 differentiation and secretion of IFN-γ
IL-13	Activated T cells (TH2), mast cells, and basophils	Biologic functions closely related to those of IL-4 but of lower magnitude
IL-14	Activated T cells	Growth factor for B cells
IL-15	Monocytes, macrophages	Stimulates growth and development of NK cells; stimulates activation and proliferation of T and B cells
IL-16	T cells, mast cells, eosinophils, airway epithelial cells	Immunomodulatory and chemoattractant for $CD4^+$ T cells
IL-17	Activated memory $CD4^+$ cells	Induces cytokine production by epithelial and endothelial cells, and fibroblasts; promotes neutrophilic inflammation
IL-18	Activated macrophages and Kupffer cells	Induces IFN-γ production by T cells and NK cells; favors TH1 induction
IL-19	Monocytes	Suspected to participate in the regulation of pro-inflammatory cytokine expression
IL-20	Cell type unknown	Appears to have a role in skin development and is suspected of regulating inflammation in the skin
IL-21	Activated $CD4^+$ T cells	TH1 cytokine; stimulates proliferation of activated T cells and cytotoxicity of NK cells
IL-22	TH1 cells and mast cells	Increases production of acute phase proteins in hepatocytes
IL-23	Activated dendritic cells	Acts on memory $CD4^+$ T cells to promote their proliferation and differentiation into TH1 effectors during a secondary immune response

Continued

Table 40-1

Cytokines—cont'd

Cytokine	Cell Sources	Predominant Effects
IL-24	Human melanoma and other tumor cells	Promotes induction of apoptosis in some cancer cells
IL-25	Activated TH2 cells, mast cells	Enhances allergic responses and promotes TH2 inflammation
IL-26	Activated memory T cells	May act as an autocrine growth factor for transformed and/or virus-infected T cells
IL-27	Activated monocytes, dendritic cells, and macrophages serving as antigen-presenting cells	Promotes development along the TH1 phenotype and suppresses the TH2 phenotype
IL-28 and 29	Induced by viral infection in various cell lines	Induce an antiviral state in infected cells
The Interferons		
IFN-γ	T cells, NK cells	Macrophage activation, increased expression of MHC molecules and antigen-presenting components, Ig class switching, suppression of TH2 response
IFN-α	Leukocytes	Antiviral; increases MHC class I expression
IFN-β	Fibroblasts	Antiviral; increases MHC class I expression
Tumor Necrosis Factor and Related Molecules		
TNF	Activated monocytes/macrophages, T, B, and NK cells	Major inflammatory mediator induced by the presence of gram-negative bacteria and their components; potent immunoregulatory, cytotoxic, antiviral, and procoagulatory activities
LTα (lymphotoxinα) Previously called TNF-β	Activated TH1, B, and NK cells	Promotes inflammation, has antiviral activity, and kills tumor cells by apoptosis
LTαβ	Activated TH1, B, and NK cells	Has a specialized role in secondary lymphoid organ development
OPGL (osteoprotegerin ligand)	Osteoblasts, bone marrow stromal cells, activated T cells	Stimulates osteoclasts and bone resorption
BAFF (B-lymphocyte–activating factor belonging to the TNF family)	Monocytes, macrophages, dendritic cells	Survival factor required for the maturation of B cells
Transforming Growth Factor (TGF)		
TGF-β	Chondrocytes, monocytes, T cells	Inhibits cell growth; is anti-inflammatory; induces IgA secretion by B cells; plays a role in adhesion, proliferation, differentiation, transformation, chemotaxis, and immunoregulation
Hematopoietic Growth Factors		
SCF (stem cell factor)	Stromal cells in the fetal liver, bone marrow, and thymus, in the central nervous system, and in the gut mucosa	Supports the survival and growth of the earliest hematopoietic precursors in vivo
GM-CSF	Activated T cells, macrophages, stromal cells, and endothelial cells	Stimulates growth and differentiation of myelomonocytic lineage cells, particularly dendritic cells and inflammatory leukocytes
G-CSF	Activated T cells, endothelial cells, fibroblasts, and mononuclear phagocytes	Stimulates neutrophil development and differentiation
M-CSF	Endothelial cells, fibroblasts, mononuclear phagocytes	Influences CFU-GM cells to differentiate into monocytes and macrophages in vitro

CFU, colony-forming unit; CSF, colony-stimulating factor; G, granulocyte; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LT, lymphotoxin; M, macrophage; MHC, major histocompatibility class; NK, natural killer; TH, helper T; TNF, tumor necrosis factor.

Table 40-2

Chemokines

Systematic Name	Common Name(s)/Ligand(s)	Target Cell(s)
CXC Chemokines		
CXCL1	GROα/MGSAα	Neutrophil
CXCL2	GROβ/MGSAβ	Neutrophil
CXCL3	GROδ/MGSAδ	Neutrophil
CXCL4	Platelet factor-4	Fibroblast
CXCL5	Epithelial neutrophil activating-78	Neutrophil
CXCL6	Granulocyte chemotactic protein-2	Neutrophil
CXCL7	Neutrophil-activating peptide-2	Neutrophil
CXCL8	Interleukin-8	Neutrophil, basophil, T cell
CXCL9	Monokine induced by IFN-γ	Activated T cell
CXCL10	IFN-γ–inducible protein-10	Activated T cell
CXCL11	IFN-inducible T-cell α chemoattractant	Activated T cell
CXCL12	Stromal cell–derived factor-1a/b	$CD34^+$ bone marrow cell, T cell, dendritic cell, B cell, activated CD4 cell
CXCL13	B-cell–attracting chemokine-1	Naïve B cell, activated CD4 cell
CXCL14	Breast and kidney–expressed chemokine	
CXCL15	Unknown	
CXCL16	Unknown	T cell, NK T cell
CC Chemokines		
CCL1	I-309 (a nameless human chemokine)	Neutrophil, T cell
CCL2	MCP-1/monocyte chemotactic and activating factor/ tumor-derived chemotactic factor	T cell, monocyte, basophil
CCL3	MIP-1α/LD78α	Monocyte, macrophage, T cell, NK cell, basophil
CCL3L1	LD78β	
CCL4	MIP-1β	Monocyte, macrophage, T cell, NK cell, basophil
CCL5	Regulated upon activation, normal T cell–expressed and secreted (RANTES)	Monocyte, macrophage, T cell, NK cell, basophil, eosinophil, dendritic cell
CCL6	None	
CCL7	MCP-3	T cell, monocyte, eosinophil, basophil, dendritic cell
CCL8	MCP-2	T cell, monocyte, eosinophil, basophil
CCL9/10	None	
CCL11	Eotaxin	Eosinophil
CCL12	Unknown	
CCL13	MCP-4	T cell, monocyte, eosinophil, basophil, dendritic cell
CCL14	HCC-1	Monocyte
CCL15	HCC-2/leukotactin-1/MIP-1δ	T cell, monocyte, dendritic cell

Continued

Table 40-2

Chemokines—cont'd

Systematic Name	Common Name(s)/Ligand(s)	Target Cell(s)
CCL16	HCC-4/liver-expressed chemokine	Monocyte
CCL17	Thymus- and activation-regulated chemokine	T cell, immature dendritic cell, T cell, thymocyte
CCL18	Dendritic cell–derived CC chemokine/pulmonary and activation-regulated chemokine/activation-induced, chemokine-related molecule-1	Naïve T cell, T cell
CCL19	MIP-3β/EBL-1 ligand chemokine/exodus-3	Naïve T cell, mature dendritic cell, B cell
CCL20	MIP-3α/liver- and activation-regulated chemokine/exodus-1	T cell, bone marrow dendritic cell
CCL21	6Ckine/secondary lymphoid tissue chemokine/exodus-2	Naïve T cell, B cell
CCL22	Macrophage-derived chemokine/stimulated T-cell chemoattractant protein-1	Immature dendritic cell, T cell
CCL23	MPIF-1/CK□8/CK□8-1	Monocyte, T cell
CCL24	Eotaxin-2/MPIF-2	Eosinophil, basophil
CCL25	Thymus-expressed chemokine	Macrophage, thymocyte, dendritic cell
CCL26	Eotaxin-3	
CCL27	Cutaneous T cell–activating chemokine/interleukin-11 receptor alpha-locus chemokine	T cell
CCL28	Mucosae-associated epithelial chemokine	T cell, eosinophil
C Chemokines		
XCL1	Lymphotactin/SCM-1β/activation-induced, chemokine-related molecule	T cell, NK cell
XCL2	SCM-1β	
CXC3C Chemokine		
CXC3CL1	Fracktalkine	T cell, monocyte

CK, chemokine; GRO, growth-related oncogene; HCC, human CC chemokine; IFN, interferon; MCP, monocyte chemoattractant protein; MGSA, melanoma growth stimulatory activity; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NK, natural killer; SCM, single C motif.

Type III, immune complex–mediated reactions (IgG, IgM complex mediated), involve antibody-mediated inflammation whereby the antibody and its antigen form low-solubility immune complexes, which are deposited in normal tissues, activate complement, and set off an inflammatory response characterized primarily by neutrophil influx, which inflicts tissue injury. Knowledge of this immunologic disease became widespread in the early 1900s, when physicians began using immune animal sera, usually equine sera, to treat bacterial infections, a practice that led to serious illness and even death of the treated subjects, a disease known as serum sickness.[101] Immune complex vasculitis in the skin can also occur in a series of clinical conditions, such as systemic lupus erythematosus, rheumatoid arthritis, drug reactions, and infections. *Type IV,* delayed hypersensitivity (DTH) reactions (T cell–mediated), are caused by antibody-independent mechanisms involving T cells or NK cells. These reactions are the pathologic variants of a normal T cell–mediated immune response in which the T-cell response to an environmental antigen becomes exaggerated. A clinical example of such a reaction, as previously described, is the cutaneous reaction to challenge with the purified protein derivative of *M. tuberculosis* in previously infected or vaccinated patients.

Allergic Rhinitis

Allergic rhinitis is a clinical hypersensitivity of the nasal mucosa to foreign substances mediated through IgE antibodies. It has a prevalence of between 10% and 20% and affects 20 to 40 million individuals in the United States annually.[102-107] The prevalence of seasonal allergic rhinitis is higher in children and adolescents than in adults,[108] and in childhood, boys outnumber girls; the gender ratio becomes approximately equal in adults, however, and may even favor women. Because individuals require low-dose exposure to an offending allergen over many years before development of symptoms, seasonal rhinitis rarely occurs in children younger than 2 years. Most patients with allergic rhinitis have symptoms before age 20.[109,110] The severity of the disease remains relatively constant throughout childhood and early adulthood, usually improves in middle age, and is seldom a problem in the elderly. A family history of allergic rhinitis increases the odds that a child will have the disease. Atopy, the predisposition to respond to environmental allergens with the production of specific IgE antibodies, occurs in only 13% of children for whom neither parent is atopic, but in 29% of children with one atopic parent or sibling and in 47% for whom both parents are atopic.[111] A history of asthma is also important,

because allergic rhinitis is significantly more likely (up to 4-6 times) to develop in individuals with asthma than in the general population.

Hygiene Hypothesis

Epidemiologic data provide strong evidence of a steady rise in the incidence of allergic (asthma, rhinitis, and atopic dermatitis)[112-123] and autoimmune diseases (multiple sclerosis,[124] insulin-dependent diabetes mellitus,[125] and Crohn's disease[126]) in developed countries since the beginning of the 1970s. Concomitantly, the incidence of many infectious diseases in developed countries has decreased as a result of antibiotics, vaccination, or improved hygiene. A hypothesis thus emerged that the decrease in infectious diseases is causally linked to the increase in the incidence of allergic disease, the "hygiene hypothesis." Strachan[127] observed that the risk of allergic rhinitis was inversely linked to birth order and the size of the family. He proposed that infections within households in early childhood have a role in preventing allergic rhinitis.

The geographic distribution of allergic and autoimmune diseases in the world also shows interesting patterns. The incidence of disease decreases from north to south in the Northern Hemisphere and reciprocally from south to north in the Southern Hemisphere. Underdiagnosis of allergic and autoimmune diseases in underdeveloped countries could explain these geographical differences but it is not likely. Although this explanation might be proposed for allergic rhinitis and atopic dermatitis, relatively benign diseases, it is not likely to apply to type I diabetes and multiple sclerosis, which lead to significant symptoms and are not likely to go undiagnosed. Environment seems to play an important role in this incidence gradient.

In developed and industrialized countries, a higher prevalence of atopy and asthma is observed than in undeveloped and less affluent countries. Immigration to allergy-prevalent countries causes more allergies and asthma in immigrants in comparison with the prevalence of atopy in their countries of origin. This difference probably involves exposure to a new set of pollutants and allergens and several socioeconomic and cultural issues, such as housing conditions, diet, and accessibility to medical services, all of which are likely to affect migrants' health. The increase in allergy and asthma is usually not related to ethnicity but in certain populations may play an important role. Studies on migrants support the notion that lifestyle and environmental factors in Western industrialized countries facilitate atopy and asthma.[128] An obvious factor in the north-south gradient is socioeconomic differences. Several studies have found a lower frequency of immunologic diseases in populations with a low socioeconomic status. Some infections have been found to be distributed according to a south-north gradient in European countries that mirrors the gradient for autoimmune diseases. Low socioeconomic levels and high temperatures, two common features of southern countries, may predispose to infections in a number of ways: Less stringent control of microbial contamination of water and food, an increased risk of bacterial proliferation with higher ambient temperatures, and poorer housing conditions may all affect the risk of contamination between persons.

When infections are an incriminating factor, they often occur in childhood. Young children with older brothers and sisters at home and those who attend a daycare center during the first 6 months of life subsequently have a lower incidence of asthma[129] and type I diabetes[130] than children who do not attend a daycare center and have no older siblings. The administration of antibiotics to children has been suspected to raise the risk of asthma and allergy. Droste and colleagues[131] observed that the use of antibiotics in the first year of life increased the risk of asthma or other allergic diseases in children with a genetic predisposition to atopy. Antibiotics might act by decreasing the number of infections or by modifying intestinal flora.

The increase in atopic diseases in the northern parts of the hemisphere in comparison with the southern parts has been linked to sun exposure and levels of vitamin D. In addition to its traditional role in the endocrine system, vitamin D diminishes the risk of many chronic illnesses, including cancer, autoimmunity, infection, and cardiovascular disease.[132] This vitamin has also been implicated in the development of atopic diseases, such as asthma, allergic rhinitis, and anaphylaxis.[133-135] In a later study, our group demonstrated lower levels of vitamin D in a cohort of African Americans with chronic rhinosinusitis than in same-race controls.[136] Anaphylaxis, measured in proxy on the basis of prescription of EpiPens (Dey Laboratories, Napa, Calif), varies with geographic latitude; the finding of higher levels being found in areas with less sun exposure supports the preceding theory.[137] The possible mechanisms by which vitamin D might affect these diseases, characterized by chronic inflammation, could be related to its immunologic effects, including those on T cells, dendritic cells, and macrophages[138,139] as well as to the ability to promote IL-10 production by regulatory T cells.[140]

Differences in disease incidence between urban and suburban dwellers have been observed, and factors other than air pollution have been implicated. In 1999, Braun-Fahrländer and colleagues found that children whose parents were farmers and who lived on the farm were less likely to become allergic than children from the same rural region who were not raised on a farm.[141] Since then, a large number of studies has documented that people raised on farms have a lower prevalence of hay fever and atopic sensitization in childhood, as well as in adulthood, whereas effects on asthma are more consistent for the atopic than the nonatopic phenotype.[142-151] The timing of the exposure played a crucial role because the protection was strongest when the exposures occurred in the first years of life rather than in later years.[142,152] One such study showed that allergies were less frequent when the children were exposed early and for a prolonged period to farm animals and cow's milk.[142] In that study, a clear maternal effect was also seen because the mother's exposure to animal sheds during her pregnancy had a protective effect of the offspring.[142] An inverse correlation between endotoxin levels in bedding and the incidence of atopic diseases among children living in rural areas was also found, suggesting that a subject's environmental exposure to endotoxin may have a crucial role in the development of tolerance to ubiquitous allergens found in natural environments.[153] However, although endotoxin was inversely related to atopy and related phenotypes, it was a risk factor for nonatopic asthma, increased airway hyperresponsiveness, and low lung function.[153,154]

Animal studies support the preceding epidemiologic observations, because autoimmune diseases in susceptible strains of mice or rats develop earlier and at a higher rate among animals bred in a specific pathogen-free environment than among animals bred in a conventional environment. The same has been observed relating to allergic diseases. Administration of *Mycobacterium bovis* and *Mycobacterium vaccae* can attenuate the late phase response, airway hyperresponsiveness, and bronchoalveolar lavage eosinophilia in a mouse model of bronchial asthma.[155]

Several mechanisms might explain these relationships. The development of most autoimmune diseases depends on the TH1 cytokines IL-2 and IFN-γ, whereas the development of allergic diseases requires the TH2 cytokines IL-4 and IL-5. Initial reports that suggested an inverse relationship between the incidences of autoimmune diseases and allergic diseases[156] led to speculation that the reciprocal down-regulation of TH1 cytokines by TH2 cytokines, and the reverse, might account for these observations. However, later evidence supports an association between the incidences of allergic and autoimmune diseases.[157,158] These observations would fit with the concept of common mechanisms underlying infection-mediated protection against autoimmunity and allergy.

Another potential mechanism involves Tregs and cytokines. The decrease in antigenic stimulation related to the decreased frequency of childhood infections has resulted in a decrease in the levels of regulatory cytokines, specifically, IL-10 and, possibly, TGF-β. $CD25^+$ T cells and other regulatory T cells produce these two cytokines, which in turn act to down-regulate both TH1- and TH2-mediated responses. Data from humans and animal models tend to support the concept that infectious agents stimulate the production of regulatory cells whose effects extend beyond the responses to the invading microbe.[159,160] IL-10 and TGF-β, which may be produced by $CD25^+$ and other regulatory T cells,[161] can inhibit both TH1 and TH2 responses, and thus are plausible candidates for mediators of the inverse relationship between infections on the one hand and allergic and autoimmune diseases on the other. Another hypothesized mechanism relates to stimulation of the innate immune system by viruses and bacteria and

their components. Pathogen-associated molecular patterns that are structural components of microbes are recognized by receptors of the host's innate immune system, the pattern recognition receptors (PRRs).[162] Examples for pathogen-associated molecular patterns are LPS, a component of endotoxin, and muramic acid, a component of peptidoglycan that is part of the cell wall of most bacteria. Examples of human pattern recognition receptors are CD14 and the human TLRs discussed previously. In the context of the development of allergies, TLR4, serving as a receptor for LPS, and TLR2, which recognizes peptidoglycan of gram-positive bacteria, have been implicated. Polymorphisms in the genes for TLR4 and TLR2 have been shown to interact with these environments, modulating the allergy protective effect.[163] The observation that the peripheral blood leukocytes of farmers' children, who live in an environment with a high load of endotoxin, express higher levels of TLR2 and CD14 than those of less exposed children supports a modulation of the innate immune response by microbial compounds even in the absence of infection.[164]

Another interesting observation relates to the presence of pets in the house and the risk of asthma. Farm animals have not been common in big European and American cities, but domestic pets are extremely common. They are a prolific source of allergen, and sensitization to these allergens is strongly associated with asthma.[165] Reports from Europe suggest that the presence of a cat in the home decreases the risk of sensitization to cat allergens.[166] Because of studies that suggest that the same effect occurs in countries where domestic animals are equally common in the homes of families with a history of asthma as in the homes of families without such history, the initially proposed explanation that this effect could be secondary to decisions by families with allergic disease not to have pets is unlikely. Ownby and colleagues[167] strengthened these initial observations. They reported that children in a birth cohort raised in a house with two or more dogs or cats in the first year of life have not only less allergic sensitization to dog and cat, as determined by skin prick tests and allergen-specific IgE levels, but also less sensitization to allergens in general at age 6 to 7 years. Because domestic animals can be a source of endotoxin, this finding suggests the possibility that the effects of pets as these researchers described in the United States could be comparable to those of cows and farm animals in Europe. Mechanisms similar to those discussed earlier in this chapter involving regulatory T cells and inhibitory cytokines are being investigated to explain these findings.

Therefore, the interesting relationships between infections and immune-mediated diseases, such as allergic and autoimmune diseases, and between early exposure to some allergens and the lowered risk of future allergic sensitization, potentially create new therapeutic strategies. The challenge will be to elucidate the responsible immune mechanisms involved and to determine the extent of exposure that will ensure safety and the desired outcome—the development of healthy children with a very low risk of allergic and autoimmune disease.

Burden of the Disease

Health-related quality of life (HRQL) is the component of overall quality of life that is determined primarily by a person's health and that can be influenced by clinical interventions. Using both generic and disease-specific tools, several investigations have documented a significant impairment of quality of life in allergic rhinitis.[168-172] The disease-specific tools are more sensitive to change in health-related quality of life than the generic instruments. The most commonly used disease-specific tool is the rhinoconjunctivitis quality of life questionnaire (RQLQ) developed and validated by Juniper and Guyatt.[172] Modifications of this questionnaire are also validated and tested for patients with perennial rhinitis, adolescents (12-17 years old), and children (6-12 years old).

Poorly controlled allergic rhinitis has been shown to contribute to sleep loss or disturbance, and seasonal allergic rhinitis leads to increased daytime sleepiness.[173-175] Allergic rhinitis also contributes to learning problems during school in children either through direct interference or indirectly through its adverse effect on sleep.[176] Treatment with sedating H_1 antihistamines aggravates these problems, and nonsedating antihistamines only partially reverses this effect.[177,178] In adults, similar adverse effects on proper functioning ability lead to an impairment in work ability and induce both work absenteeism as well as reduction in work productivity and presenteeism.[179,180] In one study, the mean total productivity losses per employee per year were $593 for allergic rhinitis, which was more costly than all other prevalent and chronic disorders, such as migraine, depression, respiratory infections, diabetes, asthma, and coronary artery disease.[181]

For all these reasons allergic rhinitis is a costly disease. Estimates of the annual health care costs have ranged from $2 billion to $5 billion with the wide range related to the parameters used to make these estimates.[182]

Pathophysiology of Allergic Rhinitis

Sensitization and Immunoglobulin E Production

During the initial stage of the disease, low-dose exposure leads to the production of specific IgE antibodies. Antigen that is deposited on the nasal mucosa is engulfed by APCs (macrophages, dendritic cells, Langerhans cells) and partially degraded within their phagolysosomes. Portions of the antigen are then exteriorized on the surfaces of APCs and are recognized by helper T cells and class II MHC molecules. IL-1-activated helper T cells then secrete cytokines, which promote the growth and differentiation of other cells involved in the immune response. TH2 $CD4^+$ cells are important contributors to allergic reactions. They secrete the cytokines IL-4, IL-5, and IL-13, which are all central to the production of IgE and to the recruitment and survival of eosinophils at sites of allergic reactions. Antigen-specific IgE then attaches to high-affinity receptors on mast cells and basophils and to low-affinity receptors on other cells, thereby sensitizing the nasal mucosa. On subsequent exposure to the offending allergen, the IgE antibodies on the surfaces of these cells serve as receptors for the antigen molecules. Cross-linking of adjacent IgE molecules on mast cells leads to the release of inflammatory mediators that stimulate nerves, glands, and blood vessels to cause the clinical manifestations of the disease, namely, sneezing, pruritus, rhinorrhea, and nasal obstruction. These events are known as the early allergic response.

Early Response to Antigen

Within minutes after exposure of an allergic patient to antigen, an inflammatory response occurs. The patient first senses tingling and pruritus, followed by sneezing, rhinorrhea, and, last, nasal congestion. These subjective feelings correlate with physiologic changes that are measured after antigen provocation, such as increases in nasal secretions and nasal airway resistance (NAR).[183] In addition to these physiologic changes, increases are noted in the levels of several mediators, including histamine,[184] kinins, tryptase,[185] PGD_2,[186] leukotriene C_4 (LTC_4),[187] leukotriene B_4 (LTB_4),[188] MBP,[189] and platelet-activating factor (PAF).[190] These mediators lead to the various symptoms of allergic rhinitis by their effects on end-organs and nerves of the nasal mucosa. Histamine and tryptase are found in mast cell granules, and their detection in nasal secretions after antigen provocation provides support for mast cell degranulation during the nasal allergic reaction. PGD_2, and the cysteinyl leukotrienes, newly synthesized mediators of the arachidonic acid pathway, are also secreted by mast cells. Further evidence for the role of nasal mast cells in the immediate allergic reaction was provided by the demonstration of degranulated mast cells in nasal mucosal biopsies of allergic patients after allergen challenge.[191]

Neuronal Contribution

Sneezing and itching during the early response to allergen provocation involve the nervous system. Unilateral intranasal antigen challenge experiments have supported the role of the nervous system in amplifying the allergic response as challenge leads not only to an increase in sneezes, rhinorrhea, nasal secretions, histamine, nasal airway resistance,[192] and PGD_2[193,194] on the side of challenge but also to an increase in rhinorrhea, secretion weights, and PGD_2 contralateral to the challenge.[194] The contralateral secretory response was rich in glandular markers[193] and was inhibited by atropine, an anticholinergic,[192] suggesting that the efferent limb was cholinergically mediated. It has also become clear that the nasal response to allergen is accompanied by an ocular, pulmonary, and even a sinus response that can, at least in part,

be explained by a neural reflex. Monitoring ocular symptoms and secretions after unilateral allergen challenge has shown an ocular symptomatic and secretory response that is inhibited by pretreatment with an intranasal antihistamine, suggesting that histamine's action on nasal afferent nerves initiates this reflex.[195] This nasal ocular reflex has also been shown to be potentiated by repeated allergen challenges, which lead to priming, a process inhibited by pretreatment with intranasal steroids because of their anti-inflammatory actions.[196] Similar unilateral challenge studies with allergen have shown an influx of eosinophils into the ipsilateral maxillary sinus hours after allergen provocation that parallels the increase in these cells seen in nasal secretions, albeit of a lesser magnitude.[197] Similarly, challenge of the nose with allergen has been shown to lead to up-regulation of inflammatory markers in bronchial biopsy specimens obtained 24 hours later.[198] Besides a reflex initiated in the nose, another possible explanation of these findings has included the theory of systemic allergic inflammation, whereby an allergic reaction at one site generates an inflammatory response that reaches the systemic circulation and then leads to the involvement of other predisposed end-organs.[199]

Several neuropeptides—in addition to sympathetic and parasympathetic nerves and their transmitters—are found in the nasal mucosa. These neuropeptides are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene–related peptide [CGRP], neurokinin [NK], gastrin-releasing peptide), parasympathetic nerve endings (vasoactive intestinal peptide [VIP], peptide histidine methionine), and sympathetic nerve endings (neuropeptide Y). Substance P (SP), a member of the tachykinin family, is often found as a co-transmitter with neurokinin A and calcitonin gene–related peptide; it has been found in high density in arterial vessels and, to some extent, in veins, gland acini, and epithelium.[200] Several studies support the concept that neuronal mechanisms mediated by these peptides amplify the inflammatory allergic reaction.[201-207]

Mosimann and colleagues[208] were able to demonstrate significant increases in the levels of substance P, calcitonin gene–related peptide, and vasoactive intestinal peptide immediately after antigen challenge in allergic individuals; in patients who experienced a late reaction, only substance P increased slightly. These experiments suggest that neuropeptides are released in vivo in humans after allergen challenge and might be partly responsible for symptoms of the allergic reaction. Repetitive application of capsaicin, the essence of chili peppers, releases substance P and calcitonin gene–related peptide from sensory nerves and initiates both central and axonal reflexes.[209] Capsaicin causes a burning sensation and profuse bilateral rhinorrhea when applied to one side of the nasal cavity, and repeated administration causes tachyphylaxis.[210,211] The capsaicin-induced nasal secretory response in humans is glandular and is not caused by increased vascular permeability.[212] Furthermore, capsaicin desensitization reduces sneezing in response to antigen and histamine challenges.[213] All these findings point to the importance of the participation of neurogenic elements to the allergic response, and more specific delineation of the role of each of these neuropeptides awaits the development of specific antagonists.

Late Response to Antigen

The response to allergen exposure is not limited to the acute events that occur minutes after exposure. Hours after antigen challenge, some patients experience a recurrence of symptoms, most notably nasal congestion. This is termed the late response. Several investigators have documented elevations in nasal airway resistance 4 to 10 hours after antigen challenge, with a peak around 6 hours and resolution by 24 hours.[214,215] After nasal challenge with antigen, the early response was followed by a recurrence of symptoms and increases in the levels of histamine, tosyl-L-arginine methyl ester (TAME)–esterase, and kinins, but not PGD_2.[216] Other mediators, including eosinophil products, have also been detected.[189] These events are accompanied by an inflammatory cellular influx.

In addition to the different preformed and newly generated inflammatory mediators secreted by mast cells and other inflammatory cells during the allergic reaction, cytokines have been identified in the nasal mucosa and in nasal secretions of allergic patients during natural exposure and allergen provocation. In different allergen challenge experiments, increased levels of IL-1β, TNF-α and GM-CSF were detected during the early hours after provocation and levels of IL-5, IL-6, IL-8, GM-CSF, TNF, and soluble intercellular adhesion molecule-1 (ICAM-1) were detected during the late phase response.[217-221] Furthermore, significantly elevated baseline levels of IL-1β, IL-6, and IL-8 were detected in nasal lavages of patients with seasonal allergic rhinitis compared with those of healthy subjects.[219]

Investigations relating to the role of cytokines in allergic rhinitis have been performed using nasal biopsies during the season or after challenge looking either for protein expression using immunohistochemistry or mRNA using in situ hybridization. Compared to healthy subjects, nasal biopsies from patients with perennial allergic rhinitis show significantly more IL-4^+ cells, which seems to be primarily (78-100%) localized to mast cells as evidenced by positive staining of the same cells on consecutive sections with an antibody against mast cell tryptase.[222,223] Immunoreactivity for IL-5, IL-6, and IL-8 was present in most biopsy specimens from perennial rhinitis patients and healthy subjects with no significant differences between the two populations. Most IL-5^+ cells were mast cells, with some eosinophils. IL-6 also colocalized to mast cells, and IL-8 was localized to the cytoplasm of epithelial cells.[222] No cytokine reactivity was localized to $CD3^+$ or $CD4^+$ cells. These data suggest that IL-4, IL-5, and IL-6 proteins are localized to mast cells in the nasal mucosa of patients with perennial allergic rhinitis. The lack of localization of any of the cytokines to T lymphocytes is attributed by the authors to the fact that cytokines generated by activated T cells are rapidly transported from the cell, and do not accumulate in sufficient concentrations to be detected by the techniques used. This work supports the role of mast cells in contributing to the cytokines released in the local milieu after exposure to allergen. The same investigators, studying seasonal allergic rhinitis, showed that pretreatment with intranasal corticosteroids suppressed the increases in mucosal eosinophils and epithelial mast cells, and also led to a significant suppression of IL-4^+ cells in the nasal submucosa, without significant effects on the number of IL-5 and IL-6 immunoreactive cells.[224]

Looking for mRNA for the different cytokines in nasal biopsy specimens after allergen challenge of allergic subjects, Durham and others found significant increases in cells bearing mRNA for IL-3, IL-4, IL-5, and GM-CSF, but not for IL-2 or IFN-γ compared with biopsies obtained after a control challenge.[225] Activated eosinophils ($EG2^+$) increased significantly after allergen challenge and correlated positively with mRNA expression for IL-5, IL-4, GM-CSF, IL-3, and IL-2 but not for IFN-γ. Most IL-5 $mRNA^+$ cells were also shown to be $CD3^+$ (83%), and the rest were positive for tryptase (16.4%).[226] The same investigators demonstrated that pretreatment with fluticasone propionate before allergen challenge resulted in significant inhibition of an allergen-induced increase in activated eosinophils ($EG2^+$) and cells expressing mRNA for IL-4 but not for IL-5.[227] Immunotherapy, in addition to inhibiting cellular influx into the nasal mucosa, also induced a TH1 cell response, with a significant increase in cells expressing mRNA for IFN-γ.[228] Other biopsy studies have also shown significant increases in mRNA positive cells for IL-10 and IL-13 after allergen challenge.[229]

These findings suggest that both T lymphocytes and mast cells are contributors to cytokine production during the allergic reaction, with technical differences in detection probably accounting for the differences in the quantitative distribution of the cytokines between these two cell types. The cytokine profile observed after exposure to allergen emphasizes the importance of TH2 cells and their cytokines in the allergic reaction. The effects of TH2 cytokines are all conducive to the promotion of allergic inflammation: IL-5 promotes the differentiation,[230] vascular adhesion,[231] and in vitro survival of eosinophils[232] and enhances histamine release from basophils[233]; IL-4 is a mast cell growth factor[234] and promotes the switching of B cells to the production of IgE[235]; and IL-13, independent from the other two cytokines, is necessary and sufficient to induce key features of inflammation such as eosinophil recruitment, mucus hyperproduction, and airway hyperresponsiveness.[236]

Cellular Events

Along with the physiologic changes and inflammatory mediator production that occur hours after antigen provocation, inflammatory cel-

lular influx occurs in the nasal mucosa and in recovered nasal secretions after experimental provocation and in seasonally exposed patients. The sampling techniques in the various studies differ, with some targeting nasal secretions and the superficial layers of the mucosa (lavage, scraping, brushing) and others targeting the actual mucosa and submucosa (biopsy). Studies suggest that these techniques yield different cellular predilections for allergic inflammation, with polymorphonuclear cells and eosinophils predominating in nasal secretions, , and mononuclear cells predominating in the nasal mucosa, suggesting that nasal secretions and the nasal mucosa are two separate compartments with different inflammatory cellular predominance during allergic inflammation.[237]

Typically, a slight initial increase in eosinophils in nasal secretions is observed within 1 to 2 hours of challenge and is usually followed by a peak 6 to 8 hours later.[238] MBP, a mediator secreted by eosinophils, is also recovered in nasal lavages hours after antigen provocation, and its levels correlate with the number of eosinophils, suggesting that these cells flow into nasal secretions and release inflammatory mediators.[189] Basophils constitute 1% of the recovered cells. Their number correlates significantly with levels of histamine recovered in nasal secretions during the late phase response, suggesting that these cells are the source of the late rise in histamine.[238]

Similar cellular changes have been observed during seasonal exposure of allergic patients, lending credibility to the observations after experimental allergen challenge. Nasal biopsy specimens collected from allergic patients during the pollen season showed significant increases in total MBP and activated ($EG2^+$) eosinophils in the submucosa compared with preseasonal eosinophil numbers and with numbers in biopsy specimens from nonallergic subjects.[239] Basophilic cells were observed in nasal secretions during seasonal exposure of allergic patients to pollen.[240,241] In contrast to nasal secretions, examination of nasal mucosal scrapings[242,243] or biopsy specimens,[243,244] which sample deeper layers, showed that most metachromatic cells in these compartments were mast cells. A seasonal increase in mast cells occurs on the surface of the nasal epithelium after 4 or 5 days of exposure to pollen, which seems to be the result of migration of mast cells from the deeper layers of the lamina propria to the surface.[244] The consensus of most researchers is that basophils predominate in nasal secretions, whereas mast cells are more abundant in the epithelium and lamina propria of allergic patients exposed to antigen either experimentally or naturally.

Although eosinophils and mast cells are found in the nasal submucosa, most cells in this location are mononuclear cells (lymphocytes and monocytes). Numbers of $CD4^+$ (helper T) lymphocytes and $CD25^+$ cells are significantly higher after antigen challenge than after sham challenge.[245] The preceding discussion of cytokines stresses that a significant source of cytokine production in the nasal mucosa in allergic inflammation are helper T cells of the TH2 subtype.

Another important cell type detected in the nasal mucosa of allergic patients is Langerhans cells, large mononuclear dendritic cells that are important in antigen presentation. Although the numbers of intraepithelial $CD1^+$ (Langerhans) cells in healthy subjects and grass-allergic patients before and after the pollen season are not different, the numbers of intraepithelial $CD1^+$ cells are significantly increased during the allergy season.[246] In a study involving patients with perennial allergic rhinitis, a significant decrease in numbers of Langerhans cells in the epithelium was seen after 3 months of treatment with fluticasone propionate.[247] Thus, Langerhans cells appear important in the allergic reaction and seem to not be constitutively more numerous in patients with allergic rhinitis but are more likely to be up-regulated upon exposure to allergen.

Adhesion Molecules and Cellular Recruitment

Cellular trafficking is integral to human immune response because it allows cells to be selectively recruited from the bloodstream into sites of tissue inflammation. Cellular recruitment into sites of allergic reactions is an example of such trafficking. Numerous inflammatory cells are present in the nasal mucosa and in nasal secretions of allergic patients during allergen exposure but not in healthy subjects. Mechanisms should therefore exist for the migration and accumulation of these effector cells during allergic inflammation. Recruitment of cells such as eosinophils and activated T lymphocytes are mediated, in part, by interactions between adhesion molecules on the cells themselves and those on vascular endothelial cells, with cytokines playing various regulating roles in these interactions.

The molecules responsible for adhesion on leukocytes belong to different families, such as the integrin family, the very late antigen (VLA) family, and the selectin adhesion molecule family.[248-250] Adhesion molecules on the vascular endothelial cell surface include ICAM-1 (CD54), ICAM-2, E-selectin, P-selectin (granule membrane protein-140 [GMP-140], CD62), and VCAM-1.[251] Receptor–counter-receptor pairs for adhesion molecules include leukocyte function–associated antigen-1 (LFA-1) with ICAM-1 and ICAM-2, the macrophage differentiation antigen Mac-1 with ICAM-1, VLA-4 with VCAM-1, the carbohydrate structure sialyl–Lewis X with E-selectin and P-selectin, and glycosylation-dependent cell adhesion molecule 1 (GlyCAM-1) for L-selectin.[248,250]

It is currently thought that a series of events occurs during the migration of circulating leukocytes into tissues (Fig. 40-6). The cells initially undergo reversible margination and can be seen rolling along the endothelial surface on intravital microscopy.[251] These changes are mediated by interactions between carbohydrates and selectins. Leukocyte activation occurs next, presumably as a result of exposure to chemoattractants or other activating factors released by endothelial cells or by nearby tissue-dwelling cells. Leukocyte activation is associated with changes in affinity and expression of adhesion molecules on the leukocyte surface. Leukocytes may also be activated directly by their interaction with adhesion molecules on activated endothelial cells.[252] Activated leukocytes then attach to endothelial cells and migrate across the endothelium into the extravascular space. These events are mediated by one or more members of the integrin, selectin, and immunoglobulin families of adhesion molecules. Furthermore, it is likely that the preferential recruitment of leukocytes involves multiple steps, such as leukocyte activation, vascular endothelial cell expression of adhesion molecules, adhesion of leukocytes to vascular endothelium, transendothelial migration, chemotaxis, and localized survival within the tissues. Multiple cytokines and other factors are important in up-regulating adhesion molecules on circulating leukocytes and vascular endothelium and are crucial in chemotaxis and leukocyte survival within the tissues.

Clear evidence shows that endothelial activation occurs during allergic rhinitis in vivo. Enhanced expression of ICAM-1 and VCAM-1, but not E-selectin, has been described in the mucosa of allergic patients.[253] The expression of VCAM-1 was found to be significantly up-regulated in biopsy specimens obtained from allergic patients 24 hours after antigen challenge concomitantly with a significant increase in the number of eosinophils.[254] These studies of adhesion molecules in vivo suggest that these molecules, along with their counter-ligands on circulating leukocytes, have an important role in cellular recruitment to allergic inflammatory sites. Further studies are needed for better definition of the role of these adhesion mechanisms in allergic rhinitis and for determination of whether interfering with the process of adhesion would modify the course and severity of the disease.

Hyperresponsiveness

One of the hallmarks of allergic rhinitis is the hyperresponsiveness of allergic patients to specific stimuli such as antigen (a phenomenon known as priming) and nonspecific stimuli.

Specific Hyperresponsiveness

Many allergic patients report worsening of symptoms as the allergy season progresses, despite unchanged or decreased pollen counts. This phenomenon is probably caused by a shift in the threshold of responsiveness. Connell[255] found that the dose of pollen necessary to create symptoms decreased more than fivefold by the fourth day of consecutive antigen challenges. Consecutive nasal allergen challenges have also demonstrated the priming phenomenon, in that patients challenged 24 hours after earlier exposure had significantly more sneezes and a reduction in the threshold dose necessary to elicit the response.[256] Concomitant with the priming response observed for sneezes, significantly higher levels of histamine and kinins and an increase in the number of neutrophils, eosinophils, and basophils were observed in nasal lavage samples. These observations suggest that mechanisms of priming

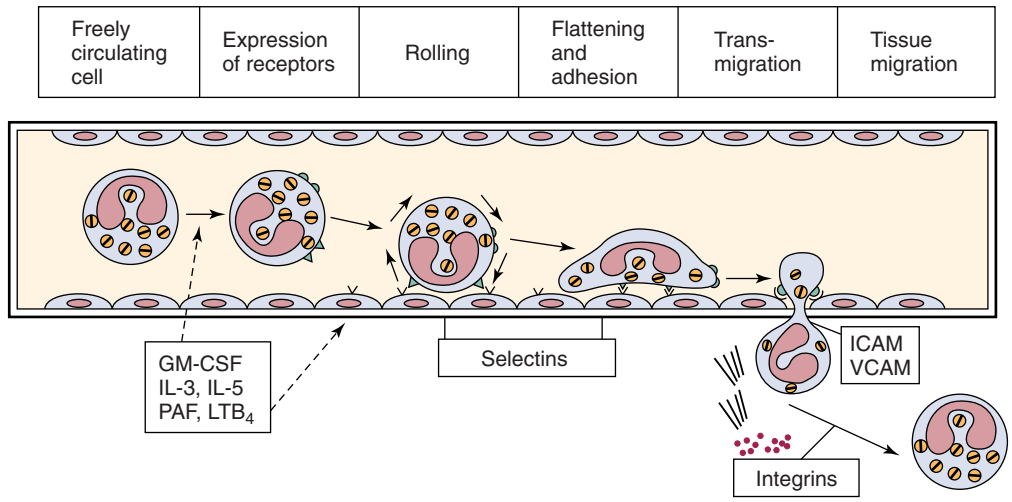

Figure 40-6. Cellular adhesion and recruitment. An eosinophil is seen from the early stage of free circulation to rolling, adhesion to the vascular endothelium, transendothelial migration, and, finally, tissue migration. In the case of the eosinophil, these events are regulated and mediated by multiple cytokines and adhesion molecules. GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; LTB_4, leukotriene B_4; PAF, platelet-activating factor; VCAM, vascular cellular adhesion molecule. *(From Mygind N, Dahl R, Pedersen S, Thestrup-Pedersen K, eds.* Essential Allergy. *2nd ed. Oxford: Blackwell Scientific Publications; 1996.)*

involve cellular infiltration, increased mediator production, and possibly increased end-organ responsiveness. Inflowing inflammatory cells are hypothesized to alter the mucosal penetration of antigen and to provide additional targets for antigen stimulation and increased generation of inflammatory mediators, which would, in turn, encounter more responsive end organs, thus leading to the exaggerated response noted after repeated antigen exposure.

Nonspecific Hyperresponsiveness

Increased reactivity to irritant stimuli is often reported by allergic patients. This phenomenon has been studied by observation of the nasal response to nonantigenic nasal secretagogues, such as histamine and the cholinergic agonist methacholine. Patients who underwent an antigen challenge followed 24 hours later by a histamine challenge showed increased sensitivity to histamine compared with those undergoing only a baseline histamine challenge,[257] and this response was inhibited by pretreatment with topical corticosteroids.[258,259] The number of eosinophils in nasal secretions 24 hours after antigen challenge correlated with the magnitude of reactivity to histamine, and inhibition by topical corticosteroids was accompanied by an inhibition of the increase in eosinophils.[259] Similar studies show nasal hyperresponsiveness to the cholinomimetic agonist methacholine.[260-263] In allergic patients during the allergy season, the hyperresponsiveness caused by nonspecific irritants probably reflects complex interactions among inflammatory cellular influx, epithelial injury, and increased end-organ responsiveness caused by exposure to antigen.

The pathophysiologic mechanisms in allergic rhinitis can be synthesized in the following scenario (Fig. 40-7): Sensitization of the nasal mucosa to a certain allergen entails multiple interactions among APCs, T lymphocytes, and B cells that lead to the production of antigen-specific IgE antibodies, which then localize to mast cells and basophils. Subsequent exposure leads to cross-linking of specific IgE receptors on mast cells and their resultant degranulation, with the release of a host of inflammatory mediators that are, in large part, responsible for allergic nasal symptoms. Other proinflammatory substances are also generated after antigen exposure, the most prominent being eosinophil products and cytokines. Cytokines are thought to be generated in part by lymphocytes, which are abundant in resting and stimulated nasal mucosa, and also by mast cells, which have an important role in the storage, production, and secretion of cytokines. Cytokines up-regulate adhesion molecules on the vascular endothelium, and possibly on marginating leukocytes, leading to the migration of these inflammatory cells into the site of tissue inflammation. Various cytokines also promote the chemotaxis and survival of these recruited inflammatory cells, leading to a secondary immune response by virtue of their capability to promote IgE synthesis by B cells. Also important is the nervous system, which amplifies the allergic reaction by central and peripheral reflexes that result in changes at sites distant from those of antigen deposition, such as the eye, sinuses, and lower airway. These inflammatory changes lower the threshold of mucosal responsiveness to various specific and nonspecific stimuli, making allergic patients more responsive to stimuli to which they are exposed every day.

Evaluation and Diagnosis

History

The classic symptoms of seasonal allergic rhinitis are recurrent episodes of sneezing, pruritus, rhinorrhea, nasal congestion, and lacrimation that occur after exposure to the offending allergen. Itching is the symptom most suggestive of an allergic etiology and involves not only the nose but also the palate, throat, eyes, and ears. Rhinorrhea is usually clear and can be anterior, resulting in sniffing and nose blowing, or posterior, resulting in snorting, throat clearing, and postnasal drip. If the rhinorrhea is purulent, the physician should consider other etiologies, such as viral upper respiratory infections and bacterial rhinosinusitis. Nasal obstruction may be bilateral or could manifest as exaggeration of the nasal cycle with alternating unilateral obstruction. If the obstruction is constant and fixed, the physician should think about coexisting mechanical causes for the obstruction, such as septal deviation. If the congestion is severe, it can be associated with a loss of smell secondary to obstruction to airflow or to inflammation in the olfactory cleft and usually manifests as a loss of taste. Ocular symptoms, including itching, tearing, and conjunctival injection, occur frequently. Eustachian tube dysfunction, manifested as ear popping and clicking, is an occasional manifestation. Systemic symptoms that may accompany allergic rhinitis include general malaise, fatigue, irritability, snoring, and sleep problems.[174,264] The history for rhinitis should also include query about family history of allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis, because a positive family history for allergic diseases makes it more likely that the patient's nasal symptoms are secondary to allergic rhinitis.

The traditional classification of allergic rhinitis is seasonal, perennial, or episodic. *Seasonal allergic rhinitis* is defined by symptoms that occur during exposure to seasonal allergens, such as ragweed, grasses, outdoor molds, and tree pollens. *Perennial allergic rhinitis*, defined as nasal symptoms for more than 2 hours per day for more than 9 months

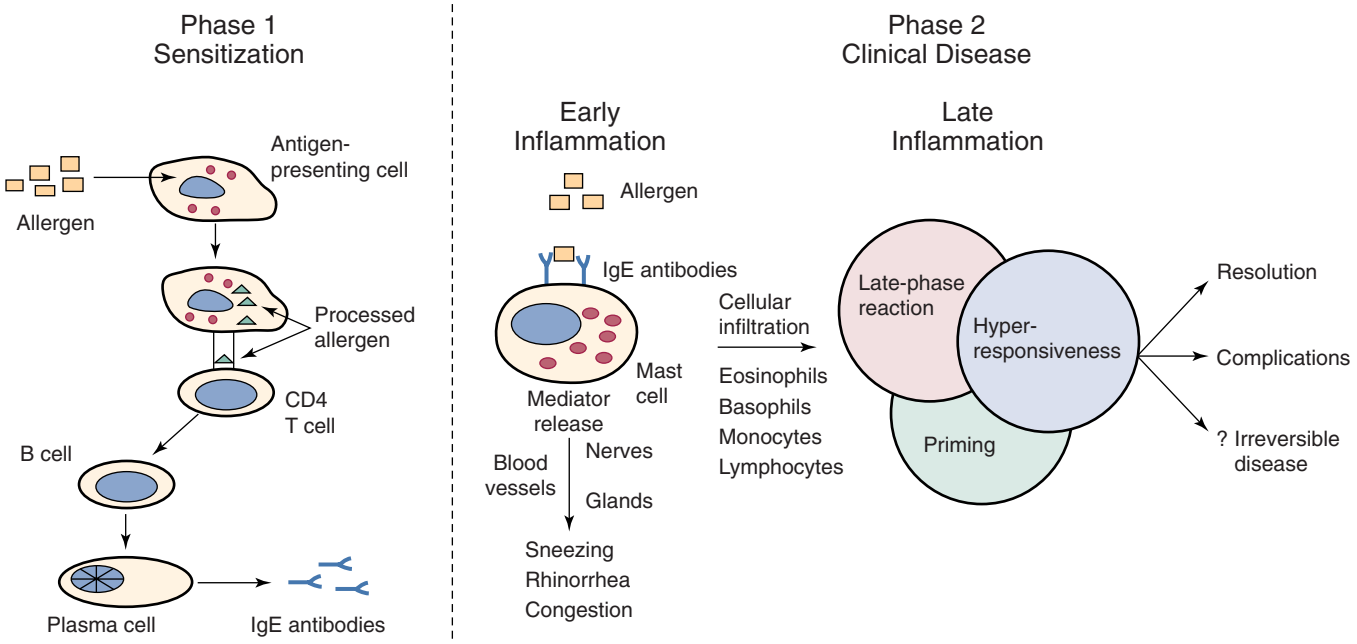

Figure 40-7. Pathophysiology of allergic rhinitis. The first stage of development of allergic rhinitis involves antigen processing and the production of specific immunoglobulin E (IgE) antibodies, which attach to mast cells, basophils, and other inflammatory cells. On subsequent exposure to the same allergen, IgE receptors on the surface of mast cells are cross-linked, leading to the degranulation of these cells and the release of preformed and newly synthesized mediators that are responsible for symptoms of the disease. Recruitment of inflammatory cells to the nasal mucosa also occurs, as does a resultant state of chronic inflammation with a heightened state of reactivity to specific and nonspecific stimuli, a hallmark of allergic nasal disease. In addition to the early and late inflammatory responses, exposure to allergen leads to a secondary immune response with increased production of specific IgE and a perpetuation of the state of susceptibility to allergen. *(From Naclerio RM. Allergic rhinitis.* N Engl J Med. *1991;325:860.)*

of the year, occurs when allergies develop to house dust mites, indoor molds, animal danders, and cockroaches. *Episodic rhinitis* refers to symptoms on exposure to allergens that are not normally present in the environment, such as a cat-allergic individual becoming symptomatic upon entering the home of relatives who have a cat.

A newer classification was proposed in 1999, during the ARIA (Allergic Rhinitis and its Impact on Asthma) World Health Organization (WHO) workshop, on the basis of the facts that the preceding, more traditional, classification did not always fit all disease presentations and that most patients were polysensitized with both perennial and seasonal allergens.[265] The new definition introduced the terms intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER), with the emphasis that these terms were not synonymous with *seasonal allergic rhinitis* and *perennial allergic rhinitis*, respectively. A degree of severity was also attached to this classification. Thus according to the ARIA classification, *intermittent allergic rhinitis* refers to symptoms present for less than 4 days a week, or for less than 4 consecutive weeks, and *persistent allergic rhinitis* refers to symptoms present for more than 4 days a week and for more than 4 consecutive weeks, with the realization that patients usually suffer almost every day. The severity is designated as mild or moderate to severe. *Mild* implies that the symptoms are present but not troublesome. Importantly, there is the absence of sleep disturbance and of impairment of leisure/sport/school/work daily activities. *Moderate to severe* implies the presence of one or more of the following: sleep disturbance, impairment of leisure/sport/school/work daily activities, and troublesome symptoms. The ARIA classification is used to suggest a treatment algorithm, whereas the traditional classification is used to help define the offending antigens.

It is important for the treating physician to familiarize himself or herself with the pattern of environmental allergens in the area of practice. Once allergic symptoms are present, they may be exacerbated by irritants such as strong odors or perfumes, tobacco smoke, paint, newspaper ink, soap powders, and air pollutants. This exacerbation represents nonspecific hyperresponsiveness. Several clinical entities should be considered in the differential diagnosis of the patient who presents with nasal obstruction and rhinorrhea; they are listed in Box 40-1.

Physical Examination

A complete ear, nose, and throat examination is essential in the workup of every patient suspected of having allergic rhinitis and is useful in identifying other problems rather than in confirming the diagnosis. The ear examination may show otitis media with effusion, suggesting nasopharyngeal problems. Examination of the face may show puffiness of the eyelids and periorbital cyanosis, usually due to venous stasis secondary to chronic nasal obstruction and often referred to as "allergic shiners." Other facial anomalies associated with long-standing obstruction are elongated facies, open mouth, flattened malar eminences, pinched nostrils, raised upper lips, high arched palate, and retracted jaws, a complex of signs usually referred to as "adenoid facies." Localized facial tenderness on palpation, especially in conjunction with purulent anterior or posterior nasal discharge, suggests rhinosinusitis. External nasal examination may show a gross deformity due to previous trauma or bony expansion by an underlying lesion. A supra tip crease at the junction of the upper and lower lateral cartilages is a result of frequent pushing upward of the nasal tip, the "allergic salute."

A nasal speculum or an otoscope, fitted with the largest speculum, is then used to inspect the inner aspect of the nasal cavities. The anterior portion of the nose is examined for possible folliculitis and anterior septal deviations. The inferior turbinates are then inspected along the lateral nasal wall. These structures are often described as being pale, bluish, and edematous, and coated with thin, clear secretions. It is important to remember that there is no pathognomonic appearance of the nasal mucosa in allergic rhinitis. A topical decongestant, such as oxymetazoline, can be applied and the nasal cavity examined a few minutes later. This step allows evaluation of the reversibility of nasal congestion and facilitates inspection of the area of the middle meatus.

For better examination of the nasal cavity, and in cases in which the existence of pathology not readily accessible to anterior rhinoscopy

Box 40-1

Differential Diagnosis of Rhinorrhea and Nasal Obstruction

Allergic Rhinitis

Seasonal/perennial/episodic or intermittent/persistent.

Nonallergic Rhinitis

Perennial (vasomotor): Constant symptoms of profuse, clear rhinorrhea and nasal congestion without correlation to specific allergen exposure or signs of atopy.

Cold air–induced: Nasal congestion and rhinorrhea upon exposure to cold, windy weather; occurs in both allergic and nonallergic individuals.

Nonallergic rhinitis with eosinophilia syndrome (NARES): Most often seen in adults; characterized by eosinophilia on nasal smears and with negative test results for specific allergens.

Infectious Rhinitis

Bacterial, viral, fungal.

Granulomatous Rhinitis

Sarcoidosis, Wegener's granulomatosis.

Drug-induced Rhinitis

Oral contraceptives, reserpine derivatives, hydralazine hydrochloride, topical decongestants (rhinitis medicamentosa), β-blockers (eye drops).

Mechanical Obstruction

Septal deviation: Common, and might exacerbate nasal obstruction in allergic rhinitis.

Foreign body: Unilateral purulent nasal discharge is the usual manifestation of a foreign body and resolves after removal.

Choanal atresia or stenosis: Bilateral choanal atresia is usually diagnosed early in life, but unilateral choanal atresia or stenosis can go unnoticed for several years. Easily diagnosed by nasal endoscopy and axial computed tomography of the midfacial skeleton.

Adenoid hypertrophy: Common cause of nasal obstruction in children.

Others: Encephaloceles, lacrimal duct cysts, dermoids.

Neoplastic Rhinitis

Benign: Polyps, juvenile angiofibroma, inverted papilloma.

Malignant: Adenocarcinoma, squamous cell carcinoma, esthesioneuroblastoma, lymphoma, rhabdomyosarcoma.

is suspected, nasal endoscopy should be performed. This procedure is usually done with the use of a flexible or rigid fiberoptic instrument and is well tolerated by adults and by children older than 5 years. Nasal endoscopy allows visualization of the middle meatus to rule out the existence of purulent discharge or small polyps originating from the sinuses. In cases in which adenoidal hypertrophy or choanal atresia is suspected, endoscopy can visualize the nasopharynx.

Diagnostic Tests

The two most common tests used to confirm the diagnosis of allergic rhinitis are skin testing and in vitro testing for serum levels of specific IgE antibodies. Skin testing is performed by applying antigen extracts to the skin either epicutaneously (puncture skin tests) or intradermally (intradermal tests). Intradermal testing is usually not required for the diagnosis of inhalant allergy when standardized extracts are available[266,267] and might induce false-positive reactions. Testing is always accompanied by an introduction of the diluent for the allergen extract, used as negative control, and histamine or codeine (a mast cell degranulating agent), used as a positive control. A wheal and flare reaction, seen within 15 minutes of injection, occurs if a patient is sensitive to a specific antigen. A positive reaction indicates the existence of specific IgE antibodies on intradermal mast cells and the reaction of the skin to released mediators.

Skin testing is rapid and inexpensive but, like all clinical tests, has certain disadvantages, as follows: (1) skin reactivity might be affected by previous ingestion of antihistamines or other drugs, (2) children often do not tolerate multiple skin needle pricks, (3) prior or coexisting dermatologic conditions, such as eczema or dermatographism, may preclude the performance of skin tests, (4) the potency of antigen extracts needs to be maintained, and (5) systemic reactions may occur. Potentially interfering medications must be discontinued prior to skin testing; montelukast does not appear to affect skin test reactivity, however, and does not need to be discontinued prior to skin testing.[268] Most physicians test with a panel of allergens that are prevalent in their areas in addition to allergens that seem relevant from the history, such as cat, dog, and cockroach.

Both total and specific serum IgE levels can be measured in vitro. Total IgE is elevated in 30% to 40% of patients with allergic rhinitis, and can be elevated in patients with nonallergic conditions and normal subjects; thus, total IgE determination is of limited use in the diagnosis of allergic rhinitis. The detection of specific IgE antibodies in the patient's serum is useful in the diagnosis of allergic rhinitis. Although less sensitive than skin testing, in vitro IgE measurements correlate well with the results of skin testing and the clinical picture. These tests eliminate the need for multiple skin pricks but are more expensive, and the results take longer to obtain than those of skin testing. It is important to obtain simultaneous total IgE levels because false-positive radioallergosorbent test (RAST) results may occur in sera with extremely high levels of IgE because of nonspecific binding. Other tools, such as nasal challenges and measurement of blood basophil histamine release, other peripheral blood activation markers, or eosinophils in nasal smears, are primarily utilized for research purposes.

The clinical history should guide the clinician to test the patient with a panel of the most relevant antigens. Testing with the six most common antigens is effective in picking up 95% of the allergens to which a patient is sensitive. It is always important to remember that a positive in vitro or skin test result alone does not confirm the diagnosis of allergic rhinitis in the absence of supporting clinical history, particularly because the last National Health and Nutrition Examination Survey study showed that a prevalence of positive test results exceeded 50% but full expression of allergic disease affected only 20% of the study population.

Therapeutic Options

Avoidance

Avoiding the offending allergens is potentially an effective treatment for allergic rhinitis. Multiple measures for avoidance have been advocated over the years, including removing a pet from the house, covering pillows and mattresses, washing bedding with hot water, and vacuuming mattresses and pillows. These measures are targeted toward indoor allergens, especially dust mites. Unfortunately a systematic review of many of these avoidance measures has shown that single measures are not effective in reducing symptoms in patients with allergic rhinitis.[269] In a large study investigating the effects of the use of allergen-impermeable bedding covers in the bedrooms of patients with dust mite–associated perennial allergic rhinitis, these covers reduced the concentrations of mattress *Dermatophagoides pteronyssinus* by 30% of baseline but resulted in no difference in the clinical symptoms of allergic rhinitis.[270] Limited evidence suggests that preventive measures (removing carpeting, using tannic acid, washing bedding, washing the cat) result in a reduction of levels of the allergen Fel d 1 in the house and a subsequent improvement of clinical symptoms of allergic rhinitis due to cat allergy.[271] Good evidence supporting the use of

high-efficiency particulate air (HEPA) filters is also lacking.[272] Outdoor allergens such as grasses, trees, and weeds are even more difficult to control, and some of the proposed measures that lack scientific evidence for efficacy include avoiding lawn mowing and driving with the car windows closed. The lack of effectiveness of avoidance measures makes it less important to define what specific allergens patients are sensitive to, if pharmacotherapy is the planned treatment.

Antihistamines

H_1 antihistamines block histamine at the H_1 receptor level and are commonly used in the treatment of allergic rhinitis. They include older first-generation, drugs, such as diphenhydramine, which are lipophilic and have varying degrees of anticholinergic and sedating side effects, and newer, second-generation, antihistamines, such as loratadine, which have minimal or no sedative effect. The latter are less lipophilic with a reduced ability to cross the blood-brain barrier and have lower sedating and anticholinergic side effects. Oral H_1 antihistamines are effective in controlling histamine-mediated symptoms such as sneezing, itching, rhinorrhea, and eye symptoms such as itchy and watery eyes, but are not as effective in alleviating nasal congestion.[273] Furthermore, several agents in this category have been demonstrated to improve quality of life as measured by generic and disease-specific tools.[274-276] They are rapidly absorbed after oral administration and begin to provide relief within 1 hour. Oral H_1 antihistamines have been shown to be safe and effective in children, and many are available in liquid form.[277] They are also safe when utilized for long-term treatment (years).

In addition to antagonizing histamine at the H_1 receptor, some antihistamines have anti-inflammatory properties, such as inhibiting histamine release, reducing the production of leukotrienes, inhibiting allergen-induced nonspecific responsiveness, and reducing soluble ICAM-1 levels in nasal secretions.[278-281] These additional properties, however, do not seem to translate into enhanced clinical efficacy and thus their clinical importance is not clear.

The side effects of first-generation antihistamines can be bothersome. The most important of these is sedation, which is reported in approximately 20% of patients. It is therefore important to warn the patient receiving such a drug about its potential effect on daily activities, such as driving or operating heavy machinery. The development of nonsedating antihistamines in the 1980s eliminated this problem. The newer nonsedating antihistamines have few effects on performance and a low reported incidence of sedation. The second-generation antihistamines include loratadine, cetirizine (both available over the counter), desloratadine, fexofenadine, and, the latest, levocetirizine. Both cetirizine and levocetirizine are labeled by the U.S. Food and Drug Administration (FDA) as sedating, but they cause less sedation than the first-generation antihistamines.

H_1 antihistamines are also available for intranasal administration. Azelastine, a phthalazinone derivative, is available in the United States for the treatment of allergic rhinitis. It is comparable in efficacy to other antihistamines, is usually given twice daily, can cause somnolence, and may cause a sensation of altered taste immediately after use.[282] This agent has been shown to be effective in reducing itching, sneezing, runny nose, and nasal congestion.[283,284] Olopatadine hydrochloride (0.6%) has been shown to be safe and effective for the treatment of seasonal allergic rhinitis and is usually administered as 2 puffs/nostril twice daily. The most commonly reported adverse reaction to this drug is bitter taste, and the incidence of somnolence is minimally higher than that for the placebo vehicle.[285]

Decongestants

Both topical and systemic decongestants act by α-adrenergic stimulation. They cause vascular constriction and a reduction of both the nasal blood supply and the volume of blood in the sinusoids. Topical decongestants, which can be either catecholamines (such as phenylephrine) or imidazoline derivatives (such as xylometazoline or oxymetazoline), have a rapid onset of action and are usually more efficacious than systemic decongestants. They do not have systemic side effects except in children, in whom seizures have been reported. Continued use of these agents leads to progressively shorter duration of action, until almost continued application provides no relief—a condition known as rhinitis medicamentosa. Therefore, the use of topical decongestants in allergic rhinitis should be limited to a short duration for the following purposes: to facilitate the penetration of intranasal steroids in patients in whom severe congestion precludes it, to allow proper physical examination, and to facilitate sleep during severe rhinitic exacerbations.

Commonly used in the United States, oral decongestants do not cause rhinitis medicamentosa but are not as effective as their topical counterparts. Pseudoephedrine hydrochloride and phenylephrine are the most commonly used. Phenylpropanolamine has been taken off the market in the United States because of the increased risk of hemorrhagic stroke in women associated with its use as an appetite suppressant.[286] Pseudoephedrine decongestant–containing products are now sold from behind the pharmacy counter in the United States because of the potential for their conversion into stimulants. They are used most frequently in combination preparations with antihistamines (pseudoephedrine) or over the counter in cough and cold products in combination with analgesics and antitussives. Phenylephrine is another over-the-counter decongestant also used in combination products, but a 2007 meta-analysis showed lack of efficacy for this agent on both objective and subjective measures of nasal congestion in comparison with placebo.[287] In addition to nasal vasoconstriction, oral decongestants cause vasoconstriction in other vascular beds, accounting for their side effects, the most common of which are insomnia and irritability, which can be seen in as many as 25% of patients. An overdose of these agents causes hypertension, nervousness, renal failure, arrhythmias, psychosis, strokes, and seizures. They should therefore be administered with caution to patients who have hypertension, heart disease, seizure disorders, hyperthyroidism, or prostatic hypertrophy or who are undergoing monoamine oxidase inhibitor therapy.

Anticholinergics

Anticholinergic drugs are useful in the treatment of those subjects in whom rhinorrhea is the predominant complaint. Ipratropium bromide has little or no systemic effects when administered intranasally and has been shown to be effective in controlling watery nasal discharge in perennial allergic and nonallergic rhinitis.[288] It has no effect on sneezing or nasal obstruction. This agent can be used in conjunction with other modalities, such as antihistamines or intranasal steroids, for the satisfactory control of rhinorrhea.

Cromolyn Sodium

Cromolyn sodium, which is available over the counter as a 4% solution for intranasal use, has been shown to be clinically effective in the treatment of allergic rhinitis. Like antihistamines, it is more helpful for sneezing, itching, and rhinorrhea and less effective in relieving nasal congestion. Its mode of action is unclear, and it is most effective when started before the onset of symptoms. The dosage is four to six times daily, causing compliance problems, but cromolyn sodium is very safe, especially in children and pregnant women.

Leukotriene Modifiers

Because leukotrienes are generated in allergic rhinitis, the effects of inhibitors of the 5-lipoxygenase pathway (zileuton) and leukotriene receptor antagonists (montelukast and zafirlukast) have been investigated. By far the most commonly used agent in this category is montelukast, which is approved in the United States for the treatment of seasonal and perennial allergic rhinitis in adults and children. In placebo-controlled studies, montelukast has repeatedly been shown to be more effective than placebo and equal in effectiveness to antihistamines for all ocular and nasal symptoms of allergic rhinitis, including congestion, rhinorrhea, and sneezing.[289-291] Furthermore, the combination of montelukast and loratadine was found to be superior to each agent alone in the treatment of seasonal allergic rhinitis in one study, although these results have not been duplicated consistently in subsequent investigations.[292] Ciebiada and colleagues[293] conducted a placebo-controlled, crossover study to evaluate the effect of montelukast, desloratadine, and levocetirizine, alone or in combination, in patients with persistent allergic rhinitis. These researchers showed that all treatments were superior to placebo in the control of total nasal symptoms and that the

combination of either of the antihistamines with montelukast was more effective than each of the treatments used individually. A combination product containing loratadine and montelukast was not approved by the FDA.

Intranasal Steroids

Intranasal steroids (INSs) are the most potent drugs available for allergic rhinitis, a feature likely related to their diverse anti-inflammatory effects. In nasal allergen challenge models of allergic rhinitis, pretreatment with INSs results in significant inhibition of mediator release during both the early and late phase reactions along with a significant inhibition of the influx of basophils, eosinophils, neutrophils, and mononuclear cells in nasal secretions.[238,294] These agents also lead to a reduction in the number of inflammatory cells and TH2-type cytokines within the nasal mucosa of patients with allergic rhinitis.[295] INSs also were found to reduce the antigen-induced hyperresponsiveness of the nasal mucosa to subsequent antigen[294] and histamine provocation.[259] Coupled with these favorable anti-inflammatory effects of INSs, several placebo-controlled clinical trials using a variety of these agents demonstrated their effectiveness in the reduction of all nasal symptoms in both seasonal[296] and perennial[297] allergic rhinitis. Studies have also shown the efficacy of INSs in controlling ocular symptoms.[298,299] In comparative studies, INSs have been shown to have superior efficacy to both H_1 antihistamines[300,301] and leukotriene receptor antagonists.[302] Because of their superior efficacy especially in controlling nasal congestion, and their safety, INSs are regarded as first-line treatment of allergic rhinitis, except for the mildest forms of the disease.

Efficacy appears after 7 to 8 hours of dosing,[303] although maximum efficacy requires days of INS administration. On the other hand, some patients have been shown to benefit within as little as 2 hours of dosing.[304] It is often reasonable, although difficult to accomplish, to start treatment a week or so before the beginning of the pollen season in subjects with known seasonal allergic rhinitis. One should start treatment with the recommended dosage and reevaluate the patient in 2 weeks. During the reevaluation visit, the nose should be examined for signs of local irritation due to the drug or mechanical trauma from the applicator itself, and the patient's response to treatment should be assessed. If a favorable clinical response is reported, the dose of INS can be lowered, keeping in mind the load of allergen in the environment, with the aim of reaching the minimal dose that provides symptomatic relief. Although continuous use of INSs is usually recommended, some studies have demonstrated the superiority of the as-needed use of intranasal fluticasone propionate over placebo.[305,306]

Local nasal irritation, the principal side effect of INSs, occurs in about 10% of patients. The incidence of epistaxis with different preparations ranges from 4% to 8% over a couple of weeks, with higher incidences in studies carried over a year, and septal perforations, although rare, have been reported. Biopsy specimens from the nasal mucosa of patients with perennial rhinitis who had been treated with fluticasone propionate or mometasone furoate continuously for 1 year showed no evidence of atrophy[307] and a higher percentage of pseudostratified ciliated columnar epithelium after active treatment, suggesting normalization of the epithelium.[295] *Candida* overgrowth in the nose with the use of INSs is rare. The long-term use of the newer INSs has been shown to be free of the concerns associated with the use of systemic steroids, such as growth retardation and interference with the hypothalamic-pituitary axis.[308,309] It is recommended that the growth of pediatric patients receiving INSs should be monitored regularly (every 3 to 6 months) with an accurate instrument (stadiometer) by trained staff in a consistent way.

Systemic Glucocorticosteroids

The role of systemic steroids in the treatment of allergic rhinitis is limited because of their adverse effects and the limited morbidity of the disease. They are best reserved for patients who present in the middle of the pollen season with total nasal obstruction. Because oral decongestants, with or without antihistamines, would not be effective in these patients and the intranasal steroid preparations cannot be delivered because of nasal obstruction, a short course of systemic steroids is effective in relieving nasal obstruction. A short course of systemic steroids is also useful in reducing the nasal obstruction associated with rhinitis medicamentosa and facilitates weaning of patients from topical decongestants. Treatment with intramuscular injections of depo-steroids should not be used for the treatment of seasonal allergic rhinitis unless there are extenuating circumstances, because there is always a potential for decreased resistance to infection during the 4 to 6 weeks after the injection. Furthermore, depo-steroid injections have long-term effects on bone density, cause systemic suppression of the hypothalamic-pituitary axis, and have other systemic effects associated with systemic steroids.

Immunotherapy

Allergen-specific immunotherapy involves the repeated administration, sublingually or subcutaneously, of increasing doses of antigen extract in an attempt to alter patients' immunologic responses and improve their symptoms. Immunotherapy is usually reserved for patients who find it difficult to avoid allergens and who have not experienced adequate responses to pharmacologic treatment.

Subcutaneous Immunotherapy

Since the introduction of subcutaneous immunotherapy (SCIT) in 1911, many studies have supported its effectiveness in the treatment of pollen allergies. Several immunologic changes occur in patients receiving SCIT; they include (1) a rise in serum-specific IgG, (2) an increase in the levels of IgG and IgA antibodies in nasal secretions, (3) a variable reduction in the reactivity and sensitivity of peripheral basophils to antigens, (4) reduced in vitro lymphocyte responsiveness to allergens, (5) a reduction in inflammatory cells in the nasal mucosa and nasal secretions and a shift from the TH2 to the TH1 cytokine profile, and (6) suppression of the seasonal rise in IgE antibodies followed by a slow decline in the level of specific antibodies during the following several years of treatment.[310] The clinical efficacy of SCIT is well established for allergic rhinitis,[311] and the therapy improves quality of life of patients with allergic rhinitis.[312] The treatment offers relief, but the onset of action is slow, with improvement starting within 12 weeks and increasing over a period of 1 to 2 years after treatment. Because the treatment involves multiple visits, requires a high degree of patient compliance, has significant adverse effects, such as death, is highly specific and effective only for the allergens administered, and needs months to achieve clinical improvement, careful identification of all allergens responsible for the patient's symptoms before initiation of treatment is important.

The duration of SCIT is usually 3 to 5 years, and several studies have shown persistence of benefit for various periods of time after cessation of therapy, supporting the conclusion that SCIT alters the natural history of allergic rhinitis.[313-315] In one such blinded, placebo-controlled study, Durham and colleagues[315] showed that 3 to 4 years of immunotherapy with grass pollen extract resulted in prolonged clinical remission accompanied by a persistent alteration in immunologic reactivity as demonstrated by reduction in the late skin response and associated $CD3^+$ T-cell infiltration and IL-4 mRNA expression 3 years after discontinuation of therapy. SCIT has also been shown to prevent the development of new sensitizations in monosensitized children,[316] and it may reduce the development of asthma in patients treated for rhinitis.[317,318]

Immunotherapy causes local and systemic adverse reactions. Lockey and associates[319,320] reported 46 fatalities associated with immunotherapy and skin testing in the United States for the period 1945 to 1985 and 17 fatalities associated with immunotherapy for the years 1985 to 1989. Analysis of these data with special attention to risk factors suggested that, although death from immunotherapy is uncommon (risk estimated at 1 fatality for every 2 million injections), special precautions must be taken in patients with asthma, and a waiting period of 20 minutes after the administration of the shot is recommended for all patients, with longer intervals (30 minutes) being appropriate for high-risk patients. Treatment should also be administered in an office ready to handle anaphylaxis.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT), whereby extracts are administered sublingually, was controversial for many years but has gained wide

acceptance in European and other countries and is starting to be investigated in the United States. In 2005, Wilson and colleagues[321] performed a meta-analysis, the results of which supported the safety and efficacy of SLIT in allergic rhinitis. Multiple other studies have been published since then with results to the same effect.[322,323] Studies using grass tablets have also shown efficacy and safety in allergic rhinitis.[324,325] A meta-analysis has also supported the efficacy of SLIT in children with allergic rhinitis[326] and patients with asthma.[327] Limited data support the potential of SLIT in altering natural history of the disease.[328,329]

The obvious advantage of this treatment over SCIT is ease of administration and the avoidance of coming to a doctor's office to receive the treatment. This is primarily related to the safety of SLIT. Indeed, safety has been demonstrated in multiple studies in adults and children.[330-332] Described local side effects have included itching and swelling of the lips and the sublingual oral mucosa that resolve without treatment. Systemic anaphylactic reactions have been described, one with latex immunotherapy,[333] one with an ill-defined multi-allergen vaccine,[334] and the last with pollen mix administered in conjunction with dust mite extract during the peak of the spring season in a child.[335] Clear directions should therefore be given to parents about what to do in the event of an adverse reaction, and the extracts should be kept in a safe place out of the reach of children. It is of note that no extracts are currently approved by the FDA for immunotherapy using the sublingual route. However, a couple of leading developers and providers of allergy immunotherapy are in the process of performing clinical trials with SLIT using their standardized allergenic extracts in an effort to bring an approved sublingual-oral immunotherapy treatment to the United States.

SCIT is probably best reserved for patients with perennial rhinitis because they are symptomatic all through the year and are willing to undergo prolonged treatment. Medical treatment is probably more suitable for patients with seasonal or episodic rhinitis who have symptoms for much shorter periods of the year. SLIT has been studied primarily in and is available mostly for seasonal allergens; its use with multiple allergens has not been fully evaluated.

Novel Extracts

Recombinant DNA technology has allowed the production of allergens with improved purity, consistency, composition, and dosage. The use of such extracts is being investigated for the immunotherapy of allergic rhinitis, and initial results are promising.[336] Animal studies are also ongoing to test the efficacy of a mucoadhesive formulation of allergens that would enhance adhesion of allergen extracts to the sublingual mucosal membrane and would thus augment treatment via the sublingual route.[337]

Anti-IgE

Recombinant, humanized, monoclonal anti-IgE antibody forms complexes with free IgE and blocks its interaction with mast cells and basophils. Anti-IgE has been shown to be beneficial and cost-effective in the treatment of moderate to severe asthma, for which it is currently indicated in the United States.[338,339] Although it has also been shown to be effective in decreasing nasal symptoms and improving quality of life in patients with allergic rhinitis, the lack of cost-effectiveness as well as the inconvenient route of administration (subcutaneous) make this agent ill-suited as the mainstay of treatment of allergic rhinitis.[340-342] In a clinical trial in patients with ragweed allergic rhinitis, anti-IgE therapy was shown to enhance the safety of a rush (accelerated dosage increase) immunotherapy regimen, allowing a significant reduction in the time required for treatment.[343]

Treatment of Eye Symptoms in Allergic Rhinoconjunctivitis

Allergic rhinitis involves eye symptoms that are probably a combination of the direct effects of allergen deposition on the conjunctiva and reflexes between the nose and the eye. Oral H_1 antihistamines and leukotriene receptor antagonists are effective in controlling eye symptoms.[273,289] Antihistamines given intraocularly have been shown to be effective for the control of allergic eye symptoms.[344,345] They have a rapid onset of action and are associated with lower rates of sedation and dry eye than first-generation oral H_1-antihistamines.[346] They usually require twice-a-day dosing, although a newer preparation (olopatadine) is effective when used once daily.

Interestingly, multiple studies have shown that the administration of intranasal steroids is effective in controlling ocular symptoms in seasonal allergic rhinitis.[347-350] In a meta-analysis comparing H_1 antihistamines with INSs, there was no difference in the efficacy of these two agent classes in the control of ocular symptoms, suggesting that INSs were at least as effective as H_1 antihistamines in the control of ocular symptoms in patients with allergic rhinitis.[300] Furthermore, another meta-analysis examining the findings from clinical trials that compared the effects of INSs and intranasal antihistamines on ocular symptoms in allergic rhinitis demonstrated no overall significant difference between the two treatment modalities.[301] The mechanism of this favorable effect of INSs is speculated to be reduced intranasal inflammation, which in turn inhibits the nasal ocular reflex initiated by allergen contact with the nasal mucosa.[196]

Combination Treatments

Combinations of drugs have been tested for treatment of allergic rhinitis, and results were partly covered in the discussions of decongestants and leukotriene modifiers. Additionally, the use of antihistamines, in various forms, with INSs has been investigated. Addition of intranasal azelastine to intranasal fluticasone propionate in patients with Texas mountain cedar allergic rhinitis showed a synergistic effect of the combination treatments in comparison with each agent alone in the control of nasal symptoms.[351] Studies on the combination of systemic H_1 antihistamines and INSs have reported variable results, with one study showing no additional benefit in the control of nasal symptoms for fluticasone and loratadine given in combination over fluticasone administered alone.[352] A similar study showed no palpable added benefit for the addition of cetirizine or montelukast to intranasal fluticasone propionate in comparison with the nasal spray alone for the control of seasonal allergic rhinitis.[353] Furthermore, in the same study, intranasal fluticasone propionate was more effective than the combination of cetirizine and montelukast. In an ocular allergen challenge study combining intranasal fluticasone propionate and intraocular olopatadine produced significantly greater improvements in ocular itching after challenge than the combination of fluticasone and fexofenadine.[354] Finally, an older study showed additive efficacy of intranasal beclomethasone and ipratropium bromide in comparison with the individual agents in the control of severity and duration of rhinorrhea in perennial rhinitis.[355] It is common in clinical practice to use combination treatments in patients with symptoms that are difficult to control; these treatments typically include an INS with an additional agent such as an H_1 antihistamine (systemic, intranasal, or intraocular) or a leukotriene modifier.

General Treatment Planning

Various organizations have published guidelines for the management of allergic rhinitis, including a joint effort by the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology[356]; ARIA[265,357]; and the Global Allergy and Asthma European Network (GA2LEN).[358] The interested reader is referred to these publications for more detail. We have tried to keep the discussion of management simple and recommend the following general guidelines for the treatment of allergic rhinitis. If disease is mild, we treat with as-needed (PRN) intransasal steroids, and if it is moderate to severe, we recommend the regular use of INSs. If patients are not willing to use an intranasal medication, or are bothered by local irritation, we recommend treatment with antihistamines.

We generally reevaluate patients after 2 weeks to assess the response to therapy. If they have an excellent response, we consider their anticipated exposure and treat accordingly. If there is a partial response, we identify residual complaints and add agents targeting these symptoms. For residual eye symptoms, we treat with intraocular antihistamines/mast cell stabilizers. If there is significant redness of the eye, we refer the patient to an ophthalmologist. For residual nasal congestion, we consider the addition of an antihistamine decongestant combination or montelukast. For residual rhinorrhea, we consider adding

ipratropium bromide. If the patients do not improve after maximal medical therapy, we reconsider the diagnosis. If they have significant perennial disease and have no response to maximal medical treatment, we evaluate the patients for immunotherapy. We do not routinely perform allergy testing unless immunotherapy is planned, because avoidance is great in theory but not proven in practice.

We also consider special patient groups. In pregnant women, we use budesonide as the INS of choice and loratadine, cetirizine, and levocetirizine as the antihistamines of choice, because these agents are all considered pregnancy category B agents by the FDA. In the elderly, we avoid sedating antihistamines because of the increased risks of falls in such patients. In competitive athletes, systemic decongestants are banned substances and are therefore avoided. In patients taking ritonavir, an inhibitor of human immunodeficiency virus protease, and potentially other protease inhibitors, we avoid INSs. Concomitant use of ritonavir and intranasal/inhaled fluticasone propionate may increase plasma concentrations of fluticasone, resulting in possible systemic corticosteroid effects and adrenal suppression with reduced serum cortisol concentrations.[359] In patients taking protease inhibitors, safer options appear to be budesonide, triamcinolone, and flunisolide.[359]

Conclusion

This chapter provides an overview of immunology of the upper airway and discusses innate and adaptive immunity as well as cell-mediated immune responses. As a model of an immunologic disease involving IgE antibodies to foreign substances, allergic rhinitis, an important and frequently encountered disease in otolaryngology practices, is also discussed. A detailed review of the pathophysiology, diagnosis, and treatment options of this disease are presented.

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CHAPTER FORTY-ONE

Physiology of Olfaction

Donald A. Leopold

Eric H. Holbrook

Key Points

- The olfactory epithelium is a pseudostratified columnar neuroepithelium containing supporting cells, bipolar olfactory receptor neurons, and dividing basal cells located in the superior cleft between the middle and superior turbinates and the septum.
- The axons extending from the receptor neurons coalesce into bundles (cranial nerve I) that travel through the cribriform plate to make primary synapses with the olfactory bulb.
- As identified in rodents, an olfactory map exists in which individual odorant receptor types that are randomly distributed among zones within the olfactory mucosa converge to form synapses in specific glomeruli. This receptor map formation appears to extend to higher processing centers.
- Multiple testing mechanisms for olfactory ability exist and are commercially available and accessible for all physicians. Testing allows for an assessment of extent of olfactory loss and measures change in ability over time.
- The most common reasons for olfactory loss include chronic rhinosinusitis and polyps, upper respiratory infections, head trauma, and aging. Patient history is extremely important in determining etiology of olfactory disorders.
- Patchy replacement of olfactory mucosa with respiratory epithelium appears to be common with aging. Alzheimer's disease is closely correlated with olfactory loss independent of aging.
- Chronic rhinosinusitis can cause both a conductive loss of olfaction and a sensorineural loss. Nasal endoscopy is extremely useful in assessing obstruction of the olfactory cleft.
- Computed tomography scans are helpful in assessing conductive losses and chronic rhinosinusitis. Magnetic resonance imaging can be helpful if there are neurologic signs suggesting mass lesion or neurodegenerative disease.
- Available therapies for olfactory disorders continue to be limited. Patient support and counseling of hazards associated with the loss of smell are an important part of the patient visit.

The perception of odors adds a quality to life that is difficult to express. Odors are part of our everyday life, from the pleasures of perfume, to the satisfactions of toast and coffee, to the warnings of skunks and fire. As the molecules of substances are transported through the nose, the possibility of their being perceived occurs. The quality and intensity of that perception depend on the anatomic state of the nasal epithelium and the status of the peripheral and central nervous systems.

This chapter explores the physiology of olfaction, noting pertinent research data. The initial discussion focuses on the pathways and obstacles that odorant molecules must negotiate as they come in contact with the olfactory receptor cells. A consideration of the neural processing of odorant stimulation and the pathways projecting to the brain gives some insight into the mechanisms underlying olfactory perception. Olfactory testing explores the assessment and method of this perception. The chapter ends with a section on clinical olfactory problems in humans and includes suggestions for their diagnosis and management.

The study of olfaction poses many tantalizing questions. For example, do humans, like many animal species, communicate through odorant signals (pheromones)? Why are primary olfactory receptor cells able to regenerate entirely but other special sensory primary neurons are not? Can olfactory tissue be transplanted in humans as demonstrated in rodents? The study of olfaction has attracted the attention of researchers in the fields of endocrinology, anatomy, biochemistry, neurophysiology, and others. Through these efforts, the ability to diagnose and help individuals with chemosensory problems is improving.

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Anatomy of Olfactory Stimulation

Nasal Passageways

Experiencing an odor is a result of input from the olfactory, trigeminal, glossopharyngeal, and vagus nerves. Apparently, the properties of any given odorant determine the particular "mix" of these various inputs. Olfactory nerve (cranial nerve I) stimulation, which is necessary for identification of most odorants, depends on the odorant molecules' reaching the olfactory mucosa at the top of the nasal cavity. Although molecules can reach the olfactory cleft by diffusion, essentially olfaction requires some type of nasal airflow, usually as part of inhalation (orthonasal flow). During eating, there is a retronasal flow of odorant molecules that stimulate the olfactory receptors at the top of the nose and contribute greatly to the flavor of the food.[1,2] This airflow can be very small, such as that generated by the mouth and pharyngeal motion.[3-5] Additional data from a large-scale model indicate that at physiologic airflow rates, approximately 50% of the total airflow passes through the middle meatus, with approximately 35% flowing through the inferior meatus (Fig. 41-1). About 15% flows through the olfactory region.[6]

Mathematical models of the nose, created from digitized computed tomography (CT) anatomy slices and predicted mass transport

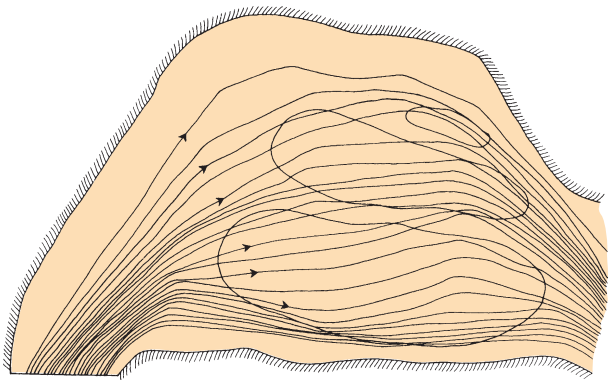

Figure 41-1. Streamline patterns for resting inspiratory flow (250 mL/sec) through an expanded (20× normal size) scale model of a healthy human adult male nasal cavity (sagittal view). *Lines* show the paths taken by small dust particles entering at the external nares. *(From Scherer PW, Scherer PW, Hahn II, Mozell MM. The biophysics of nasal airflow.* Otolaryngol Clin North Am. *1989;22:265.)*

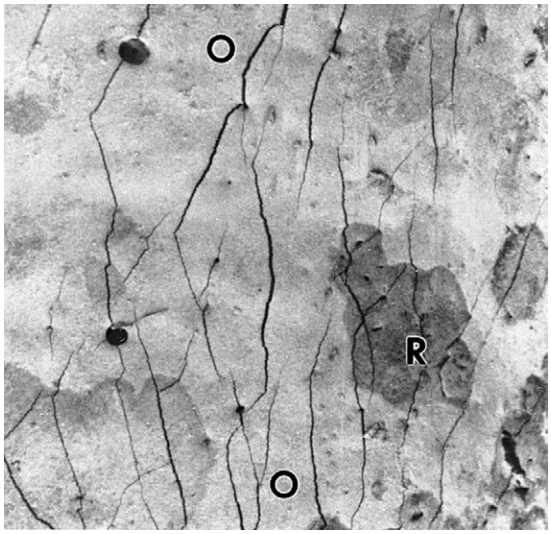

Figure 41-2. Low magnification of the surface of the nasal cavity taken from a transition region. Patches of respiratory (R) epithelium (*dark areas*) can be seen within the olfactory (O) region (×28). *(From Morrison EE, Costanzo RM. Morphology of the human olfactory epithelium.* J Comp Neurol. *1990;297:1, Copyright 1990. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons.)*

functions, can predict odor intensity for varying amounts of olfactory epithelium, the character of the carrier gas, and the solubility of the odorant molecules.[7-9] These theoretical results show agreement with human and animal experimental data.

The effect of a rapid change in flow velocity, such as with a sniff, on the in vivo airflow pattern remains unknown. Scherer and colleagues[6] have found in their large-scale model studies that the percentage and velocity of airflow to the olfactory region are similar for various steady-state airflow rates in the physiologic range. The fact remains, however, that sniffing is an almost universally performed maneuver when a person is presented with an olfactory stimulus. It is possible that its purpose is to momentarily increase the number of olfactory molecules in the olfactory cleft by means of a transient change in the airflow pattern of the nose. A sniff also may allow the trigeminal nerve to alert the central olfactory neurons that an odorant is coming. Sniffing duration, flow velocity, and volume are quite different among subjects but remain remarkably constant for any one subject.[10] Furthermore, Laing[11] has shown that different sniffing paradigms do not improve a subject's olfactory perception. The naturally chosen sniff seems to be optimal for that subject's nasal anatomy.

For molecules to reach the olfactory area, they must pass through the tall but narrow nasal passageways. The epithelium lining the walls of these passageways is wet, has variable thickness, and is aerodynamically "rough." Schneider and Wolf[12] have observed that olfactory ability is best when this epithelium is moderately congested, wet, and red, such as during an upper respiratory infection. Furthermore, olfactory ability seems to improve with narrowed nasal chambers,[13,14] but the changes in nasal patency that occur during the natural rhythmic engorgement and thinning of the nasal epithelium (nasal cycle)[15] do not have any effect on olfactory ability.[16-18]

The sorption of molecules to these mucus-lined walls extracts some of them from the air stream and increases their travel time. This process could influence the spectrum of chemicals reaching the olfactory cleft or spread their arrival over time. Moncrieff[19] described this phenomenon in the variable times required for odorants to traverse the nasal passageways of sheep. The sorption of molecules may separate or sort the odorants before they reach the olfactory mucosa. Highly sorbable chemicals may have minimal or no odor simply because they sorb to the nasal walls before they reach the olfactory cleft, thereby accentuating the trigeminal component. Could it be that our world would smell different if we had no external nose to lengthen the path of the olfactory region? Does an animal with a long snout, such as the dog, smell the world differently as a result of these sorptive effects?

Olfactory Mucus

After the odorant molecules reach the olfactory region, they must interact with the mucus overlying the receptor cells. The mucus apparently comes from both Bowman's glands deep in the lamina propria (only of serous type in humans)[20,21] and the adjacent respiratory mucosa (goblet cells). Researchers have observed that the supporting (sustentacular) cells of the human olfactory epithelium are not histologically equipped to secrete mucus.[21-23] The supporting cells of most other species, however, do secrete mucus, often in response to odorants.[20,24-26]

The partitioning of an odorant's molecules between the air phase and the mucus phase is most certainly another determinant of its being perceived. To reach the olfactory receptors, the odorant molecules must be soluble in the mucus but, as Laffort and associates[27] argue, not so "strongly captured" that they are unable to interact with the receptors. In addition, changes in the thickness or composition of the mucus can influence the diffusion time required for odorant molecules to reach the receptor sites.[28] Adrenergic, cholinergic, and peptidergic agents have caused these changes in the mucus overlying the olfactory receptors through their effects on the secretory activities of the mucosal glands. Moreover, these same agents have influenced the sensitivity of the olfactory receptor cells themselves.[29-31]

Once in the olfactory mucus-epithelial system, the rate at which the odorant is cleared also is important. Hornung and Mozell[32] showed that 79% of a radioactively labeled odorant (butanol) remained trapped in the mucus 30 minutes after inspiratory exposure, whereas radioactively labeled octane cleared rapidly. The mucus may exert a differential role in deactivating, removing, or desorbing odorants from the olfactory area.

Olfactory Epithelium

Located 7 cm inside the nasal cavity, the olfactory sensory neurons are protected in a 1-mm-wide crevice of the posterosuperior nose. At the epithelial surface, these bipolar neurons are exposed to the outside world through their dendrites and cilia. Proximally, axons of these same neurons synapse at the base of the brain (olfactory bulb). Although the olfactory receptor region is a solid sheet of olfactory mucosa housed in a protected environment in human fetuses and laboratory animals, a number of research groups have shown that there is mixing of olfactory and respiratory epithelial tissues in adult humans (Fig. 41-2).[22,33-36] The number of these clumps of respiratory epithelium, which are found in the olfactory area, increases with age, suggesting that a loss of primary olfactory neurons at least partially explains the decreased olfactory ability associated with aging.[37]

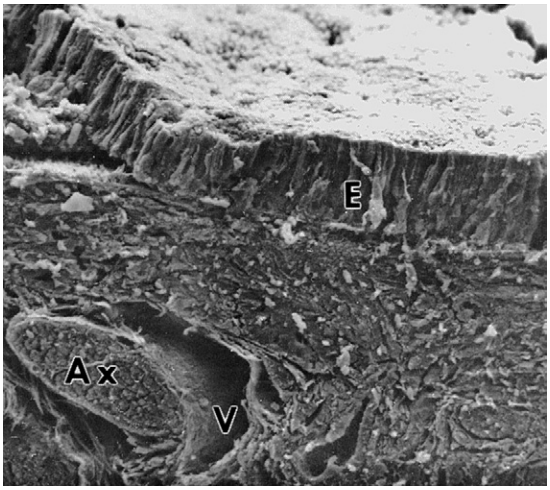

Figure 41-3. Low-power three-dimensional scanning view of the olfactory epithelium and lamina propria. The olfactory epithelium (E) overlies a thick connective tissue lamina propria that contains olfactory axon fascicles (A x) and blood vessels (V) (×248). *(From Morrison EE, Costanzo RM. Morphology of the human olfactory epithelium.* J Comp Neurol. *1990;297:1. Copyright 1990. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons.)*

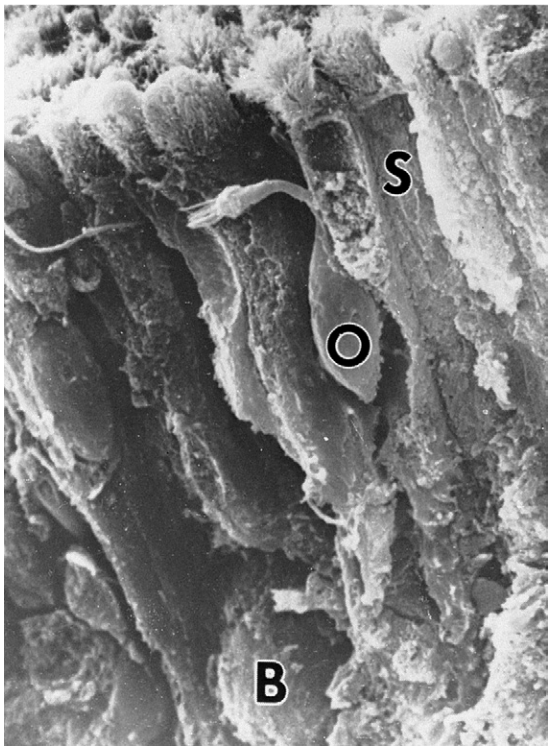

Figure 41-4. Cross-sectional view of the olfactory epithelium showing the columnar supporting cells (S) that extend the full length of the epithelium. An olfactory neuron (O) with its dendrite and basal cell (B) can be seen among supporting cells (×1241). *(From Morrison EE, Costanzo RM. Morphology of the human olfactory epithelium.* J Comp Neurol. *1990;297:1. Copyright 1990. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons.)*

The human olfactory epithelium covers an area of roughly 1 cm^2 on each side. The epithelium is pseudostratified columnar, and it rests on a vascular lamina propria with no submucosa (Fig. 41-3). In most mammals studied, four main cell types have been identified (Figs. 41-4 and 41-5): ciliated olfactory receptors, microvillar cells, supporting (sustentacular) cells, and basal cells.[22,23,35,38] Research that uses immunohistochemical staining of olfactory elements continues to provide information on growth, maturation, function of specific cellular elements, and similarities with other neural tissue.[39-45] One possible use for this technique may be to clarify the etiology of the patient's olfactory dysfunction and possibly offer a prognosis regarding improvement of olfactory ability.[18,46] Equally important to analysis of the epithelium is the evaluation of the olfactory axon bundles that travel within the lamina propria of the mucosa. Given that these bundles arise from receptor neurons distributed along a region of the epithelium, the identification of mature olfactory axons in comparison with the abundance of immature axons or collagen replacement within these bundles suggests a healthy functional olfactory mucosa. This may be a truer representation of the status of the epithelium as a whole than what can be deduced from analysis of the epithelial surface alone in a small biopsy specimen.[47]

The olfactory receptor neuron is bipolar and has a club-shaped peripheral "knob" that bears the cilia (Fig. 41-6). The surface of human olfactory epithelium is covered with cilia extending from the dendritic knobs of olfactory receptor neurons, but two electron microscopic studies show that there are no dynein arms on these cilia.[21,23] The researchers in these studies conclude from this observation that neither dynein arms nor motility is essential for human olfaction. After widening for the nucleus, the olfactory receptor neuron tapers to a long, thin, nonmyelinated axon that can travel several centimeters to the olfactory bulb. Bundles of these fibers form in the lamina propria and become surrounded as a group by the plasma membranes of the Schwann-type ensheathing cells, forming the olfactory nerve (cranial nerve I), which traverses the 15 to 20 foramina in the cribriform plate to synapse in the bulb. Allison and Warwick[48] estimate the rabbit to have approximately 50 million olfactory axons, whereas Jafek[21] estimates humans to have only 6 million bilaterally.

The olfactory ensheathing cells are unique in that they share characteristics that are common with Schwann cells and central glial cells. Because olfactory neurons have the ability to regenerate and make functional synapses with the olfactory bulb, there has been interest in the role of the ensheathing cells in this process and its possible therapeutic potential for repair of peripheral neuronal injury. The glial-type cells that ensheathe olfactory neurons support axonal growth of both olfactory and nonolfactory neurons.[49] Because of their ability to promote long-distance growth of regenerating axons in vivo and their ability to remyelinate axons of the adult mammalian spinal cord, these cells have received great interest as potential agents for reversing spinal cord injuries and demyelinating diseases.[50] Guntinas-Lichius and others[51] compared transplants of olfactory mucosa with buccal mucosa laid over a primary reanastomosis of the facial nerve in rats. Use of the olfactory mucosa resulted in better vibrissal movements, less branching of motor neurons, and greater accuracy of reinnervation.

The microvillar cell occurs about one tenth as often as the ciliated olfactory neurons.[21,22] The cell body is flask-shaped, is located near the epithelial surface, and has an apical membrane containing microvilli that project into the mucus overlying the epithelium (see Fig. 41-5).[23,52] The deep end of the cell tapers to a thin, axon-like cytoplasmic projection that proceeds into the lamina propria. Although there is no electrophysiologic evidence that these cells respond to chemical stimuli, Rowley and others[38] have hypothesized that the cells are a morphologically distinct class of sensory receptors. The evidence for this hypothesis is the backfilling of a cytochemical tracer macromolecule (horseradish peroxidase) into the ciliated olfactory receptors and the microvillar cells when it is injected into the olfactory bulb.

In among these two receptor-type cells are the supporting or sustentacular cells. These tall cells have an apical membrane that joins tightly with the surface of the receptor cells and the microvillar cells. They seem positioned to separate the receptor cells from each other; however, intimate apposition between receptor cells does occur.[21-23] Whether this proximity allows some receptor cells to influence each other's firing patterns is unknown. Sustentacular cells do not generate

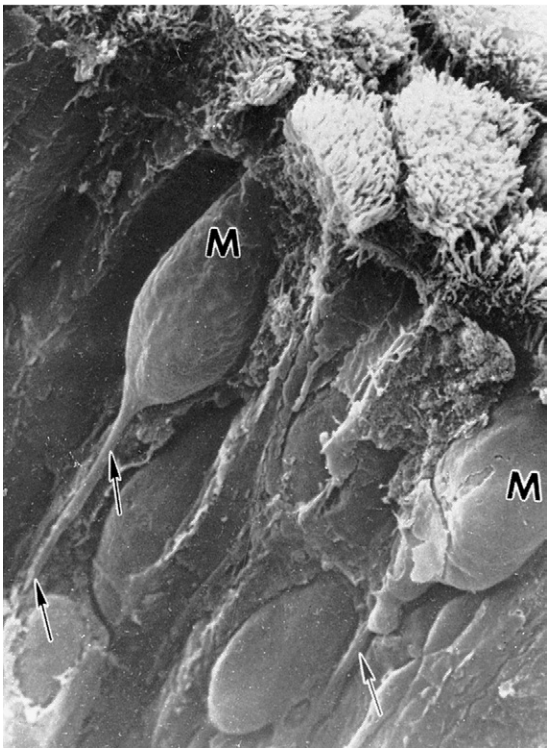

Figure 41-5. Low-power magnification of fractured olfactory epithelium illustrating the axon-like processes (*arrows*) from microvillar cells (M), which extend basally between supporting cells (×3060). *(From Morrison EE, Costanzo RM. Morphology of the human olfactory epithelium. J* Comp Neurol. *1990;297:1. Copyright 1990. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons.)*

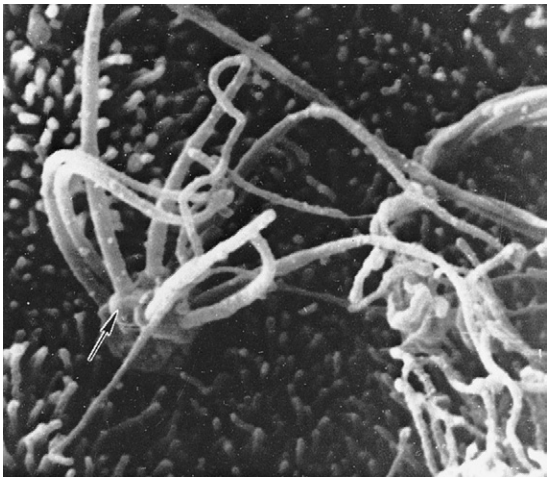

Figure 41-6. High-power magnification of an olfactory knob with long cilia gradually tapering as they extend over the epithelial surface. At the base of individual cilia, a necklace-like structure (*arrow*) can be seen on the surface of the olfactory knob (×14,220). *(From Morrison EE, Costanzo RM. Morphology of the human olfactory epithelium.* J Comp Neurol. *1990;297:1. Copyright 1990. Reprinted by permission of Wiley-Liss, a division of John Wiley & Sons.)*

action potentials, nor are they electrically coupled to each other[53,54]; thus, they do not seem to contribute directly to the olfactory transduction process and the elicitation of generator potentials by odorant stimuli. However, they do appear to play a role in ion and water regulation[55] and, along with Bowman's gland duct cells, contain xenobiotic

Figure 41-7. Photograph from the right nasal cavity demonstrating the vomeronasal organ "pit" in the right central part of the image; it is on the anterior septum. Note the inferior turbinate and floor of the nose to the left.

enzymes such as cytochrome P-450 that likely contribute to odorant metabolism.[56]

Deep to all of these cells, the basal cells sit along the basal lamina. The basal cells are divided into two groups of replicating cells. The horizontal basal cells are just above the basal lamina, and the globose basal cells are positioned between the horizontal basal cells and immature neurons. The globose basal cells seem to be responsible for the continuous replacement of olfactory receptor neurons; however, during severe insult, they may repopulate the nonneuronal components of the epithelium as well.[57-60] This function identifies the globose basal cell as the bona fide stem cell located within the olfactory mucosa, but new evidence for the horizontal basal cell as the neural stem cell has also been presented.[61] The ongoing renewal of these special sensory neurons is not known to occur in other sensory systems. The replication cycle is between 3 and 7 weeks.[62,63] When the new receptor cell forms, it also projects its axon to the olfactory bulb, where it synapses with second-order neurons, thereby ensuring continual olfactory function and continual olfactory neuron replacement.

Vomeronasal Organ

Many mammals have an identifiable pit or groove in the anteroinferior part of the nasal septum that contains chemosensitive cells.[64] In most of these animals, a nerve can be identified connecting these cells to the central nervous system, often to an accessory olfactory bulb. In some situations, this system has been receptive to pheromones.[65] There have been investigations into the possibility that humans have some type of vomeronasal system.[66] Biopsy studies of the nasal mucosa in the small pit often seen along the anteroinferior nasal septum (Jacobson's organ) show olfactory-like histology but no central connection (Fig. 41-7). Electrophysiologic studies have shown negative action potentials from this vomeronasal area in response to specific chemical stimuli but without a subjective response from individuals tested.[67] These same stimuli did not cause negative potentials in the olfactory system. Similar electrical activity elicited by certain compounds directly delivered to the vomeronasal area has been shown to cause changes in blood pressure, heart rate, and hormonal levels.[68] Because no identified central brain connection seems to exist, and an accessory olfactory bulb seen in other mammals has never been identified in humans, it is possible that this system functions as a neuroendocrine system, emitting a substance in response to a specific chemical stimulus. Positron emission tomography (PET) scanning after presentation of a putative pheromone show detection of the compound executed in higher cortical regions different from those usually activated in the perception of odors, and in contrast to PET scanning results in the olfactory system, responses to the putative pheromone show gender differences.[69] *V2R* genes encoding for vomeronasal receptors have been found in mammals; however, in humans putative vomeronasal receptors are nonfunction-

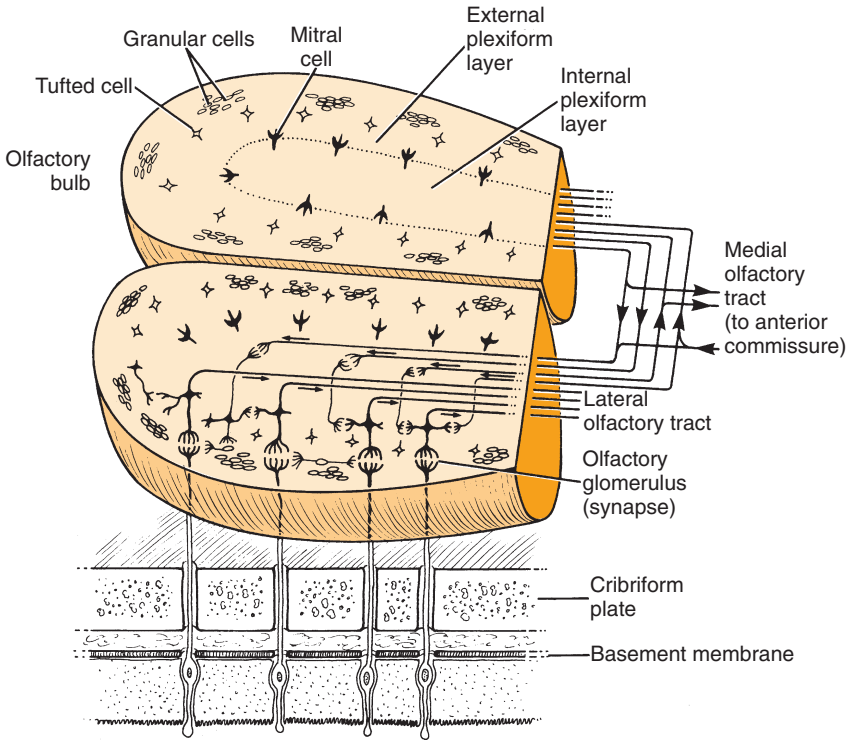

Figure 41-8. Structure of olfactory bulbs and their neural connections to one another, the olfactory mucosa, and the brain.

ing pseudogenes.[70] It may be that human vomeronasal receptors are unrelated to olfaction and that other mammalian receptors have yet to be identified. Genetic, biochemical, and electrophysiologic data now suggest that some pheromone-based behaviors in vertebrates are mediated through the main olfactory epithelium.[71,72] At present, no good evidence for symptom-related importance of the human vomeronasal organ exists, but prudence suggests that this anatomic area should not be disturbed during surgery unless it is necessary.[73]

Olfactory Bulb

The olfactory bulb lies at the base of the frontal cortex in the anterior fossa (Fig. 41-8). It serves as the first relay station in the olfactory pathway, where the primary olfactory neurons synapse with secondary neurons. These synapses and their postsynaptic partners form dense aggregates of neuropil called *glomeruli*. In humans, projections of mature olfactory axons into the bulb end in glomeruli as well, but misrouted projections commonly occur, usually into the external plexiform layer.[74] In the adult rabbit, approximately 26,000 olfactory axons enter each glomerulus, where they contact roughly 100 second-order neurons.[75] This relationship indicates a considerable convergence of information, because these neurons pass from the periphery onto this first central station. (The interconnections among the various glomeruli in one bulb, the interconnections between bulbs, and the afferent and efferent connections with the brain indicate that considerable processing also occurs at the bulb level.)

The neuronal projection of the olfactory mucosa onto the bulb displays some anatomic restrictions but is not strictly point-to-point. In other words, a given region of the bulb receives its most dense input from a particular region of the mucosa,[76] but inputs to a particular region of the bulb converge from many receptor cells distributed throughout a certain zone of the mucosa.[77] Conversely, a small focus in the epithelium projects widely, but within a restrictive region of the bulb.[78] These dense and diffuse inputs possibly represent excitatory and inhibitory influences, which, as in other sensory systems, narrow the neural stimulus representation as the processing moves centrally. Alternatively, the convergence and divergence of projections from neurons in the epithelium may serve to coalesce inputs from receptor cells of sensitivity to odorants. Evidence to support this notion emerges from the coherent activation of single glomeruli or sets of glomeruli by specified odorants.[79,80] Therefore, it is clear that the microcircuitry of the bulb is specialized to narrow the spatial pattern of the glomerular activation elicited by an odorant or mixture of odorants.

In line with the regenerative capacity of the olfactory epithelium, there is a mechanism for neuronal replacement in the olfactory bulb. In mammals, the olfactory bulb is closely associated with dividing cells in the lateral ventricles that migrate via the rostral migratory stream (RMS) into the bulb and become mature neurons. In humans, the rostral migratory stream appears to be located around an extension of the lateral ventricle into the olfactory bulb, and at least some of the cells derived from the stream relocate to the periglomerular region.[81]

Olfactory Connections in the Brain

The more central olfactory connections include the olfactory tubercle, the prepiriform cortex, part of the amygdaloid nuclei, and the nucleus of the terminal stria, with further projections to a number of structures, including the hypothalamus. Although these structures receive olfactory input, they also serve other functions, such as food intake, temperature regulation, sleeping cycles, vision, memory, hearing, and taste. These connections may explain the strong memories and emotional context of various odors. It also is possible that these structures influence the olfactory process by efferent connections.[82,83]

The organization of like olfactory receptors projecting into the olfactory bulb with the formation of an olfactory map (described later) appears to also occur to some degree in higher cortical areas. In mice, single odorants activate distinct patterns in the anterior piriform cortex. Exposure to different odorants results in different but overlapping maps of activity in the piriform cortex that are similar in individual mice. Odors that are related in structure also stimulate similar patterns of activity within the piriform cortex. These findings suggest an organization of axonal projection and stimulation in response to odorant stimulation within the cortex.[84]

Common Chemical Sense

Free nerve endings of three cranial nerves—trigeminal (the most important), glossopharyngeal, and vagus—provide added chemoreceptivity in the mucosa of the respiratory tract.[85,86] The trigeminal nerves are

sensitive to the burn of ammonia and the bite of hot pepper. In the nose, virtually all odorants stimulate olfactory and trigeminal nerves, even when no apparent pungency can be perceived. The peripheral anatomic pathways for these cranial nerves have long been known; however, the central connections that allow their interaction and how they interrelate with other senses are just beginning to be determined.[85,87,88] Cometto-Muniz and Cain[89] have shown that when tested with ammonia, the common chemical sense behaves more like a total-mass detector than a concentration detector (i.e., at a given concentration, the perceived magnitude increases with the time of presentation). It is even possible that the trigeminal nerve interprets pungent or chemically irritative stimuli as being painful or nociceptive in nature.

Olfactory Transduction and Coding

At each level of the olfactory system, different factors control or shape how the system works. The nose has narrow passageways lined by wet mucus and swept by alternating air currents. The hydrophilic olfactory mucus presents the incoming odorant molecules with constraints of sorption, solubility, and chemical reactivity. Once the odorant molecule is dissolved in the olfactory mucus, another group of events influences whether it can interact with the olfactory receptor cells. Soluble binding proteins, like odorant-binding protein, have been described in air-breathing vertebrates, and it has been suggested that these proteins enhance the access of odorants to the olfactory receptors.[90-94] This enhancement is said to be accomplished by binding and solubilizing of hydrophobic odorant molecules, thus increasing their concentration in the environment of the receptor cell by as much as 1000 to 10,000 times more than their concentration in the ambient air.[95,96] In addition, these same odorant-binding protein molecules may act to remove odorant molecules from the region of the receptor cell after transduction. Other workers, however, have suggested that mammalian odorant-binding protein is too slow to be able to bind and release the odorant in the mucus.[97,98] They conclude that the role of odorant-binding proteins is purely hypothetical and most likely not related to odor protein transport. It also is possible that the olfactory systems of air-breathing vertebrates may have a chemical-sensing system like that of unicellular and multicellular organisms. This system can produce degradative enzymes that transform stimulants into inactive products, and vice versa.[99] Therefore, many perireceptor events occur in the olfactory mucus before the odorant actually comes into contact with the cilia of the olfactory receptor cell.

In mammals, it is generally accepted that the actual transformation of odorant chemical information into an electrical action potential occurs as a result of specific interactions between odorant molecules and receptor proteins on the surface of olfactory cilia.[100,101] At least the first stages of odorant discrimination occur at the primary neuron level.[102-104] This process is mediated by a family of approximately 1000 genes encoding for variations of a seven–transmembrane domain receptor protein.[19] The human genome is composed of approximately 30,000 genes, thus making the olfactory receptors the largest gene family in the entire genome.

As this transduction process moves through the receptor cell membrane, several second-messenger systems assist in depolarizing the cell and initiating the action potential. Patch clamp recordings have demonstrated that cyclic adenosine monophosphate (cAMP) and inositol phosphate (IP_3) are the primary signaling pathways that can mediate olfactory transduction, depending on the species and the odorants.[102,105] In mammals, the olfactory receptors are members of G protein–coupled receptors (G_{olf}), and this G protein seems to be exclusively localized to the olfactory epithelium.[106] With the binding of the receptor to an odorant, adenylate cyclase is activated by G_{olf} and converts adenosine triphosphate (ATP) into cAMP. The cAMP then binds to a Na,Ca ion channel to allow influx of these ions. As more channels open, the cell depolarizes, and an action potential is produced (Fig. 41-9). Clinical evidence supporting the cAMP pathway comes from patients with type 1a pseudohypoparathyroidism, who have a deficiency in stimulatory G_{olf}, which is needed for the second messenger transduction, and also have olfactory losses.[107-109] With high doses of odorant, and in other parts of the olfactory pathway (like the olfactory bulb), another second messenger system involving nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) has been identified.[110,111]

Once the peripheral olfactory receptor cells are depolarized, there begins a convergence of electrical information toward the olfactory bulb. In the nasal cavity, a broad, genetically determined pattern of organization is emerging that becomes more specific as the information is passed through the glomeruli and mitral/tufted cells of the olfactory bulb.[104,112,113] How that electrical information is coded for the thousands of odorants that can be recognized and discriminated is just beginning to be understood. In the mid–20th century, Adrian[114-119] suggested several mechanisms on the basis of his electrophysiologic recordings. Taken together, all of these mechanisms could produce different activity patterns across the mucosa, which would explain the different activity patterns he observed from anterior and posterior locations in the bulb. One mechanism is the odorant-selective sensitivity of the individual receptors, such that incoming odorants would excite different patterns of receptors along the mucosal surface. A second mechanism extends this concept, suggesting that receptors of like sensitivity are aggregated into particular regions of the mucosa, thus giving a different spatial representation for each odorant. The final mechanism Adrian suggests proposes that each odorant, having different physiochemical properties such as solubility, would spread differentially both

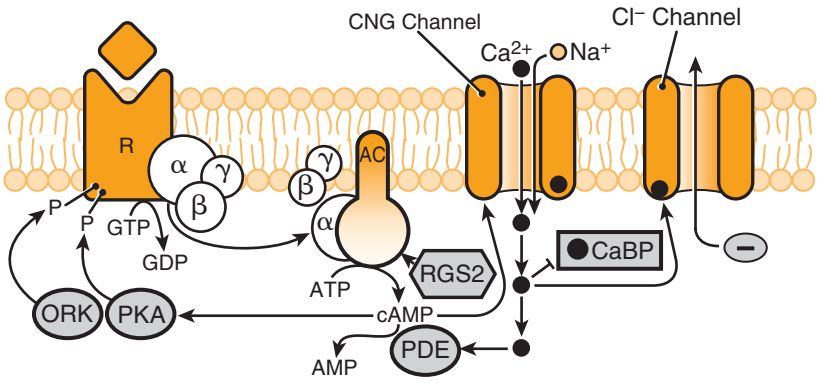

Figure 41-9. A diagram of the cascade of enzymatic activity transducing the binding of an odorant molecule to a receptor into an electric signal that can be transmitted to the brain. AC, adenylyl cyclase; ATP, adenosine triphosphate; CaBP, calmodulin-binding protein; cAMP, cyclic adenosine monophosphate; CNG channel, cyclic nucleotide–gated channel; ORK, olfactory receptor kinase; PDE, phosphodiesterase; PKA, protein kinase A; RGS, regulator of G proteins (but here acts on the AC). *Arrows* indicate stimulatory and inhibitory (feedback) pathways. *(From Firestein S. How the olfactory system makes sense of scents.* Nature. *2001;413:211.* Reprinted by permission from Macmillan Publishers Ltd.)

in time and space across the mucosal sheet. Adrian's proposals have been supported by later investigators.

Over the years, evidence for an olfactory odor map has been growing. Besides the electrophysiologic evidence described previously, anatomic evidence comes from special patterns identified through horseradish peroxidase tracing of receptor neurons to the bulb[120] and the discovery of differential cell adhesion molecules specific to olfactory axon pathways leading to the olfactory bulb.[121,122] However, genetic advances have helped solidify the argument for odor maps. It is now known that the olfactory epithelium of the mouse is roughly divided into four zones. Each zone contains a group of different olfactory receptor subtypes that seem to be confined within the designated zone. These zones are then reproduced by receptor projections to the olfactory bulb. What is more amazing is that the axons from each identical olfactory receptor subtype converge and synapse with mitral cells within only a few glomeruli of each olfactory bulb. Therefore, a specific odorant may activate certain olfactory receptor types that then send signals to specific glomeruli and create a pattern of activity much like patterns of other sensory systems in the brain.[123-125] Inability to perceive particular odorants (specific anosmia) has been associated with loss of specific odor receptor genes, yielding clinical evidence for receptor specificity of odorants.[113,126,127]

The contribution made by the central nervous system to olfactory coding and discrimination is unclear. It may be that the olfactory code is complete by the time it leaves the olfactory bulb. Alternatively, the code may need to be completed by additional central neural processing. Whatever the status of the olfactory code, it is clear that the central nervous system uses olfactory information for many purposes. One such purpose, for instance, is in the area of feeding. Glucose-sensitive cells in the lateral hypothalamus of the monkey integrate many chemosensory inputs from both endogenous and exogenous sources, whereas glucose-insensitive cells from the same area distinguish among fewer, more specific chemosensory cues to control food acquisition behavior.[128] In another area, the alpha 2 power on electroencephalogram (EEG) recording is increased after an unpleasant smell exposure (valeric acid) but not after a pleasant exposure (phenylethyl alcohol).[129]

Where the central nervous system processes and stores the olfactory information is also unclear. Studies on laterality have suggested that humans have a better side for olfactory ability.[14,130] Zatorre and Jones-Gotman[131] have suggested that the right side is the better one on the basis of their observation of no deficits in olfactory identification ability in patients after left central, parietal, and posterior brain excisions. This suggestion is supported by the finding that patients with right parietal and frontotemporal lesions have difficulty with the lateralization of odorants.[132] Brand and Jacquot,[133] who looked at electrodermal activity responses, showed a predominance of the right hemisphere in treatment of olfactory information that did not depend on quality of the odor and with no difference in the side of the nostril involved. Alternatively, Hong and coworkers[18] have correlated olfactory function with nasal anatomy by use of CT scanning. They learned that most people are using only their left side when perceiving olfactory information. Handedness may be a determinant of this trend,[134] or the preferred side may be related to learning. Both PET scanning and functional magnetic resonance imaging (MRI) have been used to look at brain responses to unilaterally and bilaterally presented odors. Many control measures must be instituted with these studies, because most odorants are not purely olfactory, and the introduction of trigeminal stimulation adds activation through contralateral inputs. In addition, the act of sniffing alone without an odorant present causes activation in certain higher brain centers, and the memory of an odorant activates others. It is not surprising that results have been inhomogeneous, but there tends to be more evidence for a right hemisphere dominance in olfactory functioning.[135,136]

Olfactory Cognition

Odors are understood largely on the basis of experience, and each person develops his or her own hedonic code within cultural restraints.[137-139] Odor associations, once established, are notoriously difficult to erase from memory,[83,140,141] even though the incident that formed the association is forgotten or seems irrational. In one study, odor memory was shown to last at least 1 year, whereas visual memory lasted only a few months.[83] Interestingly, odor memory is facilitated by bilateral nasal stimulation, suggesting that people who have one-sided nasal obstruction may form poorer odor memories.[142] An odor aversion can be formed to a perfectly good food by overindulgence. Similarly, becoming ill for another reason while eating an otherwise innocuous food can have the same effect.[83] This same phenomenon is used effectively in animal training, in which lithium chloride, an emetic, is given with food to induce an aversion. For many of these reasons, the memory system that exists for odors may be distinct from other memory systems.[142,143] The exciting molecular advances made in understanding olfactory transduction and coding suggest that learning and memory might also be a "hard-wired" system. The adaptive ability to meet specific biologic needs, like those described previously, require that no matter how the system is wired, it needs flexibility.[144]

Whether newborn human babies discriminate between pleasant and unpleasant odors or whether the sense of smell enters into their enjoyment of food is debatable.[83] They can, however, identify odorants that have biologic meaning. In one study, 30 women who had just given birth underwent washing of one breast, and their newborns were placed prone between their breasts; 22 of the 30 newborns selected the unwashed (odorous) breast.[145] Macfarlane[146] has shown that, by the age of 6 to 10 days, infants prefer a pad from their own mother's breast to one from a strange mother. Other studies have shown that between the ages of 3 and 5 years, odor perception plays a role in a child's attachment to his or her mother.[93] Between the ages of 2 and 7 years, children start to show odor preferences, which are similar to those of the adults living in the same area.[147-149] Nevertheless, the olfactory sensitivity of prepubescent children to specific odorants can be quite different from that of teenagers and adults.[150] All these observations of early human olfactory development have parallels in other mammals. Several researchers have suggested that this development is related to the marked growth that occurs in the neural circuitry of the olfactory epithelium and olfactory bulb from birth until adult size is reached.[151,152]

Pheromones, which are pervasive throughout the subhuman animal kingdom, are chemicals released by one member of a species and received by another member, resulting in a specific action or developmental process.[153] Thus, the male hamster knows whether the female is receptive to mating,[154,155] and the ant knows the trail laid by a conspecific to a particular food.[156] (A more complete listing of messages that are probably conveyed among mammals by means of olfaction is given in Box 41-1.[157,158]). The search for a human pheromone has been going on for many years, and various biologic odorants refined from human urine, axillary secretions, and vaginal secretions have been touted, often in the popular press, as being pheromones. Both anatomic and behavioral studies support the possibility of human communication through odorants (see earlier discussion of the vomeronasal organ); however, additional studies with double-blind techniques are needed before adequate conclusions can be made.[13,159-161] One example of the type of human biologic activity on which chemosensory control can be exerted is menstrual cycle synchrony. Russell and associates[162] placed a mixture of alcohol and underarm secretion from one woman on the upper-lip skin of five women subjects and alcohol only on the skin of six control women subjects. Over a period of 5 months, there was a statistically significant (0.01) greater tendency for menstrual synchrony with the woman who donated the axillary secretions among the experimental group than in the control group. Similarly, Preti and colleagues[163] applied male axillary extract on the upper lips of a group of women and observed changes in luteinizing hormone pulses. In addition, responses in these women to a mood scale indicated an overall reduction in tension and an increase in relaxation. These studies do not discriminate between activation of the olfactory and vomeronasal systems but argue for a chemosensory communication system that seems to occur in humans.

Liberles and Buck[164] have discovered a second family of odorant receptors that occur in the olfactory epithelium of mice and humans. These trace amine–associated receptors (TAARs) also communicate through G proteins, but are located in olfactory neurons that lack odorant receptors. The receptors detect various amines that are found in mouse urine and are important in pheromone related activity. This

Box 41-1

Types of Messages Conveyed by Mammals by Means of Olfaction

Age appraisal
Alarm
Attention seeking
Defense
Distress signaling
Encouraging approach
Frustration
Gender appraisal
Greeting
Gregariousness
Group membership appraisal
Identification with home range
Individual appraisal
Pain indication
Predator
Prey
Reproductive stage indication
Social status appraisal
Species membership
Submission
Territory marking
Trail marking
Warning

From Doty RI: Odor guided behavior in mammals. *Experientia*. 1986;42:257; and Mykytowycz R. The role of skin glands in mammalian communication. In: Johnston JW Jr. Moulton DG, Turk A, eds. *Advances in Chemoreception, Vol 1: Communication by Chemical Signals*. New York: Appleton-Century-Crofts, 1970.

would provide an explanation for pheromone-like activity in humans even with the lack of a centrally connected vomeronasal organ.

Stimulation and Measurement of Olfaction

For many years, the clinical evaluation of olfactory ability was simply to determine whether the patient could detect any odorant at all. However, just as this type of yes-or-no testing is no longer acceptable in the evaluation of vision or hearing, it also is not acceptable for olfactory evaluation. Careful clinical practice demands quantitative, repeatable tests that can be used to document olfactory ability during the course of medical management or over time. The two aspects of olfaction most commonly tested are threshold and identification ability. Of these, identification is more closely related to everyday olfactory functioning.

The measurement of the detection threshold attempts to quantify the most dilute concentration of a particular odorant that an individual can detect. The general format of this test is to use a series of bottles containing a range of concentrations in predetermined steps. Although pyridine and *n*-butyl alcohol (1-butanol) are two of the most widely used test chemicals because of their water solubility, easy identifiability, and history of successful use, phenylethyl alcohol, which has a roselike smell, may be a better choice, because it has less trigeminal reactivity.[165] The odorants are presented from lowest to highest concentration until the subject correctly identifies four odorants at a given concentration. This order of presentation avoids the adaptation (i.e., the loss of sensitivity from mere stimulation) that might occur if strong concentrations were to be used first.[166] In the test situation, the subject is presented with two bottles, one containing the odorant and the other a blank. The subject is asked to choose the bottle that contains the odorant (two-alternative, forced-choice procedure).[167,168] Discretion should be used, however, in the interpretation of olfactory detection threshold scores, because the test-retest reliability of this test has been reported to be low.[169,170]

Identification tests allow the subject to smell a number of odorants and name them correctly. The test is a suprathreshold test; that is, the stimuli are presented at a concentration above threshold that the subject considers normal for that odorant. In addition, identification tests presume normal cognitive ability. Without this ability, a low olfactory test score may be due to poor testing in someone with normal olfactory ability. Several versions of this test are available and commonly used. Cain and associates[171] have developed an identification test that is administered along with a threshold test. In this test, eight common household items (e.g., baby powder, coffee, Ivory soap) are presented to the subject in screw-top jars. The subject is graded on how many of the odorants he or she can identify correctly.

Doty and colleagues[172,173] have developed a method of testing identification ability using scratch-and-sniff booklets containing 40 microencapsulated odorants. This commercially available test is self-administered and can be either mailed to test subjects or used during the examination. Material accompanying the booklets allows percentile score ranking of test results by age and gender, which are known determinants of olfactory ability (see "Factors Affecting Olfactory Testing"). Because the subject is asked to choose the correct answer from a list of four possible answers, a chance performance would be 25% correct. Obviously, anyone scoring much less than this should be considered for malingering. The portability of the booklets, the freshness of the stimulus, and the fun of taking the test contribute to its popularity.

A simple olfactory screening test has been described that is available to all clinicians and is based on the ability to detect the odor of an opened alcohol pad. The patient is told to close the eyes, and the open pad is slowly brought closer to the nose. The patient notifies the test giver when an odor is detected, and the measured distance between the alcohol pad and the nose correlates with the extent of olfactory impairment.[174] The test has been able to differentiate hyposmic and anosmic patients and can be modified for unilateral testing.

In other parts of the world olfactory testing also is being performed, sometimes with one of the tests noted previously and sometimes with locally designed tests. In Japan, the standard test is the T & T olfactometer, which is a rack containing eight concentrations of five different odorants. From this test, both detection and recognition thresholds can be determined, and they are charted on a graph similar to an audiogram.[175] In Germany, an odorant identification forced-choice test that uses odorant-impregnated felt-tip pens has been developed (Sniffin' Sticks, Burghart Modizintechnik, Erlangen, Germany). It has the advantage of a long shelf-life, the ability to be reused, and short test administration times.[176]

It is well known that odorants reach the nasal olfactory receptors from the front through the nostrils (orthonasal stimulation) and from the back through the posterior choanae (retronasal stimulation). Pierce and Halpern,[177] using small film canister lids containing odorants that were placed on subjects' tongues, were able to test these two stimulation pathways separately and show that they are independent. Heilmann and coworkers[178] have developed a clinical testing kit to assess retronasal olfactory function with oral stimulus presentation. Testing of these two different routes has shown differential neural recruitment in the brain,[179] which may explain differences in flavor perception with route of odor presentation. With this new knowledge, an improved clinical test of human olfaction will need to ensure whether it is testing orthonasal olfaction, retronasal olfaction, or both.

Doty and colleagues[180] reviewed nine different olfactory tests, including tests of odor identification, discrimination, detection, memory, and suprathreshold intensity and pleasantness perception.[181] Using a principal components analysis, they were able to determine that most of these tests measure a common source of variance. This result is borne out in clinical practice, in which it is rare to find a major discrepancy between olfactory tests.

For all these olfactory tests, especially those measuring threshold, control of stimulus concentration is obviously important. In general, the two main techniques to control or vary odorant concentration are (1) dilution of the liquid-phase odorant in varying amounts of solvent and (2) dilution of the vapor-phase odorant with air. Racks of sniff

bottles can be designed with a gradient of concentrations. Although they are conveniently portable, the liquids can become contaminated by oxidation, or the odorant concentration can be changed by oxidation or evaporation.[181] Therefore, the solutions must be changed frequently when open-bottle tests are used. More precise control over the stimulus intensity has been achieved with a variety of olfactometers. With mixing of pure air and odorized air streams, the odorant concentrations reaching the nose can be precisely controlled. Although these olfactometers are quite accurate in the control of the stimulus, their cost and size have restricted their use to research laboratories.

In an attempt to circumvent the problems of the air stream–delivered stimulus, some Japanese researchers have included intravenous smell testing in their olfactory evaluation.[182] In such a test, the subject is asked to perceive the mercaptan (garlic) smell of injected Alinamin, a thiol-type derivative of vitamin B_1. The time between the injection and the recognition of the smell is designated as the latent time, and the time between the recognition and the disappearance of the smell as the duration time. The researchers report that the latent time is influenced by olfactory acuity and that the duration time depends on adaptation to the odorant. Central olfactory disorders are suspected in patients with decreased duration times, and nonresponders to this test are said to have a poor prognosis for olfactory recovery. Although it is tantalizing to speculate that this intravenous test directly stimulates the olfactory receptor cells through the blood stream, studies by Okabe[183] indicate that the mechanism of the test by the discharge of Alinamin's metabolic by-products from the blood stream into the pulmonary alveoli, from which it reaches the olfactory receptors via the nasopharynx through the exhaled air stream.

A problem often encountered in testing of olfactory sensitivity is that many patients confuse the loss of the sense of smell with the loss of the sense of taste. Westerman[184] has developed a simple test for such an evaluation, whereby the odorant is placed on the tongue and the subject is asked to describe the flavor of the material. This test also may be used to identify malingerers, because few individuals know that flavor is largely mediated through the sense of olfaction. When asked, therefore, to identify the taste of the coffee placed on the tongue, the blindfolded olfactory malingerer, who should report a bitter taste, identifies its taste as coffee but disclaims any ability to identify the coffee odor when it is held in front of the nose. Further development of these taste-odor tests by Laing and colleagues[185] in Australia show that humans have a limited capacity to identify the components of taste-odor mixtures.

Electrophysiologic testing of olfactory ability in humans has been developed and is available in laboratories. Accurate delivery of the odorant molecules to the nose in warmed and humidified air is mandatory in all of these objective studies.[186,187] The most peripheral of these tests, the electro-olfactogram (EOG), is obtained by placement of an electrode directly on the olfactory epithelium.[188] When an odorant stimulates the receptor cells, a slow negative shift in voltage is seen. This has been shown in multiple animals, including humans, and is thought to represent a summation of the many generator potentials from single-receptor cells.[26,53,189,190] Although the olfactory epithelium is relatively inaccessible in the human, some researchers, including Furukawa and associates,[191] have succeeded in recording these electro-olfactogram potentials and have shown decreased potentials in hyposmic subjects that are commensurate with their olfactory loss. As these researchers have said, the electro-olfactogram provides the only objective method currently available for the differential diagnosis of anosmia caused by disorders of the olfactory epithelium versus the central olfactory tract.

A second objective testing method, used with success in other sensory systems such as hearing and vision, is measurement of brain-evoked potentials. In this test, the summated percutaneous brain electrical activity is averaged after multiple timed exposures to an odorant. Using this test in their research center, Kobal and Hummel[192] have succeeded in determining when the olfactory stimulation arrives at the receptors and have shown differences between pure olfactory stimulation and trigeminal stimulation. Maximal amplitudes of potentials evoked by substances that partly or exclusively excite the trigeminal nerve (high concentrations of carbon dioxide, menthol, acetaldehyde) were found at the vertex and are defined as *chemosomatosensory-evoked potentials*. Substances that exclusively, or to a great extent, excite the olfactory nerve (hydrogen sulfide, vanillin) caused maximal responses in the parietal area and are defined as *olfactory-evoked potentials*. This method would correlate best with subjective testing of odor perception.

Another type of induced brain wave activity is the endogenous component, called the contingent negative variation (CNV).[193] The brain waves are called "endogenous" because their presence depends on subjective response strategies rather than stimulus characteristics. The method would correlate best with subjective testing of odor discrimination. When the olfactory-evoked potentials and contingent negative variation are measured simultaneously, objective assessments of clinical status can be made.[194,195] When both are absent, anosmia is present. When just contingent negative variation is present, there likely is an olfactory distortion. Finally, in hyposmia, when the odorant presented is just above the discrimination threshold, the amplitude of the contingent negative variation is enhanced, and the olfactory-evoked potential is undetectable. This technique is clearly a useful clinical tool, although it is not generally available.

Much work, mostly in the setting of research, has focused on blood oxygen level–dependent signals in the brain through the use of PET and functional MRI. Currently, the clinical use of these modalities in olfactory disorders is not practical; however, they have significantly contributed to the understanding of odorant processing. Both imaging modalities are based on the regional cerebral blood flow differences in the brain between presentation of a stimulus and baseline levels. PET is limited by the fact that a radioactive substance is needed. Spatial resolution is 3 to 6 mm, but distinction between two areas of activation is limited to 10 to 12 mm. In addition, PET collects data over a 60-second period and may miss short signals. Functional MRI, on the other hand, does not involve radiation, and subjects can be scanned multiple times. Temporal resolution is also better with functional MRI than with PET; however, limitations caused by surrounding areas of bone and air can reduce signals in certain regions. Collectively, these modalities have increased our understanding of where olfactory processing occurs. It seems to be closely associated with activation of the trigeminal and limbic systems even in the simplest processing of passive perception of odors, a concept that explains the immediate recall of emotions related to a source of smell. With increasing complexity of olfactory processing tasks, areas outside those used for passive perception (amygdala, piriform cortex, orbitofrontal cortex, and thalamus) are recruited with each combined set of regions specific for the task at hand.[196]

Factors Affecting Olfactory Testing

Age

The testing of olfactory ability in children presents special problems. Richman and associates,[197,198] using an identification test designed for adults, found no consistent results in testing children younger than 10 years, but by the age of 14 years, the children's performance was equal to that of adults. Through the use of pictures to represent the odorants instead of words, reliable results could be obtained from children as young as age 6 (Richman RA: Personal communication, 1991). With an abbreviated odorant identification task, Richman and associates[199] have successfully tested olfactory function in children starting at age 8 years.

The other popular method for testing olfactory ability in adults, the detection threshold method, has been used in 5- to 15-year-old patients with a forced-choice, single-staircase method,[200] but the clinical relevance of this testing, especially in children, is unclear. Engen[83] found it very difficult to test a hedonic preference in children younger than 4 years. These subjects answered "yes" to the query regardless whether the question was phrased positively or negatively (i.e., both "Do you like it?" and "Do you dislike it?" yielded affirmative answers). Studies that used happy and sad faces or puppets have yielded more consistent results.[148,149]

Using a technique not often used in testing adults, Richman and colleagues[201] have developed a match-to-sample odorant discrimination task that has been useful in testing children as young as age 5 years. To date, this approach seems the most reliable way to test young children.

Testing older adults is generally a problem only if there has been a major loss of olfactory function or the patient has dementia. For individuals with poor olfactory ability, the testing can be boring, disheartening, and frustrating, and so can lead to inadequate measurement of real olfactory ability. For testing olfactory ability in the demented individual, the tests used in children have been useful. Obviously, if someone is severely demented, any type of interactive testing is futile.

Gender

In humans, test results averaged over many chemicals have consistently shown that women have a better olfactory ability than men, both in threshold and in identification tasks.[202] For specific odorants, however, there may be no difference.[203] In addition, the menstrual cycle influences womens' olfaction threshold levels, which are best at ovulation and poorest during menstruation.[159,173,204] The reasons for this pattern are not simply hormonal variations, because Doty and coworkers[161] have shown olfactory cycling even in women who were taking oral contraceptives, whose hormone levels did not vary. In animals, a clear relation exists between olfaction and sexual functioning. Pregnancy in mice can be blocked by the odor of a strange male.[205]

Adaptation and Habituation

The perception of a strong odor noticeable on entering a barn will disappear after a time. This adaptation response in humans, as measured by Stuiver,[206] generally occurred within 1 to 5 minutes for the chemicals studied. Data suggest that adaptation occurs both at the receptor-cell level[189,207] and more centrally.[206,208,209] Central adaptation is supported by the finding that, in humans, continued stimulation through one nostril leads to adaptation in both nostrils.[206]

Olfactory cross-adaptation is the ability of one chemical to decrease the subject's responsiveness and sensitivity to another chemical. It has been proposed that the greater the cross-adapting effect on one odorant by another, the more likely they are to share common sensory channels.[210-214] The manner and degree to which the odorants cause the receptors to adapt may not result from a simple mechanism, because even if two different odorants are matched in subjective intensity, their cross-adapting effects may be asymmetric.[214,215] For example, pentanol seems to have a strong cross-adapting effect on propanol, whereas propanol has only a small cross-adapting effect on pentanol.[216]

Clinical Olfactory Problems

Decreased and Distorted Olfactory Ability

Life for the person with anosmia has a very "flat" quality to it. Patients say that they select food by texture, color, and custom. Some state, for example, that they must identify sour milk from its lumpy character. Others do not use perfumes for fear of overapplication. Many express concern regarding fire and noxious or dangerous gases, and in fact, most anosmic patients have been involved in at least one accident stemming from this problem. Smoke alarms are an absolute necessity for people with anosmia.

In contrast to this lack of sensory input, there are individuals who have a distorted perception of odorants (*parosmia*) or the constant perception of an odor (usually foul in character) (*phantosmia*). These people are miserable and spend a great deal of time and money trying to rid themselves of their problem, often without success.

Human Olfactory Dysfunctions

The report of the Panel on the Communicative Disorders to the National Advisory Neurological and Communicative Disorders and Stroke Council estimates that approximately 2 million American adults have disorders of taste and smell. The literature lists more than 200 conditions that have been associated with changes in chemosensory ability.[13,217-220] Through the use of careful history taking, physical examinations, chemosensory testing, and imaging studies, several chemosensory centers have categorized most cases of olfactory losses into etiologic categories (Table 41-1). The following sections describe the common etiologic categories in detail. Those rare patients who have a distortion of the sense of smell (parosmia or phantosmia) with no change in intensity are not included in the classification.

Obstructive Nasal and Sinus Disease

Total nasal obstruction, such as caused by nasal polyps (Fig. 41-10), extreme mucosal swelling (Fig. 41-11), or simply finger occlusion of the nostrils produces anosmia. When the obstruction is released, olfactory ability should return (Fig. 41-12), although the minimal nasal opening at which the return occurs is not known. The location of this opening, or the area through which air flows to get to the olfactory cleft, is thought to be medial and anterior to the lower part of the middle turbinate.[221,222] This area may function as a regulator of airflow to the olfactory cleft, and changes in its anatomy clearly affect olfactory ability. Consequently, obstruction at this area or above it by swollen mucosa, polyps, tumors, or nasal bony deformities can decrease or eliminate olfactory ability.[223-225] This obstruction sometimes occurs even when the lower nasal cavity seems normal. It has been known that systemic steroid management reverses anosmia in most patients with nasal obstruction that is caused by nasal polyps and chronic rhinitis.[220,226-228] Although management with long-term systemic steroid therapy has many drawbacks,[229] a 1- or 2-week course may serve as a diagnostic test for nasal disease. What is still unclear is the etiology of anosmia in the rare patient with a patent nasal airway whose olfactory ability can be improved by long-term systemic steroid therapy.[230]

Although several workers have proposed that traumatic nasal cavity deformity can cause olfactory loss,[231-233] none of their reports used reproducible olfactory testing, nor was any meaningful change in olfactory ability brought about by surgical changes in the nasal anatomy; therefore the olfactory losses reported may have been caused by neural problems. In our experience, it is rare to identify an individual whose nasal anatomy is so deformed from external trauma that not even a small amount of air can reach the olfactory cleft. Scarring from previous surgery between the middle turbinate and the nasal septum, however, can be effective in closing off the olfactory area to airflow.

Obstruction of the olfactory cleft with edema and polyps has been thought to be the mechanism of olfactory dysfunction in patients with chronic rhinosinusitis. This conclusion may be only partly accurate. Kern[234] analyzed olfactory mucosa biopsy specimens from patients with chronic rhinosinusitis and found inflammatory changes within olfactory epithelium in a large number of subjects who performed poorly on odorant identification testing. This finding suggests that an inflammation-driven, primary neuron dysfunction may be contributing to olfactory disability with or without a concurrent obstructive process. In fact, evidence exists for active apoptosis of olfactory receptor neurons in patients with chronic rhinosinusitis,[235] which may explain the finding of smell loss unresponsive to oral steroids in patients with a long history of sinus disease.

Another form of obstructive olfactory loss can be seen in patients with a long-standing deficit, lack of trauma or sinonasal disease, and absence of a previous upper respiratory infection. Enlargement or medialization of the middle turbinate, of the superior turbinate, or of both, can be seen on nasal endoscopy and CT. Systemic steroids as well as surgery seem to be ineffective in reversing the deficit, possibly because of congenital lack of olfactory neurons or chronic sensory deprivation of olfactory neurons.[236,237]

Olfactory Loss after Upper Respiratory Infection

Many people volunteer that at one time or another they have lost their sense of smell completely during an upper respiratory infection (URI). In general, these olfactory losses are due to nasal airway obstruction and resolve when the nasal airway becomes patent again (1-3 days).[238] Of greater concern is the small number of patients whose olfactory ability never recovers after the other symptoms of the URI resolve. These people tend to be otherwise healthy individuals in the fourth, fifth, or sixth decade of life, and they are overwhelmingly women (70%-80%).[221,226,239,240] The reason for this female preponderance is unclear but may relate to the fact that women tend to have more URIs.[241] Biopsy specimens of the olfactory cleft in these patients show either decreased numbers of olfactory receptors or a complete absence of them.[242-244] MRI measurements of olfactory bulb volume in these patients reveals a decrease in size that correlates with severity of loss as well as duration of the hyposmia.[245] The prognosis for recovery from this olfactory loss is generally poor. Hendriks[240] combined several

Table 41-1

Spectrum of Olfactory Loss as Reported at Four Chemosensory Centers

	Goodspeed and Colleagues (1987)[239]*	Davidson and Colleagues (1987)[226]†	Leopold and Colleagues (1987)[222]‡	Heywood and Costanzo (1986)[169]§
Total no. patients	441	63	198	133
Etiologic category (%):				
Obstructive nasal and sinus disease	30	33	29	20
Post–upper respiratory infection	19	32	15	17
Head trauma	9	10	19	32
Aging	0	0	8	6
Congenital	0	5	8	0
Toxins	1	11	3	0
Miscellaneous	14	10	8	16
Idiopathic	26	0	10	10

*Connecticut Chemosensory Clinical Research Center, Farmington, Connecticut.
†Chemosensory Perception Laboratory, University of California, San Diego.
‡Clinical Olfactory Research Center, SUNY Health Science University, Syracuse, New York.
§Smell and Taste Clinic, Medical College of Virginia, Richmond, Virginia.

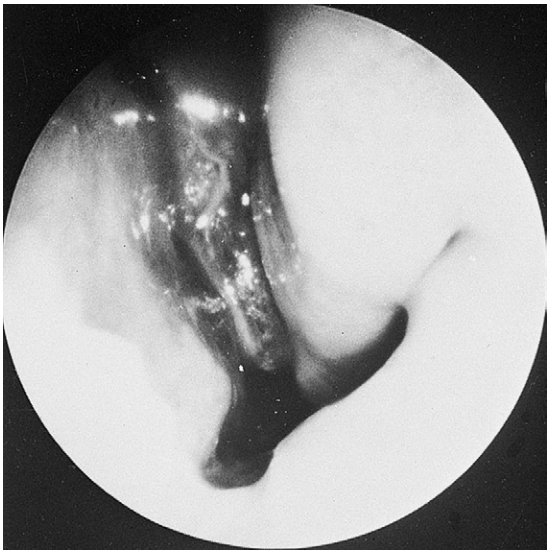

Figure 41-10. The lower left nostril with a large polyp between the inferior turbinate and the septum.

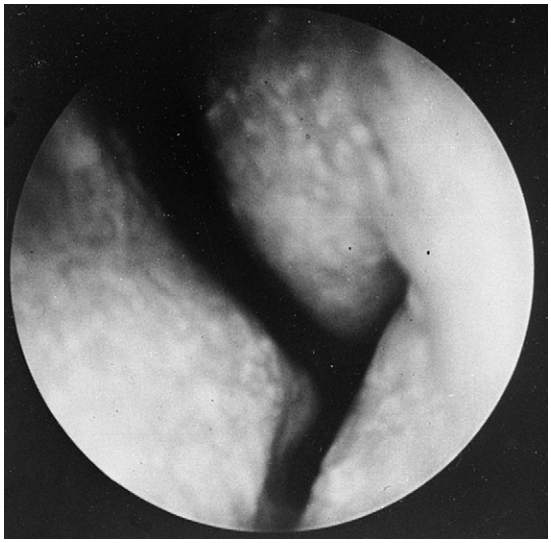

Figure 41-11. The lower left nostril with a narrowed airway caused by mucosal edema.

reported studies of patients with olfactory dysfunction and found that approximately one third of the patients recovered their olfactory ability, regardless of whether they were treated. Duncan and Seiden[246] have measured a light to moderate improvement in two thirds of their sample of 21 patients that took years to occur. The problem with these studies is that an upper nasal obstruction from mucus or swollen mucosa may remain after the URI has resolved. Without concurrent imaging of the nasal cavity, it would be impossible to determine whether a return of olfactory ability after a URI loss was due to clearing of the olfactory cleft or recovery of neural function.

Head Trauma

A review of several large series of mostly adult patients with head trauma (containing both minor and major trauma) reveals that the reported incidence of olfactory loss is between 5% and 10% (Leigh,[247] 1000 cases; Hughes,[248] 1800 cases; Sumner,[249] 1167 cases; Zusho,[250] 5000 cases). In contrast, the rates of olfactory loss after childhood head trauma have been reported to be 3.2% (transient loss) and 1.2% (permanent loss) (Jacobi and colleagues,[251] 741 cases). The degree of olfactory loss is generally associated with the severity of the trauma; however, even minor trauma can produce total anosmia.[252,253] Most studies of patients who complain of olfactory loss after trauma find the average loss to be in the anosmic range.[18,174] Fikentscher and Mauuller,[254] who classified 77 of 122 patients as anosmic, also support this tendency for the post-traumatic loss to be complete. The degree of olfactory loss is also partly determined by the site of cranial trauma. Frontal blows most frequently cause olfactory loss; however, total anosmia is five times more likely with an occipital blow.[240,255] The onset of a traumatic olfactory loss is generally immediate, although in some instances the patient either does not appreciate the loss or does not experience the loss until months after the injury.[18,256] Rate of recovery of olfactory function is less than 10% according to most large studies; however, Duncan and Seiden[246] showed that one third of their group of 20 patients had slight to moderate improvement in identification ability after the trauma. The quality of the returned olfactory ability is usually quite poor.

The exact injury to the olfactory system produced by trauma is unknown but is thought to be due either to shearing of the olfactory nerves as they exit the top of the cribriform plate[257] or to contusion of the olfactory bulbs or other central processing areas.[258] After trauma,

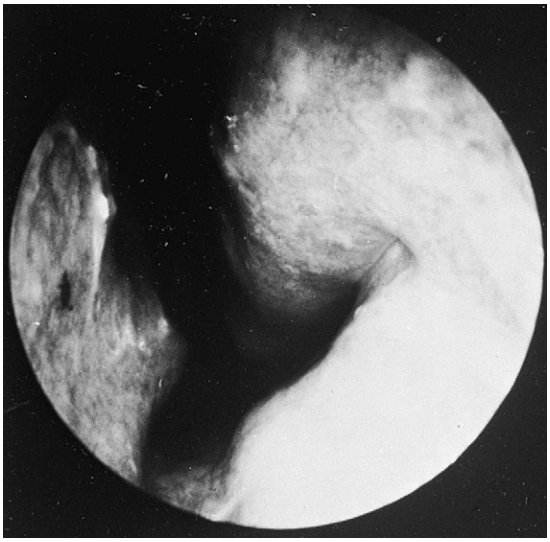

Figure 41-12. The same patient as in Figure 41-10 after polyp removal.

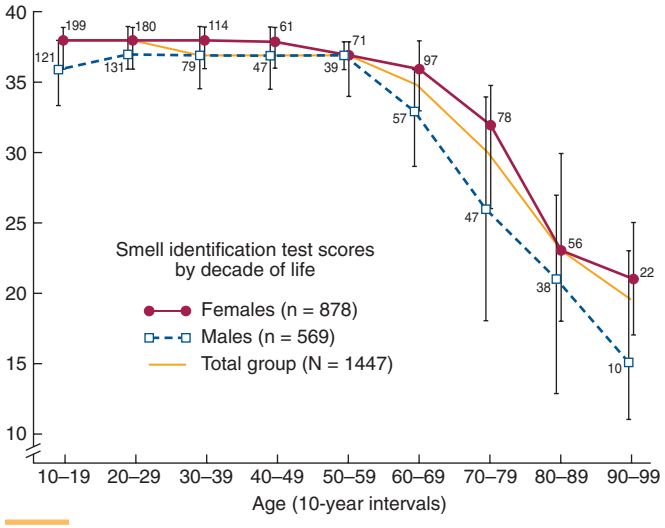

Figure 41-13. Relationship between the University of Pennsylvania Smell Identification Test scores, age, and gender in a large heterogeneous group of subjects. *(From Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function.* Physiol Behav. *1984;32:489.)*

the olfactory cells are generally distorted, have proliferation of axons and axon tangles in the lamina propria, and have few olfactory knobs and cilia.[244,259] The olfactory nerve bundles contain immature axons, and reentrant neuromas are found within the epithelium.[47] These findings suggest the following scenario: (1) the olfactory nerves were damaged at the time of the trauma, perhaps at the cribriform plate; (2) the normal response of the olfactory nerves is to regenerate, but the axons cannot form functional synapses because of either scar formation at the cribriform plate or irreversible damage to the olfactory bulbs; and (3) without this connection with the bulb, the cells will not produce olfactory knobs or cilia. The key, therefore, in helping patients with traumatic olfactory loss is to reestablish contact between the olfactory axons and the olfactory bulb if viable. At present, however, there is no known method to accomplish this task. Another possible area of olfactory system injury after head trauma may be in the frontal cortex. In a study of 40 patients who had traumatic total anosmia, all had major vocational problems.[260] Most of these patients showed psychosocial defects associated with frontal cortex injury. Similarly, Levin and others[261] observed impaired olfactory recognition in patients who had a traumatic hematoma or contusion in the frontotemporal region.

Aging

Although older individuals can have an olfactory loss from any of the other causes discussed here, they also can have losses caused by dementia-related diseases and from the aging process itself. In fact, in otherwise healthy individuals, deficits in balance, olfaction, and visual pursuit best discriminate between people older than 85 years and those younger than 74 years.[262] Olfactory identification ability has been shown to drop sharply in the sixth and seventh decades of life such that more than one half of those aged 65 to 80 years show major olfactory declines.[263] This pattern of change with respect to age is similar to that seen for visual acuity and speech intelligibility.[264] Olfactory thresholds also have been found to decline with age; this effect is slightly less dramatic in women (Fig. 41-13).[60,172,263,265,266] From the National Geographic Smell Survey, Wysocki and Gilbert[267] determined that the degree and rate of olfactory loss are odorant specific and vary from individual to individual. Other measured effects of aging on the sense of smell are decreased magnitude matching,[263] changes in the perception of pleasantness,[267,268] association with decreased nutritional status,[269,270] and the ability to discriminate flavor in everyday foods.[271,272]

The perceptual losses in olfactory ability that accompany aging are not surprising when the anatomic changes are noted. Bhatnagar and associates[273] carefully studied olfactory bulbs from individuals aged 25 to 95 years. From a total of 50,935 mitral cells at age 25, these researchers observed a linear decline that averaged 520 cells per year. Likewise, from a total olfactory bulb volume of 50.02 mm at age 25, they noticed a decline of 0.19 mm per year. In addition to the decline in the number of cellular elements, Liss and Gomez[274] noted extensive degeneration in the bulb with aging.

At least two dementia-related diseases are often accompanied by a smell disorder: Alzheimer's disease and Parkinson's disease. In patients with these diseases, it is likely that there has been some damage to the olfactory bulb or the central olfactory cortex and that this damage is, at least in part, responsible for the accompanying loss in olfactory detection and recognition ability.[275] Alzheimer's disease is characterized by the presence of neurofibrillary tangles and neuritic plaques in most of the central olfactory pathways.[276-279] These tangles and plaques are presumed to account for the clinical deficits of the disease.[280,281] The fact that similar pathologic changes and testing abnormalities are seen in patients with Down syndrome suggests a possible genetic link.[282] Furthermore, as Pearson and coworkers[281] have pointed out, the involvement by the olfactory system contrasts strikingly with the minimal abnormality seen in other areas of the brain. This finding has raised the possibility that the olfactory system is the portal of entry for an environmental agent that causes the disease.[283] Abnormalities in the nasal olfactory epithelium identified by Talamo and colleagues[284] may give additional support for this theory. An alternative theory is that the olfactory system is simply attacked preferentially over other neural elements.[285] There are a number of nonmotor defects in patients with Parkinson's disease, including depression and cognitive losses.[286] A reduction in the ability to detect and identify odorants is one of these defects, and the extent of this defect is related to, and may help in the diagnosis of, the clinical subtype of Parkinson's disease.[287,288] The olfactory changes have been shown to be independent of the cognitive and motor symptoms,[289] and they occur early in the disease. After measuring olfactory ability in patients with Parkinson's disease and normal patients of varying ages, Hawkes[290] has hypothesized that Parkinson's disease starts as an acute event and that the olfactory and neural losses progress. Neuronal losses have been identified in the olfactory bulb and tracts of individuals who died with Parkinson's disease, with a strong correlation to disease duration.[291] Because the loss of olfactory ability also occurs early in Alzheimer's disease and is not noticed by the patient, decreased olfactory ability on clinical testing may be an important early signal for the development of these diseases.[292] Indeed, if a patient has a diagnosis of Alzheimer's or Parkinson's disease but testing does not detect decreased olfaction, a different diagnosis should be considered.[293] An interesting study of first-degree relatives of patients with Parkinson's disease suggested that lower lifetime caffeine consumption is associated with decreased olfaction scores.[294]

Congenital Dysfunction

The usual history of the person with a total congenital loss of the sense of smell is that he or she is otherwise healthy and began to learn at about age 8 that friends, parents, and siblings could perceive something he or she could not. In most of these people the other chemosensory functions are intact, so that pungency, irritating odors, and tastes can be detected normally.[295] Many more people have an isolated loss of sensitivity to a particular chemical or group of chemicals (also known as *specific anosmia*), for example, musks, trimethylamine (a fishlike odor), hydrogen cyanide (almond-like), butyl mercaptan (an additive to natural gas), and isovaleric acid (a locker-room odor).[296,297]

Jafek and associates[295] have proposed that the pathophysiology of congenital olfactory loss is a degeneration or atrophy of the olfactory epithelium or the olfactory bulb late in the developmental process. They base this theory on the total lack of peripheral receptors or supporting cells and the routine finding of respiratory epithelium in olfactory cleft biopsy specimens from people with a history consistent with a congenital loss. On olfactory testing, individuals in this congenital group scored either at or slightly better than chance performance.[226,295] Because members of groups with olfactory loss from other etiologies (e.g., head trauma, post-URI) have been shown to have at least some olfactory epithelium (albeit often abnormal), it is not surprising that this group with congenital loss has the lowest olfactory scores of all the etiologic groups.

Perhaps the best-known type of congenital anosmia is associated with hypogonadotropic hypogonadism and is known as Kallmann's syndrome.[298,299] This disorder affects approximately 1 in 8000 males and 1 in 40,000 females, mostly in a sporadic manner. Mutations in the X chromosome–located *KAL1* gene, which encodes the protein anosmin-1, accounts for 11% to 14% of cases. An autosomal dominant mutation in the *KAL2* gene or the gene for fibroblast growth factor receptor-1 (FGFR-1) is thought to account for another 10% of cases, and other mutations in genes involved in the migration of gonadotropin-releasing hormone neurons during development are being discovered.[300] At least some patients with Kallmann's syndrome have been shown to have agenesis of the olfactory bulbs and stalks and incomplete development of the hypothalamus.[301-303] The one patient with Kallmann's syndrome studied by Jafek and associates[295] also had no olfactory epithelium in the olfactory cleft, although patient studies by Schwob and colleagues[303] did show abnormal olfactory epithelium. Other defects sometimes seen in Kallmann's syndrome are renal abnormalities, cryptorchidism, deafness, midline facial deformities, and diabetes. The existence of this syndrome brings to light the strong association between sexual development and olfaction in other mammals. Male mice, for example, do not show mating behavior or sexual development if their olfactory bulbs have been removed shortly after birth.[304-306]

Toxic Exposure

The history of olfactory loss in conjunction with exposure to a particular chemical is currently the clinical method used to make the diagnosis of a toxic exposure–related loss. The loss may occur over a period of days, as was the case for a dentist who was using a new compound for dental work. Conversely, it may be years until the loss is apparent, such as with exposure to formalin. Even common substances, such as cigarette smoke, can be associated with olfactory loss.[307] The literature has many reports of olfactory loss after exposure to toxins, some of which are reversible usually after removal of the affected person from the source, and some permanent.[226,308-310] Scott,[220] Feldman and colleagues,[217] and others[311] have listed many of the known agents related to olfactory loss. Their lists are long. Most of the agents are either gases or aerosols and enter the nose with the respiratory air stream. Obviously, the concentration and duration of exposure must be considered, and employers in occupations that use such agents must be aware of these factors.[312,313]

Neoplasms

Both intranasal and intracranial tumors can affect the sense of smell. The intranasal tumors most commonly seen are inverting papillomas, adenomas, squamous cell carcinomas, and esthesioneuroblastomas.[314] These intranasal tumors decrease olfactory ability mostly by blocking the airflow to the olfactory cleft. Intracranial meningiomas, pituitary tumors, and gliomas can cause local destruction to the olfactory apparatus. Approximately 25% of temporal lobe tumors have been estimated to cause an olfactory disturbance.[315] Symptoms of nasal obstruction, epistaxis, anosmia, hyposmia, visual lesions, or other central nervous system signs should be a warning of these tumors. Intranasal tumors do not usually manifest as olfactory loss because of the intact function of the contralateral side. Uninasal olfactory testing is a good way to diagnose them.

Human Immunodeficiency Virus Infection

Patients infected with human immunodeficiency virus (HIV) have been found on testing to have decreased olfactory ability. These losses are variable and do not correlate with measures of health such as human immunodeficiency virus helper T cell (CD4) count, body weight, body composition, management, and diet.[316-318]

Epilepsy

Olfactory auras are sometimes associated with epilepsy. The prevalence of olfactory auras has been estimated between less than 1% and less than 30%.[319] These auras often last for only a few minutes or less and are often unpleasant in character.

Psychiatric Disorders

Patients with depression, schizophrenia, and hallucinations may have olfactory complaints. Olfactory identification deficits are observed only in schizophrenic patients, however.[320-322] Although depressed patients do have some altered gustatory ability, their ability to identify odorants is generally normal.[323] Therefore, the source of the olfactory complaints these people have is likely to be located in the central nervous system, and it may be that the same chemicals that are thought to cause the symptoms of depression affect the neural connections between the limbic system and the hypothalamus.[324] Pryse-Phillips[325] differentiates intrinsic olfactory hallucinations (in which the patient believes the smells emanate from his or her own body) from extrinsic hallucinations (in which the odors seem to come from a source other than the patient's own body). The *olfactory reference syndrome* describes patients who are obsessively concerned about minor or absent odors. Because these concerns are often in reference to body odor, these people bathe frequently and use perfumes in an abnormal way. In the "Marcel Proust" syndrome, individuals conjure up memories based on odors in such dramatic ways as to interfere with their daily routines. Careful attention to the patients' descriptions of their concerns often points to a need for psychiatric referral.

Parosmia and Phantosmia

Distortion of the sense of smell clearly bothers patients more than the loss of the sense of smell. It is difficult for patients with parosmia (distortion of inhaled odorants) to learn new names for the smells of familiar items. They are disturbed that nothing smells normal. On the other hand, patients with phantosmia (perception of smell without an odorant present in the environment) might continuously perceive an unpleasant odor, such as rotten eggs or feces. Both these distortions can be intermittent or continuous and can be brought on by specific triggers, such as strong odors, loud sounds, and stress. The distortions can also be present in only one nostril, and simple nostril blockage can diagnose this situation. Parosmias and phantosmias have been reported to accompany many disorders, some of which are associated with brain or psychiatric disease, such as temporal lobe tumors or seizures.[219,326] For this reason, they have been believed to be of central nervous system origin. Studies by Leopold and colleagues[327] suggest that some individuals with phantosmia may have diseased neurons in the peripheral olfactory system that are amenable to management. The etiology of phantosmias and parosmias is most often associated with a specific URI, head trauma, or the aging process.[327,328] Other investigators also have noted the disorders in patients with nasal disease.[220,329] Patients with these distortions of odor quality are more likely to be women and generally have decreased olfactory ability when tested.[220,327,330]

Medications

Although medications seem to affect the taste system more than the olfactory system, many can cause olfactory dysfunction (Table 41-2). Usually the olfactory ability returns after the offending medication is discontinued, but sometimes the change is permanent.[331]

Surgery

Alterations of either the respiratory airflow path or the region around the olfactory nerves can be expected to affect olfactory ability. Although septal deformities that can affect olfactory ability have been described,[332] and septal surgery has been reported to improve olfactory ability,[333,334] deformities severe enough to obstruct a nasal airway are extremely rare. Losses of olfactory ability after rhinoplasty have also been reported. Champion,[335] reviewing the records of 100 consecutive rhinoplasty patients, found that 20% of them complained of the loss of the sense of smell from 6 to 18 months after surgery; 95% of these losses were temporary. No olfactory testing was used in this study. Goldwyn and Shore[336] tested 97 patients before and after nasal surgery and found 3 patients with decreased postoperative olfactory ability. In contrast, Kimmelman[337] tested 93 patients before and after a range of nasal and sinus procedures and found that 34% had decreased olfactory ability. These losses could be caused by neural damage at the time of the surgery or the narrowing of the nasal airways by anatomic changes or scar tissue.[338] Fortunately, the advances in endoscopic sinus surgery have allowed more accurate surgery and less olfactory damage.[339]

In patients who undergo a total laryngectomy, inspired air has been rerouted away from the nasal cavity. These patients complain of decreased olfactory ability,[340] but some can perceive odors when the stimulus is under their noses.[341] Mozell and associates[342] and Schwartz and colleagues[5] have shown that olfactory ability can be restored to patients after laryngectomy through shunting of respired air again through their noses, indicating that the olfactory receptors were intact and functional even after many years. Continued use of maneuvers to move air in the nasal cavity can successfully rehabilitate smelling ability in patients after laryngectomy.[343]

Much of the cranial and skull base surgery in the region of the olfactory bulbs has been associated with a total and permanent loss of olfactory ability. However, techniques have been developed for preservation of the olfactory tract.[344-346]

Idiopathic Loss

After an extensive workup including many tests, some patients still have no obvious reason for their olfactory dysfunction. They are usually young or middle-aged adults in otherwise good health. Some olfactory biopsy specimens from patients in this category have shown the presence of olfactory epithelium, but the changes observed are not characteristic enough to be diagnostic.[46,244]

Diagnostic Assessment

The most important thing the physician can offer the patient with an olfactory dysfunction is an accurate diagnosis and concern for his or her plight. Obtaining a detailed medical history is of utmost importance. Having the patient estimate the severity of olfactory loss and the time over which the loss occurred (e.g., days, weeks, or months) provides useful information. Events that occurred around the time of the loss, such as trauma or URI, also need to be determined. A thorough review of systems and general medical health helps rule out side effects of medications and problems caused by diseases such as hypothyroidism. Careful assessment of the patient's problem may lead to diagnosis of a seemingly unrelated entity, such as a metabolic disease, in a patient previously thought to have psychological problems.[347] The physical examination should include special attention to the nose, mouth, and neurologic system. Nasal endoscopy has been particularly useful in assessing the nasal airways in the region just below the olfactory cleft. Mandatory tests for the workup of patients with chemosensory complaints include testing of their gustatory and olfactory abilities.[348,349] In general, identification tests (like the Smell Identification Test, Sensonics, Inc., Haddonfield, NJ) have been more useful than threshold tests in the clinical situation.[348] Bilateral and uninasal olfactory testing has been useful in detecting both nasal and cranial

Table 41-2

Drugs Affecting Taste and Smell

Classification	Drug(s)
Amebicides and anthelmintics	Metronidazole; niridazole
Anesthetics, local	Benzocaine, procaine hydrochloride (Novocain), and others; cocaine hydrochloride; tetracaine hydrochloride
Anticholesteremics	Clofibrate
Anticoagulants	Phenindione
Antihistamines	Chlorpheniramine maleate
Antimicrobial agents	Amphotericin B; ampicillin; cefamandole; griseofulvin; ethambutol hydrochloride; lincomycin; sulfasalazine; streptomycin; tetracyclines; tyrothricin
Antiproliferatives, including immunosuppressive agents	Doxorubicin and methotrexate; azathioprine; carmustine; vincristine sulfate
Antirheumatic, analgesic-antipyretic, anti-inflammatory agents	Allopurinol; colchicine; gold; levamisole; D-penicillamine; phenylbutazone; 5-thiopyridoxine
Antiseptics	Hexetidine
Antithyroid agents	Carbimazole; methimazole; methylthiouracil; propylthiouracil; thiouracil
Agents for dental hygiene	Sodium lauryl sulfate (toothpaste)
Diuretics and antihypertensive agents	Captopril; diazoxide; ethacrynic acid
Hypoglycemic drugs	Glipizide; phenformin and derivatives
Muscle relaxants and drugs for treatment of Parkinson's disease	Baclofen; chlormezanone; levodopa
Opiates	Codeine; hydromorphone hydrochloride; morphine
Psychopharmacologics, including antiepileptic drugs	Carbamazepine; lithium carbonate; phenytoin; psilocybin; trifluoperazine
Sympathomimetic drugs	Amphetamines; phenmetrazine theoclate and fenbutrazate hydrochloride (combined)
Vasodilators	Oxyfedrine; bamifylline hydrochloride
Others	Germine monoacetate; idoxuridine; iron sorbitex; vitamin D; industrial chemicals, including insecticides

Modified with permission from Schiffman SS. Taste and smell in disease (second of two parts). *N Engl J Med*. 1983;308:1275.

tumors and unsuspected neural losses.[350] If the patient's medical situation warrants blood testing (such as for thyroid hormone levels), it should be performed, but routine blood tests have not been useful.[239] Rhinomanometry can be useful in assessing the general status of the nose; however, if the upper nasal airways are patent, any small nasal airflow allows olfaction to occur.

If an anatomic deformity or obstruction is suspected, if there is any history of nasal or sinus disease, or if the diagnosis is not perfectly clear, a CT scan of the nasal and sinus cavities should be performed in the coronal plane. MRI of this region does not permit visualization of the fine bony detail of the upper nasal cavity, but it can be useful for soft tissues, sometimes including the olfactory sulci.[351-353] Plain radiographs of this region are too imprecise to be of any help in the workup. Another advantage of the coronal CT scan is that it helps rule out tumors and deformities in the anterior cranial fossa. In a few centers around the country, olfactory biopsies are being performed to assess the status of the olfactory epithelium. These biopsy studies require a great deal of time and expertise and are still considered research tools.[46,242,244,295,354]

Management

The management of olfactory disorders depends on the type of disorder and the determined cause (Fig. 41-14). The major olfactory dysfunction for which treatment has been useful is that caused by nasal disease. As previously described, the problem is obstruction of airflow to the olfactory cleft. Management aimed at opening the air passageways while preserving the olfactory epithelium will improve olfactory ability. Medical therapy, including intranasal steroids, antibiotics, and allergic therapy, is the mainstay of management.[355] Oral steroids have been particularly useful in shrinking thickened nasal mucosa; however, the

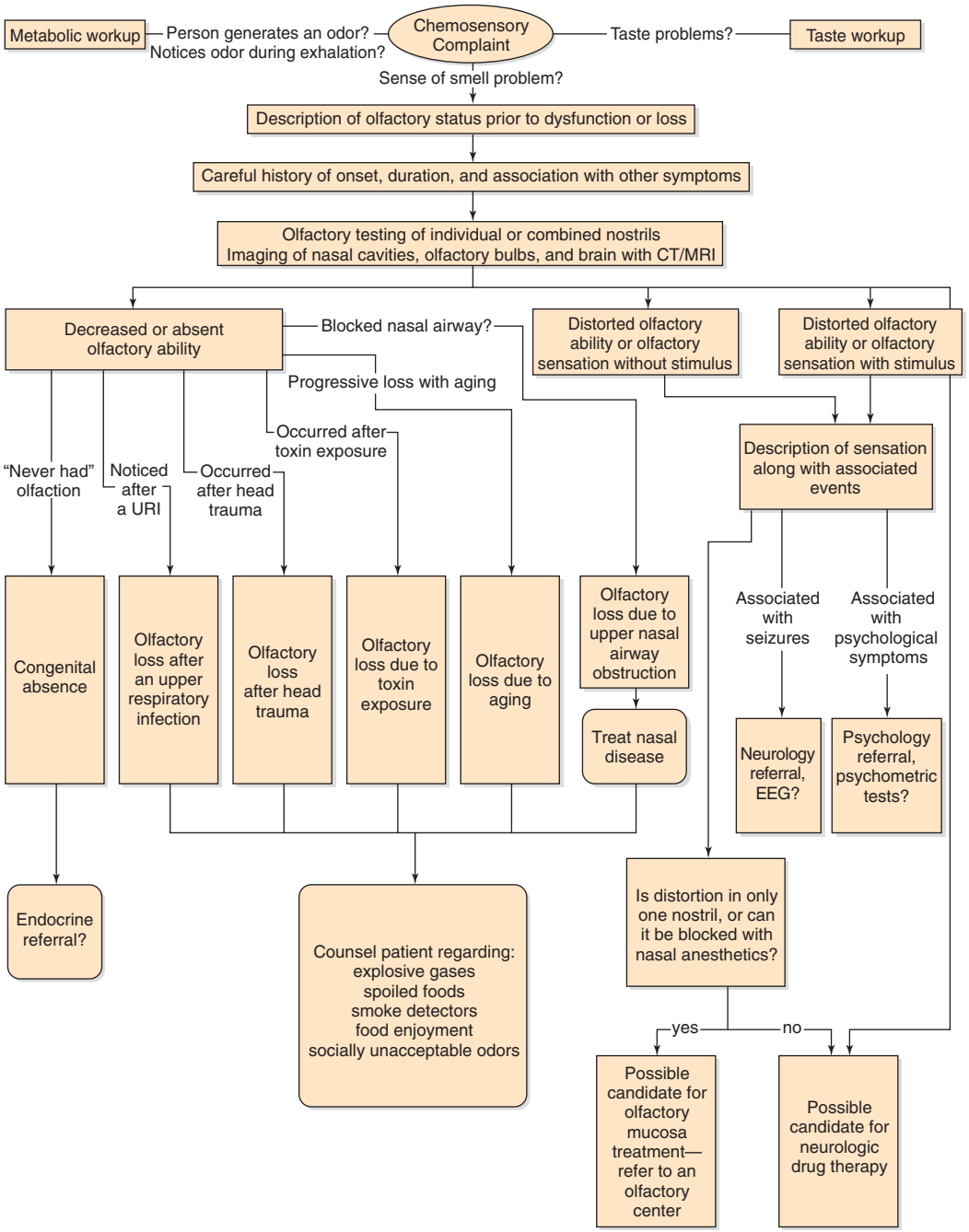

Figure 41-14. Algorithm of how to manage the patient with an olfactory disorder. CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; URI, urinary tract infection.

side effects of this therapy must be weighed against its potential benefits.[220] Patients whose olfactory loss is resistant to medical therapy or those who have tumors often can benefit from surgical therapy. Tumors are managed according to usual oncologic principles. Often the nasal disease is associated with (or perhaps caused by) adjacent ethmoid sinus disease. Functional ethmoidectomy, often conducted with the use of an endoscope, can improve the health of these sinuses and, in turn, allow the olfactory cleft to open.[356-360] Even those patients who have had surgery may need long-term medical management to control the disease and prevent recurrence.

For cases that have been placed in any of the other diagnostic categories, there is no proven therapy. In general, the problem is either a total lack of olfactory receptor neurons (e.g., congenital) or damage to olfactory nerves that do not seem to be functioning normally (e.g., trauma). Multiple management strategies have been proposed, often using vitamins or minerals. Vitamin A was thought to be an effective management strategy because (1) it is necessary for the repair of epithelium, (2) white rats apparently become anosmic on a diet deficient in vitamin A,[361] and (3) assays performed on mammalian olfactory epithelium showed considerable amounts of vitamin A.[362] In an uncontrolled study, Duncan and Briggs[362] used vitamin A successfully to restore at least partial olfactory ability in 50 of 56 of their subjects. Unfortunately, other observers have been unable to reproduce their success.[240,363] B vitamins have also been tried for the management of anosmia, once again without success.[362,363]

Mackay-Sim and Dreosti[364] demonstrated that zinc-deficient adult mice do not show a food odor preference. This finding supports the administration of oral zinc by Henkin and coworkers[365] as a management option for losses of taste and smell associated with a zinc deficiency. It is known that severe zinc deficiency is rare and difficult to substantiate.[366] Nevertheless, occasional reports of patients whose olfactory problems have improved with zinc therapy are available.[367,368] These reports must be evaluated, however, with the understanding that some olfactory disorders do improve spontaneously. Indeed, in a randomized, double-blind crossover study of the effects of zinc on 106 patients with taste and smell problems, Henkin and colleagues[255] noted that zinc was no more effective than placebo. Zinc is generally not a recommended therapy for olfactory disorders.[220] Henkin and colleagues[255] also have suggested that aminophylline is useful for anosmic and hyposmic patients. This suggestion is based on the observation that cAMP plays a role in the transduction of olfactory responses. Unfortunately, corroborative data supporting its use are not available. The use of short-term systemic steroids has resulted in some improvement in a proportion of patients with various forms of olfactory loss unrelated to chronic rhinosinusitis,[369,370] but further evaluation on its efficacy is needed.

Once patients have been identified as having one of the olfactory losses for which we have no assured treatments, they should be reassured that there are others with similar deficits. Because olfaction plays such an important role in the appreciation of foods, these patients should be counseled on possible ways to improve the variety or seasoning of the diet to enhance whatever sensory modalities remain (e.g., emphasizing the taste, color, texture, viscosity, and "mouth feel" of foods). Attempts should be made to ensure that the normosmic persons living with such patients understand the problem and can be relied on to volunteer information of social concern regarding odors. Smoke and fire detectors are mandatory. Anosmic persons living alone should elicit the confidential help of friends on matters of odor. The dangers of natural gas and liquid petroleum gas can be avoided by switching to electric appliances and nonexplosive heating or cooling fuel.[371]

The management of phantosmia is varied. One simple and safe therapy that has been effective in multiple cases is for patients to instill four nasal saline drops in the affected nostril with the head positioned down and forward. This is likely effective through a blockage of the upper nasal airways and reproduces a phenomenon that many of the patients notice with crying or excessive tearing. In Europe, Zilstorff[372] and Fikentscher and Rasinski[328] have used topical cocaine hydrochloride directly on the olfactory mucosa; however, multiple re-treatments have been required, and other clinicians have been unable to duplicate their results.[220] In addition, one of us (DAL) has documented the total loss of olfactory ability in one patient who used this treatment daily over several years. Neurosurgeons have performed olfactory bulbectomies through a neurosurgical craniotomy approach to alleviate the phantom odor.[373,374]Although the patients who have had this surgery are pleased to be rid of their phantom odor, they are left with no olfactory ability on the operated side. If both sides are operated on, they will be totally anosmic. Leopold and associates[327,330] have successfully managed phantosmia by removing olfactory epithelium from the underside of the cribriform plate. The advantage to this procedure seems to be that the olfactory ability is not irreversibly destroyed in some people. This is difficult surgery that entails repair of CSF leakage.

Summary

Although the basic mechanisms of olfaction are still being discovered, what has already been learned forms an exciting foundation for further research. The process of odorant delivery to the receptors differs from person to person and may be an adaptation to the differences in upper nasal cavity anatomy. The receptors regenerate throughout adult life, but why does this process not continue after head trauma? How does the olfactory system distinguish the thousands of odorants to which humans are exposed? What is the relationship of the olfactory loss in Alzheimer's and Parkinson's diseases to the progression of disease? The answers to these questions and many others are being explored. Through evaluation and diagnosis of patients with olfactory problems, a better understanding of the olfactory system is being obtained, and these patients are being helped in the process.

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CHAPTER FORTY-TWO

Evaluation of Nasal Breathing Function with Objective Airway Testing

Jacquelynne Corey

John Pallanch

Key Points

- During optimal nasal respiration, air passes over the maximum amount of nasal mucosa with resulting humidification, cleansing, and warming but without the sensation of dyspnea.
- Increased awareness of normal physiologic phenomena like the nasal cycle or increase in nasal congestion when lying down may signify the presence of nasal obstruction.
- The nasal valve is a slitlike opening between the caudal edge of the upper lateral cartilage and the nasal septum.
- Rhinomanometry and the nasal peak flowmeter both measure transnasal flow. Rhinomanometry also simultaneously measures transnasal pressure, allowing calculation of nasal resistance (pressure/flow).
- For the same designated transnasal pressure on both sides of the nose, the flows of the right and left side of the nose can be added to obtain the total nasal airflow for that pressure.
- In a graph with pressure plotted on the *x*-axis and flow on the *y*-axis, the greater the pressure-to-flow ratio (resistance), the closer the curve is to the pressure axis. Thus curves representing a more obstructed airway lie closer to the pressure axis than curves for a less obstructed airway.
- It is apparent that there is a difference in objective test results between the group of subjects with nasal obstruction and the group with no symptoms; however, there is a significant overlap between the airway values for these two groups (see Fig. 42-21).
- There is no single population threshold for the airway at which symptomatic obstruction would occur. Instead it appears that there is a range of individual threshold values that vary from person to person.
- Some individuals might have decreased airflow receptor activity, and therefore, even if their airways are unrestricted, they may feel that nasal airflow is not adequate. There is less likelihood of helping such patients' symptoms with treatment aimed at increasing the size of the nasal airway.
- Patients in whom airway testing results do not match their symptoms are precisely the ones in whom the results may be of significant benefit, because the mismatch will lead to additional discoveries about the nature of their symptoms.
- Simultaneous assessment of symptoms, nasal examination, and objective testing is a key element in the application of objective testing of the nasal airway.
- Objective testing of the nasal airway can aid in the evaluation of patients with nasal obstruction, providing further information about the effectiveness of medical or surgical treatment, and of patients who have allergic rhinitis or disturbance of the airway during sleep.

Nasal Breathing Function

During normal nasal breathing, air passes through the anterior nares over the nasal mucosa to the nasopharynx, with resulting humidification, cleansing, filtering, and warming of the air but without the sensation of obstruction. These functions are influenced by changes in the natural environment, normal physiologic reflexes, normal anatomic variations, and pathologic conditions. In this chapter, we discuss objective measures that can be used to evaluate nasal breathing. Most of these tests attempt to assess the airflow through the nose by measuring (1) area, (2) changes in airflow corresponding to pressure, or (3) volume. Other nasal functions are discussed in separate chapters; they include detection of odors and toxins, immunologic defense against pathogens, and mucociliary clearance.

Physiologic Factors

Although the sensation of unrestricted nasal breathing is a complex phenomenon that may be influenced by factors other than airflow,

there is a correlation between the amount of airflow and the symptom of nasal obstruction.[1-3] Factors affecting the stimulation of cold receptors in the nasal vestibule, skin, and mucosa and changes in the atrophic mucosa of rhinitis sicca may be interpreted by a patient as nasal obstruction despite the presence of unrestricted airflow.

"Normal" changes in airflow and the sensation of obstruction occur during the nasal cycle.[4] During quiet nasal respiration, one side of the nose is usually more "congested" than the other. This cyclic engorgement of the nasal turbinates is part of normal physiologic function of the nose that warms and humidifies the air. We do not currently understand why the cycling occurs, but it allows us to have at least one nostril that is unobstructed relative to the other during normal breathing. In most people, these cycles last around 2 to 4 hours. In some subjects, however, there is no "cycle" at all, cycles are extremely shortened or elongated, or cycles involve nostrils being concurrently either "blocked" or "open." Another normal response of the nose is the "opening up" of the nose associated with an elevated pulse that occurs during exercise. It is also normal for the nose to become more congested when a person is lying down and for relative congestion to occur on the dependent side when a person is lying in the lateral recumbent position. These normal physiologic phenomena have been studied with objective testing of the nasal airway.

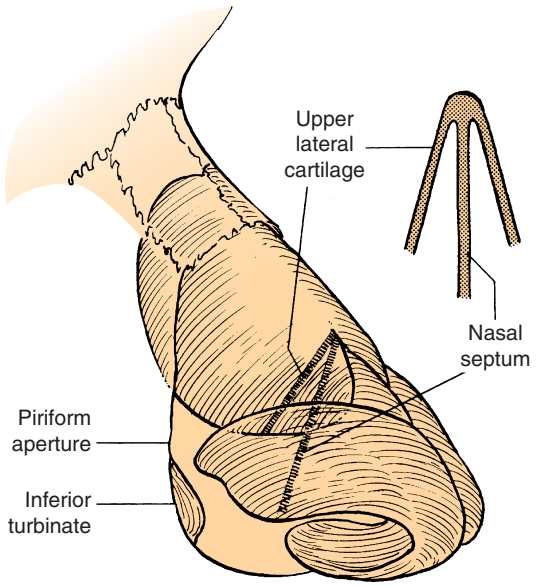

Figure 42-1. Anatomy of the valve region.

Anatomy

Septum and Turbinates

Variations in shape of the nasal septal shape and protuberances of the turbinates that encroach on the airway can contribute to nasal airway restriction.

The Nasal Valve

Distinction between Valve and Valve Area (Region)

Kern[5] distinguished between the nasal valve and the nasal valve area. The *nasal valve* is a slitlike opening between the caudal edge of the upper lateral cartilage and the nasal septum. The valve is only a part of the *nasal valve area*. Dutch otolaryngologist and physiologist Pieter J Mink (1859-1941) called this slitlike opening the "ostium internum" and considered it to be the narrowest part of the nasal airway.[6] Other names are os internum, limen vestibuli, limen nasi, liminal valve, and "liminal chink." *Limen nasi* (limen vestibuli) refers to a specific anatomic ridge (boundary) on the lateral nasal wall formed by the lower end of the upper lateral cartilage that separates the vestibule from the remainder of the nasal cavity.[7] The valve has also been called the narrowest part of the nasal airway,[8] and it would thus generally be the main determinant of nasal resistance. Plastic casts show that the smallest area is at the isthmus nasi close to the piriform aperture.[9] A model based on magnetic resonance imaging data suggests that the greatest drop in pressure occurs anterior to the inferior turbinate.[10]

Description of Valve Area (Region)

The nasal valve area (Fig. 42-1) is the functional unit that "includes the distal end of the upper lateral cartilage, the head of the inferior turbinate, the caudal septum, and the remainder of the tissues surrounding the piriform aperture" (floor of the nose, lateral fibrofatty tissue, and frontal process of the maxilla).[11] This is the "flow-limiting segment" with the "Mink" valve as its distal orifice.[11a] Other designations for the valve area are "valve region," minimal cross-sectional area (mCSA), and cross-sectional area 2 (CSA2).[5] In the rest of this chapter, we use the term *valve region* to refer to this anatomic unit in order to avoid confusion of the term "area" with the measurement of a cross-section. The valve region is the anterior part of the nose where the minimal cross-sectional area occurs. Bridger and Proctor,[12] using rhinomanometry and a plastic catheter passed along the floor of the nose, found that instead of a solitary highest resistance point, the resistance was spread across the valve region and that beyond that only a little additional resistance was noted. Using a similar method, Haight and Cole[8] found that the greatest resistance drop occurred at the anterior end of the inferior turbinate in the first few millimeters of the bony cavum. They demonstrated that the site of greatest resistance was in the same location even after decongestion. Extending this study to a larger group of subjects, Hirschberg and associates[13] found that before decongestion, the most restrictive portion of the nose (78% of the resistance) was in the first 4 cm, with 56% of the resistance in the first 2 cm. After decongestion the greatest resistance (88%) was in the first 2 cm. This finding demonstrated that the anterior tip of the inferior turbinate is the site of most resistance in the nasal airway for some patients before but not after decongestion.

The valve region is bounded by compliant and mobile as well as rigid components, giving the region a dynamic character.[14] Any change in dimension can alter the cross-sectional area and thus affect airway resistance exponentially. Therefore, the effect of changes in the valve region is greater than elsewhere in the nose. This fact reinforces the importance of not distorting the anterior nasal structures during performance of an objective test. This region of the nose has been noted to account for half of the airflow resistance of the entire respiratory tract. It is the most common site of pathology causing significant obstruction.[14]

Site of Sensation of Obstruction

Vestibular Skin versus Caval Mucosa

Exposure to aromatic substances such as menthol, camphor, and eucalyptol causes the sensation of increased nasal patency despite the absence of change in nasal resistance.[15,16] These volatile oils increase the sensitivity of cold receptors by raising the temperature at which they respond. With the increase in cold receptor reactivity in nerve endings, the subject feels that the nose is more open.[17]

Lidocaine injected in the nasal vestibule causes the sensation of nasal obstruction in subjects, without any change in nasal resistance. This finding supports the hypothesis that the level of activity of the cold receptors affects the sensation of obstruction. Cold receptors reside primarily in the vestibular skin; this location is supported by the finding that, when an air jet is directed at the inside of the nose, the area of greatest sensitivity to the sensation of airflow is in the nasal vestibule.[18]

Investigators have also found evidence for menthol-sensitive receptors in the nasal mucosa.[19,20] Most of the nasal mucosa is located posterior to the vestibule in the cavum of the nose. Conflicting results have been obtained when the nasal mucosa was anesthetized, with investigators finding that it caused a sensation of more, unchanged, or less patency.[20] Clarke and Jones[21] reported that if airflow is carefully controlled, nasal mucosal anesthesia has little effect on sensation, suggesting that the most important receptors for the sensation of patency are in the vestibule.[21] Aldren and Tolley[19] concluded that both ves-

tibular skin and the caval mucosa contribute to the sensation of patency or obstruction, but that the nerve endings in the vestibule have the greatest effect. Clarke and Jones[21] thought that, rather than cold receptors detecting airflow, it is more likely that flow sensation results from an interplay of "peripheral signals—tactile, thermal and perhaps chemical."[21] Eccles[16] believed that any damage to trigeminal sensory nerve endings, whether vestibular or caval, may cause a sensation of nasal stuffiness even though resistance is unchanged or decreased.

Wight and colleagues[22] found that radical turbinectomy results in a greater likelihood of improvement in symptoms than anterior turbinectomy, even though both lead to a decrease in resistance. There are two possible explanations for this finding. One is that more than airflow is involved in the experience of symptoms in the patients who had turbinate surgery. The second is that an airflow phenomenon occurs along the unresected portion of the turbinate, which causes persistent symptoms. It is of smaller magnitude than the larger anterior pressure drop and so is not reflected in the result of improved resistance. This theory would suggest that it might still be important to correct pathologic conditions in a more posterior location to provide symptomatic relief. This suggestion is consistent with the statement by Bachmann[23] that the effect of the anatomy in the posterior sector of the nose has been undervalued.

Pathologic Conditions

Most patients are aware of the nasal "congestion" that occurs with certain illnesses or pathologic conditions. These include responses to upper respiratory infection, allergy, sinusitis, and other conditions, such as mucosal hyperreactivity, septal, valve, or other structural deformities of the nasal airway, infections, polyps, tumors, crusting, granulomatous conditions or vasculitides, neoplasms, perforations, and synechiae.

Physicians, whose goal in treating patients is to help improve the patients' quality of life, seek to choose the therapeutic intervention that has the best chance of being helpful. Many therapeutic interventions are directed at increasing the dimension of the nasal airway. Therefore, having the maximal amount of data about each patient's airway gives the physician a greater chance of success in treating the patient. Objective testing can provide such information.

Assessment of Nasal Breathing Function

Patient History

The first way of assessing nasal breathing function is by taking a patient's history. The patient is asked specifically about the symptom of nasal obstruction. If it is present, the side of obstruction, its severity, frequency, and duration, and exacerbating factors are recorded. In addition, questionnaires are sometimes used for assignment of specific scores for symptoms and quality-of-life issues related to nasal obstruction.[1] A good questionnaire should be valid, reliable, and responsive to changes. Questionnaires may be generic (measuring general health), such as the Medical Outcome Survey Short Form 36 (SF-36), or disease-specific, such as the Rhinitis Quality of Life Questionnaire (RQLQ), the Sino-nasal Outcome Test (SNOT-20), and the Rhinosinusitis Disability Index (RSDI).[24] Several other methods have been used for recording the severity of symptoms.[25-27] A common method asks the patient to record the severity of a blockage by using the descriptors "none," "mild," "moderate," and "severe." Sipilä and coworkers[28] used four categories for severity of symptoms, including "very patent" for the sensation that the airway was more open than normal. All of these descriptions represent the patient's subjective evaluation of nasal breathing function.

Nasal Examination

Another way of evaluating nasal breathing is the physical examination of the nose. Methods of recording rhinoscopic findings can be detailed.[29] These methods include an assessment by the physician of the appearance of the intranasal anatomy, the cross-sectional area, and the condition of the lining tissues of the nose. This assessment is made with the aid of a speculum and headlight or head mirror. In addition, endoscopy may be performed, typically with a small flexible scope but sometimes with a rigid scope.

The endoscope has the advantage of visualizing parts of the nasal airway, such as polyps and other pathology, that may not be seen with a headlight and speculum. The endoscopes may also be used for visualizing the area of the internal valve without any potential speculum effect. Endoscopes, however, have the disadvantage of a two-dimensional "fish-eye" view that may not give a clear assessment of relative adjacencies of structures that may contribute to obstruction. These observations are the examiner's subjective assessments of anatomic factors that might affect the patient's nasal breathing. There have been attempts to "objectify" nasal endoscopy digitally by recording the endoscopic examination and measuring photographs. These measurements are influenced by lighting, equipment, positioning, and so on.

Maneuvers performed as part of the examination can help elucidate the nature of a nasal obstruction. One simple test is to occlude one side of the patient's nose at a time and ask the patient to compare the nasal breathing through the two sides. It is very important that the examiner then looks to see whether his/her visual assessment of the airway matches the patient's subjective impression. To assess the effect of the nasal valve, the patient's cheek can be drawn back (as in the presence of Cottle's sign)[30] to see whether a significant decrease in obstruction occurs. Alternatively, the patient can be asked how much improvement in breathing is noted when the valve area is held open with a nasal speculum, with one of the commercially available adhesive plastic strips or dilators, or with a wax curette. These tests are easy to perform and are noninvasive; however, they require subjective appraisal by the patient and clinician and thus are not easily quantified objectively.

Objective Testing of the Nasal Airway

The next step in the evaluation of the nasal airway is an objective measurement of the physical parameters affecting nasal breathing; this is the focus of the rest of this chapter. An objective assessment can involve measurement of the intranasal anatomy, including the cross-sectional area and volume, or measurement of properties of the air stream through the nose, including the transnasal pressure and airflow. Other tests have measured the volume of air in each breath and even the amount of nasal sound transmitted by the nasal airway.

History of Objective Testing of the Airway—Starting with Some Simple Office Maneuvers

At the turn of the 20th century, objective testing methods used included having the patient breathe on a mirror or glass plate (rhinohygrometry), assessing the sound of a forced expiration through the nose, and evaluating the pitch of the sound made by a patient humming while first one and then the other side of the nose was occluded.[31,32] The mark made by warm airflow in rhinohygrometry has been quantitated.[33] Foxen and colleagues[31] and Kosoy[34] have described the history of the development of rhinomanometry. Various types of equipment and methods have been developed for performing this measurement.[35] *Rhinomanometry*, the assessment of transnasal pressure and flow, has been a useful tool. The early rhinomanometers had a long warm-up time, producing variations in measurements when the machine was first turned on. In the past, recordings of pressure and flow have been made with strip-chart recorders, oscilloscopes, and x-y plotters. In the late 1970s rhinomanometry was first performed using the then-newer technology of the desktop computer. The computerization of airway testing allowed simultaneous storage, calculation, analysis, and printing of test results.[36,37] In the early 1980s, the first reports of acoustic rhinometry emerged. Because of its relative ease of use, acoustic rhinometry became one of the more widespread methods of objective airway assessment.

Criteria for a Good Objective Test of the Nasal Airway

A number of desirable criteria for a nasal airway test have been described.[38] They include ease of performance with readily available equipment; no discomfort for the patient; no interference with the nasal anatomy or airflow; an objective means of assessment that is accurate, reproducible, and standardized; availability of normal values; use of physiologic levels of the parameters measured; and clinical usefulness. Available tests vary in their ability to fulfill these criteria.

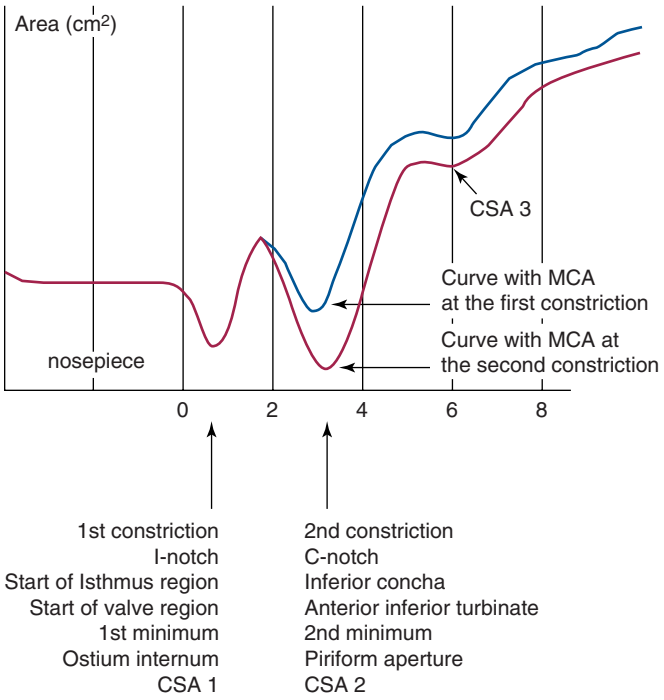

Figure 42-2. Typical area-distance curves obtained with the use of acoustic rhinometry. Two curves are shown, with the first parts overlapping. The different synonyms for the two minima on the curves are shown. The upper curve shows the minimal cross-sectional area at the first constriction, and the lower curve shows the minimal cross-sectional area at the second constriction. CSA, cross-sectional area; MCA, minimal cross-sectional area.

Tests That Assess Intranasal Dimensions and Cross-Sectional Area

The cross-sectional area of the nose can be assessed by computed tomography (CT), magnetic resonance imaging, fiberoptic endoscopy,[39] rhinostereometry, and acoustic rhinometry. *Acoustic rhinometry*, the most commonly used of these methods, analyzes the changes in a reflected incident sound wave ("click") that is passed into the nose. The various anatomic structures inside the nose, such as the inferior turbinates, septum, and middle turbinates, cause changes and distortions in the reflected wave. The cross-sectional area may be estimated from the magnitude of the distortions, and the distance of the reflected anatomy can be estimated from changes in the reflected sound wave. Acoustic rhinometry gives a profile of the cross-sectional areas through the nose and the volume of the nasal cavity (Fig. 42-2). Investigators have found a correlation between cross-sectional area as measured by CT scanning and that measured by acoustic rhinometry.[32,40] In addition, magnetic resonance imaging data have been correlated with cross-sectional area as measured by acoustic rhinometry in the decongested nose.[41] There is a correlation between volume measured by acoustic rhinometry and that measured by use of a water displacement method.[32] The application of acoustic rhinometry is described in more detail later on.

Rhinostereometry involves the use of a microscope for assessing changes in nasal congestion.[42] Rhinostereometry has been shown to be useful for the detection of the nasal cycle; however, a good correlation of results with those of acoustic rhinometry is not observed when the two are directly compared.[43] This method has been used for research into the effects of medication on nasal mucosal blood flow.

There has been growing interest in the use of CT with computational fluid dynamics (CFD). This method entails using high-resolution CT images to define the airspace of the nose. Then computer software is applied to this airspace to calculate its fluid dynamics and to derive the airflow vectors throughout the nasal airway. This technique is being explored as investigators continue the quest for optimal parameters that correlate with the symptom of nasal obstruction.[44]

Tests That Assess the Air Stream through the Nose

Rhinomanometry and the nasal peak flowmeter both measure transnasal flow. Rhinomanometry also measures transnasal pressure, allowing the calculation of nasal resistance (pressure/flow).

Nasal Airflow and Transnasal Pressure

Airflow through the nose occurs because there is a difference in pressure across the nasal airway, with the airflow occurring from an area of higher pressure to an area of lower pressure. Although the pressure outside the nose is relatively constant, the pressure in the nasopharynx changes with the respiratory movement of the chest. This change creates a pressure differential (the transnasal pressure) across the nose, and air moves back and forth through the nose with the phases of respiration.

Physical Factors Affecting Nasal Airflow

Airflow through the nose depends on the length and cross-sectional area of the nasal airway, the pressure gradient across the nose, and the character of the airflow (laminar vs. turbulent). The cross-sectional area of the nose is a major factor in the determination of airflow. At a given transnasal pressure, the airflow is greater as the cross-sectional area increases. The cross-sectional area varies along the length of the nose. The effect of turbulence in the nasal airway has not been quantified precisely. Laminar flow occurs in a smooth-walled, straight tube at low flow rates, but turbulence can occur when irregularities are encountered in the tube or at higher velocities. Computational fluid dynamics has suggested that more of the nasal airflow is laminar than was previously thought, with turbulence occurring along the boundaries where exchange of moisture and particles occurs. Turbulent flow requires more energy but results in better mixing of the air, thereby enhancing the humidification function of the nose.

Measurement of Peak Nasal Airflow

The readily available peak *expiratory* flowmeter has been used for assessment of the nasal airway, and the results are correlated with nasal resistance,[45] but may be unreliable possibly due to changes in effort.[46] A nasal peak *inspiratory* flowmeter has been studied.[47] In children, the measurement of peak nasal inspiratory flow has the drawback of depending on the extent of cooperation of the child and on the subjective impression of the observer about when a maximal effort has been made.[48] Measurement of peak inspiratory flow is less sensitive than rhinomanometry for detecting changes in nasal patency after histamine challenge[49] and with increasing doses of xylometazoline.[50] Measurements with the portable nasal spirometer have been shown to correlate well with results of rhinomanometry for the detection of the nasal cycle.[51] This is a simple measurement that requires minimal equipment.

Simultaneous Measurement of Transnasal Pressure and Airflow: Rhinomanometry

Rhinomanometry is the simultaneous measurement of transnasal pressure and airflow. Rhinorheomanometry, rhinomanometry, rhinometry, and rhinomanography are names that have been applied to these measurements. The International Standards Committee for the Objective Assessment of the Nasal Airway has chosen the term rhinomanometry.[52] In subsequent sections, we describe equipment and methods for performing rhinomanometry as well as reported results and clinical applications.

Other Methods of Objective Assessment of the Nose

Other objective tests have been performed for assessment of various components of the nasal airway. Investigators have used laser Doppler velocimetry to study mucosal blood flow in the nose.[53] Manometric rhinometry[54] is a technique in which the volume of air in the nose is assessed by closing off the nose, removing a volume of air, and then recording the resultant pressure change. In forced oscillation rhinomanometry,[55-57] the oscillation of a loudspeaker provides a complex signal

of sinusoidal sound waves, which is coupled to the patient through a small mask and a pneumotachometer. Nasometry measures the oral and nasal acoustic ratio across a specified frequency range. This test may be performed more easily than rhinomanometry, particularly in children, because it does not require a mask or a pressure cannula.[58] Olfactory testing and tests of ciliary function are objective assessments of nasal function covered in other chapters.

Comparison of Acoustic Rhinometry and Rhinomanometry

Of all the methods described, rhinomanometry and acoustic rhinometry are the most commonly used. With the current microprocessor-assisted devices, equipment capable of rapid and sophisticated airway assessment has become readily available. There is a correlation between the cross-sectional area of the nasal airway measured by acoustic rhinometry and the area found from calculations based on data from rhinomanometry.[32] The results of both acoustic rhinometry and rhinomanometry are abnormal in habitual snorers.[59] There is a correlation between the results of rhinomanometry and acoustic rhinometry in a study of normal subjects before and after decongestion, but the relationship is weak.[60] Investigators have found comparable results for acoustic rhinometry and rhinomanometry when performing nasal challenge testing.[61,62] The two techniques provide complementary information.[14] Rhinomanometry determines nasal patency in terms more representative of how difficult it is for a person to breathe, and acoustic rhinometry is preferable to study rapidly changing mucovascular conditions and nasal volume changes. Both methods can give information about a site of obstruction, but acoustic rhinometry gives more precise anatomic information.

Intranasal Sites Assessed by Rhinomanometry and Acoustic Rhinometry

Various Sites of the Minimal Cross-Sectional Area Verified by Rhinomanometry and Acoustic Rhinometry

The *MCA* is the anatomic site of the minimal cross-sectional area. It would seem appropriate to designate the anatomic site of the MCA as the valve, but this would be confusing because, historically, the valve is the specific anatomic area described in the first section of this chapter. Consequently, we use the term MCA to refer to the location of smallest cross-sectional dimension which is thus likely to be the location of greatest restriction. Is the site of greatest constriction (MCA) located at the ostium internum or in the region posterior to this, or at the head of the inferior turbinate at the piriform aperture? Apparently it varies in location within the valve region. This conclusion is supported by data from acoustic rhinometry. Normal variations in anatomy may explain these differences.

Usually two constrictions are noted on the typical area-distance curve obtained with acoustic rhinometry. Calibrated probes have shown that the first constriction occurs at the triangular entrance of the valve region, and the second is at the entrance of the bony cavum. The first constriction as well as the second can be reduced by decongestion. With decongestion, the resistance decreases across both the nasal vestibule and the first part of the cavum. Erectile tissue related to the valve region can be found not only in the turbinate but also in the caudal septum and the lateral nasal wall. The septal erectile body in the medial wall of the valve explains the opening of the first constriction with decongestion, as noted with acoustic rhinometry.

In some patients, the MCA before decongestion corresponded to the anterior tip of the inferior turbinate (second minimum). After decongestion, it shifted forward to the first minimum (ostium internum, start of valve region). The average distance to the MCA before decongestion was 2.23 cm (range 0.6-3.3 cm), and after decongestion it was 1.53 cm (range 0.44-3.03 cm). The MCA in 134 normal individuals is usually at the first constriction and does not decrease with decongestion. Because the MCA is usually at the first constriction, this is called the "I-notch," for isthmus nasi. The first constriction at the opening to the valve region (ostium internum) is the MCA before decongestion and the second constriction (the anterior edge of the inferior turbinate) is the "isthmus nasi" posterior to the ostium internum. Some confusion arises from the association of both the first and second constrictions with the isthmus nasi. This can be considered the "isthmus region" rather than a single location. Decongestion affects the second minimum more than the first.

The acoustic rhinometry area-distance plot for the normal patient has the smallest dimension (lowest minimum) in the anterior valve region (sometimes referred to in European publications as the "ascending" or "rising" w), whereas in a patient with mucosal disease before decongestion, or a patient who has had allergen challenge, the smallest dimension might be in the area of the anterior tip of the inferior turbinate (the "descending w"). With decongestion, the MCA moves anteriorly, probably owing to shrinkage of the inferior turbinate. In patients with severe septal deflection anterior to the inferior turbinate, no anterior shift in MCA occurs with decongestion. After correction of the septal pathology, the MCA may move anteriorly with decongestion as in the normal patient.

Rhinomanometry, when performed with the use of the pressure drop across the entire nose, largely reflects this narrowest effective cross-sectional area of the nasal airway, because the greatest part of the resistance drop occurs at the narrowest site. We call this assessment of the smallest dimension found by rhinomanometry the *physiologic* MCA estimate. Acoustic rhinometric measurements yield an area-distance display that allows the measurement of the smallest cross-sectional area for the anatomic presentation of the instrument. We refer to this smallest dimension determined by acoustic rhinometry the *anatomic* MCA estimate. Acoustic rhinometry also yields the distance to the narrowest area. Figure 42-2 illustrates how the MCA can move after decongestion. One of us (JC) suggests naming the cross-sectional areas found by acoustic rhinometry CSA1, CSA2, and CSA3. The ability of acoustic rhinometry to evaluate the valve region has been confirmed by CT and endoscopy. The extent to which the *physiologic* MCA estimate and the *anatomic* MCA estimate are similar reflects the extent to which acoustic rhinometry and rhinomanometry provide similar assessments of the nasal airway.

Acoustic Rhinometry

Equipment

A hollow plastic tube conducts a sound pulse ("click") generated by a trigger module into the nasal cavity. An appropriate external nosepiece is placed against the nares, with care taken not to distort the nasal alae. (Most testers no longer use internal nosepieces because they may cause distortion of the nasal valve.) The acoustic wave is reflected from the nose and recorded as digital impulses by an analog-to-digital converter for computer analysis. Calculated area-distance graphs and volumes are generated onscreen and printed with the use of mathematical algorithms.

Technique

Testing should be performed in a quiet room, with the patient seated comfortably. A test acoustic wave is used for calibrating the equipment. The patient's head may be stabilized by fixing the gaze on a faraway object. The subject may be requested to hold their breath, but this is not mandatory. The nosepiece is aligned against the nares at an angle parallel to the nose and held gently without causing alar distortion. A seal is facilitated by use of a surgical lubricant on the tip of the nosepiece. The acoustic pulse is then generated; the nosepiece should be held still for 10 seconds. An appropriate curve is generated on the computer screen. The procedure is then repeated on the other side. A second set of readings may be taken 10 minutes after application of oxymetazoline or another suitable topical decongestant. The graphs before and after decongestant application offer a way of quantifying both mucosal and structural components of obstruction. The curve generated on the computer from the reflected sound waves shows an estimated distance in centimeters on the *x*-axis and estimated cross-sectional areas in square centimeters on the *y*-axis. "0" is the nosepiece. The distance is commonly measured at 2, 4, and 6 cm; the results become less accurate after 6 cm.

A typical graph before and after administration of decongestant is shown in Figure 42-2. The minimal cross-sectional areas (CSAs)

usually observed are CSA1, CSA2, and CSA3. Some publications may describe these as "valleys" or I-notch (isthmus-notch). Recommended standards and interpretation methods have been recorded for adults and children.[63-66]

Reporting Results

The graph is usually printed with results "before" and "after" decongestion; cross-sectional areas CSA1, CSA2, CSA3, and estimated volume are recorded. The congestion factor may be calculated and the sides compared with each other. A consensus report from the European Community by Clement and Gordts[67] provides standardization recommendations. CSA1 is usually the nasal valve area; CSA2 may be located at the anterior head of the inferior and/or middle turbinate. Nasal examination, endoscopy, or both should be used for correlating the area of CSA2 for an individual patient. The values of CSA1, CSA2, and CSA3 (mid-posterior end of the middle turbinate) are recorded and compared with normative values.

Technical Concerns and Testing Pitfalls

The accuracy of acoustic rhinometry decreases after 6 cm. Results are also distorted if there is a very small nasal constriction anteriorly. The room should be quiet and should have controlled temperature and humidity. The selection of nosepieces used, the quality of the seal, the position of the patient's head, probe position, and movement can also throw off readings. These are minor and can be avoided easily with instruction and standardization of the technique by the test operator.

Interpretation of Results

Mucosal "congestion" may be measured by calculation of the "congestion factor." The severity of blockage is calculated by comparison with normative standards. More than 2 standard deviations at *each* CSA is considered abnormal. The congestion factor may be designated as normal, mild, moderate, severe, or markedly severe.

$$\text{Congestion factor} = \frac{(\text{decongested CSA2 value} - \text{baseline CSA2 value})}{\text{baseline CSA2 value} \times 100}$$

Rhinomanometry

Equipment

Various types of equipment have been developed for performing these measurements. A mask is attached to a device that measures transnasal pressure and flow and interfaces with a computer. Polymeric silicone (Silastic) tubing comes with the device. The manufacturer should provide a source for tape to connect the tubing to the nostril for pressure detection. Current manufacturers of rhinomanometers can change with time and can be searched for on the Internet.

Technique

Before proceeding with the testing, the tester should calibrate the device as recommended by the manufacturer. The International Committee on Standardization of Rhinomanometry has concluded that active anterior rhinomanometry is the preferred method of measurement.[52,68,69] Refer to Figures 42-3 to 42-11 for the description and illustration of the method of rhinomanometry.

For children, a smaller face mask can be used, but the test is performed in the same way as for adults. For patients whose chief complaint is nasal obstruction when recumbent, additional studies can be performed with the patient in the supine, right-side lying, and left-side lying positions, preferably with appropriate delay after positioning before testing. For patients with suspected allergic rhinitis, nasal provocation testing can be performed. Often, simultaneous display of the pressure-flow curve is provided so that mask leaks or other problems with data collection can be detected and corrected during the test. After the pressure and flow data are collected with the use of rhinomanometry, various parameters can be calculated from these data that are stored in the computer.

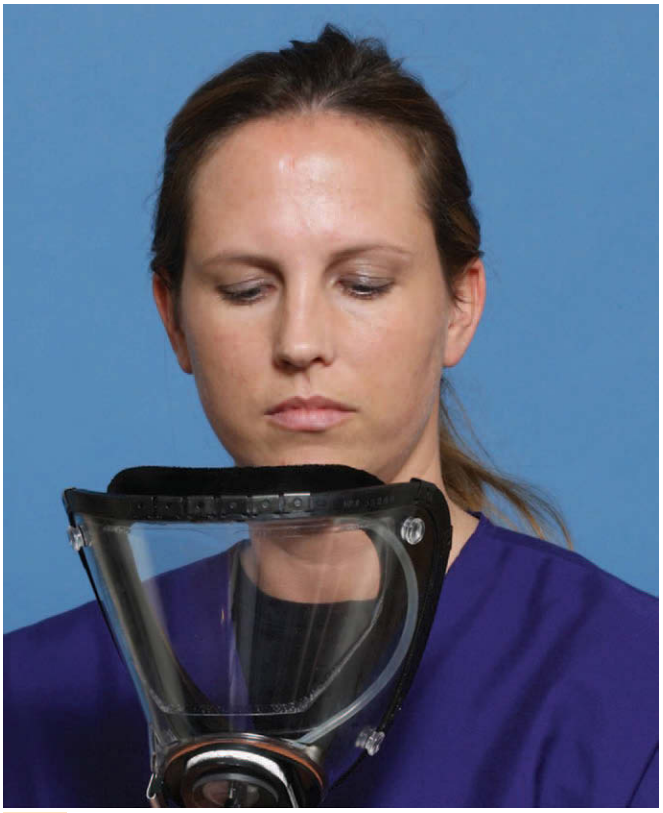

Figure 42-3. The technique of anterior rhinomanometry. The patient is in a sitting position (supine position may be added for patients with a history of nighttime congestion). The patient's name, number, and other information are entered into the computer database on the rhinomanometer. The patient is given the mask to hold, and then is instructed to put it on the face with the chin in the appropriate location and to take several breaths with the mouth closed. This relieves any apprehension about wearing the mask and also verifies appropriate fit. The mask is then removed from the face.

Figure 42-4. The technique of anterior rhinomanometry (*continued*). If the machine requires a baseline collection (similar to adjusting a digital bathroom scale to zero), it is performed before any connection to the device.

Technical Concerns and Testing Pitfalls

Measurement of Transnasal Pressure in Rhinomanometry: Anterior versus Posterior Rhinomanometry

Pressure across the nose must be measured at the front and back of the nose so that the transnasal pressure difference can be determined. Three

Figure 42-5. The technique of anterior rhinomanometry (*continued*). The right nasal airway is tested first. **A,** The appropriately shaped tape to cover the left nostril is fastened to the pressure tube that comes into the inside of the mask (for nasopharyngeal pressure detection). **B,** This in turn is attached to the left nostril, leaving the right nostril open for testing its airflow.

Figure 42-6. The technique of anterior rhinomanometry (*continued*). The mask is then put in place on the patient's face **(A)**, and the pressure tubing is adjusted as the tester views it through the mask and verifies that it is correctly positioned and not kinked **(B)**.

methods of transnasal pressure detection are currently in use: anterior rhinomanometry, posterior (peroral) rhinomanometry, and postnasal (or pernasal) rhinomanometry.[70] The major difference in these three approaches is the location of the pressure detector at the back of the nose. In the anterior method, it is placed at the opening to the nostril not being tested (see Figs. 42-5, 42-9, and 42-12). In the posterior method, the pressure detector is placed transorally in or close to the posterior oropharynx (Fig. 42-13). For the postnasal (pernasal) technique, the tube is placed in the posterior nose through one of the nostrils (Fig. 42-14).[70] The tube is connected to a pressure-measuring device which allows a computer to record the transnasal pressure as the patient is breathing.

In general, anterior rhinomanometry is most widely used as a clinical tool because it is easily performed.[71] Anterior and pernasal methods require little patient effort or cooperation, and the anterior method does not require a tube in the nose or mouth. By contrast, for the posterior method, the patient must be coached in the correct positioning of the tongue and palate to keep both the oropharynx and nasopharynx open so that the technique can be performed. It has been shown that 15% of patients are not able to perform this positioning.[70] A limitation of the anterior method is that it cannot be used for measuring the nasal airway in patients who have a nasal septal perforation. None of the rhinomanometric methods can be used if the nose is totally obstructed.

Measurement of Nasal Airflow in Rhinomanometry

Nasal airflow is best measured with the use of a face mask large enough so that it does not distort the external nasal structures. The nasal airflow is measured by a device attached to the front of the mask (see Figs. 42-4, 42-6, and 42-7) that sends the flow readings to the computer. A nozzle can also be used, but it has a greater potential to distort nasal structures.

Plethysmography is another way of assessing airflow. The patient sits in a volume-displacement body plethysmograph, which detects changes in the volume of the thorax by measuring the amount of air displaced from the plethysmograph during respiration. This respiratory volume change corresponds to the nasal airflow; therefore, a mask is not needed. This method has the advantage of allowing instrumentation of the nose during the test, which can be useful for research. The body plethysmograph is less portable, however.

Active versus Passive Rhinomanometry

Active or passive methods can be used for measuring the pressure and flow of air through the nose. In one passive method, pressure is measured as the subject holds their breath while air is pumped through the nose at a known rate. Active methods use the patient's own respiratory efforts as a source of pressure and flow. Active rhinomanometry is the method used today for two reasons: It is easier to perform, because it

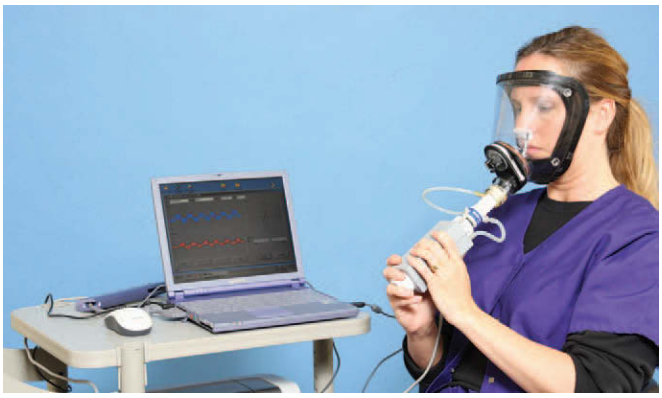

Figure 42-7. The technique of anterior rhinomanometry (*continued*). The patient is instructed to close the mouth and to breathe in and out. The pressure-flow curve is visualized on the computer display, and any needed adjustments are made. The collection is completed, and the pressure-flow data are saved on the computer.

Figure 42-8. The technique of anterior rhinomanometry (*continued*). The mask is removed, and the tape is removed from the left nostril. If the machine requires a baseline collection, it is performed before any connection to the device for the next measurement.

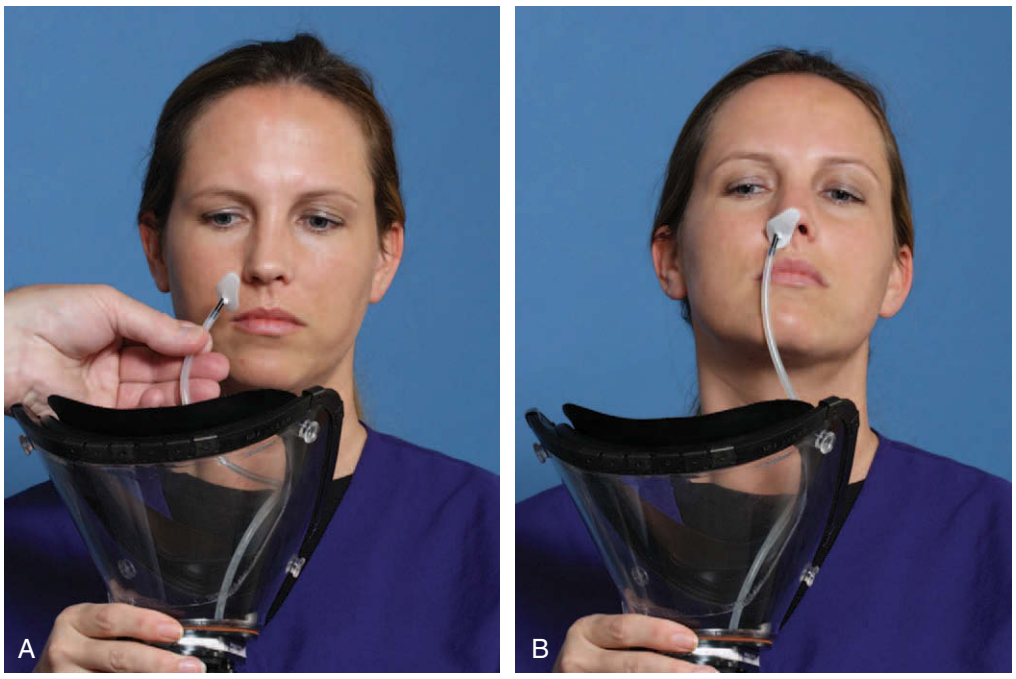

Figure 42-9. The technique of anterior rhinomanometry (*continued*). **A** and **B,** The tape is applied to the right nostril, leaving the left nostril open for testing.

Figure 42-10. The technique of anterior rhinomanometry (*continued*). The mask is then put in place on the patient's face and the pressure tubing is adjusted as the tester views it through the mask and verifies that it is correctly positioned and not kinked. The patient is instructed to close their mouth and to breathe in and out. The pressure-flow curve is visualized on the computer display, and any needed adjustments are made. The collection is completed, and the pressure-flow data are stored on the rhinomanometer computer. The data are stored and printed out.

Figure 42-11. The technique of anterior rhinomanometry (*continued*). If testing will be performed with dilating plastic strips or other dilating devices, these are placed and the preceding procedures are repeated for both sides of the nose. The results are stored and printed out. If testing will be done after both dilation and nasal decongestion, the decongestant spray is placed in the nose. Five minutes later the nose is again sprayed. Ten minutes later both sides of the nose are tested in the manner described previously. Results are stored and printed. If testing will be done with nasal decongestion alone, the dilators are removed (if they were used), and testing is performed as described previously. Results are stored and printed out.

does not require an external source of airflow, and it allows assessment of the pressure-flow ratio at various locations on the pressure-flow curve rather than at a single fixed flow or pressure.

Unilateral versus Bilateral Measurements in Rhinomanometry

For measuring the total nasal airway, both sides of the nose can be measured simultaneously with posterior rhinomanometry, or the total nasal airway values can be calculated from unilateral measurements. Anterior rhinomanometry does not allow direct measurement of the total airway because one side of the nose is plugged. Thus, with the anterior method, the total nasal airway values should be calculated from the two unilateral measurements. Through parallel nasal airways, for the same given pressure on both sides of the nose, the flows of the right and left sides of the nose can be added to yield the total nasal airflow (Fig. 42-15).

Reporting Results

Once the pressure and flow data have been collected, appropriate filtering, averaging, and selection of data can be completed. The results are then assessed and reported with one of several available methods. The most common result reported is nasal resistance, which is the ratio of pressure to flow, sometimes abbreviated as NAR or Rn.

The International Committee on Standardization of Rhinomanometry has recommended that rhinomanometric values be expressed in SI units, with pressure expressed in pascals (Pa) and flow expressed in cm^3/sec (100 Pa = 1.0 cm H_2O; 1000 cm^3/sec = 1 L/sec). Nasal resistance is reported in $Pa/cm^3/sec$ (0.1 $Pa/cm^3/sec$ = 1 cm H_2O/L/sec).[52,68,69]

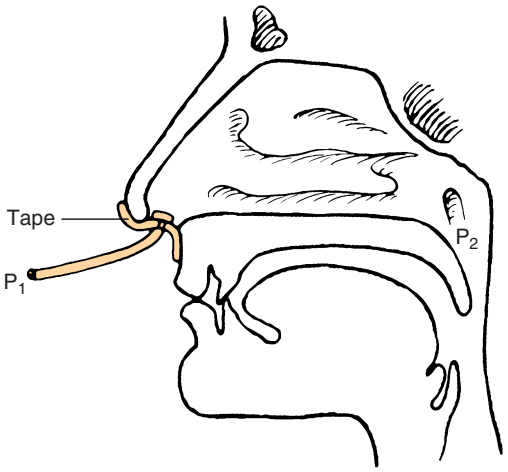

Figure 42-12. Placement of pressure tubing for anterior rhinomanometry. Tape occludes the nostril on one side; that side acts as an extension of the tubing so that the pressure at the end of the tube (P_1) equals the pressure in the nasopharynx (P_2).

Examining the Pressure-Flow Curve

One way of appraising the data is to examine the pressure-flow curve. In nasal breathing, the difference in pressure across the nose causes air to flow through the nose (Fig. 42-16A). If an increase in transnasal pressure caused an increase in flow that was always of the same propor-

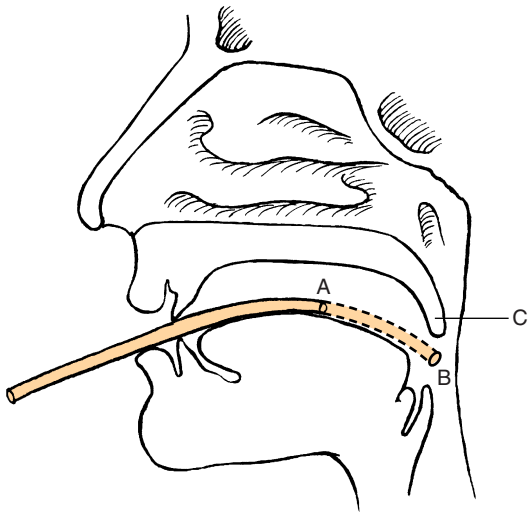

Figure 42-13. Placement of pressure tubing for posterior rhinomanometry. Site A works as well as site B and avoids stimulation of the base of the tongue. The soft palate (C) should be relaxed.

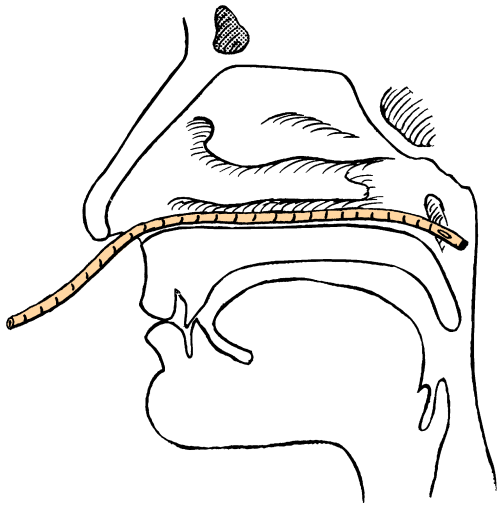

Figure 42-14. Placement of pressure tubing for postnasal (pernasal) rhinomanometry.

tion, the nasal pressure-flow plot would be a straight line. In reality, the plot is usually curved (Fig. 42-16B to E), with a sigmoid shape. The amount of curvature can vary among different pressure-flow curves. Flattening of the curve may represent limitation of flow from an airway restriction such as collapse of the valve area.

The more obstructed the airway, the greater the pressure required to generate a certain flow. The accepted standard for displaying the pressure-flow curve is to plot pressure on the *x*-axis and flow on the *y*-axis. With this arrangement, the greater the pressure-to-flow ratio (resistance), the closer the curve is to the pressure axis (Fig. 42-17). Thus, curves representing a more obstructed airway lie closer to the pressure axis.

Reporting Rhinomanometric Parameters

All Parameters Are Not the Same

Data from the pressure and flow curves can be used for calculating and reporting various parameters. The most commonly reported parameter

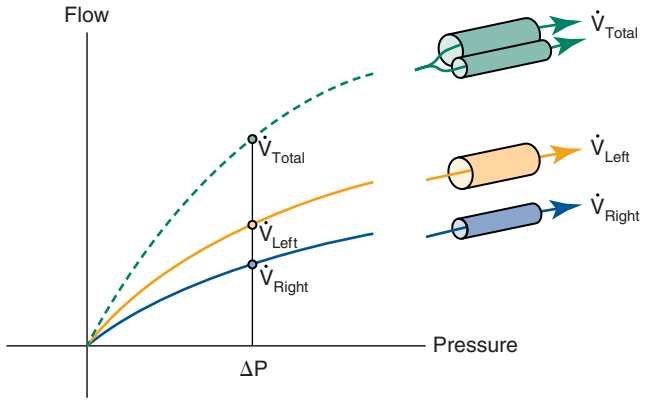

Figure 42-15. The calculation of total nasal airflow at a given transnasal pressure: $\dot{V}$ = flow; $\dot{V} = \dot{V}_{Right} + \dot{V}_{Left}$. ΔP, transnasal pressure.

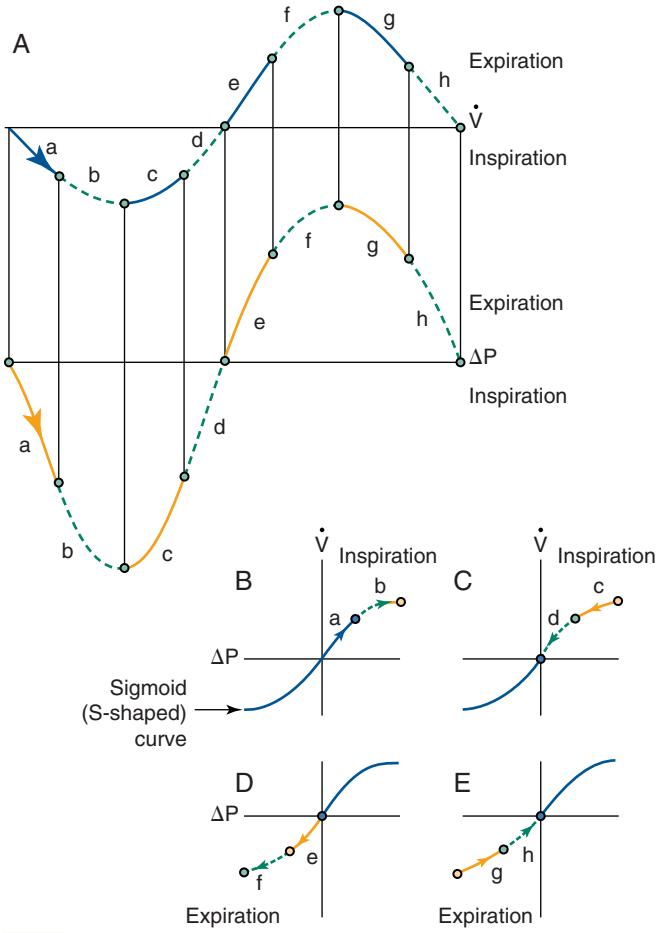

Figure 42-16. **A,** One respiratory cycle as seen on flow and pressure tracings and on the pressure-flow plot. **B** (*a-b*), Inspiration, phase of acceleration of airflow. **C** (*c-d*), Inspiration, phase of deceleration of airflow. **D** (*e-f*), Expiration, phase of acceleration of airflow. **E** (*g-h*), Expiration, phase of deceleration of airflow. ΔP, transnasal pressure; $\dot{V}$, flow.

is resistance as defined previously. Different methods of reporting resistance have yielded different results,[57,72] in part because the resistance values are obtained at different locations on the pressure-flow curve (Fig. 42-18), which is nonlinear. Pressure-flow curves may have varying amounts of curvature, causing the resistance values obtained at different points on the curve to vary in rank order, even when the same method

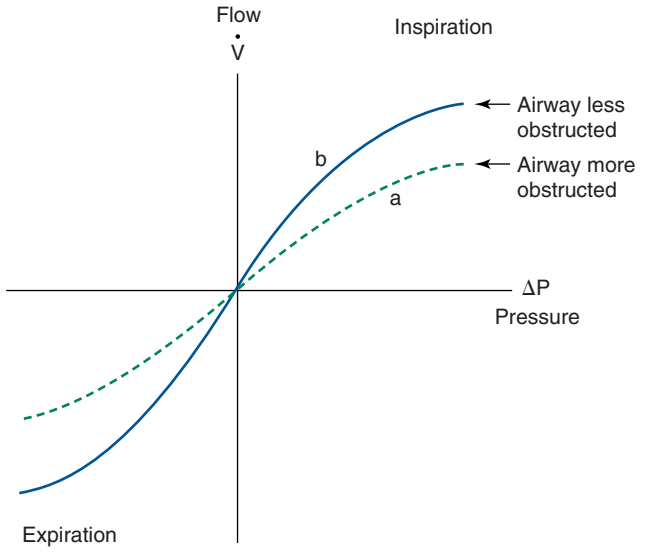

Figure 42-17. The pressure-flow curve (*a*) for a nasal airway that is more obstructed will be closer to the pressure axis than will the curve (*b*) for a nasal airway that is less obstructed. ΔP, transnasal pressure; $\dot{V}$, flow.

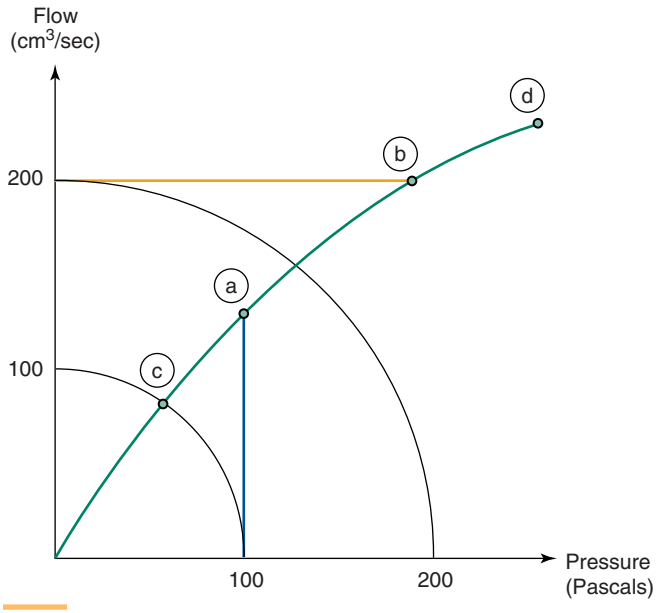

Figure 42-18. Nasal resistance can be calculated at a designated pressure (*a*), flow (*b*), radius (*c*), or maximum (*d*).

is used (Fig. 42-19). The resistance is generally higher at more distant points along the nasal pressure-flow curve. For comparisons of the results for a given patient at different times or between different patients, a consistent method would assign a consistent site on the curve for obtaining this ratio (i.e., the resistance). Furthermore, it would be best to report the parameter that has the best overall correlation with the patient's subjective symptoms.

Important Parameters to Know

A commonly used point at which the pressure-flow ratio is reported is the flow corresponding to a pressure of 150 Pascals (Pa). A voluntary increase in ventilation may be necessary for some subjects to reach a designated pressure of 150 Pa, or even 100 Pa.[73,74] This approach allows for the direct calculation of the total airway by simply adding the flows from each side of the nose at the designated pressure (see Fig. 42-15). Resistance at a designated radius (see Fig. 42-18) is also popular in

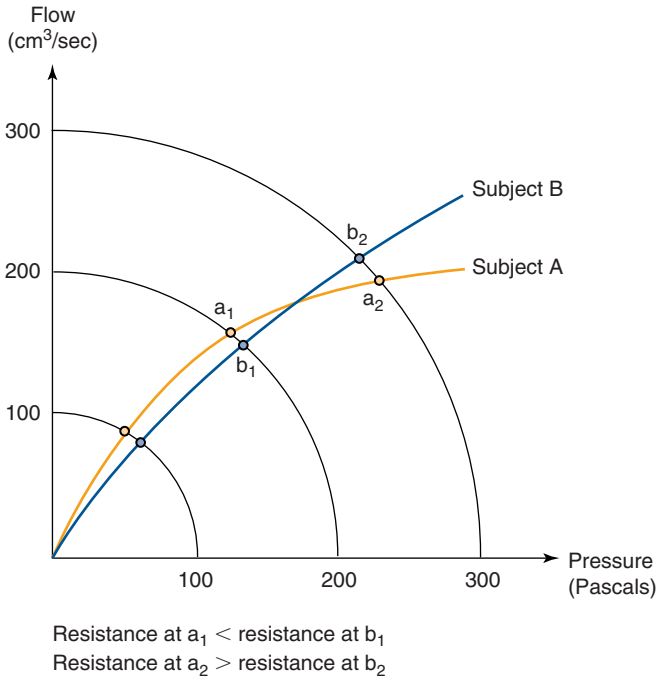

Figure 42-19. A change in the rank order of resistance values can occur when resistance is calculated at different locations on the curves from two different subjects, even though the same method (e.g., resistance at a designated radius) is used.

some countries.[75] The International Standards Committee has designated flow at 150 Pa or resistance at radius 2 to be the standard options for reporting results.[52,67] Another important parameter is the resistance at the peak pressure and flow point,[76] called the *maximum resistance* or, per Vogt,[67] the *vertex resistance*. An advantage of this method is that a result can be obtained for all patients because it is not necessary to reach a designated point on the pressure-flow curve.

Other Parameters That Have Been Used

Resistance has also been reported at a designated flow (see Fig. 42-18), at mean pressure and flow,[46] and at the origin of the pressure-flow curve.[56,77,78] Other parameters that have been reported are conductance (flow/pressure), the cross-sectional area of the nose derived from pressure-flow data,[31,79-81] the percent flow increase with a doubling of pressure (from 150 to 300 Pa),[82] power,[83] work,[36,84] the difference in resistance between the two sides of the nose,[82,85,86] the acceleration change of nasal airflow in the rapid phase from inspiration to expiration,[87] and pressure-flow curve coefficients or exponents derived by the fitting of various mathematical models to the pressure-flow-curve data. Pallanch[37] studied the ability of various mathematical models to fit the data recorded on a variety of pressure-flow curves. The best fit to the data was accomplished with a polynomial model, although polar and geometric models also worked well. Another parameter that has been used by Vogt is the "effective resistance."[67]

Comparison of the Various Parameters

With the possibility of reporting so many different parameters, it would be useful to know which is the best. The most useful clinical parameter would be the one that correlates best with the symptom of nasal obstruction. In a comparison of all of the previously listed parameters (except for the acceleration change from inspiration to expiration[87] and power[83]) for the same group of patients, the *resistance at maximum pressure and flow* (in normal respiration) (see *d* in Fig. 42-18) was found to correlate best with the symptom of obstruction.[88]

Reporting Inspiratory or Expiratory Values

Although Shelton and associates[57] found no significant difference between inspiratory and expiratory resistance values, other researchers

have reported that inspiratory resistance is significantly lower than expiratory resistance at low flows.[89-92] In quiet respiration, the resistance is higher during inspiration.[8] Most commonly, values obtained from *inspiration* are reported.

Sources of Variability in Objective Nasal Airway Testing

There are some sources of variability in rhinomanometry and acoustic rhinometry. One should try to control all nonphysiologic sources of variability without affecting the clinical information being sought. Test subjects should avoid exercise and exposure to climatic extremes for 30 minutes before testing. Patients should not be taking any interfering medications. Distortion of the alae should be avoided. Measurement should be performed in a comfortable, quiet, stable, nonirritating environment. Tobacco and coffee should be avoided before the test. By minimizing any variability caused by test conditions, investigators can obtain the most accurate and precise results.

Sources of Variability and Ways to Minimize Them

Rhinomanometry

Some variability can result from movement of the nasal alae. In persons with valve pathology or disruption of the alar muscles (e.g., after rhinoplasty), alar movement may cause variability. Alar movement is sometimes revealed by looping that occurs toward the end of the pressure-flow curve.

The rhinomanometry apparatus should be properly calibrated, and baselines set to 0. Potential variability due to the nozzle technique has been cited.[68] Masks have also introduced some variability in results.[35,78] Different mask shapes and volumes do not significantly change the results obtained in rhinomanometric measurements.[93] Visual feedback, that is, use of a real-time display of the pressure-flow curve, has been valuable in reducing variability through detection of air leaks, baseline drift, and other artifacts.[35,78,94,95]

Acoustic Rhinometry

Sources of variability in acoustic rhinometry include operator bias, the angle of incidence of the wave tube, nasal tip distortion, loss of the acoustic seal with the nostril, the size of the nosepiece, breathing or swallowing during the test, measurement beyond a severe restriction, a change in the geometry of the cavity measured, and the position or motion of the soft palate. These sources can be minimized with the use of a point for fixed gaze, placement of the tube parallel to the nose, an appropriate seal, and use of appropriate size nosepiece.

Role of Objective Testing of the Nasal Airway

Objective testing of the nasal airway can be used for clinical evaluation of the symptom of nasal obstruction, for evaluation of patients with sleep apnea, for allergy challenge testing, for pretreatment and posttreatment assessments of surgical or medical therapy, and for research in nasal physiology. Research applications in nasal physiology were covered in the earlier sections of this chapter. Evaluation of the patients with the symptom of nasal obstruction through the use of objective testing of the airway is discussed separately later.

For Patients with Snoring and Sleep Apnea

As previously mentioned, acoustic rhinometry can be used for assessment of the change in resistance that occurs when the patient is in the supine position. This change can be more severe in patients who have sleep apnea.[96] Snoring can be decreased with the use of nasal dilators that open the anterior nasal airway, thus demonstrating that nasal obstruction contributes to snoring in some patients.[97,98] Nasal obstruction due to nasal packing can cause disturbed sleep.[99] In 97% of patients with habitual snoring (some with sleep apnea), a minimal cross-sectional area (MCA) is located at the C-notch (turbinate), whereas in normal subjects, the MCA is located at the isthmus "I-notch."[59] Even with decongestion, the "C-notch" of patients who snore does not reach a normal, non-decongested size. Higher than normal nasal resistance is found in these patients, but there is no correlation between the number of apnea periods and the degree of nasal resistance.[100] Increasing the nasal airway with a dilator can reduce the apnea index.[101] In patients with allergic rhinitis, those with snoring and mild sleep apnea have significantly greater congestion at the anterior portion of the inferior turbinate as measured by acoustic rhinometry and less subjective improvement with nasal decongestion.[102] Lenders and associates[59] found that 65% of patients with habitual snoring have elevated nasal resistance but only 19% complain of the symptom of nasal obstruction. Some patients have abnormal airway study results but do not complain of nasal obstruction, and so their symptoms fall below the threshold at which they would notice obstruction. The role of objective nasal airway testing in helping to assess the contribution of the nasal airway in patients to snoring and sleep apnea will continue to evolve as investigators examine questions such as the role of airway testing in predicting compliance with continuous positive airway pressure treatment and the effect on sleep-disordered breathing of varying levels of nasal obstruction.

For Challenge Testing in Patients with Allergic Rhinitis

Nasal challenge testing is performed with the introduction of a specific allergen into the nose to assess the pathophysiologic changes that result. This use of objective testing emerged from the desire to directly test the organ affected by allergy rather than to rely on the indirect reaction manifested by skin tests.[2,103,104] Nasal provocation testing dates from 1873.[105] A technique was sought that would be reproducible, deliver a consistent concentration of the challenging antigen, and provide an objective, noninvasive assessment of the response to the challenge. Provocation testing with the use of objective testing of the airway offers the promise of fulfilling these criteria. An inflammatory reaction occurs after nasal challenge and is closely related to increases in both nasal resistance and nasal obstruction.[106] Intranasal allergen challenges with ragweed pollen in patients with ragweed allergy reproducibly cause a rise in nasal resistance with increasing doses of ragweed.[107] Rhinomanometry can provide numbers that enable calculation of the percent change from a baseline value, which is more difficult to assess with symptom scores alone.[108] Different levels indicative of a positive response or challenge have been chosen. An increase to 100% of the baseline rhinomanometric result occurs after challenge in 94% of subjects in the early phase and in 82% of subjects in the late phase; however, unilateral measurement is preferred to total measurement, because it is more sensitive in the evaluation of the late-phase nasal response.[109]

Acoustic rhinometry has also been used for challenge testing.[110] Acoustic rhinometry shows a correlation between the results of challenge testing and serum-specific immunoglobulin E (modified radioallergosorbent test) results. Acoustic rhinometry and rhinomanometry have yielded comparable results with regard to nasal challenge testing.[35,62] However, Lenders and Pirsig[111] thought that acoustic rhinometry could be more sensitive than rhinomanometry in detecting allergic rhinitis because it could reveal mucosal changes even when no change in resistance had occurred. Compared with rhinomanometry, acoustic rhinometry can be performed more quickly and requires minimal subject cooperation, which can be advantageous in challenge testing.[61] Scadding and colleagues[62] thought that acoustic rhinometry had less variability in quantifying the airway in challenge testing performed in severely congested patients.

To Assess the Effect of Treatment

For Medical Therapy

Objective testing of the nasal airway is a useful way of assessing the effect of intranasal medications, because it does not rely on subjective assessment by the patient or clinician.[112-116] Acoustic rhinometry has shown changes in cross-sectional area in patients with nasal polyps who are receiving systemic steroid treatment.[117]

For Surgical Therapy

Nasal airway testing can help in the objective assessment of the effect of surgery on the airway. Acoustic rhinometry and rhinomanometry

have value in allowing the surgeon to explain to patients why surgery has reduced or increased the severity of their nasal symptoms. Sipilä and colleagues[118] stated that objective testing could serve as "a method of quality control" by showing that nasal obstruction was not corrected in some cases. These tests have scientific value for "evaluating effects of certain surgical techniques."[119]

Documentation of Improvement in Airway Dimensions after Surgery

Investigators have found a significant decrease in nasal resistance in the more obstructed side of the nose after septal surgery[34,120-126] and after turbinate surgery.[22,123,127,128] Acoustic rhinometry showed an improvement in airway dimension after turbinate surgery,[111] but decreases in MCA after rhinoplasty.[129] Both nasal flow and cross-sectional area increase unilaterally after septoplasty on the side of obstruction, and these values decrease on the opposite side.[130] There are significant increases in nasal volume as measured by acoustic rhinometry, as well as a decrease in the sensation of congestion, after septoplasty, but not after septorhinoplasty.[131] Postoperative improvement in the severity of symptoms is associated with improvement in the nasal airway as documented by objective testing.[120,122,126,128,130,132,133]

Selection of Patients for Surgery

Is there an objective measure of preoperative nasal obstruction for which patient satisfaction will be higher after surgery? Patients with high preoperative resistance or low preoperative MCA are more likely to be satisfied with surgery than are those who have lower resistance or higher MCA preoperatively.[132,134] Patient satisfaction is highest in those with symptoms of obstruction whose nasal resistance is changed by surgery to "normal."[118] Although the MCA does not always improve with correction of septal deformities, the patient's satisfaction is correlated with the improvement in the size of the MCA and nasal volume after surgery.[135] After turbinoplasty, there is improvement in both MCA and symptoms of patency, but the amounts of improvement in the MCA and patients' satisfaction with surgery do not correlate.[136]

Suonpää and colleagues[134] questioned the possible benefits obtained when operating on patients who have normal nasal resistance preoperatively. Malm[119] suggested that it is possible to select patients for surgery on the basis of rhinomanometric data if results are obtained from the decongested nose, if correction is made for height, and if the 95% prediction limit is used.[119] Bachmann[82] thoughtfully outlined rhinomanometric indications for and against surgery and noted that "when *constant stenosis* exists and" when total flow (at 150 Pa) "is below 700 cm^3/sec then there exists a clear indication for surgery."

The Use of Objective Assessment of the Nasal Airway in the Clinical Evaluation of the Patient with the Symptom of Nasal Obstruction

If airway restriction is the suspected cause of the symptoms, objective testing results can be used together with the medical history and physical findings to aid in diagnosis and treatment. If there is a suspicion of sinusitis or other conditions that might cause symptoms of obstruction without directly restricting the airway, these can be looked for before testing is performed.

The Normal Nasal Airway

Before using objective testing to help diagnose problems with the nasal airway, the clinician must first understand how objective testing reflects the normal nasal airway. Tables 42-1 and 42-2 present unilateral and total values for normal resistance that have been reported. The values cannot always be compared directly with one another because they were obtained at different points on the pressure-flow curve. One problem in reporting of normal values lies in the criteria used for selection of normal subjects. The normal subjects listed in Tables 42-1 and 42-2 were usually considered "normal" on the basis of a lack of symptoms. Szucs and colleagues[137] concluded that lack of symptoms alone was not a sufficient criterion for the inclusion of subjects in normative studies of rhinomanometry results. Palma and associates[138] recommended that subjects described as normal also be "rhinoscopically normal."

A normal range for nasal pressure-flow curves can be indicated by a shaded area on the pressure-flow curve (Fig. 42-20).[139] Although there is no absolute level beyond which obstruction is indicated, this shaded area serves as a reference area for comparisons with a population of persons who breathe comfortably through their nose. One problem encountered in studies of a "normal" population is that resistance values are not normally distributed in a statistical sense.[1,137,139] For statistical analyses, a transformation can be performed that normalizes the distribution of the data, or nonparametric statistical methods can be used.[1,76,140-142]

Table 42-1

Unilateral Normal Mean or Median Nasal Resistance: Reported Adult Inspiratory Values

Study	Subject Description	No.	Non-decongested Value*	Decongested Value*	Side	Measured at
Pallanch et al[139]	Symptomless volunteers	80	0.33 0.42	0.22 0.28	Average Average	Radius 2 Radius 3
Unno et al[167]	No or only slight obstruction	50	0.35 0.30	— —	Right Left	50 Pa 50 Pa
Kenyon[90]	Healthy	25	0.33/0.39	0.28	Average	Radius 2
Jessen and Malm[124]	Healthy	100	0.45 0.54	0.23 0.36	Average Average	Radius 2 150 Pa
Cole[145]	Symptomless	Thousands	Varies	0.3 0.15	Average Average (with retracted ala)	Mean Mean
Sipilä et al[118]	Healthy, "normal nasal status"	97	— —	0.30 0.20	Average Average	150 Pa Radius 2

*All values rounded off and converted to Pa/cm^3/sec (0.1 Pa/cm^3/sec = [approximately] 1 cm H_2O/L/sec). In some cases, the mean value is the arithmetic mean of a skewed distribution. Ranges are not shown.

Table 42-2

Total Normal Nasal Resistance: Reported Adult Inspiratory Values

Study	Subject Description	No.	Non-decongested Value*	Decongested Value*	Method	Measured at
Rundcrantz[168]	Healthy individuals	10	0.14	—	Posterior measured	0.5 L/sec
McCaffrey and Kern[1]	Asymptomatic normal examination	23	0.22	0.15	Anterior calculated	Maximum
Connell[46]	Pedestrians on the streets of New York (some children)	263 white 30 black	0.23 0.19	— —	Anterior calculated Anterior calculated	150 Pa 150 Pa
Pallanch et al[139]	Symptomless volunteers	80	0.12 0.14 0.16 0.14 0.18 0.12	0.08 0.09 0.10 0.10 0.14 0.08	Anterior calculated Anterior calculated Anterior calculated Anterior calculated Anterior calculated Anterior calculated	Radius 2 Radius 3 Radius 4 50 Pa 100 Pa 0.2 L/sec
Unno et al[167]	No or only slight obstruction	50	— —	0.16 0.15	Anterior calculated Posterior measured	50 Pa 50 Pa
Jones et al[94]	No disease, normal examination	59	0.38	—	Anterior calculated	150 Pa
Jessen and Malm[124]	Healthy	100	0.19	0.11	Anterior calculated	Radius 2
			0.25	0.18	Anterior calculated	150 Pa
Cole[145,169]	Symptomless volunteers	800	0.26	—	Posterior measured (?)	Mean
		Thousands	0.33	—	Posterior measured (?)	150 Pa
			0.2	0.1	Posterior measured (?)	Mean
			0.25	0.12	Posterior measured (?)	150 Pa
Sipilä et al[118]	Healthy, "normal nasal status"	97	— —	0.15 0.09	Anterior calculated Anterior calculated	150 Pa Radius 2

*All values are rounded off and converted to Pa/cm^3/sec (0.1 Pa/cm^3/sec = [approximately] 1 cm H_2O/L/sec). In some cases, the value is the arithmetic mean of a skewed distribution. Ranges are not shown.

Normal MCA values are about 0.72 to 0.73 cm^2 before decongestion and 0.92 to 0.95 cm^2 after decongestion for the unilateral airway.[111,143] For the total airway, the normal MCA is about 1.46 cm^2 before decongestion and 1.88 cm^2 after decongestion.

There is a difference in airway testing results between obstructed individuals and persons with no symptoms; however, there is a large overlap between the airway values for these two groups (Fig. 42-21).[26,139,144]

The Role of Objective Testing in Revealing When Symptoms Are Not Due to Airway Restriction

The symptom of nasal obstruction can be present in a person with an open airway—for example, it can be due to atrophic rhinitis,[145] inflammation, sinusitis, psychogenic causes, or pulmonary disease. As noted previously, objective testing results correlate with symptoms and the symptom of nasal obstruction is a complex phenomenon. Airway testing can identify those patients in whom airflow restriction corresponds with obstructive symptoms and those in whom it does not. The first group has a better chance of being helped by therapy that is directed at enlarging the dimension of the nasal airway. If no airway restriction is found with testing despite the presence of symptoms, other causes must be considered. Some patients, including those with atrophic rhinitis, may have altered nasal sensation, which they misinterpret as obstruction to airflow. Edema or inflammation around the sensory nerve endings in the nasal mucosa may create a sensation of nasal obstruction by adversely affecting the function of the sensory receptors,[146] and poor pulmonary function can also lead a patient to complain of nasal dyspnea. Some patients who suffer from cardiopulmonary insufficiency find any nasal resistance load intolerable.[145]

When Airway Testing Results Do Not Match the Physical Findings or Symptoms, Further Information Can Be Discovered

It has been suggested that it may be easier just to ask patients how they feel rather than to perform objective testing.[26] Physicians continue to echo this sentiment because they believe that an operation to open the airway will help any obstructive symptoms or that airway testing results do not correlate with symptoms. The patients whose airway testing results do not match their symptoms are precisely the ones in whom the test may be of significant benefit, because it will lead to additional

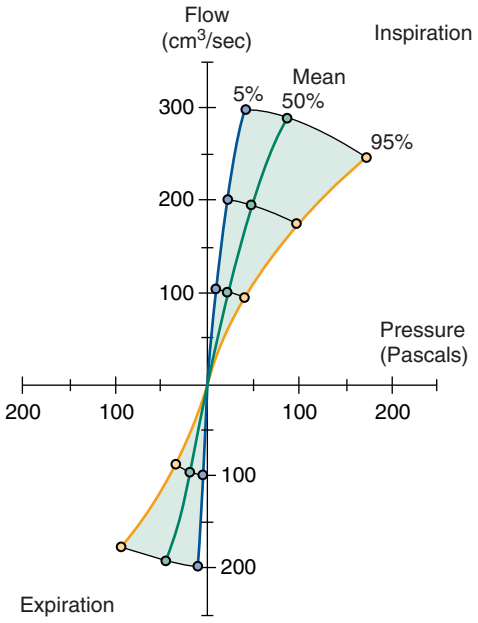

Figure 42-20. *Shaded area* defined by the 5%, mean, and 95% curves representing the range in unilateral nasal pressure-flow data after decongestion in 80 healthy adults.

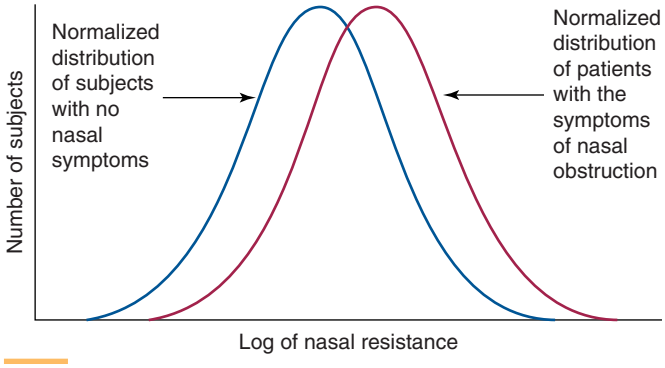

Figure 42-21. Plot of the overlap of the normalized distribution of nasal resistance data from a population of subjects with no nasal symptoms and from a population of patients with the symptoms of nasal obstruction.

discoveries regarding the nature of their symptoms. Rather than dismiss the use of objective testing because of the times when the test results do not match symptoms, "one should rather examine the causes of discrepancy," because "these causes are of considerable clinical interest."[82]

The Correlation between Airway Testing Results and Symptoms

For objective testing results to be credible when they do not match symptoms, they must in general have a correlation with symptoms.

Correlation with Side or Severity of Symptoms

The relative correlation between test results and symptoms within a given individual can be studied by checking whether the side of the nose with the greater airway restriction is the side that feels more obstructed to the patient. Another method is to determine whether the severity of obstruction correlates with the degree of airway restriction found by objective testing.

A correlation has been found between the side of symptoms and the airway test result in symptomatic patients.[88,147] Fisher and associates[148] found that side and severity of the symptoms corresponded to changes in measurements made in some subjects in whom acoustic rhinometry was used to study the nasal cycle.

It Is Easier to Find a Correlation between Objective Airway Results and Symptoms in Patients Who Have Symptoms

Some investigators have found only a weak correlation between airway testing results and the degree of obstruction in patients who do not generally have symptoms of nasal airway restriction.[60] Tomkinson and Eccles[60] conceded that the poor correlation in their study between symptoms and objective test results may have been due to lower "symptom" scores in normal subjects. A correlation *has* been demonstrated between nasal resistance and the degree of symptoms of obstruction in symptomatic patients,[2,3,28,87,106] although not in all studies.[149-151] Sipilä and colleagues[28] found that the correlation between subjective sensation and rhinomanometry results is better for unilateral than for total resistance. These findings show that the lower resistance values for normal subjects may not reflect a sufficient difference to overcome the variation in baseline (or "threshold," or "resting") resistance and thus reveal a correlation with symptoms. The lack of correlation in studies with asymptomatic patients should not pose a problem in the clinical evaluation of patients who do have the symptom of nasal obstruction.

In patients with a "nondiseased" mucosa who complain of nasal obstruction, a correlation has been found between the sensation of comfortable breathing and the results of objective testing of the airway. This finding is apparently due to disturbance of the sense that the correct amount of air is flowing past receptors in the nasal airway that many patients are able to experience. It appears to be partially a learned sensation, because patients who have never known what it is like to breathe through one side of the nose sometimes do not complain of lack of the ability to sense airflow there. A patient who is familiar with the sensation and then loses that ability (for example, with a nasal fracture) may complain of significant symptoms.

Unilateral and Total Airway Assessment

Both unilateral resistance and total resistance may be related to the patient's symptoms. It is not known whether unilateral or total results give the more meaningful correlation with symptoms. There is a significant correlation between unilateral nasal resistance and the sensation of obstruction,[87] but not always for total nasal resistance and symptoms.[152] A significant difference is found between the mean resistance of the obstructed side of the nose in patients with unilateral symptoms and the unilateral resistance in a group of normal subjects.[1,121] No difference is found with the nonobstructed side in symptomatic patients. The total resistance values for patients with moderate and severe bilateral symptoms and for patients with moderate and severe unilateral symptoms are greater than the median total resistance for normal patients.[1,121]

The total resistance may be the more important determinant of the patient's sense of well-being.[1,82] Arbour and Kern[153] described the phenomenon of paradoxical nasal obstruction in which the effect of the more open side of the nose on the total resistance is the factor determining when the patient experiences symptoms of obstruction.[153]

Correlation between Change in Symptoms and Changes in Airway Testing Results

It was noted previously that there was a correlation, in symptomatic patients, between change in symptoms and improvement in airway test results after surgical intervention.[120,122,128,132,133] Eccles[146] and Clarke and associates[155] found a correlation between changes in resistance and changes in symptoms after decongestion in normal subjects. However, Clarke and associates[155] thought that the comparison of objective test results with symptoms in normal subjects may be hampered by the large variation in resting nasal resistance and that, in normal patients, the amount of change from baseline was of greater importance for correlation with symptoms. They noted that there may be a much closer relationship between subjective and objective measures of nasal patency than they had previously thought. Cole and Roithmann[14] thought that changes in airway dimension were as useful as absolute values in many investigations.

Threshold Level at Which a Patient Feels Airway Restriction

Because there is a correlation between airway test results and symptoms, there should be a particular threshold level of airway restriction at which a patient would begin to feel obstructed.

The Concept of a Single Threshold

Some writers have estimated single threshold values for abnormal airway measurements.[1,82,121,133,156,157] At a certain threshold value, patients change to oronasal breathing. At another threshold value short of that, many (but not all) patients complain of dyspnea. On the basis of available data, at least some individuals also would be expected to be able to distinguish varying degrees of obstruction, which would correspond to various resistance values. Sipilä and colleagues,[28] who studied the sensation of breathing recorded by patients breathing through different-sized tubes attached to a face mask, demonstrated good or satisfactory agreement between test results and sensations in 89%. However, 11% of the time patients thought that the narrowest tubes were easier to breathe through, or the widest tubes were more obstructed. These researchers concluded that an objective assessment is needed because the patient does not always give a reliable assessment of the nasal airway status.

The Concept of a Spectrum of Thresholds

Because the normal values of resistance for asymptomatic patients can show a generous area of overlap with a population that has obstructive symptoms (see Fig. 42-21), there are many possible objective test values at which some patients complain of obstruction but others do not. It follows that there is not a single population threshold for the nasal airway at which symptomatic obstruction would occur. Instead, it appears that there is a range of threshold values that vary from person to person. Thus, it is not always possible to identify individuals who will feel obstructed on the basis of only airway data. There does not seem to be a single airway value at which all patients become symptomatic, because it tends to vary in each case.[158] There is a variation in "resting nasal resistance."[155] An "individual calibration curve" may be needed for each subject when a correlation of symptoms with airway results is being studied. The existence of a range of threshold resistances could explain why comparisons between groups may need relatively large changes in resistance for a correlation with symptoms to be demonstrated. It would be helpful to know the range of airway dimensions or resistances at which each patient feels the onset of uncomfortable breathing, but such a range has not been delineated. The presence in a population of multiple thresholds at which the sensation of obstruction will be noted means that the diagnostician must give credibility to a range of degrees of symptoms and test results in the course of evaluation of these patients.

High Threshold

A patient with a high threshold for the symptom of nasal obstruction is one who complains of only minimal obstruction, yet has significant airway restriction as measured by objective testing. An example is a patient who is born with a marked nasal septal deflection but has fewer complaints of nasal obstruction than would be anticipated. This situation can be due to the patient's describing the symptoms not in terms of what the general population notices but, rather, in terms of what the patient is accustomed to. A patient who is accustomed to a higher level of airway restriction may be operating at a level of restriction that would be considered "severe" by another person. The presence of a high threshold usually does not change the management of symptoms that do significantly affect quality of life, because it would still be anticipated that correction of the pathology causing the restriction would improve the symptoms.

Low Threshold

A patient with a low threshold for the symptom of nasal obstruction complains of significant obstruction yet has only mild measured airway restriction. This raises the concern that the condition may be more difficult to treat with the same level of success as treating a patient with a normal or high threshold for symptoms. The reason is that the symptoms in a patient with a low threshold have a greater likelihood of being due to factors other than structural nasal airway restriction. For instance, there may be a sensory disturbance of the nasal mucosa (e.g., some airway tissue loses some of its sensory detection with age). Thus, some individuals might have decreased cold receptor activity and, therefore, even if the airway is unrestricted, they might not receive the receptor stimulation for the same amount of airflow, and so they may feel that airflow is not adequate. In this group, there is less likelihood of relieving symptoms with treatment aimed at increasing the size of the nasal airway.

The Role of Objective Testing in Identifying the Site of Pathology Affecting the Airflow

Identification of the Side of the Nose with Greater Airway Restriction

Both rhinomanometry and acoustic rhinometry can distinguish the side with the more abnormal results. If the side of greater restriction as measured by objective testing corresponds to the observed side of greater pathology, this finding constitutes evidence that this observed pathology has the greater effect in causing airway restriction.

Use of Decongestion

If objective testing verifies opening of the airway with decongestion, then the relative amount of change due to mucosal components of the airway can be assessed.

Use of Valve Area Stenting

If objective testing verifies either change or no change with maneuvers to open the valve area, the relative amount of change due to any valve area pathology can be assessed. Stenting open the nose can help reveal the effect of the compliant part of the valve region and may improve the airway in the case of an anterior restriction.[9] The nasal airway has been held open with Tygon tubing,[159] sticks or wire,[8] a custom wire stent,[160,161] and retraction on the cheek.[81] The currently available externally applied adhesive plastic strips can also be used for this purpose.[98,162] If the method of retraction does not interfere with the test equipment, it can be used for either rhinomanometry or acoustic rhinometry.

There is a significant correlation between changes in resistance with stenting of the nares and valve pathology.[161] If stenting effects little change in resistance results, a restriction could be attributed to sites located posterior to the compliant part of the valve area. Alar retraction minimizes the effect of the compliant part of the valve on resistance, demonstrating the relative contribution of the caval parts of the valve.[14] A nasal dilator can open up the entire valve region back to the second constriction measured by acoustic rhinometry. Objective testing could reveal valve pathology better than rhinoscopy because the introduction of a nasal speculum into the nose of a white patient nose may alter tissue relationships in this area.[14] Airway testing can also be performed with both nasal dilator and decongestion to reveal the combined effect of the two interventions.

Chaudhry and associates[160] reported that resistance in 33 patients with structural pathology was reduced 26% by an internal nasal dilator, 41% by decongestion, and 62% by a combination of dilator and decongestion.[1] They noted that further studies are needed to correlate these results with "the aetiology of the nasal obstruction."

Pathology Posterior to the Valve Area

Site, size, and position of pathology can affect the magnitude of resistance to airflow. Cole and associates[163] and Chaban and colleagues[164] simulated septal deviations to study their effect on nasal resistance to airflow. These researchers showed that site, size, and position of pathology can affect the magnitude of resistance to airflow and found that in the posterior nose, only large pathology would increase nasal resistance.

Grymer and coworkers[135] found that the change in cross-sectional area at 6.4 cm from the nostrils in patients who underwent surgical correction of posterior septal deformities was small (but significant). They noted that most of the patients also had anterior pathology that had been corrected along with the posterior pathology. In another study

using acoustic rhinometry, the same research group found that the maximum effect of decongestion occurred in the middle part of the nose, where the middle turbinate is present.[143] The question of whether parts of the airway other than the MCA play a significant role in causing the symptom of obstruction due to airway restriction remains unanswered. Computational fluid dynamics may play a role in the future in answering this question.[44]

Clinical Application: Rhinoscopy, Endoscopy, Decongestion, Stenting, and Objective Testing Provide Complementary Information

Consideration of the results of the nasal examination (which may include rhinoscopy, endoscopy, decongestion, and stenting) in combination with objective test results can provide enhanced information about the nasal airway. Objective testing has some potential advantages over rhinoscopy. The results of objective testing are correlated with the degree of obstruction, whereas those of rhinoscopy are not.[29] Because these modalities can at times yield different information, they should both be used and should be performed simultaneously with the nasal examination; the *synthesis* of the information provided can be most useful in the clinical evaluation of a patient.[23,82]

Conclusions

Objective testing can further explain the relationship between symptoms and physical findings. Simultaneous assessment of symptoms, nasal examination, and objective testing is a key element.[23,82]

Objective testing of the nasal airway can aid in the evaluation of patients with nasal obstruction, particularly when airway restriction is the suspected cause. Diagnosis, treatment, and patient counseling can be refined by having this additional information. Also, objective testing can provide further information about the effectiveness of treatment and about the condition in patients who have allergic rhinitis or disturbance of the airway during sleep.

Objective testing can be, as Williams[165] stated, "an adjunctive examination to combine history, physical examination and above all, clinical experience to arrive at a well reasoned conclusion." Cottle[166] noted that those who wish to obtain all available information about the nasal airway will continue to use objective methods of assessing nasal patency for the "wider understanding of nasal functions" that such tests provide in assessing patients who complain of nasal obstruction. Future work will further define and refine the clinical applications of objective testing.

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CHAPTER FORTY-THREE

Nasal Manifestations of Systemic Diseases

Rose Stavinoha

Thomas V. McCaffrey

Key Points

- The classic triad of Wegener's granulomatosis involves the following organ systems: the upper respiratory tract, lungs, and kidneys.
- The cytoplasmic antineutrophil cytoplasmic autoantibody (c-ANCA) test is highly sensitive for Wegener's granulomatosis but a negative result does not exclude the diagnosis of the disease.
- The main agents used to induce remission of Wegener's granulomatosis are cyclophosphamide, methotrexate, and/or glucocorticoids.
- Approximately 40% of patients with sarcoidosis have granulomatous changes in extrapulmonary organs. The involvement of the nose and paranasal sinuses by sarcoidosis is relatively infrequent, and most reports are anecdotal, so the true incidence of nasal involvement is not known with certainty.
- Angiotensin-converting enzyme elevations occur in 83% of patients with active sarcoidosis.
- The most common nasal manifestation of AIDS is chronic rhinitis. Patients present with drying, crusting, nasal congestion, partial obstruction, and pain or discomfort.
- Clinical manifestations of nasal T-cell lymphoma usually start with nasal obstruction followed by purulent rhinorrhea and serosanguineous discharge. As symptoms progress, usually unilateral mucosal ulceration with extension into the palate, maxillary sinus, and upper lip help distinguish lymphoma from Wegener's granulomatosis, which is associated with diffuse nasal mucosal ulceration.
- Cicatricial pemphigoid is more likely to affect the mucosa whereas bullous pemphigoid is confined to skin. Nasal findings occur in 25% to 50% of affected patients. The usual site of involvement is the anterior nasal region, which is found to have painful, ulcerative crusting.
- Primary ciliary dyskinesia is characterized by chronic respiratory tract disease beginning in childhood and leading to a constellation of symptoms, including chronic rhinitis, sinusitis, bronchiectasis, chronic cough, otitis media, and sterility.
- Cystic fibrosis is the most common fatal inherited disease among whites. It affects 1 in 2000 live births. The disease is characterized as an exocrinopathy with clinical features of chronic lung disease, chronic sinusitis, and pancreatic insufficiency.

The nasal airway and paranasal sinuses can be affected by systemic diseases in both specific and nonspecific ways. In some cases, the nasal findings in a systemic disease may be the first indication of disease. The understanding of the various ways in which systemic disease can manifest in the nose is important for both otolaryngologists and the medical specialists who often work with them to treat these diseases.

Systemic diseases affecting the nasal airway can produce pathologic changes in three general ways. First, the general pathophysiology of the disease may affect the tissues of the nose, as in recurrent or severe epistaxis secondary to a coagulopathy. Second, the unique mucosal histology of the nose may make an otherwise minor pathologic process more severe and apparent, as seen in hereditary hemorrhagic telangiectasia. In this particular disease, telangiectasia causes few symptoms in the skin, but in the superficial, easily traumatized vessels of the nasal mucosa, severe epistaxis may occur (see Chapter 45). Third, a systemic disease may affect the tissues of the nose as part of a symptom complex, as seen in Wegener's granulomatosis.

Granulomatous Disease

Several granulomatous diseases have a predilection to involve tissue in the airways. They include Wegener's granulomatosis (WG), Churg-Strauss syndrome, and sarcoidosis. These diseases are often characterized by local inflammatory response in the airways, particularly in the upper nasal passages. WG is perhaps the most common granulomatous disease to affect the upper airway and the nasal airway in particular. Sarcoidosis and Churg-Strauss syndrome, although much less frequently found to involve the nasal airway, also have characteristic findings that may permit earlier diagnosis.

Wegener's Granulomatosis

Wegener's granulomatosis involving the nose is now being recognized at an earlier stage. Friedrich Wegener first clearly defined WG in 1939 as a systemic disease characterized by necrotizing granulomas with vasculitis of the upper and lower respiratory tract, systemic vasculitis, and focal necrotizing or proliferative glomerulonephritis.[1] The classic triad of WG involves the following organ systems: the upper respiratory tract, lungs, and kidneys. Formerly, WG was often confused with several other entities causing midline granulomas or midface destruction, including lymphomas, carcinomas, and infectious processes. WG can now be easily separated with more precise nasal biopsies, histopathologic examination, and the cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) test.

The prevalence of WG is estimated to be 3 cases per 100,000, and the mean age at diagnosis is 55 years.[2] Men and women are similarly affected, and more than 90% of all patients with WG are white according to later studies. The remaining 1% to 4% of patients are African-Americans, Hispanics, and Asians.[3]

Rhinologic symptoms of patients with WG may include nasal congestion, rhinorrhea, and anosmia. These symptoms may progress to rhinitis, sinusitis, septal perforation, and/or nasal airway stenosis. Nasal endoscopy typically reveals mucosal cobblestoning, edema, and crusting.[4]

Clinical features of WG can be divided into three categories. Patients with type 1 WG present with a limited form of the disease characterized by upper airway symptoms and few systemic findings. They typically present with several weeks of symptoms that are similar to those of an upper respiratory tract infection but are unresponsive to antibiotics. There is often associated nasal pain with serosanguineous rhinorrhea and crusting.

Patients with type 2 disease are sicker and present with systemic features although not as severe as those with type 3 disease. Their initial presentation is similar to that of patients with type 1 WG. There is a characteristic prolonged upper respiratory tract infection with a continued nasal discharge that progresses to nasal pain, tenderness, serosanguineous discharge, ulceration, and crusting. Pulmonary involvement is often present and is associated with a cough, hemoptysis, and cavitary lesions on chest radiography.

Type 3 WG is a widely disseminated form of the systemic disease, commonly consisting of upper and lower airway involvement, cutaneous lesions, and progressive renal involvement. Systemic features are more profound and, as with type 1 and type 2 disease, nasal ulcerations and symptoms are present.

Diagnosis

The clinical diagnosis of WG is suggested by the history and characteristic nasal findings. Laboratory values that are often abnormal in WG include the erythrocyte sedimentation rate (ESR) and hemoglobin, serum creatinine, and serum cytoplasmic antineutrophil cytoplasmic autoantibody (c-ANCA) levels. These serologic findings in conjunction with nasal biopsy can provide a definitive diagnosis of WG.

Immunofluorescence is a study that distinguishes antiproteinase-3 (anti-PR3) ANCAs from antimyeloperoxidase antibodies according to the pattern of staining; The cytoplasmic pattern is seen with ANCAs for anti-PR3, and the perinuclear pattern with ANCAs for antimyeloperoxidase.[5] The characteristic pattern of coarse granular staining of c-ANCAs is caused by antibodies against proteinase-3 and neutral serine protease present in the azurophilic granules of neutrophils. The c-ANCA test is highly sensitive for WG, but a negative result does not exclude the diagnosis of WG. The specificity of c-ANCA testing for WG has been confirmed in large studies and may in some cases preclude biopsy.[6-8] The c-ANCA titer may be used to monitor disease activity because a rise in the titer may be predictive of a relapse of disease, although this concept remains controversial. However, it is clinically appropriate to interpret an increase in c-ANCA titer as an indicator to closely monitor the patient for signs of relapse.

Nasal biopsy, which may be performed with use of local anesthesia and/or intravenous sedation, provides supportive evidence for the diagnosis. All visible nasal crusts must be removed, followed by liberal removal of tissue from the septum, nasal floor, and turbinates in order to provide ample tissue for stains and culture.[8] Culture is necessary to rule out granulomatous infectious agents such as fungi and mycobacteria.

Because of the nonspecific nature of many of the symptoms of WG, diagnosis and treatment may be delayed even by specialists.

Pathology

The histopathologic features of WG include vasculitis of medium and small vessels with intramural eccentric necrotizing granulomatous lesions. Typically, arteries, arterioles, capillaries, venules, and veins are involved. Large vessels are rarely affected. There may also be microabscesses that enlarge and coalesce into larger necrotic areas.

Treatment

Patients with WG often have multiorgan involvement and are best treated by a team of physicians including an otolaryngologist and internists or specialists with knowledge of the disease. Treatment algorithms are often based on disease severity and the organ system affected.[9] Patients are typically treated with immunosuppression in order to induce remission, and then dosages are adjusted to maintain the state of remission. The main agents used to induce remission are cyclophosphamide, methotrexate, and/or glucocorticoids.

Cyclophosphamide is an alkylating agent that impairs DNA replication and transcription. The current standard regimen for treatment of WG with cyclophosphamide is oral administration of 2 mg/kg per day with a maximum dose of 200 mg/day. It is typically continued for 6 months to 1 year and then the dosage is tapered gradually after the disappearance of symptoms.

Methotrexate is an alternative to cyclophosphamide in patients with limited forms of WG, such as type 1 disease. It acts as an antimetabolite and inhibits dihydrofolate reductase in order to impair folate metabolism. The standard dose begins at 0.25 mg/kg/week, which can be increased to 25 mg/week. This is typically continued for 1 year; it may be continued indefinitely, the dosage may be tapered, or the drug may be stopped abruptly.

Glucocorticoids are given concurrently whether cyclophosphamide or methotrexate is used. The recommended starting dose is prednisone 0.5 to 1.0 mg/kg/day up to a maximum of 80 mg/day.[9] Dosage tapering may begin after 1 month with the goal to discontinue the agent completely within 6 to 9 months.

After the symptoms are stabilized, the patient with WG may be effectively maintained on a regimen of trimethoprim-sulfamethoxazole.[10] Although the mechanism of action of this drug is not known with certainty, it has been shown to prevent relapses, and it has minimal side effects.

New therapeutic agents have been shown to be promising in resistant cases. Rituximab, a chimeric monoclonal antibody, has been reported to be effective in treating resistant WG.[11]

Surgical reconstruction may be used to restore function once the disease is in remission. It includes correction of saddle nose deformity and septal perforation repair. Functional endoscopic sinus surgery may benefit selected patients with chronic nasal crusting. Saline irrigations with or without antibiotics are essential to management, although nasal débridement may be helpful with mucosa-sparing techniques and frequent postoperative care to minimize scar formation.

Sarcoidosis

Sarcoidosis is a chronic systemic granulomatous disease capable of involving almost any organ in the body. It frequently involves the lymphatic system, lungs, liver, spleen, and bones. Although involvement of the epithelium of the upper respiratory tract is comparatively uncommon, nasal symptoms may be the first manifestation of this disease.

The etiology of sarcoidosis is unknown, but etiologic claims have been made for various infective agents, chemicals (including beryllium and zirconium), pine pollen, and peanut dust.[12] It has also been associated with cell-mediated and humoral immune abnormalities.

Sarcoidosis has a worldwide distribution, but the incidence is higher in northern Europe, southern United States, and Australia.

Women are slightly more often affected than men, and the disease is 10 to 20 times more prevalent in blacks than whites.

The clinical course in most cases is benign, with spontaneous resolution within 2 years, although 10% of cases may progress to pulmonary fibrosis. The lung is the primary organ affected by sarcoidosis. Ninety percent of patients have evidence of thoracic involvement, either enlarged intrathoracic lymph nodes or pulmonary parenchymal infiltrates. Approximately 40% of patients with sarcoidosis have granulomatous changes in extrapulmonary organs.

The involvement of the nose and paranasal sinuses by sarcoidosis is relatively infrequent and most reports are anecdotal, so the true incidence of nasal involvement is not known with certainty. The observed incidence of histologically confirmed nasal involvement in large populations of patients with sarcoidosis has ranged between 1% and 6%.[13,14] The most common symptom of nasal involvement is nasal obstruction, but epistaxis, dyspnea, nasal pain, epiphora, and anosmia may also occur.

Nasal sarcoidosis commonly affects the mucosa of the septum and inferior turbinate. The nasal mucosa is usually dry and friable with crusting.[15] Submucosal nodules with a characteristic yellow color may be noted. These nodules are the macroscopic presentation of intramucosal granulomas, which can be identified in mucosal biopsy specimens. In more advanced disease, irregular polypoid mucosa is seen, which is friable and bleeds readily.

Paranasal sinus involvement in sarcoidosis often accompanies nasal mucosal involvement. Mucous membrane thickening or opacification of paranasal sinuses occurs. Some patients with nasal sarcoidosis have bony lesions of the nasal bones. The lesions may appear as scattered regions of osteoporosis or zones of frank destruction. These lesions are a response to granulomas within the bone. The suture lines may disappear, but no periosteal reaction is seen.[16]

Diagnosis

The diagnosis of sarcoidosis is based on a combination of histologic, radiographic, immunologic, and biochemical data. The diagnosis of sarcoidosis of the nose and paranasal sinuses is based on the clinical findings of crusting friable nasal mucosa with either polypoid changes or characteristic yellowish submucosal nodularity. Sinus computed tomography (CT) and radiography findings are abnormal in most cases of nasal sarcoidosis. Pulmonary findings of either hilar lymphadenopathy or pulmonary fibrosis are common. A laboratory finding that may support a presumptive diagnosis of sarcoidosis is elevation of serum or urinary calcium. Radioactive gallium uptake may be increased in the nasal mucosa in sarcoidosis.[17] The diagnosis is confirmed by the presence of noncaseating granulomas in the nasal mucosa.

Serum angiotensin-converting enzyme (ACE) elevations occur in 83% of patients with active sarcoidosis. At present, this test has become very useful for the diagnosis of sarcoidosis as well as for monitoring for relapse. It must be remembered that ACE values can also be elevated in tuberculosis, lymphoma, leprosy, and Gaucher's disease.

Pathology

Multiple noncaseating granulomas are the characteristic histology feature of sarcoidosis. The sarcoid granuloma consists of a central area of tightly packed epithelioid cells surrounded by lymphocytes and fibroblasts. Multinucleated giant cells up to 150 µm in diameter are frequently found within granulomas. There is no specific histologic feature of sarcoidosis, and similar granulomas occur in tuberculosis, berylliosis, leprosy, hypersensitivity pneumonitis, fungal disease, and chronic inflammatory processes.[18,19]

Treatment

Most cases of stage I sarcoidosis undergo spontaneous remission within 2 years without specific treatment. Sarcoidosis beyond stage I with elevated ACE values or extrapulmonary involvement usually requires treatment; this statement applies to most cases of nasal sarcoidosis.

The mainstay of treatment is systemic corticosteroids. The majority of patients' symptoms can be controlled with oral prednisone in doses of 10 to 40 mg daily.[20] If nasal symptoms relapse while a patient is taking relatively high systemic doses of corticosteroid, local treatment with intranasal steroids may be used to allow reduction in the oral dosage.

Methotrexate has been used to treat nasal sarcoidosis successfully at a dose of 30 mg weekly.[21] The use of methotrexate should be considered only if there are contraindications to the use of systemic corticosteroids, because its effectiveness in sarcoidosis has not been extensively tested.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS), also known as allergic granulomatous angiitis, affects small to medium-sized vessels. It is a granulomatous vasculitis characterized by the following three phases: (1) a prodromal phase with allergic rhinitis and asthma, (2) an eosinophilic infiltrative phase with chronic eosinophilic pneumonia or gastroenteritis, and (3) a systemic, life-threatening vasculitis with granulomatous inflammation. CSS is associated with nasal crusting, and polyposis and may be distinguished from WG by the presence of both nasal polyps and asthma in CSS. The c-ANCA test result is also negative in CSS, although p-ANCAs are found in 70% of patients. CSS may be distinguished from sarcoidosis by the presence of asthma, eosinophilia, and vasculitis with necrotizing granulomas, all of which are absent in sarcoidosis.[22]

Pathology

Histopathologically, CSS is characterized by necrotizing vasculitis of small and medium-sized vessels. Necrotizing extravascular granulomas may also be present. There is prominent eosinophilia of the vessels and perivascular tissue.

Treatment

Glucocorticoids continue to be standard treatment for CSS. Cyclophosphamide may be helpful in life-threatening cases or in patients with poor prognostic factors.[23]

Neoplastic Diseases

The most notable neoplastic, systemic disease with nasal manifestations is nasal T-cell lymphoma. Leukemia and B-cell lymphomas may also have nasal manifestations. B-cell lymphomas may manifest as unilateral nasal obstruction by an enlarged nasal or nasopharyngeal mass. Acute leukemia may manifest as symptoms of an upper respiratory infection or as epistaxis secondary to friable mucosa in the anterior nose.

T-Cell Lymphoma

Previously known as midline malignant reticulosis or polymorphic reticulosis, nasal T-cell lymphoma is a rare disease that can be difficult to diagnose. The rate of long-term remission is low in patients with this disease; and 50% die from distant extranodal spread or from relapses outside the treatment field.[24,25] Nasal T-cell lymphomas differ phenotypically from lymphomas of the paranasal sinuses and in Waldeyer's ring, which tend to be of B-cell origin.

Diagnosis

Clinical manifestations of nasal T-cell lymphoma usually start with nasal obstruction followed by purulent rhinorrhea and serosanguineous discharge. As symptoms progress, usually unilateral mucosal ulceration with extension into the palate, maxillary sinus, and upper lip helps distinguish lymphoma from WG, which is associated with diffuse nasal mucosal ulceration. Mucosa is often pale and friable, and extensive crusting is often present. Oronasal fistulas often occur as well as nasal septal perforations, which have been reported in 40% of cases of nasal T-cell lymphoma.[26] Typically, there is an explosive unilateral involvement of one side of the nose, face, palate, and/or orbit. Systemic symptoms are more notable in advanced cases and include malaise, night sweats, febrile episodes, and arthralgias.[27]

Laboratory workup is similar to that for Wegener's granulomatosis. However, it is important to include human immunodeficiency virus (HIV) testing. A nasal biopsy may benefit diagnosis if there is adequate sampling of both abnormal and adjacent normal tissues.

Pathology

T-cell lymphomas have a polymorphic lymphoid infiltrate made up of mature, immature, and atypical lymphocytes, plasma cells, histiocytes, eosinophils, and macrophages. The infiltrate is characterized by angiocentricity and angioinvasion and can lead to vessel occlusion and local tissue infarction. This may cause the rapid tissue necrosis and ischemia seen with nasal T-cell lymphoma. Immunohistochemical studies of biopsy specimens typically demonstrate the presence of T cell–associated markers CD2, CD7, CD45RO, CD43, and natural killer cell marker CD57.[28]

The association of Epstein-Barr virus (EBV) and nasal T-cell lymphoma has been frequently reported. Various studies report the detection of EBV DNA and RNA in tumor cells associated with high titers of EBV antibodies in patients with T-cell lymphoma.[25,29,30] The causative role of EBV in the pathogenesis of T-cell lymphoma has been strongly suggested but remains to be definitively determined.

Treatment

Localized disease responds well to radiation therapy. Chemotherapy may benefit patients with disseminated disease or relapses. A 2004 study suggested that high-dose chemotherapy as well as autologous peripheral blood stem cell transplantation may be effective treatment options for relapsed nasal T-cell lymphoma.[24] Currently, multiagent chemotherapy in addition to radiation therapy, in an attempt to control the primary lesion and prevent early dissemination, is the initial treatment recommendation for nasal T-cell lymphoma.[25]

Immunodeficiency Diseases

There are two areas in which immunodeficiency is of special importance in rhinology: the nasal manifestations of acquired immune deficiency syndrome (AIDS) and the infectious consequences of iatrogenic immunodeficiencies resulting from chemotherapy for neoplastic and hematologic diseases. These two forms of immunodeficiency create difficult problems of diagnosis and treatment of infectious diseases of the nose, which will become an increasing component of the practice of rhinology.

Sinusitis in the Immunocompromised Patient

Rhinitis and sinusitis in immunocompromised patients are usually due to the same pathogens affecting the general population. There may be more subtle signs of bacterial infection, but treatment is similar, consisting of antibiotics and/or surgery. Complications including periorbital or orbital abscess may be more subtle, and open surgical treatment may be instituted prior to full demonstration of an abscess cavity on computed tomography.

Fungal sinusitis appears rarely in immunocompromised patients but is extremely important to the otolaryngologist in terms of diagnosis and treatment. *Aspergillus* and *Mucor* species are the most commonly involved fungi. Affected patients present with bloody nasal discharge, facial pain and swelling, fever, and edema. The disease often progresses rapidly in an invasive manner to cause facial cellulitis, gangrenous mucosal changes in the nose and paranasal sinuses, obtundation, cranial nerve palsies, vision loss, and proptosis.[31]

Diagnosis is established via physical examination findings of pale or gray mucosa of the nasal cavity or palate or the classic black middle turbinate.[32] Decreased pain and sensitivity of the nasal cavity is a suspicious sign. Small tissue biopsy specimens should be taken of the nasal lesions and sent for culture and microscopic examination, including Gomori's methenamine silver (GMS) staining. Computed tomography of the sinuses may demonstrate a destructive bony lesion but can often understate the clinical problem in a severely immunocompromised patient.

Treatment includes standard therapy for febrile neutropenia if present, blood glucose control in diabetics, as well as medical therapy for biopsy- or culture-confirmed *Mucor* or *Aspergillus* infection. Current antifungal therapies include amphotericin B given systemically and with nasal irrigations, voriconazole, and posaconazole. Aggressive surgical débridement is strongly advocated if the patient can tolerate surgical intervention. Surgical interventions range from endoscopic débridement to total maxillectomy with orbital exenteration and craniofacial resection.

Acquired Immunodeficiency and the Nasal Airway

AIDS is a syndrome characterized by the presence of one or more opportunistic diseases that indicate an underlying cellular immunodeficiency without any other known cause of immunodeficiency.[33] It is well known that the condition is caused by the human immunodeficiency virus, which attacks T-helper cells.

The most common nasal manifestation of AIDS is chronic rhinitis. Patients present with drying, crusting, nasal congestion, partial obstruction, and pain or discomfort. Purulent rhinitis may be seen secondary to cytomegalovirus. Other causative agents of rhinosinusitis reported in the literature include *Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophila, Alternaria, Cryptococcus neoformans*, and *Acanthamoeba castellani*. Initial treatment of rhinosinusitis in patients with human immunodeficiency virus or AIDS, according to Meiteles and Lucente,[34] is a trial of antibiotics and decongestants. Failure of this trial should be followed by antral lavage and culture with directed treatment. If there is inadequate response, surgical intervention should be undertaken.[34]

Benign and malignant neoplasms are also present in the patient with AIDS. Patients may complain of nasal obstruction and hearing loss or foul-smelling nasal discharge. Reported findings upon examination and biopsy of the nasal cavity and nasopharynx include benign lymphoid hypertrophy and nasal lymphomas. Kaposi sarcoma has also been documented in the nasal skin, vestibule, cavity, septum, and nasopharynx in patients with AIDS.[34] Presenting symptoms are nasal obstruction, drainage, and epistaxis. Physical examination may reveal nodular violaceous lesions. Treatment of these neoplasms ranges from supportive care to chemotherapy and radiation if warranted.

Cutaneous Diseases

Nasal findings associated with selected autoimmune or collagen-vascular disorders are uncommon. However, there are a few major disorders with nasal manifestations that may cause significant morbidity and are worthy of mention. They are pemphigus vulgaris, pemphigoid, scleroderma, and Behçet's disease.

Pemphigus Vulgaris

Pemphigus vulgaris is a common mucocutaneous bullous disorder characterized by nonscarring bullous dermatitis of presumed autoimmune origin.[35] The oral cavity is the most common involved site in the head and neck region, and only 10% of all patients have involvement of the nasal mucosa. Desquamative ulcerative lesions can be seen and ulceration of the nasal septum with anterior perforation has also been reported. The external nose is more likely to be affected. Steroids are the mainstay of treatment and may have to be combined with other immunosuppressants.

Pemphigoid

Pemphigoid is an uncommon disease characterized by blisters and scar formation that has a presumed autoimmune etiology. It can be divided into two categories, bullous and cicatricial. Cicatricial pemphigoid is more likely to affect the mucosa, whereas bullous pemphigoid is confined to skin. Nasal findings occur in 25% to 50% of affected patients.[36] The usual site of involvement is the anterior nasal region, which is found to have painful, ulcerative crusting. Scar formation is usually found in the nasal valve area but can also affect the nasopharynx. Scarring may be bilateral and may lead to partial or total nasal obstruction.[37] Treatment, which is usually managed by a dermatologist, involves dapsone and/or immunosuppressive agents.

Scleroderma

Scleroderma is a systemic disorder of unknown etiology. Its characteristics include symmetric stiffness of the skin and vascular insufficiency. Head and neck manifestations are very common and mostly affect the skin and oral cavity. Nasal findings involve telangiectasias of the mucosa leading to epistaxis. Treatment is symptomatic.

Behçet's Disease

Behçet's disease is characterized by the following triad: oral ulceration, genital ulceration, and ocular inflammation. The typical aphthous

ulceration found in the oral cavity in this disease can also be found in the nasal mucosa. These lesions typically heal without scarring but can cause rhinorrhea and pain. Treatment includes symptomatic care as well as immunosuppressive agents.

Mucociliary Diseases

A major defense mechanism of the nose and paranasal sinuses against infection is the mucociliary system. The physiology of this system has only recently come under close scrutiny. Its role in the prevention of sinusitis is demonstrated by the effects of mucociliary deficiencies in dysfunctional cilia syndrome and cystic fibrosis. New techniques for evaluating cilia function have permitted better diagnosis of these conditions, the detrimental consequences of which can be controlled by early treatment.

Normal mucociliary function in the nose is toward the nasopharynx in all parts except for the very anterior end of the septum. The direction of mucociliary transport is independent of the position of the body in reference to gravity. Mucociliary transport can be bridged, at areas lacking ciliated epithelium, by the traction exerted by the viscous mucus layer.[38] If a piece of mucosa is excised then reimplanted, the cilia continue to beat in their previous direction.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia was first described in association with Kartagener's syndrome. The dyskinesia is characterized by chronic respiratory tract disease beginning in childhood and leading to a constellation of symptoms including chronic rhinitis, sinusitis, bronchiectasis, chronic cough, otitis media, and sterility.[38] The incidence of primary ciliary dyskinesia is 1 in 15,000 to 1 in 30,000, and it is suspected to be an autosomal recessive disease.[39]

Primary ciliary dyskinesia can be diagnosed by the saccharin test, which is performed by placement of a tablet of sodium saccharinate just behind the anterior aspect of the inferior turbinate. The time required for the patient to notice a sweet taste after placement of the tablet is recorded. The maximum time is typically 30 minutes in the normal population. The test result may be influenced by many variables and does not itself identify a specific etiology of symptoms. An additional test involves the cytologic investigation of viable ciliary cells collected from the nose with small brushes. Cytologic investigation should be performed at various intervals and can confirm diagnosis by the finding of decreased ciliary beat frequency.

Management of primary ciliary dyskinesia includes antibiotics and nasal irrigations. Surgery is indicated for chronic or recurrent infections in order to establish a dependent drainage pattern. But even with appropriate surgical drainage, long-term use of antibiotic and nasal irrigations will be necessary to control symptoms.

Cystic Fibrosis

Cystic fibrosis, the most common fatal inherited disease among whites, is autosomal recessive. It affects 1 in 2000 live births and is associated with a mutation on chromosome 7q31-32.[40] Cystic fibrosis is a disease affecting the mucous component of mucociliary transport, rather than the cilia themselves as is the case in ciliary dyskinesia. The disease is characterized as an exocrinopathy with clinical features of chronic lung disease, chronic sinusitis, and pancreatic insufficiency.[40]

Diagnosis is confirmed with the sweat chloride test. Specific nasal symptoms include intermittent nasal obstruction with clear but thick rhinorrhea and nasal polyps. Patients with cystic fibrosis often have grayish green putty-like material in their sinuses, and the most common bacteria affecting these sinuses are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Radiology demonstrates underdevelopment of the sinuses, especially the frontal sinus.

Treatment of the nasal symptoms of cystic fibrosis is important to maintain a patent nasal airway and prevent infection. Long-term antibiotic therapy may be needed, and nasal irrigations are often beneficial. Nasal polyp surgery, sinus surgery, or both may be indicated in cases of failed medical management; the procedure performed depends on the degree of nasal obstruction, the severity of sinusitis symptoms, and the motivation of the patient and family. Much debate and controversy remain about the exact role of surgical intervention in patients with cystic fibrosis.

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CHAPTER FORTY-FOUR

Radiology of the Nasal Cavity and Paranasal Sinuses

Nafi Aygun

S. James Zinreich

Key Points

- The diagnosis of acute rhinosinusitis is made on clinical grounds, and imaging is reserved for cases with suspected intracranial and orbital complications.
- Because of the excellent bone detail it provides, CT is the modality of choice in imaging of chronic rhinosinusitis (CRS) and planning for functional endoscopic sinus surgery (FESS).
- Acute secretions of the sinuses are of low attenuation on CT and resemble fluid signal on MRI. With increasing dehydration of the secretions, the protein concentration increases, causing high attenuation on CT and decreasing T2 signal on MRI. The T1 signal first increases then decreases with rising protein concentration.
- Anatomic variations are very common and should not be perceived as the cause of CRS although they may be responsible for lack of response to treatment and recurrence.
- Osteitis is considered to play an active role in CRS.
- The earliest imaging signs of acute invasive fungal rhinosinusitis are edema and swelling in the perisinus soft tissues and focal bone destruction of the sinus wall.
- Allergic fungal rhinosinusitis shows characteristic high density on CT and decreased signal on T1- and T2-weighted MRI.
- The most common site of intracranial penetration or CSF leak associated with FESS is the anterior and medial cribriform plate, which is formed by the lateral lamella of the ethmoid bone, the extent and thickness of which are subject to individual variation that needs to be carefully evaluated before any surgery.
- The optic nerves and internal carotid arteries may be vulnerable to injury during FESS owing to variations in their anatomic relation to pneumatized cells and the completeness of bony coverings.

Radiologic examination of the sinuses is designed to give information that is complementary to clinical findings. Traditionally, conventional radiography was used to examine the paranasal sinuses. The standard radiographic sinus series consists of four views: lateral view, Caldwell's view, Waters' view, and submentovertex or base view.[1] The lateral view shows the bony perimeter of the frontal, maxillary, and sphenoid sinuses. Caldwell's view (Fig. 44-1) shows the bony perimeter of the frontal sinus. Waters' view (Fig. 44-2) shows the outlines of the maxillary sinuses, some of anterior ethmoid air cells, and the orbital floors. The submentovertex view evaluates the sphenoid sinus and the anterior and posterior walls of the frontal sinuses.

Standard radiography may be accurate in showing air and fluid levels in the frontal, maxillary, and sphenoid sinuses, but it significantly underestimates the degree of chronic inflammatory disease present, particularly in the ethmoid sinuses. Furthermore, the superimposition of fine bony structures on standard radiography precludes the accurate evaluation of the anatomy of the ostiomeatal channels.[2-7]

Computed Tomography

Computed tomography (CT) is currently the modality of choice in the evaluation of the paranasal sinuses and adjacent structures.[2-7] Its ability to optimally display bone, soft tissue, and air facilitates accurate depiction of anatomy and extent of disease in and around the paranasal sinuses.[2-5,7] In contrast to standard radiography, CT can clearly show the fine bony anatomy of the ostiomeatal channels.

Many writers stress the importance of initially performing CT after a course of adequate medical therapy to eliminate changes of mucosal inflammation and to better evaluate the underlying anatomic structures. To minimize mucosal edema and allow an improved display of the fine bony architecture, some writers also suggest routine management with a sympathomimetic nasal spray before scanning to reduce nasal congestion.[8]

Technique

Current state-of-the-art multi-slice multi-channel CT scanners can acquire slices as thin as 0.5 mm with contiguous coverage of the entire volume, allowing excellent quality reconstructed images in any desired plane with practically no loss of information during post-processing. This approach eliminates the need for separate scanning in axial and coronal planes. The scanning is usually done in the axial plane because the supine position is the most comfortable position for most patients and artifacts arising from the dental fillings spread in the plane in which the data are acquired, thus allowing artifact-free coronal images of the paranasal sinuses.

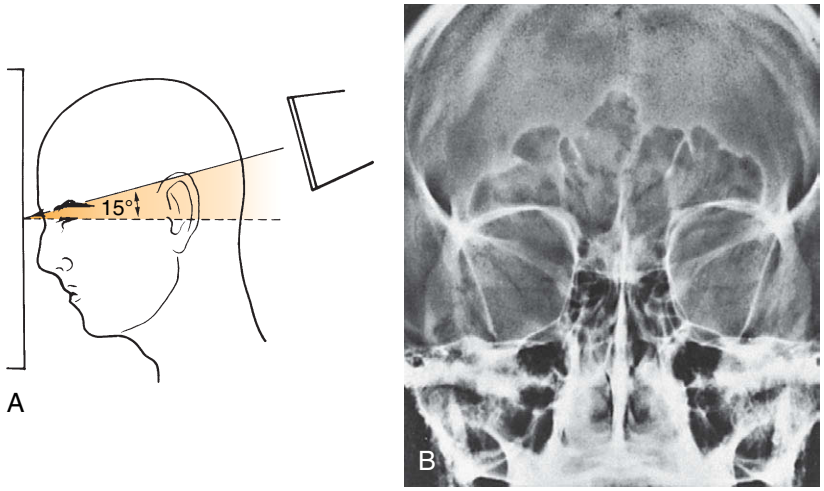

Figure 44-1. The modified Caldwell view. **A,** Positioning diagram. **B,** Sample radiograph. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Figure 44-2. The modified Waters view. **A,** Positioning diagram. **B,** Sample closed-mouth radiograph. **C,** Sample open-mouth radiograph. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Because the coronal plane optimally shows the ostiomeatal unit, the relationship of the brain and ethmoid roof, and the relationship of the orbits to the paranasal sinuses, coronal reconstructions are routinely performed (Fig. 44-3).[2-7] Coronal images correlate best with the surgical approach.[9] Axial images are complementary to the coronal reformatted images when severe disease is present in the sphenoid and posterior ethmoid sinuses and surgical management is contemplated. Axial images can be helpful in displaying the position of the internal carotid arteries and optic nerves with respect to the bony margins of the posterior ethmoid and sphenoid sinuses, as well as in demonstrating the sphenoethmoid recess. Sagittal reconstructions can be obtained for a morphologic orientation. Various distances and angles can be measured to aid in the passage of instruments during surgery. The frontal recess is best visualized on the sagittal images.

If multi-slice multi-channel CT is not available, scanning is routinely performed in the coronal plane from the anterior wall of the frontal sinus through the posterior wall of the sphenoid sinus. Contiguous 3-mm-thick images are obtained. Scanning with contiguous images is important to avoid loss of information through "skipped" areas.[10]

Windows are chosen to highlight the air passages, the bony detail, and the soft tissues. A window width of 2000 Hounsfield units with a level of 200 Hounsfield units is the most advantageous.[2-5,7]

Originally, the exposure settings for sinus CT were 125 kilovolt (peak) (kV[p]) and 450 milliamperes (mA). It has been shown that a considerable reduction in radiation exposure can be achieved without compromising the diagnostic quality of sinus CT examinations by lowering the mA setting. Recommended exposure settings are 125 kVp and 80 to 130 mA.

Radiation Exposure

See Chapter 11 for a general discussion of radiation exposure and CT scanning. Radiation-induced cataracts and thyroid cancer are the two specific concerns for paranasal sinus CT examinations. Imaging in the axial plane compared with the coronal plane results in a substantial reduction of radiation exposure to both of these structures. The average dose from a routine paranasal sinus CT examination is substantially less than the acute threshold dose of 0.5 to 2 Gy for detectable lens opacities, although the pediatric lens is more susceptible to radiation and the cumulative effects of radiation exposure to the lens is not well understood. A cumulative dose as small as 0.25 Gy can cause cataracts in children. The risk of thyroid malignancy from sinus CT examination is very low because the gland is not directly irradiated as it is with neck CT, but this small risk cannot be ignored. Furthermore, the dose received by the thyroid gland is substantially higher in young children, simply because the distance between the scanned region and the thyroid is less than in older children. In summary, a small but real risk of cataract and thyroid malignancy is associated with sinus CT examinations, particularly for children who undergo repeat studies.

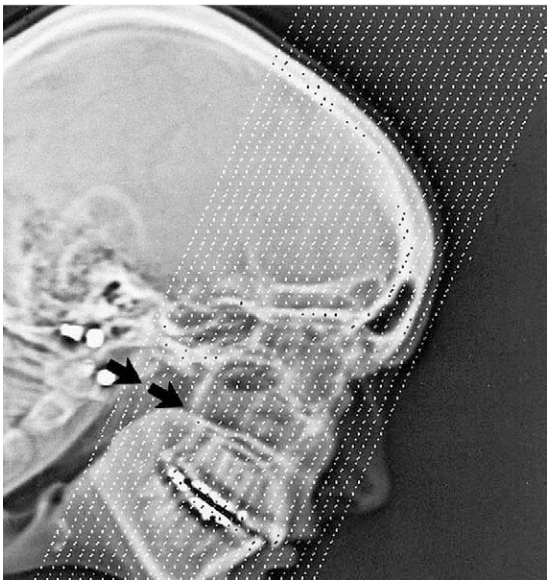

Figure 44-3. Lateral computed tomography scan shows the patient's position during the examination. *Dotted lines* represent the scanner gantry angulation, which should be as perpendicular as possible to the hard palate (*arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

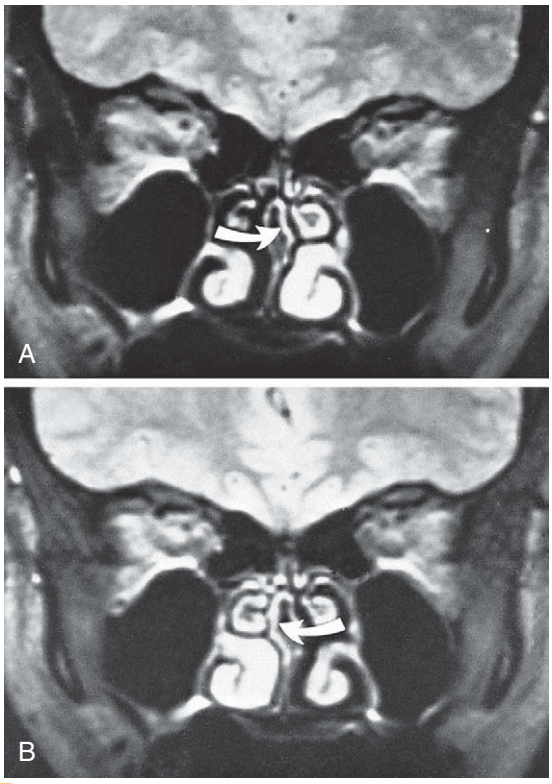

Figure 44-4. Nasal cycle. **A** and **B,** Coronal magnetic resonance images of a healthy volunteer obtained 30 minutes apart show the change in thickness of the mucosa (*arrows*) overlying the nasal septum and turbinates.

Magnetic Resonance Imaging

Although magnetic resonance imaging (MRI) better visualizes soft tissue than CT,[2,3] it does not visualize cortical bone. Because cortical bone and air have no mobile protons, they yield no MRI signal, resulting in an inability to discern the intricate anatomic relationships of the sinuses and their drainage portals. Thus, MRI is not a reliable operative road map to guide the surgeon during functional endoscopic sinus surgery (FESS).

The side-to-side cyclic variation in the thickness of the nasal mucosa is known as the *nasal cycle* (Fig. 44-4). The signal intensity of the mucosal lining of the nasal cavity and the ethmoid sinuses varies with the nasal cycle.[11,12] During the edematous phase of the nasal cycle, the mucosal signal intensity on T2-weighted MR images in these two areas appears similar to that of mucosal inflammation,[5,8] limiting the usefulness of MRI (see Fig. 44-2). Interestingly, cyclic variation of the mucosal signal does not occur in the frontal, maxillary, or sphenoid sinuses. Increased mucosal thickness and higher signal intensity on T2-weighted images are always abnormal.[11,12]

With respect to sinus imaging, MRI has proved most helpful in the evaluation of regional and intracranial complications of inflammatory sinus disease and their surgical management, in the detection and staging of neoplastic processes, and in improved display of anatomic relationships between the intraorbital and extraorbital compartments. For example, MRI is helpful in diagnosing fungal concretions, which often show low or no signal on T2-weighted images.[13-16] MRI also is useful in the evaluation of mucoceles and cephaloceles.[17]

The standard protocol to evaluate the paranasal sinuses with MRI includes sagittal and axial T1-weighted images and axial and coronal T2-weighted images. After intravenous administration of gadolinium-diethylenetriaminepentaacetic acid (DTPA), axial and coronal T1-weighted images can be obtained.

Ostiomeatal Unit and Sinus Physiology

For a clear understanding of the regional anatomy and the importance of the anterior ethmoid sinus structures, it is critical to understand (1) the flow pattern of the mucous blanket coating the major sinuses (mucociliary clearance) and (2) the concept that inflammatory sinus disease is largely the result of compromise of the drainage portals (ostiomeatal channels) of the individual sinus cavities.

The mucosal lining of the paranasal sinuses is made up of a ciliated cuboidal epithelium. In turn, a mucous blanket is found on the surface. The cilia are in constant motion and act in concert to propel the mucus in a specific direction. The pattern of flow is specific for each sinus and will persist even if alternative openings are surgically created in the sinus.[18-21] Therefore, FESS has gained widespread acceptance because it restores drainage of the sinuses through their anatomic drainage pathways.

In the maxillary sinus, the mucus flow originates in the antral floor, with the flow being directed centripetally toward the primary ostium. This pattern of mucus movement persists even after a nasal antrostomy is created.[18,20,22-26]

In the frontal sinus, mucus flows up along the medial wall, laterally across the roof, and medially along the floor. As the flow approaches the medial aspect of the floor, some mucus is directed into the primary ostium while the remainder is recirculated. The cleared mucus travels down the frontal recess and into the middle meatus, where it joins the flow from the ipsilateral maxillary sinus.[18,20,23-26]

The posterior ethmoid and sphenoid sinuses clear their mucus into the sphenoethmoidal recess. The flow enters the superior meatus and subsequently the nasopharynx.

Thus, there are two main ostiomeatal channels: (1) the anterior ostiomeatal unit, which includes the frontal sinus ostium, frontal recess, maxillary sinus ostium, infundibulum, and middle meatus; and (2) the posterior ostiomeatal unit, which consists of the sphenoid sinus ostium, sphenoethmoidal recess, and the superior meatus. These channels provide communication between the ipsilateral frontal, anterior ethmoid, and maxillary sinuses. Imaging of the paranasal sinuses should allow assessment of these ostiomeatal channels.

Normal Anatomy

An understanding of the anatomy of the lateral nasal wall and its relationship to adjacent structures is essential (Fig. 44-5).[6,27,28] The lateral nasal wall contains three bulbous projections: the superior, middle, and inferior turbinates (conchae). The turbinates divide the nasal cavity into

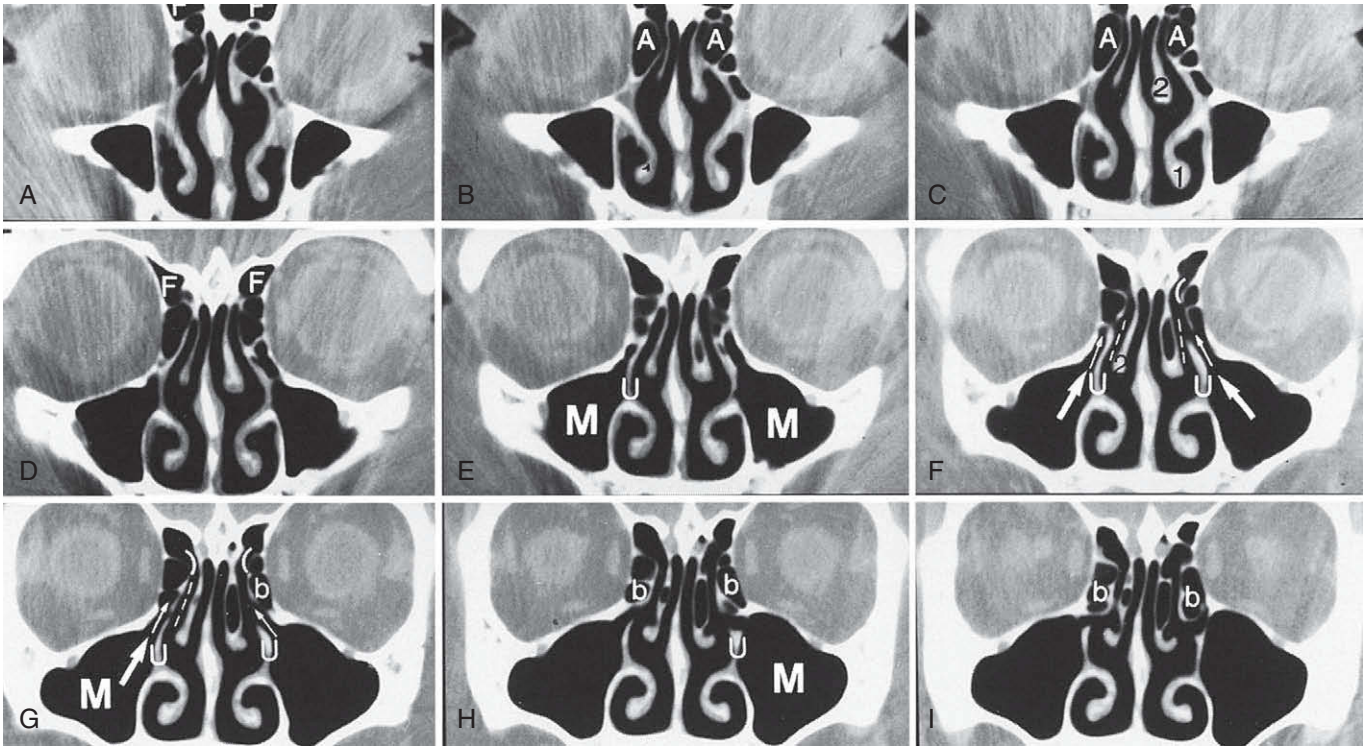

Figure 44-5. **A** through **I,** Coronal computed tomography (CT) scans of paranasal sinus anatomy as shown on thin-section coronal CT scans of a cadaver. The anterior ostiomeatal unit is shown in images **F** through **H**. The frontal recess (*small curved lines*), the middle meatus (*dashed lines*), the infundibulum (*small arrows*), and the primary ostium of the maxillary sinus (*large white arrows*) are seen. A, agger nasi cell; b, ethmoid bulla; F, Frontal sinus; M, maxillary sinus; S, sphenoid sinus; U, uncinate process; 1, inferior turbinate; 2, middle turbinate; 3, superior turbinate. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

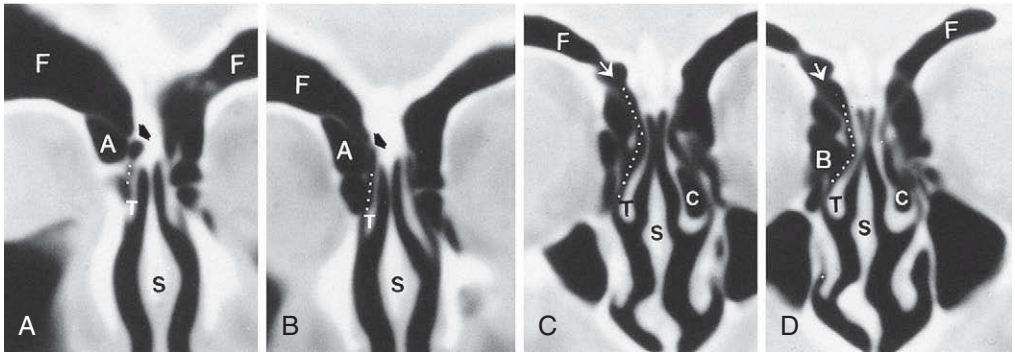

Figure 44-6. Anatomy of the frontal sinus. Coronal computed tomography scans of the frontal sinuses from anterior (**A**) to posterior (**D**), show the relationship between the frontal sinus (F) and the middle meatus (*dotted line*). Note that there is a bony strut (*heavy black arrowhead*) separating the frontal sinus and the anterior middle meatus. This separation is lost on the more posterior images, revealing the position of the frontal recess (*white arrow*). Note the position of the agger nasi cell (A) and its relationship to the frontal recess. The nasal septum (S), the ethmoid bulla (B), the middle turbinate (T), and the concha bullosa (C) are also shown. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

three distinct air passages: the superior, middle, and inferior meati. The superior meatus drains the posterior ethmoid air cells and, more posteriorly, the sphenoid sinus (through the sphenoethmoidal recess). The middle meatus receives drainage from the frontal sinus (through the frontal recess), the maxillary sinus (through the maxillary ostium and subsequently the ethmoidal infundibulum), and the anterior ethmoid air cells (through the ethmoid cell ostia). The inferior meatus receives drainage from the nasolacrimal duct.

On CT, the first coronal images display the outline of the frontal sinuses (Fig. 44-6). The frontal sinuses are funnel-shaped. Their aeration varies among patients. They can be small and occupy only the diploic space of the medial frontal bone, or they can be large and extend through the floor of the entire anterior cranial fossa posteriorly to the planum sphenoidale. In general, a central septum separates the left and right sides; however, several septa are often present. The floor of the frontal sinus slopes inferiorly toward the midline.

Close to the midline, the primary ostium is located in a depression in the floor. The frontal recess is an hourglass-like narrowing between the frontal sinus and the anterior middle meatus through which the frontal sinus drains (Fig. 44-7).[4]

Anterior, lateral, and inferior to the frontal recess is the agger nasi cell. The agger nasi cell is an ethmoturbinal remnant that is present in nearly all individuals. It is aerated and represents the most anterior ethmoid air cell. It usually borders the primary ostium or floor of the frontal sinus; thus, its size may directly influence the patency of the frontal recess and the anterior middle meatus. The frontal recesses are

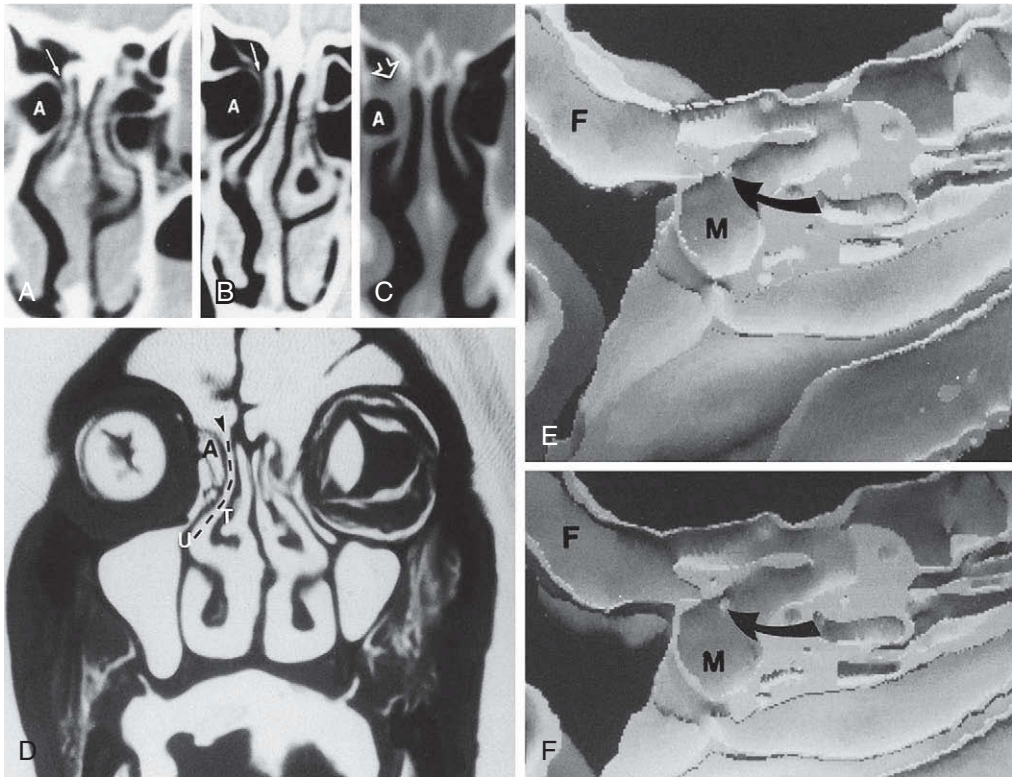

Figure 44-7. Anatomy of the frontal recess. **A** and **B,** Coronal computed tomography (CT) scans reveal a patent frontal recess (*white arrow*) despite the presence of a large agger nasi cell (A). **C,** Coronal CT scan in a different patient with an obstructed right frontal recess and mucoperiosteal thickening in the right frontal sinus (*open arrow*). An agger nasi cell (A) is seen. **D,** Density-reversed coronal CT scan in a cadaver optimally shows the position of the frontal recess (*arrow*). Also note the relationship between the middle turbinate (T), the uncinate process (U), the agger nasi cell (A), and the middle meatus (*dashed line*). **E** and **F,** Three-dimensional CT scans with sagittal cut-plane views of the paranasal sinuses show the position of the frontal recess (*curved arrow*) and show that its shape is that of an hourglass narrowing between the frontal sinus (F) and middle meatus (M). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

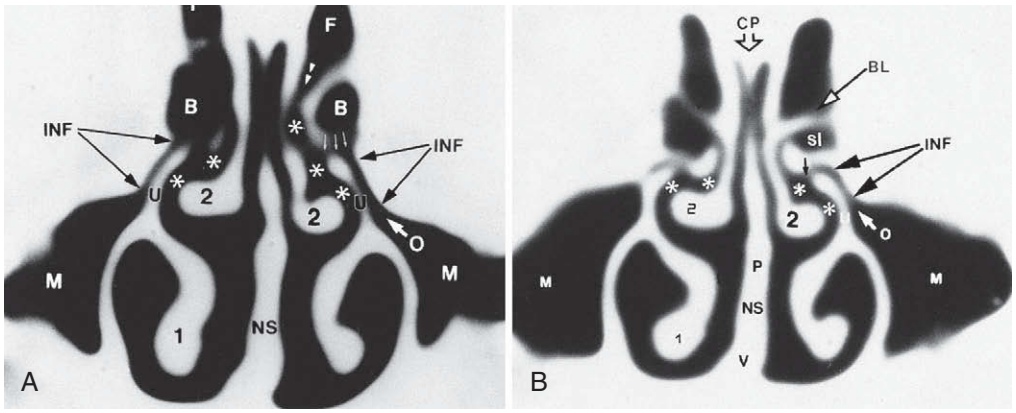

Figure 44-8. Anterior ostiomeatal channels. Coronal computed tomography scan through the anterior ethmoid sinuses shows the air passages intercommunicating with the frontal sinus (F), anterior ethmoid sinus, and maxillary sinus (M). The primary ostium (O) of the maxillary sinus communicates with the infundibulum (INF), which is bordered medially by the uncinate process (U) and laterally by the orbit. In turn, the infundibulum communicates with the middle meatus (*asterisks*) through the hiatus semilunaris (most medial *white arrow* in **A,** *black arrow* in **B**). The frontal recess (*white arrowheads*) is patent. The ethmoid bulla (B) is usually the largest air cell in the anterior ethmoid sinus. Note the vertical attachment of the middle turbinate (2) to the cribriform plate (CP) and its lateral attachment to the lamina papyracea, the basal lamella (BL). The air space between the basal lamella and the ethmoid bulla is the sinus lateralis (sl). The inferior turbinate (1), the nasal septum (NS), the vomer (V), and the perpendicular plate of the ethmoid bone (P) are also shown. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

the narrowest anterior air channels and are common sites of inflammation. Their obstruction subsequently results in a loss of ventilation and mucociliary clearance of the frontal sinus.

The uncinate process is a superior extension of the lateral nasal wall (medial wall of the maxillary sinus).[3,4] Anteriorly, the uncinate process fuses with the posteromedial wall of the agger nasi cell and the posteromedial wall of the nasolacrimal duct. The uncinate process has a free (unattached) superoposterior edge. Laterally, this free edge delimits the infundibulum (Fig. 44-8), the air passage that connects the maxillary sinus ostium to the middle meatus. Posterior to the uncinate

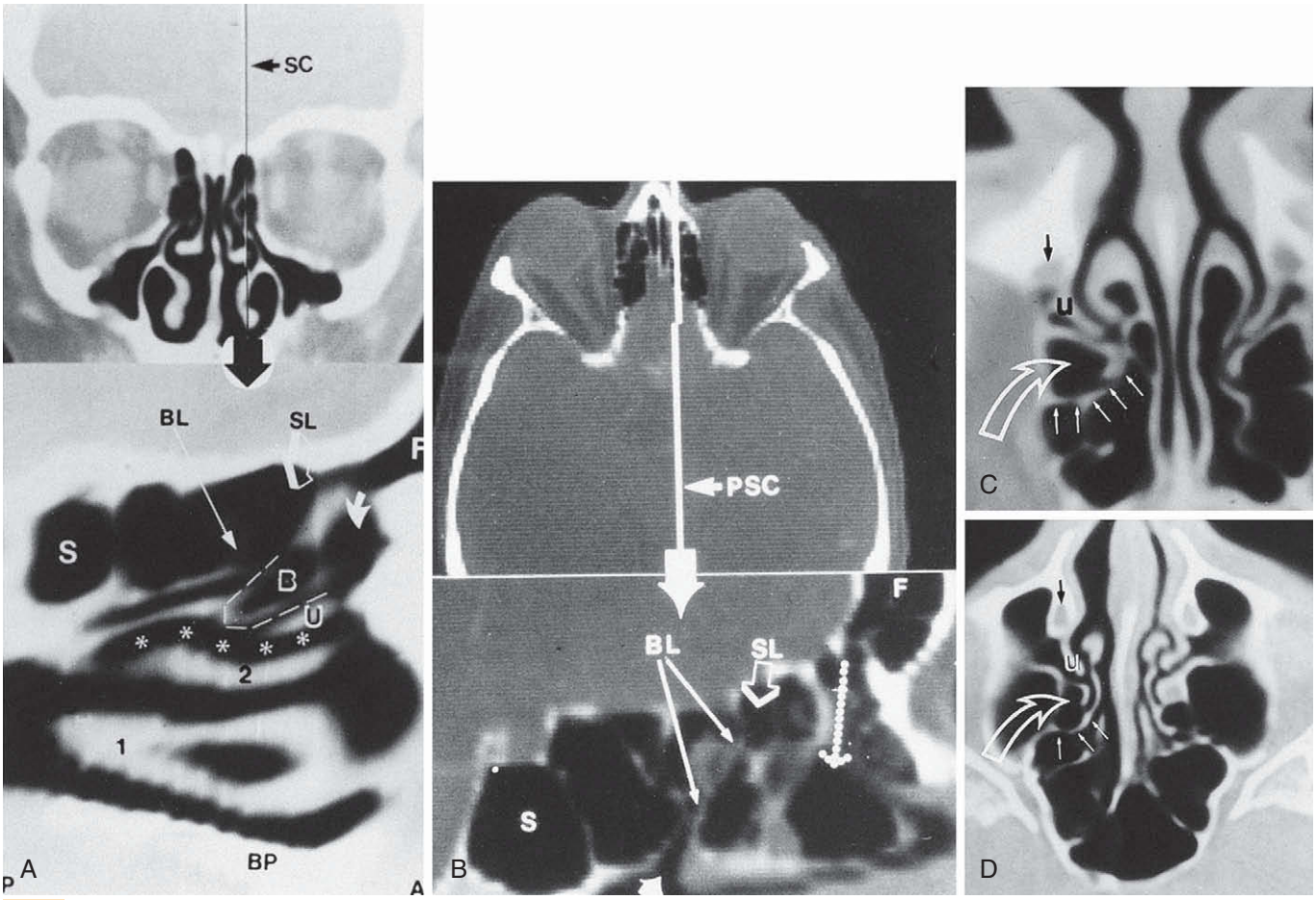

Figure 44-9. Anatomy of the basal lamella and sinus lateralis (retrobullar and suprabullar recesses). **A,** Sagittal reconstructed plane (*SC*) from direct coronal computed tomography (CT) data, and **B,** sagittal reconstructed plane (*PSC*) from direct axial CT data, show the outline of the basal lamella (BL) and the position of the sinus lateralis (SL) in between the basal lamella and the ethmoid bulla. The position of the hiatus semilunaris (*dashed U-shaped line* in **A**), the frontal recess, and the anterior middle meatus (*curved arrow* in **A**, *dotted line* in **B**) are noted. The frontal sinus (F), sphenoid sinus (S), uncinate process (U), middle meatus (*asterisks*), inferior turbinate (1), middle turbinate (2), bony palate (BP), and middle meatus–nasopharynx junction (*heavy white arrow* in **B**) are shown anterior (A) and posterior (P). **C** and **D,** Axial CT scans show the orientation of the uncinate process (u) and its association with the nasolacrimal duct (*black arrow*). Note the attachment of the basal lamella (*small white arrows*) to the lamina papyracea. The ethmoid bulla (*curved arrow*) is the air cell anterior to the basal lamella; in both of the patients in whom these scans were obtained, the posterior wall of the air cell is incomplete, providing direct communication between the ethmoid bulla and the sinus lateralis. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

is the ethmoid bulla, usually the largest of the anterior ethmoid cells. The uncinate process usually courses medial and inferior to the ethmoid bulla. The ethmoid bulla is enclosed laterally by the lamina papyracea.

The gap between the ethmoid bulla and the free edge of the uncinate process defines the hiatus semilunaris. Medially, the hiatus semilunaris communicates with the middle meatus, the air space lateral to the middle turbinate.[3,4] Laterally and inferiorly, the hiatus semilunaris communicates with the infundibulum, the air channel between the uncinate process and the inferomedial border of the orbit. The infundibulum serves as the primary drainage pathway from the maxillary sinus.[3,5]

The structure medial to the ethmoid bulla and the uncinate process is the middle turbinate. Anteriorly, it attaches to the medial wall of the agger nasi cell and the superior edge of the uncinate process. Superiorly, the middle turbinate adheres to the cribriform plate. As it extends posteriorly, the middle turbinate emits a laterally coursing bony structure, the basal or ground lamella, which fuses with the lamina papyracea posterior to the ethmoid bulla. The basal lamella demarcates the anterior ethmoid sinus from the posterior ethmoid sinus.

In most individuals, the posterior wall of the ethmoid bulla is intact, and an airspace is usually found between the basal lamella and the ethmoid bulla. This airspace is called the retrobullar recess or suprabullar recess, depending on its extent, and usually drains to the frontal recess (Fig. 44-9). Dehiscence or total absence of the posterior wall of the ethmoid bulla is common and can provide communication between these two usually separated airspaces.

The posterior ethmoid sinus consists of air cells between the basal lamella and the sphenoid sinus. The number, shape, and size of these air cells vary significantly among individuals.[2,4,5,29]

The sphenoid sinus is the most posterior sinus. It is usually embedded into the clivus and bordered superoposteriorly by the sella turcica. Its ostium is located medially in the anterosuperior portion of the anterior sinus wall, which in turn communicates with the sphenoethmoidal recess into the posterior aspect of the superior meatus. The sphenoethmoidal recess lies just lateral to the nasal septum and can sometimes be seen on coronal images but is best seen in the sagittal and axial planes (Fig. 44-10).[2-3]

The relationship between the aerated portion of the sphenoid sinus and the posterior ethmoid sinus must be accurately represented so the surgeon can avoid operative complications. Usually in the paramedian sagittal plane, the sphenoid sinus is the most superior and posterior airspace. More laterally, the sphenoid sinus is located more inferiorly, and the posterior ethmoid air cells become the most superior and posterior airspace. This relationship is well seen on axial

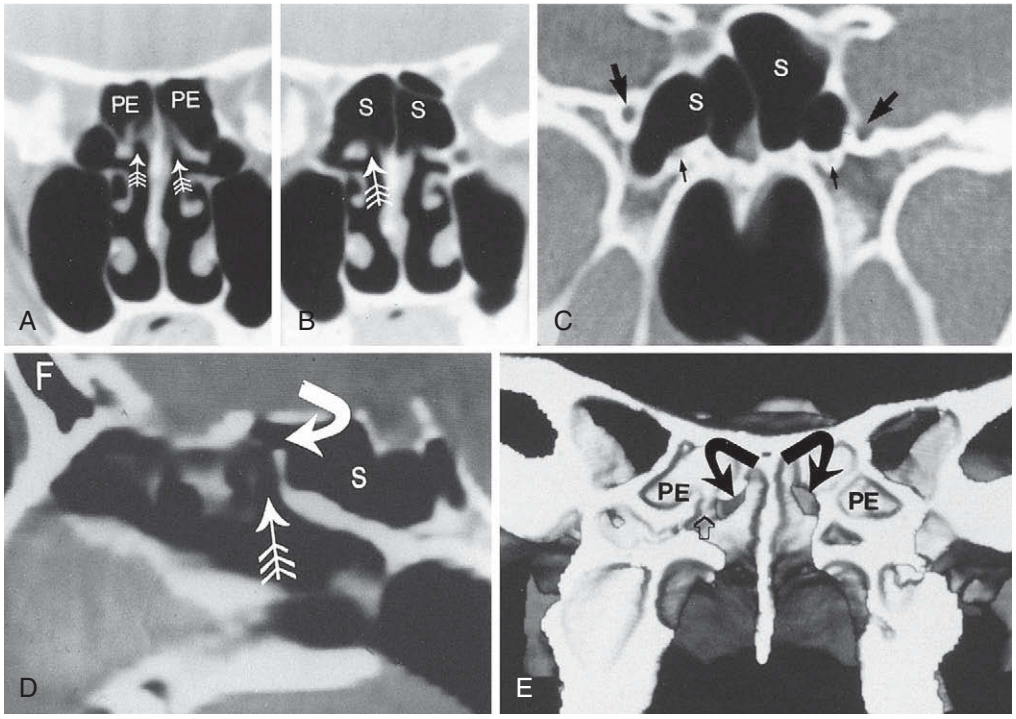

Figure 44-10. The sphenoid sinus anatomy. **A** and **B,** Coronal computed tomography (CT) scans show the boundary between the posterior ethmoid sinus (PE) and the sphenoid sinus (S). This boundary is best recognized from the position of the sphenoethmoidal recess (*feathered arrows*). **C,** Coronal CT scan through the sphenoid sinus (S) shows the number and orientation of septa within the sinus and the relationship to the foramen rotundum (*large arrows*) and vidian canal (*small arrows*). **D,** Paramedial sagittal CT scan shows the position of the sphenoid sinus ostium (*curved arrow*) and the sphenoethmoidal recess (*feathered arrow*). The frontal sinus (F) and sphenoid sinus (S) are seen. **E,** Three-dimensional CT image with a coronal cut-plane view through the posterior aspect of the posterior ethmoid sinus (PE) reveals the orientation of the sphenoethmoidal recess (*open arrow*) and position of the sphenoid sinus ostia (*curved arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

and sagittal images. The number and position of the septa of the sphenoid sinus vary. Some septa can adhere to the bony wall covering the internal carotid artery, which frequently penetrates the sphenoid sinus.[30]

Anatomically, the paranasal sinuses are in close proximity to the anterior cranial fossa, the cribriform plate, the internal carotid arteries, the cavernous sinuses, the orbits and their contents, and the optic nerves as they exit the orbits.[31-35] The surgeon should be cautious when maneuvering instruments in the posterior direction to avoid inadvertent penetration and drainage of these structures.[3,7,33,34]

Anatomic Variations and Congenital Abnormalities

Although the nasal anatomy varies significantly among individuals, certain anatomic variations are common in the general population and are often seen more frequently in patients with chronic inflammatory disease. The significance of an anatomic variant is determined by its relationship to the ostiomeatal channels and nasal air passages. The ability of the variation to obstruct the air passages may imply a role in the development and recurrence of sinusitis, although such a causal relationship has never been documented. The most common variations are discussed in the following paragraphs.[10,27,28,37-40]

Concha Bullosa

Concha bullosa is defined as an aeration of the middle turbinate (Fig. 44-11). It may be unilateral or bilateral. Less frequently, aeration of the superior turbinate can occur, whereas aeration of the inferior turbinate is uncommon. A concha bullosa in the middle turbinate may enlarge to obstruct the middle meatus or the infundibulum. The air cavity in a concha bullosa is lined with the same epithelium as the rest of the nasal cavity; thus, these cells can undergo the same inflammatory disorders experienced in the paranasal sinuses. Obstruction of the drainage of a concha bullosa can lead to mucocele formation.

Nasal Septal Deviation

Nasal septal deviation is an asymmetric bowing of the nasal septum that may compress the middle turbinate laterally, narrowing the middle meatus (Fig. 44-12). Bony spurs are often associated with septal deviation, which may further compromise the ostiomeatal unit. Nasal septal deviation is usually congenital but may be a posttraumatic finding in some patients.

Paradoxic Middle Turbinate

The middle turbinate usually curves medially toward the nasal septum. However, its major curvature can project laterally and, thus, narrow the middle meatus and infundibulum. This variant is called a *paradoxic middle turbinate* (Fig. 44-13). The inferior edge of the middle meatus can assume various shapes with excessive curvature, which in turn can obstruct the nasal cavity, infundibulum, and middle meatus.

Variations in the Uncinate Process

The course of the free edge of the uncinate process varies. In most cases, it extends slightly obliquely toward the nasal septum with the free edge surrounding the inferior or anterior surface of the ethmoid bulla, or it extends more medially to the medial surface of the ethmoid bulla.

Sometimes, the free edge of the uncinate adheres to the orbital floor or the inferior aspect of the lamina papyracea, which is termed an *atelectatic uncinate process* (Fig. 44-14). This variant is usually associated with a hypoplastic, and often opacified, ipsilateral maxillary sinus resulting from closure of the infundibulum. It is important to note this variant in the planning for surgery because there is an increased risk of orbital penetration when it is present.

Haller or Infraorbital Cells

Infraorbital cells are ethmoid air cells that extend along the medial roof of the maxillary sinus (Fig. 44-15). Their appearance and size vary.

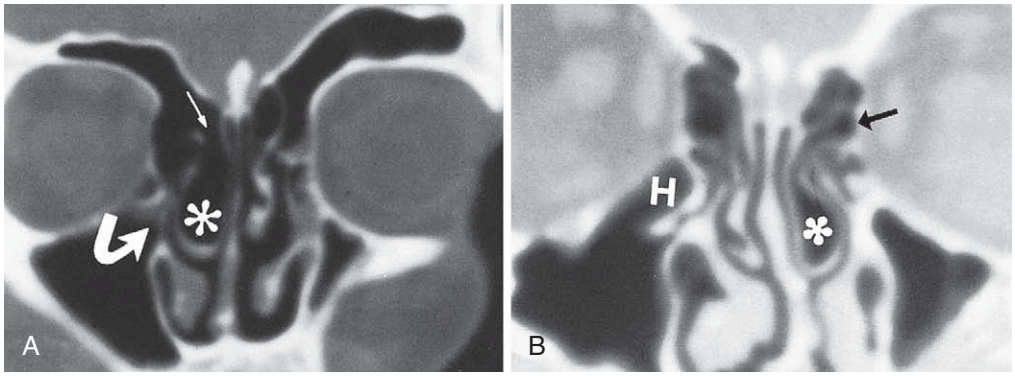

Figure 44-11. The concha bullosa in two patients. **A,** The coronal computed tomography (CT) scan shows a prominent right concha bullosa (*asterisk*) with communication to the frontal recess (*small arrow*). Note the obstruction of the right middle meatus (*curved arrow*). **B,** The coronal CT scan shows a left-sided concha bullosa (*asterisk*) with communication to the sinus lateralis (*arrow*). Note the contralateral Haller cell (H). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

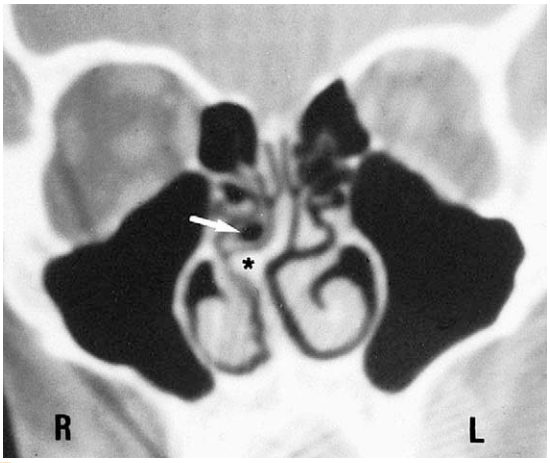

Figure 44-12. The nasal septal deviation with spurring. The coronal computed tomography scan shows deviation of the nasal septum toward the right side with a right-sided cartilaginous nasal spur (*asterisk*). Note the ipsilateral concha bullosa (*arrow*). Both of these anatomic variants contribute to marked narrowing of the right nasal cavity and ethmoid passages.

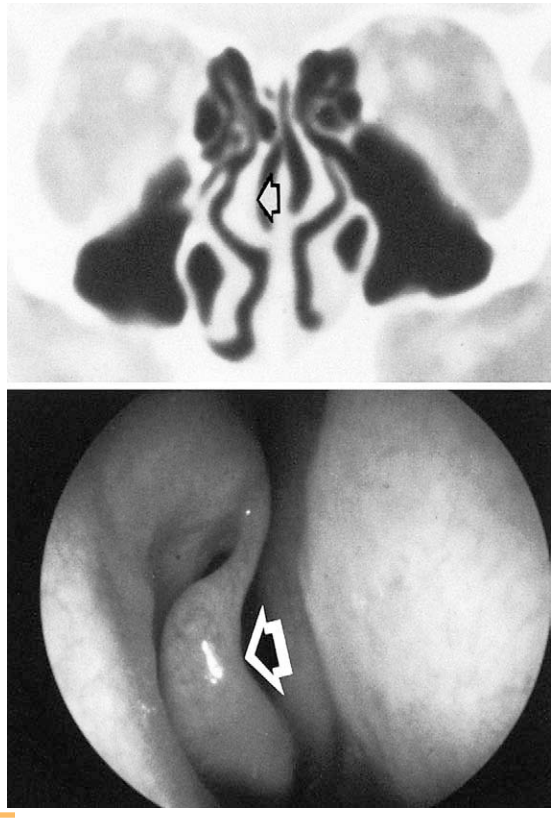

Figure 44-13. The paradoxic middle turbinate. **A,** The coronal computed tomography (CT) scan shows bilateral paradoxic middle turbinates. The right side is highlighted (*arrow*). **B,** The endoscopic view correlates with the CT findings (*arrow*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Large Haller cells may cause narrowing of the infundibulum. These cells may exist as discrete cells or may open into the maxillary sinus or infundibulum.

Onodi or Sphenoethmoidal Cells

Sphenoethmoidal cells are uncommon. They are lateral and posterior extensions of the posterior ethmoid air cells. They extend the paranasal sinus cavity very near the optic nerves as the nerves exit the orbits. These cells can surround the optic nerve tract, putting the nerve at risk during surgery.

Giant Ethmoid Bulla

The largest of the ethmoid air cells, the ethmoid bulla, can enlarge to narrow or obstruct the middle meatus and infundibulum.

Extensive Pneumatization of the Sphenoid Sinus

Pneumatization of the sphenoid sinus can extend into the anterior clinoid processes and the clivus, surrounding the optic nerves. When this situation occurs, the risk of damage to the optic nerves is increased during surgical exploration (Fig. 44-16).

Medial Deviation or Dehiscence of the Lamina Papyracea

Medial deviation or dehiscence of the lamina papyracea may be a congenital finding or the result of prior facial trauma. Regardless, the intraorbital contents are at risk during surgery because of the common dehiscences in the area and the ease of confusing this medial bulge with the ethmoid bulla. Excessive medial deviation and bony dehiscence tend to occur most often at the site of the insertion of the basal lamella into the lamina papyracea, thus making this portion of the lamina papyracea most delicate.

Aerated Crista Galli

Aeration of the crista galli can occur. When aerated, these cells may communicate with the frontal recess. Obstruction of this ostium can lead to chronic sinusitis and mucocele formation. It is important to recognize this entity preoperatively and to differentiate it from an ethmoid air cell to avoid extension of surgery into the cranial vault.

Cephalocele

Preoperative CT is useful to assess for congenital abnormalities, such as encephaloceles (Figs. 44-17 and 44-18),[37] which can be spontaneously present or can result from previous ethmoid or sphenoid sinus surgery. Their presence needs to be considered when one is dealing with an isolated soft tissue mass adjacent to the ethmoid or sphenoid roof, especially if it is complemented by adjacent bone erosion. The differential diagnosis includes mucocele, neoplasm, cephalocele, and, less likely, a polyp associated with an adjacent bony dehiscence. Coronal CT best displays the extent of bony erosion, and sagittal and coronal MRI is helpful in narrowing the differential diagnosis.

Asymmetry in Ethmoid Roof Height

It is important to note any asymmetry in the height of the ethmoid roof. The incidence of intracranial penetration during FESS is higher when this anatomic variation occurs. Intracranial penetration is more likely to occur on the side where the position of the roof is lower.[41]

Interpretation of Images

Using a systematic approach is helpful in the interpretation of sinus CT scans. While reading from anterior to posterior, one should make a mental checklist of important structures to be evaluated and commented on. The reporting system consists of the following three steps:

1. Identify and describe the important structures of the paranasal sinuses.
2. Evaluate the critical relationships when planning surgery.
3. Evaluate the bony outline of the nasal cavity and paranasal sinuses.

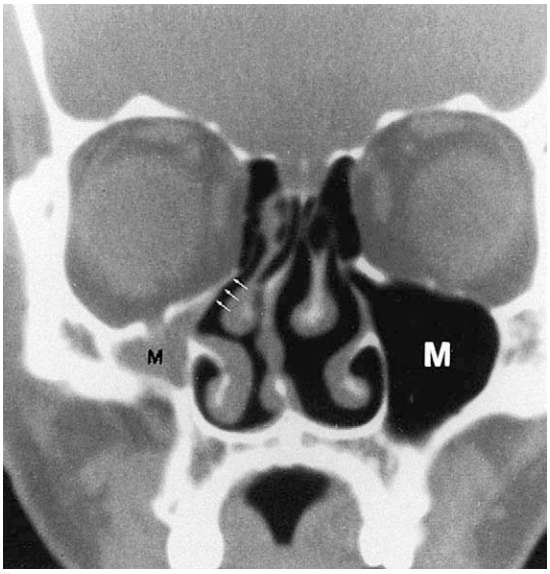

Figure 44-14. The atelectatic uncinate process. The coronal computed tomography scan shows that the right uncinate process is apposed to the inferomedial aspect of the orbit (*arrows*). The resultant obstruction of the infundibulum is usually the cause of the prominent inflammatory process in the ipsilateral maxillary sinus (*black M*). Note that this process is associated with hypoplasia of the ipsilateral maxillary sinus in comparison with its counterpart (*white M*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

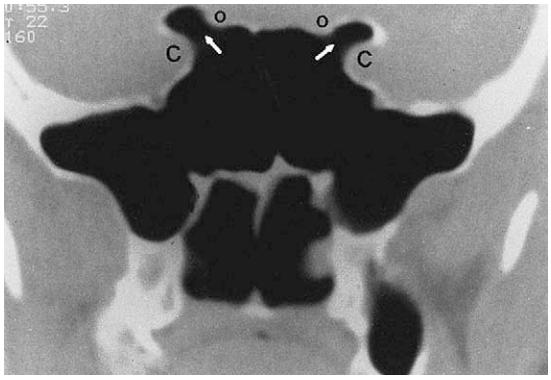

Figure 44-16. Extensive pneumatization of the sphenoid sinus. Coronal computed tomography scan shows pneumatization of both anterior clinoid processes (*arrows*) and their relationship to the optic nerves (o) and internal carotid arteries (C). The presence of anterior clinoid process pneumatization is an important indicator of optic nerve vulnerability during functional endoscopic sinus surgery. *(From Som PM, Curtin HD. Head and Neck Imaging. 3rd ed. St Louis: 1996; Mosby.)*

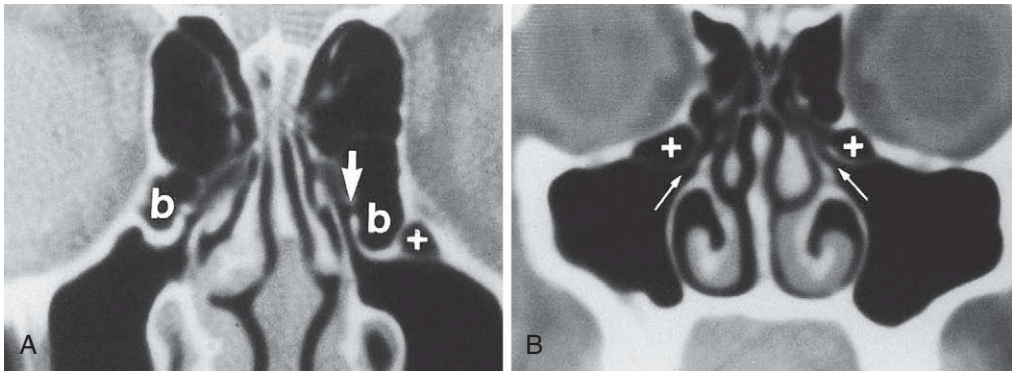

Figure 44-15. Haller cells (infraorbital). **A,** Note the left Haller cell (*plus sign*) with the ethmoid bulla (b) ostium (*arrow*) located medially opening into the infundibula. **B,** Bilateral Haller cells (*plus signs*). Note their close proximity to the uncinate process and their influence on the infundibula (*arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

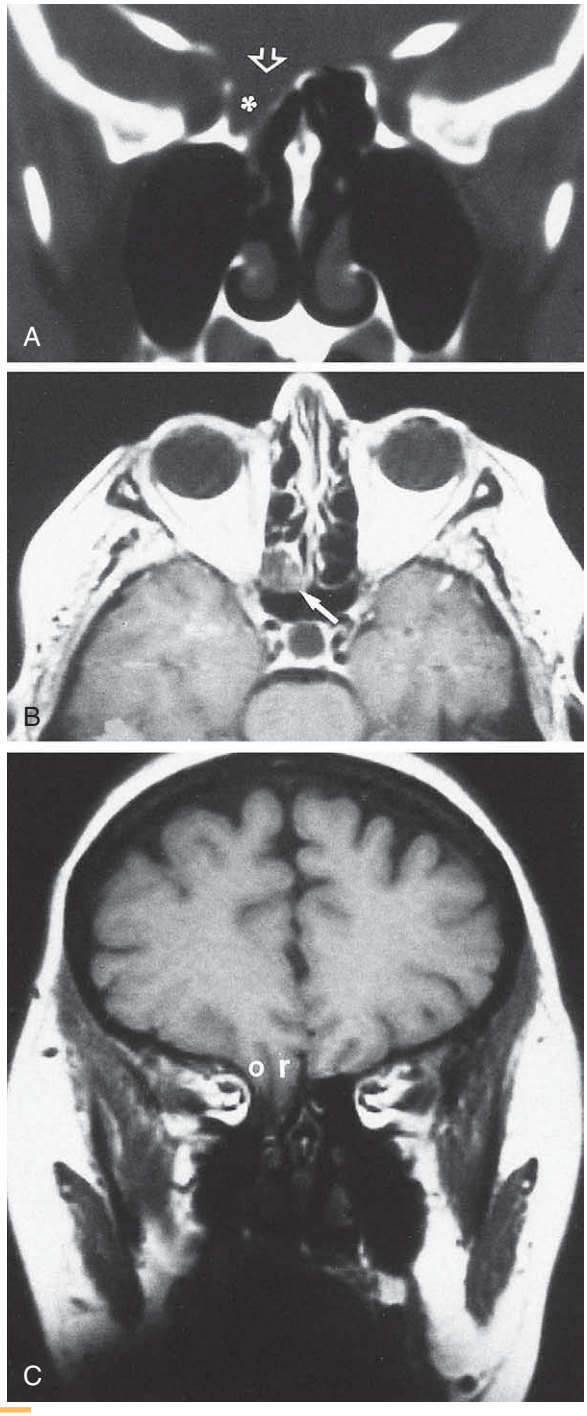

Figure 44-17. Computed tomography (CT) and magnetic resonance imaging (MRI) appearances of an encephalocele. **A,** Coronal CT scan through the posterior ethmoid sinus shows erosion of the roof of the posterior ethmoid sinus (*arrow* and *asterisk*). **B,** Axial T1-weighted MR image shows an isolated soft tissue mass within the posterior ethmoid sinus (*arrow*), which on **C,** a coronal T1-weighted MR image, is confirmed as an encephalocele. The gyrus rectus (r) and gyrus orbitales (o) are noted. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

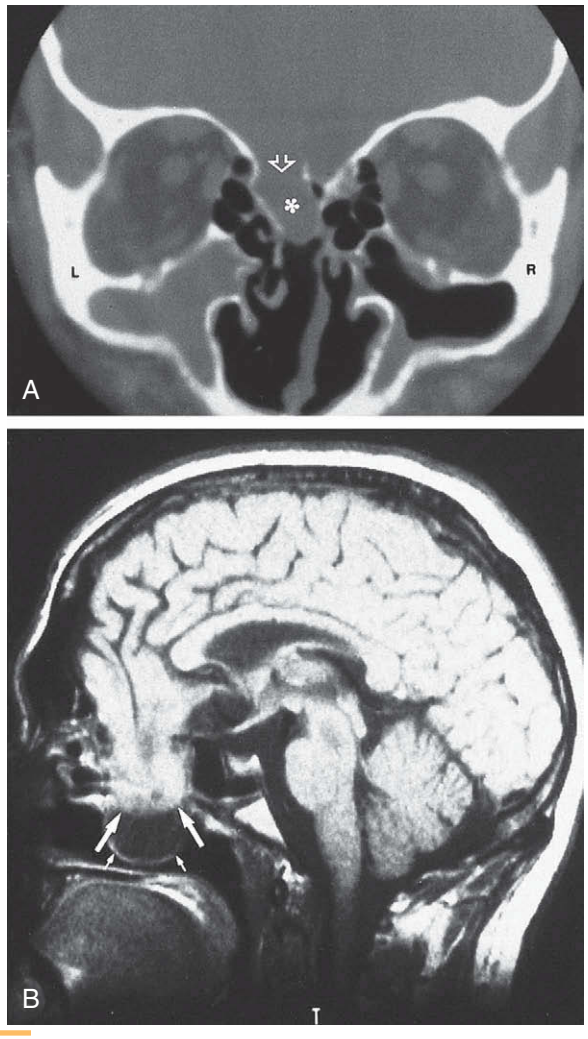

Figure 44-18. Computed tomography (CT) and magnetic resonance imaging (MRI) appearances of an encephalocele. **A,** The coronal CT scan through the posterior ethmoid sinus shows wide erosion of the ethmoid sinus roof (*arrow*) with a soft tissue mass penetrating into the ethmoid sinus (*asterisk*). **B,** T1-weighted sagittal MR image shows the outline of the brain tissue (*large arrows*) and the meninges and cerebrospinal fluid (*small arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Identification and Description of Important Structures

The structures of the paranasal sinuses that should be identified on CT scans include the frontal sinus, the frontal recess, the agger nasi cell and anterior ethmoid sinus, the ethmoid roof, the ethmoid bulla, the uncinate process, the infundibulum, the maxillary sinus, the middle meatus, the nasal septum and nasal turbinates, the basal lamella, the sinus lateralis, the posterior ethmoid sinus, and the sphenoid sinus.

Evaluation of Critical Relationships for Surgical Planning

The symmetry of the ethmoid roof should be noted. If not recognized, discrepant heights of the ethmoid roof can lead to inadvertent penetration of the cranial vault during FESS.

Careful attention should be paid to the status of the lamina papyracea, and any dehiscence or excessive medial deviation of this bone should be reported. The relationship of the sphenoid sinus and posterior ethmoid air cells with the internal carotid artery and optic nerves should be noted. Findings that put either of these structures at greater risk during endoscopic surgery should be conveyed to the referring surgeon. In particular, extensive expansion of the sinuses around the internal carotid artery or the optic nerve and bony dehiscences adjacent to either structure should be noted. The incidence of bony dehiscence around the presellar and juxtasellar portions of the internal carotid artery is 12% to 22%.[42,43] The carotid canal frequently penetrates the aerated portion of the sphenoid sinus; in many cases, the sphenoid sinus septa adheres to the bony covering of the carotid canal. The surgeon

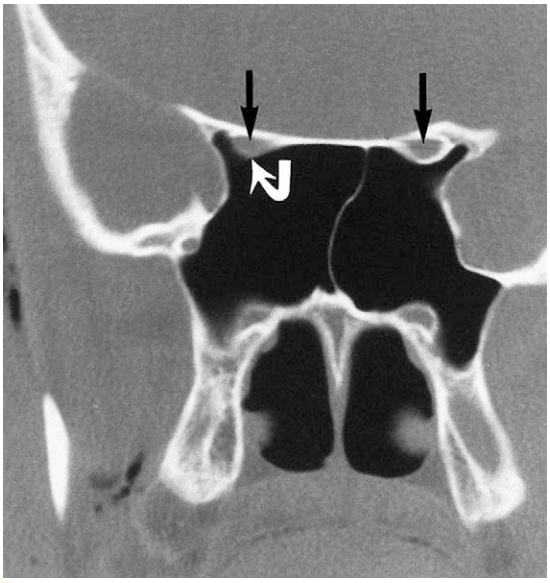

Figure 44-19. Relationship of optic nerves to sphenoid sinus. Type three optic nerves (*black arrows*) course through the sphenoid sinus with more than 50% of the nerves surrounded by air. Note that there is dehiscence of the bone covering the right optic nerve (*curved arrow*). This finding increases the risk of optic nerve damage during functional endoscopic sinus surgery. *(From Som PM, Curtin HD. Head and Neck Imaging. 3rd ed. St Louis: 1996; Mosby.)*

must be aware of this variation to prevent fracture of the sphenoid sinus septum–carotid canal junction and avoid puncturing the carotid canal.

The relationship between the posterior paranasal sinuses and the optic nerves is important to note to avoid operative complications (Fig. 44-19). Delano and associates[42] classified the relationship into four categories:

- In type 1, the optic nerves course adjacent to the sphenoid sinus without indentation of the wall or contact with the posterior ethmoid air cell. This type is most common and occurs in 76% of patients.
- In type 2, the nerves course adjacent to the sphenoid sinus, causing indentation of the sinus wall, without making contact with the posterior ethmoid air cell.
- In type 3, the nerves course through the sphenoid sinus with at least 50% surrounded by air.
- In type 4, the nerves course adjacent to the sphenoid sinus and posterior ethmoid sinus.

In this study, the optic nerve was dehiscent in all cases in which it traveled through the sphenoid sinus (type 3) and in 82% of the cases in which the nerve impinged on the sphenoid sinus wall (type 2). Delano and associates[42] also found that 85% of optic nerves associated with a pneumatized anterior clinoid process were of type 2 or 3 configuration and that 77% were dehiscent. Therefore, the presence of anterior clinoid process pneumatization is an important indicator of optic nerve vulnerability during FESS because of frequent associations with bony dehiscence and type 2 and type 3 configurations.[42]

Evaluation of Bony Outlines of Nasal Cavity and Paranasal Sinuses

Prominent thickening of the bone outlining the paranasal sinuses occurs, especially in patients who have undergone several surgical procedures and in those with repeated exacerbations of chronic inflammation (Fig. 44-20). Similar changes occur in patients with Wegener's

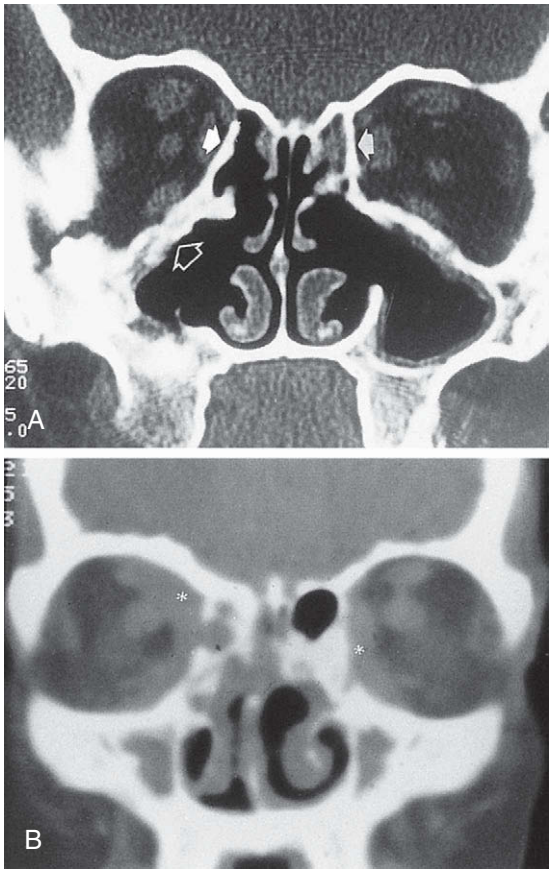

Figure 44-20. Osteitis of the paranasal sinus walls. **A,** Coronal computed tomography (CT) scan through the ethmoid sinus shows bilateral antrostomies, uncinectomies, and partial anterior ethmoidectomies. Note the bilateral pronounced thickening of the orbital floors, which is more severe on the right side (*open arrow*). There is marked thickening of the lamina papyracea bilaterally (*solid white arrows*). These changes are occasionally seen in patients who have undergone multiple surgical procedures in this area. **B,** Coronal CT scan through the anterior ethmoid sinus in a patient with Wegener's granulomatosis shows diffuse, pronounced bony thickening of the perimeter of the maxillary sinuses and lamina papyracea and the presence of soft tissue masses (*asterisks*) within the orbits. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

granulomatosis. These patients suffer with a prolonged chronic inflammation and no previous surgery. Unfortunately, no pathophysiologic explanation of this finding exists; however, the change is directly related to the underlying inflammatory process and periosteal stimulation.

Bone erosion or absence of bone may have three causes. Bone may have been removed during a previous surgical procedure, and therefore a dehiscence is noted. Evidence of prior surgery should be sought on CT scans and established through a proper medical history. These changes may also be caused by the erosion secondary to a mucocele or neoplasm. The associated mass is a clue as to the cause, and MRI may distinguish between these processes. Bony dehiscences can also be developmental; in the absence of prior surgery or additional pathology, this last possibility should be considered.

Radiologic Appearances of Inflammatory Sinus Disease

Acute (Rhino)sinusitis

Acute bacterial rhinosinusitis is usually caused by superinfection of an obstructed paranasal sinus. The obstruction is often the result of appo-

sition of edematous mucosal surfaces from an antecedent viral upper respiratory tract infection. The edema disrupts the normal mucociliary drainage pattern of the sinus, leading to obstruction of the sinus ostium. The accumulation of fluid within the sinus predisposes to a bacterial superinfection. The bacterial pathogens most often responsible include *Streptococcus pneumoniae*, *Haemophilus influenzae*, beta-hemolytic streptococci, and *Moraxella catarrhalis*.[17,44,45] Acute rhinosinusitis only rarely results from a pure viral infection. It usually only involves a single sinus; the ethmoid sinus is the most common location.[38,45] The risk of regional and intracranial complications is increased with involvement of the frontal, ethmoid, and sphenoid sinuses.[38]

Radiologically, the hallmark of acute rhinosinusitis is an air-fluid level (Fig. 44-21) in the respective sinus. However, the radiologic findings in acute rhinosinusitis may be nonspecific, with smooth or nodular mucosal thickening or complete opacification of the sinus. On MRI, the findings include watery secretions with hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images.

An air-fluid level is a pathognomonic sign of acute sinusitis in usual clinical settings. This finding is mimicked by the acute finding of blood within the sinus in patients with a history of recent trauma. Scans performed shortly after a lavage procedure may show air-fluid levels in the sinuses. Fluid is frequently present in the paranasal sinuses of intubated patients. Cerebrospinal fluid (CSF) leak is a rare cause of air-fluid level in the sinuses.

Chronic (Rhino)sinusitis

Chronic rhinosinusitis (CRS) is preferred over *sinusitis* because sinusitis is almost always preceded by rhinitis and rarely occurs without inflammation of the nasal passages.[46] The diagnosis of CRS is symptom-based and requires persistence of patient complaints for more than 12 consecutive weeks. Almost all the symptoms, however, are nonspecific and without objective demonstration of mucosal inflammation; therefore, the symptom-based diagnosis is not reliable.[46-48] Anterior rhinoscopy may not always allow for confirmation of the presence of mucosal inflammation, and nasal endoscopy is required to visualize the middle meatus and the ethmoid bulla.[25,40,48] CT—as the imaging standard for evaluation of the sinuses—is an excellent tool to confirm the presence and assess the extent of inflammation in the sinonasal cavity beyond what is permitted by endoscopy. It is possible that chronic inflammation may be manifest without CT identification of findings such as mucosal hypertrophy and retained secretions. Furthermore, a modest amount of inflammation diagnosed by CT may be present in asymptomatic persons.[49] The correlation between positive endoscopy and positive CT findings is better than the correlation between negative endoscopy and negative CT findings. Overall, the correlation of CT and endoscopy findings is about 70% to 80%.[25,47,48,50]

There is evidence that the bacteria are present in the inflamed mucosa and that treatment with antibiotics can positively affect the outcome, but the role of bacteria in the pathogenesis of CRS remains elusive. Commonly isolated pathogens include *Staphylococcus, Streptococcus, Corynebacterium, Bacteroides*, and *Fusobacterium* species, and other anaerobes.[44] Anaerobes are more commonly involved in chronic rhinosinusitis than in acute rhinosinusitis.[37,45] CT provides excellent information about the extent and distribution of mucosal disease but not much about the origin of the changes (e.g., infection, granuloma, postsurgical scarring).

The radiologic findings vary. Signs suggestive of chronic rhinosinusitis include diffuse or polypoid mucosal thickening, partial or

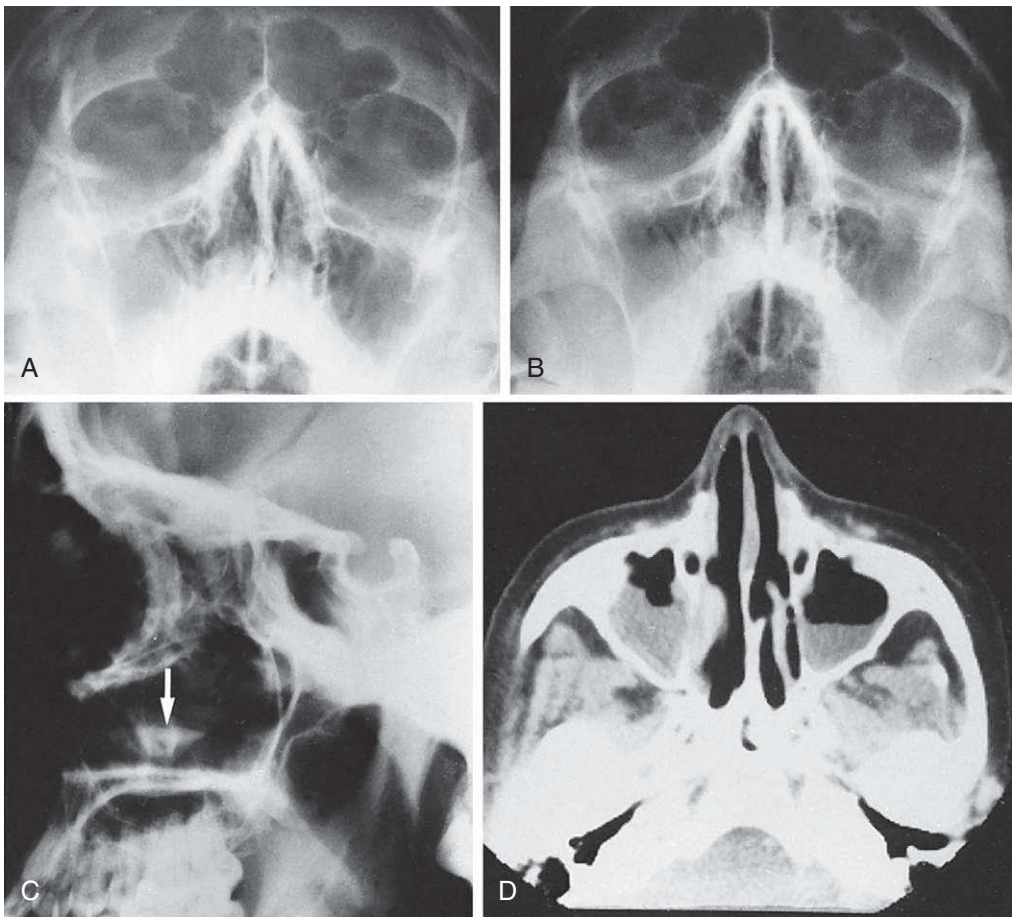

Figure 44-21. Maxillary sinus air-fluid level. **A,** Waters' view (patient prone) with right maxillary sinus opacity. **B,** View of the same patient in upright position shows the air-fluid level. **C,** The lateral view with maxillary sinus air-fluid level (*arrow*). **D,** Computed tomography scan shows bilateral maxillary sinus air-fluid levels.

complete opacification, bone remodeling and thickening caused by osteitis from adjacent chronic mucosal inflammation, and polyposis.[17,45,51]

A variety of symptom and CT or endoscopic scoring systems have been proposed to better classify patients into diagnostic and prognostic categories. It is apparent that there is no significant correlation between the severity of symptoms and the extent of inflammation identified on CT or endoscopy.[25,46,50,52] In particular, isolated symptoms of facial pain/pressure or headache do not correlate at all with CT evidence of sinus disease. The Lund-MacKay scoring system is the most popular method applied to CT description of sinus disease. A score of 0, 1, or 2 is given to each of six subsites (anterior ethmoid, posterior ethmoid, frontal, maxillary, and sphenoid sinuses and ostiomeatal complex [0 or 2]) in one side of the sinonasal cavity for normal pneumatization, partial opacification, or complete opacification, respectively.[22] The maximum score is 12 for one side.

Opacification of the ostiomeatal unit (OMU) predisposes to the development of sinusitis. Zinreich and associates[2,4,7] found middle meatus opacification in 72% of patients with chronic rhinosinusitis; 65% of these patients had mucoperiosteal thickening of the maxillary sinus. All of the patients with frontal sinus inflammatory disease had opacification of the frontoethmoidal recess. Frontal sinus opacification involving the OMU without frontal, maxillary, or anterior ethmoid sinus inflammatory disease was rare.[2,4,7] Yousem and colleagues[53] found that of patients in whom the middle meatus was opacified, associated inflammatory changes were found in the ethmoid sinuses in 82% and in the maxillary sinuses in 84%.[36] Bolger and coworkers[44] found that the maxillary and frontal sinuses were clear in 77% of patients in whom the ethmoid infundibulum was free of disease.

Babbel and associates[54] reviewed 500 patients with screening sinus CT and defined the following five recurring patterns of inflammatory sinonasal disease: infundibular OMU, sphenoethmoidal recess, sinonasal polyposis, and sporadic or unclassifiable disease patterns. The infundibular pattern (26% of patients) consisted of focal obstruction within the maxillary sinus ostium and ethmoid infundibulum that was associated with maxillary sinus disease. The OMU pattern (25% of patients) was ipsilateral maxillary, frontal, and anterior ethmoid sinus disease (Fig. 44-22). This pattern was caused by obstruction of the middle meatus. The frontal sinus was sometimes spared because of the variable location of the nasofrontal recess in the middle meatus. The sphenoethmoidal recess pattern (6% of patients) resulted in sphenoid or posterior ethmoid sinus inflammation caused by sphenoethmoidal recess obstruction. The sinonasal polyposis pattern (10% of patients) was caused by diffuse nasal and paranasal sinus polyps. Associated radiographic findings included infundibular enlargement, convex (bulging) ethmoid sinus walls, and attenuation of the bony nasal septum and ethmoid trabeculae.[27,54,55]

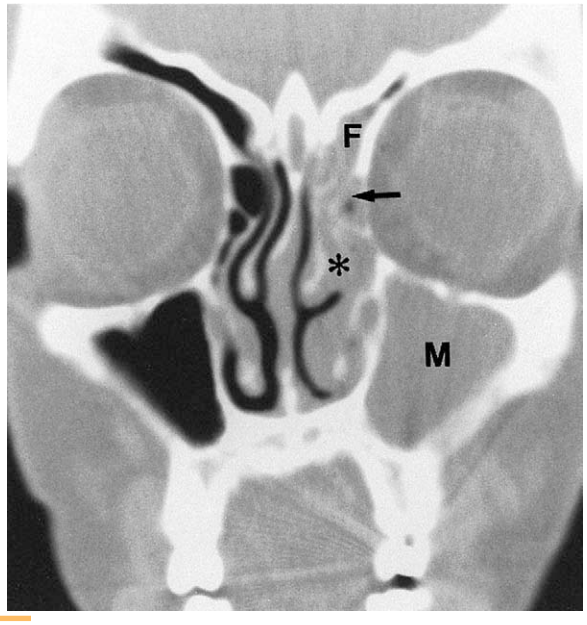

Figure 44-22. Ostiomeatal unit pattern of sinusitis. Inflammatory changes obstruct the left middle meatus (*asterisk*) with resulting opacification of the left maxillary (M), frontal (F), and anterior ethmoid (*arrow*) sinuses. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

When sinus secretions are acute and of low viscosity, they have intermediate attenuation on CT, ranging from 10 to 25 Hounsfield units. In the more chronic state, sinus secretions become thickened and concentrated, and the CT attenuation increases, having density measurements of 30 to 60 Hounsfield units (Fig. 44-23).[14]

Thickening and sclerosis of the bony walls of the sinuses have been traditionally attributed to secondary reaction of bone to chronic mucosal inflammation. Later work suggests that the bone may actually play an active part in the disease process and that, at a minimum, the inflammation associated with CRS may spread through the haversian system within the bone.[56,57] The combination of a surgical procedure and experimentally induced sinusitis creates an inflammatory process within bone with the classic histologic features of osteomyelitis. Furthermore, bone inflammation can induce chronic inflammatory changes in the overlying mucosa at a significant distance from the site of infection.

On MRI, the appearance of chronic rhinosinusitis varies because of the changing concentrations of protein and free water protons.[13,14] Initially, watery secretions visible on MRI appear as hypointense on T1-weighted images and hyperintense on T2-weighted images.[13,14] According to Som and Curtin,[14] when sinonasal secretions become obstructed, two important physiologic events occur: The number of glycoprotein-secreting goblet cells in the mucosa increases, and the mucosa resorbs free water. These events result in a transition from a thin serous fluid to a thicker mucus and, ultimately, to a desiccated stonelike plug. As the protein concentration increases, the signal intensity on T2-weighted images decreases. These changes are presumably caused by cross-linking that occurs between glycoprotein molecules. Som and Curtin[9,14] describe four patterns of MRI signal intensity that can be seen with chronic rhinosinusitis: (1) hypointense on T1-weighted images and hyperintense on T2-weighted images with a protein concentration less than 9%; (2) hyperintense on T1-weighted images and hyperintense on T2-weighted images with a total protein concentration of 20% to 25%; (3) hyperintense on T1-weighted images and hypointense on T2-weighted images with a total protein concentration of 25% to 30%; and (4) hypointense on both T1-weighted images and T2-weighted images with a protein concentration greater than 30% and inspissated secretions in an almost solid form. MRI of inspissated secretions (i.e., those with protein concentrations greater than 30%) may have a pitfall in that the signal voids on T1- and T2-weighted images may look identical to normally aerated sinuses.[13,14]

Certain anatomic variants, as described, have been implicated as causative factors in the presence of chronic inflammatory disease. Stammberger and Wolf[58] and Lidov and Som[59] found that a large concha bullosa can produce signs and symptoms by narrowing the infundibulum. However, Yousem and colleagues[53] found that the presence of a concha bullosa did not increase the risk of rhinosinusitis. This finding was corroborated by Bolger[44] who found that a concha bullosa, paradoxic turbinates, Haller cells, and uncinate pneumatization were not significantly more common in patients with chronic rhinosinusitis than in asymptomatic patients. Yousem and colleagues[53] found that nasal septal deviation and a horizontally oriented uncinate process were more common in patients with inflammatory sinusitis. Although these variants may not necessarily predispose to sinusitis, the size of a given anatomic variant and its relationship to adjacent structures are important in the development of rhinosinusitis.[29,60]

Fungal Rhinosinusitis

The clinically distinct forms of fungal rhinosinusitis are noninvasive (eosinophilic [a.k.a. allergic] fungal rhinosinusitis and fungus ball) and invasive fungal (chronic and acute). The clinical and radiologic presentation of fungal rhinosinusitis is largely determined by the host's immune response; an overreaction manifests in the form of eosinophilic

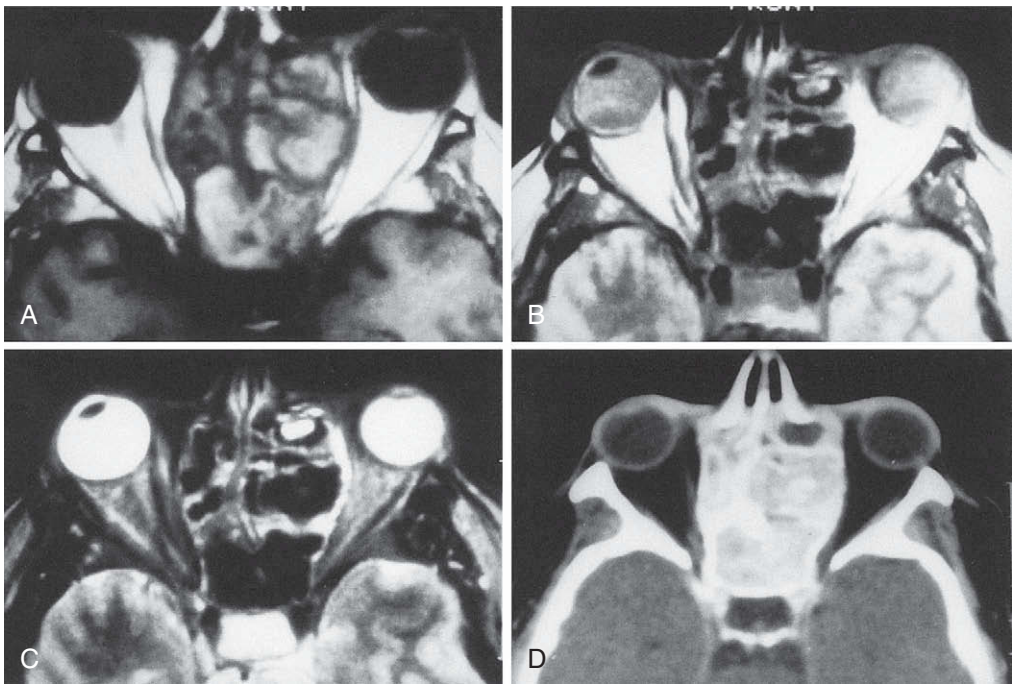

Figure 44-23. Chronic rhinosinusitis. **A,** Axial T1-weighted magnetic resonance (MR) image. **B,** Axial proton density–weighted MR image. **C,** Axial T2-weighted MR image. **D,** Axial computed tomography (CT) scan. The expanded ethmoid and sphenoid sinuses are opacified (**A**). However, if a proton density and T2-weighted series were the only MR images obtained, the dried secretions easily seen on CT (**D**) could be mistaken for aerated sinuses in **B** and **C.** *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

fungal rhinosinusitis, whereas a fungus ball is typically seen in normal hosts. Invasive fungal rhinosinusitis is seen in the setting of a lack of immune response either in a chronic form, as seen in mildly immunocompromised individuals (e.g., diabetics), or in an acute form, as seen in severely immunocompromised patients (e.g., those with hematologic malignancies).

Fungal cultures can routinely demonstrate presence of fungi in the nasal mucosa of patients with chronic rhinosinusitis, but this finding should not be taken as a proof of fungal rhinosinusitis. The role of fungi in CRS is not clearly understood but it is evident that there is a large overlap between CRS and eosinophilic fungal rhinosinusitis in both etiology and imaging features. Eosinophilic fungal rhinosinusitis usually occurs in patients with a history of atopy or asthma. This entity and sinonasal polyposis may be associated.

The fungal pathogens most commonly encountered in eosinophilic fungal rhinosinusitis are *Aspergillus* species, fungi of the order Mucorales, and *Candida* species.[29,53] Mucorales fungi and *Aspergillus* are part of the normal respiratory flora,[38] but their involvement in the paranasal sinuses can often be differentiated clinically.[14,16,61]

On imaging, the hallmarks of eosinophilic fungal rhinosinusitis are hyperdense secretions with expansion of the sinuses. Involvement of the skull base and orbits with exophthalmos or optic nerve compression is not uncommon.[62] Expansion of the sinus and bone erosion may occasionally mimic malignant disease. On MRI, sinus secretions may be very dark on all pulse sequences, sometimes causing underestimation of disease extent. A fungus ball usually manifests as opacification of a single sinus with speckled or chunky calcifications present in the sinus. It may be difficult to differentiate from regular CRS if calcifications are not present. The invasive fungal rhinosinusitis usually starts in the middle turbinate and involves the maxillary and ethmoid sinuses.[14] Air-fluid levels are uncommon, and early on it may be impossible to differentiate invasive fungal rhinosinusitis from regular rhinosinusitis on imaging studies, emphasizing the importance of a high index of suspicion for the timely diagnosis of this entity.

The imaging findings vary depending on the aggressiveness of the fungus. Nonspecific mucosal thickening or sinus opacification can occur. The allergic form of *Aspergillus* is associated with recurrent sinonasal polyps. With more invasive fungi, sinus opacification with a central mycetoma and associated bony thickening or erosion can occur.[14] With mucormycosis and invasive *Aspergillus*, vascular invasion can occur, leading to intracranial and extracranial thrombosis and infarction.

Several imaging characteristics suggest fungal rhinosinusitis (Fig. 44-24).[14-16] On CT, a focal hyperdense lesion may be seen with surrounding hypodense mucoid material. Low signal intensity on T1-weighted MR images and a signal void on T2-weighted images have been found in many patients with fungal rhinosinusitis, possibly because of the presence of paramagnetic metals (e.g., iron, manganese). Although the MRI appearance is similar in chronic bacterial infection caused by desiccated secretions, the decreased signal is not as pronounced as it is in fungal disease.

Two other circumstances suggest the presence of invasive fungal infections: soft tissue changes in the sinus with thickened, reactive bone and localized areas of osteomyelitis.[13,14] Also suggestive of fungal infection is the association of inflammatory sinus disease with involvement of the adjacent nasal fossa and the soft tissues of the cheek. These signs of aggressive infection are atypical for bacterial pathogens.

Allergic Rhinosinusitis

Allergic rhinosinusitis occurs in 10% of the population.[27] It typically produces a pansinusitis with symmetric involvement.[8] CT often shows a nodular mucosal thickening with thickened turbinates.[27] Air-fluid levels are rare unless bacterial superinfection occurs.[51]

Granulomatous Rhinosinusitis

Although many granulomatous diseases involve the sinonasal cavity, Wegener's granulomatosis is the most commonly encountered. In the early stages of this disorder, the radiologic findings are very similar to those in nonspecific rhinosinusitis. Fibrotic bands extending from turbinates to nasal walls are frequently seen in the chronic stage. Nasal septal perforation, destruction of the nasal turbinates, and marked thickening of the sinus walls are relatively characteristic features in advanced disease. Lytic bone defects and inflammatory soft tissue masses may occur in Wegener's granulomatosis and must be differentiated from lymphoma and other malignant processes.

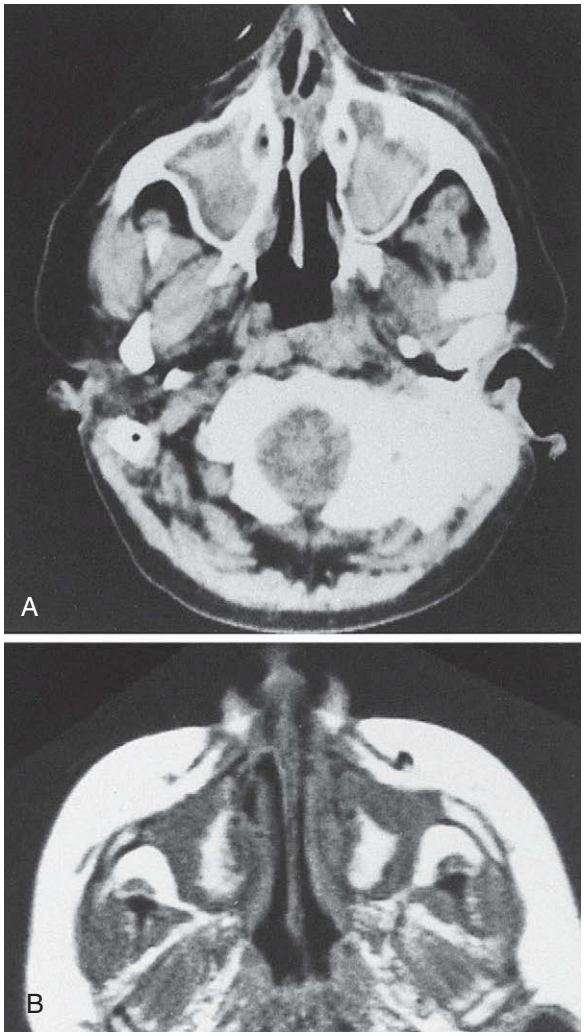

Figure 44-24. A, Axial computed tomography scan. Central areas of increased attenuation in both maxillary sinuses are separated from the sinus walls by a thin zone of low attenuation (mucoid) material. This appearance is consistent with desiccated sinus secretions, mycetoma, and hemorrhage. **B,** T1-weighted magnetic resonance image. The central areas of the antra have high T1-weighted signal intensity with surrounding low–signal intensity material, a finding diagnostic of hemorrhage with inflammation. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Complications of Inflammatory Sinus Disease

Mucous Retention Cyst

Mucous retention cyst is a small cyst that most commonly occurs in the maxillary sinus floor in patients with a history of inflammatory disease. Occurring in 10% of the population, it is the result of inflammatory obstruction of a seromucinous gland within the sinus mucosal lining.[9,27] On CT, mucous retention cyst will appear as a homogeneous, well-circumscribed hypodense to isodense mass (Fig. 44-25). On MRI, it is usually hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 44-26).

Mucocele

Mucocele is a dilated mucus-filled sinus that is lined by mucous membrane. It is the result of a chronically obstructed sinus ostium with enlargement of bony walls caused by mucous secretions filling the sinus cavity.[14,55] It is most commonly caused by inflammatory obstruction of the ostium, but can also be secondary to trauma, tumors, or surgical manipulation;[51] Sixty-six percent of mucoceles occur in the frontal sinuses, and 25% and 10% in the ethmoid and maxillary sinuses, respectively.[38] On CT, mucocele appears as a hypodense, nonenhancing mass that fills and expands the sinus cavity (Fig. 44-27). On MRI, the appearance varies because of alterations in protein concentration of the obstructed mucoid secretions.

An infected mucocele, a *mucopyocele*, may show rim enhancement.[54]

Inflammatory Polyps

Polyps in the paranasal sinuses result from local upheaval of the sinus mucosa with mucous membrane hyperplasia caused by chronic inflammation.[38,54] If large or numerous, polyps can cause local problems as a result of obstruction of the important ostiomeatal channels, including the sinus ostia. On CT and MRI, polyps are often indistinguishable from mucous retention cysts (Fig. 44-28). In chronic polyposis there is usually extensive opacification of the sinuses with expansion of the sinonasal cavity.

Orbital Complications

About 3% of patients with acute rhinosinusitis (most commonly children) have some form of orbital involvement; manifestations can be the first sign of sinus infection. Complicated rhinosinusitis is the most common cause of orbital infection, occurring in 60% to 84% of cases.[1,26,31,63] The ethmoid sinuses are the most common origin, followed, in decreasing order of frequency, by the frontal, sphenoid, and maxillary sinuses. The ethmoid and maxillary sinuses are present at birth and therefore are the source in younger children. The frontal sinuses are usually detectable radiologically in children 6 years of age but are not usually significant sources of infection until after the age of 10 years. The sphenoid sinuses also develop late and are rarely implicated in pediatric patients.

Most researchers recommend CT when clinical evidence of postseptal infection is present (i.e., when exophthalmos and limited eye movement are present) or when there is failure to improve with antibiotics.[27,54] Because the disease can be more aggressive in pediatric patients, CT should be considered when clinical evidence of preseptal inflammation is present.

Preseptal orbital edema is a common finding in sinusitis, especially in children. CT reveals diffuse soft tissue density and thickening of the preseptal soft tissues. At this stage, swelling and redness of the eyelids occur, but not exophthalmos or limited eye movement. As infection spreads from the ethmoid sinus to the orbit, the orbital periosteum becomes inflamed, thickened, and elevated, with accumulation of an inflammatory phlegmon. On CT, the phlegmon appears as an ill-defined, slightly enhancing mass on the sinus and orbital sides of the lamina papyracea. It is limited laterally by the periosteum; however, in more advanced cases, it merges with a thickened and enhanced medial rectus muscle, which is displaced laterally. Subsequently, liquefaction can occur in the subperiosteal compartment to form an abscess, which is evident on CT as regions of low density, sometimes with an enhancing rim. CT findings of low-attenuation material surrounded by an enhancing rim suggest an abscess rather than a phlegmon, although the distinction between them can be difficult, given the continuum existing between these two states.

Rare orbital complications of paranasal sinus infection include superior ophthalmic vein thrombosis, cavernous sinus thrombosis, and blindness.[64] Superior ophthalmic vein thrombosis is suspected on CT when enlargement of this vessel (best seen on coronal scans) is asymmetric with a relative lack of normal enhancement, although thrombus within the lumen can be hyperdense. MRI may show these changes more accurately. Magnetic resonance angiography, especially phase-contrast techniques, can establish the presence of superior ophthalmic vein thrombosis.

Cavernous sinus thrombosis is evident as fullness of the affected side with convexity of the lateral margin of the cavernous sinus (instead of the normal, slightly concave margin). Gadolinium-enhanced axial and coronal MR images would be expected to be more sensitive to the presence of cavernous sinus thrombosis than CT.

Permanent loss of vision is a rare complication of acute rhinosinusitis, although studies report about a 10% incidence in patients with

Figure 44-25. Axial computed tomography scans in the middle (**A**) and in the upper portion of the left maxillary sinus (**B**). In **A,** the sinus appears to be opacified. However, in **B,** air can be seen outlining the upper surface of a large retention cyst or polyp. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

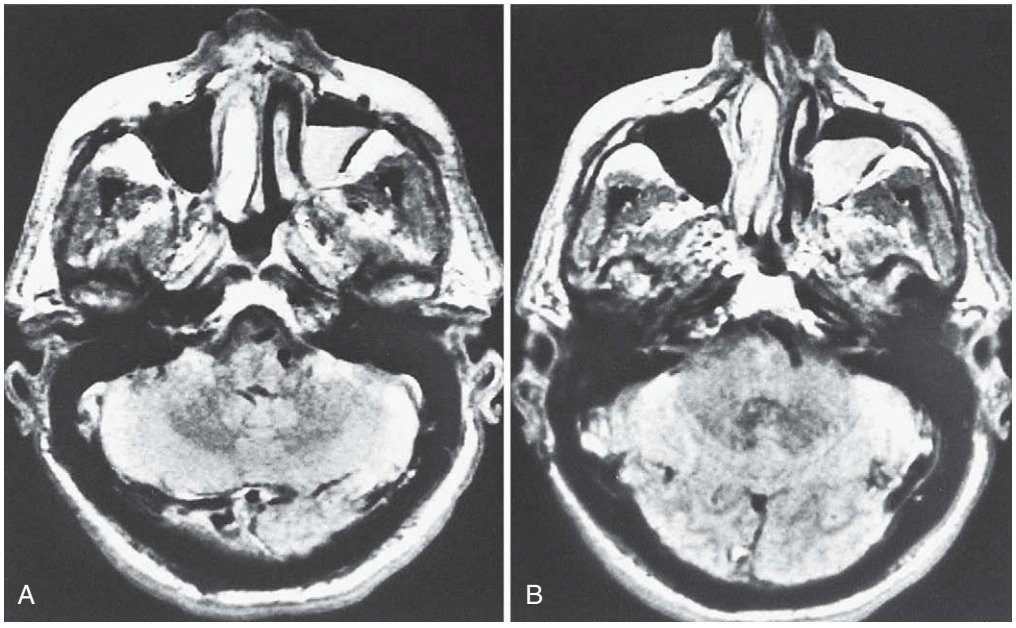

Figure 44-26. Axial proton-density magnetic resonance images low (**A**) and higher (**B**) in the antrum show a retention cyst in the left antrum. If the contour of the upper surface is not clearly noted on all scans, this cyst could be mistaken for an air-fluid level. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

postseptal infection.[1,26,62,63] A mechanism for loss of vision may be optic neuritis as a reaction to adjacent infection. Ischemia caused by thrombophlebitis, arteritis, or pressure on the central retinal artery may also result in blindness.

Radiographic Evaluation of Patients after Functional Endoscopic Sinus Surgery

Expected Findings

Postoperative evaluation of patients is similar to preoperative evaluation. Ideally, FESS should be followed by coronal CT. First, the type and extent of surgery should be established. Subsequently, the emphasis is on the anatomy. The presence or absence of important structures should be identified and mentioned. The nasal cavity, paranasal sinus boundaries, and important anatomic relationships should be inspected (Fig. 44-29). Areas of bony thickening or dehiscence should be noted. The following structures merit close scrutiny on follow-up CT.

Frontal Recess

The frontal recesses should be identified to determine their patency. Postoperatively, recurrence of disease is caused by persistent obstruction in this area, which is the narrowest channel within the anterior ethmoid complex and is difficult to access surgically. Therefore, the frontal recess is most likely to be affected with inflammatory disease in a patient who underwent previous surgery in the paranasal sinuses. The agger nasi cell (if it remains) should be noted because its persistence may continue to narrow the frontal recess.

Ostiomeatal Unit

The extent of the excision of the uncinate and removal of the ethmoid bulla should be noted. The course of the infundibulum should be examined for persistent anatomic narrowing. The outline of the

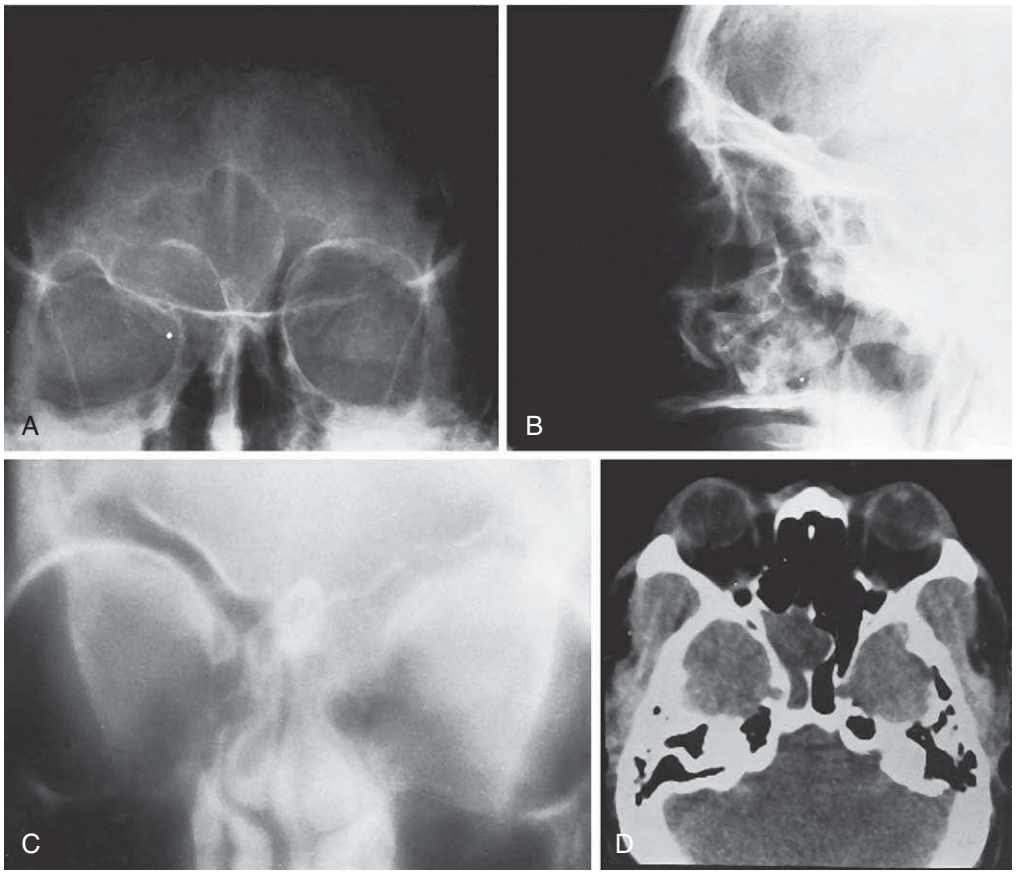

Figure 44-27. Sinus mucoceles. **A,** Frontal view of right frontal-ethmoid sinus mucocele. Right orbital border is expanded. **B,** Lateral view of same patient with expansible change in frontal sinus and ethmoidal expansion. **C,** Frontal tomogram of another patient with left ethmoid sinus mucocele. Note expansible thinning of ethmoidal cells and orbital roof thinning. **D,** Right sphenoid sinus mucocele with expanded thinning of septum. *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

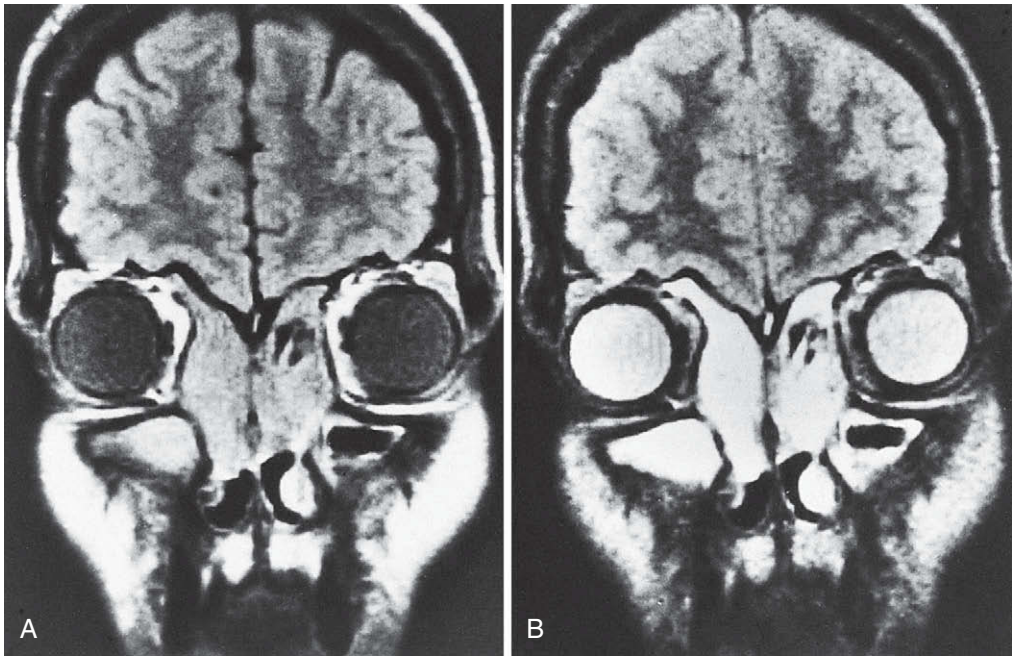

Figure 44-28. Polyposis and sinusitis. Coronal proton-density (**A**) and T2-weighted (**B**) magnetic resonance images show bilateral nasoethmoid expansile masses causing hypertelorism. These masses have the same signal intensities as the mucosal thickening in the left antrum and the material in the right antrum, namely an intermediate signal intensity in **A** and a high signal intensity in **B.** *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

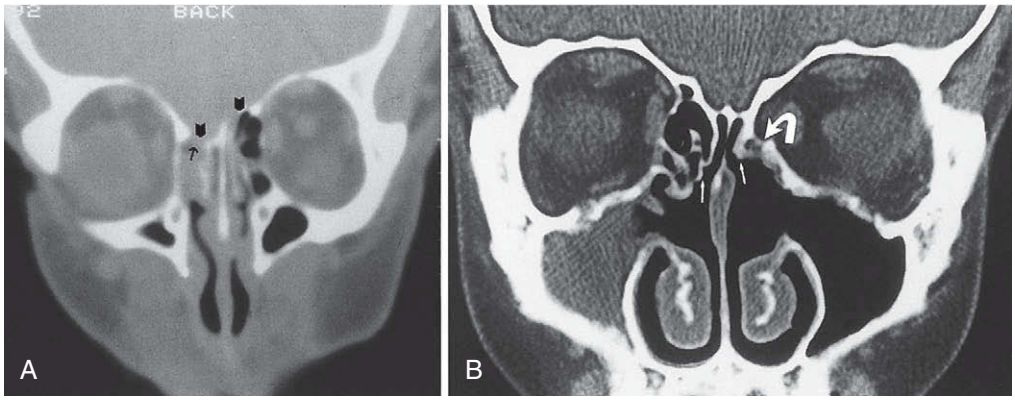

Figure 44-29. Anatomic landmarks to be evaluated in patients after functional endoscopic sinus surgery. **A,** Coronal computed tomography (CT) scan through the anterior ethmoid sinuses shows a prominent asymmetry in the position of the roof of the ethmoid sinuses (*arrowheads*). The intracranial penetration (*small arrow*) is usually on the side where the roof is lower. **B,** Coronal CT scan through the anterior ethmoid sinus in a patient after bilateral uncinate resections and partial middle turbinectomies (*small arrows*). If there is an intraorbital complication during such a surgical procedure, it usually involves the lamina papyracea at the attachment of the basal lamella (*curved arrow*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

middle turbinate should be examined to determine whether a middle turbinectomy has been performed. If so, careful attention should be paid to the vertical attachment of the middle turbinate to the cribriform plate and to the attachment of the basal lamella to the lamina papyracea. Traction on the vertical attachment and basal lamella of the middle turbinate during the course of middle turbinectomy can fracture the lamina papyracea or the cribriform plate. Breaks in the continuity of the lamina papyracea and the ethmoid roof are easily seen on coronal images.

Lamina Papyracea

The course of the lamina papyracea should be inspected to evaluate the integrity of this structure. Postoperative dehiscences are commonly found posterior to the nasolacrimal duct and can be caused by the uncinate resection.

Ethmoid Roof

Asymmetry in the position of the roof of the ethmoid sinus should be noted. Intracranial penetrations are usually on the side where the roof is lower.

Sphenoid Sinus Area

The margins of the sphenoid sinus should be evaluated for bony dehiscence or cephalocele.

Operative Complications

The incidence of FESS-related complications is related to the use of instruments, the patient's underlying anatomy, the overall health of the patient, the extent of disease, and the experience of the surgeon.[10,20,27,37-40]

The field of view available to the surgeon during FESS is quite small, and variant anatomy can make surgical landmarks difficult to identify. The surgeon's view is limited to the surface mucosa and does not extend beyond the mucosa directly in view. The presence of various anatomic variants can contribute to surgical complications if not noted prospectively.[33,65] As stated, because an accurate surgical road map is needed, all patients scheduled to undergo FESS should also undergo preoperative coronal CT.

Brisk bleeding in the operative field and extensive nasal polyposis can hinder visibility and predispose the patient to operative complications.[33] Standard surgical techniques and microscope-assisted surgery can be used when problems arise. However, they involve many of the same complications.

In general, complications can be divided into minor and major.[32,33,35,37,66] Minor complications include periorbital emphysema, epistaxis, postoperative nasal synechiae, and tooth pain. Although these complications can commonly occur, they are usually self-limited and do not require postoperative radiologic evaluation.

Major complications are rarer but can be severely devastating or fatal.[35] A preexisting loss of integrity of the lamina papyracea can permit intraorbital fat to herniate into the ethmoid sinuses. Preexisting dehiscence of the lamina papyracea may be caused by prior trauma or erosion from chronic sinus disease. Disruption of the lamina papyracea can occur during resection of the middle turbinate if the ground lamella is resected back to its attachment to the lamina papyracea (Fig. 44-30).

The medial rectus muscle, superior oblique muscle, or other orbital contents can be directly damaged if preexisting or intraoperative disruption of the lamina papyracea occurs.[24] Injuries to the orbital contents can result in postoperative diplopia, which can be caused by muscle entrapment among bone fragments or direct muscle laceration, or it can occur secondary to nerve injury. Clinically, subconjunctival hemorrhage is often associated with extraocular muscle damage.[24] If intraorbital and intraocular pressure builds up as a result of an expanding hematoma or air being forced into the orbit from the nasal cavity (through a dehiscent lamina papyracea), visual impairment or blindness secondary to ischemia can result.[24]

Temporary or permanent blindness caused by injury of the optic nerve can occur during posterior ethmoidectomy if the bony limit of the sinus is violated (see Fig. 44-29).[24,32,35] Trauma to the vessels supplying the optic nerve also can result in visual loss.

Perforation of the cribriform plate can lead to intracranial hematoma or infection.

Massive hemorrhage from direct injury to major vessels can occur. Laceration of the internal carotid artery has been reported and is often fatal.[32,33,35] Emergency angiography with balloon occlusion of the lacerated artery has been performed. Patients who report severe postoperative headache or photophobia or who have signs suggesting subarachnoid hemorrhage should undergo noncontrast CT of the head. If subarachnoid blood is found, cerebral angiography is recommended to detect vascular injury.[32,33,37]

Injury to the nasolacrimal duct can occur during anterior enlargement of the maxillary ostium in the middle meatus. Injury to the membranous portion of the duct may be self-limited and may remit by spontaneous fistulization into the middle meatus. Stenosis or total occlusion of the nasolacrimal duct can result from more severe injury.[24]

Postoperative CSF leak, another major complication of FESS,[10,24,35,66] occurs after inadvertent penetration of the dura. Extension of the injury to involve the cribriform plate, fovea ethmoidalis, anterior cranial fossa, and the skull base has been reported. Secondary nasal encephalocele or deep penetration of the cerebrum can be seen after violation of the cranial vault.[17] A CSF leak may not become clinically apparent for up to 2 years after surgery.[32,33] CSF leaks often

close spontaneously with conservative measures (e.g., lumbar drain).[32,33] However, if they persist, radiologic workup is indicated. If the presence of CSF leak is proven by detection of β_2-transferrin in nasal secretions, a high-quality CT scan is often sufficient to demonstrate the skull base defect. If there is soft tissue prominence in the vicinity of the skull base defect, MRI can often differentiate meningocele from mucosal thickening. In certain situations it may be necessary to show the site of leakage with the use of a positive contrast agent.

Traditionally, a radionuclide cisternogram is the initial radiologic screening examination in such patients.[67] Before the study, several absorbent pledgets are placed in the nasal cavity. Next, the radionuclide is injected in the subarachnoid space via lumbar puncture. The patient undergoes imaging with a gamma camera at multiple intervals up to 24 hours. Any position or activity known to provoke the leak is encouraged. Identification of radionuclide accumulation outside the cranium is diagnostic for CSF leak. Imaging over the abdomen is beneficial because swallowed radionuclide manifests as intestinal activity (Fig. 44-31). Contamination of the pledgets with radionuclide is also diagnostic of CSF leak. Pledgets showing activity 1.5 times greater than serum activity are considered "positive." Unfortunately, the sensitivity of the radionuclide cisternogram is not sufficiently high, and the specificity of the test is hampered by leakage of the radionuclide from serum to nasal mucosa. Furthermore, the anatomic detail provided is not sufficient for surgical planning. CT cisternogram, on the other hand, affords excellent anatomic detail. The sensitivity of CT cisternography is limited in cases of intermittent CSF leak. For CT cisternography, 3 to 5 mL of iodinated contrast material is administered intrathecally, and the patient is placed in reverse Trendelenburg position; then high-resolution CT of the skull base is obtained with the patient in the prone position.

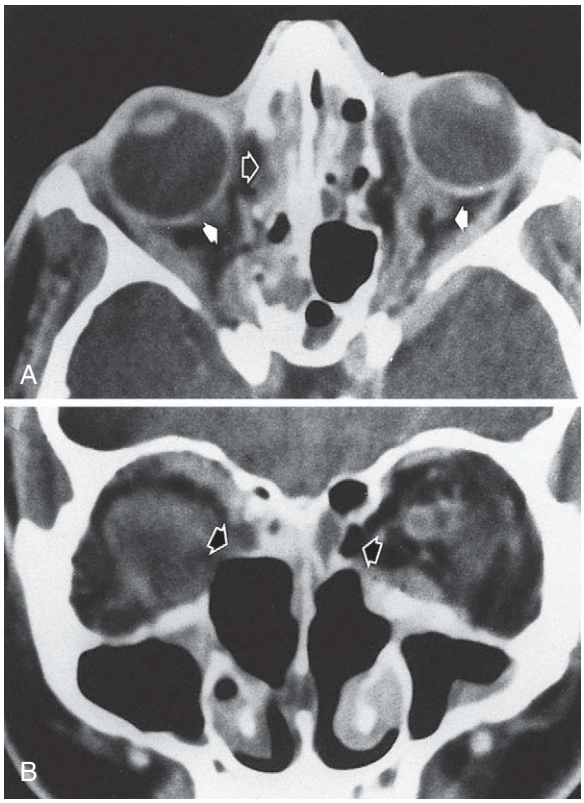

Figure 44-30. Orbital complications from functional endoscopic sinus surgery. Axial (**A**) and coronal (**B**) computed tomography scans in a patient who was found to be blind after undergoing bilateral anterior ethmoidectomies, partial bilateral middle turbinectomies, and bilateral uncinate resections. Note the bilateral defects in the lamina papyracea (*open arrows*) and the bilaterally severed optic nerves (*solid arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Image-Guided Surgery

Although it is not a replacement for anatomic knowledge, good surgical technique, and sound judgment, image-guided surgery (IGS) may allow the surgeon to accept more difficult cases and perform more comprehensive operations. Various IGS systems routinely used today share the same principle: to give the surgeon a real-time link between the preoperatively obtained image data set and the surgical field.

The fundamental functional components of IGS systems are the registration and tracking systems. The common components of various IGS systems include computer workstation, display system, software, data transfer unit, surgical instrumentation, tracking (navigation) system, and registration system.

Registration

Registration is the process of creating a link between the preoperatively obtained image data set and the operating field volume. Through registration, the computer software maps define points in the preoperative image data set with their corresponding points in the operating field. Subsequent localizations are calculated relative to these registration data. The registration process is the most important factor determining the accuracy of an IGS system.

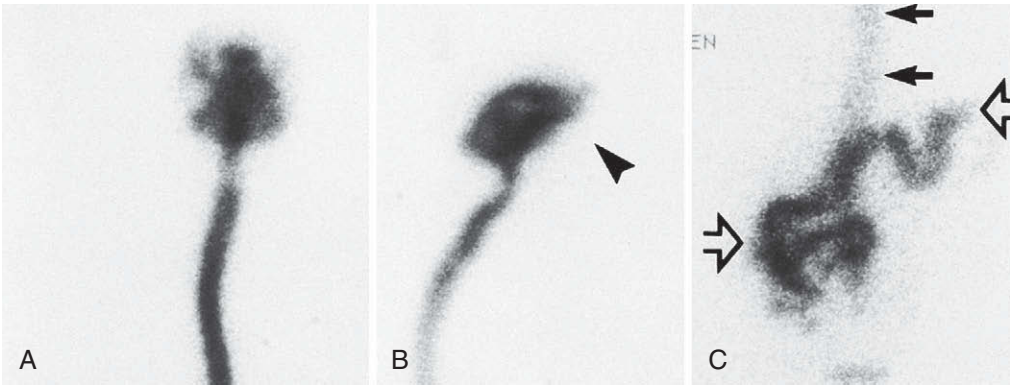

Figure 44-31. A cerebrospinal fluid (CSF) leak seen after functional endoscopic sinus surgery. An Indium-111–labeled pentetic acid CSF study in the anteroposterior (AP) (**A**) and lateral (**B**) projections shows normal activity in the subarachnoid spaces. No activity is seen within the paranasal sinuses or nasal cavity (*black arrowhead*). **C,** Delayed AP image of the abdomen shows abnormal bowel activity because of swallowed secretions from occult CSF leakage (*open arrows*). Residual activity within the subarachnoid space is noted (*black arrows*). *(From Som PM, Curtin HD.* Head and Neck Imaging. *3rd ed. St Louis: 1996; Mosby.)*

Generally, two types of registration approaches are used, intrinsic and extrinsic. Intrinsic markers are anatomic points selected directly from the patient's anatomy (anatomic fiducial or surface mapping registration). Extrinsic markers include skin-affixed markers, bone-anchored markers, and head frame–mounted reference points (autoregistration).

Tracking Systems

A tracking system constantly monitors the ever-changing position of the surgical instruments and patient's head. The location of instruments is superimposed on the preoperative image data, allowing the surgeon to navigate through the operating field. The precision of instrument localization is critical to maneuvering safely within concealed anatomy and allows the surgeon to perform a more precise and thorough operation. Today, two tracking technologies are in widespread use: electromagnetic and optical.

Optical IGS systems use infrared light for the tracking of surgical instruments and the patient's head. There are two types of optical tracking systems, active and passive. In the active system, light-emitting diodes (LEDs) are secured on the surgical instruments and the head frame worn by the patient. This system requires either a cable connection to the instrument and head frame or incorporation of batteries to power the LEDs. The passive tracking system has reflector units instead of LEDs, precluding a power source and permitting cordless instruments and head frame. The infrared light emitted or reflected by the instruments and head-piece is detected by an array of strategically placed cameras that incorporates digitizing sensors. Then through triangulation, the computer calculates the instrument tip position on the basis of its known geometry.

A clear line of sight must be maintained between the infrared camera and LEDs or reflectors mounted on the surgical instruments for the system to function correctly and continuously.

Electromagnetic IGS systems exploit the changes in local magnetic field created by movement of surgical instruments and patient's head to calculate the instrument tip position. A radiofrequency transmitter placed on a head frame and a receiver incorporated into the surgical instrument track the relative positions of the instrument and patient's head. Both the receiver and transmitter are connected to a computer, which calculates the position of the instrument and displays it on the image data.

The presence of any other ferromagnetic object in the surgical field can distort the magnetic field and disrupt the signal, although this problem is minimized through developments in coil design. The use of the IGS system is contraindicated in patients with cardiac pacemakers and cochlear implants. The other disadvantage is that the head frame may interfere with some external frontal sinus procedures. The electromagnetic IGS systems are less costly than the optical ones.

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CHAPTER FORTY-FIVE

Epistaxis

Daniel B. Simmen

Nick S. Jones

Key Points

- Epistaxis is the most common otolaryngologic emergency.
- The most common etiology of epistaxis is idiopathic, followed by primary neoplasms and traumatic or iatrogenic causes.
- The management ranges from resuscitation, through visualization, and cautery, nasal packing, and surgery (either endoscopic or external), to embolization.
- Terminal branches of the external and internal carotid arteries supply the mucosa of the nasal cavity, with frequent anastomosis between these systems.
- Various anastomoses on the ipsilateral side between the internal and external carotid systems exist as well as crossover to the contralateral side.
- The philosophy of management for epistaxis is: (1) establish the site of bleeding, (2) stop the bleeding, and (3) treat the cause.
- The majority of posterior idiopathic bleeds are from the septum, usually from the septal branch of the sphenopalatine artery.
- Endoscopic bipolar diathermy treats most cases of epistaxis.
- If a bleeding point cannot be found, ideally the nose is packed with an absorbable hemostatic agent that produces minimal mucosal trauma.
- Endoscopic sphenopalatine artery ligation (ESPAL) has replaced the need for posterior nasal packs, other than in an emergency situation to control profuse bleeding.
- The branching pattern of the sphenopalatine artery is complex—most commonly there are two or three branches medial to the crista ethmoidalis, sometimes even more.
- Persistent posterior epistaxis can be controlled by percutaneous embolization of bleeding arteries.

Epistaxis is the commonest otolaryngologic emergency, affecting up to 60% of the population in their lifetimes, with 6% of cases requiring medical attention.[1] It has been estimated that nosebleeds affect 108 per 100,000 population per year.[2] In England and Wales an average of 10.2 per 100,000 patients with nosebleed are admitted, for an average stay of 2.9 days, in a 3-month period[3]; and in the United States 17 per 100,000 or 6% of patients with nosebleed are admitted.[4] There are peaks in incidence for patients both younger than 10 years old and older than 40 years.[4-6] The etiology of epistaxis in the majority of patients is idiopathic,[7] followed in frequency by primary neoplasms and traumatic or iatrogenic causes.

Decisions about the optimum therapeutic intervention and timing are often made on an ad hoc basis, and most units do not have a protocol (systematic algorithm) for the management of epistaxis,[8] despite a 2005 published protocol aimed at junior doctors.[9] However, this protocol does not contain the timing of surgical intervention. The management of a patient with epistaxis ranges from resuscitation, through direct visualization and cautery, nasal packing, and surgery (both endoscopic and external) to embolization.

Vascular Anatomy

The nasal cavity is extremely vascular. Terminal branches of the external and internal carotid arteries supply the mucosa of the nasal cavity with frequent anastomoses between these systems (Fig. 45-1). The anterior nasal septum is the site of a plexus of vessels called Little's or Kiesselbach's area, which is supplied by both systems.

The terminal branches of the external carotid artery that supply the nasal cavity are the facial artery and the internal maxillary artery. The facial artery supplies the superior labial artery, which enters the nose and supplies the anterior nasal septum. The internal maxillary artery courses within the pterygopalatine fossa and terminates in the sphenopalatine, descending palatine, pharyngeal, infraorbital, and posterior superior alveolar arteries. The branching of the sphenopalatine artery when it enters the nasal cavity is a key point in the understanding of the management of posterior nosebleeds. The sphenopalatine artery enters the nasal cavity through the sphenopalatine foramen and then divides into conchal (posterior-lateral) and septal (posterior-medial) branches.[10,11] The descending palatine artery courses through the greater palatine canal and becomes the greater palatine artery, entering the nose through the incisive foramen, where it supplies the anterior inferior septum and anastomoses with medial branches of the sphenopalatine artery. Importantly, the vidian artery has a significant anastomosis between the internal carotid artery and a branch of the sphenopalatine artery and therefore with the external carotid system (Fig. 45-2).

The internal carotid artery supplies the nasal mucosa via the ethmoidal branches of the ophthalmic artery. The ophthalmic artery is the first branch of the internal carotid artery. The posterior ethmoidal artery passes through the posterior ethmoidal canal into the anterior cranial fossa and divides into lateral and medial branches, supplying the superior part of the posterior septum and lateral nasal wall. The anterior ethmoidal artery enters the nasal cavity through the anterior ethmoidal

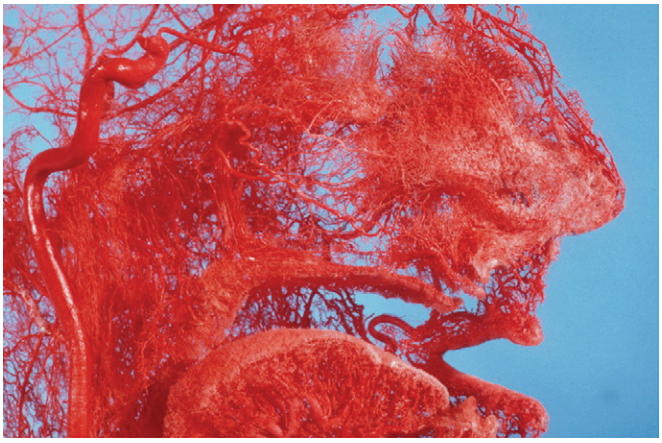

Figure 45-1. Latex-injected human skull showing the functional vascular anatomy of the nasal mucosa—internal and external artery supplies with rich anastomoses in between and also crossover anastomoses. (Courtesy of the Institute of Anatomy, University of Zürich, Switzerland.)

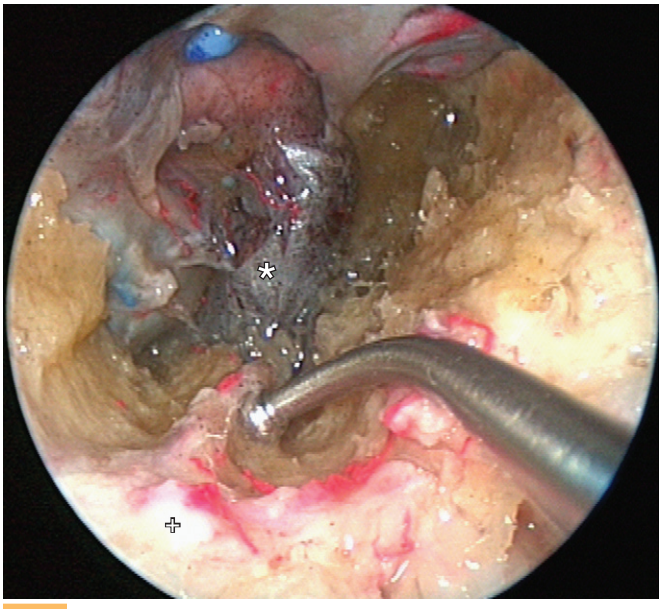

Figure 45-2. Endoscopic view of an anatomic, injected specimen showing the vidian artery along the floor of the right sphenoid with the ball probe anastomosing the internal carotid (*asterisk*) with the sphenopalatine artery system (*plus sign*).

canal and passes anteromedially to the area of the anterior skull base (Fig. 45-3). Where it crosses the anterior ethmoid roof to reach the fovea ethmoidalis and cribriform plate, a nasal branch supplies the anterior superior part of the septum (Fig. 45-4) and its other branch—the anterior meningeal artery—enters intracranially.

A fundamental aspect of the understanding of the vascular anatomy and its importance to epistaxis is the fact that various anastomoses on the ipsilateral side between the internal and external carotid systems exist as well as crossover to the contralateral side. The rich anastomoses underlie the importance of a strategy to address the most distal site of any bleeding (Figure 45-5).

The maxillary sinus ostium serves as the dividing line between "anterior" and "posterior" epistaxis. Anterior bleeding is usually easier to access and is therefore less dangerous. Posterior epistaxis is more difficult to treat because visualization is more difficult and blood is

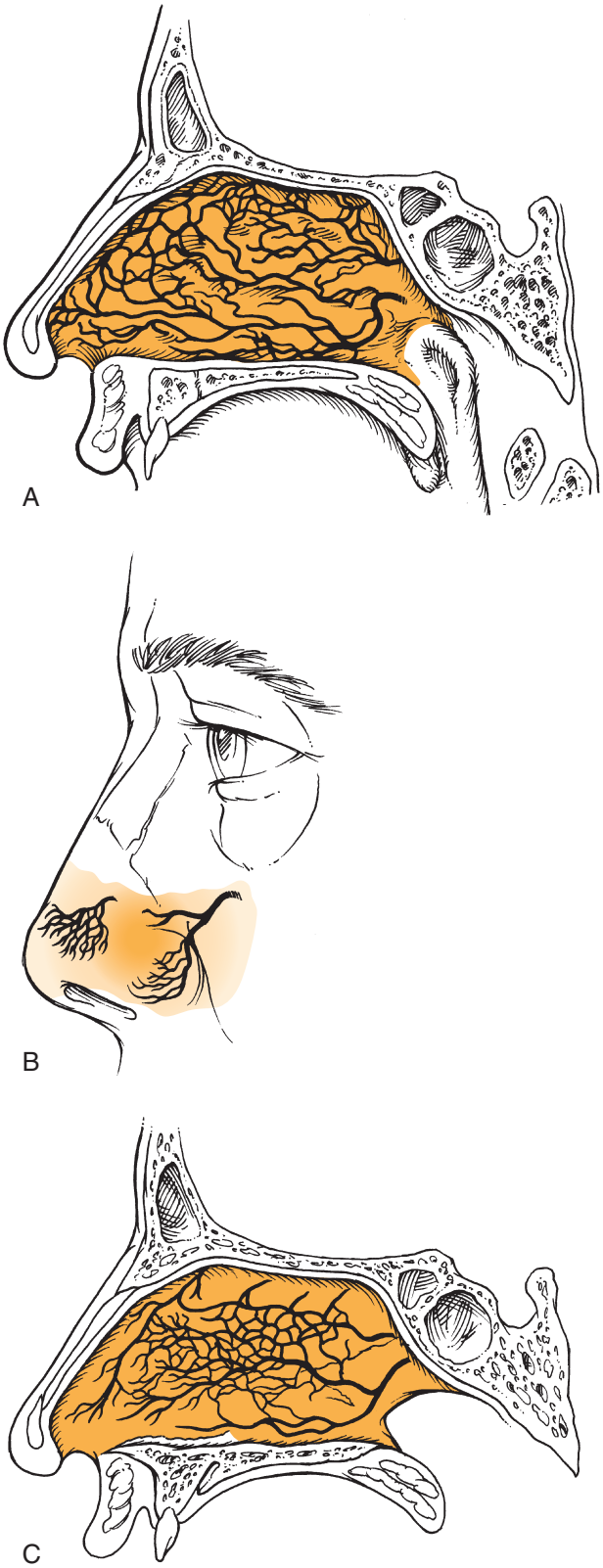

Figure 45-3. Internal and external artery supply with rich anastomoses in between and also crossover anastomoses: lateral nasal wall **(A),** external nose **(B),** and septum **(C).** *(Adapted from Zuckerkandl: Anatomie der Nasenhöhle, Taf. XIII, 1892.)*

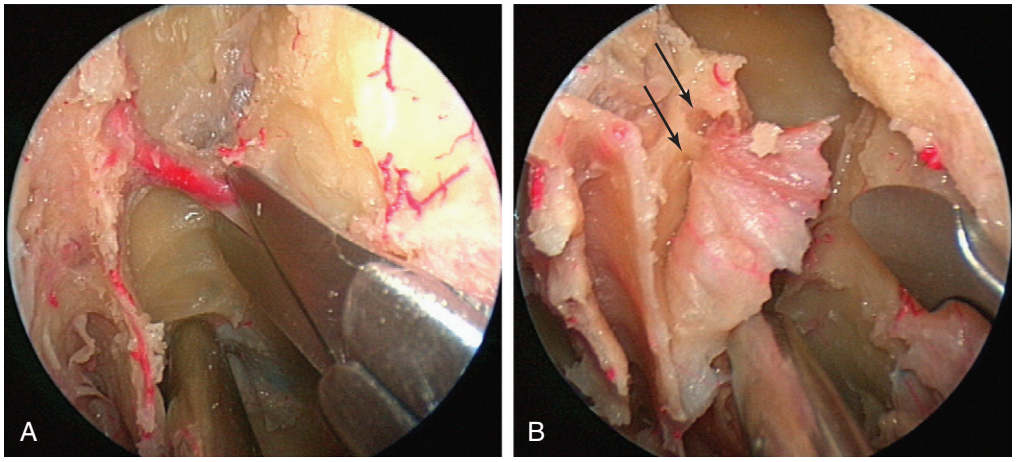

Figure 45-4. Endoscopic view of the left skull base in a injected specimen, showing the course of the anterior ethmoid artery. **A,** Zürich microscissors dividing the artery close to the orbit. **B,** Endoscopic view to the left skull base area after a median drainage procedure, showing the anterior nasal branch coming off the ethmoidal artery and the first olfactory fiber just behind (*arrows*).

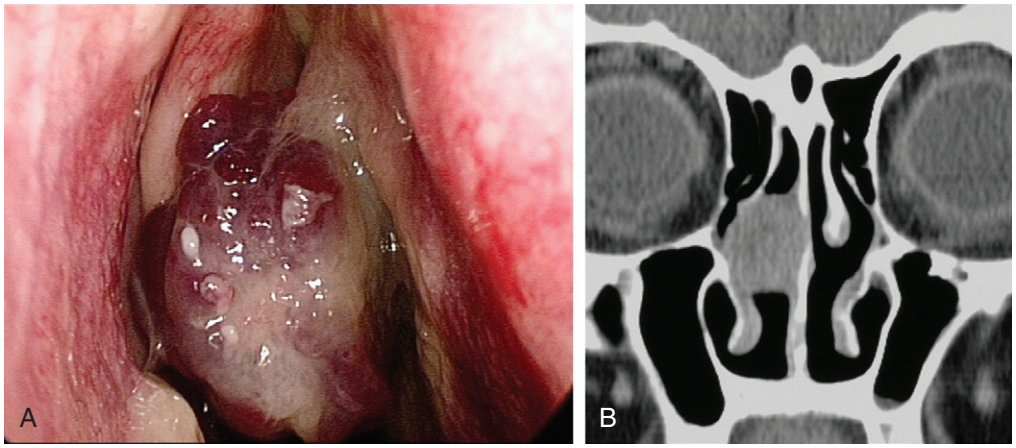

Figure 45-5. Endoscopic view **(A)** and computed tomography scan **(B)** of a cavernous hemangioma arising from the olfactory cleft on the right side that has caused a severe epistaxis.

often swallowed, making it more difficult to gauge the amount of blood loss.

The term "posterior bleeding" is all too often used incorrectly to label bleeding that cannot be visualized with a head lamp. It transpires in many cases that endoscopic examination shows the bleeding to be located high on the septum.

Management

Initial Assessment

The amount of blood loss should be estimated (the physician should ask about whether the patient has lost enough to soak a handkerchief, a facecloth, or a towel; the last would indicate a significant loss), and over what period (a regular minor bleed can cause anemia). A clinical assessment of the patient's cardiac status and circulating blood volume should include looking to see if the patient is pale, sweating, or cool, or has tachycardia; any of these findings would indicate significant hypovolemia. A reduction in blood pressure is often a late sign, particularly in young people, who can maintain blood pressure until the circulatory volume is critical.

Obtaining intravenous access, checking for and correcting any clotting abnormalities, and taking blood for "group and save" and/or crossmatching may be required. In our unit patients admitted via the emergency department can be "fast-tracked" to the otorhinolaryngologic emergency unit if stable (Box 45-1). This practice helps avoid unnecessary and counterproductive nasal packing in the emergency department as well as transfer of patients before they are fit enough to travel.

First aid measures include asking the patient to apply constant firm pressure over the lower (non-bony) part of the nose for 20 minutes and to lean forward with the mouth open over a bowl so that further blood loss can be estimated. Otherwise, blood dripping postnasally will be swallowed, and the next warning sign of a serious loss could be several hundred milliliters of blood being vomited up.

It is important to establish both the site and the cause (Box 45-2; Figs. 45-6 to 45-12) of bleeding. The philosophy of this approach can be summarized as follows:

1. Establish the site of bleeding.
2. Stop the bleeding.
3. Treat the cause.

The clinician must remember that epistaxis is frequently idiopathic but can be a manifestation of a possible underlying pathology (see Fig. 45-12). Your patient should undergo further investigation according to the history.

Box 45-1

Criteria for Emergency Department "Fast-Tracking" of a Patient with Epistaxis to an Otorhinolaryngologist

1. The patient is hemodynamically stable and shows no clinical signs secondary to hypoperfusion (cardiac/respiratory or decreased Glasgow Coma Scale score).
2. The patient does not have any severe medical comorbidities that would make transfer to an otorhinolaryngology clinic or the ward unsafe.
3. For a patient in whom the bleeding is other than minor, a blood specimen has been collected and sent for complete blood count, clotting screen, and "group & save," and an intravenous infusion has been started.
4. Digital pressure on the patient's alar cartilages and septum has been used for at least 20 minutes.

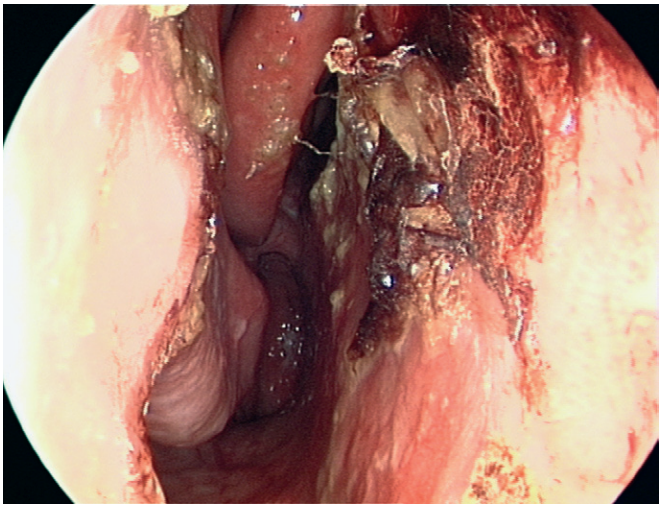

Figure 45-6. Endoscopic view in Wegener's granulomatosis.

Box 45-2

Etiology—Selected Causes of Epistaxis

Local Causes

Idiopathic—spontaneous

Trauma:
- Nose picking
- Foreign body
- Nasal oxygen and continuous positive airway pressure
- Nasal fracture

Inflammatory/infectious:
- Common cold, viral rhinosinusitis
- Allergic rhinosinusitis
- Bacterial rhinosinusitis
- Granulomatous diseases (Wegener's granulomatosis [Fig. 45-6], sarcoid, tuberculosis)
- Environmental irritants (cigarette smoking, chemicals, pollution, altitude)

Postoperative—iatrogenic:
- Nasal surgery (Fig. 45-7)

Primary neoplasm:
- Hemangioma of the septum, turbinates
- Hemangiopericytoma
- Nasal papilloma
- Pyogenic granuloma (Fig. 45-8)
- Angiofibroma (Fig. 45-9)
- Carcinoma and other nasal malignancies (Fig. 45-10)

Structural:
- Septal deformity, spurs
- Septal perforation (Fig. 45-11)

Drugs:
- Topical nasal steroids
- Cocaine abuse (Fig. 45-12)
- Occupational substances

General Disorders, Systemic Causes

Hypertension (not more common, but more troublesome)

Arteriosclerosis

Platelet deficiencies, dysfunction; coagulopathies (e.g., warfarin, liver disease)

Leukemia, von Willebrand's disease

Hereditary hemorrhagic telangiectasia

Organ failure (liver, kidney)

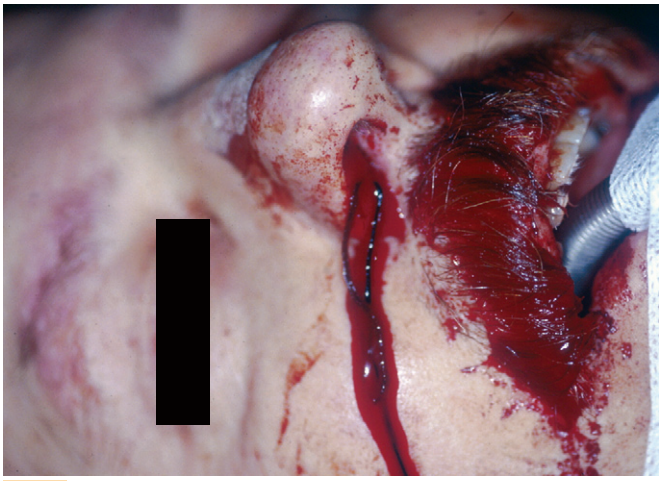

Figure 45-7. Postoperative severe epistaxis that has not been stopped by packing. Endoscopic investigation has determined that bleeding is coming from the septal branch, which was cut by sphenoidotomy performed on the right side.

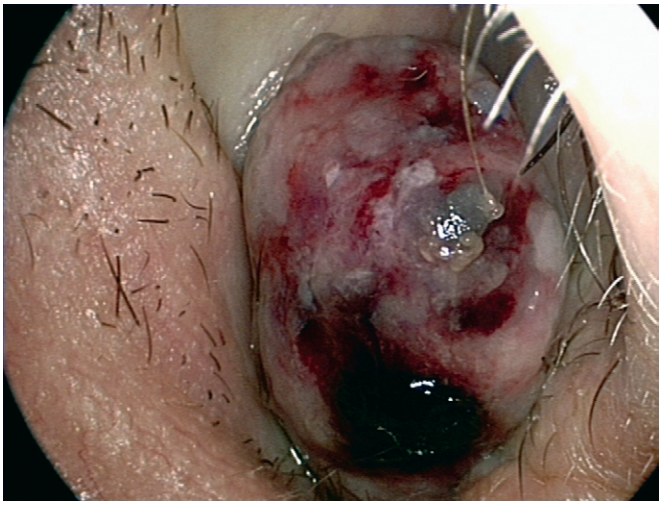

Figure 45-8. Pyogenic granuloma on the septum, right side nasal vestibule.

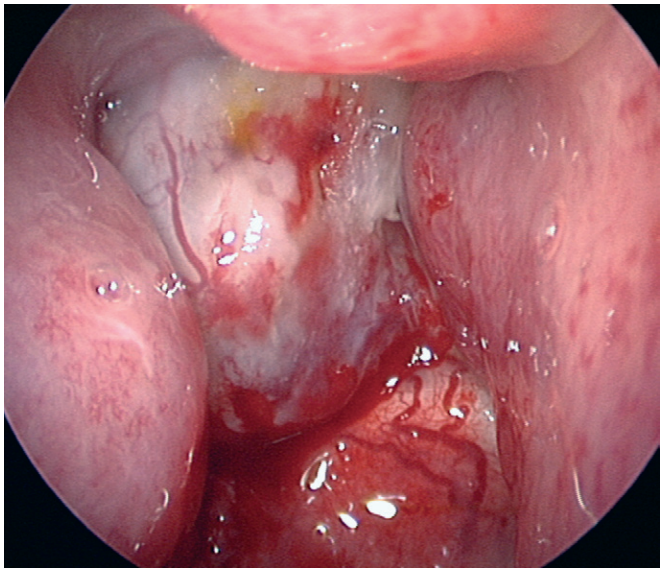

Figure 45-9. Endoscopic view of an angiofibroma occluding the right nasal cavity and choana.

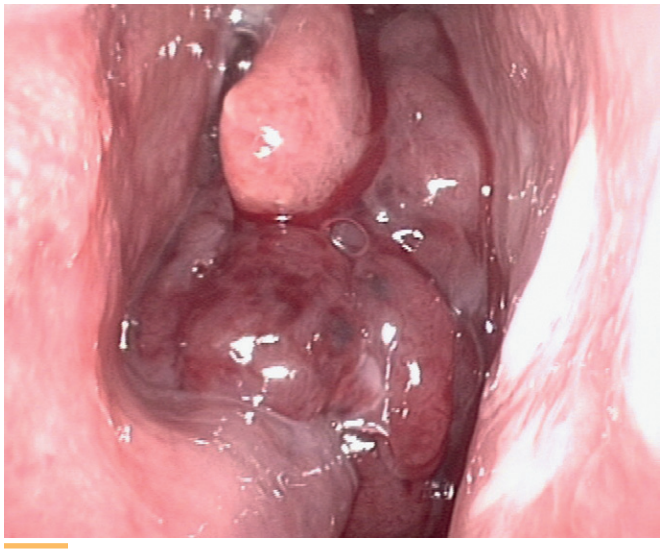

Figure 45-10. Squamous cell carcinoma of the right nasal cavity originating from the septum and occluding the olfactory cleft and middle meatus.

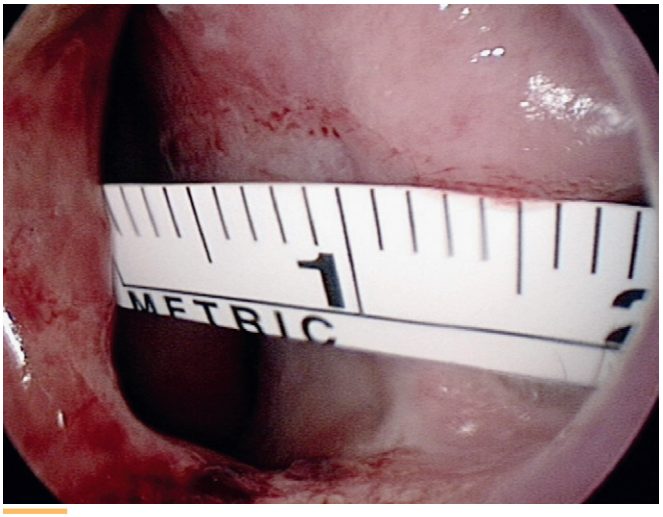

Figure 45-11. Septal perforation causing epistaxis and crusting.

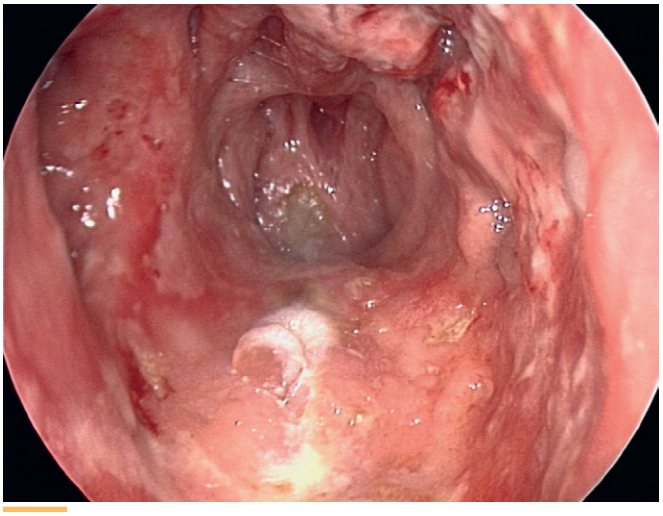

Figure 45-12. Total septal perforation causing epistaxis and crusting in a patient with cocaine abuse.

Headlamp Examination Using Local Anesthesia—Initial Overview

The key to controlling most epistaxis is to find the site of the bleeding, and although chemical cautery with silver nitrate can be used, bipolar diathermy is more effective for stopping the bleeding. Protection from blood contamination is important. A plastic apron for both parties is helpful in order to avoid staining of clothes, and eye protection is advisable if there is active bleeding because some patients have a reflex to blow away any fluid dripping down the upper lip, which can create a bloody aerosol. Once the clots have been sucked out, the nasal airway should be inspected, initially with a headlamp and then, if the bleeding point cannot be located, with an endoscope.

Epistaxis in Children

Young children usually bleed from a vessel just inside the nose at the mucocutaneous junction on the septum, and the bleeding invariably stops spontaneously. In children with epistaxis in whom no prominent vessel can be seen, the regular local application of a cream can help,[12] but petroleum jelly (Vaseline) alone does not.[13] A Cochrane Collaboration systematic analysis of the efficacy of topical treatments for idiopathic epistaxis in children concluded that the best treatment still must be defined.[14] As many as 5% to 10% of children with recurrent nosebleeds may have undiagnosed von Willebrand's disease.[15,16] Children who have leukemia or are undergoing chemotherapy often have epistaxis associated with thrombocytopenia. Older children, adolescents, and adults often bleed from Little's area or a maxillary spur.

Epistaxis in Adults

The caudal end of the septum, where several branches of the external and internal carotid anastomose in Little's area or Kiesselbach's plexus, is the most common site of bleeding in adults.[17] Less commonly bleeding, comes from further back on the septum, and a septal deviation may make it difficult to visualize (Fig. 45-13). Some patients with seasonal allergic rhinitis complain of more nosebleeds in the hay fever season, and topical nasal steroids aggravate the bleeding in approximately 4% of users. Many people believe that a nosebleed signifies a release of pressure and may herald a stroke, and it is important for the clinician to address these anxieties for the patient. Although many patients are found to be hypertensive during nosebleeds, few remain so

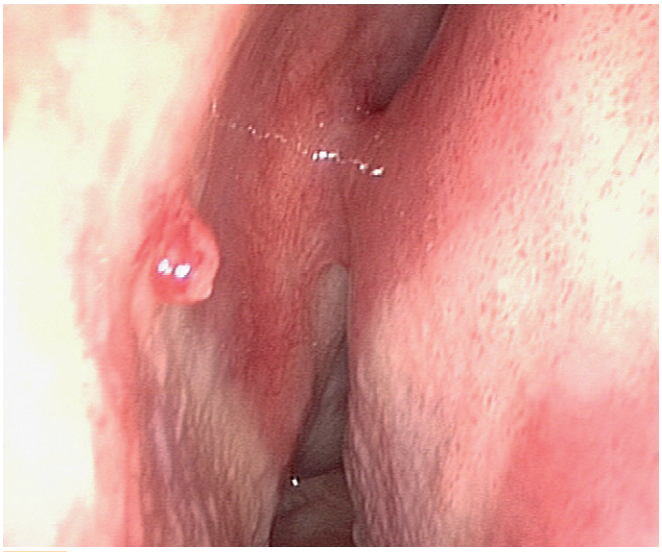

Figure 45-13. Endoscopic view of the bleeding site on the septum in epistaxis, just opposite the left middle turbinate in the olfactory cleft.

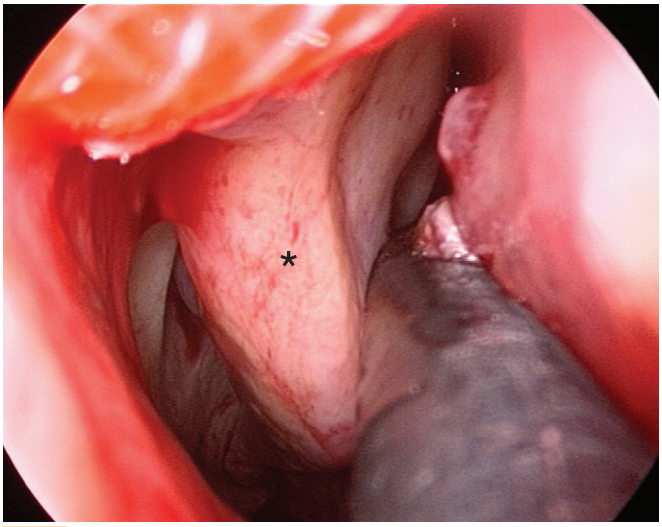

Figure 45-14. Endoscopic view of the bleeding site in severe epistaxis. The bleeding vessel was found on the septum just opposite the superior turbinate (*asterisk*) in the right olfactory cleft. Monopolar suction cautery was performed to stop the bleeding.

on follow-up. The association between hypertension and epistaxis is disputed.[18] Many clinicians report that hypertension is not related to nosebleed.[19-21] However, nosebleeds in patients with hypertension are more likely to lead to admission and to be associated with comorbidity.[22]

Bleeding disorders can manifest de novo as nosebleeds, although this situation is rare. A range of drugs has been linked with epistaxis, warfarin being one of the most common.[3,23] Nearly a third of patients admitted with epistaxis who were taking warfarin had an international normalized ratio (INR) value above the upper limit of the therapeutic range.[24] The need to reverse anticoagulation is uncertain as long as the INR value is within the therapeutic range.[25] In over-anticoagulated patients, fresh frozen plasma, clotting factor extracts, and vitamin K help. Vitamin K takes more than 6 hours to work, however, and it can delay anticoagulation for 7 days after warfarin is started. If the INR value is greater than 4, the warfarin should be stopped, and fresh frozen plasma given.[23] Clotting factor extracts should be given with extreme caution because of the risk of thromboembolic complications. Tranexamic acid, an antifibrinolytic agent, has not been shown to help.[26] Other drugs associated with bleeding are aspirin, which interferes with platelet function for up to 7 days, clopidogrel, and nonsteroidal anti-inflammatory drugs.[27,28] In patients who do not have a history of a bleeding disorder or undergoing anticoagulant therapy, routine clotting studies do not add to the management.[22,24] There is a higher incidence of epistaxis in patients with a high alcohol intake, even when there is no laboratory evidence of a coagulation abnormality.[29,30]

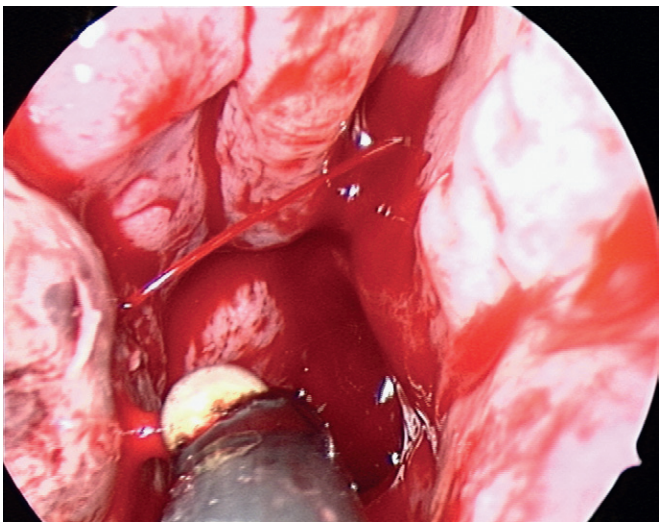

Figure 45-15. Endoscopic view of the bleeding site in severe epistaxis coming from a conchal branch of the sphenopalatine artery on the right side, just before monopolar suction cautery was performed.

Topical Treatment

A randomized controlled trial of silver nitrate cautery with topical antiseptic nasal carrier cream versus topical alone showed both to be effective.[31] A study of patients applying weekly triamcinolone 0.025% and daily petroleum jelly reported that 89% of patients had no further bleeding.[32] Various hemostatic compounds have been used but without consistent evidence of their efficacy. Collagen-derived particles with bovine-derived thrombin have been found to be better than nasal packs.[33]

Cautery

Most anterior epistaxis can be controlled with identification of the bleeding point and cautery using a headlamp. The vast majority of posterior bleeding sites can be identified by endoscopy without the use of general anesthesia.[34] The majority of posterior idiopathic bleeds are from the septum, usually from the septal branch of the sphenopalatine artery as it runs submucosally (Fig. 45-14), although some workers report bleeding from the lateral aspect of the middle or inferior meatus or the posterior end of the turbinates (Fig. 45-15).[35] When the site of bleeding cannot clearly be identified with a headlamp, the use of a rigid nasal endoscope by an experienced endoscopist is best. The key is to identify the site of the bleeding and gain control using silver nitrate cautery or bipolar suction diathermy. Studies have shown that the use of endoscopic bipolar diathermy treats most cases of epistaxis.[36,37] Preparing the nose with lignocaine and epinephrine or cocaine for its decongestant and anesthetic effects often helps. It is worth noting that cophenylcaine has a significant decongestant effect at 6 minutes and a maximum anesthetic effect after 9 minutes,[38] so time must be allowed for it to take effect. An injection of local anesthetic and epinephrine gives better analgesia if there is a sizable vessel that needs bipolar diathermy; otherwise the patient may feel a "smarting" sensation.

After cautery the patient should be advised against blowing the nose for about 10 days to allow the area to heal. A greasy antiseptic

barrier cream should be applied several times daily for 2 weeks to prevent the eschar from drying and coming off with a resulting rebleed. The ointment should not be placed directly on the area treated but is best placed inside the rim of the nostril with the tip of the finger, and "milked up" by massaging the nostril rims, and then sniffed up. This advice can also be given to patients with a crusted septal area from picking or excessive drying. Although most nosebleeds come from Little's area, or from the mucocutaneous junction in young children, a small proportion come from higher on the septum or more posteriorly. Endoscopy is very helpful in defining the bleeding point. Packing of the nose before endoscopy can complicate detection of the exact site of bleeding, because packing often causes mucosal trauma and misleads the clinician.

Rarely, nasal tumors can manifest as epistaxis, so it is important to check for a nasal mass, especially beyond a septal deviation. If there is crusting on the septum, it is worth asking whether it has been a problem. Crusting can follow an abrasion, picking, or a vasculitis such as Wegener's granulomatosis.[39] If it looks likely that the problem is being perpetuated by the patient's picking or blowing any crust off, it is usually not helpful to confront the patient about this possibility. Instead, the clinician should casually mention that nose-picking is very common ("You see people doing it in cars or waiting for a train, and many people do it when nobody is watching"), and say that dried crusts are irritating, and *then* ask whether the patient has to remove the crusts; the patient may confess to doing so, and some progress can be made.

If the bleeding point is not identified, gently packing the nose with oxidized cellulose in fine sheets avoids mucosal damage and promotes coagulation to control bleeding.

The majority of posterior idiopathic bleeds are from the septum, usually from the septal branch of the sphenopalatine artery as it runs submucosally. The key is to identify the site of the bleeding and gain control using bipolar suction diathermy. A severe septal deviation can make it difficult to define the bleeding point.[40] Controlling the bleeding avoids the discomfort associated with nasal packing and also avoids hospital admission.[40] A U.K. cost-benefit analysis of 38 adult patients with epistaxis concluded that £6804 (≈$13,600) could be saved by avoiding admission in 28 patients.[36] Endoscopic cauterization achieves hemostasis in more than 80% of patients with posterior epistaxis at the first attempt and more than 90% after a second attempt.[29] The bleeding point can be cauterized with the help of nasal endoscopy; this procedure has a reported failure rate of 17% to 33%.[41,42] Complications associated with this procedure are uncommon, but there are isolated reports of palatal numbness from thermal damage to the greater palatine nerve, damage to the lacrimal duct, and possible damage to the optic nerve if cautery is used in a patient who already has undergone an ethmoidectomy.[43]

Nasal Packing

If a bleeding point cannot be found, ideally the nose is packed with an absorbable hemostatic agent that produces minimal mucosal trauma. Various nonabsorbable packs have been used, but their insertion is uncomfortable, as is their presence once in position. The insertion of a pack can cause local mucosal trauma and complicate localization of the bleeding point.

If an anterior pack fails and there is no access to an experienced surgeon who can examine, localize, and cauterize the bleeding point, more packing to tamponade the bleeding point may be required. This procedure requires good local anesthesia and analgesia to enable adequate pressure to be applied with the packs in position. Various proprietary packs are available. The insertion of a nasal pack has conventionally meant that the patient has to be admitted, although one study discharged 46 of 62 patients whose nasal airways had been packed, with outpatient follow-up arranged for 48 hours later. However, 28% of those discharged had unplanned returns to the emergency department.[44] If anterior packing fails, a posterior balloon may have to be placed and inflated in the postnasal space. An anterior pack is then placed, and gentle traction used to pull the balloon forward against the anterior pack; this arrangement is held by placement of a clip over the catheter anteriorly as it emerges through the anterior pack.[45] It is vital that any clip used to secure the catheter does not rest on the skin of the nostril; a clip in this position could produce necrosis of the area in as little as 4 hours (Fig. 45-16). The morbidity and physical discomfort associated with nasal packing includes pain, hypoxia, alar necrosis, and toxemia, and is well described in the literature.[46-49] Unfortunately, nasal packing is used routinely in some units where expertise in nasal endoscopy is not available; for example, in only 7% of ear, nose, and throat emergency departments in the United Kingdom is suction diathermy available.[8] Packing not only traumatizes the nasal lining but also can cause cardiorespiratory complications and local infection.[46]

Figure 45-16. Necrosis of the columella after bilateral posterior nasal packing.

The role of prophylactic systemic antibiotics in patients who have nasal packs is not well established. There appears to be wide variation in current practice in England.[50] The main concern is to avoid toxic shock syndrome. We would prescribe antibiotics if the patient has any cardiac anomalies that would require antibiotic prophylaxis for surgery.

If the patient does not experience rebleeding within 12 to 24 hours, the packs should be removed. The nose should be inspected with a rigid endoscope, if this procedure has not already been performed prior to packing, to exclude any disease that may have been responsible for the bleeding.

Posterior epistaxis controlled by posterior nasal packing has a failure rate between 26% and 52% and a complication rate between 2% and 68.8%.[43,51] The complications noted in two studies were synechia, angina, periorbital cellulitis, sinusitis, toxic shock syndrome, hypoxia, and otitis media.[43,51] "Gone are the days when a patient had an uncomfortable posterior nasal pack inserted then spent several days on the ward only to bleed again on its removal."[52] Endoscopic sphenopalatine artery ligation (ESPAL; see later) has replaced the need for posterior nasal packs, other than in an emergency situation, to control profuse bleeding. The goal is to achieve a high success rate and a low morbidity. Especially elderly patients with multiple medical problems (arteriosclerosis, hypertension, diabetes, hepatic and renal disease) tolerate packing poorly, and complications occur frequently; therefore, in such patients, the clinician should consider an early surgical intervention rather than packing of the nose.[49]

Maxillary Artery Ligation

Another technique to control posterior epistaxis is ligation of the internal maxillary artery in the pterygopalatine fossa.[53] It has a reported success rate of approximately 90%.[54] Treatment failures are due to the difficulty in finding the artery and its branches. The technique is also associated with a complication rate of 28%.[54] Because this procedure is done through a Caldwell-Luc approach, complications include sinusitis, facial pain, oroantral fistula, and facial and dental paresthesia; also, dissection in pterygopalatine fossa can result in blindness, ophthalmoplegia, and decreased lacrimation.[41]

Ligation of the External Carotid Artery

Ligation of the external carotid artery has been advocated, but the rich anastomoses of vessels in the nose means that this procedure is not very effective.[55] Ligation of the external carotid artery prevents embolization that may be desirable because of bleeding that is in the distribution of that vessel but not in the vessels supplied by it, which are also supplied by cross-anastomoses from contralateral vessels. There are reports of cerebrovascular ischemia and infarction following external carotid ligation in elderly atherosclerotic patients, whose cerebral circulation has partially relied on anastomotic connections from the external to the internal carotid system.

The Role of Endoscopic Sphenopalatine Artery Ligation

If bleeding cannot be controlled after endoscopic examination and cautery and/or nasal packing, then examination with use of either a general anesthetic or a local anesthetic with sedation is indicated. Bipolar diathermy of any bleeding points or ESPAL is then the treatment of choice.[9] Clipping or diathermy of the sphenopalatine artery is now the accepted treatment for management of persistent posterior epistaxis.[40,43,56-60] The morbidity associated with ESPAL is low compared with that for ligation of the maxillary or external carotid artery and for embolization. Pooled case-series data have shown that epistaxis was controlled by this technique in 98% of patients.[61] The endoscopic sinus surgeon should locate the sphenopalatine artery at the level of the crista ethmoidalis (Fig. 45-17).[62] An incision is made over the posterior fontanelle, a submucosal flap is lifted, and the anterior branch is identified with its origin just posterior to the crista ethmoidalis. The anterior branch is then identified and then undergoes clipping or diathermy (Fig. 45-18). In the majority of cases the sphenopalatine foramen opens into the middle and superior meatus.[62]

The sphenopalatine artery normally starts to branch lateral to the crista ethmoidalis, and these branches vary widely. It is important that the surgeon who undertakes ligation or cautery of the artery is aware that more than 97% of individuals have two or more branches medial to the crista ethmoidalis, 67% have three or more branches, and 35% have four or more branches.[63] The endoscopic sinus surgeon views the sphenopalatine artery at the level of the sphenopalatine foramen or a few millimeters medial to it. With a mucosal incision made in the posterior fontanelle area, anterior to the horizontal part of the base middle turbinate as it joins the lateral nasal wall, a submucosal flap is lifted, and the artery is identified posterior to the crista ethmoidalis and clipped. Some workers describe identifying the artery and clipping it

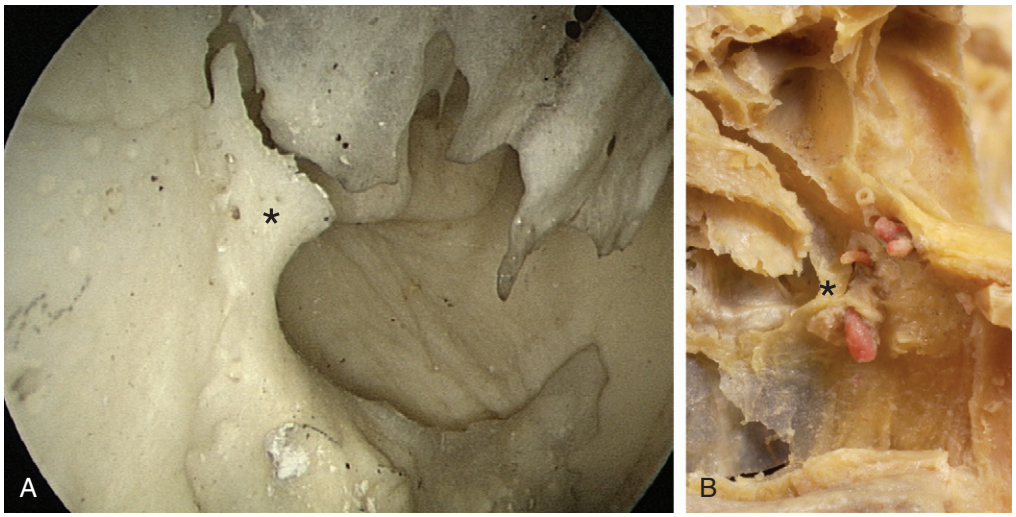

Figure 45-17. **A,** Endoscopic view of the right ethmoidal crest (*asterisk*) in a human skull. **B,** View of the right lateral wall of the nose injected with pink latex to show four branches of the sphenopalatine artery, three above and one below the crista ethmoidalis (*asterisk*).

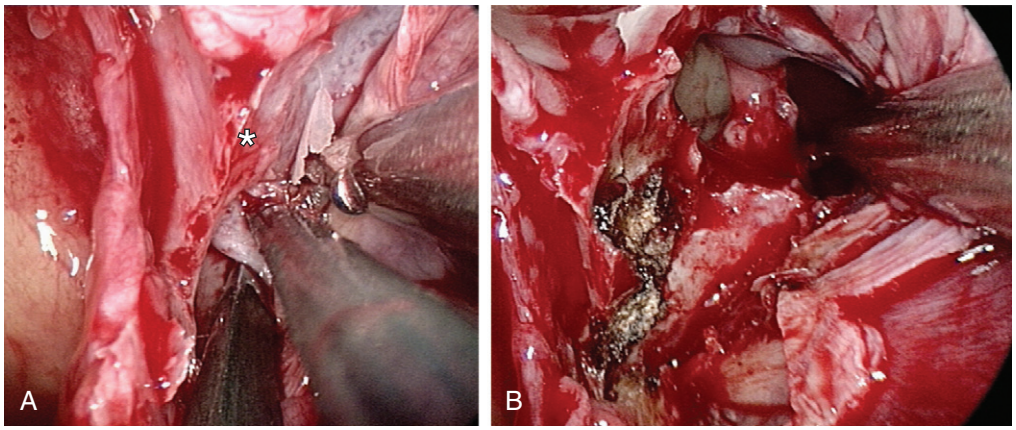

Figure 45-18. **A,** Intraoperative endoscopic view of the dissection of the sphenopalatine artery just behind the ethmoidal crest (*asterisk*). Bipolar cautery is applied to the first branch just below the ethmoidal crest. **B,** Final view after cautery of all 4 branches, two below and two above the ethmoidal crest, suction within the right sphenoid sinus.

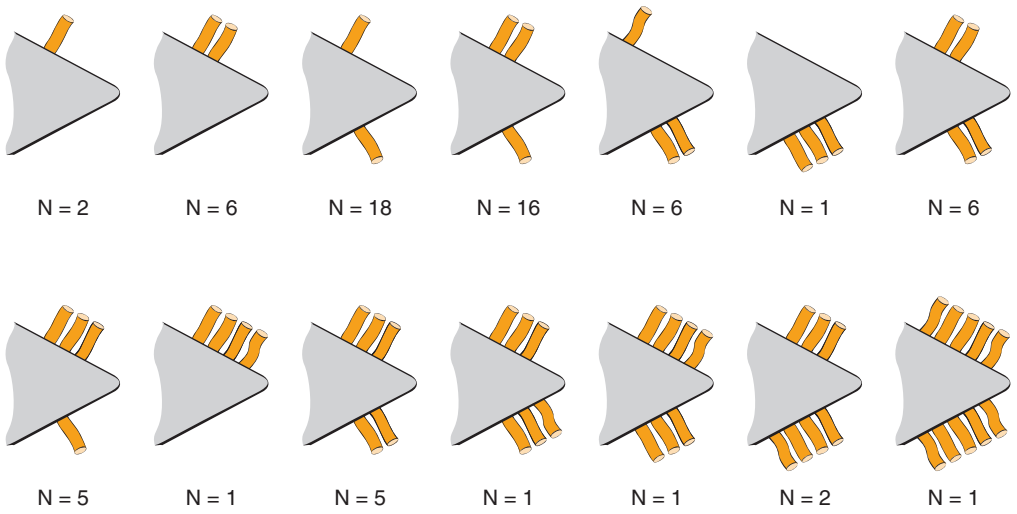

Figure 45-19. Line diagrams to illustrate the possible numbers of branches of the sphenopalatine artery superior and inferior to the crista ethmoidalis in the sagittal plane medial to it. *(Redrawn from Simmen D, Raghavan U, Manestar M, et al. The anatomy of the sphenopalatine artery for the endoscopic sinus surgeon.* Am J Rhinol. *2006;20:502-505.).*

without further dissection to verify whether there were any other branches.[56,59,60] The mistaken belief that the artery enters as a single trunk into the nose may have led to the failure of these procedures. One study specifically looked at the branching pattern of this artery from the endoscopic surgeon's point of view.[41] The researchers found two branches of the sphenopalatine artery near the sphenopalatine foramen. In their study, 16% of arteries branched within the foramen, allowing the two arteries to exit together; in 42%, the branches exited much more posteriorly; and in the remaining 42%, the septal branch exited through a separate foramen posterior to the sphenopalatine foramen.[41] Simmen and colleagues[63] reported that in more than 97% of cadaver specimens examined there were 2 or more branches medial to the crista ethmoidalis, in 30% there were 3 branches, and in one specimen there were 10 branches. The variations in 77 specimens are shown in Figure 45-19.

Various reports have claimed success rates for ESPAL between 92% and 100% in controlling epistaxis.[57,59,61] Failure to clip all the branches of the sphenopalatine artery may be the reason for continued epistaxis after the procedure. All divisions of the sphenopalatine artery take place in the pterygomaxillary fissure, and the branches enter the nasal fossa as separate blood vessels. The arrangement of these branches in relation to the sphenopalatine foramen varies widely. The largest and most anteriorly based branch is the posterior lateral nasal branch. This must be clipped and divided so that the flap can be lifted superiorly to locate the nasopalatine branch, which must be clipped and divided as well. Because there are such wide variations in the branching pattern of the sphenopalatine artery, careful dissection is required even after these two branches are clipped. A thorough search by careful dissection should be made all around the sphenopalatine foramen to find any other branches that can be clipped. Clipping or diathermy of the sphenopalatine artery has a failure rate between 0% and 8%[61] and is not associated with any serious complications. The main complication, as previously mentioned, is failure to control epistaxis, which is usually due to the surgeon's failure to clip all the branches of the sphenopalatine artery. The arrangements of these branches are unpredictable, as seen in our study, and can vary on the two sides in the same individual. In addition the branches of this artery can come out through separate foramina, and a surgeon who is not aware of this possibility can miss a few branches. Other complications are uncommon; they include nasal crusting, palatal numbness, acute rhinosinusitis, decreased lacrimation, and septal perforation.[59] A long-term study of ESPAL showed a 93% success rate.[64]

We do not advocate packing and repacking for refractory epistaxis.

Embolization

Arterial embolization has been shown to be effective in the treatment of intractable epistaxis.[65,66] However, the procedure carries a risk of complications, which include cerebrovascular accident, hemiplegia, ophthalmoplegia, facial nerve palsy, seizures, and soft tissue necrosis.[67-70] The analysis of 31 cases of embolization of internal maxillary artery by Siniluoto and colleagues[71] did not find any major and persistent complications. Because interventional neuroradiology is increasingly available, embolization has become an option when initial treatment fails. It is also important to state at this point that the arterial embolization technique is effective mainly for the external carotid artery supply and very dangerous for the internal carotid supply. Embolization for bleeding from the terminal branches of the ophthalmic artery is therefore not advocated because of the high risk of blindness due to reflux of the embolic materials.[72]

We would advocate the use of this technique for patients with refractory epistaxis who are unfit for surgery or in whom surgery has failed to control the bleeding (Fig. 45-20). Persistent posterior epistaxis can be controlled by percutaneous embolization of bleeding arteries. The success rate for this procedure is between 71% and 95%, and the complication rate is 27%.[41,54,71]

Bleeding from the Anterior Ethmoidal Artery

An uncommon cause of severe epistaxis is associated with a nasoethmoid fracture when the bleeding originates from the anterior ethmoidal artery. Patients with anterior ethmoidal artery epistaxis form a distinct subgroup whose management differs in that they require surgery to the anterior ethmoidal artery, via either a traditional external approach or an endoscopic approach, because the bleeding rarely subsides with conservative measures (Fig. 45-21).[73]

The anterior ethmoidal artery can also be damaged during sinus surgery. It is at risk as it passes through the roof of the ethmoid sinuses on its way from the orbit to the anterior cranial fossa.[74] Damage to the artery can lead to profuse epistaxis and intraorbital bleeding, and, at times, intracranial bleeding.[75] The development of a retro-orbital hemorrhage is an emergency because it can even lead to blindness. The bony canal in which the anterior ethmoidal artery crosses the skull base can be dehiscent, making it vulnerable to damage.[76] The rate of dehiscence of the anterior ethmoidal artery has been reported as 11% to 40%.[77]

There are bony protrusions from the lateral end of the bony canal of the artery where it emerges from the orbit and medially where it goes through the lateral lamella. Some authorities have stated that the artery lies behind the frontal recess and can act as a landmark in the surgical

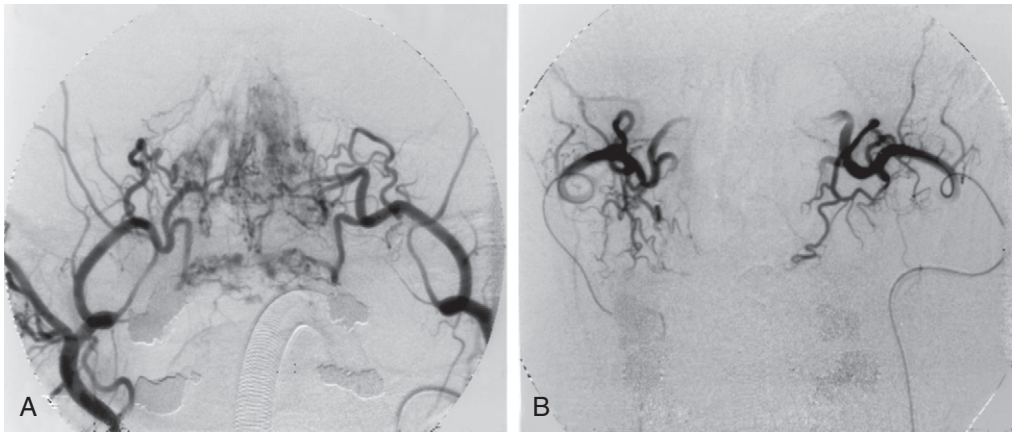

Figure 45-20. Bilateral superselective angiograms of the sphenopalatine arteries. **A,** The crossover anastomosis of the septal mucosa artery supply. **B,** Postembolization view.

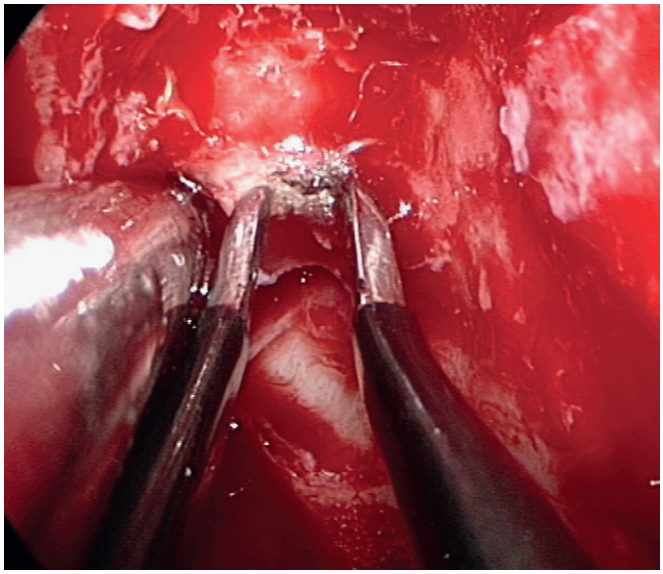

Figure 45-21. Intraoperative endoscopic view of bipolar suction cautery of the left anterior ethmoidal artery in epistaxis. Partial anterior ethmoidectomy and exposure of the vessel just below the skull base.

approach to this area.[74,78-80] Stammberger[76] located the anterior ethmoid artery 1 to 2 mm behind the junction of the posterior wall of the frontal recess and the anterior ethmoid air cells.[76] Simmen and associates[81] showed a mean distance from the posterior wall of the frontal recess to the artery of 11 mm (range 6-15 mm). In most cases the position of the artery is mirrored on the contralateral side. However, the position is very variable, so it is not safe to use the artery as a landmark for any endoscopic intervention, especially in locating the frontal recess. The anterior ethmoidal artery is always seen between the second and third lamellae, and the most common site to find it is in the suprabullar recess (85%). If pneumatization of the ethmoid sinus is marked, the artery is likely to be lying below the skull base and is more prone to surgical damage. Preoperative knowledge of the suprabullar recess and supraorbital cells through careful interpretation of computed tomography scans is helpful in avoiding damage to the anterior ethmoidal artery (Fig. 45-22).

It should be emphasized that locating the anterior ethmoidal artery is usually unnecessary, and indeed undesirable, during most procedures because doing so will increase the risk of damaging it.

Hot Water Irrigation for Epistaxis

Hot water irrigation as a noninvasive treatment for posterior epistaxis has received some renewed attention.[82] Obstetricians used hot water to irrigate a postpartum bleeding wound in the 19th century, and Guice[83] introduced this procedure for staunching blood in cases of epistaxis in 1879. Studies by Stangerup and colleagues[84] involving experiments with rabbits showed that irrigating the nose at 40° to 46°C does not lead to any histologic changes of the mucosa. Temperatures higher than 46°C result in vasodilatation and, in particular, edema of the mucosa. Only temperatures above 52°C trigger necrosis. It can be assumed that the temperature-induced mucosal edema leads to local compression of the bleeding vessel and at the same time may propagate the cascade for hemostasis.[84]

After an examination with nasal endoscopy, topical anesthesia of the relevant nasal cavity is administered using 4% tetracaine. Then Stangerup's modified bladder catheter is inserted in the affected nasal cavity. The balloon is inflated in the epipharynx and the catheter gently pulled back until the choana is blocked off. The affected nasal cavity is continuously irrigated with tap water at a temperature of 50°C. The treatment lasts approximately 3 minutes, with the patient sitting upright so that the irrigation water can flow forward from the nose into a basin. After the irrigation with 500 mL of hot water, the catheter can be removed. In a prospective study involving 84 patients, Schlegel and colleagues[82] showed a success rate of 82% for hot water irrigation without any complications. This technique avoids painful packing, hospitalization, and immediate surgery but also allows the patient to breath normally through the open nasal cavity after the treatment.[82-84]

Management of Epistaxis in Patients with Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant multisystemic disorder characterized by telangiectasia that affects cutaneous and mucosal surfaces as well as arteriovenous malformations in the pulmonary, cerebral, and hepatic circulations (Fig. 45-23). The most common symptom in patients with HHT is epistaxis, which affects more than 90% of individuals. The severity of attacks is variable; these episodes of epistaxis can be functionally and socially debilitating for the patient and may require frequent hospital admission; and for some patients, the bleeding is intractable.[85] Many methods of treatment for epistaxis due to HHT have been described in the literature, including medical strategies, such as the use of hormonal manipulation and the use of antifibrinolytic agents, as well as surgical options, including laser coagulation (see Fig. 45-23),[86]

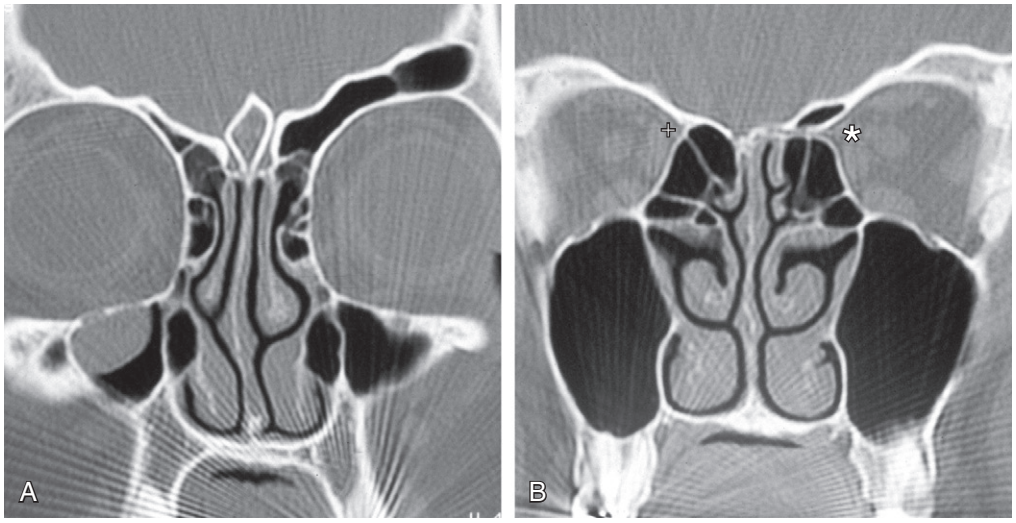

Figure 45-22. **A** and **B,** Coronal CT scans of the paranasal sinuses. The preoperative checklist information will prove that in a well-pneumatized supraorbital recess (left side), the course of the anterior ethmoidal artery is below the skull base (*asterisk*), and if the supraorbital recess is poorly or not pneumatized (right side), the course of the ethmoidal artery will be within the skull base (*plus sign*). *(From Simmen D, Raghavan U, Briner HR, et al. The surgeon's view of the anterior ethmoid artery.* Clinical Otolaryngology. *2006;31:187-191.)*

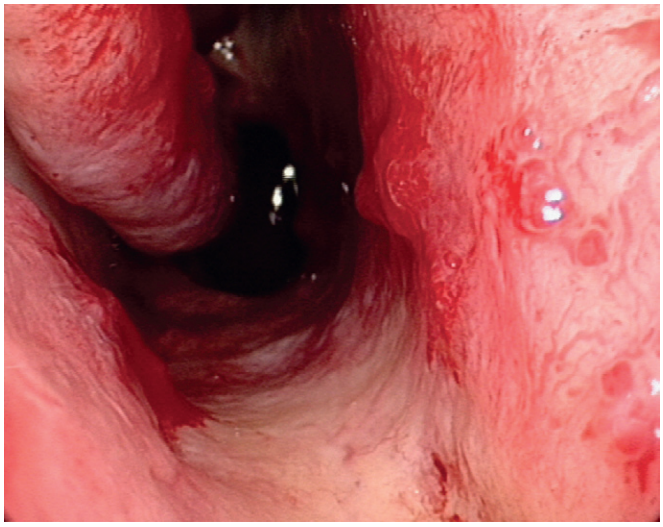

Figure 45-23. Hereditary hemorrhagic telangiectasia with arteriovenous malformations, on an endoscopic view of the right nasal cavity.

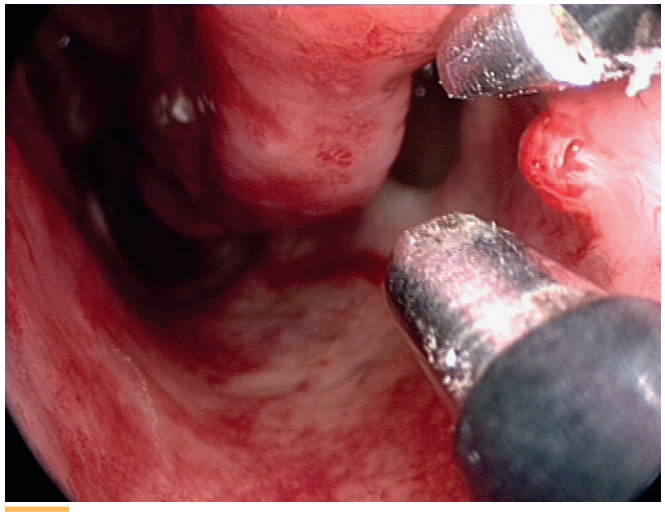

Figure 45-24. Endoscopic view of the left lateral nasal wall with an arteriovenous malformation in a patient with hereditary hemorrhagic telangiectasia during bipolar suction coagulation.

septodermoplasty,[87] and nasal closure.[88] No one method has proved itself entirely successful or without significant side effects, however.

A prospective study by Hitchings and coworkers[85] investigated the effect of various surgical options on quality of life scores in patients with HHT and epistaxis. The researchers concluded that nasal closure should be offered to patients with moderate to severe epistaxis that has proved unresponsive to other treatment options, either bipolar (see Fig. 45-23) or laser coagulation treatment (see Fig. 45-24), or septodermoplasty; 88% (7/8) of the patients in their series who were treated with nasal closure reported a complete cessation of nosebleeds. Closure of the nasal cavity—Young's procedure—is based on the principle that the absence of desiccating airflow through the nasal cavity prevents the breakdown of mucosa overlying the fragile telangiectasias. An alternative to nasal closure is the use of nasal obturators.[89]

Summary

The role of rigid nasal endoscopy as part of the initial assessment of epistaxis, with direct visualization and control of the bleeding point, is effective in the majority of patients and reduces the need for nasal packing. Endoscopic sphenopalatine artery ligation is well established as the treatment of choice when cautery and nasal packing fail. Figure 45-25 presents a protocol for management of epistaxis.

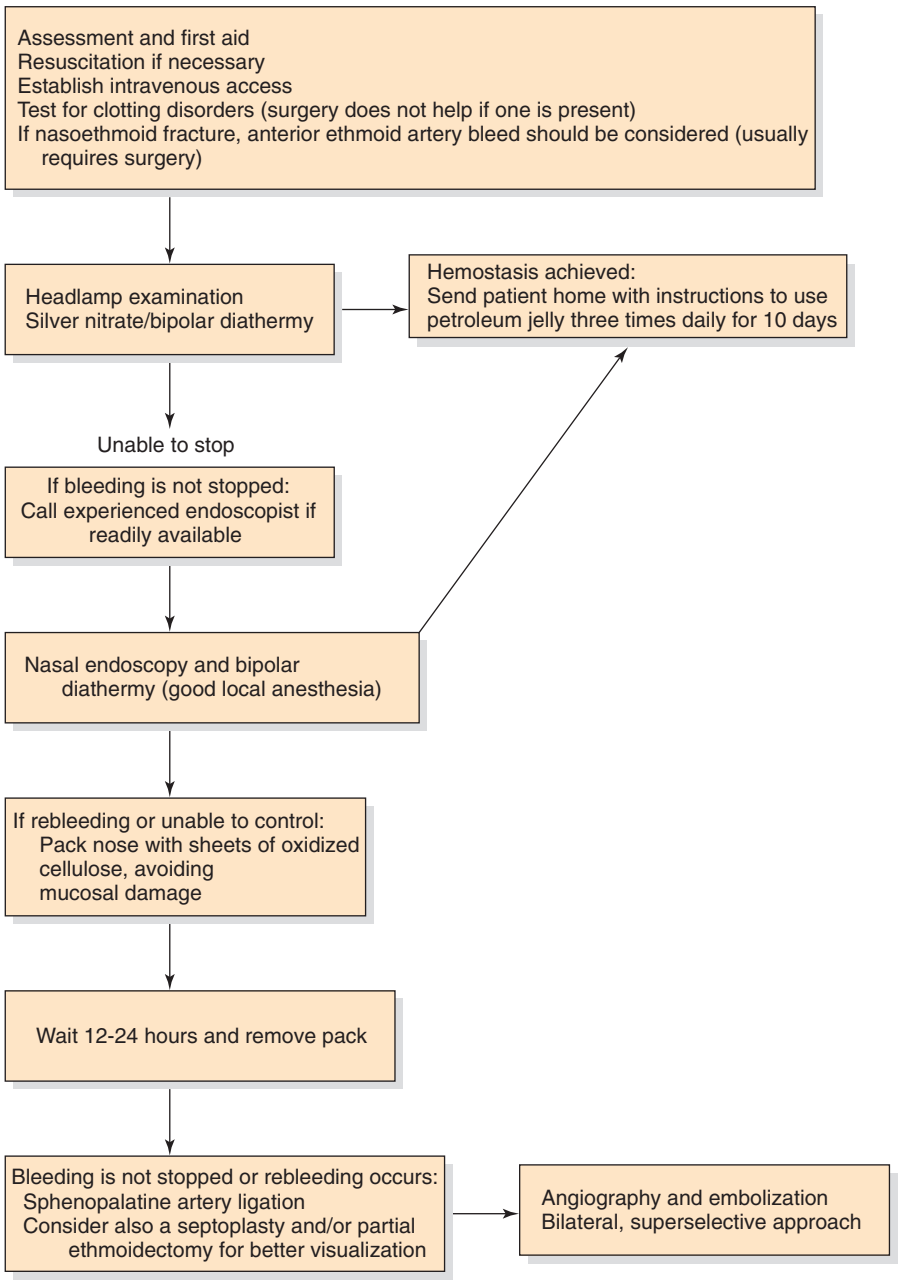

Figure 45-25. Management protocol for epistaxis. The key is to find the site of the bleed with endoscopy, if it is not seen with a headlamp. Minimize the use of packs for patient comfort. Sphenopalatine artery ligation should be performed if the site of the bleed is not located or bleeding cannot be stopped by an experienced endoscopist.

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CHAPTER FORTY-SIX

Nonallergic Rhinitis

Stephanie A. Joe

Sundip Patel

Key Points

- The incidence of chronic rhinitis is high in the United States and poses a large burden on society, school attendance, and work productivity. Nonallergic rhinitis (NAR) can be clinically present in an isolated form or in a combined form with some varying mixture of an allergic component. Concerning NAR, females tend to be afflicted more, and the incidence also increases with age. Despite what is known about NAR, much is also unknown, making the diagnosis process—along with trying to achieve good overall control—difficult, leading to frustrated patients and clinicians.
- Often the symptomatologies of NAR and allergic rhinitis (AR) are quite similar, and careful differentiation is needed. Differentiating the typical symptoms of rhinitis, which include rhinorrhea, congestion, sneezing, change in smell, and postnasal drip, into either an allergic or nonallergic category is difficult. Most often, if the etiology is not clear and results of typical allergic rhinitis testing (skin and radioallergosorbent testing) prove to be negative, then NAR must be considered. However, this is not the endpoint because effort must be taken to classify the subtype of NAR present in order to maximize therapy.
- The pathophysiology of NAR is quite complex, and much is yet to be discovered. Numerous factors play a role in nasal physiology and control, including intricate innervation by sensory, parasympathetic, and sympathetic nerves. Other factors that complicate the understanding are various inflammatory cascades and a multitude of cellular and protein reactions, most of which are not fully understood. Provocation testing has been one of the principal tools utilized in the attempt to assess the pathophysiology of NAR. Histamine, muscarine, cold air, adenosine monophosphate, and capsaicin are among the more commonly studied agents. Research is also evaluating the potential role of immunoglobulin E, mast cells, and other known factors typically thought of in AR that could also play a role in NAR, despite the absence of systemic atopy.
- Determining the numerous different types of NAR can be daunting. The various types of NAR presented and discussed in this chapter are divided into the following categories: NAR with eosinophilia syndrome, hormone-related NAR, medication-induced NAR, irritant-induced NAR, NAR due to chemical exposure, atrophic rhinitis, NAR due to anatomic obstructions, NAR due to systemic disorders, and idiopathic NAR. The rationale for this division is based on therapy and management, in that the treatment of each type of NAR within the specific category has a similar basis. Despite the numerous types, the foundation of NAR is the same: some exposure or alteration in the nasal mucosa, either external to the body or within the body, that alters the normal homeostasis of the nasal mucosa, inducing the resulting NAR symptoms. The diagnostic picture can be complicated by the presence of coexistent AR.
- If after an exhaustive search, no clear etiology is noted, the condition is termed *idiopathic* or *vasomotor* rhinitis. This seems to be the most common form of NAR and often the most difficult to treat. Historically, idiopathic rhinitis was thought to be related to excessive parasympathetic or reduced sympathetic activity of the nasal mucosa. This process is likely to be only part of the whole picture of vasomotor rhinitis, because other theories have also been proposed.
- The single most important factor in attaining a proper diagnosis is a complete history. Absolute points that must be covered are detailed symptomatology, potential inciting agents or triggers, past and present medication use, and other systemic disorders. A complete examination for local and/or anatomic factors is also necessary, which should include a nasal endoscopy.
- The best overall treatment tool is avoidance of known inciting agents. Medical therapy should be an adjunct to this step. Medications that have proved to be effective include topical nasal corticosteroids, antihistamines, and anticholinergics. Oral preparations of these agents have limited value and their use minimized compared with direct, topical therapy. Decongestants, either oral or topical, should also be used in a limited way and only in combination with topical therapies.
- Surgical intervention for NAR is usually reserved for those whose symptoms are not controlled with conservative medical therapy. Surgery is also beneficial for those with clear, overwhelming anatomic obstructions. Various surgical procedures described for NAR include septoplasty, inferior turbinate reductions, vidian neurectomy, and other procedures to relieve anatomic obstructions.

Chronic rhinitis presents a tremendous problem for the health care industry; 10% of the population is affected by chronic or recurrent nasal symptoms, with an estimated 17 to 19 million Americans affected by nonallergic rhinitis (NAR).[1,2] The prevalence of patients with NAR among otolaryngology and allergy clinic populations ranges from 28% to 60%, and its incidence rises with age.[3,4] Of the patients who present to the otolaryngologist's office, 50% are diagnosed with a form of NAR, and the rest are diagnosed with allergic rhinitis (AR).[1,5] In a survey of 975 patients visiting allergists' offices for chronic rhinitis, the National Classification Task Force found that 43% were diagnosed with pure AR, 23% with NAR, and 34% with mixed AR and NAR. Thus, 57% of patients with chronic rhinitis have some component of NAR.[6] Women seem to be more affected by rhinitis, with one study noting 70% of women aged 50 to 64 years experiencing some form of rhinitis during a 1-year period.[7,8]

Problems that result from chronic rhinitis include sinusitis, the development of polyps as a result of chronic inflammation and obstruction, eustachian tube dysfunction, laryngeal dysfunction, chronic otitis media, hearing loss, sleep-disordered breathing, disorders of the sense of smell, malaise, and fatigue. In fact, rhinitis is present in as many as 80% of patients with chronic fatigue syndrome.[9] These symptoms often interfere with school or work performance, and a lack of productivity is worsened by the need for frequent doctor visits. In a survey of rhinitis patients, one fourth noted restricting their choice of occupation or residence to reduce their symptoms.[10] In addition, medications—although usually helpful—may elicit undesirable side effects, such as drowsiness, epistaxis, palpitations, and nasal dryness, compounding the overall effect of NAR.[11]

NAR and AR have similar presentations, manifestations, treatments, and effects on school and work performance. Thus, statistics for AR can be used to infer the economic impact of NAR. In many instances, AR and NAR are often indistinguishable and coexist.[1,2] Twenty million to 40 million Americans are affected by AR, and the direct costs for doctor visits and medication expenses are at least $1.9 billion annually. The cost of lost productivity approaches $3.8 billion annually.[12]

Despite all of the preceding facts, defining NAR is difficult. Symptom presentation is nonspecific, and patients may present in a variety of ways. Most commonly a patient complains of rhinorrhea, nasal congestion, and sneezing despite having no history of allergies and negative results of skin testing and nasal cytology. Unfortunately, after allergy has been ruled out as the etiology of the rhinitis, these patients may be diagnosed with "vasomotor rhinitis," a blanket term used to diagnose affected patients.[2,13,14] Because no unifying criteria exist for this broad class of problems, further investigation and workup are generally abandoned by most clinicians, especially because there are no clear diagnostic tests. Treatment is indiscriminate, with varied responses seen among patients. The results are often unsatisfactory and frustrating for both the physician and the patient.

Chronic rhinitis has been described in the literature under many terms. Historically, *vasomotor rhinitis* has been favored, but distinct vascular or motor nerve dysfunction has been difficult to identify.[4] Other terms used in the literature include *perennial rhinitis, idiopathic rhinitis, perennial NAR,* and *nonallergic, noninfectious perennial rhinitis*.[6,15,16] Nonallergic rhinitis (NAR) is the term used here to describe the variety of rhinitis-related problems that cause intermittent rhinorrhea, nasal congestion, and nasal obstruction unrelated to allergy. Nasal itching and sneezing with NAR occur to a lesser extent than seen in AR.

Various forms of and contributing factors for chronic NAR are outlined in this chapter; the research into its pathophysiology is also briefly reviewed. This chapter provides the background for the development of a systematic evaluation and treatment plan for patients with NAR.

Pathophysiology

Nasal Function and Innervation

The effects of NAR cannot be fully appreciated without a brief review of nasal function. Nasal function includes temperature regulation, olfaction, filtration, and humidification of inspired air. The nasal lining also produces secretions that contain immunoglobulin (Ig) A, protein, and enzymes to provide lubrication and protection. Secretions trap particulate matter, and then nasal cilia propel the matter toward the natural ostia. The cilia move at a frequency of 10 to 15 beats per minute, and the mucous blanket streams at a rate of 2.5 to 7.5 mL per minute.[17]

Innervation of the nasal mucosa is highly organized and very complex. Regulation of mucosal vasculature and glandular secretions is controlled by the autonomic system. The sympathetic nerves form one half of the efferent nasal reflex arc. Once stimulated, sympathetic nerves release norepinephrine and neuropeptide Y, which cause vasoconstriction of the nasal vasculature. The parasympathetic nerves constitute the other half of the efferent nasal reflex arc. After they have been stimulated, parasympathetic nerves release acetylcholine, norepinephrine, and vasoactive intestinal peptide. Cholinergic neuropeptides and neurotransmitters stimulate the serous glands of the nasal mucosa and increase mucus secretion. Unilateral stimulation of the efferent reflex arc leads to a bilateral response.[17,18]

Sensation originates primarily from the trigeminal nerve. Afferent ethmoidal nerves provide sensory innervation to the epithelium, vessels, and glands. C fibers, which are unspecialized afferent sensory nerves that react to pain and to changes in temperature and osmolarity, are the most relevant type of sensory fibers in NAR. They are stimulated by inflammatory mediators such as histamine and bradykinin and are involved in centrally mediated reflexes. Research has also elucidated their stimulation by inhaled irritants like nicotine, smoke, formaldehyde, and capsaicin, which is discussed later. Once stimulated, C fibers depolarize and release neuropeptides such as substance P and calcitonin gene–related peptide, which increase vascular permeability and activate the submucosal glands. The result is the acute stimulation of glandular cells, endothelial cells, and epithelial cells within the nasal mucosa, thereby causing the sensation of itching, rhinorrhea, and/or burning.[5]

A disorder of any component of the nasal mucosa may lead to NAR. The efferent parasympathetic nervous system produces glandular secretions and the sympathetic limb causes nasal decongestion, both of which are normal physiologic activities. However, hyperresponsiveness of the afferent sensory limb causes an exaggerated efferent response to neuronal stimuli; the result is the oversecretion of mucus and increased nasal congestion due to capillary plasma exudation. The same symptoms are seen with normal afferent input and a hyperreactive efferent arc. Less commonly, an intrinsic epithelial problem or central nervous system dysregulation is the source of disordered responsiveness. Unfortunately, given the complex interaction of mucosal regulation, it has been difficult to isolate a source for specific study.[16] The nonspecific and variable symptoms of NAR are confounding; this situation compounds the difficult task of identifying the exact pathophysiologic source. One suggested mechanism in the complex pathophysiology of NAR involves the inflammatory cascade, including prostaglandin and leukotriene products, but there is still equivocal and contradictory evidence as to the importance of these substances.[19]

Provocation Testing

Various nasal provocation tests have been used in attempts to characterize NAR and nasal reactivity. The methacholine challenge test is used to study glandular responsiveness; this provocation bypasses sensory nerve stimulation, vascular effects, and, thus, complaints of congestion. It also determines glandular responsiveness independent of allergen or immunologic mediation.[4,15] Methacholine is a muscarinic cholinergic receptor agonist that stimulates cholinergic receptors in the submucosal glands. Intranasal administration leads to a dose-related increase in glandular secretions and rhinorrhea. Patients with NAR have higher glandular activity than controls.[16] However, this hyperresponsive reaction is not unique to patients with NAR. Patients with AR respond to methacholine in a similar fashion[4,16]; therefore, methacholine can be used to differentiate patients with AR as well as patients with NAR from controls but not to differentiate these patient groups from each other.

Histamine placed in the nose stimulates symptoms of rhinitis and is widely used to study both AR and NAR.[4,5,20,21] Histamine provoca-

tion increases vascular permeability, thus causing sneezing, pruritus, rhinorrhea, and nasal obstruction.[4,16] Patients with NAR have a higher response than controls.[21] The response experienced by patients with NAR is less than that seen in patients with AR, but there is significant overlap in the responsiveness of these two patient populations. Definitive indications of histamine as an influence in the physiologic mechanism of NAR are lacking.[5,16] However, these results suggest that vascular hyperreactivity may be a contributing factor in NAR.

The effects of cold, dry air on nasal mucosa have been extrapolated from asthma research.[22,23] The studies demonstrate that nasal inhalation of cold, dry air causes drying of the nasal mucosa; this drying induces symptoms of rhinorrhea, congestion, and occasional sneezing in susceptible patients. Cold, dry air increases the tonicity and osmolality of nasal secretions, causing release of inflammatory mediators, afferent stimulation, activation of the parasympathetic reflex arc, increased epithelial shedding, production of mucus, and symptoms of rhinitis. One of the current thoughts regarding the physiology of cold air rhinitis is that the cold, dry air causes sensorineural stimulation, which leads to hyperosmolarity; these changes, in turn, lead to mast cell activation. However, there is also evidence supporting a variation of this theory, which suggests that the cold air induces nasal mucosa water loss with resulting hyperosmolarity. This effect would then stimulate sensory nerves, activate mast cells, and damage nasal epithelium. The role of mucosal mast cells is to release mediators that increase fluid movement, decrease hyperosmolality, and reestablish homeostasis by altering nasal vasculature, epithelium, and glandular cells.[23,24] Regardless of the specific mechanism, the general hypothesis of cold air–induced rhinitis is the inability of the mucosa to compensate for the high water loss that results from this specific environmental exposure.[25] Togias and associates[26] proposed that studying such mast cell mediator release with resultant inflammation and increased vascular permeability through either immunologic or physical stimuli provides models for the study of multiple forms of rhinitis.

Stjarne and colleagues[27] have looked at capsaicin as it relates to nasal mucosal provocation. Placement of capsaicin on the nasal mucosa leads to sensory nerve stimulation, with specific stimulation of the C fibers. The result is cholinergic parasympathetic reflex activation, which causes rhinorrhea, congestion, sneezing, and nasal burning.[27,28] The symptoms occur independent of histamine release or mast cell activation, suggesting that these results are selective for patients with NAR.[27]

In 1991, Stjarne and colleagues[27] published studies of nasal mucosal desensitization with capsaicin, the results of which have been reproduced by other groups.[29,30] Local treatment of the inferior turbinate with capsaicin for 3 consecutive days led to sensory nerve release, neuropeptide depletion, and disrupted function of capsaicin-sensitive nerve endings. Subjects reported a more than 50% reduction of complaints of nasal blockage and discharge when challenged with a dose of capsaicin at 1-month follow-up. These results correlated with an improved appearance of the mucosa and were maintained at 3-month follow-up; symptoms and mucosal appearance reverted to pretreatment levels by 6 months. A selective effect on patients with NAR was again suggested.[27]

The preceding tests represent examples of ways to study the pathophysiology of NAR, but no test has been found to be a specific model for the study of this disorder. For each of the provocation tests, there are studies that support the contrary argument; also, various methods are used in these studies to assess the responsiveness, further clouding the results. It has been difficult to find a response that definitively distinguishes between patients with NAR and those with AR.[4,16]

Allergic Component

Later research has evaluated the role of mucosal IgE production with and without provocation testing in patients diagnosed with NAR. IgE production within nasal mucosa in conventional AR has been studied extensively. Rondon and colleagues[31] reported that a subgroup of NAR patients also produce local IgE upon nasal provocation testing. This response has also been studied and demonstrated in a clinical study by Wedbäck and associates.[32] These results suggest there may be a subgroup of NAR patients who have an allergic disease pathway while still exhibiting negative systemic atopy; this group could possibly be those with NAR with eosinophilia (NARES).[33]

Classification

Nonallergic Rhinitis with Eosinophilia

A classification scheme for the major forms of NAR is listed in Box 46-1. Jacobs and colleagues[34] first described NARES in 1981, separating it from traditional NAR. The complex consists of perennial symptoms with episodes of watery rhinorrhea, pruritus, epiphora, and sneezing in patients with negative or irrelevant reactions to common allergens on skin or in vitro testing. The majority of patients deny having specific triggers, although some complain that weather changes or exposure to irritant chemicals is troublesome. Cytologic examination of nasal secretions from such patients shows marked eosinophilia. This reaction may occur as part of a continuum of chronic sinusitis, nasal polyps, and Samter's triad or as an isolated disorder in up to one third of patients presenting with NAR.[1,5,35,36] Unfortunately the exact pathophysiology of this condition is not clear. However, as noted previously, studies have shown that numbers of mast cells, IgE-positive cells, and eosinophils are increased in the nasal mucosa of patients with AR and NAR, possibly as a consequence of localized IgE-mediated reactions. In addition, nasal neural dysfunction has also been described to contribute to the symptomatology in patients with NARES.[33,37,38]

Hormonal

Through direct effects on the nasal mucosa, hormones may cause mucous gland hyperreactivity and increased rhinorrhea.[1] Hypothyroidism and acromegaly are metabolic conditions that result from hormone imbalances and that are associated with nasal symptoms and rhinitis.[5] Fluctuating serum hormone levels during menstruation can lead to nasal symptoms in women of childbearing age. Similarly, rhinitis may arise as a result of changing blood hormone concentrations during puberty.[3,5]

Rhinitis during pregnancy is a well-known entity, affecting 22% of pregnant women. This proportion increases by 69% in women who also smoke.[39] The prevalent nasal symptoms are rhinorrhea and congestion, and a review of the patient's history frequently elicits prior problems with rhinitis. During pregnancy, vascular changes and physiologic expansion of circulating blood volume may contribute to increased nasal vascular pooling and progesterone-induced vascular smooth muscle relaxation.[1,40] The severity of rhinitis during pregnancy has been shown to parallel blood estrogen levels.[5] Direct nasal effects from changes in levels of estrogen, progesterone, prolactin, and placental growth hormone are thus possible causes of the development of this condition. However, no current theory regarding the etiology is convincing, and a multifactorial etiology seems most plausible.[40,41]

Medication-Induced

Rhinitis is a common side effect of a myriad of medications; a list of such medications is shown in Box 46-2. Aspirin and nonsteroidal antiinflammatory medications are well known for their association with airway reactions, including sinusitis and asthma. Nasal symptoms and congestion are associated with several psychotropic agents (e.g., thioridazine, amitriptyline, perphenazine) and antihypertensives (e.g., β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, vasodilators). Hormonal replacement and oral contraceptives can also lead to NAR.[5,42] Asking a patient with rhinitis about medication overuse and abuse is critical; rhinitis medicamentosa is a unique entity that results in rebound congestion after persistent use of topical nasal decongestants or cocaine.

Atrophic

Prior to the availability of antibiotics, primary atrophic rhinitis in westernized countries was commonly associated with infection from bacteria such as *Klebsiella pneumoniae* subsp *ozaenae*. Today, atrophic rhinitis is seen more often as a result of aggressive surgery for nasal obstruction, trauma, manifestations of granulomatous diseases, chronic cocaine abuse, and radiation therapy. It is also associated with increasing age.[43] Sanico and Togias[16] postulate that mucosal changes, along

Box 46-1

Classes of Nonallergic Rhinitis

- Nonallergic rhinitis with eosinophilia
- Hormone-related disorders:
  - Hypothyroidism
  - Acromegaly
  - Puberty
  - Pregnancy
  - Postmenopausal status
- Medications (see Box 46-2) (rhinitis medicamentosa)
- Irritant:
  - Temperature
  - Humidity
  - Barometric changes
  - Gustatory exposure
- Chemical exposure:
  - Immunologic:
    - Animal proteins
    - Wheat
    - Latex
    - Pyrethrum in the insecticide and garden industries
    - Acid anhydrides in the adhesive industry
    - Toluene in auto body spray paints
  - Annoyance:
    - Perfumes
    - Exhaust fumes
    - Pesticides
    - Cleaning agents/ammonia
    - Room deodorizers
    - Floral fragrances
    - Cosmetics
  - Irritant:
    - Air pollution (indoor and outdoor)
    - Ozone
    - Tobacco smoke
    - Carbonless copy paper/paper dust/printing ink
    - Paint fumes
    - Volatile organic compounds (building materials, furnishings)
    - Formaldehyde
    - Oxides of nitrogen
    - Toluene and xylene
  - Corrosive:
    - Ammonium chloride
    - Hydrochloric acid
    - Vinyl chloride
    - Chlorine
    - Organophosphates
    - Acrylamide
- Atrophic:
  - Cocaine abuse
  - Surgery
  - Aging
  - Infectious causes
  - External beam radiation treatment
- Associated systemic disorders
- Idiopathic
- Emotional
- Exercise-induced

Box 46-2

Medications Contributing to Rhinitis

- Intranasal preparations:
  - Cocaine
  - Intranasal decongestants
- Antihypertensives:
  - α- and β-adrenoceptor antagonists
  - Reserpine
  - Hydralazine
  - Angiotensin-converting enzyme inhibitors
  - β-blockers
  - Methyldopa
  - Felodipine
  - Guanethidine
  - Phentolamine
- Anti-inflammatory agents:
  - Nonsteroidal anti-inflammatory medications
  - Aspirin
- Agents for prostatic hypertrophy:
  - Doxazosin
  - Tamsulosin
- Phosphodiesterase type 5 inhibitors:
  - Sildenafil
  - Tadalafil
  - Vardenafil
- Hormones:
  - Oral contraceptives
  - Hormone replacement therapy
- Anti-platelet agent:
  - Clopidogrel
- Anti-depressants:
  - Selective serotonin reuptake inhibitors
- Non-benzodiazepine hypnotic:
  - Zolpidem
- Psychotropic agents:
  - Thioridazine
  - Chlordiazepoxide
  - Chlorpromazine
  - Amitriptyline
  - Perphenazine
  - Alprazolam

with aging, lead to decreases in function, ability to condition inspired air, and secretion production that result in rhinitis symptoms.

The nasal mucosa in atrophic rhinitis gradually changes from a functional, ciliated respiratory epithelium to a nonfunctional lining of nonciliated squamous metaplasia, with a loss of mucociliary clearance and neurologic regulation. Crusting, fetor, mucosal atrophy, and widely patent nasal cavities are seen in patients who complain of nasal congestion.[43] The normal pattern of airflow is changed, likely contributing to the sensation of congestion and obstruction as well as decreased olfactory function. Treatment, which is limited and frequently unsatisfactory, consists of antibiotics, nasal irrigations/humidification, and other medical approaches, discussed later. Various operations to alter nasal airflow have brought relief to some patients.

Irritant

Temperature changes, alterations in barometric pressures, ingested foods, and inhaled irritants are other inciting causes of NAR. Physical stimuli with weather changes are known triggers. As mentioned earlier, cold, dry air is a known factor in the development of profuse rhinorrhea.[22,44] Altitude and pressure changes result in facial pressure, head-

aches, and nasal symptoms in susceptible individuals who work, for example, in the aviation field.

The ingestion of certain foods leads to mucoid or watery rhinorrhea, referred to as *gustatory rhinitis*.[1,5,45] Hot, spicy foods are the most common culprit; the onset is acute and lasts for as long as the food is ingested. Other symptoms characteristic of AR are absent, and the result of skin testing with extracts of the suspected foods is negative. Stimulation of afferent sensory nerves is the most likely pathophysiologic mechanism; this stimulation activates the parasympathetic nerves that supply the nasal mucosal glands and could also explain the sweating and epiphora that sometimes accompany this reaction.[45]

Occupational

A more complex form of inhalant-induced rhinitis is occupational NAR. The incidence is estimated to be 5% to 15% and it should be differentiated from occupationally induced allergic or immunologic rhinitis.[46] Owing to a lack of clear diagnostic tests in this clarification process, the medical and workplace history is especially important. Along with the typical symptoms of NAR, victims of occupational rhinitis also have impaired sense of smell, nosebleeds, crusting, and reduced mucociliary transport; they often also have nasal hyperreactivity.[47]

Box 46-1 outlines various forms of chemical exposure as classified by Baraniuk and Kaliner[48]: immunologic, annoyance, irritant, and corrosive. *Immunologic* aeroallergens associated with rhinitis in the workplace include animal proteins, wheat, latex, pyrethrum in the insecticide and garden industries, acid anhydrides in the adhesive industry, and toluene in auto body spray paints. Many patients complain of symptoms in association with perfumes, exhaust fumes, cleaning agents, room deodorizers, floral fragrances, and cosmetics; such *annoyance* reactions occur in patients with heightened olfactory awareness. *Irritant* reactions occur with inhalation of respiratory irritants beyond threshold levels. Air pollution and ozone levels are discussed daily in susceptible areas. Tobacco smoke, paint fumes, formaldehyde, oxides of nitrogen, and toluene are other examples of irritants. Exposure to high concentrations of soluble chemical gases can cause inflammation of nasal and oral mucosa, skin, and eyes along with mucosal burns and ulcerations. Ammonium chloride, hydrochloric acid, vinyl chloride, organophosphate, and acrylamide exposures are known to cause such *corrosive* reactions.[1]

Evidence indicates that many of the irritant forms of rhinitis are mediated by neurogenic mechanisms, particularly those that are related to chemical exposures. Neurogenic inflammation has been discussed as a pathway model in chemical sensitivity syndromes, including rhinitis and asthma.[49] As discussed earlier, the proposed mechanism is the stimulation of chemical irritant receptors on sensory nerves (i.e., C fibers) to induce neuropeptide release. The neuropeptides produce vasodilation and edema associated with inflammation independent of immune-mediated inflammation.

Idiopathic

Idiopathic or vasomotor rhinitis is diagnosed when other identifiable causes have been excluded and there is no cytologic evidence of mucosal inflammation.[1] This form is thus a diagnosis of exclusion and is the most common form of NAR. However, for this reason it poses a difficulty in treatment for the clinician.[8] Historically, idiopathic rhinitis was thought to be due to an imbalance of the autonomic nerve supply in the nasal mucosa—either excessive parasympathetic or reduced sympathetic activity. The relationship between vasomotor rhinitis and the autonomic nervous system was first speculated on more than 50 years ago.[2,13] As mentioned previously, nasal mucosal reactivity, which is a balance of the sympathetic and parasympathetic systems, controls vascularity and glandular expression. Jaradeh and colleagues[50] used an autonomic nervous system laboratory to compare nasal reactions in control patients with those in patients with vasomotor rhinitis. Their studies demonstrated a relationship between vasomotor and autonomic nervous system dysfunction and hypoactivity of the sympathetic nervous system relative to the parasympathetic system. These specific neural defects may contribute to the diverse symptomatology in vasomotor rhinitis.[51]

Associated Factors

Several local and systemic conditions can result in nasal symptoms and rhinitis. Local anatomic factors are apparent from examination and can exacerbate underlying rhinitis. Nasal symptoms may be the first sign of neoplasms; infectious etiologies may be the primary causes of nasal symptoms because of underlying obstructive and chronic nasal disease. Diagnosis and control of systemic disease must be addressed to effectively treat coexisting NAR. Boxes 46-3 and 46-4 list several local and

Box 46-3

Local Factors in Rhinitis

- Anatomic factors:
  - Septal deviation
  - Hypertrophic turbinates
  - Nasal valve collapse
  - Antrochoanal polyp
  - Adenoid hypertrophy
  - Choanal atresia/stenosis
  - Septal perforation
  - Cleft palate
- Infectious and inflammatory sources:
  - Acute and chronic rhinosinusitis (viral, bacterial, fungal, eosinophilic)
  - Sinonasal polyposis
  - Tuberculosis
  - Leprosy
  - Syphilis
  - Rhinoscleroma
  - Rhinosporidiosis
- Neoplasms:
  - Benign (e.g., inverting papilloma)
  - Malignant

Box 46-4

Systemic Conditions Associated with Rhinitis

- Autoimmune/rheumatic disorders:
  - Systemic lupus erythematosus
  - Sjögren's syndrome
  - Scleroderma
  - Relapsing polychondritis
  - Immunoglobulin deficiency syndromes
- Vasculitides:
  - Wegener's granulomatosis
  - Sarcoidosis
  - Churg-Strauss syndrome
  - Pyogenic granuloma
  - Microscopic polyangiitis
  - Cryoglobulinemic vasculitis
- Ciliary dysmotility syndromes:
  - Primary ciliary dyskinesia (a.k.a. Kartagener's syndrome)
  - Young's syndrome
- Cystic fibrosis
- Hormonal disorders/imbalance:
  - Acromegaly
  - Hypothyroidism
  - Pregnancy
  - Perimenopausal/postmenopausal status
  - Puberty

systemic disorders that contribute to rhinitis or in which rhinitis is a component.

History and Diagnosis

History

Diagnosis of NAR is based on thorough history, complete head and neck examination, and diagnostic tests to rule out inflammation and infectious etiologies. A complete history includes questions about the presentation and history of the symptomatology; details of the pattern and timing of symptoms, exacerbating and alleviating factors, environmental triggers, and the exclusion of common environmental allergens. Box 46-5 provides a list of questions to help the clinician focus the patient's history, which can be formulated into a questionnaire for expeditious and efficient patient evaluation. Brandt and Bernstein[52] formulated a questionnaire to aid in the diagnosis of NAR. Their results showed that patients in whom onset of symptoms occurred after 35 years of age and who had no family history of allergies, no outdoor or cat-related symptoms, and no symptoms around perfumes/fragrances had a 96% likelihood of having NAR. As discussed previously, several systemic conditions are associated with symptoms of rhinitis, ranging from vasculitides to hormonal imbalances to infectious causes such as chronic sinusitis. Boxes 46-3 and 46-4 list conditions that may contribute to rhinitis.

When a child presents with NAR symptomatology, some important factors must be evaluated. Points in the history that should be reviewed include snoring, sleep history, school performance, birth history, and evidence of recent trauma. Among adolescents, onset of puberty should also be discussed. Although the most common trigger of rhinitis in children is the common cold, important other conditions should be considered, including environmental irritants, foreign bodies, thyroid disorders, adenoid hypertrophy, polyposis, immunodeficiency disorders, ciliary dyskinesia, reflux, and cystic fibrosis.[53]

Box 46-5

Useful Patient History Questions for Diagnosis of Nonallergic Rhinitis

What are your nasal and sinus symptoms?
Are your symptoms intermittent or persistent?
Which of the following do they include?
- Nasal discharge
- Congestion/blockage
- Postnasal drainage
- Episodes of sneezing
- Nasal itching
- Itchy eyes
- Epiphora

Do you have environmental allergies (e.g., hay fever)?
Have you undergone allergy testing?
Have you been treated for allergies?
Are there certain situations or environments in which your symptoms are worse or in which they are better? For example, home, work, indoors, or outdoors?
Are there certain times of the day or year during which your symptoms are worse or better?
What type of work do you do?
Are you exposed to chemicals in your occupation?
Have you noticed an increase in nasal or sinus symptoms around certain chemicals/aromas/foods?
Did your symptoms begin when you started taking certain medications?
What medications have you tried for your symptoms?
Of the medications you have tried, have any resulted in the improvement of your symptoms?
When using nasal sprays, have you used them regularly?
Do you have a history of chronic sinusitis? Nasal and/or sinus polyps?
Are you sensitive or allergic to aspirin?
Have you undergone sinus surgery?
Do you have asthma?
Do you have a history of head or nasal trauma?

Physical Examination

A comprehensive head and neck examination includes the findings of nasal endoscopy. The mucosa is usually boggy and edematous with clear mucoid secretions. Mucosal injection and lymphoid hyperplasia involving the tonsils, adenoids, and base of the tongue may be seen. Areas of blanched mucosa surrounding prominent vessels have been reported in chemical exposures.[54] The presence of inflammation and purulent discharge from the middle meatus and sphenoethmoid recess indicates active infection. Polyps are an indication of chronic inflammation and obstruction. Atrophy of the mucosa is seen in cases of aging, prior surgery, and drug abuse. Anatomic obstruction can be diagnosed with a septal deviation, hypertrophic turbinates, choanal stenosis, or atresia. Nasal valve collapse is often overlooked when patients complain of nasal obstruction; septal perforation with crusting and epistaxis can be associated with similar symptoms. Examination of the nasal cavity and nasopharynx also helps identify adenoid hypertrophy or unusual mucosal lesions suggestive of sarcoidosis or Wegener's granulomatosis.

Diagnostic Testing

The diagnostic workup should include skin testing and/or serum testing for serum specific Ig E antibodies to relevant allergens (radioallergosorbent testing), results of which are typically negative in NAR. Nasal cytology provides information about the cell types present in the mucosa and determines whether there is evidence of inflammation. Scrapings from the inferior turbinate mucosa, nasal lavage, or nose blowing are methods described to provide epithelium for the analysis of cell types, particularly to look for eosinophils. The finding of 5 to 25 eosinophils per high-power field is compatible with a diagnosis of NARES.[55]

Acoustic rhinometry is an adjunct in the diagnostic workup and may also provide objective measures of nasal patency.[56] Gosepath and colleagues[57] published a protocol that uses nasal provocation testing as a standardized method for evaluating NAR. They expose a patient to a respective allergen and then assess the clinical response along with collecting objective data with rhinomanometry and acoustic rhinometry. Chronic rhinitis has also been associated with smell impairment, and validated smell testing is useful in the diagnostic workup.[58]

Imaging using plain radiographs or even computed tomography is not particularly useful in uncomplicated rhinitis, especially after initial nasal endoscopy is performed. However, computed tomography is useful for evaluating sinus disease, the extent of sinonasal polyposis, a concha bullosa, and skull base defects with cerebrospinal fluid rhinorrhea. Magnetic resonance imaging is useful for investigating the possibility of a mass lesion.

Treatment of Nonallergic Rhinitis

Avoidance

Patient education is of utmost importance in treating NAR. Patients frequently are not aware of the specific trigger that incites their symptoms, but a thorough and accurate history can often elucidate the cause of an individual's problem. After being informed, the patient can take an active role in his or her health care and control his or her environment. Avoidance of inciting factors such as perfumes, tobacco smoke, cleaning supplies, and certain foods or wines can usually be accomplished without great difficulty. If a change in environment is not feasible, occupational exposures can be eliminated with the use of masks and protective coverings. The associated medications can be discontinued or changed. Unfortunately, in many circumstances, inciting exposure cannot be avoided and there is no substitute for an essential medication. In these cases, rather than simply accepting rhinorrhea and

congestion, the patient can undergo medical therapy to help control the symptoms of NAR. Additionally, it is important to remember that diagnosis and treatment can be complicated by the presence of coexistent AR.

Topical Nasal Corticosteroids

Topical nasal steroids are widely used for the treatment of NAR. Several different preparations are available; they are listed in Table 46-1. These agents work on the nasal mucosa, thereby decreasing neutrophil and eosinophil chemotaxis, reducing mast cell and basophil mediator release, and thus decreasing edema and inflammation.[59] The effectiveness of nasal steroids requires that the drug come in contact with and penetrate the nasal mucosa. Optimal administration requires propelling the medications into the nasal cavity. Pointing the spray nozzle upward and away from the nasal septum is recommended. Anatomic obstruction resulting from polyps and turbinate hypertrophy may prevent topical steroids from reaching their destination.

Decongestants—either topical or systemic—can be used to decrease mucosal edema and assist with the application of topical nasal steroids. After the topical steroids consistently and successfully reach the nasal mucosa, decongestant use should be tapered and discontinued. Physiologically normal saline is another useful adjunct to therapy; rinsing with this substance increases steroid efficacy at the mucosal level. In addition to cleansing the nose, saline improves ciliary function and mucociliary clearance.

Topical steroids are generally tolerated quite well, and side effects are infrequently encountered. The most commonly reported side effects include septal irritation, nasal dryness and crusts, epistaxis, throat dryness, and headaches. Septal perforation has been reported but is uncommon[60]; even rarer are systemic side effects. Approximately 20% of any intranasal steroid preparation is absorbed into the nasal mucosa; the majority of the remaining 80% is swallowed and undergoes first-pass hepatic metabolism in the portal circulation. There is conflicting evidence regarding whether the portion absorbed by the nasal mucosa can cause systemic complications.[61-65] Concern about the bioavailability of steroid preparations after topical use has arisen, and a definitive answer is not entirely clear; exceeding the recommended dosage and using topical steroids in conjunction with other steroid inhalants certainly increase this risk. The "margin of safety" for any such agent refers to the multiple of the recommended initial dose that will suppress cortisol production and cause systemic problems.

Given the findings of eosinophils and inflammation on nasal cytology, NARES responds well to topical nasal steroids, which are the mainstay of treatment.[1] Topical intranasal steroids vary in efficacy, and studies have shown inconsistencies. Fluticasone propionate and beclomethasone are currently the only topical steroid preparations approved by the U.S. Food and Drug Administration (FDA) for treatment of NAR; they have both been found to be effective in patients with this disorder.[66,67] Budesonide has also shown good efficacy and is currently the only topical nasal steroid assigned to pregnancy category B; all others are category C. [67-69] On the other hand, mometasone, in a separate study, did not show better efficacy than placebo in reducing rhinitis symptoms over a 6-week period in patients with perennial NAR.[70]

Antihistamines

Antihistamines can be administered orally, parenterally, or topically. First-generation agents include diphenhydramine, chlorpheniramine, and clemastine; they are the most potent and most effective antihistamines available. However, these drugs are lipophilic and cross the blood-brain barrier. As a result, central nervous system depression that causes sedation, drowsiness, and motor and cognitive impairment is their primary limitation. Other side effects are related to their anticholinergic properties, which in turn are also the likely mechanism for their reduction of rhinorrhea.[55] The successful second- and third-generation, nonsedating, lipophilic antihistamines loratadine, desloratadine, cetirizine, levocetirizine, and fexofenadine have now come to be more useful. Oral antihistamines tend to have a limited role in treating NAR, although they may be beneficial for patients who have NAR with sneezing.[71]

Histamine release is the pathophysiology indicated in AR. For this reason, antihistamines would seemingly be a poor choice for treatment of NAR. However, azelastine—a topical antihistamine—is approved for use in both AR and NAR. Azelastine is an H_1 receptor antagonist. In addition, it inhibits the synthesis of leukotrienes, kinins, and cytokines, the expression of intercellular adhesion molecules, and the generation of superoxide free radicals. These anti-inflammatory effects, which are unrelated to H_1 receptor antagonism, allow azelastine to provide relief in NARES and vasomotor rhinitis.[72,73] Two multicenter,

Table 46-1

Commonly Prescribed Nasal Corticosteroids*

Generic Name	Trade Name	Dose Frequency (Adult)	Systemic Bioavailability (%)
Dexamethasone	Dexacort	tid	Very high, no first-pass liver metabolism
Beclomethasone	Vancenase	bid-qid	44
	Vancenase AQ DS	qd	44
	Beconase AQ	bid	44
Flunisolide	Nasalide	bid	49
	Nasarel	bid	49
Triamcinolone	Nasacort	qd-bid	NA
	Nasacort AQ	qd	NA
Budesonide	Rhinocort	qd-bid	34
	Rhinocort AQ	qd	34
Fluticasone propionate	Flonase	qd	<1
Fluticasone furoate	Veramyst	qd	<1
Mometasone	Nasonex	qd	<1

*Not all are available in the United States.
NA, data not available.

Table 46-2

Commonly Prescribed Antihistamines

Generic Name	Trade Name	Dose
First-Generation Agents		
Diphenhydramine	Benadryl	25-50 mg q 4-6 hours prn 12.5 mg q 4-6 hours prn (6- to 12-year-old patients)
Clemastine	Tavist	1.34 mg bid, or 2.68 mg daily to tid prn 0.76 to 1.34 mg bid prn (6- to 12-year-old patients)
Chlorpheniramine	Chlor-Trimeton	4 mg q 4-6 hours 2 mg, 3 to 4 times a day prn (6- to 12-year-old patients)
Second-Generation Agents		
Acrivastine	Semprex D	8 mg, 4 times a day
Loratadine	Claritin	10 mg qd 5 mg qd (2- to 5-year-old patients)
Desloratadine	Clarinex	1.25 mg qd (12-month to 5-year-old patients) 2.5 mg qd (6- to 11-year-old patients) 1.5 mg qd (11-month to 5-year-old patients) 1 mg qd (6- to 11-month-old patients)
Third-Generation Agents		
Fexofenadine	Allegra	60 mg bid or 120 mg qd 30 mg bid (6- to 12-year-old patients)
Cetirizine	Zyrtec	5-10 mg qd 2.5 mg qd up to 5 mg qd or 2.5 mg bid (2- to 6-year-old patients)
Levocetirizine	Xyzal	5 mg qd as an evening dose 2.5 mg qd as an evening dose (6- to 11-year-old patients)
Topical		
Azelastine	Astelin	1-2 sprays per nostril bid 1 spray per nostril bid (5- to 11-year-old patients)

randomized, double-blind studies clearly showed azelastine to achieve significant reduction in NAR symptomatology, including nasal obstruction, rhinorrhea, and nasal edema.[72,74] The high incidence of mixed rhinitis also allows this medication to be quite useful. Furthermore, studies have shown that the medication is generally well tolerated, with a discontinuation rate of only 2.3%.[75] Table 46-2 provides a list of antihistamines and their dosages.

Anticholinergics

Anticholinergic medications provide relief from bothersome and unrelenting rhinorrhea in NAR. Oral preparations cause blurred vision, drying of the mouth and eyes, and thickened secretions; these systemic side effects are disturbing and outweigh the potential benefits of these agents. Alternatively, ipratropium bromide, which is a topical anticholinergic, acts locally and blocks parasympathetic input to the nasal mucosa glands only. Systemic side effects are uncommon with intranasal ipratropium bromide; epistaxis and nasal dryness may occur, but they are rarely intolerable, and they decrease in incidence with prolonged use of the medication.[76] Two strengths are available, 0.03%, which is approved by the U.S. Food and Drug Administration for treatment of AR and NAR, and 0.06%, which is approved for use in acute viral rhinitis. Intranasal ipratropium bromide can be used in children as young as 6 and also in pregnant women because it is assigned to a pregnancy category B. Initially, two sprays are given three times a day. Symptom control should become apparent within 1 week. When symptoms abate, the dosage can be lowered by one spray at a time. One spray two times daily is the lowest recommended maintenance dose.

Surgery

Surgery is also used in recalcitrant cases to address specific symptoms in NAR. Nasal polyps, hypertrophic inferior turbinates, and septal spurs or deviation may completely obstruct a nasal passage. As stated, topical medications must reach the nasal mucosa to be effective. In circumstances of obstruction, surgical intervention may be warranted. Little debate exists about the performance of surgery for sinonasal polyps that are resistant to medical therapy. Tissue conservation and mucosa-sparing techniques are used whenever possible to retain physiologic function and reduce the risk of atrophic rhinitis.

In addition to highly vascular mucosa, the membranes of the inferior turbinates contain venous sinusoids surrounded by smooth muscle fibers under autonomic control[43]; there is also a rich supply of mucous and serous glands. Therefore, turbinate hypertrophy contributes to nasal obstruction and drainage. Hypertrophy that is unresponsive to medical therapy can be addressed in a variety of ways: electrocautery, laser ablation, microdébrider resection, submucosal resection, lateral displacement, partial turbinectomy, and radiofrequency ablation. The goals are to use conservative approaches to minimize interference with turbinate function and to preserve mucociliary transport, secretion, filtration, temperature modulation, and regulation of nasal airflow. A variety of techniques are also available for septoplasty; the specifics of these procedures are described elsewhere in this volume and are beyond the scope of this discussion.

In 1959, Malcomson[77] demonstrated that overactive parasympathetic input resulted in vasomotor rhinitis. In subsequent years, Golding-Wood[78] produced clinical evidence to support Malcomson's work, supporting the development of surgical procedures for the treatment of

obstinate cases of chronic rhinitis. Initially attempts were made to section the greater superficial petrosal nerve, but the risk of facial palsy was unacceptably high, so a new approach was desired. In 1961, Golding-Wood[79] popularized the transantral vidian neurectomy.

During years since then, several different approaches to the vidian nerve have been utilized to address persistent rhinorrhea that is resistant to more conservative measures. The transantral approach requires resection of the anterior and posterior walls of the maxillary sinus, putting the adjacent internal maxillary artery, maxillary nerve, superior alveolar nerve, and sphenopalatine ganglion at risk. Transpalatal nerve section can lead to oronasal or orosinusal fistulas. Risks of transethmoidal approaches include bleeding (as a result of damage to ethmoidal arteries) and vision damage. Current trends favor endoscopic transnasal approaches. Although technically more challenging, this transnasal approach has a lower morbidity than other methods described.[64,80,81] Other complications, which are independent of approach, include decreased lacrimation, mucosal engorgement in the supine position, dysesthesia, and recurrence of initial symptoms, presumably from reinnervation.

General Considerations in Treatment

The first part of this chapter describes the classification of the multiple causes of NAR. For the consideration of treatment, these can be organized into the following broad subject headings: NARES, hormonal causes, medications, irritant etiologies, atrophic rhinitis, anatomic obstruction, systemic disorders, and idiopathic rhinitis. This organization is preferred, because the treatments of irritant forms of rhinitis—chemical sensitivity, temperature-induced rhinitis, gustatory rhinitis, and their many subsets—are essentially identical, depending on the prevailing symptoms. Similarly, hormonal rhinitis encompasses menstrual changes, pregnancy, and hypothyroidism and requires the adjustment of these underlying causes. As discussed previously, medication-induced rhinitis is relieved by the substitution of other medications.

Conservative management is appropriate in the majority of pregnant patients who present with rhinorrhea; patients can be reassured that symptoms will almost certainly cease within 2 to 4 weeks of delivery. If required, a number of therapeutic regimens are available for pregnant women. However, before starting such a patient on a new medication, the clinician should consult her obstetrician. Nasal saline irrigations may help and are of no risk. Diphenhydramine and chlorpheniramine may be used when needed, although caution is warranted during the first trimester. Decongestants can also be used, but gastroschisis has been reported in the infants of women who took such agents during the first trimester. The effects of topical steroids have been extrapolated from their use in pregnant patients with asthma.[42] Steroids, either systemic or intranasally injected, have been described to effectively control rhinitis and congestion and do not appear to pose a risk to the fetus when used cautiously and in limitation; however, no controlled studies exist regarding these treatments.[82,83] Other hormonal causes of rhinitis are responsive to the same medications as described earlier.

To address other forms of NAR, similar management can be undertaken. Conservative management, including the avoidance of irritating substances, cold weather, and certain foods and wine, should be attempted first. The treatment of underlying diseases and the adjustment of associated medications can bring significant relief. If pharmacologic therapy is initiated, ipratropium bromide is an excellent choice for patients who are complaining mainly of rhinorrhea. Topical steroids or azelastine given with or without nasal saline and decongestants, if necessary, are also efficacious. Finally, surgical correction should be considered if symptoms are recalcitrant to conservative or medical management. Vidian neurectomy can be a viable treatment option for persistent rhinorrhea when these other therapies have failed. Inferior turbinate surgery as well as septoplasty can relieve related anatomic obstructions and are beneficial in many cases.

As mentioned earlier in the chapter, many rheumatologic diseases have otolaryngologic manifestations. Wegener's granulomatosis, Churg-Strauss syndrome, sarcoidosis, and relapsing polychondritis are the four conditions most likely to affect the nose and nasal passages. Treatment of these conditions is primarily accomplished through a multidisciplinary approach and the use of immunosuppressive medications, antibiotics, or both.

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CHAPTER FORTY-SEVEN

The Pathogenesis of Rhinosinusitis

Michael S. Benninger

Key Points

- The pathogenesis of rhinosinusitis depends on defining specific types of rhinosinusitis: acute bacterial rhinosinusitis (ABRS), chronic rhinosinusitis (CRS), and acute exacerbation of chronic rhinosinusitis (AECRS).
- A number of environmental and host factors predispose to the development of rhinosinusitis, including allergy, anatomic variants in the nose, and environmental exposures such as tobacco exposure.
- Although acute rhinosinusitis usually is the result of a viral infection, ABRS occurs primarily because of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis,* or *Staphylococcus aureus*.
- Invasive fungal rhinosinusitis is an aggressive, life-threatening infection that occurs in immune-compromised individuals and is caused most often by *Mucormycosis* and *Aspergillus*.
- CRS is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration. Many potential pathophysiologic mechanisms have been described to account for CRS, but in most cases these factors apply only in susceptible hosts. Bacteria may play a role through multiple mechanisms, including chronic infection, osteitis, the production of superantigens, and support through biofilms. Fungi can result in a classic chronic fungal inflammation in either allergic fungal rhinosinusitis or immunoglobulin (Ig) E–mediated inflammation. A non-IgE inflammatory etiology also occurs in a group of susceptible individuals.
- AECRS is a sudden worsening of symptoms in a patient with CRS. It is often associated with an increase in bacteria that are prominent in the exacerbation. Although there is an increase in the organisms typically associated with ABRS—*S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus*—there is also a high percentage of anaerobic organisms.

Definitions of Acute and Chronic Rhinosinusitis

In order to understand the pathogenesis and pathophysiology of rhinosinusitis one must realize that there are different forms of rhinosinusitis with dramatically different inciting mechanisms. Although *sinusitis* is commonly used for any inflammation or infection of sinuses, this term has largely been replaced by *rhinosinusitis* because the nose is almost always involved with the infection or inflammation at the same time as the sinuses.[1] Many potential factors can result in the development of rhinosinusitis, so there has been some debate concerning the exact definitions.

More recently, rhinosinusitis has been defined as "a group of disorders characterized by inflammation of the mucosa of the paranasal sinuses."[2] In 1997 the Rhinosinusitis Task Force of the American Academy of Otolaryngology–Head and Neck Surgery[3] developed a now well-accepted classification of rhinosinusitis, which was reported by Lanza and Kennedy.[1] This classification relies on two major criteria that help to identify whether or not a patient has rhinosinusitis primarily on the basis of symptoms (Box 47-1) and then to classify rhinosinusitis types based primarily on temporal time frames from the onset of symptoms. The symptoms are divided into major and minor categories, with purulent nasal drainage, nasal congestion, facial pressure or pain, decreased smell, and posterior purulent drainage serving as the major symptoms.[1]

An inflammatory response is an expected sequela of an infectious process. Inflammation in the nose and sinuses from a variety of causes can result in sinus ostia obstruction and can predispose to the development of an infection. Many factors have been described as playing a role in the development of acute bacterial rhinosinusitis (ABRS).[1,4,5] These include the following factors related to the host: genetic factors such as immotile cilia syndrome and cystic fibrosis; anatomic variants such as a concha bullosa, septal spur, and paradoxical turbinate; certain systemic diseases or medical treatments that predispose individuals to infections; neoplasms; and allergic or immune disorders. Rhinosinusitis may also develop in relationship to environmental factors, as follows: bacterial, viral, or fungal infections, or inflammation that occurs secondary to fungal or bacterial colonization[2,6]; trauma; primary or secondary tobacco smoke exposure[7] and chronic or acute irritants or noxious chemicals; and iatrogenic factors, including surgery, medications, nasal packing, and nasogastric tube placement.[8] There is growing evidence that individuals with allergies have a higher incidence of both acute and chronic rhinosinusitis, and an association of acute bacterial rhinosinusitis with asthma has also been suggested, although this may also relate to the presence of allergic rhinitis.[9-11]

Box 47-1

Symptoms and Signs of Rhinosinusitis*

Major Symptoms/Signs

Facial pain/pressure
Facial congestion/fullness
Nasal obstruction/blockage
Nasal discharge/purulence, discolored posterior drainage
Hyposmia/anosmia
Purulence on nasal examination
Fever (acute rhinosinusitis only)

Minor Symptoms/Signs

Headache
Fever (nonacute rhinosinusitis)
Halitosis
Fatigue
Dental pain
Cough
Ear pain/pressure/fullness

*Diagnosis requires presence of either two major factors, or one major and two minor factors.

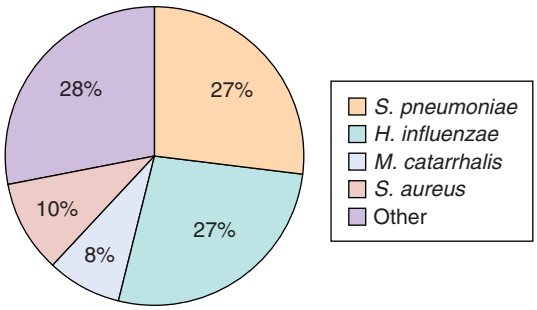

Figure 47-1. Pathogen distribution in acute bacterial rhinosinusitis (ABRS) as shown by a recent meta-analysis. *(From Payne SC, Benninger MS.* Staphylococcus aureus *is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis.* Clin Infect Dis. *2007;45:e121-e127.)*

The distinctions between acute rhinosinusitis (ARS), recurrent acute rhinosinusitis (RARS), subacute rhinosinusitis (SARS), chronic rhinosinusitis (CRS), and acute exacerbation of chronic rhinosinusitis (AECRS) are based on the temporal differences in the presentation and, in some cases, on the clinical presentation. Each of these subcategories may be associated with different pathophysiologic processes, and the predisposition to their development may vary from patient to patient. Given these differing etiologies, the pathogenesis is described here on the basis of this classification.

Acute Rhinosinusitis

Acute rhinosinusitis is a very common disorder that at one time or another affects most people. From a temporal standpoint acute rhinosinusitis lasts for up to 4 weeks.[1] The disorder is almost always due to an infectious process, principally from viruses and bacteria, with viruses accounting for the majority of the cases. There have been attempts at estimating the prevalence of acute rhinosinusitis. It is estimated that children have between six to eight upper respiratory (tract) infections (URIs) per year and that adults average two or three.[12] If an assumption is made that 90% of patients with colds have sinusitis (bacterial or viral) and that each person has an average of four URIs per year, then it can be estimated that in the United States there are more than a billion cases of viral and bacterial rhinosinusitis annually (260 million people × 4 episodes = 1.040 billion cases).[13]

Acute bacterial rhinosinusitis has been defined as sudden in onset and with duration of less than 4 weeks.[1] Because most cases of rhinosinusitis are caused by a self-limited viral infection and bacterial infections usually occur after a viral URI, ABRS has been diagnosed after at least 7 to 10 days of symptoms or in patients whose symptoms are worsening after 5 to 7 days.[1,4,14] This distinction has been endorsed in most of the guideline development for the treatment of ABRS.[4] The diagnosis may be more difficult in children, because they often have difficulty describing their symptoms.

Streptococcus pneumoniae (20%-45%) and *Haemophilus influenzae* (22%-35%) are the predominant organisms in ABRS in adults, whereas *S. pneumoniae* (30%-43%), *H. influenzae* (20%-28%), and *Moraxella catarrhalis* (20%-28%) are the predominant organisms in ABRS in children.[4,14] Although *Staphylococcus aureus* was previously thought to be a contaminant, a 2007 meta-analysis has confirmed that this organism should now be considered a real pathogen in ABRS, accounting for 8% to 10% of adult cases (Fig. 47-1).[15] Because *M. catarrhalis* infection is largely a self-limited disease, and methicillin-resistant *S. aureus* (MRSA) is becoming a bigger health care issue, *S. aureus* may be more important to treat. *S. aureus* is also well recognized in both CRS and AECRS.[14-16]

ABRS is a self-limited disease in many cases. Evaluation of placebo-controlled antibiotic trials has shown that there is a high self-resolution rate.[4,13,14] Infections with *M. catarrhalis* are most likely to resolve without antibiotic treatment, those with *H. influenzae* less likely, and those with *S. pneumoniae* least likely to resolve without treatment. It may become important therefore to determine which patients have which organism. The most reliable way is to obtain a culture, with a maxillary sinus tap being the traditional method of obtaining sinusitis cultures. The invasiveness of this test and the advancement of endoscopically guided selective middle meatal culture collections have resulted in a shift to this latter method in clinical practice.[16,17] An evidence-based review has shown that cultures of endoscopic middle meatal specimens are as sensitive and specific as those of maxillary sinus tap specimens.[17] In clinical practice, however, cultures are rarely performed unless there has been a failure of treatment. The severity of the symptoms and radiographic findings may help identify different pathogens, in that patients infected with *S. pneumoniae* have been found to have more significant symptoms and worse radiographic findings than those infected with *H. influenzae*.[18]

With the widespread utilization of pneumococcal 7-valent conjugate vaccination, there has appeared to be a shift in the overall distribution of pathogens in ABRS. In a 2006 study assessing the pathogenesis of ABRS, the proportions of the recovery of pathogens from cultures of endoscopically obtained specimens in adults with acute maxillary sinusitis were compared for the periods 4 years prior to and 5 years after the introduction of the conjugate pneumococcal vaccine. Recovery rate for *H. influenzae* increased from 36% to 43%, making it the most common pathogen. At the same time, the rate for *S. pneumoniae* was found to decrease from 46% of isolates to 35%. There also were increases in the proportions of cases caused by *M. catarrhalis* and *S. aureus*.[19] In a similar study, nasopharyngeal cultures were obtained in children with acute maxillary sinusitis before and after the widespread use of pneumococcal conjugate vaccination. *S. pneumoniae* decreased from accounting for 43% to 25% of isolates, whereas *H. influenzae* increased from 35% to 41%. The rate for *M. catarrhalis* remained stable, changing from 13% to 14%. The rate for *Streptococcus pyogenes* increased from 7% to 12%, and that for *S. aureus* from 4% to 8%.[20]

With the widespread use of pneumococcal vaccination a change also seems to have occurred in the serotypes of *S. pneumoniae* responsible for not only ABRS but also acute otitis media (AOM), with an increase in serotypes not found in the vaccine.[21-23] There has been some speculation that this serotype replacement may reduce the long-term efficacy of the pneumococcal 7-valent conjugate vaccine.[23] Multiple studies have shown a reduction in culture rates for both the nonsusceptible and highly resistant strains of *S. pneumoniae* in AOM and to a lesser extent in ABRS.[24-28] Whitney and colleagues[25] showed a drop of 35% in rate of strains not susceptible to penicillin.[25] High-level resistance of *S. pneumoniae* to penicillin also appears to have dropped,

from 15% to 5% in one report.[27] There has been an associated increase in the β-lactamase–producing strains of *H. influenzae*.[28] Although the data related to the shift in pathogens is less well supported in ABRS than in AOM, there have been clear and parallel shifts in the pathogens associated with ABRS and AOM. This finding is not unexpected because the pathogenic organisms are similar for ABRS and AOM and the shift in the microbiology of ABRS has been suggested to have occurred because of the involvement of the same pathogens in AOM and ABRS.[29]

The mechanism by which the viral inflammation of a viral URI can lead to ABRS has been suggested in a number of reports.[5,30] As previously mentioned, acute rhinosinusitis typically develops in conjunction with an acute viral URI. The propensity for development of a viral URI may occur more commonly in predisposed individuals. The viral infection can result in swelling of the mucosa of the nose or sinuses, and the resultant swelling can produce occlusion or obstruction of the sinus ostia. A reduction in oxygen tension occurs that in turn can reduce mucociliary transport and transudation of fluid into the sinuses.[5] The inflammation also results in changes in the mucus, which becomes more viscous, and often in alterations in cilia beat frequency. These changes in the nasal-sinus environment lead to reduced clearance, stasis of mucus, and bacterial colonization. If the sinuses remain obstructed or the mucociliary transport system does not return to normal, a bacterial infection can ensue. The ability of the body to respond to the viral challenge and reduce the inflammation may, in part, determine whether a secondary bacterial infection occurs.

The role of allergies in the development of rhinosinusitis has been strongly suggested but not proven.[9-11] Antigen-antibody reactions result in the release of histamine and other mediators of inflammation. These mediators cause changes in vascular permeability, destabilization of lysosomal membranes, and other reactions that produce inflammation, mucosal swelling, and ostia obstruction.[5] Although infectious agents can be primary causes of sinus inflammation, they may also represent a secondary infection. The type and magnitude of the reaction may be related to the host response and how it relates to the disease process and progression.

Recurrent acute rhinosinusitis is defined as 4 or more episodes of acute rhinosinusitis per year, with each lasting longer than 7 to 10 days, and an absence of intervening signs or symptoms that would suggest an ongoing or chronic rhinosinusitis.[1] Although recurrent viral respiratory tract infections are common, in general it is rare for people to develop true recurrent episodes of ABRS to meet the preceding criteria for recurrent ABRS. When they do, it is expected that the bacteriology and pathophysiology would be similar to those of individual episodes of ABRS.

Invasive Fungal Rhinosinusitis

In a very small subset of patients with acute rhinosinusitis the inciting pathogen is neither viral nor bacterial. They have acute *invasive fungal rhinosinusitis (IFRS)*. This disorder is almost always confined to patients with altered host defenses. A review of 43 patients with IFRS has shown that 65% were immunosuppressed because of a hematologic malignancy or its treatment. Twenty-three percent had diabetes, 7% were taking long-term steroid therapy, and 2% had acquired immunodeficiency syndrome.[31] Any disorder that results in immune suppression or an immunodeficiency can lead to the development of IFRS in some individuals.

Historically the most common organism reported in IFRS has been *Mucormycosis*, but in the past decade, *Aspergillus* has become more common.[31] *Alternaria* species and *Pseudallescheria boydii* have also been identified in IFRS. *Aspergillus* is particularly common in diabetic persons with IFRS. On examination, however, it is very difficult to distinguish between the two organisms on the basis of clinical presentation or physical examination. IFRS is suspected when the immunocompromised patient demonstrates a fever and localization of symptoms suggesting a complication of sinusitis, such as orbital swelling, change in vision, or significant facial pain. Patients may present with anesthesia of the face, mucosa, or palate and may have nasal bleeding**.** Nasal endoscopy may show necrosis of the nasal mucosa, or there may even be a blackish color, suggesting *Mucormycosis*. If there is significant necrosis, the tissue may not bleed when manipulated or sampled for biopsy. One of the major challenges is that early in the disease it may be difficult to distinguish IFRS from nonfungal or noninvasive fungal causes of rhinosinusitis. On rare occasions oral examination may show invasion through the hard palate from the sinuses.

If the diagnosis of IFRS is suspected, sinus computed tomography (CT) and often magnetic resonance imaging (MRI) should be obtained. Because abnormal sinus radiographic findings are common in immunocompromised patients—up to 42% of patients with leukemia in one series had abnormal sinus radiographs[32]—the suspicion for IFRS should rely on clinical symptoms and findings as well as CT or MRI features. Changes of IFRS seen on sinus CT scans or plain radiographs are usually indistinguishable from those of bacterial rhinosinusitis, although the former may include bony erosion or soft tissue invasion. Cultures help identify the causative organism, and histopathologic evaluation of biopsy or surgical specimens often shows the fungus within and invading tissue. IFRS was once considered nearly universally fatal, but early detection and the maintenance of a high index of suspicion leading to early aggressive medical and surgical treatment have reduced the mortality rate to less than 30%.[31]

Chronic Rhinosinusitis

Because it has become clear that inflammation is the major universal finding in all patients with rhinosinusitis, newer definitions have been developed to describe its types. The definitions are as follows: *Rhinosinusitis* is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses. *Chronic rhinosinusitis* is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration.[1,2,6] Patients with CRS may have intermittent acute flare-ups; in such cases, the disorder is called *acute exacerbation of chronic rhinosinusitis*.[1]

ABRS is a common disorder, the criteria used to make the diagnosis are fairly well established, and the treatment is relatively straightforward. Definitions and subsequent treatment for CRS, however, have been particularly difficult to establish owing to the wide variety of conditions that have been found to be associated with it. Unlike for ABRS, the role of bacteria in CRS is not well supported. Therefore, the use of symptoms to define CRS is not as effective as for ABRS, and the original criteria for the use of clinical symptoms has been largely abandoned for this entity.[2,6]

With this new focus on inflammation, it can be seen that inflammation in the nose and sinuses from a variety of causes can result in sinus ostia obstruction and can predispose to the development of further inflammation or an infection. There are many potential causes of inflammation, and current medical treatment options have been designed to treat the inciting factor, reduce the subsequent inflammatory reaction, or both. Although bacteria, fungi, and viruses can be primary causes of sinus inflammation, they may also occur as secondary infections or even as colonizers of the mucus. Much attention has focused on the host response to the inflammatory precipitant and how it relates to the disease process and progression. A number of cells and proteins have been identified as being involved with the nasal-sinus inflammatory response. This is particularly true in CRS, in which eosinophils, interleukins, neutrophils, mast cells, T and B cells, immunoglobulins, tumor necrosis factor, major basic protein, along with a host of other mediators of inflammation have been identified and may play important roles in selective patients. In addition, other factors have also been identified that may participate in the development or perpetuation of CRS. These include bacterial biofilms, superantigens, and osteitis.[2,6,33-35]

One of the major problems with identifying the pathogenesis of CRS is that neither symptoms, findings, nor radiographs, taken independently, are sufficient basis for the diagnosis. One study showed that current symptom-based criteria had only a 47% correlation with a positive CT scan result.[36] Furthermore, in patients who have sinus disease, objective patient-based descriptions and measures do not correlate with the severity of CT findings.[37] Bhattacharyya and Fried[38] performed CT in two group of patients who had been evaluated with an established grading scale for disease severity. One group had been diagnosed with CRS and were to undergo surgery; the other group,

control patients, did not have sinus disease. These researchers found that CT scans exhibited good sensitivity and specificity for CRS, but only at the 85% and 59% levels, respectively. There are also a number of conditions that have been found to clinically masquerade as CRS. These include rhinitis, laryngitis associated with reflux, and headaches.[39,40]

To discuss all the potential pathophysiologic mechanisms that may play a role in the development or perpetuation of sinusitis is beyond the scope of this chapter; they are listed in Box 47-2. The multiple theories related to pathophysiology have been well discussed in other reports.[2,6] Given the definition suggesting that the key criteria is an inflammatory reaction, any mechanism that can cause inflammation in the nose and sinuses could theoretically lead to CRS. Trying to identify the pathophysiologic mechanisms in CRS has been very difficult for a number of reasons. The first is that there were no well-accepted definition or criteria for the diagnosis until the Sinus and Allergy Health Partnership report, published in 2003.[2] The second is that knowledge of this disease is still dramatically evolving, thereby complicating identification of the mechanisms resulting in the disease. Another significant reason is that there has been a tendency to try to identify a single, unified etiology for all cases of CRS. On the new definitions of this entity as "a group of disorders," such a unified concept may not be easily identified or perhaps even possible. Some pathophysiologic mechanisms are becoming more established.

It is fairly well established that CRS may be associated with bacterial infection. Whether the bacteria play a role in the disease via a classic infectious mechanism, a mechanism related to inflammation, or both, is not yet known, but in some patients, eradication of the bacteria improves symptoms or can even resolve the CRS. Although the bacteria involved in ABRS are well established, studies looking at the bacteriology of CRS have revealed significant differences in the microbial pathogens present. *S. pneumoniae* and *H. influenzae* are often identified in CRS, but in much lower concentrations. Rather, a number of other bacteria are commonly found. *S. aureus*, coagulase-negative staphylococci, as well as anaerobic and gram-negative bacteria, are frequently reported.[2,41-43] Whether or not these bacteria have their relationship with the chronic inflammation via a classic infectious process or through an allergic or inflammatory mechanism is debated. For whatever reason, many cases respond to antibiotic therapy, prompting an interest in the role of the anti-inflammatory properties of certain classes of antibiotics such as the macrolides.

One of the other mechanisms by which bacteria may participate in the pathogenesis in CRS may be the ability of some organisms to release exotoxins or bacterial "superantigens." For example, *S. aureus* can release exotoxins, which can be pathogenic and cause significant, sometimes life-threatening, reactions in humans.[44] *Superantigens* are a group of proteins or particles produced by bacteria that can elicit an aggressive inflammatory response.[2,6,34,41,44,45] It has been proposed that exotoxins can also be released locally into the tissues and elicit a local inflammatory response without resulting in the overwhelming systemic effects seen in toxic shock syndrome. Such could be the case in CRS, in which bacteria could release exotoxins that cause inflammation.[2,34,45] This inflammation is not due to a classic infectious response, although it may occur as a secondary effect once there has been a breakdown in the mucosa and local defense mechanisms allowing for bacterial invasion, colonization, and infection.

Another area in which bacteria have been implicated in CRS is through the interaction with bacterial biofilms.[2,35,46] Bacterial *biofilms* are defined as "an assemblage of microbial cells enclosed in a self-produced polymeric matrix that is irreversibly associated … with an inert or living surface."[35] Biofilms do appear to be present in a large number of patients with CRS. One study reported that biofilms were identified in specimens from 80% of patients undergoing surgery for CRS.[46] The role of biofilms is not yet established, but there is growing interest in methods to break up biofilms as a treatment for CRS. Another proposed pathophysiologic mechanism is the effect of osteitis on the perpetuation of the chronic inflammatory response.[47,48] Although most workers now believe that the osteitic changes noted are a secondary reaction to the inciting inflammatory precipitant, these changes may either play some role in prevention of the response to treatment or increase the likelihood of recurrence.

Just as with ABRS, one of the factors that appears to be associated with CRS is allergy (Fig. 47-2). There seems to be an increasing rec-

Box 47-2

Factors Associated with Chronic Rhinosinusitis

Host Factors

Systemic

Allergic/immunologic
Genetic/congenital
Mucociliary dysfunction
Endocrine
Neuromechanism

Local

Anatomic
Neoplastic
Acquired mucociliary dysfunction

Environmental

Microorganisms:
- Viral
- Bacterial
- Fungal

Trauma
Noxious chemicals/pollutants/smoke
Iatrogenic
Medications
Surgery

From Benninger MS, Ferguson BJ, Hadley JA, et al.; Sinus and Allergy Health Partnership. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg.* 2003;129:S1-S32.

Figure 47-2. Computed tomography scan of sinuses in a patient with allergic fungal rhinosinusitis in whom a mucocele with extension into the left orbit has developed.

ognition of the relationship between allergies, particularly allergic rhinitis and CRS.[2,9,49] A direct cause-and-effect relationship has not been established, but in theory, allergies can cause inflammation that, if it persists long enough, can manifest as CRS. The prevalence of allergy in patients with CRS has been reported from 25% to 50%, which is greater than would be expected in the general population.[2] Allergy could potentially lead to CRS through a number of different mechanisms, including allergy-induced inflammation alone or obstruction of the sinus ostia from nasal inflammation and swelling leading to infection. It is also possible that allergies induce neurogenic stimulation or predispose to secondary bacterial or fungal infection independent of an obstructive mechanism.[2,50] There is also a strong relationship between asthma, CRS, allergy, and, in some cases, aspirin hypersensitivity. This finding would support the suggestion that some people suffer from a more diffuse hyperactive airway disease, or common unified airway, which involves both the upper and lower airways. Such patients also seem to be more prone to other mucosal inflammatory conditions, such as acute or chronic otitis media.

A number of other inflammatory participants play a role in the development of CRS. In addition, it has been suggested that anatomic variants may predispose to earlier obstruction of the sinuses, allowing for the development of CRS, although strong evidence is lacking. One area of growing interest is the effect of inflammation caused by environmental irritants, such as industrial pollution, on secondary environmental tobacco exposure (ETS). ETS is becoming more strongly associated with a number of airway conditions, including asthma and acute and chronic rhinosinusitis and rhinitis.[7,51] Although epidemiologically it may be difficult to control for such exposures, stronger associations are being identified.[51] The Sinus and Allergy Health Partnership's Task Force on Chronic Rhinosinusitis identified a large number of systemic host, local, and environmental factors that have been suggested to play a role in CRS; and they are listed in Box 47-2.[2]

One of the more widely explored theories for the pathogenesis of CRS is the role of fungi.[2,6,33,41,52-55] There are likely a number of different ways that fungi can play a role in CRS. For some patients with chronic sinus disease, obstruction of the sinuses can lead to an accumulation of mucus and debris along with noninvasive fungal colonization in the sinuses. This fungal colonization is readily amenable to surgical removal, and these patients usually have good outcomes with no long-term inflammatory sequelae.

Another group of patients have fungal disease secondary to a more classic type I, immunoglobulin (Ig) E–mediated hypersensitivity reaction or more classic allergic (atopic) disease.[53,54] These patients have "allergic fungal sinusitis" (AFS) (see Fig. 47-2). AFS is identified in patients who demonstrate five characteristics features with nasal polyps, eosinophilic mucin containing noninvasive fungal hyphae, characteristic radiographic findings, particularly on CT scans, allergy, and immunocompetence.[6,52,53,55] There are therefore patients who are hyperresponsive to fungi through this IgE-mediated reaction.

There are other mechanisms by which fungi can participate in or are related to the development of CRS. In some patients, an inflammatory response to fungi develops through a non-IgE mechanism. In some cases this may be due to a type III (immune-complex) hypersensitivity reaction.[2,6,33,52,56] It has been found that fungus can be cultured from the noses of almost all people.[33,56] People, therefore, are continually exposed to fungi. In most people, colonization by fungi does not result in any noticeable reaction or inflammation. There is a small subset of individuals, however, who have a more intense inflammatory reaction that is believed to be a response to the presence of the fungus.[6,33,52,56,57] In such cases, eosinophils appear to play a very important role in this reaction, prompting recommendation of a new term, "eosinophilic fungal sinusitis."[33,56,57] It has been proposed that this eosinophilic reaction to fungi may play an important role in nearly all episodes of CRS. With the multiple potential etiologic or associated conditions recognized with CRS, this assumption of a common fungal etiology would seem a significant simplification and may be important in only a selective group of patients with CRS.

The role of the eosinophil, however, may be much more important than previously recognized.[2,33,53,54,56,57] Whether through classic type I hypersensitivity, eosinophilic reaction to bacteria, viruses, or fungi, or as a common inflammatory step, eosinophilic inflammation is being recognized as being involved in a majority of cases of CRS.[2] Some workers speculate that "eosinophilic inflammation may occur as a common pathway in response to a number of different inflammatory starting points."[54] The studies in fungal rhinosinusitis may have helped not only to create a great interest in the role of fungi but also to have substantially improved the understanding of the various inflammatory mediators involved with CRS.

Acute Exacerbation of Chronic Rhinosinusitis

Acute exacerbation of chronic rhinosinusitis is used to describe an acute flare-up in a patient with CRS. Oftentimes, their persistent but somewhat stable symptoms become acutely worse, usually with an increased production of nasal mucus, which may become more purulent, increased nasal congestion, further loss of smell, and associated systemic symptoms such as fatigue, malaise, and even fever. AECRS is a sudden worsening of the baseline CRS symptoms (Fig. 47-3).[58,59] In such cases, there may be a change in the bacteriology of the disease, so that a blend of bacteria is seen in both CRS and ABRS. Whereas ABRS is associated with primarily aerobic organisms and CRS with a high proportion of gram-negative organisms and anaerobes, AECRS is associated with both. There is an increase in the numbers of the common ABRS organisms, such as *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* but with a large percentage of anaerobic organisms such as *Peptostreptococcus* species and *Fusobacterium*. Although the effectiveness of antibiotics in CRS is debatable, antibiotics that cover both the common ABRS and CRS organisms are effective in reducing the exacerbation of AECRS. Aggressive anti-inflammatory agents such as systemic steroids may also be necessary. With acute treatment, patients tend to return to their "steady CRS state" following the exacerbation.

Summary

The pathogenesis of rhinosinusitis largely depends on the classification of the rhinosinusitis. Environmental factors such as allergy, smoke, and chronic irritants appear to predispose to any episode. Viruses and aerobic bacteria are the major causes of ABRS. Invasive fungal sinusitis occurs in immunocompromised hosts and is largely secondary to

Figure 47-3. Computed tomography scan from a patient with acute exacerbation of chronic rhinosinusitis. The scan shows evidence of mucosal hypertrophy in both maxillary sinuses and left ethmoid but also air-fluid levels in the left maxillary sinus.

Mucormycosis and *Aspergillus*. Chronic rhinosinusitis is a disease with a heterogeneous group of potential causes or associated etiologic factors. In any individual host, there may also be more than one factor. Bacteria, fungi, allergies, biofilms, osteitis, and superantigens, along with a number of other factors, have been implicated. There is also a group of patients who have diffuse inflammatory upper and lower inflammatory disease associated with CRS. Currently, no single common pathway or etiology can be associated with CRS. Acute exacerbation of CRS is a sudden and severe change in symptoms from baseline. This is generally associated with an increase of pathogenic bacteria, both aerobic and anaerobic. The investigation of the pathogenesis of rhinosinusitis is very dynamic and will likely continue to evolve for some time to come.

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CHAPTER FORTY-EIGHT

Fungal Rhinosinusitis

Berrylin J. Ferguson

Key Points

- Categorization of fungal rhinosinusitis as acute invasive, chronic invasive, fungus ball, allergic fungal, or nonallergic eosinophilic fungal rhinosinusitis has important prognostic and management implications.
- The early CT findings in acute invasive fungal rhinosinusitis are nonspecific and similar to those in rhinosinusitis of nonfungal cause.
- Invasive mucormycosis is most common in patients in diabetic ketoacidosis.
- The earliest symptom of mucormycosis is often anesthesia of the nose, followed by rapid development of ischemic darkened mucosa.
- Rapid diagnosis of invasive fungal rhinosinusitis in the immunocompromised patient, with the use of immediate fungal staining, culture, and biopsy, if possible, is critical to rapid implementation of therapy.
- The treatment of invasive fungal rhinosinusitis is reversal of the source of immunocompromise, appropriate antifungal therapy, and directed surgery.
- Paranasal sinus fungus balls may show as calcifications on CT.
- The treatment of sinus fungus balls is removal by endoscopic surgery.
- Allergic fungal rhinosinusitis is diagnosed histopathologically from the finding of eosinophilic mucin plugs containing fungal hyphae in patients with an elevation of immunoglobulin E antibodies specific to the cultured fungus.
- The treatment of allergic fungal rhinosinusitis is endoscopic surgical removal of allergic mucin and polyps and systemic steroid therapy. Systemic or topical antifungals may have a role, but evidence for their effectiveness is weak. Immunotherapy may be indicated after surgical removal of all allergic mucin.
- Nonallergic eosinophilic fungal rhinosinusitis is a controversial category of disease for which topical antifungals have to date shown no benefit in well-designed trials that excluded patients with allergic fungal rhinosinusitis.

Fungal rhinosinusitis can be categorized as invasive or noninvasive on the basis of histopathology. These manifestations also depend on the host's immunologic health. Acute invasive fungal rhinosinusitis occurs in patients with severe immunologic compromise, whereas chronic invasive and the noninvasive forms occur in patients with intact immune systems. Noninvasive forms of fungal rhinosinusitis include fungus balls (in which the immune system is neither over- nor under-responsive) and eosinophilic fungal sinus disease (which is secondary to an over-responsiveness, either allergic or nonallergic, to fungus). These noninvasive eosinophilic manifestations are subdivided into allergic fungal rhinosinusitis (AFRS) and nonallergic eosinophilic fungal rhinosinusitis (NA-EFRS). This latter category, introduced in the late 1990s, is controversial because its proponents contend that fungi mediate a nonallergic eosinophilic immunologic response that is the basis for almost all sinus disease (Table 48-1).

In describing fungal rhinosinusitis, it is important to use the category that best describes the manifestation, because the prognosis and therapy are different for the various manifestations. The specific fungal species causing the disease is less important than the host's immunologic response or nonresponse to it. Determining the fungal species through fungal culture aids in antifungal selection and is particularly important for those fungal manifestations responsive to antifungal therapy.

Invasive Fungal Rhinosinusitis

Acute Invasive Fungal Rhinosinusitis

Also called fulminant or rapidly invasive fungal rhinosinusitis, acute invasive fungal rhinosinusitis is almost always confined to the patient with altered host defenses, such as a patient undergoing transplantation, a diabetic patient in ketoacidosis, or a patient with leukemia. As the name implies, the time course is rapid and on histopathologic inspection shows the fungus invading tissue (Fig. 48-1). Invasive fungal rhinosinusitis is suspected when the immunocompromised patient demonstrates a fever and localization of symptoms to the nose or paranasal sinus area, such as orbital swelling, facial pain, or nasal congestion. Nasal endoscopy may show necrosis of the nasal mucosa, which is indicative of mucormycosis, and, in rare situations, actual fungal sporulation. It is more usual to note only edema and changes indistinguishable from those seen in rhinosinusitis from nonfungal causes.

The most common invasive fungal species in both the acute invasive and the indolent or chronic invasive forms of fungal rhinosinusitis varies geographically but is usually an *Aspergillus* species, frequently *Aspergillus fumigatus* or *Aspergillus flavus*. However, many species can become invasive in the setting of immunocompromise, including *Scedosporium apiospermum* or *Pseudallescheria boydii, Fusarium,* the Zygomycetes (which cause mucormycosis), and even, rarely, Basidiomycetes

(mushrooms).[1] With mucormycosis, anesthesia of the nasal mucosa or cheeks, independent of topical anesthetics, is common and precedes the onset of ischemic darkened necrosis of the nasal cavity. The oral cavity should always be examined for invasion through the hard palate from the nose. If the diagnosis is suspected, sinus computed tomography (CT) should be obtained. Changes seen on sinus CT scans or plain radiographs usually are indistinguishable from those in other causes of rhinosinusitis, although in advanced disease, CT may show bony erosion or soft tissue invasion. Unfortunately, abnormal imaging findings are common in immunocompromised patients. Up to 42% of patients with leukemia in one series, for example, had abnormal sinus radiographic findings.[2]

Fungal infections in the at-risk population of severely neutropenic patients, such as those undergoing bone marrow transplantation, can be reduced by preventing fungal exposure with the use of high-efficiency particulate air filter systems and by eliminating fungal sources such as potted plants.

Aspergillus

The *Aspergillus* species most commonly responsible for invasive disease in the United States is *A. fumigatus*. *A. flavus* is commonly associated with the more indolent, chronic invasive fungal disease seen primarily in the Sudan and in India, but it can also be responsible for fulminant invasive disease regardless of geographic location.[3] Therapies and prognosis do not differ among *Aspergillus* species. *Aspergillus* species can be angioinvasive, but they do not cause the obliterative invasion seen with mucormycosis. Hemorrhagic infarcts can be seen if there is cerebral involvement.[4]

Table 48-1

The Manifestations of Fungal Rhinosinusitis According to Host Immunologic Status

Host Immunologic Status	Manifestation of Fungal Rhinosinusitis
Immunodeficient	Invasive, acute Invasive, chronic
Immunocompetent	Invasive, granulomatous Fungus ball
Allergic or altered cell-mediated hyperresponsiveness	Allergic fungal rhinosinusitis (AFRS) Nonallergic eosinophilic fungal rhinosinusitis (NA-EFRS)

Mucormycosis

Mucormycosis is a term commonly used to designate all fungal species within the order Mucorales in the class of the Zygomycetes. The most virulent and common species is *Rhizopus oryzae*. Mucormycosis has earned the reputation as the most acutely fatal fungal infection known to humans. It is rapidly growing, and within 24 hours, cultures of *Mucor* species can grow to the top of the culture plate. It is important, if the diagnosis is suspected, that the suspicion be acted on immediately. *Mucor* has a propensity for vascular invasion and obliteration leading to ischemia. Unusual species in the family, such as *Apophysomyces elegans*, may afflict the immunocompetent patient, but usual treatment is curative.[5,6]

The growth of *Mucor* is facilitated by acidotic conditions, and as the fungus grows, it facilitates its propagation by this vascular invasion, leading to ischemia. The use of hyperbaric oxygen in this setting is theoretically attractive because it reduces the ischemia and acidosis, but no controlled studies have shown its efficacy. Hyperbaric oxygen is a relatively benign therapeutic option, and in these life-threatening situations it can be added to the therapeutic regimen. Patients with poorly controlled diabetes, particularly with diabetic ketoacidosis, are uniquely at risk for invasive mucormycosis. Normal human serum can inhibit the growth of *Rhizopus* (the most virulent of the species within the order Mucorales), but the serum of patients with diabetic ketoacidosis actually may enhance fungal growth.[7,8] The mechanism of this increased susceptibility to mucormycosis may be attributable to altered transferrin binding in diabetic patients, which makes iron more readily available.[9] Patients receiving renal dialysis and deferoxamine also are at higher risk for mucormycosis.[10] The importance of iron in the physiology of invasive mucormycosis is demonstrated in clinical scenarios and in vitro studies, although the growth of *Aspergillus* or *Candida* is affected to a much lesser degree by the availability of iron.[11] Other causes of immunocompromise also lead to mucormycosis, including defects or reduction in neutrophils and the immunosuppression caused by steroids. Unlike leukemia or bone marrow failure, diabetic ketoacidosis is readily reversed. The survival rates in those with invasive mucormycosis reflect the variation in ability to reverse the underlying predisposing cause. Up to 80% of diabetic patients survive the disease, whereas less than 50% of nondiabetic patients do so.[12]

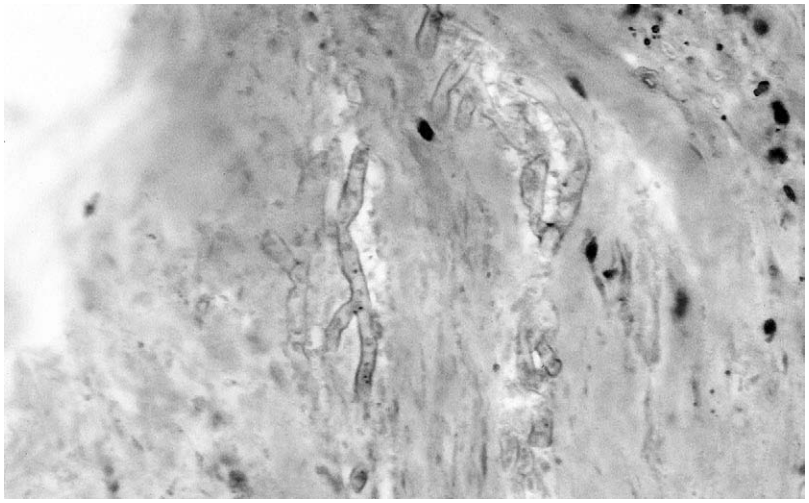

Figure 48-1. Histopathologic section demonstrating invasive fungal rhinosinusitis on frozen section in a patient with leukemia. Subsequent cultures grew an *Aspergillus* species. Note that some of the hyphae appear swollen, suggesting mucormycosis; this is an artifact of the frozen section. The 45-degree branching typical of *Aspergillus* species and septated hyphae are present.

Chronic or Indolent Invasive Fungal Rhinosinusitis

Chronic, also known as indolent, invasive fungal rhinosinusitis more frequently occurs in patients with no or with limited immunocompromise. Symptoms are slowly progressive over many weeks to months, in contradistinction to the rapidly fatal course of untreated acute invasive fungal rhinosinusitis. The diagnosis of chronic invasive rhinosinusitis should be suspected in patients with any element of immunocompromise or with complications of rhinosinusitis such as cranial neuropathy or orbital extension. Chronic invasive fungal rhinosinusitis is rare. It has been detailed most compellingly in articles from the Sudan, where the pathogenic organism was always *A. flavus*. The histologic picture is that of a granuloma in which giant cells contain the hyphae. In this setting, immunocompetent patients present with painless proptosis.[13] Other fungal species that can cause an indolent invasive fungal rhinosinusitis with extension to the orbit or palate are *A. fumigatus*,[14] *Alternaria*,[15] *P. boydii, Sporothrix schenckii*,[16] and *Bipolaris* species.[16] The host is seemingly immunocompetent, and the disease course is variable. In some patients, surgical exenteration is curative, and in others, the disease is relentless despite multiple therapies, including systemic antifungal drugs and surgery, and may end in blindness, cerebral extension, or death.[17] Patients who live in Africa or India are disproportionally afflicted with granulomatous invasive fungal rhinosinusitis.

Therapy and prognosis are currently the same for both granulomatous and nongranulomatous forms of chronic invasive fungal rhinosinusitis. Therapy usually involves surgery and antifungal therapy. Very few centers perform fungal cultures with determination of antifungal sensitivities. Culture specimens can be sent to the University of Texas Fungus Testing Laboratory at the University of Texas Health Science Center in San Antonio for determination of sensitivity to various antifungal agents. In the United States, nongranulomatous chronic invasive rhinosinusitis is more common, but still rare. Usually there is no identifiable immunodeficiency.[15,18]

Diagnosis

Biopsy of the suspected tissue for pathology and culture is critical to making the diagnosis of invasive fungal rhinosinusitis. Histopathologic findings of hyphae within tissue establish the diagnosis of invasive fungal rhinosinusitis, with detection enhanced by the use of special stains for fungus. Fungal culture specimens should be obtained, preferably before the initiation of systemic antifungal therapy. Initiation of therapy, prior to culture, decreases the likelihood that the fungus will grow on culture. It is critical that the diagnosis, once suspected, be made as quickly as possible. Therefore, a frozen section of the pathologic specimen or evaluation of the material submitted for culture by immediate fungal stains, such as calcofluor white (Fig. 48-2) should be requested, and if results of either of these examinations are positive for fungus, appropriate antifungal therapy and extended surgical resection can be initiated without delay.[19]

Neither frozen section of the involved tissue nor special stains for fungus will definitively distinguish between fungal species, although mucormycosis can be suspected if the fungal elements seen are broad ribbon–like (10 to 15 µm), irregular, and rarely septated (Fig. 48-3). The artifacts of frozen section may cause *Aspergillus* hypha elements to appear swollen and similar to those of mucormycosis. Generally, the distinction between mucormycosis and *Aspergillus* species can be made on permanent histopathologic sections. The *Aspergillus* species demonstrate more narrow hyphae with regular septations and 45-degree branching on histopathology (Fig. 48-4). Cultures are important for distinguishing *Aspergillus* species from less common pathogenic fungal species that are septated, such as *Fusarium, Alternaria,* and *P. boydii*.[20]

The pseudohyphae in *Candida* infections are distinct from the true hyphae of fungal species, although the ubiquity of *Candida* requires either the presence of a large number of organisms on culture or deep rather than superficial invasion of the tissues to distinguish saprophytic *Candida* growth from invasive *Candida* fungal infection.

Therapy

Therapy of invasive fungal rhinosinusitis requires reversal of the underlying predisposing condition, appropriate systemic antifungal therapy, and surgical débridement. Of these, the most important is reversal of the underlying cause of immunocompromise.[21] If the source of immunocompromise is profound and irreversible, the treatment will not be successful, and mutilating and painful adjuncts should be avoided. Some patients may benefit from infusion of granulocytes in an attempt to reverse immunocompromise, although reports of this procedure are anecdotal.

Invasive fungal rhinosinusitis in the immunocompetent patient is rare and the course is generally chronic, although it may still be lethal.

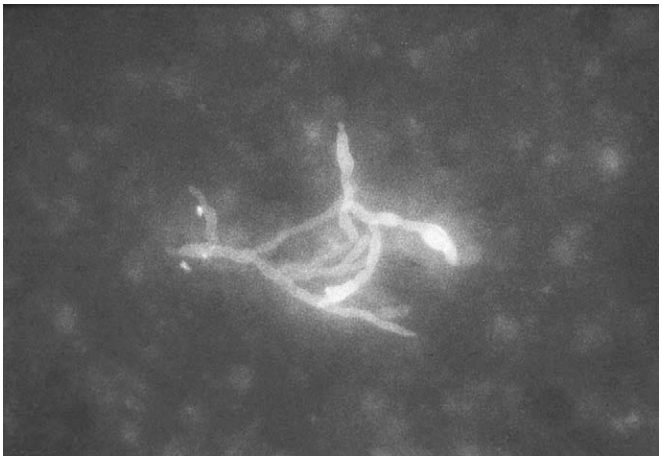

Figure 48-2. Calcofluor white stain demonstrating hyphal elements. This immunofluorescent stain can be used for immediate identification of fungal elements.

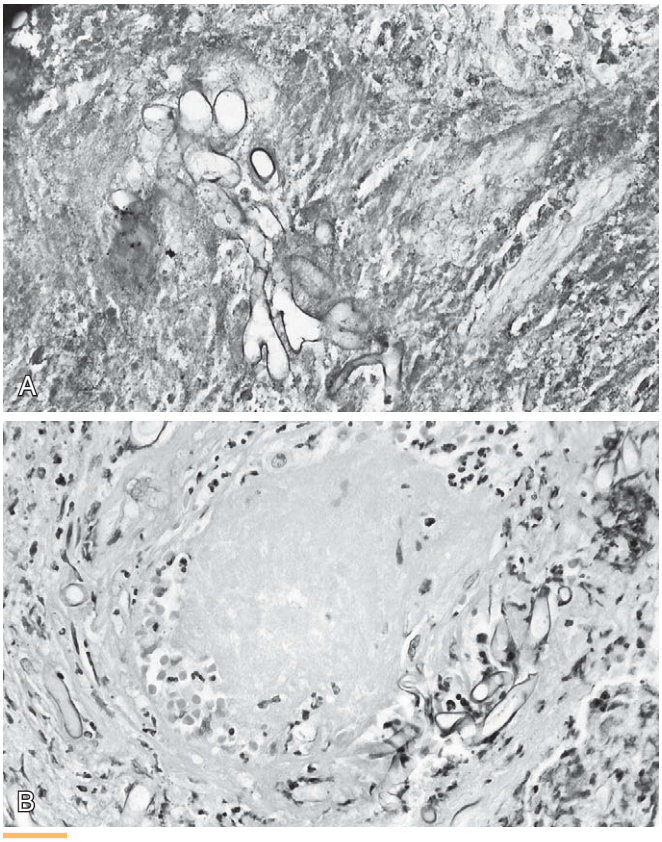

Figure 48-3. **A,** Mucormycosis on histopathologic section demonstrating broad hyphae (periodic acid–Schiff stain). **B,** The hyphae of mucormycosis can be seen invading the vessel wall. The vessel is thrombosed (hematoxylin-eosin stain).

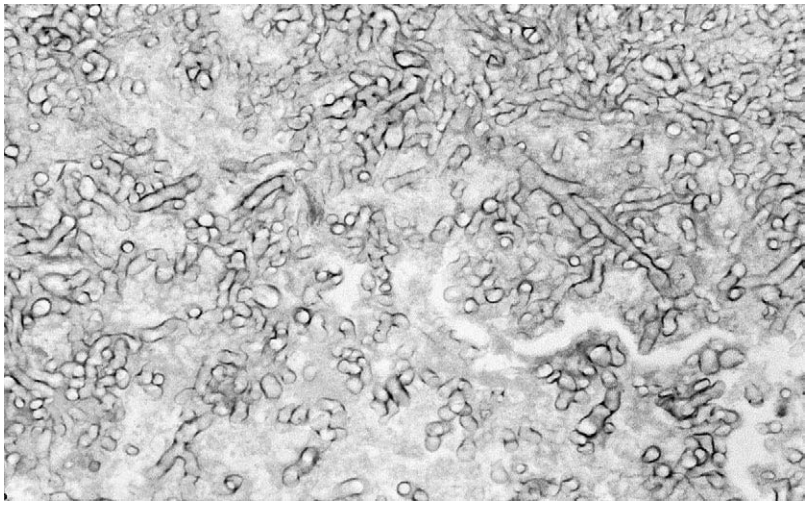

Figure 48-4. Fungus ball showing hyphae of *Aspergillus*. The entire specimen was composed of a tangled mass of hyphae. No tissue invasion was seen.

The therapy for chronic invasive fungal rhinosinusitis, both granulomatous and nongranulomatous, is similar to that for acute invasive fungal rhinosinusitis, except for correction of immunodeficiency.[16,22] Management includes endoscopic débridement, often on multiple successive occasions, combined with both systemic and topical antifungal therapies targeted to the sensitivities of the fungus isolated. This approach has largely replaced external surgical approaches. External débridement may be required for orbital exenteration or if bleeding precludes endoscopic diagnosis and débridement.[23]

For the majority of patients with invasive fungal rhinosinusitis, systemic amphotericin B continues to be the drug of choice, at intravenous doses of 0.6 to 1.0 mg/kg/day until a favorable response is seen, up to a total dose of up to 3 g. Nephrotoxicity, the major dose-limiting complication, can be reduced with sodium loading. Fever, chills, nausea, and hypotension frequently accompany the first few doses. These toxicities can be reduced or eliminated with the use of amphotericin B lipid complex, which is amphotericin B delivered through liposomes. The usual starting dose is 5 mg/kg daily. The liposomes have an affinity for the reticuloendothelial system and so bypass tissues that would otherwise be affected by amphotericin B toxicity. Certain fungi also respond to other antifungal agents, so occasionally another antifungal agent is the drug of choice. Approximately half the cases of invasive *Aspergillus* infections in one series were salvaged with itraconazole.[24] Table 48-2 lists the various fungal agents commonly used to treat fungal rhinosinusitis.

Voriconazole is not approved by the U.S. Food and Drug Administration for invasive fungal rhinosinusitis; however, success has been reported with its use in chronic invasive fungal rhinosinusitis.[25]

Posaconazole also is not approved for fungal rhinosinusitis, but its efficacy in *Mucor* rhinosinusitis and *Aspergillus* rhinosinusitis has been reported, and this agent may well become the antifungal of choice for mucormycosis in the future.[26] Because posaconazole is an oral agent, it is also an option for step-down therapy from IV amphotericin B.

Fungus Balls of the Paranasal Sinuses

Paranasal sinus fungal balls are common and grow in the wet, moist cavities of the paranasal sinuses of a host with normal immunologic status. In a patient who is immunocompromised by systemic steroid therapy or, occasionally, by surgical abrasion, it is possible for a previously contained fungal growth to become invasive. Paranasal fungus balls cause symptoms indistinguishable from those of chronic rhinosinusitis or may be asymptomatic and discovered incidentally. Figure 48-4 shows the tangled hyphae characteristic of a fungus ball in histologic examination. At surgery, the gross appearance of a fungus ball is that of a darkened, often crumbly mass, occasionally with visible sporulation. This characteristic gross appearance has a positive predictive value of 100% for histologic appearance of a fungus ball and a very high negative predictive power as well (Table 48-3).[27]

The term "mycetoma" has been incorrectly used to refer to paranasal fungus balls; in fact, *mycetoma* is a fistulous fungal skin infection. A variety of fungal species cause fungus balls, including *A. flavus, A. fumigatus, Alternaria*,[3] and *Mucor*.[28]

CT findings of metallic or calcified densities within an opacified sinus cavity have a positive predictive power of around 60% for a fungus ball and a high negative predictive power. Thus mycologic and histologic studies are essential to confirm the diagnosis (see Table 48-3).[27] A sinus CT scan demonstrating characteristic calcifications of a fungus ball is shown in Figure 48-5.

Nongrowth on fungal culture can occur in more than 30% of specimens, even though histologic evidence of hyphae is present on pathology. In one of the largest series to date of patients with paranasal sinus fungus balls in central France, the majority of fungus balls were in the maxillary sinus and the usual fungal organism was an *Aspergillus* species. Treatment by endoscopic surgical removal was successful in 172 of 173 of the cases.[29]

Ferreiro and colleagues[30] reported death as a surgical complication in some cases of sphenoid sinus fungus balls.

Saprophytic Fungal Infection

Saprophytic fungal infections occur when ubiquitous fungal spores land and germinate on mucous crusts, which fail to clear the sinonasal cavity. This development is commonly seen after sinonasal surgery. The treatment is removal of the crust supplying the substrate on which the fungal spores are growing. These spore-encrusted, hardened mucous secretions can frequently be removed by nasal cleaning or nose blowing, and no further therapy is required.

Allergic Fungal Rhinosinusitis

Allergic fungal sinusitis or rhinosinusitis (AFRS) was described first in 1981 by Millar and colleagues[31] and then in 1983 by Katzenstein and associates,[32] who detailed the unique histopathologic findings. Both groups recognized the histologic similarity of AFRS to the previously described allergic bronchopulmonary aspergillosis (ABPA). AFRS is considered a sinonasal form of ABPA. The diagnosis is made histopathologically from the finding of an allergic mucin characterized by necrotic inflammatory cells, eosinophils, and Charcot-Leyden crystals (a by-product of eosinophil degranulation). In this allergic mucin are hyphal elements usually best appreciated with fungal stains.[33] Culture of the allergic mucin reveals a variety of fungal species. Associated fungal causes vary geographically. In North America most cases of AFRS are caused by dematiaceous or pigment-producing species, such as *Bipolaris*, *Exserohilum robustum*, *Curvularia lunata*, and *Alternaria*.

Table 48-2

Antifungal Agents Commonly Used in the Treatment of Fungal Rhinosinusitis

Antifungal	Dosage	Activity	Comments
Amphotericin B IV, lipid and non-lipid	0.25 up to 1.0 mg/kg qd IV in 5% dextrose; dose varies with lipid formulation	Active against most pathogenic fungi; variably active against some *Aspergillus* species and Zygomycetes; *Pseudallescheria boydii* and *Fusarium* species are resistant	Nephrotoxicity reduced with more expensive lipid formulations
Amphotericin B topical	100 µg/mL, 20 mL bid	As above	Not absorbed via oral route; unproven efficacy in noninvasive fungal rhinosinusitis
Itraconazole	100 mg 1-2 po bid with meals	Active against many dematiaceous fungi; variably active against *Aspergillus* species; not active against Zygomycetes	Best absorbed in acidic stomach; co-administer with cola or cranberry juice; if used long term, liver function must be monitored
Posaconazole	Oral suspension of 40 mg/mL; dosage is 400 mg bid, given with fatty foods to enhance absorption	Indicated for the treatment of a broad range of invasive fungal infections, including Zygomycetes, *Fusarium*, and *Aspergillus,* in patients who have refractory infections or cannot tolerate other antifungal therapies	Safety in patients younger than 18 years not assessed; use with caution with other drugs metabolized through the cytochrome-P3A4 system
Terbinafine	250 mg po qd	Variable in vivo anti-fungal activity; utilized chiefly for dermatophytosis	Not effective in a randomized controlled trial against noninvasive chronic rhinosinusitis[55]
Voriconazole	200 mg bid po 1 hour before or after meals; IV formulation given as loading dose, followed by 4 mg/kg bid	Indicated for treatment of a broad range of fungal pathogens	Liver function and creatinine must be monitored; unusual adverse effect is visual disturbance

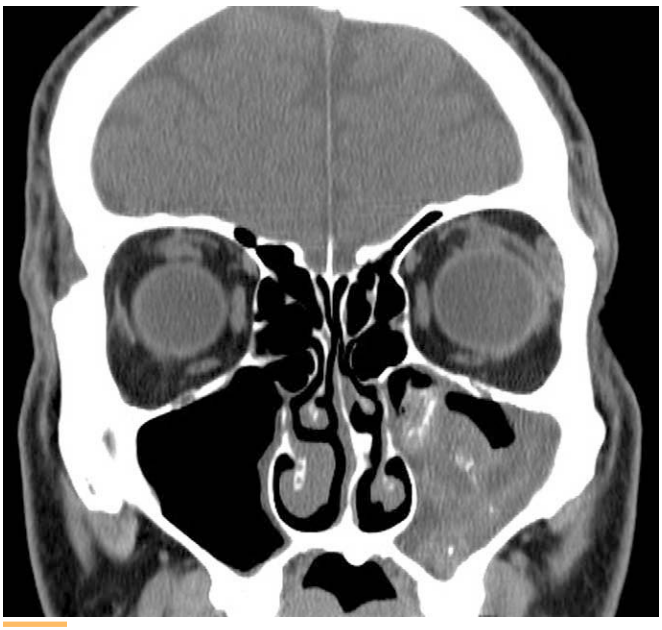

Figure 48-5. Coronal sinus computed tomography (CT) scan demonstrating calcifications within the partially opacified left maxillary sinus consistent with a maxillary sinus fungus ball.

In northern India the majority of AFRS cases are caused by *A. flavus*, and in the Persian Gulf countries, *Aspergillus* species predominate.

The most rigorous criteria for the diagnosis of AFRS require elevation of immunoglobulin (Ig) E antibodies specific to the fungus found on culture of the eosinophilic mucin containing the fungus. There must be no evidence of fungal invasion. Cases of fungal rhinosinusitis with absence of any of these criteria fall into a less well-defined category NA-EFRS.[34]

The therapy and prognosis of patients with AFRS is independent of the fungal species cultured. Clinically, patients with AFRS are atopic and have nasal polyps. Up to 40% of patients with AFRS have asthma, which usually is mild. Many of these patients have undergone multiple nasal polypectomies. On sinus CT, bony erosion is common,[35] and the inspissated mucus causes a heterogeneous soft tissue density (Fig. 48-6).[36]

Epidemiology and Geography

The incidence of AFRS varies geographically.[37] Endemic areas include areas of high humidity in the United States along the Mississippi River and in the South, in Northern India (51% occurrence in patients undergoing sinus surgery), Adelaide, Australia (8.6% occurrence in patients undergoing sinus surgery),[7,38] and areas of the Persian Gulf. In 1998 the highest reported rate in the United States was in Memphis, Tennessee, where 20% of surgical endoscopic sinus procedures were performed for AFRS. Most telling is the absence of AFRS in certain regions, such as the Northwestern part of the United States, where the climate is cooler. The presence of mold spores is necessary for AFRS

Figure 48-6. Axial CT scan of a patient with allergic fungal rhinosinusitis. Note the heterogeneity of densities in the ethmoid and bony erosion of the right lamina papyracea and the posterior wall of the sphenoid.

Table 48-3

Presence of Fungus Balls, Correlated with Computed Tomography Findings and Gross Operative Appearance

	Presence of Fungus Ball*	Absence of Fungus Ball*
Computed tomography findings: Hyperdensities/calcium, ferritin (positive for fungus ball)	32	9
Negative for fungus ball	20	1129
Operative appearance: Positive for fungus ball	52	11
Negative for fungus ball	0	1127

*As confirmed by pathology.
Adapted from Dhong HJ, Jung JY, Park JH: Diagnostic accuracy in sinus fungus balls: CT scan and operative findings. *Am J Rhinol.* 2000;14:227.

to occur. Outdoor mold spore counts vary widely geographically and seasonally.

Pathophysiology

The development of AFRS requires that an individual genetically predisposed to fungal allergy be exposed by inhalation of the mold spore. The spore must elude mucociliary clearance and expulsion by sneezing or coughing for long enough to allow germination.

It is estimated that an average person inhales 5.7×10^6 spores of various species in a 24-hour period.[39] Occasionally, because of mucociliary transport disruption, dryness, or a large inoculum, the mold spore may not be cleared. Germination increases the antigenicity of the fungus,[40] leading to greater production of allergic mucin in which the fungus continues to grow. A "positive feed-back loop" results, in which growth of the antigenic fungus induces the production of more allergic mucin, which leads to increased growth of antigenic fungus. The sticky allergic mucin resists clearance by normal mucociliary action, and the inflammatory cytokine milieu promotes the growth of nasal polyps. If the mold spore randomly becomes lodged in just one side of the nose, unilateral AFRS develops. The immunology of AFRS includes increases in IgE and IgG antibodies to the specific fungus. With the exception of the *Aspergillus* species, specific IgG to other fungal species is not available commercially. Extreme elevation of total serum IgE is usually present and decreases as the disease is controlled.

Box 48-1

Pathogenesis of Allergic Fungal Rhinosinusitis

Elements Currently Required

Noninvasive fungal growth

Eosinophilic mucin

Type I allergy to the fungus cultured

Elements Probably or Possibly Required

Superantigen from bacterial co-infestation

HLA subtype susceptible to superantigen stimulation

Both ABPA and AFRS are associated with certain class II genes of the major histocompatibility complex (HLA-DR2 and HLA-DR5). Certainly not all patients with AFRS have this genotype and not all patients with this genotype experience either ABPA or AFRS. Schubert and colleagues[41] reported that HLA-DQB1 *03 was a significantly more common finding in patients with AFRS than in those with chronic rhinosinusitis without fungus, although it was more common in both groups than in normal controls. Such a finding is compatible with a role for bacterial superantigen exposure in genetically susceptible patients leading to the nonspecific up-regulation and activation of T cells, which can set the stage for a TH2-mediated reaction to a fungus that may be only incidentally present (Box 48-1).[42]

Therapy

Surgery and Steroids

Treatment of AFRS consists of conservative, nonmutilating surgical removal of the nasal polyps and inspissated allergic mucin, which can usually be accomplished endoscopically. The mucin is tenacious, and the Microdebriders can facilitate the removal. Use of Microdebriders adjacent to areas of orbital or cranial bony dehiscence is dangerous. Even if the surgical resection is incomplete, adjunctive systemic steroid therapy, usually beginning perioperatively at a prednisone dose of 40 to 60 mg for several days with tapering over 2 to 4 weeks, can result in remission. Preoperative systemic steroid therapy may resolve the eosinophilic component of the process, leading to a pathology misdiagnosis of fungus ball. When steroids are withdrawn the eosinophilic context for the fungus usually returns, and a second sampling may yield the histopathologic diagnosis of AFRS.[43]

Unfortunately, the predisposition to this allergic response can result in recurrence. Once large sinus cavity openings have been created, recurrences can often be managed in the office with endoscopic débridement, systemic and topical steroids, and, possibly, antifungal therapy.

Immunotherapy

Initially immunotherapy was considered contraindicated in AFRS because of a theoretical potential to worsen the disease through the formation of immune complexes. Mabry and colleagues[44] initially showed that fungal-specific immunotherapy after endoscopic sinus surgery for AFRS did not cause harm and could lead to improvement within the first several years postoperatively. These researchers found, however, that after 4 to 10 years, remission rates were the same whether or not immunotherapy was given.[45]

Box 48-2

Therapies of Allergic Fungal Rhinosinusitis

Definitely Helpful

Steroids, systemic or topical

Surgery

Nasal lavage

Probably or Possibly Helpful

Immunotherapy

Oral antifungals*

Anti–immunoglobulin E*

Not Helpful or Effect Unclear

Topical amphotericin B

Leukotriene modulators

Calcineurin inhibitors

Antibiotics

*These agents have demonstrated efficacy in allergic bronchopulmonary aspergillosis.

The humanized monoclonal antibody to the Fc portion of IgE, omalizumab, is currently approved for use in patients with severe allergic asthma. There are no reports of its use in patients with AFRS, although I have seen a case that responded within a week of initiation of omalizumab therapy. Also, van der Ent and coworkers[46] reported that a patient with ABPA showed a dramatic and rapid response to a single dose of omalizumab.

Other Modalities

Antibiotics have on occasion been reported to improve AFRS, but there are no trials to support their use for this indication. If AFRS does require the presence of a bacterial superantigen, perhaps antibacterial therapies may be useful, but their role remains to be elucidated. If superantigen stimulation is important, the calcineurin inhibitors may be helpful, as they are in atopic dermatitis, for which picrolimus and tacrolimus have proven efficacy. These agents have not been studied for this indication. Saline lavage also has not been studied for this condition, but it is a prominent tool in most physicians' armamentarium, being used before the application of a topical steroid. Saline irrigations are widely utilized in India for these conditions.

Antifungal therapies are discussed in the section on NA-EFRS. To date no randomized controlled trials of antifungal therapy in patients with classic AFRS have been performed. For the pulmonary equivalent of the disease, ABPA, the antifungal itraconazole, at a dose of 200 mg twice daily for 16 weeks, was shown to significantly improve the disease in a randomized, placebo-controlled multicenter study.[47]

Therapies of definite, probable, or possible benefit for AFRS are summarized in Box 48-2.

Nonallergic Eosinophilic Fungal Rhinosinusitis

The confusion over the role of fungus in the etiology of chronic rhinosinusitis (CRS) was heightened by the assertion of Ponikau and colleagues[48] in the late 1990s that fungi were responsible for most cases of CRS. They reported that in 93% of patients undergoing sinus surgery, both eosinophilic mucin and fungus were present in nasal lavage samples. These researchers based their conclusion—that there is a nonallergic etiology for eosinophilic fungal rhinosinusitis—on the fact that less than half of their sample of almost 100 patients in whom eosinophilic mucin and fungus were present were allergic. They also noted that fungus could be grown from the nasal washings of 100% of normal controls.[48] The researchers proposed that cell-mediated responses provoked by fungus in a susceptible host were responsible for eosinophilic fungal rhinosinusitis (EFRS). In order to highlight the nonallergic nature of the categorization proposed by Ponikau and colleagues,[48] I refer to this entity as *nonallergic eosinophilic fungal rhinosinusitis*.

Since the proposal of Ponikau and colleagues[48] that fungus was causal in nearly all cases of CRS, three large studies have examined the demographics of eosinophilic sinus disease relative to the presence or absence of fungus, and their findings are conflicting. In 2000 Ferguson[49] reported that clinical characteristics of patients with eosinophilic mucin rhinosinusitis without fungus differed significantly from those of patients with AFRS, although there was overlap. This study's database consisted of cases from a comprehensive literature review of AFRS and nonfungal eosinophilic mucin rhinosinusitis (NF-EMRS) combined with Ferguson's cases accrued from the northeastern United States. The review, comparing 69 cases of NF-EMRS with 431 cases of AFRS, found that patients with AFRS were significantly younger (30.7 years vs. 48.0 years), less likely to have asthma (41% vs. 93%) and less likely to be aspirin sensitive (13% vs. 54%), had significantly higher total IgE levels (mean 1941 mg/dL, with a range of 12-13,084 mg/dL, vs. mean 267 mg/dL, with a range of 14-1162 mg/dL), and were less likely to have bilateral disease (55% vs. 100%) than patients with EMRS. More than 90% of this entire database was drawn from North America.[49]

In 2006, Saravanan and associates[50] prospectively categorized 70 patients in northern India who were undergoing sinus surgery and found that 36 (51%) patients had AFRS, 12 (17%) had NF-EMRS, 4 (6%) had fungus balls, and the remaining 18 had noneosinophilic CRS from other causes. As in the report by Ferguson,[49] the AFRS patient mean age in this study was lower (28 ± 13 years vs. 41 ± 10 years) and bilateral disease was less likely (75% vs. 100%) in the AFRS group than in the NF-EMRS group, but these findings did not reach statistical significance. Bony erosion (100% vs. 40%) and heterogeneity of densities on CT scan (97% vs. 67%) were significantly more common in the AFRS group than in the NF-EMRS group.[50]

In a 2006 prospective evaluation of 188 patients with EMRS in Adelaide, Australia, Pant and colleagues[51] found that patients with classic AFRS were significantly younger than patients with other forms of EMRS; however, there was no difference in the subgroups for any other parameters examined, including presence of aspirin sensitivity, bilaterality of disease, immunoglobulin levels, and asthma. Virtually 100% of patients in southern Australia with AFRS have bilateral disease.[51]

Possible explanations for the differences between these three large series include the effect of variations introduced by climate, genetic susceptibility, and socioeconomic factors. In Ferguson's[49] literature and retrospective review, 93% of the patients were from across North America, whereas those in the two large prospective series were each from a single location, central northern India or Adelaide, Australia. It is possible that in northern India and southern Australia, conditions could exist that lead to a higher mold inoculum and more frequent bilateral disease.

Pant and associates[51] found that fungal IgE levels were similar in patients with NF-EMRS and fungal allergy to those in patients with AFRS.[8] This finding implies that presence of fungal allergy alone is not sufficient for development of AFRS. Patients also have fungal allergy without EMRS. Thus, the presence of IgE antibodies to fungal antigens in patients with NF-EMRS may represent cases in which fungi have not become entrapped in the nose or sinuses. In other words, the mucociliary/host defenses have been adequate to prevent entrapment of fungal spores or a cofactor such as superantigen may be absent.

The controversy involving the definition of AFRS has been intensified by reports of mucosal invasion as indicated by granulomatous inflammation and branching septate fungal hyphae in the submucosal tissues in patients with presumed extensive AFRS.[52,53]

Therapy

Antifungal Agents

Early nonrandomized, noncontrolled studies reported 70% improvement in symptoms and CT findings after irrigation of the nose with

Table 48-4

Studies of Topical Amphotericin B in Chronic Rhinosinusitis

Study	Entry Criteria	Design	No. Patients	Amphotericin B Dose	Result
Ponikau et al (2002)[56]	CRS	NR NB	51	20 mL bid 100 µg/mL × >3 months	Imp in 75%
Ricchetti et al (2002)[57]	NP	NR NB	74	20 mL bid 1:1000 × 4 weeks	Resolution of NP in 42%-62% of moderate & mild cases, but in 0% of severe cases
Weschta et al (2004)[58]	NP without AFRS	R DB PC	74	200 mL spray (3 mg/mL) qid × 8 weeks	NS imp*
Ponikau et al (2005)[59]	CRS	R DB PC	24	20 mL bid 100 µg/mL × 6 months	8% imp in CT findings
Ebbens et al (2006)[54]	CRS, prior endoscopic sinus surgery, without AFRS	R DB PC Multicenter	116	25 mL bid 100 µg/mL × 13 weeks	NS difference found objectively, subjectively, or by quality-of-life assessment

*Three patients randomized to Amphotericin B wash had a ≥50% improvement in sinus CT findings compared with no patients randomized to placebo wash.
AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; CT, computed tomography; DB, double-blinded; imp, improvement; NB, nonblinded; NP, nasal polyps; NR, nonrandomized; NS, no significant; PC, placebo-controlled; R, randomized.

20 mL of amphotericin B twice a day for 4 months. Studies to assess the effect of intranasal antifungal agents have evolved (Table 48-4). In the best-designed study to date, Ebbens and coworkers[54] reported no benefit from use of amphotericin irrigation, as assessed either objectively or subjectively, but their study specifically excluded patients with AFRS. No benefit from high-dose oral terbinafine was shown in a randomized, placebo-controlled multicenter study of patients with CRS not restricted to AFRS.[55] Endoscopic sinus surgery and topical and/or oral corticosteroids remain the main therapies for NA-EFRS.

Conclusion

Within each classification of fungal rhinosinusitis, gray areas exist. Our understanding of the causes of fungal rhinosinusitis and the best treatments, particularly in the noninvasive classifications, is incomplete and changing. The classification of fungal rhinosinusitis along an immunologic spectrum, ranging from invasive to allergic, serves as a guide to appropriate treatment and prediction of clinical outcomes in patients with fungal rhinosinusitis.

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CHAPTER FORTY-NINE

Benign Tumors of the Sinonasal Tract

Piero Nicolai

Paolo Castelnuovo

Key Points

- Unilateral nasal obstruction is the most common symptom in patients with either benign or malignant tumors of the sinonasal tract. Therefore, any patient with this complaint should be assessed with endoscopy, imaging studies, and, if required, histologic examination to establish an accurate diagnosis.
- Osteoma and inverted papilloma are the first and second most frequent benign tumors of the sinonasal tract, respectively. However, because osteomas do not always require surgery, inverted papilloma is the most common surgical indication for benign tumors of the sinonasal tract.
- The key point for successful removal of inverted papilloma is resection along the subperiosteal plane with drilling of the bone underlying the diseased mucosa.
- Most inverted papillomas can currently be resected through an endoscopic approach, the extent of which is modulated according to the site and size of the lesion.
- The need for an external or combined approach for localization of frontal sinus inverted papilloma should be anticipated and discussed with the patient because of the difficulties with preoperative assessment of the extent of disease along the sinus mucosa.
- Juvenile angiofibromas extending to the nasopharynx, the nasal cavity, the sphenoid, the maxillary sinus, the ethmoid, the pterygomaxillary/infratemporal fossa, the orbit, and the paracavernous area can be removed with endoscopic surgery.
- Juvenile angiofibromas that extensively involve the floor of the middle cranial fossa, those that encase the internal carotid artery, and those that involve critical areas after a previous treatment are better managed with a combined external/endoscopic approach.
- Because most persistent juvenile angiofibromas are located in the basisphenoid and grow submucosally, postoperative surveillance should include periodic endoscopic examinations and imaging studies.
- Osteomas more frequently involve the frontal sinus. Lesions originating medial to a sagittal plane tangential to the medial wall of the orbit and not involving the anterior wall of the frontal sinus are amenable to endoscopic resection. To gain transnasal access to the lesion, the frontal sinus should have an anteroposterior diameter of at least 1 cm.
- Cavitation, which is achieved by drilling of the central part of the osteoma and leaving a peripheral shell of bone that is subsequently more easily dissected off the adjacent structures, is a key aspect for removal of even large osteomas using a limited access.

Significant refinements in imaging techniques and the widespread application of endoscopic surgery have led to revived interest in the management of benign tumors of the sinonasal tract. Not unexpectedly, this anatomic region may be involved by a large variety of different histopathologic entities that, according to the World Health Organization (WHO) classification, include epithelial tumors (papillomas and salivary gland–type adenomas), soft tissue tumors (myxoma, leiomyoma, hemangioma, Schwannoma, neurofibroma, meningioma), and tumors of bone and cartilage (giant cell lesion, giant cell tumor, chondroma, osteoma, chondroblastoma, chondromyxoid fibroma, osteochondroma, osteoid osteoma, osteoblastoma, ameloblastoma, nasal chondromesenchymal hamartoma).[1] Although originating from the pterygomaxillary fossa, juvenile angiofibroma is habitually included in the group of sinonasal tract tumors because of its common presentation as a nasal or nasopharyngeal mass.

Apart from osteomas, which are usually serendipitously diagnosed on computed tomography (CT) of the brain or orbits or are associated with frontal headache in the absence of any other nasal complaint, the heralding symptom of most benign tumors of the sinonasal tract is unilateral nasal obstruction, which nowadays requires initial investigation with endoscopy of the nasal cavities after appropriate decongestion. This examination usually reveals a mass of variable aspect that is narrowing or obstructing the nasal passage. In some lesions, such as inverted papilloma and angiofibroma, the endoscopic appearance may even suggest the nature of the lesion itself. At this point, it is our common policy to obtain imaging studies, which can help define the

Table 49-1

Distribution of Benign Tumors of the Sinonasal Tract by Histology and Surgical Approach

	Surgical Approach			
Tumor Histology	**Endoscopic**	**Combined**	**External**	**Total**
Inverted papilloma	260	28	12	300
Juvenile angiofibroma	74	—	34	108
Osteoma	56	29	9	94
Lobular capillary hemangioma	45	1	—	46
Fibrous dysplasia	13	2	1	16
Cavernous hemangioma	11	—	—	11
Schwannoma	7	3	1	11
Ossifying fibroma	6	—	1	7
Hamartoma	6	—	—	6
Glioma	5	—	1	6
Pleomorphic adenoma	5	—	—	5
Miscellaneous	18	7	—	25
Total	506	70	59	635

Data from a series of 635 patients treated at the University Hospitals of Brescia and Varese from 1994 to 2008.

vascularization of the mass and its relationships with adjacent structures, and to rule out a diagnosis of encephalomeningocele. In general, our preference is for magnetic resonance imaging (MRI), because it can clearly differentiate tumor from retained secretions, allows higher contrast resolution, and may even suggest the nature of a soft tissue lesion. CT with contrast medium enhancement can be considered as a reasonable alternative. A biopsy is required whenever a diagnosis cannot be established by imaging studies but should be avoided if an angiofibroma is suspected.

Even though most benign tumors of the sinonasal tract can nowadays be managed through an endoscopic approach, there are still situations that require an external or a combined procedure. Need for an external or combined procedure may be clearly suggested by imaging studies, but there are cases in which a definitive decision can be taken only during surgery. Consequently, the possibility of switching from an endoscopic to an external procedure must be discussed with the patient preoperatively.

This chapter discusses in detail inverted papilloma, osteoma, and juvenile angiofibroma, which are the most common histologic types seen in our series of 635 benign tumors of the sinonasal tract encountered over 15 years at two University Hospitals (Table 49-1). We also provide information on other benign tumors of less common observation.

Inverted Papilloma

Inverted papilloma (or Schneiderian papilloma, inverted type), which is included in the group of sinonasal papillomas together with the oncocytic and exophytic variants, is the second most common benign tumor of the sinonasal tract after osteoma, even though it represents the most common surgical indication for a benign sinonasal tumor. The lesion is estimated to represent 0.4% to 4.7% of all surgically removed nasal tumors, with an incidence ranging from 0.6 to 1.5 cases per 100,000 inhabitants per year.[2,3] Men are more commonly affected than women, and the lesion is prevalently observed in the fifth and sixth decades of life.

With regard to the histologic appearance, inverted papilloma is composed exclusively or almost exclusively of hyperplastic ribbons of basement membrane–enclosed epithelium that grow endophytically into the underlying stroma. The epithelium is multilayered and formed of squamous or ciliated columnar cells mixed with mucocytes.[4]

Inverted papilloma most frequently arises from the lateral nasal wall in the fontanelle area. The maxillary sinus is the second most commonly affected site, and frontal and sphenoid sinuses are rarely involved primarily. Often the lesion extensively involves more than one sinus, making it impossible to assess the exact site of origin.

The association of inverted papilloma with squamous cell carcinoma has been overemphasized, with reported frequencies as high as 56%.[5] Recent data clearly show that the prevalence varies between 3.4%[6] and 9.7%[7] and that synchronous occurrence is more common than metachronous.

Inverted papilloma is suspected to have a viral etiology. Human papillomavirus DNA has been demonstrated by in situ hybridization or the polymerase chain reaction in papillomas, with a prevalence of serotypes 6, 11, 16, and 18.[8,9] The last two serotypes have been specifically found to be associated with inverted papillomas that show histologic signs of malignant transformation. Not unexpectedly, in this setting an increase in levels of epidermal growth factor receptor and tumor growth factor-α has been demonstrated.[10]

Unilateral nasal obstruction with watery rhinorrhea is the most common symptom prompting the patient to seek otolaryngologic consultation, whereas epiphora, proptosis, diplopia, and headache may be associated with advanced lesions involving the orbit or the skull base. Endoscopy of the nose, usually showing a pale, polypoid lesion with a papillary appearance protruding from the middle meatus (Fig. 49-1), may easily suggest the diagnosis, which is sometimes made less obvious by the concomitant presence of inflammatory polyps. A biopsy per-

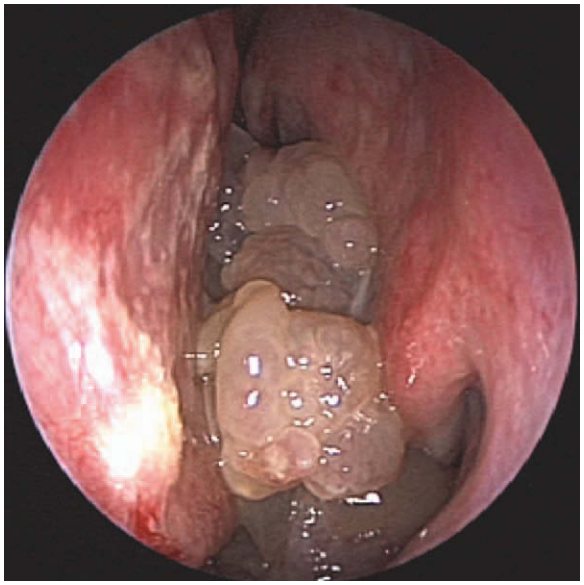

Figure 49-1. Typical endoscopic appearance of an inverted papilloma. A polypoid lesion with a pale, papillary surface protrudes from the middle meatus and extensively fills the left nasal cavity.

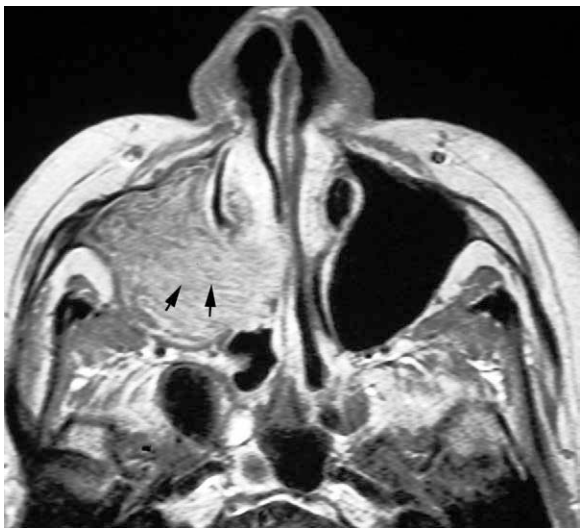

Figure 49-2. Inverted papilloma on an axial contrast-enhanced, T1-weighted, spin-echo magnetic resonance image. The maxillary sinus is occupied by a solid mass protruding into the nasal fossa through an accessory ostium. The lesion exhibits a cerebriform-columnar pattern, which is typically seen in inverted papilloma (*arrows*).

formed under endoscopic guidance is indicated to establish the histologic diagnosis.

Imaging studies are required to assess the extent and three-dimensional configuration of the lesion and to disclose its relationship with surrounding structures (i.e., orbit, skull base, optic nerve, internal carotid artery). In our experience, these goals are best achieved by MRI with gadolinium enhancement, which also has the advantage over CT of better differentiating tumor from inflammatory mucosal changes and to disclose the so-called cerebriform-columnar pattern (Fig. 49-2). This reflects the histologic arrangement of inverted papilloma characterized by the alternation of regular parallel folds made of a highly cellular metaplastic epithelium and of an underlying less cellular stroma. It is therefore highly predictive for inverted papilloma diagnosis.[11] However, even MRI has limitations, especially in lesions completely filling the maxillary, sphenoid, or frontal sinus, in differentiating inverted papillomas growing inside the sinus but arising from a small area of insertion from those extensively involving the mucosa. Recent studies indicate that focal hyperostosis[12] and osteitic changes[13] upon CT may be considered reliable predictors of tumor origin. These findings may also be identified by MRI (Fig. 49-3).

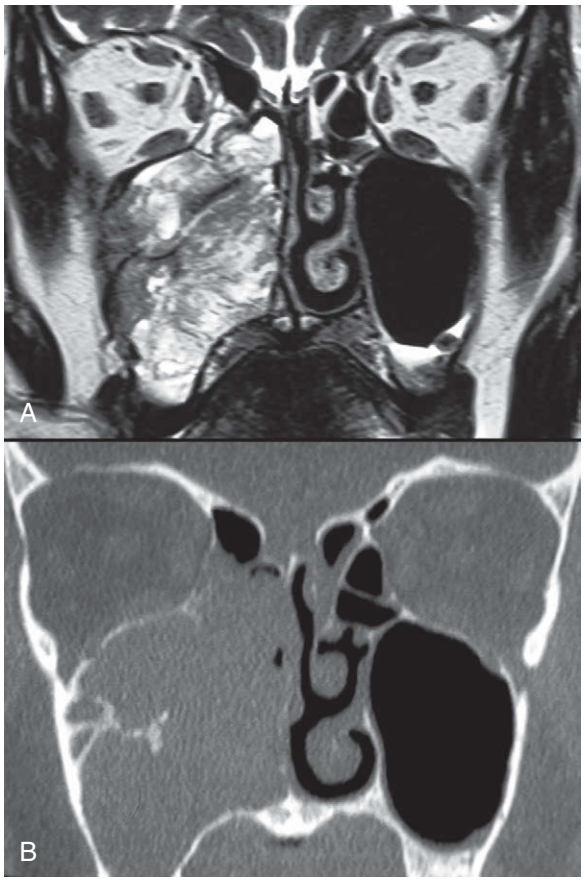

Figure 49-3. Inverted papilloma on a magnetic resonance (MR) image and a computed tomography (CT) scan, both in the coronal plane. The maxillary sinus is completely occupied by an expansile lesion that destroyed the medial wall and invaded the right nasal fossa. **A,** The T2-weighted spin-echo MR image demonstrates the cerebriform-columnar pattern of the lesion and permits visualization of the bony spur along the lateral maxillary sinus wall where the lesion originates. **B,** The CT scan does not provide a good characterization of soft tissue density opacification but gives a superior view of the sclerotic bony spur.

As clearly shown by a 2006 meta-analysis[14] and by our experience based on 300 inverted papillomas, endoscopic surgery is a reliable alternative to traditional external techniques for the vast majority of lesions. An exclusive endoscopic approach may be contraindicated in the following situations: (1) massive involvement of the mucosa of the frontal sinus and/or of a supraorbital cell, (2) intradural extension or transorbital extension, both of which are very uncommon situations usually found in patients who have already undergone one or more surgical procedures, (3) concomitant presence of a malignancy involving critical areas, and (4) presence of abundant scar tissue from previous surgery.

One criticism of endoscopic approaches is the impossibility in always obtaining an en bloc resection. However, it is not the concept of en bloc resection per se that has to be fulfilled to achieve complete removal; the key point is to dissect the involved mucosa along the subperiosteal plane and to drill the underlying bone whenever required by imaging and/or intraoperative findings.[15] The extent of the operation is dictated by the site of the lesion and the area of mucosa involved by the lesion. Apart from cases with a clearly identifiable small attachment of the lesion, which can be managed with a very conservative

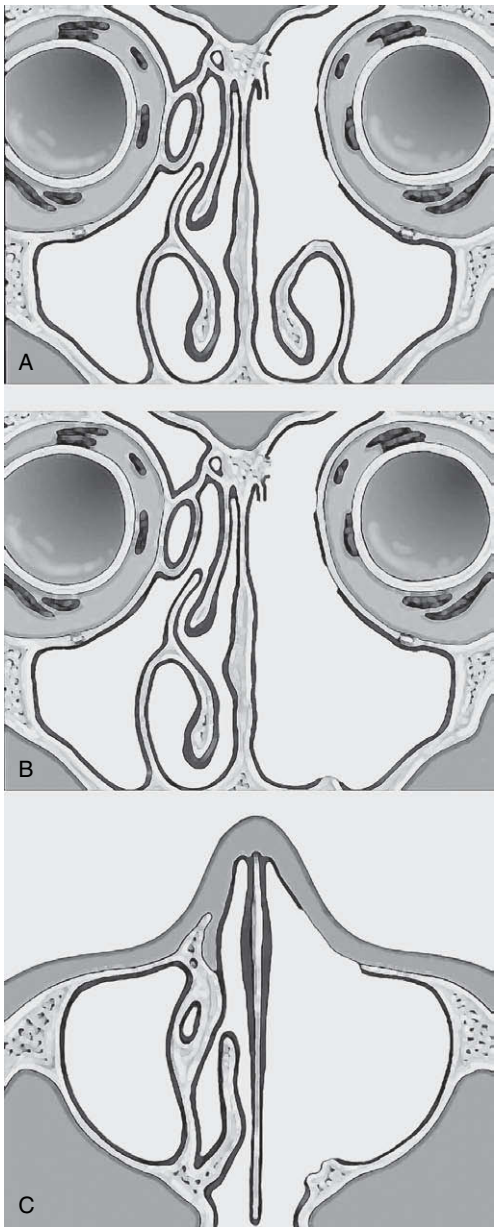

Figure 49-4. Schematic drawings summarizing the different endoscopic resections used for inverted papillomas of the naso-ethmoid-maxillary region. **A,** type I resection; **B**, type II resection; **C,** type III resection. See text for explanation.

approach,[16] there are basically three different types of endoscopic resections available, according to our classification.[17] Type I resection (Fig. 49-4A) is indicated for inverted papillomas involving the middle meatus, ethmoid, superior meatus, sphenoid sinus, or a combination of these structures; even lesions protruding into the maxillary sinus without direct involvement of the mucosa are amenable to this approach. Type II resection (Fig. 49-4B), which corresponds to an endoscopic medial maxillectomy, is indicated for tumors originating within the nasoethmoidal complex and secondarily extending into the maxillary sinus or for primary maxillary lesions not involving the anterior and lateral walls of the sinus itself. The nasolacrimal duct can be included in the specimen to increase the exposure of the anterior part of the maxillary sinus. Type III resection (Fig. 49-4C), also known as the Sturman-Canfield operation or endonasal Denker operation,[18] entails removal of the medial portion of the anterior wall of the maxillary sinus to enable access to all the antrum walls. It is therefore recommended for inverted papillomas extensively involving the anterior compartment of the maxillary sinus.

Figure 49-5. Inverted papilloma on a sagittal contrast-enhanced magnetic resonance image. The advantage of this acquisition plane is the excellent assessment of tumor growth into the most caudal part of the frontal sinus. The upper part of the sinus is filled with inflammatory secretions (*asterisk*). The sagittal plane also permits accurate evaluation of the relationships between the tumor and the floor of the anterior cranial fossa, which is not invaded (*arrow*).

Frontal sinus involvement can be observed in different scenarios, ranging from a limited lesion marginally growing from the ethmoid into the frontal recess (Fig. 49-5) to very complex cases in which most or all of the sinus mucosa is diseased. Because the key point for ultimate success is removal of the lesion along the subperiosteal plane with the possibility to drill out the underlying bone, the surgical choice may involve a Draf IIB or Draf III endoscopic sinusotomy or a combination of an endoscopic approach with external sinusotomy through an osteoplastic flap depending on the extent of frontal sinus mucosa involvement, a finding that can usually be definitively assessed only at the time of surgery. Even the involvement of an extensively pneumatized supraorbital cell is frequently challenging. Exposure through the nose may be increased by coagulation and sectioning of the anterior ethmoid artery and by displacement of the orbit after drilling of the upper portion of the lamina papyracea. However, whenever the lesion involves a cell that extends far posteriorly and/or laterally over the orbit and complete resection cannot be achieved transnasally, the surgeon should resort to a frontal osteoplastic flap.

Regardless of the access selected for inverted papilloma resection, the operation should end with the creation of a largely marsupialized cavity that will give wide access during follow-up for endoscopic inspection, which should be periodically performed in order to diagnose residual or recurrent lesions early. Postoperatively, MRI or CT is indicated only when a sinus that was originally involved by the lesion is not accessible for exploration owing to scar closure, the patient is symptomatic, or a residual or recurrent lesion has been histologically documented.

In the era when transnasal resection without endoscopic or microscopic assistance was the most commonly used technique, the rate of recurrences ranged from 40%[19] to 78%.[20] These extremely high values indicate that these "recurrences," mostly occurring at the site of primary resection, should have been more appropriately regarded as residual lesions. They reflected the inadequacy of transnasal surgery in affording a radical excision of the lesion. In view of such limitations, medial maxillectomy through lateral rhinotomy was established in the 1970s and 1980s as the gold standard for treatment of inverted papilloma. Although the frequency of recurrences decreased, reportedly from 0%[21] to 29%,[22] this technique was associated with potential aesthetic sequelae. Therefore, midfacial degloving became the most popular approach for the management of inverted papilloma. The routine use of available staging systems specific for inverted papilloma[23-27] would facilitate the comparison of results among different institutions.

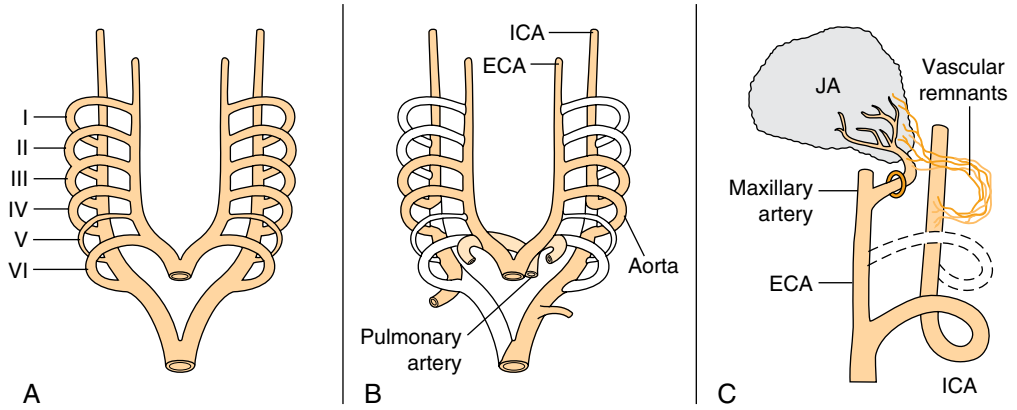

Figure 49-6. Schematic drawing summarizing the theory postulated by Schick and colleagues[29] on the origin of juvenile angiofibroma (JA) from remnants of the branchial artery. **A,** During embryogenesis the sixth branchial arch arteries temporarily connect the ventral and dorsal aortas. **B,** Physiologic regression of several vascular structures (*white vessels*) subsequently occurs, leading to definitive configuration of the vascular system. **C,** Regression of the first branchial arch artery takes place via the formation of a vascular plexus, which is usually complete at birth. Incomplete regression of this structure can explain the typical blood supply for juvenile angiofibromas, from the maxillary and sphenopalatine arteries, with persistent vascular connections to the internal carotid pathway. I through VI, six branchial arteries; ECA, external carotid artery; ICA, internal carotid artery.

Juvenile Angiofibroma

Juvenile angiofibroma is a benign lesion histologically characterized by vascular endothelium–lined spaces embedded in a fibrous stroma that typically affects young male adolescents. Immunohistochemical and electron microscopy studies suggested that the lesion could be considered a vascular malformation (or hamartoma) rather than a tumor.[28] These observations led Schick and colleagues[29] to postulate that juvenile angiofibroma might develop from incomplete regression of a branchial artery, which arises in embryogenesis between day 22 and 24 and forms a temporary connection between the ventral aorta and dorsal aorta. This artery commonly regresses and forms a vascular plexus that either involutes or may leave remnants, potentially leading to development of juvenile angiofibroma (Fig. 49-6). This theory is supported by the finding that juvenile angiofibroma vessels express laminin α_2, which is considered a marker for early angiogenesis.[30]

The lesion has a pathognomonic epicenter of origin at the level of the pterygopalatine fossa and subsequently grows through different pathways of spread that typically follow foramina and fissures of the skull base. The bone may be involved basically with two mechanisms, resorption by pressure coming from subperiosteal growth or invasion of the cancellous component initially at the level of the root of the pterygoid process, with subsequent expansion within the greater wing and erosion of the floor of the middle cranial fossa. In its early phase, juvenile angiofibroma extends through the sphenopalatine foramen into the nasopharynx and the nasal cavity and along the vidian nerve into the floor of the sphenoid sinus. Lateral extension through the pterygomaxillary fissure leads to invasion of the infratemporal fossa, which in advanced lesions may be completely filled. When the lesion expands anteriorly, the posterior wall of the maxillary sinus is progressively pushed forward. Although benign, juvenile angiofibroma may extend intracranially through the orbit via the inferior and superior orbital fissure or along the maxillary nerve to the parasellar region. Encroachment upon the anterior skull base through the ethmoid is less commonly observed. Regardless of the site and pattern of intracranial involvement, transdural growth of the lesion is very rare.[31]

Unilateral nasal obstruction and epistaxis are the most common heralding symptoms of small to intermediate-size juvenile angiofibromas. In advanced lesions, swelling of the cheek, proptosis, or headache may be present, indicating an involvement of the infratemporal fossa, the orbit, or the cranial fossa, respectively. The endoscopic finding of a smooth, hypervascularized lesion originating behind the middle turbinate, which is usually laterally displaced against the lateral wall (Fig. 49-7), in a teenage boy strongly suggests a diagnosis of juvenile angiofibroma, which is usually confirmed by CT and MRI. Therefore, resorting to a biopsy, which is associated with a high risk of hemorrhage, is rarely if ever justified.

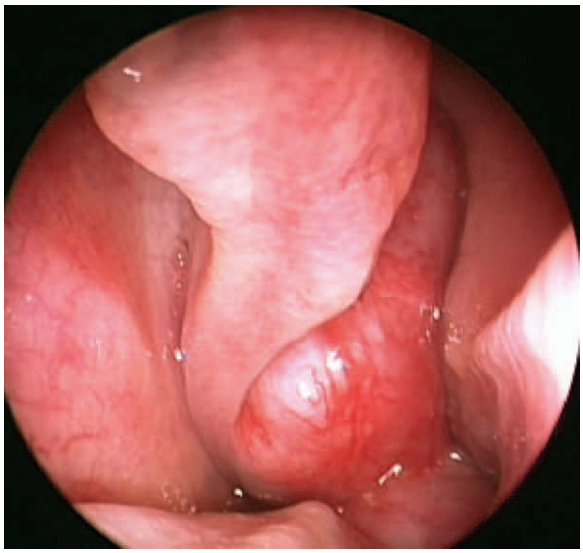

Figure 49-7. Juvenile angiofibroma. On endoscopy, the lesion typically appears as a polypoid hypervascularized mass bulging from the lateral wall behind the middle turbinate, which is laterally compressed. The choana is completely obstructed.

On CT and MRI the diagnosis of juvenile angiofibroma is based on the following three features: the area of origin invariably located at the level of pterygopalatine fossa, its hypervascular appearance after contrast enhancement, and its pattern of growth.[32] On MRI, the presence on both T1- and T2-weighted sequences of several signal voids within the lesion, indicating major intralesional vessels, further corroborates a diagnosis of juvenile angiofibroma. Sometimes differentiation of this lesion from lobular capillary hemangioma, hemangiopericytoma, and schwannoma can be difficult in view of a similar pattern of enhancement. However, these other lesions do not commonly involve the pterygopalatine fossa and occur in a different age group.

Intraoperative bleeding has always been considered one of the most challenging issues in the management of juvenile angiofibroma, leading in the past to a high rate of persistent disease and to a notable

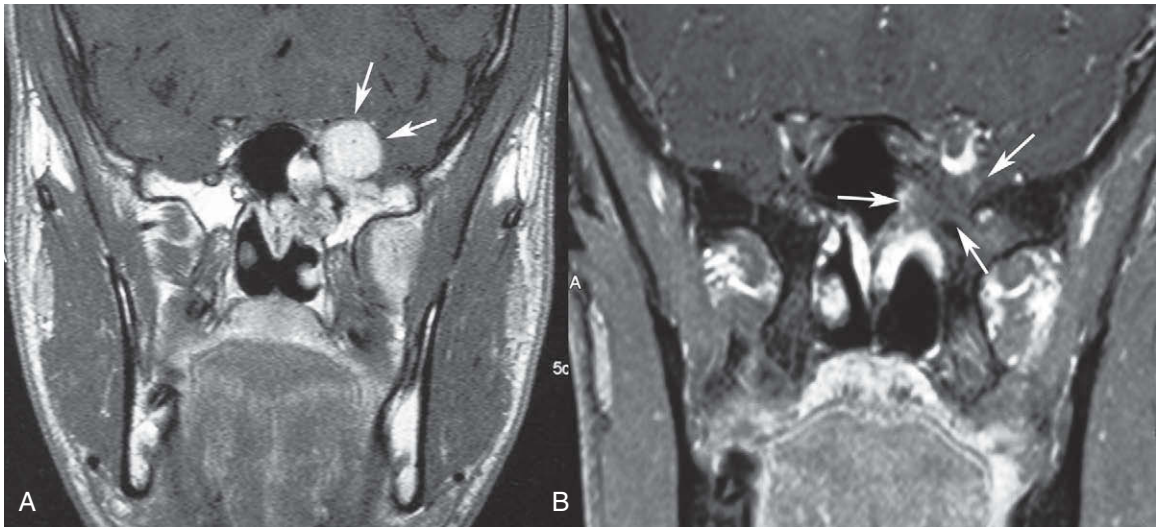

Figure 49-8. Juvenile angiofibroma on coronal contrast-enhanced magnetic resonance (MR) images obtained before and after endoscopic resection. **A,** Pretreatment image shows encroachment of both the floor and lateral wall of the left sphenoid sinus and infratemporal fossa. Intracranial extension is demonstrated in close proximity to the superior orbital fissure (*arrows*). **B,** MR image obtained after surgical resection shows solid tissue (*arrows*) along the lateral sphenoid sinus wall; the lack of contrast enhancement suggests residual scar tissue.

morbidity. The introduction in the early 1970s of preoperative embolization,[33] which is commonly performed 48 hours before surgery, has revolutionized the treatment of this lesion by dramatically decreasing intraoperative bleeding and therefore making the assessment of tumor borders at dissection more accurate. Nowadays, the availability of intra-arterial digital subtraction angiography, microcatheters, and embolic agents such as polyvinyl-alcohol particles makes superselective embolization of feeding vessels even easier.[34] Furthermore, angiography provides a detailed map of the lesion's vascular supply, showing connections with the internal carotid artery, the vertebral artery, and branches of the contralateral carotid system. Although the currently available methods of embolization provide excellent devascularization of feeding vessels from the internal maxillary artery and its branches as well as from the ascending pharyngeal artery, control of major vascularization from the internal carotid artery is demanding. Devascularization by direct tumor puncture and embolization is associated with an unacceptable risk of major neurologic complications[35] and has therefore been abandoned. In case of encasement of the internal artery, which is indeed a very rare event, a balloon occlusion test and sacrifice of the internal carotid artery or, as a less invasive procedure, stenting of the intratemporal carotid artery[36] may be considered.

Not all authorities concur about routinely performing preoperative embolization. In fact, the modifications induced by this procedure at the tumor periphery have been shown to increase the likelihood of leaving residual tissue behind.[37]

Several classification systems for juvenile angiofibroma are available in the literature.[38-41] They should be used with the intent to stratify cases according to lesion extent and to make comparison among different series easier.

Surgery is considered the mainstay in the management of juvenile angiofibroma. Several approaches are currently available, ranging from microendoscopic techniques to midfacial degloving and infratemporal fossa resection. Independent of the technique selected, the key steps to minimizing bleeding and achieving radical resection are the dissection of the lesion in the subperiosteal plane with the help of bipolar coagulation and an extensive drilling of the basisphenoid where the tumor is growing with digitations that are difficult to identify even under magnification. The importance of this latter surgical step has been emphasized by Howard and associates,[42] who have observed a dramatic reduction of recurrences in their series with the systematic removal of the cancellous bone of the sphenoid involved by the lesion.

Endoscopic surgery has also emerged as a viable alternative to traditional external approaches in the management of small to intermediate size juvenile angiofibroma.[43-45] Involvement of the infratemporal fossa, orbit, and parasellar region cannot be considered contraindications to endoscopic surgery (Fig. 49-8), but advanced lesions with extensive involvement of the cavernous sinus or encasement of the internal carotid artery (Fig. 49-9) are better treated through a combined endonasal-external approach. Midfacial degloving or an infratemporal fossa approach may be selected according to the location of the intracranial component and the surgeon's preference. For lesions with a large intracranial extension, another option is resecting the extracranial component and the intracranial component in two sessions. For residual lesions involving critical areas, the possibility of switching to a combined procedure should always be discussed with the patient, in view of possible scarring that makes dissection through an exclusively endonasal approach problematic. One should also keep in mind that radiotherapy at a low dose (30-36 Gy) has been demonstrated to be effective in cases of advanced or recurrent lesions deemed not amenable to complete resection with acceptable morbidity.[46] The availability of new techniques such as Gamma knife radiosurgery[47] and the Cyberknife system[48] might be alternatives with a low morbidity when used for lesions of limited size.

Postoperative surveillance is based on periodic endoscopic and imaging examination. However, because most of the residual lesions tend to grow submucosally, contrast-enhanced CT or MRI plays a key role in their early detection. Imaging studies performed in the immediate postoperative period would identify residual juvenile angiofibroma tissue more easily, because of the absence of any inflammatory changes.[49] The actual frequency of residual lesions, although difficult to assess, ranges from 6% to 39%.[47] Even though there is a great variability in postoperative surveillance with respect to the timing and imaging techniques used by different investigators, most residual lesions are diagnosed within 1 year after surgery. Independent of the surgical approach used (external vs. endoscopic), invasion of the sphenoid or pterygoid process, involvement of the infratemporal fossa, foramen lacerum, and/or cavernous sinus in more advanced lesions have a negative impact on local control.[41] Endoscopic surgery, when appropriately planned, is associated with a low rate of residual lesions, which are reported in 6.6%[43] to 17%[41] of patients.

Because the understanding of the biologic behavior of residual lesions is still limited, we commonly monitor residual lesions with MRI to assess their pattern of growth. Treatment, in the form of surgery or radiotherapy, is scheduled only when there are clear signs of constant increase in size.

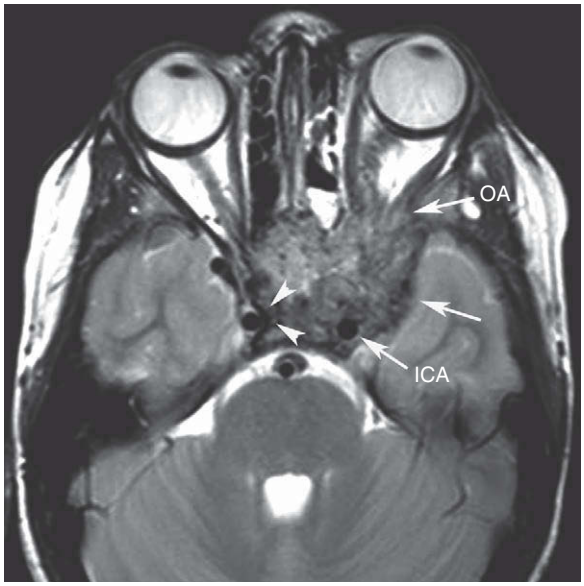

Figure 49-9. Juvenile angiofibroma on axial T2-weighted, spin-echo magnetic resonance image. The lesion invades the left orbital apex (OA), the lateral wall of the left sphenoid sinus (*white arrows*) is completely destroyed, and the internal carotid artery (ICA) is encased. On the right side, a bony barrier (*arrowheads*) still separates the lesion from the internal carotid artery.

Figure 49-10. Osteoma on a coronal computed tomography scan. A huge ivory osteoma is shown in the right ethmoid, encroaching on the crista galli and the cribriform plate and invading the anterior cranial fossa. The right orbit is not invaded, and the thin lamina papyracea can still be detected (*arrows*).

Osteoma

Osteoma, a benign, slow-growing osteoblastic lesion, is the most common benign tumor of the sinonasal tract. It is found in 1% of subjects undergoing plain sinus radiographs and in 3% of those undergoing CT for sinus symptoms.[50] Osteomas are generally diagnosed between the second and fifth decades of life, with a slight male preponderance commonly reported in the literature. The frontal sinus is the most frequently involved anatomic site (approximately 80% of cases), followed by the ethmoid, the maxillary sinus, and, more rarely, the sphenoid sinus. Osteomas can be observed in conjunction with Gardner's syndrome, a genetic disorder characterized by multiple polyps of the colon in association with osteomas of the skull and multiple soft tissue tumors.

Macroscopically, most osteomas appear as hard, white, multilobulated masses. The area of origin is easily recognizable in small lesions, whereas in large osteomas its identification can be problematic.

According to the Fu and Perzin[51] classification, osteomas are histologically divided into the following three categories:

- Ivory or "eburnated" osteoma: lobulated, made of compact, dense bone, containing a minimal amount of fibrous tissue, and without evidence of haversian ducts.
- Mature osteoma or osteoma spongiosum: composed of spongy, mature bone in which the bony trabeculae are divided by a conspicuous amount of fibrous tissue, containing fibroblasts in different stages of maturation, and a great number of collagen fibers. The connective tissue may often contain distended thin-walled vessels.
- Mixed osteoma, which features findings typical for both ivory and mature osteoma.

There is no general agreement on the mechanisms leading to the development of osteomas. Three main theories have been proposed. The embryologic theory, which proposes that osteoma develops at the junction between the embryonic cartilaginous ethmoid and the membranous frontal bone, does not explain the occurrence of osteomas distant from the area where the frontal bone and the ethmoid labyrinth join together. The traumatic theory correlates the development of osteoma with a previous trauma, whereas the infective theory is based on the belief that local inflammation may alter adjacent bone metabolism by activating osteogenesis.[32] One additional possibility is that the etiology of osteomas is variable and the lesions should be more properly considered slow-growing osseous hamartomas arising in childhood.[52]

Most osteomas are asymptomatic and are occasionally diagnosed during radiographic examinations performed for unrelated reasons. In its more typical frontal or frontoethmoidal localization, an osteoma may interfere with sinus drainage and therefore cause a sinusitis or even a mucocele, with consequent frontal pain. If the lesion involves the outer table of the frontal bone, the patient may complain of aesthetic deformity, whereas tumors growing toward the orbit can cause orbital or lacrimal symptoms (i.e., proptosis, diplopia, orbital pain, epiphora, decreased visual acuity, and even transient blindness). Osteomas extending into the anterior cranial fossa carry the risk of cerebrospinal fluid leak, pneumocele, meningitis, and brain abscess. According to the different patterns of growth, maxillary osteomas impair the sinus drainage, causing symptoms such as pain in the maxillary area, compress the infraorbital nerve and cause neuralgic symptoms, or modify the aesthetic profile of the maxillary region.

Endoscopic examination of the nasal cavity is usually normal, because the lesion is deeply located inside a paranasal cavity. Only in very rare instances in which the osteoma is growing toward the nasal cavity can it be visualized as a firm mass covered by normal or atrophic mucosa.[32]

Imaging assessment of osteomas is currently based on CT. According to the amount of mineralized bone within the lesion, osteomas may exhibit a very high density, resembling cortical bone (Fig. 49-10), or a gradually decreasing density to a ground-glass pattern (Figs. 49-11 and 49-12). Contrast enhancement is usually unnecessary to reach a diagnosis.[32] Multiplanar reconstructions may help identify the sinus wall of origin of the lesion, which is a relevant finding for selecting the best surgical approach. Whenever the lesion is massively eroding the bony interface with the anterior skull base or the orbit, MRI may better delineate the relationship between the osteoma and adjacent soft tissues (i.e., dura, brain, orbital content).

Because osteomas are slow-growing, there is general consensus in the literature for a "wait and see" policy for any lesion that is asymptomatic, does not encroach upon critical structures such as the optic nerve (risk for intracranial complication), and is not extensively invading the anterior skull base or the orbit (risk for orbital complication). In this setting, it is advisable to monitor the lesion with periodic cross-sectional imaging examinations, which preferably include MRI. In all other situations, surgery is recommended.

Figure 49-11. Coronal computed tomography (CT) scan showing a frontoethmoid osteoma exhibiting a mixed CT pattern, ivory in the anterior ethmoid and spongiosum into the frontal sinus.

Figure 49-12. Coronal computed tomography scan showing a right ethmoid osteoma that displays a ground-glass density typically seen in the spongiosum variant. The lesion is adjacent to the frontal recess, which is unobstructed (*arrows*).

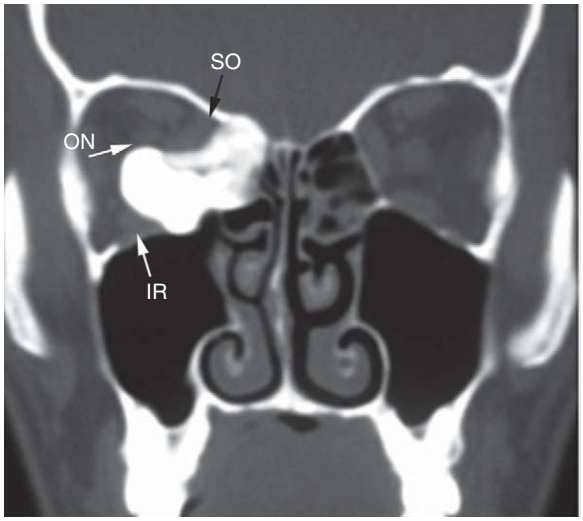

Figure 49-13. On a coronal computed tomography scan, a large ethmoid osteoma can be seen invading the orbit and displacing the optic nerve (ON), the superior oblique muscle (SO), and the inferior rectus muscle (IR). The high and quite homogeneous density is characteristic of the ivory variant. The lesion was resected via an endoscopic approach.

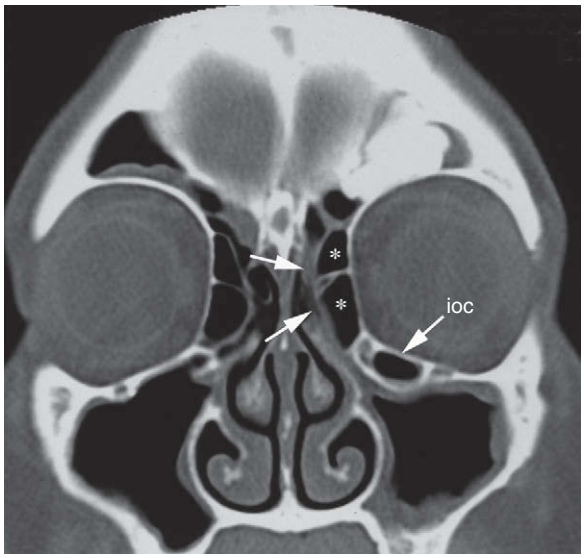

Figure 49-14. An ivory osteoma is shown in the most lateral aspect of the left frontal sinus in this coronal computed tomography scan. The lesion is rather distant from the frontal recess (*arrows*), which is narrowed by large agger nasi cells (*asterisks*). The osteoma was managed with a combination of an endoscopic approach with an osteoplastic frontal sinusotomy. ioc, infraorbital cell.

Different external surgical approaches (i.e., frontoethmoidectomy through a Lynch-Howarth incision, midfacial degloving, lateral rhinotomy, Caldwell-Luc procedure, and osteoplastic frontal sinusotomy via a coronal incision) have all been extensively used in the past according to the site and size of osteomas. The introduction and subsequent refinement of microendoscopic techniques led to a revolution in the surgical management of these lesions, and most are now treated through a transnasal approach (video clip available on website). A surgical trick that helps resect even large osteomas through the nose is cavitation, which consists of drilling the core of the lesion with a diamond bur, thus leaving a very thin shell of bone that can be easily fractured and dissected from the adjacent tissues.[53] The possibility of using a device inducing ultrasound bone emulsification has also been proposed.[54] Cerebrospinal fluid leak can be expected during these maneuvers if the lesion is in contact with dura. Consequently, the patient should be informed about this possibility and the need to repair the defect with a multilayer technique.[55]

Schick and colleagues[56] have precisely established the indications for and limits of endoscopic removal of osteomas. Lesions involving the ethmoid, the sphenoid, the medial wall of the maxillary sinus, and, in some selected cases, even the inferior and medial wall of the orbit can be resected transnasally (Fig. 49-13). Frontal osteomas are amenable to endoscopic surgery if they are located medial to a virtual sagittal plane prolonged upward from the lamina papyracea, if they originate from the inferior portion of the posterior frontal sinus wall, and if the anteroposterior diameter of the frontal sinus is at least 10 mm. Performing a Draf III procedure may sometimes help resect the lateral part of an osteoma of the frontal infundibulum extending over the orbit. However, for lesions extending far laterally in a well-pneumatized frontal sinus, radical removal cannot be achieved with a purely endoscopic procedure (Fig. 49-14). Such a lesion can be completely exposed and drilled out through the combination of an endoscopic approach with an image-guided frontal trephination[57] or, in more extensive lesions, with osteoplastic flap sinusotomy. In our experience, obliteration of the frontal sinus is contraindicated whenever a large frontal

sinusotomy, which can maintain satisfactory sinus drainage, is performed. On the other hand, when a frontal osteoma is located laterally and does not involve the frontal infundibulum, resection is better achieved through an exclusive osteoplastic flap without disturbing the frontal sinus outflow. In the case of a lesion that is massively eroding the anterior wall of the frontal sinus, reconstruction is required to maintain a regular frontal contour. This can be accomplished through the harvest of a split calvarial graft from the parietal bone, which is fixed in place by microplates.

Because osteoma recurrences are very rare, routine periodic postoperative surveillance by CT is not justified. We usually perform CT examination 1 year after surgery and, on the basis of its results, make a decision about further radiologic follow-up. The presence of a symptomatic stenotic frontal or maxillary sinusotomy is another situation calling for CT examination.

Lobular Capillary Hemangioma

Lobular capillary hemangioma is a rapidly growing lesion characterized by a proliferation of capillaries arranged in lobules and separated by a loose connective tissue stroma, often infiltrated by inflammatory cells.[58] The tumor has been commonly reported in the literature as "pyogenic granuloma," which is currently considered inadequate in view of the fact that the lesion is neither the result of a bacterial infection nor a true granuloma.

Most mucosal lobular capillary hemangiomas of the head and neck arise in the oral cavity, and fewer in the nasal cavity. In a series of 40 patients reported by Puxeddu and colleagues,[59] age ranged from 10 months to 72 years, with a mean age of 42 years and a peak incidence in the fifth decade of life. No gender preponderance was observed.

The etiopathogenesis of lobular capillary hemangiomas is still obscure. Trauma, hormonal influences, viral oncogenes, underlying microscopic arteriovenous malformations, and the production of angiogenic growth factors have been all advocated as potential etiopathogenetic factors. The relevance of trauma such as habitual nose picking and nasal packing is supported by the fact that most lesions are located in the anterior half of the nasal cavity at the level of Little's area or on the head of inferior and middle turbinates.

In its typical presentation, lobular capillary hemangioma appears at endoscopy as a red to purple mass, not larger than 1 cm, associated with epistaxis.[59] However, in more rare instances the lesion reaches a considerable size, filling the nasal cavity entirely and leading to a complaint of unilateral nasal obstruction. In this setting, differential diagnosis from other hypervascularized lesions, such as angiofibroma, angiomatous polyp, hemangioma, hemangiopericytoma, paraganglioma, angiosarcoma, and metastases from highly vascularized tumors (i.e., kidney or thyroid carcinoma), can be problematic and requires appropriate imaging studies as a first step. On CT, the lesion appears as a unilateral mass with soft tissue density, whereas the MRI pattern consists of T2 hyperintensity and spontaneous T1 hypointensity; on both sequences, vivid enhancement can be observed after administration of paramagnetic contrast medium.[32] Once angiofibroma is excluded, because of its peculiar location and epidemiologic profile, only histologic examination may establish a definitive diagnosis.

Surgery is the treatment of choice for lobular capillary hemangioma, and radical resection can be performed through an endoscopic approach even in large lesions.[32] In our experience, only in one case was formal anterior craniofacial resection necessary; in that case, the lesion extensively involved the orbit and anterior skull base and was associated with intravascular papillary endothelial hyperplasia (Fig. 49-15).[60]

Ossifying Fibroma and Fibrous Dysplasia

In the past, ossifying fibroma and fibrous dysplasia were traditionally grouped together because of their histologic similarities. In 1963, however, Reed[61] suggested that they should be regarded as two distinct entities. Ossifying fibroma is a true benign neoplasm, whereas fibrous dysplasia is a genetically based developmental anomaly of the bone-forming mesenchyme with a defect in osteoblastic differentiation and maturation that leads to a replacement of normal bony tissue by fibrous tissue of variable cellularity and immature woven bone. The main

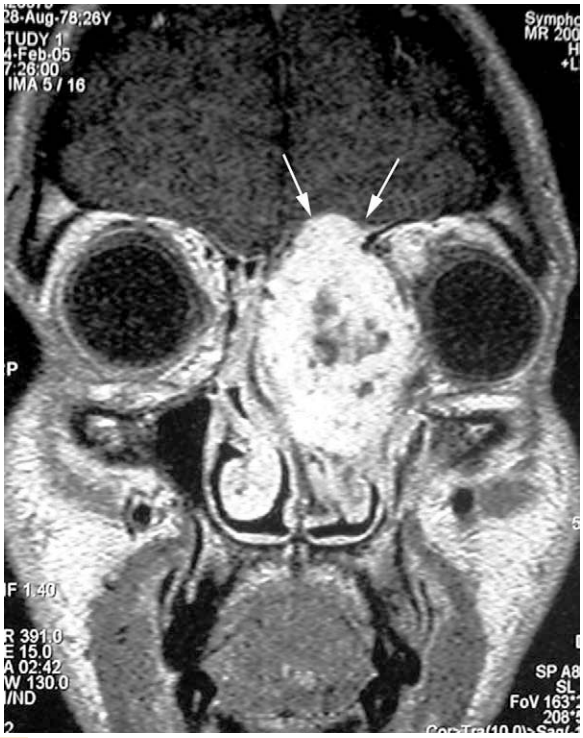

Figure 49-15. A lobular capillary hemangioma appears on a coronal contrast-enhanced magnetic resonance image as a large ethmoid lesion abutting the orbit and encroaching on the floor of the anterior cranial fossa. The sharp borders of the intracranial part of the lesion and the subtle dural enhancement suggest extradural invasion (*arrows*).

histologic differences between the two lesions lie in the absence of a capsule and the presence of more immature bone without osteoblastic activity in fibrous dysplasia.[62] Psammomatoid ossifying fibroma is a variant of ossifying fibroma characterized by the presence of numerous small ossicles in stroma that resemble psammoma bodies found in extracranial meningiomas, which are indeed acellular and test positive for epithelial membrane antigens.[63]

Ossifying fibroma of the sinonasal tract generally occurs in the third and fourth decades of life, preferentially in black women, whereas its psammomatoid variant typically affects men at a younger age and displays a more aggressive local behavior. Fibrous dysplasia is commonly diagnosed within the first two decades of life and may present in the following three forms: monostotic, polyostotic, and disseminated, the last also known as McCune-Albright syndrome.

Neither ossifying fibroma nor fibrous dysplasia is associated with specific symptoms. However, the former more frequently manifests as a space-occupying lesion in the nasal cavity that is evident at endoscopic examination and causes nasal obstruction, whereas the latter in an advanced stage may interfere with frontal or maxillary sinus drainage resulting in pressure or pain in the corresponding area, compress the optic nerve or the orbit with impairment of the vision or diplopia, respectively, or result in aesthetic deformities. Endoscopic findings are usually unremarkable or, as with osteoma, may consist of a lesion covered by intact mucosa.

The CT appearance of fibrous dysplasia is strictly related to the degree of mineralization of the tissue. In the early phases, associated with a high density of fibrous tissue, the lesion displays a radiolucent or lytic appearance, which is difficult to differentiate from a simple bone cyst. As the amount of bony tissue increases, a ground-glass (Fig. 49-16) or sclerotic appearance is seen. On MRI, the signal is reported as rather variable on T2-weighted sequences, whereas the T1 signal is more commonly hypointense. Nonhomogeneous enhancement may be obtained after gadolinium administration.[32]

Although differentiation on imaging between fibrous dysplasia and ossifying fibroma may be problematic, the latter more commonly

Figure 49-16. Coronal computed tomography scan showing fibrous dysplasia. An expansile lesion can be seen in the right ethmoid with a mixed density pattern, including calcifications, ground-glass appearance, and low-density areas. This pattern reflects the different degrees of mineralization of the fibrous tissue replacing normal bone. The lamina papyracea is interrupted (*arrowheads*) but the orbit is not invaded. The cribriform plate is thickened and displays a ground-glass pattern (*arrows*), suggesting fibrous dysplasia.

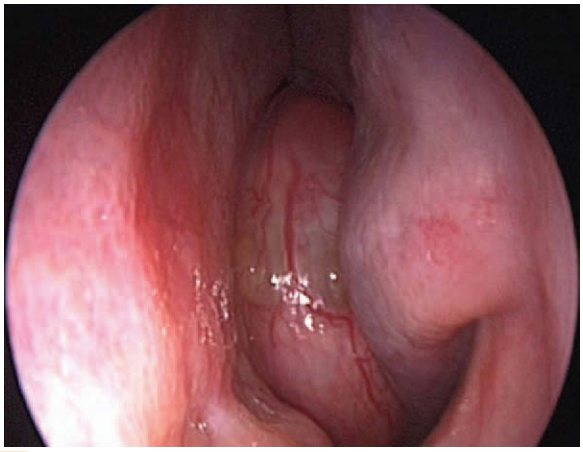

Figure 49-17. This benign schwannoma appears on endoscopy as a large polypoid mass entirely filling the left nasal cavity. A network of capillaries on the surface of the lesion may suggest a diagnosis of hypervascularized tumor.

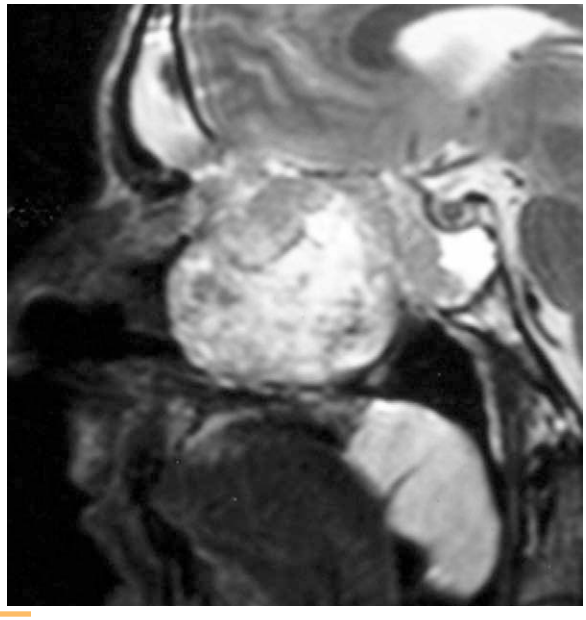

Figure 49-18. Benign schwannoma on a sagittal T2-weighted, spin-echo magnetic resonance image. A large hyperintense mass obliterates the nasal fossa and protrudes into the sphenoid and frontal sinus. The ethmoid roof is eroded, and the crista galli cannot be recognized. A concomitant hemangioma of the soft palate is also visible.

appears on CT as a well-defined, multiloculated lesion, bordered by a peripheral eggshell-like dense rim.[64] On MRI, ossifying fibroma displays a hyperintense signal on T2-weighted sequences, but on T1-weighted sequences, the signal is intermediately intense to hyperintense in the central part of the lesion and hypointense in the outer shell.[32]

The objective of surgical treatment is different for the two lesions. Ossifying fibroma requires radical resection, in view of both the high rate of relapses, accounting for 44% of lesions localized in the ethmoids,[65] and the aggressive behavior of recurring tumors, with local destruction and potential invasion of adjacent vital structures.[66] Successful removal of ossifying fibroma via an endoscopic approach has been reported in the literature.[67-69] For fibrous dysplasia, surgery is intended to relieve symptoms such as visual impairment due to compression of the optic nerve or to correct aesthetic deformities, but not to remove the entire lesion. Optic nerve decompression has been traditionally achieved through external transfacial, neurosurgical, or combined approaches, although most cases can nowadays be managed with endonasal endoscopic surgery.[67,70-73] Radiotherapy is contraindicated because of the risk of malignant transformation and the possible side effects on facial skeleton growth in young patients.

Medical treatment of fibrous dysplasia based on the use of bisphosphonates (i.e., pamidronate), which inhibit osteoclastic activity, has been used with success in patients with extensive lesions associated with significant disfigurement and pain.[74,75]

Schwannoma

Schwannoma is a neurogenic tumor arising from the Schwann cells of the sheath of myelinated nerves. This is a rare neoplasm that can be found in any part of the body; in 25% to 45% of cases, it is localized at the level of the head and neck. Only 4% of the lesions involve the sinonasal tract, where the ethmoid, maxillary sinus, nasal fossa, and sphenoid are involved (listed in order of decreasing frequency). According to a review of 160 cases,[76] the age distribution ranges from 6 to 78 years, with most patients between 25 and 55 years of age, and no gender preference. The lesion has been only rarely observed in association with von Recklinghausen's disease.

Sinonasal schwannomas are considered to arise more frequently from the ophthalmic and maxillary divisions of the trigeminal nerves, but they can also originate from sympathetic fibers of the carotid plexus or parasympathetic fibers of the pterygopalatine ganglion. Particularly in large lesions, identification of the nerve of origin at surgery is extremely difficult.

Macroscopically, the tumor appears as a well-delineated but nonencapsulated globular, firm to rubbery yellow-tan mass.[77] Histologically, schwannomas are composed of cellular Antoni A areas with Verocay bodies and hypocellular myxoid Antoni B areas. Tumor cells are strongly and diffusely immunoreactive for S-100 protein. The pathologist should differentiate schwannoma from neurofibroma, solitary fibrous tumor, leiomyoma, fibrous histiocytoma, and fibrosarcoma.

At endoscopy, the appearance of a sinonasal schwannoma is quite nonspecific; the presence of a network of capillaries on the surface may sometimes suggest a diagnosis of a hypervascular lesion (Fig. 49-17). CT findings are not usually diagnostic, but MRI reflects the histologic features of the lesion (Fig. 49-18). Specifically, lesions with a prevalent

Antoni A component have an intermediate signal on both T1- and T2-weighted images, whereas in those with a predominant Antoni B pattern, which is related to a loose myxoid stroma, hyperintensity is observed on T2-weighted images.[78,79]

Radical surgery is the treatment of choice for sinonasal schwannoma. Before the advent of endoscopic surgery, a large variety of external approaches were employed in relation to the site and size of the lesion. After the initial report by Klossek and coworkers[80] on the endoscopic management of sinonasal schwannomas, other cases with successful outcome have appeared in the literature,[81-83] thus supporting the idea that even for this tumor, endoscopic surgery can be considered a viable alternative to traditional techniques.

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CHAPTER FIFTY

Medical Management of Nasosinus Infectious and Inflammatory Disease

Scott C. Manning

Key Points

- Recurrent or chronic rhinosinusitis is multifactorial with potential predisposing conditions such as viral illness, allergic rhinitis, immunodeficiency, ciliary dyskinesia, cysteinyl leukotriene imbalance, and environmental irritants.
- A large percentage of cases of recurrent or chronic rhinosinusitis represent underlying inflammation at times aggravated by infection. Studies show a spectrum ranging from a more TH1 (nonallergic) cytokine profile with nonatopic chronic rhinosinusitis to a more TH2 (allergic) cytokine profile with atopic chronic rhinosinusitis associated with nasal polyps.
- Because of the ambiguities in diagnostic criteria and the lack of correlation of imaging findings with symptom scores, validated quality of life instruments are probably the best tools for assessing efficacy of treatment modalities.
- Treatments with the strongest level of evidence to date include: topical glucocorticoids for acute and chronic rhinosinusitis with or without polyps; nasal saline lavage; long-term macrolide treatment for chronic rhinosinusitis; and short-term antibiotics for well-defined, imaging-proven acute rhinosinusitis.
- Surgery is considered last, after medical therapeutic options have been exhausted, but there is a paucity of comparative efficacy studies for surgical treatment of rhinosinusitis.

The incidence of rhinosinusitis as defined by health surveys in the United States has been estimated at 14% of the adult population.[1] A review of the Canadian National Health Survey from 1996 and 1997 found a 5% overall incidence in that country.[2] A history of rhinosinusitis was more common in women than in men and in adults than in children. Lower socioeconomic status, cigarette smoking, allergic rhinitis, and asthma were all associated with a higher incidence of sinusitis history. Sinusitis ranks in the "top 10" diagnoses associated with loss of productivity for U.S. businesses (just behind spine and back conditions).[3] Approximately 200,000 patients per year are estimated to undergo sinus surgery in the United States for rhinosinusitis symptoms that are unresponsive to medical therapy.[4]

In the patient presenting with infrequent episodes of acute rhinosinusitis complicating viral upper respiratory infection, the disease is usually easily managed with short courses of antibiotics administered by the primary care physician. Unfortunately, chronic or recurrent rhinosinusitis implies a multifactorial etiology and is not solved simply by an empiric selection of antibiotic. Predisposing factors for recurrent or chronic rhinosinusitis include viral illness, allergic rhinitis, anatomic obstruction, immunodeficiency, ciliary dyskinesia, cystic fibrosis, and environmental irritants. Genetic factors obviously play a role, although they are poorly understood at present for allergic diathesis and other key predisposing conditions. The role of bacteria and fungi, obvious in cases of culture-proven acute bacterial or invasive fungal rhinosinusitis, is much less clear in chronic disease. This form of disease was previously thought to be mostly infection aggravated by underlying host factors, but the pendulum of thought is now swinging toward the view that a large percentage of cases of chronic or recurrent sinus disease represent underlying inflammation at times aggravated by infection.[5]

Diagnosis

Definitions

The symptoms of rhinosinusitis overlap with predisposing conditions such as viral illness and allergic rhinitis. Current consensus-defined, symptom-based definitions of chronic rhinosinusitis (CRS) usually include congestion and nasal discharge (anterior or posterior) possibly with facial pain or pressure and loss of smell, continuing beyond the expected 7- to 10-day course of a viral illness. Supporting evidence includes rhinoscopically determined presence of purulent rhinorrhea, polyps, or mucosal edema and imaging findings of sinus or ostiomeatal mucosal inflammation.[6]

Because of the ambiguities in defining *recurrent or chronic rhinosinusitis*, the U.S. Food and Drug Administration (FDA), in November 2006, issued guidelines for industry studies.[7] The FDA has defined *chronic rhinosinusitis* as symptoms lasting more than 8 weeks and *recurrent rhinosinusitis* as more than three episodes of rhinosinusitis per year. In contrast to historic views, the FDA made the statement that "chronic sinusitis is not usually caused by bacterial infection" (Table 50-1).[7]

Table 50-1

List of Abbreviations

FDA	Food and Drug Administration
CT	Computed tomography
IL	Interleukin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
CRS	Chronic rhinosinusitis
ARC	Acute rhinosinusitis
VAS	Visual analog scale
ECP	Eosinophilic cationic protein
QOL	Quality of life
RSV	Respiratory syncytial virus
IFN	Interferon
TGF	Transforming growth factor
CYSLTS	Cysteinyl leukotrienes
PG	Prostaglandin
ASA	Acetylsalicylic acid
SE	Staphylococcal enterotoxin
LPR	Laryngopharyngeal reflux
NO	Nitric oxide
MRSA	Methicillin-resistant *Staphylococcus aureus*
AERD	Aspirin exacerbated respiratory disease

The term "sinusitis" is used in the media as a synonym for headache from any cause, congestion in general, and even low energy. It is vital that the clinician carefully delineate the specific symptoms that the patient describes rather than assume that the patient's complaint of "sinusitis" means the same thing to the patient as it does to the physician. A specific diagnosis matching the patient's major complaints is a vital first step toward making an effective treatment plan. And because nasal and sinus mucosa represents a continuum with no clear border, *rhinosinusitis* is probably better suited to describe upper airway inflammation.

Imaging

The first role of imaging is to potentially exclude rhinosinusitis in the differential diagnosis of congestion, rhinorrhea, headache, facial pain, and so on. In other words, the presence of rhinosinusitis symptoms in the absence of sinus mucosal inflammation with imaging is, by definition, not rhinosinusitis. On the other hand, the common situation of incidental sinus mucosal inflammation on imaging in a patient with no symptoms corresponding to rhinosinusitis does not determine a need for therapeutic intervention.

Plain radiographs have fallen out of favor in many clinical centers because of their low sensitivity compared with computed tomography.[8] However, mucosal inflammation too minimal to be apparent on plain films probably correlates well with absence of clinically relevant rhinosinusitis. Specifically, plain films, if findings are normal, can help to rule out rhinosinusitis as a cause of congestion in a patient with allergic rhinitis or as a cause of headache in a patient with a family history of migraine (Fig. 50-1).

Figure 50-1. A coronal computed tomography (CT) scan demonstrating an opacified, hypoplastic right maxillary sinus in a pediatric patient presenting with night-time cough.

Studies have documented the incidence of incidental sinus mucosal abnormalities on computed tomography (CT) to be 20% in normal adults[9] and to be as high as 60% in children younger than 8 years in temperate latitudes in winter.[10] Presumably, these findings relate to the fact that viral upper respiratory infection causes rhinosinusitis with inflammation of nose and sinuses that can persist radiographically up to several weeks.[11]

Results of studies correlating CT scores with symptom scores and outcomes are mixed. Stewart and colleagues,[12] in a prospective study of 57 adults, found that high preoperative CT scores correlated with more symptom improvement after sinus surgery. In a retrospective study of children, Kim and associates[13] reported that high preoperative CT stage, along with nasal polyposis and cigarette smoke exposure, was associated with worse outcomes after surgery. Other studies have found an association between bony hypertrophy[14] and frontal and sphenoid disease (factors that presumably indicate a more severe level of inflammation) and symptom scores. On the other hand, other prospective studies in adults have not shown correlation between preoperative CT scans by any (Lund-Mackay, Kennedy, or Harvard) staging system and symptom scores or outcomes.[15,16]

Differences in study conclusions regarding the extent of CT evidence of sinus inflammation and patient symptom scores and outcomes are probably due in part to patient selection biases. Presumably, patients with more severe disease in general have higher symptom scores and more measurable response to therapy, but the final word will have to await larger and better-designed studies. Some of the lack of correlation between symptoms and imaging is due to differences in underlying patient perception. Davis and colleagues, who used the SNOT-16 (Sinonasal Outcome Test 16), SF-36 (36-item Medical Outcomes Short Form Survey), BSI, (Brief Symptom Inventory) and PHQ (Patient Health Questionnaire)[17] to assess adult patients with CRS selected for surgery, found a high rate of somatization, anxiety, and depression in the study population. Somatization in particular was associated with higher SNOT-16 scores (independent of imaging findings), although all groups of patients showed improvement after surgery.[17] Facial pain and headache, in particular, among sinusitis symptoms correlate poorly with imaging findings.[18,19]

In the United States at present, medical insurance reimbursement patterns are favoring ownership of medical infrastructure such as CT scanners and diminishing payment for procedures such as surgery. The result may be a tendency for greater utilization of imaging. The clinician must keep in mind that the goal of treatment is to improve the patient's symptoms, not necessarily to make the imaging findings improve. It is not necessary to repeat imaging in a patient with symptom improvement.

Rhinoscopy

Nasal endoscopy is generally considered a necessary part of any comprehensive assessment of rhinosinusitis. Rigid or fiberoptic endoscopes provide excellent visualization of the nasal cavities, but in their absence, an otoscope placed in the nostril can give an excellent magnified view up to the middle meatus and beyond. Polyps, rhinorrhea, turbinate hypertrophy, and other types of congestion can be evaluated and roughly quantified. Also, many authorities have shown fairly good correlation between culture results for endoscopically guided middle meatus specimens and maxillary sinus aspirates.[20]

Smell and Nasal Airflow

Smell can be measured objectively, and subjective responses on validated outcome measures correlate fairly well with objective test results.[21] Subjective reports of nasal obstruction correlate fairly well with objective measures of nasal airflow such as rhinomanometry but less well with acoustic rhinometry, a measure of nasal airway volume.[22]

Outcome Measures and Quality of Life

The FDA recommends that the following measures be considered for new trials evaluating efficacy of medical therapies for rhinosinusitis: symptom profile with visual analog scale (VAS; mild, moderate, severe), nasal endoscopy with a scoring system, imaging with scoring, documentation of other medications, cigarette smoking, comorbid conditions such as asthma, and additional tests such as smell and mucociliary function.[6]

Rhinosinusitis is rarely health threatening but represents a significant quality of life issue for a large number of people. Because of the ambiguities in diagnostic criteria and the lack of correlation of imaging and symptom scores, validated quality of life instruments are probably the best tools for assessing efficacy of treatment modalities. This field is still young and instruments are constantly being refined.

Several quality of life instruments have been utilized in studies of acute and CRS, although not all have been validated. The most commonly utilized general health status instrument has been the Medical Outcomes Study Short Form 36 (SF-36). Several disease specific instruments have been developed for rhinosinusitis; a sample of studies utilizing these instruments is shown in Table 50-2.[23-30]

The Rhinosinusitis Outcome Measure (RSOM) has 31 items, permitting an assessment of symptom severity and importance. The Sinonasal Outcome Test (SNOT-20) has perhaps been the most utilized to date. A revision, the SNOT-22, adds questions about nasal congestion and smell. SNOT-5 is a short evaluation directed at the pediatric population and completed by parents. The Rhinosinusitis Disability Index (RSDI) links symptoms to their effect on daily life. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) emphasizes allergic symptoms. The RhinoQOL focuses on symptom impact.

Predisposing Factors

Viral Illness

Upper respiratory viruses are probably the most common predisposing factors for acute rhinosinusitis, especially in children. The link between viruses and CRS is less clear.[31] A multiplicity of viruses has been implicated in the common cold, including influenza, parainfluenza, ade-

Table 50-2

Rhinosinusitis Quality of Life Studies

Study	Outcomes	Study Design	Findings
Ragab et al[23]	SF-36, Visual Analog Scale, SNOT-20, nitric oxide, computed tomography, AR, endoscopy	PRCT: surgery vs. medical treatment for CRS	Both groups significantly improved but there was no difference, except for increased nasal volume by AR in surgical group
Winstead and Barnett[24]	SF-36	Cohort of adult patients with sinus surgery, compared before and after surgery	Improvement in symptom scores at 6 and 12 months postoperatively
Hissaria et al[25]	RSOM, magnetic resonance imaging, endoscopy	PRCT: oral prednisone vs. placebo for adult patients with nasal polyps	More improvement in RSOM scores in prednisone group; also, reduced polyps
Browne et al[26]	Sinonasal Outcome Test-22	Adult patients with polyps: polypectomy alone vs. polypectomy with additional sinus surgery	Slightly more improvement on SNOT-22 results in group with more extensive surgery
Senior et al[27]	Rhinosinusitis Disability Index	Adult patients with CRS vs. controls	Patients with CRS and allergic rhinitis had the worst scores
Friedman et al[28]	Standardized Rhinoconjunctivitis Quality of Life Questionnaire, endoscopy	Hypertonic saline vs. Dead Sea salt nasal lavage in adult patients with CRS	Both groups improved, more with Dead Sea salt
Atlas et al[29]	RhinoQOL	Adult patients with ARS and CRS vs. controls	Good internal consistency for symptom impact in patients with ARS and CRS
Rudnick & Mitchell[30]	Sinonasal Outcome Test-5	Cohort of children with CRS having adenoidectomy or undergoing endoscopic sinus surgery	Overall symptom improvement lasting 24 months postoperatively—no difference between groups

AR, acoustic rhinometry; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; PRCT, prospective randomized controlled trial; RSOM: Rhinosinusitis Outcome Measure; SF-36, 36-item Medical Outcomes Short Form Survey; SNOT-20, Sinonasal Outcome Test–20.

novirus, rhinovirus, and respiratory syncytial virus. Because of the number and antigenic variability of potential causative agents, viral vaccine therapy is not likely to become an effective weapon in the battle against the common cold.

Most spread of viral illness occurs via hand-to-hand contact, and studies have demonstrated reduced viral illness with protocols of hand washing and alcohol gel.[32] Parents of children with recurrent sinusitis are encouraged to find child-care settings with the fewest possible children in order to reduce their children's viral exposure. Sometimes coordinating vacations or child-care with relatives to remove the patient from the daycare setting for several weeks allows enough mucosal recovery to break a cycle of recurrent infection.

Vitamin C has long been proposed as both prevention and therapy for the common cold, but studies have failed to demonstrate significant benefit. Similarly, zinc gluconate may have a mild effect in reducing cold symptoms, but its mechanism of action is poorly understood.[33]

Antiviral agents have received much attention for the prevention and possible treatment of the common cold. A 2007 Cochrane review concluded that although interferons had some efficacy, their side effects were often equal to the cold symptoms.[34] Other antiviral agents, including dipyridamole, palmitate, and pleconaril, show potential efficacy with fewer side effects. Currently there are no antiviral agents with FDA approval for prevention or treatment of the common cold.

Of particular interest in CRS is the possible association between early viral infection and a subsequent shift from an immune response dominated by type 1 helper T cell (TH1) cytokines (nonallergic) to TH2 cytokines (allergic). Respiratory syncytial virus (RSV) and rhinovirus infection at an early age have been associated in some studies with subsequent reactive airways disease and asthma.[35,36] An individual's susceptibility to a shift to a TH2 immune response and future refractory respiratory disease is probably related to several factors, including genetic predisposition, timing of the initial and subsequent viral infections, and exposure to environmental antigens.[37]

Environmental Irritants

More than half of the people in the United States are estimated to live in areas where exposure to ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide, lead, and particulates exceeds the National Ambient Air Quality Standards. The reunification of Germany has provided an interesting laboratory for examining the possible effects of air pollution on incidence of rhinosinusitis. As levels of particle emissions and sulfur dioxide dropped with the modernization of the former East German industry, the incidence of rhinosinusitis reported on standardized questionnaires for pediatric patients has also fallen significantly.[38]

Air pollution may impair respiratory mucociliary protection and potentially augment sensitivities to common aeroallergens.[39] Exposure to outdoor and indoor pollutants is therefore one possible factor explaining the dramatic increase in rates of immunoglobulin (Ig) E–mediated disease, including asthma and allergic rhinitis, reported from most industrialized areas over the past 20 years.

A careful history of environmental exposures should be a part of the evaluation of every patient with recurrent or chronic rhinosinusitis. Indoor sources include cigarette smoke,[40] smoke from wood-burning stoves, formaldehyde, copier fluid, latex, chlorine, paint, and perfumes.

Allergy

Allergy may be a predisposing factor, a comorbid state, or even part of the definition of rhinosinusitis. Up to 30% of the adult population of the United States is allergic according to skin test results, and the percentage appears to be greater overall in populations of patients with rhinosinusitis. Studies have shown a higher prevalence of allergic rhinitis in patients with acute rhinosinusitis[41] and more CT evidence of mucosal inflammation with viral illness.[42] The association between allergic rhinitis, defined as atopy, and CRS is less clear. For example, Gelnick and colleagues[43] studied 115 adults with CRS and found that allergy was not significantly associated with asthma or chronic sinusitis. Interestingly, CT scores and global health outcome measures were worse in the nonatopic group. However, in children, some studies have shown a strong association between a diagnosis of rhinosinusitis and allergic rhinitis.[41]

Inflammation

The last few years have witnessed a dramatic increase in the number of published studies linking chronic mucosal inflammation in general to chronic or recurrent rhinosinusitis. In aggregate, studies show a spectrum in inflammation from a more TH1 cytokine profile in nonatopic CRS to a more TH2 profile with atopic CRS associated with nasal polyps.[6,44] These studies have led to a fundamental shift in treatment philosophy away from exclusively antimicrobial strategies towards a more balanced approach that includes anti-inflammatory treatments also.

Histologic studies of adult patients with long-standing CRS demonstrate sinus mucosal changes similar to those seen with remodeling in asthma, with greater basement membrane thickness, increases in goblet cells and submucosal mucous glands, and eosinophilic infiltrates.[45] Epithelial damage from eosinophil-mediated cytotoxicity may promote a vicious circle of increased antigen interaction and/or infection, which in turn leads to even greater inflammation. Studies have shown that pediatric patients with CRS also demonstrate increases in basement membrane thickening and eosinophilic infiltrate in comparison with controls, but not as much as adult patients with CRS.[46] The assumption is that the adult patients exhibit more remodeling as a function of more damage and repair over a longer period.

Peripheral eosinophilia has been associated with sinus CT stage, history of asthma, and presence of polyps in patients with CRS.[47,48] Tissue eosinophilia has also been related to greater severity and worse prognosis in patients with CRS.[49,50] Cytokine expression is up-regulated in patients with CRS in comparison with controls, showing a TH1 profile in nonatopic CRS with increases in interferon-γ and tumor growth factor-β and a TH2 profile in patients with nasal polyps showing increases in interleukins IL-5 and IL-13.[51] Nasal polyps exhibit a special inflammatory profile, with decreased tumor growth factor β_1, increases in IL-5, eotaxin, and eosinophilic cationic protein, and an imbalance of metalloproteinases (Fig. 50-2).[52,53]

Eicosanoids and Aspirin Sensitivity Triad

Abnormal regulation of arachidonic acid metabolism pathways with elevated cysteinyl leukotrienes has been associated with allergic rhinitis, asthma, CRS, nasal polyposis in general and aspirin triad (steroid-dependent asthma, nasal polyposis, and aspirin intolerance). Cysteinyl leukotrienes promote airway inflammation and fibrosis. The extent of up-regulation of these leukotrienes in such disorders appears to be linked to the level of eosinophilic inflammation as indicated by IL-5 and eosinophilic cationic protein measurements.[54] Patients with nasal polyps in particular may also have a down-regulation of the cyclooxygenase pathway with decreased production of prostaglandin E_2, an anti-inflammatory mediator.[55] These abnormalities do not seem to be related to allergy (Fig. 50-3).

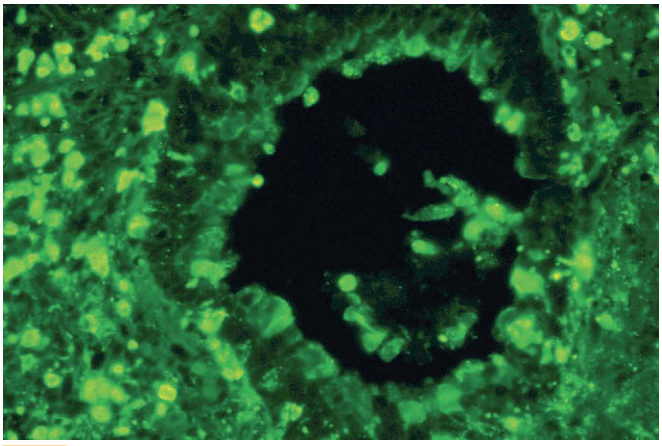

Figure 50-2. Immunohistochemical stain for major basic protein in a surgical specimen from a patient with classic allergic fungal rhinosinusitis. Degranulating eosinophils can be seen surrounding a mucous gland.

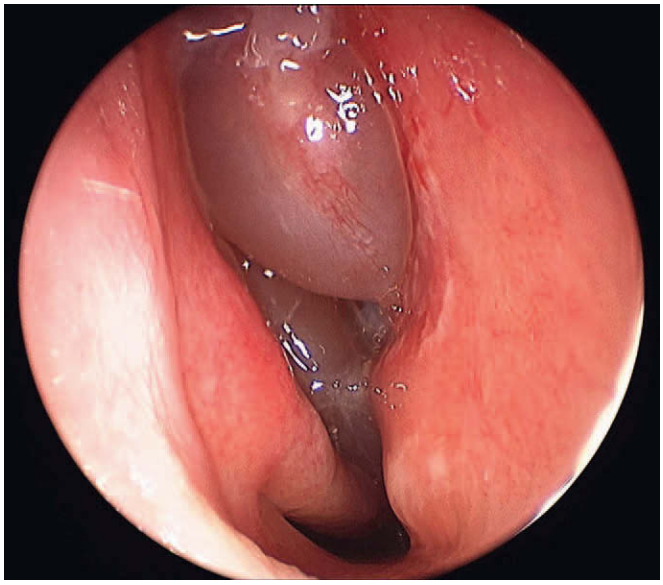

Figure 50-3. Nasal polyposis in a patient with aspirin-exacerbated respiratory disease.

There appears to be a spectrum of severity with aspirin sensitivity, and up to 20% of patients who have steroid-dependent asthma without overt nasal polyps can have exacerbation of asthma with aspirin exposure.[56] Also, some patients without overt asthma have respiratory symptoms with ASA exposure. Perhaps as much as 20% of patients with CRS and tissue eosinophilia experience upper and lower airway disease flare-ups with ASA exposure. The average age of onset of aspirin-exacerbated respiratory disease (AERD) is young adulthood, and a majority of patients are women. The definitive diagnosis is made with an oral challenge of aspirin in a controlled setting (anaphylaxis management), during which the physician looks for symptoms such as flushing, sneezing, wheezing, conjunctivitis, rhinorrhea, and periorbital edema. Oral aspirin challenge is being replaced in some centers by nasal challenge with lysine aspirin, which has nearly the same sensitivity and specificity but is much safer.

Superantigens

In 2001, Schubert[57] wrote that "superantigen amplification of preexisting immunopathology is the proposed mechanism for disease induction and maintenance" in a large proportion of patients with CRS. In other words, microbial infection in a patient with an underlying hyperinflammatory state leads to amplified inflammation with chronicity and recurrence. Staphylococcal bacterial antigens such as enterotoxins A and B (SEA, SEB) and toxic shock toxins could potentially bind at the T-cell V beta site, thus bypassing normal antigen processing and dramatically up-regulating IgE-mediated inflammation.[58,59] A significant percentage of people have staphylococcal colonization at any given time, affording a source for inflammation amplification.[60] Similarly, antigenic fungi such as *Alternaria* species could potentially act as superantigens.[61] Ferguson and associates,[62] in a study of patients with CRS and eosinophilic mucin, found that more than half of the patients had histologic evidence of bacteria within the mucin.[62] These researchers hypothesized that perhaps a significant proportion of patients with culture-nonspecific CRS may have bacterial superantigen inflammation amplification.

Laryngopharyngeal Reflux

Laryngopharyngeal reflux could potentially inflame nasal mucosa and predispose to CRS. On the other hand, gastroesophageal reflux in general can be associated with an allergic diathesis, and laryngopharyngeal reflux may be more of a comorbid state than a cause of CRS. *Helicobacter pylori* has been detected within sinuses of patients with CRS, but a causal relationship has not been demonstrated.[63]

Nitric Oxide

Nitric oxide, which is produced by nasal and sinus mucosa, has a role in inflammation and presumably also in local immune defense. In fact, healthy sinuses contain a higher concentration of nitric oxide than the nasal cavities and may serve in part as reservoirs. Nitric oxide metabolites have been found to be elevated in sinus lavage fluid from patients with CRS, and nasal nitric oxide levels have been found to decrease with successful treatment of CRS.[64-66]

Bacteria

Sinus health is a result of adequate ventilation through patent ostia, adequate mucociliary clearance, and competent local and systemic immune defense. When conditions allow, opportunistic bacterial flora of the nasal cavities can proliferate and colonize sinus mucosa, leading to a circle of infection leading to secondary mucosal edema and dysfunction followed by further loss of mucosal immune defense and further infection.

Acute Rhinosinusitis

It has been estimated that up to 2% of all cases of routine viral rhinosinusitis progress to acute bacterial rhinosinusitis (ABRS). In culture studies, the most common organisms are *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae,* and *Moraxella catarrhalis* (more common in children). A 2008 study reported that the use of polyvalent pneumococcal vaccines in children with secondary herd immunity effects in adults may be causing an overall decrease in the number of *S. pneumoniae* infections.[67] The subsequent loss of bacterial interference from *Streptococcus* species may in turn be causing a rise in disease and colonization secondary to *Staphylococcus aureus*, with implications also in terms of superantigen inflammation. Studies also point to an increase in the recovery of methicillin-resistant *S. aureus* (MRSA) in acute and chronic rhinosinusitis.[68] A significant percentage of *S. pneumoniae* isolates show intermediate penicillin resistance, and a growing percentage of *Haemophilus* isolates are positive for beta-lactamase.[69]

Chronic Rhinosinusitis

The role of bacteria in CRS is uncertain. A 2003 study comparing middle meatus and maxillary sinus culture specimens from patients with CRS and from healthy controls showed an 80% correlation between findings in middle meatus and maxillary specimens as well as recovery of similar bacteria in similar frequencies in the two populations.[70] In the CRS group, the most common isolates were *S. aureus* (36%), coagulase-negative *Staphylococcus* (20%), and *S. pneumoniae* (17%). In a 2007 study, the researchers found no microbiologic culture difference between patients with CRS and controls but the patients with CRS did have more white blood cells in their secretions.[71]

Studies from cohorts of patients undergoing surgery for CRS sometimes show a greater prevalence of gram-negative rods.[72] Not surprisingly, writers are reporting steady increases in antibiotic resistance among cultured organisms, including MRSA.[73,74] And one study has shown an association between intracellular presence of *S. aureus,* as determined by confocal microscopy of surgical specimens, and persistent clinical disease (Fig. 50-4).[75]

Biofilms

Biofilm formation may explain in part some of the mysteries of CRS, including indolent course and poor response to antibiotic therapy. Several studies in humans and in animal models of sinusitis have demonstrated evidence of biofilm formation by confocal microscopy and other techniques.[76] Biofilm formation is probably more likely with gram-negative rods such as *Pseudomonas* species. In one study, researchers performed in vitro assays of nasal secretions from patients with CRS and found that 28% had bacteria with a "severe biofilm-forming capacity."[77]

Fungi

Fungi can cause invasive sinonasal infections in profoundly immunocompromised patients, but over the last decade, some workers have put forth the controversial proposal that a large percentage of CRS is caused

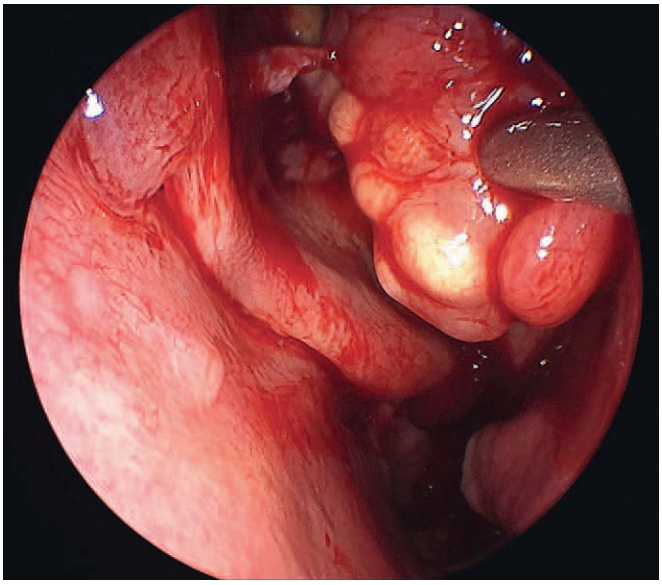

Figure 50-4. Focal nasal polyposis in an 18-year-old man with an ongoing methicillin-resistant *Staphylococcus aureus* (MRSA) infection of his foot. The yellow areas proved to be microabscesses, culture specimens of which also grew MRSA.

by reaction to fungi. Fungal spores are more ubiquitous than pollen in normal inspired air, so it is not surprising that, through the use of techniques to bring spores in contact with culture media, fungi can routinely be cultured from nasal mucus from patients with CRS as well as from normal patients.[78] In terms of inciting inflammation, the majority of molds (as with pollens) are not antigenic, particularly the basidiospores or leaf molds, which predominate in the inspired air of more temperate latitudes. More antigenic fungi include *Bipolaris*, *Alternaria,* and *Aspergillus* (after germination), spores of which are much more commonly seen along the subtemperate latitudes around the 30th parallel.[79,80]

In the United States, skin testing shows that about 4% of adults are allergic to some type of common mold, and the highest incidence of fungal allergy is seen in urban pediatric patients with asthma.[81,82]

A significant percentage of patients with CRS have *allergic nasal mucin*, defined as evidence of eosinophilic inflammation, and the controversy regarding fungi as inciting factors continues.[83] At the furthest point along the continuum of sinonasal fungal allergy is the entity *allergic fungal rhinosinusitis*, defined most strictly as the presence of allergic mucin—defined histologically as sheets of eosinophils with Charcot-Leyden crystals and fungal elements—in an atopic, immunocompetent patient. Reports of these cases tend to cluster along the 30th parallel of latitude, and when culture results are positive, dematiaceous fungi such as *Bipolaris* and *Alternaria* are seen most commonly in the Western Hemisphere, and *Aspergillus* species in the Eastern Hemisphere.[84]

In conclusion, there is little question that fungi can contribute to CRS—especially in atopic patients breathing antigenic fungi (30th parallel). There may well be a continuum among patients with nasal eosinophilia, and one study has shown that the extent of eosinophilic inflammation within "allergic mucin" is proportional to the presence and number of fungal elements seen histologically.[85] But for the majority of patients with CRS who do not have classic allergic fungal rhinosinusitis, the role of fungi in the pathogenesis of chronic inflammation remains uncertain.

Treatment

Tables 50-3 and 50-4 summarize the medical therapies for rhinosinusitis, both with and without proven benefit in comparative trials.

Antibiotics

Oral Antibiotics

Acute rhinosinusitis outcome studies are easily influenced by the "Pollyanna phenomenon," whereby differences in treatment outcomes with different therapies are difficult or impossible to demonstrate because of vague diagnostic criteria and vague outcome measures.[86] For example, studies that rely solely on vague clinical entry criteria without imaging in pediatric patients subject to more viral infections than adults usually show no outcome difference between antibiotic therapy and placebo.[87]

However, adult studies with strict entry criteria have shown benefit for antibiotic treatment. A Cochrane review summarized in the 2007 European position paper on nasal polyps[6] found 49 studies of acute rhinosinusitis suitable for analysis. The review concluded that antibiotics were more effective than placebo in reducing symptom scores and improving imaging findings. Overall, no difference between antibiotics was noted. However, the clinician must always keep in mind local resistance patterns and the risk of side effects when choosing therapy. Therapy should always be guided by culture results (from endoscopically guided collection of middle meatus specimens) whenever possible. The most common recommendation remains amoxicillin or amoxicillin-clavulanate as first-line therapy in patients not allergic to penicillin who have uncomplicated disease.[69]

CRS is even more difficult to define in clinical studies, and to date there are no randomized placebo-controlled trials demonstrating efficacy of short courses of oral antibiotics. Uncontrolled retrospective studies have shown improvements in patient symptoms with oral antibiotics and topical or oral steroids.[88,89] In one randomized study of adults with CRS, ciprofloxacin achieved a better cure rate than amoxicillin-clavulanate in patients for whom initial middle meatus cultures were positive for bacteria.[90] With our current lack of placebo-controlled studies, however, whether symptom improvements in these studies represent an antibiotic treatment effect or simply the natural history of the disease course remains uncertain.

Long-Term Macrolide Antibiotic Therapy

Long-term macrolide therapy was first reported in Japan to be effective for treatment of pulmonary peribronchiolitis and later to be effective for CRS. The effect appears to involve anti-inflammatory mechanisms independent of antimicrobial effects, including reducing the production of IL-5, IL-8, and granulocyte-macrophage colony-stimulating factor and decreasing neutrophil inflammation.[91] Uncontrolled studies have shown improvements in outcome measures for adult patients with CRS. Cervin and associates,[92] monitoring 17 patients treated with erythromycin or clarithromycin for 3 months, found that a majority improved as measured by VAS for congestion and rhinorrhea symptoms.[92] These researchers also measured improvements in saccharin transport time but not ciliary beat frequency. Ragab and colleagues[23] showed equal improvements as assessed by VAS, SNOT-22, and the 36-item Medical Outcomes Study Short Form in a cohort of adults with CRS randomly assigned to either endoscopic sinus surgery or 3 months of erythromycin therapy.[23]

Wallwork and associates[93] reported in 2006 on the results of a double-blind, randomized placebo-controlled study in which 64 adult patients with CRS received either roxithromycin therapy or placebo for 3 months. The researchers found significant improvements in the treatment group for SNOT-20 and nasal endoscopy scores, saccharin transit time, and IL-8 levels.[93] In a 2007 overview of studies of long-term macrolide therapy for CRS, Cervin and Wallwork[94] concluded that macrolides can possibly also decrease biofilm formation and overall bacterial virulence. Those workers recommended macrolide administration as part of primary therapy in nonatopic patients with bilateral disease.

Intravenous Antibiotics

Intravenous antibiotic therapy has been shown to reduce symptoms in some patients with CRS, but controlled trials are lacking. Tanner and Fowler,[95] in a review of five retrospective trials, found a short-term success rate of 29% to 89% but high relapse rates. Other reviews of retrospective studies have found high complication rates.[96] Intravenous

Table 50-3

Medical Treatment of Rhinosinusitis: Therapies with Proven Benefit in Comparative Trials

Class	Examples	Indications	Level of Evidence	Comments
Topical glucocorticoids	Budesonide Flunisolide Fluticasone Mometasone	ARS and CRS with or without polyps	Strong	Mucosal adverse effects (drying and bleeding) minimized by concurrent use of nasal saline and by proper technique
Nasal saline lavage		ARS, CRS with or without polyps	Strong	Lavage more effective than spray
Long-term macrolide	Clarithromycin Erythromycin Roxithromycin	CRS with or without polyps	Strong	Studies show benefit with treatment for 3 months or longer
Oral glucocorticoids	Methylprednisone Prednisone	CRS with or without polyps	Strong for CRS with polyps Good for CRS without polyps	Risk of serious side effects
Short-term antibiotics	Amoxicillin-clavulanate Cefuroxime Quinolones	ARS	Moderate	Studies show benefit when ARS is strictly defined and confirmed with imaging or a sinus aspiration and culture Quinolones are not the first-line therapy because of their risk profile
Aspirin desensitization	Oral aspirin or nasal lysine—aspirin spray	AERD (polyps)	Moderate	Open studies show benefit especially for patients with AERD and nasal polyposis after surgery
Antivirals	Dipyridamole Interferon Pleconaril	Viral ARS	Moderate	Side effects of treatment equal to ARS symptoms
Antihistamines	Azelastine Cetirizine Loratadine Olopatadine	ARS in patients with allergic rhinitis	Weak	Intranasal preparations may be more efficacious for nasal symptoms

AERD, aspirin-exacerbated respiratory disease; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis.

antibiotics are possibly best reserved for treatment of CRS due to culture-proven, oral-antibiotic resistant organisms.

Topical Antibiotic Therapy

The idea of topical antibiotic therapy is compelling as a potential way to deliver high concentrations of antibiotics to the nose and sinuses without significant systemic absorption. Also, the ability to deliver high concentrations topically provides theoretical advantages in terms of both the treatment of resistant organisms and the lower risk of inducing resistance than is associated with systemic antibiotics. Studies in the 1980s proved that topical therapy with mupirocin could be an effective means of at least temporarily treating the *S. aureus* nasal carrier state in individuals.[97,98] This treatment has growing relevance for controlling or preventing outbreaks of methicillin-resistant *S. aureus*, treating severe eczema (exacerbated by *Staphylococcus*), and, possibly, in treating CRS by reducing the superantigen effect in predisposed individuals.

The best method of delivering topical antibiotics has yet to be determined. Topical ointment applied to the nostrils appears to stay confined mostly to the nasal floor and inferior turbinates.[99] Sniffing, positive-pressure sprays, and nebulizers appear to distribute the medication better intranasally, but sinus penetration is usually poor.[100,101]

Topical antibiotic preparations have included nebulized forms of common intravenous antibiotics and antibiotics in saline, such as gentamicin or tobramycin 80 mg/L, ceftazidime 0.1% solution, mupirocin 7.5 to 22 g/L, clindamycin 600 mg/L, and ciprofloxacin 500 mg/L.[102]

Uncontrolled studies have implied symptom improvements with some topical regimens. Vaughan and Carvalho,[103] for example, found that adult patients with CRS who received 3 weeks of nebulized treatment using agents indicated by results of culture and sensitivity testing had longer symptom-free intervals than historic controls, who were treated with systemic antibiotics. Scheinberg and Otsuji[104] reported on the use of 3 to 6 weeks of nebulized antibiotics in 41 patients with CRS that had failed to improve with endoscopic sinus surgery and oral antibiotics; the results were overall good symptom response with few side effects.[104] To date, the literature contains one comparative trial assessing topical therapy for CRS. Desroisiers and Salas-Prato[105] randomly assigned 20 patients to therapy with either saline with tobramycin or plain saline via a large-particle nebulizer for 4 weeks and reported similar outcomes.[105]

In 2008, Lim and coworkers[106] reported on their systematic review of all English language studies of topical therapy for CRS. Overall, they noted better results with antimicrobial irrigation than with nebulizer therapy. Regarding antibiotic studies, they found the highest level of evidence in the study by Moss and King,[107] which demonstrated less need for subsequent surgery in patients with cystic fibrosis who were treated with tobramycin irrigations than in patients who did not

Table 50-4

Medical Treatment of Rhinosinusitis: Therapies without Proven Benefit in Comparative Trials (or with Insufficient Evidence to Date)

Class	Examples	Indications	Comments
Topical antibiotics	Mupirocin 0.4% solution Tobramycin 0.08% solution	CRS, cystic fibrosis, carrier of methicillin-resistant *Staphylococcus aureus*	Mupirocin solution may be beneficial for *S. aureus* carriers; topical antibiotics have not proved superior to nasal saline in comparative trials
Topical antimycotics	Amphotericin B 100 µg/mL	CRS?	Equal to plain saline lavage in comparative studies
Systemic antimycotics	Terbinafine Voriconazole	CRS?	One placebo-controlled trial showed no benefit
Intravenous antibiotics	Cefuroxime	CRS with culture-proven resistant bacteria?	Short-term improvement in retrospective studies, but high relapse rates
Leukotriene modifiers	Montelukast Zileuton Zafirlukast	CRS	Benefit for nasal polyposis in a few open studies
Anti-reflux therapy	Proton pump inhibitors	CRS?	No comparative studies showing benefits to date
Decongestants	Oxymetazoline Phenylpropanolamine	?	No benefits in comparative trials
Mucolytics	Guaifenesin	Cough?	Few trials for analysis
Anti–Immunoglobulin E	Omalizumab	Nasal polyps?	No trials to date; use is limited by cost and parenteral delivery
Immune globulin intravenous		CRS with primary immunodeficiency	Some benefit in noncomparative retrospective reviews
Alternative	Vitamin C Zinc *Echinacea*	ARS, CRS?	Vitamin C and *Echinacea* may have a mild decongestant effect

ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis.

undergo such irrigations.[107] Moss and King noted, however, that saline alone seemed to provide benefits equal to those from saline plus antibiotics, as in the controlled study by Desroisiers and Salas-Prato.[105]

Disruption of biofilms may become a new approach for topical antimicrobial therapy. In one study, 1% baby shampoo was effective in disrupting *Pseudomonas* biofilms in vitro and appeared to achieve some symptom improvement in an uncontrolled clinical trial involving 17 patients with CRS.[108]

Systemic Antifungal Therapy

The idea of systemic antifungal treatment of CRS probably first derived from studies suggesting a possible effect of antifungal treatment of allergic bronchopulmonary aspergillosis. A few single case reports have suggested a treatment effect of oral voriconazole in patients with classic allergic fungal sinusitis,[109,110] but controlled studies for this disease are lacking. The one prospective placebo-controlled trial to date involved treatment of adults with routine CRS.[111] In this study, 53 adults were randomly assigned to receive either oral terbinafine at 625 mg/day or placebo. Outcomes were assessed with CT scores, the Rhinosinusitis Disability Index, and VAS. Both groups improved slightly over the course of the study, with no difference between the groups.

Even if one subscribes to the idea that fungal spores within nasal mucus are inciting inflammation, it is difficult to postulate a mechanism whereby systemic antifungal therapy would have an effect, because little or no drug would likely reach the mucus and spores would be relatively unaffected. By definition, fungus-induced CRS is not histologically an infection but, rather, an inflammatory reaction to extramucosal fungal elements. To date, there is no strong evidence that systemic antifungal therapy is useful in the treatment of CRS.

Topical Antifungal Therapy

Topical antifungal therapy seems to make more sense in terms of potentially inhibiting fungal spores from progressing to a more antigenic mycelial state within nasal mucus. Ponikau and associates[112] were early proponents of topical antifungal therapy for CRS, and they even patented the concept of topical nasal antifungal use in the United States. In their comparative study of 24 patients with CRS who received either amphotericin B (250 µg/mL) or saline nasal irrigation, CT and endoscopy scores were slightly better in the treatment group but there was no difference in patient outcomes according to SNOT-20 scores.[112] In a similar but more strongly powered study, Weschta and colleagues[113] found no significant difference between topical amphotericin B and saline given over 8 weeks in 78 adult patients with CRS. In a subsequent study, the same group found no effect of amphotericin B topical treatment on levels of eosinophilic cationic protein or tryptase or on post-treatment detection of fungus.[114] In the largest controlled trial to

date, Ebbens and colleagues[115] studied 116 adult patients with CRS who were randomly assigned to receive nasal irrigation with either amphotericin B, 25 mL of a 100 µg/mL solution, or saline. Outcomes as indicated by high values for VAS scores, nasal endoscopy scores, polyp scores, and quality of life scores were similar for the two groups. Topical antifungals may have a nonspecific anti-inflammatory effect similar to that seen with macrolides,[116] but to date, controlled studies have not shown superiority of antifungal therapy over nasal saline.

Antimicrobial Treatment Issues

Potential problems related to antimicrobial use include alterations in the natural ecology by reduction of bacterial interference, selection of resistance genes, allergic reactions, interactions with other drugs, and enterocolitis. No doubt, some of the inflammation issues behind CRS relate to the so-called hygiene hypothesis, whereby factors such as urbanization, smaller families, vaccinations, high-fat diet, and early introduction to food antigens other than mother's milk may contribute to the shift from a TH1 to a TH2 immune response profile in genetically predisposed individuals. Ironically, overuse of antibiotics may be another factor in the hygiene hypothesis. Later studies have confirmed that the normal gastrointestinal carrier state of *H. pylori* in young children has been significantly reduced in recent years, presumably as a herd effect from adult treatment for gastritis and ulcer disease. In one fascinating study of 7412 children in the National Health and Nutrition Examination Survey, *H. pylori* seropositivity was found to be inversely associated with early diagnosis of asthma and also with a history of allergic rhinitis and eczema.[117]

Prolonged use of antibiotics may promote chronicity of infection by creating beta-lactamase–producing normal flora organisms that can protect potentially sensitive pathogens from antibiotic effects. In addition, antibiotics may inhibit normal flora such as viridans streptococci and nonhemolytic streptococci, which could otherwise competitively inhibit colonization by pathogenic organisms. *Clostridium difficile* enterocolitis is being reported with much greater frequency since 2000, and risk factors for this disorder include the use of multiple antibiotics, such as cephalosporins and quinolones, over prolonged periods. *C. difficile* infections are increasingly virulent and resistant, resulting in a true health care crisis, especially in large hospitals.

The quinolones present special problems besides enterocolitis risk and probably should not be regarded as first-line drugs in the treatment of rhinosinusitis. The FDA has issued warnings about prolonged QT interval and alterations in glucose homeostasis with use of gatifloxacin, and about QT prolongation with use of moxifloxacin. The quinolones in general should not be used in conjunction with other drugs that may prolong the QT interval, such as erythromycins, antipsychotics, and antidepressants. Moxifloxacin should also be used with caution in patients with central nervous system disorders. Use of quinolones, especially ciprofloxacin, has been associated with tendinitis and Achilles tendon rupture. The risk is probably greatest in patients undergoing concomitant steroid therapy.

Topical Nasal Steroids

Glucocorticoids bind to glucocorticoid receptor-α and trigger several potential anti-inflammatory pathways. They can reduce inflammation in both allergic and nonallergic patients, and many controlled studies have shown their benefit in both acute and chronic rhinosinusitis. Topical budesonide, flunisolide, and mometasone furoate, when used in conjunction with oral antibiotic therapy, have all been shown to improve symptoms in patients with ARS.[118-120] In one placebo-controlled trial, mometasone twice daily was superior to both placebo and amoxicillin in reducing symptoms.[121] Similarly, topical nasal steroids are usually found to reduce symptoms in patients who have CRS without polyps, but the level of evidence is not as strong as in ARS.[6,122] Many controlled studies have demonstrated reduction of polyp size as well as objective and subjective improvement in nasal congestion with long-term use of intranasal steroids in patients with CRS and nasal polyps.[6,122]

The currently approved intranasal preparations show similar efficacies in available studies as well as low systemic bioavailability and systemic steroid effect. Epistaxis is greater in nasal steroid users in placebo-controlled trials,[123] and the risk may be increased by dry climate, use of fluticasone propionate, and improper technique (such as a right-handed person spraying directly into the right distal septum). Use of intranasal steroids in children appears to be safe, involving possible mild short-term delays in linear growth with some preparations but no evidence of long-term effects.[124]

Systemic Steroids

Placebo-controlled trials of systemic steroids in adult patients with ARS have shown some short-term symptom improvements, particularly with pain, but no differences at study completion.[125]

Placebo-controlled trials overall show some effect of systemic corticosteroids for CRS without polyps but a much stronger effect for CRS with polyps.[6] In patients with CRS who have significant nasal congestion or polyps, many clinicians utilize systemic steroids for short periods to increase nasal patency and allow for penetration of topical nasal steroid sprays. The potential complications of systemic steroids are well-known, and these medications must be used with extreme caution in patients with diabetes, osteoporosis, glaucoma, or a history of mental health issues.

Leukotriene Modifiers

Leukotriene modifier therapy has been shown to improve symptoms in patients with allergic rhinitis, but controlled studies of the use of these agents in rhinosinusitis are lacking. In one noncontrolled study of zileuton, a 5-lipoxygenase inhibitor, the addition of this agent to standard therapy resulted in improvements in the nasal symptoms of loss of smell, rhinorrhea, and congestion in patients with aspirin-intolerant asthma.[126] Montelukast, a leukotriene receptor antagonist, has been shown in a few open studies to benefit patients with nasal polyposis.[127,128] Patients using zileuton or zafirlukast must be monitored with liver function testing.

Nasal Saline Lavage

Nasal saline has shown benefits in the treatment of rhinosinusitis in several controlled studies. Rabago and colleagues[129] found greater improvements in outcome, as assessed with the Medical Outcomes Survey Short Form 12 (SF-12) and the Rhinosinusitis Disability Index, with use of hypertonic saline lavage than with standard therapy over 6 months in a cohort of adult patients with CRS. Similar improvements have been demonstrated in pediatric patients.[130] Other studies have shown no benefit for hypertonic solution over normal saline, with more patient discomfort for hypertonic solutions.[131] Nasal saline irrigation has been shown to potentially provide more benefit than nasal saline spray in patients with CRS evaluated with SNOT-20 scores and medication usage.[132] A 2007 Cochrane review concluded that nasal saline appears to have benefits as an adjunctive treatment for CRS.[133] This beneficial effect must be taken into account in the interpretation of results of comparative trials using saline as a "control."

Decongestants

Decongestants are α-adrenergic agonists that cause varying levels of tachyphylaxis and are best utilized for short-term (3-5 days) relief of symptomatic congestion. Prospective studies have not demonstrated more rapid resolution of overall sinus symptoms with use of decongestants in adult or pediatric patients with CRS.[134] Both topical (phenylephrine, oxymetazoline) and oral (phenylpropanolamine, pseudoephedrine) decongestants have side effects, including insomnia, palpitations, and elevated blood pressure. They should be used with caution or avoided in patients with high blood pressure or thyroid disease and in patients taking monoamine oxidase inhibitor medications.

Mucolytics

Guaifenesin, the most commonly used mucolytic agent, is often dispensed in combination with a decongestant. High doses (up to 2400 mg/day for adults) are required for effect, and at those doses, emesis and abdominal pain are frequently reported as mild adverse effects. The only prospective trials for the use of mucolytics in CRS to date involve bromhexine, and results are mixed.[135]

Antihistamines

Antihistamines are commonly prescribed for patients with rhinosinusitis, although so far there are no controlled studies demonstrating efficacy of these agents for CRS. One prospective controlled trial showed symptom benefit with loratadine in patients with ARS and known allergic rhinitis.[136] Two intranasal spray antihistamines, azelastine and olopatadine, are approved in the United States for use against allergic rhinitis.

Omalizumab

Omalizumab is a recombinant monoclonal antibody to IgE with indication for treatment of refractory allergic asthma. It has also been shown to be effective for treatment of allergic rhinitis. No studies have been published to date regarding the use of omalizumab for rhinosinusitis, but a one paper has hypothesized that this agent may be effective for nasal polyposis, given the fundamental role of IgE inflammation in polyposis.[137] Use of omalizumab is limited by its high cost and the need for parenteral delivery.

Anti-Reflux Therapy

Prospective controlled studies of the use of anti-reflux therapy for CRS are lacking. A meta-analysis of published reports concluded that there is an association between laryngopharyngeal reflux and CRS at a grade C level of evidence.[138] A 2006 Cochrane review concluded that we have insufficient evidence at present to conclude that proton pump inhibitor therapy is useful for the cough associated with CRS.[139] If there is an association between laryngopharyngeal reflux and CRS, it may be more of a comorbid state in the spectrum of allergic diathesis rather than directly causal.

Intravenous Immune Globulin

Primary immunodeficiency can manifest initially as recurrent or chronic rhinosinusitis. In a review of 252 patients with common variable immunodeficiency, the most common symptoms were respiratory tract infections, including sinusitis, otitis media, bronchitis, and pneumonia.[140] Intravenous immune globulin therapy results in significant initial improvements for these patients, but the overall natural tendency over time is toward progressively more sinus and pulmonary disease.[141] The diagnosis of common variable immunodeficiency is often delayed by several years, and clinicians should have a low threshold for performing immunologic evaluations, including IgG subclass analysis, in patients with CRS.[142]

Aspirin Desensitization Therapy

Although no placebo-controlled studies have been conducted on this issue, evidence is growing that aspirin desensitization therapy can alleviate CRS symptoms in patients with aspirin-exacerbated respiratory disease, especially those with nasal polyps. At least two thirds of patients with this disorder show response to aspirin desensitization with clinical improvements in symptoms and decreases in serum cysteinyl leukotrienes.[58] In open, noncontrolled studies, aspirin desensitization is shown to reduce the number of episodes of sinusitis and to decrease polyp recurrence and the need for additional surgery.[143,144] In a prospective study comparing 100 mg with 300 mg aspirin daily in patients with aspirin-exacerbated respiratory disease , the 300-mg cohort showed significantly more improvement in smell and no recurrences of nasal polyps during the study period.[145]

Special Considerations

Elderly

Older patients may complain more of chronic postnasal discharge, throat clearing, and morning cough. First-generation antihistamines are poorly tolerated in older patients owing to the agents' higher rate of anticholinergic adverse effects, such as urinary retention and reduced visual accommodation. Ipratropium nasal spray may be a more appropriate alternative for chronic rhinorrhea in such patients, and daily saline nasal spray and oral gargle are often helpful. Oral decongestants must be used with caution because of the potential for adverse cardiovascular and central nervous system effects.

Children

Children with recurrent or refractory rhinosinusitis have a higher overall incidence of allergic rhinitis than adults, and anti-inflammatory therapy should be considered as an adjunct to antibiotics. Second-generation antihistamines such as loratadine and cetirizine may be more effective for congestion and better tolerated in children than the first-generation agents. Some nasal steroid preparations are approved in the United States for use in children 2 years and older, in whom they are generally well tolerated.

The overall strategy in caring for children with CRS is to address suspected predisposing factors, beginning with the least costly and least invasive appropriate therapeutic interventions. Most children experience spontaneous improvement in symptoms with natural maturation of systemic immunity.

Athletes

For athletes subject to drug testing, the first consideration in treating rhinosinusitis should be to avoid medications proscribed by the relevant testing authority. Commonly proscribed medications include α-agonists, such as phenylephrine, ephedrine, and pseudoephedrine, and systemic corticosteroids. Athletes are generally allowed to use topical nasal steroids if they can present letters to the testing authority about the therapy from their treating physicians.

Pregnancy

Increased nasal congestion due to hormonal effects is common in pregnancy, usually starting in the second trimester. Conservative measures such as nasal saline and cromolyn can be tried first, but topical corticosteroids appear to have no teratogenic potential and have a long record of safe use in pregnancy. The second-generation antihistamines have demonstrated no teratogenic potential in animal studies and are generally considered safe.

Conclusion

Acute rhinosinusitis and chronic rhinosinusitis are at best significant quality of life issues and at worst threats to health when they trigger or aggravate underlying pulmonary disease in patients with asthma or cystic fibrosis. ARS is often triggered by viral illness and is self-resolving. CRS is multifactorial, and the pendulum is swinging toward the view that chronic inflammatory factors may be more important than infection. A balanced approach aimed at likely triggers is necessary to break a circle of recurrent disease. Patients must be educated about their risk factors before they can understand the process of treatment, a necessary step for improving compliance with recommended therapies. Logically, therapeutic options should be considered along a hierarchy starting with the least difficult and most risk-free options, with more intense therapeutic options added only after initial failure to improve. Surgery for CRS should be considered last, after medical options have been exhausted.

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CHAPTER FIFTY-ONE

Primary Sinus Surgery

Devyani Lal

James A. Stankiewicz

Key Points

- The choice of open versus an endoscopic approach depends on the exposure needed and on the surgeon's training and experience.
- Primary surgery for chronic rhinosinusitis is now almost exclusively performed endoscopically.
- Functional endoscopic sinus surgery aims to re-establish physiologic sinus ventilation and mucociliary clearance.
- Surgery for chronic rhinosinusitis is adjunctive to medical therapy; the ostiomeatal complex is its primary target.
- Identification of anatomic landmarks and variations helps limit complications.
- Inadvertent penetration of the orbit or the skull base may occur in the following situations: lamina papyracea lying medial to maxillary ostium or dehiscence of the lamina; maxillary sinus hypoplasia; low or sloping fovea ethmoidalis; sphenoid sinus septations attached to the carotid canal; and carotid canal or optic nerve dehiscence.
- The anterior skull base is highest anteriorly and slopes downwards posteriorly.
- The anterior wall of the sphenoid sinus is convex toward the surgeon; the skull base is concave, sloping away from the surgeon.
- The maxillary antrostomy helps identify the medial orbital wall; intranasal herniation of orbital fat upon pressing of the eyeball increases chances of orbital trauma.
- Major complications of endoscopic sinus surgery are cerebrospinal fluid leak, blindness, diplopia, and internal carotid artery injury.
- Functional endoscopic sinus surgery provides significant improvement in overall general health.
- Common causes of failure of endoscopic sinus surgery are lateralized middle turbinate, missed middle meatal antrostomy, maxillary ostium stenosis, frontal recess scarring, residual ethmoidal air cells, and adhesions.
- Endoscopic approaches may be used for sinonasal tumors and skull base surgery.

The maxillary sinus has been the focus of surgical attention since the 17th century. An approach through the anterior maxillary wall was described as early as 1675 by Molinetti.[1] Other methods were also described, but none of these was satisfactory until Caldwell, Spicer, and Luc added a counter-opening into the nose in the 1890s.[1,2] The Caldwell-Luc procedure remained popular as the primary choice of treatment in chronic rhinosinusitis (CRS) through the early 20th century. Although Hirschmann conducted the first endoscopic examination of the nose with a modified cystoscope in 1901,[3] the modern era of endoscopic sinus surgery (ESS) evolved with the development of Hopkins rods in the 1950s. Messerklinger[5] pioneered the study of the endoscopic anatomy and pathophysiology of the paranasal sinuses, publishing his experience with ESS in 1978.[4,6] He highlighted the role of the ostiomeatal complex (OMC) in the pathophysiology of rhinosinusitis and directed attention to it during surgery. His resident, Stammberger,[4,6-10] was instrumental in popularizing this technique outside Germany and Austria.[3] Kennedy[7] is credited with the introduction of ESS to the United States in 1985.[3] Primary surgery for CRS is now performed almost exclusively endoscopically. Endoscopic approaches also now dominate the surgical treatment of many other sinonasal disorders. Understanding of the anatomy and pathophysiology of each disease process is necessary before one can embark on surgery.

Anatomy

Identification of anatomic landmarks and recognition of variations are imperative to maximize the benefit and limit the complications of ESS.[11] This chapter offers a concise review of the relevant anatomy. Although this review focuses on the endoscopic anatomy, the surgeon must be familiar with external landmarks and the three-dimensional orientation. Standardized nomenclature based on the recommendations of the Anatomic Terminology Group at the International Conference on Sinus Disease is used in this chapter.[12]

Ostiomeatal Complex

The OMC is a functional entity of the anterior ethmoidal complex representing the final common pathway for drainage and ventilation of the ethmoid, maxillary, and frontal sinuses. Its exact boundaries are not defined. It comprises the uncinate process, the ethmoid infundibulum, anterior ethmoid cells, and the ostia of the anterior ethmoid, maxillary and frontal sinuses (Fig. 51-1). The uncinate process lies in the sagittal plane and runs from anterior-superior to postero-inferior. Laterally, the uncinate process covers the infundibulum, which is the three-dimensional space where the anterior sinuses drain. The hiatus semilunaris inferior, commonly referred to as the hiatus semilunaris, is a two-dimensional space between the uncinate process and the ethmoid bulla. Superiorly, the uncinate process may attach either to the lamina papyracea, the skull base, or the middle turbinate (Fig. 51-2).[11] Because this attachment causes variations in frontal sinus drainage, its preoperative identification is important.

Middle Turbinate

The middle turbinate has three attachments. Superiorly and anteriorly, it is in a sagittal plane and attaches to the skull base along the cribriform plate. The middle part is in a coronal plane and attaches to the lamina

papyracea. Posteriorly, the middle turbinate angles into an axial plane and then attaches to the posterior aspect of the lamina papyracea. The most posterior end attaches to the perpendicular process of the palatine bone. The middle and the posterior parts, which lie in the coronal and axial planes, respectively, are part of the basal lamella of the middle turbinate.

Ethmoid Complex

The ethmoid complex is divided by the basal lamella into the anterior and posterior ethmoid cells. The anterior ethmoids are further divided into infundibular cells and the ethmoid bulla. Infundibular cells include the agger nasi cell, the terminal cell, and the suprainfundibular cell. The agger nasi lies at the attachment of the middle turbinate to the lateral nasal wall and, when pneumatized, forms the agger nasi cells. These cells, the most anterior of the ethmoid cells, can frequently be identified on preoperative computed tomography (CT). On endoscopy, they appear as a projection of the lateral nasal wall anterior to, or at the attachment of, the middle turbinate. The terminal cell can be found at the superior extent of the infundibulum that does not end in a blind sac. The suprainfundibular cell lies at the superior aspect of the infundibulum. The ethmoid bulla is the largest and most constant cell of the ethmoid complex. It is often the first cell encountered posterior to the uncinate process during entry into the anterior ethmoids. Its lateral wall is the medial wall of the orbit, and it drains into the suprabullar or retrobullar recess (sinus lateralis). The suprabullar recess and the retrobullar recess are a cleft rather than a cell. They are bordered superiorly by the ethmoid roof, laterally by the lamina papyracea, inferiorly by the roof of the ethmoid bulla, and posteriorly by the basal lamella. The hiatus semilunaris superior or hiatus secondarius is the two-dimensional space that opens into these recesses. Haller cells are infraorbital ethmoid cells that can narrow the maxillary sinus ostium.

The posterior ethmoid sinus consists of one to five cells that drain into the superior or the supreme meatus. When highly pneumatized, this sinus may extend into the lamina papyracea and anterior wall of the sphenoid. The sphenoethmoidal cell (Onodi cell) is a posterior ethmoidal cell that extends laterally and superiorly to the sphenoid sinus. Both the internal carotid artery (ICA) and the optic nerve can be exposed within it. The sphenoid sinus lies inferomedial to the posterior ethmoids.

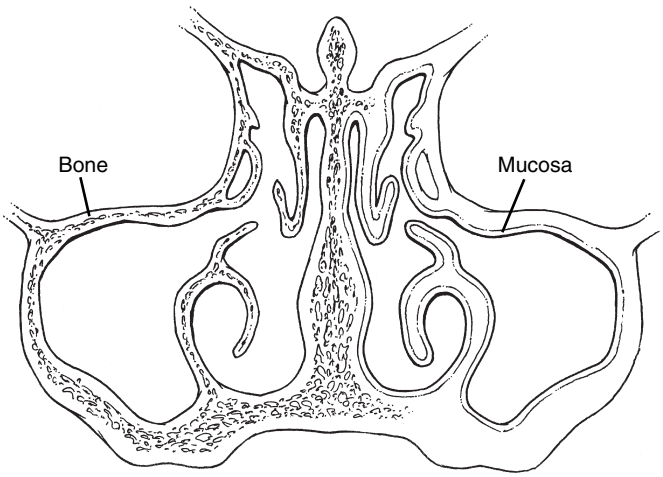

Figure 51-1. Coronal view of the ostiomeatal complex. The uncinate process lies in a sagittal plane. The maxillary sinus ostium drains into the infundibulum.

Maxillary Sinus

The natural ostium of the maxillary sinus drains into the infundibulum and is found just below the orbital floor in the medial wall of the sinus. It usually lies halfway between the anterior and posterior walls.[13] It is located in the superior third of the infundibulum in 10%, the middle third in 25%, and the inferior third in 65% of cases.[14] The natural ostium is elliptical; accessory ostia are round and are present in 10% of patients.[13]

Sphenoid Sinus

The sphenoid sinus is the most posterior paranasal sinus. Its natural ostium opens into the sphenoethmoid recess. This recess lies posterior to the superior turbinate, and anterior to the anterior wall of the sphenoid. The sphenoid ostium is located approximately halfway up the anterior wall of the sinus. It is medial to the posterior end of the superior turbinate in 83% of cases.[15] The ostium lies at a distance of 6.2 to 8.0 cm (average, 7.1 cm) from the nasal spine, at an angle of 30 to 34 degrees with the floor (Fig. 51-3).[15-18] The surgeon must identify the natural ostium to safely enter this sinus. The sphenoid is surrounded by several critical structures, such as the ICA, the optic nerve, and the skull base. Septations in the sphenoid frequently have attachments to the ICA.

Frontal Sinus

The frontal sinus drains into the middle meatus through the frontal recess. The frontal recess is located at the junction of the frontal sinus and the most anterosuperior part of the ethmoid sinus. The medial wall of the frontal recess is made by the anterior-most part of the middle turbinate, and its lateral wall is the lamina papyracea.[12] The anterior wall of the frontal recess is the posterior wall of the agger nasi cell. The recess is hourglass shaped, with the narrowest part at the frontal ostium. The ostium of the frontal sinus can drain anterior to the uncinate

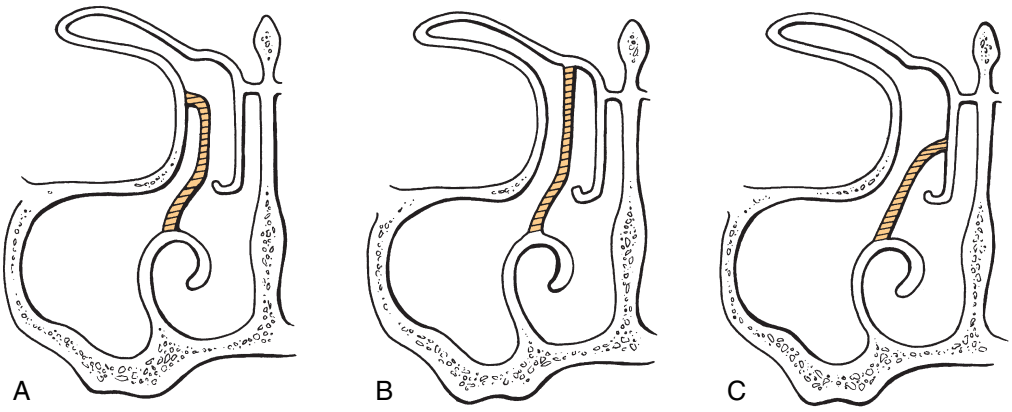

Figure 51-2. The superior attachment of the uncinate process can attach to the lamina papyracea **(A)**, the roof of the ethmoid **(B)**, or the middle turbinate **(C)**. If the uncinate process attaches to the roof of the ethmoid or to the middle turbinate, the frontal sinus drains into the infundibulum. If the uncinate attaches to the lamina papyracea, the frontal sinus drains medially, next to the middle turbinate.

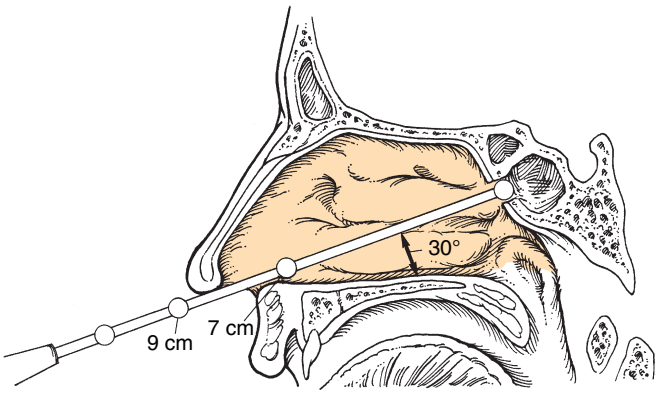

Figure 51-3. The sphenoid ostium lies at a distance of 6.2 to 8.0 cm (average, 7.1 cm) from the nasal spine, at an angle of 30 to 34 degrees to with the floor.

process or, more commonly, posterior to the uncinate process, usually in the ethmoid infundibulum.[19] The frontal or frontoethmoid cells lie superior to the agger nasi cells and can show variable pneumatization. Kuhn[20] identified the following four pneumatization patterns:

Type 1: a single cell superior to the agger nasi.

Type 2: a tier of two or more cells above the agger nasi cell.

Type 3: a single cell extending from the agger cell into the frontal sinus.

Type 4: an isolated cell within the frontal sinus.

Cells posterior to the frontal sinus, pneumatizing superior to the orbit, are termed *supraorbital ethmoid cells*.[20]

Anterior Skull Base

The anterior skull base is formed by the cribriform plate medially. The fovea ethmoidalis extends laterally from the cribriform plate to form the roof of the ethmoid sinuses. The fovea ethmoidalis may lie higher than the cribriform plate. The lateral lamella of the cribriform plate joins the fovea ethmoidalis and is considerably thinner than the lateral part of the ethmoid roof. Keros[21] classified the skull base into three types according to the depth of the olfactory groove: type 1, 1 to 3 mm; type 2, 4 to 7 mm; and type 3, 8 to 16 mm. Because the lateral lamella forms most of the steeply inclined ethmoid roof in a type 3 configuration, patients with this configuration are especially vulnerable to penetration of the anterior skull base during ESS. The anterior skull base is highest anteriorly and slopes downwards posteriorly.[22] This fact is important to remember during opening of the sphenoid sinus through the posterior ethmoids. Dissection must be directed inferiorly and medially.

Anatomic Variations

Anatomic variations include structures such as a concha bullosa, agger nasi cells, infraorbital (Haller) cells, sphenoethmoid (Onodi) cells, and paradoxic middle turbinates. *Concha bullosa* is the term used for an aerated middle turbinate or a cell found within the middle turbinate. These structures appear as a widened area of the middle turbinate, and they may obstruct the OMC. In the absence of a history of sinusitis, the incidental finding of widened middle turbinate during endoscopy or concha bullosa on CT does not mandate further investigation.[23] Most patients with such variations remain asymptomatic. In a review of 172 coronal sinus CT scans, a concha bullosa was found in 28% of patients with sinus disease and in 26% of patients without sinus disease.[24]

Indications for Primary Sinus Surgery

Any sinonasal pathology may be approached endoscopically or externally. There is no absolute indication for an endoscopic approach for any sinonasal disease. Although the majority of sinus procedures are performed endoscopically to treat CRS, the indication for surgery is relative. In contrast, surgery is absolutely mandated in certain sinonasal conditions, such as impending orbital or intracranial complications of acute rhinosinusitis, invasive fungal rhinosinusitis, cerebrospinal fluid (CSF) rhinorrhea, sinonasal tumors, and expansile mucoceles and polyps that cause orbital or skull base erosion.

As with the indications, there is no absolute contraindication to using the endoscopic approach. The decision to use an external or an endoscopic approach depends on the amount of exposure needed as well as the surgeon's training and experience. Box 51-1 lists the sinonasal disease processes for which surgery is indicated. In the past, most of these processes have been treated with an external approach, but ESS is increasingly being used for them.

Box 51-1

Indications for Sinus Surgery

- Chronic rhinosinusitis
- Recurrent acute rhinosinusitis
- Complications of rhinosinusitis
- Sinonasal polyposis
- Mucoceles
- Intractable epistaxis
- Cerebrospinal fluid rhinorrhea and anterior meningoencephaloceles
- Noninvasive fungal ball
- Invasive fungal rhinosinusitis
- Foreign body removal
- Choanal atresia repair
- Headaches and facial pain
- Tumors
- Expanded transnasal approaches to the skull base and orbit

Chronic Rhinosinusitis

CRS is a relative indication for surgery. Surgery is indicated in patients in whom maximal medical therapy has failed. ESS is the exclusive surgical procedure in primary sinus surgery, with external or headlamp-guided procedures being rarely used now.

Recurrent Acute Rhinosinusitis

Surgery is indicated for patients with four or more episodes of acute rhinosinusitis annually that are refractory to medical therapy.[25] Disease must be documented endoscopically or on CT scan while the patient is symptomatic before any surgical intervention is undertaken.

Acute Complications of Rhinosinusitis

Acute complications, both orbital and intracranial, that are unresponsive to medical therapy require immediate surgical intervention. Traditionally, external procedures have been used because nasal edema and inflammation can compromise endoscopic exposure. However, in experienced hands, ESS is safe and effective.[26]

Sinonasal Polyposis

Nasal polyps that erode through the skull base or the lamina papyracea must be removed to prevent impending complications. A relative indication for surgery is polyps that cause nasal obstruction and do not respond to medical therapy. However, polyps cannot be eradicated, and the goal of surgery is to provide a nasal passage for airway and drainage. Surgery is adjunctive to medical therapy—for instance, with topical and systemic steroids. Polyps can often be "cured" by surgery in patients without asthma but frequently recur in patients with asthma. Polyps in patients with Samter's triad (nasal polyps, asthma, and aspirin sensitivity) are very difficult to treat.

Mucoceles

Mucoceles are epithelium-lined, mucus-containing sacs that completely fill a paranasal sinus. They are expansile and cause bony erosion. They must be removed or drained to prevent intracranial and orbital complications. Mucoceles are more commonly found in the frontal and ethmoidal sinuses, although isolated sphenoid mucoceles have been reported.[27,28] In the past, open approaches have been used to completely remove the lining of the mucocele. However, this practice can be dangerous because mucoceles can erode through the skull base or through the lamina papyracea into the orbit. Endoscopic management with marsupialization is safe in this situation, because complete removal of the cyst lining is not required. Although technically more challenging, this latter approach is very effective, with recurrence rates near 0%.[29] A review of 108 mucoceles managed endoscopically found that 60 mucoceles had eroded the skull base, and 31 had significant intracranial extension.[29] This review reported one recurrence and one postoperative CSF leak.

Intractable Epistaxis

Uncontrolled posterior epistaxis can be controlled with endoscopic assistance in identification of the bleeding vessel[30]; this subject is described in Chapter 45.

Cerebrospinal Fluid Rhinorrhea and Anterior Meningoencephaloceles

Endoscopic repair is now standard for CSF rhinorrhea, with success rates higher than 90%.[31] Meningoencephaloceles may also be repaired endoscopically.[32] They are both described in detail in Chapter 54.

Noninvasive Fungal Rhinosinusitis

Allergic fungal rhinosinusitis and noninvasive fungal balls are usually treated endoscopically. A large antrostomy or ostioplasty is created. The fungal debris is irrigated and removed. See Chapter 48 for details.

Invasive Fungal Rhinosinusitis

Invasive fungal rhinosinusitis is almost exclusively a disease of the severely immunocompromised. All insensate mucosa and dead tissue must be débrided till healthy, bleeding tissue is encountered. An open approach may be required in extensive disease. The prognosis remains grim in spite of optimal débridement by any approach, as patients have multi-systemic comorbidities. See Chapter 48 for details.

Removal of Foreign Bodies

Endoscopy is helpful in visualization of foreign bodies and aids in their atraumatic removal.

Choanal Atresia Repair

Endonasal endoscopic approaches can be used to treat choanal atresia.[33] Schraff and colleagues[34] state that unilateral choanal atresia in children with the CHARGE association (*c*oloboma [ocular], *h*earing deficit, choanal *a*tresia, *r*etardation of growth, *g*enital defects [boys only], and *e*ndocardial cushion defect) can be managed successfully with a transnasal approach. However, patients with bilateral atresia should undergo primary transpalatal repairs owing to the high failure rate for the transnasal approach.[34] To improve success rates, some writers advocate postoperative stenting, but others condemn it.[35] Postoperative dilatation and mitomycin C therapy have been used.[35] Endoscopic repair with use of an image guidance system may improve the success rate.[36]

Headache and Facial Pain

The role of surgery for treatment of headaches is controversial. Levine and associates[37] described a multidisciplinary consensual approach on diagnosis and treatment of "sinus headache." They stated that a stable pattern of recurrent headaches with headache as the presenting complaint is most likely migraine. Recurrent self-limited headaches associated with rhinogenic symptoms are also most likely migraine. Prominent rhinogenic symptoms with headache as one of several complaints should be evaluated for otolaryngologic pathology. Headache with associated fever and purulent nasal discharge is likely rhinogenic in origin, best assessed by nasal endoscopy and sinus CT.[37] Moretz and Kountakis[38] studied the effect of ESS on subjective headache scores in patients diagnosed with CRS. In a retrospective analysis of 201 patients, they compared headache scores preoperatively and 2 years postoperatively. An overall decrease in mean headache scores was noted at the 2-year follow-up.

For patients with normal CT findings and no rhinogenic cause of headache, the role of sinus surgery is debated. Becker and Cunning[39] believe that limited ESS may cure headaches in patients with headaches that are frontal, retro-orbital, or both, in whom mild mucosal edema is found on endoscopy and sinus CT findings are normal. Parsons and Batra,[40] and Clerico and associates[41] hold that the finding of contact points on CT and/or endoscopy is a prerequisite for surgery. They also emphasize that the presence of contact points is not pathognomonic, because many patients with contact points have no headache. Clerico and associates[41] state that it is important to "prove" the correlation of the contact point with headaches by noting the response to medical therapy or a diagnostic anesthetic block. Surgery should be offered only if patients have a clear reduction in headache in response to intranasal decongestants and anesthetic sprays, or obvious findings on endoscopy, CT, or both. In a retrospective series of 34 patients, Parsons and Batra[40] reported a reduction in the intensity and frequency of headaches (91% and 85%, respectively) in patients who underwent ESS to relieve the contact points identified on CT. However, others are less optimistic. Stankiewicz[42] states that surgery should be resorted to only after both thorough neurologic and radiographic evaluation and failure of medical therapy. A directed, targeted endoscopic sinus, septal, or turbinate operation should be used only if relief from medications point to a specific anatomic problem or if specific physical or radiographic data indicate a problem site. Even with these prerequisites, surgery has variable results, may be unsuccessful, and may worsen the headache. Long-term results may be poor, and a follow-up of at least a year is necessary to confirm a successful outcome.[42]

Tumors

Benign and malignant tumors of the nasal and paranasal cavities may be resected endoscopically or with endoscopy-assisted approaches.[43-48] See Chapters 49 and 83 for a detailed description.

Expanded Utilization of Transnasal Endoscopic Sinus Approaches

The nose and the paranasal sinuses are being utilized as a pathway to approaching territories in the anterior and middle skull base, the intracranial cavity, and other regions in the skull. The endoscopic transnasal approach has gained widespread popularity for resection of pituitary tumors.[49,50] Expanded approaches to the infratemporal fossa clivus, anterior and middle cranial fossa, and petrous apex have been described.[51-55] These procedures are performed by a combined team of neurosurgeons and otolaryngologists and with the use of image guidance. Endoscopic transnasal approaches are also being applied to orbital procedures.[56-61] The endoscopic dacryocystorhinostomy procedure is gaining popularity.[56,57] Transnasal orbital decompression for Graves' ophthalmopathy, optic canal decompression, and endoscopic transnasal strabismus surgery have also been described.[58-61]

Endoscopic Sinus Surgery for Rhinosinusitis

Pathophysiology of Chronic Rhinosinusitis

The nose and paranasal sinuses are lined by pseudostratified ciliated columnar epithelium with goblet cells. Functional cilia and normal mucus production are necessary to clear the sinuses of inhaled particulate matter and bacteria. Normal mucociliary transport is also needed to maintain ostiomeatal patency.[62] The cilia of the maxillary and frontal sinuses transport mucus in specific patterns only toward the natural ostia, despite the presence of accessory ostia.[63] Rhinosinusitis is usually preceded by a viral upper respiratory infection that impedes mucociliary clearance, causing blockage of the natural sinus ostia. The ensuing series of events create a milieu that is conducive to bacterial proliferation. This bacterial infection then perpetuates further mucosal thickening and worsens blockage.[62] Allergies, likewise, can cause mucosal inflammation and edema. Anatomic obstruction of the ostia can be

caused by septal deviations, concha bullosa, paradoxic middle turbinate, infraorbital cells, agger nasi cells, and nasal polyps. Cystic fibrosis, ciliary dyskinesia, and immunodeficiencies can impair mucociliary clearance and predispose to CRS.

The Principles of Functional Endoscopic Sinus Surgery

The primary objective of functional ESS (FESS) is to restore paranasal sinus function by re-establishing the physiologic pattern of ventilation and mucociliary clearance. Surgery is always used as an adjunct to medical therapy. The goal is to remove diseased mucosa and bone, preserve normal tissue, and judiciously widen the true natural ostia of the sinuses. The OMC is most often the primary target of ESS because minimal inflammation in this area can lead to disease in the maxillary, anterior ethmoid, and frontal sinuses. Bony septations should be removed, but aggressive removal of mucosa is inappropriate and causes postoperative problems with healing. Uninvolved sinuses should be left alone. In spite of adequate surgery, mucosal disease may persist and require further medical therapy, a development that is predictive of revision surgeries. More extensive surgery may be necessary for complicated acute rhinosinusitis, extensive fungal or polyp disease, and tumors. For CRS, the concept of FESS should always be adhered to. Each patient is individually assessed to determine the site of pathology and obstruction, and surgery is tailored to address them.

Minimally invasive sinus technique (MIST)[64] is a targeted endoscopic intervention introduced in 1994. Its goals are similar to that of FESS with some differences that aim to standardize the procedure.

Preoperative Assessment

History

A thorough history is key. Specific review of CRS symptoms such as facial pain, congestion, nasal obstruction, drainage, and hyposmia is made. A detailed history of prior medical therapy for CRS is critical in determining whether the patient needs surgery. Current optimal medical therapy includes at least a 4-week course of antibiotics, nasal decongestants, topical nasal steroids, and, possibly, systemic steroids.[65] One could make a strong argument that if CRS is an inflammatory disease, oral steroids should be part of the treatment protocol. Also, in the absence of any purulence, the role of antibiotics is currently questioned by many writers.[65,66] Patients must have experienced failure of such treatment to be considered candidates for surgery. History of associated diseases and their treatment is obtained. These include allergy, asthma, polyps, aspirin sensitivity, and rhinitis medicamentosa. Exposure to smoking and environmental irritants is explored. Smoking causes mucosal inflammation and is associated with worse outcomes after ESS. Patients are counseled on the possibility of a poorer surgical outcome if they continue to smoke and are advised to stop smoking.[67] The patient's response to medical therapy, previous operations, and preexisting comorbidities influence their candidacy for surgery.

Examination

Office examination comprises a complete head and neck examination, a basic ocular examination, anterior rhinoscopy, and nasal endoscopy. Anterior rhinoscopy detects any significant septal deviation that may cause problems with nasal endoscopy. The condition of the mucosa, drainage, masses, and polyps are grossly visualized. Next, nasal endoscopy is conducted in a systematic fashion with a rigid or flexible endoscope. With rigid scopes, the examination is divided into three passes.[68] The nasal floor, nasolacrimal duct, and nasopharynx are examined on the first pass. The second pass is carried out at a 30-degree angle with the nasal floor to examine the middle meatus, OMC, and sphenoethmoid recess. Lastly, the scope is directed superiorly toward the frontal recess. The character of the mucosa, appearance of the sinus drainage pathways, and the presence of anatomic variations, structural abnormalities, purulent drainage, and polyps is noted.

Radiographic Assessment

CT is more sensitive and specific for CRS than plain radiography.[69] CRS is diagnosed on the basis of history and physical findings. CT scans are ordered either in patients with symptoms of rhinosinusitis but without examination findings or for planning of surgery for CRS. In all cases, care must be taken in interpreting "positive" CT findings and correlating them with symptoms. Prospective studies have shown that symptoms of rhinosinusitis frequently do not correlate with CT findings[70] and that incidental sinus opacifications can be found on up to 27% of sinus CT scans.[71] The severity of rhinosinusitis on preoperative CT scan does not predict the severity of symptoms as assessed by the Sinonasal Outcome Test-20 (SNOT-20) inventory in patients undergoing FESS.[72] Further, CT scores fail to predict the amount of symptomatic improvement after FESS.[72] In one prospective series, 146 adult patients undergoing ESS were evaluated with CT and the rhinosinusitis symptom inventory (RSI) preoperatively and at a minimum of 12 months postoperatively.[73] The preoperative CT scans were staged according to three systems: Lund-Mackay, Kennedy, and Harvard. No significant correlation of CT stage with symptom domains was demonstrated.

Patients with CRS must be treated medically before a sinus CT is ordered. The CT should be obtained 3 to 4 weeks after therapy to evaluate the effect of treatment.[74] If the CT scan then reveals evidence of persistent inflammation, surgery may be indicated. CT is performed to assess sinonasal anatomy and disease pattern so as to guide surgery.

Most sinus CT evaluations include coronal and axial views, with 2- to 5-mm intervals. Coronal views show the ostiomeatal unit and the relationship of the brain and orbit with the paranasal sinuses. These views are most useful in planning surgery. Axial CT views complement coronal views and must be obtained for planning of surgery for severe disease in the posterior ethmoid and sphenoid sinuses. Many institutions offer "screening sinus CT," which includes a limited number of coronal views in the bone window. Screening sinus CT has been shown to be useful for the evaluation of sinusitis, but coronal CT with a maximum of 5-mm slices to avoid loss of information through skipped areas is needed for full appreciation of the anatomy of a surgical candidate.[75] Modern CT scanners can perform 0.5-mm slices without prolonging scanning time.

The CT scans are carefully reviewed before surgery and must be available for review during the procedure to enable evaluation of the extent of disease and to assist with operative planning (Table 51-1). Meyers and Valvassori[22] reviewed 400 preoperative CT scans with attention to anatomic variations. They found six specific variations that may predispose a surgeon to inadvertent penetration of the orbit or the anterior cranial cavity. These variations are (1) lamina papyracea lying medial to the maxillary ostium; (2) maxillary sinus hypoplasia; (3) fovea ethmoidalis abnormalities such as low or sloping fovea; (4) lamina papyracea dehiscence; (5) sphenoid sinus wall variations such as septa attached to the carotid, or dehiscence of the carotid or optic nerve; and (6) sphenoethmoidal cells. Hyperpneumatization of the frontal sinus, or presence of a frontal cell, may be associated with a deep fovea ethmoidalis.[76] Blockage of any of the sinus drainage pathways can usually be identified from the presence of retained fluids within the sinuses. The cause of the blockage can also frequently be determined from the presence of thickened mucosa, polyps, or anatomic abnormalities. Calcifications or hyperintense signals can be evidence of fungus or tumors.

If there is bony dehiscence or erosion, magnetic resonance imaging (MRI) may be indicated, particularly if intracranial extension is suspected. This imaging modality is also helpful in differentiating tumors from fluid within the sinuses and for evaluating dehiscent areas of the skull base for possible encephaloceles.

Other Preoperative Preparation

Antibiotics are frequently started 7 to 10 days before surgery to reduce inflammation from purulent CRS. This reduction helps diminish bleeding during surgery. Preoperative steroids can also help decrease inflammation, especially in patients with polyps, chronic disease, or reactive airways. For maximum benefit, oral steroid therapy should be started at least 10 days prior to surgery.

Intraoperative Considerations

Image-Guided Navigation Systems

An inherent problem with endoscopic surgery is the two-dimensional view afforded by the use of the single lens. Navigational systems were

Table 51-1

Key Points to Be Reviewed on Preoperative Computed Tomography Scan Prior to Endoscopic Sinus Surgery

Disease	Extent and pattern Clinical correlation
Bony integrity (erosion/ expansion/ dehiscence)	Skull base Lamina papyracea Optic canal Carotid canal
Skull base	Height Symmetry Slope of cribriform plate and fovea ethmoidalis
Maxillary sinus	Location and attachment of uncinate process to medial orbital wall Pneumatization and height (hypoplastic maxillary sinus has low orbital floor) Presence of infraorbital cells
Ethmoid sinus	Location of anterior and posterior ethmoidal arteries Height of posterior ethmoid cells (determines slope of the skull base) Large sphenoethmoid (Onodi) cells and their relationship to the optic nerve
Sphenoid sinus	Location of sphenoid ostium Sphenoid septations and relation to carotid canal
Frontal sinus	Extent of pneumatization (deeper fovea ethmoidalis noted on side with a frontal cell and/or hyperpneumatized frontal sinus)[93] Natural drainage pathway Presence of agger nasi/frontal/supraethmoid cells Anteroposterior diameter of frontal recess in sagittal section
Miscellaneous	Septal deviations and their clinical correlation Abnormalities within the orbit

developed to help reduce the risks of ESS. These systems use thin-cut CT scans that are reformatted in various planes to create a three-dimensional configuration. This three-dimensional view is then correlated with actual patient anatomy intraoperatively with the help of a computer (Fig. 51-4). The surgeon can place a probe on any structure to get a real time, three-dimensional view of the position of the probe. These computer-assisted navigation systems, which can be extremely helpful for difficult cases and for revision surgery, are gaining in popularity. Metson[77] showed a 70.6% increase in the number of procedures using image guidance and a 92.8% increase in the number of surgeons using it in the first 2 years that this technology became available.

However, navigation systems are aids to the endoscopic sinus surgeon; they do not substitute for thorough understanding of the surgical anatomy. Even under ideal circumstances, they are associated with some degree of inaccuracy or error.[77,78] Accuracy to within 2 to 3 mm is acceptable for image guidance systems, making them most useful in confirming identity of large compartments (posterior ethmoid versus sphenoid sinus) rather than distinguishing between millimeter increments such as in the skull base. Potential sources of error include variables during CT scanning, fiducial (reference device) or headset shift, soft tissue effects during surface registration, and operator-dependent errors during registration. Also, navigation systems are not needed for every case of ESS. There is an associated increase in operative time and cost. Depending on the system used and the medical facility charges, operating time and hospital cost may be significantly higher with use of a navigation system.[77,78]

As the use of image guidance systems becomes more popular, there is a question whether it is now the standard of care.[79] The American Academy of Otolaryngology–Head and Neck Surgery[80] endorses use of these systems in the following example situations: (1) revision sinus surgery; (2) distorted sinus anatomy of developmental, postoperative, or traumatic origin; (3) extensive sinonasal polyposis; (4) pathology involving the frontal, posterior ethmoid, and sphenoid sinuses; (5) disease abutting the skull base, orbit, optic nerve or ICA; (6) CSF rhinorrhea or conditions in which there is a skull base defect; and (7) benign and malignant sinonasal neoplasms. Tabaee and colleagues,[81] comparing 60 patients undergoing image-guided surgery with 179 patients undergoing ESS without image guidance, found no statistically significant difference in the incidences of major intraoperative complications, major postoperative complications, revision procedures, and postoperative SNOT-20 symptom scores.[81] However, a higher incidence of intraoperative CSF leak was noted in the group undergoing surgery without image guidance—2.2%, vs. 0% in the image-guided surgery group. Javer and Genoway[82] report that though the long-term effect of image-guided surgery as measured by patient quality of life (QOL) remains unknown, there appears to be a significant trend indicating greater QOL improvement in the short term over non–computer-assisted FESS techniques.[82]

Intraoperative Computed Tomography Scans

The major disadvantage of image-guided surgery is that the CT scans are obtained before the procedure and may not reflect the intraoperative disease process. Attempts have been made to overcome this drawback. Brown and associates[83] reported that near–real time image-guided sinus surgery using intraoperative fluoroscopic CT is feasible.[83] Jackman and colleagues[84] described the use of intraoperative CT scanning in 20 subjects undergoing ESS. In their study, intraoperative CT scans were obtained successfully in less than 40 seconds and could be loaded into the image guidance system within minutes. New information obtained from these intraoperative scans led to performance of additional surgery in 30% of their patients. Suzuki and coworkers[85] reported use of real-time magnetic resonance imaging guidance in ESS through the use of an optical tracking system during ESS.

Choice of Anesthesia

The choice of anesthesia for ESS is determined by variables such as the extent of surgery, age and health of the patient, experience of the anesthesiologist, and patient choice.

Local Anesthesia

ESS using purely local anesthesia can be performed. The biggest drawback of local anesthesia is poor sedation. A talented, interested, and experienced anesthesiologist is required for good sedation. Without this key medical colleague, general anesthesia should be used. Sedation with local anesthesia calms patients, stabilizes blood pressure, and minimizes bleeding. ESS with use of local anesthesia may, in theory, improve safety because awake patients can report manipulation of the orbital periosteum or dura. Local anesthesia works well for young patients undergoing primary sinus surgery that lasts less than 2 hours. If the patient becomes unstable during surgery, bleeding should be quickly controlled, intravenous sedation should be stopped, the procedure should be halted, and general anesthesia should be administered. In a retrospective review of 177 patients, Fedok and associates[86] compared complication rates and recovery times in patients undergoing elective septoplasty or ESS using local anesthesia with sedation with rates in patients undergoing the same procedure using general anesthesia. Total operative and recovery times were shorter in patients receiving local anesthesia with sedation. The frequency of emesis, epistaxis, and nausea

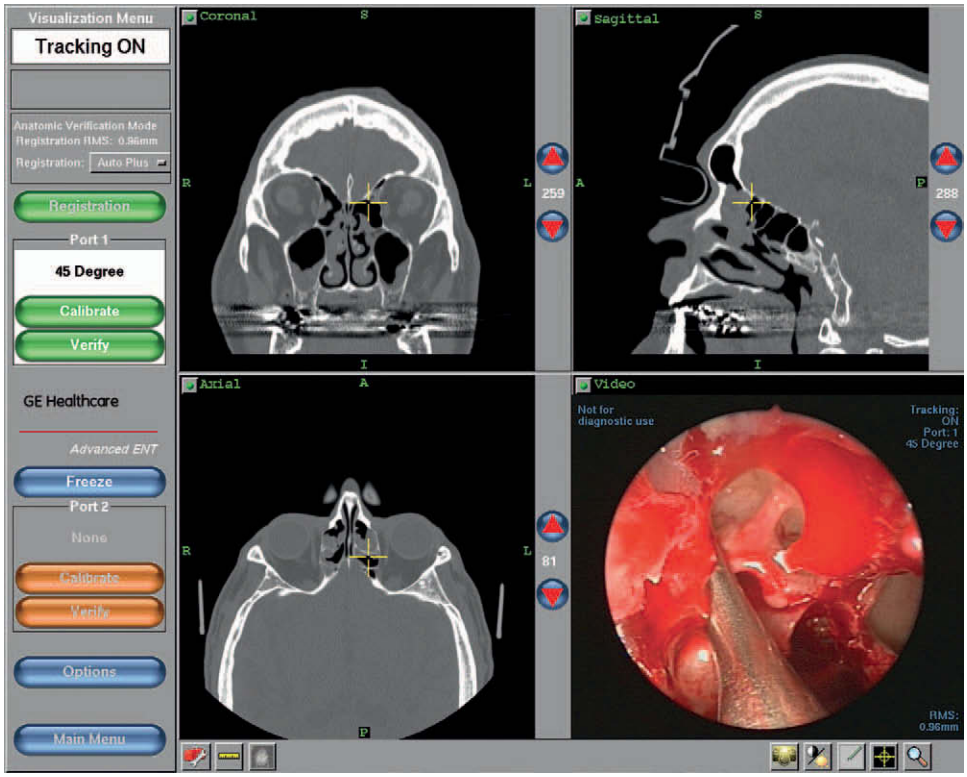

Figure 51-4. Image-guided navigation systems use reformatted thin-cut computed tomography scans (*top* and *bottom left*) to create a three-dimensional view that is correlated intraoperatively with actual patient anatomy as seen through the endoscope (*bottom right*).

was less in the local anesthesia group. Three patients who received general anesthesia required unplanned admissions. An older, retrospective review of 232 patients showed a slightly higher complication rate for local anesthesia with sedation than for general anesthesia.[87] Another study found no appreciable difference between local with sedation and general anesthesia in terms of postoperative pain, nausea, vomiting, and overall tolerance of ESS.[88]

General Anesthesia

The principal advantages of general anesthesia are independence from patient cooperation and the control of the airway. Reasons to choose general anesthesia include patient anxiety, operation in a child, and anticipation of a long procedure.[88] General anesthesia is also indicated if computer-assisted navigation systems are used, because any patient movement may disrupt the reference device. Even if general anesthesia is used, topical nasal decongestant sprays and local injections are still helpful for vasoconstriction and postoperative pain.

In a prospective randomized controlled trial with 56 patients, Wormald and colleagues[89] reported that total intravenous anesthesia (propofol with remifentanil) may be superior to inhalational anesthesia (sevoflurane with fentanyl) in providing a better surgical field, especially for patients with polyposis, allergic fungal rhinosinusitis ,and higher Lund-Mackay scores. These findings are supported by Ahn and coworkers,[90] who report lower blood loss and better surgical field with propofol-remifentanil intravenous anesthesia than with sevoflurane-remifentanil anesthesia in a prospective randomized controlled trial involving 40 patients. However, Beule and associates[91] report that under conditions of balanced circulatory parameters, equal blood loss and endoscopic vision can be achieved with the two tested anesthetic regimens. In a prospective randomized controlled trial of 46 patients (22 sedated with sevoflurane/fentanyl, 24 sedated with propofol/fentanyl), these researchers found no difference in total blood loss, blood loss per minute, or endoscopic vision. Platelet function was significantly impaired 45 minutes after onset of surgery in both groups but was more pronounced after propofol anesthesia.

Patient Preparation and Positioning

A topical nasal decongestant spray is administered in the preoperative holding area. The spray causes nasal decongestion and vasoconstriction and also retards systemic uptake of topical cocaine or tetracaine hydrochloride. The patient is brought to the operating room and laid supine on the operating room table. After administration of general anesthesia or intravenous sedation, local anesthetic is injected prior to draping of the patient; this procedure allows adequate time for the anesthesia and vasoconstriction to take effect.

A solution of lidocaine 1% with epinephrine 1:100,000 is injected with use of a nasal speculum and headlamp. The nasal septum, inferior turbinate, and middle turbinate are injected. Injection of the nasal dorsum, and infraorbital and greater palatine blocks may be used when local anesthesia is being used. After injection, cotton pledgets soaked in cocaine, tetracaine-ephedrine, or concentrated epinephrine (1:10,000) solution are placed into the nasal cavity for additional topical anesthesia and vasoconstriction. All containers of topical medications should be labeled or stained to prevent inadvertent injection. When local anesthesia is used, an expandable sponge or a No. 8 pediatric Foley catheter is placed in the nasopharynx, and the balloon inflated with10 to 15 mL of water. For operation with general anesthesia, a throat pack is placed, with care taken to have one end come out through the mouth. The throat or nasopharyngeal pack helps prevent aspiration. If the patient is under general anesthesia, the eyes should be lubricated and taped in a vertical fashion, with the medial part of the eye kept clear for observation. A preoperative dose of an antibiotic that covers common sinus pathogens should be considered, particularly if there is an active infection.

The table should be positioned as for otologic procedures. The patient is put in slight reverse Trendelenburg position and rotated toward the surgeon to help to reduce blood loss and provide a more comfortable position for the surgeon. With the positioned patient thus prepared, it is also good practice to carefully review the CT scan before surgery is begun. The surgeon then scrubs and dresses for surgery. Draping is accomplished either with a head drape (e.g., Memorial) or

by triangulation of the nose with surgical towels. The eyes are included within the surgical field. The surgeon may either sit or stand, depending on whether he or she uses direct visualization through the endoscope or a camera and monitor for visualization. It is helpful to have the scrub nurse on the same side as the surgeon, with a Mayo stand holding commonly used instruments over the patient. When the patient has been draped and all suctions and powered instrumentation have been connected and tested, surgery can proceed.

Surgery

Basic Techniques: Messerklinger and Wigand

The technique of FESS has developed from the approaches described by Messerklinger[5,63] and Wigand.[92] Both techniques are well described in the literature.[5-10,92] The Messerklinger technique involves an anterior-to-posterior approach.[5] The procedure begins with visualization with a 0-degree scope, and starts with removal of the uncinate process with a sickle knife to expose the infundibulum. The dissection is then carried on as clinically indicated, progressing with removal of the ethmoid bulla, exposure of the frontal sinus ostium, and identification of the roof of the ethmoid. Once the skull base is identified, the dissection continues posteriorly with removal of the remaining anterior ethmoid cells, removal of the posterior ethmoid cells, and finally opening of the sphenoid sinus. The ostium of the maxillary sinus is then identified with use of a 30-degree telescope and is widened if necessary.

Wigand agrees with most principles outlined by Messerklinger. The difference with the former's technique is the posterior-to-anterior approach for completing ethmoidectomy.[92] This technique begins with the partial resection of the middle turbinate, opening of the posterior ethmoid cells, and then removal of the anterior wall of the sphenoid sinus. Once the skull base is identified within the sphenoid sinus, dissection is continued anteriorly through the posterior and anterior ethmoids. The major advantage of this technique is early exposure of the skull base. The technique described next is based on the preceding principles and outlines the procedure that the senior of us (DL) follows.

Basic Steps of Endoscopic Sinus Surgery

(See Key Indicator Video on website.)

Nasal Endoscopy

A thorough endoscopic examination of the nasal cavity is first performed to look for landmarks. The condition of the mucosa, the presence of any polyps or pus, and any significant differences from the preoperative examination findings are noted. Structural abnormalities seen preoperatively are again identified. At this time, additional injections can be made to the lateral nasal wall and middle turbinate.

Resection of the Uncinate Process

The uncinate process is identified with the 0-degree endoscope passed into the middle meatus (Fig. 51-5). The uncinate process is usually crescent shaped. It is sometimes necessary to gently rotate the middle turbinate medially with a Freer elevator to expose the uncinate (Fig. 51-5A). Aggressive manipulation of the middle turbinate should be avoided because it can lead to destabilization of the turbinate and fracture the skull base. When polyps are present, the uncinate is identified from its posterior free end, which often has a rolled edge or anterior eversion. A ball-tipped probe is slid into the infundibulum to find this posterior free edge (Fig. 51-5B). A backbiter punch is used to incise the uncinate process via the hiatus semilunaris in an axial plane (Fig. 51-5C). This initial horizontal incision is made between the inferior one third and superior two thirds of the uncinate process (Fig. 51-5D). The incision is continued anteriorly until the harder lacrimal bone is encountered. Penetration of this bone can damage the lacrimal duct. Once the uncinate incision is complete, the inferior aspect is rotated medially with a Lusk probe and is removed with a Microdebrider.[93] Alternately, a sickle knife or an elevator can be used to resect the uncinate process via a vertical incision that starts on its anterior aspect and is then continued inferiorly and posteriorly along the crescent-shaped anterior margin. Regardless of the technique used, care is taken to not breach the medial orbital wall, which may lie lateral to the uncinate process superiorly. Any remaining uncinate process is then removed with a backbiter. There has been debate on whether the uncinate process should be preserved; we prefer to remove it.

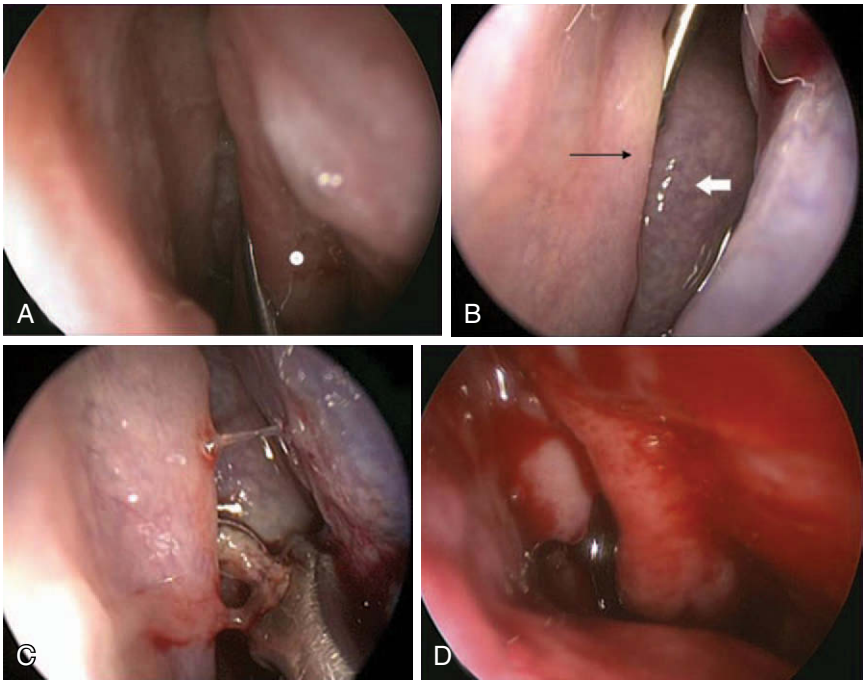

Figure 51-5. **A,** Right middle meatus. The middle turbinate (*dot*) is medialized with a Freer elevator. **B,** View of the uncinate process (*black arrow*) and ethmoid bulla (*white arrow*). A ball-tipped probe is slid into the infundibulum to find the posterior free edge of the uncinate process. **C,** A backbiter punch is used to incise the uncinate process via the hiatus semilunaris in an axial plane. **D,** This initial horizontal incision is made between the inferior one third and superior two thirds of the uncinate process.

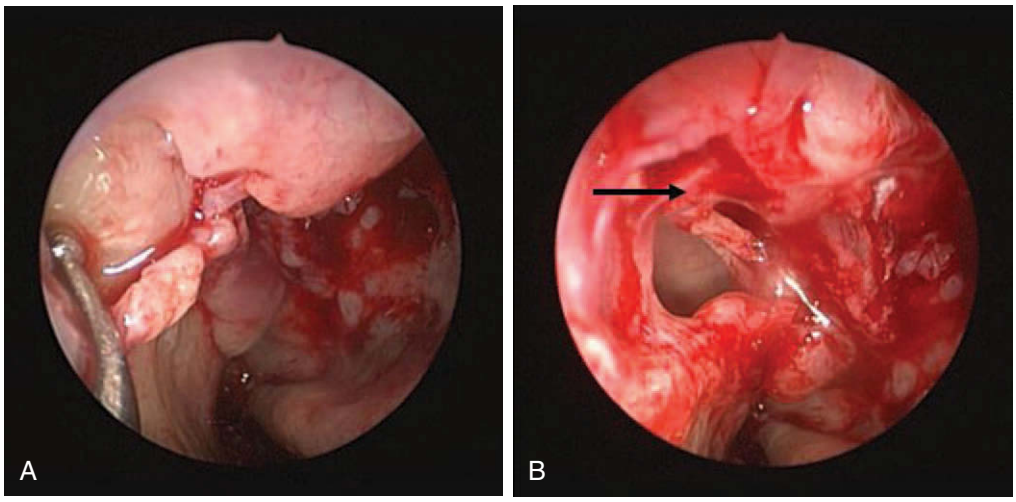

Figure 51-6. **A,** A Lusk probe is slid gently down the infundibulum; the natural ostium is identified when the probe passes easily into the maxillary sinus. **B,** The maxillary antrostomy is created; the medial orbital wall is identified at its superior margin (*arrow*).

Maxillary Antrostomy

The removal of the uncinate process exposes the infundibulum, which is the central drainage pathway for the anterior sinuses. The maxillary sinus ostium is found first, not only to allow for drainage but also to help with identification of the orbit. The maxillary sinus ostium is elliptic and is usually found within the infundibulum, behind the lower third of the uncinate.[14] Accessory ostia are more circular and are commonly found within the posterior fontanelle. The drainage of the maxillary sinus occurs through the natural ostium; opening an accessory ostium of the sinus and missing the natural ostium leads to mucus recirculation and persistent infection.

If there is significant mucosal edema, the maxillary ostium may not be easily identified. A Lusk probe can be gently passed into the infundibulum to help identify the natural ostium (Fig. 51-6). Sliding the probe gently down the infundibulum, the surgeon can identify the ostium when the probe easily passes into the maxillary sinus. To avoid penetration of the orbit, the probe is never forced through the bony wall. If the natural ostium is patent, it should not be manipulated. If it is edematous and obstructed, the Lusk probe can be used to dilate it posteriorly. A straight punch can then be used to open it further both posteriorly and inferiorly if necessary.

Larger antrostomies are preferred for patients with polyps. Placing one free edge of the punch into the ostium under direct visualization enables widening of the ostium to be safely carried posteriorly without damage to the orbital wall. The punch should never be forced into the sinus. A backbiter can also be used to open the anterior aspect of the ostium, with care taken to remove only residual uncinate process. Biting anteriorly in the natural ostium is usually unnecessary and may damage the nasolacrimal duct. It is important not to strip mucosa off the walls of the maxillary sinus, so as to prevent scarring and mucociliary dysfunction.

Once the maxillary antrostomy is complete, the sinus is carefully examined with a 30-degree endoscope. Disease in the sinus can be removed with curved endoscopic instruments, the Microdebrider, or irrigation via a medial and/or inferior antrostomy. Any pus or debris should be sampled for culture. All landmarks, including the medial and inferior orbital wall, are carefully identified (Fig. 51-6B). Occasionally, an infraorbital cell may block the antrostomy from above. This cell can now be safely opened.

Anterior Ethmoidectomy

The ethmoid bulla is the largest cell of the anterior ethmoid complex and is usually the first, most prominent cell seen within the middle meatus (Fig. 51-7). This cell forms the posterior border of the hiatus semilunaris. With use of a Microdebrider or a punch forceps, the ethmoid bulla should be entered along its inferior and medial aspect (Fig. 51-7B). Once this opening is formed, the anterior and medial walls can be easily taken down to expose the posterior wall. Some surgeons leave the inferior wall intact as a strut to keep the turbinate medial. The lateral wall of the ethmoid bulla is the lamina papyracea, which can be identified as soon as the cell is opened (Fig. 51-7C). Mucosa should be preserved laterally. Opening the agger nasi and suprabullar cells completes the anterior ethmoidectomy, but the opening is performed only after the sphenoid sinus has been opened and the skull base identified. Dissection should never be carried out medial to the superior vertical attachment of the middle turbinate because such extension carries the risk of penetrating the cribriform plate and fovea ethmoidalis. Dissection should continue posteriorly till the basal lamella is identified, which is the posterior limit of the anterior ethmoid. Care is taken to preserve mucosa over the lamina papyracea. The Microdebrider window should always face up when the surgeon is working along the lamina papyracea, to allow for mucosal preservation and to prevent inadvertent injury of the periorbita in the presence of a dehiscence.

Posterior Ethmoidectomy

To open the posterior ethmoids, the inferior and medial aspects of the vertical basal lamella must be removed with the Microdebrider (Fig. 51-7D). These cells can be large, and the skull base is often prominently exposed at this point in the dissection. Care is taken not to open the horizontal basal lamella, because to do so not only destabilizes the middle turbinate but also exposes the vessels coming from the internal maxillary artery, causing acute or delayed hemorrhage. If a sphenoethmoid cell is present, the posterior ethmoids will extend lateral and superior to the sphenoid sinus. These cells can usually be identified in the preoperative CT scan and are important to identify during surgery because the optic nerve may be dehiscent within the lateral aspect of the cell. Dissection should remain low in the posterior ethmoids until the skull base and sphenoid sinus are identified. A calibrated probe or computerized navigation system is often useful at this point in the dissection to identify the anterior wall of the sphenoid sinus. In an average adult, this structure is approximately 7 cm from the nasal sill at a 30-degree angle (Fig. 51-8). Continued dissection in a posterior and inferior direction will open the posterior ethmoidal cells into the superior meatus. Examination medial to the middle turbinate should be undertaken to ensure that posterior ethmoid drainage is patent. The inferior half of the superior turbinate may have to be removed for full visualization of the sphenoethmoid recess and the anterior wall of the sphenoid sinus. The anterior wall of the sphenoid sinus is usually convex, toward the surgeon, whereas the skull base is concave, away from the surgeon. During the initial dissection through the posterior ethmoids, septations and smaller cells found superiorly should not be

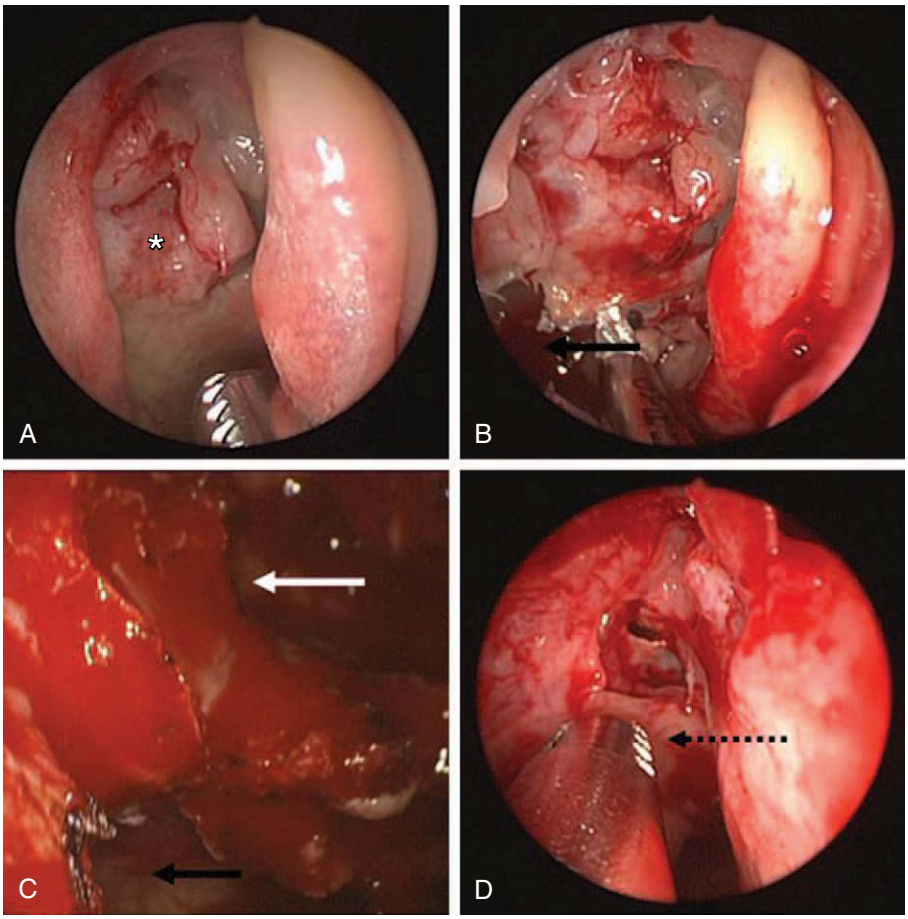

Figure 51-7. **A,** Polypoid right ethmoid bulla (*asterisk*). **B,** With a Microdebrider, the ethmoid bulla is entered along its inferomedial aspect. The maxillary antrostomy can also be seen (*arrow*). **C,** The bulla has been opened to show the lamina papyracea, which forms its lateral wall (*white arrow*), seen above the maxillary antrostomy (*black arrow*). **D,** The inferomedial aspect of the vertical basal lamella is removed with the Microdebrider to open the posterior ethmoids (*dashed arrow*).

explored until the skull base is identified via the sphenoid sinus. These cells are removed later as the dissection is continued superiorly in a posterior-to-anterior direction.

Sphenoid Sinusotomy

The ostium of the sphenoid sinus can be approached lateral to the middle turbinate, after inferior dissection of the posterior ethmoids, to expose the superior turbinate and meatus (Fig. 51-8B). The ostium can also be identified medial to the middle turbinate through the nasal cavity if there is no septal obstruction. The easiest way to find the sphenoid ostium is to remove the lower third to half of the superior turbinate, with use of cutting forceps to avoid tearing olfactory fibers. In most cases this maneuver exposes the ostium just medially or directly posteriorly. The ostium is located approximately half the distance between the superior and inferior borders of the anterior wall (Fig. 51-8C). The natural ostium can be located by gentle sliding of a probe along the anterior wall until it easily passes (Fig. 51-8B). The probe should never be forced, so as to avoid penetration of the skull base. The probe should also not be forced against the posterior wall of the sphenoid sinus, where a dehiscent ICA may lie.

Once the ostium of the sphenoid sinus is identified, it should be enlarged. The surgeon widens the ostium by inserting a small straight forceps, opening it, and out-fracturing the anterior sphenoid wall as the forceps is pulled out. A sphenoid punch or Microdebrider can then be used to safely widen the ostium as needed, but not in a circumferential fashion, which would cause stenosis (Fig. 51-8D). As the sphenoid ostium is enlarged, the surgeon should be aware that small arteries may be present medially or laterally that could cause bleeding. Simple cautery nicely controls this bleeding. Any purulence, fungus, polyps, or debris should be suctioned or irrigated from the sphenoid sinus, with care taken to preserve the mucosa. Any instrumentation to remove disease posteriorly, posterolaterally, or superiorly in the sphenoid sinus should be avoided unless guided by a well-calibrated computer navigation system to denote exact anatomy. This guidance helps avoid injury to the ICA, optic nerve, and skull base. The sphenoid sinus can be extremely variable with regard to size. Any septations should not be removed because they often attach posteriorly to the anterior carotid wall, which may be weak or dehiscent.

Complete Ethmoidectomy

The skull base, which can be easily visualized within and superior to the opening of the sphenoid sinus, becomes the major landmark during completion of the ethmoidectomy. At this point two major landmarks, the orbit and skull base, have been identified. The posterior-to-anterior dissection of the superior ethmoids can now proceed. With either a curved suction or other blunt curved instrument, the remaining septations and cells of the posterior and anterior ethmoids are removed in a posterior-to-anterior direction (Fig. 51-9). This maneuver is safe because, as the skull base rises superiorly, the instrument will go up and behind superior ethmoid projections, which are then pulled forward (Fig. 51-9B). The tip of the probe or suction should always be behind a partition before its removal; otherwise the surgeon might be biting on the skull base. The dissector is never thrust upward if it appears flush with a structure. Only tangential dissections are performed.

Remembering that the roof of the ethmoid is thin medially and may actually lie higher than the cribriform plate, the surgeon should avoid dissection along the medial aspect of the middle turbinate or lateral lamella at this level (Fig. 51-10). The mucosa covering the

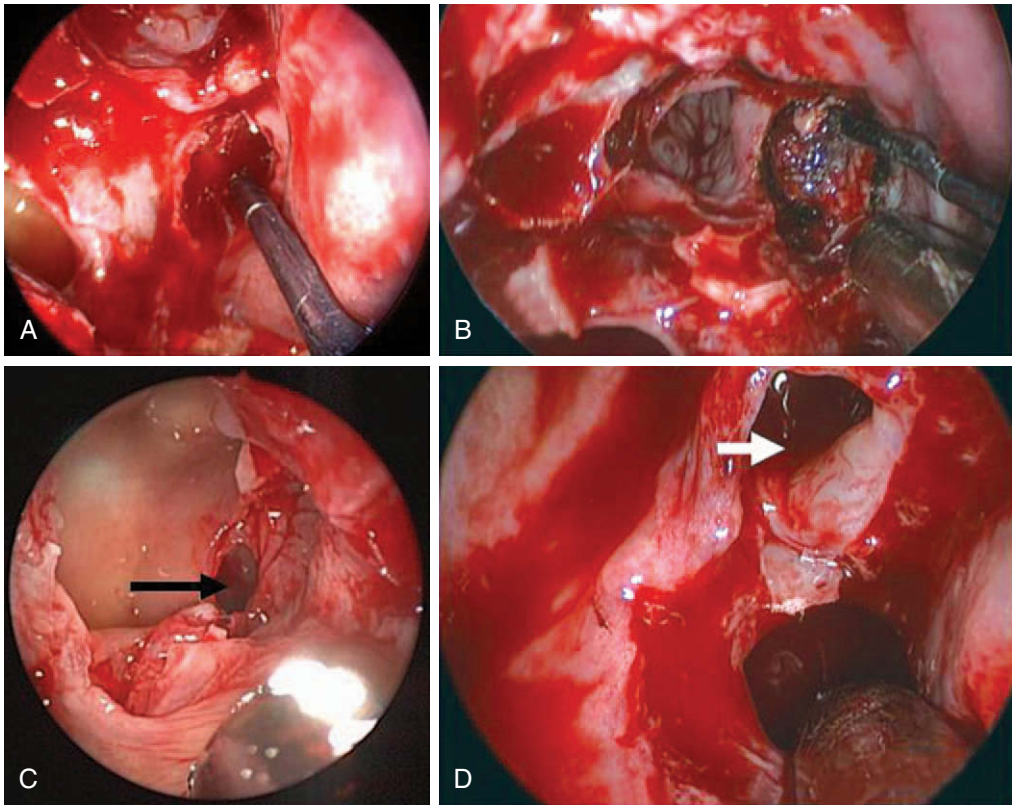

Figure 51-8. **A,** A calibrated probe can be useful to identify the anterior wall of the sphenoid sinus, which is approximately 7 cm from the nasal sill at a 30-degree angle. **B,** The surgeon can locate the natural ostium by gently sliding a probe along the anterior wall until it passes easily. **C,** The ostium (*arrow*) is located approximately halfway between the superior and inferior borders of the anterior wall. **D,** Once the ostium of the sphenoid sinus is identified, it should be enlarged. Note also the sphenoethmoidal (Onodi) cell (*arrow*) lying superior and lateral to the sphenoid sinus.

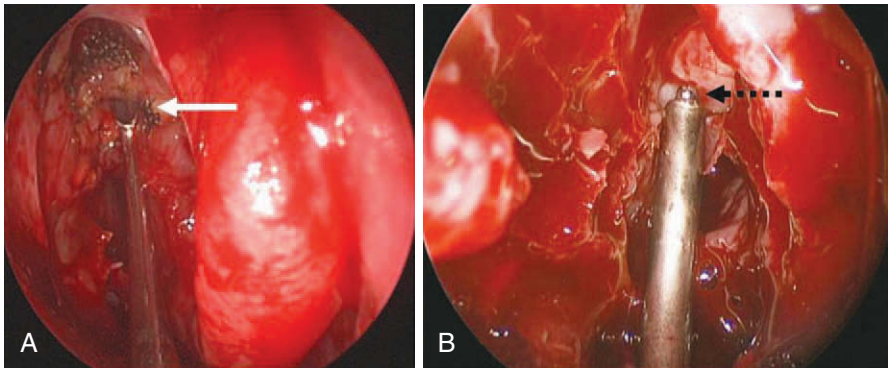

Figure 51-9. Completing ethmoidectomy. **A,** With a curette, remaining septations and cells of the posterior and anterior ethmoids are removed in a posterior-to-anterior direction, with the tip of the curette always kept behind a partition before removing it. **B,** The dissector is never thrust upward if it appears flush with a structure; otherwise the surgeon might be biting on the skull base (*arrow*).

lamina papyracea should be preserved for proper healing. Also remembering that the ethmoid is wider posteriorly as the orbit narrows, the surgeon should carefully avoid penetrating the lamina papyracea. Application of gentle pressure on the orbit externally during visualization of the lamina with the scope allows identification of any dehiscent areas (Fig. 51-11). Herniation of orbital fat during this maneuver should raise concern for orbital trauma. The posterior ethmoidal artery can be identified just superior to the sphenoid sinus. The anterior ethmoidal artery lies just posterior to the frontal recess. In most cases, these vessels are enclosed in the skull base and are not visible. Preoperative survey of the coronal CT scan can identify low-lying ethmoidal arteries. If traumatized, these vessels should be cauterized. It is important to not transect them so as to prevent their retraction into the orbit, which would cause formation of an orbital hematoma.

As the ethmoidectomy approaches the most anterior extent, the suprabullar cells are opened (Fig. 51-12). The frontal recess and agger nasi area are opened last in a complete or anterior ethmoidectomy because bleeding from above can reduce endoscopic visualization and hamper dissection of lower cells. This area is also most at risk for scarring and iatrogenic injury, and so requires meticulous dissection. The superior aspect of the agger nasi may lie close to the skull base, and the lateral or anterior aspect may be contiguous with the lacrimal sac and orbit. It is safely opened from the inferior, medial, or posterior to anterior aspect after the skull base has been identified.

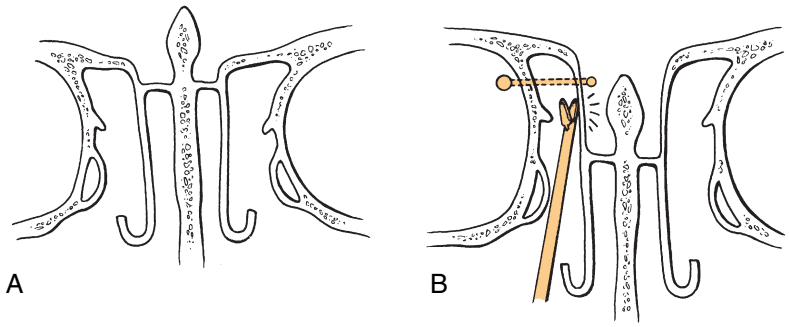

Figure 51-10. Dissection should be avoided along the medial aspect of the middle turbinate because the roof of the ethmoid may lie higher than the cribriform plate. **A,** Shallow cribriform-fovea ethmoidalis complex. **B,** Low-lying cribriform with long lateral lamella. Instrument points to most common area of iatrogenic cerebrospinal fluid leak.

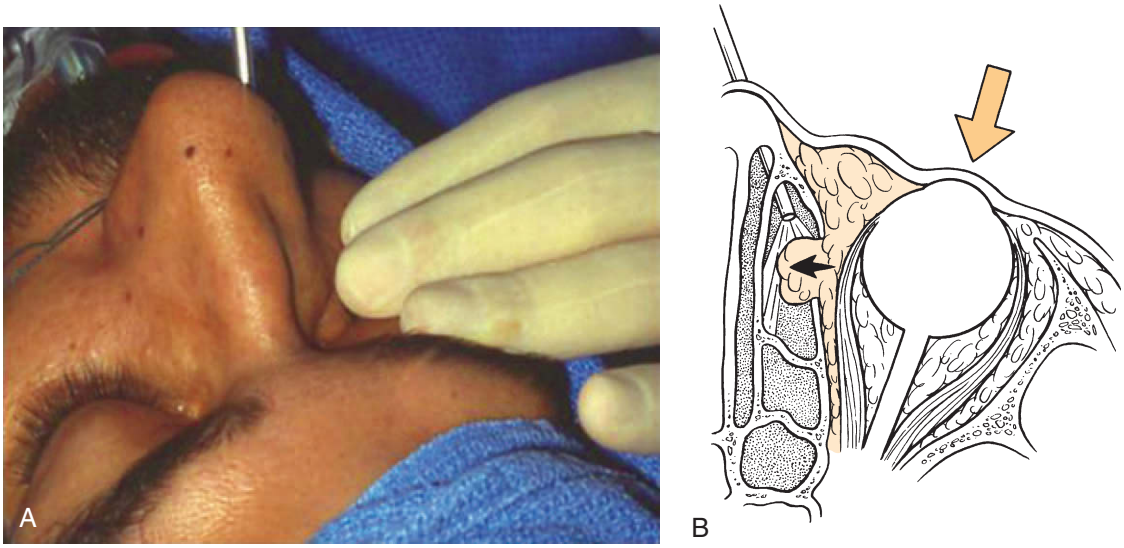

Figure 51-11. **A** and **B,** By gently applying pressure to the globe while visualizing the lamina papyracea, the surgeon can identify any dehiscent areas. Protrusion of orbital fat (*arrow*) indicates a violation of the orbital periosteum and should raise concern for possible orbital trauma.

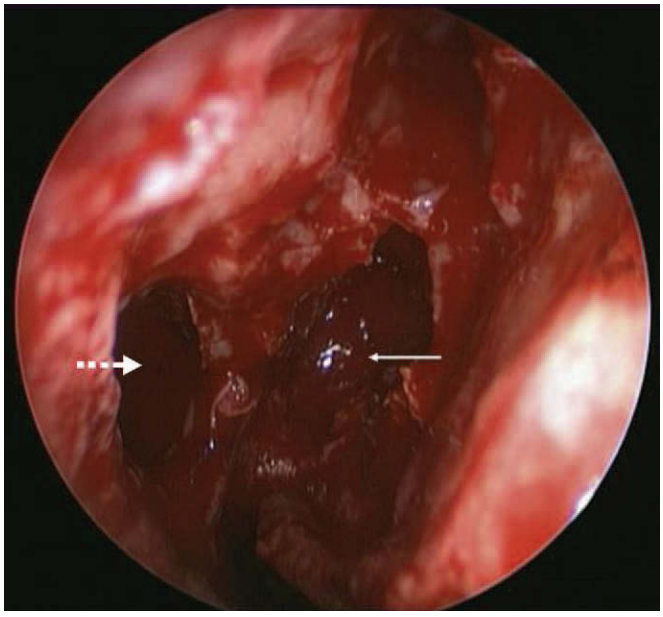

Figure 51-12. Right complete ethmoidectomy. The maxillary antrostomy (*dashed arrow*) and the enlarged ostium to the sphenoid sinus (*arrow*) can be seen.

Frontal Sinusotomy

The decision to open the frontal recess is confusing to many surgeons. In general, if the frontal sinus is not diseased, it should be left alone. If frontal disease is present, opening the frontal recess is warranted, with care taken to minimize mucosal injury and prevent middle turbinate lateralization. Frontal ostioplasty is unnecessary in asymptomatic nasal polyposis because polyps routinely recur at the frontal sinus and recess. The risk of causing frontal sinus symptoms in a patient who has been without them should be considered. Anteriorly, the frontal recess is a cone-shaped space below the ostium of the frontal sinus. The medial wall of the frontal recess is the most anterior aspect of the middle turbinate, the lateral wall is the lamina papyracea, and the anterior wall is the posterior wall of the agger nasi.[12]

If there are remnants of the uncinate process superiorly, they should be carefully removed. The superior attachment of the uncinate process should be determined through both review of the preoperative CT scan and endoscopic examination to help identify the frontal recess. This may not be possible if there are significant opacifications of the frontal and anterior ethmoids. If the uncinate attaches to the middle turbinate or to the fovea ethmoidalis, the frontal recess is found draining into the infundibulum. Removal of the most superior aspect of the uncinate provides access to the frontal recess. When the uncinate attaches to the lamina papyracea, as it usually does, the frontal recess is found between the middle turbinate and the superior extent of the uncinate process. With a curved probe and a curved curette, gentle dissection performed along the skull base helps identify the frontal recess. A 30- or 45-degree endoscope aids visualization. Both a terminal

cell and an agger nasi cell can easily be confused with the frontal recess. Once the frontal recess is identified, any remaining polyps and disease should be removed to provide an adequate drainage area. The position and stability of the middle turbinate should be examined to ensure that it will not scar into a lateral position that may obstruct the frontal recess. If necessary, measures should be taken to prevent its lateralization.[94]

Treatment of the Middle Turbinate

The vertical attachment and the posterior horizontal attachments of the middle turbinate should be carefully preserved to prevent its destabilization and lateralization. Lateralized middle turbinates cause postoperative obstruction of the sinus drainage pathways, resulting in persistent inflammation and infection. This situation is a common finding during revision surgery. The middle turbinate should, in most cases, be preserved. In some situations, its partial or complete removal is necessary. Removal should be considered only when disease has caused severe destabilization. The middle turbinate can be removed with a straight punch, starting at its anterior attachment to lateral nasal wall and proceeding posteriorly. The posterior stump of the middle turbinate often bleeds, necessitating the use of suction cautery. A partial turbinectomy in which the anterior bulbous middle turbinate is removed but the anterior-superior and basal lamella attachments are preserved is another consideration. Postoperative observation is essential, because if the turbinate is partially removed, lateralization can still occur. Another option is to débride a small area of mucosa on the medial aspect of the turbinate and a corresponding area on the nasal septum to promote the formation of an adhesion (Fig. 51-13). This can be done with a sickle knife or Microdebrider. Light packing is used postoperatively for 4 to 7 days to push the turbinate into the septum and to allow formation of the adhesion. Other options are packing alone, suturing the turbinate to the septum, and using stents.

Concluding the Procedure

Before the procedure is terminated, all small bone fragments are removed and hemostasis is achieved. Cotton soaked in an epinephrine solution can be placed over areas that are bleeding. The areas of the sphenopalatine, posterior septal, anterior ethmoidal, and posterior ethmoidal arteries are carefully examined. If these vessels have been injured, they should be cauterized. Cautery should be used sparingly to reduce scarring. Anticoagulant gels and packing products are available if there is persistent oozing, but some of them can cause granulations and scarring. A small pack is placed into the middle meatus to keep the middle turbinate medialized, especially if an adhesion procedure was performed. This pack is left in place for 3 to 5 days. A pack can also be placed inferiorly along the floor of the nasal cavity if septoplasty has been performed. Inferior packing can usually be removed before the patient is discharged, greatly improving patient comfort. Although many variations of postoperative packing have been described, from no packs to dissolvable packs to longer durations of pack, there is little evidence to support one method over the others.[95] If a throat or nasopharyngeal pack was placed preoperatively, it should now be removed, and the stomach suctioned.

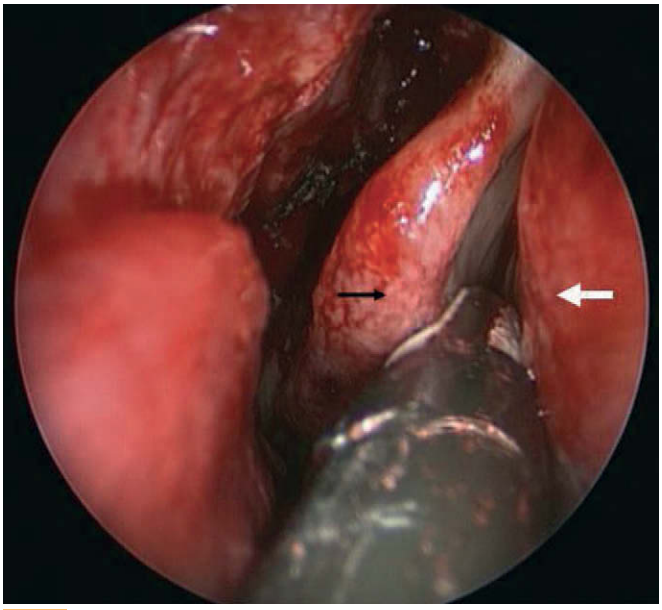

Figure 51-13. The Microdebrider is used to create an adhesion between the middle turbinate (*black arrow*) and the septum (*white arrow*) to prevent lateralization of the turbinate.

Special Situations

Nasal Septal Deviation

Significant septal deviations can cause lateral displacement of the middle turbinate, obstructing the OMC. Septal deviations can make ESS technically difficult. If the patient has no symptoms from the deviation, septoplasty may be added to the endoscopic sinus procedure. Addressing asymptomatic deviation is more debatable. If septoplasty makes the endoscopic procedure simpler, or makes postoperative endoscopy and débridement easier, it should be performed during ESS. It may be easier to perform ESS on the side with adequate exposure, then perform a septoplasty and continue the procedure on the contralateral side.

An elegant alternative to formal septoplasty is endoscopic submucosal septoplasty, performed as follows: With endoscopic visualization, a small incision is made through the septal mucosa just anterior to any deviation or spur. The mucosa is elevated on both sides of the deviation after an incision is made through the septum, and the deviated bone or cartilage is removed. As with formal septoplasty, care must be taken not to create mucosal tears on both sides of the septum. Endoscopic septoplasty quickly and conveniently creates room for endoscopic sinus procedures. Packing is required only on the side of the incision, and no sutures are necessary.

Concha Bullosa

The concha bullosa should be addressed in patients with rhinosinusitis undergoing surgery, primarily because their removal improves visualization of the middle meatus. There are also reports of mucoceles within a concha bullosa causing symptoms of rhinosinusitis.[96] With a sickle knife, the anterior wall of a concha bullosa is incised to open the cell (Fig. 51-14). A Microdebrider may also be used as long as the normal mucosa of surrounding structures is preserved. The lateral wall is removed posteriorly to the basal lamella. Care must be taken not to destabilize the middle turbinate. As a last resort, or if there is a risk of lateralization of the middle turbinate, complete resection of the turbinate may be considered.

Mucoceles

The surgical goal in treatment of a mucocele is to widely open it to allow for drainage (marsupialization). The opening must be performed in a safe fashion, however, because mucoceles often cause skull base or orbital dehiscences, which obviously should not be opened. Care must be taken to prevent scarring in order to avoid recurrence. Use of intraoperative image-guided navigation systems may help in identifying and safely opening mucoceles.

Polyps

In a primary procedure, polyps are easy to approach endoscopically because they are gelatinous and have minimal blood supply. Revision polyp surgery is technically more difficult. Polyps obstruct visualization and often cause heavy bleeding. A Microdebrider can help reduce blood loss and improve visualization by quickly removing nasal polyps. The instrument also suctions blood, keeping the surgical field clear.[97,98] In all cases with extensive polyposis, it is advisable to clear the polyps anteriorly and inferiorly until the middle turbinate and other landmarks can be identified. Surgery should progress only when the orbit and skull

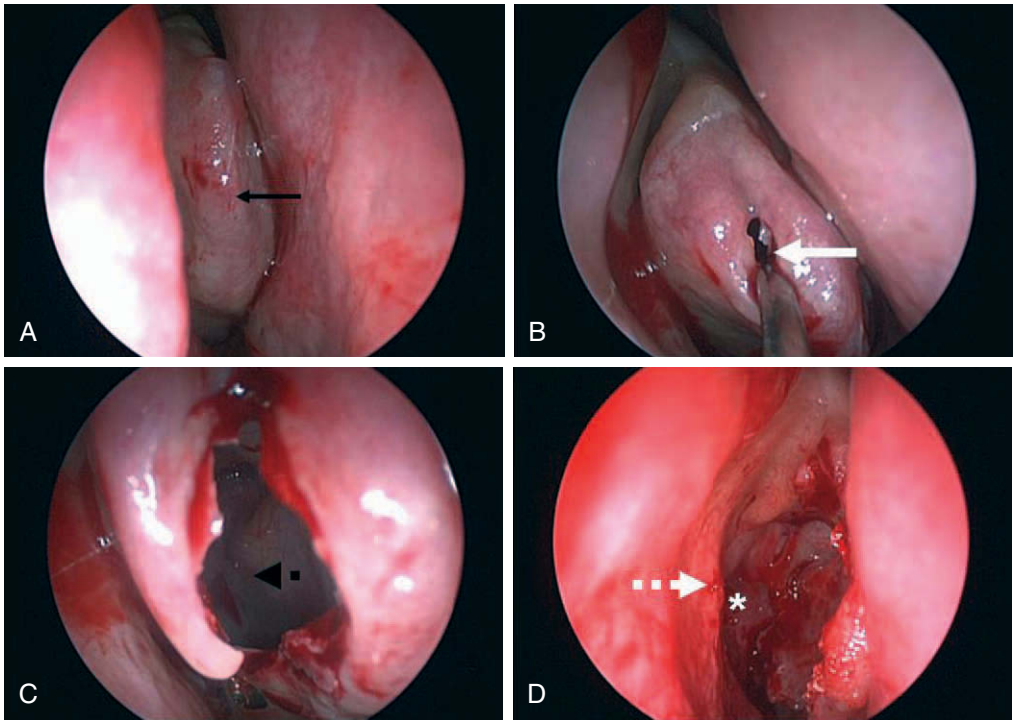

Figure 51-14. **A,** Right concha bullosa (*arrow*). **B,** A vertical incision is made with a sickle knife (*arrow*). **C,** Inner mucosal lining of the concha bullosa (*arrow*). **D,** The lateral part of the concha bullosa has been removed, exposing the uncinate process (*arrow*) and the bulla (*asterisk*).

base have been identified. Primary polyp surgery can be conducted without marked blood loss. Sinuses should be opened widely except for the frontal sinus. Polyps tend to recur first in the upper frontal area, but most patients have asymptomatic disease in the frontal recess. Manipulation of the frontal recess is not necessary and may create problems, particularly if there is any surrounding osteitis and if the frontal ostium appears narrow on sagittal CT scans. The middle turbinate is involved in most cases of polyposis, and if it is, removal of the middle turbinate is appropriate.

Antrochoanal polyps have traditionally been treated through a Caldwell-Luc approach to the maxillary sinus or through a combined endoscopic and transcanine approach.[99] The creation of an endoscopic inferior meatal antrostomy affords better access for polyp removal along with the wide middle meatal antrostomy created by the disease process. This avoids the need for a Caldwell-Luc procedure. Endoscopes and curved powered or grasping instruments are very helpful in removal of the maxillary portion of the polyp, which is the key to avoiding failure.[100]

Extent of Surgery: Limited versus Extended Approaches

Kuehnemund and associates[101] studied whether postoperative results from a limited surgical approach differed from a more extended approach in ESS for patients with CRS.[101] The 65 patients in the study were examined preoperatively and reassessed at 3 months, 6 months, and long-term follow-up visits after surgery. Using endoscopy, saccharin transport time, and the assessment of symptoms, these researchers found that surgical results and symptoms were similar in the two groups, suggesting that a conservative approach may be sufficient.

Minimally Invasive Sinus Technique

MIST upholds Messerklinger's functional concepts perhaps more strictly than FESS, with the surgeon performing a very minimal initial intervention.[64] Surgical intervention is limited to the sinus transition spaces (i.e., ethmoid infundibulum, hiatus semilunaris superior, and retro-agger space). Catalano and Strouch[64] describe MIST as a targeted intervention, or "threshold" surgical procedure. The MIST philosophy is based on tissue preservation and transition space surgery. The procedure consists of a stepwise, anatomic progression of surgery that has a defined beginning and end for all patients regardless of disease severity. In contrast, other forms of conventional ESS are far less structured. In MIST, sinus ostia are rarely enlarged and the middle meatal antrostomy is not performed. Catalano and Roffman[102] assessed the long-term postoperative outcome of MIST using the duration-based Chronic Sinusitis Survey (CSS) QOL instrument in a prospective study of 85 patients. At follow-up, there was 62.0% improvement in the mean CSS total score ($P < .00001$). An overall improvement was found in 78.8% of patients; 12.9% of patients were worse, 8.2% of patients were unchanged, and 5.9% needed a revision MIST procedure. Controversy persists about the use of MIST primarily because of an absence of comparative outcome data.

Sinus Balloon Catheterization

Sinus balloon catheterization is a surgical technique by which dilation of a paranasal sinus ostium is accomplished through use of a balloon catheter. The procedure involves insertion of a balloon dilation catheter over a guidewire that has been positioned within the involved paranasal sinus under the direction of endoscopy and fluoroscopy (Fig. 51-15). Inflation of the balloon results in dilation of the targeted ostium. This procedure can be used for all sinuses except the ethmoid cells.

After cadaveric[103] and preliminary studies,[104] Bolger and colleagues[105] published the first prospective, multicenter evaluation on the safety and outcome of balloon catheter sinusotomy in 115 patients.[105] Of these, 106 underwent balloon catheter sinusotomy. In 6 patients, the catheterization procedure had to be converted to endoscopic dissection with traditional instruments. Sinusotomy was attempted in 358 sinuses, of which 347 (96.9%) were successfully cannulated; 11 sinuses had to be dissected with traditional endoscopic instrumentation because cannulation was not possible secondary to scar tissue, anatomic restrictions, and polypoid mucosal edema. In 5 sinuses, cannulation and dilation were accomplished but the opening was insufficient. Sinusotomy using balloon catheters was successfully performed in 143 maxillary ostia, 75 sphenoid ostia, and 124 frontal recesses. Sinusotomy using balloon catheters was the only sinus intervention in 52 of 109 patients, (47.7%). There were no serious adverse events. No patient experienced CSF leak, orbital injury, or nasal bleeding that required

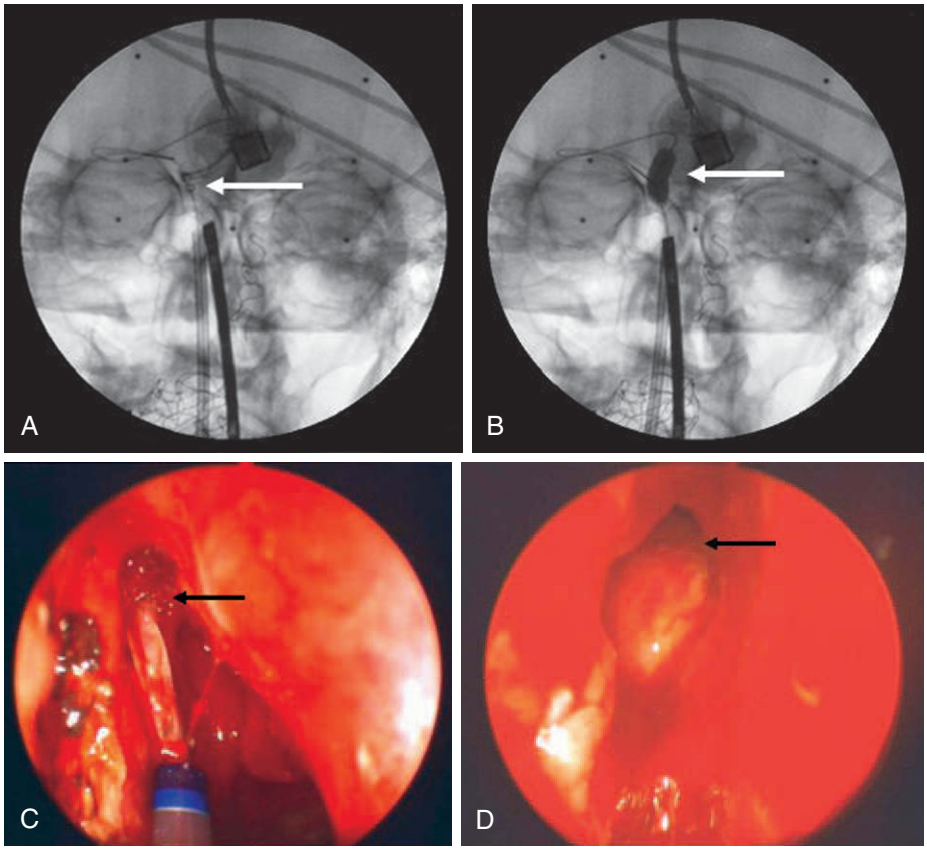

Figure 51-15. **A,** Fluoroscopic image of balloon dilation guidewire that has been positioned within the right frontal sinus under endoscopic guidance (*arrow*). **B,** Fluoroscopic image of balloon dilation guidewire with the balloon inflated (*arrow*). **C,** Endoscopic image of dilation guidewire and balloon, which have been positioned within the right frontal sinus (*arrow*). **D,** Endoscopic appearance of the frontal recess after inflation of the balloon catheter (*arrow*).

packing. There were nine cases of bacterial sinusitis after dilation that resolved with oral antibiotic treatment. The median fluoroscopy time per sinus was 0.81 minutes; the average radiation dose per patient was approximately 730 mrem. Devices malfunctioned in 12 of 358 (3.35%) applications/sinuses.

At the end of the 24-week follow up, endoscopy of 307 sinuses demonstrated patency in 80.5%, nonpatency in 1.6%, and indeterminate patency in 17.9%. Revision treatment was required in 0.98% of the sinuses and 2.75% of the patients. Symptoms were evaluated at baseline, 1 week, 12 weeks, and 24 weeks with the SNOT-20 questionnaire. Patients treated with balloon catheter alone, as well as those patients treated with balloon catheter sinusotomy in conjunction with endoscopic instrumentation in different sinuses, experienced symptomatic improvement. For each group, and for the overall study group, all changes were statistically significant ($P < .0001$).

Chandra[106] estimated the radiation dose to the lens during fluoroscopy-assisted balloon dilation as well as the length of fluoroscopy time that would be tolerated.[106] Mean exposure varied from 0.041 (right eye) to 0.284 (left eye) mGy/sec ($P = 0.037$), more in the left eye as it lies closer to the radiation source during the lateral projection. The threshold for lenticular opacity has been estimated as 500 mGy, which would be attained in the left eye after approximately 29 minutes of fluoroscopy. He concluded that the lens may tolerate less than 30 minutes of fluoroscopy during balloon sinuplasty. Further advances in technology are leading to reduction or elimination of fluoroscopy. Outpatient clinic procedures using balloon catheterization technology performed with local anesthesia are now available.

Postoperative Care

Once a patient has emerged from sedation or general anesthesia, the head should be elevated and ice applied to the nose to help reduce facial swelling. In the recovery room, a quick visual and mental status examination is performed. Most healthy patients can be discharged home from the recovery room. Patients with comorbidities or complications may need overnight observation. Appropriate pain medication is administered. If the packing is removed, saline nasal spray and a short course of a nasal decongestant are prescribed. For patients with purulent drainage or nasal packing, appropriate antibiotics are dispensed. Patients with reactive airways, fungal disease, or extensive polyps often benefit from steroid "burst" therapy to reduce postoperative mucosal edema. Patients are advised to avoid strenuous activity, nose blowing, and any medications that may increase the risk for bleeding.

The postoperative period is almost as critical to the success of surgery as the surgery itself. All patients should undergo an initial postoperative examination to ensure that crusting and scarring are not obstructing the sinus ostia and that the middle turbinate is not lateralized. The first postoperative visit should occur within the first 3 to 6 days after surgery. During this visit, any packing is removed and the sinuses are examined endoscopically. Crusts and clots, which may impede drainage of mucus, must be débrided.[107] Débriding helps promote healing of the mucosal lining of the nose and restore normal mucociliary function. Fixed clots or crusts should not be removed. It is important not to damage the mucosa or cause bleeding because doing so may slow healing and cause scar formation. There is debate about the frequency and thoroughness of postoperative débridement. Originally, it was recommended that patients be seen daily until the sinus cavities were stable. This practice is neither practical nor necessary. Patients who have undergone minimal surgery with minor bleeding may need only daily irrigations to clean debris from the sinuses. More aggressive and frequent débridement may be necessary for patients who had extensive surgery, polyps, allergic fungal rhinosinusitis, or underwent frontal sinus surgery. Some patients require frequent cleaning, and others little to none.[108] Other problems, such as a lateralized middle turbinate, can often be dealt with in this period, avoiding the need for

Box 51-2

Complications of Endoscopic Sinus Surgery

Minor Complications

Minor epistaxis
Hyposmia
Adhesions
Headache
Periorbital ecchymosis or emphysema
Dental or facial pain

Major Complications

Major epistaxis
Anosmia
Nasolacrimal trauma
Carotid injury, intracranial hemorrhage, stroke
Orbital hematoma, diplopia, decreased visual acuity, blindness
Cerebrospinal fluid leak, pneumocephalus, meningitis

revision surgery. Allergy management, antifungal agents, steroids, leukotriene inhibitors, antibiotics, and irrigation should all be used as needed. If stenting has been used, stent removal is planned. Stents can be removed, cleaned, and replaced if necessary. Further follow-up visits, endoscopic examinations, and additional débridements are individually tailored for each patient to help achieve favorable results.

Complications

Complications related to ESS can be divided into minor and major categories (Box 51-2). Minor complications can usually be treated with minimal consequences. The most common minor complication is synechia formation, which does not require any type of revision.[109] However, catastrophic complications do occur rarely. They can be treated safely if recognized early. Major complications include major hemorrhage, blindness, and intracranial injury. Hopkins and colleagues[110] carried out a prospective multicenter study of 3128 patients who underwent sinonasal surgery in England and Wales. Major complications—orbital or intracranial complications, bleeding requiring ligation or orbital decompression, return to the operating room—occurred in 11 patients (0.4%). Minor complications (all other untoward events) occurred in 207 patients (6.6%). The most commonly reported minor complications were excessive perioperative hemorrhagic bleeding (5.0%) and postoperative hemorrhage requiring treatment (0.8%). The complication rate was linked to the extent of disease, which was measured in terms of symptom severity and health-related QOL, the extent of polyposis, level of opacity of the sinuses on CT, and the presence of comorbidity, but not on the basis of surgical characteristics (extent of surgery, use of endoscope or Microdebrider, grade of surgeon, and adjunctive turbinate surgery). An older large review of complications of ESS found a minor complication rate of 6.9% and a major complication rate of 0.85%.[111]

The first step in avoiding complications is prevention. Technically difficult cases should not be attempted by an inexperienced sinus surgeon until he or she has mastered the procedure through cadaver dissections, courses, and surgical training.[11,112] Prevention also involves a thorough preoperative assessment of the patient's history, physical findings, and radiographic evaluation. An informed consent procedure, in which the rate of complications for the operating surgeon is discussed, is essential.

Hemorrhage

Bleeding may be minor or major. Minor intraoperative or postoperative bleeding is common and usually requires minimal intervention. Meticulous dissection with instruments such as the Microdebrider helps reduce blood loss. Surgery of extensive polyposis can routinely be associated with heavier blood loss. Intraoperatively, application of cotton pledgets soaked in epinephrine solution and sparing use of cautery are usually effective in controlling bleeding. Postoperatively, administration of topical decongestants, packing, and local cautery are useful. Major postoperative bleeding is an indication for immediate return to the operating room. The posterior septal artery below the sphenoid sinus is frequently the cause of such bleeding. Other branches of the internal maxillary artery into the middle turbinate can also cause marked bleeding. Bleeding can be controlled endoscopically in most cases. External procedures or embolization is rarely necessary. Injury to the internal carotid artery requires immediate control of hemorrhage and angiography for balloon occlusion.[113] Lippert and associates[114] reported two cases with massive bleeding of the ICA caused by ESS.[114] In both cases, bleeding could be stopped sufficiently by implantation of a stent graft, which preserved the lumen of the artery; no neurologic sequelae were observed.

Ophthalmic Complications

The use of powered cutting instruments has been a useful advance in ESS but has also been implicated in rapid, irreversible, and devastating orbital complications. Bhatti and Stankiewicz[115] reviewed neuro-ophthalmic complications associated with ESS, which they categorized according to anatomic sites as follows: orbit, optic nerve, extraocular muscle, and lacrimal drainage system. Orbital complications, which occur in 0.12% of ESS procedures,[111] include orbital hemorrhage, enophthalmos, orbital emphysema, lipogranuloma formation, and intraorbital foreign body reaction. Orbital hemorrhage is the most common ophthalmic complication of ESS and is potentially blinding if it is not promptly diagnosed and treated. Ophthalmic complications after ESS may also involve direct trauma to the lamina papyracea, orbital contents, and the extraocular muscles, the nasolacrimal sac or duct, and the optic nerve. Prevention begins with preoperative planning that includes review of the orbital anatomy. The eyes should always be included in the surgical field and should be loosely taped so they can be easily examined during surgery. The maxillary antrostomy is the key landmark to finding the lamina papyracea, which is always above its superior border. Simultaneous endoscopic viewing of the lateral wall with orbital palpation will show the slightest breech in the lamina papyracea and is a useful preventive tool. With any orbital complication, an immediate ophthalmologic consultation should be obtained, and intraorbital pressures should be measured. Any intraoperative eye complications should be recognized immediately and should be dealt with both during surgery and postoperatively. Orbital hemorrhage, proptosis, pupillary changes, and changes in visual acuity are ominous signs.

Orbital hematoma may be arterial or venous in origin.[116] Bleeds from the anterior or posterior ethmoidal arteries may lead to rapidly expanding hematomas, which in turn cause sudden increase in intraorbital pressures and must be treated aggressively. Simultaneous efforts are made to relieve the elevated intraorbital pressure and stop the bleeding. A lateral canthotomy and cantholysis may be necessary to relieve intraorbital pressure. If the artery has retracted into the orbit, an endoscopic orbital decompression with cautery or clipping is helpful. If this maneuver is not possible, an external ethmoidectomy can be performed to isolate the vessel and decompress the orbit. Other therapies include orbital massage and the administration of osmotic agents. Venous bleeding, such as that from the veins lining the lamina papyracea, leads to slowly progressive orbital hematomas. These lesions may not be recognized until the patient is in the recovery room or at home. Treatment should be similar to that for arterial orbital hematomas.

Blindness from ESS is a devastating complication and can have several causes. Elevated intraorbital pressure causes blindness after 60 to 90 minutes or even sooner with rapid arterial hemorrhage.[117] Blindness can also result from injury to the optic nerve in the orbit, in the sphenoid sinus, or within a sphenoethmoidal cell. An ophthalmologic consultation is obtained immediately. In addition, any nasal packing is removed. Orbital decompression, which may include decompression of the optic nerve, may be needed. Steroid administration may be beneficial. Inflammatory optic neuropathy may also cause amaurosis after sinus surgery. Haller and coworkers[118] reported on two patients with dramatic visual decrease occurring 2 weeks after sinus surgery as a result

of inflammatory posterior paranasal sinus disease. They were treated with orbital or optic nerve decompression, systemic steroids, and antibiotics, which resulted in a significant improvement in visual acuity in one patient and a complete vision restoration in the other.

Diplopia results from damage to the ocular musculature, most commonly the medial rectus and the superior oblique muscles.[119] Diplopia can be caused by breaching of the lamina papyracea and entry of the orbit, or by pulling of orbital contents through a dehiscence into the ethmoid sinus with a Microdebrider. It is important to always to keep this instrument tangential to the lamina papyracea. Diplopia caused by injury to the muscle must be treated by an ophthalmologist and generally has a poor prognosis.

The nasolacrimal sac and duct are in close relation to the natural ostium of the maxillary sinus as well as to the anterior ethmoids. To avoid injury, dissection should never be performed anterior to the anterior margin of the middle turbinate. The inferior antrostomy should be at least 1 cm posterior to the anterior margin of the middle turbinate so as to avoid the nasolacrimal duct. Inferior or middle antrostomies should not be opened anteriorly. Occult damage to the nasolacrimal duct was probably a common event when antrostomies were opened anteriorly as first described.[120] When patients are symptomatic, a dacryocystorhinostomy may be necessary. It can be performed endoscopically.

Subcutaneous emphysema can result from a small fracture of the lamina papyracea. If the patient is subjected to large amounts of positive pressure after extubation, or if the patient coughs, vomits, or blows the nose, air can become trapped in the subcutaneous and orbital tissues. The eyes should be examined for any other complications. No treatment is usually necessary, and the emphysema resolves in 7 to 10 days.

Intracranial Complications

Penetration of the anterior skull base can occur in any location, but several areas are more prone to injury. The bone of the lateral skull base is usually quite hard, in contrast to the medial skull base, where it can be thin, particularly in the area posterior to the anterior ethmoidal artery. Often the fovea ethmoidalis and cribriform plate lie lower than usual, and any dissection occurring superiorly along the medial aspect of the middle turbinate risks penetration of the skull base. Defects of the skull base that result in CSF leak can be treated intraoperatively if they are recognized. A variety of patches, such as nasal mucosa, temporalis fascia, fat, muscle, and acellular dermal grafts, can be used alone or in combination to help seal the leak. Overlay and underlay grafting techniques work equally well. Fibrin glue is useful in sealing and healing. If there is a large skull base defect, bone or cartilage is used to bridge the gap and prevent encephalocele formation. Penetration of the skull base can lead to brain injury as well as major hemorrhage from vascular injury. These complications are rare and require immediate neurosurgical intervention. Because of nasal packing, CSF leaks may not be apparent during surgery or immediately postoperatively. Delayed leaks are challenging because it is difficult to ascertain the site of leak. If endoscopic examination fails to identify the source, a CT cisternogram or intrathecal injection of fluorescein (off-label use) with endoscopy may be helpful (Fig. 51-16). Small CSF leaks often close spontaneously. Surgery should be considered for any leak lasting longer than 2 to 3 weeks.

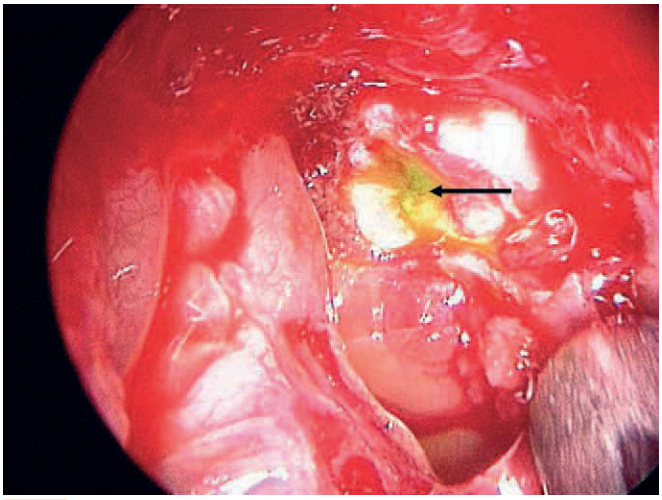

Figure 51-16. Intrathecal injection of fluorescein helps identify a cerebrospinal fluid leak (*arrow*).

Results

Results of ESS are difficult to compare because of variations in disease severity, procedures and techniques used, and length of patient follow-up. There are also no prospective studies comparing medical with surgical management or comparing techniques used. In a prospective study, Khalid and associates[121] utilized the 36-item Medical Outcomes Short-Form Survey at baseline and at 3 years after ESS to assess the general health status of patients. One hundred and fifty (75%) of randomly selected respondents completed follow-up surveys. Baseline sf-36 QOL scores indicated significant differences between patients with CRS and published norms in six of eight subscale parameters (role-physical, bodily pain, general health, social function, vitality, and mental health). Significant improvement in all six categories was maintained at the end of the study period ($P < 0.05$) with QOL scores within the limits of published norms for the general population. These researchers concluded that FESS combined with appropriate postoperative care is effective at maintaining a significant improvement in the overall general health status of patients for at least 3 years after surgical intervention and that the overall scores return to a range of normative values for the general population.[121] A large review by Smith and colleagues[122] concluded that the vast majority of articles on outcomes of sinus surgery represent level 4 (retrospective case series) evidence. All articles generally support that ESS improves symptoms and/or QOL in adult patients with CRS. Older patients with CRS present with symptoms and patient factors that are comparable to those in younger patients and have a similar degree of improvement on endoscopy scores and QOL measures after ESS.[123] Smoking is associated with statistically worse long-term outcomes after ESS, on the basis of average SNOT-16 scores.[67] However, in the short term, both smokers and nonsmokers may achieve a highly significant benefit from ESS. Smokers achieved a greater short-term benefit than nonsmokers in one retrospective study.[124] Patients with CRS and depression present similarly but have worse preoperative and postoperative QOL scores and experience similar disease-specific QOL improvements from sinus surgery in comparison with other patients with CRS. Sinus surgery is not effective in alleviating the effect of depression on disease-specific QOL.[125]

These newer studies validate the earlier finding of others. In 1990, Levine[126] reported success rates of 89.7% for relief of sinonasal polyposis and 80.2% for relief of chronic sinusitis in 221 patients with mean follow-up of 17 months. After following up 200 patients for a mean period of 17 months, Smith and Brindley[127] found that 88% of patients were symptom free or had improvement in symptoms; additional medical therapy was required in 41.5% of the cases. Hoffman and coworkers[128] found that 88% of 114 patients reported the surgery to be of some overall health benefit. A large number of their patients reported improvements in breathing difficulty, nasal congestion, headache, recurrent sinus infections, and postnasal drip. Damm and colleagues[129] reported that QOL was restricted by rhinosinusitis preoperatively in 94% of 279 patients, with 74% considering this restriction to be severe or intolerable. Postoperatively, 85% of the patients had an improvement in QOL.

Patients who have comorbidities such as severe allergies, asthma, and aspirin sensitivity have less favorable results, frequently needing revision surgery.[92,130] However, Robinson and associates[131] found that although their patients with acetylsalicylic acid intolerance had significantly worse preoperative CT ($P < .0001$) and endoscopy scores ($P < .0001$), 57% to 74% of patients after ESS improved as determined by endoscopy scores, 63% to 71% improved as determined by the Rhinosinusitis Disability Index (RSDI), and 58% to 73% improved as determined by the Chronic Sinusitis Survey (CSS). These

researchers reported that improvement did not significantly differ with ASA status.

Gender has also not been found to be predictive of QOL or ESS outcome.[132] Despite similarities in objective disease measures, women report significantly worse QOL scores preoperatively and postoperatively. However, Mendolia-Loffredo and coworkers[132] report that postoperative improvement does not differ according to sex, nor is sex predictive of outcome. Gender differences in QOL may reflect gender differences in ASA intolerance and depression, which are more prevalent in women and have been associated with poorer outcome. Preoperative CT scan scores do not predict surgical outcome.[73] In one series, 146 adult patients undergoing ESS were evaluated with CT and the Rhinosinusitis Symptom Inventory (RSI) preoperatively and at a minimum of 12 months postoperatively, with a mean follow-up of 19.4 months. No significant correlation was identified between preoperative CT stage and percentage change in symptom domain scores on the Inventory.[73]

Causes of Failure of Primary Endoscopic Sinus Surgery

The combination of careful surgical technique and meticulous postoperative care can provide lasting results and improvements in patient health. The most common causes of surgical failure are lateralization of the middle turbinates, missed middle meatal antrostomy with recirculation, maxillary ostium stenosis, residual air cells and adhesions in the ethmoidal area, and frontal recess scarring.[133] The rate of revision surgery has been reported at 10%, with a 78% success rate.[134]

External Procedures

Caldwell-Luc Procedure

The technique of creating an opening in the canine fossa with an intranasal antrostomy was described by George Caldwell[2] in 1893 and Henry Luc in 1897.[135] Until the advent of the endoscope, it was the primary approach used for accessing the maxillary sinus. The creation of an intranasal antrostomy allowed for both dependent drainage of the maxillary sinus and an opening for irrigations after closure of the gingivobuccal sulcus incision. The benefits of the Caldwell-Luc procedure, compared with intranasal antrostomy, are better visualization of antral disease, removal of all disease, and the creation of a window for permanent drainage.[136] Today, the Caldwell-Luc procedure has limited indications in the management of complicated acute or chronic rhinosinusitis, pterygomaxillary space surgery, trauma, foreign bodies, and benign tumors.[136] Combined with an endoscopic approach, the procedure can also be helpful for orbital decompression and removal of inverting papillomas.[137,138]

The Caldwell-Luc procedure is usually performed with the use of general anesthesia. The gingivobuccal sulcus is injected with 1% lidocaine with 1:100,000 epinephrine. Cotton pledgets soaked with a vasoconstrictor are placed in the nasal cavity. The incision is made in the gingivobuccal sulcus, above the canine fossa (Fig. 51-17). An adequate cuff of tissue is left on the gingiva to allow easier suturing during closure. In children the incision should be placed above the secondary dentition; plain radiographs can help determine this level. The incision is carried through the periosteum over the maxilla. The periosteum is then elevated superiorly until the infraorbital nerve is identified. A 4-mm osteotome or a drill is used to outline a window into the maxillary antrum. The anterior wall of the sinus is generally very thin and can be entered with gentle tapping of the osteotome. Once the window is opened, a punch forceps or a drill can be used to enlarge the window as needed. Injury to the secondary dentition and the infraorbital nerve is carefully avoided. The intranasal antrostomy is created by passing a curved hemostat under the inferior turbinate and into the sinus. This window should be made at least 1 cm posterior to the anterior end of the middle turbinate to avoid damage to the nasolacrimal duct. Endoscopic inferior antrostomy allows for localization of the nasolacrimal duct and precise placement of the antrostomy. Partial removal of the membranous inferior turbinate or stenting helps prevent postoperative closure. The maxillary sinus can be visualized endoscopically both from the antrostomy through the natural ostium and through the canine fossa. Placement of an absorbable patch or tissue graft over the bony opening in the maxillary sinus may prevent scar ingrowth, which may be responsible for chronic pain in some patients. The incision is closed with an absorbable suture.

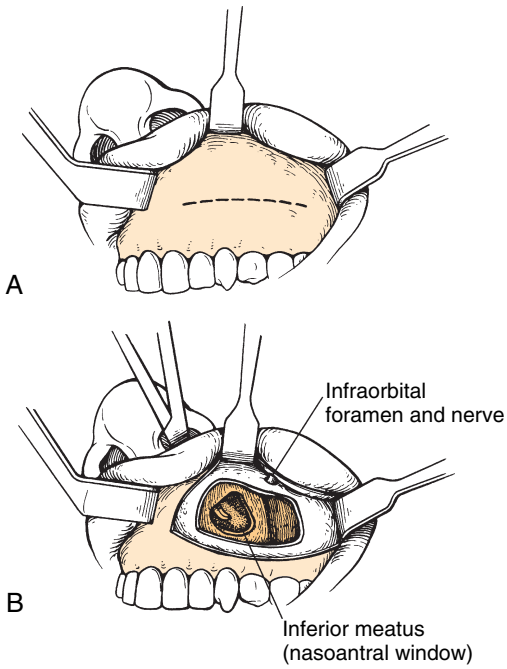

Figure 51-17. **A,** The incision for a Caldwell-Luc procedure is made in the gingivobuccal sulcus, above the canine fossa. **B,** An osteotome or drill is used to create a window into the antrum. A nasoantral window can then be created.

In a review of 670 Caldwell-Luc procedures, the most frequent complication was recurrent nasal obstruction, which occurred in 28% of the patients.[139] Other complications were facial asymmetry, facial numbness, oroantral fistulas, wound dehiscence, dacryocystitis, devitalized teeth, recurrent sinusitis, and recurrent polyposis. Techniques that may help reduce complications include gentle tissue retraction, protecting the infraorbital nerve, limiting the size of the anterior antrostomy, and avoiding cracks in the bony wall of the antrum.[140] Robinson and Wormald[141] wrote that the most suitable area for performing the canine fossa puncture without injuring the infraorbital nerve or anterior superior alveolar nerve was at the intersection of the midpupillary line and a horizontal line through the floor of the nasal vestibule. The same group later described the complications arising from the canine fossa puncture technique.[142] Punctures were performed with endoscopic guidance in addition to use of the predetermined landmarks in 67 patients. Thirty canine fossa punctures were performed without endoscopic guidance, but utilizing the described landmarks. The researchers found that the use of the landmarks to place the site of the canine fossa puncture resulted in statistically fewer complications, such as numbness, tingling, and pain; this rate was further reduced if the puncture was performed with endoscopic vision.

Intranasal Ethmoidectomy

Intranasal ethmoidectomies have largely been replaced by endoscopic approaches. The indications for an endoscopic ethmoidectomy apply for an intranasal ethmoidectomy. They include polyps, tumors, foreign bodies, and CRS unresponsive to medical therapy. The procedure is generally performed with use of general anesthesia but can be done with use of local anesthesia with sedation. An intranasal injection of 1% lidocaine with 1:100,000 epinephrine should be given, as well as placement of cotton pledgets soaked with a topical decongestant. The eyes should be exposed during surgery so they can be easily inspected. A nasal speculum and a headlamp are used for visualization.

Once the middle turbinate has been injected, the procedure begins with gentle medial displacement of the middle turbinate with an eleva-

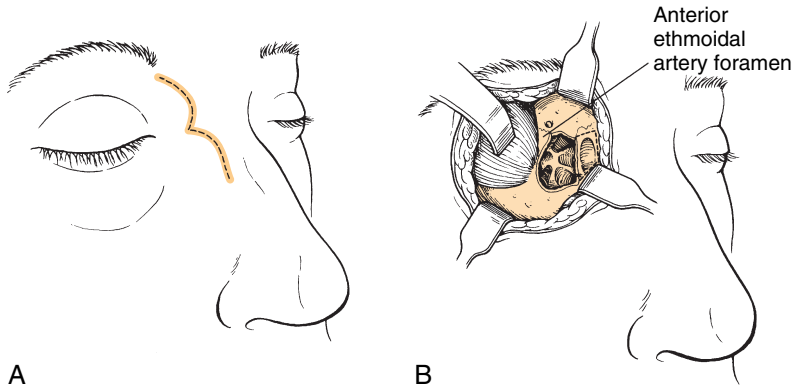

Figure 51-18. **A,** The gull-wing incision for external ethmoidectomy is made midway between the medial canthus and the nasal midline. **B,** The anterior ethmoidal artery is found in the frontoethmoid suture line, which is also the superior extent of the dissection. Bone is removed from the lacrimal fossa and lamina papyracea to provide additional exposure.

tor to improve middle meatal exposure. Often a total middle turbinectomy is performed. With a small curette, the bulla is opened and the anterior ethmoids are removed. Great care must be taken not to violate the orbit or the skull base. Frequent suctioning and placement of cotton pledgets soaked in an epinephrine solution help control bleeding and improve visualization. Dissection is continued into the posterior ethmoids as indicated. At the end of the procedure, packing is placed into the middle meatus. As with endoscopic procedures, the packing is removed after 3 to 4 days, and saline nasal irrigation is initiated. The safety of the intranasal ethmoidectomy has been questioned. Complication rates range from 1.1% to 2.8%.[143,144] Few surgeons now perform this procedure.

External Ethmoidectomy

An external ethmoidectomy is an alternative approach but is rarely used for CRS. However, it is still useful for treating orbital complications of acute rhinosinusitis, such as a subperiosteal abscess. Although endoscopic techniques can be used for draining a subperiosteal abscess, inflammation and edema can limit endoscopic visualization. An external approach should always be discussed with patients as a backup plan. The procedure is usually performed with use of general anesthesia, and the nasal cavity is topically decongested. A tarsorrhaphy is performed on the ipsilateral eye to protect the globe. The surgeon should mark the incision before injection by making an impression with the thumbnail midway between the medial canthus and the midline of the nose (Fig. 51-18). The area is then injected with 1% lidocaine with 1:1,000,000 epinephrine. A gull-wing incision may help reduce postoperative contracture of the medial canthus. The incision is made with a No. 15 scalpel and continued through the periosteum. With an elevator, a small cuff of tissue is elevated medially to aid in closure. Lateral elevation lifts the lacrimal sac from its fossa, along with its attachments, superiorly and inferiorly. A malleable retractor is used to protect the orbital contents during further dissection.

The periosteum is elevated posteriorly into the orbit until the anterior ethmoidal artery is identified. This vessel should be ligated to allow for more posterior exposure. If a subperiosteal abscess is present, pus will be encountered, and should be sampled for culture. A probe is then used to enter the ethmoid complex through the lacrimal fossa or through the lamina papyracea if it is not already dehiscent. Identification of the basal lamella guides the limits of the dissection. The skull base can usually be identified clearly in the posterior ethmoids. This identification helps with any additional dissection of the anterior ethmoids. Dissection should not be carried higher than the frontoethmoid suture line, which marks the level of the skull base. Once the ethmoids are opened, any diseased mucosa, polyps, or tumors can be removed. At the end of the procedure, the incision is closed in two layers and drained externally with a rubber band. Any packing should be removed after 3 to 4 days. Frequent nasal irrigations help reduce postoperative crusting. Complications include diplopia from injury to the trochlea or medial rectus, blindness, exposure keratitis, corneal abrasions, skull base injury, and CSF leak.[145]

External Approaches to the Frontal Sinus

Frontoethmoidectomy, frontal sinus trephination, and frontal sinus obliteration are procedures performed on the frontal sinus via an external approach. They are discussed in Chapter 53.

Approaches to the Sphenoid Sinus

Transseptal and transethmoid approaches to the sphenoid may be performed with a headlamp or a microscope but are now usually carried out with endoscopic guidance.

Conclusions

Patients with CRS experience significant improvement in overall general health after sinus surgery. Endoscopic sinus surgery is remarkably safe and effective, but a thorough familiarity with the three-dimensional anatomy is essential. External approaches are indicated in certain unique situations and also may be utilized in patients for whom multiple endoscopic procedures fail.

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CHAPTER FIFTY-TWO

Concepts of Endoscopic Sinus Surgery: Causes of Failure

James N. Palmer

David W. Kennedy

Key Points

- The concept of functional endoscopic sinus surgery is to surgically remove inflamed tissue and involved bone from critical points in the mucociliary clearance pathways.
- Chronic rhinosinusitis is a disease of inflammation, and therefore the successful approaches to treatment, including surgery, are directed at that inflammation.
- In the overall spectrum of radical to minimal surgery of the sinuses, the successful practitioner of functional endoscopic sinus surgery is somewhat radical in the involved regions of the ethmoid cavity, removing all partitions while carefully leaving a mucosa-lined cavity on the skull base and medial orbital wall.
- In appropriately selected patients, the long-term success rate of functional endoscopic sinus surgery, combined with appropriate medical therapy, is 80% to 90%.
- Absolute indications for surgery in sinus disease include the development of complications of rhinosinusitis, expansile mucoceles, allergic or invasive fungal rhinosinusitis, and suspected neoplasia.
- Relative indications for surgery in inflammatory rhinosinusitis include the presence of symptomatic nasal polyps that are unresponsive to medical therapy and symptomatic chronic or recurrent acute rhinosinusitis that persists despite appropriate medical therapy.
- Anatomic variations are no longer considered important in the pathogenesis of chronic rhinosinusitis, as was previously believed.
- Poor indicators of successful functional endoscopic sinus surgery include persistent environmental exposures after surgery, uncontrolled allergies, continued chemical exposures, and smoking.
- Prior to surgery, the computed tomography scan must be reviewed and the relevant anatomy conceptualized by the surgeon so as to decrease complications and minimize surgical trauma.
- Postoperative medical care augmented by endoscopic examination and débridement as necessary is required for success.

The hallmark of chronic rhinosinusitis (CRS) is inflammation, which may be incited by many different mechanisms. Therefore, therapies used for treatment of CRS are aimed at the inflammation and the inciting factors causing that inflammation rather than specifically at disease identified on imaging. In many cases microbial contamination is a significant factor in this inflammatory process. Chronic or recurrent bacterial infection with or without fungal presence is associated with a change in the inflammatory profile and an inability of the body's own mucociliary clearance mechanisms to function normally, giving rise to the symptoms of CRS. Unfortunately, medical therapy alone directed at this inflammation may be unable to clear the disease, and surgical treatment of what is ultimately an inflammatory disease is considered after failure of medical treatment. Small areas of persistent inflammation that are poised at critical areas can block mucociliary clearance and allow further inflammation to appear at those distal areas. Removing the inflamed mucosa and bone of the obstructed area allows appropriate drainage of the distal sinuses. Therefore the concept of functional endoscopic sinus surgery (FESS) is to surgically remove inflamed tissue from critical points in the mucociliary clearance pathways.

The extent of surgery is somewhat flexible in the overall concept of FESS—that is, the extent of surgery performed, the number of sinuses opened, and the inflamed diseased mucosa and bony partitions removed depend on the amount of disease identified on preoperative evaluation. It is therefore not a "one size fits all" operation but, rather, a procedure that is tailored to each patient's set of findings from history, endoscopy, and radiologic evaluation. Optimally, surgery removes diseased bone and mucosa in the critical areas, with the recognition that the more distal linings of the maxillary, ethmoid, sphenoid, and frontal sinuses do not contain "condemned" mucosa, as was once taught. In the overall spectrum of radical to minimal surgery, the successful practitioner of FESS is probably somewhat radical in removing all bony partitions in areas of the ethmoid cavity involved in the disease process but is also able to preserve a mucosa-lined cavity on the skull base, medial orbital wall, and middle turbinate (Fig. 52-1).

Figure 52-1. Computed tomography scans of a patient with an ethmoid mucocele. **A,** A middle meatal antrostomy has not been performed on the patient's right side. **B,** Scan taken 1 year after surgical drainage of the mucocele and middle meatal antrostomy demonstrates clearance of the ostiomeatal complex.

It should be noted that the importance of the ostiomeatal unit was highlighted in the early years of FESS as a critical final common pathway in the disease process.[1-3] Appropriate surgery in this critical area was found to have exceptionally good results in reversing patient symptoms, with positive outcomes in 80% to 90% of patients.[4,5] However, over subsequent years, anatomic abnormalities in the ostiomeatal complex (OMC) came to be seen by some as the underlying cause of sinusitis, and not merely as a critical point in disease pathogenesis—that is, as a "bottleneck" for the sinonasal drainage pathways. The overemphasis of the importance of the role of the OMC in CRS led to an inappropriate overemphasis on surgically correcting abnormalities in the OMC. Anatomic variations should be regarded only as potential predisposing or potentiating factors in CRS, and not the underlying etiology of the disease; therefore appropriate surgery is only an adjunct treatment for chronic and recurrent rhinosinusitis, not primary therapy.

As discussed, surgery plays an adjunctive and important role in the treatment of rhinosinusitis, but medical therapy is the cornerstone of management of inflammatory disease.[6] CRS is a multifactorial disease. The underlying pathogenesis can be broken into categories of causes that are environmental, generalized host factors, or local host factors. Environmental issues include smoking, allergy, mold/fungus exposure, and, possibly, emotional stress. General host factors include reactive airways disease, Samter's triad, and genetic influences such as immunodeficiency. Local host factors include iatrogenic disease, nasal polyps, and diseases of poor mucus transport. Except in the cases of potential complications such as an expansile mucocele, the adjunctive procedure of surgical intervention (FESS) should be instituted when appropriate environmental control and medical therapy have failed. Continued medical therapy is usually required after surgery to avoid disease recurrence, and failure of the original surgery is often associated with abandonment of the basic concepts of FESS.

Extent of Surgery

Debate about the appropriate extent of surgery for CRS will most likely continue until the pathogenesis is better understood. However, the concept of "irreversibly diseased" or "condemned" mucosa that requires surgical removal is incorrect. In fact, Moriyama and colleagues[7] have shown that denuding of bone results in extremely delayed healing. The bone may remain exposed for 6 months or more, and ciliary density may never return to normal at these sites. The underlying bone of an area of stripped mucosa is also prone to long-term inflammation and is a cause of failure, especially when associated with narrow areas such as the frontal recess. Therefore great emphasis should be placed on mucosal preservation in all sinuses during surgery, especially within the ethmoid sinus, owing to its central position in the paranasal sinuses.

The initial understanding of FESS has been modified, on the basis of continued improvement of the understanding of the disease process. Simply draining involved cells or sinuses may be insufficient in chronic disease. The surgery should be extended one stage beyond the diseased mucosa, which is identified either by computed tomography (CT) or at the time of surgery. Close endoscopic observation of postsurgical healing cavities led us to suspect that the underlying bone may play a significant part in the overall chronic disease process. The inflammatory aspects of the disease usually persist in localized areas, and the disease tends to recur at that same site.[8-10] The inflammation of the mucosa typically resolves after the underlying bone is resected, but it will not improve if only the inflamed mucosa is removed. In experimental animals there is evidence of early bone involvement in sinusitis; chronic osteomyelitis and inflammation spread within the haversian canals of bone despite an inability to demonstrate the organisms within the bone. These clinical and experimental findings lead us to believe that resection of inflamed bone is important to the success of FESS. We hold that reduced viability and inflammation of the underlying bone may be a significant factor in the disease process, at least in more severe cases of CRS.

Because of the inflammation in the bone, the underlying osteitic bony partitions should be removed as completely as possible from the sites of mucosal disease involvement during surgery. In addition to the fact that these partitions may potentiate persistence of the disease, they tend to thicken up in the presence of persistent and ongoing inflammation, making them less easy to remove. Removal of these osteitic partitions is especially important in the uncinate process and partitions of the ethmoid sinuses. Advocates of transition space or minimally invasive surgical therapy (MIST) recommend removing only enough tissue to allow sinus ventilation and mucociliary clearance. There are good aspects to this concept, owing to its advocacy of meticulous atraumatic and mucosal preservation techniques. However, there is also significant concern that the MIST approach is suitable primarily in children and, in adults, for early and mild disease that might be better treated by aggressive medical therapy. The current recommended approach in adults tends toward more complete removal of the underlying bony partitions in the areas where the mucosa is involved with disease with preservation of both the normal mucosa and the mucoperiosteal layer over any remaining bone. The avoidance of leaving exposed bone is an important goal, especially in areas prone to scarring and stenosis.

Surgical Indications in Inflammatory Disease

Absolute indications for surgery in sinus disease include the development of complications of rhinosinusitis, expansile mucoceles, allergic or invasive fungal rhinosinusitis, and suspected neoplasia. Relative indications for surgery in inflammatory rhinosinusitis include the presence

of symptomatic nasal polyps that are unresponsive to medical therapy and symptomatic chronic or recurrent acute rhinosinusitis that persists despite appropriate medical therapy.

As discussed, there are several absolute indications for surgical intervention in sinus disease, but there are essentially no absolute indications for an endoscopic approach rather than other endonasal or external operations. Several publications have demonstrated both better results and lower morbidity with FESS, and therefore it is normally the approach of first choice in CRS. Patients with recurrent acute rhinosinusitis benefit from endoscopic surgical intervention when low-grade mucosal disease persists between episodes. The relation between anatomic variations and recurrent disease is more controversial, but it is reasonable to consider surgery when such obstructing anatomic variations correspond to the area of recurrent symptomatology.

Chronic Rhinosinusitis

In evaluating patients with CRS, it is worthwhile to identify on evaluation some overall factors that are associated with good and poor outcomes. Good outcomes are associated with less severe total mucosal disease and associated obstructive abnormalities that can be corrected. A decision to intervene surgically is relatively easy in patients with persistent severe symptomatic sinus disease despite medical treatment or in patients with impending complications. Nasal obstruction and nasal congestion, the most common symptoms of uncomplicated ethmoid sinusitis, normally respond well to surgery. Additionally, a history of severe pain with pressure change during air travel is strongly suggestive of sinus obstruction that often has a good outcome from surgery.

Headache or facial pain alone requires careful evaluation. In the absence of symptoms of nasal congestion, obstruction, and postnasal drainage, a surgeon should be very cautious about ascribing a complaint of pain to sinus disease. Additionally, several publications have demonstrated a radiographic incidence of mucosal thickening of between 30% and 50% in patients undergoing CT for indications other than sinus complaint. However, it should be noted that the normal sinus mucosa appears to be more sensitive than chronically thickened mucosa to pain from ostial obstruction. Thus, localized, minor ostiomeatal disease may result in severe pain in a dependent sinus, whereas it is less common for a patient with massive polyposis to identify marked facial pain or headache as a major complaint.

Several identified factors are associated with poor outcomes from FESS for CRS. Poor indicators of successful FESS include persistent environmental exposures after surgery, uncontrolled allergies, continuing chemical exposures, and smoking. Allergic patients with middle meatal and OMC disease may be relatively protected from their environmental allergens by their disease; after surgery, however, virgin mucosa is widely exposed to nasal airflow. Cigarette smokers have such bad outcomes with FESS that smoking is a relative contraindication to elective ESS. In patients who continue to smoke, a significantly greater than usual amount of granulation tissue develops over any areas of exposed bone, and the incidence of frontal recess stenosis is higher. In a long-term follow-up study, smoking was the most significant factor in the need for revision surgery and a significantly greater factor than prior surgical procedures, allergies, and asthma in determining the need for revision surgery.[11-13]

Complicated Acute Rhinosinusitis

Endoscopic sinus surgery has been demonstrated to be effective in acute rhinosinusitis that is not resolving with appropriate medical therapy and in cases with threatened or established complications. However, certain cautions must be observed in performing surgery in acute disease. The acutely inflamed mucosa tends to be hyperemic and to bleed easily, with greater potential for the intraoperative bleeding to obscure surgical vision. This difficulty with surgical vision is also complicated by the fact that if a diseased cell is not opened, such an omission can be serious or even life-threatening. Thus, it is important that the surgeon be very skilled in endoscopic surgical techniques undertaking an endoscopic surgical procedure for orbital or intracranial complications of sinusitis. In some cases, a surgeon chooses to perform the operation in acute sinusitis through an open approach to ensure that all cells targeted are cleared of disease and to avoid potential complications such as entry into the orbit.

Mucoceles

In general, the functional endoscopic approach is of most benefit when extensive sinus disease results from a limited cause. Thus, frontal sinus obstruction resulting in an extensive frontal sinus mucocele with posterior table erosion is an ideal case for endoscopic intervention. Such an approach maintains the bony framework of the frontal recess and allows wide marsupialization with minimal morbidity. Indeed, in the presence of posterior table erosion, sinus obliteration is not a good alternative because of the difficulty of completely removing the lining mucosa from exposed dura (Fig. 52-2).

Preoperative evaluation of the patient with frontal sinus mucocele should include careful evaluation of the lesion relative to the skull base. At surgery, the skull base is identified within the posterior ethmoid and then followed anteriorly until the bone of the lesion is identified and the inferior portion removed. It is important that all the osteitic bone be removed from the region of the obstruction. If the bony margins are not made flush with the surrounding wall, narrowing of the opening due to scarring and even closure of the opening may occur. Occasionally upon surgical entry into the lesion, clear fluid drainage may be identified, raising suspicion of a cerebrospinal fluid leak. It appears that this fluid, assuming an intact skull base, represents marked hypersecretion from the mucosa of the lesion.

In the postoperative period, the mucosa lining the mucocele cavity may undergo significant hypertrophy, and secretions may reaccumulate, necessitating suctioning from time to time. However, mucociliary clearance becomes re-established, typically in a few weeks, and the mucosal hypertrophy resolves over time.

Fungal Rhinosinusitis

Fungal rhinosinusitis is classifiied as invasive or noninvasive. Fungal balls and allergic fungal rhinosinusitis are categorized as noninvasive fungal rhinosinusitis. Invasive fungal rhinosinusitis includes both chronic invasive fungal rhinosinusitis and the more common fulminant invasive disease that occurs in the immunosuppressed patient.

Complete removal of a fungal ball results in resolution of the disease, although associated bacterial sinusitis is often also present and frequently requires antibiotic treatment. Fungal balls can usually be removed from the maxillary sinus with a curved suction through a very wide middle meatal antrostomy. If the mass cannot be satisfactorily removed in this fashion, a canine fossa trocar can be introduced and used as a spoon to scoop the mass toward the antrostomy. Angled telescopes (45- and 90-degree) are required for looking into the sinus transnasally to ensure that the mass has been adequately removed.

Allergic fungal rhinosinusitis may be associated with marked bone remodeling that may distort anatomic relations dramatically. In addition to dural exposure, erosion of bone and displacement of the optic nerve and carotid artery may occur when the disease involves the sphenoid or posterior ethmoid sinuses (Fig. 52-3). The aim of surgery in allergic fungal rhinosinusitis is complete removal of all of the inspissated material and polypoid mucosa. It is important to achieve complete removal of the intersinus partitions throughout the ethmoid and sphenoid cavities as well as a very wide middle meatal antrostomy and wide frontal sinusotomies. However, as in all surgery for inflammatory disease, care should be taken to maintain mucoperiosteal coverage of the bone within the cavity. Intensive medical therapy, both preoperative and postoperative, is important for success.[14]

Chronic invasive fungal rhinosinusitis typically requires both a "conservative radical" open approach and a full course of antifungal therapy. The procedure in this case should include all involved soft tissue and bone that can be safely removed, but care should be taken to avoid resecting or violating the dura and orbital periosteum, because both are relatively good barriers to the fungus.

Nasal endoscopy and biopsy are very helpful in the diagnosis of fulminant fungal rhinosinusitis. Wide resection of the invaded tissue, typically via an open approach, combined with the use of intravenous antifungal agents and reversal of the underlying agent of immunocompromise remains the gold standard of therapy for this disease.

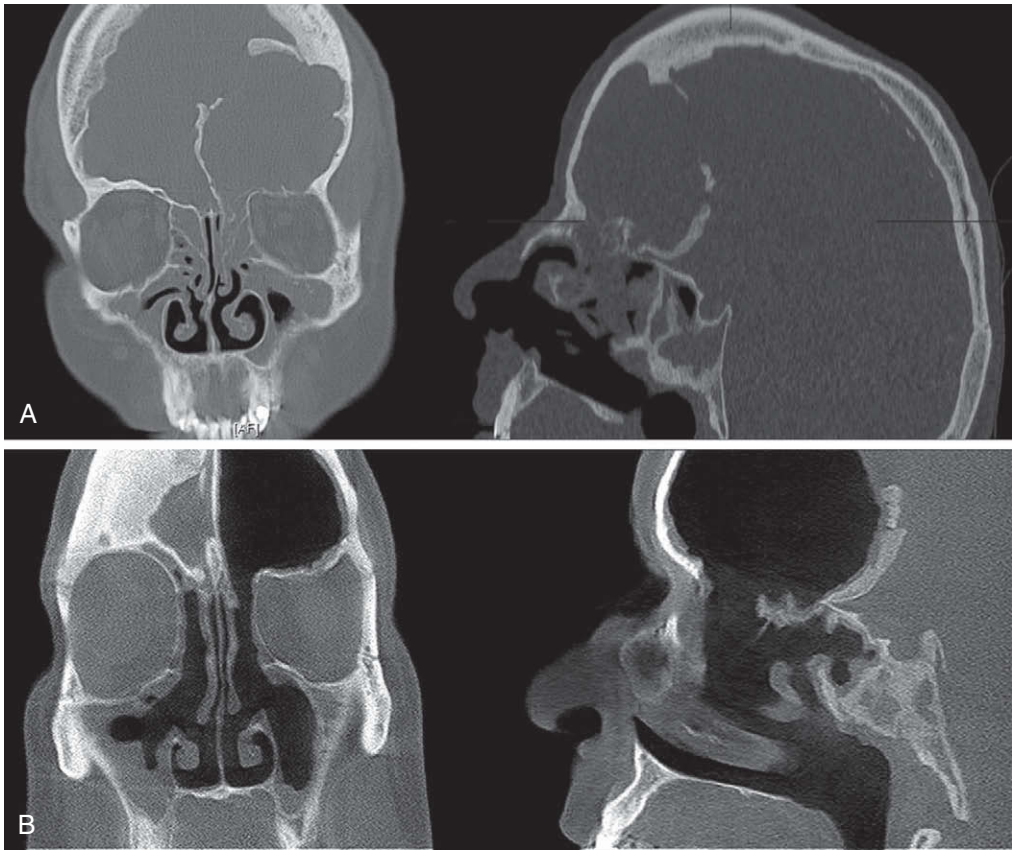

Figure 52-2. **A,** Preoperative computed tomography scans of a patient who presented with frontal lobe compression symptoms. The massive, long-standing frontal sinus mucocele had eroded bone. **B,** The mucocele was treated by endoscopic drainage, as can be seen in these scans, which demonstrate an open draining cavity at 6 months after surgery.

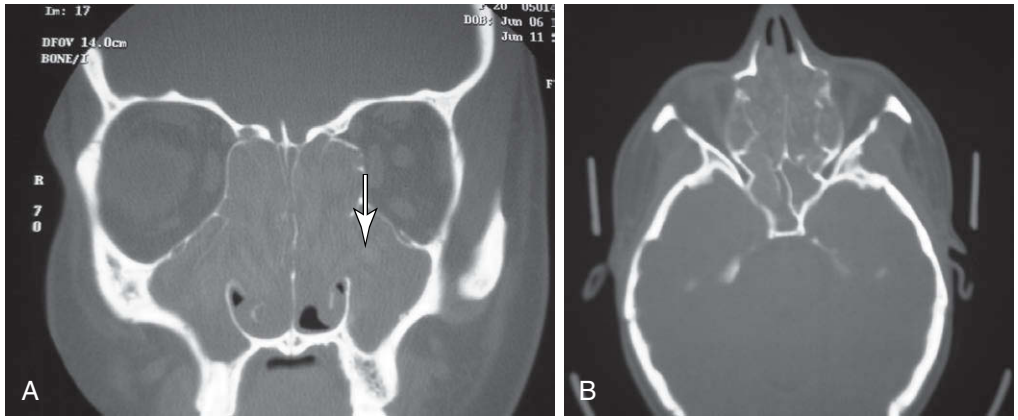

Figure 52-3. **A** and **B,** Computed tomography scans of a patient with allergic fungal rhinosinusitis. Note the differential density of the mucus secretions, as highlighted by the *arrow* in the maxillary sinus in **A**.

Surgical Indications for Tumors, Skull Base Defects, and Other Noninflammatory Lesions

Endoscopic sinus surgery is also an effective approach to other lesions, including benign tumors, skull base defects, and orbital problems. The approaches for these disorders are described in greater detail in other chapters; however, a few comments are warranted here. The most important change that has allowed the development of extended surgical approaches is development of reliable methods for the closure of skull base defects. Using free mucosal grafts and, for lesions of greater than 6 mm, free bone grafts, we have demonstrated a 95% success rate. However, the importance of using an initial layer of bone placed intracranially remains unproven, and others have subsequently reported similar success rates with different graft materials and with the use of flaps based on the septal branch of the sphenopalatine artery. This ability to close skull base defects effectively has allowed endoscopic surgical resection of tumors to be extended to include elective resection of fairly extensive portions of the of skull base.

Additional changes that have assisted in the development of extended endoscopic approaches include advances in instrumentation. The introduction of the EndoScrub Lens Cleaning System (Medtronic ENT, Jacksonville, FL), which enables the tip of the endoscope to be

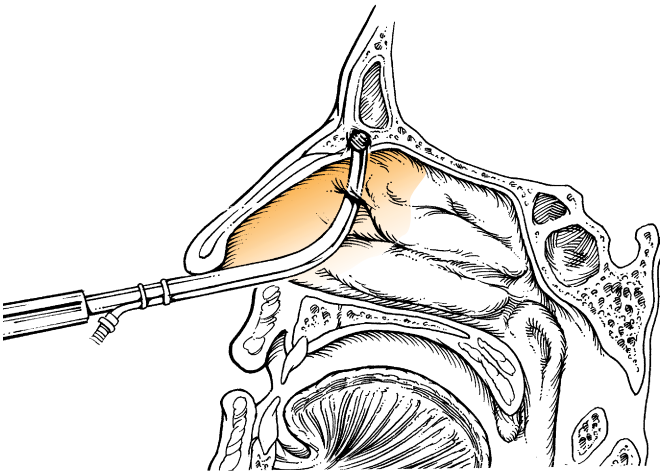

Figure 52-4. Depiction of a 70-degree diamond drill on sagittal section. The curve of the drill allows not only removal of bone at difficult angles but also endoscopic visualization of the working tip. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

kept clean, has made it more possible to operate in the presence of bleeding. Fine slender 70-degree angulated drills, which perform simultaneous irrigation and suction, have significantly improved our ability to remove bone with precision through an endoscopic view (Fig. 52-4). Finally, the refinement of computer-assisted navigation, intraoperative CT scanning with real-time navigation, and CT–magnetic resonance imaging (MRI) merge technologies have allowed more accurate intraoperative localization of adjacent critical anatomy.[15-17]

Tumor control in benign lesions such as inverted papilloma requires precise preoperative imaging and endoscopic evaluation. If the tumor might be attached at a site beyond the reach of the endoscope, preoperative patient consent for an external procedure is necessary. At surgery careful attention is paid to remove or bur the underlying bone at the site of attachment. The dura and periorbita usually provide excellent barriers against spread of the lesion and should be left intact. Therefore, in areas of dural or periorbital exposure where the overlying bone has been eroded, only bipolar cautery rather than resection at the site or sites of attachment is performed. A major surgical aim in tumor surgery must be to create and maintain a widely patent surgical cavity to facilitate long-term endoscopic follow-up. Therefore, we advocate a very complete sphenoethmoidectomy, frontal sinusotomy, and very wide antrostomy in these cases. The nasolacrimal duct is sacrificed whenever necessary.[18]

Endoscopic removal of vascular lesions such as juvenile angiofibroma requires excellent interventional angiography and preoperative embolization in addition to a high level of experience. Juvenile angiofibroma is often best approached by separation of the lesion from any blood supply posteriorly in the nasopharynx with the use of curved bipolar suction forceps administered perorally under direct endoscopic visualization with the soft palate retracted. The lateral limit of the lesion is approached transnasally by creation of a wide maxillary antrostomy and entry of the pterygoid fossa. This allows the primary vascular supply to be clipped and sectioned before manipulation of the tumor itself. Finally, the tumor may be mobilized, displaced medially, and resected.

Malignant tumors require removal of the site or sites of attachment with a margin of normal tissue. Even with limited areas of attachment, such endoscopic oncologic procedures may require moderately extensive skull base and dural resection with clearly delineated margins. In both benign and malignant tumors with more widespread skull base and intracranial involvement, endoscopic techniques may aid craniofacial en bloc resection. The endoscopic approach may provide excellent visualization for the intranasal cuts as well as aid placement of the vertical cuts from above. An extensive resultant skull base defect can be closed with a flap through the cranial approach.

Endoscopic endonasal techniques have become the approach of choice for the closure of the majority of accessible skull base defects. However, lesions within the distal or lateral frontal sinus or defects in a supraorbital ethmoid sinus are best addressed through an external approach. In addition to reduced morbidity, endoscopic resection of encephaloceles and meningoceles and endoscopic closure of cerebrospinal fluid rhinorrhea offer significantly higher success rates than surgery from above.

Endoscopic orbital surgery may be used for orbital decompression, optic nerve decompression, or the biopsy of lesions in the medial aspect of the orbital apex. Endoscopic transnasal dacryocystorhinostomy (DCR) offers some advantages over an external approach, also allowing excellent intraoperative visualization and the ability to remove any granulation tissue during the healing phase.

The variety of procedures currently being performed endoscopically, from endoscopic cauterization or clipping of sphenopalatine epistaxis to endoscopically directed olfactory biopsy, precludes discussion of all the possibilities for the use of transnasal endoscopic approaches. The range of procedures for which endoscopic intervention is performed will continue to expand as the instrumentation develops and techniques are refined. However, the most significant advance will occur when robotic arms are developed that are small enough to be utilized intranasally.

Preoperative Evaluation and Management

To identify the proper diagnosis of the underlying factors involved in CRS, evaluation through careful history, nasal endoscopy, and radiologic imaging is appropriate. A careful history is important to match symptoms with disease process so that therapy can be initiated. In many cases, the patient will have been treated to a variable extent by primary care physicians—it is important to identify the amount and duration of antimicrobial and anti-inflammatory treatments previously given in order to tailor an appropriate medical regimen. Although the primary imaging modality is CT, MRI is performed as an adjunct when indicated.

Medical Treatment and Nasal Endoscopy

The patient should undergo a second diagnostic nasal endoscopy so the surgeon can review the anatomy and pathology, ensure that there has been no acute exacerbation after medical therapy, and, if indicated, take culture specimens to guide intraoperative and postoperative antibiotic therapy. During endoscopy, access to the ethmoid cavity is evaluated. If the 4-mm 0-degree telescope cannot be introduced to the anterior attachment of the middle turbinate because of septal deviation, it will be evident that at least a limited septoplasty is required at the time of surgery.

Prior to elective surgery for inflammatory disease, infection should be minimized to reduce intraoperative bleeding. Patients with severe polyposis or markedly hyperreactive mucosa also are best treated with a course of oral steroids to reduce mucosal bleeding, unless there is a contraindication to the use of these agents. Patients with reactive nasal mucosa can be identified from their tendency for development of marked congestion, sneezing, and hypersecretion during diagnostic endoscopy despite the use of topical decongestion and anesthesia. If untreated, a similar tendency will result intraoperatively in intermittent profuse nasal bleeding in response to mucosal stimulation, even if the site of intranasal stimulation is at a distance from the site of surgery. Typically, a course of 20 to 30 mg of prednisone for 3 to 10 days preoperatively is sufficient, with the longer preoperative treatments being reserved for severe polypoid disease and allergic fungal sinusitis. The course of steroids additionally stabilizes the lower airway in patients with asthma and decreases the chance of intraoperative or postoperative bronchospasm.

Radiographic Evaluation

Computed Tomography

Presurgical evaluation of CT scans should be performed in a routine checklist fashion to ensure careful review of each area for anatomic variations (Table 52-1). Special care should be taken to evaluate the

Table 52-1

Computed Tomographic Evaluation before Functional Endoscopic Sinus Surgery

Site	Evaluation
Skull base	Slope, height, erosions, areas of relative thickening and thinning
Medial orbital wall	Integrity, erosion, shape, infundibular size, and uncinate position
Ethmoid vessels	Position of anterior and posterior ethmoid vessels relative to skull base
Posterior ethmoid	Vertical height, presence of sphenoethmoidal (Onodi) cell
Maxillary sinus medial wall	Infraorbital ethmoid cells, accessory ostia
Sphenoid sinus	Relative sizes, position of intersinus septum, relationship to carotid arteries, and optic nerves
Frontal recess and frontal sinus	Frontal sinus pneumatization, frontal recess size, agger nasi and supraorbital ethmoid pneumatization, frontal sinus drainage

Figure 52-5. Coronal computed tomography scan demonstrating protrusion of the medial rectus. This patient had no history of trauma and no abnormality of extraocular movement.

lateral cribriform plate lamella, because this medial part of the ethmoid roof is usually the thinnest part of the skull base and is exposed to potential trauma during frontal recess surgery. In general, the skull base is significantly thicker laterally than medially. Any areas of hyperostosis should be identified, because in these areas, the skull base can probably be approached with relative impunity.

The medial orbital wall is evaluated for areas of erosion and for any irregularities (Fig. 52-5). The relative position of the uncinate process to the orbital wall and the presence of any infundibular atelectasis are noted so that inadvertent orbital entry will not occur during the initial infundibulotomy incision.

The anterior ethmoidal artery usually can be identified as a medial indentation ("nipple") pointing medially from the medial orbital wall. This may be seen either at the level of the skull base or some distance below it (Fig. 52-6). The posterior ethmoidal artery is typically within the skull base and is significantly more difficult to recognize.

An evaluation of the vertical height of the posterior ethmoid should be performed. This is the vertical distance between the posteromedial roof of the maxillary sinus and the roof of the ethmoid sinus. This vertical height determines the working room available within the posterior ethmoid for access to the sphenoid sinus. Failure to recognize a narrow vertical height in this area may result in inadvertent intracranial entry (Fig. 52-7).

Maxillary sinus pneumatization is evaluated with respect to the presence of any infraorbital ethmoid cells, and the medial wall is evaluated for the presence of any accessory ostia that might have been missed during nasal endoscopy. The presence of a medially retracted posterior fontanelle in conjunction with an atelectatic infundibulum suggests that gaining entry into the maxillary sinus will be challenging.

Should surgery be necessary in the region of the sphenoid sinus, this structure is best evaluated in both the axial and the coronal planes. The axial plane demonstrates the relation of the intersinus septum to the carotid arteries and the relative size of the two sphenoid sinuses, and the coronal view demonstrates the relation of the optic canal with the sinus.

The frontal recess requires triplanar views (axial, coronal, and sagittal) to achieve understanding of the three-dimensional anatomy of the area. The ability to scroll through the anatomy in multiple planes is even more preferable. If significant trauma is to be avoided in this critical region, it is essential that the surgeon have a complete understanding of the anatomic relationships, particularly with regard to the anteroposterior diameter of the frontal sinus, as well as the relationship to adjacent agger nasi and supraorbital ethmoid cells.

Magnetic Resonance Imaging

Although CT is clearly the primary diagnostic modality for sinus disease, MRI is adjunctive and required in certain situations. MRI is essential when CT reveals disease adjacent to skull base erosion. In this situation, MRI identifies whether the erosion is caused by sinus disease or secondary to a prior skull base erosion or trauma with resultant meningoencephalocele. The evaluation of dehiscent areas becomes even more important when there are sphenoid erosions and the possibility of a carotid artery aneurysm. MRI also enables differentiation of sinus from intranasal soft tissue masses as well as of tumor from retained secretions (Table 52-2).

Concepts of Antrostomy

Several theoretic considerations need to be kept in mind when one is considering the most appropriate size for antrostomy in FESS. In rabbits, experimental exposure of the maxillary sinus to airflow results in dramatic slowing or cessation of mucosal clearance. Therefore, the maxillary sinus ostium and the maxillary sinus mucosa should ideally remain protected from airflow. It also has been demonstrated that nitric oxide is actively liberated from the sinus mucosa at levels that may reach bacteriostatic concentrations, theoretically creating another advantage for keeping the surgically created ostium small. Conversely, a significant part of the medial wall of the maxillary sinus is composed of the uncinate process, a bone that frequently displays osteitic changes. When the uncinate process is diseased and is not completed resected, persistence of disease and scarring are typically seen at this site. Therefore, if disease is very mild, a minimal opening of the ostium is preferable. However, in the presence of long-standing diffuse chronic sinusitis, especially with evidence of osteitis, or when there is a strong likelihood that significant local care of the maxillary sinus may be required after surgery, a wide middle meatal antrostomy is preferred. The wide middle meatal antrostomy would include careful and complete removal of the uncinate process both anteriorly and inferiorly. If the maxillary sinus extends medially into the nasal cavity so that the medial wall posterior to the antrostomy is displaced into the nasal airflow, this medially displaced wall creates an "air scoop" that will preferentially dry the mucosa of the posterior maxillary sinus wall. In this instance it is better

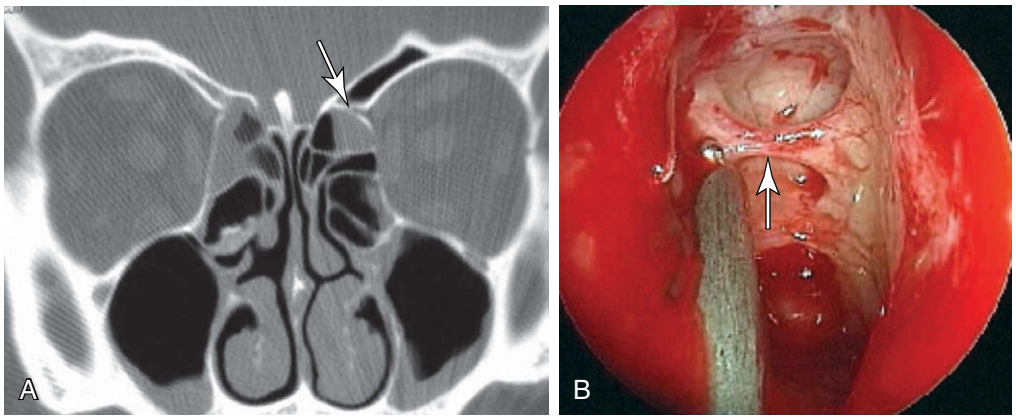

Figure 52-6. Paired coronal computed tomography scan **(A)** and endoscopic view **(B)** of the anterior ethmoidal artery (*arrow*). Note that the artery comes through a foramen that is demarcated by the convergence of the medial rectus and superior oblique muscles.

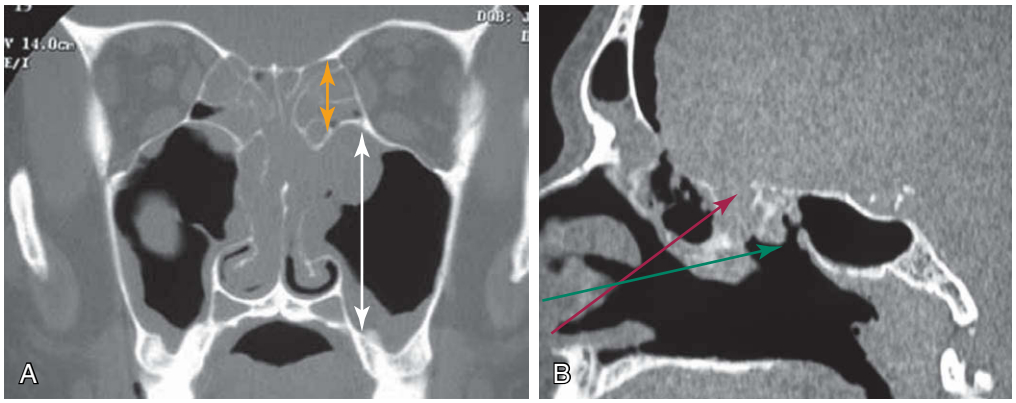

Figure 52-7. **A** and **B,** Paired coronal and sagittal computed tomography scans demonstrating the importance of the ratio of maxillary height (*white arrow*) to ethmoid height (*orange arrow*). When the maxillary sinus is larger, the ethmoid height is relatively shorter, and vice versa. The larger the maxillary sinus, the more superior the basal lamella attachment—therefore, the higher the "angle of attack" through a 0-degree scope into the posterior ethmoid, and the higher the risk of skull base penetration in the posterior ethmoid. In **B,** the *red arrow* indicates a larger maxillary sinus; the *green arrow* indicates a smaller maxillary sinus.

Table 52-2

Appearances of Sinus Lesions on Magnetic Resonance Imaging (Simplified)

Image	Tumor	Mucocele	Fungus Ball	Meningocele	Encephalocele
T1-weighted	Low	Variable (brighter as protein rises)	Variable	Low	Low
T2-weighted	Low-intermediate	Variable (brighter in high-water, low-protein fluids)	Variable; often drops out	High	Low
T1-weighted with contrast enhancement	Solid, central bright	Peripheral enhancement	Peripheral bright	Rim enhancement	Low

to extend the antrostomy in the posterior direction to the pterygoid plate.

Whatever the size of antrostomy created, it is important that the opening communicates with the natural ostium to prevent failure of surgery. One of the more common causes of persistent maxillary sinus disease after surgery is the presence of a middle meatal antrostomy that does not connect with the natural ostium anteriorly.[19] If the natural ostium is not opened, persistent disease may remain in the periostial area, with pooling of secretions and continued recurrent and persistent disease. Additionally, if the natural ostium does reopen and a noncontiguous middle meatal antrostomy is present, recirculation of mucus frequently occurs, with the mucus re-entering the maxillary sinus through the iatrogenic ostium. Such recirculating mucus will, almost of necessity, become more acutely infected from time to time. Confirming that a middle meatal antrostomy communicates with the natural ostium may not be easy. The bone of the uncinate process may become thickened after infection, and the ostium may become tightly closed and difficult to reopen. Additionally, there are no easy landmarks for the extent to which an antrostomy should be brought anteriorly. Inspection with a 45-degree or 70-degree telescope frequently is helpful

in this regard and is definitely required to exclude with certainty the presence of a noncontiguous antrostomy (Figs. 52-8 and Fig. 52-9). Another anatomic abnormality that bears mention is the diseased infraorbital (Haller) cell, which even when opened may have residual osteitic partitions, creating persistent localized mucosal hypertrophy. Use of angled telescopes is important to evaluate the drainage pathways. Occasionally, when such bony partitions are clearly a cause of localized persistent disease and they are inaccessible from the intranasal route, a limited sublabial approach may be indicated for their removal (Fig. 52-10). Other long-term causes of antrostomy failure are osteoneogenesis from stripped mucosa, retained foreign body, and mucus draining into the sinus from persistent frontal recess inflammation.

Ethmoidectomy

The surgeon must work from "known" to "unknown." Once the middle turbinate is medialized and the uncinate removed in its entirety, the maxillary sinus may be addressed, and antrostomy performed as discussed. If the sinus is opened, the posterior and superior walls of the sinus can be used as landmarks for subsequent dissection. The medial orbital wall is identified and is the first critical ethmoid landmark. Failure to identify the medial orbital wall early can lead to dissection in the medial part of the ethmoid cavity, where the skull base is both thin and downsloping, at a point in the surgery at which adequate visualization of the anatomy has not been achieved. The ethmoid sinus is in close proximity to the other three paranasal sinuses, and often FESS includes a complete ethmoidectomy to allow access to each diseased sinus. In primary CRS, surgery is focused to areas of disease, and when complete ethmoidectomy is performed, the goal is to create a marsupialized cavity lined by healthy, intact mucosa. Ethmoidectomy is most safely performed with a 0-degree telescope and Microdebrider or straight and 45-degree through-cutting forceps. After positive identification is made of the medial orbital wall, the skull base provides the second critical landmark so it must be identified carefully. We advocate dissection low in an anterior-to-posterior direction, across the basal lamella to the sphenoid face, and then identification of the skull base in the posterior ethmoid or sphenoid sinus, followed by completion of the dissection from posterior to anterior.

Some of the more common postoperative results of failure of correct complete ethmoidectomy are lateralized middle turbinate, retained uncinate process, failure of removal of the uncinate superiorly (persistent recessus terminalis), and residual agger nasi cells. Careful attention to bony lamellar remnants, the use of through-cutting forceps,

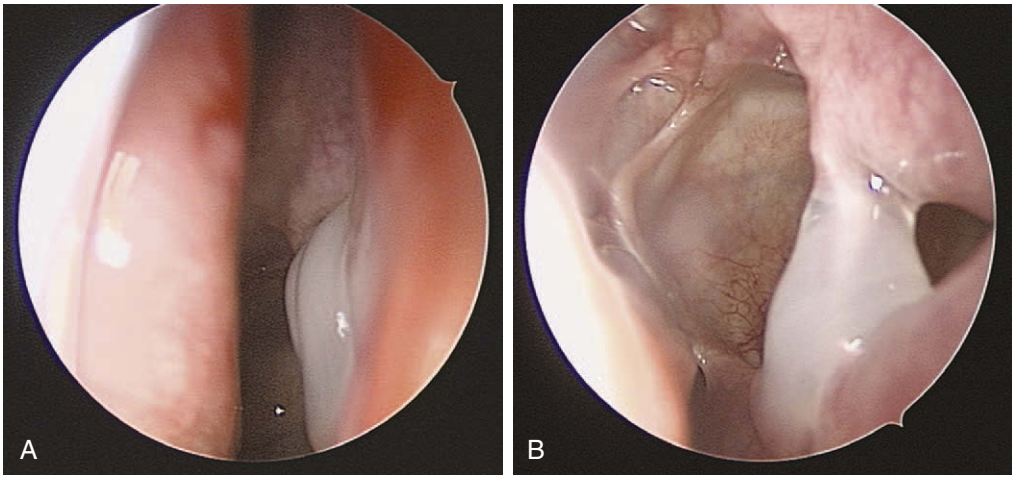

Figure 52-8. Paired images from 0-degree **(A)** and 70-degree **(B)** endoscopes. It is easy to imagine that if the surgeon were to use only a 0-degree endoscope in this patient, the adhesion that is allowing recirculation of mucus in the maxillary sinus would not be identified and subsequently addressed.

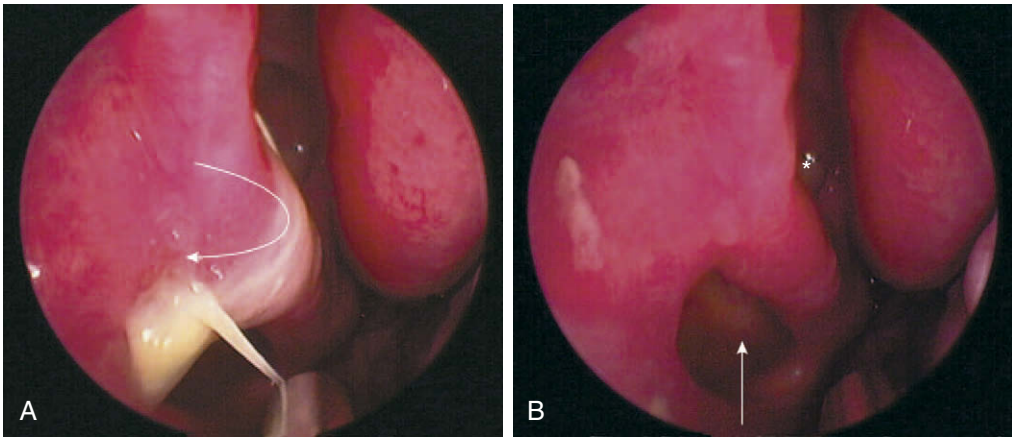

Figure 52-9. **A** and **B,** Endoscopic views of the right middle meatus through a 0-degree telescope demonstrating recirculation of infected secretions. Normal mucociliary flow sweeps contents from the maxillary sinus out the surgically enlarged maxillary sinus ostium. **A,** In this case, secretions re-enter the maxillary sinus through a patent antral nasal window. As these secretions continue to recirculate, they are prone to becoming infected. **B,** Structures shown immediately after suctioning. The *star* denotes the surgically enlarged maxillary sinus ostium, and the *arrow* the nasal antral window. Secretions are rotating around a previously amputated inferior turbinate.

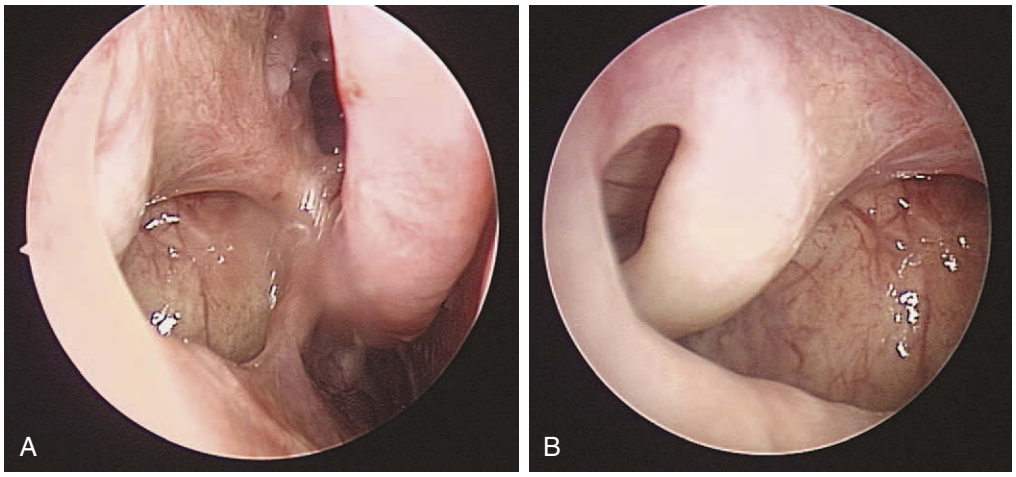

Figure 52-10. Paired images from 0-degree **(A)** and 70-degree **(B)** endoscopes. It is easy to imagine that if the surgeon were to use only a 0-degree endoscope in this patient, any disease in the left infraorbital (Haller) cell would not be addressed.

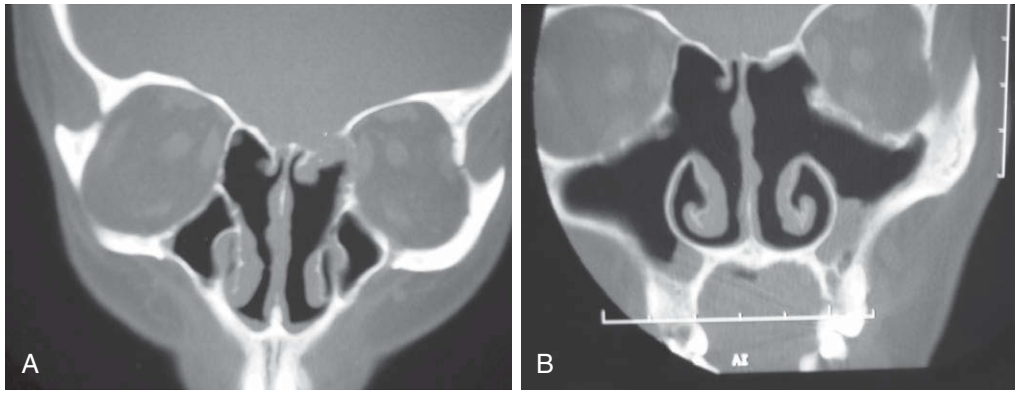

Figure 52-11. Patient who had undergone endoscopic ethmoidectomy presented with an encephalocele that had not been diagnosed because the endoscopic appearance was similar to that of nasal polyposis. **A,** Preoperative computed tomography scan. **B,** Scan obtained 6 months after endoscopic repair with a bone graft.

and the use of a Microdebrider helps achieve resection of disease while leaving a mucosa-lined cavity. Unresected bony partitions trap mucosa and mucosal secretions and will frequently thicken and become difficult to remove after surgery, so it is important to remove them at the first operation. On occasion, particularly in revision surgery, a drill may be needed to remove osteitic bone if it cannot be removed with forceps.

Iatrogenic disease can also include a meningocele or encephalocele. In a case in which a skull base dehiscence is identified and a meningocele is suspected, intrathecal injection of fluorescein before the surgery (0.1 mL of 10% fluorescein injected slowly in 10 mL of the patient's own cerebrospinal fluid) can be considered, to help distinguish encephalocele from surrounding mucosa (Fig. 52-11).[20]

Sphenoidotomy

Before entry of the sphenoid sinus, it is advisable to re-review the radiographic anatomy in both the coronal and axial planes. In addition, the surgeon should review the course of the optic nerve and the carotid artery, especially if a sphenoethmoidal (Onodi) cell is present. The surgeon should also remember that the carotid artery is "clinically dehiscent" in 23% of sphenoid sinuses, making the potential for serious complication in this region significant (Table 52-3). The importance of preoperative diagnosis through radiologic studies must be emphasized (Fig. 52-12). Once the diagnosis is more firmly established and risk to surrounding structures is evaluated, multiple approaches to the sphenoid can be considered.

The transethmoid/transnasal approach is ideal when sphenoidotomy is combined with ethmoidectomy or when wide unilateral sphenoid exposure is required. Following complete ethmoidectomy, the sphenoid face, skull base, and superior turbinate are identified. In cases in which the last structure may be difficult to identify in the presence of severe disease, a ball-tipped seeker may be helpful in locating the superior meatus medially within the cavity. It can also be helpful to resect the posterior portion of the middle turbinate with a backbiter to further expose both the superior meatus and the turbinate. Once the appropriate structures are identified, the inferior third of the superior turbinate is sharply resected; then the natural ostium of the sinus is identified medial to it and is widened. It is important to create a very wide opening that extends to both the skull base and medial orbital wall to avoid the risk of postoperative stenosis (Figs. 52-13 and 52-14).

The other two approaches used for isolated sphenoid sinus disease are the transseptal and the endoscopic transnasal approaches. Before the endoscopic era, a transseptal approach to the sphenoid was frequently used because it provided the advantage of keeping the surgery in the midline of the nasal cavity. The endoscopic transnasal approach provides an excellent approach in isolated sphenoid disease. The advantage is that is quick and avoids disruption of ethmoid sinus anatomy. However, it offers the smallest total exposure to the sinus of any approach.

The most common local causes of failure leading to persistent sphenoid disease are missed or inadequate entry and stenosis, the latter occurring either as a result of inadequate sinusotomy or because of limited postoperative care and scarring of the lateral superior turbinate.

Table 52-3

Possible Complications of Sphenoid Sinus Surgery

Complication	Associated Structure(s)
Vascular hemorrhage	Posterior ethmoidal artery, internal carotid artery, cavernous sinus, sphenopalatine artery
Hematoma	Retrobulbar
Intracerebral injury	Cerebrospinal fluid leak, meningitis, cerebritis, abscess, brain injury, pituitary trauma
Fistula	Cavernous sinus: carotid artery
Cranial nerve (CN) injury	Optic nerve: blindness, pupillary defects Oculomotor nerve (CN III): diplopia, pupillary defects Trochlear nerve (CN IV): diplopia, pupillary defects Abducens nerve (CN VI): diplopia, pupillary defects Trigeminal nerve (CN V_1 to V_x): facial numbness

Frontal Sinusotomy

The frontal sinus continues to present the surgeon with the most challenge, in terms of both the surgical procedure and the potential for persistent and recurrent disease. At minimum, exploration of the frontal recess commits both the patient and the surgeon to a prolonged period of postoperative care and endoscopic observation. At worst, unnecessary exploration of the frontal sinus or inadvertent stripping of mucosa in this area can result in prolonged morbidity and multiple surgical procedures. Therefore, the most difficult decision in FESS is whether the frontal recess should be explored. In some cases of frontal sinus involvement, it is clearly better to perform just an ethmoid dissection and then monitor the patient to see whether the frontal recess disease resolves. The decision should depend, in addition to the pathology present, on the surgeon's experience and ability to preserve mucosa, the regional anatomy as seen on CT, and the availability of through-cutting mucosal-sparing instrumentation.

Preoperative evaluation of the frontal sinus and frontal recess anatomy requires careful evaluation of coronal and axial CT views. A reconstructed sagittal view, as provided in computer-assisted stereotactic navigation, is also of benefit, particularly in cases of complicated frontal recess pneumatization. In evaluation of the frontal recess for potential surgical intervention, attention is paid to its size in both the anteroposterior and lateral diameters, the presence of neo-osteogenesis, and an evaluation of the underlying disease process. Additionally, attention should be paid to the extent of the pneumatization of the frontal sinus itself, because a hypoplastic frontal sinus appears to be significantly more likely to lead to frontal recess stenosis than a sinus that is well pneumatized, irrespective of the anatomy of the frontal recess. One possible explanation for this phenomenon is that mucociliary clearance from a well-pneumatized sinus is greater than

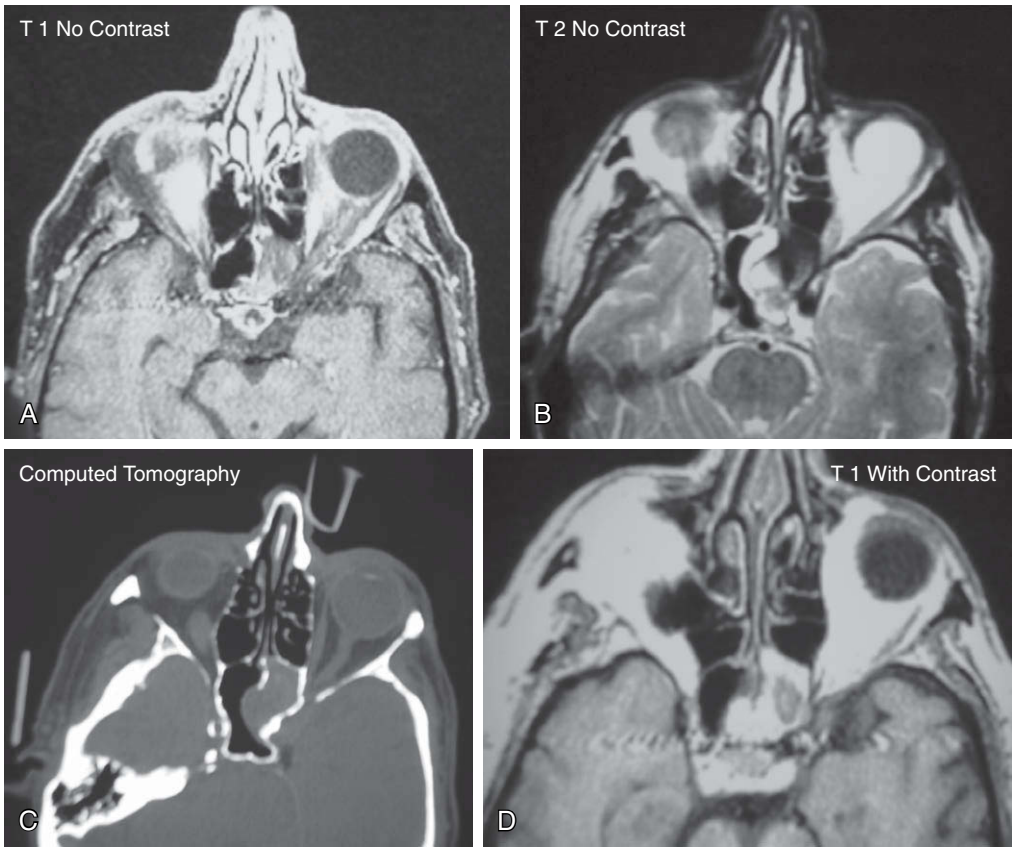

Figure 52-12. Imaging of a patient with a fungus ball in the sphenoid sinus. The heterogeneous mass in the left sphenoid shown on the T1-weighted magnetic resonance image **(A)** drops out on the T2-weighted image **(B)**. The bright areas around the fungus ball are from associated inflammation. **C,** Computed tomography scan. **D,** On a T1-weighted gadolinium-enhanced magnetic resonance image, contrast agent lights up the associated mucosal inflammation around the fungus ball.

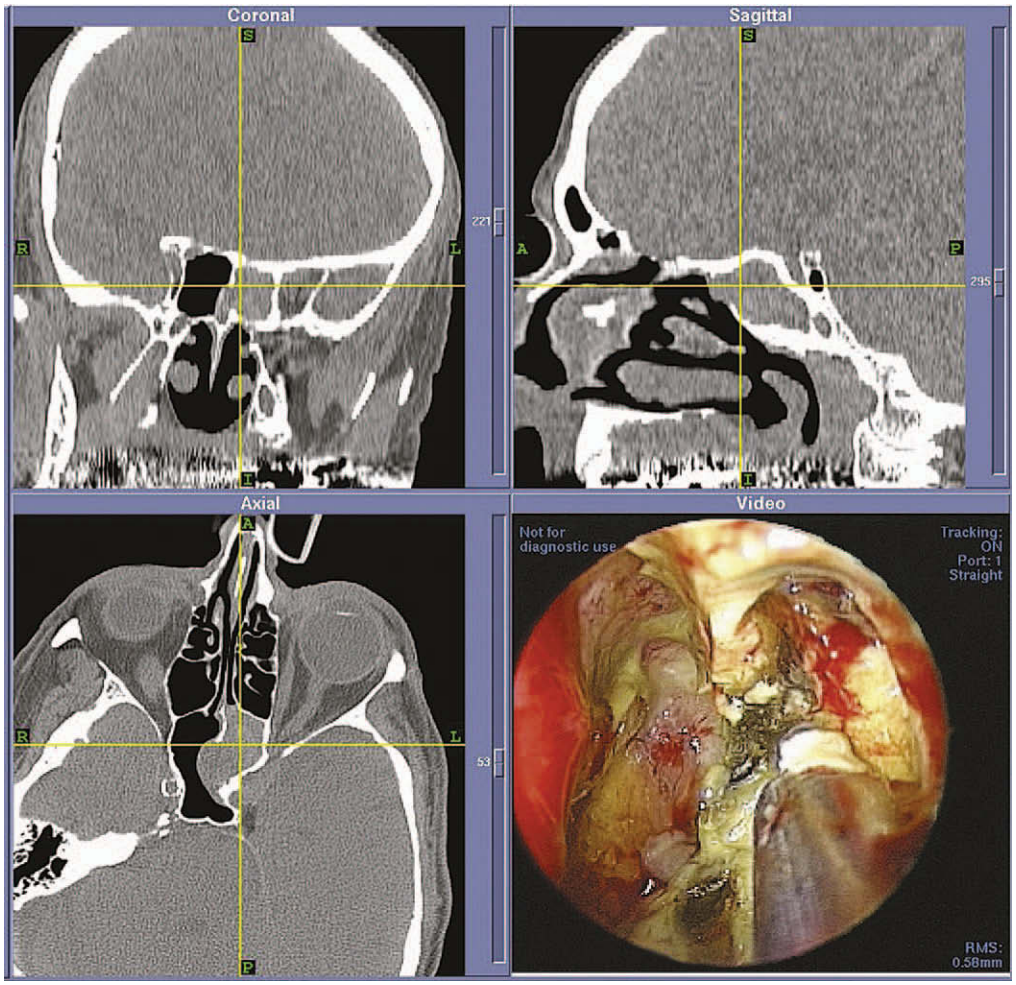

Figure 52-13. Intraoperative images from endoscopic sphenoethmoidectomy using an image-guided navigation system performed in the patient from Fig. 52-12. The cross hairs on the reformatted three-dimensional computed tomography scans (*top, bottom left*) denote placement of the probe as seen in the endoscopic view (*bottom right*). The remains of the fungal ball as well as the associated inflammation can be seen in the endoscopic view. After its removal, the patient had complete relief of symptoms with an uneventful postoperative period.

from a hypoplastic sinus, and mucociliary flow may aid in maintaining patency.

In our clinical experience, the most common immediate cause of frontal sinus disease is the presence of infundibular disease displacing the uncinate process medially, thereby obstructing a frontal sinus. Indeed, in some cases, the medially displaced uncinate process may undergo fusion to the middle turbinate. The second most common cause of frontal sinus disease appears to be mucosal disease and expansion of an agger nasi cell, with resultant posterior displacement of the frontal sinus ostium.

The concept therefore in FESS with respect to the frontal sinus is to work in a stepwise progression to remove all bony septae from cells present, in a procedure termed a *frontal recess dissection*. The initial step in frontal recess dissection involves identification of the appropriate boundaries and the drainage pathway of the frontal recess on CT scan, as well as correlation of this anatomy with the endoscopic view through a 45- or 70-degree telescope (Box 52-1 and Table 52-4). A fine malleable probe can be very helpful in locating the access to the frontal sinus. Once the inferior wall of the agger nasi cell is identified, the surgeon can resect it by sliding a 90-degree frontal sinus curette between the skull base and the posterior agger nasi cell wall and fracturing wall in an anterior and inferior direction (Fig. 52-15). Stammberger has very aptly described this gently performed maneuver as "uncapping the egg." The remaining medial agger nasi cell wall is then removed. After the bone is fractured, the loose bony fragments can be teased out with a fine malleable hook and removed with giraffe forceps with preservation of the mucosa. Mucosal preservation is critically important during frontal recess dissection, but redundant mucosa can be removed with through-cutting forceps or gentle application of curved, powered dissection blades. In general, frontal sinus stents are less satisfactory in maintaining patency than meticulous postoperative care. However, if a stent is used, it should be made of a soft, conformable material.

Frontal cells originate as anterior ethmoid cells that pneumatize into the frontal recess, creating the potential for compromise of the frontal sinus outflow tract and thus serving as a significant potential cause of persistent disease.[21] Because these are the second most anterior of the ethmoid cells, the origins of the frontal cells are located posterior to the agger nasi cell. Each frontal cell then pneumatizes superior to the agger nasi cell into the frontal recess and up into the frontal sinus, where it can cause frontal recess obstruction. A classification of four types of frontal sinus cells has been described, and the nomenclature for them expresses the distance they pneumatize into the frontal sinus, from a type I cell, which is just above the agger nasi cell, to a type IV cell, which pneumatizes completely into the frontal sinus itself. However, for a surgeon performing ESS, the relationship of the cell to the opening of the frontal sinus outflow tract is typically more important than the extent of the cell within the frontal sinus. The surgeon best determines this relationship by using triplanar CT reconstructions or, even better, by scrolling through the triplanar "cuts" on an image guidance system screen until he or she has developed a true three-dimensional conceptualization of the anatomy and how it will appear endoscopically. Frontal recess obstruction by frontal cells occurs in a

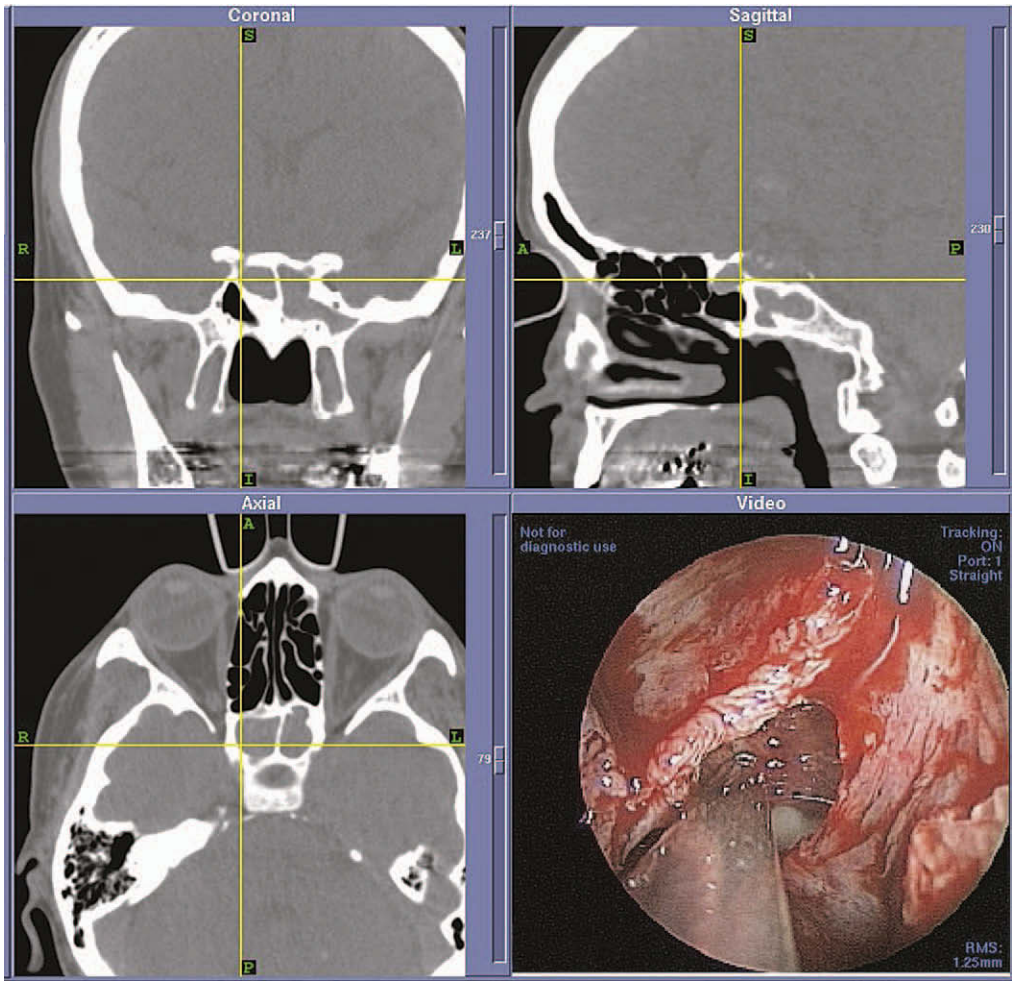

Figure 52-14. Intraoperative images from endoscopic surgery using an image-guided navigation system for chronic sphenoid sinusitis. The cross hairs on the reformatted three-dimensional computed tomography scans (*top, bottom left*) denote placement of the probe as seen in the endoscopic view (*bottom right*). A drill was required to open the sphenoid on account of the extreme neo-osteogenesis.

Box 52-1

Cells and Structures Important in Frontal Recess Disease

Agger nasi cell
Supraorbital ethmoid cell
Frontal cells of types I through IV
Interfrontal sinus septal cell
Suprabullar cell
Frontal bullar cell
Recessus terminalis

Table 52-4

Boundaries of the Frontal Recess

Medial	Superior attachment of the middle turbinate
Lateral	Lamina papyracea
Superior	Internal os of the frontal sinus
Anterior	Posterior buttress nasal spine—nasofrontal "beak"
Posterior	Superior extension of the ethmoid bulla to the skull base
Inferior	Nasal communication of the frontal recess

similar fashion to that of obstruction of an agger nasi cell; that is, edema in very small, tight pathways or in an iatrogenic scar after surgery can close off the frontal recess.

The supraorbital ethmoid cell or cells develop posterior to the frontal sinus, and either failure to address disease within these cells or subsequent scarring is another potential reason for persistent frontal sinus disease. The important feature of these cells is that they pneumatize laterally out over the orbit, and they also may pneumatize forward from their lateral position and appear to be part of a septated frontal sinus. Understanding the spatial relationship of a supraorbital ethmoid cell with the frontal sinus, orbit, and skull base is key to performing frontal recess dissection. As with the other cells in this region, triplanar CT reconstructions are helpful in identifying the exact anatomic relationships. Typically, one or two supraorbital ethmoid cells, with variable degrees of pneumatization, lie posterior to the opening of the frontal sinus. Because of its proximity to the frontal sinus, a well-pneumatized supraorbital ethmoid cell can be easily confused with entrance into the frontal sinus ostium. Once the individual cells have been identified, it is important to remove the common wall between the supraorbital ethmoid cell and the

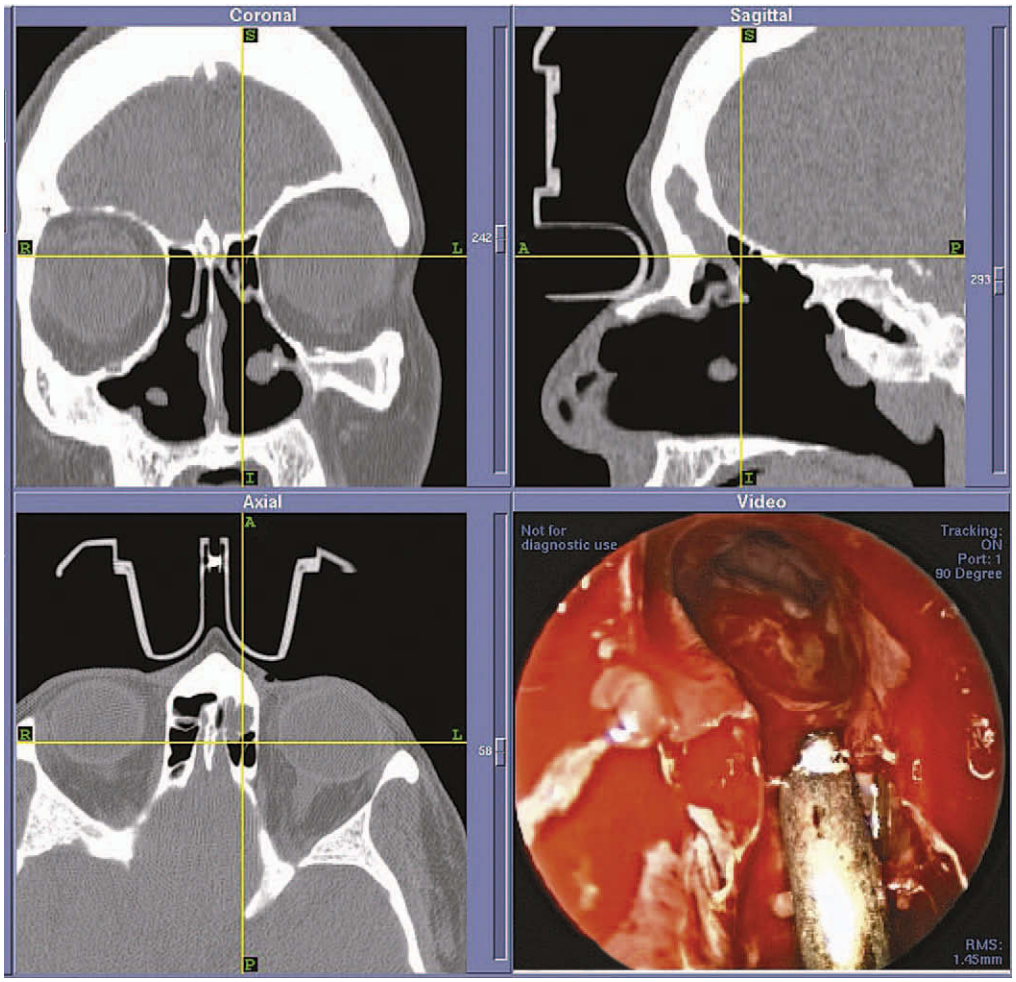

Figure 52-15. Intraoperative images from endoscopic surgery using an image-guided navigation system. The cross hairs on the reformatted three-dimensional computed tomography scans (*top, bottom left*) denote placement of the probe as seen in the endoscopic view (*bottom right*). The patient underwent surgery for recurrent frontal sinusitis from residual agger nasi cell cap adherent to the superior attachment of the ethmoid bulla, which was causing stasis and mucocele. The endoscopic view depicts appropriate findings after frontal recess dissection. The mucosa of the frontal recess is intact. Note the excellent view afforded by the 70-degree telescope.

frontal sinus as far superiorly as possible, preferably to the level of the skull base.

The interfrontal sinus septal cell appears less frequently than the agger nasi or supraorbital ethmoid cell and develops in the septum between the two frontal sinuses. The cell may pneumatize to different extents, varying from just the lower septum all the way to the frontal sinus apex or into a pneumatized crista galli. This cell empties into one frontal recess, usually medial and anterior to the internal frontal ostium and, in some situations, into the frontal sinus. With the endoscopic approach, it should be opened inferiorly, and then as much of the common wall as possible should be removed.

If the uncinate process inserts on the medial orbit wall, the ethmoid infundibulum will end in a blind pocket called a *recessus terminalis*. This common anatomic variation (occurring in up to 50% of people) forces the frontal sinus drainage pathway down the medial surface of the uncinate process and thereby directly into the middle meatus. Because of the proximity of the downsloping skull base, dissection of this variant can be tricky, and failure to identify and meticulously dissect this structure is a common cause of surgical failure (Fig. 52-16).[22]

In all instances of frontal recess dissection, external approaches ranging from frontal sinus trephine to osteoplastic flap can be used as an adjunct to allow access to disease and completion of a thorough frontal recess dissection. The extended frontal sinus approaches, Draf IIB (Fig. 52-17) and Draf III (or transseptal frontal sinusotomy or modified Lothrop approach), have also offered new possibilities for the management of frontal sinus disease.[23-25] In particular, the combination of a Draf III approach with an osteoplastic procedure enables the management of frontal sinus lesions such as tumors without the necessity of frontal sinus obliteration. This combination of endoscopic and external approach means that the big disadvantage of obliteration, the loss of subsequent accurate imaging, is eliminated and the frontal sinus can be monitored directly via endoscope, with either angled rigid scopes or a flexible endoscope, during routine follow-up.

Turbinate Management

At the end of the procedure, attention should be directed toward the middle turbinate to help ensure a good postoperative result. Any exposed bone should be removed. A floppy middle turbinate should be stabilized; frequently this is done via a controlled scar to the nasal septum. At 1 month or more in the postoperative period, the adhesions between the septum and middle turbinate may be lysed to return the middle turbinate to its normal profile.[26] Another option to stabilize the middle turbinate and prevent a lateralized one is to suture the turbinate to the septum with an absorbable suture. Routine amputation or resection of the middle turbinate is not recommended because it alters whatever is left of normal physiologic actions of the turbinate and because the stump often lateralizes anyway, causing iatrogenic frontal sinus disease.

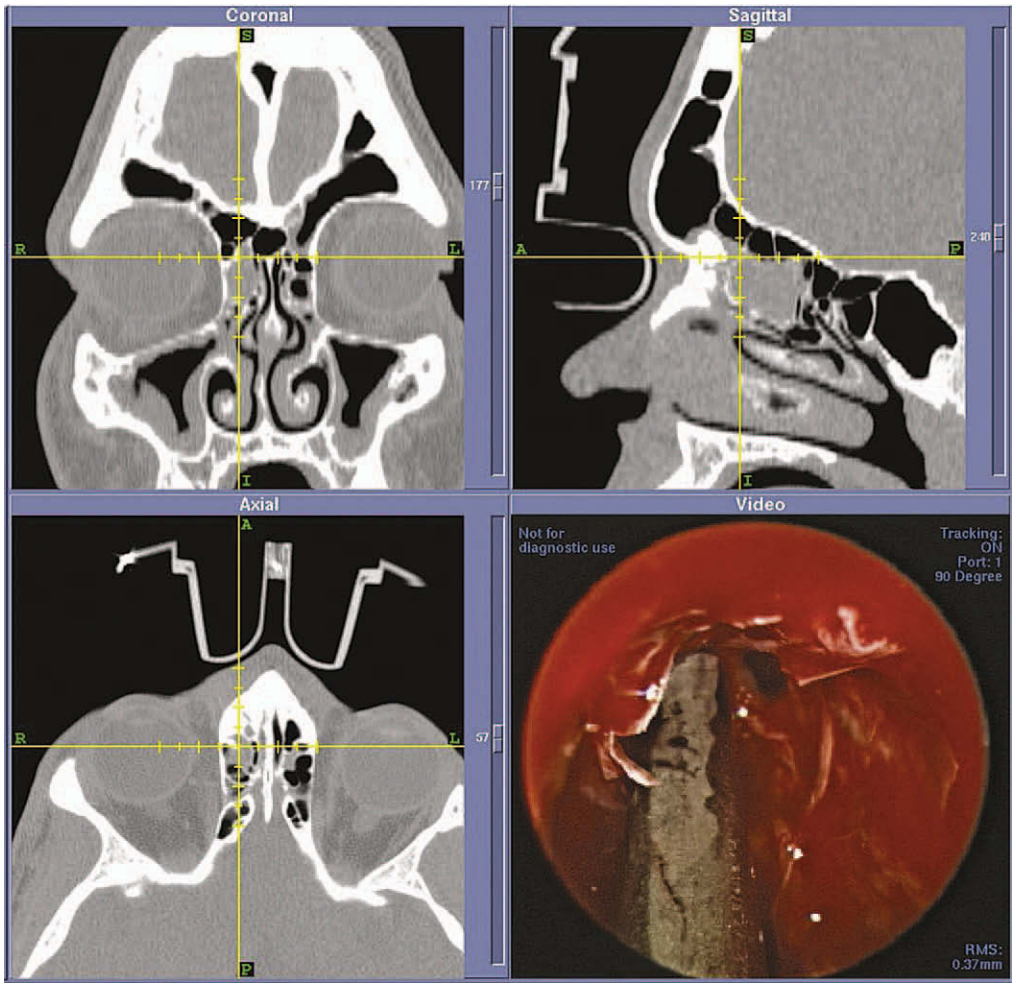

Figure 52-16. Intraoperative images from endoscopic surgery using an image-guided navigation system. The cross hairs on the reformatted three-dimensional computed tomography (CT) scans (*top, bottom left*) denote placement of the probe as seen in the endoscopic view (*bottom right*).The sagittal CT image (*top right*) demonstrates both a frontal bullar cell and a suprabullar cell, whereas the axial image (*bottom left*) shows an interfrontal sinus septal cell, a supraorbital ethmoid cell, an agger nasi cell, and a type I frontal cell. The endoscopic view shows the image-guided probe at the top of an agger nasi cell cap.

Computer-Assisted Navigation and Intraoperative Imaging

One of us (JNP) has used computer-assisted navigation devices during selected ESS procedures for the past 18 years. However, the early devices were based on rigid arms, had software that was not user-friendly, and required that the patient undergo general anesthesia and rigid head fixation. Additionally, a repeat CT was required the day before surgery with fiducial markers in place, so as to allow accurate registration of the patient's head during surgery.

Significantly more user-friendly devices based on either electromagnetic or infrared tracking have become available in the past decade. These newer devices allow head movement and yet provide reasonable accuracy (generally within 2 mm) for ESS. No devices have yet been demonstrated to clearly reduce complications during surgery, but they do provide the surgeon with additional information and probably also permit more complete surgery to be performed. The technology is changing, but at the time of writing, it appears that all devices have relative advantages and disadvantages.

The ability to check the anatomy with computer-assisted imaging may have an advantage in any given case, but computer-assisted navigation is particularly important during a transseptal frontal sinusotomy (Draf III) procedure and is almost essential for removal of a large fibro-osseous tumor that is based in a critical area. Similarly, computer-assisted imaging is helpful during transnasal endoscopic pituitary surgery to help ensure that the pituitary dissection is performed in the midline despite a slightly oblique transethmoid approach.

Because computer-assisted surgery is based on computer storage and manipulation of the preoperative CT data, the limitation of this technology is that it does not record any changes in the relative anatomy that occur intraoperatively. Unlike intracranial surgery, however, endoscopic sinus surgery is generally performed within a stable space delimited by boundaries of bone, so the limits of the dissection are generally fixed, and this is not generally a critical issue. Nevertheless, it becomes an issue when surgery is performed within the sella turcica or intracranially or where there is marked loss of bone. These problems can be overcome with the use of intraoperative MRI or intraoperative CT, both of which provide a real-time image. Unfortunately, intraoperative MRI currently is prohibitively expensive for use in routine sinus surgery, in terms of both the cost of the magnet and the special nonferromagnetic instrumentation required for the surgery. Intraoperative CT involves additional radiation exposure for both patient and surgeon. The newest intraoperative CT scanners have the advantage of using a volumetric protocol rather than helical slices. This change in protocol allows the radiation exposure to the patient to be $\frac{1}{7}$ to $\frac{1}{10}$ that of a standard head CT scan, and therefore worth the added radiation when one considers the clinical information garnered, which can then be uploaded to the image guidance system. We suspect the future will combine the advantages of intraoperative CT scanning with computer-assisted surgery in one machine.

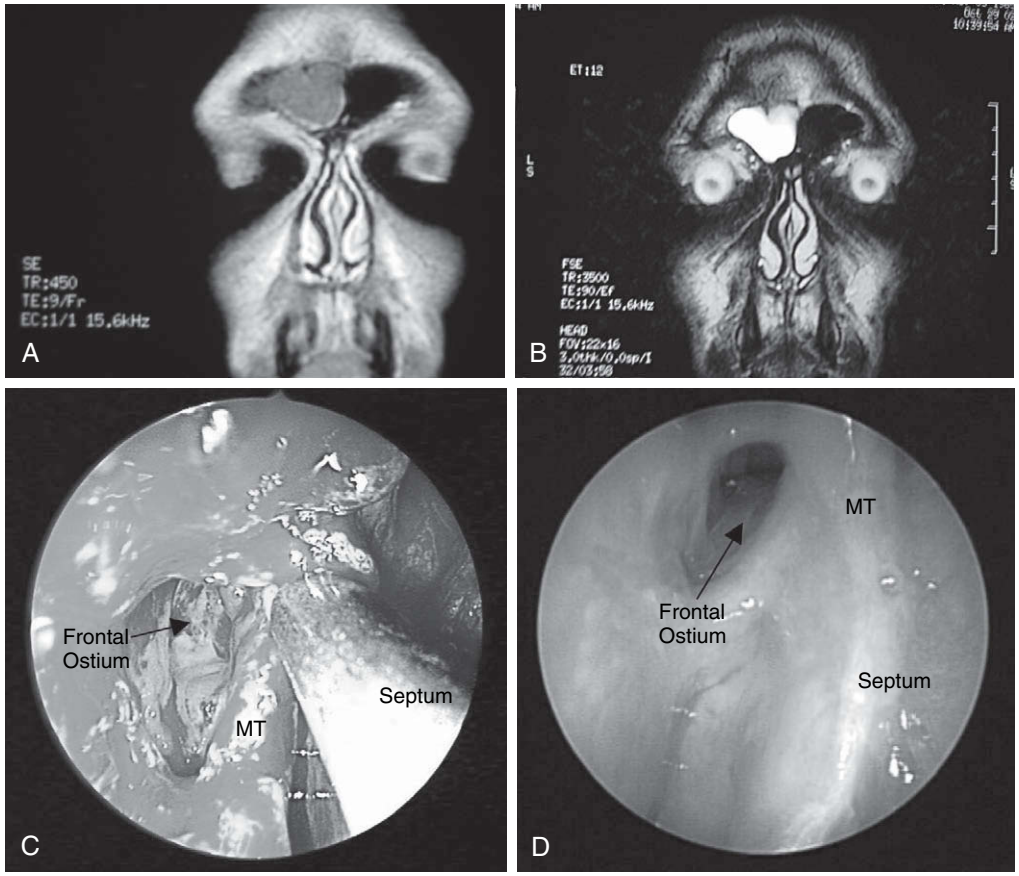

Figure 52-17. A patient with recurrent frontal sinusitis after endoscopic sinus surgery that included amputation of the middle turbinate (MT). Appearances on T1-weighted **(A)** and T2-weighted **(B)** magnetic resonance images are consistent with mucocele. **C,** Intraoperative photograph of the mucoperiosteal flap advancement onto the skull base medially. **D,** Endoscopic view (with 70-degree telescope) demonstrates a patent ostium 1.5 years after surgery; the patient had no symptoms.

Postoperative Medical Management and Débridement

Medical therapy in the postoperative period includes antibiotic coverage instituted in the operating room and, when possible, adjusted postoperatively according to results of culture of intraoperatively collected specimens. Long-term antibiotic therapy may be indicated in a patient with evidence of significant bone inflammation. In many patients undergoing revision procedures in which there is significant bony change but *Pseudomonas* is not present, a combination of clindamycin and trimethoprim-sulfamethoxazole is a consideration for treatment. At any point in the postoperative period, if the inflammation increases and pus is seen, the cavity is resampled for culture, and appropriate antibiotics are instituted.

All patients are given long-term topical steroid sprays to minimize postoperative edema, to reduce the need for oral steroid use, and to decrease the potential for late recurrence. The most common site for disease persistence and recurrence remains the frontal recess. Therefore, multiple ways have been described to increase topical steroid deposition in this area. The Moffat head-down position and the Mygind head-hanging in hyperextension are two positions in common use. The following alternative approach may allow the patient to maintain the position and hold the spray in the nose for a longer period: The patient is instructed to place a couple of large pillows on the bed, to spray the nose while sitting on the bed, and then to roll over, lying prone with the head alongside the pillows with the neck flexed and the forehead dependent. This relatively comfortable position (Kennedy position) can be maintained for at least 5 minutes. The dosage of any oral steroid administration begun in the preoperative setting is slowly tapered on the basis of the endoscopic appearance of the mucosa over days to weeks, but in severe disease the course may need to be prolonged or the dosage even slowly reduced to an alternate-day, low-dose maintenance regimen.

Patients are instructed to use saline spray frequently in the postoperative period and may be instructed to irrigate the nose with a saline solution using either a bulb syringe or Waterpik. However, meticulous attention must be paid to cleaning and aseptic technique to prevent the introduction of gram-negative organisms. An antibiotic may be added to the saline solution, either in Wilson's solution (80 mg gentamicin in 1 L normal saline) or mupirocin (7.5 mg mupirocin in 1 L normal saline). Multiple topical preparations of antifungal medications have been tried, including nystatin, amphotericin B, and itraconazole. The administration of topical antifungal medications seems rational in the patient with fungal sinusitis, but the data on their efficacy are difficult to interpret.

Débridement begins at postoperative day 1, when the polyvinyl acetal (Merocel) sponges are removed, and the cavity is suctioned. We believe that this ability to suction mucus postoperatively from the dependent sinuses, before it becomes heavily contaminated with bacteria and mold, is a significant advantage of a removable rather than an absorbable spacer in the middle meatus. Débridement is then initially performed weekly and continued as necessary until the entire cavity is healed, all exposed bone is mucosalized, and the mucosa itself has stabilized. The frequency and the amount of débridement are determined primarily by the amount of inflammation present, because greater inflammation increases the tendency for scarring. In severe disease, débridement can be a labor-intensive process that requires both topical analgesia and, frequently, an oral narcotic/analgesic. Any persistent exposed bone is removed, crusts are cleaned, and any pools of blood clots or mucus are suctioned from the cavity. Any cells not removed at

surgery and discovered in the postoperative period can be removed at this time. Areas of possible stenosis, scarring, or synechiae are lysed and removed with through-cutting forceps. Such visits may take as long as 30 minutes, and it might seem as if the surgeon is "doing the surgery again." The tendency to form scarring slowly decreases as the inflammation decreases with continued medical management. In the office setting, local anesthesia can be achieved using 1% lidocaine (Xylocaine) with 1:100,000 adrenaline administered with a long, 27-gauge needle attached to a tuberculin syringe. The needle can be bent to allow infiltration directly at the site. For more posterior access, an angled tonsil needle or spinal needle can be used.

Long-term follow-up and medical management are required for patients who undergo revision surgery. Because patients who have had surgery are at risk for persistence of disease, and because persistent disease is frequently asymptomatic in the early postoperative period, the critical factor guiding care is the appearance of the cavity on nasal endoscopy rather than symptoms. The postoperative care for a patient who has had revision surgery can easily last at least a year with a decreasing frequency of visits, but in severe disease it is commonly even longer.[27] Over this period, while the inflammation is settling down, multiple courses of oral steroids and culture-directed antibiotics may be required. The occurrence of a viral upper respiratory infection during this period may need additional attention, with either prophylactic antibiotic coverage or a short course of oral steroids to manage the hyperreactive mucosa. However, over time, the mucosa typically stabilizes and returns to more normal function. Symptoms should be monitored closely. Pain and pressure in the postoperative period are uncommon and should prompt further investigation, because they are frequently signs of persistent inflammation. Postnasal discharge is common, resolving slowly and sometimes incompletely. Loss of olfaction is a sensitive sign of return of disease and also an indication for repeat endoscopic evaluation and, possibly, additional medical management.

Patients undergoing revision surgery may require endoscopic follow-up for years if a stable cavity is not obtained. In terms of the goal of disease resolution, it is much more effective to intervene earlier in the disease process with débridement, steroids, and antibiotics than to wait until the patient requires another revision procedure for removal of hyperplastic or polypoid disease. In the setting of well-performed surgery, the appearance of mucosal hypertrophy or inflammation or any return of symptoms, especially loss of olfaction or nasal congestion, requires aggressive medical treatment. However, in all situations, the goal is to minimize oral steroid therapy and replace it with a combination of topical and mechanical treatments whenever possible. In addition to environmental and allergy management, adjunctive therapy with antihistamines, antileukotrienes, and anti–immunoglobulin E monoclonal antibody may be considered. Imaging with another CT scan is not typically required as long as a nicely patent cavity is achieved. However, postoperative CT can be help evaluate whether any cells were missed in the original procedure or whether frontal stenosis has reccurred.[28-30]

Conclusion

The concept of functional endoscopic sinus surgery is to surgically remove inflamed tissue and bone from critical points in the mucociliary clearance pathways. In inflammatory disease, it is one tool of an armamentarium of therapies utilized in an overall management aimed at the inflammation and the inciting factors causing that inflammation in the nose and sinus cavities. However, the same surgical techniques have been extended to manage a variety of neoplastic and other lesions of the nose and skull base, and continued refinements in technique and instrumentation will further expand the opportunities for these techniques in the years ahead.[31]

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CHAPTER FIFTY-THREE

Management of the Frontal Sinuses

Nick S. Jones

Key Points

- Use instruments in the frontal recess only with good reason.
- In most circumstances it is desirable to establish drainage.
- Preserve mucosa around the frontal recess.
- Maintain bony support around the frontal recess.
- Avoid pressure necrosis of mucosa if a stent is used (rarely necessary).
- If obliteration of the sinus is required, remove all mucosa.

Acute Frontal Sinusitis

Acute bacterial frontal sinusitis is relatively uncommon and it normally follows a viral upper respiratory tract infection. Typically the patient with frontal rhinosinusitis presents with a low-grade fever, malaise, and a frontal headache often accompanied by marked tenderness of the medial aspect of the infraorbital margin. The infection usually responds to antibiotics with the correct antibacterial spectrum, which varies from area to area depending on the prevalence of resistance to amoxicillin. The most common organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, anaerobic streptococci, *Bacteroides*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus milleri*, and microaerophilic *Streptococcus*. Culture results–directed prescription is desirable for severe infections or for the complications of sinusitis.

Occasionally the infection does not respond and needs to be drained. It is worth placing a topical decongestant via endoscopy high in the middle meatus, because doing so sometimes allows spontaneous drainage through the frontal recess. If this maneuver does not work, the options are to trephine the frontal recess through an incision in the medial aspect of the eyebrow or to open the frontal sinus endoscopically by removing the ethmoid air cells surrounding the frontal recess while trying to preserve the mucosal lining of the recess.

Acute frontal sinusitis is normally a single infection, and the patient is unlikely to go on to have a further sinus infection. An argument can be made, particularly in children, for trephining the frontal sinus in order to reduce the chance of physician-induced stenosis of the frontal recess. Endoscopic drainage of the frontal sinus can be difficult in these circumstances because the hyperemia associated with infection can result in a lot of bleeding. Damage to mucosa in the area of the recess may result in adhesions or stenosis, leading to further problems.

Frontal sinusitis can be complicated by periorbital cellulitis or the formation of a periorbital abscess. The indications for an urgent computed tomography (CT) scan are the presence of signs of central nervous system involvement, inability to assess vision accurately, gross proptosis, ophthalmoplegia, deteriorating visual acuity or color vision, bilateral edema, no improvement or deterioration after 24 hours, and a spiking pyrexia not resolving within 36 hours.[1] Intracranial complications include a subdural empyema, intracerebral abscess, extradural abscess, meningitis, and, more rarely, cavernous and superior sagittal sinus thrombosis. It is important to be aware that almost 50% of patients with intracranial complications present with a periorbital cellulitis or frontal swelling. Therefore it does not follow that a collection of infection that spreads around the orbit excludes any intracranial involvement.[2] It is important to look for the symptoms or signs of intracranial involvement—namely, an altered mental state, headache, vomiting, seizure, neck stiffness, papilledema, unilateral weakness, and signs of cranial nerve involvement. If there is intracranial involvement, sinus surgery has a role in obtaining pus for culture as well as draining the collection if the sinus is in continuity with the intracranial collection.

Chronic Frontal Sinus Disease

Before a discussion of the specific management of this condition, it is worth considering the history of frontal sinus surgery.

In the pre-endoscopy era, the principles of surgical treatment of the frontal sinus were essentially the same as they are now; namely, when antibiotics failed, drainage of the frontal sinus was the primary goal.

Jurasz was the first surgeon to describe an intranasal approach to the frontal sinus. Ogston[3] in the late 1880s and Luc[4] in the next decade described trephination and widening of frontonasal duct through the anterior ethmoid sinuses. Brieger[5] first described the osteoplastic operation in the 1890s. Riedel[6] described a technique in 1889 wherein he removed its anterior and inferior walls. This technique resulted in a cosmetic deformity that would require a second operation if an improvement in cosmesis was sought. In 1908 Knapp[7] advocated an extensive ethmoidectomy through the medial orbital wall, leaving the anterior wall of frontal sinus intact but removing the diseased mucosa and enlarging the frontonasal duct. Lothrop[8] in 1912 resected the frontal floor between the frontal recesses and the intersinus septum along with the upper aspect of nasal septum after an ethmoidectomy

via an external approach as described by Lynch. By 1921 Lynch[9] and Howarth[10] had surgically entered the frontal sinus through an external approach via the medial orbital wall and, like Knapp, removed sinus mucosa and left a stent in position to try to maintain a patent duct. The osteoplastic flap with fat obliteration then became popular for the treatment for persistent frontal sinus disease. Macbeth[11] and Bosley[12] later postulated that fat obliteration is not necessary, as they claimed that the cavity is filled by osteoneogenesis. However, I and others have found that, unless the frontal sinus is obliterated in this procedure, loculated areas within the sinuses are more likely to form, which may become infected or form mucoceles.

With the introduction of CT and endoscopes, it became possible to open the frontal recess to a greater or lesser extent, with mucosal preservation dependent on the extent of disease and the skill of the operator.

The bacteriology of chronic rhinosinusitis differs from that of acute rhinosinusitis, in that there is a higher prevalence of anaerobic organisms with the chronic form. Typical infections include *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and, when there has been previous surgery, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, and *Enterobacter*. Obtaining a culture and determining antibiotic sensitivities of the organisms grown is vital in the treatment of purulent disease, and care in the taking and culture of specimens is important in culturing anaerobic organisms.

In the medical treatment of bilateral chronic rhinosinusitis without purulent secretions, there is growing evidence that some antibiotics work not only through their antibacterial action but also by down-regulating inflammation.[13] Long-term (12 weeks to 6 months), low-dose therapy with erythromycin, clarithromycin, and other macrolides along with douching has been shown to be beneficial.[14] The efficiency with which an antibiotic disperses biofilms may also be of importance.

Indications for Surgery in Chronic Frontal Sinusitis

Disease in many patients with chronic frontal sinus disease appears to have been initiated by unnecessary instrumentation of the frontal recess. In order to make a diagnosis of chronic frontal sinusitis, the clinician must find out whether the periodicity of symptoms correlates with upper respiratory tract infections or changes in barometric pressure or are associated with a purulent discharge, because many patients with frontal symptoms have tension-type headache. Opacification of the frontal recess alone is not a reason to use instruments in the frontal recess, because the opacification is often due to retained secretions that will clear if the ostiomeatal complex is opened and medical treatment is given.

The primary indication for instrumentation of the frontal recess is when maximum medical treatment has failed to help frontal sinus symptoms, and a partial anterior ethmoidectomy and medical treatment have not succeeded.

There are few other reasons for operating on the frontal recess before trying a partial anterior ethmoidectomy along with medical treatment; these reasons include the presence of fungal disease in the frontal sinus, barotrauma, mucocele (Figs. 53-1 to 53-3), an osteoma causing obstruction with evidence of mucosal disease, and other pathology, such as osteomyelitis (Fig. 53-4) and tumors.

The normal frontal recess is narrow, raising a question as to the role of anatomic variations in the pathogenesis of rhinitis. The frequency of such "variations" and anatomic "restrictions" appears to be no higher in a control population than in a patient with proven rhinosinusitis.[15] It seems likely that the primary problem is the mucosal pathology or a patient's immunity—the reason why one individual experiences chronic rhinosinusitis and another does not.

The variability of the anterior ethmoid air cells makes them a fascinating subject on their own. In more than 94% of people there are anterior ethmoid air cells over the lacrimal bone or adjacent to the anterior aspect of the middle turbinate; these are called *agger nasi cells*. A high anterior ethmoidal cell that has pneumatized into the frontal bone, known as the *bulla frontalis,* can displace the frontal recess posteriorly and medially. The bulla frontalis can be so large that it can mimic the frontal sinus, almost forming a sinus within a sinus. Not infrequently a *supraorbital cell*—that is, a posterior cell in the anterior ethmoid complex that is well pneumatized—can extend laterally into the frontal bone over the orbit and also can narrow the frontal recess by pushing it forward. Occasionally air cells exist within the frontal sinus itself, the ostia of these cells draining within the frontal sinus.[16] Another variation is the intersinus septal cell that may extend into the crista galli; this cell often drains into the frontal recess. The prevalence of these variations does not appear to correlate with the presence or absence of frontal sinus disease.

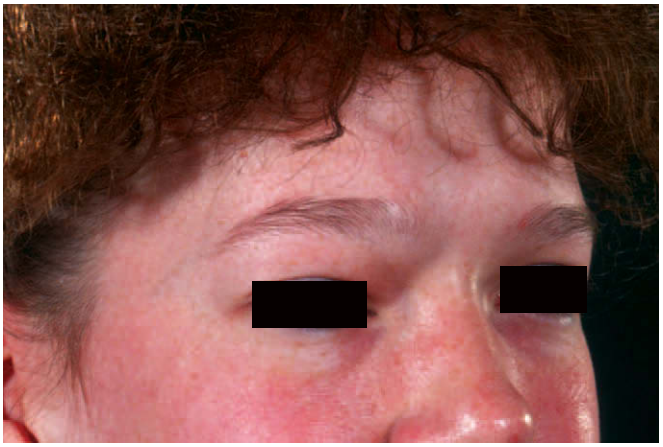

Figure 53-1. A right frontoethmoid mucocele.

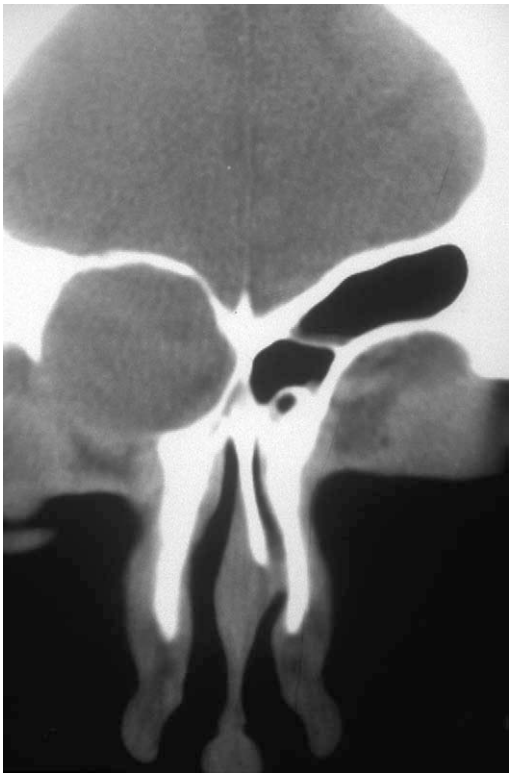

Figure 53-2. Computed tomography scan of the right frontoethmoid mucocele shown in Figure 53-1.

Endoscopic Frontal Sinusotomy

There are two main approaches to opening the frontal recess, each with the aim of "deflating" the cells or "balloons" of the ethmoid air cells and preserving the mucosa around the recess as much as possible. To this end a submucosal dissection, removing the thin walls of the agger

Figure 53-3. Postoperative view of patient in Figure 53-1 after endoscopic marsupialization of the right frontoethmoid mucocele.

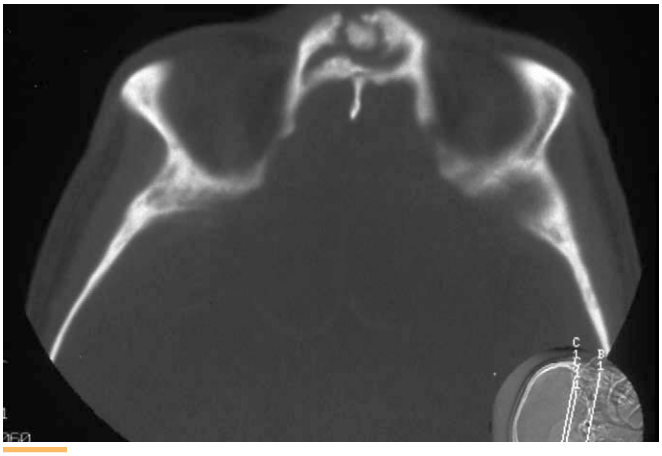

Figure 53-4. Osteomyelitis of frontal bone with bony sequestra.

nasi cells and using through-cutting instruments to remove excessive mucosa, leaves a mucosa-lined recess that is far less likely to stenose.

One method of accessing the frontal recess involves removing the superior remnant of the uncinate process with a 45-degree through-cutting forceps or a punch. A 45- or 70-degree endoscope is then used to examine the area. Careful palpation, not prodding, with a ball probe next to the middle turbinate reveals a crevice between the middle turbinate and the agger nasi cells. The aim is to open this crevice, which will turn out to be the pathway to the frontal recess and the frontal sinus, by "deflating" the cells. This is best done by passing the ball probe well above them and gently fracturing them to one side. The shaft of a Kuhn curette works well for this maneuver (Figs. 53-5 and 53-6). If visibility is good, it may be possible to do this by submucosal dissection. Fragments of bone are removed, with care taken not to grab the mucosa, because doing so might leave bone exposed and predispose to scar tissue and stenosis.

When they are opened, agger nasi cells, the terminal recess, and the ethmoid bulla can all form concave domes of a variable size and give the appearance of the frontal sinus, but the sinus itself has a convex posterior surface that is distinctive. It is possible to confirm that an instrument is actually in the frontal sinus by using a ball probe, a Kuhn curette, or a curved sucker as a sound, passing it into the area in question and then registering the angle and length of this ball probe in relation to the maxillary spine. To ensure that the instrument is within the frontal sinus, the surgeon can grip the shaft of the ball probe between the thumb and the index finger next to the nasal spine, noting the angle of the instrument at the same time. The surgeon then withdraws the instrument and places it alongside the outside of the nose,

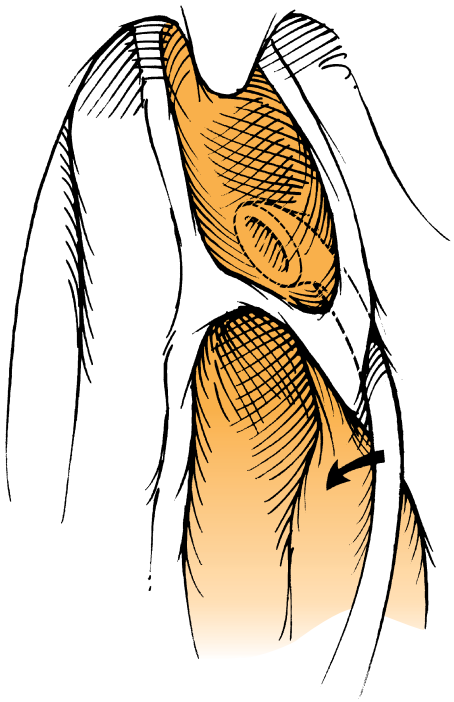

Figure 53-5. A Kuhn curette is used, submucosally if possible, to pull down and remove the roof of an ethmoid air cell. Fragments of bone from the agger nasi cell are removed, but the mucosa is preserved. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

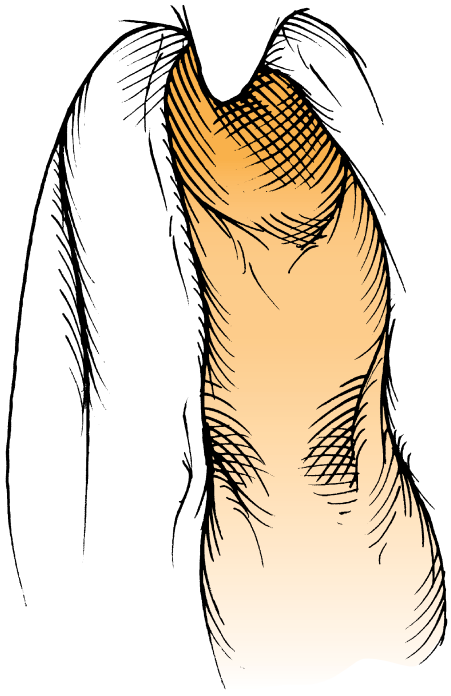

Figure 53-6. The right frontal recess after removal of the ethmoid air cells. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

at the same angle it had in the sinus and with the pinch grip placed alongside the nasal spine (Figs. 53-7 and 53-8). If the end of the ball probe is then higher than the eyebrow line, the instrument was probably in the frontal sinus. If the instrument is around or just above the medial canthus, then the ball probe is likely not within the frontal recess

Figure 53-7. Confirming location of instrument in the frontal sinus. The surgeon "pinches" the instrument against the maxillary spine, noting the angle of the instrument. (See Figure 53-8.)

Figure 53-8. Confirming location of instrument in the frontal sinus (see Figure 53-7). The surgeon then aligns the instrument outside the nasal airway at the same angle, keeping the fingers at the same place on the instrument against the nasal spine. If the end of the probe is well above the medial canthus, it is likely to be within the frontal sinus when reinserted. (The exception is a large bulla frontalis, presence of which can be checked for on the computed tomography scan.)

but is within an agger nasi cell. If the handle of the ball probe is noted to have been turned laterally when it passes up through what is thought to be the frontal recess, it may have been channeled in this direction by a bulla frontalis or a supraorbital cell, and the surgeon should correlate this possibility with the CT scan.

It is vital not to prod with any instrument medially as it is passed toward the frontal recess, because the lateral lamella is usually the thinnest part of the skull base and it would be easy to cause a cerebrospinal fluid leak in this area. To avoid entering the orbit, the surgeon should not push in any way laterally. Instead the surgeon should check the proximity of the orbit and the pattern of air cells on CT and ask the assistant to ballotte the eye while this area is being examined to make sure the orbit has not been entered.

An alternative method is to approach the frontal recess anteriorly with a 0-degree scope if there is a large agger nasi cell. An anteriorly based mucosal flap on the lateral nasal wall is raised over the prominence of agger nasi cells. A punch is used to remove the "armpit" of the area where the middle turbinate attaches to the lateral nasal wall, the agger nasi cells are removed submucosally, and the lateral flap is placed over any raw bone to further reduce the chance of stenosis.

Figure 53-9. Ten previous external ethmoidectomy procedures have resulted in a loss of lateral bony support and scar tissue around the frontal recess. Small mucoceles have also formed.

If previous surgery has caused stenosis and there are few landmarks, access to the frontal recess can be difficult. In such cases it is safest to palpate anteriorly, where the bone is very thick, and any probe must be angled vertically to reduce the risk of a cerebrospinal leak or of entering the orbit. A "mini-trephine" can help define the site of the frontal recess. An incision is made within the medial aspect of the eyebrow, and a small bur hole is made into the sinus. Fluorescein dye can then be placed into the frontal sinus and then sought endoscopically within the nose to see where it comes out.

Lynch-Howarth External Ethmoidectomy

The Lynch-Howarth external ethmoidectomy has largely been replaced by endoscopic techniques because stenosis developed in approximately a third of patients who underwent the procedure.[17,18] An external scar, the necessary loss of bone lateral to the frontal recess, and loss of mucosa often result in scar tissue and stenosis of the frontal recess.

A curved incision is made from the inferomedial aspect of the eyebrow and extended along the upper third of the nose, with a break in it shaped like the silhouette of a seagull (to produce less webbing). If the area of the trochlea—the sling of the superior oblique muscle attached to the superior-anterior-medial aspect of the orbit—is involved, it must be cut cleanly away from the periosteum, not torn, to avoid damaging it and causing diplopia. The anterior ethmoidal artery may have to be clipped or ligated. The thin medial wall of the orbit is perforated, and the opening is enlarged with a punch. The ethmoid air cells are removed, and the frontal recess is opened. As much medial bony support to the recess is retained as possible. Historically, as large a stent was placed in the frontal sinus as it would accept. It is now recognized, however, that the stent causes pressure necrosis of the mucosa, leading to medium- and long-term stenosis. Local mucosal flaps have been advocated but are rarely possible, and a free mucosal or composite graft can be used with a loose stent.

It is possible to support and reconstruct the lateral wall of the frontal recess to prevent its collapsing or to deal with collapse of that area. The problematic circumstances affecting this area are large mucoceles and previous surgery in the area, particularly when an external ethmoidectomy has led to a loss of bone lateral to the frontal recess (Fig. 53-9). There is often a great deal of fibrosis in the area of the frontal recess if it has stenosed after an external ethmoidectomy. It is rarely possible to reflect a septal flap that can extend into this area and provide the lining for a new channel; a free turbinate graft is the main option. A free cartilage graft from the septum or conchal bowl is sutured in position with mucosa over it, and a loose stent is placed to hold it open (Figs. 53-10 and 53-11). The stent is loose in order to avoid any pressure necrosis on the graft. Its placement provides lateral support and reduces the chance of further stenosis. Two weeks after the proce-

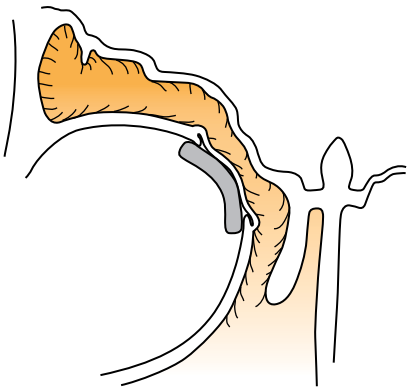

Figure 53-10. A line diagram illustrating how a composite septal graft can be used to reconstruct the lateral wall of the frontal recess. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

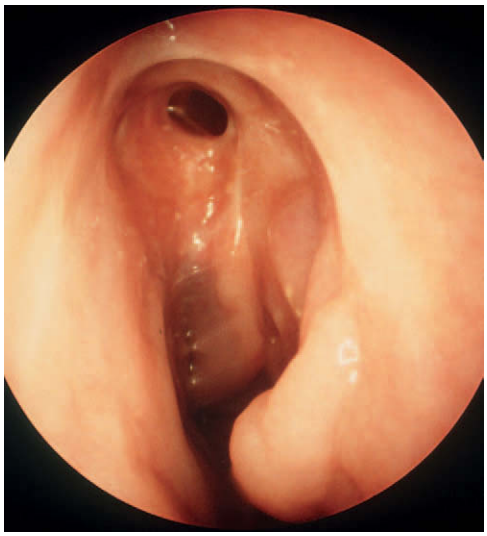

Figure 53-11. An endoscopic view of the left frontal recess now that it has been reconstructed via an external approach and with use of a composite graft to overcome stenosis occurring after a previous external approach.

Figure 53-12. A coronal computed tomography scan to show the appearance after an endoscopic median drainage procedure.

Figure 53-13. Paget's disease of the frontal bone, an indication for an external approach.

dure, endoscopy shows that the stent is loose and surrounded by healthy mucosa in the frontal recess.

Median Frontal Sinus Drainage Procedure

In the median frontal sinus drainage procedure, the frontal recesses are opened to create a central drainage channel by removal of the top of the septum, the frontal intersinus septum, and the anterior beak of the frontal bone (Fig. 53-12).[19] The procedure is indicated when the lateral support has been removed in an external procedure, allowing medial collapse of the orbital contents or as a method to address stenosis of the frontonasal recess.

The nasal process of the frontal bone is thick posteriorly, forming a "beak" that can be removed to help create a large central drainage channel. The frontal intersinus septum varies greatly in its position. The main concern with this procedure is that the cribriform plate is positioned behind the posterior limit of the coronal plane that connects the frontal recesses. Laterally, the bone of the lamina papyracea is preserved to avoid prolapse of the orbital contents, which might impair drainage.

Both frontal recesses are identified, and then the bone anterior to and between them is removed. Image-guided equipment can help *confirm* the position of instruments, but the definition is not reliable enough to operate by. Unlike with other procedures in the frontal recess, it is not possible to preserve mucosa around more than a minority of its circumference.[20]

Obliteration of the Frontal Sinuses

Obliteration of the frontal sinuses is a more invasive procedure, particularly if the sinuses are well pneumatized, as is often the case. The surgeon should beware if the patient has Paget's disease of the bone, because the bleeding can be torrential (Fig. 53-13). A coronal flap using a zigzag incision disguises the scar well in patients with male-pattern baldness. Alternatively, the sinus can be approached through an eyebrow incision (Figs. 53-14 and 53-15). A sterilized template of the frontal sinus can be constructed either from a preoperative Caldwell's view radiograph of the frontal sinus or from a three-dimensional model based on digital CT data. A plain radiograph fails to account for some pneumatization, so if a template alone is used to remove the anterior plate, it will leave some overhang because areas of pneumatization often occur superiorly and laterally, even extending to the zygomatic process. An alternative is for the extent of the sinus to be gauged by image-guided surgery. It is worth dissecting the periosteum off the frontal

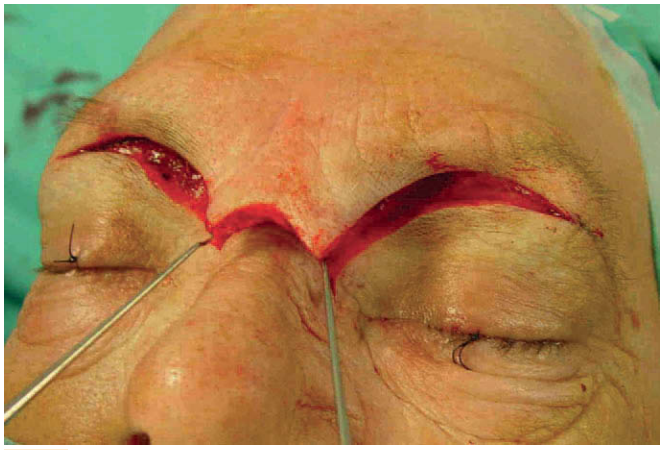

Figure 53-14. An eyebrow incision.

Figure 53-15. Postoperative appearance 9 months after an eyebrow incision.

bone down to the supraorbital margins. This description differs from conventional descriptions, in which the anterior wall is hinged on a flap of periosteum inferiorly. Such a hinge arrangement is rarely possible without putting the periosteum in tatters between the areas where bone has been divided along its inferior margin. Past descriptions of retaining intact periosteum on the frontal bone are misleading. It is important to remove all the mucosa from the whole of the frontal sinus, because if any is left, a mucocele forms. The mucosa is removed not only from the posterior wall but also from the anterior flap, and this removal is difficult to perform thoroughly while the flap is still attached to the periosteum.

The outline of the frontal sinus is estimated with the use of a template, image-guided surgery, or shining an endoscope transnasally into the frontal recess, and an initial hole is made into the sinus in its medial third. A blunt-ended hook can be used to check the outline of the extent of the frontal sinus,[21] and by rotating the hook to where its end reaches the limit of the frontal sinus, the surgeon can follow the outline around with a fissure bur (Fig. 53-16). This maneuver reduces the amount of overhang left after the anterior wall is removed and makes removal of the mucosa easier. It is unwise to make an entry hole high in the midline, where the venous sinuses are large, because entry there can cause torrential bleeding. Before the whole anterior plate is removed, it is worthwhile to fix miniplates onto its anterior wall (to be removed subsequently) and to make bur holes into the cranium to match them; this step makes replacement of the plate at the end of the procedure not only more accurate but quicker.

It is vital to remove all the mucosa of the frontal sinuses before they are obliterated, to avoid formation of a mucocele; a Mitchell's trimmer is an ideal shape for this maneuver. Donald[22] has shown that mucosa follows the veins of Breschet into the posterior wall of the frontal sinus, so these structures must be cleared by drilling of the posterior wall a fraction of a millimeter. The remaining bony walls, including the back wall of the anterior frontal plate, should be drilled with a diamond bur to ensure that all the mucosa has been removed. Care must be taken not to enter the orbit. The floor of the frontal sinus can be very thin, and if it is entered, orbital fat can prolapse upwards, making it difficult to remove the mucosa around this area. If fat does prolapse into the orbit, it can be ablated with bipolar diathermy, but it should not be pulled or pushed. Entering the orbit causes a periorbital ecchymosis, and the vision and orbital pressure must be checked postoperatively to ensure that the vasculature of the optic nerve is not compromised by any bleeding into the posterior-septal compartment of the orbit.

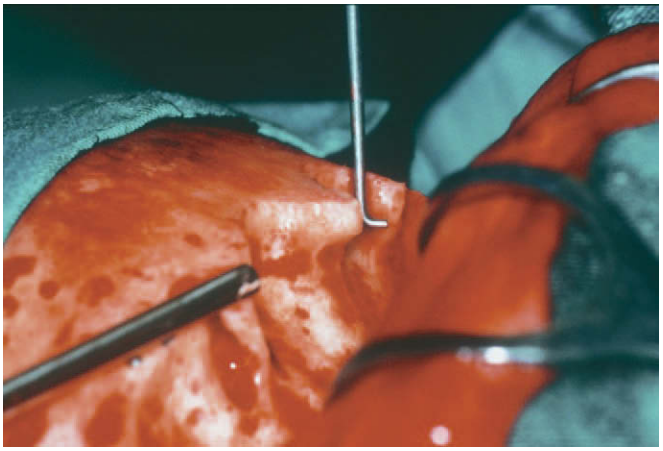

Figure 53-16. A blunt-ended hook can be used to palpate the limit of the frontal sinus and help reduce the amount of overhang. Here the hook is shown after the anterior wall has been removed to better illustrate how it is used.

Once all of the mucosa has been removed, the frontal recess is separated from the nasal airway with a sheet of fascia lata, and fat is used to obliterate the sinuses. The bony plate with its attached mini-plates is then secured, and the pericranium and coronal flap are closed with 2-0 polyglactin 910 (Vicryl) sutures and skin staples. The anterior bone flap is susceptible to infection, so prophylactic antibiotic coverage should be prescribed. A relatively tight cotton elastic bandage is placed to ensure that no hematoma develops between the flap and the bony plate; the bandage is kept in place for at least 3 days.

Various materials have been used to obliterate the sinuses, ranging from muscle to bone to synthetic materials. All have their proponents, but infection of foreign material and bone implants poses a particular challenge because infected materials have to be removed.[23] Fat is readily obtained and gives results as good as, if not better than, any other material. It is important to close the frontonasal duct and to remove the mucosa along with the inner bony cortex of the frontal bone. If the anterior bony wall is also infected, Riedel's procedure is required to rescue the situation.

Postoperative monitoring of the sinuses can be a problem with this obliterative procedure, because when persistent symptoms occur it can be difficult to distinguish recurrent disease from neuropathic pain. The most helpful form of imaging appears to be magnetic resonance imaging, which although the most accurate still has its limitations. The detection of a small recurrent mucocele and the differentiation of vital adipose tissue from fat necrosis in the form of oil cysts prove to be the main difficulties. The most disastrous complication of frontal sinus surgery is infection, because the anterior plate of bone is inevitably involved and because of the incidence of resistant organisms. Even in the 1970s infection was a major concern, with reputable surgeons reporting a complication rate of 18%.[24] If infection occurs in this situ-

Figure 53-17. A laterally placed mucocele.

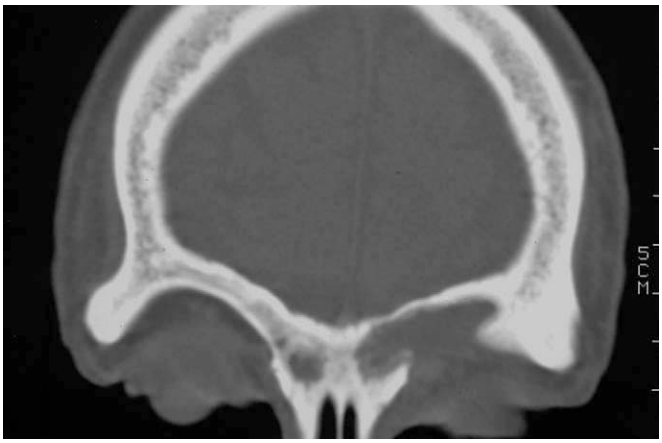

Figure 53-18. New bone formation just weeks after an infection, a contraindication to an endoscopic approach.

ation, it is best to remove the anterior wall and the remains of any sinus content with Riedel's procedure.

Indications for an External Approach

Situations in which removal of pathology and/or drainage is difficult to achieve endoscopically are as follows:

- Laterally placed mucocele
- Lateral loculation within the frontal sinus (Fig. 53-17)
- Fibrosis or new bone around the frontal recess (Fig. 53-18)
- Marked loss of bony support of frontal recess and floor of frontal sinus (previous external surgery or large mucocele)
- Coexisting malignancy
- Other pathology, such as Paget's disease of the frontal bone (see Fig. 53-13), large osteoma, osteomyelitis (see Fig. 53-4), verrucous carcinoma, squamous cell carcinoma, and inverted papilloma
- Gross prolapse of the orbital contents with a small medial anteroposterior diameter of frontal sinus preventing a wide median drainage procedure
- Narrow anteroposterior diameter of frontal sinus (even allowing for removal of the "beak" of the frontal bone)

Surgical options when there is a lack of lateral bony support and frontal recess stenosis is present are as follows:

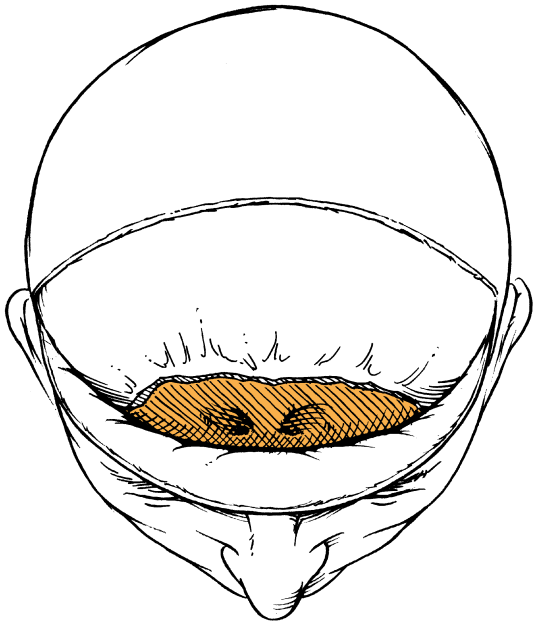

Figure 53-19. Preoperative appearance. The anterior wall of the frontal sinus has been removed.

- Median drainage procedure
- Reconstruction of bony support and mucosal lining of the frontal recess
- Obliteration

Options when endoscopic drainage is unlikely to work are as follows:

- Frontal sinus obliteration
- Riedel's procedure

Riedel's Procedure

Riedel's procedure is used for the following situations:

- Osteomyelitis of the anterior wall of the frontal sinus
- Failure of frontal sinus obliteration
- Some tumors of the frontal sinus

Most large studies of patients undergoing sinus obliteration have reported recurrent disease, yet the management of patients with recurrence is rarely discussed. The larger series reporting obliterative procedures have found a 3% recurrence rate for infection[24,25]; Weber and colleagues[26] reported a 10% chance of recurrent infection. Riedel's procedure has an important role in the management of patients with recurrent infection. Riedel's procedure can help eradicate frontal sinus disease and symptoms when drainage and obliteration have failed and there is persistent disease involving the anterior wall of the frontal sinus or the sinus itself. Although cranialization has a role in removing the mucosa or contents of the frontal sinus in craniofacial resection, the morbidity associated with it make an extradural Riedel's procedure preferable in dealing with chronic infection or locally invasive disease. Riedel's procedure maintains a barrier in the form of the posterior wall of the frontal sinus and the intracranial contents. Postoperative disfigurement, the main criticism of this procedure, can be reduced to some extent by chamfering the margins of the frontal sinus along with the supraorbital rims (Figs. 53-19 to 53-21).[27] Reconstruction of the anterior wall can be performed at a later date if necessary.

Figure 53-20. Postoperative appearance after the mucosa of the frontal sinus has been removed and the edges of the frontal sinus have been drilled down to make a smooth contour.

Figure 53-21. The bony shoulders of the cranial part of the frontal bone are removed and the supraorbital rims are reduced.

If there is a tumor in the frontal sinus, radical clearance is required. In this situation Riedel's procedure is useful. It involves removing the anterior wall and floor of the frontal sinus and all its mucosal lining.

Riedel's procedure has a useful role in the management of a small proportion of patients in whom drainage of the frontal sinus cannot be established, in whom frontal sinus obliteration has failed, or who have osteomyelitis of the anterior wall of the frontal sinus. Because the frontal sinus mucosa is completely removed, the chance of recurrent complications are few, and if recurrence happens, it can easily be recognized.

Cranialization

Cranialization of the frontal sinuses is performed in the following situations:

- When resection of the posterior wall of the frontal sinus is indicated
- For anterior skull base tumors
- In severe comminution of the posterior wall of the frontal sinus

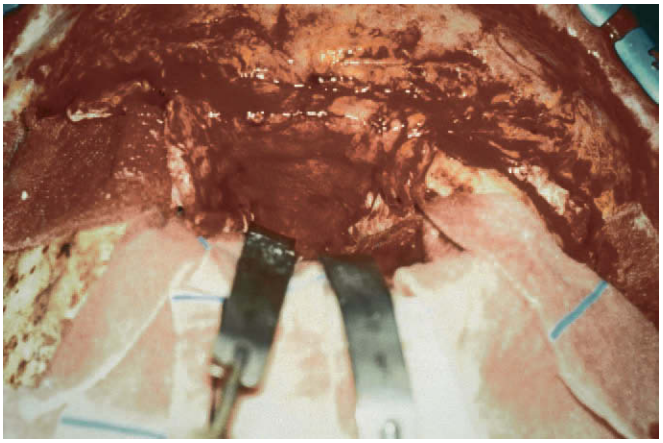

Figure 53-22. A pericranial flap is folded over the anterior skull base to separate the remaining sinuses from the intracranial contents.

In the majority of patients with either an infective or a neoplastic condition within the frontal sinus, cranialization is not desirable because it removes the barrier between the frontal sinus process and the brain. Cranialization does have a role, however, in removal of the potential problems of infection and mucocele formation that can occur after craniofacial surgery that involves the frontal sinus, as well as in trauma in which the posterior wall and, inevitably, the anterior wall of the frontal sinus have been significantly disrupted. All of the posterior wall of the sinus is removed, along with the mucosa attached to the anterior wall, which is then reconstructed. The anterior intracranial contents are separated from the paranasal sinuses and nasal airway by either a fascia lata or pericranial flap (Fig. 53-22).

Balloon Catheter Sinusotomy

The concept of using a balloon to dilate sinus ostia was introduced in 2006.[28] The idea that the balloon can dilate ostia to aid aeration and mucociliary clearance of sinuses and to minimize the risk of causing stenosis because mucosa is preserved around the ostia is attractive. Initial studies have been encouraging.[29] There are technical problems with dilatation of the maxillary sinus ostia because the uncinate process limits the introduction of the balloon; even if this problem is overcome, the narrow crevice between the uncinate process and the mucosa of the medial wall of the maxilla remains.[30] More long-term data are required before the role of this technique can be substantiated.[31] The current evidence is based on a 24-week follow-up, and a longer period of monitoring outcome is needed to eliminate the placebo effect and the cognitive dissonance as well as to ensure that the sinus ostia remain patent.

A key question is, What are the indications for balloon catheter sinusotomy? Acute frontal sinusitis usually resolves with antimicrobial treatment and is an isolated event. The immune status should be checked in patients who have more than two episodes of acute bacterial sinusitis a year,[32] because an immune problem is more likely than an anatomic irregularity to be the primary problem. Chronic bacterial infective frontal sinusitis is uncommon. The majority of patients with pain or pressure over the forehead have tension-type headache or migraine and do not require surgery, which would exacerbate the symptoms in a third of patients.[33-36] The majority of patients with rhinosinusitis and involvement of the frontal sinus have nasal polyposis, which is not amenable to balloon catheter sinusotomy—nor is osteomyelitis, mucoceles, or neoplasia. Similarly, infective sphenoid sinusitis that is unresponsive to medical treatment is uncommon. The majority of patients with symmetric facial symptoms of pressure have a version of tension-type headache that affects the midface.[37]

When balloon catheter sinusotomy was introduced, a guidewire was placed into the sinus under fluoroscopic control, but in one cadaveric study the balloon was introduced into the frontal recess on its own.[38] Researchers were unable to dilate the maxillary ostia with balloon catheter sinusotomy.[38] Is this a technique looking for a patho-

Figure 53-23. A superior view of a patient with pneumosinus dilatans of the frontal sinuses; it is more marked on the left side.

logic process to treat?[30] Its use should be studied with well-defined entry criteria, good outcome measures, and a follow-up period that would negate the effect of cognitive dissonance.

Specific Pathologic Conditions

Pneumosinus Dilatans

Pneumosinus dilatans is a rare condition characterized by the benign expansion of an aerated sinus beyond the normal margin of the frontal bone. The precise etiology and pathogenesis of pneumosinus dilatans are unknown, although a large number of mechanisms have been proposed. A *hypersinus* is an enlarged sinus with normal walls that do not extend beyond the normal boundaries of the frontal bone. A *pneumocele*, unlike pneumosinus dilatans, has walls with either generalized or focal thinning and total or partial loss of its integrity within the contours of the frontal bone.

Pneumosinus dilatans has a fluctuating course: It may be slowly progressive or may develop suddenly following a refractory period. Most cases are asymptomatic and are diagnosed only when a deformity is noticed, such as frontal bossing, or when the mass effect due to involvement of surrounding structures leads to symptoms (Fig. 53-23). Depending on the site and rate of expansion and the vulnerability of the surrounding structures, this deformity may result in diplopia, reduced visual acuity, headache, and other local pressure symptoms. Pneumosinus dilatans has been associated with pathologic conditions such as planum meningiomas and other brain tumors, arachnoid cysts, fibrous dysplasia, prolonged cerebrospinal fluid shunting and cerebral hemiatrophy infantile meningoencephalitis, von Recklinghausen's disease, and acromegaly. It can also be idiopathic. Six different hypotheses have been advanced to explain the etiology of these cases of pneumosinus dilatans; they are the presence of a gas-forming microorganism, spontaneous drainage of a mucocele, the presence of a one-way valve, congenital origin, programming of osteoblastic and osteoclastic activity, and hormonal origin.

Chronic inflammatory changes are occasionally noted histologically, although the surrounding "nonaffected" paranasal sinuses have rarely been examined; in paranasal sinuses that have been evaluated, minor chronic inflammation of the other paranasal sinus has been seen. It has been proposed that inflammation of the surrounding sinuses stimulates the pneumatization power of the subepithelial layers of the sinus mucosa, causing pneumosinus dilatans.[39,40]

The most commonly proposed pathogenic mechanism, and the one that has acquired the most credibility, is a local process involving obstruction of the sinus ostium with a one-way valve mechanism.[41] In this hypothesis, the one-way valve results in long-term air trapping in the affected sinus, by which air entering under positive pressure after events such as nose blowing is subsequently prevented by the valve from escaping. The best experimental evidence for a one-way valve mechanism comes from antral pressure studies showing the absence of patent ostia together with a loss of normal antral pressure variation with the respiratory cycle and increased sinus pressure for several minutes after Valsalva's maneuver. Other evidence for a one-way valve comes from the pain experienced in the affected sinus by some patients during changes in atmospheric pressure, such as flying or diving, or with nose blowing.

Evidence against this "trapdoor" theory includes the normal drainage of sinus secretions in the affected sinus; one would expect mucus to be trapped by the partial obstruction of the valve. In addition, none of the involved sinuses has notable mucoperiosteal thickening or other evidence of infection, which would be expected with ostial obstruction. Complete occlusion of the sinus would be expected to lead to negative antral pressures and effusion but not sinus expansion. Furthermore, the highly vascularized nature of the mucosal lining would be expected to reduce the pressure of the gases by diffusion in a relatively short time, preventing any long-term effects; in fact the pressures demonstrated after Valsalva's maneuver have been shown to be normal in some patients with pneumosinus dilatans. For there to be a trophic effect on bone, a sustained pressure would probably be required. This theory would not explain the focal cases of pneumosinus dilatans.

The congenital conditions associated with pneumosinus dilatans, such as the finding of an association with polyostotic fibrous dysplasia (McCune-Albright syndrome) may help support the theory that a genetically altered sinus becomes enlarged after it is acted upon by a programmed alteration in the balance between osteoclastic and osteoblastic activities—hence the association of pneumosinus dilatans with conditions such as acromegaly. This theory is as yet unsubstantiated.

A variety of surgical options for treating this condition, based on a presumed etiology of occlusion of the sinus ostium by a one-way valve, have been proposed. In the majority of cases, opening the sinus ostium has been shown to arrest expansion of the sinus. In patients who have a functioning ostium, the cosmetic deformity is of primary importance and can be corrected by resection and a bone graft from the cranial vault.

Mucoceles

A paranasal sinus mucocele is an epithelium-lined sac containing inspissated mucus.[42] Obstruction of a sinus ostium has been suggested as the primary etiologic factor. The obstruction may be due to a mass lesion or secondary to fibrosis, inflammation, osteoma, fibrous dysplasia, Paget's disease, or, rarely, malignancy, trauma, or previous surgery. Local production of bone resorption factors such as prostaglandins, interleukin-1, and tumor necrosis factor have been identified at the interface between the mucocele and bone.[43,44] Other researchers suggest that expansion occurs through the direct effect of positive pressure within the mucocele.[45] Irrespective of the method by which expansion arises, subsequent intraorbital or intracranial extension can occur.

Prior to surgery, assessment of the size and location of the lesion on CT is important. The accepted, preferred method of managing paranasal sinus mucoceles is endoscopic marsupialization, if possible. The significant early, medium-term, and long-term recurrence rate, between 9% and 15%, should be explained to the patient as part of the consent process.

Osteoma

Osteomas rarely cause symptoms except when they are large enough to cause a cosmetic deformity (Fig. 53-24) or a mucocele.[46] The presence of other symptoms, such as pain, should prompt clinical suspicion of another cause, because an osteoma rarely causes such symptoms. Osteomas are so common that they are likely to be a coincidental finding; approximately 3% of people have an osteoma in the paranasal sinuses. Often, the lesions are blamed for causing headaches or excision is recommended before they do cause symptoms. Actually, however, osteomas rarely cause any problems other than cosmetic. If an osteoma does cause symptoms by obstructing the frontal recess, the history should include symptoms that are worse after upper respiratory tract infections and there should be endoscopic and CT findings of mucosal disease. All too often tension-type headaches are blamed on an osteoma that is coincidental.

Figure 53-24. An axial view of a right frontoethmoid osteoma that is causing marked proptosis.

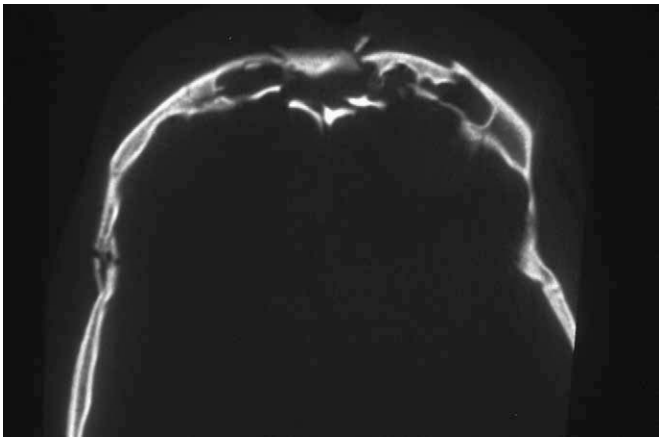

Figure 53-25. A fracture of the anterior and posterior walls of the frontal sinuses, which is best managed by cranialization and reconstruction of the anterior wall.

The removal of an osteoma depends on how accessible it is. The endoscope can be used to shell out the osteoma, and then its walls can be removed or fractured inwards. Because the most symptomatic lesions are in the frontal recess, it is important to establish drainage, which usually requires removal of the osteoma combined with a median drainage procedure.

Fractures of the Frontal Sinus

Frontal sinus fractures that are restricted to the anterior wall do not require exploration unless there is a significant cosmetic defect. The exception to this rule is when a fracture affects the frontonasal duct—these are often overlooked. Undisplaced posterior wall fractures without any complications such as cerebrospinal fluid leak can be managed conservatively. In a patient with a compound comminuted fracture affecting the posterior wall (Fig. 53-25) or near the frontonasal duct, cranialization of the frontal sinus by removal of the posterior wall along with all the mucosa and obliteration of the frontonasal recess is the best treatment.[47,48]

Split calvarial and corticocancellous grafts are best for reconstructing the anterior wall if there is a large defect. When initial débridement is undertaken, any fragments of bone can be cleaned and left in the wound for later use if needed.

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CHAPTER FIFTY-FOUR

Cerebrospinal Fluid Rhinorrhea

Martin J. Citardi

Samer Fakhri

Key Points

- Cerebrospinal fluid rhinorrhea may be classified as traumatic (>90%) or nontraumatic (<10%). Approximately 80% of all traumatic leaks occur in the setting of accidental trauma, and the remaining traumatic leaks occur after neurosurgical and rhinologic procedures. Nontraumatic etiologies include neoplasms and hydrocephalus.
- Idiopathic nontraumatic cerebrospinal fluid rhinorrhea has been linked with elevated intracranial pressure. Numerous studies have confirmed an association of this entity with both benign intracranial hypertension and empty sella syndrome.
- Clinical presentation includes unilateral watery drainage with a characteristic metallic or salty taste, often in the clinical setting of possible etiologic factors.
- The differential diagnosis for watery rhinorrhea includes allergic rhinitis, vasomotor rhinitis, and retained nasal saline irrigation fluid as well as cerebrospinal fluid otorrhea that is draining through the eustachian tube.
- Confirmation of a cerebrospinal fluid leak can be achieved through detection of β_2-transferrin or β-trace protein in nasal secretions.
- Cisternogram studies provide diagnosis confirmation and localization information. Both CT cisternography and radionuclide cisternography require lumbar puncture for the administration of tracer agent, whereas MRI cisternography can be achieved solely through specific imaging protocols. Radionuclide cisternography has poor sensitivity and poor spatial resolution. Both CT cisternography and MRI cisternography offer much greater spatial resolution but still require the presence of a relatively large, active leak for reliable detection.
- Endoscopic examination after the administration of intrathecal fluorescein can confirm the diagnosis of a cerebrospinal fluid leak and indicate its location. Dilute fluorescein must be used; serious neurologic sequelae have been reported after higher intrathecal doses of this agent.
- Endoscopic repair has emerged as the preferred modality for most cases of cerebrospinal fluid rhinorrhea requiring operative repair. During endoscopic repair, the leak site is identified and then closed with autogenous graft materials (fascia, free bone graft, fat), allograft (acellular dermal allograft), and xenogeneic collagen dural substitutes, or a combination. A free mucosal graft is typically placed over these materials, and the reconstruction is secured with surgical sealant and resorbable and nonresorbable packing material.
- The role of prophylactic antibiotics remains controversial. Some data suggest that antibiotics should be administered after detection of a cerebrospinal fluid leak, but the data are far from conclusive. Certainly, in the presence of active infection adjacent to the leak site, antibiotics are prudent.
- Traumatic cerebrospinal fluid leaks are likely to resolve with conservative measures (lumbar drainage and bed rest); operative repair is reserved for those cases in which these measures fail or in which massive injury requires urgent formal operative exploration and repair.
- Cerebrospinal fluid leak that is recognized at the time of surgery should be repaired during that procedure. Cerebrospinal fluid rhinorrhea that develops after surgery may be managed conservatively at first, but most cases require operative repair.
- Nontraumatic cerebrospinal fluid rhinorrhea is unlikely to resolve spontaneously. After potential etiologic factors (brain tumor) have been excluded, operative repair is warranted.

Cerebrospinal fluid (CSF) rhinorrhea results from a direct communication between the CSF-containing subarachnoid space and the mucosalized space of the paranasal sinuses. Because it may serve as a path for the spread of bacterial pathogens and other microorganisms, CSF rhinorrhea may lead to meningitis and intracranial infections, which carry significant morbidity even today. In addition, the skull base defect through which CSF drains may provide a route for the development of pneumocephalus and secondary brain compression. Although CSF rhinorrhea is a simple concept, its diagnosis and localization may be problematic; fortunately, contemporary strategies now provide a more direct means of diagnosis and localization. Over the past two decades, the optimal treatment strategy has undergone significant evolution as minimally invasive, endoscopic techniques have gained acceptance and supplanted more traditional techniques requiring external incisions or craniotomy.

Historical Perspective

CSF rhinorrhea was first reported in the 17th century.[1] In the early 20th century, Dandy[2] reported the first successful repair, which used a bifrontal craniotomy for placement of a fascia lata graft. Although this surgical strategy provided direct access for the repair, reported failure rates were quite high and the procedure entailed the morbidity of craniotomy. In fact, reported recurrent rates were as high as 27%,[3] and in one series only 60% of leaks were successfully repaired.[4]

Extracranial approaches were introduced in the mid-20th century. In 1948, Dohlman[5] presented a patient whose CSF leak was repaired through a standard naso-orbital incision. Several years later, Hirsch[6] reported the successful closure of two sphenoid sinus CSF leaks through a pure endonasal approach. In 1964, Vrabec and Hallberg[7] described the repair of a cribriform defect through an endonasal route. All of these endonasal procedures were performed before the advent of surgical nasal endoscopy.

Endoscopic approaches were introduced and popularized in the 1980s and early 1990s. Both Wigand[8] and Stankiewicz[9] described closure of incidental CSF leaks during endoscopic sinus surgery. In 1989, Papay and colleagues[10] introduced rigid transnasal endoscopy for the endonasal repair of CSF rhinorrhea, and in 1990, Mattox and Kennedy[11] presented another series of cases in which the CSF rhinorrhea was addressed with use of endoscopic visualization. Since then, numerous series have been published,[12-14] and endoscopic repair has emerged as a mainstay of surgical management.[15]

Classification

Box 54-1 summarizes a classification system for all cases of CSF rhinorrhea. This approach, which is based on the established pathophysiology of CSF rhinorrhea, has important clinical implications for the selection of treatment strategies as well as patient counseling about prognosis.

Box 54-1

Classification of Cerebrospinal Fluid Rhinorrhea

Traumatic

Accidental

Immediate

Delayed

Surgical

Complication of neurosurgical procedures:

- Transsphenoidal hypophysectomy
- Frontal craniotomy
- Other skull base procedures

Complication of rhinologic procedures:

- Sinus surgery
- Septoplasty
- Other combined skull base procedures

Nontraumatic

Elevated Intracranial Pressure

Intracranial neoplasm

Hydrocephalus:

- Noncommunicating
- Obstructive

Benign intracranial hypertension

Normal Intracranial Pressure

Congenital anomaly

Skull base neoplasm:

- Nasopharyngeal carcinoma
- Sinonasal malignancy

Skull base erosive process:

- Sinus mucocele
- Osteomyelitis
- Idiopathic

The importance of accurate classification was first recognized by Ommaya and associates,[16] who proposed dividing CSF rhinorrhea into traumatic and nontraumatic forms. These researchers believed that the application of the term "spontaneous" to cases of CSF rhinorrhea was inappropriate because comprehensive investigations of all cases of CSF rhinorrhea should reveal the true proximate cause. Most cases of so-called spontaneous rhinorrhea have a specific etiology, so the term "spontaneous" is probably best reserved for cases of true idiopathic CSF rhinorrhea, in which various investigations cannot determine a specific cause.

Data about the incidence of CSF rhinorrhea are sparse. Only 4% of all CSF leaks are nontraumatic, and 16% occur as a direct result of intracranial and extracranial procedures.[17] The vast majority result from accidental or surgical trauma. Approximately 80% of all cases of CSF rhinorrhea occur in the setting of accidental trauma, mostly in the form of closed-head injury. Conversely, CSF rhinorrhea is noted in only 2% to 3% of cases of serious head trauma.[17] The presence of a skull base fracture is associated with a CSF fistula in 12% to 30% of cases.[18] More than 50% of CSF fistulas resulting from accidental head trauma are located at the anterior cranial base, most of them involving the cribriform plate.[19,20] The majority of traumatic CSF leaks become clinically evident within 2 days, and almost all manifest within 3 months after the traumatic event.[21] Most CSF fistulas resulting from accidental head trauma resolve spontaneously or with conservative management, including lumbar drainage and bed rest.

Pathophysiology

CSF is produced by the choroid plexus in the ventricles at a rate of 20 mL per hour in adults. The CSF circulates from the ventricles through the foramina of Luschka and Magendie to the subarachnoid spaces around the cerebral hemispheres, cerebellum, and spine. Total CSF volume is 140 mL, consisting of 20 mL in the ventricles, 50 mL in the intracranial subarachnoid space, and 70 mL in the paraspinal subarachnoid space. The typical upper limit of normal CSF pressure ranges from 40 mm H_2O in infants to 140 mm H_2O in adults. CSF pressure fluctuates with respirations and arterial pulse pressures as well as with changes in head position. CSF pressure is maintained by a relative balance between CSF secretion (from the choroid plexus) and CSF resorption (by the arachnoid villi). Because CSF secretion occurs at a steady rate, the rate of CSF resorption plays the major role in determining CSF pressure.[22] Processes that disrupt CSF resorption tend to lead to increased intracranial pressure (ICP).

The presence of active CSF rhinorrhea requires a disruption of the barriers that normally separate the contents of the subarachnoid space from the nose and paranasal sinuses; that is, the leak incorporates defects of the arachnoid and dura mater, paranasal sinus mucosa, and the intervening bone. Furthermore, a pressure gradient is also required to produce flow of CSF.

From these apparent observations, the possible etiologies for CSF leaks may be inferred. Various surgical interventions, including routine sinus surgery, can lead to inadvertent disruption of the skull base. Complex intracranial and skull base procedures often directly violate the normally sturdy barrier; however, reconstitution of that barrier may be incomplete. Severe head trauma can lead to skull base fractures with dural laceration. Direct erosion of the skull base by neoplasm or infection can also create a CSF fistula.

The other major factor in the pathogenesis of CSF rhinorrhea is increased ICP. Both an intracranial mass and hydrocephalus are associated with elevated ICP. Strong coughing and the Valsalva maneuver both serve to transiently increase ICP. Elevated ICP is also an important factor in cases of apparent idiopathic CSF rhinorrhea. In a series of publications, Schlosser and coworkers[23,24] have noted that all patients who underwent clinically indicated lumbar puncture or drainage after successful endoscopic repair of nontraumatic CSF rhinorrhea had elevated ICP (mean 26.5 cm H_2O in the first report[23] and 32.5 cm H_2O, in the second report[24]), suggesting that occult elevation of ICP may be an etiologic factor in even so-called idiopathic or spontaneous CSF rhinorrhea. It could be postulated that in patients with occult elevated

CSF pressure, the CSF leak may serve as a release valve that decompresses the elevated pressure. (If the patient has an active leak at the time of lumbar puncture, the opening pressure may be normal—because the leak has decompressed the ICP. Thus, the increased pressure may be apparent only after a site of leakage has been surgically repaired.)

In at least certain instances, nontraumatic CSF rhinorrhea seems to result from abnormally elevated ICP. Given that elevated ICP is a primary characteristic of benign intracranial hypertension (BIH), the pathophysiology of nontraumatic CSF rhinorrhea and that of BIH may be similar. *Benign intracranial hypertension,* also known as *idiopathic intracranial hypertension* and *pseudotumor cerebri,* is a syndrome of increased ICP in the absence of specific causes such as intracranial masses, hydrocephalus, and dural sinus thrombosis. Clinical manifestations of BIH include headache, pulsatile tinnitus, papilledema, and visual disturbances including abducens nerve palsy. Most patients with BIH are obese, middle-aged women. In fact, the demographics of the population with spontaneous CSF leak are quite similar to those of the average population of patients with BIH.[25] Thus the diagnosis of BIH must be examined in the setting of spontaneous CSF rhinorrhea. In fact, Schlosser and coworkers[26] demonstrated that 8 of 11 patients (72%) with apparent idiopathic CSF rhinorrhea strictly fulfilled the modified Dandy criteria used by neuro-ophthalmologists to make the diagnosis of BIH.[26] The other 3 patients fulfilled most but not all the criteria.

In a separate publication, Schlosser and Bolger[27] assessed the incidence of an empty sella in 15 patients with apparently spontaneous CSF rhinorrhea and in 9 patients with nonspontaneous CSF rhinorrhea and noted a statistically significant ($P = .01$) greater incidence of empty sella in the nontraumatic CSF leak group (100% vs. 11%, respectively). An empty sella may therefore serve as a marker of elevated ICP.[28] Normally, the pituitary gland fills the entire sella turcica; however, if arachnoid and CSF herniate through the sellar diaphragm, this CSF-filled sac may partially or completely compress the pituitary gland. When this compression occurs, an "empty sella" results. The clinical manifestations and demographic profile of patients with empty sella syndrome (ESS) are highly similar to those for patients with BIH and patients with nontraumatic CSF leaks. The clinical presentation of ESS includes headache, memory losses, cerebellar ataxia, papilledema, and visual field defects. In addition, many patients with ESS are obese, middle-aged women with elevated body mass index (BMI). In a later report, Silver and colleagues[29] demonstrated that the radiographic signs displayed in 14 patients with nontraumatic, apparently idiopathic, CSF rhinorrhea were largely similar to those seen in patients with ICP and BIH. The signs included arachnoid pits in 79% of patients, empty sella in 50% of patients, meningoencephaloceles in 50% of patients, and dural ectasias in 35% of patients. Because ESS is associated with altered CSF circulation dynamics,[30] treatment of nontraumatic CSF rhinorrhea, which has a demonstrated association with ESS, should include consideration of the concomitant diagnosis of ESS as well as the potential clinical impact of ESS.

These associations among nontraumatic CSF rhinorrhea, BIH, and ESS have important clinical implications, because these three entities may all be manifestations of the same underlying pathophysiologic derangement that leads to elevations in intracranial and CSF pressures. Persistent headache after successful surgical repair may indicate occult ICP hypertension. Similarly, recurrent or persistent CSF rhinorrhea often represents decompression of abnormally high ICP. Thus, the issue of abnormal CSF dynamics should be considered in instances of apparently idiopathic CSF rhinorrhea.

The bony architecture of the skull base plays a role in the development of CSF rhinorrhea. Certainly bony dehiscences or even partial thinning weakens the normal barrier that separates the subarachnoid space from the paranasal sinus space. Alternatively, these weaknesses can be considered congenital anomalies. In addition, specific areas of the skull base are normally quite thin. In particular, the lateral lamella of the cribriform plate (LLCP) has been well recognized as an area of potential weakness (Fig. 54-1). The length of the LLCP shows considerable variation; if the LLCP is especially long, this anatomic variation weakens a significant portion of the skull. Congenital dehiscences in the lateral sphenoid roof, occurring from persistence of the lateral craniopharyngeal canal (Sternberg's canal), have also been implicated in the pathogenesis of sphenoid CSF leaks and meningoencephaloceles.[31,32] In all instances of thinning of the bony skull base, the pressure from the overlying intracranial contents coupled with constant dural pulsations may further erode the weakened area with the resultant development of CSF rhinorrhea.

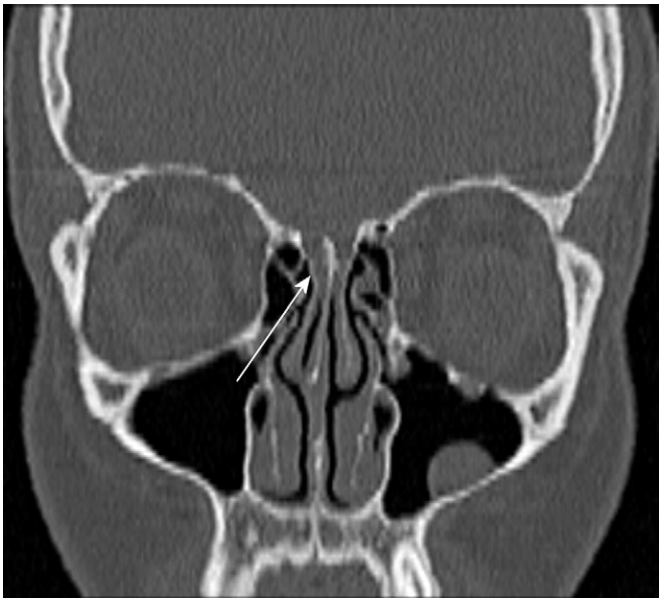

Figure 54-1. The lateral lamella of the cribriform plate (indicated by an *arrow* in this coronal sinus computed tomography scan) forms the weakest part of the skull base. The length of the lateral lamella is quite variable. In this example, it is quite long; hence, the skull base is at increased risk of inadvertent injury.

Although skull base trauma leading to CSF rhinorrhea during or after routine endoscopic sinus surgery is a rare event, the frequency of this procedure makes this complication an important cause of CSF rhinorrhea today.[9,33,34] Inadvertent pressure along the thin skull base may fracture the skull base and lacerate the dura. Because the LLCP is the weakest part of the skull base, even minor trauma in this region may cause CSF rhinorrhea. Aggressive middle turbinate retraction or resection (Fig. 54-2) may be associated with LLCP injury. The mechanism of injury during the procedure should also be considered. It is likely that powered instrumentation produces a greater skull base injury than the standard sinus forceps and through-cutting forceps. Powered instrumentation is invariably associated with greater removal of tissue; as a result, the resultant skull base defect may be quite extensive. Later generations of powered instrumentation may increase the risk of this complication, because they can remove tissue more quickly and easily. CSF rhinorrhea may occur both intraoperatively and postoperatively. When patients report symptoms that are consistent with CSF rhinorrhea after sinus surgery, the diagnosis of CSF rhinorrhea should be considered, even if the procedure itself was seemingly uneventful.

A meningocele or meningoencephalocele may occur in association with CSF rhinorrhea, although each of these lesions may occur independently. Meningoceles and meningoencephaloceles develop from the constant pressure exerted by the dura over a weakened portion of the skull base. Over time, a portion of dura may protrude through the bony defect into the paranasal sinuses and nose. If the defect is large enough and sufficient time has elapsed, meningoencephalocele may eventually develop. Often CSF rhinorrhea is the presenting symptom of a meningocele or meningoencephalocele, but not universally so.

In many patients, it is difficult to determine a precise etiology. Conceivably, multiple factors may play a role in the pathogenesis. A long LLCP increases the risk of a spontaneous leak, although most

Figure 54-2. Intraoperative images from endoscopic surgery using an image-guided navigation system for repair of bilateral cerebrospinal (CSF) leaks. The cross hairs on the reformatted three-dimensional computed tomography scans (*top, bottom left*) denote placement of the probe as seen in the endoscopic view (*bottom right*). Middle turbinate resection may result in inadvertent skull base trauma and CSF leak. The instrument tip rests on the anterior skull base defect. The coronal sinus CT shows bony loss of the skull base and middle turbinate on both the left and right sides.

individuals with this skull base feature do not have such a leak. However, the combination of a long LLCP and elevated ICP—perhaps owing to a variant of ESS and/or BIH—may lead to CSF rhinorrhea. It is important to remember this multifactorial etiology, especially in patients with recurrent or persistent CSF rhinorrhea after surgical repair. Of course, surgical failure may result from other unrecognized factors.

Diagnosis

Intuitively, the diagnosis of CSF rhinorrhea may seem simple; in practice, however, it may be problematic. In selected instances, the presence of CSF rhinorrhea may be obvious. For instance, the development of unilateral watery rhinorrhea after head trauma with resultant anterior skull base fracture warrants little effort for diagnosis confirmation. However, the establishment of the diagnosis of a CSF leak as well as its precise localization often represents a major clinical challenge for a number of reasons. First, CSF rhinorrhea is relatively rare, but other rhinopathies, including seasonal allergic rhinitis, perennial nonallergic rhinitis, and vasomotor rhinitis, are relatively common. These more innocuous conditions may mimic some of the signs and symptoms of CSF rhinorrhea or may occur simultaneously with CSF rhinorrhea. Second, CSF rhinorrhea is often intermittent. As a result, a diagnostic test performed at a time when the CSF rhinorrhea is quiescent may lead to a false-negative result. Finally, the CSF drains from a low-pressure system; therefore, the quantity and duration of drainage may be quite low, because the pressure gradient that drives the CSF flow is intrinsically low, even in the presence of relative increases in CSF rhinorrhea.

The diagnosis of CSF rhinorrhea is typically a two-step process: First, the presence of a CSF leak must be confirmed through the documentation of objective evidence of extracranial CSF. Second, the position of the skull base defect or defects through which the CSF is draining must be determined.

Differential Diagnosis

Occasionally, CSF otorrhea may manifest as CSF rhinorrhea. In this circumstance, a skull base defect communicates between the intracranial space and pneumatized spaces of the middle ear and mastoid behind an intact tympanic membrane. The CSF collects in the middle ear space and then drains down the eustachian tube to the nose, where it appears as watery nasal drainage.

Patients who perform sinonasal saline irrigations may note watery nasal drainage that occurs even hours after they have completed the irrigation. Retained irrigation fluids may be more problematic when the surgically opened sinuses hold the saline until the patient tips the head. When this situation occurs in the immediate postoperative period, distinguishing between a true CSF leak and the release of retained saline irrigation fluid can be somewhat challenging; however, discontinuing the irrigations quickly eliminates any problems caused by them, but will not diminish a true CSF leak.

A large number of sinonasal inflammatory conditions, including both seasonal and perennial allergic rhinitis, and noninflammatory conditions, including vasomotor rhinitis, may produce watery rhinorrhea. Associated features typically serve to separate these conditions from true CSF rhinorrhea.

History

The patient's clinical history provides important cues about CSF rhinorrhea. A patient with active CSF rhinorrhea reports unilateral watery nasal discharge that occurs on the side of the presumed CSF leak. Often, the rhinorrhea is associated with a salty taste, but this may not necessarily be so. Of course, the patient with a septal perforation is not able to reliably localize the side of the skull base defect, and the patient with bilateral defects describes bilateral watery rhinorrhea. Rhinorrhea caused by a CSF leak has a typical characteristic of positional variation; that is, the rhinorrhea occurs only when the patient lowers the head. For instance, such a patient indicates that the watery drainage occurs when he or she bends over to tie his or her shoelaces.

In the situation of a traumatic CSF leak, the history of the antecedent event provides obvious cues about the presence of a skull base defect. Unilateral watery drainage that develops after a head injury from a motor vehicle accident or fall or unilateral drainage that is first noted after sinus surgery or skull base surgery must be regarded as possible CSF leak.

CSF leaks that are seemingly idiopathic may be preceded by transient increases in ICP. Clinical anecdotes suggest that some patients experience CSF rhinorrhea after strong nose blowing. In this situation, the CSF leak may best be classified as a traumatic leak.

If the skull base defect involves the cribriform plate, the patient may report hyposmia, anosmia, parosmia, or a combination of these disorders. A skull base neoplasm, causing a skull base defect, may produce remarkably minimal symptoms, aside from those associated with skull base defect, until the lesion is relatively massive and encroaches upon and destroys adjacent cranial nerves and other structures.

A detailed history of nasal and sinus health is also warranted in patients with suspected CSF rhinorrhea. First, the presence of inflammatory paranasal sinus disease may influence the treatment strategy if a true CSF leak is present. Second, inflammatory conditions may mimic the symptoms of a CSF leak, and fluctuating nasal symptoms due to varying inflammation may complicate the clinical history. Finally, many patients with suspected CSF leak may have undergone surgery, although not recently. In such cases, unrecognized skull base injury may manifest as CSF rhinorrhea years or decades after the initial procedure.

A history of headache must be explored in detail. Some patients with idiopathic, nontraumatic CSF rhinorrhea report severe diffuse headache that improves when the rhinorrhea occurs and worsens when the rhinorrhea stops. The pathophysiology of these headaches probably reflects variations in ICP. When the ICP is elevated, the headache occurs; however, when the CSF leak, appearing as watery rhinorrhea, releases the ICP elevation, the headache improves. Chronic headache may also result from other causes of elevated ICP, including BIH and ESS, which have been associated with CSF rhinorrhea (as described previously). Rarely, a chronic headache may result from an unrecognized intracranial neoplasm. Severe chronic headache may also occur from low ICP caused by chronic depletion of CSF through a persistent CSF leak.

A history of bacterial meningitis, especially of multiple episodes of bacterial meningitis, may suggest a possible skull base defect that provides a route for the intracranial extension of bacterial pathogens from the paranasal sinuses.

Physical Examination

During the physical examination of a patient with a suspected CSF leak, the physician should attempt to demonstrate the unilateral watery rhinorrhea by having the patient lean forward. Failure of such a maneuver to produce the watery drainage should not be considered definitive proof that a CSF leak is not present, especially if the clinical history supports the diagnosis of a CSF leak.

Traditionally, the so-called halo sign has been considered an important marker of CSF rhinorrhea after head trauma. The halo sign is considered present when a clear ring surrounds a central bloody spot after bloody nasal discharge is dropped upon a handkerchief or paper towel. However, the presence of either tears or saliva is likely to yield a falsely positive halo sign.

Results of the nasal examination, including traditional anterior rhinoscopy and nasal endoscopy, are often nonspecific. Glistening, moist nasal mucosa may be identified on the side of the CSF leak. A stream of clear fluid may herald an active CSF leak. Nasal examination may demonstrate the mass of a meningoencephalocele and also provides important cues about other nasal conditions that may mimic a CSF leak.

In patients with elevated ICP, papilledema may be present. Elevated ICP associated with BIH may also be associated with abducens nerve palsy. Stigmata of maxillofacial trauma may be present in patients with traumatic CSF rhinorrhea.

Diagnostic Testing

Strategies for diagnostic testing for CSF rhinorrhea may be divided into two groups. The first group focuses on the identification of a substance that can serve as a chemical marker of CSF. The second group relies upon the administration of agents that can document the presence of communication between the intradural space and extradural space.

Chemical Markers

For many decades, glucose was considered a sensitive and specific marker of CSF. Proponents of this marker applied nasal discharge to glucose oxidase test strips; the presence of glucose—indicated by a color change—was believed to represent CSF mixed with the nasal secretions. Numerous reports describe a very high false-positive rate for glucose oxidase strips as a test for CSF rhinorrhea,[35,36] because reducing substances in tears and nasal mucus react with these glucose oxidase strips.[37] In addition, false-negative results may occur in the presence of active bacterial meningitis, which typically reduces CSF glucose levels.

β_2-transferrin has now emerged as the preferred biochemical marker of CSF. In 1979, Meurman and colleagues[38] performed protein electrophoresis of CSF, tears, nasal secretions, and serum and noted a β_2-transferrin fraction only in the CSF samples. Several years later, Oberascher and Arrer[39] further described the technique for this marker and noted no false-positive results in a series of 42 tests performed. The techniques used in these reports were not overly sensitive (although they were quite specific); technical improvements have enhanced sensitivity and even simplified the technique.[40] Because β_2-transferrin is a reliable marker of CSF, it has been proposed that a negative β_2-transferrin test result in a patient with a suspected CSF leak may be sufficient justification for not performing additional invasive procedures.[41]

Important caveats about the β_2-transferrin test must be stated, however. First, a reliable test result requires that the laboratory receives an adequate sample. Because the test is not commonly available, transportation time may degrade the sample. Furthermore, a patient may be unable to obtain a sufficient volume of nasal drainage if he or she has a very slow or intermittent CSF leak. In addition, some elderly, disabled, or uncooperative patients may be unable to collect the nasal drainage because of difficulties in the actual collection process. Finally, although β_2-transferrin seems quite specific for CSF, it has been detected in aqueous humor[42] and in the serum of patients with alcohol-related chronic liver disease.[43]

Beta-trace protein (βTP) is another chemical marker that could be used for the detection of CSF. The second most common protein found in CSF after albumin, βTP has been identified as a prostaglandin D_2 synthase. It is produced by the meninges and choroid plexus and released into CSF. This protein is also present in other body fluids, including serum, but at much lower concentrations than in CSF. Detection of βTP has 100% sensitivity and specificity in cases of confirmed CSF rhinorrhea.[44] It is important to mention that the βTP test cannot be reliably used in patients with renal insufficiency or bacterial meningitis, because serum and CSF levels of βTP have been shown to substantially increase with reduced glomerular filtration rate and to decrease with bacterial meningitis.[45] βTP testing is a rapid and cost-effective procedure that should be included in the diagnostic battery for CSF rhinorrhea.

A novel strategy for the detection of CSF is the "electronic nose," a system that uses organic semiconductors for identification of volatile gases; Thaler and colleagues[46] reported that the electronic nose was able to distinguish between CSF and serum in 18 of 19 instances.

Cerebrospinal Fluid Tracers

Intrathecal agent tests provide information that can confirm the presence of a CSF leak; these tests also may provide information about the location of the skull base defect associated with the leak. All of these tests require a lumbar puncture for the introduction of a tracer agent into the subarachnoid space. Complications of the use of the intrathecal agent can be quite severe, and intrinsic properties of the agent may limit the specificity and sensitivity of the test. Agents may be categorized as visible dyes, radionuclide markers, and radiopaque dyes. Any of these tests are considered to have a positive result if the agent is visualized within the nose and paranasal sinuses.

Intrathecal fluorescein is probably the most popular visible agent. Kirchner and Proud[47] introduced the technique in 1960, and Messerklinger[48] later refined and popularized it. In brief, a lumbar puncture is performed for the introduction of fluorescein into the intrathecal space, the patient is kept in the head down-position, and nasal endoscopy is performed to identify fluorescein within the nose and sinuses. Because the fluorescein has a characteristic green color, it is quite easy to identify even in minute quantities. Specific blue-light filters may be used to enhance visual detection of fluorescein, but typically they are not necessary. Intrathecal fluorescein has been associated with various but isolated catastrophic complications, including grand mal seizures and even death. However, in most of those instances, the complication either was nonconclusively linked to the administration of fluorescein or resulted from the injection of an unusually high dose. In a large study of 420 administrations of intrathecal fluorescein in Europe and the United States, Keerl and associates[49] concluded that fluorescein is very useful in localizing CSF fistulas and that low-dose fluorescein (50 mg or less) is unlikely to be associated with adverse events because most complications seem to be dose-related. The recommended dilution of fluorescein is 0.1 mL of 10% fluorescein (the intravenous preparation, not the ophthalmic preparation) in 10 mL of the patient's own CSF[12]; this dilution should be infused slowly over 30 minutes. Patients should be counseled about the risks of intrathecal fluorescein, because this use of fluorescein is clearly not approved by the U.S. Food and Drug Administration.

Radioactive iodine (I^{131})–labeled serum albumen (RISA), technetium Tc 99m–labeled serum albumen or diethylenetriamine/pentaacetic acid (DTPA), and radioactive indium (In^{111})–labeled DTPA have all been used for radionuclide cisternography, which involves the intrathecal administration of a radionuclide tracer via a lumbar puncture and subsequent monitoring of the distribution of tracer with a scintillation camera. Typically, intranasal pledgets are also placed in close proximity to the suspected skull base defect and assayed for tracer 12 to 24 hours later with a gamma counter. Pledget counts should be determined per unit mass of dry pledget, and a radionuclide ratio that compares tracer counts in the pledget with counts in a unit volume of peripheral blood should be calculated.[50] An elevated ratio suggests the presence of a CSF fistula; the distribution of counts across the pledgets may suggest the location of the defect. Because radionuclide cisternography requires active CSF flow for the documentation of a CSF leak, the technique of overpressure radionuclide cisternography (ORNC), which incorporates a constant tracer infusion to increase the intrathecal pressure and thereby enhance flow, may improve the sensitivity of radionuclide cisternography.[51] In practice, the utility of radionuclide cisternography has been limited by the poor spatial resolution of the scintillation cameras. Despite its apparent advantages, this modality has an unacceptable rate of false-positive or indeterminate results, and thus, it cannot be the sole test to confirm CSF leak.

Computed tomography (CT) cisternography, which incorporates CT scanning after the intrathecal administration of radiopaque contrast (metrizamide), may also be used to document the presence of a CSF leak (Fig. 54-3).[52,53] Approximately 80% of CSF leaks can be confirmed through CT cisternography.[54]

Magnetic resonance (MR) cisternography is a noninvasive method for assessing the presence of intranasal or intrasinus CSF (Fig. 54-4).[55] In this technique, a heavily T2-weighted image with fat suppression

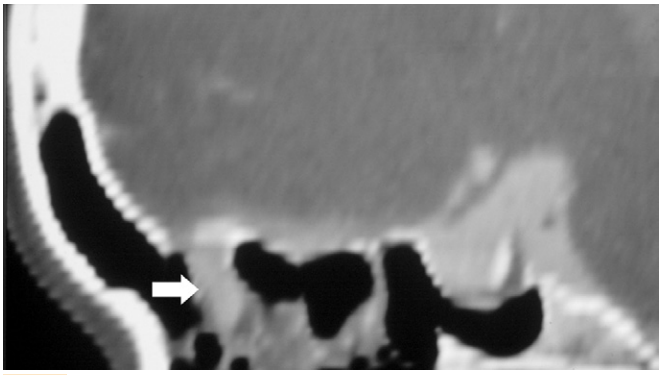

Figure 54-3. A cerebrospinal fluid leak on computed tomography (CT) cisternography is characterized by the presence of contrast material within the pneumatized paranasal sinuses. The contrast material should be in direct continuity, so that a precise site of communication can be reliably demonstrated, as shown in this sagittal CT reconstruction from a positive CT cisternogram. The *arrow* points to the area of the contrast material within the ethmoid sinuses.

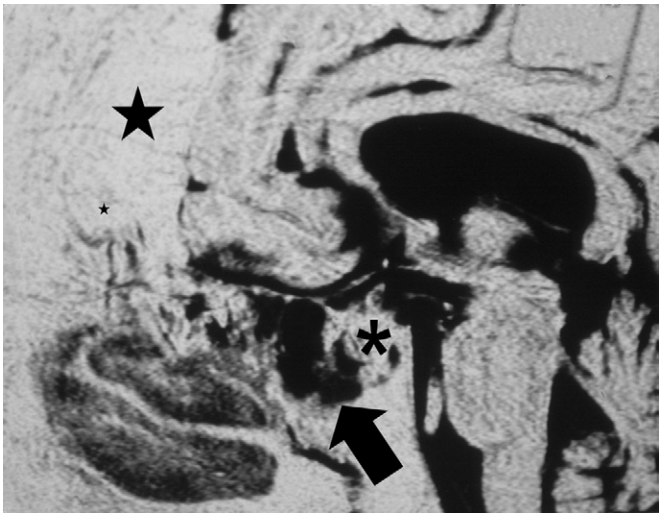

Figure 54-4. Magnetic resonance (MR) cisternography provides a noninvasive way to confirm and localize cerebrospinal fluid (CSF) leaks. In this sagittal image, obtained during a positive MR cisternogram in a patient with a CSF leak after transsphenoidal hypophysectomy, the CSF signal, which appears black, is present in the sphenoid sinus (*arrow*). The *asterisk* shows the position of the sella. The anterior cranial fossa shows minimal signal because of a pneumocephalus (indicated by the *star*).

and video reversal provides a means to image CSF; extension of the characteristic signal from the intracranial space to the paranasal sinuses represents a CSF leak. Reported sensitivity, specificity, and accuracy of MR cisternography are 0.87, 0.57, and 0.78, respectively.[56]

Localization Studies

The diagnostic tests that rely on CSF tracers also provide information about localization of the skull base defect through which the CSF is draining. Such information is critical for the development of a strategy for the surgical repair of CSF leaks. The extent to which these studies can provide anatomic information varies. For instance, even under the best of circumstances radionuclide cisternography has notoriously poor spatial resolution. Even when results of such a study are positive, they may only suggest a general region (i.e., cribriform plate) or even just a side. MR cisternography provides greater anatomic information, but the long image acquisition times required by contemporary MR imagers produce relatively thick image slices that are not thin enough to show small skull base defects. Even metrizamide CT cisternography may be difficult to reliably interpret, although scan slices may be as thin as 1 mm. It is important to remember that all of these studies assume the presence of active CSF flow; if the leak is intermittent or very small, any of these studies may yield a false-negative result.

Nasal endoscopy after intrathecal administration of fluorescein provides a means for direct confirmation of the presence and location of a CSF leak. This study, too, requires active CSF flow to identify a leak. Typically it plays a role in two circumstances. First, intrathecal fluorescein may be administered at the beginning of a procedure aimed at repairing a CSF leak confirmed by other means (typically β_2-transferrin testing). Second, intrathecal fluorescein with nasal endoscopy may be employed for diagnosis alone; this procedure should be performed with use of anesthesia in the operating room to enhance patient safety and comfort.

The specificity of β_2-transferrin testing has significantly altered the role of the various cisternography tests. Because β_2-transferrin testing is both reliably specific and noninvasive, it has relegated these other imaging-based studies to use in selected cases only. After the diagnosis of a CSF leak has been confirmed through β_2-transferrin testing, high-resolution CT (either 1-mm direct coronal images or coronal images reformatted from 1-mm axial data through a robust software algorithm) and MR imaging (MRI) of the skull base may provide adequate anatomic information about the integrity of the skull base. Endoscopic exploration for identification and repair of the defect site (described later) may be performed with attention directed at the area or areas of suspected skull base dehiscence. In fact, Zapalac and associates[57] recommended β_2-transferrin testing for diagnosis and high-resolution CT for localization. In this strategy, CT and MRI are complementary; that is, CT provides detail about the bony anatomy, including bony skull base dehiscences (Fig. 54-5), and MRI provides detail about soft tissues, including coincident meningoencephaloceles and incidental intracranial masses (Fig. 54-6). CT scans also provide information about meningoencephaloceles but often lack the soft tissue detail present in MRI studies (Fig. 54-7). Improvement in imaging software and computer-aided surgery (CAS) technology has enabled the application of CT-MRI fusion. In this modality, high-resolution CT scans are fused with MR images to create a hybrid image with excellence of both bony detail and soft tissue and fluid signal. Using this application, Mostafa and Khafaqi[58] were able to accurately localize the site of CSF leakage in 17 of 19 cases with a sensitivity of 89.5%.

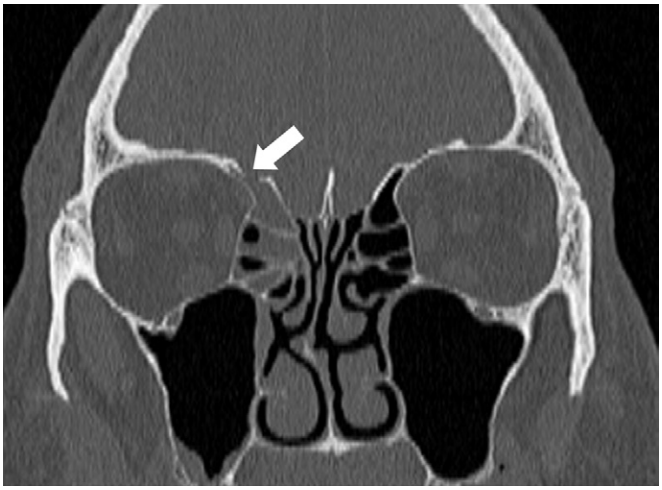

Figure 54-5. High-resolution sinus computed tomography (CT) may be used to image even small bony defects of the skull base. This coronal CT scan was reconstructed from 1-mm direct axial CT image data using a robust image processing software system. It should be noted that not all reformatted coronal images are of sufficient quality to permit this precise examination of the skull base. A bony dehiscence (indicated by the *arrow*), together with a positive β_2-transferrin study result, represents a likely site for an active CSF leak; however, in the absence of a positive β_2-transferrin study result, the presence of a CSF leak should not be assumed from the presence of such a finding.

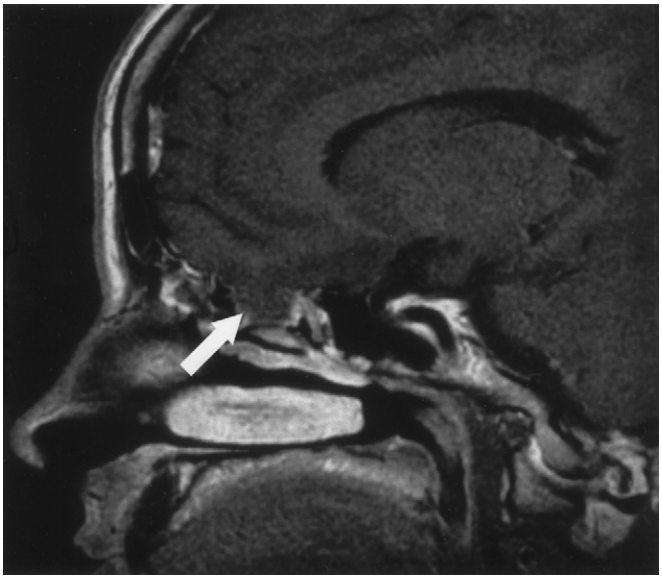

Figure 54-6. Magnetic resonance (MR) imaging provides excellent visualization of anterior skull base meningoencephaloceles. The *arrow* shows the characteristic appearance of such a finding on this sagittal MR image.

Management

After confirmation of the presence of a CSF leak and localization of the skull base defect, optimal management of CSF rhinorrhea focuses on the selection of an appropriate treatment strategy. That decision-making process should include consideration of the leak's etiology and probable natural history.

Optimal treatment requires cooperation among various disciplines, including otorhinolaryngology, neurosurgery, and neuroradiology. Even if the otorhinolaryngologist will manage the CSF rhinorrhea primarily, he or she should seek the input of neurosurgery colleagues. In addition, consultation with infectious disease specialists may be helpful for the selection of appropriate antibiotics in the situation of suspected meningitis.

Conservative Treatment

Conservative treatment of CSF rhinorrhea includes a 1- to 2-week period of strict bed rest with head elevation as well as several days of continuous subarachnoid drainage through a lumbar catheter (or intermittent drainage through serial spinal taps) (Box 54-2). In addition, patients are advised to avoid coughing, sneezing, nose blowing, and

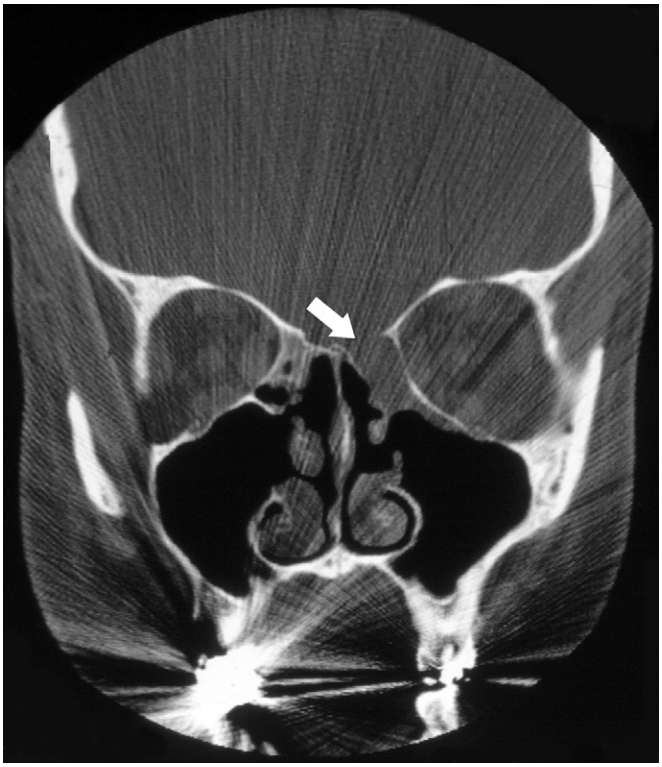

Figure 54-7. Computed tomography (CT) may be used to visualize the bony structures of the skull base, but it cannot reliably distinguish between a meningoencephalocele and a mucocele with bony resorption. This coronal CT scan shows a bony skull base dehiscence (*arrow*) and an adjacent area of opacification. In this case, a meningoencephalocele was confirmed by magnetic resonance imaging.

Box 54-2

Conservative Treatment of Cerebrospinal Fluid Rhinorrhea

Subarachnoid drainage through a lumbar catheter
Strict bed rest
Head elevation
Stool softeners
Advising patient to avoid coughing, sneezing, nose blowing, and straining
Prophylactic antibiotics (possible)*

*Routine administration of prophylactic antibiotics is controversial. The best data support the use of antibiotics after a traumatic leak, but even these data are far from conclusive. Data for the use of antibiotics for other etiologies are sparse.

straining. Stool softeners are often recommended. The goal of these measures is to reduce the CSF leak flow by decompressing the ICP; in this way, healing at the defect site may seal the leak without surgical intervention.

Although lumbar drains are passive devices, they require active management. CSF specimens for cell count, protein and glucose measurements, and culture should be collected daily. An hourly drainage rate of 10 mL is desirable. Of course, higher rates produce a greater decompression of ICP; however, higher rates may lead to abnormally low ICP, which can produce severe headache. Low ICP also may cause pneumocephalus as air is drawn through the skull base defect. If low ICP is suspected, the rate of drainage should be decreased or the drain should be clamped until the ICP equilibrates at a higher level.

Complications of lumbar drainage are significant, so this technique should be used cautiously.[59] In the scenario of markedly elevated ICP, it should be avoided. In addition, lumbar drainage carries a risk of meningitis. Despite that risk, routine antibiotic therapy for prophylaxis of meningitis is not warranted, because it is probably ineffective and may even induce resistance in likely pathogens.[17,60] Nonetheless, a first-generation cephalosporin (or similar agent) for coverage of skin flora may minimize the risk of cellulitis at the puncture site with secondary ascending meningitis. In addition, it is reasonable to administer antibiotics in those patients with a history of suppurative bacterial rhinosinusitis.

Transcranial Techniques

The concept of transcranial repair of CSF rhinorrhea is quite simple: After craniotomy, the defect site is identified, and then a tissue graft is placed to close the defect. Fascia lata grafts, muscle plugs, and pedicled galeal flaps may be used. A tissue sealant, such as fibrin glue, may be used to hold the grafts in position. Access to the cribriform plate region and roof of the ethmoid requires a frontal craniotomy; extended craniotomy and skull base techniques with even greater brain compression provide access to the sphenoid sinus defects.

The well-recognized and potential morbidities of these techniques include brain compression, hematoma, seizures, and anosmia. Despite direct access to the skull base defect, failure rates are quite high; in fact, reported failure rates may exceed 25%.[3] For these reasons, extracranial techniques are now preferred in most circumstances.

Extracranial Techniques

Early extracranial techniques required an external incision for transsinus access to the skull base defect., Endoscopic techniques, which rely upon transnasal, trans-sinus access to the defect, have supplanted the older techniques. Both extracranial techniques attempt to seal the defect by the placement of graft at the defect site, although endoscopic techniques provide superior visualization. Since the initial descriptions of the endoscopic repair of CSF rhinorrhea in the 1980s, endoscopic management has emerged as the primary technique for the surgical management of skull base defects.[15]

The initial steps for endoscopic repair of CSF rhinorrhea consist of the standard endoscopic dissection so that the defect site is adequately visualized. Intrathecal fluorescein (discussed previously) may be administered to facilitate identification of the defect. The defect site must be prepared for grafting. Bipolar cautery or potassium-titanyl-phosphate (KTP) laser may be used to fulgurate a concomitant meningoencephalocele, which must never be reduced by simply being pushed intracranially. Bipolar cautery and KTP laser may also be used to remove sinus mucosa that is adherent to dura. Mucosa within 5 mm of the margins of the skull base defect must also be removed to facilitate mucosal grafting. Middle and superior turbinate resection is not routinely necessary for access.

The specific details of graft selection have generated considerable controversy. Potential grafts include temporalis fascia, fascia lata, muscle plugs, pedicled middle turbinate flaps (mucosa alone or mucosa and bone), autogenous fat, free cartilage grafts (from the nasal septum or the cartilaginous auricle), and free bone grafts (from the nasal septum or calvarium as well as other sites). Acellular dermal allograft may also serve as a graft.[61] Although pedicled intranasal grafts may be used, they have been associated with a relatively high failure rate; as a result, free grafts seem preferable for most circumstances.[62] In a meta-analysis of 289 CSF fistulas, Hegazy and colleagues[63] found that the choice of the grafting material did not seem to alter the outcome of the repair.

The selection of grafting material largely depends on the availability of the material and the experience and preference of the surgeon. Interest in the use of xenogeneic collagen dural substitutes—for example, Durepair Dural Regeneration Matrix (Medtronic Inc., Minneapolis, MN), DuraGen Dermal Graft Matrix (Integra, Plainsboro, NJ), and Dura-Guard Dural Repair Patch (Synovis Surgical Innovations, St. Paul, MN)—for closure of skull base defects has increased. This increase is partly due to advances in the endoscopic management of complex skull base pathology, which results in relatively large skull base defects. The collagen implant provides a scaffold for the native

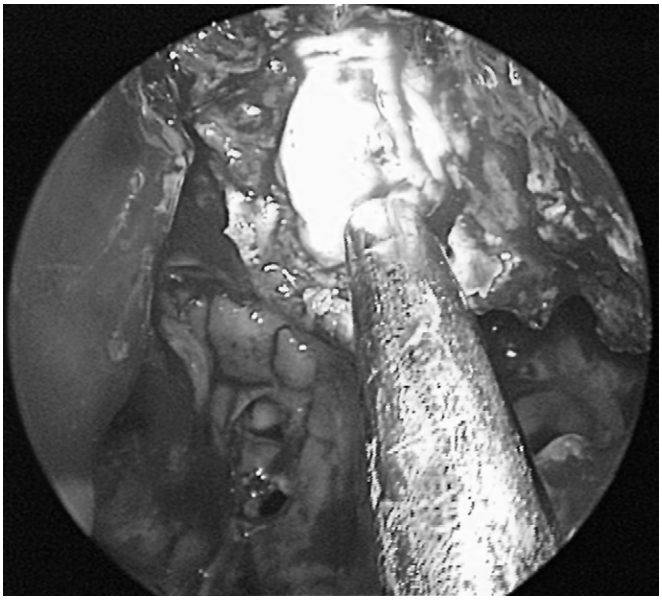

Figure 54-8. Appropriate graft placement is critical to successful repair of cerebrospinal fluid leak. In this endoscopic image, the instrument tip rests on an acellular dermal allograft, which has been tucked beneath the edges of an anterior skull base defect.

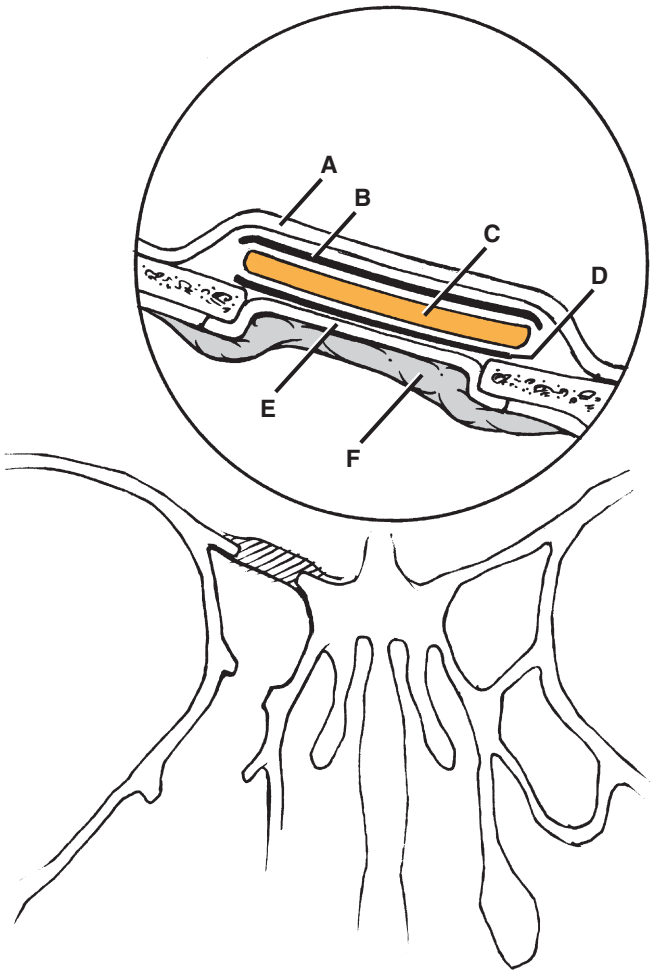

Figure 54-9. Layered skull base reconstruction provides a stronger barrier. In this illustration of a repair of a defect of the roof of the left ethmoid, representative layers are depicted as follows: *A,* dura; *B,* fascial autograft (or acellular dermal allograft); *C,* bone or cartilage autograft; *D,* fascial autograft (or acellular dermal allograft); *E,* mucosal free autograft; *F,* surgical sealant. *(Redrawn with permission from Lorenz RR, Dean RL, Hurley DB, Chuang J, Citardi MJ. Endoscopic reconstruction of anterior and middle cranial fossa defects using acellular dermal allograft.* Laryngoscope. *2003;113:496-501.)*

fibroblasts to produce a collagen layer that blends and eventually replaces the implant. In an animal study comparing the three dural substitutes listed previously, all three implants were found to be safe and effective in healing surgically created defects in the dura mater.[64]

Appropriate graft placement is critical for successful endoscopic repair (Fig. 54-8). Ideally, grafts of fascia (or similar materials) should be placed on the intracranial side of the defect with use of an underlay technique. Ambient ICP serves to hold the graft in position. Wormald and McDonogh[65] have described the "bath-plug" technique, which incorporates an intracranial fat graft; the patient's ICP helps to hold the graft in the desired position.[65] Larger defects may require a layered reconstruction including solid support such as cartilage or bone grafts placed in the epidural space (Figs. 54-9 and 54-10). In fact, this layered reconstruction offers a more robust boundary and may reduce the risk of delayed recurrence and/or meningoencephalocele formation, especially in patients at risk for elevated ICP (namely patients with suspected BIH or ESS). It should be mentioned, however, that data in the literature do not show better outcomes for use of rigid support or multilayered reconstruction of larger defects.[66] In addition to defect size and location, the CSF pressure gradient across the skull base defect is an important factor in the choice of surgical technique (underlay vs. overlay) and graft material.

Mucosal grafts should never be placed intracranially, and care should be taken to ensure the correct placement, which avoids inadvertent intracranial placement. Intracranial mucocele after endoscopic CSF leak repair has been reported; this complication probably resulted from incorrect placement of mucosal grafts.[67]

After the grafts are placed, a surgical sealant (such as fibrin glue) may be used to help hold them in place. Typically, absorbable nasal packing is placed adjacent to the grafts, and traditional nonabsorbable packing is used to support the absorbable packing. The nasal packing supports the grafts and provides some hemostasis.

Pure endoscopic approaches provide excellent access to the ethmoid roof, cribriform plate, and most of the sphenoid sinus. Lateral sphenoid leaks may require an extended approach, which incorporates endoscopic dissection of the medial pterygomaxillary space.[68,69] An osteoplastic flap or a simple trephine may be required for repair of defects through the posterior table of the frontal sinus (Fig. 54-11).

Postoperative care includes strict bed rest for several days as well as antistaphylococcal antibiotics (for prophylaxis against complications from the nasal packing). In the immediate postoperative period, patients must be monitored for potential intracranial complications (such as hematoma); observation in the intensive care unit is appropriate for the first 24 hours (or longer if necessary). If a lumbar drain was placed intraoperatively, CSF drainage, which decompresses the pressure on the repair site, should be continued for 4 or 5 days, and standard lumbar drain management principles should be closely followed (as discussed previously). Nasal packing is removed several days after surgery, and the operative site may be checked through serial nasal endoscopy sessions. Patients should be advised to avoid strenuous activity, sneezing, coughing, and so on, for approximately 6 weeks after surgical repair. The long-term postoperative management of patients with increased ICP and apparent spontaneous CSF rhinorrhea should be aimed at lowering the ICP. The reduction may be achieved with diuretic therapy, such as acetazolamide,[70] or less commonly through a CSF diversion procedure, such as ventriculoperitoneal shunting or lumbar peritoneal drain.

Endoscopic techniques offer several advantages. The excellent visualization afforded by nasal endoscopy facilitates identification of the defect and placement of the grafts. Endoscopic repair is also well toler-

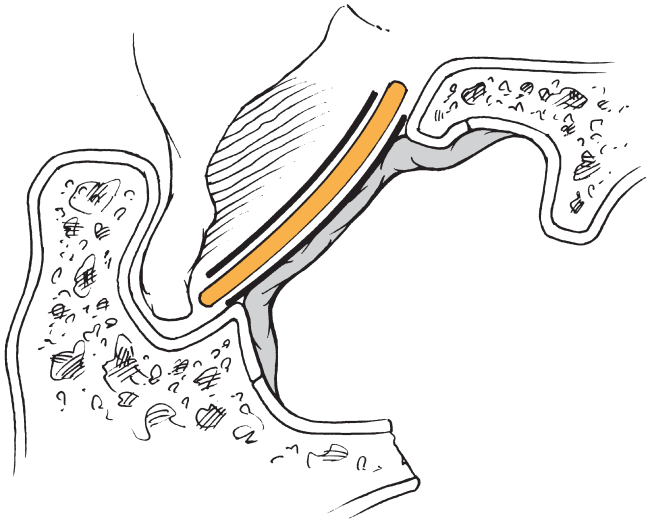

Figure 54-10. Layered reconstruction also provides an optimal barrier for sphenoid cerebrospinal fluid leaks, as shown in this illustration of such a repair of a midline sphenoid defect (after transsphenoidal hypophysectomy). Layers are as indicated in Figure 54-9. *(Redrawn with permission from Lorenz RR, Dean RL, Hurley DB, Chuang J, Citardi MJ. Endoscopic reconstruction of anterior and middle cranial fossa defects using acellular dermal allograft.* Laryngoscope. *2003;113:496-501.)*

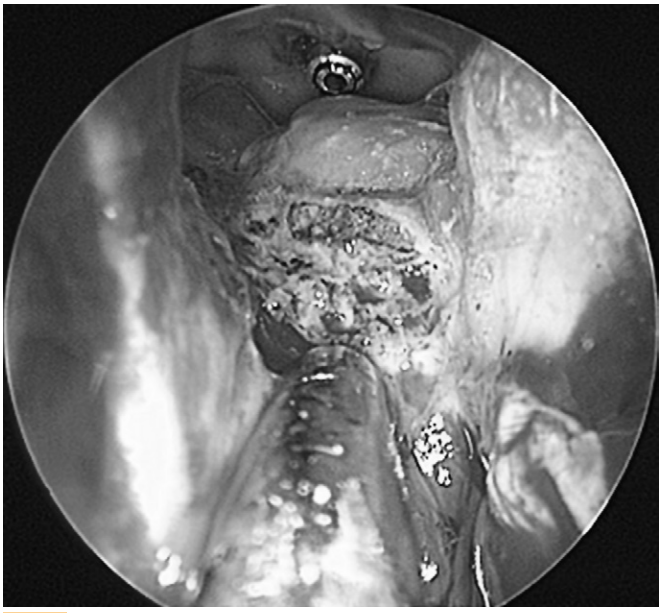

Figure 54-11. Endoscopic repair of a frontal sinus posterior table defect may require an anterior table trephination. In this endoscopic image of the left frontal recess (obtained through a 70-degree telescope), the inferior suction rests on the inferior edge of a small meningocele, and the superior bipolar suction cautery, which was passed through the trephine, rests on the superior edge of the meningocele.

ated, especially in comparison with intracranial techniques. Reported outcomes are excellent.[12-14,57] Successful repair may be anticipated in more than 85% to 90% of primary procedures; secondary endoscopic repair is also associated with a high likelihood of success.

Precautions for CSF Rhinorrhea

Patients who have confirmed CSF leak and are awaiting definitive management as well as patients who have suspected CSF leak should be counseled about the pathophysiology of CSF rhinorrhea. For many patients, watery rhinorrhea may seem trivial, but aggressive patient education is warranted to correct that potentially fatal misconception. In particular, patients must understand the early symptoms of meningitis, so that they can seek appropriate medical care quickly if such symptoms start to develop. In addition, these patients should be advised to minimize actions that can increase ICP and exacerbate a CSF leak.

Bacterial meningitis is the major cause of mortality and morbidity in patients with CSF fistulas. Considering the contaminated surgical field during the endoscopic repair of CSF fistulae, most surgeons elect to use perioperative antibiotics. Typically an agent with good CSF penetration, such as ceftriaxone, is administered. The efficacy of long-term prophylactic antibiotics for the prevention of meningitis in patients with active CSF rhinorrhea, however, remains a very controversial issue. The primary concern about unwarranted use of antibiotics is the potential for selection of resistant organisms. The reported incidence of meningitis in patients with posttraumatic CSF fistulas varies greatly (2% to 50%).[71-73] Multiple factors, including the duration of CSF leakage, delayed onset of CSF leakage, site of the fistula, and concomitant infections, seem to affect the occurrence of meningitis. Patients with posttraumatic CSF leaks lasting more than 7 days have at least 8- to10-fold increase in risk of meningitis.[71,72] Strong consideration should therefore be given for surgical repair of posttraumatic CSF leaks persisting more than 7 days despite appropriate conservative management.

MacGee and associates[74] reported one of the main studies frequently cited in arguments against the use of prophylactic antibiotics in posttraumatic CSF fistulas. They described a series of 58 patients and reviewed data on 344 patients from the literature, for a total of 402 patients with posttraumatic CSF leaks. There was a 14% incidence of meningitis in the group who received prophylactic antibiotics, compared with 5% in the group treated without antibiotics. However, the difference in incidence of meningitis between the two groups did not reach statistical significance. In a meta-analysis of six studies involving 324 patients with posttraumatic CSF leaks, Brodie[73] found a 2.5% incidence of meningitis in patients who received prophylactic antibiotics and a 10% incidence in those who did not receive antibiotics. The difference was statistically significant ($P = .006$). Individually, however, none of the studies included in this analysis demonstrated a significant difference in incidence of meningitis with prophylactic antibiotic therapy. It is important to mention that there is a paucity of studies examining the incidence of meningitis in nontraumatic, idiopathic CSF leaks.

For patients with persistent leaks, immunization against *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Neisseria meningitidis* may be considered.

Comprehensive Management Strategy

Indications for operative CSF leak repair include failure of conservative management, intraoperative recognition of a leak (during sinus surgery, skull base surgery, or craniotomy), large defects or leaks (especially in association with pneumocephalus), idiopathic leaks, so-called spontaneous leaks, and open traumatic head wounds with CSF leakage.

A single management strategy cannot be utilized for the treatment of all CSF leaks. Instead, selection of the appropriate treatment should reflect the natural history of CSF rhinorrhea as well as potential morbidity. Therefore, treatment should be targeted to the underlying etiology of the CSF leak. It is practical to consider management options in the following four scenarios: traumatic (nonsurgical) etiology, intraoperative injury with immediate recognition or onset, operative injury with delayed recognition or onset, and nontraumatic ("spontaneous") leaks.

Traumatic (Nonsurgical) Etiology

CSF rhinorrhea due to head injury should be managed initially with conservative measures that reduce ICP and promote spontaneous closure of the CSF leak. If the rhinorrhea does not resolve within several days, operative exploration and repair is necessary. Often, extracranial endoscopic techniques are applicable; however, open transcranial procedures may be warranted. An important exception to the use of con-

servative measures is the situation of massive head injury requiring urgent operative exploration; in this scenario, direct closure of the skull base defect should be performed.

Massive skull base trauma is often associated with intracranial and maxillofacial injuries. Such cases are typically managed in an interdisciplinary fashion with immediate attention given to address life-threatening neurologic injuries. Pneumocephalus should be treated promptly because rapid air accumulation may lead to a catastrophic outcome. Most cases of massive head and skull base trauma are initially handled by a trauma neurosurgeon in conjunction with an otorhinolaryngologist, a maxillofacial surgeon, and an ophthalmologist, depending on the extent and location of injuries.

The vast majority of cases of CSF rhinorrhea due to head trauma do not require operative intervention, because the leaks tend to resolve with conservative measures only.

The administration of prophylactic antibiotics for CSF rhinorrhea due to trauma is controversial, as discussed previously. Certainly, in instances of contaminated, open wounds, most surgeons would employ intravenous antibiotics, but in most circumstances, the decision to administer intravenous antibiotics should be made on a case-by-case basis.

Intraoperative Injury with Immediate Recognition or Onset

CSF leaks that are noted intraoperatively should be repaired at the time that they are recognized. If a CSF leak is suspected during routine endoscopic sinus surgery, the surgeon should attempt to confirm its presence. If a leak is confirmed, endoscopic repair should be performed. Deliberate breach or resection of the dura in operations on the anterior skull base should be closed to provide a watertight seal at the end of the procedure.

Operative Injury with Delayed Recognition or Onset

In some instances, the presence of CSF rhinorrhea may not be confirmed until days, weeks, months, or even years after a surgical procedure. A trial of conservative therapy for a few days is warranted in most instances, because at least some of these leaks close with use of simple measures. However, it is reasonable to pursue operative intervention for massive leaks early. In addition, if there has been a significant delay (i.e., more than several weeks at most) between the time of the surgery and the time of CSF leak diagnosis, conservative measures are less likely to be successful, and early surgical intervention is warranted. Of course, when conservative measures fail, surgical repair is the next step.

Nontraumatic Leaks

In general, nontraumatic CSF leaks are likely to require surgical repair, but in selected instances, a trial of conservative measures may be attempted. Treatment of nontraumatic CSF rhinorrhea due to neoplasm, hydrocephalus, and so on, should involve treatment of the specific etiologic factors. Commonly, nontraumatic leaks occur "spontaneously"—that is, there is an absence of obvious antecedent factors. In this scenario, consideration of unrecognized elevation of ICP due to BIH or ESS must be considered. Regardless, operative repair will likely be necessary.

Conclusions

CSF rhinorrhea occurs when a skull base defect permits the drainage of CSF from the intracranial space to the nose and paranasal sinuses. CSF leaks are best categorized as traumatic or nontraumatic. Accurate diagnosis has been problematic, although the β_2-transferrin test now provides a relatively specific testing modality. Several CSF tracer studies are available; however, all of these studies suffer from suboptimal precision, specificity, and sensitivity. High-resolution CT provides detailed information about the bony skull base anatomy, and MRI assesses soft tissue issues, including unrecognized tumors and coincidental meningoencephaloceles. Many CSF leaks respond to conservative management (observation plus measures to minimize ICP); in particular, traumatic CSF rhinorrhea tends to resolve with conservative measures alone. In contrast, nontraumatic CSF rhinorrhea is especially likely to require direct operative repair. Although transcranial techniques for CSF leak closure have been present for many decades, they are often second-line choices in the contemporary management of CSF rhinorrhea. Extracranial techniques were developed in the middle of the 20th century, but the incorporation of endoscopic visualization and instrumentation over the past 20 years has made endoscopic repair the preferred surgical modality for those instances in which operative repair is warranted.

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CHAPTER FIFTY-FIVE

Endoscopic Dacryocystorhinostomy

Erik Kent Weitzel

Peter-John Wormald

Key Points

- Chronic epiphora should be investigated with a dacryocystogram and possibly a scintillogram prior to surgery to localize the site of obstruction to ensure that it is amenable to dacryocystorhinostomy.
- Although anatomic obstructions of the lacrimal system are associated with excellent surgical outcomes, functional obstructions have less impressive responses to surgery. It is important to differentiate between these two types of obstruction to determine a patient's prognosis.
- The superior edge of the lacrimal sac is located well above the insertion of the middle turbinate. Surgical outcomes are improved when the entire sac is marsupialized.
- The primary surgical goal is to lay the marsupialized lacrimal sac flat without tension in direct contact with surrounding mucosa for primary intention healing. This concept allows outcomes of endonasal dacryocystorhinostomy to equal those of the external procedure.
- Advantages of endonasal over external dacryocystorhinostomy include the lack of an incision and no disruption of the lacrimal pump mechanism.

Endoscopic dacryocystorhinostomy (DCR) was first described in the otolaryngology literature by McDonogh[1] in 1989. Over the ensuing years, there has been a steady improvement in outcomes owing to advances in surgical technique, instrumentation, and comprehension of the anatomy. Specifically, once the superior extent of the lacrimal sac was recognized to extend significantly above the middle turbinate, surgical outcomes improved.[2] Today's endoscopic DCR is a reliable and effective technique that is comparable to external DCR in outcome measures.[3-6] In 2007, endoscopic DCR was reported to be economically superior to the external technique.[7]

Pathophysiology

Obstructions of the lacrimal apparatus can occur anywhere along its course. DCR surgically bypasses the most distal portion of the lacrimal apparatus, creating a new outflow in the lateral wall of the nasal cavity instead of below the inferior turbinate. Thus, DCR is specifically designed to manage obstructions of the lacrimal sac and duct. It is important to note that DCR is not capable of reliably managing obstructions within the lacrimal apparatus proximal to and including the common canaliculus (Fig. 55-1). In selected cases, a stenosis of the common canaliculus immediately proximal to its entry into the lacrimal sac can be managed by temporary stenting with O'Donoghue tubes.

E. Weitzel has no financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the subject of this paper. P-J. Wormald has a financial interest/arrangement with Medtronic Xomed for royalties received from design of surgical instruments.

There are two principal categories of lacrimal obstruction, anatomic and functional. Anatomic obstructions are more common than functional obstructions, the approximate rates being 70% and 30% respectively.[5] Anatomic obstructions are complete blockages most commonly noted between the lacrimal sac and nasal cavity. Functional obstructions are caused by either critical narrowings within the lacrimal system that delay normal lacrimal flow or a failure of the proximal pumping mechanism. Both anatomic and functional obstructions may be managed with endoscopic DCR; however, surgery of anatomic obstructions is noted to have superior outcome.

Evaluation

The clinical evaluation of the patient presenting for DCR excludes other causes of epiphora, including entropion, ectropion, lid malposition, punctal abnormalities, and blepharitis. The discovery of reflux of purulent material from the lacrimal puncta during medial canthal palpation indicates obstruction of the nasolacrimal system that is amenable to DCR. Probing of the lacrimal system with a Bowman's lacrimal probe adds a more detailed clinical picture to the level of blockage. A "hard stop" implies that the probe has impacted against the lacrimal bone, suggesting a patent lacrimal system up to the lacrimal sac. A "soft stop" implies that distal progress of the probe is impeded by soft tissue, suggesting either stenosis of the common canaliculus or a tight common canaliculus-sac junction. Further information is gleaned by syringing of the lacrimal apparatus. A 25-gauge blunt lacrimal needle is inserted into the inferior puncta, and saline is gently flushed. The taste of saline confirms a patent system, although the test is not diagnostic because the pressures developed during the test are much higher than normal

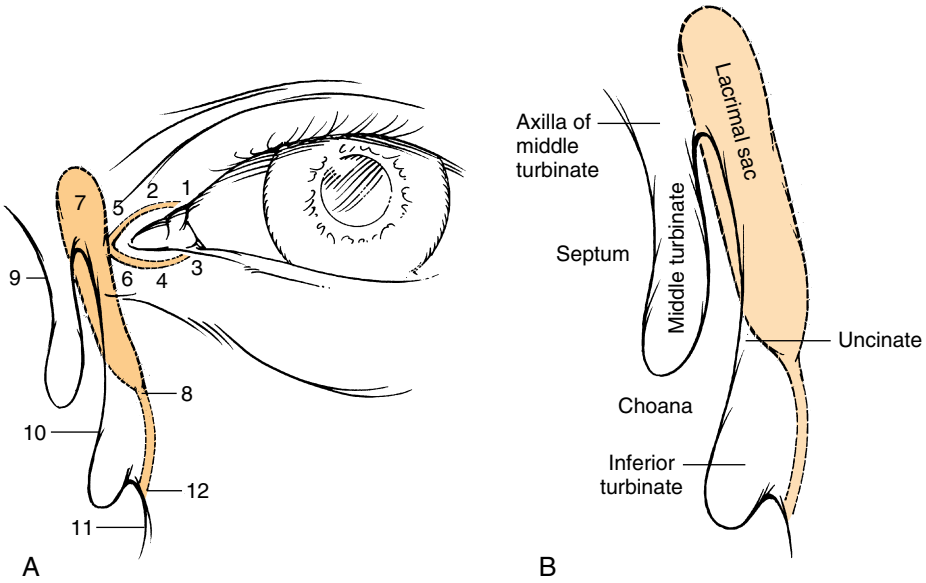

Figure 55-1. **A,** Anatomy of the left lacrimal apparatus: 1, superior punctum; 2, superior canaliculus; 3, inferior punctum; 4, inferior canaliculus; 5, medial canthal ligament; 6, common canaliculus; 7, lacrimal sac; 8, lacrimal duct; 9, middle turbinate; 10, lacrimal bone; 11, inferior turbinate; 12, Hasner's valve. **B,** Position of lacrimal sac as seen during endonasal visualization. The lacrimal sac is located under mucosa and the frontal process of the maxilla. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

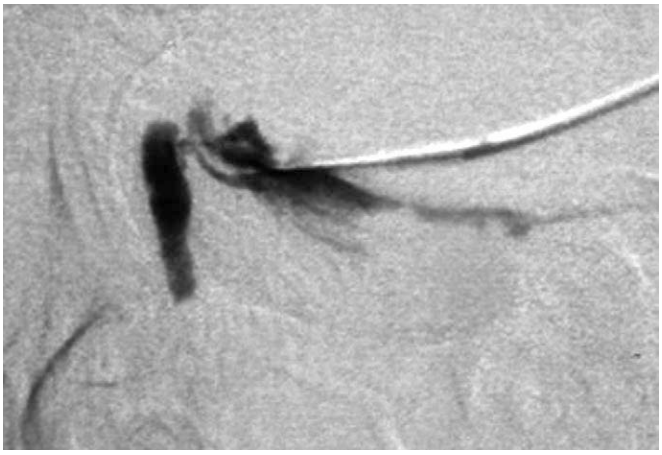

Figure 55-2. Anatomic obstruction. This left-sided dacryocystogram shows dye failing to penetrate past the lacrimal sac/duct junction.

and thus cannot identify functional constrictions within the system. An anatomically blocked system causes reflux through the superior punctum during irrigation. More proximal canalicular obstructions can cause reflux out of the punctum being injected.

Radiologic evaluation of lacrimal obstructions begins with the dacryocystogram (DCG). Because it, like saline irrigation, causes elevated pressures within the lacrimal system, this study is capable of diagnosing only anatomic obstructions (Fig. 55-2). Failure of DCG to identify a blockage in a symptomatic patient necessitates lacrimal scintilligraphy. Unlike DCG, scintilligraphy is a physiologic test of the lacrimal system; thus functional obstructions cause delays in the flow of radioisotopes from the conjunctiva into the nasal cavity over the 30-minute duration of the test. If isotope delay is detected in the lacrimal sac during the test, a narrowed segment is more likely than a failure of the lacrimal pump mechanism (Fig. 55-3). However, if the isotope does not penetrate the lacrimal system, a pump failure is then more likely. Studies have shown that outcome of DCR performed for anatomic obstructions is superior to that of DCR done for functional obstructions.[5] The ability to confirm an obstruction with scintilligraphy and to differentiate anatomic from functional obstruction with DCG allows the surgeon to better prepare the patient for the prognosis of the procedure.

Surgical Technique

(Video clip available on website.)

Nasal preparation is performed with both pledget-applied vasoconstrictor and lateral nasal wall injection of 2% lidocaine with 1:80,000 adrenaline. The injection is performed in two places: superior to the axilla and well anterior to the uncinate process. If a septoplasty must be performed, the septum is likewise injected. Endoscopic septoplasty is performed in 48% of cases,[8,9] because any narrowing of the anterior nasal cavity increases the complexity of the procedure dramatically. Generally, the septoplasty is very limited and specifically addresses the most anterior and superior portion of the bony septum. This area is checked for adequacy by gentle medialization of the septal mucosa to ascertain mobility in the region medial and anterior to the axilla (Fig. 55-4).

A 30-degree scope angled superolaterally is used during the entire procedure to improve visualization around the frontal process of the maxilla. The posteriorly based DCR flap is created with the underlying lacrimal sac in mind. Because approximately half of the sac extends above and posterior to the insertion of the middle turbinate, the superior incision for the flap is created 5 mm posterior and 10 mm superior to the axilla (Fig. 55-5). The flap is brought 10 mm anterior to the middle turbinate, because a shorter flap would limit the ability to marsupialize the lacrimal sac fully. The inferior incision is created at the insertion of the inferior turbinate about two thirds of the way down the middle turbinate.

A suction Freer elevator is used to establish a subperiosteal plane along the incisions onto the frontal process of the maxilla. The flap should be developed over the broadest possible area and mobilized over the frontal process of the maxilla until the lacrimal bone is identified. The easiest place to identify the lacrimal bone is in the region directly adjacent to the inferior horizontal incision just above the inferior turbinate. The junction of the hard bone of the frontal process of the maxilla and the soft thin lacrimal bone is a critical landmark and must be identified in all cases. Posteriorly, the flap is elevated past the lacrimal bone and just onto the uncinate process. Superiorly the flap elevation is carried well on to the insertion of the middle turbinate (Fig. 55-6).

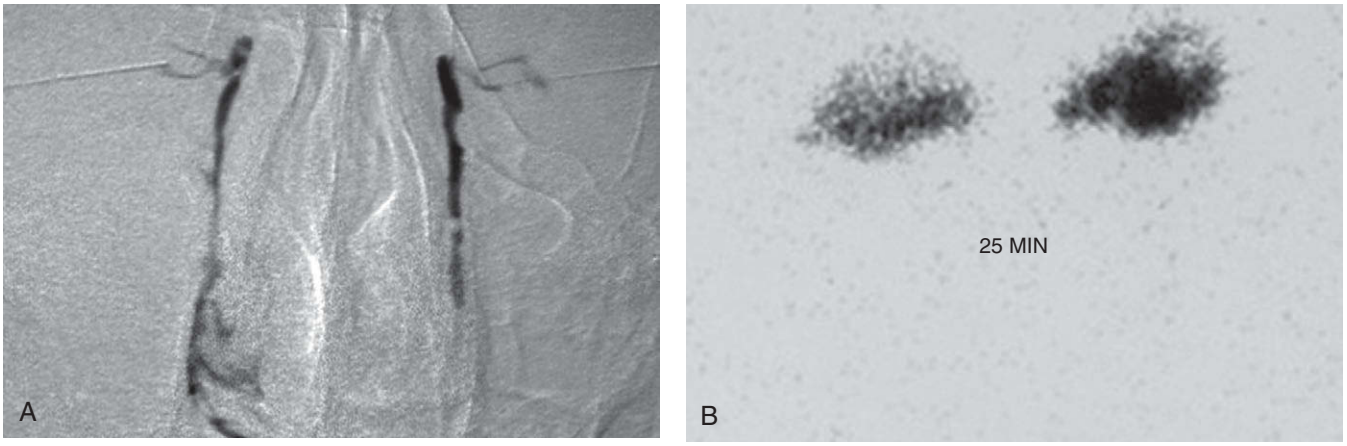

Figure 55-3. Functional obstruction. Dye penetrates the nasal cavity on the right-sided dacryocystogram (**A**), but after 25 minutes, scintilligraphy fails to show any penetration (**B**).

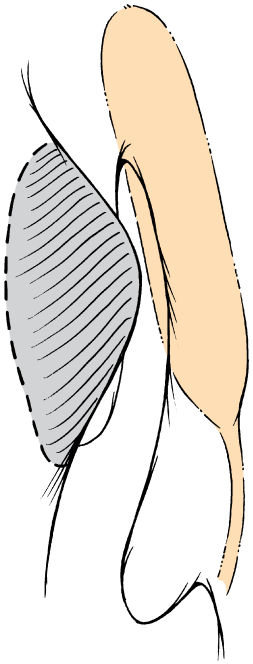

Figure 55-4. High endoscopic septoplasty. Ideal area of bone removal for dacryocystorhinostomy (DCR) is indicated by the *dashed line*. This subsequently pliable region of septum will be a potential space to give additional freedom of endoscope movement. All endonasal DCRs require a septoplasty if the axilla is not completely visualized. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

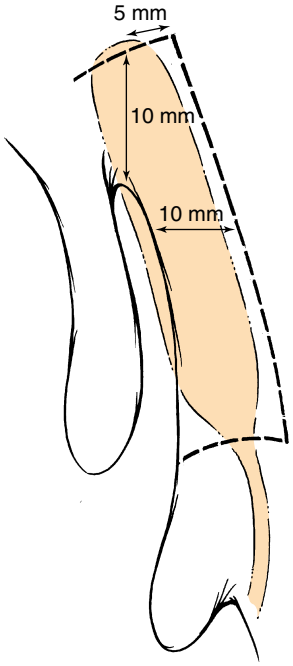

Figure 55-5. Detail of dacryocystorhinostomy flap with measurements. Superior margin of the flap is 5 mm posterior to the insertion of the middle turbinate and 10 mm above the axilla. The inferior limit of the flap is 10 mm anterior to the uncinate and just at the superior margin of the inferior turbinate. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

When completed, the posteriorly based DCR flap is pedicled inferiorly off the superior aspect of the inferior turbinate and insertion of the uncinate. In the midportion of the flap, the pedicle is rather weakly attached to the uncinate bone, and tears in this portion of the flap may occur.

A round knife (from the ear instrument set) is used to identify the frontal process–lacrimal bone junction and to flake off the lacrimal bone. This region is difficult to see if a 0-degree scope is used; this maneuver exposes the posteroinferior aspect of the lacrimal sac and adjacent nasolacrimal duct. Next, a forward-biting Hajek-Koffler punch is used to remove the frontal process of the maxilla overlying the anteroinferior aspect of the lacrimal sac. After each bite the surgeon opens the punch to release the bone before closing the punch and carefully removing the bone; this maneuver prevents the lacrimal sac that may be adherent to the medial side of this bone from being torn, as it would if the punch were simply closed and the bone removed. As this bone removal continues superiorly, the bone thickens and it becomes increasingly difficult for the Hajek-Koffler punch to grip the bone. The completion of this task requires drilling, for example with a 25-degree angled DCR diamond bur (Medtronics ENT, Jacksonville, FL). The bur is used to thin the remaining visible bone within the limits of the DCR flap, avoiding the bone-sac junction. Once this bone is thin, the bone-sac junction is addressed, with care taken to ensure that the bur does not slip under the junction and thereby place excessive pressure on the sac wall.

As the bone removal continues to the edges of the mucosal flap incisions, the lacrimal sac begins to "stand proud" of the lateral nasal wall, so that when it is opened it will lie flat on the lateral nasal wall. Effectively the sac is marsupialized into the lateral nasal wall. As the bone is removed over the posterolateral region of the lacrimal sac, the

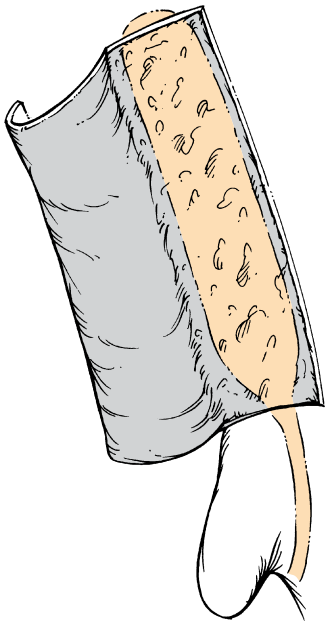

Figure 55-6. Mucosal flap elevated off the frontal process of the maxilla and rolled over the middle turbinate. The flap must be aggressively mobilized off the axilla of the middle turbinate to allow adequate superior and posterior bony removal. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

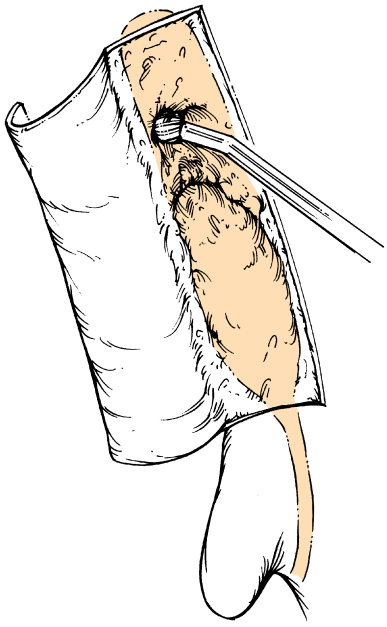

Figure 55-7. Bony work. A bone punch is used to remove frontal process of maxilla off the lacrimal sac. Next a diamond bur is used to saucerize remaining visible bone to the margins of the dacryocystorhinostomy flap. Finally, the bone overlying the agger nasi cell is removed until the cell's mucosa can be marsupialized. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

mucosa of the agger nasi cell is exposed. The bone between the anterior aspect of the agger nasi cell and the lacrimal sac forms an inverted pyramid and must be carefully removed to establish complete exposure of the lacrimal sac. A sickle knife is used to open the agger nasi mucosa, thus creating the posterior mucosa to which the lacrimal sac will approximate (Fig. 55-7).

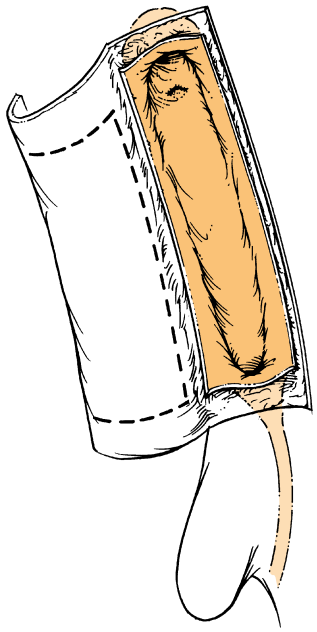

Figure 55-8. The lacrimal sac is open and laid out flat on the lateral wall of the nose. The dacryocystorhinostomy flap is then cut (indicated by *dashed lines*) to cover any exposed bone. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

When bony work is completed, the lacrimal puncta are inspected and are dilated if too small to accommodate a lacrimal probe. The sinus endoscope provides adequate lighting and magnification to assist with this part of the procedure. An assistant holds the endoscope while the primary surgeon passes a Bowman's lacrimal probe along the inferior canaliculus and into the lacrimal sac. Passing the lacrimal probe to the assistant, the surgeon then identifies the metal of the lacrimal probe visible within the translucent sac wall. If the probe is not creating a sharp-pointed projection, but instead is causing a more generalized movement of the sac, the probe has not yet emerged from the common canaliculus and requires further manipulation until its point is clearly seen within the sac. A spear knife (Medtronics ENT) is then used to cut down on the lacrimal probe and open the sac superiorly and inferiorly with a rotating cutting movement. A lacrimal mini-sickle knife (Medtronics ENT) is used to make the superior and inferior flap cuts in the anterior lacrimal sac. These cuts allow the anterior lacrimal sac to be rolled out over the frontal process of the maxilla, approaching the anterior vertical mucosal incision. The posterior cuts are made with a microscissors in the most superior and inferior aspects of the sac again, allowing the posterior sac to be rolled posteriorly, resulting in a complete marsupialization.

The mucosal flap is then positioned to evaluate where it needs to be cut to create flaps to ensure that approximation of the nasal mucosa to the lacrimal mucosal occurs. Usually a superior flap is required to cover the exposed bone above the lacrimal sac, and occasionally an inferior flap is required to cover bone. The middle portion of the flap is removed until the posterior aspect of the flap approximates the posterior edge of the lacrimal sac. The flaps are then positioned with a ball probe (Fig. 55-8).

The common canaliculus should be visible in the lateral sac wall in every case and is easily located by placement of a lacrimal probe back through the inferior canaliculus. Stenting the system during recovery is now considered. Lacrimal tubes do not have to be placed if the passage of the lacrimal probe was without resistance through the canaliculus and the common canaliculus valve of Rosenmüller. However, if there is any doubt about the possibility of common canaliculus tightness, then stents such as O'Donoghue tubes (BD Visitec, Bidford-Upon-Avon, UK) are placed through the superior and inferior canaliculi and brought out of the common canaliculus. This is done in order to

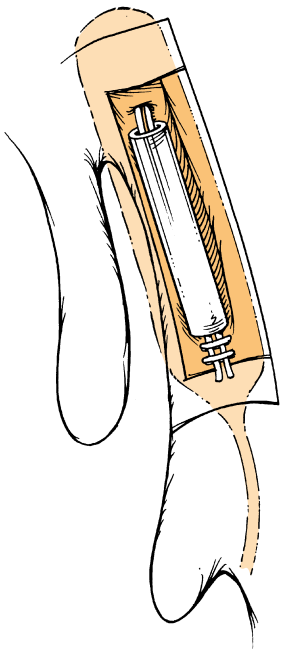

Figure 55-9. Close-up view of completed dacryocystorhinostomy (DCR). O'Donoghue tubes stent open the common canaliculus. The marsupialized lacrimal sac is in direct approximation to the cut margins of the DCR flap. No bone is left exposed, and no force is required to keep the sac in an open position. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

dilate the common canaliculus and treat any functional obstruction of the proximal lacrimal system. The tubes are not placed to keep the sac open; the sac should lie open without the stenting action of the tubes. A 1.5-cm circular piece of gelatin sponge (Gelfoam) is loaded on the O'Donoghue tubes, followed by a 1-cm segment of 4-mm silicone tubing. The tubing is used to push the gelatin sponge into the lacrimal sac. A loop of tubing is pulled in the medial canthus to prevent "cheese-wiring" of the puncta. Two titanium Liga clips are crimped below the silicone tubing, and the tubes are cut just below these clips (Fig. 55-9). The gelatin sponge is raised out of the lacrimal sac to allow inspection of the flaps to ensure that they remain fully rolled out and that the nasal mucosal flaps do not cover any part of the lacrimal sac.

Outcomes

A number of series have shown that 90% to 95% of patients are asymptomatic after a DCR regardless of the type of approach (endonasal or external).[3-5,10-14] Subgroup analyses in these studies have shown that success with DCR is related to the type of obstruction. When Tsirbas and Wormald[6] evaluated outcomes with endonasal DCR, regardless of obstruction type, they noted a 95% rate of lacrimal sac patency, as indicated by clear flow of fluorescein placed in the conjunctiva. However, in terms of symptom control, 95% of anatomic obstructions became asymptomatic, whereas only 81% of patients with functional obstructions had complete relief of symptoms. The higher rate of symptomatic failures in the functional obstruction group was thought to be due to tear collection by the eyelids off the globe, which is not addressed by DCR. It is important to note that despite the diminished number of asymptomatic patients within the functional obstruction group, the patients who did not meet the criteria for success (asymptomatic) still enjoyed an appreciable amount of improvement.[8,9]

Revision Endoscopic Dacryocystorhinostomy

The principles of revision DCR are similar to those of primary DCR. The most important factor that determines the success of revision surgery is the size of the lacrimal sac. Preoperative DCG should be obtained for all patients who have undergone prior DCR (either external or endoscopic) to evaluate the size of the lacrimal sac. If the sac is of normal size, then the success rate of the procedure is similar to that of a primary procedure. However, if there is scarring and cicatrization of the sac, the success rate is lower, because even with full sac exposure only a small amount of lacrimal mucosa can be marsupialized. This leads to a higher risk of repeated scarring and stenosis. Analysis of outcomes shows that revision surgery has very acceptable rates of success (89% success with multiple attempts).[8,9] In cases in which there is significant scarring and stenosis of the lacrimal sac, the agger nasi mucosa has been used as a free graft to create functional mucosa surrounding the common canaliculus–sac junction.

Complications

Theoretical complications of endonasal DCR are similar to those for endoscopic sinus surgery. The most common complication is epistaxis, occurring in 2% of cases. All cases of epistaxis in a large series were managed solely with nasal packing.[8,9] Other possible complications are postoperative frontal or maxillary sinusitis from damage to the drainage pathways, orbital penetration with damage of the ocular muscles, and skull base penetration with subsequent cerebrospinal fluid leak. All significant complications occurring as a result of an endonasal approach are due to a surgeon's inexperience with the endoscopic surgical anatomy of the nose and have been reported only in series not involving otolaryngologists.[6,15-19] It is for this reason that an oculoplastic surgeon and an endoscopic otolaryngologist should work together as a team so that all aspects of this technique are mastered quickly with minimal associated learning morbidity.

Conclusions

Endonasal DCR is a highly evolved surgical technique with outcomes comparable to those of traditional techniques. Advantages of endonasal DCR include a lack of skin incisions, preservation of the lacrimal pump, cost-effectiveness, and the safety profile. The technique remains useful in revision situations despite multiple previous operations.

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Evaluation and Management of Laryngeal and Pharyngeal Disorders

CHAPTER FIFTY-SIX

Laryngeal and Pharyngeal Function

Gayle Ellen Woodson

Key Points

- The upper aerodigestive tract serves the competing functions of respiration and swallowing.
- The anterior ends or the vocal folds are fixed at the anterior commissure.
- All motion of the vocal folds is caused by muscles that move the arytenoid cartilage.
- The posterior cricoarytenoid muscle is the only muscle that actively opens the larynx.
- The recurrent laryngeal nerve supplies all intrinsic laryngeal muscles except for the cricothyroid muscle.
- The cricothyroid muscle is supplied by the motor branch of the superior laryngeal nerve.
- The internal branch of the superior laryngeal nerve carries sensory information from the larynx.
- Vocal sound is produced by passive vibration of the vocal folds, powered by exhaled air.

The upper aerodigestive tract serves the competing functions of respiration and swallowing. The nose is the primary respiratory orifice, and the mouth is the portal for ingestion of food. Both open into a common cavity, the pharynx. The patency of the upper airway must be actively supported during breathing, yet total and forceful collapse is required to propel food into the esophagus during swallowing. The airway must be protected during a swallow so that ingested food or water does not spill into the trachea. Aspiration of food or foreign material can lead to serious consequences, such as asphyxia or lung infection. In humans, the function of the upper aerodigestive is considerably more complex, owing to the demands of speech as well as to a significant structural difference. In infants and in all nonhuman mammals, the pharynx is functionally compartmentalized into separate passages for breathing and alimentation. The epiglottis interdigitates with the uvula to form a respiratory channel from the nose into the larynx and two lateral pathways from the mouth to the esophagus through the pyriform sinuses.[1] During postnatal development in humans, enlargement of the cranium with flexion of the base of the skull results in a downward displacement of the larynx. This displacement elongates the pharynx and distracts the uvula and epiglottis so that they are no longer in contact. The result is a common pharyngeal cavity for breathing and swallowing (Fig. 56-1).[2,3] The larynx begins its descent at the age of about 18 to 24 months. There are two positive outcomes. Vocal power is greater because of increased resonance, and articulatory diversity is expanded.[4]

This complicated and potentially hazardous configuration of the upper airway results from embryology and reflects evolution. The lower respiratory tract has evolved as an offshoot of the digestive tract, first appearing in the lungfish as a simple muscle sphincter to protect the lungs from water.[5] Consequently, during embryologic development, the foregut is the common origin of the larynx, trachea, and esophagus.

Normal function of the larynx and pharynx requires precise timing and coordination of competing functions of this system. Thus, function is easily disrupted by structural or neurologic pathology. Further, the treatment of any disease or disorder of this region may have an impact on more than one function. For example, surgery to improve the glottic airway can impair the voice or lead to aspiration during swallowing. It is therefore imperative for otolaryngologists to understand the function of the upper aerodigestive tract. This chapter focuses on the functions of breathing and speech; swallowing is addressed in another chapter of this book.

Laryngeal Motion

Applied Anatomy

In the illustrations of many textbooks, the membranous vocal folds are depicted as moving solely in the axial plane, with rotational motion similar to that of a windshield washer. Details of motion of the posterior, cartilaginous portions of the larynx have been largely ignored. The reason is that early concepts of motion were based on observing laryngeal motion with a mirror, and then recording the observations with two-dimensional freehand drawings. However, with the advent of flexible endoscopy, stroboscopy, videorecording, and computerized imaging, it has become clear that laryngeal motion is more complex than previously recognized. Vocal folds move in three dimensions and undergo conformational changes in length, shape, and volume (Fig. 56-2).[6] The terms *cadaveric* and *paramedian* have been commonly used to describe the position of paralyzed vocal folds. These terms are inadequate to describe the three-dimensional changes in configuration of the glottis in paralysis.[7] Motion of the larynx is best understood as the net result of the interaction of its component parts.

The laryngeal skeleton consists of the hyoid bone and a series of cartilages. The hyoid bone is a U-shaped structure, open posteriorly, which is suspended from the base of the skull and mandible by muscles and ligaments. The thyroid cartilage, the largest cartilage in the larynx, is suspended from the hyoid bone. The word thyroid means "shield"

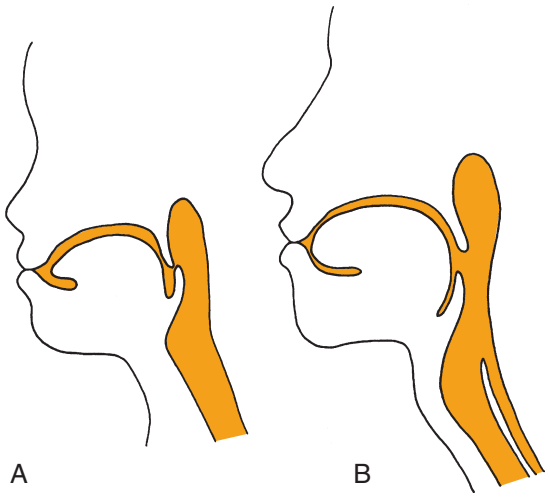

Figure 56-1. Postnatal descent of the larynx. Migration of epiglottis away from the uvula results in loss of pharyngeal compartmentalization for breathing and feeding. **A,** Sagittal view through the head and neck of a neonate. **B,** Sagittal view through an adult head and neck.

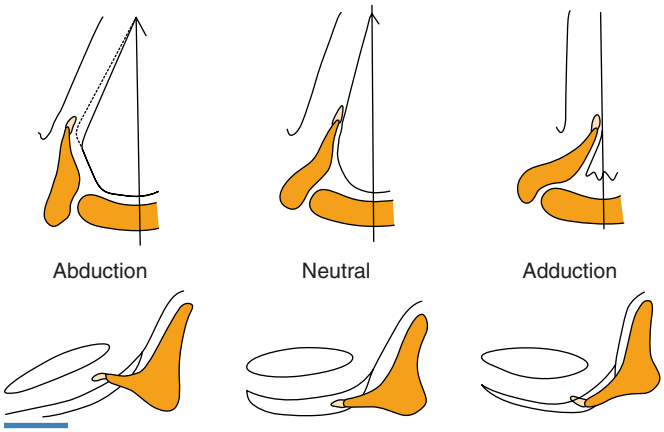

Figure 56-2. Three-dimensional motion of the arytenoid cartilage and vocal fold. *(From Hirano M. Anatomy and behavior of the vocal process. In: Baer T, Sasaki C, Harris K, eds.* Laryngeal Function in Phonation and Respiration. *Boston: College-Hill Press; 1987.)*

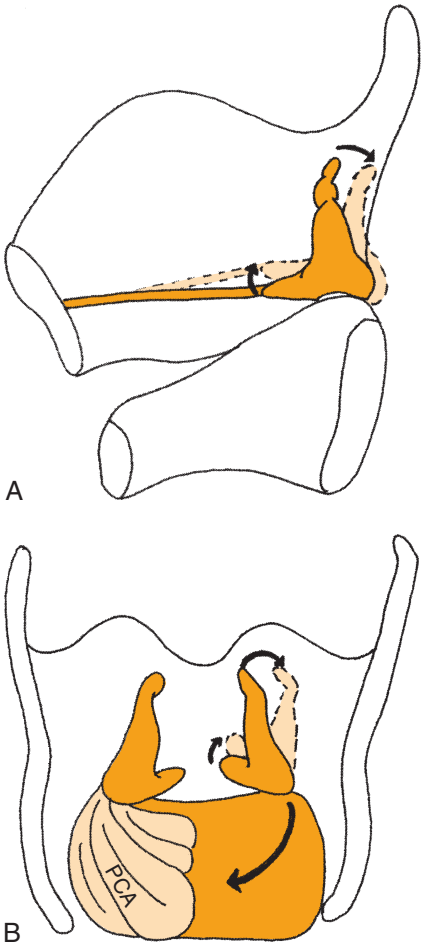

Figure 56-3. Three-dimensional effects of posterior cricoarytenoid muscle contraction. **A,** Sagittal view. **B,** Posterior view.

and this name is appropriate, because the structure is not only shaped like a shield but also provides support and protection for the vocal folds. In the axial plane, the thyroid cartilage is shaped like a V, with two wings that project posteriorly. Like the hyoid bone, the thyroid cartilage is open posteriorly. The vocal folds attach to the anterior inner surface of the thyroid cartilage. The posterior ends of the vocal folds are anchored to the arytenoid cartilages, which are the chief moving parts of the larynx. The arytenoid cartilages sit atop the posterior rim of the cricoid cartilage and articulate via shallow ball-and-socket joints. The cricoid cartilage is the only complete rigid ring within the airway. It is shaped like a signet ring and is broadest posteriorly. Inferiorly, and just lateral to the cricoid joints, the inferior cornua of the thyroid cartilage articulates with the cricoid in two hingelike joints, creating a visor-like, or "bucket handle" structure, with motion that controls the space between the anterior rims of the thyroid and cricoid cartilages.[8]

The epiglottic cartilage is a leaf-shaped structure that is attached inferiorly to the anterior interior surface of the thyroid cartilage. The upper margin is free and projects into the hypopharynx above the glottic opening. The mucosa covering the epiglottis spreads laterally on both sides and is continuous with the mucosa over the arytenoid, to create the aryepiglottic folds, the lateral borders of the supraglottis. There are some muscle fibers within each aryepiglottic fold that contribute to constriction of the supraglottis. Two small sesamoid cartilages, the corniculate and cuneiform cartilages, sit just above each arytenoid within the aryepiglottic fold.

Most intrinsic laryngeal muscles connect the arytenoid cartilages to either the cricoid or thyroid cartilages. These include the thyroarytenoid muscle, the lateral cricothyroid muscle, the interarytenoid muscle, which act to adduct the vocal folds, and the posterior cricoarytenoid muscle, which is the only active abductor of the larynx. As mentioned above, the arytenoid cartilages are the chief moving parts of the larynx. The membranous vocal folds are suspended between the thyroid cartilage and the arytenoids, and the position of each membranous vocal fold is determined by the motion of the arytenoid cartilage. The arytenoid rotates upward and outward to open the larynx, and rotates inward to close it. Contraction of the posterior cricoarytenoid muscle pulls the muscular process of the arytenoid posteriorly and caudally. The structure of the cricoarytenoid joint prevents the entire arytenoid from being pulled along this vector. Instead, the arytenoid rotates, displacing the vocal process upward and laterally, abducting the vocal fold (Fig. 56-3).[9] Conversely, the lateral cricoarytenoid muscle pulls the muscular process of the arytenoid anteriorly and caudally, which rotates the arytenoid, moving the vocal process medially and adducting the vocal fold. The interarytenoid muscles pull the arytenoid cartilages together. The thyroarytenoid muscles exert some adductor force, but their major action is to shorten or tense the vocal fold and increase its cross-sectional area (Fig. 56-4).

In addition to the diverse force vectors of individual laryngeal muscles, there is also segmental compartmentalization within muscles, increasing the possibilities for fine control. For example, the human posterior cricoarytenoid muscle is divided into two compartments. These are supplied by separate nerve branches, differ in fiber type, and

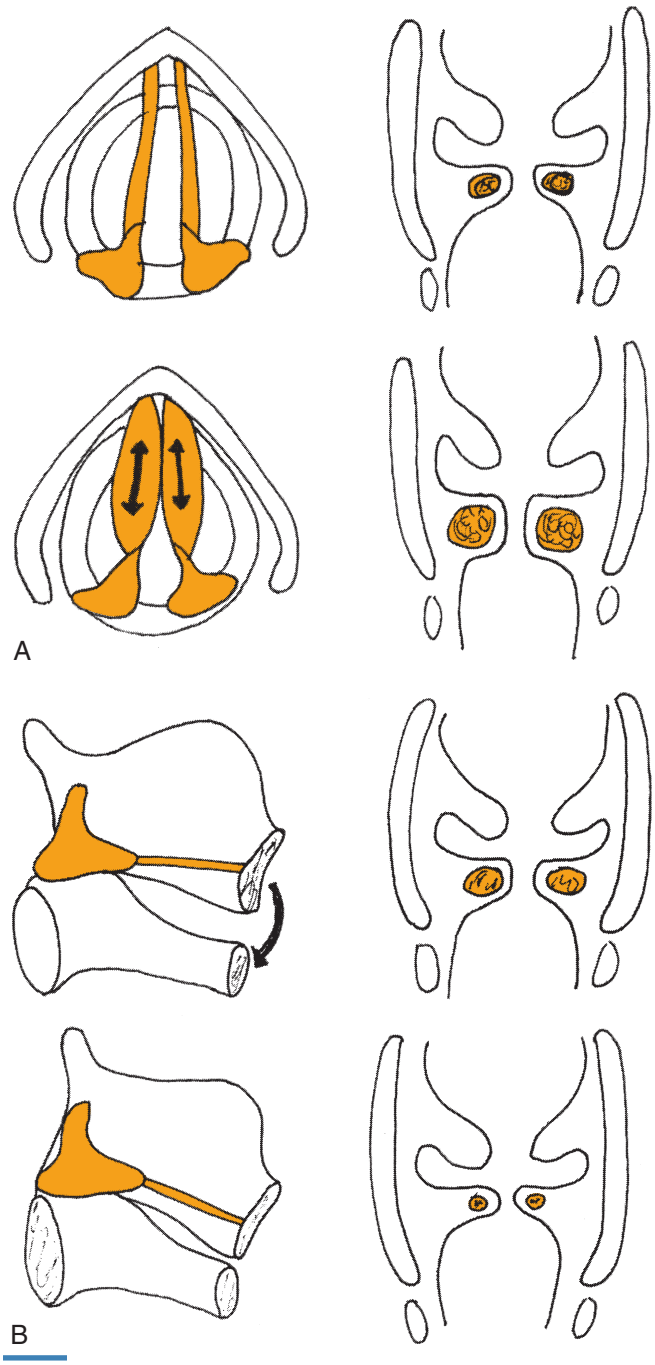

Figure 56-4. Effects of **(A)** thyroarytenoid and **(B)** cricothyroid muscle contraction on the thickness of the vocal fold.

insert on opposing sides of the muscular process (Fig. 56-5).[9,10,11] The human thyroarytenoid muscle is also compartmentalized: It has long been regarded to have a separate medial compartment, the "vocalis."

In contrast to other intrinsic laryngeal muscles, the cricothyroid muscle does not insert on the arytenoid cartilage and therefore has no direct action on arytenoid motion. Instead, the cricothyroid muscle connects the anterior edges of the thyroid and cricoid cartilages. Contraction of this muscle pulls the two cartilages closer together, which increases the distance between the anterior commissure and the cricoid. The result is stretching of the vocal fold, increasing its length and tension. Because both vocal folds insert on the anterior commissure, contraction of either cricothyroid muscle affects both ipsilateral and contralateral vocal folds. Contraction of both right and left cricothyroid muscles results in maximal anterior traction.[8]

Figure 56-5. Compartmentalization of the human posterior cricoarytenoid muscle. Posterior view of a cadaver larynx.

Muscles that are extrinsic to, but connect with, the larynx can also affect glottic function by exerting traction on the laryngeal cartilages. The sternohyoid, thyrohyoid, and omohyoid muscles, innervated by the ansa cervicalis, exert caudal traction on the larynx. This action, as well as downward traction on the trachea during inspiration, causes abduction of the vocal folds.[12,13] Muscles that exert a cephalad force include the geniohyoid, anterior belly of the digastric, mylohyoid, and stylohyoid muscles. In patients with hyperfunctional dysphonia, excess activity can usually be palpated in the extrinsic laryngeal muscles.

The nerve supply to the larynx is via the superior laryngeal nerves and the recurrent laryngeal nerves, both of which are branches of the vagus nerves. The superior laryngeal nerve leaves the vagus nerve high in the neck, at the nodose ganglion. Its internal branch exits the lateral thyrohyoid membrane and carries sensory afferent fiber from the supraglottis and vocal folds, whereas the external branch of the superior laryngeal nerve supplies motor fibers to the cricothyroid muscle. All other intrinsic laryngeal muscles are supplied by the recurrent laryngeal nerves, which leave the vagus nerve in the chest and then travel back up to enter the larynx near the cricothyroid joint. The course of the recurrent laryngeal nerve is much longer on the left side, because it runs under the ligamentum arteriosum, a vestigial remnant of embryonic connection between the aorta and pulmonary artery. On the right side, the recurrent nerve travels only as far caudally as the subclavian artery before returning cephalad.

The laryngeal mucosa is richly supplied with sensory receptors. In fact, there are many more sensory receptors in the larynx than in the lungs, which have a vastly larger area of surface mucosa. Laryngeal sensory receptors respond to a variety of stimuli, including mechanical, thermal, chemical, and taste. These receptors provide important input for protection of the larynx and also information on the movement of air in and out of the lungs. The receptors provide the afferent limbs of a variety of reflexes.

Laryngeal Function in Breathing

The primary and most primitive function of the larynx is to protect the lower airway. In evolution, the larynx first appeared as a sphincter to prevent the ingress of water into the airway of the lungfish.[5] Subsequently, dilator muscles evolved to permit active opening of the larynx. In more evolved animals, the larynx is not just an open or shut valve but, rather, a variable resistor, capable of regulating airflow. Other laryngeal functions are the Valsalva maneuver and coughing. The larynx

is also a sensory organ, providing information about airway function and the purity of inhaled air and serving in the afferent limb of many reflexes.

Protection

When the larynx is mechanically stimulated, it closes abruptly, and respiration ceases. Apnea can also occur in response to such diverse chemical agents as ammonia, phenyl diguanide, and cigarette smoke. These are appropriate and beneficial responses that prevent the entry of foreign matter into the lower airway, although strong laryngeal stimulation may result in responses that appear to be maladaptive, such as laryngospasm and prolonged bronchoconstriction.[14] These reflexes may be produced in experimental animals by electrical stimulation of the superior laryngeal nerve and probably represent an oversaturation of pathways that serve a useful function at lower levels of input.

The larynx occupies a protected position in the body, and it is rarely subject to direct stimulation. Therefore, laryngospasm and apnea are not everyday occurrences. Severe laryngeal reflexes are most often encountered in patients in the operating room in response to direct stimulation during intubation, endoscopy, or extubation. These reflexes most likely occur in patients during light anesthesia and in those who are well oxygenated.

Recurrent paroxysmal laryngospasm is occasionally encountered in clinical practice. In some patients, it is caused by gastroesophageal reflux, which responds to acid-suppressing medication. In other patients, the pathophysiology appears to be a hypersensitive laryngeal closure reflex, because such patients report some triggering event such as eating or inhaling steam or odors. The onset frequently occurs during an upper respiratory infection, but it also can occur after surgical trauma to the recurrent laryngeal nerve. Most often the condition resolves spontaneously within a few months, but it may become a permanent and debilitating problem. The laryngeal closure reflex is particularly sensitive in infants and can be elicited by a stimulus as weak as water. During early infancy, the strength of this reflex increases, then decreases, along a time course similar to that of the incidence of sudden infant death syndrome, suggesting that laryngeal reflexes may play a role in its cause.[15]

Cough

Another important protective reflex involving the larynx is the cough, which ejects mucus and foreign material from the lungs.[16] Cough can be a voluntary action or a reflexive response to stimulation of the larynx or receptors in the lungs. The cough reflex is suppressed during sleep, so that a greater stimulus is required with progressive stages of sleep. During deep sleep, a cough cannot be elicited unless the stimulus first results in arousal to a lighter level of sleep.

The first phase of a cough is inspiratory. The larynx opens widely to permit rapid and deep inhalation. In voluntary cough, the extent of inspiratory effort is varied according to the intended strength of the cough. The second phase is compressive, involving tight closure of the glottis and strong activation of expiratory muscles. The effectiveness of the cough is impaired by glottic incompetence. Finally, the larynx suddenly opens widely, resulting in a sudden and rapid outflow of air, at speeds of as much as 10 L/second. Cough plays an important role in cleaning the tracheobronchial tree and in maintaining patency of the lower airways. Abnormal cough can be a serious clinical problem that interferes with normal daily function and impairs quality of life.

Control of Ventilation

The role of the larynx as an active organ of respiration is not widely recognized. Abduction and adduction of the larynx in phase with respiration has been acknowledged for many years.[17,18] It has been postulated that all respiratory motion of the larynx is passive, resulting from biomechanical coupling of the larynx to the tracheobronchial tree.[12,19] There is some evidence that downward traction on the larynx dilates the glottis.[13] But clinical observations and experimental evidence indicate that the larynx moves actively in respiration and, in fact, plays an important role regulating respiration. The larynx is located at the entrance into the trachea and is capable not only of rapid opening and closure but also of sudden alterations in resistance. Hence, the larynx is better adapted than any other portion of the respiratory tract for regulating airflow. The resistance changes resulting from laryngeal responses to respiratory stimuli, such as negative airway pressure and blood gas changes, have a beneficial effect on ventilation.[20]

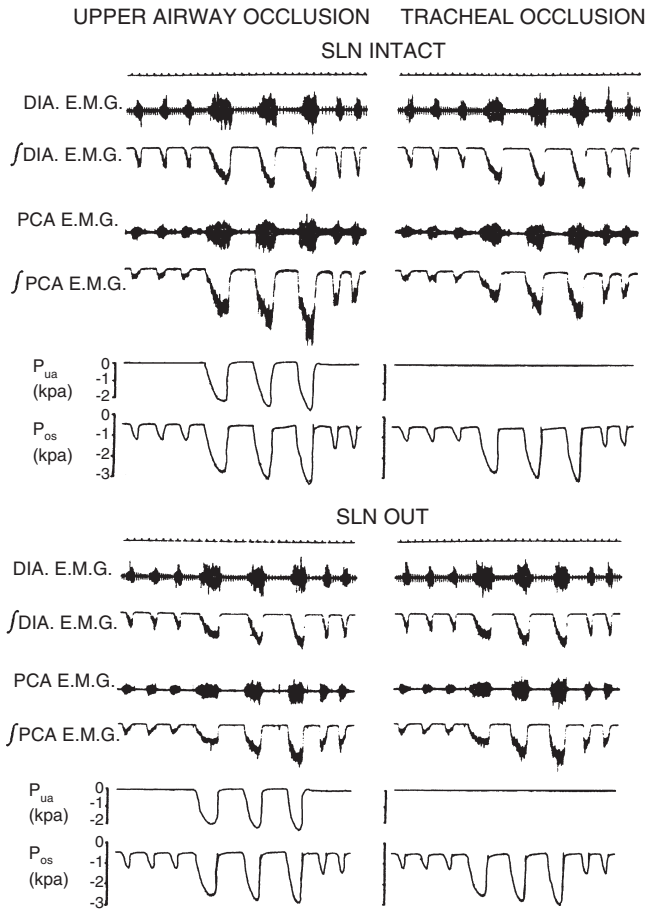

Figure 56-6. Effects of upper airway and tracheal occlusions in an anesthetized dog, before and after a section of the superior laryngeal nerve (SLN). In each panel, the top trace is time in seconds, and the second and third traces are integrated electromyographic activity of the diaphragm (DIA E.M.G.) and posterior cricoarytenoid muscle (PCA E.M.G.). The lower two traces in each panel are pressure in the upper airway (P_{ua}) and esophagus (P_{os}) (intrathoracic pressure). Tracheal occlusion affects only intrathoracic pressure, whereas upper airway occlusion also affects upper airway pressure, which is sensed by the SLN. *(From Sant'Ambrogio FB, Mathew OP, Clark WD, Sant'Ambrogio G. Laryngeal influences on breathing pattern and posterior cricoarytenoid muscle activity.* J Appl Physiol. *1985;58:1298.)*

Widening of the glottis during inspiration is a primary action of ventilation that ceases only during deep anesthesia or sleep. The posterior cricoarytenoid muscle (PCA), the only active dilator of the larynx, begins to contract with each inspiration before activation of the diaphragm.[5,21,22]

The level of PCA activity, and hence laryngeal movement with breathing, varies. Laryngeal motion may be imperceptible during unlabored, quiet breathing. With increasing respiratory drive, peak inspiratory PCA activity increases proportionately with diaphragmatic activity. There are important differences between PCA activity and diaphragmatic behavior (Fig. 56-6). When the upper airway is partially occluded, inspiration generates negative airway pressure, which is a potent stimulus to the PCA and the several other upper airway muscles that dilate the upper airway.[20,23] In contrast, the diaphragm responds by actually decreasing inspiratory force and by increasing the duration of inspiration.[14] This response occurs because, during partial airway obstruction, the PCA and the diaphragm have opposing effects on

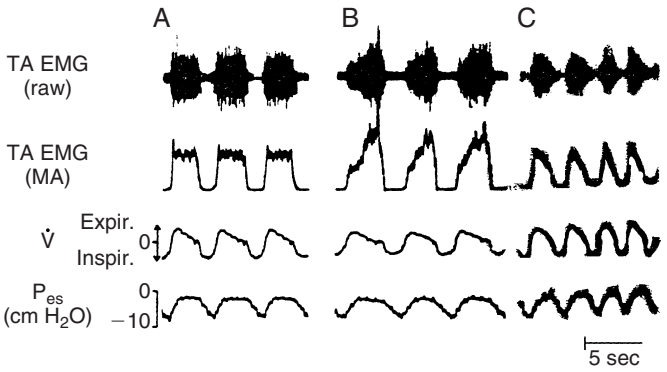

Figure 56-7. Laryngeal adductor activity during breathing as shown on electromyography. **A,** Plateau in thyroarytenoid muscle activity (TA EMG) correlates with decreasing flow. **B,** Progressive increase in TA activity correlates with flattened airflow trace and longer exhalation. **C,** Decreasing activity during expiration correlates with shorter exhalation. Expir., expiration; Inspir., inspiration; MA, averaged; P_{es}, esophageal (intrathoracic) pressure; $\dot{V}$, airflow. *(From Kuna ST, Insalaco G, Woodson GE. Thyroarytenoid muscle activity during wakefulness and sleep in normal adults. J Appl Physiol. 1988;63:1332.)*

patency of the lumen. Increasing diaphragmatic force raises the negative pressure, favoring airway collapse. To inspire the same volume, the diaphragm extends the duration of inspiration. PCA contraction dilates the airway, opposing the effects of the diaphragm. During strong respiratory demand, the PCA continues contracting during expiration after the diaphragm has relaxed, thus delaying expiratory adduction and facilitating the outflow of air. During panting, the glottis sustains an abducted posture, ensuring maximal airflow. Because of these physiologic differences, the phrenic nerve is not an ideal choice for reinnervation of the PCA in patients with laryngeal paralysis.

There has been some controversy in the literature as to whether laryngeal adduction during expiration is an active or passive process. Some electromyographic studies have not confirmed any expiratory activity of laryngeal adductor muscles, suggesting that expiratory narrowing of the glottis is passive, a result of relaxation of the PCA.[24,25] Other researchers have documented phasic expiratory activity of laryngeal adductors.[26,27] These conflicting observations have been reconciled by the finding that respiratory activity of laryngeal adductor muscles is much less consistent than that of the PCA. Expiratory adduction of the larynx is either active or passive, depending on breathing strategy. During baseline conditions, such as sleep, laryngeal adductor muscles are silent. During consciousness, expiratory activation of laryngeal adductor muscles is frequently detected, but at highly variable levels. Correlations of laryngeal adductor muscle activity with expiratory airflow, ventilatory pattern, and transglottal resistance suggest that this is an important mechanism for controlling the rate of breathing (Fig. 56-7).[28] Glottic adduction increases expiratory resistance to airflow, prolonging exhalation. During normal breathing conditions, respiratory rate is primarily controlled by variation in the rate of exhalation.[29] Exhalation is slowed by partial contraction of the diaphragm during expiration. Abdominal muscle pushing increases the rate of exhalation, although during tidal breathing under baseline conditions, the larynx appears to be the primary mechanism for controlling the ventilatory pattern.

Laryngeal regulation of breathing is not essential for life, as evidenced by the fact that patients ventilate satisfactorily through a tracheotomy, although the inability to breathe and speak normally through natural orifices has a devastating impact on quality of life. Optimal function of the upper aerodigestive tract requires normal laryngeal function.

Sensory Receptors

The larynx is not only a motor organ. It also is the location of a variety of sensory receptors that exert influences on breathing and cardiovascular function. The larynx is densely supplied with sensory receptors; sensory fibers from the larynx are several times more numerous than those from the lungs. This finding is remarkable when one considers that the internal surface area of the lungs is several square meters, whereas the larynx is a small orifice. Single nerve fiber recordings from the superior laryngeal nerve have identified three major types of laryngeal respiratory receptors: negative pressure, airflow, and "drive."[30] These receptors are activated by the process of breathing and influence the central control of breathing. Airflow receptors actually respond to a decrease in temperature because the larynx is cooled by inspired air. Thus, flow receptors do not respond to air that has been warmed and humidified by the nose. They are activated by air that comes in through the mouth, particularly in cold and dry weather. "Drive" receptors are probably proprioceptors that respond to the respiratory motion of the larynx. Laryngeal sensations of touch and chemical stimuli are not activated during normal breathing conditions, but stimulation can profoundly affect ventilation.

Circulatory Reflexes

Stimulation of the larynx can alter heart rate and blood pressure. During induction of general anesthesia, endotracheal intubation can result in bradycardia. The direct result of experimental laryngeal stimulation on blood pressure is hypertension,[31] although in the clinical situation, the effects of bradycardia or ectopy usually prevail, resulting in hypotension. In patients with obstructive sleep apnea, negative airway pressure may stimulate receptors in the larynx so strongly that cardiac arrhythmias occur. Animal experiments show that the afferent limb is the superior laryngeal nerve because transection of this nerve abolishes cardiovascular responses (Fig. 56-8). The efferent limb for bradycardia is the vagus nerve, and the efferent limb for blood pressure elevation is via sympathetic nerve fibers, but intervening central connections have not been identified.[32]

Pharyngeal Function in Breathing

The upper airway is a conduit with several points wherein the shape and cross-sectional area can be dynamically altered. The pharynx is the largest but most compliant region, and it is susceptible to passive collapse. Maintenance of patency requires the action of striated upper airway muscles in coordination with the activity of respiratory pump muscles.[33] Upper airway muscles also determine whether air is inspired through the nose or the mouth. The anatomy and intrinsic properties of upper airway muscles indicate that they are primarily adapted for nonrespiratory functions but can be used in respiratory tasks. Most of the muscles acting on the pharynx show no respiratory activity during awake, tidal breathing, but they are recruited by increased respiratory drive or upper airway obstruction (Fig. 56-9).[34]

In healthy patients, the nose is the preferred route of breathing, because the relaxed position of the mandible closes the mouth and the relaxed palate occludes the oropharyngeal inlet. Furthermore, the nose warms, humidifies, and filters inspired air. The selection of oral or nasal breathing is performed primarily by the soft palate, a band of moveable soft tissue suspended from the posterior bony palate. Oral breathing requires activation of the levator veli palatine to elevate the soft palate as well as activation of the musculus uvula. Nasal breathing is favored by constriction of the oropharyngeal passage, which is accomplished primarily through activation of the palatoglossal muscles, medialization of the faucial arches, and elevation of the base of tongue. This activity is highest during forced nasal breathing with the mouth open.[35]

Little objective information is available regarding the respiratory function of the pharyngeal constrictors. It is widely assumed that some active tone in these muscles increases the stiffness of these muscles, thereby decreasing the tendency of the pharynx to collapse with the negative pressure generated during inspiration. Conversely, flaccidity of the constrictors is considered to destabilize the airway, promoting collapse, although there are no physical data to support this concept.[5] On the contrary, contraction of the constrictor muscles actively collapses the pharyngeal lumen. Spontaneous activity in the respiratory cycle has been detected in the superior constrictor muscle, but this activity occurs during the expiratory phase and disappears with bronchoconstriction, suggesting that it plays a role in modulating expiratory airflow resistance.[36]

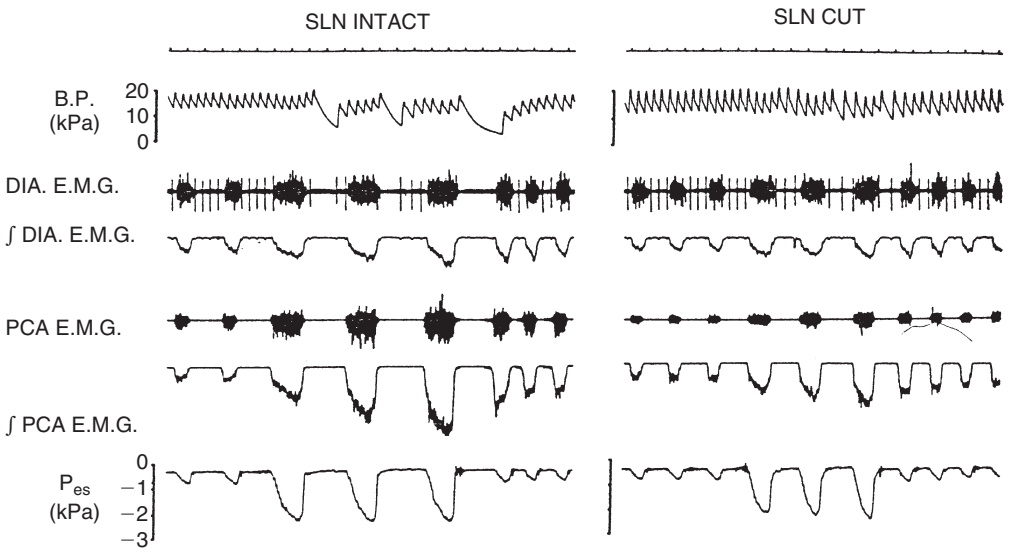

Figure 56-8. The effects of upper airway occlusion on arterial blood (B.P.) pressure in an anesthetized dog before and after transection of the superior laryngeal nerve (SLN). In each panel the top trace marks time in seconds. The third and fifth traces are raw and integrated electromyographic activity of the diaphragm (DIA) and posterior cricoarytenoid muscle (PCA). The bottom trace is intraesophageal pressure (P_{es}) as an indicator of respiratory effort. *(From Sant'Ambrogio FB, Mathew OP, Clark WD, Sant'Ambrogio G. Laryngeal influences on breathing pattern and posterior cricoarytenoid muscle activity.* J Appl Physiol. *1985;58:1298.)*

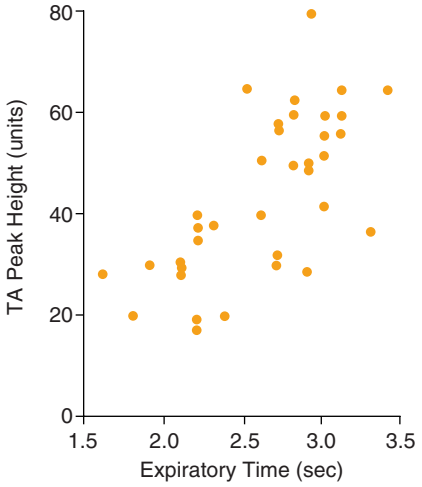

Figure 56-9. The peak electromyography activity of the thyroarytenoid muscle (TA peak height) as a function of expiratory time in an awake human. Correlation coefficient = 0.680. *(From Kuna ST, Insalaco G, Woodson GE. Thyroarytenoid muscle activity during wakefulness and sleep in normal adults.* J Appl Physiol. *1988;63:1332.)*

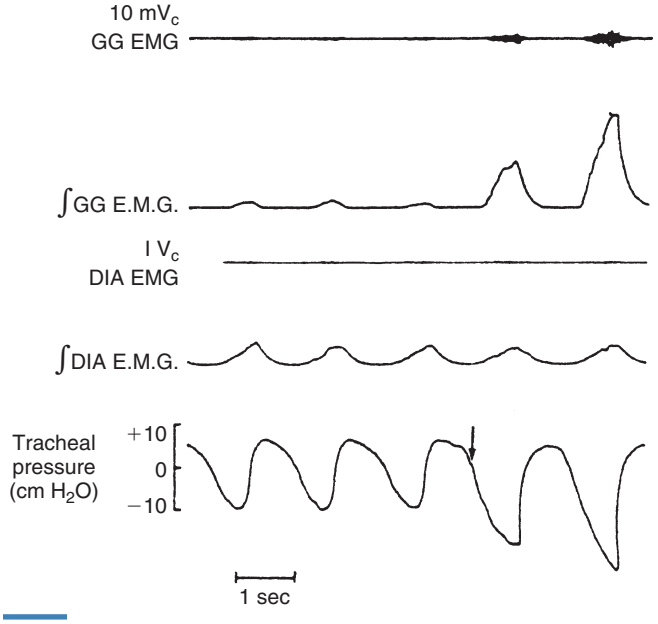

Figure 56-10. The diaphragm (DIA) and genioglossus (GG) muscle responses to nasal occlusion (beginning at *arrow*) in an anesthetized vagotomized rabbit. The upper trace is raw electromyographic activity (EMG) of the genioglossus muscle (GG) in millivolts, and the second trace is integrated GG activity in volts. The third and fourth traces are raw and integrated EMG of the diaphragm (DIA). *(From Mathew OP, Abu-Osba YK, Thach BT. Influence of upper airway pressure changes in respiratory frequency.* J Appl Physiol. *1982;52:483.)*

The dilator muscles of the pharynx are located anteriorly and laterally. The best-studied and probably most important pharyngeal dilator is the genioglossus (GG), a fan-shaped muscle that originates from the anterior mandible and spreads out to insert into the tongue. Although no studies have conclusively established what muscles are responsible for pulling the base of the tongue forward to dilate the airway, evidence strongly supports the role of the GG. In animal experiments, increased electromyographic activity of the GG is associated with a greater capacity of the pharynx to withstand negative collapsing pressure.[37] GG electromyographic activity increases reflexively in response to negative upper airway pressure (Fig. 56-10).[14,23] In humans with obstructive sleep apnea, decreased GG electromyographic activity has been noted during obstructive events, whereas obstruction is relieved with recovery of GG activity.[38]

The hyoid bone supports the hypopharynx. In humans, as in other primates, the hyoid does not articulate with any other skeletal element; rather, it is suspended by muscles and ligaments. Contraction of muscles attached to the hyoid has been shown in animal experiments to increase the size and stability of the upper airway.[39] Muscles attached to the hyoid are also believed to resist the downward traction exerted on the airway by the trachea during inspiration.[35,40]

Function in Speech

Human speech requires coordinated interaction of the mouth, pharynx, larynx, lungs, diaphragm, and abdominal and neck muscles. The three

Box 56-1

Requirements for Phonation

Adequate breath support
Approximation of vocal folds
Favorable vibratory properties
Favorable vocal fold shape
Control of length and tension

fundamental components in the processes are phonation, resonance, and articulation. *Phonation* is the generation of sound by vibration of the vocal folds. *Resonance* is the induction of vibration in the rest of the vocal tract to modulate laryngeal output. *Articulation* is the shaping of the voice into words.

Phonation

The role of the larynx in sound production has been recognized for centuries,[41] although the mechanism of how the larynx generates sound from exhaled air was not clear until the mid-20th century. In 1950, Husson[42] presented the neurochronaxic hypothesis, which held that glottic vibrations were caused by rhythmic impulses in the nerves to the larynx, synchronous with the frequency of the sound produced, so that each vibratory cycle was caused by a separate neural impulse. This hypothesis is physiologically impossible.

In the 1950s von Leden used high-speed motion pictures to document the motion of the vocal folds during vibration and subsequently reported his theory of the mechanism of phonation; now widely accepted, the theory holds that the interaction of aerodynamic forces and the mechanical properties of the laryngeal tissues are responsible for inducing vocal fold vibration and generating vocal sound.[43]

Normal phonation requires that five conditions be satisfied, as listed in Box 56-1. There should be adequate breath support to provide power, and the vibratory edges of the vocal folds should be aligned and separated by an appropriately small gap. The physical properties of the vocal fold should be conducive to vibration, and its three-dimensional contour should be favorable. Finally, a normal voice requires volitional control of glottic length, tension, and shape.

The process of phonation begins with the inhalation of air, and then glottic closure, to position the vocal folds near the midline. A simplified explanation of phonation is that exhalation causes subglottic pressure to increase until the vocal folds are displaced laterally, producing a sudden decrease in subglottic pressure. The forces that contribute to the return of the vocal folds to the midline include this pressure decrease, elastic forces in the vocal fold, and the Bernoulli effect of airflow. When the vocal folds return to the midline, pressure in the trachea builds again, and the cycle is repeated. Vocal fold structure determines whether the resulting vibration is periodic or chaotic.

Actual phonation is more complex than the previous model because the vocal fold is not a homogeneous structure and also because it vibrates in three dimensions.[44] Moreover, the pattern of vibration varies with pitch and vocal register. The "body-cover" concept of phonation is that vibration of the mucosa does not correspond directly to that of the rest of the vocal fold.[45] Instead, the "body" of the vocal fold is relatively static, whereas the wave is propagated in the mucosal "cover." This mucosal wave begins on the inferomedial aspect of the vocal fold and moves rostrally (Fig. 56-11). As the superior edges of the vocal fold begin to separate, the lower edges close, and this temporal relationship is accounted for by the two-mass model proposed by Ishizaka and Flanagan.[46] As the superior edges of the vocal folds separate, airflow through the divergent glottis generates greater negative pressure at the lower edge of the vocal folds, accelerating closure of the inferior glottis. The body-cover theory and the two-mass model are consistent with most of the observed motion during modal phonation (e.g., chest register, in the middle range of pitch), although the mucosal wave decreases at higher pitches and is not visible during falsetto, suggesting that the motions of the mucosa and the underlying tissue become coupled. In this mode, elastic recoil, rather than the Bernoulli effect, is the primary force driving the closing phase of phonation. The closing phase is much shorter, and only the superior edges of the vocal folds make contact. The vibratory characteristics of falsetto have been attributed to increased tension and decreased thickness of the vocal fold. During phonation at low pitches, the vocalis muscle is relaxed so that the "body" of the fold participates in oscillation.

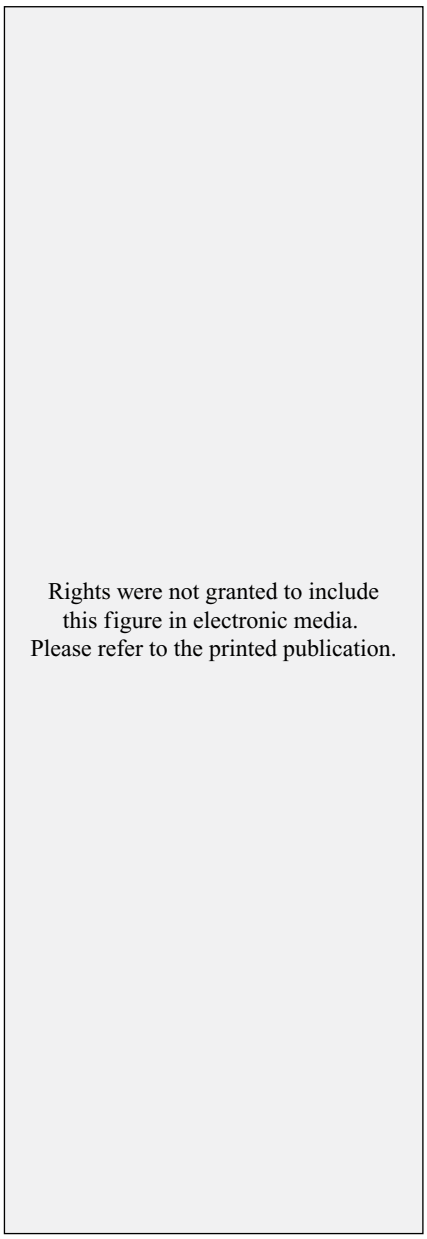

Figure 56-11. Movements of different portions of vocal folds during one cycle of vibration shown schematically in coronal plane (*left*) and from above (*right*). Mucosal upheaval begins caudally (1) and then moves rostrally. The lower portion is closing as the upper margin is opening (5). (*From Hirano M.* Clinical Examination of Voice. *New York: Springer-Verlag; 1981.*)

Expiratory Force

The force available to drive phonation depends on the volume of air in the lungs, the elastic recoil in the chest wall and diaphragm, and the strength in abdominal and intercostal muscles. Normally, passive expiration is sufficient to power conversational speech. Shouting and singing require deeper prephonatory inspiration for larger lung volume and for active expiratory effort. Because the amount of breath support required for normal voice use is small compared with lung capacity, voice loss generally is not a presenting complaint of pulmonary disorders. Breath support available for phonation becomes a clinical issue in

two situations: First, in patients with functional dysphonia, there is insufficient prephonatory inspiration, so excessive glottic pressure is required to produce an acceptable volume, which may lead to stress-induced injury of the vocal folds. Second, in a patient with an organic voice disorder and impaired pulmonary function, the capacity to compensate for the glottic defect is limited. For example, a patient with laryngeal paralysis is more symptomatic when there is coexisting emphysema. An important component of vocal training is instruction on control of breathing to maximize the power of vocal output.

Vocal Fold Positioning

Phonation requires a critical relationship between the gap between the medial surface edges of the vocal folds and the expiratory airflow. The folds should be close enough together so that airflow entrains oscillations. If the gap is too wide, the voice is breathy, or aphonic, with only turbulent airflow noise and no periodic sound. The gap may be wider if airflow is greater; conversely, low airflow requires a narrower gap. If the vocal folds are too tightly apposed, excessive pressure is required, and phonation sounds strained or might not even be possible. An analogy to phonation is the sound generated by air released from a toy balloon. The pitch and volume may be varied by adjustments in the tension across the neck of the balloon. The sound is louder with more air in the balloon. If pressure on the neck is sufficient to interrupt airflow, then sound ceases. With decreasing closing pressure, the sound becomes increasingly turbulent.

Vibratory Capacity of the Vocal Folds

The physical properties of the vocal folds are crucial in determining vocal function. During normal modal phonation, the mucosa undulates freely over the underlying vocal ligament and vocalis muscle. Hirano's[47] important histologic studies showed that this undulation is possible because the mucosa and muscle are separated by a specialized layer of connective tissue that serves as a shock absorber. This highly specialized tissue is characterized by stratified concentrations of elastin and collagen. The most superficial layer is made up of loosely connected fibers of collagen and elastin. This layer also is known as Reinke's space. The intermediate layer is composed predominantly of elastic fibers, and the deep layer is constructed of densely arranged collagen fibers. Together, the intermediate and deep layers form the vocal ligament.

Vocal Fold Shape

In falsetto mode, only the superior edges of the vocal folds contact during the closing phase, although during modal phonation, which is more efficient, the mucosal wave begins on the inferior surface of the vocal fold. This requires a favorable configuration of the glottis in the coronal plane, with the medial surfaces of the vocal folds nearly parallel. If the vocalis muscle is atrophic or paralyzed, then the medial surface of the vocal fold is convex, and the glottal tract is too convergent for optimal phonation. A divergent glottis is also unfavorable.

Pitch Control

Changes in vocal fold length and tension are used to control the fundamental frequency of vocal fold vibration to produce dynamic inflections of the voice. Such adjustments involve fine motor control. In the lower vocal range, contraction of the thyroarytenoid results in a lowering of pitch because it decreases tension in the vocal cover. During contraction of the cricothyroid muscle, which increases length and tension, strengthening thyroarytenoid muscle contraction results in rising pitch. Contraction of the cricothyroid muscle in the absence of thyroarytenoid muscle activity is generally accepted to be the mechanism of falsetto.

The size and physical properties of a larynx determine the range of pitch that can be produced. A child has a smaller larynx and a higher pitch range than an adult. During puberty in boys, the rapid increase in size of the larynx results in unstable pitch control until adaptation to the new anatomy occurs. Size is not the only determinate of pitch range, because age-related loss of elasticity and increasing ossification of the thyroid lamina result in an elevation of pitch. The lowest pitches are produced by young men, whose vocal folds are longer and heavier than those of women and more compliant than those of older men.

Resonance

The raw sound produced by the glottis in isolation from the rest of the vocal tract does not sound like human voice but is harsh and sounds something like a goose call. Phonated sound acquires the characteristics of a human voice through the resonance of the chest, upper airway, and skull. Resonance is the prolongation, amplification, and filtering of sound by the induction of sympathetic vibration. The vocal frequencies that are enhanced by resonance are termed *formants*. The pharynx itself does not resonate because its walls are too compliant to support sympathetic vibration. The primary resonating structure is actually the air column contained in the pharynx. The length of the vocal tract and the locations of constricted segments confer characteristic resonant frequencies, which are excited by any sound fed into the tract, whether from the glottis or from an artificial larynx. These resonant frequencies are called formants. A speaker controls resonance of the voice by altering the shape and volume of the pharynx, by raising or lowering the larynx, by moving tongue or jaw position, or by varying the amount of sound transmission through the nasopharynx and nose. Vocal training for singing, acting, or public speaking concentrates heavily on refining and maximizing resonance. The goal is to produce the loudest and most pleasing sound possible with minimal strain or pressure on the larynx.

Articulation

The source-filter hypothesis of speech states that the larynx is the source of a constant sound, which is shaped into words by the upper vocal tract. In this generally accepted model, consonants and vowels are formed by the action of the lips, tongue, palate, and pharynx. Participation of the larynx during articulation is generally considered to be limited to the onset and offset of phonation, coordinating with upper articulators to produce voiced and unvoiced sounds. In computerized simulation, this model seems to account for speech fairly well, although evidence now suggests that the position and shape of the glottis may actually vary with production of different vowels, so that the contribution of the larynx to phonation may be more complex than previously recognized.[48]

Sensory Input to Speech Control

One obvious mechanism for controlling phonatory output during speech is auditory feedback. This sensory input is most important while one is learning speech and is not essential for everyday use. Prelingually deaf persons never develop completely normal-sounding speech, although those who become deaf after language acquisition are able to maintain fairly normal speech patterns, in part because of ballistic speech production but also probably because of the use of nonauditory cues for feedback. An example of the importance of nonauditory cues in voice control is the ability of well-trained singers to perform with good control of pitch and loudness even when they cannot hear their own voices. Tactile sensations of induced vibration in the face, throat, and chest are important cues. There are many sensory receptors in the larynx, responding to such cues as air pressure and flow and joint motion, but the degree to which laryngeal sensation influences vocal control is not known.

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For complete list of references log onto www.expertconsult.com.

CHAPTER FIFTY-SEVEN

Visualization of the Larynx

Robin A. Samlan

Jackie Gartner-Schmidt

Melda Kunduk

Key Points

- Laryngeal endoscopy, using flexible or rigid endoscopes, is used to examine vocal fold structure and gross function.
- Videostroboscopy is used to examine vocal fold vibration patterns and the relationship between the body and the cover.
- High-speed digital imaging complements endoscopy and stroboscopy, showing details of short and aperiodic vibration as well as quantifying vibration parameters.
- Narrow-band imaging is a newer visualization technique that uses the tissue's light absorption characteristics to show vascular detail.
- Each vocal fold visualization tool makes a unique contribution to the assessment puzzle.

In this chapter, we describe several tools for laryngeal visualization and how to analyze and interpret the images. Laryngeal videoendoscopy and stroboscopy (LVES), high-speed digital imaging (HSDI), and narrow-band imaging (NBI) are discussed.

Laryngeal videoendoscopy is a clinical tool that is used to examine vocal fold structure and gross function. It is used to diagnose and document voice and laryngeal disorders, plan treatment, make longitudinal comparisons, educate patients, provide biofeedback for voice and breathing therapy, and provide a record for medicolegal proceedings. Both rigid and flexible endoscopes can be used for endoscopy.

Stroboscopy is a lighting technique that helps clinicians examine vibration patterns and the relationship between the vocal fold body and cover. It is valuable for describing mucosal disease and its effect on vocal fold vibration. Stroboscopy is necessary to determine glottic closure and mucosal pliability, to make inferences about tension, and, sometimes, to identify or differentiate lesions. The decisions to use continuous or strobe light and rigid or flexible endoscope are largely based on whether the examiner is more interested in gross structure and function or mucosal health and vibration patterns. Often, both rigid and flexible examinations are used as part of a dynamic assessment to thoroughly evaluate laryngeal function during a variety of voicing conditions and therapy probes.

Examination with *high-speed digital imaging systems* complements endoscopy and stroboscopy; details of short and aperiodic vibration can be observed, and the image analysis allows quantification of vibratory details that is not otherwise possible.

Narrow-band imaging is a new endoscopic imaging technique that uses the absorption characteristics of light to enable a detailed analysis of mucosal and vascular structures. The technique holds promise for becoming a powerful tool to screen for malignancies by identifying high-yield areas to sample for biopsy.

In most states, LVES, HSDI, and NBI can be performed by either an otolaryngologist or a qualified speech-language pathologist.[1] Each professional brings a different perspective and training to the process, and the most thorough examinations are typically conducted in a team setting. The otolaryngologist is responsible for assessing mucosal health and diagnosing laryngeal pathology; the speech-language pathologist is interested in the vibratory patterns during various voicing conditions, the behavior of the laryngeal and supralaryngeal structures during phonation, and how treatment probes alter phonatory physiology. As team members work together over time, they often learn from each other and develop common skill sets.[2]

The advantages and disadvantages of rigid and flexible endoscopes are described in the first section of this chapter, with recommendations for technique and troubleshooting. The second section details the assessment process for endoscopy and stroboscopy. The third section discusses HSDI, its advantages and limitations, and how images are processed and analyzed. The final section is an introduction to the emerging technology of NBI.

Endoscopes

Rigid Endoscopes

Advantages

Rigid endoscopes used with LVES are usually 70- or 90-degree scopes. Rigid scopes have the advantage of high resolution with bright, clear pictures. Contrast is excellent, there is a large selection of viewing angles, and the image is more accurately magnified than with a flexible endoscope. The examination is simple and does not usually require topical anesthesia.[2-4]

Disadvantages

The primary limitation of the rigid endoscope is that phonation is limited to sustained vowels, most commonly "ee." Because visualization with a 70-degree rigid endoscope usually requires an extended neck and protruded tongue, the size of a glottic gap might appear exaggerated with the rigid endoscope.[5] To counteract this problem, Rammage and

colleagues[2] suggest a lateral approach to the larynx to decrease neck extension during the examination. Alternatively, a 90-degree endoscope does not require the same amount of neck extension as the 70-degree endoscope does. A second limitation is that the mobility of the arytenoids might not be accurately assessed via rigid endoscopy; often, it appears as if there is a vocal fold paresis when the perceived lack of motion is, in actuality, an artifact of the tongue protrusion and neck extension. Lastly, disorders more evident in connected speech than in sustained vowels (e.g., muscle tension dysphonia and spasmodic dysphonia) are not as well documented with rigid endoscopy as they are with flexible endoscopy.

Technique

The laryngeal examination with a 70-degree rigid endoscope is conducted with the patient bending slightly forward from the hips while maintaining a straight back. The neck and chin are extended, and the tongue is protruded. The examiner wraps the tongue in gauze and holds it gently during the examination. The endoscope is advanced just under the uvula or between the uvula and faucial pillars until the epiglottis is visualized. Turning the endoscope tip to face the cheek during insertion, to prevent tongue residue from coating the lens, might keep the lens cleaner. Having the patient vocalize a sustained "hey" lowers the tongue base, facilitating placement. The patient is then instructed to sustain "ee," which moves the epiglottis anteriorly for a better view of the vocal folds. The examiner might need to flex the wrist to tilt the endoscope tip inferiorly. The angle can be varied for differing levels of magnification and differing fields of view. The patient is then guided through the examination tasks listed in the following "Assessment" section. Examination with the 90-degree endoscope is similar, but the patient does not need to bend forward or extend the neck. Another difference is the angle; the tip of the 90-degree scope is positioned with minimal tilt so that the light is parallel to the surface of the vocal folds. This type of endoscope is often preferable for viewing the larynx when a wider viewing angle is desired. A longer lens or a zoom lens might be necessary for adequate visualization of vocal fold details.

Defogging the endoscopes can be a challenge, because sterilizing beads can cause damage to both the lens and the patient. Alternatives include liquid defogger, hot (not boiling) water, soap film, surgical wax, and holding the endoscope lens briefly against the patient's cheek or the side of the tongue. The examination is generally tolerated without topical anesthesia, but a small amount of benzocaine topical spray or a similar product is sometimes useful and does not appear to affect examination results.[6]

Troubleshooting

A good-quality examination means that the image is in focus, that it is large enough to show small mucosal irregularities, and that it is bright enough to show details (but not so bright as to obscure them). Contrasting color is important for differentiating subtle lesions and vascular changes. Ideally, an examination includes both a wide-angle view of the larynx and a close-up view of the vocal folds. The stroboscopic portion of the examination should include several complete stroboscopic cycles at the patient's most comfortable pitch and loudness (MCPL) in addition to the rest of the protocol (see "Assessment"). Common imaging problems and solutions are listed in Table 57-1.

Flexible Endoscopes

Advantages

The primary advantage of the flexible endoscope is the ability to view the larynx dynamically—that is, during natural functions such as speech and singing. Arytenoid mobility and the glottic gap can be more accurately described with flexible than with rigid endoscopy because of the neutral tongue and neck positions.[5] Flexible endoscopy also allows the clinician to assess the nasal cavity and velopharyngeal port during the same examination. Flexible endoscopy is preferred when the question is one of movement rather than structure or mucosal health. It is particularly useful for disorders such as spasmodic dysphonia and muscle tension dysphonia, in which the voice problem is more obvious during speech than in sustained vowels, and vocal fold motion impairment, where having the patient sniff through the nose allows the examiner to assess subtle motion.

Disadvantages

The primary limitation of flexible endoscopy is that light transport and magnification of the image are inferior to those of rigid endoscopy. There is also a distortion of the periphery of the image and a trade-off between adequate focus and light fiber mismatch, so that when the image is in focus, there is a moiré or honeycomb effect that is enhanced by the edge-detection software of digital imaging systems. The honeycomb effect is not a concern with the newer-technology flexible endoscope with a charged-coupled device (CCD) camera in the tip. These "chip-tip" endoscopes eliminate the fiberoptic bundle and provide superior optics. Although the chip-tip endoscope represents a significant improvement, the new technology comes at a significant cost increase, and the quality of resultant examinations is not equal to that achieved with rigid endoscopy. In addition, many patients find the flexible examination to be more invasive than the rigid examination, and the flexible technique carries the risks of nosebleed, adverse reactions to the anesthetic, and vasovagal reaction.

Technique

The flexible endoscope is typically inserted after the application of a topical anesthetic and a vasoconstrictor. It can be passed through the inferior or middle meatus of the nose. The higher path is preferred for examination of the velopharyngeal port, but the paths are equivalent for visualizing the larynx. The examiner should raise the endoscope slightly as the patient swallows to avoid triggering a cough or laryngeal closure reflex, which can occur if the endoscope touches the rising larynx during a swallow.

Troubleshooting

As with the rigid endoscope, a good-quality flexible examination means that the image is in focus, large enough to show small lesions, bright enough to show details, and not so bright that details are obscured. Varying the field of view of the flexible endoscope is easy, but it is sometimes challenging to bring the endoscope close enough to the vocal folds for optimal light and vibratory detail. Patients generally allow a more complete examination when they are fully informed about the procedure, have some feeling of control (e.g., they know the examiner will respond if they say they have had enough), and have received adequate anesthetic.

Videoendoscopy and Stroboscopy

Endoscopy: Assessment Using Continuous Light

Protocol

Endoscopic parameters that require only continuous light (as opposed to the xenon light of stroboscopy) include laryngeal structure, arytenoid and vocal-fold motion, color and quantity of mucus, vascularity, supraglottic activity or compression, and deformation of vocal fold edges. The tasks during this portion of the examination include rest breathing, deep breathing, easy cough or throat clear, and laryngeal diadochokinesis, which consists of rapid repetitions of "ee" with glottal stops between productions. Laryngeal diadochokinesis is a useful measure, and production rates of four to six syllables per second are considered normal.[7] Difficulty with accurately and rhythmically producing the voice onset/offset gesture has been found in patients with neurologic impairment.[8,9] If a flexible endoscope is used, several other parameters can be assessed, including repetitions of a short "ee" followed by a quick sniff through the nose, a standard set of phrases or sentences, and conversational speech if voice quality during the endoscopic examination is not consistent with what was heard before it. Examination of velopharyngeal function is indicated if nasal emission or hypernasality is heard. At a minimum, soft palate and lateral pharyngeal wall motion should be assessed during a sustained vowel and a voiceless fricative, as well as during words or phrases with nasal-oral consonant transitions. A sample protocol is outlined in Box 57-1.

Table 57-1

Common Problems and Solutions for Laryngeal Endoscopy and Stroboscopy

Problem	Solution(s)
Foggy image	Warm the endoscope. Apply defogger. Clean the endoscope lens; mucus or dried disinfectant might be obscuring the image. Turn the endoscope so that the lens is facing the cheek during insertion, to prevent tongue residue from coating the lens.
Fuzzy image	Check or adjust the focus. Whenever possible, set the focus on the endoscope (if there is one) prior to connecting it to the camera, and then leave it alone. Clean the endoscope lens.
Dark image	Clean the lens of the endoscope, the eyepiece, or the camera. Increase light. Different techniques are used for different light sources and cameras. For some systems, decreasing the shutter speed or turning the electronic light control (ELC) on/off can increase brightness. Change the position of the endoscope; the light might not be directly over the vocal folds or area of interest. If it is the xenon light that is too dark, check the number of hours on the bulb. The brightness of the xenon light fades with use, whereas the halogen bulb burns out all at once.
Grainy image	Decrease the gain. Slightly defocus the endoscope. Consider a shorter camera lens.
Image is tilted or the vocal folds appear to have different widths	Modify the alignment of the endoscope and camera. Be sure your arm and wrist are straight, not tilted, when approaching the patient. Have a third party hold the laryngeal microphone to the patient's neck or attach it to a hook-and-loop strap.
Image is mostly of the valleculae and epiglottis or anterior commissure cannot be seen	Insert the endoscope farther into the oropharynx. Tilt the tip of the endoscope. Ask the patient to "smile down" around the endoscope (decreases mouth opening). Check the patient's position: legs uncrossed, back straight, neck slightly extended, jaw jutted. Ask the patient to produce a high-pitched "ee" to lengthen the vocal folds.
Mostly arytenoids and posterior vocal folds are seen	Withdraw the endoscope slightly from the oropharynx. Tilt the tip of the endoscope. Have the patient phonate in a high pitch. Request that the sound be more "ee-like."
The base of tongue is high	Ask the patient to produce sustained "hey" or "ā." Ask the patient to allow the back of the tongue and jaw to release and be "floppy." Have the patient hold his/her own tongue.
Uvula is "in the way"	Direct the endoscope around the uvula. Have the patient breathe through the mouth, not the nose. Ask for the sound to be more "ee-like." Have the patient plug the nose or use nose clips.
Abnormal color	Solution depends on the particular system; color can often be adjusted by controls on the monitor, camera, or videoprinter. Check the brightness settings. Check the focus; slight defocusing might be needed.
Omega-shaped epiglottis	Use a 90-degree endoscope. Have the patient (1) bend farther forward so that the elbows rest on the knees and (2) extend the neck as much as possible. Try a lateral approach.

Continued

Table 57-1

Common Problems and Solutions for Laryngeal Endoscopy and Stroboscopy—cont'd

Problem	Solution(s)
Strobe is "not tracking"	Modify placement of the laryngeal microphone or electroglottograph electrodes. They should be placed flat on the neck over the thyroid laminae. Have the patient phonate louder. Try the other fundamental frequency extractor (i.e., use the laryngeal microphone if fundamental frequency is not tracking with the electroglottograph). Vibration might be aperiodic; try other vocalization tasks, such as high pitch, low pitch, quiet voice, phonation on inhalation, instruction to take a better breath, and relaxing the shoulders. Some systems allow the examiner to select an approximate fundamental frequency as an override. If the system does not have the override feature, a third party can phonate at the approximate fundamental frequency to trigger the strobe light.
"Plica ventricularis": ventricular folds closed so the true vocal folds cannot be seen	Ask the patient to produce a soft, gentle, breathy "hhheee," almost like a sigh. Model such a production. Ask the patient to laugh "hee hee hee." Have the patient phonate on inhalation. Perform voice therapy and then repeat the evaluation.
Gagging	Reduce anticipation by educating the patient about the exam. It is sometimes helpful to use a model to show that the vocal folds are in view with the endoscope placed far above them. Talk the patient through the exam in a calming voice, reminding him/her to breathe slowly through the mouth and start phonating in a relaxed, breathy voice. Distract the patient by having him/her focus on a certain spot, think the alphabet backwards, or try not to blink (attenuation of the blink reflex can suppress the gag reflex). Ask the patient to keep the tongue protruded and to pant when breathing in. Have the patient hold his/her own tongue. Alter the approach (e.g., lateral versus anterior; elevate or lower the endoscope tip). Apply topical anesthetic. Use a flexible endoscope.

Box 57-1

Protocol for Laryngeal Videoendoscopy (Continuous Light)

Rigid Endoscopy

Rest breathing
Deep breathing
Easy cough or throat clear
Laryngeal diadochokinesis "ee"
Laryngeal diadochokinesis "hee"

Flexible Endoscopy

All components of rigid exam
"ee" followed by a quick sniff (×3)
Whistling
Sentences and/or conversation as needed
Observation of velopharyngeal function during sustained sounds such as "ee" and "s"
Observation of velopharyngeal function during sentences loaded with nasal-oral contrasts

Laryngeal Structure

The valleculae, pyriform sinuses, epiglottis, aryepiglottic folds, ventricular folds, and posterior glottic rim should be examined. Lowered pitch during sustained "ee" widens the angle, allowing better visualization of the valleculae. Abnormalities and asymmetries of laryngeal structure are noted. An omega-shaped epiglottis is a common variant in men, but it is rare in women.[7,10] Signs of laryngeal irritation or possible laryngopharyngeal reflux are noted; these primarily include edema, erythema, surface irregularities, and lesions of the posterior larynx.[11-14] The specificity of signs for reflux is still being evaluated. In particular, interarytenoid bar, arytenoid medial wall erythema, and posterior pharyngeal wall cobblestoning have been found in a substantial number of "normal" volunteers.[13]

Arytenoid and Vocal Fold Motion

Movement and position of the arytenoids inform the examiner about the integrity of the cricoarytenoid joint and the recurrent laryngeal nerve. Arytenoids are typically described as mobile or immobile, symmetric or asymmetric, and upright or rotated. Immobility is further described by position: median, paramedian, intermediate, or lateral. Motion of the arytenoid should be described separately from movement of the posterior third of the vocal fold because sometimes the arytenoid is mobile when the vocal fold is fixed. Mobility is rated when patients phonate then breathe, and during laryngeal diadochokinesis, cough, whistling, and sniff. The etiology of the motion impairment, along with particular characteristics such as arytenoid position, gap size, shape, and vocal-fold plane difference, can influence management strategy as described in Chapters 66 through 68.

Mucus

Thickened mucus often adheres to the vocal fold edges or superior surface. The presence of thick mucus generally relates to a lack of hydration or to chronic irritation from sources such as mechanical trauma, smoking, or laryngopharyngeal reflux. Mucus pooling in the pyriform sinuses can indicate poor laryngeal sensation, weak lateral pharyngeal walls, or inefficient swallow. Thickened mucus adhering to the vocal folds can masquerade as a lesion or mask an abnormality. To

allow differentiation of mucus from underlying structures or lesions, patients should be instructed to try to clear the mucus by swallowing or gentle cough.

Vascularity

The vocal folds are generally pearly white. A blush throughout the tissue is considered erythema or hyperemia. If capillaries are visible, they are generally aligned parallel with the free edge; horizontal vascularity is cause for concern. Abnormally dilated and tortuous vessels, called *capillary ectasias* or *microvarices*, might represent areas of stiffness or risk for hemorrhage. Hemorrhage occurs when enough blood cells have escaped from a vessel to lend a diffuse coloring to the vocal fold. Post-hemorrhage vocal folds often appear yellow-brown, similar to healing bruises in other areas.

Supraglottic Activity

Supraglottic activity refers to any abnormal motion above the true vocal folds. Examples are tremor of the larynx or pharynx, other involuntary contractions (e.g., myoclonic movements), and compression of the supraglottic structures. Supraglottic movements help tease apart neurologic voice disorders from disorders caused by abnormal muscle tension; tremor and myoclonic movement are evidence of a neurologic disorder, whereas sustained constriction is more typically found in muscle tension disorders. Constriction is often categorized by direction (anteroposterior or lateromedial) and frequency (constant or intermittent). Anteroposterior constriction during phonation is shown in Figure 57-1, and lateromedial constriction in Figure 57-2. The Stroboscopy Evaluation Rating Form proposed by Poburka[15] displays a superior view diagram of the vocal folds with superimposed concentric circles on which raters estimate the extent of constriction. Aryepiglottic narrowing or dilation and pharyngeal shape for different vowels can alter vocal-fold vibratory characteristics.[2,16,17]

The frequency and severity of supraglottic constriction in subjects without voice disorders is still somewhat uncertain, although it is clear that both anteroposterior and lateromedial constrictions are sometimes normal variants.[18-20] Stager and associates[20] found that supraglottic movements were present at the initiation of phonation in normal controls. Behrman and colleagues[18] showed a greater severity of anteroposterior constriction in dysphonic subjects than in normal controls.

Ventricular fold closure with or without vibration is not considered a normal variant. It can be the primary disorder[2] or compensation for another problem, such as incomplete glottic closure or a lesion.[21,22] In other words, the patient can have a primary muscle tension dysphonia, in which the muscle tension causes the voice disorder, or can present with a secondary muscle tension dysphonia, in which a vocal-fold abnormality is causing the muscle tension. To tease apart the etiology, voice therapy maneuvers should be used to reduce the amount of constriction, and then visualization should be repeated.

Other supraglottic activity occurs in people with normal voices. Lateral wall constriction, for example, is frequently observed with increasing pitch. Anteroposterior narrowing of the epilaryngeal space during singing might be a desired pattern that helps create the singer's formant.[23]

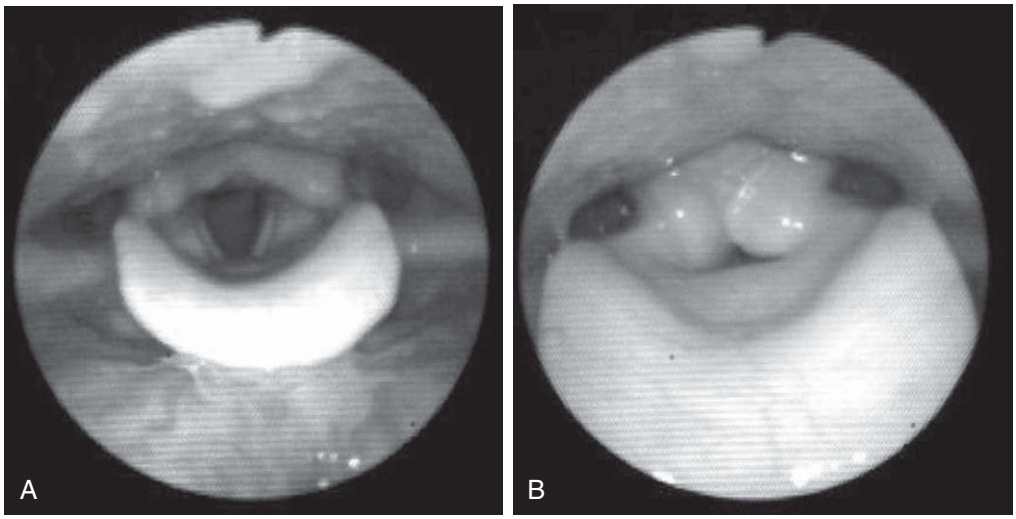

Figure 57-1. **A,** Vocal folds during respiration. **B,** Vocal folds with anteroposterior constriction during phonation.

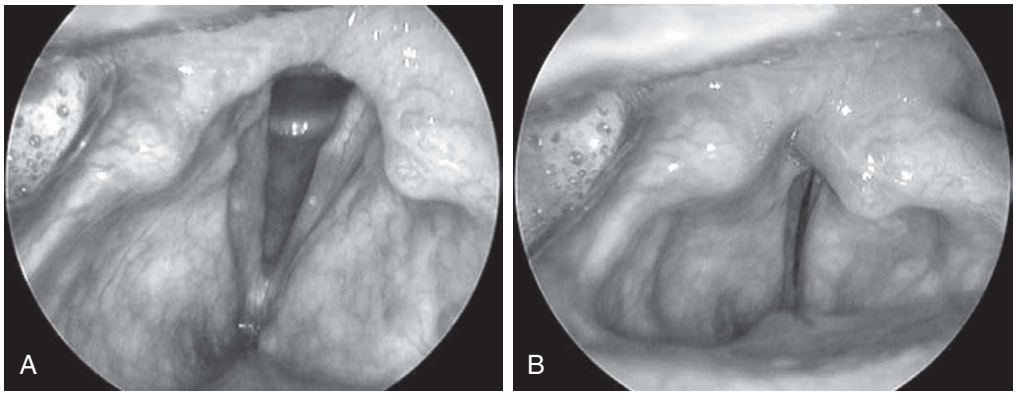

Figure 57-2. **A,** Vocal folds during respiration. **B,** Vocal folds with lateromedial constriction during phonation.

Vocal Fold Edges

Vocal fold edge shape can be rated on two scales, straight to smooth and rough to irregular.[15] Along the straight-smooth continuum, abnormalities should be further described as convex or concave ("bowed"), along with the degree of deviation. Bowing is not a pathognomonic symptom; rather, it is a symptom of several underlying disorders.

Assessment Using Stroboscopy

A *stroboscope* is defined as "an instrument for determining the speed of cyclic motion (as rotation or vibration) that causes the motion to appear slowed or stopped."[24] Videostroboscopy is not slow-motion photography; it is an illusion of slow motion. The illusion is possible because images linger on the retina for 0.2 second, and only five distinct images can be viewed per second. If more than five per second are presented, the viewer perceives the images as connected and sees the result as a smooth motion; this phenomenon is referred to as *Talbot's law*.[3] For videostroboscopy to be used for the analysis of vocal fold vibration, the light must flash at specific points in the glottic cycle, or the illusion of slow motion vibration will crumble. Extraction of the vocal fold fundamental frequency (rate of vibration) facilitates the process. The strobe light can be used to create two effects, the running phase (often called strobe) and the stop or locked phase. In the running phase (the more frequently used mode), the light flashes slightly faster or slower than a rate matched to the frequency of vibration, thereby creating the illusion that the vocal folds are vibrating in slow motion. Because each image is from a different glottal cycle, the cycles must be fairly regular to show a smooth stroboscopic cycle during the running phase. If the vocal fold vibration is aperiodic, the illusion of slow motion will not occur; rather, the vocal folds will appear to "flutter." In the stop phase, the light flashes at a rate that is matched with the frequency of the vocal fold vibration, thereby creating the illusion that the vocal folds are not moving at all.

Videostroboscopy is used to assess vocal fold vibration patterns, mucosal pliability, the underlying layered structure of the vocal folds, and the undersurface of the vocal fold edges. It is particularly valuable for assessing stiffness, scar, or submucosal injury; detecting small vocal fold lesions; estimating the depth of invasion of a tumor; identifying asymmetric mass or tension; or determining the resumption of phonation after phonosurgery.

Understanding normal vocal fold physiology for different modes of phonation is essential to interpreting stroboscopic examinations, although a thorough review is beyond the scope of this chapter. Detailed descriptions of vibratory physiology can be found in several sources cited.[2,3,16,17] In brief, it is helpful to think of the vocal folds as having three functional divisions; cover, transition, and body. The cover is composed of the epithelium and the superficial layer of the lamina propria. The transition consists of the intermediate and deep layers of the lamina propria (i.e., vocal ligament), and stiffness increases from the superficial to the deep layers of the lamina propria as the proportion of dense collagen fibers increases and that of elastin fibers decreases. The body of the vocal fold is the thyroarytenoid muscle, which is even less pliable.[3,25,26]

The vocal folds are set into vibration through a combination of aerodynamic, muscular, and elastic forces. As they vibrate, each vocal fold moves away from the midline and back. In spite of simplified explanations to patients, the vocal folds do not move like French doors; rather, the inferior vocal fold edges separate before the superior edges, and they return to midline in the same order (a vertical phase difference). Additionally, the folds separate at the anterior aspect before the posterior aspect, and they close in the same order (a horizontal phase difference). The ability of the vocal folds to move with these phase differences is critical to the initiation and sustenance of vibration. Furthermore, the inertia of the supraglottal air column, particularly the portion just superior to the vocal folds, aids in initiating and sustaining vibration. Alterations to vocal fold structure, occurring with disorders or postoperatively, can significantly affect the vibratory patterns; in the extreme, such perturbations may prevent vibration from occurring at all.

As the vocal folds move back and forth in whatever pattern their particular structure allows, they cyclically open and close the airspace between them, which is called the *glottis*. This time-varying glottal area transforms the steady tracheal airflow into a series of air pulses called the *glottal flow*. A particular pattern of vocal-fold vibration and the influence of the supraglottal air column determine the temporal characteristics of each glottal flow pulse. For example, a rapid movement of the vocal folds toward the midline creates a sharp cutoff of the pulse (rapid declination of flow). The shape of the glottal flow pulses determines the amount of acoustic energy available at the fundamental frequency and all of its harmonics.

Normally, vibration patterns are different for high and low pitch as well as loud and quiet phonation. For example, the vocal folds are stretched during high-pitch phonation, thereby increasing stiffness of the cover. During low-pitch phonation, they are shortened, and the cover is lax. Stiffness and mass are intricately linked with fundamental frequency, in that a decrease in stiffness or increase in mass can cause frequency to decrease, and vice versa.[16] Most stroboscopic parameters are rated at most comfortable pitch and loudness (MCPL), and then their variation with pitch and loudness changes is described.

Stroboscopic parameters include closure pattern, phase closure, amplitude of vibration, mucosal wave, adynamic segments, vertical closure level, symmetry, and regularity. Of these, closure and mucosal wave are often considered key indicators of function. Although it is tempting to consider judgments of these parameters as objective data, they are visual perceptual ratings and subject to reliability and validity errors.

Protocol

The protocol for stroboscopy includes several productions of sustained "ee" at MCPL; phonation on inhalation; pitch glide from midrange to high, sustaining the high note; pitch glide from midrange to low, sustaining the low note; quiet "ee," loud "ee"; "ee" at MCPL with locked phase; and, possibly, physical manipulation of the larynx or trial therapy. These tasks are listed in Box 57-2.

During the examination, it is important to monitor the patient's voice so that all of the necessary information is recorded. For example, the patient may initially sustain phonation quietly and at a high pitch

Box 57-2

Protocol for Laryngeal Videostroboscopy (Xenon Light)

Rigid Endoscope

Sustained "ee" at patient's most comfortable pitch and loudness (MCPL) (several)
"ee" on inhalation
Glide midrange to high, sustaining the high note
Glide midrange to low, sustaining the low note
Quiet "ee"
Loud "ee"
Sustained "ee" at MCPL using locked mode
Trial therapy or laryngeal manipulation as needed

Flexible Endoscope

All components of rigid exam
Consensus Auditory Perceptual Evaluation for Voice (CAPE-V)[27] sentences:
- "The blue spot is on the key again."
- "How hard did he hit him?"
- "We were away a year ago."
- "We eat eggs every Easter."
- "My mama makes lemon muffins."
- "Peter will keep at the peak."

Singing tasks as necessary
Conversation as necessary
Humming or other trial therapy tasks as needed

rather than at MCPL. Most vibratory parameters are rated from "ee" at MCPL, and the examiner should attempt to elicit several of these productions so that the vibration patterns can be accurately analyzed. Monitoring the voice quality is also important; sometimes the patient complains of roughness when talking, but the sustained vowel during stroboscopy is clear and normal. In this case, the examination would be most useful if the examiner can also elicit some productions that are similar to the patient's typical patterns or symptoms. Sometimes stroboscopic assessment is not possible when the patient uses a typical voice (e.g., the vocal folds do not vibrate quasiperiodically or are not visible). When this is the case, the examiner should indicate in the report that the stroboscopic examination was not congruent with the auditory perceptual findings before and after it.

Several components of the protocol just described might not be intuitive or might be left out at a busy clinic. Each task, however, contributes unique data to the assessment puzzle. Phonation on inhalation, for example, is useful when supraglottic constriction interferes with visualization of the vocal folds.[2] It also highlights edema or lesions of the inferior compartment of the vocal fold edge.

The patient should produce a variety of pitches during the examination. Bilateral and symmetric lengthening of the folds during ascending pitch glides confirms that gross cricothyroid muscle function is intact. High-pitch phonation is useful for highlighting midmembranous edema and stiff or scarred segments along the edge.

The locked phase is useful for assessing the regularity of vibration, which is the extent to which one vibration cycle is similar in duration to the next. It is also useful for highlighting lesions of the vocal fold edge. Most stroboscopy systems have foot-pedal control of the phase so that the examiner can select the point in the cycle that best shows the lesion. Vocal-fold plane differences are sometimes more easily seen in the locked mode.

When the flexible endoscope is used, connected speech should be an examination task. The sentences included in the Consensus Auditory Perceptual Evaluation for Voice (CAPE-V)[27] are a good standard sample, because each sentence has different characteristics:

"The blue spot is on the key again" contains many English vowel sounds.

"How hard did he hit him?" emphasizes easy onset.

"We were away a year ago" is all-voiced.

"We eat eggs every Easter" elicits glottal onsets.

"My mama makes lemon muffins" uses nasal sounds.

"Peter will keep at the peak" is loaded with voiceless plosive sounds.

If the patient's concern is related to the singing voice, that should also be assessed with the use of glides, vocalizes, and songs. If the patient's voice is different during the examination and typical conversation, engaging the patient in a dialogue might uncover habitual maladaptive laryngeal and supraglottic posturing.

Trial (probe) therapy techniques are often used during a flexible examination to "unload" the larynx or change vibration patterns for a more accurate diagnosis; they are also helpful to assess potential for change and to guide therapy. There are many such techniques, and some of the most useful are listed here. Pitch and loudness changes and phonation on inhalation were described earlier. Humming can alter glottic closure, symmetry, and regularity or decrease supraglottic activity. Twang, sighs, or descending glides with high airflow can alter supraglottic postures or the closure pattern. Trills, breathy voice, flow phonation, coughing, pushing, abdominodiaphragmatic onsets, and visual feedback are also useful probes. Leonard and Kendall[22] describe the combination of a traditional voice evaluation and flexible endoscopy as a "phonoscopic" evaluation. In their retrospective study of 100 cases, the findings from the phonoscopic evaluation differed from the findings of the referring physician in 42 cases. In an additional 32 cases, the findings were consistent with the referral diagnosis, but the phonoscopic examination provided additional detail (e.g., there was indeed hyperfunction, but it appeared as a result of an underlying pathology, such as atrophy or a lesion).

Closure Pattern

Closure pattern indicates how well the vocal folds come together at midline during the closed phase of the vibratory cycle. There are two principal options: Is the glottis completely closed (Fig. 57-3A) or not completely closed? If the vocal folds are not completely apposed, it is helpful to characterize the shape of closure. Patterns of incomplete closure are posterior gap (Fig. 57-3B), anterior gap (Fig. 57-3C), spindle-shaped gap (Fig. 57-3D), hourglass-shaped gap (Fig. 57-3E), irregular, and variable. With complete closure, there is no space between the folds; complete closure is the most common pattern for men,[28] and it occurs in some women at MCPL or with increased loudness.[5,28,29]

An *incomplete closure pattern* occurs when the gap extends for the entire length of the folds. Incomplete closure most often occurs with vocal fold motion impairment, scar, and the muscle tension dysphonia/aphonia variant in which the patient does not fully adduct the folds for phonation.

A *posterior glottic gap* can vary from small to large, and the extent of the gap should be indicated. Posterior glottic gap is one of the most common closure patterns for women,[28,30,31] and it might be a normal variant for men.[28] The gap is typically limited to the space between the cartilaginous folds during MCPL, but it can extend into the membranous folds during quiet productions.[28] Rammage and colleagues[2] categorize extended glottic gap as a laryngeal isometric pattern of muscle tension dysphonia.

An *anterior gap* is a condition in which there is closure of the arytenoids and cartilaginous folds but a gap between part or all of the membranous folds. Anterior gaps occur as a normal variant in men of any age and in older women.[7,30] They are also present in patients with disordered voices and can occur with tissue deficit of the membranous folds as a result of scarring, prior surgery, atrophy, superior laryngeal nerve deficit, or sulcus vocalis; at other times, they appear because of edematous posterior folds.

Spindle-shaped gap refers to a condition in which there is closure of the arytenoids but otherwise a gap that extends the length of the folds. Spindle-shaped gaps occur as normal variants in men of all ages and in older women[7]; they also occur with bowing as a result of vocal fold motion impairment, superior laryngeal nerve injury, sulcus vocalis, or tissue deficit due to aging or prior surgery.

Hourglass closure refers to a pattern of an anterior gap and a posterior gap with a point of closure in between. This pattern is typical for bilateral lesions (e.g., nodules) or a cyst or polyp and a contralateral reactive lesion; it can also occur with large unilateral lesions.

Irregular closure is a pattern that involves multiple gaps or that does not quite classify as another pattern. Irregular closure is most common with multilobular lesions or irregular vocal fold edges, which often occur with malignant lesions.

Sometimes the closure alternates between two or more patterns; it is then called *variable*, with the multiple patterns delineated. The closure pattern is rated at MCPL. For most people, vocal fold vibration patterns change as pitch and loudness change. With increasing pitch, the vocal folds lengthen, and only the medial edge is involved in vibration. Closure pattern can become incomplete, and the amplitude of vibration and mucosal wave can decrease. In the description of glottic closure, it is often helpful to describe it in multiple conditions. For example, the closure pattern for a patient with bilateral lesions may be described as follows: "Closure pattern is variable at MCPL; it is sometimes hourglass shaped, and, at other times, a posterior gap extends to the midmembranous folds. At higher pitch, closure is always hourglass. At low pitch and loud voice, glottic closure becomes complete."

Phase Closure

Although "*closure pattern*" describes the extent of closure, "*phase closure*" describes the duration of closure. During vibration at MCPL, the glottis is typically open (opening, fully open, or closing) for approximately two thirds of one vibratory cycle and maximally closed for the remaining third. This parameter is typically rated by counting of "frames" with

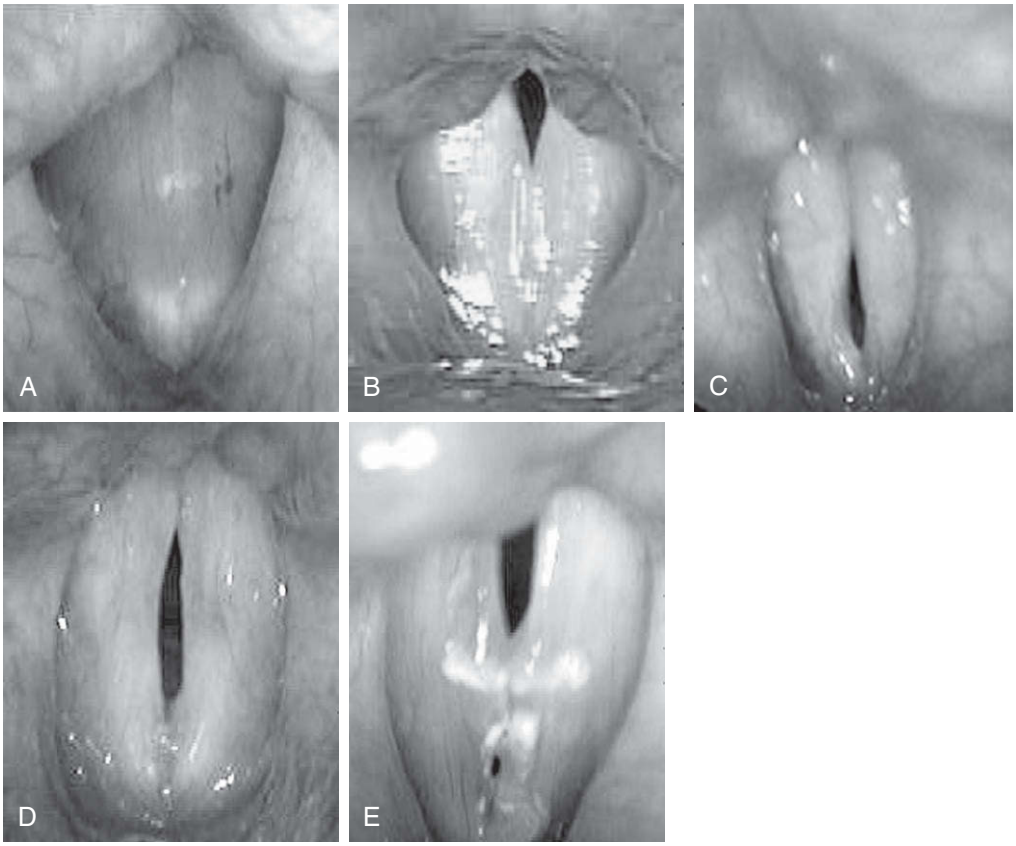

Figure 57-3. Glottal closure and gap patterns. **A,** Complete closure; **B,** posterior glottic gap; **C,** anterior glottic gap; **D,** spindle-shaped gap; **E,** hourglass-shaped gap.

the use of clicks of a computer mouse. Closed time generally decreases with higher pitches and in older women; it increases in older men.[10] Phase closure is a useful measurement in a patient who sounds breathy but achieves complete closure or during hyperfunctional patterns when the vocal folds open only briefly.

Amplitude of Vibration

Amplitude of vibration refers to the fold's horizontal excursion from midline. Normal is defined as approximately one third of the width of the fold (Fig. 57-4).[3] In normal conditions, the vocal folds are symmetric in amplitude; that is, the maximum amplitude of the left fold is similar to the maximum amplitude of the right fold. Amplitude can be rated as a percentage of the width of the fold[15] or on a five- or seven-point equal-appearing interval scale from normal to reduced.[3] Amplitude of vibration is typically smaller in women than men, it generally covaries with loudness, and it varies inversely with pitch.[10] Decreased amplitude of vibration can be the result of glottic incompetence, tight glottic closure, or increased vocal-fold mass or stiffness. Decreased amplitude is common in lesions such as firm polyps, cysts, papilloma, carcinoma, Reinke's edema, scarring, and hyperfunction.[3] Increased amplitude may be a sign of decreased tonicity, as observed in vocal-fold paresis or atrophy.

Mucosal Wave

Mucosal wave is the vertical upheaval of the cover over the body. It occurs because of the vertical phase shift (the timing difference between the upper and lower margins of the vocal folds) that is vital to the self-oscillation of the folds.[16,17,32] The wave is propagated from the infraglottic lip of the vocal fold, then travels up the medial edge and across the superior surface of the fold. The velocity of the mucosal wave is linked to the amount of pressure that is needed to establish phonation,[33,34] and we judge mucosal wave as the distance it travels across the superior surface of the fold. Normally, this wave moves approximately half the width of the vocal fold during phonation at MCPL.[41] Increased mucosal wave (i.e., it moves farther across the fold) is observed when mucosa is abnormally pliable, such as in polypoid degeneration or when there is increased subglottal air pressure. As such, it is normally greater than half of the width of the fold for loud phonation, when subglottal air pressure is increased. Mucosal wave is decreased or even absent when the mucosa is stiff or there is minimal differentiation of the vocal fold layered structure; this occurs normally with increasing pitch[3] and with aging.[30] In pathologic conditions, decrease or absence of mucosal wave is seen with some lesions, scarring, or sulcus vocalis. Incomplete glottic closure resulting from aging, atrophy, or motion impairment can also lead to decrease or absence of mucosal wave.[30,35,36]

Adynamic Segments

Adynamic segments refers to nonvibrating areas of the vocal fold (i.e., areas that have no mucosal wave and poor amplitude of vibration). They are described by location and by the percentage of the vocal-fold surface that they cover. These stiff areas are generally related to a lesion or to a scarred segment.

Symmetry

Symmetry is a timing parameter. It refers to the extent to which the vocal folds appear as mirror images of each other during vibration. The vocal folds should depart from midline at the same time and arrive back at midline at the same time. The asymmetry should be described whenever possible; for example, "the excursion of the right fold lags behind that of the left," or "the folds are asymmetric at the end of tasks." Depending on the rating scale, the parameter can be rated as either the percentage of the examination during which vibration was asymmetric or the extent of asymmetry. Asymmetric vibration raises questions about differences in mechanical properties or neurologic status between the folds.[3] Differences between the vocal folds in position, mass, tension, elasticity, or viscosity should be further assessed.

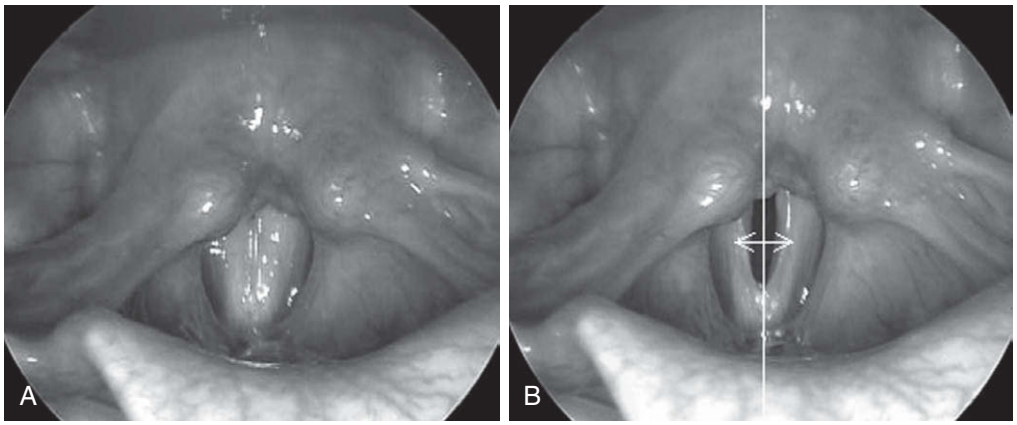

Figure 57-4. **A,** Complete glottic closure. **B,** Maximum amplitude of vibration/excursion.

Regularity

Regularity (or periodicity) describes the degree to which one phonatory cycle is similar in both amplitude and time to the next phonatory cycle.[3] The goal is to answer the question "Do the vocal folds vibrate in a regular, rhythmic pattern?" Regularity is best assessed in the locked or stop mode, but it can be estimated from the running phase as well. In the stop mode, the image appears static if the vibration is regular and appears to quiver or shake if the vibration is irregular. In running mode, the strobe light cannot adequately track fundamental frequency and adjust the illumination rate if vibration is irregular, and so quiver or shimmer appears. Vibratory regularity is rated just like symmetry, either by describing the percentage of time that the vibration was regular or irregular or by describing occurrences of irregularity. It is difficult to assess the amount of aperiodicity from stroboscopy; this would require acoustic analysis.

Incidence of aperiodicity rises with age. Biever and Bless[30] found that 85% of geriatric women demonstrated aperiodicity, compared with 30% of young women. Regular vibration depends on a steady balance between pulmonary pressure and the vocal folds. Irregular vibration can be caused by asymmetry of the mechanical properties of the vocal folds, interference with the homogeneity of the vocal folds, flaccidity, unsteady tonus, or inconsistent force. Examples are paralysis (asymmetry); a small cyst or carcinoma (homogeneity); paralysis, atrophy, or edematous lesion (flaccidity); spasmodic dysphonia or another neuromuscular disease (tonus); and functional pulmonary disease (inconsistent force).[3] Aperiodic vibration gives rise to acoustic noise, which can be perceived as roughness or hoarseness.

Vertical Closure Level

Whether the vocal folds meet on the same plane is typically rated as on-plane or off-plane. Closure is off-plane typically because of either neuromuscular differences between the folds (paralysis or paresis) or laryngeal trauma or surgery.

High-Speed Digital Imaging

Even though videostroboscopy is one of the most frequently used visualization techniques of vocal-fold vibration and is a powerful tool to examine symmetric and regular vibration,[3,35,38,39] stroboscopic analysis of irregular vibration, which is frequently observed in disordered voice production, is limited. Videostroboscopy requires a long enough phonatory segment to trigger the strobe light and cannot provide information about the phonation onset and offset, because they are very short and irregular. Currently, only HSDI[37,40,42-44] and high-speed kymography[45-47] allow the examiner to see the patterns of vocal-fold vibration regardless of their length, in most voice disorders, and during voicing initiation and termination phases. Both techniques capture images much faster than the vibration rate of the vocal folds; therefore, they allow the examiner to view vocal-fold vibration without the pitch-tracking requirement that exists for LVES. Kymography and HSDI are capable of demonstrating actual, real-time vibratory characteristics of the vocal folds. Video kymography allows the observation of movements at a single horizontal line from a laryngeal image, added together in real time to represent the vibratory pattern. It can be considered a one-dimensional version of HSDI. In contrast, HSDI allows the observation of the full length of vocal folds (Figs. 57-5 and 57-6).

Since the first recordings of vocal fold vibrations were made with high-speed photography,[48-50] high-speed recordings have shown promise for clinical applications. These recordings provided the foundation upon which much of our subsequent knowledge of vocal-fold vibration is based. Technologic advances in cameras, image resolution, and computers have resulted in development of HSDI, which permits recording of 2000 to 4000 (and higher) frames per second (fps) as opposed to the 25 or 30 fps available in videostroboscopy. This technique holds great promise for overcoming the limitations of currently available techniques for direct observation of laryngeal function. Images of stroboscopy and HSDI for a person with normal voice and a patient with a history of laryngeal cancer can be viewed in online video segments.

Equipment

Two HSDI systems are commercially available at present: the KayPENTAX Color High Speed Video system 9710 (KayPENTAX, Lincoln Park, NJ), which has spatial resolution of 160 × 140 pixels, and the Wolf High Speed Endocam 5562 (Richard Wolf Medical Instruments Corporation, Vernon Hills, IL), which has spatial resolution of 256 × 256 pixels. As a frame of reference, a typical LVES system has spacial resolution of 750 × 500 pixels. Both HSDI systems use the conventional 70- or 90-degree endoscopes to visualize the vocal folds, as in the LVES system. The flexible endoscopes have been used only in limited research settings with very few subjects because the image is generally not bright or clear enough. With a rigid endoscope, each of these systems requires a 300-watt cold light source to achieve sufficient clarity and the brightness of HSDI images. The recording time and capturing rate of the Wolf system are 2 seconds and 4000 fps, respectively, and the system stores color images as in an LVES system. The KayPENTAX HSDI system captures 2000 fps for 4 seconds. Faster capture rates are possible for less time and with smaller image size. Images using a capture rate of 4000 fps will still be color and 10,000 fps will be black and white. Both HSDI systems allow the examiner to play back the captured images at different playback rates. Even though synchronized audio playback is not available with either system, both systems allow simultaneous recordings of the endoscopic and acoustic signals and later analysis and comparisons of endoscopic and acoustic data.

Deliyski[51] reported in 2007 on the ongoing development of another HSDI system, which is equipped with temporal resolution of 10,000 fps, spatial resolution of 640 × 480, and sample duration of 32 seconds. At present, powerful HSDI systems like the one Deliyski's group is developing are impractical for clinical use owing to the equipment size, the magnitude of the data acquired, the lengthy duration of reviewing the captured data, and the image processing.

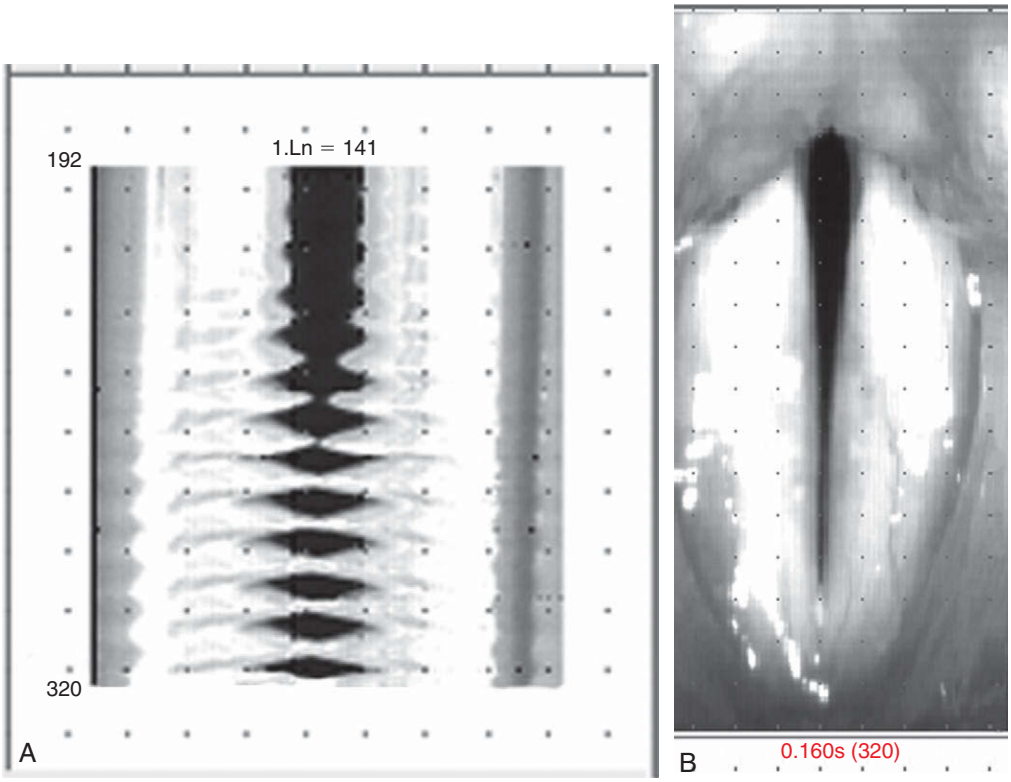

Figure 57-5. Kymographic images (**A**) based on endoscopic high-speed digital imaging (**B**), showing the vocal-fold vibration from the initiation to regular vocal-fold vibration in a normal voice. Note the number of cycles and detail during initiation in comparison with those in Figure 57-6.

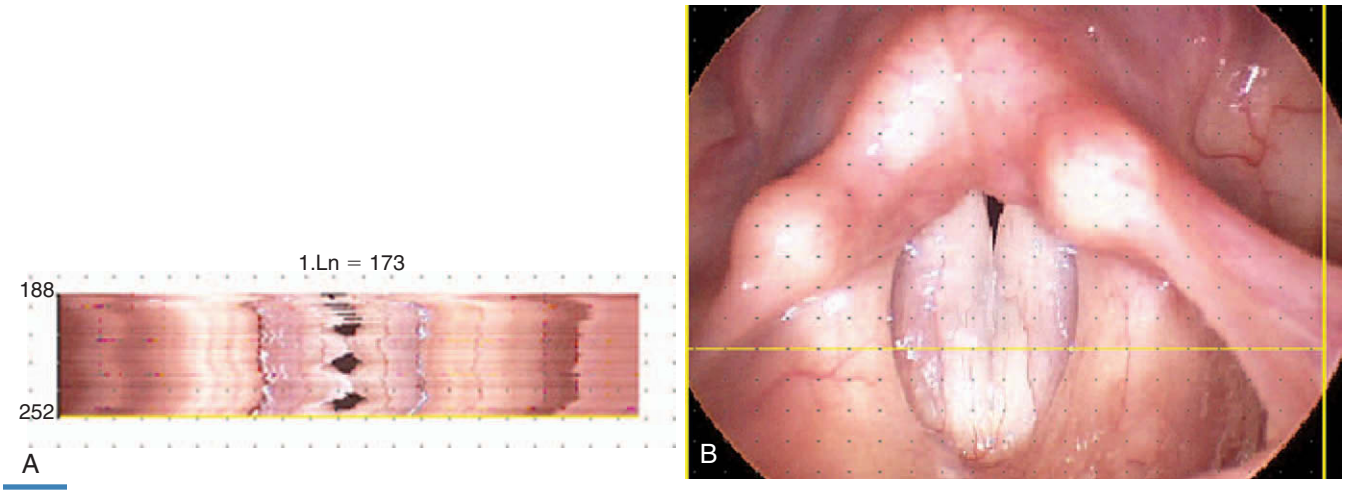

Figure 57-6. Kymographic images (**A**) based on laryngeal videoendoscopy and stroboscopy (**B**), showing vocal-fold vibration from the initiation to regular vocal fold vibration in a normal voice. Note the number of cycles and detail during initiation in comparison with those in Figure 57-5.

Assessment

Some of the parameters used in high-speed image analysis are the same as those for LVES: closure pattern, phase symmetry, amplitude of vibration, mucosal wave, pliability of tissue, adynamic segments, symmetry, regularity, vertical closure level, and vocal-fold edges. In addition, HSDI allows the observation of phonation onset and offset,[52,53] vibration in the surrounding structures such as ventricular folds,[54] intermittent vibration breaks, asymmetry between right and left vocal fold vibration, and the differences in frequency of vibration along different portions of the same vocal fold.[55] The primary challenge in analyzing high-speed images has always been managing the vast amount of data generated (a 2-second recording requires ~90 MB of digital storage).[48-50] The analysis was previously subjective, and reviewing the whole captured phonation segment took a very long time. This problem has been eliminated by higher computer processing speed, storage capacity, and newer image-processing techniques.[56-58] Current image-processing techniques allow rapid and objective data analysis and introduce easily recognizable visual representations of vocal-fold vibratory patterns in normal and disordered voice production. The Wolf system includes an automated image-processing system that provides quantitative informa-

tion regarding right and left vocal-fold asymmetry and the glottal perturbation measures (e.g., open quotient, speed quotient, jitter, and shimmer). The other image-processing systems used to process HSDI data are not commercially available at this time.

Limitations

Many challenges prevent HSDI from replacing LVES as a clinical tool: short duration of the recording, prolonged saving time of the captured images (which will lengthen the examination session if the tester wishes to obtain several phonation tasks in one session), cost, lack of synchronized audio playback, decreased spatial resolution, and no medical insurance billing code for the procedure.

In addition, information about normal and disordered vibratory characteristics is still being collected and reported. The parameters used to rate vocal-fold vibration are still being refined. Research showing firm evidence for the clinical relevance of HSDI is in its infancy. Only when standard parameters and normative data are identified will the added benefit of observing real-time vocal-fold vibration be realized in a clinical setting.

Image distortion secondary to the distance between the endoscope and the vocal folds, endoscope angle, or movement of the endoscope during the image-capturing process are inherent to any endoscopic procedure and make comparison of images taken from different visits difficult. The calibration issue has been addressed by the development of a laser projection system,[59] but laser projection is not available with the current HSDI systems. Each of the image-processing systems[57,58] can compensate for some of the endoscope movement during the imaging. The examiner's endoscopic skills, training in, and understanding of the HSDI technique further improve the quality of the data collection and analysis.

Applications

Results of studies using HSDI have already improved our understanding of normal and pathologic voice production. Kiritani and colleagues[40,60] found that, during diplophonia, the left and right vocal folds vibrate at different frequencies and the phase difference between the movements of vocal folds varies with time. Lindestad and associates[54] used HSDI techniques to study the relationship between ventricular fold vibration, vocal-fold vibration, and voice quality. High-speed analysis might be useful in quantifying the effects of neurologic diseases such as spasmodic dysphonia and vocal tremor[61] on vocal-fold vibration, possibly helping with differential diagnosis. HSDI has also been used to investigate different singing styles and their effects on laryngeal configuration.[62,63]

It appears that HSDI techniques will further our understanding of the voice source and biomechanics of vocal-fold vibration. With continued improvement of spatial and temporal resolution and image-processing systems, HSDI has the potential to become an excellent tool to show the efficacy of medical, surgical, and behavioral interventions for voice disorders.

Narrow-Band Imaging

Narrow-band imaging (NBI) is a new endoscopic imaging technique that employs the absorption characteristics of light for the detailed analysis of mucosal and vascular structures. This technique was initially developed to improve the recognition of Barrett's esophagus at the squamocolumnar junction of the lower esophageal sphincter.[64,65] NBI takes advantage of the differential absorption characteristics of tissues. Blue light with its shorter wavelength is better absorbed by hemoglobin. With the use of mechanical light-filtering technology to pass only the blue subset of the white light spectrum, structures with high hemoglobin concentration become more apparent with increased visualization of tissue's vascular pattern.[66] This creates a sharper contrast for better visualization of fine mucosal detail and helps to better identify subtle abnormalities (Figs. 57-7 and 57-8).

The applicability of this new technology to identify mucosal pathology in the aerodigestive tract is under investigation. To date, the technique has been shown to improve identification of abnormalities at the gastroesophageal junction, stomach, and colon.[65-71] NBI shows promise for improving the yield of biopsies by directing the examiner to the more "suspicious" areas, a type of optical biopsy. It is currently available for gastroscopes including transnasal esophagoscopes and flexible laryngoscopes. Clinicians are beginning to explore the utility of NBI in laryngeal[72] and hypopharyngeal[73] lesions. The real benefits and

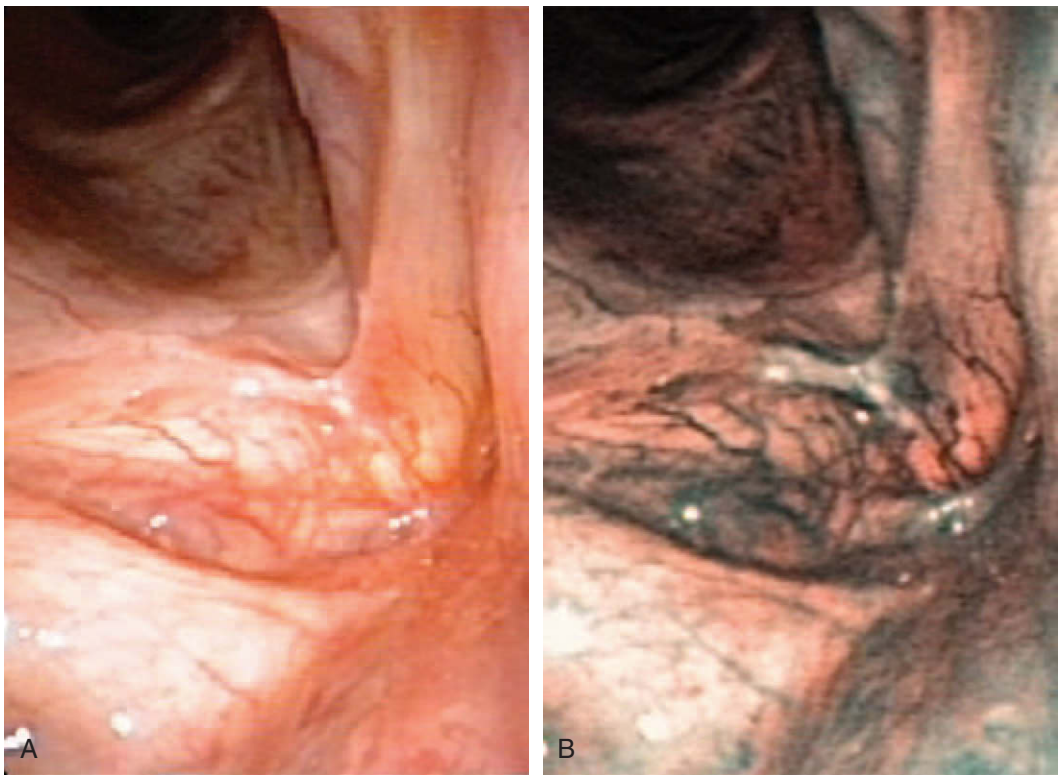

Figure 57-7. True vocal-fold scar at the anterior commissure. **A,** White light; **B,** narrow-band imaging.

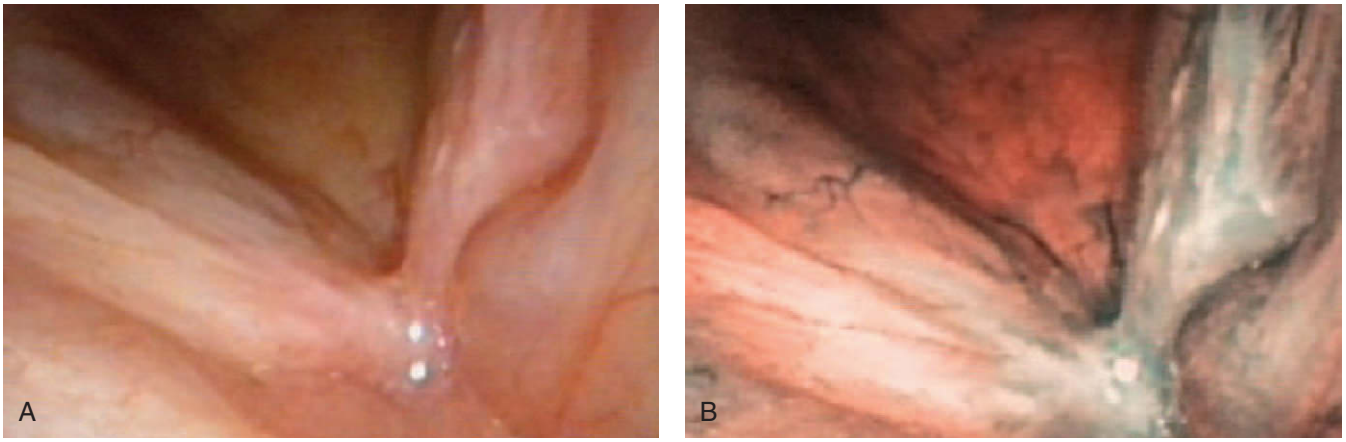

Figure 57-8. Carcinoma in situ of the left true vocal fold. **A,** White light; **B,** narrow-band imaging.

limitations of NBI will emerge with future studies employing this technique.

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CHAPTER FIFTY-EIGHT

Voice Evaluation

Robin A. Samlan

Julie Barkmeier-Kraemer

Key Points

- The voice is multidimensional, so voice assessment should be.
- The patient's perception of the problem is an important component of the evaluation. Several published scales can be used to report various aspects of handicap or quality of life.
- Perceptual assessment is notoriously unreliable yet remains important. Auditory, visual, and tactile perceptual examinations are key components of a voice evaluation.
- Vocal function measurements are less "objective" than they sound; standardization of tasks, instructions, and recording situations helps make them more useful.
- Specific measurement techniques contribute different information to the process, and the constellation of results is more useful than any one component.

Voice is produced by interactions among the respiratory, laryngeal, and resonance systems. The speech-language pathologist's voice evaluation is multifactorial, assessing each system in addition to the speech output. The purpose of this chapter is to describe the typical components of a voice evaluation and how to interpret the results. The focus of this chapter is on the perceptual, physical, and physiologic evaluation; the patient history and videostroboscopy are detailed in other chapters.

Both clinical and research requirements factor into decisions on how to measure voice. In the clinical arena, vocal function measures are used in both the diagnosis and treatment of voice disorders. Vocal function testing helps clinicians document the status of the voice source and the supraglottic vocal tract, characterize the type and severity of the voice disorder, and explain discrepancies between voice quality and stroboscopic evaluation by providing cycle-to-cycle information that is not available with stroboscopy. Vocal function measures can help the voice care team determine treatment goals and can be used as visual feedback during behavioral treatment. Repeated testing over time allows clinicians to monitor and document changes that result from treatment and also to monitor disease progression or recurrence. From a research perspective, voice measurements can improve our understanding of voice production, help identify links between laryngeal disease and voice production, and document change with interventions.

Many of the instrument-based tests yield numbers that lead some clinicians to view the results as "objective"; however, examiners influence results through their specific instructions to the individual as well as the selection of stimulus, token, measure, and equipment. In addition, the testing environment, time of day, day of week, and the number and type of prior tests conducted on the same individual can affect measurements. Results of vocal function testing should, therefore, be interpreted with these considerations in mind. To be considered reliable, measures must be made with the use of standard protocols, recording procedures, patient instructions, and test environments. Because of the multidimensional nature of the voice, one measure cannot adequately characterize an individual's voice. Thus, a group of measures is frequently selected to capture the primary elements of the voice, such as pitch, loudness, and quality.

The following discussion describes a typical voice evaluation, with a focus on how to interpret the results. The evaluation is divided into the following categories: patient scales, perceptual evaluation, measures, and diagnostic therapy. Within each category, measures can reflect typical voice use or maximum performance capabilities. The particular measures performed vary from one speech-language pathologist to the next, depending on equipment available as well as on the examiner's education and philosophy.

Patient Scales

Individuals have different requirements and expectations of their voices; thus, the same level of dysphonia can differentially limit participation in typical daily activities. As part of a complete voice evaluation, the effect of the voice problem on each individual's life should be assessed. Patient measures are scales completed by the patient and sometimes a caregiver or significant other. These scales typically measure patient satisfaction, quality of life, general health, handicap or loss as a result of the voice disorder, or some aspect of voice production (e.g., ease of phonation, effort, quality). Several scales specific to voice have been published in the last decade. The scales vary in length, construction, and what they assess.

Each published scale measures a different aspect of the voice. Some scales were constructed more carefully than others, so reliability and validity characteristics differ. Scale selection should be made according to variables of interest and reliability requirements. In general, patient scales are a wonderful addition to a voice evaluation and provide novel information about the patient's point of view. A patient scale can guide discussion between health care providers and patients and help the team determine treatment goals.

Two commonly used scales, the Voice Handicap Index (VHI)[1] and Voice-Related Quality of Life (V-RQOL),[2] are described here. Details and information about scale construction can be found in the

Table 58-1

Patient Scales

Scale	Abbreviation	Total No. Items	Domains
Voice Handicap Index[1]	VHI	30	Function, physical, and emotional
Voice-Related Quality of Life[2]	V-RQOL	10	Physical and social-emotional functioning
Voice Activity and Participation Profile[7]	VAPP	28	Severity, effect on: job, daily communication, social communication, and emotion
Voice Symptom Scale[4,6]	VoiSS	30	Impairment, emotional response, physical symptoms
Reflux Symptom Index[9]	RSI	9	Symptoms associated with laryngopharyngeal reflux
Patient Questionnaire of Vocal Performance[10,11]	VPQ	12	Physical, social, and emotional
Voice Outcome Survey[12]	VOS	5	Symptoms associated with unilateral vocal fold paralysis

reference articles, and a synopsis of current scales can be found in Table 58-1.

Voice Handicap Index

The Voice Handicap Index was designed to assess handicap, "a social, economic, or environmental disadvantage resulting from an impairment or disability."[3] The instrument consists of 30 statements that patients rate on a 5-point equal-appearing interval scale that reflects the frequency of occurrence. The total possible score is 120, with higher scores reflecting greater handicap. Although the initial publication suggests division into functional, physical, and emotional subscales,[1] other writers have questioned the subscale structure,[4,5] suggesting that total score appears more meaningful. Since its publication in 1997, the Voice Handicap Index has been widely used to show voice handicap in specific groups of patients, comparisons between handicap and vocal function measures, and change with treatment.

Voice-Related Quality of Life

The Voice-Related Quality of Life comprises 10 items divided into physical functioning and social-emotional functioning subscales. Each item is scored on a 5-point interval scale that reflects the severity of the problem. For the subscales and the total score, 100 is the highest possible score and reflects the highest quality of life.

Other Patient Scales

The Voice Symptom Scale (VoiSS)[4,6] is a psychometrically sound 30-item scale representing physical impairment, emotional response, and related physical symptoms. The Voice Activity and Participation Profile (VAPP)[7] follows the terminology and framework of the World Health Organization's 1997 revision[8] of the International Classification of Functioning, Disability, and Health. Patients indicate their extent of limitation in daily activities and restriction of participation in corresponding activities.

The Reflux Symptom Index (RSI), the Patient Questionnaire of Vocal Performance (VPQ), and the Voice Outcome Survey (VOS) are more limited in scope. The Reflux Symptom Index, made up of 9 items, is designed to document patient symptoms of laryngopharyngeal reflux.[9] The Patient Questionnaire of Vocal Performance is a 12-item scale designed to assess the physical, social, and emotional impacts of a nonorganic voice disorder.[10,11] The Voice Outcome Survey is a 5-item survey designed for patients with unilateral vocal fold paralysis.[12]

Perceptual Evaluation

Auditory Perceptual Assessment

Several formal measures and scales have been proposed to rate voice quality; two of the most commonly used scales are described here. Auditory perceptual ratings are appealing because the ultimate goal of voice treatment is to improve perceived voice quality. Unfortunately, such measures are fraught with definition, rating, and interpretation difficulties. Voice quality is difficult to define, leading to many, often circular, definitions of each term. Raters have different internal representations of the parameters and severity. It is difficult to differentiate between related qualities, and univariate ratings do not often correlate well with global ratings or measurements (for a detailed discussion, see Kreiman and Gerratt[13]). Although auditory perceptual assessment often results in a number, the number represents a perceptual judgment rather than a measurement and should be treated accordingly.

GRBAS

GRBAS is a well-known standard scale that was developed by the Committee for Phonatory Function of the Japanese Society of Logopedics and Phoniatrics. As described by Hirano,[14] the *G* represents grade or overall quality. The other four letters represent dimensions of voice quality, as follows: *R* for roughness, *B* for breathiness, *A* for asthenia, and *S* for strain. Descriptions of each parameter are given in Table 58-2. Each parameter is rated on a 4-point scale: 0 means that there is no deficit in this parameter, 1 is a mild deficit, 2 is a moderate deficit, and 3 indicates a severe deficit. There is no standard recommendation for the type of utterance(s) to use with GRBAS, so specific information about testing conditions should be documented in the report.

CAPE-V

The Consensus Auditory-Perceptual Evaluation–Voice (CAPE-V) was developed at a 2003 consensus conference sponsored by the American Speech-Language-Hearing Association Special Interest Division 3, Voice and Voice Disorders.[15] Six core and additional examiner-selected parameters are rated on a visual analog scale. The clinician uses a tick mark to rate function on a 100-mm line and then measures the distance from the left end of the line to establish a score; higher scores reflect a more severe deviation from normal quality. Core parameters are overall severity, roughness, breathiness, strain, pitch, and loudness. The judged parameters are identified as consistent or intermittent, and resonance differences can be noted. The CAPE-V is to be scored from two sustained vowels, six standard sentences, and at least 20 seconds of natural running speech. Recommendations about testing and recording environments are included.

Other Aspects of Speech Production

The speech-language pathologist might comment on other aspects of speech production that can indicate structural or neurologic disorders that affect voice production. Examples are imprecise articulation, resonance, and prosody disturbances. *Resonance* is described as hypernasal,

Table 58-2

GRBAS Scale for Auditory-Perceptual Evaluation

Parameter	Hirano Definition*	National Center for Voice and Speech Definition†
Grade (G)	Overall severity	
Roughness (R)	Psychoacoustic impression of irregular vocal-fold vibration	An uneven, bumpy quality that appears to be unsteady in the short term but stationary in the long term; acoustically, the waveform is often aperiodic, with the modes of vibration lacking synchrony, but voices with subharmonics can also be perceived as rough.
Breathiness (B)	Psychoacoustic impression of air leakage through the glottis	Containing the sound of breathing (expiration) during phonation; acoustically, breathy voice, like falsetto, has most of its energy in the fundamental, but a significant component of noise is present owing to turbulence in the glottis. In hyperfunctional breathiness, air leakage may occur in various places along the glottis, whereas in normal voice, air leakage is usually at the vocal processes.
Asthenia (A)	Weakness or lack of power in the voice	A voice that appears too low in effort, weak; hypofunction of laryngeal muscles is apparent.
Strain (S)	Psychoacoustic impression of a hyperfunctional state of phonation	A voice that appears effortful; visually, hyperfunction of the neck muscles is apparent; the entire larynx seems compressed.

*From Hirano M. *Clinical Examination of Voice*. New York: Springer-Verlag; 1981.
†From Titze IR. *Workshop on Acoustic Voice Analysis: Summary Statement*. Iowa City, IA: National Center for Voice and Speech; 1995.

hyponasal, or cul-de-sac. *Prosody* refers to rate, repeated or prolonged syllables, rushes of speech, intonation (i.e., monopitch or monoloudness), and stress patterns.

Auditory perceptual correlates of speech breathing are often assessed. Breath group length, average loudness, loudness variability, and inspiratory duration provide important information about lung volume expended, adequacy and consistency of alveolar pressure, and shape of rib cage and abdominal walls during talking.

Visual Perceptual Examination

The *visual perceptual examination* refers to visible and physical aspects of voice production related to etiology, maintenance, or effect of dysphonia. Koschkee and Rammage[16] have divided the visual perceptual examination into the following five categories: (1) general appearance; (2) posture, breathing, and musculoskeletal tension; (3) neurologic dysfunction; (4) physical dysmorphology; and (5) clinical manifestations of disease. Several components of the visual perceptual evaluation are described in more detail here.

General appearance factors, such as apparent age, height and weight, facial expression, skin, hair, and nails, personal hygiene and dress, and head and neck observations, can be indicative of underlying systemic disease, previous treatment, or emotional disorder. One example is the masked face of parkinsonism.

Posture, breathing, and musculoskeletal tension are key components of a voice evaluation because they frequently affect pitch, loudness, and quality. Postural assessment likely involves information about the alignment of the head, neck, torso, pelvis, and legs. Visual assessment of breathing includes observations of neck, shoulder, chest, and abdominal movement. Reports of musculoskeletal tension contain information about extent of jaw motion, chin jut, neck extension, bulging of the neck muscles while talking, or raised shoulders.

Neurologic dysfunction is indicated by observations such as unsteadiness, asymmetry, rigidity, hesitation, slowness, weakness, incoordination, inconsistency, and extraneous movements. Weakness, asymmetry, and incoordination of the tongue, jaw, lips, or soft palate are especially noteworthy. The presence of focal dystonias, such as writer's cramp, blepharospasm, torticollis, and oromandibular dysphonia, usually leads the examiner to consider a neurologically based voice disorder, such as spasmodic dysphonia.

Tactile Perceptual Evaluation

The manual examination of laryngeal musculoskeletal tension includes palpation of the suprahyoid muscles, the major horns of the hyoid bone, the superior cornu and the lateral aspects of the thyroid cartilage, the thyrohyoid space, and the anterior border of the sternocleidomastoid muscle. It is useful to assess suprahyoid tension and thyrohyoid space both at rest and during phonation. The examiner should also attempt to move the thyroid cartilage from side to side.[17-19] Figure 58-1 depicts this evaluation. Some authors recommend palpating the thyrohyoid, cricothyroid, and pharyngolaryngeal (inferior constrictor and posterior cricoarytenoid) muscles as well.[20,21] Normal findings include palpable space between the hyoid bone and the superior border of the thyroid cartilage and mobility of the laryngeal complex. Findings indicative of excessive musculoskeletal tension include pain with palpation (frequently more severe on one side), decrease or absence of thyrohyoid space at rest or with phonation, muscle "knots," high carriage of the hyoid bone and thyroid cartilage, and difficulty rotating the larynx.[17-21]

A drawback of the examination is that it is subjective, and examiner's skill and experience likely affect ratings. In addition, there are currently no intra- or inter-examiner reliability data for the technique, and the sensitivity and specificity of abnormal findings are unknown. Even given these limitations, tactile perceptual evaluation is a powerful technique to rapidly assess the contribution of muscle tension to the observed voice quality. Teasing apart the muscle tension and other components of the dysphonia can help ensure proper diagnosis and management; the tactile examination is one tool used in this endeavor.

Measures

Many different types of measurements can be used in the voice evaluation to describe pitch, loudness, and quality. Most speech-language pathologists use a subset of these measures, depending on their particular philosophy, education, and the equipment available to them. The measures described here are grouped into several categories based on measurement technique: chest wall displacement, aerodynamic assessment, and acoustic analysis. A fourth category, vocal fold measures, includes noninvasive evaluation techniques designed to assess vocal fold vibration patterns.

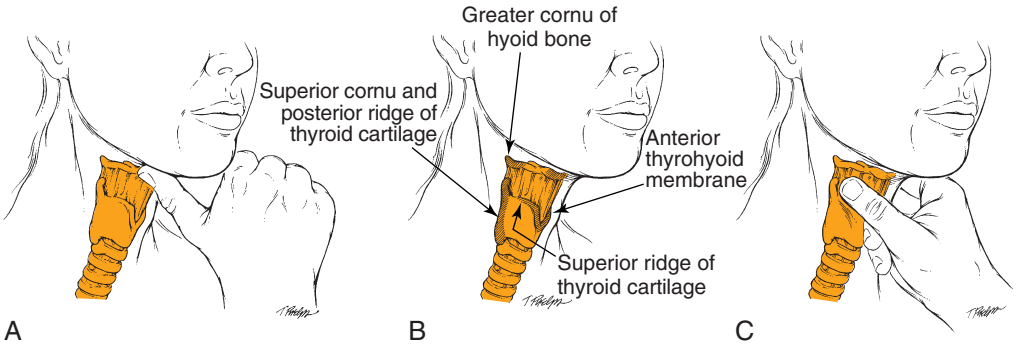

Figure 58-1. Manual musculoskeletal tension evaluation. **A,** Palpation of suprahyoid musculature. **B,** Palpation of greater cornu of the hyoid bone, superior cornu of the thyroid cartilage, and lateral aspects of the thyroid cartilage. **C,** Palpation of the thyrohyoid space.

Table 58-3

Perceptual Correlates of Aerodynamic Measures

Measure	Perceptual Correlate
Subglottal air pressure (Ps)	Phonatory effort
Phonation threshold pressure (PTP)	Effort to initiate phonation
Airflow	Breathiness
Laryngeal airway resistance (R_{law})	Phonatory effort, vocal strength, strain
Velopharyngeal measures	Nasal emission, strength of pressure consonants

Chest Wall Displacement

Measurements of chest wall movement can be used to estimate volume changes during voice production. Reports typically include information about the lung volumes used and chest wall shape during phonation. Lung volume variables of interest are the volumes at which the patient initiates and terminates speech. In general, people tend to initiate phonation around 20% of vital capacity above resting tidal end-expiratory level and to terminate phonation around resting tidal end-expiratory level.[22] Shape is usually described in terms of rib cage wall and abdominal wall movement. Because some shapes are more mechanically advantageous to phonation, the patient's typical shape and ability to change shape might be reported.

Aerodynamic Assessment

Aerodynamic evaluation involves measuring air pressures and airflows. Many calculations from these measures appear to be useful for vocal function analysis. Equipment can range from "low-tech" to "high-tech." Measurements are listed, along with their perceptual correlates, in Table 58-3.

MAXIMUM PHONATION TIME. *Maximum phonation time* (MPT) has long been used to describe both breath support and phonatory efficiency. The maximum length of time a patient can sustain phonation, however, is not fully explained by either vital capacity or laryngeal function.[23] Respiratory capacity and function, phonatory function, resonance, practice, frequency, intensity, instructions, and vowel choice all influence maximum phonation time.[23-29] Because of the variety of influences and because maximum phonation time is so dissimilar to conversational speech, the measure is neither accurate nor meaningful, especially when it is the sole measure reported.[23] When maximum phonation time is used, the longest of three trials should be reported. The normative range is quite large; for healthy young adults, the normal range is 6.6 to 69.5 seconds.[30]

SUBGLOTTAL AIR PRESSURE. *Air pressure* is defined as the force per unit area. The airway pressures important to voice production are tracheal pressure (*subglottal pressure*, or P_s), intraglottal air pressure (P_g), vocal tract input pressure (supraglottal pressure), and intraoral pressure (P_o). Relatively constant P_s and variable P_g are required to sustain vocal fold vibration. Measuring tracheal pressure (P_t) requires a tracheal puncture; thus, the intraoral air pressure (P_o) during a voiceless consonant (when the glottis is open) is typically used clinically for noninvasive estimation of P_t.[31] The magnitude of a normal pressure peak varies with loudness, age, gender, consonant, and speech context.[30] Normative values of 6.43 cm H_2O (standard deviation, 1.07) in men and 7.52 cm H_2O (standard deviation, 2.17) in women are reported.[32] Abnormal values can indicate a lack of driving pressure, an incompetent or insufficient velopharyngeal or laryngeal valve, or increased vocal fold mass or stiffness. Intraoral air pressure is useful to document clinician perceptions of weak pressure consonants, such as with velopharyngeal incompetence or dysarthria.

The minimum P_s needed for vocal fold vibration is called *phonation threshold pressure* (PTP),[33] and it is often measured at different pitches. At high pitches, phonation threshold pressure is sensitive to increased viscoelasticity of the vocal folds and has been useful in demonstrating subtle changes after dehydration, vocal fatigue, and vocal warm-up.[34-40] The measure is useful for documenting a patient's perception of increased effort to phonate, a common symptom of patients with vocal fold lesions, muscle tension dysphonia, and adductor spasmodic dysphonia.

AIRFLOW. *Airflow,* a change in volume of air over a specific time, is measured as volume (mL or L) per time (second or minute). Mean airflow is commonly assessed during sustained phonation, although it is sometimes measured during connected speech. Airflow measures are influenced by gender, age, fundamental frequency, and intensity. Normal values for women range from 91 to 156 mL/second, with a standard deviation range of 16 to 71 mL/second. Mean values for normal men range from 101 to 183 mL/second, with a standard deviation range of 16 to 77 mL/second.[30] Mean airflow is typically increased when there is poor vocal fold closure, such as for vocal fold motion impairment.[14,41] The shape of the airflow trace can also be useful; it is common with motion impairment to see a burst of air at the beginning of phonation and low airflow by the end. With hyperfunction, mean airflow might be reduced owing to over-closure of the vocal folds during phonation.[24]

LARYNGEAL AIRWAY RESISTANCE. *Laryngeal airway resistance* (R_{law}) is the ratio of translaryngeal air pressure to translaryngeal airflow.[30] Smitheran and Hixon[31] demonstrated that it can be estimated using P_o and mean airflow from repetitions of the syllable /pi/ at a rate of 1.5 syllables per second. Average values range from 24 to 45 centimeters of water per liter per second (cm H_2O/LPS) for adult men and 27 to 51 cm H_2O/LPS for adult women.[30] Higher R_{law} can occur with increased intensity, a long closed phase, or a higher force of closure.[24] Because it is a ratio, the R_{law} might be normal when the P_o

Table 58-4

Acoustic Measures and Their Perceptual Correlates

Measure	Perceptual Correlate
Frequency (Fo)	Pitch
Intensity (sound pressure level [SPL])	Loudness
Voice range profile (VRP)	Interaction of pitch and loudness ranges
Variability measures	Quality (e.g., roughness, breathiness, timbre)
Spectral displays	Quality
Fast Fourier transform (FFT)	Quality
Linear predictive coding (LPC)	Quality
Long-term average spectrum (LTAS)	Quality
Cepstral peak prominence (CPP)	Quality
Nasalance	Hypernasality, hyponasality

and airflow values are not. It is therefore a good idea to know the individual values used in the calculation.

AERODYNAMIC ASSESSMENT OF VELOPHARYNGEAL FUNCTION. The *velopharyngeal system* can be assessed aerodynamically with the use of P_o and nasal airflow (V_n) during stop consonants (usually /p/). Comparing the V_n and P_o traces during a transition between nasal and stop consonants (e.g., "mp" in the word "pamper") shows the timing of the velopharyngeal closure. If nasal cavity pressure is also measured, velopharyngeal orifice area can be calculated.[42,43]

Acoustic Analysis

The acoustic speech signal is the system's output and is rich in information about pitch, loudness, and quality. The signal is quite complex and is therefore broken down for analysis into the dimensions of frequency, amplitude (intensity), and time. Acoustic measurements are best made from signals recorded on high-quality equipment in a quiet environment and with the use of standard instructions. Data should be interpreted in light of subject age and gender, interactions between parameters, speech sample selected for analysis, and number of tokens. It is also important to know whether the samples were consistent with typical voice use or maximum/best performance. Commonly used acoustic analysis measurements are described here and are listed, along with their perceptual correlates, in Table 58-4.

FREQUENCY. *Frequency* is the number of repeating cycles in the acoustic waveform each second. Pitch is the perceptual correlate of frequency. In truth, many additional factors contribute to perception of pitch, but frequency is the most salient one. Lower pitches are associated with a longer glottal cycle as reflected by fewer cycles per second and a lower fundamental frequency. Higher pitches are associated with shorter glottal cycles, as reflected by more cycles measured per second and a higher fundamental frequency. Altered pitch and restricted pitch range are common symptoms of voice disorders and can represent a significant concern for patients. Average speaking fundamental frequency and maximum phonational frequency range (MPFR) are the most common clinical parameters used to examine frequency. Normative values are influenced by intensity, speech sample, vowel type, age, and gender.[30,44] Average speaking fundamental frequency ranges from approximately 100 to 125 Hz for normal adult men into their 70s and from 190 to 225 Hz for normal adult women.[30] The maximum

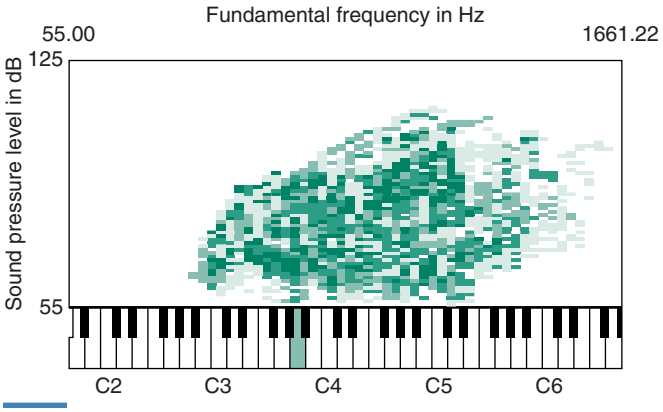

Figure 58-2. Sample Voice Range Profile (VRP).

phonational frequency range is frequently reported through the use of a semitone scale, whereby perceived changes in pitch are equalized across the frequency range. The semitone scale corresponds with the musical scale, with 12 semitones in an octave. Maximum range for men and women is typically two-and-a-half to three octaves, or approximately 29 to 36 semitones.[30]

INTENSITY. Sound pressure level (SPL), often referred to as *intensity*, is the acoustic correlate of loudness. Many factors influence the perception of loudness, but intensity is the primary one. Sound pressure level is measured in decibels (dB) and is influenced by frequency, vowel, speech sample, equipment, distance from the sound source, and ambient noise.[44] The most common measures are average speaking, minimum, and maximum sound pressure levels. On average, men and women speak at approximately 70 dB,[30] although there can be large variability in conversational speech. Maximum range is typically less than 60 dB to at least 110 dB.[24,45] Intensity measures are useful to document concerns about decreased loudness levels, which are common for patients with Parkinson's disease or impairment of vocal fold motion, and they help identify patients who have difficulty speaking quietly, such as people with vocal fold scarring or lesions.

COMBINED FREQUENCY AND INTENSITY. A frequency-by-intensity plot for an individual's total range is called a *phonetogram* or a *voice range profile* (VRP). The minimum and maximum intensities an individual can produce are plotted for every frequency in that person's range. There is a typical shape to the plot, which is demonstrated in Figure 58-2. Visual inspection of the voice range profile highlights the interaction between frequency and intensity, with the highest frequencies generally produced at greater intensities than the lowest frequencies. The middle of the frequency range is usually the location of the individual's maximum intensity range.[33] There is no standard for analyzing the voice range profile, but several writers have proposed methods of quantifying the plot.[46-51] Even though it is difficult to describe a voice range profile with one number, the profile is very useful for tracking changes and for documenting difficulty with specific pitch and loudness combinations (e.g., trouble singing particular notes quietly).

VARIABILITY MEASURES. Acoustic measurement of voice quality remains elusive. Theoretically, measures that document variability in the sound wave or noise in the spectrum should correspond well with roughness, breathiness, and strain. Unfortunately, how well the measures relate to voice quality ratings remains uncertain,[44,52-59] and no particular measure or group of measures has emerged as indispensable for the diagnosis of voice disorders. The best-known short-term perturbation measures are jitter and shimmer, which are the most likely to be included in a report because normative values are reported in the literature. *Jitter* is cycle-to-cycle variation in frequency, and *shimmer* is cycle-to-cycle variation in amplitude. Various measures of harmonics or signal to noise have also been proposed. An excellent review of acoustic measures and algorithms can be found in a chapter by Buder.[60] One important limitation to perturbation analysis is that it can be reliably performed only for nearly periodic signals. If the signal has no

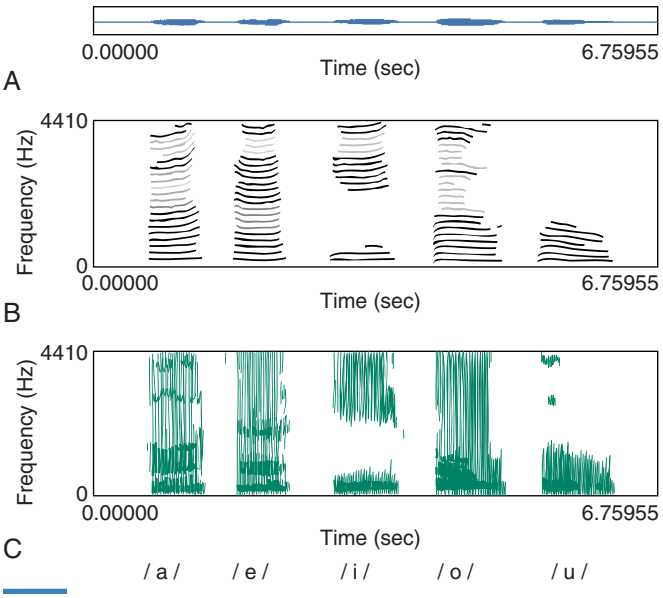

Figure 58-3. **A,** Audio signal; **B,** narrow-band spectrogram; **C,** wide-band spectrogram for /a/ /e/ /i/ /o/ /u/.

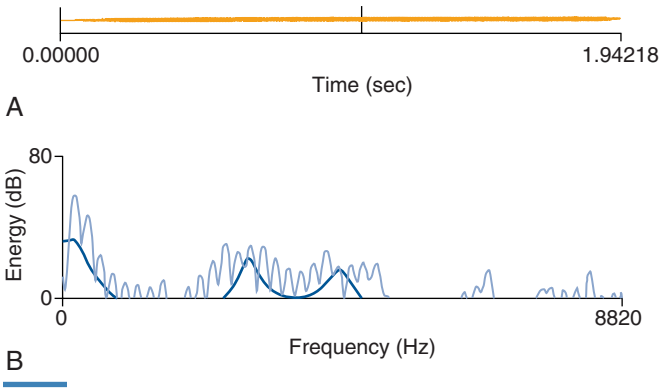

Figure 58-4. **A,** Audio signal of sustained /i/; **B,** Fast Fourier Transform (*light blue*) and linear predictive coding (*dark blue*) spectra from the marked portion of the /i/.

single fundamental frequency or has qualitative changes (common for patients with disordered voices), perturbation analysis is not appropriate.[61]

SPECTRAL DISPLAYS. Vocal fold vibration produces a (source) signal that has a fundamental frequency and multiples of that frequency, called *harmonics*.[62] This source signal is modified as it passes through the supraglottic vocal tract, called the *filter*. The vocal tract structures change position for different vowels, changing the location of resonant peaks, called *formants*.[30] Because the voice that people hear is a combination of source and filter characteristics, the harmonics and the formants each tell part of the story of voice production.

A *spectrogram* is the most common visual depiction of an acoustic wave. It displays time on the x-axis, frequency on the y-axis, and amplitude on a gray scale. Changing the bandwidth of the analysis window allows us to view details of either the source or the filter. A narrow-band spectrogram, with its greater frequency resolution, emphasizes the fundamental frequency and the harmonics. A wide-band spectrogram, with its greater time resolution, highlights the formants.[30] Figure 58-3 shows both a narrow-band spectrogram and a wide-band spectrogram of /a/ /e/ /i/ /o/ /u/. Spectrograms clearly show noise versus harmonic structure, tremor, phonation breaks, and pitch breaks. The relative amplitude of the first harmonic has been shown to correlate with ratings of breathiness,[63,64] as have increased noise in the higher harmonics and increased bandwidth of the first formant.[65] Spectrograms are useful for tracking change and can be used in real time during voice therapy for visual feedback.

ADDITIONAL ACOUSTIC MEASURES. A *Fast Fourier Transform (FFT) analysis* converts the signal so that the individual frequencies from a narrow time band can be identified. The display shows frequency on the x-axis and intensity on the y-axis. *A linear predictive coding (LPC) spectrum* shows a smoothed line that highlights the formant structure but that again reveals the amplitude of frequencies for a narrow band of time. Figure 58-4 shows the Fast Fourier Transform and linear predictive coding spectra for the marked location in the audio signal of a sustained /i/.

Long-term average spectra (LTAS) show the amount of energy at each frequency over a long period (e.g., a standard reading). Because the measure is averaged over such a long sample, the effects of speech context are minimized. Measurements of the long-term average spectra typically compare the amount of energy in different frequency bands. The resultant values, which are often referred to as *spectral tilt*, indicate whether low or high frequencies dominate the spectrum.[66] Increased spectral tilt is linked with breathy voice.[65]

Cepstral peak prominence (CPP) is a measure of signal periodicity that does not rely on fundamental frequency extraction, but instead corresponds to the regularity of harmonic peaks. The measure has been found to correlate with breathiness and overall dysphonia ratings.[63,64,67] A lower cepstral peak performance reflects less periodic vibration.

Acoustic assessment of velopharyngeal function: Oronasal resonance balance can be assessed acoustically using a commercial program such as the Nasometer (KayPENTAX, Lincoln Park, NJ). This instrument computes *nasalance*, a ratio of nasal sound energy to total (oral plus nasal) sound energy. There has been some debate about the validity of nasalance because of inconsistent correlation between nasalance and the perceptual evaluation of hypernasality. Proposed hypernasality cutoff scores have varied according to testing centers and raters but appear to range from 25% to 33% for a standard passage without nasal consonants (zoo passage). That is, mean nasalance scores of 25% to 33% or greater are generally associated with perceived hypernasality; hyponasality is generally perceived when mean nasalance falls below 50% for nasal sentences.[68-71] There is evidence to suggest that regional normative data should be collected, because resonance patterns vary according to dialect.[68] Documenting hypernasality due to velopharyngeal dysfunction can be an important factor in narrowing potential sites of lesions.

Measures of Vocal Fold Vibration

ELECTROGLOTTOGRAPHY. Electroglottography (EGG) measures the conductance of a low-frequency electric signal across the neck between two surface electrodes.[24,30,72] The conductance of the signal varies with the vibration of the vocal folds; when the vocal folds contact each other, conductance increases, and the resultant EGG trace has a positive slope. As vocal folds separate, conductance decreases, and the trace has a negative slope. Because the traces display the extent of contact relative to the rest of the signal, maximum contact does not necessarily indicate complete vocal fold closure. The waveform's shape is potentially meaningful for describing the pattern of vocal fold vibration. Baken and Orlikoff[30] summarize a variety of EGG shapes and the corresponding glottic cycles. Specific measures of increasing contact, decreasing contact, and speed quotients have been proposed over the years, but some researchers question their validity.[73]

In EGG, abnormalities in the signal are not always the result of abnormalities in vocal fold motion; the signal can be affected by the placement of electrodes, movement of the larynx during phonation, irregularities of neck tissue, and mucous bridges. Even given its limitations, EGG is an excellent measure of fundamental frequency and offers a unique opportunity to study the vocal fold vibration without any influence of supraglottic structures or shaping. It is noninvasive, relatively inexpensive, and can be used at the same time as other measures (e.g., airflow, videostroboscopy).

INVERSE FILTERED FLOW. In inverse filtered flow, the effects of the vocal tract (resonances) are filtered out of either the acoustic or the

aerodynamic waveform, and the glottic source signal is left. From this trace, several measures can be made, including *skewing quotient* (the ratio of the positive slope to the negative slope) and *open quotient* (the ratio of the time open to the period of the waveform).[33] Inverse filtered flow is quite useful because it allows us to study the glottal flow signal, yet it is technically complicated and therefore challenging to incorporate into clinical assessment protocols.

Diagnostic Therapy

Diagnostic therapy (i.e., probe therapy) is used to determine whether voice quality can be modified and in what situations. Response to therapeutic probes can guide intervention decisions and even help determine the diagnosis. Therapy probes often include modification of extrinsic laryngeal muscle tension or posture. They also include techniques to modify the breath, phonation, and resonance subsystems.

Summary

Voice evaluation and measurement should be multidimensional, reflecting the complexity of the voice. Evaluation includes patient scales, perceptual evaluation, vocal function measures, and diagnostic therapy. Individual measures are influenced by many factors that must be considered by the clinician or researcher interpreting the data. Each of the measures addresses a piece of the puzzle, and none stands alone as the perfect answer to all questions. A set of measures should be selected that documents the patient's particular concerns or that parallels the questions that are of interest to the examiner. The development of standard protocols and testing conditions among centers will improve the ability of clinicians and researchers to communicate and hasten further understanding of the human voice.

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CHAPTER FIFTY-NINE

Neurologic Evaluation of the Larynx and Pharynx

Gayle Ellen Woodson

Andrew Blitzer

Ronda E. Alexander

Nazaneen N. Grant

Key Points

- Evaluation of the larynx and pharynx is a multidisciplinary endeavor and may involve otolaryngologists, neurologists, speech-language pathologists, and radiologists.
- Normal functions of the larynx include regulation of respiratory mechanics, airway protection during deglutition, and phonation.
- Normal function of the pharynx includes maintenance of patency for respiration and effective constriction for swallowing with prevention of reflux into the nose or mouth.
- Neurologic evaluation begins with observation of voluntary and involuntary movements and having the patient perform various phonatory tasks.
- Flexible laryngoscopy and stroboscopy give information on vocal cord movement, compensatory mechanisms, laryngeal sensation, mucosal wave and pliability, and velopharyngeal competence.
- Video recording of physical examinations facilitates later review and consultation with colleagues.
- Acoustic analysis gives objective measures of fundamental frequency, perturbation, and spectral analysis.
- Electromyography can be used to assess the integrity of a neural pathway. It is useful to prognosticate the potential for recovery of motion in a patient with a fully immobile vocal fold.
- Sensory testing quantifies sensory loss and can give information for evaluating the site of a neurologic deficiency.

The upper aerodigestive tract serves the diverse purposes of breathing, eating, and communicating. These activities require some orthogonal functions. For example, pharyngeal patency should be maintained during respiration, but the pharynx should be forcibly constricted during swallowing. In addition, the anatomic structure of the upper aerodigestive tract is precarious, with ingested food and inspired air traversing the same space. Precise coordination of motor activity and appropriate response to sensory feedback are essential for normal function. Neurologic disorders may impair upper aerodigestive tract function by diverse mechanisms, including motor weakness, incoordination, and impairment of sensation.[1,2]

The diagnosis of disorders in patients with neurologically impaired function of the upper aerodigestive tract is often elusive, particularly when the problem is isolated to that region. The reason is that the ability of the throat and larynx to function cannot be directly observed. Patients with complaints of hoarseness, dysarthria, dysphagia, aspiration, or airway obstruction are often seen by otolaryngologists, whose training emphasized morphologic rather than functional evaluation. Neurologists, whose forte is functional assessment, generally confine their evaluations to structures that are more accessible, such as limbs. If the anatomy is normal and if no functional deficit is noted on a traditional neurologic examination, a patient who actually has a neurologic impairment is often incorrectly assumed to have a functional or psychiatric disorder. Thus, the diagnosis of a generalized neurologic disorder, such as myasthenia gravis or amyotrophic lateral sclerosis (ALS), may be delayed until the disease process is more widespread and apparent. As a result, patients may receive well-intentioned but ineffective therapy instead of potentially effective treatment.[3-5]

In patients whose neurologic diagnosis has been established, assessment of laryngeal and pharyngeal function is an important component and may be lifesaving. Optimal treatment and rehabilitation of patients with swallowing, speech, or phonation disorders require identification of the precise pathophysiology of the problem so that appropriate therapy may be designed.

The diagnosis of neurologic impairment of the upper airway requires an awareness of the possibility of neural dysfunction, familiarity with the signs and symptoms of neural dysfunction, and a systematic approach to the examination of the throat and pharynx. Box 59-1 lists some symptoms that suggest neurologic impairment. The patient's interests are best served by the collaborative efforts of the otolaryngologist, who is highly skilled in visualizing the throat and larynx, and the neurologist, who is knowledgeable in the pathophysiologic processes. This chapter reviews normal physiology and salient features of specific neurologic diseases that affect function, outlines the approach

Box 59-1

Laryngeal and Pharyngeal Symptoms Suggesting Neuropathology

Speech Problems
Lack of volume
Breathiness
Instability of pitch or volume
Lack of voice inflection
Abnormal resonance
Dysarthria

Swallowing Problems
Oral incompetence
Velopharyngeal incompetence
Inability to initiate a swallow
Aspiration

Breathing Abnormalities
Fluctuating inspiratory stridor
Weak breathy cough
"Gurgly" breathing noises

to the history and physical examination of patients in whom such diseases are suspected, and discusses how ancillary tests may be useful.

Normal Function

Phylogenetically, the most important function of the larynx is protective; the larynx prevents ingested food and drink from entering the lungs. To fulfill this role in humans, the larynx should be open during breathing and tightly closed during swallowing. Phonation is a more advanced evolutionary function. Glottic closure during forced exhalation results in an effective cough to clean the lungs and prevent atelectasis. Laryngeal closure is required to generate positive intrathoracic pressure for defecation, childbirth, and lifting heavy objects and for the stabilization of the thorax. The larynx also seems to play a sophisticated role in controlling airflow and pressure during breathing. The vocal folds open just before respiration and then close gradually during exhalation, braking expiratory airflow and thereby influencing the rate of breathing. The sensory feedback loops that control these respiratory functions of the larynx are not well understood, but it is clear that feedback from a variety of receptors is involved.[1,2,6]

Swallowing is a deceptively simple function. Food prepared in the mouth is ejected into the pharynx and then rapidly propelled downward around the glottis, through the pyriform sinus, and into the esophagus. During the swallow, the same pharynx that remains patent during breathing is responsible for constricting tightly in an organized sequence from top to bottom. Regurgitation into the nose or reflux into the mouth is prevented by actions of the soft palate, tonsillar pillars, and base of the tongue. The larynx is pulled upward and forward, away from the flow of the bolus. This action also decompresses the sphincter between the pharynx and esophagus. Flexion of the epiglottis and closure of the glottis prevent the entry of any errant material into the airway. After this complex and coordinated activity, the cricopharyngeal muscle should be relaxed when the bolus reaches the caudal end of the pharynx to permit passage into the esophagus. If pharyngeal peristalsis is inadequate or if the upper esophageal sphincter is insufficiently opened, residual material in the pharynx could penetrate the airway during the next inhalation. The unique anatomic configuration in humans after infancy renders swallowing more difficult. In all other mammals, the feeding and breathing channels are offered a degree of separation by interdigitation of the epiglottis and uvula. In humans, these structures are separated during early development by the descent of the larynx relative to the palate.[7-9]

Speech is audible communication that results from phonation, resonance, and articulation. The production of sound *(phonation)* requires several conditions. Expired airflow and pressure should be sufficient to induce oscillation of the vocal folds. The vocal folds should be appropriately approximated. If they are closed tightly, excessive expiratory force is required, resulting in a strained, harsh voice or complete aphonia. If the vocal folds are too far apart, increased expiratory airflow volume is required, so that the voice becomes weaker and breathier or even fades to a whisper. The three-dimensional shape of the vocal fold is also important in imparting favorable aerodynamic features to the glottis. Atrophy of the vocal fold causes concavity in the axial and coronal planes. The former results in incomplete glottal closure even during tight approximation of the vocal processes. Concavity in the coronal plane results in a convergent airflow tract. Control of length and tension is required to produce normal inflections in pitch and tone. In the absence of such control, the voice may be flat and expressionless, or it may be distorted by uncontrolled pitch breaks. The mucosa of the vocal folds should be supple to permit free vibration. All but the last of these requirements for phonation are susceptible to derangement by neurologic dysfunction.[10,11]

Resonance is the modification of phonation to produce voice. Pure phonated sound as produced by the vocal folds does not sound like a human voice; it is a strident and unpleasant noise. This sound is modified by resonance of the head, neck, and chest so that component frequencies are selectively amplified or dampened. Vocal resonance is largely determined by anatomy, but it also is significantly modulated by motor activity of the pharynx, soft palate, and oral cavity. This principle may be used in speech therapy to achieve stronger voices in patients with impaired function. Certain neurologic disorders, such as ALS, stroke, and Guillain-Barré syndrome, result in altered vocal resonance. The characteristic sound of the voice in patients with these disorders may be a valuable physical sign to aid in early diagnosis.[10,11]

Articulation is the shaping of voice into words by actions of the lips, tongue, palate, pharynx, and larynx and is highly susceptible to neurologic impairment. Whereas dysarthria in children is caused most often by a hearing deficit, acquired dysarthria in adults usually indicates neurologic impairment. Dysarthria may be a result of impaired motor output, such as weakness, paralysis, or incoordination, but may also result from cognitive or language defects or from apraxia of speech.[10,11]

Neurologic Examination of the Mouth, Larynx, and Pharynx

Listening to the patient is the first step of the examination in the patient with a voice complaint. Often, it is possible within minutes to make a working diagnosis on the basis of the sound of the voice and the patient's description of the problem. The patient should be questioned carefully about vocal fatigue, pain with speaking, increased effort required for speech, glottal tightness, pitch breaks, and tremor.

The standard neurologic examination does not address the relatively inaccessible regions that are familiar to the otolaryngologist. The following protocol is suggested as a systematic approach to detecting neurologic dysfunction. The objectives are to assess the integrity of the lower cranial nerves and to seek signs of central nervous system disorders.[10]

Oral Cavity

Observe the lips, palate, and tongue for abnormal spontaneous movement. Involuntary, slow, athetoid movements of the tongue occur in patients with tardive dyskinesia, which is usually a reaction to a major tranquilizer. A quivering, "bag of worms" appearance indicates fasciculations, a characteristic sign of ALS. Spasmodic motions, in particular excessive blinking and jaw thrusting, are characteristic of Meige's syndrome. Assess range of motion, strength, and symmetry of the mouth and palate muscles as usual. Ask the patient to purse the lips, to protrude the tongue and move it from side to side, and to open the mouth and say the traditional /ah/ to test for palate motion and symmetry. The best way to assess tongue strength is to have the patient push the tongue against the buccal mucosa while the physician palpates the cheek externally.[10]

It is important to test not only the strength but also the central control of lip and tongue muscles. Rapid repetition of the syllable /Pa/

shows lip function. A healthy person is able to maintain a regular rhythm at a rapid rate. A lower motor neuron lesion decreases the strength of this action. Upper motor neuron involvement reduces the rate at which the patient can repeat the syllable, but regular rhythm should be preserved. In patients with cerebellar dysfunction, the rhythm is erratic. Myasthenia gravis involvement results in fatigue with repetitive motion. Other syllables address other muscle groups. /Ta/ tests the tip of the tongue, and /Ga/ tests the posterior tongue.[10]

Flexible Laryngoscopy

Neurologic function of the larynx is difficult to assess without the use of flexible laryngoscopy. This technique permits observation during both quiet breathing and a variety of tasks. The addition of a video camera is invaluable, because it produces an enlarged image on the monitor that may be recorded for detailed evaluation and saved for comparison with future evaluations.[12,13]

Attention is first directed to the soft palate. With the scope in the posterior choana, the soft palate is observed for any tremor or spasmodic movement at rest. The patient is instructed to swallow and say "kitty cat." These tasks show the symmetry and competence of velopharyngeal closure.[12,13]

The scope then is advanced to visualize the base of the tongue. Alternating phonation of /ee/ and /ah/ should result in first anterior and then posterior movement of the tongue. Assessment of the pharynx is more difficult, because during a normal swallow, the view through the flexible scope is totally obscured. In those with pharyngeal paralysis or paresis, closure is impaired, and impairment of motion on the involved side may often be detected. Pooling of secretions in the hypopharynx is indicative of poor swallowing function, which could be attributed to either sensory or motor impairment.[12,13]

The most detailed assessment is focused on the larynx. During quiet breathing, the vocal folds may appear motionless and partially abducted, but abduction usually occurs just before inspiration, and gradual adduction during exhalation. The degree of motion varies with the respiratory effort and with the level of upstream resistance. With deep inspiration, the vocal folds abduct widely. During panting, the vocal folds remain fixed in an abducted position. Nasal breathing in most patients offers more resistance than mouth breathing, so the range of vocal fold movement is usually greater with the mouth closed.[12,13]

Having the patient perform a vigorous voluntary cough is a good way to assess the strength and range of motion of the larynx. The vocal folds abduct during the inspiratory phase, close tightly for the compressive phase, and then suddenly open widely. The cough is a useful way to differentiate psychogenic stridor from true bilateral laryngeal paralysis.[12] Aphonic malingering patients may not adduct their vocal folds completely when asked to phonate but adduct them normally with cough. During phonation, the vocal folds should adduct smoothly and symmetrically. Recurrent laryngeal nerve paralysis can usually be diagnosed through observation of the vocal folds during breathing and phonation, although paresis may become evident only if the patient performs repetitive brief phonations. Asking the patient to sniff and then say /eee/ repetitively may elucidate a paresis. Repetitive phonations also reveal fatigue in patients with myasthenia gravis. For assessment of the cricothyroid muscle, which is innervated by the superior laryngeal nerve, the patient is asked to perform a pitch glide, phonating from a low pitch to a high pitch and back down. The pitch should rise as the vocal folds become longer and thinner.[12,13]

It is sometimes difficult to differentiate a functional or psychiatric voice problem from a neurologic disorder. It is helpful if the physician is familiar with characteristic distortions of the larynx in hyperfunctional dysphonia. Some common distortions are compression of the glottis in the anteroposterior dimension, contraction of the aryepiglottic folds, and false vocal fold adduction, which may be severe enough to totally obscure the true vocal folds. Patients with hyperfunctional dysphonia also characteristically elevate the larynx and speak with a low lung volume. Such dysfunction is usually amenable to voice therapy. It is important to remember that neurologic and functional conditions commonly coexist and that some patients may use hyperfunction to compensate for a neurologic defect.

Video recording of the endoscopy may enhance the examination, because the record can be reviewed repeatedly or viewed by other consultants. An objective record is also provided for monitoring the progress of the disorder or the patient's response to therapy. Transoral telescopic laryngoscopy with a rigid-rod quartz lens system provides a clear, magnified view of the larynx. This is the best technique for demonstrating laryngeal morphology and documenting even minute laryngeal lesions. The use of the telescope has limitations. The patient's mouth should be open with anterior traction on the tongue, although this position prevents examination of the larynx during speech or swallowing. The examination also requires topical anesthesia in many patients.[12,13]

The stroboscope provides a flashing light to simulate a slowed vocal cord vibration. The stroboscope has a microphone to sense the fundamental frequency of the vibrations and to coordinate the flashing light to the same frequency. If the light flashes at the fundamental frequency, the stroboscope freezes one image in the vibratory cycle. The slowed motion allows the most accurate assessment of the mucosal wave, which may be impaired by scarring, edema, or subtle defects in the mucosa. Lesions such as subtle edema, vocal cord cysts, and early carcinoma may be best seen as an adynamic segment of the vocal cord on stroboscopy. Stroboscopy also allows accurate evaluation of the closing and opening pattern of the larynx and may be able to indicate the probable underlying cause of a faulty closure. Probable causes that can be detected with a stroboscope include vocalis muscle atrophy, posterior laryngeal edema, and faulty vocal technique. The stroboscope has limitation in patients in whom an unstable voice does not allow for a steady frequency of slow motion. This occurs in patients with vocal cord paralysis or vocal cord scarring and in some patients with spasmodic dysphonia.[14]

Ancillary Tests

Rating Scales

In the past, assessment of voice disorders has focused on objective measures of voice quality and aerodynamic tests. These measurements, however, do not account for global voice function and its effect on quality of life, which is the ultimate goal of therapy and surgical intervention. Several rating scales have thus been validated to quantify the degree of disability attributable to a voice disorder. The Voice Handicap Index (VHI) is a patient-based self-assessment tool consisting of 30 items equally distributed over three domains—functional, physical, and emotional aspects of voice disorders. A modified, 10-item rating scale known as the VHI-10 was subsequently developed and validated. Other measures have been developed as well, including the voice-related quality of life (V-RQOL) instrument, a 10-item outcome instrument with a social-emotional domain and a physical-functional domain.[15] In interpreting the scores from such scales, the physician must keep in mind that the output is ordinal ranking only, rather than rational number values.

Acoustic Analysis

The sound of a voice can be assessed quantitatively by mathematical processing of the recorded sound. Voice is not a simple sine wave; rather it is a complex group of waves of varying frequency. In a pure periodic waveform, all frequencies above the fundamental frequency are multiples of f_0 called *harmonics*. Lack of periodicity is perceived as noise and is described as frequencies between the harmonics. A Fournier analysis is a computational method of simplifying complex waveforms into component parts. Transmission of sound through the vocal tract with its characteristic resonant properties alters the sound by enhancing the resonant frequencies. Most commercial packages for acoustic analysis provide measures of f_0 (a correlate of pitch) as well as perturbation measures that track variations in loudness (shimmer) and pitch (jitter). Acoustic measures have only limited clinical relevance. Although they can be used to document severity and to track changes over time and with treatment, they provide little diagnostic information. For neurogenic disorders, acoustic parameters do not differentiate voices of patients with neurologic disorders such as Parkinson's disease, ALS, and Huntington's disease.[16] Furthermore, validity diminishes with the

severity of hoarseness, and it is impossible to analyze a severely dysphonic voice sample. The one acoustic measure that is very useful in neurologic voice disorders is the documentation of breaks in the acoustic signal. These events are quite characteristic of spasmodic dysphonia but rare in subjects with habitual or psychogenic hyperfunctional dysphonia.[17] Thus, detection and measurement of voice breaks can be very useful in diagnosing spasmodic dysphonia.

Performance Measures

Performance measures evaluate the capacity of the patient to produce vocal sound. Maximum phonation time is a clinically valuable parameter that is very simple to measure. It is the maximum duration that a subject can sustain phonation of a vowel. It can be measured by a computerized program or just with an ear and a stopwatch. If the glottis is incompetent, excess air escapes during phonation and the duration of maximum phonation time decreases; in some cases of excessive glottic closure, it increases. Maximum phonation time can also be decreased by poor respiratory function or inadequate patient effort, and these factors should be considered in interpretation of results.

A more complex assessment of vocal capacity can be acquired by the phonetogram, which tracks the minimum and maximum loudness that the subject can produce across a spectrum of pitch. This technique, which is not widely used in the United States, is time and effort intensive.

Aerodynamic Assessment

Whereas acoustic measures address the sound of the voice, measurements of airflow and air pressure provide important information about the mechanics of vocal production. Phonatory and respiratory airflow can be easily measured directly and are useful in monitoring the effects of therapy. Accurate interpretation of airflow data requires concurrent measurement of subglottic pressure—the driving force for phonation. Direct measurement of subglottic pressure requires invasive procedures, such as transglottic placement of a transducer or tracheal puncture. More commonly, phonatory subglottic pressure is estimated from measures of intraoral pressure during repetitions of the syllable /pi/. This technique was developed in normal subjects and has not been validated in pathologic conditions.

Other means of assessing aerodynamic ability are body plethysmography (measurements of chest wall movement), spirometry, and airflow measurement with a hot wire anemometer (to determine rapid changes in airflow).[7,18]

Glottography

Photoglottography and electroglottography are tools that track motion of the edges of the glottis during phonation. Photoglottography is performed by shining a light on the larynx. The amount of light that passes through the glottis is proportional to the size of the glottic opening. The light transmission may be measured by a photosensor overlying the subglottic neck skin. Electroglottography is a technique based on a change in electrical resistance and is related to movement of the vocal cords. Low-voltage electrical current is applied through surface electrodes that have been placed on the skin over the thyroid alae. The electrodes then measure a change in electrical resistance that is representative of the surface area of contact of the vocal folds. Changes in the electroglottography amplitude and duration of the opening-and-closing phase may characterize abnormal function. The electroglottography results suggest an abnormal condition through variance from normal rather than with a pathognomonic sign.[7,19]

Electromyography

Electromyography (EMG) can be used to assess spontaneous and voluntary activity of laryngeal muscles. Its chief value is in assessing nerve integrity, and it can be used to assess the prognosis of recovery from a nerve injury. It is occasionally useful in the diagnosis of myasthenia, motor neuron disease, and myopathy.

Laryngeal EMG makes use of standard equipment. Topical anesthetic is not used because it has been shown to affect the electrical signal.[20] The thyroarytenoid muscle, supplied by the recurrent laryngeal nerve, is most commonly sampled. The needle is introduced between the thyroid and cricothyroid cartilages and directed superiorly. One approach is to enter the subglottic airspace in the midline and then to divert the needle into the right or left vocal fold. This step frequently stimulates coughing, because sensory receptors in the vocal fold mucosa are activated. An alternative approach is to enter the cricothyroid space off the midline so the muscle may be entered without violating mucosa. To verify needle location, the examiner asks the patient to phonate. The cricothyroid muscle is commonly tested by insertion of the needle in the midline, down to the superior edge of the cricoid cartilage. The tip of the needle is then "walked" over the cartilage superiorly and laterally to avoid the strap muscles. There usually is a palpable pop as the needle enters the cricothyroid muscle. To verify needle placement, the examiner asks the patient to begin phonating at a comfortable pitch and then to glide to a higher, falsetto pitch. The cricothyroid muscle may be active or silent at the comfortable pitch, but it is activated at higher pitches.[21]

One important clinical use of the laryngeal EMG is for needle guidance in injecting botulinum toxin for treatment of spasmodic dysphonia. It is helpful to confirm needle placement into thyroarytenoid muscle for adductor spasmodic dysphonia and into the posterior cricoarytenoid muscle in the less common abductor spasmodic dysphonia.

The most common application of laryngeal EMG is the assessment of laryngeal nerve integrity in vocal fold immobility. If abnormalities are detected on EMG, the diagnosis of a neural lesion is confirmed. A normal EMG supports, but does not confirm, mechanical fixation of the vocal fold. It does not necessarily rule out a nerve lesion, because spontaneous reinnervation is quite common after nerve injury and neuropathic signs can be subtle and difficult to detect. EMG can be used to differentiate between a vagus nerve and recurrent laryngeal nerve (RLN) injury, because cricothyroid function should be intact after RLN injury. EMG is often used to counsel the patient about the prognosis for recovery of function. When a nerve is completely severed, voluntary activation of the muscle is abolished. After 3 weeks, fibrillation potentials may appear and indicate denervation. In such patients, recovery is extremely unlikely, and early surgical intervention is prudent. Most patients with RLN paralysis do not have electrical silence, because either the lesion was not complete or reinnervation has occurred. Polyphasic action potentials, which can also be detected on laryngeal EMG, are discoordinate nerve signals that indicate reinnervation. Although there is a potential for recovery in a patient with polyphasic action potentials, the rate of that potential is unclear. If the nerve regenerates synkinetically so that nerve fibers do not connect with the functionally appropriate muscles, the vocal fold may remain immobile despite recovery of a vigorous interference pattern. EMG is also used to assess severity of vocal fold paresis; however quantification of reinnervation on the basis of EMG is controversial, because the amplitude and activity pattern can vary greatly with many factors, including electrode impedance, position in muscle, and volitional activity.

The clinical utility of laryngeal EMG is currently limited by the lack of standards for electrodes and testing protocols as well as the lack of normative data.

Edrophonium Test

The edrophonium test is important in the diagnosis of myasthenia gravis. When symptoms are confined to the larynx or pharynx, this test may require observation of laryngeal and pharyngeal function before and after edrophonium is administered. To accomplish this, an intravenous line is established, and the nose is topically anesthetized. The patient is asked to perform repetitive tasks to produce fatigue, and a baseline endoscopic video recording is made. A small test dose of edrophonium is administered, and if there is no adverse reaction, the full test dose is given. The patient is instructed to perform the same tasks, and another recording is made.

Cineradiography

Cineradiography uses a modified barium swallow, and it is useful in assessing pharyngeal function and in planning therapy for patients with swallowing problems. The technique is most commonly performed with the collaboration of a radiologist and a speech pathologist. It is important in planning swallowing therapy and diet modification, for

identification of surgically correctable problems, and for detection of aspiration.

Sensory Assessment

Laryngopharyngeal sensory testing is a method of evaluating the causes of aspiration. The sensory apparatus may be tested with a pressure-controlled and duration-controlled puff of air delivered to the anterior wall of the pyriform sinus and arytenoid (the area innervated by the superior laryngeal nerve). The air puff is delivered from the internal port of a flexible fiberoptic laryngoscope made especially for this purpose (Pentax Precision Instrument Corporation, Orangeburg, NY) or a port that is part of a disposable sheath. To determine a patient's sensory pressure threshold, air pressure is varied according to the psychophysical method of limits, whereas the duration of the air puff is held constant at 50 msec. Thus, the severity of sensory loss can be recorded. The right and left sides of the pharynx and supraglottic larynx are studied to reveal any asymmetry that can indicate the side of the lesion.[22]

Summary

During the past decade, a greater understanding of neurologic disorders of the larynx has led to earlier diagnosis and treatment of these disorders. New technology and the collaboration of neurologists and laryngologists have created a better understanding of the neuromuscular physiologic abnormalities found in patients with motion disorders of the larynx. Because new treatment modalities are available, it is imperative to make accurate neurolaryngologic diagnoses.

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CHAPTER SIXTY

Neurologic Disorders of the Larynx

Andrew Blitzer

Ronda E. Alexander

Nazaneen N. Grant

Key Points

- Neurologic disorders of the larynx may be focal diseases or local manifestations of systemic disorders. Characteristic deficiencies found on clinical examination may aid in ascertaining the site of a lesion.
- Hyperfunctional disorders include dystonia, myoclonus, essential tremor, stuttering, and muscle tension dysphonia.
- Hypofunctional disorders include focal disorders such as vocal fold paresis, and central causes such as Parkinson's disease, multiple sclerosis, neuromuscular junction disorders, poliomyelitis, myopathies, medullary disorders, and psychogenic disorders.
- Spasmodic dysphonia is an idiopathic focal laryngeal dystonia characterized by either breathy or halting speech breaks.
- Botulinum toxin is an important treatment for spasmodic dysphonia and other dystonias.
- Vocal fold paresis can result from trauma, tumor, neurologic, idiopathic, or other medical diseases. Vocal fold positioning can vary on presentation.

Neurologic conditions that affect the larynx span a wide spectrum. They may be focal diseases or local manifestations of systemic disorders. These lesions can produce stereotyped patterns of abnormal function that the otolaryngologist should strive to recognize. Evaluation should include a complete head and neck examination, neurologic examination, and visual recording of the functional disability for documentation. For systemic disorders, consultation with a neurologist is useful for diagnosis and for optimizing medical management. In general, neurologic dysfunction results from one or more insults within the central or peripheral nervous system.

A few important generalized neurologic disorders are characterized by specific patterns of involvement of the larynx and pharynx. In early stages of involvement, patients with these disorders may consult otolaryngologists because symptoms are located in the head and neck region. At any stage of these disease processes, otolaryngologic consultation may be vital to differentiate manifestations of the disease from problems caused by other concurrent disorders and to ensure appropriate management. The neurologic disorders affecting the larynx are best understood when characterized as hypofunctional disorders. Although this is a general categorization, often both types can exist concurrently, particularly when hyperfunctional activity, such as muscle tension dysphonia, works to overcome a hypofunctional deficit.

Laryngologic Manifestations of Neurologic Diseases

Cortical lesions may result from strokes, tumors, or trauma and may impair memory as well as the planning and execution of actions. Because of the diffuse and bilateral representation of laryngeal structures in the cortex, cortical lesions, such as those caused by tumors or strokes, do not produce classic flaccid or spastic paralysis. Inappropriate vocal fold adduction with inspiration may have the symptom inspiratory stridor.[1,2] Extrapyramidal system defects are characterized by abnormal motor control, which may manifest as inappropriate or excessive muscle tension, tremor, and involuntary spasmodic muscle contractions. Vocally, it translates into strain, arrests, pitch breaks, and pitch instability. The dysfunction may be focal, regional, or generalized. In addition to problems caused by tumors or trauma, the extrapyramidal system is disrupted by conditions of uncertain etiology such as Parkinson's disease, tremor, and dystonia.[3] Cerebellar lesions impair coordination of motor activities. Patients' problems are generalized rather than focal. "Scanning speech" is regarded as characteristic of cerebellar involvement. Diagnosis is based on the presence of attendant physical signs, such as intention tremors, dysdiadochokinesia, dysmetria, ataxia, and nystagmus.[4] Brainstem lesions result in flaccid paralysis. Because the cranial motor nuclei are densely packed within the brainstem, lesions at this level affect multiple outputs. Strokes and tumors of the brainstem produce severe dysfunction related to paralysis of the larynx, pharynx, or tongue and are associated with sensory deficits.[2] The site of lesion is best identified from the type of motor disruption, because observable clinical signs are predominantly disruptions of motor acts (Table 60-1).[5,6] Diffuse central nervous system (CNS) lesions result from specific neurologic disorders, such as multiple sclerosis and amyotrophic lateral sclerosis (ALS), and have a myriad of signs and symptoms. Patients with movement disorders have a paucity of movement (akinesia or bradykinesia), excessive or hyperfunctional movement (hyperkinesia), or a combination of the two. The hyperkinetic motor programming errors can produce spasms, tremors, jerks,

Table 60-1

Signs Indicating Site of Lesion in Neurologic Disorders of the Larynx

Site of Lesion	Signs
Cortex	Aphasia Aphonia Dysarthria Dysphonia Stridor
Extrapyramidal system	Vocal strain and pitch breaks Tremor Spasmodic movements Focal, regional, or generalized dystonia
Cerebellum	Ataxia Dysmetria Tremor Incoordination
Brainstem	Flaccid paralysis Never isolated

or tics as well as symptoms related to the body part involved. For those with laryngeal manifestations, a multidisciplinary approach that includes the involvement of an otolaryngologist, a neurologist, and a speech pathologist is key to successful diagnosis and management of hyperfunctional disorders of the larynx.[7,8]

Hyperfunctional Disorders

Dystonia

Dystonia is a syndrome dominated by sustained muscle contractions of skeletal muscles that frequently causes twisting and repetitive movements or abnormal postures that may be sustained or intermittent. Because the condition is rare and the movements and resulting postures are often unusual, dystonia is among the most commonly misdiagnosed neurologic conditions.[9] The prevalence is unknown, but there are an estimated 50,000 to 100,000 cases of idiopathic dystonia in the United States. Classification is important because it can inform prognosis and the approach to management. The classification scheme is outlined in Box 60-1.

Dystonia can begin at nearly any age. Presenting signs have occurred as early as 9 months and as late as 85 years. In general, onset has a bimodal distribution, with peaks at ages 8 and 42 years. Early-onset dystonia begins to manifest before age 26 years, whereas in the late-onset form, the signs appear at older ages. Patients are also categorized according to symptom distribution. Focal dystonia involves one small group of muscles in one body part, segmental disease involves a contiguous group of muscles, and generalized dystonia is widespread. The more common examples of focal dystonia are listed in Box 60-2.[7]

History, physical examination, and laboratory studies may not identify the cause of a patient's dystonic symptoms (idiopathic dystonia). Therefore, there should be a normal perinatal and early developmental history; no history of neurologic illness or exposure to drugs known to cause acquired dystonia (e.g., phenothiazines); normal intellectual, pyramidal, cerebellar, and sensory examination findings; and normal diagnostic study results. The clinical phenomenology is often a clue to the cause. Primary dystonia is typically action induced and normal at rest, but secondary dystonia frequently results in fixed dystonic postures. The presence of extensive dystonia limited to one side of the body (hemidystonia) also suggests a secondary cause.[7,9]

Box 60-1

Classification of Dystonia

Primary

Without hereditary pattern
With hereditary pattern
Autosomal dominant
Autosomal recessive
X-linked recessive
Undefined

Secondary

Associated with other hereditary neurologic disorders (e.g., Wilson's disease, Huntington's disease, ceroid lipofuscinosis, progressive supranuclear palsy, Hallervorden-Spatz disease, olivopontocerebellar atrophy, acquired hepatocerebral degeneration, Tourette's syndrome)
Environmental
Posttraumatic
Postinfectious
Vascular
Neoplastic
Toxic
After antipsychotic drug therapy (phenothiazines, piperazines, butyrophenones, molindone, thioxanthenes)
Antiemetics (prochlorperazine, promethazine, metoclopramide)
Antiparkinsonian drugs (levodopa, bromocriptine, lisuride, pergolide)
Associated with parkinsonism
Hysterical

Box 60-2

Distribution of Dystonia

Focal:
- Blepharospasm (forced, involuntary eye-closure)
- Oromandibular dystonia (face, jaw, or tongue)
- Torticollis (neck)
- Writer's cramp (action-induced dystonic contraction of hand muscles)
- Spasmodic dysphonia (vocal cords)

Segmental (cranial, axial, or crural)
Multifocal
Generalized (ambulatory, nonambulatory)

Because up to 16% of patients with dystonia and primary laryngeal involvement experience spread of the disease to another body part, patients should be advised of this potential and should be reexamined on a regular basis for signs of other dystonic involvement. Approximately 10% of patients with primary laryngeal dystonias have a family history of dystonia.[10]

In most cases of childhood-onset idiopathic dystonia, family studies show an autosomal dominant inheritance with reduced penetrance. A marker for some cases of childhood-onset dystonia has been found on chromosome 9.[11] There are heterogeneous genetic patterns among patients with idiopathic dystonic symptomatology, including a linkage to the X chromosome and parkinsonism,[12-14] a dopamine-responsive form.[15]

Family and linkage studies have identified several subtypes with different genetic bases, including the autosomal dominant dopamine-responsive dystonia already mentioned,[15] X-linked Filipino torsion dystonia,[12-14] and an autosomal dominant (non–dopamine-responsive)

idiopathic torsion dystonia related to the DTY1 gene mapped to chromosome 9q34. Both dopamine-responsive dystonia and X-linked torsion dystonia are rare forms of idiopathic torsion dystonia associated with parkinsonism.[6,11,16,17]

Clinically, spasmodic dysphonia is an idiopathic focal dystonia of the larynx.[17a] Although the disease was initially described by Traube[18] in 1871, Fraenkel[19] and Gowers[20] later recognized the relationship with other dystonias, such as writer's cramp. The vast majority of cases of laryngeal dystonia cause spasmodic adduction of the vocal folds during speech, which results in a strained and strangled voice. Fewer patients have abductor dysphonia, with intermittent or sustained opening of the larynx during speech[21] that leads to breathy voice breaks or a whispering voice. Some patients display a combination of adductor and abductor signs and have been classified as having "mixed laryngeal dystonia."[7,22] Patients with spasmodic dysphonia have reported that symptoms momentarily improve when he or she pinches the nares, presses the hand against the back of the head, presses the hand into the abdomen, pulls on an ear, or touches the clavicular notch (personal experience). Many patients observe that they speak better after a yawn or sneeze or when they sing or yell; these sensory tricks are also common for patients with other craniocervical dystonias.[9,23] Systemic pharmacotherapy provides little relief of symptoms. Dedo and Izdebski[24] described dramatic relief of symptoms with sectioning of the recurrent laryngeal nerve. The initial favorable reports were temporized by a review of 33 patients by Aronson and De Santo[3,25] that addressed surgical management. Three years later, only 36% of patients had some persistent improvement, and only 3% achieved a persistent normal voice. At present, the symptoms are most effectively managed with use of an individualized regimen of chemodenervation with botulinum toxin.

Another rare form of laryngeal dystonia is adductor breathing dystonia, in which patients adduct their vocal cords while inspiring. The adduction causes stridor and dyspnea, but these patients do not become hypoxic and do not need tracheostomy. Localized injection of botulinum toxin into involved muscles is an effective way to diminish the symptoms of patients with dystonia, particularly those with adductor spasmodic dysphonia.[26-30] Patients with more generalized dystonia that also involves the larynx have vocal dysfunction, which is clinically indistinguishable from idiopathic spasmodic dysphonia. Meige's syndrome, a regional dystonia of the head and neck, may be evident in those with blepharospasm, oromandibular dystonia, torticollis, or spasmodic dysphonia.

Botulinum Toxin Therapy

The bacterium *Clostridium botulinum* produces eight immunologically distinct toxins that are potent neuroparalytic agents: A, B, C_1, C_2, D, E, F, and G.[31,32-36] Botulinum toxin exerts its effect at the neuromuscular junction by inhibiting the release of acetylcholine, causing a flaccid paralysis.[4,37-39] Botulinum toxin type A (Botox; Allergan, Inc., Irvine, CA) is most commonly used, and type B (Myobloc; Elan Pharmaceuticals, Inc, San Francisco) is also available for clinical application.

Although botulinum toxin has been used therapeutically in humans since the mid-1970s without evidence of a direct effect on uninjected muscles, the later consequences of long-term injections are unknown. Weakness and routine electromyography (EMG) changes in muscles distal to the site of injection have not been reported. However, there are detectable abnormalities on single-fiber EMG.[40] It is not known how long these abnormalities persist or whether they have any clinical significance. There is a paucity of data regarding use of botulinum toxin during pregnancy. Currently, injection should be avoided in pregnant or lactating patients. Caution is warranted for the management of patients with conditions such as myasthenia gravis, Eaton-Lambert syndrome, and motor neuron disease, particularly when large doses are required (e.g., in the management of cervical dystonia). However, the amount of toxin entering the circulation after injection is thought to be minute, and this theoretic concern should be balanced against the severity of the hyperkinetic symptoms.[40]

In patients with adductor spasmodic dysphonia, botulinum toxin injection has been demonstrated to improve speaking to 60% to 100% of normal function,[41] with a mean of 90%; the duration of effect was between 3 and 4 months. Adverse effects include a mild breathy dysphonia for less than 2 weeks (45%), mild choking on fluids for the first several days (22%), hyperventilation and dizziness when trying to speak while hypophonic, a sore throat or coughing up blood-tinged sputum, and itching (without rash).[42-45,81] In patients with abductor laryngeal dystonia, injection of botulinum toxin into the posterior cricoarytenoid muscle produces marked improvement, with a return to mean maximal functional performance of 70% of normal. Adverse effects include mild dysphagia without aspiration and mild stridor on exertion.

The effective treatment dose is variable for each patient and for each muscle injected; therefore, injections are individualized.[46] The dose range for adductor spasmodic dysphonia is 0.05 to 20 units of Botox, with an average dose of less than 1 unit per vocal fold.[24,29,30,47,48] In general, a starting dose of 1.0 units in 0.1 mL of saline is used for bilateral thyroarytenoid injections. Subsequent doses are varied according to clinical response and adverse effects. A trend toward lower doses has been observed and may be useful in reducing adverse effects.[49] Injections are given by means of a tuberculin syringe with a 27-gauge monopolar polytef-coated hollow EMG recording needle. Adductor laryngeal injections are performed percutaneously through the cricothyroid membrane and into the thyroarytenoid-vocalis muscle complex, with use of EMG guidance for optimum placement (Fig. 60-1). Injections for abductor spasmodic dysphonia are administered to the posterior cricoarytenoid muscle. The physician reaches muscle by manually rotating the larynx, placing the EMG needle behind the posterior edge of the thyroid lamina, and advancing the needle to the cricoid cartilage to arrive at the posterior cricoarytenoid muscle. Alternatively, a transcricoid injection can be made. When the patient is instructed to sniff, which maximally uses the posterior cricoarytenoid muscle, there is a burst of activity on the EMG, and the toxin is administered.[42,43,47,50]

After an injection, the patient typically reports improvement in voice within 24 hours followed by a breathy, hypophonic period lasting 1 to 2 weeks (45%), occasionally causing hyperventilation and dizziness when trying to speak. Mild choking on fluids for the first several days (22%) is also common; in addition, sore throat or coughing up blood-tinged sputum may occur in the first 1 to 2 days after injection.[42-44]

Patients with abductor spasmodic dystonia are also managed with an EMG-guided percutaneous injection. The larynx is manually rotated away from the side of intended injection, and the hollow EMG needle with syringe is placed posterior to the posterior edge of the thyroid lamina (Fig. 60-2).

For treatment of adductor spasmodic dysphonia, Ford and colleagues[51] reported an indirect laryngoscopic approach for injecting the toxin into the vocal fold. They reported that the technique has the advantage of being "familiar to the otolaryngologist and requires no special EMG equipment or training." The onset of response to toxin appears delayed (mean, 9.1 days), but the level of benefit and duration of efficacy appear comparable with those of EMG techniques. Nevertheless, at initial management, the muscle appears to be electrically active at multiple sites throughout the course of the muscle. On follow-up, the electrical recruitment pattern, an index of muscle contraction, may be patchy. EMG guidance has the advantage of controlled administration into the more actively contracting regions of the muscle.[7,44]

Regardless of technique, botulinum toxin injections have several advantages over surgical therapy in the management of intractable disease. The patient is awake for the procedure, and there is no risk of the complications that would be involved with anesthesia. Graded degrees of weakening can be achieved by varying of the dose. Most adverse effects are transient and are caused by an extension of the pharmacology of the toxin. If the patient has a strong response to therapy and too much weakness occurs, strength gradually returns. Follow-up therapy is carefully individualized. The response to therapy should be meticulously documented.[40]

Pseudobulbar Palsy

Pseudobulbar palsy (PBP) results from bilateral lesions of the corticobulbar tracts. Patients have muscle spasticity and hyperreflexia of the pharynx, palate, lips, tongue, and larynx. The voice in the patient with PBP is harsh, strained, and strangled, and it sounds somewhat like that of a patient with spasmodic dysphonia. Patients with PBP are easily distinguishable clinically, because they have associated signs of

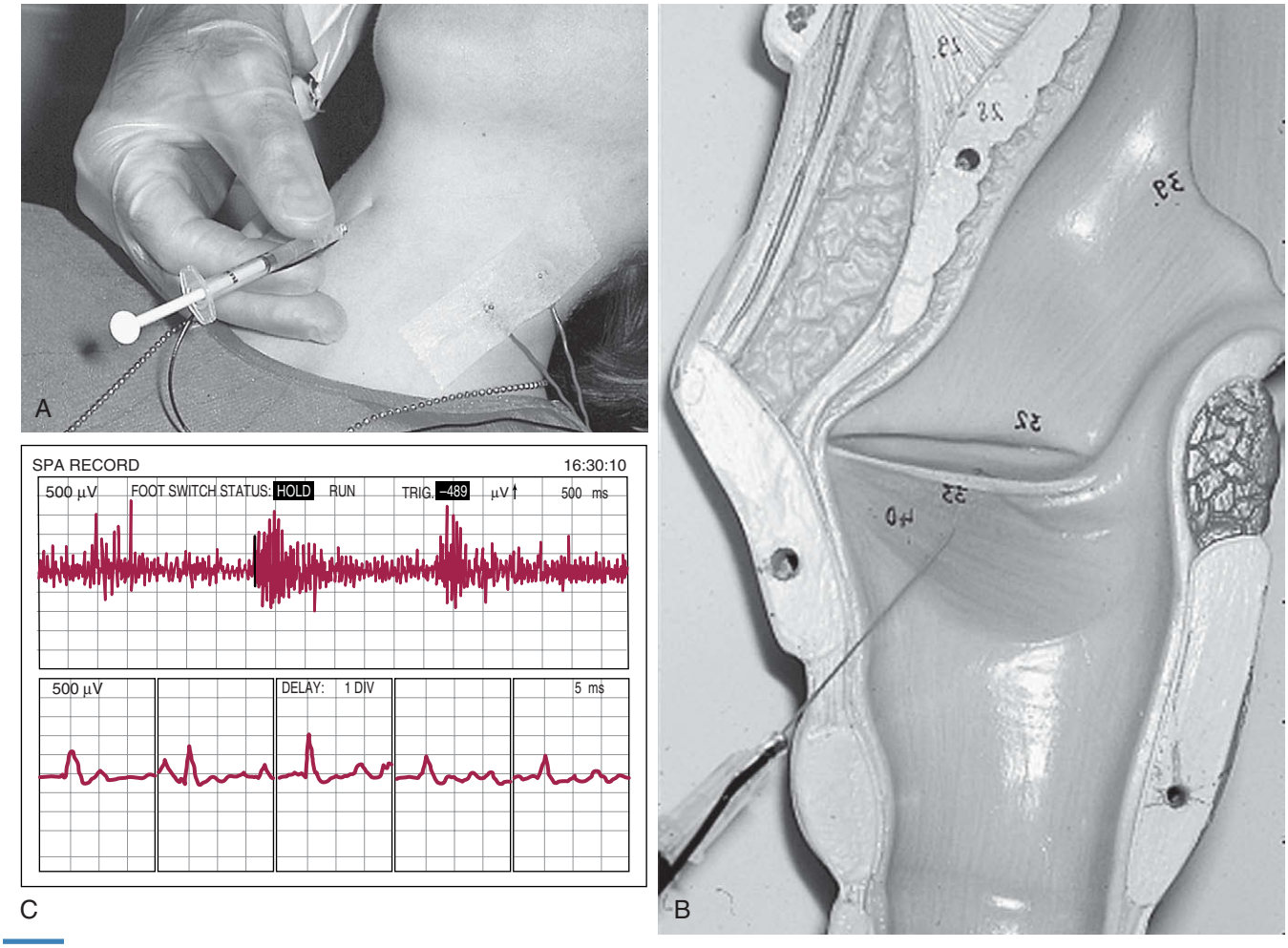

Figure 60-1. **A,** Anterior approach to the thyroarytenoid muscle through the cricothyroid membrane. The injection needle is passed into the airway and directed laterally and superiorly into the thyroarytenoid muscle. **B,** Model depicting placement of 27-gauge injection needle into the thyroarytenoid-vocalis muscle. An acute angle places the injection into the anterior belly of the thyroarytenoid muscle. **C,** Electromyogram obtained during injection of the thyroarytenoid muscle. The patient is asked to say "ee," resulting in recruitment and increased motor unit activation and confirming accurate placement of the electrode before injection.

hypernasality as well as slow, labored articulation, emotional lability, and subcortical cognitive impairments.[2]

Myoclonus

Oculopalatolaryngopharyngeal myoclonus is an uncommon disorder consisting of rhythmic contractions of the soft palate, pharynx, and larynx at a rate of one or two contractions per second. This condition may affect only the palate, all of the laryngopharynx, and even the eyes, and is caused by a lesion in the central tegmental tract. It may result in a speech that sounds like a choppy voice with intermittent hypernasality. The palate and vocal folds may be treated with injections of botulinum toxin to decrease the severity of the contractions and thereby reduce the symptom. A patient complaint of clicking in the ears, thought to be caused by involvement of the eustachian tube and tensor veli palatini muscles, was first noted in the 19th century by Muller and then Politzer.[52] The clicking can often be heard by family and examiners. Laryngeal involvement may produce a broken speech pattern, simulating that heard in laryngeal dystonia or tremor (personal observation). Examination of the vocal cords often shows slow rhythmic adduction and abduction of the vocal cords at the same timing and frequency as the palatal, pharyngeal, and occasional diaphragmatic contractions. This causes the broken speech pattern and a respiratory dysrhythmia. Although oculopalatolaryngopharyngeal myoclonus is usually unresponsive to pharmacotherapy, isolated cases have reportedly responded to serotonin,[27,53] carbamazepine,[54] clonazepam,[55,56] tetrabenazine,[56] and trihexyphenidyl.[57,58] Several patients whose symptoms were unresponsive to drug therapy have been managed with local injection of botulinum toxin into the thyroarytenoid muscles.

Essential Tremor

Tremor is an involuntary, purposeless rhythmic movement of a part of the body. It causes a 6- to 8-Hz shaking of the hands, head titubation, and a tremulous voice. The proposed underlying neural bases for tremor include a central mechanism[59-61] and a peripheral mechanism.[62] Tremors have been classified according to cause or clinical appearance and are characterized by their frequency, amplitude, distribution over the body, and exacerbating and relieving factors.[63] Of patients with essential tremor, 60% have a family history of tremor, and 30% of these had voice involvement.[64]

The involuntary, rhythmic, oscillatory movements that affect the distal musculature in patients with tremulous diseases can also affect the muscles of speech production and generate rhythmic alterations in pitch and loudness, termed *vocal tremor*. Vocal tremor can result in either rapid decreases and increases in loudness and pitch or complete phonation stoppages. Intelligibility and rate of speech may be decreased. Vocal tremor has been described perceptually as "tremulous voice,"[30,65] "wavy voice,"[66] or "tremulous, quavering speech"[66] and has been associated with neurologic disorders such as essential tremor, Parkinson's disease, cerebellar ataxia, and flaccid dysarthria.[21,67]

Essential tremor is typically absent at rest, maximal during maintenance of a posture, attenuated during movement, and often accentuated at the termination of movement.[7,68,69] Vocal tremor occurs in

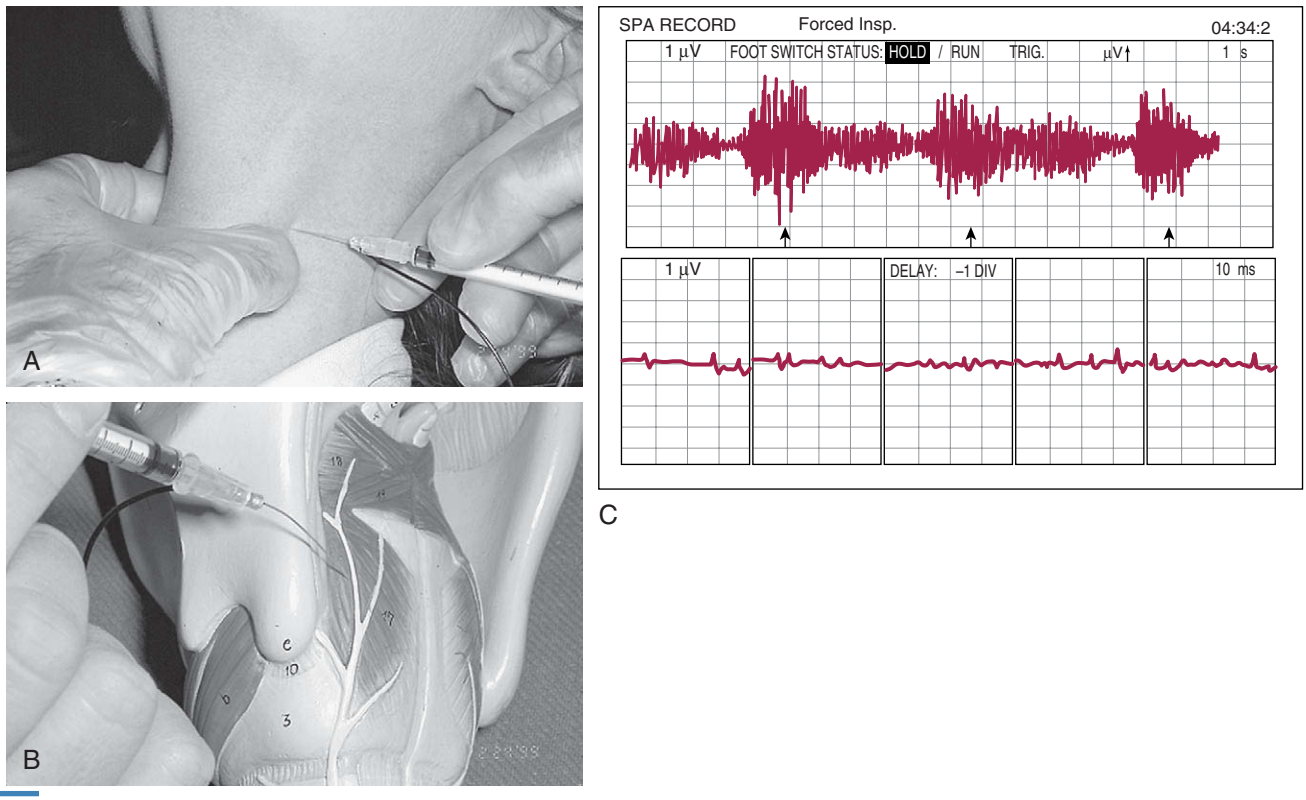

Figure 60-2. **A,** Lateral approach to the posterior cricoarytenoid (PCA) muscle. The thyroid cartilage is rotated laterally with simultaneous anterior displacement, exposing the posterior lateral border of the thyroid cartilage. The 27-gauge injection needle is inserted into the posterior lateral aspect of the cricoid cartilage. **B,** Model depicting placement of the injection needle into the PCA muscle using a posterior lateral approach. **C,** Electromyogram obtained during injection of the PCA muscle. *Vertical arrows* indicate volitional "sniff" maneuvers with recruitment of PCA motor units.

approximately 10% to 20% of patients with essential tremor.[70] It may be the first[65] or only sign of the disease,[38] or it may accompany tremors in other body parts.[71] Vocal tremor may parallel the onset of other symptoms or may have a sudden onset and cause rapid deterioration in speech intelligibility.[65,71] Vocal tremor has been reported to be greater with emotional stress or fatigue.[27] Pitch breaks (octave breaks to a lower frequency) and phonation arrests have been reported in some cases of essential tremor[70,72] and have been associated with visible vertical oscillations of the larynx.[73]

The effect of medication on reducing vocal tremor is equivocal. Certain researchers have reported reductions in vocal tremor with administration of propranolol,[70,72] primidone,[27,74] and a combination of clonazepam, propranolol, and diazepam.[54] Limited, clinically significant changes in vocal tremor have been found with administration of propranolol[66,75] and primidone.[55] One report describes a better than 70% improvement of vocal tremor with thalamotomies.[76] Preliminary studies have also shown reduction of tremor with long-term electric stimulation of the thalamic nucleus through surgically implanted neuropacers.[77] Local injection of botulinum toxin in the management of essential vocal tremor has shown a dramatic benefit in preliminary studies. The injections are given into the muscles that seem to be most tremulous. In many cases, the most active muscles are the sternohyoid and sternothyroid muscles, which rhythmically elevate and lower the larynx in the airway (resonator), causing oscillations and producing a tremulous voice quality. In these cases, injecting botulinum toxin into the strap muscles diminishes the up-and-down motion of the larynx, thereby diminishing the amplitude of the tremor and making speech more fluent. Generally, 5 units in 2.5-unit aliquots are injected on each side. If the vocal folds are tremulous, they are injected at a second session. Although the toxin does not eliminate the tremor, it decreases the amplitude, thereby reducing the severity of the symptom. Tremor commonly accompanies spasmodic dysphonia and other focal dystonias.[3]

Stuttering

Stuttering might best be considered a movement disorder because it characteristically includes abnormal, involuntary, and inappropriate use of the muscles of speech production resulting in dysfluency. The abnormal movements are task specific and may be repetitive and stereotyped. Stuttering occurs in three subsystems of speech: respiratory, phonatory, and articulatory. Stuttering is a result of increased muscle tension in these three subsystems, which causes the muscles to move too quickly and too far.[78] This increased muscle tension results in postures that are sustained for longer than expected or in quick repetitive movements of the same posture. In addition, other cranial musculature may inappropriately contract, including the eyelids and other muscles of facial expression.[79-81] One report describes stuttering followed by the development of jaw-opening dystonia.[82]

As in other movement disorders, competing stimuli, such as emotional arousal, sensory stimuli, motor actions (e.g., walking), and the use of rhythmic patterns (e.g., a metronome), increase fluency. Communicative pressures such as audience size, listener reactions, concern about social approval, time pressure, and the extent to which the stutterer is responsible for conveying a meaningful message to a listener are found to increase stuttering.[83]

The use of antidepressants does not improve fluency.[84] Most persons with a stuttering disorder respond to traditional speech therapy and training. For cases resistant to traditional therapy, chemodenervation of the thyroarytenoid muscles may be considered; in a group of patients with stuttering and glottal block, this maneuver initially achieved promising results.[82] Small doses of botulinum toxin (1 unit or less, given bilaterally) has produced improvement in 50% of patients. The number of glottal blocks and the duration of the glottal blocks significantly diminish with management. The most significant advances in treatment of stuttering have been achieved with altered auditory feedback in-the-ear devices.[74,85,86] With the use of both delayed and frequency-altered auditory feedback, significant improvement in

fluency and normalcy of speech has been demonstrated. Improvement was demonstrated for both young and adult subjects, and these devices are currently marketed under the trademark SpeechEasy (Janus Development Group, Inc, Greenville, NC).

Muscle Tension Dysphonia

In muscle tension dysphonia, which is functional, a patient postures the vocal folds. This hyperfunction causes tightness and dysphonia, with harshness, breathiness, choppy vocal production, or tremor. Patients are best treated with speech therapy to learn to use their voices in a less strained manner.

Hypofunctional Disorders

Central Causes of Vocal Fold Paresis

Central nervous system disorders that may produce vocal fold paralysis/paresis are syringobulbia, Arnold-Chiari malformations, stroke (including Wallenberg's lateral postmedullary syndrome, posterior, inferior cerebellar artery occlusion) and other lower motor neuron disorders. Vocal fold paresis as a result of peripheral nerve injury or compression is discussed separately later in the chapter.

Neuromuscular Junction Disorders

Neuromuscular junction disorders include myasthenia gravis and the less common Eaton-Lambert disease. In such disorders, muscles fatigue quickly with use.

The incidence of myasthenia gravis is less than 10 per 100,000 people. Specific patient complaints may vary, depending on the distribution of muscles involved. Many patients have ptosis or double vision, because ocular muscles are most commonly affected. General fatigue is also a common complaint. Sometimes the disease is localized to the throat, and patients have difficulty speaking, breathing, or swallowing. Careful examination of the larynx and palate in such patients may reveal fatigue as a result of repetitive movements. For example, asking the patient to repeat "ee-ee-ee" can elicit laryngeal fatigue. Electromyography and an edrophonium test are used for rapid diagnosis and treatment of myasthenia gravis. Blood testing is used to detect antibodies against acetylcholine. Early detection of this disorder is invaluable, because medical treatment is effective and may be lifesaving.[16,87]

Poliomyelitis

Poliomyelitis (polio) is essentially nonexistent today, thanks to vaccination programs. However, there are survivors of polio who experienced postpolio syndrome with a recurrence of motor weakness. The exact cause of postpolio syndrome is unknown, but it is thought that the syndrome is derived from the natural loss of motor neurons during the aging process. Patients who have recovered from polio function by virtue of a small pool of surviving neurons that sprout to supply expanded numbers of muscle fibers. Thus, these patients are particularly susceptible to the loss of even a small number of neurons. Acute bulbar polio causes pharyngeal and laryngeal paresis but spares the cricopharyngeus muscle. The resulting symptoms are hoarseness, dysphagia, and aspiration. Because the cricopharyngeus muscle retains tone, cricopharyngeal myotomy often is helpful in the patient with recent onset of polio; however, in those with postpolio syndrome, the effectiveness of myotomy has not been established.[87]

Myopathies

Examples of myopathies are dermatomyositis, muscular dystrophy, and metabolic myopathies. Dermatomyositis manifests as dermatitis in conjunction with muscle weakness. This disorder may be associated with lung cancer, systemic lupus erythematosus, or poliomyelitis. The muscular dystrophies vary in age at onset and anatomic distribution of involvement. The infantile variety often presents with oculopharyngeal weakness. Metabolic myopathies may result from abnormalities in acid maltase, glycogen brancher enzyme, and cytochrome c-oxidase. Also, some episodic myopathies with periodic paralysis are drug induced.

Medullary Disorders

Medullary disorders that affect motor neurons include ALS, primary lateral sclerosis, postpolio syndrome, Arnold-Chiari malformations, and medullary strokes. ALS (also known as Lou Gehrig's disease) is an idiopathic and progressive degeneration of upper and lower motor neurons that results in muscle wasting, fasciculations, and weakness. Incidence in the United States has been estimated at 1 to 2 per 100,000 people. As many as 25% of patients with ALS initially have complaints related to speech and swallowing. In many patients, limb symptoms predominate. The clinical course varies in its rate of progression and is inevitably "downhill." Approximately 25% of patients survive from 5 to 10 years after the onset of the disease. Death is most often related to respiratory insufficiency due to weak breathing muscles and aspiration pneumonia. Therefore, prognosis for a more rapid demise is higher in patients with throat involvement.[25]

When ALS involves the upper airway, the voice is monotonous and raspy with abnormal hypernasal resonance. Speech is commonly dysarthric and labored and has velopharyngeal incompetence. The dysarthria is related to tongue involvement. Patients have slurred speech as a result of weakness and slowed activity of the tongue. The tongue often has visible fasciculations. There also is weakness in the palate, pharynx, and larynx, along with an inability to make rapid muscle adjustments or repetitive motions. Secretions pool in the hypopharynx, and aspiration often occurs during swallowing. Certain characteristics distinguish ALS from myasthenia gravis. Symmetric facial weakness is common in patients with ALS, although extraocular motion is preserved; this characteristic contrasts with the proclivity of myasthenia to involve the eyelids and extraocular muscles. ALS results in muscle wasting and fasciculations that are most easily observed in the tongue and the intrinsic muscles of the hand. Tongue fasciculations have a classic "bag of worms" appearance.[25,30]

Therapeutic options for patients with ALS are essentially limited to supportive care. In some patients, a palatal lift prosthesis may improve speech intelligibility and reduce nasal regurgitation during speech. In most patients, nothing can be done to improve speech. Eventually, the only options for avoiding aspiration are nasogastric feeding and gastrostomy. Tracheostomy often is necessary for airway protection and assisted ventilation.[25,49]

The lower motor neuron disorders that affect the laryngopharynx include progressive spinal muscular atrophy (PSMA) and progressive or pseudobulbar palsy (PBP). PBP results from bilateral lesions of the corticobulbar tracts. Patients have muscle spasticity and hyperreflexia of the pharynx, palate, lips, tongue, and larynx. The voices of these patients are harsh, strained, and strangled, like those of patients with spasmodic dysphonia. Patients with PBP are easily distinguished clinically, however, because they have associated signs of hypernasality, slow labored articulation, emotional lability, and subcortical cognitive impairments.

Parkinson's Disease

The criteria for diagnosis of Parkinson's disease require at least two of the following findings: a resting tremor, rigidity, bradykinesis, and a loss of postural reflexes. Parkinson's disease is an extrapyramidal syndrome caused by cell death in the substantia nigra. It may be idiopathic or secondary and may be caused by drugs, encephalitis, stroke, toxins, tumors, or head trauma. Affected patients typically have a flat facial expression and abnormal posture. Tremor is often present in the distal parts of the extremities and the lips when patients are at rest. "Pill-rolling" tremor of the hands is typical. Speech abnormalities in Parkinson's disease are nearly universal, manifesting as defects in articulation and voicing. The patients have a hypokinetic dysarthria (45% of patients) with a reduced range of articulation for linguals and labials. They also have decreased loudness, monopitch, and prosodic insufficiency because of poor air presentation to the vocal apparatus (sound generator), which is due to decreased airflow from a bradykinetic bellows mechanism. The vocal folds may be adynamic and/or bowed. On testing, patients with Parkinson's disease show an increased shimmer and jitter, a decreased harmonic/noise ratio, and a tremor. Less commonly, these patients experience a predominant effect of rigidity of the larynx and produce a strained voice with frequent breaks that

are similar to the voice of a patient with spasmodic dysphonia. Swallowing usually is not noticeably impaired in patients with this syndrome, but patients may drool because of the inability to voluntarily swallow.[3,37,40,47]

Parkinson's disease may also be accompanied by autonomic nervous system dysfunction or failure of supranuclear functions. The Parkinson's-plus syndromes include progressive supranuclear palsy (PSP) and multiple system atrophy. In the latter, there is an autonomic nervous system failure with orthostatic hypotension, impotence, sphincter dysfunction, and anhidrosis. One form of multiple system atrophy is known as Shy-Drager syndrome. Patients with this disorder have failure of vocal fold abduction with inspiration that is worse during sleep. Many require tracheotomy for maintenance of the airway. The progression of multiple system atrophy may be rapid and may lead to death.[3]

Multiple Sclerosis

Multiple sclerosis is a diffuse demyelination process with an incidence of approximately 3 per 100,000 people in the United States. The signs and symptoms are protean but basically consist of relapsing and remitting sensory and motor deficits. Visual problems, numbness, and limb weakness are common. As many as 50% of patients with multiple sclerosis have problems that lie within the domain of the otolaryngologist. These problems include vertigo, tremor, scanning speech, and dysphagia. The clinical course in some patients is intermittent and slowly progressive, whereas others experience a rapid and inexorable decline. There have been some promising developments in experimental drug therapy for this disorder.[87]

Psychogenic, Malingering, and Mixed Causes

Psychiatric voice disorders can mimic all of the preceding disorders and hence are very difficult to distinguish from neurogenic voice disorders. Complete aphonia is most often due to a conversion disorder.

Vocal Fold Paresis

Vocal fold paresis is most commonly due to injury of the recurrent laryngeal nerve resulting in vocal fold immobility. It may or may not involve the superior laryngeal nerve, and thus, sensation of the larynx is variably affected. The term *paralysis* implies a complete denervation of the vocal fold with no motor activity, as proven by EMG. *Paresis* implies that there is some residual nerve function, as is most often the case. *Vocal fold immobility* as a broad term encompasses impaired motion from either a neurogenic or a rare mechanical cause, such as arytenoid dislocation, joint fixation, or web formation.

The causes of vocal fold paresis can be divided into the broad categories of trauma, idiopathic, tumor, and neurologic or other medical diseases. Trauma can be surgical, such as from thyroidectomy, anterior cervical spine surgery, or thoracic procedures, or from endotracheal intubation. Skull base tumors, mediastinal lymphadenopathy, and esophageal cancers are examples of tumors that can impinge at various points on the vagal nerve or its recurrent branch; for this reason, neck and chest imaging is obtained in the evaluation of vocal fold paresis. Systemic neurologic diseases that can cause vocal fold paresis are discussed earlier in the chapter; it can also manifest as a peripheral neuropathy in disorders like Charcot-Marie-Tooth disease, sarcoidosis, and Lyme disease. Up to a third of cases of vocal fold paresis are diagnosed by exclusion as idiopathic.

Clinically, the patient with vocal fold paresis presents with an effortful, weak, breathy, and hoarse voice. Vocal fatigue is common, because lack of proper vocal fold closure (glottic insufficiency) due to paresis requires greater effort to create subglottic pressure against a leaking laryngeal valve. This is especially apparent when a patient makes unfruitful attempts to yell. Increased subglottic pressure pushes the flaccid and paretic vocal cord even further away. Dysphagia can also be present from glottic insufficiency and sensory deficits. Maximum phonation time, measured as the length of time that the patient can phonate a sustained vowel, is often decreased.

Vocal fold positioning can vary on examination. Despite prior characterizations, it is now clear that the traditional terms for vocal fold position (e.g., intermediate, paramedian, and cadaveric) do not adequately characterize glottic configuration and that the distance of the vocal fold from the midline is not a reliable indicator of lesion site.[23] The effect of an isolated superior laryngeal nerve lesion on the level of the vocal fold and rotation of the glottis also is controversial. Some writers report rotation of the glottis to the side of the lesion in patients with unilateral cricothyroid muscle paralysis, although the preponderance of the evidence indicates that the cricothyroid muscle does not appreciably influence the spatial orientation of either the vocal fold or the glottis as a whole. Clinically observed variations in glottal configuration are chiefly determined by the extent of the nerve lesion (complete or incomplete) and the extent and accuracy of nerve regeneration. Information on the cricothyroid joint structure now indicates that the two cartilages interact in a visor fashion, similar to a bucket handle, with little translational movement. Thus, a unilateral cricothyroid muscle paralysis may decrease the strength of motion along the arc of rotation but has no differential effect on one vocal fold.[25]

When the cause of vocal fold paresis is not obvious from history, such as recent surgery, further workup, including a detailed medical history and imaging, is needed to rule out other causes. Computed tomography of the neck and chest to examine the full course of the recurrent laryngeal nerve is usually indicated. Magnetic resonance imaging can be considered when skull base lesions are suspected. Blood tests, such as rheumatoid factor and antinuclear antibody tests, Lyme titer, and measurement of erythrocyte sedimentation rate, are not typically performed unless prompted by clinical history.[88] Electromyography can assist in estimating potential for recovery, particularly if the paresis is less than a year old, and is discussed in another chapter. Surgical management of vocal fold paresis is also discussed in other chapters.

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CHAPTER SIXTY-ONE

The Professional Voice

Mark S. Courey

Gregory N. Postma

Robert H. Ossoff

Key Points

- Management of patients with voice disorders is most effectively performed by a multidisciplinary team that includes a laryngologist, a speech language pathologist, and a vocal pedagogue; and current standard of care mandates that all patients with voice disorders receive the same level of care regardless of their level of voice use.
- Voice and speech are produced according to the source-filter theory of voice production. In this theory, the vocal folds provide a harmonic sound source that is filtered by the vocal tract. During filtering of the sound source, the vocal tract attenuates and amplifies certain frequencies of the harmonic sound source to create sounds characteristic of speech.
- Regardless of vocal style, patients all use the same basic mechanism to produce voice. The intrinsic laryngeal musculature contracts to bring the vocal folds into a nearly closed position appropriate to allowing vocal fold vibration to occur, while the abdominal, thoracic, and/or pelvic musculature is used to control the rate and volume of air intake and egress to drive the vocal folds into vibration. The patient uses the extrinsic laryngeal muscles to position the larynx within the neck. This positioning controls the length of the vocal tract. The patient uses the tongue, lips, and teeth to control the shape of the vocal tract. The length and shape of the vocal tract determine which frequencies of the harmonic sound source are attenuated and which resonated.
- Vocal efficiency is achieved when the patients are able to produce their desired vocal output with minimal input.
- Laryngeal stroboscopy is currently the best method for evaluating patterns of vocal fold vibration. To be used most effectively, laryngeal stroboscopy should be performed at multiple vocal pitches and intensities to enable study of the vocal fold vibratory patterns under different requirements.
- Voice analysis with acoustic and aerodynamic measures may be helpful to quantify or measure voice disorders; however, perceptual analysis of the voice by a trained observer remains the most sensitive test to semi-objectify vocal changes.
- Often, vocal professionals complain of a change in vocal effort or slight change in voice quality before other people and trained clinicians can identify a change. “Hoarseness,” a term often used to describe voice changes, is therefore inadequate. Clinicians must strive to describe the voice changes in terms of the specific alterations in effort of production and in vocal quality (roughness, breathiness, weakness, and strain) as well as which portion of the vocal range is most disturbed.
- Physical examination of patients with voice disorders should include palpation of the anterior cervical structures in the region of the larynx and tongue base for tension and tenderness at rest and during phonation. Excess tension or tenderness indicates excessive extralaryngeal muscular effort for voice production. Findings of tension or tenderness may be secondary to habitual inefficient vocal mechanisms or to compensation for suboptimal laryngeal vibration from loss of mucosal pliability or loss of laryngeal closure.
- Benign, nonneoplastic vocal fold lesions are most commonly a response to injury. The most common source of injury is the use of excessive, loud, and abusive voice production methods.
- Even if distinct anatomic abnormalities are identified within the larynx, the patient with a voice complaint should be evaluated by a speech language pathologist and/or a vocal pedagogue, to assess the efficiency of voice production and ability to improve the voice through behavioral changes.
- *Voice rest* means complete vocal silence. It is useful primarily as a diagnostic tool. By eliminating vocal behaviors, it allows the clinician to assess what portion of the acute vocal changes are due to the patient’s abusive vocalization patterns. The period of voice rest rarely needs to exceed 1 week. Voice rest may also be useful in patients with acute injuries or illness, to allow quicker recovery.
- Speech-language pathologists and vocal pedagogues help patients modify their voice use techniques through vocal hygiene techniques and techniques of direct voice therapy.
- Surgical intervention is appropriate if malignancy is suspected or if the patient has been compliant with speech therapy recommendations but the voice has not improved.

Care of patients who use their voices professionally requires knowledge and skills not easily mastered within the field of otolaryngology alone. It is part of the discipline of performing arts medicine. The laryngologist enlists the expertise of speech language pathologists and vocal pedagogue retrain and rehabilitate the professional voice patient. A team approach is mandatory and has been strengthened over the past decade by the establishment of several multidisciplinary voice centers.

Professional voice patients are a diverse group. Limiting the definition to singers and actors is too narrow. All people who depend on speaking or singing skills for employment (e.g., salesmen, receptionists, telephone operators, lawyers, clergy, teachers, politicians, public speakers, and most physicians) should be considered professional voice users, because all of them place diverse yet significant demands on their voices.

Singers and actors (*performing* vocal professionals) put the greatest demand on the vocal apparatus. The extraordinary amount of practice and performance stress they are under exceeds that of any other type of vocal professional. They are often highly trained and push their voices to their physical limits. No other patients are as sensitive to subtle changes in their vocal abilities. Singers and actors with voice disorders often challenge the most experienced laryngologist. The knowledge and expertise gained from managing such patients can and should be generalized to care for other professional and nonprofessional voice users with voice disorders. It is no longer appropriate to treat voice problems in nonprofessional voice users differently from those in professional voice users.

Anatomic Considerations

Voice and voice use patterns can be affected by emotional status and general health. Therefore, in the evaluation of the patient with a voice disorder, the entire body and psyche should be considered. The body itself is the vocal instrument, and the larynx is its most sensitive part. Altered function in nearly any area of the vocal professional's body can result in vocal changes. The larynx, therefore, should not be evaluated as an isolated entity.

Sound generation of any type requires a power source, a vibrator, and a resonator. The lungs are the power supply, the larynx is the vibratory source, and the supraglottal vocal tract (supraglottic larynx, pharynx, oral cavity, and, potentially, the nasal cavity) is the resonator, which shapes the sound into words and song. The sound of the voice is affected by changes in any of these three systems, which should be regarded as a unit during evaluation of the professional voice patient.

Laryngeal function depends on extrinsic and intrinsic laryngeal musculature. The extrinsic laryngeal muscles alter the position of the larynx, which in turn can affect the length of the vocal tract resonator. Classically trained singers use the extrinsic musculature to stabilize the larynx within the neck when singing.[1] The intrinsic laryngeal muscles allow delicate control of adduction, abduction, and tension of the vocal folds.

Within the larynx, the human vocal folds are unique structures with no correlates in another animal species. Hirano,[2,3] who contributed greatly to the understanding of the laminar structure of the human vocal fold, described the *cover-body theory* of vocal fold vibration. The vocal fold is covered by a layer of stratified squamous epithelium. The subepithelial tissue, the lamina propria, is divided into superficial, intermediate, and deep layers. The superficial layer, often called Reinke's space, is composed of fibroblasts, which produce proteins and glycoproteins to form an extracellular matrix of loose connective tissue. The intermediate layer is composed chiefly of elastin fibers, and the deep layer is composed primarily of collagen fibers. Collagen fibers from the deep layer blend into the underlying thyroarytenoid muscle, which forms the main bulk of the vocal fold (Figs. 61-1 and 61-2).

According to the cover-body theory of vocal fold vibration, the cover is composed of the overlying epithelium combined with the superficial layer of the lamina propria. The intermediate and deep layers of the lamina propria, known as the vocal ligament, form a transition zone, and the body is composed primarily of the thyroarytenoid muscle. The contrasting masses and physical properties of the vocal fold cover and the body causes them to move at different rates as air passes between the vocal folds. This movement, or vibration, creates sound at the level of the vocal folds by disturbing the local pressure equilibrium within the area of the glottis. The sound, a buzzing-like tone, is modulated and radiated by the supraglottal vocal tract into audible speech or song.

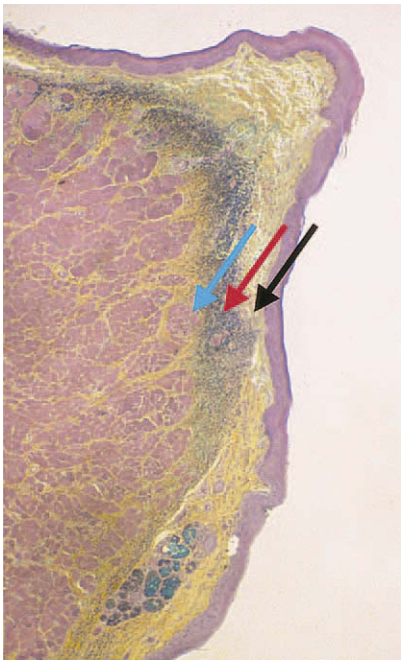

Figure 61-1. Cross section of a true vocal fold stained for elastin (*black*) and collagen (*yellow*). The trilaminar arrangement to the lamina propria is shown. Nonkeratinized squamous epithelium forms the mucosal layer over the superficial portion of the lamina propria. The *black arrow* indicates the superficial portion, the *red arrow* indicates the intermediate layer, which is rich in elastin, and the *blue arrow* is pointing to the deep layer, which is rich in collagen (Movat stain, ×40).

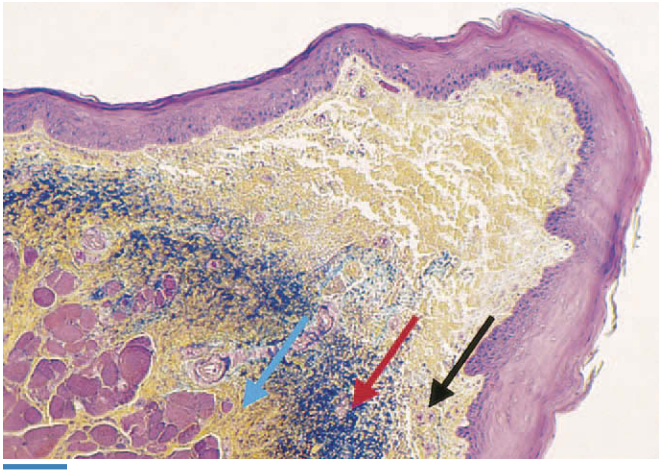

Figure 61-2. Cross section of a true vocal fold under higher magnification. Collagen with increased cross-linking appears deeper yellow (*blue arrow*) compared with less cross-linked collagen in the superficial portion of the lamina propria (*black arrow*) (Movat stain, ×100). The *red arrow* indicates the intermediate layer, which has a high concentration of elastin. In this Movat stain elastin fibers are black.

Blood vessels enter the vocal fold anteriorly and posteriorly. Vessels run parallel to the longitudinal axis of the fold. This arrangement allows the cover to vibrate over the body without placing excessive stretch or shearing forces on the vessels. Electron microscopy has shown that several arteriovenous shunts are present in the vocal fold microcir-

culation. These shunts may allow autoregulation of blood flow to this area.[4]

Gray and colleagues[5] began to identify the contents of the basement membrane zone and the lamina propria. The basement membrane zone is a complex area anchoring the epidermis to the superficial layer of the lamina propria (Fig. 61-3). It is the site of tremendous shearing forces in the human vocal fold that occur during vocal fold vibration. Excessive shear forces can lead to disruption of the basement membrane zone and the development of infiltrates in this area.[6] This process is important in the formation of vocal fold lesions. In the superficial layer of the lamina propria, collagen type III and VII fibers intertwine. This arrangement fixates the basement membrane zone to the superficial layer of the lamina propria yet allows passive stretch during vibration (Fig. 61-4).[5,7-9]

Immunohistochemical analysis has also been used to study the basement membrane zone and extracellular matrix of the lamina propria. In diseased states, which correlate clinically with vocal fold nodules, the basement membrane zone is widened significantly. In lesions that are clinically labeled polyps, collagen type IV within the basement membrane zone appears less pronounced than in the healthy state. Perhaps this relative weakness predisposes patients to polyp formation under phonotraumatic stress.[10,11]

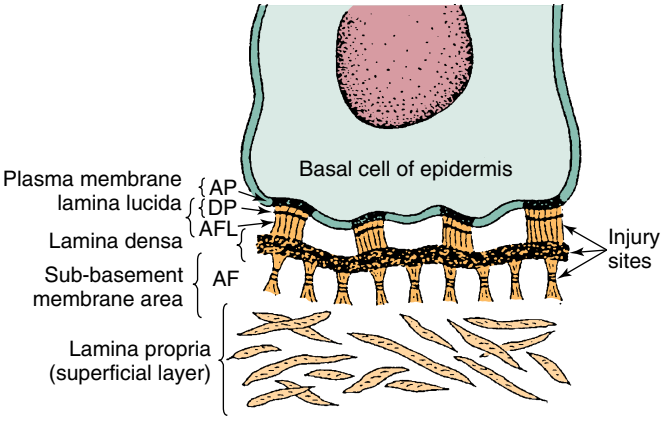

Figure 61-3. Arrangement of structures visible with the electron microscope from the basement cell to the fibers of the superficial layer of the lamina propria. AF, anchoring fibers; AFL, anchoring filaments; AP, attachment plaques; DP, subbasal dense plate. *(From Gray SD, Hirano M, Sato K. Molecular and cellular structure of vocal fold tissue. In: Titze IR, ed.* Vocal Fold Physiology. *San Diego: Singular Publishing Group; 1993.)*

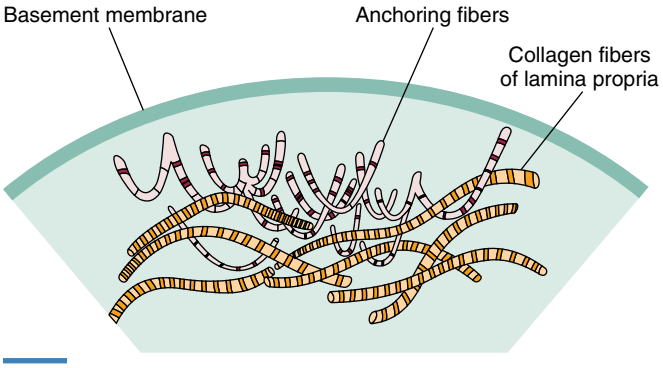

Figure 61-4. The basement membrane and basal lamina of cell anchoring fibers that attach to the lamina densa of the basement membrane, and type III collagen fibers passing through the loops of the anchoring fibers. *(From Gray SD, Pianatni SS, Harding P. Morphologic ultrastructure of anchoring fibers in normal vocal fold basement membrane zone.* J Voice. *1994;8:48.)*

Voice Production

Vocalization begins with the air or power supply. The lungs supply the essential energy for sound production by presenting the larynx (oscillator) with a stream of air. The diaphragm, the intercostal, back, and abdominal musculature, and the elastic recoil of the chest wall work in concert during inspiration and expiration to control the release of air.[12,13] Classically trained singers use the abdominal and thoracic musculature to regulate exhalation; they tend to use a greater percentage of total lung capacity than non–classically trained singers to produce sound in a more efficient manner.[14,15] This enhanced efficiency of air propulsion to the larynx is a key difference between trained and untrained voice users.

As the diaphragm relaxes and the chest wall recoils to a resting state, air is pushed through the nearly closed vocal folds. Because the air passage at the glottal level is smaller than the air passage of the trachea and subglottis, pressure in the region of the glottis drops as the velocity of the air column increases. The relative vacuum created by this drop in pressure draws the pliable rima glottal tissues of the membranous vocal fold region together; this phenomenon is known as the *Bernoulli effect*. After closure at the membranous vocal fold at the glottal level, the air column from the lungs and trachea continues to flow into the subglottal region. The rising subglottal air pressure forces the vocal folds back open. The vocal folds, or rima glottal tissues, open from inferiorly to superiorly (inferior to superior lip), forming an alternating convergent and divergent glottal configuration. The aerodynamic forces of the air column and the inherent myoelastic properties of the vocal folds, particularly in the region of the vocal fold cover, are responsible for the repeated opening and closing of the rima glottal tissues that pulses the air column as it flows out of the glottis. These disruptions in the steady state of the tracheal air pressure by glottal activity result in sound production. The sound produced by the vibratory source has a buzzlike quality. In professional voice production, glottal sound production can be further complicated by voluntary muscular activity that can influence the intensity and frequency characteristics of the glottal sound before its presentation to the supraglottal vocal tract.

The intensity of the sound source is related directly to subglottic pressure—that is, as subglottal pressure increases, sound intensity also increases. Humans can alter subglottal pressure, and therefore sound intensity, by two methods. The first and probably more efficient method is to modify the force of the expelled air from the trachea. This is accomplished through activation of the abdominal and thoracic musculature to increase the amount of air inspired and then, partially through elastic recoil properties of the thoracic cavity and partially through voluntary muscular activity, controlling the rate of air egress. The varied regional schools of classical singing all emphasize different areas of muscular control to accomplish this phenomenon.[16] However, the effect is the same in that the percentage of air used during singing is greater.[17] The second method used to control subglottal pressure is to modify the force of vocal fold adduction. This method is somewhat less efficient. Increasing the force of laryngeal closure through activity of the thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscles achieves greater resistance to the glottal opening. This in turn raises subglottal pressure, which increases sound intensity. However, frequency of vocal fold vibration is directly related to tension within the vibratory system. Therefore, if sound intensity is controlled by the addition of tension in the vibrating system, the frequency of vibration can be inadvertently affected.

Well-trained vocal professionals can independently modulate the frequency characteristic of the source signal from vocal fold vibration through voluntary behaviors. They do so through adjustments in cricothyroid, thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscle activity. The cricothyroid muscle, when activated, elongates the vocal fold, thus tensing the cover and elevating the frequency of vibration. Fine control of the amount of tension is accomplished by balancing these cricothyroid contraction forces against thyroarytenoid, lateral cricoarytenoid, and interarytenoid muscle forces to keep the vocal folds in an appropriate position for phonation. Unopposed cricothyroid muscle contraction leads to increases in the glottal width, which negatively affect the vibratory cycle. In addition, fine control of this mechanism allows the blending of the registers of the singing voice for a smoother transition between what singers term the "chest" and "head"

voice regions. Inappropriate or unbalanced changes lead to what is perceived as voice breaks. Although these breaks may be unappealing in a classically trained singer, they can be used for stylistic effects in commercial singing voice production. The yodel is probably the most commonly appreciated stylistic technique using the break in registers to produce a desired sound.

The sound source signal produced by vocal fold oscillation has a fundamental vibratory rate termed the *fundamental frequency*. Owing to the characteristics of the larynx as a natural vibrator, the sound that is produced has harmonic qualities—that is, as the vocal fold tissue vibrates to disturb the local air pressure, the pressure waves created are refracted. Refracted pressure waves that are out of phase with the fundamental frequency cancel each other out. Waves that are in phase with the fundamental frequency, on the other hand, are also radiated. These in-phase waves may be faster or slower by a whole-number multiple of the fundamental frequency. They create the harmonic or subharmonic frequencies produced by the laryngeal sound source. Again, each harmonic is a whole-number multiple of the fundamental frequency. This harmonic sound source is presented to the supraglottal vocal tract. In turn, the supraglottal vocal tract, on the basis of its physical characteristics (length, shape, and size of the opening at the distal end), amplifies or attenuates particular regions in the source harmonic spectrum.

The harmonic frequencies that are amplified are referred to as *formant regions*. They shape the output from the sound source into sounds appreciated as vocal communication. Through spectral analysis of the voiced signal, we can measure four or five formant regions significant in vocal sound production. The first two of these regions are primarily responsible for vowel determination, whereas the third, fourth, and fifth formant regions color the sound or provide timbre. Vocal professionals, particularly classically trained singers, are able to alter the characteristics of the vocal tract to modulate or shift these formant regions. When the third through fifth formant regions are brought closer together by the voluntary changes in characteristics of the vocal tract, they amplify one another and a ring, termed the *singer's formant*, is produced. This formant region, in the range of 2300 to 3200 cycles/second, is detected by the human auditory system preferentially over other frequencies, allowing the singer to be heard and understood above the sound of an orchestra or other instruments.[18-20] Appropriate use of these principles may give a professional voice user greater vocal efficiency, that is, greater radiated output with less physical effort. A trained vocal professional provides an aesthetically pleasing sound quality for the listener by modulating the formant regions of the sound produced in the following ways: (1) altering the length of the vocal tract through actions of the abdominal, thoracic, and cervical musculature, (2) altering the shape of the vocal tract through the action of the pharynx, tongue, jaw, and lips, and (3) altering the size of the distal opening primarily through the actions of the jaw and lips. The purpose of all vocal training, either commercial or classical, is to teach the performer to control these vocal subsystems to produce the desired, and hopefully aesthetically pleasing, sound.

From this simplified discussion of voice science and the source-filter theory of voice production, the reader should understand that voice and speech production for complex human communication involves the interplay of several subsystems of the human body. These subsystems are:

- The respiratory tract
- The abdominal cavity and abdominal wall musculature
- Perhaps the pelvic cavity and pelvic musculature, depending on the patient's respiratory technique
- The anterior cervical musculature
- The paraspinous musculature
- The pharyngeal musculature
- The laryngeal musculature

Changes in any one of these subsystems can affect the vocal output. Therefore, coordination of these subsystems, for complex vocalization, is not an innate activity. Like any complex activity or sporting skill, such as a golf swing or tennis swing, people have a natural ability that is affected by their muscular set pattern, which in turn is determined in part by their genetics and epigenetics.

Laryngeal Stroboscopy

Although first reported by Oertel[21,22] in 1878, stroboscopic examination of the larynx has only recently become popular in the United States. Stroboscopy is necessary to evaluate the vibratory patterns of the vocal folds that occur too rapidly to be visualized by the unaided human eye.[23-25] According to Talbot's law, the retina is able to resolve only five images per second. Therefore, images presented to the retina for less than 0.2 seconds (5 images/sec) persist and are fused together by the ocular cortex to produce apparent motion. Because the vocal folds vibrate at rates of 75 to 1000 cycles/second, even the slowest vibratory patterns cannot be visualized without assistance. During stroboscopy the larynx is visualized with a xenon light source. Characteristics of xenon light allow rapid on-and-off bursts. In this manner, the larynx is visualized for only brief periods in the range of $\frac{1}{1000}$ second. These brief images, sampled from various points across many vibratory cycles, are then fused together to provide apparent slow motion of the laryngeal vibratory tissue. In modern stroboscopic equipment, the rate of laryngeal vibration is sensed by a microphone and used to control the rate of xenon light firing. When the rate of visual sampling of the laryngeal image is out of phase with the rate of vibration, the laryngeal tissue appears to move. When the sampling rate is in phase with the vibratory rate, the laryngeal tissue appears to stand still.

Stroboscopy permits observation of the vibratory action of the vocal folds, which is not possible with still-light examination (Fig. 61-5). As previously described, this vibratory action is responsible for sound production. Therefore, by using stroboscopy, the examiner can observe how small lesions alter the normal laryngeal vibratory pattern and glottal closure. The significance of a given lesion can then be determined.

In addition to providing information about vibratory status, examinations captured in video format can be reviewed for comparison with previous examinations and for consultation. This information improves accuracy in the diagnosis of vocal problems. Ideally, a baseline laryngeal stroboscopic examination should be performed in each professional voice patient while the health and voice are good. The findings can be compared with the vocal fold appearance during dysphonic states, and conclusions regarding the effects of vibration patterns on the cause of dysphonia can be made.

Recorded laryngeal stroboscopic examinations can be used to follow changes in the glottal vibratory pattern over days, weeks, and years. This process, known as *interval examination*, helps determine the effects of behavioral, medical, and surgical interventions on the larynx. Changes in laryngeal stroboscopy findings can be shown and documented on videotape, computerized formats, and still prints.

Interpretation of laryngeal stroboscopy requires knowledge of the stroboscopic appearance of the healthy larynx phonating at various frequencies and intensities. A regular format for evaluation also enables a more objective interpretation of this subjective test. Standardized checklists for laryngeal stroboscopy interpretation are available.[2,25-27] Evaluation criteria include symmetry, amplitude, periodicity, mucosal wave propagation, and glottal closure (Table 61-1). These vibratory characteristics are evaluated at a comfortable loudness level and modal speech frequency. In professional voice patients, it is beneficial to perform laryngeal stroboscopy during high and low pitch and loud and soft phonation. This approach provides additional data about the vibratory characteristics. If a professional voice patient is having difficulty at a particular point in the vocal range, stroboscopy and laryngoscopy should be performed while the patient phonates within the troubled range. With this approach, the clinician may observe subtle vibratory changes that may be the source of the patient's vocal difficulties.

Symmetry refers to the paired appearance of the vocal folds, which are mirror images of each other during glottal vibration. Any difference in the mechanical properties of the vocal folds—mass, tension, pliabil-

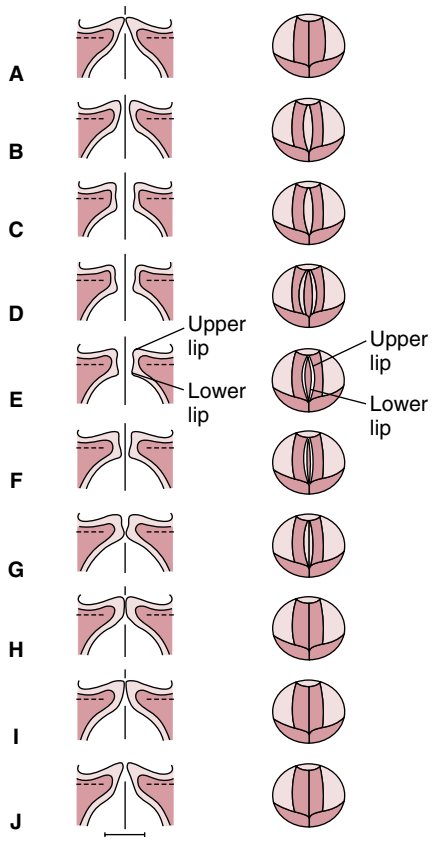

Figure 61-5. Vocal fold vibration. The frontal section (*left column*) and the view from above (*right column*). *(From Hirano M, Bless DM.* Videostroboscopic Examination of the Larynx. *San Diego: Singular Publishing Group; 1993.)*

ity of the superficial layer of the lamina propria or mucosa, elasticity, position, or inflammation—can alter symmetry. Asymmetry of vibration can result in dysphonia.

Amplitude of vibration refers to the lateral excursion of the midmembranous portion of the vocal fold during vibration. This movement is normally one third to one half of the width of the visible fold. As with symmetry, lesions that affect the mass, tension, or pliability of the vocal fold alter amplitude. Vocal pitch and vocal intensity or loudness also alter vibratory amplitude. Vocal folds vibrating at high pitch are stiffer and thinner, so their vibratory amplitude is reduced both in total and in relative relation to the visible size of the vocal fold. On the other hand, when volume is increased, particularly by increases in the force of expelled air, the vibratory amplitude increases as well. This phenomenon occurs at all pitches of phonation.

Periodicity, or the regularity of successive glottal cycles, is ascertained by synchronizing the stroboscopic flash with the frequency of vocal fold vibration. The vocal folds are visualized at approximately the same point in each cycle. This maneuver "freezes" the image or makes the vocal folds appear to be standing still. Any perceived motion of the folds indicates aperiodicity. Any alteration in the balance of the vocal folds and the lungs can result in aperiodic vibrations. During a single phonation, vibratory cycles can range from periodic to aperiodic. Therefore, it may be helpful to determine whether the vibratory pattern is completely periodic, mostly periodic, mostly aperiodic, or completely aperiodic.[28,29]

Mucosal wave propagation has both vertical and horizontal components. The vertical component, known as the *vertical phase*, is visualized during stroboscopic examination along the medial surface of the vocal fold. During vocal fold vibration, owing to characteristics of the mucosa and the vocalis muscle, two distinct ridges appear to form. These ridges are referred to as the upper and lower masses or lips of the vocal fold. The position of the *upper lip* is determined by the reflection of the vocal fold mucosa as it turns from horizontal to vertical over the superior surface of the vocal fold. The position of the upper lip is relatively fixed by the physical characteristics of the vocal fold. The *lower lip* is determined by the change in the physical properties of the mucosa covering the vocal folds from those of the mucosa covering the respiratory tract. Mucosa is technically defined as epithelium and submucosal tissue. Respiratory mucosa consists of a columnar epithelial layer supported by a relatively thin submucosal layer with occasional mucus-producing cells and minor salivary glands. Vocal fold mucosa, however, consists of a stratified nonkeratinized epithelium supported by a relatively thickened and specialized submucosa (see the section on vocal fold anatomy and physiology). The transition between the two types of epithelia is known as the *inferior arcuate line* or the *conus elasticus*. As the air pushes through the glottis, the specialized submucosa of the vocal fold separates from the underlying structure. This is the point of mucosal upheaval. As the vocal fold mucosa is tensed

Table 61-1

Interpretation of Laryngovideostroboscopy

Criteria	Result
Symmetry	Normal Side to side Teeter-totter Vertical O not symmetric
Amplitude	Right equals left Right is greater than left Left is greater than right Both decreased
Periodicity	Yes, consistent Yes, inconsistent No, inconsistent No, consistent
Mucosal wave	Right normal Right great Right abnormal pattern Right decreased Right adynamic (where) Left normal Left great Left abnormal pattern Left decreased Left adynamic (where)
Closure	Complete, long Complete, short Small posterior chink Large posterior chink Slit Elliptic 50% Elliptic Hourglass Asymmetric hourglass Other

RECORDING QUALITY (1 = Poor, to 4 = Great)
Focus _____ Size _____ Brightness _____
Color _____ Notable feature _____
Videotape number: _____
Verbal diagnosis: _____

through the action of the cricothyroid muscle, the submucosal tissue is thinned three-dimensionally in the same manner that a rubber band thins as it is stretched. This thinning causes the lower lip to move in a cephalad direction relative to the upper lip. In this manner, the tension in the vocal fold is increased and the mass of vocal fold tissue available for vibration is reduced to allow pitch elevation. Because the lower lip moves closer to the upper lip, the vertical phase and the time difference between closure of the lower lip and upper lip regions, known as the *vertical phase difference*, is also reduced.

In short, with tensing of the vocal fold for elevation of pitch, the vocal fold cover thins in three dimensions and the time difference between closings of the lower lip of the vocal fold and upper lip (the vertical phase difference) is reduced. This action, which can be witnessed under stroboscopic light examination, is a critical feature in professional voice patients. Often a small lesion or stiffness along the medial surface of the vocal fold will become noticeable only as the vocal fold is stiffened by elevation pitch. The action of elevating pitch limits the vibratory motions of the vocal fold to the superficial region of the cover. This is one of the first areas injured by prolonged or excessive phonation.[11] It is visualized as a reduction in the distinctness of the upper and lower mass formation from one vocal fold to the other.

The *horizontal phase* of vocal fold vibration has been described as a "ripple of light across the superior surface" of the vocal fold.[30] It is a reflection of light either from the upper lip of the vocal fold as it travels from medial to lateral or from motion of the mucosa created by a shock wave as the two upper lips meet during closure. This wave is similar to the wave moving across the surface of a pond after disturbance of the water by a pebble. Lesions that stiffen the mucosa and reduce its pliability lead to loss of this light reflex. This is an important characteristic when visualized under stroboscopic light examination, particularly when the vocal folds are compared with each other at various pitches of phonation. Lesions that fill the superficial layer of the lamina propria and abut or infiltrate the vocal ligament tend to restrict or eliminate both components of the mucosal wave. In contrast, small to moderate-sized lesions limited to the superficial portion of the superficial layer of the lamina propria usually allow propagation of the wave, although it may be decreased and asymmetric.[31,32] Finally, large and exophytic lesions may disrupt the mucosal vibratory characteristic even if they do not infiltrate deeply into the lamina propria, by altering the glottal shape and impairing glottal closure.

Closure of the membranous glottis is vital to laryngeal efficiency. Men usually have complete glottal closure, whereas up to 70% of women normally show a small posterior glottal chink.[33] This glottal chink, however, is considered normal only when it extends from the vocal process of the arytenoid posteriorly. This region from the vocal process to the posterior commissure, referred to as the *cartilaginous glottis,* is not typically important in phonation unless the closure deficiency is large enough to create alterations in closure of the membranous portions of the rima glottic tissue. Berry and colleagues[34] determined that the most efficient glottal output occurred when the vocal folds were approximately 1 mm apart at the region of the vocal process. Glottic closure patterns can be described as complete, long or short, small or large posterior chink, slit, elliptic, and hourglass or asymmetric hourglass. Closure can be altered by a mass lesion, scarring, muscular tension, and neurologic abnormalities, which become clinically significant when they involve deficiencies of closure at the membranous vocal fold level.

High-speed digital video is currently a research instrument but holds great promise for the evaluation of the vibrational function of the vocal folds, especially in patients with severe aperiodic dysphonia, in whom stroboscopy is of limited value.

Voice Analysis

Several methods can be used to quantify voice or measure vocal vibration. No single test is considered the gold standard for documenting vocal fold function. All tests have significant limitations. In addition, intrapatient and interpatient variability exists. Therefore, in professional voice patients, perceptual analysis by a trained observer and patient satisfaction with vocal outcome are often the most useful indicators of a successful intervention. Most laryngologists consider objective and semiobjective voice analysis to be important, particularly regarding preoperative and postoperative voice documentation. Little agreement exists as to the optimal tests and their performance, relative importance, or interpretation.

Acoustic Measures

Acoustic analysis has been used to objectively document voice and to compare preoperative and postoperative surgical results. Acoustic measures include fundamental frequency, perturbation or cycle-to-cycle variation in frequency and amplitude, and maximal phonation range. Comparison of interval examinations requires a high-quality microphone and recording system with strict, standardized recording techniques and patient tasks. Although several computer-integrated acoustic analysis systems are available, they are of limited benefit for the average patient. The reliability of acoustic measures, secondary to variation in patient effort, is limited. In addition, the validity of acoustic measures designed to evaluate periodic vibration is questionable in dysphonic voices because dysphonia results from aperiodic vibration.

Spectrometry

Spectrometry provides a visual display of vocal harmonics and noise. In spectral analysis of sound, time is plotted on the vertical axis against frequency and intensity. This display shows the impact of resonance (formant structure) and articulation on the laryngeal buzz. Spectral analysis can evaluate and compare resonance changes and may be useful in documenting vocal alterations after surgical procedures on the pharynx. Some laryngologists have found it to be valuable in singers and other professional voice patients.[35,36]

Electroglottography

Electroglottography measures the efficiency of glottal closure by graphically recording the contact time of the vocal folds. It shows the opening and closing rates of the vocal folds, which are not well visualized by stroboscopy. Electroglottography is performed by the passage of a low-voltage, high-frequency current between two electrodes placed on either side of the patient's neck. It measures the electrical impedance, which varies with opening and closing of the glottis. Some clinicians consider this measure objective and reproducible. Electroglottography may provide clinically useful information when combined with laryngeal stroboscopy or other measurements of layrngeal function.[37-39]

Aerodynamic Measures

Aerodynamic studies are based on the fluid mechanics of airflow and involve the measure of airflow, volume, and pressure. Some are related to Ohm's law ($R = P \div F$, in which R is laryngeal resistance, P is subglottal pressure, and F is airflow).

Normative aerodynamic data are very broad, making comparisons among patients almost useless. However, changes in measures after intervention in individual patients are quite useful, particularly in the evaluation of changes in laryngeal closure.

Standard pulmonary function testing may be used to objectively evaluate the lungs. Mild obstructive or restrictive pulmonary disorders may be the basis of a patient's vocal fatigue or dysphonia. Bronchodilator trials and methacholine challenge may rule out cough-variant asthma and other types of reactive airway disease.

Subglottal pressure is usually measured indirectly rather than by tracheal puncture or esophageal balloon. It is measured via oral pressure when the glottis is open. The oral pressure achieves equilibration with the subglottal pressure across the open vocal folds for voiceless stop consonants, such as /p/ and /t/.[40]

Maximum phonation time is an average of the (1) phonation length in one breath voicing the vowel /a/ at a comfortable pitch and (2) loudness after deep inspiration. It is highly variable but can reasonably estimate laryngeal competence and glottal closure.

Mean airflow rate (airflow volume ÷ phonation time) of a sustained vowel /a/ is occasionally tested. In general, low flow rates suggest laryngeal hyperfunction, obstruction, or primary pulmonary disorders. Higher values imply abnormalities in glottal competence that allow air loss.

Perceptual Analysis

For evaluation of the professional voice, the "trained" ear remains the most discerning instrument.[41-43] Perceptual improvement or degradation of the professional voice to the performer, manager, other performers, the laryngologist, the speech language pathologist, and the vocal pedagogue is critical. To make perceptual vocal analysis more objective, vocal characteristics can be evaluated independently in a systematic manner. In addition, judges are trained in vocal evaluation to decrease subjective bias. However, agreement on the terminology of vocal characteristics is not universal. Hirano[44] proposed the GRBAS (grade, rough, breathy, asthenic, strained) scale, which is widely used. However, Sundberg[45] and Kreiman and associates,[46] who performed research in this area, concluded that the clinical application of perceptual analysis was difficult, and it remains so even today.[45,46]

Voice Outcomes

Because of daily variation in vocal measures, vocal quality is frequently best judged by measures of patient satisfaction or direct comparisons of voice at different times. Patient satisfaction can be assessed through direct questioning or specially designed questionnaires for rating perceived vocal problems. Voice can be directly compared with the use of taped samples. By eliminating dates and other identifying factors, blinded analysis of vocal changes can be determined. A panel of judges can thus evaluate objective qualitative changes in a blinded manner over time. This approach is useful to determine the effect of a specific therapeutic intervention.

Outcomes research for judging patient satisfaction with voice and treatment is a valuable tool for studying vocal disorders. A voice handicap index has been developed to quantify a patient's perception of his or her voice and its change in response to therapy.[47] Cohen and associates[48] have validated a voice handicap index specifically designed to measure self-perceived vocal handicaps among patients who sing.[48] Both of these self-rating questionnaires are useful for measuring patients' self-perceptions about voice and the changes in voice after medical, behavioral, or surgical intervention.

Evaluation

Medical History

A complete history of the present illness and past medical problems is necessary. Several laryngologists have developed patient questionnaires to obtain the most complete history possible and to streamline the evaluation process.[49]

Salient points regarding a patient's past medical history and general health include diseases that affect pulmonary status, posture, and hydration as well as any of the other body systems involved in voice production, as described in the introductory portion of this chapter. Any underlying chronic or acute pulmonary condition can significantly affect a singer's voice. Asthma, emphysema, or chronic bronchitis, all of which impair pulmonary function, decreases a singer's power supply to the voice. Musculoskeletal injuries alter posture and impair a patient's ability to position the larynx within the neck, leading to vocal dysfunction. Prescription and nonprescription drugs change the voice through direct effects on the autonomic nervous system and indirect effects on the larynx and vocal tract.[50,51] Drugs that alter a patient's emotional status affect the manner in which the patient approaches the vocal task. Drug-induced changes in hydration lead to poor laryngeal lubrication, which affects vocal fold vibration. History taking in a female singer should include questions about oral contraceptives and hormonal drugs (e.g., danazol), which may adversely affect the voice.[52-54]

A singer's personal habits should also be reviewed. Moderate use or abuse of alcohol is detrimental to the voice through dehydration and effects on judgment. Caffeine (a diuretic) and high-fat dairy products affect the voice by thickening mucous secretions, thereby decreasing the efficiency of vocal fold vibration. Certain foods and alcohol exacerbate gastroesophageal and extraesophageal reflux.[50] Finally, tobacco use should be evaluated. Inhaled smoke is particularly irritating to the mucosa acutely and may induce esophageal reflux, which reduces vibratory efficiency. In addition, exposure to carcinogens can lead to neoplastic changes.

A history of any surgery is important to learn in patients with vocal dysfunction. In addition to questions concerning head- and neck-related procedures, any history of endotracheal intubation should be identified because it may adversely affect the larynx. Procedures in the neck can alter a patient's ability to stabilize the larynx during voice production either through injury to the muscles and nerves controlling the extrinsic musculature or through pain from the surgical intervention itself. Recent abdominal or thoracic surgery could also greatly restrict a singer's capacity for inspiration or expiration for many weeks or months after the operation.

The identification of endocrine dysfunction is often useful. The laryngeal manifestations of hypothyroidism may create subtle changes in Reinke's space, leading to alterations in the voice.[55] Even mild hypothyroidism can cause a muffling of the voice, decreased range, and vocal fatigue.

Less well understood are the vocal changes caused by hormonal fluctuations in women just before and during menstruation. Flach and coworkers[56] reported that 75% of female singers show a premenstrual change in their voices, manifested as decreased range and vocal fatigue. Using cytologic smears, Abitbol and colleagues[57] objectively showed cyclical changes in vocal fold epithelial cells corresponding to the menstrual cycle; these changes have been called *laryngopathia praemenstrualis*.[58] The common increases in size of vocal fold varices before and during menstruation have been associated with a higher incidence of submucosal vocal fold hemorrhage.[59,60] Vocal fold varices are most commonly found in female professional voice patients.[59,61-63]

Finally, the history must also address what type of professional voice use the patient requires as well as the amount and type of formal vocal training the patient has received. Professional voice users who primarily speak have different vocal demands from those who primarily sing. Speakers often lower the pitch of the voice to sound more authoritative. This practice is particularly common among female newscasters and physicians. Prolonged artificial pitch lowering often leads to muscular strain and early vocal fatigue. Such patients can lose flexibility in the speaking voice over time, a loss that is often perceived as an increased sense of roughness.

In patients who sing, the clinician must ascertain the style of singing. Those who sing commercial rock music have different demands from those of country and western or bluegrass musicians. Classically trained vocalists in opera and those in legitimate Broadway performance have completely different sets of demands from each other as well as from the other types of performers previously mentioned. It is helpful for the clinician to become familiar with the demands and requirements for each type of performer. If the otolaryngologist caring for the voice patient does not have an interest in obtaining this knowledge, he or she must work jointly with someone who does. The clinician should determine whether the patient has a current voice coach or they have worked with one in the past. It is helpful to determine the level of vocal performance education as well. What are the patient's long-term goals? A trained vocalist may be able to correct the vocal technique more easily than an untrained vocalist.

History of Present Illness

The exact nature of a singer's complaint should be reviewed with care. A vocal professional may simply complain of "hoarseness." This common term is used to describe most vocal abnormalities, including loss of upper register, roughness, pitch instability, difficulty in transition between singing registers, and early vocal fatigue. These are frequently symptoms of laryngeal edema, muscle tension dysphonia, extraesophageal reflux, upper respiratory infections, nonneoplastic lesions, or poor vocal technique. Patients, therefore, should be questioned specifically about range, pitch breaks, anterior cervical discomfort, esophageal reflux, and stamina. An understanding of the required type of voice use is helpful in evaluating these complaints and their effect on vocal production. Professional speakers usually speak in and around their most common vocal pitch; in speech language pathology this is referred to as the *modal register* of voice production. If professional patients attempt to artificially lower the pitch to slightly below the natural speaking pitch, they often complain of vocal fatigue and/or increased effort. After prolonged inefficient use patterns, the speakers

may also complain of increased vocal roughness even though examination does not reveal any discernible lesions.

Singers, on the other hand, divide their modal voice register into chest voice, head voice, and a transition register between head and chest voice. *Chest voice* is the lower portion of the modal register in which the singer feels the sensation that the voice is resonating from the chest. *Head voice* production includes the upper portion of the modal register in which the singer has the sensation that the voice is coming from the head. The area between head voice and chest voice is referred to as the *transition voice* or *transition register* by most singers. In this register the classically trained performer attempts to blend the chest voice into the head voice so that the register shift is not apparent. These register shifts are most likely secondary to physical vocal fold mass and absolute laryngeal size. As the singer attempts to elevate pitch, cricothyroid muscle activation elongates the vocal fold and tenses the vocal fold cover. In addition, cricothyroid activity slightly abducts the vocal folds. To maintain the vocal folds in an efficient posture for vibration, the singer must delicately adjust vocal fold adduction by increasing activity in the thyroarytenoid, lateral cricoarytenoid, and/or interarytenoid muscles. The abductory force on the vocal fold from the cricothyroid muscle pull is most likely responsible for the break between the chest voice and the head voice. The "break" region is termed the *passagio*. The specific notes are called the *primo passagio* for the lower break point and the *secundum passagio* for the upper break point. These points vary for different singers but can be broken down into expected regions according to a singer's overall pitch range. These break points or regions, along with the singer's overall range, help determine whether the singer is a bass, baritone, tenor, contralto, or soprano. There are also many divisions among classically trained singers within each one of these categories. A more complete discussion of this topic can be found in Miller.[16] Commercial or pop performers may not be aware of their vocal range classification. It may be unimportant to them because they may often sing in a different vocal register termed the *falsetto*, *flagelette*, or *whistletone* register. These terms essentially imply voice production with light or incomplete vocal closure and are often used somewhat interchangeably by both speech language pathologists and vocal pedagogue.

The onset and offset of the vocal difficulty can often provide clues about the cause. Specifically, time of the difficulty throughout the day, situations that aggravate the dysphonia, events that immediately precede the onset of the difficulty, and the association between dysphonia and voice use are significant in determining the cause and may aid in management.

Professional activities that can contribute to these problems include air travel, performing on older indoor stages with poor acoustics, exposure to chemicals and fumes, required excessive use of the speaking voice for promotion, and overscheduling of performances. Air travel remains a problem for the serious voice user because the air on planes is very dry (5%-10% relative humidity) and affects the larynx; also, the high background noise tempts the patient to speak more loudly.[8] Performing on older stages, which may be dusty, and traveling in areas with a large amount of allergens can degrade a patient's voice. Exposure to other types of irritants, including tobacco smoke at parties or at performances in smoke-filled rooms, also affects the voice. Vocal professionals required to give multiple interviews often experience dysphonia of various degrees. A singer's schedule may make it difficult for the singer to drink large quantities of water to lubricate the vocal cords, and although a singer may complain of singing problems, the main difficulty may be voice abuse caused by excessive speaking. Significant abuse of the speaking voice leads to eventual singing difficulties.

Often, a younger vocal professional does not seek help until the problem becomes significant or the performer is about to go on tour or has a performance in the near future. Management of the problem may vary according to when the next performance is to take place. This should be considered in the development of a management plan.

Physical Examination

Every voice patient presenting to the otolaryngologist or laryngologist should undergo complete examination of the head and neck. The physical evaluation of the vocal professional begins with observation of gait and posture as the patient walks into the physician's office. Does the patient stand comfortably erect with shoulders slightly back or slouched? Does the patient appear tense and anxious?

While taking the history, the physician should evaluate the quality of the patient's speaking voice. The frequency or pitch should be appropriate for the performer's age, gender, and body habitus. Volume or vocal intensity should be appropriate for conversational speech. The timing of voice onset should be studied, including speech breaks and the overall rhythm. Finally, vocal quality is evaluated for roughness, breathiness, asthenia, and strain.

Neck palpation, specifically of the anterior cervical musculature, cricothyroid space, thyrohyoid space, and tongue base above the hyoid bone, is performed with the patient at rest and while phonating. These areas should be nontender. They should remain supple and should tense or move only minimally during phonation if the patient is producing voice efficiently. Excessive tenderness indicates excessive extralaryngeal muscular tension or effort. Excessive tensing during voice production indicates excessive effort to produce glottal closure. This is common in patients with inefficient patterns of voice production, often termed *functional dysphonia*. Tension during phonation without tenderness at rest may indicate that a patient needs to use extralaryngeal muscular effort to compensate for impairment of laryngeal closure from paresis, paralysis, or a large mucosal lesion

Certain areas of the nonlaryngeal examination are also significant. Jaw range of motion should be checked, and the temporomandibular joint should be palpated. Temporomandibular joint dysfunction can create significant muscular tension difficulties in a professional voice patient. The ears should be examined for any abnormalities, and an audiogram should be obtained. Hearing loss, particularly if sensorineural, can cause a singer to sing too loudly, resulting in excessive trauma to the vocal folds.

The nasal examination can provide information about mucous membrane disease. Pale and edematous nasal mucosa suggests the presence of significant allergies. Evidence of a chronic infection with purulent discharge or crusting should be sought. Nasal obstruction can lead to chronic mouth breathing. The subsequent exposure of the larynx to unfiltered dry air can cause significant dysphonia by thickening the secretions and therefore raising the phonation threshold pressure. In addition, the physician can determine the nature of the patient's secretions by noting their consistency in the nose and oral cavity. Cough resulting from chronic postnasal drip can also lead to vocal fold edema.

Laryngeal and pharyngeal examination can be performed by various methods. There are three ways to examine the larynx: with a laryngeal mirror, with a rigid telescope, or with a flexible transnasal laryngoscope. The first and classic method is with a laryngeal mirror. It gives the most natural color to the tissues being examined and potentially allows a panoramic view of the entire larynx.

Vocal professionals may be evaluated with the rigid telescope and/or a flexible transnasal laryngoscope. Single-point light sources, however, can distort color, and this fact should be considered in the evaluation. Rigid indirect endoscopy and flexible laryngoscopy are complementary; each has certain advantages. Using both methods in the professional voice patient enables a full evaluation.. Use of the rigid telescope requires that the examiner gently grasp the patient's tongue and draw it forward. This maneuver alters the patient's normal use of the supraglottal vocal tract and articulators, making glottal closure and laryngeal hyperfunction difficult to interpret. Most efficient voice users can compensate for these changes and actually use the larynx relatively efficiently while being able to sing scales on vowel sounds. The rigid rod lens endoscope provides the best illumination and magnification, allowing an unparalleled view of the larynx during vibration and inspection of the laryngeal mucosa for disease. Small lesions or areas of vascular abnormality in the larynx, which may be missed with the mirror or flexible laryngoscopy, can be identified with a 70- or 90-degree telescope. In addition, laryngovideostroboscopy is performed better through the rigid telescope than with the flexible device. The picture is clearer, larger, and brighter and therefore allows the examiner to better evaluate the laryngeal vibratory pattern.

Flexible laryngoscopy with either a distal chip camera or older fiberoptic technology allows examination of a vocal professional without

Table 61-2

Laryngeal Examination

	Laryngeal Mirror	Flexible Fiberoptic Laryngoscope	Rigid Telescope
Operator ease	+++	+++	++++
Patient tolerance	+++	+++	++
Photographic quality	−−	++	++++
Magnification	−−	+	++++
Color	++++	++	+++
Laryngovideostroboscopy	−−	++	++++
Observation of speech/singing	−−	++++	−−−
Evaluation of vocal mechanics	−−	++++	−−−−

+, Advantageous; − disadvantageous.

traction on the tongue. Although the presence of the flexible endoscope may induce some discomfort and therefore alter laryngeal behavior, most patients can use connected speech or can sing during evaluation of the supraglottal vocal tract and larynx. This provides an opportunity to evaluate laryngeal biomechanics, particularly in a hyperfunctioning larynx, but does not give the examiner the opportunity to directly palpate tongue tension. Drawbacks of fiberoptic systems include the well-known fish-eye distortion of the peripheral image, decreased resolution, linear color stripe distortion on video imagery (moiré effect), and decreased illumination, which makes stroboscopy findings more difficult to interpret (Table 61-2).[64] These problems are reduced or eliminated by flexible endoscopes, which use a distal chip camera to transmit the image rather than the older standard fiberoptic technology. The presence of a large mucosal lesion or paralysis of the vocal folds may be apparent to the examiner using an endoscope. Subtle laryngeal findings may be less apparent. The presence of thick, tenacious mucous secretions should be noted and compared with the usually seen watery lubrication, which is preferable. Evidence of vocal fold swelling, ventricular effacement, and erythema, swelling, or granular tissue in the posterior glottis may indicate recurrent trauma due to chronic coughing or extraesophageal reflux. Areas of vocal fold edema, particularly in the middle third of the fold, may be present in a vocal professional who complains of slight dysphonia. Evidence of hyperfunction should be sought; it can manifest in its most subtle form as widening of the posterior glottis. More severe hyperfunction could cause closure of the false vocal folds (plica ventricularis) as well as anterior-to-posterior contraction of the supraglottis. If these findings are present, subtle vocal fold paresis should be considered.

The vocalist should be evaluated by a vocal pedagogue even if an obvious laryngeal problem is identified. The singer's posture and general stance should be noted. The "singer's stance" is a fully upright position with the feet about shoulder-width apart and the weight slightly forward on the balls of the feet. Frequently, commercial performers are required to play instruments while singing. In this instance, the patient should be observed while holding the instrument. Facial, shoulder, or cervical tension should be noted if present when the patient is singing. Is the singer using the abdominal muscles appropriately to support the singing voice or breathing only with the use of chest and shoulders? The presence or absence of laryngeal elevation with rising pitch should be noted; this is considered poor technique in a classically trained singer and can lead to vocal fatigue due to excessive muscular tension. In commercial singing, however, laryngeal elevation can often be used to achieve a desirable sound, and elimination of elevation causes an uncharacteristic vocal quality for many styles of commercial music.

Problems in Singers

Professional singers have the same maladies that affect the general population. However, because of the tremendous demands placed on their voices, these vocalists are highly sensitive to problems affecting the larynx and the associated areas involved in voice production.

Extraesophageal Reflux

Gastroesophageal reflux is a common problem often manifested as heartburn, belching, or an acidic taste on waking. Patients may have significant reflux with no abdominal or chest complaints; this type is called extraesophageal or laryngopharyngeal reflux.[50,65-69] The symptoms are often frequent throat clearing, mild dysphonia, cough, a sensation of phlegm or a foreign body sensation in the throat (globus), vocal fatigue, cervical dysphagia, and decreased singing range.[70,71] Singers and other vocal professionals with extraesophageal reflux often have hoarseness in the morning and require longer vocal warm-up. Signs of reflux laryngitis should always be sought during the physical examination.[72,73] If signs or symptoms suggest extraesophageal reflux, conservative management directed at diet and general lifestyle is initiated. Adhering to these measures might be difficult for performers with a demanding travel schedule. Extraesophageal reflux is partially managed with proton pump inhibitor. This agent is taken 30 minutes to an hour before a meal and, for extraesophageal reflux, is often used twice daily. It is uncertain whether the addition of drugs to enhance gastric emptying makes any definite contribution in the management of extraesophageal reflux. Patients with a confusing clinical picture or those who do not show a good response to maximal-dose proton pump inhibitors undergo 24-hour pH monitoring. Some cases of reflux may be resistant to proton pump inhibitors.[74-77]

Laryngeal Hygiene

Laryngeal hygiene can be problematic in professional singers. The key to good laryngeal hygiene is adequate hydration. Poor hydration causes an increase in mucus viscosity, resulting in less efficient vocal fold vibration.[78-80] Singers should drink larger amounts of water. The noted otolaryngologist and voice specialist Van Lawrence is quoted as stating that singers should "pee pale" (ingest so much water that they exhibit lightly colored urine), and vocal professionals should not drink a set amount of water but allow their kidneys to "tell" them how much to drink. At least eight glasses (64 ounces) of water per day appears to be needed, and the amount should be increased if the voice user is traveling by air, is ill, or has a demanding or excessive performance schedule. The use of caffeine is discouraged because of its diuretic effect. Dairy products also appear to increase the viscosity of secretions and hinder the healthy smooth vibratory function of the vocal folds. Guaifenesin

can thin the secretions in some patients. The use of tobacco by the professional voice patient also contributes to poor laryngeal hygiene.

Vocal Abuse and Misuse

Vocal abuse refers to phonation that is excessive in length or is produced in an overly loud manner. Loud phonation and excessive phonation lead to increased trauma in the mucosal membrane during voicing. After periods of vocal abuse, patients complain of a sense of vocal fatigue and tightness in the larynx. If voice abuse is long-term, patients can experience a response to the trauma, with lesions appearing on the vibratory surface of the vocal folds. Common forms of voice abuse in professional voice users are: (1) over-rehearsing, (2) spending too much time working in the studio, (3) singing too loudly, and (4) singing outside the singer's capable range. In addition, commercial singing frequently incorporates artificial roughness to render "validity" to the performance.

Vocal abuse behaviors can also occur if performers give too many interviews or shout and talk excessively in areas of loud background noise (e.g., restaurants, airplanes). The vocal professional should conserve the voice by limiting unnecessary speaking, exercising what is called *modified voice use*. This is particularly important if the vocalist is having vocal difficulties or is ill. Punt[81] advises singers "not to say an unnecessary word unless they are paid for it," especially if they are ill or have an excessively demanding performance schedule.

Vocal misuse refers to dysphonia caused by inefficient methods of voice production. Inefficient vocal patterns occur when voice is produced with inappropriate laryngeal tension and/or poor respiratory support. This often leads to early vocal fatigue, increased vocal roughness, or pain with phonation. Most of the time, patients who misuse their voices have a relatively normal vocal fold appearance; this condition is often referred to as *muscular tension dysphonia*. Long-term misuse coupled with loud and excessive phonation (abuse) can eventually lead to organic changes in the vocal folds. These changes most commonly appear as vocal nodules and disrupt the normal laryngeal vibratory pattern, causing dysphonia. Elimination of the inefficient/inappropriate vocal behaviors lessens or eliminates the dysphonia. With time, the organic changes may reverse, and healthy vibratory patterns may return.

Voice misuse or muscular tension dysphonia is not limited to vocal professionals, and voice misuse can be the primary or secondary cause of dysphonia. Singers are not immune from voice misuse despite misconceptions that vocal training should eliminate such difficulties. This problem is common, particularly as a maladaptive, compensatory behavior after an upper respiratory infection. The singer attempts to maintain a normal voice while the vocal folds or pharynx are swollen from illness or too much use and develops inappropriate vocal behaviors. Such a patient often complains of hoarseness, vocal fatigue, loss of range, and neck or ear discomfort.

Koufman and Blalock[82,83] formulated a grading or classification system for muscular tension dysphonia. Class I muscular tension dysphonia is defined as an increase in muscular tension manifested as an enlarged posterior glottal chink, an elevated larynx, and palpable neck tension or tenderness. It may produce a breathy or strident voice and commonly occurs in patients with vocal nodules. Class II muscular tension dysphonia is a lateral to medial constriction of the larynx with the false vocal folds adducted. This problem causes greater vocal fatigue. In its most severe form, the false folds are used for phonation, so-called *plica ventricularis*. It is often seen as a compensatory maneuver after laryngitis or laryngeal surgery. Class III muscular tension dysphonia is an anterior-to-posterior constriction of the supraglottis when the epiglottis and the arytenoids obscure at least 50% of the laryngeal aditus. Class IV muscular tension dysphonia is present when the epiglottis and arytenoids contact one another, and lateral constriction is often seen.

Koufman[84] reviewed laryngeal biomechanics during singing. In this study, 100 singers of various singing styles were evaluated with fiberoptic laryngoscopy. Koufman found that vocal training, warming up before singing, and singing classical musical styles decrease muscular tension. This finding supports the belief that vocal training increases vocal efficiency and decreases muscular tension. Koufman also found that singers with asymptomatic vocal nodules had significantly higher levels of laryngeal muscular tension than those without nodules. The management of muscular tension dysphonia is directed by the speech language pathologist and the vocal pedagogue. It aims to retrain the patient to improve speaking and singing efficiency, thereby decreasing laryngeal tension and vocal fold trauma.

An interesting type of vocal misuse in professional voice patients is an inappropriately low-pitched speaking voice. This deepening of the voice gives it a more authoritative quality. It requires a significant amount of muscular tension to maintain.[85]

Laryngitis

Acute laryngitis (inflammation of the laryngeal mucosa) is common in adults and can be devastating to a professional voice patient. Inflammation of the vocal folds causes irritation and edema and hinders the pliable motion of the mucosa, leading to dysphonia. To compensate, singers may exert extra effort to maintain the normal voice. Singers may correctly compensate by decreasing the volume, increasing the amplification, altering the repertoire, and other measures.

A very mild case of laryngitis can be managed conservatively with voice rest. Some singers may, however, elect to continue to perform. A singer who elects to perform while the vocal folds are inflamed should be aware of the risk of permanent damage to the vocal folds and the greater risk for submucosal hemorrhage. Preferred management of laryngitis involves an increase in fluid intake and humidification of the room. If cough is present, an antitussive agent may be of benefit. Conservative voice use is key. The singer should speak little, if at all, to allow the vocal folds to heal.. Before the performance, the singer should warm up in a normal fashion and should be told not to force the voice to produce the usual or normal sound. The performer should be instructed to sing by feel and not by sound. This technique may avoid exacerbating the injury. The singer should speak in a normal, unforced voice without whispering. If a bacterial infection is suspected, antibiotics should be prescribed. The use of corticosteroids, although not empirically tested, is clinically beneficial in most patients with acute laryngitis.

Severe laryngitis should be managed like acute laryngitis, but in the case of severe laryngitis, every possible effort must be made to persuade the vocalist to agree to vocal rest. Serial examinations enable the physician to advise the vocal professional when it is safe to return to vocal activity.

Anxiety

Apprehension before a performance is normal. A few professional voice patients may have dramatic stage fright. Professional vocalists should learn to cope with this anxiety by working with a vocal coach and laryngologist. Several medications have been used, but all have potential adverse effects, and none replaces good training and the confidence that comes with repeated performance under such stress.

The use of β-blockers to decrease the tachycardia that often accompanies the anxiety is common, but this medication has adverse effects. Gates and coworkers[86] stated that β-blockers decrease anxiety but also take some of the dramatic edge and excitement away from the singer. These agents should be used only on rare occasions (e.g., when a crisis occurs before a performance) and never on a regular basis.

Pulmonary Disease

Any respiratory ailment alters the amount of power available for singing or phonation and limits the vocalist's ability to modulate it. Pulmonary health and good conditioning are important for proper voice support.[87,88]

An uncommon but reported type of exercise-induced asthma exists in some singers when they have been singing for a lengthy period. This airway reactivity–induced asthma in singers[89,90] can be diagnosed with pulmonary function testing performed before and after prolonged singing.

Vocal Fold Varices

A true *vocal fold varix* is a dilated, tortuous, or elongated blood vessel stemming from the microcirculation of the vocal fold; it occurs mainly in female professional vocalists. The cause of this relatively uncommon lesion is uncertain, but its preponderance in female singers suggests that hormones and vocal trauma are major factors.[59,91,92] The laryngologist

should determine whether the patient's symptoms correlate with the menstrual cycle. Varices may enlarge premenstrually and menstrually and can increase a singer's dysphonia.

If a vascular lesion is found, its functional significance should be determined. This determination is best made with serial laryngovideostroboscopy. The lesion's effect on the laryngeal vibratory pattern can be accurately determined, including whether the vascular lesion is the cause of the singer's problems. The lesion should be examined periodically throughout the menstrual cycle for changes in size or leakage of blood. Nonsurgical management of vascular lesions involves improvement in vocal hygiene, particularly with increased water intake and the avoidance of caffeine. In addition, working with a speech pathologist and vocal pedagogue to improve vocal efficiency is important. Hormonal manipulation has been advocated by some writers but has not been proven to be beneficial. Indications for surgery include recurrent hemorrhage, an enlarging varix, and continued dysphonia despite maximum medical and behavioral management.

Performance Cancellation

Possible cancellation of a performance can be very stressful for a professional singer and the laryngologist. The performer and the manager have many concerns beyond the singer's health—for example, the singer's professional image, perceived reliability, and financial obligations. The musical style and the importance of the performance are also important variables; slight vocal roughness would be acceptable in a contemporary rock or country performer but unacceptable in an opera singer.

The physician's recommendations for performing are categorized by (1) conditions in which damage to the larynx will not be significant and (2) conditions that place the performer at significant risk for development of chronic vocal difficulties (Box 61-1). However, the decision to perform ultimately belongs to the performer. Singing will still be problematic during and after the performance. Examples of conditions that pose a mild risk to the performer are a mild viral upper respiratory infection and mild to moderate vocal fold edema. In an upper respiratory infection, the postnasal drip and generalized congestion can be managed, but the supraglottal vocal tract is altered and the singing voice will not be normal. To produce the usual perceived sound, the vocalist can exert significant extra effort, possibly leading to the development of maladaptive singing behaviors that could take time for the vocal pedagogue and speech language pathologist to correct. The singer and manager should also decide whether a decrease in vocal quality would alter the performer's image or reputation.

Conditions that are likely to cause permanent vocal changes include submucosal vocal fold hemorrhage, enlarging varix, and a vocal fold mucosal break (see Box 61-1). In the presence of any of these conditions, absolute voice rest is essential. The usual conservative care of the larynx should also be undertaken. Aggressive antireflux therapy should be initiated in patients with laryngeal mucosal breaks. These individuals should be followed closely for the development of submucosal scarring, granulation tissue, or polyps.

Management

Medical Therapy

The mainstay of medical therapy for a singer is appropriate lifestyle change. This begins with maintenance of adequate hydration. In addition, for many problems, a period of conservative voice use is the best remedy. A humidifier should be used when the singer is traveling or sleeping in rooms with inadequate humidity. Altering the diet to avoid reflux-inducing foods and avoiding irritants are always important, particularly when the singer is ill. In general, these interventions improve laryngeal hygiene primarily through their effect on lubrication and avoidance of further vocal trauma.

The special needs of vocal professionals require the avoidance of certain commonly used medications, including inhaled corticosteroids, antihistamines, decongestants, aspirin, topical analgesics, and mentholated preparations.

The application of topical corticosteroids on the larynx should be avoided. They directly irritate the laryngeal mucosa and are associated with a higher incidence of fungal infections of the larynx.

Systemic corticosteroids are indicated for conditions in which there is little chance of permanent laryngeal damage (Box 61-2). They can be used when a patient with vocal fold edema has an upcoming performance. This approach is combined with improvements in laryngeal hygiene and conservative voice use. Laryngeal edema commonly occurs during repetitive recording sessions or after extensive rehearsals before major tours or performances. Corticosteroids are also beneficial when singers have mild viral laryngitis, to decrease the vocal fold edema and to help control significant allergic reactions. Corticosteroids can be given for a severe case of laryngitis, but the vocalist will risk laryngeal damage by performing. Systemic corticosteroids are frequently given for vocal fold hemorrhage to decrease the deposition of scar tissue in the superficial layer of the lamina propria, to prevent polyp formation, and to decrease the overall inflammatory response. However, no scientific evidence exists that corticosteroids are beneficial in this clinical situation.

Management with corticosteroids varies according to the severity of the problem. Combinations of short- and long-acting corticosteroids (dexamethasone 4 mg with methylprednisolone 80 mg) can be given intramuscularly if a performance is to be given within 24 hours. In subacute situations, stress-dose corticosteroids taken orally for 3 to 5 days with a rapid taper are appropriate.

Idiosyncratic reactions to corticosteroids can occur, in which case the performer's voice actually worsens rather than improves. In addition, corticosteroid-induced psychiatric changes may occur. Because of these reactions, systemic corticosteroids should not be used for the first time in any patient before a performance except in the most dire of circumstances. Corticosteroids are best used initially before routine studio recordings or song-writing sessions. This situation allows the physician and the performer to gauge the response and creates a better understanding of how the patient would respond to corticosteroids in other situations. The singer should not depend on corticosteroids but use them only when required.

Most antihistamines have a significant drying effect on mucous membranes because of their anticholinergic effects. In patients requiring significant management of allergies, it is best to begin with topical nasal corticosteroids. These are effective for the relief of allergic rhinitis and do not adversely affect the voice. Some of the newer, nonsedating antihistamines may be useful.[93] For patients with more severe allergic symptoms, formal allergy testing should be performed early. After the identification of the specific allergens, avoidance or environmental therapy is attempted, but this approach can be difficult because of travel. If possible, the performer's travel schedule should be arranged to avoid certain environments where seasonal plants are in bloom. Allergic immunotherapy is very helpful in patients with allergies.

Box 61-1

Conditions Requiring Performance Cancellation

Submucosal hemorrhage
Enlarging vocal fold varix
Break in vocal fold mucosa
Significant systemic illness
Severe laryngitis

Box 61-2

Indications for Systemic Corticosteroid Therapy in the Professional Voice Patient

Edema from episodic abuse
Mild to moderate laryngitis
Allergic vocal fold edema
Vocal fold hemorrhage

Decongestants often provide symptomatic relief in a performer with an upper respiratory infection. Combination preparations that include an antihistamine should be avoided in professional voice patients because of the drying effects of medications on mucous membranes.

Aspirin use is not advised in vocal professionals. Aspirin inhibits platelet function and can increase the risk of submucosal vocal fold hemorrhage. Professional voice patients should check the labels of nonprescription medications and should avoid those with aspirin.

Although once very popular with vocalists, topical anesthetic solutions for sore throats or laryngitis can harm the voice. By decreasing the sensitivity of the oropharynx or supraglottal larynx, these solutions allow the patient to overwork an injured area, possibly leading to submucosal hemorrhage, mucosal tears, or a granuloma. If a performer believes that work is not possible without such an analgesic, he or she should not perform.

Patients complaining of a dry throat or a cough often initiate management with nonprescription cough or topical preparations. These preparations frequently contain menthol, which is initially soothing. Menthol, however, is a drying agent and is habit forming in some patients.

Antibiotics are prescribed for singers in accordance with standard management indications. Overdispensing of antibiotics, a major problem in our health care system, should be avoided. Antibiotics can be prescribed to a singer who is about to go out of town or on an extended tour. Written instructions outlining when to use the antibiotics should be given. If the performer feels the need to use the medication, he or she should contact the physician.

Mucolytic agents (e.g., guaifenesin) are commonly used by singers as a pharmacologic adjunct to thin secretions, thereby improving the lubrication of the vocal folds. Although not proven to be effective, guaifenesin and similar agents appear to benefit some vocal professionals.

Role of the Speech Language Pathologist and Vocal Pedagogue

The speech language pathologist and vocal pedagogue work with patients to improve singing and speaking efficiency, to eliminate vocal abuse, to correct misuse, and to encourage vocal hygiene. Singers should understand that vocal abuse during speaking is intimately connected with the singing voice. They are taught to avoid cervical strain, and they learn proper breathing patterns, improve posture, and develop a soft glottal attack when speaking. The goal is to improve laryngeal efficiency and thereby limit laryngeal trauma during singing and speaking.[30]

The role of the vocal pedagogue is complex. Classical vocalists should improve classical technique. Commercial singers, however, should optimize glottal efficiency when singing without producing a classical sound. Training, therefore, differs for classical and commercial vocalists. Areas emphasized for classical artists include breath support, body alignment, stable laryngeal position low in the neck, and maintenance of a lower subglottal pressure than for other singing styles.[94] This lower pressure enables the classical vocalist to produce the singer's formant, allowing greater voice projection with less vocal effort. Nonclassical or commercial singers should also concentrate on breath support and body alignment, but they do not incorporate the singer's formant. Therefore, these performers must sing more loudly to be heard over instruments and other singers. Commercial singers must be educated on the proper use of electronic amplification, which is a substitute for loud singing. Other considerations for commercial singers are precise vowel integrity, phrasing similar to that of speech, and delayed onset of vibrato. Vocal efficiency should be improved without changing the performer's style or developing a classical sound. The use of full-length mirrors and videotaped recordings while performing help educate the performer. Vocal efficiency is also improved with appropriate warm-up and range-building exercises.[95] Sabol and associates[33] used objective aerodynamic testing to show the benefit of vocal exercise in singers.

Surgical Therapy

Before surgical intervention, behavioral and medical interventions should be maximized. Vocal hygiene, avoidance of vocal misuse, and resolution of vocal abuse should be accomplished. Patients failing to achieve these goals will have recurrent problems. Surgery is relatively contraindicated in patients who cannot comply with the recommendations of hygienic voice production from a speech language pathologist and vocal pedagogue. All patients learn to develop a soft glottal attack, which is vital for postoperative rehabilitation. The overall effect of maximizing medical and behavioral management is to reduce the need for surgery, lessen the incidence of lesion recurrence, shorten the postoperative recuperative time, and improve the overall postoperative outcome.

The decision to operate on the larynx of a vocal professional is often difficult. The singer should evaluate the risks and benefits and obtain a second opinion. It is important to realistically counsel the patient about the possible outcomes. The singer should understand that the singing or speaking voice may never be the same and that he or she may never perform at the same level again. Rehabilitation and healing after microsurgery of the larynx require 3 to 9 months and are often frustrating for the vocal professional. It is this period, working with the speech language pathologist and vocal pedagogue, during which the vocal professional needs the greatest amount of determination and encouragement. In most cases, surgery is performed only when the patient cannot perform at the required level or cannot maintain an acceptable performance schedule. Recurrent vocal fold hemorrhage from a varix and an enlarging lesion in the presence of efficient voice production styles are other indications for surgery.

After the need for surgery has been determined, atraumatic establishment of the airway in the surgical suite is the next concern. This task should be performed not by an inexperienced physician but by the surgeon or an experienced anesthesiologist. Gentle intubation should be performed with an endotracheal tube of the smallest possible caliber. The laryngologist should consult with the anesthesiologist before a vocal professional is intubated for any procedure. If possible, the laryngologist should offer his or her services for the intubation. Photographic documentation in the operative suite is performed immediately before and after the procedure. Zero-, 30-, 70-, and 120-degree telescopes can be used as needed to obtain optimal views of the vocal folds and to examine areas difficult to access, such as the depths of the laryngeal ventricle and the undersurface of the vocal folds.[96,97] The procedure is videotaped through the operating microscope.

The major determinants of a good postoperative result during laryngeal microsurgery are the conservation of normal mucosa, integrity of the vocal ligament, and the creation or maintenance of a straight vocal fold edge (see Fig. 61-5).[53,98,99]

Superficial Vocal Fold Lesions

Vocal fold nodules that have not resolved with medical and speech therapy and polyps that cause dysphonia can be surgically excised. Bilateral vocal fold lesions are of significant concern. It is common to remove the larger lesion in the hope that the smaller lesion will resolve. However, a lesion of any sort on the opposite fold may imply technical problems or hyperfunctional technique. Bilateral lesions predispose the patient to a less than optimal result; because bilateral lesions are more likely to be associated with hyperfunctional techniques, the resolution of the smaller lesion is the exception rather than the rule. Often, both lesions should be surgically removed, creating the risk of scarring and stiffness on both vocal folds.

Surgical therapy is always individualized. The choice of surgical approach is based on a thorough understanding of vocal fold anatomy and physiology. The goal of surgery is to restore the normal glottal configuration without the removal of uninvolved surrounding mucosa or excessive dissection in the superficial layer of the lamina propria. Superficial lesions represent a response to injury and reside almost exclusively in the superficial layer of the lamina propria. Therefore, surgery is limited to this region. A microflap approach with a medially placed incision is well suited to removal of these types of lesions.[100] After vasoconstriction of the laryngeal mucosa, an incision is made just over the lesion; the vocal ligament is identified through the use of a combination of blunt and sharp dissection with microsurgical instruments. The mucosa and superficial layer of the lamina propria encompassing the lesion are freed from the underlying vocal ligament by dissection in the superficial layer of the lamina propria, with great care

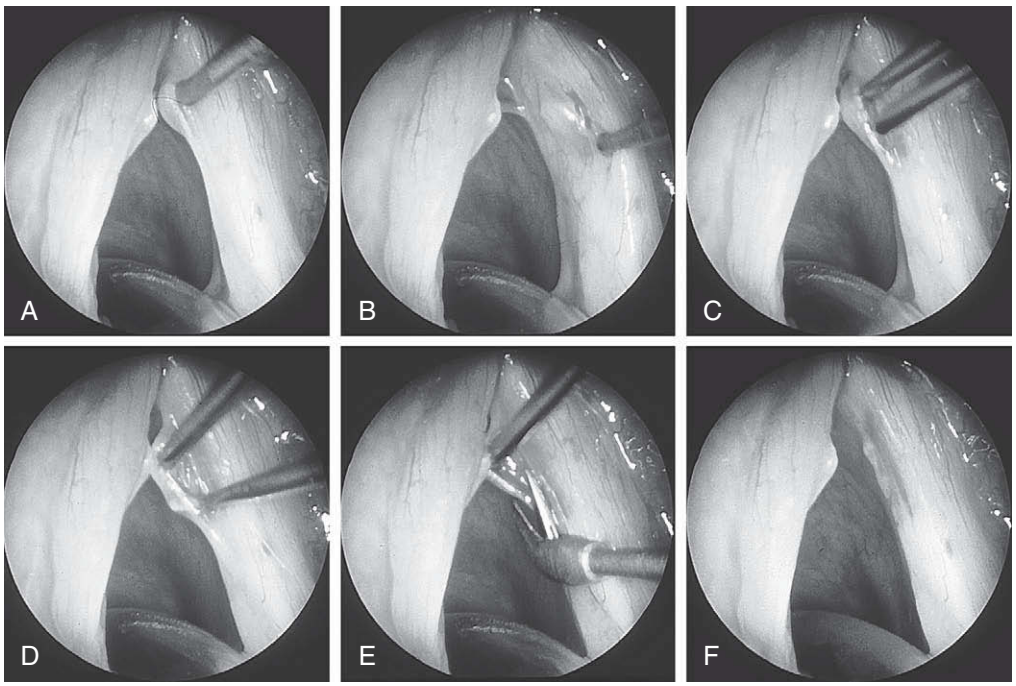

Figure 61-6. Intraoperative photographs of lesion excision through a medial microflap approach. **A,** The sickle knife is used to make an incision over the lesion on the medial surface of the vocal fold. **B,** A small angled probe, a flap elevator, is used to elevate mucosa from the medial and superior surfaces of the vocal fold around the lesion. **C,** The lesion is bluntly dissected free from the underlying vocal ligament. **D,** The lesion is peeled off a portion of the overlying vocal fold cover. **E,** The lesion and a small portion of the cover are excised. **F,** The previously created flaps are redraped in position to cover the medial surface of the vocal fold. *(From Courey MS, Garrett GG, Ossoff RH. The medial microflap for excision of benign vocal fold lesions.* Laryngoscope. *1997;107:340.)*

taken to remove only the involved mucosa. This approach often leaves a nearly imperceptible mucosal defect at the conclusion of the procedure (Fig. 61-6).

Cysts

Vocal fold cysts are diagnosed and differentiated from nodules or polyps by laryngovideostroboscopy. Cysts that fill the superficial layer of the lamina propria are often tethered to the vocal ligament, frequently resulting in a loss of the mucosal wave over the lesion. More superficial lesions such as nodules tend to be associated with a dampened yet perceptible mucosal wave.[32] Cysts and other lesions that do not separate easily from the vocal ligament on intraoperative palpation are approached via a lateral microflap technique.[31,101] This technique involves an incision along the superior aspect of the vocal fold lateral to the intracordal lesion. The vocal ligament is identified, and dissection occurs in the superficial layer of the lamina propria medially toward the lesion. The microflap is gently retracted medially, usually with a velvet eye microlaryngeal suction or with a flap elevator, and the cyst is sharply and bluntly removed from the vocal ligament and the overlying mucosal cover layer. After it is removed, the mucosal flap is redraped in place (Fig. 61-7).

Vocal Fold Varix

Varices of the vocal fold are evaluated under high magnification, and palpation is used to alternately occlude and examine the feeding and draining vessels. Then the vessels undergo vasoconstriction with chilled 1 : 10,000 epinephrine, and an iced saline pledget is placed deep to the vocal fold to protect the endotracheal tube cuff. The carbon dioxide laser is slightly defocused and used at 1- to 2-W power. The feeding and then the draining vessels are photocoagulated. The medial surface of the vocal fold is avoided. The vascular malformation is then coagulated. If still present, the mass is removed with use of the medial microflap approach.[59] Clinical experience from a few centers using angiolytic lasers (pulsed potassium titanyl phosphate and pulsed dye laser)[102] suggests that they may play a role in the treatment of these lesions; however, large feeding vessels may still require excision (Fig. 61-8).

Postoperative Care

After the surgery, general laryngeal hygiene is reemphasized to the patient. In addition to hydration and the use of guaifenesin, perioperative antireflux medications are strongly recommended for most patients. Complete voice rest is instituted after surgery. In patients with minimal mucosal excision and limited disruption of the submucosal layer of the lamina propria, this period may last 5 to 7 days. Ten to 14 days of complete voice rest is recommended in cases in which extensive vocal fold dissection or revision surgery has been performed.

Healing after laryngeal microflap surgery can be divided into four phases (Table 61-3). The first phase in the immediate postoperative period lasts 5 to 14 days and consists of complete voice rest and hydration. Healing occurs between the vocal fold cover and the underlying vocal ligament. In cases in which mucosal excision is required, healing by secondary intention occurs.

The second phase begins 1 to 2 weeks after surgery. This is a time of voice rehabilitation that occurs under the guidance and observation of a speech language pathologist. Laryngovideostroboscopy is usually performed after the second or third week. Pliability of the vocal fold and return of the mucosal wave are assessed. Rarely, vocal fold hemorrhage is noted, and further voice rest is required. This phase begins with graduated voice use. The first day, the patient speaks for 5 minutes. The phonation time is doubled each day until the patient is returned to full conversational speech, usually by the end of the third or fourth postoperative week. If voice use causes pain, the patient is asked to decrease the amount of speaking and to contact the physician. The speech language pathologist stresses easy-onset phonation, avoidance of vocal abusive behaviors, and the need to use appropriate pitch and vocal intensity. Biofeedback retraining is used during this time.

The third phase of healing occurs during the second and third months after surgery. The behaviors learned from the speech language pathologist are continued, and vocal and singing reeducation is begun

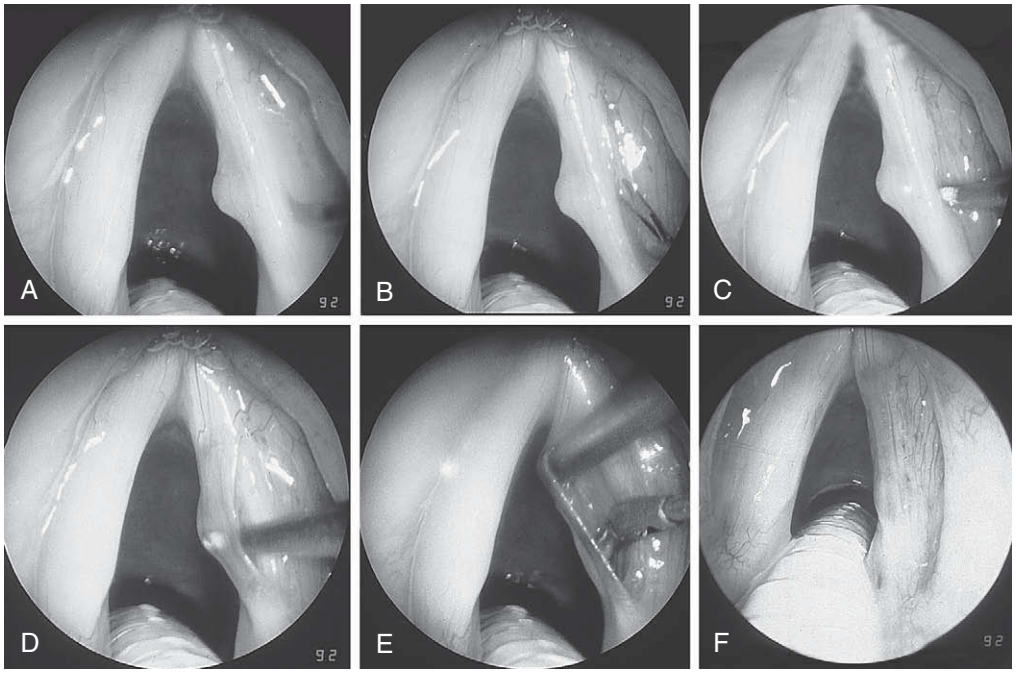

Figure 61-7. Intraoperative photographs of lesion excision through a lateral microflap approach. **A,** A sickle knife is used to make an incision on the superior surface of the vocal fold. **B,** The incision is further defined with upcutting scissors. **C,** A flap elevator is used to elevate the microflap. **D,** Dissection occurs between the vocal ligament and mucosa. **E,** The lesion is removed from the vocal ligament. **F,** The mucosal microflap is redraped into position. *(From Courey MS, Gardner GM, Stone RE, Ossoff RH. Endoscopic vocal fold microflap: a three year experience.* Ann Otol Rhinol Laryngol. *1995;104:267.)*

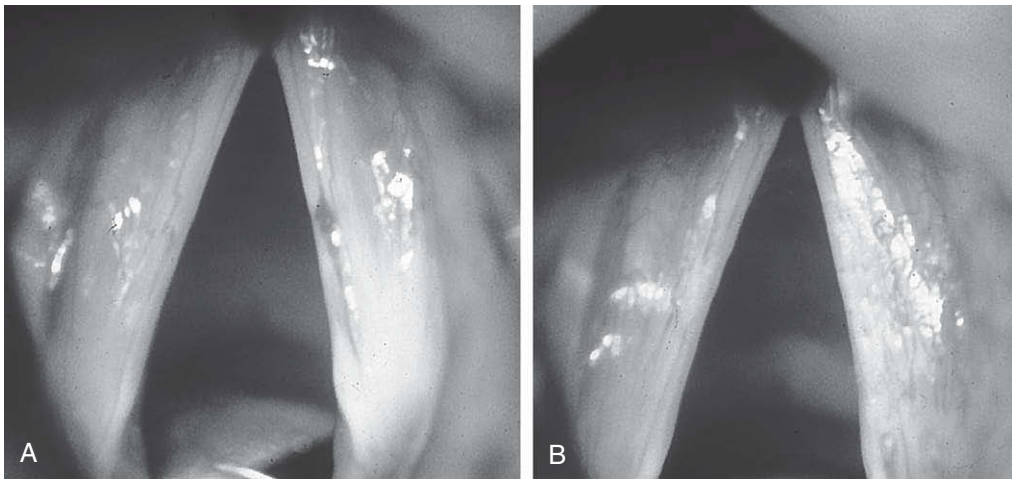

Figure 61-8. A professional singer with a microvascular lesion of the true vocal fold. **A,** Preoperative photograph. **B,** Postoperative appearance immediately after photocoagulation with the carbon dioxide laser at 1500 watts/cm^2. *(From Rubin JS, Sataloff RT, Korovin GS, eds.* Diagnosis and Treatment of Voice Disorders. *Clifton Park, NY: Thomson/Delmar Learning; 2003.)*

under the guidance of a vocal pedagogue. All singers work with a vocal pedagogue regardless of their style of singing or previous vocal training. The patient relearns how to sing from the basic level. Maladaptive behaviors are noted early and addressed by the pedagogue.

After 3 months, the average patient can return to professional activity, which constitutes the fourth phase of healing. Patients should be monitored with interval examinations for 24 months after surgery to assess for continued improvement or potential recurrence of the lesion.

Related Surgical Procedures

Professional voice patients undergo many nonlaryngeal surgical procedures involving the upper airway. They should understand that any procedure that potentially alters the anatomy or function of the supraglottal vocal tract (e.g., tonsillectomy, septoplasty, sinus surgery, palatal surgery) can alter the vocal resonance. Professional voice patients should be counseled about this possibility.

A well-performed tonsillectomy should not cause vocal professionals significant long-term difficulty. It does, at least transiently, affect the ability to modify that area of the resonator.[103] Tonsillectomy alters the frequency of the fourth formant in nonsingers but not in classically trained vocalists.[104] However, any significant palatal or faucial arch scarring could lead to laryngeal hyperfunction, which is caused by altered oropharyngeal sensation. The singer's vocal feel or sensory feedback is altered, resulting in a change in the singer's delivery.

Table 61-3

Phases of Postoperative Recovery after Laryngeal Microflap Surgery

Phase	Time	Activity
I	7-14 days	Voice rest
II	7-28 days	Graduated voice use with speech language pathologist
III	4-12 weeks	Vocal reeducation (singing with pedagogue)
IV	3-18 months	Professional activity

Laser-assisted uvulopalatoplasty has become a popular management for snoring. This procedure should result in at least a temporary voice change. Compensation should be possible for well-trained vocalists, much as for those undergoing tonsillectomy. If the surgery is performed, the stages should be spread out over many months to allow the artist to compensate for the palatal changes.

Adenoidectomy, septoplasty, sinus surgery, or turbinectomy in a singer with a significant nasal obstruction should be done very conservatively, if at all. The development of even a small degree of hypernasality could significantly alter the patient's singing voice.[105,106]

Hearing is often neglected in singers. Classical singers are taught to sing by feel and not by what they hear. However, many singers have difficulty in doing so. Baseline audiometric evaluations are recommended in all professional and serious amateur singers. Ear-level monitors with selective input have been of benefit to commercial singers. These monitors deliver stage sounds, mixed by the sound engineer, back to the performer at a comfortable intensity. They allow singers to protect their hearing, sing at the proper intensity level, and not succumb to the tendency of oversinging in the concert environment (the Lombard effect).

Conclusion

A singer's body is a vocal instrument, of which the larynx represents the most important portion. Education and behavior modification can enable singers to maximize their gifts. The maintenance of good vocal hygiene and regular reminders about abusive speaking and singing behaviors are part of this process. Even the most experienced singers may have to return to work with a vocal pedagogue after an upper respiratory infection or when they are busy recording or touring.

Professional vocalists are an interesting and challenging group of patients. Management should be undertaken by a coordinated team of professionals well versed in their care.

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CHAPTER SIXTY-TWO

Benign Vocal Fold Mucosal Disorders

Robert W. Bastian

Key Points

- The two most common risks for vocal fold mucosal vibratory injury are high intrinsic tendency to use the voice (talkativeness, extroversion) and a high extrinsic "opportunity or necessity" to use the voice (driven by occupation, family needs, social activities, and avocations).
- Visible vocal fold lesions from overuse may not cause an audible change in the *speaking* voice.
- Visible vocal fold lesions causing phonatory mismatch at the free margin or mucosal stiffness are "always" detectable *audibly*, in the singing voice, provided that the examiner knows how to elicit upper-range vocal tasks.
- Small or subtle vocal fold lesions may escape *visual* detection until the larynx is viewed with high magnification, sometimes requiring topical anesthesia, with vocalization in the upper range.
- With few exceptions, brief initial speech pathology evaluation and treatment are indicated when vocal fold injury is clearly due to overuse, misuse, or abuse of the voice. Speech therapy alone may suffice if vocal improvement is adequate to patient needs, otherwise it serves as preparation for vocal fold microsurgery.
- Key requirements for successful vocal fold microsurgery are (1) detailed knowledge of vocal fold microarchitecture and vibratory physiology to guide surgical precision, (2) proven technical ability of the surgeon, (3) preoperative and postoperative laryngeal videostroboscopy examination to diagnose clearly at patient presentation, and to assess results, with the patient as a participant, after surgery, and (4) access to voice-qualified behavioral (speech pathology) support.
- Singing voice symptoms of mucosal injury are loss of high soft singing, increased day-to-day variability of singing voice capabilities, phonatory onset delays, reduced vocal endurance, and a sense of increased effort.
- Capillary ectasia can be an incidental finding not requiring treatment. Surgical intervention may be indicated, on the other hand, when the ectasia causes one or more of the following: a tendency to decreased vocal endurance (reduced voice use time to huskiness), intermittent bruising, and a hemorrhagic polyp.
- Contact ulcer and granuloma are best thought of as an exuberant healing response to injury. Injury may be from aggressive chronic throat clearing, aggressive coughing, or endotracheal tube injury. Some believe that acid reflux is a major contributor. Treatment is generally supportive over many months during the wait for maturation, pedunculation, and spontaneous detachment; surgical removal is nearly always followed by recurrence.
- Marsupialization of saccular cysts is sometimes followed by recurrence. Therefore, when possible, complete removal of saccular cysts appears to be preferred.
- Recurrent respiratory papillomatosis is caused by the human papillomavirus.

Benign vocal fold mucosal disorders (e.g., vocal nodules, laryngeal polyps, mucosal hemorrhage, intracordal cysts, mucosal bridges, glottic sulci) seem to be caused primarily by *vibratory injury* (excessive amount and/or manner of voice use). Review of thousands of patients reveals that an expressive, talkative personality correlates best with most of these disorders. Occupational and lifestyle vocal demands appear to be additional but lesser risks, unless these demands are extreme. Occasionally, injury can occur as a "fluke" based on one episode of vocal strain in an otherwise moderate voice user. Cigarette smoking is a cofactor for smoker's polyps (Reinke's edema). Infection, allergy, and acid reflux may also potentiate vibratory injury.

Nonsingers with benign vocal fold mucosal disorders present because of change in the sound or capabilities of the *speaking* voice. By contrast, *singers* may have no issues with their speaking voices but may seek help because of *singing* voice limitations, usually in the upper range. Benign vocal fold mucosal disorders are significant because of the importance of spoken or sung communication and the voice's contribution to identity.

Benign vocal fold mucosal disorders are common. More than 50% of patients seeking medical attention because of voice change have a benign mucosal disorder. Even before the laryngeal videostroboscopy era, when subtle and small lesions may have been missed, Brodnitz[1] reported that 45% of 977 patients had a diagnosis of nodules, polyps, or polypoid thickening. From the same era (1964-1975), Kleinsasser[2] reported that slightly more than 50% of 2618 patients seen for a voice complaint had one of these benign entities.

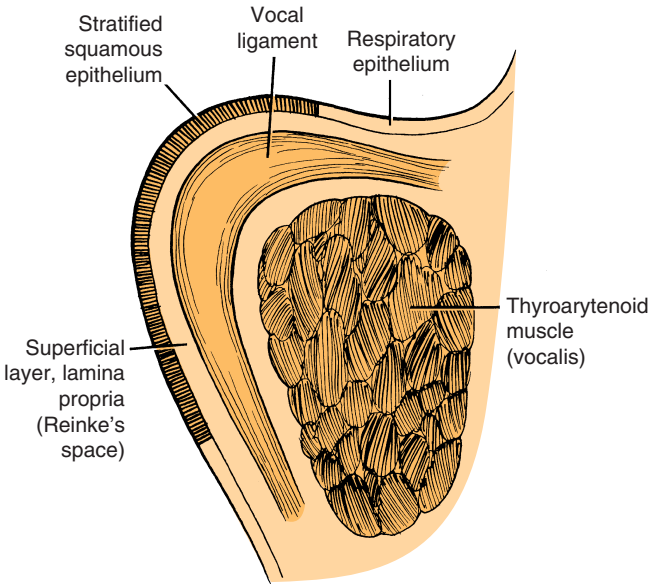

Figure 62-1. Cross section of the vocal fold.

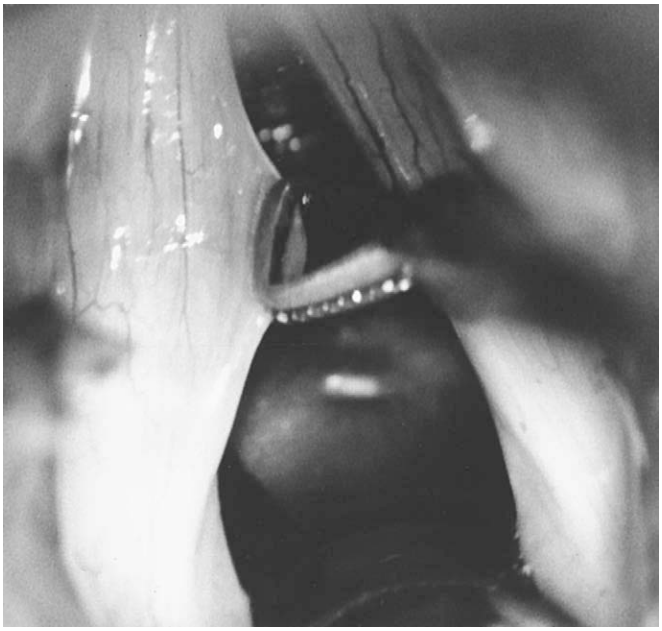

Figure 62-2. Gentle medial retraction shows the relative decoupling of the mucosa from the underlying, nondeformed vocal ligament.

Anatomy and Physiology

The anatomy most relevant to the benign vocal fold mucosal disorders is the microarchitecture of the vocal folds, as seen on whole-organ coronal sections in a study of cancer growth patterns[3,4] and in the work of Hirano.[5] Medially to laterally, the membranous vocal fold is made up of squamous epithelium, Reinke's potential space (superficial layer of the lamina propria), the vocal ligament (elastin and collagen fibers), and the thyroarytenoid muscle. Perichondrium and thyroid cartilage provide the lateral boundary of the vocal fold (Fig. 62-1).

The vocal folds move *as a whole* between abducted and adducted positions for breathing and phonation, respectively. The mucosa (epithelium and superficial layer of the lamina propria [Reinke's potential space]), which covers the vocal folds, is the chief oscillator during phonation (continuous adduction during expiratory flow of pulmonary air); thus, one might speak of vocal fold *mucosal* vibration rather than vocal *fold* vibration. In a canine study that supports this idea, Saito and associates[6] placed metal pellets at varying depths into the vocal fold (e.g., epithelially, subepithelially, intramuscularly) and used radiographic stroboscopy to trace their coronal plane trajectories during vibration. Pellet trajectories of the mucosa were far wider than those of the ligament or the muscle. Thus, primarily the vocal fold mucosa oscillates to produce sound.

'The work of Hirano[7] provides an explanation for these observations. Hirano described the vocal fold muscle as the body of the fold, the epithelium and superficial layer of the lamina propria (Reinke's potential space) as the cover, and the intermediate layers of collagenous and elastic tissue (vocal ligament) as the transitional zone (see Fig. 62-1). Because of the different physiologic stiffness characteristics of these layers, they are somewhat decoupled mechanically from each other during phonation. Decoupling is graphically illustrated in Figure 62-2 (mucosa being stretched). This decoupling allows the mucosa to oscillate with some freedom from the ligament and muscle. An analogy can be made to the relative freedom from the paddle experienced by the red rubber ball and elastic band in a child's paddleball toy. During phonation, pulmonary air power supplied to adducted vocal folds is transduced into acoustic power. To accomplish this, pulmonary air is passed between appropriately adducted vocal folds. At this point, the vocal fold mucosa vibrates passively according to the length, tension, and edge configuration determined by the intrinsic muscles and elastic recoil forces of the vocal fold tissues. Figure 62-3 shows the maximum open and closed phases of one vibratory cycle, as seen during laryngeal videostroboscopy. Further details concerning the mucosa's vibratory behavior can be found in the works of Baer[8] and Hirano[5] and in Chapter 57.

Other important microanatomy includes glands in the supraglottic, saccular, and infraglottic areas, which produce secretions that bathe the vocal folds during vibration.

Evaluation of the Patient: General Principles

The *necessary* and *sufficient* elements for diagnosis and management of benign mucosal disorders are (1) a skillful history, (2) a perceptual assessment of vocal capabilities and limitations, particularly through elicitation of vocal tasks designed to detect mucosal disturbances, and (3) a high-quality laryngeal examination (often including laryngeal videostroboscopy). In addition, certain measures of phonatory function (aerodynamic, acoustic), although not crucial for diagnosis, may be of interest for study, documentation of the disorder's physiologic effects, and assessment of improvement after treatment.

History

Besides the usual items in the general medical history, the voice history should focus in particular on the following list of items, which may be best captured via use of a questionnaire[9,10]:

1. Onset and duration of vocal symptoms.
2. Patient beliefs about causes or exacerbating influences.
3. Common symptom complexes.
4. Talkativeness profile (intrinsic, personality-based tendency to use voice).
5. Vocal commitments or activities (extrinsic requirement, invitation, or opportunity to use voice), including voice type and training, if patient is a performer.
6. Other risk factors.
7. Patient perception of the severity of the disorder.
8. Vocal aspirations and consequent motivation for rehabilitation.

Onset

It is appropriate during history-taking to test the hypothesis that a patient who complains of frequently recurring bouts of vocal dysfunc-

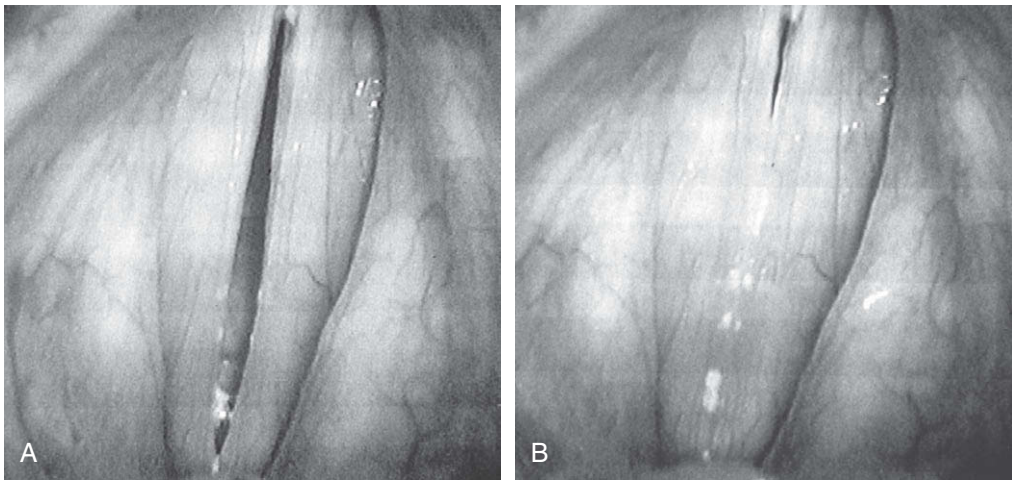

Figure 62-3. The maximum open **(A)** and closed **(B)** phases of an apparent single vibratory cycle as seen during videostroboscopy. The moving part is primarily mucosa, with little participation of ligament or muscle.

tion may be experiencing exacerbations of a more chronic overuse disorder. Such a patient, who is often found to be living "at the edge" vocally on the basis of an assessment of vocal personality, lifestyle, vocal commitments, and voice production, may present because a small increase of vocal activity or an upper respiratory infection has thrown him or her "*over* the edge." In this situation, without appropriate care, both the patient and the clinician may tend to focus on the recent or current upper respiratory infection (e.g., providing supportive treatments or antibiotics) rather than seeing past this acute issue to recognize the need for the more sophisticated behavioral therapy appropriate for a chronic "vocal overdoer."

Patient Beliefs about Causes

Clinicians may prudently maintain flexibility in their own minds regarding patient beliefs. Example: A patient may insist that the voice disorder results from allergies or acid reflux. After thorough consideration, the clinician may instead find that the patient's "vocal overdoer" status (see later) is primary, and that allergy and acid reflux in that patient actually happen to be inconsequential by comparison—if present at all! Of course, in this instance, considerable time for teaching, meeting objections, and so on, at the conclusion of the consultation is required.

Common Symptom Complexes

As for many other types of voice disorders, a characteristic symptom complex accompanies benign mucosal disorders. Nonsingers, who often have moderate to large mucosal disturbances before they seek medical attention, usually describe chronic hoarseness with exacerbations at times of increased voice use. Singers may *not* note speaking voice symptoms but rather describe (1) exaggeration of day-to-day variability of singing capabilities, (2) increased effort necessary for singing, (3) reduced vocal endurance, (4) deterioration of high soft singing, and (5) delayed phonatory onset and air wastage (breathiness).

Talkativeness Profile (The "Vocal Overdoer" Syndrome)

The factor that correlates most strongly with the formation and maintenance of many benign vocal fold mucosal disorders appears to be personality. A simple but powerful way to assess this issue is to ask the patient to rate himself or herself on a 7-point talkativeness scale, in which 1 is very untalkative, 4 is averagely talkative, and 7 is unusually talkative. (In asking this question, one must stress that this scale deals with innate predisposition, not the demands of work or lifestyle.) Virtually all patients with nodules and polyps, and even cysts and sulci, rate themselves at 6 or 7, except for persons who work in vocally extreme occupations (e.g., financial trading).

Vocal Commitments

To assess vocal commitments and activities, the clinician or questionnaire should inquire briefly about occupation, voice type and level of training, and the nature and extent of vocal activities related to family life, child-care, politics, religion, hobbies, athletics, and musical rehearsal and performance.

Other Risk Factors

Other risk factors are tobacco and alcohol use, acid reflux, insufficient fluid intake, certain drying medications, systemic illnesses, and allergies. Even when the history is positive for one of these factors, it is usually a secondary issue in comparison with "7-ness."

Patient Perception of Severity and Vocal Aspirations and Consequent Motivation for Rehabilitation

Exploration of the patient's perception of the severity of the voice problem, vocal aspirations, and motivation also is important. For example, the clinician may be confronted by a patient who only wants to be reassured that the problem is not cancer. Even with a diagnosis of large smoker's polyps with severe range virilization and dysphonia, management for such a patient might appropriately be short-term and supportive, consisting primarily of counseling about smoking cessation education. Another patient may have a normal speaking voice but have upper singing voice limitations caused by small nodules. In this patient, therapy might be intense and eventually include surgery for the patient with a normal speaking voice who, to pursue a competitive singing career, must be relieved of extreme upper singing voice limitations due to small nodules.

Vocal Capability Battery

The vocal capability battery is an auditory-perceptual assessment of vocal capabilities and limitations. It assesses, macrophenomenologically, the two crucial questions "What can't this voice do that it should be able to?" and "What does this voice do that it shouldn't?" This process involves *elicitation* of a variety of vocal tasks, followed by auditory-perceptual assessment of the voice production that results. The vocal capability battery is an often-neglected part of the diagnostic process that provides the best means of understanding the nature and severity of the voice disorder. To be most efficient, this part of the diagnostic process is performed by the same clinician who takes the history and performs the laryngeal examination. Alternatively, a second clinician can perform this assessment, but for best results, the findings of vocal capability elicitation are immediately correlated with the other two components of the diagnostic process.

Vocal capability elicitation and interpretation require that the examiner have good pitch-matching abilities, a reasonably normal

voice, extensive familiarity with his or her own vocal capabilities (and limitations, if any), intimate familiarity with normal singing voice capabilities according to age, sex, and voice classification, and the willingness to model and elicit with his or her own voice. Also needed is a frequency reference, such as a small electronic keyboard.

In voice clinics where expert vocal capability elicitation and assessment are not available or are not immediately correlated with history and laryngeal examination, clinicians may overlook or reject the power and centrality of this part of the evaluation. They may instead rely on various items of equipment that measure components of vocal output (e.g., acoustic, aerodynamic). Although useful for quantification, documentation, and some biofeedback applications, this equipment is cumbersome and expensive, and the data it collects are time-consuming to interpret and, most importantly, diagnostically weak in comparison with those of the vocal capability battery, which can answer far more quickly, powerfully, and synthetically the question "What's wrong with this voice?"

The basic vocal capabilities and phenomena to be tested are (1) average or anchor speech frequency, (2) maximum frequency range, (3) projected voice and yell, (4) very-high-frequency, very-low-intensity tasks that detect mucosal disturbances,[11] (5) register use and phenomena, (6) maximum phonation time, and (7) instability and tremors.

The ability to perform high-frequency, low-intensity tasks is the single most important part of the vocal capability battery in persons with benign mucosal disturbances. Upon elicitation of these sorts of tasks, mucosal disorders are suggested by a loss of expected range under these performance constraints, as well as onset delays, air escape, and lack of tonal clarity. The clinician should also search for inconsistencies between spoken and sung capabilities and should informally note the patient's sincerity of effort and skill. Basic vocal capability testing requires only a few minutes to perform because the examiner focuses primarily on the extremes of physical capability and secondarily on vocal skill.

As stated, the vocal capability battery—coupled with the initial voice history and then subsequent laryngeal examination—is crucial in diagnosing a voice disorder and in directing subsequent management. For example, signs of a mucosal disturbance (e.g., detection of air escape, onset delays, loss of clarity and range) during assessment of the ability to perform high-frequency, low-intensity tasks minimize the possibility that a singer's normal-sounding speaking voice during history-taking will subconsciously bias the clinician to selectively perceive normal vocal folds when, in fact, small vocal nodules are present.[11a] The vocal capability battery also provides insight into the severity of the patient's vocal limitations, which can then be correlated with the visual examination to help determine, along with the patient's needs and motivation, the intensity and direction of management.

Office Examination of the Larynx

The laryngeal mirror should provide three-dimensional viewing and good color resolution but, in practice, offers poor visualization in many cases. In other cases, visualization is good, but only during phonation, because the view is obstructed by the epiglottis during respiration. In addition, no permanent image of the larynx results from this examination technique. Because the physician must therefore remember the lesion or document it with a simple sketch, precise critique of the effectiveness of the therapy chosen may not be possible. Rigid and also flexible laryngeal scopes often allow a clearer view, particularly during respiration. When used with the naked eye, however, they have similar disadvantages to those of the mirror. The fiberoptic nasolaryngoscope or a newer "chip-tip" video-endoscope is especially important in a patient who is difficult to examine because of unusual anatomy or an exceptional gag reflex. Even with these technologies, however, it is possible to overlook subtle-to-small mucosal changes unless the larynx is topically anesthetized to allow a close approach of the tip of the fiberscope to the vocal folds. With topical anesthesia, the vocal folds, subglottis, and trachea can be examined easily (Fig. 62-4).[12,13]

Strobe illumination added to any of these examining instruments allows mucosal vibratory dynamics to be evaluated in apparent slow motion (e.g., to understand mucosal scarring, to distinguish cysts from nodules). Adding a video camera and recording device (computer hard drive or tape) to the rigid or flexible scopes brings additional advantages; for example, a patient's understanding and motivation are facilitated if he or she views the video documented examination. Also, such recordings enable other clinicians (otolaryngologists, speech pathologists, voice teachers) to participate more easily in assessment and management, serve as permanent records that document the result of voice therapy or surgery, and enhance teaching of residents.

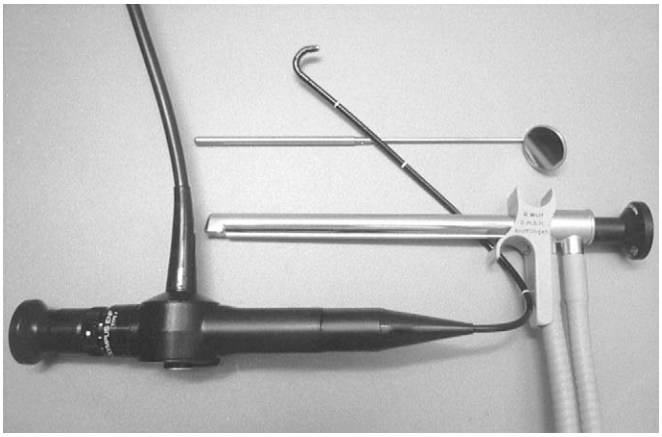

Figure 62-4. Three of the most commonly used tools for viewing the larynx: a mirror, a 90-degree telescope, and a flexible fiberoptic nasolaryngoscope. A later addition, the distal chip endoscope, which looks nearly identical but has an internal video chip rather than optics, is supplanting the fiberoptic scope.

Objective Measures of Vocal Output

Skillful "triangulation" on the voice problem through the use of the voice history, auditory-perceptual evaluation of vocal capabilities and limitations, and high-quality laryngeal examination is sufficient for a clear diagnosis and description of the problem. Although weak diagnostically due to nonspecificity, aerodynamic and acoustic information may be useful to quantify and document severity and change in response to treatment, to deepen understanding in the research arena, and to assist in some helpful biofeedback applications.

Direct Laryngoscopy and Biopsy

When videostroboscopy with magnified viewing is available, lesions that are suspicious for cancer or papillomatosis can nearly always be distinguished easily from nodules, polyps, and cysts. Therefore, removal of these latter entities is appropriate only within a comprehensive plan for treatment or voice restoration and rarely, if ever, for preliminary tissue diagnosis.

General Management Options

Hydration

Adequate hydration promotes free flow of lubricating secretions, which help the vocal fold mucosa withstand the rigors of vibratory collisions and shearing forces. Consistent supply of fluids seems to be particularly important. An expectorant, such as guaifenesin, may also help when secretions are viscid.

Sinonasal Management

Patients often incorrectly attribute chronic hoarseness to sinonasal conditions. Existing sinonasal problems should be managed on their own merits; however, the clinician may need to help diminish the patient's perception of the contribution of these problems to a voice disorder in favor of more likely behavioral causes. When optimal laryngeal function is of concern, as in a vocal performer, nasal conditions should be managed locally (topically) when possible. The reason is that many systemic drugs (e.g., oral decongestants, antihistamine-decongestant combinations) dry not only nasal secretions but also secretions in the larynx, where a continuous secretional flow is important for proper vibratory function and mucosal endurance, particularly under demand-

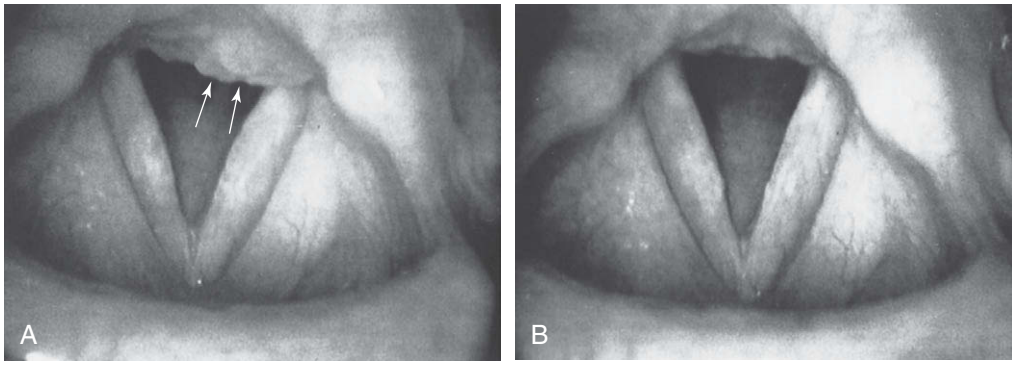

Figure 62-5. Chronic laryngitis in a patient with severe acid reflux, a history of smoking, and excessive voice use. **A,** Note the interarytenoid pachyderma (*arrows*) and loss of normal color differential between the true folds and supraglottic mucosa. Broad-based convexity of the true vocal fold margins suggests diffuse submucosal edema. **B,** Appearance 3 weeks after institution of antireflux measures. Note the resolution of the interarytenoid pachyderma.

ing phonatory conditions. Medications that affect voice minimally are the topical nasal decongestants, which should be used for only a few days before the nasal mucosa is allowed to rest, so as to avoid *rhinitis medicamentosa*. Profuse rhinorrhea that accompanies the common cold can also be managed with ipratropium bromide inhalations.[14,15] Corticosteroid inhalers are invaluable for the management of nasal allergies. Activating pump-action nasal inhalers without any inspiratory airflow avoids the alleged risk of the effects of nasally applied corticosteroid on the vocal folds.

Management of Acid Reflux Laryngopharyngitis

In a person with an incompetent lower esophageal sphincter or hiatal hernia, acid reflux into the pharynx and larynx during sleep can lead to chronic laryngopharyngitis. Such persons may or may not experience one or more of the following symptoms: exaggerated "morning mouth," excessive phlegm, scratchy or dry throat irritation that is usually worse in the morning, habitual throat clearing, and huskiness or lowered pitch of the voice in the morning. The larynx may show characteristic erythema of the arytenoid mucosa, interarytenoid pachyderma, or contact ulcers; laryngeal findings may, however, be subtle (Fig. 62-5).

Basic management of this condition consists of avoiding caffeine, alcohol, and spicy foods; eating the last meal of the day (preferably a light one) no fewer than 3 hours before retiring; using bed blocks to place the bed on a mild head-to-foot slant; and taking an antacid at bedtime, an H_2 blocker 2 or 3 hours before bed, or a proton pump inhibitor 30 to 60 minutes before dinner.

Acute Mucosal Swelling of Overuse

Public speakers or singers may sometimes perform of necessity despite acute, noninfectious mucosal swelling resulting from recent overuse of the voice. A careful strategy of *relative* vocal rest in context is needed, and pre-performance warm-up, along with solid vocal technique, may be sufficient for the patient to "get through." A short-term, high-dose, tapering regimen of corticosteroids can also be useful in this context, as part of a larger strategy to help the patient through the performance.

Laryngeal Instillations for Mucosal Inflammation

In past years more so than currently, laryngologists have used drugs such as mono-*p*-chlorophenol, topical anesthetics, mild vasoconstrictors, sulfur vapors, certain oils, and other substances for reduction of swelling, soothing effect, or promotion of healing. Some physicians and patients believe in the efficacy of such management, though it is supported only by anecdotal reports.

Systemic Medicines that May Affect the Larynx

Medicines that patients take for other reasons (e.g., antidepressants, decongestants, antihypertensives, diuretics) may dry and thicken normal secretions, thereby reducing their protective lubricating effect on the vocal folds and conceivably making the vocal fold mucosa more vulnerable to the development of benign disorders. History-taking should include inquiry about these medicines.

Voice Therapy

A course of therapy by a voice-qualified speech pathologist is frequently appropriate in patients with benign vocal fold mucosal disorders, given the common relationship of such disorders with vocal overuse, abuse, or misuse. Vocal nodules in particular are expected to resolve, regress, or at least stabilize under a regimen of improved voice hygiene and optimized voice production. In some cases, however, success is defined as having achieved a more consistent voice, without the exacerbations of hoarseness and even aphonia, even if that now-more-reliable voice remains somewhat husky. In other cases, success may require resolution of all upper voice limitations. If surgery becomes an option because the mucosal disorder has not resolved completely and the patient regards residual symptoms and vocal limitations as unacceptable, voice therapy will have optimized the patient's surgical candidacy, by educating him or her additionally about the surgical process, and decreased the risk of postoperative recurrence.

During evaluation, the speech pathologist gathers information on behavior that may adversely affect the voice and establishes a program to eliminate injurious behavior. Voice-qualified speech pathologists also model and elicit a battery of spoken and sung vocal tasks to make plain to themselves and patient the type and degree of impairment from the lesion. They also assess the skill and appropriateness of voice production for both speaking and singing. Depending on the results of this second part of the evaluation, the speech pathologist may help the patient optimize the intensity, average pitch, registration, resonance characteristics, overall quality, general and vocal tract posture, and respiratory support for voice production. For singers, the singing teacher plays an invaluable role in this process, particularly with respect to singing voice production.

Finally, in this technologic era, voice clinicians increasingly document various aspects of vocal tract output, using acoustic analysis, spirometric measures to test respiratory adequacy, frequency and loudness measures, translaryngeal airflow rates, and other measures under various conditions. Speech pathologists may use this equipment for biofeedback (e.g., using a visual electronic frequency readout to modify average pitch for speech in a tone-deaf patient). For obligate false vocal fold phonation and intractable psychogenic disorders of voice production with visible vocal fold posture abnormalities, therapy room videoendoscopy can also be converted into an effective biofeedback tool (Fig. 62-6).[11,16]

Surgery

Some lesions are known at diagnosis to be irreversible other than via surgery. Aside from these exceptions, vocal fold microsurgery should follow an appropriate trial of voice therapy. Patients are typically reexamined (vocal capability battery and videostroboscopy) at 16-week intervals after diagnosis. When a compliant patient does not improve

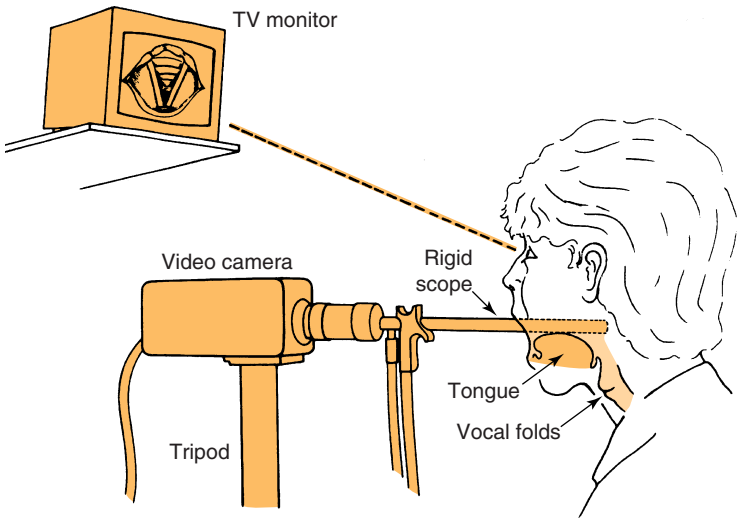

Figure 62-6. A patient learning to modify laryngeal posture by use of laryngeal image biofeedback. With a telescope rather than a fiberscope, pure vocal fold behavior is retrained initially (without speech gestures). Clearer optics and less mobility of the epiglottis permit a clearer and more stable view.

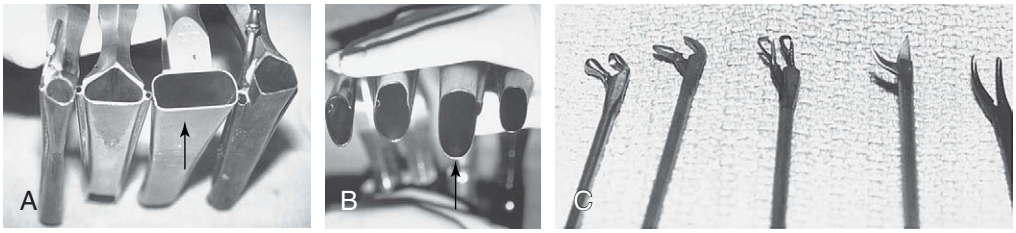

Figure 62-7. **A,** The viewing ends (*left to right*) of the Holinger hourglass, Jako-Cherry, Bouchayer, and Dedo laryngoscopes. **B,** The distal ends of these laryngoscopes (*same order*). The Bouchayer scope (*arrow*) is most useful for microsurgery. **C,** *From left*, The up-cup forceps, smaller biting forceps, Bouchayer microring forceps, curved scissors, and curved alligator forceps.

after two or more successive examinations and remains unhappy with the voice's capabilities, surgery may be considered. Good surgical results are directly related to diagnostic accuracy, surgical judgment and precision, and the patient's compliance with proper voice care.

Although specific techniques vary for each disorder, the basic requirements for successful laryngeal microsurgery for all benign vocal fold mucosal disorders are the same. An understanding of vocal fold microarchitecture and vibratory dynamics (see earlier discussion) is a prerequisite, and preoperative and postoperative videostroboscopic evaluation is necessary so that the patient and surgeon can see the results together.

The first principle of surgery is that microlaryngoscopy (not direct laryngoscopy with the unaided eye) and extreme technical precision are required to minimally disturb mucosa. Because the disorder is benign and confined to the mucosa, including Reinke's potential space, the cancer concept of surgical margins does not apply. Every case should be approached with the awareness that overly aggressive or imprecise surgery of the vocal fold mucosa can have disastrous results caused by scarring of regenerated or surgically manipulated mucosa to the underlying vocal ligament.

A set of laryngoscopes, microlaryngeal forceps, scissors, dissectors, and knives should be on hand. In the face of the plethora of instruments currently available, the comment by Kleinsasser[2] that a relatively simple set suffices the experienced surgeon remains true (Fig. 62-7)!

The carbon dioxide laser has become an important part of the surgeon's armamentarium, and many have discussed its application to benign laryngeal disorders. Tissue effects of the laser depend on spot size and focus, wattage, duration of beam activation, waveform mode (pulsed vs. continuous), and, perhaps most important, surgical precision. Cold microdissection may be safer than laser techniques, provided that the surgeon is equally proficient in both. Norris and Mullarky,[17] comparing continuous-mode carbon dioxide laser with the cold scalpel for incising pig skin, reported that a short-term advantage resulted after laser incision with regard to the speed of reepithelialization; no long-term difference in healing was noted. However, although the fact was not noted in their report, these investigators' histologic sections clearly showed a wider zone of tissue destruction beneath the epithelium with laser than with scalpel. Duncavage and Toohill[18] compared healing response in dogs after traditional fold stripping and after carbon dioxide mucosal vaporization. They concluded that, until late in healing, more edema and giant-cell reactions to bits of charred debris, and greater subepithelial fibrosis occurred with the laser technique than with the cup forceps alone. Manipulation of wattage, focus, and mode of laser irradiation of tissues may decrease thermal injury, charring, and other adverse effects of the laser.

The preceding studies date from the early era of the carbon dioxide laser. The microspot carbon dioxide laser appears to diminish these disadvantages,[19,20] although a systematic comparison of functional results (including vocal capabilities and videostroboscopy) is not available to guide the surgeon in choosing between laser and microdissection methods. With a caseload approaching 1000 singers and double or triple that number of non-singers—for whom laser and non-laser methods have been used on an individualized basis—I believe that surgical technique and skill are preeminent over the specific tools used.

After surgery, vocal *quality* and *capabilities* should show good to excellent improvement; however, patients should be counseled preoperatively what the risk of worsening the voice is predicted to be: For *nodules* it may be appropriate to say, "This surgery typically restores the voice to 'original equipment status,' but there is a *small risk* that you will experience a large improvement but not to fully normal; and there is a *remote, rare risk* that your voice will be worse after surgery." By contrast, one may say to the person with bilateral sulci in whom mucosa

is thin, "I am expecting a modest improvement of your voice, but it will take many months to experience this improvement, and there is a quite significant chance your voice will be no better, and even possibly worse." For the experienced surgeon who uses dissection, rather than microavulsion techniques, along with preoperative and postoperative videostroboscopy as his or her "teacher," the question in the general case becomes not so much one of possibly making the voice worse, but rather, "Can I make this patient's speaking and singing capabilities normal, and if not, how close can I come?" Cornut and Bouchayer's[21] experience operating on 101 singers and Bastian's[22] experience in the same population established a role for laryngeal microsurgery in restoring vocal capabilities and in abolishing or diminishing limitations.

Specific Benign Vocal Fold Mucosal Disorders

Vocal Nodules

The term nodules should be reserved for lesions of proven chronicity. Recent or acute mucosal swellings, which disappear quickly in response to simple voice rest and perhaps supportive medical management, are thus excluded when one is referring to *nodules*.

Epidemiology

Vocal nodules occur most commonly in boys and women. Such persons are almost always vocal overdoers (i.e., rating 6 or 7 on the 7-point talkativeness scale). Intrinsic talkativeness correlates more consistently than occupation, unless the occupation is extraordinarily demanding vocally (e.g., rock singer, stock trader). Comparatively, nodules develop frequently in children with cleft palates, presumably from their use of glottal stops to compensate for velopharyngeal incompetence.

Pathophysiology and Pathology

Only the anterior two thirds (membranous portion) of the vocal folds participates in vibration because the arytenoid cartilages lie within the posterior third of the glottic aperture. Vibration that is too forceful or prolonged causes localized vascular congestion with edema at the midportion of the membranous (vibratory) portion of the vocal folds, where shearing and collisional forces are greatest. Fluid accumulation in the submucosa from acute abuse or overuse results in submucosal swelling (sometimes unwisely called incipient or early nodules). Long-term voice abuse leads to some hyalinization of Reinke's potential space and, in a subset of cases, some thickening of the overlying epithelium. This pathophysiologic sequence explains the easily reversible nature of most acute nonhemorrhagic swellings, in contrast to the slower, incomplete, or failed resolution of chronic vocal nodules. Whether acute edema or more chronic nodules, the change in mucosal mass, lessened ability to thin the free margin, and incomplete glottic closure caused by the nodules account for a constellation of vocal symptoms and limitations that is characteristic of mucosal swelling.[11,22]

Diagnosis

History

A pediatric patient with vocal nodules is usually described by the parent as vocally exuberant. An adult patient, virtually always a woman who rates herself as a 6 or 7 on the talkativeness scale (discussed earlier), describes experiencing chronic hoarseness or repeated episodes of acute hoarseness. Sometimes the initial onset is associated with an upper respiratory infection or acute laryngitis, after which the hoarseness never clears completely, leading the patient to incorrectly attribute the voice problem to the infection and to neglect more relevant ongoing behavioral causes. Singers with chronic nodules are usually relatively unaware of speaking voice limitations unless the nodules are at least moderate in size. More sensitive symptoms of vocal nodules, including very small ones, are as follows:

- Loss of the ability to sing high notes softly
- Delayed phonatory onset, particularly with high, soft singing
- Increased breathiness (air escape), roughness, and harshness
- Reduced vocal endurance ("I get husky more easily than others.")
- A sensation of increased effort for singing
- A need for longer warm-ups
- Day-to-day variability of vocal capabilities that is greater than expected for the singer's level of vocal training

Vocal Capability Battery

In patients with moderate to large vocal nodules, the speaking voice is usually lower than expected, husky, breathy, or harsh. Patients with subtle to moderate swellings often have speaking voices that sound normal; the speaking voice is an insensitive indicator of mucosal disorders in comparison with the singing voice. In patients with subtle or small swellings (usually only singers present with small mucosal disturbances), vocal limitations (e.g., delayed phonatory onset with preceding momentary air escape, diplophonia, inability to sing softly at high frequencies) may become evident only when high-frequency, low-intensity vocal tasks for detecting swelling are elicited.[11a] At high frequency, short-segment vibration may occur; in other words, the nodules stop vibrating and the short segments of mucosa anterior or posterior to them, or both, vibrate.

Many patients with nodules may have undergone indirect laryngoscopy and have been told that their vocal folds were normal or have been given a nonspecific diagnosis such as "laryngeal irritation." Use of vocal tasks that detect swellings and videostroboscopy, when indicated (see Figs. 62-3 and 62-4), protect the laryngologist from missing the most subtle vocal fold swellings. The ability to diagnose tiny nodules is crucial, because failure to make such a diagnosis can have serious consequences for the professional voice user.

Laryngeal Examination

Nodules can vary in size, contour, symmetry, and color, depending on how long they have been present, the amount of recent voice use, and interindividual differences in mucosal response to voice abuse. Also, some variability exists in the correlation between size of nodules and their effect on vocal capabilities. Nodules do not occur unilaterally, although one may be larger than the other. It is important to distinguish between nodules and cysts, because management of these conditions differs. The correlation between nodule appearance and reversibility with voice therapy is imperfect. The larynx should be examined at high frequency (500-1000 Hz) to visualize subtle to small swellings, which can be poorly appreciated at lower frequencies.

Management

Medical

Good laryngeal lubrication should be ensured through general hydration. Allergy and reflux, when present, should be treated.

Behavioral

Vocal nodules arise from the vocal overdoer profile, so speech (voice) therapy plays a primary role initially. Typically, the nodules and their more obvious symptoms regress, particularly if the patient is not a singer. However, the most skilled behavioral (voice) therapy sometimes fails to achieve complete visual resolution of nodules that have been present for many months to years. Sensitive singing tasks that detect impairment (not the size of persistent swellings) are generally more helpful in the decision whether to consider their surgical removal.[11,22]

Surgical

Surgical removal becomes an option when nodules of whatever size persist and the voice remains unacceptably impaired (from the patient's perspective) after an adequate trial of therapy (generally a *minimum* of 3 months). Some writers prefer precise removal using microdissection techniques (Fig. 62-8). Vocal fold stripping has no place in the surgery of nodules. The proper duration of voice rest is controversial; some

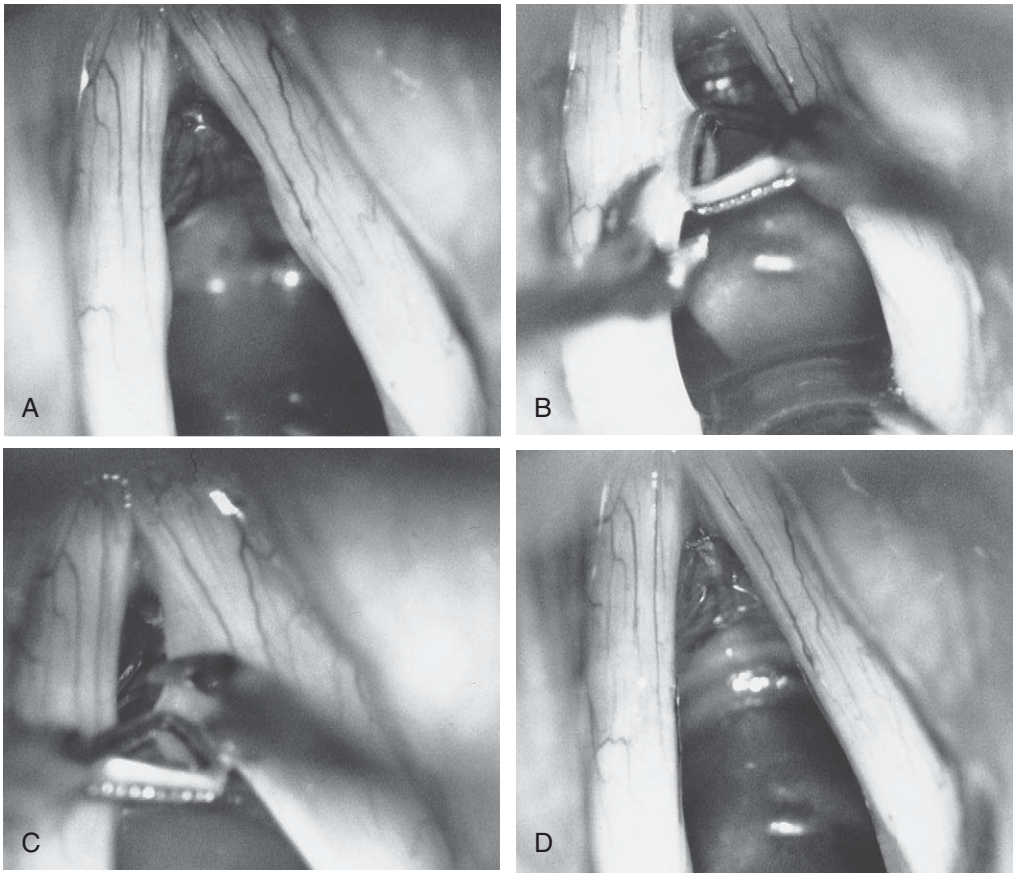

Figure 62-8. The operative sequence in a professional musical theater actress who had been experiencing vocal symptoms and limitations compatible with fusiform vocal nodules for more than 2 years. **A,** The operative view after many months of conservative management. Not all fusiform swellings are reversible with conservative measures alone. **B** and **C,** A polypoid nodule is grasped superficially and tented medially with Bouchayer forceps. Scissors, which curve away from the vocal fold, are used for removal. The nodule is thus removed in a very superficial plane, thereby minimizing the risk of engendering scar between the remaining and regenerated mucosa and the underlying vocal ligament. **D,** The vocal fold appearance after excision. The patient experienced dramatic normalization of vocal capabilities, and there was no evidence of scarring on postoperative stroboscopic examination. The dilated capillaries may predispose to recurrent nodule formation and can be spot-coagulated with a micro-spot laser.

writers prefer a relatively short period. Typically, the patient is asked not to speak for 4 days, although sighing sounds begin 1 day after surgery. Beginning on the fourth day, the patient gradually progresses over 4 weeks to full voice use under a speech pathologist's supervision. Early return to nonstressful voice use, as described in Table 62-1, seems to promote dynamic healing. The results of precision surgery are typically remarkably good, even in singers. Cornut and Bouchayer[21] stated, in their study of approximately 160 singers treated with surgery, "As long as certain management principles are followed in a majority of cases, laryngeal microsurgery enables the singing voice to regain the whole of its functioning."

Capillary Ectasia

Epidemiology

Capillary ectasia seems to happen most often with vocal overdoers (Figs. 62-9 to 62-11). Because of the female preponderance of this disorder, some writers have speculated about an estrogen effect.

Pathophysiology and Pathology

Repeated vibratory microtrauma can lead to capillary angiogenesis. In a circular fashion, abnormally dilated capillaries seem to increase the mucosa's vulnerability to further vibratory trauma. In particular, mucosal swelling, when present with capillary ectasia, appears to be larger on the side with greater ectasia. It seems that capillary ectasia predisposes to one or more of the following: increased vulnerability to mucosal swelling (reduced vocal endurance), a small incidence of vocal fold hemorrhage, and hemorrhagic polyp formation.

Diagnosis

History

Capillary ectasia is diagnosed most often in female singers who complain that they become a little hoarse after relatively short periods of singing (reduced vocal/mucosal endurance). When this complaint is associated with mucosal swelling, additional symptoms reminiscent of nodules (e.g., delayed phonatory onset, loss of high soft singing, increased effort) may also be noted. The occasional singer with capillary ectasia may have experienced one or more episodes of acute vocal fold hemorrhage, which may precipitate the patient's first visit; capillary ectasia may be discerned only after the bruising has resolved.

Vocal Capability Battery

Without mucosal swelling, the voice's capabilities in a patient with capillary ectasia may be entirely normal. With swelling, vocal limitations may be similar to those detected in the patient with nodules. If mucosal hemorrhage is recent, the speaking voice and singing voice may be very hoarse.

Laryngeal Examination

Capillary ectasia may manifest as abnormal dilation of the long arcades of capillaries that proceeds mostly from anterior to posterior (see Figs.

62-9 to 62-11). However, aberrant clusters of dilated capillaries also may be seen. Occasionally, a vascular dot may appear when a loop comes from within Reinke's space to the surface and doubles back down into the submucosa. Finally, some dilated capillaries are confluent or become so large as to almost resemble a chronic hemorrhage; this variant can be termed a *capillary lake*.

Table 62-1

General Guidelines for Initial Voice Use after Vocal Fold Microsurgery

Time After Surgery*	Talking†	Singing (for Singers)
Days 1 to 4	None	Gentle attempts at yawn or sigh for approximately 30 sec, 6-8 times per day‡
Week 2 (begins day 5)	3	Same exercise 5 min twice per day (after first postoperative exam)
Week 3	4	Same exercise 10 min twice per day§
Week 4	5	Same exercise 15 min twice per day§ (after second postoperative exam)
Week 5	4 or 5	Same exercise 20 min twice per day§
Weeks 6-8	4 or 5	Same exercise, up to 20 min three times per day¶

*After fourth examination, return to performance should be considered.
†Based on a 7-point talkativeness scale, in which 1 = very untalkative, 4 = average, and 7 = extremely talkative.
‡Accept what comes out, even if it is only air or is very hoarse.
§With emphasis on ease, clarity, and agility, not voice building. The entire expected range should be practiced in each session, with gentle insistence on high notes that do not want to sound. In general, practice mostly a mezzo piano dynamic and only occasionally a mezzo forte.
¶Same as preceding footnote, with the addition of gradually increasing the dynamic range and insistence.

Management

Medical

Use of drugs that have anticoagulant effects (aspirin, nonsteroidal anti-inflammatory drugs) should cease if medically appropriate. These drugs do not appear to increase the *incidence* of hemorrhage but may increase the *severity* of bruising when it does occur. In addition, acid reflux may have an amplified effect on the mucosa when capillary ectasia is visible; thus, management of reflux is particularly important.

Behavioral

Many persons with capillary ectasia are vocal overdoers; therefore, the behavioral changes appropriate for persons with nodules are advocated. In particular, patients are warned about sudden, explosive use of voice. The duration of voice use per practice session should also be reduced (e.g., three 20-minute sessions per day vs. one 1-hour session).

Surgical

If the patient cannot accept residual vocal symptoms and limitations (e.g., decreased vocal endurance) after medical and behavioral management, laryngeal microsurgery is an excellent option.[22,23] Dilated capillaries are spot-coagulated to interrupt blood flow every few millimeters (see Fig. 62-9C). Capillaries proximal to each interrupted segment may subsequently dilate. Even so, not all visible dilations should be ablated; those that remain visible at the end of the procedure and even at the first postoperative visit routinely involute within a few weeks. If mucosal edema is minimal, management of the capillaries alone often leads to edema resolution.

Vocal Fold Hemorrhage and a Unilateral (Hemorrhagic) Vocal Fold Polyp

Epidemiology

The occurrence of vocal fold hemorrhage (see Fig. 62-10) and a unilateral hemorrhagic vocal fold polyp is more common in men, particularly those who engage in intermittent severe voice abuse or who work in noisy environments. Some patients have a history of aspirin or other anticoagulant use.

Pathophysiology and Pathology

Shearing forces acting on capillaries within the mucosa during extreme vocal exertion lead to capillary rupture. Capillary ectasia seems to predispose to this sort of injury. Breakage of *superficial* capillaries may lead to a thin, widely suffused, superficial bruise without vocal fold margin convexity. Within a few days, this type of hemorrhage often may have little effect on mucosal oscillation. Resolution of the bruise may be complete within 2 weeks. By contrast, extravasation of blood from a *deeper* capillary may lead to focal accumulation of blood, similar to a

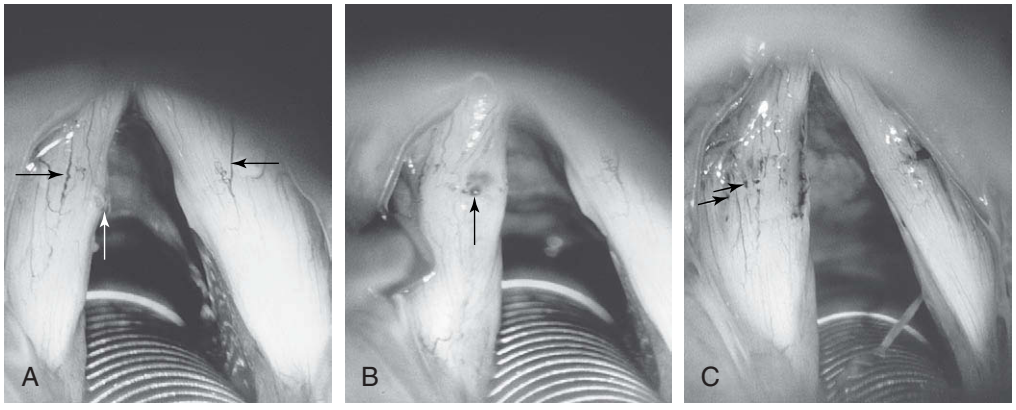

Figure 62-9. Vocal nodules with associated capillary ectasia. **A,** Superficial ectasia is seen (*black arrows*); the *white arrow* indicates deeper ectasia seen within left-sided nodule. **B,** The left vocal fold margin is rolled up onto the superior surface of the fold so that ectasia within the nodule can be seen more clearly (*arrow*), particularly the knuckle variant. **C,** Nodules have been removed (see Fig. 62-8), but spot-coagulation of dilated capillaries is present at approximately 2-mm intervals (*arrows*).

blood blister. This type of hemorrhage alters the margin contour and stiffens the mucosa, as seen stroboscopically. It causes significantly more and longer-lasting hoarseness and may be the precursor of a hemorrhagic polyp. In this case, microscopic examination would reveal a relatively rich vascular stroma and areas of hyalinization, although a unilateral, nonhemorrhagic, often pedunculated polyp may also be seen as the end stage of a hemorrhagic polyp.

Diagnosis

History

The history of abrupt onset of hoarseness during extreme vocal effort, such as at a party or sporting event, or even after a loud sneeze is classic but not universal in patients with vocal fold hemorrhage and a unilateral hemorrhagic vocal fold polyp.

Vocal Capability Battery

Vocal capabilities vary according to the size, age, turgidity, and pedunculation of the polyp. Some patients have a normal-sounding speaking voice, except for intermittent subtle aberrant sounds. Other patients have a normal speaking voice but an impaired or nonexistent falsetto register. Some patients also manifest chronic vocal huskiness.

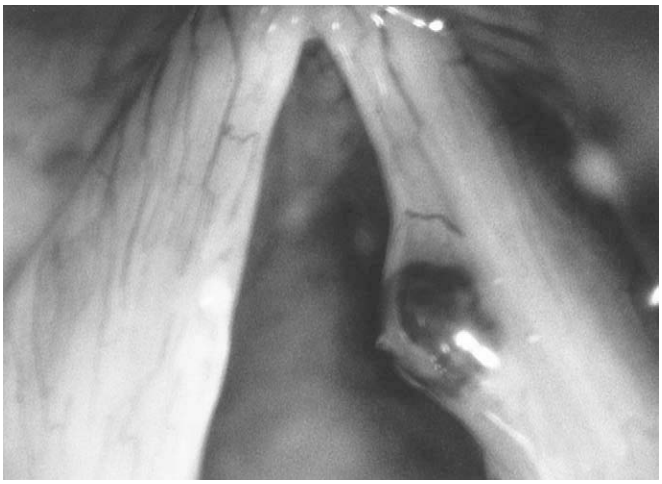

Figure 62-10. Operative view of a hemorrhagic polyp on the right true vocal fold of 14 months' duration. Note the capillary ectasia.

Laryngeal Examination

Laryngeal examination demonstrates a largely unilateral lesion in the node position, a contact reaction—or nodule if the person is a vocal over-doer-—on the fold opposite the polyp. In the case of the chronic vocal overdoer, a hemorrhagic polyp may represent an acute injury superimposed on chronic nodules. The hemorrhagic polyp is usually much larger than the typical nodule and may appear dark and filled with blood in early stages. Depending on when the submucosal bleeding occurred, discoloration may be in any stage of bruise evolution. Long-standing, hemorrhagic polyps may lose their vascular appearance and become pedunculated, moving in and out of the glottis with inspiration and expiration, respectively. During phonation, this end-stage polyp may be displaced upward onto the fold's superior surface, interfering little with basic phonation.

Treatment

Medical

If possible, the intake of anticoagulant medications (e.g., aspirin, nonsteroidal anti-inflammatory drugs, warfarin) should be stopped. Because acid reflux can increase hyperemia and dilate normal and abnormal capillaries, this condition should be controlled.

Behavioral

A short course of voice therapy is appropriate, mainly to instruct the patient in voice care. The occasional small, early hemorrhagic polyp resorbs completely with many months of conservative measures, but typically, surgical removal is required to return the vocal fold to its normal appearance and vibratory function and the voice to normal capabilities.

Surgical

Evacuation of blood through a tiny incision in a recent large hemorrhage that looks like a blood blister may be appropriate, because one would expect a long wait for resorption (in the best case) and likely progression to a chronic hemorrhagic polyp. After microsurgical evacuation of the hematoma, care should be taken to detect the large capillaries within Reinke's space, because these also should be interrupted, although a slightly deeper coagulation may be required to reach the level of the capillary. A long-standing polyp—whether hemorrhagic or

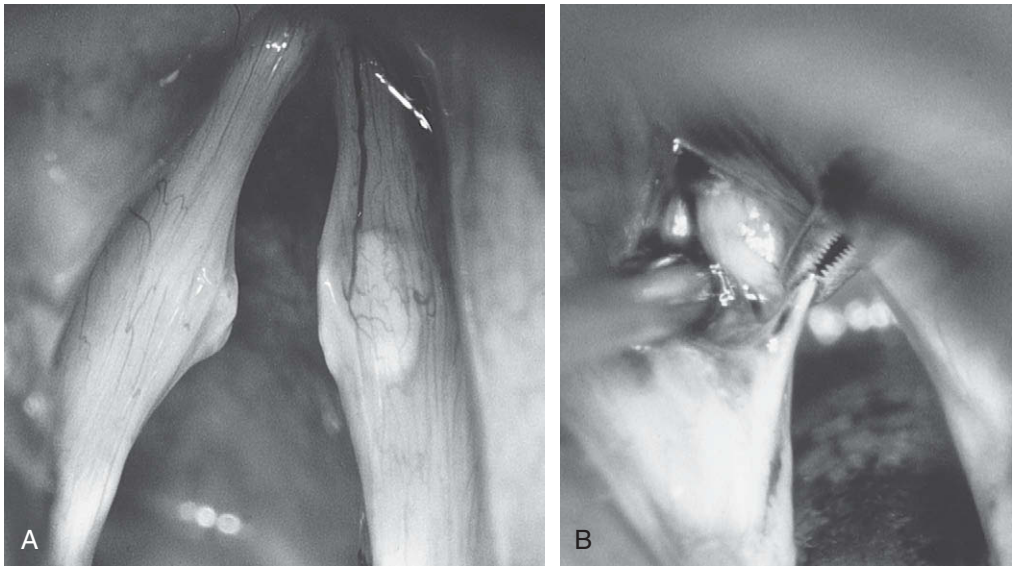

Figure 62-11. **A,** A large right epidermoid inclusion cyst with a characteristic dilated capillary. Note the large left nodule. **B,** An epidermoid inclusion cyst in another patient is delivered through a cordotomy incision.

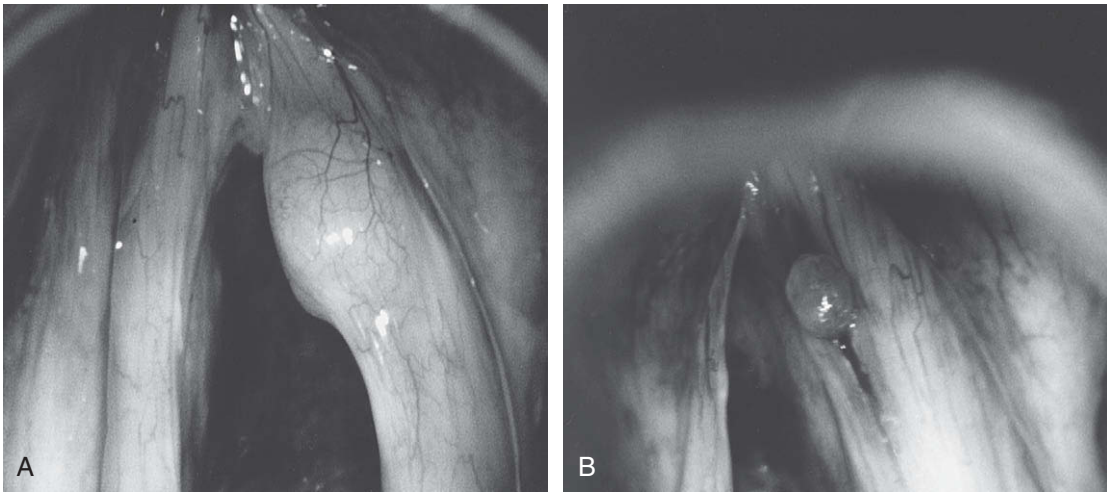

Figure 62-12. **A,** A mucus retention cyst of the right vocal fold. Note the relatively greater margin deformation caused by this cyst in comparison with that caused by an epidermoid inclusion cyst. **B,** In another patient, a cyst is delivered through cordotomy incision.

end-stage and pale—should be trimmed away superficially at the time the spot coagulations take place. Prognosis for full return of vocal functioning after precision surgery is excellent.

Intracordal Cysts

Epidemiology

The most prominent epidemiologic finding is a history of vocal overuse. This is routine for the epidermoid cyst, but less so for the mucus retention variety.

Pathophysiology and Pathology

Histologically, intracordal cysts are classified as either mucus retention or epidermoid inclusion types (Figs. 62-11 to 62-13). Mucus *retention (ductal) cysts* (see Fig. 62-12) arise when the duct of a mucus gland becomes plugged and retains glandular secretions; *epidermoid cysts* (see Fig. 62-13) contain accumulated keratin.[24-27] Two theories state that the epidermoid cyst results from a rest of epithelial cells buried congenitally in the subepithelial layer or from healing of mucosa injured by voice abuse over buried epithelial cells. In time, cysts may rupture spontaneously. If the resulting opening is small in relation to the overall size of the cyst, some epidermoid debris may be retained and may create an *open cyst*; if the opening is as large as the cyst, the resulting empty pocket becomes a *glottic sulcus*.

Diagnosis

History

A patient with epidermoid cysts has many of the same symptoms and voice abuse factors as a patient with nodules. Mucus retention cysts can arise seemingly spontaneously, without relation to amount or manner of voice use.

Vocal Capability Battery

The vocal capability battery uncovers vocal limitations similar to those for a patient with vocal nodules. Patients with epidermoid cysts are more likely to experience diplophonia in the upper voice, and they may manifest an abrupt and irreducible transition to severe impairment at a relatively specific frequency rather than a more gradual transition to greater degrees of impairment, as often noted in patients with nodules. Mucus retention cysts often cause less vocal limitation than anticipated from the laryngeal appearance; epidermoid inclusion cysts often cause more limitation than expected.

Laryngeal Examination

Mucus retention cysts often originate just below the free margin of the fold with significant medial projection from the fold. For this reason, mucus retention cysts are sometimes misdiagnosed as nodules or polyps. Epidermoid cysts project less from the fold and are harder to diagnose when small. An inexperienced clinician may be more aware of what appear to be nodules than the faint cyst outline on the superior surface of the fold (see Fig. 62-13). In an open cyst, the sphere may be less discrete and may have a more mottled appearance on the superior surface of the vocal fold (Fig. 62-14). Under strobe illumination, as the fundamental frequency of phonation increases, the mucosa overlying the cyst often stops vibrating before the mucosa anterior and posterior to the cyst. Even so, diagnosis can be confirmed in some patients only at the time of microlaryngoscopy.

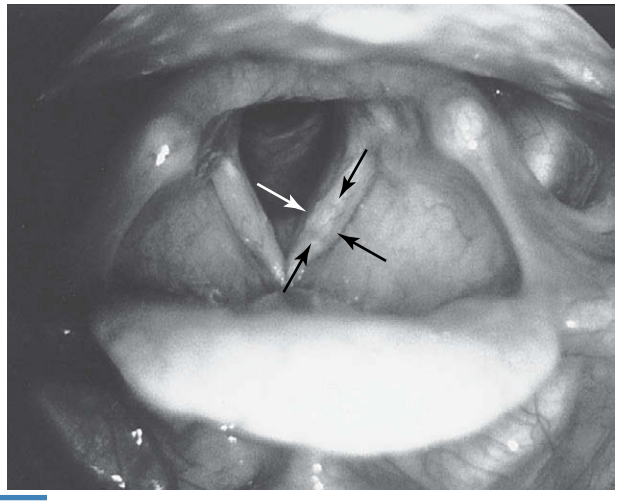

Figure 62-13. A 90-degree telescope view shows the faint spherical outline of a small epidermoid inclusion cyst (*arrows*).

Treatment

Medical

General supportive measures (e.g., hydration, potential acid reflux management) may be helpful but will not resolve this problem.

Behavioral

Voice therapy is more appropriate for persons with epidermoid cysts and often is not needed (beyond teaching in preparation for surgery) in those with the mucus retention variety. The reason is that persons with epidermoid inclusion cysts are by far the more likely of the two to be vocal overdoers. Of course, speech (voice) therapy may also be

warranted for the mucus retention variety if the person is a vocal overdoer, not to resolve the lesion, which is "surgical," but to avoid the risk of another (this time vibration-induced) lesion.

Surgery

Patients with large mucus retention cysts and no history of voice abuse may be scheduled for surgery promptly. If under the edge of the vocal fold and extremely superficial and translucent (resembling a polyp), the cyst may be removed in its entirety with a small slip of overlying mucosa when its wall is so thin as to make its dissection from the overlying mucosa virtually impossible. In this case, mucosal oscillation will still be normal after healing is complete. More typical mucus retention cysts are removed as described in the following paragraph, via dissection that leaves overlying mucosa intact.

A small, extremely shallow incision is made on the fold's superior surface. Careful dissection reveals that the swelling is indeed caused by a cyst. Taking care to avoid any injury to mucosa, other than that of the incision, the surgeon dissects the cyst free of the mucosa and vocal ligament (Fig. 62-15). The opposite fold should be examined carefully because of the possibility of a more subtle cyst or sulcus. Results are not as uniformly good as for nodules and polyps. Considerable improvement is expected, however, and some patients achieve excellent results. Patients should also know that postoperative recovery takes longer than for nodule or polyp surgery (many months rather than a few weeks). Bouchayer and colleagues[26] reported a series of 148 patients managed for cysts, sulci, or mucosal bridges (very difficult surgical problems compared with nodules and polyps), of whom 10% had an overall excellent result, 42% a good result, 41% a fair result, and 5% a poor result. Follow-up supportive voice therapy from the speech pathologist or singing teacher assists vocal rehabilitation. A return to active voice use or training should occur within a few days of surgery, because the amount of mucosal disturbance required leads to a greater tendency to mucosal adherence and stiffness.

Figure 62-14. Bilateral open cysts. Because the openings are small in relation to the size of the cysts, partial emptying of the keratin contents causes a mottled appearance.

Glottic Sulcus

Epidemiology

Although some writers believe sulci to be congenital, this entity appears to occur exclusively in vocal overdoers (Figs. 62-16 to 62-18).

Pathophysiology and Pathology

Bouchayer and colleagues[26] reviewed acquired and congenital theories for these conditions. They described the appearance of the sulcus as an epithelium-lined pocket whose lips parallel the free edge of the folds and suggested that a sulcus may represent an epidermoid cyst that has spontaneously emptied, leaving the collapsed pocket behind to form a sulcus. In effect, a mucosal bridge is the result of two parallel sulci arising from a single cyst (see Fig. 62-18).

Diagnosis

History

The patient with a glottic sulcus often has a history of voice overuse and complains of chronic hoarseness.

Vocal Capability Battery

Typically the voice is noticeably hoarse. Upper voice limitations, particularly diplophonia, are obvious. As is the case for cysts, the transition between hoarse phonation and aphonia may occur abruptly, almost at a specific frequency, generally in the middle of the singing range.

Laryngeal Examination

Laryngeal examination may initially reveal fewer findings than expected to account for the abnormal speaking voice or reduced singing voice capabilities. Because the patient is likely a vocal overdoer, associated fusiform vocal fold margin swellings might also be seen. Stroboscopic evaluation shows a segment of reduced vibration. The entire length of the mucosa may oscillate at lower frequencies; at higher frequencies,

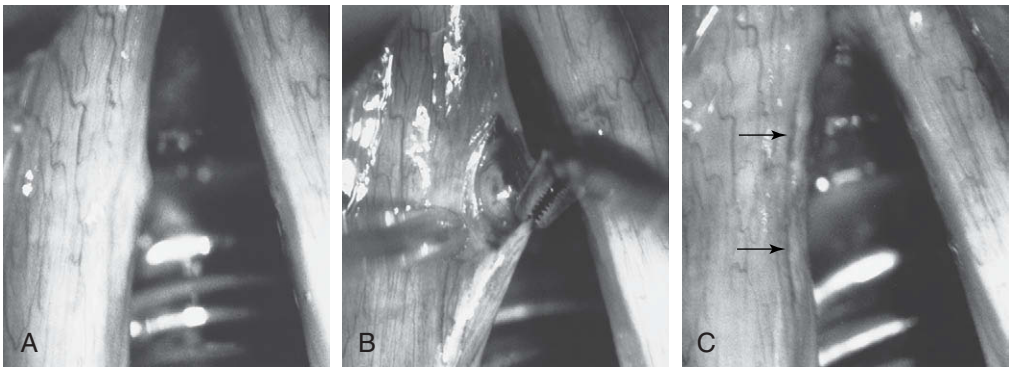

Figure 62-15. Operative sequence for removal of a small mucus retention cyst in a patient previously diagnosed as having vocal nodules. **A,** Initial operative view, left vocal fold. **B,** The cyst is exposed through an incision made on the superior surface of the fold. **C,** After removal of the cyst and redraping of undamaged overlying mucosa, only an incision line is seen (*arrows*). The patient's vocal fold was stiff under strobe illumination for several weeks postoperatively but ultimately regained full vibratory amplitude and mucosal wave as compared with the unoperated cord. Vocal capabilities also returned to normal. With larger cysts, some postoperative stiffness can be permanent, particularly as the patient phonates at high frequencies.

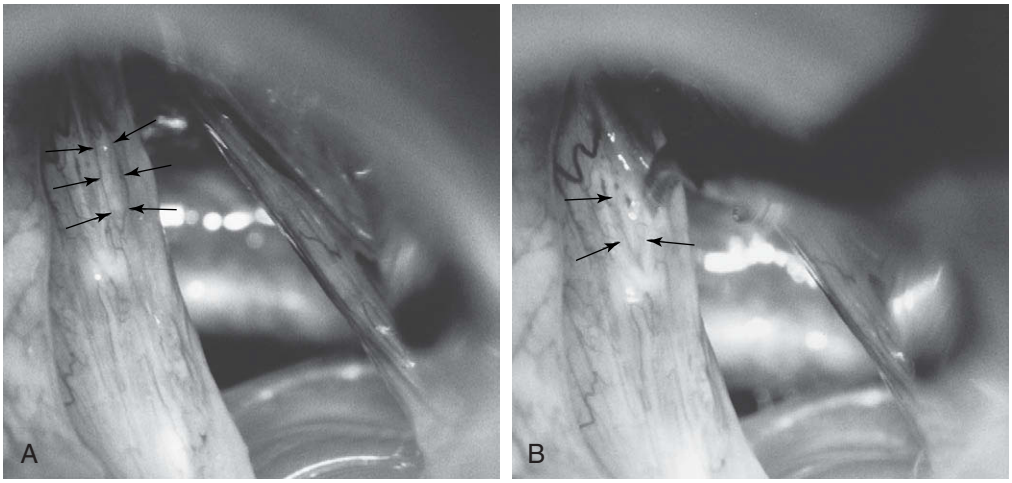

Figure 62-16. Sulcus of the left true vocal fold seen **(A)** undisturbed and **(B)** with forceps used to spread open its lips.

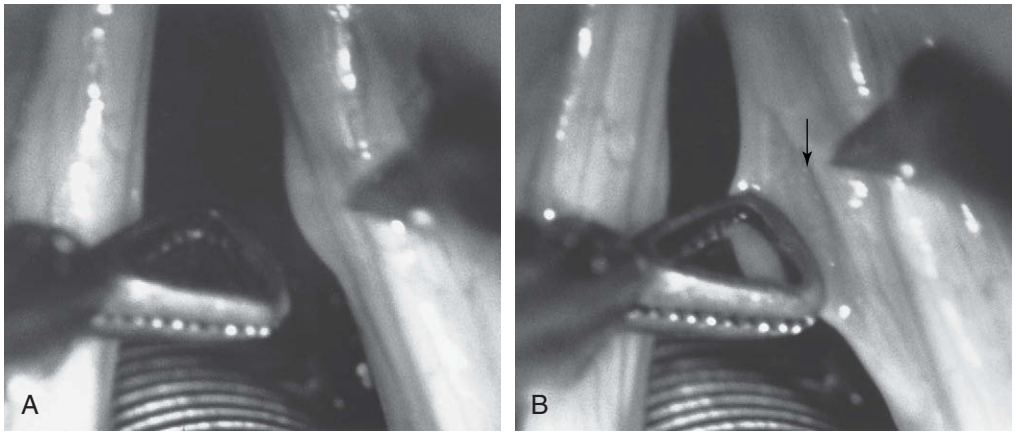

Figure 62-17. **A,** Operative view of a chronic polypoid nodule. **B,** At the time of medial tenting of the mucosa preparatory to excision, a previously unsuspected sulcus is discovered (*arrow*). In this case, excision of the polypoid nodule alone without specifically addressing the sulcus resulted in marked improvement of vocal capabilities and eliminated this nonsinging patient's chronic hoarseness of the speaking voice.

Figure 62-18. A mucosal bridge of the right vocal fold (with forceps passed under it) in the same patient seen in Figure 62-16.

the midportion of the mucosa stops oscillating and short-segment vibration begins to occur. Microlaryngoscopy is often required for definitive diagnosis because the lips of the sulcus are not always visible with inspiratory phonation during the office or voice laboratory examination.

Management

Medical

Medical management for glottic sulcus is supportive as appropriate, but it is not expected to resolve this structural abnormality.

Behavioral

A short preoperative course of voice therapy is indicated if the patient with glottal sulcus is a confirmed vocal overdoer, because the behavioral goal for patients with cysts initially is selection and preparation for surgery; restoration of the mucosa to normal cannot be achieved by medical or behavioral treatment.

Surgical

Sulcus removal is technically demanding, and it involves considerable surgical disturbance of the vocal fold mucosa in comparison with surgery for nodules. Bouchayer and colleagues[26] described the steps for removal of a glottic sulcus (Fig. 62-19), including cordal injection to make the sulcus lips spread and the sulcus more shallow and to accomplish some hydrodissection. This step is followed by circumcision of

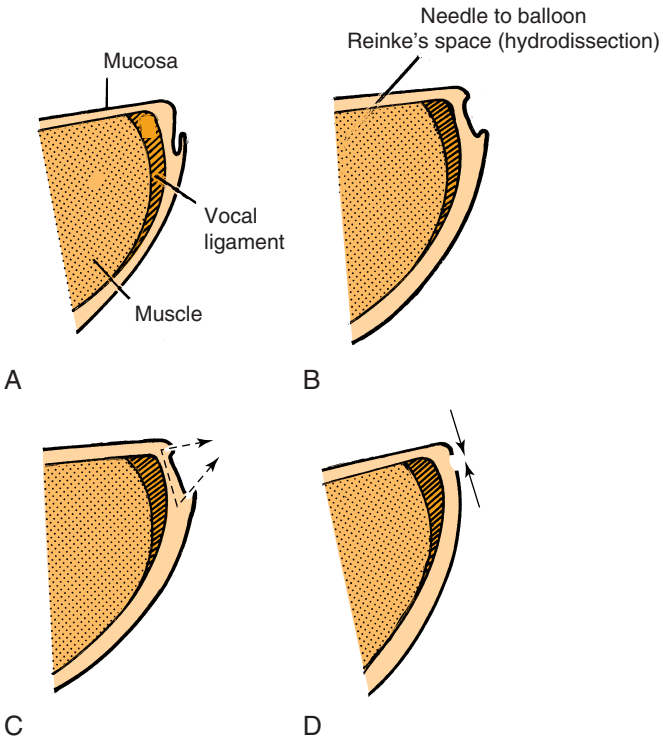

Figure 62-19. Removal of a glottic sulcus. **A,** A vocal fold coronal section shows the sulcus. **B,** Injection of 1% lidocaine with epinephrine into Reinke's space spreads the lips of the sulcus. **C,** Incisions at the sulcus lips and dissection off the vocal ligament. **D,** After removal of the sulcus.

the lips of the sulcus and dissection of the invaginated mucosal pocket from the underlying fold without injuring the vocal ligament. Results seem to depend not only on excellent surgical skill but also on the thickness of the mucosa. A thick, almost polypoid mucosa may yield a normal voice on occasion. In the patient in whom the mucosa is very thin and more widely adherent to the ligament, voice is typically better than before surgery but residual mucosal stiffness may occur even after optimal surgery.

Bilateral Diffuse Polyposis

Epidemiology

Voice change caused by bilateral diffuse polyposis (chronic Reinke's edema or smoker's polyps) (Fig. 62-20) typically becomes noticeable enough to prompt a laryngeal examination in middle-aged, *talkative* women who have been long-term smokers.

Pathophysiology and Pathology

There seems to be an individual susceptibility to this condition because it develops in only a small percentage of persons at risk (e.g., smokers who use their voices a lot). As detailed by several writers, chronic smoking and voice abuse result in edema, vascular congestion, and venous stasis.[28,29] These conditions cause diffuse polypoid changes that become permanent, although the degree of edema or turgidity and consequent voice disturbance may rise and fall with voice use.

Diagnosis

History

The combination of smoking and avid voice use is classic for this entity. A woman with smoker's polyps may complain of being called "sir" on the phone, or she may have problems with increasing hoarseness during the day.

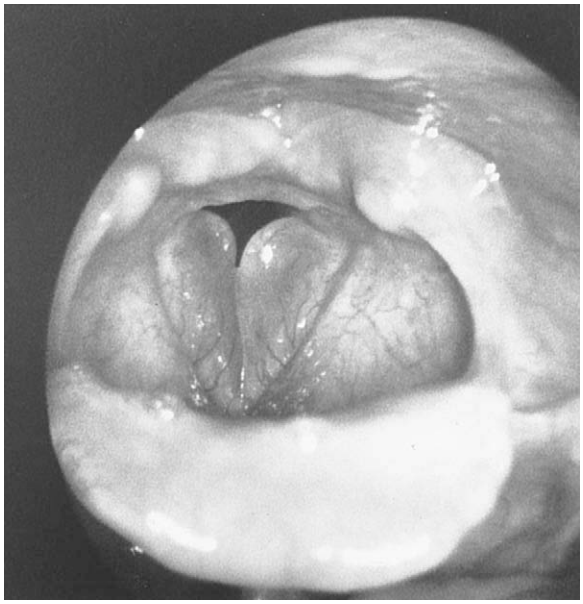

Figure 62-20. Moderately large unilocular smoker's polyps (inspiratory view through a rigid laryngeal telescope).

Vocal Capability Battery

The voice examination demonstrates lower pitch than would be expected, often well into the masculine range when the condition is seen in women. Upper voice is lost, and the female patient can often phonate through the range of a true bass singer! With large polyps, the voice may even be hypermasculine.

Laryngeal Examination

Laryngeal examination usually reveals pale, watery bags of fluid attached to the superior surface and margins of the folds. Large smoker's polyps may cause an involuntary laryngeal snore on sudden inhalation. A to-and-from motion is often seen with respiration. In severe cases, clusters of polyps on polyps may be seen. Small smoker's polyps are easily overlooked unless the patient is instructed to phonate on inspiration, when the polypoid tissue is drawn from the superior surface of the folds into the glottic aperture and thereby made more visible as a greater-than-normal convexity of the margin. (Virilization of the singing range noted during the vocal capability battery directs the examiner to elicit inspiratory phonation and look for this type of lesion.)

Management

Medical

The patient with bilateral diffuse polyposis is encouraged to give up smoking. Thyroid function tests can be performed if hypothyroidism is suspected. This latter entity has often been invoked as causal in this condition, although diffuse polyposis is extremely rare in the absence of smoking and avid voice use.

Behavioral

Short-term voice therapy may be appropriate to introduce optimal vocal behavior. These measures alone may reduce the polyps' turgidity, with a corresponding modest improvement in vocal functioning.

Surgical

Microsurgery for polyp *reduction* is necessary when the voice remains objectionable to the patient. The older common practice of stripping the polyps away often results in aphonia for many weeks postoperatively, and the final voice achieved may sound unacceptably high and husky to the patient. Polyp reduction with mucosal sparing (Fig. 62-21) is recommended for earlier and optimal return of voice (usually begin-

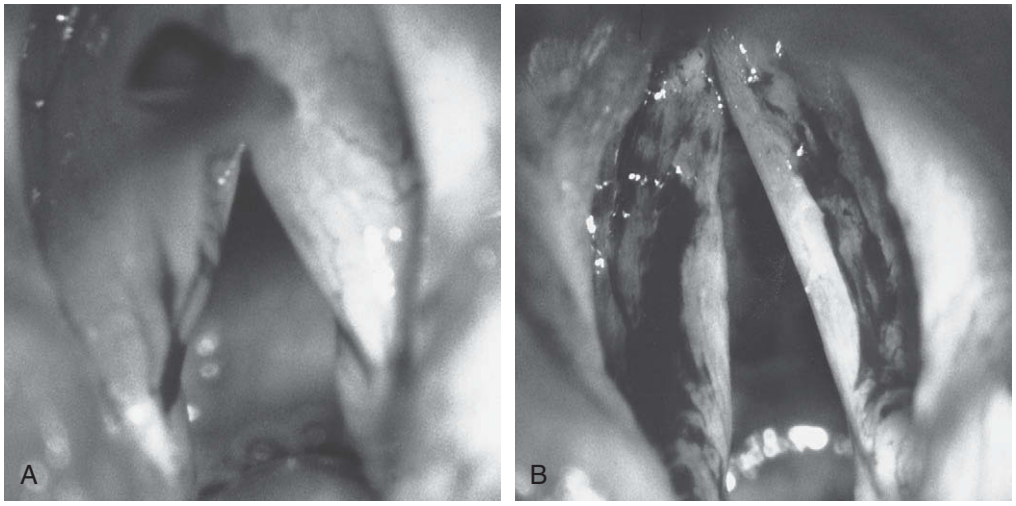

Figure 62-21. **A,** This operative view is seen after a left vocal fold polyp has been bivalved in the axial plane. Bouchayer forceps are holding the superior half of the polyp in preparation for removal. **B,** The final view after the upper part of the polyp has been removed and myxoid material has been suctioned and dissected from between the mucosal flap and vocal ligament; the resulting inferiorly based mucosal flap has been redraped over a free edge of the vocal fold. This female patient's speaking voice was markedly virilized preoperatively and considerably feminized postoperatively. The patient was aphonic for only 7 days postoperatively, whereas after traditional stripping, she may not have regained voice for many weeks.

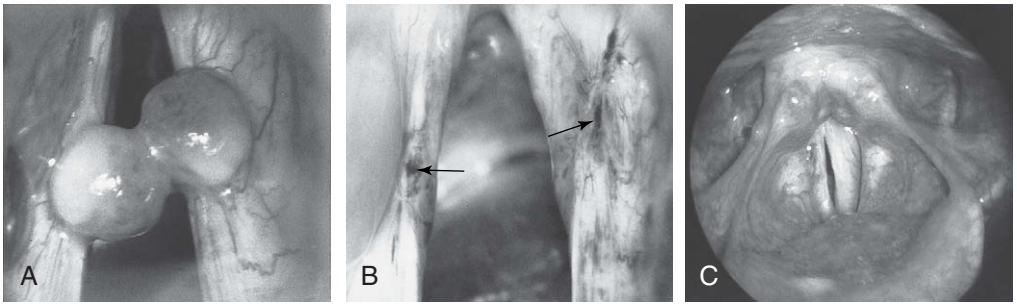

Figure 62-22. Iatrogenic mucosal scarring. This patient underwent bilateral vocal fold "stripping" elsewhere for persistent dysphonia, which was subsequently diagnosed as spasmodic dysphonia. The patient was reportedly aphonic for many weeks postoperatively. **A,** This operative photograph was taken 4.5 months after the original surgery. Granulomas are highly pedunculated and may have eventually detached or regressed spontaneously. Note the medial-to-lateral reorientation of vocal fold capillaries, a common finding after vocal fold stripping. **B,** The same patient after granuloma removal. Attachment points of the granulomas are marked at *arrows*. In this view, the vocal folds are rolled superiorly, and considerable scarring is evident, particularly on right vocal fold. **C,** The same patient as viewed through a laryngeal telescope a few weeks later. The larynx shows pseudobowing caused by mucosal loss rather than by vocal fold atrophy. Under strobe illumination, these vocal folds were very stiff with minimal mucosal wave evident even at low frequencies. With a voice-building regimen and scar maturation, a serviceable but limited voice was achieved.

ning within 10 days). It is better to leave the patient with a voice that still sounds rich (even with some residual polyposis and mild vocal virilization) than to strip the folds and leave the patient with a voice that sounds thin, insubstantial, and effortful.

Postoperative Dysphonia

Epidemiology

Vocal fold surgery performed without extreme precision can lead to permanent *postoperative* dysphonia (Figs. 62-22 and 62-23) that can be worse than the hoarseness of the lesion that was operated on.[30,31] The prior surgeon may have performed vocal fold stripping or laser vaporization of the mucosa. The pathology report from that operation frequently describes a fairly large specimen that may contain fibrous tissue or even muscle, suggesting that the removal went deeply into the vocal fold.

Pathophysiology and Pathology

Dysphonia can result from a scarred, stiff vocal fold cover, from phonatory mismatch of the vocal fold margins, or from both. Scarring adheres mucosa to underlying vocal ligament, abolishing the ability of mucosa to oscillate with any freedom from the underlying vocal ligament. Mismatch may arise from a divot caused by overzealous removal or from pseudo-bowing, such as that from not sparing enough mucosa during smoker's polyp reduction. With few exceptions, postoperative dysphonia can be avoided by use of an appropriately precise surgical technique and by early graduated resumption of voice use after surgery (see Table 62-1).

Diagnosis

History

A history of prior surgery is common to all cases, but a clear understanding of the original lesion should be sought, as well as any history indicating continuing vocal abuse that might indicate recurrent mucosal injury, rather than scarring, as a possible explanation.

Vocal Capability Battery

The voice may vary from aphonia to a harsh whisper to a relatively normal speaking voice, but it is accompanied by disastrous limitation

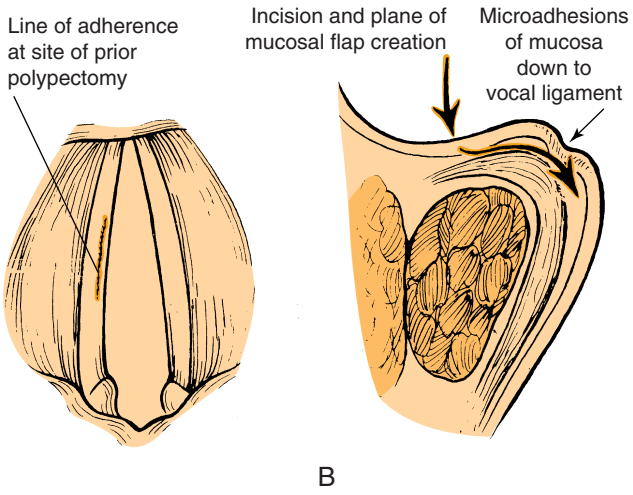

Figure 62-23. Postoperative dysphonia (severe diplophonia) from suspected overly aggressive polypectomy. **A,** The operative view from above shows a longitudinal scar. **B,** Cross-sectional view shows the surgical approach releasing microadhesion of mucosa down to the vocal ligament. The patient experienced immediate and enduring relief of diplophonia.

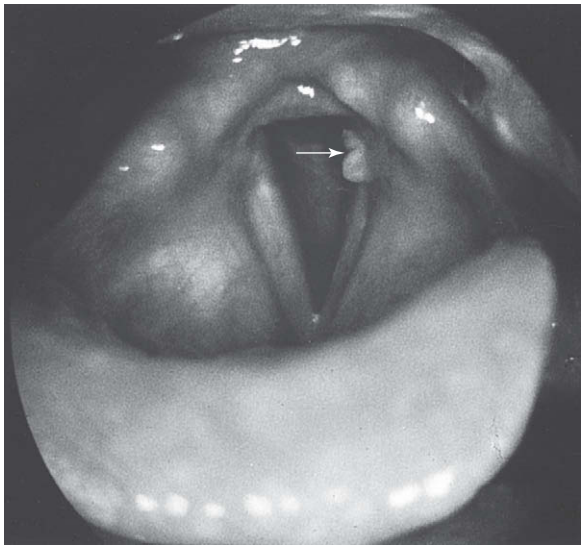

Figure 62-24. Contact granuloma, left vocal fold. The general appearance and the cleft (*arrow*) where the opposite vocal process fits are typical.

of the upper singing voice with diplophonia and loss of the expected upper range.

Laryngeal Examination

Laryngeal videostroboscopy is essential for patients with possible postoperative dysphonia. The technique allows careful analysis of mass lesions, areas of asymmetry, and the mucosa's vibratory pattern, from which a clear diagnosis and a therapeutic plan can be generated.

Management

Medical

General medical issues that relate to the voice should be optimized in the course of management.

Behavioral

If stiffness, scarring, and tissue loss are problems, voice therapy is tried first, with a voice-building approach. A person who is resting the voice should instead resume talking per routine. In addition, the individual is coached to sing with moderately great vigor for 10 minutes two or three times per day at all vocal frequencies of his or her range. Using the facilitating vowel /oo/ is helpful in cases of severe dysphonia. When only a very narrow frequency range is available to a patient because of postoperative scarring, the patient is asked to start phonating at a frequency that works (often quite high in the expected vocal range) and to coax the voice lower and higher from this small area of working frequencies. Some remarkable improvements may be seen with this approach. However, even with achievement of a serviceable speaking voice, the voice's singing capabilities will remain limited in comparison with a normal voice. Proof for this approach is difficult to procure. However, improvement does not seem to arise only from spontaneous softening of scar tissue, because improvement can occur with the preceding "voice-building" strategy in patients more than 1 year after surgery or another scarring event.

The rationale for this aggressive, voice-building strategy may require some explanation for patients whose voice abuse is what caused the problem for which they underwent surgery. A voice-qualified speech pathologist who is comfortable with teaching vigorous voice production throughout the expected range should monitor voice-building exercises initially. Some patients can work independently because of the short duration of exercise sessions and because the overall idea of the voice-building approach is not to scream abusively or, primarily, to enhance vocal skills. Rather, the goals are to strengthen the laryngeal musculature to compensate for—to overdrive—the damaged mucosa and to encourage the mucosa to oscillate more freely because of this sort of "phonatory massage" of the mucosa.

Reoperation is occasionally an option. Ample time (9-12 months) should pass before this idea is entertained, however, because the voice may improve and iatrogenic lesions may diminish slowly for many months after the first operation. A second procedure can be planned to correct the videostroboscopically identified defect in mucosal mass, mobility, or edge configuration. For example, if an iatrogenic mass (granuloma) is causing poor phonatory closure, it should first be allowed to mature and possibly to resolve spontaneously. If it remains after a minimum of 6 months, it can be removed. Injection of collagen into an area of depression has been advocated,[32] but this approach does not yield more than very modest results, and even these occur on an inconsistent basis. Incision and simple mucosal elevation across a limited line of adherence with early postoperative phonation may cure diplophonia or lessen dysphonia, occasionally to a surprising extent. It should be stressed, however, that in some instances little can be done beyond voice building, and avoidance of this problem altogether through precision surgery is the ideal. Some authorities have written of fat injection or medialization thyroplasty, but these approaches remain to be systematically validated and make some sense theoretically primarily if there is a significant gap between the folds, and not simply mucosal stiffness.

Contact Ulcer or Granuloma

Epidemiology

Contact granuloma or ulceration is seen primarily in men (Fig. 62-24). Chronic coughing or throat clearing and reflux of acid from the stomach into the posterior larynx during sleep also seem to cause contact ulceration.[33] Some writers have also suggested that patients with this entity are experiencing psychological stress or conflict.

Pathophysiology and Pathology

The thin mucosa and perichondrium overlying the cartilaginous glottis become inflamed, perhaps as a result of overly forceful apposition (slamming together) of the arytenoids at the onset of voicing (glottal stroke) or during chronic coughing or throat clearing. Acid reflux may also increase inflammation of the vocal process area. The traumatized area ulcerates or produces a heaped-up granuloma.

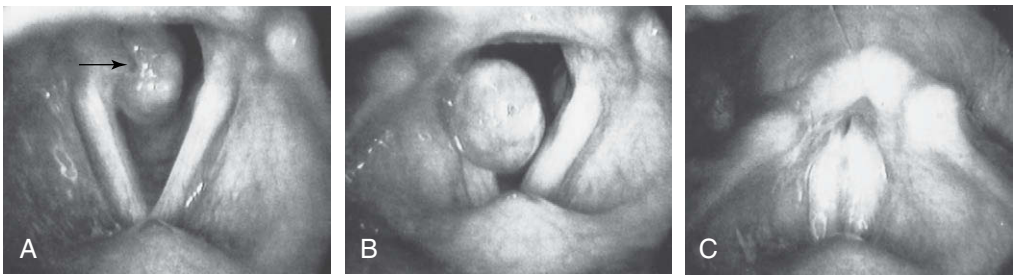

Figure 62-25. Video photographs through a laryngeal telescope of highly pedunculated right contact granuloma. **A,** The granuloma is drawn into the subglottis during sudden inspiration, thereby revealing its pedicle more clearly (*arrow*). **B,** Sudden exhalation blows the granuloma upward into the laryngeal vestibule. **C,** During phonation, the granuloma remains below the level of the vocal fold. Vocal fold closure is thus excellent, and speaking voice quality is remarkably undisturbed.

Diagnosis

History

The clinician inquires about caffeine and alcohol consumption as well as late-night eating, along with more specific acid reflux symptoms (e.g., acid eructations, raw throat in the morning with sour taste, unusually low-pitched, gravelly morning voice, heartburn). Frequent symptoms include unilateral discomfort over the midthyroid cartilage, occasionally with referred pain to the ipsilateral ear. When contact granulation tissue becomes large, hoarseness can occur.

Vocal Capability Battery

The speaking voice of a patient with contact ulcer or granuloma may sound normal or only slightly husky. The patient may be noted to be speaking habitually in an overly low frequency range, often with a "held back" vocal quality but sometimes with a kind of "constrained emphasis." In particular, the voice characteristics of the held-back quality, habitual coughing or throat clearing, and low and monotone voice use are typical.

Laryngeal Examination

A depressed, ulcerated area with a whitish exudate clinging to it or a bilobed, heaped-up lesion on the vocal process may be noted. At the instant of glottal closure, the vocal process of the uninvolved side can be seen to fit into the cleft of a bilobed granuloma. Erythema is also usually apparent on the vocal process and coming upward on the medial surface of the arytenoid cartilage. A mature, soon-to-detach granuloma may be pedunculated and may flip above and below the plane of the vocal fold margin with expiratory and inspiratory phonation, respectively (Fig. 62-25).

Management

An antireflux regimen should be started on an empirical basis even for patients with no symptoms of reflux. The necessity of routine barium or pH monitoring studies remains controversial. Maturation and resolution of the granuloma can often occur spontaneously over 3 to 6 months. Thus, the role for voice therapy to abolish throat clearing, raise average pitch for speech, and so forth, is indeterminate.

Indirect injection of a depot corticosteroid directly into the lesion and the area around its base can be accomplished in a videoendoscopy procedure room with the patient sitting in a chair.[12] Anecdotally, this technique has worked especially well for some granulomas but poorly for contact ulcers. Visible lesions tend to diminish in size, and the symptoms disappear. The use of inhaled triamcinolone (Azmacort, Abbot Laboratories, North Chicago, IL) 150 µg orally 3 times a day for 6 to 8 weeks has also been used for treatment and avoids systemic side effects.

Surgery should be a last resort because postoperative recurrence of the ulcer or granuloma is predictable. Furthermore, when the lesion has a classic appearance and can be visually monitored, there is little need for tissue diagnosis: visual criteria are sufficient. Microlaryngoscopy may be justified, however, if after a several-month trial of management an uninflamed, pedunculated lesion remains and is causing symptoms. Removal should be limited, leaving the base or pedicle undisturbed.

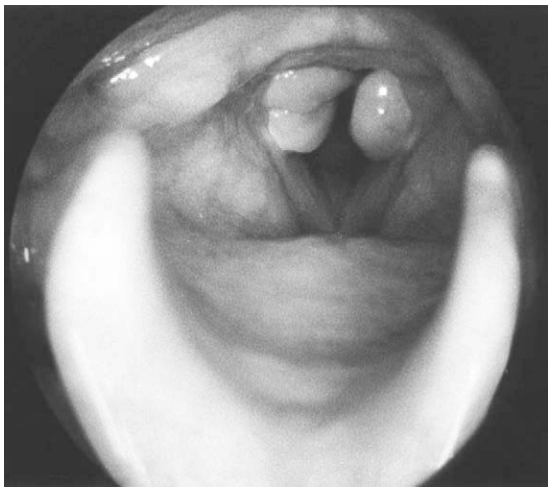

Figure 62-26. Postintubation granulomas.

Intubation Granuloma

Epidemiology

Intubation granuloma occurs in patients who have undergone endolaryngeal surgery affecting the arytenoid perichondrium, acute or chronic intubation, rigid bronchoscopy, or other direct laryngeal manipulations (Fig. 62-26).

Pathophysiology and Pathology

Granuloma after intubation can occur because of direct abrasion of the arytenoid perichondrium, a break in the mucosa covering it as a result of coughing on an endotracheal tube, or long-term pressure necrosis of the vocal process area. The resulting reparative granuloma may initially progress from fairly sessile to large and pedunculated, but it may then regress entirely with maturation over several months.

Diagnosis

History

The history of a patient with intubation granuloma includes a fairly recent event during which the larynx was subjected to direct instrumentation or intubation.

Vocal Capability Battery

The speaking voice of a patient with intubation granuloma may not sound abnormal because the membranous (vibratile) portion of the vocal folds may be unaffected by the granuloma, which may sit above or below the vocal process during phonation. The laryngeal appearance,

however, is characteristic. The granuloma can vary in size but is often large and spherical with some pedunculation. The granulomas are attached directly to the vocal process and are frequently bilateral. In cases of long-standing intubation, there may be associated findings such as tissue loss with resulting posterior glottic incompetence. In even more severe cases, there may be partial or complete fixation of one or both arytenoid cartilages. An interarytenoid synechia may also be noted on occasion.

Management

Regarding the management of intubation granuloma, if the history and physical examination findings are unequivocal, patience is recommended. If the injury is recent, antibiotic coverage for several weeks seems to be helpful. Voice therapy may have a role on a highly individualized basis. With time and use of these measures, intubation granulomas usually mature and "fall off." If they become mature and persistent, however, surgery or a trial of indirect corticosteroid injection in the office may be an option. During microlaryngoscopy, corticosteroid injection into the base of the granuloma before its removal is suggested. Any identifiable stalk should be left with the patient to minimize the size of the surgical wound. Topical application of mitomycin C has also come into use, to inhibit fibroblast proliferation that might lead to the reformation of granulation tissue.

Summary

The benign vocal fold mucosal disorders are important because of their impact on identity and communication and their commonness. For optimal results, diagnosis should include a skillful history, vocal capability elicitation, and laryngeal videostroboscopy. Intervention, whether medical management, voice therapy, surgery, or some combination, should match the diagnosis.

Saccular Disorders

At its anterior end, the normal laryngeal ventricle has a small outpouching called the *saccule* or *laryngeal appendix*. This structure is a blind sac that extends upward between the false vocal fold and thyroid cartilage, just posterolateral to the edge of the epiglottis at the level of the petiole. Containing many mucous glands, the saccule empties through an orifice in the anterior part of the ventricle. In a study of 100 random cadaver larynges, Broyles[34] found significant variation in the size of this normal structure, with 75% measuring 6 to 8 mm in length, 25% measuring 10 mm or greater, and 7% of the 25% measuring 15 mm or more. Although these structures may represent vestigial air sacs, their function is unknown in humans, besides perhaps to supply lubrication to the true folds via the many glands that line a saccule. For review of this anatomy, see Figure 62-27A.

Etiology of Saccular Disorders (Laryngocele and Saccular Cysts)

In infants, saccular disorders appear to be congenital. Otherwise, the cause of an air-filled laryngocele may be uncertain for the individual case. Some writers have cited an increase in transglottic pressure, such as that seen in trumpet players, glass blowers, and people using the voice in unusually forceful ways. Others, such as Stell and Maran,[35] believe that the relationship of laryngocele to these activities may have been overstated, because few reported patients with such disorders described in the world literature had hobbies or occupations requiring high transglottic pressures. A perhaps more clearly documented, although uncommon, cause of saccular cysts is laryngeal carcinoma, which causes obstruction of the saccular orifice.[36] I have also seen saccular cyst months or years after successful excision of a large supraglottic carcinoma with the laser, which left remnants of the saccule buried.

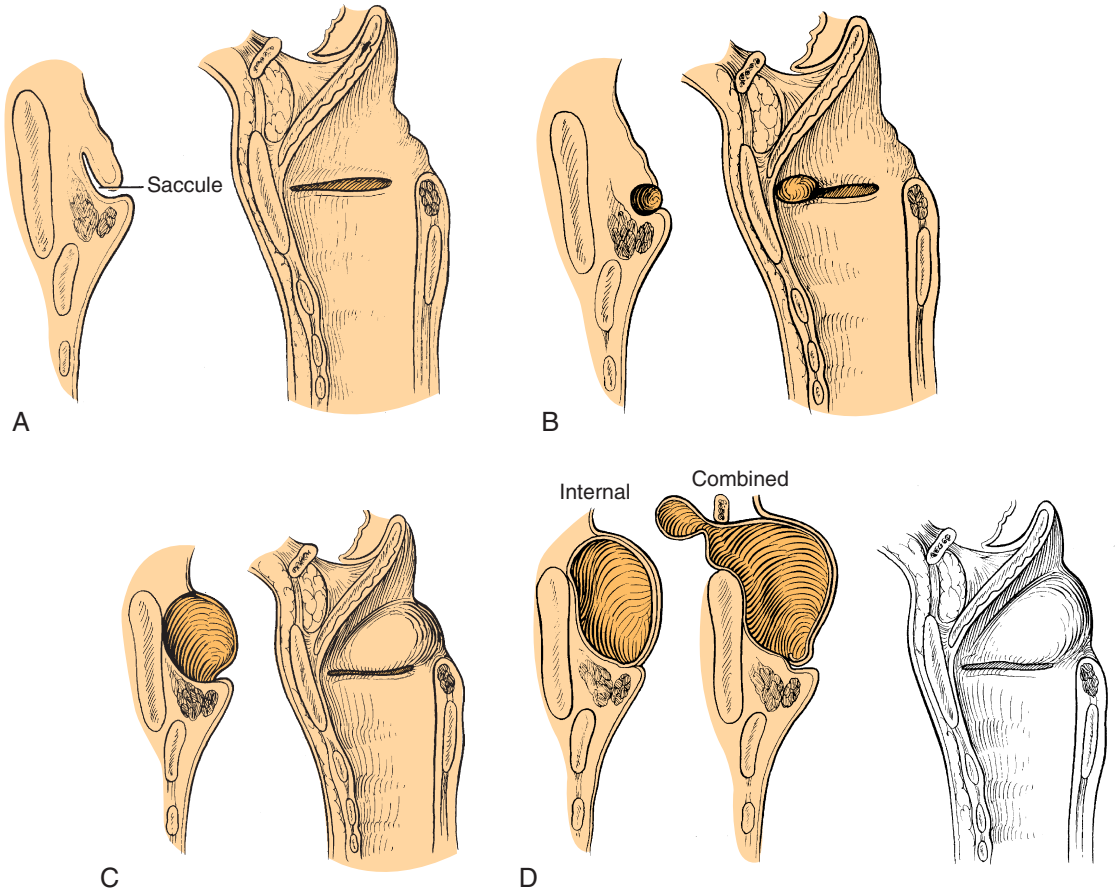

Figure 62-27. The classification scheme for a laryngocele or saccular cyst. **A,** Normal anatomy. **B,** Anterior saccular cyst. **C,** Lateral saccular cyst. **D,** Laryngocele types.

Clinical Scenario

Holinger and associates,[37] in their review of 46 patients with laryngocele or saccular cyst, found that in the 41 cases involving a saccular cyst, 10 occurred in infants and children and 31 in adults. Of the 31 adult cases, 22 were anterior saccular cysts and 9 were lateral saccular cysts. Four cysts in the infants and children were anterior, and 6 were lateral. When a saccular cyst occurs in infancy, it usually appears early, even at birth, as respiratory distress with inspiratory stridor. The infant's cry is abnormal, and cyanosis and dysphagia can occur. In adults, hoarseness seems to be the most common complaint, although dyspnea, dysphagia, pain, and a neck mass can occur with large or infected lateral saccular cysts (laryngopyoceles).[37]

Classification

Saccular disorders can be classified in various ways (Figs. 62-27 to 62-30).[37-40] It seems reasonable to think first of the *contents of the dilated saccule,* as in the following classification:

- Air-filled = *laryngocele* with patent saccular orifice
- Mucus-filled = *saccular cyst* with blocked orifice
- Purulence-filled = *laryngopyocele* with blocked orifice

A second classification might be by the *size and direction of cyst dissection* within the larynx, as follows:

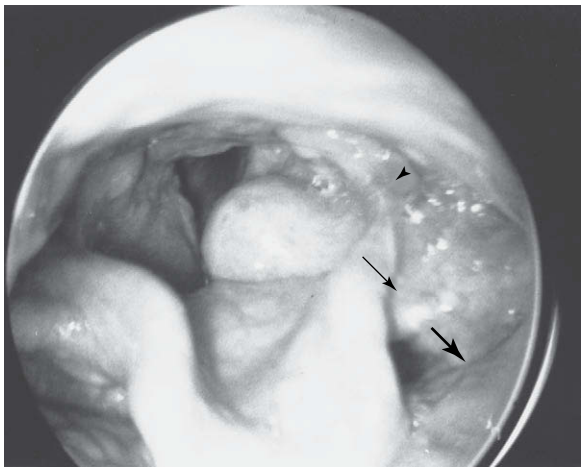

Figure 62-28. A saccular cyst, left, obscures most of the left vocal fold. A slightly larger cyst can be seen at the medial wall of the pyriform (*arrowhead*), at the pharyngoepiglottic fold (*small arrow*), or through the thyrohyoid membrane and into the neck (*large arrow*).

Anterior saccular cyst. Tends to protrude from the anterior ventricle toward the laryngeal vestibule. When large, it may "push down" on the vocal fold and cause dysphonia.

Lateral saccular cyst or laryngocele, internal only. This lesion tends to dissect more superiorly and laterally up into the false and aryepiglottic folds, sometimes bulging not only those structures (medially), but also the medial wall of the pyriform sinus (laterally) or even to fill the vallecula.

Lateral saccular cyst or laryngocele, internal/external. This variant tends to dissect as described for the lateral cyst, but also to penetrate through the thyrohyoid membrane and to appear as a swelling palpable in the neck.

Diagnosis

The diagnosis and classification of disorders of the laryngeal saccule are made through a combination of careful history, detailed examination of the larynx and neck, and computed tomography to determine contents (air vs. fluid) as well as the precise size and direction of expansion or dissection of the process. *Symptoms* depend somewhat on whether the laryngocele is internal, external, or combined. The usual symptoms are hoarseness, generally from downward pressure on the vocal fold or premature closure of the laryngeal vestibule at the false fold level during phonation, and (in decreasing order of frequency) stridor, dysphagia, sore throat, snoring, and cough.

Examination of the head and neck in a person with laryngocele reveals submucosal swelling protruding from the anterior ventricle in the case of an anterior saccular cyst or of the false vocal fold and aryepiglottic fold to a degree commensurate with the laryngocele's size. If a component of the laryngocele extends through the thyrohyoid membrane, a mass is palpable in the lateral neck in that location.

Treatment

Management is surgical. In infants with congenital lateral saccular cysts who have weak cry, stridor, and cyanosis, the airway should first be secured. This is followed by aspiration of the cyst contents through a direct laryngoscope or by endoscopic marsupialization with or without stripping of the cyst lining. Abramson and Zielinski[41] described application of the carbon dioxide laser to incise the cyst and to vaporize its lining. Booth and Birck,[42] reporting on laryngocele and lateral saccular cyst in neonates, described using simple cup forceps to unroof both lesions, followed by a 3-day intubation to act as a stent and to maintain the infant's airway. A 5-year follow-up revealed no recurrences. Frederick[43] describes endoscopic excision of internal laryngoceles. Holinger and coworkers,[37] in their report of 10 infants with saccular cysts, described direct laryngoscopy and aspiration of the cyst. They noted that a mean of 7.5 aspirations were required for each infant, 5 of whom later needed endoscopic marsupialization. One child had external excision of a persistent laryngeal cyst after 11 direct laryngoscopies. These

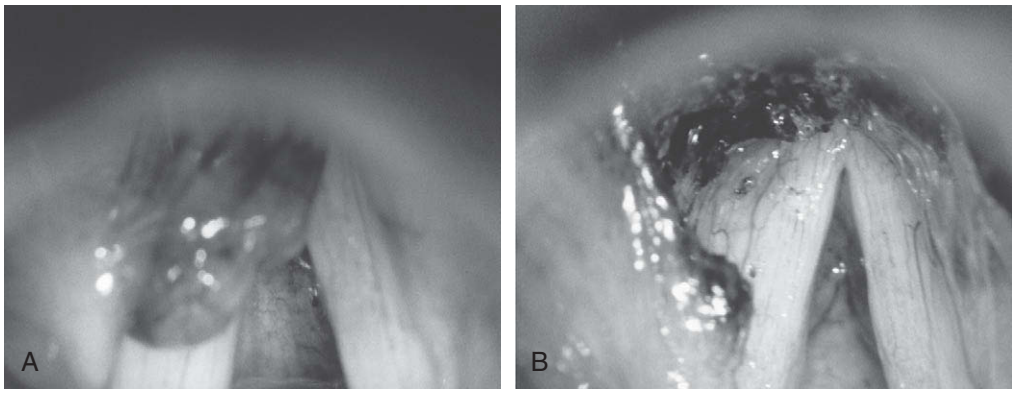

Figure 62-29. **A,** A moderate-sized anterior saccular cyst obscures the anterior left true vocal fold. **B,** After complete excision with a laser (not marsupialization).

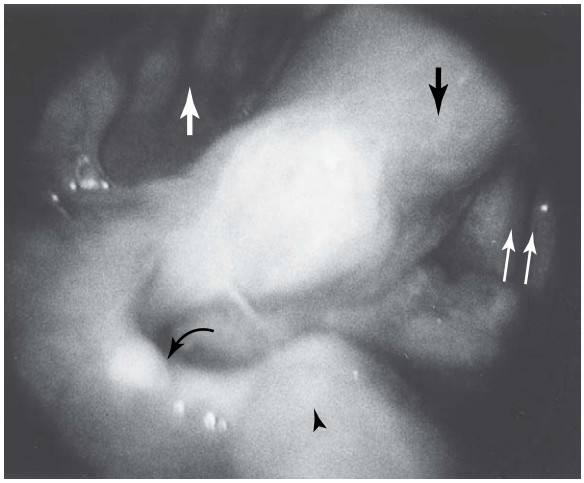

Figure 62-30. A voice laboratory view 1 week after complete endoscopic excision (not marsupialization) of a large lateral saccular cyst that had penetrated above the thyroid cartilage (direction of *curved arrow*) and outside the confines of the larynx. Parallel *small white arrows* demarcate the vocal folds. The *large white arrow* indicates the right pyriform sinus, and the *large black arrow* shows the right arytenoid apex. The wall of the cyst was followed surgically through the aryepiglottic fold, detaching the cyst from the epiglottis (*arrowhead*).

investigators also described the necessity for tracheotomy in 6 of 10 children, with a mean tracheotomy duration of 17 months. On the basis of this report, earlier definitive removal or aggressive marsupialization seems like a better option.

DeSanto and colleagues[38] reported on adult patients with saccular cysts and described endoscopic cyst avulsion for 29 cases of anterior cysts. Only one patient had recurrence of the cyst, which was later removed via laryngofissure. These researchers found anterior saccular cysts in association with laryngeal carcinoma in two of their cases, another finding that points to the need to rule out a small ventricular cancer in cases of saccular cysts or laryngoceles.

The experience of Holinger and coworkers[37] concerning 22 adults with anterior saccular cysts involved direct laryngoscopy and endoscopic removal with cup forceps. With this method, no cyst recurred. I have found that anterior saccular cysts are not infrequently incidental findings on examination performed for another reason; they can be followed if they are not causing symptoms.

For the larger lateral saccular cysts and laryngoceles, some controversy exists in the literature on the merits of primary endoscopic marsupialization versus an external approach.[35-45] Most writers seem to prefer the external approach for definitive removal in adults, particularly when an external component is present. This transcervical approach involves following the external portion (neck presentation) of the laryngocele or cyst sac through the thyrohyoid membrane. Some writers believe that removal of the upper portion of one side of the thyroid cartilage may be necessary to provide easier access to the endolarynx. The lesion is then transected as close as possible to the orifice of the saccule.

Many writers have cited the need for careful endoscopic examination and multiple biopsies to rule out laryngeal carcinoma in the ventricle as the cause of the laryngocele before definitive surgery. Removal of small internal laryngoceles, which are relatively rare, through laryngofissure or microlaryngoscopic techniques has been reported. Much of the literature seems to favor an external approach, but Hogikyan and Bastian[45] described complete endoscopic removal of large or recurrent saccular cysts. Their report on seven large lateral saccular cysts is well documented with preoperative and postoperative computed tomography scans and endoscopic photos. These researchers affirm complete *endoscopic excision* instead of endoscopic marsupialization or transcervical removal, even for large recurrent lateral saccular cysts. In this series, complete excision was possible on an outpatient basis for four of seven patients, and three were admitted for a single night's observation. None of the patients required tracheotomy, and none of the lesions has recurred several years later (Fig. 62-30). Since the time of this publication, I have also removed two combined internal-external saccular cysts with palpable neck components completely via endoscopic methodology. This approach requires following the cyst wall *endoscopically* over the top of the thyroid cartilage and into the neck.

The reader attempting complete removal of a saccular cyst via the endoscopic approach should note that even a large lateral cyst bulging dramatically during awake endoscopy can virtually disappear under conditions of direct laryngoscopy with general anesthesia. I have found that when that happens, one can begin by excising the false fold, during which maneuver the wall of the cyst is invariably encountered. In small and moderate lesions, one can often deliver the entire cyst intact by dissecting carefully along its external wall. When the lesion is unusually large, one may need to transect the presenting part of the cyst, decompress its gluelike contents, and then deliver the rest of the cyst by retracting or releasing its wall progressively into view through the laryngoscope.

Summary

Saccular disorders, whether laryngoceles or saccular cysts, can be easily diagnosed through appropriate history-taking, physical examination, and radiologic evaluation. Initial evaluation in adults should exclude the presence of an occult laryngeal carcinoma involving the ventricle, the region of the saccular orifice, or the saccule. Whether to use an endoscopic or external approach depends on the classifications of laryngocele or saccular cyst, its size, patient factors, and, perhaps most of all, surgeon experience and preference.

Benign Mesenchymal Neoplasms

Compared with the benign vocal fold mucosal disorders (e.g., nodules, polyps, cysts, sulci, contact ulcers), neurologic disorders, scarring or stenosis problems, malignant tumors of the larynx, and benign tumors of the larynx are rare. The literature sometimes incorrectly includes nonneoplastic mucosal reactive disorders (i.e., response to chronic injury), such as polyps and nodules, in the category of benign neoplasms.[46,47] Even when nonneoplastic reactive lesions are excluded, the cases of benign tumors in the literature are comparatively few when one considers the number of years covered by the reviews describing them. And if papillomas are excluded, laryngologists can expect to see only a few nonmalignant laryngeal neoplasms during their careers.

Epithelial Tumors

Recurrent Respiratory Papillomatosis

Squamous papillomas caused by the human papillomavirus (HPV), are the most common benign neoplasms seen by laryngologists (Figs. 62-31 and 62-32). Jones and colleagues,[47] who found that 84% of the benign laryngeal tumors they managed were papillomas, noted that this statistic matches those of other large series. On the basis of physician questionnaires about patients with recurrent respiratory papillomatosis, it is estimated that this entity occurs at a rate of 4.3 per 100,000 children and 1.8 per 100,000 adults.[48] HPV infection can be separated into many different serotypes by means of polymerase chain reaction methodology. The majority of infections are the result of subtypes 6 and 11. Type 11 appears to predispose to more aggressive disease, more frequent need for surgical intervention, and a higher risk of tracheopulmonary involvement.[49,50] Weiss and Kashima[51] reviewed 39 cases and also reported that a history of tracheotomy, a high number of endoscopic procedures, and a long duration of the disease seem to correlate with an increased incidence of tracheal involvement. I have also seen types 16 and 18, which are known to pose a higher risk of malignant transformation.

An association between genital condylomata in the mother and recurrent respiratory papillomatosis (RRP) in the child is known; however, the fact that only approximately 1 in 400 children at risk because of maternal infection actually experience RRP, as reported by Shah and associates,[52] suggests relatively low infectivity. Another study of 3033 births to mothers with genital condylomata yielded 57 cases

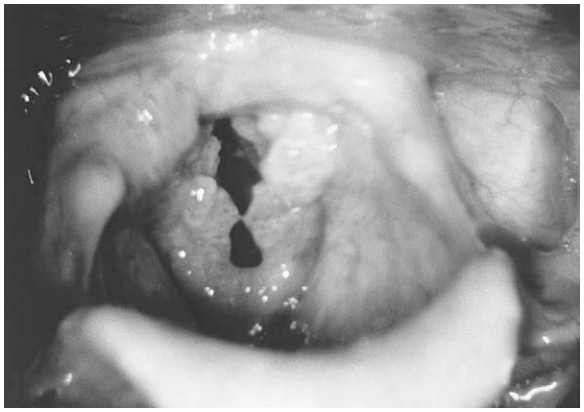

Figure 62-31. Diffuse recurrent respiratory papillomatosis distorts the contour of both true vocal folds and the right arytenoid apex. The dark dots represent the fibrovascular core within each papilloma.

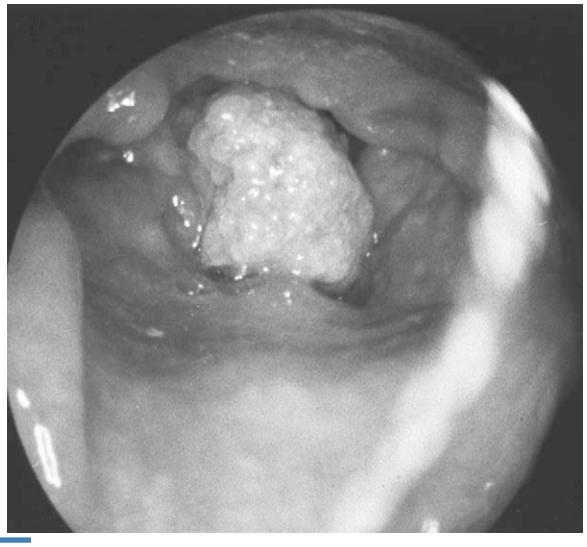

Figure 62-32. A large mass of papillomas obscures the vocal folds and airway. The patient has a tracheostomy tube.

of RRP, for a rate of 7 per thousand births to genitally infected mothers, a markedly greater incidence than that seen in uninfected mothers. Nevertheless, somewhat counterintuitively, cesarean delivery was *not* found to be protective against respiratory papillomatosis.[53] These kinds of findings make the question whether to perform cesarean section in the context of maternal infection controversial. A different question is whether children born to women with RRP (genital status unspecified) are likely to develop RRP themselves. Gerein and colleagues[50] found no cases of RRP among children and grandchildren of a group of German mothers with RRP or among those of a second group of Russian women with this disease. All the same, Mammas and associates[54] found HPV DNA in the specimens of 9 of 106 (8.5%) children after removal of hyperplastic tonsils and adenoids in whom no clinical papillomas were found.[54]

RRP may commence in childhood or adulthood. The juvenile form, almost always due to type 6 or 11 and commonly designated papillomatosis because of diffuse involvement of the larynx, usually manifests in infancy or childhood as hoarseness and stridor. This form of papillomatosis is often aggressive and rapidly recurrent, requiring frequent laryngoscopic removal for management. Rarely, papillomas may regress spontaneously, especially at puberty. On laryngoscopic examination, exuberant tissue resembling miniature clusters of grapes may be seen, especially on the anterior part of the true vocal folds, the false folds, and the epiglottis (see Fig. 62-32). The bulk of papilloma tissue can be so great as to obscure normal laryngeal landmarks.

Adult-onset papillomas are occasionally solitary or at least more localized than juvenile-onset lesions and are more likely to be of the "carpet variant." The latter morphology does not show the typical exophytic growth pattern, instead causing a velvety appearance with little projection from the surface. The red "dots" on the surface representing the fibrovascular core of each papilloma are still visible, however. Behavior of adult-onset papillomatosis may also be less aggressive, and, rarely, a single removal leads to "cure." However, adult-onset papillomatosis can also behave like the more aggressive juvenile-onset form.

The carbon dioxide laser remains the most widely accepted management for papillomas in the larynx; more than 100 laryngoscopic removals may be required to control these lesions during childhood, and sometimes they must occur every few weeks. The laser is useful because of its hemostatic properties (papillomas tend to be friable and vascular). In addition, the precision of the micro-spot laser allows for vaporization of the lesion plane by plane to avoid harming the underlying vocal fold. The microscopic débrider instrument is particularly useful in friable, exuberant cases that would require markedly more time to remove via laser "excision" or planar coagulation. That tool, however, is not very useful for the precise removal of the last "5%," nor for very flat "carpet" morphology.

Many other management modalities have been tried. Systematic reviews of the English literature suggest that the strongest current interest might be in the antiviral agent cidofovir.[55-57] Options such as cryotherapy, irradiation, photodynamic therapy, and vaccines such as Gardasil (Merck & Co., Inc., Whitehouse Station, NJ) are not yet validated or are even rejected by some for *treatment* of existing disease, although Freed and Derkay[58] have advocated use of the vaccine to *prevent* not only genital HPV infection but also RRP.

Although dramatic responses to interferon have been observed in some cases, the agent's long-term role in the management of laryngeal papillomatosis appears to be limited at best. In 1983, McCabe and Clark[59] reported a series of 19 patients with moderate to severe RRP that was managed with interferon. They found that 6 patients were disease free by visual criteria, 7 had a small amount of visible disease but not enough to require surgery, and 2 showed no response to interferon. These investigators also noted that the papillomas tended to regrow upon cessation of interferon therapy. Overall, they thought that during the time administered, interferon spared patients the need for multiple operations. In a later study, Leventhal and colleagues,[60] using higher doses and longer duration of interferon therapy, noted a significantly higher response rate; some responses appeared to be long-term. Similar findings arose in an even larger study by Gerein and coworkers.[50] Ogura and associates[61] reported the recurrence of papilloma after a 6-year interval in a patient who seemed to have achieved a durable response to interferon. I have used interferon according to the Leventhal criteria in 12 adults. Three achieved long-term remission after 6 months of treatment. Most of the rest had notable reduction of growth rate of the disease, sometimes on a durable basis, but not remission. Better understanding of the role of interferon in RRP awaits further study.

Another newer medical management modality uses indole-3-carbinol, a natural derivative of cruciferous vegetables such as cabbage and broccoli.[62] Anecdotal reports suggest that some patients who take this medication experience significant benefit. An estimated 30 of 110 patients in my adult practice have used this nutritional supplement, but with somewhat disappointing results. Case reports suggesting good results can be achieved, but perhaps they are more common in persons with more rapid growth of RRP than is often seen in adults.

Avidano and Singleton[63] reported the use of methotrexate in three patients with severe RRP that did not respond to interferon or *cis*-retinoic acid. All three experienced a prolonged interval before repeat surgery and reduced disease severity, but regression was not complete.

European investigators first wrote about the use of intralesional cidofovir as a treatment for DNA viruses, including HPV.[64-66] At least one anecdotal report showed disappearance of a papillomatous lesion of the esophagus injected serially with cidofovir.[67] Subsequently, others have shown good results with this medicine, either for regression or

remission of existing lesions or as an adjunct to surgery.[67-76] In my experience with more than 30 patients, rapidly growing and focal lesions seem to respond best. Some durable remissions are indeed achievable, and pending further experience, long-term remission appears feasible in approximately one in four adult patients when patients with slowly growing papillomas are included. Neither the investigators described nor I have seen scarring believed to be due to the use of cidofovir, except when an overly aggressive "bleb" was raised, depriving the mucosa of blood supply. Chhetri and colleagues,[76] however, in a study using a canine model, found atrophy and scarring that appeared to be worse with number of times injected and with increasing concentration of cidofovir. In this model, use of concentrations higher than 20 mg/mL, in particular, seemed to have this effect. The same group found no change in leukocyte count or renal parameters in doses up to 4.26 mg per kg body weight. The carcinogenic potential has never to my knowledge been proven for intralesional use of cidofovir, and it bears remembering that HPV infection itself has a documented risk for cancer.[50,77,78]

In a pilot study, McMillan and associates[79] described use of the 585-nm pulsed dye laser on three patients with RRP. As had previously been found by Tan and colleagues[80] for cutaneous warts, the hemoglobin in microvasculature selectively absorbed laser energy. In the McMillan study, either the carbon dioxide or the pulsed dye laser was used on different areas of papilloma growth. Papilloma response to both laser treatments appeared to be good, at least to the limited time of follow-up reported. Early edema seemed to be less on the side of the pulsed dye laser. This laser coagulates the microvasculature, owing to the red color of hemoglobin, but leaves the overlying epithelium relatively uncoagulated. The mechanism of action for regression of papillomas was said to be deprivation of oxygen and nutrients to the lesions. Franco and colleagues[81] subsequently used the pulsed dye laser on lesions in 41 patients. In about half of these, papillomas were treated with the laser but not removed. This group also noted marked response without evident scarring. As a continuation of long-established office-based surgery,[12,13] I use two office-based lasers. I use the pulsed potassium titanyl phosphate (KTP) laser, with hemoglobin as the chromophore, for small to moderate disease and especially for carpet-variant papillomas. The less selectively coagulating thulium laser (with the water molecule as the chromophore) is more useful for larger amounts of disease (Figs. 62-33 and 62-34).

Some of these medical management modalities hold promise; all need further investigation and validation. Thus, optimal management for RRP is careful serial laser laryngoscopic treatments with consideration of the investigational use of interferon, indole-3-carbinol, cidofovir, and, perhaps, the HPV vaccine if or when validated for this disease process.

Vascular Neoplasms

Polypoid Granulation Tissue

Fechner and colleagues[82] reviewed 639 vascular lesions of the head and neck, 62 of which were found in the larynx or trachea, and reported that polypoid granulation tissue is the most common vascular tumor in the larynx. They also noted that pyogenic granuloma does not occur in the larynx. Pyogenic granuloma, as seen most often on the tongue, consists of distinct lobules of capillaries separated by fibromyxoid stroma, whereas polypoid granulation tissue consists of radially arranged capillaries. These investigators attribute formation of polypoid granulation tissue in the larynx to one of several forms of trauma (i.e., caused by laryngeal biopsy, intubation, direct external trauma to the larynx, and an external penetrating wound). Granulation tissue in the larynx should be handled primarily by conservative measures, including removal of the source of any ongoing irritation (e.g., from inappropriate voice use or acid reflux laryngitis) and intralesional corticosteroids. For nonresponse and continuing symptoms, careful endoscopic removal may be considered after the granulation tissue has been allowed to mature and to become less active and vascular.

Laryngeal Hemangiomas

Infants with laryngeal hemangiomas often have associated cutaneous hemangiomas. These infants typically have respiratory symptoms

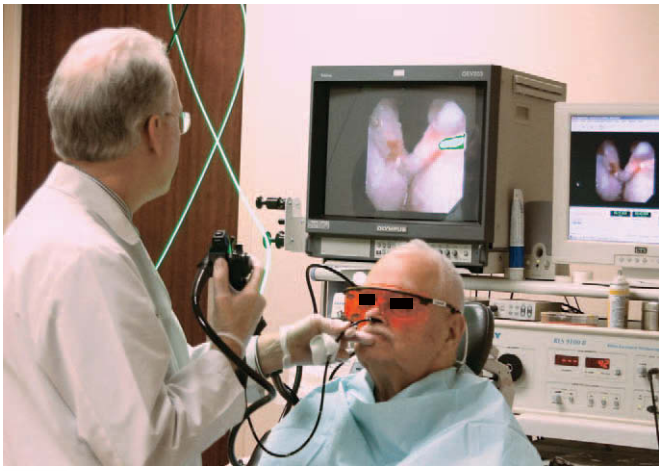

Figure 62-33. Pulsed KTP (potassium titanyl phosphate) laser treatment of chronic and recurrent keratosis with atypia.

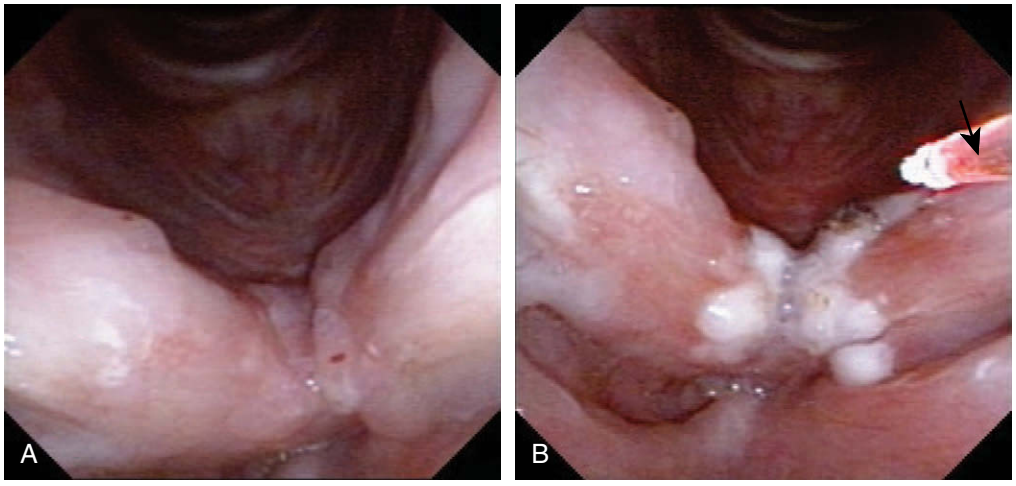

Figure 62-34. A, Papillomas primarily at the anterior commissure, before pulsed-KTP (potassium titanyl phosphate) laser treatment. **B,** Same larynx after treatment. Note the delivery glass fiber (*arrow*).

such as stridor and pseudocroup, usually within the first 6 months of life.

During direct laryngoscopy, a mucosa-covered mass with or without bluish coloration may be seen in the subglottis. Other suggestive findings are compressibility with palpation and shrinkage with administration of epinephrine.

In his review of the management of subglottic hemangioma in 1968, Calcaterra[83] addressed the then-prevalent practice of low-dose irradiation for subglottic hemangioma in infants. On the basis of experience in an infant with a large cavernous hemangioma that did not respond to irradiation as well as general knowledge of radiation's effect on vascular tissues, Calcaterra[83] suggested that this therapy was inadvisable. He suggested that tracheotomy be done when indicated for airway protection. This step allows the tracheal lumen to enlarge with growth of the child and, more importantly, gives the hemangioma an opportunity to involute spontaneously, as most such lesions do if they are left alone.

Later reports by Healy and colleagues[84] and Mizono and Dedo[85] explored the usefulness of the carbon dioxide laser for the management of this lesion. On the basis of 11 cases in the three centers reported by the authors, the researchers concluded that for the usual capillary hemangioma in the infant subglottis, the carbon dioxide laser is clearly superior to radiotherapy or corticosteroid therapy. They described the procedure as beginning with removal of tissue for histologic examination followed by simple vaporization of remaining abnormal tissue. These researchers also believe that if the tracheotomy was not required before the procedure for airway maintenance, it is probably unnecessary, provided that intense humidification is supplied in the immediate postoperative period. None of the patients reported in this series had significant complications, although four required a second treatment with laser for a satisfactory final result. All patients with previously placed tracheotomy tubes were successfully decannulated.

Adult hemangiomas are usually found at or above the level of the vocal folds. Because they are more often the cavernous form and are usually covered by thinner mucosa than the congenital hemangioma, adult hemangiomas appear more often as bluish, discolored masses.

Bridger and associates[86] reviewed literature on hemangioma in the adult patient, noting that in contrast to the congenital form, symptoms of this lesion may have been present for many years. Hoarseness is the expected symptom, and respiratory distress never occurs. Although hemorrhage may occur spontaneously, it is usually a surgical complication. These investigators advised that adult laryngeal hemangiomas be left alone if at all possible. They recommended that corticosteroid therapy or radiotherapy be used when necessary and that surgery of adult laryngeal hemangioma be undertaken when the hemangioma shows a tendency to involve progressively additional parts of the larynx, as occurred in one reviewed study. The carbon dioxide laser is not generally advised for adult cavernous hemangioma because the diameter of the vascular spaces exceeds this laser's coagulating ability.

Muscle Neoplasms

Rhabdomyoma

Most extracardiac rhabdomyomas are found in the head and neck region, especially in the pharynx and larynx. Winther[87] found 53 cases involving the hypopharynx or larynx in the literature up until 1976 and also supplied two case reports. He noted that none of these tumors recurred after local excision and advised that the approach be as conservative as possible for complete removal. He also noted that rhabdomyoma can be confused with a granular cell tumor or a rhabdomyosarcoma. Modlin[88] also stressed the need to differentiate between rhabdomyoma and granular cell tumor and noted that complete local excision is curative.

Neoplasms of Adipose Origin

Lipoma

Zakrzewski,[89] in his review of the literature through 1965, believed that only 70 of many cases reported as laryngeal lipomas actually involved the larynx and were sufficiently described to allow for analysis of this entity. He noted, however, that 23 of the 70 cases had some other tumor characteristics, such as fibrolipoma, myxolipoma, nervous tissue, cyst fragments, and angiolipoma. Although laryngeal lipomas were sometimes seen among persons with numerous lipomas in other body areas, most were isolated occurrences.

Of 70 cases, 54 were designated extrinsic, whereas only 16 were classified as true intrinsic laryngeal tumors. Because lipomas occurred more frequently in parts of the larynx in which fat was a normal part of the subepithelium, most tumors arose on the aryepiglottic fold and epiglottis (the periphery of the laryngeal vestibule). Of the intrinsic tumors, the most common site of origin was the false vocal fold. Only one case involved a true vocal fold.

Because lipomas are slow growing, symptoms were often present for many years before diagnosis. In general, respiratory symptoms were most common, and hoarseness was relatively infrequent.

Surgical management was successful. Procedures such as endoscopic removal, subhyoid pharyngotomy, lateral pharyngotomy, and laryngofissure were used according to tumor size and location. The guiding principle was conservative with complete removal or enucleation because incompletely removed lipomas regrow.

Benign Neoplasms of Glandular Origin

Benign Mixed Neoplasm

Benign mixed tumors (pleomorphic adenomas) are extremely uncommon in the larynx. Som and coworkers[90] found only 27 cases of this tumor involving the larynx in the literature up to 1979, and they supplied one case report. Most of these tumors involved the subglottic laryngeal region, and only 6 involved the supraglottis. These researchers described the typical appearance as that of a smooth, ovoid submucosal mass. As is the case for most other benign laryngeal tumors, the approach to surgical excision of a benign mixed neoplasm of the larynx depends on the tumor's size and location.

Oncocytic Neoplasms of Larynx

According to the literature, oncocytic tumors are actually oncocytic metaplasia and hyperplasia of the ductal cell portion of glandular tissue. Gallagher and Puzon[91] found that 18 of 19 cases in their series were cystic and concluded that these lesions represent duct metaplasia and hyperplasia rather than true neoplasia. One solid tumor in their series was considered an oncocytic adenoma, as seen in the parotid gland.

Lejeune and associates[92] reported a case of a woman with numerous cystic oncocytic lesions of the epiglottis, aryepiglottic folds, false vocal fold, and right true vocal fold, supporting the opinion of Gallagher and Puzon.[91] Lundgren and colleagues[93] presented a series of seven oncocytic cysts of the larynx and agreed that these lesions represent glandular duct metaplasia and hyperplasia rather than true neoplasia.

All of these writers seem to agree that simple excision, by whatever approach necessary according to lesion size and location, is the management of choice.

Cartilaginous Neoplasms

Chondroma

Although an attempt to differentiate histologically between chondroma and low-grade chondrosarcoma has been made, Mills and Fechner[94] believe that the behaviors of the chondromas and the low-grade chondrosarcomas are so similar that histologic distinction has little practical significance. Because neither grows quickly or metastasizes, the clinical approach to these entities can be the same. Neel and Unni,[95] in their experience with 33 patients, noted that most patients had an "obvious smooth rounded mass covered by mucous membrane in the subglottic region of the larynx," and in most cases this mass was situated posteriorly and laterally.

Neel and Unni[95] did not tabulate symptoms separately for benign and malignant cartilaginous tumors; symptoms consisted mainly of hoarseness, dyspnea, neck mass, and dysphagia. These writers used laryngofissure most often for tumor removal and total laryngectomy for high-grade malignant tumors.

Singh and associates,[96] in a review of laryngeal tumors seen at four major hospitals between 1960 and 1977, found only two cartilaginous tumors of the larynx, but they found 177 cases reported in the English literature. Of cartilaginous tumors, 70% arose in the cricoid cartilage, primarily from the posterior plate. The growth of these tumors is mostly intraluminal, with a rare case appearing externally into the neck. These writers believed that because chondrosarcomas are usually indolent and rarely metastasize, local resection, if technically feasible, is adequate management. They described laryngofissure with submucosal resection as the most common approach to these tumors, unless the cricoid would be collapsed entirely by its subtotal removal.

Hyams and Rabuzzi,[97] in a series of 31 cartilaginous tumors of the larynx, found 15 chondromas and 16 chondrosarcomas. The chondromas occurred in a slightly younger age group than the chondrosarcomas. However, the chondromas included nine "chondromas of the true vocal cord," which probably represent metaplasia of the elastic connective tissue of the vocal fold rather than true chondromas.

Neoplasms of Neural Origin

Granular Cell Neoplasms

Mills and Fechner[94] noted evidence indicating that granular cell tumors originate in Schwann cells; these tumors had previously been called granular cell myoblastomas because they resemble muscle tissue with standard staining techniques. A notable characteristic of granular cell tumors is frequent association with overlying pseudoepitheliomatous hyperplasia of the mucosa. Insufficiently deep biopsy of this lesion can lead to an incorrect diagnosis of epidermoid carcinoma.

Although granular cell neoplasm can involve any part of the larynx, the middle to posterior part of the true vocal fold is the most common site, and hoarseness is thus the most common complaint. Conservative but complete local excision is considered definitive therapy.[98-101]

Neurofibroma

Chang-Lo[102] reviewed 19 previously reported cases of von Recklinghausen's disease with laryngeal involvement and supplied 1 case. Supance and colleagues[103] reported that solitary neurofibromas of the larynx not associated with von Recklinghausen's disease were more common than those associated with the disease. The most common symptoms in patients with laryngeal involvement by von Recklinghausen's were hoarseness, dyspnea (most striking), and dysphagia. On physical examination, lobulated nodules ranging from less than 2 to 8 cm in diameter were noted, and the most common site of origin was the arytenoid or aryepiglottic fold.

Because these lesions are benign, the surgical approach should balance conservatism with the need for complete excision. For larger tumors, an external approach (e.g., lateral pharyngotomy, laryngofissure, lateral thyrotomy) may be needed.[104]

Neurilemmoma

Neurilemmomas are less common than neurofibromas and usually involve the aryepiglottic fold and false vocal fold. Symptoms correspond with the slow growth of these lesions and can include a sensation of fullness in the throat, voice change, and slow development of respiratory distress. Management should consist of conservative but complete removal by an approach consistent with tumor size and location. Neurilemmomas are more encapsulated than neurofibromas; simple enucleation (e.g., by a lateral thyrotomy) with removal of a portion of the thyroid cartilage is believed to be adequate management.[105,106]

Summary

True benign neoplasms of the larynx do not include benign (reactive) vocal fold mucosal disorders. If papillomas are excluded, the number of persons with laryngeal neoplasms is small; busy laryngologists infrequently see these lesions. The basic management principles are similar for these tumors, regardless of the cell of origin. Removal should be complete but conservative (to spare the voice), with the approach determined primarily by tumor size and location.

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CHAPTER SIXTY-THREE

Acute and Chronic Laryngitis

Albert L. Merati

Key Points

- Acute and chronic laryngitis overlap and do not correspond to causes of inflammation.
- The impact of laryngitis includes both short-term dysfunction during the acute phase of inflammation and secondary effects of the inflammatory process, such as scar formation.
- The most common cause of *chronic laryngitis* in patients cared for by otolaryngologists is reflux. The most common cause of *acute laryngitis* in the general population is viral, as part of an upper respiratory infection. The true incidence of these two entities is not known.
- Candidal laryngitis is common and can occur in immunocompetent individuals.
- New investigation into individual susceptibility to various laryngeal injuries may explain the variation of clinical presentations in gastroesophageal reflux.

Of all the terms in the realm of the otolaryngologist, "laryngitis" may feature the greatest discrepancy between its familiar meaning for the lay public and its broad implications for specialists in the field. Although *laryngitis*, or inflammation of the larynx, does indeed include many varied and complex abnormalities, the basic distinction between *acute* and *chronic* laryngitis is reasonable and will serve to organize this chapter. In the following sections, disorders resulting in laryngeal inflammation are presented along with general concepts about laryngeal tissue response to injury and the larynx as an immunologic organ.

Why Does Laryngitis Matter?

There are several broad reasons why laryngitis is significant. *Functio laesa*, the often overlooked "fifth sign" of inflammation (along with *rubor, tumor, dolor,* and *calor*), describes the loss of function in an inflamed organ, be it the liver in hepatitis or the hoarse voice of a patient with vocal fold edema related to viral laryngitis. The inflamed larynx does not phonate, swallow, or breathe well. In the extreme, this condition can lead to airway obstruction as seen in *epiglottitis*. Function may also be impaired after the resolution of the inflammatory process. In an important paper, Squire and associates[1] demonstrated that the introduction of bacteria into an acquired airway injury in the rabbit model resulted in a higher rate of stenosis than seen in the controls; this effect was muted by the addition of antibiotics to the model. Fine degrees of dysfunction from bacterial infection have not been clearly described, however. In an innovative study, Reidy and colleagues[2] exposed subjects to aerosolized antigens (to which they were known to have skin-test responsiveness). In this investigation, the subjects' larynges did demonstrate greater mucus and other signs of irritation after exposure; their objective laryngeal parameters, such as acoustic voice parameters, did not change.

Finally, although it is not proven, many have suspected the relationship between laryngeal inflammation and malignant transformation. The most commonly considered mechanism is injury from refluxed materials. It was proposed many years ago by Ward and Hanson[3] and has been further supported by the work of Koufman[4] and Qadeer and associates.[5-8]

Acute Laryngitis

Phonotrauma

Vocal abuse, misuse, and overuse can contribute to phonotrauma. This may result in vocal fold hemorrhage and edema in addition to incurring changes at the molecular level.[9,10] Although this process does not represent the usual concept of infectious or "exogenous" sources of inflammation, the tissue response to injury can be quite profound. The problem of vocal abuse and strain may be exacerbated by dehydration through its effect on phonation threshold pressure.[11,12] On the basis of common clinical experience, many practitioners believe that vascular lesions of the vocal fold may begin or may be exacerbated by acute phonotrauma. In the case illustrated in Figure 63-1, a young singer noted the moment her voice changed during a performance. Examination of her vocal folds in the clinic revealed a left true vocal fold lesion with feeding vessels. Despite excellent hygiene, voice therapy, and conservative management, the lesion did not resolve, and she required phonosurgical intervention.

In the great majority of cases involving phonotrauma, medical attention is not sought. A patient who does seek care from an otolaryngologist is most likely to have recurrent or severe symptoms—or to be particularly sensitive to his or her vocal health. Clinical examination should include a detailed history and fiberoptic examination and stroboscopy, if available. There is little to no scientific basis for the usual treatments—voice rest, steroids, and other medications. Anecdotally, however, voice rest is quite useful to reduce further acute injury, particularly if there is a hemorrhagic component to the laryngeal injury. Paradoxically, some degree of mechanical strain (in the truest physics sense of the word) may be beneficial to appropriate vocal healing. Branski and colleagues[13] have elegantly shown that low levels of mechanical activity may actually reduce inflammatory activity in vocal fold fibroblasts. This finding may be elucidated by further investigation

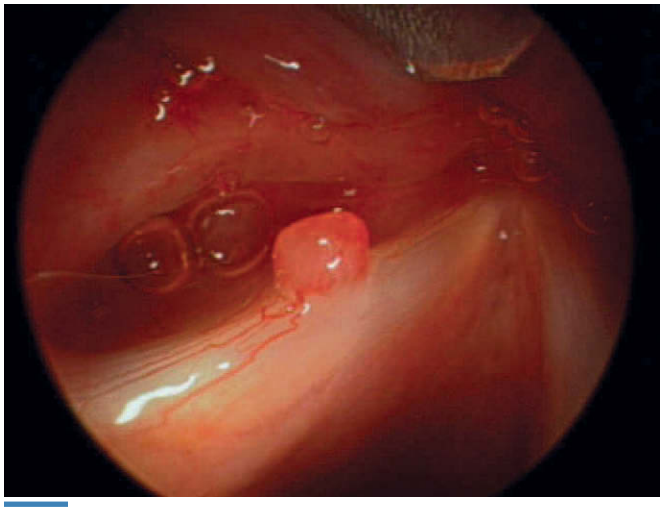

Figure 63-1. Intraoperative photograph from a 70-degree telescope of the left true vocal fold of a young singer who reported acute vocal changes during a performance. Clinical examination revealed this pedunculated lesion with surrounding inflammatory vessels. Medical and speech language intervention did not resolve her condition. She underwent successful phonosurgical removal of the lesion. Note the absence of pathologic vessels on the right vocal fold.

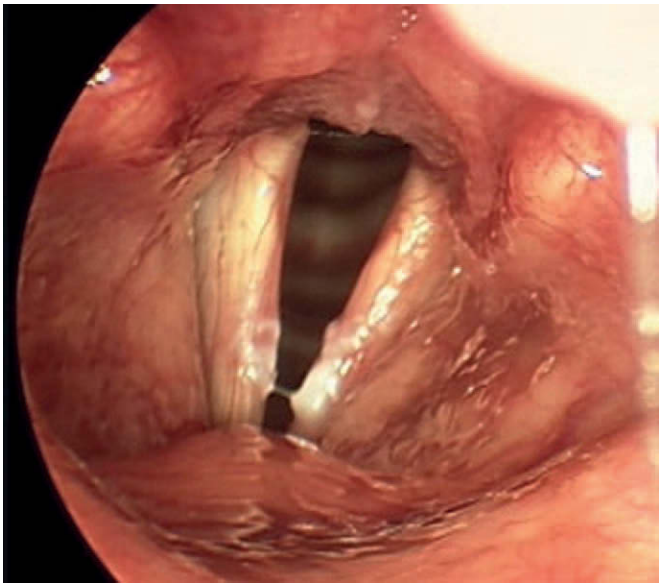

Figure 63-2. 60-year-old woman with several months of hoarseness. She had been using a steroid inhaler. Examination with a transoral rigid laryngoscope showed raised whitish plaques of the membranous vocal folds. These responded promptly to antifungal treatment. *(Image courtesy of Lucian Sulica, MD, Cornell University School of Medicine, New York.)*

as our understanding of the molecular basis of vocal fold injury improves.

Viral Laryngitis

The precise incidence of viral laryngitis is not known, reflecting its familiarity and its association with the ubiquitous viral "upper respiratory infection." When it does occur, it may be due to typical "common cold" viruses, such as the rhinovirus. Many other viruses have been implicated in cases of acute viral laryngitis, including herpes zoster,[14,15] coronavirus,[16] as well as less familiar agents. There is no specific knowledge that antiviral treatments have any predictable impact on the clinical course of viral laryngitis. Supportive care, including rehydration and vocal rest, are commonly recommended. In one double-blind, placebo-controlled study, flurbiprofen, an anti-inflammatory medication, was shown to decrease discomfort in patients with viral laryngitis.[17]

In severe cases resulting in airway embarrassment, this aspect of clinical care naturally takes precedence. Medical management of the impaired and inflamed airway is familiar to readers from the airway chapters in this volume; it includes the use of steroids, antibiotics for secondary infections, proton pump inhibitors, and humidification. Although much of this approach has remained experiential and anecdotal, one prospective, double-blind, randomized study in children demonstrated better outcomes when dexamethasone was used in acute laryngotracheitis (croup) if given in the first 24 hours of treatment.[18]

Acute Bacterial Laryngitis

Much of this discussion, historically as well as in this edition, deservedly rests in the pediatric section. Epiglottitis—or, more properly, supraglottitis—continues to be a life-threatening infection of the upper airway in adults as well. Despite the great success of the *Haemophilus influenzae B* vaccine in limiting the frequency of this disorder,[19] the clinical entity acute upper airway obstruction from bacterial infection of the larynx continues to occur. The presentation is often quite dramatic, with an urgent call to the emergency department for a drooling, febrile patient in respiratory distress. Depending on the acuity of the airway embarrassment, the *adult* patient may be examined fiberoptically to characterize the nature of the obstruction; determination of the severity of the obstruction and the clinical decision-making, however, are based on a generalized assessment of the patient's overall appearance in addition to nonlaryngeal airway considerations, such as body habitus, jaw and mouth opening, and neck extension. If the patient requires airway intervention, intubation in a controlled setting (such as the operating room) or awake tracheotomy may be appropriate. This having been said, a review of 23 adult supraglottitis cases revealed that the minority (3/23) of cases required airway intervention.[20] The remainder may be managed supportively, with humidification, intravenous antibiotics, close observation, and even with steroids.[21]

Laryngeal infection with *Klebsiella rhinoscleromatis*, part of the disorder known as rhinoscleroma, is another clinical entity that can affect the larynx. The disease may progress to airway obstruction with tracheal involvement but may be limited to rhinologic and vocal fold involvement. The disease is diagnosed from the identification of the causative organism, a gram-negative coccobacillus, within macrophages obtained from mucosal biopsy specimens. These are the characteristic Mikulicz cells of rhinoscleroma. The disease may be treated with fluoroquinolone antibiotics, tetracycline, and supportive airway management.[22] Patients with this disease may also need acute as well as long-term surgical airway management; Amoils and Shindo[23] reported on a series of 22 patients with rhinoscleroma, 13 of whom had laryngeal involvement.[23] Of these 13, 3 had undergone tracheotomy at some point during the clinical course.

Acute Fungal Laryngitis

In this section, laryngeal dysfunction from *Candida albicans* is discussed; several other pathogenic fungal species are more appropriately reviewed in the chronic laryngitis section. As in many sections of this chapter, the distinction between acute and chronic inflammation is somewhat arbitrary; many of the disorders feature both acute and chronic inflammation.

Candidal laryngitis is probably quite common, although its recognition as a clinical entity has increased. Sulica[24] provided a succinct review of this disorder in 2005. Patients typically present with hoarseness with or without accompanying throat discomfort. The most characteristic finding is a diffuse, whitish speckling of the vocal folds or supraglottis (Fig. 63-2); this can be quite similar to that seen in thrush affecting the oral cavity and soft palate. Perhaps the most important lesson in the clinical recognition of laryngeal candidiasis is for the

physician to suspect its presence in both immunocompromised and immunocompetent individuals. There are very few causes of white lesions on the surface of the vocal fold epithelium; the differential diagnosis includes hyperkeratosis/leukoplakia, malignancy, thick mucus, and candidal infection. Although formal culture is required to confirm the diagnosis, it is neither practical nor common. It has been theorized that patients with local risk factors, such as the recent use of broad-spectrum antibiotics or topical (inhaled) corticosteroids, are more prone to development of this problem. This theory is clinically reasonable but such an association is not exclusively the case; *Candida* should be included in the differential diagnosis of a great range of patients with epithelial abnormalities of the larynx.[25]

Candida may also become invasive with fulminant inflammation and erosion. This development requires aggressive medical treatment, including consideration for parenteral antifungal medication and airway support.[22]

Chronic Laryngitis

As noted previously, the distinction between acute and chronic laryngitis is not necessarily a strict one; many of the disorders discussed in the section on acute laryngitis may also contribute to chronic dysfunction. In this section, several key infectious causes of chronic laryngitis are reviewed along with reflux-associated laryngeal inflammation.

Bacterial Laryngitis

Although most otolaryngologists associate bacterial infection of the larynx with an acute process, chronic, even life-threatening disease may arise in this situation. Superinfection of the larynx may complicate intubation injuries or larynges already damaged from relapsing polychondritis, for example. Eliashar and colleagues presented several case examples of this occurrence.[26] In each of the three cases outlined, purulent chondritis was noted in patients with prolonged (longer than 1 month) of hoarseness and stridor. These patients required surgical drainage and ongoing medical treatment. In two of the three cases, the pathogen was *Staphylococcus aureus*. Clinicians should suspect bacterial infection, regardless of its relative rarity, in patients who have persistent chronic inflammation of the larynx. Culture and drainage of abscess spaces may be required. The role of hyperbaric oxygen is not widely agreed upon for this disorder or even for chondroradionecrosis of the larynx, which is discussed elsewhere in this volume.

Fungal Laryngitis

The larynx may also become infected with pathogenic fungal species. The organisms include *Blastomyces, Histoplasma, Coccidioides, Paracoccidioides,* and *Cryptococcus* spp. In general, the clinical presentation of laryngeal fungal infection is not specific to the pathogen, but reflects general disturbance of laryngeal function—that is, consists of hoarseness and throat discomfort. Tissue biopsy and fungal stains are needed to confirm the diagnosis. The less common pathogens are not discussed in detail, although laryngeal infection with *Sporothrix,*[27] *Aspergillus,*[26,28] and *Cryptococcus* spp.[29,30] have been reported.

Blastomycosis

Blastomycosis is endemic in several areas, including the southern parts of the United States.[31] Although this fungus enters the system by inhalation, laryngeal infestation is thought to arise, like infestation of other organs, from hematogenous spread.[32] In a major paper from the Mayo Clinic, 102 cases of blastomycosis were found in a retrospective review of patients seen between 1960 and 1990.[33] In these 102 cases, the minority affected the head and neck area; in blastomycosis of this area, the skin was the most common site impacted. Only 5 of the 102 cases featured laryngeal involvement. The diagnosis is made when suspicious lesions are noted in the larynx, often involving the glottis. Fungal stains of the involved tissue may reveal the broad-based budding yeast. Treatment includes systemic therapy, such as with amphotericin B, ketoconazole, or itraconazole. The practitioner must be particularly cautious to distinguish blastomycosis from laryngeal carcinoma; like many inflammatory disorders, fungal laryngitis may manifest in a clinical picture similar to that seen in a new laryngeal cancer; furthermore, biopsies of involved tissue may reveal *pseudoepitheliomatous hyperplasia,* which may be mistaken for the advancing front of an epithelial malignancy.[34]

Paracoccidioidomycosis

Paracoccidioides appears to be one of the leading pathogens in invasive fungal laryngitis. Although not common in comparison with other laryngeal maladies, paracoccidioidal infection of the larynx affects a significant fraction of patients in South America. As in most of these disorders, the primary manifestation is dysphonia with dyspnea.[35] Most of the patients in the series reported by Sant'Anna and associates[35] were male farm workers. Laryngeal examination revealed both ulcerative and exophytic lesions, which like those in blastomycosis resembled carcinoma. Silva and colleagues[35a] looked retrospectively at a series of 24 patients with granulomatous laryngitis, 10 of which proved to have paracoccidioidal infection. Treatment is with systemic antifungals.

Coccidioidomycosis

Coccidioidomycosis is a disease of the southwestern United States and Mexico; it is thought that the larynx may be the site of inoculation in some patients. Little has been written about this disorder, however. A 1991 review from Boyle and coworkers[36] noted 12 cases of laryngeal coccidioidomycosis, 7 of which were in children. Most cases were in boys or men, who presented with airway obstruction.

Histoplasmosis

The causative agent in histoplasmosis, *Histoplasma capsulatum*, is a fungus endemic to areas of the United States; it is found in the Ohio and Mississippi River valleys, and its spores may be inhaled, leading to localized pulmonary infection or dissemination. It is possible for this infection to occur outside of endemic areas. There are few reported cases of laryngeal histoplasmosis; Gerber and colleagues[37] reviewed a series of 115 patients with disseminated disease in order to characterize the incidence of otolaryngologic findings. Seven of these patients had oral cavity/oropharyngeal infection; only two cases featured laryngeal disease. Eight of the 9 patients with otolaryngologic manifestations were immunocompromised, such as from human immunodeficiency virus disease, kidney transplant medication, and diabetes. In 8 of these 9 patients, the response to fungal staining of the acquired tissue sample was positive. Gerber and colleagues[37] reported better treatment results with amphotericin than with fluconazole. As with other fungal and atypical laryngeal infections, writers have cautioned against the misdiagnosis of histoplasmosis as carcinoma.[38]

Mycobacterial Laryngitis

Laryngeal tuberculosis may affect patients with and without disseminated tuberculosis (TB). The bulk of this discussion reviews existing knowledge regarding laryngeal TB. One other mycobacterial infection, *leprosy*, also deserves mention here. In this generally tropical disease, the causative agent, *Mycobacterium leprae*, is transmitted via aerosolized droplets and may remain highly contagious, although it does not always lead to clinical disease.[32] This disease is found in South America, Africa, and the Asian subcontinent; the countries with the highest incidence are Brazil, Mozambique, and India. More than a third of patients with disseminated leprosy in India were noted to have laryngeal involvement.[32] As in TB, staining of tissue biopsy specimens demonstrates acid-fast bacilli and granuloma formation (Fig. 63-3). Multiple-drug regimens may be required for more than 1 year to eradicate the disease.

The recognition and treatment of laryngeal TB requires an awareness of the typical clinical scenario and laryngeal findings associated with the disorder. In the past, laryngeal TB was highly associated with disseminated disease or at least with active pulmonary TB. In a paper from Korea, however, Lim and colleagues[39] reviewed 60 cases of laryngeal TB over a 10-year period. The mean age of the patients was 50 years; there was a 2:1 male preponderance in the series. Hoarseness was nearly uniform in these patients. Laryngoscopic findings were divided between granulomatous and ulcerative lesions, with an increasing likelihood of polypoid and unilateral findings. The true and false vocal folds were the most commonly affected sites. Twenty-eight of the

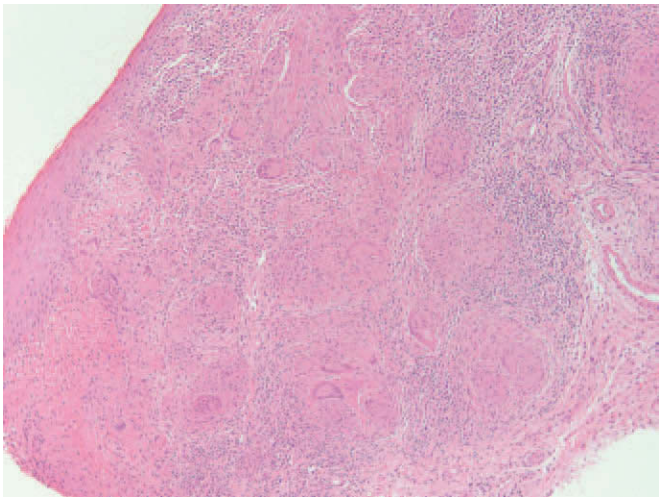

Figure 63-3. Hematoxylin and eosin stain of laryngeal tuberculosis demonstrating granuloma formation. *(Image courtesy of Hong-Shik Choi, MD, Yonsei University College of Medicine, Seoul, Korea.)*

60 patients (47%) had *active* pulmonary disease; 20 of the 60 (33%) had inactive pulmonary TB, and 9 (15%) had isolated laryngeal TB. Lim and colleagues[39] made special note of the focal, atypical, and unilateral laryngeal findings in patients without active pulmonary disease. In another study, a series of 319 Turkish patients with pulmonary TB were assessed for laryngeal disease[40]; 5 of the patients (1.5%) had apparent laryngeal symptoms and findings. In this study, odynophagia, not hoarseness, was the most common complaint. In a separate paper, several of the authors of the first paper demonstrated perceptual and objective improvement of vocal parameters in patients with laryngeal TB who were undergoing medical therapy.[41]

Noninfectious Laryngitis

The most clinically significant causes of laryngitis in the otolaryngologist's practice are often related to poor laryngeal hygiene (tobacco, alcohol, and caffeine consumption) or to the refluxate of gastric and duodenal contents. A detailed description of the impact of reflux on the larynx as well as other organs in the head and neck is given elsewhere in this volume. The topic deserves some discussion here, however.

Reflux Laryngitis

The larynx may be affected by contact with refluxed material from the lower foregut. The vast majority of such contact events are thought to be acidic in nature; the recognition of acidic injury to the larynx has been one of the key advancements in laryngology in the past few decades.[4] This issue is not without controversy, however. The rates of medical management of presumed reflux affecting the larynx and pharynx have risen[42] despite the lack of compelling evidence in double-blind, placebo-controlled trials.[43] The complete discussion of the impact of acidic refluxate on the larynx is found elsewhere in this text. It is possible, however, that investigation into nonacidic reflux as well as into the significance of patient susceptibility to injury in reflux (and perhaps other laryngeal disorders) will yield a deeper understanding of this issue.

Bile has been implicated as a possible source of laryngeal injury for many years. The presence of biliary (alkali reflux) continues to be a possible explanation for the lack of response to anti-acid therapy in chronic laryngitis. In an elegant animal study, however, Adhami and colleagues[44] showed that bile was injurious to laryngeal mucosa, but only in the presence of acidification. In contrast, Sasaki and coworkers[45] demonstrated epithelial injury in the rat laryngeal model when the larynx was exposed to certain bile salts at neutral pH, that is, in the absence of an acidic environment. Although this key theoretical foundation of our understanding of bile injury continues to be evaluated, Galli and associates[46] have provided some interesting observations

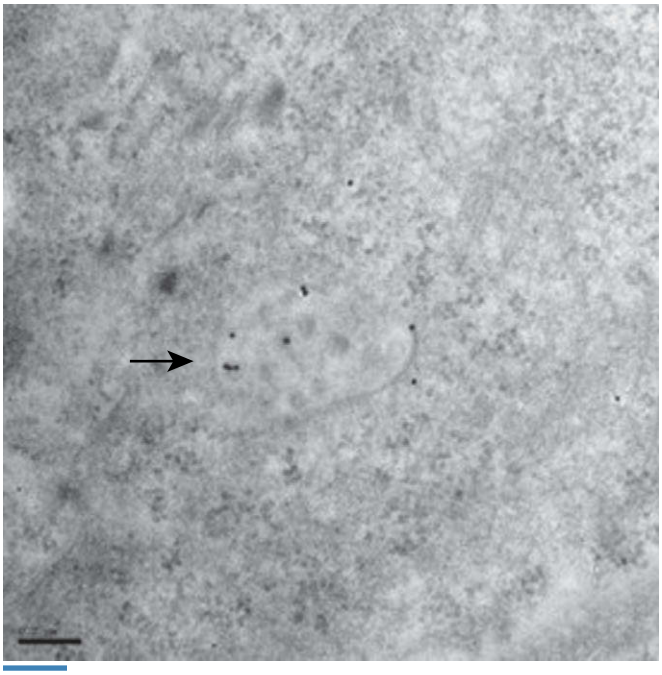

Figure 63-4. Pepsin (*arrows*) within an intracellular vesicle of human laryngeal epithelium from a patient with laryngopharyngeal reflux (*bar* = 0.2 μ). *(Image courtesy of Nikki Johnston, PhD, Medical College of Wisconsin, Milwaukee.)*

about reflux and its association with laryngeal carcinoma; their case-control study of 21 patients with laryngeal and hypopharyngeal carcinoma revealed a higher than suspected incidence of malignancy in patients who had undergone previous gastrectomy, suggesting a correlation to chronic exposure to duodenal contents and biliary reflux.

Pepsin is another agent suspected in the ongoing description of laryngeal injury from reflux. The main proteolytic agent produced by the stomach, pepsin is active principally at acidic pH. In the animal study previously cited,[44] pepsin clearly demonstrated the ability to create laryngeal epithelial injury at acid pH. Later studies, however, have expanded our understanding of pepsin's role in laryngeal damage. Johnston and colleagues[47] demonstrated that pepsin is present intracellularly in patients with the clinical diagnosis of laryngeal reflux and is not present in controls; its presence was also correlated with the depletion of intracellular carbonic anhydrase (type III). Pepsin was found to maintain its proteolytic activity at pH above 4 and was able to be "reactivated" even after being in a neutral environment.

The significance of these findings may prove to be great; the model for treating acidic injury of the larynx has depended on neutralization of the proton pump in the stomach. If indeed pepsin can maintain the ability to damage tissue even after neutralization (particularly after receptor-mediated uptake into epithelial cells[48]), the paradigm of reflux disease and the larynx must be reconsidered (Fig. 63-4). Patient-to-patient variability in ability to prevent and withstand injury, such as manifested by differing levels of protective intracellular enzymes, may also play an important role in this clinical entity. In two patients with the same DeMeester score or acid exposure time on a 24-hour pH probe, for example, laryngeal injuries may differ greatly.

The Larynx as an Immunologic Organ

Although great attention has understandably been focused on other areas of the head and neck with regard to immunologic manifestation of disease, the larynx's role is not well defined. Barker and colleagues[49] have described the presence of major histocompatibility complexes (MHCs) in the porcine larynx and have estimated that this finding is a marker of the role that the larynx might play in the afferent aspect of environmental allergy and defense. Interestingly, the immunogenicity of the larynx has been investigated not for the ubiquitous issues of

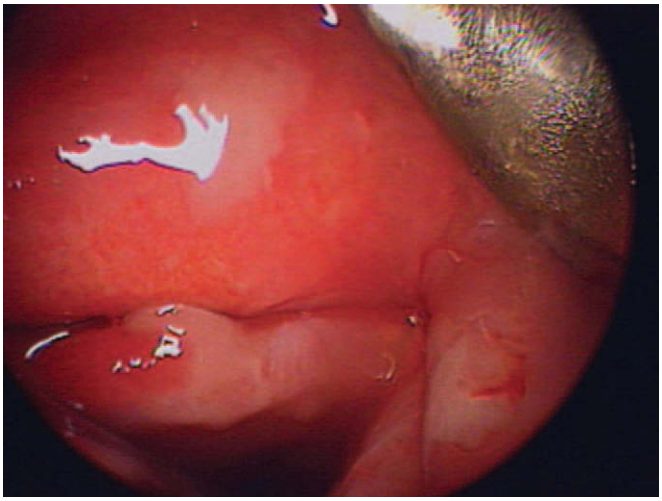

Figure 63-5. Pemphigus vulgaris in a 57-year-old woman who presented with throat pain and hoarseness. This image of the left false and true vocal folds was obtained with a 70-degree telescope during direct laryngoscopy.

mild chronic laryngitis but in order to better understand and potentially overcome obstacles in the path towards the lofty (and controversial) goal of human laryngeal transplantation.[50] Rees and associates[51] have also investigated a particularly compelling aspect of laryngeal immunology as it relates to possible carcinogenesis. Laryngeal mucosal biopsy specimens from 63 patients were assessed for various cell surface markers; those from smokers, for example, had increased numbers of $CD4^+$ T cells. Older patients also had higher numbers of these cells, but in contrast, female patients had lower counts of $CD4^+$ positive cells. Several other markers were tested as well, with some being affected by patient factors and some not. The investigators concluded that laryngeal T-cell populations may be influenced by smoking (as well as age and gender), and that this influence itself contributes to the genesis of inflammatory and even neoplastic disease of the laryngeal epithelium.

The larynx may be the end-organ affected by autoimmune disorders, such as pemphigoid and pemphigus (Fig. 63-5). Severe epithelial loss and inflammation may occur from the effect of either intraepithelial (pemphigus vulgaris) or subepithelial (pemphigoid) antibodies. Hale and Bystryn[52] noted that as many as 80% of the patients with pemphigus in their study had otolaryngologic signs and symptoms, of which 40% were laryngeal in nature. Several patients had coexistent fungal infection. Alexandre and coworkers[53] published a prospective paper describing the manifestations of *pemphigoid* in a series of 110 patients over an 8-year period. Thirty-eight of these patients (35%) were found to have some symptoms related to the head and neck; 87% of these 38 patients had physical findings at that time. The majority had nasal symptoms; 19 (50%) had pharyngeal complaints, and 10 (26%) had laryngeal symptoms; nearly 50%, however, had laryngeal findings, indicating that laryngeal involvement was asymptomatic in a large fraction of patients. The presence of advanced ocular pemphigoid was predictive of laryngeal involvement, as was the presence of concomitant nasal and pharyngeal disease.

Conclusion

As we move forward in our understanding of the pathophysiology of laryngeal inflammation and infection, a complete appreciation of each patient's inherent tissue response to injury and genetic resistance may be of greater importance to the clinician. This may manifest through diagnosis and management of laryngeal immunologic abnormalities or by affecting a patient's ability to negate the effect of intracellular pepsin, for example. At present, however, we must recognize the varied pathogens and agents that may induce inflammation of the larynx and affect its function. The possibility of neoplasm should always be considered when signs point to infection; the possibility of infection, however, should be considered when neoplasm seems like the "obvious" clinical diagnosis.

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CHAPTER SIXTY-FOUR

Laryngeal and Tracheal Manifestations of Systemic Disease

Kevin P. Leahy

Key Points

- The spectrum of laryngeal and tracheal symptoms of systemic disorders can vary from mild to severe, including hoarseness, cough, stridor, and airway compromise.
- Many systemic disorders that affect the larynx may mimic laryngeal carcinoma.
- A systemic process should be suspected in a hoarse patient with no obvious lesion.
- Many systemic disorders require a multidisciplinary approach to achieve optimal results, involving a speech pathologist, rheumatologist, infectious disease specialist, and otolaryngologist.

The number of problems that can affect the larynx and trachea are protean. Their manifestations can range from mild hoarseness to airway obstruction. Thankfully, most manifest as the former. In evaluation of a patient with a laryngeal or tracheal complaint, the problem may be classified as either malignant or nonmalignant. However, this is not accomplished so easily, because many nonmalignant processes can mimic malignancy, at least prior to biopsy. It is therefore up to the otolaryngologist to remain suspicious and think on a broader scale. Such an approach requires that a basic understanding of the variety of disease states that affect the larynx is an integral part of the otolaryngologist's armamentarium.

This chapter focuses on nonmalignant diseases that affect the larynx and trachea. Many of the infectious processes otolaryngologists encounter, especially those affecting the pediatric population, are covered in other chapters. This chapter provides a summary of the many systemic and infectious diseases that can manifest as laryngeal and tracheal dysfunction and describes their etiology, diagnosis, and treatment.

Wegener's Granulomatosis

Wegener's granulomatosis is a multisystem inflammatory disease characterized by necrotizing granulomatosis and necrotizing vasculitis of small arteries, arterioles, capillaries, and venules.[1,2] It primarily involves the upper and lower respiratory tracts, including the larynx and trachea, and kidneys.[1] Other areas of involvement are the oral cavity, skin, joints (polyarteritis), and orbit.[1] In the airway, the subglottis and trachea are more commonly affected (Fig. 64-1).

Airway involvement usually occurs in the presence of systemic disease but may be the only sign of the illness. Specifically, 10% to 20% of patients with Wegener's granulomatosis present with subglottic involvement and subsequent stenosis.[1,3,4] As a result, patients may be incorrectly diagnosed as having asthma when stridor is mistaken for wheezing. Glottic involvement manifests as voice changes. Most patients with Wegener's granulomatosis have a positive ANCA (antineutrophil cytoplasm antibody) test result, but up to 20% of patients who have the disease with respiratory involvement have negative ANCA test results.[2]

Common symptoms of Wegener's granulomatosis of the airway include hoarseness, cough, hemoptysis, dyspnea, stridor, and wheezing. Progressive respiratory difficulty with stridor can be the first signal of airway involvement. Pulmonary function testing with flow-volume loops can be helpful in distinguishing a fixed extrathoracic lesion (i.e., subglottic stenosis) from parenchymal disease.[2] The typical pattern of flattening of both inspiratory and expiratory phases is seen in fixed lesions.[2]

Management of the disease is complex and usually requires a multidisciplinary approach. Systemic manifestations are treated with systemic corticosteroids and other immunomodulating agents, depending on disease severity. First-line treatment is with steroids plus cyclophosphamide.[2,4] Once remission has been achieved, methotrexate or azathioprine is used.[2] Airway disease in Wegener's granulomatosis presents a complex challenge because it frequently behaves independently of the systemic disease. Treatment should be tailored to the presenting symptoms and level of distress.

In the presence of acute airway obstruction, tracheostomy placement can be lifesaving. With current endoscopic techniques, however, many patients can be managed without tracheostomy.[3-5] Although techniques differ, dilation of the stenosis with injection of intralesional steroids is the mainstay of treatment. There are reports of the use of topical mitomycin C after dilation.[6] Depending on the severity of narrowing or the level of the stenosis, dilation can be achieved with rigid dilators or balloon dilation.[2-4] The carbon dioxide laser has also been used to treat subglottic stenosis.[6] In patients with difficult stenoses, stents or tracheostomy can be used. Finally, resection and

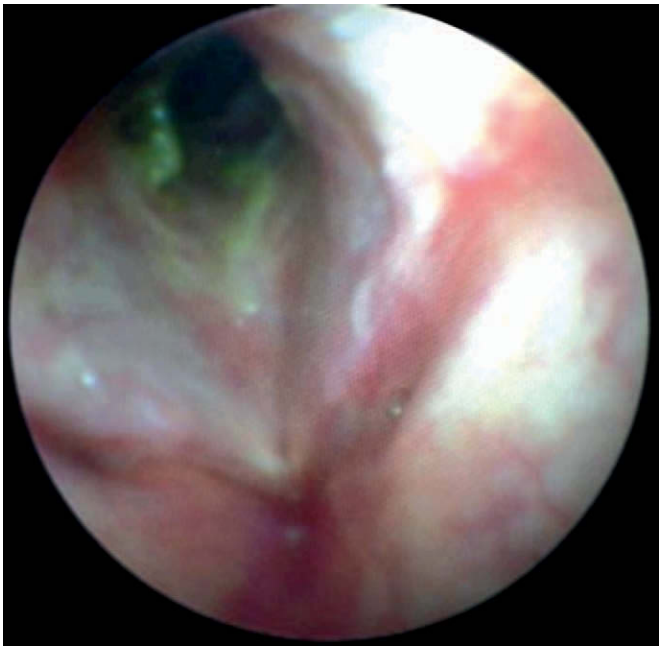

Figure 64-1. Active Wegener's granulomatosis. Yellow crusting and subglottic narrowing can be seen.

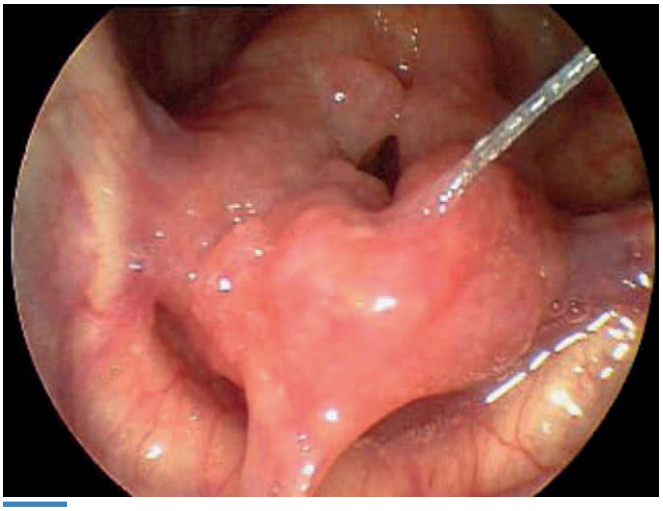

Figure 64-2. Laryngeal sarcoidosis. Note the hyoepiglottic ligament and the prominence of the hyoid bone. The epiglottis has its classic appearance, nodular and "turban-like."

reanastomosis have been used to remove the stenotic segment, but this step is usually reserved for mature stenoses and inactive disease.

Relapsing Polychondritis

Relapsing polychondritis is a rare inflammatory disease of unknown etiology that causes episodic inflammation of cartilaginous structures throughout the body.[7] Commonly affected areas are the ears, nose, eyes, larynx, bronchi, costal cartilages, and articular joints. Males and females are affected equally, with an annual incidence of 3.5 per million.[8] All ages can be affected, but peak onset is somewhere in the fourth to fifth decade. Only about 14% of patients present with airway symptoms, but 50% to 55% of patients eventually have them.[7] Diagnosis is based on the presence of multiple criteria, first described by McAdam and colleagues[7] and later modified by Damiani and Levine.[9] The most common finding is bilateral auricle chondritis. Respiratory involvement is less common but more damaging. In 25% to 35% of patients with relapsing polychondritis there is a preceding autoimmune process.[8,10]

Involvement of the respiratory tract can have serious consequences. Typically patients present with hoarseness, cough, choking, wheezing, dyspnea on exertion, stridor, or tenderness of the laryngeal framework.[7-9] Mortality rates are reported anywhere from 10% to 50% when the laryngotracheobronchial tree is involved.[8] The airway can be involved at various levels, making treatment difficult. Upper airway obstruction can occur with laryngeal involvement. Collapse of the trachea or bronchi happens when the more distal airway is affected. Respiratory distress may occur by either of two mechanisms, collapse of the central airway from destruction and fibrosis of the laryngeal and tracheal cartilages or peripheral airway narrowing from inflammation and cicatricial fibrosis.[11] Patients may ultimately require tracheostomy for airway stabilization.

Imaging can be helpful in the diagnosis of relapsing polychondritis. Plain films can demonstrate the nonerosive arthropathy seen in the disease.[9] Airway fluoroscopy has been implemented to evaluate for central airway collapse during expiration.[11] Magnetic resonance imaging and computed tomography are complementary in the diagnosis of relapsing polychondritis. Typical computed tomography findings include subglottic stenosis, tracheobronchial luminal narrowing, dense calcification and thickening of tracheal cartilages, peripheral bronchial narrowing, and bronchiectasis[11]; the most common finding is increased attenuation and smooth thickening of the airway walls.[11] Magnetic resonance imaging is very sensitive for visualization of soft tissue inflammation. Such inflammation tends to be hyperintense on T_2-weighted images, and to enhance with gadolinium on T_1-weighted images.[8]

Histologic examination shows chondritis with a mixed inflammatory cell infiltrate composed of polymorphonuclear leukocytes, lymphocytes, plasma cells, and eosinophils, depending on the stage at which the lesion is sampled.[7,9] The primary change is the loss of matrix mucopolysaccharides followed by a secondary perichondrial inflammatory reaction.[12]

In addition to surgical measures, relapsing polychondritis is managed with high-dose corticosteroids. Maintenance therapy consists of methotrexate and low-dose corticosteroids. Azathioprine, cyclophosphamide, cyclosporine, and dapsone have been tried in refractory cases.[8] There have also been case reports of the use of infliximab, which blocks tumor necrosis factor α, to treat refractory cases.[13]

Sarcoidosis

Sarcoidosis is a chronic granulomatous disease of unknown etiology. It is characterized by noncaseating granuloma formation with clusters of tubercles in the same stage of development.[14,15] It can affect any organ system within the body.[14] Nine percent of all patients with sarcoidosis have head and neck manifestations.[14] The first histopathologic diagnosis of laryngeal involvement was confirmed by Poe in 1940, despite its earlier description in the literature.[14,15] The estimated incidence of laryngeal sarcoidosis is between 1% and 5%.[14] Although rare, laryngeal sarcoidosis can be the only manifestation of the disease.

Symptoms are generally mild despite extensive tissue involvement. The progression of the disease is slow and is characterized by many relapses and remissions.[15] With respect to laryngeal involvement, symptoms typically include hoarseness, dyspnea, stridor, dysphagia, and cough.[14,16,17] However, patients can be asymptomatic. Rarely, airway obstruction may be the presenting symptom.[14]

The supraglottic larynx is affected most often, followed by the subglottis. The vocal folds are frequently spared. The epiglottis is the most common subsite, followed by the arytenoids, aryepiglottic folds, and false vocal folds.[14] When airway involvement is suspected, laryngoscopy is a key step in the diagnosis.

The classic appearance of the larynx affected by sarcoidosis is described as "turban-like thickening" (Fig. 64-2).[15] This thickening is due to the pale, pink, diffuse induration and swelling of the supraglottis. Flexible fiberoptic examination may reveal the presence of edema and erythema, punctate nodules, mass lesions, and ulcerations.[14] Biopsy of affected areas shows lymphocytic infiltration and noncaseating epithelioid granulomas.[14] The pathologic findings can be confused with those in other granulomatous diseases, and additional studies and cultures are recommended.[14]

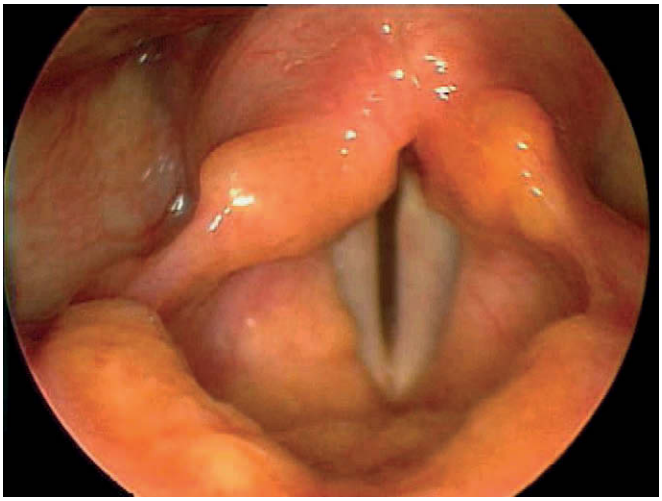

Figure 64-3. Laryngeal amyloid deposition in the supraglottis (right ventricular fold, laryngeal surface of epiglottis) and sparing of the true vocal folds. The patient presented with hoarseness and a nonproductive cough.

Treatment of the laryngeal manifestations of sarcoidosis can be achieved with systemic corticosteroids. For lesions that are small and well circumscribed, some writers have performed intralesional injection of corticosteroids.[14,17] In cases in which there is airway obstruction, excision with the carbon dioxide laser or Microdebrider can be performed to prevent the need for a tracheostomy. It is preferable to treat lesions when they are nonobstructing so as to avoid the need for a tracheostomy.[17] Due to the risk of laryngeal involvement, it is recommended that patients with sarcoidosis who begin to have airway symptoms be evaluated by an otolaryngologist.[15]

Amyloidosis

Amyloidosis is an idiopathic disorder characterized by the extracellular deposition of insoluble fibrillar proteins. Interestingly, the origins of these fibrillar proteins are their normally soluble variants. These deposits were initially described by Rokitansky in 1842.[18] The first laryngeal case was described by Borow in 1873.[18] Since then it has rarely been described as affecting the larynx, accounting for as little as 0.2% of benign tumors of the larynx.[19] However, laryngeal deposition of amyloid is the most common involvement within the head and neck.[18] Other deposits can occur anywhere in the upper and lower aerodigestive tract.

Amyloidosis is classified on the basis of the following three parameters: the fibrillar protein making up the deposits, the precursor protein from which the amyloid protein was derived, and the clinical description of the associated disease process (primary, secondary, myeloma-associated, familial, or hemodialysis-associated amyloidosis).[18] Laryngeal amyloidosis is usually a localized and primary disease but may be found in association with an underlying disorder, such as multiple myeloma.[18]

Presenting symptoms vary with the amyloid deposition. The most common location within the larynx is deposition in the true and false vocal folds and the ventricles (Fig. 64-3).[20] Frequently complaints revolve around hoarseness or cough, but if deposition is significant, dyspnea or stridor may also be seen.

Biopsy of the primary lesion is the mainstay of diagnosis. On light microscopy, amyloid exhibits an acellular, amorphous, homogeneous, eosinophilic appearance after hematoxylin and eosin staining.[18] The classic findings of bright green birefringence under polarizing light microscopy are seen after staining with Congo red. Other diagnostic tests that should be performed are complete blood count, liver function tests, renal function studies, and urinalysis to look for the Bence-Jones protein.[18] A referral to a hematologist or oncologist is appropriate, given the association of amyloidosis with multiple myeloma.

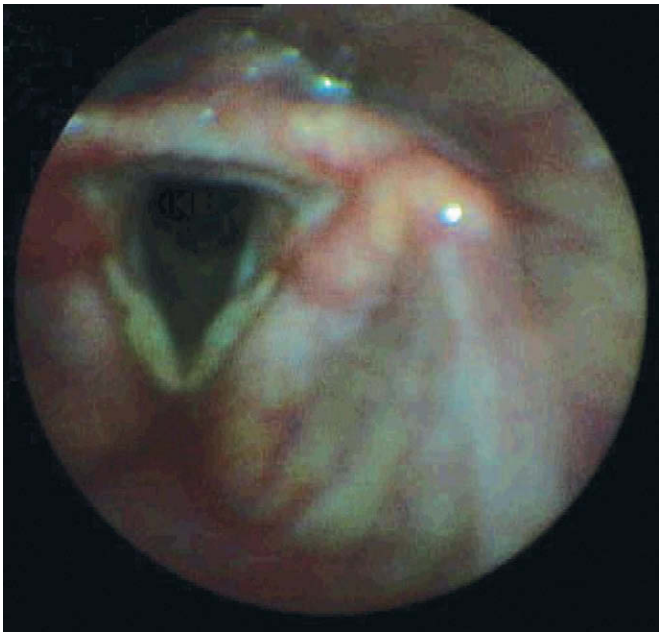

Figure 64-4. This patient was known to have rheumatoid arthritis. She experienced hoarseness, and fiberoptic examination showed bilateral midfold thickening.

Treatment is focused on maintaining airway patency and improving hoarseness while minimizing the effects on voice quality.[18,20] The treatment is routinely performed during suspension microlaryngoscopy with excision. Microdebrider excision and carbon dioxide laser excision are two modalities currently employed. Recurrence of amyloid deposits is common and is managed with reexcision. Rarely, tracheostomy is needed.

Rheumatoid Arthritis

Rheumatoid arthritis is a common autoimmune disease that involves inflammation of the synovial tissue.[21] Women are two to three times more likely to have the disease. The larynx is involved in 25% to 30% of cases. The symptoms vary from hoarseness and dysphagia to globus sensation and even stridor.[22]

Rheumatoid arthritis affects the larynx in two forms. In the active form, there is acute involvement of the larynx with tenderness and erythema. Laryngoscopic examination often shows red, swollen arytenoids.[23] The chronic form typically causes cricoarytenoid joint involvement with ankylosis.[23] This can result in bilateral impairment of vocal fold motion requiring urgent intervention, with both medical and surgical treatments.[24,25]

In addition to joint involvement, submucosal nodules can develop on the vocal fold (Fig. 64-4). Their histologic appearance is similar to that of rheumatoid nodules found elsewhere in the body. Most often, these nodules lead to hoarseness, and when removed, the voice quality improves.[22] There have been case reports of patients treated with methotrexate in whom giant rheumatoid nodules developed within the larynx, causing airway obstruction.[21,23]

Pemphigus

Pemphigus is a rare autoimmune disease that affects the skin and mucous membranes. The loosening of the epidermal-dermal junction leads to the characteristic formation of blebs. The disease is most commonly encountered by dermatologists; however, in the experience of Hale and Bystryn,[26] laryngeal complaints were not uncommon when nasal complaints were also present. Pemphigus may be isolated to the larynx, but this is unusual.[27] Most often, precedent nasal or oral lesions are found. The most common laryngeal presentation of this disease is hoarseness, although progressive stridor and dyspnea may be the presenting symptoms.[28] On fiberoptic examination, one will typically see supraglottic involvement affecting the laryngeal surface of the epiglottis,

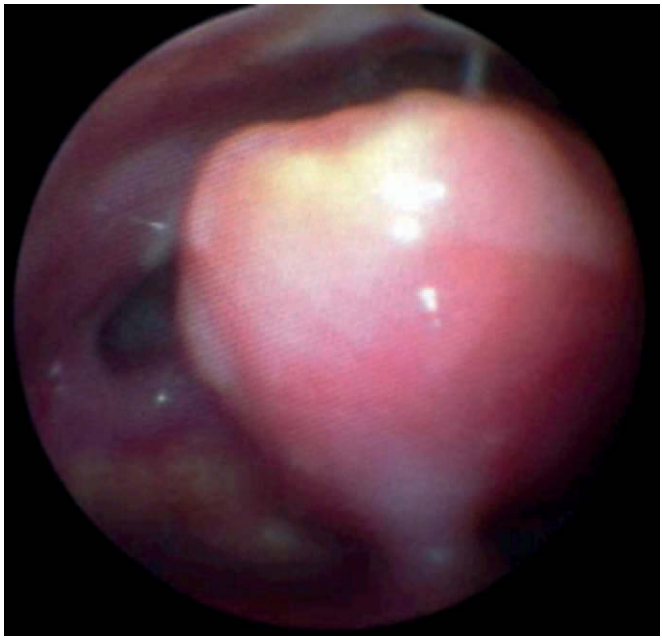

Figure 64-5. Progressive dyspnea. The fibrinous exudate is classic for pemphigus. Bullae typically are not seen in the upper aerodigestive tract because they rupture and slough off, leaving behind the fibrinous exudate as seen here.

aryepiglottic folds, and the arytenoid mucosa. The lesions that are encountered do not have the typical bleb appearance because the epidermis is sloughed off by swallowing. What is left is a tan fibrinous base with a halo of erythema (Fig. 64-5).[28,29] If this condition is encountered, a thorough inspection of the oral cavity mucosa (most common site in the head and neck)[27] and nasal cavity may reveal other lesions.[26] Because of the underlying inflammatory response, scarring can be prevalent and can lead to supraglottic narrowing.

Diagnosis relies on tissue biopsy. Because of the fragile nature of the mucous membranes, care should be taken in the performance of endoscopy. The classic histologic finding is intraepithelial acantholysis.[28,29] Pemphigus typically has acantholytic lesions that are subepithelial with basement membrane involvement. Direct immunofluorescence in pemphigus has an intracellular pattern. Indirect immunofluorescence can measure the amount of circulating antibodies and correlates with disease severity.[27]

Treatment is based on oral corticosteroids. High doses are given at first and are then tapered to a maintenance regimen. Azathioprine, cyclophosphamide, and cyclosporine have been used as maintenance medications for pemphigus.[27,28]

Whooping Cough

Whooping cough, caused by *Bordetella pertussis*, has been increasing in frequency in the United States.[30] Originally a disease of childhood, it is now more commonly seen in infants, adolescents, and adults. The reason for this increase is unknown. It is believed that despite vaccination, the maximum protection is conferred for 3 years, with decreasing effectiveness each year thereafter.[31]

Adults who become infected do not typically experience the catarrhal stage with fever and leukocytosis,[32] but instead have a severe protracted cough. Treatment with antibiotics, typically erythromycin, does not change the clinical course but does prevent transmission.[30] Azithromycin has also been found helpful in prophylaxis.

Tuberculosis

Over the years, the clinical presentation of laryngeal tuberculosis has changed. Usually laryngeal tuberculosis developed in the presence of severe pulmonary tuberculosis, secondary to expectorated secretions containing the organism.[33] Most patients who present today are without pulmonary symptoms or a history of pulmonary tuberculosis. It is theorized that laryngeal disease is the result of hematogenous or lymphatic spread.[34,35] Despite these changes, the most common presenting symptom is hoarseness.[34-36] Other symptoms are dysphagia, odynophagia, cough, and weight loss.[34,36] Despite the lack of pulmonary involvement, the purified protein derivative test result is usually positive.[37,38]

The location within the larynx has also changed with time. The most common location was the posterior glottis. It has been supplanted in frequency by various other subsites of the larynx: vocal folds, ventricular folds, aryepiglottic folds, as well as the posterior glottis.[33,36] The lesions may be nodular, exophytic, or ulcerative.[33,36-38] Because of the appearance of the lesions, laryngeal tuberculosis can be mistaken for squamous cell carcinoma.[36]

Diagnosis is usually made by the combination of sputum culture, biopsy specimens testing positive for acid-fast bacilli, and chest radiographs.[36] Medical therapy can alleviate symptoms and expedite the improvement in hoarseness. During the workup for laryngeal tuberculosis, patients should be screened for human immunodeficiency virus, given the high incidence of co-infection with the two pathogens.

Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*.[39,40] Endemic regions in the United States include the Ohio and Mississippi river valleys. Infection varies according to the initial exposure. It may manifest as either an acute or chronic pulmonary infection or an acute or chronic disseminated infection with systemic symptoms.[40] Both of the pulmonary processes are usually self-limited, unless concomitant immunosuppression is present (i.e., due to human immunodeficiency virus).[39,40] Acute disseminated histoplasmosis is almost always fatal.[41] Chronic disseminated disease usually manifests as focally destructive lesions.[39,40]

Mucosal involvement is common and can resemble lesions of squamous cell carcinoma or tuberculosis.[42-44] Biopsies can show the presence of poorly defined granulomas with macrophages and multinucleated giant cells.[40,42] Periodic acid–Schiff and Grocott stains can show intracellular *H. capsulatum*.[42-44] These ulcers begin as flat, plaque-like, nontender elevations that become painful after ulceration.[43] Treatment is with intravenous amphotericin B.

Blastomycosis

The organism responsible for blastomycosis is the dimorphic fungus *Blastomyces dermatitidis*. This soil saprophyte can be found throughout the United States and Canada but is endemic along the Mississippi and Ohio river basins. The primary portal of entry is through the lungs.[39] Hematogenous spread accounts for other organ involvement. Skin is the most commonly affected system, in contrast to the larynx, which can be involved in about 2% of cases.[39,45] Prior to antifungal therapy, the mortality of blastomycosis exceeded 60%.[39]

Laryngeal involvement typically leads to hoarseness as the chief complaint.[45,46] Examination typically reveals exophytic masses, but ulcerative lesions have been described. The true vocal folds are the most common subsite, with extension to the ventricular folds. Because these lesions can be mistaken for squamous cell carcinoma, biopsy is critical for diagnosis.

The typical histologic findings include acute and chronic inflammation, microabscesses, and giant cell formation. The hallmark finding is pseudoepitheliomatous hyperplasia.[39] Fungal stains (e.g., Gomori methenamine silver) show the organism as a double-walled sphere 8 to 15 mm in diameter with single broad-based buds.[39] In addition to histologic identification, culture of the organism is performed in enriched agar medium. For uncomplicated cases, prolonged oral ketoconazole or itraconazole treatment can be given. Amphotericin B is also effective, especially in cases with central nervous system involvement.

Cryptococcosis

Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans*, a yeastlike fungus with a thick polysaccharide capsule.[39] It is found in areas contaminated with pigeon droppings.[39] As in blastomycosis, infection is through inhalation of the spores. The pulmonary disease in nonimmunocompromised patients is generally subclinical. However, in

immunocompromised patients, systemic involvement is typical. The most commonly affected system is the central nervous system, leading to meningitis. Most cases of laryngeal involvement occur in immunocompromised patients, but there are rare cases in immunocompetent patients.[39,47] The true vocal folds are the only site affected, with subsequent hoarseness. On biopsy, budding yeast can be seen. As seen in blastomycosis, pseudoepitheliomatous hyperplasia may be identified. Depending on the severity of the infection, treatment involves amphotericin B or fluconazole.[39,47]

Coccidioidomycosis

Coccidioides immitis, the fungal organism responsible for San Joaquin Valley fever, is endemic to the southwestern United States and northern Mexico.[39] Spores are inhaled, and 60% of infections go unrecognized. In the remaining 40%, flulike symptoms occur 1 to 3 weeks after infection.[39] Most cases of laryngeal involvement occur in disseminated coccidioidomycosis. Symptoms range from hoarseness, pain, and odynophagia to airway involvement with stridor.[48,49] Amphotericin B is the mainstay of treatment.

Actinomycosis

Actinomycosis is a chronic suppurative infection characterized by the presence of purulent drainage from chronic discharging sinus tracts containing the pathognomonic sulfur granules.[39] The causative organism is *Actinomyces israelii*, an anaerobic or microaerophilic, non–acid-fast, gram-positive organism. These organisms are endogenous to the oral cavity and can be found in carious teeth, plaque, and tonsillar crypts.[39] Cervicofacial actinomycosis accounts for 50% to 60% of all cases.[39] Laryngeal and tracheal cases have been reported.[50] Treatment involves prolonged antibiotic therapy; the mainstay is penicillin, although clindamycin has also been used.[39,50]

Candidiasis

Candidiasis affecting the larynx tends to be associated with oral and esophageal involvement as well. Affected patients are typically immunocompromised owing to chemotherapy or acquired immunodeficiency syndrome. Isolated laryngeal candidiasis has been seen, especially in patients using inhaled corticosteroids.[51-53] The lesions are usually white sessile plaques on an erythematous base; however, ulceration may be noted.[51] Therapy is focused on eliminating the causative agent (i.e., steroid inhaler) and the addition of an oral antifungal agent, such as fluconazole.[51,53] Also, candidal overgrowth is associated with failure of a tracheoesophageal puncture voice prosthesis.

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CHAPTER SIXTY-FIVE

Upper Aerodigestive Manifestations of Gastroesophageal Reflux Disease

Jonathan E. Aviv

Savita Collins

Key Points

- Laryngeal edema, not laryngeal erythema, is the clinical hallmark of laryngopharyngeal reflux disease.
- Office-based transnasal esophagoscopy without sedation is becoming a viable alternative to facility-based transoral esophagoscopy with sedation for examining the esophagus.
- Extraesophageal symptoms of acid reflux disease, in particular cough and hoarseness, better predict the presence of esophageal adenocarcinoma than traditional gastroesophageal reflux symptoms, such as heartburn and regurgitation.
- Multichannel intraluminal impedance testing with a pH sensor will become an increasingly essential part of the workup of the patient with acid reflux disease.

Gastroesophageal reflux (GER) is defined as the retrograde movement of material from the stomach into the esophagus in the absence of belching or vomiting.[1-3] *Gastroesophageal reflux disease* (GERD) occurs when GER is associated with symptoms or complications. When GER affects the laryngopharynx, the disease entity is called *laryngopharyngeal reflux* (LPR). Another term used to describe nonesophageal manifestations of the regurgitation of gastric contents is *extraesophageal reflux* (EER).[4,5]

It has been estimated that 30% of Americans suffer from GERD, with 7% to 10% of adults experiencing daily heartburn and 29% to 33% having symptoms weekly.[1,6-8] Twenty-five million to 75 million people in the United States are affected by GERD, and 13% of Americans use indigestion aids at least twice weekly.[8] The incidence of GERD in patients presenting to an otolaryngology practice has been estimated to be 4% to 10%.[5] GERD is not rare in children; it has been described in 18% of children, with a higher incidence in children with esophageal atresia, tracheoesophageal fistula, or neurologic impairment.[9] Unfortunately, accurate estimates of the incidence of LPR are not available. Koufman and colleagues[10] reported that 50% of all patients presenting to their center with laryngeal and voice disorders had LPR as documented by dual pH probe studies. A retrospective review of patients presenting with common cervical symptoms demonstrated that GERD was detected in 73% of patients, and symptomatic relief after antireflux medical treatment resulted in symptomatic improvement in 84%.[11]

The role and incidence of LPR in the development of otolaryngologic disorders are controversial among otolaryngologists. A survey of members of the American Broncho-Esophagological Association showed that 75% of respondents estimated that less than 50% of their patients had disorders related to LPR, and there was a lack of consensus regarding evaluation and treatment modalities.[12] LPR has been implicated in several clinical disorders, including chronic laryngitis,[10,13,14] chronic dysphonia,[10,13,14] laryngotracheal stenosis,[15,16] head and neck carcinoma,[17-21] cough,[22-26] asthma,[22,25-27] otitis media,[28] dental caries and erosion,[29] laryngeal papilloma,[30] vocal fold granulomas and ulcers,[22,31-33] laryngospasm,[34-37] recurrent croup,[9] paradoxic vocal fold movement disorder,[38,39] and laryngomalacia.[40] The goals of this chapter are to review the pathophysiology, clinical manifestations, diagnoses, and treatment of EER.

Pathophysiology

The esophagus is the conduit for the transfer of material from the pharynx to the stomach. The esophagus acts as a vent for the stomach, allowing some normal retrograde flow of gases and gastric contents.[41] The gatekeepers for the ingress and egress of material are the upper esophageal sphincter (UES) and lower esophageal sphincter (LES). The four main constituents of the barrier to reflux are the UES, the LES, esophageal acid clearance, and epithelial resistance.[14,42] Laryngopharyngeal diseases associated with EER are thought to result from both direct and indirect pathways,[11,34,43] which are detailed in the section on mechanisms.

Upper Esophageal Sphincter

The UES is functionally defined as the area of the distal pharynx and proximal esophagus that maintains a closed pharyngoesophageal segment and opens for specific physiologic demands (e.g., swallowing, belching). Anatomically, the UES is made up of the cricopharyngeus, the thyropharyngeus, and the proximal cervical esophagus.[41,42,44] Unlike other muscular sphincters, the UES is not a complete muscular circle

but rather a C-shaped sling that attaches to the cricoid cartilage. The pharyngeal plexus innervates the UES and receives contributions from the vagus nerve (superior and recurrent laryngeal nerves), the glossopharyngeal nerve, and the sympathetic nerves from the superior cervical ganglion.[44] The motor neurons that control the cricopharyngeus are found in the brainstem in the nucleus ambiguus, and stimulation of the nucleus tractus solitarius (the afferent nucleus of the vagus) results in contraction of the cricopharyngeus.[44] In canine studies, vagal nerve stimulation produced UES relaxation, and sectioning of both vagus nerves produced severe dysphagia.[14] Sensory information from the UES is transmitted via the glossopharyngeal nerve and the sympathetic nerves.[44]

The UES maintains a closed pharyngoesophageal segment via tonic contraction of the cricopharyngeus.[41,44] During swallowing, UES relaxation occurs, and the cricoid cartilage is pulled upward and anteriorly by the laryngeal musculature, thereby resulting in a stretching of the cricopharyngeus, thus allowing for bolus passage.[41] The UES tonic pressure is increased in response to laryngeal stimulation (laryngo-UES contractile reflex).[7,42] UES pressure is increased with acidification of the distal esophagus.[14,42,44] UES pressure increases with slow balloon distention of the distal esophagus.[44] General anesthetics, sleep state, cigarette smoking, and peppermint consumption are associated with decreased UES pressure.[14,42,44] Koufman[14] reported that smoking and peppermint consumption produced a 50% reduction in UES resting pressure in healthy volunteers within minutes.

The UES is the final gatekeeper in the antireflux barrier, and UES dysfunction may be associated with head and neck manifestations of EER. Deveney and collegues[45] showed an increased incidence of UES hypotonia in patients with pulmonary problems associated with GERD. In patients with inflammatory lesions of the larynx, they found UES pressures that were somewhat lower than normal.[45] Ulualp and Toohill[42] did not see significant differences between resting UES pressures in patients with posterior laryngitis and normal controls.

Lower Esophageal Sphincter

The LES is the most critical antireflux defense mechanism.[1,46] It is located at the gastroesophageal junction, and it is not as anatomically distinct as the UES. Contraction of the LES results in circular closure that prevents the egress of gastric contents. Relaxation of the LES occurs during swallowing, belching, and vomiting. The LES is anatomically surrounded by the diaphragmatic crura, which mechanically augment the sphincter mechanism and are believed to contribute to 25% of LES competence.[14] Manometric measurements at the LES reflect the combined contributions of the esophageal LES and the diaphragmatic crura. The intrinsic resting pressure of the LES varies with the phase of the respiratory cycle as a result of differential diaphragmatic contraction.[46] During episodes of straining, LES pressure is increased as a result of greater diaphragmatic activity, yielding a stronger diaphragmatic squeeze of the LES.[41,46] Hormonal control of LES activity is complex. Gastrin, pitressin, angiotensin II, and motilin increase contractile tone, whereas secretin, cholecystokinin, glucagon, and vasoactive intestinal peptide reduce LES pressure.[14,46]

To prevent GER, the LES must maintain a resting pressure that is higher than the gastric pressure. GER occurs when there is a reversal of this gastric-to-LES pressure gradient.[41,46] Retrograde flow occurs with relaxation of the LES, with chronic hypotonia of the LES, or with increases in gastric pressure that overcome the LES resting pressure. Transient relaxation of the LES occurs in normal healthy adults and children.[46] Research has shown that transient relaxation of the LES is the most critical mechanism in the production of GER.[21,94] Dent[46] demonstrated that 63% to 74% of GER episodes were associated with transient LES relaxation. Chronic hypotonia of the LES is thought to be associated with GER episodes in a smaller percentage of patients, but perhaps with more severe esophagitis.[46] Lower LES's resting pressures are seen in patients with CREST (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia) syndrome, scleroderma, and isolated Raynaud's phenomenon. Although chronic hypotonia of the LES results in more severe reflux, it is an uncommon mechanism for GERD.[46,47] Large hiatal hernias may result in disruption of the relationship of the LES to the diaphragmatic crura, which may in turn impair the ability of the LES to act as an antireflux barrier by removing the additional pressure generated by the squeeze of the diaphragm.[14,46] Although hiatal hernias may play a role in GERD in some patients, not all patients with hiatal hernias have GERD.[1] Box 65-1 lists agents that affect the LES pressure.[1,14]

Box 65-1

Factors That Increase or Decrease Lower Esophageal (LES) Pressure

Increase

Protein
Bethanechol
Metoclopramide
Antacids
α-adrenergic drugs

Decrease

Fat
Carbohydrates
Alcohol
Cigarettes
Carminatives (peppermint, spearmint)
Theophylline
Calcium-channel blockers
Nitrate drugs
Atropine
β-adrenergic drugs
Dopamine
Sedatives

When gastric pressure exceeds LES pressure, reflux can occur. "Stress reflux" is seen with increased intra-abdominal pressure during bending over, heavy lifting, straining, and coughing.[14] Excessive gastric distention resulting in higher gastric pressure can occur postprandially after a large meal and with severe gastroparesis. Impaired gastric emptying is more common in patients with GERD.[47] Pregnancy, in which abdominal pressure is increased, is a risk factor for GERD.

Esophageal Acid Clearance

Because some GER is normal, mechanisms exist to clear and neutralize gastric contents when they pass into the esophagus. Esophageal peristaltic waves—along with the effect of gravity—act to mechanically clear the esophagus. Weakened or ineffective peristalsis allows for refluxed materials to have longer contact time with esophageal tissues.[47a] Knight and colleagues[47] studied 100 subjects with EER and noted that 52% had ineffective esophageal motility. Primary esophageal peristalsis in patients with GERD and posterior laryngitis has been shown to be similar to that in normal controls.[42] In patients with GERD, secondary esophageal peristalsis was noted to be decreased in comparison with that in normal controls.[42] Increased numbers of GER episodes seen in patients with GERD, when supine, can be partially explained by the loss of gravitational effects. Acidic refluxate left in the esophagus can be neutralized by gastric glandular secretions and buffering agents in saliva.[14] Xerostomia, which can be caused by Sjögren's disease, certain medications, and previous radiotherapy, may abolish this important antireflux barrier.[14] The low pH of gastric material is damaging to epithelium, but alkaline pH pancreatic and bile juices, when present, can also injure tissues.[1,14]

Epithelial Resistance Factors

When the antireflux barriers fail, the severity of tissue damage is determined by epithelial resistance factors. There are pre-epithelial, epithelial, and intracellular protective mechanisms. The epithelium is preceded by a mucus layer and an aqueous layer with high bicarbonate content.[14,42] Mucus resists penetration by large molecules such as

pepsin, but it does not prevent the ingress of acid. The aqueous layer is alkaline, and it buffers acid material. At the cellular level, the cell membrane and the intracellular junctions resist acid and pepsin.[14] Different tissues have variable epithelial resistance, with esophageal epithelium being more resistant than respiratory epithelium.[11,14,42,43,45] Even slight amounts of GER in the hypopharynx or larynx may cause significant injury, whereas reflux to the same degree in the distal esophagus would be easily resisted.[11,14,42,43,45] Hanson and Jiang[31] postulate that the posterior glottis is especially susceptible to the effect of EER. They theorize that the cilia beat material to the posterior glottis, thereby resulting in longer contact with refluxate and, therefore, more injury to this epithelium.

Mechanisms of Symptoms due to Extraesophageal Reflux

Head and neck disorders associated with EER are postulated to occur via the following mechanisms: direct mucosal damage and direct effect on mucociliary clearance from exposure to gastric contents; GER-related distal esophageal damage that results in vagally mediated, referred symptomatology; and laryngeal reflexes mediated by the stimulation of distal esophageal afferents.[11,34,43] Gaynor[32a] studied the effects of direct exposure of gastric contents on rabbit and canine larynges. In the rabbit, direct exposure at a pH of 4.0 resulted in an inflammatory response that involved the submucosa and muscle, and the extent of damage worsened with longer durations of exposure. When a pH of 1.4 was used, "severe mucosal ulceration, submucosal and deeper hemorrhage with marked inflammatory response as well as necrosis were noted."[43] In canines, an effect on mucociliary flow was noted to begin at a pH of 5.0, and no mucociliary flow was observed at pH of 2.0. Ciliary activity persists after the cessation of mucociliary flow. Alteration of pH has a direct effect on mucociliary transport and may lead to increased viscosity of the mucus blanket.[43] A reduction in mucociliary transport may decrease resistance to infection and has been theorized to contribute to the pathogenesis of subglottic stenosis.[43]

Pepsin, which is found in gastric contents, is maximally active at pH 4.5, and its enzymatic activity produces tissue damage.[14] Koufman[14] demonstrated the importance of pepsin in the production of epithelial damage in canine larynges. He created subglottic mucosal injuries in dogs and then compared healing and injury in control, acid-only, and acid- and pepsin-exposed conditions. The acid-only group had inflammatory lesions that healed in twice the time it took for the control group lesions. None of the acid- and pepsin-treated larynges showed healing, and they were noted to develop ulceration and granulation.[14]

Gaynor,[32a] monitoring patients receiving intensive care who were intubated for prolonged periods, found lower pharyngeal pH readings ranging from 2.4 to 7.0. Forty percent of the patients were noted to have reflux episodes with pH less than 4.0. In patients treated with antacids or histamine H_2 blockers, pH readings ranged from 4.7 to 8.9. The works of Koufman,[14] Gaynor,[32a] and Maronian[47b] support the use of anti-acid therapy in cases of potential subglottic trauma (e.g., intubation), because it may help prevent irreversible mucosal damage.

Direct stimulation of sensory receptors in the larynx by aspirated or refluxed material can result in reflexive vocal fold adduction or laryngospasm.[34,36,48] This laryngeal chemoreflex is associated with bradycardia, central apnea, and hypotension.[9] Partial or complete laryngospasm and cough can also be triggered by GER to the distal esophagus via a vagally mediated reflex.[1,7,27,34] Laryngospasm associated with distal esophageal GER can be associated with bronchospasm, increased secretions, tachycardia, and hypertension.[9] These reflexes have implications for respiratory manifestations of EER and in the mechanisms involved with sudden infant death syndrome and recurrent laryngospasm.[34,36,43,48]

Diagnostic Evaluation

History

A good case history is very critical to both diagnosis and treatment in patients with EER. The clinician must identify not only symptoms but also behavioral and medical risk factors. It is also critical to patient compliance with treatment that the patient be actively involved in the identification of the risk factors that he or she can modify. Common symptoms described in association with EER are listed in Box 65-2.[1,5,11,12,22-24,31,49-56]

Box 65-2

Common Symptoms of Extraesophageal Reflux*

- Hoarseness/dysphonia (episodic or chronic)
- Globus sensation
- Chronic throat clearing
- Vocal fatigue
- Voice breaks
- Sore throat
- Neck pain
- Excessive throat mucus
- Chronic or nighttime cough
- Dysphagia
- Odynophagia
- Postnasal drip
- Halitosis
- Ear pain
- Laryngospasm
- Asthma exacerbation
- Loss of upper singing range
- Prolonged warmup time in singers
- Heartburn/regurgitation

*Listed in order of frequency.

In a retrospective review of 216 patients with cervical symptoms that were believed to be associated with EER, Rival and associates[11] found that the most common complaint was cervical dysphagia (33%), followed by globus (19%), sore throat (17%), and chronic throat clearing (14%). The researchers found that 66% of the patients complained of classic symptoms of GERD, such as acid regurgitation and heartburn.[11] Fraser and coworkers[52] prospectively reviewed patients with symptoms believed to be associated with EER in whom pH probe study results were positive and found cough and hoarseness as the most common symptoms; 77% of their patients also complained of classic symptoms of GERD. Other investigators report lower rates of symptomatic GERD in patients with EER, with estimates of 20%,[5] 43%,[14] and 55%.[54] In a survey of American Broncho-Esophagological Association members, respondents believed that the most common symptoms related to EER were throat clearing, persistent cough, heartburn/dyspepsia, globus sensation, and voice quality change.[12] The importance and relevance of these findings are supported by the work of Reavis and associates,[57] who showed that laryngopharyngeal manifestations of acid reflux, specifically cough and hoarsenesss, better predict the presence of adenocarcinoma of the esophagus than "classic" GERD symptoms such as heartburn and regurgitation.

Belafsky and colleagues[49,50,58] developed the Reflux Symptom Index (RSI), a self-administered survey of nine questions used to assess patients with EER (Box 65-3). They demonstrated that the instrument is reliable and that it provides reproducible and valid findings. Normative data gathered by these researchers support that an RSI of more than 10 is associated with a high likelihood of positive results of a dual-channel pH probe study.[59] They prospectively evaluated 40 patients with EER documented by dual pH probe studies and 2 months of medical management. The RSI was noted to show improvement before changes were seen in physical findings. The mean RSI at initiation of the study was 19.3, which improved to a mean of 13.9 after 2 months.[49]

Physical Examination and Laryngeal Endoscopy

The physical examination can yield several clues to EER. Observations of the quality of the voice, frequent throat clearing, cough or stridor, muscle tension in extralaryngeal musculature, and general body habitus are important to the evaluation. The larynx can be evaluated with indirect laryngoscopy along with rigid and/or flexible laryngoscopy.

Box 65-3

The Reflux Symptom Index

Within the past month, how did the following problems affect you? Rank them from 0 (no problem) to 5 (severe problem).

1. Hoarseness or a problem with your voice
2. Clearing your throat
3. Excess throat mucus or postnasal drip
4. Difficulty swallowing food, liquids, or pills
5. Coughing after you have eaten or after lying down
6. Breathing difficulties or choking episodes
7. Troublesome or annoying cough
8. Sensations of something sticking in your throat or a lump in your throat
9. Heartburn, chest pain, indigestion, or stomach acid coming up

From Belafsky PC, Postma GN, Amin MR, Koufman JA. Symptoms and findings of laryngopharyngeal reflux. *Ear Nose Throat J*. 81(Suppl 2):10, 2002.

Table 65-1

The Reflux Finding Score

Pseudosulcus	0, absent; 2, present
Ventricular obliteration	0, none; 2, partial; 4, complete
Erythema/hyperemia	0, none; 2, arytenoids only; 4, diffuse
Vocal fold edema	0, none; 1, mild; 2, moderate; 3, severe; 4, polypoid
Diffuse laryngeal edema	0, none; 1, mild; 2, moderate; 3, severe; 4, obstructing
Posterior commissure hypertrophy	0, none; 1, mild; 2, moderate; 3, severe; 4, obstructing
Granuloma/granulation	0, absent; 2, present
Thick endolaryngeal mucus	0, absent; 2, present

From Belafsky PC, Postma GN, Amin MR, Koufman JA. Symptoms and findings of laryngopharyngeal reflux. *Ear Nose Throat J*. 81(Suppl 2):10, 2002.

Videoendoscopy and stroboscopy are very useful, especially for documenting treatment effects and for visualizing subtle signs associated with acid reflux.

The majority of laryngeal findings seen in patients with chronic laryngitis associated with EER are edematous changes, as opposed to erythematous changes, seen in the posterior larynx. Posterior laryngitis manifests as edema, loss of clear epithelial markings, and increased vascularity of the posterior commissure and arytenoids.[5,13,60] Chronic irritation can result in a thickening of the posterior laryngeal mucosa with hyperkeratosis, which is also called pachydermia laryngeus.[5,13] Hanson and colleagues[13] describe this posterior mucosal thickening with increased granularity and rough cobblestone appearance as "granular mucositis." Increased mucus formation and thickness, along with mucus stranding and pooling, may result from chronic irritation and alterations of mucociliary flow.[5,43] Laryngeal ulceration, granuloma formation, scarring, and stenosis may indicate more severe EER.[13,30-32] Cherry and Margulies first identified extraesophageal reflux of gastric acid as being associated with contact ulcers.[43]

Although it has been traditionally thought that erythema of the posterior larynx is the key sign of EER,[13,31] it is really the edema consequent to acid reflux–induced trauma to the larynx that is the clinical hallmark of EER.[59,61-63] Habermann and colleagues,[60] reviewing the endoscopic findings in 29 patients with chronic dysphonia and chronic laryngitis, showed that edema of the posterior glottic mucosa was the most common finding. The researchers noted significant improvement in these changes with therapy. Alterations of the true vocal fold mucosa and false vocal folds were also noted to improve with treatment. Shaw and Searl[64] assessed 96 patients who had symptoms suggestive of EER and noted that posterior glottic edema and nodularity were the most "severe and frequent" findings. Only 47% of patients were found to have ulceration, and 3 patients were found to have granulomas. Branski and coworkers[62] performed a prospective, randomized, blinded study to assess the reliability of the laryngoscopic evaluation of patients with EER. They found that both intrarater reliability and inter-rater reliability were poor; raters demonstrated a poor agreement on the severity of endoscopic findings for LPR. The investigators concluded that using laryngoscopic findings alone for the diagnosis of EER was highly subjective.

Pseudosulcus has been described as a common endoscopic finding in EER.[50,59,65] The term *pseudosulcus* refers to the edematous changes that take place along the undersurface of the vocal fold from the anterior to the posterior commissure.[50,50,65] By contrast, true sulcus vocalis involves the free edge of the fold and terminates at the vocal process. Belafsky and colleagues,[59] evaluating pseudosulcus in 30 patients with EER (i.e., with positive pH probe results) and 30 control patients, found pseudosulcus in 70% of patients with EER and in 30% of controls. Patients with pseudosulcus were 2.3 times more likely to have pH probe–documented EER. The sensitivity and specificity of pseudosulcus were estimated to be 70% and 77%, respectively.[59] Hickson and colleagues[65] prospectively assessed, with dual-channel pH probe studies, 20 patients in whom endoscopic evaluation had confirmed pseudosulcus; EER was identified with positive pH probe results in 18 of the 20 patients. These researchers estimated that the positive predictive value of pseudosulcus for EER was 90%.[65]

Belafsky and coworkers[59] have developed an endoscopic grading scale for EER. The Reflux Finding Score (RFS) consists of eight findings, seven of which are related to edematous changes in the endolarynx and only one to redness of the endolarynx, that are graded as to severity to a score from 0 to 26 (Table 65-1). The researchers report that an RFS of more than 7 is associated with a high likelihood that dual pH probe results will be positive.[59] The RFS was tested in 40 control subjects and 40 patients with clinical history positive for EER and pH probe studies. This review showed excellent interobserver and intraobserver reliability for the RFS. The mean RFS for control subjects was 5.2, whereas the mean RFS at entry for the EER group was 11.5, and an individual with an RFS of more than 7 was noted to have EER with 95% certainty.[58]

Beaver and colleagues[61] conducted a prospective study of the videostroboscopic images of 49 patients diagnosed with laryngopharyngeal reflux disease on the basis of two or more symptoms (i.e., throat clearing, hoarseness, cough, globus, or excessive mucus) along with physical findings of chronic laryngitis. Subjects were evaluated before and after 6 weeks of high-dose proton pump inhibitor (PPI) therapy. Ten control patients without any symptoms of EER were included. Three otolaryngologists evaluated the photographs in a blinded manner and in random order and gave each a score using the Laryngopharyngeal Reflux Disease Index (Box 65-4). The mean index value for patients was significantly higher than that of controls (9.50 vs. 2.92, respectively), and posttreatment mean scores were significantly lower than pretreatment scores (7.35 vs. 9.50, respectively). The most useful items on the scoring system were as follows: supraglottic edema and erythema, glottic edema and erythema, and subglottic edema and erythema. Items 7 through 12 were not believed to be as useful, and very few patients had positive scores on these items. The key factor in the endoscopic assessment of acid reflux–induced changes in the laryngopharynx is that edema, not erythema, is the clinical hallmark of EER.

Box 65-4

The Laryngopharyngeal Reflux Disease Index

Grade each using a scale of 0 to 3 (0, absent; 3, most severe):

1. Edema of posterior supraglottis
2. Edema of vocal folds
3. Edema of subglottis
4. Erythema of posterior supraglottis
5. Erythema of vocal folds
6. Erythema of subglottis

Grade as 1 if present and 0 if absent:

7. Leukoplakia
8. Nodules or prenodules
9. Polyp(s)
10. Posterior pachydermia
11. Web (may be anterior microweb)
12. Contact granuloma

From Beaver ME, Stasney CR, Weitzel E, et al. Diagnosis of laryngopharyngeal reflux disease with digital imaging. *Otolaryngol Head Neck Surg*. 128:103, 2003.

Voice Analysis

Hanson and colleagues[66] reviewed voice quality and measures of jitter, shimmer, and signal-to-noise ratios in 16 patients undergoing treatment for chronic posterior laryngitis. Perceptual analysis did not show correlation with acoustic measures, and it did not show significant change with treatment. The investigators did demonstrate that measures of jitter, shimmer, and signal-to-noise ratio improve significantly with antisecretory and antireflux treatment of chronic posterior laryngitis. Shaw and Searl[64] noted significant improvement in measurements of jitter, shimmer, habitual frequency, and frequency range with antireflux treatment in their series of patients with a pretreatment complaint of hoarseness. Hamdan and coworkers[53] did not find any change in acoustic parameters in patients undergoing medical treatment of EER.

Esophagram

Barium esophagram is a convenient, inexpensive, and noninvasive diagnostic test. It is a useful method to diagnose structural and functional abnormalities of the esophagus, including hiatal hernia, erosive esophagitis, strictures, Barrett's esophagus, esophageal rings, extrinsic compression, motility disorders, diverticula, possible malignancy, cricopharyngeal spasm, aspiration, and esophageal shortening.[5,9,14,67,68] Barium studies have significant use for planning of antireflux surgery. Fluoroscopic evaluation is often used to look for the presence of reflux, and it is often combined with provocative maneuvers, such as Valsalva's maneuver, cough, rolling from the supine to the right lateral position, and the water siphon test (the patient drinks 60 mL of water through a straw while supine). The sensitivity of barium esophagram to detect GER is between 20% and 60%, with a specificity of 64% to 90% and an accuracy of 69%.[9] Thompson and associates[68] assessed 117 patients with clinical GERD and compared the results of esophageal pH probe studies with those of barium esophagrams. They demonstrated that barium studies showed unprovoked reflux in 26% of subjects with positive pH probe study results. The addition of the water siphon test increased the sensitivity of barium esophagram in the evaluation of reflux to 70%, with a specificity of 74% and a positive predictive value of 80%.[68]

The relevance of barium esophagography in patients with EER is less clear. In Toohill and Kuhn's[5] series of 286 patients with dysphonia and various laryngeal disorders, 79.9% had abnormal esophagram findings. Rival and colleagues[11] showed that 22 out of 73 patients with EER symptoms had normal barium swallow study results, with 50% of these patients demonstrating EER on subsequent diagnostic testing. Giacchi and colleagues[2] reviewed 28 patients with otolaryngologic manifestations of EER, reporting that barium esophagram revealed reflux in 45% of patients and that 50% had normal findings.

Laryngeal Sensory Testing

Laryngeal sensory testing alone, without evaluation of swallowing, can be used to diagnose EER.[68a,b] The concept is that the posterior laryngeal edema that results from acid reflux can be quantified with laryngeal sensory testing. With laryngeal sensory testing, a pressure- and duration-controlled pulse of air is administered to the arytenoid epithelium in order to induce the laryngeal adductor reflex, a brainstem-mediated, airway-protective reflex. The practical way to regard laryngeal sensory testing is that an edematous arytenoid would require a stronger air pulse pressure to cause indentation of the arytenoid epithelium than the air pressure required to "indent" arytenoid epithelium that is not edematous.

Two studies have demonstrated that laryngeal sensory testing can be used to quantify the edema that results from LPR. In one study, 76 patients were prospectively evaluated to determine the relationship between double-probe pH testing results, laryngopharyngeal sensory testing results, and transnasal flexible laryngoscopy (TFL) findings.[69] All 76 patients underwent dual channel 24-hour pH testing after 7 days with no PPI treatment, laryngopharyngeal sensory testing, and TFL performed by otolaryngologists who were blinded as to the patients' pH status and laryngopharyngeal sensory testing results. There were three patient groups: Group A (the study group) consisted of patients with GERD who had LPR symptoms; Group B (GERD controls) had GERD but no LPR symptoms; and group C (normals) had no GERD and no LPR symptoms. GERD was defined as a distal probe pH of less than 4 more than 5.4% of the time during a 24-hour period.[70] Patients with GERD and LPR symptoms (group A) had significantly higher posterior laryngopharyngeal sensory thresholds than both patients with GERD but no LPR symptoms and controls with no GERD and no LPR symptoms. Sensitivity of blinded TFL findings versus dual-channel 24-hour pH testing was 50%, and specificity was 83%. However, adding the finding of air pulse pressure greater than 5 mm Hg on laryngopharyngeal sensory testing increased the sensitivity to 88% and specificity to 88%. This study showed that LPR is associated with a posterior laryngeal sensory neuropathy with impairment of the laryngeal adductor reflex. The investigators reasoned that because a greater air pulse strength was required to elicit the laryngeal adductor reflex in the patients with documented acid reflux than in the controls without acid reflux, this finding effectively represented an alteration in laryngeal sensory nerve function; hence their use of the term "neuropathy." Furthermore, the combination of sensory testing, specifically a sensory deficit greater than 5 mm Hg air pulse pressure, TFL findings were essentially as sensitive and specific as 24-hour pH testing for diagnosis of acid reflux disease.

Another key prospective study compared 15 patients who had chronic cough (no asthma, no rhinitis) and 24-hour pH probe–documented GERD with 10 healthy controls.[71] The patients in both study groups had laryngeal sensory testing before and after laryngopharyngeal infusions of normal saline and 0.1 N hydrochloric acid (on separate days). The baseline threshold for eliciting the laryngeal adductor reflux was significantly greater for both patients with pH probe–documented acid reflux disease and patients and controls exposed to 0.1 N HCL. The researchers concluded that the sensory integrity of the laryngopharynx is significantly impaired after exposure to even small amounts of acid and that patients with cough and proven GERD have reduced laryngopharyngeal sensitivity compared with healthy controls—which could result in a higher risk of aspiration.

Practically, what these studies mean for the patient and for the clinician is that a brief in-office test, laryngopharyngeal sensory testing, can serve the same purpose as a 24-hour pH probe test to diagnose reflux disease. Therefore, these results suggest that with the application of sensory testing techniques, identification of reflux disease can be made quite readily by most practicing physicians who see patients with laryngopharyngeal reflux symptoms. This is not to suggest that patients who might be contemplating surgical treatment of acid reflux disease, such as a laparoscopic fundoplication, avoid pH probe testing. Rather, there are reliable office-based alternatives to diagnose acid reflux disease

enabling immediate diagnosis so that treatment may be initiated at the time of testing.

Esophageal Endoscopy—Transoral and Transnasal Esophagoscopy

The esophagus can be examined endoscopically via either a transoral approach or a transnasal approach. The transoral route is performed either in an operating room with use of a rigid scope and the patient under general anesthesia or in an endoscopy suite with use of a flexible scope and the patient under intravenous, or conscious, sedation. The reason patients typically need general anesthesia or intravenous anesthesia for transoral esophagoscopy is that, in both instances, a rather large-caliber endoscope is passed along the dorsal surface of the tongue, thereby necessarily engaging the gag reflex. Alternatively, esophagoscopy can be performed transnasally with an ultra-thin-caliber endoscope passed via a topically anesthetized nasal cavity. The transnasal approach is called transnasal esophagoscopy (TNE). Peroral rigid esophagoscopy has been performed by otolaryngologist–head and neck surgeons since the 1890s.[72-74] Flexible esophagoscopy, performed transorally in the endoscopy suite with use of conscious sedation, has been performed by gastroenterologists since the late 1950s.[75,76]

The transnasal era of esophagoscopy was first reported by Prescott,[77] an otolaryngologist, who described TNE in children in 1993. In 1994, Shaker,[78] a gastroenterologist, published the first paper on unsedated, transnasal EGD in adults, performed with the patients sitting upright in an examining chair. In 1998, at the annual meeting of the American Broncho-Esophagological Association, an otolaryngologist performed TNE live on a healthy control in order to demonstrate the ease and reliability of the technique.[79] Since that time, TNE is fast becoming, in the otolaryngology world and beyond, a safer alternative to both traditional flexible esophagoscopy with conscious sedation and rigid esophagoscopy with general anesthesia.[80-82]

Since 1996 numerous studies have compared unsedated transnasal and sedated transoral upper endoscopy. These studies showed no difference between the two techniques with respect to safety, feasibility, and patient tolerance.[83-86] As to whether an endoscopic examination of the esophagus, without a detailed examination of the stomach and small intestine, is sufficient to diagnose acid reflux disease, Wildi and colleagues[87] demonstrated that for patients who have traditional esophageal reflux symptoms—heartburn, regurgitation, dysphagia—but who do not have other gastric or duodenal symptoms—abdominal pain, nausea or history of gastric or duodenal ulcer—an endoscopic examination of the esophagus alone is sufficient. Furthermore, two studies have clearly shown that TNE with small-caliber endoscopes is as accurate as conventional upper endoscopy to detect Barrett's esophagus.[88,89] The implication here is that TNE is not only technically feasible and well tolerated but also accurate in screening for Barrett's esophagus, despite yielding a smaller biopsy specimen. In the not too distant future, office-based, unsedated TNE has the potential to eliminate the infrastructure and cost required by intravenous sedation for screening for and surveillance of Barrett's esophagus.

It is essential to endoscopically examine the esophagus in patients with suspected acid reflux disease because of the proven relationship between acid reflux esophagitis and esophageal adenocarcinoma.[90-94] Patients with acid-induced reflux esophagitis may have pathologic changes in the esophageal epithelium whereby the normal stratified squamous epithelium of the distal esophagus is replaced by columnar cells that typically are found in the stomach lining. This condition is called Barrett's esophagus. In 1975, GERD was linked to Barrett's esophagus and esophageal adenocarcinoma.[95]

The incidence of esophageal adenocarcinoma has been rising markedly since the 1970s in both the United States and Western Europe.[96,97] The risk factors for esophageal adenocarcinoma are presence of Barrett's esophagus and gastroesophageal reflux. As Barrett's esophagus may be seen in 5% to 15% of Americans with GERD, the potential public health problem in this country is daunting.

Unlike laryngeal squamous cell carcinoma, which can cause symptoms—hoarseness, cough—when a vocal fold lesion is miniscule, esophageal adenocarcinoma generally manifests when the esophageal lesion is so large that the patient presents with dysphagia. As a result, most esophageal cancers are detected at an advanced stage when the chance of survival is dismal. Specifically, the 5-year survival rate of symptomatic esophageal adenocarcinoma is less than 10%.[98,99] However, in the rare instances that esophageal cancer is detected early, usually as an incidental finding during an otherwise routine upper endoscopy or barium swallow study, it becomes a curable disease, with 5-year survival rates between 80% and 90%.[100]

So how can early detection of esophageal cancer be achieved? One way is for physicians and their patients to be educated about the presenting symptoms of the disease. As mentioned earlier, laryngopharyngeal symptoms such as cough and hoarseness are better predictors of the presence of esophageal cancer than heartburn and regurgitation.[101] Therefore, for patients with persistent laryngopharyngeal symptoms despite antacid therapy, an endoscopic examination of the esophagus is indicated. Patients may balk at the notion of having to undergo an endoscopic procedure that requires conscious sedation. This is a reasonable concern because most complications related to esophagogastroduodenoscopy (EGD) are related not to perforation but to the risks of conscious sedation. Cardiac and respiratory problems as a consequence of conscious sedation account for more than 60% of all major complications of EGD.[102-104] With TNE, no sedation, intravenous or otherwise, is required. So the major risk associated with conventional upper endoscopy is suddenly removed.

Esophagogastroduodenoscopy is useful for the direct visualization of the esophagus, along with collection of biopsy and culture specimens in patients with esophagitis and gastritis. In patients with GERD, EGD may be valuable in the search for esophageal mucosal irritation and to rule out Barrett's esophagus. Deveney and colleagues[45] evaluated a small series of patients with laryngeal inflammatory lesions and found that three out of seven (43%) had esophagitis, although none had Barrett's esophagus. Smit[105] found pH probe–proven GER in 72% of patients with globus and hoarseness, in 35% of patients with hoarseness alone, and in 30% of patients with globus alone. Abnormal EGD findings were noted in 65% of the patients in this group who had concurrent GER. On the basis of the findings of a high prevalence of pathologic GER in subjects with globus and hoarseness, Smit[105] recommended that patients with symptomatic EER and concurrent GERD be evaluated with EGD. In a small prospective study in patients with chronic laryngeal symptoms associated with EER and concomitant GER as documented by pH probe study, EGD showed grade II or higher esophagitis in all of the subjects and Barrett's esophagus or peptic esophageal stricture in 50% of these individuals.[54,106]

Tauber and associates[107] prospectively evaluated the incidence of gastroenterologic diseases in patients presenting with nonspecific laryngopharyngeal symptoms that were believed to be associated with EER. Thirty such patients refused pH probe studies and were evaluated with EGD. GERD was seen in 43%, gastric culture was positive for *Helicobacter pylori* in 23%, and 73% had some form of gastrointestinal disease diagnosed by EGD or biopsy. Medical therapy for reflux and *H. pylori* (in patients found to have the infection) resulted in a 90% therapeutic success rate for symptom resolution.[107]

McMurray and colleagues,[37] studying pediatric patients who were undergoing evaluation for airway reconstruction, found that significant reflux as demonstrated by the lower esophageal pH probe did not correlate with positive esophageal endoscopic findings or biopsy-proven inflammation of the upper or lower esophagus. A weak correlation was seen between laryngoscopic findings of EER and postcricoid biopsy findings.[37] The necessity of esophageal endoscopy in patients with EER without GERD is unclear, and the procedure may be unnecessary.[14]

Manometry

The use of manometric evaluation for patients with GERD is well documented. Knight and coworkers[47] documented the significance of esophageal dysmotility in patients with EER. These investigators used manometric studies of 100 patients with EER to show that 29% had normal motility, 48% had ineffective motility, 10% had a hypertensive lower esophageal sphincter, 9% had nutcracker esophagus, and 4% had esophageal achalasia. Rival and associates[11] noted low LES pressure in 60% of the patients they studied who had cervical symptoms of EER. Esophageal manometric evaluation is critical to surgical planning for

antireflux surgery.[67] Although manometry is valuable in a certain subset of patients with EER, it may not be useful as a diagnostic test for EER. Because it is only one measurement in time and transient relaxations of the LES are important in the pathogenesis of EER, manometry may not accurately assess patients for the absence of relaxations of the LES and, therefore, for EER.[9]

pH Probe Monitoring

Continuous pH monitoring studies are believed to be the "gold standard study" for diagnosing GERD and EER.[9,14,108] Probes that sense pH changes can be placed in different locations in the esophagus, pharynx, and hypopharynx. Probe placement can be verified with manometry, endoscopy, or fluoroscopy. Manometric localization of pH probe location is the most commonly used technique. Single pH probe techniques that involve the use of a probe placed 5 cm above the manometrically determined site of the LES are commonly employed for the evaluation of patients with GERD. With the recognition of extraesophageal symptoms of EER, the importance of adding a second probe above the UES has been elucidated. Postma[108] describes a review of patients with otolaryngologic complaints associated with EER who underwent dual pH probe testing at Wake Forest University, 59% of whom would have been inappropriately assumed to have a negative pH probe study result if the diagnosis had been based solely on the readings from the esophageal probe. In these patients, the pharyngeal sensor was needed to document EER.[109] In a similar study, Koufman and colleagues[110] showed that 11% of patients had a positive upper probe result with normal esophageal pH probe acid exposure time. Little and associates[111] demonstrated the importance of the proximal probe in children and noted that 46% (78 of 168) of subjects were found to have EER by proximal probe in spite of negative lower esophageal probe results.

Although the advent of dual pH probe studies has added significantly to our diagnostic armamentarium, it is not without its limitations. It is an invasive test, and its sensitivity is no more than 75% to 80%.[95] Hanson and colleagues[112] stated that the false-negative rate may approach 50%. Noordzij and associates[113] compared dual pH probe findings with symptom severity in patients with EER and showed that a dual pH probe positive result had poor predictive value for symptoms or signs of EER. Small variations in technique for probe placement or calibration can significantly affect accuracy.[108] Careful documentation of patient position (supine or upright), diet, and symptoms are equally important during the study. The patient should maintain his or her usual dietary and smoking habits and activity level during the study.[108,114,115]

Although there is a consensus about norms for the distal esophageal pH probe, considerable controversy exists with regard to findings in the proximal pharyngeal probe. Some researchers report that a single pharyngeal reflux event as determined by a drop in pH to 4 or less is diagnostic of EER.[108,114] Unfortunately, several studies have documented that a small percentage of normal subjects have proximal probe pH drops to less than 4.[55,116,117] Vincent and colleagues[55] showed that normal subjects were judged positive for reflux with the proximal probe (median of one event), with 80.4% of the events occurring while the subjects were upright. In addition, these investigators examined the Reflux Area Index, which incorporates the number and duration of events of pH less than 4. They state that "the reflux area index appears to be the most useful parameter to measure laryngopharyngeal reflux severity."[55] Normative data for pediatric patients is also lacking, and there appears to be considerable age-related variation.[9,40] Bauman and associates[35] performed a retrospective review in pediatric patients undergoing pH probe testing at their institution. Sixty-eight patients were noted to have EER symptoms, underwent empiric medical treatment, and were reviewed. Chronic cough, apnea, and recurrent pneumonia were the most commonly documented extraesophageal symptoms. Eight-five percent of subjects were noted by their caretakers to have symptomatic benefit from antireflux therapy. The positive predictive value of the distal esophageal probe study was more than 90%, but the negative predictive value was less than 50%. The researchers noted that the reproducibility of results on different days was poor; only a small number of subjects underwent dual pH probe study, and for those subjects, the mean percentage of time that the pH was less than 4 in the upper probe was 2.6%.[35]

Contencin and Narcy,[118] Hanson and colleagues,[112] and Koufman[14] have argued that the criteria of the pH being below 4 may be too stringent. Contencin and Narcy[118] showed that drops in pH to 6 or less at the proximal probe in children with laryngotracheitis may be significant. Pepsin, which has been shown to be critical in the pathogenesis of tissue damage, is active at pH levels of up to 5.[14] Hanson and Jiang[31] cautioned against stringent use of the pH value of 4 criterion in patients who have had prior radiotherapy, because irradiated tissue may be less resistant to reflux trauma.

Several writers have shown the importance of a positive proximal pH probe result, yet one must be careful when interpreting a negative study result in patients with EER. Many patients with respiratory tract manifestations of EER may not have reflux into the proximal esophagus, but they may have symptoms as a result of a vagally mediated reflex, as discussed previously.[114] In addition, there is a potential for sampling error, because EER may potentially cause disease but it may be infrequent and therefore not documented in a 24-hour study period.

There are several problems with catheter-based, ambulatory esophageal pH probe testing, including patient discomfort, the alteration of the patient's typical activities because a catheter is taped to the cheek for 24 hours, and early removal of the catheter.[119] A solution to these issues has been developed with the advent of wireless esophageal pH monitoring systems.[120] The wireless systems may ultimately replace the more uncomfortable, unwieldy catheter-based pH probe systems. The wireless system involves attachment of a pH capsule to the esophageal mucosa at the time of an upper endoscopy. The pH capsule can be delivered to the esophagus either transorally or transnasally.[121] Data from the pH signal is then wirelessly transmitted to a receiver that is on or near the patient. The patient may be monitored for 24 or 48 hours.[122] Wireless pH testing technology is more comfortable for the patient, is more reliable than catheter-based techniques, and provides more time to obtain pH data so that the diagnosis can be more securely made.[123]

Impedance Testing

The introduction of the multichannel intraluminal impedance technology using a pH sensor (MII-pH) allows the detection of nonacidic gastroesophageal reflux.[124] With impedance testing one can detect the presence of liquid or gaseous boluses within the esophageal lumen on the basis of changes in electrical conductivity of what is travelling within the esophagus. MII testing allows one to detect the direction of material flow, antegrade or retrograde. Furthermore, adding pH monitoring to the impedance analysis can detect both acid and nonacid reflux events.[125] It is believed that in EER, it is very often the nonacid reflux events that are responsible for persistent symptoms despite aggressive antiacid pharmacotherapy.[126,127] MII-pH likely will have a significant and growing role in diagnosing patients with EER, because studies have shown that during prolonged monitoring of pH levels, typical GER symptoms are related more to acid reflux events than to nonacid reflux events. However, symptoms that persist during acid-suppressive therapy are often related to nonacid reflux events.[128,129]

The therapeutic options for the nonacid component of the refluxate are varied and, in addition to acid suppression, include prokinetics, baclofen, and mucosal protective agents like alginates. Laparoscopic Nissen fundoplication is an option as well.[128,130]

Treatment

Behavioral Modification

Behavioral changes that are aimed at reducing episodes of reflux may be critical to the successful management of EER. Hanson and colleagues[13] have shown that nocturnal reflux precautions alone result in symptomatic improvement in approximately 50% of patients with posterior laryngitis and chronic dysphonia. Common modifications recommended include the following: avoidance of eating or drinking 3 hours before lying down; avoidance of tobacco products, alcohol,

fried foods, fatty foods, chocolate, caffeine, spicy foods, and peppermints; avoidance of tight-fitting clothing; and elevation of the head of the bed by 6 to 8 inches.[13,42,64] No controlled studies have evaluated behavioral modifications.[42] Giacchi and associates[2] evaluated patient compliance with treatment for EER and found that compliance with behavior modification varied widely. The extent of symptomatic improvement correlated positively with both medical therapy and behavior modification. The changes that most significantly correlated with symptom reduction were avoidance of food and liquid before bedtime and elevation of the head of the bed.[2] Multiple researchers have shown that acid exposure to the lower esophagus is reduced with decreases in fat intake, smoking, elevation of the head of the bed, and allowing at least 3 hours between eating and lying down.[42] Chewing gum for 1 hour after food intake resulted in reduced acid contact time in both controls and patients with reflux,[131] and it raised esophageal and pharyngeal pH.[132] The benefit was more pronounced in patients with reflux and lasted for up to 3 hours.[131] Avidan and colleagues[131] noted that walking for 1 hour postprandially caused a mild reduction of acid reflux, but only for a short time.

Over-the-Counter Antacids

Aluminum- and magnesium-based, bismuth, and bicarbonate-based antacids are very effective, low-cost, nonprescription antacid medications that can alleviate traditional GERD symptoms such as heartburn and regurgitation. These substances neutralize the pH of stomach acid, and they can thereby prevent the tissue damage caused by bile salts and deactivate pepsin at a higher pH.[8] Antacids have been shown to increase LES resting pressure.[1] Gaviscon (GlaxoSmithKline, Uxbridge, UK) contains alginic acid and is effective for reducing GER, but it does not appear to change LES pressure. Gaviscon's mechanism of action is not fully understood.[43] Antacids may be used as first-line therapy in patients with minor EER or as an adjunct to other treatment modalities.[133]

H_2 Blockers

Several H_2 blockers are currently available by prescription and over the counter. These drugs act at the histamine type 2 receptor by competitive binding, and they reduce gastric acid secretion along with pepsin production.[8,43] Some of the H_2 blocker effect is on the hepatic metabolism of other drugs, so patients should consult with their physicians and pharmacists to avoid drug-drug interactions. H_2 blockers may be used as first-line therapy in patients with minor EER, as adjunct therapy, or as step-down therapy to wean patients from PPIs.[133,133a,133b] Of patients with chronic laryngitis who were treated with H_2 blockers and behavioral modifications, 54% noted symptomatic relief after 6 weeks of therapy, with 92% reporting some recurrence of symptoms after cessation of H_2 blocker therapy.[13] Long-term high-dose H_2 blocker therapy was not found to be as effective or as cost effective as PPI therapy for the treatment of significant esophagitis.[134]

Proton Pump Inhibitors

PPIs act against the enzyme hydrogen-potassium adenosine triphosphatase in the parietal cell, thus blocking the final step of gastric acid production.[43] These drugs are more effective than H_2 antagonists for the long-term reduction of basal and stimulated levels of gastric acid production.[134a,134b,134c] Postma and colleagues[133] make the following recommendations: Patients with significant EER are started on twice-daily PPI therapy, along with behavioral modifications (especially if the patients are positive for GERD or have positive lower esophageal pH probe results); they should be reevaluated at 2-month intervals. H_2 blockers may be added to limit nighttime acid breakthrough, but the decision to add them should be based on the pattern of reflux seen on dual-channel pH probe study. Patients are assessed with the RFS and RSI; for the patient with RFS values less than 5 and RSI scores less than 10 on two consecutive examinations, Postma and colleagues[133] recommend tapering PPI therapy. Their recommended protocol for tapering medications involves initially stopping the nighttime dose of PPI and substituting an H_2 blocker. Two weeks later, the morning medication also becomes an H_2 blocker. If the patient experiences breakthrough symptoms, PPI therapy is resumed. For patients who do not show symptomatic improvement at the 4-month mark—despite high-dose PPI therapy—the pH probe study is repeated while the patient is taking medication.[133] A significant number of patients with chronic laryngitis on PPI therapy may show relative PPI resistance.[135] Other reasons for treatment failure are poor compliance and breakthrough with acid suppression therapy.[135]

An immediate-release preparation of the PPI omeprazole has been developed for which the phenomenon of nocturnal acid breakthrough does not occur.[136] A small, prospective, double-blind, placebo-controlled study of the efficacy of twice-daily dosing of omeprazole for patients with chronic laryngitis and at least four episodes of LPR on pH probe study demonstrated a placebo effect.[137] Most symptom scores improved over time for both the omeprazole group and the placebo group. The researchers did not see significant changes in endoscopic laryngeal findings in either group. Hoarseness (when scored low) and chronic throat clearing were noted to improve in the omeprazole group. The duration of this study was short; patients were evaluated at 1 and 2 months.

Promotility Agents

Metoclopramide, a dopamine antagonist, is effective against GER. It raises LES pressure, improves gastric emptying, and may improve esophageal clearance.[43,138] Metoclopramide is the only prokinetic agent that is currently available on the market, although new serotonin agonists are being evaluated by the U.S. Food and Drug Administration. Unfortunately, up to a third of patients may experience side effects from metoclopramide.[43] Patients with diabetes mellitus, dystrophia myotonica, and anorexia nervosa may have significantly delayed gastric emptying and thus may benefit from prokinetic agents.[138] Erythromycin may be used as a prokinetic agent, and it acts as a motilin agonist.[139]

Other Medical Therapy

Sucralfate has been shown to enhance mucosal resistance to trauma, is effective for promoting the healing of duodenal ulcers, and has been shown in animal studies to protect esophageal mucosa against injury from acid.[43] Sucralfate is a salt of sucrose, and it is well tolerated by patients. Its value as a treatment for patients with EER is not well elucidated. Bethanechol is an anticholinergic agent that has been shown to increase LES pressure, decrease GER, and improve salivary flow.[43]

Surgical Treatment

Antireflux surgery involves replacing the LES into the abdomen and then augmenting the LES as an antireflux barrier. The Nissen fundoplication involves the use of a 360-degree wrap of the gastric fundus around the intra-abdominal esophagus.[67] Ten-year success rates for the use of this procedure in treatment of GERD are quoted to be around 90%, with a mortality rate of 1%.[67] Fundoplication can be performed via an open or a laparoscopic approach. Complications of fundoplication are rare and include bleeding, the need for splenectomy, dysphagia, slippage of the fundoplication into the chest, early satiety, bloating, diarrhea, pneumothorax, and gastric ulceration. Deveney and colleagues,[45] assessing 13 patients with persistent laryngeal inflammatory lesions and voice disorders who underwent Nissen fundoplication, found that 73% (11 patients) showed a resolution of symptoms and endoscopic changes. Lindstrom and associates[140] performed a retrospective review of patients with EER who underwent Nissen fundoplication and found that 25 out of 29 patients had near total symptomatic relief and were not taking any antireflux medications. Wright and Rhodes[141] reviewed 145 patients with EER symptoms who underwent the laparoscopic Hill repair and saw statistically significant improvement in EER symptoms postoperatively.

Otolaryngologic Disorders Associated with Extraesophageal Reflux

Chronic Laryngitis

Hanson and colleagues[13,31,66] define chronic laryngitis as a 3 months' or longer history of one or more of the following: hoarseness that worsens with voice use; persistent or recurrent sore throat without throat infec-

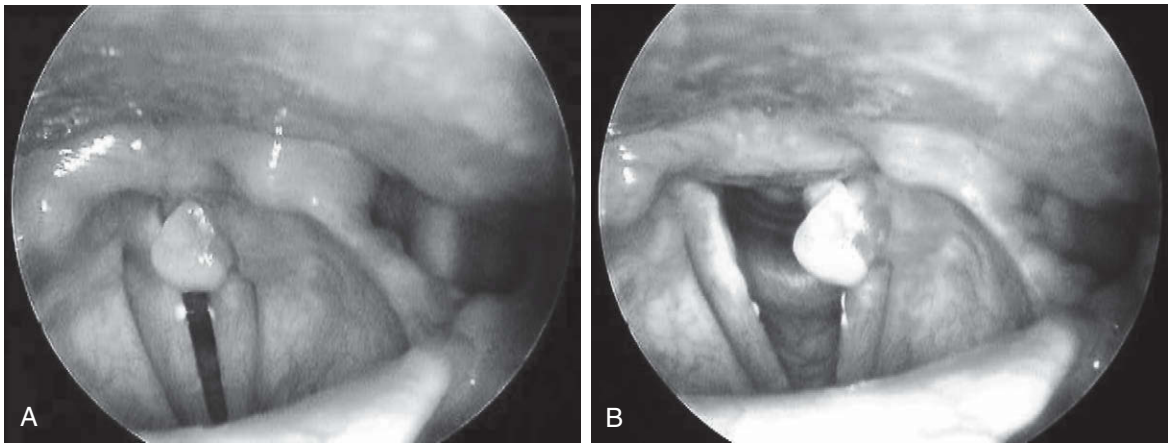

Figure 65-1. A 60-year-old patient with left vocal fold granuloma before treatment. **A,** Vocal fold adduction. **B,** Vocal fold abduction.

tion; sensation of postnasal drip; and throat clearing or cough in the absence of lower respiratory tract or pulmonary disease. The researchers report that the sensation of chronic postnasal drip is the most common and earliest manifestation of chronic irritative laryngitis, throat discomfort and dysphonia being the second and third most common symptoms, respectively. The sensation of constant secretions in the back of the throat is thought to be a result of ciliary dysfunction in the posterior larynx and pharynx.[31] Hanson and Jiang[31] studied 182 patients with chronic laryngitis that was believed to be associated with EER. Ninety-six percent of patients experienced relief with antireflux treatment within 12 weeks. Fifty-one percent (93 patients) showed response to nocturnal antireflux management alone; 48 patients required the addition of an H_2 blocker nightly, and 34 required the addition of 20 mg of nightly omeprazole. Seven patients in the study required higher dosages of omeprazole, all of whom were noted to have severe laryngeal changes at their pretreatment examinations. Symptomatic relapse was common with the discontinuation of therapy. Habermann and colleagues[60] showed that hoarseness, globus pharyngeus, sore throat, heartburn, and coughing were symptoms in patients with chronic laryngitis that showed significant improvement with an empiric 6-week course of a PPI.

Rival and others[11] demonstrated that 84% of patients with cervical symptoms associated with EER had symptomatic improvement with antireflux therapy. Koufman and colleagues,[4,142] Fraser and coworkers,[52] and Postma and associates[133] point to the need for longer duration of treatment, stating that up to 6 months of treatment may be necessary. Koufman and colleagues[4] showed that, with 6 months of antireflux treatment, 85% of patients with chronic laryngitis had evidence of treatment efficacy. They noted that half of these "responders" demonstrated an effect in 3 weeks to 3 months, with the remaining showing an effect by 6 months.[4,49,133] In a prospective study of patients with chronic laryngitis who were treated with a combination therapy of behavioral modifications, PPI therapy, and cisapride, significant therapeutic benefit was noted in patients with chronic hoarseness, but not in those with intermittent dysphonia.[53]

Contact Ulcer and Laryngeal Granuloma

Proposed etiologies for vocal process granulomas include EER, vocal misuse, intubation trauma, smoking, chronic cough, chronic throat clearing, infection, and allergies.[32,32a] In a retrospective review of 55 patients with vocal fold granulomas, there was a 76% incidence of associated EER or GERD.[32] A 50% recurrence rate was seen with surgical excision alone. All but 4 of the 55 patients who were treated with antireflux measures, medications, and voice therapy showed resolution of granulomas. In the recalcitrant four cases, antireflux surgery resulted in resolution of the granulomas.[32] In a retrospective study of 58 men with vocal contact ulcers and granulomas, esophageal dysfunction was found in 74%.[143] Hoffman and colleagues[33] recommend a treatment algorithm for laryngeal granulomas and ulcers that uses surgical intervention as a last step, with the medical management of reflux and voice therapy as the mainstay of treatment; intralaryngeal botulinum toxin is recommended for recalcitrant cases. The use of inhaled triamcinolone (Azmacort, Abbott Laboratories, North Chicago, IL), 150 µg three times a day for six to eight weeks, has also been used for treatment and avoids systemic side effects. Surgical management is reserved for cases in which conservative management has failed, in which airway obstructive symptoms are present, or in which the diagnosis is in doubt.[33] Figures 65-1 through 65-4 show some clinical examples of vocal fold granuloma and its treatment.

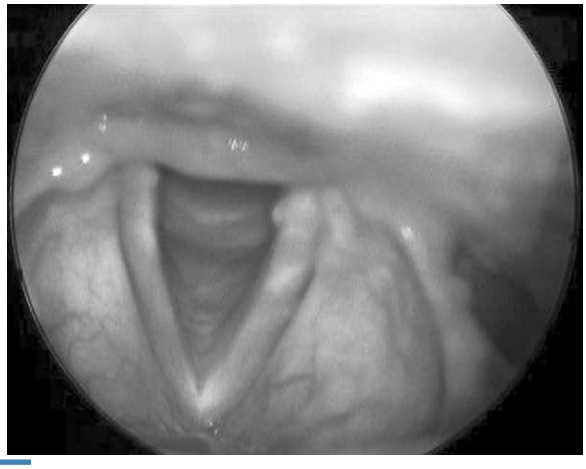

Figure 65-2. The same patient as seen in Figure 65-1, after 4 months of twice-daily proton pump inhibitor therapy and behavioral modifications.

Extraesophageal Reflux and Head and Neck Cancer

EER may play a role in the development of head and neck squamous cell carcinoma, although it has not been established as a cocarcinogen.[19-21] EER may contribute to complications of both surgical management and radiation treatment of head and neck carcinoma.[17] Copper and colleagues[17] prospectively evaluated 24 patients with laryngeal and pharyngeal squamous cell carcinoma and 10 patients who had previously received radiotherapy, all of whom had undergone 24-hour dual pH probe testing before treatment. In 11 of the 24 patients, pathologic reflux was confirmed by both probes, and only 4 patients (17%) had negative results for both probes.[17] In the irradiated patients, pathologic reflux was documented by the upper probe in 60%, by the lower probe in 70%, and by both probes in 40%.[17] A high incidence of LPR was seen in patients with premalignant and early glottic carcinomas, with 85% having positive pH probe results.[19] No significant correlations with severity of reflux or histologic stage was seen.[19] Sung and colleagues[20] studied the effect of bile acid on cultured human pharyngeal

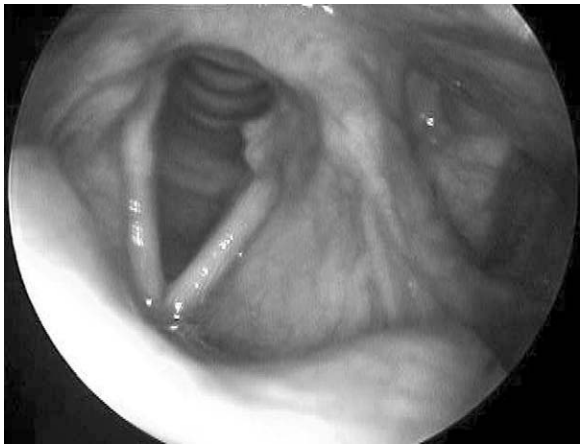

Figure 65-3. A 45-year-old man with recalcitrant left vocal fold granuloma. Prior treatment included removal, voice therapy, and high-dose proton pump inhibitor therapy with botulinum toxin injection. Dual pH probe study revealed moderate reflux in both probes.

Figure 65-4. The same patient as seen in Figure 65-3, 2 months after an endoscopic antireflux procedure.

cells. Bile acid is known to be associated with tumor formation in the esophagus through the overexpression of cyclooxygenase-2. Bile salts or acidic conditions were noted to induce cyclooxygenase-2 expression in normal pharyngeal mucosa, which may imply a role in tumorigenesis in the pharynx.[20]

Conclusion

There is substantial evidence that many otolaryngologic and respiratory symptoms and disorders can be associated with EER. EER should be considered in patients presenting with laryngeal, pharyngeal, and airway complaints. The evaluation and management of these patients must be individualized. No single diagnostic test available is a definitive gold standard; medical management offers these patients substantial symptomatic relief and often requires a multidisciplinary approach.

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Management of Unilateral Vocal Fold Paralysis

CHAPTER SIXTY-SIX

Medialization Thyroplasty

Carole Fakhry

Paul W. Flint

Charles W. Cummings

Key Points

- Both medialization thyroplasty and vocal fold injection can be used successfully to manage glottal insufficiency associated with unilateral vocal fold motion impairment, vocal fold bowing, and soft tissue deficits.
- The choice of medialization thyroplasty, vocal fold injection, or injectable should account for anatomic considerations, duration of symptoms, potential for improvement, and patient health and life expectancy.
- Videostroboscopy is useful for both preoperative and postoperative evaluation of patients with vocal fold motion impairment. Electromyography is the only test available to evaluate the integrity of the laryngeal motor unit.
- Vocal fold injections can be performed percutaneously or transorally with local anesthesia or via direct laryngoscopy with general anesthesia.
- Injections for vocal fold medialization should target the paraglottal space lateral to the vocalis muscle, whereas intracordal injections for soft tissue deficits are more superficial, but deep to the lamina propria, avoiding Reinke's space.
- Complications of vocal fold injections include under-injection, misplaced injection, over-injection, and reaction to foreign material, all of which negatively affect vocal quality.
- Type I thyroplasty makes static changes to laryngeal framework; its lack of effect on vocal fold muscle mass, innervation, and vocal fold motility is the inherent limitation of this procedure.
- Medialization thyroplasty may be performed alone or in conjunction with arytenoid adduction or reinnervation procedures for management of vocal fold paralysis.
- Complications of type I thyroplasty include failure to achieve adequate medialization, penetration of the endolaryngeal mucosa, wound infection, chondritis, implant migration or extrusion, and airway obstruction.

Since the first writing of this chapter, laryngeal phonosurgery has undergone evolution comprising a continuum of procedures designed to rehabilitate the dysfunctional larynx. Phonosurgical procedures may be classified into the following categories: (1) microlaryngeal procedures for excision of benign or malignant disease, (2) vocal fold injection for augmentation and medialization, (3) laryngeal framework surgery, (4) laryngeal reinnervation procedures, and (5) reconstructive and rehabilitative procedures after tumor resection. Laryngeal framework surgery has been further categorized by Isshiki and associates[1] into the following four types of surgical procedures on the basis of the functional alteration of the vocal folds: medial displacement (type I), lateral displacement (type II), shortening or relaxation (type III), and elongation or tensioning procedures (type IV).[2-5] This chapter focuses on laryngeal framework surgery and vocal fold injection in the context of rehabilitation of the paralyzed larynx while specifically addressing the management of glottal insufficiency from unilateral vocal fold motion impairment, vocal fold bowing, and soft tissue deficits.

Historical Aspects

The predominant focus of phonosurgical procedures has been rehabilitation of the paralyzed larynx. With a few exceptions, primary repair by end-to-end anastomosis after injury to the recurrent laryngeal nerve has been universally unsuccessful.[6] Failure of primary repair is ascribed to a random process of axonal regeneration at the site of injury that results in the simultaneous contraction of antagonistic muscle groups, otherwise known as *synkinesis*.[7,8] Alternative methods of reinnervation using ansa hypoglossus nerve–muscle pedicle implants into the posterior cricoarytenoid muscle and phrenic nerve–recurrent laryngeal nerve anastomosis for bilateral vocal fold paralysis have been explored.[9-12] Ansa hypoglossus nerve–nerve anastomosis and nerve-muscle implant techniques have also been applied to unilateral vocal fold paralysis.[11,13] Despite significant efforts in establishing appropriate reinnervation and function after injury to the recurrent laryngeal nerve, debate continues about the efficacy of these procedures. Reinnervation procedures applied to laryngeal rehabilitation are covered in greater detail in Chapter 68.

Vocal Fold Medialization

The first report of a phonosurgical procedure appeared when Brunings[14] introduced the concept of vocal fold medialization by injection of paraffin within the body of the paralyzed fold. This was followed by Payr's[15] description of an external approach for medialization that used a posterior vertical incision through the thyroid lamina, whereby the anterior flap was collapsed inward, resulting in limited medialization. Neither approach gained acceptance.

Almost four decades later, Meurman[16] reported a series of patients with vocal cord paralysis in whom external medialization procedures

were performed with use of a vertical parasagittal incision in the anterior thyroid cartilage and autologous rib cartilage grafts placed between the thyroid ala and the inner perichondrium. Meurman's procedure resulted in a high incidence of complications, probably as a result of perichondrial and mucosal perforations occurring with the anterior midline approach.

In the 1960s, Arnold[17] reintroduced vocal fold injection but with use of an alloplastic material, polytetrafluoroethylene (Teflon). Over the ensuing years, experience with this material has demonstrated a rising frequency of problems related to granuloma formation.[18-20] Subsequently, an absorbable material (absorbable gelatin sponge [Gelfoam]) was applied, allowing temporary vocal fold medialization by injection. Autologous fat has also been used to attempt permanent medialization.[21-23] However, the long-term effectiveness of autologous fat has been shown to be unpredictable, with an overall success rate of 62% at 12 months.[24] Reports of the use of bovine collagen injections for medialization were initially promising; however, soft tissue response led to variable results with respect to phonatory function.[25] At the beginning of this century, micronized AlloDerm Regenerative Tissue Metrix (Cymetra; LifeCell Corporation, Branchburg, NJ) has been applied for vocal fold injection, with early reports indicating improvements in soft tissue response, tissue compliance, and overall phonatory function. Like bovine collagen, Cymetra may last 3 to 9 months and can be used for temporary medialization in patients for whom recovery is likely to occur after recurrent laryngeal nerve injury.[26,27]

Although numerous modifications of external approaches have been reported,[28-32] Isshiki and associates[29] were the first to introduce the concept of alloplastic implant material for medialization. Using an external approach with a Silastic implant, these investigators are credited with the ultimate success and popularity of type I medialization thyroplasty. We are proponents of prefabricated implants with sizing systems. Two systems, VoCoM hydroxyapatite implants (Gyrus ACMI, Southborough, MA) and Montgomery Silastic implants (Boston Medical Products Inc, Westborough, MA), are currently available.[33] More recently, Gore-Tex strips have been used to maintain vocal fold medialization with and without arytenoid adduction.[34-36]

Although type I medialization procedures result in dramatic improvement in glottal efficiency and sound production, a small group of patients continue to have difficulty during phonation as a result of a large posterior glottal chink or vocal folds at unequal levels. To address this specific problem, Isshiki and associates[29] introduced the arytenoid adduction procedure for unilateral vocal cord paralysis. Placement of a suture around the muscular process of the arytenoid with traction in the direction of the lateral cricoarytenoid and thyroarytenoid muscles results in medial rotation of the arytenoid and downward displacement of the vocal process. The posterior gap is reduced, and the paralyzed vocal folds are placed at equal levels. Arytenoid adduction and related procedures are covered in greater detail in Chapter 67.

The advantages of an external approach to modify vocal fold tension and position without altering the structural components (mucosal fold and underlying muscle body) have expanded the role of laryngeal framework surgery. Isshiki and associates[37,38] and Koufman[39] have reported their experiences with medialization and tensioning procedures for the management of vocal fold bowing and dysphonia resulting from sulcus vocalis and soft tissue deficits.

Management of Glottal Insufficiency Associated with Unilateral Vocal Fold Motion Impairment and Soft Tissue Deficits

Several procedures are available to manage glottal insufficiency, including vocal fold injection for medialization, medialization thyroplasty, arytenoid adduction, adduction arytenoidopexy,[40] and a variety of reinnervation procedures. Selection of the appropriate procedure depends on the duration of symptoms, severity of impairment, presence of anatomic or surgical defect, and potential for recovery. In addition, the patient's overall condition and life expectancy should be considered before one embarks on a procedure that may predispose the patient to added morbidity.

Patient Evaluation and Selection

Severity of impairment can be determined from subjective criteria based on the patient's symptoms, such as breathiness, aspiration, and exertional intolerance, or on more objective criteria obtained through a variety of tests. Currently available studies for the objective assessment of laryngeal function include perceptual assessment, simple phonatory function tasks such as mean or maximum phonation time, acoustic parameters (i.e., spectrographic analysis, measurement of fundamental frequency, perturbation of frequency and amplitude, signal-to-noise ratio), and measurement of phonatory airflow. The objective assessment of laryngeal function is covered in greater detail in Chapters 57 to 59.

Videostroboscopy remains the most useful subjective and objective test for preoperative and postoperative evaluation of patients with unilateral vocal fold impairment, providing visual assessment of glottal closure and of the status of the mucosal wave. Reinnervation or denervation may be determined from the presence of abnormal or asymmetric mucosal wave patterns during stroboscopy; however, the absence of a mucosal wave does not necessarily imply denervation. Because the mucosal wave is a passive phenomenon established by adequate vocal fold tension and subglottal pressure, the presence of functional motor units is not a prerequisite for the development of the mucosal wave.[41]

Electromyography (EMG) is the only test available at this time for evaluating the integrity of the laryngeal motor unit in the presence of vocal fold motion impairment. Laryngeal EMG is useful for determining the presence of denervation or reinnervation potentials and is assuming a more active role in the prognostication, timing of intervention, and choice of surgical procedures for the paralyzed larynx.[42,43] Despite normal voluntary electric activity, however, vocal fold immobility may be present as the result of laryngeal synkinesis, joint ankylosis, or cicatricial web formation. Distinction among these processes can be made only by palpation of the vocal process during direct laryngoscopy.

With documentation of denervation by EMG, medialization thyroplasty should be considered early in the presence of aspiration or severe dysphonia. If there is evidence of recovery on visual examination or EMG, medialization by injection using a resorbable material such as collagen may be considered as a temporizing procedure. Patients with mild to moderate symptoms of dysphonia only may be counseled to allow spontaneous recovery to occur before considering permanent medialization procedures. Although type I thyroplasty is considered reversible, voice quality after the removal of implants has not been studied.

Prognosis, when combined with results of objective studies, is useful for choice of treatment. Vocal fold paralysis with a favorable prognosis occurs after blunt trauma, endotracheal intubation, idiopathic vocal fold paralysis, and paralysis associated with viral pathogens (Ramsay Hunt syndrome). In this setting, severity of aspiration, dysphonia, and EMG findings can be used to determine the choice of procedure and timing of intervention, as outlined previously. The group of patients with paralysis who have poor prognosis for recovery includes those with injury after complete nerve section during surgical resection of tumor, with invasion of cranial nerves by tumor, with paralysis associated with thoracic aneurysm, and with paralysis due to progressive neurologic disorders. Unlike peripheral recurrent laryngeal nerve injuries, high vagal injuries can result not only in loss of abductor/adductor function but also in loss of cricothyroid muscle function and deafferentation of sensory fibers. In this condition, vocal folds are more likely to be lateralized with marked bowing and atrophic changes. Patients with such injuries generally have greater difficulty with dysphonia, dysphagia, and aspiration. When denervation is documented or history portends a poor outcome, early medialization by thyroplasty is warranted.

Percutaneous medialization by injection should be considered in patients with short life expectancy and aspiration or severe dysphonia. In this situation, the time and expense of medialization thyroplasty or reinnervation procedures might not be justified.

Vocal Fold Medialization by Injection

Vocal fold medialization by injection remains a standard procedure for laryngeal rehabilitation. In the absence of arytenoid fixation and when

adequate residual vocal fold structure remains to allow needle placement for augmentation, medialization of a paralyzed vocal fold by injection can be performed with use of a variety of materials. Autologous fat and Cymetra are the materials most commonly used today. Cymetra has been shown to provide excellent phonatory results lasting 6 to 12 months with little or no inflammatory response.[44] The hyaluronic acid formulations, such as Hylan B gel (Hylaform, Genzyme Biosurgery Inc., Cambridge, MA), used as an injectable material for medialization have also been shown to have favorable viscoelastic properties.[45,46] Collagen, although not specifically approved by the U.S. Food and Drug Administration for laryngeal injections, has been shown to be effective for management of vocal fold paralysis, sulcus vocalis, and soft tissue deficits.[47] Inflammatory changes associated with soft tissue response after bovine collagen injection can result in greater tissue stiffness and less than satisfactory results. Permanent adverse effects are unlikely to occur, however, because the collagen is ultimately resorbed. The use of polytetrafluoroethylene paste (polytef) for vocal fold injection is discouraged unless long-term patient survival is not anticipated. Adverse effects from development of polytetrafluoroethylene granuloma are well documented and include dysphonia caused by soft tissue reaction and airway obstruction from mass effect.[8]

Calcium hydroxyapatite (Radiesse dermal filler, Bioform Medical, Inc., San Mateo, CA) has also been introduced as a viable material for injection laryngoplasty with longer duration of effect.[48] However, this material has been associated in case reports with a foreign body granulomatous reaction.[49] Affected patients have presented with dysphonia, pain, and vocal cord erythema visualized on fiberoptic examination. In our experience and the other reportable case, patients required suspension microlaryngoscopy, which demonstrated multiple irregular mass lesions on the true vocal folds. In both cases, microflaps were made to excise the injectable material. Histologically, a chronic inflammatory infiltrate with surrounding foreign body giant cells was observed. Therefore, we advocate caution in the use of calcium hydroxyapatite as an agent for vocal fold medialization.

Transoral and percutaneous approaches have added a new dimension to the management of vocal fold paralysis.[50,51] In most patients, medialization can be accomplished quickly and effectively in the office setting. These procedures are relatively simple and yield immediate results with little discomfort to the patient. If recovery of vocal fold function is likely, fat and polytetrafluoroethylene are usually contraindicated, and alternative methods must be considered. Cymetra can be used as a temporizing measure in this setting. Percutaneous injections are performed without sedation, local anesthesia alone being sufficient. Flexible fiberoptic laryngoscopy is required to visualize position and adequacy of injection. Given their advantages and ease of performance, percutaneous injections are becoming the preferred method in many centers. However, when airway management is a potential problem, injection in a controlled setting during direct laryngoscopy should be considered.

Percutaneous Injection

We prefer a lateral, percutaneous approach through the thyroid ala at the level of vocal fold determined by palpation of the thyroid notch and inferior border of the thyroid ala anteriorly (Figs. 66-1 and 66-2). The vocal fold lies perpendicular to this line at the midpoint. Alternatively, an anterior approach can be used through the cricothyroid membrane, with the vocal folds approached from below.[50,51] As the needle is inserted, it is angled superiorly and laterally under direct visualization with a flexible fiberoptic nasopharyngoscope. Rees and colleagues[52] reported their technique using a transthyrohyoid approach with fiberoptic visualization. The primary disadvantage of this technique is related to potential deposition of injectable material within Reinke's space. Given that the material injected in this report is calcium hydroxyapatite, there is potential for adverse outcomes resulting in permanent dysphonia. This issue is addressed by Chheda and coworkers in a report of revision laryngeal surgery after suboptimal injection with calcium hydroxyapatite.[53]

When Cymetra is used for this procedure, it is reconstituted in saline and placed in a Luer-Lok 1-mL syringe with a 1-inch, 23-gauge needle. Controlled pressure is required to pass the needle through the thyroid lamina. Visualization is best achieved with a flexible fiberoptic nasopharyngoscope with digital imaging system. The position of the needle can be visualized easily before the superficial layers of the fold are entered. Optimal results are obtained with placement of the injection just anterior and lateral to the vocal process and on a plane level with the lower border of the medial edge. Material in this location builds up the undersurface of the true fold and minimizes the risk on injecting into Reinke's space. With this technique, approximately 0.5 to 1.0 mL of Cymetra is adequate. In general, slight over-injection with Cymetra and autologous fat is preferred because resorption is anticipated. Patients should be counseled to expect voice change over time.

Figure 66-1. Percutaneous injection with fiberoptic visualization. A lateral approach is used with the needle passed through the thyroid cartilage. The needle is visualized in the paraglottic space anterior and lateral to the vocal process.

Transoral Injection

Transoral injection can be performed in selected patients. Topical 4% lidocaine solution is applied to the pharyngeal and laryngeal mucosa. With the patient holding the tongue forward, allowing indirect visualization, the injection is performed with a curved laryngeal needle. Right and left needles are available, so that the bevel is directed away from the midline to minimize the possibility of an intramucosal injection.

Laryngoscopic Injection

In patients who do not tolerate the flexible fiberoptic examination, laryngoscopic injection via a percutaneous or transoral approach may be necessary. Injection via microlaryngoscopy is also used during ablative procedures in which recurrent laryngeal or vagal nerve resection is anticipated and temporary medialization is performed to minimize immediate postoperative symptoms. The injection can be performed with the patient under general anesthesia with spontaneous ventilation, controlled intermittent apnea, or jet ventilation using the Sanders device.

With the patient in the supine position, and after initiation of appropriate anesthesia, the laryngoscope is introduced and suspended using a suspension apparatus. Care is taken not to place unnecessary tension at the anterior commissure, which would result in distortion of the vocal folds. The arytenoid cartilages are palpated with a spatula to ensure mobility, and the false vocal fold is lateralized, exposing the ventricle (Fig. 66-3).

For injection of Cymetra, a 23-gauge butterfly needle is modified by removing the flange completely on one side and leaving a small flange on the other to grasp with a small alligator forceps. Visualization is best achieved with a 0- or 30-degree, 5-mm laryngeal telescope and digital video system. Telescopic visualization provides better assessment of the depth of injection. The needle is then inserted anterior and lateral

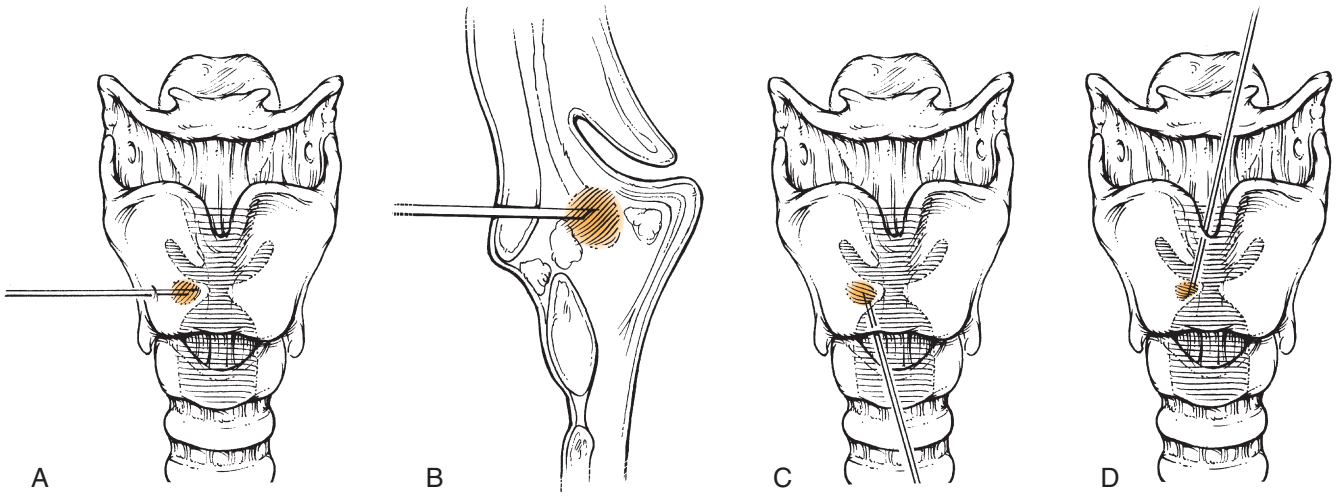

Figure 66-2. **A,** A lateral percutaneous approach for vocal fold injection. **B,** Site of injection. **C,** An anterior subglottic percutaneous approach for vocal fold medialization. **D,** Superior transthyrohyoid space approach. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

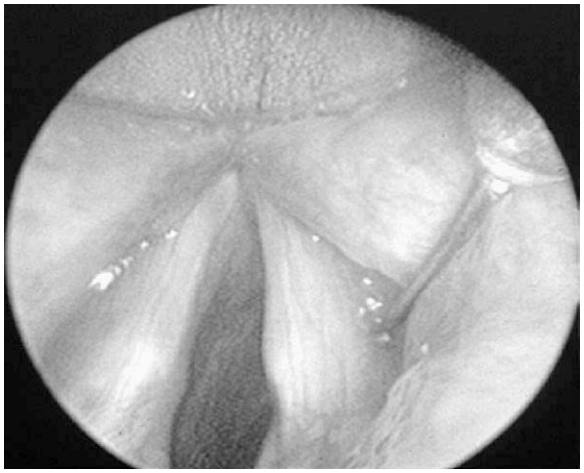

Figure 66-3. Vocal fold injection performed by direct laryngoscopy using a Brunings syringe. The injection needle is placed lateral to the vocal process and vocal ligament to prevent infiltration into Reinke's space.

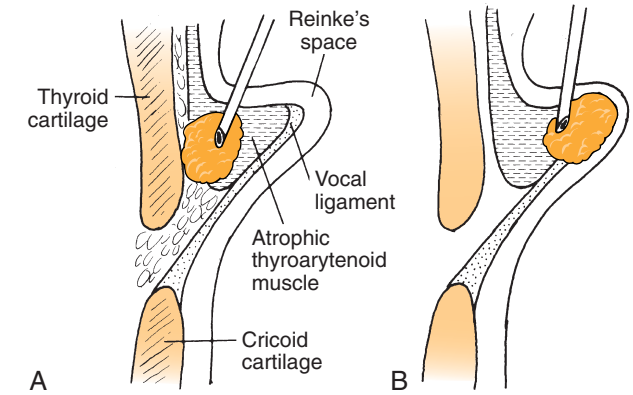

Figure 66-4. Types of vocal fold injection. **A,** Intrachordal injection for vocal fold paralysis showing the bevel of the needle directed away from the medial edge of the vocal fold. **B,** Intramucosal injection resulting from misplaced injection with the bevel of the needle directed toward the medial edge of the vocal fold. *(From Cummings CW, ed.* Otolaryngology–Head and Neck Surgery: Update I. *St. Louis: Mosby; 1989.)*

to the vocal process approximately 2 mm deep or at the plane level with the lower margin of the true fold. Autologous fat is more viscous and may require an injection gun, such as a Brunings syringe. After injection, a spatula or suction can be used to massage the vocal fold to distribute the injected material more evenly.

Laryngoscopy can also be performed with the patient under local anesthesia to monitor the changes in vocal quality during injection. Superior laryngeal nerve blocks with lidocaine should be avoided because they would alter vocal fold tension through cricothyroid muscle paralysis and thus adversely affect voice quality. After the initial injection, the scope is relaxed and the patient is asked to phonate. Repeat injections are performed as necessary.

A distinction should be made between vocal fold medialization and intracordal injection. With injections for medialization, the material is placed in the paraglottal space lateral to the vocalis muscle, leaving the mucosa overlying the vocal fold unaltered. With intracordal injections to eliminate soft tissue defects, the injectable material (collagen or Cymetra) is placed more superficially, into the area just deep to the lamina propria, avoiding Reinke's space (Fig. 66-4). Polytetrafluoroethylene is contraindicated for intracordal injections because granulomatous reactions to the material can increase vocal fold stiffness and mass, adversely affecting vocal fold vibration.[54,55]

Complications of vocal fold injection include under-injection requiring repeat procedures, over-injection with airway compromise, improper placement causing subglottal extension, and potential stenosis. Migration of polytetrafluoroethylene particles, intracordal injection of polytetrafluoroethylene impairing vibratory capability, and granuloma formation may occur (Fig. 66-5). Management of polytetrafluoroethylene over-injection is a challenging problem and should be counteracted immediately by incising the mucosa over the site of injection and removing excess material with suction. Immediate removal is preferred because delayed removal is made difficult by migration of polytetrafluoroethylene, granuloma, and scar formation. If necessary, delayed removal is generally attempted during microlaryngoscopy using cupped forceps or the carbon dioxide laser. Koch and associates,[56] evaluating the safety of using the carbon dioxide laser on polytetrafluoroethylene, found no evidence or reports of untoward side effects. Endoscopic removal should be attempted initially, although open procedures (thyrotomy) may be required in cases of persistent granuloma. Similarly, Cymetra has been found to migrate and result in a mass extending from the aryepiglottic fold to the piriform sinus, which required suspension microlaryngoscopy and resection. Histologically, the mass was consistent with a foreign body reaction. Of note, in the reported case the patient had received three injections within 12 weeks.[57]

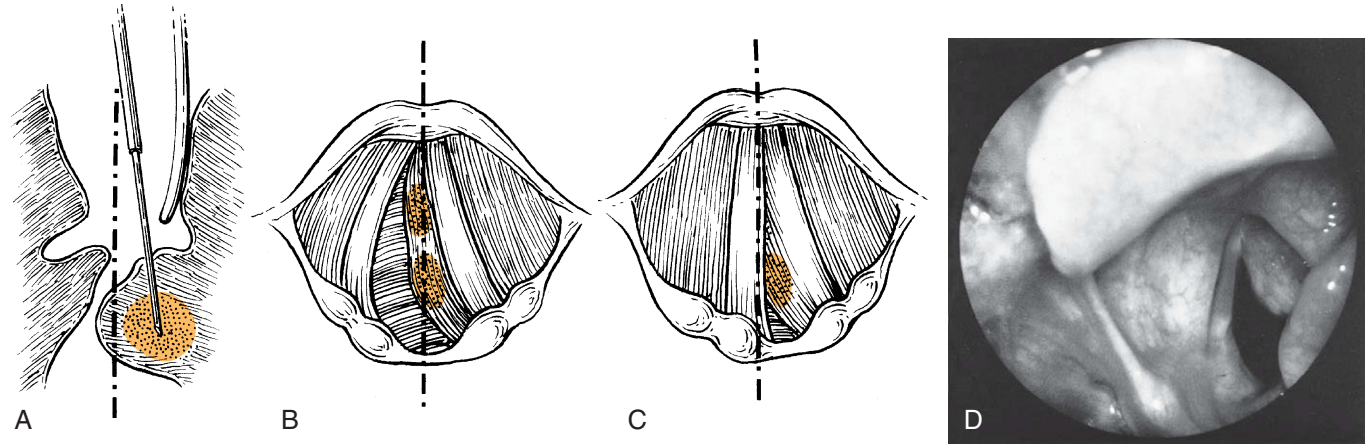

Figure 66-5. Complications of vocal fold injection. **A,** Excessive and incorrect placement of injected polytef. **B,** Inspiration with partial obstruction. **C,** Phonation with vocal fold overlap. **D,** Polytef granuloma developing 2 years after injection, resulting in dysphonia and airway obstruction. *(From Cummings CW, ed.* Atlas of Laryngeal Surgery. *St. Louis: Mosby; 1984.)*

Medialization Thyroplasty

Medialization thyroplasty is now considered by many in the surgical community to be the procedure of choice for management of the paralyzed vocal fold. The procedure can be performed alone or in conjunction with arytenoid adduction or reinnervation procedures. Also classified as a type I thyroplasty by Isshiki and associates,[29,37] this procedure offers the following advantages: (1) it is performed with local anesthesia with minimal or no discomfort to the patient, (2) patient positioning is more anatomic, allowing better assessment of voice during the procedure, (3) it is potentially reversible, and (4) because the prosthesis is placed lateral to the inner perichondrium of the thyroid lamina, structural integrity of the vocal fold is preserved, allowing medialization with effective closure of the prephonatory gap—the end result being a decrease in oscillation threshold and improved vocal efficiency.[2,58,59] Disadvantages include the following: (1) the patient is subjected to an open procedure, (2) the procedure is technically more difficult, and (3) closure of the posterior glottis may be limited.

Medialization thyroplasty is currently used for management of vocal fold paralysis, vocal fold bowing due to aging or cricothyroid joint fixation, sulcus vocalis, and soft tissue defects resulting from excision of pathologic tissue.[1,60] Treatment for paralytic dysphonia is indicated when the likelihood of recovery is negligible. When recovery is anticipated, medialization thyroplasty may be considered for management of aspiration or severe dysphonia as an alternative to repeated injections with Cymetra. Generally, dysphonia by itself should be managed conservatively if recovery is anticipated; however, our experience has not shown an adverse effect in patients who have received a thyroplasty and subsequently recovered function.

Although modifications of Isshiki's description of medialization thyroplasty are abundant, the basic principles remain the same. Factors that affect outcome include size and shape of the implant, position of the implant, maintaining proper position of the implant, and limiting the duration of the surgical procedure. In our experience, the duration of the procedure is directly related to the predictability of the end result. Carved Silastic implants, prefabricated Silastic implants (Montgomery),[31] and dense hydroxyapatite (VoCoM) implants are routinely used. Prefabricated implants with matched-sizing templates allow for more rapid determination of the correct implant position and size (Fig. 66-6). Gore-Tex strips have also been used with success and, in some situations, may provide greater adaptability than prefabricated systems.[36] However, Gore-Tex has not been immune from the potential granulomatous inflammatory responses associated with polytetrafluoroethylene products. In a laryngectomy specimen of a patient who had previously undergone Gore-Tex implantation for recurrent aspiration, histopathologic changes of multinucleated giant cells at the periphery of the Gore-Tex implant were observed.[61]

Figure 66-6. Prefabricated implant system made from hydroxyapatite. Implants vary from 3 to 7 mm of displacement. The implant is stabilized with a 0- to 3-mm offset shim (2-mm offset shim is shown with 6-mm displacement shim).

Technique

With the patient in the supine position and prepared for a sterile procedure, a paramedian horizontal incision is outlined over the middle aspect of the thyroid lamina. Local anesthesia is administered subcutaneously and in four quadrants over the ipsilateral lamina. A 5-cm incision is made through the platysma. Superior and inferior flaps are elevated in the subplatysmal plane, exposing the thyroid notch and inferior border of the thyroid cartilage. The strap muscles are split in the midline and retracted laterally off the thyroid lamina, leaving the outer perichondrium intact. A single large skin hook is implanted in the anterosuperior aspect of the contralateral ala and retracted laterally, providing exposure of the ipsilateral lamina. The cartilage window is outlined by scoring the perichondrium sharply, or with electrocautery applied to a window template. For the VoCoM system, the window measures 6 mm (vertical) by 10 mm (horizontal) (Fig. 66-7). The anterior aspect of the window is positioned 5 to 8 mm posterior to the ventral midline in women, and 8 to 10 mm in men. The superior aspect of the window should be placed at the level of the true fold. A point half the distance between the anterior-inferior border of the thyroid cartilage and the notch defines the level of the true fold. From this point, a line drawn posterior and parallel to the inferior border of the thyroid cartilage will approximate the level of the true fold. The outer perichondrium is incised and elevated from the thyroid cartilage within the confines of the window. Cartilage and osteoid material are removed precisely, preserving the dimensions of the window. If ossification has occurred, the window can be drilled out or removed with a Kerrison

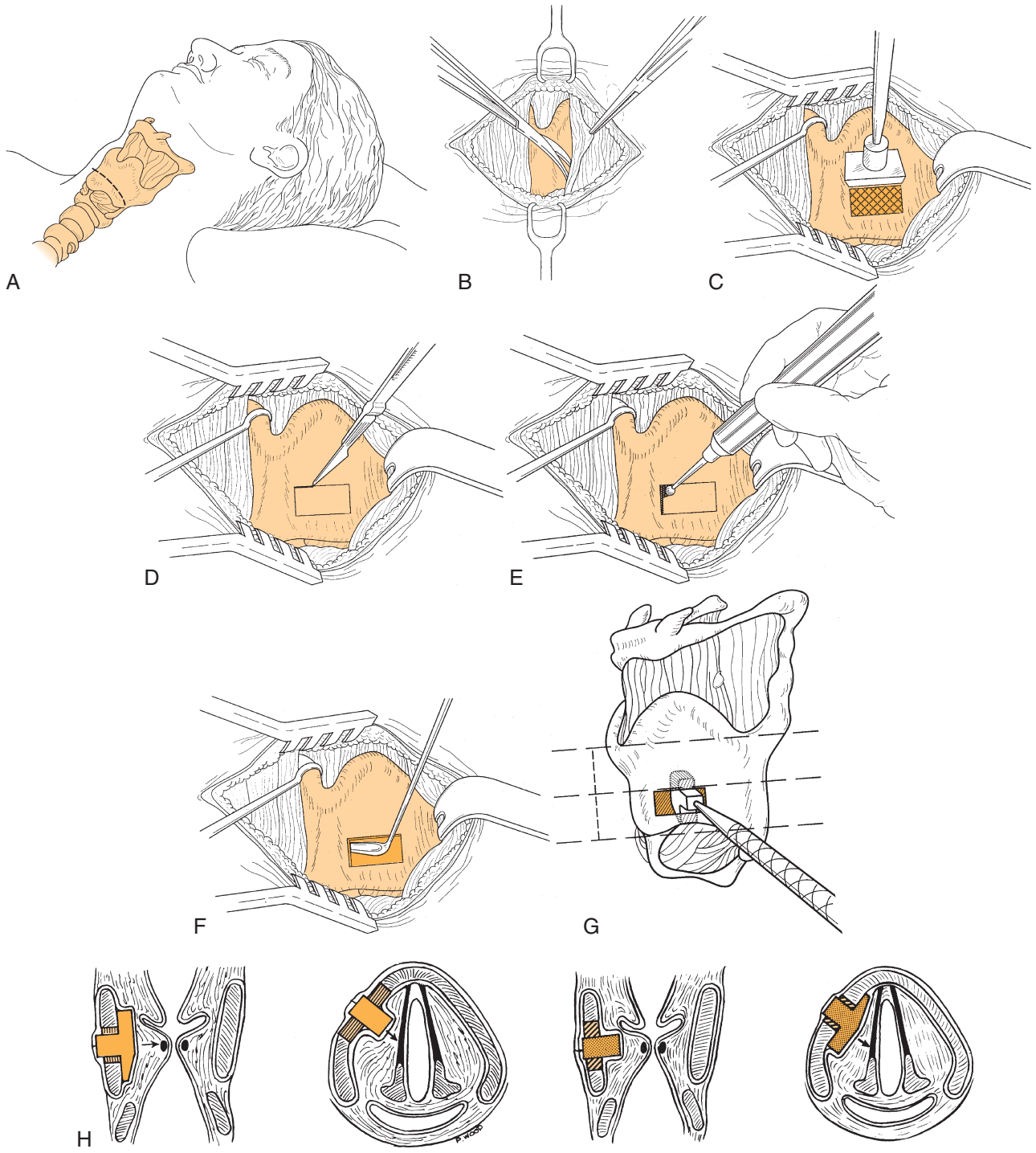

Figure 66-7. Medialization thyroplasty. **A,** Skin incision. **B,** Sternohyoid muscle is elevated off the thyroid cartilage. **C,** The muscle is retracted posterior to thyroid lamina; a cautery template marks the fenestra (6 × 10 mm), and the superior aspect of the window is at the vocal fold level. **D,** The outer perichondrium is incised and removed. **E,** A cutting bur, followed by a diamond bur, is used to remove cartilage and protect underlying periochondrium; a small Kerrison punch may facilitate removal of cartilage from the fenestra. **F,** The inner perichondrium is circumferentially elevated with a blunt dissector. **G,** A template or appropriately sized prosthesis is placed in the most effective position; the appropriate position of the fenestra is shown relative to the vocal fold level based on external landmarks. **H,** Variations in placement of the implant, showing vertical and horizontal implants relative to the plane of the true vocal fold.

punch. Care is taken to preserve the inner perichondrium, which is now elevated in circumferential fashion off the thyroid lamina by means of a laryngeal elevator.

With the VoCoM system, one of five sizing prosthesis templates (3-8 mm) is inserted through the window and rotated 90 degrees with the bevel directed superiorly (Fig. 66-8). This orientation is more likely to produce optimum voice quality; however, placing the bevel of the implant inferiorly or anteriorly in the horizontal plane can be tried. Precut Silastic implants with progressively greater displacement (3-8 mm) may also be used. Rarely are implants with displacement greater than 7 mm required. All retractors are removed, and the patient is asked to phonate while the template is moved through all four quad-

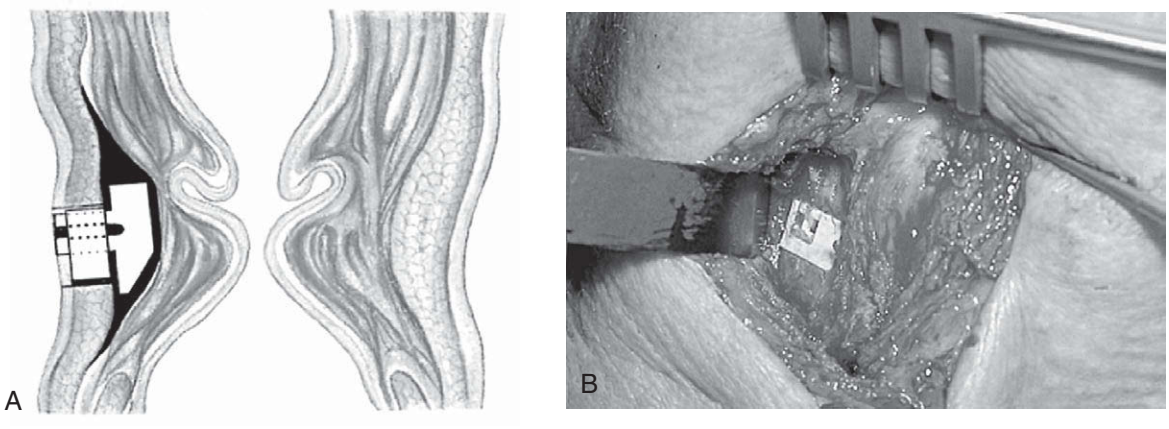

Figure 66-8. **A,** Schematic rendition of an implant positioned within the fenestra and secured with a shim. **B,** Intraoperative view of hydroxyapatite implant (VoCoM system, Gyrus ACMI, Southborough, MA) secured with shim.

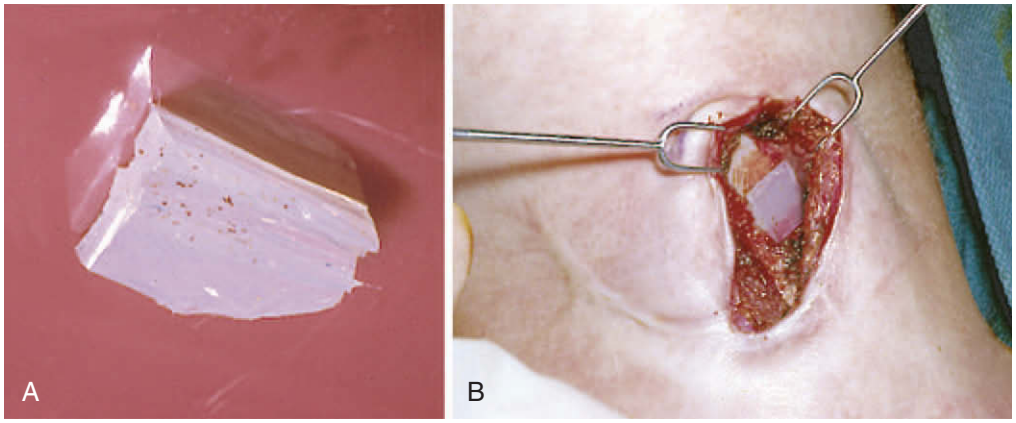

Figure 66-9. **A,** Carved polymeric silicone (Silastic) implant with medial and lateral flange to engage the thyroid lamina. **B,** Implant secured within fenestra in thyroid lamina.

rants of the window to determine the optimal position. Smaller or larger templates can be selected as needed. If medialization appears to be limited by the inner perichondrium and the thyroid cartilage is bowed outward, the inner perichondrium can be incised, releasing tension and enhancing medialization. Once the appropriate size and position have been determined, the retractors are replaced and the implant is inserted and secured with the appropriate shim. If the window is fashioned correctly, the shim will fit securely, preventing migration of the implant. If the shim is not stable, or the cartilage is thin, a suture is passed through the neck of the implant and tied over a titanium mini-construction plate, thus securing the shim. When one is using carved Silastic, the implant can be fashioned with medial and lateral flanges to engage the thyroid cartilage and thus secure it (Fig. 66-9). The wound is then irrigated with antibiotic solution. A small suction drain is placed deep to the strap muscles. Strap muscles and platysma are approximated with 4-0 absorbable suture, and skin is closed with a running 5-0 subcuticular suture. Dexamethasone (Decadron) is given preoperatively to minimize edema, and administration of prophylactic antibiotics is continued for 5 days.

We prefer to use the largest prosthesis possible that maintains quality of voice. Overcorrection is supported by Isshiki and associates,[1] who found deterioration in voice quality over time as intraoperative edema resolved in the postoperative period. When medialization is performed early after the onset of paralysis, muscle atrophy can lead to postoperative voice deterioration. Minimizing operative time is critical in obtaining optimal results.[1] Fabricating implants before the procedure facilitates the intraoperative determination of size and position and optimizes the end result.

Thyroplasty performed with Gore-Tex, as described by McCulloch and Hoffman,[35] is performed in a similar manner. Window location and dimensions do not need to be as precise. The inner perichondrium is opened, and the implant material is simply layered into the paraglottal space (Fig. 66-10).

After its first description in 1999,[62] Nishiyama and colleagues described[63] a modification of thyroplasty using autologous temporalis fascia grafts. In this procedure, temporalis fascia is harvested, dehydrated, rolled, and inserted into the vocal fold under microlaryngoscopy. Among the eight patients these researchers evaluated, phonation time was significantly improved.[63] This technique has been implemented for large glottic gaps, unilateral vocal fold palsy, post-radiotherapy scar tissue, and atrophic vocal fold.

Limitations of type I thyroplasty relate to the mechanical nature of the procedure. The procedure imparts static change to the laryngeal framework but has no influence on dynamic function. There is no effect on vocal fold muscle mass, innervation, or vocal fold mobility. Closure of the posterior glottis may be limited by narrowing of the paraglottal space as the cricoid and thyroid cartilage converge posteriorly. Furthermore, type I thyroplasty may not affect vocal fold level in the vertical plane.

Objective and subjective outcome measures of medialization thyroplasty have revealed significant patient improvements. A prospective cohort study reported significantly improved voice in terms of hoarseness ($P < .001$) and breathiness ($P < .001$). Average phonation time increased from 4.6 to 15 seconds, and voice amplitudes were significantly higher (62.9 dB vs. 68.0 dB, $P < .01$), although preoperative and postoperative frequencies were similar.[64]

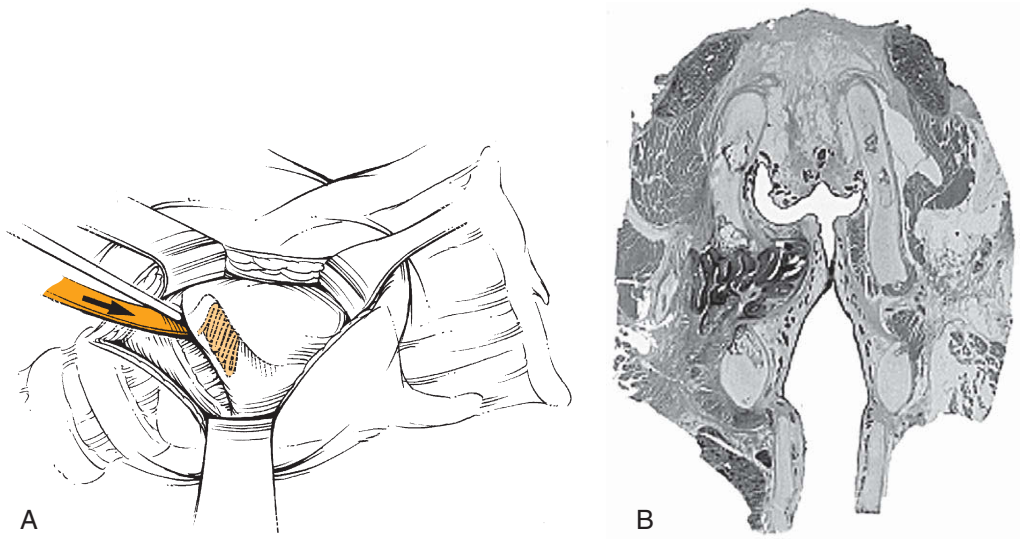

Figure 66-10. **A,** Schematic diagram of thyroplasty technique using porous polytetrafluoroethylene (Gore-Tex) strip. The strip can be placed through a standard fenestra or via an inferior approach. **B,** Postmortem whole-organ section of human larynx obtained 6 months after Gore-Tex thyroplasty, demonstrating medialization of implanted vocal fold. (*A, © 2008 by Johns Hopkins University, Art as Applied to Medicine. B, Photomicrograph generously provided by Timothy McCulloch, M.D., University of Washington, Seattle.*)

Complications associated with type I thyroplasty include penetration of the endolaryngeal mucosa, wound infection, chondritis, implant migration or extrusion, and airway obstruction. Airway compromise, the most serious potential problem, requires overnight inpatient observation.[65,66] Combined medialization thyroplasty and arytenoid adduction increase this risk.[65] Penetration of the endolaryngeal mucosa raises the risk of implant extrusion into the airway and infection. Before placement of the implant, the surgeon should assess the window for air leak by filling the wound with saline while the patient phonates. If communication with the airway has occurred, as determined by air escape, the procedure should be terminated. Intubation soon after medialization can result in displacement of the prosthesis or mucosal erosion resulting from endotracheal tube pressure.

Although the overall complication rate with type I thyroplasty is less than 3%, incomplete glottal closure resulting from undercorrection or improper placement of the implant occurs in approximately 10% to 15% of patients. Incomplete glottal closure is more likely to occur in patients undergoing acute implantation as a result of progressive vocal fold atrophy occurring after denervation. The surgical menu for management of incomplete closure includes revision thyroplasty, vocal fold injection with autologous fat or Cymetra, reinnervation procedures, and arytenoid adduction. Revision thyroplasty is surgically feasible and results in a high rate of improvement over the preexisting condition.[67] Silastic implants may be repositioned, or a larger prosthesis may be fashioned and reinserted through the previously created fenestra. However, removal of the implant with recreation of the surgical envelope and reintroduction of a new prosthesis is more difficult than the initial step in the procedure. In our experience, revision of VoCoM implantations resulted in dramatic improvement over the pre-revision condition (CW Cummings, PW Flint, unpublished data).

Medialization thyroplasty alone offers a simple solution to the management of unilateral laryngeal paralysis. With recognition of the limitations of this procedure, there are situations in which more than one procedure is required. Combining medialization thyroplasty with arytenoid adduction or reinnervation is, at times, necessary. These surgical approaches are discussed in Chapters 67 and 68.

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CHAPTER SIXTY-SEVEN

Arytenoid Adduction

Gayle Ellen Woodson

Key Points

- Arytenoid adduction mimics the action of the lateral cricoarytenoid muscle to close the glottis by rotating the arytenoid cartilage.
- Arytenoid adduction is indicated for treatment of laryngeal incompetence due to flaccid laryngeal paralysis.
- This procedure is usually performed simultaneously with a thyroplasty.

The arytenoid adduction procedure addresses laryngeal incompetence in patients with unilateral laryngeal paralysis.[1] It mimics the action of the lateral cricoarytenoid muscle to close the glottis via rotation of the arytenoid cartilage rather than direct displacement of the membranous vocal fold.[2] An adduction suture is placed in the muscular process of the arytenoid, which is the origin of the lateral cricoarytenoid muscle. This suture is passed forward through the paraglottic space and secured to the inferior thyroid ala (Fig. 67-1). This anterior traction pulls forward on the muscular process so that the arytenoid rotates. The vocal process, which is orthogonal to the muscular process, moves medially, dragging the membranous vocal fold with it. Arytenoid adduction can be performed in conjunction with type I thyroplasty. Research in animal models indicates that a combination of the two procedures is more effective than either alone.[3]

Arytenoid adduction is a more invasive procedure than type I thyroplasty and is technically more difficult. It has been reported to carry somewhat greater surgical risks, including airway obstruction, joint dislocation, fistula, and carotid injury.[4,5] A 2001 study compared outcomes of type I thyroplasty alone or in combination with arytenoid adduction in 237 patients. The complication rate was 19% in patients undergoing arytenoid adduction versus 14% in those receiving thyroplasty alone. However, the difference in the complication rate was not statistically significant, and the 2 patients who required emergency tracheotomy for airway obstruction had thyroplasty alone.[6] Arytenoid adduction does provide better closure of the posterior glottis, and research in animal models has objectively documented that acoustic and aerodynamic results for this procedure are better than for those of thyroplasty alone.[7,8] Thus, arytenoid adduction is a valuable component of the therapeutic armamentarium for rehabilitation of patients with laryngeal paralysis, particularly those with significant glottal incompetence.

The clinical impact of laryngeal paralysis varies greatly.[9] Some patients with unilateral paralysis are completely asymptomatic. At the other end of the spectrum, some patients are aphonic and have severe problems with aspiration during swallowing. Such severe symptoms result from laryngeal incompetence—the inability of the glottis to close completely. Two key factors that influence glottal closure in patients with laryngeal paralysis are the configuration of the paralyzed vocal fold and the compensatory function of the contralateral fold.

Several theories have been proposed to explain variations in symptoms and vocal fold positions in patients with laryngeal paralysis, ranging from selective damage to abductor fibers[10] to adductor action of the cricothyroid muscle (Wagner-Grossman hypothesis).[11,12] However, it has been demonstrated that the cricothyroid muscle does not exert an adductor force on the vocal fold.[13-15] It is now generally accepted that a medial vocal fold position results from residual or regenerated innervation of laryngeal muscles.[16-19] When there is significant innervation of adductor muscles, the paralyzed fold is located near the midline, and compensatory activity of the normal side of the larynx can often close the glottis during phonation. In such cases, aspiration is rare, and hoarseness or breathiness responds well to surgical medialization of the membranous vocal fold performed by injection or thyroplasty. On the other hand, complete flaccid paralysis results in a cadaveric position of the vocal fold with more severe glottal incompetence, often referred to as a posterior gap.

It has long been recognized that vocal fold injection, such as with polytetrafluoroethylene (Teflon), cannot restore glottal competence when there is a large glottal gap.[20] There is some controversy regarding the efficacy of Isshiki type I thyroplasty in closing a posterior gap. It has been contended that a posterior extension of the thyroplasty implant can close a posterior gap, based on clinical observation.[21] However, other clinical reports as well as experimental studies indicate that arytenoid adduction is much more effective than thyroplasty in closing the posterior glottis.[7,8]

The concept of a "posterior gap" is not entirely accurate, in that the maximal glottic opening is between the vocal processes. The open glottis actually converges posterior to the vocal processes because lateral displacement of the vocal process involves external rotation of the arytenoid cartilage, not lateral displacement of the arytenoid.[22,23] In other words, the angle between the membranous vocal fold and its posterior cartilaginous portion decreases as the vocal fold abducts (Fig. 67-2).[24] Thus, the posterior portion of the cartilaginous vocal fold is medial to the vocal process in abduction, and it prevents glottic closure even with vigorous hyperadduction of the normal vocal fold (Fig. 67-3). Procedures that medialize the membranous vocal fold may achieve some medial displacement of the vocal process; however, the force vectors created by such procedures are inadequate to effect significant internal rotation of the arytenoid cartilage.

Vocal fold injection and type I thyroplasty do not address differences in the level of vocal folds. The paralyzed vocal fold often lies in a different plane from that of the mobile vocal fold. Although both folds are firmly attached to the anterior commissure, the vocal process may sag on the paralyzed side or lie above the glottic plane, as it does in physiologic abduction. Thus, there can be a significant vertical gap between the edges of the vocal folds, even when they appear to be touching when viewed from above in a two-dimensional image. The paralyzed fold can lie either above or below the glottal plane. In cadaver specimens from subjects who had chronic vocal fold paralysis,

the vocal fold has been reported to be caudally displaced with a wide ventricle and shift of the conus elasticus to a horizontal plane.[25,26] Other reports describe superior displacement of the paralyzed vocal fold, essentially the same position assumed by an actively abducted vocal fold.[2,27]

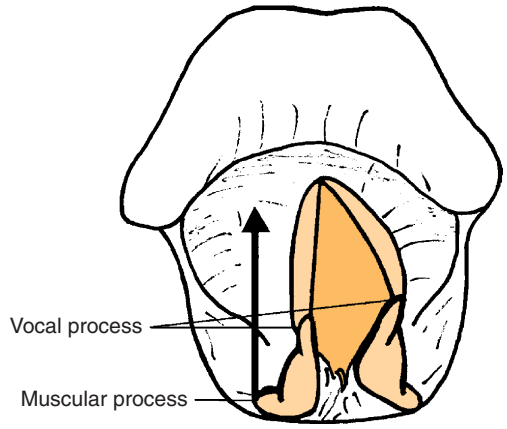

Figure 67-1. Arytenoid adduction procedure. Anterior traction (*arrow*) on the muscular process rotates the arytenoid so that the vocal process moves medially.

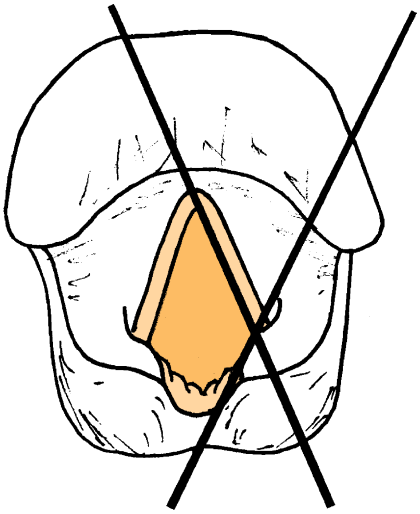

Figure 67-2. Vocal fold angle (*X*) formed by membranous and cartilaginous portions of the vocal fold.

A difference in the level of the vocal folds can often be appreciated with indirect mirror laryngoscopy, which permits binocular vision. In 1932, noting observations with mirror laryngoscopy, New and Childrey[28] stated, "In the absence of any innervation from the recurrent nerve fibers, the cord is somewhat relaxed or bowed; it is, therefore, shortened, somewhat narrowed and depressed, lying at a lower level than normal." In a two-dimensional video image, a level difference is not apparent. What can be perceived is a difference in the apparent length of the vocal folds. Brewer and colleagues[29] noted that a paralyzed vocal fold generally appears shorter than its mobile mate. In patients with significant glottal incompetence, the apparent length of a paralyzed vocal fold during inspiration is approximately two thirds that of the mobile side. During phonation, the mobile vocal fold appears to shorten to nearly the same length as its paralyzed mate (see Figure 67-3). Successful arytenoid adduction increases the apparent length of the paralyzed vocal fold.[30]

Three-dimensional motion analysis in cadaver larynges indicates that the arytenoid adduction procedure does not actually lengthen the vocal fold but instead moves the vocal process caudally. It is this vertical component of motion that is endoscopically perceived as a length change; the visual image shortens owing to rotation of the vocal fold out of the optical plane.[31] In arytenoid adduction, the arytenoid rotates about an oblique helical axis. As the vocal process moves medially, it is displaced caudally as well (Fig. 67-4).[32] Conversely, when the posterior cricoarytenoid muscle abducts the vocal fold, the vocal process moves laterally, rostrally, and caudally (Fig. 67-5).[23] An abducted vocal fold appears shorter when viewed from above because the vocal process has moved rostrally; the vocal fold slopes upward, out of the plane of the image. In adduction and during arytenoid adduction, the vocal process moves caudally, toward the level of the anterior commissure, so that the vocal fold is parallel to the image plane, and the apparent length is longer.[31]

The cricoarytenoid joint is a shallow ball-and-socket, and therefore, it is multiaxial. That is to say, vocal folds do not open and close along a fixed "track," and the rostrocaudal level of the vocal process is not completely dictated by internal and internal rotation. Cadaver studies of simulated muscle contraction demonstrate that the axis of rotation for the posterior cricoarytenoid is quite different from that for the lateral cricoarytenoid muscle (see Fig. 67-5).[23] This means that varying the force of individual muscles enables the rostrocaudal position of the vocal process to be varied independent of its mediolateral position. This is a likely mechanism of compensation by the active vocal fold in patients with laryngeal paralysis.

Because of the multiaxial nature of the cricothyroid joint, the vocal process of a paralyzed vocal fold is not necessarily located along the path of physiologic motion. In a normal larynx, the vocal process moves upward as the vocal fold is adducted. But in flaccid paralysis, the pull of the posterior cricoarytenoid muscle is lost, so that the arytenoid may "tip" forward (see Fig. 67-3A). The vector of the pull in the arytenoid

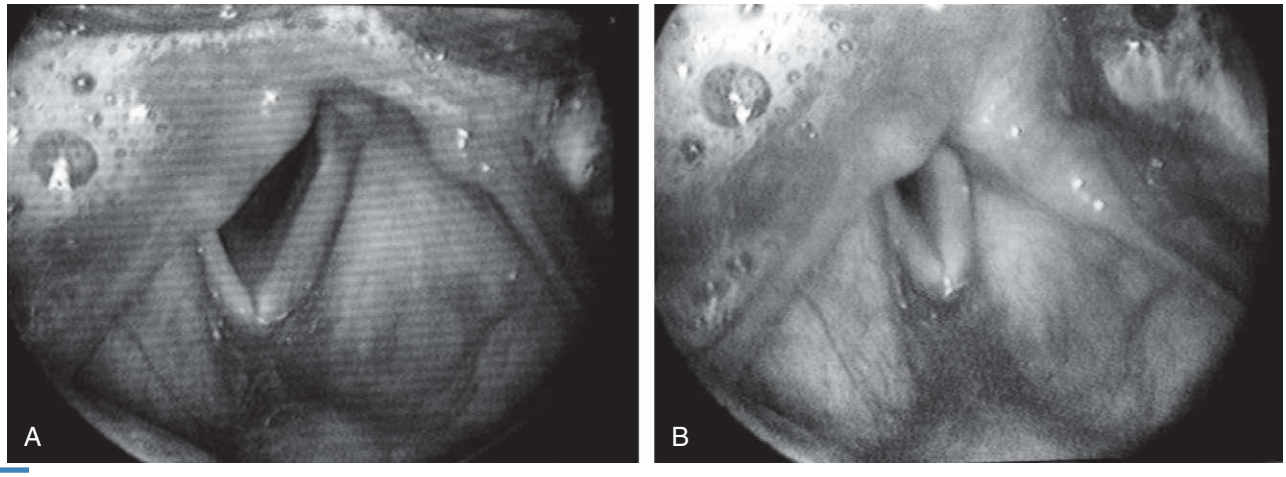

Figure 67-3. **A,** Apparent vocal fold shortening in laryngeal paralysis. **B,** Compensatory shortening of the mobile focal fold.

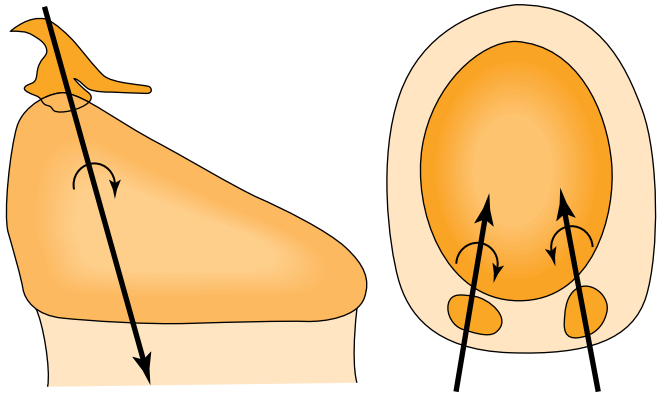

Figure 67-4. Axis of rotation (indicated by *arrows*) in arytenoid adduction, as determined in three-dimensional motion analysis in cadaver larynges.

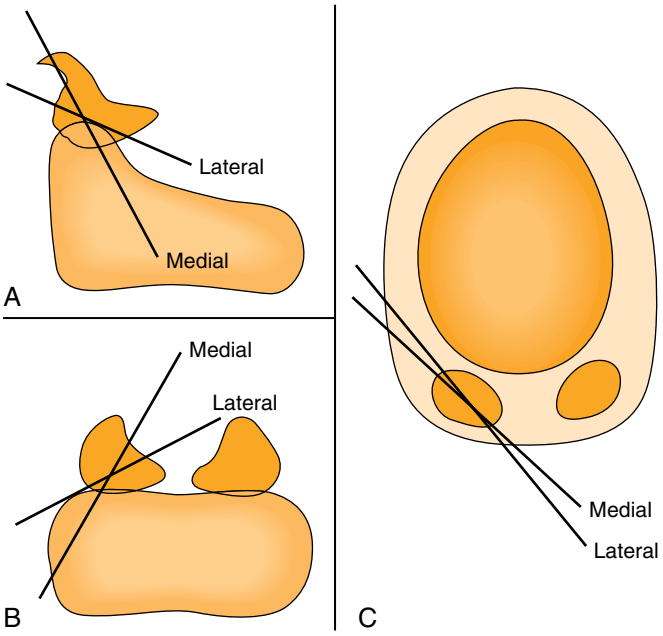

Figure 67-5. Axes of rotation (*X*) with simulated individual contraction of the two bellies of the posterior cricoarytenoid muscle in cadaver larynges. **A,** Sagittal view; **B,** posterior, coronal view; **C,** axial view. These data, as well as those from the study depicted in Figure 67-4, illustrate the multiaxial nature of the cricoarytenoid joint.

adduction procedure is similar to that of the cricoarytenoid muscle, anteriorly and slightly inferiorly. Thus, the procedure cannot correct, and may exacerbate, anterior tip. One approach to correcting the "sagging" arytenoid is a posterior suspension suture, which pulls posteriorly and inferiorly on the vocal process, to "rock" the arytenoid into a position that is nearer than that assumed during normal phonation (Fig. 67-6).[33] Another approach to the sagging arytenoid is adduction arytenoidopexy.[34] However, adduction arytenoidopexy fixes the arytenoid to the cricoid posteriorly and does not provide a medial vector of force at the vocal process. Thus, the vocal process can be pushed laterally by the adduction force of the normal vocal fold during phonation.

The membranous vocal fold is moved medially by arytenoid adduction. However, if the thyroarytenoid muscle is atrophic (which is frequently the case in cadaveric paralysis), there is still a glottal gap anterior to the vocal process. This gap can be addressed by concomitant or subsequent medialization by injection or type I thyroplasty.

Dysphagia can be a significant problem when laryngeal paralysis is the result of a vagus nerve injury. Pharyngeal propulsion is impaired

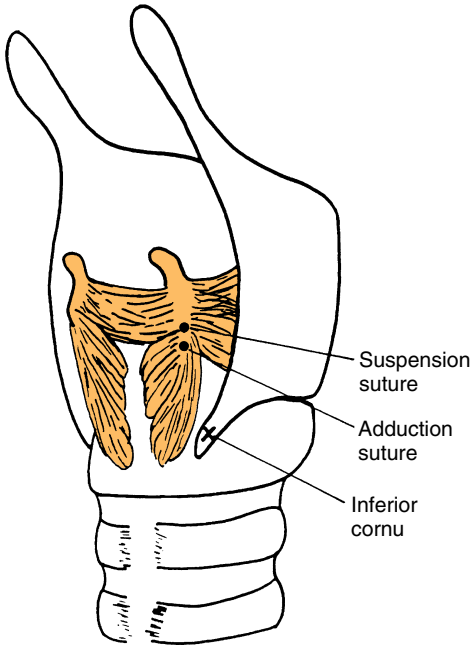

Figure 67-6. Posterior view of larynx demonstrating muscular process attachment of the arytenoid adduction suture and the suspension suture. The suspension suture is anchored to the inferior cornu of the thyroid cartilage.

owing to ipsilateral paralysis of constrictor muscles. But the cricopharyngeal muscle retains tone because it is a continuous muscular sling that receives bilateral innervation. There is inadequate pharyngeal pressure to push the bolus into the esophagus, resulting in stasis of secretions and ingested food in the hypopharynx. In such cases, a cricopharyngeal myotomy can be effective in improving swallowing and reducing aspiration.[21] Cricopharyngeal myotomy is easily performed in conjunction with the arytenoid adduction procedure.[35]

Arytenoid adduction is less effective in patients with long-standing laryngeal paralysis. This limitation does not appear to be due to joint fixation, because the arytenoid can be successfully internally rotated, with objective improvements in maximum phonation time and mean phonatory airflow. But the apparent length, and presumably the vertical position of the arytenoid, is not improved, so compensatory hyperfunction is still required for speech.[30] It is possible that contracture and fibrosis of soft tissues, such as muscle and mucosa, prevent correction of the vertical position of the vocal fold. The outcome of the arytenoid adduction procedure is also less favorable in patients with paralysis due to central neural lesions, such as tumor or stroke, because of associated sensory, reflex, and/or cognitive deficits.

Operative Technique

Anesthesia

Local anesthesia is preferred for arytenoid adduction in most patients so that the changes in voice can be monitored intraoperatively. The correct degree of arytenoid adduction can be ensured, and the potential need for a concomitant thyroplasty can be assessed, by transnasal flexible laryngoscopy. Moreover, glottic configuration can be adjusted without the confounding presence of an endotracheal tube. Finally, the risks of general anesthesia are avoided. Despite the fact that the larynx is rotated 90 degrees or more during the procedure, the airway is usually not appreciably compromised. Intraoperative swelling can compromise the airway and alter glottic closure, making intraoperative assessment less accurate. Therefore, preoperative steroids are recommended to minimize intraoperative swelling. Patients must be sufficiently alert during the procedure to cooperate. A patient who is overly sedated may actually become agitated during the procedure. Thus, sedation is recommended only during injection of local anesthesia. A field block

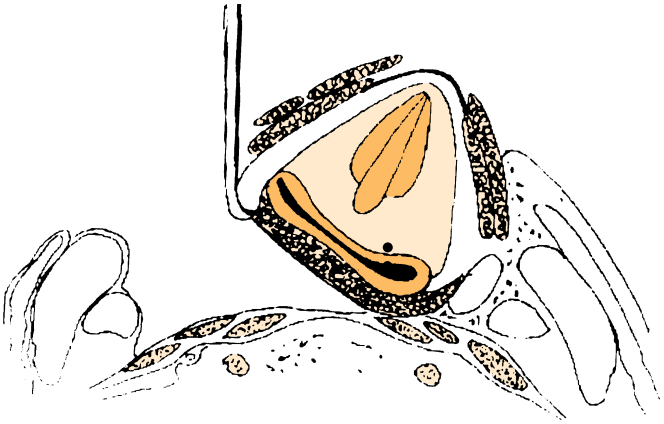

Figure 67-7. Surgical approach to the arytenoid, lateral to cervical strap muscles. The larynx is rotated to the opposite side, by means of traction on the superior cornu of the thyroid cartilage.

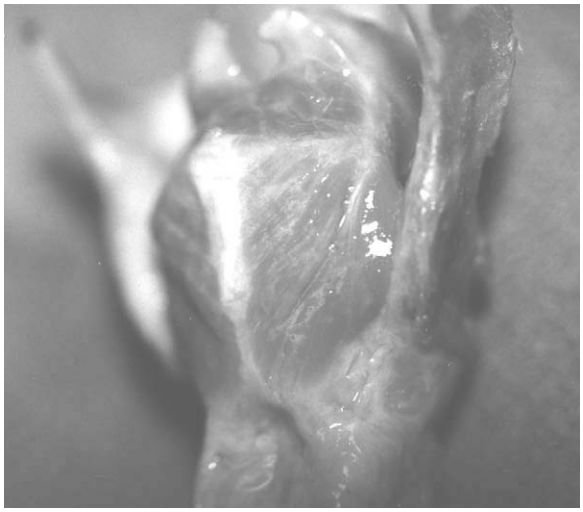

Figure 67-8. Muscular process of the arytenoid cartilage, located at the convergence of posterior cricoarytenoid muscle fibers.

provides adequate anesthesia at the outset; however, supplemental injections are required because the dissection proceeds posteriorly. An ipsilateral superior laryngeal nerve block minimizes coughing during intralaryngeal dissection.

General anesthesia can be used in uncooperative or very anxious patients or in those in whom dissection is anticipated to be difficult, such as very obese patients or those with extensive scarring in the operative field. General anesthesia is also a good option for patients with an existing tracheotomy. When the procedure is performed with the patient under general anesthesia and intratracheal intubation, direct laryngoscopy is used for intraoperative assessment. Obviously, this task is not precise when an endotracheal tube is present. Another approach is to use a laryngeal mask for the airway and flexible endoscopy to monitor the larynx.

Surgical Procedure

The larynx is approached through a horizontal skin incision at the lower border of the thyroid cartilage, extending from the ipsilateral sternocleidomastoid muscle to approximately 1 cm past midline. It is most efficient to create a thyroplasty window at the outset of the procedure. This provides a route for the arytenoid adduction suture to be passed later in the operation, and it also sets the stage for concomitant thyroplasty if it is necessary.

After the thyroplasty window is created, the next objective is to expose the muscular process of the arytenoid. Several approaches have been described. I prefer to dissect lateral to the cervical strap muscles, rotating the larynx away from the opposite side. This rotation displaces the larynx away from the carotid sheath, minimizing risk to those structures. Dissection should "hug" the strap muscles, continuing posteriorly to the inferior constrictor muscle and superiorly to identify the superior cornu of the thyroid cartilage. A sturdy cricoid hook should then be placed on the superior cornu of the thyroid cartilage to rotate the larynx away from the field (Fig. 67-7). Dissection should be continued inferiorly, medial to the thyroid gland, down to the level of the cricoid.

Next, the inferior constrictor muscle is transected over the posterior edge of the thyroid cartilage. Inferiorly, the cricopharyngeal muscle comes into view, and this muscle can then be resected if needed. The muscle can be defined by blunt dissection just behind its attachment to the cricoid, and then a 1- to 2-cm segment of muscle is excised.

A critical step in the procedure is identification and displacement of the pyriform sinus mucosa, to expose the arytenoid cartilage and to avoid entry into the hypopharynx. The pyriform sinus is separated from the medial surface of the thyroid ala by blunt dissection. Identification of the posterior and inferior limits of the pyriform sinus is facilitated by having the patient utter plosive phrases (such as "puppy") that generate gentle positive intrapharyngeal pressure. The pressure distends the pyriform sinus and makes its edges apparent. The sac is then reflected superiorly and anteriorly, exposing the posterior cricoarytenoid muscle. The fibers of this muscle are then followed to their convergence and insertion on the muscular process of the arytenoid. In a man with a large thyroid cartilage, adequate exposure may require transaction of the thyrohyoid ligament to permit greater laryngeal rotation. Alternatively, a posterior portion of the thyroid cartilage could be resected, as described by Netterville and colleagues.[36] Maragos[37] has reported performing arytenoid adduction via a posterior thyroplasty window.

In their original description, Isshiki and colleagues[1] recommended transection of the cricothyroid joint as well as opening of the cricoarytenoid joint to locate the muscular process. These steps potentially destabilized the larynx, and most later writers have not found it necessary to compromise these structures.[38]

The muscular process appears as a white prominence between the attachments of the anterior and posterior bellies of the posterior cricoarytenoid muscle (Fig. 67-8). This is where the adduction suture is placed—a 4-0 permanent suture with a sturdy but small-radius curved needle (I prefer a cardiac valve needle). The muscle tendon is grasped near its insertion, and the needle is passed from back to front through the cartilage process; care should be taken to not injure the pyriform mucosa. The surgeon should then tug the suture while palpating the arytenoid, to assess the "purchase." If the entire arytenoid does not move with traction on the suture, the stitch was passed through soft tissue rather than the cartilage. The suture is then used to provide traction, to stabilize the arytenoid, and to ensure placement in the cartilage. When a satisfactory suture has been placed, it should be tied down securely, leaving two long ends.

The next step is to create a paraglottic tunnel, deep to cartilage and lateral to muscle, extending from the site of the suture to the window that was previously created in the thyroid cartilage. One strand of the suture is then passed through this tunnel. At this point, the larynx should be observed endoscopically to detect arytenoid motion during alternating traction on the anterior and posterior ends of the adduction suture. If appropriate rotation of the arytenoid is not observed, the suture attachment is reassessed.

Once adequate rotation is ensured, the second, posterior end of the arytenoid adduction suture is passed forward through the tunnel, bringing it out under the thyroid cartilage rather than through the window. This allows the stitch to be secured by tying of the suture over the inferior thyroid strut, at the posterior inferior corner of the window (Fig. 67-9). Sutures in this position will not be affected by a thyroplasty implant.

Next, the patient is asked to phonate with the vocal fold adducted so that the need for thyroplasty can be assessed. The thyroplasty can be performed in many ways, as covered in another chapter in this book.

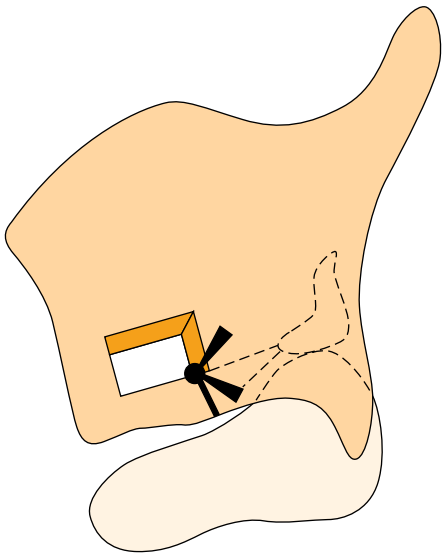

Figure 67-9. Position of arytenoid adduction suture in the posterior inferior corner of the thyroplasty window to allow simultaneous thyroplasty.

A rigid implant is preferred, rather than flexible ribbon, because the paraglottic space dissected to create a passage for the adduction sutures is much larger than needed to accommodate the medialization implant. If a rigid implant is used, the soft tissues will contract around it. However, if flexible ribbon is packed into the space, a larger volume will be required to medialize the vocal fold, and there may be excess or inappropriately positioned medialization.

If the arytenoid sags forward and the vocal fold is in a lower plane than the normal fold, a posterior suspension suture should be considered. The suspension suture is placed in the arytenoid cartilage a few millimeters superior to the muscular process of the arytenoid, on the ridge that extends from the muscular process to the apex of the cartilage (see Fig. 67-6). The suture is then passed through or around the inferior cornu of the thyroid cartilage, and is tied down to provide inferior traction. The larynx is observed endoscopically while tension is adjusted to rock the larynx posteriorly, without canceling out the adduction achieved by the arytenoid adduction suture.

Postoperative Care

In general, patients can resume oral intake within 1 to 2 hours after surgery. I keep patients overnight in the hospital after the procedure to observe for possible airway obstruction. Bleeding into the paraglottic space is the primary cause of postoperative airway obstruction. Thus, it is imperative to leave an adequate drain, to suppress coughing, and to control blood pressure. Maragos[39] has described postoperative airway obstruction due to herniation of pyriform mucosa into the airway. He reports that suture stabilization of pyriform mucosa at the close of the procedure is effective in preventing this complication.

Arytenoid Abduction for Bilateral Paralysis

A variation of arytenoid adduction is arytenoid abduction.[40] The procedure is identical to arytenoid adduction, except that the suture through the vocal process is anchored posteriorly rather than anteriorly. This vector of force rotates the larynx externally to abduct the vocal fold. Arytenoid abduction has been described as a surgical option to improve the glottic airway in patients with bilateral laryngeal paralysis. It can be performed in lieu of an emergency tracheotomy in patients with airway distress. Alternatively, it can be performed in patients with a tracheotomy to facilitate decannulation. In contrast to adduction, arytenoid abduction is performed with the patient under general anesthesia. For patients without an existing tracheotomy, an endotracheal tube provides a stable airway. When a tracheotomy is in place, dissection is more difficult, and the surgery is better tolerated with use of general anesthesia.

Arytenoid abduction, in contrast to other procedures to widen the glottis, has the potential to preserve phonatory adduction in patients who have primarily abductor paralysis with active adduction during phonation. This is a result of the three-dimensional nature of the cricoarytenoid joint. As mentioned previously in this chapter, the axes of rotation for thyroarytenoid and posterior cricoarytenoid muscle activities are different. Therefore, posterior traction on the muscular process moves the vocal fold laterally for an improved airway during inspiration, but does not abolish rotation about the axis for the thyroarytenoid muscle. Arytenoid abduction is less effective for patients who have significant synkinetic reinnervation, with reinnervation of the adductor muscles by nerve fibers that fire in inspiration and originally supplied the posterior cricoarytenoid muscle. In such a situation, the traction exerted by the abduction suture is counteracted by inappropriate inspiratory adduction.

Future Directions

Arytenoid adduction is an effective means of altering the position of the arytenoid. However, the ideal position of the arytenoid has yet to be determined. Moreover, there are currently no means of precisely measuring the spatial displacement accomplished by arytenoid adduction in vivo. It is likely that the "ideal" position varies, not only among patients, but also with variation in vocal pitch, amplitude, and quality. Advances in three-dimensional imaging will provide important information about laryngeal motion that will allow refinement of this procedure or development of better ways of restoring dynamic laryngeal function.

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CHAPTER SIXTY-EIGHT

Laryngeal Reinnervation

George S. Goding, Jr.

Key Points

- Ideal rehabilitation of unilateral vocal fold paralysis would involve restoration of vocal fold movement, position, bulk, and tone.
- Complete recovery from unilateral paralysis can happen only through the spontaneous and appropriate regeneration of the recurrent laryngeal nerve.
- Reinnervation options for laryngeal paralysis include (1) the neuromuscular pedicle procedure, (2) ansa hypoglossi (cervicalis)–recurrent laryngeal nerve anastomosis, and (3) direct implantation of a nerve (ansa hypoglossi) into the denervated muscle.
- Laryngeal reinnervation as yet does not result in coordinated movement of the vocal fold and is used clinically for unilateral paralysis.

Complete recovery from laryngeal denervation may occur with spontaneous and appropriate regeneration of the recurrent laryngeal nerve (RLN). Surgical intervention cannot reliably provide appropriate vocal fold movement or the rapid and fine adjustments required for continuous vocal fold symmetry. Vocal cord medialization and augmentation allow for improved positioning of the paralyzed vocal fold. The RLN, however, supplies both adductor and abductor laryngeal muscles. Reinnervation procedures designed to generate muscle movement must bypass the main trunk of the nerve and address individual muscles directly or at the most distal branches of the RLN. Reinnervation at the level of the RLN trunk can provide improvement in laryngeal muscle tone and mass.

In 1909, Horsley[1] reported the first successful vocal cord reinnervation. He performed a neurorrhaphy of the RLN in a patient who had been shot in the neck, who had nearly complete recovery of laryngeal function. A number of writers have independently reported recurrent nerve repairs with return of function.[2-4]

In most cases vocal fold motion does not return after RLN anastomosis. Instead, a laryngeal synkinesis occurs with adductor and abductor nerve fibers nonselectively innervating the laryngeal muscles.[5-8] The result of this neuromuscular mismatching is that counteracting forces are applied to the arytenoid by all the muscles innervated by the RLN and little or no functional movement occurs.[9] An inspiratory medial bulging is seen that is thought to arise by the inappropriate activation of the thyroarytenoid muscle by abductor axons. The majority of RLN repairs, however, are incapable of producing abduction and adduction in functional coordination with the respiratory cycle.

The activity of the phrenic nerve during inspiration makes it an excellent candidate for reinnervation of the posterior cricoarytenoid (PCA) muscle. A similar muscle fiber–type profile between the diaphragm and the PCA also exists.[10] Abductor mobility of the vocal fold had been obtained in multiple animal models.[11-15] Experimental reinnervation with the phrenic nerve after a 9-month delay is successful but the functional recovery is reduced.[16] Attempts at creating vocal fold motion with phrenic nerve reinnervation in humans, however, were unsuccessful.[17]

Because of the inability to consistently obtain cyclical motion of the vocal cords in coordination with respiration, reinnervation at the level of the nerve trunk has not gained acceptance as a clinical modality for bilateral vocal cord paralysis.[18] Selective innervation of individual laryngeal muscles (in particular the PCA muscle) by neuromuscular transfer technique,[19] selective anastomosis,[20,21] or direct nerve implantation[22,23] is required.

Although desirable, cyclical vocal cord motion is not mandatory for the successful rehabilitation of unilateral vocal cord paralysis. This fact has led to the successful use of vocal cord medialization techniques to improve the primary functions of the larynx (closure, respiration, and phonation). The vocal cord medialization techniques currently in use include thyroplasty, arytenoid adduction, and vocal fold injection. Laryngeal reinnervation at the level of the RLN can also take advantage of the resultant synkinesis to provide vocal fold position, bulk, and tone.

The two most common reinnervation techniques that have been applied to the problem of laryngeal paralysis in patients are the neuromuscular pedicle (NMP) and the ansa cervicalis–recurrent laryngeal nerve (ansa-RLN) anastomosis. The two techniques take advantage of the same donor nerve (ansa cervicalis), but otherwise they differ.

The NMP procedure, developed in the 1970s, involves placement of the distal portion of the ansa cervicalis branch to the omohyoid muscle along with a small block of muscle into a denervated laryngeal muscle. The procedure is indicated in patients with either unilateral or bilateral vocal fold paralysis, with different muscles being treated in each case. Depending on the success of reinnervation and the nature of the stimulus, there is a potential for recovery of vocal fold motion. In patients with unilateral vocal fold paralysis, the technique can be combined with a thyroplasty.[24]

The ansa-RLN anastomosis as an attempt to restore vocal fold movement was first reported by Frazier[25] in 1924 and Frazier and Mosser[26] in 1926. The current use of the technique was reported in 1986.[27] An end-to-end anastomosis of the proximal ansa cervicalis nerve to the distal stump of the RLN is performed. The procedure is indicated for unilateral paralysis because vocal fold motion is not restored. Instead, muscle tone is restored to the entire hemilarynx,

providing appropriate vocal fold position, bulk, and tone. The result is the potential for a near normal vocal ability.

Physiologic and Anatomic Issues in Laryngeal Reinnervation

There is substantial evidence that reinnervated muscle takes on the characteristics of the donor nerve (see Talmadge[28] for review). This process appears to happen as the reinnervating nerve imposes a pattern of activity on the muscle fibers it contacts. Thus the selection of a donor nerve should ideally take into account the fiber type and contraction characteristics of the muscle to be reinnervated.

Nerve Characteristics

The RLN contains 1000 to 4000 motor axons, efferent axons, and sympathetic and parasympathetic secretomotor fibers, depending on the level at which the count is made. The RLN gives off branches to the cricopharyngeus and upper esophageal muscles[29] as well as a sensory branch that communicates with the superior laryngeal nerve prior to entering the larynx. Five hundred to a thousand fibers are in the motor branches of the RLN.[30] Before branching within the laryngeal framework, the motor fibers to the various muscles are intermixed throughout the RLN nerve trunk, making selective reinnervation at this level impractical.[31] The anterior motor branch of the RLN enters the larynx posterior to the cricothyroid joint. The first branches that emerge from the RLN innervate the PCA muscle and often have connections to the midline interarytenoid muscle. The branch to the PCA muscle has characteristics of a slow-twitch motor nerve, with axons containing 200 to 250 muscle fibers in each motor unit.[32] The interarytenoid muscle also receives a separate branch from each RLN, resulting in bilateral innervation. The terminal branches of the RLN innervate the lateral cricoarytenoid (LCA) and thyroarytenoid (TA) muscles. The axons in this branch are more characteristic of fast-twitch fibers, with motor unit sizes of 2 to 20 muscle fibers.[33] In some larynges a connection between the superior laryngeal and the terminal fibers of the RLN can be seen within the TA.[34]

Except for proprioceptive fibers carried within the nerve, the ansa cervicalis is a purely motor derivative of the ventral rami of the cervical plexus. Fibers from the first cervical nerve join the hypoglossal nerve until it curves anteroinferiorly. At this point the first cervical nerve fibers leave the hypoglossal nerve to form the superior root of the ansa cervicalis. The geniohyoid and thyrohyoid are supplied entirely by these fibers. The branch to the superior belly of the omohyoid muscle typically originates from the superior loop of the ansa cervicalis. Because of its proximity to the thyroid ala and infrahyoid position, this branch has been frequently used as a donor for reinnervation using the NMP technique. The other strap muscles receive motor fibers from second and third cervical nerves primarily via the inferior root of the ansa cervicalis. The lower portions of the sternothyroid and sternohyoid muscles receive terminal nerves that branch off the loop of the ansa cervicalis as it passes deep to the omohyoid muscle.[35]

Muscle Fibers in General

The performance of a particular muscle depends on the character of the individual muscle fibers it contains. On the basis of their histochemical and contraction properties, the fibers of skeletal muscle can be classified as slow fatigue-resistant (type 1), fast fatigue-resistant (type 2A), or fast fatigable (type 2B). Several other classifications and subtypes exist (see Staron[36] for review). Type 1 fibers are characterized by a low peak tension, slow contraction time, a low threshold of recruitment, fatigue resistance, and a dependence on aerobic metabolism. Muscles that are required to produce low tension over a prolonged period generally have a high proportion of type 1 fibers. Type 2 fibers are found to play a prominent role in muscles that can generate high tension for short periods. Type 2B fibers have a fast contraction time and can generate a higher tension. They are more easily fatigued, have a higher threshold of activation, and depend on anaerobic metabolism. Type 2A fibers are intermediate in tension, fatigability, and threshold, and they make use of both aerobic and anaerobic metabolism. The laryngeal muscles also have a high-velocity, low-tension fiber types (2L or mixed fiber type) that may be similar to those found in extraocular and jaw-closing muscles.[37-40]

Most mammalian skeletal muscles are made up of multiple fiber types. Because of these combinations the various whole muscles have a variety of contraction and relaxation characteristics. The peak contraction time of the extraocular muscles is the fastest and that of the soleus muscle is the slowest.

Laryngeal Muscles

Activity of the PCA muscle is synchronous with inspiration and precedes activation of the diaphragm by 40 to 100 msec.[41] The amount of activity varies directly with ventilatory resistance. Activity of the PCA produces lateral turning of the arytenoid, resulting in abduction of the vocal fold. Loss of PCA muscle tone results in instability of the arytenoid cartilage. On the basis of gross anatomy[42] and innervations,[43] the PCA muscle in humans can be divided into a horizontal compartment and a vertical/oblique compartment.[43] Some researchers have reported that the PCA in laryngectomy specimens consists of nearly equal percentages of type 1 and type 2 fibers.[44] A similar ratio is seen in the primate PCA.[45] Other writers have found the PCA to have a higher percentage of type 1 fibers.[10] The remainder of the muscle fibers appears to be mostly of the intermediate (type 2A) variety. These findings are consistent with the peak contraction time of the PCA, which is approximately 40 msec.

Reinnervation occurs most easily at the sites of the original motor end plates. It is possible that placement of a reinnervating NMP near a large population of motor end plates could improve the end result.[46] The motor end plates of the human PCA muscle are distributed in a loosely arranged arc in the midportion of the muscle. The density of end plates is higher in the deeper portions of the PCA.

TA activity increases with phonation and reflex protection of the airway. Contraction of the TA is critical to the fine control of the mass and tension of the phonating edge of the vocal fold. Atrophy of the TA muscle results in a reduced vocal cord volume and glottic incompetence. Paralysis of the LCA and interarytenoid muscles severely compromises the ability to adduct and stabilize the vocal process of the arytenoid. Bilateral innervation of the interarytenoid muscle is not sufficient to compensate for this loss.

The TA and LCA are faster muscles. Their peak contraction times of 14 msec (TA) and 19 msec (LCA) make them some of the more rapid muscles in the body.[45,47] The composition of muscle fibers in the TA is approximately 40% type 1, 55% type 2A, and 5% type 2B. The higher frequency of oxidative fibers characterizes the muscle as having aerobic metabolism, resistance to fatigue, and fast contraction.[48] The faster response characteristics of these muscles are appropriate for their phonatory and protective functions.

The pattern of motor end plate distribution in the TA and cricothyroid (CT) muscles is more diffuse than that in the PCA. In the CT muscle the majority of the motor end plates are in the medial two thirds of the muscle[49] while in the TA the end plates are scattered throughout the muscle.[50] Placement of a NMP, or a direct nerve implant in precise locations, therefore, may offer a limited advantage in reinnervating the PCA and CT muscles. These diffuse patterns differ from skeletal muscles elsewhere in the body where they form a narrow band at the midpoint of the muscle.[49]

Both adductor and abductor laryngeal muscles contribute to the position and stability of the arytenoid cartilage.[51] Restoration of adductor and abductor muscle tone should allow appropriate arytenoid position and stability.

The CT muscle participates in deep inspiration, expiration and phonation. The CT is innervated by the superior laryngeal nerve and is not addressed by ansa-RLN reinnervation. Cricothyroid contraction pulls the vocal process in an anterior and slightly medial direction. This anterior pull is offset by the stabilizing effect of PCA and LCA contraction.

Infrahyoid Muscles

The ansa cervicalis provides motor supply to the infrahyoid muscles and is the most commonly used donor nerve in laryngeal reinnervation. The peak contraction times of the thyrohyoid and sternothyroid

muscles are approximately 50 msec.[52] Approximately two thirds of the muscle fibers are type 1.[53] The infrahyoid muscles have enzyme profiles similar to those of limb muscles and lack the faster mixed fibers found in the laryngeal muscles.[54]

In the hope of obtaining vocal fold movement, the activity of the various infrahyoid muscles has been examined. The strap muscles extending below the larynx function as accessory muscles of inspiration in varying degrees. The sternohyoid muscle has consistently shown little to no consistent activity with respiration. In the canine, a regular contraction of the sternothyroid muscle is seen with quiet respiration, but all strap muscles lack phasic activity in the primate. With greater airway resistance and hypoxia, inspiratory activity in the primate is greatest in the omohyoid, followed by the sternothyroid muscle .[55] The sternothyroid in labored respiration can result in vocal cord lateralization even if the larynx is paralyzed, by means of the sternothyroid muscle's effect on the laryngeal skeleton.[56]

The thyrohyoid muscle can similarly assist in adduction of the vocal cords. Medial positioning of the vocal folds is assisted by this muscle's action of displacing the thyroid cartilage upward. On the basis of activity relative to the respiratory cycle, the nerve supply to the sternothyroid and omohyoid muscles would be acceptable candidates for use in reinnervation for laryngeal abduction. The thyrohyoid muscle's activity makes its branch of the ansa cervicalis nerve an appropriate choice for laryngeal adduction. Because specific laryngeal muscles are not reinnervated in isolation with the ansa-RLN anastomosis, the activation patterns of the infrahyoid muscles become less meaningful with this technique. Denervation of an infrahyoid muscle does occur and may result in a change in vocal quality immediately after surgery. Sacrifice of the sternothyroid muscle can result in a decrease of lateral pull on the thyroid ala and a medialization effect. The opposite effect can occur with sacrifice of the thyrohyoid muscle.

The infrahyoid muscles are a less than perfect histochemical match to the recipient laryngeal muscles. After reinnervation for unilateral vocal fold paralysis with the ansa cervicalis, changes in the fiber type composition of the laryngeal muscles would be expected.

Effects of Denervation

With denervation, the area of sensitivity to acetylcholine, which is limited to the end plate region in the intact muscle, spreads out over most of the external membrane.[57] Denervation also eliminates both the trophic and activity-related influences on the muscle, resulting in muscle atrophy. Without reinnervation there is progressive atrophy and eventual destruction of the muscle despite an adequate supply of all nutrients.

Reinnervation becomes less effective the longer a muscle is denervated. The different laryngeal muscles appear to atrophy at different rates that vary with the muscles' fiber composition. In a study on primate larynges, the faster TA muscle showed a far greater reduction in fiber size than the slower CT or PCA muscle. By 8 weeks of denervation, however, all laryngeal muscles were fibrosed.[58] Muscle atrophy in human skeletal muscles apparently proceeds at a slower pace, with muscles surviving at least 3 years after denervation. Successful laryngeal reinnervation has been claimed as much as 50 years after onset of laryngeal paralysis.[59] It is possible that some nerve sprouting occurs, resulting in a low-grade but functionless innervation that preserves the muscle's ability to be reinnervated.[60] Innervation of laryngeal muscles can also come from misdirected reinnervation from autonomic nerves.[61]

Restoration of Function

Successful regeneration of injured nerves requires (1) a neuron responding to the injury with the metabolic changes necessary to support axonal regrowth, (2) an environment around the injured axon that permits axon growth, and (3) guidance clues for restoration of function.

Regeneration is pointless unless the regenerating axons grow back to reinnervate the original targets. Motor axons preferentially reinnervate distal motor branches of a severed nerve. The specificity is gained primarily through pruning of misdirected fibers.[62] Some evidence for a neurotrophic mechanism of directional nerve regrowth exists,[63] but the usual outcome of nerve injury suggests the specificity is low. A major problem is that after division of a nerve, a functional specificity in motoneuron regeneration for the original muscle does not exist.[64-66] The result, in a regenerating nerve supplying several muscles such as the RLN, is synkinesis.

Muscle fiber types can change under the influence of activation pattern[67] and altered innervation.[68] The changes following reinnervation with a different donor nerve may be related to a different pattern of activity imposed by the new nerve supply. Fiber type grouping is thought to be a result of this process.[69] Mechanisms for directing the regenerating motor axons within a single muscle leading slow- and fast-twitch axons to the appropriate muscle fibers have some influence on reinnervation.[70] The effect, however, is not enough to prevent changes in muscle fiber type. Reinnervation with a new donor nerve would be expected to change the fiber type composition of the reinnervated muscle and thus its contraction characteristics.

The Neuromuscular Pedicle

The NMP technique attempts to transfer a nerve with a portion of its motor units intact to a denervated muscle. Preservation of motor units is brought about by the inclusion of a small block of muscle at the distal end of the donor nerve. This inclusion distinguishes the technique from nerve anastomosis, implantation of a nerve stump, and direct electrical stimulation of muscle fibers.

Reinnervation with the Neuromuscular Pedicle

Successful reinnervation with an NMP depends partly on the ability of the transplanted axons to reach receptive sites on the recipient muscle fibers and partly on the ability of the muscle fibers to accept innervation from foreign nerves. With partial denervation of the transferred nerve, the remaining intact motor neurons develop sprouts that provide reinnervation preferentially at the original end plate sites of the denervated muscle fibers.[71,72] This phenomenon is important to successful transfer of the NMP, because a portion of the nerve fibers in an NMP may have an intact motor unit.[73] Axon sprouting results in a larger number of motor fibers innervated by each nerve. Mature nerve terminals appear to be limited in functional expansion to three to five times the normal terminal field.[74]

Laboratory Investigations

In early experiments a block of muscle containing the terminal branches of the recurrent laryngeal nerve was removed and reimplanted into the larynx.[73,75] A small portion of muscle was incorporated at the distal end of the transferred nerve to transfer intact nerve fibers. The short time to functional recovery (2 to 6 weeks) was thought to be secondary to the avoidance of degeneration and regeneration before effective reinnervation.

In 1973, reinnervation of the canine larynx with an NMP derived from the ansa cervicalis nerve and its insertion into the sternohyoid muscle was described.[76] The technique was modified because of the unavailability of the RLN in most cases of laryngeal paralysis and the unsuitability of preserving a portion of the larynx in the presence of cancer.[77] Return of function was seen at approximately 6 weeks after surgery. Reinnervation could be successful up to 6 months after denervation.[78]

Evidence for reinnervation with the NMP has included muscle response to pedicle stimulation, demonstration of neural tracer in the central motor nuclei of the donor nerve,[79] and glycogen depletion in fiber of reinnervated muscles.[80] Successful use of the NMP technique in animal models has been reported by multiple researchers.[19,81-85] In their studies, electrical stimulation of the transferred nerve or induction of greater respiratory effort was required to produce gross motion.

In other studies, the presence of vocal fold movement under hypercarbic conditions was not associated with evidence of reinnervation by either direct stimulation[86-88] or histologic evaluation.[88] Other maneuvers, such as division of the inferior pharyngeal constrictor[86] or of the superior laryngeal nerve or the strap muscles,[87] were effective in eliminating the observed vocal fold motion. Postoperative scarring, which could stabilize the arytenoid and lateral tethering of the arytenoid to the thyroid cartilage, is a potential explanation for vocal fold motion not related to reinnervation.[89]

A modification of the NMP technique involves using a transferred NMP as a means of providing access to a denervated muscle for long-term electrical stimulation.[90-92] A cuffed electrode can be placed around the nerve component of an implanted NMP. This should avoid deterioration at the electrode-muscle interface. Successful pacing was accomplished for the sternothyroid[90] and PCA[91] muscles with the use of tracheal motion with respiration as the triggering signal.

Indications

Bilateral Paralysis

The NMP technique can be considered for any patient with bilateral vocal cord paralysis that has persisted for 6 months[59] to a year.[93] In practice, however, only half of such patients are suitable candidates.[94] Fixation or limitation of the cricoarytenoid joint is the most common contraindication, affecting approximately one third of patients.[93] Direct laryngoscopy and palpation of the arytenoids prior to proceeding with the NMP procedure is recommended.

The ansa cervicalis nerve and its insertion into the appropriate strap muscle must be available for this technique. Any prior surgery or trauma that may have injured the ansa cervicalis should be carefully reviewed. Other causes of airway obstruction should be resolved before reinnervation.[93]

Central nervous system disease resulting in vocal cord paralysis is a relative contraindication. Tucker[93] has reported only a 40% to 50% success rate in patients with such diseases, which may also disrupt the function of the ansa cervicalis nerve.

Finally, the laryngeal muscles must be able to accept reinnervation. Although successful reinnervation has been reported after 22 and 50 years of denervation, muscle atrophy probably plays a role in hampering the outcome. The incidence of cricoarytenoid fixation may increase with time[95] but this finding has not been confirmed hstologically.[96]

Unilateral Paralysis

Consideration of reinnervation is usually delayed in patients with unilateral paralysis until enough time has passed to make spontaneous recovery unlikely. In patients who have difficulty with aspiration, vocal fold injection has been recommended. Prior injection of polytetrafluoroethylene (Teflon) into the vocal cord, however, has had a poor vocal result.[97] The procedure has also been limited to patients who require above-average vocal quality.

Like patients with bilateral vocal cord paralysis who are being considered for an NMP procedure, the patient with unilateral paralysis must be able to tolerate the procedure, and the ansa cervicalis nerve must be intact, the selected adductor muscle must be in suitable condition for reinnervation, and there must be a mobile arytenoid muscle on the paralyzed side. Inability to visualize the larynx by normal endoscopic methods, which precludes transoral injection, is an additional indication for NMP reinnervation.[97]

Technique

The description of the NMP procedure below is that first described by Tucker[59]with modifications by other writers as noted (Fig. 68-1).[77,93,95,98]

In Bilateral Paralysis

When performed in a patient with bilateral paralysis, the procedure begins with laryngoscopy and palpation of the arytenoids with the patient under general anesthesia and muscular paralysis but with no endotracheal tube. Once it is determined the arytenoids are freely mobile, the patient is intubated, and a tracheotomy is performed if one is not already present.

A horizontal incision is made near the lower border of the thyroid cartilage. The anterior border of the sternocleidomastoid muscle is exposed and retracted laterally. Dissection of the anterior belly of the omohyoid muscle and the fascia overlying the internal jugular vein is completed. The branch of the ansa cervicalis supplying the anterior belly of the omohyoid muscle can be identified in either of the following two ways: (1) by finding the main trunk of the ansa cervicalis as it crosses the internal jugular vein and tracing it proximally and distally until the appropriate branch is recognized or (2) by mobilizing the medial border of the omohyoid near its attachment to the hyoid and dissecting in a medial to lateral direction along the muscle. The nerve is usually accompanied by a small arterial vessel, which is preserved. If the nerve is injured, the branch to the sternothyroid is also acceptable.[89,99]

After the point of entry into the muscle is determined, dissection of the nerve is continued distally until its terminal branches are identified. This may require an additional 2 to 3 mm of dissection from the entrance of the nerve into the muscle. A block of muscle large enough to include the terminal branches (usually 2-3 mm on a side) is dissected free with the attached nerve. The muscle block is kept as small as possible because it will act as a free graft. The proximal portion of the omohyoid branch of the ansa cervicalis is mobilized, with care taken to preserve the accompanying vessel.

The lateral margin of the thyroid cartilage is identified and is used to rotate the larynx toward the opposite side. With the dissection kept close to the lateral edge of the thyroid ala, the fibers of the inferior constrictor are bluntly separated. Dissection is continued until either the pyriform sinus is encountered or the PCA muscle is seen. The mucosa of the pyriform sinus is bluntly displaced superiorly if necessary. The PCA muscle can be recognized from its fibers, which pass at right angles to those of the inferior constrictor.

The NMP is then sutured to the PCA with two or three sutures of 5-0 nylon. Abrasion of the surface of the PCA is not necessary for reinnervation to occur. Closure of the fibers of the inferior constrictor muscle is not necessary. A drain is placed, and the wound is closed in layers. Postoperative antibiotics are not routinely used.

Unilateral Paralysis

The direct laryngoscopy and harvesting of the NMP are the same for unilateral vocal cord paralysis as for bilateral paralysis. No tracheotomy is performed. The recipient muscle in unilateral paralysis is the LCA, and the second portion of the operation varies accordingly.

The thyroid cartilage on the denervated side is exposed, and the lower half of the perichondrium of the thyroid cartilage is incised in the midline. A posteriorly based perichondrial flap exposing the lower half of the thyroid ala is created. A block of thyroid cartilage is removed from this area, leaving the underlying perichondrium and the inferior margin of the thyroid cartilage intact. The inner perichondrium is incised to expose the denervated LCA muscle, and the NMP is sutured in place with two or three sutures of 5-0 nylon. The outer perichondrial flap may be sutured back in place, and the wound is closed in layers with a drain. One modification consists of placement of two pedicles (each from a separate strap muscle) into the recipient muscle.[100]

Intravenous dexamethasone has been given to reduce laryngeal edema in the early recovery period after NMP in unilateral vocal paralysis.[99] Voice rest and postoperative antibiotics are not necessary.

Reported Results

In 1976, Tucker[77] reported using the NMP in humans for bilateral vocal fold paralysis. All five patients he studied demonstrated vocal cord abduction with inspiration within 6 to 8 weeks after the procedure. In two patients with a marked improvement in exercise tolerance, vocal cord motion was not seen without an increased respiratory effort. In 1978, Tucker[59] reviewed 45 cases of NMP laryngeal reinnervation for bilateral vocal cord paralysis, reporting an 88.8% (40/45) success rate. Duration of follow-up ranged from 3 months to 4 years, and duration of paralysis ranged from 6 months to 50 years. The time to return of function varied from 6 to 12 weeks.

In 1982, Tucker[93] divided results of NMP reinnervation for bilateral vocal cord paralysis into three categories. In approximately 40% of his cases, airway improvement was accompanied by visible motion of the vocal cord with inspiratory effort; 20% of patients had no airway improvement. The remaining patients had airway improvement but little vocal cord motion. Most of the patients in this last group demonstrated vocal cord motion or tonic abduction only with increased respiratory demand. A second NMP procedure to the opposite PCA muscle has been performed successfully in patients in whom the first procedure had an inadequate result.[93]

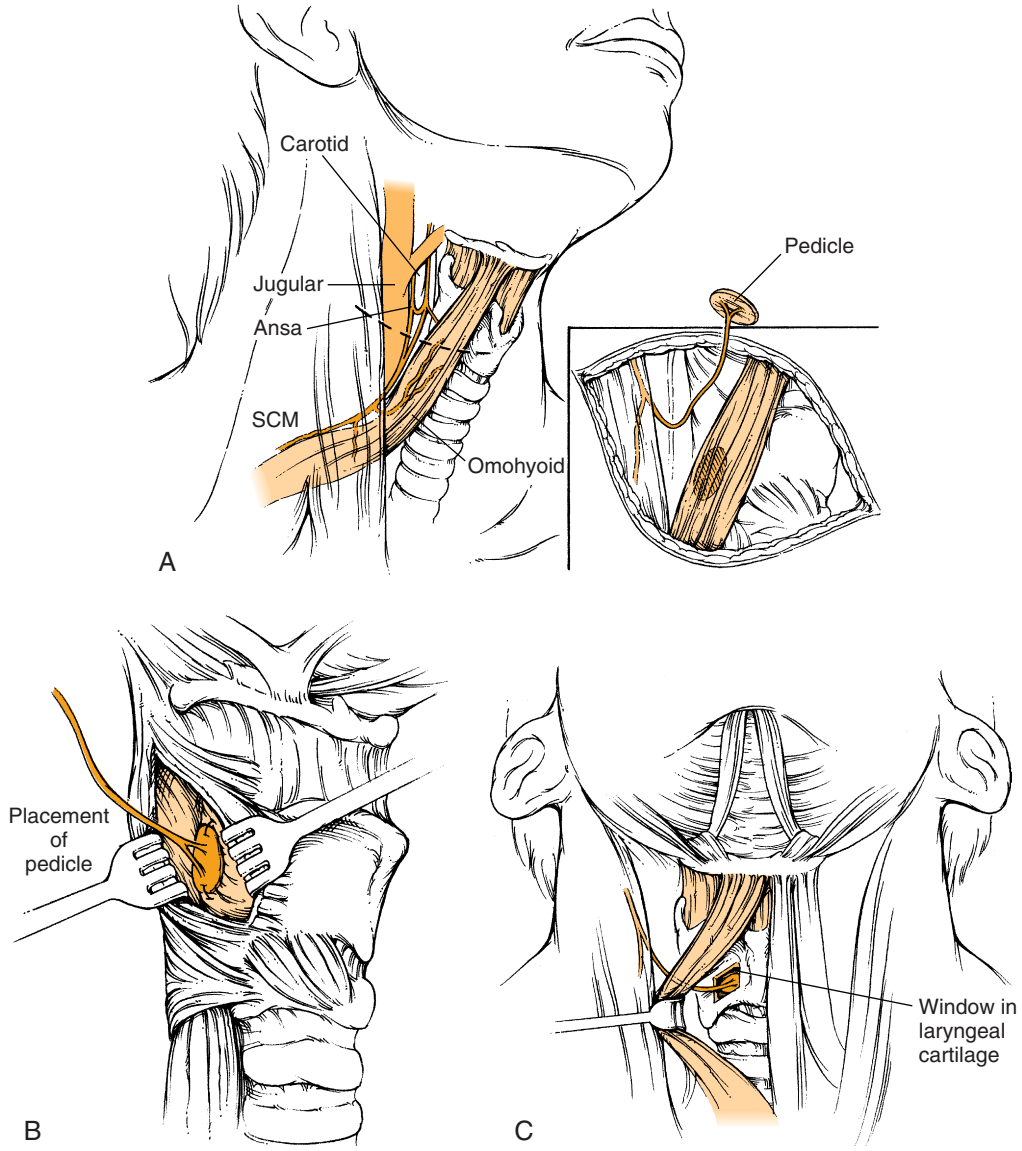

Figure 68-1. Neuromuscular pedicle (NMP). **A,** NMP harvested from omohyoid muscle. The branch of the ansa cervicalis nerve to the omohyoid is removed with a 2- to 3-mm attached block of muscle. SCM, sternocleidomastoid muscle. **B,** NMP placed into the posterior cricoarytenoid muscle after rotation of the larynx and separation of the fibers of the inferior constrictor for the treatment of bilateral paralysis. **C,** NMP placed into the lateral cricoarytenoid muscle via a window in the thyroid ala for the treatment of unilateral paralysis.

A review of 214 patients with bilateral vocal cord paralysis demonstrated a 74% long-term success rate.[94] In 48% of patients, tracheotomy was performed at the time of reinnervation. Success was defined as decannulation with improved airway that did not limit regular daily activities or exacerbate acute upper respiratory disease. Minimum follow-up was 2 years. Six-month results showed an 89% success rate, but 31 patients had subsequent deterioration of the airway. In a majority of patients with late failure who were evaluated, fixation of the cricoarytenoid joint was identified.

In 1977, Tucker reported the use of the NMP procedure in 9 patients with unilateral vocal cord paralysis.[98] Recovery of adductive function was seen 2 to 12 weeks after surgery in all of the patients. Only 6 patients had a satisfactory improvement in vocal quality, and a subsequent polytetrafluoroethylene injection was required in the other 3. In a subsequent report on the use of the NMP in unilateral vocal cord paralysis, improvement was found in 25 of 27 patients undergoing a NMP procedure to the LCA.[99]

In a 1989 study, NMP procedures for unilateral paralysis were reported to have a success rate of 88%.[94] Success was established by voice improvement, vocal cord adduction, and change in cord tension with elevated pitch. Voice results were noted to improve for several months and were aided by the addition of speech therapy.

May and colleagues[101] reported their results with the NMP procedure in 1980. Of 8 patients undergoing NMP reinnervation of the PCA for airway obstruction only 3 experienced improvement; 13 of 15 patients with disordered phonation and/or deglutition were improved by NMP reinnervation of the LCA. Applebaum and associates[100] reported successful results in all 6 of their patients undergoing the NMP technique. Four of the patients had bilateral vocal cord paralysis, with 1 requiring a tracheostomy. Dyspnea and stridor were relieved in all 4 patients, in whom vocal cord movement was seen only after physical exertion.

For isolated unilateral recurrent laryngeal paralysis, May and Beery[97] reported improvement in the voice in 19 of 20 (95%) patients treated with NMP implantation into the LCA muscle. Observable movement of the reinnervated cord was seen in only 1 patient, suggesting that enhanced muscle tone or a slight change in position was responsible for voice improvement. The degree of voice improvement was substantially less in patients with multiple cranial nerve deficits or vocal cord fixation.

Complications

The main complication of the NMP technique is failure to obtain a satisfactory result. Many of the patient selection factors listed previously as contraindications are a result of these experiences. Relatively few operative complications associated with the NMP procedure are described. In 214 patients undergoing an NMP procedure for bilateral vocal cord paralysis, Tucker[99] noted only four complications. Three were wound infections, and the fourth was related to the previously placed tracheotomy. No complications were reported in 73 patients undergoing NMP for unilateral paralysis. No operative complications were reported in other series.[97,100]

Future of the Neuromuscular Pedicle Procedure

Despite its successful use in a few writers' experiences, widespread use of the NMP has not materialized. Reinnervation can occur with implantation of an NMP into denervated muscle, but the ansa cervicalis continues to be an imperfect source for neural input. Even in the absence of movement with respiration, the NMP can maintain muscular tone.

The NMP can provide a mechanism to access a denervated muscle for long-term pacing.[90,91] With electrical pacing, the options for a potential triggering source and the stimulus for muscle contraction are increased, providing a potentially more effective treatment of airway impairment secondary to bilateral vocal fold paralysis.

Ansa Cervicalis–Recurrent Laryngeal Nerve Anastomosis

The current use of the ansa-RLN anastomosis is in unilateral vocal fold paralysis. No motion of the reinnervated vocal fold with respiration or phonation is expected. A variation of this technique involves a hypoglossal nerve–RLN anastomosis.[102,103] Use of the ansa cervicalis as a donor nerve has gained the widest acceptance because of the lower morbidity associated with the sacrifice of this nerve.

Advantages

The procedure is relatively easy to perform in an unoperated neck for any surgeon familiar with head and neck anatomy. The primary difficulty is associated with identifying the appropriate nerves when excessive scar is present. There is typically no "learning curve" with respect to the ultimate vocal result, because fine adjustments of vocal fold position are not required. In contrast, the ultimate vocal result for vocal cord injection and thyroplasty is determined at the time of surgery and depends on the expertise of the surgeon.

The ansa-RLN procedure provides tone, position, and bulk to the denervated muscles, resulting in less asymmetry between the normal and reinnervated vocal cords. This result offers the opportunity for an outstanding rehabilitation of unilateral vocal cord paralysis. Improvement in vocal quality can also continue to occur after the initial improvement seen during the first year after surgery.

The sacrifice of the sternothyroid muscle is clinically insignificant and may theoretically improve vocal function. The resting tone of the sternothyroid muscle slightly lateralizes the normal vocal cord.[56] Loss of this tone may result in a slight medialization of the paralyzed vocal cord and an improvement in vocal quality early after surgery.[60]

The procedure is primarily extralaryngeal and can be reversed by division of the anastomosis at a later time. Because the thyroid ala and intrinsic muscles of the larynx are not violated, the subsequent use of vocal fold injection or thyroplasty is not limited. The impact of the delay prior to reinnervation can be reduced when the procedure is combined with injection of absorbable material into the vocal fold at the time of surgery. No permanent implant material is used, so the potential for implant migration or foreign body reaction at the level of the vocal cord is eliminated.

Disadvantage

The ansa-RLN transfer procedure requires a deeper level of dissection in the neck and typically takes longer to perform than thyroplasty or vocal fold injection. The time for completion of the ansa-RLN is estimated at 2 hours.[104] Although thyroplasty is typically performed with the patient under sedation and vocal fold injection can be performed in the clinic, ansa-RLN anastomosis is performed under general anesthesia.

The possibility of spontaneous recovery of vocal fold function is eliminated with the division of the RLN prior to ansa-RLN anastomosis. It is important to wait until the possibility of spontaneous recovery is minimal before performing this procedure.

There is a delay of 5 to 9 months before substantial improvement in the voice occurs, in addition to the several-month delay of waiting for the possibility of spontaneous recovery before the procedure is performed. Often an initial improvement can be seen as early as 3 to 4 months after surgery. Improvement, however, can continue for several years.

The procedure requires one intact ansa cervicalis and the intact distal stump of the RLN. This requirement can be difficult to satisfy after thyroid surgery or impossible after bilateral neck surgery in which the ansa cervicalis is sacrificed. In cases of unilateral neck surgery the contralateral ansa cervicalis can be used. Unlike in thyroplasty, the consequences of performing the procedure on the wrong (nonparalyzed) side are severe. With division of the only remaining intact RLN, a bilateral vocal fold immobility and resultant airway obstruction are likely consequences.

Surgical Indications and Contraindications

Ansa-RLN anastomosis is indicated for the treatment of unilateral vocal fold paralysis in which there is minimal chance for spontaneous recovery. The most common waiting period prior to consideration of reinnervation is 12 months. The distal stump of the RLN must be available for anastomosis. In the presence of extensive scar, the RLN can be found behind the cricothyroid joint. A donor nerve must also be available. The ansa cervicalis, however, can be prepared from either the ipsilateral or contralateral side. The patient must be able to tolerate both general anesthesia and the wait for substantial improvement from reinnervation.

Absolute contraindications include glottic airway compromise, bilateral vocal fold paralysis, absence of the distal RLN, bilateral absence of the ansa cervicalis, and poor general health.

The relative contraindications to ansa-RLN anastomosis include limitations of time, voice, and surgery. Time limitations primarily focus on the delay after surgery for the voice improvement. Is the wait worthwhile for the patient? Time can be limited by either social or work considerations or by the patient's life expectancy. If the patent's life expectancy is less than 5 years, the delay for improvement with reinnervation may not be worthwhile. The procedure also appears to be less successful in the elderly and in patients who have had paralysis for several decades. Voice limitations focus on the fact that ansa-RLN anastomosis fixes only the position, bulk, and tone of the paralyzed vocal fold. Is there other pathology that will limit the voice result, such as dysarthria associated with multiple cranial nerve defects or stroke? Other vocal fold pathology that will limit the ultimate result, such as the presence of a vocal fold scar, web, or polyp, must be considered. If a near-normal voice is not the anticipated result, the use of ansa-RLN anastomosis should be considered carefully. Fixation of an arytenoid in a lateral position also has an adverse effect on the expected outcome.

Surgical considerations also come into play when prior surgery has occurred in the area of the RLN. Is there extensive scarring or atrophy of the nerve? The possibility of not finding an adequate nerve for anastomosis must be considered, and alternative plans for intraoperative management reviewed with the patient.

Surgical Technique

An incision in a natural crease of the neck is made below the level of the cricoid cartilage, often at the level of a thyroidectomy incision (Fig. 68-2). The incision need not cross the midline, and 4 cm is usually adequate. The strap muscles are separated vertically in the midline, and the RLN is identified in the tracheoesophageal groove. The nerve is dissected to its entrance into the larynx. In the presence of local scar tissue, the RLN can be found behind the cricothyroid joint. A vessel loop can be placed around the nerve. The anterior border of the sternocleidomastoid muscle is identified. The ansa cervicalis nerve can be

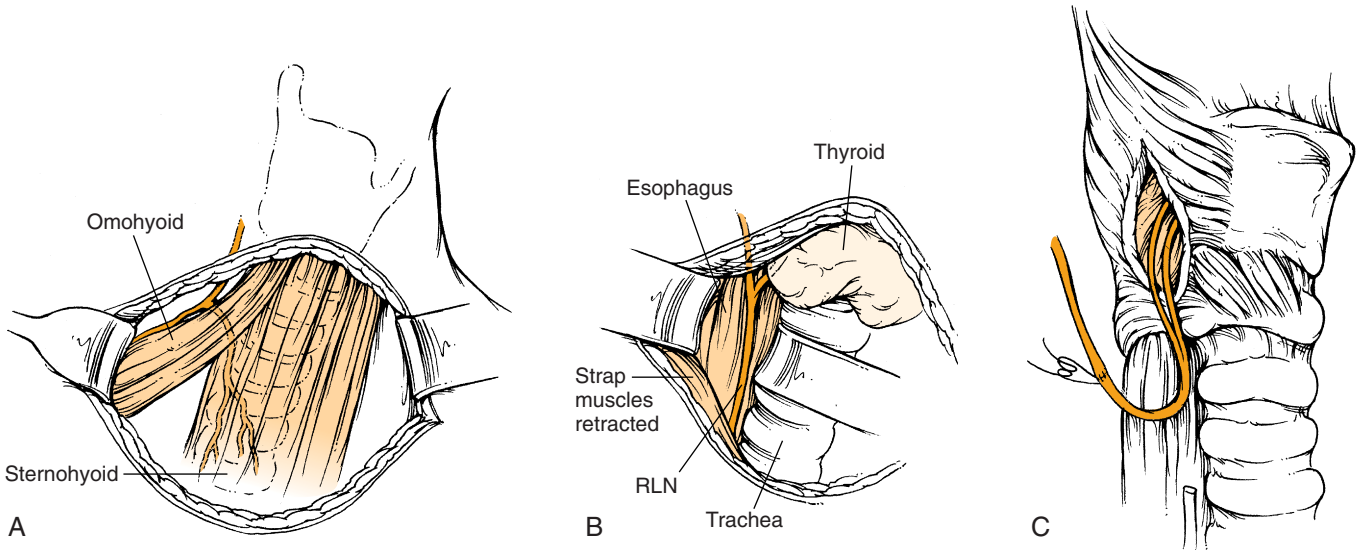

Figure 68-2. Ansa cervicalis to recurrent laryngeal nerve (RLN) anastomosis. **A,** Exposure of branch to sternohyoid muscle. **B,** Exposure of RLN in the tracheoesophageal groove. **C,** Ansa-RLN anastomosis.

identified along the lateral border of the sternothyroid muscle, at the level of the omohyoid muscle, or along the internal jugular vein.

After both nerves are identified and the distal RLN is confirmed to be intact, the ansa cervicalis nerve and RLN are transected. Each nerve should be divided inferiorly enough to allow a tension-free anastomosis. A tunnel deep to the sternohyoid and sternothyroid muscles connects the two operative sites and facilitates the anastomosis. The anastomosis is performed with the use of 9-0 or 10-0 nylon sutures. Two or three epineural sutures are adequate. Magnification with either a surgical microscope or loupes can be used. The wound is closed in layers with an appropriate drain.

An absorbable material can be injected at the time of surgery to provide an initial improvement in vocal quality. After 2 to 3 months the voice may deteriorate to the preoperative level. At 4 to 6 months after surgery, a gradual improvement in vocal quality begins. On laryngeal examination after ansa-RLN transfer, the reinnervated cord is immobile or demonstrates only minimal movement. The procedure produces a synkinesis that allows the mobile vocal fold to approximate the reinnervated fold in the midline.

Clinical Results

Ansa-RLN anastomosis has produced near-normal vocal quality in most reports. The initial two reports by Crumley and colleagues[27,105] described success in two patients and four patients. In one of these patients the contralateral ansa cervicalis nerve served as the donor nerve. No motion of the reinnervated vocal fold was seen in reinnervated patients. The vocal improvement was believed to be secondary to precise positioning of the reinnervated vocal fold. Reinnervation of the of PCA, LCA, and TA muscles appears to provide the needed tone to stabilize and position the arytenoid properly.[51]

A series of 20 patients undergoing ansa-RLN anastomosis was reviewed by Crumley[60] in 1991. Vocal quality was judged to be normal or near normal in 18 of 20 cases. In the one failure, identification of the RLN was in doubt secondary to local scar formation from multiple prior procedures. A second patient demonstrated improvement but to a lesser extent. Lateralization of the arytenoid and the patient's age (65 years) were cited as possible factors contributing to the lesser result. Several patients in whom the delay between injury and reinnervation exceeded 8 years had successful results.

Ansa-RLN anastomosis was successful in two elderly patients (66 and 71 years old) following resection of mediastinal tumors with early reinnervation.[106] Zheng and coworkers[107] presented eight cases with one disappointing result. They used an anterior branch of the RLN. Slight improvement was seen early after surgery, with additional improvement seen at 2 to 3 months. Electromyographic confirmation was obtained in five patients. Passive arytenoid mobility was important in achieving good results and was related to the one substandard result.

Similar results in terms of mean phonation time and vocal fold position are seen after a direct anastomosis of the RLN, a free nerve graft reconstructing the RLN, a vagus nerve–RLN anastomosis, and an ansa-RLN anastomosis performed during the course of thyroid surgery.[108] The ansa-RLN anastomosis has several advantages over other means of reconstruction of a divided RLN during the course of thyroid or other neck surgery. These include the requirement of only one anastomosis performed at a relatively accessible level in the neck, a relatively short time to recovery because the anastomosis is close to the larynx, and availability when the RLN is injured within the mediastinum. Performing the anastomosis behind the thyroid cartilage[108] as well as using the contralateral ansa cervicalis as a donor nerve[109] improves the chances of successful reconstruction.

Olson and colleagues[110] performed a quantitative analysis of 12 patients with ansa-RLN anastomosis for unilateral vocal fold paralysis. Improvement in vocal quality was demonstrated. Results of acoustic analyses in postoperative patients were similar to those in a control group of normal subjects. Patients with isolated vocal fold paralysis had the best results. Improvement in overall severity, roughness, and breathiness of the patient's voice more than 6 months following ansa-RLN anastomosis has also been demonstrated.[111] The greatest improvement was seen with breathiness measures. Postoperative electromyographic studies of patients undergoing reinnervation with an ansa-RLN anastomosis as well as NMP implantation into the TA have shown activation of the reinnervated muscle with speech and head elevation.[112] Head elevation maneuvers that directly activate the strap muscles were routinely found to result in greater activation of the TA and LCA muscles. Activation of the TA muscles with speech was found to increase with time.

Chhetri and colleagues[113] reported that the addition of ansa-RLN anastomosis to arytenoid adduction did not result in better acoustic results than arytenoid adduction alone. All patients in their series had significant perceptual improvement in voice, but these investigators questioned the relationship of surgical repositioning of the arytenoid and reinnervation in unilateral paralysis.

Direct Nerve Implant

Early in the 20th century, direct implantation of a nerve into a denervated muscle was shown to produce successful reinnervation in experimental models.[114-116] Insertion of a nerve ending into skeletal muscle results in the establishment of neuromuscular junctions.[117,118] Using

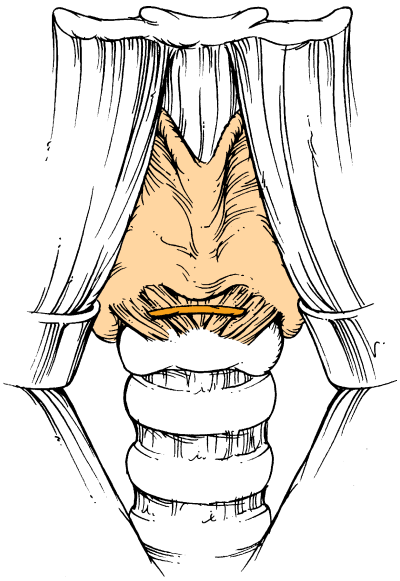

Figure 68-3. Muscle-nerve-muscle graft between the innervated and denervated cricothyroid muscle.

multiple implants distributed over a wide area increases the effectiveness of reinnervation with the direct nerve implantation technique.[119] Direct nerve implants have been successfully used in 10 patients, with active muscle movement occurring in all 10 patients.[120] A short period of denervation, a healthy donor nerve, and a wide distribution of nerve fibers entering the muscle had a positive effect on the outcome.

Early experiments investigating direct nerve implantation also examined the value of the technique in laryngeal reinnervation.[121,122] Direct implantation of the RLN into the PCA muscle was successfully performed in the canine and proposed as a promising method for reinnervation.[4,123]

Comparisons of the NMP procedure with direct implantation of the ansa cervicalis nerve into denervated muscle have shown mixed results. Meikle and associates[82] showed no advantage of one method over the other, whereas Hall and colleagues[83] found the NMP procedure to produce stronger evoked contractions and to involve a shorter time to return of function. Both groups judged that their results were consistent with the action of the NMP as a source for multiple direct nerve implants rather than a predominant reliance on transfer of intact motor units. Because of the need to support a distal muscle pedicle, the NMP procedure was inferior to the direct nerve implantation when the reinnervation procedure was extended with a cable graft.[84]

Direct nerve implantation of the TA muscle was performed in ten patients with unilateral paralysis.[124] Improvement of voice was seen in eight, with a return to "normal" or "great improvement" in 6 patients. Reinnervation was supported by electromyography in all four patients tested.

A variant of this technique, in which a nerve acts as a conduit from an innervated muscle to the contralateral, denervated muscle (muscle-nerve-muscle), has been successfully used.[125] Selective cricothyroid reinnervation with a muscle-nerve-muscle graft from the contralateral cricothyroid was used in combination with ansa-RLN anastomosis in three patients (Fig. 68-3). All patients had improved voice and electromyographic evidence of cricothyroid muscle reinnervation.

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Management of Acquired Disorders and Trauma

CHAPTER SIXTY-NINE

Chronic Aspiration

Steven D. Pletcher

David W. Eisele

Key Points

- Intractable aspiration results in chronic soilage of the lower respiratory tract and life-threatening pulmonary infections.
- In adult patients, cerebrovascular accident with subsequent lower cranial nerve palsies is the most common cause of intractable aspiration; other causes are neuromuscular disorders, tumors (brainstem or laryngeal), postoperative aspiration, and traumatic or anoxic brain injury.
- Causes of intractable aspiration in pediatric patients include cerebral palsy, anoxic encephalopathy, sequelae of neurologic trauma or surgery, tracheoesophageal fistula, and other severe congenital or acquired neurologic disorders.
- Initial conservative treatments of chronic aspiration include nothing-by-mouth status with an alternative route of alimentation, head of bed elevation, and aggressive pulmonary toilet.
- Patients who continue to aspirate despite such conservative measures are deemed to have intractable aspiration; surgical management should be considered in these patients.
- Control of aspiration, phonation, and swallowing should all be considered in the choice of surgical approach for aspiration.
- The Lindeman procedures (tracheoesophageal diversion and laryngotracheal separation) have gained popularity owing to their high rate of success in controlling aspiration as well as their technical simplicity.

The three major functions of the larynx—respiration, phonation, and airway protection—are intimately related. Impairment of laryngeal protective function can result in aspiration, the laryngeal penetration of secretions such as saliva, ingested liquids or solids, or refluxed gastric contents below the level of the true vocal cords.

A certain amount of aspiration is known to occur normally. Scintigraphic evaluation of healthy persons during sleep reveals aspiration in nearly 50%.[1] A certain amount of aspiration may be tolerated without complications, provided that tracheobronchial clearance is normal and defense mechanisms are intact. Contamination of the respiratory tract associated with aspiration can result in a spectrum of bronchopulmonary complications. The severity of complications depends on the volume and the character (e.g., pH) of the aspirated material. Respiratory complications of aspiration include bronchospasm, airway obstruction, tracheitis, bronchitis, pneumonia, pulmonary abscess, sepsis, and death.[2-4] Significant aspiration results in a high mortality rate.[5]

Aspiration may be an isolated event related to temporary impairment of normal swallowing mechanisms and airway protection. Typically, isolated aspiration occurs secondary to neurologic dysfunction. This dysfunction may in turn be secondary to a depressed state of consciousness related to drugs, alcohol, or metabolic derangement. In addition, seizure, injury, or infection may cause isolated aspiration. Elderly patients are more likely to experience aspiration, presumably in relation to physiologic and neurologic changes associated with age.[6-8] Patients with dentures experience impaired swallowing with decreased oral sensation and oral control, which may contribute to aspiration.

Chronic or intractable aspiration entails repeated episodes of aspiration. Patients with chronic aspiration require evaluation and effective management to prevent life-threatening complications. This chapter discusses the evaluation and management of patients with chronic aspiration and emphasizes surgical management.

Etiology

Chronic aspiration usually results from a severe loss of laryngeal protective function related to impaired motor activity or sensory loss. Chronic aspiration can occur, despite healthy laryngeal function, if dysfunctional swallowing is significant.

Box 69-1 lists causes of chronic aspiration. The most common origin is associated with cerebrovascular accidents, particularly those involving the brainstem with bilateral cranial nerve (CN) deficits.[9] In addition, degenerative neurologic diseases are frequently associated with chronic aspiration. Peripheral nerve disorders, particularly those involving the cranial nerves, as well as neuromuscular diseases and muscular disorders, can cause recurrent aspiration. Diffuse neurologic dysfunction from head injury, anoxic brain injury, infection, or drug toxicity can cause severe dysfunction and chronic aspiration.[10-12] Chronic aspiration also can result from disorders of the pharynx and the esophagus, including neoplasms, postoperative and postirradiation dysfunction, Zenker's diverticulum, stricture, and severe gastroesophageal reflux.[13]

Chronic aspiration can occur in pediatric patients, in whom it is usually related to severe neurologic dysfunction resulting from cerebral palsy, anoxic encephalopathy, sequelae of neurologic trauma or surgery, tracheoesophageal fistula, or other severe congenital or acquired neurologic disorders.[14]

Symptoms

Patients may be aware of recurrent aspiration and describe episodes of coughing or choking during swallowing. Some patients, however, may

Box 69-1

Causes of Chronic Aspiration

Cerebrovascular Accidents
Atherosclerotic thrombosis
Embolism
Intracranial hemorrhage

Degenerative Neurologic Diseases
Parkinson's disease
Amyotrophic lateral sclerosis
Progressive supranuclear palsy
Multiple sclerosis

Neuromuscular and Muscular Disorders
Poliomyelitis
Myasthenia gravis
Muscular dystrophy
Myopathies

Peripheral Nerve Disorders
Cranial nerves
Guillain-Barré syndrome
Intracranial neoplasms
Primary dysfunction related to neoplasm
Postsurgical dysfunction

Trauma
Closed-head injury
Hematoma
Anoxic brain injury
Intracranial infection

Pharyngeal Disorders
Neoplasms
Postsurgical dysfunction
Postirradiation dysfunction
Zenker's diverticulum
Cricopharyngeal dysfunction
Stricture

Esophageal Disorders
Reflux
Achalasia
Caustic injury

Miscellaneous
Severe illness
Multisystem disease
Drug intoxication

experience silent aspiration, whereby cough does not occur after laryngeal penetration.[15-17] Fever and respiratory symptoms such as productive cough with purulent sputum may occur, indicating an infectious complication. Patients may have weight loss, dysphonia, pain, dysphagia, odynophagia, or other symptoms, depending on the cause of the underlying disorder.[9] Frequently, patients are severely ill because of their disease and secondary infectious complications.

Evaluation

In the evaluation of a patient with chronic aspiration, a detailed medical history is important. Frequently, the cause of aspiration is apparent from the history. The medical history and history of prior surgery or injury should be thoroughly investigated.

A multidisciplinary approach to patients with chronic aspiration is important.[18] Frequently, an otolaryngologist–head and neck surgeon is consulted after complications of chronic aspiration have occurred. Once chronic aspiration has been identified, consultation with specialists in speech-language pathology, neurology, internal medicine, rehabilitation medicine, radiology, gastroenterology, thoracic surgery, and psychiatry may be beneficial. A cooperative effort in which each specialist provides special expertise ensures optimal care for the patient.

Physical examination should be thorough, with careful examination of the head and neck, including cranial nerve evaluation. Examination of the hypopharynx and larynx is performed with indirect mirror examination or fiberoptic nasopharyngoscopy. If these structures are not adequately visualized by these methods (e.g., in an endotracheally intubated patient), direct laryngoscopy is recommended. Esophagoscopy is performed if an esophageal abnormality is suspected. Pulmonary function tests help assess pulmonary function and reserve.

Radiography provides important diagnostic information and should include chest radiography and swallowing evaluation. A videofluoroscopic swallowing study reliably provides information about the precise physiologic nature of aspiration and swallowing disturbance and about the severity of aspiration.[19,20] Logemann[21] described a modified barium swallow study in which small amounts of barium are used because of the risk of aspiration. Different consistencies of contrast material are used to assess whether consistency alteration has any effect on aspiration reduction. A videofluoroscopic swallowing study performed in conjunction with a speech-language pathologist allows radiographic assessment of the effects of swallowing therapy and maneuvers on control of aspiration.[22,23]

Functional endoscopic evaluation of swallowing (FEES) was proposed by Langmore and associates[24] in 1988 as an alternative to videofluoroscopy for the evaluation of dysphagia. In this study, dyed pudding and liquids are swallowed by the patient during nasopharyngeal fiberoptic observation. The swallow is recorded and reviewed for evidence of oral leakage, pharyngeal stasis, laryngeal penetration, and aspiration. Evaluation of FEES suggests that it is similar in sensitivity and specificity to videofluoroscopic examination with the advantages of lower cost, decreased radiation exposure, and bedside availability.[25-29] In general, the choice between videofluoroscopy and FEES depends on multiple factors, including physician and speech-language pathologist preferences and hospital availability.

Scintigraphy may help quantify the magnitude of aspiration[30,31] but in general adds little information, beyond that obtained from a FEES or a videofluoroscopic swallowing study, for the management of aspiration. Other imaging studies that may provide important information are computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, and soft tissue radiography of the neck.

Comprehensive evaluation of the patient with aspiration ideally determines the cause of the underlying disorder or disorders causing the aspiration. A thorough search for any correctable cause of aspiration (e.g., obstructing lesion, Zenker's diverticulum, cricopharyngeal muscle dysfunction, esophageal motility disorder) is important to management.

Frequently, progressive functional deterioration can be anticipated for certain degenerative neurologic diseases and malignant neoplasms. It can be extremely difficult, however, to predict the time course of improvement and recovery for cerebrovascular accidents, head injuries, anoxic brain injuries, postoperative dysfunction, and other disorders. Multispecialty input is helpful in planning management for these difficult cases.

Nonsurgical Management

Initial management of the patient with chronic aspiration should include appropriate antibiotics for any infectious complications. Aggressive pulmonary therapy is instituted. All oral intake is discontinued, and an alternative route of alimentation is provided. Enteral routes of alimentation include small, soft nasogastric feeding tubes, cervical esophagotomy, piriform sinusotomy, gastrostomy, and jejunostomy. Gastrostomy can easily be performed percutaneously with minimal morbidity. Patients with significant reflux may benefit from a tube passed through a gastrostomy into the small intestine or jejunostomy.

Depending on the cause of aspiration, alimentation by nasogastric feeding tube decreases but does not eliminate the risk of aspiration.[32] Some researchers believe that nasogastric feeding tubes may actually predispose to aspiration.[33,34] In addition, nasogastric feeding tubes can be uncomfortable and aesthetically displeasing when used for long periods. Gastrostomy alone has been shown not to reduce aspiration in neurologically impaired patients. [35,36] Some patients may be candidates for parenteral hyperalimentation if gastrointestinal function is impaired (e.g., patients with acute severe brain injury).[37]

Proper nursing care includes special positioning of the patient, such as elevation of the head of the bed for patients with severe reflux. However, one study showed no significant difference in aspiration with respect to patient position in the patient with endotracheal intubation.[34] Frequent suctioning of the oral cavity and oropharynx is also important.

Tracheotomy

A tracheotomy tube with a low-pressure cuff provides comfortable airway control for patients requiring intubation and facilitates pulmonary toilet in patients with copious secretions. Tracheotomy also effectively reduces the pulmonary dead space. Despite these advantages, tracheotomy cannot be relied upon to eliminate aspiration.[38,39] In addition, tracheotomy has been implicated as a causative factor in aspiration. The proposed mechanisms include esophageal compression via inflated tracheotomy cuff,[40] desensitization of the larynx from diversion of airflow through the tracheotomy,[41] impairment of laryngeal elevation through tethering of the larynx by the tracheotomy tube,[42] disruption of the normally closed aerodigestive system,[43] disorder of laryngeal reflexes due to chronic upper airway bypass,[1,44,45] reduced effectiveness of cough to clear secretions from the upper airway,[43,46] and the inability to generate subglottic air pressure.[47,48] Despite these proposed mechanisms, no clear causal relationship between tracheotomy and aspiration exists. In a study of 20 patients evaluated with FEES before and after tracheotomy (within 1 month), no causal relationship between tracheotomy and aspiration was demonstrated.[49]

The use of a tracheotomy tube for aspiration control requires close attention and skilled care, particularly for the debilitated patient. Several studies have examined the effect of endotracheal and tracheotomy tube cuffs on the prevention of aspiration. Although low-pressure, high-compliance cuffs are the most effective in minimizing cuff leak, they do not prevent aspiration.[50-52]

Vocal Cord Medialization

Vocal cord paralysis can result in chronic aspiration, particularly when combined with a laryngeal sensory deficit (e.g., a high vagal lesion). Vocal cord injection with materials such as collagen derivatives or hydroxyapatite can be performed endoscopically or transcervically to achieve vocal cord medialization and may prevent aspiration related to vocal cord paralysis.[53-55] Bilateral vocal cord injection with permanent materials such as polytetrafluoroethylene, however, has been shown to be an unreliable method for the prevention of chronic aspiration.[56]

Alteration of the laryngeal framework by medialization laryngoplasty using an implant is another excellent technique for vocal cord medialization.[57,58] Carrau and associates[59] reported that 94% of patients with high vagal lesions experienced improved swallowing after medialization thyroplasty with or without arytenoid adduction. In the same study 79% of patients who presented with tracheotomies underwent successful decannulation following laryngeal framework surgery.

Surgery

Sometimes a correctable cause of chronic aspiration is not identified, and nonsurgical and minor surgical procedures (e.g., tracheotomy, vocal cord medialization) do not prevent chronic aspiration. In these cases, surgical separation of the upper digestive tract from the upper respiratory tract is necessary to prevent the morbidity and mortality of recurrent respiratory tract soilage. A reasonable probability and duration of survival are necessary prerequisites for this surgery.

Clinical judgment should be used to determine the likelihood of recovery of laryngeal protective function and to identify patients who require prompt surgical intervention to separate the upper digestive and respiratory tracts to prevent death. The patient's general medical and mental status, severity of illness, and potential quality of life should be addressed.[60] Patients may have to sacrifice normal phonation and laryngeal respiration to ensure restoration of airway protection. This difficult issue requires thorough discussions of management options and sequelae with the patient and family members.

Box 69-2

Surgical Management of Chronic Aspiration

Reversible Procedures

Laryngotracheal separation
Tracheoesophageal diversion
Epiglottic flap laryngeal closure
Endolaryngeal stent
Double-barrel tracheostomy
Partial cricoidectomy
Vertical laryngoplasty

Irreversible Procedures

Subperichondrial cricoidectomy
Narrow-field laryngectomy
Glottic closure

"Ideal" Surgical Procedure for Chronic Aspiration

The ideal surgical procedure for chronic aspiration would be uniformly effective in preventing aspiration, be simply achieved, and have few complications and low morbidity. This procedure could be performed with local anesthesia for debilitated patients. In addition, the ideal procedure would allow phonation and deglutition and would be reversible if the underlying cause of aspiration were to improve. Many surgical options have been described for the management of chronic aspiration (Box 69-2).

Laryngectomy

Before 1970, laryngectomy was considered the surgical procedure of choice for management of chronic aspiration. This procedure provides definitive separation of the upper digestive and respiratory tracts. Narrow-field laryngectomy (Fig. 69-1) is used, in contrast to the total laryngectomy performed for malignancy. It preserves the hyoid, strap muscles, and as much hypopharyngeal mucosa as possible. Closure without tension and with reinforcement minimizes the potential postoperative complications of pharyngeal stenosis and fistula.[61] A staple-assisted laryngectomy technique designed specifically for treatment of aspiration may provide technically straightforward method to decrease the postoperative fistula rate.[62]

Laryngectomy also is practical because of the low likelihood of recovery of most patients with chronic aspiration.[63,64] However, because of the negative psychosocial aspects of laryngectomy, most patients and family members are reluctant to consent to laryngectomy for chronic aspiration. Narrow-field laryngectomy can be performed with local anesthesia. Tracheoesophageal puncture and placement of a voice prosthesis can be used for vocal rehabilitation after laryngectomy in selected patients. Because of the disadvantage of irreversibility of laryngectomy and the observation that some patients with chronic aspiration recover, other surgical procedures have been developed since the 1970s for the surgical management of chronic aspiration.

Subperichondrial Cricoidectomy

An option for definitive surgical separation of the upper respiratory and digestive tracts when recovery of function is expected is subperichondrial cricoidectomy (Fig. 69-2).[65] In this technique, the anterior aspect of the cricoid cartilage is exposed. The perichondrium of the anterior cricoid cartilage is divided vertically in the midline to expose the cricoid cartilage. The outer cricoid perichondrium is elevated with an elevator to the posterior cricoid lamina, and the inner cricoid perichondrium is elevated from the cricoid cartilage circumferentially. The cricoid carti-

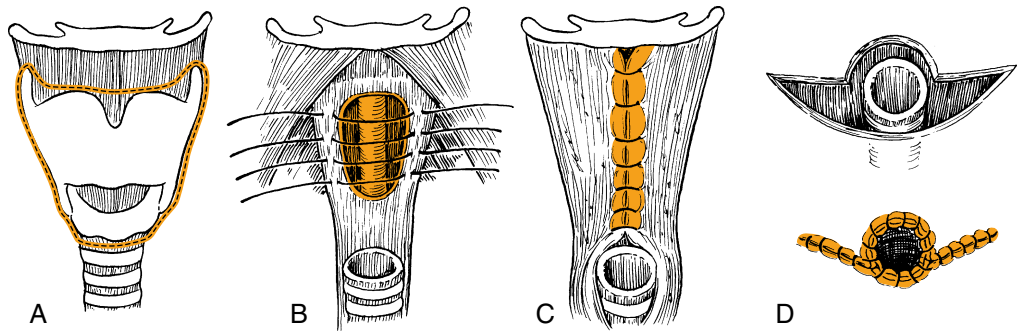

Figure 69-1. Narrow-field laryngectomy. **A,** Outline of larynx removal; the hyoid is preserved. **B,** Closure of the pharynx. **C,** Closure is reinforced with sternohyoid muscles. **D,** A tracheostoma is created.

lage is then removed piecemeal bilaterally with biting forceps, and the posterior cricoid lamina is preserved. The inner perichondrium and subglottic mucosa are transected horizontally, inverted, and closed, creating a subglottic pouch. The closure is buttressed by approximation of the strap muscles, and the wound is closed in layers over a drain. A tracheotomy is necessary.

Advantages of this technique include a high success rate, simplicity, and low morbidity. For these reasons, subperichondrial cricoidectomy may be preferable to narrow-field laryngectomy and other procedures for chronic aspiration when recovery of laryngeal protective function is not expected. This procedure can be performed easily with use of local anesthesia. Disadvantages include the need for a tracheotomy and the remote possibility of fistula into the upper trachea. The procedure was not designed to be reversible, and no reversals have been reported.

Partial Cricoidectomy

Krespi and associates[66] described subtotal and submucosal cricoid resection for the control of chronic aspiration after extensive surgical resection of pharyngeal and base-of-tongue tumors, particularly for patients undergoing myocutaneous flap reconstruction. The posterior cricoid perichondrium is elevated, and the posterior half of the cricoid lamina is removed without entering the mucosa. A cricopharyngeal myotomy also is performed. A tracheotomy is necessary. Partial cricoidectomy enlarges the pharyngeal inlet, facilitating deglutition, and narrows the laryngeal inlet, reducing aspiration and preserving the voice.

Biller and Urken[67] described partial cricoid collapse for the prevention of aspiration after extended horizontal partial laryngectomy. Vertical segments of the hemicricoid are removed. The hemicricoid is then collapsed with stabilization of the cricoid segments to a midline position, narrowing the laryngeal opening and correcting glottic incompetence.

Endolaryngeal Stents

Several types of endolaryngeal stents have been used to prevent chronic aspiration. Weisberger and Huebsch[68] reported the use of a solid silicone laryngeal stent, which was placed endoscopically and secured transcervically with sutures (Fig. 69-3). A tracheotomy tube was necessary. Aspiration was prevented and oral intake tolerated in three of seven patients with chronic aspiration. Perioperative mortality was high in this series and was thought to be related to tracheotomy tube obstruction. Endoscopic reversal of the stent procedure was reported in two patients; however, both required stent replacement for aspiration control.

Eliachar and coworkers[69,70] reported two types of vented silicone laryngeal stents for control of aspiration (Fig. 69-4). The newer of the two stents is inserted through a tracheotomy and secured by a flexible strap of silicone extending from the tracheotomy tract above the tracheotomy tube. Eliachar and Nguyen[69] reported aspiration control in 11 of 12 patients with chronic aspiration with the newer stent. For 1 patient in whom the initial procedure failed, placement of a larger stent achieved aspiration control. The stent was reportedly used for up to 9 months. Of 3 patients who survived and underwent successful stent removal, 1 experienced laryngeal granulation tissue requiring laser excision, and an anterior subglottic web developed in another.

Laryngeal stents are easily introduced and, if properly sized for the patient, prevent aspiration.[69,71] Laryngeal stents, however, have the disadvantages of a lack of uniform success caused by leakage around the stent or extrusion. Because of the potential for endolaryngeal injury from the stent or tracheotomy tube displacement with airway occlusion by the stent, short-term use is recommended. Other disadvantages of stents are patient discomfort, the need for stents of different sizes, and the potential for life-threatening complications such as stent dislodgement. For these reasons, endolaryngeal stents have failed to gain wide acceptance for control of chronic aspiration.

Epiglottic Flap Closure of the Larynx

Habal and Murray[72] described an epiglottic flap technique of supraglottic closure. With this technique, the supraglottic larynx is approached through an infrahyoid pharyngotomy. The supraglottic larynx is closed after the edges of the epiglottis, aryepiglottic folds, and arytenoids are denuded (Fig. 69-5). A tracheotomy is required.

Since this initial report, several modifications and refinements of the procedure have been described. Strome and Fried[73] described (1) diminishing the tensile strength and elasticity of the epiglottic cartilage by morcellation, linear striations, or wedge excision and (2) severing the hyoepiglottic and thyroepiglottic ligaments. These modifications lessened dehiscence of the posterior flap.[72,74,75] However, this frequent complication allowed speech in some patients.

A further modification of the epiglottic flap closure procedure purposefully leaves the posterior laryngeal inlet open to allow phonation.[74,76] Another modification of this procedure suspends the larynx to the mandible to provide additional laryngeal protection.[75] Denuding the false vocal cords of mucosa and approximating the false vocal cords provide an additional layer of closure for laryngeal inlet obliteration.[77]

Epiglottic flap closure of the larynx prevents chronic aspiration in only approximately 50% of the procedures reported, although revision surgery is successful if the first procedure fails.[78] Reports of reversal of epiglottic flap closure are uncommon; successful reversal with endoscopy has been achieved.[73]

Advantages of epiglottic flap closure include reversibility, allowance of deglutition, and speech preservation if the posterior laryngeal inlet is left open or if dehiscence of the closure occurs. In addition, the true vocal cords are not injured by this procedure. Disadvantages of the epiglottic flap closure procedure include a high rate of flap dehiscence and failure and the need for a transcervical approach and tracheotomy. Supraglottic stenosis is a potential complication after reversal.[74]

Vertical Laryngoplasty

Biller and coworkers[5] described vertical laryngoplasty for the prevention of aspiration in patients who required total glossectomy for advanced carcinoma of the tongue (Fig. 69-6). In this technique, an incision is made along the outer borders of the epiglottis and carried inferiorly and posteriorly along the aryepiglottic folds over the arytenoids and

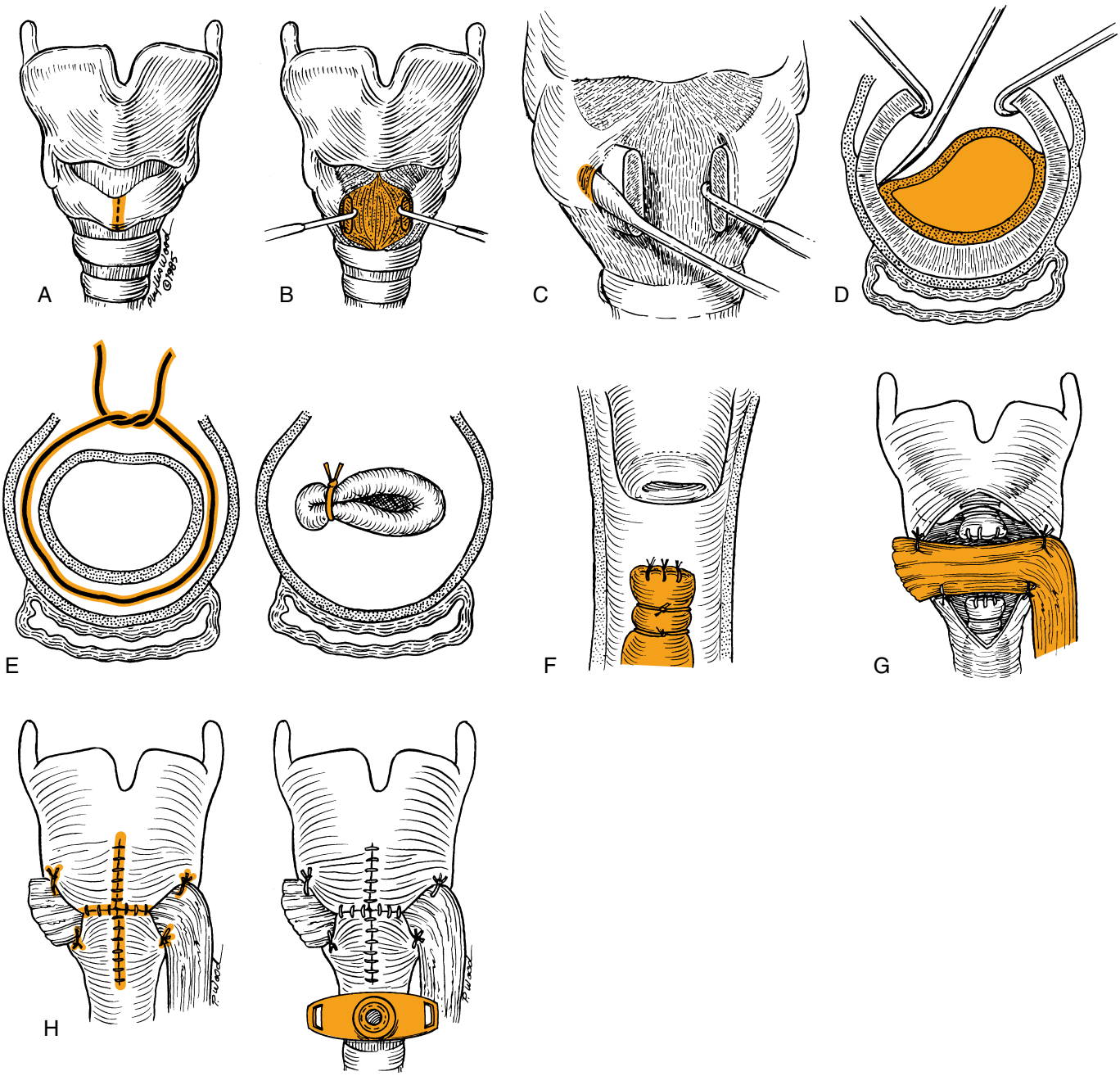

Figure 69-2. Subperichondrial cricoidectomy. **A,** Cricoid incision. **B,** The cricoid cartilage is opened. **C,** Outer cricoid perichondrial dissection. **D,** Inner cricoid perichondrial dissection. **E,** The inner perichondrium and mucosa are divided and closed. **F,** Both proximal and distal cut ends of the inner mucosal tube are folded in, and the sutured end is closed. **G,** The sternohyoid muscle is insinuated into the cricoid space. **H,** Closure with the outer perichondrium closed over muscle.

into the interarytenoid area. The epiglottis and supraglottic larynx are then closed vertically in two layers as a tube, with a small opening left superiorly. This technique also has been applied to patients with chronic aspiration with satisfactory results, allowing deglutition and speech.[60] Failure secondary to posterior dehiscence may limit the efficacy of this technique. Attempts to perform this procedure through an endoscopic approach have also been limited by posterior dehiscence and persistent aspiration.

Several modifications of the procedure have been proposed. Miller and Eliachar[71] described scoring the epiglottic cartilage in order to eliminate the cartilaginous spring and thus minimize dehiscence of the closure. A variation of the Biller vertical laryngoplasty has also been combined with a partial closure of the posterior glottis in an attempt to minimize failure due to persistent aspiration. This modified technique requires a permanent tracheotomy, but speech may still be attained with occlusion of the tracheotomy site.[79]

Glottic Closure

Glottic closure was described by Montgomery.[80] In this procedure, the larynx is closed at the level of the true and false vocal cords (Fig. 69-7). A midline thyrotomy is performed initially, exposing the endolarynx. The true and false vocal cords, ventricles, and posterior commissure are denuded of mucosa. Nonabsorbable monofilament sutures are used to approximate the glottic surfaces to provide glottic closure. In addition, absorbable sutures are used to approximate margins of the false vocal cords. A tracheotomy tube is necessary. Sasaki and colleagues[45,81] modified glottic closure, adding a sternohyoid muscle flap to provide an additional layer of laryngeal closure.

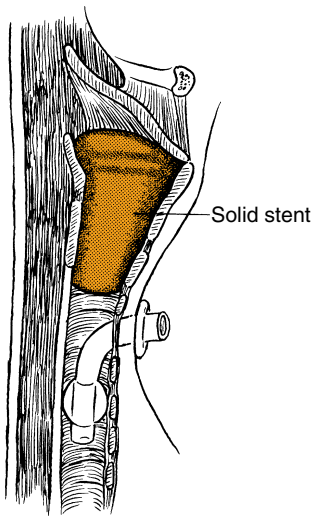

Figure 69-3. Endolaryngeal stent.

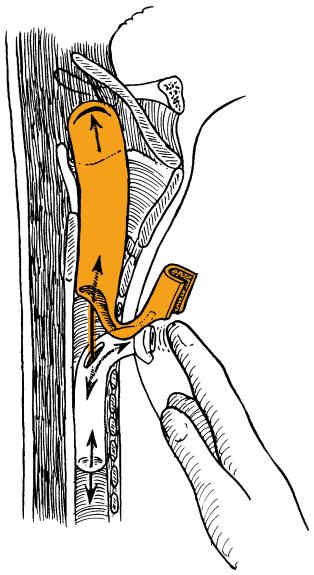

Figure 69-4. Vented endolaryngeal stent.

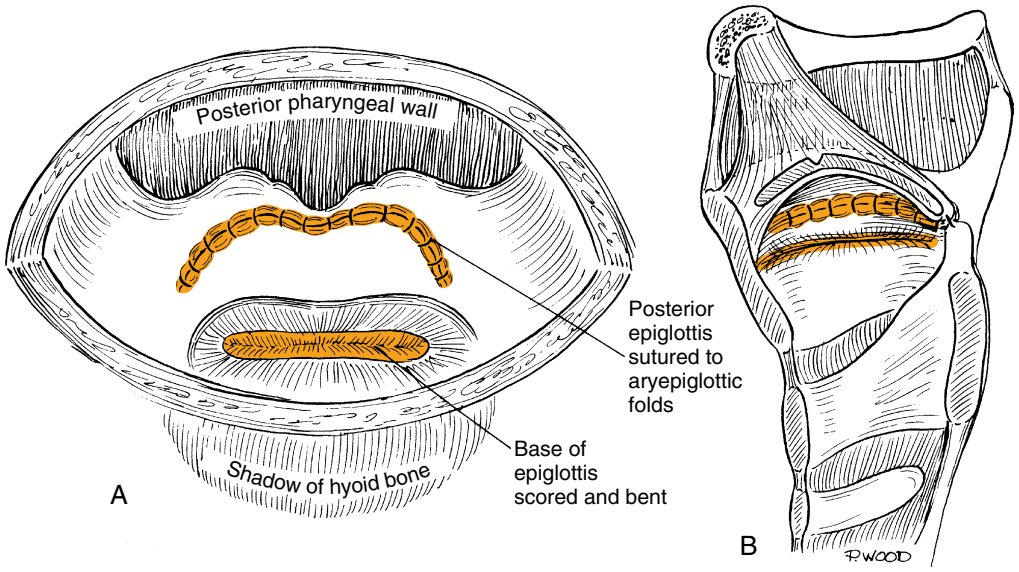

Figure 69-5. Epiglottic flap closure of larynx. **A,** Superior view. **B,** Lateral view.

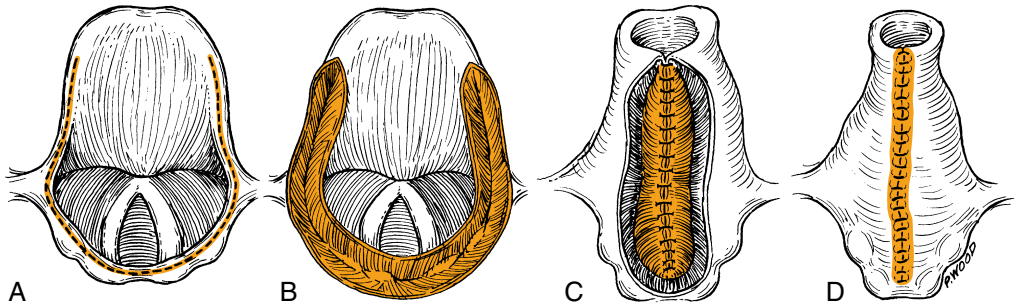

Figure 69-6. Vertical laryngoplasty. **A,** Incision along epiglottis, aryepiglottic folds, arytenoids, and interarytenoid area. **B,** Submucosal flaps are created. **C,** Inner layer closure. **D,** Outer layer closure.

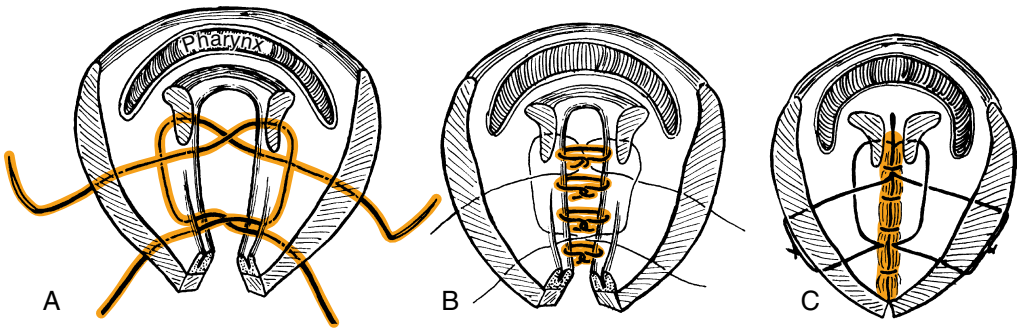

Figure 69-7. Glottic closure procedure. **A,** Midline thyrotomy, removal of the glottic mucosa, and placement of transglottic sutures for closure. **B,** False vocal cords are approximated. **C,** The glottis is closed.

The results of glottic closure for the prevention of aspiration are reported to be excellent (success rate, approximately 95%). There has been only one report of successful reversal of the glottic closure procedure.[82]

Advantages of the glottic closure procedure include high success rate for prevention of aspiration, allowance of deglutition, and potential reversibility. Glottic stenosis, however, makes reversal difficult. Disadvantages of the glottic closure procedure include the need for a transcervical approach and thyrotomy, loss of phonation, need for a tracheotomy, and endolaryngeal injury involving the true vocal cords. Performing the procedure is technically challenging; the interarytenoid closure is the most difficult step. A preexisting laryngeal abnormality is a contraindication for this procedure.

A dynamic glottic closure technique using implanted electrodes to stimulate the recurrent laryngeal nerve at the time of swallow has been proposed as a new method for prevention of aspiration without surgical manipulation of the endolarynx.[83] Along with the obvious benefit of preservation of respiration and phonation, a preliminary report of the use of these electrodes in two patients with stroke suggests efficacy in control of aspiration.

Tracheoesophageal Diversion and Laryngotracheal Separation

Lindeman[84] described tracheoesophageal diversion in 1975. This procedure for chronic aspiration was devised with the objective of developing a reliable surgical technique that would control aspiration for an indefinite period while preserving the larynx and the integrity of the recurrent laryngeal nerves. The procedure was designed to be reversible if healthy laryngeal protective function returned.

Tracheoesophageal diversion is performed by horizontal division of the trachea at the fourth and fifth tracheal rings (Fig. 69-8). The proximal tracheal segment is anastomosed in an end-to-side fashion to an opening in the anterior esophagus. The distal tracheal segment is used to create a tracheostoma.

In 1976, a similar surgical procedure for chronic aspiration, laryngotracheal separation, was described.[85] Laryngotracheal separation was designed for patients with chronic aspiration who had previously undergone high tracheotomy, which prevents establishment of a tracheoesophageal anastomosis, as performed in tracheoesophageal diversion. Laryngotracheal separation is performed by division of the trachea horizontally between the second and third tracheal rings or at the level of an existing tracheotomy (Fig. 69-9). The proximal tracheal edges are closed onto themselves anteroposteriorly as a blind pouch. The tracheal closure is buttressed with rotated sternothyroid muscles. The distal tracheal segment is used to create a tracheostoma.

A modification of tracheoesophageal diversion has been described; an anterior tracheal flap is created by removal of the inferior half of the cricoid cartilage and the anterior aspects of the first and second tracheal rings (Fig. 69-10).[12] This modification creates a soft flap, which allows tracheoesophageal diversion in patients who have undergone prior tracheotomy. This modification may jeopardize the reversibility of the procedure.

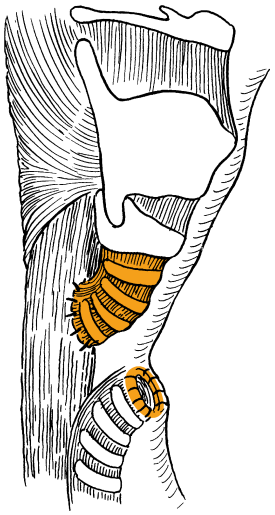

Figure 69-8. Tracheoesophageal diversion.

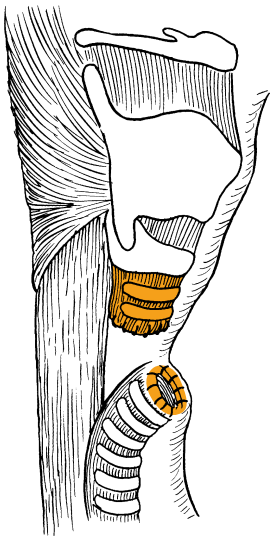

Figure 69-9. Laryngotracheal separation.

Tucker[86] proposed division of the trachea and externalization of the proximal trachea between the fibers of the sternocleidomastoid muscle to the cervical skin. It was theorized that sternocleidomastoid muscle compression would collapse the trachea, thus limiting external leakage of secretions. This procedure effects definitive separation of the respiratory tract and the digestive tract and prevents aspiration. Tra-

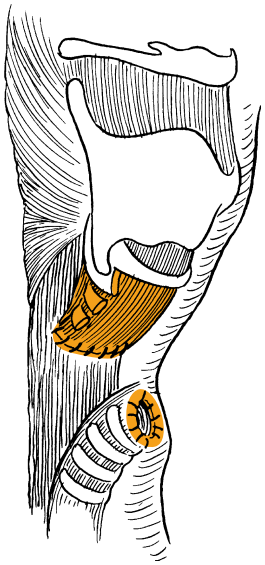

Figure 69-10. Modified tracheoesophageal diversion.

cheal secretions draining onto the neck, however, are aesthetically displeasing and require local care.

Many writers have reported uniform success in control of chronic aspiration with tracheoesophageal diversion and laryngotracheal separation.[11,87-92] Postoperatively, most patients can tolerate a normal diet, depending on their neurologic function. Reversals of both procedures with restoration of voice, deglutition, and respiration have been reported.[89,90,92-95] Both procedures can be performed with local anesthesia if necessary. Zocratto and associates[92] describe the use of laryngotracheal separation in conjunction with ablative surgical treatment of upper aerodigestive tract malignancies to prevent postoperative aspiration. Subsequent surgery for reversal was performed in 38% of their patients with aspiration. Tracheal stenosis occurred in more than 50% of patients who underwent reversal.[92]

Tracheoesophageal diversion has been recommended for patients with chronic aspiration who have not had high tracheotomy.[96] Tracheoesophageal diversion allows secretions and oral intake that have penetrated the larynx to pass into the esophagus. However, laryngotracheal separation is technically easier to perform than tracheoesophageal diversion. These techniques appear equally effective in controlling chronic aspiration. Complications are uncommon; they include postoperative fistula, which usually closes spontaneously with local care and antibiotics. Fistula formation is more common in patients with prior tracheotomy.[88] Ultimately, the decision whether to perform the diversion or separation procedure is determined by the presence of a tracheotomy and the surgeon's experience.

Candidates for reversal of tracheoesophageal diversion or laryngotracheal separation are considered on the basis of neurologic improvement and the results of laryngoscopy and videofluoroscopic swallowing evaluation. Reversals of these procedures have been performed most commonly in patients who have recovered from cerebrovascular accidents or who have undergone resection of benign intracranial tumors.[88] Surgical reversal may require partial resection of scarred tracheal remnants and mobilization of the laryngeal and tracheal segments in order to achieve a tension-free closure.[55,94] Excellent long-term speech and swallowing capabilities have been demonstrated in patients who have undergone reversal procedures.[55,94]

Advantages of tracheoesophageal diversion and laryngotracheal separation are that they are the most dependable of the reversible techniques for preventing chronic aspiration. These procedures allow oral alimentation and are reversible because the endolarynx is avoided and the larynx is not injured. Tracheoesophageal diversion has also demonstrated shorter operative time and less intraoperative blood loss than narrow-field laryngectomy.[97]

Disadvantages include the need for a transcervical approach and the loss of capacity for air-powered speech. Most patients, depending on their neurologic function, communicate with an electrolarynx after these procedures. Tracheotracheal and tracheoesophageal puncture with placement of a Blom-Singer voice prosthesis and resultant successful speech rehabilitation have been reported after laryngotracheal separation.[98-101] Carefully followed criteria, including sufficient manual dexterity and visual acuity, are necessary to select candidates for these rehabilitative procedures after laryngotracheal separation.

Tracheoesophageal diversion and laryngotracheal separation have also been successfully performed with satisfactory results in children with chronic aspiration.[14,26,91,102]

Summary

Chronic or intractable aspiration is a serious problem usually related to severe neurologic dysfunction. Chronic aspiration requires a thorough evaluation and the management of any correctable causes. Surgical separation of the upper respiratory and upper digestive tracts may be necessary to prevent repeated soilage of the respiratory system with recurrent infectious complications and to avoid death.

If there is no chance of recovery of neurologic function, surgical options for control of chronic aspiration include subperichondrial cricoidectomy and narrow-field laryngectomy. If recovery is possible, laryngotracheal diversion and separation are effective and reversible surgical techniques that prevent chronic aspiration.

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Zocratto O, Savassi-Rocha P, Paixao R, et al. Laryngotracheal separation surgery: outcome in 60 patients. *Otolaryngol Head Neck Surg*. 2006;135(4):571.

For complete list of references log onto www.expertconsult.com.

CHAPTER SEVENTY

Laryngeal and Esophageal Trauma

Guri S. Sandhu

S. A. Reza Nouraei

Key Points

- Laryngeal trauma is rare (1:137,000) but acutely life-threatening and, if not promptly recognized and treated, can cause significant long-term morbidity.
- External laryngeal trauma can be blunt or penetrating. Internal trauma is most commonly due to translaryngeal intubation but can also be secondary to caustic ingestion or inhalation burns.
- The first priority in managing laryngeal trauma is establishing a safe airway. Definitive treatment must be provided within 24 hours.
- External laryngeal trauma should be managed by a multidisciplinary trauma team, and associated cervical and remote injuries should be systematically sought and treated.
- Approximately 40% of patients with laryngeal trauma can be managed conservatively, and in those patients who require surgical treatment, the extent of the original injury correlates with the long-term outcome.
- The incidence of laryngeal injury is 10% after short-term translaryngeal intubation and rises to 90% after long-term intubation and ventilation. It can be prevented with early tracheotomy in the intensive care unit.
- Inhalation injury to the larynx occurs in 6% of patients with burns and in 40% of patients with caustic ingestion. Both types of injuries, if not recognized and treated promptly, can lead to severe long-term complications.
- Esophageal injuries occur in 6% of patients with penetrating neck trauma and 14% of patients with laryngotracheal trauma. They can be managed conservatively if recognized early but may require surgical exploration and drainage.
- Caustic esophageal injuries are almost always accidental in children but due to suicide attempts in adults. They are associated with stricture formation in 10% to 35% of cases as well as with a markedly elevated incidence of esophageal carcinoma.

The larynx contains the narrowest region of the ventilatory conduit,[1] houses the phonatory apparatus, and functions to protect the airway during swallowing. External laryngeal trauma—the primary focus of this chapter, is an acutely life-threatening injury[2-4] that, if not promptly recognized and adequately treated, can also cause significant long-term morbidity in as many as a quarter of patients owing to any combination of dysphonia, aspiration, and airway stenosis.[4-6] Laryngeal trauma is often associated with concomitant cervical and intracranial injuries and frequently occurs as part of multisystem polytrauma.[4] It is vital therefore that all patients with suspected laryngeal injury be managed by a multidisciplinary trauma team according to Advanced Trauma Life Support guidelines.

Mechanisms of Injury

Laryngeal and esophageal trauma can be broadly divided into external trauma, which can be blunt or penetrating, and internal trauma, which can be caused by iatrogenic, thermal, caustic, or foreign body injuries (Fig. 70-1).

Laryngeal Trauma

External Laryngeal Trauma

Incidence

External laryngeal trauma is rare. It has a population incidence of 1 in 137,000 in adults[4] and accounts for 0.5% of trauma admissions in children.[7] Other studies estimate the incidence of this injury to be between 1 in 5000[8] and 1 in 30,000[9] emergency room visits.

Etiology

The larynx is well shielded by the mandible superiorly, the sternum inferiorly, the sternomastoid muscles laterally, and the spinal column posteriorly. Further protection is afforded through its mobility. It is however susceptible to crushing anterior cervical trauma, which compresses the organ against the spinal column (Fig. 70-2). Laryngeal injury is also compounded by the process of calcification that begins during the third decade of life and affects men to a greater degree than women.[10]

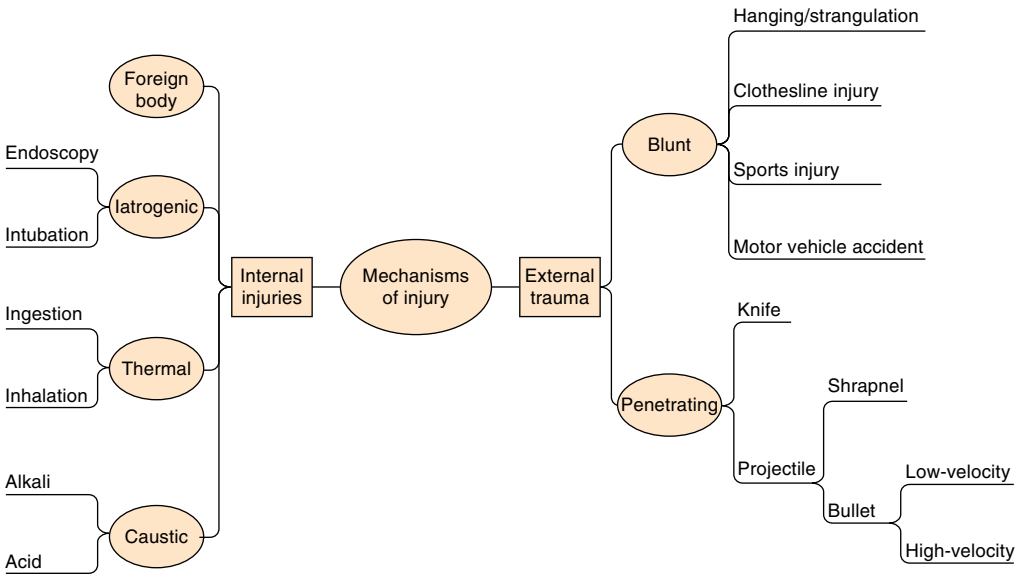

Figure 70-1. An overview of the mechanisms of laryngeal and esophageal injury.

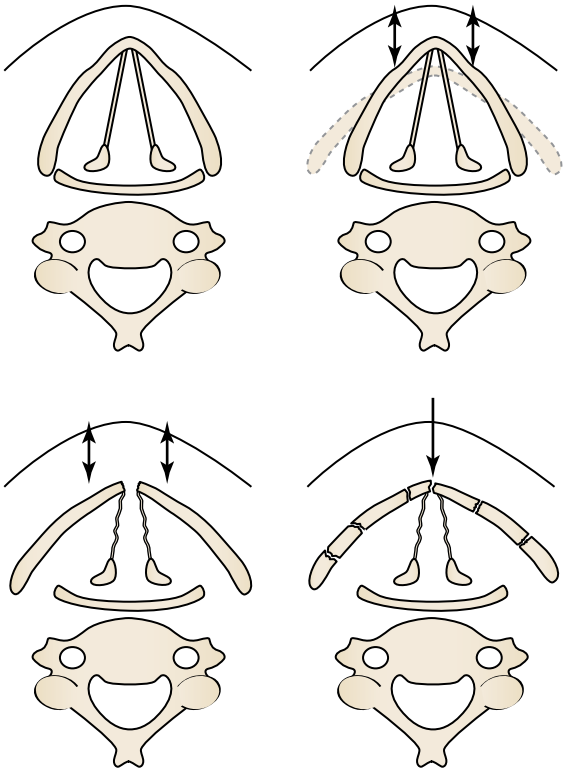

Figure 70-2. Impact of anterior cervical trauma on the larynx. *Top,* Uncalcified thyroid cartilage may spring back. *Bottom,* Calcified cartilage may shatter, and the larynx appears flattened.

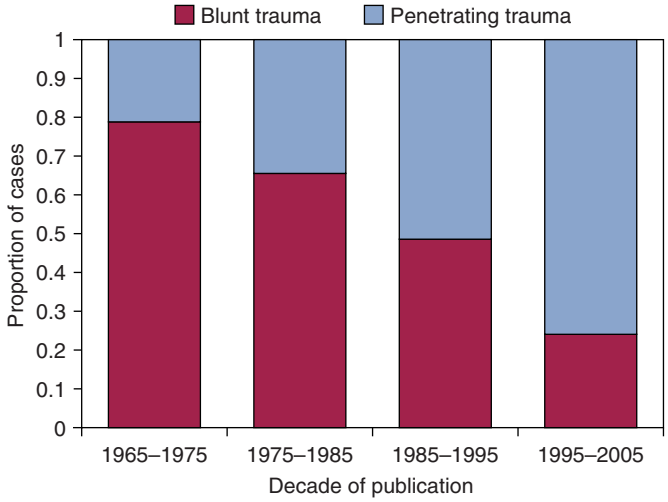

Figure 70-3. Change in the relative composition of blunt and penetrating laryngeal trauma as reported in several sources from 1965 through 2005. *(Data from references 2, 3, 6, 8, 9, and 16-21.)*

Being often asymmetric in respect to the extent of calcification of both the inner and outer surfaces of the thyroid cartilage and each hemilamina,[11] laryngeal calcification increases the likelihood of fractures after trauma and creates stress risers that can cause framework comminution. Motor vehicle accidents have historically been the main cause of external laryngeal trauma.[12] The injury typically occurs when a person not wearing a seat belt or wearing only a lap belt is subjected to rapid deceleration, which thrusts the hyperextended neck onto the dashboard or the steering wheel.[13] Other causes of blunt external laryngeal trauma are clothesline injury (in which the rider of a motorcycle encounters a fixed horizontal object at neck level), sports-related injuries,[14] and suicidal or homicidal strangulation. Penetrating laryngeal trauma is due predominantly to interpersonal violence in civilian practice and is the main cause of laryngeal injuries sustained in the theater of war.[15] Over the past four decades the composition of laryngeal trauma in the United States has changed substantially, due on the one hand to reductions in speed limits, mandatory seat belt laws, and better public education—reducing the incidence of blunt trauma due to motor vehicle accidents—and on the other hand to an increase in penetrating trauma secondary to a greater use of guns and knives (Fig. 70-3).[2,3,6,8,9,16-21]

Diagnosis

Pertinent Features in the Mechanism of Injury

The mechanism of injury has a significant bearing on the likely pattern and severity of laryngeal trauma. Speed and configuration of the vehicles involved in an accident and the use of lap and shoulder seat belts should be determined. Clothesline injuries are often associated with major trauma to the neck because they impart a large force over a small area.[22,23] There are also significant differences in the pattern of injury

Table 70-1

Symptoms and Signs of External Laryngeal Trauma in 33 Cases

Symptom or Sign	No. of Cases (%)
Hoarseness	28 (85)
Dysphagia	17 (52)
Pain	14 (42)
Dyspnea	7 (21)
Hemoptysis	6 (18)

From Juutilainen M, Vintturi J, Robinson S, Back L, Lehtonen H, Makitie AA. Laryngeal fractures: clinical findings and considerations on suboptimal outcome. *Acta Otolaryngol.* 2008;128:213-218.

between suicidal and homicidal strangulation,[24] with the latter being more likely to cause laryngotracheal separation and concomitant neurovascular injuries. Strangulation injuries can cause loss of airway due to laryngeal edema some time after the event, despite minimal initial findings. Penetrating trauma is more likely to damage additional cervical structures, with the extent of injury being proportional to both the weight and velocity of the penetrating projectile ($E = \frac{1}{2}\ mv^2$, where E is energy, m is mass, and v is velocity). As such, information about the type of weapon used and the distance from which it was fired is useful. With knife injuries, information about the blade and depth of entry is helpful.

Symptoms of Laryngeal Trauma

Laryngeal trauma manifests as a spectrum of symptoms and signs ranging from cardiopulmonary arrest due to airway obstruction to subtle changes in voice quality. The most common presenting feature of laryngeal trauma is hoarseness, followed by dysphagia and pain (Table 70-1).[5]

Examination and Initial Management

Examination and initial management of laryngeal trauma should be part of primary and secondary surveys according to Advanced Trauma Life Support guidelines, to ensure that concomitant injuries are not missed (Table 70-2).[4] The over-riding priority is to establish a safe airway with cervical spine protection, which may, and often does, necessitate performing an emergency tracheotomy with the use of local anesthesia. Endotracheal intubation is not a preferred method of airway control in laryngeal trauma, because it can exacerbate a laryngeal injury[25] and precipitate total airway obstruction. Endotracheal intubation can be particularly difficult to perform in the presence of concomitant maxillofacial injuries in a patient with an immobile neck. If endotracheal intubation has been performed, it is converted at the earliest opportunity to a tracheotomy to prevent long-term laryngeal injury. In selected cases transtracheal jet ventilation or cricothyroidotomy may be a helpful temporizing measure. No manipulation of the neck is permissible until the cervical spine has been "cleared"—that is, until injuries to the cervical spine have been ruled out in a systematic manner.

The neck is inspected for evidence of injury such as skin abrasions, bruising, and entry and exit wounds in penetrating trauma, and is palpated for crepitations, laryngeal tenderness, and any obvious changes in laryngeal anatomy, such as loss of the prominence. Open wounds should not be explored at this stage because instrumentation may restart hemorrhage. Flexible nasoendoscopy is then performed, and the oropharynx and hypopharynx are examined for injuries. The laryngeal mucosa is examined for lacerations and hematomas, and particular care is taken to assess the vibratory edge of the vocal cords and the anterior commissure. Arytenoid adduction is examined during phonation, and abduction is assessed by asking the patient to sniff. Impairment of arytenoid mobility may be secondary to structural damage or due to recurrent laryngeal nerve injury. Note is taken of any exposed or protruded cartilage or submucosal distortion of the framework. A sign of cartilaginous injury is failure of the vocal cords to meet in the same horizontal plane.

Table 70-2

Concomitant Primary Diagnoses Recorded along with Laryngeal Trauma

Injury	Percentage of Cases
Open neck injury	18
Maxillofacial fractures	18
Intracranial injuries	17
Cervical spine fracture	13
Chest injury	13
Other facial injury	10
Skull fracture	7
Open pharyngeal injury	4

Adapted from Jewett BS, Shockley WW, Rutledge R. External laryngeal trauma: analysis of 392 patients. *Arch Otolaryngol Head Neck Surg.* 1999;125:877-880.

Box 70-1

National Emergency X-Radiography Utilization Study (NEXUS) Criteria for Cervical Spine Imaging in Trauma Patients

According to NEXUS low-risk criteria, cervical spine radiography is indicated for trauma patients unless they exhibit *all* of the following criteria (sensitivity 99%):

- No posterior midline cervical tenderness
- No evidence of intoxication
- Normal level of alertness
- No focal neurological deficit
- No painful distracting injuries

Use of Computed Tomography

In our practice, multislice computed tomography (CT) (Fig. 70-4) is performed in all patients presenting with "impending airway obstruction" once their airways have been secured, and in those patients with "stable airway" who are found, on flexible nasoendoscopy to have endolaryngeal abnormalities, because imaging may reveal further injuries not readily identifiable with flexible nasoendoscopy. CT scanning can be deferred only in those patients with a history of relatively minor trauma to the neck, no laryngeal tenderness or surgical emphysema, stable airway, and the finding of minimal laryngeal injuries on flexible laryngoscopy. It is important to appreciate that laryngeal trauma is associated with a cervical spine fracture at a rate approaching 10%.[4] At the same time, injuries that occur close to the cervical spine are known to be more likely to mask a spinal injury than injuries further away.[26] We take the view therefore that all but the most minor of laryngeal injuries constitute a "distracting injury" and mandate cervical spine radiography under National Emergency X-Radiography Utilization Study (NEXUS) criteria (Box 70-1).[27] Our practice of using CT to clear the cervical spine irrespective of plain radiography findings is informed

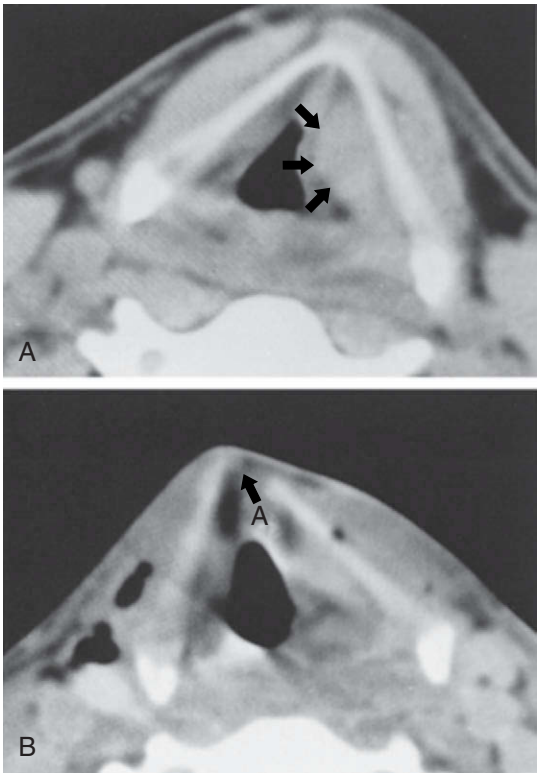

Figure 70-4. A, Computed tomography shows a hematoma involving the right vocal fold (*arrows*) with the thyroid cartilage intact. The injury was completely resolved with only medical management. **B,** Fracture of the right anterior thyroid lamina with angulation (A, *arrow*) is seen. The management consisted of open reduction and internal fixation.

by a growing body of evidence demonstrating a much higher sensitivity for CT over plain radiography in diagnosing spinal injuries.[28,29] Overall, therefore, detailed radiologic imaging of the larynx is available in the majority of patients with laryngeal trauma both because of primary laryngeal indications and as a by-product of "clearing" of the cervical spine.

Classification

Laryngeal trauma can be classified according the Schaefer-Fuhrman[25,30] (Table 70-3) or Lee-Eliashar[31] system. We use the Schaefer-Fuhrman system but also formally and separately document the extent of injuries to the laryngeal mucosa and framework, the vibratory mechanism, and the laryngotracheal complex (Table 70-4).

Management

Airway Management

The first priority in managing laryngeal trauma is to assess and secure the airway while protecting the cervical spine. We take a stepwise approach to securing the airway based on information available at the different stages of clinical assessment (Fig. 70-5). A stridulous patient with respiratory distress at presentation should immediately undergo tracheotomy with local anesthesia. If the airway is judged to be stable following initial history and examination, the patient undergoes flexible nasoendoscopy. In a small number of cases, unexpected airway-encroaching injuries are identified at this stage and tracheotomies are performed. More subtle endolaryngeal injuries are further assessed with CT, and again, if airway-encroaching injuries are identified, a tracheotomy is performed.

Surgical versus Nonsurgical Therapy.

The decision as to the most appropriate therapy for laryngeal trauma rests on assessing the stability of, and the extent of injury to, the *laryngeal framework*, the extent of *mucosal injuries*, the presence of injury to the *vibratory apparatus*, and the integrity of the *laryngotracheal junction*. Jewett and colleagues[4] showed that 37% of patients with laryngeal trauma could be managed with no airway intervention and that a further one sixth of patients required only a tracheotomy.

Table 70-3

Schaefer-Fuhrman Classification of Laryngeal Trauma

Group 1	Minor endolaryngeal hematomas or lacerations No detectable fracture
Group 2	Edema, hematoma, minor mucosal disruption without exposed cartilage Nondisplaced fracture Varying degrees of airway compromise
Group 3	Massive edema, large mucosal lacerations, exposed cartilage Displaced fracture(s) Vocal cord immobility
Group 4	Same as group 3 but more severe with: Severe mucosal disruption Disruption of the anterior commissure Unstable fracture, two or more fracture lines
Group 5	Complete laryngotracheal separation

Conservative Management

Patients in whom nasoendoscopy has found the endolarynx normal, as well as patients with minimal endolaryngeal abnormalities and a stable laryngeal framework whose airway patency has been confirmed by CT, can be conservatively managed (see Fig. 70-5). Conservative management consists of a minimum of a 24-hour admission to a high-dependency unit, with regular observations, serial flexible nasoendoscopy examinations, and use of humidified oxygen. A mixture of oxygen and helium should be on standby in case respiratory embarrassment develops. The patient's head is elevated to reduce further edema, and corticosteroids are administered if presenting within 24 hours of injury. All patients are prescribed a proton pump inhibitor and, if the laryngeal mucosa has been breached, are also given prophylactic broad-spectrum antibiotics.

Surgical Management

Patients with more significant injuries require surgical intervention. The optimal timing of repair is a subject of debate, and in patients with polytrauma, laryngeal surgery may have to be coordinated with other procedures. We aim to repair all laryngeal injuries within 12 hours of presentation and are reluctant to accept delays beyond 24 hours. Delays in treatment can lead to granulation and scar tissue formation, which can progress to laryngeal stenosis (Fig. 70-6), a difficult surgical problem to correct.

DIAGNOSTIC OR THERAPEUTIC ENDOSCOPY. All patients who are not managed conservatively should undergo microlaryngoscopy and tracheoscopy, direct pharyngoscopy, and direct esophagoscopy. In a proportion of patients definitive, endolaryngeal treatment can be undertaken endoscopically. Hematomas can be drained, mucosal and selected vocal cord lacerations can be repaired, and dislocated cricoarytenoid joints can be reduced. If there have been extensive injuries to opposing laryngeal mucosal surfaces, stents can also be deployed endoscopically to prevent adhesions.[32]

OPEN LARYNGEAL REPAIR. The main indications for open repair are unstable or comminuted laryngeal fractures, cricotracheal separation, detachment of the anterior commissure, and extensive mucosal

Table 70-4

A Systematic Approach to Documenting Laryngotracheal Injuries and Determining the Need for Surgical Intervention

Laryngeal framework	Stable: No fractures A single undisplaced fracture Unstable: A single displaced fracture >1 fracture line Cricoid fracture Potentially nonviable: Framework comminution with devitalized cartilage fragments
Laryngeal mucosa	Intact/minimally injured: No mucosal injuries Small submucosal hematoma Linear laceration with no exposed cartilage Injured: Jagged/multiple linear lacerations Large hematoma(s) Exposed cartilage Massively injured: Significant loss of mucosa Devitalized mucosal tissue
Vibratory apparatus	Intact Injured: Anterior commissure Vibrating edge of the vocal cord(s) Arytenoid dislocation
Laryngotracheal junction	Intact Any degree of laryngotracheal separation

disruption. For open exploration, a transverse neck incision is placed over the cricoid, and subplatysmal flaps are elevated. Strap muscles are separated in the midline and retracted. In some patients with unstable laryngeal fractures but with minimal or endoscopically treatable endolaryngeal injuries, a thyrotomy can be avoided. Repair of the anterior commissure or significant endolaryngeal injuries is achieved through an anterior vertical laryngofissure. However, a paramedian fracture close to the midline may also be used. Hematomas are evacuated and mucosa tears repaired with 5-0 or 6-0 absorbable sutures. Mucosal loss can often be reconstructed with local mucosal flaps, and, in particular, posterior commissure injuries can and should be reconstructed with piriform fossa or supraglottic mucosa to prevent laryngeal stenosis. The anterior margins of the vocal folds are attached to the anterior limit of the thyroid cartilage or its outer perichondrium with a slow-absorbing monofilament suture. It is very important to reestablish the appropriate height of the vocal folds to optimize voice outcomes. Thyroid cartilage fractures are repaired with the use of permanent or resorbable miniplates. Even in the older patient, the cricoid arch is not fully calcified and can be repaired with suture material alone (Fig. 70-7).

ENDOLARYNGEAL STENTING. The indications for stenting are controversial because the need for endolaryngeal support must be weighed against the potential for further mucosal injury. Our primary indication for stenting is significant framework comminution. Stents can also be used to prevent anterior commissure webbing in cases of bilateral vocal fold epithelial loss. We prefer to use soft polymeric silicone (Silastic) stents for this purpose (Figs. 70-7B and 70-8) in order to *minimize* further mucosal injury and foreign-body reaction associated with the use of stents fashioned from endotracheal tubes. Endolaryngeal stents are commercially available but can also be fashioned from the vertical limb of a Montgomery T-tube that is oversewn at the top. The stent is held in place with a 2-0 polypropylene (Prolene) suture passed through the anterior stent and laryngeal ventricles and knotted over the larynx after closure of the laryngofissure. The stent is removed endoscopically 10 to 14 days later. The securing suture can be cut flush with the endoluminal airway or removed via a small neck incision.

TREATMENT OF VOCAL CORD IMMOBILITY. Vocal cord mobility can usually be determined during preoperative flexible laryngoscopy. Cricoarytenoid joint mobility can be assessed preoperatively, but definitive assessment of joint mobility requires microlaryngoscopy and instrumentation. Vocal cord immobility due to cricoarytenoid joint dislocation can often be managed with endoscopic manipulation and reduction. Recurrent laryngeal nerves can be severed in penetrating trauma or during cricotracheal separation, or crushed during laryngeal trauma. Only if a complete palsy is confirmed should exploration of the affected nerve be considered. Anatomically intact nerves should be allowed to regenerate. When possible, severed nerves should be repaired in a tension-free manner. If such repair is not possible, a cable graft using the greater auricular or sural nerve should be considered. The other option is to consider ansa cervicalis–recurrent laryngeal nerve repair. Nerve repairs do not restore the intricate motor function of the larynx but may provide sufficient muscle tone to improve vocalization.

MANAGEMENT OF CRICOTRACHEAL SEPARATION. After surgical exposure in a patient with cricotracheal separation, a tracheotomy is fashioned or moved to a healthy part of the lower trachea prior to reanastomosis. A small reinforced endotracheal tube is placed through the tracheotomy for ventilation during surgery and is replaced with a small tracheotomy tube at the end of the procedure. The surgeon begins the repair with the posterior anastomosis, using a combination of 3-0 absorbable and nonabsorbable sutures, and works toward the anterior trachea (see Fig. 70-7C). All knots are extraluminal, and the sutures are run through the submucosal plane. Avascular and damaged tissue is resected. If there is an associated crush injury to the trachea, a temporary soft polymeric silicone stent may have to be placed in the lumen prior to anastomosis.

PARTIAL OR TOTAL LARYNGECTOMY. In cases of massive laryngeal injury with significant tissue loss (Fig. 70-9), partial or total laryngectomy may be indicated, although this situation is rare in civilian practice.[9]

Postoperative Care

Any repairs to the vocal folds should be followed by strict voice rest for 48 to 72 hours. A nasogastric tube should be inserted at the time of surgery and should remain in situ until the safety of swallowing is confirmed. All patients with mucosal tears should be started on antireflux and prophylactic antibiotic therapy. The patient is nursed in the head-up position to minimize edema, and standard tracheotomy care is provided. Early ambulation is encouraged. Stents are removed at 10 to 14 days, and the patient is decannulated. Regular endoscopic examinations are undertaken, during which granulation tissue is removed to prevent long-term scarring. In patients with cricotracheal separation, the neck is kept in flexion for 7 days postoperatively to prevent traction on the anastomosis. A large monofilament suture from the submental skin to the anterior chest skin, placed at the time of surgery, may be necessary for the first few days after surgery. The tracheotomy can be removed at 7 days, and the airway stent can be removed endoscopically at 10 to 14 days.

Sequelae

All patients with laryngeal trauma should be regularly monitored for a minimum of 12 months. Long-term morbidity occurs from any combination of laryngeal stenosis, dysphonia, and aspiration, owing to both structural and neurovascular injuries. Vocal cord paralysis should be

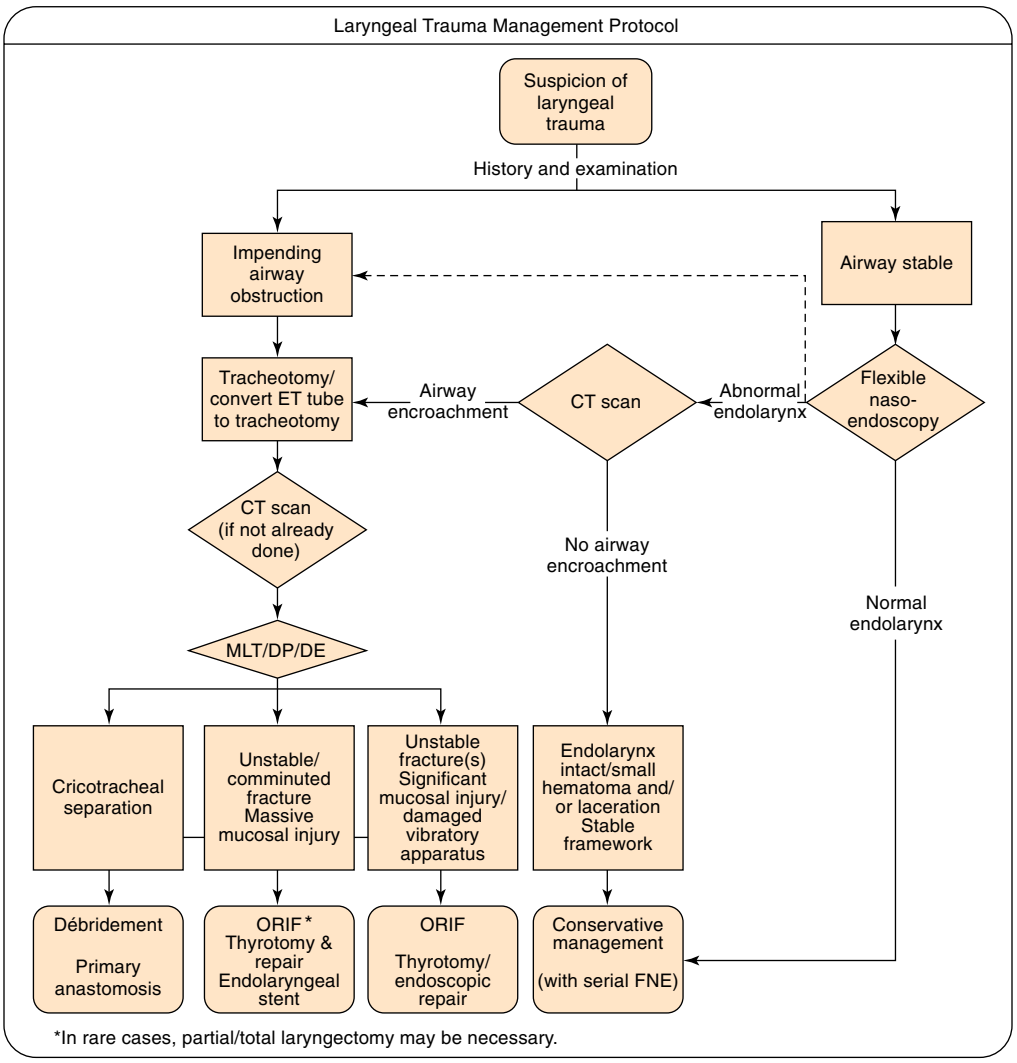

Figure 70-5. A proposed protocol for managing laryngeal trauma. CT, computed tomography; DE, direct esophagoscopy; DP, direct pharyngoscopy; ET, endotracheal; FNE, flexible nasoendoscopy; MLT, microlaryngoscopy; ORIF, open reduction and internal fixation.

carefully observed for recovery, and in patients with a normal vibratory apparatus structure and unilateral vocal cord paralysis, definitive medialization procedures should be attempted only after 9 to 12 months of observation for functional recovery. In the interim, the voice can be temporarily improved by collagen or fat injection. In cases of bilateral vocal cord palsy causing laryngeal inlet obstruction, consideration should be given to retaining the tracheotomy in preference to performing an early laser arytenoidectomy, in anticipation of return of vocal cord function. Laryngeal stenosis due to posterior commissure or tracheal granulation tissue should be promptly treated with intralesional steroid injections and reduction of granulation tissue. The granulation tissue should not be allowed to mature into a scar, because it is a much more difficult problem to manage.[33] In our experience, the most difficult injury to manage is laryngeal inlet obliteration (Fig. 70-10), followed by interarytenoid scarring or webbing (Fig. 70-11). The treatment of glottic stenosis is almost always a compromise between voice, airway, and swallowing; gains in one domain are often made at the expense of another.

Outcome

Outcome depends both on the nature and severity of the original injury and on whether it was promptly recognized and adequately treated. Schaefer[9] and more recently, Juutilainen and colleagues[5] found that the voice outcome, but not the airway outcome, correlates with the severity of the initial injury as determined by Schaefer's classification system (Table 70-5), whereas Bent and associates[8] reported that intervention within 48 hours was associated with an improved outcome. Delays in intervention can lead to complete laryngotracheal stenosis (Fig. 70-12).

Special Considerations in Pediatric External Laryngeal Trauma

The larynx lies at the level of C3 in the neonate and descends during the first 3 years of life to its adult position at the level of C6. The pediatric larynx is smaller in absolute and relative dimensions compared with the adult larynx. Furthermore, laryngeal mucosa is less firmly adherent to the cartilaginous framework in infants and children than in adults. The result of this combination of factors is that, although the pediatric larynx is better shielded and is therefore less liable to injury, an injury is more likely to result in loss of the airway owing to mucosal edema and hematoma formation.[7,34] Furthermore, it is usually not possible to perform a tracheotomy with use of only local anesthesia in a child. The child is therefore managed along the same lines as a patient with acute epiglottitis. The surgeon is prepared for an emergency tracheotomy, but in most cases the airway can be secured with an endotracheal tube or ventilating bronchoscope, followed promptly by a tracheotomy performed using general anesthesia. CT scanning may then be considered prior to airway reconstruction. As with adult patients, selected, more limited injuries can be managed endoscopically and without tracheotomy.[35]

Iatrogenic Laryngeal Trauma

Incidence

Despite major advances in the design of endotracheal tubes and developments in the management of difficult airways, endotracheal intubation remains by far the most common cause of laryngeal trauma. Approximately 10% of patients have demonstrable laryngeal pathology 1 day following short-term intubation for surgery.[36] With longer-term intubation and mechanical ventilation for critical illness, the incidence of laryngotracheal injuries approaches 90%, with long-term sequelae occurring in 11% of patients.[37] The annual incidence of postintubation laryngotracheal stenosis requiring surgical correction is 1 in 204,000 in adults[38] and 4.9 in 100,000 in children.[39]

Etiology

Endotracheal intubation can cause pharyngeal or laryngeal lacerations, cricoarytenoid joint dislocation, and neuropraxia of the lingual, hypoglossal, and laryngeal nerves. There is no period of endotracheal intubation before which no injury occurs, and after which injury is inevitable. The subglottis is the narrowest part of the pediatric airway, accounting for the fact that most postintubation injuries in children occur at this level. In adults, translaryngeal intubation can lead to pressure necrosis, most commonly of the medial surface of the posterior commissure, on which the tube rests.[40] This can lead to perichondritis, granulation tissue formation,[41] and, in a proportion of patients, interarytenoid scarring and airway compromise due to bilateral vocal cord immobility (see Fig. 70-11). Intubation trauma can also cause bilateral intubation granulomas, which can coalesce to fix the vocal cords in adduction (Fig. 70-13). The larynx can also be injured by a poorly sited tracheotomy either through or adjacent to the cricoid cartilage, with the potential for subglottic airway stenosis. Another iatrogenic cause of laryngeal injury is aggressive treatment of benign laryngeal diseases such as respiratory papillomatosis. Excessive damage to the epithelium can lead to laryngeal scarring with the potential to affect the voice or airway.

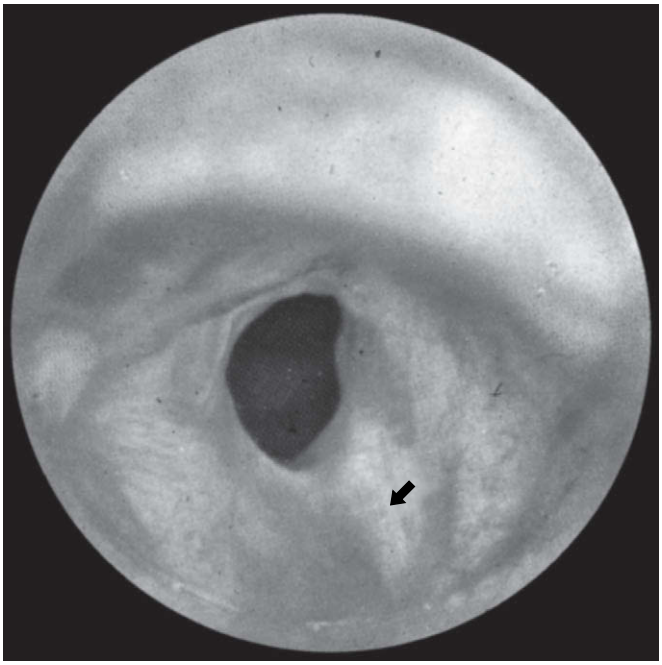

Figure 70-6. Post-traumatic laryngeal stenosis. The *arrow* points to the remnant of the right arytenoid cartilage.

Management

A detailed account of the management of laryngotracheal stenosis is given elsewhere. Laryngeal stenosis—in particular, posterior commissure stenosis due to interarytenoid scarring (see Fig. 70-11)—carries a poor prognosis. Tracheal stenosis, which predominantly affects the airway, is amenable even in its more severe forms to curative therapy with minimal long-term sequelae.[42] Treatment of laryngeal stenosis, as discussed previously, involves compromise among voice, airway, and swallowing functions, and gain in one domain is often achieved through compromise in the function of another. As such, prevention is the best approach in relation to this injury. Posterior commissure stenosis occurs exclusively with translaryngeal intubation, and the likelihood of its occurrence can be significantly reduced by performing early tracheotomy in the intensive care unit. Although tracheotomies are not without complications themselves and can precipitate airway stenosis, tracheotomy-related airway stenosis carries a much better outlook than laryngeal stenosis,[43] and from a laryngologic perspective, preventing the latter injury is sufficient justification to recommend universal early tracheotomy in patients receiving mechanical ventilation for a protracted period. This recommendation is also supported by the findings of a randomized controlled trial that patients undergoing mechanical ventilation who received early tracheotomy (<48 hours) had a 30% absolute risk reduction in mortality and a fivefold reduction in pneumonia in comparison with patients who had prolonged translaryngeal intubation.[44]

Caustic or Thermal Laryngeal Trauma

Incidence

Upper aerodigestive tract injury due to ingestion of caustic substances occurs in 5000 to 15,000 persons in the United States annually, and

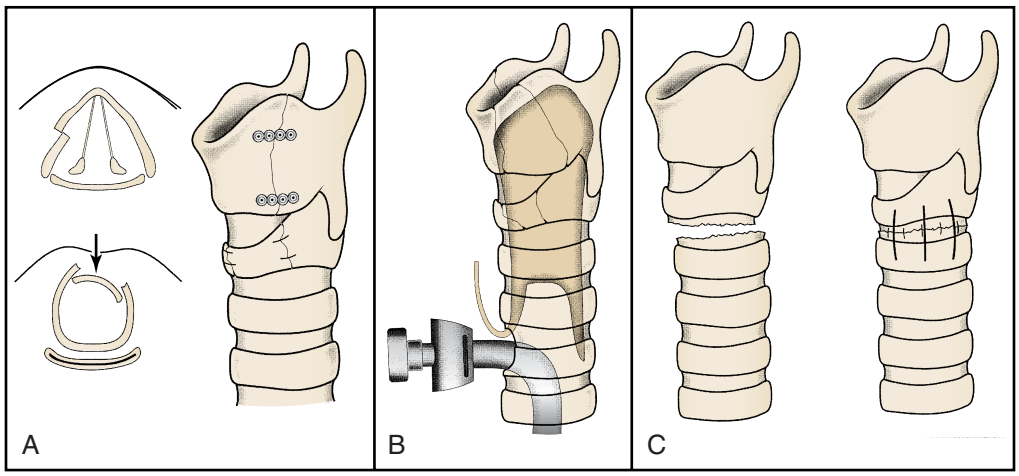

Figure 70-7. **A,** Plate and suture repair of laryngeal cartilage and the cricoid arch. **B,** Extensive laryngeal framework injuries require endolaryngeal stenting prior to fracture fixation. **C,** Cricotracheal separation requires débridement and primary anastomosis.

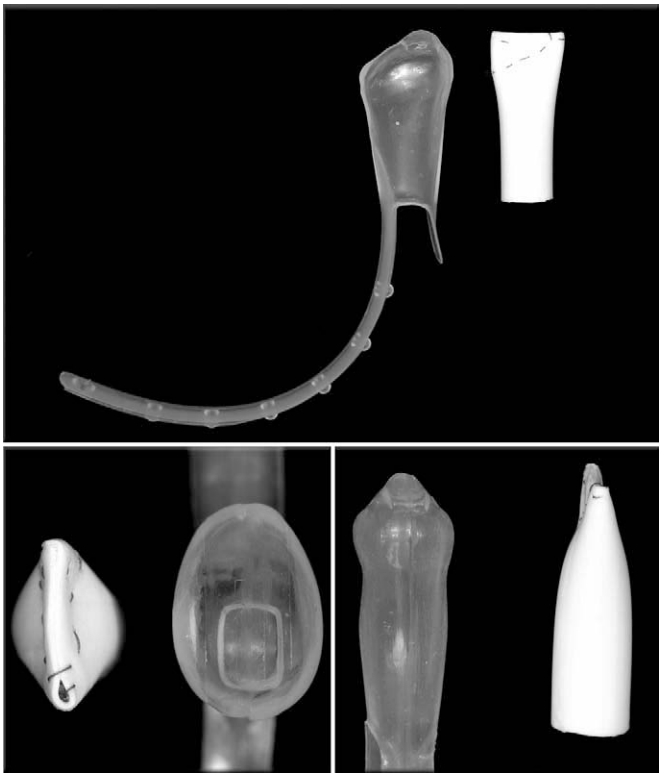

Figure 70-8. Pictures of a custom-made stent manufactured from the limb of a polymeric silicone (Silastic) T-tube that has been oversewn (*white*) and a commercially available endolaryngeal stent (Eliashar) (*gray*).

Figure 70-9. Severe laryngeal injury caused by a high-velocity military bullet.

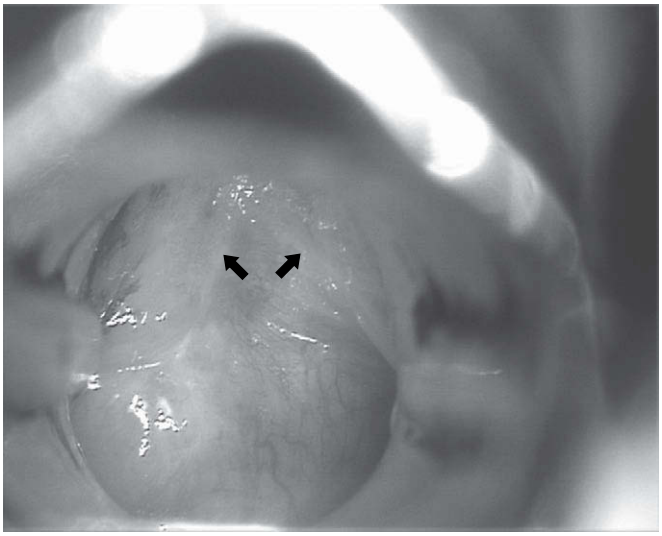

Figure 70-10. Post-traumatic laryngeal inlet obliteration due to scarring (*arrows* indicate vocal fold remnants).

Figure 70-11. Postintubation laryngeal stenosis due to interarytenoid scarring.

the majority of injuries are caused by ingestion of alkaline substances.[45] The larynx is involved in approximately 40% of cases.[46] Thermal injury to the larynx is a result of inhaling superheated air. Inhalation burns occur in 30% of all patients with burns, and 20% of patients with inhalation injury have extensive laryngeal injury. A further 7% of patients with inhalation injury have both laryngeal and tracheobronchial injuries.[47]

Etiology

Ingestion of alkali causes liquefaction necrosis of muscle, collagen, and lipids and creates an injury that worsens with time. By contrast, acids cause coagulation necrosis of the superficial tissues. Ingestion of a caustic substance is virtually always accidental in children, in whom small amounts of liquids are taken, but is almost always due to attempted suicide in adults, in whom large volumes of liquid are

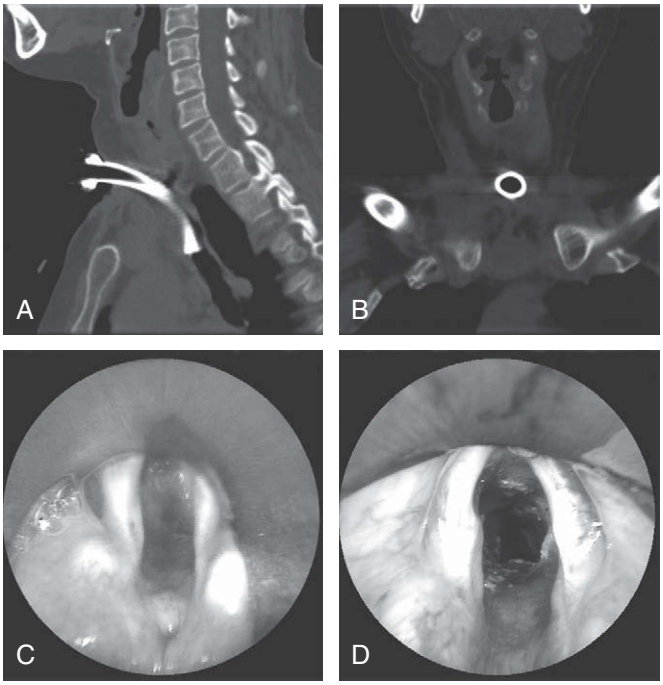

Figure 70-12. Sequelae of inappropriate initial management of laryngotracheal separation. The patient had laryngotracheal separation secondary to penetrating anterior neck trauma and was treated with tracheotomy placement through the tracheal wound. **A** and **B**, Computed tomography scans of the airway showing complete luminal obliteration. **C,** Endoscopic appearance of the airway prior to tracheal resection. **D,** Endoscopic airway appearance 6 weeks after tracheal resection.

Table 70-5

Voice and Airway Outcome by Group

Schaefer-Fuhrman Group	Voice Outcome			Airway Outcome		
	Good	Fair	Poor	Good	Fair	Poor
Results from Schaefer*						
1	20	0	0	20	0	0
2	38	3	0	40	1	0
3	18	3	0	21	0	0
4	22	10	0	31	0	2
Results from Juutilainen et al†						
2	12	4	0	16	0	0
3	7	6	0	13	0	0
4	1	3	0	4	0	0

*Data from Schaefer SD. The acute management of external laryngeal trauma. A 27-year experience. *Arch Otolaryngol Head Neck Surg.* 1992;118:598-604.
†Data from Juutilainen M, Vintturi J, Robinson S, Back L, Lehtonen H, Makitie AA. Laryngeal fractures: clinical findings and considerations on suboptimal outcome. *Acta Otolaryngol.* 2008;128:213-218.

involved.[46] The type of liquid taken varies widely with geography, alkaline ingestion being more common in developed countries and acid ingestion in developing countries.[45,48] Inhalation injury typically is a consequence of fires in closed spaces and causes a sixfold increase in the mortality rate associated with the burn.[47]

Figure 70-13. Coalescence of intubation granulomas, as seen at extubation, causing acute airway compromise due to bilateral vocal cord immobility in adduction.

Management

All patients with caustic or thermal laryngeal injuries should be admitted for a minimum of 24 hours for airway observation. The first priority is the establishment of a safe airway, followed by cardiovascular resuscitation as per standard burn care protocols. Presence of facial or body burns and soot in the oral cavity and finding at endoscopy of laryngeal edema predict the need for airway intervention.[49] Endotracheal intubation plays an even lesser role in management of these cases than in cases of external laryngeal trauma. Arevalo-Silva and colleagues[46] found a 100% association between endotracheal intubation and subsequent tracheotomy for airway stenosis in patients with laryngeal injury due to caustic ingestion. The situation with airway management in thermal injuries is somewhat less clear, because there have been reports of higher stenosis rates with tracheotomy than with intubation in patients with inhalation injury.[50] However, unless there are strong contraindications to performing a tracheotomy, such as extensive cervical burns, we iterate the view that because glottic stenosis has a far worse prognosis than tracheal stenosis, a possible increase in the change of post-tracheotomy stomal stenosis is an acceptable tradeoff.

If patients are to undergo microlaryngoscopy, tracheobronchoscopy, or esophagoscopy, the procedure should be performed within 24 hours of injury. Beyond this period edema and ulceration are more marked, and instrumentation may exacerbate subsequent problems. The upper aerodigestive tract should be irrigated in cases of caustic injury to remove any residual substances. Further treatment depends on the nature and extent of injuries found and the consequences of healing and scarring.

Caustic and thermal injuries can cause laryngeal and tracheal airway strictures, whose severity is reported to be greater than that of strictures associated with postintubation laryngotracheal stenosis.[51] Dysphonia is present in as many as 70% of patients with inhalation injuries 16 to 25 years after initial injury.[52]

Esophageal Trauma

Traumatic Injuries

Esophageal injuries are reported in 14% of patients with laryngotracheal trauma[8] and 6.5% of patients with penetrating trauma to the neck.[53] Isolated esophageal trauma due to external trauma to the neck is uncommon, but it can occur as a result of barotraumatic perforation of Killian's

dehiscence and injury caused by the thyroid cartilage. Iatrogenic injuries also occur from attempted endotracheal intubation and esophagoscopy.

Cervical crepitus or surgical emphysema often accompanies esophageal injury, although both signs occur more commonly in patients with hypopharyngeal and laryngeal injuries.[54] Other presenting features are pain, dysphagia, and aspiration, and patients with a delayed presentation or diagnosis may also exhibit symptoms and signs of sepsis. Plain radiographs and CT scans of the neck and chest may demonstrate surgical emphysema, pneumomediastinum, or pneumothorax, all of which point toward the diagnosis, although in many cases esophageal injury is identified during panendoscopy or following radiocontrast swallow studies.

Conservative management, consisting of "nothing by mouth" status, broad-spectrum antibiotics, and peripheral nutrition, is the cornerstone of managing esophageal injuries, provided that they are recognized early. When there has been a significant delay in presentation or recognition of the injury, and the patient exhibits signs of infection, exploration and drainage of any purulent collection is urgently indicated. Nothing by mouth status is usually maintained for 8 to 10 days, and healing is assessed with a radiocontrast swallow study. The prognosis of traumatic cervical esophageal injuries is favorable, and survival rates between 90% and 100% have been reported.[54]

Caustic Injuries

Details about the incidence and etiology of caustic upper aerodigestive tract injuries were given in the discussion of caustic and thermal laryngeal injuries. The management of caustic ingestion depends on the extent of injury. Esophageal injuries can be endoscopically graded as follows[46]:

- Normal
- First-degree injury: of mucosal erythema
- Second-degree injury: erythema with noncircumferential exudation
- Third-degree injury: circumferential exudation
- Fourth-degree injury: circumferential exudation with esophageal wall perforation

As many as 30% of patients with caustic esophageal injury do not show any evidence of oropharyngeal damage,[48] so the absence of oropharyngeal injury does not exclude an esophageal injury. Evaluation with the patient under anesthesia should be deferred unless it can occur within 24 hours of injury,[48] and endoscopes should not be forced beyond areas of circumferential mucosal injury. The earliest opportunity should be taken to irrigate the upper aerodigestive tract to remove any remaining caustic substances. The severity of injury is greater in adult patients than in children, given the fact that caustic ingestion in adults almost exclusively occurs in the setting of attempted suicide, in which large volumes of the caustic substance are taken. Management consists of insertion of a large-bore nasogastric tube to maintain esophageal patency, steroids, broad-spectrum antibiotics, and antacid therapy.[46] In the most severe cases, esophageal resection with gastric pull-up or bypass surgery may be necessary.[55] Peripheral nutrition is continued until safety of swallowing is confirmed.

The incidence of esophageal stricture after caustic ingestion is 10% to 35%.[46,56] In many cases the stricture can be managed with endoscopic dilatation. It is very important to note, however, that as many as 1 in 7 patients with a caustic esophageal stricture go on to have esophageal carcinoma.[57] Many authorities therefore advocate regular esophageal surveillance after caustic ingestion, although the latent period for the development of cancer may be as long as 50 years.[58]

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CHAPTER SEVENTY-ONE

Surgical Management of Upper Airway Stenosis

Ayesha N. Khalid

David Goldenberg

Key Points

- Accurate preoperative assessment of laryngotracheal stenosis is critical to a successful repair, including use of multiple staging systems to evaluate diameter and levels of airway stenosis.
- The primary goals of surgical intervention are to establish an adequate airway and enable eventual decannulation.
- Timing of surgical intervention is important; chronic airway stenosis may be electively repaired following proper preoperative evaluation of possible inflammatory and autoimmune etiologies in idiopathic stenosis cases.
- The advent of endoscopic microlaryngeal instrumentation has enabled photodocumentation and decreased morbidity of neck incisions when performed by experienced surgeons.
- Laryngeal lesions may undergo microsurgical débridement or laser therapy, and each technique has its advantages and disadvantages; similarly topical applications (such as mitomycin C).
- Successful surgical repair hinges on providing an adequate skeletal framework as scaffolding, followed by the need for grafts to avoid scarring and tethering.
- Sources of cartilage grafts include vascularized thyroid and hyoid, as well as auricular and nasal cartilages. Sources of muscular flaps (for example, skin) and mucosa may also be utilized.
- Stents are useful in limited instances, with the need to maintain a patent airway being balanced by risk of ischemic mucosal injury and increased risk of infection of underlying grafts.
- Controversy surrounding the effect of endotracheal intubation leading to airway stenosis from compression has led to improvements in endotracheal tube design, with the largest impact on the size of the tube and its cuff on the posterior glottic region.
- Traumatic laryngotracheal stenosis may lead to airway stenosis, with surgical intervention ranging from tracheotomy to tracheal resection with postoperative stent placement.

Successful repair of upper airway stenosis requires establishing an adequate airway while preserving the laryngeal functions of airway protection, phonation, and sustained glottic closure to increase intrathoracic pressure. Laryngotracheal injuries vary widely and can differ in location, severity, duration, cause, and extent of functional impairment. Selection of the appropriate surgical repair should consider all these factors within the context of the patient's concurrent injuries and medical stability.

Pathophysiology

Adult laryngotracheal stenosis has numerous etiologies (Box 71-1). The pathophysiology of the specific cause plays a role in the timing of surgical management as well as the surgical procedure chosen.

The most common causes of laryngotracheal stenosis are external trauma to the neck and prolonged endotracheal intubation. Both may result in acute stenosis and chronic stenosis; which occur through different pathophysiologic processes. Anatomically, the larynx and trachea can be regarded as a semirigid tubular structure. When the laryngotracheal complex is injured by external trauma, disruption of the cartilaginous framework, hematoma in the laryngeal spaces, and mucosal disruption usually result. Resorption of the hematoma can cause cartilage loss and extensive deposition of collagen. Subsequent scar contracture leads to stenosis and loss of mobility. The location, mechanism, and severity of the laryngeal injury caused by external trauma vary.[1]

In contrast, the injury from endotracheal intubation is usually initiated by ischemic necrosis of the mucosa from pressure of the cuff of the endotracheal tube or the endotracheal tube itself.[2] Mucosal ulceration in the presence of bacterial infection can lead to perichondritis and chondritis with subsequent cartilage resorption. Healing occurs by secondary intention with subsequent submucosal fibrosis and scar contraction. Injuries from endotracheal intubation occur primarily in the posterior glottis as a result of pressure exerted by the wall of the tube and the pressure of the cuff on the tube's tip. The latter injury has been reduced significantly with low-pressure, high-volume cuffs. Other factors, including tube size and composition, duration of intubation, and laryngeal movement, contribute to the development of laryngotracheal stenosis. With the widespread acceptance and use of endotracheal intubation to provide ventilatory and airway support, efforts have been directed to modifying endotracheal tube design.[3]

Box 71-1

Causes of Adult Laryngeal and Upper Tracheal Stenosis

Trauma
External laryngotracheal injury
- Blunt neck trauma
- Penetrating wound of the larynx

Internal laryngotracheal injury
Prolonged endotracheal intubation
- Tracheotomy
- Surgical procedure
- Irradiation therapy
- Endotracheal burn
  - Thermal
  - Chemical

Chronic Inflammatory Disease
Bacterial diphtheria
Syphilis
Fungal histoplasmosis
Tuberculosis
Leprosy
Sarcoidosis
Scleroma

Benign Neoplasms
Intrinsic
- Papillomas
- Chondromas
- Minor salivary gland
- Neural

Extrinsic
- Thyroid
- Thymus

Malignant Neoplasms
Intrinsic
- Squamous cell carcinoma
- Minor salivary gland
- Sarcomas
- Lymphoma

Extrinsic
- Thyroid

Collagen Vascular Diseases
Wegener's granulomatosis
Relapsing polychondritis
Other

Patient disease has also shown to be correlated with the development of subglottic and tracheal stenosis. Diabetes mellitus, congestive heart failure, and a history of stroke have been shown to be associated with a higher incidence of severe acute laryngeal injury from intubation. In some cases, this condition prompts early tracheotomy.[4] Laryngopharyngeal reflux in the setting of gastroesophageal disease has also been demonstrated to be a causative agent and potentiator of laryngotracheal stenosis. Treatment with H_2 blockers and proton pump inhibitors in the perioperative and acute injury phases has been demonstrated to prevent scar formation and subsequent contracture.[5]

Classification of Stenosis

Multiple staging systems exist for airway stenosis; these are based on function or location of the stenotic section. As shown in Table 71-1, the most prevalent is the Cotton-Myers classification; however, the McCaffrey system and others also add to the diagnostic and therapeutic plan in providing not only size of stenosis but location and inclusion of multiple subsites, which are associated with a poorer prognosis following surgery.

Table 71-1

Classification and Staging Systems for Airway Stenosis

Myers-Cotton Classification: circumferential stenosis limited to subglottic region	
Grade I	Obstruction of 0%-50% of the lumen
Grade II	Obstruction of 51%-70% of the lumen
Grade III	Obstruction of 71%-99% of the lumen
Grade IV	No detectable lumen; obstruction of 100% of the lumen
McCaffrey Classification: laryngotracheal stenosis based on the subsites and length of the stenosis	
Stage I	Subglottic or tracheal lesions < 1 cm long
Stage II	Subglottic lesions > 1 cm long
Stage III	Subglottic/tracheal lesions not involving the glottis
Stage IV	Glottic lesions
Lano Classificaiton: based on number of subsites involved	
Stage I	One subsite involved
Stage II	Two subsites involved
Stage III	Three subsites involved

Surgical Principles

Goals and Assessment

The goal of any surgical procedure addressing laryngotracheal stenosis is to establish a satisfactory airway, and eventually, to decannulate the patient. In addition, every effort should be made to preserve other important laryngeal functions—phonation, airway protection, and glottic closure. Surgical procedures designed to improve the airway often compromise other laryngeal functions. The anticipated overall function of the larynx should be carefully discussed with the patient so that expectations are reasonable.

Several factors should be considered, including the location, dimensions, and quality (soft vs. fibrous) of stenosis, associated vocal fold motion impairment, and extent of functional impairment. Initial evaluation should involve a thorough history that includes details of the degree of subjective impairment (perceived by the patient) along with objective measures (e.g., observing the patient walking 200 feet, climbing a flight of stairs, pulmonary function testing).[6] Pulmonary function testing is helpful in delineating the site of obstruction and severity of airway compromise (Fig. 71-1).

Physical examination, including an indirect laryngeal examination followed by direct laryngoscopy and bronchoscopy, is essential (Fig. 71-2). High-resolution computed tomography of the larynx and trachea may be useful in assessing the level and extent of the stenosis. Three-dimensional computed tomography with volume rendering or virtual endoscopy has been employed to evaluate the extent or severity of the stenosis.[7,8]

An important consideration is whether the site of stenosis requires reestablishment of structural support, usually by repositioning of existing cartilage or, more commonly, through the use of cartilage or bone grafts.[9] Even with grafts, the preservation of existing mucosa and the judicious use of antibiotics, stents, skin or mucosal grafts are all adjunctive treatments intended to minimize formation of granulation tissue, and subsequent deposition of collagen.

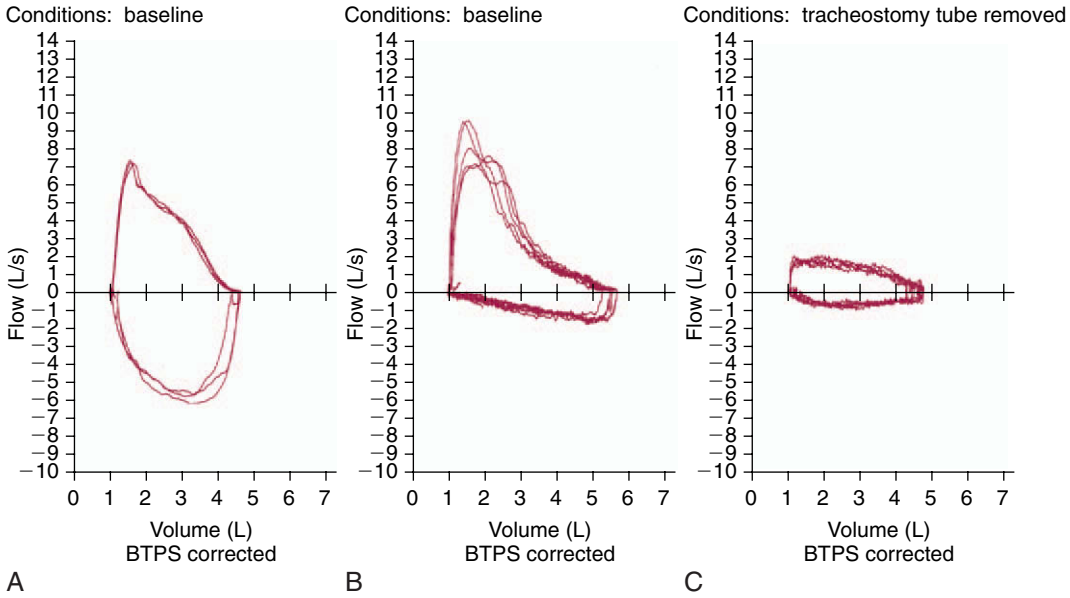

Figure 71-1. Flow-volume loop for assessing adequacy of the upper airway. **A,** Normal result shows expiratory flow, indicated by positive deflection, and inspiratory flow, indicated by negative deflection. **B,** Loop from a patient with bilateral vocal fold motion impairment shows variable extrathoracic obstruction with a mid–vital capacity inspiratory flow rate (Vi_{50}) of less than 1.5 L per second. **C**, Loop from a patient with an infiltrative tumor and a fixed obstruction. BTPS, body temperature, pressure saturation.

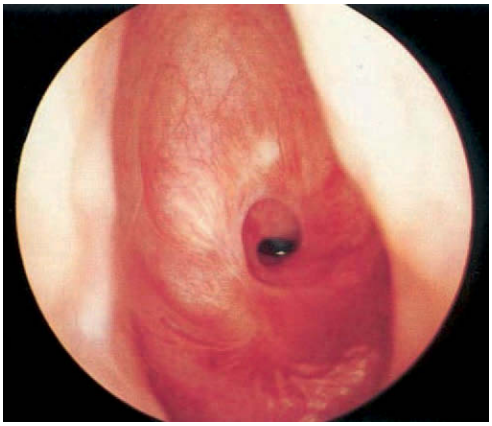

Figure 71-2. Endoscopic view of subglottic stenosis for preoperative staging and evaluation.

Timing of Repair

A chronic laryngotracheal stenosis repair is generally elective, once the appropriate workup is completed. The onset of symptoms may be insidious, depending on the extent of scar formation and contracture, and in intubated patients, several attempts at extubation usually fail, requiring tracheotomy.[13] Such patients subsequently cannot be decannulated or, after a brief decannulation, experience gradually progressive upper airway symptoms. Irreversible stenosis is usually diagnosed at this time, and repair can be performed electively after thorough evaluation. A key consideration is that patients with inflammatory or autoimmune diseases require stabilization of their underlying disease processes before surgical management of the stenosis.

Endoscopic versus Open Repair

Beginning in the 1940s, the literature describes the use of endoscopic division of webs and subsequent keel placement. These early endoscopic techniques included scar removal via instruments or lasers followed by application of mitomycin-C. The evolution of powered instrumentation such as better microlaryngeal instrumentation and refinements in laryngoscopes have both enhanced visualization and maneuvering and have led to an increase in the numbers of laryngeal lesions removed via endoscopic techniques that previously required open approaches. Duration of inpatient hospital stay and morbidity of procedures have both declined with endoscopic techniques; however, the skill and comfort level of the surgeon with these newer tools cannot be overemphasized.

The last few decades have seen the growing popularity of the carbon dioxide (CO_2) laser, which offers the advantages of delayed formation and maturation of collagen in wounds, thus allowing reepithelialization before scar formation as well as minimal deep tissue injury. The laser has enabled precise control of the areas removed and hemostasis with the aim of preserving existing mucosa that may be utilized for the repair. Limitations of the CO_2 laser include the risk of an airway fire, and the danger of the laser plume for the surgeon and hospital staff if they are working with infectious lesions.[10] In addition, it is often difficult to control thermal injury, which may result in perioperative edema and postoperative scarring of the vocal folds.[11] "Due to these risks," some authors advocate initial endoscopic management of chronic laryngotracheal stenosis, reserving open repair for patients whose stenosis does not resolve with endoscopic management.[12] The advantage of this approach is that an open surgical repair may be avoided in some instances; however, several endoscopic procedures may be required for long-term success. Current recommendations include treatment of mild stenosis (Cotton-Myer grades I and II) with endoscopic techniques. Failure of initial endoscopic technique is associated with previous surgery, circumferential scarring, loss of cartilaginous support, exposure of cartilage leading to chondritis, posterior inlet scarring with subsequent arytenoid fixation, postoperative bacterial infection, and initial poor choice of candidates, such as patients with combined laryngeal and tracheal stenosis or vertical scar length greater than 1 to 1.5 cm. With prudent choice of candidates and careful postoperative care and monitoring, success of decannulation at 1 year after endoscopic surgery for stenosis has risen from 60% to 65% to 80% to 85%.

Postoperative management should include antibiotics for 1 to 3 weeks, antireflux management, and subsequent wound reassessment in 6 weeks via endoscopy. Patients with more severe stenosis may be better served with an initial open technique, although this does not guarantee higher success rates in such difficult cases.

Box 71-2

Indications for and Contraindications to Usage of a Laryngeal Microdebrider

Indications

Internal laryngoceles
Tumor debulking
Supraglottic, glottic, subglottic, and tracheal lesions
Removal of polytetrafluoroethylene (Teflon) granulomas
Subglottic and tracheal stenotic lesions
Excision of tracheostomal granulation tissue
Respiratory papillomatosis
Laryngeal cysts
Anterior commissure lesions (only in conjunction with CO_2 laser or monopolar suction cautery for hemostasis)

Relative Contraindication

Vascular lesions

Microsurgical Débridement

Much like the impact of advanced instrumentation for endoscopic techniques in laryngeal surgery, the success of powered instrumentation in many arthroscopic procedures has led to the popularity of microsurgical debriders in airway surgery. This technique combines the use of flexible forceps and a microsurgical debrider with videoendoscopic control.[14] The debrider has a powered rotating blade and suction so that soft tissue lesions are aspirated into the tip of the blade and cleanly cut. Use of this instrumentation in endoscopic sinus surgery provided for more efficient and precise tissue removal and reduced injury to normal mucosa. Development of a laryngeal microsurgical shaver in the 1990s allowed for removal of bulky, exophytic laryngeal papilloma in patients with recurrent respiratory papillomatosis, obstructing carcinoma, and Reinke's edema.[15-17] In comparison with the carbon dioxide laser, the laryngeal microsurgical debrider eliminates the risk of airway fire because there is no laser plume and therefore a lower infectious risk for the operating room staff. Anecdotal data show that use of this instrument in patients with recurrent respiratory papillomatosis, which was previously treated with the laser, have less postoperative pain and a quicker return to a usable speaking voice. A decrease in operative time has also been observed, thus reducing both the patient's exposure to a general anesthetic and overall operating room costs.[18]

We use the microdebrider for many laryngeal lesions (Box 71-2) by maneuvering the rigid telescope with the laryngeal shaver, thus promoting camera steadiness and good visualization of the blade tip relative to the lesion as it is removed. Subglottic and tracheal stenotic lesions are typically removed with a surgical microdebrider (4-mm) subglottic blade to excise the fibrous scar. Softer, bulky lesions, such as laryngeal and tracheal papilloma, are rapidly removed with the 4.0-mm round window (skimmer) blade. Papillomas and other lesions involving the true vocal folds are removed with the 3.5-mm round window (skimmer) laryngeal blade (Figs. 71-3 and 71-4).

Local Application of Mitomycin C

Topical mitomycin C may be useful for the treatment and prevention of subsequent re-stenosis and scar formation in the larynx and trachea. Mitomycin C is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting DNA and protein synthesis. It can inhibit cell division, protein synthesis, and fibroblast proliferation.[19]

The use of topical mitomycin C remains controversial, with one study demonstrating that after 15 months of mitomycin application, all patients had clinical improvement of symptoms without evidence of recurrence.[19] Another study performed on the pediatric airway found no statistical difference between a single topical dose of mitomycin and isotonic sodium chloride after laryngotracheal reconstruction.[20] Animal studies have shown a statistically significant reduction in the rate of restenosis after surgical lysis with the use of mitomycin C.[21]

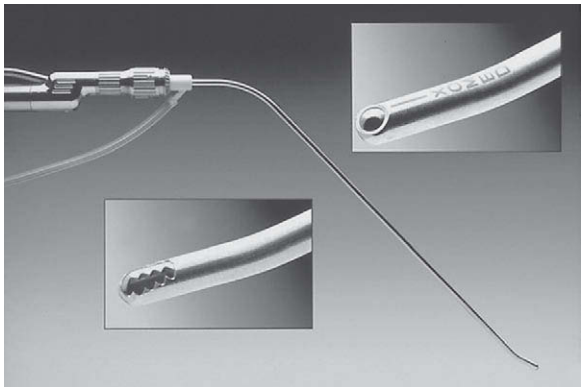

Figure 71-3. Powered instrumentation. Microdebrider blade (*upper inset*), for use in larynx, subglottis, and trachea, and skimmer blade (*lower inset*), for removal of mucosal lesions.

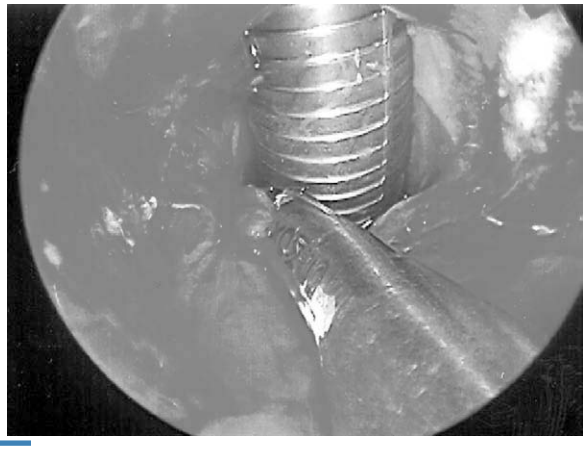

Figure 71-4. Endoscopic view of endolaryngeal lesion removal using the round blade of a microdebrider.

Surgical Planning for Repair

The first consideration for successful repair of acute or chronic laryngotracheal stenosis is the establishment of an intact, reasonably shaped skeletal framework to provide a scaffold for the airway. Acute, blunt injuries to the larynx, in which cartilage is fractured and displaced, are generally best managed with open reduction and stabilization of the fragments. In contrast, chronic injuries often are devoid of cartilage as a result of resorption of devitalized segments or of chondritis and subsequent chondromalacia or necrosis. The cartilage has often been replaced by scar tissue, so cartilage or bone grafts are necessary to reestablish structural support and to provide luminal augmentation. There is no consensus as to the ideal graft materials, and the grafts described in the literature use rib, iliac crest, hyoid bone, epiglottis, thyroid cartilage, composite auricular cartilage, and nasal septal cartilage.

Each of these graft materials may be limited by size, lack of pliability, and variable resorption due to lack of blood supply. The rib or costal cartilage graft is most commonly used because of its size, strength, and relative ease of harvesting. Vascularized hyoid and thyroid cartilage grafts have shown considerable success[22,23] but are limited by the amount of cartilage available. Composite auricular and nasal septal cartilage has the advantage of providing simultaneous epithelial repair, but it generally lacks adequate size and rigidity for cases in which large grafts are required. Vascularized perichondrial grafts and periosteal grafts have been evaluated for their chondrogenic or osteogenic capabilities and show potential for providing a pliable, vascularized graft that generates viable rigid bone or cartilage. In a rabbit model, vascularized perichondrium was shown to form significantly more cartilage when placed in a subglottic defect, and it tolerated a 2-hour ischemia time[24]; it has also been successfully maneuvered into tube form for

reconstruction of a segmental tracheal defect.[25] The sternocleidomastoid myoperiosteal flap has been successfully used for subglottic and tracheal reconstruction, with a low incidence of bony overgrowth on long-term follow-up.[26]

Use of Skin and Mucosal Grafts

The second consideration of the successful repair of acute and chronic laryngotracheal stenosis is the establishment of a completely epithelialized lumen of reasonably normal size and shape. In acute injuries, the ideal method is primary closure of mucosal lacerations after minimal débridement of nonviable tissue. In chronic stenosis, scar tissue should be excised, with preservation of as much overlying mucosa as possible. Small mucosal defects can be left to remucosalize, resulting in minimal detrimental effects.[27] The controversy arises in the use of epithelial grafts to resurface large defects in acute and chronic stenosis. Wounds that heal by secondary intention form granulation tissue and deposit collagen, which may contract until later covered by epithelium.[27] When the denuded area is secondarily infected—particularly after tracheotomy—epithelialization can be prolonged, leading to excessive granulation tissue and scar formation.[28]

Epidermal grafts have been advocated to interrupt this process and to result in healing similar to that of primary intention with minimal collagen deposition. When a stable cartilaginous framework is present, the tendency for the epidermal graft to contract is less, because the laryngeal skeleton acts as an external splint.[29] The techniques of skin grafting as an important adjunct in laryngotracheal reconstruction have been well described.[30]

However, the disadvantage of epidermal grafts in laryngotracheal reconstruction is that the larynx is not an ideal site to accept free epidermal grafts. The larynx is in constant motion with swallowing and neck movements, and the bed is potentially contaminated when a tracheotomy is present. A nonvascularized epidermal graft in the airway can become infected, thereby exacerbating the process of healing by secondary intention. The benefit of an epidermal graft must be weighed against the possibility of infection, especially in the context of an underlying skeletal reconstruction.

Stent Placement

Internal laryngeal and subglottic stenting is widely used with acceptable results; however, questions about the indications for stenting, the optimal type of stent, and the duration of stenting are largely unanswered. Internal stenting with soft or firm materials increases the risk of local infection, mucosal ulceration, and granulation tissue, which is directly related to the duration of stenting. Capillary blood flow ceases with a pressure of 20 to 40 mm Hg in mucosa closely adherent to cartilage, possibly initiating ischemic mucosal injury.[31] Therefore, several writers advocate avoiding internal stenting (unless absolutely necessary) and minimizing the duration of stenting. However, internal stenting is commonly used for the following specific indications: (1) to provide support for cartilage and bone grafts or to splint displaced cartilage fragments in the desired position, (2) to allow approximation and immobilization of epidermal grafts to a recipient site, (3) to separate opposing raw surfaces during healing, and (4) to maintain lumen in a reconstructed area that lacks adequate cartilaginous support and requires scar formation.

The optimal stent has not been determined, and a variety of options exist. A tantalum[32] or umbrella silicone[33] keel is useful for anterior glottic webs, but for more severe laryngotracheal stenosis, various stents are commonly used, including the Montgomery laryngeal stent (Fig. 71-5), the Aboulker stent, the "Swiss roll" siliconized rubber stent, and the finger cot stent; each has proponents who describe good results.[34,35] In general, a soft stent should be used to minimize pressure on mucosal surfaces when cartilaginous support is satisfactory and when the indication for stenting is to splint an epidermal graft or to separate opposing raw mucosal surfaces. A finger cot with a povidone-iodine–soaked sponge is an excellent soft stent; an alternative is a Montgomery laryngeal stent, which is firm but conforms to endolaryngeal contours. A firm stent is needed when the cartilaginous framework or graft requires splinting or when inadequate cartilage is present, thereby requiring that luminal support be achieved through collagen deposition and scar contraction. A solid stent is preferable to a hollow stent to minimize aspiration. However, a soft, hollow stent such as the Montgomery T-tube allows phonation. The T-tube is commonly used for subglottic and upper tracheal stenosis; appropriate patient selection and education are essential, because this is a single-lumen tube with a greater risk of airway obstruction.[36] An Aboulker stent can be used for subglottic or combined subglottic and laryngeal stenosis. The advantage of this stent is that it is used with a double-cannula metal tracheostomy tube, and is secured to the tube, thus preventing removal. Modifications of this technique that allow tracheotomy changes have been described.[37]

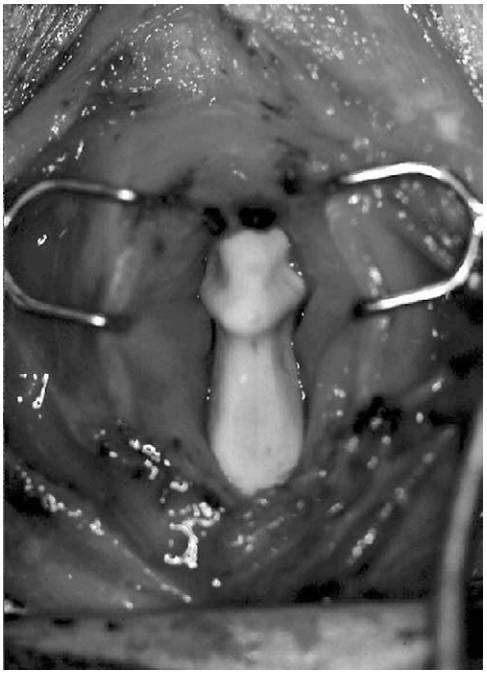

Figure 71-5. Thyrotomy with Montgomery stent in place.

There is no uniformly accepted optimal duration of stent placement. Most authorities recommend 6 to 8 weeks, but the duration varies from 2 weeks to several months.[38] Usually 1 to 3 weeks is sufficient if only mucosal healing or epidermal graft take is required. If the laryngeal skeleton is adequate but requires splinting to maintain the appropriate position, 6 to 8 weeks is the generally accepted time frame.

However, if the cartilaginous framework is deficient and mature scar is important for structural strength, prolonged stenting is indicated to allow scar contraction around an inert, firm object. Successful prolonged stenting has been reported for intervals of up to 14 months. In this situation, the problem arises in premature stent removal, usually before sufficient scar contraction has occurred.[38] The presence of a paratubal air envelope, which manifests as linear air densities between the outside wall of the stent and the inside wall of the larynx and trachea, is reported to be a reliable indicator of laryngotracheal structural integrity and functional stability and is a useful measure to determine optimal timing for stent removal.[39]

Surgical Management of Chronic Stenosis

Supraglottic Stenosis

Chronic hypopharyngeal stenosis usually results from unrecognized acute blunt injury to the hyoid and thyrohyoid membrane. The direction of force is posterior to superior and results in the following discrete injuries: (1) the epiglottis can be adherent to the posterior or lateral hypopharyngeal walls, (2) the hyoid bone can be fractured and displaced posteriorly with the epiglottis, thereby producing laryngeal inlet stenosis, (3) a horizontal web of the posterior hypopharyngeal wall may form at the level of the superior aspect of the epiglottis, or (4) postcricoid stenosis may result in stenosis of the esophageal introitus.[40]

The surgical approach is through a transhyoid pharyngotomy. Tracheotomy is essential if it has not been previously performed. A horizontal skin incision is made over the hyoid bone, which is then identified. If the hyoid is fractured, attempts are made to reduce and wire it into its normal anatomic position; otherwise, the body of the hyoid can be excised. The vallecula is entered, and the mucosal incision can be extended to a lateral pharyngotomy, if needed, with care taken to preserve the superior laryngeal neurovascular pedicles and hypoglossal nerve. After satisfactory exposure has been provided, attention is directed to repair of the stenosis.

Adhesions of the epiglottis to the hypopharyngeal walls may be managed by division of the adhesion along its long axis, submucosal excision of scar tissue, and primary mucosal closure. When a horizontal web or shelf is present, a vertical incision is made through the web, and scar tissue is excised. Mucosal flaps are undermined to allow closure of the incision in a horizontal line. If necessary, superiorly based mucosal advancement flaps can be used. If the hypopharyngeal stenosis is extensive, the division of bands and the excision of scar tissue may result in an extensive denuded area over the constrictor muscle, and skin grafting should be considered. Hollow silicone esophageal stents have also been used to assist in the healing of a skin graft.[40] If resection of scar tissue results in an extensive full-thickness pharyngeal defect, a radial forearm revascularized flap may be used to provide thin, pliable, soft tissue, which may, however, result in an adynamic hypopharyngeal segment.

Laryngeal inlet stenosis results from posterior displacement of the hyoid and epiglottic cartilage and can be accompanied by a fracture through the thyroid notch. This injury is approached through a laryngofissure approach with division of the thyrohyoid membrane and elevation of the mucoperichondrium on the laryngeal surface to allow for excision of this inverted wedge of the base of the epiglottic cartilage, perichondrium, fascia, and scar. With suturing of the resultant flaps to the free edge of the anterior epiglottic perichondrium, the thyrotomy is closed, and stenting is not required.[40]

Glottic Stenosis

Anterior Glottic Stenosis

Anterior glottic stenosis may be caused by external trauma resulting in a thyroid cartilage fracture and mucosal disruption or from circumferential scarring after denuding of mucosa by an endotracheal tube. A thin web that extends more than 3 to 4 mm posteriorly along the vocal fold can produce hoarseness, whereas a thicker web or a web that extends farther posteriorly can cause significant airway obstruction.[41] Hoarseness or airway compromise is an indication for surgical intervention. Excision of the anterior glottic scar recreates the conditions that caused the original stenosis. Successful surgical repair requires physical separation of the opposing edges until remucosalization is complete; this may be done endoscopically when the web does not extend below the inferior edge of the true vocal fold and the posterior commissure is normal.[42] Microlaryngeal instruments allow for better development and preservation of mucosal flaps than are possible with the laser. Excess scar tissue is removed, and a keel is placed and secured externally with wires or with a heavy suture placed through the thyrohyoid membrane. Alternatively, a mini-cricothyrotomy may be performed to place the keel with endoscopic visualization. Differing keel designs and compositions have been described. In principle, the keel should be composed of an inert material of sufficient length to extend from the cricothyroid membrane to at least 2 to 3 mm above the anterior commissure; if the keel extends superiorly over the petiole of the epiglottis, the anterior edge of the keel should make a 120-degree angle (i.e., the angle of the epiglottis and the anterior tracheal wall) to minimize granulation tissue formation at the petiole of the epiglottis. Of note, the posterior wing of the keel should lie at the vocal processes and should not touch the posterior commissure.[41,42] The keel is usually removed after 2 to 4 weeks with any granulation tissue adherent to it.

If the anterior subglottic stenosis extends more than 5 mm subglottically, an external laryngofissure approach should be utilized. Resection of scar tissue should not be overzealous, and mucosa should be preserved whenever possible. When mucosa is deficient, Isshiki and others[52] have described obtaining superior voice results by resurfacing the vocal fold with labial mucosa instead of split-thickness skin grafts and short-term stenting. Successful results have been achieved with the Montgomery umbrella silicone keel used for 2 to 3 weeks or with the McNaught tantalum keel.[41]

Posterior Glottic Stenosis

Posterior glottic stenosis is most commonly caused by endotracheal intubation, although mechanical fixation may also occur from cricoarytenoid joint arthritis. Posterior glottic stenosis may be confused clinically with bilateral vocal fold paralysis before direct laryngoscopy. It should be considered when the history is appropriate and when there are indirect laryngoscopy findings of anteromedial displacement of the arytenoid cartilages, which thus obscure the posterior commissure scar, with a pseudo-foreshortening of the anteroposterior length of the membranous folds or glottic aperture.

Mechanical fixation and neurogenic paralysis are differentiated by direct laryngoscopy, and palpation of the arytenoid to assess mobility is essential. Joint excursion should be uninhibited. Passive medial movement of the contralateral arytenoid when the ipsilateral arytenoid is displaced laterally suggests interarytenoid scar. Electromyography findings of denervation or action potentials of the vocalis muscle are very useful to document neurologic integrity, particularly when results of direct observation of the vocal fold movement are equivocal. Patients with such findings may have a preexisting tracheotomy, which decreases posterior cricoarytenoid muscle activity, thereby making active lateral vocal fold excursion difficult to visualize unless the tracheotomy is plugged temporarily.

The extent of injury is variable. Type III and type IV posterior glottic stenoses are difficult to manage successfully, particularly when they are associated with subglottic stenosis.[3,43] The major therapeutic challenges are to reestablish a satisfactory airway and to preserve the voice, which is often normal.

Endoscopic repair of posterior glottic stenosis is successful in carefully selected cases. Patients with an interarytenoid web and posterior sinus tract have been managed with a simple division of the web. Many patients experience restenosis, particularly those who have had a tracheotomy.[44] A soft, sponge-filled finger cot stent has been advocated in this situation to separate the raw opposing surfaces; it can be placed endoscopically and remain for 2 weeks.[45]

Posterior commissure stenosis can be managed endoscopically with a CO_2 laser or a laryngofissure approach. Creation of a posterior micro-trapdoor flap is successful when a posterior sinus or a 3- to 4-mm posterior interarytenoid scar is present.[44] This technique fails when there is arytenoid fixation or a scar that is more than 1 cm in height. When posterior interarytenoid mucosa is insufficient to create a trapdoor flap (>3-4 mm), interarytenoid scar tissue is resected, with the mucosa preserved through a hockey-stick incision.

A synthetic implantation fabric keel may be placed endoscopically and left in place for 4 to 6 weeks to cause sufficient widening of the interarytenoid mucosa to allow for a micro-trapdoor flap. However, Dedo and Sooy,[44] who first described this procedure, reported that failures occurred in all of their patients who had arytenoid fixation. Several other writers recommend open repair through a laryngofissure approach.[45,46] The surgeon effects such a repair by developing a superiorly based mucosal flap, excising scar tissue and fibrosed interarytenoid muscle, and repositioning the mucosal flap to provide immediate epithelial coverage. Internal stenting is not required when both arytenoids are mobile. Care is taken to not enter the cricoarytenoid joints if both arytenoids are mobile. Successful surgical repair is an elusive goal.

Posterior glottic stenosis with arytenoid fixation has been traditionally managed through an external approach. If, after development of a mucosal flap and resection of scar, one arytenoid is freely mobile, resection of the fixed arytenoid is unnecessary. When bilateral arytenoid fixation exists, removal of the less mobile arytenoid is necessary to achieve a satisfactory airway. Denuded mucosal surfaces are covered with mucosal flaps, skin, or mucosal grafts. Stenting for 2 to 3 weeks with a conforming silicone laryngeal stent or with a soft finger cot stent is required. A posterior cricoid split with rib graft may also be considered (Fig. 71-6).

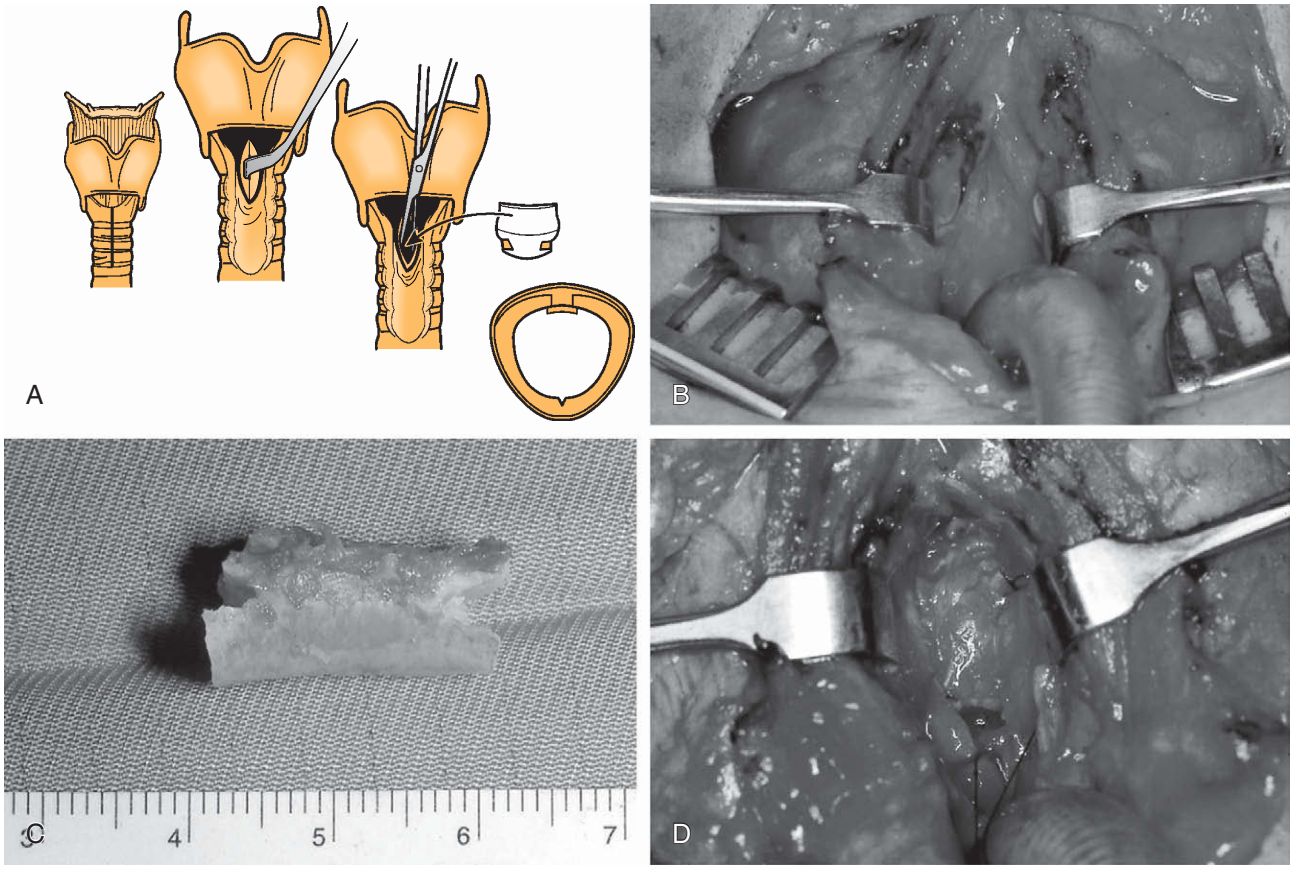

Figure 71-6. Rib graft for posterior subglottic stenosis. **A,** Schematic of anterior wall defect and graft placement. **B,** Anterior wall defect (intraoperative photo). **C,** Rib graft. **D,** Rib graft in place.

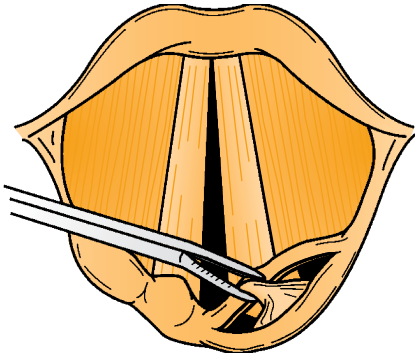

Figure 71-7. Endoscopic view of an arytenoidectomy.

In 1983, Ossoff and associates[47] first described complete arytenoidectomy via an endoscopic approach. Endoscopic laser arytenoidectomy is also useful for managing type IV posterior commissure stenosis when subglottic involvement is limited, because this procedure avoids the complications of an external approach and allows for the immediate assessment of airway size (Fig. 71-7). Endoscopic laser arytenoidectomy requires the removal of the entire arytenoid except for the muscular process. Arytenoid perichondritis is a potential complication, and the administration of perioperative antibiotics and antireflux measures, as always, are recommended. The degree of vocal fold lateralization obtained is variable, and the use of a lateralization suture or a finger cot stent may improve the final result by controlling the extent of lateralization.

The external approaches for an arytenoidectomy are through a laryngofissure or a Woodman arytenoidectomy. The latter approach exposes the arytenoid cartilage through a posterolateral extralaryngeal approach and the entire arytenoid cartilage is resected, except for the vocal process. A submucosal suture is placed through the vocal process and anchored around the inferior thyroid cornu to lateralize the vocal fold (6 mm in men, 5 mm in women).[48] Other writers believe that tethering the vocal process around the inferior thyroid cornu may reposition the vocal fold inferior to the opposite fold; they recommend suturing to the thyroid lamina at the vocal fold level[5] or around the superior cornu (success rate, 60%-80%).[43] If the procedure is unsuccessful, completion arytenoidectomy through a laryngofissure approach with suture lateralization of the vocal fold can be performed.[49]

Exploration of the fixed cricoarytenoid joints with lysis of adhesions without arytenoidectomy has also been advocated. Fibrous bands on the medial aspect of the cricoarytenoid joints are divided, and the arytenoids are stented in full abduction for 2 to 3 weeks; stent removal and aggressive speech therapy follow. Return of vocal cord mobility has been described in 90% of patients managed in this way.[50]

Complete Glottic Stenosis

Complete glottic stenosis usually results from unrecognized severe extralaryngeal trauma, in which injury is rarely isolated to the glottis and associated subglottic injury is common. Endoscopic management is rarely indicated because of the severity and nature of the injury, and only a few instances have been reported in the literature. The mainstay of management involves an open laryngofissure approach. The stenosis should be divided at the midline and excessive scar tissue resected; the mucosa is preserved and mucosal flaps are developed from the aryepiglottic folds for coverage. If extensive areas are devoid of mucosa, epithelial grafts of buccal mucosa, grafts of nasal septal mucosa, or split-thickness skin grafts may be used. Large split-thickness skin grafts may cause excessive crusting. The grafts are sutured in place and stented with a form-fitting laryngeal stent for 4 to 8 weeks.[51] When the stent is removed, an umbrella keel is placed into the anterior commissure for 2 weeks.

An alternative approach is reconstruction with an epiglottic flap. This approach is indicated in the following situations: severe glottic stenosis, a more than 50% reduction in the anteroposterior dimension of the glottis, glottic-subglottic stenosis, and glottic-supraglottic stenosis with an intact epiglottis.[52,53] The repair is approached through a midline thyrotomy, and the thick scar is transected in the midline. Submucosal excision of scar tissue can be attempted, and the mucosa can be repositioned and secured with chromic suture. The base of the epiglottis is identified, and the median thyroepiglottic ligament is transected. The epiglottis is pulled inferiorly to reach the anterior cricoid arch, and the epiglottic flap is sutured to the outer anterior edges of the thyroid cartilage laterally and to the cricoid cartilage inferiorly. This procedure results in an epithelialized, widened anterior commissure. Several cartilage-splitting incisions may be used to allow the petiole to be folded onto itself to make a sharper anterior commissure.[36]

Subglottic Stenosis

Endoscopic management of subglottic stenosis requires careful patient selection. The predictive factors for failure were described earlier.[43,54,55] CO_2 laser excision followed by repair with a micro-trapdoor flap is moderately reliable for managing circumferential subglottic stenosis; it requires laser incision of the superior surface of the scar and the submucosal excision of scar tissue. An inferiorly based rectangular mucosal flap is created by two lateral knife incisions. The preserved flap does not completely cover the lasered area, but it does divide the raw concave area into two flat lateral raw areas, which heal rapidly. One study reported a 90% success rate in all patients undergoing the procedure, in whom scars that were less than 10 mm in height.[43] A large flap that can potentially obstruct the airway through a ball-valve effect should not be created. Other writers[44] have confirmed the efficacy of this procedure in adults and emphasize that it is useful when the stenosis is less than 10 mm in height, but a tracheotomy should be performed if the flap is longer than 4 mm. The procedure is uniformly unsuccessful in children, however.[55] Failure also occurs if associated posterior glottic stenosis or arytenoid fixation is present. Shapshay and coworkers proposed an alternative method, consisting of radial incisions followed by bronchoscopic dilation.[56] Their series of patients was small, however, and follow-up observation was only 1 year; thus, success was not assumed.

Subglottic and tracheal stenotic lesions may be microsurgially debrided with use of a microdebrider (4-mm) subglottic blade. External repair is indicated when endoscopic techniques fail or when the extent of the stenosis is severe and factors are unfavorable for an endoscopic approach. Various techniques are available, and the selection of the appropriate repair technique should anticipate the amount of rigid support required for luminal augmentation and the possibility that scar resection requires epithelial grafting. Subglottic stenosis due to extensive mature scar with adequate cartilaginous support can be repaired via a laryngofissure approach.

Subglottic scar is resected to cricoid perichondrium and is relined with the buccal mucosa or a split-thickness skin graft. The graft is preferably sewn around a stent that is fixed in place. When cartilaginous support or luminal augmentation is also required, various autogenous cartilage grafts are available. The hyoid-sternohyoid muscle interposition graft has been extensively used, with a success rate of approximately 70% in adults.[57] This technique can be applied to isolated subglottic stenosis or subglottic stenosis in combination with anterior glottic or tracheal stenosis.

The procedure uses a vascularized segment of the body of the hyoid pedicle on the sternohyoid muscle and its adjacent periosteum. The length of bone can be tailored to the length of the stenosis; it is interposed vertically into the stenosis and secured with four-point fixation. A stent is not used unless an epidermal graft is required after scar excision to minimize possible graft resorption by pressure necrosis.

The advantages of this technique include immediate reconstruction with a single operative field, theoretically better tissue survival with minimal graft remodeling, and versatility in augmenting glottic, subglottic, and upper tracheal stenosis. The long-term survival of the bone graft has not been conclusively shown; the graft is limited in the amount of augmentation it provides because of its narrow width and concave shape. Additional procedures are often required to remove granulation tissue. The thyroid-cartilage-sternothyroid pedicle composite graft was developed to overcome the limitation of the hyoid-sternohyoid graft. A large central piece of thyroid ala attached to the sternothyroid muscle through its perichondrium is harvested. A flap of contralateral thyroid alar perichondrium is harvested in continuity with the ipsilateral perichondrium and serves as internal lining when the composite graft is transposed. Stenting for 1 to 6 weeks is required. This technique also offers the advantages of the hyoid-sternohyoid graft, except that it cannot be used for glottic stenosis. A larger piece of cartilage, however, is available to reconstruct more extensive defects. The internal perichondrial transposition allows for remucosalization with minimal granulation tissue formation.

Various free autogenous cartilage grafts have been used for luminal augmentation. These grafts have variable amounts of resorption and require prolonged stenting to allow resorbed graft to be replaced by firm, mature scar tissue. Costal cartilage grafts have the advantage of providing large grafts that are easily sculpted. Specific details of graft tailoring have been well described.[55] Composite nasal septal cartilage grafts have been used successfully in patients with stenosis of the larynx and upper trachea.[15] Stenosis of up to 3 cm in height can be repaired, and the respiratory epithelium is a theoretic advantage, because it provides immediate resurfacing with a match of epithelium from the stenotic area. In children, a stent is not used, and the graft is not used so as to prevent injury to nasal growth centers. Various other autogenous grafts, including auricular cartilage, clavicular bone, and free hyoid bone, have been used but they have not received uniform acceptance.

Division of the posterior cricoid lamina should be considered when severe subglottic stenosis is present with posterior glottic stenosis or for complete glottic and subglottic stenosis. It is approached through an anterior cricotracheal fissure, avoiding disruption of the anterior commissure. The entire posterior cricoid lamina is divided vertically in the midline to the level of the postcricoid submucosa. Scar tissue excision is not necessary, and the interarytenoid muscle is divided if it is fibrosed. Prolonged rigid internal stenting is required for at least 3 months. Interposition cartilage grafts with perichondrium can be harvested from the thyroid lamina for posterior support, and anterior luminal augmentation can be performed.

Partial cricoid resection with thyrotracheal anastomosis is considered when other methods have failed. Several investigators reported good results and specific technical details. This procedure should be performed only in adults and is limited to stenosis involving the cricoid and upper trachea. There should be approximately 1 cm of normal lumen below the glottis. The main risks of this procedure are injury to the recurrent laryngeal nerves and anastomotic dehiscence with restenosis.

The procedure involves exposure of the involved laryngotracheal section with preservation of the recurrent laryngeal nerves. Identification of the nerves is often risky because of extensive scarring; therefore, dissection of the trachea is performed in the subperichondrial plane. The inferior resection line is immediately below the stenosis, beveling the anterior tracheal wall. The superior limit can include the cricoid up to the posterior lamina just below the cricothyroid joint. Care is taken to not injure the recurrent laryngeal nerves, which pass immediately posterior to the cricothyroid joints. The tracheotomy can be lowered if three of four tracheal rings can be interposed between the anastomosis and the tracheotomy; otherwise, the patient should be intubated and the anastomosis accomplished with 3-0 interrupted sutures placed submucosally and tied extraluminally. Laryngeal release procedures are usually necessary, and the neck is kept in flexion for 7 to 10 days postoperatively to minimize tension on the anastomosis. If a tracheotomy is not used, the patient is extubated in the operating room in 3 to 4 days.

Grillo and others[58,59] refined this procedure to incorporate a posterior membranous tracheal wall flap to resurface the bared cricoid cartilage. In a series of 80 patients with subglottic and upper tracheal stenosis, these researchers reported failure in only 2 out of 77 patients with at least 6 months follow-up; one perioperative death occurred. Of 77 patients, 66 had no restriction of daily activities due to dyspnea, and tracheotomy was rarely required.

Box 71-3

Surgical Management of Tracheal Stenosis

Open resection and repair
Endoscopic dilatation/laser excision
Stent placement:
- Silicone stent (e.g., Dumon, Rusch Y)
- Expandable stent (e.g., Gianturco Z, Wallstent, Nitinol)
- Flexible silicone stent (e.g., PolyFlex)

A sliding flap tracheoplasty has been described, which is a variation of the cricoid resection and thyrotracheal anastomosis. The procedure involves resection of the anterior cricoid arch and the first two tracheal rings, with development of an inferiorly based anterior tracheal wall flap from the third through sixth rings; this is advanced and anastomosed to the thyroid cartilage superiorly. Patients for whom this procedure is selected should have a subglottic stenosis involving only the anterior cricoid arch and the first ring, an intact posterior wall, mobile vocal folds, and an uninvolved segment of mucosa below the glottis.

Cervical Tracheal Stenosis

Cervical tracheal stenosis in adults most commonly results from trauma produced by either intubation or tracheotomy, or blunt external trauma to the neck. Other causes are benign and malignant neoplasms, inflammatory diseases, and systemic autoimmune disease.

When surgical repair of tracheal stenosis is considered (Box 71-3), regardless of the cause, it is essential to determine the location, length, composition, extent of airway stenosis, and neurologic integrity of the larynx through indirect laryngeal examination, bronchoscopy, and radiography. In most instances, cervical tracheal stenosis can be categorized as cicatricial membranous stenosis, anterior wall collapse, or complete stenosis. Airway management should be considered preoperatively and discussed with the anesthesiologist, as for all of these procedures. If a tracheotomy is not present or is not planned, it is safest to have the patient breathe spontaneously until the airway is secured. If a Montgomery T-tube is used as part of the reconstruction, the patient should breathe spontaneously after the T-tube is inserted (Fig. 71-8). If the airway is 5 mm or smaller at the time of reconstruction, dilation is performed initially with use of general anesthesia; microsurgical debridement resection may also be performed. If the lumen is larger than 6 mm in diameter, intubation is carried out above the lesion, and dissection is performed carefully to prevent airway obstruction. If a postoperative tracheotomy is planned, it should be performed with use of local anesthesia at the outset of the reconstruction procedure.

Cicatricial Membranous Stenosis

Granular or fibrous stenosis of the cervical trachea with intact cartilage can initially be managed endoscopically. CO_2 laser excision of granular stenosis is useful because tracheotomy can be avoided, and the granular stenosis can be resected accurately with minimal bleeding. If the stenosis is circumferential, partial resections should be staged 2 to 4 weeks apart to prevent the formation of a circumferential denuded area of trachea in which restenosis can occur. Fibrous stenosis can be excised with a micro-trapdoor technique.[44]

Open repair of a cicatricial membranous stenosis requires approaching the stenosis via a vertical midline incision through the anterior tracheal wall to expose the entire length of the stenosis. Care is taken to prevent lateral dissection, because the vascular supply to the cervical trachea from the inferior thyroid artery enters laterally. Submucosal excision of scar tissue is accomplished under direct visualization, and the tracheotomy may be moved to below the stenosis. An epidermal graft is useful to cover the denuded area, and it is usually fixed over a stent. Luminal augmentation is often required, and the type of graft used depends on the size of the graft needed and the surgeon's experience and preference. The pedicled thyroid-cartilage-sternothyroid graft or a composite septal cartilage–mucoperiosteal graft seems to be reasonably successful.

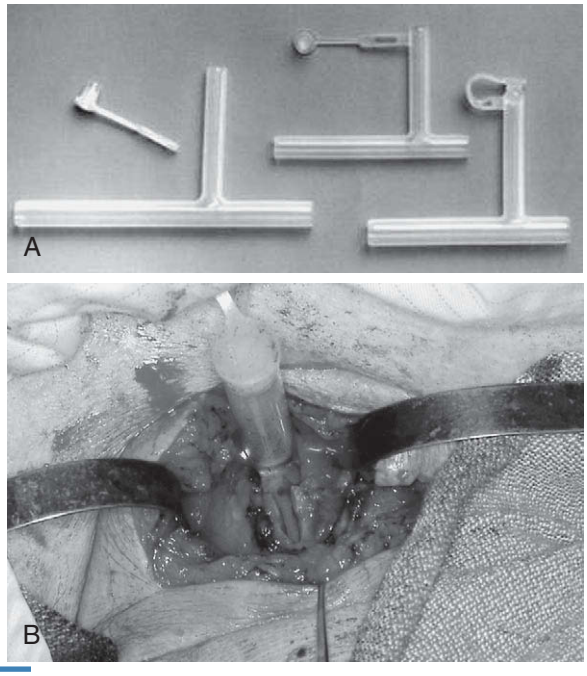

Figure 71-8. A, Silicone T-tube stents for tracheal stenosis. **B**, Open placement of a T-tube.

Anterior Wall Collapse

Collapse of the anterior laryngeal wall can result from anterior blunt neck trauma, but it more commonly results from tracheotomy. Montgomery categorizes these injuries as suprastomal, stomal, or infrastomal.[32] In this type of stenosis, a well-mucosalized posterolateral wall and residual cartilage in the area of the stenosis should be present.[36]

A suprastomal and stomal stenosis can be approached and managed as described for cicatricial membranous stenosis. However, restoration of the anterior wall is essential. The surgeon can accomplished this restoration by (1) stenting the lumen open with a T-tube or a firm stent of a tracheostomy tube, such as the Aboulker stent, and repairing the anterior wall with a cartilage graft or (2) mobilizing the sternohyoid muscles and securing them together over the defect. In both instances, prolonged stenting is required.[36]

Wedge resection of an anterior tracheal wall stenosis can be considered if (1) the stenosis is limited to two or three rings, with significant loss of cartilage that would preclude stenting, (2) the posterior wall mucosa is intact, or (3) the stenosis is stomal or suprastomal. The procedure involves adequate exposure of the involved trachea, including at least one ring above and one ring below the stenosis. Subperichondrial dissection is carried out carefully around the involved trachea to prevent injury to the recurrent laryngeal nerves. The stenosis is resected, with care taken to preserve posterior tracheal wall mucosa. An oroendotracheal tube is passed through the anastomosis, and the cartilaginous trachea is reanastomosed with submucosal sutures tied extraluminally. The patient is extubated when awake and alert, and granulation tissue is excised endoscopically as early as possible.[36]

Complete Tracheal Stenosis

Segmental resection and primary anastomosis provide optimal results for complete tracheal stenosis. The average length of the adult trachea is 11 cm (range, 10-13 cm), and there are 14 to 20 tracheal rings. With hyperextension of the neck, 50% of the trachea is cervical. Approximately 50% of the trachea (5-7 cm) can be safely resected and anastomosed primarily with appropriate mobilization techniques. Other factors also should be considered in the determination of how much

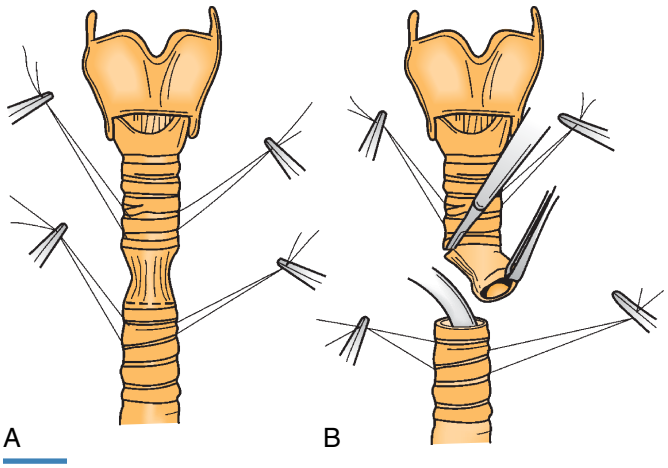

Figure 71-9. **A,** Near-complete tracheal stenosis. **B,** Segmental resection with primary anastomosis.

trachea can be resected. Older patients with calcification between tracheal rings may have less tracheal elasticity; a patient with a short, thick neck may have a deep trachea, with the cricoid at the level of the sternal notch. Tracheal mobilization is limited in a patient with decreased ability to extend the neck. The procedure is essentially the same as a wedge resection, except that dissection requires excision of the posterior membranous wall. The anterior cricoid arch and the posterior cricoid lamina are resected to just below the cricothyroid joints. An oroendotracheal tube is passed distal to the anastomotic site, and the anastomosis is performed with submucosal sutures placed around a trachea ring and tied extraluminally. Adequate mobilization of the larynx and trachea is required to relieve tension from the anastomosis. The neck is placed in extreme flexion, and a stay stitch is placed from chin to sternum.[36]

Segmental resection with primary anastomosis shows promise as the most efficacious procedure for managing near complete or complete tracheal stenosis (Fig. 71-9). In patients in whom stenosis is limited to the trachea and subglottis and the glottis is normal, success rates in several large series are 95% to 97%.[59] When the stenosis also involves the glottis, resection with end-to-end anastomosis has been performed simultaneously with laryngofissure and decannulation repair of the glottic stenosis, which is achieved in approximately 95% of patients. In these instances, a Montgomery T-tube and prolonged stenting were uniformly used.

Extensive cervical and laryngotracheal stenosis not amenable to segmental resection and anastomosis can be managed with a multistaged trough reconstruction technique. The essential steps require the creation of a large tracheostoma by sewing cervical neck skin to residual tracheal mucosa. The second stage requires the formation of a rigid anterior wall by the insertion of Marlex mesh under adjacent cervical skin. Finally, the closure is obtained by tubing skin and Marlex mesh anteriorly to close the stoma and then advancing cervical neck skin as a second layer.

Laryngeal Release Procedures

Tracheal mobilization and laryngeal release techniques are required when a gap greater than 3 cm in tracheal continuity occurs in young patients. Older patients lose elasticity of the annular ligaments of the trachea and therefore require release procedures when more than 1 to 2 cm is resected. Three techniques can gain extra length for end-to-end anastomosis. The first is incision of the annular ligaments, which can add up to 2.5 cm but is most useful in younger patients. Incisions should be placed on one side of the lateral trachea above the anastomosis and on the opposite side below the anastomosis to preserve the blood supply to both tracheal segments. The second technique is superior mobilization of the distal trachea from the thorax, which can result in the achievement of 6 cm of mobilization. This technique requires transection of the left mainstem bronchus and end-to-side anastomosis with the right mainstem bronchus, and it carries a risk of mediastinal dissection. The third technique involves laryngeal release procedures, which can gain 5 cm of tracheal mobilization. The infrahyoid release involves transecting the sternohyoid, omohyoid, and thyrohyoid muscles at the level of the superior border of the thyroid cartilage. The greater cornua of the thyroid cartilage are divided bilaterally, and the thyrohyoid membrane is sectioned. This procedure carries a risk of injury to the superior laryngeal nerve and is associated with prolonged dysphagia.

Suprahyoid laryngeal release is often preferred. This technique requires transection of the insertion of the mylohyoid, geniohyoid, and genioglossus muscles to expose the preepiglottic space. The stylohyoid insertions are transected, and the body of the hyoid is transected medial to the insertion of the digastric tendon. This procedure allows the body of the hyoid, the thyroid cartilage, the cricoid cartilage, and the proximal trachea to drop inferiorly. Flexion of the neck affords an additional 1 to 2 cm of length.

Conclusion

Management of the patient with airway stenosis requires a comprehensive operative and perioperative team and an adequate preoperative workup to determine the most appropriate procedure for each patient. Whether the procedure is performed endoscopically or via an open approach, the results of any of these operations may be very gratifying if the surgeon and patient have reasonable expectations and are prepared for possible complications.

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CHAPTER SEVENTY-TWO

The Esophagus: Anatomy, Physiology, and Diseases

Michael F. Vaezi

Key Points

- Primary symptoms of underlying esophageal disorders, most often due to mechanical or motility disturbance, include heartburn, dysphagia, odynophagia, and regurgitation.
- Indications for endoscopy are presence of weight loss, upper gastrointestinal bleeding, dysphagia, odynophagia, chest pain, poor response to therapy, and for evaluation for Barrett's esophagus.
- Esophageal manometry measures coordination of intraluminal pressure activities of the three functional regions of the esophagus: the lower esophageal sphincter, esophageal body, and upper esophageal sphincter; it is used in patients with dysphagia and noncardiac chest pain suggesting motility disorders.
- Indications for 24-hour pH monitoring are to document excessive acid reflux in patients with suspected gastroesophageal reflux disease without endoscopic findings and to assess the efficacy of medical or surgical therapy.
- Development of the wireless pH monitoring capsule has improved sensitivity for detecting reflux events through prolonged monitoring, improved patient compliance, reduced impairment of patients' daily activity, and decreased likelihood of catheter movement during the study.
- Multichannel intraluminal impedance probes measure both acidic and nonacidic reflux of liquid or gas by measuring the resistance to current flow between adjacent electrodes.
- Empiric therapy for classic gastroesophageal reflux disease is recommended. Additional studies are considered in patients with no response and in patients with dysphagia, odynophagia, weight loss, chest pain, or choking.
- Antireflux surgery is not advised in patients whose reflux disease is unresponsive to proton pump inhibitor therapy and who have no evidence of esophageal acid exposure or nonacid regurgitation.
- Patients with Barrett's esophagus require continued endoscopic surveillance to detect the development of dysplasia and adenocarcinoma.
- The cardinal symptom of infectious esophagitis, commonly found in immunosuppressed patients, is odynophagia.

Normal Esophageal Anatomy and Physiology

The *esophagus* is a muscular tube connecting the pharynx to the stomach that acts as a channel for the transport of food. However, its structure and function are much more complex. A thorough understanding of the anatomy and physiology is essential to understanding esophageal disease states.

The proximal margin of the tubular esophagus is the upper esophageal sphincter (UES), the functional unit correlating anatomically with the junction of the inferior pharyngeal constrictor and cricopharyngeus.[1] The esophagus extends distally 18 to 26 cm within the posterior mediastinum as a hollow muscular tube to the lower esophageal sphincter (LES) (Fig. 72-1). The LES is a 2- to 4-cm–long focus of tonically contracted thickened circular smooth muscle that lies within the diaphragmatic hiatus.[2]

The esophageal wall is composed of four layers: mucosa, submucosa, muscularis propria, and adventitia. The esophagus has no serosa, making it unique to the rest of the gastrointestinal tract. The mucosa is normally composed of stratified squamous epithelium, lamina propria, and the muscularis mucosa. Lymphatic drainage begins in the lamina propria. The muscularis propria consists of both skeletal muscle and smooth muscle. The proximal 5% to 33% is skeletal muscle, the middle 35% to 40% is mixed, and the distal 50% to 60% is smooth muscle.[3] The muscles are arranged into inner circular and outer longitudinal layers.

The smooth muscle portions of the esophageal body are innervated by the vagus nerve, which controls peristalsis under physiologic conditions. Neural innervation of the esophagus is from the myenteric or Auerbach's plexus, located between the two muscle layers, and Meissner's plexus, located in the submucosa.[4] The myenteric plexus is responsible for esophageal peristalsis, whereas Meissner's complex is the site of afferent sensory input (Fig. 72-2). Although the precise interaction between morphology and function of the nerve plexuses is not entirely clear, there are two main neurotransmitters within the myenteric plexus. Excitatory stimulation from acetylcholine mediates contraction of both the longitudinal and circular muscle layers. Inhibitory neurons predominantly affect the circular muscle layer via nitric oxide (NO). Excitatory stimulation from acetylcholine has its largest effect proximally, whereas the inhibitory effect of nitric oxide is seen distally.[5]

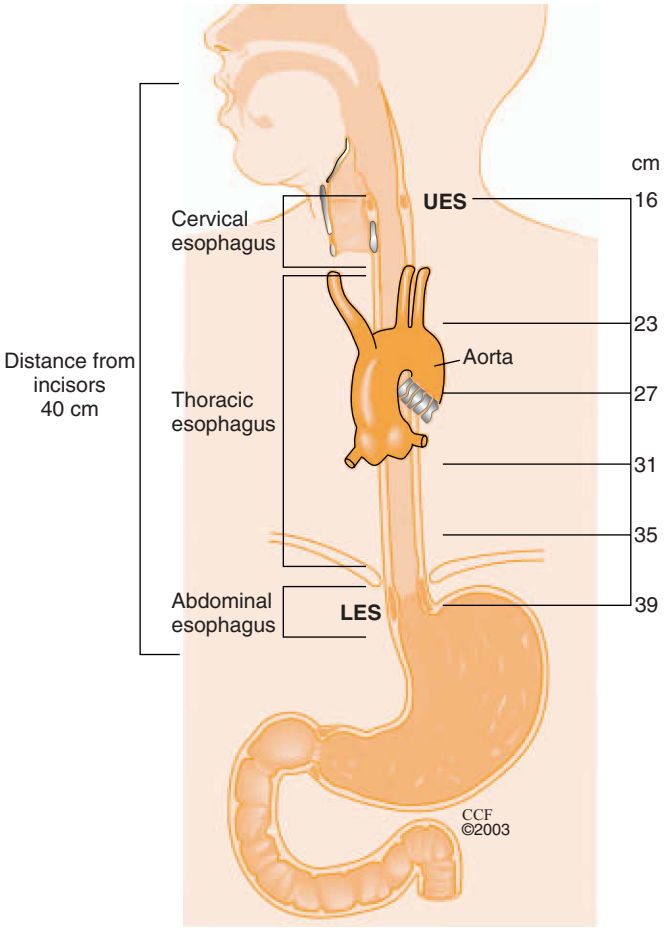

Figure 72-1. Schematic view of the esophagus and its relationship to neighboring structures. LES, Lower esophageal sphincter; UES, upper esophageal sphincter. *(Reprinted with the permission of the Cleveland Clinic Foundation.)*

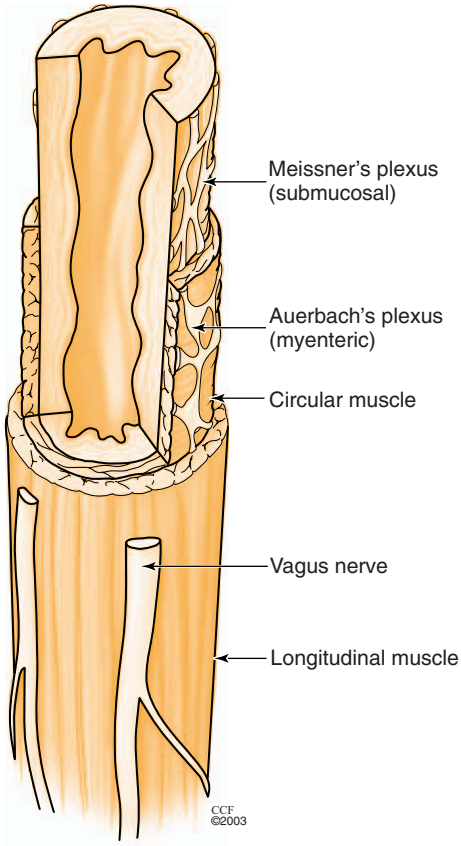

Figure 72-2. Cross-sectional anatomy of the esophagus. Note the outer longitudinal layer and inner circular layer of smooth muscle. Auerbach's plexus, which is responsible for peristalsis, is located between the two muscle layers. Meissner's plexus, responsible for sensation, is in the submucosa. *(Reprinted with the permission of the Cleveland Clinic Foundation.)*

Functionally, the UES, the esophageal body, and the LES act in a coordinated manner to allow normal swallowing. Swallowing begins when a food bolus is propelled into the pharynx from the mouth. This oropharyngeal phase of swallowing is voluntary, but the esophageal phase that follows is involuntary. In rapid sequence and with precise coordination, the larynx is elevated and the epiglottis seals the airway. A rapidly progressing pharyngeal contraction then transfers the bolus through the relaxed UES into the esophagus. As the UES closes, a progressive circular contraction begins in the upper esophagus and proceeds distally along the esophageal body to propel the bolus through the relaxed LES (Fig. 72-3). Peristaltic pressures normally ranging from 30 to 180 mm Hg are generated.[6-8] The measured pressure tends to be lower in the more proximal portions of the esophagus and greater in the distal smooth muscle portions.[8] The pressures may also vary with the consistency of the bolus itself. The LES subsequently closes with a prolonged contraction, preventing movement back into the esophagus. The mechanical effect of peristalsis is a stripping wave, so called because it strips the esophagus clean from its proximal to its distal end.

Secondary peristalsis is a progressive contraction in the esophageal body that is induced by stimulation of sensory receptors, rather than a swallow. Distention by residual food bolus or the refluxed gastric contents is usually the stimulant. It begins approximately at or above the level of the stimulus and resembles primary peristalsis. Its function is to clear the esophagus of food contents that were poorly cleared by the primary peristalsis and to push refluxed gastric contents back into the stomach.

Both the UES and LES are tonically contracted at rest. The closed state for the UES is a result of continuous neural excitation, with a small passive component to tone.[9] The UES pressures are asymmetric, being higher anteriorly and posteriorly. During general anesthesia or sleep, this pressure falls to 10 mm Hg as a result of cessation of neural discharge.[10] It is believed that the tonic contraction of the LES is a function of the muscle itself and is not dependent on neural innervation. Stimulation of inhibitory fibers results in LES relaxation. The resting tone of the LES is typically between 15 and 45 mm Hg and is affected by a wide array of events, foods, drugs, and hormones.[8] LES relaxation occurs not only in response to swallowing but also in response to esophageal distention (secondary peristalsis) or without peristalsis. The latter is referred to as a *transient lower esophageal sphincter relaxation* (TLESR). TLESR is a vagally mediated reflex that is a part of normal digestion and is triggered by gastric distention. It represents the primary mechanism for gastroesophageal reflux in normal individuals and patients with mild gastroesophageal reflux disease (GERD).[11]

Esophageal Symptom Assessment

Primary symptoms suggesting the presence of an underlying esophageal disorder typically include heartburn, dysphagia, odynophagia, and regurgitation. Heartburn, or pyrosis, is classically described as a substernal burning sensation usually occurring within 30 minutes to 2 hours after meals and made worse by lying down or bending over. Large meals, especially if containing fat, chocolate, coffee, or alcohol, are particularly likely to precipitate heartburn. Relieving factors often include drinking milk and taking an antacid. The presence of recurrent heartburn, as an isolated symptom, strongly suggests the diagnosis of GERD.

Dysphagia refers to the sensation of food being delayed in its normal passage from mouth to stomach. Patients often complain of a sensation of food "sticking." It may be classified anatomically into two

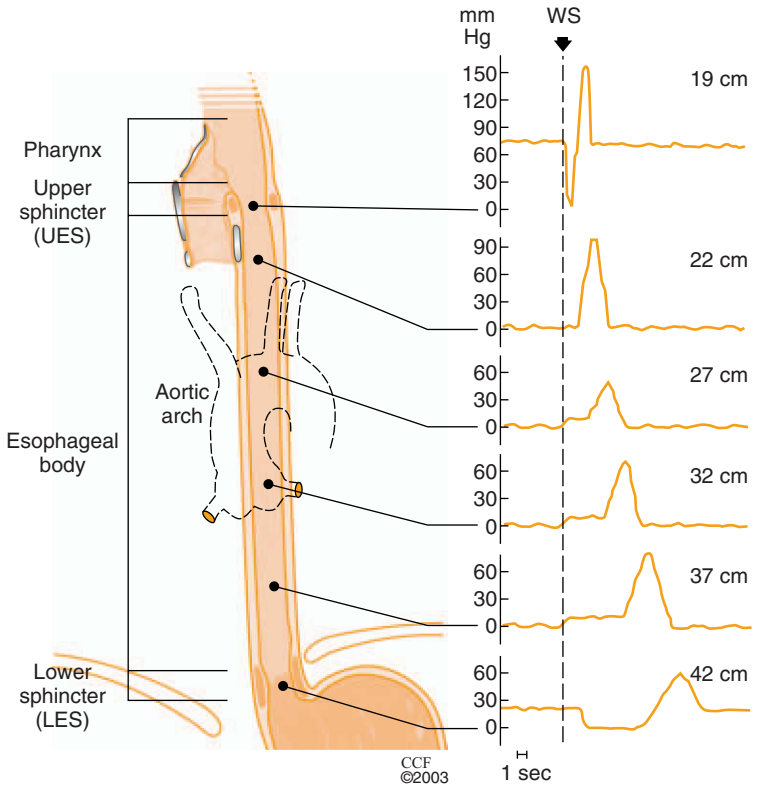

Figure 72-3. Normal esophageal peristalsis. The esophageal body and sphincters are intricately coordinated. Upper esophageal sphincter pressure (located at 19 cm) falls quickly at swallow initiation (wet swallows [WS]), followed by initiation of esophageal body peristalsis, and then lower esophageal sphincter relaxation (located at 42 cm). The peristaltic pressure tends to be lower in the proximal and middle esophagus and higher in the distal smooth muscle portion of esophagus. *(Reprinted with the permission of the Cleveland Clinic Foundation.)*

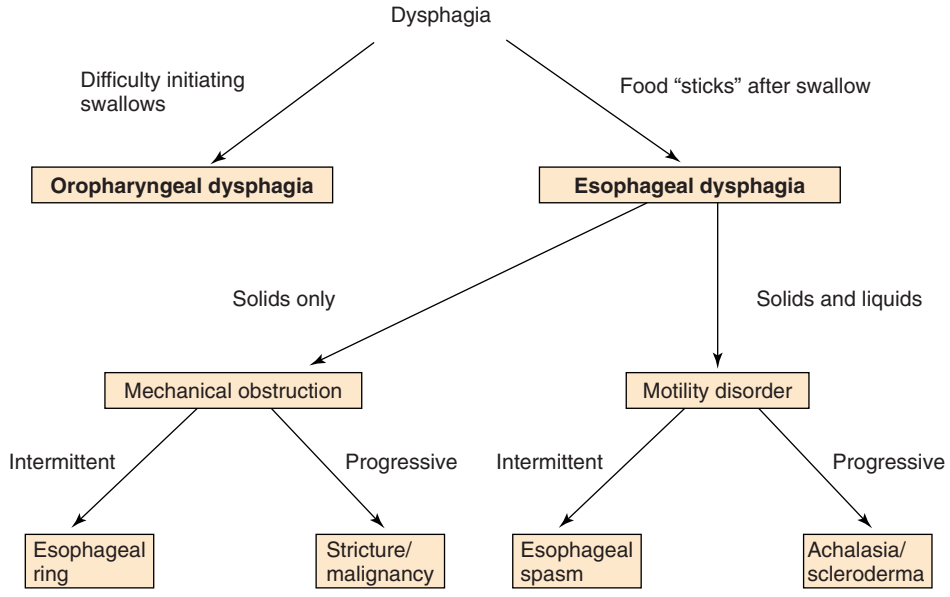

Figure 72-4. Algorithm for the evaluation of dysphagia.

separate clinical entities, oropharyngeal and esophageal. Oropharyngeal dysphagia, discussed later in this chapter, is the difficulty in initiating a swallow. Esophageal dysphagia results from difficulty transporting food down the esophagus secondary to structural or neuromuscular defects in the smooth muscle portion of the esophagus. Further history can often establish the diagnosis in patients with esophageal dysphagia (Fig. 72-4). Patients with primarily solid food dysphagia typically have a structural lesion, such as a peptic stricture, ring, or malignancy. Esophageal rings tend to cause intermittent solid food dysphagia, whereas strictures and cancer cause progressive dysphagia. Patients with both solid and liquid dysphagia are more likely to have a motility disorder such as achalasia or scleroderma. The site at which a patient localizes dysphagia is of limited value. Although dysphagia in the retrosternal or epigastric areas frequently corresponds to the site of obstruction, dysphagia localized to the neck may be from either lower in the esophagus or the hypopharyngeal area.[12,13]

Oropharyngeal or transfer dysphagia is an abnormality related to the movement of a food bolus from the hypopharynx to the esophagus. Oropharyngeal dysphagia arises from disease of the upper esophagus, pharynx, or UES, in contrast to esophageal dysphagia, which is the difficulty in propagating food down the esophagus. Esophageal dysphagia arises within the body of the esophagus, as a result of either a mechanical or motility disturbance. A careful history may be adequate to make this distinction.[14] Patients with oropharyngeal dysphagia typically present with difficulty initiating a swallow and immediately experience coughing, choking, gagging, or nasal regurgitation when attempting to swallow. Although patients with oropharyngeal dysphagia accurately localize the problem to the cervical or throat region, up to 30% of patients with esophageal dysphagia secondary to distal esophageal obstruction can localize the problem to the same area.[12,13] Dysphagia must be distinguished from globus sensation. *Globus* is a sensation of a lump in the throat in which food transport is not limited. A key distinction is that globus is not related to swallowing and, in fact, may improve with swallowing. Most patients with globus do not give a history of dysphagia with food.

The distinction between oropharyngeal dysphagia and esophageal dysphagia is crucial, because the conditions have distinctly different causes (see Fig. 72-4). Oropharyngeal dysphagia is most commonly caused by disruptions in the finely coordinated act of swallowing secondary to neuromuscular dysfunction. In this setting, the symptoms may be more severe during the swallowing of liquids. History and physical examination should concentrate on neurologic signs and symptoms. Both sensory and motor injury may result in an inability to accomplish the transfer of a bolus to the esophagus. Any disease that affects the nerves or muscles can produce oropharyngeal dysphagia; the more common associations are cerebrovascular accidents, amyotrophic lateral sclerosis (ALS), Parkinson's disease, myasthenia gravis, and tardive dyskinesia. Rarely, structural abnormalities, such as cervical osteophytes, hypopharyngeal diverticulum (Zenker's diverticulum), tumors, and postcricoid webs, can cause oropharyngeal dysphagia. Affected patients typically note difficulty with a solid food bolus leaving the mouth. Although these structural abnormalities occur rarely, they are important to identify, because they may be amenable to endoscopic or surgical therapy.

The oropharyngeal swallow is best assessed by videofluoroscopy, also known as the modified barium swallow study. Videofluoroscopy not only serves to confirm the presence of oropharyngeal dysfunction but also can assess the degree of aspiration. It is helpful to have an experienced speech pathologist present at the time of videofluoroscopy to identify these abnormalities and assist with specific swallow therapies. Assessment of aspiration risk and its treatment are essential in the management of patients with such problems, because aspiration carries a high risk of morbidity and mortality.

Dysphagia must be distinguished from *odynophagia*, which is pain caused by swallowing. This important symptom is clearly indicative of a pharyngeal or esophageal problem. Most often it is an inflammatory condition of the esophagus, such as erosive esophagitis, pill-induced esophagitis, or infectious esophagitis.

Regurgitation is the effortless appearance of an acid or bitter taste in the mouth. Regurgitation may be particularly severe at night and may awaken a patient from sleep with coughing and choking. Esophageal problems do not cause true vomiting, but patients may complain of "vomiting" when they are experiencing regurgitation. The term *water brash* describes the sudden filling of the mouth with clear, slightly salty fluid. The fluid is salivary secretions, not regurgitated gastric contents, and the mechanism is vagally mediated.

A number of other ancillary symptoms may be of esophageal origin. *Chest pain* is a common atypical symptom of esophageal disorders. Esophageal disorders are probably the most common causes of noncardiac chest pain. Chest pain can be indistinguishable from angina, but chest pain of esophageal origin tends to be of longer duration, positional, related to meals, and associated with other gastrointestinal symptoms. Esophageal causes of chest pain include GERD and motility disorders. The easily recognized hiccup may be associated with esophageal reflux or obstruction. *Globus* sensation, defined as feeling of a lump, fullness, or "tickle" in the throat, is another frequently encountered symptom. This symptom is usually psychologic and related to increased visceral sensation, but a thorough investigation of the pharynx, larynx, neck, and esophagus should be pursued. Asthma, cough, hoarseness, sore throat, and repetitive throat clearing may be secondary to atypical reflux disease.

Esophageal Testing

Endoscopy

Endoscopy is the technique of choice to evaluate the mucosa of the esophagus and detect structural abnormalities. The modern endoscope uses fiberoptic technology to capture and transmit the image from the distal end of the endoscope. Four-way tip deflection is permitted by use of two control knobs, one with up/down movement and the other with right/left movement. The endoscope is equipped with internal channels for air, water, and suction. Air is used to insufflate the esophagus and stomach, which are normally decompressed. A separate instrument channel is present, allowing the passage of biopsy forceps, heater probes, injection needles, and other equipment that will be used for biopsy and treatment of upper gastrointestinal disorders. The standard upper endoscope measures 9 mm in diameter, but both smaller and larger scopes are available. The "therapeutic" endoscope contains a larger instrument channel that permits passage of "jumbo" biopsy forceps and larger coagulation devices. Endoscopes as small as 4 mm are also available, allowing transnasal or oral endoscopy without sedation.

In the United States, upper gastrointestinal endoscopy is routinely performed with the patient under conscious sedation. After local anesthetic is sprayed on the posterior pharynx and intravenous sedation is given, the examination begins with insertion of the endoscope into the posterior pharynx. The posterior pharynx and larynx are examined for abnormalities. The endoscope is advanced under direct vision into the tonically closed UES. The patient is asked to swallow in order to relax the UES, and the endoscope is advanced into the proximal esophagus. The esophageal mucosa normally appears smooth and light pink. The mucosa should be thoroughly inspected for any abnormalities, including mucosal breaks, ulcers, strictures, and lesions. The area of the gastroesophageal junction (GEJ) must be carefully examined in order to identify specific landmarks. The squamocolumnar junction can be recognized from the irregular Z line demarcating the interface between the light pink esophageal squamous mucosa and the red columnar gastric mucosa (Fig. 72-5).[15] The GEJ is defined by the proximal margin of the gastric folds. Although, the squamocolumnar junction and GEJ are normally located at the same level (Fig. 72-6A), the two

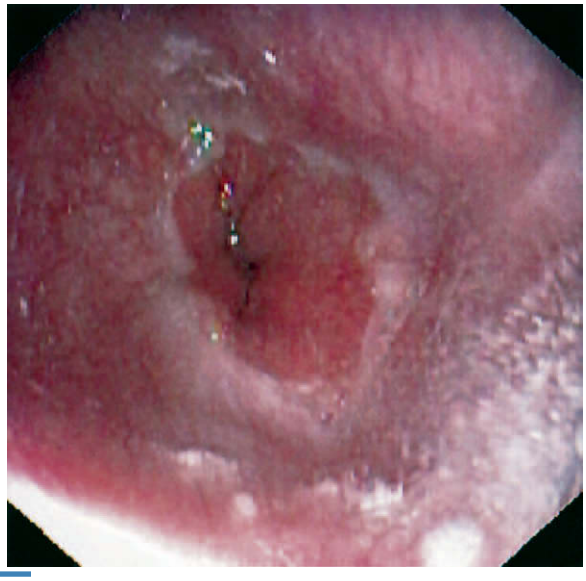

Figure 72-5. Normal squamocolumnar junction. The squamocolumnar junction is recognized from the irregular Z line marking the interface between the light pink esophageal squamous mucosa and the red columnar gastric mucosa.

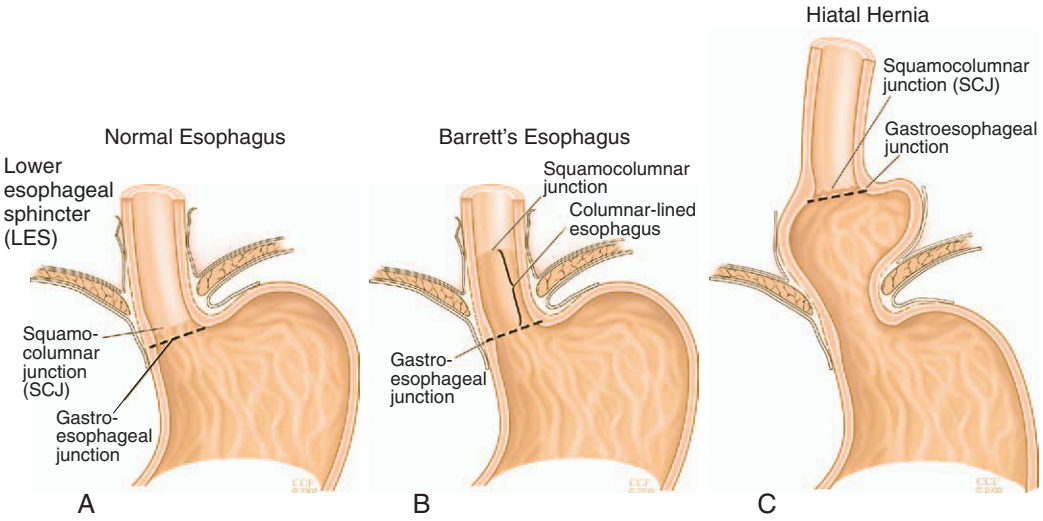

Figure 72-6. Anatomy of the gastroesophageal junction. **A,** Normal gastroesophageal junction, the squamocolumnar junction, and diaphragmatic hiatus are all at the same level. **B,** Barrett's esophagus; the squamocolumnar junction is proximal to the gastroesophageal junction. **C,** Hiatal hernia; the gastroesophageal junction is proximal to the diaphragmatic hiatus. *(Reprinted with the permission of the Cleveland Clinic Foundation.)*

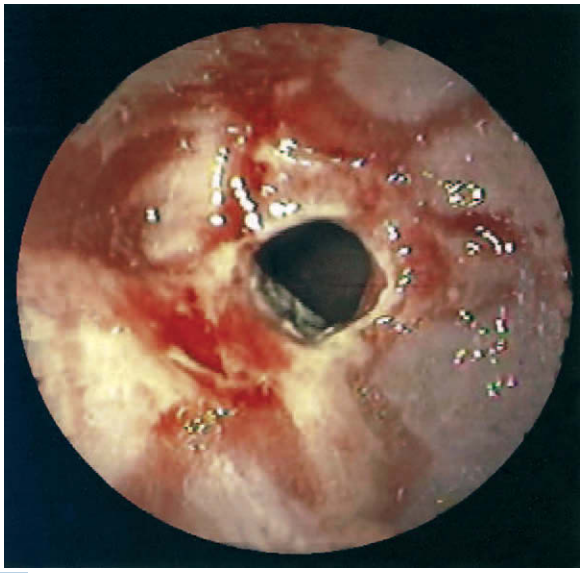

Figure 72-7. Endoscopic view of the gastroesophageal junction with severe esophagitis. There is circumferential ulceration with surrounding erythema and a moderate-size stricture.

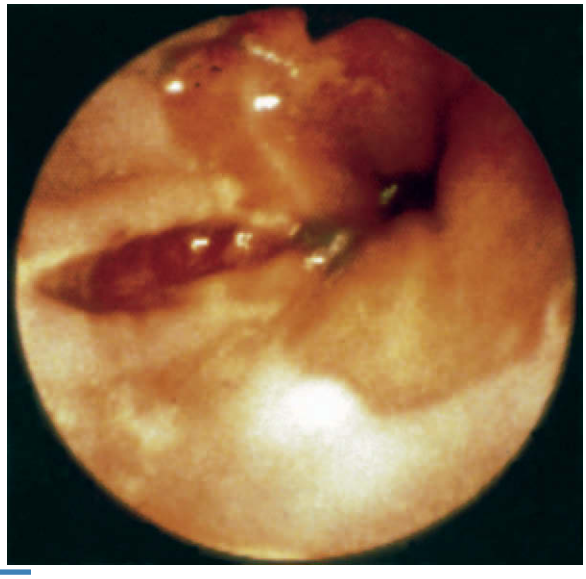

Figure 72-8. Endoscopic view of the gastroesophageal junction with a Mallory-Weiss tear. The tear is the mucosal break located on the *left* side of the figure. Mallory-Weiss tears, which often occur after vomiting or retching, are common causes of upper gastrointestinal bleeding.

are not synonymous. In patients with Barrett's esophagus, the squamocolumnar junction is more proximal in the esophagus than the GEJ (see Fig. 72-6B). Endoscopy can also be used to diagnose the presence of hiatal hernia. In patients with a hiatal hernia, the GEJ is more proximal than the diaphragmatic indentation (see Fig. 72-6C) visualized by diaphragmatic contraction noted during patient respiration.

The current indications for endoscopy include presence of warning symptoms such as weight loss, upper gastrointestinal bleeding, dysphagia, odynophagia and chest pain, partial or no response to empiric therapy, and evaluation for Barrett's esophagus. Esophageal causes of bleeding include severe esophagitis (Fig. 72-7), Mallory-Weiss tears (Fig. 72-8), and esophageal varices (Fig. 72-9).

Esophageal Manometry

Esophageal manometry is a diagnostic test that measures intraluminal pressures and coordination of the pressure activities of the three functional regions of the esophagus: LES, esophageal body, and UES. Manometry is commonly used in the assessment of patients with symptoms suggestive of esophageal motor dysfunction, such as dysphagia and noncardiac chest pain. A manometric study is also indicated for evaluation of esophageal peristalsis prior to antireflux surgery.

Manometry is commonly performed with the use of a water-infusion catheter and less commonly with a solid-state catheter system. Solid-state catheters contain embedded microtransducers that directly measure the esophageal contractions, but they are limited by a small number of recording sites. Water-perfused catheters contain several, small-caliber lumens that are perfused with water from a low-compliance perfusion device. When a catheter port is occluded by an esophageal contraction, water pressure builds within the catheter, exerting a force that is conveyed to an external transducer. With either catheter system, the electrical signals from the transducers are transmitted to a computer, which produces a graphic record.

The technique of manometry involves inserting the catheter into the esophagus via the nares. The catheter is then advanced to approximately 60 cm, which should be well within the stomach. At this point,

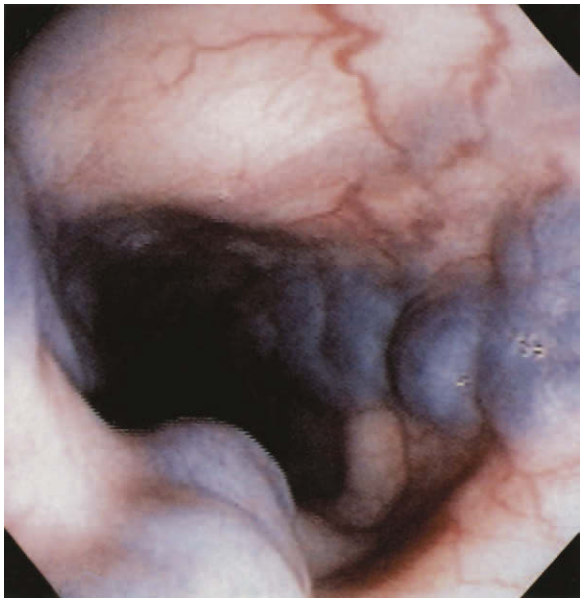

Figure 72-9. Endoscopic view of the distal esophagus. Three columns of esophageal varices (*blue*) are present.

the patient is placed supine on the left side, and the catheter calibrated. The station pull-through technique is then employed. This involves slowly withdrawing the catheter through the LES, esophagus, and UES. Resting LES pressure and relaxation, esophageal peristalsis, and UES pressure and relaxation are thus evaluated with a series of wet swallows (Fig. 72-10).

Manometry is the accepted standard for diagnosis of motor disorders of the esophageal body and LES. Manometric evaluation of the LES can accurately assess basal pressure and relaxation of the sphincter during swallowing. The esophageal body can be assessed for amplitude and duration of contractions and peristalsis. Peristalsis is defined by a coordinated contraction sequence and is quantified by the percentage of swallows with peristalsis. Through the use of these characteristics of the LES and esophageal body, a number of esophageal manometric disorders can be diagnosed (Table 72-1).

Manometric evaluation of UES often yields limited information, partly because of a great variability in what are considered normal values for UES resting pressure. Resting UES pressure is asymmetric, with greater values anteriorly and posteriorly than laterally.[16] Also, the technique of measurement may stimulate sphincter contraction. In addition, the duration of UES relaxation depends on the volumes of swallow boluses. Because of these limitations, disorders of the UES may be better defined by barium radiography.

A solid-state high-resolution system has become available that is able to monitor esophageal function without the need for water perfusion. The solid-state manometry probe has 36 circumferential sensors spaced at 1-cm intervals. Each of the 36 pressure-sensing elements contains 12 circumferentially isolated sectors detecting pressure over a 2.5 mm length. The procedure involves simply placing the catheter in the esophagus, allowing a brief adjustment period, recording 10 swallows, and withdrawing the probe. Pressures detected by each sector are averaged to obtain a mean pressure measurement for each sensor, making each of the 36 sensors a circumferential pressure detector. The data are processed by a computerized program to create the plots that can be viewed as conventional line traces or switched to high-resolution plots. This method has significant potential advantages over conventional methods. It is simple, faster, and more precise. The software simplifies data collection and gives more accurate diagnostic information while shortening procedure time by 50% to 200%. Additionally, this novel technique provides a complete observation of motor function from the pharynx to the esophagus to the stomach without the need for catheter repositioning. The computer program is customized for processing the data into an isocontour pressure plot (Fig. 72-11).

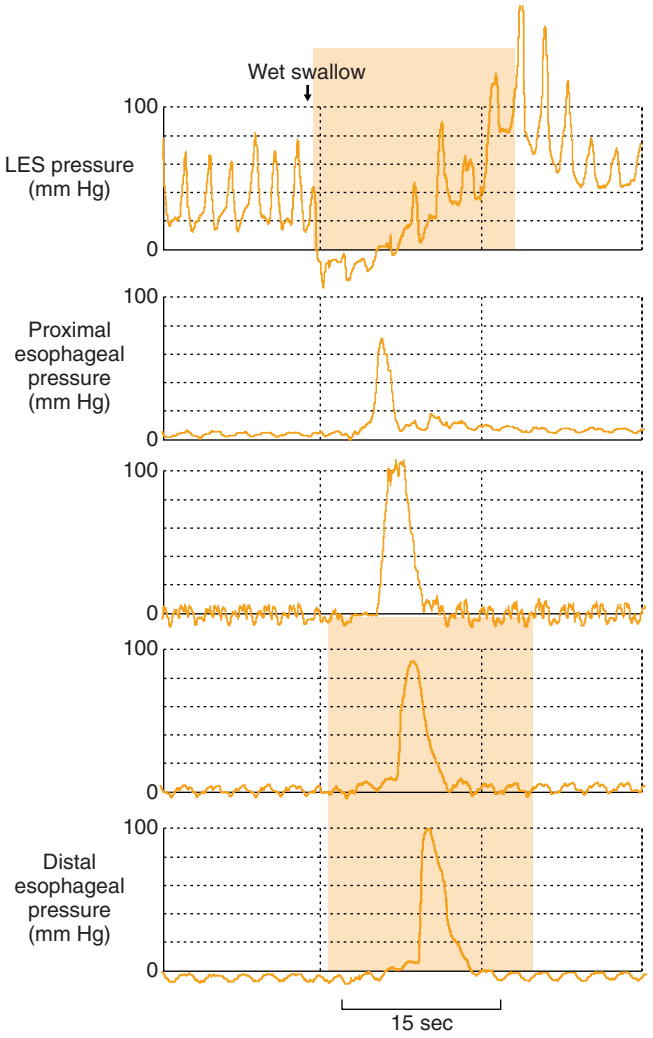

Figure 72-10. Normal esophageal manometry. The wet swallow initiates a progressive peristaltic contraction in the body of the esophagus with wave amplitudes of 30-180 mm Hg. The lower esophageal sphincter (LES) relaxes completely to gastric baseline at the end of peristalsis.

Ambulatory 24-Hour Esophageal pH Monitoring

Ambulatory 24-hour esophageal pH monitoring is an important tool in the diagnosis and management of GERD. Esophageal pH monitoring can detect and quantify gastroesophageal reflux and correlate symptoms temporally with reflux. The primary indications for ambulatory 24-hour esophageal pH monitoring are (1) to document excessive acid reflux in patients with suspected GERD but without endoscopic esophagitis, and (2) to evaluate the efficacy of medical or surgical therapy.

Standard pH monitoring measures distal esophageal acid exposure by using a single pH electrode catheter that is passed through the nose and positioned 5 cm above the superior margin of the manometrically determined LES. Although other techniques for electrode placement exist, such as pH step-up (rise in pH from stomach to esophagus), and endoscopic and fluoroscopic placement, they are less accurate and not standardized.[17-19] After catheter placement, the patient is encouraged to have a typical day without dietary or activity limitations. The pH is recorded every 6 to 8 seconds, and the data are transmitted to an ambulatory data logger. Typical pH units have an event marker that can be activated by the patient during the study to indicate the timing of symptoms, meals, and recumbence (Fig. 72-12). The patient also records these events on a diary card so that specific symptoms can later be correlated with the esophageal acid exposure recorded by the pH

Table 72-1

Esophageal Manometric Findings in Normal Patients and in Patients with Motility Disorders

Finding	Normal	Achalasia	Diffuse Esophageal Spasm	Nutcracker	Ineffective Esophageal Motility
Basal lower esophageal sphincter (LES) pressure	10-45 mm Hg	Normal or high	Normal	Normal	Low or normal
LES relaxation with swallow	Complete	Incomplete	Normal	Normal	Normal
Wave progression	Peristalsis	Aperistalsis	Peristalsis with at least 20% simultaneous contractions	Normal	30% or more failed nontransmitted contractions
Distal wave amplitude	30-180 mm Hg	Usually low (may be normal or high)	Normal	High	30% or more <30 mm Hg

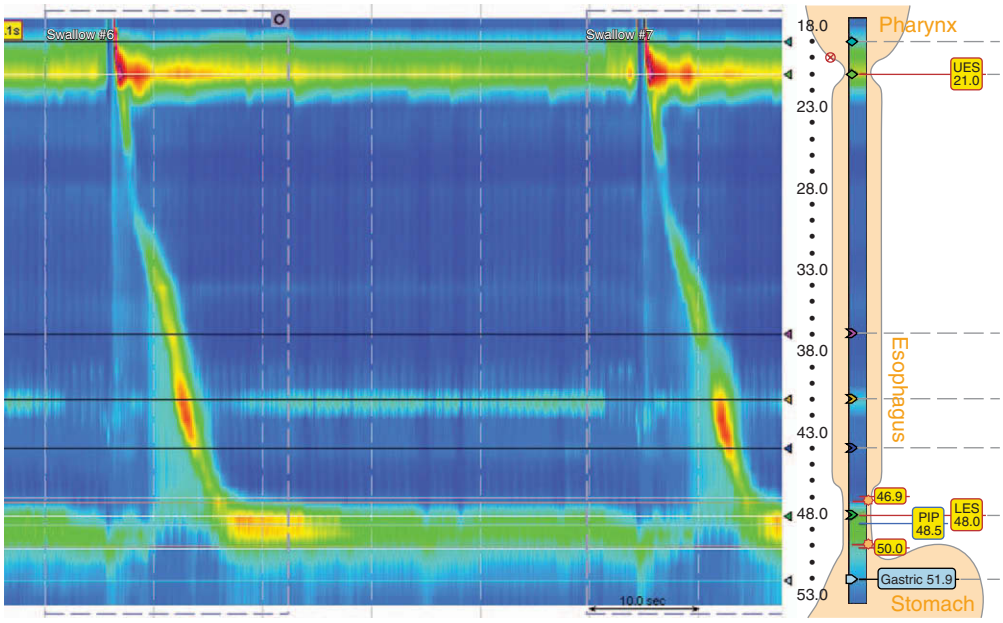

Figure 72-11. Isocontour plot of two swallows showing relaxation of the upper esophageal sphincter (Swallow #6) and peristaltic contractions in the esophagus. The pressure profile typically is low pressure (*blue*) to high pressure (*red*).

Figure 72-12. Typical pH unit used for ambulatory pH monitoring. The unit has buttons that can be activated by the patient during the study to indicate symptoms, meals, and recumbency.

probe. At the end of the study, data are downloaded to a computer, which generates a pH tracing and a data summary (Figs. 72-13 and 72-14).

A reflux episode is defined when the esophageal pH drops below 4.0. This value is chosen on the basis of the proteolytic activity of pepsin, which is most active at and below this pH. Additionally, a pH value less than 4.0 best distinguishes between symptomatic patients and asymptomatic controls.[20-23] Some gastroesophageal reflux is physiologic and may be seen in normal individuals, especially after meals. Although many scoring systems and parameters have been evaluated, the percentage of time that the pH is less than 4 is the single most important parameter to measure and is calculated in most software programs used in the analysis of pH monitoring. Results are generally considered abnormal when the total time that the pH is less than 4 is exceeds 4.2% of the study period.[24,25] Stratification by supine time and upright time is also reported by all software programs.

Although the pH software automatically calculates the total, upright, and supine reflux times, manual review of the pH tracing to exclude artifact is essential for precise interpretation. A typical reflux event involves an abrupt drop in pH (see Figs. 72-13 and 72-14). This

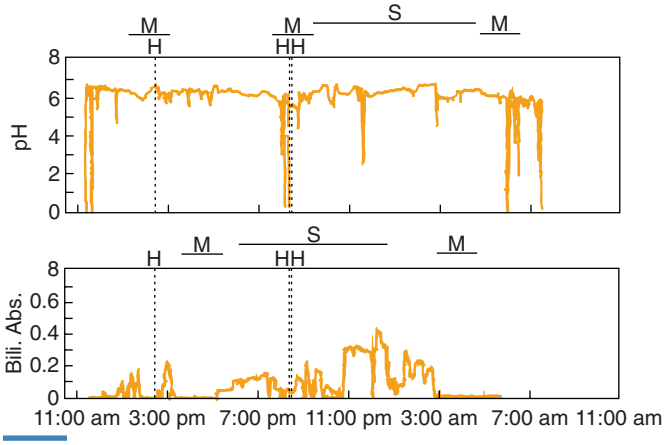

Figure 72-13. Normal pH tracing as generated by computer software. Symptoms, meals, and recumbency are recorded on the tracing. A reflux event occurs when the baseline pH drops abruptly to less than 4.0. Several short episodes of reflux with meals are demonstrated, as well as one spontaneous event related to recumbency. Although there are several reflux events, the total time during which the pH value is less than 4 is normal, and this patient would not be considered to have gastroesophageal reflux disease. Bili. Abs., bilirubin absorbance; H, heartburn; M, meal; S, supine.

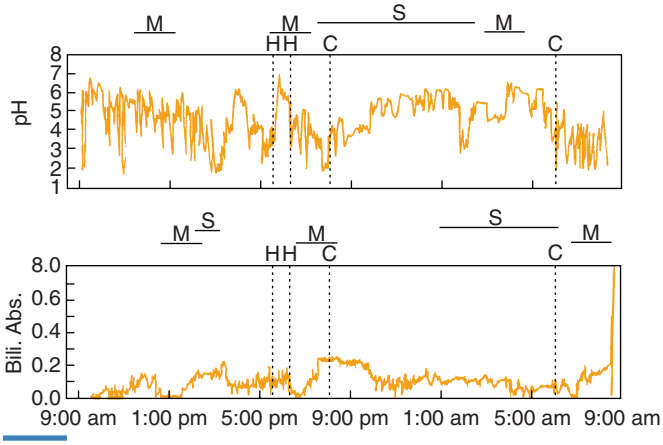

Figure 72-14. pH tracing of a patient with gastroesophageal reflux disease (GERD). Although the baseline pH varies considerably, several long episodes of reflux with pH less than 4 are shown. These events occur postprandially, not exclusively in relation to a meal as such events are in Figure 72-13. The total time during which the pH value is less than 4.0 is abnormal, and thus, the patient has GERD. The patient's symptom of chest pain (C) correlates with episodes of reflux. Bili. Abs., bilirubin absorbance; H, heartburn; M, meal; S, supine.

must be distinguished from a slowly drifting pH value, which may be secondary to the probe's losing contact with the esophageal mucosa and drying out. Probe dysfunction or disconnection can result in a reading that drops to zero. In addition, some patients may sip on acidic carbonated or citrus beverages, causing prolonged periods during which pH is less than 4. These artifacts should be identified and their corresponding time excluded from the calculation of acid exposure times.

One potential advantage of ambulatory pH monitoring is the ability to correlate symptoms with reflux episodes. However, even in patients with well-documented GERD, less than 20% of reflux episodes are associated with symptoms. This observation has led to the development of several scoring systems. The "symptom index score" is defined as the percentage of symptom episodes related to reflux events during the study period.[26] Good correlation is considered to be 50%. The "symptom association probability" (SAP) score is a statistical probability calculation in which the entire pH tracing is separated into 2-minute intervals and each segment is evaluated for reflux and symptom episodes; a modified chi-square test is used to calculate the probability that the observed distribution could have occurred by chance.[27] Unfortunately, no clinical trials prove that either of these symptom scores predicts a cause-and-effect relationship. This relationship can be confirmed only by the response to appropriate antireflux therapy.

Monitoring of pH may be performed with or without medical therapy. In monitoring performed without medical therapy, patients are asked to stop proton pump inhibitor (PPI) therapy for at least one week, histamine H_2 blocker therapy for 48 hours, and antacid use for 2 hours.[28] Whether the study should be performed with or without therapy depends on what information the clinician desires to gain. A pH study without therapy simply documents whether acid reflux is present, such as in a patient considering antireflux surgery or with atypical GERD symptoms. The study performed in a patient undergoing therapy documents whether continued acid reflux is the cause of symptoms in patients with poor or incomplete response to therapy.

Multiple-probe catheters have additional pH electrodes located more proximally in the esophagus or the hypopharynx. These electrodes allow the detection of proximal esophageal and pharyngeal acid reflux events, which may be useful in the evaluation of extraesophageal GERD symptoms, particularly laryngitis, chronic cough, and asthma. The conventional location of the proximal esophageal pH probe is 15 cm to 20 cm above the LES, with a normal value for total time with pH below 4.0 being less than 1%.[29,30] The hypopharyngeal probe is usually placed 2 cm above the manometrically determined UES. Although normal values are not clearly defined, more than two or three episodes of hypopharyngeal reflux is considered abnormal. It is again critical to review the pH tracings to be sure that proximal esophageal or hypopharyngeal reflux events are accompanied by distal esophageal reflux and are not secondary to artifacts. The clinical utility of these multiple-probe catheters is considered later in the atypical reflux discussion.

Ambulatory 24-Hour Bile Monitoring

Duodenogastroesophageal reflux (DGER) refers to regurgitation of duodenal contents through the pylorus into the stomach, with subsequent reflux into the esophagus. DGER may be important because factors other than acid, namely bile and pancreatic enzymes, may play a role in mucosal injury and symptoms in patients with GERD.[31-33] Initially esophageal pH greater than 7.0 during pH monitoring was considered a marker of such reflux, but alkaline reflux was later proved to be a poor marker for DGER.[31] This finding led to the development of a fiberoptic spectrophotometer (Bilitec 2000, Synectics, Stockholm), that detects DGER in an ambulatory setting independent of pH (Fig. 72-15).[34] This instrument utilizes the optical properties of bilirubin, the most common bile pigment. Bilirubin has a characteristic spectrophotometric absorption band at 450 nm. The basic working principle of this instrument is that absorption near this wavelength implies the presence of bilirubin and, therefore, represents DGER.

As in pH monitoring, data from the bilirubin spectrophotometer are usually measured as percentage of time that bilirubin absorbance is greater 0.14 and can be analyzed separately for total, upright, and supine periods (Fig. 72-16). Percentage of time bilirubin absorbance exceeds 0.14 is commonly chosen as a cutoff because studies show that values lower than this number represent scatter owing to suspended particles and mucus present in the gastric contents.[34] In a study using 20 healthy controls, the 95th percentile values for percentage of total, upright, and supine times that bilirubin exceeded 0.14 were 1.8%, 2.2%, and 1.6%, respectively.[35] Several reports have indicated a good correlation between Bilitec fiberoptic spectrophotometer readings and bile acid concentration measured by duodenogastric aspiration studies.[34,36-38] Validation studies have found that this instrument underestimates bile reflux by at least 30% in an acidic medium because of bilirubin isomerization with a shift in wavelength absorption.[35] Therefore, the instrument's measurement of DGER must always be accompanied by simultaneous measurement of esophageal acid exposure by means of prolonged pH monitoring. Furthermore, a variety of substances may result in false-positive readings by this instrument, because it indiscriminately records any substance with an absorption band

Figure 72-15. The Bilitec 2000 monitor (Synectics, Stockholm) for detection of duodenogastroesophageal reflux. The probe is a fiberoptic spectrophotometer designed for the detection of bilirubin in the distal esophagus.

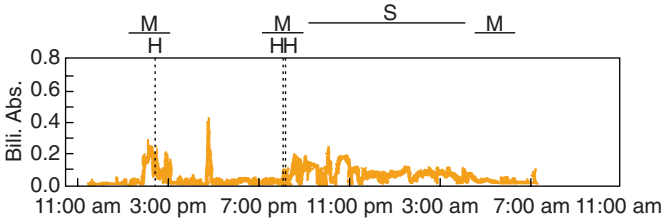

Figure 72-16. Tracing from a Bilitec 2000 monitor (Synectics, Stockholm) for a patient with duodenogastroesophageal reflux. *Reflux* is defined as bilirubin absorbance (Bili. Abs.) value > 0.14. This patient has several postprandial episodes of reflux associated with heartburn (H). Also note the prolonged episode of duodenogastroesophageal reflux while the patient was supine (S).

around 470 nm. This fact necessitates the use of a modified diet to avoid interference and false readings.[34,38] Also, it is important to remember that the Bilitec spectrophotometer measures reflux of bilirubin and not bile acids or pancreatic enzymes, thereby assuming that the presence of bilirubin in the refluxate is accompanied by other duodenal contents.

Development of this instrument was an important advancement in the assessment of DGER, but its clinical role is limited, and it is no longer available. Esophageal studies with this device were instrumental in showing that acid reflux and bile reflux occur together, making it difficult to incriminate duodenal contents alone as the cause of damage to the esophagus.

New Technologies

Because of the limitations of standard 24-hour pH monitoring, several new diagnostic modalities for GERD are under investigation. These include multichannel intraluminal impedence (MII) and the wireless Bravo pH Monitoring System (Medtronic Inc, Minneapolis, MN) and the Restech pH probe (Restech Respiratory Technology Corporation, San Diego, CA).

The Bravo is a catheter-free monitoring system in which a pH monitoring probe approximately the size of a medication capsule is placed endoscopically (Fig. 72-17). A standard upper gastrointestinal endoscopy is performed to locate the GEJ. The endoscope is removed, and an introducer with an attached pH capsule probe is inserted. The introducer is advanced and the capsule probe is placed 6 cm above the GEJ (Fig. 72-18). pH data are then transmitted to a recording device on the patient's waist. Besides being catheter free, the wireless system has the advantage of recording 48 hours of pH data. The capsule pH probe falls off after 4 to 10 days and is passed in the stool. The wireless system is significantly better tolerated, causing less interference with daily activities, and having a higher overall satisfaction rate and better quality of life for patients with GERD. The second, often discussed, and important advantage of the Bravo system is its greater sensitivity for detecting reflux events due to (1) prolonged monitoring (48 hours vs. 24 hours), (2) improved patient compliance, (3) reduced impairment of patients' daily activity, and (4) decreased likelihood of catheter movement during the study.

Figure 72-17. The Bravo wireless pH capsule (Medtronic Inc, Minneapolis, MN). It is approximately the size of a medication "gel cap." Placement of the capsule onto the esophageal mucosa with endoscopic assistance eliminates the need for a pH catheter.

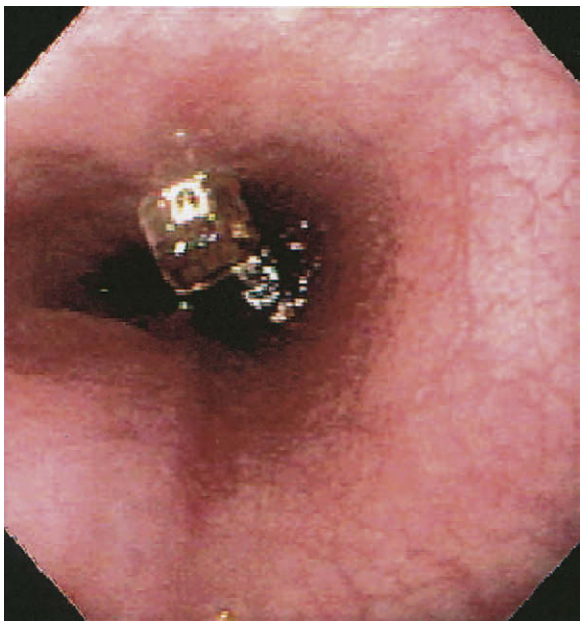

Figure 72-18. The Bravo wireless pH capsule (Medtronic Inc, Minneapolis, MN) attached to the distal esophageal mucosa after deployment.

The latest pH monitoring system is the Restech Dx–pH Measurement System, a highly sensitive and minimally invasive device for detection of acid reflux in the posterior oropharynx. It uses a nasopharyngeal catheter able to measure pH in either liquid or aerosolized droplets. The probe is a 1.5-mm–diameter oropharyngeal catheter with a wireless digital ZigBee transmitter attached to the shirt collar. The catheter employs a 3.2-mm teardrop tip to aid in insertion and to ensure that the sensor is positioned in the airway. The tip has a colored light-emitting diode (LED) for oropharyngeal visualization, to aid proper placement (Fig. 72-19). The sensing element consists of a circular 1-mm antimony surface and a reference electrode separated by a 0.05-mm polymer insulator (Fig. 72-20). Moisture from exhaled air condenses on the sensor surface, creating a fluid layer that bridges the gap between the antimony and reference sensor elements. The sensor records pH values twice every second (2 Hz), and it features a hydration monitor to eliminate data if the tip dries out. Special circuitry monitors each reading to ensure sufficient sensor hydration. This circuitry prevents the inclusion of dryout-related "pseudo-reflux" events in the data. The potential clinical utility of this device is in patients with extraesophageal reflux disease. Clinical data are needed to assess the future role of this device.

Multichannel intraluminal impedance (MII) is a relatively new technique that measures both acidic and nonacidic refluxates of liquid or gas consistency.[39] This ZepHR impedance/pH recorder (Sandhill Scientific Inc, Highlands Ranch, CO) is capable of measuring characteristics of gastroesophageal reflux that are not detectable by the current "gold standard," the pH probe. *Impedance*, a measure of the total resistance to current flow between adjacent electrodes, is capable of differentiating between liquid and gas refluxates on the basis of their inherent current and resistance properties. Combined MII-pH measurement has an advantage over standard pH monitoring, which does not detect nonacidic reflux. Hence, clinically this approach may be most useful for further evaluation of typical or atypical reflux symptoms refractory to acid suppression therapy, in assessing the role of nonacid and/or nonliquid reflux. Although there is no doubt that MII-pH measurement is currently the most accurate and detailed method to detect reflux of all kinds, the clinical indications for its use are still evolving, and its role in the management of patients with GERD awaits further definition for two main reasons: (1) the relevance of nonacid reflux in specific clinical settings has to be further discerned, and (2) there is a paucity of high-quality blinded, randomized, controlled studies examining the benefit of treating nonacid reflux.

Provocative Testing

Provocative testing in the esophagus is mostly of historical value. Such testing arose because of the difficulty in evaluating patients with noncardiac chest pain. The Bernstein test, introduced by Bernstein and Baker[40] in 1958, is an acid perfusion test used as an objective method to reproduce symptoms of acid related injury. After a brief control period, consisting of intraesophageal saline infusion, 0.1 N hydro-

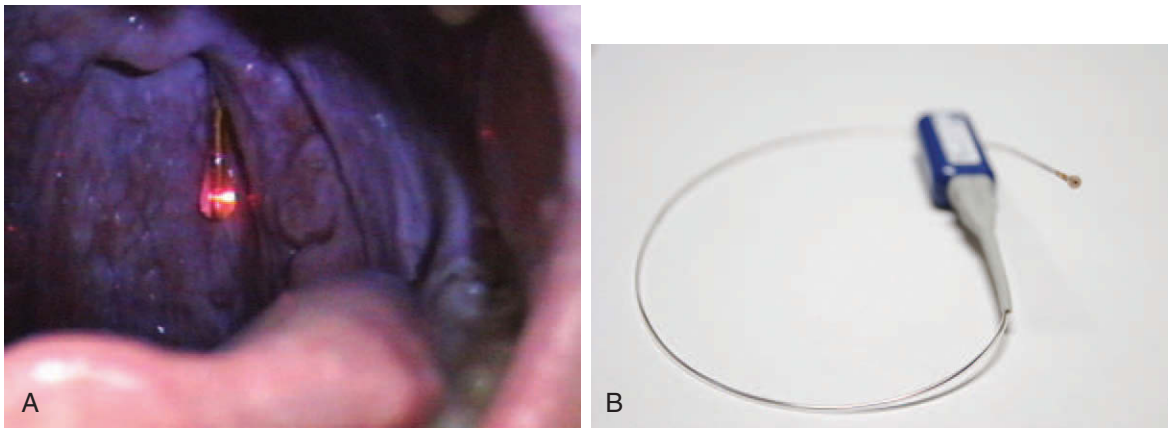

Figure 72-19. **A,** Oropharyngeal pH probe with light-emitting diode (LED) tip in the posterior aspect of the mouth. **B,** The probe transmitter.

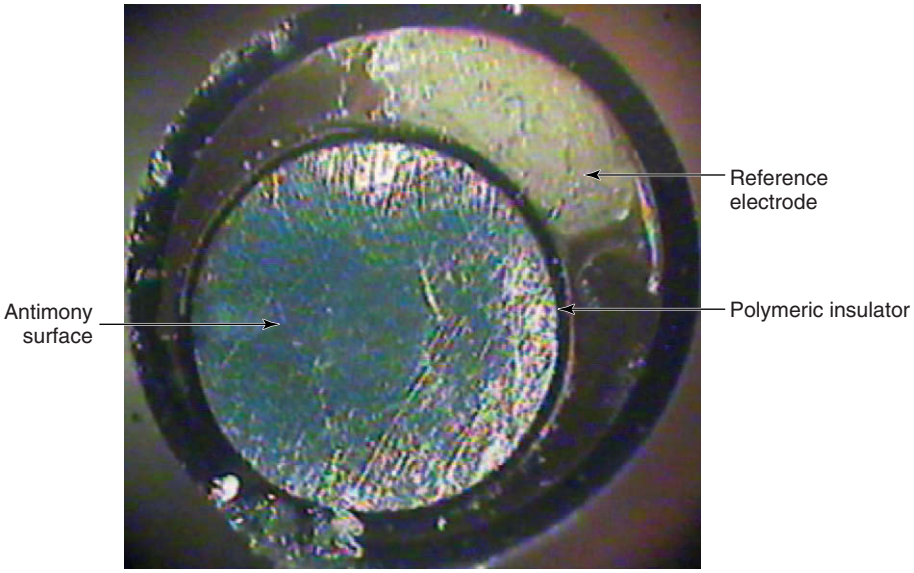

Figure 72-20. Magnified cross-sectional view of the Dx–pH probe (Restech Respiratory Technology Corporation, San Diego, CA) (×75).

chloric acid is infused in the esophagus. If the infusion produces the patient's chest pain and saline does not, the result is considered positive. Because of its low sensitivity, especially in comparison with pH monitoring, the Bernstein test is now rarely used.[41,42]

The edrophonium test is a provocative test designed to implicate esophageal motility disorders as a cause of chest pain. Edrophonium, a parasympathomimetic, increases the amplitude and duration of esophageal contractions. The tests consists of an intravenous injection of 80 μg of edrophonium, which reproduces esophageal manometric changes and chest pain in 20% to 30% of patients with noncardiac chest pain.[43,44] As with the Bernstein test, the sensitivity of this test is low and varies widely in the literature. Also, studies have shown poor correlation between increased amplitude and duration of esophageal contractions and patient's symptoms of chest pain.[44-46]

Esophageal Disease States Causing Dysphagia

Esophageal Motility Abnormalities

Box 72-1 highlights the latest classification system for esophageal motility disorders.[47] This system categorizes such disorders according to four major patterns of esophageal manometric abnormalities: inadequate LES relaxation, uncoordinated contraction, hypercontraction, and hypocontraction.[47] Most esophageal motility abnormalities fall predominantly into one of these four major categories, although there can be considerable overlap.

Processes that affect the inhibitory innervation of the LES (e.g., achalasia) can interfere with LES relaxation and thereby delay esophageal clearance. In the body of the esophagus, abnormal motility is characterized by uncoordinated contraction, hypercontraction, and hypocontraction. Uncoordinated esophageal contractions (i.e., contractions that are not peristaltic and directed toward the stomach) can delay esophageal clearance. Such uncoordinated contractions are the hallmark of diffuse esophageal spasm. Hypercontraction abnormalities are those that are characterized by contractions that are of high amplitude, long duration, or both. The putative disorders of hypercontraction (e.g., "nutcracker esophagus," isolated hypertensive LES) are perhaps the most controversial of the abnormal esophageal motility patterns, because it is not clear whether esophageal hypercontraction has any pathophysiologic significance. In contrast, hypocontraction abnormalities that result from weak (low-amplitude) muscle contractions can cause ineffective esophageal motility, which delays esophageal clearance, and LES hypotension can result in GERD.

Achalasia

Achalasia is a primary esophageal motility of unknown etiology characterized by insufficient LES relaxation and loss of esophageal peristalsis. Available data suggest hereditary, degenerative, autoimmune, and infectious factors as possible causes.[48,49] Pathologic changes occur in the myenteric plexus, consisting of a patchy inflammatory infiltrate of T lymphocytes, eosinophils, and mast cells, loss of ganglion cells, and myenteric neural fibrosis.[50] These changes result in selective loss of postganglionic inhibitory neurons, which contain both nitric oxide and vasoactive intestinal polypeptide. The postganglionic cholinergic neurons of the myenteric plexus are spared, leading to unopposed cholinergic stimulation.[51] This condition produces high basal LES pressures, and the loss of inhibitory input results in insufficient LES relaxation. Aperistalsis is related to the loss of the latency gradient along the esophageal body—a process mediated by nitric oxide.

The most common symptoms of achalasia are dysphagia for solids and liquid, regurgitation, and chest pain. Most patients are symptomatic for years before seeking medical attention. Patients with achalasia tend to localize their dysphagia to the cervical or xiphoid areas. Initially, dysphagia may be for solids only, but most patients have dysphagia for solids and liquids at the time of presentation.[48] Patients tend to accommodate for their problem by using various maneuvers, including lifting the neck or drinking carbonated beverages to help empty the esophagus. Regurgitation occurs in 75% of patients with achalasia and becomes a greater problem as the esophagus dilates with progression of the disease.[52] It occurs most commonly in the recumbent position and may awaken the patient from sleep because of choking and coughing. Chest pain is experienced by approximately 40% of patients with achalasia.[52] Weight loss occurs in 60% but is usually minimal.[53]

When the diagnosis of achalasia is suspected, a barium esophagram with fluoroscopy is the best initial diagnostic study. This test reveals loss of primary peristalsis in the distal two thirds of the esophagus. In the upright position, there is poor emptying, with retained food and saliva often producing a heterogeneous air-fluid level at the top of the barium column. The esophagus may be dilated (Fig. 72-21). In early disease the dilation is often minimal, but in chronic disease it can

Box 72-1

Classification of Esophageal Motility Abnormalities

Inadequate relaxation of lower esophageal sphincter (LES)
Classical achalasia
Atypical disorders of LES relaxation
Uncoordinated contraction
Diffuse esophageal spasm
Hypercontraction
Nutcracker esophagus
Isolated hypertensive LES
Hypocontraction
Ineffective esophageal motility

Data from Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut.* 2001;49:145-151.

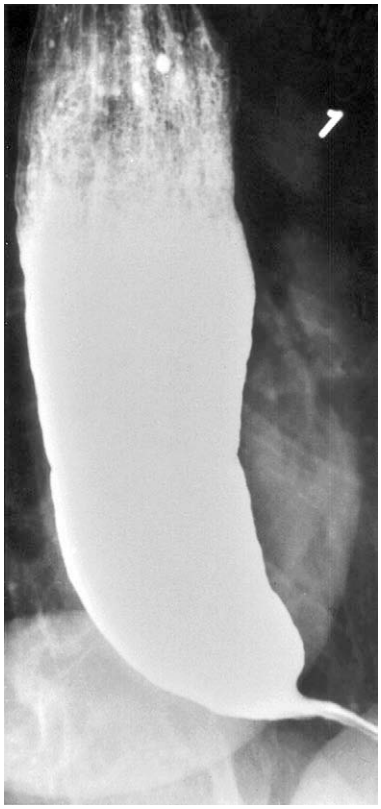

Figure 72-21. Classic esophagram of a patient with achalasia. The esophagus is dilated with a "bird's beak" tapering of the distal esophagus. Retained secretions form the heterogeneous air-fluid level seen at the top of the barium column.

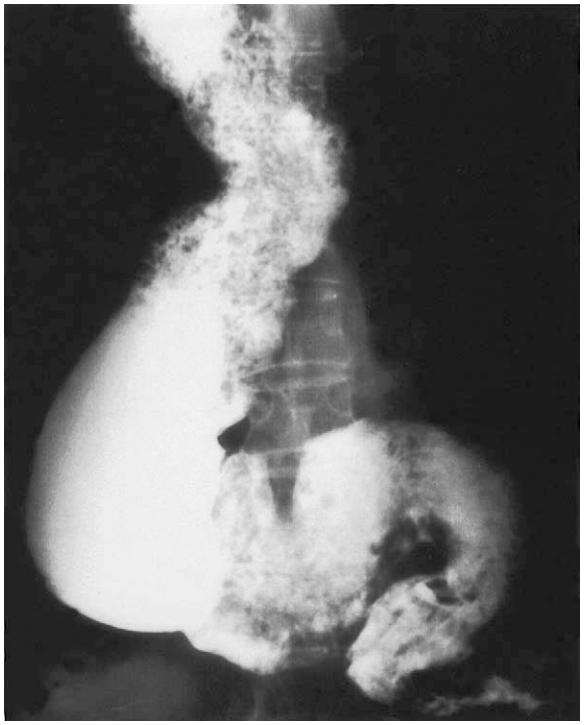

Figure 72-22. Esophagram of late-stage achalasia. The esophagus now has a sigmoid-like tortuosity with a large amount of retained debris.

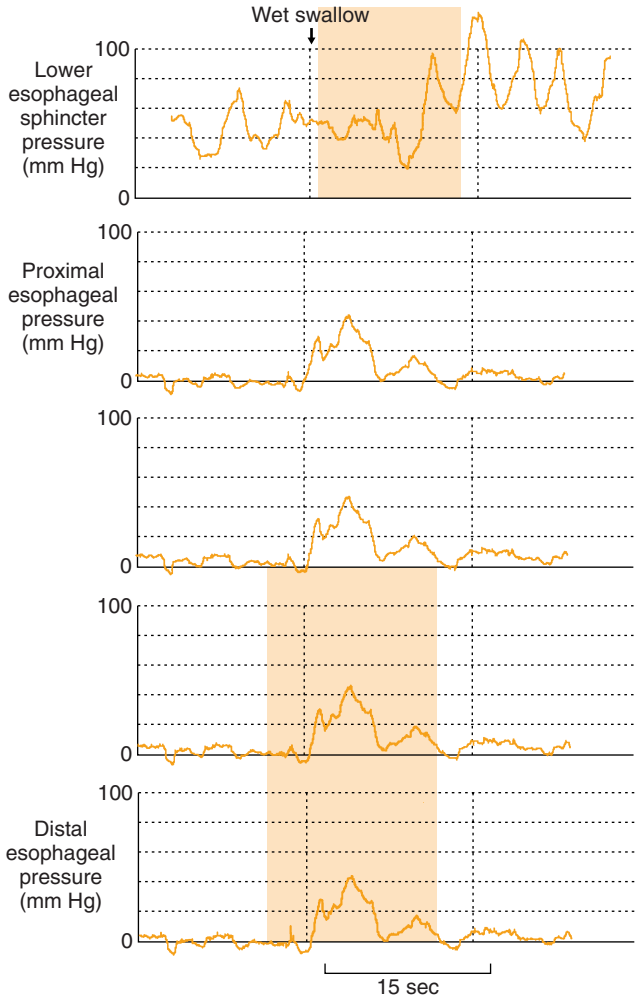

Figure 72-23. Manometric findings in achalasia. There is aperistalsis, manifested by isobaric contractions without propagation. The lower esophageal sphincter pressure, which is elevated, shows minimal relaxation with swallowing.

be massive with a sigmoid-like tortuosity (Fig. 72-22). There is a smooth tapering of the lower esophagus leading to the closed LES that resembles a bird's beak. The presence of an epiphrenic diverticulum may also suggest the diagnosis of achalasia.[54]

Esophageal manometry may also be used to establish the diagnosis (Fig. 72-23).[55] In the body of the esophagus, aperistalsis is always present. This means that all swallows are followed by simultaneous contractions, typically with low contraction amplitudes. Abnormal LES relaxation is seen in all patients with achalasia. About 70% to 80% of patients have absence or incompleteness of LES relaxation with swallows; in the remainder, the relaxations are complete but are of short duration. The baseline LES pressure is usually elevated but may be normal in up to 45% of patients; however, a low LES pressure is never seen in untreated patients with achalasia.

All patients with achalasia should undergo upper endoscopy to exclude pseudoachalasia arising from a tumor at the GEJ. Pseudoachalasia may mimic classic achalasia both clinically and manometrically. This diagnosis should be suspected in patients of older age with a short duration of symptoms and more significant weight loss.[56] At endoscopy, the esophageal body in classic achalasia often appears dilated and tortuous. Retained secretions and food debris may be encountered (Fig. 72-24). The LES region usually appears puckered and remains closed with air insufflation; however, with gentle pressure the endoscope can transverse this area. The GEJ and gastric cardia must be examined closely for the presence of tumors in order to rule out pseudoachalasia.

There is no cure for achalasia, but most patients can obtain relief of symptoms and improvement in esophageal emptying. The two most effective treatments are graded pneumatic dilation and surgical myotomy. All patients considered for pneumatic dilation should be surgical candidates, because the procedure is associated with a 2% to5% risk of esophageal perforation.[49,57] Pneumatic dilation, performed endoscopically, uses air pressure to dilate and disrupt the circular muscle fibers of the LES. Balloon dilators, available in three diameters (3, 3.5, and 4 cm) are positioned over a guidewire at endoscopy. The most important aspect of an effective pneumatic dilation is accurate positioning of the balloon across the LES, followed by fluoroscopic visualization of effective obliteration of the balloon waist. After pneumatic dilation,

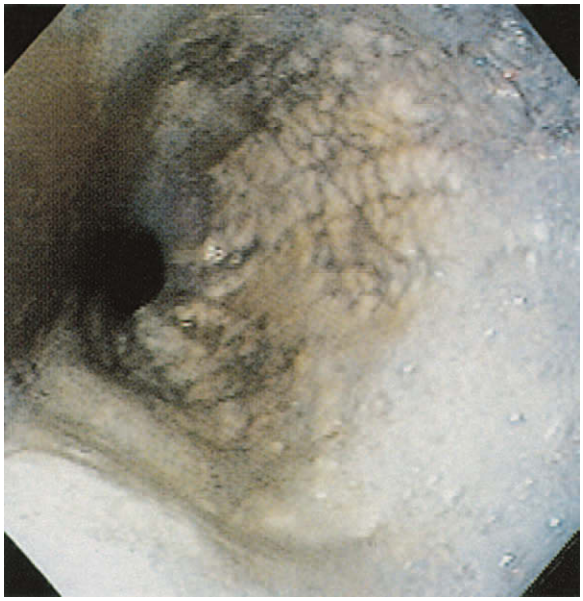

Figure 72-24. Endoscopic view of the distal esophagus in a patient with achalasia. The esophagus is dilated with retained fluid and debris.

all patients should undergo a (Gastrografin) study followed by barium swallow to exclude esophageal perforation.[58] Studies to date indicate good-to-excellent relief of symptoms in 50% to 93% of patients in whom the graded dilators were used.[49] The clinical response improves in a graded fashion with increasing size of the balloon diameter.[57] Surgical myotomy for achalasia involves performing an anterior myotomy across the LES (Heller's myotomy) usually associated with an antireflux procedure. Myotomies are increasingly being performed by laparoscopy, which has a good-to-excellent response rate of 80% to 94%.[49] A potential complication of myotomy is GERD, which occurs in 10% to20% of cases.[59]

For patients who are at high risk for pneumatic dilation or surgery, endoscopic injection of the LES with botulinum toxin (Botox) or pharmacologic treatment with nitrates or calcium channel blockers may be acceptable alternatives. Botulinum toxin injection, which inhibits the release of acetylcholine from nerve terminals, is initially effective in about 85% of patients.[49] However, symptoms recur in more than 50% of patients at 6 months.[60] Therefore, botulinum toxin injection is reserved for elderly patients for whom surgery poses a high risk. Calcium channel blockers and long-acting nitrates are effective in reducing LES pressure and temporarily relieving dysphagia but do not improve either LES relaxation or peristalsis.[61,62] The clinical response is short acting, the agents usually do not provide complete symptom relief, and their efficacy decreases with time. Given these limitations, pharmacologic therapy is recommended only for patients who are not candidates for pneumatic dilation or surgical myotomy and in whom botulinum toxin injections fail.[63]

Nonachalasia Motility Disorders

There are a number of other described primary motility disorders of the esophagus. These disorders are defined on the basis of presence of specific manometric criteria (see Table 72-1 and Box 72-1),[47] but, for most, the clinical relevance of these manometric findings is questionable.[64] Most often they are noted on manometry performed in patients with chest pain or dysphagia.

Diffuse esophageal spasm is the best recognized of these conditions. Manometric changes include the presence of simultaneous and repetitive contractions in the esophageal body, but unlike in achalasia, some normal peristalsis is maintained. LES relaxation is also normal in diffuse esophageal spasm (Fig. 72-25). The classic finding on esophagogram is the "corkscrew" esophagus (Fig. 72-26). Patients with this disorder may present with chest pain, if the contraction amplitudes are high, or dysphagia, if the contraction amplitudes are low. The treatment of diffuse esophageal spasm consists of medications that relax the esophagus, such as nitrates and calcium channel blockers, but is usually not completely effective.

"Nutcracker esophagus" is another common manometric diagnosis in patients with noncardiac chest pain. It is defined by high-amplitude peristalsis. This condition appears unlikely to be a true primary motility disorder but rather a marker for increased visceral pain perception.

Ineffective esophageal motility is a hypocontractile disorder with relevant clinical associations. It is defined by a distal esophageal contraction amplitude of less than 30 mm Hg in 30% or more of wet swallows. Ineffective esophageal motility has been demonstrated to be reproducible manometrically, and studies have demonstrated a higher incidence in patients with GERD, especially in those with respiratory symptoms.[65,66] Given the ineffective nature of the contractions, a food bolus may not be effectively transported, resulting in dysphagia in some patients.

Secondary motility disorders are commonly a result of systemic conditions. The most common condition affecting esophageal motility is scleroderma, or progressive systemic sclerosis (PSS). Other systemic conditions that can result in esophageal hypomotility are hypothyroidism, diabetes mellitus, and amyloidosis. These disorders are discussed in more detail later.

Strictures

An *esophageal stricture* is defined as any loss of lumen area within the esophagus. The normal esophagus measures 20 mm in diameter. The

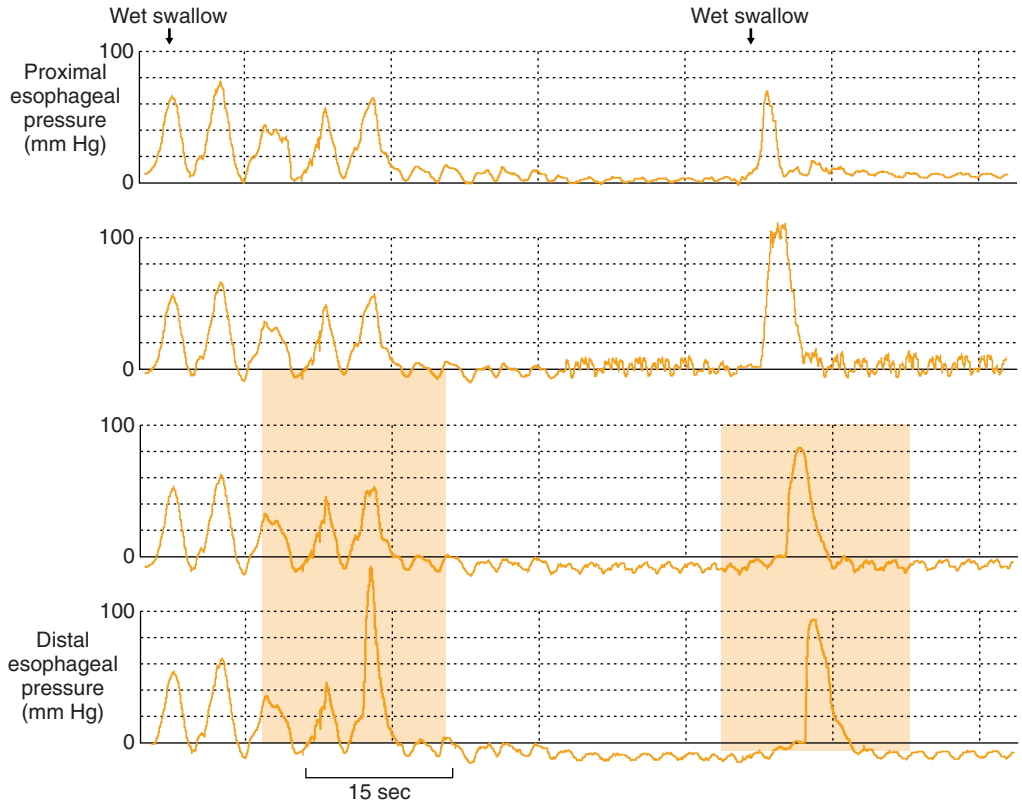

Figure 72-25. Manometric findings in diffuse esophageal spasm. There are repetitive simultaneous contractions in the esophageal body, but some normal peristalsis is maintained. Lower esophageal sphincter relaxation is normal and complete.

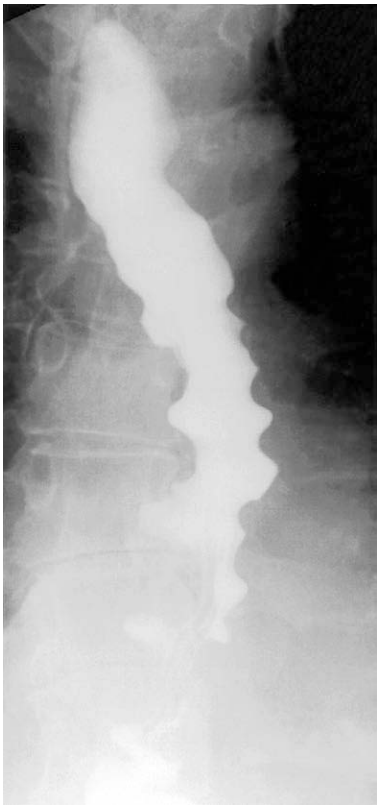

Figure 72-26. Esophagram of a patient with diffuse esophageal spasm, showing the classically described "corkscrew" esophagus.

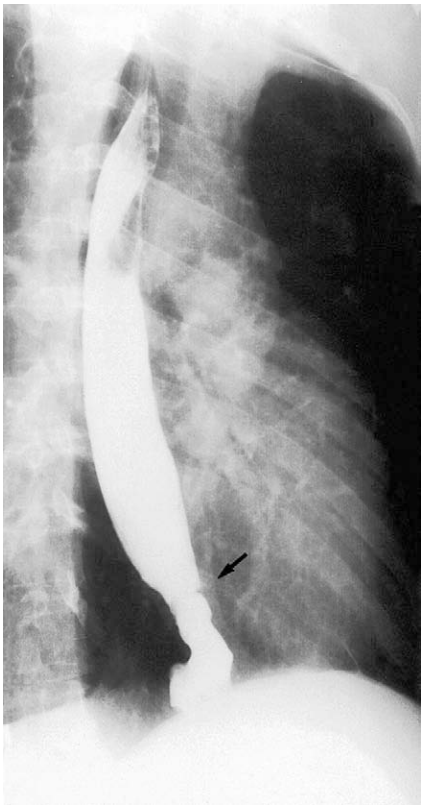

Figure 72-27. Esophagram with a distal esophageal stricture. There is a smooth taper of the distal esophagus consistent with a benign peptic stricture (*arrow*). A subtle Schatzki's ring is also present.

Box 72-2

Etiology of Esophageal Strictures

Intrinsic Strictures

Acid peptic
Pill-induced
Chemical/lye
Post-nasogastric intubation
Infectious esophagitis
Sclerotherapy-induced
Irradiation-induced
Esophageal/gastric malignancies
Surgical anastomotic
Congenital
Systemic inflammatory disease
Epidermolysis bullosa

Extrinsic Strictures

Pulmonary/mediastinal malignancies
Anomalous vessels and aneurysms
Metastatic submucosal infiltration (breast cancer, mesothelioma, adenocarcinoma of gastric cardia)

predominant clinical symptom of strictures is dysphagia, which is usually most prevalent when the luminal diameter is less than 15 mm. Even less severe strictures can cause intermittent dysphagia to large food pieces such as meat and bread. There are multiple intrinsic and extrinsic causes for esophageal strictures (Box 72-2). Intrinsic strictures are most common, with acid or peptic causes accounting for the majority of cases (60% to 70%) (Figs. 72-27 and 72-28).[67] Rings or webs and malignant strictures are discussed later separately.

Regardless of etiology, the foundation for treatment of benign stricture disease is esophageal dilation. The different types of dilators are (1) mercury-filled, rubber Maloney bougies, (2) wire-guided rigid Savary-Gilliard dilators, and (3) balloon dilators, which can either be through-the-scope (TTS) or wire-guided. Choice of dilator often depends on anatomy of the stricture and operator experience. In general, Maloney bougies are used in uncomplicated short straight strictures. The wire-guided Savary-Gilliard dilator and TTS balloons are both best suited for long, tight, or tortuous strictures. Complications of esophageal dilation are uncommon, but perforation (0.5%), bleeding (0.3%), and bacteremia (20% to 50%) are not rare.[68] Patients with radiation-induced or malignant strictures are at higher risk of perforation. To minimize the risk of perforation, the "rule-of-threes" applies—that is, no more than three sequential dilators to be used per session. The goal of esophageal dilation is to obtain an objective diameter greater than 15 mm. Approximately 90% of patients in whom the esophagus was dilated to 15 mm have no recurrence at 24 months.[69]

Refractory esophageal strictures are defined by lack of response to two or more dilations. The causes for refractory stricture include ongoing insults from pills or nonsteroidal anti-inflammatory drugs (see discussion of pill-induced injury), uncontrolled acid reflux, and inadequate lumen diameter achieved by dilations. PPIs are superior to H_2 blockers in preventing recurrence of acid-related strictures.[70] Treatment of refractory strictures includes elimination of offending agents (pills and acid) and gentle dilation to 15 mm. Intralesional injection of steroids before dilation is safe and probably effective for refractory strictures.[71] Surgery is now extremely rare for benign disease but may be considered in strictures that fail to respond to aggressive medical therapy and dilation.

Rings or Webs

Esophageal rings and webs are common findings on upper endoscopy, and many are asymptomatic. However, some patients do experience significant symptoms from these structural abnormalities. Symptoms

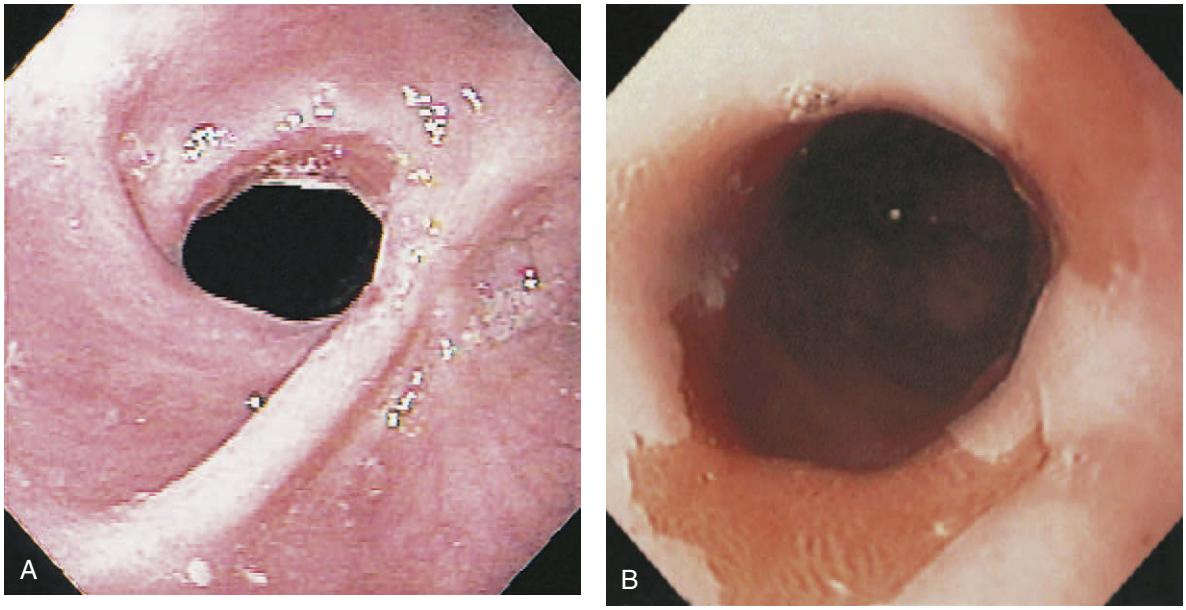

Figure 72-28. Endoscopic views of esophageal strictures. **A,** Anastomotic stricture with normal smooth mucosa. **B,** Subtle distal esophageal stricture with Barrett's metaplasia (salmon-pink mucosa extending above the strictured area).

include intermittent solid food dysphagia, aspiration, and regurgitation. Although the terms "esophageal ring" and "esophageal web" have been used interchangeably, there are subtle differences in what defines each. Rings are circumferential, can consist of mucosa or muscle, and most commonly occur in the distal esophagus.[15] Esophageal webs occupy only part of the esophageal lumen, are always mucosal, and are usually located in the proximal esophagus.

Esophageal webs can in found in as many as 5% of asymptomatic individuals.[72] When symptomatic, they usually cause dysphagia. An association between esophageal webs and iron deficiency was noted by gastroenterologists Plummer and Vinson in the United States and otolaryngologists Paterson and Kelly in the United Kingdom.[73-75] Their descriptions have given the name Plummer-Vinson or Paterson-Kelly syndrome to the triad consisting of proximal esophageal webs, iron deficiency anemia, and dysphagia.[76,77] Barium radiography is the most sensitive means of diagnosing esophageal webs (Fig. 72-29). Endoscopic visualization is also possible, in which the web will appear as a thin, eccentric lesion with normal-looking mucosa. Some webs are located so proximally that routine passage of the endoscope through the UES fractures the web before its presence is known. Treatment of symptomatic esophageal webs consists of mechanical disruption, which can be accomplished with bougie or balloon dilators.

Schatzki's ring (also known as B ring) occurs at the GEJ at the distal margin of the LES and is the most common cause of intermittent solid food dysphagia and food impaction (Figs. 72-30 and 72-31). The presence of symptoms depends on the luminal diameter. If the ring diameter is less than 13 mm, the patient has symptoms; if the diameter is greater than 20 mm, the patient almost never has symptoms.[78] For diameters between 13 and 20 mm, which account for the majority of Schatzki's rings, symptoms are variable. The pathogenesis of esophageal rings is controversial. Some writers believe that the rings are congenital lesions, and others suspect a role for GERD.[79-81] The most sensitive test for detecting a Schatzki's ring is the barium swallow study, but with patience and air insufflation, most rings can also be identified at endoscopy. Treatment is required only in symptomatic patients, in whom mechanical bougienage is usually employed. Recurrent symptoms requiring repeat dilation are not uncommon, and some authorities recommend maintenance therapy with acid suppression, given the possible association of Schatzki's ring with GERD.

The second type of esophageal ring is the A ring, a muscular ring most commonly detected on barium swallow study. This lower esophageal muscular ring, which is rarely symptomatic, occurs at the proximal margin of the LES approximately 2 cm proximal to squamocolumnar junction.

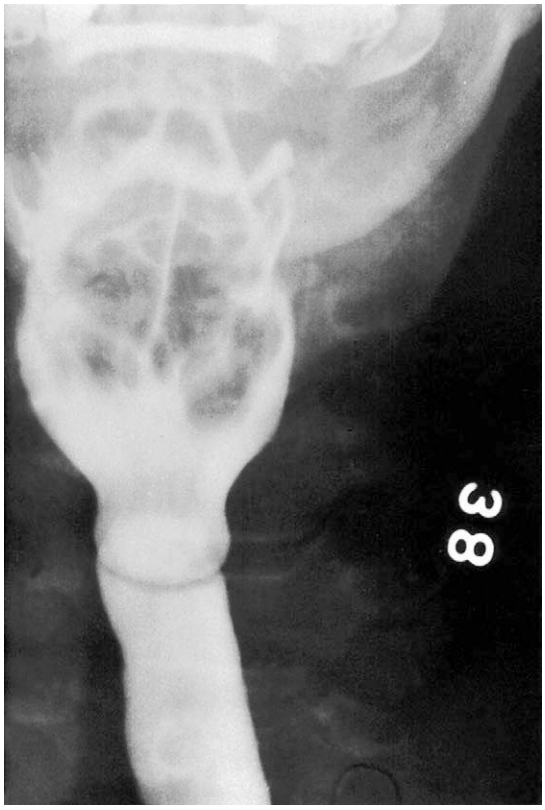

Figure 72-29. Proximal esophageal web on barium swallow study in a patient with Plummer-Vinson syndrome.

Eosinophilic Esophagitis

Also known as "ringed," "feline," or corrugated esophagus, eosinophilic esophagitis has rapidly become an increasingly recognized cause of dysphagia and often food impaction in young adults.[82,83] The syndrome

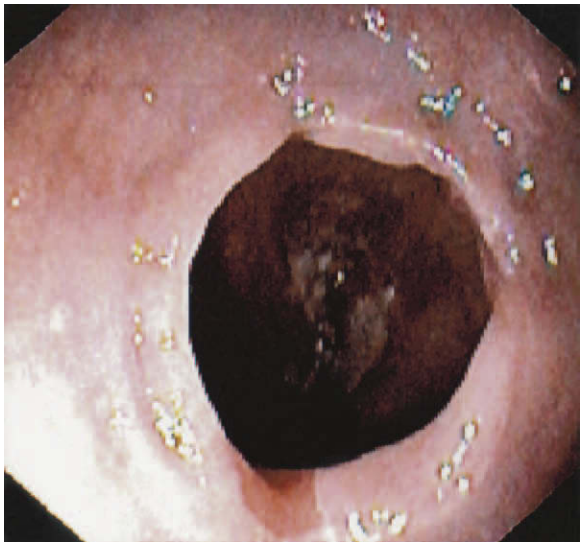

Figure 72-30. Endoscopic view of a Schatzki's ring. Note the significant narrowing in the esophageal lumen.

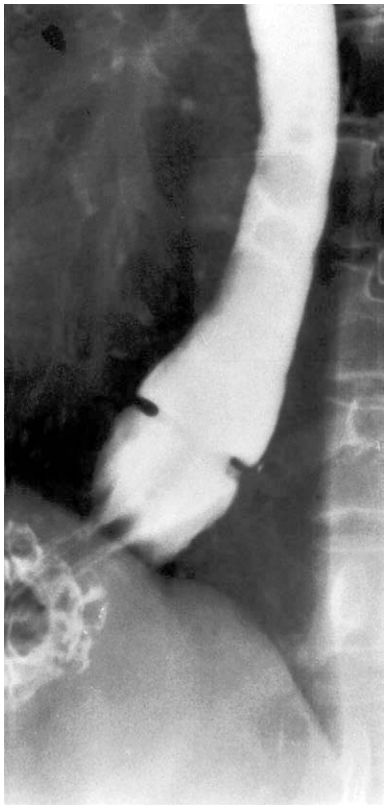

Figure 72-31. Esophagram of the Schatzki's ring in the patient from Figure 72-30.

consists of endoscopic findings of multiple esophageal rings in patients with dysphagia (Fig. 72-32). The etiology is unclear, but GERD, congenital abnormality, and possible allergic conditions have been implicated.[84-86] Eosinophilic esophagitis is characterized by esophageal eosinophilia of greater density than found in acid reflux. The eosinophil density required for the diagnosis of eosinophilic esophagitis is more than 15 eosinophils per high-power field (eos/hpf) in the mucosa that does not clear after appropriate treatment with PPI.[83] Eosinophilic esophagitis is often associated with other atopic diseases. Patients may also have a strong family history of atopy.[83]

Given the limitations of the unknown natural history of eosinophilic esophagitis and the lack of consensus on the therapeutic goal, a number of medical, dietary, and endoscopic therapies are reported. Current studies do not support a significant role for GERD in the majority of patients with eosinophilic esophagitis, but there is clearly a role for acid suppression in those complaining of GERD symptoms. Treatment consists of dilation with bougienage with or without acid suppression. In many cases more than one treatment session is required to obtain a desired esophageal lumen of 15 mm. Patients with eosinophilic esophagitis are also at higher risk of painful deep mucosal tears with dilation. Pharmacologic treatment of eosinophilic esophagitis has been shown to improve clinical symptoms and histology in the majority of patients. Therapeutic options include pharmacologic treatments such as oral and topical corticosteroids and leukotriene receptor antagonists. Dietary modification and food elimination have been effective in the pediatric population, suggesting that certain foods may serve as environmental triggers for the eosinophilic infiltration. Because many adults present with strictures, endoscopic esophageal dilation is another management modality. Despite these treatment options, several controversies exist as to the recommended treatment strategy. Whether the goal of therapy is resolution of symptoms or of tissue eosinophilia or both remains unclear owing to a paucity of data on the natural history of the condition.

Other Esophageal Disease States

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is defined as chronic symptoms or mucosal damage secondary to the abnormal reflux of gastric contents into the esophagus.[87] *Reflux esophagitis* refers to a disorder in a subgroup of patients with GERD consisting of histopathologically demonstrated characteristic changes in the esophageal mucosa. *Nonerosive reflux disease* is the presence of typical GERD symptoms in a patient without endoscopic findings of esophageal erosion. In the spectrum of GERD, nonerosive reflux disease accounts for approximately 50% of cases, reflux esophagitis for 30% to 40%, and Barrett's esophagus for 10% to 20%.[88]

GERD occurs when the normal antireflux barrier between the stomach and the esophagus is impaired, either transiently or permanently. Therefore, defects in the esophagogastric barrier, such as LES incompetence, TLESRs, and hiatal hernia, are the primary factors involved in the development of GERD.[89] As discussed previously, TLESRs are short relaxations of the LES that do not occur in response to swallow. Studies have demonstrated that TLESRs are the primary mechanism for gastroesophageal reflux in normal individuals and in patients with mild GERD. Conversely, those with severe GERD and complications are more likely to have a permanent structural alteration, such as low LES pressure or a large hiatal hernia.[90] Delayed gastric emptying can also be a contributing factor to the development of GERD. Symptoms develop when the offensive factors in the gastroduodenal contents, such as acid, pepsin, bile acids, and trypsin, overcome several lines of esophageal defense, including esophageal acid clearance and mucosal resistance. As more components of esophageal defense break down, the severity of reflux increases.

Symptoms

Classic symptoms of GERD are heartburn, defined as a retrosternal burning discomfort, and acid regurgitation. Symptoms often occur after meals and may increase when a patient is recumbent. Other ancillary symptoms seen in typical reflux are dysphagia, odynophagia, and belching. Atypical GERD symptoms (discussed later) include asthma, chest pain, cough, laryngitis, and dental erosions.

Diagnosis

There is no diagnostic gold standard for the detection of GERD. Classic symptoms of acid regurgitation and heartburn are specific but not sensitive for the diagnosis of GERD, as determined by abnormal 24-hour pH monitoring. Therefore, it is reasonable to consider an initial empiric trial of antisecretory therapy in a patient with classic GERD symptoms in the absence of alarm signs, such as dysphagia,

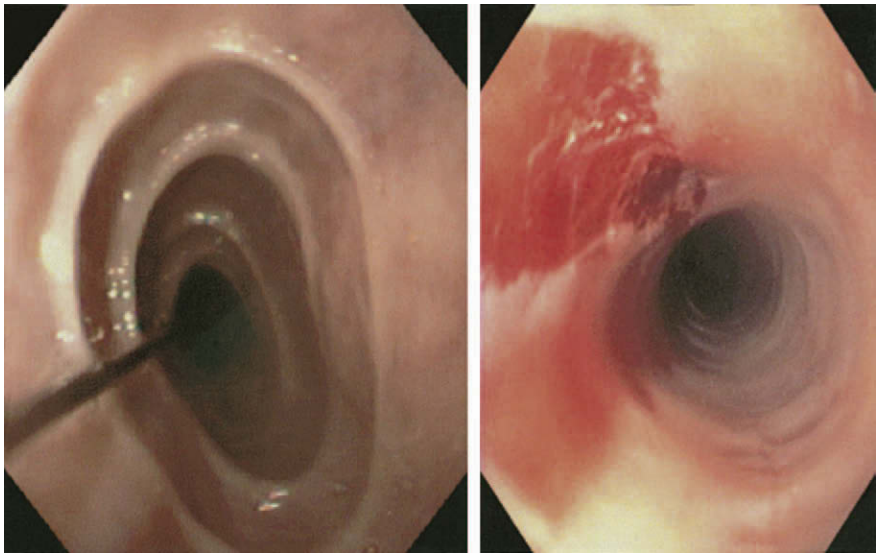

Figure 72-32. Endoscopic views of the esophagus of a 25-year-old man with a 3-year history of severe dysphagia. *Left,* There are multiple rings consistent with "ringed esophagus." *Right,* After bougie dilation, a deep mucosal tear is evident; this is a common complication after dilation for "ringed esophagus."

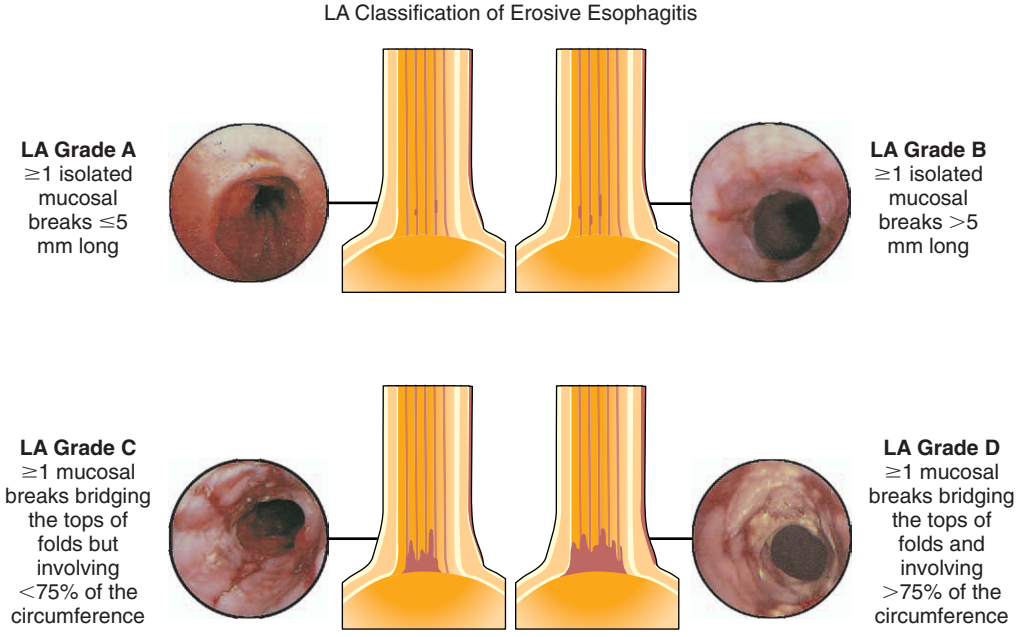

Figure 72-33. Los Angeles (LA) classification of erosive esophagitis. Note that mucosal breaks are necessary for a diagnosis of esophagitis. Subtle findings such as erythema and edema of the gastroesophageal junction are not a part of this classification scheme because they are not specific to gastroesophageal reflux disease.

odynophagia, weight loss, chest pain, and choking. Further diagnostic testing should be considered if there is no response to an empiric course of antisecretory therapy or if alarms signs are present.

Endoscopy is the technique of choice to evaluate the mucosa in patients with symptoms of GERD. Reflux esophagitis is present when erosions or ulcerations are present at the squamocolumnar junction (see Fig. 72-7). There are many grading systems to characterize the severity of esophagitis, the most common of which is the Los Angeles (LA) classification (Fig. 72-33).[91] The presence of esophagitis as well as the finding of Barrett's esophagus are diagnostic of GERD. Although ambulatory 24-hour pH monitoring has long been thought to be the gold standard for the diagnosis of GERD, this test has limitations that remain underappreciated. Results are normal in 25% of patients with erosive esophagitis and in approximately 33% of patients with nonerosive reflux disease.[92] Nevertheless, 24-hour pH testing can be useful to quantitate esophageal acid exposure and allows for the correlation of symptoms to reflux events. Given the lack of a reliable standard test, clinical response to acid suppression is a good indication that a patient's symptoms may be due to GERD.

Treatment

The goals of treatment in GERD are to relieve symptoms, heal esophagitis, prevent recurrence of symptoms, and prevent complications. A variety of lifestyle modifications are recommended in the treatment of GERD. These include avoidance of precipitating foods (fatty foods, alchohol, caffeine), avoidance of recumbency for 3 hours postprandially, elevation of the head of the bed, smoking cessation, and weight loss.[93] However, although these measures make sense physiologically,

little data are available in the literature to support them. Additionally, with the availability of potent acid-suppressive agents, dietary modification as the primary therapy for GERD is no longer overly emphasized.

Antacids and alginic acid can provide temporary relief of episodic heartburn. Despite the wide use of these over-the-counter products, surprisingly few data are available as to their utility for healing reflux esophagitis or for the long-term management of GERD symptoms. Sucralfate, a complex metal salt of sulfated sucrose, is an exceptionally safe medication that has some demonstrated efficacy in the treatment of mild reflux esophagitis. Few published data are available on the use of sucralfate in GERD, however, and the drug has never achieved popularity as antireflux therapy.

In theory, prokinetic agents may decrease gastroesophageal reflux by raising LES pressure and enhancing esophageal and gastric clearance. Currently, metoclopramide is the only prokinetic agent available in the United States for the treatment of GERD. Metoclopramide is a dopamine antagonist, and its use is limited by side effects such as agitation, restlessness, somnolence, and extrapyramidal symptoms, which occur in up to 30% of patients. Cisapride, a serotonin-4 (5-HT_4) receptor agonist, demonstrated efficacy in mild GERD, but this agent was withdrawn when it was found to cause lethal cardiac arrhythmias in patients with a number of predisposing conditions.

The cornerstone of GERD therapy is the administration of agents that decrease gastric acid secretion, thereby reducing esophageal acid exposure. Histamine receptor antagonists (H_2 blockers) in standard divided doses achieve complete symptom relief in approximately 60% of patients and heal esophagitis in about 50%. The H_2 blockers are most useful for patients with GERD of mild to moderate severity, in whom the highest rates of healing can be anticipated. However, healing rates with these agents are poor in patients who have severe reflux esophagitis. High doses of H_2 blockers (up to eight times the conventional dose) have been used effectively to treat esophagitis in severe cases of GERD, but this approach is generally not recommended. Few data document the long-term efficacy of H_2 blockers used in any dosage, and tolerance to the antisecretory effects of these agents develops in many patients. For patients with severe GERD, most authorities prescribe PPIs rather than high-dose H_2 blocker therapy.

PPIs are superior to H_2 blockers in both healing erosive esophagitis and relieving symptoms, with healing rates approaching 90%.[94] For most patients, GERD is a chronic relapsing disease with almost universal recurrence of symptoms after treatment withdrawal; thus, it requires maintenance therapy in many patients. Long-term therapy with PPIs, which maintains remission in 80% of patients, is superior to that with H_2 blockers, which achieve a remission rate of 50%.[95] With more than a decade of clinical experience with PPIs in the United States, initial concerns regarding the long-term safety of these agents remain unsubstantiated.[96] In clinical practice, "step-down" therapy is recommended in patients in whom GERD is suspected. Patients are initially treated with PPIs; and once clinical response is noted, patients are treated with H_2 blockers or PPI on an as-needed basis.

Antireflux surgery, now performed primarily by the laparoscopic approach, remains an option for carefully selected patients with well-documented GERD.[97] The ideal candidate is the patient with typical symptoms that respond completely to antisecretory therapy. The patients who opt for surgery typically have concerns about the cost or potential adverse effects associated with long-term PPI therapy. Patients with large hiatal hernias and predominant regurgitation symptoms are also good candidates. However, in some patients, GERD is refractory to acid suppression with high-dose PPI therapy; any consideration of surgery in such patients must be guarded, and the clinician should document continued evidence of ongoing esophageal acid exposure or damage during therapy. Studies with impedance pH monitoring in patients with GERD refractory to PPI therapy suggest a possible benefit of surgery in those with continued nonacid reflux; however, controlled studies are needed before surgery can be recommended in this group. At this time, surgery is not advised in patients with GERD unresponsive to PPIs who have no evidence of esophageal acid exposure or nonacid regurgitation.

There has been some interest in endoscopic therapy for GERD.[98,99] Several such therapies have become available and are undergoing clinical trials. These techniques include endoscopic suturing, injectable agents for bulking the GEJ (Enteryx, which was withdrawn from the market; and Gatekeeper Reflux Repair System, Medtronic, Inc., Minneapolis, MN), and radiofrequency energy delivery to the GEJ. All are shown to result in improved LES pressure; however, most studies of endoscopic therapy have only limited follow-up information in a relatively small number of patients. Therefore, the durability of these devices is unknown. Serious adverse events were reported with Enteryx, which led to the voluntary withdrawal by the manufacturer in September 2005 and suspension of the Gatekeeper clinical program in late 2005. A number of other endoscopic antireflux procedures are under investigation. Small studies describe promising results, but the safety and efficacy of these procedures are not yet known, and their role in the treatment of GERD is not clear.

Extraesophageal Gastroesophageal Reflux Disease

GERD may manifest as symptoms other than heartburn and regurgitation. They include asthma, chest pain, chronic cough, laryngitis, and dental erosions. Although the relationship between each atypical symptom and GERD varies, there are some common themes. In addition to the lack of the classic heartburn and regurgitation symptoms, esophagitis or Barrett's esophagus is usually not present. Additionally, response to antireflux therapy in patients with these symptoms is often less predictable. In general, an empiric trial of twice-daily PPI therapy is indicated as initial treatment because there is no definitive diagnostic standard for GERD. If treatment fails, full investigation with ambulatory pH testing is recommended to ensure that medical therapy has been intensive enough (Fig. 72-34). The diagnosis of GERD can be confirmed only when the symptom is relieved consistently with specific antireflux therapy.

Laryngitis

There is increasing evidence that GERD causes laryngeal signs and symptoms. This is often referred to as "reflux laryngitis" or "laryngopharyngeal reflux." In fact, it is estimated that 4% to 10% of patients presenting to otorhinolaryngologists do so because of symp-

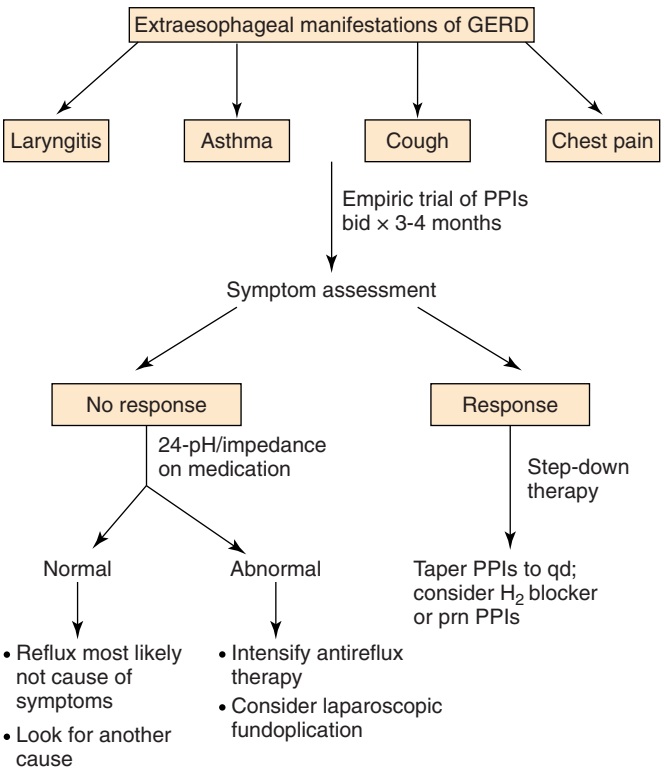

Figure 72-34. Treatment algorithm for extraesophageal manifestations of gastroesophageal reflux disease (GERD). bid, twice daily; pm, evening dose; qd, once daily; PPIs, proton pump inhibitors.

toms in part related to GERD.[100] Symptoms of reflux laryngitis include hoarseness, throat clearing, dysphagia, increased phlegm, and globus sensation.

GERD may be responsible for causing significant laryngeal changes, including erythema, edema, pharyngeal ulcerations, vocal cord nodules and polyps, granulomas, and even leukoplakia and cancer. Although some writers believe that these laryngeal signs are specific for acid-related problems, others suggest that these changes may also be secondary to smoking, excessive alcohol use, allergies, asthma, viral illnesses, or voice abuse. One study investigated the baseline prevalence of laryngeal signs in 105 healthy subjects without reflux or laryngeal complaints; the majority of these normal subjects (87%) had at least one abnormal finding in the larynx.[101] The three most common laryngeal findings were interarytenoid bar, arytenoid medial wall erythema, and posterior pharyngeal wall cobblestoning, all of which had previously been considered pathognomonic for GERD. Importantly, these signs in healthy subjects were associated with the presence of other ear, nose, and throat irritants, including chronic nasal congestion, postnasal drip, alcohol use, and asthma. Therefore, this study suggests the potential for overdiagnosis of GERD due to the poor specificity of some of the currently designated laryngeal signs of the disease. Studies comparing laryngeal signs in normal volunteers with those in patients with GERD suggest that two laryngeal findings may be more specific for GERD-induced laryngeal injury, vocal cord lesions, and arytenoid medial wall erythema and edema.[102] These encouraging data suggest a likelihood of identifying more specific laryngeal sites in patients with GERD.

Despite compelling epidemiologic data, there is still controversy about the prevalence of GERD-related laryngeal signs and symptoms, in part because of the lack of consensus about the utility of 24-hour esophageal pH monitoring in diagnosing this disorder. Studies have clearly shown that 24-hour pH monitoring may not be the perfect test for diagnosing atypical GERD. Overall, only 50% of patients with laryngoscopic signs of GERD have abnormal esophageal acid exposure, irrespective of the location of the pH probe (distal or proximal esophagus or hypopharyngeal). This low rate may be due either to overdiagnosis of GERD as the cause of laryngeal pathology or to the lack of sensitivity of the pH probes in diagnosing acid-related disease in this group of patients. Distal and proximal esophageal pH probes are at best 75% and 50% sensitive, respectively, for detection, of acid reflux in a group of patients with classic acid reflux disease (i.e., heartburn, acid regurgitation, and, possibly, esophagitis).[103] Furthermore, studies using distal, proximal, or hypopharyngeal probes in patients with laryngeal pathology yielded conflicting data on the ability to predict clinical improvement on the basis of abnormal findings for each of the pH probes.

Owing to the unpredictable response to acid suppression, there are currently no accepted protocols for the most cost-effective treatment of patients with GERD and laryngeal signs and symptoms. H_2 blockers usually produce only mild to moderate improvements, at best. However, PPIs may be more effective and should be the first line of therapy in patients in whom reflux-related laryngeal signs and symptoms are suspected.[104,105] Clinical response rates ranging from 60% to 98% have been reported with medical therapy. However, there is a lack of consensus on dosing, frequency, and duration of therapy in this group of patients. Initial aggressive therapy with twice-daily dosing followed by tapering to once-daily in patients showing response to therapy is the treatment approach currently recommended (see Fig. 72-34).

The negative results for PPI therapy obtained by placebo-controlled studies in this field[106] reflect the lack of a standard in identifying patients with a true GERD-related cause for their laryngeal signs and symptoms. Nonetheless, results of open-label studies suggest that PPIs may be more effective than H_2 blockers and should be the first line of therapy in patients suspected of having reflux-related laryngeal signs and symptoms.[107,108]

Asthma

There is a clear association between asthma and GERD. Approximately 70% to 80% of patients with asthma have GERD.[109-111] The two major pathophysiologic mechanisms proposed for acid-induced asthma are (1) proximal esophageal reflux leads to microaspiration/bronchospasm, and (2) a vagally mediated esophageal-bronchial reflex results in bronchospasm.[112] Patients with adult-onset asthma, no family history of asthma or atopy, and heartburn, especially if it precedes the onset of asthma, may have GERD-related asthma. Similarly, wheezing that is exacerbated by meals, exercise, or the supine position and nocturnal wheezing may be GERD related.[113] As with laryngitis, diagnostic testing with ambulatory pH monitoring for asthma possibly related to GERD is controversial, especially because vagally mediated bronchospasm may not be associated with proximal reflux. Clinical data, based on meta-analysis, suggest that treatment of GERD in patients with asthma usually improves respiratory symptoms in 69% of patients and reduces asthma medication use by 62%.[109,112] However, objective improvements in pulmonary function tests have not been consistently reported. In clinical practice, most patients with asthma are treated with a PPI to suppress GERD and possibly help with control of GERD and asthma symptoms.

Chest Pain

Noncardiac chest pain has been a clinical conundrum for decades. Patients classically present with recurring angina-like, substernal chest pain for which the cardiac workup results are negative. Noncardiac chest pain may have a pulmonary, musculoskeletal, or esophageal cause, with the esophagus often implicated as the culprit. The primary esophageal cause is GERD, present in 40% to 60% of patients.[113] Once cardiac disease is ruled out, the most cost-effective initial therapy is a trial of PPIs for 3 months (see Fig. 72-34). One study reported a 92% rate of response, defined as more than 50% improvement in symptoms, in patients with noncardiac chest pain undergoing PPI therapy.[114] Another prospective placebo-controlled study in 36 patients with noncardiac chest pain and GERD demonstrated a reduction of chest pain score in 81% of the treated group, compared with 44% in the placebo group.[115] Endoscopy has a limited role in noncardiac chest pain. The prevalence of erosive esophagitis in patients with noncardiac chest pain is less than 10%.[116] Endoscopy is indicated only if there are other symptoms, such as dysphagia, odynophagia, and weight loss, and in patients with chronic reflux symptoms.

Chronic Cough

GERD is the third most common cause (after postnasal drip and asthma) of chronic cough, which is defined as cough duration greater than 3 months, accounting for 21% of cases of chronic cough.[117] The pathophysiology of GERD-related cough includes both irritation of the upper respiratory tract (with or without aspiration) and stimulation of an esophageal-bronchial cough reflex. Patients with chronic cough from GERD have normal chest radiograph findings, are nonsmokers, are not taking medications known to cause cough (such as angiotensin-converting enzyme inhibitors), and have had no response to treatment for asthma and postnasal drip. Between 43% and 75% of patients with GERD-related cough have no typical reflux symptoms.[117,118] The best initial evaluation is a trial of PPI therapy, which must be maintained for 3 months because GERD-related cough can take this long to resolve (see Fig. 72-34).[119] Despite the limitations noted previously, 24-hour pH monitoring may be helpful in the management of GERD-related cough. It also allows temporal correlation between reflux events and cough. If the cough is produced by GERD, the pH drop should occur simultaneously or within 5 minutes after a reflux episode.[118,120] On the other hand, cough preceding a pH drop suggests secondary reflux. Patients who have normal pH study results with a poor relationship to symptoms have no response to acid suppression, and GERD-related cough is excluded. Alternatively, a positive pH study result does not adequately predict response to therapy. In one study of patients with chronic cough and abnormal pH testing results, only 35% had relief with sustained acid suppression.[121]

Dental Erosion

Dental erosion is a loss of tooth structure secondary to a chemical rather than bacterial cause. An association of dental erosion with GERD has

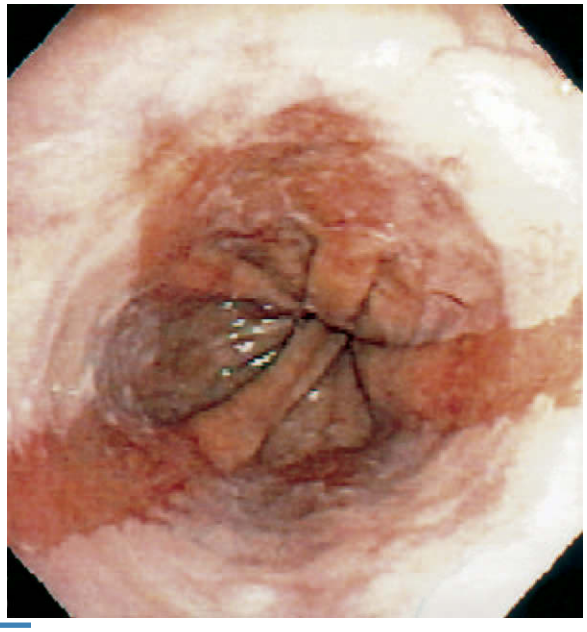

Figure 72-35. Short-segment Barrett's esophagus. "Tongues" of red columnar mucosa extend less than 3 cm above the gastroesophageal junction.

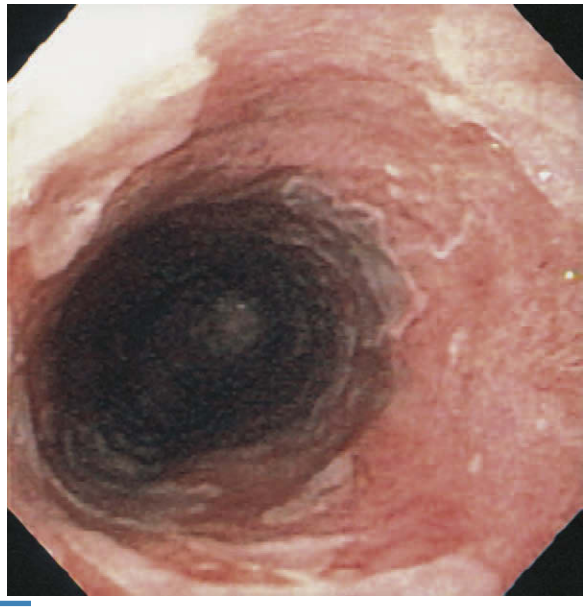

Figure 72-36. Long-segment Barrett's esophagus. The columnar mucosa extends longer than 3 cm above the gastroesophageal junction. Islands of normal squamous mucosa are present within the Barrett's metaplasia.

been demonstrated, and thus dental erosions are considered an atypical expression of GERD. The reported prevalence of dental erosions in patients with GERD has varied from 17% to 68%.[122] The pathophysiology is simple: Chronic exposure to acid can lead to loss of enamel and tooth substance. This complication of GERD is important to recognize because treatment can limit the damage. In addition, referral to a dentist can lead to prompt diagnosis and treatment of dental lesions and institution of preventive dental therapy.

Barrett's Esophagus

Barrett's esophagus is a potentially serious complication of long-standing GERD. Barrett's esophagus is present when the normal stratified squamous epithelium of the distal esophagus has been replaced by intestinal columnar metaplasia. It is the most significant outcome of chronic GERD and predisposes to the development of esophageal adenocarcinoma.

Barrett's esophagus is suspected endoscopically when the pale pink squamous mucosa of the distal esophagus is replaced to various length with salmon-pink columnar mucosa (Figs. 72-35 and 72-36). In Barrett's esophagus, the squamocolumnar junction is displaced proximal to the GEJ, and the diagnosis is confirmed with a biopsy finding of intestinal metaplasia, which is different from normal esophageal mucosa lined by stratified squamous mucosa (Figs. 72-37 and 72-38). Intestinal metaplasia is characterized by mucin-containing goblet cells, which can be detected by routine hematoxylin and eosin stain or accentuated with an alcian blue stain. Barrett's esophagus may be divided into short segment (SSBE) and long segment (LSBE) types (see Figs. 72-35 and 72-36) according to whether the metaplasia is longer or shorter than 3 cm. It is more common to find to dysplasia and cancer in a patient with LSBE, but patients with SSBE are also at increased risk.

It is estimated that 6% to 12% of patients undergoing endoscopy for GERD are found to have Barrett's esophagus.[123] The risk is highest in the older white males. Unfortunately, most cases of Barrett's esophagus go undetected in the general population, and it is estimated that for every known case of Barrett's, 20 cases are not identified.[124] Although there are no specific symptoms related to Barrett's esophagus, it is clearly associated with more severe gastroesophageal reflux. Patients with this disorder tend to have reflux at a younger age, have a long duration of reflux symptoms, are more likely to have nocturnal symptoms and hiatal hernias, and have increased complications from GERD,

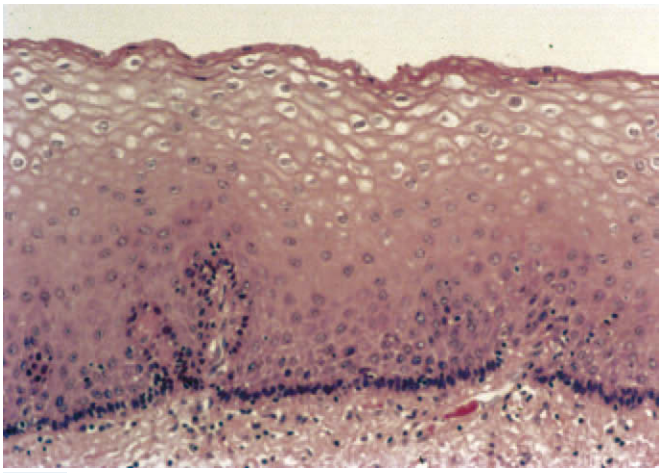

Figure 72-37. Histologic appearance of normal esophagus with stratified squamous epithelium.

such as esophagitis and strictures. However, some patients have impaired sensitivity to acid and their symptoms are no worse than those of uncomplicated GERD. Thus it is recommended that patients with prolonged GERD symptoms, especially middle-aged white men, undergo endoscopic screening for Barrett's esophagus.[125]

If Barrett's esophagus is confirmed, these patients require continued endoscopic surveillance to detect the development of dysplasia and adenocarcinoma. The risk of esophageal adenocarcinoma in Barrett's esophagus is approximately 0.5% annually.[126] The goal of surveillance is to detect cancer at an earlier and potentially curable stage. Several retrospective studies demonstrate that for patients with Barrett's esophagus in whom adenocarcinoma was detected in a surveillance program the cancer is detected at an earlier stage and 5-year survival is better than for similar patients not undergoing routine surveillance.[127-129] Current endoscopic surveillance guidelines suggest 4-quadrant biopsies at 2-cm intervals along the entire length of Barrett's esophagus every 3 years.[125] Special attention should be paid to any and all mucosal

Figure 72-38. Histologic appearance of distal esophageal biopsy specimen showing goblet cells diagnostic of Barrett's metaplasia.

Table 72-2

Surveillance of Barrett's Metaplasia

Dysplasia	Confirmation	Intervention
None	Two EGDs with four-quadrant biopsy specimens every 2 cm	Surveillance endoscopy every 3 years
Low-grade	Highest grade on repeat EGD with biopsy remains low	Surveillance endoscopy every year until no dysplasia
High-grade	Repeat EGD with four-quadrant biopsy specimens every cm Expert pathologist confirmation	Focal high-grade dysplasia: surveillance endoscopy every 3 months Multifocal high-grade dysplasia: esophagectomy, ablation therapy, or esophageal mucosal resection

EGD, esophagogastroduodenoscopy.

abnormalities. Even with this extensive biopsy protocol, there is potential for sampling error because the distribution of dysplasia and cancer is variable. Surveillance endoscopy should not be performed until any active inflammation of GERD is controlled, because landmarks are more difficult to identify in the presence of inflammation, and reparative changes make interpretation of biopsies for dysplasia difficult.

Surveillance biopsy specimens are examined for the presence and degree of dysplasia. Dysplasia should be categorized on the basis of expert consensus into one of the following categories: (1) negative for dysplasia, (2) indefinite for dysplasia, (3) low-grade dysplasia, (4) high-grade dysplasia, and (5) carcinoma.[130,131] Surveillance intervals for Barrett's esophagus are based on the presence and extent of dysplasia, as outlined in the updated practice guidelines of the American College of Gastroenterology (ACG) (Table 72-2).[125] Patients with no evidence of dysplasia on two consecutive biopsies can be followed every 3 years. Those in whom low-grade dysplasia is the highest grade after follow-up endoscopy with concentrated biopsies in the area of dysplasia should be followed annually until there is no dysplasia. The natural history of low-grade dysplasia is variable, but the variability may in part be due to interobserver variability in establishing the diagnosis. In one study of patients with low-grade dysplasia who were followed up for a mean of 26 months, 28% progressed to have high-grade dysplasia or adenocarcinoma, 62% had regression of the dysplasia, and 12% continued to have low-grade dysplasia.[132]

High-grade dysplasia is a concerning finding that requires further investigation. Unsuspected carcinoma has been detected in esophagectomy specimens in approximately 40% of patients with high-grade dysplasia.[133] On the other hand, progression to adenocarcinoma can take many years and is not inevitable. Studies have shown variable rates of progression to cancer, as high as 59% at 5 years and as low as 20% at 7 years.[134,135] Given these facts, the treatment of high-grade dysplasia is controversial. It is essential that an expert gastrointestinal pathologist confirm that high-grade dysplasia is present.[125] Focal high-grade dysplasia may be followed with intensive surveillance (3-month intervals), and intervention should be considered in patients with multifocal disease. Intervention may involve esophagectomy, mucosal ablation with photodynamic therapy, or endoscopic mucosal resection for mucosal irregularities.

Neoplasia

Neoplasia in the esophagus is relatively uncommon but when present is typically malignant. Approximately 12,000 cases of esophageal carcinoma occur in the United States each year.[136] The two main culprits are esophageal squamous cell carcinoma and esophageal adenocarcinoma. More than half the U.S. cases are now adenocarcinoma, which has been increasing in frequency dramatically over the past half-century.

Although the two malignancies have similar presentations and staging, their epidemiologic patterns are quite different. Squamous cell carcinoma (SCC) of the esophagus is typically a disease of African-American men and is associated with alcohol and tobacco abuse. Patients with a history of caustic esophageal injury are also clearly at increased risk. Other conditions, including achalasia, Plummer-Vinson syndrome, tylosis, and a history of head and neck SCC, may also confer increased risk. Esophageal dysplasia and SCC have also been associated with human papillomavirus. On the other hand, adenocarcinoma is predominantly a disease of white men and has a well-documented association with GERD and Barrett's esophagus, as discussed previously.[137] The midesophagus is the most common site of SCC, followed by the distal esophagus, and then the proximal esophagus, whereas adenocarcinoma occurs predominantly in the distal esophagus and at the GEJ (Fig. 72-39).

Patients with esophageal malignancy typically present with rapidly progressive solid food dysphagia secondary to mechanical obstruction. Less commonly, patients may present with odynophagia, iron deficiency, or hoarseness from recurrent laryngeal nerve injury. Up to 75% of patients experience weight loss prior to presentation. SCC is an aggressive locally invasive malignancy, and complications related to local invasion are common. These include tracheoesophageal fistulas and recurrent laryngeal nerve injury with vocal cord paralysis. Distant metastases occur to the lung, liver, bone, and brain. Adenocarcinomas, although not as locally invasive, often have lymphatic and liver metastases. Most patients have advanced disease at the time of presentation because the esophagus has a rich lymphatic supply extending into the lamina propria.

Once a malignancy has been diagnosed by endoscopy with biopsy, rigorous staging is employed. The stage of the disease at diagnosis determines outcome and treatment options. Staging is accomplished through a combination of computed tomography and endoscopic ultrasonography. Computed tomography can accurately identify metastatic disease, but evaluation of the depth of invasion is best accomplished by endoscopic ultrasonography. Staging is based on the TNM classification (Box 72-3).[138] Patients who have early stage disease, namely T1 or T2 without nodal or metastatic disease, can be treated with surgery alone. Patients with more advanced disease, such as T3 or N1, may benefit from neoadjuvant chemotherapy/irradiation before surgical

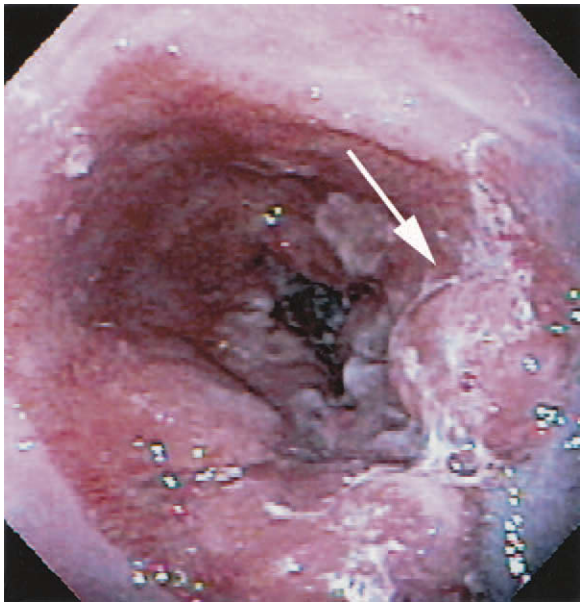

Figure 72-39. Esophageal adenocarcinoma arising in Barrett's esophagus. *Arrow* indicates the nodular mass.

Box 72-3

TNM Staging Classification for Esophageal Cancer

Primary Tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1a: Tumor invades lamina propria
T1b: Tumor invades submucosa
T2: Tumor invades muscularis mucosa
T3: Tumor invades adventitia
T4: Tumor invades adjacent structures

Regional Lymph Nodes (N)

NX: Lymph nodes cannot be assessed
N0: No evidence of lymph node metastasis
N1: Lymph node metastasis

Distant Metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No evidence of distant metastasis
M1: Distant metastasis

resection. Those with late stage disease receive palliative treatment. Palliative endoscopic measures include repeated dilation, laser/photodynamic therapy ablation, esophageal stent placement, and percutaneous endoscopy gastrostomy tube placement.

Under most circumstances, esophageal cancer is identified at a late, incurable stage. Five-year survival rates for SCC are predictably less than 10%. Esophageal adenocarcinoma has a similar poor prognosis, with 5-year survival rates below 15%.[139] Survival is stage dependent, T1 lesions being associated with a 5-year survival of 46%, and T4 lesions with a survival of 7%.[140] There is some hope that with increased screening and surveillance for Barrett's esophagus in patients with GERD, adenocarcinoma can be detected at an earlier and potentially curable stage.

Figure 72-40. Midesophageal traction diverticulum. The true esophageal lumen is located inferiorly. Traction diverticula are the only true diverticula that form in the esophagus.

Esophageal Diverticula

An *esophageal diverticulum* is a sac that protrudes from the esophageal wall. As in the rest of the gastrointestinal tract, a true diverticulum is one that contains all layers of the wall. A false diverticulum contains mucosa and submucosa that have herniated through the muscular wall. Esophageal diverticula are most practically classified anatomically into the following four categories: Zenker's diverticula, midesophageal diverticula, epiphrenic diverticula, and intramural pseudodiverticulosis.

Zenker's diverticulum, first described in 1877, is often referred to as an esophageal diverticulum.[141] However, it is located proximal to the esophagus, above the UES, and should be considered a hypopharyngeal diverticulum. Zenker's diverticula are believed to form as a result of an area of weakness, Killian's triangle, which exists between the cricopharyngeal sphincter and the inferior pharyngeal constrictor muscle. The primary abnormality that leads to the development of the diverticula is incomplete relaxation of the UES. An association between Zenker's diverticulum and reflux has been suggested but not confirmed. Typical symptoms include oropharyngeal dysphagia, regurgitation of undigested food, halitosis, cough, and aspiration pneumonia. The barium swallow study is an excellent test for the diagnosis of Zenker's diverticulum. Many small diverticula are asymptomatic, but symptomatic patients with large diverticula should be offered treatment. The classic treatment is an open surgical resection of the diverticulum with division of the cricopharyngeus muscles.[142] Another option for extremely large diverticula is diverticulopexy, or suspension of the diverticulum in a cranial direction.

Midesophageal diverticula are most commonly asymptomatic and, as their name implies, occur in the mid-esophagus (Fig. 72-40). Traction diverticula form as a result of external pulling of the esophageal wall by neighboring inflammatory or fibrotic tissue, such as adjacent tuberculous mediastinitis.[143] Traction diverticula are located in the middle third of the esophagus. Midesophageal traction diverticula are the only true diverticula in the esophagus. A second type of midesophageal diverticulum is a pulsion diverticulum, which results from internal forces applied to a portion of the esophageal wall. These often relate to motility disorders, and their pathogenesis is similar to that of Zenker's and epiphrenic diverticula.

Epiphrenic diverticula, which are located near the diaphragmatic hiatus, occur in the distal esophagus near the LES (Fig. 72-41). These diverticula are often the result of a motility disorder, such as achalasia or diffuse esophageal spasm.[144,145] It is imperative to obtain manometric studies in patients with epiphrenic diverticulum to rule out an associated motility disorder. Most diverticula are asymptomatic, but

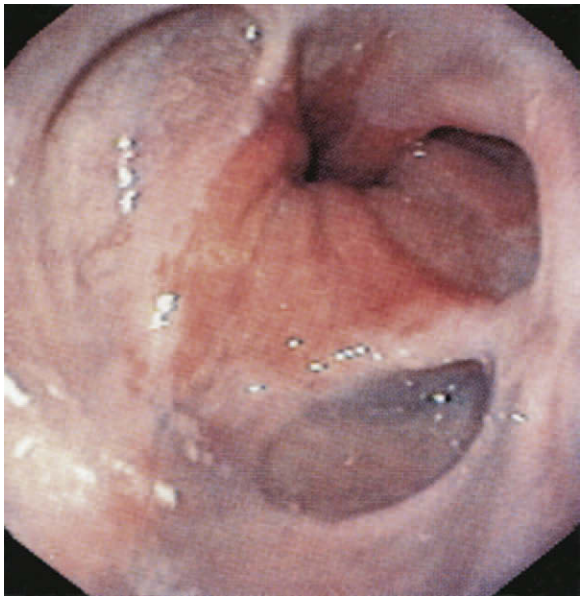

Figure 72-41. Multiple epiphrenic diverticula. Epiphrenic diverticula are located in close proximity to the gastroesophageal junction. These diverticula are strongly associated with motility disorders such as achalasia.

occasionally chest pain or regurgitation can be prominent symptoms. Treatment consists of managing the underlying motility disorder and, for symptomatic diverticula, diverticulotomy with or without myotomy.

Esophageal intramural pseudodiverticula are multiple small outpouchings apparent on barium swallow study or endoscopy (Fig. 72-42). These rare outpouchings are not diverticula but rather dilated submucosal glands. The etiology is not clear, but they are associated with acid reflux, esophageal strictures, and esophageal cancer.

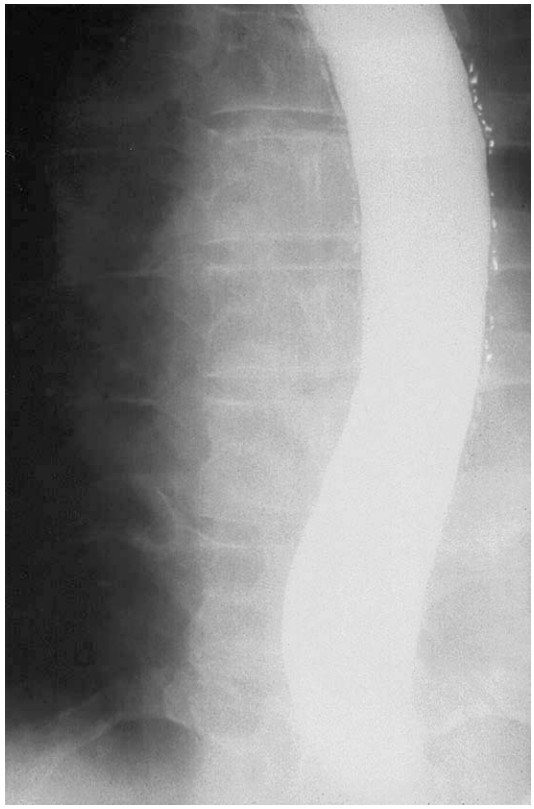

Figure 72-42. Esophageal pseudodiverticulosis. Multiple small outpouchings can be seen emanating from the esophagus. These pseudodiverticula are actually dilated submucosal glands.

Foreign Body

Foreign bodies in the gastrointestinal tract are a common clinical problem. Ingestion of a foreign body, either accidental or intentional, is common in pediatric patients, psychiatric patients, and prisoners. Elderly patients with loose-fitting dentures also pose a unique risk. Management principles are based on the nature of the ingested foreign body and its location within the gastrointestinal tract. The esophagus is one of the foreign body locations for which intervention is often required. Underlying alterations in the lumen of the esophagus play an important role in the risk that a swallowed object may become lodged. The esophagus has several areas of physiologic narrowing where a foreign body may become impacted: the UES, the level of the aortic arch, and the diaphragmatic hiatus/LES. The key to the management of foreign bodies is understanding that different foreign bodies require different interventions. It is important to distinguish a true foreign body from a food impaction.

Food impactions tend to occur in adults with benign structural abnormalities of the esophagus. Patients usually present with the sudden onset of dysphagia in relation to swallowing a large piece of beef, hot dog, or bread. Patients may complain of chest pain and difficulty swallowing their own saliva. Typically, the patient has a history of intermittent solid food dysphagia. Management includes obtaining anteroposterior and lateral chest radiographs to assess for free air and look for bones in the food bolus. A trial of pharmacologic therapy with glucagon, 1 to 2 mg intravenously, which relaxes the LES, can be performed but is rarely successful in relieving a food impaction. The primary therapy for food impaction is prompt endoscopy. If the patient is able to manage his or her own saliva and is comfortable, endoscopy can be performed as a nonurgent procedure, but preferably within 12 hours.[146,147] There is no role for barium swallow studies, except to confirm disimpaction. Endoscopic removal of impacted food can be a difficult procedure, because usually some digestion has taken place and the impacted food cannot be removed easily in its entirety. Although blind pushing with the endoscope is discouraged, the food bolus often passes with a gentle push from the endoscope. If the endoscope can be maneuvered around the impaction and luminal patency confirmed, it is reasonable to attempt once more to push the bolus into the stomach. If the bolus cannot be safely pushed into the stomach, it must be removed with the endoscope. This may require piecemeal extraction with the use of grasping forceps and multiple passes of the endoscope. Other equipment, including snares, nets, and baskets, can also be used under direct visualization. Because of the need for multiple passes and to protect the airway, an overtube is often used. Sometimes, once the bolus has been debulked with a forceps, it passes into the stomach with gentle pressure.

After removal of the foreign body, the esophagus should be assessed for underlying pathology, which is present in approximately 90% of patients.[148,149] It can be difficult to assess because usually some inflammation, edema, and erythema are present. If a benign structural abnormality is present, dilation should be arranged at a later date. If only minimal inflammatory change is present, dilation may be performed safely in the same session.

True foreign bodies are classified according to their physical characteristics: small and blunt, sharp or pointed, or long. Plain neck, chest, and abdominal radiographs are essential to evaluate for perforation and to attempt to localize a foreign body. Any foreign body in the esophagus must be removed because pressure necrosis with resultant perforation might otherwise occur. Sharp or long objects, which carry a risk of perforation of 15% to 35%, should be removed regardless of location.[150] Conversely, most small blunt objects that have passed the esophagus will also pass through the remainder of the gastrointestinal tract without incident.

Small blunt objects, such as coins, can become lodged at areas of physiologic or pathologic narrowing even if they are smaller than the usual esophageal diameter of 20 mm. Small objects can be removed endoscopically from the esophagus, with use of a variety of specialized

Box 72-4

Medications Implicated in Pill-Induced Esophagitis

Alendronate
Aspirin
Captopril
Clindamycin
Doxycycline
Ferrous sulfate
Glucocorticoids
Nonsteroidal anti-inflammatory drugs
Oral contraceptives
Phenytoin
Potassium chloride
Quinidine
Tetracycline
Verapamil
Vitamin C

forceps designed for foreign body extraction. As with food impaction, an overtube is often required for airway protection. In children, the procedure is usually performed with the use of general anesthesia and endotracheal intubation to protect the airway.

The presence of a sharp or long foreign body in the esophagus is an emergency, whereas the presence of a foreign body that has passed into the stomach can be addressed urgently. In any attempt to remove a sharp foreign body endoscopically, the object must be grasped from its blunt end, with its sharp end directed distally,[151] to minimize the risk of perforation. Many sharp objects pass through the gastrointestinal tract without difficulty. If the object is not within reach of the endoscope, the patient should be monitored closely with radiographs, and surgery should be considered if there is evidence of perforation, obstruction, or nonprogression.

Pill-Induced Injury

Pill-induced injury to the esophagus is an underappreciated entity. It is estimated that well over 70 drugs are capable of injuring the esophagus.[152] Drugs commonly associated with pill-induced injury are potassium chloride tablets, doxycycline, quinidine, nonsteroidal anti-inflammatory drugs, iron, and alendronate (Box 72-4). Pills damage the esophagus by various mechanisms, such as acidity, size, and contact time with esophageal mucosa. There is a wide spectrum of injury, from acute self-limited esophagitis to refractory strictures. The typical sites of pill-induced injury are at the level of the aortic arch and the distal esophagus, where there is anatomic narrowing. Most patients with pill-induced esophageal injury do not have other esophageal problems, such as strictures and motility disorders. They typically present with chest pain and odynophagia. Dysphagia usually reflects a stricture within the inflammatory changes. In a patient with symptoms, the diagnosis is often made by endoscopy. Mucosal changes found at endoscopy can also vary widely; they include ulcer formation, plaques resembling *Candida* infection, and strictures. Management can be difficult. It involves repeated dilations for strictures and avoidance of the offending agent. To prevent further damage, all medicines should be taken in liquid form. All medications should be taken with sufficient fluids, and the patient should remain upright for 15 to 30 minutes after swallowing pills. Symptoms and endoscopic findings usually resolve within weeks after the patient stops taking the culprit pill.[152]

Infectious Esophagitis

Infectious esophagitis is common, especially in immunosuppressed hosts such as patients with human immunodeficiency virus, patients with transplants, and patients undergoing chemotherapy. The cardinal symptom of infectious esophagitis is odynophagia. However, immunodeficient patients can present with a variety of symptoms, including heartburn, nausea, fever, and bleeding. The three most common causes of infectious esophagitis are *Candida albicans*, cytomegalovirus (CMV), and herpes simplex virus (HSV).

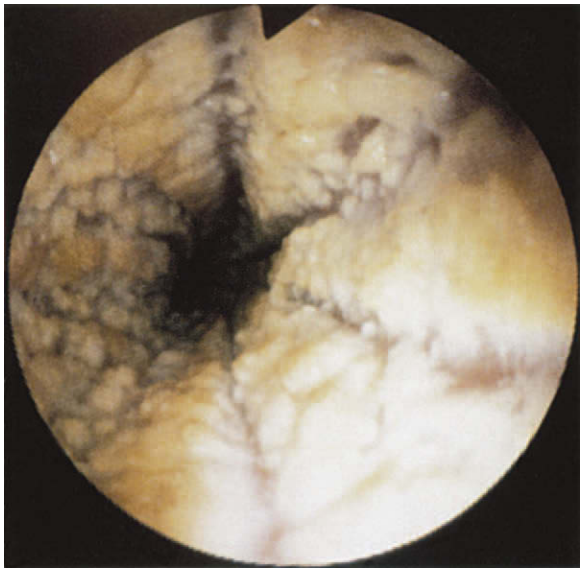

Figure 72-43. Endoscopic view of severe *Candida* esophagitis. The esophageal lumen is obscured by thick adherent white-yellow plaques.

C. albicans, which is normally found in oral flora, is the most common cause of infectious esophagitis in immunocompromised hosts including those with diabetes mellitus, alcoholics, and users of glucocorticoids, in addition to those mentioned previously.[153] Other predisposing factors are advanced age, hypochlorhydria, and motility disorders. Oral thrush, if present, is a helpful diagnostic finding, because 75% of patients with esophageal symptoms also have candidal esophagitis.[63,154] Many patients at risk are treated empirically with antifungal medications, but a definitive diagnosis is made by endoscopy with biopsy and brushings. The classic endoscopic appearance consists of adherent white to pale yellow plaques (Fig. 72-43). It should be noted that this appearance is not pathognomonic for *Candida*, because it can occur with any cause of esophagitis. Examination of brushings of the plaques reveals hyphae and budding yeast in the presence of *Candida*. Treatment consists of antifungal therapy, most commonly with fluconazole, 100 to 200 mg per day for 10 to 14 days. In patients with only mild immunologic deficiencies, the topical antifungals clotrimazole and nystatin are reasonable alternatives. These agents are virtually devoid of side effects but require administration four or five times a day. Patients who are granulocytopenic and more severely compromised may need treatment with amphotericin B to prevent disseminated candidal disease.

CMV is another common cause of esophagitis. This virus infects the submucosal fibroblasts and endothelial cells rather than the squamous epithelium. Because CMV may be a more systemic infection, patients often present with several gastrointestinal symptoms, including abdominal pain, nausea, and vomiting, in addition to painful swallowing. The typical endoscopic findings are serpiginous erosions and ulcers, which may coalesce and form deep, larger ulcers (Fig. 72-44). Tissue diagnosis is needed to confirm the infection. Biopsy specimens should be taken from the bases of the ulcers because CMV infection is subepithelial.[155] The characteristic histologic findings of CMV-infected cells are intranuclear and cytoplasmic inclusions and a halo surrounding the nucleus. Tissue from the ulcer base should also be sent for viral culture, which is more sensitive than histology alone. Both ganciclovir and foscarnet are treatment options. Most immunocompromised patients require maintenance therapy for several weeks after an initial 2-week regimen at the full dose.

Herpes simple virus esophagitis occurs in both immunocompetent and immunocompromised hosts. Most often this is reactivation of

latent viral infection, but it can occur with primary HSV infection as well. The diagnosis is best made by endoscopy. The characteristic early findings include esophageal vesicles, which rupture to create ulcers with raised edges (Fig. 72-45). Unlike CMV, HSV infects epithelial cells. Therefore, biopsy specimens must be taken from the ulcer margins, where squamous mucosa is present. Histologic examination demonstrates multinucleated giant cells and ground-glass intranuclear inclusion bodies, but viral culture is more sensitive for diagnosis (Fig. 72-46). Treatment consists of intravenous acyclovir, 5 to 10 mg/kg every 8 hours, until the patient is able to tolerate oral therapy. Duration of treatment should be 7 to 10 days.

Other infections can rarely cause esophagitis. They include varicella-zoster virus (human herpesvirus 3), Epstein-Barr virus, human papilloma virus, bacteria, diphtheria, syphilis, and human immunodeficiency virus. Of these, human immunodeficiency virus is the most common and can lead to aphthous ulceration in the absence of any pathogens. After other infectious etiologies are ruled out in patients with HIV, the patients are treated with prednisone with good response.

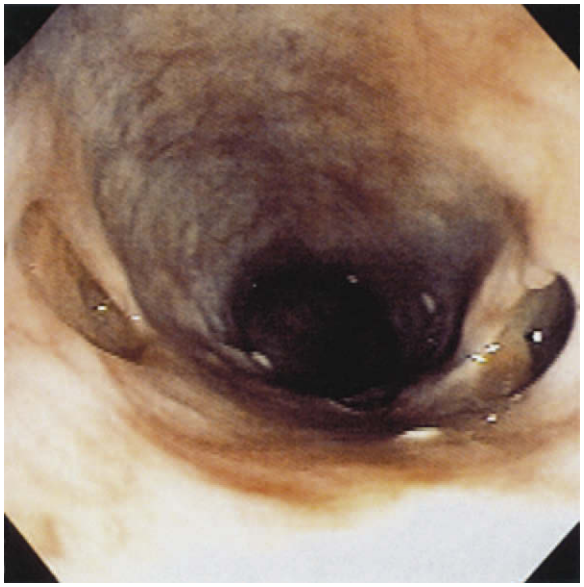

Figure 72-44. Endoscopic view of cytomegalovirus esophagitis. Several deep ulcers are present in the midesophagus. Biopsy specimens should be taken from the ulcer base to make the diagnosis.

Caustic Injury

Caustic ingestion can result in severe injury to the esophagus and stomach. Most ingestions occur accidentally in children, and the remainder in suicidal, psychotic, or alcoholic adults. It is estimated than more than 5000 caustic ingestions occur annually in the United States, and the incidence is rising.[156] A variety of chemicals can be ingested, but strong alkali and acids are most likely to produce injury. Strong alkali is contained in drain cleaners and other household cleaning products. *Lye* is a generic term for a strong alkali, usually sodium or potassium hydroxide, used in these cleansing agents. Injury to the esophagus is more severe with alkali substances than with acid substances,[157] because alkaline materials produce liquefactive necrosis and result in rapid and deep tissue injury. In the stomach, partial neutralization of the ingested alkali by gastric acid results in a more limited injury. Acidic agents produce a coagulation necrosis in the esophagus that may limit penetration and injury.

The clinical features of caustic ingestions vary widely. Early signs and symptoms often do not correlate with the severity and extent of tissue injury.[158,159] Patients may complain of oropharyngeal, retrosternal, or epigastric pain, dysphagia or odynophagia, or hypersalivation. Persistent severe pain may indicate esophageal perforation and mediastinitis. Hoarseness, stridor, and respiratory difficulties are uncommon but can result from burns of the epiglottis and larynx. All patients should be examined for evidence of oropharyngeal injury, and if airway compromise is present, intubation may be necessary. The absence of oropharyngeal burns does not preclude the presence of esophageal or gastric injury. Thus, upper endoscopy should be performed during the first 24 to 48 hours after ingestion in order to evaluate the extent of esophageal and gastric damage, which will establish prognosis and guide therapy. A grading system for esophageal injury to predict subsequent clinical outcome has been developed (Table 72-3).[160]

Patients with grades 1 and 2A injury have an excellent prognosis without acute morbidity or chronic stricture formation. These patients can be started on a liquid diet and advanced to a regular diet in 1- to 2 days. Strictures develop in 70% to 100% of patients with grade 2B or 3A injury. Grade 3B carries a 65% early mortality rate and high need for esophageal resection. Despite this poor prognosis, there is no evidence that medical therapy, such as antibiotics and steroids, is of any

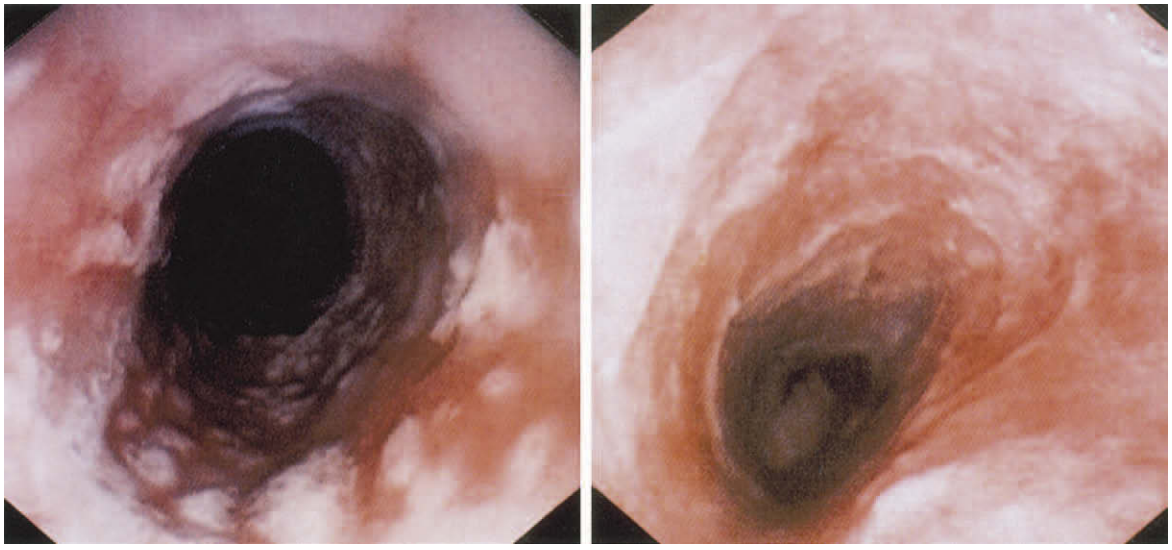

Figure 72-45. *Left*, Early herpes simplex virus esophagitis. Multiple small vesicles and surrounding ulceration. Biopsy specimens should be taken from the squamous epithelium at the edge of an ulcer to make the diagnosis. *Right*, Late herpes simplex virus esophagitis. Vesicles have ruptured to form large shallow ulcers. The esophagus is significantly denuded of squamous epithelium.

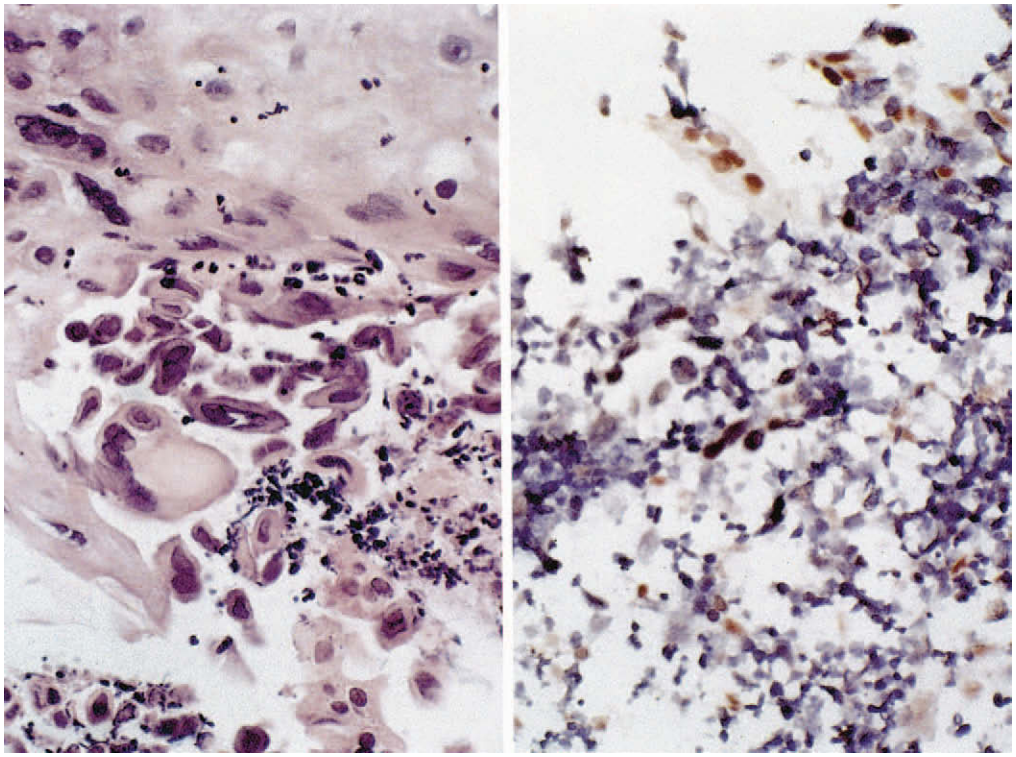

Figure 72-46. Histologic appearance of herpes simplex virus esophagitis. Note the multinucleated giant cells (*left*) and ground-glass intranuclear inclusion bodies (*right*).

Table 72-3

Grading of Caustic Esophageal Injury

Grade	Feature(s)
0	Normal
1	Mucosal edema and erythema
2A	Superficial ulcers, bleeding, exudates
2B	Deep focal or circumferential ulcers
3A	Focal necrosis: deep ulcers with brown, black, or gray discoloration
3B	Extensive necrosis
4	Perforation

Figure 72-47. Tight esophageal stricture resulting from caustic ingestion.

benefit. In-hospital observation for perforation is recommended. If the patient with caustic injury is able to swallow without pain or vomiting, liquids can be started after 48 hours.

If esophageal strictures form, they require esophageal dilation. Esophageal strictures are usually located where caustic agents pool, at the cricopharyngeus, the level of the aortic arch, and the LES. These caustic strictures tend to be longer and tighter than benign strictures of other causes (Figs. 72-47 and 72-48). Thus, they are often refractory to and have a higher rate of complications with dilation. In fact, a significant portion (10% to 50%) may require surgery because of lack of response to dilation.

The other late complication of caustic esophageal injury is SCC of the esophagus. It is estimated that there is more than a thousand-fold increase in the risk of SCC after caustic injury.[161] The mean time to formation of cancer is approximately 40 years after ingestion. This fact has led some groups to suggest endoscopic surveillance for SCC in patients with a distant history of caustic ingestion.[162]

Esophageal Manifestations of Systemic Disease

A variety of systemic diseases can affect the esophagus. Connective tissue diseases, diabetes mellitus, thyroid disease, amyloidosis, and Behçet's disease are the more common systemic disorders with esopha-

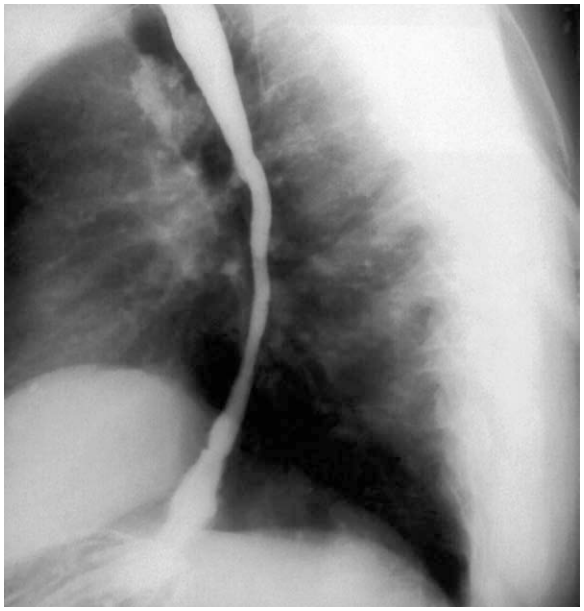

Figure 72-48. Barium esophagram of the stricture shown in Figure 72-44. The stricture extends the entire length of the esophagus.

geal involvement. The severity and frequency of esophageal symptoms vary both within and between these diverse systemic diseases.

Scleroderma, or progressive systemic sclerosis (PSS), reliably has significant esophageal involvement. Gastrointestinal involvement occurs in 90% of patients with PSS, and approximately 50% of these patients experience serious symptoms.[163] Patients with esophageal involvement present with heartburn, regurgitation, and dysphagia. PSS is characterized by small-vessel vasculitis and proliferation of connective tissue with fibrosis of multiple organs. The fibrosis predominantly affects smooth muscle in the gastrointestinal tract, leading to motility abnormalities. In patients with PSS, there is progressive loss of peristalsis in the esophagus and eventual ablation of the LES pressure. This process yields the classic manometric findings of aperistalsis in the distal two thirds of the esophagus and very low LES pressure. Barium esophagrams typically demonstrate a dilated esophagus, a patulous GEJ, and free reflux into the proximal esophagus (Fig. 72-49). Because of the disruption of the antireflux barrier and the inability to clear reflux from the esophagus, patients with PSS are often afflicted with severe, complicated GERD. The sequelae of severe GERD are common: Barrett's metaplasia (up to 37%), esophagitis, and strictures (3% to 42%).[164-166] Dysphagia may result from impaired peristalsis or peptic strictures. Treatment consists of aggressive acid suppression, dilations of strictures, and surveillance of Barrett's esophagus if present. Control of the underlying disease is important but to date is unsatisfactory.

In other connective tissue diseases, including mixed connective tissue disease, inflammatory myopathies, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, esophageal involvement can be a minor manifestation. The myopathies are distinct in that they affect striated muscle with resultant dysfunction in the oropharynx and proximal esophagus and oropharyngeal dysphagia. The other rheumatologic disorders can manifest as hypomotility and, rarely, dysphagia.

Diabetes mellitus is a common disease with potential involvement of many organs in the body, including the stomach and esophagus. Studies have demonstrated predominantly decreased peristalsis and esophageal emptying in diabetic patients with esophageal symptoms. Many patients with diabetes may have gastroparesis, resulting in secondary GERD symptoms. Both the gastric and esophageal changes likely have a neurologic basis. Treatment with promotility agents has been tried for symptomatic patients; it is largely ineffective for the esophageal dysmotility but may help patients with gastroparesis.

Figure 72-49. One view from an upper gastrointestinal radiographic series in a patient with scleroderma. The esophagus is dilated with a patulous gastroesophageal junction. On fluoroscopic imaging, free gastroesophageal reflux was visualized.

Behçet's disease, an idiopathic inflammatory disorder typified by recurrent oral and genital aphthous ulceration, can infrequently involve the esophagus. Esophageal manifestations include ulcerations, erosions, esophagitis, and perforation. When the esophagus is involved, there is usually small bowel or colonic ulceration as well, making this disorder difficult to distinguish from Crohn's disease.

Hypothyroidism is a rare cause of dysphagia. Manometry has documented decreased amplitude and velocity of peristalsis, which improve with thyroid replacement therapy. Esophageal manometric abnormalities may also be seen in up to 60% of patients with amyloidosis.[167] Aperistalsis, hypomotility, incompletely relaxing LES, and decreased LES pressure have all been reported. It is believed this dysmotility results from neurogenic dysfunction rather than amyloid deposition in the esophageal wall. Despite these common manometric findings, esophageal symptoms are rarely prominent in amyloidosis.

Cutaneous Diseases and the Esophagus

Several dermatologic diseases have been associated with esophageal involvement. The most important dermatologic disorders that involve the esophagus are the blistering skin diseases: epidermolysis bullosa, bullous pemphigoid, cicatricial pemphigoid, and pemphigus vulgaris. Epidermolysis actually consists of several disorders typified by initiation of blisters after minor trauma. Dystrophic epidermolysis bullosa is an inherited disorder with autosomal dominant and recessive forms. Esophageal involvement is more common in the recessive form, with blisters of the skin, mouth, and esophagus developing during childhood. Esophageal bullae result from minor trauma from food and can lead to severe dysphagia and odynophagia. The lesions heal with fibrosis, leading to constriction of the mouth and esophageal strictures, which can potentially lead to malnutrition. Endoscopy is relatively contraindicated because it may cause bullae to form, but it may be necessary for the gentle dilation of strictures. Some patients require esophageal resection and replacement, and others need lifelong parenteral nutrition.

Bullous pemphigoid is the most common bullous skin disease. Patients with this disorder have antibodies to the basement membrane, and histologic examination demonstrates subepidermal bullae. The skin lesions consist of pruritic plaques that evolve into bullae. Esophageal involvement is rare and consists of bullae. Glucocorticoid treatment is effective.

Cicatricial pemphigoid is a bullous disorder involving mucosal surfaces, with a minimum or absence of cutaneous lesions. It involves the esophagus in less than 5% of cases but is less responsive to treatment than bullous pemphigoid. Because these bullae heal by fibrosis as well, endoscopic findings include not only bullae but also webs and strictures, usually in the proximal esophagus. Although steroids may be effective, stricture dilation is often required. Both bullous pemphigoid and cicatricial pemphigoid may predispose to esophageal carcinoma.

Pemphigus vulgaris is characterized by formation of intraepidermal bullae in the skin and mucous membranes. It is an autoimmune disease characterized by antibodies to cell adhesion molecule desmoglein 3 in stratified squamous epithelium. The esophagus is frequently involved, along with the mouth, with bullae and erosions. Glucocorticoid treatment is usually effective.

Lichen planus is a disease characterized by skin papules, and mucosal hyperkeratosis and erosions. Esophageal involvement is unusual but can manifest as strictures and dysphagia.

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CHAPTER SEVENTY-THREE

Transnasal Esophagoscopy

Neil N. Chheda

Gregory N. Postma

Key Points

- Unsedated transnasal esophagoscopy is a well-tolerated, cost-effective, and safe examination.
- The accuracy of the transnasal esophagoscopy examination is similar to that of conventional endoscopic evaluation.
- Common esophageal indications for endoscopy include dysphagia and screening for Barrett's esophagus. Among the extraesophageal indications are head and neck carcinoma screening, laryngopharyngeal reflux, and chronic cough. Esophageal adenocarcinoma is more frequently heralded by extraesophageal symptoms, such as chronic cough, rather than esophageal complaints.
- A multitude of in-office procedures can be facilitated with use of the transnasal esophagoscope.

History

The work of many pioneers has enabled the modern physician to visualize and study the esophagus.[1] Bozzini, in 1806, was the first physician to report the ability to visualize the proximal esophagus.[2] After studying the performances of sword swallowers, Kussmaul performed the first rigid esophagoscopy in 1868. Advances in equipment continued to be made through the work of physicians such as Von Mikulicz (1881, first electrically lighted esophagoscope), Einhorn (1897, distal illumination in an esophagoscope), and Jackson (advances in endoscopic instruments). Interestingly, Jackson did not use anesthesia, general or local, for esophagoscopy of adults.

While advances in equipment, lighting, and optics were being made in rigid instrumentation, a major advance toward flexible esophagoscopy was made through the work of Hirschowitz and associates,[3] who presented the first fiberoptic gastroscope in 1957. Since that time, the examination of the esophagus has been conducted primarily by gastroenterologists with flexible endoscopes and patient sedation. Shaker,[4] a gastroenterologist, published the first report of unsedated transnasal esophagogastroduodenoscopy (EGD) in 1994. Although initially met with limited interest from gastroenterologists, the appeal of unsedated transnasal esophagoscopy (TNE) grew among the otolaryngology community, particularly after the reports of Herrmann and Recio[5] and the live demonstration by Aviv and colleagues[6] in 2001.

Equipment

One of the primary differences between a transnasal esophagoscope and a standard flexible oral esophagoscope is the instrument diameter—3.1 to 5.1 mm versus 10 to 12 mm. Most transnasal endoscopes are able to suction and insufflate air, and contain a working channel. The working channel can be used for passing biopsy forceps or brushes, laser fibers, guidewires for balloon dilators, and the topical application of anesthesia. However, ultrathin transnasal esophagoscopes may lack these capabilities and require an add-on sheath, which may increase the diameter by 1.3 mm. The length of a flexible laryngoscope is 30 to 35 cm, but that of transnasal esophagoscopes is typically at least 60 cm to allow visualization of the entire esophagus, including a retroflexed view of the gastroesophageal junction.

Two main camera systems exist for TNE. The proximal "add-on" camera is familiar to most otolaryngologists who perform endoscopy. Endoscopes utilizing this tool typically lack a working channel and require an add-on sheath. Alternatively, distal videochip technology has emerged, whereby optical impulses are converted to electric signals without the need for optical fibers.[7] A separate video processor is required for visualization in this system (Fig. 73-1).

Tolerance of Unsedated Examination

Historically, examination of the esophagus has been performed with patient sedation. Analyses of the complication patterns during endoscopy reveal that most adverse events are related to sedation. Cardiopulmonary complications account for more than 50% of all reported complications, with the majority being due to aspiration, over-sedation, hypoventilation, vasovagal episodes, and airway obstruction.[8] A 2007 national survey of endoscopists confirmed that unplanned cardiopulmonary events secondary to conscious sedation constitute the majority of endoscopy complications—67% of complications and 72% of mortalities were cardiopulmonary related.[9]

In addition to the medical risks of sedation, economic factors arise. The increased direct costs of conventional esophagoscopy include a longer procedure time, longer recovery time, and the costs associated with the needed medications, sedation, and recovery teams.[10] Unsedated TNE has been found to be up to two thirds less expensive than conventional esophagoscopy.[11,12] Indirect costs accrued with conventional esophagoscopy include the loss of work time for both the patient and an adult for patient transportation. In contrast, with an unsedated examination, patients are able to resume routine daily activities shortly after completion of the study.

Physiologic studies have verified that unsedated esophagoscopy is a safe procedure. In a prospective study, the changes in systolic and diastolic blood pressures, pulse rate, and rate-pressure product, as well as the drop in arterial oxygen saturation experienced by patients who had conventional transoral EGD, were significantly greater than in those undergoing either transnasal or transoral small endoscopy. Between the two small endoscope groups, these same parameters had a significantly greater change in the transoral group than in the transnasal group

Figure 73-1. Video chip transnasal esophagoscope. An add-on camera is not needed with this system.

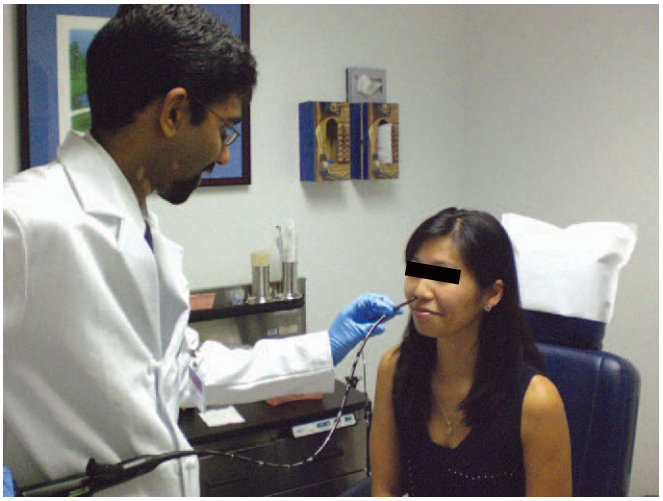

Figure 73-2. Examination technique. The unsedated patient is seated comfortably throughout the entire examination.

at 2 minutes after esophageal intubation.[13] Additional studies have shown that a significant increase in heart rate and a significant decrease in oxygen saturation occur in those undergoing transoral esophagoscopy but not in those undergoing transnasal esophagoscopy.[14]

Although initial patient anxiety is higher before unsedated TNE, numerous studies have demonstrated a very high patient satisfaction rate, usually greater than that for conventional or transoral approaches.[15-18] Crossover studies have shown that in patients who have undergone both sedated and unsedated endoscopy, the unsedated examination was better tolerated.[19] Dumortier and coworkers[20] found that 91% of patients who had undergone unsedated TNE who had also previously had a conventional EGD stated that they preferred the TNE examination. TNE was associated with fewer gagging sensations and was rated with higher patient satisfaction than unsedated transoral examinations.[21-23]

Accuracy of Examination

Dean and associates[24] reported a high degree of correlation between the endoscopic findings (sensitivity 89%, specificity 97%) of TNE examinations and of conventional EGD. Although the biopsy sample size obtained with TNE is generally smaller than that obtained with conventional endoscopy, numerous studies have verified the accuracy of TNE-guided biopsies. In patients with known Barrett's metaplasia, Saeian and colleagues[25] found that the congruence between biopsy samples obtained with conventional endoscopy and those obtained with TNE was 97%. In a crossover study of 121 patients, Jobe and colleagues[26] compared the endoscopic findings and the histologic detection of Barrett's esophagus from biopsy specimens obtained from unsedated TNE and conventional esophagoscopy. A moderate to very good extent of agreement was present for endoscopic findings, such as hiatal hernias and esophagitis, between the two endoscopic modalities. In addition, although the biopsy specimen size was significantly smaller with TNE, there was a moderate extent of agreement in pathologic findings.[26]

Technique

The most important step in performing TNE is proper nasal anesthesia and decongestion. With the patient in a sitting position, the more patent nasal cavity is sprayed with a mixture of a topical anesthetic and decongestant and then packed with a cotton pledget soaked in the same mixture. A topical anesthetic may be administered to the oropharynx. Too much anesthesia may actually make the TNE procedure more difficult owing to the accumulation of secretions in the hypopharynx that may be aspirated and induce coughing.

The endoscope is lubricated and introduced into the naris. It may be passed either along the floor of the nose—the preferred method—or between the middle and inferior nasal turbinates. As the scope approaches the post-cricoid region, the patient's head is flexed toward the chest. The patient performs a swallow as the endoscope is gently introduced into the esophagus. Air insufflation and suction are used, as needed, to improve visualization. The scope is advanced only when the lumen is clearly seen.

The endoscope is advanced into the distal esophagus for visualization of the gastroesophageal junction and the squamocolumnar junction (SCJ), also known as the *Z-line*. The endoscope is advanced more deeply into the stomach and retroflexed to visualize the gastric cardia. The mucosa of the entire esophagus is examined while the instrument is withdrawn. The post-cricoid region is visualized by insufflation of a burst of air as the endoscope is withdrawn from the esophagus (Fig. 73-2).[15]

Normal Findings

The anatomy of the esophagus viewed through a thin endoscope appears different from that obtained through a rigid esophagoscope or a conventional oral esophagoscope.[27] By nature of the smaller size of the scope, TNE does not distort the anatomy of the esophagus, thereby allowing the natural curvatures and external compressions to be easily seen.

Three major curvatures of the esophagus are encountered before the endoscope enters the stomach. At the base of the neck, the esophagus curves to the left with a gentle return to midline at the level of T5. Another left curve is encountered at T7. Finally, an anterior curve occurs in the distal esophagus as it passes through the diaphragm.

Three external compressions are seen during a TNE examination. The first encountered is a pulsatile compression of the left anterolateral wall from the aorta. Approximately 2 cm more distal, the left main bronchus produces an anterior compression. In the distal esophagus, the diaphragm produces a circumferential constriction best visualized by having the patient sniff.

A network of terminal linear vessels can be seen in the distal esophagus that end at the gastric rugae. These vessels do not normally extend below the level of the SCJ. Folds of the gastric rugae form may extend up to 2 cm above the pinch of the diaphragm. Proximal extension of the rugae beyond 2 cm indicates a hiatal hernia. The presence of a hiatal hernia may also be suggested by visualization of a loose diaphragm crus on the retroflexed view.

Esophageal squamous epithelium normally appears as a gray-white color, whereas the gastric columnar epithelium is of a salmon-pink hue. The SCJ occurs at the meeting of the esophageal mucosa and gastric mucosa. An irregularly shaped SCJ may be found and is not always pathologic. The junction of the gastric rugae and the network of terminal linear vessels marks the level of the gastroesophageal junction.

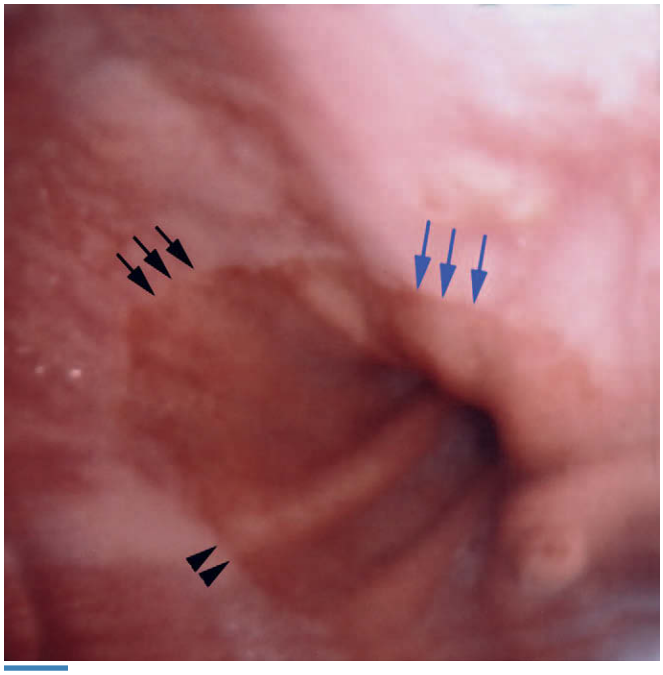

Figure 73-3. Normal transnasal esophagoscopic appearance of the distal esophagus. The junction of the terminal vessels (*short arrows*) and the gastric rugae (*arrowheads*) corresponds to the level of the gastroesophageal junction. The squamocolumnar junction (*long arrows*) coincides with the gastroesophageal junction in this patient. *(From Postma GN, Belafsky PC, Aviv JE.* Atlas of Transnasal Esophagoscopy. *Philadelphia: Lippincott Williams & Wilkins; 2007:18).*

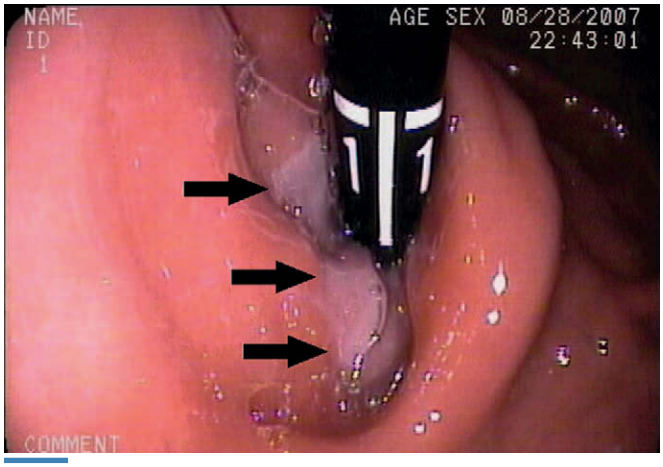

Figure 73-4. Retroflexed view of the squamocolumnar junction (*arrows*). The diaphragm is tight around the endoscope.

The SCJ and the junction should normally coincide. However, finding the SCJ above the gastroesophageal junction represents clinical Barrett's esophagitis (Figs. 73-3 and 73-4).

Indications

The rate at which pathology is found on TNE performed in an otolaryngology practice is high, approaching 50%.[15,28] Indications for TNE can be divided into three major categories: esophageal, extraesophageal, and procedure-related. Esophageal indications include dysphagia, refractory or long-standing gastroesophageal reflux, abnormal radiographic study, and screening for Barrett's metaplasia. Extraesophageal indications include globus pharyngeus, head and neck cancer, laryngopharyngeal reflux, and chronic cough. Reavis and colleagues[29] found that patients with esophageal adenocarcinoma exhibited extraesophageal reflux symptoms more frequently than typical gastroesophageal reflux complaints, with chronic cough being the most common single complaint.[29] Procedures for which TNE may be used are detailed in the following sections.

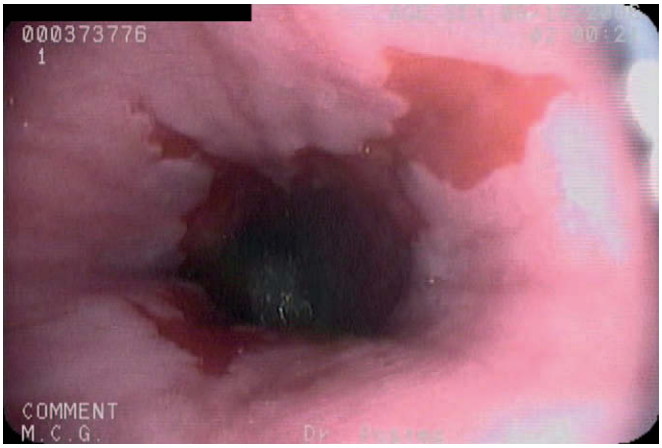

Figure 73-5. Barrett's esophagus. Tongues of gastric columnar epithelium can be seen extending into the squamous epithelium of the mid-esophagus.

Transnasal Esophagoscopy in Head and Neck Oncology

Panendoscopy is considered part of the standard evaluation of patients diagnosed with head and neck squamous cell carcinoma. Often, these patients possess comorbidities that increase the risks of general anesthesia. Unsedated office TNE allows for an examination of the aerodigestive tract without the morbidity of anesthesia. A complete examination can be performed in a high percentage of patients, with series reporting up to 99%.[30] Biopsy specimens can also be obtained on the day of the in-office endoscopy. In patients with presumed head and neck squamous cell carcinoma, a high degree of congruence has been shown between specimens obtained through TNE and those obtained from standard operating room panendoscopy.[31]

Patients requiring extensive resection of a head and neck malignancy may need complex reconstruction, including the use of free tissue flaps. TNE may be used for surveillance of the reconstruction and to check the integrity of the flap both in the immediate postoperative period and during further follow-up examinations.[32]

Transnasal Esophagoscopy in Barrett's Esophagus

Although most cancers in the United States are showing a decline in prevalence, the rate of esophageal adenocarcinoma is on the rise. Barrett's esophagus represents a premalignant state for this type of esophageal neoplasm. TNE is a useful screening examination for this condition. Limitations of TNE include the inability to use jumbo forceps or comfortably to obtain a full four-quadrant range of biopsy specimens spaced every 1 to 2 cm, which are standard during conventional Barrett's esophagus surveillance. Therefore, TNE is not currently recommended for the *surveillance* of Barrett's esophagus (Fig. 73-5).

Transnasal Esophagoscopy in Dysphagia

Dysphagia is a growing clinical concern, particularly among the elderly. TNE complements other diagnostic tools, including manometry, flexible endoscopic evaluation of swallow (FEES), flexible endoscopic evaluation of swallowing with sensory testing (FEESST), and radiographic studies such as the barium esophagram and the modified barium swallow. Unlike these other studies, TNE allows direct visual inspection of the mucosa. An additional advantage of this unsedated examination is the ability to subjectively assess peristaltic activity. A pill, food, or a liquid can be swallowed and observed to travel through the esophagus, in order to localize areas of decreased peristalsis or narrowing. Transit time for a liquid is usually less than 13 seconds. Conditions found during TNE for dysphagia include esophagitis, strictures,

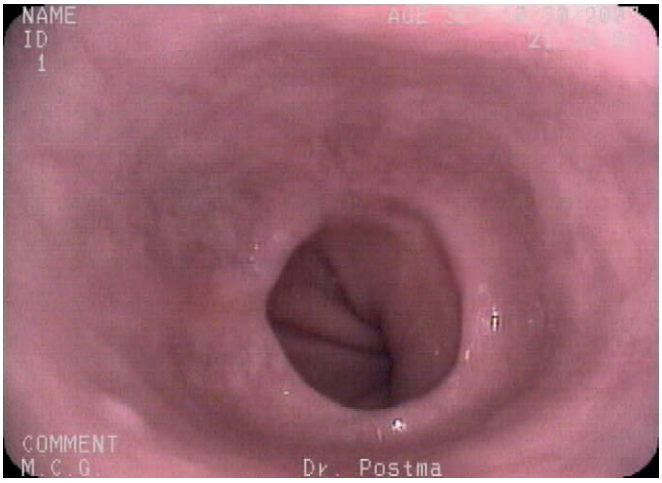

Figure 73-6. Esophageal ring. The type B ring (Schatzki's ring) represents the most common cause of dysphagia to solids in adults.

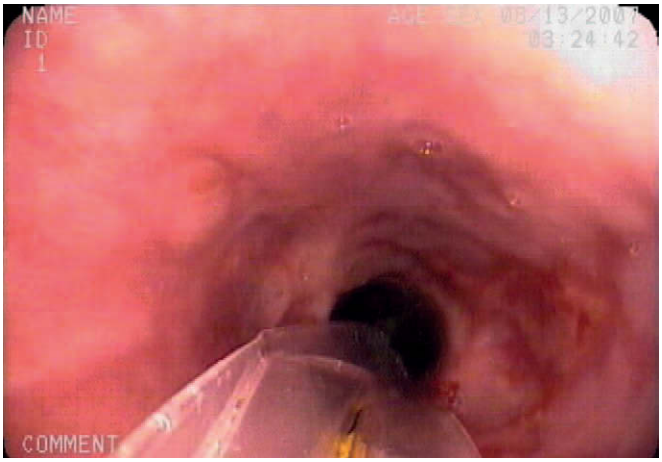

Figure 73-7. Balloon dilation of an esophageal stricture. A partially inflated controlled radial expansion balloon can be seen within an esophageal stricture.

rings, large hiatal hernias, webs, primary or metastatic neoplasms, eosinophilic esophagitis, vascular anomalies, and diverticula. A tight lower esophageal stricture found on endoscopy can also suggest the diagnosis of achalasia rather than the presence of a tumor (pseudoachalasia) (Fig. 73-6).

Additional Diagnostic Applications of Transnasal Esophagoscopy

New indications for TNE are continually being developed. Among its novel applications are documenting the resolution of *Helicobacter pylori* infection and the detection and grading of esophageal varices.[33] The ability to evaluate esophageal pathology without sedation is particularly valuable in patients with cirrhosis in order to avoid the risk of postsedation encephalopathy.[34] Similarly, serial evaluations after a caustic ingestion can be accomplished with TNE without the need for repeated anesthesia. Foreign bodies, such as impacted food, may be diagnosed with TNE and "pushed" into the stomach. It is our opinion that unsedated TNE should not be used for the *removal* of foreign bodies because of airway concerns. Finally, technologic innovations, such as narrowband imaging, may further improve the diagnostic accuracy of TNE.[35]

Procedures

Stricture Dilation

When patients complain of a primarily solid rather than liquid dysphagia, an anatomic etiology is often present, such as a stricture or web. Traditionally, the treatment of esophageal strictures involves mechanical dilation, often with bougies, in the operating room or with sedated endoscopy. Patients may need multiple treatment sessions. The need for numerous anesthetics and "blind" dilation is avoided with the use of unsedated TNE.[36] Controlled radial expansion (CRE) balloons can be passed over a guidewire to dilate narrowed segments.[37,38] Evidence suggests that these balloons may be less traumatic than bougies.[39] Unsedated TNE has been used to successfully dilate esophageal strictures in conditions such as epidermolysis bullosa as well as those induced by reflux or radiation.[40,41] The endoscope can also guide placement of controlled radial expansion balloons to treat radiation-induced stenosis of the nasopharynx. Neopharyngeal strictures that may occur after total laryngectomy have been successfully dilated with the use of office unsedated TNE as well (Fig. 73-7).[42]

Tracheoesophageal Puncture

Tracheoesophageal puncture (TEP) is one of the most commonly used vocal rehabilitation pathways following total laryngectomy.[43] TNE can be used for secondary TEP placement. Traditionally, secondary TEP placement is performed with general anesthesia and a rigid esophagoscope. In addition to the risks associated with general anesthesia, this technique can be complicated by difficulty passing the rigid esophagoscope in patients lacking neck flexion or passing the instrument through friable tissue.[44]

The procedure begins with the endoscope's being passed into the neopharynx. A needle is then passed through the posterior tracheal wall and through the anterior wall of the esophagus, which is observed under direct visualization. Air is insufflated into the neopharynx to promote visualization and protect the posterior esophageal wall from accidental needle penetration. The incision is enlarged and then either a catheter or the TEP prosthesis itself may be inserted. A study found that in-office, unsedated secondary TEP placement was successful in 10 of 11 patients.[45] TNE can also be used to diagnose and replace a TEP device that has failed because of malposition.[46]

Additional Therapeutic Applications of Transnasal Esophagoscopy

Laser fibers can be passed through the working channel for ablation of esophageal papillomas or other small tumors. Unsedated TNE has also been used successfully to position wireless telemetry devices in the esophagus for pH monitoring.[47]

Complications

One of the most feared complications of esophagoscopy is esophageal perforation. Among the thousands of cases performed, only one case of esophageal perforation has been reported, when unsedated TNE was performed by a gastroenterologist.[16] There have been no reported cases of esophageal perforation during TNE performed by an otolaryngologist. Minor complications have been reported. In two of the largest series reported, involving 700 patients from the United States and 1100 patients from France, rates of epistaxis were reported between 0.85% and 2% and those of vasovagal events to be 0.3%.[15,20] Mild, self-resolving nasal discomfort was reported at 1.6%.

Conclusion

Transnasal esophagoscopy is a well tolerated, safe, and efficacious method to evaluate the esophagus without many of the risks associated with conventional endoscopy. Better patient care along with a significant potential cost savings can be achieved with use of TNE rather than the conventional procedure.

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CHAPTER SEVENTY-FOUR

Zenker's Diverticulum

Richard L. Scher

Key Points

- Zenker's diverticulum is the most common of the hypopharyngeal diverticula.
- Patients with this disorder most commonly present with dysphagia with food regurgitation.
- Diagnosis is confirmed by contrast radiography of the pharynx and esophagus.
- Treatment is directed toward elimination of symptoms and prevention or treatment of complications such as aspiration and malnutrition.
- Endoscopic treatment with the staple technique has proved to be an effective and safe method of therapy and should be considered the first-line approach.
- Any external surgical approach to treatment should include a cricopharyngeal myotomy.
- Regardless of technique, the most significant complication of surgical therapy is perforation of the hypopharynx or esophagus with associated mediastinitis.

Esophageal diverticula are classified on the basis of anatomic location (pharyngoesophageal, midesophageal, or epiphrenic) and mechanism of origin (pulsion or traction). *Traction diverticula* are a result of pulling forces external to the esophagus that are secondary to inflammatory or neoplastic processes and usually occur on the anterior wall of the esophagus near the bifurcation of the trachea. In contrast, *pulsion diverticula* are a result of herniation of esophageal mucosa and submucosa through an area of weakened esophageal musculature. Of the various types of esophageal diverticula, Zenker's diverticulum (ZD), a pulsion-type diverticulum, is one of the most common symptomatic esophageal diverticula, with an annual incidence of 2 per 100,000 people per year, with men being affected 2 to 3 times more commonly than women.[1-6] For patients referred for an examination of the upper gastrointestinal tract, the incidence can reach 1 in 1000.[4,6,7] ZD is extremely rare in Asia and Africa, where gastroesophageal reflux disease is also uncommon, suggesting that reflux may play a role in its etiology.[5,7,8] Most esophageal diverticula are acquired lesions found in adults, particularly in the seventh and eighth decades. Pediatric hypopharyngeal diverticula along with true ZD are extremely rare, with most cases being congenital in nature and fatal secondary to massive aspiration pneumonia.[9-19]

Zenker's diverticulum is classically defined as a pulsion diverticulum between the cricopharyngeal muscle and inferior constrictor muscle in an area of weakness called Killian's dehiscence or triangle, first described by Killian[20] in 1907 (Fig. 74-1). However, there are other areas of weakness where pulsion diverticula may form, including Killian-Jamieson's area, between the oblique and transverse fibers of the cricopharyngeal muscle, and Laimer's triangle, formed between the cricopharyngeal muscle and the most superior esophageal wall circular muscles (Fig. 74-2).[21] More rarely, pharyngoceles may be found in the posterolateral or lateral areas of the pharynx and hypopharynx (Fig. 74-3).[22] Cases of double pharyngeal pouches have also been described (Fig. 74-4).[23] Interestingly, ZD is found almost exclusively in humans, a fact hypothesized to be secondary to the large size and relatively caudal cervical location of the larynx in comparison with lower animals.[8,21] The caudal location of the larynx results in an oblique orientation of the pharyngeal constrictor muscles, resulting in regions of weakness. Such muscular vulnerabilities are absent in animals because the pharyngeal and esophageal musculatures have a coherent parallel orientation throughout the upper aerodigestive tract. Indeed, ZD has been found in only one animal, the Mangabay monkey, in a single case so far.[21]

Theoretically, a diverticulum herniates to the side of less resistance. Accordingly, it is hypothesized that ZD is more prone to herniate to the left because the carotid artery is more laterally located on this side of the neck, making it less adherent to the adjacent prevertebral fascia, and because there the cervical esophagus has a slight convexity to the left.[21,24] According to one series, although two thirds of Zenker's diverticula are found in the midline, nearly 25% protruded to the left, and only 10% to the right.[25,26]

Presentation

Patient history alone may raise suspicion for ZD. The predominant symptom is progressive dysphagia, which may occur in excess of 90% of patients presenting with the disorder.[27] Regurgitation of food even hours after a meal, unprovoked aspiration, and noisy deglutition (borborygmi) specifically suggest ZD. Other symptoms are belching, hypopharyngeal mucus collection, halitosis, choking, coughing, hoarseness, globus pharyngeus, weight loss, and recurrent respiratory infections. Symptoms may last for weeks to many years before diagnosis and are generally more severe with a larger ZD. Minimal physical findings may include mucus pooling in the hypopharynx that initially clears with swallowing then recurs, emaciation or dehydration, and, only rarely, Boyce's sign, a swelling in the neck that gurgles on palpation.[28] However, it is more often the case that patients are without any specific findings on physical examination. Diagnosis is confirmed by barium swallow radiography, which can also define the size and position of the sac (Fig. 74-5). Fiberoptic endoscopy is also performed to help rule out other potential causes of dysphagia (Table 74-1). Occasionally, ZD may be first discovered during esophagogastroduodenoscopy or rigid cervical esophagoscopy as an incidental finding during the course of a gastrointestinal evaluation. The size of the sac may range from less than

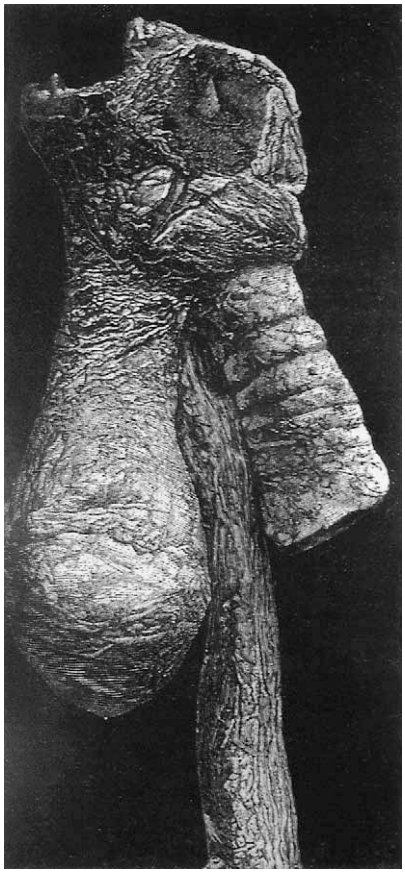

Figure 74-1. Large Zenker's diverticulum discovered by Zenker during an autopsy on a 67-year-old man. Drawing from *Krankheiten des Oesophagus* by Zenker and von Ziemssen, 1877. *(From Westrin KM, Ergun S, Carlsoo B. Zenker's diverticulum—a historical review and trends in therapy.* Acta Otolaryngol [Stockh]. *1996;116:351-360.)*

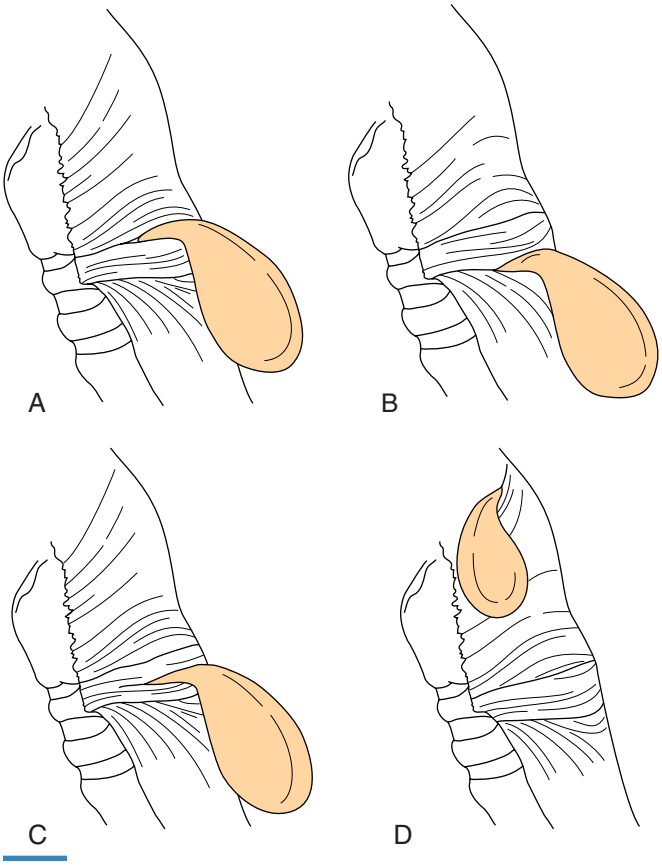

Figure 74-2. Types of esophageal diverticula. **A,** Killian's triangle: region between the cricopharyngeal and inferior constrictor muscle. **B,** Laimer's triangle: region between the cricopharyngeal and most superior esophageal circular muscle. **C,** Killian-Jamieson's triangle: region between the oblique and transverse fibers of the cricopharyngeal muscle. **D,** Lateral pharyngocele: variable location above and lateral to the cricopharyngeus.

1 cm to a truly enormous 12 cm or more. Rarely, a large diverticulum may be seen on a regular chest radiograph (Fig. 74-6).

Through the years, physicians have attempted to classify ZD on the basis of contrast radiology findings (Table 74-2). In 1930, Lahey[29] described three stages based on radiologic appearance. Morton and Bartley,[30] along with subsequent writers, also described three stages but based them on size.[31] van Overbeek and Groote[5] used cervical vertebral bodies as a standard for comparison rather than absolute size measurements. Brombart and Monges[32] expanded the classification into four stages, incorporating size, appearance, and stage of deglutition. Other workers have created increasingly more complex categories incorporating elements from both Brombart and Monges's and van Overbeek and Groote's systems.[33] Although useful in terms of classifying ZD, these arrangements have limited clinical utility.

Pathophysiology

Although it is widely accepted that ZD is an acquired pulsion diverticulum, considerable controversy exists about the mechanism of its formation. Ludlow[34] in Bristol, England, gave the first anatomic description of a pulsion diverticulum of the hypopharynx in 1769. He believed that this condition was induced in his subject by trauma after the swallowing of a cherry stone. Subsequent pathologists hypothesized traumatic rupture or burn, congenital upper esophageal stricture, thyroid goiter, or foreign bodies as triggers for ZD formation.[21] It was not until 1877 that these hypotheses were rejected as erroneous and the basic pathophysiology was described by, and the diverticulum named after, Zenker, a German pathologist.[35] The original German description was later translated into English in New York in 1878, allowing wider dissemination of Zenker's findings.[21] However, before Zenker, Bell[36] (best known for describing facial nerve palsy) proposed in 1816 that incoordination of the inferior constrictor muscle against a closed cricopharyngeal muscle resulted in this type of outpouching at regions of inherent weakness. This etiology was later supported by other researchers.[37-46] Similarly, the congenital theory describes an unusually weak or large Killian's triangle from birth that with time herniates with normal pharyngeal contraction.[47] Variations on this theme for the mechanism of formation of ZD have been debated ever since.

Patterson[48] in 1919 first proposed cricopharyngeal achalasia as an etiology for ZD. Others noted a higher incidence of reflux and hiatal hernia in patients with ZD as well as epidemiologic observations that ZD occurs predominantly in populations with a high incidence of reflux, suggesting a possible relationship between the two.[7,49] Several writers in the early 1970s suggested that spasm or persistently elevated resting tone of the cricopharyngeus secondary to reflux could cause ZD, although others refuted a direct causal association.[7,49-51] On the basis of histologic studies, Lerut[52] in 1988 proposed a structural abnormality of the cricopharyngeal muscle itself. Cook and associates[53] in 1992 suggested partial, but incomplete, opening of the cricopharyngeal muscle because of fibroadipose tissue replacement as an etiology. Six years later, Walters and colleagues[54] proposed that ZD might be a manifestation of central or peripheral neurologic disease. Regardless of the theory, the cricopharyngeal muscle is the common theoretical culprit behind the formation of ZD, and whether to address this muscle during surgical management has been debated through the years.[55]

Management

The treatment of ZD, as well as other forms of hypopharyngeal diverticula, is surgery. The presence of ZD is an additional risk factor in the

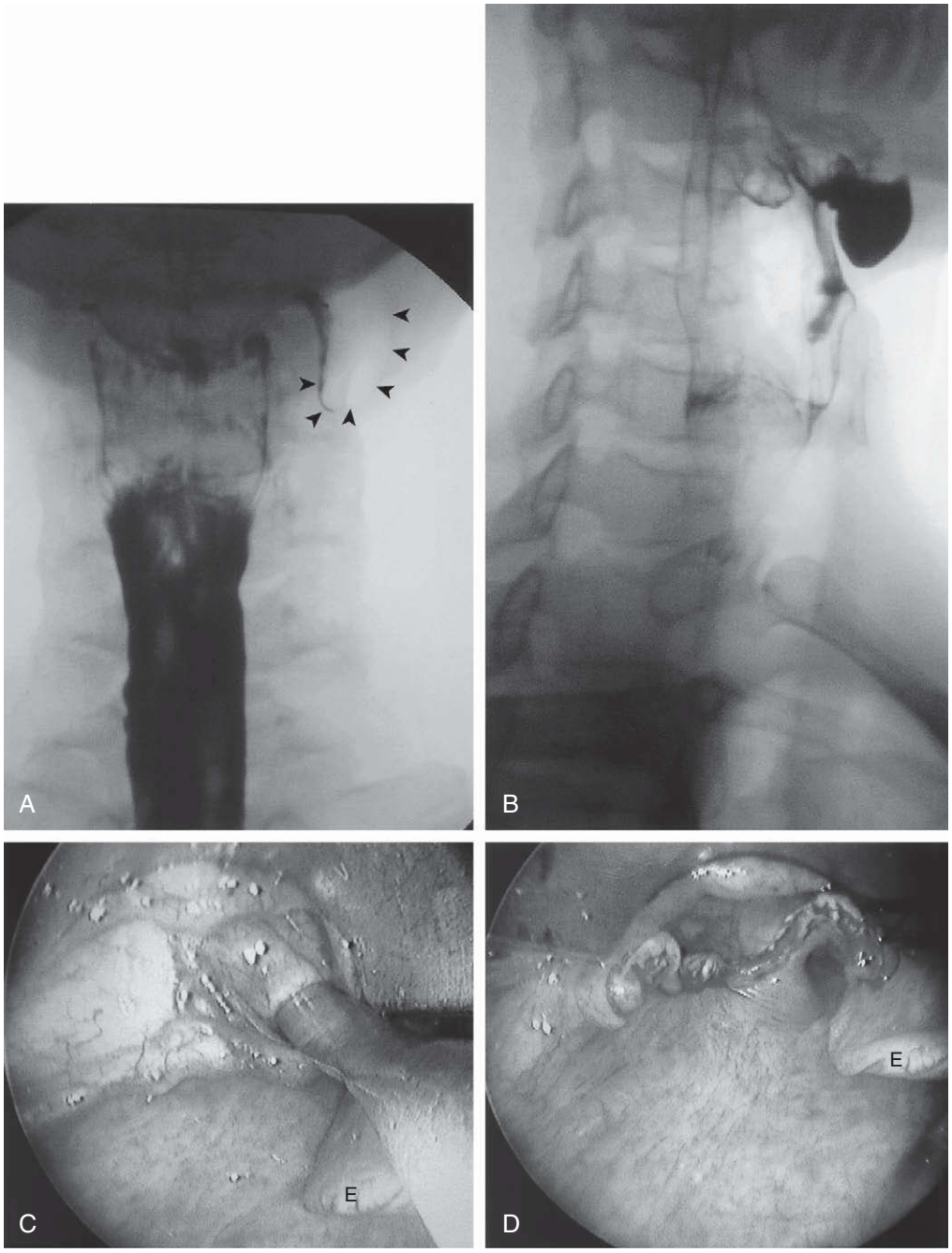

Figure 74-3. Left lateral pharyngocele in a 45-year-old man. **A,** Barium swallow study, anterior view. A faint outline of the diverticulum can be seen in the left neck anterior and superior to the thyroid cartilage (*arrowheads*). Barium is outlining the medial wall of the diverticulum. **B,** Barium swallow study, lateral view. **C,** Direct laryngoscopy view demonstrating pharyngeal pouch. Spatula probe is within pouch. **D,** Direct laryngoscopy view after endoscopic staple diverticulostomy. **E,** epiglottis.

overall health of the elderly patient, who may have concomitant pulmonary, cardiac, and other morbidities. With symptomatic ZD, the patient may have persistent aspiration causing deterioration of pulmonary function. Furthermore, with severe symptoms of dysphagia and aspiration, patients with ZD often become cachectic and dehydrated because of fear or inability to eat or drink. Definitive surgical management is mandated in these patients to prevent continued pulmonary compromise and malnutrition. Generally, all operative procedures addressing esophageal diverticula should be performed with the use of general anesthesia and as elective operations before complications have occurred. However, surgery may become urgent once problems have arisen and a patient's condition is unlikely to be optimized before definitive treatment. In these patients, it is also important to fully evaluate and treat for other etiologies of dysphagia to obtain maximal benefit from surgery (see Table 74-1). Surgery is not necessary if the patient is asymptomatic or if the diverticulum is causing the patient minimal, if any, problems, but the patient does require long-term monitoring.

External Techniques

History

A variety of open, external surgical approaches to treating ZD have been performed, with and without the inclusion of cricopharyngeal myotomy. The first-recorded, but unfortunately fatal, treatment was performed in Vienna in 1877 by Nicoladoni,[56] who established a fistula

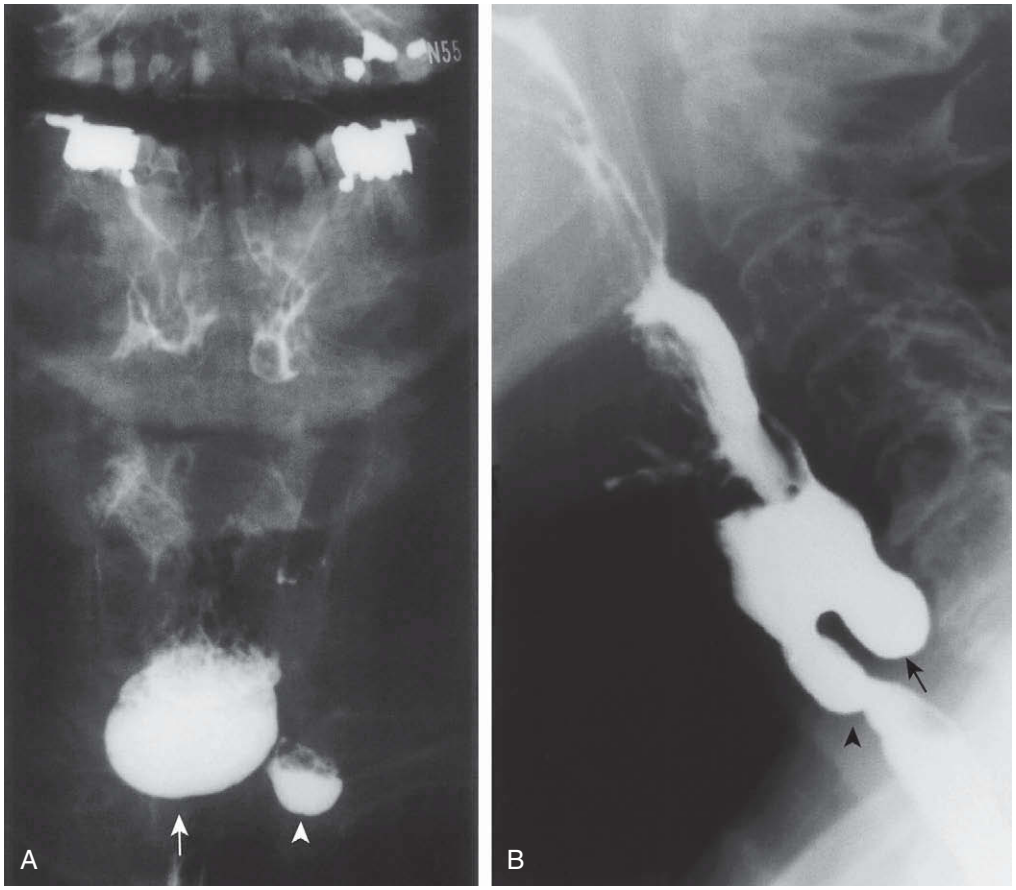

Figure 74-4. Barium swallow study revealing a double esophageal diverticulum. **A,** Anterior view. This 80-year-old woman was found to have a 3-cm Zenker's diverticulum (*arrow*) and a 0.5-cm right Killian-Jamieson diverticulum (*arrowhead*). **B,** Lateral view. Patient underwent successful endoscopic staple diverticulostomy of the Zenker's diverticulum. No attempt was made to correct the remaining diverticulum.

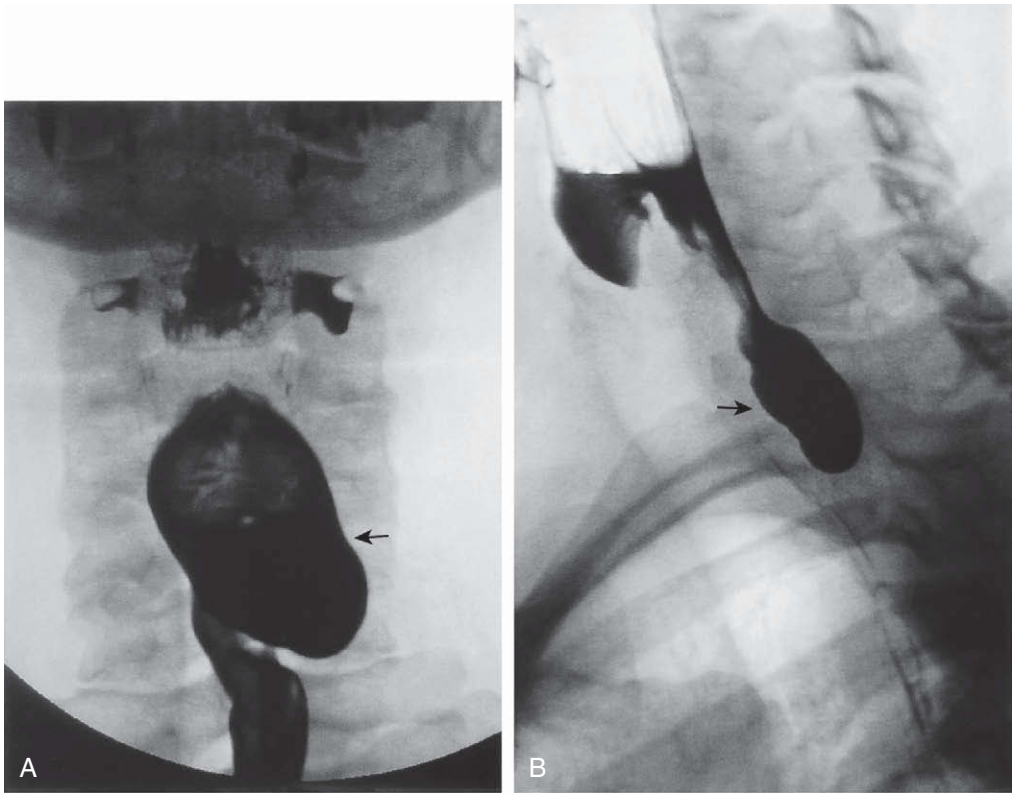

Figure 74-5. Zenker's diverticulum (*arrow*) in a 63-year-old patient who underwent a barium swallow study. **A,** Anterior view. **B,** Lateral view.

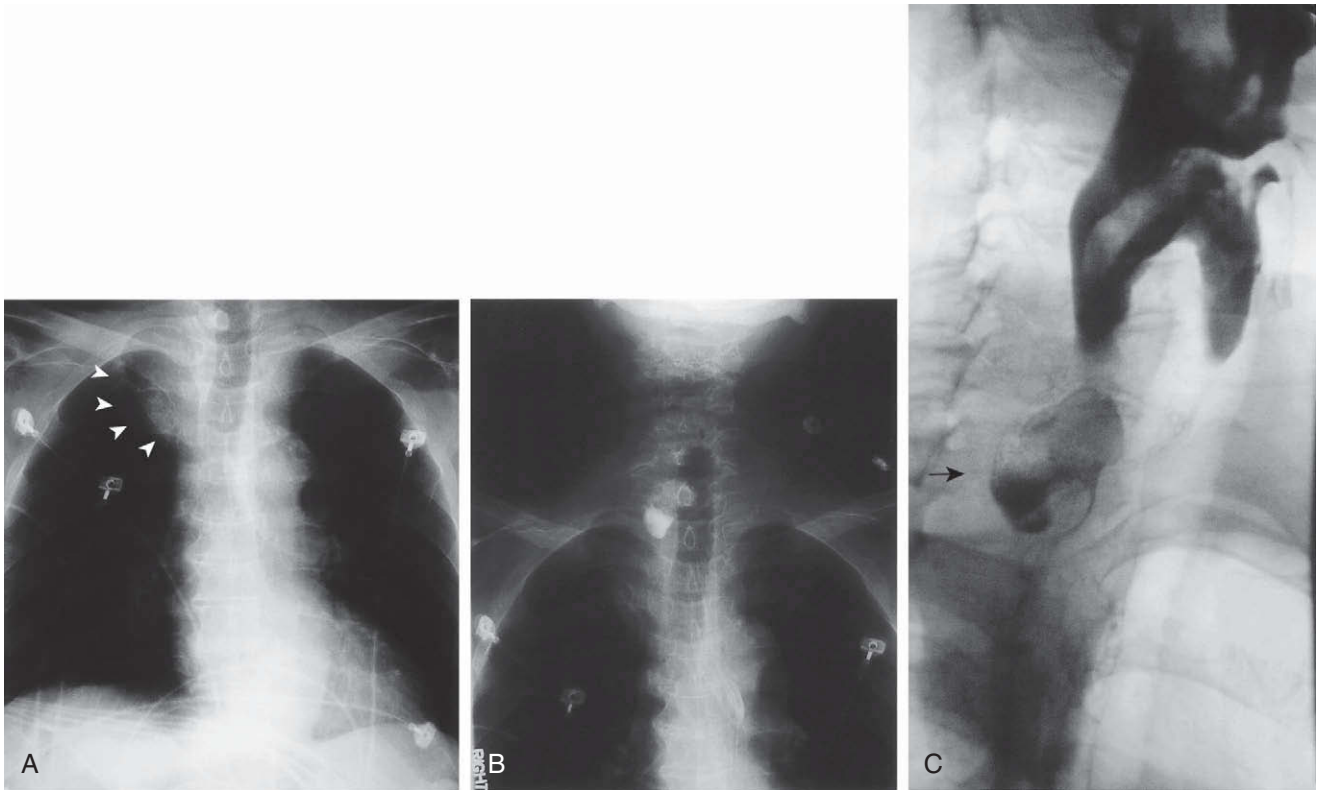

Figure 74-6. **A** and **B,** Chest radiographs of a 75-year-old patient with a 6-cm Zenker's diverticulum. **A,** Before barium swallow. Note the hazy soft tissue mass in the right upper lung field (*arrowheads*) representing the Zenker's diverticulum. **B,** After barium swallow. An air-fluid level can be seen within the Zenker's diverticulum. **C,** Barium swallow study shows the diverticulum (*arrow*).

Table 74-1

Differential Diagnosis of Dysphagia

Congenital or acquired	Esophageal stenosis, stricture, web Extrinsic compression from neck mass Carcinoma Trauma or iatrogenic (prior surgery) Inflammatory or infectious masses Tumor Plummer-Vinson syndrome Esophageal diverticulum
Motility disorders	Achalasia Esophageal spasm
Muscular incoordination	Myasthenia gravis Muscular dystrophy Thyrotoxicosis Carcinomatosis
Central neuropathic	Stroke Bulbar palsy Trauma
Peripheral neuropathic	Trauma Neuritis Collagen-vascular disorders
Idiopathic	Idiopathic

to drain the sac, a procedure Bell[36] first proposed in 1816. Zenker and von Ziemssen[35] in 1877 recommended dilations of the esophageal inlet.[21] Niehans[58] unsuccessfully attempted ZD excision in 1884. This procedure, first suggested by Kluge in 1850, resulted in the death of his patient from hemorrhage from the superior thyroid artery.[21,57] Wheeler,[59] 2 years later, successfully excised a diverticulum. Kocher[60] in 1892 performed a diverticulectomy with primary closure. Girard[61] in 1896 inverted the diverticulum, a procedure first described by Keyrat in 1866.[21] Schmid[62] in 1912 described the method of diverticulopexy, which was performed by Hill[63] in 1917. Unfortunately, these procedures, which often necessitated multiple stages, were associated with high mortality, particularly before the discovery of antibiotics to help reduce the morbidity and mortality. With technical advances and the availability of antibiotics, one-stage procedures became standard.

Despite the numerous different theories on the formation of ZD, the vast majority point toward the cricopharyngeal muscle as the etiologic factor. It thus follows that performing a cricopharyngeal myotomy does have a logical role in the surgical management of ZD. Although Richardson[64] in 1899 performed the first cricopharyngeal myotomy with good results, albeit accidentally, it was not until 1936 that Aubin[65] proposed cricopharyngeal myotomy as a useful adjunct to surgical diverticulectomy. Instead of a myotomy, Lahey[66] in 1946 recommended cricopharyngeal dilation. Beginning in the 1950s, performance of a myotomy became a planned component of the surgical treatment of ZD and, in some cases, the sole treatment.[1,67] It is now commonly accepted that surgical treatment of ZD without a cricopharyngeal myotomy is associated with a high recurrence rate.[39,55,57,68-71]

Procedure

Generally, all external procedures (excluding cricopharyngeal muscle dilation) use a transcervical approach to the ZD, using a left lateral neck incision unless the ZD is found on the right side by preoperative barium esophagram. Before incision, however, cervical esophagoscopy is performed to identify the diverticulum and pack it with gauze to help

Table 74-2

Zenker's Diverticulum Classification Schemes

Researcher	Stage 1	Stage 2	Stage 3	Stage 4
Lahey (1930)[29]	Small mucosal protrusion, spherical in shape	Pear-shaped	Glove-fingered shape	
Brombart & Monges (1964)[32]	Thornlike diverticulum (longitudinal axis of 2-3 mm) visible only during contraction phase of upper esophageal sphincter	Clublike diverticulum (longitudinal axis of 7-8 mm) visible only during contraction phase of upper esophageal sphincter	Bag-shaped diverticulum (caudally oriented axis > 1 cm in length) without compression of the esophagus	Compression of the esophagus, which is displaced ventrally
Morton & Bartley (1993)[30]	<2 cm	2-4 cm	>4 cm	
van Overbeek & Groote (1994)[5]	1 vertebral body	1-3 vertebral bodies	>3 vertebral bodies	

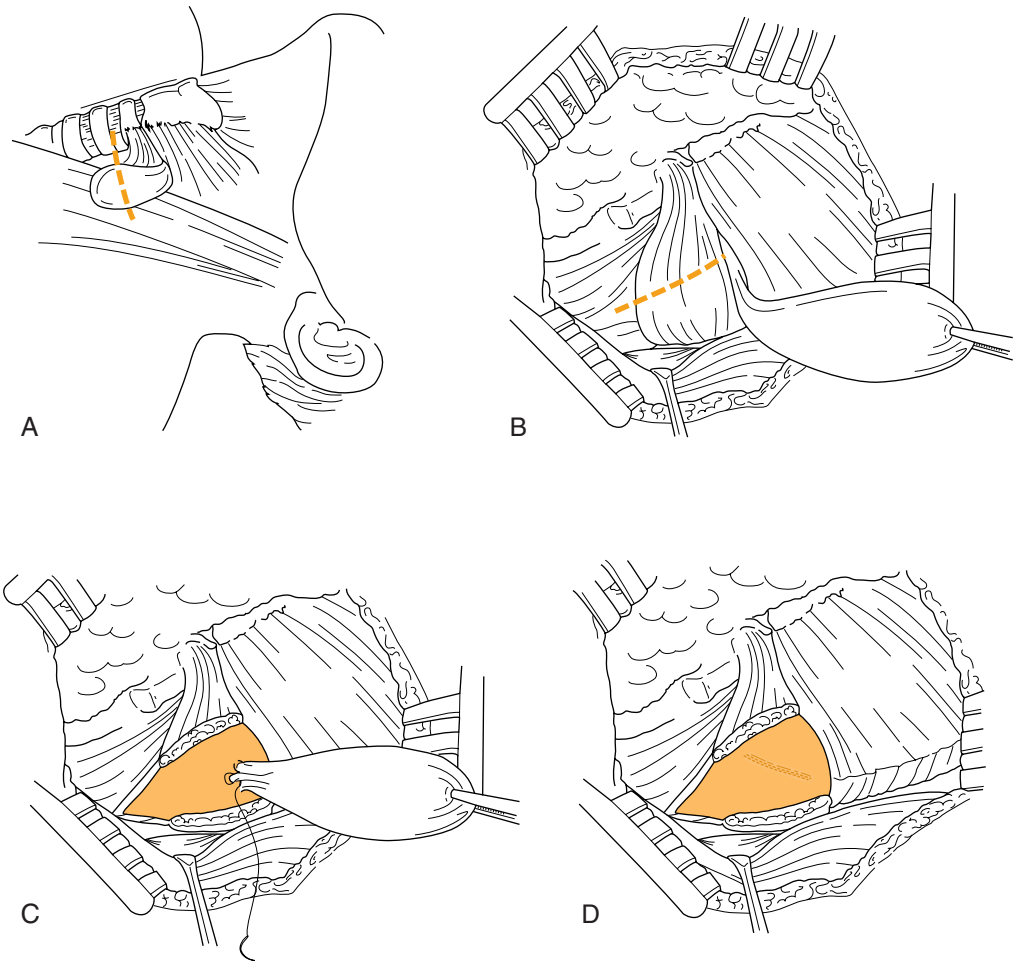

Figure 74-7. Steps of a transcervical diverticulectomy. **A,** Incision line is illustrated. An alternative incision line may be along the anterior border of the sternocleidomastoid muscle. **B,** Soft tissues are dissected away. The trachea, strap muscles, and thyroid gland are retracted medially, and the sternocleidomastoid muscle is retracted laterally. The omohyoid muscle may also be retracted laterally or, alternatively, divided for exposure. Once the diverticulum and cricopharyngeus muscle are identified, a cricopharyngeal myotomy is performed. The diverticulum itself may be excised and the defect closed with a purse-string suture (**C**) or a stapler (**D**).

in identification during transcervical surgical exposure. An esophageal dilator is inserted into the esophagus under direct visualization to assist in cricopharyngeal myotomy and to minimize the risk of esophageal stenosis. A nasogastric feeding tube is also inserted to be used for feeding after surgery.

The standard incision is usually made along the anterior border of the sternocleidomastoid muscle from the level of the hyoid bone to several centimeters above the clavicle. However, a curvilinear transverse incision along a neck crease between the hyoid and clavicle is preferable for cosmesis (Fig. 74-7). Subplatysmal flaps are then raised,

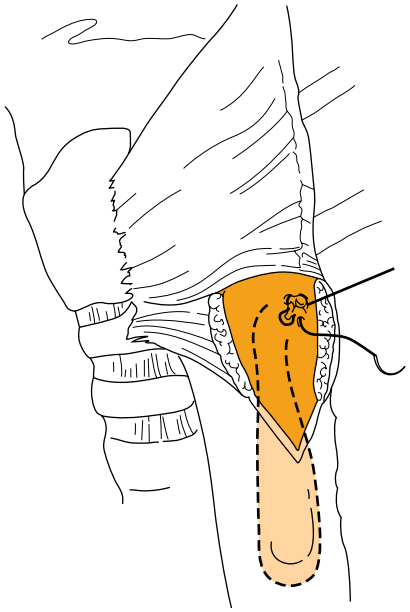

Figure 74-8. Inversion technique. After a cricopharyngeal myotomy is performed and the diverticulum freed, a purse-string 3-0 absorbable (polyglactin) suture is passed extramucosally around the neck of the diverticulum. The pouch is then inverted, and the purse-string suture pulled tight. The muscle fibers may then be approximated over the defect. In this method, no feeding tube is required if the mucosa was not violated.

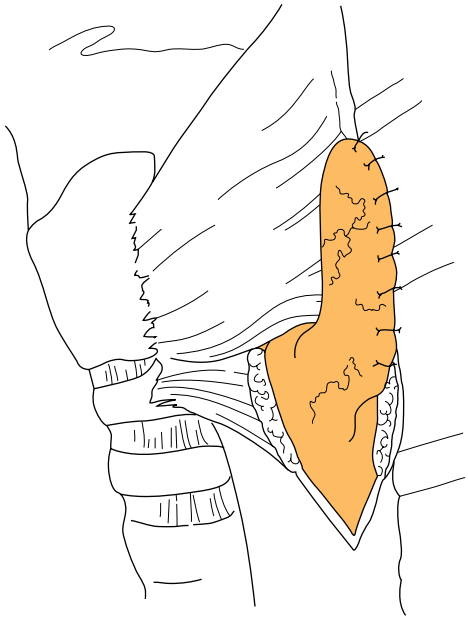

Figure 74-9. Diverticulopexy technique. After a cricopharyngeal myotomy is performed and the diverticulum is freed, the sac is tacked with 2-0 silk sutures superiorly to the prevertebral fascia.

followed by lateral retraction of the sternocleidomastoid muscle. The fascial attachments along the anterior border are divided. The strap muscles may be retracted anteromedially, but for better exposure, the anterior belly of the omohyoid muscle may be divided inferiorly. As blunt dissection is carried out to expose the posterior aspect of the pharynx, larynx, and esophagus, the recurrent laryngeal nerve is identified and protected before the thyroid vessels are ligated and divided, if necessary. Once the diverticulum is identified and freed from the surrounding tissues down to its base attachment to the esophagus, a long cricopharyngeal myotomy is performed. The pouch itself can then be excised, inverted, or suspended by a suturing or stapling technique (Figs. 74-8 and 74-9).[72-74] Each of these techniques has had its advocates.[2,30,68,72,75-82] For small diverticula (1-2 cm), a cricopharyngeal myotomy alone may be sufficient.[28,83,84] The patient generally is fed postoperatively through a feeding tube for several days, after which an oral diet may be resumed.

External procedures for treatment of ZD have long been associated with significant morbidity. Although this association is partly a result of the surgery itself, the vast majority of patients are elderly, often with other medical problems. Despite refined surgical techniques, the rate of symptomatic relief has been reported between 80% and 90%, and complication rates of 10% to 30% (with up to 3% mortality) have persisted for external approaches.[3,68,81,84-87] Engel and Panje[88] summarized the results of surgical complications observed from transcervical approaches in a large series of cases published in the English literature and covering the period from 1985 to 1991. Their compilation reported the following complication rates in 245 patients: fistulas 6.3%, recurrent laryngeal nerve palsy 3.6%, pneumomediastinum 0.8%, mediastinitis 3.1%, and mortality 2%. Payne[84] at Mayo Clinic reported a morbidity rate of 7.9%, a mortality rate of 1.2%, and a recurrence rate of 3.6% in 888 patients. Feeley and colleagues[77] reported a 37% complication rate. In a review of the literature of all studies published in the English literature between 1990 and 2002 by Chang and associates,[27] external techniques had an overall 1.6% mortality and an 11.8% complication rate.

Endoscopic Techniques

History

In an attempt to improve outcome, Mosher[89] in 1917 first described endoscopic esophagodiverticulostomy using a knife to divide the common wall, but he abandoned the procedure after his seventh patient died from mediastinitis. Two decades later, Sieffert[90] re-introduced the endoscopic technique using scissors, but Dohlman and Mattson[91] popularized the procedure in 1960 when they presented the endoscopic management of ZD in a series of approximately 100 patients without deaths or serious complications, 93% of whom reported relief of symptoms, and only 7% symptom recurrence (Fig. 74-10).

Despite these successes, endoscopic management of ZD was not as readily accepted as external techniques because of concerns about dividing the common wall in a "sutureless" manner with the potential for pneumothorax, bleeding complications, or mediastinitis. Various refinements in the endoscopic technique have been introduced to alleviate these concerns and minimize the risk of severe complications. van Overbeek and coworkers[92] introduced the use of the operating microscope and carbon dioxide (CO_2) laser in 1984, and Kuhn and Bent[93] the use of the potassium titanyl phosphate (KTP)/532 laser in 1992. Gastroenterologists Ishioka and associates[94] in Brazil and Mulder and colleagues[95] in the Netherlands simultaneously introduced flexible endoscopic incision using electrocautery in 1995. Two years earlier, Martin-Hirsch and Newbegin[96] in England and Collard and associates[97] in Belgium had simultaneously introduced an endoscopic stapling technique of performing an esophagodiverticulostomy for ZD. The technique later was refined and introduced to the United States by Scher and Richtsmeier.[98,99]

Procedure of Endoscopic Staple Diverticulostomy

Endoscopic techniques involve visualization of the ZD through a modified laryngoscope with division of the common wall between the diverticulum and esophagus using electrocautery, CO_2 laser, or staples (Figs. 74-11 to 74-13). It has been our experience that the endoscopic staple diverticulostomy (ESD) has proved to be the treatment method of choice for patients with ZD. Briefly, the ESD procedure, as with other endoscopic techniques, is performed with the patient under general endotracheal tube anesthesia. After a dental guard is placed to protect the maxillary teeth, the Weerda bivalved laryngoscope (Karl

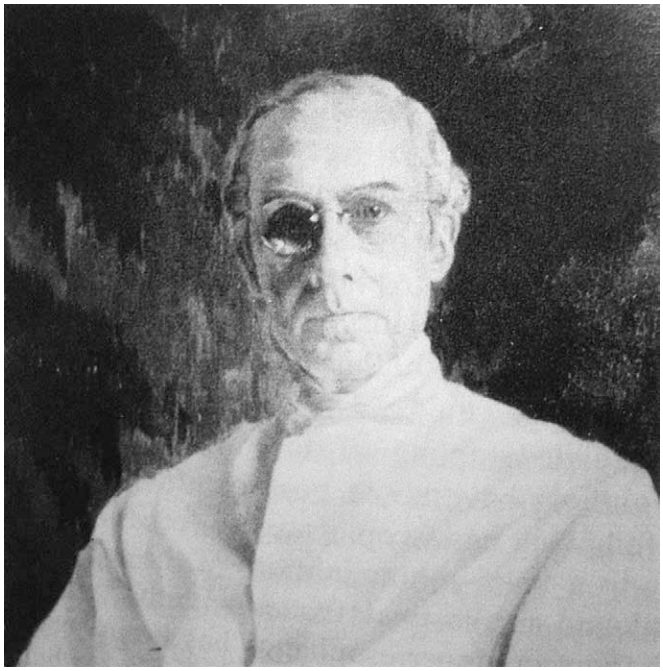

Figure 74-10. Portrait of Gosta Dohlman, Professor of Oto-rhino-laryngology at Lund University who introduced endoscopic diathermic diverticulostomy. *(From Westrin KM, Ergun S, Carlsoo B. Zenker's diverticulum—a historical review and trends in therapy.* Acta Otolaryngol [Stockh]. *1996;116:351-360.)*

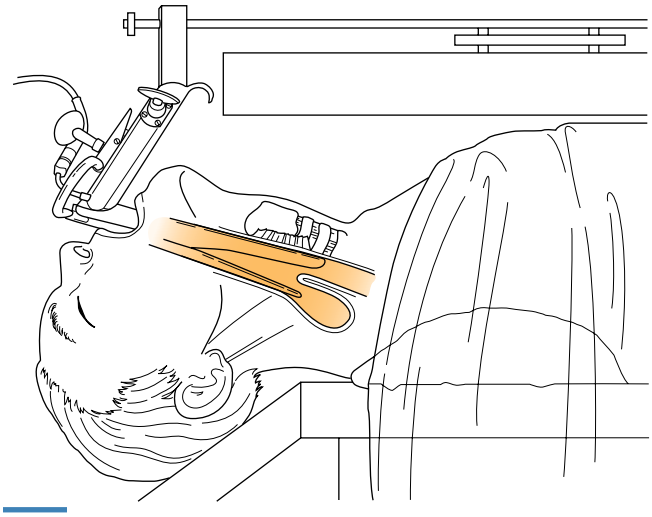

Figure 74-11. General patient positioning for endoscopic techniques.

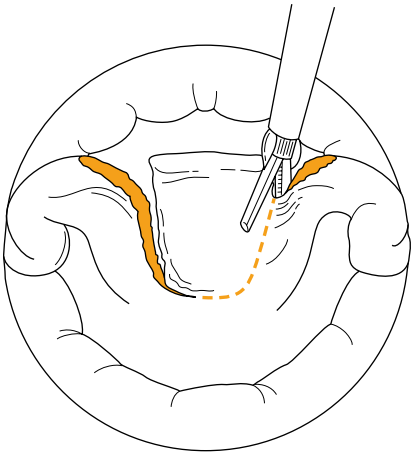

Figure 74-12. Endoscopic electrocautery technique.

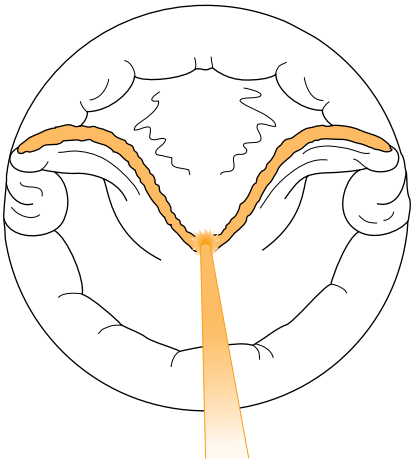

Figure 74-13. Laser technique.

Storz Endoscopy-America, Inc, Culver City, CA) is introduced into the oral cavity and used to expose the common wall between the esophageal and diverticular lumen (Fig. 74-14). A magnified view of the operative field and all manipulations are visualized using a rigid 0- or 30-degree telescope connected to a video camera (Fig. 74-15). The diverticular pouch is carefully examined and, if any lesions are noted, biopsy specimens are obtained for frozen-section diagnosis. The procedure is aborted and an external diverticulectomy is performed if a malignancy is identified.

Before division of the common wall, 2-0 silk retraction sutures are placed through the lateral edges of the common wall with the ENDOSTITCH autosuture device (Covidien Autosuture, Mansfield, MA). These sutures allow tension to be placed on the common wall to help with stapler positioning for small diverticula (less than 2.0-2.5 cm) to allow effective insertion of the stapler blades, or for assistance in countertraction when the stapler blades are re-inserted for a second or third cut in large diverticula (more than 3.5 cm). The diverticular common wall is then divided with the disposable MULTIFIRE ENDO GIA 30 stapler (Covidien Autosuture). The stapler blade containing the stapler cartridge is placed into the esophageal lumen, and the opposite blade is placed into the diverticulum. The stapler blades are closed around the common wall, and their position is confirmed with the telescope. Activation of the stapler simultaneously cuts and staples the divided mucosal edges of the common wall. Multiple applications may be necessary for large diverticula. By dividing the common wall, an internal cricopharyngeal myotomy is performed, creating a single lumen without removal of the pouch. The retraction sutures are removed after the esophagodiverticulostomy is completed. The telescope is then used to closely examine the esophagus, diverticulum, and incised common wall for any evidence of perforation or foreign debris such as loose staples, which are promptly removed.

The patient is discharged home on the day of surgery after 3 to 4 hours of observation to assess for complications (fever, chest or back pain, subcutaneous emphysema, hemoptysis, tachycardia, tachypnea, respiratory distress). The patient is instructed to have only a clear liquid diet that night, which may be advanced as tolerated to the regular diet the next day. Antireflux medications are prescribed for all patients. Although many observers have used antibiotics in the perioperative period, use of antibiotics on a routine basis before, during, or after surgery has been found to be unnecessary. During the postoperative period, no role for barium esophagography has been found except for evaluation of possible recurrence.[8,100,101] Such radiographic studies,

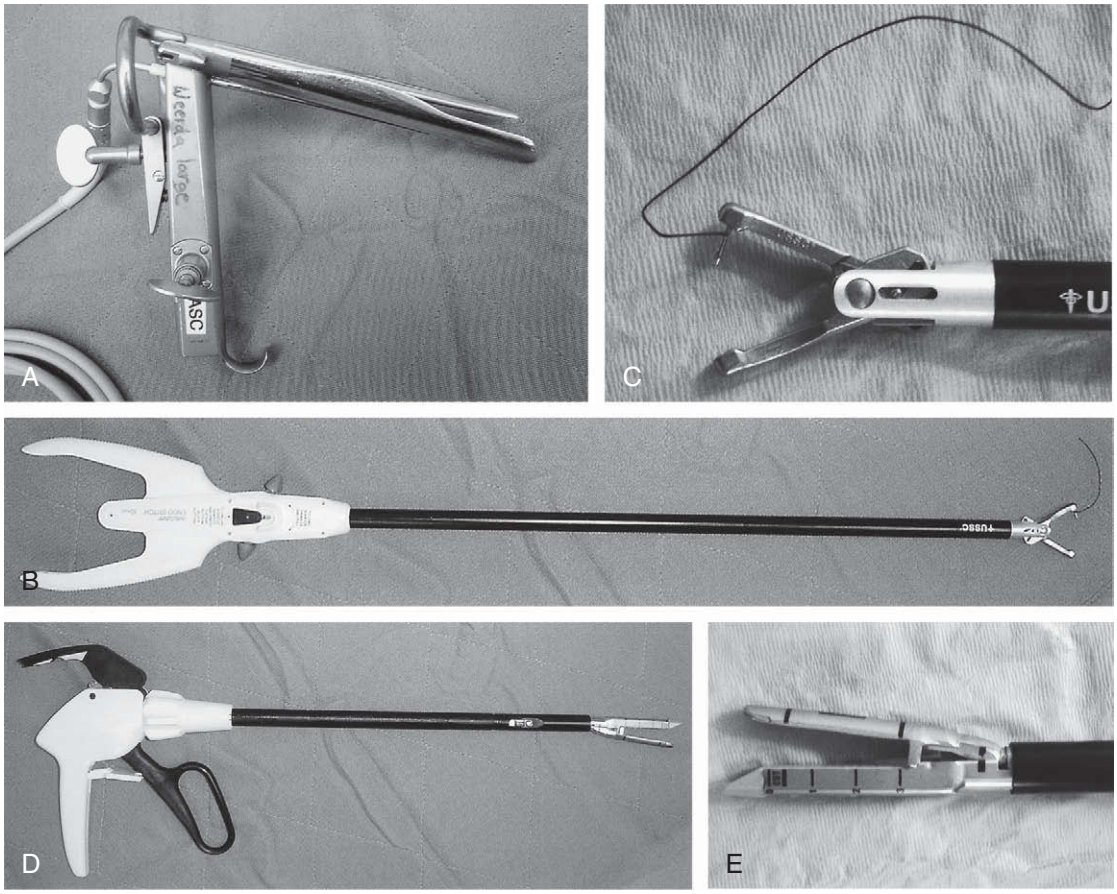

Figure 74-14. Instruments for endoscopic staple diverticulostomy. **A,** Weerda laryngoscope. **B,** ENDOSTITCH suturing device (Covidien Autosuture, Mansfield, MA). **C,** ENDOSTITCH tip. **D,** Endo-GIA 30 stapler. **E,** Stapler cartridges.

when performed in the asymptomatic patient, usually reveal a residual diverticulum that does not retain barium and so has no clinical bearing on, or correlation with, outcome.[100-103]

The procedure itself takes about half an hour to perform.[27] Patients resume an oral diet within 24 hours.[27] Compared with external approaches, endoscopic techniques have shorter, if any, inpatient stay, shorter anesthesia times (which is important in the elderly or the medically infirm), and more rapid convalescence.[98] Furthermore, in patients whose diverticula have recurred after primary external or endoscopic approaches, ESD may be performed without any increase in technical difficulty or morbidity.[27,31,98,104-106] One hospital charge analysis reported that ESD procedures were potentially more cost-effective than external techniques, an important consideration in today's world of health care economics.[107]

The stapling technique does have its limitations, although they are few. Exposure of the diverticulum may be difficult or impossible because of patient anatomy, such as kyphosis, large cervical osteophytes, or a small oropharyngeal opening. In patients with a small ZD (less than 2 cm), an insufficient cricopharyngeal myotomy may be performed, although placement of retraction sutures improves the exposure and divisibility of the common wall. Even with these sutures, retraction of the common wall may not be possible in the patient with recurrent small ZD from an earlier external approach, because of scarring.[98] Collard and associates[97] proposed that by sawing off the distal part of the Endo-GIA 30 stapler anvil, a section of the common wall more distal to the bottom of the diverticulum could be accomplished. However, in addition to its introducing avoidable risks to the procedure by potentially affecting the integrity of the staple closure, we have found such a modification unnecessary.[108]

Last, although the pouch can be inspected thoroughly and biopsy specimens obtained, a complete specimen is not obtained for pathologic assessment. This lack of complete specimen could prevent the discovery of carcinoma within the pouch. Fortunately, carcinoma in a diverticulum is extremely rare, found in less than 0.25% to 0.50% of cases, although in one review of 50 excised ZDs, Bradley and coworkers[25] reported an unusually high percentage, 8% of diverticula in their series containing squamous cell carcinoma or carcinoma in situ. The main factor in ZD carcinoma development is thought to be chronic inflammation of the diverticulum lining through many years from food retention, which would be minimized after ESD.[25,112] Along with intraoperative assessment, possible malignancy may be suggested when there is a sudden increase in severity of symptoms such as progressive dysphagia, pain, hemoptysis, or more marked regurgitation of food.[25,112] A barium swallow study may also suggest a malignancy when it reveals a loss of smooth contour within the pouch interior and a filling defect that does not move between films, although most often it is a result of retained food particles.[25] In these rare situations, ESD is contraindicated and external approaches to excise the diverticulum are recommended.[112]

Current experience suggests that ESD is superior to external, as well as other, endoscopic approaches.[27,31] Because the common wall edges are simultaneously divided and "sutured" with staples, there is a reduced risk of perforation that would allow salivary egress into the mediastinum, predisposing to mediastinitis. Furthermore, thermal damage to the recurrent laryngeal nerve from cautery is avoided, and there is no need for any expensive equipment such as a laser source. ESD procedures are performed faster, and patients recover more quickly than with external and other endoscopic techniques.[27,75,107,113] In addition, ESD may be used not only for ZD but also for other forms of hypopharyngeal and pharyngeal diverticula (see Fig. 74-3).[22,31,98,104-106] Overall, ESD has a reported 2.6% complication rate and 0.3% mortality, which compare favorably to external approaches (11.8% complica-

tion rate and 1.6% mortality) and other endoscopic approaches (7.4%-8.1% complication rate and 0.2% mortality).[27] The 1996-1997 report from the National Confidential Enquiry into Perioperative Deaths in head and neck surgery also concluded that endoscopic surgery is a quicker, less invasive, and safer technique.[114]

Complications unique to ESD exist, but are rare and described in case reports. Esophageal perforation was reported secondary to possible technical failure of the endo-stapler or excessive width of the common wall.[115] However, Richtsmeier and Monzon[116] brought to light that differences do exist between stapler cartridges and discovered that one particular type (TR45B 3.5-mm cartridge for the Endopath ETS Flex45 Endoscopic Articulation Linear Cutter stapler, Ethicon, Inc., Somerville, NJ) was more prone to leaks at the incisional apex at lower intraluminal pressures.[116] Persistent foreign body sensation and odynophagia were reported after ESD because of retention of a clump of staples in one case and a piece of silk retention suture in another.[106,117] Removal of the staples and stitch, respectively, resulted in symptomatic relief. Finally, a fatal case of mediastinitis as a result of delayed perforation on postoperative day 2 has also been reported, although in this case report, no mention was made whether the pouch and divided wall were examined carefully for perforation intraoperatively, a practice that needs to be performed at the conclusion of every procedure.[118]

Recurrence

Regardless of the technique used, whether external or endoscopic procedures, postoperative relief of symptoms has been found to be achieved in more than 90% of patients in the short term. However, the rate of

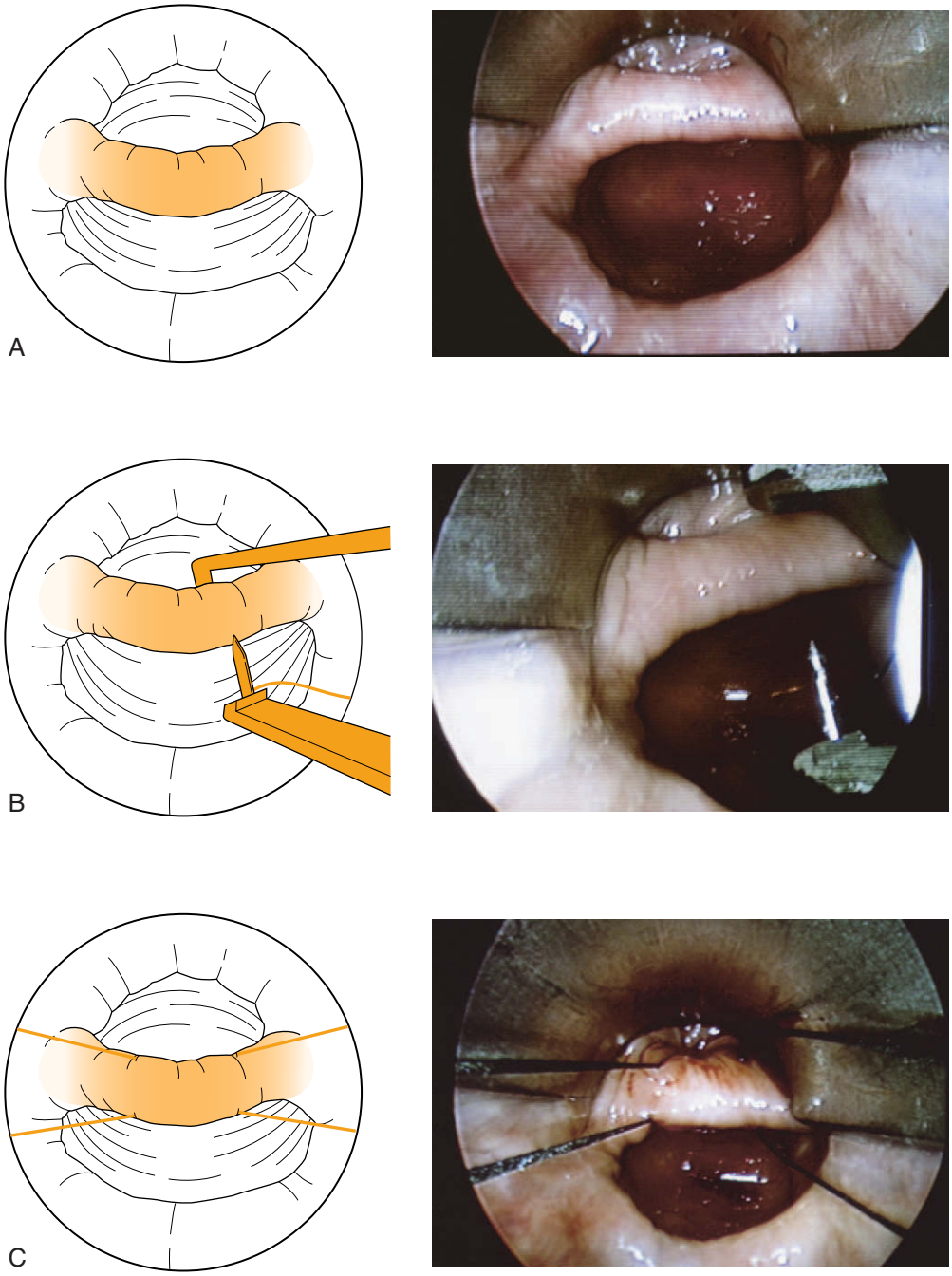

Figure 74-15. Technique of endoscopic staple diverticulostomy as seen with a rigid telescope. Drawings are accompanied by corresponding intraoperative photographs of the procedure. **A,** Common wall visualized with a Weerda laryngoscope. **B** and **C,** With an ENDOSTITCH suturing device, retraction sutures are placed on the lateral aspects of the common wall.

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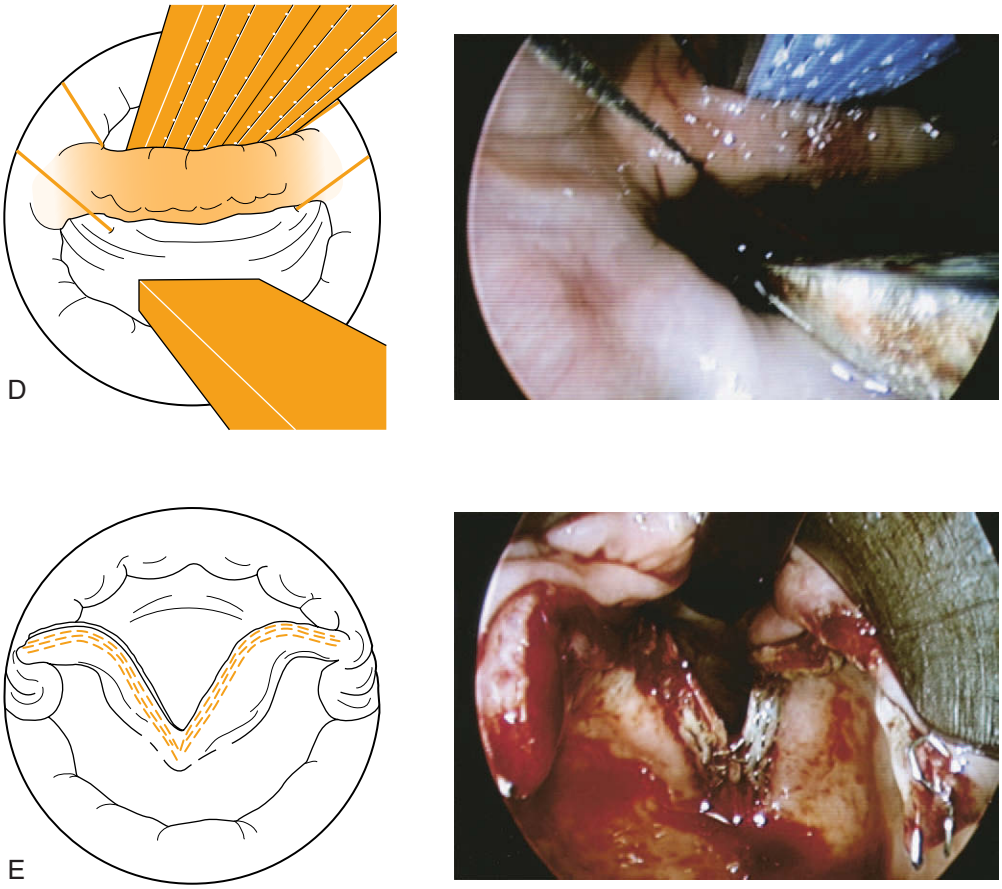

Figure 74-15, cont'd. **D,** The common wall is positioned between the blades of the stapler. **E,** The common wall is divided after the stapler is activated. The retraction sutures are cut and removed.

recurrence of preoperative symptoms after surgery has been found to be variable with the different surgical approaches. Recurrence rates of 0% to 19% for external approaches have been reported with variable length of follow-up.[27] For endoscopic approaches, recurrence rates between 0% and 22% have been reported, also with variable length of follow-up.[27] In a large cohort study of 159 ESD cases with 32.2 months average follow-up, there an 11.8% recurrence was reported.[27] Interestingly, this last study exhibited a bimodal distribution of recurrences, with partial return of symptoms occurring on average 33.9 months after ESD and complete return of symptoms occurring earlier, on average 8.5 months after ESD. Several reasons may explain this distribution. The relatively short interval before complete recurrence may be a result of incomplete division of the cricopharyngeal muscle as well as restenosis of the common wall from scarring. In one patient, the procedure made symptoms worse within 6 weeks. This patient was found at the time of revision ESD (5 months later) to have scar formation across the diverticulostomy of the common wall. Theoretically, reflux may irritate the freshly divided edges of the common wall and encourage scar tissue formation during the healing process, resulting in early restenosis of the common wall and recurrence of symptoms at an earlier time point. Findings of a partial or complete scar band at the earlier ESD diverticulostomy site for revision ESD support such inflammatory factors in wound healing. Furthermore, gastroesophageal reflux has been postulated to lead to cricopharyngeal spasm, which may predispose to the development of ZD.[42,77] Many patients with ZD also have gastroesophageal reflux, correction of which has been shown to lead to normalized upper esophageal sphincter pressures.[42,77]

Patients with minimal return of symptoms, however, may have reformation of ZD because of slow processes similar in pathophysiology to that of the processes that led to its initial formation, a process that takes years, unlike scar formation from aberrant healing, which takes only weeks. It is possible in some of these patients that the cricopharyngeal muscle was incompletely divided, leading to partial reformation of ZD during many months to years that results in partial, but not complete, return of symptoms. However, without performance of a direct laryngoscopy on these patients to assess the ZD, it is impossible to say with certainty, given the aging population, whether other factors unrelated to ZD may be developing, contributing to the appearance of these symptoms (see Table 74-1).

Intraoperative measures to decrease the chance of recurrence and complications include the use of retraction sutures to help position the common wall and allow the stapler to have total access to the cricopharyngeal muscle for maximal sectioning, as well as for the removal of any loose staples or retained sutures immediately after the common wall is divided to prevent mucosal edge irritation and subsequent restenosis.[31] After ESD, several measures may be pursued to help minimize inflammation, which otherwise may lead to restenosis of the common wall. Proton pump inhibitors are routinely prescribed for 2 to 3 months after surgery regardless of whether the patient had symptomatic reflux. Even in the literature for external approaches, some surgeons have advocated treatment of reflux postoperatively to reduce risk of recurrence, although others dispute any role of reflux in recurrence.[7,83] Endoscopic staple diverticulostomy does not induce thermal injury and inflammation to the tissues, as do CO_2 laser and electrocautery, which may encourage scar tissue formation. Finally, control of factors that may affect swallowing other than ZD must be performed to achieve greatest chance of symptom relief.[98]

The vast majority of patients who experience recurrence of ZD after primary excision by the transcervical route or any manner of endoscopic diverticulostomy may undergo revision ESD without any increase in technical difficulty or greater morbidity.[27,31,98,103-105] However, revision ESD may not be the best option for those patients

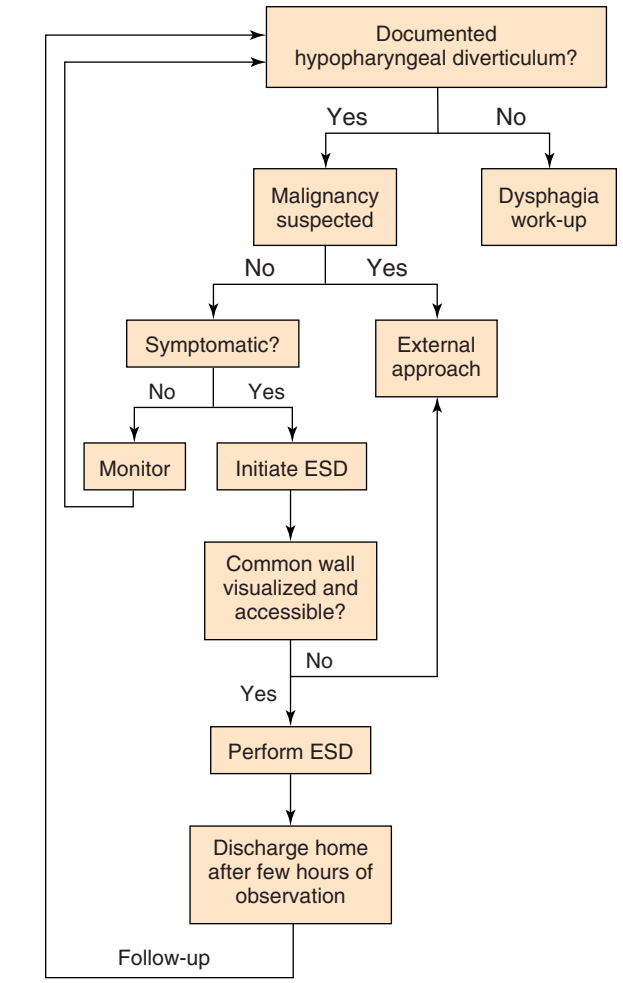

Figure 74-16. Algorithm for the approach to a patient in whom Zenker's diverticulum is suspected. ESD, endoscopic staple diverticulostomy.

with a very small recurrent pouch (1 cm or less) who have had previous external diverticulectomy, because scarring from earlier treatment and small diverticular size make retraction of the common wall into the stapler blades difficult.[98] Such patients should be counseled to undergo observation or external reoperation, depending on symptom severity.[98] Unlike revision ESD, external reoperations are technically demanding and have a much higher incidence of complications secondary to adhesions and distorted anatomy.[1,84] Indeed, Payne[84] reported much higher complication rate (51% vs. 2%) and mortality (3% vs. 0.9%) for further external operations than for primary procedures performed during the same period.

Summary

Zenker's diverticulum is a common acquired pulsion esophageal diverticulum found in the elderly population. Patients become symptomatic, with dysphagia, regurgitation, and aspiration, necessitating surgical correction. The etiology remains unknown but centers on cricopharyngeal muscle abnormalities. Historically, diverticulectomy with cricopharyngeal myotomy has been performed for this condition. However, with technical advances, endoscopic approaches, particularly endoscopic staple diverticulostomy, have become the treatment of choice for both initial presentation and recurrences, because of lower treatment-associated morbidity and mortality as well as shorter convalescent periods. Knowing how to perform all the various external approaches to address ZD is important in the armamentarium of the otolaryngologist–head and neck surgeon for those patients in whom ESD cannot be performed or diverticular carcinoma is suspected. A recommended treatment algorithm is offered in Figure 74-16. As new surgical advances occur, recommendations will be expected to evolve.

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CHAPTER SEVENTY-FIVE

Tracheobronchial Endoscopy

Rex C. Yung

Emily F. Boss

Key Points

- The most common standard nomenclature for the bronchi is to label them by generation, whereby the trachea is the zero-generation bronchus, right and left mainstem bronchi are the first-generation bronchi, and so forth.
- Indications for bronchoscopy include the evaluation of respiratory symptoms such as hemoptysis, cough, or dyspnea; the assessment of an endobronchial or mediastinal mass noted on radiographic studies; as guidance during a difficult intubation; and the evaluation of congenital airway anomalies.
- In preparation for diagnostic or interventional bronchoscopy, a contrast-enhanced CT scan is useful to provide spatial relationships between lung pathology and vasculature and to minimize risk of injury during interventional procedures.
- Although flexible fiberoptic bronchoscopy offers great diagnostic and therapeutic opportunities, an important advantage of rigid bronchoscopy is that its wider lumen affords access to larger instruments, which may be necessary for foreign body removal, placement of airway stents, and control of hemoptysis.
- Numerous methods exist to diagnose pulmonary pathology, including bronchial wash, bronchiolar lavage, transbronchial biopsy, and transbronchial needle aspiration. Endobronchial ultrasonography may assist in directing biopsy.
- Tissue débridement via bronchoscopy is generally assisted using freezing, heating, or biochemical methods of causing cell death. Cold techniques include use of forceps, powered microdebrider, or cryotherapy. Heat-assisted resection is performed using laser, argon plasma coagulation (APC), or electrocautery. Photodynamic therapy (PDT) and endobronchial brachytherapy (EBBT) are biochemical destructive methods.
- Balloon bronchoplasty and endobronchial stent placement are techniques that assist in maintaining airway patency in an airway that is narrowed or has been reopened by débridement.
- Autofluorescence bronchoscopy is an evolving method for early detection of preinvasive lung cancers.

Careful consideration of the central and peripheral airways, pulmonary parenchyma, and vasculature is germane to the evaluation of the head and neck. Rapid advances in technology of the realm of imaging are making possible ever more accurate characterization of the anatomic distribution and metabolic properties of normal tissues and pathologic lesions in the head, neck, and thoracic structures. However, there remains no substitute for tracheobronchial endoscopy in the performance of a detailed examination of the airway mucosa and in directing biopsies and interventional procedures.

This chapter reviews the current technology of tracheobronchoscopy with a focus on the advances in flexible bronchoscopy and incorporation of various ancillary diagnostic technologies, such as endobronchial ultrasonography (EBUS) and autofluorescence (AF) bronchoscopy. Therapeutic airway interventions for both benign and malignant lesions will also be briefly reviewed.

Airway Anatomy and Nomenclature

The basic pulmonary function of gas exchange occurs at the level of the alveolus, located in the distal acinus beyond respiratory bronchioles, but for the purpose of the bronchoscopist, it is more important to recognize the more proximal airway divisions. Distal to the trachea and the mainstem bronchi, the lobar bronchus defines the division of the lobes, and the segmental bronchi the pulmonary lobules (Fig. 75-1). There are thus three lobes in the right lung, with normally ten segmental lobules, although there may be some anatomic variants. In the left lung, the left upper lobar segments and the lingular subsegments come off the same left upper lobe bronchial division, which also explains why resection of the left upper lobe often requires inclusion of the lingular, and vice versa. Because of the anatomic divisions, the left lung is often divided into nine segmental lobules, although here again there are anomalies, and the bronchoscopist should be familiar with the variations. Because of the location of the heart, the right lung usually accounts for 55% to 60% of the total lung parenchyma, and the left lung the smaller remainder. This information becomes important in estimations of residual pulmonary function after a planned lobar resection or pneumonectomy.

An additional source of frequent confusion in the naming of the segmental and subsegmental bronchi has to do with the frequent but incorrect interchange of the terms *generation* and *order* of the bronchial segments. Standard nomenclature of the human airways denotes the trachea as the zero-*generation* airway, with each of the right and left mainstem bronchi being the first generation, lobar bronchi the second generation, lobar segmental bronchi the third generation, and so forth. Conversely, *order* of airway segment refers to the retrograde counting from the "lobular bronchiole," which is the first airway segment with a diameter of less than 0.7 mm. Hence, more central airways of a larger

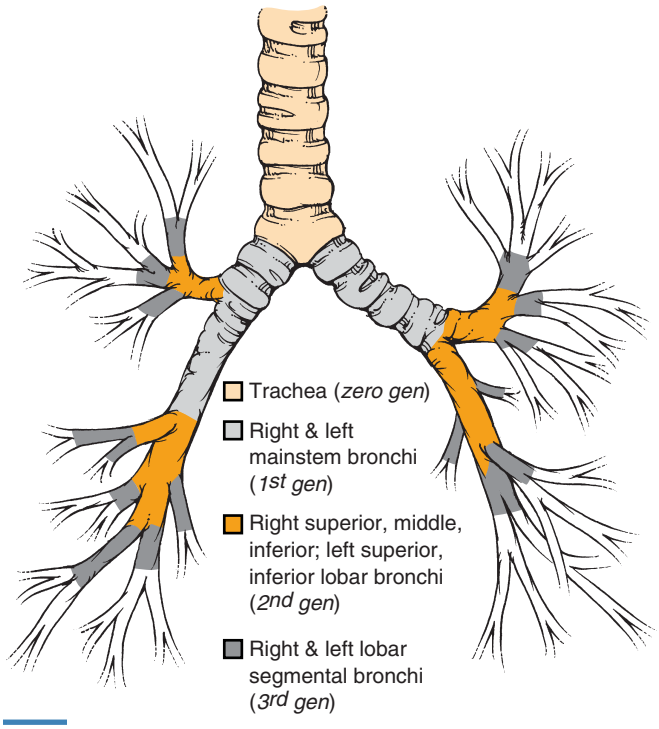

Figure 75-1. Tracheobronchial schema. Gen, generation. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

dimension actually have a higher order.[1,2] However, given the uneven segmentation and subsequent diminution of airway calibers, there is far less uniformity of division of airway in the different lobes, and lobules narrow down to 0.7 mm. Hence, the standard textbook description of the 0.7-mm lobular bronchiole located in the 10th- to 14th-generation bronchi does not match the bronchoscopic findings of airways navigable by a bronchoscope significantly wider than 0.7 mm beyond the number of branchings described previously.[2-4] In summary, it is best to use the term *generation* in the description of sequential airway branching, starting from the trachea. Dr. Shigeto Ikeda,[5] regarded as the founder of modern fiberoptic bronchoscopy, also developed a detailed system of naming segmental and subsegmental airways branchings, but that topic is beyond the scope of this chapter.

Indications and Preparations for Tracheobronchoscopy

Indications

Indications for tracheobronchoscopy include the evaluation of acute or chronic respiratory symptoms such as hemoptysis, nonresolving and worsening cough, and acute or worsening subacute dyspnea that may be accompanied by wheezing or stridor, pleurisy, chest pain, fever, or other symptoms suggestive of a pulmonary process (Box 75-1). Symptoms may be accompanied by radiographic abnormalities suggesting an endobronchial lesion, extrinsic compression of the airways by a mediastinal or lung mass, or presence of an infiltrate. Patients are often also referred for evaluation of asymptomatic lung or mediastinal masses and nonresolving parenchymal lung infiltrates. Pleural effusions usually lead to evaluation of the pleural fluid; however, effusions most often have an underlying parenchymal pulmonary cause, and a nonresolving effusion without an established cause after thoracentesis or thoracoscopy should prompt an examination for endobronchial obstruction. Bronchoscopy is helpful in assessing the placement of endotracheal tubes, especially in difficult intubation cases or when double-lumen tubes are required. A flexible fiberoptic bronchoscope (FOB) can be used to guide placement of an endotracheal (ET) tube in a difficult airway; in such cases, the ET tube is prepositioned and advanced over the bronchoscope. An FOB can also be used to guide percutaneous tracheostomy. Indications for tracheobronchoscopy in children include suspected foreign body, respiratory distress secondary to tracheomalacia or bronchomalacia, and evaluation of other congenital anomalies. Depending on the findings on radiography or during a diagnostic bronchoscopy, therapeutic interventions may be performed with an FOB to maintain airway patency and improve gas exchange.[6,7]

After consideration of the indication for the procedure, the next steps of planning should include the multimodality team of otolaryngologists, pulmonologists, radiologists, anesthesiologists, nurses, respiratory therapists, "backups" in thoracic surgery and interventional radiology if their services may be needed, and, not least, the patient and family for careful discussion and informed consent.

Box 75-1

Indications for Tracheobronchoscopy

Diagnostic Evaluation

Chronic nonresolving or worsening cough, especially with signs of aspiration
Voice change, hoarseness
Stridor
Wheezing unresponsive to bronchodilator
Hemoptysis
Pulmonary infections: acute processes not responsive to empiric therapy; recurring pneumonias in the same location
Progressive dyspnea
Radiographic abnormalities:
- Volume loss with suggestion of central airways obstruction
- Isolated lung mass(es)
- Infiltrate(s), localized or diffuse
- Mediastinal masses, adenopathy
- Nonresolving atelectasis
- Nondiagnosed pleural effusion with underlying lung consolidation

Interventional

Assistance in securing the airway: intubation over the bronchoscope; confirmation of position of endotracheal tube; assistance with double-lumen intubation
Removal of foreign body
Therapeutic aspiration of blood clots, inspissated mucus
Relief of central airways obstruction, both benign and malignant causes:
- Thermal ablation and mechanical removal of tumor
- Débridement of benign stenosis
- Balloon dilation
- Airway stent placement to maintain airway patency
- Guidance of percutaneous tracheostomy

Radiology

Given the millimeter-range high-resolution and rapid multiplanar reconstruction of the airways achievable with multislice spiral computed tomography (CT) scanners, a preprocedural CT scan can help pinpoint the location and extent of disease and reduce the time spent on exploration in patients with limited cardiopulmonary reserve. A contrast-enhanced CT scan is especially useful to provide the spatial relationship between pathology and vasculature and, hence, to minimize the risk of accidental and potentially life-threatening vascular injury from interventions such as laser or mechanical débridement. Contrast-enhanced atelectatic lung parenchyma can often also indicate whether there is viable lung tissue beyond central obstruction. Three-dimensional measurements of airway stenosis length and diameter facilitate the preselection of balloons for bronchoplasty and of airway stents for maintaining patency in an obstructed airway segment. A

thoracic surgeon or interventional radiologist should be consulted before the bronchoscopic investigation of massive hemoptysis, in case the bleeding source can only be identified—but not quelled—by bronchoscopic interventions.

Sedation and Airway Management

Maintaining gas exchange is critical during bronchoscopy, together with the desire of minimizing patient discomfort and anxiety. Some level of sedation, monitoring, and augmentation of oxygenation and ventilation is carried out with the assistance of an anesthesiologist or nursing personnel certified in sedation and airway management. Conscious sedation usually involves intravenous sedation with short-acting benzodiazepines (midazolam is most commonly used) or other anxiolytic agents plus a short-acting narcotic (e.g., fentanyl, meperidine, or morphine sulfate) to help suppress the cough reflex. My colleagues and I also find promethazine (Phenergan) useful in patients who are difficult to sedate or who have a strong gag reflex. The medications are given in measured, small boluses and the patient is appropriately monitored with hemodynamics, cardiac monitors, and pulse oximeters. Not yet routinely used but increasingly available is transcutaneous capnography. Deep sedation with propofol (Diprivan) provides for rapid on-and-off titration of sedation and can be very helpful in some patients who are difficult to sedate. General anesthesia with inhalational anesthetics with or without intravenous sedation provides the greatest control, but this would mandate the use of an ET tube, laryngeal mask airway (LMA) ventilation, rigid endoscopy with side-port ventilation, or a previously placed tracheostomy. It is also contingent on the presence of an anesthesiologist or a nurse anesthetist, who may not be readily available for bronchoscopies performed in endoscopy units separate from the operating rooms.

For patients undergoing bronchoscopy under conscious sedation, topical anesthetics are commonly used to reduce the amount of systemic sedative-narcotics needed to suppress cough, and also to diminish local discomfort in the nasopharynx during the passage of the bronchoscope. Lidocaine and its derivatives are most commonly used and applied topically as a gel to the nasal passage or as a spray to the posterior oropharynx. Solutions with concentrations between 1% and 4% are available, but the operator must pay attention to the total dosage applied because systemic lidocaine toxicities, including inadvertent deaths in healthy research subjects, have been reported when more than 500 to 1000 mg is delivered topically in a single session.[8] Therefore, except for spraying to the posterior oropharynx, we limit the use of topical lidocaine injected via the operating channel of the bronchoscope onto the vocal cords and airway mucosa to less than 3 to 4 mg/kg total dosage (1% lidocaine has 10 mg of lidocaine per 1 mL solution). Cocaine is also a very effective topical anesthetic that has the advantage of vasoconstricting the nasal mucosa membrane; it is, however, not generally available for use in the average endoscopy suite.

Miscellaneous medications that can be used in bronchoscopy include atropine or glycopyrrolate in patients with excessive secretions. Chronic bronchitis patients with acute bronchitis and patients with preprocedural problems handling bronchial secretions may be good candidates for parasympathomimetic agents. Caution should be used because such agents can precipitate tachycardia.

Patient Positioning and Route of Bronchoscope Entry

In a patient under conscious sedation with or without a previously placed tracheostomy, a flexible bronchoscope can be introduced with the patient supine or in a sitting position. It is generally easier for the bronchoscopist to be standing at the head of the bed. If a nasal approach is chosen, a cotton swab soaked with a lidocaine solution or gel is used to determine which of the nares permits easier passage. Studies have found shorter and smaller patients to experience greater postprocedural nasal discomfort when the same-sized bronchoscope is used; hence, for such patients, an oral approach may be preferable. Conversely, because of the sharper angulation of the bronchoscope at the posterior oropharynx when introduced orally, patients tend to have a greater gag response; therefore, a more thorough application of topical anesthetics to the posterior oropharynx is recommended. Because of the risk of trauma to the teeth and the instrument being used, a properly secured bite block is mandatory in this approach. For rigid bronchoscopy, although the early pioneers performed the procedure on fully conscious patients placed in a sitting position, the procedure should be carried out with the patient supine and the neck extended. The patient is almost always fully anesthetized with paralysis to facilitate the passage of the rigid bronchoscope. The rigid bronchoscope can most easily be introduced via the oral route. The insertion and maneuvers of the rigid bronchoscope as well as the proper ventilation and anesthesia are discussed later.

Ventilation and oxygenation can be better maintained in a more upright patient under lighter sedation. With a flexible FOB, the approach is made from the front of the patient. The approach via the nares or an oral passage is similar, although the view on the monitor is inverted because of the position of the bronchoscope tip relative to the approach. Once past the vocal cords, the bronchoscope can easily be turned to regain the familiar view with the ventral or anterior surface of the body facing the top.

In patients under deep sedation or general anesthesia, either a flexible FOB or a rigid bronchoscope can be used to examine the airways. For a flexible FOB, gas exchange is maintained with either an ET tube or a laryngeal mask; the latter is usually sufficiently large such that bronchoscope size is not a factor in limiting adequate ventilation and oxygenation. Prior discussion with the anesthesiologist ensures that a sufficiently large ET tube is inserted to permit smooth passage of the bronchoscope. For therapeutic cases using bronchoscopes with a diameter of 6.0 mm or greater, an ET tube of at least 7.5 mm is needed. Additional options are (1) to perform direct suspension laryngoscopy with intermittent ventilation via an ET tube alternating with bronchoscopic examination and intervention and (2) to perform direct suspension laryngoscopy using spontaneous ventilation and passive oxygenation.

To facilitate passage of the flexible bronchoscope, water-soluble lubricants are applied to the sheath of the bronchoscope. Lubricant jelly has the disadvantage of drying rather quickly, leading to stiffness in maneuvering, especially when the scope is introduced nasally. Lidocaine jelly is a good alternative that also provides some local anesthesia. Newer compounds, such as Endo-Lube (Covidien, Mansfield, MA) provide excellent lubrication and are ideal when the bronchoscope has a tight fit through devices such as an ET tube. Its cost may be higher, and caution is necessary to prevent accidental dislodgement of the ET tube from the ventilator because the lubricant also makes the various connections between the ET tube and ventilator circuit slippery. Mineral oil should not be used if at all possible because of the potential of oil aspiration leading to a lipoid pneumonia.

Patient Discussion and Informed Consent

Well-informed and educated patients and families are more likely to be compliant with therapy. In the case of bronchoscopy, especially in patients undergoing conscious sedation, an explanation of the steps helps alleviate the anxiety over the coughing and gagging that can sometimes force premature termination of the procedure. Ancillary diagnostic and therapeutic procedures, especially on hyperemic inflamed or malignant tissue, often lead to bleeding and postprocedural hemoptysis that should taper off. Similarly, a substantial portion (25%-50%) of patients may experience transient postprocedural fever during the first 24 hours. The cause need not be infectious and may be more common after bronchoalveolar lavage (BAL), which can result in surfactant washout. Informing patients of these two possible minor complications can obviate anxious midnight calls to the physician after a procedure. Conversely, patients should also be warned about prolonged bleeding and delayed pneumothoraces that may not be detected immediately after the procedure. Persistent or high spiking fevers, hemoptysis, and worsening dyspnea should prompt the patient to immediately contact a physician, who may perform a reevaluation with radiograph, physical examination, and other laboratory tests, as indicated.

Rigid Bronchoscopy

Rigid bronchoscopy retains certain important advantages over flexible fiberoptic bronchoscopy, including the much larger lumen that affords access to larger instruments, which may be necessary to remove foreign

bodies, to provide adequate suction in brisk hemoptysis, to place noncompressible polymeric silicone (Silastic) airway stents, and to use the bronchoscope itself to core out tumors and provide direct tamponade to a bleeding source. Rigid bronchoscopy today is performed almost exclusively in patients under general anesthesia, and rarely with the use of only topical anesthesia and conscious sedation without paralytics. More commonly, intravenous deep sedation, with or without inhalational anesthetics, is used. A variety of ventilatory strategies are used, from intermittent apneic ventilation to spontaneous/assisted ventilation. Oxygenation and ventilation can be provided by tidal volume through a closed system or via an open system with side-port Venturi jet ventilation.

Before insertion of the rigid bronchoscope, either alone or with a telescope lens through it to provide a better distal view, the patient must be examined for neck stability and for any loose teeth or dentures. A shoulder roll may give room for added extension of the neck. With or without a tooth guard to protect the upper teeth, the operator's left thumb is placed over the upper teeth and the index finger scissors open to lift up the lower teeth of the relaxed jaw. The bronchoscope with the bevel up is then directed midline and almost perpendicularly toward the hypopharynx until the uvula is passed. The operator thereafter slowly levels the bronchoscope angle toward the horizontal, seeking out the epiglottis while lifting the base of the tongue. When the vocal cords are clearly visualized, the bronchoscope is rotated 90 degrees such that the beveled edge can enter the trachea along the length of the vocal cord, thereby limiting trauma to the cords. Once the tip of the rigid bronchoscope is clearly in the trachea, it is rotated back to its starting position with the bevel up. The operator's left hand and finger positions are maintained to protect the teeth, although it is also necessary to occasionally use the left hand to provide a better seal around the cuffless rigid bronchoscope at the level of the cricoid and thyroid cartilages when ventilation is applied. Because larger operative rigid bronchoscopes with diameters of 11 to 12 mm are now available for insertion of silicone stents, upper airway and vocal cord edema may be a more severe problem at the end of a prolonged procedure; hence careful examination of the cords and hypopharynx is important to avoid postprocedural stridor and upper airway obstruction. With the advent of flexible fiberoptic bronchoscopy, the number of pulmonary teaching programs routinely including rigid bronchoscopy in their training curriculum is falling. Therefore, even though rigid bronchoscopy should be a skill acquired by all bronchoscopists, generally only those being trained in otolaryngology–head and neck surgery, thoracic surgery, or interventional pulmonology generally receive adequate exposure to and practice with this technique.[9]

Flexible Fiberoptic Bronchoscopy

Advances in fiberoptics, illumination, and image capture, including the use of true color-chip charged couple device cameras embedded in the distal tip of the FOB, have greatly improved the imaging capabilities of the FOB. Most new flexible FOBs are now videoscopes with high-resolution true-color rendition of the image captured by the distal chip. The illumination is still delivered via fiberoptic bundles. The improved imaging quality and the ease of recording areas of interest with digital still images or video segments are offset by the cost of these instruments as well as those of the dedicated processor and high-quality video display units. The startup cost of such a setup with two videobronchoscopes is in the $60,000 to $80,000 range. Conventional FOBs, in which the image is relayed via fiberoptic bundles and viewed at the proximal end of the FOB by the eyepiece or connected to a video display, continue to have a role. This is especially true for FOBs used at the bedside or during operations to confirm the position of standard or dual-lumen ET tubes and for the attachment of special illumination and visualization devices, such as during autofluorescent bronchoscopy.

Range of Flexible Bronchoscopes and Special Features

Although there remains the tendency to subdivide bronchoscopes into "adult" and "pediatric" categories depending on their outer diameters, this distinction is arbitrary. Because bronchoscopists venture more peripherally with FOBs to sample focal lesions, and more interventional procedures via a flexible FOB are performed in the pediatric population, it makes more sense to describe the bronchoscopes and leave their judicious application to the bronchoscopist according to experience and the situational need.[3,4]

All FOBs have an illumination fiberoptic bundle and imaging fiberoptics or a camera. With the exception of the very few "ultrathin" bronchoscopes, there is also a channel for suction of secretions and blood, for the passage of topical medication and fluid for washing, and for the passage of various instruments for diagnostic retrieval of tissues or for therapeutic procedures (Table 75-1). The "average" diagnostic bronchoscope has an outer diameter of 5.0 to 5.5 mm and an operating channel of 2.0 to 2.2 mm. This caliber channel admits most cytology brushes, bronchial biopsy forceps, and transbronchial aspiration needles with sheathed outer diameters between 1.8 and 2.0 mm. Smaller bronchoscopes, in the range of 3.0 to 4.0 mm at the outer diameter and correspondingly smaller channels, are usually given a "P" designation (for pediatrics), but they can, of course, be used in the adult airways when narrowing is present because of benign strictures or malignant stenosis. Newer generations of "slim" video and fiberoptic bronchoscopes have a 2.0-mm operating channel with a 4.0-mm outer diameter. The one disadvantage of these bronchoscopes is the sacrifice of a smaller image area because of fewer optical bundles.

Larger "therapeutic" bronchoscopes (often designated with a "T" in the model number) can, of course, also be used for diagnostic purposes, but the larger outer diameter can cause greater discomfort and mucosal trauma in a conscious patient and can be harder to pass through an ET or tracheostomy tube, and thus can also impair gas exchange to a greater degree. Such therapeutic bronchoscopes have outer diameters between 6.0 and 6.3 mm, with operating channel lumens between 2.6 and 3.2 mm. Certain therapeutic instruments, including larger laser fibers, larger electrocautery forceps designed for gastrointestinal endoscopes, cryotherapy probes, and expandable balloons for bronchoplasty, require these larger diameters for their use through FOBs. Prototype bronchoscopes with a 9-mm outer diameter and a 5-mm operating channel have been made, the main application of which is to provide access for therapeutic instruments to airway segments that cannot normally be reached by rigid open-tube bronchoscopes and telescopes (Fig. 75-2).

At the other extreme are the ultrathin bronchoscopes, with outer diameters smaller than 3 mm. The Olympus production models fiber BF-XP40 and video BF-XP160F (Olympus America, Center Valley, PA) have outer diameters of 2.8 mm and operating channels of 1.2 mm. Special instruments (e.g., reusable cytology brush and forceps) of the proper caliber are available for tissue sampling (Fig. 75-3). Handling of these ultrathin bronchoscopes is often more challenging because their very floppy tips make steering more difficult. Suction via the narrow channels is also much more limited. Nevertheless, with practice and the use of small amounts of saline to flush open the distal airways in guiding the bronchoscope forward, the ultrathin bronchoscopes can traverse 12 to 16 generations of airways and, under fluoroscopic or CT guidance, are seen to approach the periphery of the lungs to sample focal lesions.[3,4] The passage of a 2.8-mm instrument beyond the mid-teens division of the lobular bronchiole (measured at 0.7 mm in fixed tissue) calls into question some of the accepted measurements of the adult human airways. To permit the greater distance traversed, such ultrathin bronchoscopes usually have an operating length of 60 cm, 5 cm longer than the older bronchoscopes, although the current generation of videobronchoscopes are all built with a 60-cm working length.

New bronchoscopes manufactured today usually have a white ceramic insulated tip; this feature permits the safe use of electrocautery instruments with reduced risk of retrograde electric shock to the bronchoscopist and damage to the bronchoscope (see Figure 75-2).

Certain bronchoscopes designed for autofluorescence imaging have built-in filter wheels that are adjustable to facilitate imaging at specific spectral frequencies. Autofluorescence bronchoscopy is briefly mentioned in a later section of this chapter.

Care of the Flexible Fiberoptic Bronchoscope

Unlike the sturdy rigid bronchoscope, the flexible FOB is much more delicate, with glass fiberoptic bundles that can be easily damaged by

Table 75-1

Available Flexible Bronchoscopes, Dimensions, and Features

Manufacturers and Model Numbers	Features	Outer/Channel Diameters (mm)	Length (cm)
Fujinon, Inc. (Wayne, NJ)			
CHO-SP	Fiber	4.9/2.0	40
BRO-YP2	Fiber	4.8/2.0	57.5
BRO-Y35	Fiber	5.7/2.0	57.5
BRO-YL2	Fiber therapeutic	6.4/2.6	57.5
EB-270S	Video	4.9/2.0	60
EB-270T	Video therapeutic	5.9/2.8	60
EB-470S	Video	4.9/2.0	60
EB-470T	Video therapeutic	5.9/2.8	60
Karl Storz Endoscopy-America, Inc. (Culver City, CA)			
11001B11*	Fiber	5.2/2.0	55
11004B11*	Fiber therapeutic	6.4/2.8	55
Olympus America (Center Valley, PA)			
BF-N20	Fiber view only (no operating channel)	2.2	55
BF-XP160F	Video ultrathin	2.8/1.2	60
BF-XP40	Fiber ultrathin	2.8/1.2	60
BF-3C40	Fiber slim	3.6/1.2	55
BF-MP160F	Video thin	4.0/2.0	60
BF-P160	Video	4.9/2.0	60
BF-P40	Fiber slim (older)	5.0/2.2	55
BF-160	Video	5.2/2.0	60
BF-1T40	Fiber therapeutic	5.9/2.8	55
BF-40	Fiber Standard (old)	6.0/2.2	55
BF-1T160	Video therapeutic	6.0/2.8	55
BF-XT160	Video therapeutic	6.2/3.2	60
BF-XT40	Fiber therapeutic	6.3/3.2	55
Pentax Medical Company (Montvale, NJ)			
FB-8V	Fiber ultrathin	2.7/1.2	60
FB-10V	Fiber thin	3.4/1.2	60
FB-15V	Fiber	4.9/2.2	60
EB-1530T3	Video 30 series	5.3/2.0	60
EB-1570K†	Video K series	5.5/2.0	60
FB-18RX	Fiber	5.9/2.2	60
FB-18V	Fiber therapeutic	5.9/2.8	60
EB-1830T3	Video therapeutic	6.0/2.6	60
FB-19TV	Fiber therapeutic	6.2/3.2	60
EB-1970K†	Video k therapeutic	6.3/2.8	60

*Built-in filter wheel for tissue autofluorescence and drug-induced autofluorescence examination.
†Pentax's version of advanced color-chip camera.

rough handling or accidental patient bites. Repair of bronchoscopes is costly and makes the use of the instrument temporarily unavailable. The narrow operating channel can also be damaged by a number of instruments, especially when these are too large for safe passage. The two especially vulnerable portions of the flexible FOB are the angulated entry port of the working channel and the distal tip of the bronchoscope. Incompletely retracted transbronchial needle aspiration (TBNA) needles are most frequently the culprits, tearing the channel during their introduction or retrieval by an inexperienced user. Such damages are noted during the "leak test" that should be performed after each use of the bronchoscope and before machine washing. It should also be emphasized that the tip of the bronchoscope should be kept as straight as possible during introduction and retrieval of the instruments. The same care must be exercised in the use of the entire range of diagnostic and therapeutic instruments because tears can also occur with biopsy forceps improperly opened within the channel, pushing and pulling of semirigid instruments through the flexed tip of the bronchoscope, burning on the inside of a bronchoscope channel by improper activation of electrocautery instruments, or firing of laser fibers.

There is growing focus on nosocomial infections resulting from defective endoscopes (loose valves) or from improper cleaning techniques. Thus far, outbreaks of nosocomial bacterial infections (e.g., gram-negative bacilli and *Mycobacterium*) are rare, and there have not been confirmed reports of viral transmission. The prevalence of such infections is very low and should not discourage the appropriate performance of bronchoscopy when it can provide important diagnostic information or can aid therapy. There are a number of accepted cleaning techniques ranging from gas sterilization (ethylene oxide) to formaldehyde-based approaches. It is under the purview of the endoscopy unit or operating room director and nursing director to develop quality control measures.

Figure 75-2. *Left to right,* Range of fiberoptic bronchoscopes with outer/channel diameters of 4.9/2.0 mm and 6.0/2.8 mm, and a prototype therapeutic scope with diameters 9.0/5.0 mm. Note the insulated white ceramic plate, which is necessary for safe use of electrosurgery.

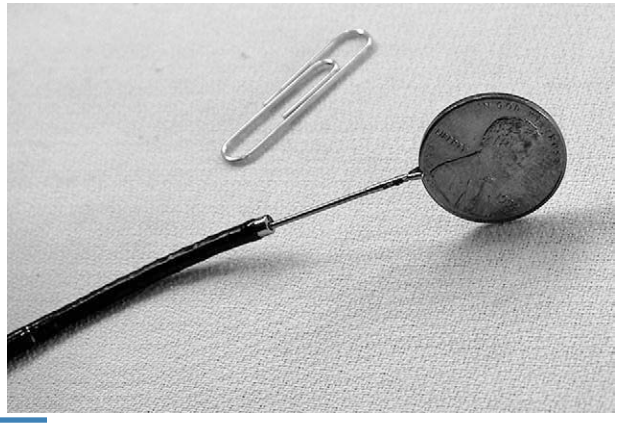

Figure 75-3. An "ultrathin" bronchoscope, with an outer diameter of 2.8 mm and a working channel of 1.2 mm, and a custom forceps holding up a U.S. penny and shown next to a paperclip for size comparison.

Diagnostic Fiberoptic Bronchoscopy

General Approaches

Although there is usually one primary indication for bronchoscopy, an orderly and uniform approach should be taken for airway examination so that important pathology will not be missed because of impatience to attend to the primary focus. Starting at the upper trachea, mucosal integrity should be examined. Even when there are no gross endobronchial lesions, the presence of extrinsic tracheal deviation and compression due to paratracheal masses should be noted. TBNA can often successfully provide a tissue diagnosis of extrinsic lesions.[10,11] Still under development is an array of ultrasound devices, balloon probes, and actual dedicated EBUS bronchoscopes that should help in the localization and characterization of such lesions. The posterior membranous portion of the trachea is sometimes the site of airway compromise caused by tracheomalacia or tumor invasion from esophageal cancers, and it is also the site of tracheoesophageal fistula. However, because of inflammation and redundant tissue, a tracheoesophageal fistula may be difficult to locate. Having the patient swallow 15 mL of methylene blue dye or food coloring immediately preceding bronchoscopy can aid in the localization of a tracheoesophageal tear or fistula. The distal trachea and main carina are important sites for examination because malignant diseases often metastasize to the surrounding mediastinal lymph nodes. The subcarinal, anterior carinal, and low paratracheal lymph nodes bilaterally are particularly suitable for TBNA.[10,12]

There is no set rule whether the left-sided or right-sided airways should be examined first. In general, unless marginal pulmonary reserve or cardiovascular instability severely limits the time available for bronchoscopic examination, both sides of the lungs should be examined because unexpected, radiographically occult airway pathology can occur in up to 10% of cases of primary bronchogenic carcinoma, and a smaller percentage in cases of metastatic disease. A thorough lobar and segmental review should not take more than 5 to 10 minutes. Countering the instinct to approach the area of suspected pathology, the bronchoscopist should first focus on the contralateral lung. Furthermore, unless the lesion is central and unavoidable, the bronchoscopist should examine apparently uninvolved lobes and segments to look for unexpected pathology. There are several reasons to practice this patience. First, once the main disease is visualized or diagnostic procedures are started, the bronchoscopist is often too distracted to return to a thorough and careful examination of the remainder of the airways. Second, once the site of primary pathology is sampled, bleeding can degrade the quality of the FOB image, and coughing and oxygen desaturation will limit the time to complete the procedure. Third, there is a danger that samples retrieved from a secondary site that appear abnormal and are found to contain malignant cells can actually represent contamination from cells dislodged during earlier examination of a primary cancer site. Although such false-positive results may have little significance in advanced obstructing central airways disease, this confusion could have the devastating effect of "over-staging" a potentially curable peripheral lesion.

Visual Examination

Less experienced bronchoscopists often regard confirming a positive tissue diagnosis as the main measure of a successful bronchoscopy. One should not, however, discount the value of getting a good "lay of the land" in terms of the dimensions of the airway, any significant anomalies in anatomy, and whether these are normal anatomic variants of the number of airway segments and the location of their branchings or are distortions resulting from prior surgery or endobronchial or extrinsic pathology. Such a "scouting" bronchoscopy with measurements of the length and the extent of airway compromise is especially important to planning potentially complex interventional procedures.

Bronchial Wash

Most often, some form of specimen is retrieved to diagnose pathology or, in the case of suspected opportunistic infections, to rule out with a greater certainty pulmonary infection by certain pathogens. Because there are always some airway secretions and, furthermore, aliquots of lidocaine solution and sterile saline are used to numb the airway mucosa and to clear the view of the airway, collecting a bronchial wash entails no more effort than connecting a "trap" in line between the suction port of the bronchoscope and the vacuum source providing suction. Care should be taken to secure the container used as a trap because if it is left dangling loose, the container could easily be inadvertently tilted or tipped over, with loss of sample easily occurs. The bronchial wash can be sent for cytology and culture. Concerns that the injected lidocaine may act as a bacteriostatic agent and hence may inhibit bacterial pathogen growth are unwarranted when one considers the overall dilutional effect. A much more valid criticism is that pathology such as malignancy or infections uncovered from examination of the wash may represent contamination introduced from the oropharynx and upper airways by the passage of the bronchoscope via the nares or oral cavity. For more peripherally located lesions, such as a lung mass or localized infiltrate, the bronchial wash seldom adds to the more specifically targeted sampling techniques listed here.

Bronchoalveolar Lavage

Accounting for the variations in airway compliance and caliber, the standard diagnostic bronchoscope and even the "pediatric" bronchoscopes with an outer diameter of between 3.5 and 5.0 mm can traverse through, at most, 7 to 10 generations of airways. This means that most

pulmonary masses and infiltrates are not directly visualized. With experience, and especially with the aid of radiographic guidance by fluoroscopy or by CT scanning, such lesions can be successfully diagnosed with different transbronchial techniques; however, the yield always depends on the skill of the operator and also tends to be lower than that of visible lesions, owing to sampling errors arising from the small size of samples retrieved. BAL is a technique that can provide a larger sample volume and also sampling of a larger lung field.

After identification of the region of the lung of interest, preferably down to the lobar segmental or subsegmental level, the bronchoscope is guided into the segment and "wedged" into place—that is, with gentle forward pressure, it is advanced and kept snug against the side walls of a bronchial segment. After the bronchoscope tip is maneuvered to obtain the best straightforward view into distal airway segments, aliquots of sterile saline ranging from 20 to 50 mL are gently infused. There should be a slight blanching of the airways. After each aliquot is infused, often with a column of air within the syringe to help propel the lavage fluid distally, suction is applied, either by depression of the suction button that activates the valve or by withdrawal on the syringe recently used to infuse the saline. The initial return is scant until a certain volume (possibly up to the functional residual capacity) is filled; thereafter, return should be more generous.

No set "standard" aliquot volume or total volume of normal saline is used for BAL, and the amount used depends on the amount of return and an estimate of how much sample is required for the desired battery of studies. In general, for the same total volume infused, a larger number of smaller aliquots of 20 to 30 mL (e.g., 4×25 mL vs. 2×50 mL) will yield a higher percentage of total volume recovered. Small-volume lavage return also appears to better reflect the peripheral lung cellular content. This finding may be the result of a longer dwell time in between aliquots, and because a greater number of sequences of infusion and suctioning can cause greater airway turbulence and agitation with better resultant washout of distal conducting airways and alveolar content.

In a supine patient, the yield is generally also better with BAL of anterior segments of the lungs—that is, lavage of the lingular and left upper lobe anterior segments and of the right middle lobe and right upper lobe anterior segments. In circumstances in which the infiltrate is in a dependent segment, such as the lower lobe superior segments or the posterior segments of the upper lobes, the return can be improved by positioning the patient in an appropriate decubitus position during the BAL. The yield from BAL is higher with infectious causes than with malignancy, although this difference is contingent on the expertise of the microbiology laboratory or cytology services. For certain infections, such as *Pneumocystis carinii* pneumonia (PCP) in a patient who has tested positive for human immunodeficiency virus, cytologic staining of a BAL specimen for PCP has a diagnostic sensitivity greater than 90%, and therefore transbronchial biopsies are not routinely necessary during the initial study. Conversely, other potential opportunistic organisms, such as *Aspergillus* species and cytomegalovirus (CMV) recovered from the BAL may be airway colonizers, and more definitive biopsy proof of tissue invasion may be needed before toxic therapy is initiated. The yield from BAL for malignant invasion of the lung parenchyma by primary bronchogenic or metastatic diseases ranges from 15% to 40% but is generally lower than that from more specifically targeted biopsies.

Complications from BAL are generally self-limited. Increased coughing after BAL is the most common. Whether coughing is due to induced bronchospasm or to washout of surfactant is unclear, and some practitioners advocate using saline warmed to body temperature to reduce bronchospasm. An excessive amount of lavage volume can potentially aggravate hypoxemia in a diseased lung, although the lung's central and peripheral airspace normally has a great reserve to resorb excess fluid, except in the presence of cardiogenic or noncardiogenic pulmonary edema. As previously mentioned, BAL can also increase the incidence of post-bronchoscopy fever, which is usually self-limited.

Endobronchial and Transbronchial Biopsy

A number of biopsy forceps are available for biopsy of bronchial mucosa or endobronchial lesions, and for transbronchial biopsy of airway and parenchyma beyond direct bronchoscopic vision (Fig. 75-4). The catheters are of various diameters and lengths, with larger "therapeutic" forceps fitted with larger forceps cups. The edges of the cups are either smooth-cutting or jagged "alligator" type. A number of the larger forceps are designed primarily as forceps for use in upper and lower gastrointestinal endoscopes, and hence their cables are much longer than the 55 to 60 cm of the bronchoscope working channel. There are additional forceps with a needle or "spike" in the center of the opened jaw near the fulcrum of the opened forceps; this spike aids in the anchoring of the forceps on mucosa, scar tissue, or tumor. These needle forceps are most useful for endobronchial biopsy, especially when the target may be along an airway wall tangential to the bronchoscope and thus cannot be easily grasped by forceps opening at a very shallow angle to the lesion. Some forceps also have an attachment for electrocautery. These may be useful for sampling or removing friable tissue that bleeds, because electrocautery can effectively provide thermal hemostasis.

Figure 75-4. Instruments for use with a flexible fiberoptic bronchoscope *Top to bottom*, Reusable forceps with steel wire catheter sheath (Olympus America, Center Valley, PA); disposable forceps with coated catheter (Microvasive, Boston Scientific, Natick, MA); disposable needle forceps; large electrocautery forceps, which requires a 2.8-mm channel; electrocautery snare; handle with wire attachment for electrosurgical instruments.

The technique for endobronchial biopsy is fairly straightforward. After careful positioning of the opened jaws of the forceps, the forceps is advanced toward the target lesion and is closed when the lesion is within grasp. The challenge comes when the target is small, the airways are moving in response to respiration, or the patient is agitated and coughing. The opened jaws of the forceps can further obscure the view from the bronchoscope. Under these circumstances, the resultant tug of a fairly floppy forceps catheter may yield a disappointingly small specimen. One technique to improve the accuracy and yield of the biopsy is to advance with the bronchoscope closer to the target lesion before advancing the biopsy forceps outward. With closure of the forceps cups, one should pull back gently until the forceps are almost but not fully retracted into the bronchoscope channel. The bronchoscope itself should be pulled back slowly but firmly, and the much larger instrument (bronchoscope vs. the forceps) generally helps pull out a much larger specimen.

Complications from endobronchial biopsy most often involve bleeding due to trauma. Flushing small aliquots (1-2 mL) of a topical vasoconstrictor followed by a saline "chase" of 2 to 3 mL to clear the medication out of the bronchoscope channel helps stem the bleeding. Tamponade with the tip of the bronchoscope until a clot forms may also help, but this is often less effective and risks further obscuring the view with coagulum. Oxymetazoline (Afrin) 0.05% and lidocaine with epinephrine (1:10,000 dilution) are two vasoconstrictors commonly used for this purpose, although oxymetazoline is preferred because it causes less tachyarrhythmia and hypertension. Airway perforation is a theoretic risk but it rarely occurs, except in severely necrotic airways already distorted and destroyed by invasive cancer. Damage to the

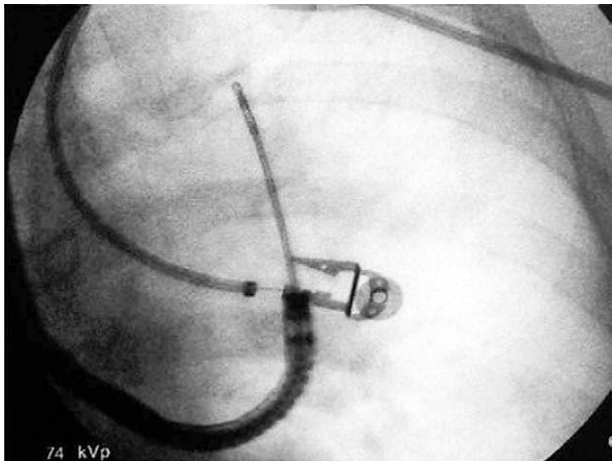

Figure 75-5. Transbronchial biopsy of a peripheral (left upper lobe) lung mass under fluoroscopic guidance.

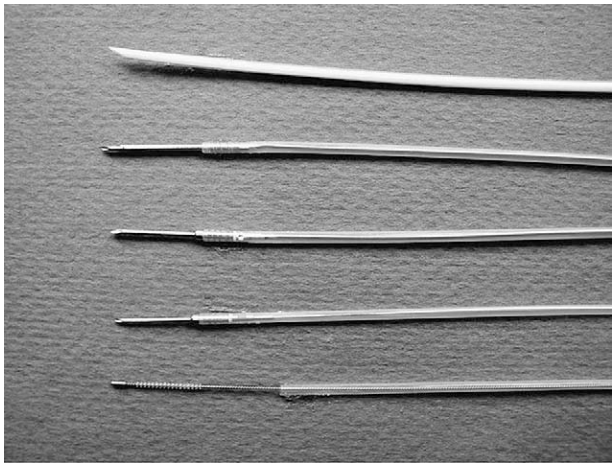

Figure 75-6. Transbronchial needles and cytology brush. *Top to bottom,* 18-gauge Microvasive Sofcor plastic (Boston Scientific, Natick, MA); 19/21-gauge MW 319 histology steel, 15-mm length (Bard/Mill-Rose Laboratories, Mentor, OH); 21-gauge SW121 cytology steel, 15 mm (Bard/Mill-Rose Laboratories); 22-gauge MW122/222/522 cytology steel, 13 mm (Bard/Mill-Rose Laboratories); cytology brush.

bronchoscope is a real concern; this can occur if an inexperienced operator attempts to open the forceps while it is still within the channel, or if an incompletely closed forceps or one with a kinked set of cups is forcibly withdrawn back into the channel. When there is any doubt or if there is obvious kinking of the forceps that cannot be corrected within the airways, the entire bronchoscope must be withdrawn, and the problem fixed outside the patient's airways.

Transbronchial biopsy uses the same instruments, although there is much less reason to use the needle forceps. This procedure is usually directed toward a focal mass lesion most often suspicious for lung carcinoma, or toward focal or diffuse infiltrates suggestive of infection, inflammatory lung processes, fibrotic lung parenchyma, or metastatic carcinoma with lymphangitic or diffuse hematogenous spread. Although it is possible to perform successful transbronchial biopsy without radiographic guidance, the yield is lower and the risk of complications increased; therefore, we prefer the availability of fluoroscopy to guide transbronchial biopsy, especially of smaller, more focal, and more peripheral lesions (Fig. 75-5).[11,13]

For more diffuse peripheral disease, whether guided by fluoroscopy or with use of a "blind" approach, the forceps are advanced slowly in a closed position until gentle resistance is felt or until the tip of the instrument is seen to approach the pleura. Because of the angulation of the segmental airway branchings and the effects of foreshortening, the advancing forceps may not appear to approach the lung periphery on the planar fluoroscope. Once resistance is felt, the forceps are retracted about 2 to 3 cm, the cups are opened, and the instrument is gently pushed forward. After firm closure, the position of the forceps is confirmed by fluoroscopy and the instrument withdrawn. In a patient under conscious sedation, especially when fluoroscopy is not available, we also ask whether there is chest wall pain, which would suggest focal pleural irritation caused by the tip of the forceps and would warn us of the increased risk of pneumothorax. The yield from transbronchial biopsy varies depending on pathology, location and size of lesion, and availability of fluoroscopy. In general, the diagnostic yield for transbronchial biopsy in malignant lesions located centrally and larger than 2 cm is about 50%, compared with only 25% in lesions smaller than 2 cm located in the peripheral one third of the lung.

Complications of TBBX are bleeding and pneumothorax. As aforementioned, performing fluoroscopy and querying for symptoms of pleurisy reduce the risk of pneumothorax to less than 10%, with overall rates of 3% to 20% reported.[11] Significant bleeding is not increased in patients taking aspirin and cannot be predicted by routinely ordering measurements of platelet counts and coagulation parameters. Nevertheless, in critically ill or pancytopenic patients, an attempt is made to keep the platelet counts above 50,000/μL, to correct coagulopathy if present, and to temporarily suspend anticoagulation. Bleeding, when brisk, is managed by tamponading of the bleeding subsegment with the bronchoscope tip. Depending on operator preference, suction can be applied to collapse the segmental airways to prevent further retrograde bleeding into the central airways, and lavage with room-temperature or cooled saline can be performed to slow the bleeding. There are no randomized trials to suggest efficacy of one approach over another. Needless to say, life-threatening hemorrhage from transbronchial biopsy is rare but reported.

Transbronchial Needle Aspiration

TBNA has traditionally been used to sample mediastinal lymph nodes and cysts. Initially TBNA was performed using needles on a long rigid stem introduced via a rigid bronchoscope tube; in fact, the earliest cannulation of the left atrium for measurements of left atrial pressure was performed using this TBNA approach. Diagnosis of benign mediastinal adenopathy (e.g., sarcoidosis) and malignant tissue (e.g., lymphoma, nodal metastases of bronchogenic carcinoma) can be made via rigid TBNA; however, the lymph nodes sampled are often limited to the subcarina and, possibly, the precarina because of the limited angulations achievable with rigid instruments.

The introduction and refinement of TBNA needles attached to a flexible catheter has permitted sampling, with a flexible FOB, of a larger number of lymph node regions, endobronchial lesions in the segmental and subsegmental bronchi, and peripheral, endoscopically occult lesions. The majority of the needles are made of stainless steel with calibers ranging from 22 to 19 gauge (Fig. 75-6). There remains one plastic needle with a flexible tip (Microvasive Sofcor, Boston Scientific, Natick, MA) that may be bent to facilitate passage into subsegments of the upper lobes and certain lower-lobe subsegments that are otherwise often not reachable with metal transbronchial needles because the 13- to 15-mm lengths of these rigid needles reduce the tip angulations of the flexible FOBs.

Although the flexible needles have been divided into smaller gauge (20, 21, and 22 gauge) "cytology" needles and larger gauge (19-gauge metal and 18-gauge Sofcor) "histology" needles (see Figure 75-6), the choice of the needle depends on operator experience, because the larger "histology" needles still provide tissue for cytologic examination by slide smear, and samples aspirated with smaller "cytology" needles can be spun down into a cell block and cut for histologic examination. The longer needle lengths (15 mm) of the 21-gauge and larger needles offer the advantage of greater depth penetration. However, a 19-gauge needle is more unwieldy to maneuver, takes more practice for penetration of the bronchial mucosa, and can potentially cause more trauma. It is often reserved for the sampling of larger lymph nodes suspected of

harboring lymphoproliferative tissue (e.g., lymphoma, Castleman's disease) or granulomatous diseases (e.g., sarcoid, mycobacterial, and fungal adenitis) because, with practice, a 21-gauge core sample can be retrieved.

Mediastinoscopy remains the "gold standard" for examination and sampling of mediastinal lymph nodes; however, access to the subcarina, posterior tracheal, subaortic left-paratracheal/aortopulmonary window and hilar lymph nodes is limited. TBNA via FOB has the advantage of access to a larger number of lymph node stations and of being a less invasive procedure that can be combined with the endoscopic examination of the airways plus as-needed sampling of peripheral lung disease (see Figure 75-6). Therefore, TBNA may be one of multiple procedures performed in a sequence of "one-stop" diagnosis and staging of thoracic malignancies. Certain lymph node stations are also inaccessible to TBNA via FOB; these include the paraesophageal and lateral aortopulmonary-window lymph nodes, which can be sampled by real-time endoscopic ultrasonography–guided fine-needle aspiration (FNA) via the esophagus and by anterior median sternotomy (Chamberlain procedure), respectively.

Technical Aspects

The "abnormal" lymph node has been classified radiographically as one with a short axis measuring more than 1 cm. However, thorough lymph node staging of bronchogenic carcinomas has demonstrated a diagnostic sensitivity and specificity of only about 60% to 70% with this rule applied. 18-Fluorodeoxyglucose positron emission tomography may identify metabolically abnormal lymph nodes and lung nodules even when they do not fulfill this size criterion. After identification of an accessible lymph node suspicious for harboring pathology, a TBNA needle is carefully introduced with tip retracted via the operating channel of the bronchoscope. Regardless of the location of the chosen target, it is best to pass the TBNA through the lumen with the bronchoscope in a fairly central location (i.e., the trachea or mainstem bronchi) with the tip straight or minimally angulated in order to protect the expensive equipment that can be most easily damaged by instruments at its distal flexible end. With the TBNA needle still in its protective hub, the bronchoscope is then maneuvered into a position proximal to the target lesion. After the bronchoscope is centered away from the side-walls, the needle is deployed and locked in place, as care is taken to avoid mucosal trauma that will cause bleeding and obscuration of the bronchoscopic view. The catheter tip housing the beveled metallic needle usually has a protective metal hub that helps prevent inadvertent perforation of the bronchoscope channel. During positioning for TBNA, a portion of the needle or the catheter hub should always be visible; otherwise it is possible that the exposed needle was pulled back into the distal bronchoscope tip, again risking damage. If for any reason the needle is not visible, it should be retracted into the catheter and the entire catheter should be removed from the bronchoscope and properly reset for redeployment.

The actual mucosal penetration and spearing of the mediastinal target can be performed by one of two techniques, the "stab" or the "push-jab."[10] The stabbing approach entails holding the bronchoscope in place and pushing the deployed needle catheter forcefully forward, thus traversing the bronchial mucosal into a lymph node or tumor mass. The limitation of this technique is that it is suited only for lesions that are situated directly in the line of sight of the bronchoscope; the needle will more than likely take a somewhat more oblique pathway across the bronchial mucosa, thus leaving less needle length to penetrate the lesion. In a spontaneously breathing patient, subtle airway motion can translate to missing the lesion or having the needle hang up on bronchial cartilage instead of passing through the membranous portion of the mucosa. Finally, if the bronchoscope-needle setup is positioned too far away from the bronchial mucosa point of entry, pushing the flexible TBNA catheter outside the bronchoscope channel will allow the catheter to bend and kink, further limiting its effectiveness.

For these reasons, the piggy-back "push-jab" technique is preferred. In this approach, the deployed and locked needle is kept partially withdrawn into the distal bronchoscope and the sharp needle tip is carefully directed toward a selected entry point; the membranous mucosa between cartilage rings is chosen. The bronchoscope tip can be partially flexed such that the bronchoscope and needle catheter behave as a curved needle set, with the needle anchored at about a 45-degree angle. Control of both the catheter and bronchoscope is obtained, either by the bronchoscopist alone or with an assistant holding the proximal end of the catheter and being ready to advance it on command, and the bronchoscope is pushed forward firmly as the piggy-backed needle-catheter is jabbed forward. With practice, the TBNA needle can be made to traverse the mucosa at a nearly 90-degree angle, thus affording sampling of lesions in the distal left and right paratracheal angles, anterior precarinal space, and right bronchial lymph nodes (Fig. 75-7). Once the locked needle-catheter set is advanced until the entire length of the needle is buried up to the hub, the clear catheter is pushed from the proximal end until a bit of it is visibly protruding from the distal bronchoscope tip. At this point, inadvertent penetration of one of the major vascular structures, such as the aorta, pulmonary artery branches, superior vena cava, or azygous vein would be obvious from the complete backfill of the distal catheter with blood even without any suction applied. If there is no unexpected return of blood, a cytology or histology sample can be obtained with the forward-and-backward movement of the needle. Although suction has most often been applied by syringe attached to the proximal end of the TBNA catheters, this manipulation is not always necessary because it is really the capillary action plus the regular agitation motion that draws tissue into the lumen of the needle. This principle is especially applicable for looser, less organized malignant tissue, whereas suction may be required for acquisition of an adequate sample of a denser granulomatous or reactive lymph node.

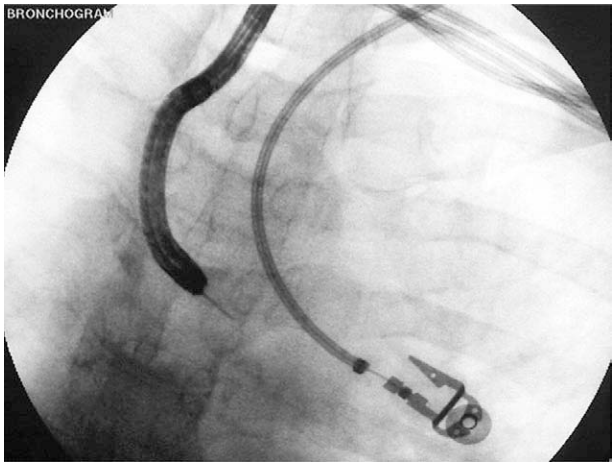

Figure 75-7. Transbronchial needle aspiration of a left paratracheal lymph node, resulting in successful staging of stage IIIA disease.

The same TBNA needles can be used for the transbronchial sampling of peripheral lung masses, although as mentioned earlier, the acute bending of certain lobar segments may preclude successful passage of the TBNA needle into the desired airway segments.[11,13] Unlike in sampling of central mediastinal lesions or endobronchial pathology, the needle is not deployed until the catheter hub with the protected needle tip is advanced into position as indicated by fluoroscopy or CT.

There is some debate as to the ideal method to retrieve the needle-catheter and how to process the sample thereafter. Some experienced practitioners of TBNA withdraw the still extended and locked needle back into the bronchoscope and out the channel while simultaneously straightening the tip of the bronchoscope. The rationale for not first retracting the needle into the safety of the hubbed tip is to avoid sucking back bronchial epithelial cells that may dilute the presumed pathologic cells of interest within the needle. The obvious risk, however, is the much greater chance of damage wrought on the bronchoscope even if the needle is only pulled back, because a rigid needle measuring 13 to 15 mm can scratch and perforate the bronchoscope channel, which can be in a 130- to 180-degree angulation. Current teaching is therefore to always fully retract the needle before pulling the catheter backward, while still straightening the distal tip of the bronchoscope.

The retrieved samples can be prepared and preserved in a number of ways. Generally, more than a single pass is made to ensure adequate sampling, with the maximum yield leveling off after between four and seven passes at a particular site. The presence of rapid on-site evaluation by a pathologist or an experienced cytopathology technician is a helpful adjunct that improves the diagnostic yield of TBNA.[14] The immediate feedback will direct the need for additional TBNA passes. Even when disease is noted, such as carcinoma or abnormal lymphocytes, extra passes for additional material to be spun down for immunostaining or preservation in media for flow analysis may aid in making the identification of a tumor source or cell type, with important implications for prognosis and as a guide for therapy. In the absence of cytopathology assistance, samples can also be injected into an aliquot of preservative solution such as Saccomanno's fixative and spun down in the laboratory for further analysis. Flushing out the needle with 1 to 2 mL of saline after each pass, as reported earlier, is no longer practiced because this dilutes out small quantities of sample, and the needle loses some of its capillary effect when flushed with liquid. We therefore eject the sample from the needle with an air-filled syringe.

Published series quote a diagnostic yield rate of 75% to 90% for TBNA sampling of mediastinal lymph nodes, with lower rates for peripheral pulmonary lesions, once again depending on the location and size of the targets.[10,11,13] TBNA, however, remains an underused minimally invasive sampling technique because of uneven teaching of the technique and the average low yield for the occasional practitioner of this technique.[9] A number of radiographic techniques have been used or are being developed as adjuncts to help in localization and to guide TBNA sampling of lung pathology. Fluoroscopy can help visualize the proper penetration of a lesion in the lung parenchyma but is generally less useful in accurately localizing mediastinal adenopathy and central masses that may be obscured by the cardiac silhouette and other normal mediastinal structures. Spiral CT, either with stopped frames or fluoroscopic, can be used to help localize and prove TBNA penetration of target lesions, but it is cumbersome to perform these bronchoscopic procedures in the CT scanner, and the patient and staff are exposed to a much higher levels of radiation.

The advent of rapid multislice detector CT scanners and the development of software to improve three-dimensional rendering may soon make available a number of high-fidelity "virtual bronchoscopy" programs, including the capability of rendering the airway wall "transparent" and highlighting the adjacent mediastinal structures of interest. The purpose of these programs is not to obviate the need for tissue diagnosis but to guide the approach for procedures such as TBNA and transbronchial biopsy. Another real-time guidance technique is the use of EBUS to localize lymph nodes and other mediastinal structures of interest for tissue sampling.[15,16] Most EBUS procedures use a radial balloon probe introduced via the working bronchoscope channel. After EBUS imaging is completed, the probe is withdrawn and TBNA is performed. Report of simultaneous imaging and sampling via a double-lumen bronchoscope is not generally applicable owing to the rarity of these bronchoscopes, which are largely being phased out, and by the imminent introduction of a dedicated EBUS bronchoscope with an angled side-port for TBNA. EBUS is currently available for clinical use, but in only at a limited number of centers because of the lack of experienced practitioners and the equipment cost.

The primary complication from TBNA of mediastinal structures is bleeding into the airways from puncture of vascular structures or vascular tumors. Less commonly, pneumothorax, pneumomediastinum, or hemomediastinum may occur. Bleeding is generally self-limited, and the bronchoscopist should be focused on clearing the airway of blood that would otherwise obscure the bronchoscopist's view and induce coughing and desaturation. Suction should be directed downstream from the TBNA entry site, presenting no interference with the local formation of a small clot. TBNA of peripheral lung lesions entails the same risk as transbronchial biopsy, including bleeding and pneumothoraces.

Bronchoscopic Brush

The use of a cytology brush for the sampling of an endobronchial lesion or its use under fluoroscopic guidance for the sampling of a peripheral lesion appears a simple enough procedure, but a review of the yield and complications is warranted. Because the stiff metallic bristles of the cytology brush can be traumatic over a larger area, bleeding from bronchoscopic brushing can be severe. In spite of a vigorous effort to retrieve sample, the yield can be disappointingly low for carcinoma and generally ranks below directed-forceps biopsy and endobronchial needle aspiration.[11,13] There are multiple explanations for this apparent paradox. Much as with TBNA, in which active negative-pressure aspiration can cause more trauma and bleeding than agitation without suction, the nonspecific trauma induced by the bristles leads to a usually bloody sample that can obscure the malignant cells behind a field of red blood cells, fibrin, and other debris. The superficial endobronchial layer of a central tumor can often consist of a biofilm of mucus, necrotic cell debris, and recruited inflammatory cells, thus sampling along the surface with a cytology brush may pick up only these nondiagnostic contaminants and miss the underlying true pathology. The yield of a cytology brush for the sampling of peripheral lesions is equally disappointing, also because of the sampling issue of picking up mostly normal or inflamed bronchial or bronchiolar epithelial cells. In a number of instances, unless an airway leads directly up into a tumor mass, the catheter of the cytology brush is directed away from the tumor that pushes away adjacent bronchi.[17] In a similar circumstance, the needle of a TBNA can be extended directly toward a tumor, penetrating the smaller airways as necessary. Therefore, except as a poor substitute for directed-forceps biopsy and TBNA of central endobronchial and peripheral lesions, bronchoscopic brushing for cytology has relatively low merit and rarely adds to the other sampling procedures in cancer diagnosis.

To address the issue of nonspecific bronchial wash or BAL cultures from contamination by upper airways colonizers, a protective microbiologic brush has been developed as an adjunctive method to sample the lower airway. A plastic-bristled brush housed within a catheter capped with a plug is introduced into the airway's segment of interest, and the plug is ejected by the deployed brush, which will then pick up a "true" lower respiratory tract sample. The brush has furthermore been designed to adsorb a fixed quantity of bronchial secretions (0.1 mL), which can be serially diluted 100-fold in the microbiology laboratory to yield a semiquantitative "protected" microbiologic culture. By this method, growth of 1000 colonies of a particular organism would be significant. It is advisable for the bronchoscopist to confer with the institution's microbiology staff before embarking on collecting specimens with the protected catheter brush.

Interventional Bronchoscopic Procedures

General Principles

Virtual bronchoscopy is becoming more popular in simulating diagnostic bronchoscopy to diagnose airway pathology as a prequel to therapy, and minimally invasive therapies are now more and more favored over aggressive operations because of improved technology. Therefore the paradigm of bronchoscopy is shifting slightly from diagnostic implications to treatment with bronchoscopic interventional procedures.[18-20]

Careful selection of a patient eligible for interventional bronchoscopy is critical to maximize benefit to patients who are generally quite ill. Depending on the particular intervention, the nature of the disease state, and the patient's functional status, the risks associated with interventional procedures can be significant. The majority of our currently performed interventional procedures, such as repair of tracheobronchial-esophageal or bronchial-mediastinal fistulas, all strive to maintain airway patency and reestablish normal gas exchange, or to reestablish the airway structure to as near normal as possible.

It is important to recall that for ideal gas exchange to take place, there should be minimal ventilation-perfusion mismatching. Therefore, whereas the removal of a foreign body such as an aspirated object in a toddler or child can lead to immediate and full recovery, simply reestablishing airway patency may not be sufficient in other instances. For thoracic malignancies blocking the airways, whether primary or metastatic, débridement of airway tumor and debris when the accompanying vasculature is also infiltrated and obliterated may simply lead to

increased "dead space." Reestablishing ventilation of nonperfused lung segments can in fact worsen hypercapnia and not improve hypoxemia. A good-quality contrast-enhanced CT scan of the chest is therefore mandatory for review in all cases of airway obstruction, with the exception of patients with recent aspiration of a foreign body.

Knowledge of the position of the vasculature is furthermore critical for the interventional bronchoscopist to avoid potentially life-threatening complications of vascular injury by laser or mechanical débridement. The intravenous contrast agent in the CT scan serves another very important purpose. In the cases of known or highly suspected malignancies blocking the central airways, knowledge of whether there is functioning lung distal to the obstruction will help to predict the likelihood of success and to determine whether patients with tenuous medical status should be subjected to deep sedation or general anesthesia with mechanical ventilation from which they may not be successfully weaned. Experienced radiologists provide a reasonable estimate as to whether an interventional expedition from within the airway lumen will only reveal disease that is the "tip of the iceberg." They can also comment on the presence of concomitant pleural disease that may portend the very poor prognosis of a "trapped" lung, even when the central airways are reopened and pleural fluid removal attempted.

Preparation of the Patient and Selection of Instruments

Careful history-taking should include any use of anticoagulants and antiplatelet agents. Physical examination, review of radiographs (preferably including a recent contrast CT scan), and measurement of platelet counts and other relevant bleeding parameters are routine. Because many of the patients undergoing interventional bronchoscopic procedures often have more advanced pulmonary diseases and possible comorbidities, a baseline electrocardiogram is often requested. Because the purpose of the procedures is often palliative in nature and the procedures are accompanied by higher risk than a standard diagnostic bronchoscopy, a detailed discussion of possible complications and the realistic likelihood of achieving subjective relief should be discussed with the patients and their families. In an airway interventional series of laser débridement in 1585 patients by Cavaliere and associates,[21] the overall procedure-related mortality was 0.3% and the rate of major complications (including significant hemorrhage, pneumothorax, and pneumomediastinum) was 1.5%.

Most interventional procedures can be performed via an FOB, a rigid bronchoscope, or an FOB introduced via a rigid bronchoscope or via direct suspension laryngoscope. There are pros and cons to both approaches, but the operator should be capable of converting a procedure begun with an FOB into one using a rigid bronchoscope when the need arises.[9,18] The larger channel of the rigid bronchoscope facilitates the use of larger-caliber instruments, and certain rigid silicone stents require rigid instrumentation for their deployment. The bronchoscope itself can be used to core out tumor tissue or to tamponade hemorrhage from the side walls. It is also easier to remove noncancerous foreign bodies and to dilate benign stenotic segments via a larger rigid tube. Conversely, the larger and rigid instruments are more liable to cause trauma to the vocal cords and potentially cause a fistula when used to débride necrotic tissue in distorted airways. The constrained angulation provided by manipulation of the patient's head and neck positions can limit the bronchial segments reachable for intervention. The rigid instruments also mandate the use of general anesthesia. When a flexible FOB is chosen for interventional procedures, larger-channel "therapeutic" bronchoscopes that can accommodate flexible interventional instruments are selected, but it is often helpful to also have available thinner pediatric bronchoscopes that can be used to bypass critical narrowings.

In the management of airway obstruction, the choice of the specific intervention depends on the location and severity of narrowing. Certain techniques, such as cryotherapy, photodynamic therapy, and endoluminal brachytherapy, simply do not work on malignant tissue rapidly enough to relieve critical stenosis. The short-term effect is, in fact, tissue edema as tumors undergo cell death and necrosis. In such instances, mechanical débridement with or without one of the heat thermal therapies would be more appropriate. In significant cases of central airway narrowing, in which both mainstem bronchi may be partially compromised, attention should first be directed to the less affected side, most often also the healthier lung, so that adequate single lung ventilation can be established. Even though the majority of airway interventions result in improved pulmonary function, the operating team of otolaryngologists, pulmonologists, anesthesiologists, and nursing personnel should always be prepared for and ready to perform interventions for acute and potentially catastrophic complications. These include turning the patient laterally and keeping the functioning lung upward in case of massive hemorrhage; keeping handy equipment for intubation, including double-lumen ET tubes for split lung ventilation, or at least bronchial blockers to tamponade a bleeding lung; and maintaining the capacity to perform rigid endoscopy if the situation is less dire but larger airway access is needed.

Foreign Body Removal

Although foreign body aspiration (FBA) is classically a pediatric problem, with the highest incidence occurring in children younger than 5 years, bronchial foreign body can occur in adults as well, albeit often with less acute symptoms.[22] The classic signs—witnessed acute choking, wheezing, loss of unilateral breath sounds with corresponding volume loss, or hyperinflation due to air-trapping on the radiographs—have a high sensitivity (about 70%) but variable specificity for FBA. Other findings, such as chronic cough, recurrent pneumonias in the same chest region, atelectasis, and even pneumothoraces or pneumomediastinum, are more common in adults, who may or may not recall an episode of possible aspiration.[18]

Rigid bronchoscopy has been the standard procedure for removal of airway foreign bodies and remains so in the pediatric population. Conversely, in adults, a trial of foreign body removal with instruments compatible with a flexible FOB would be reasonable, although there should always be the backup plan for rigid bronchoscopy should the aspirated foreign body prove too stubborn for removal by the smaller flexible bronchoscopy instruments. Flexible bronchoscopy is indicated for patients with cervical spine instability and skull and jaw fractures, and such trauma patients may be particularly at risk for the aspiration of broken teeth or dentures, or a preceding aspiration leading to near asphyxiation and loss of consciousness may even be the cause of the subsequent head and neck trauma from a fall or a vehicular accident. Helpful adjuncts in directing the foreign body centrally include repositioning the patient in a Trendelenburg or decubitus position, movements that would not interfere with flexible FOB but may prove more challenging with a rigid bronchoscope. A number of "nonpulmonary" instruments can be adapted to assist in the retrieval of a foreign body; these include a Fogarty catheter pushed distal to the foreign body, then inflated and slowly pulled back, simulating the retrograde clot removal from a vascular lumen. Snares and baskets, such as the Roth basket developed for gastrointestinal procedures, can also be used to retrieve smooth or rounded items that are difficult to grasp, such as peanuts and marbles that are akin in texture and size to biliary stones. Cryotherapy probes used primarily for tumor and granulation tissue ablation can also be used to retrieve a foreign body that has a layer of aqueous condensation or secretions around it by virtue of the process of cryoadhesion.[23] (Recall the unfortunate child testing this hypothesis on a cold winter's day and getting his tongue stuck to the metal pole.)

Hemorrhage can occur as a result of inflammation and granulation formation induced by the foreign body; this finding is especially true for certain pill fragments and other caustic compounds, oily food such as nuts, and on a more long-term basis, metal pins and other sharp objects. The manipulation of the various instruments can further aggravate this process. Therefore, having the capacity to provide hemostasis with vasoconstrictor compounds and mucosal surface coagulation is desirable. The routine use of corticosteroids to reduce airway edema has not been rigorously studied but is commonly recommended.

Tissue Débridement

The discussion of interventional bronchoscopic approaches in the débridement of malignant or scar tissue causing airway obstruction often becomes a catalog of technology and devices to deliver these tissue-destructive techniques. However, it is fair to say that the underlying common denominator is mechanical resection assisted by

freezing, heating, or biochemical methods of causing cell death. Cold techniques include use of forceps, powered microdebrider, or cryotherapy. Laser, argon plasma coagulation (APC), and electrocautery are three methods of heat-assisted mechanical resection. Finally, photodynamic therapy (PDT) and endobronchial brachytherapy (EBBT) are biochemical destructive methods. Methods for tissue débridement are detailed in Table 75-2.

Balloon Bronchoplasty

In addition to reopening an obstructed airway, there is the task of maintaining airway patency. Furthermore, endobronchial débridement is not useful when the obstruction is extrinsic in nature. Dilation of a narrowed airway segment by mechanical means may be helpful in reestablishing airway patency, albeit temporarily, until more definitive solutions can be instituted. Through a rigid bronchoscope or a suspended laryngoscope, metal mechanical dilators can be gently corkscrewed through a length of tracheal stenosis from fibrotic tissue or tumor. However, areas beyond the proximal right or left mainstem bronchi are seldom accessible. For more distal portions of the right and left mainstem, and for narrowed lobar and segmental bronchioles, balloon bronchoplasty with fluid-expandable catheter balloons offer another option for mechanical dilation. These balloons were originally designed for endoscopic dilation of the biliary tract and the upper (esophageal and pyloric) or lower (colonic) gastrointestinal tracts. Their diameters at full deployment range from 6 mm (biliary) to 18 mm. The lengths of the balloons are fixed, ranging from 2 cm (biliary) to 8 cm (esophageal and colonic). Dedicated bronchoscopic balloons with a length of 3 cm mounted on shorter catheters have also been introduced. These controlled radial expansion (CRE Pulmonary Balloon Dilator, Boston Scientific) balloons have the additional benefit of being expandable to three sequential diameters, depending on the amount of fluid pressure applied, which can be monitored on a manometer supplied with the balloon kit. The fluid can be sterile water or saline or diluted contrast material, which will render the expanded balloon more visible under fluoroscopy.

Endobronchial Stent Placement

Placement of airway stents may be the definitive treatment or may maintain airway patency long enough for adjunctive treatment to control the underlying disease in a number of obstructive conditions. A large number of endobronchial stents have been developed or adapted for airway use over the past 20 years.[9,18,20,24] A detailed discussion of all of the individual types and their variants goes beyond the scope of this chapter. The stents can be grouped into metallic and silicone types. Most but not all of the metallic stents are self-expanding, whereas most of the silicone stents are fairly rigid and require rigid bronchoscopy or direct suspension laryngoscopy for placement.

The earliest airway stent was the Montgomery T-tube, a stiff acrylic polymer tube later replaced by silicone, but its placement required a tracheostomy. A number of silicone stents, some reinforced with metallic struts embedded circumferentially or three-quarters around to simulate the tracheal cartilage (e.g., Orlowski and Freitag Dynamic Stents, Rüschag, Germany), are available in various lengths and diameters, and there are optional limbs to fit the carina and proximal mainstem. With the exception of a single self-expanding polyester reinforced thinned-walled silicone stent (i.e., Polyflex, Rusch), these stents require rigid instrumentation for placement. Because of the intrinsic thickness of the stent material and the method of insertion, they are useful primarily for placement within the trachea and first- to second-generation airways only.

The earliest metallic stents used in the airways were Gianturco-Z stents adapted from their intended endovascular application. This type of noncovered stent has to be ballooned open, has no protection against ingrowth of tumor, and is associated with an unacceptably high rate of induction of severe granulation and airway or vascular perforation. Therefore, it has no role today in endobronchial stenting, given the number of dedicated endobronchial stents now available. The current generation of metallic stent is self-expandable, comes packaged in a much slimmer profile, can be delivered over a guidewire into the distal mainstem and lobar segments, and hence can be deployed without the need for rigid instrumentation. These self-expandable metal stents are made from stainless steel (e.g., Wallstent, Boston Scientific) or the nickel-titanium blend of nitinol (e.g., Ultraflex, Boston Scientific and Alveolus TB-STS, Alveolus, Inc. Charlotte, NC). They are available in a variety of lengths and diameters, with or without an outer polypropylene covering that helps prevent tumor ingrowth. There can still be the problem of tumor or granulation overgrowing the ends of the stents, and proper sizing is important to prevent excessive movement or excessive tension against the airway wall, either of which may promote the proliferation of granulation tissue. Once deployed, the stainless steel Wallstent with its sharp opened prongs is generally fixed in place, whereas the more pliable nitinol stents are maneuverable at least until granulation or tumor overgrows the open ends.

Complications of stent placement include trauma to a compromised airway during stent insertion, such as inadvertent tears to the tracheobronchial mucosa already compromised by tumor invasion. An improperly sized covered stent can occlude functioning airway segments because it is too large or too long; if it is too small, it can subsequently migrate. All stents, covered or otherwise, interfere with normal mucociliary clearance and, as foreign bodies, will promote biofilm formation. Stents can therefore become quickly overgrown with a variety of microorganisms. The problems of granulation and tumor ingrowth have been mentioned. The metallic stents can suffer metal fatigue and undergo fracture and, with the single strand weave of nitinol, can unravel.[25] This problem is especially prominent with tracheal stents in which the constant change in curvature of the posterior tracheal membrane with breathing in and out results in metal fatigue. We have therefore avoided placing self-expandable metal stents in the trachea if we anticipate long-term need for the stent in benign conditions such as tracheobronchomalacia or if the patient with a malignant condition has an anticipated survival beyond several months.

Esophageal-tracheal and esophageal-bronchial fistulas deserve special mention. The majority of such cases result from malignancies originating from the esophagus and, less commonly, from the bronchus. Fistula formation and poor healing may also be due to radiotherapy. Less commonly, such fistulas are congenital or are caused by acute trauma or chronic erosion from a tracheostomy tube. The most common presenting symptoms are coughing with feeding and other signs of aspiration. Swallow studies using a contrast agent (e.g., Gastrografin) and, occasionally, three-dimensional CT reconstructions may localize the fistula, but failure to demonstrate the defect should be followed by direct visual examination. Having a conscious patient swallow 15 to 30 mL of methylene blue or other dye immediately before the induction of anesthesia may be helpful in pinpointing the site of a small but clinically significant fistula. In the absence of an adequate tracheal replacement and the rarity of being able to resect the length of involved trachea for primary anastomoses, stenting to cover the fistula can provide palliation of symptoms, including aspiration of oral secretions and recurring lower respiratory tract infections, and can allow the patient to swallow for oral gratification in the terminal phase of a malignancy. Close collaboration with an interventional gastroenterologist is necessary for this application.

Innovations and Future Developments

Autofluorescence Bronchoscopy

Autofluorescence bronchoscopy is used to detect early, preinvasive lung cancers and can also help thoracic surgeons in planning lung cancer resection. Since the early 1990s, trials have been ongoing to test and improve systems to detect alteration of tissue autofluorescence in dysplastic and cancerous bronchial tissues. Reduction of tissue autofluorescence in precancerous and cancerous tissue results in a change in the green autofluorescent hue of normal bronchial mucosa toward red-brown to blue-black tints. U.S. trials of several systems, including the LIFE (Laser Imaging Fluorescence Endoscope, Xillix Technologies, Richmond, BC, Canada) and D-Light (Karl Storz Endoscopy-America, Inc., Culver City, CA), validate a higher yield in the detection and localization of severely dysplastic and carcinoma in situ lesions in comparison with conventional white-light broncoscopy.[26-28]

Table 75-2

Interventional Bronchoscopic Methods for Tissue Débridement

	Technical Details	Advantages	Disadvantages
Cold Techniques			
Cold steel débridement	Tip of rigid bronchoscope may be used to core out tumor Forceps may assist with débridement	Readily available equipment Rigid bronchoscope may assist with tamponade	Ineffective for dense scar Length of rigid bronchoscope scope may limit access Hemorrhage may obscure visualization
Powered microsurgical debrider	Longer custom-made blades (37 cm) and curved tips (Xomed Corp) assist with subglottic and tracheal access Microsurgical debrider directed by rigid telescopes	Rapid technique Allows for good visualization	Can be bulky to manipulate Aggressive débridement may endanger walls of airway
Cryotherapy	Allows sudden expansion of compressed gases (nitrous oxide) or liquid nitrogen to cool the metal cryoprobe tip in order to promote cell death, cryothrombosis of vessels, and tissue necrosis (Joule-Thomson effect)	Units are inexpensive and easy to use Little risk of airway or vascular wall perforation Normal nonvascular tissue is cryoresistant and heals almost completely	Slower-growing tumors (carcinoids) may be cryoresistant because of rapid warming effect Not helpful for high-grade central airway obstruction because of need for follow-up débridement
Thermal Ablation			
Laser	Neodymium:yttrium-aluminum-garnet and potassium-titanyl-phosphate most commonly used Pulses should be delivered in a noncontinuous mode starting from a lower power setting	Easy to maintain Ability to achieve powerful débridement without contact	Expensive Risk of airway fire Risk of vascular perforation
Argon plasma coagulation	Achieved by ignition of a charged argon gas plasma generated by a high-voltage, high-frequency electrode Ionized plasma seeks out conductive tissue and can therefore be sprayed onto a surface tangential to the aiming beam	Good for cleaning prostheses, stents overgrown by granulation, tumors, recurrent respiratory papillomatosis, scars Less fire risk	Shallow depth of tissue penetration Lesser capacity to quickly débride bulky tumor Risk of airway fire Risk of vascular perforation Risk of air embolism Risk of electrocution if patient and argon plasma coagulation generator are not grounded properly
Electrocautery	Direct-contact thermal tissue destruction Monopolar and bipolar instruments available	Fast Powerful high-voltage current	Risk of airway fire Risk of vascular perforation Risk of retrograde conduction of current
Photodynamic therapy	Photochemical reactions generate cytotoxic oxygen radicals using hematoporphyrin-derived photosensitizers and photon light source 48-hour interval between drug infusion and light activation	May provide therapy for invasive carcinoma and preinvasive carcinoma in situ Relatively longer duration of response in maintaining airway patency	Delayed response Not good for relief of acute/severe obstruction Systemic photosensitivity for 30-60 days Potential allergy Expensive Enhanced toxicity with chemotherapy or radiotherapy
Endobronchial brachytherapy	Directs high-intensity radiation (iridium-192) originating from a source within the tracheobronchial tree Radiation source passed through temporary bronchoscopic hollow catheters (remote afterloading)	Ability to treat advanced endobronchial cancers in patients who have received the maximal dose of external beam radiation therapy or as a boost to planned external beam radiation therapy in patients with significant endobronchial compromise May be curative for carcinoma in situ or small-volume visible invasive carcinoma May have use in benign stenosis or granulation	Delayed response Radiation exposure Risk of radiation bronchitis Risk of fatal hemoptysis (reported between 2% and 25%)

Endobronchial Ultrasonography

Endoscopic application of ultrasonography for characterization and localization of extraluminal structures such as lymph nodes, masses, and blood vessels has been mostly developed in the gastrointestinal field. The adaptation of a balloon-tipped ultrasound probe for use within the airway lumen allows for a more precise localization of regional lymph nodes for tumor staging and for diagnosis of lymphoma and other lymphoproliferative disorders. Ultrasound probes introduced through the working channel of the bronchoscope and directed peripherally have also been used to characterize pulmonary consolidation and may distinguish malignant from nonmalignant causes.[15,16,18] Higher-frequency high-resolution EBUS can also provide additional information about extrabronchial invasion of the serosal surface or submucosal infiltration by cancer, again with prognostic and therapeutic impact. Currently, sampling with EBUS-directed TBNA requires imaging followed by the removal of the probe and substitution of a sampling needle into the working channel. The next adaptation of ultrasound technology into the airways will be the introduction of a dedicated EBUS bronchoscope with a side-directed radial probe and aspiration port that will allow real-time aspiration.

Endoscopic/Bronchoscopic Lung Volume Reduction

The National Emphysema Treatment Trial established the benefit of surgical lung volume reduction surgery as an alternative to lung transplantation in selected patients with COPD.[29] Parallel studies have been undertaken to examine the possibility of affecting lung volume reduction through selective blockage of segmental bronchi leading to regional atelectasis. A number of such endoscopic/bronchoscopic lung volume reduction studies using biologic or synthetic adhesives, such as fibrin glue and removable valves, are currently ongoing. These procedures hold the promise of either being effective and less invasive methods of lung volume reduction surgery or of offering a less invasive and reversible trial of lung volume reduction before patients are subjected to the rigors of thoracic surgery.[30,31]

Summary

Tracheobronchial endoscopy is an integral part of the multimodality examination of aerodigestive tract diseases. The widespread availability of flexible FOBs facilitates an extended examination of the lower respiratory tract with minimal conscious sedation of the patient. The introduction of high-resolution and easily maneuverable videobronchoscopes coupled with innovative imaging technologies is advancing the ability of bronchoscopists to identify early airway dysplasia, locate extrabronchial targets such as lymph nodes and mediastinal masses for biopsy, and characterize the depth and lateral spread of malignancies with greater accuracy. Diagnostic bronchoscopy is also improved by the availability of an expanding array of instruments that can be deployed through both rigid and flexible bronchoscopes to sample visible central endobronchial lesions or, transbronchially, to sample peripheral lesions. Furthermore, evolving technology in tissue débridement and destruction is aiding the palliation and treatment of airway disease.

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General Considerations

CHAPTER SEVENTY-SIX

Biology of Head and Neck Cancer

Steven Chang

Patrick Ha

Key Points

- Head and neck squamous cell cancer results from the accumulation of DNA damage in an entire mucosal field. A molecular progression model has been determined for the evolution of a lesion from mild dysplasia to malignancy.
- The hallmarks of cancer, increased cell proliferation and decreased cell death, are mediated through the inactivation of tumor suppressor genes, the activation of oncogenes, or both. The ways in which these genes are turned on or off may vary, but ultimately all can fit into this scheme.
- The combination of high-throughput molecular biologic techniques and bioinformatics is revolutionizing the way research is being done. It is also accelerating the pace and efficiency with which discoveries are made.
- The molecular biology of head and neck squamous cell cancer is complex and develops from the dysfunction of several interrelated pathways. No single mechanism, pathway, or molecule is responsible for carcinogenesis.
- Molecular biomarkers and targeted therapy are a reality for the treatment of head and neck squamous cell cancer. However, in order for any discovery to affect clinical care, well-run clinical trials must be performed.

There has been an explosion not only of knowledge regarding the molecular biology of head and neck squamous cell carcinoma (HNSCC) but also in the techniques available to study it. With each new discovery, the increasing complexity of cancer has been progressively revealed. Fields of study originally thought to be separate have merged, weaving a complex web of interrelated pathways. The purpose of this chapter is to attempt to break these interrelated pathways into discrete sections for discussion. However, it should not be forgotten that none of these pathways is the sole source of cancer development but simply one piece of the entire puzzle. Part of this complexity is the result of the integration of various high-throughput approaches to studying cancer and the subsequent complex bioinformatics analysis needed to interpret the results. The information technology age has finally pervaded and bolstered the molecular biology field and will continue to be intimately tied to the future of this research. Therefore, the aim of this chapter is both to provide a review of our current understanding of HNSCC and to preview advances in the field. Finally, advances in molecular detection and surveillance of HNSCC are discussed, in addition to the molecular basis for novel, targeted therapies based on molecular alterations in HNSCC.

Background

There are more than 40,000 new cases of head and neck cancer every year in the United States, and 500,000 worldwide, predominantly consisting of squamous cell carcinoma of the upper aerodigestive tract.[1] Despite aggressive multidisciplinary treatment approaches, including preoperative or postoperative chemotherapy, radiotherapy, or both, with reconstructive surgery, there has been only modest improvement in outcomes over the past 20 years. Treatment failures still occur in the form of locoregional recurrence, distant metastases, and second primary tumors. Further insight into the molecular basis of head and neck cancer in general could lead to advances in screening, diagnosis, and treatment with improved clinical outcome.

The mechanisms underlying carcinogenesis in the head and neck are similar to those mechanisms and principles found in other solid tumors. It is generally accepted that cancer arises from the progressive accumulation of genetic alterations that lead to a selection of a clonal population of transformed cells.[2] In an attempt to classify and understand the biology of sporadic and hereditary retinoblastoma, Knudson[3] first put forth his model of the "two-hit" hypothesis in 1971. He described a model in which two copies of the parentally inherited Rb gene were inactivated either by mutation or by loss of chromosomal material, leading to development of hereditary or sporadic retinoblastoma. A model of tumor progression was synthesized by Fearon and Vogelstein[2] into the following three basic tenets:

1. Cancer arises as the result of inactivation of tumor suppressor genes (TSGs) or activation of proto-oncogenes.

2. There is a defined order of genetic events that leads to development of a malignant phenotype.

3. Variations in the order of events can occur, however, and it is ultimately the net accumulation of genetic events that determines the phenotypic expression of malignancy.

In 1993, Renan[4] put forth a statistical model suggesting that between 6 and 10 independent genetic alterations need to accumulate before the development of HNSCC. Although the precise number of events required for HNSCC carcinogenesis is unlikely to be defined, the conclusion from this analysis is that HNSCC requires more genetic alterations in its development when compared to other solid tumors. This series of genetic changes that must occur for frank malignancy to arise is a result of the 20- to 25-year latency period seen in head and neck cancer. During this time, a cumulative exposure to carcinogens—particularly tobacco and alcohol—is believed to be the predominant

cause of specific genetic alterations acquired during HNSCC progression.

Through the examination of premalignant and invasive lesions, many of these initial genetic alterations have been well described in head and neck cancer, and a genetic progression model has been created to detail the evolution of genetic alterations.[5] Using microsatellite analysis, Califano and associates[5] were able to correlate allelic imbalance due to chromosomal loss and gain with varying grades of dysplasia in premalignant lesions. The histologic progression of hyperplasia, dysplasia (mild, moderate, and severe), carcinoma in situ, and, finally, invasive carcinoma provided the structure in which genetic alterations were framed. A genetic progression model was created to examine lesions in each of these categories for similar patterns of allelic imbalance.[5] Even in the earliest of lesions, there were clonal, genetic changes; 30% of benign hyperplastic lesions had loss at 9p21 or 3p, indicating that these losses and the corresponding inactivation of p16 and p14/aRF and putative 3p TSGs are among the first genetic alterations to occur in the progression to cancer. In addition, a transcriptional progression model has been described.[6] These genetic and transcriptional alterations have been correlated with the histopathologic stages of premalignant and malignant mucosal lesions to define the order and time course of molecular alterations in the development of HNSCC.

Later, however, it was found that not just the tumor but the entire field of mucosa undergoes these changes. Slaughter and colleagues[7] first coined the term *field cancerization* in a histologic study examining the epithelium surrounding invasive cancers. They recognized there were histopathologic changes in the epithelia surrounding invasive oral tumors and reported an increased incidence of second primary tumors, usually close to the initial tumor. Other investigators subsequently confirmed a higher incidence of second primary tumors in the upper aerodigestive tract in those patients with initial head and neck primary tumors.[8-10]

Thus, field cancerization originally was a clinical concept describing a mucosal surface in the region near an invasive tumor with premalignant changes and the propensity for second primary tumor development in adjacent mucosa. With the advent of contemporary molecular genetic understanding of malignancy, two theories provide possible explanations for this finding; they are (1) the areas of abnormality represent independent clones, with a unique pattern of genetic alterations, and (2) these areas of abnormality are genetically related and originate from a common cellular clone. Although these theories are not exclusive, it was shown that there was indeed lateral spread of progenitor clones throughout squamous mucosal surfaces rather than independent clones. Further studies looking at second primary head and neck tumors found that these second lesions tended to originate from a common clone.[11] Another study examining serial biopsy specimens of head and neck premalignant lesions that ultimately progressed to invasive cancer showed a pattern of accumulated microsatellite loss, with the cancer demonstrating losses identical to those found in the previous premalignant lesions.[5,12] Therefore, the theories of field cancerization and the genetic progression model for cancer work hand in hand to describe how the molecular and histopathologic changes occur and lead to malignancy.

The breadth of possible genetic alterations previously discussed as leading to a phenotypic expression of malignancy has grown, although the end targets of genetic alterations almost always involve inactivation of TSGs, activation of proto-oncogenes, or both. TSGs are those genes that are normally present in cells and whose function is to regulate and repress cellular functions that, when left unchecked, would lead to expression of a cancer phenotype. *Proto-oncogenes* are those genes that, when altered either by aberrant, constitutive activation or DNA copy number amplification, result in inappropriate overexpression or increased activity that results in expression of a malignant phenotype. Alterations of both TSGs and proto-oncogenes can be caused by several mechanisms, including endogenous mutation, environmental carcinogens, and the result of the disruption of normal cellular functions by viral, chemical, or other factors. These alterations in the DNA may lead to changes in sequence or quantity of messenger ribonucleic acid (mRNA) intermediates, with subsequent translation into aberrant protein products or an altered level of normal proteins. (This model has been modified with the discovery of noncoding RNAs that regulate translation of mRNA, a topic discussed in another section.) Ultimately, these genetic alterations lead to a malignant phenotype that can include altered cell proliferation, invasion, metastasis, altered immunogenicity, resistance to therapy, and genetic instability, as well as other phenotypic characteristics common to malignancy.

With these principles of malignancy in mind, we proceed to discuss many specific molecular changes that occur in HNSCC and the clinical implications of these advances in knowledge. Although the topics have been separated for the purposes of this chapter, it is important to keep in mind that they are all intimately related.

Environmental Exposures and Risk Factors

The primary risk factors for the development of HNSCC are two environmental toxins, tobacco and alcohol (tobacco exposure being a much higher risk). These two factors combine synergistically to increase the risk of HNSCC. In addition to studying the mechanisms by which these toxins can alter cellular proliferation and death, investigations into the endogenous enzymatic systems dedicated to metabolize these toxins into inert molecules have been performed and are discussed. A third risk factor, which acts independently of the other two, is a history of an oral human papillomavirus (HPV) infection,[13] which is addressed in more detail later in the chapter. D'Souza and coworkers[13] discovered that oral HPV infection increased the risk for oropharyngeal cancer. Oropharyngeal HPV infections were detected by multiplex polymerase-chain-reaction analysis of saline rinses after cytology brushings of patient posterior oropharyngeal walls, as well as ELISA analysis of patient serum with antibodies specific for HPV viral oncoproteins and viral capsid proteins.[13]

Processed tobacco contains at least 30 known carcinogens. Tobacco smoke contains a high concentration of reactive oxygen species and more than 50 known carcinogens and procarcinogens.[14,15] In addition to the direct physical trauma to the upper aerodigestive tract from smoking and drinking, several enzymatic systems are in place to metabolize and deactivate these compounds. It has been proposed that the genetic polymorphisms of these systems to detoxify carcinogens can potentiate putative carcinogens and lead to the development of cancer by either failing to deactivate carcinogens or activating pro-carcinogens.

Cytochrome P-450

The cytochrome P-450 system of enzymes, which is responsible for the oxidative metabolism of most chemicals encountered, consists of more than 20 subfamilies and 60 separate P-450 genes. These enzymes, which are found primarily in the liver tissue, are also found in the aerodigestive tract tissue.[16] Of these, the most studied is CYP1A1, which is present in oral tissue.[17] Several studies into two specific mutations of this enzyme have revealed only a mild risk association between CYP1A1 exon 7 polymorphism and the development of HNSCC.[18] Of particular note, statistical significance was noted only in studies of Asians, whereas results of studies in whites were equivocal. Other systems that have been studied but for which there are insufficient data or inconclusive evidence are CYP1B1, CYP2D6, and CYP2E1.

Glutathione S-Transferase

One of the family of enzymes responsible for the detoxification and processing of such harmful chemicals is known as glutathione S-transferase (GST). There are five separate loci for the production of different GST subtypes that are responsible for detoxifying many different compounds. There also exist several polymorphisms within these subtypes, which may delineate those people more at risk for the development of cancer in the presence of tobacco smoke exposure. In a large meta-analysis, Geisler and Olshan[15] reported inconsistent results among 24 studies looking at the role of GSTM1 and GSTT1. They concluded that there are likely subtle effects of polymorphisms on detoxifying enzyme function and the complexity of detoxification processes in general, and that large population-based studies must be performed before the effects of tobacco smoke in subjects with these alterations can be correctly ascertained. In 2003, Hashibe and associates[19] performed a pooled analysis and a meta-analysis of studies looking at GSTM1, GSTT1, GSTP1, and CYP1A1. They concluded that in the

33 studies reviewed, there is a modest association of GSTM1 and GSTT1 genotypes with head and neck cancer risk. They further concluded that their pooled analysis "supports the notion of greater risk when multiple GST loci are considered."[19]

Other Enzymatic Systems

Variations in other detoxifying enzymes, such as uridine diphosphate–glucuronosyl transferase (UDPGT) have been implicated in an increased risk of head and neck cancer as well.[20] A low-activity UDPGT genotype was associated with 3.7-fold greater odds of development of laryngeal cancer in smokers; the odds ratio increased to 6.1 in heavy smokers and was not increased in those who never smoked. Another interesting study, by Elahi and colleagues,[21] found that human 8-oxoguanine-DNA glycosylase (hOGG1) polymorphism is an important risk factor for the development of orolaryngeal cancer in smokers and alcohol drinkers. The hOGG1 gene encodes a DNA glycosylase that is involved in the excision repair of 8-hydroxy-2′-deoxyguanine (8-OH-dG) from oxidatively damaged DNA. These researchers found that nonsmoking, nondrinking patients with mutant hOGG1 were not at greater risk of orolaryngeal squamous cell cancer. However, smokers and drinkers with this mutation had 4.8 and 6.9 greater odds of development of orolaryngeal cancer, respectively.[21] These two studies suggest that these enzymes are involved in tobacco smoke detoxification and that the genotype can predict the phenotype.

Much study has also been devoted to examining *N*-acetyltransferases, reduced nicotinamide adenine dinucleotide:quinone oxidoreductase 1, aldehyde dehydrogenases, and alcohol dehydrogenases. Some data implicate these substances in the development of cancer. However, larger studies are required to clearly and definitively determine whether they contribute to the development of cancer.[18]

In summary, the molecular mechanisms behind tobacco smoke detoxification are beginning to be elucidated, but further work must be performed to enable accurate prediction as to which people are more susceptible to the development of cancer when subjected to this environmental exposure. Gronau and colleagues[22] have shown that detoxification enzymes are functionally redundant and that only the simultaneous deficiency of several detoxification enzymes increases the risk for oral cancer. Furthermore, a follow-up study by the same group showed that it is probable that the enzymatic activity rather than the actual genotype can influence the risk of cancer.[23] Complicating the issue even more is the influence of ethnicity on the prevalence of polymorphisms; a study in the Netherlands found that two groups of people less than 125 km apart showed statistically significant differences in the prevalence of the GSTT1 genotype.[24]

Other studies have evaluated the enzymes as prognostic markers. Although these detoxifying enzymes play a role in clearing carcinogens, they may also inactivate chemotherapeutic agents delivered in an attempt to kill offending tumor cells. One study examining a different subtype of GST, GST p, found that those patients with high levels of this enzyme had a worsened overall survival when treated with neoadjuvant chemotherapy, likely owing to the clearance of the drug by the GST p.[25] Another study examining GSTT1, a known activator of carcinogens,[26] found that individuals with the functional genotype were two times more likely to die from any cause during the course of HNSCC and three times more likely to die from disease-specific causes after adjustment of data for age, stage, and primary therapy.[27]

Lastly, there has now begun to be some study into the role of saliva and its antioxidative abilities. One group found that the saliva of nonsmoking patients with oral squamous cell carcinoma had highly oxidized DNA and protein, increased levels of reactive nitrogen species, and profoundly reduced levels of antioxidants.[28] Other studies have also examined antioxidant levels after tobacco smoke exposure and shown statistically significant decreases in antioxidants, but as yet no definitive link to the development of HNSCC has been demonstrated.[29]

Human Papillomavirus in Head and Neck Squamous Cell Cancer

Oral HPV infection, like alcohol and tobacco, is now recognized to play an important role in the pathogenesis of a subset of oropharyngeal HNSCCs.[30-36] These lesions are primarily from the lingual and palatine tonsils in the oropharynx and, to a lesser extent, the oral cavity.[31,34,37-42] Furthermore, HPV-related HNSCC has distinguished itself as a separate entity with better prognosis and response to therapy than those of non–HPV-related HNSCC, which is discussed later. It has also been proposed that oral HPV infection is the reason for the rising incidence of oropharyngeal HNSCC relative to all other anatomic sites in the head and neck. We first review in brief what is known about the molecular biology of HPV and how it relates to cancer.

The human papillomavirus is an approximately 7.9-kilobase, nonenveloped, double-stranded, circular DNA virus. It has a specific tropism for squamous epithelium. The virus infects cells in the basal layer of squamous epithelium, and the different types have been traditionally separated on the basis of tropism for cutaneous and mucosal sites as well as of high, intermediate, and low risk, depending on their association with malignancy.[43] The sequences for more than 320 different types of HPV have been identified. Low-risk types, such as HPV-6 and HPV-11, can induce benign hyperproliferations of epithelium such as papillomas and warts. The high-risk types have been implicated in cervical cancer, anogenital cancer, and HNSCC. HPV-16 and HPV-18 are the two types most pertinent to HNSCC and are the focus of this discussion.

The HPV genome typically consists of nine open-reading frame sequences, located on only one of the strands of DNA, and is divided into seven early-phase genes (E) and two late-phase genes (L). The early genes serve to regulate the transcription of DNA, and the late genes encode for proteins involved in viral spread, such as capsid proteins.[44] The E1 and E2 gene products are specifically involved in regulating the transcription and replication of viral proteins. The E6 and E7 oncoproteins are normally under control of E2 and E1 inhibitory genes; these inhibitory genes can be deleted or altered upon integration, leading to unchecked transcription of E6 and E7,[45] which are then able to disrupt the function of Rb and p53, well-known tumor suppressor genes.[46] p53 and Rb are tumor suppressor genes in that they regulate cell-cycle checkpoints at the G1 phase. If these genes are inactivated, cells are more prone to push through division and replication, even in the setting of harmful gene mutations, which can lead to malignancy.

The E6 gene is able to inactivate p53[47] through interaction with the E6-associated protein. This complex then binds with p53 and facilitates ubiquitin-dependent degradation of p53.[48] E7 is able to bind and interact with the Rb gene product.[49] E7 has the ability to phosphorylate the Rb proteins, leading to degradation by ubiquitination.[50] This process subsequently leads to E2F activation, which produces a family of transcription factors resulting in cell proliferation. Many other possible mechanisms have been discovered by which these proteins can induce malignancy so that their role in carcinogenesis is ensured.[51] It has also been shown that p53 sequence alterations are decreased in the setting of HPV infection, because there is an alternative means of p53 silencing with the production of E6, further delineating HPV-related cancers.[31,46,52,53]

The idea that HPV causes HNSCC was first proposed when the cytopathic effects of HPV (koilocytosis) were noted on light microscopy of oral lesions.[54] In situ hybridization later confirmed the presence of HPV DNA in oral pre-malignancies (4/5 leukoplakias) and malignancies (3/6 carcinomas), thereby suggesting a causal association of HPV and carcinogenesis in oral lesions as well.[55] It is now established that histopathologically, HPV-positive tumors tend to have a poorly differentiated and frequently basaloid histology that often lacks keratin.[30,31,36,56] Since then, researchers also discovered that human keratinocytes expressing E6 and E7 genes from HPV-16 become immortal,[57] as do oral epithelial cells.[58-60] It should be noted that the virus must integrate into genomic DNA to have its oncogenic effect.[61,62]

Further study finally confirmed the link between HPV and oropharyngeal HNSCC. In a 2005 meta-analysis, HPV genomic DNA was detected in approximately 26% of all HNSCCs by sensitive polymerase chain reaction–based methods.[63] However, in the majority of studies, 50% or more of oropharyngeal tumors contained the HPV genome.[62] In a multinational study conducted by the International Agency for Research on Cancer (IARC), only 18% of oropharyngeal tumors were HPV positive, indicating that this proportion likely varies by geography.[64] Regardless of the study population, high-risk HPV-16

accounts for the overwhelming majority (90%-95%) of HPV-positive tumors.[63] In addition to the ability to reliably detect HPV in a subset of oropharyngeal cancers, detection of HPV in cervical lymph nodes of patients presenting with an occult primary may be used to establish, with high specificity, the location of the primary within the oropharynx.[65] Tonsillectomy has been shown in retrospective analyses to identify the primary site of cervical metastases as the contralateral or ipsilateral tonsil in approximately 10% or 30% of cases, respectively.[66-69] Therefore, HPV-related cancer is a distinct established entity that can be reliably diagnosed.

The patient population that presents with HPV-positive HNSCC is also distinct. On average, patients with HPV-positive HNSCC are approximately 5 years younger than patients with HPV-negative HNSCC, with equal distribution between the sexes.[41,70-73] HPV-positive HNSCC is more likely than HPV-negative HNSCC to occur in the nonsmoker and nondrinker.[31,32,39,40] In a study restricted to patients with oropharyngeal cancers, nonsmokers were approximately 15-fold more likely than smokers to have a diagnosis of HPV-positive HNSCC.[74] However, whether there is a synergistic, additive, or no relationship between smoking or alcohol use and HPV infection remains to be seen, and research has supported all three possibilities.

Risk factors for HPV-related HNSCC include a high lifetime number of vaginal-sex partners (26 or more), a high lifetime number of oral-sex partners (6 or more),[13] and seropositivity for HPV-16 viral capsid protein antibodies,[33] which carries a 15-fold higher risk for HNSCC.

In the majority of studies, patients with HPV-positive tumors have a better prognosis—as much as 60% to 80% lower risk of dying from the cancer—than patients with HPV-negative tumors, after data are controlled for other risk factors.[31,71,74-77] The reason for their improved survival is unclear; however, better radiation responsiveness, immune surveillance against viral antigens, and the absence of field cancerization in these patients, who tend to be nonsmokers, have been postulated as possibilities. In addition, E6-related degradation of p53 in HPV-positive cancers may not be functionally equivalent to HPV-negative p53 mutations, and therefore, HPV-positive tumors may have an intact apoptotic response to radiation and chemotherapy.

Therapeutic implications of an HPV-positive diagnosis are an active area of investigation. The belief that HPV-positive HNSCC is more responsive to treatment than HPV-negative HNSCC is being considered in the design of future clinical trials. A clinical trial of an HPV-16–specific therapeutic vaccine is also currently being evaluated. The vaccine is administered in the adjuvant setting and is intended to enhance the cytotoxic T-cell response to the HPV-16 oncoproteins.[78] With regard to prevention, a prophylactic vaccine composed of the HPV-16 viral capsid protein has been shown to prevent persistent HPV-16 infection and the development of cervical dysplasia.[79,80] However, the clinical trials have not included an evaluation of the impact of the vaccine on oral HPV infection. The vaccine does have the potential to affect HNSCC incidence, because the current vaccines are targeted to HPV-16 and because animal models demonstrate the vaccine to have a protective effect and a reduction in the development of HPV-related oral lesions.

Possible future diagnostic tests that would likely have high specificity but low sensitivity for a diagnosis of HPV-associated HNSCC include the detection of HPV-16 DNA in plasma,[81] which can be used for surveillance. Other screening tests, such as fluorescence in situ hybridization (FISH) on Papanicolaou smears obtained directly from tumors and HPV-16 E6 and E7 seroreactivity, are currently being tested. And the impact of a positive test result on a patient's risk for the development of cancer is still unclear.

Chemoprevention

As discussed previously, there are well-defined risk factors for the development of HNSCC. In addition to avoiding exposures, there is the possibility of both preventing the development of HNSCC and preventing progression of early disease. Currently, most of the therapy for head and neck cancer is focused on treating the disease after it has already progressed to malignancy. However, because head and neck cancer often manifests initially as premalignant disease and because there is a defined set of high-risk individuals, many researchers have begun the search for agents that can prevent disease from occurring, prevent recurrent disease, or prevent disease progression.[82]

The concept of chemoprevention was first proposed by Sporn and colleagues,[83] who looked at the protective effects of vitamin A and its derivatives on carcinogenesis. The mechanism of action was thought to be via binding of retinoic acid receptor molecules,[84,85] which then function as angiogenic and growth-regulating factors.[86,87] In a landmark study, the utilization of high-dose 13-*cis* retinoic acid in patients with known head and neck cancers proved helpful in preventing the development of second primary tumors[88] and in the treatment of oral leukoplakias,[89] although significant toxicity was associated with this therapy, including skin lesions, conjunctivitis, and cheilitis. Furthermore, when therapy was discontinued, the risk of disease development returned to baseline after about 2 years.[90] A follow-up study looked at use of low-dose fenretinide (a synthetic retinoid) for leukoplakia, and early results were promising for prevention of malignant transformation.[91] Unfortunately, the trial was ended because of low recruitment. In a large trial, 1384 patients were treated with isotretinoin to prevent second primary HNSCC. Treatment showed no benefit, and only smoking cessation correlated with a decreased risk of recurrence.[92] Another large trial by the Italian Head and Neck Chemoprevention Study Group found that treatment with 13-*cis* retinoic acid for 1 year after resection showed no benefit.[93] However, the question is not completely answered; there has been evidence that in cell lines, the combination of 13-*cis* retinoic acid, interferon-alpha-2a, and alpha-tocopherol can cause cell cycle arrest and apoptosis.[94] Another study showed that a synthetic retinoid, MX3350-1, could induce the extrinsic and intrinsic pathways in head and neck squamous carcinoma cells.[95] Whether this combination or any other combination will be beneficial still remains to be seen.

Cyclooxygenase-1 (COX-1) and COX-2 inhibitors have also been studied as possible mediators of prostaglandins and the inflammation that often accompanies many different tumors. Prostaglandin levels have long been known to be raised in head and neck cancers as well, presumably owing to the up-regulation of COX-1 and COX-2.[96,97] Animal models suggested that aspirin or ibuprofen could inhibit the formation of buccal tumors.[98,99] Colon cancer was among the first tumors studied widely in humans, beginning with epidemiologic evidence that aspirin reduced the risk of colon cancer development.[100] Sulindac was shown prospectively to reduce the number and size of colonic polyps in patients afflicted with this disease.[101] Studies of the use of these agents in colorectal, breast, lung, and esophageal carcinomas followed. The mechanism behind the effect of COX-2 inhibitors appears to be multifactorial.[102,103] The overexpression of COX-2 leads to decreased apoptosis, thereby prolonging the life span of abnormal cells. Furthermore, inflammation may be a risk factor for epithelial carcinogenesis because it is often found in these malignancies. Angiogenesis may also be tied into the COX-2 pathway, because vascular endothelial growth factor (VEGF) expression is elevated by high COX-2 levels.[104] Thus, there are several mechanistic reasons why COX-2 inhibitors would be beneficial in preventing recurrence, development, or progression of head and neck lesions, especially in high-risk patients. There have been some promising results in animal models, but study in humans has only begun.[105] In addition, the use of epidermal growth factor receptor (EGFR) inhibitors as chemopreventive agents, both individually and in combination, is also being studied.[105]

Clinical Implications

The ultimate goal of understanding the molecular biology of HNSCC is to use that knowledge to improve patient outcomes. The keys to improving patient care in HNSCC therefore are (1) better diagnostic tests that allow earlier detection of disease, improved surveillance after treatment, and more accurate margin analysis, (2) more accurate prognostic indicators that allow us to tailor therapy to the individual and better predict a patient's course, and (3) additional therapeutic targets. Molecular biomarkers have the potential to improve in all those areas and are specifically discussed later. This section discusses the molecular changes occurring in cancer that form the basis of the biomarkers currently under study.

Genetic Alterations

In this section we address traditional genetic alterations in HNSCC; epigenetic changes are discussed later. The genetic alterations lead to actual sequence or code disruption by deletion, addition, substitution, or translocation of DNA. These alterations may be the result of an inherited defect or of an acquired defect secondary to environmental exposures. With the advent of many new technologies, this area of research has rapidly changed.

Cytogenetics

Cytogenetics is the study of the structure of chromosomal material. The field of cytogenetics has progressed from gross examination of a karyotype to detailed mapping of chromosomal translocations, breakpoints, and areas of loss or gain. Consistent regions of alteration in primary tumors have been correlated with the presence of important genes involved in carcinogenesis. For instance, an area of loss may contain a tumor suppressor gene, whereas an area of amplification may contain an oncogene. Newer techniques allowing for fine mapping of areas of loss or gain combined with the Human Genome Project have greatly increased our ability to focus on the relevant regions or genes involved in HNSCC.

The most basic form of cytogenetics is karyotype analysis, which entails a visual analysis of cells that have undergone short-term culture and have been arrested in the metaphase state to screen for abnormalities in copy number gain or loss and chromosomal breaks or rearrangements. Data have confirmed frequent loss of material on chromosomes 3p, 8p, 11q, 13p, 14p, and 15p with gains on chromosomes 1q, 3q, 8q, and 15q.[106] The limitation of karyotype analysis lies in its resolution. Each region carries numerous genes that could be lost or gained.

Other techniques with different strengths and weaknesses have been employed to evaluate the tumor genome. Spectral karyotyping (SKY) adds the use of chromophores to karyotype analysis; it provides a unique fluorescent background for each of the chromosomes. SKY makes characterizing complex rearrangements or chromosomal aberrations easier. The technique of SKY has been used on HNSCC, and frequent losses were identified at 3p, 8p, 9p, 11q, 14p, and 15p along with gains at 1q, 3q, 8q, and 15q.[107] Comparative genomic hybridization (CGH) is a technique utilized to detect unbalanced chromosomal gains or losses whereby normal DNA and tumor DNA are labeled and hybridized to normal metaphase chromosomes. The relative fluorescence at the different regions is determined, and regions of loss or gain can be detected. The resolution is accurate to about 20 megabases. FISH uses sequence-specific fluorescent probes that are detected through light microscopy after hybridization. It also allows for the specific detection of areas of loss and gain; however, FISH is limited in its genome-wide application.

The use of a combination of SKY, FISH, and CGH on the same samples has the benefit of balancing out the weaknesses and ensuring the consistency of these techniques. Several investigators have used such an approach in evaluating HNSCC.[108,109] As in other studies, common chromosomal losses were found to occur at 1p, 3p, 4p, 8p, 10p, and 18q with gains at 3q, 5p, 8q, 9q, and 14q, and amplification at 3q13, 3q25-26, 5q22-23, 7q21, 8q24, 11q13-14, 12p13, 14q24, and 20q13.1. There was good correlation between SKY and CGH results, and FISH was generally employed to further delineate the nature of aberrations with its sequence specificity. One study identified PIK3CA, a member of the Akt pathway, as a candidate oncogene on chromosome 3q involved in HNSCC.[109]

Cytogenetic alterations may also predict prognosis. CGH analysis of 82 primary head and neck carcinoma samples demonstrated that amplification of 11q13 correlated with a poor outcome.[110] A similar finding was shown in 12 laryngeal cancer cell lines whereby 11q13 amplification was associated with shorter patient survival.[111] Thus, these alterations can be used as markers for prognosis, because they are associated with genetic changes that can influence the development or aggressiveness of HNSCC.

Although these cytogenetic techniques were used as a screen to implicate certain regions of chromosomal losses as harboring tumor suppressor genes or areas of gain with oncogenes, a bit of a disconnect occurs once these assays have been completed. For example, loss of chromosome 3p is one of the most common aberrations identified by cytogenetic applications, but the identification of the specific gene relevant to HNSCC has been difficult. Fine mapping and loss of heterozygosity (LOH) analysis must be performed to identify the significant region of loss. Functional studies then must be performed to pinpoint the gene(s) with tumor-suppressive properties.

With the advent of microarray technology, the application of cytogenetics has begun to take on a new form. CGH-array now hybridizes the normal DNA and tumor DNA to millions of probe sequences, allowing for a much finer map down to 5 to 1010 kilobases. This technique has been shown to have application in HNSCC[112,113] and has been used to identify a novel region of gain on 8q22 and the LRP12 gene.[114]

Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when one nucleotide in the genome sequence is altered. For a variation to be considered an SNP, it must occur in at least 1% of the population. SNPs are scattered throughout the coding and noncoding regions of the genome and account for about 90% of all human genetic variation. Although most SNPs have no effect on cell function, these variations in the DNA sequence can have several uses. Because SNPs are highly conserved, they can be used for profiling cancers and subsequently as clinical biomarkers. In addition, SNPs have been used to reliably map out the locations of genes of interest. For instance, SNP arrays have been created to scan the entire genome, have been used to provide finer mapping of areas of loss or gain, and have identified a region on 6q that is implicated in some cases of HNSCC.[115]

Microsatellites

Microsatellite repeats are tandem repeats of noncoding sequences scattered throughout the genome. Use of these conserved regions as markers in the human genome enabled areas of loss to be found in cancer. Once a microsatellite was found to be deleted or missing in cancer in comparison with normal tissue, the region was identified as having a possible TSG in its proximity. Finer mapping or sequencing could then be performed to identify the gene of interest. Out of this technique came the HNSCC progression model that was discussed in the chapter's introduction. This study by Califano and colleagues[5] demonstrated that TSG deletions occurred early in the precancerous lesions and that there was an accumulation of alterations with progressive disease in HNSCC.

Oncogenes

The genetic amplifications noted in cytogenetic studies are thought to lead to the overexpression of oncogenes. *Oncogenes* encode for products that are normally produced at some time during the life of a cell but that, when aberrantly overexpressed, lead to a selective growth advantage. Thus, they may include anti-apoptotic factors, angiogenic or growth stimulators, or protein stabilizing agents. For technical reasons, the identification of oncogenes can be more challenging than that of their counterparts, TSGs. Because oncogenes are often normally expressed at lower levels, or may not necessarily incorporate any DNA sequence abnormalities, the molecular techniques to detect abnormal oncogenes are more limited. We have largely depended on the cytogenetic work in order to identify these oncogenes by looking at the chromosomal regions that are amplified and then determining which genes are important for function.

One of the best-studied oncogenes in HNSCC is the epidermal growth factor receptor (EGFR). EGFR is a cell surface receptor that is a member of the ErbB family of proteins that has many downstream signaling consequences. The story of EGFR is promising in that its study has led to its use as a therapeutic target. This receptor is discussed in more detail later in the chapter.

Matrix metalloproteinases (MMPs) are genes encoding for a variety of proteins that are thought to be involved in cell adhesion, proliferation, and migration. MMP-2 was one of the first in the family noted to be related to lymph node metastasis in HNSCC,[116] but several other studies have seen other members of MMP overexpression.[35,117] MMP

expression may also be predictive of advanced disease and tumor metastasis in HNSCC.[35,117-119] Interestingly, MMP expression may be influenced by EGFR up-regulation,[120] so there is likely to be overlap between many of the pathways involved in HNSCC. Furthermore, it appears that there are stromal elements that produce MMPs and thus could play a role in the development of metastatic disease.[121]

One of the p53 family members, ΔNp63-α, is known to be amplified and overexpressed in HNSCC cell lines and to have oncogenic properties.[122] It is also known to be created through the alternative splicing of the p63 protein, which encodes for several other putative oncogenes. One possible mechanism of action of ΔNp63-α is through the accumulation of the transcription factor β-catenin.[123] Later data demonstrate that ΔNp63-α functions through the inhibition of p73, and it is through this inhibition that ΔNp63-α is able to repress apoptosis via bcl-2.[124]

Many other oncogenes have been implicated in HNSCC, including VEGF, PIK3c/Akt, and members of the STAT (signal transducer and activator of transcription) family. The exact contributions of these mechanisms to carcinogenesis are constantly being refined. As the basic pathways are further elucidated, they represent possible targets for intervention. The targeting of pathways has the potential for greater specificity and reduced toxicity of therapeutic agents. Compounds designed to inhibit or counteract oncogene expression continue to emerge and to be incorporated into clinical trials.

Tumor Suppressor Genes

Tumor suppressor genes are the counterparts to oncogenes. In general, these genes have a role in growth suppression activities such as apoptosis, cell cycle regulation, DNA repair, and cell adhesion. Thus, when TSGs are deleted or silenced, the cell develops a selective growth advantage and becomes a cancer.

One of the earliest significant TSGs identified in HNSCC was p53. A transcription factor the gene for which has been mapped to chromosome 17p13, p53 is activated in times of cellular stress such as irradiation, hypoxia, and environmental toxin exposure. Interestingly, early reporters of p53 believed that it was an oncogene, because it was found to be overexpressed in cancers. However, it is now known that the p53 gene is inactivated most often by point mutations, although overexpression of the mutant forms still occurs.[125] Activated p53 serves to send cells into apoptotic pathways or can regulate growth through cell cycle control; thus, it plays a critical role in the maintenance and proliferation of cancer cells. Indeed, p53 is the most commonly mutated TSG among all human cancers,[126] and HNSCC is no exception.[127] Premalignant head and neck lesions have also been shown to harbor p53 mutations, suggesting that this mutation can be an early event.[128] Mutations in p53 have been correlated with poorer survival and poorer response to treatment.[129-133] Thus, p53 serves as an excellent marker for disease and has been the target of many therapeutic interventions.

As described previously, cytogenetic data indicated that deletion of 9p21 is a common event in HNSCC, and the LOH data confirmed that it is a common, early event.[134,135] The CDKN2a locus codes for p16 and p14(ARF), which have been accepted as the relevant genes contributing to HNSCC. The p16 gene plays a role in cell cycle regulation at the G1 state through cyclin-dependent kinases 4 and 6, and the p14(ARF) gene is thought to function in the stabilization of p53 through MDM2, a gene that is a negative regulator of p53. Thus, there are two prominent TSGs at this locus that show mechanistic evidence of their function in regulating cell growth and division. Studies suggest that loss of p16 expression may be associated with poorer prognosis in patients with HNSCC.[136,137] Although p16 was frequently found to be down-regulated in HNSCC, there was a surprisingly low incidence of point mutations or homozygous deletions that would explain its contribution to HNSCC.[138] The tumor-suppressive function of p16 was indeed confirmed, although it became evident that there were other mechanisms involved in its silencing (discussed later).

The deleted in colorectal cancer (DCC) gene is located on chromosome 18q21, a region that was shown to have LOH in dysplastic head and neck lesions,[139] in oral cancer cell lines,[140] and in a significant percentage of primary HNSCC.[141] Furthermore, loss of this region was shown to be more common in the metastatic and locally recurrent lesions, suggesting that it played a significant role in more aggressive lesions.[142]

However, there did not appear to be a higher incidence of tumor formation in heterozygous DCC mice than in homozygous deleted DCC mice. Thus, there was some confusion as to its true role in tumorigenesis. One study demonstrated that DCC's function was related to binding with netrin-1 and thus that DCC acts as a conditional TSG. Gene silencing via promoter hypermethylation was confirmed in primary HNSCC and cell lines, and subsequent growth assays showed that transfection of DCC into DCC-cell lines was able to arrest growth, whereas the addition of netrin-1 led to the resumption of cell growth.[143] Thus, the mechanism of the tumor-suppressive effects of DCC is not as simple as that of other models and also suggests that there may be many other ways in which TSGs may function.

The discovery of genetic alterations has been rapidly accelerating with the advent of various microarrays. The importance of understanding the mechanisms of HNSCC carcinogenesis lies in their use as clinical biomarkers and as possible therapeutic targets.

Tumor Suppressor Gene in Fanconi's Anemia

Fanconi's anemia is an autosomal recessive DNA repair disorder that leaves patients uniquely vulnerable to DNA damage and the subsequent development of a multitude of cancers. Thus far, 11 genes have been identified in this disorder that ultimately are involved in the regulation of the BRCA-1 and BRCA-2 pathway (involved in the repair of double-stranded DNA breaks). Previously, patients succumbed to aplastic crises or hematologic malignancies. However, with advances in bone marrow transplantation and longer life spans, patients with Fanconi's anemia have been found to be at profound risk for development of various cancers, in particular HNSCCs. Patients with this disorder are atypically young (<50 years of age) and are usually women who do not smoke tobacco or drink alcohol. The relative risk of HNSCC in patients with Fanconi's anemia is 700 times greater than that in the general population.[144] After bone marrow transplantation, which is performed to prevent a fatal aplastic crisis or hematologic malignancy, the risk is further increased by fourfold.[145] Patients with this disorder should be treated with surgery rather than irradiation or chemotherapy, to prevent further DNA damage and the development of other malignancies.

Epigenetics

The field of epigenetics has greatly furthered our understanding of not only cancer but all of molecular biology. *Epigenetics* is a term used to describe the regulation of gene expression that does not involve DNA sequence alterations but, rather, is a heritable modification of the DNA molecule itself and/or the proteins associated with it. One way in which this modification can occur is through the covalent addition of a methyl group to the 5′ carbon of the cytosine ring, resulting in 5-methylcytosine. However, in order for this methyl group to be added, a cytosine base pair must be followed by a guanine base pair in the DNA sequence, a so-called CpG dinucleotide. Overall, CpG dinucleotides occur at lower than expected frequencies throughout the human genome. However, they are found more frequently in the promoter regions of genes as small stretches of DNA called *CpG islands*.[146] The addition of the methyl group to the cytosine prevents binding of transcriptional activators and RNA polymerase, effectively silencing the gene. Once methylated, the modification is then passed to progenitor cells, making it a heritable or permanent modification to gene expression. DNA methyltransferases (DNMTs) are responsible for maintaining the methylation status of a gene in the progeny. Because CpG islands are most commonly found in promoter regions of the genome, they are believed to be one mechanism of gene expression regulation. In summary, hypermethylation and hypomethylation are epigenetic means of regulating gene expression (Fig. 76-1).

In addition to the methylation of promoters, histones have been shown to play an active role in regulating gene expression. Once thought to be static packaging proteins, histones are now recognized to be dynamic molecules that can physically determine whether transcription factors have access to promoters. Histones may undergo many post-translational chemical modifications, such as acetylation, meth-

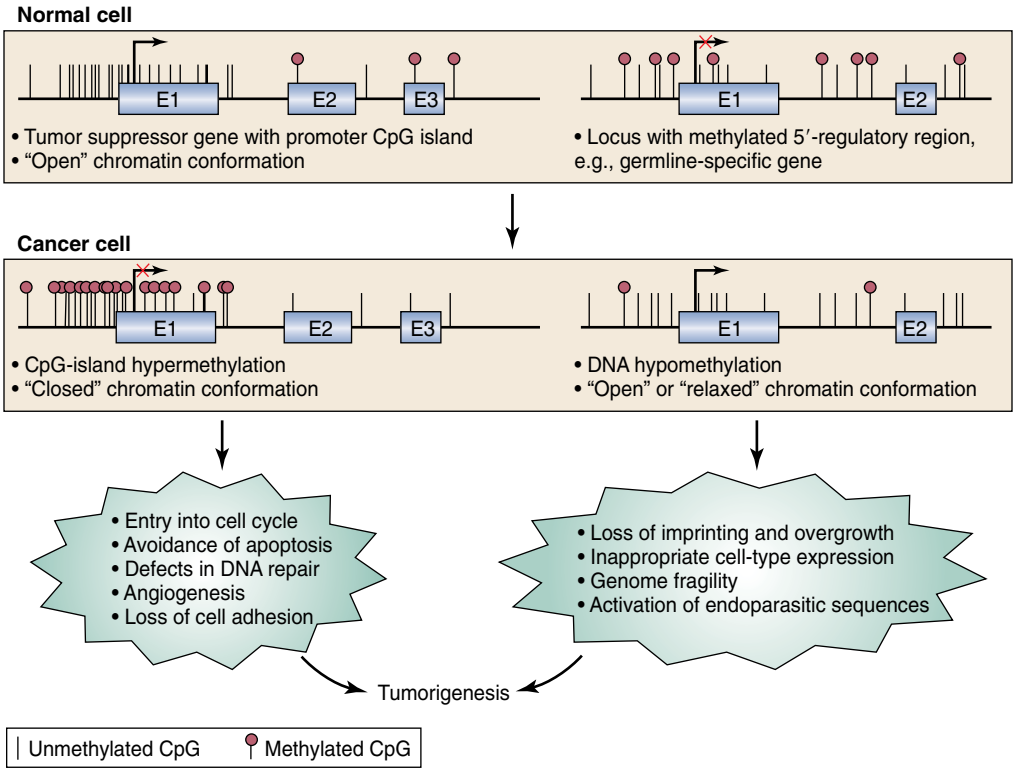

Figure 76-1. Diagram showing the altered DNA methylation patterns in tumorigenesis. The hypermethylation of CpG islands of tumor suppressor genes is a common alteration in cancer cells that leads to the transcriptional inactivation of these genes and the loss of their normal cellular functions. At the same time, the genome of the cancer cell undergoes global hypomethylation at repetitive sequences, and tissue-specific and imprinted genes can also show loss of DNA methylation. In some cases, this hypomethylation is known to contribute to cancer cell phenotypes and contribute to the genomic instability that characterizes tumors. E, exon. *(Redrawn from Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps.* Nat Rev Genet. *2007;8(4):286-298.)*

ylation, phosphorylation, ubiquitylation, and sumoylation.[147] Histone modifications and DNA methylation play a significant role in the organization of nuclear structure, ultimately influencing what genes may be suppressed or expressed.[148]

The phenomenon of methylation as a regulator of gene expression was first recognized in development, during which the coordinated expression and silencing of genes needs to take place in an organized fashion.[149] It was quickly proposed that epigenetic control of TSGs, as a novel mechanism of gene regulation, could be an important mechanism of carcinogenesis.[150,151] Initially, studies of the global methylation status were performed in animals, and cell culture showed mixed results. Many workers believed that the observed hypomethylation of tumors was simply a marker of an actively dividing cell or the result of malignant transformation rather than the cause. But Feinberg and Vogelstein[150,151] were the first to analyze primary tissue from resected cancers and examine both global methylation and methylation of specific known oncogenes. Interestingly, they found that cancers were globally hypomethylated (10%) and that Ras oncogenes were specifically hypomethylated.

Although hypomethylation was the originally identified epigenetic change in cancer, it was overlooked in preference for hypermethylation for many years and is only now undergoing a renaissance. This situation occurred, in part, because of previous bias in experimental design; if one looks for altered methylation only at sites that are normally unmethylated, then one will observe only hypermethylation.[152] Furthermore, the early success of Baylin and Herman (discussed later) in finding specific regions of hypermethylation prompted many other researchers to search for similar regions with similar techniques.

One of the earliest genes to be characterized as being under epigenetic control is the retinoblastoma gene. Looking in primary tissues of resected retinoblastomas, Sakai and coworkers[153] found that in 10% of the tumors analyzed, the promoter of Rb was hypermethylated in the absence of any other mutations. Since that discovery, many different tumor types have been shown to exhibit various TSG methylation.

Significant promoter hypermethylation has been demonstrated in many of the known TSGs in head and neck cancer. One of the more interesting findings is the high incidence of p16 hypermethylation. It has long been puzzling that p16 expression has been found to be decreased in a majority of HNSCCs, whereas point mutations and homozygous deletion are rare and the incidence of LOH is not. Promoter hypermethylation of p16 has been shown to be quite frequent in HNSCC, explaining the apparent discrepancy between the incidence of deletions or mutations and low expression.[146,153-156] Thus, Knudson's "two-hit" hypothesis could include promoter hypermethylation as one of the hits along with the more traditional sequence mutation or chromosomal deletion.

Many other genes have emerged as putative TSGs in HNSCC based on promoter hypermethylation, including lhx-6 (DIME-6), ATM, p15, TIMP-3, MGMT, RARB-2, DAP-K, E-cadherin, Cyclin A1, RASSF1A, and DCC.[157-167] The list of TSGs that are silenced through promoter hypermethylation continues to grow every year. Furthermore, it has been recognized that many other avenues of research cross paths with epigenetics. For instance, microRNAs (small non-coding RNA molecules; see later) that have tumor-suppressor function have been demonstrated to also undergo DNA methylation–associated silencing in cancer and therefore are under the same epigenetic control[164,168,169] (see Fig. 76-1).

However, one must recall that in general, DNA is hypomethylated in cancer despite local regions of hypermethylation. This apparent paradox was attributed to overall cell activation after carcinogenesis was initiated. Evidence is now emerging on the importance of the hypomethylation of genes. Studies have now shown that the regions of hypometh-

ylation correlate with genes that were important to development and were subsequently "turned off" by methylation. These genes, once reactivated, have proved to be oncogenic. Some of these genes are HOX11, MAGE family, CAGE-1, uPA, MTS1/S100A4, MASPIN/SERPINB5, and BCSG/SNCG.[170] Specific data on genes that are activated in HNSCC are yet to be published, although a 2007 study demonstrated that there is indeed global hypomethylation in HNSCC.[171]

The natural question regarding any of the previously mentioned discoveries regarding epigenetics is how they will ultimately affect clinical practice, if at all. Translational epigenomics has been an exciting area of research that has grown with the field of epigenetics itself. There are several methods to translate epigenetic discoveries into clinical practice. The first is the use of the *epigenetic profile*, which refers to the fact that unique profiles of hypermethylation define each cancer type.[172,173] Once defined, the profile of HNSCC could be used as a marker of prognosis and possibly to predict responsiveness to treatment. Second, the hypermethylated genes themselves are potential therapeutic targets. Promoter hypermethylation is an attractive route for therapeutic intervention because it does not involve loss of DNA or sequence alterations. Selective demethylation is not feasible at this point, but it could eventually become a reasonable means of cancer therapy. Third, detection of methylated DNA in body fluids is a potential marker for screening and surveillance. Studies have already proven the ability of such markers to be detected, but further work is needed to improve their sensitivity and specificity.[165,174] Lastly, it may be possible, with the development of more rapid detection strategies, to perform molecular margin analysis of cancers. These topics are more thoroughly addressed in the molecular diagnostics section of this chapter.

There are still several questions yet to be answered. What is the role of hypomethylation? And why is there global demethylation in cancer? How does DNA become methylated or demethylated? It has been theorized that DNA methylation and histone deacetylation are a means to stabilize chromatin after trauma, but this theory has not been proven. Whether the enzymes that normally maintain methylation are in dysfunction or the DNA is methylated first remains to be seen. It also has become apparent that carcinogenesis is caused not by the activation or deactivation of one or two promoters but, rather, by several hundreds of promoters and histones interacting synergistically.

Epidermal Growth Factor Receptor

One of the best-studied areas of the molecular biology of HNSCC is the role of EGFR and its associated pathways in carcinogenesis. Expression of EGFR is a normal finding in many tissues, including the dermis, gastrointestinal tract, and kidneys. However, dysfunction of this receptor and its associated pathways occurs in most epithelial cancers[175] and in 80% to 90% of HNSCCs specifically.[176,177] What is unique about this area of inquiry is that the research into the biology of EGFR has led directly to clinically beneficial targeted therapies. Before delving into therapies, we examine the basic molecular biology of EGFR.

Biology

A general understanding of the EGFR-related pathways is necessary to comprehension of the therapies directed against it (Fig. 76-2). EGFR is a cell surface receptor that is a member of the larger ErbB family of proteins, which includes the Her2, Her3, and Her4 receptors. EGFR possesses an extracellular ligand-binding domain, a transmembrane region, and an intracellular domain. The intracellular domain includes the tyrosine kinase domain and multiple phosphorylation sites. Once the extracellular portion of the receptor binds a ligand, homodimerization or heterodimerization of EGFR with other ErbBs follows, which then results in the autophosphorylation of the receptor. Currently, 12 ligands of the ErbB family have been identified. Once phosphorylated, the receptor can signal via the MAPK, Akt, ERK, and Jak/STAT pathways. These pathways are related to cellular proliferation, apoptosis, invasion, angiogenesis, and metastasis.[175,177,178] There is also some evidence that the receptor may localize to the nucleus and act as a transcriptional activator. Finally, one study has even linked the effects of tobacco smoke to increased EGFR expression and cellular proliferation.

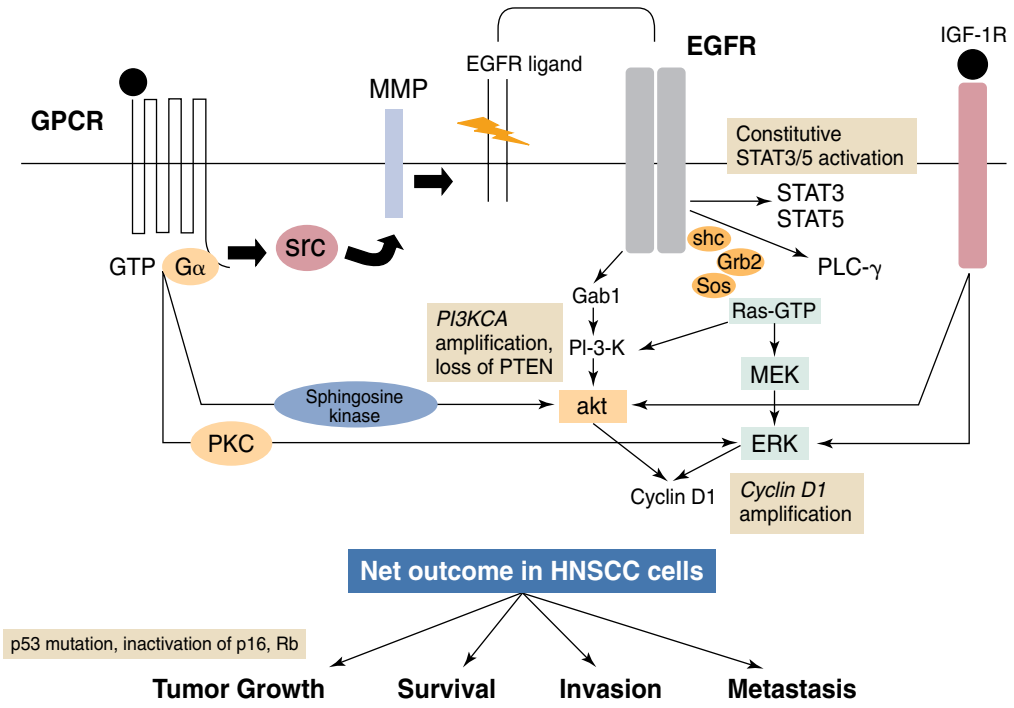

Figure 76-2. Epidermal growth factor receptor (EGFR)–associated pathways. Oncogenic pathways activated by EGFR that lead to head and neck squamous cell carcinoma (HNSCC). ERK, extracellular signal-regulated kinase; Gα, g-alpha subunit; GPCR, g-protein coupled receptors; IGF-1R, insulin-like growth factor-1 receptor; MEK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; PKC, protein kinase; Rb, retinoblastoma; STAT, signal transducer and activator of transcription. *(Modified from Kalyankrishna S, Grandis JR. Epidermal growth factor receptor biology in head and neck cancer.* J Clin Oncol. *2006;24(17):2666-2672.)*

Clinical Implications

The pathologic manifestations of EGFR in HNSCC are achieved by at least four major mechanisms, as follows: (1) overexpression of EGFR ligands and establishment of autocrine/paracrine loops, (2) mutational activation of EGFR, (3) amplification of EGFR, and (4) transactivation by other receptor and nonreceptor tyrosine kinases. Although EGFR-driven molecular pathway aberrations are important and are altered in 90% of HNSCCs, they cannot be considered the dominant or sole genetic alteration in the molecular pathogenesis of HNSCC. Initially, EGFR was first found to be up-regulated in HNSCC cell lines[179] as well as in a high percentage of primary HNSCCs.[179-181] Further study showed that histopathologically normal mucosa adjacent to cancer had a high degree of overexpression of EGFR.[182] It was also later found that the up-regulation of EGFR occurs in the transition from dysplasia to HNSCC.[183] All of these revelations, however, should not be surprising, given the field cancerization hypothesis and progression model discussed in "Background".

Furthermore, increased levels of expression were found to predict a worse disease-free and cause-specific survival.[184] Copy number amplification has also been shown to be associated with poorer prognosis in HNSCC.[185] Mutations of the EGFR tyrosine kinase domains have been detected but are infrequent in HNSCCs (1%-7%).[186,187] Further work has demonstrated the association of STAT and Src activation as contributing to the up-regulation of EGFR.[188-190] One study has demonstrated that the overexpression of EGFR is a biomarker for an improved response to therapy that could serve as a predictive marker to distinguish patients for assignment to different arms of therapeutic trials.[191]

In addition, EGFR axis alterations have been intensively researched as markers for response to treatment and as therapeutic targets. General strategies for targeting the EGFR axis are specific tyrosine kinase inhibitors, blocking of dimerization with monoclonal antibodies, and blocking of mRNA expression with antisense oligodeoxynucleotides or small interfering RNA (siRNA). A 2006 clinical trial evaluating EGFR inhibitors as adjuvants to radiotherapy demonstrated both a survival benefit and a lower side effect profile in comparison with radiotherapy alone.[192] This was the first randomized study showing a survival benefit with an EGFR-targeting agent (cetuximab, a monoclonal antibody) in locally advanced HNSCC.[193] Conversely, gefitinib (a tyrosine kinase inhibitor) has shown no survival benefit in recurrent or metastatic HNSCC.[193,194] However, several ongoing trials are looking at various methods of targeting the EGFR axis—one evaluating gefitinib plus docetaxel versus placebo for recurrent or metastatic disease, one examining cetuximab as an adjuvant to cisplatin and 5-fluorouracil therapy for recurrent or metastatic disease, and one studying cetuximab as an adjuvant to radiotherapy and cisplatin treatment for locally advanced disease.[193] A shortcoming of all of these clinical trials is that none incorporates the presence of EGFR-activating mutations, EGFR gene copy number, or both into their primary analyses, even though both factors have emerged as predictors of treatment efficacy.[193] However, retrospective analysis of these factors within the context of prospective therapeutic trials should provide some information.

As alluded to previously, there is evidence that in non–small cell lung cancer (NSCLC), activating somatic mutations in the EGFR tyrosine kinase domain can predict a patient's response to treatment. These mutations, which are present in about 10% of NSCLCs[195,196] and 1% to 7% of HNSCCs,[186,187] correlated with prolonged survival in patients with advanced NSCLCs treated with chemotherapy regardless of EGFR tyrosine kinase inhibition.[197] Moreover, in several studies of NSCLCs, EGFR mutations were predictive of survival in patients treated with EGFR tyrosine kinase inhibitors.[198-200] As a result, multiple clinical trials are evaluating EGFR tyrosine kinase inhibitors in chemotherapy-naïve patients with advanced NSCLC and EGFR-activating mutations.[193,201,202] Both gefitinib and erlotinib have demonstrated response rates of 75% to 82%.[193,201,202] Whether the same correlation and response to therapy will be found in HNSCC for other EGFR alterations has not yet been determined.

Immunotherapy

Immunotherapy, defined broadly as any manipulation of the immune system to achieve a desired treatment effect, is an attractive therapeutic strategy for the treatment of cancer. Theoretically, immune cells can be specifically targeted without the need for potentially toxic foreign chemicals or agents. In addition, immunotherapy can be integrated with and even enhanced by existing therapies such as surgery, chemotherapy, and irradiation. Like vaccination against infectious diseases, tumor vaccines rely on the concept of exploiting antigenic components of target cells. This therapeutic modality is based on the assumptions that (1) the tumors express antigens or neoepitopes that either are not found or are present in low levels on normal cells and (2) the immune system can be appropriately activated to exterminate such cells. However, unlike many microbial organisms, neoplastic cells derived from a patient's own tissues vary only slightly from normal cells. In addition, many potential antigens expressed by these cells have been constitutively present throughout development and therefore are not recognized as foreign. This is because the immune system has evolved a network of sophisticated checkpoints to prevent autoimmunity, collectively known as *tolerance*. This network includes mechanisms such as positive and negative thymic selection as well as peripheral means such as anergy, suppression, and ignorance, all designed to prevent recognition of "self" antigens as "other."

In HNSCC, the presence of tolerance is further confounded by the fact that in T cells of patients with HNSCC, lymphocytes that coordinate recognition of foreign antigens in normal cells are often dysfunctional. A high proportion of both tumor-infiltrating lymphocytes and peripheral blood lymphocytes (in patients with HNSCC) have fragmented DNA and express markers such as annexin V, indicating the occurrence of apoptosis.[203-207] In addition, both tumor-infiltrating lymphocytes and peripheral blood lymphocytes have an impaired ability to proliferate and transduce integral signaling pathways.[205-209] This functional inactivation may be related to a lack of expression of the z portion of the CD3 T-cell receptor complex that is essential for signaling transduction, as well as increased expression of FAS ligand.[206] It is predominantly CD8 T cells that display these dysfunctional attributes, whereas CD4 T cells remain comparatively unaffected.[207,210] The means by which cancer cells escape immunologic detection is still being actively researched. The exact mechanism by which these cells escape detection is still unclear, and much of this realization arose from the poor results of several early-phase clinical trials.[211,212] It has been proposed that the issue lies in a defective HLA class I receptor as well as dysfunctional antigen-presenting cell interactions, but this remains an active area of study.[212,213]

The deficits seen in both tumor-infiltrating lymphocytes and peripheral blood lymphocytes appear to have significant clinical significance in patients with HNSCC. Patients with a high percentage of apoptotic tumor-infiltrating lymphocytes have a significantly lower 5-year survival rate than those with a lower percentage.[208] Patients with HNSCC have significantly lower levels of thymic output of naïve T cells than healthy control subjects.[207] This finding indicates that patients with such deficits do not compensate well for frequent T-cell apoptosis.

Despite the fact that patients with HNSCC display this degree of relative immunosuppression, there has been an increase in the number of translational and clinical immunotherapeutic trials in HNSCC. The types of trials are numerous but are generally categorized into studies of the following: manipulation of cell signaling (such as cytokines), preventive vaccines, and T cell–based, dendritic cell–based, and antibody-based strategies (discussed in the EGFR section).[214]

Early attempts at immunotherapy in patients with HNSCC mainly focused on the administration of nonspecific agents such as the cytokine interleukin-2 (IL-2).[215,216] However, it was found that only a small minority of cases of HNSCC responded to IL-2 and similar agents, and these responses were usually of short duration. Later studies have focused on ways to improve response rates and extend remissions with cytokines through a variety of strategies. Treating peripheral blood mononuclear cells from patients with HNSCC using the combination of IL-2 and IL-12 resulted in higher cytolytic activity than treatment using either alone.[217] In addition, the lack of response to IL-2 may be due to inadequate expression of this cytokine at the tumor site[218]; this hypothesis was reinforced by the demonstration of regression of a significant proportion of implanted murine floor-of-mouth tumors after peritumoral injection of vaccinia virus that had been transduced with

IL-2.[219] Other investigators have hypothesized that the potential reason for lack of efficacy with IL-2 and other cytokines in HNSCC may be a lack of sufficient costimulation, an essential element for T-cell activation.[220]

One phase 2 clinical trial used the natural cytokine mixture IRX-2 in 15 patients with stage II to stage IV HNSCC.[221] Patients were given a 21-day cycle of perilymphatic IRX-2 in combination with cyclophosphamide, indomethacin, and zinc with surgery, irradiation, or both. Although it is difficult to draw substantial conclusions from this study because of the low number of patients enrolled with a variety of clinical presentations, a complete response was seen in 1 patient, and a partial response in several others. The treatment regimen was well tolerated, and all patients enrolled in the trial had evidence of a histologic response. On the basis of these encouraging results, a phase 3 trial involving a larger number of patients is planned for the near future.

In a 2005 study comparing expression of the chemokine CXCL-14 in patients with HNSCC and normal subjects, Shurin and colleagues[222] found a significant difference.[222] CXCL-14 was not expressed in patients with HNSCC or in HNSCC cell lines. In HNSCC cell lines, the researchers were able to demonstrate that re-expression of CXCL-14 would chemoattract dendritic cells. In dendritic cells, the addition of recombinant CXCL-14 caused the cultured cells to display markers of maturation.[222] This was a very promising study that has many therapeutic implications.

Much effort is also being spent to develop immunotherapeutic strategies that induce adaptive (T cell–based) immune responses that are sufficient to eradicate tumor while not affecting normal host tissues. One study examined the efficacy of an autologous whole-cell vaccine and adoptive T-cell immunotherapy in 17 patients with unresectable HNSCC.[223] Patients were first given an injection of irradiated autologous T cells at a single site, followed by three injections of granulocyte-macrophage colony-stimulating factor (GM-CSF) at that site. Approximately 10 days later, the draining lymph nodes were excised and the T cells isolated. The cells were then expanded in culture in the presence of IL-2 and enterotoxin A, and then reinjected into the patients. Overall, the vaccines were well tolerated with minimal adverse effects. Three patients experienced stabilization of disease, and one patient was disease free 4 years after the implementation of therapy. Another success was reported in metastatic melanoma by Dudley and colleagues.[224,225] They demonstrated an objective clinical response in 50% of 35 patients treated. Although these results are promising, it should be noted that autologous tumor vaccines are expensive and labor intensive.

There was also a promising study of the ability of mutant p53 proteins to stimulate T cells in patient serum in comparison with wild-type p53.[226] Furthermore, in a subset of patients with HNSCC (HLA-A*0201-positive patients), it was found that specific missense mutation (Y220C) in p53 not only was immunogenic but also was found in 12% of 50 examined tumors.[227] This may be the first steps in breaking the "tolerance" to cancer cells and identifying patients who may benefit from immunotherapy.

In addition to whole-cell vaccines, dendritic cell–based vaccines are being developed for HNSCC. Dendritic cells are powerful professional antigen-presenting cells that have the ability to phagocytose apoptotic cells and then present peptides to T cells, a process called *cross-priming*.[228] Dendritic cells exposed to the proper antigenic proteins and cytokines can serve as a vehicle for antigen presentation and T-cell priming. This concept was illustrated in a DBA2/J mouse model of HNSCC.[229,230] Mice that were treated with this vaccine regimen demonstrated a greater decrease in tumor burden than did control mice, with little evidence of toxicity.

Despite the fact that using irradiated tumor cells is an efficacious therapeutic technique, targeting antigens known to activate T cells has the potential to lead to a more specific and robust immune response. Although there are no HNSCC-specific antigens as of yet, a variety of immunogenic proteins present in these tumors have been shown in other tissue types to be effective targets of vaccination. HPV-related cancer, the best example of the use of a tumor vaccine for prevention and possibly for treatment, is discussed in the section on HPV. Other examples are the carcinoembryonic antigen (CEA), which has been shown to be a safe and efficacious target in patients with tumors of the digestive tract.[231] In addition, patients can mount CEA-specific T-cell responses that are capable of lysing colorectal carcinoma cells.[232] Kass and associates[233] evaluated the feasibility of targeting CEA with a vaccine in head and neck cancer. This group demonstrated that CEA was expressed in between 50% and 100% of HNSCC tumors, depending on the site. In a slightly different vein, Lee and colleagues[234] found that a high percentage of patients with various head and neck cancers expressed several isoforms of the melanoma antigen E (MAGE) tumor–associated antigen.[234] This protein is an attractive target for immunotherapy because it is expressed in a variety of tumors and is comparatively absent in noncancerous tissues. MAGE proteins have been shown to be effective targets in melanoma and therefore offer a potential target for immunotherapy in HNSCC.[235]

Immunotherapy for HNSCC is a relatively new but promising therapeutic strategy. Difficulties with achieving efficacy with this approach are due mainly to problems with host tolerance and the relative immunosuppression of patients with HNSCC. Despite this fact, both clinical and translational trials with cytokines, monoclonal antibodies, and a variety of other strategies have yielded promising results with little evidence of host toxicity. In HNSCC and other tumor types, immunotherapy has been implemented successfully in patients undergoing a variety of other therapeutic modalities, and often in patients with end-stage disease. It is to be hoped that future efforts find ways to circumvent immune tolerance and overcome malignancy-related immune dysfunction to produce regimens with better efficacy.

Mitochondrial Mutations

The role of mitochondria as the oxidative phosphorylation "power plants" in cellular function has long been known. However, they also have a role in carrying out apoptosis, cellular proliferation, and the processing of reactive oxygen species within a cell. Mitochondria are therefore central to two phenomena of HNSCC, impaired apoptosis, which is a central characteristic of neoplastic and malignant transformation,[236,237] and the Warburg effect, which is the preferential use of the glycolytic pathway rather than oxidative phosphorylation by cancer cells (Fig. 76-3).[238,239] Furthermore, mitochondrial DNA differs from genomic DNA in being uniquely sensitive to oxidative damage because of the lack of protective histones. Smoking exposes the aerodigestive tract to more than 10,000 oxidant molecules, so it is not surprising that mitochondrial dysfunction is evident in HNSCC given its unique susceptibility to oxidative damage.

The body of literature linking mitochondrial function to cancer has been growing steadily although definitive mechanisms of action are yet to be identified. There has been some evidence in cancer cell line studies that mitochondrial dysfunction in cancer involves both the apoptotic and metabolic pathways.[240,241] Mitochondrial mutations also open the door to more sensitive molecular detection techniques. Every cell has several hundred copies of mitochondrial DNA, so the number of cells required for such assays is much lower[242] than with genomic DNA detection.

Studies have demonstrated that there is a progressive increase in mitochondrial DNA content from mild dysplasia to invasive cancer[243] as well as in the saliva of patients with head and neck cancer.[244] Interestingly, the investigators in the second study also found that the salivary mitochondrial DNA content decreased after definitive treatment of patients with head and neck cancer, suggesting that it is at least a marker of disease status.[245] However, how these observations relate mechanistically to the development of cancer is an active area of research.

For instance, a study of a "hot spot" of mitochondrial genome mutation, known as the D-loop, revealed frequent alterations in oral premalignant lesions that rose in incidence with disease severity in oral cavity lesions.[246] Similar D-loop alterations have been detected in lung,[247] gastric,[248] and colorectal cancers.[249] A follow-up study in which the mitochondrial genome was sequenced in 83 HNSCC specimens found that there were mutations in 49% of the samples tested and, furthermore, that these mutations tended to reside in the mitochondrial enzyme complex components.[241] There was a statistical increase in the

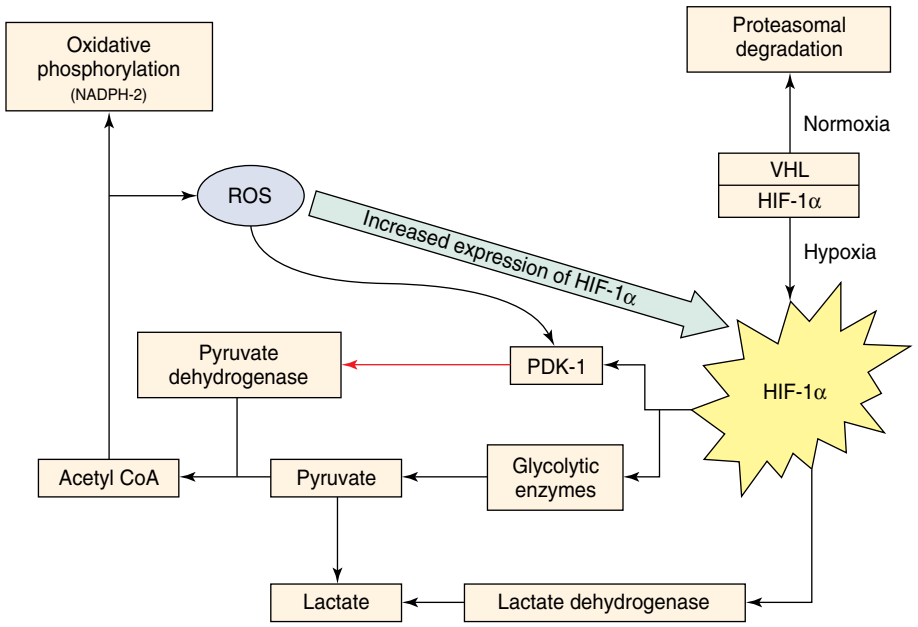

Figure 76-3. Mitochondria and the Warburg effect. During hypoxic conditions, the Von Hippel–Lindau (VHL) protein is associated with hypoxia inducible factor (HIF) and causes the activation of several pathways that lead ultimately to increased lactate production, increased glycolysis, and decreased oxidative phosphorylation. In addition these molecules are shunted toward creating excess reactive oxygen species (ROS). ROS are known to increase HIF-1 expression, to play a role in carcinogenesis, and to further increase genomic instability. CoA, coenzyme A; PDK-1, pyruvate dehydrogenase kinase-1.

number of mutations identified in NADH subunit 2. Mutation of this gene causes increased cellular reactive oxygen species, anchorage-independent growth of tumor cells, preferential glycolytic metabolism (Warburg effect) and hypoxia inducible factor-1α (an oncogene linked to metastasis and angiogenesis in cancer).[241] Another study, in renal carcinoma cell lines, found that the mutation of succinate dehydrogenase (another mitochondrial enzyme in metabolism) leads to the accumulation of succinate which inhibits hypoxia inducible factor-1α degradation enzymes in the cytosol.[250] Subsequently, Mithani and coworkers[251] analyzed HNSCC tumor tissue, adjacent dysplasia, and adjacent normal tissue histologically for mitochondrial mutation. These workers found that the majority of mitochondrial mutations occur during or after the transition of preneoplastic epithelium to cancer in HNSCC, indicating that these are a late event in the head and neck carcinogenesis progression model.[251]

Other cell line studies have revealed several avenues to explore in determining the mechanistic role of mitochondrial dysfunction and cancer. For instance, there is some evidence that mitochondrial DNA repair is hampered in HNSCC cell lines, which might help explain the propensity for mutations.[252] There is also evidence that head and neck cancer cell lines are resistant to mitochondrial depolarization–induced apoptosis.[240] Cisplatin also appears to have direct effects on mitochondria that can trigger the apoptotic pathway independent of nuclear DNA.[253] Mitochondrial mutations are an exciting field of study in HNSCC and in cancer overall. The growing evidence has broad implications in the mechanisms of carcinogenesis and provides for other potential avenues of therapy.

Expression Microarrays and Integrative Genomics

Expression microarrays examine the level of expression of mRNA of thousands of genes in a single assay, thus determining the translational makeup of any sample. In its simplest form, this powerful technology allows us to simultaneously determine which genes are over-expressed or under-expressed in cancer in comparison with normal tissue. One of the first studies did so in head and neck cancer, identifying 91 statistically significantly up-regulated genes (putative oncogenes) and 122 down-regulated genes (putative TSGs).[254] Thus from a list of thousands of genes, the number of differentially expressed genes has been greatly reduced. Through other screening methods, this list can be further reduced to a more manageable number, as discussed later.

The global expression pattern can accurately distinguish HNSCC samples from normal mucosa to delineate those genes that are characteristic of each population.[255,256] Another study identified expression patterns for premalignant disease, frank malignancy, and normal mucosa.[6] Most interesting was the finding that the majority of expression differences occurred between the normal and premalignant cohorts rather than between the premalignant and malignant cohorts. This finding confirms that significant expression alterations have already occurred in the premalignant lesions, as referred to in the progression model of cancer discussed in "Background". Further subset analysis has allowed for the detection of expression differences that might help explain cisplatin resistance,[257] recurrent disease,[258,259] metastatic disease,[260] and human papillomavirus–associated cancers.[261] Once the targets are identified by expression array to be statistically significantly differentially expressed, these genes require further study by more traditional approaches to confirm their significance.

The next step is then to find a high-throughput method to confirm the findings of these expression arrays. One method that has been used to identify the best candidates from the list of hundreds of genes is to combine techniques such as CGH and SNP arrays (which identify areas of loss and gain, respectively) with expression arrays. For example, one would anticipate there to be chromosomal amplification as well as increased expression at the locus of an oncogene. With array technology, one could search for putative oncogenes and TSGs throughout the entire genome with minimal time expenditure. Combining array data might increase the yield and likelihood of finding significant targets. This strategy has been successfully utilized in lung cancer[262] and bladder cancer.[263] This integration of data from multiple approaches further increases the likelihood of finding a TSG or oncogene. Using multiple high-throughput approaches to determine significant genes in cancer is known as *integrative genomics*. This process is an extremely powerful approach to studying the molecular biology of HNSCC. Integrative approaches to HNSCC are currently being utilized to identify novel targets.

Molecular Biomarkers

Having reviewed the molecular changes in HNSCC, we now discuss their role as biomarkers. A biologic marker, or *biomarker,* is any characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[264] Ultimately, a biomarker must be studied in a randomized clinical trial to prove that there is a reliable clinical endpoint (a characteristic or variable that reflects how a patient feels, functions, or survives), in which case it would be referred to as a *surrogate endpoint*.[264] A molecular biomarker for HNSCC can be derived from many sources that can be classified into three general categories—primary tissue, surgical margin tissue, and bodily fluid markers. Three basic types of molecules can be extracted from these sources—DNA, RNA, and protein, respectively.

Practitioners rely heavily on the histopathologic and radiographic assessments of tumors and their margins to make decisions about treatment and prognosis. The current system can fail to adequately stratify specific risk of metastasis, locoregional recurrence, or second primaries. Furthermore, though it is well known that early detection is the key to improving patient survival in HNSCC,[265] two thirds of patients present with advanced disease.[266] Biomarker research ultimately strives to fulfill one (or more) of the three inter-related categories—diagnosis, prognosis, and therapy. Success of this research would be defined as identification of a biomarker of interest that is statistically significant and independent of currently used parameters. An ideal biomarker would fulfill the requirements of all three categories, as follows: (1) the biomarker could be used to accurately diagnose cancer and recurrence, as well as screen asymptomatic populations for the presence of disease (diagnosis); (2) the biomarker could accurately stratify the risks of a patient's course or predict response to therapies (prognosis); and (3) the biomarker itself could be a therapeutic target (therapy). The final hurdle for any biomarker is logistical. Is the biomarker cost effective and practical for everyday use? The following discussion describes three biomarkers that have been extensively studied and the clinical utility of which has been established.

Human Papillomavirus Infection

As a biomarker, HPV infection and the subsequent genomic integration in HNSCC offers diagnostic, prognostic, and possibly therapeutic opportunities. Multiple studies have shown that HPV-associated oropharyngeal cancers are a distinct subset of head and neck cancers. These tumors can be reliably diagnosed and distinguished from other HNSCC tumors by several molecular biologic methods. HPV-associated tumors appear to have a better prognosis than other HNSCC tumors. In addition, because these tumors respond well to chemotherapy and radiation, HPV infection and integration appear to be good markers for responsiveness to nonsurgical treatment. Please refer to the previous HPV section for a more complete discussion of HPV-related head and neck cancers.[30-80]

Epidermal Growth Factor Receptor

Another well-studied biomarker of HNSCC is the EGF receptor. EGFR's role in HNSCC has continued to expand rapidly, and with this expansion its use as a biomarker has developed. It has been proven to be reliable from a diagnostic standpoint. There are several methods by which EGFR dysfunction leads to HNSCC, and for each dysfunction there is a reliable molecular diagnostic technique.[179-181] From a prognostic standpoint, EGFR over-expression and amplification have been demonstrated in retrospective studies to be reliable markers for poor prognosis.[184] Furthermore, there is suggestive evidence that a specific EGFR tyrosine kinase mutation may be a marker for response to chemotherapy.[197] The EGF receptor is an attractive target for chemotherapy because EGFR is a cell-surface marker, which allows it to be readily targeted, and EGFR activation corresponds to an entire pathway that is dysfunctional in cancer, which allows for the simultaneous targeting of multiple portions of the pathway. Preliminary studies have demonstrated some benefit from targeting the EGFR pathway, but further study into its ability to define a clear subset of tumors that is responsive to targeted therapy is needed. For a complete discussion of EGFR, please refer to the previous EGFR section.[175-202]

Loss of Heterozygosity

As discussed previously, the inactivation of TSGs can lead to the development of cancer. If one allele is already inactivated by DNA damage or by hereditary mechanisms, LOH can lead to inactivation of TSG through the physical loss of chromosomal material that contains the remaining allele of that particular TSG. Several regions of chromosomal loss are commonly found in cancer. For instance, the loss of chromosome region 9p21-22 is the most common of all genetic changes in HNSCC, at a frequency of 70%, and it occurs early in the progression of head-and-neck tumors.[267] Another example is the loss of chromosome region 3p.[268] Thirty percent of benign hyperplastic lesions, the earliest of precancerous lesions, have been found to exhibit loss at either 9p21 or 3p.[268] These studies indicate that LOH is commonly found in both malignant and premalignant lesions.

In a retrospective study, premalignant lesions demonstrating loss of chromosomes 9p21 and 3p14 were determined to be more common in patients whose premalignant disease eventually developed into HNSCC.[269] In another study, investigators showed that patients whose premalignant or benign leukoplakic lesions exhibited losses of only 3p and 9p had a 3.8-fold higher risk of progression to cancer, whereas those whose lesions showed the additional losses of 4q, 8p, 11q, or 17p had a 33-fold higher risk.[270] Another research group screened premalignant lesions for LOH for several markers, including 3p21, 8p21-23, 9p21, 13ql4.2, 17p13.1, and 18q21.1, and showed that having LOH in two more of these regions carried a 73% probability of development of cancer in 5 years.[271] Lastly, some smaller studies looking at tumor margins that are histologically normal have also shown that LOH of the field of cancerization may lead to cancer and that these cells originated from the same clonal lineage.[272,273]

Other Biomarkers

This section evaluates the latest research on other biomarkers of disease, organized by the source of biologic material. Although there is evidence that tumor DNA can be detected in serum or salivary rinses, as will be discussed, some issues make population screening with these tests impractical. First, no one common panel of tests or genetic alterations can encompass all patients with HNSCC. Because HNSCC is a relatively rare cancer, the sensitivity and specificity of a screening test would need to be very close to 100% for it to be useful. Second, genetic alterations arise in patients who smoke or have premalignant lesions that are indicative of DNA damage, but not necessarily the presence of malignancy. However, surveillance after treatment is a feasible application of these molecular tests, in the form of either oral rinses or serum analysis.

Oral Rinses and Saliva

Oral rinses have been shown either to harbor naked DNA or to shed cells that might harbor cancer DNA that could be used for detection or surveillance. Studies have been performed demonstrating that one can detect common mutations in saliva that are shared with the primary tumor. For example, p53 mutations detected in primary tumors were detected in five of seven salivary rinse specimens.[274] Microsatellite alterations in the primary tumor were detected in a significant majority of salivary rinse samples as well.[275] Promoter methylation has also been studied in salivary DNA and found to have a 65% concordance rate with primary tumor methylation status.[276] The detection of methylation in oral rinses has also been shown to be a good surrogate marker for the presence of disease.[277] Furthermore, mitochondrial DNA content has been shown to be higher in the salivary rinses of patients with HNSCC.[244] Patients with HNSCC also exhibited a statistically significant decrease in content after treatment.[245]

Serum

Serum analysis has also been studied as a possible way to detect circulating DNA that might harbor mutations specific to HNSCC. Microsatellite alterations in the primary tumor have been shown to shed DNA such that detectable levels of the common mutations were detected in 6 of 21 patients in one of the early studies[268] and in 68 of 152 patients in a subsequent study.[278] Serum analysis of promoter hypermethylation patterns in HNSCC showed a 42% concordance

between primary tumor and serum methylation pattern,[279] and a later study looking at p16 methylation found a 64.7% correlation in HNSCC patients.[280] In addition, serum analysis frequently detected LOH or allelic imbalance in patients preoperatively, but as patients progressed beyond treatment, the percentage of positive markers in their serum decreased. Furthermore, the patients in whom persistently high levels of serum markers were detected after surgery eventually developed disease recurrence.[281]

Molecular Margins

Margin analysis has also been studied to determine whether the molecular detection of genetic alterations is predictive of disease recurrence. There is evidence that patients whose surgical margin specimens were found by molecular analysis to be positive for p53[282] or the proto-oncogene eIF4E[283] but that histopathology classified as negative for pathology may have an increased risk of recurrence. A prospective study looking at p53 mutations in the histologically clear margins of 76 patients showed that the presence of p53 mutations led to a relative risk of 7.1 for locoregional recurrence.[284] Another use of molecular margin analysis is to determine whether real-time information could be provided to the surgeon in the intraoperative setting to help determine the extent of resection. In a pilot feasibility study, investigators were able to provide molecular margin assessment, using methylation-specific polymerase chain reaction analysis, within a timeframe that could be used in a clinical setting.[285]

Primary Tissue

Polymorphisms detected in DNA repair enzymes have been shown to correlate with the response of HNSCC responses to cisplatin and with patients' overall prognosis.[286] MMP3 polymorphisms have also been shown to be associated with sensitivity to 5-fluorouracil and cisplatin.[287] Amplification of CCND1 and c-myc along with p16 deletion has been shown to lead to a statistically higher chance of disease recurrence or metastasis.[288] Interestingly, even stromal genetic alterations have been shown to be associated with tumor aggressiveness, which might be a precursor to the progression of HNSCC.[289]

Summary

Biomarker research ultimately strives to achieve success in one (or more) of three inter-related categories, diagnosis, prognosis, and therapy. A successful biomarker is defined as being statistically significant and independent of current parameters. HPV and EGFR have been able to fulfill several of these criteria, and LOH markers have been validated in premalignant disease. HPV has proved to be a good diagnostic and prognostic tool, and attempts to exploit this marker for therapeutic purposes are ongoing. With the advent of widespread use of a polyvalent HPV vaccine in young girls in the United States, it is possible that the incidence of HPV-related oropharyngeal cancers will decrease, and its role as a biomarker may be useful only in regions without access to vaccination.

EGFR has similarly fulfilled several of the criteria but has shown more promise in the therapeutic realm as a target. However, better studies that account for EGFR amplification and mutations are needed. LOH has shown great promise in defining the risk of progression for premalignant lesions. However, prospective studies would be helpful in defining the utility of LOH as a risk factor in larger populations, so that guidelines regarding surveillance and testing can be implemented. Furthermore, there has been little progress in treating histologically normal but molecularly premalignant regions with chemoprevention or gene therapy.

Currently studies are under way to determine the unique signature of HNSCC via high-throughput techniques, examining DNA methylation, genomic copy number, microRNA, and protein or mRNA expression. Therefore, it will likely be possible to classify tumors beyond simply TNM staging and HPV, p53, and EGFR status. In addition, future therapies will depend on characterization of individual tumors for specific molecular pathway alterations for specifically tailored therapy. These alterations will also likely be useful for surveillance and detection of disease in a variety of settings. However, the ultimate utility of these biomarkers will be in their ability to add information independent of previously known clinical and biomarker parameters.

Novel Fields in Cancer Research

In addition to the study of established biomarkers, whole new fields of research have been revealed that may provide more opportunities for better biomarkers and improved targeted and tailored therapy. As our understanding of cancer biology has become refined, it is evident that the mechanisms of carcinogenesis go beyond genetic alterations and the simplified notion of TSGs and oncogenes. These alternative pathways regulating cellular function can also be used as biomarkers and novel therapeutic targets. This section discusses a few of the exciting developing fields in cancer research. In particular, we discuss the role of microRNA in HNSCC, the cancer stem cell hypothesis, biomarker profiling, and bioinformatics. Although these novel fields of research extend our understanding of the molecular biology of HNSCC, it is necessary to keep in mind that there is still much to be investigated in the current fields of study. Proper study of current biomarkers and therapeutic agents (individually and in combination) still have yet to be undertaken.

MicroRNAs

MicroRNA (miRNA or miR) molecules were discovered in *Caenorhabditis elegans* in 1993.[290] MiRs are small noncoding RNA molecules often found in introns (≈22 nucleotides) that regulate post-transcriptional gene expression.[291] With this discovery, a novel method of gene expression regulation was revealed (Fig. 76-4).[290] However, because of their short sequence, miRs have relatively nonspecific binding; a single miR may regulate the expression of several genes, making their study difficult. Various prediction algorithms identify several thousand targets per miR. It has been proposed that miRs may potentially regulate more than one third of all protein-coding genes.[292] As a result, they are involved in a variety of cellular processes, including the regulation of cellular differentiation, proliferation, and apoptosis.[293] Once miRs were discovered in the human genome, there was intense interest in their role in human diseases. It has been shown that these molecules play a role in cancer, and many studies have established that increased or decreased miR expression plays an important role in cancer biology.[294] Other studies have demonstrated that there is a unique expression profile or miR signature for certain cancer types.[294]

Results of some preliminary studies suggest that there is dysregulation of microRNA in HNSCC. A study comparing microRNA expression levels of 27 tumors and 8 normal tissue specimens revealed eight differentially expressed miRs. Of these, miR-494 (under-expressed in cancer) and miR-21 (over-expressed in cancer) were shown to be able to modulate cellular proliferation.[295] Mir-21 has been examined in several areas of molecular biology in addition to cancer biology.[296-298] Mir-21 has been implicated in chronic lymphocytic leukemia, lung adenocarcinoma, breast carcinoma, pancreatic cancer, hepatocellular carcinoma, papillary thyroid carcinoma, glioblastoma, T-cell differentiation, ovarian cancer, resistance to 5-fluorouracil, cervical carcinoma, multiple myeloma, B-cell lymphoma, uterine leiomyomas, chromosomal instability, and even hypertrophic heart muscles and vascular formation.[297,299-313] Mir-494 appears to be a marker unique to HNSCC.

Other studies have also attempted to study miR-21 as an antiapoptotic agent. Zhu and colleagues[314] proposed that miR-21 exerts some of its oncogenic effects through regulation of the tumor suppressor gene tropomyosin-1. Si and associates[298] proposed that miR-21 is able to decrease cell death through association with bcl-2. In addition, Chan and coworkers[297] proposed that caspase activation occurred with knockdown of miR-21. Interestingly, studies have shown that there is no association with other apoptosis-related proteins, such as p53, PUMA, FasL, and CDC25A. Other studies have shown that miR-21 is involved in invasion and metastasis. Meng and associates[309] proposed that miR-21 works through PTEN signaling in hepatocellular cancer to modulate matrix metalloproteases-2 and matrix metalloproteases-9.[309] Lastly, Loffler and coworkers proposed that in multiple myeloma, miR-21 is in the control of IL-6 via a Stat3 mediated pathway.[307]

There also has been some study showing miR-21 as a marker for response to therapy[310] and as a target for therapy. A study in a xenograft

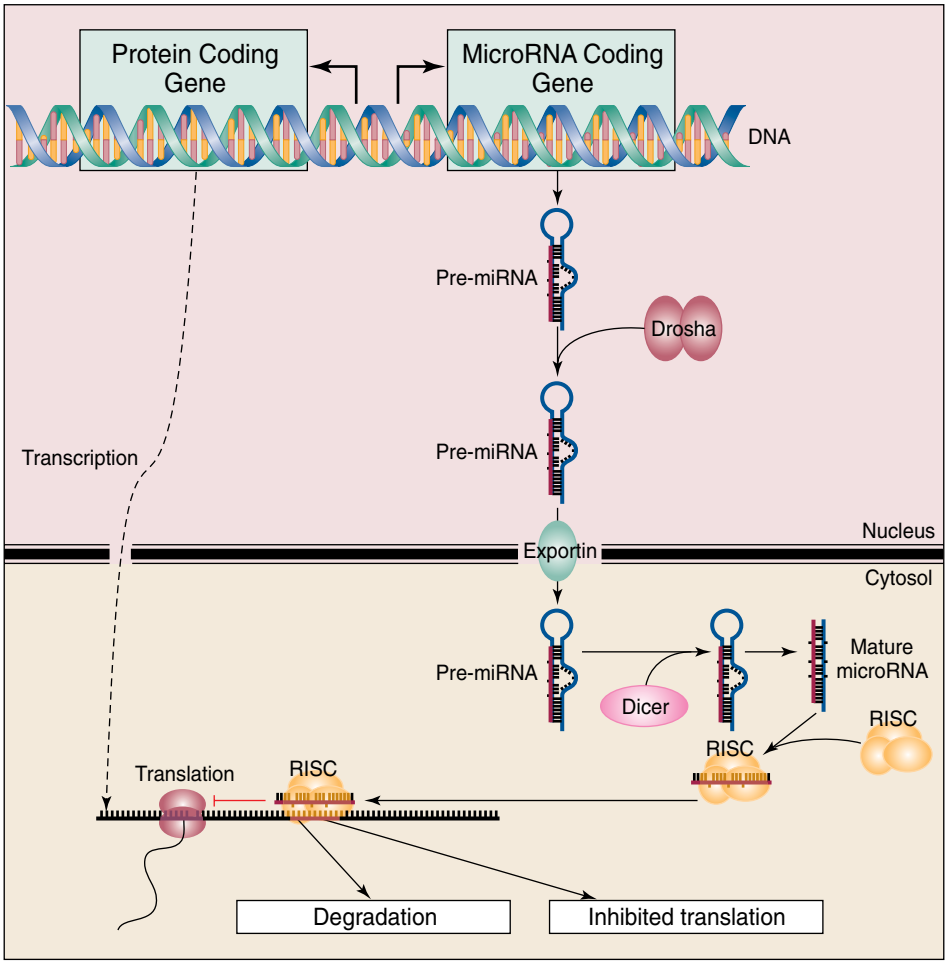

Figure 76-4. MicroRNA pathway and mechanism of action. Mature functional microRNAs (miRNAs) of approximately 22 nucleotides are generated from long primary microRNA (pre-miRNA) transcripts. First, the pre-miRNAs, which usually contain a few hundred to a few thousand base pairs, are processed in the nucleus into stem-loop precursors (pre-miRNA) of approximately 70 nucleotides by the RNase III endonuclease Drosha and its partner Pasha. The pre-miRNAs are then actively transported into the cytoplasm by exportin 5 and further processed into small RNA duplexes of approximately 22 nucleotides by the Dicer RNase III enzyme. The functional strand of the miRNA duplex is then loaded into the RNA-induced silencing complex (RISC). Finally, the miRNA guides the RISC to the cognate messenger RNA (mRNA) target for translational repression or degradation of mRNA. *(Modified from Chen CZ. MicroRNAs as oncogenes and tumor suppressors.* N Engl J Med. *2005;353(17):1768-1771.)*

mouse model showed that inhibiting miRs can reduce tumor growth by intravenous therapy.[311] This is a blossoming field in both cancer biology and molecular biology in general, and we are sure to see many more future studies of this interesting topic.

Cancer Stem Cell Hypothesis

The cancer stem cell hypothesis is the theory that a tumor is an aberrant organ that is sustained by a progenitor stem cell that drives tumorigenesis. These cells are the basis for the differentiated cells that make up the bulk of a tumor. This finding is based on the clinical observation that epithelial tumors, HNSCC included, contain cellular heterogeneity.[315-317] It is also based on the laboratory observation that only certain cells are able to recreate tumors in immunodeficient mice. For instance, tumorigenic and nontumorigenic populations of breast cancer and central nervous system cancer cells can be isolated on the basis of their expression of cell surface markers. Furthermore, these isolated tumorigenic cells, but not the nontumorigenic ones, have been shown to have the unique ability to form new tumors.[318-323]

Using methods similar to those employed in breast cancer, several groups of researchers have found a distinct population of cancer cells in HNSCC tissues that could produce not only tumors in mice (NOD/SCID mice and Rag2γDKO mice) but also the supporting stromal microdomains associated with cancer. These researchers used the cell surface expression of CD44, nuclear expression of BMI1 (a gene previously implicated in self-renewal and tumorigenesis),[324-328] positive staining for cytokeratin 5/14, and negative staining for involucrin to select out putative cancer stem cells. These cells, which were a small percentage of CD44-positive cells (<10% of cells are typically CD44-positive in a tumor), had the ability in culture to be serially passaged and to differentiate, two hallmarks of stem cells.

These findings elucidate the possible molecular mechanisms mediating the self-renewal of cancer cells and the ability of cancers to recur. In addition, this finding supports the need for research into targeted therapy against cancer stem cells. However, it must be first conclusively established that cancer stem cells indeed drive tumorigenesis. As this notion is still a theory, it cannot fully explain several clinical observations of HNSCC behavior. First, there is no explanation as to how these stem cells are able to escape surgical excision. Presumably these cells reside within the bulk of tumors, and for them to be the source of a local recurrence would imply that they are not within the surgical resection zone. Second, there has been no evidence that these cells are uniquely insensitive to chemotherapy. Furthermore, presuming that these cells have a high rate of replication, one would expect that they would be uniquely susceptible to our current chemotherapeutic regimens.

Bioinformatics

Bioinformatics and data mining have revolutionized our approach to both cancer detection and treatment. Many of the techniques and

experiments described in this chapter were based on the findings determined by genome-wide array-based approaches. As these results become publicly available as databases of the cancer genome, the efficiency of cancer research should improve exponentially. For instance, if a microarray is run on a tumor set by one institution and put in a publicly available database, any other institution will have access to this data set for research without having to recapitulate the experiment. The ability to manage and glean relevant information from these large data sets has become a field of study unto its own. The National Cancer Institute Center for Bioinformatics is currently working on this issue.

Proteomics

Another field that is still in its clinical research infancy but is well established in the basic science community is the field of *proteomics*, the study of protein structure and function. Whereas there are approximately 25,000 human genes, there are estimated to be more than 500,000 proteins in humans. This higher number is due to alternative splicing and post-translational modifications. This area of study is still new, but with the advent of high-throughput techniques, its progress has greatly increased. Two-dimensional gel electrophoresis and antibody arrays have been utilized as well as newer matrix-assisted laser desorption-ionization–time-of-flight (MALDI-TOF) and surface-enhanced laser desorption ionization–time of flight (SELDI-TOF) techniques, which have allowed for rapid identification of protein peaks involved in HNSCC. However, the greatest challenge is in identifying not the differentially expressed proteins but rather the in vivo functions of proteins and how they contribute to cancer.

Several proteins have been identified as being significantly upregulated in HNSCC on the basis of proteomic approaches.[329-332] However, although several proteins correspond to genes known to play a role in carcinogenesis, it is often difficult to identify the protein merely on the basis of its peak. Interestingly, the signature pattern of peaks can be used as a biomarker of disease that is able to classify normal mucosa and HNSCC with a high degree of accuracy.[330,333] More time is needed to determine whether there is any clinical significance to these findings. However, another study found that factors such as tobacco and alcohol use as well as gender could confound the data and lead to only moderate success in differentiating the cancer and normal test groups.[334] Serum biomarkers have also been studied as a means of early detection in a cohort of patients with hypopharyngeal carcinoma, with a sensitivity of 92% and a specificity of 82% in a training set.[335] Another similar study in HNSCC patients looked at plasma protein levels with SELDI-TOF and found that the pattern of peaks was more important than the actual identification of the corresponding proteins.

As mentioned previously, the field of proteomics is at its relative infancy. The next steps in this field will be to identify which proteins are reliable biomarkers of disease and to elucidate their functional role in carcinogenesis. Both aims are lofty goals, although they are essential to our understanding of HNSCC.

Conclusion

In this chapter, we have reviewed the current understanding of the molecular biology of HNSCC, introduced the future directions of research in this field, and discussed the clinical implications. With the accelerating pace of research discovery using high-throughput technology coupled with growing use of bioinformatics, advances in clinical care should also improve significantly. We should expect to see advances in all aspects of patient care but specifically in the fields of molecular biomarkers and targeted therapy. Better screening and surveillance tests, improved prognostic markers, and tailored and targeted therapies for patients are all on the horizon. There are several challenges to bringing these improvements to clinical reality. First, it is necessary to study any prospective biomarker and therapy in properly run clinical trials. Poorly run trials are both a waste of resources and provide no worthwhile clinical conclusions. Second, it is imperative that the right treatments and markers are chosen for study, either individually or in combination. Currently, many potential markers and therapies are available. Choosing the right dose, combination, and patient population is essential to optimizing the chances for a successful trial and maximizing efficient use of research resources.

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CHAPTER SEVENTY-SEVEN

Radiotherapy for Head and Neck Cancer: Radiation Physics, Radiobiology, and Clinical Principles

Aron Popovtzer

Avraham Eisbruch

Key Points

Basic Radiation Physics

- The unit of measure for radiation is the gray (Gy), which corresponds to 1 joule being deposited per kilogram of material.
- The two main energy sources in use are electrons and photons.
- Electrons differ from photons in that electrons travel only a certain (short) distance within tissue. The deposition of the majority of their dose is in superficial tissues, so they are mainly used for treating superficial tumors.
- Radiation treatment includes the following processes: simulation, treatment planning, verification, dose delivery, and quality assurance.
- Planning targets includes gross tumor volume; clinical target volume, which includes areas at risk for spread, such as adjacent tissues or draining lymphatic regions; and planning target volume, which includes margin to correct for possible variability in daily positioning and patient motion during treatment.

Radiation Biology

- The main radiation biology principles are the four Rs of radiotherapy, as follows: (1) repair (of sublethal damage); (2) redistribution (across the cell cycle); (3) repopulation; and (4) reoxygenation.
- Rapidly dividing tissues, such as the skin, mucous membranes, bone marrow, and tumor cells, are responsible for the acute toxicity. Acute toxicity correlates with the total treatment time, while late-responding tissues such as the spinal cord, brain cells, and connective tissue are responsible for the late toxicity from radiation therapy. The level of this toxicity depends mainly on total dose and dose per fraction.

Clinical Principles of Radiotherapy

- Altered fractionation (accelerated or hyperfractionation) achieves better local control and higher overall survival than conventionally fractionated radiation but has not yet been compared with conventional chemoradiation.
- The concurrent addition of chemotherapy to radiation in advanced head and neck cancer improves organ preservation and survival.
- In the postoperative setting, the addition of concurrent chemotherapy to radiation improves survival in cases with extracapsular extension and/or microscopically involved surgical margins.
- The use of intensity-modulated radiation therapy in advanced head and neck cancer may offer sparing of vital organs, including major salivary glands, minor salivary glands dispersed within the oral cavity, mandible pharyngeal musculature, inner and middle ears, temporomandibular joints, temporal brain lobes, and optic pathways.
- Intensity-modulated radiation therapy offers a potential for better tumor control by reducing the constraints on the tumor dose that are due to critical organs that occasionally limit the tumor boost doses in conventional radiation therapy.
- Acute side effects occur during radiation therapy and in the following weeks. They include mucositis, odynophagia, dysphagia, hoarseness, xerostomia, dermatitis, and weight loss. Late toxicity includes xerostomia, osteoradionecrosis, fibrosis, thyroid dysfunction, carotid artery rupture, and radiation-induced myelitis. These toxicities may become apparent many months or even years after treatment.

The aim of this chapter is to provide an outline of the basic principles of physics and biophysiology that lie behind modern radiotherapy. This overview is intended to enable the clinician to understand the physics background of the various radiation treatments, with a special focus on head and neck treatment technologies.

Toward the closing years of the nineteenth century, many investigations into electricity characteristics were conducted, one of them demonstrating that electric potential placed across two separated platinum electrodes produces a spark.[1] British physicist William Crookes demonstrated that if the two electrodes were placed within an evacuated glass tube, the vacuum would eventually cause the walls of the vessel to fluoresce.[2] On November 8, 1895, Wilhelm Roentgen, while performing an experiment with the Crookes tube, accidentally left a piece of paper painted with barium platinocyanide nearby; he noted that the paper fluoresced and realized that this fluorescence of the paper could have been caused by a new, invisible type of ray that the tube was now emitting. Thus, the x-ray was discovered.

Radioactivity was discovered shortly after by Henri Becquerel, who investigated the capability of different substances to produce x-rays. He observed the darkening of photographic plates by uranium salts and concluded that the same x-rays were emitted spontaneously and continuously from the uranium.[3] Pierre and Marie Curie, who read his results, coined the term *radioactivity* to describe this phenomenon. In 1898 they isolated a material with radioactivity 60 times higher than uranium and called it radium.[4]

These discoveries led to radiation biology experiments. The first documented experiment was performed unintentionally at about the same time, when Antoine Becquerel developed a "burn" on his chest from carrying a vial of radium salt in his vest pocket. It soon became apparent that radiation had the ability to produce profound biologic changes. In the beginning it was believed to be a magical cure for almost every known illness. The first documented success was reported in 1899 in Stockholm[5] by Thor Stenbeck, who treated a 49-year-old woman's nasal basal-cell carcinoma. He delivered 100 treatments in the course of 9 months, and the patient was alive and well 30 years after the treatment. In 1901, Dr. Frand Williams in Boston reported on the successful treatment of a lip cancer.[5] The early treatments often involved very large single exposures that resulted in extensive skin toxicities and other complications. Therefore, only superficial sites were originally treated by the direct application of radium.[6] Eventually, physicians started to insert radium directly into deep-seated tumors, effectively beginning the field of brachytherapy.[7]

The use of external beam treatments made its leap in 1922 when Coutard and Hautant reported a new concept of fractionated treatments: advanced laryngeal cancer could be cured without severe toxicities using fractionated treatments.[8] Advances in measurements were also achieved when the skin erythema dose (the dose of x-rays required to give a light skin reaction) was replaced by the roentgen in 1928,[9] which was later replaced by the rad. The *rad* is the unit of absorbed dose and is a measure of the energy deposition per unit mass by all types of ionizing radiation. The next step was achieved with the development of higher-energy machines capable of depositing dose at depth.

As technology has progressed, radiation therapy (RT) has become increasingly sophisticated, with computer controls to deliver exact and modulated doses to depths and specific areas within the treatment field. The advances in energy technologies led to the routine use of high-energy and accurate deep-penetrating radiation produced by linear accelerators. Nuclear physics innovations produced many artificial radioisotopes, enabling the use of high-dose brachytherapy, which shortens treatment time and simplifies the radioprotection procedures.

Aside from the technology advances, radiation treatment has a special role in head and neck cancer (HNC), in which it has in many cases a major advantage over traditional surgery in its ability to preserve organs, improving quality of life without compromising the survival rate.

Basic Physics

Characteristics of Radiation

Radiation refers to the propagation of energy through space or a medium (Fig. 77-1). Radiation can be broadly classified as either particulate or electromagnetic. If the radiant energy is carried off by a particle that has rest mass, the radiation is called "corpuscular" or "particulate" radiation. Examples of particulate radiations are electrons, beta particles, protons, neutrons, and heavy charged particles.

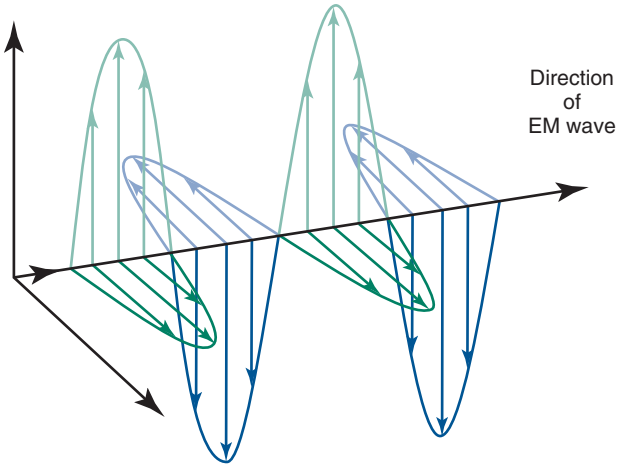

Figure 77-1. Propagation of electromagnetic (EM) radiation with oscillating electric and magnetic fields. *(From Saw CB. Foundation of Radiological Physics. Omaha, NE: C. B. Saw Publishing; 2004:10, with permission.)*

Electron beams, which are produced in a linear accelerator, are widely available for the treatment of superficial lesions in clinical radiation oncology practice. In addition, mixed beams consisting of electron beams and photon beams are used to treat lesions that require higher surface doses. Negatrons from strontium Sr-90 are used in the treatment of restenosis in intravascular coronary brachytherapy. Although other forms of particulate radiation have been used experimentally in the past, their use has been limited to a few centers. The use of protons is gaining popularity in many centers specifically for pediatric tumors.

Electromagnetic radiation is a packet of energy (a photon) that propagates through space. It has no rest mass and propagates at the speed of light. This discrete energy (E) is related to its associated frequency (ν) as follows:

$$E = h\nu \qquad \text{(Eq. 77-1)}$$

where h is Planck's constant, having a value of 6.626×10^{-34} joule-second (J.s). The energy of a photon is often expressed in electron volts (eV). One eV represents the amount of energy required to accelerate an electron through a potential of one volt. The frequency (v) of a photon is related to its wavelength (λ) as follows:

$$\nu = c/\lambda \quad 2 \qquad \text{(Eq. 77-2)}$$

where $c = 3.0 \times 108$ m/sec, the speed of light in a vacuum. The waves of electromagnetic radiation are composed of oscillating electric and magnetic fields that are orthogonal to each other and to the direction of propagation, as shown in Figure 77-1. The electromagnetic spectrum spans a broad and continuous range from radiowaves to x-rays with wavelengths from 106 to 10^{-13} m. Radiation with wavelengths shorter than visible light is classified as ultraviolet rays, x-rays, and gamma rays. The boundaries between these regions are not sharply defined. For example, x-rays and gamma rays are indistinguishable except for their origins, one from the orbital electrons and the other from the nucleus, respectively. Different types of electromagnetic radiation interact differently with the same material (see Fig. 77-1).

Radiation Production by Radioactive Decay

As previously discussed, radioactivity is the phenomenon in which radioactive materials disintegrate by emitting radiation to achieve

nuclear stability. The amount of radioactivity is measured in units of curie (ci), named after the Polish-born French scientist, Madame Curie. A curie is equal to 3.7×10^{10} disintegrations per second. A smaller unit, the millicurie (mci), is routinely used in the field of radiologic physics. The SI unit of radioactivity is the *becquerel*. It is equal to 1 disintegration/sec, typically denoted as the reciprocal of 1 second (s-1).Unstable nuclei decay by emitting alpha particles, beta particles, or gamma rays. An alpha particle (denoted by the symbol α) is actually stripped helium consisting of two protons and two neutrons. A negative beta particle (β^-) carrying a unit negative charge (−1e) is called a negatron; a positive beta particle (β^+) carrying a unit positive charge (+1e) is called a positron.

Unstable atoms de-excite by emitting x-rays. An atom is said to be in an excited state if any orbital electron is not in its lowest energy state. When an atom is in an excited state, an electron from the higher energy shell jumps into the vacant position. As a consequence of this transition, an x-ray is emitted. A cascade of x-rays can be emitted after a tightly bound electron is ejected. The process of ejecting an orbital electron is called *ionization radiation*.

Radiation Production from Linear Accelerators

Another type of radiation is termed bremsstrahlung[11] (German for "braking radiation"), electromagnetic radiation produced by a sudden slowing down or deflection of charged particles (especially electrons) passing through matter near the strong electric fields of atomic nuclei.

Internal bremsstrahlung arises in the radioactive process of *beta decay*, which consists of the production and emission of electrons by unstable atomic nuclei or the capture by nuclei of one of their own orbiting electrons. These electrons, deflected from their own associated nuclei, emit internal bremsstrahlung. During the deceleration process, the electrons interact with the atomic nuclei, resulting in the emission of bremsstrahlung radiation. Before 1950, external beam RT was accomplished in this way, with a maximum energy of about 300 keV. As just stated, these x-rays are low in energy compared to what is used today, with the disadvantages of poor penetration and maximal deposition of dose at the skin.

Today, other types of radiation are produced in nuclear reactors, cyclotrons, and linear accelerators.

Interaction of X-Rays with Matter

After these high-energy x-rays are produced successfully, they can interact with matter via several different processes. Each interaction type has a probability, based on the composition of the matter and the energy of the x-rays. These interactions cause some photons (x-rays) to be removed from the forward-moving x-ray beam, an effect called *attenuation*, which is basically the loss of intensity and subsequent decrease in the deposition of dose as the beam reaches greater depths. The five possible interactions of x-rays with matter are as follows:

- Coherent scattering
- The photoelectric effect
- The Compton effect
- Pair production
- Photodisintegration

The most important of these interactions in RT are represented in Figure 77-2.

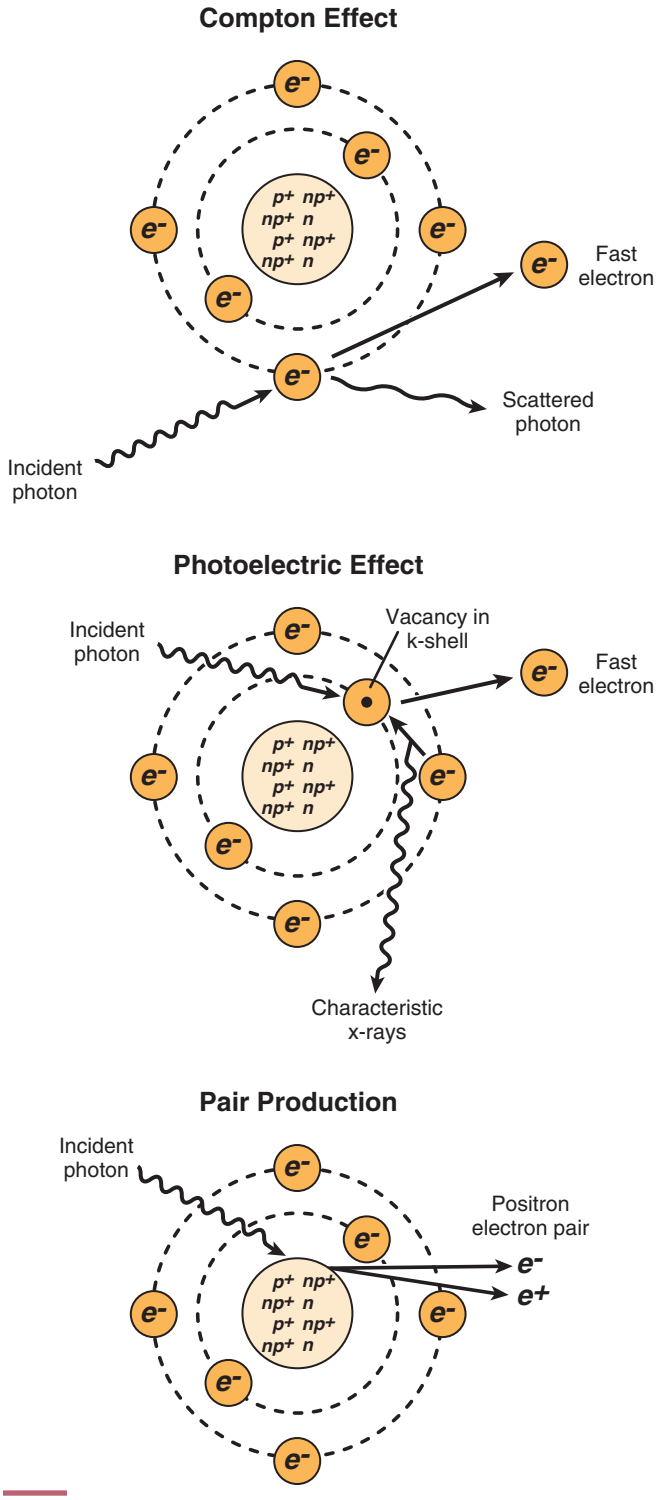

Figure 77-2. The major radiation interactions. e, electron; n, neutron; p, proton. *(Redrawn from Cox JD, Ang KK, eds.* Radiation Oncology: Rationale, Technique, Results. *8th ed. St. Louis: Mosby; 2003:5.)*

Coherent Scattering

Also called classic scattering, coherent scattering occurs when x-rays are of low energy. In coherent scattering, a photon is separated from an electron with a resultant change in direction but no change in energy. The amount of coherent scattering that occurs in therapeutic (and even diagnostic) radiation is negligible. Coherent scattering is important in processes such as x-ray crystallography. It is a dominant process at low photon energies (below 10 keV) and in material with a high atomic number. Because of its low photon energy, coherent scattering does not contribute to either diagnostic radiology or RT.

Photoelectric Effect

The photoelectric effect was first described by Albert Einstein, and it was this contribution to physics, not his discoveries regarding relativity, that led to his being awarded the Nobel Prize in 1921. In the

photoelectric effect, a photon interacts with a tightly bound inner-shell electron of the target tissue. Complete absorption of the photon's energy occurs, with the ejection of the electron from the orbit. The probability of a photoelectric interaction is highly dependent on the atomic number (Z) of the material through which the photon is passing, and thus the photoelectric effect is very important in diagnostic radiology. It is the process that is the basis for the radiographic contrast between tissues (e.g., between bone [calcium and phosphorus] and fat [carbon and hydrogen]). The photoelectric effect is in most instances undesirable in RT. Typically, we do not want bony structures to be shielding underlying tumors. With higher-energy x-rays such as are used in radiotherapy, however, the contribution of the photoelectric effect is relatively small. In comparison this effect is high in low-energy radiation used for diagnostic radiology, in which the difference between bone and tissue absorption provides the necessary tissue contrast.

Compton Effect

Compton scattering is the most important interaction in energies within the range used for RT. In Compton scattering, a photon transfers energy to an electron of the target tissue, causing the ejection of this electron. In contrast to the photoelectric effect, however, the energy of the photon is not completely absorbed, and is scattered at an angle relative to the forward direction of the original photon. This secondary photon interacts with tissue again and again, ionizing and depositing dose with each interaction. These interactions and subsequent ionizations are responsible for the biologic effects on tissues during RT.

In contrast to the photoelectric effect, Compton interactions are independent of the atomic number of the tissue because the interactions tend to be with the loosely bound outer electrons in atoms, where the energy binding an electron to the atom is much less dependent on the atomic number (Z). This results in a fairly even probability of interaction and, hence, in fairly even deposition of dose throughout the different biologic tissues with which the x-rays would interact in a patient.

Pair Production

Pair production occurs at high energies as a result of interaction of a photon with a nucleus, with the spontaneous disappearance of the photon and the production of an electron and a positron. Pair production occurs at higher energies and becomes dominant at ranges above standard treatment, at about 25 megaelectron volts (MeV); thus it rarely has a role in treatment.

Photodisintegration

At very high energies, x-rays can deposit so much dosage into the nucleus of the target tissue that partial disintegration of the nucleus occurs, with emission of neutrons from the nucleus. Although this process has little importance in the clinical interactions used in RT, the production of neutrons is important in the planning of shielding around high-energy linear accelerators for the sake of protecting patients and personnel from potentially carcinogenic low-dose radiation.

Deposition of Dose

The absorbed dose from an x-ray beam is the measure of the energy deposited by the beam and absorbed by the target. Radiation doses were historically measured by roentgen, which was a unit of exposure but did not quantify the dose the patient absorbs. In the late 1950s the *rad*, an abbreviation for "radiation-absorbed dose," was introduced. The rad is equivalent to the deposition of 100 ergs (10^{-7} joules) per gram of material.

More recently, an international commission has agreed that radiation doses should be specified in terms of gray (Gy), which corresponds to the deposition of 1 joule per kilogram of material. Numerically, doses in rad can be converted to equivalent doses in Gy by dividing by 100 (i.e., 100 rad = 1 Gy). This is closely related to the observed biologic effects, how and where the dose is deposited is obviously very important. Because the amount of radiation absorbed by the target is assumed to be as stated previously, x-rays in the megavoltage energy range, such as those used in RT, exhibit the phenomenon of skin sparing, whereby the dose deposited in tissue is relatively low at the surface but increases rapidly over the first few millimeters. The region of rapidly increasing dose is known as the *buildup region*. This rapid increase occurs because of the forward-moving photons interacting with electrons of the target tissue via the interactions described previously. Because these electrons are also propelled forward but have a shorter course than the photons, there becomes an area at depth at which the number of electrons entering the plane of interaction from superficial interactions is exactly equal to the amount leaving the plane from interactions in that plane. This plane is termed the D_{max}, as it represents the maximum number of ionization events past this point; as more interactions between the photon beam and tissue occur, fewer photons are available to travel forward and deposit dose at greater depths. This process, as previously described, is called *attenuation*. How quickly a photon beam is attenuated (i.e., how much dose it deposits at depth) depends on qualities both within the beam and within the target tissue. The most substantial effect on depth dose from the photon beam itself is the beam's energy.

Deposition of Energy

As a high-energy photon beam traverses through a medium, the atoms are excited and ionized. Of the two interacting processes, ionization is disruptive to atoms, changing the molecular integrity and leading to cell death in tissue. The ejected electrons undergo further interactions and deposit their energies to the medium through excitation and ionization. The amount of energy transferred to the electrons at the initial point of interaction is called *kerma*. The second stage of the energy-transfer process is called the *absorbed dose*. Not all the energy transferred to the medium at the initial point of interaction is absorbed. Some of the energy is radiated away as bremsstrahlung, and the remaining is called *collision kerma.* The absorbed dose is the energy retained in the medium along the path of the electrons. If the electron track has an appreciable length, the transfer of energy (kerma) and the absorption of energy (absorbed dose) take place at separate locations.

When a photon beam enters a medium, the initial ionization of atoms takes place at the surface. The energy is directly transferred to the ejected electrons, and therefore kerma has a maximum value at the surface. As the beam proceeds farther, the photon intensity decreases as a result of absorption and scatter. Hence kerma decreases as a function of depth into the medium. On the other hand, absorbed dose is initially low at the medium surface, increases to a maximum, and thereafter decreases as a function of depth. The region from the surface to depth of maximum dose is called the *buildup region*. The position of maximum absorbed dose is called the *point of equilibrium*, and the region beyond the maximum dose is the region of *transient electronic equilibrium*.

Radiation in Conventional Medicine

External beam radiotherapy is the most frequently used form of radiotherapy. With this technique, the patient lies on a bed and an external source of radiation is pointed at a particular part of the body. Kilovoltage (which may be either superficial or deep) x-rays are used for treating skin cancer and superficial structures. Megavoltage x-rays are used to treat deep-seated tumors (e.g., bladder, bowel, prostate, lung, brain). Megavoltage electrons are used mainly for treating superficial tumors.

The energy of diagnostic and therapeutic gamma rays and x-rays is expressed in kilovolts (kV)or megavolts (MV), whereas the energy of therapeutic electrons is expressed in terms of megaelectron volts (MeV). In diagnostic and therapeutic situations, this voltage is the maximum electric potential used by a linear accelerator to produce the photon beam. The beam is made up of a spectrum of energies: the maximum energy is approximately equal to the beam's maximum electric potential times the electron charge. Thus, a 1-MV beam will produce photons of no more than about 1 MeV. The mean x-ray energy is only about a third of the maximum energy. Beam quality and hardness may be improved by special filters, which improve the homogeneity of the x-ray spectrum.

In the medical field, useful x-rays are produced when electrons are accelerated to a high energy. Some examples of x-ray energies used in medicine are as follows:

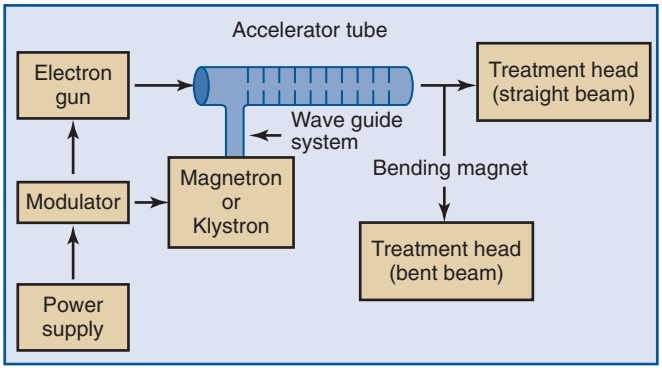

Figure 77-3. Block diagram of a typical medical linear accelerator. *(From Leibel SA, Phillips TL, eds.* Textbook of Radiation Oncology. *Philadelphia: WB Saunders; 1998:110.)*

Diagnostic x-rays: 20 to 50 kV

Superficial x-rays: 50 to 200 kV

Orthovoltage x-rays: 200 to 500 kV

Supervoltage x-rays: 500 to 1000 kV

Megavoltage x-rays: 1 to 25 MV

Of these energy ranges, megavoltage x-rays are by far the most common in radiotherapy. Orthovoltage x-rays do have limited applications, and the other energy ranges are not typically used clinically.

Medically useful photon beams can also be derived from a radioactive source such as cobalt Co-60, iridium Ir-192, cesium Cs-137 and radium Ra-226 (which is no longer used clinically). Such photon beams, derived from radioactive decay, are more or less monochromatic and are properly termed gamma rays.

Orthovoltage x-rays are produced by linear accelerators operating at 200 to 500 kV. These are also known as "deep" or "superficial" machines, depending on their energy range. Orthovoltage units have essentially the same design as diagnostic x-ray machines. These machines are generally limited to less than 600 kV.

Linear accelerators (linacs) produce megavoltage x-rays. Commercially available medical linear accelerators produce x-rays and electrons with an energy range from 4 MeV up to around 25 MeV.[11] The x-rays themselves are produced by the rapid deceleration of electrons in a target material, typically a tungsten alloy, which produces an x-ray spectrum via bremsstrahlung radiation. The shape and intensity of the beam produced by a linear accelerator may be modified or collimated by a variety of means. Thus, conventional, conformal, intensity-modulated, tomographic, and stereotactic radiotherapy are all produced by specially modified linear accelerators (Fig. 77-3).

As the particle bundle passes through the tube it is unaffected, and the frequency of the driving signal and the spacing of the gaps between electrodes is designed so that the maximum voltage differential appears as the particle crosses the gap. This accelerates the particle, imparting energy to it in the form of increased velocity. At speeds near the speed of light the incremental velocity increase will be small, with the energy appearing as an increase in the mass of the particles

Additional magnetic or electrostatic lens elements may be included to ensure that the beam remains in the center of the tube and its electrodes (see Fig. 77-3).

Linear Accelerators

Linear accelerators typically produce beam energies ranging from 6 to 18 MeV, and the dose at depth increases with beam energy. Therefore, an 18-MeV photon beam would deliver more dose to a given depth in a patient than would a 6-MeV photon beam. An 18-MeV beam would also have more skin sparing (i.e., it would have a greater D_{max}). Another aspect that affects the depth dose is the size of the field of radiation used to treat the patient. With a larger field size, there is greater scattering of photons within the field during the interactions with electrons. This scatter effect leads to more interactions, which translate into a higher deposition of dose at depth. In other words, the dose at 10-cm depth within a patient from a photon beam that has a field size of 20 cm × 20 cm would be higher than the same photon beam with a field size of 5 cm × 5 cm. Many other factors go into the calculation of dose delivered at varying depths in a patient, including scatter from the collimators in the machine, blocks to shield normal tissue, and wedges and compensators (which are used to shape the photon beam). Another main modifier in the target tissue that affects dose at depth is the density of the tissue being treated. Lung, for example, being less dense than soft tissue, allows more photon transmission. Additionally, the inverse square effect, first noted by Roentgen, must be taken into account. All of these factors must be taken into consideration in the determination of the dose being delivered to structures within the patient. Calculation of the dose given to a tumor or other volumes within a patient is thus complex, requiring much more knowledge than simply how much x-ray dose the machine is putting out.

As an energy source, electrons differ from photons in that electrons travel only a certain (short) distance within tissue. They are very light particles compared with the nuclei of the target tissue with which they interact. Hence, the electrons lose a large fraction of their energy in a single process. This leads to much less skin sparing and the deposition of the majority of the dose in superficial tissues. Consequently, however, they are very useful for treatments in which the target of the radiation lies close to the surface of the patient, such as skin tumors (Fig. 77-4).

Particle Beams

High-energy charged particle beams interact with tissues in a unique way. At first, the charged particles lose energy gradually, but there is an intense release of energy at the end of the range. This intense energy deposition is called the *Bragg peak*. This feature provides a means of delivering the maximum dose to a target at a specified depth. Often in clinical practice, the particle beams are modulated to change the energy, and hence the depth, to widen the dose deposition to cover the target, and this change is in addition to allowing optimized dose delivery.

In the strictest sense, the electron beams used in conventional radiotherapy facilities are a type of particle radiation, but this section is devoted to the heavier charged particles (e.g., protons, α-particles, heavy ions, π-mesons, and fast neutrons) used experimentally at a small number of radiotherapy centers throughout the world. These particles are of special interest because of their different radiobiologic properties or their better depth-dose characteristics, which allow for higher tumor doses without causing a commensurate increase in the dose to the surrounding healthy tissues.

One particle for which there has been a great amount of clinical work is the *fast neutron*.[12,13] Fast neutrons are of clinical interest because of their radiobiologic properties, which occur because of the much greater amount of energy they deposit when they go through tissue. Neutrons are neutral particles and interact with the atomic nuclei, producing "heavy" charged particles such as protons, α-particles, or nuclear fragments that in turn create a dense chain of ionization events as they go through tissue. The distribution of these secondary particles depends on the energy spectrum of the neutron beam, so the biologic properties of the beam depend strongly on its energy spectrum. Neutrons used in therapy generally are produced by accelerating charged particles, such as protons or deuterons, and impacting them on a beryllium target.

There is considerable interest in using charged particle beams directly for therapeutic purposes, which generally requires beams of much higher energy than those used to produce neutrons. The lighter particles, such as protons[14] and α-particles, are of interest because of their extremely favorable depth-dose characteristics. The radiobiologic properties of these beams are similar to those of conventional photon or electron beams. Heavy charged particles combine the favorable depth-dose properties of the proton and α-particle beams with the

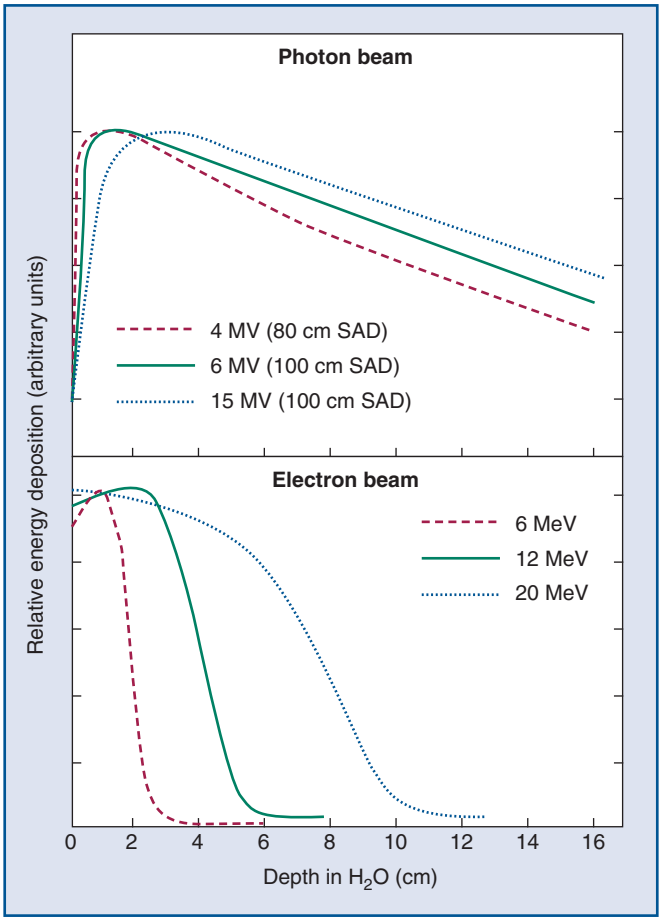

Figure 77-4. Typical depth-dose curves for megavoltage photon and electron beams commonly used in the therapy of head and neck cancers. The *upper panel* shows curves for 10 cm × 10 cm fields for a 4-megavolt (MV) (80-cm source axis distance [SAD]) linear accelerator *(dashed line),* a 6-MV (100-cm SAD) linear accelerator *(solid line),* and a 15-MV (100-cm SAD) linear accelerator *(dotted line)*. The *lower panel* shows depth-dose curves for 10 cm × 10 cm fields for 6–megaelectron volt (MeV) *(dashed line),* 12-MeV *(solid line),* and 20-MeV *(dotted line)* electron energies.

favorable biologic properties of the neutron beams. Energies are on the order of several hundred MeV per nucleon, rather than the few MeV per nucleon for the recoil fragments produced by neutrons. These highly energetic particles do not deposit much energy in tissue until they reach the end of their path, where they are moving slowly. Hence, they do not produce much radiation damage in the intervening tissues. Because of their extremely high cost and general unavailability, however, these beams are not widely in use. Interest in proton beams has grown, and the number of radiotherapy facilities using protons in the United States is expected to rise.

Treatment Aspects of External Beam Radiation

A series of technical tasks must be performed to prepare a patient to undergo external beam RT. The purpose of these tasks—simulation, treatment planning, verification, dose delivery, and quality assurance—is to ensure that high radiation doses are delivered to the patient in an accurate and controlled manner. Usually the processes of simulation, treatment planning, and verification take 1 to 3 days. The setup and treatment planning must be individualized to maximize the dose delivered to the target while minimizing the irradiation of surrounding normal tissue. Any inaccuracy in this process could cause further delay in the initiation of the radiation treatment.

During simulation, the patient setup is assessed for ease of positioning and daily reproducibility. This process involves the use of

Figure 77-5. Photograph of a linear accelerator.

immobilization devices (anything that can hold a patient in position during treatment) and treatment aids (any kind of support to make patient comfortable). In most HNC cases, a mask that immobilizes the head and neck is used.

After the patient is immobilized, at least two reference points are marked on the patient with x-ray markers to define a reference plane close to the internal tumor target. The marking of the reference points is aided by the use of lasers. Next, the region of interest on the patient is scanned using computed tomography (CT), often using a dedicated CT-simulator scanner to obtain CT images for image-based treatment planning. The images are scanned to a treatment planning station. The radiation oncologist then outlines the tumor target region and critical surrounding normal structures on the axial images on the basis of the CT scan, and a prescribed dose with appropriate normal tissue margin is provided. On the basis of this information, a medical physicist or a medical dosimetrist designs an individualized treatment plan. The challenge in the plan is to deliver the prescribed dose uniformly to the tumor or tumor bed target while maintaining a very low dose to the critical normal structures. Although these goals are achievable, it takes time to arrive at an optimized individualized plan.

Aside from delivering the prescribed dose to the target and minimal dose to the surrounding critical structures, the individualized plan must be evaluated for *deliverability*—that is, the selected beam orientation must be such that the linear accelerator does not collide with the patient or the table, and the technical parameters of the patient's plan must comply with the technical requirements of the delivery machine. Next, the individualized machine-delivery parameters are downloaded into a record verification system database. Patient *verification* is the process of ascertaining that the individualized plan is correct and deliverable. *Correct* here means that the patient is easily placed into treatment position, relatively comfortable, and immobile, the setup is reproducible, and the target is at the appropriate position relative to the isocenter according to the plan. Finally, there is clearance to avoid patient-equipment collision. During verification, orthogonal radiographs or individualized field radiographs are taken, with films or a portal imager, for assessment and for documentation of the setup. In addition, machine parameters are captured into the database. These images can be used to assist in repositioning the patient as necessary.

Typically, the radiation dose is delivered to the patient using a linear accelerator (Fig. 77-5). The radiation beam as produced is a forward peak; that is, it has extremely high intensity along the beam axis. It must pass through a conical metallic flattening filter to create a uniform field beam for clinical use. As the clinical beam exits the linear accelerator, it is collimated by a pair of jaws or a multileaf collimation

(MLC) system (see Fig. 77-5). The multileaf collimation system is used to shield and protect normal structures (replacing the antiquated and cumbersome lead blocks). In addition, the system is used to modulate beam intensity in intensity-modulated RT. The linear accelerator has a gantry that allows the rotation of the treatment head around the patient. Hence, the radiation beam can be directed at the target from multiple positions to reduce dose to the normal tissues. Because of the high voltage, moving parts, and high dose, the linear accelerator must be properly calibrated and properly maintained for its safe use (see Fig. 77-5).

In addition to external beam therapy, radiation oncology departments offer brachytherapy services. In brachytherapy (*brachy* is derived from the Greek word for "short"), sealed radioactive sources are implanted near or directly into tumors. The principal advantage of brachytherapy has been its rapid dose fall-off away from the source. Brachytherapy is generally invasive. When the implant requires short-lived radioactive sources, preimplant dosimetry is performed to determine the number of sources required. After the number of sources has been determined, they are ordered from the vendors. When the sources arrive, they must be assayed and prepared for implantation. On the day of implantation, a final dosimetry plan is created and the sources (often in the form of seeds, as used in prostate brachytherapy) are implanted according to the new treatment plan. For cases involving sources with long half-lives, catheters are provided to the radiation oncologist for implantation. After the implantation, the patient must undergo simulation, and a final treatment plan is generated, similar to the process already described for external beam RT. With advances in computer technology, remote afterloading brachytherapy is now being practiced, in which radioactive sources are remotely loaded into a patient and can be retracted at any time if necessary.

Treatment Planning

Successful treatment planning is imperative to the success of a radiation treatment course. The goal is to identify the full extent of the tumor and areas of possible spread. Several considerations must be taken into account. They include the tumor histology, the extent of the gross disease, regions of microscopic spread but no gross disease, whether the treatment is being given postoperatively or in an undisturbed tumor bed, and the tolerances of adjacent structures. A plan must then be devised to treat this entire region to the dose desired for each region while keeping the volume of each normal tissue below its tolerance. After the image data sets are obtained in any type of simulation, careful review of the clinical data must be made to delineate the tissue in need of treatment. This volume to be treated is defined as the target volume and is created by adding three components together. First, the gross tumor volume (GTV) is noted. This volume is expanded to create the clinical target volume (CTV) by accounting for the areas at risk for spread, such as adjacent tissues or draining lymphatic regions. The planning target volume (PTV) is calculated by adding margin to correct for possible variability in daily positioning and patient motion during treatment.

The remainder of the planning process involves choosing the number of radiation beams required, the energy of these beams, and the angles and weighting of the beams needed to deliver the required radiation dose to the tumor with optimal sparing of normal tissues. After these beams are designed, digitally reconstructed radiographs are produced to reflect the designed treatment fields. The availability of three-dimensional treatment planning has allowed for greater complexity of plans in the attempt to increase the therapeutic ratio via the designing of radiation fields, because the doses to the tumor and normal organs can be evaluated accurately and three dimensionally. This evaluation process allows assessment of the possible toxicity that could result from the radiation treatment via the evaluation of a dose volume histogram, which shows the dose delivered throughout the volume of the organ.

Once treatment planning is completed, the patient begins the course of RT. The first step is to set up the patient to verify the simulation fields on the actual treatment machine. Each day, the patient is repositioned into the exact position in which the simulation and subsequent treatment planning were done. To aid in the repositioning, immobilization devices are often used, consisting of foam body casts or plastic head masks, as previously described. These are made prior to simulation and are kept for use throughout the entire radiation course. Laser lights that converge on the exact isocenter (the point around which the treatment machine rotates) of the treatment machine are available within the treatment room and are used to assist in this repositioning. As three-dimensional techniques allow for greater refinement of treatment volumes and of the increasing complexity of plans, exact daily repositioning is absolutely imperative.

When planning radiation treatment, one must keep in mind the dosages needed to control gross tumor-positive margins and microscopic disease. The probability of tumor control correlates with both the dose of radiation and the volume of the cancer. Radiation cell kill is basically an exponential function of dosage. As a result, the necessary dosage of radiation is roughly proportional to the number of cells in the tumor (tumor volume). Control of microscopic disease in HNC usually requires a dosage of approximately 50 Gy, whereas positive margins require 60 Gy, and adequate control of large (stages T3 and T4) tumors requires dosages in the range of 70 Gy.

Radiobiology

Radiation biology is the study of the effect of radiation on biologic systems. It includes everything from DNA strand breaks to genetic mutations to cellular nongenetic events such as apoptosis.

Radiation cell killing occurs when critical targets within the cell are damaged by radiation.[15] A number of biologic molecules or structures are potential targets for radiation damage. According to most studies DNA is the most critical target for the biologic effects of radiation. On a molecular level, this effect requires the production of ionizations, which is why we refer to the process as *ionizing radiation*. The damage can occur directly when the radiation is absorbed by the DNA itself, because the atoms of the DNA become ionized and damaged. More commonly, however, it occurs indirectly through the following three modes of action[15,16]:

- The effect of x-rays or gamma rays requires the generation of an intermediate ion. (By contrast, particulate types of ionizing radiation, such as α-particles, are directly ionizing and do not require an intermediate ion for effect.)
- The intermediate ion in most cases produces intermediate free radicals, which affect the DNA by breaking chemical bonds (the intermediate ion can also generate DNA damage directly: a less common event for photon ionizing radiation).
- Water molecules surrounding the DNA are ionized by the radiation, creating hydroxyl radicals, peroxide, hydrated electrons, and oxygen radicals.[17]

All of these species are highly reactive free radicals that, in turn, interact with the DNA and cause damage. Both ways eventually cause broken bonds in the DNA backbone, which can cause double-strand breaks, ultimately resulting in mitotic death (Fig. 77-6).

These broken bonds can result in the loss of a base or of the entire nucleotide, or in complete breaking of one or both of the strands of DNA. Single-strand breaks are easily repaired with use of the opposite strand as a template. Therefore, single-strand breaks show little relation to cell killing, although they might result in mutation if the repair is incorrect. Double-strand breaks, on the other hand, are thought to be the most important lesion in DNA produced by radiation.[18] Double-strand breaks, as the name implies, results in snapping of the chromatin into two pieces. These double-strand breaks can result in mutations or, most important, in cell killing.

A growing body of experimental data suggests that radiation damage to DNA is not the only mechanism by which ionizing radiation damages cells. Other mechanisms are apoptosis, cell cycle arrest, and mitotic death. One study has suggested that apoptosis can be triggered by radiation energy deposition in cell membranes.[19] It has also been reported that direct radiation damage to mitochondria can trigger apoptosis.[20]

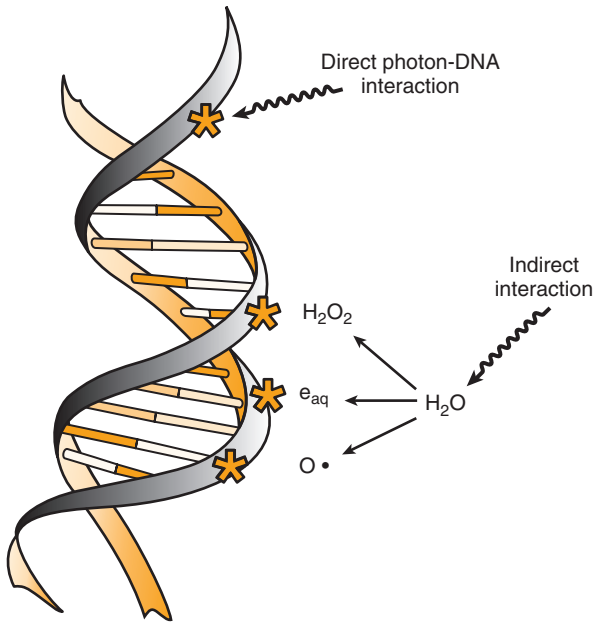

Figure 77-6. Two types of interactions are possible between x-rays and DNA: Direct interaction, in which x-ray interacts with the DNA molecule itself (this interaction is relatively rare); and indirect interaction, in which x-rays ionize water and the reactive species that are created interact secondarily with DNA, causing damage and DNA strand breakage. *(Redrawn from Lichter AS. Radiation therapy. In: Abeloff M, ed.* Clinical Oncology. *2nd ed. London: Churchill Livingstone; 2000:423-470.)*

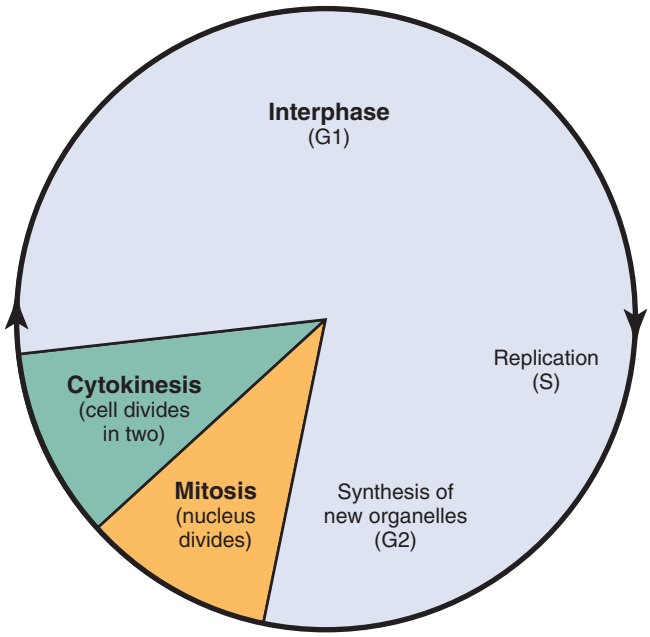

Figure 77-7. Cell cycle.

Cell Cycle Arrest

Radiation triggers signaling cascades leading to arrest, usually at the G1 and G2 checkpoints in the cell cycle.[21] Cell cycle perturbations (Fig. 77-7) are seen characteristically after radiation exposure and were among the earliest observed biologic effects of radiation. Cells can show checkpoints or arrest in any phase of the cell cycle, although the best-described checkpoints with respect to radiation damage are the G1 and G2 checkpoints. Normal cells and those cancer cells that retain p53 function are blocked in the G1 phase of the cell cycle. This is a p53-mediated event.

Mitotic Death

Many cancer cells (typically those with loss or mutation in the p53 protein pathway) have lost the ability to stop in G1. These cells retain the ability to arrest in the G2 phase of the cell cycle. Even in cells that re-enter the cycle after the G2 checkpoint, however, cell death can still be seen and can take several forms. Some cells fail in cytokinesis and form multinucleated giant cells. Some undergo mitotic catastrophe as they attempt to undergo mitosis.

Radiosensitivity

Our main interest in radiobiology is in figuring out ways to improve the treatment toxicity ratio. One of the main concepts is *radiation sensitivity*, which refers to the relative susceptibility of cells, tissues, tumors, or organisms to radiation. However, tumor regression is not solely a function of tumor cell death, but is influenced by many factors, including the amount of extracellular stroma, the propensity of the tumor cells to undergo rapid rather than delayed death, and the resorption of radiation-inactivated cells (depopulation). A frequent misconception is that tumors should be more radiosensitive than normal tissues because they proliferate more rapidly. This misconception may go back 100 years. In 1906, only 11 years after the discovery of x-rays, Bergonie and Tribondeau formulated a "law" for the relationship between cellular radiosensitivity and reproductive capacity.[22] They postulated that cells that have a higher proliferation rate are more radiosensitive than slowly proliferating cells. On a purely cellular basis, it is correct that cells in mitosis at the time of irradiation are more radiosensitive than cells in other phases of the cell cycle. However, many other factors, such as tissue- and host-specific factors, have important influence. In 1906, there was no appreciation of late-occurring normal tissue complications. Nowadays, we know that many slowly proliferating or nonproliferating normal tissues, such as the kidney, are highly radiosensitive; they just express radiation injury much later than rapidly proliferating tissues. Similarly, the proliferation rate of tumors does not predict their radio-curability. For example, rapidly proliferating tumors such as glioblastoma multiforme can be highly radioresistant.

Cell Survival

Loss of reproductive integrity in long-term survival assays is important to our understanding of the response of either a tumor or a normal tissue to radiation. When cells are exposed to lethal doses of radiation, they may not die immediately or within a few hours of treatment, or even sometimes within a single division of radiation. When cells have been observed by time-lapse cinematography after irradiation, some cells survive and go on to form colonies, and some die quickly. Others go through up to several rounds of abortive cell division before finally ceasing to divide. Radiation biologists have demonstrated that it is the proportion of cells capable of forming a colony by sustained cell division that most fully predicts the effects of a dose of radiation.[23] In order to eradicate or control a tumor; one must inactivate all clonogenic tumor cells. In other words, the treatment may fail if only one clonogen survives, because that cell can give rise to a regrowing tumor. In order to understand tumor control better, plots of the surviving fraction of cells as a function of the radiation dose have been performed. An example is shown in Figure 77-8.

By convention, the surviving cell fraction is plotted on a logarithmic scale, and the radiation dose is plotted on a linear scale. This curve is representative of most mammalian cells. Consider the solid curve in Figure 77-8, which represents the survival data. Note that there are two distinct regions to the curve. There is an initial region for low radiation doses, where the slope of the curve is shallow. In this region, small incremental changes in the amount of radiation are not very effective at increasing the number of cells killed. This is called the *shoulder region*, and its width is characterized by the parameter D_q. It is the distance along the dose axis at a surviving fraction of unity between the abscissa and the point where the extrapolated linear portion of the curve is intersected. It is a measure of the ability of the cells to repair small amounts of radiation damage. At higher doses of radiation, the curve

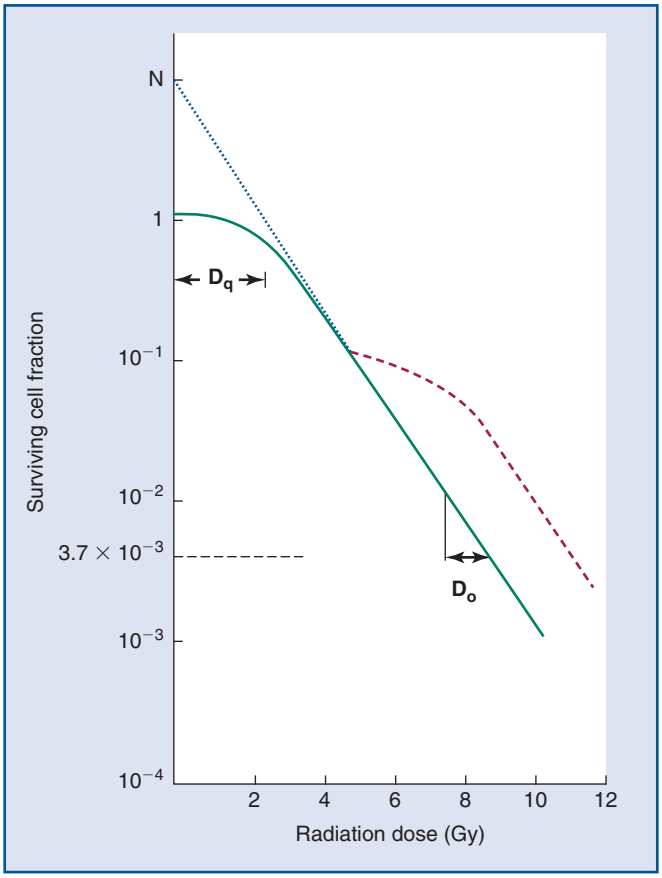

Figure 77-8. A representative cell survival curve *(solid line)* for mammalian cells exposed to single doses of radiation. The surviving cell fraction is plotted on a logarithmic scale, and the radiation dose is plotted on a linear scale. D_q characterizes the width of the shoulder region, which in target theory also may be characterized by the extrapolation number, N. D_o characterizes the slope of the "straight line" portion of the curve. The *dotted line* shows the extrapolation of the linear portion of the curve back to the abscissa. The *dashed line* shows the regeneration of the cell survival curve if, after a certain amount of radiation is given, 6 to 8 hours are allowed to pass before additional radiation is given. *(Redrawn from Hall EJ.* Radiobiology for the Radiologist. *Philadelphia: JB Lippincott; 1994.)*

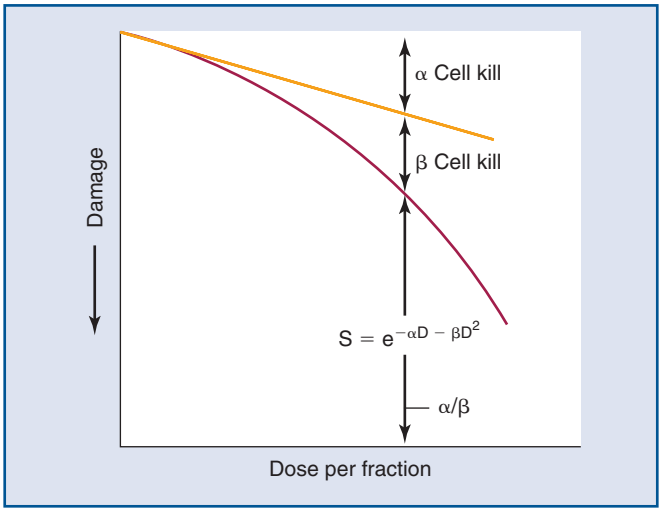

Figure 77-9. Dose-response curves for mammalian cells are adequately fitted by the linear-quadratic relationship, at least over the range of doses of concern in radiation therapy. The form of the equation is where S is the fraction of cells surviving a dose (D), and α and β are constants. Cell killing by the linear and quadratic term are equal when $D = \alpha/\beta$. *(From Cox JD, Ang KK, eds.* Radiation Oncology: Rationale, Technique, Results. *8th ed. St. Louis: Mosby; 2003:14.)*

becomes a straight line on a semilog plot. Its slope is characterized by D_o, which is the incremental dose change required to reduce the surviving cell fraction to 1/e of its value. The steeper the slope in this region, the smaller is the value of D_o and the more radiosensitive is the cell line. When extrapolated back to a zero radiation dose, it intersects the abscissa at a value N. A curve of this type can be modeled using the following equation:

$$S = 1 - [1 - \exp(-D/D_o)]^N \qquad \text{(Eq. 77-3)}$$

where *S* is the surviving fraction, *D* is the radiation dose, and *N* and D_o are as indicated in Figure 77-8. In target theory, *N* can be thought of as the number of distinct targets in the cell that should receive one radiation "hit" before the cell is inactivated.

A number of mathematical models have been devised to attempt to describe the shape of the cell survival curves that are observed experimentally, with an initial shallower slope, an eventual bending (the "shoulder"), and a final, steeper slope. These include target models, lethal and potentially lethal damage models, and repair saturation models. Some of these have been based on simple mathematical modeling without any real attempt to model known molecular events involved in cell killing, whereas others have been based on attempts to model some of the known molecular events (e.g., chromosome breaks or DNA repair) that are involved in cell killing. All of the models can describe the shape of the survival curve to a first approximation. None does so perfectly, and none takes into account all the events and all of the possible mechanisms involved in cell death. A model that has been most influential on clinical practice is the linear quadratic model,[24] because it is one of the models that best fits the behavior of cells after exposure to radiation doses within the range used in the clinic. The linear-quadratic model was devised by Keller and Rossi,[25] who proposed that radiation-induced cell killing resulted from two potential events, one with a linear relation to dose ($\exp[-\alpha D]$), the other having a quadratic relation to dose ($\exp[-\beta D^2]$). This was expressed mathematically by the "alpha-beta" equation, as follows:

$$S = e^{-(\alpha D + \beta D^2)} \qquad \text{(Eq. 77-4)}$$

where *S* represents survival of a cell population after a dose, *D* (Fig. 77-9). It has been hypothesized that this equation actually represents a molecular reality.[26] Double-strand breaks in the DNA are lethal lesions that are produced by either one energy deposition, an event termed (αD), or by two separate events, each involving a single strand of DNA (βD^2), which then interact. This hypothesis is now thought to be unlikely because of the low probability of two tracks interacting within a single double helix.

The α/β ratio, which is derived from Equation 77-4, represents a point on the survival curve at which the components of cell killing are equal to each other—that is, $\alpha D = \beta D^2$, or $D = \alpha/\beta$. In other words, for each cell population there is a dose of radiation in which the linear (α) and quadratic (β) contributions to cell killing are equal. The α/β ratio is specific to each cellular population and reflects the sensitivity of the cell to the two types of damage. Tissues that have an early response to radiation (skin, mucosa, and tumor cells) have a high α/β ratio. In other words, their survival curves stay straight for a longer period before the bend occurs, in which there is a higher contribution of single-event or α killing. Late-responding tissues, such as spinal cord, kidney, and muscle, have survival curves that bend earlier, with resultant lower α/β ratios. These late-responding tissues have shoulders on their survival curves within the range of doses commonly used in RT. This understanding led to the concept that altered fractionation sched-

ules could be used to treat tumor populations more effectively with respect to damage to late-responding tissues.

Tissue-Radiation Characterizations

The main intent in clinical radiotherapy is to irradiate tumoral tissues while minimizing the damage to the surrounding healthy tissues. The four main concepts of clinical radiotherapy are known as "the four Rs of radiotherapy": repair (of sublethal damage), redistribution (across the cell cycle), repopulation, and reoxygenation. Radiotherapy basically works not because tumors are more radiosensitive than normal tissue but because normal tissues are better at repair and repopulation. These four Rs also account for different response rates of tumors.[27-29]

Dividing the total dose into a number of smaller fractions allows for normal tissue sparing because of the *repair* of sublethal damage between fractions; however, doing so may also influence tumor cells. Cells show increased survival with split-dose radiation because the shoulder of the survival curve must be repeated with every fraction. In other words, the shoulder of the survival curve represents the accumulation and repair of sublethal damage.

Fractionating the therapy also allows for reassortment or *redistribution* of tumor cells into radiosensitive phases of the cell cycle, according to several studies. The cells are radiosensitive early in the M phase but become more resistant toward the end of this phase. They are resistant in the early G_1 phase but then become more sensitive in the late G_1 and early S phases. They then become more resistant again in the late S and early G_2 phases. The exact mechanisms underlying this change in radiosensitivity are not clear, but it is interesting to note that at the beginning of mitosis, the DNA in the chromosomes aggregates into a discrete state; in the late S phase, the DNA content of the cell has doubled. These points in the cycle correspond, respectively, to the points of maximum and minimum radiosensitivity.

Reoxygenation of the tumor cells causes the cells to be more radiosensitive. The response of cells to ionizing radiation is strongly oxygen dependent, with well-oxygenated cells showing up to threefold greater sensitivity to the killing effects of ionizing radiation than the same cells under hypoxic conditions (Fig. 77-10).[30] Tumors tend to have a much higher proportion of hypoxic cells than normal tissues do. Therefore it is important to allow tumor cells to reoxygenate. However, if too much time occurs between fractions, *repopulation* or proliferation of the tumor cells could occur. Therefore the main issue is creating a balance between reoxygenation of the tumor and its repopulation and repair, and at the same time minimizing the damage to the surrounding tissue.

Rapidly dividing tissues, including tissues such as the skin, mucous membranes, bone marrow, and tumor cells, are responsible for the acute toxicity following RT. The severity of acute toxicity correlates with the relationship between the rates of cell killing of early-responding tissues counteracted by regeneration by those tissues' surviving stem cells. This balance is based mainly on total treatment time. Prolonging overall treatment time spares the patient from the severe acute toxicity caused by shorter, intense treatment courses. If the therapy is so intense and does not allow a sufficient number of stem cells to survive, the acute toxicity can progress to consequential late effects. Late-responding tissues are responsible for the late toxicity from RT. These tissues, such as the spinal cord, brain cells and connective tissue, are composed mostly of terminally differentiated cells with no reproducible cell population. Thus, there is usually no turnover of such cells within a radiation treatment course, and no opportunity or need for regeneration to occur during treatment. Therefore, unlike in early-responding tissues, the overall treatment time has little importance in determining toxicity in late-responding tissues. Instead, late toxicity depends mainly on total dose and dose per fraction.

Provided that full recovery occurs after each fraction, most late radiation effects show no dependence on the duration of treatment. In contrast, overall treatment time has a large effect on both acute toxicity in early-responding tissues and the cure of tumors. This implies that the tumors that show a decrease in curability with longer treatment times have a rapid regeneration in response to the cell killing that occurs with radiation.

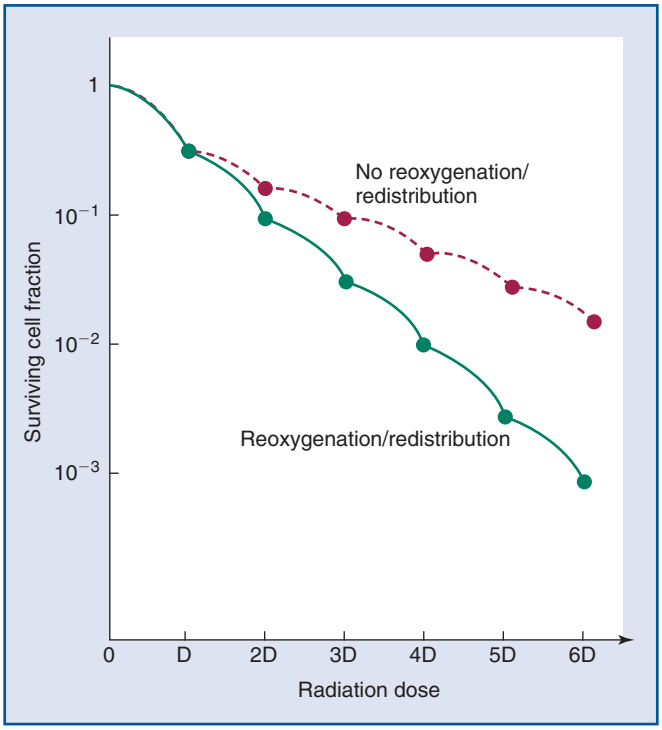

Figure 77-10. Illustration of the effects of fractionated radiotherapy on a heterogeneous cell population. Surviving cell fraction is plotted along the abscissa as a function of the radiation dose. The dose is given in increments, D, with the time interval between successive doses being long enough to allow for sublethal damage repair. The initial dose increment kills a greater fraction of well-oxygenated cells than it does their hypoxic counterparts. It also preferentially kills those cells in the radiosensitive phases of the cell cycle. The *solid curve* indicates when the remaining cells reoxygenate and redistribute along the cell cycle before the next radiation dose is given. The *dashed curve* indicates when there is no reoxygenation or redistribution, and successive radiation doses are delivered to a more radioresistant cell population. The figure is schematic and is not meant to represent any particular cell line.

In order to evaluate the impact of a radiation treatment, time-dose considerations are important in estimating the effect of a given total radiation dose.[31] If the dose were given in a single fraction, then the healthy tissues would experience more cell killing than if it were given in a fractionated manner. This difference occurs because single fractions allow no opportunity for repair of sublethal damage. In general, smaller total radiation doses given over shorter total treatment times can produce the same normal tissue effects as larger total radiation doses given over longer intervals.

The classic measurements that illustrate this point are the isoeffect measurements on skin that were made by Strandquist.[32] He showed that the isoeffect lines for various degrees of skin damage and for curing skin cancer were straight when plotted on a log-log scale of total dose versus time. Moreover, the lines appeared to have the same slope (i.e., were parallel). The required dose to produce a given effect was proportional to time to the 0.33 power. Ellis[33] extended this concept to clinical radiotherapy by allocating a portion of the exponent 0.33 to the overall treatment time, *T*, and a portion to the number of fractions, *N*. He defined the nominal standard dose (NSD) with the following equation:

$$NSD = D^t / T^{0.11} N^{0.24} \qquad \text{(Eq. 77-5)}$$

where D^x is the total radiation dose. The exponents in this expression are for skin and no doubt vary for other tissues.

Clinical Applications

Radiation Fractionation

Altered Fractionation Schedules

The highly fractionated radiotherapy protocols used today are based on the notions just discussed. They are a result of many years of clinical experience, and are extremely crucial for patients with HNC, in whom the radiation in most cases is a curative treatment. Side effects of treatment may have an impact on treatment and therefore may influence survival. In order to further improve the outcome, many studies have suggested different types of dosage prescriptions. The two main treatment methods that have been explored are hyperfractionation and accelerated fractionation treatment.

Several trials suggested the use of *hyperfractionation*, which involves the administration of multiple daily doses of radiation of such a size that the overall treatment time is about the same as for a conventionally fractionated course of once-a-day radiotherapy. The decreased size of each radiation fraction should permit utilization of a higher total dose without increasing late morbidity. Because normal tissues that show delayed toxicity (and hence long-term morbidity) are more dependent on the size of the individual dose than are tumors, decreasing the size of each radiation fraction should permit utilization of a higher total dose without increasing late morbidity. In practice, multiple daily treatments with smaller than conventional fraction sizes are given over approximately the same treatment duration. Typically, 1.1 to 1.2 Gy/fraction, two fractions per day, to total doses of 74 to 80 Gy have been employed.

Four prospective randomized trials comparing hyperfractionation with standard irradiation alone (without chemotherapy) have been performed.[34-37] In all studies locoregional control was significantly better for those patients treated with hyperfractionation and accelerated fractionation with a concomitant boost than for those treated with standard fractionation. The advantage ranged from an 8% to a 20% 2-year locoregional control rate. There was also a trend toward better disease-free survival with hyperfractionation. In one of the studies, which dealt specifically with oropharynx tumors, there was an improvement in overall survival: Overall survival rate at 42 months was 27% for the hyperfractionation arm and 8% for the conventional treatment arm ($P = .03$).[36] Survival rates were 40% for the hyperfractionated arm and 18% for the conventional RT arm ($P = .06$). All groups treated with altered fractionation RT had significantly greater late side effects than those undergoing conventional fractionation. The acute side effects of hyperfractionation were slightly more intense and common than with standard fractionation, but the long-term effects appear to be very similar.

Accelerated fractionation is the administration of multiple daily radiation doses of larger size to reduce the overall treatment time. The goal of accelerated fractionation is to prevent tumor repopulation during a course of radiation therapy. Clinical support for tumor cell proliferation during therapy is found in numerous studies that have shown a loss in tumor control with prolongation of overall treatment time in HNC. In general, accelerated treatments that employ continuous (rather than split-course) RT schedules without compromise in the total dose result in better local control. However, whether the added mucosal toxicity from this approach is justified by meaningful gains in survival remains an open question. The studies present a trend toward better primary tumor control in the hyperfractionation arm but no significant difference in overall survival. Comparison of accelerated RT with conventional RT for locoregionally advanced HNC has been tested in a considerable number of randomized trials.[34-41] All of these trials used somewhat different dose fractionation schedules, and the results (in terms of both locoregional control and survival) are inconsistent. The only trial suggesting a survival benefit for this approach was the smallest.[39]

The reasons for these inconsistent findings may be the differences in treatment regimens used. In some studies overall treatment time was decreased by more than 50%, necessitating a decrease in total dose by approximately 10% to 20%.[38,40,41] This approach resulted in significantly better locoregional control in only one trial,[38] and none showed gains in overall survival. Another approach involved moderate reduction in the overall treatment time without a relevant compromise in total dose, with the use of split-course RT regimens.[34,35,38] With this strategy, no benefit in local control or survival has been observed, except for a significant improvement in local control in one of the trials.[35] This improvement did not translate into an improvement in overall survival, however. This lack of survival benefit has been attributed, at least in part, to the significantly higher rate of severe late toxicities in the accelerated treatment arm, which resulted in an increase in the non–cancer-related death rate.

Moderate reduction of the overall treatment time without a relevant compromise in total dose has also been achieved in two studies, with the use of six or seven fractions per week (compared with the usual five fractions weekly) without a split course.[39,42] Both of these studies showed a significantly improved local control rate in the accelerated treatment arm, and one demonstrated a trend for an improvement in overall survival.[39] Both studies demonstrated a significant increase in acute side effects. Whether late toxicity is also worse with the accelerated treatment approach is unclear. The available data are conflicting, with some trials suggesting no increase in late toxicity,[38] and others suggesting the opposite.[35]

The benefit of altered fractionation RT for squamous cell HNC was addressed in a meta-analysis of 6515 patients enrolled in 15 selected trials comparing hyperfractionated or accelerated fractionation RT with conventional fractionation RT.[43] The majority were treated for stage III or IV disease. Compared with conventional fractionation RT, altered fractionation RT resulted in a statistically significant 18% reduction in rate of local failure at the primary site, corresponding to a 6.4% absolute reduction in rate of locoregional failure at 5 years. The improvement in locoregional control was more pronounced in patients undergoing hyperfractionated RT and in those treated with accelerated RT without dose reduction. A significant benefit in overall survival was also found; altered fractionation regimens reduced the risk of dying by 8%, which translated into an absolute survival benefit of 3.3% and 3.4% at 2 and 5 years, respectively. The magnitude of benefit was statistically significant in patients treated with hyperfractionated RT, but not for those undergoing accelerated fractionation RT, with or without a dose reduction. Although this meta-analysis demonstrates the advantage of hyperfractionation versus conventionally fractionated radiation, the standard of care today is chemoradiation, and these studies do not demonstrate superiority of any RT regimens over chemoradiation.

The benefit of combining radiosensitizing chemotherapy with hyperfractionated RT (CRT) schedules was shown in one study in which 116 patients with HNCs (approximately 53% of which were unresectable) were randomly allocated to undergo hyperfractionated RT either alone or with 5-fluorouracil (5-FU) and cisplatin.[44] At 3 years, CRT was associated with significantly higher rates of locoregional control (70% vs. 44%), a trend toward better relapse-free survival (61% vs. 41%, $P = .08$), and better overall survival (55% vs. 34%, $P = .07$). Toxicity, although high, was equivalent in the two groups. However, no trial has compared a regimen using hyperfractionated RT with or without chemotherapy directly with a regimen using concomitant CRT and conventional fractionation RT, the widely accepted standard of care, at least in the United States, for locoregionally advanced laryngeal and oropharyngeal cancers. These twice-daily treatments place greater time demands on the patient as well as on the treatment facility and may create problems with compliance. As a result, hyperfractionated regimens have not been widely adopted, at least in the United States.

Radiosensitizers

The two main options for improving radiation treatment outcome are modulation of the radiation itself, as already discussed, and helping the radiation to become more effective, known as *radiosensitizing*. A number of mechanisms have been proposed to explain radiation resistance or failure. These can be divided into mechanisms based on radiation dose and schedule, and genetic and epigenetic factors that affect

the tumor and its response to radiation therapy. In this section the following existing strategies are discussed: (1) reducing hypoxia, (2) concomitant chemotherapy, and (3) targeted therapy.

Reducing Hypoxia

Within the tumor cell microenvironment, radiation therapy effectiveness is closely dependent on oxygen availability at the time of treatment. Hypoxic cells are 2.5 to 3 times less radiosensitive than well-oxygenated cells.[45,46] The hypoxic cell fraction in solid tumors ranges from less than 1% to more than 50%.[47] Hypoxia in the tumor microenvironment may be a result of increased interstitial pressure, which leads to vascular collapse with resulting areas of transient or persistent hypoperfusion, local hypoxia, and acidosis.[48] Many patients with cancer are anemic, a factor that may also contribute to localized hypoxia and that has an adverse effect on curability of a tumor by radiation therapy.[49] In order to overcome the hypoxia, specific trials addressing this issue were performed. These explored the concept of increasing the delivery of oxygen, also known as hyperbaric oxygen therapy (HBO), which increases the amount of oxygen in the blood. The use of carbogen, also raises the local oxygen level. Although the use of HBO was associated with significant increases in response rate (clinical complete response rate 84% with HBO vs. 52% without it),[50] there were no significant differences in 5-year rates of local control or survival. Inhalation of carbogen (95% oxygen–5% carbon dioxide) during radiation therapy, often combined with accelerated radiation and oral nicotinamide (ARCON treatment)[6,7] has been suggested in several trials, and its benefit has not been confirmed.

A second approach to decreasing the impact of hypoxia is the use of hypoxic cell sensitizers, some of which have been used in concomitant chemotherapy regimens, including nimorazole and tirapazamine. Although results of initial clinical trials have been promising, so far there is no proven evidence for survival benefit.[51-53]

Several trials have evaluated the hypothesis that outcomes might be improved through correction of preexisting anemia using recombinant human erythropoietin (epoetin or darbepoetin); this hypothesis was supported by the results of uncontrolled studies.[52] However, subsequent randomized trials directly testing this hypothesis did not confirm benefit and, in fact, suggested significantly worse locoregional control and overall survival outcomes, or both, in patients who received epoetin during therapy for HNC.[54,55]

Concomitant Chemotherapy

In general, there may be a synergistic effect between radiotherapy and chemotherapy that alters the radiobiologic parameters (α and β) or there may be an additive effect.

The *additive effect* may occur in two different ways, as follows:

1. The chemotherapy may be effective at eradicating micrometastases, thus reducing the incidence of distant metastases.

2. Spatial cooperation, meaning independent activity of each treatment modality (i.e., radiation within the treatment field and chemotherapy inside and outside the field) may occur. Toxicity independence (i.e., non-overlapping toxicity) allows for administration of each treatment modality at near full dose without a significant increase in normal tissue damage, although almost all chemoradiotherapy regimens are associated with higher rates of mucositis and other regional toxicities than radiation alone.

Alternatively, a *synergistic effect* may occur, through increased cytotoxic activity within the radiation field as a direct result of the interaction of chemotherapy with radiation. In this case, the drug is acting as a sensitizer, enhancer, or potentiator of radiation. A number of chemotherapy drugs act as direct cellular radiosensitizers in vitro. They include cisplatin, mitomycin C, 5-FU, hydroxyurea, bleomycin, paclitaxel, docetaxel, and cetuximab, a monoclonal antibody that is directed against the epidermal growth factor receptor, which is over-expressed in the majority of HNCs.

Synergistic or additive effects are thought to be due to the following mechanisms[56-58]:

- The drug may interfere with cellular DNA repair after sublethal or potentially lethal damage. This may be part of the mechanism of action of cisplatin.[56]

- The drug may reduce tumor cell repopulation by enhancing the cytotoxic effect, particularly following fractionated RT.[57]

- The drug may reduce the population of hypoxic tumor cells. Tumor cell oxygenation can be improved by reduction of interstitial pressure that follows successful cytoreduction.[56-58] Alternatively, hypoxic cells can be sensitized to radiation (or chemotherapy). Hypoxic cells can be killed with a hypoxic cell toxin; for example, mitomycin is preferentially activated in hypoxic cells,[58] and tirapazamine is another hypoxic cell toxin.

- The drug may kill radioresistant cells in the S phase of the cell cycle and increase cell cycle synchronization.[59] Hydroxyurea is an S phase–specific agent that inhibits ribonucleotide reductase. Therefore, it may have additive effects with radiation because it is toxic to S-phase cells that are considered radioresistant. It has also been shown to synchronize cells by inhibiting the entry of cells from the radiosensitive S phase. Paclitaxel works similarly as a cell cycle modifier: It causes accumulation of cells at the G2/mitosis phase of the cell cycle, at which both it and radiation are most effective.[60]

Concomitant chemoradiation has been tested in several settings, for example as up-front curative treatment in resectable and unresectable tumors, postoperatively.

UNRESECTABLE TUMORS. Several meta-analyses have been performed to analyze the use of chemoradiotherapy in unresectable tumors. One meta-analysis of trials evaluating locoregional treatment with or without chemotherapy suggested that the magnitude of the absolute survival benefit with chemotherapy (given in any fashion with RT) was 4% at five years.[61] The hazard ratio (HR) for death was 0.81 (95% confidence interval [CI] 0.76 to 0.88) with concomitant chemoradiotherapy compared with locoregional therapy alone, and the benefit was more pronounced with multiple-agent chemotherapy regimens (hazard ratio 0.69).

A second meta-analysis of randomized trials testing curative intent RT alone or with concurrent or alternating chemotherapy concluded that the addition of concurrent (but not induction) chemotherapy to conventional or altered fractionation RT prolonged survival by an average of 12 months.[62] Benefit was most pronounced in those trials that used 5-FU or cisplatin-based chemotherapy (average survival prolongation 24 months and 16 months, respectively).

INDUCTION CHEMOTHERAPY. Some writers have suggested that the optimal regimen should include induction chemotherapy prior to chemoradiation. The rationale for using induction chemotherapy is that a reduction in the overall tumor burden will permit more effective local therapy: Radiotherapy can be directed against a smaller number of tumor cells, and early treatment of micrometastases may diminish the chance of developing gross metastatic disease. The reduction in tumor size and healing prior to definitive RT may improve functional outcomes. The response to chemotherapy may be an important predictor of survival, because various studies have shown that patients with a good response to induction chemotherapy have a better overall survival.

The majority of studies suggest that there is no obvious role for induction chemotherapy. Tumor cells that remain after chemotherapy are likely to be chemoresistant and to show cross-resistance to radiation therapy as well.[63] Delaying radiation treatment can lead to accelerated repopulation of surviving tumor clonogens, which occurs during an extended total treatment time. There are also practical issues. Induction chemotherapy is associated with increases in toxicity (compared with local therapy without chemotherapy), cost, and overall duration of treatment. Some patients receiving induction chemotherapy do not go on to receive definitive therapy because of the toxicities.

Several trials have compared different regimens of induction chemotherapy.[64,65] The triple regimen of docetaxel or paclitaxel plus cisplatin and 5-FU has been compared with a regimen using cisplatin

plus 5-FU in the setting of induction chemotherapy. The studies demonstrated that the taxane-containing regimen (with docetaxel or paclitaxel) provided superior outcomes, reporting a 14% improvement of overall survival at 3 years and improvement in median survival from 30 to 71 months.[65] However, neither of these studies compared induction chemotherapy with direct chemoradiation. In the study by Hitt and associates,[64] 13% of the patients assigned for the better-tolerated PCF induction regimen dropped out and did not receive the definitive treatment, a situation that might lead to worse survival than that with standard treatment. In order to answer this question, three large randomized trials have been initiated to test the benefit of adding induction chemotherapy to chemoradiotherapy. Until these trials are completed, this approach should be considered investigational.

ORGAN PRESERVATION. One of the main goals in chemoradiation treatment in HNC is the ability to preserve organs that would have been destroyed by surgery. Many studies have dealt with producing the optimal combination in order to preserve function.

The U.S. Department of Veterans Affairs (VA) Laryngeal Cancer Study was the first published randomized trial using neoadjuvant chemotherapy with the major endpoint of organ preservation.[66] In this study, 332 patients with advanced laryngeal cancer, either stage III (53%) or stage IV (47%), were randomly assigned in equal numbers to one of the following two regimens:

Arm 1—Induction chemotherapy followed by RT, with surgery reserved for salvage. Chemotherapy was given on a 21-day cycle. Clinical tumor responses were reassessed by physical examination and indirect laryngoscopy 18 to 21 days after the start of the second cycle of chemotherapy. The patients undergoing definitive RT received 66 to 76 Gy to the primary tumor site. The doses to the nodes varied according to initial nodal size, ranging from 50 Gy to 75 Gy. Patients with persistent disease in the larynx after RT underwent salvage laryngectomy, and patients with persistent disease in the neck underwent neck dissection alone. In addition, patients with late relapses underwent salvage laryngectomy.

Arm 2—Standard surgery and RT. These patients underwent total laryngectomy and most also underwent neck dissection. This surgery was followed by postoperative RT (PORT) (50 to 74 Gy). The results were as follows: 15% of patients had less than a PR and received standard laryngectomy, 31% had a clinical CR at the primary site, and 85% had a complete response (CR) or partial response (PR) of the primary and involved regional lymph nodes.

Outcome was reported at 33 months' follow-up, and outcome measures of both survival and organ preservation were clearly delineated. Two-year survival was equivalent at 68% in the two treatment arms.

A second publication from the same study reported long-term survival in the chemoradiation group only.[67] At the time of that report, 53% survival was noted at 3 years. Patients who had a histologic CR had better survival than patients with persistence of tumor after chemotherapy.

The most significant findings in the VA studies were those related to organ preservation. In the patients randomly assigned to neoadjuvant chemotherapy followed by definitive radiotherapy, 66% of the survivors had a preserved larynx at 2-year follow-up, and 39% of the overall group were alive at 2 years with a functional larynx. A major conclusion of this study was that a significant number of patients could remain alive with a functional larynx after neoadjuvant chemotherapy with definitive RT. However, no survival advantage was seen.

Subsequently, Forastiere and colleagues[68] compared RT alone with either induction chemotherapy followed by RT or concomitant CRT, with larynx preservation as the primary end point. In their initial report, 2-year laryngectomy-free survival rates significantly favored the concomitant chemoradiotherapy group (88% vs. 75% for neoadjuvant chemotherapy and 70% for RT alone), and the rates of local control were also significantly better (80%, 64%, and 58%, respectively).[68] There were no significant differences when induction chemotherapy followed by RT was compared with RT alone, and overall survival was nearly identical in all three groups (2-year and 5-year survival rates 74% to 76%, and 54% to 56%, respectively).

In a later report that this group presented at the 2006 meeting of the American Society of Clinical Oncology, there were no longer any differences in laryngectomy-free survival between the groups receiving concomitant chemoradiotherapy and induction chemotherapy followed by RT (47% versus 45% at 5 years, respectively, compared with 35% for RT alone).[69] However, the overall laryngeal preservation rate still favored concomitant therapy (84% versus 71% respectively, compared with 66% with RT alone), as did locoregional control rates. This study has established concomitant CRT as a standard of therapy in this setting.

POSTOPERATIVE TREATMENT. The treatment goals for patients with resectable locally advanced HNC are to maximize cure and to maintain functional status through organ preservation. Historically, surgery with postoperative radiotherapy (PORT) has been used for most patients with potentially resectable stage III or IV HNC. Indications for PORT include involved surgical margins, perineural involvement, bone or cartilage invasion, and advanced primary (T3 or T4) or nodal (N2 or N3) disease.

Two large trials have reported a survival benefit for combined chemotherapy and conventional fractionation over radiation alone after surgical resection among patients with locally advanced but resectable disease.[70,71] These benefits came at the cost of enhanced acute mucosal toxicity, although late toxicities were not more common.

In a multi-institutional trial sponsored by the European Organization Research and Treatment of Cancer (EORTC), 334 patients with high-risk resected squamous cell cancer (SCC) of the oral cavity, oropharynx, larynx, or hypopharynx were randomly assigned to RT alone or the same dose of RT with concomitant cisplatin.[62] High-risk disease was defined as a T3 or T4 primary with any nodal stage (excepting T3N0 laryngeal cancer), involved surgical margins, extracapsular extension, perineural invasion, vascular invasion, or oral cavity/oropharyngeal primary sites with involvement of level IV or V lymph nodes.

At a median follow-up of 60 months, concomitant chemoradiotherapy was associated with significantly better 5-year rates of progression-free survival (47% vs. 36%) and overall survival (53% vs. 40%), fewer locoregional relapses (18% vs. 31%), and a significantly longer time to progression (55 versus 23 months) than those for PORT alone. In a similarly designed Radiation Therapy Oncology Group (RTOG) trial, 459 patients with resectable high-risk SCC of the oral cavity, oropharynx, larynx, or hypopharynx were randomly assigned to RT alone or the same doses of RT with concomitant cisplatin on days 1, 22, and 43.[70] The definition of "high-risk" differed somewhat from that used in the EORTC trial, consisting of positive resection margins, involvement of two or more lymph nodes, or extracapsular nodal extension. At a median follow-up of 46 months, chemoradiotherapy was associated with a significantly better 4-year disease-free survival (40% vs. 30%) and fewer locoregional relapses (19% vs. 30%) than those for PORT alone. The difference in overall survival was not statistically significant (hazard ratio 0.84, $P = .19$). As in the EORTC trial, the incidence of acute severe mucosal toxicity was significantly greater in the chemoradiotherapy group (77% vs. 34%). Long-term toxicity rates were comparable in the two groups, although data derived from larger numbers of patients undergoing definitive treatment suggest that the rate of long-term toxicity is higher in patients receiving chemoradiotherapy than in those undergoing RT alone.

In order to suggest treatment guidelines, risk stratification was addressed in a pooled analysis comparing the selection criteria, clinical and pathologic risk factors, and treatment outcomes of the EORTC and RTOG studies.[71] The findings can be summarized as follows: Extracapsular extension and/or microscopically involved surgical margins were the only risk factors for which the effect on survival of adding chemotherapy to RT was statistically significant in both trials. There was a trend toward better survival in favor of chemoradiotherapy in the group of patients who had stage III or IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV or V lymph nodes secondary to tumors arising in the oral cavity or oropharynx, but the differences were not statistically significant.

Patients in whom two or more histopathologically involved lymph nodes without extracapsular extension was the only risk factor that did not seem to benefit from the addition of chemotherapy.

Targeted Therapy

In order to reduce side effects and optimize treatment, several studies have substituted chemotherapy with molecular targeting antibodies. The most prominent molecule thus far investigated has been cetuximab (Erbitux, IMC225), which is a monoclonal antibody that is directed against the epidermal growth factor receptor and often over-expressed in the majority of HNCs. Cetuximab inhibits receptor activity by blocking the ligand binding site. The benefit of cetuximab as a radiation sensitizer was tested in a multicenter trial[72] in which 424 patients with locoregionally advanced SCC of the oropharynx, hypopharynx, or larynx were randomly assigned to RT (once daily, twice daily, or with a concomitant boost, with the specific approach selected by each participating institution) with or without weekly concurrent cetuximab. The majority of patients underwent concomitant boost RT (56%), whereas once daily and twice daily fractionation schedules were used in 26% and 18% of patients, respectively. Cetuximab was administered at a dose of 400 mg/m^2 over 2 hours 1 week prior to RT, then at 250 mg/m^2 over 1 hour for subsequent weekly doses during the RT weeks. At a median follow-up of 54 months, the cetuximab-treated group had significantly better median (49 vs. 29 months) and 3-year survival rates (55% vs. 45%) than the group receiving RT alone. Locoregional control rates were also significantly better (50% vs. 41%, respectively), and there was also a suggestion of a higher laryngeal preservation rate in the cetuximab group (88% versus 80% at 3 years, respectively).[72] The cumulative rates of distant metastases at 2 years were similar (16% versus 17%, respectively).[72] Although cetuximab did not appear to exacerbate the toxic effects commonly associated with RT (i.e., mucositis, xerostomia, dysphagia, and weight loss), patients receiving combined therapy had a greater incidence of grade 3 or 4 skin toxicity (17% vs. 1% rate of acneiform rash, respectively).

These results are encouraging; however, cetuximab has not been directly compared with other agents as a radiosensitizer. Thus, its role, particularly in comparison with the current standard cisplatin-based chemoradiotherapy, remains uncertain. Nevertheless, it is approved in the United States in combination with RT for the treatment of locally or regionally advanced head and neck SCC. It could be considered in older patients with a borderline performance status (PS2) whose ability to tolerate cisplatin-based chemoradiotherapy is questionable.

The next generation of clinical trials is focusing on combinations of RT, cetuximab, and conventional cytotoxic chemotherapy agents. Although early reports using this approach are promising, it may result in greater toxicity, and incorporation of this strategy into clinical practice would be premature.[73]

Advanced Radiation Technologies

In traditional irradiation of HNC, the placement of the radiation fields and their shapes were based on the bony anatomy acquired by the simulator diagnostic-quality films. During the late 1980s, advancements in computer technology and imaging introduced methods to identify the targets on CT scans and display the radiation beams in three dimensions relative to the anatomy. In addition, calculation and display of the radiation dose distributions and methods to evaluate and compare rival plans with dose-volume histograms (DVHs) became available. The introduction of multileaf collimators facilitated an increase in the number of beams that could be delivered without a large extension of treatment time. The result was the emergence of three-dimensional conformal radiotherapy (3DCRT), which allowed better precision of irradiation delivery to image-based targets and some improvements in the sparing of noninvolved critical tissue. Early studies of the utility of 3DCRT in HNC examined larynx,[73] nasopharynx,[74] hypopharynx,[75] and paranasal sinuses cancers.[76] These studies demonstrated a significant benefit for 3DCRT—better coverage of the tumors and reduced doses to critical tissue—over standard techniques.

Another step forward in the mid-1990s was the development of intensity-modulated radiotherapy (IMRT), which facilitated a higher degree of dose conformality and offered opportunities for additional clinical gains. More recently, imaging-guided radiotherapy (IGRT) has emerged, providing opportunities for better precision of patient setup and for tracking of tumor regression and anatomical changes in the noninvolved tissue during the course of radiation therapy. Other emerging technologies are new imaging modalities that enable study of the customization of the radiation dose according to the expected tumor biology, and the use of heavy particles like protons and carbon ions, which offer additional advantages in dose conformality.

Intensity-Modulated Radiotherapy

IMRT implies the use of radiation fields whose intensity varies across the field, depending on the thickness of the target and the existence of critical organs or critical noninvolved tissue in their path. Treating the targets with multiple beams of varying intensity allows a relatively uniform dose in an irregularly shaped target while avoiding a high dose to the surrounding structures. Two technologic developments made IMRT possible: the introduction of computer-controlled multileaf collimators, and the development of computerized optimization, or "inverse planning," which determines the intensity of the beams required to satisfy a specified set of dose distributions. Inverse planning demands the planner to state the treatment goals, usually in terms of the dose and/or dose/volume goals for the targets, and the constraints for the critical normal tissue (the objective, or cost function). The computer attempts to achieve the desired outcome by iteration through numerous possible beam intensities. The desired solution is the dose distribution that minimizes the variance of the delivered dose relative to the objective function. For each target and noninvolved organ or tissue, an importance factor or weight is assigned, and the objective function is the sum of the variance terms representing each structure of interest, multiplied by the importance factor.

Intensity-Modulated Radiotherapy in Head and Neck Cancer

The anatomy of the neck is complex, with many critical and radiation-sensitive organs in close proximity to the targets. Tight dose gradients around the targets that limit the doses to the noninvolved tissue, features characteristic of IMRT, are desirable and offer the potential for therapeutic gains (Fig. 77-11). Noninvolved tissues, the sparing of which may offer tangible gains, include the major salivary glands, minor salivary glands dispersed within the oral cavity, the mandible, and the pharyngeal musculature. In the cases of nasopharyngeal and paranasal sinus cancers, critical normal tissues that may be partly spared using IMRT are the inner and middle ears, the temporomandibular joints, temporal brain lobes, and the optic pathways.

In addition to sparing of noninvolved tissues, IMRT offers a potential for improved tumor control by reducing the constraints on the tumor dose due to critical organs. Examples include the spinal cord, brainstem, and optic pathways that occasionally limit the tumor boost doses in conventional RT. This goal is achieved by specifying a maximal dose to the critical organs and a high penalty in the optimization process if that dose is exceeded. In addition, IMRT eliminates the need for posterior neck electron fields, commonly used in conventional RT, and their associated dose deficiencies. Although IMRT in the head and neck is more feasible than in other sites because breathing-related organ motion is practically absent, other factors must to be taken into account, such as patient setup uncertainties, swallowing-related organ movements, and changes in target and organ positions related to tumor shrinkage and patient weight loss during therapy; these are discussed later.

Not every patient is expected to benefit from IMRT. Those who would benefit most are patients with paranasal sinus cancer in whom the targets are near the optic pathways, patients with oropharyngeal or nasopharyngeal cancer in whom standard RT fields would encompass most of the salivary glands, and patients in whom standard techniques would require a compromise in the tumor dose because of proximity of the tumor to the spinal cord or brainstem. For patients with laryngeal cancer and clinically noninvolved neck, who are receiving treatment to the larynx alone or who require irradiation of the neck encompassing the jugulodigastric nodes but not extending to the base of skull, IMRT may not be better than simpler techniques. The same applies to patients requiring irradiation to the ipsilateral neck alone.

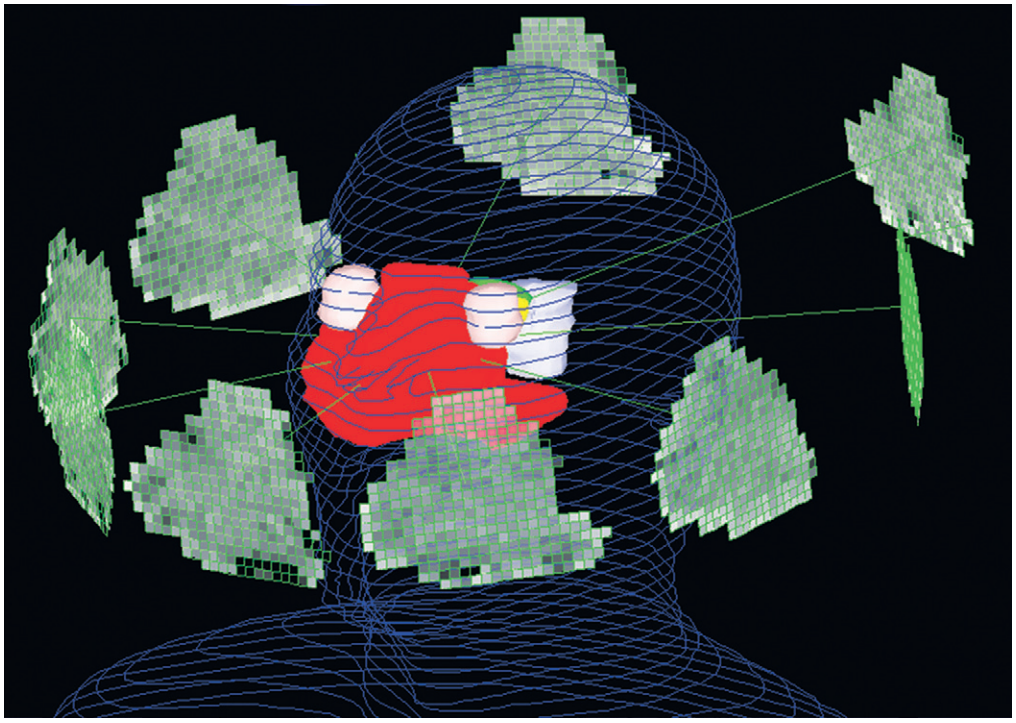

Figure 77-11. Intensity-modulated radiation therapy of head and neck cancer. Each *green* field represents a radiation field. The *red* field is the target, and the eyes are avoided.

Defining the Target: Imaging

The simulation contrast-enhanced CT is in most cases the only imaging modality required for the delineation of the targets. Magnetic resonance imaging (MRI) is a necessary adjunct to CT for tumors close to the base of skull, such as nasopharyngeal and paranasal sinus cancer, where it provides better details of tumor extension and of the parapharyngeal and retropharyngeal spaces than CT.[77,78] Another potential imaging modality for this purpose is fluorodeoxyglucose-positron emission tomography (FDG-PET). However, in a series of HNCs in which CT, MRI, and FDG-PET were obtained, and surgery was then performed to validate the primary tumor extent and lymph node involvement, a rather limited benefit of FDG-PET over CT and MRI was found.[79] PET-derived gross tumor volumes were smaller than those derived from CT and MRI, and surgical specimens were even smaller. However, when examined in detail, despite overestimation in most dimensions, all three imaging modalities actually underestimated the mucosal extent of disease.[79] Therefore, physical examination and laryngoscopy findings should be part of the definition in addition to image modalities such as CT and PET.

Selection and Outlining of the Targets

Target Definitions in the Head and Neck

As described previously, the gross tumor volume (GTV) consists of the primary tumor and of lymph nodes with apparent or suspected metastasis. The clinical target volume (CTV) surrounding the primary tumor consists of tissue perceived to contain microscopic, subclinical tumor extension. In addition to the primary tumor CTV, the lymphatic CTVs consist of nodal areas that are at risk for metastatic disease but that do not match the radiologic criteria for involved nodes.

Selection and Delineation of the Lymphatic Clinical Target Volumes

Our knowledge of the pattern and risk of lymphatic drainage from different head and neck sites is based on the classic anatomical work of Rouviere,[80] which has been reviewed,[81] the assessment of the location and prevalence of clinical neck metastasis by Lindberg[82]; and the large experience with elective neck dissections providing information about microscopic metastases, which was reported by Byers and colleagues[83] and Shah.[84] A division of the neck into six levels has been developed by surgeons from Memorial Hospital and revised by Robbins and associates.[85,86] The retropharyngeal nodes, which are not routinely dissected surgically, are not considered in the surgical neck levels classification but are important targets in the irradiation of nasopharyngeal and other advanced HNCs.[87]

The Planning Target Volumes

Once the GTVs and CTVs are outlined on the axial CT scans, a uniform expansion of these targets is performed to obtain the PTVs that accommodate setup uncertainties. Typically the magnitude of the margin is 3 to 5 mm, which means that an extra 5-mm ring of normal tissue around the target receives full dose. In a region with targets and organs at risk in close proximity, reducing this margin can potentially reduce treatment-related toxicity. Indeed, it has been estimated that each 1 mm of margin adds 1.3 Gy of dose to the parotid gland, which is particularly sensitive to low doses of radiation.[88] In order to reduce setup uncertainty, many groups have advocated daily imaging, with a position correction if the displacement from the original plan exceeds a threshold value. An example of the delineation of the targets and noninvolved structures in a case of oropharyngeal cancer is provided in Figure 77-12. The delivery of a single IMRT plan throughout the course of treatment provides better dose conformality than the use of several consecutive plans common in conventional radiotherapy, which consist of initial fields encompassing all targets followed with a boost to the gross tumor.[89] When a single plan is prescribed, the gross tumor PTV receives both a higher total dose and a higher dose per fraction than the PTVs of the subclinical disease. Owing to the differences in the daily fraction doses, a correction of the total dose to yield the normalized total dose for a 2-Gy fraction regimen is required. Therefore a standard IMRT plan would include 70 Gy over 35 fractions to the GTV, and lower fraction doses to the subclinical disease PTVs: 63 Gy to the high-risk and 56 to 59 Gy to lesser-risk elective targets, over 35 fractions (1.8 Gy and 1.6-1.7 Gy).

Dose and dose/volume specifications are made to impose constraints on the dose-volume histograms of the targets, noninvolved tissue of interest, and nonspecified tissue outside the targets. Radiation Therapy Oncology Group protocol H-0022 specified the prescription dose as the dose that encompasses at least 95% of the PTV. No more

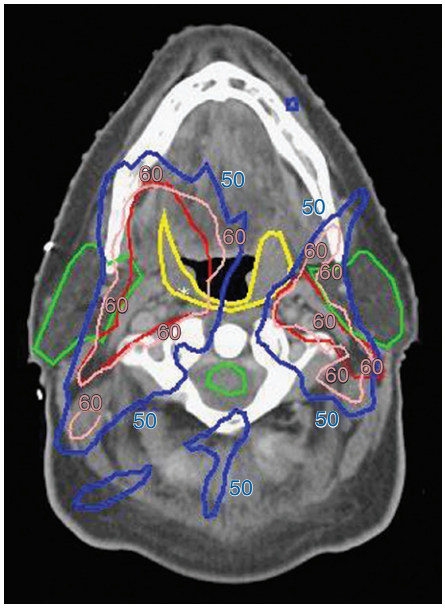

Figure 77-12. Dose prescription and specification and normal tissue dose constraints. *Green* represents the parotid gland; *red* represents CTV; *yellow* represents the constrictor muscle; and *blue* represents the 50 Gy line.

than 20% of the PTV can receive more than 110%, and no more than 1% of the PTV can receive less than 93%, of the prescribed dose.

Dose constraints regarding critical organs are usually stated in terms of the maximal dose. Commonly applied constraints in the head and neck are maximal doses of 45 Gy to the spinal cord, 54 Gy to the brainstem, 70 Gy to the mandible, and 50 to 55 Gy to the optic pathway.

The Optimization Process: The Number and Directions of the Beams

Although tomotherapy uses arcs around the patient, IMRT using multileaf collimators requires decisions regarding the number and orientation of the beams. It was suggested early on that if the number of segments (or beamlets) is large enough, the direction of the beams is not important, and coplanar beams arranged at equal distances around the patient's head and neck would achieve satisfactory results. Most investigations of IMRT of the head and neck with multileaf collimators use this approach. The beam number should be odd, to prevent opposed beams, which would increase hot spots near their entrances to the neck. Nine beams arranged equidistantly (40 degrees apart) were found to be optimal: They provided better dose distributions than five or seven beams, whereas fifteen beams did not seem to improve the plans.[90]

Clinical Results

Most studies comparing IMRT with conventional treatments are retrospective and therefore have a potential selection bias. IMRT is far more complex and time consuming than conventional radiotherapy. It is likely that different selection factors play a role in each institution: In patients who cannot tolerate lengthy treatment, those judged to be too sick to benefit from complex therapy, those requiring urgent start of therapy, more simple, conventional treatment may be selected. Therefore the comparison of IMRT with conventional RT in such situations would be futile. With this in mind, we would like to briefly summarize the existing results for specific sites.

Nasopharynx

The use of IMRT for the nasopharynx represents opportunities to spare many critical noninvolved structures and to improve tumor coverage, as detailed previously. These improvements have been demonstrated in several treatment planning exercises in nasopharyngeal and oropharyngeal tumors, in which IMRT plans were compared with "standard 3D" plans in the same patients.[91,92]

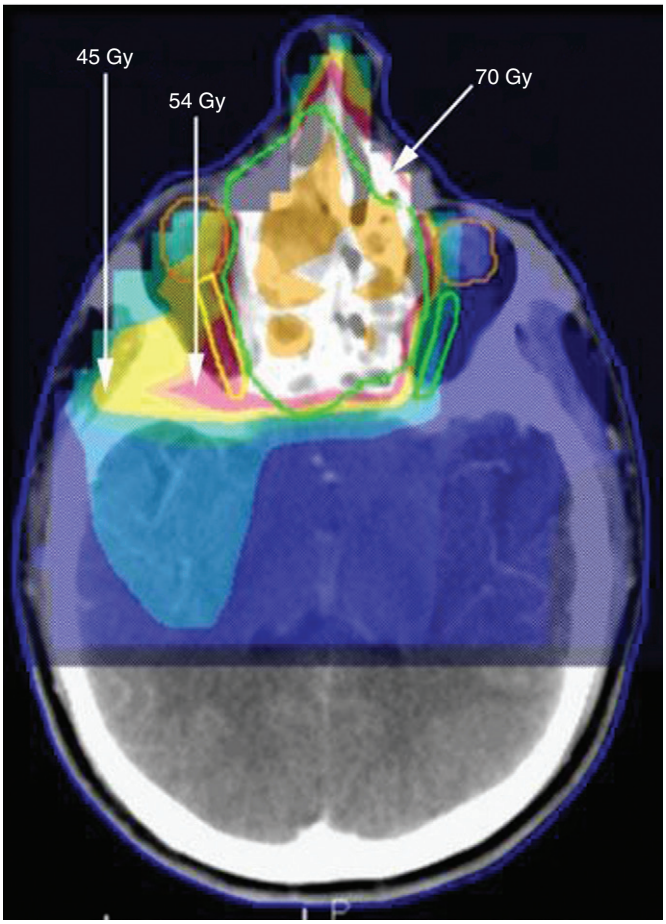

Figure 77-13. Radiation of sinuses with sparing of the optic nerves. *Green* represents GTV, to Gy dose; *yellow* is US Gy; and *pink* is SU Gy.

Two randomized prospective studies compared IMRT treatment with conventional treatment in early stage nasopharyngeal cancer.[93,94] Both showed similar high rates of tumor control and a benefit for IMRT for sparing of salivary flow. One of these studies demonstrated a benefit for IMRT in patient-related xerostomia.[93]

A large clinical series of IMRT of nasopharyngeal cancer has been reported by investigators at the University of California in San Francisco.[95] They studied 67 patients treated in the years 1995 to 2000. The GTV dose was 1.12 to 2.25 Gy/fraction to a total of 65 to 70 Gy, and the CTV dose was 1.8 to 2.0 Gy/fraction to a total of 50 to 60 Gy. In order to prevent under-dosing of the targets, the prescribed doses were typically the minimal doses encompassing the targets. The resulting delivered mean GTV dose was 74.5 Gy, at mean GTV fraction doses of 2.24 to 2.4 Gy. The resulting normalized total dose (calculated for late-responding tissue) was 80 Gy. This regimen yielded excellent locoregional tumor control: The rate was 97% at median follow-up of 31 months, with reasonable rates of acute toxicity. For re-irradiation of nasopharyngeal cancer, IMRT offers dose distribution advantages because it significantly reduces the extent of irradiation of the previously irradiated tissue volume. Lu and coworkers[96] described their experience with re-irradiation using IMRT for recurrent nasopharyngeal cancer. The rate of acute toxicity was acceptable, and at a median follow-up of 9 months, the locoregional control rate was 100%. Although longer follow-up is necessary, the preliminary toxicity and local control data for these recurrent cases are promising.[96]

Paranasal Sinuses

The main obstacle to adequate irradiation of tumors of the paranasal sinuses is the proximity of the optic pathways to the target in advanced cases. In these cases, IMRT can provide adequate target coverage while sparing the optic pathways (Fig. 77-13).

The group from the Royal Marsden Hospital found that compared with 3DCRT using the same beam arrangement, IMRT significantly reduced the dose to the optic nerves and improved PTV coverage.[97] Tsien and colleagues[98] at the University of Michigan found that IMRT planning in patients with nonresectable maxillary sinus cancer revealed no substantial difference between plans using an anterior field and two lateral fields and plans using nine equidistant beams arranged around the patient. Optimization using normal tissue complication probability (NTCP) of the optic nerves as an objective function was found to facilitate planning and to provide a basis for the assessment of the clinical trade-off between PTV coverage and ipsilateral optic nerve sparing.[98]

A large clinical series of IMRT for paranasal sinuses was reported from Ghent University in Belgium.[99] 39 patients were treated postoperatively, and the 4-year actuarial local control after surgery and IMRT was more than 80% for patients with T1-4aN0M0 disease. In the group undergoing IMRT, there was significantly lower incidence of severe dry-eye syndrome than in the historical cohort.

Oropharynx

In general, all series investigating IMRT for oropharyngeal cancer have reported outstanding locoregional control rates.[92,100] These series reported 2-year locoregional tumor control rates of 90% to 98% for patient populations who mainly had stage III or IV tumors. However, these results should be evaluated in the context of a likely selection bias and, importantly, with consideration of the emergence of human papillomavirus–related oropharyngeal cancer, which is associated with better prognosis.[101]

Some of the most reliable information gained from clinical series of IMRT for HNC in general, and oropharyngeal cancer in particular, relates to the pattern of tumor recurrences relative to the targets and the locally delivered doses. These data allow an assessment of the adequacy of target selection and delineation. In all reported cases, it seems that careful selection and delineation of the targets resulted in very few or no marginal or out-of-field recurrences. De Arruda and colleagues[100] reported that all recurrences in their series were in-field. In the series by Chao and coworkers,[102] most marginal recurrences were in the lower neck, which was treated with an anterior field that was matched to the IMRT-treated upper neck. In the series reported by Eisbruch and associates,[87] in which the majority of patients had oropharyngeal cancer, almost all recurrences were in-field, in high-risk volumes that had received the full prescribed doses.

Larynx and Hypopharynx

IMRT can improve target dose homogeneity for laryngeal and hypopharyngeal SCC while reducing the dose to the normal tissues at risk.[103-105] Clinical data on IMRT for laryngeal and hypopharyngeal SCC are scarce, however, and include limited numbers of patients within large heterogeneous series of multiple HN tumor sites.[87,95,105] In general, these series showed lower tumor control rates than those reported for oropharyngeal sites. Potential reasons could be patient selection factors. For example, at the University of Michigan, only patients with laryngeal cancer and advanced nodal disease receive IMRT. The reason is that for patients with nodal stage 0 to 1, the uppermost nodes at level II are the subdigastric nodes, which can be treated with conventional techniques while sparing the majority of the parotid glands and avoiding the oral cavity; the retropharyngeal nodes or level II near the base of skull are not at risk in these patients. Another small study has suggested a benefit in xerostomia without a compromise in local control (94% at 2 years) in advanced node-negative laryngeal cancer.[106]

In general the main intent in IMRT planning is preservation of function. One of the main issues is reducing xerostomia via the sparing of the parotid salivary glands and submandibular glands. According to one study, the mean dose of 26 Gy is the threshold for parotid gland sparing (see Fig. 77-12),[107] and patients in whom at least one functioning parotid gland was spared enjoyed significant preservation of salivary flow and reduced xerostomia.

Other potential functional gains from IMRT compared with conventional RT include reduced long-term dysphagia. Sparing of pharyngeal constrictors and the glottic and supraglottic larynx may be beneficial in this regard.[108]

Proton Therapy

Currently, all centers utilize photons, or high-energy x-rays, for their IMRT treatments. However, because of their inherent physical characteristics, protons are better able to concentrate dose inside targets and minimize dose to surrounding normal tissues. Most of the energy of a proton beam is deposited near the end of the beam path (Bragg peak), the location of which is determined by the energy of the beam. Thus, the target can be included in the tissue volume receiving the high dose while little is delivered before or after the beam passes through the target, and the integral dose delivered outside the targets is lower than the dose delivered using IMRT. Use of proton beams would be expected to reduce the risk of secondary malignancies, which is especially important in pediatric cancer patients.[109] With the use of inverse planning, intensity-modulated proton therapy (IMPT) can further improve the therapeutic index of radiotherapy. Several groups have published treatment planning comparisons of (photon) IMRT with IMPT.[110-112] Using IMPT, mean doses to the organs at risk—the parotid glands, in particular—have been reduced by as much as 50%. However, because IMPT has been used for only a few years, long-term clinical treatment results are not yet available. The areas in the head and neck that could benefit from the added conformality achievable with protons are the paranasal sinuses and nasopharynx, which are often in close proximity to the optic nerves and chiasm, as well as the brain. Retrospective reviews of 3D conformal proton therapy suggest high local control rates with minimal toxicity, including preservation of vision in patients with advanced sphenoid sinus cancers.[113]

Neutron and Carbon Ion Therapy

In addition to protons, other particles have been used to treat HNCs. Neutrons have found a niche in treatment of salivary gland tumors, after a small trial randomly assigning patients to photon or neutron radiotherapy demonstrated a survival benefit for neutron therapy.[114] Other ions, including helium, neon, and carbon, have been investigated over the past 50 years. Currently, carbon ion therapy shows the most promise. Compared with photons, carbon ions have the conformality advantage of protons, with the additional advantage of a greater relative biologic efficacy (RBE): A smaller dose of carbon ions is required to achieve the same biologic effect as a reference dose of photons. This difference is due to a higher linear energy transfer with carbon ions, which theoretically causes more irreparable DNA damage, is more effective in hypoxic cells, and is less subject to variation in radiosensitivity with cell cycle. Currently, few centers worldwide are able to treat with this modality. Initial results in adenoid cystic carcinoma and locally advanced SCC of the head and neck, which demonstrate excellent local control rates with low toxicities, are promising.[115] However, long-term results are not yet available.

Imaging-Guided Radiotherapy

The term *imaging-guided radiotherapy* relates to the performance of patient and tumor imaging with electronic portal imaging devices (EPIDs) or CT before each fraction or every few fractions of therapy in order to ensure tracking of the tumor by the treatment beams. In cancer of the head and neck, where breathing-related motion is inconsequential, imaging-guided radiotherapy has two main goals, minimizing setup uncertainties, thereby enabling reduction of the PTV margins, and assessing anatomic changes in tumor and critical tissue during the course of therapy.

Tracking Anatomic Changes during Therapy

During the 6- to 7-week course of radiotherapy, many anatomic changes can occur. Because dose distributions achieved using IMRT have steep gradients, and PTV "safety" margins are becoming smaller, it is especially important to understand the consequences of anatomic changes during therapy for the dose to both targets and normal tissues. In definitive cases, the primary tumor, nodes, or both can shrink, whereas in postoperative cases, inflammation and edema can resolve. Additionally, weight loss, a common consequence of acute treatment toxicity, can lead to muscle wasting and shifting of both normal tissue and tumor positions. Barker and associates[116] conducted a detailed study of such anatomic changes during radiotherapy for HNC.[116] The

primary tumors and nodes were noted to shrink at a median rate of 1.8% of the initial volume per treatment day, so that on the last day of treatment, the median overall volume loss was close to 70%. The parotid glands moved medially during treatment, the median displacement at the end of therapy being 3.1 mm. These changes were highly correlated with patient weight loss. After publication of these findings, several investigators suggested replanning during treatment to minimize parotid gland dosage while maximizing tumor dosage. This issue is subject to ongoing studies.

Brachytherapy

As described previously, brachytherapy is localized radiotherapy that uses many radioactive isotopes, such as radium Ra-226 and cesium Cs-137 needles for implants in certain cases or afterloading techniques using iridium Ir-192 sources.[117] These sources produce a lower-energy gamma ray, thus simplifying the radiation protection requirements associated with routine patient care. The sources are left in place for a specified time and then are removed. Alternatively, permanent implants using gold Au-198 and iodine I-125 can be used. These implants deliver their total radiation dose over the effective lifetime of the radioactive material. The obvious advantages of implants are better dose localization, which results in less radiation damage to the healthy tissue surrounding the tumor, and the relatively prolonged time over which the radiation is delivered. The disadvantages include lack of addressing subclinical disease and the requirement for general anesthesia in many cases.

External-beam radiation is given at the rate of 1.5 to 2.0 Gy per minute.[118] A typical Ir-192 implant delivers its dose at the rate of 0.4 to 0.8 Gy per hour. High-dose-rate (HDR) remote afterloading devices have also been developed. These devices push a single, high-activity Ir-192 source through a set of interstitial catheters, and a computer program controls the source dwell time at various points throughout the implant. Typically, about 3.0 to 3.5 Gy is given to a distance of about 1 cm from the periphery of the catheters each treatment, and up to two daily treatments are given about 6 hours apart. Each treatment takes about 15 to 30 minutes, depending on the strength of the radioactive source and the complexity of the implant.

Radiation Side Effects

Acute Side Effects

Acute reactions that can occur during irradiation with or without chemotherapy are predictable toxicities, and depend on the dose and schedule of radiation therapy used and the accompanying chemotherapy. Such effects include mucositis, odynophagia, dysphagia, hoarseness, xerostomia, dermatitis, and weight loss. These effects occur to some degree in the majority of patients, but they are self-limited in duration.

Acute complications can interfere with and delay treatment. Even short delays can be deleterious, interfering with local tumor control.[119,120] In one study, for example, a 5-day delay in completing RT was associated with a 3.5% to 8% reduction in local control for laryngeal cancers.[120] The effect was greater in tumors with a higher probability of local failure. In addition to treatment-related factors, the nature, frequency, and severity of complications are heavily influenced by tumor-related factors (e.g., location, invasion of vital structures) and patient-related factors (e.g., oral hygiene, nutritional status, continued tobacco use, and history of diabetes, collagen vascular disease or human immunodeficiency virus).

The following sections discuss the most common acute side effects:

Dermatitis

Radiation damage to stem cells in basal layers of the skin can give rise to a sunburn-like desquamation. This can be aggravated by chemotherapeutic agents such as 5-FU. These effects can occur as early as 2 weeks after the start of radiotherapy.

This side effect can be minimized through appropriate skin care, avoidance of exposure to potential chemical irritants, limitation of direct sun exposure, and avoiding application of lotions, ointments, or fragrances to the head and neck region to minimize the bolus effect that might alter the depth at which the maximum RT dose is delivered. IMRT typically worsens skin reaction because of the multiple target beams, but this effect can be reduced by specifying the skin as an avoidance structure and by treating the lower neck with an anterior beam rather than including it in the IMRT plan.

Xerostomia

The severity of xerostomia resulting from RT for HNC depends on the volume of salivary tissue irradiated. Temporary loss of saliva is significant after about 10 Gy is delivered to the salivary glands, whereas administration of doses significantly higher than 26 Gy can cause permanent loss of function. Alteration in taste can also occur, and decreased oral intake may contribute to reduced saliva production.

Prevention of this side effect can be performed by reducing salivary gland dosage in formal planning. Some suggested that the use of amifostine may reduce xerostomia. The benefit of amifostine was shown in a landmark trial of 315 patients receiving RT alone (60 to 70 Gy in 1.8- to 2.0-Gy daily fractions), who were randomly assigned to receive either amifostine or no amifostine.[121] Amifostine reduced the incidence of significant acute xerostomia from 78% to 51% and the incidence of significant chronic xerostomia at 12 months from 57% to 34%. This agent had no impact on rates of mucositis or on tumor control at 2 years.[121] However, data on the effect of amifostine in the chemoradiation setup are conflicting,[122,123] other than that it has severe side effects and is expensive and therefore has not been widely used.

Mucositis

Radiation-induced loss of stem cells in the basal layer interferes with the replacement of cells in the superficial mucosal layers when they are lost through normal physiologic sloughing. The subsequent denuding of the epithelium results in mucositis, which can be painful and can interfere with food intake and nutrition. Mucositis usually develops 2 to 3 weeks after the start of RT. The incidence of mucositis is variable, depending on the field, the total dose and duration of RT, and the concomitant administration of chemotherapy.[124] In one series, clinically significant mucositis occurred in 64% of patients receiving RT to the head or neck for any malignancy.[125] Both incidence and severity are higher in patients receiving chemoradiotherapy than in those undergoing RT alone. Chemotherapy can have a similar effect on the mucosa, and the combination of chemotherapy with RT increases the rate of mucositis especially when the modalities are delivered concurrently. Mucositis is managed symptomatically with scrupulous oral hygiene, dietary modification, and topical anesthetics. A variety of agents have been evaluated for use either prophylactically or after the onset of symptoms; their role in the treatment of radiation-induced mucositis is uncertain (Fig. 77-14).

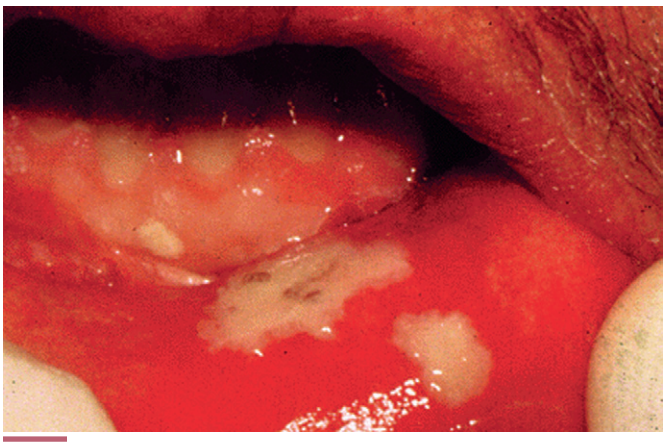

Figure 77-14. Acute mucositis.

Late Toxicities

Xerostomia

Xerostomia is a frustrating side effect that may lead to many other effects. It often improves with time,[126] but it can be long-lasting or even permanent. Regarding treatment, several strategies may minimize the incidence of xerostomia. When possible, sparing one parotid gland and, if possible, the submandibular glands can greatly diminish the incidence of xerostomia.[127] Commercially available salivary substitutes or artificial saliva (oral rinses containing hyetellose, hyprolose, or carmellose) relieve the discomfort of xerostomia by temporarily wetting the oral mucosa. Although they can provide temporary relief, especially prior to eating, many patients must take frequent sips of water to remain comfortable. In addition to being inconvenient, this can lead to secondary problems such as nocturia from late night fluid intake in men with prostatic hypertrophy and in men and in women with small bladder capacity. In patients in whom untreated or unaffected residual salivary tissues are intact, sialagogues that stimulate salivary production may be used. Sialagogues can be characterized as gustatory, tactile, or pharmacologic. Gustatory stimuli such as acidic or bitter substances are most effective at stimulating salivary flow.[128] Sweet substances such as sugar-free hard candy also stimulate the flow of saliva, but to a lesser extent. Pharmacologic sialagogues, which are typically agonists of the muscarinic (M3) receptor, include pilocarpine and cevimeline. Of these, pilocarpine has been the most extensively investigated. Pilocarpine may improve or prevent xerostomia when given after completing radiotherapy. Improvement in symptoms may occur only after many weeks of treatment, and cholinergic side effects, in particular sweating, may stop a significant number of patients from continuing to use the drug.[128]

Osteoradionecrosis

Osteoradionecrosis (ORN) of the jaw is a severe complication of RT for HNC. The presentation of post-RT ORN ranges from small asymptomatic bone exposures that remain stable for months to years and heal with conservative management, to severe necrosis necessitating surgical intervention and reconstruction. Depending on the location and extent of the lesion, symptoms can include pain, bad breath, dysgeusia, dysesthesia or anesthesia, trismus, difficulty with mastication, deglutition, and/or speech, fistula formation, pathologic fracture, and local, spreading, or systemic infection. The mandible is the most commonly affected bone, because in the majority of patients undergoing treatment for HNC, a large part of it is inevitably exposed to high RT doses. Another reason is the blood supply of the mandible, which is unilateral; the maxilla has bilateral blood supply. Maxillary ORN is reported infrequently, usually in the setting of irradiation for nasopharyngeal cancer (in which both jaws are at risk).

Mandibular ORN occurs in 5% to 10% of patients treated with conventional RT or high-dose-rate brachytherapy, and is severe in about 2%.[129,130] The incidence of this complication appears to be higher with hyperfractionated regimens, especially with a short inter-fraction interval. In one study of 168 patients with oral cancer treated with hyperfractionated or conventional RT, the incidence of ORN was higher with hyperfractionated therapy (23% vs. 9%, respectively).[130] Tooth extraction and dental disease in irradiated regions are major factors in the development of both mandibular and maxillary ORN.[129,130] Although opinion differs as to whether extraction of diseased and nonrestorable teeth should be performed before or after irradiation, many writers report that postirradiation extraction of such teeth produces a higher rate of mandibular ORN.[131] Furthermore, at least some data suggest that mandibular ORN associated with postirradiation tooth extraction more often requires radical resection than does ORN that develops after pre-irradiation extraction (45% vs. 12%, respectively).[132] Repair of nonrestorable and diseased teeth prior to RT may reduce the risk of this complication. However, most authorities do not recommend the pre-irradiation extraction of healthy or restorable teeth.

Ben-David and colleagues[133] demonstrated that rates of ORN could be significantly lower if the following rules were observed: reducing the mandibular volumes receiving high doses, improved salivary flow rates and associated improved oral health, and uniform prophylactic dental care. For mild ORN, treatment with conservative débridement, antibiotics, and occasionally ultrasound is usually successful.[134] However, when bone and soft tissue necrosis are extensive, radical resection of the mandible with immediate microvascular reconstruction may provide better results.[135] Persistence of ORN despite aggressive treatment should raise the suspicion of recurrent cancer.[135]

Hyperbaric oxygen therapy (HBO) has been suggested as a beneficial therapeutic maneuver in patients in whom ORN of the jaw develops after RT. ORN may be triggered by a predominantly fibroatrophic mechanism.[136] At least in theory; HBO simulates the function of monocytes and fibroblasts, increasing collagen synthesis and vascular density. Despite this theoretical rationale, the available data are conflicting, as to clinical benefit, of HBO for both prevention and therapy of ORN. The benefit from HBO was called into question by results of a randomized multicenter trial in which 68 patients with overt mandibular ORN were randomly assigned to receive either 30 to 40 exposures to HBO or a placebo at 2.4 absolute atmospheres for 90 minutes.[137] Healing rates were equivalent in the two groups and in fact trended toward worse in the HBO group (19%, compared with 32% for placebo; $P = .23$). Although this was only a single study and did not include patients receiving HBO prior to dental extraction, its results raise doubt about the efficacy of HBO for ORN.

Fibrosis

A serious complication of RT in the treatment of cancer patients is the late-onset of fibrosis in normal tissues, including the neck, pharynx, esophagus, and temporomandibular joint. Radiation-induced fibrosis (RIF) is similar to inflammation, wound healing, and fibrosis of any origin. Typical histologic features include the presence of inflammatory infiltrates (particularly macrophages in the earlier stages of fibrosis), differentiation of fibroblasts into postmitotic fibrocytes, and changes in the vascular connective tissue with excessive production and deposition of extracellular matrix proteins and collagen. RIF can cause a wide range of clinical manifestations, including cutaneous induration, lymphedema, restrictions in joint motion, strictures and stenoses in hollow organs, and ulcerations. Specifically in the head and neck region it may cause trismus, which can progress over time. RIF in the esophagus and hypopharynx may lead to strictures, ulcerations, and fistula formation. Radiation fibrosis to the constrictor muscles may lead to chronic dysphagia. The best way to prevent this side effect is conformal planning to spare unnecessary radiation.

Thyroid Dysfunction

Irradiation of the low neck is associated with hypothyroidism. The incidence varies widely and is dose-dependent as well as time dependent, increasing with time elapsed since treatment. RT-induced hypothyroidism develops at a median of 1.4 to 1.8 years (range 0.3 to 7.2 years) after RT.[138] It is more common in patients undergoing both neck surgery and RT but is not higher in patients who undergo chemotherapy in addition to RT than in those who have RT alone.

Vascular Complications

Carotid artery rupture (also called carotid blowout syndrome) and oropharyngocutaneous fistula are major complications associated with RT to the neck. These sequelae occur almost exclusively in patients who have received combined surgery and RT. As an example, in one series of 46 patients with carotid artery rupture, 43 had undergone extensive primary and salvage radical surgery with intraoperative brachytherapy, external beam irradiation, or both.[119] Both retrospective and prospective studies show that both carotid artery rupture and oropharyngocutaneous fistula occur more often with preoperative than postoperative irradiation.

Carotid rupture and fistula are rarely observed after definitive RT with or without concomitant chemotherapy but may be more common when tumor is invading the carotid sheath or extending into and occupying a large volume of the soft tissue of the neck.[139] Patients with ORN of the temporal bone after definitive treatment for nasopharyngeal cancer are also at risk for carotid artery rupture.

The most common angiographic abnormality seen in one study was one or more pseudoaneurysms.[140] Although this devastating complication can sometimes be managed with endovascular therapy, it recurs in up to 25% of patients, often as a manifestation of recurrent tumor or of multifocal iatrogenic arteriopathy and occasionally wound complications.

Neurologic Complications

Radiation therapy can cause toxicity to either the central or peripheral nervous system when these structures are included in the treatment field. Nervous system toxicity is usually subdivided into acute (during the course of radiation), early delayed (weeks to three months after radiation), and delayed reaction (after more than 3 months). Late toxicity is the most common.

A transient myelopathy may develop 2 to 6 months following spinal irradiation. This condition is widely believed to be due to temporary demyelination of the posterior columns of the spinal cord. Self limiting, it is generally not a precursor of chronic progressive myelitis. The characteristic manifestation is the development of Lhermitte's sign, a nonpainful but unpleasant electric shock–like sensation that shoots down the spine during neck flexion. Increased spinal cord metabolic activity and PET imaging have been described in association with Lhermitte's sign.

Radiation myelopathy may begin acutely, but more often the onset is insidious. Paresis, numbness, and sphincter dysfunction developing 6 to 12 months after irradiation are the typical manifestations of progressive radiation-induced myelitis. However, the initial signs can be subtle, such as decreased temperature sensation and decreased proprioception. These signs may stabilize or slowly progress inexorably to lower extremity weakness, footdrop, the Brown-Séquard syndrome, incontinence, hyperreflexia, loss of bowel and bladder function, and complete paresis below the irradiated section of the spinal cord. The risk of chronic radiation myelopathy rises progressively with the dose of radiation.[141] Evidence derived from several large series suggests that the incidence of myelopathy is less than 0.5% after 50 Gy with conventional fractionation.[141] The best estimate of the dose expected to cause a 5% risk of myelopathy within 5 years (sometimes called the TD 5/5) is approximately 60 Gy if the radiation is given in 1.8- to 2.0-Gy daily fractions. This dose value appears to be independent of the region or length of spinal cord treated. The risk of myelopathy increases rapidly with doses above 60 Gy, with one series reporting an incidence of 50% in patients receiving between 68 and 73 Gy to the spinal cord.[141]

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CHAPTER SEVENTY-EIGHT

Chemotherapy and Targeted Biologic Agents for Head and Neck Cancer

William N. William, Jr.

Merrill S. Kies

Key Points

- Combined-modality therapy is an acceptable treatment option for patients with locally advanced squamous cell carcinoma of the head and neck in three clinical scenarios: (1) chemoradiation delivered concurrently for organ preservation, (2) chemoradiation as adjuvant therapy after definitive surgical resection, and (3) induction chemotherapy, also termed neoadjuvant chemotherapy, delivered before definitive treatment with surgery or irradiation.
- In the setting of organ preservation for cancers of the larynx and hypopharynx, chemotherapy followed by radiation therapy has been shown to produce similar survival, but higher larynx preservation rates, in comparison with surgery followed by postoperative irradiation. Chemotherapy delivered concomitantly with radiation therapy has better laryngeal preservation rates than single-modality radiation therapy.
- In the setting of adjuvant therapy after definitive surgical resection, cisplatin delivered concomitantly with radiation therapy results in higher overall survival than single-modality radiotherapy, especially in patients with high-risk features in the surgical specimen (i.e., positive margins, extracapsular nodal extension).
- Induction chemotherapy is not yet considered standard of care for patients with locally advanced head and neck cancers. However, when induction chemotherapy is used, regimens containing docetaxel, cisplatin, and 5-fluorouracil are associated with longer survival time than cisplatin–5-fluorouracil doublets.
- In the setting of recurrent/metastatic disease, regimens containing two cytotoxic drugs produce a higher response rate than single-agent regimens; however, this rate does not translate into an increase in survival.
- Molecular targeted agents directed at the epidermal growth factor have emerged as important strategies for the treatment of head and neck cancers. Cetuximab has been shown to improve survival, when added to radiation therapy, for patients with locally advanced disease. Cetuximab added to platinum/5-fluorouracil doublet chemotherapy achieves better survival than platinum/5-fluorouracil in patients with recurrent/metastatic disease. In this setting, cetuximab is also active as monotherapy in patients in whom a platinum-based regimen has failed.

The otolaryngologist frequently cares for patients with head and neck cancer who will receive chemotherapy as a component of treatment. Often, these patients have locally advanced squamous cell cancer or metastatic disease not amenable to curative therapy with surgery or irradiation. Chemotherapy may be administered concomitantly with radiotherapy (concurrent therapy), before definitive radiotherapy or surgery (induction/neoadjuvant therapy) or as a single-modality treatment for patients with recurrent or metastatic disease not amenable for cure (palliative approach). Biologic agents targeted at specific molecular pathways involved in carcinogenesis (e.g., the epidermal growth factor receptor [EGFR] pathway) have been increasingly used in these settings as well. This chapter focuses on chemotherapy and targeted biologic therapy for squamous cell carcinoma of the head and neck (SCCHN).

Surgeons treating SCCHN should be familiar with (1) the basic principles of integrating systemic therapy as a component of combined-modality programs, (2) the design and results of the key clinical trials that support the use of chemotherapy and/or biologic agents in the concomitant, induction, and palliative therapy settings, and (3) promising experimental approaches of chemotherapy and targeted agents under study for the treatment of these tumors.

Squamous Cell Carcinoma

Before 1970, chemotherapy had a limited role in the management of squamous cell cancer of the head and neck in community practice and at academic centers. Part of the reason was the paucity of available drugs with documented antitumor activity for this disease. The only drug

with clearly established activity, used worldwide, was the folic acid analogue methotrexate. Many other drugs have since been tested, although the assessment criteria used to define response years ago were not uniform. Hence, the reported response rates tended to be unreliable, representing an accumulation of observations of any degree of tumor regression. In contrast, during the past decade, more rigid criteria have been applied to the testing of potentially useful drugs. There are now clearly defined parameters for the objective evaluation of response and survival time as well as statistical guidelines for the design of clinical research trials to establish efficacy or to show improvement in comparison with standard therapies.

The serendipitous identification of the metal compound cisdiamine-dichloroplatinum (II) (cisplatin) as a potential anticancer agent by Rosenberg[1] in 1968 spurred clinical research efforts to test new agents and to develop combination chemotherapy regimens for the palliative benefit of patients with locally recurrent and metastatic cancers. After highly active chemotherapy regimens were identified, drug therapy was incorporated into combined-modality approaches for treating the newly diagnosed patient. The objectives then changed, with more focus on increasing tumor eradication in order to improve survival time. It became clear that if administered as the initial treatment, chemotherapy could result in rapid regression of tumor in the majority of patients without substantially increasing the morbidity of subsequent surgery or irradiation. Moreover, in a proportion of patients with responding tumors, there is no histologic evidence of tumor in resected specimens. This observation led to consideration of altering standard surgical approaches to some primary tumors with the objective of organ preservation. In addition to investigational trials using chemotherapy before definitive local therapy, adjuvant radiation and chemotherapy administered after surgical resection and chemotherapy used as a radiosensitizer concomitant with radiotherapy have been under active study.

A new class of drugs (i.e., targeted biologic agents or molecular targeted agents) has become available for the treatment of cancer. These compounds have a distinct mechanism of action, blocking specific molecular pathways key to the carcinogenic process. As a result, molecularly targeted drugs exhibit antiproliferative, proapoptotic, antiangiogenic and chemotherapy/radiotherapy-sensitizing properties that contribute to antineoplastic effects. Adverse events associated with these drugs are very distinct from the classic side effects observed with cytotoxic agents and are largely determined by the target pathway inhibited. Bonner and colleagues[2] demonstrated that cetuximab (a biologic agent targeted at EGFR), given concomitantly with radiotherapy, improves survival of patients with head and neck cancer, with no increased incidence of severe radiotherapy-induced side effects. This study can be accepted as proof of principle that biologic agents may become substantial therapeutic agents for this disease. Moreover, the report inaugurates an exciting era for both research and clinical management of SCCHN.

In the next sections, the roles of chemotherapy and biologic therapy in the treatment of locally advanced and recurrent or metastatic squamous cell carcinomas are discussed. Systemic therapy as a single-modality treatment has a limited or no role as a curative treatment option. However, the addition of chemotherapy given concomitantly with radiotherapy has been demonstrated to improve local control and survival, both as definitive treatment with organ preservation and after surgical resection. For locally advanced disease, chemotherapy given as an induction strategy before definitive irradiation or chemoradiation (induction) may also affect survival, especially with combination regimens utilizing a taxane, cisplatin, and 5-fluorouracil (5-FU).

A role for human papillomavirus (especially subtype 16) has now been recognized in the pathogenesis of a substantial percentage of oropharyngeal squamous cell carcinomas.[3] Transmission is sexual. The E6 and E7 viral oncogenes are overexpressed and associated with degradation of wild type p53. Indeed, molecular studies[4] suggest that human papillomavirus–positive tumors have relatively minimal genomic alterations and that, stage for stage, prognosis is better than that for human papillomavirus-negative tumors, which tend to have multiple cytogenetic changes, p53 mutations, loss of p16, cyclin D1 overexpression, and increased surface expression of EGFR.

Combined-Modality Therapy

Although surgery and radiotherapy achieves cure in a high percentage of patients with early-stage SCCHNs, conventional treatment does not achieve cure for the majority of those with locally advanced disease, and treatment for recurrent disease with chemotherapy is far from satisfactory. Thus, much effort has been directed toward improvements in primary treatment programs with advances in combined-modality therapy. To this end, the following three general approaches have been established:

- Chemoradiation for organ preservation, in which chemotherapy is given simultaneously with radiotherapy to enhance its effect as a definitive, potentially curative treatment
- Chemoradiation as adjuvant therapy, in which chemotherapy and radiotherapy are simultaneously administered after surgery in high-risk patients in an effort to improve local control and to decrease the metastatic disease burden, thus improving survival
- Induction chemotherapy, also known as neoadjuvant therapy, in which chemotherapy is given before surgery or radiotherapy in a sequential format

Concomitant Chemoradiation

For early-stage cancers of the larynx, definitive radiotherapy or conservation laryngeal surgery produces excellent tumor control with preservation of speech and swallowing functions. These approaches are discussed in Chapter 112. A majority of patients with SCCHN present with stage III to IV M0 disease and may require extensive or radical surgery, with potential deleterious effects on speech or swallow function, depending upon the primary tumor site. Of course, general appearance may also be altered. In the 1990s, the dual objectives of improving survival and preserving organs represented a major challenge and became a focus for clinical trial development. This led to the Department of Veterans Affairs (VA) Laryngeal Cancer Study,[5] which tested a nonsurgical alternative for locally advanced squamous cancer of the larynx, matching induction chemotherapy followed by definitive radiation against laryngectomy with postoperative radiotherapy. Thus, initial drug treatment as a component of primary treatment in sequence before definitive radiotherapy was tested in a prospective, phase III randomized trial.

Induction chemotherapy with cisplatin-based regimens is highly active, with clinical partial and complete responses observed in 80% to 90% of previously untreated patients. It was postulated that a substantial response to initial treatment with chemotherapy would lead to an improvement of therapeutic efficacy for surgery or radiotherapy. If so, radiotherapy might then become an acceptable alternative to laryngectomy with preservation of prospects for tumor control and organ function. In the VA Study, 332 patients with stage III or IV squamous cell carcinoma of the larynx were randomly assigned to receive either induction chemotherapy consisting of cisplatin and 5-FU followed by radiotherapy or surgery with postoperative radiotherapy.[5] Patients who experienced no tumor response to chemotherapy or those who had locally persistent or recurrent cancer underwent salvage laryngectomy. Two-year survival for both treatment groups was 68%, and 41% of patients randomly assigned to the experimental arm were alive with a functional larynx at 2 years. Thus, the efficacy of chemotherapy followed by radiotherapy (with surgical salvage) was similar to that of surgery followed by radiotherapy, establishing organ preservation as a realistic goal of nonsurgical treatment administered with curative intent. Lefebvre and colleagues[6] later reported data from a European trial involving patients with cancers of the hypopharynx. In this randomized study, comparing induction chemotherapy followed by irradiation in subjects who had complete response with surgical resection and postoperative radiotherapy, overall survival rates in the two arms were considered equivalent, again demonstrating that larynx preservation could be achieved in some patients without jeopardizing their survival. Calais and associates[7] presented data from GORTEC (Groupe d'Oncologie Radiotherapie Tête et Cou) 2000-01, which compared induction chemotherapy using cisplatin and 5-FU with 5-5-FU (TPF)

Table 78-1

5-Year Update for Radiation Therapy Oncology Group 91-11

Therapy Protocol	% RT Compliance	% Laryngectomy-Free Survival	% Larynx Preserved
PF → RT	84	45 (P = .01 vs. RT)	71
RT + P	91	47 (P = .01 vs. RT)	84 (P < .01 vs. RT)
RT alone	95	34	66

F, fluorouracil; P, cisplatin; RT, radiation therapy; →, followed by.
Data from Forastiere A, Maor M, Weber RS, et al. Long-term results of intergroup RTOG 91-11: a phase III trial to preserve the larynx—induction cisplatin/5FU and radiation therapy versus concurrent cisplatin and radiation therapy versus therapy. *Proc Am Soc Clin Oncol.* 2006:24(No 18S); 5517.

or without docetaxel for organ preservation in hypopharynx and larynx cancer. In 220 patients, preliminary results show a superior overall response rate of 83% with TPF, versus 61% for cisplatin and 5-FU. The rate of larynx preservation was also better, offered in 80% of patients in the TPF arm, versus 58% in the cisplatin and 5-FU arm. Neutropenia was greater in the experimental arm (57% vs. 35%). On balance, TPF demonstrated a significantly superior tumor response rate, was tolerated with acceptable toxicity, and appeared to be associated with better larynx preservation.

In the VA study,[5] there were observed trends in patterns of tumor relapse, with 20% of patients in the chemotherapy arm having locoregional recurrence, compared with 7% in the surgery arm. Distant disease recurrence was more likely in the surgical arm, affecting 17% of patients in that group, but only 11% in the chemotherapy/radiotherapy arm. Salvage laryngectomy was required more often in patients with glottic cancers than in those with supraglottic primary sites (43% vs. 31%, respectively), in patients with fixed vocal cords than in those with mobile vocal cords (45% vs. 29%), and in patients with gross invasion of thyroid cartilage than in patients without (41% vs. 35%). Notably, salvage laryngectomy was required in 56% of patients with T4 cancers but in only 29% of patients with smaller primary tumors (P = .001).

The VA study has prompted further investigations of chemotherapy and radiotherapy in the treatment of intermediate-stage laryngeal cancer using the sequential administration of induction chemotherapy, consisting of cisplatin and 5-FU, followed by radiotherapy as the control arm.[8] In a study reported in 2003 by Forastiere and colleagues,[8] called the Intergroup Radiation Therapy Oncology Group (RTOG) 91-11 trial, this modality was compared with concomitant cisplatin and radiotherapy and with radiotherapy administered as a single treatment modality. For all groups, totaling 547 patients, surgical salvage was reserved for patients with persistent or locally recurrent disease. Eligible patients had stage III or IV disease, but all of those with T1 and most of those with T4 disease were excluded. The rate of preservation of the larynx was greatest in patients receiving concomitant chemoradiotherapy, and the difference between it and the preservation rate in patients receiving radiotherapy as a single modality reached statistical significance. Survival was not affected by treatment assignment. Acute mucocutaneous toxic effects of treatment were greatest in the patients who received radiotherapy with concomitant cisplatin.

In 2006, Forastiere and colleagues[9] provided a 5-year analysis of Intergroup RTOG 91-11 data (Table 78-1). Most notably, laryngeal preservation was greatest in those patients randomly assigned to concomitant radiotherapy with cisplatin (84% vs. 66% with radiotherapy alone; P = .0002). Data for patients living with preservation of the larynx was similar when contrasted with the cisplatin and 5-FU induction arm with concomitant chemoradiation. Moreover, overall survival was 59% in the induction arm compared with 55% in the concomitant chemoradiation arm, not a statistically significant difference. Disease-free survival was similar for the sequential and concomitant chemoradiation strategies.

These trials indicate that for patients with intermediate-stage squamous cell carcinoma of the larynx, a combined treatment program with the objectives of tumor eradication and laryngeal preservation is feasible. It should be emphasized that patients with destructive T4 primary laryngeal cancers were not included in the RTOG 91-11 trial. These patients may require total laryngectomy for optimal tumor control and to preserve swallow without aspiration. Treatment planning should be multidisciplinary for accuracy in staging and most effective decision-making. Moreover, to optimize long-term function, patients should also be followed up by qualified speech pathologists, further emphasizing the value of multispecialty care in managing complex cancers of the head and neck.

Within the past decade, concomitant chemoradiotherapy has become the standard-of-care treatment option for patients with locally advanced squamous cell carcinomas of the larynx, oropharynx, and hypopharynx (Table 78-2). The theoretical rationale of and mechanism for the interaction between cytotoxic drugs and irradiation that results in additive or synergistic enhancement have been reviewed in detail.[10] This biologic phenomenon rests on several mechanisms, as follows: (1) inhibition of DNA repair, (2) redistribution of cells in sensitive phases of the cell cycle, and (3) promotion of oxygenation of anoxic tissues. The net effect is to improve cellular cytotoxicity.[11] The benefits of adding chemotherapy delivered during irradiation are notably demonstrated in two meta-analyses.[12,13] Concomitant administration of chemotherapy and irradiation was reported to achieve better local control and an 8% survival advantage at 5 years over radiotherapy administered as a single modality. Notably, however, this approach to improved tumor control appears to be associated with increased acute and chronic toxicities, inanition, esophageal stenosis with gastrostomy tube dependence, and recurrent infection related to aspiration.

The choice of the best chemotherapy regimen to be used in conjunction with irradiation has not been well addressed in randomized trials, but cisplatin 100 mg/m^2 administered on days 1, 22, and 43 of a daily radiation treatment plan is widely accepted as a standard. The major drugs with efficacy for SCCHN and in vitro evidence of radiation enhancement capability have been tested as single agents since the 1960s. Most of the single agents used to treat patients with head and neck cancer have been combined with irradiation. Multiagent chemotherapy given concomitantly with radiotherapy has also been evaluated in several studies. Data from selected randomized trials of combined therapy are shown in Table 78-2. In general, to date, there is no convincing evidence to suggest that multiagent chemotherapy is superior to single-agent chemotherapy when given concomitantly with radiotherapy. Additionally, nearly all reported trials of concomitant chemotherapy (single-agent or multi-agent) and radiotherapy have noted enhanced acute radiation-induced toxicity, primarily mucosal, which may result in dose reductions and interruptions in the radiation fractionation schedule. This result violates a guiding principle of radiation therapeutics. Thus, in combining these two treatment modalities, especially when multi-agent chemotherapy regimens are used, it is essential that sensitizing drug-related toxicity not compromise an optimal radiation dose and volume plan. As a result, single-agent cisplatin therapy has evolved as a predictable and effective regimen and is commonly accepted as a standard in the United States in chemoradiation programs

Table 78-2

Selected Randomized Trials Comparing Radiotherapy with Concomitant Chemoradiotherapy

Study	Year	No. of Patients	Chemotherapy Agent(s)	Radiation Dose (gy)	Survival Benefit?	Locoregional Control Benefit?
Jeremic et al[104]	1997	159	P	70	Yes	Yes
Al-Sarraf et al[14]*	1998	147	P	70	Yes	Yes
Jeremic et al[105]	2000	130	P	77	Yes	Yes
Adelstein et al[106]	2003	295	P	70	Yes	Yes
Adelstein et al[107]	1997	100	PF	66-72	Yes[‡]	Yes
Wendt et al[108]	1998	270	PFL	70.2[†] (split)	Yes	Yes
Brizel et al[109]	1998	116	PF	70-75[†]	Yes	Yes
Calais et al[110]	1999	226	CpF	70	Yes	Yes
Staar et al[111]	2001	240	CpF	69.9[†]	Yes[§]	Yes[§]
Budach et al[112]	2005	384	MF	70.6-77.6[†]	Yes	Yes
Bensadoun et al[113]	2006	163	PF	75.6-80.4[†]	Yes	Yes

Cp, carboplatin; F, fluorouracil; L, leucovorin; M, mitomycin; P, cisplatin.
*Disease-free survival.
[†]Altered-fractionation radiation.
[‡]Relapse-free survival.
[§]Oropharynx cancer subset.
Modified from Adelstein DJ, Rodriguez CP. Current and emerging standards of concomitant chemoradiotherapy. *Semin Oncol.* 2008:35;211-220.

for head and neck cancers of any site. In part, this development has been due to favorable results observed in the Intergroup 0099 trial for nasopharyngeal carcinomas.[14] In this study, patients were to receive either radiotherapy alone or cisplatin (100 mg/m^2 on days 1, 22, and 43) during radiotherapy, followed by adjuvant chemotherapy with cisplatin and 5-FU (three cycles). An analysis of 147 randomly assigned patients revealed significant differences in 3-year survival time (78% vs. 47%) and progression-free survival time (69% vs. 24%) favoring the chemotherapy group.

An alternative approach to combined drug therapy and radiotherapy has been developed by Robbins and Homma,[15] with rapid infusion of high-dose intra-arterial cisplatin followed by the systemic neutralizing agent sodium thiosulfate and administered with concomitant irradiation, a technique known as RADPLAT. Drug is infused selectively into the tumor bed after technically demanding placement of microcatheters with the intent of concentrating the cytotoxic compound within the tumor and minimizing systemic exposure, in order to gain a marked therapeutic effect with modest toxicity. In a 2008 report on a series of 240 patients with T3 or T4 squamous cell cancers of the oral cavity, oropharynx, and hypopharynx, in whom RADPLAT was used, local disease control ranged from 69% to 89% and was most favorable for oropharyngeal lesions.[16] These control data approximate what may be achieved with concomitant intravenous chemotherapy. Severe mucositis was observed in 31% of patients. The precise risk of long-term complications, such as osteonecrosis and neurologic deficits, is under scrutiny. Continued research is anticipated.

Biologic agents have been studied in combination with radiotherapy as well, with EGFR-targeted agents representing the class of drugs in the most advanced stages of clinical development. See Figure 78-1 for a depiction of signaling pathways that are considered potential targets for new drugs in development. In an important study, Bonner and associates[2] conducted a prospectively randomized phase III trial in 424 treatment-naïve patients with stage III and IV SCC of the oropharynx, hypopharynx, and larynx. Patients were randomly assigned to radiotherapy as a single modality or radiotherapy with cetuximab administered in a weekly schedule at 250 mg/m^2 after an initial loading dose of 400 mg/m^2. The experimental regimen was generally well tolerated. Three per cent of patients receiving the targeted agent demonstrated severe hypersensitivity reactions, but notably, severe "in-field" mucocutaneous toxicity was not increased in the combined-modality treatment arm. Moreover, locoregional tumor control (median 24.4 months vs. 14.9 months for radiotherapy only) and overall survival (hazard ratio for death 0.74; $P = .03$) were higher in the combined-modality arm. In a retrospective subset analysis, the survival advantage was most favorable for patients with oropharyngeal primary cancers, although the study was not sufficiently powered for a survival analysis according to primary site. This is a landmark study, the first to demonstrate a survival advantage for targeted therapy in the primary treatment of SCCHN.

In summary, organ preservation strategies are feasible for the treatment of squamous cell carcinomas of the head and neck. For adequately selected patients, combined-modality treatment confers survival that is similar to if not greater than that with surgical approaches while avoiding extensive resections and maintaining anatomic organ preservation. Of concern in patients receiving chemoradiotherapy is the level of long-term organ function and quality of life. For selected patients with oropharyngeal and hypopharyngeal squamous cell cancers, concomitant chemotherapy and radiotherapy have been demonstrated to be superior to radiotherapy alone and are considered a standard of care for the treatment of locally advanced disease that is not judged amenable to surgical resection. Oral cavity and locally advanced laryngeal cancers are more often treated with surgical resection as the optimal definitive local therapy. Single-agent cisplatin therapy administered every 3 weeks with radiotherapy administered once daily is the most widely accepted regimen in the United States. Biologic agents, such as cetuximab, are currently being studied for the treatment of this disease as well. Their optimal application has not been well defined to date, but the combination of cetuximab and radiotherapy may be a suitable treatment

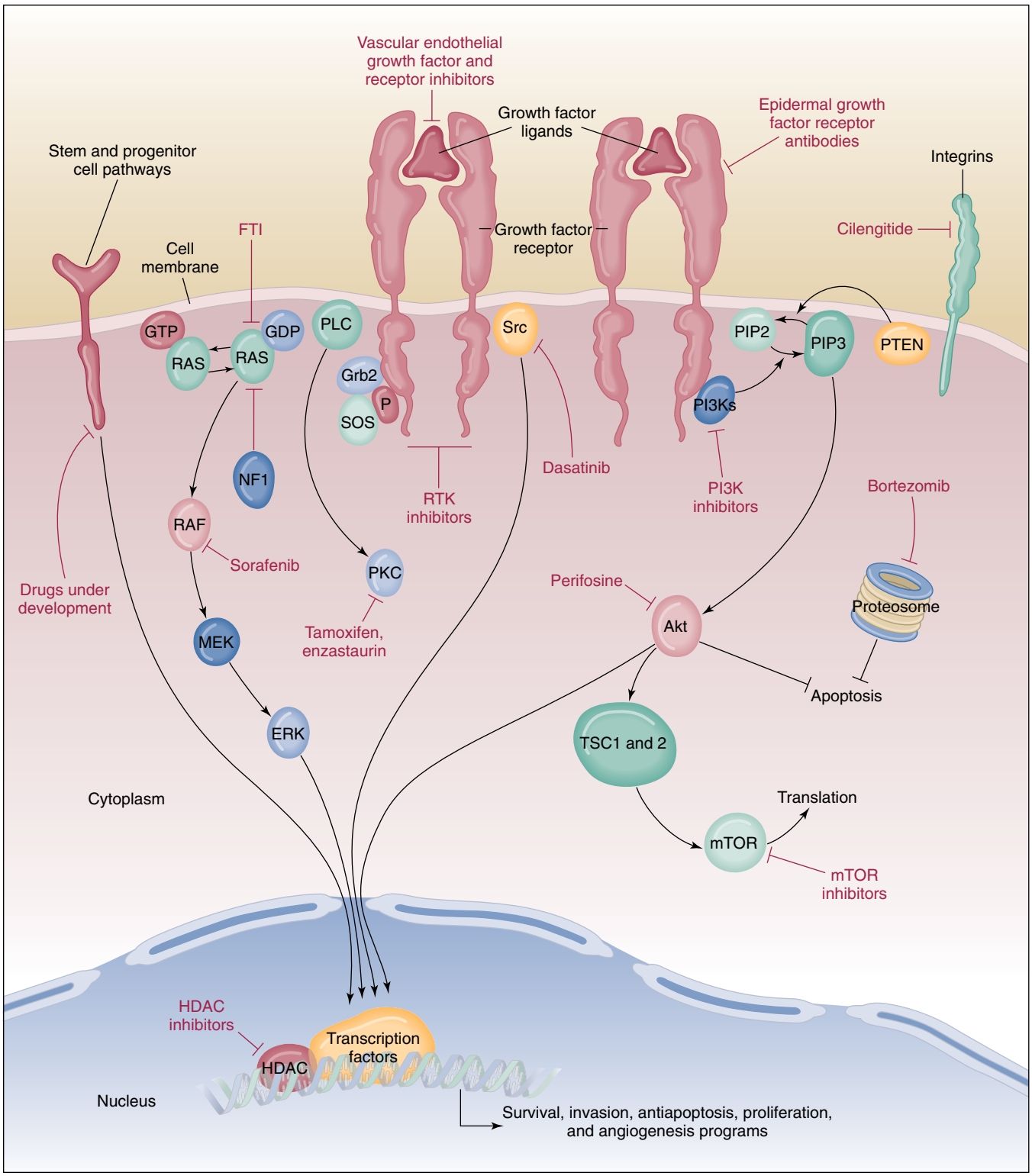

Figure 78-1. Major signaling pathways and corresponding targeted agents in development. Akt, denotes murine thymoma viral oncogene homologue; ERK, extracellular signal regulated kinase; FTI, farnesyl transferase inhibitors; GDP, guanine diphosphate; Grb2, growth factor receptor-bound protein 2; GTP, guanine triphosphate; HDAC, histone deacetylase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol (4,5) biphosphate; PKC, protein kinase C; PLC, phospholipase C; PTEN, phosphatase and tensin nomologue; RAF, v-raf 1 murine leukemia viral oncogene homologue 1; RAS, rat sarcoma viral oncogene nomologue; RTK, receptor tyrosine kinase inhibitor; SOS, son of sevenless; Src, sarcoma (Schmidt-Ruppin A-2) viral oncogene homologue; TSC1 and 2, tuberous sclerosis genes 1 and 2. *(Modified from Wen PY, Kesari S. Malignant gliomas in adults.* N Engl J Med. *2008:359;492-507.)*

alternative for older patients who have intermediate-stage head and neck cancers or who are not good medical candidates for chemotherapy.

Concomitant Chemoradiation as Adjuvant Therapy

Adjuvant chemotherapy after definitive surgery is a treatment strategy used in many types of cancer with the goal of eradicating residual micrometastatic disease and thus ultimately improving long-term survival. In head and neck cancer, adjuvant chemotherapy as a single-modality treatment is still not widely accepted because previous trials have shown difficulty with completing the treatment plan and efficacy has not been demonstrated. Through the Head and Neck Intergroup organization, a large multi-institutional trial was conducted to test whether the addition of chemotherapy to surgery and radiotherapy prolonged survival time or altered the pattern of recurrence.[17] Patients with stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, or larynx and patients with stage II, III, or IV of the hypopharynx in whom resection margins were pathologically negative were eligible. Randomization was to either immediate postoperative radiotherapy or three cycles of cisplatin plus 5-FU chemotherapy followed by radiotherapy. An analysis of the 503 patients in the study showed no significant difference in disease-free survival time, overall survival time, or locoregional control between the two treatment groups. However, there was a significantly lower rate of distant metastases as a site of failure ($P = .016$) at any time for patients treated with adjuvant chemotherapy. Perhaps more important was the finding that a high-risk subset of patients (those with extracapsular extension, carcinoma in situ, or narrow surgical margins) appears to benefit from adjuvant chemotherapy, with increases in survival time and local control that approached statistical confidence in comparison with those receiving radiotherapy alone.

Two trials testing induction chemotherapy added maintenance chemotherapy to one treatment group and observed differences in outcome. The Head and Neck Contracts Program[18] trial of one course of cisplatin and bleomycin induction chemotherapy before surgery and irradiation also planned for 6 months of maintenance chemotherapy in one of the three treatment arms. A significant decrease in the distant metastatic rate was observed for patients in that arm. Ervin and associates[19] randomly assigned patients showing a response to cisplatin, bleomycin, and methotrexate induction chemotherapy to receive either three additional cycles or observation after definitive surgery and radiotherapy. The 3-year disease-free survival time for patients receiving maintenance chemotherapy was 88%, compared with 57% for the control subjects ($P = .03$). In a phase II pilot study, Johnson and colleagues[20] treated 42 patients who had extracapsular spread of tumor in cervical lymph node metastases with 6 months of methotrexate and 5-FU after resection and radiotherapy. The 2-year disease-free survival rate was 66%, which was better than the control rate of 38% that was expected on the basis of historical experience.

Considered together, the results of these trials indicated that adjuvant chemotherapy can affect micrometastatic disease and decrease the rate of distant recurrence. The data also suggested that disease-free survival time might be improved. However, impediments to successfully conducting adjuvant or maintenance chemotherapy in patients with head and neck cancer are patient noncompliance and physician fatigue. The morbidity of the primary treatment, combined with the medical and social situations of many patients, makes classic adjuvant chemotherapy difficult or sometimes not feasible. In addition, there appears to be no role for adjuvant chemotherapy in low-risk patients, although high-risk patients may benefit. Certainly, improved patient selection remains to be clarified in definitive randomized phase III trials.

More recently, prospective phase III studies conducted in the United States[21] and Europe[22] testing the value of concomitant cisplatin and radiotherapy in patients considered at high risk for recurrence after surgery because of tumor margin involvement of the resected specimen, nodal extracapsular spread, or both have demonstrated better local tumor control and overall survival.[23] Although the entry criteria were slightly different in the two studies, patients were randomly assigned to either radiotherapy alone or combined treatment. The rate of acute mucocutaneous side effects was higher in the combined-modality arm, but the chronic toxicity was not reported to be elevated. There was an overall 42% reduced risk of locoregional treatment failure. Thus, for patients who have undergone surgery and have the selection factors previously indicated, postoperative drug therapy with concomitant radiotherapy is now considered the standard of care.

Induction Chemotherapy

Theoretically, treatment with chemotherapy before surgery or irradiation—known as induction chemotherapy—has several advantages. Initial treatment with chemotherapy is feasible. Patients are not debilitated because of surgery or radiotherapy. Clearly the drug activity is optimal in the previously untreated patient, probably because there had been no disruption of normal vascularity. Effective systemic therapy induces primary and nodal disease response in a high percentage of patients, and further, there may be a systemic effect with a reduction in risk of distant disease recurrence.[24]

With the introduction of cisplatin into clinical trials in the mid-1970s, Hong and coworkers[25] combined cisplatin with a 5- to 7-day continuous infusion of bleomycin and observed an overall response rate of 75%, with a 20% complete response rate. Other investigators added vinblastine, vincristine, or methotrexate to the two-drug combination and had similar results. An alternative and probably more effective regimen tested in the 1980s at Wayne State University was cisplatin (100 mg/m^2) followed by a 5-day infusion of 5-FU (1 g/m^2 per day by continuous infusion). In phase II trials, this regimen produced an overall response rate as high as 93% and a 54% complete response rate when three cycles were administered.[26] Although the toxicity from cisplatin is the same, 5-FU appeared to be better tolerated than bleomycin, without the associated allergic phenomena or lung toxicity.

Ensley and colleagues[27] from Wayne State University have reported a high complete response rate with the use of five or six courses of cisplatin and 5-FU alternating with methotrexate, leucovorin, and 5-FU. In one study, the complete response rate was 65% in 31 patients completing the protocol, although toxicity was formidable and approximately one third of patients withdrew from the study early. Despite the potential for improvement in response rate, the applicability of alternating regimens has yet to be demonstrated. This group of investigators and others showed that a response to induction chemotherapy correlated with a response to subsequent radiotherapy.[28-30] Thus, patients whose tumors are resistant to cisplatin-based induction chemotherapy had a high likelihood of not having a response to radiotherapy.

Most authorities agree that randomized trials incorporating appropriate stratification factors and prognostic variables, and with adequate follow-up periods, are necessary to draw conclusions about the effects of induction chemotherapy on disease-free survival and overall survival.[24,31] The results of numerous randomized controlled trials of induction chemotherapy before surgery, radiotherapy, or both, have been published.

The previously mentioned Head and Neck Contracts program,[18] a Southwest Oncology Group trial,[32] and the VA Laryngeal Cancer Study Group trial[5] were large multi-institutional randomized studies. The patients in all studies had advanced resectable head and neck cancer, and the treatment arms were well balanced as to TN stage and primary site. The Head and Neck Contracts program randomly assigned patients to receive one of the following three treatments: (1) surgery followed by irradiation, (2) induction chemotherapy with one cycle of cisplatin plus bleomycin followed by surgery and irradiation, and (3) induction chemotherapy, surgery, irradiation, and maintenance chemotherapy with cisplatin for 6 months. The 5-year survival rates for the three regimens were 35%, 37%, and 45%, respectively; the differences were not statistically significant. However, the time to development of distant metastases and the frequency of distant metastases as a site of first recurrence were significantly lower in patients in the maintenance chemotherapy arm than in the other two groups.[18] Subgroup analysis also found a significant difference in disease-free survival time for patients receiving maintenance chemotherapy for oral cavity primary tumors and for N1 or N2 disease.[33] In retrospect, it is not surprising that this trial did not show improvement in overall survival time because only one cycle of cisplatin and bleomycin was administered before surgery, resulting in a low response rate of 37%.

In the Southwest Oncology Group trial, patients were randomly assigned to receive either three cycles of cisplatin, bleomycin, methotrexate, and vincristine before surgery and radiotherapy or standard treatment with surgery and radiotherapy. The median survival time was 30 months for patients in the standard treatment arm and 18 months for those in the induction chemotherapy arm. The distant metastatic rate was 49% with standard treatment and 28% with induction chemotherapy. Although differences in survival time and pattern of recurrence are striking, they did not reach statistical significance. This trial fell short of its accrual goals and had a high rate of noncompliance, with only 56% of patients assigned to induction chemotherapy completing the treatment per protocol.[32]

Domenge and associates[34] have reported a phase III trial in which 318 patients with locally advanced oropharyngeal squamous cancers were randomly assigned to receive either induction chemotherapy with cisplatin and 5-FU followed by locoregional treatment or locoregional therapy alone. Overall survival was better in the chemotherapy group (median, 5.1 vs. 3.3 years; $P = .03$).

Encouraging data emerge from induction chemotherapy trials and in the area of organ preservation concurrent chemoradiotherapy. The VA Laryngeal Cancer Study Group[5] completed a randomized trial in patients with resectable stage III and IV squamous cell cancer of the larynx. Patients were randomly assigned to receive either standard therapy with total laryngectomy and postoperative radiotherapy or a maximum of three cycles of cisplatin and 5-FU chemotherapy followed by radiotherapy. Surgery was reserved for salvage in patients with persistent or recurrent disease. If patients did not have at least a partial response at the primary site after two cycles of chemotherapy, they underwent immediate surgery. The complete and partial response rate after two cycles of chemotherapy was 85%, and after three cycles it was 98%. The pathologically confirmed complete response rate at the primary site was 64%. At a median follow-up period of 33 months, there was no significant difference in survival time. However, the patterns of relapse differed: recurrence at the primary site was 2% for the surgery group compared with 12% for the chemotherapy group ($P = .0005$); regional node recurrence rates were similar ($P = .305$); rates of distant metastases were 17% and 11%, respectively ($P = .016$); and the rates of second primary malignancies were 6% and 2%, respectively ($P = .029$). After 3 years of follow-up, 66% of surviving patients in the induction chemotherapy treatment group had a preserved, functional larynx. Similar results were reported by a European Organisation for Research and Treatment of Cancer study comparing cisplatin and 5-FU induction chemotherapy followed by radiotherapy with laryngopharyngectomy and irradiation in patients with locally advanced cancer of the hypopharynx. There was no survival difference between the arms, and 28% of patients receiving sequential chemotherapy and radiation were alive with a functional larynx at 3 years. The larynx preservation rate was 42% at 3 years, only deaths from local disease being regarded as treatment failure.[6]

In the follow-up to the VA study, the Head and Neck Intergroup conducted a prospective three-arm study comparing (1) induction chemotherapy with cisplatin and 5-FU followed by radiotherapy, (2) radiotherapy alone, and (3) radiotherapy with concomitant cisplatin.[9] Entry criteria involved stage III or IV disease, but T1 and advanced T4 lesions conferred ineligibility. Tumors infiltrating more than 1 cm into the tongue base or demonstrating thyroid cartilage destruction were also barred from the study. Five hundred forty-seven patients were entered, 65% of whom had stage III disease. Two thirds of patients had supraglottic primary tumor sites. No unexpected toxicity was observed. With no difference in overall survival, the concomitant treatment arm resulted in superior larynx preservation; the rate for that group was 88%, compared with 74% for sequential chemotherapy and irradiation and 69% for radiotherapy alone. Notably, patients with destructive T4 primary tumors were excluded from this study. Long-term outcomes, including quality of life and functional data, are awaited.

Two trials showed an improvement in survival time for chemotherapy-treated patients after subset analysis. In a large Italian study, Paccagnella and others[35] observed an improvement in local control, metastatic rate, and survival time for patients with inoperable tumors. In a follow-up study to the Head and Neck Contracts Program study, Jacobs and others[33] reported an improvement in survival time for the subgroup with oral cavity primary tumors and limited nodal disease. Multiple trials have shown a decrease in the rate of distant metastasis.[6,24,32,33,35]

These trials have helped clarify many issues. First, the overall response rates to cisplatin-based chemotherapy range from 60% to 90% with clinical complete response rates of 20% to 50%. Survival time is better in patients with a complete response than in patients with no response, and complete pathologic responses can be seen in about 30% of patients with complete clinical responses. Second, a response to chemotherapy predicts for a response to radiotherapy. Tumors that show no response to chemotherapy do not respond well to irradiation. Third, neoadjuvant or induction chemotherapy increases neither surgical nor radiotherapy complication rates. Fourth, the most critical prognostic factors for response have been TN stage and type of chemotherapy. Biologic behavior appears to differ per site. Fifth, although no benefit in overall survival time has yet been shown, a significant reduction in the rate of distant metastases has been observed with induction chemotherapy. Finally, this modality can achieve organ preservation and improved quality of life. For patients with advanced laryngeal cancer who would require a total laryngectomy, the available data indicate that laryngeal function can be maintained in two thirds without jeopardizing survival time. However, much more work in this area as well as longitudinal follow-up are needed, especially with respect to preservation of functional swallow in the setting of induction chemotherapy followed by chemoradiotherapy, particularly in patients with cancers of the oropharynx and hypopharynx.

There has been increased interest in the study of induction chemotherapy, with the development of potentially more effective three-drug combinations (Fig. 78-2). These trials reflect attempts to improve on the cisplatin and infusional 5-FU regimen. Hitt and coworkers[36] compared cisplatin and 5-FU with a three-drug combination of paclitaxel, cisplatin, and modified dose of 5-FU (PCF). Responses were significantly better in the experimental program (33% complete response vs. 14% for the two-drug group), without an overall increase in the rate of acute toxicity. Indeed, rates of mucositis seemed reduced with the modified 5-FU dosage. Grades 2 to 4 mucositis affected 16% of patients who received PCF compared with 53% of patients treated with cisplatin and 5-FU. Significant peripheral neuropathy occurred in 8% of patients who received PPF. Following induction chemotherapy, patients received concomitant chemoradiation with cisplatin (100 mg/m^2) administered on days 1, 22, and 43. Patients who received the three-drug combination showed a trend to longer overall survival ($P = .06$); however, the subset of patients whose disease was defined as "unresectable" experienced a clearer benefit ($P = .004$).

Later studies[37,38] have generated considerable excitement. A 358-patient phase III European Organisation for Research and Treatment of Cancer study compared cisplatin and 5-FU with docetaxel, cisplatin, and 5-5-FU (TPF). After induction chemotherapy administered for four cycles, all patients received radiotherapy as a single modality. With a median follow-up of 32 months, TPF produced superior tumor responses, with a significant progression-free survival advantage hazard ratio of 0.72 and an overall survival hazard ratio of 0.73. Also, more toxic deaths (5.5% vs. 2.3%) were observed in the cisplatin and 5-FU arm. In the TAX 324 phase III trial,[38] 501 patients were randomly assigned to receive either induction chemotherapy with docetaxel (75 mg/m^2), cisplatin (100 mg/m^2), and continuously infused 5-FU (1000 mg/m^2/day) for 4 days or the standard cisplatin and 5-FU schedule. Three treatment cycles were administered before patients underwent an examination under anesthesia followed by chemoradiation, with weekly carboplatin area under the curve 1.5. Next, a fraction of patients underwent surgery either for residual disease or for advanced node involvement at diagnosis. There was a significant disease-free and overall survival advantage for patients receiving TPF. With a hazard ratio of 0.70, 62% of patients who received TPF were alive at 36 months, compared with 48% of patients who received standard cisplatin and 5-FU. Analysis of the sites of treatment failure also is of note. There was an unexpected, but statistically significant difference with respect to locoregional disease control favoring the TPF group as well

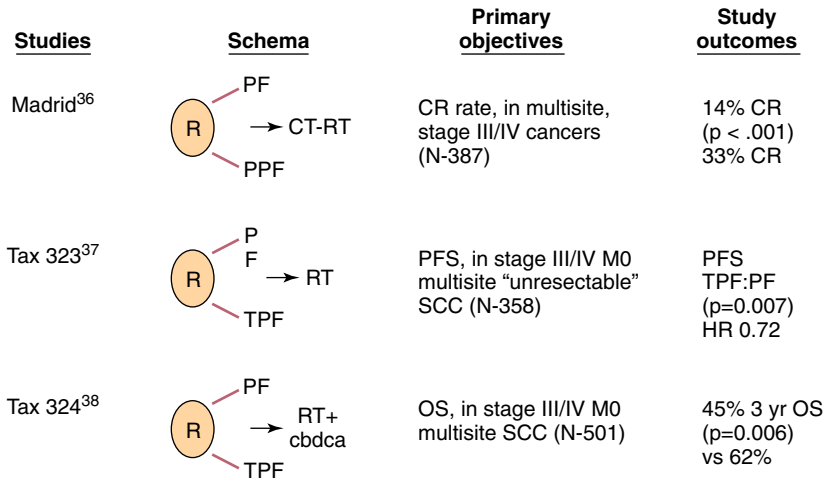

Figure 78-2. Selected induction taxane trials. PF, cisplatin and fluorouracil; PPF, paclitaxel, cisplatin and fluorouracil; RT, radiotherapy; cbdca, carboplatin; PFS, progression-free survival; OS, overall survival. *(Data from references 36, 37, and 38.)*

Table 78-3

TAX 324 Trial of Induction Chemotherapy plus Chemoradiotherapy for Head and Neck Squamous Cell Carcinoma: Analysis of Failures*

	TPF	PF	All
Total no. patients treated	255	246	494
Total no. failures	88 (35)	110 (45)	198 (40)
No. with LRF†:	77 (30)	93 (38)	170 (34)
Primary	43 (17)	49 (20)	92 (19)
Neck	22 (9)	33 (13)	55 (11)
Both	12 (5)	11 (4)	23 (5)
No. with distant metastases‡:	14 (5)	21 (9)	35 (7)
Distant only	11 (4)	17 (7)	28 (6)
Distant and LRF	3 (1)	4 (2)	7 (1)
No. with second primaries	9 (4)	10 (4)	16 (3)

F, 5-fluorouracil; P, cisplatin; T, docetaxel.
*Numbers in parentheses are percentages.
†Hazard ratio for death 0.73 (0.54-0.99), $P = .04$.
‡Hazard ratio for death 0.60 (0.30-1.18), $P = .14$.
Modified from Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007:357;1705-1715.

as a more modest reduction in the distant metastasis rate with the addition of the third drug (Table 78-3).

Previous experience with induction chemotherapy has not led to a consensus regarding overall benefit. There is the potential for added chemotherapy toxicity and a delay of or compromise in definitive local therapy. However, the data of the recent randomized trials are promising, and we strongly support ongoing randomized studies designed to more precisely define the value of induction chemotherapy in patients with locally advanced disease who are then to proceed to concomitant chemoradiation. Treatment planning for induction chemotherapy is likely to be most applicable in patients with advanced or lower neck nodal metastases, at diagnosis—patients at greatest risk for development of distant metastases after effective local therapy. Two such trials are currently accruing patients in North America, both testing docetaxel, cisplatin and 5-FU followed by concomitant chemoradiotherapy. Survival is the primary end point. These studies are summarized in Table 78-4. We anticipate that future phase I and II studies will evaluate innovative and novel systemic therapy programs with integration of molecularly targeted agents. We look forward to a day when individual patient characteristics, tumor site and stage, and tumor biologic markers will prompt individualized therapy based on validated selection factors.

Induction chemotherapy is highly active, with tumor responses observed in a large percentage of patients. TPF is the current model for further testing; the induction strategy has been demonstrated to reduce risk of distant metastases but also represents a vehicle for the evaluation of other clinical and molecular end points. The development of increasingly effective induction chemotherapy may eventually result in better local local disease control after radiotherapy. However, we must await the results of ongoing randomized trials, as well as better identification of the subgroups of patients who may be most likely to benefit from this approach, before we accept induction chemotherapy as a standard treatment.

Systemic Chemotherapy for Recurrent or Metastatic Disease

Systemic management of recurrent head and neck cancer is a major concern, because 30% to 50% of patients with locally advanced SCCHN at diagnosis eventually die of recurrent local or regional disease within 5 years. Distant metastases may be clinically present in about one third of patients with recurrent disease, but autopsy may determine the presence of disease in up to 60%.[39] The primary goal of conventional chemotherapy used for palliation should be to ease discomfort and prolong survival time. Patients with locally advanced or disseminated recurrent SCCHNs have a median survival time of 6 to 9 months, and 20% survive 1 year. Patients with tumors showing a substantial response to chemotherapy have better symptom control and overall survival.

Prognostic Factors

Many chemotherapy trials have been analyzed to determine factors that would predict a favorable response to chemotherapy and prolonged survival time. Most single-institution trials have only modest numbers of patients, so firm conclusions about their results cannot be drawn with statistical confidence. For patients with recurrent disease, poor prognostic factors are a low performance status, poor nutrition, a large tumor burden, and extensive previous radiotherapy and surgery.[40] Tumor progression during or shortly after surgery or radiotherapy is also an

Table 78-4

Ongoing Randomized Induction Chemotherapy Trials in Squamous Cell Carcinoma of the Head and Neck

Location of Study	Stages	Sites	Regimen for Induction Chemotherapy	Regimen for Concurrent Chemotherapy	Survival End Point	Targeted Improvement (%)	Accrual Goal (No. of Patients)
University of Chicago	N2-N3	All	DPF × 2	DFHX	3 yrs	50-65	400
Dana-Farber Cancer Institute	Stage III-IV	All	DPF × 3	Various	3 yrs	55-70	300

D, docetaxel; F, fluorouracil; H, hydroxyurea; P, cisplatin; X, hyperfractionated radiation administered on alternate weeks.

ominous sign. In these circumstances, any response to chemotherapy is likely to be marginal and brief, without an impact on overall survival time. However, it seems clear that survival time may be prolonged in patients who demonstrate a complete response to chemotherapy. These patients, in general, have good performance status, they are not malnourished, and they have not received previous chemotherapy for recurrent disease.

In the next sections, we discuss the use of single agents and combination chemotherapy for the palliative treatment of recurrent or mestastatic SCCHN. Last, we describe the promising results obtained with selected molecularly targeted agents, which are currently being evaluated in both locally advanced disease and metastatic disease.

Single Agents

The response rate (complete and partial) of recurrent or metastatic squamous cell cancer to commonly used agents is 20% to 40%, and the drugs most commonly used are the platin compounds (cisplatin and carboplatin), taxanes (docetaxel and paclitaxel), 5-FU, methotrexate, and ifosfamide. In general, the older literature indicates that about one third of patients have response to treatment. Response criteria previously were somewhat less stringent than today. According to the Response Evaluation Criteria in Solid Tumors (RECIST), a partial response is defined as a reduction in the largest tumor dimension by 30%. The majority of responses to single agents are partial, as indicated by clinical and imaging criteria, with less than 5% of patients having a complete response to chemotherapy alone. Response duration tends to be brief, on the order of 2 to 4 months, and median survival time is 6 to 9 months. Methotrexate and cisplatin are the most extensively studied single agents for this disease, and they may still be considered to be of standard use, but most practitioners recommend a platin and taxane drug combination regimen for patients medically able to tolerate it.

Methotrexate was previously widely used for management of SCCHN. Therapy with this drug is relatively nontoxic, inexpensive, and convenient. Response rates to conventional doses vary between 10% and 50%, averaging 30%.[41] Weekly treatment with doses in the range of 40 to 60 mg/m^2, if tolerable, is superior to twice monthly or monthly treatments. Levitt and associates[42] have shown in vitro that when moderate to high doses of methotrexate are used with leucovorin rescue, an enhanced therapeutic index results from the high intracellular levels of drug associated with selective rescue of healthy tissue. The initial results of pilot trials of moderate- or high-dose methotrexate suggested improvement in response rates for patients with head and neck cancers. However, there has been no clear benefit to the higher dose levels (e.g., as much as 5000 mg) from prospective randomized trials comparing conventional-dose with moderate- or high-dose methotrexate, with or without leucovorin rescue,[43,44] and the approach has fallen out of use.

Cisplatin is associated with response rates ranging from 10% to approximately 30%, with some reported complete responses and a duration of response of approximately 2 to 4 months.[45,46] Two controlled trials comparing methotrexate with cisplatin found no difference in response rate or survival time between the two, but noted quite different toxicities.[47,48] Advantages of cisplatin over methotrexate are a relatively rapid response rate and the need for less frequent administration, every 3 or 4 weeks. Cisplatin has been studied at different doses to determine whether a dose-response effect exists. In a comparison of 60 mg/m^2 and 120 mg/m^2, Veronesi and coworkers[49] found no difference in response rates. Forastiere and colleagues[50] conducted a pilot trial evaluating 200 mg/m^2 and observed a 73% response rate, or double that expected with conventional dosing. Although these findings suggested a benefit from the higher dose, ototoxicity and neurotoxicity occurred frequently, limiting the feasibility of this approach.

Combination Chemotherapy

In an effort to improve response rates and, hopefully, survival time, combination chemotherapy was developed. Many combination chemotherapy regimens have been evaluated in phase II trials involving a few patients with recurrent head and neck cancer. Often, the results indicate a high response rate that suggests improvement over that expected from single-agent therapy with methotrexate or cisplatin. However, the median duration of response ranges from 2 to 4 months, and there has not been a clear demonstration of a median survival advantage for conventional cytotoxic chemotherapy combinations. Moreover, these regimens may be complex to administer and have greater toxic effects than single-agent therapy.

Most often, prospective comparative trials with patients randomly assigned and stratified for prognostic variables are needed to best determine therapeutic benefits of new or innovative drug regimens. Large multi-institutional trials well designed with respect to prognostic factors tend to show a significant difference in response rates between the combination treatment and single-agent control arms.[51-55] The Eastern Cooperative Oncology Group (ECOG) compared an outpatient regimen of cisplatin, bleomycin, and methotrexate with weekly methotrexate.[55] The rate of response to single-agent therapy with methotrexate was 35%, and that to the combination 48%—a significant improvement ($P = .04$). However, toxicity was greater for the combination, with no difference in survival time.

The Southwest Oncology Group reported a comparison of cisplatin with 5-FU, carboplatin with 5-FU, and weekly methotrexate.[52,53] The response rates for the three arms were 32%, 21%, and 10%, respectively. There was a significant difference in response rates between the cisplatin combination and methotrexate ($P < .001$); the difference between the response to the carboplatin combination and the response to methotrexate approached statistical significance ($P = .05$). Cisplatin with 5-FU was associated with significantly more toxicity than methotrexate; carboplatin with 5-FU was intermediate in toxicity. Despite these findings, the median survival times were no different, varying between 5.6 and 6.6 months. The third study to show a difference in response rates compared the combination of cisplatin and 5-FU with each drug used alone.[54] The response rate to the combination was 40%, compared with 18% for cisplatin and 15% for

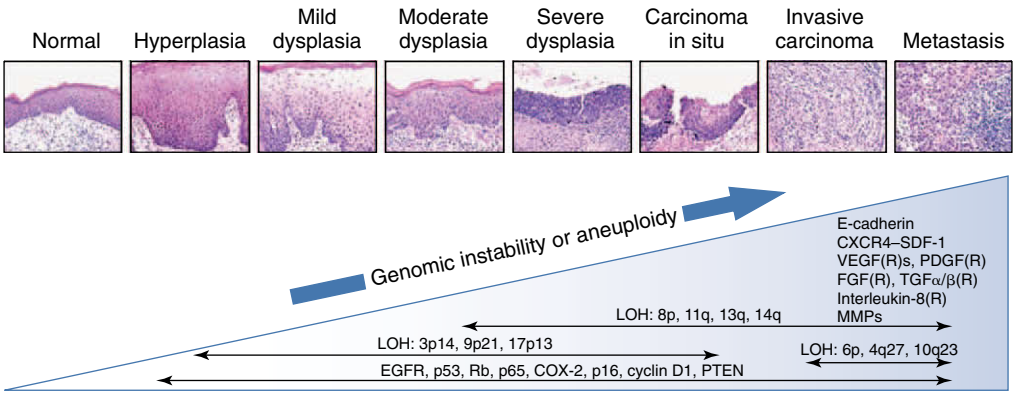

Figure 78-3. Head and neck cancer is considered to progress through a multistep process from normal histologic features to hyperplasia through mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, invasive carcinoma, and metastasis. Underlying genetic instabilities, including the loss of heterozygosity (LOH) of certain chromosomes (3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27, and 10q23) and amplification or deletion or up-regulation or down-regulation of certain oncogenes or tumor suppressor genes, including epidermal growth factor receptor (EGFR), p53, Rb, p65, cyclooxygenase 2 (COX-2), p16, cyclin D1, and phosphatase and tensin homologue (PTEN), have been identified as genetic alterations in each of the pathologic stages of this disease. Several genes—including those encoding E-cadherin (CDH1), chemokine (C-X-C motif) receptor-stromal-cell-derived factor (CXCR4-SDF-1), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factors α and β (TGF-α and TGF-β), interleukin-8, and the respective receptors, along with matrix metalloproteinase (MMP)—are involved mainly in the progression of metastasis and in early stages of tumor progression. (R), randomization. *(From Haddad RI, Shin DM. Recent advances in head and neck cancer.* N Engl J Med. *2008:359:1143-1154.)*

continuous-infusion 5-FU ($P < .01$). Although the median survival times were not different, an analysis of patients surviving longer than 9 months showed a 40% survival rate for the combination treatment group, compared with 27% for cisplatin and 24% for 5-FU ($P < .05$). The latter two trials are also of interest because of the similar response rates observed for cisplatin and 5-FU, which were administered with the same dose and schedule. Cisplatin with 5-FU is a commonly used drug regimen for the treatment of patients with head and neck cancer both for palliation and in combined-modality programs. The results of these large trials have served to establish that a response rate of 30% can be expected from the cisplatin and 5-FU combination in patients with recurrent head and neck cancer. Clavel and associatess[51] also observed differences between combination chemotherapy and single agents. They found higher response rates for two cisplatin-based combinations than for single-agent methotrexate therapy—34%, 31%, and 15%, respectively.

From these randomized trials, it appears that higher response rates can be achieved with some combination chemotherapy regimens. Toxicity is more severe, and overall median survival time is not notably improved.

In an attempt to compare the efficacy of cisplatin with 5-FU with that of cisplatin with paclitaxel, the Eastern Cooperative Oncology Group conducted a prospective phase III trial on 218 patients with locally advanced, recurrent metastatic disease. Patients were randomly assigned to cisplatin 100 mg/m^2 on day 1 followed by 5-FU infusion 1000 mg/m^2 per day for 4 days or cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2 on day 1. Tumor responses were observed in 27% of the cisplatin–5-FU group and 26% of the cisplatin-paclitaxel group, with similar toxicity. There was no survival difference.[56]

Targeted Therapy

The histologic prognostic factors for head and neck cancer are the presence of locoregional metastases, perineural invasion, vascular or lymphatic invasion, positive surgical margins, and extracapsular spread of tumor cells from involved lymph nodes into soft tissues of the neck. There is a major effort[4] to identify molecular signatures and to better understand mechanisms of tumor progression as this may facilitate the identification of more precise biomarkers and vulnerable therapeutic targets.

Metastatic progression of tumor cells is a multistep and complicated process.[57] Each step appears to involve interdependent molecular interactions among tumor cells and between tumor cells and the surrounding microenvironment. Multilayered systems are under study with genomic and proteomic techniques. See Figure 78-1 for a conceptualization of potential molecular targets. DNA microarray and other techniques posit multiple potential factors affecting metastases:[58-60] keratins, cell-surface proteases, mesenchymal-cell markers, cell-matrix adhesion molecules, chemokines, and modulating elements for the extracullular matrix and epithelial-to-mesenchymal transition.[61] Chemokine (C-X-C motif) receptor (CXCR4), and its ligand, stromal-cell-derived factor (SDF-1), may combine to direct primary tumor cells to metastatic sites.[60] This activity may be crucial in the evolution of metastatic patterns and relate to enhanced secretion of angiogenic factors, such as vascular endothelial growth factors (VEGFs), and surface receptor concentration. Figure 78-3 provides a model of genetic instability and tumor progression in SCCHN.

Antiangiogenic compounds target VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factors α and β (TGF-α and TGF-β), and interleukin-8, along with the receptors of these proteins.[4] Phase I and II trials are examining VEGF inhibitors, single agents or in combination with chemotherapeutic agents, in SCCHN. We have observed tumor responses in 25% of patients receiving cetuximab and bevacizumab in a phase II inter SPORE project with no significant hemorrhagic toxicity as yet.[62]

EGFR is overexpressed in SCCHN.[63,64] The development of monoclonal antibodies and small-molecule tyrosine kinase inhibitors has led to "inhibition" of EGFR signaling and associated molecular networks. EGFR consists of four family members. EGFR-1 (HER1) and EGFR-2 (HER2/neu) are the best characterized.[65] Ligands for EGFR are epidermal growth factor (EGF), TGF-α, amphiregulin, epiregulin, betacellulin, and heparin-binding EGF-like growth factor (HB-EGF). HER2 has no known natural ligands. After binding receptor, dimerization obtains and activates subsequent phosphorylation of tyrosine kinases, downstream signaling mediators and ultimately cellular proliferation. Nuclear translocation of EGFR and other growth factor receptors is important for signaling in rapidly growing cells, and the activity is largely abrogated by treatment with cetuximab, which also strongly inhibits phosphorylation of EGFR. EGFR and the ligands, EGF and TGF-α, are overexpressed in SCCHN, and linked to a poor prognosis after treatment. For these reasons, EGFR is a target for experimental therapeutics.[4,66]

Chimeric and humanized IgG antibodies target the extracellular domain of EGFR epitopes and have been shown to prevent EGFR signaling.[65] Antibodies have been shown to have single agent antitumor

activity. Small molecule EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, bind within the intracellular domain to inhibit kinase activity, thus modulating transcription, cell-cycle progression, cell survival, and motility, all of which facilitate invasiveness and metastasis. In early clinical trials, these agents have independent activity, with response rates from 5% to 15% depending upon dose and schedule.[24]

Most recently, there have been efforts to identify targeting agents which would exploit tumor cell vulnerabilities. Cetuximab is a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFR), and has been found to be quite an active agent in SCCHN, when used as a single compound,[67] or in combination with cisplatin or radiotherapy. In a important phase III trial,[68] 117 patients with metastatic or recurrent SCCHN were randomized to receive cisplatin as a single agent or in combination with cetuximab. The addition of cetuximab improved the overall response rate from 10% to 26% ($p = 0.03$) and median survival from 2.7 to 4.2 months. These data suggested benefit associated with the combination, over single agent cisplatin.

In a landmark study, Vermorken and colleagues[69] randomly assigned 442 eligible patients with untreated recurrent or metastatic squamous cell carcinoma to receive a platin/fluorouracil regimen with or without cetuximab, in a prospective phase III trial. This led to significant prolongation of overall survival from 7.4 months to 10.1 months in the group of patients receiving cetuximab, $P = 0.04$. The addition of cetuximab prolonged median progression free survival from 3.3 to 5.6 months ($P < 0.001$) and increased the response rate from 20% to 36%. There was no crossover treatment. This study marks the potential for targeted systemic drug therapy to have an impact on survival, as a component of treatment for patients with metastatic disease.

Chemoprevention of Head and Neck Cancer

Chemoprevention is defined as the administration of pharmacologic agents to inhibit the events occurring during the multistep process of carcinogenesis or the reversal of a premalignant condition[70,71] The key concepts underlying chemoprevention are that carcinogenesis is multistep (i.e., it results from accumulated genetic and epigenetic alterations), multipath (i.e., multiple functional pathways are involved, such as self-sufficiency in growth signals, insensitivity to anti-growth signals, apoptosis evasion, limitless replicative potential, tissue invasion and metastasis and sustained angiogenesis), and multifocal (both multiclonal, i.e., "field cancerization," and clonal, i.e., cloning expansion leading to intraepithelial spread).[72]

Drug development for chemoprevention purposes is challenging, given that the cancer risk for the overall population is relatively low, especially for head and neck cancers. Chemoprevention interventions usually have to be administered over extended periods of time and long-term follow-up is necessary to ascertain the true benefits (i.e., reduced incidence of invasive cancer) of any given treatment. In an effort to expedite advances in the field, in 2002, the American Association for Cancer Research recommended the development of chemoprevention strategies focused on carcinogenesis, not necessarily invasive cancer, as a measure of clinical benefit. This recommendation specified the prevention and regression of clinical/histopathologic intraepithelial neoplasia (i.e., pre-malignant lesions).[70] A 2006 update of these recommendations highlighted the importance of molecular intra-epithelial neoplasia (i.e., molecular alterations detected early in the target histopathologic intra-epithelial neoplasia) as a potential surrogate marker for invasive cancer and an end point for chemoprevention studies.[71]

The setting of head and neck pre-malignant lesions provides an excellent model for chemoprevention studies, given that these lesions can be easily followed by physical examination, and are readily assessable for biopsies, both for histopathologic evaluation and biomarker discovery. Furthermore, there has been increasing knowledge on the carcinogenic pathways leading to transformation of head and neck premalignant lesions into invasive cancer, thus providing strong rationales for developing strategies for cancer risk assessment, treatment and prevention, as well as identification of surrogate markers of invasive cancer that could serve as intermediary end points in chemoprevention studies.

As a result, many head and neck cancer prevention trials have focused on patients with pre-malignant lesions (i.e., leukoplakia and erythroplakia) to test a variety of pharmacologic compounds (e.g., retinoids[73-79] and non-steroidal anti-inflammatory agents[80,81]). The majority of these trials relied on histopathologic or clinical response of the oral pre-malignant lesions as the primary end point (as opposed to invasive cancer incidence), and none resulted in the development of chemopreventive agents that could be used routinely in the clinic (either due to toxicity or lack of long-term efficacy). A second set of trials focused on the prevention of second primary tumors/tumor recurrence after definitive treatment of a head and neck cancer.[82-86] So far, these trials also failed to identify drugs that could be routinely used in the clinic for this indication.

In the next paragraphs, we will summarize the seminal head and neck chemoprevention studies with retinoids (the most widely investigated class of drugs in this setting). Subsequently, we will briefly discuss how the molecular knowledge gained from the translational component of these and other trials is now shaping the design of the next generation of molecular-targeted, chemoprevention clinical studies in head and neck cancer.

Retinoids are the synthetic and natural analogues of vitamin A. β-carotene is a precursor and the major source of vitamin A in the diet. Although the exact mechanism by which retinoids inhibit carcinogenesis is not known, retinoids have been shown to modify genomic expression at the level of messenger RNA synthesis and to regulate transcription of specific genes.[87,88]

The major limitation in the use of retinoids is associated toxicity. Acute toxicity includes dryness of conjunctival and oral mucous membranes, cheilitis, skin desquamation, hypertriglyceridemia, bone tenderness, arthralgias, and myalgias. Chronic toxicities include hepatotoxicity and bone remodeling.[89] The most commonly used retinoids in the clinic are vitamin A (retinol); β-all-transretinoic acid; 13-cis retinoic acid (isotretinoin); and an aromatic ethyl ester derivative, etretinate. In contrast to the retinoids, the major toxicity of the carotenoids is yellowing of the skin.

In patients with pre-malignant lesions, Stich and others[76,90] reported two trials conducted in India and the Philippines in betel nut chewers. In one placebo-controlled trial, β-carotene was compared with β-carotene plus vitamin A. Complete response was observed in 3% of the patients taking placebo, in 15% of β-carotene-treated patients, and in 28% of those taking the combination. These patients demonstrated significant suppression of micronuclei expression and index of DNA damage on serial cytologic examinations. In a subsequent study, patients were randomly assigned to receive placebo or twice the dose of vitamin A (200,000 IU/wk) received in the first trial. A 57% complete response rate was observed with total suppression of the development of new leukoplakic lesions. In the placebo group, the complete response rate was 3%, and there was a 21% rate of new lesion formation.[76] In a small pilot study, Garewal and others[91] observed a 71% complete and partial response rate in 24 patients treated with β-carotene. There was no significant toxicity. Other investigators reported complete and partial response rates ranging from 60% to 100% with 13-cis retinoic acid.[92,93]

These results led Hong and others[73] to conduct a randomized placebo-controlled trial of 13-cis retinoic acid (1 or 2 mg/kg per day) in oral leukoplakia with dysplastic change. All patients were assessed with pretreatment and post treatment biopsies. Patients were treated for 3 months and observed for 6 months. There was a highly significant difference in response rate, 67% vs. 10%, comparing the treated group with those taking placebo. Histologic reversal of dysplastic change was documented in 54%. Unfortunately, after stopping treatment, the relapse rate was high within 2 or 3 months, and the regimen was associated with considerable toxicity. In a follow-up trial,[74] 56 patients received 13-cis retinoic acid (1.5 mg/kg per day) for 3 months, followed by randomization to low-dose 13-cis retinoic acid (0.5 mg/kg per day) or β-carotene maintenance therapy for 9 months. 13-cis-retinoic acid proved superior in maintaining remissions and had an acceptable level of toxicity in this low dosage. Nonetheless, the beneficial effects of therapy diminished over time (23% and 25% of patients in the low-dose isotretinoin and beta carotene arms, respectively, developed either

in situ or invasive carcinoma after a median follow-up of 66 months).[75] Three other placebo-controlled trials reported increased response rates or decreased recurrence rates of oral leukoplakia in patients treated with retinoids (vitamin A[76] or fenretinide[77,78]). Recently, Papadimitrakopoulou and colleagues published the final results of the longest-term study of retinoids in patients with oral pre-malignant lesions.[79] This trial randomized 162 patients with oral pre-malignant lesions to receive low-dose 13-cis-retinoic acid or beta-carotene plus retinyl palmitate for 3 years. After other randomized trials established an adverse effect of beta-carotene on lung cancer incidence/mortality, beta-carotene was dropped and patients were randomized to 13-cis-retinoic acid alone or retinyl palmitate alone. There was a higher incidence of adverse events in the 13-cis retinoic acid group. The clinical response rate of retinyl-palmitate alone was significantly lower than the other experimental treatments. However, the oral cancer-free survival in all arms was similar. Most importantly, there was no correlation between clinical response rate of the oral pre-malignant lesions and subsequent cancer incidence. This study illustrates many of the difficulties with the use of retinoids for head and neck oral pre-malignancies: 13-cis-retinoic acid is not well tolerated for long-term use, even at low doses. Moreover, even though short-term clinical response might be demonstrated following retinoid administration (particularly 13-cis-retinoic acid), evidence that clinical response correlates with long-term cancer development is still lacking, and this may not be considered a validated intermediary end point (despite its widespread use as a primary end point in many clinical trials).

Chemoprevention is also particularly relevant to patients who are curatively treated for an early stage head and neck squamous cell cancer. It is recognized that second primary malignancies develop at a rate of 3% to 4% per year in these patients.[94,95] The explanation for this risk is based on the concept of field cancerization first formulated in the 1950s.[96,97] Repeated exposure of the entire epithelial surface to carcinogens, such as tobacco and alcohol, can lead to the development of multiple sites of premalignant and malignant change.

The pioneer randomized placebo-controlled trial by Hong and coworkers demonstrated fewer second primary tumors in curatively treated head and neck cancer patients receiving high-dose 13-cis-retinoic acid for one year versus placebo (4 and 24%, respectively, $P = 0.005$) at a median follow-up of 32 months. This preventive effect persisted after 54.5 months of follow-up (14 versus 31% for the retinoid and placebo arms, respectively, $P = 0.042$). However, overall survival was not statistically different between the groups (57 and 52%, $P = 0.39$), nor was the annual second primary tumor rate. Again, the patients in the high-dose retinoid arm experienced increased toxicity with roughly 48% of the cohort requiring dose reductions or therapy discontinuation, thus limiting the clinical applicability of this strategy.[82,83] In an attempt to reduce the side-effects profile, a large randomized trial with 1218 patients (with prior stage I or II squamous cell carcinoma of the head and neck) evaluated the effects of low-dose 13-cis-retinoic acid versus placebo for three years in the incidence of second primary tumors. There were no statistically significant differences in the primary end point, disease recurrence, nor overall survival between the two groups after 7 years of follow-up.[84] Two other large trials enrolling patients with previous lung or head and neck cancer (EUROSCAN—2592 patients)[85] or oral cavity/oropharynx cancer (316 patients)[86] also failed to demonstrate a beneficial effect of retinoids (retinyl palmitate[85] or etretinate[86] in the second primary tumor rates or overall survival.

The lack of consistent benefit from retinoids for head and neck cancer prevention, as well as the advances of molecular-targeted approaches for the treatment of invasive/advanced disease have prompted a shift in the research focus of the chemoprevention field. This has been driven by two major aspects evolving from basic and translational studies of head and neck cancer biology: refining of assessment of invasive cancer risk (using molecular tests), and development of molecular-targeted agents for both cancer treatment and prevention.

The ability to identify individuals at increased risk for developing invasive cancer allows for the design of clinical trials enriched with a population likely to experience a high number of events, thus maximizing the chances for successful and accelerated development of chemoprevention strategies. This might ultimately translate into potentially meaningful benefits in the clinic. Perhaps the most promising risk assessment tool currently being incorporated in clinical trials of chemoprevention is the evaluation of allelic imbalances in patients with oral pre-malignant lesions: loss of heterozygosity of specific loci in chromosome 3p and/or 9p have been demonstrated to be associated with increased cancer risk, both in patients with and without a history of prior oral cancer.[98-100] As an example, in a Canadian series of curatively treated oral cancer patients who subsequently developed an oral pre-malignant lesion adjacent to the cancer site, the 5-year cancer risk was 72% in patients with loss of heterozygosity at 3p and/or 9p versus 6% in patients without the allelic imbalance.[100] These findings are currently being evaluated prospectively in the erlotinib prevention of oral cancer (EPOC) study.[101] One of the entry criteria of this ongoing U. S. multi-institutional clinical trial is presence of loss of heterozygosity at specific loci in the oral pre-malignant lesions of patients with or without a prior oral cancer. Eligible patients (who are considered to be at highest risk for cancer, based on the aforementioned molecular assessment) are then randomized to receive placebo or erlotinib for one year. Unlike the previous retinoid studies discussed above, the primary end point of the trial is cancer development, thus allowing for a definitive assessment of erlotinib's preventive activity in this enriched, at-risk population.

EPOC also highlights the second hallmark of the newer generation of chemoprevention trials: use of molecular-targeted agents directed at pathways relevant to the carcinogenic process. Erlotinib, the oral investigational drug used in EPOC, inhibits EGFR, a key molecule in head and neck cancer development.[102,103] Moreover, cetuximab (an anti-EGFR monoclonal antibody) has been shown to increase survival when used in combination with radiation therapy[2] or chemotherapy[69] in patients with intermediate and advanced stage head and neck cancer. This further supports the development of pharmacologic strategies inhibiting this pathway earlier on in the course of the disease.

In summary, abundant trials using retinoids have failed to demonstrate a consistent benefit from this class of agents in the treatment of oral pre-malignant lesions and/or prevention of recurrent/second primary tumors. Nonetheless, they have set the stage for the development of newer generations of clinical trials based on improved risk assessment and use of molecular-targeted drugs directed at relevant pathways of carcinogenesis. Hopefully this will advance the field of chemoprevention research, leading to the design of effective preventive strategies, ultimately resulting in decreased cancer incidence and mortality.

Summary

Tumors of various histologic types occur in the head and neck. Excluding thyroid malignancies, approximately 80% are squamous cell carcinomas. Data evaluating the impact of chemotherapy on survival time, particularly for combined-modality treatments, are limited to this common histologic type for which patient numbers are available for randomized comparative trials. Phase I, II, and III studies in patients with locally recurrent or metastatic disease have shown that chemotherapy can produce response rates of 30% to 40%, and combination chemotherapy is more effective than single agents. However, responses historically have tended to be brief, 2 to 4 months, and may not be associated with longer survival time. The addition of cetuximab to cytotoxic chemotherapy may augment efficacy. Nonetheless, chemotherapy for these patients is palliative. An exception to this is patients with tumors of the nasopharynx in whom higher response rates and a small proportion of long-term disease-free survivors are observed. Prognostic factors have been identified that should be used by the physician to select patients most likely to benefit from palliative treatment.

In newly diagnosed patients with locally advanced disease, high response rates have been achieved with induction chemotherapy; and this approach remains under study. An important role for chemotherapy may be to preserve organ anatomy and function at selected sites. Three large multicenter randomized trials have been conducted showing preservation of the larynx in a substantial fraction of patients. Chemotherapy administered concomitantly with radiotherapy has

improved local control and survival in selected series, particularly in the setting of oropharyngeal cancers. The potential for increased acute mucocutaneous toxicity associated with these regimens should be carefully considered when selecting patients for combined treatment. Moreover, long-term follow-up is needed to best assess tumor control, risk of metachronous cancers, and functional outcomes after intensive combined-modality regimens. The concomitant administration of cetuximab and radiotherapy shows promise for advancing non-surgical therapy without an apparent increase in severe grade toxicity.

Patients with earlier-stage disease (i.e., stage I or II) should receive conventional therapy with either surgery, radiotherapy, or both. Negative prognostic factors such as an endophytic growth pattern may be an indication for chemoradiotherapy either as definitive or postoperative treatment. Patients with stage III or IV disease can be divided into those for whom surgical resection is indicated or not. Those with disease not to be resected should often be treated with chemotherapy and radiation or entered into a combined chemoradiation treatment protocol. Those with stage III disease may also benefit from combination treatment as part of a clinical trial. Patients with metastatic disease should receive chemotherapy with palliative intent if performance status is favorable.

Patients with resectable disease can be further divided by site. Those with primary oral cavity tumors would most likely be best served by surgery followed by radiotherapy, whereas patients with oropharyngeal, hypopharyngeal, or laryngeal tumors are often treated with radiation, with or without chemotherapy depending on the precise site and stage. Many patients with hypopharyngeal cancers and T4 cancers of the larynx should be considered for possible laryngectomy.

Chemoprevention will continue to be an important area of research in the coming decade. Multiple new strategies are to be considered for further testing.

The management of head and neck cancer is a multidisciplinary activity. The identification of effective targeted and chemotherapeutic agents and their integration into the initial curative therapy of head and neck cancer has the potential to improve survival time and preserve organ function. Systemic therapy has become an accepted component of primary therapy. The increasing appreciation of human papillomavirus as an etiologic and favorable prognostic factor can be expected to affect patient management and the conduct of future studies. Through well-designed and well-executed clinical trials, coupled with basic research of the biology of upper aerodigestive tract tumors, further advances in the management and prevention of these cancers can be achieved.

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CHAPTER SEVENTY-NINE

Skin Flap Physiology and Wound Healing

Eugene A. Chu

Patrick J. Byrne

Rick M. Odland

George S. Goding, Jr.

Key Points

- Flap survival depends on adequate perfusion to meet the metabolic demands of the mobilized tissue.
- The primary insult affecting flap survival is impaired vascular supply and the resultant ischemia.
- Current research for improving flap survival has focused on modulating the cascade of cytokines and intercellular signaling molecules involved in wound healing.
- Wound healing is a dynamic process involving soluble mediators, blood cells, extracellular matrix, and parenchymal cells.
- At present there are no data to support the routine use of growth factors or other wound mediators to aid wound healing. However, continued research and development of substances that stimulate wound healing are under way.

A comprehensive discussion of the physiology of the skin as it applies to surgery is essentially one of vascular supply. Local skin flaps, like pedicled flaps and free tissue transfer, depend on the maintenance of adequate perfusion to meet the metabolic demands of mobilized tissue. An understanding of this physiology allows the surgeon to plan flaps intelligently to ensure a favorable outcome. In addition, an understanding of flap physiology provides a conceptual basis with which to optimize the management of the challenging defect or the tenuous flap.

The vascular supply to the skin serves two purposes, thermoregulation and nutritional support. Nutritional support is regulated largely by the capillary network, which is under the control of the precapillary sphincters. Local hypoxemia causes vasodilation of the precapillary sphincters. Thermoregulation is controlled by arteriovenous shunts, which are located more superficially in the skin. The sphincters of the arteriovenous shunts are under sympathetic control. When body temperature increases, the resulting decrease of norepinephrine leads to lesser sphincteric contraction, thus allowing greater blood flow to the skin; the opposite occurs with decreased body temperature.

The creation of a flap applies specific stresses to healthy skin. These stresses include local tissue trauma and reduced neurovascular supply to the affected tissue. The extent to which skin can survive these injuries is a reflection of the anatomy and physiology of skin and of the cutaneous response to injury. Knowledge of these principles has led to improved skin flap survival rate by means of better flap design. Increasing cutaneous flap survival rate by minimizing the deleterious physiologic effects of flap transposition is an area of active research that has yet to produce techniques that have widespread clinical application.

An important concept in skin vascular physiology as it applies to flaps is that of the *angiosome.* In 1987, Taylor and Palmer[1] coined the term *angiosome* to refer to the tissue supplied by a named artery. The head and neck region has several such angiosomes, including the important thyroid, facial, buccal, ophthalmic, superficial temporal, and occipital.[1] Adjacent angiosomes are in communication with each other via choke vessels. This relationship becomes important in the design of various flaps. It has been demonstrated that axial pattern flaps (to be discussed in this chapter) are capable of supplying adequate blood flow to an adjacent angiosome. The incorporation of tissue on an additional angiosome beyond this adjacent angiosome, however, invites vascular compromise and likely flap failure. Techniques to extend this vascular supply, such as delay, may be necessary.

Zones of Perfusion

Maintenance of cell function and viability is the objective of the circulatory system at macrocirculatory, capillary, interstitial, and cellular levels. The importance of tissue vascularity is well recognized, but the complexity and diversity of tissue perfusion mechanisms require that the process be divided into components. Each level of perfusion has unique physiologic characteristics, and optimal management is possible only if these differences are recognized. Johnson and Barker[2] described two levels of risk zones for flap failure, making a distinction between thrombosis at the arterial and capillary levels. By extension of this concept, four zones of the circulatory system can be considered for all hazards (Fig. 79-1). Proper function of each zone is crucial to tissue viability.

Zone I consists of the cardiopulmonary system, the conduits for blood flow (arteries and veins), neural control of those conduits, and the lymphatic system. Zone I has historically been recognized as essential for flap survival. The delay phenomenon is primarily a zone I effect.

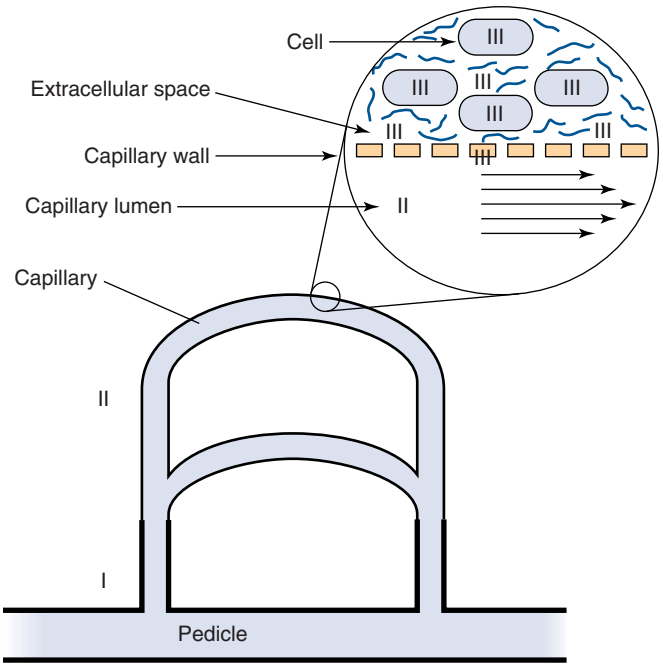


Figure 79-1. Zones of perfusion. Zone I is the macrocirculatory system consisting of cardiopulmonary, neurovascular, and lymphatic function. Zone II is the capillary circulatory systems composed of arterioles, capillaries, venules, and arteriovenous shunts. The interstitial system is zone III and entails the capillary membranes and interstitial ground substance. The cell membrane, organelles, and intracellular space constitute zone IV, the cellular system.

The development of the pedicled flap[3] underscores the importance of zone I in extending flap survival time. Free microvascular tissue transfer is also a zone I manipulation.

Zone II comprises the capillary circulation. The importance of the capillary circulation is shown by the "no-reflow phenomenon," wherein a loss of nutritive blood flow occurs in the presence of an adequate vascular supply.[4]

Zone III is the interstitial space and its mechanisms of nutrient delivery. The capillary wall is included in zone III because capillary permeability is a main determinant of interstitial space properties. Failure of metabolites to enter and traverse the interstitial space can result in loss of cell viability, even though there is adequate zone I and even zone II function. Interstitial systems are an important link in skin flap survival rate.[5]

The cell and its membranes constitute *zone IV*. Maintaining viable cells is the ultimate determinant of flap survival. Prolongation of cell survival through selective changes in cell permeability and uptake is a potential intervention that may improve flap survival rate.

Anatomy and Physiology of Skin

The skin serves as a sensory organ and a protective organ. The thick epidermal layers are largely impermeable to gases and most liquids. Therefore many agents that could have beneficial effects on skin flaps are ineffective when applied topically to intact skin.

The epidermis of the skin is derived from ectoderm in the early embryo. The glandular appendages of the skin (i.e., sebaceous glands and hair follicles) develop from tubes and solid cords that invaginate from the covering ectoderm.[6,7] The epidermis is a metabolically active, but avascular, stratified squamous epithelium. The average epidermal thickness for most of the body is 0.1 mm. The majority of cells undergo keratinization and form the various epithelial layers.[8] The superficial keratinized cells of the skin are continuously replaced by cells originating from the mitotic activity in the basal layer of the epidermis. Melanocytes derived from neural crest cells also are found in the epithelium of skin and constitute a second cell type.

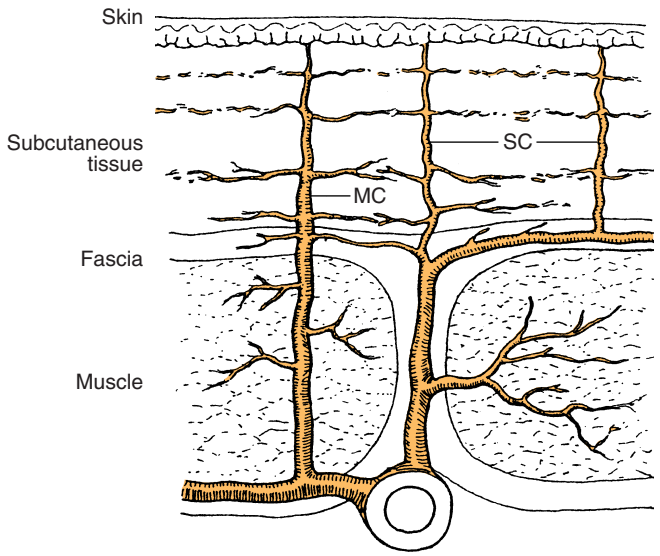


Figure 79-2. Varying pathways to skin define musculocutaneous (MC) and septocutaneous (SC) arteries.

The dermis, derived from embryonic mesoderm, consists primarily of noncellular connective tissue. This relatively noncellular layer has metabolic requirements far less than those of the epidermis. Nerves, blood vessels, lymph vessels, and the base of the epidermal glandular appendages are found within the dermis.[8] The dermis is 15 to 40 times thicker than the epidermis, with a maximum width of 4 mm on the back.[9] The outer surface of the dermis has an uneven border contacting the epidermis that is known as the papillary layer. The papillary dermis is characterized by an abundant ground substance, irregularly arranged collagen bundles, and a highly developed microcirculation. The reticular dermis is composed of thick bundles of collagen and coarse elastic fibers, and fibrocytes and blood vessels are proportionally less numerous.

Deep to the reticular layer of the dermis, the subcutaneous layer consists of loose connective tissue and a varying amount of fat cells. It is a deeper continuation of the dermis and collagenous fibers continuous with those in the dermis. The density of the collagenous fibers is related to the degree of cutaneous mobility over the underlying structures. In the palms and soles, for example, these fibers are particularly numerous. The deep surface of the subcutaneous layer is attached to the superficial fascia of underlying muscle where it is present.

Zone I: Macrocirculatory System

Blood vessels travel by one of two main routes to terminate in the cutaneous circulation. Musculocutaneous arteries pass through the overlying muscle to which they provide nutrition; septocutaneous arteries[10] (also referred to as direct cutaneous arteries) travel through fascial septa that divide the muscular segments (Fig. 79-2).

The cutaneous portion of a septocutaneous artery typically runs parallel to the skin surface, providing nutrition to a large area of skin. Septocutaneous arteries are usually accompanied by pairs of veins and run above the superficial muscular fascia.[11] The more common musculocutaneous arteries leave the muscle and enter the subcutaneous tissue to supply a smaller region of skin.

Septocutaneous and musculocutaneous arteries empty into a diffuse interconnecting vascular network of dermal and subdermal plexuses. This network provides a redundancy in the vascular supply to the skin. A collateral blood supply supports the vascular territory of each artery. Lymphatic vessels form a plexus running parallel and deep to the network of blood capillaries. The lymphatic capillaries, which end in blind sacs, conduct extracellular fluid back into the blood stream. Lymphatic function is affected by inflammation and loss of blood vessel pulsations.[8]

The neural supply to the skin originates from sensory nerves and sympathetic nerves. The sensory nerves are distributed in segmental fashion, forming dermatomes, and participate in the skin's protective function. The postganglionic terminals of cutaneous sympathetic nerves contain the neurotransmitter norepinephrine and are found in the area of cutaneous arterioles.[12]

Zone II: Capillary System

The cutaneous capillary system, along with the arteriovenous shunts, serves the two important functions of nutritional support and thermoregulation. Primarily because of its thermoregulatory function, the rate of blood flow through the skin is one of the most variable in the body. During ordinary skin temperatures, the amount of blood flowing through the skin (approximately 9 mL/min per 100 g of tissue) is greater than the flow required for nutritional support.[13,14] Blood flow can increase to 20 times this value with maximal vasodilation. When the body is exposed to extreme cold, blood flow can be reduced to levels that are marginal for cutaneous nutrition.

Before entering the capillary bed, the arterioles branch into small vessels (e.g., terminal arterioles or metarterioles) that are surrounded by a discontinuous layer of smooth muscle. A simple ring of smooth muscle forms a sphincter at the point where the capillaries originate from the metarteriole. This sphincter can completely stop blood flow within the capillary. The capillary bed can be bypassed by arteriovenous shunts that allow the arterioles to empty directly into venules. During conditions of adequate systemic vascular pressure, preshunt and precapillary sphincters regulate the distribution of cutaneous blood flow.[16]

The preshunt sphincters are involved in regulating the changes in blood flow that affect thermoregulation and systemic blood pressure.[16,17] Release of norepinephrine by the postganglionic sympathetic fibers results in contraction of the preshunt sphincters. This contraction diverts blood away from the skin surface, where heat loss could occur. With increased body temperature, the sympathetic vasoconstrictor impulses decrease, allowing for greater blood flow to the skin.

Local production of bradykinin may play a role in regulating skin blood flow by causing vasodilation.[15] The cutaneous circulation also is extremely sensitive to circulating norepinephrine and epinephrine. Even in areas of skin that have lost their sympathetic innervation, a mass discharge of the sympathetic system still results in intense vasoconstriction in the skin.

The precapillary sphincter, which controls the amount of nutritive blood flow to the skin, responds to local hypoxemia and increased metabolic byproducts by dilating.[16-18] Capillary blood flow is also affected by elevated interstitial pressure, which can compress the capillary and decrease transcapillary flow. Conversely, as pressure decreases in the interstitium, the capillary expands and flow increases.[19] Acute rises in systemic blood pressure cause an immediate increase in local blood flow followed by return of flow to near normal levels in less than 1 minute. This normalization of capillary blood flow is called *autoregulation*.[20] The metabolic theory for autoregulation proposes that an excess of oxygen and nutrients results in arteriolar constriction. This process is believed to be the primary functional mechanism of autoregulation. The myogenic theory suggests that stretching of the arteriolar muscle results in reflex contraction and may be a mechanism to protect capillaries from excessively high blood pressures. Reduction of blood flow may also occur as a result of increased interstitial pressure.

Zone III: Interstitial System

The interstitial space is filled with proteoglycans and collagen.[13] In many tissues, hyaluronic acid filaments make up the interstitial ground substance. These filaments are normally woven through the interstitium, producing a medium that exhibits high resistance to fluid movement unless the tissue is well hydrated. In tissues with excess edema, the filaments do not overlap, producing shear planes of free fluid within the interstitium.[5]

Two processes by which substances can move across the interstitial space are diffusion and convection.[21,22] Diffusion is the process wherein a molecule passively moves to a lower concentration. Molecular movement by diffusion is affected by many factors. An important characteristic is lipid solubility. Lipid-soluble molecules tend to traverse cell membranes more easily and quickly than non–lipid-soluble agents. Large molecules diffuse more slowly than small ones. As molecules diffuse away from the capillary, the concentration of that molecule decreases by the inverse square law. As edema occurs, diffusion distances increase.[23]

Convective flow, or bulk flow, is another way for molecules to move across the interstitium. Rather than diffusing to a lower concentration, an agent is swept along with the current of plasma that flows across the interstitial space in microchannels. The agent then diffuses the short distance from the microchannels to the cells.

The relative importance of diffusion and convective flow is controversial. Some writers believe that diffusion is primarily responsible for cell nutrition. Convection becomes relatively more important for certain tissues, molecules, or pathologic states.

Convective flow of nutrient-laden plasma out of the capillaries and across the interstitial space is produced by a combination of hydrostatic and osmotic pressures as described by Starling in 1896.[24] The equation is as follows:

$$Jv/A = L_p[(P_c - P_i) - \pi_s(\pi_c - \pi_i)]$$

In descriptive terms, flow of plasma out of the capillary per unit area (Jv/A) is related to the product of the water permeability of the membrane (Lp) multiplied by the difference between hydrostatic pressure in the capillary (P_c) and interstitial space (P_i) minus the difference between osmotic pressure in the capillary (π_c) and the osmotic pressure in the interstitial space (π_i). The osmotic pressures are adjusted by the osmotic coefficient, (π_s), a measure of the "leakiness" of a semipermeable membrane.

In functional terms, over the length of the capillary, hydrostatic pressure decreases as fluid exits the capillary and hydraulic resistance is overcome. At the same time, oncotic pressure within the capillary increases as fluid exits the capillary and plasma proteins are retained. These changes in gradients favor return of fluid at the venular end of the capillary and in the immediately postcapillary venule. Pressure gradients also are responsible for bulk flow of fluid across the interstitial space in fluid microchannels.

A net change of 2 mOsm is sufficient to increase interstitial pressure beyond transmural capillary pressure, thereby compressing the capillary. Increased venous pressure limits interstitial resorption of fluid and contributes to formation of an interstitial transudate.[25] Inflammation in a flap is probably a result of nociceptor pathway stimulation by handling of the flap. Even the relatively minor trauma of inserting a fine needle causes a "very large" increase in capillary permeability within minutes after insertion, as evidenced by rapid influx of proteins into the interstitium.[26] Ischemia also produces inflammation. Capillary hyperpermeability has been found throughout ischemic flaps.[27,28] The lymphatic system has two functions that affect zone III, to remove excess fluid and to remove interstitial protein. There is some controversy in the physiology literature regarding the magnitude of the latter function.[21] If the lymphatic system is malfunctioning, interstitial fluid and interstitial protein accumulate.[29,30]

Zone IV: Cellular Systems

The intracellular space is the endpoint for nutrient transport and the origin of metabolic waste. The cell wall is a fluid lipid bilayer 7.5 to 10.0 nm thick. The lipid bilayer is a major barrier to movement of solutes across the membrane. The primary function of the cell membrane is to maintain or to vary in a controlled fashion the separation of the extracellular and intracellular environments. This separation is achieved by specific membrane proteins, which act as solute pumps and solute and solvent leaks. The osmotic pressure between the two environments also should be maintained to preserve normal cell volume. The sodium-potassium pump is important in maintaining osmotic equilibrium across the cell membrane and has a requirement for energy in the form of adenosine triphosphate (ATP).[31] A loss of energy substrate (oxygen and consequently ATP) produces an intracellular movement of sodium and an increase in intracellular osmotic pressure.[25] These changes occur quickly,[32] within 10 minutes after arterial occlu-

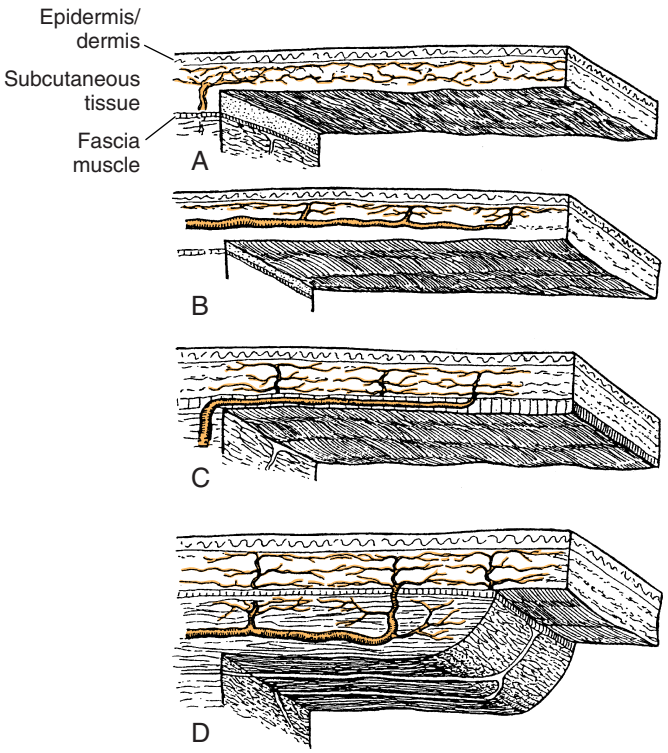


Figure 79-3. Classification of skin flaps based on vascular supply. **A,** Random. **B,** Arterial cutaneous. **C,** Fasciocutaneous. **D,** Musculocutaneous.

sion. Within seconds of hypoxia, levels of ATP begin to decrease, and cells begin to swell.[29] Relatively brief periods of ischemia result in a reversible swelling of the cell and organelles. If the ischemic insult is severe and prolonged, cell lysis and flap necrosis occur.

Classification of Flaps

Flaps are commonly classified according to their principal blood supply. They include random, arterial cutaneous (i.e., axial), fasciocutaneous, musculocutaneous, and venous flaps (Fig. 79-3). Venous flaps to this point have had no application in head and neck reconstruction. Flaps may also be described according to site of origin relative to the area to be reconstructed. Thus, flaps utilized in the head and neck are local, regional, or distant. Distant flaps may be pedicled or free flaps (microvascular free tissue transfer).

Random Cutaneous Flaps

The vascular supply to a random flap is from the subdermal plexus. The subdermal vascular plexus is supplied by unnamed musculocutaneous artery perforators near the base of the flap. The random cutaneous flap is commonly used in local flap reconstruction. The plane of dissection is through the subcutaneous fat. Examples of local random flaps are advancement, rotation, a combination of rotation-advancement, transposition, and tubed flaps. The survival of such flaps is determined by the perfusion pressure supplying the flap, and is not necessarily related to simple length-to-width ratios.

Arterial Cutaneous (Axial) Flaps

Arterial cutaneous flaps (also called axial pattern flaps) are supplied by a defined septocutaneous artery that runs beneath the longitudinal axis of the flap. These flaps typically have a better survival length than random cutaneous flaps. The plane of dissection must include the septocutaneous vessel within the subcutaneous fat. The axial flap may be designed to include tissue distal to that supplied directly by the artery. In such a case, the more distal portion of the flap is essentially a random flap, and caution must be exercised to avoid overextending the design beyond viability.

Use of arterial cutaneous flaps is limited by the availability of direct cutaneous arteries. Examples of arterial cutaneous flaps used in head and neck reconstruction are the deltopectoral flap, based on the anterior perforators of the internal mammary artery, and the paramedian forehead flap, based on the supratrochlear vessels.

Myocutaneous and Fasciocutaneous Flaps

Myocutaneous flaps represent an additional modification to improve flap survival. They are based on distal segmental vessels, leaving the local vasculature (perforators and cutaneous vessels) intact, which requires incorporation of muscle with the flap. Myocutaneous flaps are typically named for the donor muscle. Examples are the pectoralis myocutaneous flap, based on the pectoral branch of the thoracoacromial artery, and the latissimus dorsi myocutaneous flap, based on the thoracodorsal artery.

The greater blood flow and higher tissue oxygen tensions available with myocutaneous flaps[33] make this design superior in the management of contaminated or infected defects.[34,35] Improved phagocytotic and bactericidal activity of leukocytes is seen in myocutaneous flaps in comparison with random pattern flaps in the canine model.[36] These physiologic benefits contribute to the ability of myocutaneous flaps to resist bacterial inoculation more effectively than random pattern flaps.

As for arterial flaps, it often is desirable to extend the surface area of the flap in clinical situations. A random portion of the flap based on the subdermal plexus can be incorporated. This random extension is usually the portion of the flap most at risk for ischemic necrosis.

Fasciocutaneous flaps use direct arterial (septocutaneous) vessels with the cutaneous branches at the level of the deep fascia forming a plexus, which supplies the subdermal plexus.[37] The appropriate size of fasciocutaneous flaps is less well defined than axial pattern flaps with their obvious arterial supply.[38] Fasciocutaneous flaps appear to rely more on potential skin vascular territories. Four types of fasciocutaneous flaps have been described on the basis of the pattern of blood supply incorporated into the fascial component of the flap. Examples are the parascapular flap and the radial forearm flap.[39,40]

Free Microvascular Flaps

Free flaps have become the standard of care for many types of reconstruction and hold several advantages over regional flaps. Free flaps may be fasciocutaneous, musculocutaneous, myofascial, osseous, or osteocutaneous, or a combination of these. Tissue from a distant site can be harvested according to the characteristics of the donor site and the needs of the defect. Vascularity of the flap is maintained by microvascular anastomosis of the artery and vein. The flap can be harvested and customized to the defect in terms of absolute size and relative amounts of bone, muscle, skin, and nerve needed. Careful design of a free flap can eliminate the risk of partial necrosis associated with a random extension.

Physiology of Acutely Raised Flaps

A number of changes detrimental to skin survival occur when a cutaneous flap is created. That flaps survive at all is a testimony to the minimal nutritional requirements of skin. The primary insult affecting flap survival is impaired vascular supply and the resultant ischemia. In the presence of adequate blood flow, complete flap survival occurs. Nerve section and inflammation influence flap survival primarily by affecting blood flow. Recovery from ischemia also can occur through the timely formation of new vascular channels between the transposed flap and the recipient bed.

Impairment of Vascular Supply

Partial interruption of the vascular supply (zone I) to the skin is the most obvious and critical change that occurs with elevation of a cutaneous flap. Flap survival depends on the severity of ischemia and the amount of time before recovery of nutrient blood flow. Flaps can tolerate and survive an average of 13 hours of complete avascularity.[41] Limitation of the vascular supply results in a local decrease in perfusion pressure to the skin. In arterial or myocutaneous flaps, the blood supply to the skin overlying the vascular pedicle is usually adequate.[42] In random flaps or random extensions of flaps, the decrease in perfusion

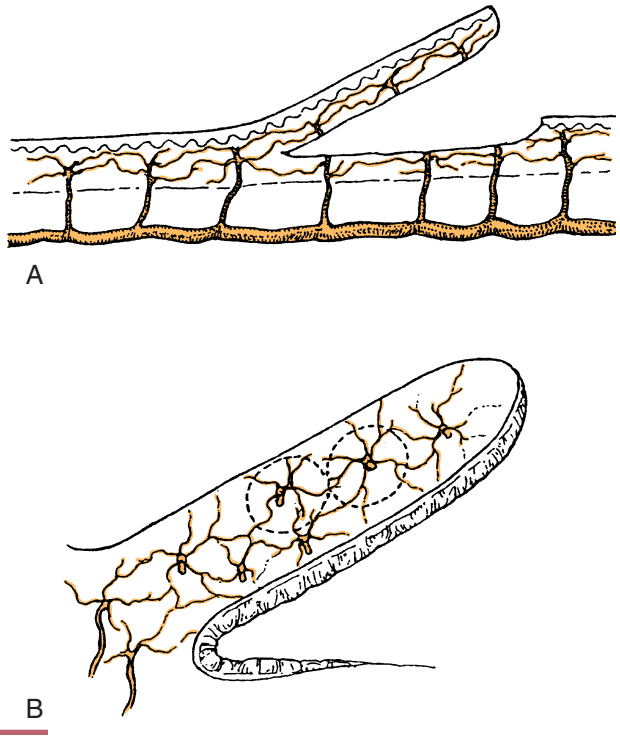


Figure 79-4. **A** and **B,** Vascular territories in skin flaps. Multiple perforating vessels exist and are interconnected at the periphery of their vascular territory. When some of these vessels are cut, blood supply can be replaced from nearby perforating vessels, and then tissue necrosis does not occur.

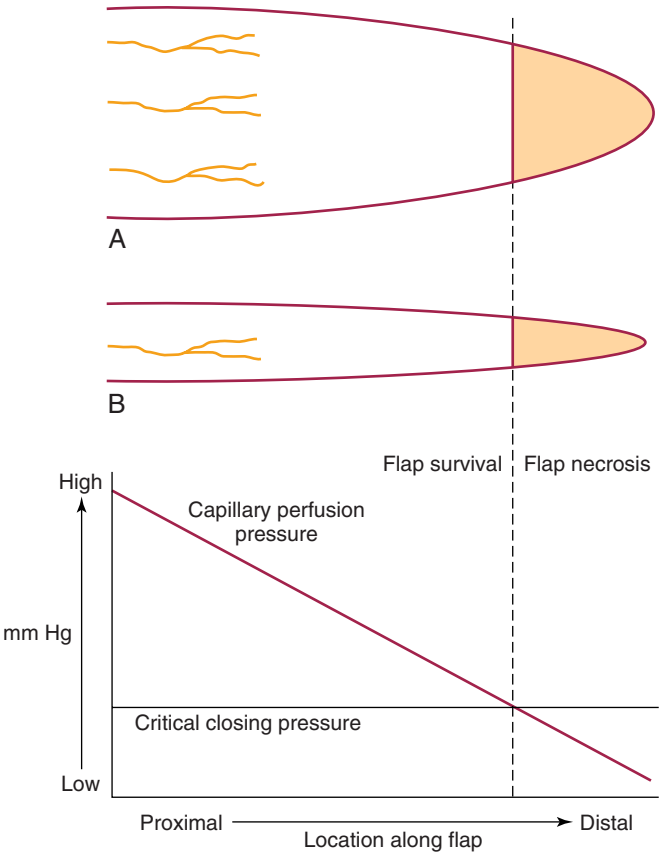


Figure 79-5. Fallacy of the length-to-width ratio. The slope of decreasing perfusion pressure versus flap length does not change with incorporation of additional vessels (flap *A* versus flap *B*) with the same perfusion pressure. Flap necrosis occurs when perfusion pressure decreases below critical closing pressure of the capillary bed.

pressure becomes more pronounced with increasing distance from the base of the flap.[43,44] When perfusion is reduced in one area of a random flap, the adjacent vascular territories supplied by a separate perforating vessel can provide a low-pressure blood supply through the subdermal plexus (Fig. 79-4). Because the nutritional requirements of skin are relatively low, a number of vascular territories can be compromised before necrosis results.

The surviving length of the random portion of the flap depends on the physical properties of the supplying vessels (intravascular resistance) and the perfusion pressure.[45,46] When the perfusion pressure drops below the pressure in the interstitial space, capillary blood flow ceases. The pressure at which there is no longer enough intravascular blood pressure to maintain capillary blood flow is called the *critical closing pressure*.

In the past, random cutaneous flaps often were designed according to a desired length-to-width ratio, a wider base being needed to successfully transfer a longer flap. The wider random flap includes only additional vessels with the same perfusion pressure. The relationship between perfusion pressure and critical closing pressure is not altered, and there is no change in survival length (Fig. 79-5).[9,47]

In free flaps, a secondary ischemia can occur when thrombus forms at the anastomosis. Anastomosis failure is related to exposure of the vascular intima to platelets.[48] Platelet activation is caused by superficially exposed subendothelium or, with deeper vessel injury, exposure to collagen types I and III. The geometry of the vascular arrangement is often a critical factor when experienced surgeons lose a free flap., Measurements of transcutaneous oxygen pressure ($TcPo_2$) and transcutaneous carbon dioxide pressure ($TcPco_2$) have been investigated for monitoring of compromised flaps. In experimental studies $TcPo_2$ was found to be more sensitive to flap ischemia; however, in clinical studies it was difficult to distinguish between flap ischemia and congestion on the basis of $TcPo_2$ alone. Instead, a $TcPco_2$ greater than 90 mm Hg in a congested flap proved a more useful guideline for warranting further treatment.[49]

The venous outflow from the skin also is impaired with flap elevation. Venous flow can occur through the subdermal plexus or via venous channels that accompany the feeding artery in the pedicle. Complete venous occlusion in the early postelevation period may be more damaging to flap survival than inadequate arterial supply.[48] Fortunately, the subdermal plexus alone is often able to provide adequate venous outflow. Care should be taken to preserve venous outflow in flaps pedicled solely on the feeding vessels.

Impairment of lymphatic drainage with flap elevation also occurs. Reduction of the cutaneous lymphatic drainage results in a rise in interstitial fluid pressure that is compounded by increased leakage of intravascular protein associated with inflammation. The resulting edema leads to increased interstitial pressure, which decreases capillary perfusion by raising the critical closing pressure (Fig. 79-6).[24,45] Alterations in the Starling forces result in further ischemic swelling of cells and the interstitial space, setting a positive feedback circle in motion.

Microcirculatory Changes

Necrosis in flaps is caused by prolonged loss of nutritional blood flow.[50,51] There are several proposed mechanisms for loss of nutritional flow, each of which may play a role. Erythrocyte sludging has frequently been noted in capillaries undergoing ischemia, often without thrombus formation. Therefore, sludging is not necessarily caused by platelet activation unless a microvascular anastomosis or other vessel injury is involved, such as tearing, stretching, laceration, or crushing. Microemboli are commonly generated from a microvascular anastomosis.[52]

The reason for the erythrocyte sludging is multifactorial. Erythrocytes become turgid and lose their flaccid, biconcave disk shape in the acidic environment of ischemia. Narrowing of the capillaries,[9,53] presumably a result of external compression, also contributes to

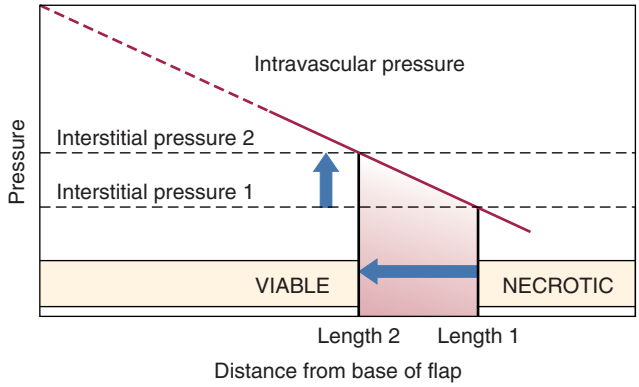


Figure 79-6. The relationship between increased interstitial pressure and decreased surviving flap length. Intravascular perfusion pressure decreases along the length of the flap. At the distal end of the flap, intravascular perfusion pressure becomes less than interstitial pressure, causing the capillaries to collapse (critical closing pressure). As edema is generated by ischemia and inflammation, interstitial pressure increases, resulting in a decrease in surviving length from length 1 to length 2.

stacking of erythrocytes within the lumen of ischemic tissue capillaries. Sludging is seen less often if the hematocrit value is kept below 30%.[54]

Capillary blood flow is further hindered by leukocyte adherence to the capillary wall.[55] The leukocytes are probably responding to cytokines released from the cells in response to initial injury. The leukocytes first roll along the capillary wall and then begin to stick. As time progresses, the leukocytes flatten onto the endothelial cell and eventually pass into the interstitium. Each step of the process has biochemical mediators. In patients undergoing heart transplantation, leukocyte depletion decreases ultrastructural evidence of reperfusion injury.[56] Ischemic cells of all tissues swell because of the loss of energy substrate needed to continue maintaining the osmotic gradient. Swelling of extravascular cells causes compression of the vascular lumen,[57] but endothelial cell swelling has a greater effect on capillary blood flow.[58] Histologic evidence of edema can be used to grade the severity of free flap injury.[59] Nitric oxide synthase, an endothelium-derived vasodilator, has been studied for its effect in skin flaps.[60-64]

Neovascularization

In surviving flaps, blood flow gradually increases. If the flap is in a favorable recipient site, a fibrin layer forms within the first 2 days. Neovascularization of the flap begins 3 or 4 days after flap transposition.[65,66] Revascularization adequate for division of the flap pedicle has been found as early as 7 days in animal models and humans.[67]

During revascularization, vascular endothelial cells play a major role in the formation of new vessels. Normally, endothelial cells are in a quiescent state, although when stimulated by angiogenic growth factors, they can dramatically proliferate. This proliferation normally occurs only during certain conditions, such as wound healing and ovulation.

Beginning with an angiogenic stimulus, the angiogenic process involves a number of discrete yet overlying steps (Fig. 79-7). Initially, the vessels become dilated and permeable with retraction of the endothelial cells and a decrease in endothelial junctions. The basement membrane is then dissolved by proteases, and the endothelial cells migrate from the vascular wall toward the angiogenic stimulus. Behind the leading front of migrating endothelial cells, endothelial cell replication begins, forming a capillary sprout that elongates toward the angiogenic source. The nearby capillary sprouts then anastomose to each other, forming capillary loops. As capillary loops and sprouts continue, the loops become patent, developing newly formed blood vessels. These blood vessels differentiate and lay down basement membrane consisting of type IV collagen, laminin, and proteoglycans. Pericytes and fibroblasts then migrate to the capillary loop sites.[68]

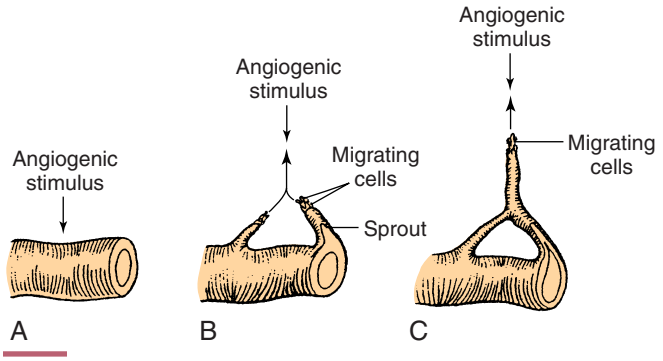


Figure 79-7. Steps in angiogenesis. **A,** Initial stimulus with retraction of endothelial cells and thinning of basement membrane. **B,** Migration of endothelial cells and formation of capillary sprout. **C,** Formation of capillary loops, which become patent to form new blood vessels.

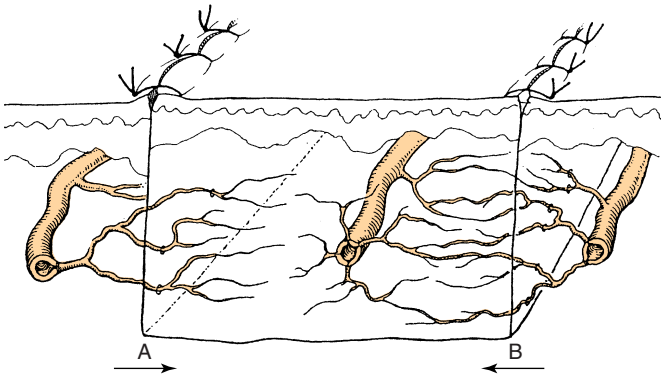


Figure 79-8. Ingrowth of angiosomes. Cross section of the flap showing direct ingrowth (*A*) versus inosculation (*B*).

With the continued presence or absence of the angiogenic stimulus, substantial remodeling, regression, and rearrangement of the new capillaries occur.[69] Some capillaries join preexisting flap vessels (*inosculation*), but the majority of revascularization appears to involve direct ingrowth of recipient vessels into the flap (Fig. 79-8). New capillaries can grow toward an angiogenic source at a mean rate of 0.2 mm/day. When the angiogenic stimulus is discontinued, the capillary vessels regress and eventually disappear over a period of weeks. Angiogenic growth factors can stimulate capillary growth over distances of 2 to 5 mm.[70] It is believed that mechanisms to inhibit angiogenesis exist to prevent an uncontrollable cascade of neovascularization. Evidence suggests that pericytes can suppress endothelial growth by direct contact.[66] Thus, the physiologic response of angiogenesis may be analogous to the blood coagulation pathway that should be maintained at a steady state of control. In soft-tissue wound repair, macrophages, lymphocytes, mast cells, and platelets are involved in releasing various factors that modulate angiogenesis.[71,72]

Nerve Section

Sensory and sympathetic nerves are severed in the process of flap elevation. Although loss of sensation may limit the usefulness of the flap after transfer, adrenergic denervation has implications for flap survival. When a sympathetic nerve is divided, catecholamines are released from the nerve terminal, and the mechanism for catecholamine reuptake is eliminated.[73-75] A local "hyperadrenergic state" exists, which produces vasoconstriction mediated by α-adrenergic receptors in the cutaneous vasculature.[73]

The vasoconstricting effect of sympathectomy further reduces total flap blood flow.[76,77] which has already been decreased by division of supplying vessels. This further reduction negatively affects the ratio of perfusion pressure to the critical closing pressure of the arterioles in

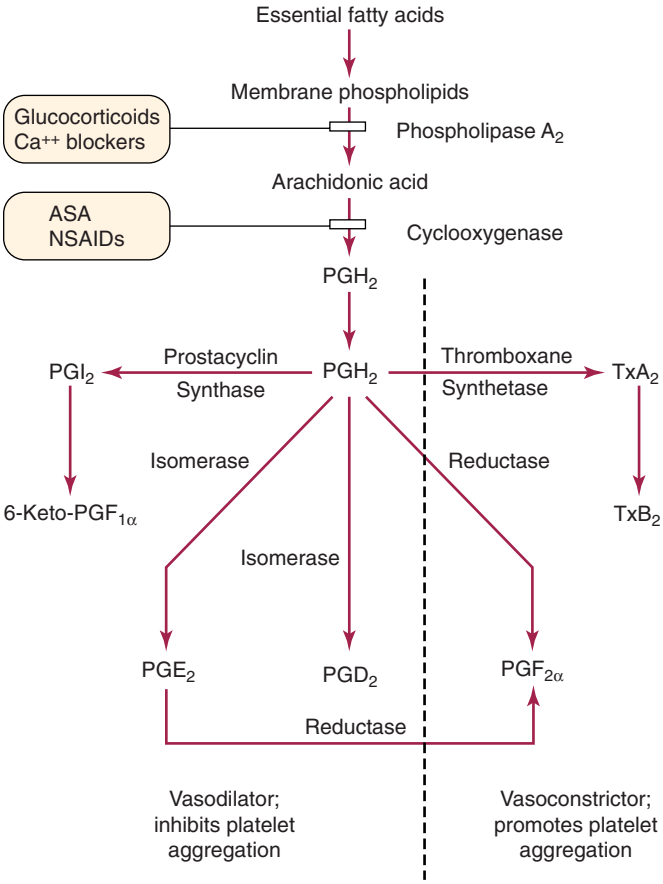


Figure 79-9. Synthesis of prostaglandins (PG) and thromboxanes (Tx) and their general effects in the cutaneous circulation. ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

the subdermal plexus. A greater proportion of the distal flap is excluded from the blood supply, and necrosis becomes more likely. The stored transmitter is depleted within 24 to 48 hours,[73] and blood flow increases as the concentration of norepinephrine declines.[77] In critical areas of the flap, the time to recovery of nutrient blood flow may be delayed sufficiently to produce additional necrosis.

Inflammation and Prostaglandins

The surgical trauma and ischemia associated with an acutely raised flap result in an inflammatory response. Histamine, serotonin, and kinins are released into the extracellular compartment after flap elevation, increasing the permeability of the microcirculation. The result is a rise in the concentration of proteins and cells within the extracellular space. The presence of nonbacterial inflammation beginning a few days before flap elevation has been shown to improve flap survival,[78-80] presumably as a result of an increase in local blood flow.

The inflammation created during flap elevation may have deleterious effects because of the resultant edema formation. In addition to compromising capillary blood flow and altering the relationships of the Starling equation, interstitial edema increases the diffusion distances between cells. The effect is enhanced because of the inverse square law for diffusion. Edema also can constitute a direct barrier to diffusion.[23,29]

The action of the primary mediators of the inflammatory response (histamine, serotonin, and kinins) is short-lived. After kinin formation and in the presence of complement, prostaglandins are synthesized by injured cells. Prostaglandins play an important role in the later stages of the inflammatory reaction while simultaneously initiating the early phases of injury repair.

Prostaglandins are derived from essential fatty acids that are incorporated in membrane phospholipids (Fig. 79-9). Activation of phospholipases results in the production of prostaglandin (PG) H_2 by cyclooxygenase. Prostaglandins E_1 and E_2 can be synthesized from PGH_2 by isomerases in the vascular endothelium. PGE_1 and PGE_2 produce vasodilation. PGD_2 also is formed by an isomerase reaction and is the principal cyclooxygenase product of the mast cell. Its effects on the cutaneous microvasculature are similar to those of PGE_1. Prostacyclin (PGI_2) is a vasodilating agent and inhibitor of platelet aggregation that is derived from PGH_2 through the action of prostacyclin synthase. In the skin, PGI_2 is produced primarily in the endothelial cells of blood vessels.[81,82]

Thromboxane synthetase, which converts PGH_2 into thromboxane (Tx) A_2, is located primarily in the platelets. Its effects include vessel constriction and promotion of platelet aggregation.[83] TxA_2 is unstable and is rapidly converted into TxB_2. $PGF_{2\alpha}$ is derived from PGH_2 by a reductase reaction. A marked increase in resistance is seen in cutaneous arteries, arterioles, and venules in the presence of $PGF_{2\alpha}$.[84] The synthesis of prostaglandins and thromboxane can be altered by pharmacologic manipulation. The action of phospholipase A_2 can be inhibited by drugs that reduce the availability of calcium. Glucocorticoids also affect phospholipase A_2 activity by inducing the synthesis of a protein that inhibits the enzyme.[85] Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with the cyclooxygenase enzyme, inhibiting the synthesis of PGH_2.

Prostaglandins clearly play a role in the inflammatory response after flap surgery. Prostacyclin levels increase after flap elevation, with a peak concentration around 7 days, and then decrease to postoperative day 21.[81] PGE_2, $PGF_{2\alpha}$, and TxB_2 levels also rise after the creation of a flap.[86] The increase in PGE_2, $PGF_{2\alpha}$, and TxB_2 can be blunted by creation of a bipedicled flap. Conversion to a single-pedicle flap ("delay") results in decreased levels of thromboxane and a higher level of PGE_2, which remain elevated for at least 7 days.[87] Whether these changes in prostaglandin levels represent a cause or a side effect of the observed phenomenon remains to be seen.

Reperfusion Injury

Controversy and, often, confusion surround the terms no-reflow and reperfusion injury. *No-reflow phenomenon* connotes the condition in which zone I perfusion has been reestablished but zone II or III failure prevails.[76,80,83,86,88-90] *Reperfusion injury* describes the observation that tissues tolerate short periods of total ischemia fairly well but exhibit histologic injury after return of perfusion—thus, injury apparently caused by reperfusion.[91,92] Both terms imply a period of ischemia, and both conditions result in microcirculatory failure.

All flaps experience some ischemia, and return of blood flow may result in microcirculatory impairment.[53,93] Free radicals form during reperfusion and cause tissue injury, but other factors, such as hyperosmosis from lactic acid accumulation,[94] have also been implicated.[95,96]

Free Radical Formation

When oxygen becomes available with reperfusion, an additional menace to flap survival is produced—the free radical. This byproduct of reperfusion can cause damage at the cellular and subcellular levels,[97,98] contributing to postischemic tissue necrosis. The neutrophil appears to play a major role in the mediation of reperfusion injury.[99]

Free radicals are extremely reactive compounds because of an unpaired electron in their outer orbits. Oxygen free radicals are formed by the sequential univalent reduction of molecular oxygen. The superoxide anion radical (O_2^-) is formed by the addition of a single electron to molecular oxygen. Superoxide is a byproduct of ATP production in the mitochondria and other oxidation-reduction reactions.[98] Polymorphonuclear cells, a second source of superoxide radicals, are released in response to bacterial inflammation.[97]

A major source of free radicals in ischemic tissue is the enzyme xanthine oxidase (Fig. 79-10).[100] With ischemia, high-energy phosphate compounds are converted to hypoxanthine, which accumulates in the tissues. When oxygen becomes available with reperfusion, xanthine oxidase catalyzes the conversion of hypoxanthine into uric acid, producing superoxide in the process. This reaction is believed to be an important mechanism in ischemic tissue injury in skin flaps.[50] The role of xanthine oxidase has been brought into question by the fact that some investigators have found xanthine oxidase activity in ischemic

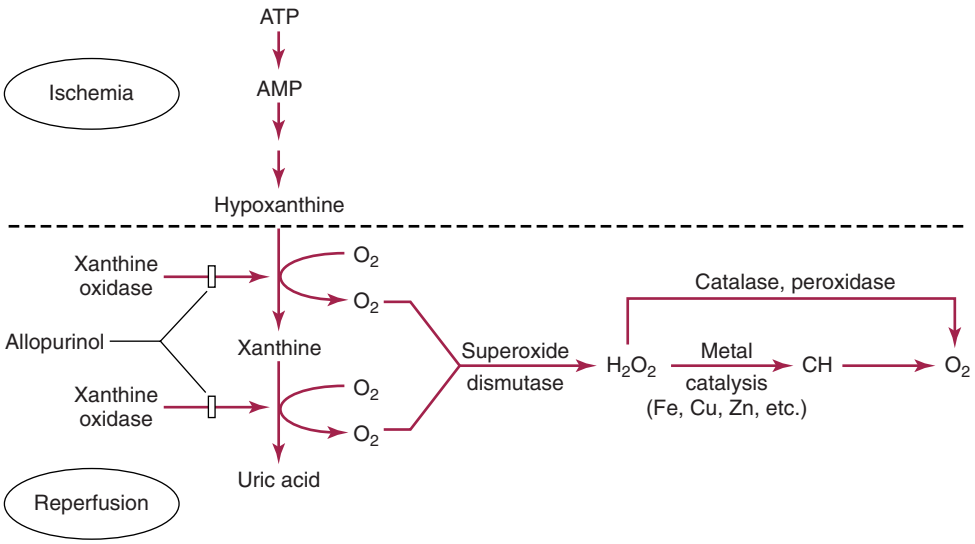


Figure 79-10. Xanthine oxidase. Possible mechanism for formation of oxygen-derived free radicals during reperfusion after ischemia and the subsequent reduction of the superoxide. AMP, adenosine monophosphate; ATP, adenosine triphosphate.

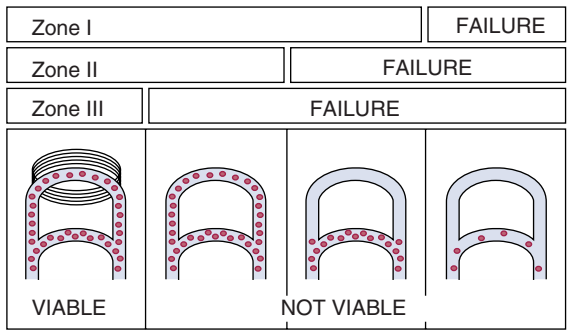
skin[27,101] but others have not.[102] Xanthine oxidase activity has been found in normal rat skin and increases its activity after venous occlusion, reperfusion,[27] and flap elevation, with the highest levels present distally.[43] Tissue damage resulting from production of free radicals can occur through lipid peroxidation of the cellular membrane and denaturation of the intracellular matrix.[98] Delayed neovascularization has been proposed as another consequence of free radical damage affecting proliferating endothelial cells.[103]

Capillary Obstruction (No-Reflow Phenomenon)

Arterial and random flaps can tolerate several hours of total avascularity and remain viable.[104] When the critical ischemia time for a flap is exceeded, an ischemia-related obstruction to blood flow, known as the *no-reflow phenomenon*, develops. Even though large vessels (zone I) have adequate flow, there is no perfusion in zone II or III. The no-reflow phenomenon was described in skin flaps by May and colleagues.[105] Swelling of the endothelial and parenchymal cells, coupled with intravascular stasis and eventual thrombosis, leads to loss of nutritive flow. Interactions between polymorphonuclear cells and endothelial cells appear to play a fundamental role in the generation of a reperfusion injury.[96] Both cell groups produce cytokine and proadhesive molecules that affect the inflammatory response.[93] Polymorphonuclear cells adhere to the vascular wall and generate proteases and oxygen free radicals that injure the endothelial cells.[106]

Flap Biomechanics

Skin flap biomechanics are governed principally by collagen and elastin.[107,108] The interplay of these components has a direct influence on the results of flap wound closure. Collagens I and II constitute the principal structural framework of the extracellular matrix.[109] Elastic fibers, meanwhile, are responsible primarily for the elasticity and compliance of the skin. When skin is stretched, the fine elastin network initially allows easy deformation. This is demonstrated on the stress-strain curve (Fig. 79-11).[110] As the force (stress) applied to the skin increases, randomly arranged collagen fibers begin to lengthen in the direction of the force and deformation becomes more difficult (section II). Further lengthening becomes difficult. Once the collagen fibers have all become oriented longitudinally with the force, little further deformation is possible with increasing stress (section III). Skin in section III of the curve behaves like elderly skin, suggestive of the maintenance of collagen biomechanics with aging. As patients age, there is a progressive decrease in elastic fibers.[111] Thus, less force is necessary to produce lengthening. Older patients can therefore be expected to have less wound tension.



Temp	True pos	False pos	False pos	True neg
Doppler	True pos	False pos	True neg	True neg
$TcPo_2$	True pos	True neg	True neg	True neg
Fluoro	False neg	True neg	True neg	True neg

Figure 79-11. Perfusion types. Zones of circulatory impairment. The relationship of microcirculatory impairment and anomalous readings of common measurements of flap perfusion is shown. All zones should be functioning for cell viability, and zone III is the first to fail. Zone III failure is shown as a loss of interstitial flow, even though capillary blood flow is potentially still present. Zone II failure occurs with loss of capillary blood flow; arteriovenous shunt flow may still be present, but it is not nutritive. Finally, with zone I failure, the flap is ischemic. See text for a discussion of the monitors of perfusion. Doppler, laser Doppler velocimetry; Fluoro, fluorometry; $TcPo_2$, transcutaneous oxygen tension; Temp, temperature measurement.

Wound tension is an important factor in flap survival as well as scar formation. Excessive tension in skin flaps is associated with greater flap necrosis.[112,113] This is probably secondary to a drop in blood flow with increasing wound tension.

Creep refers to the increase in strain (change in length relative to original length) seen when a constant stress (force) is applied to the skin. *Stress relaxation*, on the other hand, refers to the decrease in stress that occurs when skin is held under tension at a constant strain.[3,114] Thus, the physiology of skin is altered over time by the application of a constant stress. These properties are responsible for the effects seen with tissue expansion and serial excisions of lesions.

Flap undermining is routinely performed during flap elevation and wound closure. It is the release of the attachments of the skin to

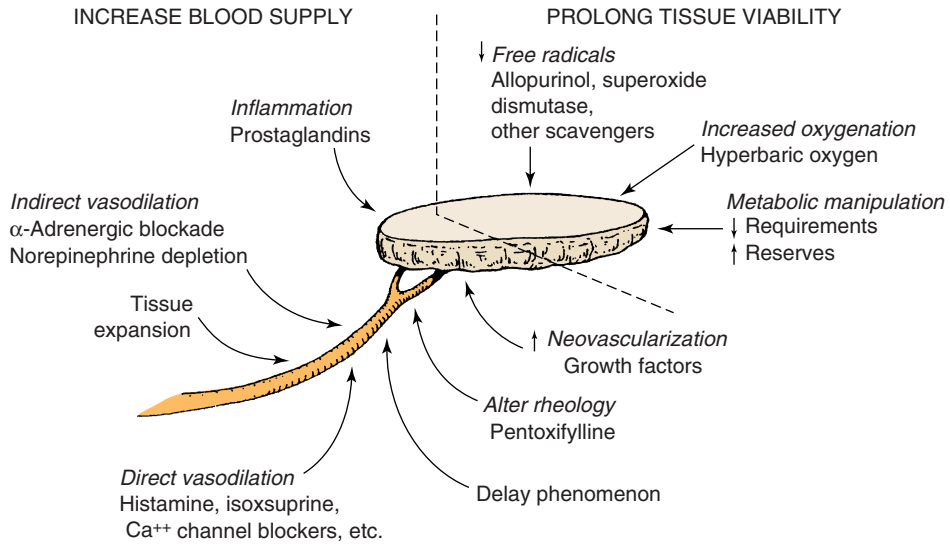


Figure 79-12. Experimental attempts to affect flap survival.

the underlying tissue that results in a decreased wound tension when undermining is performed.[115] The force required to counteract the resistance between the dermis and underlying tissue is the shearing force. In an animal model, the reduction in the shearing force, and thus wound tension, was found to decrease with undermining up to 4 cm. Further undermining did not produce more improvement in wound tension.[114]

Attempts to Alter Skin Flap Viability

Increased Blood Supply

Skin flap failure can occur from extrinsic and intrinsic causes.[116] Extrinsic reasons for flap necrosis are reasons not resulting from the design of the raised flap. Examples are systemic hypotension, infection, and pedicle compression. These factors often can be overcome in the clinical situation. The primary intrinsic factor affecting flap survival is inadequate blood flow. Numerous experimental attempts have been made to influence flap microcirculation or decrease the deleterious effects of inadequate flap blood flow (Fig. 79-12). The most successful has been flap delay. Table 79-1 shows the zones of perfusion affected by various interventions to increase flap survival.

Delay

Four things are accepted about the delay phenomenon. First, surgical trauma is required to cause it. Second, a large percentage of the neurovascular supply to the flap should be eliminated. Third, delay results in increased flap survival at the time of tissue transfer. Fourth, the beneficial effects can last up to 6 weeks in humans.[117] To explain this phenomenon, three theories regarding the mechanism of delay have been developed: (1) delay improves the blood flow, (2) delay conditions the tissue to ischemia, and (3) delay closes arteriovenous shunts.[118] Most later studies support a mechanism resulting in increased circulation to the flap; how this occurs remains to be proven.[117]

The percentage of arteriovenous shunt flow to total blood flow is similar in delayed flaps and acute flaps.[77] Delayed flaps simply have an increase in total blood flow. The addition of systemic norepinephrine decreases the blood flow in delayed flaps to the level seen in acute flaps. Thus, one effect of delay is a decrease in vasoconstriction in the distal portion of the flap.

Flaps delayed as few as 24 hours survive to a greater length and can tolerate longer periods of ischemia.[119,120] Distal perfusion in the pig flank flap increases with a bipedicled flap delay up to 4 days. No further increase in perfusion occurs, extending delay up to 14 days.[121,122] Pang and colleagues[77,93] theorized that after a delay, reduced vasoactivity of the small arteries allows delivery of more blood to the distal portion of the flap. This modulation could occur by release of vasoconstrictive substances (i.e., norepinephrine, thromboxane, and serotonin) during elevation of the bipedicled flap. Degeneration release of norepinephrine occurs soon after flap elevation, with norepinephrine stores largely depleted in the first 24 to 48 hours.[82,123] In bipedicled flaps, Cutting and associates[121,124] found the catecholamine level beginning to rise 4 days after flap construction; other researchers have found the catecholamine levels to be depressed over a greater period. Necrosis is not seen with the first stage of delay because the bipedicled flap has an adequate blood supply. After depletion of the catecholamines, a relative state of sympathectomy develops. Because of the catecholamine depletion, conversion of the delayed flap to a single pedicle is not accompanied by the same degree of vasoconstriction.[75]

Early after elevation, the vasculature to the flap has a greater sensitivity to the effects of adrenergic drugs. Intravenous norepinephrine decreases blood flow to a myocutaneous flap, even in the presence of increased blood flow to control skin.[125] This hypersensitivity to exogenous norepinephrine can be partially blocked by management with phenoxybenzamine, an α-adrenergic blocking agent. The period of hypersensitivity to norepinephrine lasts slightly less than 1 week[73]

Table 79-1

Zones of Perfusion Affected by Various Interventions to Increase Flap Survival

Intervention	Affected Zone(s)
Flap design	I
Delay	I, II
Vasodilators	II
Neovascularization	II
Rheology	II
Inflammation	II, III
Antioxidants	II, III, IV
Metabolic manipulation	II, IV
Increased oxygenation	IV

and correlates with the period of decreased tissue norepinephrine found after flap elevation.[121] Recovery from the hyperadrenergic state also appears to play a role in the delay phenomenon.

Vasodilators

Indirect Vasodilators

The intense vasoconstriction associated with the release of norepinephrine after flap elevation should hinder flap survival. One of the benefits of flap delay seems to be depletion of norepinephrine before creation of the flap to be transferred. If this vasoconstriction could be blocked or reversed, the duration and severity of distal flap ischemia should be lessened. The result would be increased flap survival without the need for delay.

α-Adrenergic blocking agents are directed against the catecholamine-induced vasoconstriction seen after flap elevation. In some studies using the rat model, phenoxybenzamine resulted in improved flap survival.[51,126,127] Phenoxybenzamine and phentolamine ointments applied topically were also found to be effective in increasing flap survival in the rat model.[127] Other investigators have been unable to reproduce beneficial effects in the rabbit or pig.[37,128] Depletion of norepinephrine stores through the use of reserpine[129] and guanethidine[130] before flap elevation has also met with mixed results and systemic toxicity.

Several anesthetic agents have vasoactive properties and may influence flap survival. Because general anesthetics are often used during the creation of larger flaps, their potential effects on flap survival are important. Use of isoflurane (a sympatholytic vasodilator) was found to be associated with significantly better flap survival than nitrous oxide, which induces vasoconstriction.[131] Verapamil and lidocaine have also been found to decrease skin flap necrosis when used locally in the vicinity of the pedicles of axial pattern flaps.[132]

Direct Vasodilators

Multiple topical anti-ischemic agents have been found to have beneficial effect on skin flaps in experimental models.[133-135] This finding has not yet translated into widespread clinical use of these agents, however, because the experimental and clinical results have been mixed. Direct vasodilators such as histamine, hydralazine, nitroglycerin, pentoxifylline, and topical dimethylsulfoxide have been found to have both a beneficial result and no effect on skin flap survival.[43] Isoxsuprine is a phenylethylamine derivative of epinephrine having α-adrenergic receptor antagonistic and β-adrenergic receptor agonistic properties, resulting in relaxation of vascular smooth muscle. In high doses, isoxsuprine can decrease viscosity and inhibit platelet aggregation. Isoxsuprine was found to increase blood flow in the area of the dominant artery in porcine myocutaneous and arterial flaps. Unfortunately, no improvement in blood flow was seen in the distal random portion of the flaps or in flap survival.[136,137] The smaller vessels in the distal random portion of a flap were theorized to differ in sensitivity from muscular or axial arteries to vasodilator drugs. Manipulation of these distal vascular channels appears to be critical in increasing flap survival.

Calcitonin gene–related peptide is a bioactive neuropeptide found in primary sensory neurons. A potent vasodilator, it is thought to stimulate smooth muscle relaxation by an endothelial-dependent mechanism. Administration of this neuropeptide improves blood flow and survival in ischemic skin flaps and delays the onset of the no-reflow phenomenon.[138,139] Pretreatment with capsaicin, which depletes neuropeptides from primary sensory neurons, results in a decreased flap survival.[140] These findings suggest a potential role for primary sensory neurons in cutaneous vascular control and flap survival.

Prostaglandins have multiple effects on healing wounds and the vasculature to the skin, including vasodilation and decreased platelet aggregation. Prostaglandins E_1 and E_2 have been found to decrease skin necrosis in random skin flaps.[141] PGE_1 also effects leukocyte-endothelial cell adhesion, a factor in ischemia-reperfusion injury. Administration of prostaglandin E_1 may increase flap survival by decreasing the expression of anti–intercellular adhesion molecule-1, thus limiting leukocyte-endothelial cell adhesion.[86] The mechanism of delivery for these substances has been by topical application, with absorption through the skin, or by subcutaneous or intravenous injection. Attempts to improve delivery have shown promise in the laboratory. The vasoactive drug buflomedil has been delivered bound to liposomes and found to have a measured therapeutic effect on ischemic skin flaps.[142] Topical application of nitroglycerin was shown to increase flap survival in some studies but not in all.[143-145] Nitroglycerin acts as a vasodilator with more potent venodilator than arteriodilator effects. Its action on the veins was believed to contribute to the increased flap survival. The ability to reduce platelet aggregation may be the main therapeutic benefit of nitroglycerin and other direct vasodilators that affect platelet function. Nitroglycerin and nifedipine have been found effective in improving random-pattern skin flaps in laboratory animals exposed to cigarette smoke.[146]

Neovascularization

The identification of a host of biologically active growth factors and the continued development of methods of delivery of these agents into target sites have generated enthusiasm for the application of these technologies to aid in flap outcomes. The stimulation of angiogenesis through gene transfer techniques offers hope for the treatment of ischemic tissues of various types, including flaps. Vascular endothelial growth factor (VEGF) is a potent angiogenic molecule, as is basic fibroblast growth factor (FGF-2). VEGF has shown promise, having been demonstrated in the laboratory to improve flap survival in random flaps, axial flaps, and flaps treated preoperatively.[70,117,147] In a rat model, injected VEGF-transduced mesenchymal stem cells survived in vivo and were incorporated into the capillary networks in the ischemic flaps. Compared with controls, the VEGF group demonstrated better flap viability and increased ischemic flap neovascularization, as evidenced by increased capillary density and blood perfusion of the flaps.[148] Similarly, adipose-derived stem cells, which have been found to demonstrate angiogenic potential, injected into flaps in a mouse model demonstrated a statistically significant increase in flap viability and capillary density in comparison with the control group.[149] Nitric oxide synthase inhibitors may raise VEGF levels and improve ischemic flap survival.[63] Application of growth factor can generate functional blood vessels and nonsurgically anastomose divided vessels within 2 or 3 weeks.[150] The greater neovascularization also allows earlier ligation of the original vascular pedicle with complete tissue survival.[65,151] The delay phenomenon does not work by an angiogenic mechanism, however, and attempts to improve survival of the random portion of a pedicled flap with fibroblast growth factors have had mixed results.[142,152-155]

Rheology

In a homogeneous fluid that exhibits equal shear stress at different rates of shear, flow (Q) in a vessel can be approximated by Poiseuille's equation:

$$Q = \frac{\pi r^4 (\Delta P)}{8nl}$$

where ΔP equals pressure gradient; r^4 equals the fourth power of the vessel radius; l equals vessel length; and n equals viscosity.[13] Although blood is a non-newtonian fluid, the qualitative relationships in the equation remain. In larger vessels, the radius is a dominant factor, but in the capillary microcirculation, viscosity becomes more important. Decreasing the viscosity of blood may make it possible to increase flow to the distal random portion of the acutely raised flap and beneficially affect flap survival. Viscosity is influenced by the hematocrit, serum proteins, temperature, erythrocyte deformability, aggregation, and other factors.[156] Each of these factors can be potentially manipulated with a resultant change in viscosity.

Hemodilution has been shown to decrease viscosity and to have a beneficial effect on flap survival.[157,158] Reducing blood viscosity by protein depletion also results in increased flap survival in rats.[159]

Pentoxifylline and low-viscosity whole blood substitutes (Fluosol-DA) also lower viscosity. Pentoxifylline is a hemorheologic agent that increases erythrocyte deformability and decreases platelet aggregability.[156] When given 7 to 10 days before flap elevation, pentoxifylline improves flap survival.[156] Beneficial effects of limited preoperative

dosing with pentoxifylline have not been uniform, however.[81,160-163] Administration of Fluosol-DA also has failed to increase flap survival in a consistent manner.[164]

Inflammation

The surgical trauma associated with an acutely raised or a delayed flap engenders an inflammatory response. This response results in a local increase in blood flow that could benefit flap survival. Improved flap blood flow and survival can occur with different methods of creating an inflammatory response before flap creation.[78,165] The beneficial effects of inflammation on flap survival also can be seen on a flap raised adjacent to a previously delayed flap.[166] Attempts to increase flap blood flow and survival with 5 days of low-power laser burns have had mixed results.[167,168] These studies show that the inflammatory response has the potential to improve survival without sympathectomy or vascular division.

The mechanism by which inflammation produces a beneficial effect appears to involve the products of cyclooxygenase metabolism of arachidonic acid. Administration of PGI_2 leads to dilation of the arterial pedicle and increased flap blood flow.[169] The result is increased flap survival.[86,141,170] Systemic administration of PGE_1 increases flap survival at low doses but can hinder flap survival at higher doses, which cause hypotension.[171] Topical administration of PGE_1 also improves flap survival but should be applied to the area of critical ischemia to be effective.[43,172,173] Additional prostaglandin effects, such as increased erythrocyte deformity and decreased platelet aggregation, have been proposed as the mechanism of better survival with prostaglandin administration.[171,174,175]

Cyclooxygenase inhibitors, such as indomethacin and ibuprofen, have been shown to increase skin flap viability and prolong tolerance of ischemia.[141,176] Glucocorticoids, which inhibit phospholipase activity, also have improved flap survival in some studies[128,177,178] but not in others.[179] Blocking TxA_2 synthesis has had mixed results.[180,181]

Tissue Expansion

Tissue expansion has been shown to increase the size of the transferred flap in experimental animals and humans. Examination of expanded skin in the guinea pig has shown an increase in the thickness[182] and mitotic activity[115] of the epidermal layer, indicating epidermal proliferation. Blood flow in expanded tissue is greater than that in skin overlying a noninflated expander 1 hour after creation of a pedicled flap.[44] The increase in blood flow to expanded skin seems to be short-lived.[183] Apart from the acute changes seen with expander manipulation, flap viability and blood flow in expanded skin appear to be similar to those seen in delayed flaps.[184]

Prolonged Viability

Protection against Harmful Agents

The formation of free radicals with reperfusion and the return of molecular oxygen to ischemic tissue place an increased burden on flap survival. Research has focused on reducing the production of free radicals and using agents that remove free radicals (free radical scavengers) from the immediate environment.

Nitric oxide is a radical with vasodilating properties that protects tissues from neutrophil-mediated ischemia-reperfusion injury.[185] L-Arginine, a nitric oxide precursor, is converted into nitric oxide by the enzyme nitric oxide synthase. This precursor has been found to have a protective effect on myocutaneous island flaps as well as random-pattern skin flaps.[186,187] Nitric oxide inhibition decreases skin flap survival.[188]

Ischemia-reperfusion injury occurs in zones II and III, where a cascade of events may lead to flap failure upon the reestablishment of blood flow after prolonged ischemia. Platelets play a role in this cascade of events. Inhibition of platelet activation by a platelet glycoprotein IIb/IIIa inhibitor has shown promise in the enhancement of skin flap survival after a long period of ischemia.[189,190]

Preoperative administration of allopurinol (a xanthine oxidase inhibitor) prevents the increased xanthine oxidase activity seen with acute flap elevation.[191] Improved survival of dorsal rat flaps has been accomplished with allopurinol given at high doses,[27,192,193] lower doses having no effect.[192] The high doses required to obtain a beneficial effect have led to concern about the use of allopurinol to increase flap survival in the clinical setting.

A number of free radical scavengers are available to protect the tissues from destruction by free radicals. Superoxide dismutase (SOD), an intracellular free radical scavenger, catalyzes the conversion of superoxide to hydrogen peroxide (H_2O_2) and molecular oxygen. When given systemically, SOD is an effective scavenger of the superoxide radical regardless of its source.[94] SOD treatment has resulted in improved flap survival[193,194] and increased tolerance of flaps to ischemia.[95,195] Improved flap survival also has been shown with a number of other naturally occurring compounds with free radical scavenging properties. They include deferoxamine,[50] vitamin E, vitamin A, vitamin C, glutathione,[196] various amino acids,[197] and amino acid derivatives.[198]

Hyperbaric Oxygen

Improvement in flap survival with hyperbaric oxygen treatment has been documented,[12] but it has not been a consistent finding.[161,199] Hyperbaric oxygen treatment increases blood oxygen-carrying capacity by 20%.[200] This relative increase is greater with a low hematocrit because the additional oxygen is dissolved in the plasma rather than carried by hemoglobin. A greater effect of hyperbaric oxygen treatment may be increasing oxygen diffusion from surrounding perfused tissue to the ischemic portion of the flap.[3] Improved flap survival also occurs with treatments using hyperbaric air, showing that increased oxygen can be delivered with a rise in ambient pressure alone.[201]

The beneficial effect of hyperbaric oxygen in pedicled flaps includes decreased leukocyte adherence, reduction of edema caused by vasoconstriction, and neovascularization in irradiated tissue.[200,202,203] Animal studies have confirmed that the treatment should be given early, and one study suggested that it should be used often.[161,204] There is little benefit from hyperbaric oxygen if the treatment is given 24 hours or more after flap elevation.[200]

In a retrospective study of 65 patients with pedicled flaps that were determined by the surgeons to be in a high-risk group, hyperbaric oxygen was beneficial.[202] Although there is evidence that hyperbaric oxygen is effective for impaired flaps, it is not cost effective to treat every flap.[205] Determining which flaps need treatment and which flaps will benefit is key. French investigators found that a hyperbaric oxygen challenge test (test dive) was predictive of successful outcome if the transcutaneous oxygen measurement rose 50 mm Hg or more. Still, the researchers noted the need for further studies to determine indications for hyperbaric oxygen.[19]

Metabolic Manipulation

Additional strategies for increasing flap survival include reducing the metabolic requirements and enlarging the metabolic reserves of skin. These approaches are based on the idea that flap necrosis occurs when tissue metabolic demand is greater than what the blood supply can deliver. Decreasing temperature is an effective way to reduce metabolic activity and delay necrotic changes, but improvement in flap survival is not seen with this maneuver.[206]

Administration of ATP–magnesium chloride complex increased survival in the rat abdominal flap.[43] The metabolic support provided by this compound was believed to delay the onset of irreversible cell damage. Difluoromethylornithine (DFMO) was found to increase survival of abdominal flaps in rats.[207] It appears to decrease metabolic demand by inhibiting the synthesis of polyamines, which are required for protein synthesis and cellular proliferation.

The use of a vacuum-assisted closure (VAC) device was first described in 1997 for the stabilization of skin grafts.[208] Shear stresses, hematoma, and seroma collection can contribute to flap failure or poor skin-graft take. Immobilization of the flap with the device limits shear stresses, eliminates fluid collections, and decreases bacterial contamination. Traditionally vacuum-assisted closure devices have been used in abdominal wounds and chronic leg ulcers,[209] but their use has expanded to the treatment of complicated head and neck wounds[210] and in securing skin grafts to microvascular free flaps as well as to the donor sites.[211] The negative pressure provided by the vacuum-assisted closure device

has circumvented the limitations of conventional tie-over bolster dressing and has allowed successful graft take in complex three-dimensional flaps.[210,211] Even irradiated wounds, previously thought to be a contraindication to split-thickness skin graft reconstruction, have been successfully managed with split-thickness skin grafts and vacuum-assisted closure.[212]

Impaired Flaps

In the majority of flaps carefully designed and accomplished in healthy patients, flap survival is the rule, and methods to improve survival and extensive monitoring or treatment of the flap are not warranted. The exceptions to the rule should be identified so extra efforts to ensure survival are reasonable and cost effective. Several factors place the patient in a higher risk category.

Smoking tobacco is associated with an increased chance of flap necrosis in facelift operations.[213] Exposure to tobacco smoke resulted in greater flap necrosis of dorsal flaps in rats[146] and hamsters.[214] The deleterious effects of nicotine appear to increase with prolonged exposure. The mechanism by which tobacco or nicotine decreases flap survival is unknown but may involve direct endothelial damage, vasoconstriction caused by catecholamine release, or local concentrations of prostaglandins.[215,216] Long-term, low-dose nicotine (comparable with human smoking exposure) was used in a rat model to document decreased capillary blood flow and survival; these effects could be avoided if the nicotine was withdrawn 2 weeks before the flap was raised.[215]

Irradiation has been shown to be deleterious to flap survival in some studies[2] but not in others.[161,217-219] The reason for this discrepancy is probably differences in the radiation regimen administered (i.e., radiation dosage, fractionation, and surgical timing in respect to the irradiation). Radiation treatment results in endarteritis obliterans and altered wound healing. Even in previously irradiated tissue, the delay phenomenon continues to improve flap survival.[217,220,221] Flap neovascularization is delayed but not eliminated after irradiation. The use of angiogenic growth factors has the potential to increase the viability of irradiated skin flaps by means of accelerated revascularization.[151]

The ischemia time during the transfer of free flaps (called primary ischemia) appears to hinder the flap's ability to tolerate a second ischemic insult. The longer the period of perfusion after the microvascular anastomosis (called the reperfusion period), the better a flap will tolerate secondary ischemia. Porcine ventral arterial island flaps initially exposed to 2 hours of ischemia followed by 12 hours of blood flow had a 50% survival rate after a subsequent 7.2 hours of "secondary ischemia,"[222] The same researchers found that 13 hours was required for the initial ischemic event to produce a 50% survival rate.[223]

Vascularity of the recipient bed is an important factor in free flaps. Experimentally, a pedicle can be divided 6 days after flap creation.[65,67] Typically in clinical situations, the pedicle is no longer monitored after 1 week, although there are cases of late flap failure.[224,225] If the flap is placed into a bed with poor vascularity, dependence on the pedicle may be prolonged. If late pedicle failure occurs in a flap with a poor vascular bed in which neovascularization has not occurred, the chance of late complications could be greater.

Diabetes may be considered a risk factor because of the small vessel disease in diabetes, although investigators did not find decreased flap survival in streptozotocin-induced diabetic rats. They did find slower endothelial growth at the anastomosis but concluded that diabetes is not a contraindication to the use of a free flap.[226] In a study on rats, older rats were found to have less tolerance to muscle ischemia than young rats, and this difference was assumed to be related to decreased mitochondrial function.[227] Fluid management also can have an impact on flap survival. Fluid overload increases flap edema, and at the other extreme, intraoperative systemic hypotension has been shown to be detrimental.[228] Central venous pressure monitoring was not found to be helpful.[229,230]

Flap Salvage

Once a flap is identified as being at risk for necrosis, action can be taken to improve survival. Zone I manipulations are the most effective. In pedicled flaps, efforts to enhance zone I perfusion are limited to preoperative planning, flap execution and design, and surgical delay. If a pedicled flap is effectively executed, its loss results from failure of zones II and III, which will develop slowly and involve the distal or random portion of the flap. Clinical efforts to improve zone II or III failure are limited to methods such as hyperbaric oxygen and leeching. Of the hundreds of pharmacologic agents that have been tested for this application, none has gained widespread clinical use.

In contrast, the global ischemia of free flap failure often relates to a zone I failure—thrombosis or compression of the pedicle. This failure often is acute and relatively easy to detect and repair. If the zone I failure is not quickly resolved, the injury progresses to zones II and III.

Free flaps need intensive postoperative monitoring. There are several different methods of monitoring free flaps, but none is foolproof, and frequent observation by experienced personnel is still the gold standard. Pedicle failure can be determined early, and the flap can be salvaged in many cases by exploration of the anastomosis and clearing of the thrombus.

Because of the accessibility of the vessels and a short period of nonperfusion (primary ischemia), the question was raised whether washing out flap vessels could potentially improve survival in the event of secondary ischemia,[224] analogous to organ transplantation. University of Wisconsin solution has been used to effectively decrease perivascular swelling in the microvasculature of organ systems.[169] Babajanian and and colleagues[231] used it as a washout solution to improve survival in free flaps.

An intriguing application of perfusion washout technology is extracorporeal circulation,[232] which investigators theorize could be used if there were no suitable donor site vessels. Extracorporeal circulation was studied in a flow-through venous free flap. Only a plasma solution was able to maintain viability over 3 days of extracorporeal infusion, although three other test perfusates caused massive edema and total obstruction to perfusion.

Perfusion washout also has been studied for its ability to improve survival after the thrombosis is cleared from the anastomotic site. University of Wisconsin solution caused greater improvement when used during secondary ischemia than during primary ischemia, indicating that it may be better for flap salvage than for prophylaxis.[232] Urokinase has been used for the antithrombotic effects at the anastomosis and, because of microemboli, at the capillaries (zone II).[233,234] Intravascular heparin was not useful after thrombus formation.[235] Medicinal leeches have been used clinically.[236] The leeches are thought to relieve microcirculatory congestion during active feeding and for several hours afterwards because of the antithrombotic effect of the leeches' salivary fluid. There is a risk of *Aeromonas* infection with their use, however. The "chemical leech" and mechanical leeches have been described.[237] Relief of vascular congestion and edema may also be possible with microdialysis techniques, which have been used to reduce skin flap edema in a rat model.[238]

Hyperbaric oxygen has been used for free flap salvage. In a study of a rat epigastric free flap after 8 hours of global ischemia, hyperbaric oxygen increased survival and increased distal blood flow as shown by laser Doppler velocimetry.[203] In a similar model, hyperbaric oxygen inhibited the xanthine oxidase system and improved free flap survival after 18 hours of nonperfused storage.[239] Hyperbaric oxygen therapy will not be effective treatment unless the thrombosis has been cleared, but it may prolong viability and increase neovascularization.

Wound Healing

The creation of a surgical flap results in a cutaneous wound that requires repair. A series of overlapping and closely coordinated events is initiated with disruption of the skin surface. The events associated with wound repair are relatively consistent regardless of the causative agent. Multiple cell types participate in wound repair (Table 79-2).

Disruption of the protective layer of skin results in exposure of the subepithelial layers and vascular endothelium along with extravasation of blood products. A blood clot is formed that both provides a wound matrix for cell migration and initiates the inflammatory response. This is the beginning of tissue repair. After establishment of an inflammatory phase, a phase of tissue proliferation occurs that

Table 79-2

Cell Types Shown to Be Involved with Wound Repair

Tissue	Cell Types
Vascular	Platelets, macrophages, neutrophils, endothelial cells, smooth muscle
Epidermis	Keratinocytes, melanocytes, Langerhans cells
Adnexal structures	Outer root sheath cells, hair dermal papilla cells
Dermis	Fibroblasts, myofibroblasts
Nervous system	Neurons
Subcutaneous fatty layer	Adipocytes

involves the formation of granulation tissue, reepithelialization, and wound contraction. Finally, a prolonged phase of tissue remodeling completes the healing process. All three phases of wound healing overlap in time and appear to be tightly coordinated. Much of the later work in wound repair has involved the regulation of and communication between the involved cell types that result in a well-healed wound.

Inflammatory Phase

The initial injury to the skin results in disruption of blood vessels and extravasation of blood constituents. The vascular response to injury begins with a brief period of vasoconstriction that aids in hemostasis.[106] Platelets respond by aggregating at the injury site; along with fibrinogen, fibrin, and fibronectin, they form a blood clot that reestablishes hemostasis. The clot covers the wound and provides an initial matrix for cell attachment and migration.[240] The clot contains a variety of cytokines and growth factors. Platelets release three substances[241]: (1) Platelet-derived growth factor (PDGF) plays roles in chemotaxis for macrophages and fibroblasts, macrophage activation, fibroblast proliferation, matrix production, and angiogenesis.[242,243] (2) Transforming growth factor-β (TGF-β) is involved in keratinocyte migration, chemotaxis for macrophages and fibroblasts, and fibroblast matrix synthesis and remodeling.[107,244-246] (3) Epidermal growth factor (EGF) is active in keratinocyte migration and replication.[244,247]

Tissue injury is associated with the onset of acute inflammation and the arrival of polymorphonuclear granulocytes (neutrophils). One day after tissue injury, neutrophils constitute nearly 50% of all cells at the wound site.[248] Neutrophils help remove foreign material and bacteria from the wound. They are subsequently extruded with the eschar or cleared by macrophages. Neutrophils also release interleukin (IL)-1α and IL-1β and tissue necrosis factor-α (TNF-α),[99] all of which are early activators of growth factor expression in macrophages, keratinocytes, and fibroblasts.

Neutrophils are highly abundant in the circulation, and quite a number are collected passively along with platelets at the wound site in the blood clot. Neutrophils also appear to be specifically attracted by a subset of cytokines referred to as *chemokines*. Along with growth factors, platelets release the chemokine connective tissue–activating peptide-III (CTAP-III), which is converted into neutrophil-activating peptide-2 (NAP-2) by proteases released from neutrophils already attached to the thrombus.[249] Neutrophil-activating peptide-2 stimulates migration and extravasation of neutrophils via the chemokine receptor 2 (CXCR2). In addition, vascular endothelial cells and pericytes secrete growth-related oncogene-α (GRO-α),[99] which supports movement of neutrophils to the wound. An additional method of attracting neutrophils involves the strong and selective expression of IL-8 under the wound surface that stimulates the CXCR2 and CXCR1 (not targeted by growth-related oncogene-α) receptors. IL-8 is expressed by neutrophils and macrophages immediately below the denuded wound surface. The expression of IL-8 is induced by pro-inflammatory cytokines such as IL-1, tissue necrosis factor-α (expressed initially by neutrophils and later by macrophages), bacterial products (lipopolysaccharides), and hypoxia.[250]

Monocytes infiltrate the wound early after injury and become activated macrophages. On the third day following an injury, with wound closure and the decline of neutrophils, monocytes represent the largest blood cell population.[251] Monocytes/macrophages are attracted to the wound by the chemokine monocyte chemoattractant protein-1 (MCP-1). This chemokine is produced by resident and infiltrating mononuclear cells, keratinocytes at the wound edge, and endothelial cells. Macrophages play a central role in the inflammatory phase of wound healing. In addition to their immunologic functions as antigen-presenting cells and phagocytes, macrophages are an important source of growth factors. Macrophages release TGF-α. TGF-β, insulin-like growth factor I (IGF-I), heparin-binding epidermal growth factor (HB-EGF), FGF, PDGF, and VEGF.[70,252] TGF-α, like EGF, has a stimulatory effect on keratinocyte migration and replication.[245,253] IGF-I—also produced by keratinocytes, fibroblasts, and platelets—promotes reepithelialization and granulation tissue formation. Heparin-binding EGF, basic FGF (bFGF, or FGF-2), PDGF, and VEGF promote angiogenesis.[147,241,254,255] As its name implies, FGF also enhances fibroblast growth.[142,153]

Lymphocytes are attracted to the wound site and after 14 days are the dominating leukocyte subset. Lymphocytes interact with Langerhans cells in the epidermis and nerve endings in the dermis to play an antimicrobial role. Leukocytes also produce growth factors (e.g., heparin-binding EGF and basic FGF).[250] Lymphocytes are attracted to wound sites initially by MCP-1. After day 4, lymphocytes are attracted to wound sites by interferon-γ–inducible protein-10 (IP-10) and monokines induced by interferon-γ (Mig). The presence of these two chemokines after day 4 reflects a shift in the cytokine profile from TNF-α/IL-1 to interferon-γ.[250]

Nitric oxide (NO) is a short-lived free radical that exerts its effects at many levels.[256] Nitric oxide synthase is frequently produced in response to acute inflammatory stimuli such as wounding. NO may have a capacity for selective regulation of gene expression.[63] This would be important during the inflammatory phase of wound healing, when NO production is greatest. Production of NO is catalyzed by nitric oxide synthases (NOSs), a group of three isoenzymes, neuronal (nNOS), endothelial (eNOS), and inducible (iNOS).[64,257] NOS catalyses the oxidation of the amino acid L-arginine to release citrulline and NO.[258] NO appears to participate in the regulation of skin homeostatic functions such as circulation, ultraviolet B–mediated melanogenesis, sunburn erythema, and the maintenance of the protective barrier against microorganisms.[185] During the inflammatory phase, iNOS is elevated, with infiltrating macrophages being a major source of its expression.[257,259]

Proliferation Phase

The successful development of an inflammatory phase results in the recruitment of keratinocytes, fibroblasts, and endothelial cells. The arrival of these cells marks the transition from a process of clearing and stabilizing the wound to one of proliferation and repair. The proliferation phase consists of reepithelialization, formation of granulation tissue, and wound contraction. Like the three major phases of wound healing, these three aspects of the proliferation phase overlap in time and are closely interrelated.

Reepithelialization

Reepithelialization attempts to restore the protective barrier of the skin. It begins within hours of injury and is the result of keratinocyte migration and proliferation.

Keratinocyte Migration

Changes leading to keratinocyte migration begin early after wounding. Growth factors that enhance keratinocyte migration are EGF, TGF-α, FGF-7 (keratinocyte growth factor), TGF-β1, hepatocyte growth

factor, IGF-I, and insulin.[244,260] IL-8 is also capable of stimulating keratinocyte migration and proliferation.[250] IL-8 is highly expressed along the denuded wound surface. Keratinocytes express the receptor for IL-8 and growth-related oncogene-α. These findings suggest that the interaction of the keratinocyte with its ligand plays a role in reepithelialization.

Under the influence of these growth factors and cytokines, epithelial cells at the wound margin undergo changes that set the stage for cell movement. These changes include filament reorganization, reduction of the number of intercellular attachments, and the expression of members of the integrin superfamily of cell surface receptors.[261]

Integrin receptors are transmembrane, heterodimeric glycoproteins consisting of one α chain and one β chain. Keratinocytes, at the leading edge of the wound, express integrins that allow them to interact with fibronectin (αvβ6, α5β1), vitronectin (αvβ5), and collagen (α2β1) present at the wound margin and interwoven with the fibrin clot.[240,262] The keratinocytes are guided into the wound, migrating between the fibrin clot and the collagenous dermis through the interaction of the integrin receptors and the extracellular matrix proteins. Keratinocytes produce plasminogen activators,[263] which activate plasmin and collagenase-1 (matrix metalloproteinase-1 [MMP-1]).[189] Plasmin and MMP-1 must dissolve fibrin and collagen type I, respectively, in order for migration to occur. In partial-thickness wounds, keratinocyte migration also occurs from skin appendages, including the hair follicle.[260]

The relationship between the enzyme production of MMPs, extracellular matrix proteins, integrins, and keratinocyte migration has been nicely summarized by Parks.[189] Plasmin and collagenase-1 break down matrix barriers that impede cell migration. Keratinocytes migrate along a path of least resistance driven and oriented by collagenase-1.[109] Collagenase-1, acting on its principal substrate in the dermis (i.e., type I collagen), provides migrating keratinocytes with a mechanism to maintain their course and directionality in the wound environment during reepithelialization. In wounds, basal keratinocytes dislodge from the basement membrane and contact dermal collagen type I. The integrin α2β1 becomes concentrated at the forward-basal tip of the migrating keratinocyte. α2β1 binds dermal collagen with high affinity, and this interaction induces collagenase-1 expression. Collagenase-1 cleaves type I collagen and converts it to a gelatin, allowing the cell to migrate. The high affinity of α2β1 with dermal collagen, but not with gelatin, favors establishment of attachment to native, uncleaved, and exposed dermal collagen in the open wound surface. When continually repeated, this process provides the migrating cells with a mechanism to control their direction and to remain superficial to the dermis but deep to the fibrin clot during reepithelialization.

Keratinocyte Proliferation

Migrating keratinocytes are found on the advancing epithelial margin. Proliferating keratinocytes are found within the epithelial margin and the nearby hypertrophic epithelium behind the actively migrating cells. Keratinocyte proliferation begins 1 to 2 days after injury. The growth factors known to enhance keratinocyte replication are EGF, TGF-α, FGF-7, IGF-I, IL-1, IL-6, hepatocyte growth factor, nerve growth factor,[247,260-262] and IL-8.[250] Neuropeptides are also thought to have growth-stimulatory effects on keratinocytes through the activation of cyclic adenosine-5-monophosphate. Examples are calcitonin gene–related peptide, vasoactive intestinal polypeptide, peptide histidine-methionine, and growth hormone–releasing factor.[264] Leptin, produced in the subcutaneous layer, is reported to have growth-stimulatory effects on keratinocytes as well.[265]

Keratinocytes can express all three forms of NOS.[258] NO serves as a mediator that regulates gene expression and proliferation in keratinocytes. Proliferating keratinocytes at the wound margin and, to a lesser extent, fibroblasts express iNOS. Wound closure in iNOS-deficient mice[259] and inhibition of iNOS in normal mice[256] are delayed. These findings suggest an important role for iNOS in the regulation of epithelial movements and the reepithelialization process.

With the reestablishment of an epithelial layer, basement membrane proteins reemerge, progressing inward from the wound margin. Keratinocyte behavior returns to normal with adhesion of basal keratinocytes to the basal lamina and restoration of intercellular attachments.[251]

Formation of Granulation Tissue

At approximately 3 to 4 days following injury, a new stromal framework, known as granulation tissue, begins to enter the wound and replace the fibrin clot. Granulation tissue consists of a dermal matrix that provides a framework for cell migration, which is enhanced by new vessels migrating into the wound (i.e., angiogenesis).

Dermal Matrix

The cell that is most important in the production of the dermal matrix is the fibroblast.[266] Fibroblasts enter the wound by 2 to 3 days, and within the first week, they become the dominant cell population in the wound. As fibroblasts invade, the fibrin clot is lysed and fibronectin and hyaluronic acid are deposited, forming early granulation tissue. These molecules serve as scaffolding to which the fibroblasts can migrate and adhere.

To facilitate migration into a wound filled with cross-linked fibrin or later with a tightly woven extracellular matrix (ECM), migratory fibroblasts secrete a range of proteolytic enzymes (i.e., collagenase-1, gelatinase-A, and stromelysin-1, or MMP-1, MMP-2, and MMP-3, respectively).[267] This process occurs initially in the periphery of the clot and later more centrally as the granulation tissue grows into the wound space. At any given time, the ECM of the wound margin differs from the ECM located centrally.

The fibroblast is critical to the production of the dermal matrix producing type I and III collagens, fibronectin, elastin, and proteoglycans. Fibroblasts also contribute to growth factor production, providing connective tissue growth factor (CTGF). Connective tissue growth factor stimulates migration and proliferation of fibroblasts. Keratinocyte growth factor stimulates epidermal cell motility and proliferation. VEGF stimulates angiogenesis.[147] MCP-1, involved in neutrophil recruitment early in the inflammatory process, also attracts mast cells. The mast cells produce high levels of IL-4, which in turn stimulate proliferation of fibroblasts and decrease the expression of MCP-1 and IL-8,[268] limiting the inflammatory reaction.

NO in granulomas seems to exert an organizing influence,[269] allowing the host to assemble macrophages, directing vascular ingrowth, and compartmentalizing the inflammatory nidus.[61,270] Peak NOS activity is noted 24 hours after wounding and then declines but remains subsequently elevated for at least 14 days.[271] The macrophage is the primary cell type implicated in iNOS activity and NO production during inflammation.[272] Fibroblasts may also participate during the time coincidental with active collagen synthesis. Fibroblasts are able to produce NO linked either to endothelial NOS or, after stimulation with interferon-γ or bacterial lipopolysaccharide (LPS), to iNOS.[64,186]

When NO is inhibited experimentally, granulomas tend to become larger and have a higher bacterial load.[269] NO-deficient states (diabetes and protein-calorie malnutrition) are associated with decreased wound extracellular matrix deposition and impaired wound healing.[273,274] Excessive delivery of NO can also inhibit wound healing.[275] NO also affects wound collagen accumulation and the acquisition of wound mechanical strength. Inhibition of wound NO synthesis is accompanied by a lowered wound-breaking strength and decreased collagen deposition.[188,259,275] NO likely mediates an antiproliferative effect on skin fibroblasts in addition to its effects on collagen synthesis.[276]

Angiogenesis

The process of angiogenesis is closely related to the formation of granulation tissue. The newly formed granulation tissue requires a vascular supply to provide for its metabolic needs. The process of angiogenesis begins at the time of injury. Cell disruption and hypoxia, hallmarks of tissue injury, are strong inducers of angiogenesis factors. Acidic fibroblast growth factor (aFGF or FGF-1) and FGF-2 are released from disrupted cells and have potent angiogenic activity.[254,277] Hypoxia stimulates macrophages and keratinocytes to produce the angiogenic growth factor VEGF.[70,242] FGF-2 may set the stage for angiogenesis during the first 3 days of wound repair, whereas VEGF may be critical for angiogenesis during granulation tissue formation from day 4 through 7.[147]

Endothelial NOS appears to contribute to granulation tissue formation by triggering endothelial migration, proliferation, and differentiation, thus participating in capillary ingrowth into the wound site during repair.[64,258] NO stimulates VEGF production and VEGF-mediated endothelial cell migration and helps redistribute microvascular blood flow.[147] Increased VEGF production also encourages vasodilation and angiogenesis. Other growth factors known to enhance angiogenesis are PDGF, heparin-binding EGF, IGF-I, and hepatocyte growth factor.[254]

Mast cells are commonly found near capillary sprouting sites, suggesting an association between mast cells and angiogenesis. Mast cells may act at sites of new vessel formation by secreting tryptase, which also functions as an angiogenesis factor.[277] Heparin, leptin, and fibronectin also enhance angiogenesis.[254]

The process of angiogenesis has been reviewed by Tonnesen and colleagues.[255] Following stimulation by growth factors and other angiogenic agents, vessels adjacent to the wound transiently (3-5 days after injury) deposit fibronectin within their walls. Endothelial cells release plasminogen activator and procollagenase, resulting in the digestion of the basement membrane by plasmin and collagenase. On the fourth day after injury, with disruption of the confining basement membrane, the endothelial cells are able to enter the ECM as capillary sprouts.[252] The fibrin and fibronectin surrounding the tips of capillary sprouts are released from the plasma rather than being derived from wound fibroblasts.

The fibrin- and fibronectin-rich provisional ECM induces capillary sprouts to express αvβ3 integrin with the most pronounced expression at the capillary tips. Appearing to have a functional role in wound angiogenesis,[240] αvβ3 allows the capillary sprouts to migrate through the basement membrane (infiltrated with fibronectin) and into the fibrin- and fibronectin-rich wound clot.

The endothelial sprouts extend, branch, and create networks, pushed by cell proliferation (stimulated by FGF and VEGF) from the rear and pulled by chemotaxis from the front. These events require an interaction among endothelial cells, angiogenesis factors, and surrounding ECM proteins. At first, the developing blood vessels are surrounded by a provisional matrix containing fibronectin and proteoglycans, but eventually a mature basement membrane is formed. Blood flow begins with the formation of capillary arcades. VEGF, FGF, and mast cell tryptase induce new sprouts to extend from these loops, further extending into the dermal matrix. With maturation of wound granulation tissue and accumulation of collagen, most of the new vessels degenerate, and the density of blood vessels declines.[260] The coverage of endothelial cells by periendothelial cells (smooth muscle cells) is necessary for vascular maturation.[242] This coverage appears to be regulated by PDGF and VEGF. The mature vessels no longer express αvβ3.[242]

Wound Contraction

During the second week of healing, fibroblasts acquire smooth muscle cell features by presenting cytoplasmic microfilament bundles.[251] These fibroblasts are called myofibroblasts. Myofibroblasts contain α-smooth muscle (αSM) actin and provide the contractile forces produced in wound granulation tissue.[278-280] During wound healing, α-smooth muscle actin is transiently expressed by fibroblasts (myofibroblasts). In a mouse model, the staining intensity of α-smooth muscle actin increased from the 6th to the 15th day of injury, decreased thereafter, and disappeared at the 30th day.[281] TGF-β1 is thought to induce expression of α-smooth muscle actin in fibroblasts.[278]

Fibronectin plays a role in wound contraction by binding to fibrin in the provisional and forming a scaffold for fibroblast and keratinocyte migration and tissue support.[282] Fibronectin binds to cell surface integrin receptors to form fibrils, allowing interaction between the cell and ECM. The fibroblasts, having already migrated into the wound, begin to interact with each other and the matrix, resulting in wound contraction.

Remodeling Phase

By the third week after an uncomplicated injury, wound closure has been completed, and local infections overcome. Collagen synthesis and degradation are in balance, and the remodeling phase begins. Myofibroblasts and vascular cells undergo apoptosis (programmed cell death) and are removed.[278] Granulation tissue is transformed into a scar. Lymphocytes constitute the most common leukocyte subset in human skin wounds during this phase,[252] but it is unknown whether lymphocytes are associated intimately with tissue remodeling. Tissue collagenases (MMPs) degrade and digest the excess collagen fibers. Other enzymes (hyaluronidase, bacterial collagenase, and lysosomal proteases) also function to remodel granulation tissue. A more ordered pattern of collagen arrangement is achieved under the influence of local mechanical forces.

The wound gradually gains in strength, ultimately attaining 80% of the tensile strength of normal skin.[248] Type III collagen, synthesized early in the repair process, is replaced by type I collagen until the normal skin ratio of 4:1 (type I to III collagen) is realized.[283]

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CHAPTER EIGHTY

Free Tissue Transfer

Douglas A. Girod

Terance T. Tsue

Yelizaveta Shnayder

Key Points

- Free tissue transfer involves autotransplantation of skin, soft tissue, muscle, or bone isolated on a supporting vascular supply. Although more than 40 donor sites for free tissue transfer have been described, forearm, fibula, rectus, and jejunum flaps account for 92% of all the free flaps used for head and neck reconstruction.
- A multidisciplinary team approach, especially for patients with head and neck cancer, is necessary to maximize both the oncologic and reconstructive efforts. Some situations in which free tissue transfer has become the standard of care include: oromandibular defects, especially those involving the anterior mandible, circumferential pharyngoesophageal defects, and salvage surgical resections of recurrent/persistent head and neck carcinomas following organ preservation chemotherapy or radiotherapy.
- Aspirin, heparin, and dextran have all been extensively used in the management of patients undergoing microvascular surgery. Many microvascular surgeons use some form of postoperative antithrombotic therapy on a routine basis, despite a paucity of prospective clinical trial data to guide it.
- Most ischemic complications in free flap anastomoses occur within the first 48 to 72 hours. After approximately 12 hours of ischemia, even with reestablishment of anastomotic flow, the free flap is usually not salvageable.
- Systemic medical complications are common in patients with head and neck cancer and should be recognized and treated aggressively. Local complications, such as hematoma, salivary fistula, and infections, are especially common in previously irradiated patients and may lead to late flap compromise.
- In addition to expertise, free flap reconstruction requires significant health care resources, including time, equipment, and personnel. However, the actual costs of microvascular reconstruction are either equivalent to or even lower than the costs of pedicled flap reconstruction, owing to the shorter length of hospitalization for patients receiving free flaps.

The expansion of knowledge, expertise, and training in the techniques of free tissue transfer since the early 1970s has redefined the standard of care in head and neck reconstructive surgery. *Free tissue transfer* refers to the isolation of tissues (fascia, skin, fat, muscle, nerve, and bone—individually or in combination) on a supporting vascular supply with transfer to a new location in the body, with the use of microvascular surgical techniques to revascularize the tissues in a permanent fashion. This autotransplantation of tissues relies entirely on the anastomosis of the feeding artery and draining vein to blood vessels in the head and neck for tissue survival. Upon revascularization, the transferred tissues can then be utilized to reconstruct various complex defects of the head and neck from any cause. Since the first reports of free tissue transfer for reconstruction in the head and neck in the early 1970s, the technique has gained widespread acceptance and growing availability. Advances in the understanding of surgical anatomy, operative microscopes, instrumentation, microsuture manufacture technology, and formalized training opportunities as well as unparalleled success rates have been largely responsible for this rapid growth. Because of the additional required training (e.g., microvascular reconstructive surgery fellowships) and resources, the majority of these complex procedures have been completed in larger, academic medical centers.

A multidisciplinary team approach, especially for patients with neoplastic disease, is commonly employed to maximize both the oncologic and reconstructive efforts. Postoperative management is often labor intensive and requires additional team members to achieve maximal rehabilitative potential. Although significant additional training and resources are required to perform free tissue transfer for head and neck reconstruction, the diversity of available tissues for harvest allows for the replacement of "like tissue with like tissue" in most instances, with a focus on functional and cosmetic issues. Currently, more than 40 identified sites in the human body are candidates for the harvest of tissue for transfer, with new sites being added regularly.[1] It becomes the reconstructive surgeon's mandate to determine the optimal flap for free tissue transfer for each patient and the anticipated defect. The advantages of free tissue transfer in the reconstruction of these complex defects include the following:

- Immediate reconstruction at the time of tumor resection (avoiding multiple, staged procedures)
- The transfer of well-vascularized tissue into a bed that often has salivary contamination and underlying tissue damage from earlier radiotherapy

- Significantly improved wound healing
- Immediate separation of critical compartments, including the aerodigestive tract and intracranial contents
- Improved ability to manage massive defects that might otherwise preclude surgical resection of tumors
- Better prospects for functional and cosmetic rehabilitation

Specific circumstances exist in which reconstruction using free tissue transfer has become the standard of care in most communities. These include oromandibular composite defects (particularly defects involving the anterior mandibular arch),[2,3] subtotal or total pharyngoesophageal defects,[4,5] and defects resulting from resection of recurrent carcinoma failing organ preservation nonsurgical therapy (combined chemotherapy and radiation therapy).[6] These situations have traditionally been the most challenging in head and neck reconstructive surgery and have been associated with high complication and failure rates. The introduction of free tissue transfer for reconstruction of these defects has dramatically improved the overall course for these difficult patients.

In this chapter we review the indications, patient selection, and preparation for free tissue transfer as well as the dominant "free flaps" in use today for head and neck reconstruction. We also discuss perioperative issues, management of complications, and future directions.

Historical Perspectives

The first clinical application of free tissue transfer was a 1959 case report by Seidenberg and colleagues,[7] as a transfer of a free jejunal segment for cervical esophageal reconstruction. In 1961, Hiebert and Cummings[8] transferred and revascularized a portion of the gastric antrum for pharyngoesophageal reconstruction. Other reports of the clinical application of free tissue transfer techniques began to appear in the literature in the early 1960s. The first reports of oral cavity reconstruction were made in the early 1970s by Kaplan and associates,[10] who utilized a free groin flap, and Harii and coworkers,[9] who described the microvascular distant transfer of a deltopectoral flap. Panje and associates[11] at the University of Iowa are credited with being the first otolaryngologists to report the use of free tissue transfer for the reconstruction of the oral cavity, in 1976. Subsequent years saw rapid implementation of free tissue transfer in head and neck reconstruction by both plastic surgeons and otolaryngologists. Pioneers such as Panje, Urken, Hayden, and Sullivan worked to establish head and neck microvascular reconstructive surgery as an important part of the specialty of Otolaryngology—Head and Neck Surgery.

With the recognition of the endless possibilities afforded by free tissue transfer came the progressive study and identification of vascular supply patterns and territories that could be potential donor sites. Vascular injection studies identified axial vessels and the presence of perforating vessels passing through muscles to supply the overlying subcutaneous tissues and skin. Identification of axial vessels supplying fasciocutaneous tissues without muscular perforators followed.

Taylor and associates[12] reported the first vascularized bone graft using a fibula for reconstruction of long bone injuries in 1975, and Hidalgo[13] adapted the osteocutaneous fibula flap for mandibular reconstruction in 1989. Dye-injection studies proved a reliable vascular supply to the ilium from the deep circumflex iliac artery for vascularized bone transfer.[14,15] Cadaver dissections identified the vascular branch of the circumflex scapular artery to scapula, allowing vascularized scapula transfer.[16] Throughout the 1980s, there was a progressive development and refinement of these and other vascularized bone flaps for oromandibular reconstruction, significantly expanding the availability of this technique.

Indications for Free Tissue Transfer

Free tissue transfer is just one of many options available to the reconstructive surgeon. Well-established methods of primary closure, skin grafting, local flaps, and pedicled fasciocutaneous or musculocutaneous flaps all remain viable and necessary tools in the surgeon's armamentarium. The indications for free tissue transfer continue to evolve with experience and as additional donor site options have emerged. The etiologies of defects that may require free tissue transfer are listed in Box 80-1. The advantages of free tissue transfer over less sophisticated techniques have likewise become more apparent with greater experience; they are listed, along with the method's disadvantages, in Box 80-2. The tremendous versatility offered by multiple potential donor sites can test the surgeons' imagination for new reconstructive methods. The result has been a progressive evolution of new ways to tackle old problems. Certainly, the driving force behind the expansion of free tissue transfer has been the potential for dramatically improved functional outcomes and a remarkable success rate in the head and neck of more than 90%.[17-19] For some situations, such as reconstruction of the oral cavity, free tissue transfer offers a significant improvement from a functional and cosmetic standpoint over previously available techniques, particularly for composite defects. In other situations for which no reconstructive options had been available, such as large skull base and scalp defects, free tissue transfer offers excellent reconstructive possibilities. Clinical situations commonly requiring free tissue transfer for reconstruction in the head and neck are listed in Box 80-3.

As with any new surgical procedure or technique, a significant learning curve exists.[20] As a result, these procedures have been available primarily in major academic medical centers, and multiple fellowship training programs have been developed to safely convey the necessary

Box 80-1

Etiology of Head and Neck Defects

Neoplasia
Trauma
Congenital defects
Infection, osteoradionecrosis
Secondary reconstructions

Box 80-2

Free Tissue Transfer in Head and Neck Reconstruction

Advantages

Versatility in tissue (skin, muscle, bone, nerves)
Versatility in orientation (no limitations on flap "reach" as with pedicled flaps)
Restoration of shape, function, and sensation
Single operation for complex reconstructions
Multiple potential donor sites available
Simultaneous resection and flap harvest possible
Donor sites out of field of prior treatment
Extensive amounts of tissue available for large or massive defects
Postoperative irradiation tolerance
Independent blood supply for compromised tissue beds
Improved function and cosmesis
Dental rehabilitation possible
High success rates (>90%), including for bony reconstruction
Only available option for some patients

Disadvantages

Increased technical difficulty (additional training required)
Two surgical teams required (surgeons and nurses)
Expensive instrumentation
Longer operation times
More intensive postoperative management
Donor site morbidity

knowledge and experience through advanced training. From a medical center perspective, a high level of investment in personnel and equipment is necessary. Anesthesia support is critical, and additional training and experience for dedicated microsurgical operating room nurses are advised as well. The postoperative management of patients undergoing free tissue transfer is certainly more complex, and the demands on personnel are more intensive, in comparison with those for most patients undergoing head and neck surgery. The overall cost of free tissue transfer has been examined and compared with the cost of more conventional (pedicled flap) techniques. The higher operative costs for free tissue transfer resulting from longer operating room times and instrumentation are offset by the significantly shorter lengths of hospitalization. The resulting overall cost of free tissue transfer is either comparable to[21] or less than[22] the cost of pedicled flap reconstruction.

Box 80-3

Defects or Situations Commonly Requiring Free Tissue Transfer

- Composite defects of the oral cavity
- Three-layer (through-and-through) defects of the oral cavity
- Total or near-total pharyngoesophageal defects
- Extensive skull base defects
- Extensive scalp defects
- Massive defects not readily addressed with other techniques
- Lack of other reconstructive options (failures or patient limitations)
- Salvage surgery for chemoradiation failures

Donor Site Options

Although more than 40 donor sites for free tissue transfer have been described,[1] only a handful have been found to be consistently useful in the routine reconstruction of head and neck defects. The dominant free tissue transfer flaps in use today are shown in Table 80-1. In fact, we have found that the radial forearm fasciocutaneous, radial forearm osteocutaneous, and fibula osteocutaneous free flaps are utilized in more than 80% of cases of head and neck reconstruction. Disa and colleagues[23] reported that forearm, fibula, rectus, and jejunum flaps accounted for 92% of free flaps they used for head and neck reconstruction.[23] This distribution will certainly vary according to the makeup of the surgeon's practice as well as the surgeon's preferences and experiences. Nonetheless, it is important for the reconstructive surgeon to be

Table 80-1

Free Tissue Transfer Flaps Commonly Used in Head and Neck Reconstruction

Flap	Artery	Vein	Nerve	Reconstruction Uses
Fasciocutaneous Flaps				
Radial forearm	Radial	Venae comitantes or cephalic vein	Medial and lateral antebrachial cutaneous	Oral cavity, tongue, palate, nose, face, scalp, lip, pharynx, larynx
Ulnar forearm	Ulnar	Venae comitantes or cephalic vein	Medial and lateral antebrachial cutaneous	Oral cavity, tongue, palate, nose, face, scalp, lip, pharynx, larynx, cervical esophagus
Lateral arm	Posterior radial collateral	Posterior radial collateral	Posterior cutaneous nerve of the forearm	Oral cavity, tongue, palate, pharynx
Lateral thigh	Deep femoral	Venae comitantes	Lateral femoral cutaneous	Oral cavity, tongue, palate, pharynx
Anterolateral thigh	Descending branch, lateral circumflex femoral	Venae comitantes	Lateral femoral cutaneous	Oral cavity, tongue, palate, pharynx, larynx, cervical esophagus
Scapular-parascapular	Subscapular	Subscapular	None	Oral cavity, tongue, palate, pharynx, face, lip
Muscle or Myocutaneous Flaps				
Rectus abdominis	Deep inferior epigastric	Deep inferior epigastric	Intercostals (mixed motor and sensory)	Skull base, total glossectomy
Latissimus	Subscapular	Subscapular	Thoracodorsal	Skull base, scalp
Osteocutaneous Flaps				
Fibula	Peroneal	Peroneal	Lateral sural cutaneous	Mandible reconstruction
Radius	Radial	Venae comitantes or cephalic vein	Medial or lateral antebrachial cutaneous	Mandible and midface
Scapula	Subscapular	Subscapular	None	Mandible and midface
Iliac crest	Deep circumflex iliac	Deep circumflex iliac	None	Mandible and midface
Other Flaps				
Jejunum	Superior mesenteric branch	Superior mesenteric branch	None	Pharyngoesophageal reconstruction
Omentum	Gastroepiploic	Gastroepiploic	None	Scalp coverage
Temporal-parietal	Superficial temporal	Superficial temporal	None	Bone and cartilage coverage

Box 80-4

Important Considerations Influencing Flap Selection

Skin and soft tissue volume, bulk, and color
Pedicle length and vessel caliber
Innervation capacity (sensory-motor)
Bone quality, quantity, and availability
Donor site location to allow concurrent resection and harvest
Donor site morbidity (dysfunction, cosmetic deformity)

familiar with a full array of flaps to manage the more difficult or unusual situations. Although several flap options are available for most defects, the surgeon must choose one on the basis of critical characteristics such as those listed in Box 80-4. Additionally, a thorough donor site evaluation and assessment of long-term donor site morbidity must be considered. A complete discussion of each of these flaps is beyond the scope of this chapter; however, some general comments are warranted.

Soft Tissue Flaps

For many cutaneous, mucosal, and soft tissue defects in the head and neck, the radial forearm fasciocutaneous free flap has proved to be the most versatile and reliable. Forearm skin is available in large quantities, is thin and pliable, and has excellent sensory capability that is ideal for oral cavity reconstruction (Fig. 80-1). The vascular pedicle (1) is long, (2) has a favorable vessel caliber, (3) can easily be harvested concurrently, and (4) exhibits acceptable functional morbidity at the donor site. However, as many as 12% of people have an incomplete superficial palmar arch and poor communication between the deep and superficial arches, precluding the safe harvest of the radial artery without causing hand ischemia.

The lateral arm flap is similarly thin and pliable with sensory capability but is limited in skin quantity, has a much shorter pedicle, and has vessels of small caliber.[24-29] There is no risk of vascular compromise to the hand, and the donor site can usually be closed primarily. The scapular and parascapular fasciocutaneous flaps produce the largest volume of skin but are quite bulky, have no sensory capability, and have intermediate pedicle length with large vessel caliber.[30-34] Although the donor site may be closed primarily, the donor site location (back) for these two flaps requires intraoperative patient repositioning, which precludes simultaneous resection and harvest.

In order to maximize color match, eliminate tissue bulk, and streamline the process of simultaneous flap harvest, other donor site choices, such as the anterolateral thigh flap, have been popularized.[35] The anterolateral thigh flap, based on the perforators from the descending branch of the lateral circumflex femoral artery, has been used extensively, mostly in Japanese and Taiwanese centers, as a flap of choice for defects requiring more soft tissue bulk than a radial forearm free flap can provide (see Table 80-1). Peripheral vascular disease is not a contraindication to the use of the anterolateral thigh flap, because the profundus femoris arterial system is not usually affected by atherosclerotic changes. A pedicle length up to 14 cm could be obtained by ligation of the transverse branch of the lateral circumflex femoral artery and the branch to the rectus femoris muscle. This may allow access to the neck vessels contralateral to the defect, if the ipsilateral neck has no suitable vessels. A skin paddle as wide as 12 cm may be harvested, while still allowing primary closure of the donor site. Overall, this flap may allow harvesting of a skin surface area up to 25 cm wide and up to 40 cm long as a single paddle or as multiple skin paddles.[36]

The two main reasons that the anterolateral thigh flap has been slow in gaining popularity in the United States are the thickness of the subcutaneous tissue of the thigh in the Western population and the highly variable vascular anatomy of the flap. However, the negligible donor site morbidity, primary closure of the donor site, and significant experience gained by microvascular surgeons in harvesting and thinning the flap have led to popularization of the anterolateral thigh flap in many U.S. centers.[35-39] Some writers describe using a handheld Doppler probe to identify perforators preoperatively, before designing the skin paddle.[37]

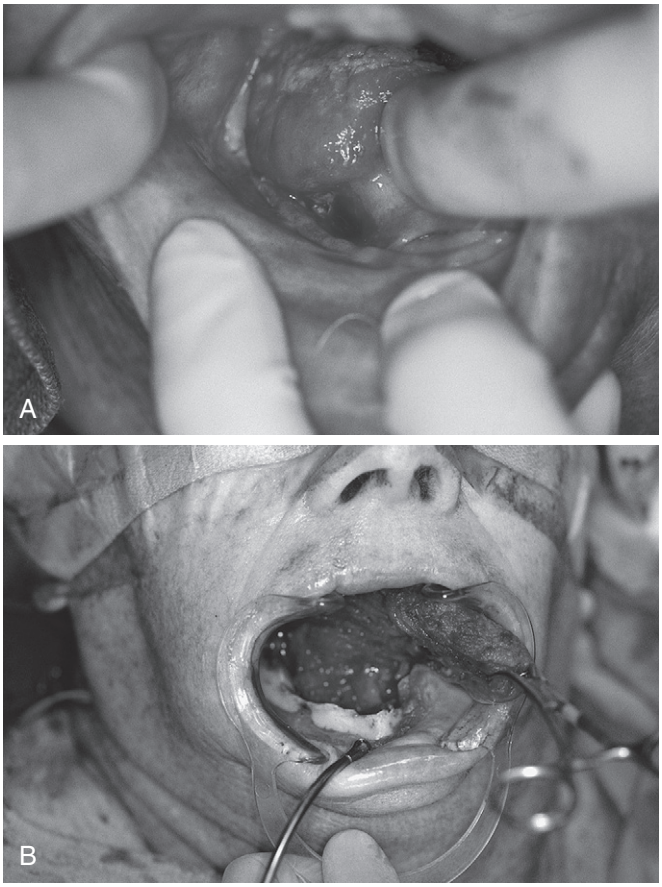

Figure 80-1. Fasciocutaneous radial forearm free flap for oral cavity reconstruction. **A,** Carcinoma involving the anterior floor of the mouth and ventral oral tongue. **B,** Extensive soft tissue defect after resection of the carcinoma.

Muscle and Myocutaneous Flaps

Muscle and myocutaneous flaps have found a niche in the reconstruction of very large defects that require significant bulk. The most common of these defects are found at the skull base, where large portions of the facial skeleton, paranasal sinuses, facial skin, and palate may be missing. The rectus abdominis flap may be harvested as a muscle or myocutaneous flap with the patient in a supine position, a long vascularized pedicle of large caliber vessels providing adequate reach to the defect site in most instances.[40-44] The skin of the rectus myocutaneous flap is useful for lining the nasal and oral cavities of the defect, and the muscle provides the needed bulk to replace the missing facial skeleton. Donor site morbidity is minimal, although abdominal hernias may occur as a result of a weakening of the abdominal wall due to the partial harvest of the anterior rectus sheath.

The latissimus flap may be harvested as a muscle or myocutaneous flap based on the subscapular vascular system.[45,46] Originally described as a pedicled flap, the latissimus flap has been found to be much more versatile as a single-stage, free tissue transfer. The large amount of muscle available for harvest is very useful for very large soft tissue defects, including the skull base and scalp. The subscapular system has additional versatility, with the option for vascularized bone (scapula bone or rib). The vascular pedicle has large vessel caliber and a length of 6 to 10 cm, and the donor site is repaired primarily without the need for a skin graft. The major disadvantage of the latissimus flap is patient positioning for harvest. As for scapula flaps, the patient must be placed in the lateral decubitus position, making harvest concurrent with the

head and neck procedure difficult or impossible. The donor site morbidity from the loss of latissimus function is well tolerated in most people. The latissimus flap has been most useful in skull base defects and larger scalp defects requiring cranial coverage (Fig. 80-2).[43,47,48]

Vascularized Bone Flaps

One of the primary indications for free tissue transfer is for the reconstruction of oromandibular defects. In this setting, no other reconstructive option offers a single-stage procedure with a greater than 90% success rate. The choices for vascularized bone flaps also dictate the need for careful evaluation and selection. Most bone reconstructions also require some soft tissue and/or mucosal reconstruction. The anticipation of the length of bone required, plans for future dental implantation, soft tissue and innervation requirements, and donor site suitability and morbidity must all be considered.

Osteocutaneous Fibula Flap

The osteocutaneous fibula free flap has become the mainstay for mandibular reconstruction at most institutions (Fig. 80-3).[49-51] The fibula is touted as "the most donateable bone in the body," with up to 25 cm of bone available for harvest and adequate bone stock to support dental implantation.[52,53] With such lengths of bone available, the entire mandible may be reconstructed with vascularized bone if required. Multiple osteotomies may be performed to shape the fibula to reconstruct the anterior arch, body, angle, or ramus of the mandible, as long as the fibular periosteum is not disrupted. The septocutaneous or musculocutaneous perforating vessels of the lower leg can be quite variable in location and quantity, affecting the placement and reliability of the skin paddle.[54-56] The skin of the lower lateral leg is thin and pliable, with fairly large amounts of skin available, and may be transferred in a sensate fashion. With smaller skin paddles, the donor defect may be closed primarily. With larger defects, a split-thickness skin graft is utilized. The fibula flap harvest can easily be performed simultaneously with the head and neck procedure.

Confirmation of three-vessel flow to the distal lower extremity should be determined preoperatively to avoid vascular compromise of the foot after harvest of the peroneal artery.[57,58] The primary disadvantage of the fibula flap is the limitations of the skin paddle. The skin is inadequate for larger soft tissue defects and most three-layer defects, requiring a second flap for soft tissue repair. The somewhat unreliable nature of the presence and location of the cutaneous perforator vascular supply can usually be minimized by inclusion of a cuff of soleus

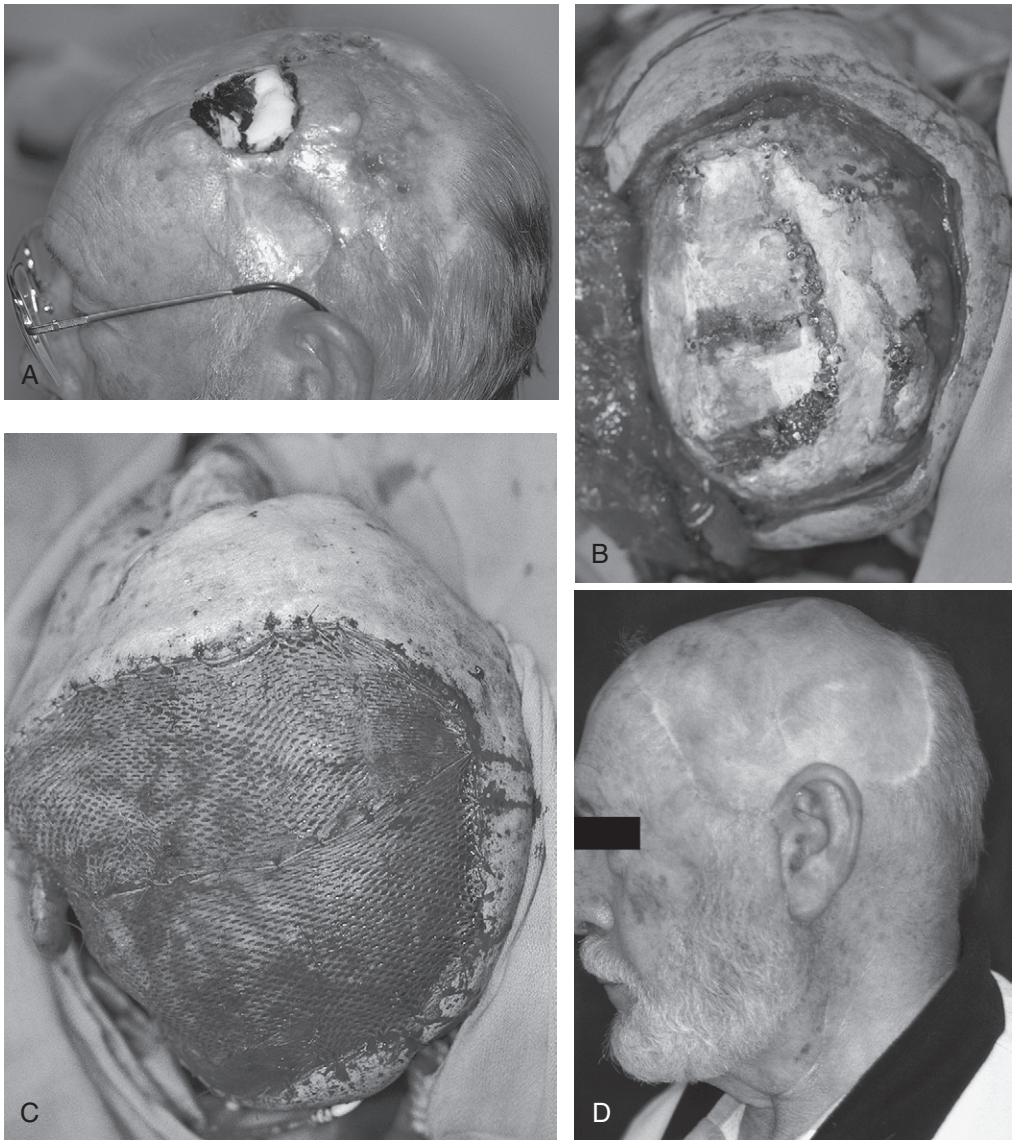

Figure 80-2. Latissimus dorsi muscle free flap to the scalp. **A,** Recurrent basal cell carcinoma after multiple operations and radiation therapy with involvement of underlying bone. **B,** Resection of the scalp, bone, and dura with cranioplasty using radiated rib grafts and bone cement. **C,** Latissimus dorsi muscle free flap with meshed split-thickness skin graft coverage. **D,** Long-term result of scalp reconstruction.

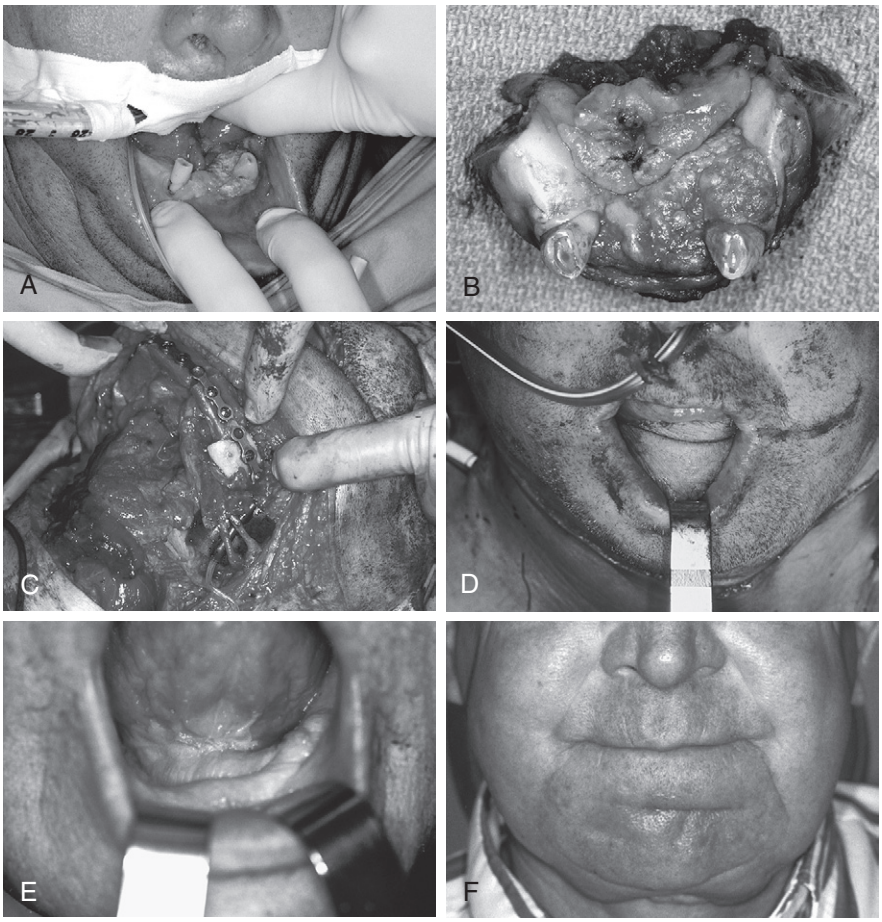

Figure 80-3. Osteocutaneous fibula free flap reconstruction of the anterior mandibular arch. **A,** Carcinoma of the anterior alveolar ridge. **B,** Resection of the anterior mandibular arch. **C,** Mandible replaced by fibula bone with osteotomies secured to a reconstruction plate. **D,** Soft tissue repair of the oral cavity defect. **E,** One-year postoperative appearance of the anterior oral cavity. **F,** Frontal view one year later.

muscle with the flap, to include musculocutaneous perforators. If dental implants are not planned, use of the fibula bone results in a very broad and rounded neomandible, which is quite difficult to fit for a tissue-borne prosthesis. The donor site morbidity of the fibula flap involves prolonged pain on ambulation for some patients.[59-63]

Osteocutaneous Radial Forearm Flap

The radial forearm free flap (RFFF) has also been described as an osteocutaneous radial forearm free flap (OCRFFF), with harvest of a portion of the radius bone based on perforators in the intermuscular septum passing to the periosteum.[64-66] This addition significantly broadened the applicability of the already widely used forearm flap in reconstructive surgery. Although the OCRFFF is seemingly the best of options, with tremendous soft tissue characteristics and an option for bone harvest, its widespread acceptance has been limited by concerns about the bone quality and possible pathologic fracture of the radius bone postoperatively.

The length of radius bone that can be safely harvested without unacceptable forearm dysfunction is limited to 10 to 12 cm (Fig. 80-4). To avoid pathologic fracture, most surgeons recommend that the thickness of the bone harvested be limited to 40% of the circumference of the radius.[67,68] This thickness generally does not provide adequate bone stock to support endosseous dental implants.[52,53] When a segment of bone is removed from the radius, the bone is significantly weakened, especially to torsional forces; the weakening previously resulted in a postoperative pathologic radius fracture rate of up to 66%, with an average of 23%.[68-71] The prophylactic internal fixation of the radius bone after OCRFFF harvest has been shown to successfully eliminate this risk (Fig. 80-5).[72,73]

Despite the limitations of bone availability with the OCRFFF, it has been used successfully for oromandibular reconstruction, with fewer complications than those associated with the fasciocutaneous RFFF with plate reconstruction.[68,74-76] For limited mandibular defects, the radius bone is quite adequate and can easily bear a tissue-borne prosthesis (denture). This characteristic has proved beneficial, because many patients do not have the financial means for dental implantation, which is frequently not covered by many third-party payers. In this setting, the radius bone provides a better contour for the support of a tissue-borne prosthesis than either the fibula or scapula bone.

Reconstruction of maxillofacial defects is a challenging problem, owing to the complex three-dimensional, esthetic, and functional roles of the midfacial structures. Cordeiro and Santamaria[77] presented a classification of maxillofacial defects and suggested an algorithm for their reconstruction. The combination of a large skin paddle to line the palatal mucosal surface, small volume of the soft tissue, and moderate vascularized bone stock are the requirements fulfilled very well by a reconstruction with OCRFFF. The radial forearm free flap is ideal to solve one of the most problematic aspects of choosing the flap for a midfacial reconstruction: a need for a long (10-13 cm) pedicle to span the distance between the midface and cervical vessels. Using an OCRFFF eliminates the need for vein grafts, shortening operative time and improving the success of the reconstruction. Chepeha and colleagues[78] expanded the use of the OCRFFF for maxillectomy defects with infraorbital rim involvement in ten patients. They advocate the choice of OCRFFF for total maxillectomy defects, with or without the orbital exenteration, that involve less than 40% of the orbital floor. Rather than using the vascularized bone to reconstruct the malar alve-

Figure 80-4. Osteocutaneous radial forearm free flap for oral cavity and lateral mandible reconstruction. **A,** Preoperative frontal view. **B,** Lateral mandibular bone defect including a larger soft tissue defect of the lateral tongue, floor of the mouth, pharynx, and palate. **C,** Harvested osteocutaneous forearm flap with skin, radius bone, vascular pedicle, and cutaneous nerves. **D,** Closure of defect repairing mandible and soft tissue defect. **E,** Postoperative frontal view after radiation therapy. **F,** Intraoral view of the oral cavity and pharyngeal reconstruction.

olar ridge, these researchers employed osteotomized radial bone to recontour the infraorbital rim and to provide support for the orbital contents when preserved. Dental rehabilitation was achieved through the use of palatal obturator and dentures.[78]

Osteocutaneous Scapula Free Flap

The osteocutaneous scapula free flap remains one of the most versatile flaps available for harvest in the human body.[30-32,34,79,80] The subscapular arterial system offers tremendous amounts of skin as well as the latissimus dorsi and serratus anterior muscles and scapular bone for harvest, all supplied by one major vascular pedicle, which is favorable in both length and caliber. Each of these different tissue components has a separate vascular branching supply, allowing for almost limitless degrees of orientation in relation to one another and to the recipient bed. The skin of the upper lateral back is usually quite thick, with considerable subcutaneous fat, resulting in significant soft tissue bulk, which can be advantageous in some reconstructive situations. This bulk reliably remains on a long-term basis, without atrophy. The skin can also be separated into scapular and parascapular skin paddles based on the transverse and descending branches of the circumflex scapular artery, respectively.[31,32,34] Inclusion of the dorsal cutaneous rami of the T1 or T2 spinal nerves into the flap, which may allow for sensate transfer of scapular cutaneous paddles, has been described.[81] A total of 10 to 14 cm of bone is available for harvest from the lateral border of the scapula, supplied by the periosteal branch of the circumflex scapular artery. The separation of the bony and fasciocutaneous components of the flap resulting from unique vascular supplies can be as much as 4 cm, allowing for significant versatility in hard and soft tissue orientation during reconstruction. Osteotomies may be safely performed for mandibular contouring, as long as the periosteum is preserved. The harvested scapular bone has a thick border along its free edge but transitions quickly to thin (1 to 2 cm) bone medial to the edge. The resulting limited bone stock may not be adequate for the support of endosteal dental implants.[52,53]

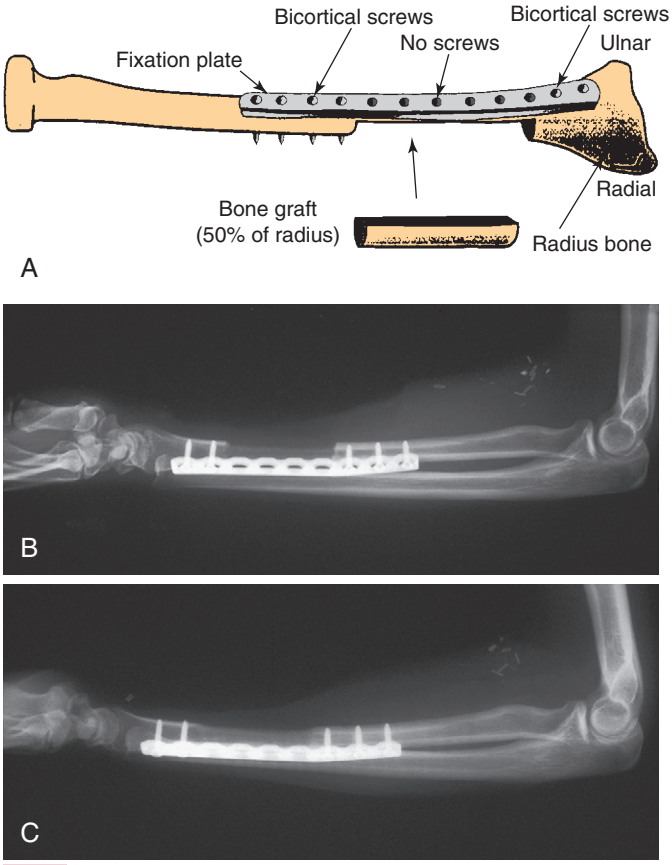

Figure 80-5. Prophylactic fixation of the radius bone after bone graft harvest. **A,** Diagram showing the harvest of the bone graft and placement of a plate spanning the defect. **B,** Postoperative radiograph of the forearm demonstrating plate fixation. **C,** One-year follow-up radiograph showing significant bone formation and remodeling in the area of the defect.

The scapular osteocutaneous flap remains an optimal choice for the reconstruction of the oromandibular complex when the surgeon is faced with large complex defects, especially those involving a large surface area, or with three-layer composite defects involving both the oral cavity and external soft tissues (Fig. 80-6).

For extremely large defects, some surgeons have employed the scapular "mega-flap," which includes not only the scapular bone and extensive skin as described earlier but also the latissimus dorsi muscle or the serratus anterior muscle for additional bulk and coverage.[82,83] The muscles are based on the thoracodorsal artery and vein that branch off the subscapular vessels, and therefore can be harvested on the same vascular pedicle, requiring only one arterial anastomosis and one venous anastomosis. The mega-flap offers significant mobilization of the various tissue components relative to one another as a result of the branching vascular supply, providing great reconstructive versatility for the largest of defects.

The major disadvantages of the scapula flap include the bulky and insensate nature of the skin paddles and the necessity to reposition the patient several times during the operation, which adds significant time to the procedure. Long-term shoulder dysfunction can result from the harvest of the scapular osteocutaneous flap, with winging of the scapula, decreased range of motion, and chronic pain. These problems can usually be minimized with careful technique and aggressive physical therapy.

Iliac Crest Flap

The iliac crest has long been a source of free bone grafts for mandibular reconstruction. A vascularized iliac crest flap harvested off the deep circumflex iliac artery may provide 14 to 16 cm of bone, which has a natural curvature for mandibular reconstruction. Studies have found that, of the available osteocutaneous flaps, the iliac crest provides the highest quality bone for the support of osseointegration for dental implantation.[52,53]

The cutaneous portion of the flap is both bulky and limited in mobility, restricting its usefulness for large composite defects. Urken and colleagues[84-87] described the addition of the internal oblique muscle based on the ascending branch of the deep circumflex iliac artery for mandibular reconstruction, which significantly increased the versatility of the flap and provided excellent results.[84-87]

Despite the high quality of the iliac bone for mandibular reconstruction, the soft tissue limitations, overall bulk, and donor site morbidity have limited the popularity of the iliac crest flap. Most surgeons utilize this flap when the other options are precluded because of peripheral vascular disease, earlier surgery or trauma, or other factors.

Dental Rehabilitation

Significant dental rehabilitation of the oral cavity after composite resection for malignancy can be achieved only with microvascular free tissue transfer of bone and soft tissue (Fig. 80-7). The placement of enosseous dental implants into the replaced bone allows for the optimal rehabilitative outcome that approaches function in the patient with normal dentition.[84,88] Appropriate contouring of the reconstructed oral cavity may allow the fitting of tissue-borne dentures. Although this reconstruction is generally cosmetically acceptable for most patients, the diet remains significantly affected.

Other Flaps

Unique situations that require the employment of less frequently utilized flaps often arise. Pharyngoesophageal defects have long presented one of the more challenging reconstructions in head and neck surgery. This is reflected by the first reported free tissue transfer in the head and neck, described by Seidenberg and colleagues[7] in 1959 as a transfer of a free jejunal segment for cervical esophageal reconstruction. The jejunal flap may be harvested off a segmental arcade of the superior mesenteric artery, for free transfer to the head and neck. As a mucus-producing tubular structure of similar size, the jejunum seems a natural replacement for the cervical esophagus. On transfer, the jejunum retains some intrinsic contractile motility, which is beneficial for swallowing (and detrimental if the jejunum is inverted on the inset or placement into the defect) (Fig. 80-8).[89-92] Through the years, experience has found the jejunum to be a fairly fragile flap that does not tolerate episodes of ischemia. The donor site morbidity of a bowel resection can be considerable. The reconstructed pharynx can successfully undergo tracheoesophageal puncture[89,93]; however, this maneuver often results in a very "wet" vocal quality. As a result, most surgeons now routinely use a radial forearm fasciocutaneous free flap, which is "tubed" to recreate the cervical esophagus (Fig. 80-9). This flap results in less donor site morbidity, provides a very functional adynamic "funnel" into the thoracic esophagus, and produces a better tracheoesophageal puncture vocal quality.[94]

Patient Evaluation and Preparation

Despite technologic advances and new options in head and neck microvascular reconstruction, the best treatment plan still depends initially on general patient factors. Multiple factors, other than the stage of cancer or surgical defect (i.e., comorbid conditions, overall performance status, occupational and recreational activities, and personal preferences) also play significant roles not only in establishing whether a patient is a safe, suitable candidate for free tissue transfer but also in dictating the possible free flap donor sites available. The reconstructive surgeon, in consultation with the patient's other health care providers, needs to expeditiously address issues such as airway status, nutritional status, and uncontrolled medical conditions. Treatment of acute issues can occur in parallel with the reconstructive surgeon's careful evaluation and often requires the input of multiple medical disciplines.

History and Current Illness

An extensive history of symptoms gathered by the reconstructive surgeon not only helps determine the size and character of the anticipated extirpative defect that needs reconstruction but also can yield

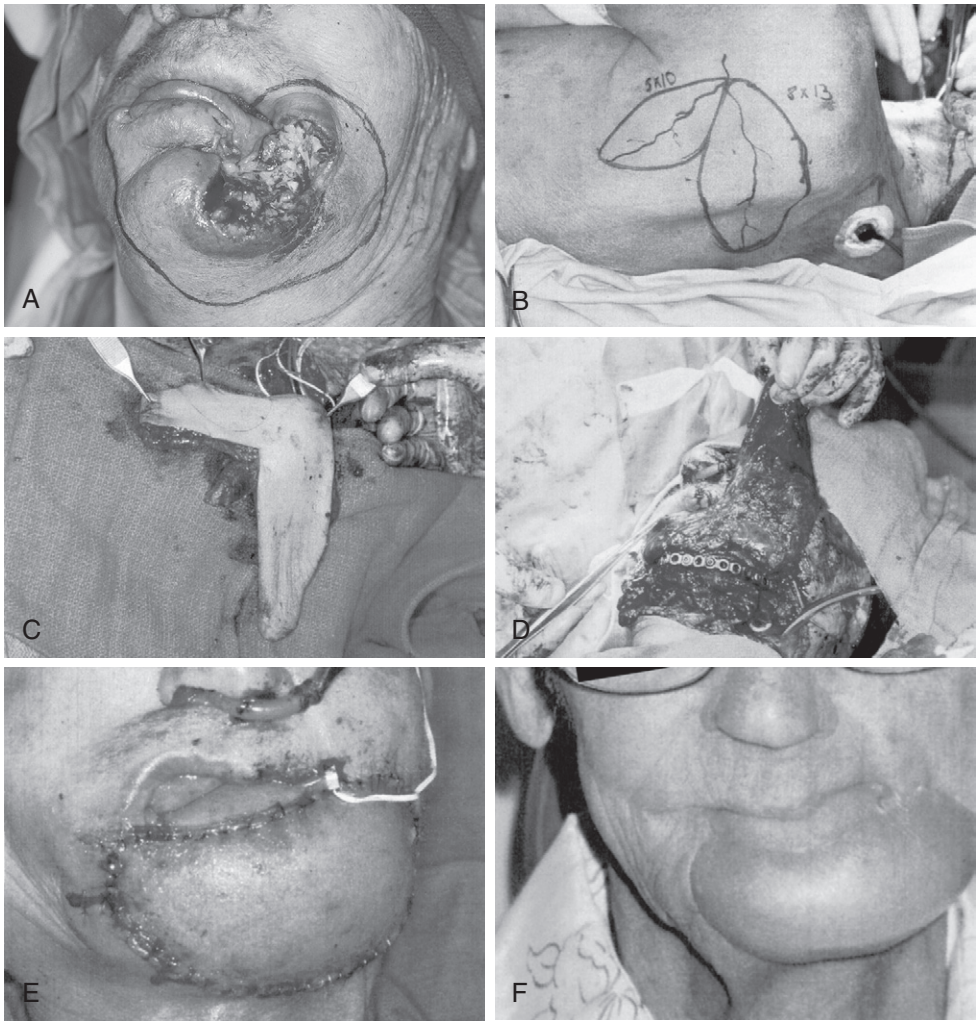

Figure 80-6. Osteocutaneous scapula free flap repair of a large three-layer defect of the anterior face and oral cavity. **A,** Larger persistent carcinoma of the lip after irradiation and chemotherapy. **B,** Planned scapula flap from the left upper back with two skin paddles. **C,** Harvested osteocutaneous scapula free flap showing both skin paddles and scapula bone. **D,** Inset of the scapula flap for oral cavity and mandibular reconstruction. **E,** Postoperative view of the defect repair. **F,** Appearance at 6-month follow-up.

hints about the possibility of a synchronous primary or metastatic disease. Complaints of unilateral conductive hearing loss, hyponasal speech, breathy voice, ptosis, diplopia, trismus, chin numbness, otalgia, and contralateral symptoms are frequently indicators of deep or extensive disease beyond that immediately apparent.

The extent of premorbid and current oral cavity function is important. The reconstructive functional result, in terms of deglutition, taste, mastication, voice, breathing, and cosmesis, generally cannot be improved beyond the premorbid state. In patients with compromised premorbid function due to neurologic disability or earlier treatments, preoperative counseling about the potential reconstructive outcome is even more crucial to providing realistic expectations.

Unfortunately, smoking and chewing tobacco are prevalent among patients with head and neck cancer. Beyond its ill effects on anesthesia and cardiopulmonary function, nicotine also has adverse vasoconstrictive effects that can compromise flap perfusion and wound healing.[95,96] A history of regular alcohol use requires aggressive perioperative withdrawal prophylaxis and nutritional supplementation. Acute withdrawal after surgery is associated with a higher rate of complications and flap loss.[97,98]

A history of previous radical neck dissections may limit the current reconstructive options at both recipient and donor sites. Careful review of old surgical reports, review of current radiographs, and discussions with previous surgeons is often necessary to supplement the patient's memory. Similarly, extensive radiotherapy can compromise recipient site vascularity and healing and cause premature vascular wall changes, but may or may not affect free flap viability.[99-101] Post-irradiation hypothyroidism should be detected and reversed to help maximize postoperative recovery and healing. Both previous surgery and prior radiotherapy can cause extensive fibrosis in the surgical bed, making safe isolation of needed recipient vessels and nerves very difficult, if not impossible.

Donor site–specific history must also be obtained. A patient's hand and foot dominances, occupation, hobbies, and recreational activities can dictate the side or site of a free flap harvest. Previous abdominal and pelvic surgery can obviate the use of some potential free flap vascular pedicles (i.e., rectus abdominis, iliac crest). Claudication or extremity rest pain is indicative of significant peripheral vascular disease and warrants aggressive assessment of extremity vascular pedicle adequacy. History of previous surgery or trauma to the donor site prompts in-depth evaluation of the donor site anatomy.

Physical Examination

The microvascular surgeon should also perform a complete head and neck examination. Direct visualization of the neoplasm or traumatic defect, along with bimanual palpation, should complement the tumor mapping anticipated by the symptom history. This step allows a discussion with the extirpative surgeon, in terms of the anticipated surgical defect size and potential structures to be removed (mucosa, skin—with

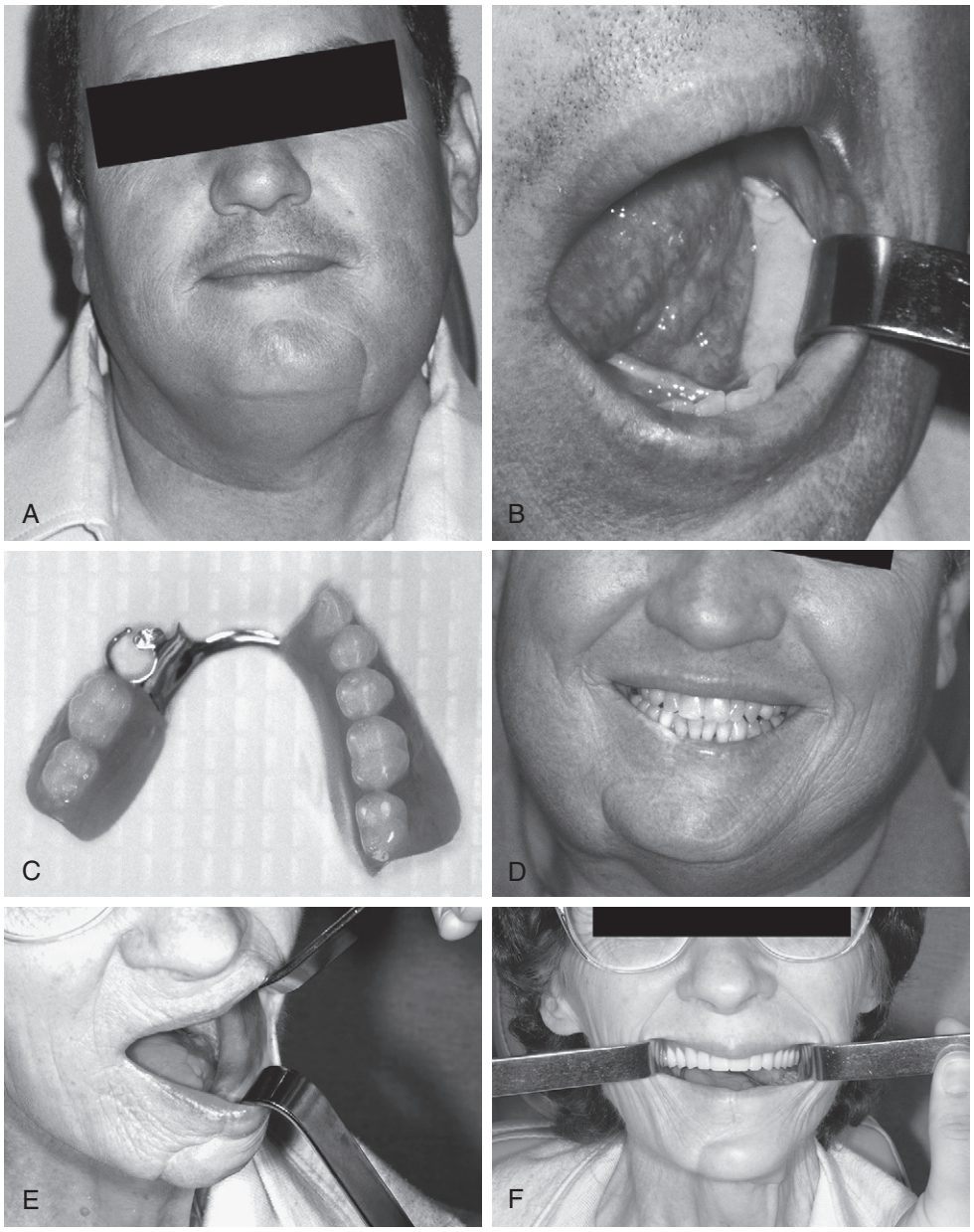

Figure 80-7. Dental rehabilitation after mandibular reconstruction. **A,** Frontal view after lateral mandibular reconstruction with fibula free flap. **B,** Intraoral appearance of intraoral reconstruction before secondary dental implant placement. **C,** Dental prosthesis for fixation with osseointegrated dental implants. **D,** Patient smile with prosthesis secured in place. **E,** In a different patient, intraoral reconstruction with an osteocutaneous radial forearm free flap. **F,** Patient seen in **E** with tissue-borne upper and lower dentures.

or without bone) or exposed (brain, orbit, bone, carotid artery). A secondary survey can then focus on the anticipated fine-tuning reconstructive procedures necessary during either the primary or secondary setting, to maximize both functional and aesthetic outcome. This survey involves status and integrity of the parotid and submandibular ducts, nasal airway, lip vermilion, oral commissure, dental occlusion, maxillary sinus, soft and hard palate, eustachian tube, facial sensation, and motor nerve function. A superinfected area of cutaneous involvement should be treated with antibiotics to help delineate infected from neoplastically involved tissue; this treatment can lead to a more efficient resection and also possibly improve pain, hygiene, and healing. The extent of neck disease determines not only prognosis but also the type of neck dissection. It influences changes in neck volume, contour, and potential available recipient vessels for microvascular anastomosis. Previous facial and neck incisions and traumatic scars must be recognized, because they will limit placement of future incisions.

Microvascular free tissue transfer has been used with success in the elderly. Chronologic age itself does not seem to contraindicate surgery, although the incidence of medical complications is higher after treatment.[18,102,103] Mental impairment, such as dementia or mental illness, is a very difficult situation to control in the debilitated postoperative patient. Serious consideration should be given to more tolerant alternative reconstructive techniques if surgery is still considered an option in a mentally impaired patient. Morbid obesity not only may influence perioperative recovery and healing but also may require alteration in available useful donor sites because of flap thickness and bulk.[104] Morbidly obese patients may also have undetected significant obstructive sleep apnea, which heavily influences perioperative airway management and can also be seriously exacerbated postoperatively by large, bulky, and swollen reconstructions. Potential airway compromise due to the bulky or edematous flap should be anticipated and should be prevented by the intraoperative tracheotomy.

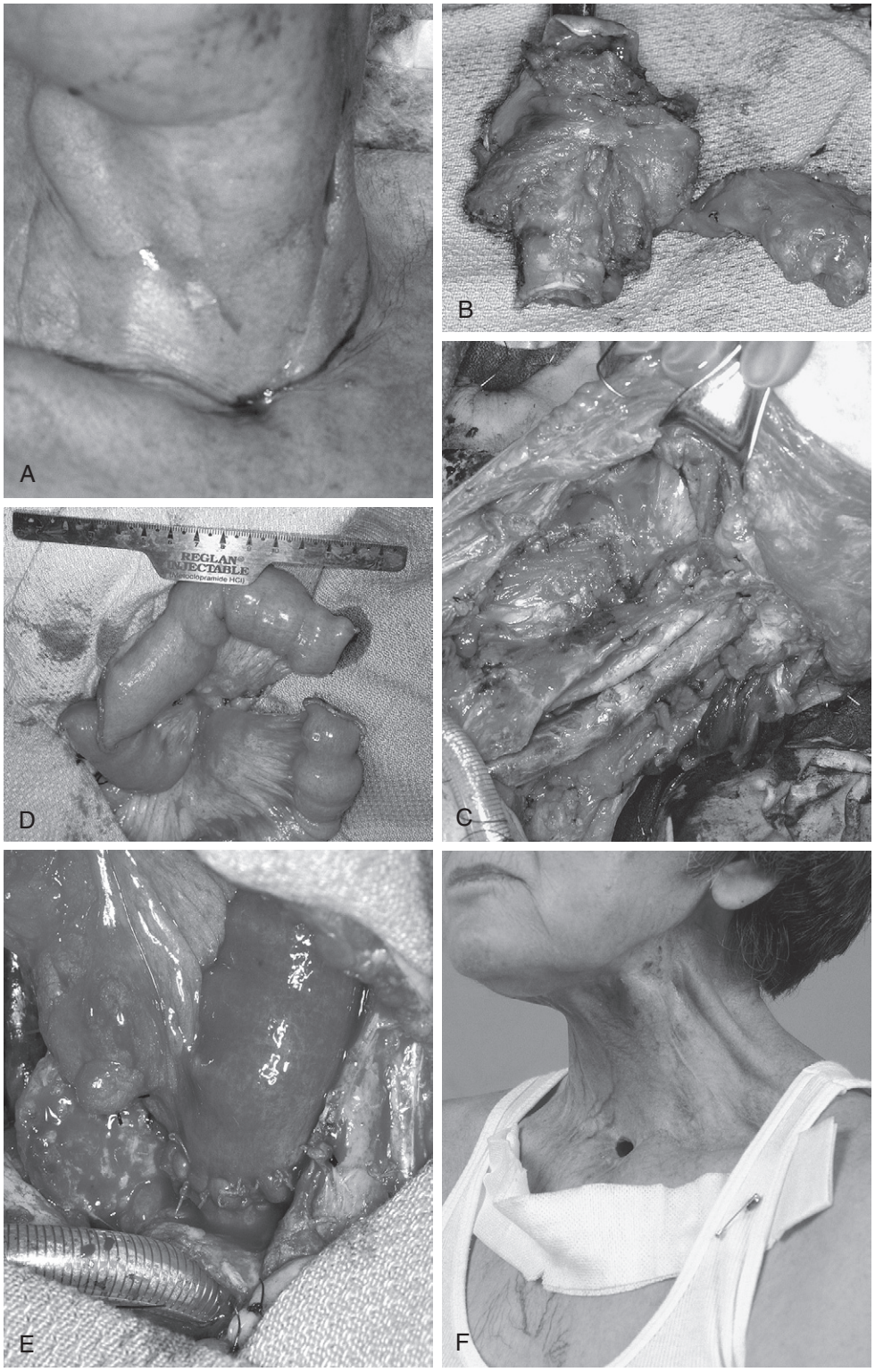

Figure 80-8. Jejunal free flap reconstruction of a complete pharyngoesophageal defect. **A,** Recurrent pharyngeal carcinoma after surgery and radiation therapy. **B,** Laryngopharyngectomy specimen with neck dissection. **C,** Surgical defect after resection. **D,** Harvest of a jejunal free flap based on a mesenteric vascular arcade. **E,** Repair of the pharyngeal and esophageal defect with the jejunal free flap. **F**, Appearance 1 year after surgery.

Examination of the potential free flap donor site for scars, asymmetries, or bony deformities can often prompt a patient's memory of an old injury or operation. Objective evaluation of the mobility, strength, and function of an extremity should confirm the patient's history. Preoperative disabilities, from previous strokes, spinal injury, or trauma, may either prompt or discourage the use of certain free flap donor sites. Nonhealing sores, cold digits, loss of sensation, as well as significant distal extremity swelling are also indicators of inadequate vascularity and commonly contraindicate the use of the involved extremity as a donor site. Palpation of distal extremity pulses (i.e., radial, ulnar, dorsalis pedis, and posterior tibial arteries) as well as the performance of subjective Allen's tests and determination of the ankle-

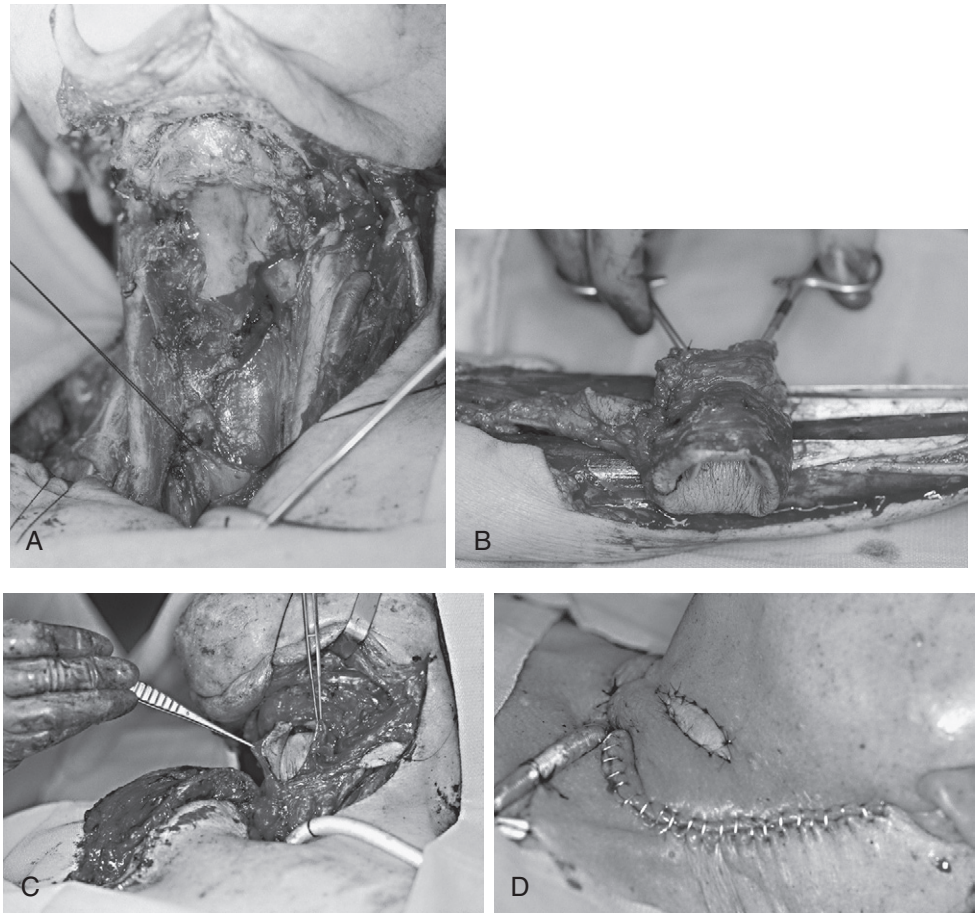

Figure 80-9. Radial forearm free flap "tubed" for reconstruction of a complete pharyngoesophageal defect. **A,** Defect after total laryngopharyngectomy for recurrent carcinoma. **B,** Forearm skin rolled onto itself, creating a "tube" for pharyngoesophageal reconstruction. **C,** Inset of the "tubed" forearm skin for pharyngoesophageal reconstruction. **D,** Closure of the neck skin, including a small monitoring paddle of forearm skin to allow postoperative monitoring of flap vascularity.

arm index can be reassuring, but adequacy determinations should be supplemented by formal vascular assessments in equivocal cases.[105-107]

Past Medical History

In all patients, special attention should be paid to optimization of any known medical conditions. Certain comorbid conditions can also affect free tissue transfer specifically, although absolutely contraindicating conditions are uncommon.[108] Certain extremity vessels are known for a tendency toward advanced atherosclerotic disease in patients with peripheral vascular disease. Radial and peroneal arteries tend to be affected frequently, but the scapular arterial system remains relatively unaffected. Poor digit perfusion can be further exacerbated by donor vessel sacrifice, yielding cold intolerance or even digit necrosis. Patients with severe extremity venous or lymphatic insufficiency should also be considered for other donor sites to prevent postoperative extremity complications. Patients with arterial vascular disease due to atherosclerosis or hypertension must also be evaluated for significant concomitant cerebrovascular and cardiovascular disease. In the patient with significant carotid disease, availability of adequate recipient external carotid artery branches may be reduced; also, intraoperative hypotension or neck extension positioning may cause perioperative strokes. Adequate cardiopulmonary reserve must be present to tolerate the often prolonged anesthesia time and intravascular fluid shifts associated with free tissue transfer operations.[109] Such comorbid disease can significantly lower the limits of resectability and reconstructability, because such procedures often require more prolonged general anesthesia and possibly even multiple trips to the operating room.

Patients who have connective tissue disorders with vasculitis are at a relatively high risk for microvascular pedicle compromise, which therefore should be a relative contraindication to microvascular reconstruction. Unfortunately, patients with well-controlled disease who have been aggressively treated with steroids or other immunosuppressive agents can experience poor healing or increased infectious complications.[110] Similarly, patients with hematologic disorders (i.e., von Willebrand's disease, hemophilia, lupus anticoagulant abnormality, thrombocytopenia, polycythemia vera, sickle cell disease, protein C deficiency) should also be strongly considered for nonmicrovascular reconstructions because of the difficulties in maintaining healthy patent anastomoses associated with prothrombotic and coagulopathy states.[111,112] Paraneoplastic hypercoagulability or extensive inadvertent preoperative use of anticoagulating medicines (i.e., aspirin, nonsteroidal anti-inflammatory drugs, vitamin E) can also compromise microvascular success. Patients who require perioperative anticoagulation because of concurrent conditions (i.e., prosthetic heart valves, deep venous thrombosis) are predisposed to compressive neck hematomas that can lead to significant blood loss, airway compromise, or flap pedicle compression.

Diabetic wounds are known to heal more slowly, so uncontrolled or previously undiagnosed diabetes should be aggressively treated. Necessary adjustments must be made in terms of incision line suturing and monitoring. The immunosuppressive effects of diabetes can lead to greater postoperative infections, which can cause delayed microvascular pedicle compromise. Untreated profound glucosuria can compound the already large changes in intravascular volume associated with these procedures. Secondary diabetic microvascular disease can cause poor fasciocutaneous paddle perfusion, yielding ischemic areas after harvest. Larger vessel disease not only can cause silent coronary artery disease that may not be detected preoperatively but can also increase both

donor and recipient vessel atherosclerosis. Poor extremity healing after harvest can lead to difficult-to-treat infections and necrosis of donor sites. Further sacrifice of extremity sensory nerves during harvest can exacerbate problems associated with diabetic peripheral neuropathy. Properly evaluated and managed diabetic patients are still suitable candidates for free tissue transfer.[113]

Laboratory and Radiologic Studies

The reconstructive surgeon should review all preoperative laboratory results and radiologic findings. Abnormalities of liver function, platelet count, blood urea nitrogen level, or prothrombin or partial thromboplastin time may lead to significant intraoperative blood loss and postoperative hematomas, with possible compressive flap loss or infection. These abnormalities must be investigated and corrected as much as possible preoperatively. Preoperative albumin, prealbumin, and leukocyte measurements can give an estimate of the level of malnourishment that can affect postoperative healing. Staging computed tomography and magnetic resonance imaging of the head and neck region complement and confirm the history, physical findings, and endoscopic evaluation by the microvascular surgeon and help to further delineate the anticipated reconstruction needs, in terms of size and structures. Magnetic resonance angiography, computed tomography angiography, Doppler ultrasonography, or conventional angiography is used in cases of potential resection for carotid artery involvement, but can also indicate the adequacy of the external carotid branches to support microvascular anastomosis.[114] Sometimes the patency of the transverse cervical arterial system for use as a recipient vessel can be determined. The integrity of potential larger recipient veins in the neck can also be detected radiographically, including predicting the need for sacrifice of the internal or external jugular venous network. Need for venous angiography is rare.

Radiographic evaluation of the determined potential free flap donor sites should help supplement the physical examination in determining safe harvest. A preoperative Allen's test is crucial for maintaining adequate hand perfusion after radial or ulnar forearm free flap harvest. In cases with an equivocal subjective Allen's test result, Doppler plethysmography can objectively document adequate collateral perfusion to the donor hand, allowing its safe use.[107] Additionally, other angiographic techniques have been used adjunctively to study donor site vasculature before harvest of extremity free flaps.[57,58,115,116] These studies can detect anatomic abnormalities, ensure adequate cutaneous flap perforator supply, and document the adequacy of distal collateral arterial flow. In patients with previous trauma or surgery, plain films can document adequate bony integrity and any compromising hardware.

Surgical Treatment Planning

After the initial workup is completed, the patient's case is presented to the institution's multidisciplinary Head and Neck Tumor Board to obtain a consensus on treatment options. Although in general, the oncologic efficacy of any therapy takes preference in the ranking of treatment options, the Tumor Board's recommendations can also be heavily influenced by the expected postoperative functional outcome, which depends somewhat on the reconstructive options available. From the preoperative clinical assessment, the microvascular surgeon can generally determine which tissue types will be required to reconstruct the anticipated surgical defect. This determination, of course, is much easier in post-traumatic defects, in which loss of further tissue is unlikely. Soft tissue considerations include volume and surface area of tissue needed, need for sensory innervation, availability of and mobility from adjoining vascularized bone graft, and other characteristics, such as motor, secretory, or peristaltic activity. The need to provide protected coverage of bone, large vessels, and brain parenchyma adds to the soft tissue volume needed. Bone considerations in choosing the appropriate free flap include length and caliber of bone required and character and mobility of associated soft tissue.

Unfortunately, there rarely is an ideal free flap that fulfills all the reconstructive requirements perfectly. In addition, the best microvascular reconstructive option may not be possible for every patient because of available expertise, previous therapy, functional or anatomic abnormality, or need for shorter anesthesia time because of medical comorbidity (shorter harvest time). A priority list should be chosen in conversations with the patient, with backup donor sites always available intraoperatively. Also, other reconstructive techniques can be used in combination with free tissue transfer, to maximize the overall reconstructive outcome. Whatever reconstructive technique is implemented, it should not hinder postoperative recovery by requiring multiple operations, possibly delaying or preventing necessary timely adjuvant therapy. Single-stage primary reconstructions are best for meeting this goal. Post-therapeutic expectations should also be discussed in detail. These conversations should include explanation of any staged or delayed procedures anticipated to yield the maximal cosmetic and functional outcome.

The planning stage is also the time to recruit and inform family and friends for the necessary physical and emotional support that complements comprehensive medical therapy. The patient's privacy concerns should, of course, be respected during this process, in accordance with his or her preferences.

Efficient postoperative recovery and early in-patient discharge involve an anticipatory and multidisciplinary approach. Therapy should begin with preoperative consultation and counseling by all involved surgical colleagues (i.e., neurosurgeon, ophthalmologist, vascular surgeon, oral surgeon) and anticipated ancillary personnel (i.e., speech pathologist, physical therapist, social worker, prosthetist). All of these experienced consultants should be familiar with the expected outcome and specific restrictions of microvascular procedures, so that the patient receives consistent information. The myriad preoperative appointments are best arranged for the patient by a patient care coordinator.

Preoperative evaluation by anesthesiologists experienced in microvascular cases is paramount. Such an evaluation ensures not only that the patient's preoperative state is maximized but also that all the necessary personnel and monitoring equipment are available at the time of surgery. An intraoperative plan can then be worked out preoperatively with the surgeon-anesthesiologist team, so that attention can be fully focused on unexpected situations.

In patients expected to undergo a prolonged period of enteral feedings—except in cases in which a gastric pull-up procedure is anticipated—preoperative percutaneous or open gastrostomy tube placement is prudent. This step helps maximize preoperative nutritional status and also removes the postoperative necessity for a nasogastric feeding tube. Postoperative tube placement can be difficult and can risk the suture lines of a free flap paddle. Transabdominal enteral routes are generally more comfortable for the patient and also decrease the incidence of sinusitis, gastroesophageal reflux, and pharyngeal swelling.[117]

Intraoperative Management

An anesthesiologist experienced in microvascular cases is essential. Even before preoperative evaluation of the patient by the anesthesiologist begins, the areas of the body that must be left available for both the extirpative and reconstructive portions of the procedure must be well communicated. Donor extremities should be visibly marked or wrapped to prevent inadvertent blood collections from or placement of intravascular catheters in potential donor vessels. The anesthesiologist should know multiple unconventional and alternate electrode and vascular access sites, in order to leave all potential donor sites available. Necessary preoperative medications, such as prophylactic antibiotics, steroids, and antacids, should be delineated and administered.[118,119] Availability of blood for transfusion should be confirmed.

In the patient undergoing head and neck surgery, airway considerations are frequently challenging. The predetermined approach to the airway is followed in the operating room, and close cooperation between the intubating anesthesiologist and the surgeon is crucial to safe airway access. Complex, lengthy, and risky intubations, including fiberoptic intubations, can be avoided by early placement of a planned tracheostomy with the patient under local anesthesia. The patient is then positioned as the anesthesiologist continues to obtain the desired adequate vascular access, because further access would be difficult once the operation is under way. Availability of lines and electrodes is necessary

during the procedure, and their routes should be planned to avoid contamination of hidden sterile donor sites by the anesthesiologist. All access and monitoring equipment must be adequately fixated to the patient, because changes in patient position are frequently necessary during the procedure. Adequate pressure point padding is confirmed by both surgeon and anesthesiologist. All remaining exposed nonsterile areas of the patient should be covered with a warmer, and unused limbs should be placed in pneumatic compression devices, even if only unilaterally.

The presence of both the extirpative and reconstructive surgeons to guide the povidone-iodine preparation of the operative sites can save a significant amount of later time and trouble. Separate draping of both recipient and donor site operative fields is necessary to prevent not only salivary contamination but also potential tumor seeding of the donor site. Draping of both alternative free and pedicled flap donor sites is also performed (i.e., pectoralis major flap). The maintenance of separate instrument sets for the recipient and donor sites on different operating room tables is necessary. Because most microvascular harvests occur concurrently with the extirpative surgery, two distinct scrub teams are often required. This practice can reduce resource utilization and overall costs.[118] Operating room personnel who are well trained and experienced, especially in microvascular instrumentation and techniques, are crucial to surgical efficiency and success.

Routine good anesthesia management applies to free tissue transfer surgery as well as to other large head and neck procedures.[120-122] Adequate blood pressure must be maintained throughout the operation to provide perfusion of both vital organs and the flap. Hypertension can lead to excess blood loss. Hypotension should be treated initially with a decrease in the inhalation agent, which can be anti-inotropic, a vasodilator, and intravenous hydration. All vasoconstrictors should be avoided, unless the situation is life-threatening, because of their intense vasospastic effect on the hypersensitive free flap pedicle.[123,124] Denervated free flaps are thought to be hypersensitive to catecholamines. Cold patient temperature, which can also cause peripheral vasoconstriction and increased afterload, should be avoided with the use of patient warmers, warm irrigation, and infused fluids.

Experienced anesthesiologists understand how judicious use of intravenous fluids is crucial to operative success. Hemodilution due to minor blood loss and intravenous hydration improves flap perfusion through blood viscosity reduction and can enhance flap ischemia tolerance.[125] Both crystalloid and colloid replacements have been advocated, with some colloids also having an antithrombotic advantage.[126] Fluid overload can cause pulmonary edema but also significant intraoperative and postoperative edema in the head and neck and the free flap. This development can impair insetting the flap or cause pedicle compression. Administration of more than 7 liters of intravenous fluid is also associated with major medical complications.[18] Appropriate hydration can generally be determined by hemodynamic parameters and urine output (0.5 mL/kg/hr), but central venous monitoring may also be necessary in the patient with a history of significant cardiac problems. Too low a hematocrit value can compromise oxygen delivery to vital organs and the flap, and the proper level varies by individual. Transfusion of packed red blood cells may be necessary but can have anticoagulation side effects. The patient should be adequately ventilated and oxygenated to assist with flap perfusion, but positive end-expiratory pressure should be avoided because of its effects on venous return.

Surgical Techniques

Surgical Incisions

Although adequate oncologic resection is paramount in the recipient site, familiarity of the ablative team with the various needs of the anticipated free flap reconstruction is also crucial. Surgical incision planning extends beyond just the purview of the oncologic surgeon. Frequently, multiple-approach options can achieve adequate access and visualization of the surgical field. The chosen surgical approach must also eventually provide sufficient visualization for adequate inset suturing of the free flap into the surgical defect. A needle holder commonly requires more maneuverable exposure than a Bovie cautery, knife, scissor, or laser. Additionally, this problem can be compounded by recipient site edema and initial flap bulk, which can be larger than the extirpated native tissue volume. These needs may require extension of the initial incision or new incisions.

Incision placement also depends on the quality of the native tissue. Previous cervicofacial incisions, traumatic incisions, skin flap elevation, prolonged steroid usage, radiation therapy, and—now more commonly—chemotherapy can all affect skin flap viability. Subplatysmal or thicker skin flap elevations are desirable but are often limited by oncologic considerations. The surgeon should attempt in all cases to use the minimum of incisions necessary for the appropriate exposure. Old incisions are the best initial choice, because the native vascularity is already compromised by them. Incisions perpendicular to or away from large vessels and the planned microvascular pedicle can decrease the exposure risk if there is incisional dehiscence. Incision breakdown often yields a poorer cosmetic result and potential exposure of large vessels, hardware, alloplast, allograft, or bone. Exposure of the microvascular pedicle can result in the rapid loss of the entire reconstruction. If it is detected intraoperatively, the options are (1) providing a vascularized muscular or fascial bed underneath the compromised skin flap area, and (2) including the devascularized area as part of the extirpative defect.

Primary Recipient Site Surgery

Throughout the operation, the extirpative and microvascular surgeons must communicate freely, and often both are working concurrently to minimize anesthesia time. Unanticipated areas of resection of tissue, tissue salvage, and areas of potential re-resection after frozen-section margin analysis should be accurately communicated to the reconstructive surgeon to allow for intraoperative adjustments. This information can affect not only the size but also the shape and orientation of the free flap cutaneous paddle. It is always helpful for the surgeon to mark transected nerve stumps that require subsequent re-anastomosis or cable grafting to innervated free flaps, because finding these areas at the end of the operation can be frustrating. Further recipient preparation includes performing as much primary closure as possible and trimming jagged wound edges to facilitate the necessary even, watertight closure.

In cases of osteocutaneous free flap reconstruction after segmental mandibulectomy, precontouring of the reconstruction plate to the buccal or labial cortex is crucial to maintaining the best postreconstruction occlusion. If there is involvement or distortion of the outer cortex of the mandible, direct plate contouring to the bone is not possible, and use of maxilla-mandibular fixation (MMF) or a mandibular fixbridge system can help maintain preoperative occlusal and joint relationships. Postresection freehand plate contouring and fixation is difficult and suboptimal. Postoperative correction of malocclusion is possible, but difficult.[127] With the currently available low-profile locking reconstruction plates, the contoured plate can closely approximate the natural mandibular projection and contour, without sacrificing durability and strength, when used in conjunction with bone grafts.[128,129] These thinner reconstruction plates are usually not visible or palpable through the external skin flap, even after some subcutaneous tissue resection. The locking plate design affords less accurate contouring of the native mandible contour, because it acts as an internal external-fixator device. Accurate measurement of bicortical screw length is paramount to minimizing readily palpable, and often bothersome, sharp lingual screw tips. The plate should be screw-fixated at the appropriate location along the native mandibular height, so that the bone graft and overlying neoalveolar soft tissue free flap paddle lie even with the remaining native occlusal surface. This fixation facilitates maintenance of the gingivobuccal, gingivolabial, and floor of mouth sulci, to help preserve tongue mobility, oral competence, and an adhesive surface area for dentures. Use of reconstruction plates to span segmental mandibular defects, without the concomitant use of vascularized bone grafts, can have a significant long-term complication rate, depending on mandibular defect location and size and the type of plate used.[130-133] The size and location of the soft tissue defect may necessitate removal of the reconstruction plate before free flap inset by the microvascular surgeon for adequate exposure to perform the paddle inset or microvascular anastomosis. Some microvascular surgeons use miniplate

fixation to attach the osteotomized vascularized bone grafts to the native mandible. Use of maxilla-mandibular fixation or a fix-bridge system is also usually required to maintain proper occlusal relationships. Some miniplate placement on these flaps can occur before pedicle sacrifice at the donor site, to reduce flap ischemia time.

Neck Recipient Site Surgery

Continuous intersurgeon communication during the extirpative neck dissection or neck vessel exploration is also important. Frequently, the range of appropriate recipient vessel size needed can be estimated from the anticipated donor site. Additionally, communication of the anticipated defect location and predicted microvascular pedicle length can guide the extirpative surgeon to save potential recipient vessels in a given area of the neck and allow faster dissection in nonessential areas. Gentle vessel dissection and preservation of lengthy stumps are important for maintaining multiple microvascular anastomosis options. This issue is important, because the best pedicle geometry may not be predictable until the time of anastomosis. Although gentle dissection and stump preservation may take extra effort and time, they usually do not compromise the adequacy of oncologic resection. Saving both the external and internal jugular veins should be attempted, although anastomotic success may be better with use of the internal jugular system.[134] All potential recipient vessels should be kept moist once exposed. Any adventitial or vessel edge dissection should be avoided at this time, until the microscope is used. Similarly, anticipated resection of the proximal external carotid arterial or jugular venous systems because of neoplastic disease must be communicated to the reconstructive surgeon so that alternative recipient vessel networks and vein grafts can be prepared.[135,136] Vein grafting can compromise anastomotic patency. Partial removal of the anterior sternocleidomastoid muscle overlying the pedicle can allow improved microvascular pedicle geometry or decrease venous pedicle compression.

In cases of across-midline resections or previous ipsilateral radical neck dissections, vessels from the contralateral neck may need to be isolated and prepared. This need may prompt the extirpative surgeon to perform a full neck dissection for oncologic reasons in a case with borderline indications for such dissection. In most patients with previous neck dissections, adequate recipient site vessels are still available.[137] Extracervical recipient vessels are sometimes available but may require a longer flap pedicle.[135] Previous anastomoses from established free flaps can also be a source of recipient vessels.[138] Reverse flow through distal ends of certain recipient arteries, such as the facial and superior thyroid arteries, is also a possibility for anastomosis in necks without normally available antegrade-flow recipient arteries.[139] In reconstructions using more than one free flap concurrently, some flaps may be sewn in series (one set of recipient vessels) rather than in parallel (two sets of recipient site vessels). The fibula and radial forearm free flaps can act as flow-through flaps, and their distal pedicles may be used for additional anastomoses.

Free Flap Harvest

An experienced head and neck team can determine the approximate size of each tissue type needed from the preoperative assessment. Communication during the resection is important if these approximations underestimate the actual need. Although many distant donor sites allow harvest of the free flap by the microvascular team to be performed concurrently with the extirpative surgery, scapular-parascapular, latissimus-based flaps require patient repositioning for harvest and so are performed after the resection, significantly increasing the overall procedure time. The separate instrument table should be set up during the extirpation and kept at a distance to remain free of contamination by oral secretions and neoplastic cells.

Although tourniquets are certainly not mandatory, many harvests allow their use to minimize blood loss and potentially improve operative site visualization and harvest speed. Use of a tourniquet can hide subtle, but significant bleeders, especially along the pedicle, that should be addressed at the time of tourniquet release and reperfusion. Certainly, any tourniquet time adds to the overall ischemia time of the free flap and should be meticulously monitored. Also, a time alarm should always be set if a tourniquet is used during donor site closure, because inadvertently leaving the tourniquet up under the drapes during the remaining part of the procedure can have disastrous results.

A flap that has been inset to be hidden deep beyond transoral inspection (i.e., pharyngoesophageal and skull base reconstructions) must have an exteriorized monitoring paddle, which is harvested in continuity with the pedicle. At times fiberoptic visualization is possible, but often difficult. Perfusion of the monitoring paddle must reliably mimic that of the main flap paddle, and this issue should be confirmed before final harvest.

The free flap is harvested until it has been isolated on the intact vascular pedicle only. As soon as the arterial and venous donor vessel diameters and pedicle length are known, these facts are communicated to the extirpative surgeon. Gentle dissection along the pedicle with minimal bipolar cautery or hemoclip hemostasis away from the pedicle vessels is important to avoid damage. Monopolar cautery can cause vessel injury well beyond the visible changes. Some microvascular surgeons microscopically separate the artery from the surrounding donor venae comitantes at this point. This conservative dissection should only be long enough to allow good pedicle anastomosis geometry, in order to minimize potential vessel damage. Copious micro-irrigation with saline or heparinized lidocaine (2% lidocaine, 100 U/mL heparin) is used to keep the vessels moist during the harvest.

Once the vessels are sacrificed distally, the tourniquet is released, and the free flap is perfused for as long as possible. This step not only enables confirmation of good flap perfusion to all portions of the free flap but also confirms adequate distal perfusion to the donor extremity. It also allows hemostasis of any bleeding on the free flap. Topical papaverine irrigation (30 mg/mL) is sometimes useful to enhance vasodilation and perfusion. The free flap paddle should be manipulated at this point as much as possible while the flap remains pedicled to its native supply (e.g., tubing, shaping, shortening). Partial closure of the donor site may also be possible at this time, with the remaining closure being done during flap anastomosis or insetting. Harvesting of any necessary vein grafts is also performed before harvest. Only when the neck recipient vessels are ready are the proximal pedicle vessels sacrificed and the free flap brought to the head and neck region. Both surgeon and anesthesiologist should note the time of harvest to indicate the beginning of flap ischemia time.

Free Flap Inset and Microvascular Anastomosis

No hard and fast rule pertains to the order of flap inset versus microvascular anastomosis. Some microvascular surgeons prefer to inset the free flap completely before performing the microvascular anastomosis, to ensure good pedicle geometry and adequate pedicle length while minimizing postanastomotic manipulation. This maneuver does lengthen the potential flap ischemia time but can usually be performed well within tolerance limits of most free flaps. Some reconstructions require this maneuver initially because of the anticipated position of the pedicle, which would otherwise block safe access to perform the flap inset. Wrapping of the finished pedicle in the drill bit during bone graft inset has been described in anecdotal reports. Other surgeons perform the anastomosis first, to minimize ischemia time, maximize exposure for the performance of the anastomoses, and allow close monitoring of the flap during the remaining portion of the procedure. It is often difficult to exactly predict the amount of pedicle compression that can be attributed to flap bulk and defect swelling after flap inset. If the anastomosis is performed first, the free flap is laid in its anticipated position. Some temporary stay sutures should be placed to keep the flap from moving or falling while under the microscope.

Extensive detail of the microvascular technique is beyond the scope of this chapter and available elsewhere.[140,141] The standard microscope used for anastomoses affords 10× to 40× magnification (250 to 300 mm focal-length lens), with opposing binocular heads for simultaneous use by the surgeon and assistant. An attached camera with monitor can help the microvascular scrub nurse anticipate instrument needs. Some surgeons use loupe magnification (3.5× to 5.5×), especially in hospitals without an adequate microscope available.[142] Anastomoses of smaller vessels (less than 1.5 mm), as seen in certain free flaps and in children, may require even more magnification. A dedicated, experienced microvascular nurse is essential for operative efficiency and

instrument maintenance. Meticulous and gentle handling of all instruments is paramount, because the ends are easily bent and broken. Basic microvascular instrumentation consists of straight and curved forceps and scissors, a microneedle holder, vessel dilators, and atraumatic single and double microvascular clamps. Micro-irrigators filled with heparinized lidocaine are useful for irrigating thrombus from open vessel lumens. Papaverine also should be available for arterial vasospasm. Nonabsorbable monofilament nylon suture (8-0 to 10-0), with various atraumatic needle sizes, is used, depending on vessel size and thickness.

Gentle microsurgical technique and good pedicle geometry are the most important factors in performing the microvascular anastomosis. Good technique involves gentle vessel handling, maintenance of smooth vessel approximating edges, and avoidance of suture line tension. Good vessel size match allows linear flow across a straight anastomosis. Good pedicle geometry includes smooth vessel transitions and avoidance of pedicle compression with a minimum of twisting and kinking. These factors also need to be checked, when the head is returned to the neutral position, which can affect pedicle geometry and, especially, venous patency.[143] Adequate recipient arterial flow should be confirmed in the chosen vessel before anastomosis, although flap arterial flow is generally more dependent on the specific flap type.[144] Good recipient vein backflow should also be confirmed before the anastomosis but may be limited by a valve. Although the most common anastomosis is end-to-end, the end-to-side anastomosis and vein grafting techniques should also be in the microvascular surgeon's armamentarium, in order to maximize pedicle geometry. Alternative methods may also be necessary if the appropriate recipient vessel size is not available (i.e., a size mismatch > 3:1) or the pedicle length is inadequate.[145]

When using the microscope, the surgeons can either sit or stand, but they must be comfortable, with good arm support on the table. No jostling of the patient by the anesthesiologists or the concurrent donor site closure team should occur during this time, because such movements are magnified under the microscope. No hard and fast rules exist about whether the arterial or venous anastomosis should be performed first.[146] Some surgeons perform the venous anastomosis initially, because it tends to be the more difficult owing to wall collapse and edge infolding. Others, however, perform the arterial anastomosis first so as to restore flap perfusion as soon as possible.

The end-to-end anastomotic technique is most common and technically the simplest. After the recipient vessel is chosen, both vessel edges are cut sharply and smoothly to provide a clean anastomotic edge, and then the vessel is gently dilated with vessel dilators. The adventitia is then sharply cleaned away from both vessel edges, to beyond where the sutures penetrate the vessel wall. Care must be taken to avoid vessel wall breeches deeper than the adventitia, which are not uncommon in the preparation of the veins. Loose connective tissue should also be trimmed so that it also does not get caught in the anastomosis and act as a thrombotic agent. Both recipient and donor vessels are placed in the sliding, double-approximating vascular clamp, so that the vessel edges approximate without tension. A blue background material provides good contrast for the fine suture.

Multiple anastomotic techniques have been described, including bisecting and trisecting the vessel circumference with simple sutures, to ensure even approximation around the entire vessel. The essence of these techniques includes placement of two or three equally spaced sutures to hold the anastomotic orientation. To minimize intimal damage, penetration of any instrument into the vessel lumen should be avoided. Either the outer vessel wall can be grasped, or a smooth jeweler's forceps can be used intraluminally, to lift the anterior vessel wall away from the posterior wall during suturing to prevent "back walling," or the inadvertant capture of the opposite vessel wall in the suture, which causes vessel closure. The suture needle is inserted perpendicularly to the vessel edge at a distance one to two times the vessel wall thickness from the edge. After the opposing vessel edge is pierced, three half knots are performed, with care taken to make them square. One of the sutures can be cut longer, to be grasped for vessel edge manipulation. Some surgeons tie each anastomotic suture as if it is thrown, but some prefer to leave them untied until half the vessel circumference sutures are placed. This latter technique allows repeated examination of the lumen to make sure no back walling has occurred, but loose sutures can become mixed. Usually, a combination of the two techniques is most successful. After the superficial vessel half wall is sutured, the double-clamp is flipped, and attention is given to closing the deeper wall. Copious micro-irrigation confirms lack of back walling and good superficial wall anastomosis, as well as the cleaning out of any accumulated blood clots. During the venous anastomosis, irrigation can also lift the superficial wall off the deep wall.

The same suture technique is used to complete the anastomosis. The interrupted suture interval can usually be larger in venous anastomosis than with arterial anastomosis, because of the lower flow pressure. A continuous suture technique can also be used but requires more experience and can constrict the vessel lumen. The clamps are then removed, the downstream ones first, and vessel filling across the anastomosis is observed. "Strip testing," which uses two smooth forceps under sliding compression, can confirm flow across the anastomosis, but can damage the endothelium.[147] The best confirmation is slow bright red blood flow from the skin paddle edge. Leaks can usually be repaired, without further interruption of flow, with simple single sutures. A Y-anastomosis has been proposed to improve blood flow across the anastomosis, but this technique is technically more difficult and not widely employed.[148]

The end-to-side anastomotic technique uses similar suturing technique. The recipient vessel is clamped both proximally and distally to the planned anastomotic site. The planned site of the arteriotomy can be grasped with a suture and stably pulled away from the recipient vessel, so that the microscissors can be used to make a clean arteriotomy. This is generally not necessary for making side venotomies. The fashioned arteriotomy or venotomy needs to be slightly larger than the donor vessel, to help keep the anastomosis splayed open in a "fish-mouth" fashion. The donor vessel can be appropriately angled slightly to aid pedicle geometry and minimize turbulence. No particular anastomotic technique is more advantageous in terms of patency.[1] Anastomotic coupling devices have also been described and have been useful for venous anastomosis (Fig. 80-10). They can speed up this portion of the procedure.[149-151]

In some cases, vein grafts are needed, resulting in a higher complication and thrombosis rate as a result of the higher number of anastomoses. Additional vein harvest sites are necessary, and usually the distal saphenous vein provides a good vessel match. Vessel size match is important for vein graft success.[152] The harvested vein graft is always longer than needed, each side branch is clipped or tied carefully, and the native direction of flow is marked, given the potential presence of valves. The flap pedicle is then placed on a sterile back table under the microscope; this location provides a much smoother and controllable

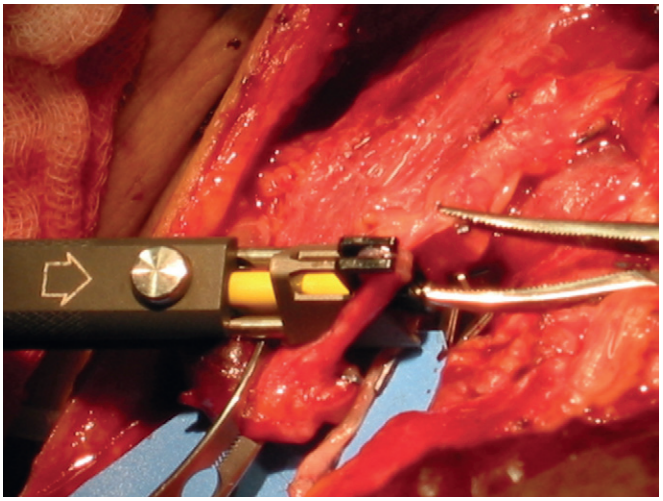

Figure 80-10. The use of a microvascular coupling device for the completion of end-to-end venous anastomosis.

surface for the vein graft anastomoses. The proximal end of the vein graft (direction of flow into vein graft) is anastomosed to the donor vein, while the distal vein graft end (direction of flow out of vein graft) is anastomosed to the donor artery. This yields a U-shaped vein graft from donor artery to vein. The flap is then brought into the head and neck region. The central portion of the vein graft is cut, depending on the needed pedicle length for both donor artery and vein, and the remaining two anastomoses are completed.

The complete inset of the free flap involves both the soft tissue and bony portions of the free flap. It is usually necessary to perform any microscopic neural anastomoses before full inset, which will limit exposure. Reinnervated flaps can adopt sensation in a pattern similar to that of the recipient bed.[153] However, even without direct neurorrhaphy, an adequate level of intraoral flap sensation is possible.[154]

Sufficient hemostasis in the recipient bed is also important, to minimize the risk of the formation of a microvascular compressing hematoma or later infected seroma. The bony inset is most difficult, because of the close proximity of the parallel vascular pedicle, the need for monocortical screw fixation, and the common need for osteotomies. If a locking plate reconstruction is used, either monocortical nonlocking or locking screws can be used; nonlocking screws allow approximation of the bone grafts to the lingual surface of the reconstruction plate. Using the fewest osteotomies as possible is desirable. Necessary osteotomies of the vascularized bone graft should be performed subperiosteally and wedge-shaped, such that bone-to-bone approximation is maximized to facilitate bony union.

Inset of the soft tissue paddle requires the gentle approximation of wound and flap edges with absorbable sutures, to form a watertight seal. Meticulous soft tissue technique is important, and suture lines should be under no tension. Multiple-layer closures are desirable but not always possible. Various techniques have been described to shape and contour the soft tissue paddle so as to mimic the resected tissue, including de-epithelization, fascia rolling, and splitting of the flap. These techniques can help maximize postoperative function and aesthetics.

Drain Placement and Wound Closure

Drain placement at the completion of the procedure is crucial. The best type of postoperative neck drainage remains controversial. A balance between adequate drainage of all potential dead spaces and minimal interruption of any reconstructive flap pedicle must be maintained. Both passive and suction drains have been advocated.[155] A tight neck skin closure can apply significant pressure to the pedicle or a drain tube if it overlies a vascular pedicle. This problem can be compounded by routine postoperative swelling or compression dressings. Drains should typically be placed parallel to flap pedicles and carotid sheath contents. Drain tips should be placed away from mucosal or skin suture lines, to avoid salivary or air leakage. Maintenance of internal drain position with postoperative head and neck movement can be ensured by loose suturing with absorbable sutures. Additionally, the drains should be externally sutured in place to prevent their inadvertent withdrawal with patient movement. Suction drains should be removed from self-suction and withdrawn carefully, according to the reconstructive surgeon's parameters.

Neck incisions are generally closed in layers, but care must be taken to avoid injuring superficial pedicles during the closure. The position of a superficial pedicle should also be marked cutaneously, so that postoperative Doppler monitoring may be employed if needed. This marking also facilitates finding of the pedicle if the neck must be re-explored.

Postoperative Management

Standardized postoperative intensive care unit (ICU) orders, ward transfer orders, and clinical pathways for microvascular cases are crucial for a consistent and efficient hospital recovery.[156] By bringing the patient directly to the ICU themselves, members of the operative team ensure that all drain and monitoring equipment are in proper working order. The operative team can also directly show the ICU nurse the microvascular paddle and monitoring sites. If a warm (80°F) room is required, the proper temperature can be confirmed. The patient is inspected in the ICU for compression by circumferential neck ties from a gown or tracheotomy straps, electrocardiogram wires, intravenous lines tightly overlying the neck, or improperly connected suction drains that may lead to early pedicle compromise. The proper head position to maintain pedicle geometry is also confirmed and maintained with bolsters in the ICU bed. As is the case during the operation, postoperative hypovolemia, hypotension, and hypothermia should be avoided. Some microvascular surgeons prefer that the patient undergo sedation and respiratory paralysis for a time, to help maintain this positioning. This preference must be balanced against the increased risk of pneumonia and deep venous thrombosis associated with prolonged ventilation. Postoperative monitoring of the neck incision is similar to that after any neck dissection. Fluid collections and dehiscences must be aggressively treated, because purulent collections can lead to rapid flap loss from pedicle compression or thrombosis.

Pharmacology

Successful free tissue transfer depends on the maintenance of blood flow through the arterial and venous microvascular anastomoses of flap vessels to the recipient vessels in the head and neck. Surgical technique is the single most important factor in patency; however, various pharmacologic therapies have been proposed in an attempt to improve anastomotic success rates.[157] The majority of these agents have attempted to address one or more of the three common mechanisms for thrombosis—stasis, hypercoagulability, and vessel injury. Of the dozens of agents that have been tried or proposed, only aspirin, heparin, and dextran have found a role in the clinical setting. There remains a paucity of prospective clinical trials on which to base treatment guidelines, with most surgeons relying on anecdotal experience to direct therapy.

Aspirin

Aspirin, or salicylic acid, is an antiplatelet agent that acts by acetylating cyclooxygenase and decreasing the products of arachidonic acid metabolism. These products include thromboxane, a potent platelet aggregator and vasoconstrictor, and prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. The desired therapeutic effect after vascular surgery is a suppression of thromboxane without effect on prostacyclin. The minimal dose to achieve this effect in humans is reported to be 100 mg.[157] Higher doses inhibit both thromboxane and prostacyclin but do so disproportionately, such that some benefit is still seen. Aspirin has been shown to reduce the risk of stroke and myocardial infarction more effectively at lower doses (81 and 325 mg). Although no microvascular surgical trials have been performed, aspirin has been shown to reduce the rate of graft occlusion in a range of vascular procedures if given preoperatively or within 24 hours of surgery. Chewing of the tablet is the most rapid administration method for anticoagulation.

Heparin

Although heparin has multiple mechanisms of action, its anticoagulation effect is largely the result of the inhibition of thrombin and, subsequently, the inhibition of thrombin-induced activation of factor V and factor VIII.[157] Heparin possesses properties to prevent both platelet-induced (arterial) and coagulation-induced (venous) thrombi. In animal models, heparin infusion has been shown to be more effective than antiplatelet agents in preventing vascular occlusion.[158] Unfortunately, systemic heparin can result in significant complications (hematoma and bleeding) in the perioperative patient, largely precluding its routine use in free flap surgery.

Topical heparin irrigation at a dose of 100 U/mL has been suggested as an alternative to systemic therapy to reduce these significant complications. Two studies, however, have not shown a significant benefit of its use for flap outcome.[159,160]

Dextran

Dextran is a heterogeneous polysaccharide that is synthesized by the action of the bacterium *Leuconostoc mesenteroides* on sucrose.[161] Two commercially available forms of dextran are available, dextran 40 (Rheomacrodex) and dextran 70 (Macrodex), which are named according to the average molecular weights of the polysaccharides in the prepara-

tions. Dextrans were initially used as colloids for fluid resuscitation; however, problems with potential anaphylactic reactions and effects on the coagulation system led to a general abandonment of the use of dextrans in this setting. It is their effects on coagulation that have been exploited in microvascular surgery. Dextrans appear to interfere with the formation of fibrin networks, increase the degradation of fibrin, decrease von Willebrand's factor and factor VII, and expand intravascular volume.[161]

Animal studies have shown better immediate postoperative vessel patency with use of dextran infusion. However, Khouri and associates[159] found no improvement in flap outcome with the use of dextran in a prospective trial of pharmacologic agents.

Although a wide variety of regimens for the administration of dextran in the perioperative period have been advocated, two are commonly followed. Johnson and Barker[162] recommend a 40-mL loading dose of dextran 40 before the release of clamps, followed by a 25-mL/hr infusion for 5 days; Buckley and colleagues[163] recommend 500 mL of dextran 40 before anastomosis and then 500 mL per 24-hour period for 3 days. Most surgeons have used dextran in a fashion similar to these protocols.

Anaphylactic reactions to dextran are probably rare, but many surgeons suggest a test dose of 5 mL of dilute dextran before initiation of therapy. More common sequelae of dextran therapy include pulmonary edema from intravascular volume overload, especially in the elderly. Nephrotoxicity and adult respiratory distress syndrome have also been reported.

On the basis of 300 digit replants and 500 free flaps, Conrad and Adams[157] suggest that dextran be used for digit replantation, but not for routine free flap surgery, especially for patients older than 50 years of age. This use also remains anecdotal, and a well-designed prospective trial remains to be performed.

Free Flap Monitoring

Close monitoring of the microvascular reconstruction is paramount, but the exact schedule and method remain controversial, so practices widely vary even within institutions. Care by ICU nurses experienced in the care of the patients who have undergone microvascular surgery is important to the avoidance and early detection of complications. This monitoring is supplemented by physician or electronic monitoring of the free flap. Visible flap inspection and pinprick constitute the most reliable method that must be mastered early by all microvascular surgeons, and should be the end-all test that determines the status of the flap. Digit palpation and Doppler monitoring of a markedly superficial pedicle can supplement direct clinical flap assessment. Both techniques have some subjectivity when there are early changes, and thus, serial monitoring by the same observer is important. Later anastomotic difficulties are not subtle.

Direct flap observation is labor intensive and can be less sensitive to early ischemic changes. Different objective monitoring methods of either pedicle blood flow or flap perfusion, both invasive and noninvasive, are being investigated, with varying success. They include radioisotope scanning, color-flow Doppler ultrasonography, temperature and oxygen tension measurements, perfusion CT scanning, photoplethysmography, and laser Doppler velocimetry.[164-169] Limitations of these methods include the cost of monitoring equipment, a wide variation in normal values with significant artifact, and the need for special expertise.

Complications and Salvage

Systemic medical complications are common in patients undergoing microvascular surgery for head and neck cancer and must be aggressively treated. Local complications to the donor site are specific to each type of free flap. Familiarity with the anatomy of the donor site is paramount to recognition of the complications, which range from pain, bleeding, and infection to more severe complications, such as permanent sensory and motor nerve damage and even loss of the donor limb. Infections under pressure in either natural or surgically created compartments can rapidly lead to compression and thrombosis of the already compromised native vascularity of the extremity. Left undetected and untreated, such developments can rapidly lead to arm or leg loss. Scarring can result in later functional and cosmetic problems that may require physical therapy or further surgery.[60] The donor site must be inspected with the same frequency and vigor as the recipient site.

Recipient site complications are similar to those seen in other patients undergoing head and neck surgery without free flap reconstruction. Hematoma, salivary fistula, infection, and wound dehiscence can occur at any time and require rapid detection and intervention. In the patient who is undergoing radiation therapy, protection of the carotid artery is important. If wound dehiscence or salivary fistula occur close to the free flap pedicle, rapid flap compromise can occur. Presence of healthy nonirradiated vascularized tissue in the heavily irradiated recipient bed can help minimize wound complications.[6]

In the animal model, ingrowth of collateral vessels may keep an inset free flap viable, independent of the pedicle, as soon as 8 days after surgery.[170] Microvascular surgeons do not rely on adequate recipient bed neovascularization until 3 to 4 weeks and probably longer in the previously irradiated patient. The bony portion of some osteocutaneous free flaps may have even longer or permanent dependence on the pedicle blood supply. Postoperative pedicle compromise should be rapidly reversed, because prolonged ischemia leads to at least partial necrosis. After approximately 12 hours of ischemia, even with reestablishment of anastomotic flow, the free flap is usually not salvageable.[171]

The ischemia tolerance of the flap tissues varies with patient and tissue type, with capillary perfusion changes seen as early as 10 minutes after venous pedicle occlusion.[172-174] Arterial insufficiency is less tolerated than venous insufficiency, and most microvascular surgeons keep the ischemia times at less than 2 hours. Ischemic tolerance is generally shortest with bowel mucosa and muscle, intermediate with skin, and longest with bone. Additionally, flap compromise later in the hospital stay tends to be more difficult to reverse. Flap monitoring is usually more relaxed, resulting in a longer undetected ischemia time. Pedicle compromise is also usually caused by localized purulence, which may have a long-term effect on the pedicle and anastomotic patency.

Most free flap anastomotic ischemic complications occur within the first 48 to 72 hours. In multiple large series, the need for pedicle reexploration or revision occurs approximately 8% to 9% of the time, with an overall flap loss rate of 1% to 11%.[174-176] Venous anastomotic thrombosis is more common, but if not remedied, both outflow and inflow will be compromised.[175,176] Early venous congestion may affect the more distal monitoring paddle before the main flap paddle, because of the proximity of the monitoring paddle to the venous anastomosis. Thus, early venous congestion changes in the monitoring paddle should be taken very seriously. Venous anastomotic thrombosis results in an increased flap turgor, rapid capillary refill with brisk bleeding of darker blood, and, finally, darkening and mottling of the skin paddle. Venous congestion may present with any or all of these changes, the color changes usually being a later sign. The arterial pulse can still be felt until the later stages. Arterial insufficiency manifests as a profound paleness and coolness, loss of flap turgor, and absence of any capillary refill or bleeding to pinprick. Usually only a serous bubble, if anything, arises from a pinprick or cut. The superficial pedicle pulse is no longer palpable or obtainable by Doppler testing. Observation of changes in free muscle flaps are more difficult to determine than in fasciocutaneous flaps. Buried flaps require an external monitor paddle for monitoring.[177]

Injury from oxygen free radicals, as well as other etiologies, contributes to flap damage from flap reperfusion after a period of ischemia.[178-180] Despite the injury from reperfusion, rapid intervention is required upon detection of pedicle insufficiency to reestablish flap perfusion if the flap is to be salvaged. This may include bedside maneuvers such as suture release, drain stripping, and opening the neck incision, because it is not always possible to move the patient to the sterile operating theater immediately. Time is of the essence, especially in cases of arterial insufficiency. The patient is urgently returned to the operating room, the neck is reopened, and the anastomoses are explored. Attention is focused on reestablishing blood flow, but the inciting factor must also be corrected to prevent recurrence (e.g., evacuation of hematoma, improvement of pedicle geometry). In the case of isolated venous outflow thrombosis, the venous anastomosis should be investigated, and thrombectomy and thrombolysis performed. When arterial pedicle thrombosis has occurred, both anastomoses must

be taken down and revised after thrombectomy. The arterial anastomosis is then revised, and thrombolysis is performed before the revision of the venous anastomosis. The timing of the release of the recipient artery vascular clamp and reestablishment of blood flow remains controversial.[181] Copious irrigation with heparinized lidocaine is used throughout to help extract gross thrombus from the pedicle. Clots should be atraumatically "milked" or pulled from all arteries and veins. Fogarty catheters may also be useful. The vessels should be trimmed back to fresh clean edges. Alternatively, new recipient vessels or vein grafts should be concurrently prepared if needed to avoid future thrombosis.

Thrombolysis is facilitated with injections of streptokinase (75,000-125,000 U/injection) or urokinase (100,000 U) using a fresh 30-gauge needle while the recipient artery is atraumatically clamped.[182] This is performed near the arterial anastomosis, in case some intimal damage is caused by the penetrating needle, which would require the anastomosis to be revised again. Microcatheterization of a side branch is also possible for instillation. The arterial clamp is then removed, and the effluent from the donor vein collected on a sponge and discarded; this maneuver prevents systemic circulation of the agent and generalized bleeding complications. The procedure is repeated until normal venous outflow from the donor vein is reestablished. Directional massage of the flap paddle can assist this process. Once flow has been reestablished and directly observed for a time exiting from the donor vein, the venous anastomosis is revised. The efficacy of thrombolytic therapy remains controversial, with early detection and treatment being the most important factors in flap salvage.[183] The patient undergoes anticoagulation with heparin, the level depending on the surgeon's preference.[184]

The use of medicinal leeches is indicated for cases of flap venous congestion in which surgical salvage has been attempted but was inadequate in reestablishing full venous outflow.[185] Prolonged use of leeches has resulted in some salvage success but requires an intense protocol. Use of leeches is also indicated as a temporary measure to relieve venous congestion until the patient can be brought to the operating room. This practice requires immediate access to medicinal leeches from the inpatient pharmacy, which may not be available in every institution. Leeches are generally available within 24 hours from a national supplier. Leeches produce both hementin and hirudin, which provide local anesthesia and anticoagulation properties at the leech bite. The leech also harbors a gram-negative beta-lactamase–producing organism (*Aeromonas hydrophila*), requiring antibiotic prophylaxis to prevent soft tissue infection and necrosis. Significant blood loss can require multiple transfusions, and wayward leeches can attach to other body areas or personnel.

Even the best salvage efforts can result in either partial or total loss of a free flap. A partially necrotic flap may be left to demarcate the necrotic from viable portions of the flap, assuming that the pedicle and major vessels are not at risk during this period. Generally, the tissues farthest from the pedicle are at highest risk. These necrotic areas should be eventually débrided down to healthy bleeding tissue. The resulting defect may be left to granulate or may be replaced with other tissue, depending on its size and location. A totally necrotic flap should be resected in a timely fashion, because of the risk of salivary contamination, infection, and disseminated intravascular coagulation. For a time, the flap can act as a nonvascularized biologic dressing, until the patient is medically stabilized and his or her status maximized for the necessary revision surgery. The resultant defect is either reconstructed with an alternative, less optimal pedicled or free flap, depending on the specific patient situation.[186] One alternative that has varying success after composite resection is to leave the fixated nonvascularized bone in place after loss of an osteocutaneous free flap. This then requires coverage with a healthy vascularized flap, separating the bone graft and protecting it from oral contamination (i.e., pedicled pectoralis major myocutaneous flap).

Costs and Outcomes

In addition to the expertise, microvascular reconstructions require significant health care resources, including time, equipment, and personnel.[187] The actual costs of microvascular reconstruction are generally comparable to those of other techniques, with costs being more dependent on comorbidities and extent of disease.[21,22,188,189]

With widespread use, further prospective evidence-based evaluation of current reconstructive techniques is warranted. As new outcome assessment tools become available, function and quality of life after microvascular reconstruction will be increasingly investigated. Focus must be placed on very specific anatomic areas of reconstruction, rather than on a general comparison of all oral cavity, oropharyngeal, and laryngeal areas. Comparisons, mostly retrospective, with alternative forms of reconstruction, including prosthetic rehabilitation and pedicled tissue reconstruction, show mostly better results for microvascular reconstruction.[3,17,18,20,190,191] These investigations should also include long-term outcomes.[192] Further comparison with results of organ preservation protocols or previous reconstruction also requires further study.[193,194]

Future Directions in Free Tissue Transfer

Enhancements to current microvascular techniques are currently being developed. Improvements in the speed of anastomoses, such as the use of mechanical anastomotic devices, must be matched with the equivalency of patency rates. The use of a microvascular anastomotic coupling device has been described in both arterial and venous anastomoses.[149-151] It has been found to be effective in end-to-end as well as end-to-side venous anastomoses, only 3 to 5 minutes being required to complete the end-to-side anastomosis.[195] Similarly, new pharmacologic agents are being investigated to assist in reducing rates of anastomotic thrombosis.[196,197]

Minimally invasive harvest techniques have been developed for some free flap donor sites, including the jejunum, gracilis, omentum, rectus abdominis, temporoparietal, and latissimus dorsi.[198-202] Although less scarring and potentially less donor site morbidity results, the longer harvest times currently required can be detrimental. Multi-institutional experience needs to be studied as these techniques become more commonly attempted, before they can be compared with current harvest techniques.[203] Endoscopic harvest of saphenous vein grafts has gained some acceptance in cardiac surgery and may also be an option for the microvascular surgeon.[204]

Allograft transplantation of whole head and neck organs has gained some media attention. The clinical experience is very small, and the necessary induced immunodeficiency certainly has serious implications for the patient with head and neck cancer. Also, return of adequate native organ function still must be demonstrated experimentally before the clinical applicability of this technique in nononcologic reconstructions can be considered.[205]

New applications and enhancements of current techniques, as well as new donor sites, are needed. Discovering new indications for current free flaps should always be encouraged, including indications such as laryngeal and tracheal reconstruction.[206] The use of prefabricated reconstructions and hybrid alloplast, or bioengineered tissue reconstructions, is slowly gaining momentum.[25,207-211] Prefabricating or prelaminating an intended free flap into a more ideal reconstruction may improve the overall aesthetic and functional result but also may be limited by the preparation time required, especially in oncology patients.[212-215] A combination of free flap reconstructions with current and future alloplastic materials may provide even more expanded indications.[216-218] Improved aesthetic and functional outcome may be possible as new combinations are developed. These techniques should also help minimize the subsequent "fine-tuning" operations that are commonly necessary to maximize overall cosmetic and functional outcomes.

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CHAPTER EIGHTY-ONE

Integrating Palliative and Curative Care Strategies in the Practice of Otolaryngology

Rhonda Johnson

Gary Johnson

Key Points

- Palliative care seeks to address symptom management for optimal patient quality of life throughout active head and neck treatment and thereafter.
- Because head and neck cancers compromise critical anatomic structures, both the disease and its treatment can be physically, socially, and emotionally debilitating, rendering palliative care essential in patients with these tumors.
- Pretreatment dental assessment by a practitioner experienced in oral oncology to address oral disease prior to cancer treatment combined with patient education directed toward ongoing good oral hygiene is important to ameliorate the side effects of treatment.
- The complex and clustered nature of symptoms among patients with head and neck cancer requires a multidisciplinary team approach to provide comprehensive palliative treatment.
- Often the behavioral and social habits of patients with head and neck cancer are predisposing factors in the development of the disease. These factors also represent an ongoing risk that influences the efficacy of treatment and therefore must be integrated into the overall treatment plan.
- Oral mucositis is a common side effect of treatment that affects virtually all patients with head and neck cancer receiving multimodality treatment. Later research has provided a model for better understanding the progression of events leading to ulceration. This model provides a framework for the development of targeted strategies to prevent and diminish the effects of treatment.
- Patients with head and neck cancer are at substantial risk for experiencing psychological distress. These patients should be assessed prior to treatment on the basis of high-risk factors, including use of tobacco and alcohol, and should be monitored carefully throughout the treatment process. Patients continue to experience significant disabling effects of their treatment months after its completion and therefore continue to be at risk for psychological distress. Palliative treatment must incorporate long-term monitoring and structured interventions for these patients.
- Approximately 50% of patients with head and neck cancer are nutritionally compromised at initial presentation. The consequences of treatment put such patients at significant risk for treatment-related delays and hospitalization secondary to the effects of nutritional insufficiency. Palliative care treatment includes careful nutritional assessment and specific interventions to alleviate nutritional deficiencies.
- Wherever possible, symptom management should utilize a portmanteau approach to the use of medications to minimize side effects and maximize treatment efficacy.

As of 2006 there were 10.5 million cancer survivors in the United States, with 1 million more anticipated each year.[1] With advances in treatment regimens that allow individuals with cancer to live prolonged periods beyond the time of diagnosis—even for cancers with trajectories that are expected to ultimately end life—symptom management becomes a critical focus of the doctor-patient relationship. Five-year survival rates for patients diagnosed with head and neck cancer (all types and stages) is 59%.[2] Although treatment has improved the disease-free interval, cure rates have not substantially improved over the last 50 years.

Treatment depends on stage of disease. For late-stage disease, treatment most often involves multimodality therapy.[3] Symptom distress that occurs commensurate with treatment and persists long term to influence both function and quality of life provides the impetus for the implementation of prevention and treatment strategies designed to alleviate these difficult conditions.

Palliative care focuses on treating acute and chronic symptoms. As a result this chapter outlines palliative care efforts that are particularly pertinent to patients with head and neck cancers. Because head and neck cancer affects structures that are critical for day-to-day functioning, including such basics as speech and swallowing, and because treatment may lead to deformities that adversely affect psychological functioning as well as debilitating short and long-term side effects, there is a special need for physicians to be attuned to distress that may be reduced by palliative intervention.

Palliative care is a relatively new construct in the epistemology of care for patients with chronic illness. It came about with the realizations that (1) individuals with ongoing illness experience physical, social, physiological, and spiritual issues that influence their quality of life and (2) treatment encompasses a more all-embracing objective than simply attempting to prolong life. The intent behind initiating palliative care, at the time of diagnosis, is to prevent and relieve suffering in order to improve quality of life throughout the disease process. It becomes imperative for the oncologist to be aware of symptoms inherent to the disease process as well as those that are associated with the treatment regimen. Comprehensive cancer care includes palliative care designed to utilize tools that identify distressing symptoms and allow for expeditious intervention.

Broadly speaking, in this chapter, we discuss palliative care strategies by addressing specific domains that include physical symptoms and emotional well-being. Although each of these issues is discussed as a separate domain of individual functioning, it is clear that each construct influences the other; while a patient is experiencing pain, for example, the patient's psychological, social, and spiritual well-being are certainly also affected. Symptoms can be the result of the disease itself or can stem from treatment. For example, malnutrition can be the direct result of the individual's lifestyle prior to the cancer diagnosis but can also result from treatment effects. Addressing one issue, usually the one that is most salient to the patient, therefore may alleviate distress in other domains.

Treatment regimens differ because head and neck cancers are a varied group of diseases comprising malignancies of the oral cavity, oropharynx, larynx, sinuses, and skull base. This difference in treatments coupled with characteristics specific to the patient (e.g. stage, co-morbid medical illness, age) influences treatment outcome and makes it difficult to describe a clearly delineated set of adverse or distressing symptoms.[4] Discussions of treatment options with patients should always include a thoughtful review of possible side effects, late effects, and quality of life consequences as well as best or most likely clinical outcome. Additionally, because both prevention and treatment of distressing symptoms involves complex and time-consuming consultation, palliative care is best delivered through the efforts of a interdisciplinary team[4] including the surgeon, medical oncologist, radiation oncologist, dentist, speech therapist, psychologist, occupational and physical therapists, nurse, and social worker.

Treatment for malignant disease involving the head and neck produces toxicities to normal cells or tissue. By virtue of its rapid cellular turnover rate, the mucosal lining of the gastrointestinal tract including the oral mucosa is a prime target for chemotherapy- and radiation-related toxicities The diverse and complex microflora that exists within the oral cavity renders the oral mucosa vulnerable to infection. Approximately 10% to 15% of patients experience oral complications during adjunctive chemotherapy.[5] This number increases to 40% to 50% when chemotherapy is administered as the primary treatment (palliative).[6] Virtually all patients with head and neck cancer who are undergoing combination chemotherapy and radiotherapy experience oral complications, the majority of whom will experience severe effects.

Treatment for patients with head and neck cancer often involves multimodality therapy. Surgery remains an integral component for most such patients. The adverse effects of surgery are distinctly different from those of chemotherapy and irradiation. Surgical effects often remain life-long and have a significant impact on daily functioning.[7]

In a 2007 Cochrane Review, less than one half of the included studies (39%) reported adverse events with treatment.[8] The writers of this review discuss the perception among oncologists that acceptance of high rates of adverse events is necessary to "tackle the bigger issue of survival." The information presented regarding adverse effects should not be used to argue against specific surgical considerations, because treatment decisions should be weighted primarily toward those that maximize survival. However, studies indicate that more than half the patients treated for head and neck cancer are disabled by their treatment.[9] Specific risk factors include previous treatment with chemotherapy and pain. Pain remains a major predictor of disability and can be disabling for many reasons. Therefore, patient education regarding expected treatment outcomes is critical to the informed consent process.

Among patients receiving treatment for head and neck cancer, the most common complications are mucositis, xerostomia, psychological distress, difficulties with speech and swallowing, taste dysfunction, and pain. These in turn may lead to complications such as dehydration, dysgeusia, and malnutrition. These secondary complications can be quite severe and can potentially cause reductions in treatment doses, delays of treatment, requirements for hospitalization, and even discontinuation of therapy.

Management of these complications consists of screening for and the identification of patients at high risk for them, patient education, initiation of pretreatment interventions, and timely management of lesions when they develop.

Pretreatment Management

Assessment of the oral status and stabilization of oral disease prior to the initiation of therapy is a critical first step to overall patient care. Primary preventive measures include patient counseling for effective oral hygiene practices and early detection of oral lesions. Involvement of a dental team experienced with oral oncology patients can reduce the risk of oral complications.[10] The evaluation itself should occur as early as possible prior to treatment. Ideally, this examination should be performed at least 1 month before initiation of cancer treatment to permit adequate healing from any required invasive oral procedures.[10] Thereafter, a program of oral hygiene can be initiated with emphasis on maximizing patient compliance throughout the course of treatment and after treatment completion.

Data that can be provided by the dental professional to the treatment care team include the presence or absence of dental caries (including amount and severity), the number of teeth requiring restoration, endodontic disease, teeth with pulpal infection, teeth requiring endodontic treatment, periodontal disease status, number of teeth requiring extraction, other urgent care that is required, and the time necessary to complete stabilization of oral disease.[10]

Routine oral hygiene care includes emphasis on tooth brushing with soft nylon–bristled brushes, with the patient instructed to brush two or three times daily and to rinse the mouth frequently. The patient should be also instructed to use a dentifrice with fluoride. The patient should floss once daily, using an atraumatic technique with modifications as needed. The use of bland rinses, either 0.9% saline or sodium bicarbonate solution, every 2 to 4 hours can soothe pain or discomfort.[11] Also, the patient should be instructed to brush a 1.1% neutral sodium fluoride gel or a 0.4% stannous fluoride gel on the teeth daily for 2 to 3 minutes and then to expectorate and rinse the mouth gently.[11]

Mucositis

For years, the development of mucositis was thought to be a direct, nonspecific consequence of the destructive side effects of irradiation and/or chemotherapy on rapidly dividing basal cells of the mucosal epithelium. Over the past several years, however, evidence has increasingly mounted to demonstrate that chemotherapy/radiation-induced mucosal injury (*mucositis*) is actually the result of a complex series of biologic and cellular events that take place predominantly in the submucosa.[12] The process by which these events occur has been modeled into a five-stage sequence as follows: initiation, primary damage response, signal amplification, ulceration, and healing. Clinically, ulceration is the most significant stage of mucositis.[12,13]

The severity of mucositis is usually expressed through the use of one of a number of grading scales. Two of the most commonly used scales are those developed by the World Health Organization (WHO) and the National Cancer Institute (NCI). The NCI's *Common Terminology Criteria for Adverse Events* (Version 3) evaluates the clinical

findings of mucositis (erythema, ulceration) and functional consequences of mucositis on two distinct scales.[12] The WHO incorporates a subjective evaluation of ulceration/erythema, a subjective evaluation of pain, and a functional evaluation (ability to eat) into a single value.[12]

Care for patients with oral mucositis remains essentially palliative. It involves strict maintenance of good oral hygiene practices as outlined previously, a nonirritating diet, and emphasis on maintaining good nutritional intake; use of oral care products such as rinses and topical anesthetics; and appropriate use of opioid analgesics as a mainstay of therapy.

The purpose of maintaining effective oral hygiene is to reduce the effect of the oral microbial flora and prevent soft tissue infections that may have systemic sequelae.[14] Basic oral care also reduces the risk of oral caries and gingivitis.[10]

The prevention and treatment of mucositis have involved the use of a wide variety of agents over many years. For the most part, however, the results of these efforts have been quite disappointing. Only lately have there been any significant advances in mechanistically based intervention, owing primarily to a greater understanding of the underlying pathophysiology of mucositis. The emphasis on quality of life during curative treatment has also engendered recognition of the importance of effectively designed and executed clinical trials that include important quality-of-life information. Comprehensive evidence-based literature reviews of published mucositis interventions by the Cochrane Collaboration and the Mucositis Study Section of the Multinational Association of Supportive Care and Cancer/International Society of Oral Oncology (MASCC/ISOO) have provided clinical recommendations or guidelines.[8,15]

On the basis of the principles of radiation biology and careful treatment planning, a number of strategies have been developed to reduce the cumulative dose of radiation therapy delivered to nontumor mucosal tissues. Midline blocking, mucosa-sparing shields, which are custom fabricated, can effectively decrease the severity of oral mucositis.[16] When metallic dental restorations (e.g. amalgams, gold crowns) exist in direct opposition to the oral mucosa, wetted cotton rolls or a number of other devices such as custom stents can be used to physically separate the tissue (3 mm or greater away from the dental restoration) and reduce mucositis secondary to localized enhanced scatter effect.[17,18] Decreased severity of mucositis has been reported after three-dimensional treatment planning and treatment with intensity-modulated radiation therapy (IMRT).[19] IMRT has come into widespread use over the last several years.[19]

Although palliative treatments do not affect the incidence, severity, or duration of mucositis, they are often indispensable in managing oral symptoms and must be considered a component of supportive care. Topical analgesics such as 2% viscous lidocaine and "magic" or "miracle" mouthwash formulations, which typically are combinations of lidocaine, benzocaine, diphenhydramine, kaolin, milk of magnesia, chlorhexidine, pectin, and/or sucralfate, can provide some relief of symptoms. These agents are swished and expectorated and can be safely used throughout the day as needed for the duration of mucositis symptoms. The lack of compelling evidence to suggest an effectiveness superior to that of normal saline prevented the MASCC/ISOO Mucosa Study Section from recommending any specific mixture for treatment in oral mucositis. The section did, however, recommend that further study of these agents is necessary to define the efficacy and potential toxicity of their use.

Given the presence of opioid receptors in the oral mucosa, topical morphine therapy and fentanyl sublingual spray have been evaluated and shown to be effective in reducing mouth pain.[20] However, it is unclear to what extent the effect is local rather than systemic, via central pathways, especially in the presence of severe ulcerations, in which transmucosal absorption is likely quite high. Systemic management with morphine and other opioid pain medications is effective and considered a standard care of therapy for severe cases, although breakthrough pain and dose-limiting toxicity are frequently encountered.[20]

Several mucosal surface protectants are available that provide relief by physically coating or soothing the oral mucosa. Caphosol (EUSA Pharma, Princeton, NJ), approved by the U.S. Food and Drug Administration (FDA), is a rinse (device) composed of sodium chloride, sodium phosphate, and calcium chloride that has been evaluated in the stem cell transplantation population and has been shown to be effective in decreasing symptoms of pain and xerostomia.[21] Gelclair (EKR Therapeutics, Bedminster, NJ) and Mucotrol (GeoPharma Inc., Largo, FL) are both FDA-approved mucoadhesive agents that coat and adhere to the inside of the mouth, exerting their effects by physically blocking painful exposed nerve endings in the damaged, ulcerated mucosa.[22] Although these agents are safe and generally well tolerated, the relief they provide is variable and additional systemic pain management is typically required.

Although not approved for use in the United States, benzydamine hydrochloride is a unique topical agent with anti-inflammatory, analgesic, and antimicrobial properties used extensively for prevention of radiation-induced mucositis in Europe and other parts of the world.[23] Amifostine, a free radical scavenger, has been found to be effective in reducing acute and long-term salivary gland hyperfunction secondary to head and neck radiation but has not consistently demonstrated efficacy in the prevention of mucositis, although clinical trials are ongoing.[24]

Palifermin, a recombinant keratinocyte growth factor (FGF-7), is approved by the FDA for prevention of oral mucositis in patients undergoing stem cell transplantation for hematologic malignancies. Spielberger and colleagues[25] reported, in a phase I/phase II trial using palifermin for reduction of mucositis in colorectal cancer patients undergoing therapy regimens containing 5-fluorouracil, that the agent demonstrated safety and efficacy.[25] Both industry and cooperative groups are sponsoring trials to evaluate the efficacy of palifermin in preventing mucositis in patients receiving chemoradiation therapy for treatment of head and neck cancers. Valifermin (FGF-20), a member of the same superclass of molecules as palifermin, is also in clinical testing.[26,27]

Several other agents, including several immunomodulators, are currently under investigation to determine their potential role in the prevention or treatment of oral mucositis in patients with head and neck cancers.

Co-morbidity with dental and oral infections may exacerbate mucositis lesions and serve as independent and serious sources of inflammation and pain. Maintaining basic oral hygiene practice during cancer therapy is paramount. Poorly fitting dentures and fractured or sharp-edged dental restorations and orthodontic brackets may all contribute to localized tissue irritation and the development of mucositis lesions. Erythematous and ulcerative lesions that may be mistaken for oral mucositis may actually represent oral candidiasis and recrudescent herpes simplex virus infection; these lesions must be recognized promptly, sampled for culture, and treated with appropriate antifungal or antiviral medications.[28]

Xerostomia

Diminished salivary gland production, induced by exposure of the salivary gland to radiation during treatment of head and neck cancer, can result in xerostomia (dry mouth syndrome).[29] The addition of chemotherapy to the treatment regimen substantially increases the likelihood of development of xerostomia.[30] Salivary gland production is critical to swallowing function, speech, and maintenance of mouth homeostasis, so its loss has a significant effect on a patient's quality of life.

Symptoms and signs of xerostomia include mouth dryness, a burning sensation of the tongue, fissures at lip commissures, atrophy of the dorsal tongue surface, difficulty in wearing dentures, and increased thirst.

Common problems associated with xerostomia also include a constant sore throat, hoarseness, and/or dry nasal passages.[31] If left untreated, xerostomia increases plaque formation, periodontal disease,[21] and the development of dental caries.[31,32] The change in pH and immune function secondary to reduced salivary flow presumably also mediates an increase in the risk of development of oral candidiasis, one of the most common oral infections seen.[32]

Salivary flow decreases within 1 week after the start of radiation treatment, and xerostomia becomes apparent when doses exceed 10 Gy. Doses larger than 54 Gy are generally considered to induce irreversible loss. The degree of dysfunction is related to the radiation dose, the

schedule (fractionation), and the volume of glandular tissue in the radiation field.[33] The parotid glands may be more susceptible to radiation effects than the submandibular, sublingual, and other minor salivary glands. Salivary gland tissues that have been excluded from the radiation portal may become hyperplastic, partially compensating for the nonfunctioning glands at other oral sites. Generally stated, some degree of a salivary gland recovery is seen over the first 6 months after radiation therapy.[34] Maximum recovery is generally reported by 12 months after therapy, but it is usually incomplete and the overall level of dryness can range from mild to severe.[35] One study demonstrated successful surgical submandibular gland transfer to the submental space, resulting in a functioning gland even after irradiation with appropriate shielding.[36] This palliative measure merits further investigation.

Amifostine, an organic thiophosphate whose action as a free radical scavenger is thought to spare normal tissue from radiation and/or chemotherapy-related effects, has been trialed in a number of studies involving patients with head and neck cancer.[37,38] The use of amifostine as a xerostomia-preventive agent has had mixed results and therefore its use remains controversial.

Dosimetric advantages of IMRT over conventional and conformal radiation therapy as it pertains to the prevention of xerostomia have been confirmed by numerous studies.[39-41] However, relatively small numbers of patients enrolled in these individual trials makes it difficult to conclude that IMRT can be recommended without reservation. Common palliation for xerostomia includes drinking water frequently to keep the mouth lubricated, use of ice chips, and artificial saliva, which combines water with lubricants.[42,43] Sucking on sugarless candy or chewing gum can also stimulate salivary flow. Pilocarpine is the only drug approved by the FDA for use as a sialogogue for radiation-related xerostomia.[43] Treatment is generally initiated at 5 mg by mouth 3 times a day; doses are then titrated to achieve optimal clinical response. The adverse effect profile, which includes sweating, rhinorrhea, and urinary frequency, limits its use.

Taste Dysfunction

Taste alterations (dysgeusia) are well described in patients with head and neck cancer who undergo radiotherapy. As the oral and pharyngeal mucosa are exposed to treatment (principally irradiation), taste receptors are damaged and taste discrimination becomes increasingly compromised. After several weeks of irradiation, it is common for patients to complain of no sense of taste. It generally takes upwards of 6 to 8 weeks after the radiation therapy for taste receptors to recover and become functional. Zinc sulfate supplements have been reported to help with recovery of the sense of taste,[44] although a 2007 phase 3 study did not find support for this measure.[45]

New evidence suggests the presence of metallic phantoms, common in patients with head and neck cancer, may be indicative of neural damage after cancer-directed treatment.[46] The presence of metallic phantoms is an independent predictor of long-term pain in this patient population.[46]

Pain

Tumor involvement of head and neck structures, cancer treatment (often multimodal), or preexisting comorbid conditions can cause pain. Pain accompanies oral infections, mucositis, xerostomia, trismus, dental caries, and osteoradionecrosis, all of which are relatively common accompaniments to head and neck cancer treatment.

The general principles of pain management apply to the treatment of patients with head and neck cancer. A careful history must be taken of the nature of the pain, its time course, and any maneuvers that increase or decrease its intensity. The assessment should also include a determination of any pain-related functional interference with activities of daily living and interpersonal relationships. Consistent monitoring of pain management intervention effects[47] is essential to determine efficacy as well to minimize treatment-related side effects. A detailed medical, neurologic, and psychosocial assessment with emphasis on a history of substance use or abuse should be conducted.

The underlying concept of good pain management is that pain is a subjective phenomenon and, therefore, the patient's perception of pain should be the dominant consideration. However, significant under-management of pain continues to persist.[48] Studies that have examined rates of drug addiction in cancer populations indicate that although tolerance and physical dependence are common, addiction (psychological dependence) is rare and almost never occurs in an individual without a history of drug abuse prior to the cancer diagnosis.[49]

Guidelines to help direct analgesic management of cancer pain include those provided by the WHO.[50] These guidelines advocate pairing the analgesic approach with the severity of pain. Under these guidelines, pain of mild to moderate severity would first be addressed with nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs). For pain that is persistent and moderate to severe in intensity, opioid analgesics of increasing potency should be utilized. A common side effect of the use of opioid analgesics is constipation. A bowel regimen should be instituted concomitant with the initiation of opioid analgesics. Psychostimulants may also prove useful in treating sedation, which also commonly accompanies opioid analgesic use.

Importantly, not all pain is somatic in origin. Neuropathic pain is a common source of pain among patients with head and neck cancer and is poorly treated by opioid medications. Neuropathic pain should be treated with the use of effective adjuvant medications that include many of the psychotropic class of medications.

Treatment effects of surgery or that occur during or after radiation treatment include the development of soft tissue fibrosis, mandibular discontinuity, and perifunctional habits associated with emotional distress caused by cancer and its treatment. Mouth pain due to these musculoskeletal conditions can be reduced by early and timely physical therapy interventions such as mandibular stretching exercises as well as the use of prosthetic aids to reduce the severity of fibrosis. Such approaches must be instituted prior to the development of trismus. If clinically significant changes do develop, several approaches, including stabilization of occlusion, trigger point injection, and other pain management strategies, as well as the use of muscle relaxants and/or pain medications, should be considered.

Additional guidance for the appropriate management of pain in patients with head and neck cancers can be found by viewing the American Pain Society (APS) website (http://www.ampainsoc.org). This organization also offers continuing medical education and certification in effective pain management methodology for health care practitioners.

Psychological Distress

Rates of depression and anxiety are particularly high in patients with head and neck cancer. The percentages of such patients who have significant depressive episodes are most often reported at around 30%.[51-53] Such patients also have higher rates of suicide than patients with other cancer.[54-57]

The loss of a normal facial appearance, changes in speech, as well as difficulties with normal communication, are distressing treatment side effects that put the patient with head and neck cancer at risk for significant psychological distress. Symptoms known to be associated with depression, such as disturbed sleep, fatigue, changes in appetite, and difficulty with attention and concentration, are also common side effects of cancer and its treatment. It is not clear whether these symptoms are the result of or the cause of depressed mood. Cytokine and neurohumoral events seemingly mediate the clustering of symptoms commonly experienced by patients with cancer. This would then provide a biologic explanation for the jointly experienced symptoms of depression, pain, and fatigue. The phenomenon of symptom clustering is the impetus for comprehensive symptom assessment and the previously mentioned portmanteau approach to intervention.

Social and economic factors predispose the patient with head and neck cancer to significant mental health–related difficulties. Often the illness causes loss of employment or significant time away from work, resulting in reduced financial resources at a time when the cost of medical care is increased.

Variables that patients with head and neck cancer bring to the treatment process can also contribute to the psychiatric risk profile. Foremost among those are patients who have a history of drug or alcohol abuse, which is common in this patient population.[58]

Because the level of distress experienced by patients changes during the course of the illness and treatment, its manifestation can become extreme, to the point that it prompts delay or discontinuation of therapy, or chronic, resulting in longer-term disability. These variable levels of impairment underlie the need for continued monitoring throughout the treatment trajectory.

The National Comprehensive Cancer Network[58a] has established guidelines for both screening for and treating cancer-related psychological distress. These guidelines suggest that every patient be screened with the distress thermometer, which both evaluates the level of distress and asks patients to identify circumstances in their lives that might be contributing to the distress.

Patients with head and neck cancer most at risk for psychological and social problems are those with the greatest levels of disfigurement, dysfunction, and physical symptoms.[59-61]

Interventions can include emotional support, referral for psychotherapy, and behavior modification specifically targeting smoking cessation and alcohol abuse.

Psychotropic medications can often be used to accomplish more than one objective. For example, mirtazapine, which can be administered as an orally disintegrating tablet, an advantage for individuals with dysphagia, is effective in alleviating anxiety and depression, sleep difficulty, and loss of appetite. Thus, it treats multiple symptoms common to individuals with head and neck cancer.

All antidepressants should be evaluated for possible adverse effects and interactions with other medications. Although anxiolytics are useful for controlling both nausea and anxiety, they can also exacerbate fatigue and can lead to delirium.[62]

Dysphagia and Speech Dysfunction

Treatment options for advanced laryngeal cancer have progressed, with studies demonstrating the efficacy of radiotherapy with concomitant chemotherapy for the purpose of preserving organ function. Unfortunately, organ preservation has been shown to result in swallowing disorders related to the dysmotility of the oropharyngeal and laryngeal structures. Frequent episodes of aspiration[63,64] may also occur as a result of the lack of normal function after organ preservation. Difficulty with swallowing is the basis for gastrostomy tube placement in 54% of patients with head and neck cancer for nutritional assistance during the course of or shortly after concurrent chemotherapy and radiotherapy.[65] Initial screening for nutritional deficiencies among patients with head and neck cancer and ongoing monitoring for the development of nutritional deficiency during therapy are essential to promote timely intervention to avoid treatment-related delays and hospitalization.

Altered speech is a common complication of surgical therapy for head and neck cancers as well as the result of treatment involving irradiation or chemotherapy. The early involvement of speech and language pathologists who specialize in the care of patients with head and neck malignancies should be a part of the comprehensive management of this patient population. Speech and language pathologists provide voice rehabilitation, including acoustic assistive devices, and teach patients modified swallowing techniques.[66]

Nutrition

Nutritional deficiencies are frequently seen in patients with head and neck cancer, approximately 50% of whom have significant weight loss at the time of initial diagnosis. High rates of malnutrition may develop or continue throughout treatment and are secondary to multiple influences, including preexisting lifestyle (smoking and alcohol use/abuse and poor dietary habits), the disease itself, and/or therapies that interfere with eating by mouth.

Options for addressing nutritional needs include parenteral and enteral therapy. Generally it is advantageous to provide enteral feeding rather than parenteral feeding owing to the balance of risks and benefits associated with these two modalities.[67] Enteral nutrition offers the advantage of providing nutrition directly to the gut, thereby reducing the risk of atrophy. Enteral feeding is also associated with fewer complications, such as infection.[68,69]

Malnutrition can progress to cachexia, a complex process of continued weight loss that involves the depletion of host reserves of skeletal muscle and adipose tissue. Importantly, this process can also involve complex and profound metabolic changes, especially in advanced cancer, characterized also by abnormalities in fat and carbohydrate metabolism. Nutritional support alone does not address the underlying catabolic metabolism. Drug treatment to attenuate the tumor-induced catabolic response should be carried out at the same time.[70] Concomitant drug treatments for cancer cachexia may slow down the wasting process by reducing anorexia, attenuating the systemic inflammation and skeletal muscle catabolism, or stimulating the muscle protein anabolism.[71]

End of Life

Although the essential components of assessing and managing symptoms continue to be an important element of palliative care, end-of-life care is differentiated in several ways. The focus of care in this setting becomes facilitation of a "good" death. What constitutes a good death is often defined differently by the individual patient and family. Each person has unique needs for information and support. Understanding of the patient and family's expectations and concerns about the end of life can be best achieved through ongoing discussions.

These discussions begin by helping the patient identify personal goals for the end of life, managing psychological and spiritual needs, assessing the patient's support system, and evaluating and communicating the estimated prognosis. End-of-life discussions between patient and health care provider are associated with less aggressive medical care near death and earlier hospice referral.[72] This issue is important in light of other findings indicating that aggressive care is associated with worse patient quality of life and worse bereavement adjustment for caregivers after the death of the loved one.[72]

Because symptom management at end of life may also involve a more complicated and intensive effort, particularly in terms of management of pain, dyspnea, and ability to urinate or empty bowels, a referral to hospice care before the patient is unable to discuss goals for the end of life is appropriate.

Palliative medicine should be a core clinical skill for all physicians who care for seriously ill patients. Several sources of information are available for physicians to develop and update these clinical skills. The National Consensus Project for Palliative Care has provided comprehensive guidelines for the administration of palliative care services at end of life.[73] These guidelines provide a framework for adoption of palliative care commensurate with diagnosis but also in the context of end-of-life care. The National Quality Forum is now developing specific strategies and guidelines for the implementation of quality palliative care throughout the continuum of a patient's treatment and life.[74]

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CHAPTER EIGHTY-TWO

The Management of Head and Neck Melanoma and Advanced Cutaneous Malignancies

Cecelia E. Schmalbach

Timothy M. Johnson

Carol R. Bradford

Key Points

- The incidence of melanoma continues to increase dramatically.
- Warning signs for melanoma are lesion asymmetry, border irregularity, color variation, and diameter more than 6 mm. However, a subset of cancers, such as nodular, amelanotic, and desmoplastic melanoma, lack these features. Any pigmented lesion that meets these criteria, has undergone change, or appears different from surrounding nevi warrants biopsy.
- The biopsy of a potential melanoma is a two-stage process. The first stage entails narrow-margin, excisional, or incisional biopsy to obtain histologic diagnosis. Shave biopsy is discouraged. This prognostic information then serves to guide the second stage, which entails wide local excision using 0.5- to 2-cm margins and, possibly, sentinel lymph node mapping and biopsy.
- The American Joint Committee on Cancer staging system for cutaneous melanoma is founded on the traditional tumor-node-metastasis (TNM) classification. Stage I and stage II represent localized disease, stage III regional disease, and stage IV distant metastasis. Nodal status is the single most important prognostic factor for patients with melanoma.
- The T classification is defined by tumor thickness (measured by even-integer cut points) and ulceration. Ulceration of the primary lesion raises the stage of the patient's disease. Clark's histologic level of invasion is applicable only in staging thin (≤ 1-mm) T1 tumors.
- Significant prognostic factors with stage III regional disease include the number of metastatic lymph nodes, tumor burden as represented by microscopic versus macroscopic disease, and primary tumor ulceration. Satellite and in-transit metastasis are also important prognostic features; they are classified as stage III regional disease regardless of the nodal status.
- The M classification is defined by anatomic site of distant metastasis and elevated serum lactate dehydrogenase value.
- The standard of care for melanoma treatment remains complete surgical excision of the primary lesion.
- Therapeutic lymph node dissection is universally accepted as the treatment for proven regional disease in the neck.
- Prophylactic, elective neck dissection for the N0 melanoma of neck has failed to demonstrate an overall survival benefit and is no longer advocated. Instead, the procedure has been replaced by sentinel lymph node mapping and biopsy, which is a minimally invasive, cost-effective, and efficient means to screen patients for regional disease. This screening modality identifies the 10% to 20% of patients with occult nodal metastasis, who then may benefit from therapeutic lymph node dissection and adjuvant therapy.
- High dose interferon-α 2b remains the only FDA adjuvant treatment approved by the U.S. Food and Drug Administration for stage III disease. It is reserved for patients at high risk for tumor recurrence, including individuals with regional metastasis or a primary lesion more than 4 mm in thickness.
- Hypofractionated radiation therapy is also an adjuvant treatment for high-risk patients with extracapsular spread or multiple node involvement. Additional roles for this modality are palliative care and, on rare occasions, as the primary treatment for extensive lentigo maligna melanomas in patients who are not candidates for surgery.

Although the overall trend in the United States demonstrates both a stabilization of cancer incidence and a decrease in cancer death rates, the incidence of cutaneous melanoma continues to rise dramatically on an annual basis.[1,2] The diagnosis is growing in men faster than any other malignancy; for women, the increase in incidence is second only to that for lung cancer.[3] Overall, cutaneous melanoma remains the sixth leading cause of cancer among men and the seventh cause among women. The current annual budget for melanoma treatment in the United States exceeds $740 million.[4]

Fortunately, the management of cutaneous melanoma is also one of fastest-evolving fields in cancer, with promising research taking place at both the molecular and clinical levels. Greater understanding of melanoma biology prompted major changes in the staging classification system set forth by the American Joint Committee on Cancer (AJCC).[5] Given its association with sun exposure, melanoma is considered a preventable disease. Decreases in incidence and mortality ultimately hinge upon increases in education, prevention, and early diagnosis, as well as improved treatment for advanced disease.

Epidemiology

Despite a decline in overall cancer trends, the incidence of invasive cutaneous melanoma continues to rise dramatically, with an estimated 62,480 new cases anticipated in 2008.[1] Over the past 50 years, the annual percentage change in invasive melanoma incidence has steadily increased by 4.3% each year. The lifetime risk for development of invasive melanoma has climbed at an epidemic rate, rising from 1 in 1500 individuals born in 1935 to 1 in 250 born in 1980.[6] This trend is expected to continue at a startling rate, with a current estimation that 1 in 41 men and 1 in 61 women will have invasive carcinoma during their lifetimes.

Melanoma is the most lethal form of skin cancer, accounting for 8110 American deaths in 2007, 8420 deaths in 2008, and an expected 8650 deaths in 2009.[1,2] These estimates average to approximately one American dying from melanoma every hour. Over the past 50 years, the annual percentage change in mortality rate has increased at a steady rate of 1.8% per year. Melanoma accounts for the second highest increase in mortality rate, especially for men older than 65 years. However, it should not be viewed as a cancer limited to the elderly because 1 in 4 patients are diagnosed before age 40, and it is the third most common cancer among women ages 20 to 39.[4,6,7] Consequently, melanoma represents one of the leading cancer causes of lost potential life years, ranking second only to leukemia.

Approximately 25% of all cutaneous melanomas arise in the head and neck region,[8] with more than 9000 cases diagnosed annually. The majority involve the cheek, scalp, and neck. A slight male preponderance is consistently reported,[9-11] and the median age at diagnosis is 55 years.[7] However, juvenile cases account for 1.66% of head and neck melanoma cases, and patients as young as 4 years are diagnosed with these lesions.[12,13]

Etiology and Risk Factors

Numerous environmental and genetic risk factors have been implicated in the development of cutaneous melanoma.[14] They are summarized in Box 82-1.

Risk Factors

Sun exposure is considered the leading cause of melanoma.[15,16] Patients who experienced peeling or blistering sunburns, even during childhood, are at particular risk.[17] Associated factors include blond or red hair, green or blue eyes, and fair skin consistent with Fitzpatrick skin types I through III.[18] Adults with more than 100 clinically normal-appearing nevi, children with more than 50 clinically normal-appearing nevi, and any patients with atypical or dysplastic nevi are also at risk.

A prior history of melanoma poses a greater risk; 5% to 10% of individuals diagnosed with melanoma experience a second primary melanoma.[16] This increased risk remains lifelong, and the melanoma can occur anywhere on the skin. For this reason, long-term follow-up with a thorough total body examination is critical.

Box 82-1

Risk Factors Associated with Cutaneous Melanoma

Environmental/Sun Exposure

Inability to tan
Fair complexion/inability to tan
Blue/green eyes
Blonde/red hair
Freckling
History of blistering/peeling sunburns
Immunosuppression
Teenage outdoor summer jobs
Tanning booth exposure

Genetic/Past Medical History

CDKN2A (p16) mutation
Family history of melanoma
History of prior melanoma
Actinic keratoses
Nonmelanoma skin cancer
Xeroderma pigmentosa
Atypical (dysplastic) nevus
Giant congenital melanocytic nevus

Adapted from Schmalbach CE, Johnson TM, Bradford CR. The management of head and neck melanoma. *Curr Probl Surg.* 2006;43:784.

Genetics

A genetic component has been implicated in the pathogenesis of melanoma[19]; 10% to 15% of patients with melanoma report a positive family history.[20] The most common chromosomal mutation associated with melanoma involves CDKN2A, which is also known as p16.[21] However, the mutation accounts for only a small percentage (0.2%) of melanoma cases observed.[22]

B-K mole syndrome is a hereditary form of cutaneous melanoma in which members acquire large, irregular, and dysplastic nevi, often in sun-protected regions of the body, such as the scalp and trunk.[23] A familial association of melanoma among individuals with atypical nevi has also been coined *familial atypical multiple mole-melanoma (FAMMM) syndrome*.[24] Today, the term "*atypical mole syndrome*" is applied to familial cases of melanoma. The syndrome is inherited in an autosomally dominant fashion.[25,26] The 10-year melanoma risk in this setting is reported to be 10.7%, compared with 0.62% in control patients.[27,28] Fitzpatrick and Ortonne[18] and Greene and associates[29] approximated a 56% cumulative risk from age 20 to 59 years, which predicts that 100% of patients with atypical mole syndrome would have melanoma by age 76.

Xeroderma pigmentosa is a rare hereditary disorder also associated with melanoma; it is inherited in an autosomally recessive fashion.[30] The fibroblasts in patients with this disease have a reduced or no ability to repair DNA that has been damaged by ultraviolet light.[31] Consequently, multiple primary cutaneous malignancies, including melanoma, basal cell carcinoma, and squamous cell carcinoma, develop. Individuals are usually diagnosed with their first cancer prior to age 10. Unfortunately for patients with xeroderma pigmentosa, the relentless development of skin cancers—as well as other cancers—ultimately leads to death at an early age.

Congenital Nevi

Congenital melanocytic nevi (CMN) are present at birth or appear within the first 6 months of life[32]; an estimated 1% to 6% of children are born with CMN. The nevi are classified by size: small CMN measure less than1.5 mm in diameter and account for the majority of lesions; medium-sized CMN measure between 1.5 and 19.9 mm in

diameter; and large CMN, which are also called giant congenital nevi, measure 20 mm or more. This large size can have significant cosmetic and psychosocial implications.[28]

The risk of melanoma development in small- and medium-sized CMN is similar to that in any other nevi. Melanoma development usually occurs after childhood and arises from the dermoepidermal junction, which makes early detection and intervention feasible. Routine prophylactic removal of small and medium CMN is rarely indicated in the absence of signs or symptoms indicative of malignant progression.

Conversely, giant CMN carry an increased risk for melanoma, with an estimated 5% to 20% of patients with these lesions eventually experiencing cancer.[33,34] Seventy percent of these individuals are diagnosed before age 10 years.[35] Melanoma in the setting of giant CMN originates deep within the epidermis, thus potentially delaying the diagnosis and treatment.

Melanoma Classification

Several histologic subtypes of melanoma are recognized within the head and neck region. It is important to note that if data are corrected for other prognostic variables, such as tumor thickness and ulceration, melanoma subtype does not generally influence prognosis.[36]

In general, superficial spreading melanoma is the most common type of cutaneous melanoma, accounting for approximately 70% of all cases. It commonly arises in the setting of a preexisting nevus, with a diagnosis rendered during the fourth or fifth decade. Characteristic features include color variation and border asymmetry. Nodular melanoma is the second most common subtype on the skin, accounting for 15% to 30% of cases. This lesion typically appears as a blue-black or blue-red nodule. For this reason, a nodular melanoma must be differentiated from hemangioma, blue nevus, pyogenic granuloma, and pigmented basal cell carcinoma.

Lentigo maligna (LM) represents intraepidermal or in situ melanoma. Histologically, it is often seen in the background of chronic sun damage. LM is the precursor to invasive lentigo malignant melanoma (LMM). The exact percentage of LMs that progress to invasive LMM remains unknown[37]; however, it is speculated that, if patients live long enough, all LMs will eventually progress to cancer. LM/LMM is most often found in the head and neck region. Traditionally, the subtype has been associated with older individuals, but the frequency in younger patients is increasing. The LM/LMM pattern warrants special comment, because this subtype is characterized by asymmetric, subclinical, and often extensive involvement of margins with atypical junctional melanocytic hyperplasia. Therefore, management with adequate wide margins can be challenging from both a functional and cosmetic standpoint. Additionally, amelanotic melanoma and invasive desmoplastic melanoma (see later) often arise within LM/LMM.

Desmoplastic-Neurotropic Melanoma

Desmoplastic melanoma (DM) describes a subtype composed of spindle cells, abundant collagen, and features resembling fibromas.[38] Some lesions demonstrate a propensity for perineural and endoneural infiltration, which prompted further subclassification of a desmoplastic neurotropic melanoma (DNM) variant.[39]

DM/DNM subtypes are rare, accounting for approximately 1% of all cutaneous melanomas.[40] However, up to 75% of the lesions manifest in the head and neck region, often in the setting of LM/LMM. The clinical presentation and biologic behavior of these tumors are distinct from those of other cutaneous melanomas. Although amelanotic cases account for only 4% to 5% of cutaneous melanomas, up to 73% of DM/DNMs are amelanotic.[40,41] As demonstrated in Figure 82-1, the neoplasms often lack the typical ABCD criteria for melanoma (described later), and they can have a difficult histologic pattern that requires interpretation by an experienced pathologist. Overall, the atypical and challenging appearance of DM/DNM is thought to result in a delay in diagnosis. This fact provides one explanation for the reason that patients with DM/DNM present with thicker, more aggressive tumors.

DM/DNM is known to be locally aggressive and highly infiltrative, often leading to cranial nerve and skull base involvement. Local recurrence has been reported in up to 50% of cases.[40] Explanations for this high rate include the association with neurotropism and the failure to recognize and adequately clear peripheral atypical junctional melanocytic hyperplasia margins. Although DM/DNM demonstrates greater tumor thickness at the time of diagnosis, the 12.5% rate of regional lymph node metastasis is lower than that for other melanoma subtypes.[39]

Figure 82-1. Desmoplastic melanoma of the nose. Note the amelanotic appearance and the absence of typical ABCD findings associated with other melanoma subtypes.

Mucosal Melanoma

Mucosal melanoma is recognized as a distinct subtype from its cutaneous counterpart. The most common site for mucosal melanoma is the head and neck, with 40% to 50% of cases arising in this location.[42] However, less than 2% of all head and neck melanomas are mucosal in origin. Of the 84,836 melanoma cases registered in the National Cancer Database from 1985 to 1994, only 1074 (1.3%) were of the mucosal melanoma variant.[43]

Although small case numbers limit research to anecdotal reports, several common trends have been noted throughout the literature. The peak age for mucosal melanoma is during the sixth to seventh decade, which is approximately 10 to 15 years later than that for cutaneous melanoma.[42,44-47] A slight male preponderance has also been reported.[45,47,49] Ethnic differences have been observed; approximately 8.8% of mucosal melanoma cases afflict blacks and Hispanics, a considerable percentage given that less than 3% of all other melanoma variants are diagnosed among this group.[48] The relative frequency is also exceedingly high in Japan, where mucosal melanoma accounts for 7.5% of all melanoma cases.[50]

Within the head and neck region, the most common site of origin is the nasal cavity, where the anterior nasal septum is most often involved, followed by the inferior and middle turbinates.[46,49,51,52] The second most common site is the oral cavity, where a predilection for the hard palate and maxillary alveolar gingivae has been found. A review of five major mucosal melanoma series by Batsakis and colleagues[51] found laryngeal primary tumors to account for less than 4% of all cases. Within the larynx, the supraglottis was the most common site of origin.

The presenting signs and symptoms of mucosal melanoma directly correlate with the anatomic site of origin. The majority of patients with nasal cavity primary tumors present with nasal obstruction and epistaxis.[49,51,52] Proptosis, diplopia, pain, and facial deformity are less common and indicate advanced disease. When present, the most common sign of an oral cavity tumor is a mass lesion.[52] However, oral cavity mucosal melanoma is often asymptomatic, going undiagnosed until a neck mass develops from metastasis.[44,49]

Many of the prognostic markers for cutaneous melanoma do not have correlates in mucosal sites.[42] Consequently, the cutaneous melanoma staging system set forth by the AJCC (see later) may be less applicable to mucosal melanoma. Most patients with mucosal melanoma present with localized disease, and in only 18.7% is regional spread detected at the time of diagnosis. The high percentage of patients with stage I disease is deceiving, because local recurrence is the major reason for treatment failure.[51] Fifty percent of patients have local recurrence,

usually within 9 to 12 months of diagnosis, and the overall 5-year survival rate is a dismal 10% to 20%.[45-47,51] Rich submucosal vasculature and lymphatics are thought to account for the aggressive behavior of mucosal melanoma.[51]

Unknown Primary

Approximately 2% to 8% of cases of melanoma involve unknown primary sites.[43,48,53] In two thirds of the cases, the patients present with regional metastasis in the absence of an identifiable primary lesion or history of melanoma; the remaining third of unknown primary cases involve distant metastasis to sites such as the subcutaneous tissues, lung, and brain.[48,53-55] Several theories have been proposed to explain melanoma of unknown primary origin. The identification of melanocytes and nevus cells within the lymph node capsule and visceral organ epithelium lends credence to the belief that unknown primary cases result from melanoma arising de novo at regional and distant sites.[43,56] Another clinical scenario is that the primary melanoma lesion undergoes complete spontaneous regression.[56,57]

The diagnosis of melanoma of unknown origin necessitates a search for the primary site with a total body skin and mucosal evaluation. A history of a previous skin biopsy or a skin lesion that spontaneously disappeared may be helpful. All pathology slides from previously excised lesions should be re-reviewed. The metastatic workup is identical to that for known primary cases (see later). After adjustment of data for tumor stage, melanomas of unknown primary origin share an overall prognosis equivalent to their counterparts with known primary sites.[43,53-55]

Diagnostic Workup

History

The majority of melanoma lesions are first detected by the patient or his/her significant other.[58,59] Less than one fourth of lesions are diagnosed during routine office physical examination, and these latter lesions tend to be thinner.[59] Overall, 80% of newly diagnosed melanomas are limited to localized, stage I/II disease.[2]

The earliest signs of melanoma are a change in color, size, or shape of a lesion, and pruritus is the earliest symptom. Later signs and symptoms, which are usually associated with a more advanced lesion, include bleeding, ulceration, and tenderness. Patients should be questioned about a personal and family history of melanoma. Information about previous skin biopsies, sun exposure, history of blistering sunburns, use of tanning booths, chronic sun exposure, and occupation should be obtained. Schwartz and colleagues[59] investigated characteristics of 1515 patients with melanoma and found that 81% elicited a history of at least one sunburn.

Physical Examination

All patients presenting with a suspicious lesion warrant full evaluation of the skin and nodal basins by a physician who is well versed in cutaneous cancers. Thorough evaluation is imperative because up to 8% of newly diagnosed patients have multiple primary cutaneous melanomas.[16,60-62]

The differential diagnosis for cutaneous melanoma is broad and includes seborrheic keratosis, hemangioma, blue nevus, Spitz nevus, pyogenic granuloma, pigmented basal cell carcinoma, and cutaneous squamous cell carcinoma. The American Cancer Society has published the ABCD checklist to educate both patients and physicians about the early detection of melanoma.[63] Under these guidelines, concerning signs for melanoma are as follows:

*A*symmetry in appearance

*B*order irregularity, such as scalloped, poorly circumscribed, or ill-defined margins

*C*olor variation within a lesion, such as shades of black, red, white, or blue

*D*iameter of more than 6 mm

Although the ABCD checklist is helpful for the identification of melanoma, it does not detect every case.[64,65] It is important to realize that a subset of cancers (e.g., amelanotic, desmoplastic, and nodular melanoma) lack the common features of the ABCD list. In one series, 88% patients with melanoma (615 of 696) recalled change in their pigmented lesions prior to melanoma diagnosis.[66] Owing to the significance of change, a proposal has been set forth to add "*E*volving changes" to the traditional ABCD warning signs.[63] Clinicians are hopeful that the new, more comprehensive ABCDE criteria will lead to even further detection of melanoma at an earlier stage.[66] Another useful screening tool is the "ugly duckling sign,"[67] whereby any pigmented lesion that appears significantly and singularly different from other surrounding lesions should be viewed with a high index of suspicion, even if the lesion lacks the traditional ABCD criteria.

Biopsy

Any pigmented lesion that demonstrates an ABCD warning sign, has undergone change, or appears different from surrounding nevi on the body necessitates histologic evaluation. The biopsy of a potential melanoma should be considered a two-step process. The first step involves biopsy not only for tissue diagnosis but also to evaluate important prognostic factors such as tumor depth, ulceration, mitotic rate, angiolymphatic invasion, and perineural spread. Ideally, a complete excisional biopsy with a narrow, 1- to 2-mm, clinical margin of surrounding skin is performed. For lesions that are not amenable to excisional biopsy because of large size or anatomic location, punch biopsy or incisional biopsy through the thickest portion of the neoplasm is recommended. Superficial shave biopsy and find-needle aspiration are discouraged, because neither procedure allows the thickness of the tumor, which dictates further diagnostic workup and treatment, to be determined. It is important to realize that punch and incisional biopsies are subject to sampling error. If a diagnosis of melanoma in this setting is not rendered, a second biopsy may be necessary.

The pathology results from this biopsy then serve as the guide for the second step, which entails wide local excision (WLE) utilizing a 0.5- to 2-cm margin of normal surrounding skin, with or without sentinel lymph node [mapping and] biopsy (SLNB). The role of SLNB ultimately depends on the final microstaging of the primary lesion and is detailed later. Although obtaining wider margins at the time of the initial biopsy seems efficient and cost effective, it is highly discouraged because clinical accuracy is uncertain and removal of significant amounts of skin surrounding the lesion may compromise the ability to accurately stage regional lymph node basins by means of lymphoscintigraphy and SLNB techniques.[68] Instead, biopsy with narrow margins in a two-step fashion is advocated.

Metastatic Workup

In an attempt to standardize staging workup for melanoma, a panel of the National Comprehensive Cancer Network (NCCN) has published guidelines.[69] The metastatic workup performed at our institution, which accords with these guidelines, is summarized in Table 82-1.

Patients presenting with localized stage I disease simply require a thorough history and physical examination. Many physicians advocate a screening chest radiograph, because the lung is the most common site for distant metastasis.[68] Although a chest radiograph is an inexpensive, noninvasive means of metastatic evaluation, the rate of detection of occult pulmonary metastasis on chest radiograph in an asymptomatic patient with stage I or II disease is exceedingly low (0.1%).[70,71] The high false-positive rate, 15%, necessitates additional and costly evaluations. Evidence supporting the use of other screening modalities, such as computed tomography (CT),[72,73] liver-spleen scans, magnetic resonance imaging, and bone scans for patients with limited stage I and II disease is also lacking.[74,75] For this reason, the National Comprehensive Cancer Network panel unanimously agreed that a search for visceral metastases, with either a chest radiograph or blood analysis, is not warranted for a patient with in situ or thin, stage IA lesions. A baseline chest radiograph is considered optional for thicker stage IB and II lesions. Imaging studies (CT, magnetic resonance imaging, positron emission tomography) may be obtained in this setting if there are specific concerning signs or symptoms.[69] Screening serum lactate dehy-

Table 82-1

University of Michigan Guidelines for Workup for Cutaneous Melanoma

Stage 0 (in situ)	History; physical examination
Stage I (<1 mm thickness)	History; physical examination
Stage I to II (1-4 mm thick)	History; physical examination Chest radiograph optional Serum acetate dehydrogenase measurement optional
Stage III (N0; >4 mm thick)	History; physical examination Chest radiograph optional Serum lactate dehydrogenase measurement optional
Stage III (N+; in transit)	History; physical examination Chest radiograph Serum lactate dehydrogenase measurement Other imaging studies, if clinically indicated
Stage IV (distant metastasis)	History; physical examination Chest radiograph Serum lactate dehydrogenase measurement Other imaging studies, per clinical trial

Adapted from Johnson TM, Bradford CR, Gruber SB, et al. Staging work-up, sentinel node biopsy and follow-up tests for melanoma: update of current concepts. *Arch Dermatol.* 2004;140:107.

drogenase (LDH) measurement carries a 15% false-positive rate, does not correlate with sentinel lymph node (SLN) status, and has not been helpful in detecting occult disease in asymptomatic patients.[76] For this reason, our institution recommends LDH measurement only when the history or physical examination reveals jaundice, abdominal pain, or other specific findings that raise concern about distant metastasis.[77]

Patients with clinically or radiographically suspicious lymph nodes, satellite lesions, or *in-transit metastasis* (defined as intralymphatic tumor dissemination between the primacy lesion and draining nodal basin) are considered to have stage III disease and are at higher risk for distant metastasis. Fine-needle aspiration is an accurate and cost-effective means of confirming metastatic melanoma within lymph nodes.[78] Additional imaging studies should be ordered according to the patient's history and physical findings. A list of symptoms that warrant a focused investigation of systemic metastasis is summarized in Box 82-2.[79] Overall, the yield of screening CT in patients with stage III melanoma has been low[77,80-82]; however, many physicians obtain the studies to serve as a baseline for future comparison.

Patients with known stage IV disseminated melanoma require a complete evaluation for systemic metastasis. LDH measurements and chest radiography or chest CT are recommended. CT of the abdomen and pelvis, magnetic resonance imaging of the head, and a positron emission tomography scan (whole body) should also be considered. In this setting, workup is often dictated by clinical trial protocols. Unfortunately, greater survival has not been demonstrated for patients who are asymptomatic when diagnosed with their distant, stage IV disease than for their symptomatic counterparts[76]; however, this thorough evaluation may lead to a better quality of life.

Prognostic Factors and Tumor Staging

As a result of a greater understanding of the biology of cutaneous melanoma, the AJCC introduced a revised staging system in 2001.[5,83]

Box 82-2

Review of Systems for Melanoma and Metastasis

Skin/Lymphatics
Change (i.e., size, shape, color)
Lesion or persistent pruritus
Enlarged lymph nodes
Mass/nodules
Nonhealing/bleeding skin lesions
Easy bruising
New pigmented skin lesions

Constitutional
Weight loss
Malaise
Decreased appetite
Weakness
Fatigue
Fever

Respiratory
Cough
Hemoptysis
Pneumonia
Pleurisy
Chest pain
Dyspnea

Hepatic
Abdominal pain
Right upper quadrant pain
Back (scapula) pain on inspiration
Jaundice

Neurologic/Psychiatric
Headache
Memory disturbance
Depression
Focal central nervous system symptoms
Visual disturbances
Balance problems
Blackouts
Seizures
Numbness
Local weakness
Paralysis
Mood swings

Gastrointestinal
Cramping
Abdominal pain
Bleeding
Nausea
Anorexia
Vomiting
Constipation

Musculoskeletal
Bone pain (e.g., rib, spine, hip)

Adapted from Johnson TM, Chang A, Redman B, et al. Management of melanoma with a multidisciplinary melanoma clinic model. *J Am Acad Dermatol.* 2000;42:820.

The goal of modifying the classification system was twofold. The main objective was to develop categories based on the most important independent prognostic markers for melanoma. Doing so may make it easier to identify cohorts of patients who have similar survival rates, thereby leading to increased homogeneity in future clinical trials. To achieve this goal, reliable prognostic markers recognized throughout the literature were studied among a cohort of 17,600 patients with melanoma from 13 major cancer institutions.[83] This investigation marks the largest analysis of its kind to date. The second goal was to provide physicians with a practical classification system that mirrors clinical practice.

Summary of Revisions

The current AJCC staging system for cutaneous melanoma remains founded upon the traditional tumor, node, metastasis (TNM) classification system (Tables 82-2 and 82-3). Stage I and stage II represent localized disease, stage III is regional disease, and stage IV is reserved for distant metastatic disease. The most important predictors for survival now serve as criteria for the definition of melanoma stage and are summarized in Box 82-3. Major revisions of the staging system are highlighted in Box 82-4.

T Classification: Localized Disease

Multivariate analysis of 13,581 patients with localized disease identified tumor thickness and ulceration as the most important predictors of outcome. Overall, tumor thickness was the most powerful prognostic indicator for this subgroup. The 1997 staging system had employed the empirically based Breslow depth of 0.75 mm to differentiate T1 from T2 lesions.[84] The revised staging system now uses even-integer cut-points of 1.0, 2.0, and 4.0 mm to delineate T stage. These new cut-points represent the best statistical fit in the correlation of tumor thickness and survival.

In the previous staging system, histologic level of invasion, as represented by the Clark scale (Fig. 82-2), was also used in the definition of T classification. However, the analysis by Balch and associates[83] found the histologic level of invasion to be prognostic only for thin T1 lesions. For tumors 1 mm or thinner without ulceration, invasion to Clark level II or III is considered T1a, whereas invasion into the reticular dermis (level IV or V) is considered T1b. With the exception of T1 lesions, Clark level of invasion is no longer used in staging melanoma.

Tumor ulceration was the second most important prognostic indicator for patients with localized disease. Ulceration is not a visible crater on gross examination but, rather, a histologic diagnosis in which intact epidermis overlying the melanoma is absent. Survival rates were found to be significantly lower for all patients with ulcerated lesions than for their counterparts without ulceration. In fact, the survival of patients with ulcerated tumors mirrored that of patients with nonulcerated tumors in the next highest T categories; for this reason, ulceration warrants classification of a tumor to a higher stage. The prognostic significance of ulceration[85] and the correlation between ulceration and mitotic rate have been reported.[86,87] Although mitotic rate was not evaluated during the revision of the AJCC staging system, it may become an important prognostic marker in the future.

Nodal Classification: Regional Disease

Similar multivariate analysis was performed in more than 1000 patients with melanoma diagnosed with lymph node metastasis. The following three prognostic factors met statistical significance, at $P < .0001$: (1) number of metastatic lymph nodes, (2) tumor burden as represented by microscopic versus macroscopic disease, and (3) primary tumor ulceration. The gross diameter of metastatic nodes was previously used in N classification but is no longer incorporated into the staging system owing to a lack of compelling evidence supporting its predictive value.[72,88]

Overall, the most important predictive marker for patients with nodal metastasis was the number of positive lymph nodes.[83] The greatest difference in 5-year survival rates was used to subclassify the N category. Patients with one metastatic node are now categorized as having N1 disease, patients with two or three metastatic nodes as having N2, and patients with four or more nodes as having N3.

The second most important prognostic indicator for patients with regional metastasis was tumor burden. Patients identified as having microscopic nodal disease, through either SLNB or elective lymphadenectomy, were found to have a significantly better survival than individuals diagnosed with macroscopic disease on the basis of clinical or radiographic examination.[83] This difference was so compelling that microscopic versus macroscopic nodal disease is now subclassified

Table 82-2

TNM Classification for Melanoma

T Classification	Thickness (mm)	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01-2.0 mm	a: without ulceration b: with ulceration
T3	2.01-4.0 mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration
N Classification	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N1	1 node	a: micrometastasis* b: macrometastasis†
N2	2-3 nodes	a: micrometastasis* b: macrometastasis† c: in-transit metastasis(es) satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in-transit metastasis(es)/ satellite(s) with metastatic node(s)	
M Classification	**Site**	**Serum Lactate Dehydrogenase Level**
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 82-3

Proposed Stage Groupings for Cutaneous Melanoma

Stage Group	Clinical Staging*			Pathologic Staging†		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0	T4b	N0	M0
III‡	Any T	N1 N2 N3	M0			
IIIA				T1-4a T1-4a	N1a N2a	M0 M0
IIIB				T1-4b T1-4b T1-4a T1-4a T1-4a/b	N1a N2a N1b N2b N2c	M0 M0 M0 M0 M0
IIIC				T1-4b T1-4b Any T	N1b N2b N3	M0 M0 M0
IV	Any T	Any N	Any M_1	Any T	Any N	Any M_1

*Clinical staging involves microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
†Pathologic staging consists of microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Patients with pathologic stage 0 or stage 1A lesions are the exception; they do not require pathologic evaluation of their lymph nodes.
‡There are no stage III subgroups for clinical staging.

Box 82-3

Summary of the Most Important Predictors of Survival that Serve as Criteria for the 2001 American Joint Committee on Cancer Cutaneous Melanoma Staging System

Stage I and II Localized Disease
Tumor thickness
Tumor ulceration
Histologic level of invasion for T1 lesions only

Stage III Regional Disease
Number of metastatic lymph nodes
Tumor burden (microscopic vs macroscopic nodal disease)
Primary tumor ulceration

Stage IV Distant Disease
Anatomic site
Elevated lactate dehydrogenase

Box 82-4

Revisions to the American Joint Committee on Cancer Staging System

1. *Tumor thickness (Breslow depth measured in mm)* and *ulceration* are now utilized in T classification. Clark's histologic level of invasion is now applicable only in the staging of thin (≤1 mm) T1 lesions.
2. The *number of metastatic lymph nodes*, as opposed to the gross size of the metastatic node, defines the N category.
3. The technique of *sentinel lymph node mapping and biopsy (SLNB)* is now incorporated into the staging system. Delineation of *occult (microscopic/subclinical)* nodal metastasis versus clinically/radiographically apparent (*macroscopic*) nodal metastasis is outlined within the N category.
4. Both *anatomic site* of distant metastasis and *elevated lactate dehydrogenase level* are utilized in the M classification.
5. *Ulceration of the primary lesions* raises the stage level of the case.
6. Primary lesions with surrounding *satellite metastasis* or *in-transit metastasis* are defined as stage III regional disease irrespective of nodal status.

From Schmalbach CE, Johnson TM, Bradford CR. The management of head and neck melanoma. *Curr Probl Surg.* 2006;43:797.

within the N category. In addition, the AJCC Melanoma Committee strongly recommends staging with SLNB for patients with T2N0M0, T3N0M0, and T4N0M0 disease before entry into clinical trials.[5] The identification of occult nodal disease enables accurate pathologic staging and greater homogeneity among cohorts under clinical investigation.

Ulceration continued to remain an important prognostic indicator, even in the presence of nodal metastasis. In fact, ulceration was found to be the only feature of the primary tumor indicative of outcome. After adjustment of data for regional metastasis, tumor thickness was no longer a prognostic marker ($P = .16$).

A fourth criterion now used in the definition of stage III regional disease is intralymphatic metastasis. The presence of satellite metastasis surrounding a primary lesion and in-transit metastasis identified between the primary melanoma and lymph node have been identified as poor prognostic indicators.[72,89] Both findings portend a prognosis similar to that for nodal metastasis. Under the new staging system, satellite metastasis and in-transit metastasis are classified as N2c disease, in the absence of nodal disease (N0). If synchronous nodal metastasis is found in a patient with satellite or in-transit metastasis, prognosis is extremely poor. Patients with these findings are automatically classified a having N3 disease, irrespective of the number of synchronous positive lymph nodes.

Overall 5- and 10-year survival rates for patients with metastatic nodal disease were 49% and 37%, respectively.[83] However, the range in survival for patients with stage III disease was significant, ranging from 13% for those with ulcerated primary lesion and macroscopic disease identified in four lymph nodes to 69% for patients with non-ulcerated primary tumor and microscopic disease confined to one lymph node. This finding confirms previous studies demonstrating that patients with stage III disease are a heterogeneous group.[88,90] In addi-

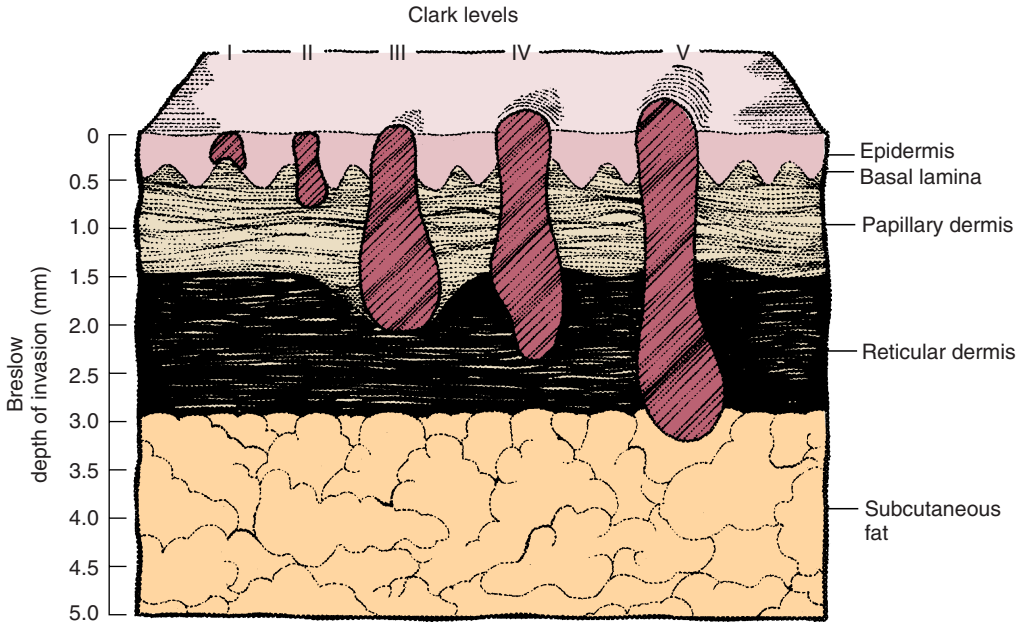

Figure 82-2. Schematic representation of cutaneous melanoma invasion according to Clark level and Breslow microstaging.

tion, it highlights the critical impact on survival afforded by the early diagnosis of regional metastasis.

M Stage: Distant Metastasis

Prognostic factors for disseminated stage IV disease were studied among 1158 patients; the most significant difference was found to be anatomic site of metastasis. Patients with distant metastasis to the skin, subcutaneous tissue, or distant lymph nodes (M1a) had a slightly higher survival rate than patients with lung metastasis (M1b). Patients with metastasis involving other visceral organs (M1c) had the worst prognosis. Previous studies have also identified elevated serum LDH as a marker of poor prognosis.[91-94] For this reason, any patient with elevated serum LDH and distant metastasis, regardless of site, is classified as having M1c disease. Additional studies correlated male gender, more than one metastatic site, Karnofsky performance status less than 80, and limited disease-free survival with a poor prognosis.[91,95] Overall, survival for patients with distant metastasis is extremely grave, measured in months as opposed to years. The median survival time following the diagnosis of disseminated disease is only 6 to 8 months, with a dismal 5-year survival rate of 6%.[91,95] For this reason, stage IV melanoma is not subclassified under the AJCC staging system.

Anatomic Site

Although anatomic site is not used within the formal staging system, prognostic differences have been reported for melanoma.[7,96] A review of 6300 cutaneous melanomas treated at the Duke Medical Center identified the worst 10-year survival rate among primary tumors of the head and neck (54%), compared with those of the trunk (61%), lower extremity (71%), and upper extremity (76%).[96] A 50% tumor recurrence rate has been reported for head and neck cutaneous melanomas.[97,98] This aggressive behavior is likely due to (1) thicker melanoma lesions in the head and neck region than in other sites and (2) inadequate removal of atypical junctional melanocytic hyperplasia at tumor margins, which leads to a higher rate of local recurrence.

Surgical Management of the Primary Tumor

Wide Local Excision and Surgical Margins

The standard of care for primary melanoma is complete surgical excision. However, the extent of surgical margins remains an unanswered question despite numerous retrospective studies, clinical trials, and meta-analyses. Historically, WLE included an extensive, 5-cm surrounding margin of normal tissue, a recommendation based on a 1907 autopsy report of a patient with advanced melanoma.[99] The use of 5-cm surgical margins was routine practice until the 1970s, when Breslow and Macht[100] challenged the concept by successfully treating 35 patients with thin melanomas through the use of narrower margins.

Two prospective, randomized trials investigating surgical margins for cutaneous melanoma have since followed. The World Health Organization (WHO) sponsored an international trial in which 612 patients with *thin* melanomas (2 mm) were randomly assigned to surgical excision with either 1-cm margins or margins larger than 3 cm.[101] At a mean follow-up of 8 years, disease-free survival and overall survival were reported to be equivalent in the two groups. For this reason, the researchers in this study concluded that wide excision did not influence survival for patients with thin melanomas. For patients with melanomas less than1 mm in thickness, they advocated "narrow," 1-cm margins to the muscular fascia plane.

Within the WHO trial, a subset of 245 patients had tumors measuring 1.1 to 2.0 mm in thickness. Although a difference in disease-free survival and overall survival was not observed with respect to margins, a local recurrence rate of 3.3% was reported among patients undergoing "narrow" excision. This finding prompted the Intergroup Melanoma Surgical Trial, which prospectively randomly assigned 740 patients with *intermediate-thickness* (1- to 4-mm) melanomas to WLE with either 2-cm or 4-cm margins.[102] Local recurrence rates and 10-year survival were reported to be equivalent in the two groups. This finding led to the recommendation of a 2-cm surgical margin for patients with intermediate-thickness melanomas—those measuring 1.1 to 4.0 mm in.

The latest prospective clinical trial, conducted by the United Kingdom Melanoma Study Group, randomly assigned 900 patients with localized cutaneous melanomas 2 mm or more in thickness to excision with 1-cm or 3-cm margins.[103] A statistically significant difference was not identified between the two groups when local, regional, and distant recurrences were compared; overall mortality rates were identical in the two groups. However, when all recurrences (local, in-transit, and nodal) were pooled together, the 1-cm margin group had a statistically higher recurrence rate. This is the first clinical trial comparing tumor margins to report a statistically significant difference in tumor recurrence. From a practical standpoint; however, it is the 1-cm versus 2-cm margin that is debated more often in this clinical setting.[104]

To date, there is no prospective randomized trial to address the optimal surgical margin for *thick* (> 4 mm) melanomas. A retrospective study of 278 thick melanomas found that surgical margins greater than 2 cm did not lead to a difference in rates of local recurrence rate, disease-free survival, or overall survival from rates for surgical margins of

Table 82-4

Recommended Surgical Margins for Excision of Primary Cutaneous Melanoma

Tumor Thickness (mm)	Surgical Margin (cm)
In situ	0.5
<1.0	1.0
1.01-2.0	1.0-2.0
>2.0	2.0

2 cm.[104] Within this study, 16% of the tumors involved head and neck subsites.

The primary goal of melanoma excision is to eliminate local recurrence secondary to persistent disease. The rate of local recurrence from narrow-margin excisions is admittedly low; however, the consequences are potentially fatal. It is estimated that 100% achievement of ideal margins would lead to a reduction in melanoma-related mortality and a 0.4-year increase in life expectancy for patients with melanoma.[105] Although this difference appears small at first glance, it equates to an estimated 11 additional years of life expectancy for patients who would have experienced local recurrence after excision with a 1-cm surgical margin but who instead experienced a disease-free state after excision with a wider surgical margin.

Current guidelines for surgical margins are based on primary tumor thickness (Table 82-4). It is important to realize that these recommendations serve only as guidelines; choices for each case of melanoma must be individualized. The depth of excision includes full-thickness skin and underlying subcutaneous tissue. Resection of fascia, perichondrium, and periosteum is required only in the setting of direct tumor invasion or if the surgical plane was violated during a previous biopsy.[106]

LMM warrants special comment, because it has a propensity for wide subclinical spread, which often results in pathologically positive margins.[107] Johnson and coworkers[108] and Anderson and colleagues[36] have reported on the use of the "square" procedure in the treatment of LM and LMM. This staged procedure entails complete excision of the peripheral margin with permanent-section histologic evaluation of 100% of the peripheral margins surrounding the entire tumor.

Closure and Reconstruction

With the use of judicious undermining, the majority of surgical sites can be closed primarily. Larger defects may require reconstruction with a split-thickness skin graft, a full-thickness skin graft, a local advancement flap, a regional flap, or free tissue transfer. The method of reconstruction depends on anatomic location, skin color and texture, depth of defect, and patient and surgeon preference. Initially surgeons were reluctant to use grafts at excision sites for fear that surveillance within the surgical bed would be hindered and future diagnosis of recurrence delayed. However, the method of closure has not been shown to affect survival.[109] After "clear" margins have been confirmed, surgeons are encouraged to close surgical defects using the technique that they believe will yield the best cosmetic result.

Melanoma of the Ear

Originally, melanoma involving the ear was thought to carry a worse prognosis than that in other head and neck sites.[98,110,111] This increased risk was attributed to rich lymphatics, complex anatomic subdivisions of the auricle, and a paucity of subcutaneous tissue between the thin auricular skin and underlying perichondrium.[112] Consequently, full-thickness excision or total auriculectomy was often advocated.

After accounting for tumor thickness, later studies demonstrated that melanoma of the ear carries the same prognosis as that in other sites.[68,113] In addition, outcome differences were not observed between auricular subsites.[112] Retrospective reviews did not demonstrate a difference in local recurrence based on the extent of surgical excision, even when perichondrium was preserved.[113] Today, the same prognostic indicators and surgical principles of obtaining wide, clear margins for treatment of cutaneous melanoma can be safely applied to the auricular region.

Surgical Management of Regional Lymph Nodes

Therapeutic Lymph Node Dissection

The most common sites for metastasis of head and neck cutaneous melanoma are the cervical and parotid lymph node basins.[114-116] The treatment of choice for regional disease remains a therapeutic lymph node dissection (TLND), which includes draining nodal basins as well as all intervening lymphatics between the primary tumor and the site of regional disease.

The location of the primary tumor dictates the type of TLND and the need for a superficial parotidectomy. Melanomas of the anterolateral scalp, temple, lateral forehead, lateral cheek, and ear, arising anterior to an imaginary coronal plane through the external auditory canals, drain via the parotid nodal basin to the jugular lymph node chain.[117] For this reason, a superficial parotidectomy and modified radical neck dissection are both recommended. In the absence of gross tumor involvement or disruption from open biopsy or previous surgical dissection, concerted efforts should be made to preserve the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle.[117] If the melanoma arises in a more inferior location (e.g., the chin or neck), a superficial parotidectomy is not warranted. Melanomas located on the scalp and occiput—posterior to the imaginary coronal plane through the external auditory canals—can drain to postauricular, suboccipital, and posterior triangle lymph nodes. These nodal basins are not addressed during routine modified radical neck dissection and necessitate a posterolateral neck dissection that includes levels II through V as well as the preceding nodes.[118]

Elective Lymph Node Dissection

One of the most controversial historic debates about melanoma surrounded the treatment of regional nodal basins in the absence of clinical metastasis (prophylactic treatment of the N0 neck).[114,116] Opponents of elective lymph node dissection (ELND) contend that melanoma metastasis is unpredictable. In Fisher's[9] retrospective review of 1444 head and neck patients with melanoma, 16% had distant metastasis in the absence of regional disease. This potential for hematogenous melanoma spread to bypass regional nodal basins theoretically limits the utility of an ELND. Opponents further argue that all four prospective, randomized trials detailed here failed to demonstrate an overall survival benefit for patients undergoing ELND in the absence of regional metastasis.[119-124]

The WHO Melanoma Group conducted the first prospective, randomized trial (Trial No.1) between 1967 and 1974, in which 535 patients with stage I and II melanoma of the extremity were enrolled.[123] A survival difference was not found between patients who underwent WLE and observation, with TLND reserved for the development of gross nodal metastasis, and patients who underwent WLE and ELND. Similarly, surgeons at the Mayo Clinic randomly assigned 171 patients with stage I disease to (1) WLE and observation, (2) WLE and delayed (30 to 60 days) ELND, or (3) WLE with concomitant ELND.[122] ELND was not found to provide a survival benefit over observation.

Although both prospective trials represent pioneering research in a challenging area, Balch[114] criticized both study designs. At the time of the studies, the prognostic significance of tumor thickness and ulceration was unknown. Later analysis of WHO Melanoma Group Trial No. 1 found significant discrepancy in the distribution of tumor thickness between the two treatment arms. Furthermore, 52% of lesions in the ELND group were ulceration compared with only 19% in the

observation group.[114] Subsequent reanalysis of these data with respect to tumor thickness and ulceration identified a subset of patients with a 22% better 10-year survival in the setting of ELND. The accuracy of clinical staging within the trial was also questioned because several institutions reported a 30% rate of occult nodal metastasis. This rate is quite high in comparison with rates reported in the literature, which range from 10% to 20%. Lastly, Balch[114] argued that the failure to detect a survival benefit with ELND was not surprising, given that both trials included patients with an overall low risk for regional metastasis at the time of diagnosis. Approximately 85% of patients enrolled in WHO Melanoma Group Trial No. 1 were women with extremity melanomas, which are recognized to have a lower rate of metastasis than melanomas at other sites. In addition, the Mayo Clinic study excluded patients with head and neck and midline trunk melanomas.

In order to address these concerns, the Intergroup Melanoma Surgical Trial was initiated.[119] This prospective, multi-institutional study involved 740 patients with intermediate tumor thickness (1 to 4 mm) melanomas of the trunk, extremity, or head and neck region. Patients were once again randomly assigned to undergo either WLE and observation or WLE and ELND. Cox regression analysis of the results identified ulceration, site, tumor thickness, and age as independent markers for survival. Overall 5-year survival rates were not found to differ in the two treatment groups. However, a significant survival benefit was found in patients 60 years of age and younger who underwent ELND, especially if their tumors were nonulcerated or measured 1 to 2 mm in thickness. Although this subgroup analysis is criticized for the shortcomings of a retrospective review and the failure to randomize by age, patients were prospectively randomized according to tumor thickness and ulceration.

The fourth prospective trial, initiated in 1982 by the WHO Melanoma Group (Trial No. 14), attempted to study patients truly at high risk for occult nodal metastasis.[121] It enrolled 240 patients with trunk melanomas measuring 1.5 mm or more in thickness. A survival difference was not observed between patients randomly assigned to observation and those who underwent ELND. In a multivariate analysis that included sex, age, tumor thickness, and treatment, only sex and tumor thickness were found to have a significant impact on survival. The study did identify a statistically significant 5-year survival difference between patients in whom micrometastasis identified during ELND (47%) and patients in the observation arm who underwent TLND only after the development of gross nodal disease (27%). For this reason, the WHO Melanoma Group advocated early detection of nodal metastasis using procedures such as SLNB (see later).

Statistical power remains one of the greatest challenges in investigating the survival benefits of ELND and early detection of nodal disease in melanoma patients presenting with localized disease in clinical trials conducted to date.[125] Only 20% of patients with melanoma presenting with localized disease actually have occult nodal metastasis. It is this 20% who would potentially benefit from early removal of nodal basins. Adjuvant melanoma therapy imparts a survival benefit in 25% to 50% of cases. If a similar survival benefit is applied to the ELND group, 25% to 50% of the 20% of patients with occult disease should benefit. In other words, only 5% to 10% of patients undergoing ELND are expected to experience a survival advantage. Detecting this small difference requires an extremely large clinical trial with enrollment numbering in the thousands. McMasters and colleagues[125] point out that the Intergroup Melanoma Surgical Trial, WHO trial, and Mayo Clinic study lacked adequate statistical power to detect this small survival benefit. For this reason, these researchers concluded that the 4% survival benefit observed in the ELND group of the Intergroup Melanoma Surgical Trial study is clinically significant, despite the fact that statistical significance was not reached.

In summary, numerous prospective, randomized trials failed to demonstrate an overall survival benefit for patients undergoing ELND.[110,119,121,123,125,126] Therefore, routine ELND is no longer advocated for melanoma. Instead, the procedure has been replaced by SLNB.

Sentinel Lymph Node Biopsy

Sentinel lymph node mapping and biopsy represents a minimally invasive, cost-effective, and efficient means of screening patients for regional metastasis.[127] Nodal status is currently recognized as the most important prognostic factor for patients with melanoma.[5] Ten percent to 20% of such patients have occult microscopic nodal disease. In an attempt to identify this small group of patients who need TLND while sparing the remaining 80% of patients without regional disease the morbidity associated with a neck dissection, Morton and colleagues[126] introduced SLNB for the evaluation of patients with trunk and extremity cutaneous melanoma. The investigators demonstrated that the status of the SLN accurately represented the status of the entire nodal basin from which it was obtained. SLNB is considered the best staging modality for regional disease, with the highest sensitivity and specificity of any modality currently available. In a multivariate model using data from 910 patients with melanoma, Peak and associates[128] identified an association between SLN positivity and increasing Breslow depth, younger age, higher mitotic rate, angiolymphatic invasion, and location on the trunk/lower extremities. The indications for SLNB are summarized in Box 82-5. Patients who have metastatic disease or who have undergone previous surgical disruption of the lymphatics or resection with wide margins are not deemed candidates for this screening.

Box 82-5

University of Michigan Indications for Consideration of Melanoma Sentinel Lymph Node Mapping and Biopsy

Breslow depth = 1 mm
Breslow depth = 1 mm in setting of adverse prognostic variables, including the following:
- Tumor extension to deep margin
- Ulceration
- Extensive regression to 1.0 mm
- Young age
- High mitotic rate[86]
- Clark level IV

The SLN technique introduced by Morton and others has since evolved to include preoperative lymphoscintigraphy.[129] Approximately 2 to 4 hours before surgery, patients undergo intradermal injection of a radioactive colloid into the four quadrants surrounding the primary melanoma tumor. Lymphoscintigraphy is then performed. This nuclear medicine scan enables the surgeon to determine the number, location, and laterality of nodal basins at risk for metastatic disease (Fig. 82-3). It is particularly helpful in the setting of midline head and neck melanomas, for which there is a risk of bilateral lymphatic drainage.

Once the patient is under anesthesia, intraoperative lymphatic mapping with isosulfan blue dye (Lymphazurin 1%; Covidien, Mansfield, MA) or methylene blue dye is performed.[126] Approximately 1 mL of dye is injected into the intradermal layer surrounding the primary melanoma lesion (Fig. 82-4). The primary tumor and draining lymphatics are in close proximity within the head and neck region. Therefore, WLE of the primary tumor is performed first to reduce radioactive "shine-through," which would render the intraoperative gamma probe useless for the identification of SLNs (Fig. 82-5) *Shine-through* refers to radioactive counts attributable to the primary site injection rather than sentinel lymph nodes.

Following WLE of the primary melanoma, the surgeon uses handheld gamma probe to identify the site(s) of sentinel lymph node(s). The procedure of identifying and removing sentinel lymph nodes continues until the gamma counts per minute (cpm) in the lymph node basin are equal or less than 10% of the "hottest" sentinel lymph node removed. We advocate this 10% rule because our data suggest that for surgeons using radioactive colloid who routinely terminate the procedure after identifying only the hottest node, or when the cpm values for nodes drop below one-half to one-third the cpm of the hottest node, the false-negative rates are higher.[130] The SLNs are removed with the use of 1- to 3-cm incisions overlying the areas of increased radioactivity. A preauricular incision is recommended for SLNB in the parotid region.

Figure 82-3. Preoperative lymphoscintigraphy is performed about 3 hours prior to sentinel lymph node biopsy. Approximately 2 µCi of technetium Tc 99m sulfur colloid is injected intradermally into the four quadrants surrounding the primary melanoma lesion located midline on the posterior occiput. The right posterior occiput primary lesion with an overlying shield to limit "shine-through" is denoted by the *small arrow*. The *larger arrow* points to two draining sentinel lymph nodes observed in the right posterior triangle of the neck.

Figure 82-4. After the administration of anesthesia, intraoperative lymphatic mapping is performed with the use of approximately 1 mL of isosulfan blue dye (Lymphazurin 1%; Covidien, Mansfield, MA) injected into the intradermal layer surrounding the primary melanoma.

SLNs are then identified through the use of a combination of the gamma probe and visual cues from the blue dye (see Fig. 82-5). Each SLN is individually dissected from surrounding tissue.

At our institution, all SLNs are sent for histologic evaluation using permanent sections. Frozen sections are less reliable, carrying a false-negative rate between 5% and 10%.[131] The evaluation involves serial sectioning (5-µm thick sections) and staining with hematoxylin and eosin. Special melanoma immunohistochemical staining for S-100 protein and melan-A (MART-1 [melanoma antigen recognized by T cells]) are performed for all SLNs with negative response to hematoxylin and eosin staining. This panel was chosen after pathologic evaluation of 99 positive SLNs from 72 patients treated at our institution.[132] The sensitivities for S-100, melan-A, and HMB-45 monoclonal antibody were found to be 97%, 96%, and 75%, respectively. In addition, HMB-45 stained a smaller percentage of cells (25% to 75%), with weaker intensity compared with S-100 and melan-A; for this reason, we no longer routinely stain for HMB-45.

Patients with a positive SLN result are returned to the operating room within 2 weeks of diagnosis for definitive TLND; patients with

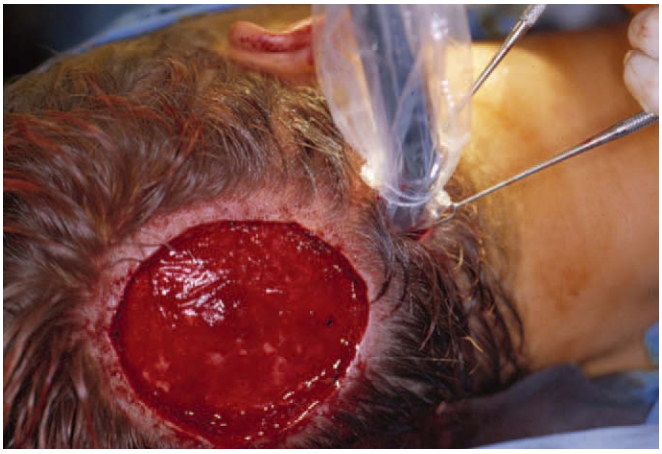

Figure 82-5. Wide local excision of the primary melanoma is performed prior to sentinel lymph node biopsy; otherwise, the close proximity of the primary lesion to the draining nodal basins within the head and neck region would cause significant radioactive "shine-through" and difficulty with localization of the sentinel lymph node. Each sentinel lymph node is then identified through the use of a combination of the gamma probe, which detects radioactive activity from the technetium Tc 99m sulfur colloid, and visual cues from the isosul-

a negative result are followed clinically. An alternative to this two-stage technique is immediate TLND on the basis of frozen-section evaluation of the SLNs. However, it is important to realize that the reliability of frozen sections for melanoma analysis has been questioned,[133] and permanent sections remain the "gold standard."

The pathologist plays an extremely critical role in the success of SLNB. Occult lymphatic metastasis from cutaneous melanoma can be difficult to detect and warrants rigorous pathologic analysis, including serial sectioning, special immunohistochemical study when indicated, and interpretation by an experienced pathologist. Wagner and associates[134] reported the mean tumor volume in SLNs positive for metastatic melanoma to be only 4.7 mm^3. Joseph and colleagues[66] reported the identification of only 73% of metastatic SLNs with the use of standard hematoxylin and eosin staining alone. In our study, 20 of the 97 positive SLNs (21%) tested negative on initial hematoxylin and eosin staining.[132] This high false-negative rate highlights the importance of immunohistochemical staining for accurate diagnosis of occult nodal disease.

The histologic analysis of SLNs is more thorough, complete, and practical than the traditional evaluation of the entire lymphadenectomy specimen, because the technique provides the pathologist with a limited number of nodes to evaluate thoroughly.[135] SLNB is particularly helpful in the diagnosis of occult DM/DNM. For this subtype, a focused histopathologic evaluation is of particular importance because the microscopic features are quite variable, often lack resemblance to the primary tumor, are limited to a paucity of tumor cells, and demonstrate inconsistencies on HMB-45 and melan-A staining.[136]

SLNB is a team effort involving experienced surgeons, nuclear medicine staff, and pathologists. The experience and technical skill of the surgeon is vital. Morton and associates[127] previously suggested a 30-case learning curve. However, long-term follow-up of their international Multicenter Selective Lymphadenectomy Trial (MSLT-1) found the 30-case learning curve to be too shallow. Analysis of the first 25 cases performed at the 10 highest-volume centers in the trial revealed a nodal basin recurrence rate of 10.3%.[131] This false-negative rate dropped to 5.2% after 25 additional cases. The researchers now conclude that a 55-case learning curve is required in order to achieve at least 95% accuracy with SLNB.

An experienced nuclear medicine staff is also necessary, because inappropriate administration of the radioactive tracer can also lead to "shine-through." Communication between the surgeon and the nuclear medicine team is helpful not only for the interpretation of the lympho-

scintigram but also to ensure that the appropriate lesion is mapped, because patients with melanoma often present with multiple pigmented lesions.

A multivariate analysis involving patients with stage I and II melanoma by Gershenwald and coworkers[137] found the pathologic status (positive or negative for metastasis) of the SLN to be the most important prognostic factor for both recurrence and overall survival. For patients with stage III melanoma, survival was better in those with occult microscopic disease than in those with palpable macroscopic disease.[5] This survival difference was so compelling that the AJCC has now incorporated SLNB into the revised staging system for cutaneous melanoma.

Although SLNB has a defined role in the evaluation of cutaneous melanoma of the trunk and extremities, several questions have been posed with respect to its application in the head and neck region.[127] The complexity of the head and neck lymphatic system has caused concern about the reliability of the SLNB to accurately reflect the status of the entire nodal basin. The interlacing network of cervical lymphatic vessels is often deemed to be watershed in nature. The complexity of this lymphatic system was demonstrated by O'Brien and colleagues,[138] who reported a 34% discordance between the clinical prediction of lymphatic drainage and lymphoscintigraphy findings in 97 cases of head and neck cutaneous melanoma. The popularity of SLNB in the head and neck region has also been limited by concern surrounding damage to vital structures such as the facial nerve,[139] technical difficulties,[139] and the necessity for nuclear medicine staff as well as pathologists who specialize in SLNB technique.

Our experience in staging 80 cases of head and neck cutaneous melanoma demonstrated that the complexity of the head and neck anatomy does not preclude the use of SLNB for the staging of cutaneous melanoma.[140] SLNB in the head and neck region accurately predicted the status of the nodal basin. Fourteen of 80 patients (17.5%) had a positive sentinel lymph node. Of 66 (4.5%) patients with negative SLNB results, only 3 experienced regional recurrence. The 17.5% positivity rate of SLNs and the 4.5% false-negative rate both mirror the results that SLNB achieved in other anatomic sites, such as the trunk and extremities.[135,141] Similar success in the application of SLNB for head and neck cutaneous melanoma has been reported by others,[142,143] and the technique has been applied successfully in pediatric head and neck cases.[13]

Approximately 25% to 30% of head and neck cutaneous melanomas drain to lymph nodes within the parotid bed.[138,140] Potential injury to the facial nerve from SLN biopsy has led some surgeons to advocate superficial parotidectomy over the mapping procedure.[139] In our retrospective analysis, staging with SNLB was successful in 28 of 30 (93.3%) patients whose tumors were draining to the parotid nodal basin.[140] One patient required a superficial parotidectomy owing to the location of the SLN deep to the facial nerve, and a second patient experienced significant bleeding from surrounding parotid tissue, which could have put the facial nerve at increased risk. A total of 39 nodes from the parotid basins of these 28 patients were removed without facial nerve injury. Continuous facial nerve monitoring for SLNB within the parotid nodal basin can be helpful when the biopsy is performed within the parotid bed.

Concern has also been expressed that SLNB causes inflammation and fibrosis that could place the facial nerve at increased risk when reoperation is required to definitively treat the parotid basin in the setting of a pathologically positive SLN.[139] In our experience, all patients with a positive parotid SLN underwent superficial parotidectomy as a subsequent procedure without facial nerve injury. Our findings are consistent with those of other reports demonstrating that SLNB can reliably and safely be performed within the parotid nodal basin.[144,145]

Other researchers have suggested that SLNB increases the risk of *in-transit metastasis* (ITM), which is defined as intralymphatic tumor dissemination within cutaneous or subcutaneous tissue located between the primary lesion and draining nodal basin.[146-150] It is theorized that ITM develops when melanoma cells detach from the primary lesion and become lodged in the dermal plexus of lymphatics prior to reaching the lymph nodes. ITM presents a therapeutic challenge and carries a poor prognosis, as indicated by the changes to the AJCC staging system previously described.[5] Original reports citing increased ITM following SLNB must by viewed with caution, because the studies often entailed pooled data from small cohorts and failed to control for important prognostic factors such as tumor thickness and ulceration.[61,148] A later prospective review comparing 4412 patients undergoing WLE alone, WLE with SLNB, or ELND identified a correlation between ITM and increasing Breslow depth, Clark level, and T stage.[61] A statistically significant difference between ITM and tumor recurrence was not found among the treatment groups, once adjustment of data was made for T stage, age, sex, tumor thickness, and site. Additional studies have concluded that it is the tumor biology, rather than the surgical procedure (SLNB; ELND), which dictates melanoma metastatic behavior.[148,151] Finally, a correlation between ITM and SLNB was not reported with MSLT-1, thus negating this concern.[131]

The impact of SLNB on overall survival remains to be determined. The answer will hopefully be provided through the multi-institutional Sunbelt Melanoma Trial, which is a prospective, randomized clinical trial that utilizes SLN staging to determine the need for adjuvant therapy.[152] While we await these results, McMasters and colleagues[153] outline the following four compelling reasons to use of SLNB for accurate regional staging of cutaneous melanoma.

1. The SLNB technique provides important prognostic information to the physician, patient, and family members in guiding subsequent treatment options.

2. SLNB helps identify patients with nodal metastasis, who then may benefit from early TLND.

3. SLNB identifies patients who are candidates for adjuvant treatment such as interferon-α 2b.

4. SLNB provides the most accurate means of regional staging. In doing so, the technique enables the identification of a homogeneous population of patients for enrollment into clinical trials. Regional metastasis is recognized as the most important prognostic factor in melanoma. Without accurate pathologic staging, stratification is impossible, and result of clinical trials will remain inconsistent and difficult to interpret.

The fifth and final analysis of MSLT-I will provide additional insight into the potential therapeutic benefit of SLNB.[131] Publication of the MSLT-I interim analysis is exciting in that it is the first randomized, prospective trial to demonstrate that SLNB accurately identifies occult nodal metastasis that would lead to advanced, palpable nodal disease if left in situ. The researchers argue that there is no reason not to perform SLNB because a zero mortality rate was reported, and the complication rate for SLNB (10%) was significantly lower than that for TLND (37%). Morton and colleagues[131] concluded that SLNB should be considered the standard of care for regional staging of primary cutaneous melanoma—the key term being "staging." At present SLNB is a diagnostic tool for regional staging, not a therapeutic modality. Although it is not 100% accurate, SLNB is the most reliable means for regional staging. It is more sensitive and specific than CT, magnetic resonance imaging, positron emission tomography, ELND, and clinical examination.[154] McMasters astutely points out that we do not expect a survival benefit from any other cancer staging test, and therefore we should not ask the same of SLNB.

Future Investigations

SLNB research endeavors hold exciting and great promise for the future. In an effort to further investigate the therapeutic potential of SLNB, research efforts have focused on identifying markers of both the primary lesion and SLN, which are predictive of tumor-containing non-SLNs.[155-157] Absence of these markers would then allow identification of the subset of patients with positive SLNB results, in whom further treatment with a formal TLND may not be warranted. Unfortunately, current studies have not identified a consistent and 100%

accurate marker. For this reason, the MSLT-II trial, currently under way, is designed to investigate the indications for TLND following a positive SLNB result. Specifically, it will determine whether immediate TLND provides a survival benefit over diligent postoperative, ultrasonographic monitoring of the draining nodal basins.[131]

Molecular staging of melanoma is also gaining increased interest. Reverse transcriptase–polymerase chain reaction (RT-PCR) analysis of SLNs for melanoma-associated genes such as MART-1, tyrosinase, microphthalmia-associated transcription factor (MIFT), and tyrosinase-related protein 2 (TRP-2) has proved helpful in identifying a subset of patients who have occult nodal disease at a submicroscopic level, which cannot be detected with traditional immunohistochemical staining.[84,158,159] In one study, in 30% (49 of 162) of patients in whom results of immunohistochemical staining of SLNs were negative, at least one melanoma marker was identified with RT-PCR.[160] This subset of patients experienced a higher rate of tumor recurrence. Currently, RT-PCR lacks specificity. The reason for the high false-positive rate may be the inability of RT-PCR to differentiate melanoma cells from occult benign nevus cells.[16] Through future research efforts, molecular staging may prove helpful in the identification of a subset of high-risk patients with melanoma in whom nodal or distant metastases develop despite presentation with a thin primary tumor. This information has the potential to change the manner in which these individuals are counseled both with respect to adjuvant therapy and follow-up surveillance.[65]

Surgical Management of Distant Metastasis

Patients with stage IV melanoma involving distant sites have an exceedingly grave prognosis. Surgical treatment has a limited role in the setting of disseminated disease. It has successfully been used as a means of palliative treatment in patients suffering from brain, lung, gastrointestinal, subcutaneous soft tissue, and distant lymph node metastasis.[161] Success of surgery in the palliative setting depends heavily on appropriate patient selection; it should be considered only if clearly identifiable and specific symptoms are associated with a metastatic lesion. Other considerations are surgical morbidity, expected quality of life, expected survival, and, most important, the patient's wishes.[162] It is imperative that the patient and his or her family understand that the goal of surgery is palliative in nature.

Several prognostic markers have been identified in patients with disseminated stage IV melanoma.[162,163] These markers are reflected in the AJCC staging system previously described above and should serve as a guide for the consideration of surgical resection of distant tumors. Patients with metastatic disease limited to one or two isolated sites experience a better prognosis as than patients who have multiple metastatic lesions. A short disease-free interval is associated with an overall poor prognosis. Patients in whom distant metastasis develops within a year of initial diagnosis have a poor prognosis, even when complete resection of the metastatic lesion is achieved.[162] Lastly, the anatomic site of the metastatic lesion is of importance. Patients with metastatic spread to nonvisceral sites (e.g., distant subcutaneous tissues, lymph nodes) have a better prognosis than those with visceral metastasis. Within the group of patients suffering from visceral metastasis, individuals with pulmonary lesions experience better survival than those with lesions at other visceral sites.

Radiation Therapy

Melanoma has traditionally been classified as a radioresistant tumor.[8,164] Although adjuvant irradiation has not been shown to have an impact on survival,[165] researchers at the MD Anderson Cancer Center completed a phase II clinical trial supporting the efficacy of hypofractionated radiation as an adjuvant to surgery for patients with head and neck cutaneous melanoma at high risk for local/regional recurrence.[166-168] Local/regional control was achieved in 88% of patients, which is an improvement over the historic control rates of 50% to 70%.[10,169] Late complications of irradiation were rare (3 of 174 patients) and included moderate neck fibrosis, mild ipsilateral hearing loss, and transient exposure of external auditory canal cartilage. Local/regional control is important, because recurrence can significantly affect quality of life by causing pain, wound breakdown, and socially debilitating cosmetic disfigurement.[170,171] However, no overall survival benefit has been demonstrated.

Ultimately the survival benefit achieved with adjuvant radiation therapy will be determined through the prospective, randomized phase III clinical trial (E3697) currently being conducted by the Radiation Therapy Oncology Group.[170] Until this trial is completed, most authorities advocate the use of adjuvant irradiation for patients demonstrating adverse prognostic markers such as neurotropism, extracapsular spread, multiple node involvement (>4), or recurrence.[172-174] These patients are often eligible to receive adjuvant interferon-α 2b (see later), which is thought to act as a radiosensitizer. Therefore, it is common practice to delay radiation therapy until the 4-week induction phase of interferon therapy is complete.[175]

On very rare occasions, primary irradiation can be used to treat extensive LM or LMM in an elderly patient who is not deemed a surgical candidate.[176] Radiation therapy can also be administered as palliative treatment in patients suffering from systemic stage IV disease, especially in the setting of brain metastasis, bone metastasis, spinal cord compression, or isolated, symptomatic visceral metastasis.[2]

Chemotherapy

Melanoma is a relatively chemoresistant tumor.[177-179] A small subset of patients is thought to benefit from chemotherapy; however, a regimen shown definitively to have an impact on survival has not emerged. The main role of chemotherapy remains as palliative treatment in the setting of disseminated stage IV disease.

Dacarbazine (DTIC) is currently the only chemotherapeutic agent approved for the treatment of advanced stage IV melanoma. Response rates following DTIC administration are modest at best, ranging from 10% to 20%.[8,87,180-182] This prognosis has not changed over the past 20 years, despite dedicated research efforts using a host of chemotherapeutic agent regimens.[178] Overall, less than 5% of individuals with stage IV melanoma experience a complete response with DTIC therapy.

Immunotherapy

Classically, immunotherapy is divided into two categories. Specific immunotherapeutic agents up-regulate the antibody and cytotoxic T-cell immune responses specifically to the patient's tumor or to known melanoma antigens; the majority of melanoma vaccines fall into this category. By contrast, nonspecific immunotherapeutic agents such as interferon, interleukin, and microbacterial products stimulate the host's immune system without targeting melanoma tumor antigens. These agents are often administered in concert with specific immunotherapeutic agents in an attempt to augment the immune system.[175,182]

Interferon

Despite myriad clinical trials involving adjuvant regimens, high-dose interferon-α 2b remains the only adjuvant treatment approved by the U.S. Food and Drug Administration (FDA) for stage III melanoma. It functions as a biologic response modifier; the mechanism of action includes direct antiproliferative effects, immune stimulation through the enhancement of natural killer cells, increased histocompatibility antigen expression on melanoma cells, macrophage phagocytosis, and enhanced T-cell–mediated cytotoxicity.[107,183] Although all three types of interferon (α, β, and γ) demonstrate antitumor activity,[183] Interferon-α 2b is the only treatment that is currently approved for the adjuvant treatment of patients with melanoma at high risk for recurrence after surgery.

Three large clinical trials involving adjuvant interferon-α 2b have been conducted by the Eastern Cooperative Oncology Group (ECOG).[184-186] In brief, ECOG trial E1684 was the first study to demonstrate the efficacy of interferon-α 2b.[184] The regimen consisted of high-dose interferon (20 million units/m^2/day) administered intravenously, 5 days a week, for 4 weeks. Maintenance treatment followed, consisting of 48 weeks of subcutaneous interferon-α 2b (10 MU/m^2/day) administered 3 days a week. The prolonged disease-free survival rate and overall survival rate in the interferon-α 2b arm of E1684 ultimately led to FDA approval of the adjuvant therapy.

Although the follow-up trial E1690 did not confirm the efficacy of high-dose interferon-α 2b,[185] the results require careful interpreta-

tion.[153] Unlike in E1684, patients enrolled in E1690 did not require pathologic staging with ELND or SLNB, nor were they stratified according to ulceration. In addition, a disproportionate number of individuals from the observation arm crossed over into the interferon-α 2b arm to receive salvage therapy for recurrent disease. Any therapeutic benefit provided to this subgroup by interferon-α 2b went unrecognized, because the crossover patients remained in the observation arm for the purposes of statistical analysis.

The latest and largest of the three studies, ECOG 1694,[186] once again confirmed the efficacy of high-dose interferon-α 2b. In fact, the difference between rates of relapse-free and overall survival observed in the high-dose interferon-α 2b control arm in the GMK ganglioside vaccine treatment arm was so compelling that the Data Safety Monitoring Committee terminated the trial early.

With close follow-up, dose modification, and pharmacologic intervention, the majority of patients with melanoma are able to tolerate the 1-year course of interferon-α 2b.[153,175,185,186] Almost all individuals experience flulike symptoms (fevers, chills, malaise) during the initial treatment course. Severe and intolerable chronic fatigue occurs in 20% to 30% of patients, and an additional 2% to 10% experience neurologic and psychiatric side effects, including depression, anxiety, suicidal ideation, and difficulty with cognition. Myelosuppression, thyroid dysfunction, and elevated liver enzyme values require close monitoring. Contraindications include a history of myocardial infarction or dysrhythmia, liver disease, central nervous system disorders, and severe psychiatric illness.[175] Approximately 50% of patients require a dose reduction or delay as a result of these side effects. The majority of patients with melanoma are willing to accept these side effects, given the potential benefit of interferon-α 2b.[187]

Although clinical trials continue to investigate alternative dosages and schedules,[188,189] high-dose interferon-α 2b remains the only proven adjuvant treatment for melanoma, with relapse-free survival prolonged by approximately 10%.[190] It remains the standard of care for adjuvant therapy against which all interventions must be compared, ideally in the setting of prospective, randomized trials.[191] Every patient with regional lymph node metastasis or a primary tumor thickness greater than 4 mm should be informed of the option to receive postoperative interferon-α 2b. To enable the patient to make an educated decision, the surgeon must have an objective discussion about the side effects of interferon-α 2b and the opportunities to enroll in other clinical trials.

Interleukin-2 and Other Cytokines

Interleukin-2 (IL-2) is another form of immunotherapy that is used in the primary treatment of disseminated stage IV disease. Unlike interferon, IL-2 lacks direct antitumor activity and in vitro activity.[107] However, in vivo, IL-2 stimulates the host's immune system by activating effector cells such as natural killer cells, monocytes, cytotoxic T cells, and helper T cells. It also induces cytokines such as interferon-γ and tumor necrosis factor-α.[107,192]

Rosenberg and colleagues,[193] of the Surgery Branch of the National Cancer Institute, successfully used high-dose IL-2 to treat 134 patients with melanoma. An overall response was observed in 17% of patients; 10% experienced a partial response, and an additional 7% had complete regression. The therapeutic benefit was substantial, lasting between 2 and 8 years.

The side effects of IL-2 are significant and potentially lethal. Acute toxic effects include myocardial infarction, arrhythmia, respiratory distress, hypotension, capillary leak syndrome, nephrotoxicity, hepatic toxicity, and sepsis.[192,194] Others are anemia, thrombocytopenia, nausea, emesis, diarrhea, myalgia/arthralgia, skin erythema, and pruritus. Only patients who demonstrate excellent cardiopulmonary health and performance status should be considered for clinical trials involving IL-2.

Subsequent efforts to enhance the response to IL-2 by altering the schedule and dose and by combining it with other therapeutic agents (e.g., lymphokine-activated killer cells) have not proved beneficial.[107,182,192,194] In addition to IL-2, other cytokines have been studied alone and in combination with various chemotherapeutic agents, including IL-1, IL-4, IL-6, and tumor necrosis factor-α.[192] Significant therapeutic benefit has not been demonstrated for any.

Future Immunotherapy Investigations

Significant advances in the field of melanoma research have been achieved in recent years.[175,182,183,195,196] Intense efforts in the areas of melanoma vaccination, gene therapy, and HLA immunoprinting will likely play important roles in future research endeavors. Until therapeutic efficacy achieves that of interferon-α 2b, all other adjuvant agents should be administered to high-risk patients only in the setting of well-designed clinical trials. Given the heterogeneous melanoma patient population, myriad immunotherapy regimens, and the limited survival of high-risk patients with melanoma, multi-institutional studies with accurate clinical staging will be imperative.

Follow-Up and Surveillance

The primary goals of melanoma follow-up are the early detection of local/regional tumor recurrence, the early identification of second primary tumors (including melanoma and other skin cancers), continuing patient education, and psychological support.[197] Each follow-up visit should include an inquiry into new or changing skin lesions. A review of systems (see Box 82-2) as they relate to distant metastasis should be performed.[79] A thorough examination of the skin and mucosa is required, with particular attention paid to the original melanoma site and associated draining nodal basins. Each follow-up visit should be viewed as an opportunity to reducate patients about the ABCD melanoma warning signs and the importance of monthly skin self-examination. Education about sun exposure—including using sunscreen, avoiding peak sunlight hours, seeking shade, wearing protective clothing, and the potential risks of tanning booths—should be emphasized.

SUGGESTED READINGS

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CHAPTER EIGHTY-THREE

Malignancies of the Paranasal Sinus

Ernest A. Weymuller, Jr.

Greg E. Davis

Key Points

- Malignant paranasal sinus tumors are rare and have relatively poor survival outcomes, often related to advanced stage at diagnosis.
- Symptoms suggesting sinus malignancy include nasal obstruction, pain, epistaxis, swelling, nasal discharge, epiphora, palate lesion, diplopia, cheek numbness, decreased vision, neck mass, proptosis, and trismus.
- Treatment for sinonasal malignant tumors varies widely according to histologic type, tumor location, and institutional experience.
- Advancements in imaging, experience with image-guided endoscopic surgery, and new chemoradiation therapy regimens have significantly altered attitudes regarding the optimal approach to sinus malignancy.
- Understanding the complex three-dimensional anatomy of the sinuses and surrounding structures is a crucial component of therapeutic decision-making.

In the first decade of the 21st century it is difficult to describe the "standard of care" for any malignant process. The rapid evolution of imaging combined with the emergence of effective nonsurgical treatment modalities and the expansion of image-guided surgical technology has created a dynamic therapeutic environment. Management of paranasal sinus malignancy exemplifies this situation, and treatment selection is additionally influenced by the proximity of the sinuses to the eyes and the brain, which limits the opportunity to achieve "clear surgical margins" for the majority of these tumors. Consideration of post-treatment quality of life has clearly influenced treatment selection in the past and is driving current management toward combined therapy and aggressive endoscopic debulking to achieve organ preservation while also preserving the probability of cure.

We present traditional topics in paranasal sinus malignancies and also discuss some of the emerging modalities, including endoscopic resection, concomitant chemoradiation therapy, and image-modulated radiation therapy. Benign lesions in the paranasal sinus and tumors of the nasopharynx are discussed elsewhere in this book.

Recognition of malignant lesions in the paranasal sinuses creates a challenge for patients and practitioners, given that the area is neither visible nor palpable and sinus malignancy initially mimics a benign process. The diagnosis usually becomes apparent only after the lesion has reached an advanced stage, thus explaining the relatively poor prognosis. The otolaryngologist has a unique obligation to be aware of these disorders and to understand the management of these complex tumors.

This chapter first reviews material common to all sinus tumors: anatomy, symptoms, physical findings, diagnostic assessment, and surgical options. Although these lesions are rare, numerous histologic subtypes must be discussed individually because management varies significantly among them (Fig. 83-1).

Epidemiology and Survival

Malignant lesions within the sinuses are uncommon, accounting for less than 1% of all neoplasms, with a frequency of 0.1 to 0.3 per 100,000 during the first decade of life that rises to 7 per 100,000 by the eighth decade of life.[1] Several histologic subtypes have been described. In one of the most widely cited papers on the incidence of malignant sinonasal lesions, Jackson and colleagues[2] reviewed 115 patients between 1957 and 1974 and reported on the histologic distribution of their tumors (Table 83-1). These rates are similar to those in a review by Sisson and associates[3] in 1989. In 2007, the Memorial Sloan-Kettering Cancer Center published their experience with paranasal sinus malignancies; the histologic prevalence remains similar to that described by Jackson 30 years earlier (see Table 83-1).[4] The most common lesions reported were squamous cell carcinomas, with a frequency of less than 1 per 200,000 per year.

A large retrospective review of 220 patients with nasal and paranasal sinus malignancies showed a 5-year survival rate of 40%.[1] The National Cancer Institute created the Survival, Epidemiology, and End Result (SEER) database in 1973. This database enables accurate estimates for cancer incidence and mortality in the United States. In 2006, Davies and Welch[5] used this database to compile recent incidence and mortality rates for head and neck cancer. The data suggest that mortality for sinus malignancies decreased by 11% between 1990 and 2001.

Numerous environmental agents are considered to have a causal relationship with carcinoma of the paranasal sinuses. The following are all associated with squamous cell carcinoma: aflatoxin, found in certain

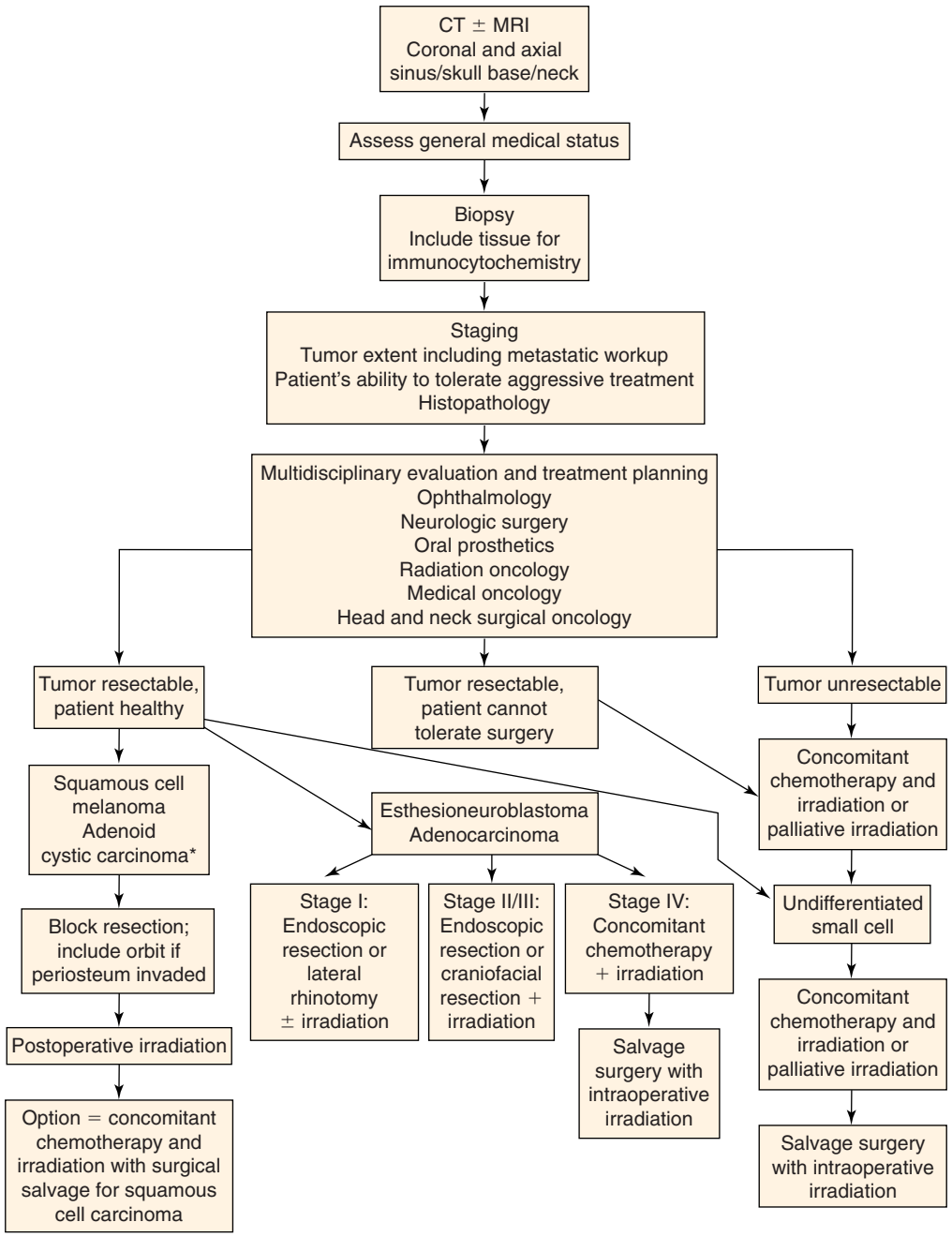

Figure 83-1. Evaluation and management of suspected paranasal sinus cancer. *Neutron irradiation is an option for adenoid cystic carcinoma. CT, computed tomography; MRI, magnetic resonance imaging.

foods and dust; chromium, nickel, mustard gas, polycyclic hydrocarbons, and other organic chemicals, usually from manufacturing processes; and mesothorium (Thorotrast), a radiopaque dye used as a contrast medium within the antrum. Wood dust has a particular association with adenocarcinoma of the ethmoid sinus. Tobacco smoke, salted or smoked foods, woodworking, heavy metal exposure, and hydrocarbon refining have all been linked with a higher incidence of these malignancies. There is a 2:1 male to female preponderance, likely due to the higher rates of male workers in the occupations listed. Additionally, human papillomavirus, including subtypes 6, 11, and 18, has been identified in inverted papilloma and associated squamous cell carcinoma.[6]

Anatomy

Assessment and management of this group of tumors demands an intense personal effort to understand the complex anatomy of the sinuses and skull base. Such knowledge is best obtained through anatomic dissection and repeated review of the anatomy of the human skull. It may be helpful to have a skull available in the operating room for inspection during complex resections, especially those that approach or traverse the skull base.

Pertinent to this discussion are the structures contiguous to each of the sinuses, because they define the extent of disease and determine the design of therapy. It is important to realize that all of the sinuses have venous communications with intracranial veins, which provide an avenue for intracranial spread.

Maxillary Antrum

As noted by Ohngren,[7] the most prognostically significant structures are above and behind the maxillary antrum. Superior to this structure are the orbit and the ethmoid sinus. The posterior boundary includes the pterygoid plates, the pterygoid space, and the infratemporal fossa.

Table 83-1

Rates of Malignant Tumors

	Number Reported (%)	
Histology	Jackson et al (1977)[2]	Hoppe et al (2007)[4]
Squamous cell carcinoma	61 (55)	42 (49)
Undifferentiated carcinoma	11 (10)	4 (5)
Adenoid cystic carcinoma	8 (7)	11 (13)
Adenocarcinoma	7 (6)	6 (7)
Melanoma	7 (6)	
Olfactory neuroblastoma	5 (4)	7 (8)
Fibrosarcoma	3 (3)	9 (11)
Papillary adenocarcinoma	2 (2)	
Transitional cell carcinoma	2 (2)	
Plasmacytoma	2 (2)	
Hemangiopericytoma	1 (1)	
Lymphoma	1 (1)	
Carcinosarcoma	1 (1)	
Chondrosarcoma	1 (1)	
Neuroendocrine	n/a	2 (3)

The other boundary areas are more easily resected en bloc and thus are less worrisome when involved. Anteriorly lies the canine fossa, inferiorly the alveolus, and medially the nasal cavity.

Ethmoid Sinus

As with the antrum, the least worrisome directions of spread from the ethmoid sinus are inferior into the antrum and medial into the nasal cavity. Of much greater concern is superior spread, in which the fovea ethmoidalis and the cribriform plate provide little barrier to intracranial spread. Evidence of intracranial spread requires consideration of an anterior craniofacial resection. The lateral wall consists of the thin bone of the lamina papyracea, which also provides little resistance to neoplastic invasion.

Sphenoid Sinus

Located in the center of the head, the sphenoid sinus is immediately adjacent to very complex and vital structures. For this reason, complete resection of a malignant tumor involving the sphenoid sinus is usually not possible. The optic nerve and the pituitary gland are superior to this sinus, and the internal carotid artery and the cavernous sinus sit laterally. The bone of the lateral wall is usually less than 0.5 mm thick and not uncommonly is dehiscent. Anterior to the sinus are posterior ethmoidal cells, and inferiorly are the vidian nerve, the clivus, and the nasopharynx.

Frontal Sinus

The sinus least frequently involved by malignant tumors, the frontal sinus, is bounded anteriorly by the soft tissues of the scalp, inferiorly by the dense frontal beak of the frontal bone, the ethmoidal cells, and the orbit, and posteriorly by the anterior cranial fossa.

Lymphatics

Ohngren[7] emphasized the importance of precise understanding of the lymphatic drainage of the nose and paranasal sinuses as a prerequisite to adequate therapy. He contested the established dictum that these tumors do not often metastasize. He held that they do metastasize but that clinical evidence of early metastasis is absent because the primary drainage is to the lateral and retropharyngeal nodes. He believed that the relative success of his therapy hinged on electrocoagulation and irradiation of the rich lymphatic channels passing from the nose and paranasal sinuses posteriorly to the retropharynx which remains an important therapeutic concept.

Symptoms

In the review of 115 patients by Jackson and colleagues,[2] the symptoms associated with malignancy were nasal obstruction (61%), localized pain (43%), epistaxis (40%), swelling (29%), nasal discharge (26%), epiphora (19%), palate lesion (10%), diplopia (8%), cheek numbness (8%), decreased vision (8%), neck mass (4%), proptosis (3%), and trismus (2%). As the disease becomes more advanced, the tumor infiltrates adjacent structures, giving rise to these symptoms as follows:

Diplopia or vision loss is most often a manifestation of tumor mass compressing or invading the orbit and may also result from direct involvement of the optic or oculomotor nerves at the orbital apex or the cavernous sinus.

Epiphora is caused by obstruction or infiltration of the lacrimal duct situated in the anteromedial aspect of the maxilla.

Facial swelling and malocclusion result from bone destruction and advancement of the tumor into the soft tissues of the face or mouth.

Trismus signals far-advanced tumor invading the muscles of mastication, most commonly the pterygoid muscles.

Neck mass; palpable metastatic adenopathy in the jugular chain is another sign of advanced disease.

Hearing loss usually results from nasopharyngeal extension of the tumor that obstructs the eustachian tube. This finding is important because nasopharyngeal extension of disease usually precludes a clear resection margin in this area.

Facial numbness is a manifestation of tumor invasion of portions of the trigeminal nerve.

Physical Findings

Until the tumor has infiltrated a cranial nerve or facial bones or has grown sufficiently to obstruct a sinus ostium, it silently advances in size and extent. Discovering an asymptomatic sinus tumor at an early stage is truly a rare and fortuitous event. The most common physical features are as follows:

Nasal, facial, or intraoral mass. The intranasal mass is often necrotic, but polypoid mucosa may obscure underlying tumor tissue in the nose. Facial swelling results when an antral tumor erodes into the soft tissues of the cheek. Widening of the upper alveolar ridge or development of loose, nonvital teeth may be the earliest sign of inferior bony invasion. A palatal mass and ulceration are evidence of more advanced disease.

Proptosis. Mild protrusion of the eye may be consistent with tumor compression of the periorbita without frank invasion, but often it reflects intraorbital tumor and implies advanced disease.

Cranial nerve deficits. The commonly involved cranial nerves are II, III, IV, V1, V2, and VI. Involvement of cranial nerves is a manifestation of advanced disease and indicates a poor prognosis.[8]

Diagnostic Assessment

The selection of diagnostic studies should be guided by thorough history-taking and head and neck examination, including a careful assessment of cranial nerve function. Once a working diagnosis of neoplasm has been inferred from the history and physical findings, subsequent studies are directed toward establishing the extent of the lesion and its histology.

Imaging Studies

Computed Tomography

Computed tomography (CT) is the initial imaging modality of choice for paranasal sinus disease. CT is superior to magnetic resonance imaging (MRI) for detection of bony involvement. CT scanning is also particularly helpful for evaluation of tumor involvement of the retro-orbital and orbital apex region, where there should be a "central low density region of fat surrounding the optic nerve with a radial arrangement of the extraocular muscles."[9] Loss of this plane implies advanced disease because the veins in this area extend directly to the cavernous sinus. CT is also valuable in assessing infiltration of the nasopharynx, where normal anatomy consists of a very thin layer of mucosa over the medial pterygoid plate. Thickening in this region implies tumor infiltration.[9] When evaluation of intracranial extension is necessary, contrast-enhanced CT may improve the definition of tumor from adjacent brain.

Magnetic Resonance Imaging

The impact of MRI on the preoperative assessment of tumor extent has been dramatic. The combination of CT to evaluate changes in the bony architecture of the cranial and facial structures with MRI to define soft tissue extent of disease has introduced a new era in staging and planning treatment for sinus neoplasms. The particular benefit of MRI is its ability to differentiate tissue density and predict with excellent accuracy the difference between tumor and retained secretions in the sinuses. By using T1 and T2 weighting with gadolinium dye enhancement, the experienced neuroradiologist is able to accurately determine the extent of the tumor.

Angiography

Angiography may be appropriate, especially if the lesion demonstrates enhancement during the initial contrast CT study or if it approximates the carotid system. This modality can also be helpful in the evaluation of unusual tumors involving the sphenoid sinus and skull base. In the instance of vascular tumors involving the sinuses, angiography is essential for assessment of tumor extent and delineation of feeding vessels and as an approach for embolization when it is deemed necessary and safe.

Positron Emission Tomography

Positron emission tomography is of little utility in assessing local tumor extent, but it can play a role in evaluating for the presence of metastatic disease before extensive oncologic surgery with or without concomitant chemoradiotherapy, in which a pretreatment positron emission tomography study provides the optimal baseline for post-treatment decision-making.

Biopsy

Often a paranasal sinus tumor presents a surface that lends itself to biopsy at the time of initial clinical presentation. In this instance a biopsy specimen obtained with use of local anesthesia and a biting forceps advances the diagnostic evaluation. Infiltration of epinephrine with a local anesthetic may decrease bleeding. Tumors contained within the sinus cavities are ideally sampled transnasally because transcutaneous or transmucosal approaches may breach the margins of a subsequent en bloc resection. One must be mindful of the possibility of a vascular tumor or an encephalocele during biopsy of unilateral nasal masses. Usually palpation of the tumor with an instrument demonstrates its solid nature. If the mass is soft or cystic, the patient should be asked to perform a Valsalva maneuver while the mass is being observed. Expansion of the mass implies an intracranial connection or a major venous connection. If doubt still exists, it is best to perform aspiration with a fine-gauge spinal needle before the biopsy. If the needle aspirate consists of cerebrospinal fluid or blood, CT, MRI, and, possibly, angiography should be considered before a biopsy is performed.

If none of the preceding methods achieves satisfactory material for histologic examination, the tumor must be approached directly. A surgical procedure appropriate to the lesion must be selected (such as frontal trephination, transseptal sphenoidotomy, intranasal antrostomy, or external ethmoidectomy). Performance of biopsy through a standard endoscopic sinus surgical approach is also appropriate when feasible. The operation should be designed to minimize disruption of later en bloc resection. Biopsy may be the only surgical procedure carried out during the patient's treatment. In that case, wide drainage of the sinus should be carried out at the time of biopsy to allow for the discharge of necrotic debris that results from subsequent therapy.

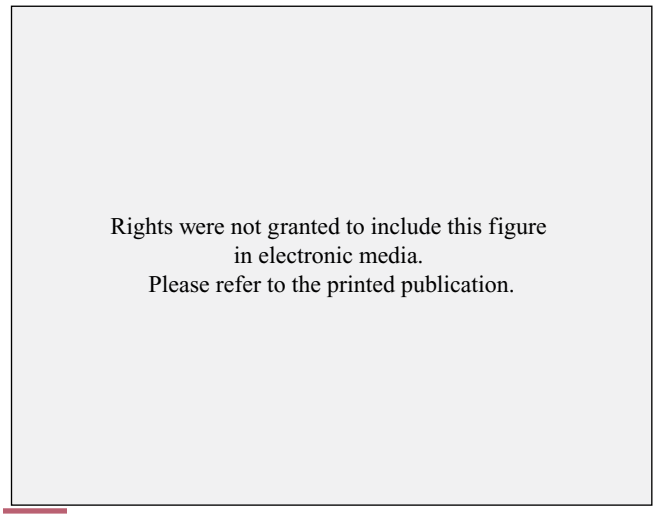

Figure 83-2. Anatomic reference for the surgical options available for treatment of malignancies of the paranasal sinuses.

Surgical Options

Extirpation of paranasal sinus tumors is a challenging exercise in surgical planning, which may be considered in three phases. First, one must assess the bony and soft tissue structures to be included for en bloc resection. Second, the approach must be designed to provide adequate exposure while preserving functional tissue and cosmetic integrity whenever possible. Third, the repair should be planned to use prosthetics or soft tissue techniques to the best advantage. See Figure 83-2 for anatomic reference.

Classic "Open" Procedures

External Ethmoidectomy

INDICATIONS. The most limited operation to be discussed, external ethmoidectomy, is appropriate for removal of small tumors of the ethmoidal region and as an approach to biopsy and drainage of tumors of the sphenoethmoid region and the medial orbit (Fig. 83-3).

BONY EXCISION. The limits of bony resection are the medial orbital wall and the ethmoidal labyrinth.

SURGICAL APPROACH. The surgical approach is through an incision on the lateral wall of the nose.

BENEFITS. The external ethmoidectomy approach allows excellent cosmesis and preservation of functional tissue.

LIMITATIONS. External ethmoidectomy will not provide en bloc excision for any but the most limited tumors (middle turbinate). There

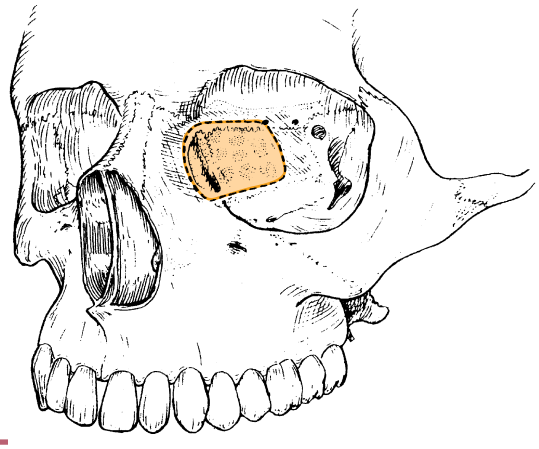

Figure 83-3. External ethmoidectomy.

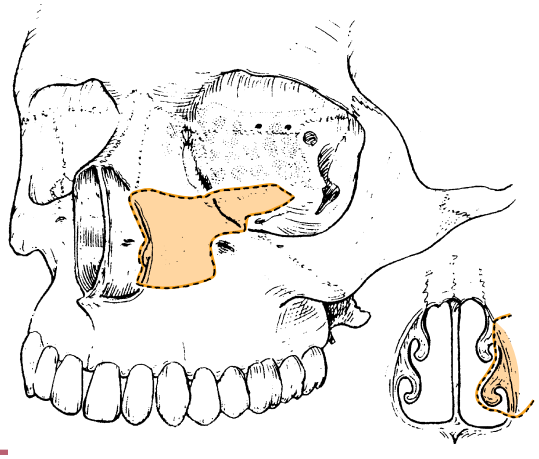

Figure 83-4. Inferior medial maxillectomy.

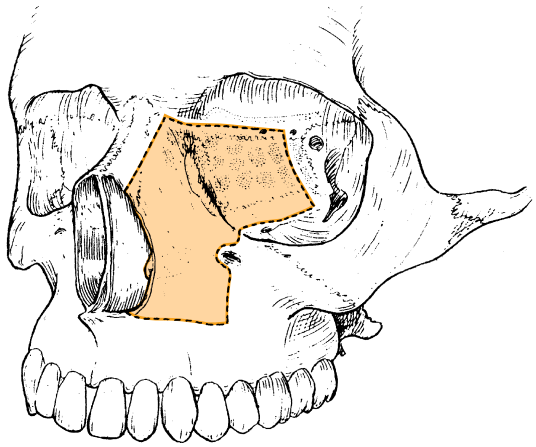

Figure 83-5. Medial maxillectomy.

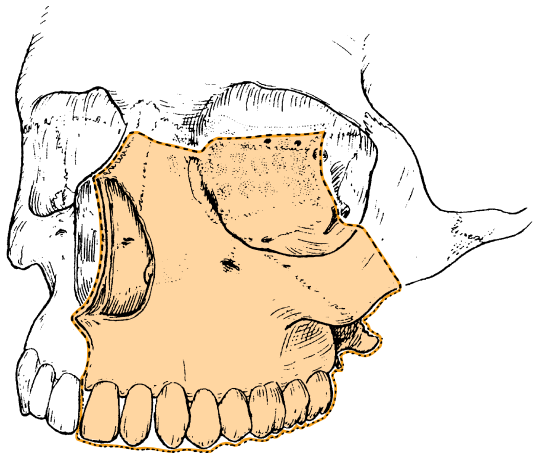

Figure 83-6. Radical maxillectomy.

is a tendency for fistula formation from the skin to the nasal cavity when this area is irradiated.

Inferior Medial Maxillectomy

INDICATIONS. Inferior medial maxillectomy is designed for resection of the medial wall of the antrum and the inferior turbinate. It is most often used for management of an inverted papilloma (Fig. 83-4).

BONY EXCISION. The margins extend laterally to the infraorbital foramen, inferiorly to the floor of the nose, superiorly to the lacrimal fossa and the middle meatus, and posteriorly to the dorsal end of the inferior turbinate.

SURGICAL APPROACH. A lateral rhinotomy incision is frequently used; the same bony excision may be achieved through a sublabial approach, although an en bloc resection may be more difficult with the latter approach.

BENEFITS. Inferior medial maxillectomy allows adequate exposure and resection for limited tumors while preserving functional tissue and providing a very acceptable cosmetic result.

LIMITATIONS. Inferior medial maxillectomy provides en bloc removal of a limited area.

Medial Maxillectomy

INDICATIONS. Medial maxillectomy may be used for larger benign or intermediate tumors involving the entire lateral nasal wall but without extension to the orbit, anterior cranial fossa, lateral maxilla, or alveolus (Fig. 83-5).

BONY EXCISION. The block removed contains the lateral nasal wall, including all turbinate tissue, and the contents of the ethmoid and maxillary sinuses.

SURGICAL APPROACH. An extended lateral rhinotomy incision provides excellent exposure. In some instances the same procedure may be accomplished by combining an ethmoidectomy incision with a sublabial incision.

BENEFITS. An en bloc resection may be accomplished with little resulting cosmetic deformity.

LIMITATIONS. Postoperative epiphora due to division of the nasolacrimal duct is not uncommon. The posterior and superior margins of resection should be monitored by means of a frozen section when indicated. Removal of all turbinate tissue results in an abnormal nasal cavity, which may require long-term management of crusting.

Radical Maxillectomy

INDICATIONS. Radical maxillectomy is the standard operation for advanced carcinoma of the maxilla (Fig. 83-6). Considerable debate exists regarding the proper application of this procedure, because the amount of tissue to be removed depends on a careful assessment of the extent of tumor involvement. Another uncertainty relates to the establishment of proper indications for removal of the orbital contents in combination with radical maxillectomy.

BONY EXCISION. Complete radical maxillectomy involves removal of the maxilla along with the nasal bone, the ethmoid sinus, and, in some instances, the pterygoid plates.

SURGICAL APPROACH. The Weber-Ferguson incision is used with extensions around the eyelids to preserve those soft tissues. A skin or dermis graft is used to line the defect.[10] A preformed obturator can be of great assistance in the immediate postoperative period because it acts as a support for packing and provides immediate dental function.

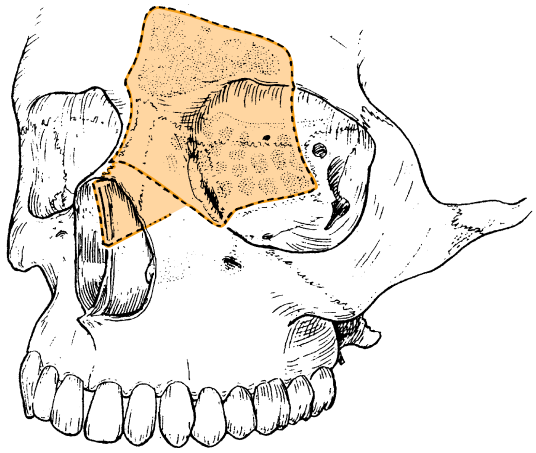

Figure 83-7. Craniofacial frontoethmoidectomy.

BENEFITS. Radical maxillectomy is adequate treatment for malignant tumors confined to the maxilla and those with extension to the facial soft tissues, lateral palate, or anterior orbit but without invasion of the eye, ethmoidal roof, posterior orbit, or pterygoid region. Historically, when the procedure was supplemented by irradiation, a cure rate approximating 30% was expected.[2] However, in the update by Sisson and associates[3] on their experience, patients who received multimodality therapy consisting of surgery, irradiation, and chemotherapy achieved a 5-year survival rate of 49%.[3]

There is little debate regarding the indications for resecting the orbital contents in patients with advanced paranasal sinus carcinoma.[10a] As indicated by Ketcham and Van Buren,[8] the decision to excise the orbital contents was made on the basis of achieving an en bloc resection of the tumor. However, those researchers implied that as imaging became more precise, more selective resection might be possible. Perry and colleagues[11] emphasized the impact of CT on surgical planning and documented that selective preservation of the orbital contents is appropriate and achieves adequate local control in properly selected cases.[11] This finding was consistent with the experience of Weymuller and coworkers,[12] who also could not demonstrate better local control or survival when the orbital contents were included in maxillectomy procedures. This position was later further supported by the experience of Larson and associates.[13]

LIMITATIONS. Even when orbital exenteration is included, a maxillectomy fails to provide an adequate resection when the tumor has escaped superiorly (ethmoidal roof) or posteriorly (orbital apex, pterygoid region). When these areas are demonstrably involved, one must decide whether to undertake craniofacial resection or use a regimen as described by Sakai and colleagues[14] that relies on chemotherapy, curettage, and irradiation.

Craniofacial Frontoethmoidectomy

INDICATIONS. Craniofacial frontoethmoidectomy is specifically designed to provide en bloc resection for tumors of the ethmoidal and frontal regions (Fig. 83-7). By including exposure of the anterior cranial fossa, the procedure makes possible complete resection of the ethmoid and frontal sinuses, and dural resection may be included when necessary. As previously noted, one or more margins of these extensive resections are often limited by proximity to the eye or brain, resulting in surgical margins that are "microscopically positive" for tumor.

BONY EXCISION. Resection may include the anterior cranium (including the frontal sinus), the floor of the anterior cranial fossa, the ethmoid labyrinth (and the eye when necessary), and the nasal septum. If the tumor crosses the midline, the procedure may be performed bilaterally.

SURGICAL APPROACH. The craniofacial frontoethmoidectomy approach described by Kaplan and associates[15] allows excellent exposure with preservation of the supraorbital rim to decrease the cosmetic impact of the procedure. Although removal of the eye is unpleasant to consider, Ketcham and Van Buren[8] have documented an improved survival when orbital resection is combined with craniofacial resection (57%, vs. 26% without exenteration).

BENEFITS. Craniofacial exposure provides direct visualization of the cribriform plate and the fovea ethmoidalis and the potential for en bloc removal. It also offers wide exposure to allow effective repair of dural tears, thus decreasing the chance of a postoperative cerebrospinal fluid leak and intracranial infection.

An international collaboration reviewing 188 patients published a report in 2005. The reported mortality associated with craniofacial resection was 4.5%, and the complication rate was 33%.[16] Surgical margins, histologic type, and intracranial extension were independent predictors of survival. Shah and associates[17] reported their experience with 71 patients, which showed an overall 5-year survival of 56% and a median survival of 4.2 years. Like the international group, Shah and associates[17] showed that intracranial involvement predicted significantly worse survival.

LIMITATIONS. If the tumor extends to the sphenoid sinus, the cavernous sinus, or transdurally, en bloc resection cannot be achieved.

Extended Craniofacial Resection

INDICATIONS. A single definitive extended craniofacial resection cannot be described (Fig. 83-8). Extensive tumors involving the anterior skull base, including certain tumors with involvement of the pterygoid plates, can be approached surgically, with the resection to include any and all of the structures outlined below. Each operation is individually tailored according to the extent and nature of the tumor to be excised.[18,19]

BONY EXCISION. The posterior line of resection is defined by the foramen ovale, the foramen rotundum, and the internal carotid artery. The excision may extend through the sphenoid sinus and up to the contralateral optic nerve. The remaining margins are those of the craniofacial frontoethmoidectomy and the radical maxillectomy.

SURGICAL APPROACH. A team consisting of a neurosurgeon and a head and neck surgeon should perform the extended craniofacial resection. A combination of coronal and anterior or lateral facial incisions is used for exposure. The closure is improved by inclusion of a split-galea flap or free tissue transfer to cover the dura.

BENEFITS. Thorough exposure and complete excision of otherwise unresectable tumors are the main benefits of extended craniofacial resection.

LIMITATIONS. In discussing the limitations of the craniofacial approach, Ketcham and Van Buren[8] cited clear-cut pterygoid plate erosion and cranial nerve invasion as indicators of unresectability. Even though this operation has extended the limit of surgical resection and in so doing has resulted in occasional cures, we must reiterate that it does not provide clear resection margins at the orbital apex, the nasopharynx, or the deep pterygoid space. Local control depends on the addition of aggressive adjuvant therapy.

Supplemental Management in Extended Craniofacial Resection

The boundary between resectability and unresectability for advanced skull base malignancy is ill defined. For reasons of palliation or for attempted cure, it is not uncommon for extended craniofacial resection to be performed for the resection of all grossly resectable tumors, with the understanding that at the most central margins of the resection there is a high probability of residual microscopic disease. In this setting, consideration of supplemental therapy is appropriate and it has a modest track record of success. In particular, using the surgical exposure as an opportunity to deliver localized supplemental irradiation is now a well-accepted technique. Intraoperative radiotherapy of the skull base has been documented as a technique to improve local control rates.[20,21]

Our unreported institutional experience with intraoperative iodine seed implantation at the University of Washington has been reviewed. Local regional control appears acceptable for tumors with indolent biologic behavior (such as adenoid cystic carcinoma). For patients with undifferentiated carcinoma and squamous cell carcinoma, the anticipated benefit for long-term survival is poor. Additionally, our experience has highlighted the risk of intracranial infection when radioactive seed implantation is used after previous irradiation. For this

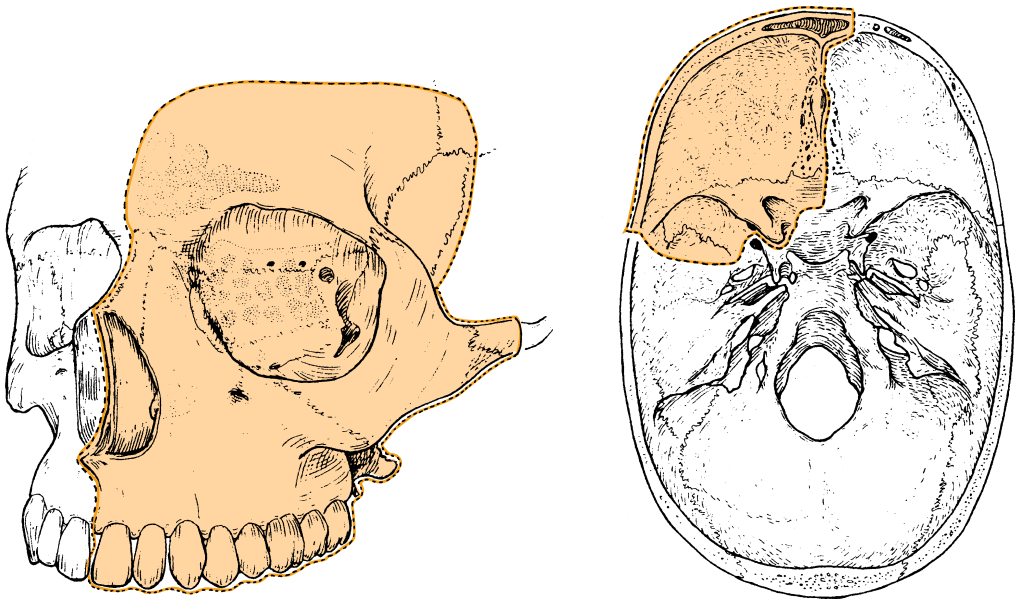

Figure 83-8. Craniofacial resection.

reason, our current posture is that whenever radioactive seeds are used as a supplement to previous irradiation, the skull base should be reconstructed with free tissue transfer to establish a highly vascularized and relatively thick separation between the airway and the intracranial contents.[22] Vikram and Mishra[23] offer support for this technique. Depending on the size of the defect, the radial forearm and rectus abdominis musculocutaneous flaps are best suited for this purpose because they are easily accessible, they provide the necessary soft tissue bulk to seal the defect, and they have sufficient pedicle length to reach recipient vessels in the neck from the skull base.

Minimally Invasive Approaches

Advancements in imaging combined with extensive experience with image-guided endoscopic surgery and new chemoradiotherapy regimens have significantly altered attitudes regarding the optimal approach to sinus malignancy. Multiple authorities have now published institutional series to document the value of endoscopic approaches. Common to all publications is a philosophy that includes endoscopic resection as one (but not the only) option to be considered in the management of individual patients. Small, purely endonasal tumors can be effectively managed endoscopically. Lesions that involve the perimeter of the sinonasal region (orbit and cranium) require consideration of combining endoscopic with the various open procedures described previously. In our experience, a surgical procedure that begins with endoscopic resection to define the truly involved areas, in combination with a flexible plan for a combined open approach (as dictated by the endoscopic findings), results in the least invasive and most accurate tumor resection. A similar surgical philosophy is reflected in a number of articles by others.[24-29]

Walch and colleagues[30] have utilized endoscopic sinus surgery, in combination with stereotactic radiosurgery, in the management of several cases of olfactory neuroblastoma. Stammberger and associates[31] also published a report on 43 destructive and invasive paranasal sinus lesions that were resected via an endoscopic approach and stated that "outcome is at least equal to standard external approaches." Kabil and coworkers[32] have also described a supraorbital endoscopic approach, although to date this has been limited to benign skull base tumors.

Intermediate Neoplasms

Inverted Papillomas

Inverted papilloma usually manifests as a polypoid unilateral nasal mass. On occasion these lesions may be found in association with allergic nasal polyps, accounting for the need in routine polypectomy to always submit labeled, separate specimens from each side of the nose. The histology consists of infolded epithelium that may be squamous, transitional, or respiratory. The incidence of frank malignant change approximates 10%.[33]

Even when not malignant, inverted papillomas must be treated with respect, because incomplete excision is likely to result in recurrence.[34] A lateral rhinotomy incision combined with medial maxillectomy to allow adequate margins is the classic approach. However, experience with endoscopic sinus surgery supports a less invasive approach. In carefully selected cases, inverted papilloma may be removed endoscopically. For example Sautter and associates[35] published a retrospective review of their experience at Cleveland Clinic Foundation of 68 patients with inverted papilloma.[35] These researchers reported the following recurrence rates: 22% in the endoscopically resected group, 39% in the open resection group, and 50% in "limited open cases."

Intermediate Neoplasms

Epithelial Malignancy

Staging

Staging is appropriately discussed only in the context of squamous cell tumors because the other lesions are so uncommon that they do not warrant such attention (or such confusion). As Harrison[36] has suggested, the staging system should allow differentiation between distinct stages of disease progression.

In 1933, Ohngren[7] emphasized the ominous importance of tumor spread in a posterior or superior direction. "*Ohngren's line*," described as an imaginary line extending from the medial canthus to the angle of the jaw, gives a rough estimate of the dividing line between tumors that may be resected with a good prognosis or a poor prognosis (Fig. 83-9). Ohngren[7] developed a staging system based on personal experience that included topography (tumor location and extent), histology (three grades), and cervical metastases (presence or absence). Tumors located below Ohngren's line involved fewer critical structures and were associated with a better survival rate than lesions arising above the line, which were more likely to involve important structures such as the orbit, optic nerve, and carotid artery. That the system was effective is borne out by this researcher's statistics, which clearly show a difference in rates of 3-year "freedom from symptoms" between groups I (82%), II (63%), and III (25%).

Other systems have been proposed by experienced surgeons. Each represents a personal variation of the generally accepted schemes, but they differ from one another sufficiently to make direct comparison of

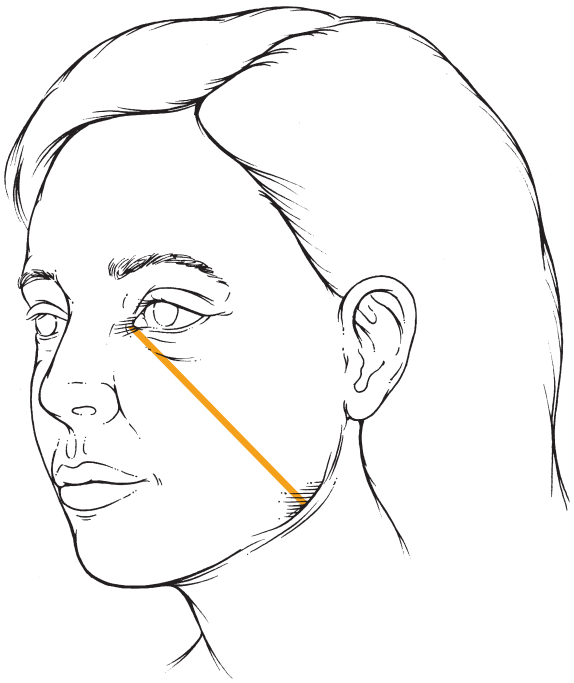

Figure 83-9. Ohngren's line—an imaginary line extending from the medial canthus to the angle of the jaw—gives a rough estimate of the dividing line between tumors that may be resected with a good prognosis (below the line) and with a poor prognosis (above the line). *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

results impossible, thus negating one of the primary goals of any staging system. The interested reader is referred to the article by Harrison[36] for further discussion and references.

According to the American Joint Committee on Cancer, staging of nasal cavity and paranasal sinus carcinomas is not as well established as for other head and neck tumors. For cancer of the maxillary sinus, the nasal cavity, and the ethmoid sinus, the Committee has designated staging by TNM classification (Box 83-1).[37] This system is well accepted, although an adjustment based on Harrison's[36] criticism of it should be seriously considered. In particular, he argued that orbital apex involvement and pterygoid muscle involvement should be placed in the T4 category. The 6th edition of the American Joint Committee on Cancer's staging manual does differentiate between resectable lesions (T4a) and unresectable lesions (T4b) of the maxillary sinus.[37]

Management

Definitive treatment has included surgery, irradiation, and electrocoagulation in varying combinations. Adjunctive chemotherapy has been introduced, but its impact on outcome is still uncertain.

Maxillary Sinus Tumors

Early (T1 and T2) lesions may be treated by surgical resection (maxillectomy) or irradiation. Although Wang[38] did not recommend definitive irradiation, he did report curing all of four patients with T2 maxillary sinus tumors with that modality alone. Bryce[10] has also stated that irradiation alone (5500 rad) is an effective way to manage early tumors but that 25% to 30% of patients will die of local recurrence.

The majority of patients have advanced (T3 or T4) disease when first seen, which most authorities agree requires combined therapy for optimal control.[10,14,38] Considerable variation exists within each reporting institution regarding the application of surgery and irradiation. All series are retrospective and present a mixture of patient populations, usually receiving the following types of management: surgery for cure, surgery with preoperative or postoperative irradiation, and irradiation with surgical salvage. This collection of retrospective data leaves one in a muddle, although some trends are becoming apparent.

Surgery Alone

Surgery alone is generally accepted as adequate management for tumors isolated to the antral mucosa. As stated previously, most investigators agree that T3 and T4 lesions require combined therapy. Terz and coworkers[39] have taken a more aggressive surgical posture and have reported dramatic improvement in survival for patients with T3 and T4 lesions when craniofacial resection was performed. According to these researchers, craniofacial resection achieved a remarkable 3-year disease-free survival of 72% (15 of 22 patients) among patients who had T3 or T4 tumors. The numbers are even more surprising when one realizes that irradiation was not used. However, reporting separately on patients from the same institution and the same time period, Amendola and colleagues[40] compared the outcome of 19 patients who underwent "radical craniofacial surgery" with that of 20 patients treated with megavoltage irradiation and a Caldwell-Luc procedure.[40] Their reported 3-year survival for the group undergoing radical craniofacial surgery was 37%, whereas that for the irradiated group was 50%. Were the surgical patients reported on by Terz and coworkers[39] identical to those reported on by Amendola and colleagues?[40] If so, how do we resolve the dichotomy of the reporting, and in what light should we hold any retrospective report concerning an uncommon disorder that is typically managed on an individual basis?

Surgical management should include consideration of immediate rehabilitation. This is usually best achieved with prosthetics that allow immediate restoration of function and yet are removable to allow inspection of the maxillary cavity. Preformed palatal plates may be used to support transoral packing in the postoperative period and may later be modified to occlude the oronasal defect. If one has access to a talented prosthetics department, the aftermath of a craniofacial-orbital resection can be reasonably well camouflaged.

Traditionally, reconstruction of maxillary sinus defects has been performed with skin graft and prosthetics. With the advent of free tissue transfer, more acceptable cosmetic reconstruction including rehabilitation of the bony hard palate for dental rehabilitation is now achievable. The fibula osteocutaneous flap has been shown to be a reliable method of midface reconstruction for lower maxillary defects. It allows for closure of the palate as well as placement of osseointegrated dental implants or implant-borne prosthetics.[41] However, this approach is of limited use when the orbitozygomatic support is the objective. In these instances, the scapula osteocutaneous flap is preferable. This flap has the advantage of better rotation of the soft tissue component around the bone, which allows for reconstruction of the orbital floor, palate, and zygoma.[42] Iliac crest osteomyocutaneous flaps can be used when additional soft tissue bulk and bone are required. Clearly one of the major potential risks is "covering recurrent disease"; however, because disease recurrence at this site, whether observed or not, is sometimes untreatable, this may be a moot point.

Combined Irradiation and Surgery

With T3 tumors, there is little survival difference between preoperative irradiation and postoperative irradiation. Postoperative irradiation often controls microscopically positive resection margins. With the more advanced lesions, especially those for which resectability is questionable, preoperative irradiation appears to be the procedure of choice. A planned preoperative dose of 5500 rad has been used successfully, followed by radical resection.[10] For patients in whom no tumor is found at operation, the 5-year survival is 77%; for those in whom tumor is found, 5-year survival is 23%; overall survival is 50%. For operable lesions (meaning those not extending to the nasopharynx, skull base, or pterygoid fossa), Wang[38] favored radical surgery to remove tumor bulk and establish drainage followed by irradiation using 5000 to 5500 cGy in 6 weeks.

Radiotherapy

Wang[38] took special care to shield the eye and the frontal lobe and reported a recurrence rate of 76% for 34 patients treated with irradiation alone.[38] In contrast, Ellingwood and Million[43] intentionally irradiated the orbit to include the probable routes of tumor extension within the irradiation field. Their cure rate of 71% suggested a successful regimen. However, all patients treated with this regimen lost vision in

Box 83-1

Staging of Paranasal Sinus Malignancies According to the American Joint Committee on Cancer

TNM Definitions

Maxillary Sinus

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
- T2: Tumor causing bone erosion or destruction including extension into the hard palate and/or the middle of the nasal meatus, except extension to the posterior wall of maxillary sinus and pterygoid plates
- T3: Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
- T4a: Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor restricted to any one subsite, with or without bony invasion
- T2: Tumor invading 2 subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
- T3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
- T4a: Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
- T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
  - N2a: Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension
  - N2b: Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
  - N2c: Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node >6 cm in greatest dimension

In clinical evaluation, the actual size of the nodal mass should be measured, and allowance should be made for intervening soft tissues. Most masses >3 cm in diameter are not single nodes but confluent nodes or tumors in soft tissues of the neck. There are 3 stages of clinically positive nodes: N1, N2, and N3. The use of subgroups a, b, and c is not required but is recommended. Midline nodes are considered homolateral nodes.

Distant Metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings

Stage 0

- Tis, N0, M0

Stage I

- T1, N0, M0

Stage II

- T2, N0, M0

Stage III

- T3, N0, M0
- T1, N1, M0
- T2, N1, M0
- T3, N1, M0

Stage IVA

- T4a, N0, M0
- T4a, N1, M0
- T1, N2, M0
- T2, N2, M0
- T3, N2, M0
- T4a, N2, M0

Stage IVB

- T4b, any N, M0
- Any T, N3, M0

Stage IVC

- Any T, any N, M1

Modified from Nasal cavity and paranasal sinuses. In: Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.

the treated eye. Amendola and colleagues[40] also documented a 3-year absolute survival of 55% for the use of an average of 6600 cGy for lesions that were primarily T4. The fields were angled posteriorly to avoid the contralateral optic nerve. No complications of irradiation were mentioned in this article, and the authors stressed the improved quality of life in patients undergoing irradiation for cure compared with those undergoing craniofacial resection.

Difficulties in the use of standard radiation therapy for paranasal sinus tumors arise from the fact that in air-filled spaces such as the sinuses, the range of particles and thus the dosimetry are subject to considerable uncertainty.[44] Treatment with conventional photon-beam technique using an anterior field and one or two wedged lateral fields either may cause significant morbidity to the eye and optic nerves or may result in significant under-dosing of portions of the posterior

ethmoid and maxillary sinuses. Improvements using conformal radiotherapy and intensity-modulated radiation therapy have allowed for more precise treatment of paranasal sinus tumors with sparing of binocular vision by improving the tumor-dose homogeneity while reducing the dose to the optic nerves and lenses.[45] These techniques allow for the treatment of tumors with large volumes and complex shapes in critical proximity to organs at risk, such as the eye and optic nerves. Although these techniques have yet to provide a therapeutic advantage (improved survival) over standard radiotherapy, they have the potential of offering better protection of adjacent normal structures.

Chemoradiotherapy

Perhaps the most significant variation from traditional management was reported by Sakai and colleagues.[14] They accumulated more than 780 patients from 1957 to 1983 at Kobe and Osaka Universities in Japan. Their cumulative experience demonstrated impressive results for their latest reported regimen, which consisted of 5000 cGy, continuous intra-arterial 5-fluorouracil infusion, tumor reduction (via the Caldwell-Luc procedure), and immunotherapy. In the years covered by this experience they observed an increase in 5-year survival from 20% (282 patients treated with 7000 cGy and maxillectomy, 1957-1966) to 54% (134 patients treated with the current regimen, 1976-1979). They simultaneously saw a substantial decrease in functional disability encountered by their patients.

An analogous regimen was reported from Rotterdam, Holland, with similarly encouraging results in a series of 60 patients (2-year survival, 76%; 5-year survival, 65%).[46] Several smaller studies have also demonstrated clinical benefit to the use of combined chemotherapy and radiation therapy. Using doses of 6920 cGy and adjuvant chemotherapy in responders, Fitzek and colleagues[47] demonstrated a local control rate of 88% in 19 patients with advanced neuroendocrine carcinoma of the sinonasal tract.Use of split-course concomitant infusion cisplatin chemotherapy with hyperfractionated radiotherapy in 21 patients with locally advanced nasopharyngeal and paranasal sinus tumors resulted in a local control rate of 94% without an increase in normal tissue injury.[48] In 33 patients with maxillary sinus carcinoma, 5-year survival rates of 86% for T3 lesions and 67% for T4 lesions were achieved by Nibu and associates,[49] who used 3000 to 4000 cGy of preoperative radiotherapy with concomitant intra-arterial infusion of 5-fluorouracil and cisplatin followed by 3000 to 4000 cGy of postoperative radiotherapy. Dramatic response with combined chemotherapy and irradiation appears to be possible even in the presence of bulky or unresectable disease, with acceptable complication rates and less morbidity than associated with craniofacial resection and conventional radiotherapy. Further study is necessary to refine this evolving therapeutic technique, because small single-institution studies have limited ability to draw definitive conclusions regarding these approaches.

Inoperable Neoplasms

Irradiation may be used to determine operability in tumors that initially appear inoperable. In this situation, Wang[38] delivered 6000 cGy in 6 weeks, with surgery to follow.He encouraged aggressive surgery if the response to irradiation appeared to make the lesion operable. If margins were subsequently positive, a further boost of local irradiation was considered. Interestingly, Wang[38] had better results in this group of patients with more advanced tumors (survival of 58% or 11 of 19 patients) than he did in those with smaller lesions, in which he favored surgery to be followed by irradiation (survival of 36%, or 5 of 14 patients). The rationale for treating patients with "curative" doses of irradiation when their lesions are initially inoperable is borne out by the number of long-term survivors seen in this group of patients.[38] This result is probably a manifestation of the heterogeneous nature of the "inoperable" patients; some are inoperable by virtue of tumor extent, whereas others either are medically unsuitable for surgery or have refused it outright.

Lee and coworkers[50] documented the potential value of intra-arterial infusion chemotherapy (5-fluorouracil) and simultaneous irradiation for initially inoperable tumors. They achieved an absolute 2-year survival of 50% in this group, which had a very poor prognosis. Survival dropped to 28% at 5 years. Unfortunately, optic nerve damage was fairly prevalent and caused bilateral blindness in two patients. The utilization of selective chemotherapy and irradiation for advanced tumors of this area has tremendous appeal when contrasted to the defects created by surgical ablation of lesions in the axial region of the skull.

Ethmoid, Sphenoid, and Frontal Sinus Tumors

Ethmoid, sphenoid, and frontal sinus tumors are especially likely to manifest at advanced stages. Tumor extension to the structures of the skull base can be expected at initial presentation in 50% of patients with these lesions.[43]

Assessment and management of ethmoidal carcinoma should be performed with a specific staging system in mind. The four-stage system introduced by Dulguerov and colleagues[1] has been modified and updated by the American Joint Committee on Cancer (see Box 83-1). This system is useful because it distinguishes tumors originating in the nasal cavity from those originating in the sinuses.[1,37] Management for esthesioneuroblastoma and adenocarcinoma is generally similar, based on craniofacial resection and postoperative irradiation when surgically feasible. The addition of chemotherapy to the management of advanced esthesioneuroblastoma (T3 and T4) is now well established, particularly in light of the experience of Spaulding and associates[51] at the University of Virginia.

In 2005 a large multi-institutional study, The International Collaborative Study, examined outcomes related to craniofacial surgery for malignant sinus tumors.[51a] This review of 334 patients revealed an overall 5-year survival rate of 48%, with craniofacial resection and multimodality therapy in a selection of these patients. Free surgical margins, intracranial extension, and histologic findings were independent predictors of survival. Suarez and colleagues showed similar findings in their review of 100 patients who underwent craniofacial resection for malignant sinus tumors.[51b] They showed 40% overall 5-year survival. Interestingly, positive surgical margins, orbital periosteum involvement, dura involvement, and frontal sinus invasion were not associated with increased mortality. Only tumor histology, brain involvement, deep orbit involvement, sphenoid sinus involvement, and previous treatment predicted decreased survival.

Ketcham and Van Buren's[8] argument for craniofacial resection in patients with malignancy extending to or primarily arising from the ethmoid sinus was presented and discussed earlier. En bloc tumor resection, improved assessment of disease extent, and better cosmesis provided the rationale for applying this technique. These researchers obtained a 5-year survival of 41% in a particularly challenging group of patients, many of whom were referred with advanced disease after failure of previous treatment. They also reported lower survival with preservation of the orbital contents (26%) than with orbital resection (57%). Further documentation of the techniques and applicability of craniofacial resection and its significant impact on improved local control and survival can be found in studies reported by Shah and associates,[17] Biller and coworkers,[52] and Panje and colleagues.[53]

Ellingwood and Million[43] stressed the importance of properly designed fields to include the whole orbit (when necessary) and skull base. Using primary irradiation, they achieved a 5-year actuarial survival of 59% and a 5-year survival with no evidence of disease of 50%. The incidence of major complications in this series was substantial; blindness occurred in every eye treated with irradiation of the whole orbit.

Primary carcinoma of the frontal sinus is a very uncommon entity. According to a review article by Brownson and Ogura,[54] the survival rate is 1 of 33 patients. One would anticipate improvement of these statistics as craniofacial resection and appropriately designed irradiation fields are used.

Involvement of Cervical Lymph Nodes

Involvement of cervical nodes occurs in about 25% to 35% of paranasal sinus tumors.[55] Most authorities agree that palpable cervical lymph nodes indicate a very poor prognosis.[12] In contrast, the experience of Shidnia[56] suggests that if neck disease is discovered at an early stage, it can be successfully managed with neck dissection. These researchers advise inclusion of the ipsilateral neck and preauricular area in the initial field of irradiation for T3 and T4 tumors.

Adenocarcinoma

Adenocarcinomas have an epidemiologic association with woodworking, furniture making, and leatherwork. They are more commonly found in the upper nasal cavity and ethmoid sinus and are usually lethal by virtue of local progression. In light of its propensity for aggressive local progression, adenocarcinoma should be treated in a surgically aggressive fashion with en bloc resection when possible.

In contrast to adenoid cystic carcinomas, adenocarcinomas have a relatively low incidence of distant metastasis, but the long-range survival is equally poor. There is a range of histologic differentiation. Patients with the poorly differentiated form have a 5-year survival no better than 20%,[33] whereas that for patients with well-differentiated papillary tumors is better.[54]

Adenoid Cystic Carcinoma

Adenoid cystic carcinomas occur with about the same frequency as adenocarcinomas but most commonly involve the antrum. They have a variable histologic pattern, and substantial biopsy tissue may be necessary before an accurate diagnosis can be established. Also part of the histologic picture is the propensity of these lesions for invasion along nerve sheath structures. Adenoid cystic carcinomas are more likely to express distant metastases than regional metastasis, although the most likely cause of death is relentless local progression at the skull base. Initially high cure rates (5-year survival of 75%) decrease as time goes on, with the Armed Forces Institute of Pathology Registry reporting a 15-year survival of 25%.[33]

More recently, the group at the M.D. Anderson Cancer Center reviewed 105 patients with adenoid cystic carcinoma of the paranasal sinuses and showed an overall 5-year survival rate of 70%.[56a] Orbital and infratemporal fossa involvement did not appear to affect survival.

Management relies on surgical resection, with irradiation added if the margins are in question.[38] Bryce[10] recommended using only one major modality (surgery or irradiation) at a time because the 5-year survival is good and late recurrence is virtually a certainty. This posture is based on a desire to hold a potentially effective treatment modality in reserve. One wonders whether this approach is treating the physician or the patient, because we do not know whether combined treatment decreases the recurrence rate or increases the disease-free interval. A contrasting opinion was offered by Horree,[57] who has recommended "three-modality therapy," including regional infusion with 5-fluorouracil, maxillary resection, and then irradiation. Neoplasms representing the entire spectrum of salivary gland malignancy have been reported to occur in the paranasal sinuses but are not discussed here.

Analysis of experience gained in the few centers that provide neutron irradiation has demonstrated improved local control in the management of salivary gland neoplasms. When confronted with an adenoid cystic carcinoma, and particularly one that is otherwise untreatable, the use of neutron beam irradiation should be seriously considered.[58,59]

Complications

The incidence of complications increases significantly when surgery breaches the intracranial space and also when high doses of irradiation are delivered to the orbit or intracranial contents. Major complications of surgery of paranasal sinus tumors are decreased by the use of perioperative antibiotics and by careful attention to dural closure, including the use of pericranial flaps. The most significant complications are meningitis, brain abscess, cerebrospinal fluid leak, and postoperative wound hemorrhage.

Cataracts are the most common complication of sinus radiotherapy. Other irradiation-induced lesions include osteoradionecrosis, keratitis, optic neuritis, and hypopituitarism. Injury to the optic nerve is made more likely with greater fraction size (250 cGy/fraction) and total dose.[38] Conformal radiotherapy and intensity-modulated radiation therapy techniques have reduced the incidence of these complications when treatment portals are in close proximity to the orbit and optic nerve. After high-dose irradiation using fields that include the whole orbit, one can expect loss of vision in 100% of cases.[43]

Therapeutic Decision-Making

Taking into consideration the data reviewed here, we make the following generalizations regarding therapy for advanced disease:

1. Most tumors are at an advanced stage when first recognized and require aggressive multimodality treatment.

2. Survival and local disease control are better when the orbit is included in the therapeutic plan (i.e., exenteration or irradiation).

3. A significant chance of metastasis to the primary (pharyngeal) and secondary (cervical) nodes exists. They should be included in the primary treatment plan.

4. Higher success rates have been reported with primary irradiation, and the associated functional and cosmetic impairment seems to compare favorably with that of surgery.

5. The best regimen may prove to be a combination of chemotherapy, irradiation, and limited surgical débridement. This, of course, requires the availability of sophisticated equipment and a cooperative effort by a multidisciplinary team.

6. The concept of intra-arterial chemotherapy for advanced skull base tumors was advocated by Lee and coworkers[50] and may see continued consideration on the basis of the experience of Robbins and associates,[60] who have pioneered the use of intra-arterial cisplatin with thiosulfate rescue and concomitant radiotherapy.

Sarcomas

Osteogenic sarcomas and chondrosarcomas of the facial skeleton are encountered more commonly in the mandible than in the maxilla. They are usually lethal by virtue of relentless local progression. In that light, the most successful therapy is based on wide en bloc resection, with 5-year survival being in the range of 10% to 20%. Irradiation seems to be an effective adjuvant for both tumors. DeFries and Kornblut[61] reported a survival of 30% with induction chemotherapy, preoperative irradiation, and wide-field ablative surgery. The multi-institutional analysis of outcome from neutron beam irradiation has identified facial sarcoma as a condition in which significant improvement was achieved. Neutron beam irradiation, when available, should be considered especially in the management of surgically unapproachable or unresectable lesions.[62]

Hyams[33] characterized a well-differentiated form and a poorly differentiated form of fibrosarcoma. One must consider the diagnosis of aggressive fibromatosis when evaluating a fibrous tumor in young adults. All tumors in this group require en bloc excision for optimal management.

Hematopoietic and Lymphoid Tumors

The paranasal sinuses are an uncommon primary site for lymphomatous tumors, but any of the multiple subtypes may occur. Because subtyping determines both the therapy and the prognosis, the most important role of the otolaryngologist is to provide adequate tissue in good condition for histologic processing. If a lymphoma is suspected, the pathology department should be notified before the biopsy is performed so that fresh specimens for flow cytometry, as well as permanent fixation, may be properly managed for subtyping and immunohistochemistry analysis.

Treatment is usually with chemotherapy, although irradiation alone is adequate for stage I and stage II Hodgkin's disease.[38]

Malignant Melanoma

Melanomas of the paranasal sinuses are usually advanced at the time of discovery. In addition to symptoms typical of sinus tumors, the patient may note a black nasal discharge and have a pigmented mass within the nose. Nonmalignant melanomas have been reported in up to 10% of cases. Frequently regional or distant metastases exist at the time of initial examination. In the Armed Forces Institute of Pathology series, the 5-year survival was 11% and the 20-year survival was 0.5%, with a mean survival of 2.3 years.[33] Although aggressive surgical removal is

the standard of care, it is obviously not very effective. Irradiation has been considered inadequate, but adjustments in fractionation may provide better results, as suggested by Berthelsen and associates,[63] who achieved local control in three of six patients with nasal melanomas treated with primary irradiation.

The Mayo Clinic reviewed a series of patients in 2008, and the study showed similar poor survival for mucosal melanoma of the paranasal sinuses.[63a] Their experience revealed an overall 5-year survival of 22%.

Paranasal Sinus Neoplasms in Children

Sinus tumors in children are usually benign. The common nasal sinus tumors of children are polyps arising on an allergic basis or in association with cystic fibrosis. The most common neoplasms are fibro-osseous lesions and tumors of dental origin. Mucoceles and hemangiomas are less frequently encountered. Embryonal rhabdomyosarcoma is the predominant paranasal malignancy.

Tumors should be assessed radiographically as discussed earlier. The diagnosis should be established by a transnasal biopsy, and a generous tissue sample should be submitted for pathologic study because special stains and electron microscopy may be necessary.

Most pediatric neoplasms are managed surgically because (1) most lesions are radioinsensitive, (2) irradiation in excess of 3000 rad has a substantial effect on growth of the facial skeleton, and (3) there is a significant risk of radiation-induced malignant transformation or secondary malignancies. Surgery should be designed to respect the developing tooth buds and facial growth centers in the palate, nose, and zygomatic process of the maxilla. The tendency is toward conservative local resection, especially with tumors of dental origin, but some lesions require en bloc resection for a curative effort.

Monostotic fibrous dysplasia is a lesion considered to be a developmental defect of bone. As such, it is most common in children and is more common in the maxilla than in the mandible. According to Schramm,[64] unlike most bony and odontogenic tumors, fibrous dysplasia sometimes requires wide local removal, including partial maxillectomy, to achieve clear margins. Resection causing a major functional or cosmetic deformity (orbital exenteration, mandibulectomy) is not often warranted. Ossifying fibromas and cementomas, in contrast, are well delineated and may be managed by local excision with minimal margins.

Rhabdomyosarcomas are the most common malignant neoplasm of the upper respiratory tract in the pediatric age group (age 15 or younger) in the Armed Forces Institute of Pathology records.[33] The tumor is aggressive, demonstrating rapid progression and dissemination. According to Hyams,[33] the histologic subcategories of juvenile rhabdomyosarcoma (alveolar, botryoid, and embryonal) have no relevance to the neoplasm's clinical behavior or the prognosis, whereas Maurer and colleagues[65] had suggested an unfavorable prognosis for cytologic anaplasia or monomorphous round cell patterns. The best survival is obtained with clear surgical margins supplemented by irradiation and chemotherapy. Maurer and colleagues[65] evaluated results from 157 nonorbital and 54 orbital rhabdomyosarcoma cases. They found patients with parameningeal involvement (as indicated by CT evidence of skull base erosion or cerebrospinal fluid analysis demonstrating pleocytosis as well as elevated protein and decreased glucose values) to have a poor prognosis. This group of patients has benefited by a treatment regimen combining intrathecal chemotherapy and craniospinal irradiation.

A report by Callender and associates[66] spanning 36 years showed that patients younger than 23 years had a 58% 5-year survival, compared with 32% for older patients. When adults and pediatric patients were combined in an analysis of treatment, the researchers found 60% 5-year survival for chemotherapy and irradiation (with or without surgery) compared with 19% for all other single-modality treatments.

Patients with a circumscribed local tumor and no evidence of distant metastases have an excellent prognosis when treated with multidrug chemotherapy and adjuvant irradiation. In most instances radical ablative surgery is not considered necessary to achieve a successful outcome.[65]

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Salivary Glands

CHAPTER EIGHTY-FOUR

Physiology of the Salivary Glands

Ravindhra G. Elluru

Key Points

- Importantly, our current understanding of salivary gland physiology is largely derived from the study of nonhuman salivary glands.
- Saliva is a complex mixture of electrolytes and macromolecules secreted from three pairs of major and numerous minor salivary glands.
- The basic unit of the salivary gland consists of an acinus, a secretory duct, and a collecting duct.
- Saliva is formed via active transport processes occurring throughout the secretory unit, and these processes are under the control of complex neuronal and hormonal signals.
- The innervation patterns of the major salivary glands differ considerably, from species to species, subject to subject, and cell type to cell type.
- The neurotransmitter acetylcholine mediates the effects of the parasympathetic nervous system, whereas norepinephrine mediates the effects of the sympathetic nervous system.
- Salivary flow rates are highly variable, stabilizing after the age of 15 years, and therefore should be interpreted in a clinical context.
- Salivary secretion is controlled by a salivary center in the medulla, which is triggered by specific stimuli: (1) the mechanical act of chewing, (2) gustatory, and (3) olfactory.
- Salivary function can be organized into five major categories that serve to maintain oral health and maintain homeostasis: (1) lubrication and protection, (2) buffering and clearance, (3) maintenance of tooth integrity, (4) antibacterial activity, and (5) taste and digestion.
- Dry mouth is a common complaint in the geriatric population and is commonly believed to arise from age-associated intrinsic salivary gland dysfunction.

Throughout the history of science, the salivary glands have been a topic of keen biologic interest and questions regarding their mechanisms of function have spurred numerous research endeavors. As early as 160 AD, Galen described the position of the major and minor salivary glands and their respective ductal openings. In 1543 Vesalius published a more detailed anatomic description of the salivary glands in a monograph entitled *De Humani Corporis Fabrica.* Interestingly, however, before the 17th century the salivary glands were thought to serve only as emunctories, the function of which was to strain excrementitious substances such as the evil spirits of the brain from the blood. Fortunately, the fortitude and dedication of scientists such as Boredu, Ludwig, Langley, Haller, Heidenhain, Mueller, Baylis, Bernard, and Pavlov allowed this notion to be dispelled and the field of salivary gland physiology to be advanced.[1] Recent technologic advances, along with a new generation of scientists, have brought this field even further, expanding our knowledge of the mechanisms of salivary gland function, disease processes that impede normal gland function, and methods by which to restore homeostasis in a diseased gland. Importantly, our current understanding of salivary gland physiology is largely derived from the study of nonhuman salivary glands.

Saliva is a complex mixture of electrolytes and macromolecules secreted from three pairs of major and numerous minor salivary glands. The major salivary glands consist of the parotid, submandibular, and sublingual glands. The minor salivary glands line the mucosa of the lip, tongue, palate, and pharynx. The secretion of saliva is tightly modulated by a multitude of factors including the autonomic nervous system, humoral factors, and disease states. Saliva performs a number of diverse and crucial roles: (1) It provides lubrication that aids in swallowing; (2) it is an emulgent that aids in the digestion of food and enzymatic cleavage; (3) it produces hormones, hormone-like substances, and other metabolically active compounds; (4) it assists excretion of endogenous and exogenous materials such as antibodies, blood-group reactive substances, iodine, and viruses; (5) it mediates taste sensations; and (6) it provides defense against bacterial pathogens. Relative to size, the salivary glands produce a large volume of saliva. The maximal rate of saliva production in humans is about 1 mL/min/g of glandular tissue. The rate of metabolism and blood flow to the salivary glands is also high, proportional to the rate of saliva secreted. To put this in perspective, the flow of blood to a maximally secreting salivary gland is approximately 10 times greater than the flow of blood to an equal mass of actively contracting skeletal muscle.[2] This chapter provides a detailed discussion of the various aspects of salivary gland function and physiology.

Principles of Salivary Gland Secretion

Anatomy of the Secretory Unit

The basic unit of the salivary gland consists of an acinus, a secretory duct, and a collecting duct (Fig. 84-1A and B). In general the area of the acinus and proximal secretory duct is called the *secretory endpiece.* The secretory duct is composed of the intercalated and striated ducts, which are intralobular. The excretory and collecting ducts are

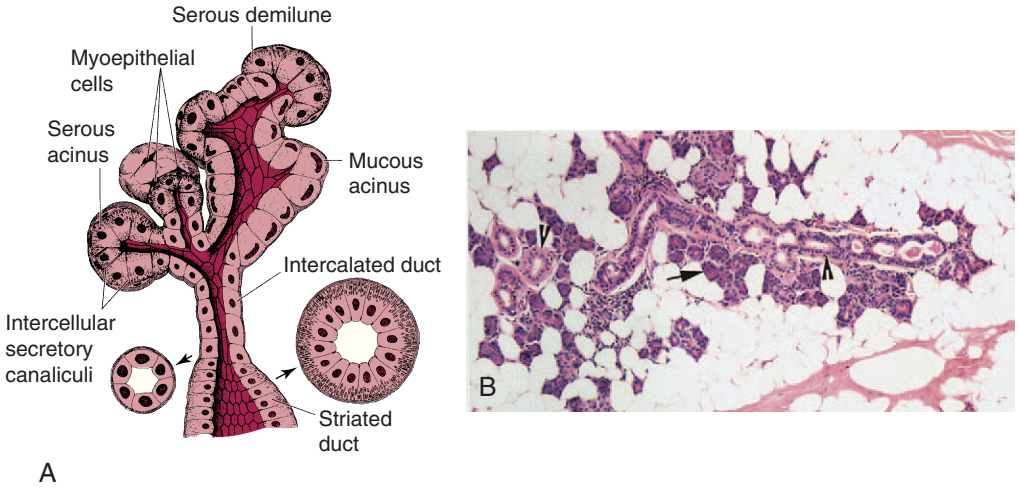

Figure 84-1. **A,** Schematic representation of a normal secretary unit. **B,** Histologic section of a normal salivary gland. Normal appearance of the ducts (*arrowhead*) and acini (*arrow*) under low power magnification (×10). (***A,*** *Reproduced with permission from Ganong WF.* Review of Medical Physiology. *New York: McGraw Hill; 1999:473).*

Table 84-1

Contribution to Saliva and Relative Viscosities of Saliva by Salivary Glands

Gland	Acinar Type	Viscosity	Percentage of Whole Unstimulated Daily Saliva
Parotid	Serous	Watery	25
Submandibular	Mixed	Semiviscous	71
Sublingual	Mucous	Viscous	3-4
Minors	Mucous	Viscous	Trace

From Mandel ID. Sialochemistry in diseases and clinical situations affecting salivary glands. *Crit Rev Clin Lab Sci.* 1980;12:321.

extralobular. The structural relationships and secretory capabilities of secretory units within different salivary glands differ widely. The parotid and submandibular glands have a single, elongated, large-caliber collecting duct, with only a few major branching interlobular ducts. These interlobular ducts in turn are connected to many intralobular ducts, each of which transports saliva from several acini. In contrast to the parotid and submandibular glands, the secretions of the sublingual gland are discharged through 10 to 12 separate collecting ducts. The minor salivary glands, which are essentially groups of individual secretory units, are distributed throughout the submucosa of the oral cavity and have short convoluted collecting ducts.[2]

The acinus comprises a central lumen surrounded by pyramidal-shaped cells (see Fig. 84-1A and B). These acinar cells are highly polarized and are bounded by a plasma membrane with two distinct domains, a basolateral domain and an apical domain. These two domains are functionally and physically separated by tight junctions that link adjacent cells just below the luminal area. Each acinus is surrounded by a layer of myoepithelial cells, which in turn is delimited by a distinct basement membrane layer. Myoepithelial cells are elongated or star-shaped nonsecreting cells with long-branching processes that surround the acinus and proximal ducts. The observation that myoepithelial cells possess adenosine triphosphate activity, have intercellular gap junctions, and contain myofilaments has led to the hypothesis that these cells have contractile properties and play a role in expelling preformed secretions.[3-5]

Acini are classified as serous, mucous, or mixed (Table 84-1). Serous acini contain pyramidal-shaped cells with round basal nuclei surrounding the lumen. The cytoplasm of the serous cells is densely packed with basophilic secretory granules, poised to discharge their contents into the acinar lumen. The number of these granules varies with the phase of secretory activity, decreasing after a period of secretion and reaccumulating following a period of synthesis. Mucous acini have a larger lumen than serous acini, and the cells surrounding the lumen have a clear cytoplasm, flattened basal nuclei, and numerous droplets of mucigen, which is the precursor of mucin. In mixed salivary glands, acini are composed of both serous and mucinous cells. Mucinous cells are found surrounding the lumen of the acini, whereas serous cells are found near the fundus of the acini forming a caplike structure, called a *serous demilune.*[6]

The acinus is contiguous with the intercalated duct, a hollow structure lined by a single layer of small cuboidal cells (see Fig. 84-1A and B). A layer of myoepithelial cells surrounds these cuboidal cell–lined ducts, similar to acini. The intercalated ducts continue as striated ducts, which are lined by columnar cells and have a brush border composed of microvilli on their luminal surface. Striated ductal cells also have prominent basal striations formed by infoldings of the plasma membrane that enclose columns of rod-shaped mitochondria. The high-energy characteristics of these cells suggest that they are involved with the transport of ions and water. The striated ducts lead into excretory ducts, which are lined by two layers of epithelium, a layer of flat cells surrounding the ductal lumen, and an outer layer of columnar cells.[6,7]

Secretory Process

Saliva consists of a complex mixture of electrolytes and macromolecules. It is now known that saliva is formed via active transport processes occurring throughout the secretory unit and that these processes are under the control of complex neuronal and hormonal signals. The secretory unit consists of two anatomically and functionally distinct regions: the acinus and the secretory duct. The acinus is the site of all fluid generation and most (≈85%) exocrine protein secretion.[7] The fluid component is derived from the local vascular bed in the form of an isotonic solution and secreted into the acinar lumen. This primary secretion traverses the ductal system before emptying into the mouth. In contrast to the water-permeable cells of the acinus, ductal cells are water impermeable. Most of the sodium (Na^+) and chloride (Cl^-) in the primary secretion is reabsorbed in the duct, and a small amount of potassium (K^+) and bicarbonate (HCO_3^-) is secreted. In addition, some proteins are added to the salivary fluid as it traverses the secretory duct.

By the time the saliva enters the mouth, it has generally been rendered hypotonic (≈25 mEq/L NaCl). The electrolyte composition of saliva, however, can be influenced by salivary flow rates. The reabsorption of salivary sodium and chloride is directly related to these rates, with decreased reabsorption and increased salivary concentrations of electrolytes with increasing salivary flow rates. Potassium reabsorption is independent of flow rates.[8,9]

Mechanisms of Primary Fluid Secretion

Fluid transport in salivary glands is thought to be driven osmotically in response to transepithelial salt gradients. These salt gradients are generated by ion transport systems localized to the luminal and basolateral membranes of the acinar cell. On the basis of studies in rabbit and rat salivary glands, three mechanisms for primary fluid secretion by the acini have been proposed. These mechanisms (Fig. 84-2) appear to operate concurrently in the same gland, and possibly in the same acinar cell. The relative importance of each of these mechanisms varies from species to species, gland type to gland type, and possibly from physiologic status to physiologic status.

Fluid secretion in the acini is the result of the combined action of four membrane transport systems: (1) a $Na^+ - K^+ - 2Cl^-$ cotransporter located in the basolateral membrane of the acinar cell; (2) a calcium (Ca^{++})-activated K^+ channel in the basolateral membrane; (3) a calcium-activated Cl^- channel localized to the apical membrane; and (4) an adenosine triphosphatase (ATPase)-driven Na^+/K^+ pump in the basolateral membrane. In the resting or unstimulated state, both K^+ and Cl^- are concentrated in the acinar cell above the electrochemical equilibrium, the former by the Na^+/K^+ ATPase and the latter via the $Na^+ - K^+ - 2Cl^-$ cotransporter.[9,10]

In the first mechanism of saliva secretion (see Fig. 84-2A), stimulation by the autonomic nervous system leads to a rise in intracellular calcium concentration, which results in the opening of the basolateral Ca^{++}-activated K^+ channels and the apical calcium-activated Cl^- channels. This increase in K^+ and Cl^- conductance allows KCl to flow out of the cell, resulting in an accumulation of Cl^- ions and their associated negative electrical charge in the acinar lumen. Sodium in the interstitium then follows Cl^-, due to electrical attraction, by leaking through the tight junctions between the cells into the acinar lumen. The resulting osmotic gradient for NaCl causes a transepithelial movement of water from the interstitium into the acinar lumen. In the continued presence of the agonist, a net transepithelial chloride flux and a concomitant secretion of fluid are sustained due to Cl^- entry via the $Na^+ - K^+ - 2Cl^-$ cotransporter and exit via the apical Cl^- channel. When the stimulus is removed, the intracellular calcium concentrations fall to resting levels, the K^+ and Cl^- channels close, and the cell returns to its resting state. In order for this model to operate continuously, it must satisfy the constraints of mass and charge balance. In other words, in the steady state ion transport must be such that neither mass nor charge is continually accumulated in or depleted from the cell. These constraints, along with the known stoichiometries of the $Na^+ - K^+ - 2Cl^-$ cotransporter ($1Na^+ : K^+ : 2Cl^-$) and the Na^+/K^+ ATPase ($3Na^+ : 2K^+ : 1ATP$), determine the relative fluxes of ions per cycle: Six chloride ions are translocated from the interstitium to the acinar lumen per ATP molecule hydrolyzed by the Na+/K+ ATPase.[9]

Mechanism 2 (see Fig. 84-2B) is similar to mechanism 1, except that in this model a basolateral Cl^-/HCO_3^- exchanger, in parallel with an Na+/H+ exchanger, replaces Na+ – K+ – $2Cl^-$ cotransporter. Decreases in intracellular chloride concentrations resulting from secretagogue-induced KCl loss lead to increased Cl^- entry in exchange for HCO_3^- via the $Cl^-/HCO3^-$ exchanger. The cytoplasmic acidification resulting from this bicarbonate loss is buffered by the Na+/H+ exchanger, which uses the extracellular-to-intracellular sodium gradient generated by the Na^+/K+ ATPase to drive protons out of the cell. The net result is the movement of NaCl into the cell in exchange for H_2CO_3, which in turn is recycled across the basolateral membrane as CO_2 after hydrolysis by carbonic anhydrase. In this model, three chloride ions are translocated from the interstitium to the acinar lumen per ATP molecule hydrolyzed. Sodium and water follow the chloride into the acinar lumen from the interstitium.[9]

In contrast to mechanisms 1 and 2, in which chloride is the secreted anion, mechanism 3 (see Fig. 84-2C) involves apical bicarbonate secretion. In this model, carbon dioxide (CO_2) enters the acinar cell across the basolateral membrane and is converted to HCO_3 plus a proton by carbonic anhydrase. The bicarbonate is lost across the apical membrane via an anion channel, possibly the same channel involved in chloride secretion, and the protein is extruded by the basolateral Na^+/H^+ exchanger. In this model, three bicarbonate ions are secreted per ATP molecular hydrolyzed. Sodium and water follow the secreted bicarbonate ions into the acinar lumen.[9]

Mechanisms of Primary Macromolecule Secretion

The protein subcomponent of saliva is derived primarily from secretory granules of the acinar and ductal cells. Secretory proteins are discharged into the lumen of the secretory unit by a process of exocytosis, wherein fusion of secretory granules with a delimited portion of the plasmalemma of the apical membrane occurs. The membrane fusion is the last of a series of steps required for the transfer of export proteins from their synthesis in the rough endoplasmic reticulum (RER) to the extracellular environment. According to the model by Palade, the secretary process can be divided into six steps: (1) synthesis, (2) segregation, (3) intracellular transport, (4) concentration, (5) intracellular storage, and (6) discharge.[11]

The synthesis of secretory proteins requires the uptake of amino acids by the cell, which is accomplished via an active transport mechanism in the basolateral surface of the cell. Transfer ribonucleic acids (tRNA) then deliver the amino acids to the ribosomes of the RER, where messenger ribonucleic acids (mRNA) are translated into polypeptides. Before transport of these polypeptides from the RER to the Golgi

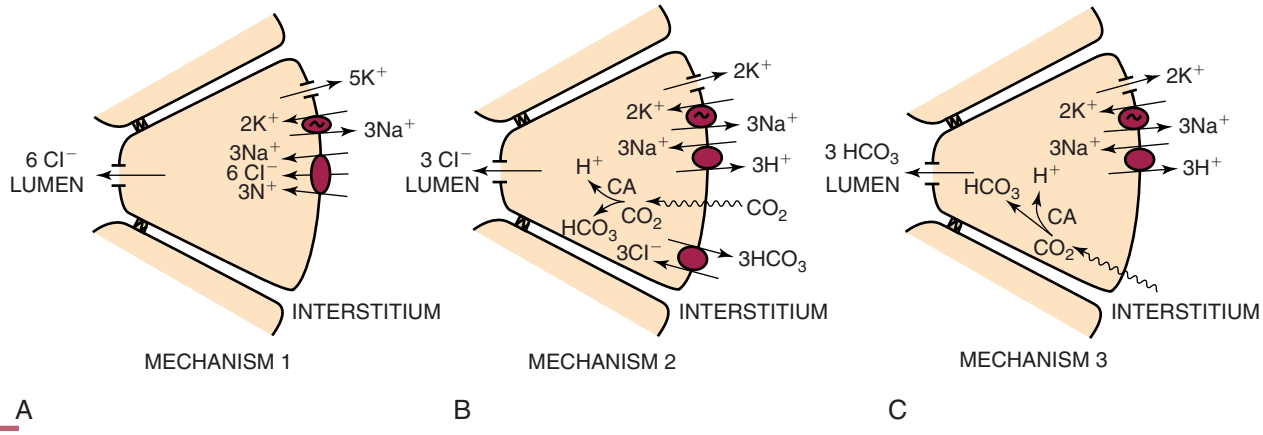

Figure 84-2. Schematic representation of three mechanisms of primary fluid secretion in acinar cells. *(From Turner RJ. Mechanisms of fluid secretion by salivary glands.* Ann N Y Acad Sci. *1993;694:24.)*

apparatus, they undergo some post-translational modifications and are segregated in the cisternal space of the RER. Segregation is regarded as an irreversible step. From the RER, polypeptides are transported to the Golgi apparatus via an ATP-dependent mechanism. In this apparatus, polypeptides undergo further post-translational modifications such as terminal glycosylation and are concentrated. At this step the polypeptides are transferred from a high-permeability membrane to a membrane with characteristics similar to the plasmalemma, forming secretory granules. On appropriate stimulation from the autonomic nervous system (discussed later), the secretory granules discharge their contents into the glandular lumen by the process of exocytosis. The membrane of the secretory granule fuses with the plasmalemma, bringing into continuity the contents of the secretory granule and the extracellular lumen, and at the same time maintaining a diffusion barrier between the interior of the cell and extracellular medium. The mechanism by which the cell recycles the apical membrane is not completely understood but likely involves the process of endocytosis and the selective degradation of endocytic vesicles.[12]

Mechanisms of Ductal Secretion

Ductal secretion is not constant and the underlying mechanisms are only partially understood. Microperfusion studies of excretory ducts have confirmed the ability of ductal cells to modify saliva by reabsorbing sodium and chloride and secreting potassium and bicarbonate to produce the final hypotonic solution.[13] In addition, ductal cells have the ability to secrete some protein into the ductal lumen. In general, when the salivary flow rate is slow, more time is available in which ion transfer can occur across the tubular cells, resulting in greater modification of the secretory fluid. When the flow rate is high, however, the contact period is shortened, diminishing the influence of the tubular cells on solute concentration. The exception to this rule is that conditions that stimulate increased flow rates also stimulate increased bicarbonate secretion.[2,6]

Neuronal Control of Secretion

In general, significant secretion from the human salivary glands occurs only in response to stimulation by the autonomic nervous system or by the action of substances that can mimic the effects of such stimulation.[14] Both sympathetic and parasympathetic nerves innervate the salivary glands, though the effects of the parasympathetic nerves predominate. Nevertheless, it is likely that the two components of the autonomic nervous system have a synergistic effect on salivary gland function. Parasympathetic stimulation is the principal impetus for salivary gland fluid secretion. In addition, parasympathetic stimulation leads to some exocytosis and protein secretion, myoepithelial contraction, and vasodilation. Sympathetic stimulation is a weak mobilizer of salivary fluid, though its effect may be additive to that of the parasympathetic system. On the other hand, sympathetic stimulation causes high levels of protein secretion, myoepithelial contraction, and maintenance of vascular tone. In general, parasympathetic stimulation leads to the output of saliva that has a large volume and low protein content, whereas sympathetic stimulation leads to the secretion of low volumes of saliva with high protein content.[2,6,12]

The innervation patterns of the major salivary glands differ considerably, from species to species, subject to subject, and cell type to cell type. The parasympathetic supply to the parotid gland originates in the inferior salivatory nucleus and travels with the glossopharyngeal nerve, and then with Jacobson's nerve to the otic ganglion, where it synapses. The postganglionic fibers are carried by the auriculotemporal branch of the trigeminal nerve to the parotid gland. The parasympathetic supply to the submandibular gland originates in the superior salivatory nucleus and travels via the nervus intermedius and chorda tympani to the submandibular ganglion. Some of these fibers synapse in the ganglion, whereas others synapse in the gland itself. The sympathetic supply to the parotid and submandibular gland originates from the superior cervical ganglion and follows major arterial blood vessels to reach the various salivary glands. Nerve fibers of the parasympathetic and sympathetic nervous system are distributed in a similar fashion around the acini, intercalated ducts, and striated, though the parasympathetic fibers predominate.[15] Myoepithelial cells are similarly liberally innervated, whereas the collecting ducts are sparsely innervated. In contrast to other organ systems such as skeletal muscles, which contain a well-defined neuronal synapse at the axon-effector organ interface, secretory cells have unmyelinated fibers of the parasympathetic and sympathetic system that lie in close proximity to the effector cell. These axonal fibers can lie either outside (epilemmal fibers) or inside the basement membrane (hypolemmal fibers) of the effector cell.[16] Neurotransmitters released from the axon presumably reach the secretory cell by diffusion. These neurotransmitters, as well as other hormones and regulatory molecules, affect the function of salivary cells in a complex manner that is poorly understood.

Neurotransmitters and Receptors

Cell surface receptors are macromolecular moieties within the cell membrane that bind ligands such as neurotransmitters in the extracellular milieu. Ligand binding activates the receptor, which then transmits a signal across the cell membrane and triggers a biologic response within the target cell (Fig. 84-3). The biologic response can be initiated directly by the receptor or, more commonly, mediated through a second messenger system activated by the receptor-ligand complex. The specific biologic response initiated and the magnitude of the response is a function of the receptor itself and not the ligand with which it binds. Receptors for neurotransmitters are typically located on the basal and lateral surfaces of the secretory cells of the salivary gland.

The neurotransmitter acetylcholine mediates the effects of the parasympathetic nervous system, whereas norepinephrine mediates the effects of the sympathetic nervous system. Adrenergic receptors, receptors for norepinephrine, are divided into two major classes, alpha and beta. Each alpha and beta class is further divided into two subtypes, yielding α_1 and α_2 and β_1 and β_2 receptors (Table 84-2).[17] The best-studied acinar cells, those of the rat parotid gland, appear to have all four subtypes of adrenergic receptors, though in general the functionally important receptors appear to be the α_1 and β_1 subtypes. The β_1 and β_2 receptors are linked to the adenylate cyclase second messenger system, and binding of ligand to this receptor activates adenylate cyclase. Alpha-2 receptors are also linked to the adenylate cyclase system; however, binding of ligand to this receptor leads to the inhibition of adenylate cyclase. Alpha-1 receptors are linked to a yet uncharacterized second messenger system that does not regulate adenylate cyclase but instead modulates calcium influx.[7]

Cholinergic receptors, receptors for acetylcholine, are divided into two categories: muscarinic and nicotinic. Acinar cells contain only muscarinic receptors, specifically the muscarinic receptor M_3 subtype. Binding of acetylcholine to the M_3 receptor leads to activation of the phospholipase C pathway and ultimately intracellular calcium mobilization. Recent evidence suggests the presence of two additional subtypes of muscarinic receptors in the rat submandibular and sublingual gland, M_1 and M_5.[18] The effect of these two receptors on acinar cell

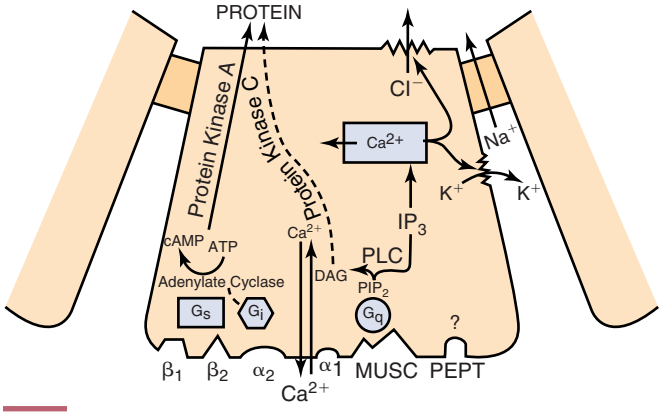

Figure 84-3. Schematic representation of acinar cell receptors and second messenger systems. *(From Baum BJ. Principles of saliva secretion.* Ann N Y Acad Sci. *1993;694:17.)*

Table 84-2

Localization and Mechanism of Action of Salivary Adrenergic Receptors

	α1	α2	β1	β2
Physiologic Response	Smooth muscle contraction in blood vessels	(1) Smooth muscle contraction in selected vascular bed (2) Inhibits release of norepinephrine (3) Stimulates secretion of K^+ and H_2O	Stimulates amylase secretion	(1) Smooth muscle relaxation (2) Assists release of norepinephrine
Location	Postsynaptic	Presynaptic, postsynaptic and without synapse	Postsynaptic	Presynaptic, postsynaptic, and without synapse
Mechanism	Changes of cellular Ca^{++} fluxes	Inhibition of adenylate cyclase	Stimulation of adenylate cyclase	Stimulation of adenylate cyclase

Data from Lefkowitz RJ, Stadel JM, Cerione RA, et al. Structure and function of beta-adrenergic receptors: regulation at the molecular level. *Adv Cyclic Nucleotide Protein Phosphorylation Res.* 1984;17:19.

function and the mechanism by which these effects are mediated are unclear at this point. Some of the effects of the M_1 receptor on salivary gland function may be indirect via nitric oxide.[7]

Parasympathetic-mediated nonadrenergic, noncholinergic secretory response and vasodilation are well-known phenomena in salivary glands, and a number of polypeptides including neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), galanin (GAL), substance P (SP), and calcitonin gene-related peptide (CGRP) have been implicated in mediating this pathway.[19] NPY-, VIP-, and GAL-immunoreactive nerve fibers are densely distributed around acini and ducts. CGRP- and SP-immunoreactive fibers are also found around these structures, but to a lesser extent. Interestingly, the density of SP- and CGRP-immunoreactive fibers around the mucous acini was significantly higher than around serous acini. The VIP system is the best studied of these polypeptide neurotransmitters in salivary glands and is similar to what has been described in the gut and pancreas.[8] Currently, the role of these different polypeptide neurotransmitters in salivary gland function is speculative; however, in view of their potential therapeutic roles, intense efforts are under way to better understand them.[19]

Signal Transduction

The formation of a receptor-ligand complex is only the first step toward initiating a biologic response within the target cell. The second step entails transmission of the ligand-receptor binding signal across the cell membrane and activation of a second messenger system. The second messenger system then activates an effector system, bringing about a specific biologic response (see Fig. 84-3).

G Proteins

A family of heterotrimeric guanine nucleotide-binding proteins (G proteins) has a well-defined role in transmitting receptor-ligand signals across the cell membrane by linking the receptor with a second messenger system.[7] G proteins consist of three distinct subunits termed α, β, and γ subunits. The α subunit is the site of guanine nucleotide binding and has generally been considered the subunit that conveys the functional and receptor specificity of the G-protein. When a neurotransmitter binds to a receptor, the affinity of the receptor for a specific G protein increases. Formation of the receptor-G protein complex leads to the replacement of the guanine diphosphate (GDP), which is bound to the α subunit with a guanine triphosphate (GTP), and dissociation of the heterotrimeric G protein into a free α subunit and a free βγ complex. The α subunit is then available to activate a specific second messenger system. The activation continues until the GTP is degraded to GDP by GTPase activity endogenous to the α subunit. The GDP-associated α subunit then reassociates with the βγ complex to generate the inactive heterotrimeric G protein. The two best-studied second messenger systems in the salivary gland are (1) the generation of cyclic adenosine monophosphate following β-adrenergic receptor stimulation leading to protein exocytosis and (2) the formation of 1,4,5-inositol triphosphate (IP_3) after muscarinic acetylcholine receptor stimulation leading to calcium mobilization and fluid secretion. Other more speculative second messenger systems involve nitric oxide, cyclic guanine monophosphate, phospholipids, cytosol pH, and membrane depolarization.

Adenylate Cyclase System

Stimulation of β-adrenergic receptors on acinar cells leads to protein exocytosis. The role of cAMP in protein secretion from acinar cells has been well documented for nearly 30 years, though some of the initial steps in this pathway have only recently been elucidated.[20,21] Binding of norepinephrine to β_1 and β_2 adrenergic receptor leads to activation of the G protein, G_s. Activation of G_s in turn leads to activation of adenylate cyclase, which then converts ATP into cAMP. Increasing concentration of cAMP then leads to the activation of cAMP-dependent protein kinase A. Both type 1 and type 2 cAMP-dependent protein kinase A are thought to be involved in this pathway.[22] Cyclic AMP-dependent protein kinase A phosphorylates several cellular proteins, the most important of which is considered to be a 26-kDa integral membrane protein.[23] As yet, it is unclear how the activation of cAMP and cAMP-dependent protein kinase A leads to protein exocytosis. Also important is that whereas ligand binding to β_1 and β_2 receptors activates the adenylate cyclase system, ligand binding to α_2 receptors inhibits adenylate cyclase via the G protein, G_i.[24]

Phospholipase C System

Researchers have long known that the stimulation of acinar cell muscarinic acetylcholine receptors leads to high levels of fluid secretion and that calcium plays a key role in this process.[7,25] In the past 25 years efforts by several investigators have led to the characterization of the specific mechanisms involved in muscarinic acetylcholine receptor-mediated fluid secretion.[7] Ligand binding to the muscarinic acetylcholine receptor activates a pertussis toxin-insensitive G protein, thought to belong to the G_q family.[26] Activation of this G protein activates the enzyme phospholipase C, which hydrolyzes a minor membrane phospholipid phosphatidylinositol 4,5-bisphosphate. This leads to the formation of two second messenger molecules, inositol triphosphate (IP_3) and diacylglycerol (DAG). Diacylglycerol is capable of activating protein kinase C leading to protein exocytosis, though this is thought to represent a minor pathway for protein secretion in acinar cells.

The other product of hydrolysis, inositol triphosphate, binds to a membrane receptor on intracellular calcium stores, causing the release of calcium into the cytoplasm. These intracellular calcium storage units are derivatives of the endoplasmic reticulum. The IP_3 receptor itself is thought to function as a calcium channel, and on ligand binding it allows calcium to move down a concentration gradient into the cytoplasm. Cytoplasmic calcium concentrations can increase 10-fold within

5 seconds of muscarinic acetylcholine receptor activation and lead to a cascade of events including a sustained influx of extracellular calcium into the cytoplasm and the activation of specific ion transport pathways, leading to fluid secretion. Currently there is little understanding of the cell membrane channels that allow calcium to move into the cytoplasm in response to increased cytoplasmic calcium concentration in nonexcitable cells such as acinar cells.[7]

Flow Rate of Saliva

Salivary flow rates are highly variable, stabilizing after the age of 15 years, and therefore should be interpreted in a clinical context.[27,28] The numbers depicted in this section are averages projected from studies on the general population. The range of normal unstimulated salivary flow is 0.1 mL/min and above, and in the stimulated state, 0.2 mL/min and above. On average the unstimulated flow rate is 0.3 mL/min and the stimulated flow rate is 7 mL/min at maximum. Stimulated saliva is thought to contribute as much as 80% to 90% of the average daily salivary production. This leads to an average daily saliva secretion of around 1000 to 1500 mL or an average flow of 1 mL/minute.[29,30] Salivary flow in the unstimulated state is produced primarily by the submandibular glands (71%) with the parotid and sublingual glands producing 25% and 3% to 4% of the flow, respectively.[30] The minor salivary glands account for trace amounts of saliva. Once stimulated, the relative contributions of the parotid and submandibular glands are reversed and the parotid gland supplies two thirds of the salivary flow.[27,31]

Studies specifically addressing hypofunction of the salivary gland have defined the critical range separating a person with normal gland function from those with salivary gland hypofunction as unstimulated whole salivary flow rates between 0.12 and 0.16 mL/min.[32] The diagnosis of salivary hypofunction is often difficult to make given the wide range of salivary flow rates that are accepted as normal. A more reliable means of diagnosing hypofunction is possible if an individual base record of saliva flow has been established. Salivary gland hypofunction can then be defined as a 50% reduction in the individual base saliva flow rate. About 30% of the population reports some degree of dry mouth. In general, oral-related effects of salivary hypofunction are (1) reduced preparation of food for digestion and taste and (2) an increased susceptibility of oral structures to disease.[33] Although decreased concentrations of salivary mucins and decreased resting salivary flow rates have been associated with increasing age, in general there are no substantial age-related changes in the secretory responsiveness of salivary cells.[34,35] Furthermore, factors endemic to the geriatric population such as polypharmacy, poor nutritional status, and systemic diseases also contribute to salivary gland hypofunction.[36] Presently, the exact role of advancing age on the average daily production of saliva and xerostomia is unknown.

Salivary secretion is controlled by a salivary center in the medulla, which is triggered by specific stimuli: (1) the mechanical act of chewing, (2) gustatory, and (3) olfactory. The stimulation of salivary flow with mastication is thought to be a reflexive response mediated by receptors in the oral mucosa, muscles of mastication, and temporomandibular joint. These receptors stimulate the salivary nucleus, which in turn increases the parasympathetic stimulation to the salivary glands, resulting in increased salivary flow.[37] Interestingly, the increase in salivary flow is thought to be directly proportional to the applied chewing force.[38] Gustatory stimuli are the most potent stimuli to the salivary center, eliciting as much as a 10-fold increase in salivary flow. Acidic tastes lead to the greatest increases in saliva flow, whereas sweet tastes are the least stimulating. Olfaction is the weakest of the salivary center triggers. Furthermore, habituation is thought to occur with repeated presentation of the same food cues, leading to a decrease in stimulation of the saliva center and saliva flow. Dishabituation occurs with presentation of novel food cues.[39-42]

Many other factors also can influence salivary flow. These factors include (1) circadian rhythm; (2) psychic factors such as pain, depression, and anticipation of food; (3) medications; (4) local or systemic diseases; and (5) hormones. Isolating and studying the effect of a specific factor is often difficult because many of these stimuli work in concert to affect salivary flow. Diurnal variation in salivary flow has been reported, with maximal flow rates in the late afternoon and minimal flow rates at night. Decreased salivary output at night may be secondary to a decrease in ambient light and/or arousal state, both of which affect salivary gland function.[43] Medications with anticholinergic properties such as most antidepressants decrease salivary flow. Dehydration can influence salivary gland output, with losses of 8% of body water, resulting in cessation of salivary flow. Decreased salivary output is also noted during the "fight or flight" response, which results from an increased sympathetic response and/or central inhibition of parasympathetic output. The sympathetic nervous system has also been proposed to play a role in the reduction of saliva flow after exercise via constriction of blood vessels that supply the salivary glands.[44]

Salivary flow is not even throughout the mouth secondary to the location of the ducts that empty the parotid and salivary glands. Intraoral flow volume is highest in the mandibular lingual area and lowest in the area of the maxillary incisors and interproximals.[45] These areas of higher and lower volume flow regions have been referred to as "salivary highways and byways." The regional clearance rate of acid produced from bacteria is directly influenced by regional variations in flow within the mouth.[46] Consequently, salivary byways are areas in which acid byproducts may remain in longer contact with oral structures unless mechanical means of cleansing are used. Furthermore, with varying amounts of saliva and salivary constituents coming from different glands, it is suggested that saliva provides different types of protection in different intraoral locations.

Composition of Saliva

Saliva comprises a variety of organic and inorganic compounds (Table 84-3), allowing its varied functional properties. The inorganic component is composed mostly of electrolytes such as sodium, potassium, calcium, magnesium, bicarbonates, phosphates, and nitrogenous products such as urea and ammonia. The organic component includes several classes of proteins such as immunoglobulins, enzymes, and

Table 84-3

Flow Rates and Composition of Saliva in Normal Adults

	Parotid Gland	Submandibular Gland
Stimulated Flow Rate (mL/min/gland)	0.7	0.6
Inorganic Constituents (mEq/L)		
K^+	20	17
Na^+	23	21
Cl^-	23	20
HCO_3	20	18
Ca^{++}	2	3.6
Mg^{++}	0.2	0.3
HPO_4^{-2}	6	4.5
Organic Constituents (mg/dL)		
Urea	15	7
Ammonia	0.3	0.2
Uric acid	3	2
Glucose	<1	<1
Cholesterol	<1	—
Fatty acids	1	—
Total lipids	2-6	2-6
Amino acids	1.5	—
Protein	250	150

Modified from Mandel ID. Sialochemistry in diseases and clinical situations affecting salivary glands. *Crit Rev Clin Lab Sci.* 1980;12:321.

mucins. Because the final saliva product is an aggregate of the saliva produced by several glands, each with different secretory characteristics, the composition of whole saliva at any particular time can be highly variable. This variability is further enhanced by the fact that the secretory characteristics of each gland will change with the type of stimulus driving the saliva production. Furthermore, the electrolyte composition of saliva will change depending on flow rates secondary to changes in the amount of inorganic compounds secreted or reabsorbed in the salivary ducts. In general, whole saliva is composed of approximately 99.5% water, has a specific gravity between 1.002 and 1.0012, and a pH that varies between 5.75 and 7.05. The osmolarity of saliva is largely determined by the major ions: sodium, potassium, chloride, and bicarbonate. The pH is largely determined by the carbon dioxide content of saliva because bicarbonate is the principal salivary buffer system. Phosphate serves a minor role in buffering saliva. The electrolyte composition of saliva is relatively independent of plasma concentrations because electrolytes are transported into saliva via an active process. On the other hand, organic compounds passively diffuse into saliva and therefore their concentrations in saliva reflect plasma concentrations.[27]

Inorganic Component

Sodium (Na^+) and potassium (K^+) are the major cations present in saliva (see Table 84-3). The salivary concentration of these ions depends on the type of gland from which it is secreted, as well as the type and amount of stimulation to the gland. In general, the concentration of these electrolytes in the parotid gland is higher than in the submandibular gland. When the salivary flow rate is low, the ratio of Na^+ to K^+ is also low. This ratio increases as the flow rate increases because of decreased reabsorption of Na^+ at higher flow rates. As with Na^+ and K^+, the salivary concentration of Ca^{++} also varies with the type of gland from which it is secreted and salivary flow rates. Salivary calcium concentrations, however, appear to be flow dependent only at high flow rates. In addition, unlike salivary Na^+ and K^+, the concentration of Ca^{++} in saliva from the submandibular gland (3.4 to 4.4 mEq/L) is almost twice that of the parotid gland (1.4 to 2 mEq/L). Calcium is distributed in saliva as a free ion, as well as bound to protein or in complexes with carbonate, phosphate, or lactate. Salivary magnesium concentrations from the parotid and salivary glands are fairly equivalent and represent roughly two thirds of the plasma concentration.[27]

The major salivary cations are chloride, bicarbonate, and phosphate. Salivary concentrations of chloride from the parotid gland and salivary gland are equivalent and lower than that of plasma. Salivary chloride concentrations are flow dependent, decreasing with decreasing flow rates. In the resting state, salivary bicarbonate concentrations can be as low as 5 mEq/L, and with stimulation bicarbonate concentrations may exceed that of plasma (27 mEq/L). Salivary bicarbonate is derived from plasma, as well as from metabolic activity in the gland. Salivary phosphate is present at concentrations appreciably higher than that of serum and serves as one of the minor buffers. About 10% of salivary phosphate is present in the ester form, mainly in phosphoproteins and trace amounts in pyrophosphate.[27]

Minor inorganic components of saliva include iodine and fluoride. The concentration of iodine in saliva is roughly 10 to 15 µg/mL. Salivary fluoride content is approximately similar to that of plasma but is elevated slightly in individuals who drink fluoridated water or use fluoridated toothpaste. In these individuals there is a prolonged release of fluoride into saliva from sparingly soluble deposits on the teeth and soft tissues. These small elevations in salivary fluoride levels are believed to be important in preventing the formation of dental caries.[27]

Organic Components

Proteins or protein-containing moieties comprise the majority of the organic components of saliva. The concentration of protein is higher in stimulated parotid than in stimulated submandibular secretions.[29,30] On average, the protein content of whole saliva is 200 mg/100 mL, which is about 3% of the protein concentration in plasma.[31] Careful analysis of whole saliva, as well as saliva from each of the major salivary glands, has revealed the presence of distinct families of proteins within saliva, each family containing multiple members. The structural variations of individual family members arise by a combination of genetic and posttranslational events. The major salivary components of saliva range in size from small histatins (2 to 4 kDa) to larger mucins (>1000 kDa) (Table 84-4).

Table 84-4

Major Salivary Macromolecules

Protein Family	Molecular Weight (kDa)
Histatins	2-4
Statherins	4-5
Lysozyme	14
Cystatins	14
Proline-rich proteins	10-30
Carbonic anhydrases	42-45
Amylase	55-60
Peroxidase	75-78
Lactoferrin	75-78
Mucin 2 (MG2)	130
Secretory IgA	380
Mucin 1 (MG1)	>1000

From Levine MJ. Salivary macromolecules: a structure/function synopsis. *Ann N Y Acad Sci.* 1993;694:11.

Evaluation of the structural and functional properties of salivary proteins has revealed several important concepts. First, the structural conformation of the protein is essential for its functional properties. For example, the alpha helical conformation of salivary statherins and histatins and the intrapolypeptide disulfide bonds of salivary amylase are essential to the functional properties of these proteins. Disruption of these secondary and tertiary structures abrogates their function. Second, most salivary proteins are multifunctional and overlap in their roles (Table 84-5). This brings up the third concept of functional redundancy, which allows deficiencies in one protein to be compensated for by another protein. In addition, the concept of functional redundancy may explain why there is a high degree of variability in the concentration of individual salivary molecules in the general population. The fourth concept is that salivary proteins can exhibit multiple functions on the basis of the situation. For example, amylase in solution has an antibacterial activity, whereas amylase bound to the tooth surface can promote bacterial adherence and the formation of dental caries. The fifth and final concept is that many salivary proteins form complexes of the same polypeptide (homotypic) or two different polypeptides (heterotypic), via covalent and noncovalent interactions, to become functionally active.[47]

One of the main protein constituents of plasma, albumin, is also present in saliva. Albumin passively diffuses into the glandular secretion from plasma and has been hypothesized to play a similar role in saliva, that of a carrier protein. The concentration of albumin in saliva depends on the salivary flow rate, decreasing in concentration with increasing flow rates. The concentration of albumin in saliva also varies with the overall medical status of the individual, increasing in concentration in the presence of chronic disease states such as immunosuppression, radiation treatment, and diabetes.[48]

The best-studied and quantitatively most prominent salivary enzyme is α-amylase, a glycoprotein with a molecular weight between 62 and 67 kDa. Six isoforms of α-amylase exist, the distribution of which differs between salivary and pancreatic secretions. Alpha-amylase is present in parotid saliva at a 60 to 120 mg/100 mL and in sub-

Table 84-5

Functions of Salivary Molecules

Functional Property	Salivary Molecule
Antibacterial	Amylase, cystatins, histatins, mucins, peroxidases
Antiviral	Cystatins, mucins
Antifungal	Histatins
Buffering	Histatins, carbonic anhydrases
Digestion	Amylases, mucins
Mineralization	Cystatins, histatins, proline-rich proteins, statherins
Lubrication	Mucins, statherins
Tissue coating	Amylase, cystatin, mucins, proline-rich proteins, statherins

Data from Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. *J Prosthet Dent.* 2001;85:162.

mandibular saliva at a concentration of 25 mg/100 mL.[31] The average total daily secretion of amylase is approximately 0.6 g, comprising 10% of the total salivary protein. Alpha-amylase hydrolyzes the α 1:4 glycosidic bond between glucose units in the polysaccharide chain of starch. Hydrolysis can take place anywhere along the polysaccharide chain, except for branching points, and is slow at hydrolyzing terminal glucose units. Therefore the end products of amylase digestion are mainly maltose, oligosaccharides, and some free glucose. The optimal pH for α-amylase activity is in the range of 6 to 8, and chloride is required as a cofactor.[31]

The major salivary glands are regarded as the principal sources of salivary antimicrobial substances such as immunoglobulin-A (IgA), lactoferrin, lysozyme, and peroxidase. Immunoglobulin-A is the predominant immunoglobulin in saliva, being present at a concentration of approximately 20 mg/100 mL, and plays an important role in the local immune system of the salivary gland.[31] Salivary IgA is found predominantly in the dimeric form in which two IgA macromolecules are covalently linked via a J chain. Dimeric IgA is formed by plasma cells in the interstitium of the salivary gland and is transported across the acinar cell into the acinar lumen via an active transport process. Unlike serum IgA, salivary IgA also contains a 70 kDa secretory component that is thought to protect dimeric IgA from digestion by proteolytic enzymes in the saliva. The secretory component is found on the basolateral surface of acinar cells and is thought to play an additional role in transporting the dimeric IgA across the cell into the acinar lumen. The role of IgA as a protective agent against dental plaque formation in humans is controversial.[49] It has been observed that the salivary IgA is increased by both sympathetic and parasympathetic stimulation.[50] Two other immunoglobulins, IgG and IgM, are also present in saliva, though at much lower concentrations.

Lysozyme is an antibacterial enzyme, which attacks components of the cell wall of certain bacteria leading to lysis and death of the bacteria. The effects of lysozyme are potentiated by specific cations in salivary secretions. Lactoferrin is an iron-binding protein, which removes free iron from saliva, depleting the supply needed for bacterial growth. Finally, sialoperoxidase oxidizes salivary thiocyanate to hypothiocyanite using hydrogen peroxide produced by oral bacteria. Hypothiocyanite has potent antibacterial activity.[31]

The major groups of salivary glycoproteins consist of two classes of mucins, mucin 1 and mucin 2, found in submandibular and sublingual saliva, as well as a group of proline-rich-glycoproteins found in parotid saliva. Mucin 1 and mucin 2 are also known after their gene designations, *MUC5B* and *MUC7*, respectively. All of the salivary glycoproteins consist of a polypeptide core with oligosaccharide side-chains. The proportion of the carbohydrate component to the protein component varies between the different groups of glycoproteins. Mucin 1 (MG1) is a high-molecular-weight multi-subunit molecule that is highly glycosylated. Mucin 2 (MG2) is a low-molecular-weight single polypeptide molecule that is glycosylated.[27] Protein-rich polypeptides are low-molecular single polypeptide molecules that are moderately glycosylated. Glycoproteins are thought to have numerous functional roles (see Table 84-5).[31]

Statherin is a small phosphoprotein, which is relatively rich in tyrosine and proline, and has the property of promoting remineralization of the enamel coating of teeth. This role is accomplished by the ability of statherin to prevent the precipitation of calcium phosphates from supersaturated solutions, which also plays a role in inhibiting the formation of salivary gland calculus.[2,27]

Since the discovery of kallikreins in submandibular glands, an increasing number of polypeptides have been either isolated and purified from, or claimed to be present in, the submandibular glands of mammals, primarily mice. Most are androgen dependent and have their secretion mediated primarily by α-adrenergic mechanisms. Nearly all are found in or considered to be synthesized by the granular convoluted tubules/striated duct cells, where they are localized in secretory granules. In addition to their presence in saliva, several of these polypeptides are also found in the blood. The presence of polypeptides in both saliva and blood raises the issue of the endocrine or endocrine-like functions of the submandibular gland. Polypeptides that have been purified from saliva and characterized include epidermal growth factor, nerve growth factor, rennin, and kallikrein.[51]

Epidermal growth factor (EGF) is a 53 amino-acid peptide that stimulates DNA, mRNA, and protein synthesis in many cell types.[51] EGF synthesized and released by the salivary glands has been implicated in a number of biologic processes. It is a potent mitotic stimulator, it enhances keratinization, and it inhibits gastric acid secretion. Studies have confirmed that oral wound healing is significantly delayed after the removal of salivary glands. This delay in oral wound healing is restored by oral administration of EGF.[52] The parotid and submandibular glands appear to be the source of salivary EGF in humans.[53] Patients with risk factors for cancer and those who have head and neck cancer have been shown to have low salivary EGF levels.[54]

The submandibular gland of mice is unique in its capacity to synthesize, store, and secrete large amounts of NGF. The role of NGF in saliva is unknown, despite its high concentration in saliva from the submandibular gland.

Salivary secretion of renin is stimulated by α-adrenergic and cholinergic mechanisms. Plasma angiotensin II concentrations do not have any impact on the release of submandibular gland rennin. The exact physiologic role of salivary rennin is currently unknown. As with salivary rennin, the physiologic role of salivary kallikrein, a serine protease that has been isolated from the submandibular glands of many mammalian species, is unknown.

Functions of Saliva

Salivary function can be organized into five major categories that serve to maintain homeostasis: (1) lubrication and protection, (2) buffering and clearance, (3) maintenance of tooth integrity, (4) antibacterial activity, and (5) taste and digestion.[27] The different components of saliva are multifunctional and have overlapping roles in accomplishing these tasks.

Lubrication and Protection

Saliva is a seromucous substance that coats the structures of the oral cavity and oropharynx, lubricating and creating a protective barrier against irritants such as proteolytic and hydrolytic enzymes produced in plaque, chemical agents, and desiccation. In addition, lubrication of oral structures is essential for such functions as speech, mastication, and swallowing. The subcomponents of saliva with the best lubricating properties are the mucins, the highest concentrations of which are found in saliva secreted from the minor and sublingual salivary glands. Intermediate amounts are found in submandibular gland saliva, and

low amounts in parotid saliva. The low solubility, high viscosity, and adhesiveness of salivary mucins enable these molecules to become concentrated on the oral mucosal lining.[55] Another class of salivary glycoproteins, the proline-rich polypeptides found in parotid saliva, also play a role in lubricating and protecting oral structures.[56] These functions are in part assisted by the fact that the carbohydrate moieties of the mucins and proline-rich polypeptides allow these molecules to bind water and therefore enhance the protective barrier and keep oral structures hydrated.

Buffering and Clearance

Saliva has a slightly alkaline pH and contains several buffer systems, the most important of which is bicarbonate.[27,31,33] Several minor buffer systems are present in saliva as well and include phosphate, urea, and low-molecular-weight histidine-rich proteins. At high flow rates a combination of the increased bicarbonate concentration in saliva and the increased volume of fluid present increases the buffering and clearance capacity of saliva. On the other hand, at low flow rates such as in situations where the salivary glands are not stimulated, the buffering capacity of saliva is at a minimum and is accomplished primarily by buffers such as phosphate and histidine-rich proteins.[27] Clearance of acids and other chemicals occurs by dilution of these substances and then spitting or swallowing the saliva. The buffering and clearance properties of saliva have a known role in the prevention of dental caries.[57]

Maintenance of Tooth Integrity

After tooth eruption, the enamel covering of the tooth undergoes processes of mineralization and demineralization, both of which are influenced by saliva. Demineralization occurs when acids produced by attached bacteria diffuse through plaque and the pellicle into the liquid phase of enamel, between enamel crystals.[27] This results in crystalline dissolution, a breakdown in the enamel coating, and the formation of dental caries. Demineralization is optimized at a pH of 5 to 5.5. Dissolved minerals diffuse out of the tooth structure and into the saliva surrounding the tooth. The buffering capacity of saliva neutralizes acids that accumulate in plaque and thereby inhibit the formation of dental caries. Plaque thickness and the number of bacteria present determine the effectiveness of salivary buffers.

Saliva also plays a role in remineralization, the process of replacing minerals lost from the crystalline matrix of the enamel. Remineralization requires the tooth to be surrounded by fluid supersaturated with minerals such as calcium, phosphorus, magnesium, fluoride, and other trace elements. Saliva has this ability, in large part to its protein subcomponents such as statherin, which stabilizes minerals in solution. Furthermore, proteins such as statherin, mucin, histatin, cystatin, and proline-rich proteins are thought to form a protective pellicle by binding to hydroxyapatite on the surface of the tooth. This protective pellicle also fosters remineralization and limits mineral egress. The remineralization process increases surface hardness, decreases permeability, and decreases the formation of caries.[27]

Antibacterial Activity

Saliva contains both immune-mediated and non–immune-mediated agents that aid in the protection of oral cavity structures. The main immunologic mediator of saliva is IgA and, to a much lesser extent, IgG and IgM. The principal actions of these antibodies are to aggregate bacteria and prevent their adhesion to oral hard and soft tissues. In addition, IgG has the ability to fix complement and cause bacterial lysis, though this represents a minor antibacterial mechanism in saliva.[27]

Nonimmunologic components include various proteins, mucins, and enzymes such as lactoferrin, lysozyme, and peroxidase, all of which are produced by the acinar cells.[27,31] Mucins perform an antibacterial function by modulating the adhesion of microorganisms to oral tissue surfaces. Mucin 1 adsorbs tightly to the tooth and thereby contributes to the enamel pellicle, which protects the tooth from acid. On the other hand, mucin 1 forms heterotypic complexes with other salivary proteins such as amylase, proline-rich proteins, statherin, and histatins. In this manner, mucin 1 allows bacteria to attach to the surface of teeth and provides them with a nutrient source. Mucin 2 also binds to enamel, but in contrast to mucin 1, mucin 2 is easily displaced. Therefore mucin 2 promotes the aggregation and clearance of bacteria.[27] Interestingly, mucin 2 predominates in the saliva of caries-resistant patients, whereas the mucin 1 predominates in caries-susceptible patients.[58]

Lactoferrin is an iron-binding protein found in saliva, whose principal function is that of scavenging free iron in fluids and inflamed areas, to suppress free radical–mediated damage and decrease the availability of the metal to invading microbial and neoplastic cells.[59] Lactoferrin is also thought to have a bactericidal effect that is distinct from its metal chelating properties.[60]

Taste and Digestion

Saliva aids in the mastication and swallowing of food through its lubricating actions. In addition, salivary amylase initiates the digestion of ingested carbohydrates by catalyzing the hydrolysis of the α 1,4 glucosidic bond. Salivary amylase is active only at neutral pH and is inactivated by the pH of gastric juice. However, because of high concentration and activity of amylase in the saliva, a fraction of the ingested starch is digested before the ingested food bolus reaches the stomach. Furthermore, studies suggest that amylase activity may continue for up to 30 minutes in the stomach if protected from the gastric acid within a bolus of food following a large meal. In general, however, most of the digestion of starch results from pancreatic amylase and not salivary amylase.[2,6]

The main role of saliva in taste sensitivity is the solubilization of ingested food particles, transport of taste substances to, and protection of taste receptors. Saliva and its subcomponents may play an additional role in taste perception by neutralizing acids, which would otherwise yield a sour taste, and binding to and neutralizing bitter tasting substances. Salivary constituents such as electrolytes also continuously stimulate the taste receptors altering the threshold of these receptors for substances such as sodium chloride. Finally, saliva bathes and hydrates the taste receptors, preventing them from desiccation, playing a long-term function in maintaining the taste function.[61]

Aging and Salivary Gland Dysfunction

Dry mouth is a common complaint in the geriatric population and is commonly believed to arise from age-associated intrinsic salivary gland dysfunction. Sixty-five percent of patients older than the age of 60 whose presenting complaint is xerostomia have objective evidence of salivary gland hypofunction.[62] However, it is important to keep in mind that extrinsic causes such as polypharmacy and chronic diseases, which are associated with xerostomia, are endemic to the elderly population.[36] A reduction in unstimulated whole saliva is associated with increasing age, when unmedicated healthy subjects older than the age of 80 years are compared with a younger control group (Fig. 84-4).[35] Elderly test

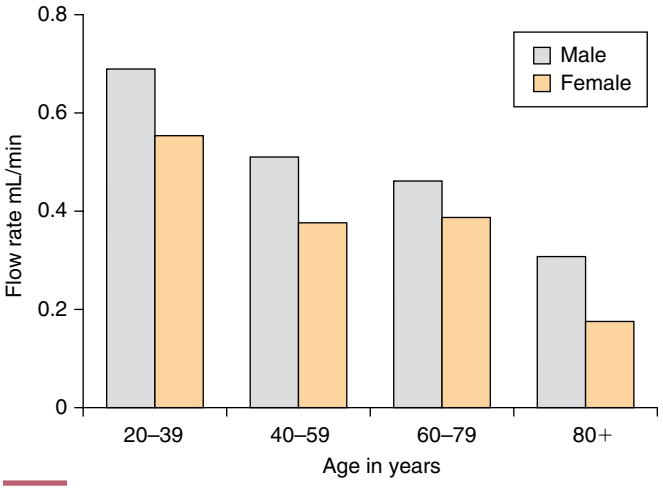

Figure 84-4. Graph demonstrating the age- and gender-specific distribution of unstimulated whole salivary gland secretions. *(From Percival RS, Challacombe SJ, Marsh PD. Flow rates of resting whole and stimulated parotid saliva in relation to age and gender.* J Dent Res. *1994;73:1416.)*

subjects, however, had no impairment in their ability to respond to sialogogues, suggesting that stimulated parotid saliva flow rates are not affected by age.[35] The significance of these findings is somewhat controversial because several other studies in the literature demonstrate a decrease in both unstimulated and stimulated whole saliva with increasing age.[63,64]

All salivary glands undergo structural changes with age. With increasing age, the compact lobular structure and uniform appearance of the ducts and acini are altered. The lobules become more loosely structured, acini assume dissimilar sizes, and intralobular ducts become more prominent. Fibroadipose tissue and acinar atrophy is found in the glands in all ages, but it increases in the elderly. Specific findings in the submandibular gland include a loss of acinar granules with shrinkage of cells, dilation of intralobular and extralobular ducts with a modest hyperplasia of intralobular ducts, oncocytic transformation after 70 years of age, fibrosis around ducts and in septae, an increased glandular adiposity that is independent of general adiposity, and focal obstructive and chronic inflammatory adenitis with intraductal calculi. In general, age-related structural changes in the parotid gland are milder than those in the submandibular gland.[2]

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CHAPTER EIGHTY-FIVE

Diagnostic Imaging and Fine-Needle Aspiration of the Salivary Glands

JoAnne Lacey

Key Points

- CT is the modality of choice for patients with inflammatory disorders of the salivary glands.
- MRI is the modality of choice for patients with a palpable lesion or expected neoplasm of the salivary glands.
- US is useful in palpable salivary lesions and has been shown to assist the diagnostic accuracy of FNA.
- Although conventional sialography is the gold standard for evaluating the ductal system in the salivary glands, MR sialography techniques are improving and can provide an alternative, less invasive method for evaluating the ducts.

Although some disorders of the salivary glands can be diagnosed and treated without the use of radiographic studies, imaging of the salivary glands can be useful in the workup of patients with a broad spectrum of salivary pathology. Imaging is used to localize the lesion, define its appearance in order to limit the differential diagnosis, evaluate for staging, and guide fine-needle aspiration for pathologic diagnosis. Various modalities including magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), and sialography are used to image and help with the diagnosis of the pathologic processes that occur in the salivary glands. Noninvasive imaging such as MRI, magnetic resonance (MR) sialography, US, and CT have improved to a point that invasive imaging techniques such as conventional sialography are much less frequently employed. Fine-needle aspiration (FNA) of the salivary glands is routinely performed, often under US guidance, for diagnosis and/or presurgical workup of salivary lesions. The role of nuclear medicine imaging in the evaluation of salivary lesions is limited.

Cross-sectional imaging is useful not only for characterization of the major salivary glands and their various pathologies, but also for the evaluation of the surrounding planes and structures revealing possible extension of salivary neoplasms into adjacent spaces, perineural or vascular spread, nonpalpable lesions and lymphadenopathy, or infiltration of the bone marrow. Lesions can also be more clearly defined as extraglandular such as would be seen with a lymph node, schwannoma, developmental cyst, or lipoma.

The clinical presentation of the patient is important in the choice of imaging modality. Patients may present with a painless palpable mass, acute or chronic pain and swelling, or with xerostomia in the setting of collagen vascular disease or radiation therapy. The correct choice of primary imaging modality will assist diagnosis in each instance.

Sialolithiasis (Fig. 85-1) can be seen in any salivary gland but is most commonly associated with the submandibular gland secondary to the more mucinous saliva and the horizontal trajectory of the submandibular duct. Symptoms of acute pain and swelling in the region of a salivary gland would raise suspicion for sialolithiasis, and a CT should be ordered because CT is the modality with the greatest sensitivity for calcification in an obstructive stone.[1]

Neoplasms can occur in any salivary gland tissue. The likelihood of malignancy is largest in the smallest glands. Lesions of the minor salivary glands, for example, have a 50% to 80% chance of being malignant. In the parotid gland, only 20% to 30% of lesions will be malignant, whereas 40% to 60% of submandibular gland lesions will be malignant. In the parotid, therefore, 70% to 80% of lesions will be benign. Of these benign lesions, 80% will be pleomorphic adenomas (Fig. 85-2).[2] Although imaging can give clues as to the pathologic diagnosis (i.e., smooth borders are more likely benign and infiltration of adjacent structures is a sign of malignancy), the role of imaging is primarily to identify the lesion and describe its association with adjacent structures.

Anatomy

It is important to understand the radiographic anatomy of the salivary glands and surrounding structures in order to better interpret the appearance of the various pathologic entities. The three major salivary glands include the parotid glands, submandibular glands, and sublingual glands.

Parotid Glands

The paired parotid glands are the largest of the salivary glands. They are located in the parotid spaces wrapping around the posterior aspects of the mandibular rami bilaterally. Each gland is divided into a superficial lobe and a deep lobe with the posterior facial vein (retromandibular vein) present as the radiographic landmark between the two lobes. The main trunk of the facial nerve exits the skull base at the stylomastoid foramen and pierces the posterior fascial border of the parotid space lateral to the surface of the posterior belly of the digastric

muscle and then courses within the parotid gland lateral to the retromandibular vein. High-resolution MR techniques can show the facial nerve and its relationship to the parotid duct, vascular structures, and, if present, intraparotid tumors.[3] On contrast-enhanced CT or when high-resolution images are not performed, the location of the facial nerve is approximated by the retromandibular vein. Approximately 80% of the parotid lies in the superficial lobe anterior and inferior to the external auditory canal extending down to the angle of the mandible. The deep lobe extends through the stylomandibular tunnel formed anteriorly by the ramus of the mandible and posteriorly by the stylomandibular ligament. The location of a mass in the parotid gland must be defined as superficial, deep, or extraglandular to best plan the surgical approach in order to limit damage to the facial nerve. The parotid duct (Stensen's duct) extends anteriorly from the superficial lobe of the parotid gland around the masseter muscle and anterior to the buccal fat where it proceeds medially to pierce the buccinator muscle. The duct then briefly runs caudally before exiting the papilla at the buccal mucosa opposite the second maxillary molar.

Frommer,[4] in his study of anatomic dissections, found that approximately 21% of parotid glands have an accessory gland. The accessory component is typically located superficial to the masseter muscle just cranial to the main parotid duct (Fig. 85-3). One excretory duct from the accessory parotid gland joins with Stensen's duct. The accessory parotid gland is subject to the same pathologies that affect the parotid gland. The rate of malignancy is estimated to be between 30% and 50%, with mucoepidermoid the most common lesion. Pleomorphic adenoma is the most common benign neoplasm of the accessory parotid gland.

The parotid glands contain many lymph nodes that drain the palatine tonsil, posterior palate, root of the nose, eyelids, frontotemporal scalp, external auditory meatus, and tympanic cavity. This network of nodes drains into the level IIA and IIB nodes of the internal jugular chain and spinal accessory chain.[5]

The parotid gland is interspersed with fat. On CT, the attenuation of the normal gland is lower than muscle and greater than fat. The greater the fat content of the gland, the easier the detection of a parenchymal soft tissue nodule. On MRI, the gland is intermediate to high signal on T1-weighted imaging and low to intermediate on T2-weighted imaging, reflecting its fat content. Flow voids are detectable on T2-weighted imaging due to vessels within the gland. Septations of lower T1 signal are seen in the gland due to interstitial tissues, ducts, and facial nerve branches. The intraparotid facial nerve can be visualized, especially on high-resolution imaging[3,6,7]; the nerve does not normally enhance. Contrast will reveal homogeneous enhancement of the normal parotid glandular tissue (Fig. 85-4).

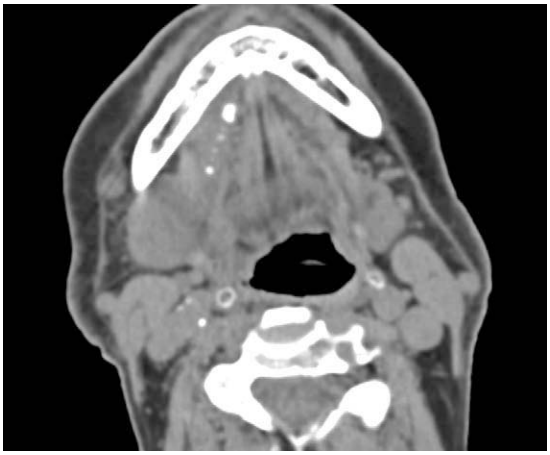

Figure 85-1. Multiple stones within the right submandibular duct (Wharton's duct) with enlargement of the right submandibular gland and periglandular inflammatory fat stranding.

Submandibular Glands

The paired submandibular glands are visible posterior to the angle of the mandible largely within the submandibular space with a small deep portion curling up cranially around the posterior border of the mylohyoid muscle. The submandibular duct (Wharton's duct) exits the deep lobe extending anteriorly and superiorly, medial to the sublingual gland in the sublingual space terminating at the sublingual papilla in the floor of the mouth. The lingual nerve and hypoglossal nerve are closely associated with the duct as it courses anteriorly through the fat-filled sublingual space. The lymphatic drainage from the glands is into the submandibular nodes (level IB).[5]

The parenchyma of the submandibular glands is less fatty than that of the parotid glands. This lends a higher attenuation to the glands on CT and, on MRI, corresponding lower signal on T1-weighted imaging and higher signal on T2-weighted imaging. Again, the use of contrast will reveal homogeneous enhancement, which should be symmetric.

Sublingual Glands

The small, paired sublingual glands are positioned up against the sublingual depressions of the inner surface of the mandible just superior to the mylohyoid muscles bilaterally. Approximately 20 ducts (ducts of Rivinus) drain into the floor of the mouth. The lymphatic drainage

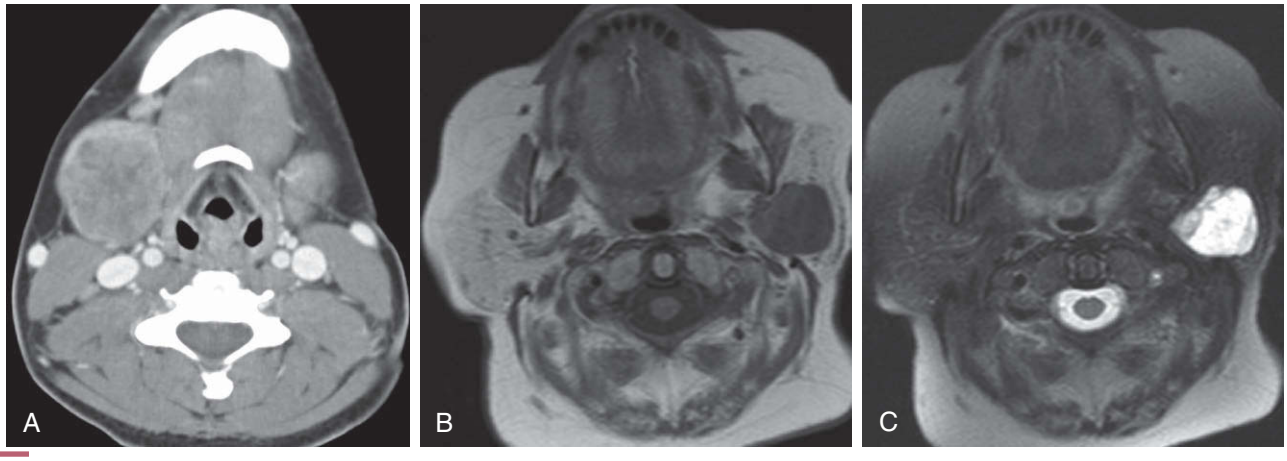

Figure 85-2. **A,** Contrast-enhanced computed tomography showing a large, well-defined, inhomogeneously enhancing right submandibular gland mass that was proven on resection to be a pleomorphic adenoma. **B,** T1-weighted noncontrast magnetic resonance image of a pleomorphic adenoma appearing as a well-defined hypointense mass in the left parotid gland. **C,** On T2-weighted imaging with fat-saturation, the pleomorphic adenoma is hyperintense, a characteristic appearance for this lesion.

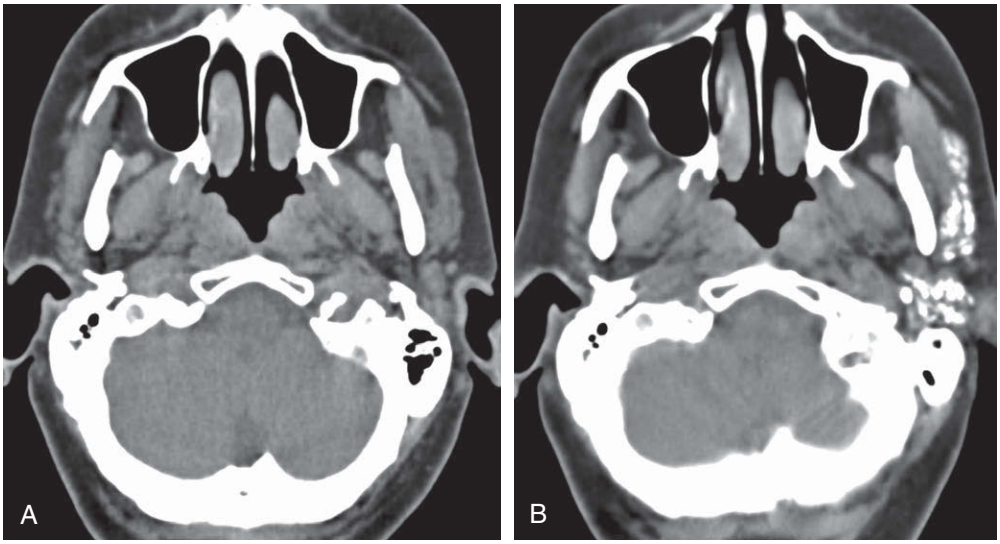

Figure 85-3. Computed tomography sialogram **(A)** before contrast injection and **(B)** after contrast injection showing accessory parotid tissue on the left.

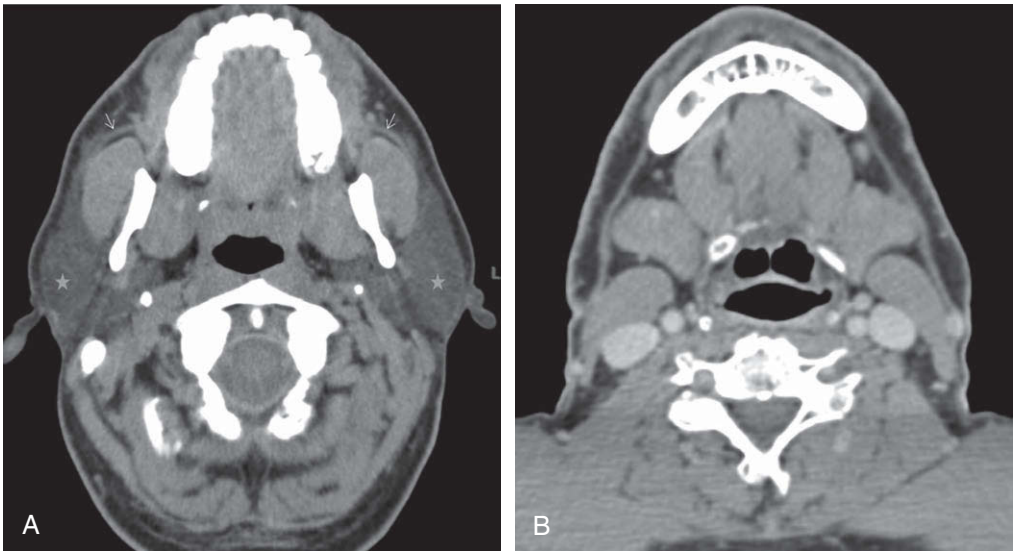

Figure 85-4. **A,** Non–contrast-enhanced computed tomography (CT) with normal parotid glands *(star)* showing the low attenuation consistent with fatty background in this gland. *Arrows* indicate the parotid ducts (Stensen's ducts) bilaterally. **B,** Contrast-enhanced CT with normal submandibular glands.

from the sublingual gland is into the submental and submandibular lymph nodes (levels IA and IB).[5]

Because the sublingual glands are small and closely approximated to the mandible, they are not well visualized on CT when they are normal. The sublingual glands lose volume with increasing age and can be more difficult to differentiate from the surrounding tissues. On MR, the glands are lower on T1WI than the surrounding fat and higher on T2WI.

Minor Salivary Glands

The minor salivary glands are numerous and are present in the deeper submucosal planes of the oral cavity (especially the lip and hard and soft palates), paranasal sinuses, pharynx, external auditory canal, nose, and paranasal sinuses. Though high-resolution MR imaging has been shown to reveal these small glands in the labia,[8] these minor salivary glands are not typically identified on imaging unless they are pathologically enlarged or involved with tumor, of which they are an important tissue of origin.

Magnetic Resonance Imaging

MRI is the modality of choice for the evaluation of salivary neoplasms. Because there is such distinct soft tissue differentiation on MRI, most lesions are identifiable on T1-weighted images, especially in the parotid gland with the fatty background. With the addition of postcontrast imaging on fat-saturated sequences, salivary lesions are easily identified.[9] The adjacent soft tissues are just as well defined, allowing for the assessment of perineal spread, intracranial extension, or marrow invasion. After fat saturation, the previously hyperintense fat on T1-weighted imaging becomes hypointense and the soft tissue mass stands out within the gland. Intravenous gadolinium contrast is helpful to further define salivary lesions and, if present, enhancement along the meninges, within the marrow of the mandible or maxilla or within the foramina of the skull base, all of which would suggest spread of tumor along these routes. Enhancement within the stylomastoid foramen (cranial nerve VII), foramen ovale (cranial nerve V-III), foramen rotundum (cranial nerve V-II), vidian canal (vidian nerve), or the pterygopalatine

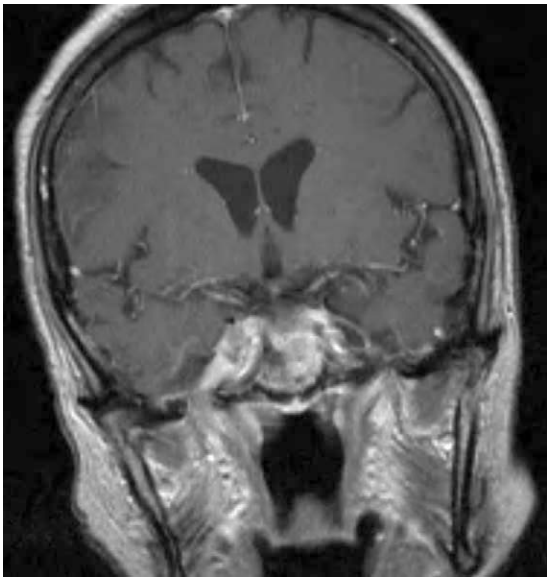

Figure 85-5. T1-weighted postcontrast coronal image showing perineural spread along the mandibular division of the right trigeminal nerve up from the masticator space through foramen ovale into Meckel's cave. This adenoid cystic carcinoma originated in a minor salivary gland of the right maxillary sinus.

fossa suggests perineural spread, and MRI is the best modality to investigate this (Fig. 85-5).

Any tumor imaged by ultrasound (US) with irregular or ill-defined borders or with malignant or suspicious cytology on FNA should be subsequently evaluated by MRI to define the extent of the lesion and possible spread of tumor that might not be identifiable by ultrasound. All sublingual and minor salivary gland tumors should be evaluated by MRI because of the higher rate of malignancy in smaller glands and the risk for perineural spread seen especially with adenoid cystic carcinoma.

Benign lesions are typically well-defined simple or lobulated lesions. Pleomorphic adenomas will have low T1 and high T2 signal intensities similar to water but with solid enhancement best seen on fat-suppressed T1WI after gadolinium. Keep in mind that although pleomorphic adenomas are thought of as benign lesions, malignant degeneration within a pleomorphic adenoma (carcinoma ex pleomorphic adenoma or malignant mixed tumor) may be as high as 25% if left untreated and may, in fact, occur in a patient known to have a previously resected pleomorphic adenoma.[2] For this reason, pleomorphic adenomas are most commonly removed when they are diagnosed.

Warthin's tumor, classified by the World Health Organization as adenolymphoma, is most common in cigarette smokers older than the age of 40 and appears most commonly as a partially cystic lesion arising in the lower portion of the parotid gland at the angle of the mandible (Fig. 85-6). The nature of the lesion results in heterogeneous signal on T2-weighted imaging with bright T2 signal in areas of cyst formation. Nodularity of the cyst wall helps to differentiate it from other cystic lesions. The outer border is well defined and there is no enhancement of the wall. Warthin's tumor is the most likely neoplasm of the salivary glands to be bilateral with up to 10% of patients presenting with bilateral and/or multifocal masses on imaging.[10] Although Warthin's tumors are classically benign, malignant transformation is known to occur, nonetheless, in less than 1% of Warthin's tumors.[11]

Many other cystic lesions affect the salivary glands. AIDS-related parotid cysts can also be bilateral and would have high T2 signal due to their cystic nature (Fig. 85-7). The walls of these cysts are smooth, helping to differentiate them radiographically from cystic Warthin's tumors. A rare first branchial cleft cyst would be seen anterior to the external auditory canal within the parotid tissue. These can become infected with thick enhancing walls and surrounding fat stranding.[2]

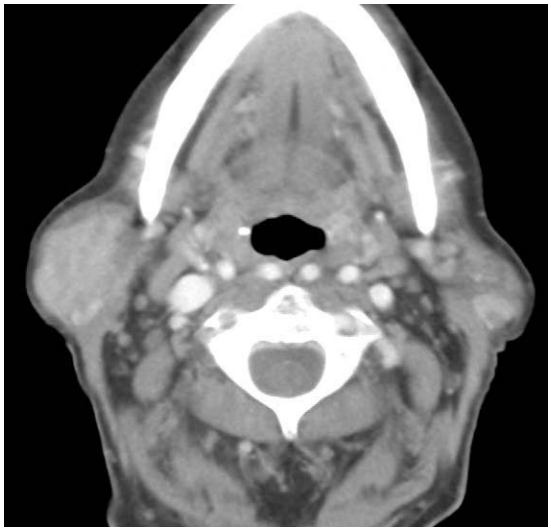

Figure 85-6. Computed tomography showing bilateral Warthin's tumors with solid and cystic components.

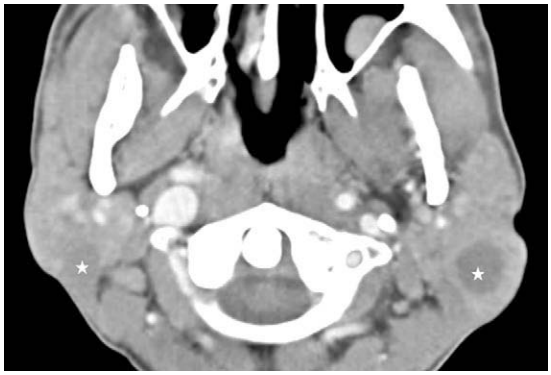

Figure 85-7. Contrast-enhanced computed tomography with bilateral acquired immunodeficiency syndrome (AIDS)-related parotid cysts *(star)* in a patient with human immunodeficiency virus/AIDS.

A ranula is a cystic lesion that arises in the sublingual gland. Two types of ranulae exist. The first, a simple ranula, is an epithelial-lined retention cyst of the sublingual gland. The epithelial border of the simple ranula is intact and the cyst remains above the mylohyoid muscle. If the wall of the simple ranula ruptures and dissects through the mylohyoid muscle into the submandibular space, it forms a mucocele and is referred to as a plunging, or deep, ranula (Fig. 85-8). A ranula of either type will be hyperintense on T2-weighted imaging following fluid on all sequences without enhancement or nodularity in the wall.[10]

Malignant salivary lesions are more likely to be low to intermediate in signal on both T1-weighted imaging and T2-weighted imaging. Most malignant salivary lesions are solitary. Presence of multiple lesions suggests Warthin's tumor, lymphoepithelial cysts, or lymphadenopathy. Lymphadenopathy can be reactive; metastatic, usually from a dermatologic origin (melanoma, basal cell carcinoma, or squamous cell carcinoma); or lymphomatous. Mucoepidermoid carcinoma, the most common salivary malignancy, can look deceptively like a pleomorphic adenoma on all imaging modalities, especially when the lesion is small. It is typically smooth walled, well defined, and may contain calcifications and cysts with mucous material (Fig. 85-9). The mucinous cysts appear as high signal on both T1- and T2-weighted images. The noncystic portions are of low signal on T2-weighted images.[12]

Adenoid cystic carcinoma is the second most common salivary gland malignancy overall and is the most frequent malignant tumor in

the submandibular and sublingual glands. Twenty-two percent of minor salivary gland tumors are adenoid cystic carcinomas. Three pathologic subtypes exist: cribriform, tubular, and solid. The solid lesions have higher cellularity and are correlated with a worse prognosis. These lesions are lower in signal on T2-weighted images. The less cellular lesions of cribriform or tubular subtype are higher in T2 signal intensity on MR imaging[12] (Fig. 85-10). This tumor is well known to spread locally and by perineural invasion. MRI is essential to evaluate the cranial nerves and skull base for this progression. Although the facial nerve is not always well seen on traditional MR sequences, high-resolution MR imaging of the intraglandular facial nerve can be performed, resulting in useful information about a parotid tumor and its relationship to the branches of the facial nerve.[3,6,7,13]

Since MR sialography was first reported in 1996 by Lomas and colleagues,[14] significant advances have been made in sequence development and coil design. These advances have produced high-resolution images of the parotid and submandibular ducts that show obstructions and ductal caliber changes, and they are reproducible.[15,16] These techniques are especially useful in patients with acute sialadenitis in whom conventional sialography is contraindicated. The techniques are also valuable in patients who are allergic to iodinated contrast. Even in cases of radiation-induced xerostomia with intraglandular ductal stenosis[17] and in Sjögren's syndrome, where fine ductal changes are being evaluated, the MR sialogram produced images that aided in the diagnosis when interpreted with the axial T1 and fat-saturated T2.[18]

Advanced MR techniques such as dynamic contrast-enhanced MR imaging, diffusion weighted imaging, and spectroscopy have been studied and show promise in differentiating between benign and malignant lesions.[19-21] These techniques are not in widespread clinical use because they have not typically changed the patient course from imaging, fine-needle aspiration, and extirpation.

Figure 85-8. Hyperintense T2 signal in a plunging ranula in the left sublingual and submandibular spaces.

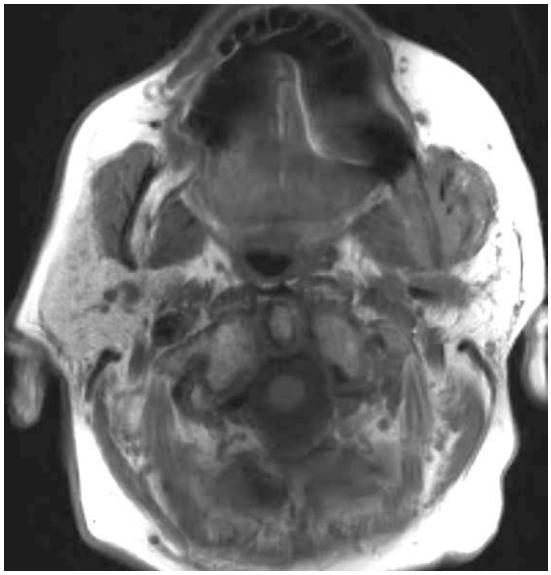

Figure 85-9. T1-weighted precontrast magnetic resonance image revealing a mucoepidermoid tumor of the left parotid gland just posterior to the ramus of the mandible. Note the dark signal in the left mandibular ramus compared with the bright marrow of the right ramus consistent with marrow invasion by tumor.

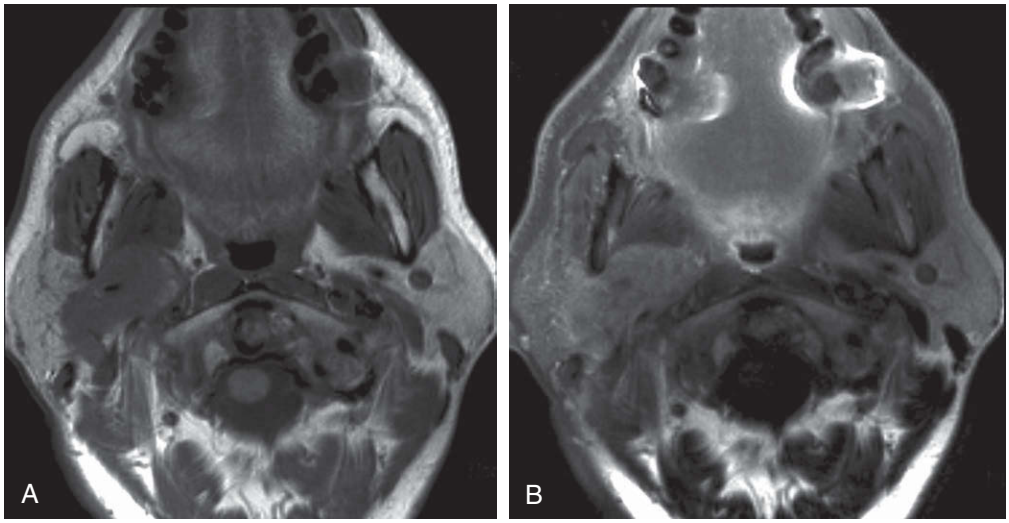

Figure 85-10. **A,** T1-weighted noncontrast magnetic resonance image (MRI) of an adenoid cystic carcinoma in the deep lobe of the right parotid gland. **B,** T1-weighted postcontrast MRI with fat saturation shows enhancement of the mass. Note that the right retromandibular vein is not visualized, raising the concern for involvement of the closely approximated right facial nerve.

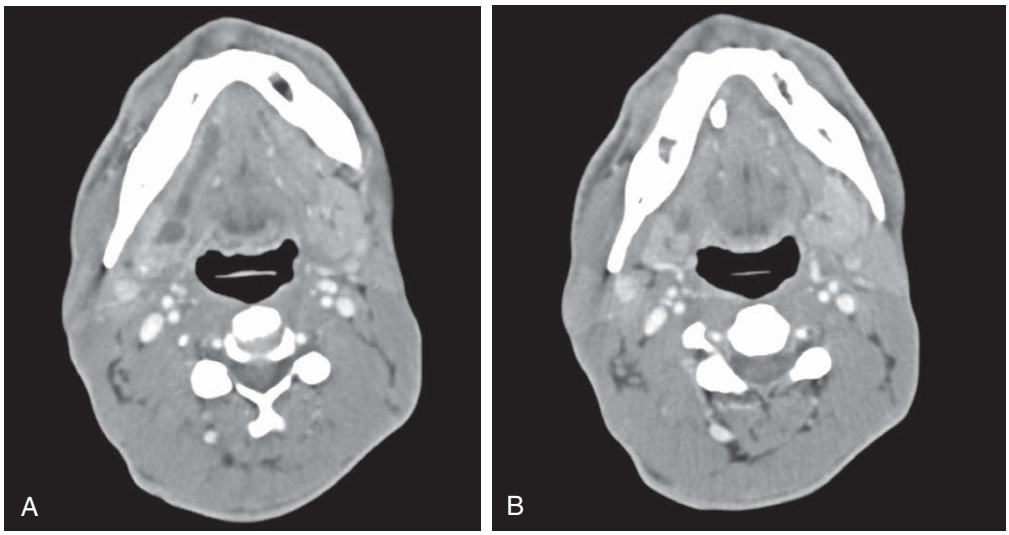

Figure 85-11. **A,** Contrast-enhanced computed tomography showing a dilated right submandibular duct (Wharton's duct). **B,** A few slices cranially in the same patient. A large sialolith is seen near the orifice of the dilated duct, as well as some intraglandular ductal dilatation.

Computed Tomography

As a modality, CT is most useful in the evaluation of calcifications and inflammatory conditions of the salivary glands.[10] The strength of CT is in its ability to show calcification, anatomy, and bony detail. Intravenous iodinated contrast increases the sensitivity of CT for the evaluation of salivary pathology. Spiral CT scans can be reconstructed in the axial, coronal, and sagittal planes to best visualize the anatomy. The fat planes of the neck allow for anatomic placement of a lesion in the correct space limiting the differential diagnosis to the structures occurring in that space. A deep parotid lobe lesion, for example, will be definable as such because it will displace the fat of the parapharyngeal space, as well as the carotid space medially.

Sialolithiasis is a condition in which the precipitation of salts in the saliva forms a stone effectively blocking the flow of saliva from the gland to the oral cavity. Most of the stones (80% to 90%) are associated with the submandibular gland (Fig. 85-11). This is thought to be secondary to the more alkaline pH of the mucinous saliva produced in that gland. The orifice of Wharton's duct is narrow and the duct has a 45% uphill course when the patient is in the erect position. On plain radiographs, 80% of submandibular stones and 60% of parotid stones are radiopaque.[2] Typically, there will be obstructive ductal ectasia with surrounding inflammation in the adjacent fat. The associated gland will be enlarged in the acute state with surrounding inflammation. If there has been chronic obstruction, the gland may be atrophic when compared with the other side.

Ascending infection is a common cause of sialadenitis. Viral infection, most commonly caused by mumps, will cause enlargement and increased density of the affected gland on CT imaging. In acute bacterial infection the gland will be enlarged and more dense than the other side. Inflammatory stranding of the surrounding fat can be seen and abscess could be present, identifiable as a low attenuation area with a thick, irregular, enhancing rim.

Although CT has an overall sensitivity for detecting neoplastic lesions approaching 100%, the distinction between benign and malignant lesions is not always clear on CT. Benign lesions of the salivary glands such as pleomorphic adenoma, Warthin's tumor, and various cystic lesions classically have a well-defined border. These benign lesions, however, can be large and nodular and have hemorrhage, fibrosis, or high protein content that make them inhomogeneous and less well-defined, suggesting a more malignant diagnosis (Fig. 85-12). In contrast, low-grade mucoepidermoid carcinoma and even small adenoid cystic carcinomas can have a pseudocapsule of compressed tissue around them that can make them look more benign. Overall, MR is more sensitive for defining neoplasms and identifying spread to adjacent soft tissues.[10]

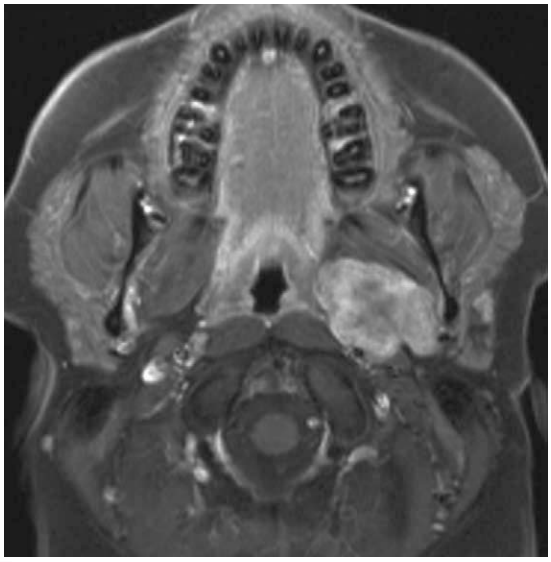

Figure 85-12. T1-weighted postcontrast magnetic resonance image with fat saturation with a pleomorphic adenoma in the deep lobe of the left parotid gland. This pathologically proven benign lesion has deceptively irregular borders, suggesting a more worrisome diagnosis.

Sjögren's syndrome, an autoimmune disease limited to the salivary and/or lacrimal glands, is the result of lymphocyte-mediated destruction of exocrine glands. Serologic markers (SS-A and SS-B antibodies) are elevated in 50% to 70% of patients with active disease. These patients are at higher risk for MALT (mucosa-associated lymphoid tissue) lymphoma. In the early stages of the disease, the gland looks normal on CT. As the disease progresses, the gland becomes enlarged and more dense with eventual development of a honeycomb appearance. Small bilateral cysts may be seen in later stages.[2]

Ultrasound

Ultrasound (US) is typically likely underused in North America in the first-line evaluation of salivary lesions.[9] CT is usually the first choice of imaging for inflammatory diseases, and MRI the first choice of imaging for neoplastic diseased. In experienced hands, however, US may serve the purpose of identifying and characterizing a lesion in the superficial

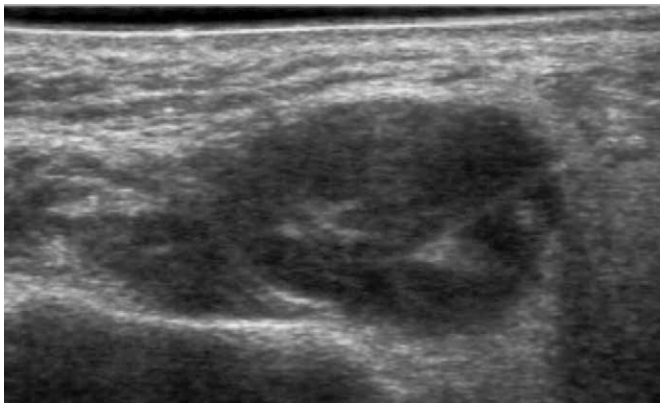

Figure 85-13. Ultrasound-guided fine-needle aspiration of a pleomorphic adenoma of the parotid gland. The needle is identified as the linear structure within the mass.

Figure 85-14. Conventional submandibular sialogram showing a normal ductal appearance.

lobe of the parotid or in the submandibular gland, as well as provide guidance for fine-needle aspiration.[22] The normal appearance of the salivary glands on US is homogeneously hyperechoic to adjacent muscles. The echogenicity of the parotid gland depends on the intraglandular fatty tissue. Higher fat content increases the echogenicity and suppresses the ultrasound waves, limiting the assessment of the deep lobe and even the retromandibular vein and external carotid branches on gray-scale images. Normal, nondilated ducts are not typically on US. Normal intraparotid lymph nodes can be visible with an identifiable fatty hilum. Malignant nodes will be more round, lack a fatty hilum, and will have abnormal peripheral vascularity on Doppler imaging.

Cystic lesions are well defined on US. Cystic neoplasms such as Warthin's tumor or low-grade mucoepidermoid carcinoma are differentiated from developmental or acquired cysts by the thickness and character of the wall of the cyst. Benign pleomorphic adenoma will be homogeneous and hypoechoic with a smooth border, whereas carcinomas will be less well defined and heterogeneous. Malignant lesions will be hypervascular on Doppler imaging. Hypervascularity, however, cannot be the only criterion for malignancy because benign lesions such as hemangiomas can also have increased vascularity. US provides good anatomic detail, and the absence of ionizing radiation in this modality makes it an attractive alternative in the workup of salivary gland lesions, especially in the evaluation of lesions in children, in whom the reduction of diagnostic radiation is crucial.

Fine-Needle Aspiration

Fine-needle aspiration (FNA) has an important role in the diagnostic workup of a salivary gland mass. If definitively positive for malignancy, for example, treatment planning, which often includes surgical resections of varying degrees, is greatly assisted. FNA can be performed without imaging if the lesion is superficial and palpable, though US-guided FNA has been shown to increase the diagnostic accuracy compared with FNA without guidance.[23] US guidance is useful not only for assuring proper needle placement in deeper lesions but also for evaluation of the overall character of the lesion, especially if cross-sectional imaging has not been performed (Fig. 85-13). Aspirates with a 22-gauge needle are usually adequate. Vascular structures are identifiable and therefore avoidable. The facial nerve is not visible on US and therefore the retromandibular vein is used as a landmark because the facial nerve is known to reside just lateral to this readily identifiable structure. Having a cytopathologist present during the procedure to check for adequacy of the specimen is important, especially if the patient is under general anesthesia. Siewert and colleagues[24] reported that the presence of a cytologist increases the likelihood of a diagnostic sample on aspiration without needing a core biopsy. CT guidance for FNA is useful as well, particularly where the lesion is deep, requiring a transbuccal approach.

Early reports raised concerns about the accuracy of cytology and frozen section concurrence with the final histology. The College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology performed a retrospective review of data from 1999 to 2003 including 6249 interpretations of benign and malignant lesions. Their data demonstrate that salivary gland FNA is 73% sensitive and 91% specific for distinguishing between benign and malignant lesions. The overall accuracy of FNA for correctly identifying the correct specific reference interpretation is 48%.[25]

Concerns have been raised regarding the effects of postbiopsy hemorrhage, squamous metaplasia, infarction, and necrosis on the final pathologic diagnosis. A report by Mukunyadzi[26] showed that though these abnormalities were indeed found in the tissues after biopsy, their presence did not alter the final histologic diagnosis. Preoperative FNA combined with intraoperative frozen section resulted in increased diagnostic accuracy than either alone.[27]

Sialography

Conventional sialography is performed to visualize the ducts of the parotid and submandibular glands. It remains the only modality capable of reliably evaluating the fine branches of the intraglandular ductal system (Fig. 85-14). Historically, sialography was useful in the diagnosis of Sjögren's syndrome and differentiating it from chronic sialoadenitis. With modern serum markers for autoimmune disorders, specifically SS-A and SS-B in Sjögren's, sialography is a less important diagnostic aid.[2] Advances in CT and MRI make these cross-sectional modalities superior for evaluation of most salivary lesions, neoplastic and inflammatory.

Conventional sialography is contraindicated in the setting of acute sialadenitis because the procedure may exacerbate the symptoms or cause ascending infection. The procedure is also contraindicated in patients with iodine contrast allergy. Both fat-soluble and water-soluble contrast agents have been used for sialography. Older, fat-soluble contrast agents such as Lipiodol and Pantopaque were reported to cause foreign body reactions following ductal perforation. Ethiodized oil (Ethiodol, 37% bound iodine, Savage Laboratories) is a newer fat-soluble agent that has excellent retention and image resolution with a low reported incidence of foreign body reaction. Water-soluble contrast agents such as diatrizoate meglumine (Sinografin, 38% bound iodine, Squibb) have similar iodine content to ethiodized oil and, if the images are obtained quickly before the contrast mixes with saliva, provide excellent contrast opacification of the ducts with no reported adverse effects with duct perforation. The water-soluble agents such as diatrizoate meglumine are therefore preferable to lipid-soluble contrast agents for silaography.[2]

The papilla for Wharton's duct is located just lateral to the frenulum in the floor of the mouth. The papilla for Stensen's duct is found on the buccal mucosa opposite the second maxillary molar. A blunt-

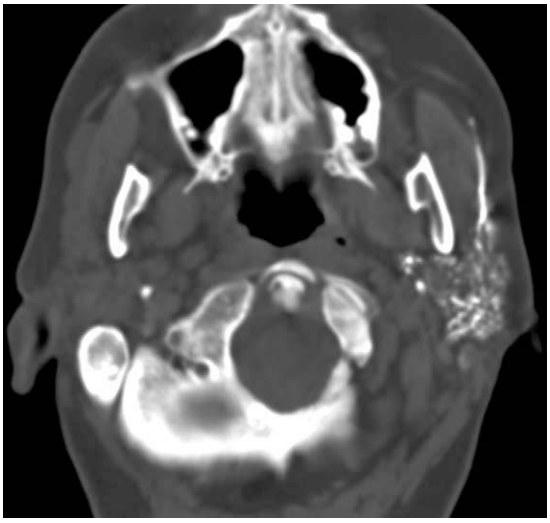

Figure 85-15. Computed tomography sialogram with contrast in a normal left parotid duct and parotid gland.

tipped sialographic cannula with attached tubing is used to access the duct. Some needles have an olive-shaped dilation 1 cm distal to the tip of the needle that, when approximated to the duct orifice, prevents backflow of contrast into the oral cavity. Lacrimal dilators may be necessary to enter the papilla.

Stensen's duct is horizontally oriented, 6 to 7 cm in length, and has a caliber of about 1 to 2 mm. Wharton's duct angles downward and laterally at about a 45-degree angle relative to the sagittal and axial planes and is about 5 cm long with a caliber of 1 to 3 mm. The papilla for Wharton's duct is small and can be more difficult to cannulate and the duct easier to perforate than the parotid duct. The mucosa around the papilla should be dried and the gland massaged to produce saliva. Alternatively, a secretagogue such as lemon juice can be used to produce saliva at the osteum of the duct. Once cannulated, the duct is slowly hand injected with a small volume of contrast under fluoroscopy using approximately 1 mL for Stensen's duct and 0.5 mL for Wharton's duct. Images in the anteroposterior, lateral, and oblique projections are then performed optimizing the visualization of the ductal system. Potential complications of sialography include local pressure or pain, which fades away in minutes and typically completely resolves within 24 hours after the procedure; postsialogram infection; and ductal perforation.

The normal sialographic appearance of the salivary ducts is smooth without filling defects or strictures. The intraglandular branching should be smooth, regular, and without pruning. Postsialogram CT may be helpful to assist localization of abnormalities within the gland (Fig. 85-15).

Nuclear Imaging

The use of nuclear medicine in the evaluation of the salivary glands is limited. It is possible to evaluate physiologic uptake and salivary excretion of intravenously administered technetium 99m pertechnetate. This technique allows for imaging of the parotid and submandibular glands. The sublingual glands and minor salivary glands are too small to evaluate by this method. One instance where nuclear imaging may be useful is in confirming the diagnosis of Warthin's tumors (cystadenoma lymphomatosum) in a patient with surgical contraindications. Pleomorphic adenomas and Warthin's tumors may be difficult to differentiate on CT and MR. Because Warthin's tumors and oncocytomas have increased pertechnetate uptake and pleomorphic adenomas typically have no significant uptake, they can potentially be distinguished with this modality.[9]

The role of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in the initial diagnosis of salivary malignancies is limited due to the high false-positive rate. Parotitis, for example, creates a highly FDG-avid environment. Some data in the literature suggest FDG-PET may be useful in the management of patients at staging and in follow-up, but more research is necessary to evaluate the potential of FDG-PET in the monitoring of these patients.[28]

Conclusion

Diagnostic imaging offers valuable tools for helping with the diagnosis, evaluation, and surgical planning of lesions and disorders of the salivary glands. US is useful in defining a palpable lesion and providing guidance for FNA. Inflammatory lesions are best evaluated by CT because the modality has a high sensitivity for calcification and reveals anatomic information crucial to diffuse or deep processes. MRI is the recommended modality to evaluate neoplastic lesions of the salivary glands. Whether the lesion is in the parotid gland or in a minor salivary gland in the sinus, MRI is the modality that will reveal extension of tumor beyond the confines of the gland, as well as complications such as perineural invasion or bone marrow involvement. MR sialography is showing promise to replace conventional sialography, which is contraindicated in patients with acute inflammation or iodine allergy. US-guided FNA is a valuable perioperative procedure to guide patient care.

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CHAPTER EIGHTY-SIX

Inflammatory Disorders of the Salivary Glands

Jeremy Rogers

Thomas V. McCaffrey

Key Points

- Sialolithiasis, more frequent in the ducts of the submandibular and sublingual glands, may also contribute to acute infection but more commonly produces chronic salivary gland infection.
- Recurrent parotitis of childhood (RPC) is an uncommon inflammatory condition of the parotid gland characterized by periodic episodes of swelling and pain. The characteristic finding is sialectasis that on conventional sialography appears as numerous scattered punctate pools of contrast.
- Sialolithiasis is the formation of calculi in the ductal system of the salivary glands. The submandibular gland is most commonly affected, with 80% to 90% of stones developing in Wharton's duct.
- Relatively recent treatment alternatives for sialolithiasis are extracorporeal shock wave lithotripsy and the use of sialoendoscopy. Lithotripsy reduces calculi to small fragments that are then flushed out of the duct. Sialoendoscopy involves the use of rigid endoscopes to visualize and remove salivary duct stones.
- The CT evaluation of patients with HIV-associated salivary gland disease demonstrates multiple cysts that appear as low-attenuation, thin-walled masses and diffuse lymphadenopathy.
- The biopsy of labial accessory salivary glands demonstrating salivary gland disease is one of the most consistent features of primary Sjögren's syndrome. The histopathologic lesion is a lymphocytic infiltrate producing a chronic focal sialadenitis.
- Sjögren's syndrome predisposes patients to the development of malignant lymphoproliferative disorders.

Salivary gland infections and inflammations have a wide range of presentations, depending on the etiologic agents involved and the chronicity of the infection. These might range from acute localized infections like bacterial sialadenitis to systemic diseases caused by viruses such as the paramyxovirus or the human immunodeficiency virus (HIV). Noninfectious inflammations such as Sjögren's syndrome may present as a chronic swelling of the salivary glands.

Bacterial Infection of the Salivary Glands

Acute Suppurative Sialadenitis

Acute sialadenitis is a bacterial inflammation of the salivary glands. Although these infections occur in all major salivary glands, the parotid gland is most commonly involved. Frequently associated with medically debilitated and postoperative patients, the incidence of acute sialadenitis is approximately 0.02% of hospital admissions. It occurs between 1 in 1000 and 1 in 2000 operative procedures.[1] Patients undergoing major abdominal and hip repair surgery have been identified as being at increased risk for acute suppurative sialadenitis. The disease is most commonly reported to occur within the first 2 postoperative weeks.[2] Of the medically ill patients affected by sialadenitis, approximately 25% have a malignant lesion and another 50% have a preexisting infection elsewhere than the head and neck. Most affected patients are between 50 and 60 years of age, with an equal incidence among men and women.[3]

Acute infection of the salivary glands is caused by retrograde bacterial contamination of the salivary ducts from the oral cavity. Stasis of salivary flow secondary to dehydration or significant hemorrhage permits retrograde migration of bacteria, producing suppurative infection of the gland parenchyma. The parotid gland is most susceptible to such infections.

In contrast to the mainly serous saliva produced by the parotid gland, the saliva made by the submandibular and sublingual glands is primarily mucoid. Serous saliva, unlike mucinous saliva, is deficient in lysosomes, IgA antibodies, and sialic acid, which have antimicrobial properties. In addition, the saliva from the submandibular and sublingual glands contains high-molecular-weight glycoproteins that competitively inhibit bacterial attachment to the epithelial cells of the salivary ducts.[4] Several predisposing factors might lead to acute sialadenitis. These include diseases such as diabetes mellitus, periodontal disease, hypothyroidism, renal failure, and Sjögren's syndrome. Medications might produce reduced salivary flow through multiple mechanisms (Fig. 86-1).

Mechanical impairment of salivary flow also predisposes to acute infection. Stenosis of the salivary ducts secondary to trauma or a foreign body has been reported to result in acute sialadenitis. Sialolithiasis,

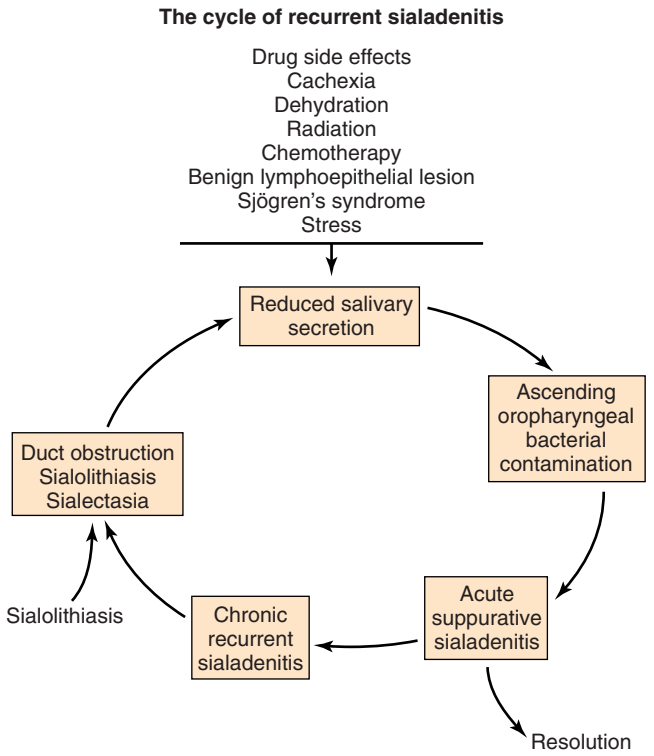

Figure 86-1. Pathophysiology and predisposing factors for the development of acute and chronic suppurative sialadenitis.

Figure 86-2. An acutely formed abscess of the parotid gland demonstrating diffuse unilateral edema.

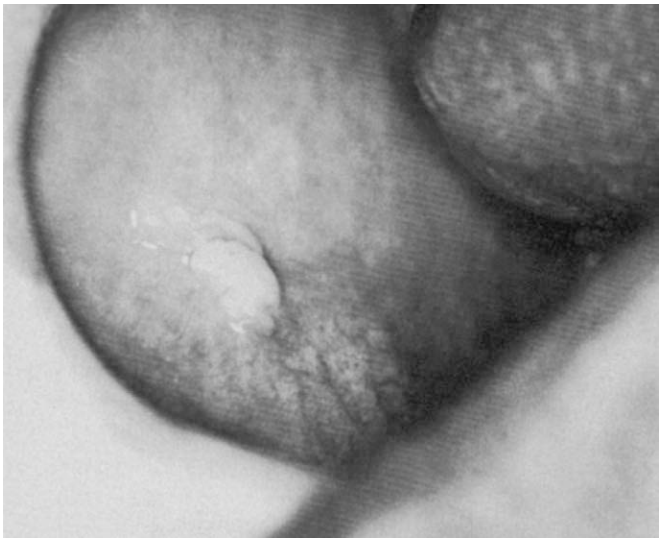

Figure 86-3. A purulent exudate emerging from the orifice of Stensen's duct.

more frequent in the ducts of the submandibular and sublingual glands, may also contribute to acute infection but more commonly produces chronic salivary gland infection.[5] The most commonly cultured organism among hospitalized patients with acute sialadenitis is penicillin-resistant *Staphylococcus aureus,* which is responsible for 50% to 90% of cases. In addition, Streptococcus species including *Streptococcus pyogenes, Streptococcus viridans,* and *Streptococcus pneumoniae,* as well as *Hemophilus influenzae,* can be isolated in community-acquired cases. More recently, the importance of anaerobic and gram-negative bacteria in acute suppurative parotitis has been established. In one study, anaerobic bacteria were isolated from 64% of cases of acute suppurative sialadenitis. The anaerobic bacteria most frequently cultured were *Peptostreptococcus,* bacteroides species, Prevotella species, and fusobacterium. In Southeast Asia, *Burkholderia pseudomallei* is a common cause of parotitis. This apparent shift in microbiology might be the result of improved anaerobic bacterial culture technique rather than a true change in the flora of acute salivary gland infections.[3,6,7]

Acute suppurative sialadenitis presents with local symptoms consisting of rapid onset of pain and swelling over the affected salivary gland (Fig. 86-2). Systemic manifestations include fever, chills, and malaise. Importantly, one should review the medical and surgical history for the previously noted risk factors that would make a patient more susceptible to acute salivary gland infection. On physical examination the patient might demonstrate signs of systemic dehydration with dry mucous membranes. Local findings include tenderness to palpation, with warmth and induration of the overlying skin. Bimanual palpation of the gland results in suppurative discharge from the duct orifice in approximately three fourths of cases (Fig. 86-3).[2] Although typically limited to one gland, multiple glands might be affected, with a reported incidence of bilateral involvement of up to 25% of cases.[8]

The laboratory evaluation will reveal a leukocytosis with neutrophilia. Generally, the serum amylase is normal. Imaging of the affected gland with computed tomography (CT) or ultrasound (US) for abscess formation is indicated in patients who do not respond to medical therapy within 48 to 72 hours. Sialography performed in the acute phases of sialadenitis provides little useful information and is contraindicated because it can exacerbate the existing inflammation. Magnetic resonance imaging (MRI) may be used to evaluate the salivary duct architecture noninvasively; however, its usefulness in acute infection has yet to be established.

Cultures of purulent drainage from the duct orifice should be obtained. Recent reports advocate the use of percutaneous needle aspiration of the involved duct. This technique limits the amount of contamination encountered by means of an intraoral culture.[6,9]

Although the diagnosis of acute parotitis is usually apparent, nonparotid swelling can mimic parotitis. Such conditions include lymphoma, lymphangitis external otitis, Bezold's abscess, cervical adenitis, dental abscesses presenting as buccal or masseteric space abscesses, and infected branchial cleft or sebaceous cysts.[10]

Initial treatment of acute suppurative sialadenitis begins with aggressive medical management. This includes prompt fluid and electrolyte replacement, oral hygiene, reversal of salivary stasis, and antimicrobial therapy. Stimulation of salivary flow is accomplished by the use of sialogogues such as lemon drops and orange juice. Antisialogogic

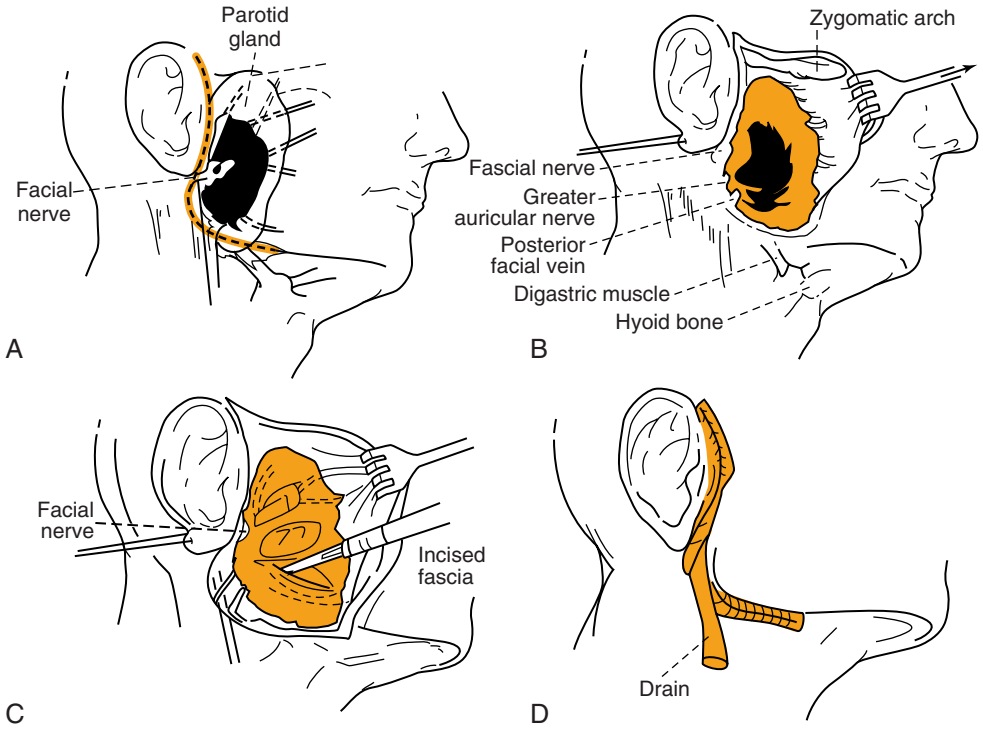

Figure 86-4. Surgical approach to the drainage of an acute parotid gland abscess. **A,** Standard curvilinear incision. **B,** Elevation of an anterior-based facial flap and identification of regional anatomic landmarks. **C,** Abscess drainage by means of incisions in the parotid fascia parallel to facial nerve branches. **D,** Marginal approximation of wound edges and drainage with the central aspect left to heal by secondary intention.

medications should be discontinued. In addition, capable patients should be instructed on regular external and bimanual massage, starting from the distal bed of the gland and working in the direction of duct drainage. Analgesics and local heat application ease the discomfort. If neither saliva nor pus can be expressed from the duct, cannulation and serial dilation may be necessary to establish patency.

Antimicrobial therapy is an essential part of the management of acute salivary gland infections. Antimicrobial therapy is initiated empirically toward gram-positive and anaerobic bacteria. However, the recovery of β-lactamase–producing bacteria in 75% of patients requires the use of augmented penicillin and antistaphylococcal penicillin or a first-generation cephalosporin.[6,11] The use of clindamycin or the addition of metronidazole to the first-line agents to broaden anaerobic coverage has been advocated by some authors.[6] In patients from nursing home environments or cases of nosocomial infection, empiric vancomycin has been advocated given the prevalence of methicillin-resistant *S. aureus*. Aminoglycosides have also been proposed by some in the treatment of critically ill patients. Culture results should be used to further direct antimicrobial treatment. Response to antimicrobial therapy is seen within 48 to 72 hours of initiating treatment and should continue for 1 week after resolution of symptoms.[1]

Rarely, conservative measures fail to eradicate the infection, and surgical drainage of a loculated abscess is necessary. The surgical approach involves elevation of an anterior-based facial flap with abscess drainage by way of radial incisions in the parotid fascia parallel to the facial nerve branches. A drain should be placed, and the wound edges should be loosely approximated, with the central aspect left to heal by secondary intention (Fig. 86-4).

Complications of acute suppurative parotitis are unusual. Suppuration confined to the duct lumen might eventually erode through the epithelium into the interstices of the parenchyma, creating multiple small abscesses that might coalesce into larger collections that can infiltrate a number of potential spaces of the neck. Osteomyelitis of the mandible and temporomandibular joint, thrombophlebitis of the jugular vein, septicemia, respiratory obstruction, and death are potential sequelae of suppurative parotitis. Rupture through the floor of the external auditory canal, spontaneous drainage through the cheek, and extension to the face, neck, and mediastinum have also been reported (Fig. 86-5).[12,13] Facial nerve paralysis, whether complete or incomplete, is uncommon. The etiology of paralysis is unknown but is thought to be due to the virulence of the offending organisms, perineuritis, or acute nerve compression. Because facial nerve paralysis is highly suggestive of parotid malignancy, all patients with paralysis should be followed until the inflammatory process has resolved and facial nerve function returned.[14] Acute suppurative sialadenitis is associated with 20% to 40% reported mortality; however, the prognosis is primarily related to the medical condition of the patient.[2]

Neonatal Suppurative Parotitis

Infections of the salivary glands are uncommon in the neonate. Neonatal suppurative parotitis (NSP) is more common in preterm and male neonates and those with dehydration. *S. aureus* is the most common pathogen, and *Escherichia coli, Pseudomonas aeruginosa*, and group B streptococci have also been implicated in NSP.[15] The oral cavity serves as the portal of entry in most patients.[16] However, transient bacteremia, usually from gram-negative bacteria, may also be responsible.[17]

Clinically, NSP manifests as fever, anorexia, irritability, and failure to gain weight. Erythema of the skin overlying the involved gland might be present. Swelling is usually unilateral initially but often becomes bilateral. The gland might be tender, and the swelling can be firm or fluctuant.

Diagnosis of NSP is made on the basis of clinical findings and Gram's stain, as well as culture of pus from the duct or from fine-needle aspiration (FNA) of the gland. Therapy consists of parenteral antibiotics directed at *S. aureus* and gram-negative bacilli until culture and sensitivity results are available. Drainage procedures should be used only when prompt clinical improvement does not occur or fluctuance of the gland increases.[15]

Recurrent Parotitis of Childhood

Recurrent parotitis of childhood (RPC) is an uncommon inflammatory condition of the parotid gland characterized by periodic episodes of swelling and pain. It can be distinguished from suppurative parotitis by the inability to express pus from the parotid duct. The age of onset

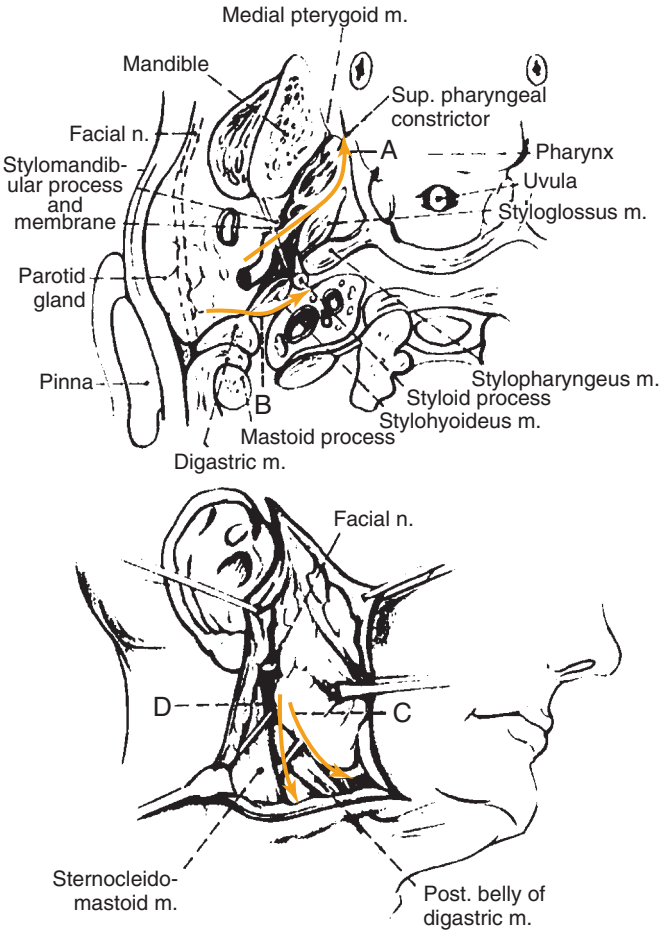

Figure 86-5. Patterns of progression of parotid abscesses. **A,** Prestyloid extension to parapharyngeal space *(arrow)*. **B,** Poststyloid extension to carotid sheath *(arrow)*. **C,** Anteroinferior extension anterior to the posterior digastric belly of the submandibular space *(arrow)*. **D,** Inferior extension posterior to the posterior digastric belly to the carotid triangle *(arrow)*.

ranges from 8 months to 16 years, with a reported peak incidence between the ages of 3 and 6 years.[17,18] Boys are more frequently affected than girls.

The cause of recurrent parotitis of childhood remains unknown, and multiple etiologies have been proposed. Several authors advocate that congenital ectasia of portions of the secondary ductal system predisposes children for bacterial colonization leading to recurrent parotitis.[17] *S. aureus* and *S. viridans* are the most commonly isolated organisms from the parotid ducts of patients. A familial form of RPC has been described with autosomal inheritance.[19] Immunologic abnormalities with isolated IgG3 and IgA deficiencies have been associated with recurrent parotitis. In addition, parotid swelling might be the sole manifestation of juvenile-onset primary Sjögren's syndrome. Several viruses might also play a role in RPC. A history of mumps parotitis often exists. Repeated multiplication of the Epstein-Barr virus in the parotid gland might be responsible for establishing repeated parotid gland inflammation, and RPC has a reported incidence of 20% in HIV-infected children.[20,21]

The histologic appearance of affected parotid glands demonstrates massive periductal lymphocytic infiltration. The intraglandular ducts are dilated and measure approximately 1 to 2 mm in diameter.[20]

Clinically, patients are seen with recurrent episodes of acute or subacute parotid gland swelling along with fever, malaise, and pain frequently after a meal. Episodes of RPC are commonly unilateral, but bilateral involvement has been reported in up to 44% of cases. Afflicted patients tend to experience exacerbations every 3 to 4 months; however, in one series with 53 patients, mean frequency was eight episodes per year. Each might last days to weeks.[17] Diagnosis is usually delayed more than 1 year.

Several imaging modalities may be used to study the ductal system of patients with RPC. The characteristic finding is sialectasis, which on conventional sialography appears as numerous scattered punctate pools of contrast. US of the parotid gland reveals an enlarged gland with multiple small hypoechoic areas. These areas represent both sialectasis of the ducts and the surrounding lymphocytic infiltration. Recently, MR sialography has been reported to be useful in the evaluation of RPC.[20] It is a noninvasive study, not requiring contrast, and may be used during acute episodes.

Treatment consists of adequate hydration, gland massage, local heat, sialagogues, and appropriate intravenous antibiotics. Empiric therapy before culture results should consist of a penicillinase-resistant antistaphylococcal antibiotic. In general, this will lead to rapid resolution of swelling and discomfort. Some authors have advocated prophylactic antibiotics, but this has not been proven effective. Fortunately most cases of recurring parotitis resolve spontaneously near the onset of puberty or in late adolescence, and surgical treatment is rarely required. Of the available options, parotidectomy is curative but carries the risk of facial nerve damage. Ductal ligation and tympanic neurectomy have been reported but with varying results.

Chronic Sialadenitis

Chronic sialadenitis is a localized condition of the salivary gland characterized by repeated episodes of pain and inflammation. The parotid gland is the most frequently affected site.[22] The initial inciting factor is believed to be salivary duct obstruction, with resulting salivary stasis. The most common cause of ductal obstruction is sialolithiasis. Stricture of the salivary duct, extrinsic compression by tumor, stenosis secondary to scar in adjacent tissue, congenital dilation, and foreign body are additional causes of duct obstruction.[23] Salivary stasis from obstruction predisposes patients to episodes of infection and inflammation. Recurrent inflammatory reactions result in progressive acinar destruction with fibrous replacement and sialectasis (Fig. 86-6).

Clinically, patients are seen with a history of recurrent swelling and tenderness of the affected gland associated with eating. Patients frequently report an initial episode of acute suppurative sialadenitis. Asymptomatic intervals might range from a few weeks to months. The physical examination reveals enlargement of the gland, and minimal saliva can be milked from the duct orifice.

Treatment of chronic sialadenitis can be frustrating, and no treatments are consistently successful. Tympanic neurectomy and parotid duct ligation are procedures advocated for chronic parotitis to induce atrophy of the gland, but these have failed to show reliable benefit. Surgical removal of the gland when conservative management has failed to control symptoms has been shown to be safe and effective.[24]

Possible complications of chronic sialadenitis include the development of a benign lymphoepithelial lesion, Kuttner's tumor, and ductal carcinoma.[25-27] A benign lymphoepithelial lesion is characterized by a lymphoreticular infiltrate with acinar atrophy, irregularly placed nuclei, and ductal metaplasia. The metaplasia results in the development of epimyoepithelial islands. Women in the fifth to sixth decade of life are more commonly affected. It has been associated with Sjögren's syndrome and has also been termed Mikulicz's disease. A benign lymphoepithelial lesion typically presents as an asymptomatic mass. FNA may be used for diagnosis and allow for a nonsurgical approach to management.[27] However, patients must be followed because there are reports of the development of malignancy from these lesions.[26]

Kuttner's tumor is a benign inflammatory process similar to a benign lymphoepithelial lesion. However, the lesion occurs almost exclusively in the submandibular gland. Kuttner's tumors are most common in middle-aged adults and present as a painless mass. Histologically, there is a heavy lymphoid infiltrate among discrete tubular structures with regularly aligned nuclei, which differentiates them from a benign lymphoepithelial lesion. Kuttner's tumor might also be followed clinically. Again, careful and routine assessment of patients with chronic sialadenitis is underscored by reports of the development of malignancies including salivary ductal carcinoma.[26]

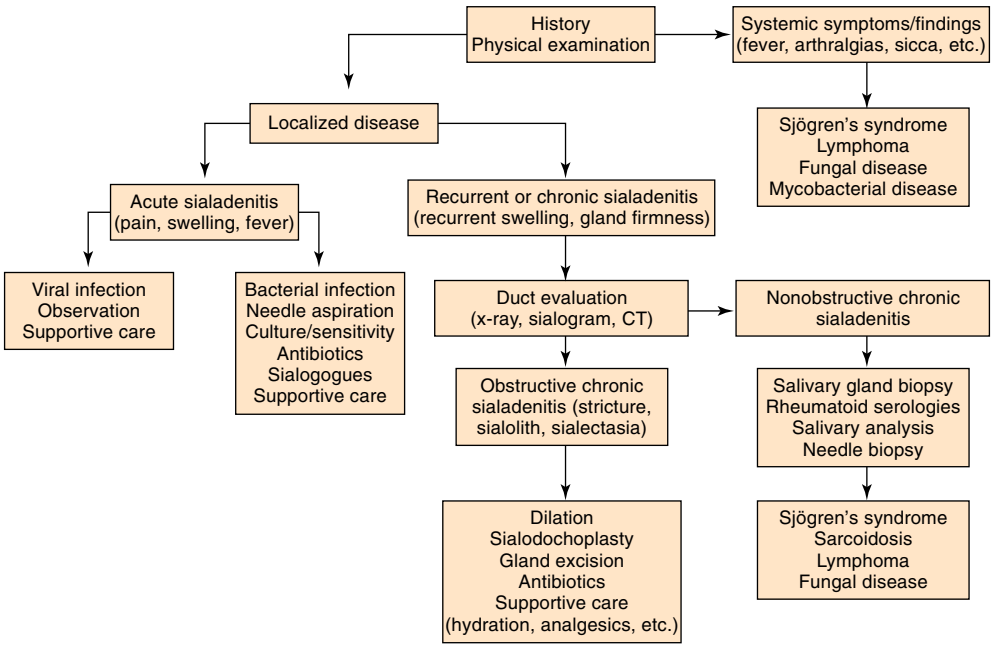

Figure 86-6. A simplified algorithm for the diagnosis and management of chronic salivary gland inflammation.

Sialolithiasis

Sialolithiasis is the formation of calculi in the ductal system of the salivary glands. The submandibular gland is most commonly affected, with 80% to 90% of stones developing in Wharton's duct. Approximately 10% to 20% of calculi form in the parotid (Stensen's) duct and 1% in the sublingual duct.[28] Patients in their fifth to eighth decade of life represent most cases. Sialolithiasis in children is rare; however, if afflicted, children most commonly are seen at 10 years of age.[6] Men tend to develop calculi much more frequently than women.

Salivary stones are composed predominantly of calcium phosphate and carbonate in combination with an organic matrix of glycoproteins and mucopolysaccharides. Small amounts of other salts such as magnesium, potassium, and ammonium are also involved in stone formation.[29]

The exact etiology of sialolithiasis is uncertain. There does not seem to be a relationship between their formation and serum calcium or phosphorous levels.[30] Salivary stasis and ductal inflammation and injury are important factors contributing to stone formation. It is believed that intermittent salivary stasis results in an alteration of the mucoid elements of saliva forming an organic gel. This gel becomes the framework for the deposition of salts, which leads to the development of calculi. The relationship between sialolithiasis and chronic sialadenitis might differ between salivary glands.[28] In the submandibular gland, development of a sialolith might be the primary event that results in stagnation of saliva and inflammation, encouraging bacterial migration and resultant sialadenitis. In contrast, inflammation and ductal injury in the parotid gland from chronic sialadenitis are believed to be the inciting processes for sialolithiasis.

Several factors might account for the propensity of salivary stones to form in the submandibular gland. Wharton's duct is longer, has a larger caliber, and is angulated against gravity as it courses around the mylohyoid muscle, all of which results in slower salivary flow rates. Also, the saliva produced by the gland itself is more viscous and has a higher calcium and phosphorous concentration.[28,31]

In the parotid gland, stones are most commonly located at the hilum or parenchyma. Sialolithiasis in the submandibular gland tends to develop in the duct.[32]

Patients with sialolithiasis are seen with recurrent episodes of postprandial salivary colic with pain and swelling. The patient might also have a history of multiple cases of acute suppurative sialadenitis (Fig. 86-7). On physical examination, bimanual palpation will reveal the presence of a palpable stone in most cases involving the submandibular duct. Parotid stones might be noted at the orifice of Stensen's duct or along the course of the duct.

Figure 86-7. Development of acute suppurative sialadenitis and abscess secondary to submandibular gland sialolithiasis.

Imaging of the salivary glands for sialolithiasis may be accomplished with plain radiographs, conventional and digital sialography, US, CT, and MRI. Plain radiographs that use intraoral or occlusal views might be used to identify radiopaque stones (Fig. 86-8). These stones are much more common in the submandibular gland than in the parotid gland, where up to 80% of stones are radiolucent. However, other calcifications in the area such as phleboliths, arterial atherosclerosis of the lingual artery, or calcified cervical lymphadenopathy make the interpretation of plain radiographs more difficult. US has proven value in the diagnosis of sialolithiasis, with the ability to detect 90% of stones greater than 2 mm.[33] CT scanning with fine cuts is extremely accurate at detecting salivary stones. Digital subtraction sialography, which lessens the interference of surrounding bony structures, has been

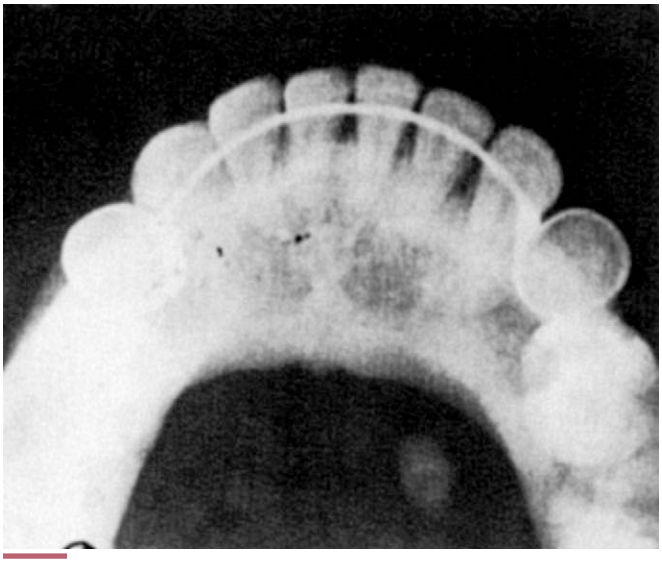

Figure 86-8. An occlusal view radiograph demonstrating an opaque calculus in Wharton's duct.

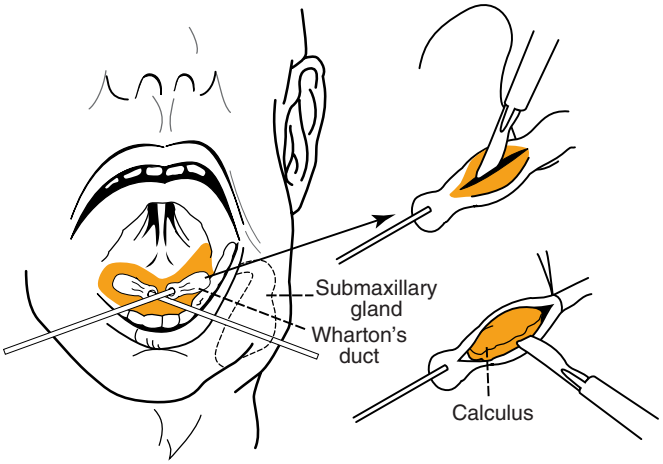

Figure 86-9. Techniques for localization and retrieval of a submandibular duct calculus.

the diagnostic test of choice for sialolithiasis. This can detect radiolucent stones and has a reported sensitivity of 95% to 100%.[27] Several disadvantages are inherent to sialography. It is an invasive technique with the possible side effects of contrast material. Sialography is also contraindicated for stones located in the oral portion of Wharton's duct and in cases of active infection. MR sialography is a relatively new and noninvasive technique being used to evaluate the salivary duct system. Studies indicate that MR sialography of the submandibular duct with evoked salivation has accuracy similar to digital sialography and superior to US.[33] This imaging modality becomes a superior alternative in patients with contraindications to digital sialography. FNA might be indicated in patients with suspected sialolithiasis when no stone is detected and the possibility of malignancy exists. However, pathologic diagnosis in this setting is difficult, and the ductal metaplasia of sialolithiasis secondary to stone formation might be misinterpreted with mucoepidermoid carcinoma.[30]

Initial nonsurgical management of patients with sialolithiasis consists of the use of sialogogues, local heat, hydration, and massaging of the involved gland. If salivary gland infection is suspected, prompt antibiotic coverage should be started.[28]

Surgical intervention for sialolithiasis depends on the anatomic location of the stone. Submandibular stones that are palpable in the mouth and are no more than 2 cm from the duct orifice may be removed using an intraoral approach. This may simply involve milking the stone through the duct opening manually or incising the duct directly over the stone without the need for closure of Wharton's duct after the procedure (Fig. 86-9). Submandibular stones located in a more posterior location will require sialadenectomy,[28] which may be performed through a transcervical or a transoral approach.[34]

The anatomy of Stensen's duct makes the management of parotid stones more difficult. An intraoral approach is limited to parotid calculi that are situated in the segment of Stensen's duct medial to the masseter muscle. In addition, manipulation of the parotid duct is complicated by a high incidence of stricture and frequently requires the use of a temporary stent. The remaining surgical option for parotid stones is a parotidectomy.

Relatively recent treatment alternatives for sialolithiasis are extracorporeal shock wave lithotripsy and the use of sialoendoscopy. Lithotripsy reduces calculi to small fragments that are then flushed out of the duct with spontaneous salivation or the use of a secretagogue.[35] Sialoendoscopy involves the use of rigid endoscopes to visualize and remove salivary duct stones. Several researchers have reported on the efficacy of this technique using a combination of baskets, graspers, and intracorporeal lithotripsy to treat sialolithiasis in both the parotid and submandibular glands.[36-38]

Viral Infections of the Salivary Glands

Viral involvement of the salivary glands most commonly occurs through hematogenous dissemination, although infection by retrograde ductal migration does occur. Viral infection of salivary parenchyma is not always locally symptomatic because transmission from blood to saliva occurs without localizing signs in many systemic viral infections including rabies, hepatitis, influenza, and poliomyelitis.

Mumps

Mumps classically defines an acute nonsuppurative viral parotitis caused by the paramyxovirus. The term "mumps" is derived from the Danish "mompen," which means mumbling (like an old man), and describes the difficulty with speech because of inflammation and trismus.[5] Mumps is the most common cause of nonsuppurative acute sialadenitis, and 85% of cases occur in children younger than the age of 15.[11] The disease is highly contagious and occurs worldwide, with a peak incidence in the spring in temperate climates and with little variation in the tropics.[39]

The paramyxovirus is a ribonucleic acid virus that is endemic in the community and is disseminated by means of airborne droplets from salivary, nasal, and urinary secretions. Interestingly, no known animal reservoir, insect vector, or human carrier has been identified. The disease is maintained by spread from acute cases.[2] Viruses other than paramyxovirus have been implicated as causes of acute viral parotitis: Coxsackie viruses A and B, enteric cytopathic human orphan virus, cytomegalovirus, and lymphocytic choriomeningitis virus.[40]

The virus enters through the upper respiratory tract and has an incubation period of 2 to 3 weeks. During this incubation period, the virus multiplies in the upper respiratory tract epithelium and parotid gland. The virus then localizes to biologically active glandular and central nervous system tissue. Patients will typically experience a viral prodrome consisting of low-grade fever, headache, myalgia, anorexia, arthralgia, and malaise just before parotid gland symptoms. The parotitis is characterized by localized pain and edema of the gland along with otalgia, trismus, and dysphagia. Eating or chewing exacerbates the pain. In 75% of cases, there will be bilateral parotid gland swelling that causes displacement of the pinna.[2] Commonly, the gland on one side will swell first, followed by enlargement of the other gland in 1 to 5 days. The submandibular gland might be affected in rare cases. Physical examination of the involved gland will demonstrate nonpitting edema that is tense and firm. The overlying skin will be stretched with a glazed appearance, but there should be no erythema or warmth.

The diagnosis of viral parotitis is confirmed through viral serology. Complement-fixing soluble (S) antibodies against the nucleoprotein

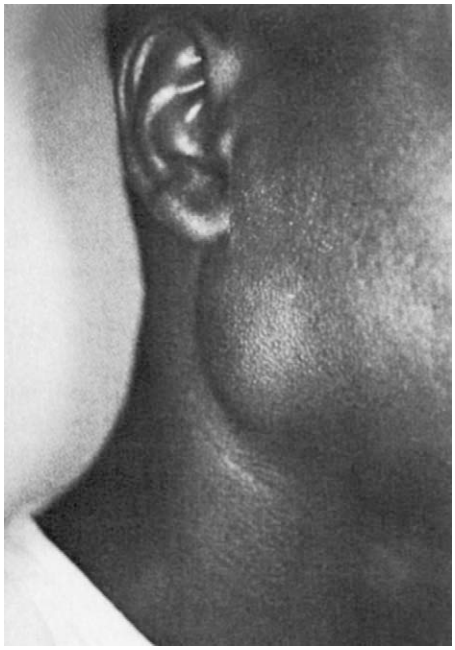

Figure 86-10. Clinical appearance of human immunodeficiency virus–related enlargement of the parotid gland. *(From Debo RF, Davidson M, Petrow CA. Pathologic quiz case 2. Benign lymphoepithelial cyst of the parotid gland associated with HIV infection.* Arch Otolaryngol Head Neck Surg. *1990;116:487.)*

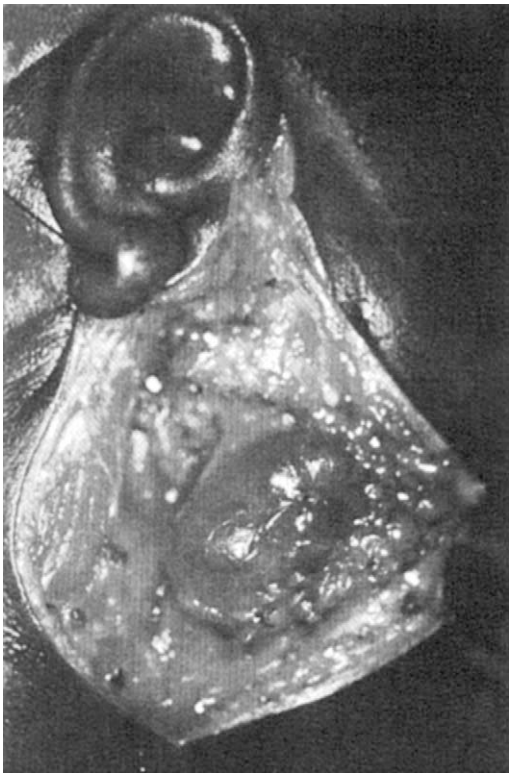

Figure 86-11. Intraoperative appearance of a parotid gland cyst occurring in a human immunodeficiency virus–seropositive patient. *(From Debo RF, Davidson M, Petrow CA. Pathologic quiz case 2. Benign lymphoepithelial cyst of the parotid gland associated with HIV infection.* Arch Otolaryngol Head Neck Surg. *1990;116:487).*

core of the virus are the earliest antibodies to appear. Their levels peak at 10 days to 2 weeks and disappear within 8 to 9 months. Therefore these S antibodies are associated with active infection. Complement-fixing viral (V) antibodies against outer surface hemagglutinin appear later than S antibodies but persist at low levels for years. If serology for paramyxovirus is negative, antibody titers for other viral agents that might also result in parotitis may be obtained. A fourfold increase in antibody titer is diagnostic for acute infection.[5] The mumps skin test has no diagnostic value in the setting of acute infection because dermal hypersensitivity does not develop until 3 to 4 weeks after exposure to the virus. A leukocyte count will occasionally be remarkable for leukopenia, and there is also an elevation in the serum salivary-type amylase.

Management of acute viral parotitis involves supportive measures that include bedrest, oral hygiene, hydration, and dietary modifications to minimize glandular secretory activity. Fever will usually subside before the resolution of glandular edema, which requires several weeks. Complications of mumps virus include orchitis, aseptic meningitis, pancreatitis, nephritis, and sensorineural hearing loss.[2]

The prevention of mumps is by means of vaccination with the live attenuated Jerry Lynn vaccine. The vaccine is administered subcutaneously, usually in combination with measles and rubella vaccines after 12 months of age. The antibodies produced persist for at least 5 years. The vaccine is contraindicated in pregnancy, immunocompromised states, allergies to neomycin, and pregnancy.[3]

HIV

HIV is associated with several pathologic processes involving the salivary glands. These include neoplasms such as Kaposi's sarcoma and lymphoma and lymphoproliferative and cystic enlargement of the major salivary glands with accompanying salivary dysfunction (Fig. 86-10). HIV-associated salivary gland disease (HIV-SGD) is a term used to describe this diffuse enlargement of the salivary glands. HIV-SGD may affect patients throughout all stages of the disease and may be the initial manifestation of HIV infection.[41] The parotid gland is the most commonly affected of the salivary glands. Salivary secretions have been shown to contain low concentrations of the virus; however, studies have failed to show infection in the epithelial cells of the salivary gland. No other viruses, such as the cytomegalovirus or Epstein-Barr virus, have been isolated in association with HIV-SGD.

The histologic findings of the salivary glands affected by HIV-SGD are varied. The enlarged intraparotid and periparotid lymph nodes demonstrate a uniform follicular hyperplasia characteristic of the generalized lymphadenopathy associated with HIV infection elsewhere in the body. In addition, there are parotid nodes containing salivary epithelial structures and epithelial-lined cysts in addition to the follicular hyperplasia. In some cases, there is diffuse infiltration of the gland by lymphoid elements with cystic dilation of the salivary ducts. It is believed that the surrounding lymphoid hyperplasia results in incomplete ductal obstruction, leading to the growth of epithelial cysts (Fig. 86-11).[42]

Patients with HIV-SGD report a history of gradual, nontender enlargement of one or more of the salivary glands. The glandular swellings might fluctuate but are generally stable and long standing. Decreased salivary gland function results in xerostomia and sicca symptoms. This sicca symptom complex clinically mimics Sjögren's syndrome and has resulted in the classification of another HIV-related salivary gland pathologic process known as the diffuse infiltrative lymphocytosis syndrome (DILS).[43]

DILS is characterized by the presence of persistent circulating $CD8^+$ lymphocytosis and visceral $CD8^+$ lymphocytic infiltration that occurs predominantly in the salivary glands and lungs. DILS might appear similar to Sjögren's syndrome but can be differentiated by the presence of extraglandular involvement involving the lung, gastrointestinal tract, and kidneys. In addition, autoantibodies present in patients with Sjögren's syndrome will be absent in DILS.

The radiographic evaluation of patients with HIV-SGD involves the use of CT and MRI. On CT, the parotid gland generally demonstrates multiple cysts that appear as low-attenuation, thin-walled masses

and diffuse lymphadenopathy. The MRI will show homogeneous masses of intermediate signal intensity on proton density and T2-weighted images.[41]

Medical treatment of HIV-SGD involves the use of zidovudine, maintenance of good oral hygiene, and the use of sialogogues. Patients with DILS and progressive visceral lymphocytic infiltration may be treated with corticosteroids and immunosuppressive therapy.[44] Some controversy exists regarding HIV-SGD and the need for surgical excision and pathologic examination of an enlarged salivary gland. In general, in patients with documented HIV-SGD, it has been demonstrated that the findings of needle aspiration and CT or MRI are sufficiently typical to provide a presumptive diagnosis, justifying conservative clinical observation.[45]

Granulomatous Infections of the Salivary Glands

Salivary gland involvement frequently arises as a manifestation of a chronic granulomatous disease involving the lymphatic network in and surrounding the parotid gland. Direct infiltration of the adjacent glandular parenchyma occurs in fulminant cases. Manifestations frequently feature asymptomatic gradual enlargement of a nodule within the gland substance, suggesting a neoplasm. Included among these granulomatous diseases are tuberculous and nontuberculous mycobacterial diseases, actinomycosis, cat-scratch disease (CSD), toxoplasmosis, and tularemia.

Tuberculous Mycobacterial Disease

The most common manifestation of *Mycobacterium tuberculosis* infection in the head and neck is cervical lymphadenopathy. The diagnosis of mycobacterial infections has become more frequent secondary to increased immigration from underdeveloped countries and the HIV epidemic. However, primary salivary tuberculosis remains an uncommon entity. The diagnosis of mycobacterial infection of the salivary glands is difficult because the differential diagnosis must include the usual spectrum of inflammatory and neoplastic diseases and lesions unique to the salivary glands.

Tuberculous salivary gland infection is most common in older children and adults. The disease is spread by close person-to-person contact. Primary salivary gland infection by *M. tuberculosis* is believed to evolve from a focus in the tonsils or gingival sulcus ascending to the glands by way of their ducts. This may then spread to the cervical nodes through the lymphatic drainage.[46] This localized, extrapulmonary type of tuberculous infection most frequently affects the parotid gland. Secondary infection of the salivary glands occurs by way of hematogenous or lymphatic spread from the lungs. Mycobacteria are encapsulated in the intraglandular lymph nodes and might be reactivated many years after the acute pulmonary infection. The submandibular gland is the more commonly involved gland after systemic tuberculous infection.[47]

Clinically, tuberculous salivary gland infection presents in two different forms. The first is an acute inflammatory lesion with diffuse glandular edema that may be confused with an acute sialadenitis or abscess. A second chronic tumorous lesion is seen as a discrete slow-growing mass that mimics a neoplasm.[27] Constitutional signs including fever, night sweats, and weight loss might be absent. Involvement of the facial nerve is rare.

The chest x-ray is commonly negative but might show evidence of healed granulomatous disease. The CT images of tuberculous infection in the head and neck are described as having three patterns. The first, early in the course of disease, demonstrates involved lymph nodes with nonspecific homogeneous enhancement. In the second pattern, there is a nodal mass with central lucency and thick rims of enhancement and minimally effaced fascial planes. The third is described as fibrocalcified nodes, usually seen in patients previously treated for tuberculosis.[30]

In the setting of a tuberculous infection, the purified protein derivative (PPD) skin test should be positive. FNA biopsy may be used for diagnosis with a lower risk of producing a draining fistula than incisional biopsy. The FNA sample is analyzed for characteristic cytologic features: granulomatous inflammation and epithelioid histiocytes. In addition, material may be sent for culture and acid-fast smears.[48]

Once diagnosed, *M. tuberculosis* infection may be treated with triple-drug therapy. In cases in which the diagnosis is uncertain or the lesion is resistant to medical therapy, complete surgical excision is both diagnostic and curative.[27]

Nontuberculous Mycobacterial Disease

Nontuberculous mycobacteria (NTM) have become an increasingly important disease of childhood. In fact, more than 92% of mycobacterial cervicofacial infections in children are a result of NTM.[49] The disease mainly affects children younger than 5 years of age, with most cases occurring between 16 and 32 months of age. The specific organisms most commonly classified as NTM are *Myocbacterium kansasii, Myocbacterium scrofulaceum,* and *Myocbacterium avium–intracellulare.* Infection by *Mycobacterium bovis* has decreased dramatically with the institution of milk pasteurization. These organisms are commonly found in soil, water, domestic and wild animals, milk, and other food items.[50] The portal of entry is believed to be through the mouth, and the tonsils have been implicated in particular.

The typical clinical presentation is of a rapidly enlarging and persistent neck mass that has failed to respond to antibiotic therapy in a pediatric patient. The skin becomes adherent to the surrounding tissues and develops a characteristic violaceous discoloration (Fig. 86-12). The infection might progress to fluctuation and the development of a draining sinus. These lesions generally produce few systemic symptoms. Associated cervical lymphadenopathy is more commonly unilateral and located in the high jugular nodes or preauricular areas.[49] The differential diagnosis should include all diseases specific to the salivary glands, as well as other granulomatous diseases, acute bacterial or viral infection, and malignancy. Chest x-ray findings are typically absent. Contrast-enhanced CT images show asymmetric cervical lymphadenopathy with contiguous low-density, necrotic, ring-enhancing masses involving the subcutaneous fat and skin. In addition, inflammatory stranding of the subcutaneous fat characteristic of bacterial inflammation is minimal or absent with NTM infection.[51]

Recently, there have been numerous approaches described to diagnose an NTM infection. FNA biopsy is one method, but it does carry the risk of fistula formation. PPD skin testing might be negative; however, NTM-specific antigens have been developed and are reported to be extremely successful for diagnosis. Newer methods that use polymerase chain reaction techniques to detect mycobacterial RNA in tissue and *Mycobacterium avium* deoxyribonucleic acid in gastric aspirates are still not widely available.[50] Traditional culture of NTM might take up to 6 weeks and is frequently negative.

Figure 86-12. A 4-year-old girl with nontuberculous mycobacterial involvement of periparotid lymph nodes.

Medical treatment of NTM with prolonged courses of antimicrobials, such as clarithromycin, has been advocated but is not well established. The treatment of choice is complete surgical excision of the involved salivary gland and nodes.[49,50]

Other Granulomatous Diseases

Actinomycosis

Actinomycosis is an infectious disease caused by the actinomyces species, a gram-positive, anaerobic, non–acid-fast bacillus. The actinomyces have a branching, filamentous appearance and are similar in appearance and pathogenicity to mycobacteria and fungi. They are a normal commensal organism found in high concentrations in the tonsils and carious teeth. *Actinomycosis israelii* is the most commonly encountered species, with the balance of cases attributable to *Actinomycosis bovis* and *Actinomycosis naeslundii*. The three major clinical infections caused by actinomyces are cervicofacial (55%), abdominopelvic (20%), and pulmonothoracic (15%).[52]

In most cases, poor oral hygiene combined with trauma to the mucosa permits invasion of the organism, leading to a slowly progressive inflammatory reaction. Diabetes, immune suppression, long-term steroid use, and malnutrition have also been implicated as predisposing factors. Isolated salivary gland involvement probably occurs by means of retrograde ductal migration and primarily occurs in the parotid gland.[53] Involvement of the salivary glands also can occur as part of direct spread of an invasive cervicofacial infection.

Patients typically have a painless, indurated enlargement of the involved gland that might suggest a neoplasm. A chronic purulent drainage might occur with granulomatous involvement and spread to adjacent tissue. The periphery of the lesion is densely fibrotic and avascular. The development of multiple draining cutaneous fistulas is quite common.[52] Facial nerve involvement has not been described. A history of recent dental disease and manipulation is common. Constitutional symptoms, malaise, leukocytosis, and lymphadenopathy are typically absent. CT scans typically demonstrate obliteration of the normal tissue planes and extensive soft-tissue destruction.[49]

Anaerobic cultures are obtained for species identification and to confirm the diagnosis; however, the recovery rate in culture is less than 50%.[52] Diagnosis is assisted by needle aspiration of the mass or a fistula swab with smears and stains to examine for the presence of sulfur granules and the organism. Sulfur granules have also been described for nocardiosis, but their identification in the presence of filamentous gram-positive rods is diagnostic for actinomycosis.[54] Biopsy specimens show firm fibrous encasement of multiloculated abscesses containing whitish yellow purulent discharge.

Antimicrobial therapy should consist of a 6-week parenteral course followed by an additional 6 months of oral management to completely eradicate the organism. The antimicrobial of choice remains penicillin because *Actinomyces* species are not known to be resistant to penicillin. Other acceptable alternatives include clindamycin, doxycycline, or erythromycin.[52] Surgical excision is necessary to remove extensive fibrosis and sinus tracts, in cases with a poor response to antibiotics, and for diagnosis. Response to management is generally favorable, with cure rates approaching 90% despite a delayed diagnosis in most instances.[55]

Cat-Scratch Disease

Cat-scratch disease (CSD) is a granulomatous lymphadenitis that most commonly results from cutaneous inoculation caused by scratch trauma from a domestic cat. The causative organism is classified as *Bartonella henselae,* a gram-negative bacillus. Approximately 90% of patients who have CSD report a history of exposure to cats, and 75% of these patients have experienced a cat scratch or bite. Dogs have been implicated in 5% of CSD cases. CSD affects approximately 22,000 persons and results in hospitalization of approximately 2000 persons each year in the United States. The head and neck is the second most common site for CSD after the upper extremity.[56] The reservoir for *B. henselae* has been shown to be kittens. The major vector by which cats themselves are believed to become infected is the cat flea.[57]

The typical history is of a papule or pustule at a scratch or bite site followed in 1 to 2 weeks by the development of lymphadenopathy in the region of inoculation. The nodes will slowly enlarge over a period of 1 to 2 weeks and might not resolve for 2 to 3 months. Erythema and fluctuance of the involved nodes with spontaneous suppuration will occur in a reported 10% to 30% of patients.[57,58] Fever and mild systemic symptoms might occur in up to one third of patients. In the head and neck, this most commonly occurs in the submandibular and cervical areas. However, preauricular adenopathy might be confused with a parotid neoplasm.

The diagnosis of CSD has changed with advances in serologic and molecular biology techniques. These methods have replaced the need for cat-scratch skin testing. Testing for the presence of antibodies to *B. henselae* is now the most commonly used test to confirm the diagnosis.[57] The two methods used for antibody detection are the indirect fluorescent antibody (IFA) and the enzyme immunoassay (EIA). The test with greatest sensitivity is a *Bartonella* polymerase chain reaction (PCR) hybridization assay with an aspirate or biopsy specimen. This test might not be as easily available as the antibody detection techniques.[59] If tissue is removed for diagnosis, histologic examination might demonstrate cat-scratch bacilli with the use of Warthin-Starry silver staining. Lymph node involvement shows reticular cell hyperplasia, granuloma formation, and widening of arteriolar walls. In more advanced stages, stellate areas of necrosis coalesce to form multiple microabscesses. *Bartonella* is a slow-growing organism, and culture requires a 6-week incubation period.

Atypical presentations of CSD in the head and neck have been reported. Parinaud's oculoglandular syndrome is a unilateral granulomatous conjunctivitis associated with a preauricular or submandibular lymph node on the affected side. In addition, a report of diffuse parotid enlargement with facial nerve palsy secondary to CSD has been described.[58] Other atypical presentations include vertebral osteomyelitis encephalitis, granulomatous hepatitis, and optic neuritis. In immunocompromised patients, systemic *B. henselae* infection might result in cutaneous proliferative vascular lesions known as bacillary angiomatosis.

In most cases no active therapy is required. The patient should be reassured that the lymphadenopathy is self-limited and usually will resolve spontaneously in 2 to 4 months. However, in patients who are systemically ill or highly symptomatic, antibiotic therapy is recommended. The β-lactam antibiotics are ineffective in the treatment of CSD. The antibiotics reported to be most effective are rifampin, erythromycin, gentamycin, azithromycin, and ciprofloxacin.[57]

Toxoplasmosis

Toxoplasmosis, an uncommon disease in the United States, is caused by the organism *Toxoplasma gondii*. The usual host for this organism is the domestic cat. Parotid gland disease might involve singular or multiple intraparotid or periparotid lymph nodes. The organism exists in trophozoite, cyst, and oocyst forms, with the latter only existing in the feline vector. Trophozoites and cysts gain entrance to the human host most often through ingestion of infected and undercooked lamb, beef, or chicken, or, less commonly, through cat feces. Digestion of the cyst capsule permits widespread hematogenous dissemination and multiplication of trophozoites in virtually all lymphoreticular organs.

Both disseminated and lymphadenopathic forms of the disease have been described. Immunocompromised individuals are most at risk for the disseminated form of the disease, which features myalgia, lethargy, and anorexia combined with hepatosplenomegaly, pericarditis, and myocarditis. Alternately, the lymphadenopathic variety occurs much more commonly, with most patients being seen with isolated cervical lymphadenopathy.[60]

Definitive diagnosis can only rarely be provided by isolation of the organism. However, there are characteristic histopathologic findings in affected lymph nodes. The lymph node architecture is preserved, with hyperplastic follicles and germinal centers showing abundant mitoses and necrotic nuclear debris. Epithelioid cells with abundant, pale eosinophilic cytoplasm, which occur singly or in groups, are found in cortical and paracortical zones and sinuses.[61] Confirmation of a presumptive histologic diagnosis is made by acute and convalescent serologic testing. Chemotherapy is generally reserved for obviously progressive infections or those involving pregnant or immunocompro-

mised individuals and consists of the combined administration of pyrimethamine and trisulfapyrimidines.

Noninfectious Inflammatory Diseases of the Salivary Glands

Sjögren's Syndrome

Sjögren's syndrome is a chronic autoimmune disorder of the exocrine glands. The disease might be systemic and involve multiple glands; however, the salivary and lacrimal glands are primarily affected. The disease is characterized by a lymphocytic infiltration, with resulting glandular hypofunction leading to dryness of the mouth and eyes.[62]

Sjögren's syndrome might have a variable clinical presentation. When Sjögren's syndrome is confined to the exocrine glands, it is defined as *primary Sjögren's syndrome. Secondary Sjögren's syndrome* refers to patients who have the characteristic signs and symptoms of primary Sjögren's syndrome associated with another autoimmune disease. The disease might even evolve into a malignant lymphoid process. The estimated prevalence of Sjögren's syndrome is believed to be 1% to 3%. The disease is most commonly seen in patients during their fourth to fifth decades of life. More than 90% of patients are women.[63]

The etiology of Sjögren's syndrome is uncertain but is believed to involve an interaction among a patient's genetics, immune system, and environmental exposures. Genetic factors involving the major histocompatibility complex and a certain group of its alleles, such as HLA-B8 and HLA-DR3, are believed to create a predisposition for the development of Sjögren's syndrome.[62] These patients are susceptible to an initial, inciting environmental event. This event is most likely a viral infection that results in an aberrant autoimmune reaction. This autoimmune reaction leads to a dense lymphocytic infiltration of the exocrine glands and the production of multiple autoantibodies. Two distinct autoantibodies found in Sjögren's syndrome are two ribonuclear proteins known as *Ro* (or *SS-A*) and *La* (or *SS-B*). The presence of these antibodies is used to assist in establishing the diagnosis of Sjögren's syndrome.[63]

The predominant clinical presentation of Sjögren's syndrome is dryness of the mouth and eyes. Patients with xerostomia will complain of difficulty chewing and swallowing food. They might also experience difficulty with phonation and with adherence of food to the buccal mucous membranes. Intolerance to acidic and spicy foods is a common complaint. Some patients might be referred by their dentists secondary to multiple dental caries. The most common ocular complaint is a foreign body sensation in the eye, which is commonly described as "gritty" or "sandy." Chronic irritation and destruction of the corneal and conjunctival epithelium results in keratoconjunctivitis sicca.

The physical examination of patients with Sjögren's syndrome will demonstrate dry, sticky oral mucosal surfaces. Multiple dental caries and the absence of pooled saliva in the floor of the mouth may be visualized. The tongue is typically smooth with fissures and atrophy of the filiform papillae occurs. Patients with Sjögren's syndrome will also commonly have an intraoral fungal overgrowth with *Candida albicans.* The examination of the salivary glands results in the expression of scant or cloudy saliva from the ducts. Salivary gland enlargement, most commonly in the parotid glands, occurs in 25% to 66% of patients.[64] This might begin unilaterally, but most patients eventually develop bilateral enlargement, which may be recurrent and episodic or chronic and fixed. Objective evaluation of salivary flow rate can be performed with Lashley cups that fit over the opening of Stensen's duct and collect saliva. Sialography demonstrates sialectasis in 85% to 97% of patients with Sjögren's syndrome.[62]

The ocular findings in patients with Sjögren's syndrome include dilation of the bulbar conjunctival vessels, pericorneal injection, irregularity of the corneal image, and occasionally enlargement of the lacrimal gland. The tear secretion rate may be assessed by means of Schirmer's test. In addition, staining of damaged corneal and conjunctival epithelia by rose bengal dye is reported to be more specific for keratoconjunctivitis sicca.[64]

The systemic nature of Sjögren's syndrome might result in a wide variety of findings other than dryness of the mouth and eyes. Systemic manifestations include generalized malaise, low-grade fever, and myalgia and arthralgia. Dryness of the pharynx and esophagus results in dysphagia, and involvement of the tracheobronchial system might lead to bronchitis or pneumonia. The renal system might be affected, resulting in renal tubular acidosis. Vasculitis is reported to occur in 20% to 30% of patients.[63] Most commonly, the vasculitis manifests itself in the skin in the form of Raynaud's phenomenon and recurrent urticaria-like lesions. Central nervous system involvement is reported to occur in Sjögren's syndrome. The neurologic involvement includes peripheral sensory and motor polyneuropathies that may mimic multiple sclerosis.

Sjögren's syndrome also predisposes patients to the development of malignant lymphoproliferative disorders. The increased risk for lymphoma in patients with Sjögren's syndrome extends even after 2 decades of a benign disease course. Patients with persistent unilateral or bilateral parotid gland enlargement are at higher risk for the development of lymphoma.

In addition to the clinical examination, establishing the presence of an autoimmune process is mandated for the diagnosis of Sjögren's syndrome, which can be done by detecting the presence of autoantibodies and minor salivary gland biopsy. Testing for autoantibodies to the ribonuclear proteins Ro (SS-A) and La (SS-B) is done by use of enzyme-linked immunosorbent assay (ELISA). The biopsy of labial accessory salivary glands demonstrating salivary gland disease is one of the most consistent features of primary Sjögren's syndrome. The biopsy should include several glandular lobes obtained from areas with normal overlying mucosa to exclude nonspecific inflammatory findings.[62] The histopathologic lesion is a lymphocytic infiltrate producing a chronic focal sialadenitis. More specifically, the lesion consists of multiple focal mononuclear aggregates that are adjacent to and replace the normal acini. Several histologic classification methods that score the number of inflammatory foci seen on salivary gland biopsy have been devised.

Several sets of diagnostic criteria, which encompass findings on history, physical examination, and laboratory testing, have been proposed for the diagnosis of Sjögren's syndrome. In general, the diagnosis consists of establishing the presence of keratoconjunctivitis sicca and xerostomia by means of clinical examination and objective testing. This testing should include objective measurements of decreased salivary and tear flow along with a minor salivary gland biopsy. In addition, laboratory evidence suggesting a systemic autoimmune disease, specifically against SS-A and SS-B ribonuclear proteins, is necessary for the diagnosis of Sjögren's syndrome.[63] The presence of another autoimmune disorder, such as rheumatoid arthritis or systemic lupus erythematosus, would mandate a diagnosis of secondary Sjögren's syndrome. Patients who have objective signs of sicca complex but no evidence of an autoimmune process should be evaluated for other causes.

Multiple factors must be considered in the differential diagnosis of patients being evaluated for Sjögren's syndrome. A patient's general state of hydration and the presence of systemic conditions such as diabetes and cystic fibrosis should be assessed. One of the most common causes of xerostomia is medications. Sedatives, antipsychotics, antidepressants, antihistamines, and diuretics are the classes of drugs most often associated with oral dryness. Salivary gland exposure to therapeutic irradiation greater than 4000 cGy will result in severe and permanent secretory hypofunction.[64]

The salivary gland enlargement frequently found in Sjögren's syndrome may also be caused by several other conditions. Unilateral salivary gland enlargement despite an established diagnosis of Sjögren's syndrome should raise the suspicion of tumor.[62] Bacterial infection, chronic sialadenitis, and ductal obstruction are all causes of unilateral salivary gland enlargement. Bilateral salivary gland enlargement might be the result of a viral infection, malnutrition, or granulomatous diseases such as sarcoidosis.

The treatment of Sjögren's syndrome involves symptomatic treatment and prevention of irreversible damage to the teeth and eyes. The management of the oral component of Sjögren's syndrome involves

increasing the secretion rate of remaining salivary glands, using saliva substitutes, treating and preventing dental caries, and eradicating fungal overgrowth.[64] Stimulation of residual salivary gland function might be accomplished by local methods such as chewing sugarless gum or candies. The muscarinic-cholinergic agonist pilocarpine is the most commonly used systemic sialogogue. The drug is administered in 5-mg doses three to four times daily; however, side effects such as sweating, flushing, and increased urination are common. Dental treatment with fluoride is used to prevent and control dental caries. The treatment for keratoconjunctivitis consists of the use of commercially available eye lubricants and eye patching if corneal ulceration develops. The use of systemic corticosteroids or cytotoxic drugs is reserved for the severe extraglandular complications such as glomerulonephritis or necrotizing vasculitis.[62]

Summary

Salivary gland infections manifest differently, depending on the agent and the patient population. The acute suppurative infection is bacterial in origin and has quick onset of signs and symptoms, usually occurring in elderly, debilitated patients. Chronic sialadenitis is characterized by repeated episodes of pain and swelling (usually after an episode of acute sialadenitis) and tends to occur throughout adulthood. Systemic viral infections such as mumps and AIDS can produce localized salivary gland disease in any age group but have different clinical courses. Granulomatous salivary gland infections can occur in children and in elderly patients. They often cause asymptomatic gradual enlargement within a gland nodule, suggesting a neoplasm. The differential diagnoses in salivary gland infections are broad, but with a careful history and physical examination and knowledge of the various etiologic agents that cause disease, the otolaryngologist can make an accurate diagnosis in most cases and recommend appropriate management.

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CHAPTER EIGHTY-SEVEN

Benign Neoplasms of the Salivary Glands

Gabriel G. Calzada

Ehab Y. Hanna

Key Points

- The salivary gland neoplasms are uncommon and generally benign.
- Most benign tumors can be easily cured by wide local excision, but pleomorphic adenoma, which is the most common salivary gland tumor, has a propensity for local recurrence. Simple enucleation is discouraged.
- The parotid gland is the most frequently affected major salivary gland, and the palate is the most commonly affected minor salivary gland location.
- Pleomorphic adenomas are the most common neoplasm of salivary glands, comprising 45% to 75% of all tumors in most series. These tumors typically affect patients in their 20s to 50s and there is a female predilection.
- Warthin's tumor is the second most common tumor of the salivary glands and constitutes approximately 14% to 21% of salivary gland neoplasms. The tumor is almost exclusively found in the parotid gland, typically affects males in their 50s to 60s, and often may be bilateral.
- Basal cell adenomas are fairly uncommon benign tumors of the salivary glands and are divided into four major histologic subtypes: tubular, trabecular, solid, and membranous.
- Oncocytomas represent roughly 1% of all salivary gland tumors. They most commonly affect the parotid and occasionally the submandibular gland. Patients are typically in their 50s with a slight female predominance.
- Canalicular adenomas are rare and most commonly affect the minor salivary glands of the oral cavity, especially the upper lip.
- Myoepitheliomas are neoplasms that consist exclusively of myoepithelial cells. These component cells are believed to be one of the two component cells of pleomorphic adenomas.
- The roles of fine-needle aspiration biopsy and high-resolution imaging in the management of patients with salivary neoplasms continue to evolve.
- Deep lobe tumors require a total parotidectomy, with facial nerve preservation. Parapharyngeal tumors are most commonly excised through a cervical-parotid approach and only occasionally in conjunction with a mandibulotomy.

The most common benign neoplasm of the salivary glands is pleomorphic adenoma originating from the parotid gland. Surgical excision is usually all that is required to provide both definitive diagnosis and adequate treatment. Despite this relatively simple algorithm, management of other types of salivary neoplasms is challenging because of their relative infrequency, inconsistent classification, and variable biologic behavior.

Better understanding of the histogenesis of neoplasms of the salivary glands, however, has allowed a more consistent and rational classification of these tumors. Recent advances in molecular biology and tumor genomics have shed some light on the genetic basis of certain types of tumors of the salivary glands.[1] The role of fine-needle aspiration biopsy and high-resolution imaging in the management of patients with salivary neoplasms continues to evolve. This chapter discusses some of the advances made in understanding the etiology and histogenesis of salivary tumors and describes a contemporary approach to the diagnosis and management of patients with benign neoplasms of the salivary glands.

Embryology

Understanding the origin of benign salivary gland tumors requires knowledge of the embryology and ultrastructure of the normal salivary gland. The major salivary glands originate from ectoderm and begin their development during the sixth week of gestation as solid, ridgelike ingrowths of the oral epithelium.[2] These ingrowths continue to develop into tubules that later become the ductal system of the salivary glands. In the major salivary glands both serous and mucous cells are arranged into acini that are drained by a series of ducts. An intercalated duct drains into a striated duct, which empties into an excretory duct. Contractile myoepithelial cells surround the acini and intercalated ducts and help in draining saliva through the ductal system (Fig. 87-1). The parotid gland consists of predominately serous acini. The submandibular gland is composed of a mixture of serous and mucinous acini, whereas sublingual gland and minor salivary glands scattered throughout the upper aerodigestive tract contain predominantly mucinous acini.

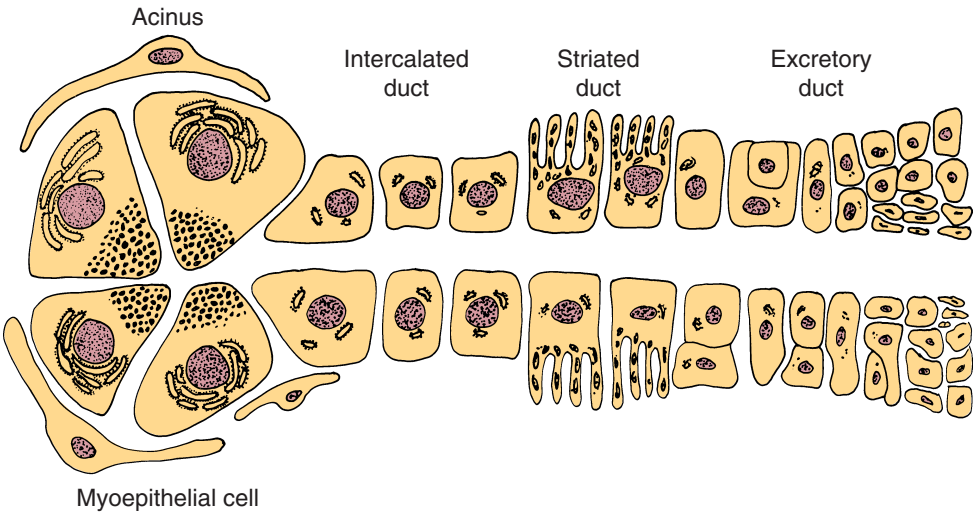

Figure 87-1. Structural elements of the salivary gland unit.

Histogenesis of Salivary Neoplasms

At least two theories of tumorigenesis have been proposed for salivary gland neoplasms.[3] In the multicellular theory, each type of neoplasm is thought to originate from a distinctive cell type within the salivary gland unit. According to this theory, Warthin's and oncocytic tumors are thought to arise from striated ductal cells, acinic cell tumors from acinar cells, and mixed tumors from intercalated duct and myoepithelial cells.[4] This theory is supported by the observation that all differentiated salivary cell types retain the ability to undergo mitosis and regenerate.[5,6] An alternative theory, the bicellular reserve cell theory, assumes that the origin of the various types of salivary neoplasms can be traced to the basal cells of either the excretory or the intercalated duct. According to this theory, either of these two cells can act as a reserve cell with the potential for differentiation into a variety of epithelial cells.[7] Hence despite the seeming heterogeneity of salivary tumors, all of them are thought to arise from one of two pluripotential cell populations. In this model, adenomatoid tumors including pleomorphic adenoma and oncocytic tumors are derived from the reserve cell of the intercalated duct, whereas epidermoid tumors, such as squamous cell carcinoma and mucoepidermoid carcinomas, are derived from the reserve cell of the excretory duct.[8] Some reports provide molecular evidence to support the reserve cell theory of salivary gland tumorigenesis.[9]

Recent efforts to identify biomarkers of salivary neoplasia have focused on methylation patterns. Williams and colleagues[10] investigated methylations status and protein expression of four tumor suppressor genes (*DAPK*, *MGMT*, *RARB2*, and *RASSF1*) in the largest cohort study of benign and malignant salivary neoplasms to date. The authors found benign and malignant salivary tumor differed in the frequency and pattern of gene methylation. They postulate methylation may aid in diagnosis and targeted therapy for salivary neoplasms.[10] Maruya and colleagues analyzed the gene expression profile of 18 primary tumors representing the major benign subtypes using a membrane-based DNA microarray platform. Of the 5000 genes arrayed, S-100 beta, galectin-9 isoform, vimentin, and tyrosine kinase receptor were more highly expressed in adenomas than in carcinomas.[11]

Etiology

The etiology of salivary gland neoplasms, like most other types of tumors, remains unknown. However, there is growing evidence that certain environmental factors such as radiation, viruses, diet, and certain occupational exposures may increase the risk of developing tumors of the salivary glands. In addition to environmental factors, specific genetic abnormalities associated with the development of some types of salivary tumors have recently been well characterized.

Radiation

There is increasing evidence to suggest that exposure to ionizing radiation may increase the risk of developing tumors of the salivary glands. In 1996 the Radiation Epidemiology Branch of the National Cancer Institute published a study on the risk of developing salivary gland tumors among atomic bomb survivors.[12] The study indicated a higher radiation-related risk of developing both benign and malignant salivary gland tumors, as compared with the general population. Dose-response analyses found statistically significant increases in risk with increasing A-bomb dose for both cancer and benign tumors. The risk was higher for malignant tumors, especially mucoepidermoid carcinoma. Among those with benign neoplasms, Warthin's tumor showed the highest dose-response–related risk.

Radiation therapy to the head and neck, especially if it encompassed the salivary glands, may also be a risk factor in the development of salivary gland tumors.[13] A recent study found a 4.5-fold increase in the incidence of salivary gland cancer and a 2.6-fold increase of benign tumors among persons exposed to scalp irradiation compared with matched controls.[14] The mean length of latency period until tumor development was 11 years for malignant tumors and 21.5 years for benign. The study also demonstrated a clear dose response effect for cancer and benign tumors, suggesting that ionizing radiation may play an important role in salivary gland tumorigenesis.

Viral

Although Epstein-Barr virus (EBV) has been consistently associated with lymphoepithelial carcinoma of the salivary gland in the Asian population, there is no evidence of a causal role of EBV in other primary salivary gland neoplasms.[15] Pollock and colleagues[16] failed to demonstrate any positive signal by in situ hybridization for EBV RNA in 42 benign salivary gland neoplasms. Other viruses including human papillomavirus, human herpesvirus-8, and cytomegalovirus do not appear to have any etiologic role in salivary gland neoplasms.[17]

Other Factors

Although tobacco use was not associated with a higher incidence of malignant salivary neoplasms, Warthin's tumor is strongly associated with cigarette smoking.[18] Occupational exposure to silica dust was linked to a 2.5-fold increased risk of cancer of the salivary gland.[19] The risk was also elevated among rubber workers exposed to nitrosamines.[20] Dietary analyses revealed a possible protective effect for a diet high in polyunsaturated fatty acids.[19,21] Similar to breast cancer, women with history of early menarche and nulliparity had an increased risk of cancer of the salivary gland, which may be due to a hormonal effect.[22] Whether these occupational, dietary, or hormonal factors have any association

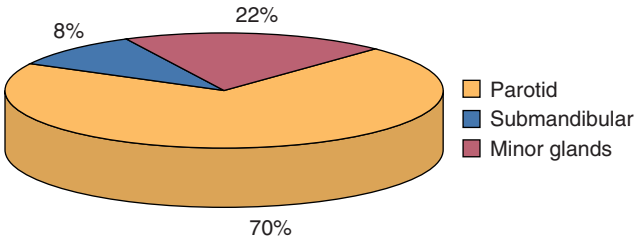

Figure 87-2. The site of origin of salivary neoplasms.

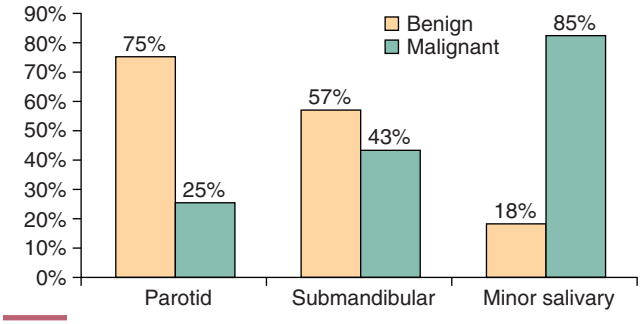

Figure 87-3. The incidence of benign and malignant salivary neoplasms according to the site of origin.

with the risk of developing benign tumors of the salivary glands remains unknown.

Genetic Factors

Recent developments in the field of molecular biology and human genomics have shed light on the genetic basis of developing several types of neoplasms including tumors of salivary gland origin. A study of several types of salivary gland tumors using comparative genomic hybridization found specific genetic alterations in different types of salivary gland tumors and involvement of several chromosomes in the alterations.[23] Genetic aberrations associated with the salivary gland neoplasia include allelic loss and point mutation, structural rearrangement of chromosomal units (most commonly translocations), the absence of one chromosome (monosomy), and the presence of an extra chromosome (polysomy). Any of these genetic aberrations may be the only karyotypic anomaly indicating an early event in tumor initiation, or several genetic alterations may coexist, which are more likely to be associated with tumor progression and more aggressive biologic behavior.[9,24]

Incidence

Salivary gland tumors are relatively rare and constitute 3% to 4% of all head and neck neoplasms. The majority (70%) of salivary gland tumors arise in the parotid gland (Fig. 87-2). Although the majority of minor salivary gland tumors are malignant, three fourths of parotid tumors are benign (Fig. 87-3). Spiro[25] reviewed the Memorial Sloan-Kettering experience with salivary neoplasms over a 35-year period. The distribution of these 2807 patients is shown in Table 87-1. Benign neoplasms constituted 54% (1529 patients) of all tumors. Pleomorphic adenoma (1280 patients) constituted 84% of benign tumors and 45% of all salivary gland neoplasms. Warthin's tumor was the second most benign tumor and comprised 12% (183 patients) of all benign tumors.

Patient Evaluation

Clinical Features

Regardless of whether they are benign or malignant, tumors of the parotid gland usually present as a painless swelling. Benign tumors are usually present for a long duration and have a slow growth rate.

Table 87-1

Distribution of 2807 Salivary Neoplasms

Histology	Number of Patients	Percent
Pleomorphic adenoma	1274	45.4
Warthin's tumor	183	6.5
Benign cyst	29	1.0
Lymphoepithelial lesion	17	0.6
Oncocytoma	20	0.7
Monomorphic adenoma	6	0.2
Mucoepidermoid carcinoma	439	15.7
Adenoid cystic carcinoma	281	10.0
Adenocarcinoma	225	8.0
Malignant mixed tumor	161	5.7
Acinic cell carcinoma	84	3.0
Epidermoid carcinoma	53	1.9
Other (anaplastic)	35	1.3
Total	2807	100

From Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg.* 1986;8:177-84. © 1986 John Wiley & Sons.

However, patients may indicate that they incidentally noticed the appearance of a "recent" lump. The acute onset of a painful swelling of the parotid gland usually indicates an inflammatory process. Acute bacterial parotitis is usually diagnosed in association with sialolithiasis of the parotid gland or in patients who are elderly, malnourished, dehydrated, or immunocompromised. Acute viral parotitis is most commonly due to "mumps"; however, other viral infections may present with acute parotid swelling. Sjögren's syndrome and other forms of autoimmune parotitis usually present with bilateral parotid swelling, although in some patients this may be asymmetric or even unilateral. Obstruction of Stensen's duct with a stone may lead to an acute painful swelling of the parotid gland. Rapid increase in size of a longstanding mass should raise the suspicion of malignant transformation of a preexisting benign tumor, but it may be due to inflammation or cystic degeneration most commonly associated with Warthin's tumor. Patients presenting with a mass in the parotid gland should be asked about a history of cancer of the scalp or facial skin. Metastasis to the parotid gland from skin cancer including melanoma may be diagnosed by a careful examination of these areas for evidence of a skin cancer or a scar of previous excision.

On examination, benign tumors of the parotid gland are usually well defined, nontender, and freely mobile. They are commonly located in the "tail" of the parotid gland but may be present anywhere in the superficial or deep lobe. Tumors may originate entirely from the deep lobe (Fig. 87-4) or extend from the superficial to the deep lobe through the relatively narrow stylomandibular tunnel, giving the appearance of a dumbbell tumor (Fig. 87-5). In either case, the tumor may extend to the parapharyngeal space and displace the oropharyngeal wall medially (Fig. 87-6). The presence of facial nerve paresis or paralysis, pain, fixation of the mass to the overlying skin or underlying structures, and associated cervical adenopathy usually indicate the presence of malignancy. It should be noted, however, that these findings usually indicate

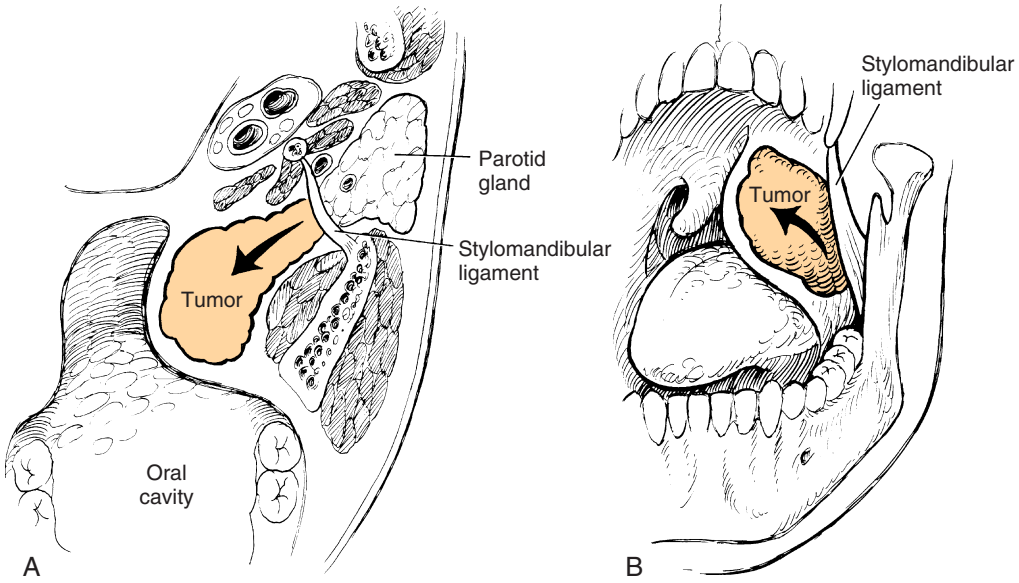

Figure 87-4. **A,** Axial and **B,** coronal diagrams of round tumor passing posterior to stylomandibular ligament to appear as mass in parapharyngeal space. *Arrows* indicate potential routes of tumor spread.

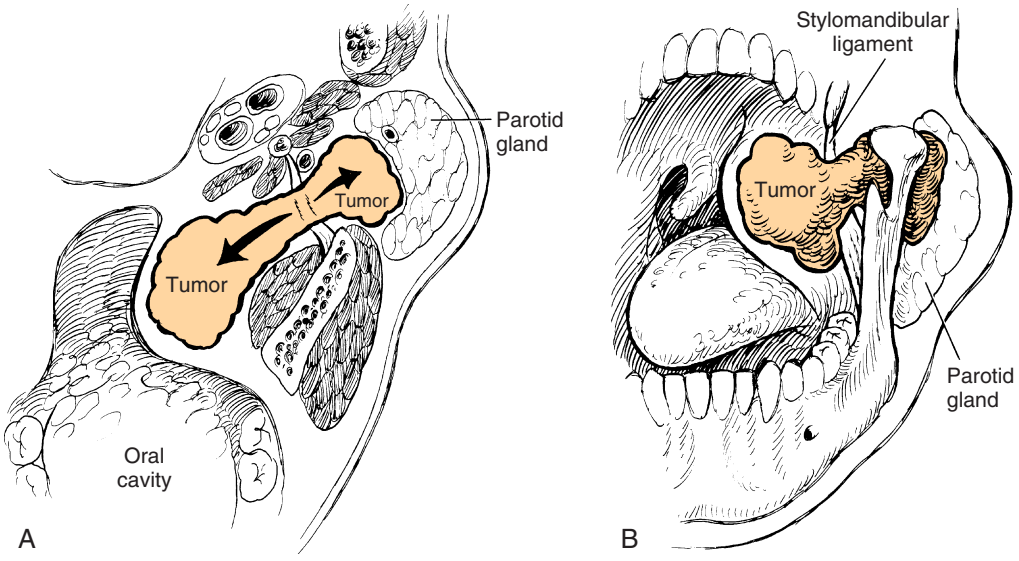

Figure 87-5. **A,** Axial and **B,** coronal diagrams of relationship of dumbbell tumor to stylomandibular ligament. Dumbbell tumor enters parapharyngeal space through stylomandibular membrane between the mandible and the stylomandibular ligament. *Arrows* indicate potential routes of tumor spread.

local or regional extension of the tumor, and the diagnosis of parotid malignancy should not await the development of these signs and symptoms. The possibility of malignancy should be ruled out in patients presenting with any mass in the parotid gland. This will usually require cytologic or histologic evaluation with a fine-needle biopsy, or parotidectomy, respectively.

Benign tumors of the submandibular gland are relatively uncommon and usually present as a painless, mobile mass in the submandibular triangle. Involvement of the overlying skin or fixation to the mandible usually indicates local extension of a malignant tumor. Ipsilateral weakness or numbness of the tongue indicates perineural spread of malignancy along the hypoglossal or lingual nerves, respectively. Weakness of the marginal mandibular branch of the facial nerve also indicates perineural extension of a malignant tumor. Enlargement of the submandibular or upper cervical lymph nodes may be due to reactive lymphadenopathy associated with submandibular sialadenitis, but it usually indicates regional metastasis of malignancy in the submandibular gland.

Benign tumors of the minor salivary glands are rare. Most tumors arising from the minor salivary glands are malignant (see Fig. 87-3). However, similar to the major salivary glands, pleomorphic adenoma is the most frequent benign tumor of the minor salivary glands. The clinical presentation depends on the site of origin, and the most common sites include the palate, parapharyngeal space, and the lacrimal gland.

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) has been widely recognized and well established as an accurate technique in the diagnosis of salivary gland neoplasms. Numerous studies have reported an exceptionally high degree of sensitivity, specificity, and predictive value for FNAB. The overall sensitivity ranges from 85.5% to 99%, and the overall

Figure 87-6. Pleomorphic adenoma of the deep lobe of a parotid gland, causing medial displacement of the palate and tonsil.

specificity ranges from 96.3% to 100%.[26-28] In general, diagnostic accuracy is higher for benign than for malignant salivary gland tumors.[29,30] The accuracy of FNAB, however, depends greatly on the experience of the cytopathologist, as well as the overall volume of patients with salivary neoplasms evaluated in any given institution. The most common source of diagnostic error of FNAB is inadequate sampling.[31] The use of ultrasound-guided FNAB may be of help in cases in which it is difficult to obtain a representative sample, and it enhances the overall diagnostic accuracy of the technique.[32,33] Despite its overall high accuracy, several significant but uncommon areas can lead to diagnostic difficulties, with the potential for clinically important diagnostic errors.[29] The most frequent problems involve variations in the expected cytology of pleomorphic adenoma. Also, there are several benign-malignant "look-alike" pairs of lesions. The first of these is related to small-cell epithelial neoplasms of low nuclear grade; the most frequent problem is between basal cell adenomas and adenoid cystic carcinoma, particularly the solid (anaplastic) type. The next area contrasts mucoepidermoid carcinoma with its cytologic mimic, benign salivary gland duct obstruction. The final difficulty in salivary gland aspiration contrasts large-cell epithelial lesions of low nuclear grade: oncocytic proliferations and acinic cell carcinoma.[34]

In addition to being accurate, FNAB is safe, simple to perform, and relatively inexpensive. However, one essential question is worth asking. Is FNAB really necessary in the evaluation of salivary gland masses? Would it change the course of management on the basis of clinical assessment? In an attempt to answer this question, Heller and colleagues[35] performed a study to determine the impact of FNAB on patient management. One hundred patients underwent FNAB of major salivary gland masses. The physician's initial clinical impression was compared with the FNAB diagnosis and the final diagnosis in each case. Overall, FNAB resulted in a change in the clinical approach to 35% of the patients. Examples of such changes in the planned management included avoiding surgical resection for lymphomas and inflammatory masses and adopting a more conservative approach with benign tumors in elderly and high-surgical-risk patients. FNAB also allows better preoperative counseling of patients regarding the nature of the tumor, the likely extent of resection, management of the facial nerve, and the likelihood of a neck dissection. Such information is not only important in treatment planning but also helps alleviate an already high level of anxiety among patients and their families.

The possibility of tumor seeding is a commonly cited argument against the routine use of FNAB in patients with salivary gland tumors. To address these issues, Mukunyadzi and colleagues[36] recently reviewed 94 resected salivary gland masses for infarction, hemorrhage, and needle track tumor seeding, as well as fibrosis after FNAB. They concluded FNAB with a 25-gauge needle is safe and does not significantly alter the histologic diagnosis because tissue effects did not preclude accurate diagnostic interpretation in any case.[36]

Imaging

The routine use of imaging in patients with small, well-defined masses of the superficial lobe of the parotid gland is probably not warranted because the results of imaging are not likely to change the treatment plan. However, tumors that present with clinical findings suggestive of malignancy, tumors arising from the deep lobe of the parotid gland or the parapharyngeal space, and, tumors of the submandibular and minor salivary gland should be evaluated with high-resolution imaging. In such cases, imaging provides accurate delineation of the location and extent of tumor, its relation to major neurovascular structures, perineural spread, skull base invasion, and intracranial extension.[37]

Computed Tomography and Magnetic Resonance Imaging

In evaluating patients with tumors of the salivary glands, both computed tomography (CT) and magnetic resonance imaging (MRI) provide information that is superior to that provided by other imaging techniques or by physical examination.[38] The normal parotid gland has a high fat content and is easily visualized on both CT and MRI. Therefore both techniques can demonstrate whether a mass in that region is intraglandular or extraglandular. Generally, neither CT nor MRI provides information regarding the specific histologic diagnosis, except rarely.[39] An example of such a rare scenario is with lipoma of the parotid gland (Fig. 87-7). The MRI signal characteristics of parotid masses, however, may be suggestive of certain diagnosis.[40] For example, if a parotid gland mass is bilateral, it is more likely to be Warthin's tumor, especially if it does not enhance. Less likely, it could be lymphoepithelial cyst or necrotic lymph node. A unilateral, nonenhancing mass with a high T2 signal is more likely to be a Warthin's tumor and less likely a necrotic lymph node or first branchial cleft cyst. If the mass is unilateral, shows postcontrast enhancement, has a high T2 signal, and does not invade surrounding tissue planes, it is more likely to be a pleomorphic adenoma (Fig. 87-8). An intermediate to low T2 signal mass, with or without invasion of surrounding tissue planes, is more likely to be a malignant mass such as adenoid cystic or mucoepidermoid carcinoma.[41]

MRI is also superior to CT in demonstrating the internal architecture of salivary gland tumors in a multiplanar fashion and in delineating the interface between tumor and normal salivary gland.[42] In contrast to benign tumors, which invariably have well-defined margins (see Fig. 87-8), malignant tumors may exhibit irregular margins (Fig. 87-9). Extension of the tumor beyond the fascial confines of the gland can be adequately seen on both CT and MRI and should raise the suspicion of malignancy.[43] Bone destruction of the mandible or skull base is best visualized on CT, whereas bone marrow involvement is better demonstrated on MRI. Both studies can adequately evaluate the neck for metastatic adenopathy. CT has the advantage of being less expensive and more available than MRI.

Although parapharyngeal space masses are well visualized by both techniques, they are better delineated with MRI than CT. This is because of the different signal intensity of tumor, fat, and muscle on MRI. The differential diagnosis of parapharyngeal masses includes deep lobe parotid tumors, minor salivary gland tumors, and neurogenic and vascular tumors. Most salivary tumors have low-to-intermediate T1 signal intensities and intermediate-to-high T2 signal intensities. Deep lobe parotid tumors and minor salivary gland tumors of the parapharyngeal space lie in the prestyloid compartment, anterior to the carotid artery, and displace the parapharyngeal fat medially (Figs. 87-10 and 87-11). Deep lobe tumors are connected to the parotid gland at least in one imaging section, whereas minor salivary gland tumors are completely surrounded by fat (see Fig. 87-11). By contrast, neurogenic tumors and glomus tumors lie in the poststyloid compartment, posterior to the carotid artery, which is displaced anteriorly (Fig. 87-12). Neurogenic tumors usually enhance intensely with gadolinium, whereas glomus tumors have characteristic serpiginous flow voids (salt and pepper appearance) on MRI.

Recently, new MR technologies such as dynamic contrast-enhanced MRI, diffusion-weighted MRI, and proton MR spectroscopy have shown promising results in the differentiation between benign and malignant salivary gland tumors.[44] Further research with larger-scale studies on these particular MR methods is necessary.

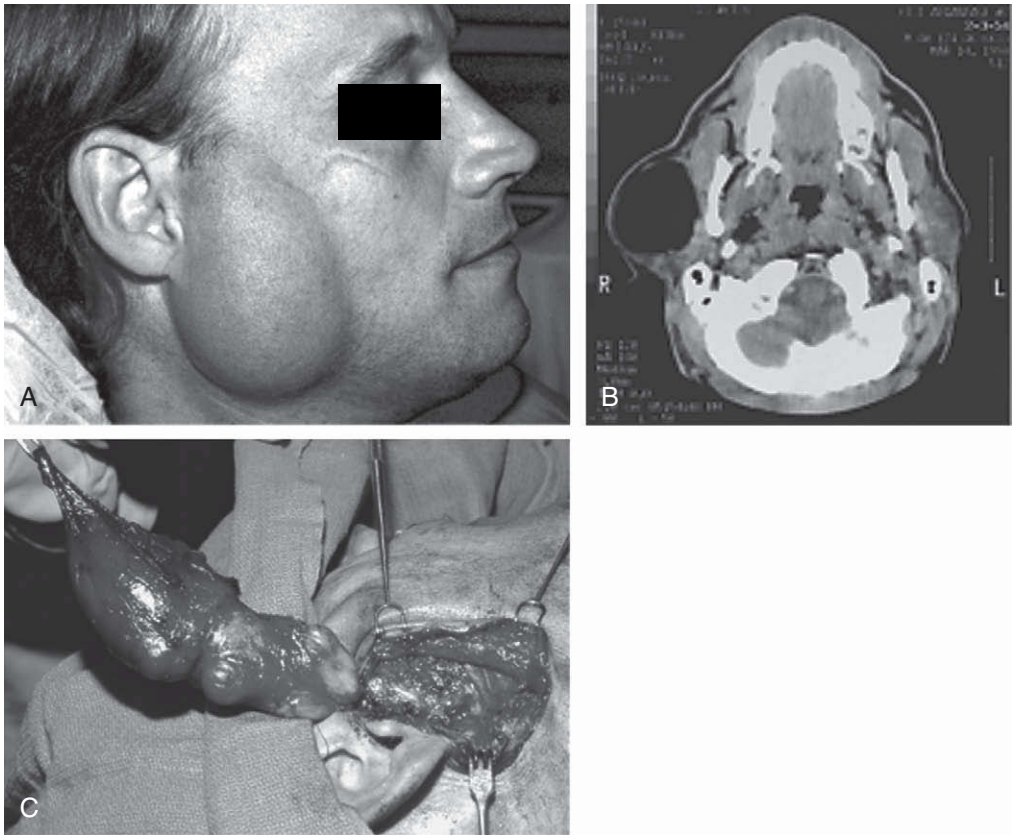

Figure 87-7. A 40-year-old male presented with a large, painless, slow-growing parotid mass. Fine-needle aspiration biopsy was indeterminate. **A,** Lateral view. **B,** An axial computed tomography (CT) with intravenous contrast demonstrating a large, rounded, well-defined mass with smooth borders in the parotid gland. The mass was nonenhancing and had the same density as the subcutaneous fat. These findings were pathognomonic of parotid lipoma. **C,** A superficial parotidectomy was performed, and the diagnosis was confirmed.

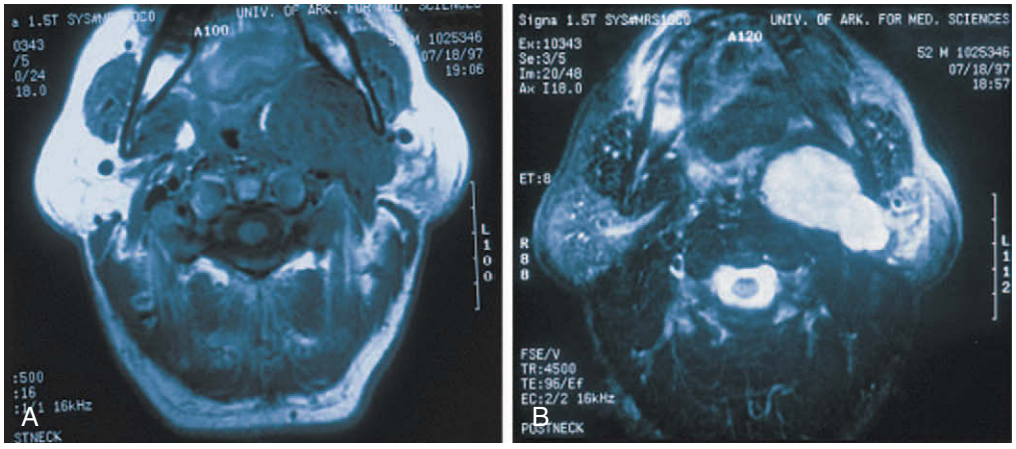

Figure 87-8. Pleomorphic adenoma of the parotid gland. The mass originated from the deep lobe of the gland and extended to the parapharyngeal space through the stylomandibular tunnel, where it was somewhat constricted, giving the appearance of a dumbbell. Note the medial displacement of the oropharynx. The mass has well-defined borders and does not invade surrounding structures. The mass is isointense on T1-weighted magnetic resonance imaging (MRI) **(A)** and has a high signal intensity on T2-weighted MRI **(B).** These signal characteristics are highly suggestive of pleomorphic adenoma.

Ultrasonography

Ultrasonography has the advantage of being inexpensive, noninvasive, simple to perform, and is virtually free of complications. It can be used to differentiate solid from cystic masses in the salivary glands, and most salivary gland diseases can be diagnosed sonographically.[32] Ultrasound guidance may also enhance the accuracy of FNAB in nonpalpable tumors and in masses with a highly heterogeneous architecture.[45]

Color Doppler Sonography

Color Doppler sonography has been recently used to evaluate the vascular anatomy of the salivary glands. It can distinguish between the

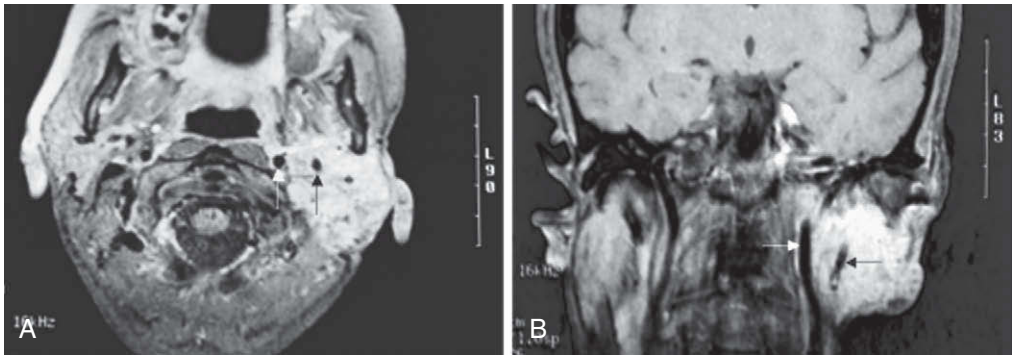

Figure 87-9. T1-weighted magnetic resonance imaging with gadolinium of a patient with mucoepidermoid carcinoma of the parotid shows the tumor to have irregular border and is indistinct from the normal parotid gland. Note complete encasement, rather than displacement of both the internal *(white arrow)* and external carotid arteries *(black arrow)* in both the axial **(A)** and coronal **(B)** images.

Figure 87-10. Large pleomorphic adenoma of the parotid gland. Axial computed tomography with gadolinium. The tumor involves the superficial and deep lobe of the parotid gland and lies anterior to the styloid process (prestyloid) *(white arrowhead)*. The fat of the parapharyngeal space is displaced medially, and the carotid artery displaced posteriorly. The isthmus of tumor between the superficial and deep components passes through the stylomandibular space and is therefore relatively narrow, giving the appearance of a dumbbell *(black arrowheads)*.

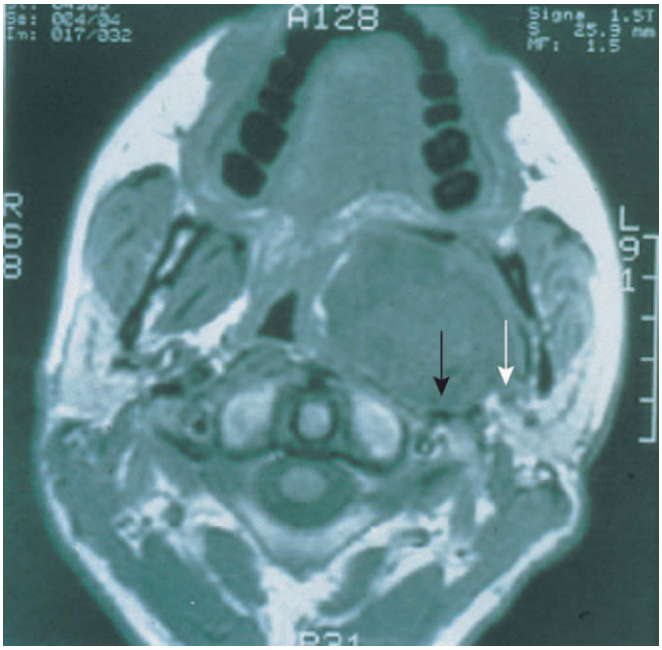

Figure 87-11. In contrast to the dumbbell tumor depicted in Figure 87-10, this pleomorphic adenoma originates entirely from the deep lobe of the parotid gland *(black arrow)* and lies entirely medial to the stylomandibular tunnel. Pleomorphic adenomas originating from the minor salivary glands of the parapharyngeal space have a similar appearance on high-resolution imaging but are not connected to the parotid gland. Regardless of their origin, salivary gland tumors of the parapharyngeal space will occupy the prestyloid compartment and displace the carotid artery posteriorly *(white arrow)*.

physiologic changes that occur during salivary stimulation in normal subjects and the flow alterations that occur in diseased glands.[46]

Positron Emission Tomography

PET scans have not gained wide application in imaging of tumors of the salivary gland for several reasons. First, tumors of the salivary glands have a variable and inconsistent uptake of F-18 fluorodeoxyglucose (FDG), which is the most commonly used radiotracer with PET scans, and therefore FDG PET is unreliable both in tumor detection and in distinguishing benign from malignant salivary tumors.[47] Second, competing techniques such as CT, MRI, and even clinical examination already have a high degree of accuracy. Third, high-resolution studies such as CT and MRI provide anatomic detail required for treatment planning that is unavailable from FDG PET images. Finally, the high cost of FDG PET prohibits its widespread use. Research is ongoing with PET scans. Uchida and colleagues[48] recently proposed combining FDG PET with Tc-99m pertechnetate salivary gland scintigraphy for differentiating various parotid gland tumors in patients with nondiagnostic needle aspiration.

Pleomorphic Adenomas

Pleomorphic adenomas, also known as benign mixed tumors, are the most common neoplasms of the salivary gland. The term *pleomorphic* was chosen to describe these tumors because they possess morphologic diversity with both epithelioid and connective tissue components in various proportions. Although highly debated in the past, most now agree that pleomorphic adenomas originate from an uncommitted reserve cell of the intercalated duct that has the potential to differentiate into epithelial and myoepithelial cells. Pleomorphic adenomas occur most frequently in the major salivary glands but may also arise from the minor salivary glands of the upper respiratory and alimentary tracts.

Pleomorphic adenomas constitute approximately 75% of all benign tumors of the major salivary glands.

In the parotid gland, approximately 90% of pleomorphic adenomas originate superficial to the facial nerve. Occasionally, tumors of the superficial lobe extend to the deep lobe medial to the facial nerve. If they extend to the parapharyngeal space through the stylomandibular "tunnel" bounded by the stylomandibular ligament, they may have a narrow isthmus connecting the superficial and deep components, giving the tumor a dumbbell appearance (see Figs. 87-5 and 87-10). Approximately 10% of pleomorphic adenomas originate entirely from the deep lobe and are usually located deep to the stylomandibular ligament. Therefore they have a more rounded appearance on high-resolution imaging (see Figs. 87-4 and 87-11). Pleomorphic adenomas may also arise from minor salivary gland tissue that naturally occurs in the parapharyngeal space. Regardless of their origin, pleomorphic adenomas of the parapharyngeal space occupy the prestyloid compartment (see Figs. 87-10 and 87-11) and, like other parapharyngeal tumors, may displace the oropharynx medially (see Fig. 87-6). Pleomorphic adenomas of the minor salivary glands most commonly occur in the palate (Fig. 87-13).[49] The second most common site is the upper lip. Despite the abundance of minor salivary glands in the lower lip, pleomorphic adenomas are exceedingly rare in this location. Pleomorphic adenomas are the most common benign tumors of the lacrimal gland (Fig. 87-14).[50-52]

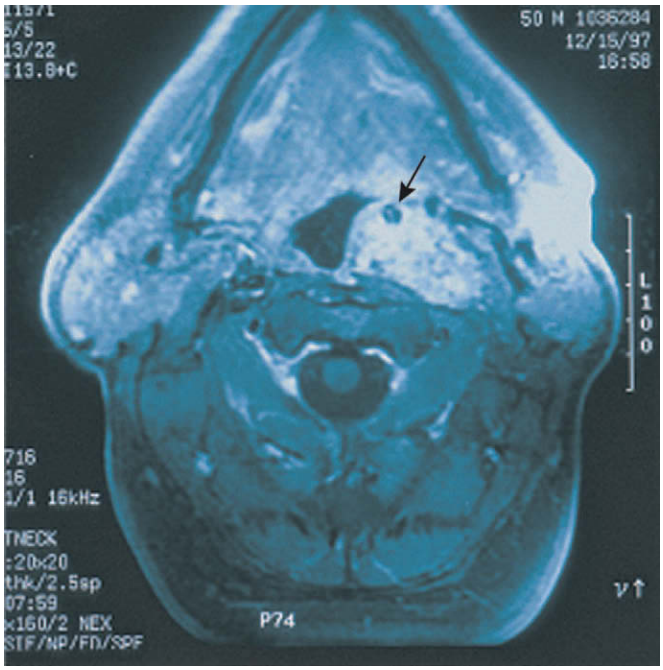

Figure 87-12. On magnetic resonance imaging (MRI), tumors of the poststyloid compartment are usually located behind the carotid artery, displacing it anteriorly *(arrow)*. Glomus tumors have characteristic serpiginous flow voids on MRI, giving a "salt-and-pepper appearance."

Clinically, pleomorphic adenomas are characterized as painless, slow-growing masses. Multiple primary pleomorphic adenomas are extremely rare, although reported.[53] Pathologically, pleomorphic adenomas are solitary, firm, round tumors. The cut surface is characteristically solid and may be hard, rubbery, or soft in consistency with a whitish gray to pale yellow color. Pleomorphic adenomas of the major salivary glands have a capsule, although varying in thickness and completeness, whereas pleomorphic adenomas of the minor salivary glands are usually nonencapsulated.[54] On histologic examination, pleomorphic adenomas consist of epithelial components that may take the form of ducts, nests, cords, or solid sheets of cells and myoepithelial cells that appear plasmacytoid or spindled in a fibrocollagenous, myxochondroid, or chondroid background. Myoepithelium in pleomorphic adenoma is considered to be responsible for the development of the characteristic myxoid or chondroid stroma. Variations in the histologic appearance of this tumor type are common and may include squamous metaplasia, calcification, cartilage-appearing tissue, oxyphilic cells, and a palisading appearance of the underlying stroma. Lipomatous[55] and osseous[56] changes have been occasionally reported in pleomorphic adenoma.

Histopathologic studies have demonstrated that almost all pleomorphic adenomas have focally thin capsules, and one fourth of pleomorphic adenomas demonstrate satellite nodules or pseudopodia.[57] Therefore the recommended treatment is surgical excision with a surrounding cuff of normal tissue to prevent recurrence from failure to address these pseudopod-like extensions of tumor.[58] In patients with tumors of the submandibular gland, the gland is generally removed with careful preservation of the marginal mandibular nerve. Tumors of the parotid gland usually involve removal of the tumor with an adequate margin and facial nerve preservation. Because most of the tumors arise from the superficial lobe, a superficial parotidectomy is often required.

Recurrent pleomorphic adenomas are an uncommon but challenging problem. Frequently, multiple foci of recurrence continue to manifest over several years.[59] This multicentric pattern is characteristic of recurrent pleomorphic adenomas (Fig. 87-15). Currently, no reliable criteria have been established to predict those tumors with a greater tendency to recur. Surgical excision, however, remains the mainstay of treatment for recurrent pleomorphic adenomas. Patients who have undergone previous surgical excision, especially those with previous parotidectomy, are at increased risk for facial nerve injury, as well as recurrence with revision surgery.[60,61] Neutron radiotherapy offers excellent local control rates and survival rates in patients with multiple recurrences who are not surgical candidates even in the presence of gross residual disease.[62]

Malignant transformation of pleomorphic adenoma is rare and occurs most frequently in patients with long-standing tumors. The risk of malignant transformation in pleomorphic adenoma is 1.5% within the first 5 years of diagnosis but increases to 10% if observed for more than 15 years.[63] Cases of benign pleomorphic adenoma metastasizing to cervical lymph nodes have been reported.[64-66]

Figure 87-13. Pleomorphic adenoma of the palate. **A,** Intraoperative view. **B,** Tumor specimen.

Basal Cell Adenomas

Most basal cell adenomas occur in the parotid gland and minor salivary glands of the upper lip. As with other benign neoplasms, they present as a slow-growing, asymptomatic mass. Gross pathologic examination reveals a well-circumscribed, solid tumor with a gray-white to pink-brown cut surface. Parotid basal cell adenomas are characteristically encapsulated, whereas those of minor salivary gland origin may lack a capsule.[67] Histologically, an intact basement membrane helps differentiate basal cell adenomas from pleomorphic adenomas. Four histologic growth patterns have been recognized: solid, trabecular, tubular, and membranous.[68] Basal cell adenomas may be difficult to distinguish from the solid variety of adenoid cystic carcinomas. Cytologic features that help differentiate basal cell adenomas from adenoid cystic carcinomas include lack of true invasion of surrounding tissues, lack of perineural invasion, a vascular stroma, and a peripheral palisading of the outer layer of basaloid cells. The cell-stroma interface is also useful in distinguishing basal cell adenomas from adenoid cystic carcinomas. In basal cell adenomas the collagenous stroma interdigitates with adjacent cells, whereas in those with adenoid cystic carcinomas the two are separated by a sharp, smooth border. Further, the stroma of basal cell adenomas may contain rare spindle cells or capillaries, but the cylinders of adenoid cystic carcinoma are acellular. The treatment of these benign tumors is surgical excision with a cuff of normal surrounding tissue.

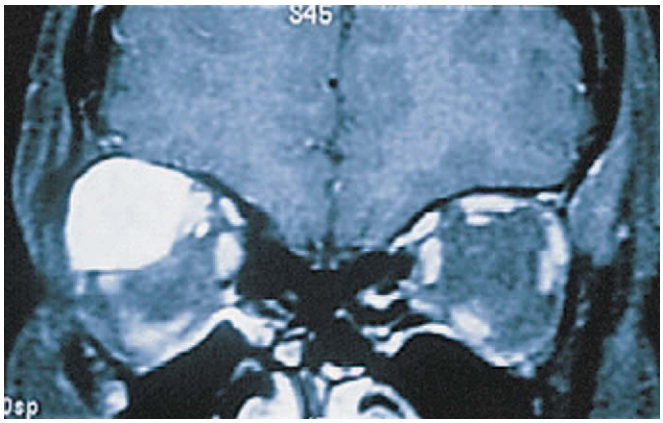

Figure 87-14. Pleomorphic adenoma of the lacrimal gland.

Canalicular Adenomas

Canalicular adenomas are benign neoplasms of predominately oral minor salivary glands, the upper lip being the most common site. They have been reported to account for less than 1% of salivary gland tumors and are rarely reported to be multifocal.[69] The patient presents with complaint of an asymptomatic, slowly enlarging mass. These tumors may be clinically similar to a mucocele or varix and may be multifocal. Histologically, they are characterized by cells arranged in parallel rows forming ductlike structures—hence the term "canalicular." Canalicular adenomas may be distinguished from adenoid cystic carcinomas by their well-circumscribed appearance and lack of perineural or soft tissue invasion. Surgical excision is the treatment of choice for canalicular adenomas.

Papillary Cystadenoma Lymphomatosum—Warthin's Tumors

First described by Aldred Warthin in 1929, Warthin's tumor is the second most common benign salivary gland neoplasm behind pleomor-

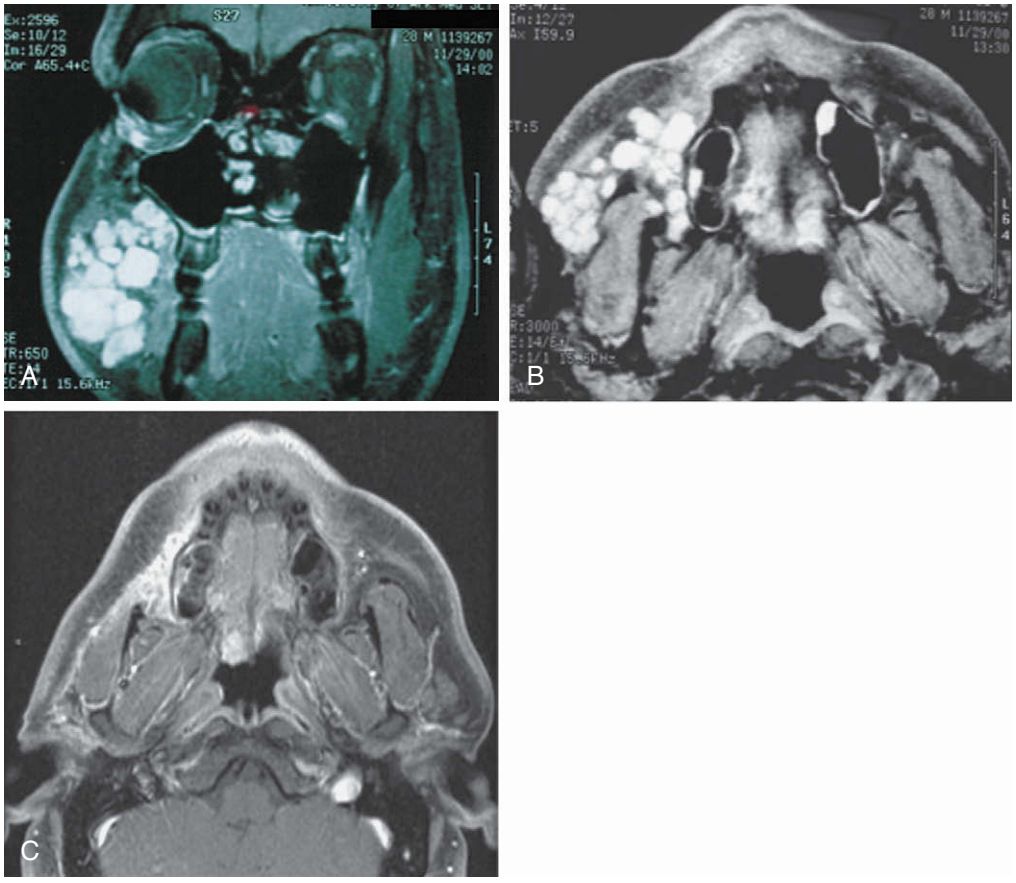

Figure 87-15. Recurrent pleomorphic adenoma of the right parotid gland. Note the multicentric pattern of recurrence in both the coronal **(A)** and axial images. **B,** T1-weighted magnetic resonance (MR) with gadolinium. **C,** The postoperative axial T1-weighted MR with gadolinium shows complete resection of all recurrent tumors.

phic adenoma. Warthin's tumor is also known as papillary cystadenoma lymphomatosum or adenolymphoma. The term "adenolymphoma" is often confused with malignant lymphoma and therefore the use of this term should be discouraged. Papillary cystadenoma lymphomatosum is an accurate descriptive term but is somewhat cumbersome compared with the most favored term of Warthin's tumor. Warthin's tumor accounts for approximately 10% of all parotid tumors and is found almost exclusively in the parotid gland. Warthin's tumor is associated with a higher male preponderance and is more prevalent in whites than in other racial groups. Bilateral Warthin's tumors occur in 10% of cases and may be simultaneous. As previously discussed, Warthin's tumor is associated with cigarette smoking, which may be due to irritation of ductal epithelium by tobacco smoke, which initiates tumorigenesis.[18]

Clinically, patients with Warthin's tumor present with an asymptomatic, slow-growing mass often in the superficial lobe of the parotid gland at the angle of the mandible. However, a few patients will present with swelling, pain, and other inflammatory changes, which may be secondary to an immunologic response of the lymphoid element.

On gross pathologic examination, Warthin's tumors are usually spheric or ovoid masses that are encapsulated with a smooth or lobulated surface. Papillary cysts are commonly found on sectioning and contain mucoid brown fluid. Solid gray tissue encapsulates white nodules of lymphoid tissue. Microscopically, the combination of papillae of eosinophilic epithelia projecting into cystic spaces and lymphoid matrices is a distinct and pathognomonic histologic feature. The typical cystic lining is arranged in two cell layers of even rows. The apical or luminar tall columnar and basal cuboidal cells contain small dark nuclei and abundant granular pink cytoplasm (oncocytes). The granular eosinophilia of oncocytes is due to abundant mitochondria present in the cytoplasm. Treatment of Warthin's tumor is surgical excision, usually a parotidectomy with facial nerve preservation. Inadequate excision or tumor multicentricity may explain tumor recurrence.

Oncocytic Papillary Cystadenoma

Oncocytic papillary cystadenoma is an uncommon tumor type to originate in the parotid gland. Most of these tumors occur in the larynx, although they have been described in the nasopharynx, palate, buccal mucosa, and the accessory tear ducts. These tumors have no gender predilection and usually occur in those aged 50 years or older. Patients usually present with a painless mass. Those with laryngeal lesions may present with hoarseness or cough. The minor salivary glands of the false vocal cords and ventricles are common sites of presentation, but this tumor type also may originate from any site in the laryngeal mucosa. Although they are usually solitary tumors, there have been reports of multiple tumors.

On pathologic examination, oncocytic papillary cystadenomas are smooth round cysts that may be pedunculated. Microscopically, these tumors look like Warthin's tumor, although the lymphoid stroma is absent. Sometimes, these tumors are referred to by some pathologists as "Warthin's tumor without lymphoid matrix." Whether these are true tumors has been debated. They may reflect metaplasia or hyperplasia of preexisting salivary gland ducts, but nonetheless, they are treated with surgical excision.

Oncocytoma

Oncocytoma accounts for less than 1% of all salivary gland tumors. They are usually benign tumors that arise most commonly in the parotid gland. These tumors may also originate in the submandibular, sublingual, and minor salivary glands. The cells of origin, oncocytes, are large epithelial cells with granular eosinophilic cytoplasm secondary to mitochondrial hyperplasia. Oncocytes may be found individually or in groups in otherwise normal major or minor salivary glands. They are also found in the pancreas, respiratory tract, thyroid, parathyroid, pituitary, adrenal glands, and kidney, although the majority of tumors occur in the superficial lobe of the parotid gland.

Most patients are in the fifth to sixth decade of life at the time of diagnosis and the gender distribution is almost equal. Oncocytomas are painless, slowly enlarging tumors that show a predilection for technetium-99m-pertechnetate and thus often enhance on radionucleotide scan.

On gross pathologic examination, oncocytomas of the major salivary glands are well circumscribed and encapsulated. Those originating from minor salivary glands have less well-defined borders and are not encapsulated. The surface is pink to rust in color. Microscopically, the tumor has a granular appearance as a result of the abundant, hyperplastic mitochondria. The concentration of mitochondria differentiates oncocytomas from other tumors. A true oncocytoma contains no lymphoid tissue. The extensive lymphoid component that is typical of a Warthin's tumor is never encountered. Histologically, oncocyte-predominant benign lesions may have a degree of epithelial atypia, squamous metaplasia, or necrosis that may mimic some types of malignant salivary tumors with oncocytic components such as adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma.[70] Metastatic thyroid carcinoma or renal cell carcinoma with a large number of oncocytes should also be differentiated from oncocytoma.

Oncocytomas originating from minor salivary glands tend to grow in an irregular and locally invasive pattern. They are less predictable than those originating in the parotid glands. Those originating from minor salivary glands in the respiratory tract may invade surrounding cartilage or bone. Although histologically benign, they have a destructive potential. Rarely do they demonstrate features indicative of malignancy such as increased mitoses and perineural or vascular invasion. Detection of cellular proliferation using immunohistochemical staining may be helpful in distinguishing a benign oncocytoma from a malignant oncocytoma.[71] Treatment of benign oncocytomas is surgical excision.

Myoepithelioma

Myoepithelioma originates from contractile myoepithelial cells that lie beneath the ductal and acinar epithelium in the salivary glands. These cells also have been identified in sweat glands and mammary glands. They have the ability to contract, and their pumping action helps expel (or discharge) secretions from the salivary glands. Diagnosing myoepitheliomas by fine-needle aspiration is difficult, and immunohistochemistry with CD 10, SMA, and S-100 markers may aid in diagnosis.[72] On gross pathology, myoepitheliomas are well demarcated and the external surface is smooth. The cut surface is homogeneous and white. Microscopically, these tumors have a thin capsule, except when they occur in the palate, wherein they lack encapsulation. The cells are benign appearing with rare mitosis and often assume spindle, polygonal, or plasmacytoid features. Clinically, these tumors are difficult to distinguish from pleomorphic adenomas due to their painless, slow-growing nature. There is no gender predilection, and they occur in the major and minor salivary glands. Histologically, they should be differentiated from plasmacytomas and any tumors with spindle cells including neurilemoma, fibroma, meningioma, and leiomyoma. The majority of these tumors behave in a benign manner, although there have been reports of local aggressiveness. The treatment is surgical excision.

Sialadenoma Papilliferum

Sialadenoma papilliferum is a rare, benign salivary gland tumor named after the skin tumor syringocystadenoma papilliferum, which it resembles on gross pathologic and microscopic examination. This tumor is painless and exhibits slow-to-moderate growth. It originates in the major and minor salivary glands, most commonly in men about 60 years of age. Microscopically, the tumor originates from the superficial extralobular salivary gland ducts. The cell of origin is thought to be the pluripotential myoepithelial cell.

Clinically, the differential diagnosis includes other papillary lesions like squamous papilloma, verrucous hyperplasia, or carcinoma. Usually it can be distinguished from other intraoral minor salivary gland tumors because it is exophytic and not a smooth, mucosa-covered mass. The treatment is surgical excision.

Inverted Ductal Papilloma

Inverted ductal papilloma is an inverted papilloma that originates from the excretory ducts of the minor salivary glands. This tumor is a different entity from the inverted oral papilloma, which is endophytic and does not bear any clinical resemblance to inverted ductal papilloma. The few cases that have been reported occur equally in men

and women. The lesions are raised but not ulcerated. The preoperative differential diagnosis includes salivary gland tumor, fibroma, and lipoma. Treatment should be conservative, but excision should be complete.

Congenital Lesions

Hemangiomas

Congenital vascular lesions are divided into two groups: hemangiomas and vascular malformations. Juvenile hemangiomas are the most common tumors of infancy, occurring in up to 10% of all births.[73] They may be present at birth but commonly appear several days to weeks later. A rapid growth phase occurs around the age of 1 to 6 months, followed by gradual involution over 1 to 12 years. During the growth phase, endothelial cells proliferate rapidly and become flat during involution. Facial infantile hemangiomas occur in two distinct patterns of tissue involvement: a focal type with a tumor-like appearance and a less common diffuse type with a plaquelike appearance. The diffuse lesions are more likely to be complicated by ulceration or airway obstruction and show a strikingly segmental distribution pattern. Focal hemangiomas, in contrast, show a predilection for regions of embryologic fusion.[74] Hemangiomas are more common in the parotid than in the submandibular gland. Hemangiomas of the parotid area are more often seen in female patients and are usually asymptomatic, unilateral, and compressible masses. The overlying skin may be normal or may be involved. It is not uncommon to see other skin lesions present. On gross pathologic examination, this tumor is dark red, lobulated, and nonencapsulated. Microscopically, these tumors are composed of capillaries lined by proliferative endothelial cells. Blood vessels are uniform in size. Mitoses occur frequently but are not indicators of behavior.[75]

Hemangiomas may become extremely large with complications such as bleeding, heart failure, and even death. Treatment initially should consist of steroids administered 2 to 4 mg/kg per day. If the hemangioma is responsive to steroids, the result is usually immediate and often dramatic. Unfortunately, the response rate to steroids is only 40% to 60%. In such patients, interferon may be useful, but it should be reserved for life-threatening situations because of its toxicity and the necessity to continue the drug for prolonged periods. Surgical excision or various types of laser treatments may be performed for select circumstances.[76] Hemangiomas usually involute completely, but they may take years and may result in medical or psychological problems for children.[77]

Vascular and Lymphatic Malformations

Vascular malformations are different from hemangiomas of the parotid gland. These vascular malformations are not true neoplasms and are divided into different categories, which are discussed briefly as follows.

Venous Malformations

Venous malformations are usually noted at the time of birth and continue to grow as the patient gets older. They may become extremely large in size by the time the child is fully grown. Unlike hemangiomas, which grow by cellular proliferation, enlargement of venous malformations is primarily by dilation of the existing vessels and does not represent cellular division.[76] Treatment is usually by surgical excision; however, large venous malformations involving the parotid gland may be difficult to remove. An MRI scan is the best imaging study to determine the extent of disease. Arteriograms are not helpful.

Arteriovenous Malformations

Arteriovenous malformations differ from arteriovenous fistulas in that the malformations are congenital (but may not manifest for several years), whereas the fistulas are acquired, usually as a result of trauma. Arteriovenous malformations involve shunting of blood from the arterial vessels directly into the venous system, causing significant enlargement of the vascular lesion. Generally these should be removed completely in order to stop the progress. They can involve the parotid gland and appear as a parotid mass. An arteriogram is essential to diagnose the presence and extent of the malformation. Surgical resection is desirable.

Lymphatic Malformations

Lymphatic malformations are usually present at birth and gradually grow. They can involve the salivary glands, causing enlargement. In some cases the lymphatic aggregates can be nodular, simulating a mass. Usually very diffuse, they infiltrate locally in the tissue planes of the adjacent structures. Treatment is surgical resection, which can be quite tedious.

Management of Benign Salivary Gland Neoplasms

Management of benign salivary gland tumors has not changed dramatically for years. Management of tumors of the salivary glands requires a detailed understanding of the anatomy and pathologic processes affecting these glands. Benign salivary gland tumors should be excised completely with an adequate margin to avoid local recurrences.[57] Generally tumors in the parotid gland are removed with an adequate cuff of surrounding normal tissue, and the facial nerve is dissected and carefully preserved. The extent of dissection of the facial nerve and the amount of parotid tissue resection depend on the size, location, and histology of the tumor.[78]

Small adenomas located in the tail of the parotid gland may require only dissection of the lower division of the facial nerve with removal of the tumor and the surrounding parotid tissue, avoiding unnecessary dissection of the upper division.

Larger tumors of the superficial lobe, however, usually require a complete superficial parotidectomy. Deep lobe tumors require a total parotidectomy, with facial nerve preservation. Parapharyngeal tumors are most commonly excised through a cervical-parotid approach and only occasionally in conjunction with a mandibulotomy.[79]

A tumor of the submandibular gland requires submandibular gland resection. If the tumor originates from a minor salivary gland, the tumor and a cuff of normal tissue should be excised. Simple enucleation should be discouraged because of the increased risk of recurrence.[58] Pediatric hemangiomas will generally involute but may be resected in special cases. Vascular malformations involving the parotid or submandibular glands may require surgical excision.

Parotidectomy (see Key Indicator Video online)

The patient is placed in the supine position, and the head turned to the opposite side. The standard incision is a modified Blair's incision (Fig. 87-16A). The skin incision is placed in a preauricular crease and extends superiorly to the level of the root of the helix. The incision extends inferiorly around the lobule of ear over the mastoid tip. It then gently curves down along the sternocleidomastoid muscle and then slightly forward in a natural skin crease in the upper neck (see Fig. 87-16A). Alternatively, a "face-lift" incision may be done in selected patients with benign tumors of the lower or mid regions of the parotid gland. The preauricular portion of the incision passes on or just inside the tragal margin. The incision is then carried below the lobule of the ear, turns posteriorly over the mastoid, and then is extended within the hairline (Fig. 87-17A). The face-lift incision is less conspicuous and therefore offers better cosmesis (see Fig. 87-17B).

To expose the parotid gland, skin flaps are elevated in the plane superficial to the parotid fascia in the preauricular region and in the subplatysmal plane in the cervical portion of the incision (see Fig. 87-16B). The greater auricular nerve and the external jugular vein are identified over the sternocleidomastoid muscle and are divided to free the tail of the parotid gland (see Fig. 87-16B). In some cases the greater auricular nerve can be preserved, but whether this preservation has a significant impact on the patients' quality of life is debatable (as will be discussed under Complications).[80,81] The posterior belly of the digastric muscle is exposed proximal to its attachment to the mastoid bone. The fascia between the parotid gland and the cartilaginous external auditory canal is dissected, and the parotid gland is retracted anteriorly. This exposes the tragal pointer. The most common method of identifying the main trunk of the facial nerve is in its course in the region located between the tragal pointer and the attachment of the posterior belly of the digastric muscle to the mastoid bone (see Fig. 87-16C). Unless displaced by tumor, the nerve is usually located approximately

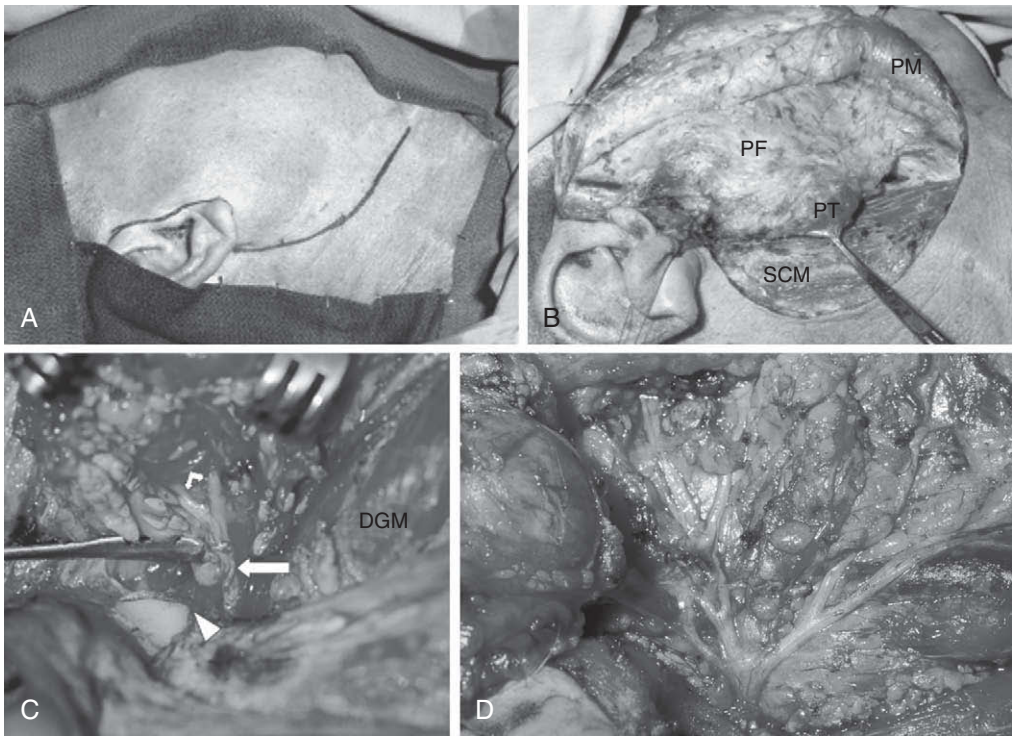

Figure 87-16. Right superficial parotidectomy. **A,** Modified Blair's incision for a right parotidectomy. **B,** Flap elevation and freeing the tail of the parotid gland. **C,** Identification of the main trunk of the facial nerve. The facial nerve is usually identified by dissecting the main trunk *(white arrow)* in the region located between the tragal pointer *(white arrowhead)* and the attachment of the posterior belly of the digastric muscle (DGM) to the mastoid bone. Unless displaced by tumor, the nerve is usually located approximately 1 to 1.5 cm deep and inferior to the tragal pointer. Dissection of the main trunk then proceeds distally until it branches *(double arrow),* and then all branches are sequentially and meticulously dissected. **D,** Complete dissection of all parotid tissue lateral to the facial nerve reveals the main trunk and the complex branching pattern of the facial nerve (pes anserinus). PF, parotid fascia; PM, platysma muscle; PT, parotid tail; SCM, sternocleidomastoid muscle.

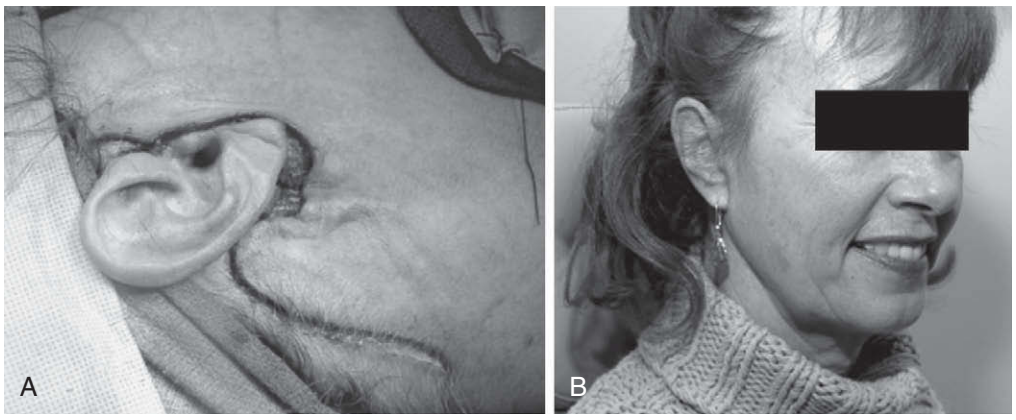

Figure 87-17. Modified "face-lift" incision for parotidectomy. **A,** Unlike the modified Blair's incision, which has a cervical extension (see Fig. 87-16A), the face-lift incision extends posteriorly and inferiorly along the hairline. **B,** The hairline portion of the incision is inconspicuous, making this approach more cosmetically pleasing.

1 to 1.5 cm deep and inferior to the tragal pointer. Another reliable, and perhaps a more constant, landmark to identify the facial nerve is the tympano-mastoid suture line, which could be followed medially to the main trunk of the nerve. The nerve is usually 6 to 8 mm deep to the tympano-mastoid suture line. In certain cases where the tumor is directly overlying the region of the main trunk of the facial nerve, one or more of the peripheral branches of the nerve are identified distally and traced proximally toward the main trunk.[82] The marginal mandibular branch can be identified below the lower border of the mandible, as it crosses superficial to the facial vessels, in the plane immediately underneath the deep cervical fascia. Alternatively, the buccal branch can be identified underneath the parotido-masseteric fascia, coursing parallel to the parotid duct.

Once the facial nerve is identified, the overlying parotid tissue is meticulously elevated from the nerve with a fine clamp and the bridge of tissue between the blades of the clamp carefully divided. If the main trunk of the nerve is identified first, then the overlying parotid tissue is progressively dissected free of the nerve to the first branching of the nerve, usually into an upper and a lower division (see Fig. 87-16C). Subsequent branching of the nerve (pes anserinus) is sequentially dissected in a similar fashion, until the entire superficial lobe of the parotid gland lying lateral to the facial nerve is

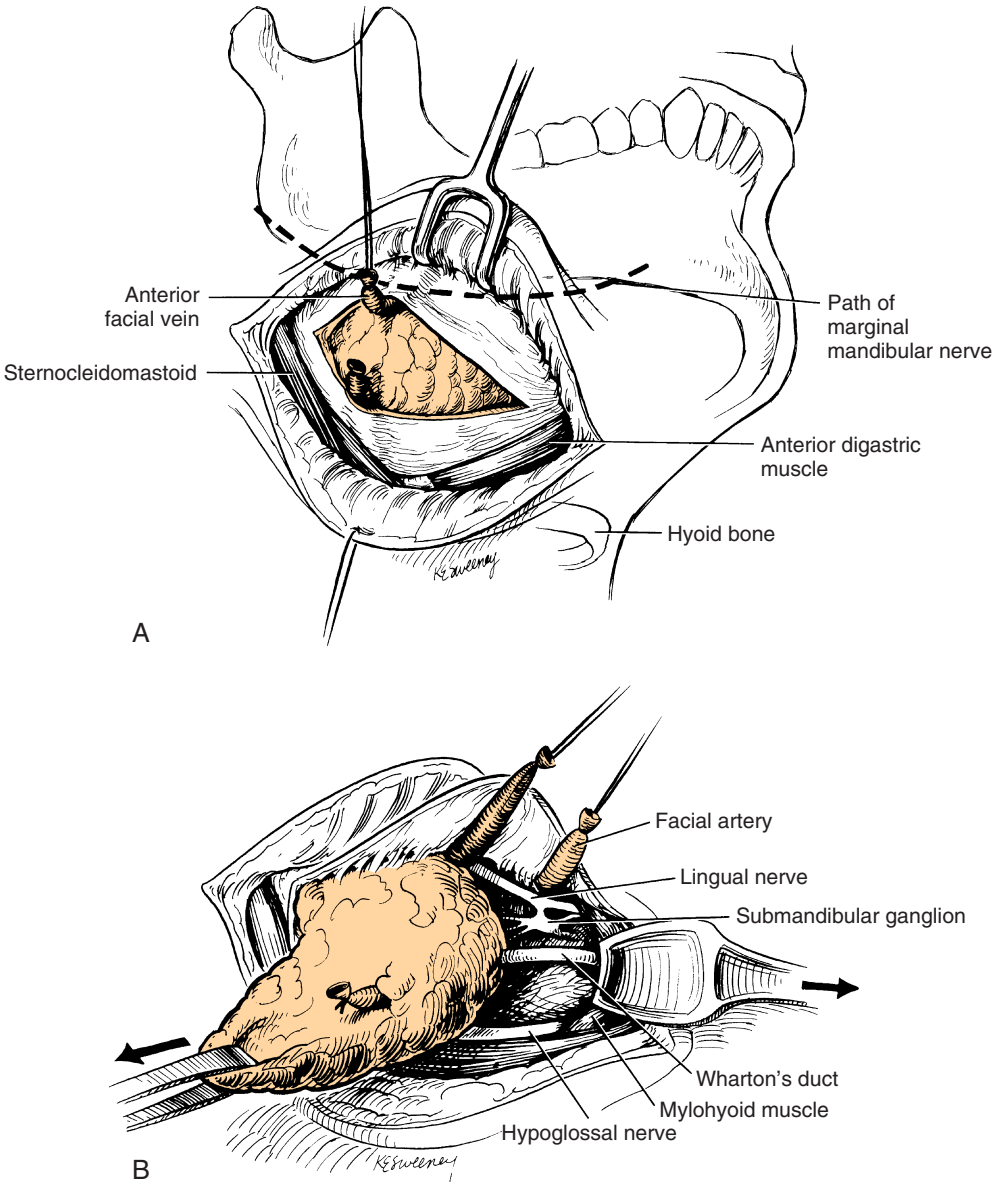

Figure 87-18. Excision of the submandibular salivary gland. **A,** Submandibular incision, made in a natural skin crease 3 to 4 cm inferior to mandible. Marginal mandibular nerve generally lies just superficial to anterior facial vein. **B,** Mylohyoid is retracted anteriorly and the gland posteriorly. This exposes the lingual nerve, submandibular ganglion, and Wharton's duct.

delivered (see Fig. 87-16D). This completes a superficial or lateral parotidectomy.

If a total parotidectomy is indicated, the procedure is extended by meticulous dissection of the main trunk and the branches of the facial nerve from the underlying parotid tissue in a gentle and atraumatic fashion. This allows the salivary tissue lying deep to the facial nerve to be delivered while preserving the nerve and its function.

Submandibular Gland Excision

A curvilinear incision is placed, preferably in a natural skin crease, 3 to 4 cm below the lower border of the mandible, overlying the submandibular gland. The incision is carried down through the subcutaneous fat, and the platysma muscle. Great care should be taken to avoid injury of the marginal mandibular nerve. The nerve lies immediately beneath the deep cervical fascia, and can be identified crossing the anterior facial vein. The vein is doubly ligated and transected well below the nerve, and upward retraction of the superior ligature displaces the nerve superiorly and protects it from injury during further dissection (Fig. 87-18A). Superior dissection proceeds by double ligation and transection of the facial artery, which frees the superior attachment of the gland. Anteriorly the vessels to the mylohyoid muscle are divided, and the gland is mobilized posteriorly, exposing the free edge of the mylohyoid muscle. The free (posterior) edge of the mylohyoid muscle is retracted anteriorly, while gentle posterior traction on the gland is maintained. This exposes the deep portion of the gland and its duct, the submandibular ganglion, and the lingual and hypoglossal nerves (see Fig. 87-18B). These structures lie superficial to the hyoglossus muscle. The contribution of the lingual nerve to the submandibular ganglion is transected, and the Warthin's duct is doubly ligated and divided. This delivers the deep portion of the gland. Care should be taken to avoid injury to the lingual and hypoglossal nerves. Finally the facial artery is divided a second time, and the gland is removed.

Excision of Parapharyngeal Salivary Gland Tumors

Surgical excision of salivary gland tumors within the parapharyngeal space is best done via an external approach.[37,79] The incision is that of a parotidectomy with a cervical extension (Fig. 87-19A). If the tumor involves the deep lobe of the parotid gland, a superficial parotidectomy is done first. If the tumor arises from the minor salivary glands of the

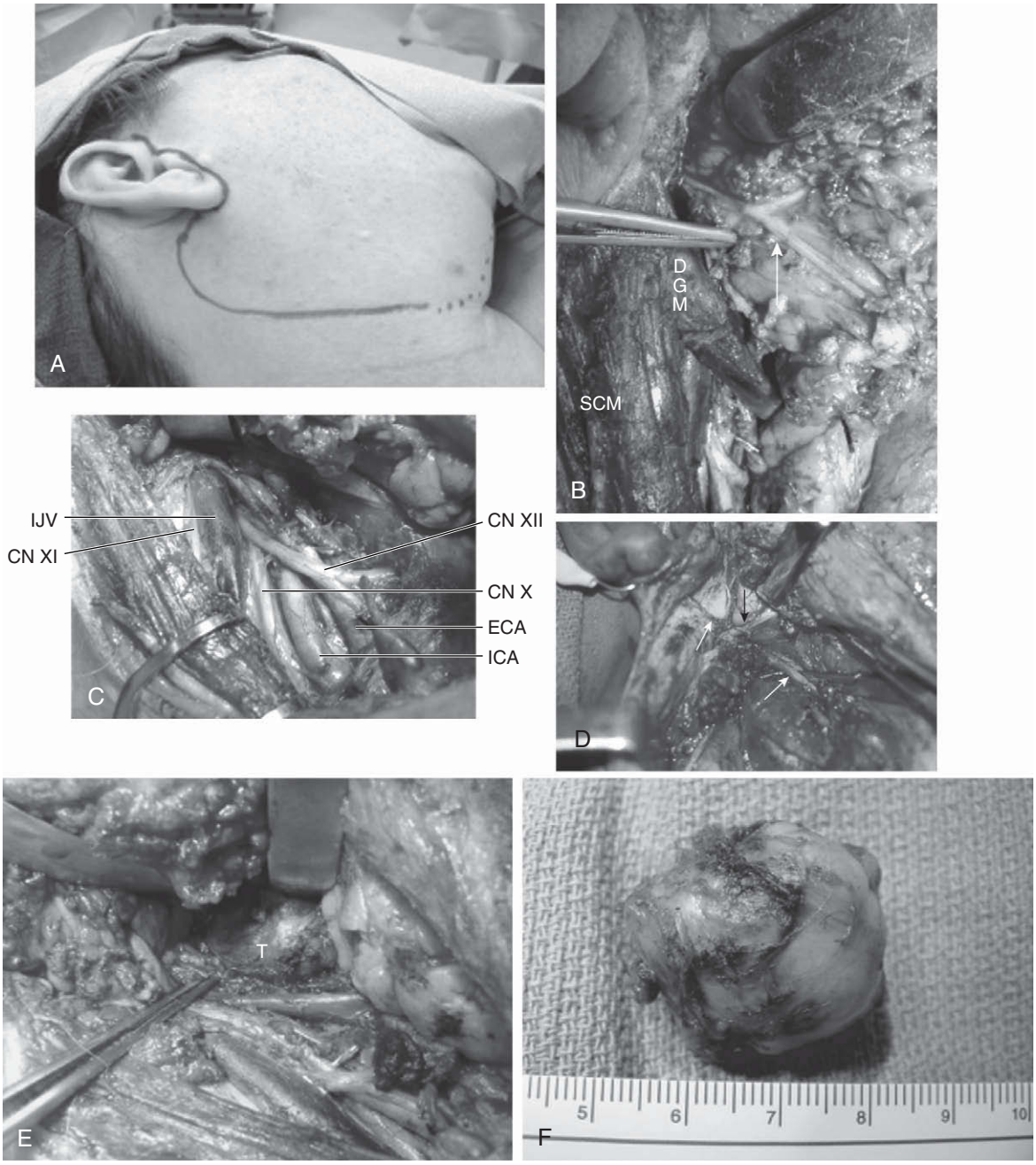

Figure 87-19. Transcervical approach to the right parapharyngeal space. **A,** Incision for transcervical approach to the parapharyngeal space. The incision can be extended to the submandibular region and can also extend as a lip-splitting incision if a mandibulotomy is necessary for added exposure *(dotted line).* **B,** The main trunk of the facial nerve is identified in the same manner as described for superficial parotidectomy. For most benign tumors of the parapharyngeal space, dissection of the facial nerve is limited to the main trunk and the inferior division of the nerve *(arrow).* Dissection of the upper division is occasionally necessary for adequate exposure and tumor resection. **C,** Exposure of the neurovascular structures in the upper cervical region. These include the internal jugular vein (IJV), internal carotid artery (ICA), external carotid artery (ECA), and cranial nerves (CN) X, XI, and XII. **D,** The stylomandibular ligament *(white arrow)* is seen overlying the curved hemostat. The relationship of the main trunk of the facial nerve *(black arrow)* and the tragal "pointer" *(white arrowhead)* is also demonstrated. **E,** Division of the stylomandibular ligament allows further anterior retraction of the mandible, and resection of the styloid process allows more cephalad exposure of the parapharyngeal space. These maneuvers allow wide access to the parapharyngeal space for adequate tumor (T) exposure. **F,** Pleomorphic adenoma of the parapharyngeal space. DGM, digastric muscle; SCM, sternocleidomastoid muscle.

parapharyngeal space, the inferior division of the facial nerve is identified and carefully preserved (see Fig. 87-19B). Next, the sternocleidomastoid is retracted laterally and the upper neck is dissected to expose the internal jugular vein, external and internal carotid arteries, and the last four (IX, X, XI, and XII) cranial nerves (see Fig. 87-19C). The posterior belly of the digastric and the stylohyoid muscle are identified, divided near their mastoid and styloid attachments, respectively, and retracted medially. This allows further superior exposure of the internal carotid artery, internal jugular vein, and adjacent nerves, as well as visualization of the stylomandibular ligament and the styloid process. The stylomandibular ligament is divided (see Fig. 87-19D), which allows further anterior retraction of the mandible and provides a wide opening into the parapharyngeal space (see Fig. 87-19E). The styloid process may be resected for further exposure and to assist delivery of

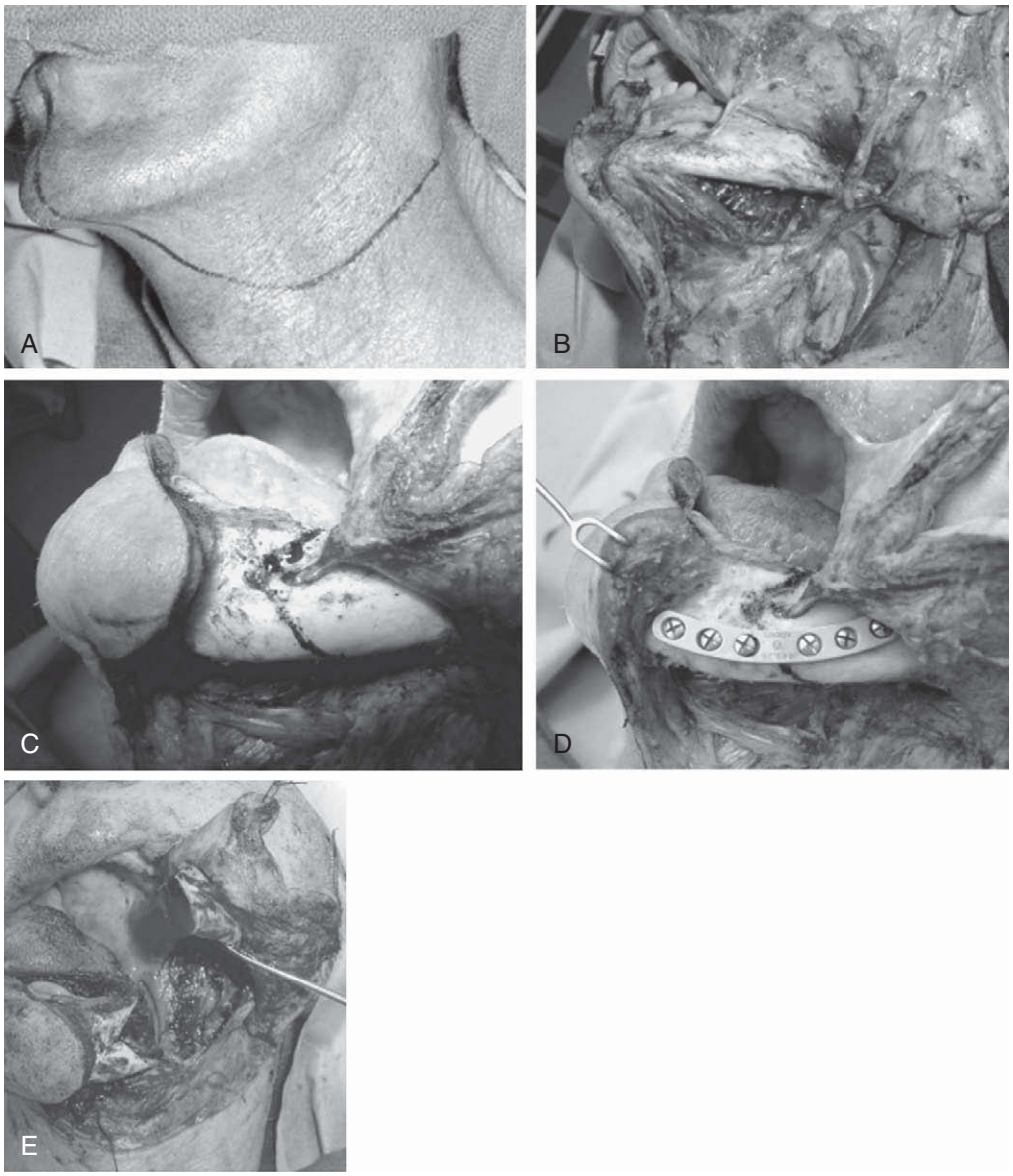

Figure 87-20. Mandibulotomy approach for excision of tumors in the parapharyngeal space. **A,** Lip-splitting incision for mandibulotomy. **B,** Upper cervical dissection and exposure of the mandible with identification and preservation of the mental nerve. **C,** A "Chevron" osteotomy is outlined anterior to the mental foramen. **D,** A metal plate is preregistered and fixed to the mandible before the planned osteotomy to avoid postoperative malocclusion. **E,** After the osteotomy is distracted, dissection is carried along the floor of mouth just lateral to the tongue, providing wider access to the parapharyngeal space.

larger tumors. Through this exposure, the tumor can be easily visualized and safely excised (see Fig. 87-19E and F).

In patients with tumors located in the superior aspect of the parapharyngeal space approaching the eustachian tube and skull base, the addition of a mandibulotomy may be necessary.[37,83] The enhanced exposure offered by the mandibulotomy allows the visualization necessary for resection of the tumor with adequate margins. First, a cervical-parotid approach is performed as described in the previous section. If a mandibulotomy is indicated, a preliminary tracheostomy is performed. Next, the cervical portion of the incision is extended through the chin to split the lower lip in the midline (Fig. 87-20A). After dissection of the upper carotid sheath, the mandible is exposed carefully, identifying and preserving the mental nerve (see Fig. 87-20B). A stair-step or "Chevron" osteotomy is outlined either in the midline (median mandibulotomy) or just anterior to the mental foramen (paramedian mandibulotomy) (see Fig. 87-20C). These types of osteotomies are more mechanically stable than a straight-line osteotomy. In order to obtain normal dental occlusion, a metal plate is preregistered and fixed to the mandible before performing the planned osteotomy (see Fig. 87-20D). The osteotomy is performed using a micro-reciprocating saw in order to minimize bony loss at the osteotomy site. A paralingual incision is then made along the floor of the mouth. The mylohyoid muscle is divided while carefully preserving the hypoglossal and lingual nerves. The tongue is retracted medially, and the parapharyngeal and retropharyngeal spaces are opened widely (see Fig. 87-20E). The tumor can now be excised safely and adequately while protecting the critical neurovascular structures of the parapharyngeal space. Closure involves a water-tight intraoral suture line and rigid fixation of the mandibulotomy. A nasogastric tube is inserted for feeding. Within 7 to 10 days most patients will have their tracheostomy decannulated and be able to resume oral feeding.

Complications

Facial Nerve Paresis or Paralysis

Facial nerve dysfunction may result from traction injury to the facial nerve during dissection. Facial nerve monitoring has helped decrease

the morbidity of a parotidectomy.[84] As long as the anatomic integrity of the nerve is preserved, this type of injury usually results in neuropraxia and, therefore, complete recovery is anticipated. The degree of weakness or paralysis may range from minimal partial weakness of one or more branches of the facial nerve to complete paralysis of all branches of the nerve. Recovery of facial nerve function may be prompt and complete within days or may be delayed for several months. In a study of 256 consecutive patients who underwent parotid surgery at the Cleveland Clinic over a period of 15 years, immediate postoperative facial nerve dysfunction was frequently encountered (46%), but permanent dysfunction was uncommon (4%).[85] The incidence of long-term dysfunction was higher in revision cases and when an extended (total or subtotal) parotidectomy was performed. In order to minimize facial nerve injury, the parotid surgeon should adhere to meticulous dissection and gentle handling of the facial nerve. Excessive traction on the nerve must be avoided, as should overzealous use of the nerve stimulator.

Transection of one or more of the branches of the facial nerve will result in paralysis of the corresponding muscles supplied by the injured nerve. The degree of paralysis may vary and depends on the presence and extent of cross-innervation of the involved muscle groups by the uninjured branches of the facial nerve. Complete transection of the main trunk of the facial nerve results in complete and permanent paralysis of all ipsilateral muscles of facial expression.

If the facial nerve is sacrificed, nerve repair may be done by using either direct neurorrhaphy of the cut edges or a cable graft, depending on the length of the resected segment (see Fig. 87-18). Immediate rehabilitation of the paralyzed face requires diligent eye care to prevent exposure keratitis. This involves liberal use of artificial tears, lubricating ointment, and protection with an appropriate eye dressing and eyewear. A gold weight implant should be used routinely in patients with complete facial paralysis. A temporary tarsorrhaphy may be necessary for patients with lower eyelid ectropion. If the facial nerve is not repaired or grafted, then one or more of the various surgical procedures for static or dynamic rehabilitation of the paralyzed face may be indicated.

Sensory Abnormalities

The greater auricular nerve (GAN) is frequently divided during the operation of parotidectomy. This usually results in sensory deficits in the dermatomal distribution of the GAN, which comprises the lower third of the pinna including the earlobe, as well as the adjacent preauricular and postauricular skin. Although many patients experienced sensory deficits, the overall quality of life was not significantly affected after GAN sacrifice during parotidectomy.[80]

Gustatory Sweating—"Frey's Syndrome"

Patients with Frey's syndrome experience flushing and sweating of the ipsilateral facial skin during mastication (gustatory sweating). The symptoms may vary in severity from barely noticeable to severe and bothersome. The syndrome is a sequela of parotidectomy and may follow other surgical, traumatic, and inflammatory injuries of the parotid and submandibular glands and the cervical and upper thoracic portions of the sympathetic trunk.[86] The true incidence of postoperative Frey's syndrome is unknown, but it is estimated to be between 35% and 60%. The incidence would probably be higher if the syndrome were searched for by directed, symptom-specific questions.[87] The presumed pathophysiology of Frey's syndrome involves aberrant cross-reinnervation between the postganglionic secretomotor parasympathetic fibers to the parotid gland and the postganglionic sympathetic fibers supplying the sweat glands of the skin.

The diagnosis of Frey's syndrome depends largely on the patient's symptoms. An objective method of confirming the diagnosis is the Minor's starch/iodine test. This involves painting the ipsilateral side of the face and neck with iodine solution, which is allowed to dry. Starch powder is then dusted over the painted area. The patient then chews on a sialagogue (e.g., lemon wedge) for several minutes. The appearance of dark blue spots along the face confirms gustatory sweating. This discoloration is the result of the reaction of the dissolved starch with iodine. If the Minor's starch iodine test is used for diagnosis, up to 96% of patients who did not complain of Frey's syndrome after surgery actually had a subclinical manifestation of this complication.[86] This is usually detected within the first year after surgery, but the onset may occasionally be delayed for many years.

If the symptoms are bothersome enough, treatment involves simply applying an antiperspirant over the involved skin. Glycopyrrolate (1%) roll-on lotion is also effective in controlling the symptoms. In cases not responding to these simple measures, surgical interruption of the secretory fibers may be attempted by performing a tympanic neurectomy. Recently, intracutaneous injection of botulinum toxin A has been described as an effective treatment in severe cases of Frey's syndrome.[87,88]

Thick skin flap and partial superficial parotidectomy are the most important techniques to minimize the risk of developing symptomatic Frey's syndrome.[89] The incidence was not altered by the use of sternocleidomastoid muscle flap or other implantation material.[90]

Salivary Fistula

This is an uncommon problem. It usually presents as a clear sialorrhea from the wound or a fluid collection under the skin flaps. In the majority of cases the problem is self-limited. Management includes repeated aspiration, pressure dressing, wound care, and patience. Oral anticholinergics (e.g., glycopyrrolate) may be helpful in temporarily reducing salivary flow until healing is complete.

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CHAPTER EIGHTY-EIGHT

Malignant Neoplasms of the Salivary Glands

John B. Sunwoo

James S. Lewis, Jr.

Jonathan McJunkin

Sunitha Sequeira

Key Points

- Salivary gland malignancies are diverse and heterogeneous. Their behavior and resulting clinical management are highly dependent on their histologic type and, often, their grade.
- High-grade histologic types include high-grade mucoepidermoid carcinoma, squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma not otherwise specified, carcinoma ex-pleomorphic adenoma, and salivary duct carcinoma.
- Treatment is primarily surgical (when resectable) with or without adjuvant postoperative radiation.
- There is controversy regarding when to treat an N0 neck; however, in general, histopathologic type, T stage, and evidence of perineural or bone invasion can guide management.
- Indications for adjuvant postoperative radiation include advanced stage, positive margins, high-grade histologic types, and evidence of local tissue invasion.

Malignant neoplasms of the major and minor salivary glands are rare, comprising approximately 3% of all head and neck malignancies.[1] The estimated incidence is only 0.9 per 100,000 in the United States, but the rate increases with age, peaking at ages 65 to 74 years.[2] Less than 5% of all salivary gland tumors occur in the pediatric age group; however, salivary gland tumors in children are much more likely to be malignant than those of adults.

Of all salivary neoplasms (benign and malignant), the vast majority occurs in the parotid gland and the fewest in the sublingual gland. There is an interesting inverse relationship between the overall incidence of neoplasms by site and the percentage that are malignant (Table 88-1). In a review of 2410 cases of salivary gland tumors,[3] 73% occurred in the parotid, and of those, only 15% were malignant. On the other hand, minor salivary gland tumors constituted only 14% of the total number of cases but 46% were malignant. Likewise, submandibular gland neoplasms constituted 11% of the cases with 37% being malignant; sublingual gland neoplasms constituted only 0.3% with 86% being malignant.

The frequency of the different histologic types of salivary gland malignancy also varies depending on the gland and site. A number of studies have found the most common primary malignancy presenting in the salivary glands to be mucoepidermoid carcinoma.[1,2,4] In one of the largest reviews of salivary gland neoplasms (2807 total), Spiro examined 1278 cases of malignant salivary gland tumors[1] and reported that 34% were mucoepidermoid carcinoma (Table 88-2). The next most common type was adenoid cystic carcinoma (22%), followed by adenocarcinoma (a mixture of tumors which has more recently been subdivided, as described below) (18%), malignant mixed tumor (13%), acinic cell carcinoma (7%), and squamous cell (epidermoid) carcinoma (4%). When considering the types by anatomic site, mucoepidermoid carcinoma was the most frequent malignancy of the parotid, but adenoid cystic carcinoma was the most frequent of the submandibular and minor salivary glands. One exception to the latter was malignant minor salivary gland tumors arising in the nasal cavity and paranasal sinuses, in which case adenocarcinoma was the most common type as opposed to adenoid cystic carcinoma.

This chapter discusses the evaluation of patients with these malignancies, histopathology of the more common types, and currently accepted treatment. Both the rarity of these malignancies and the wide variety of histologic types have made their study challenging. In fact, what is known about their clinical behavior and treatment outcomes is based almost entirely on retrospective studies.

Evaluation of the Patient

Physical Examination

The clinical presentation of malignant salivary gland neoplasms can range from indolent asymptomatic masses to rapidly growing painful masses with progressive facial nerve paralysis. In Spiro's review of 2807 salivary gland tumors, pain was a symptom in only 10% of malignant cases[1] but was more frequently seen with malignant neoplasms than with benign ones. In general, episodic swelling and pain most often indicates salivary gland obstruction and inflammation, whereas constant pain is more worrisome for malignancy. However, sialadenitis can

Table 88-1

Relationship Between Site of Primary Tumor and Frequency of Malignancy

Site	Absolute Numbers	Percentage Frequency	Percentage Malignant
Parotid	1756	72.9	14.7
Submandibular	257	10.7	37
Sublingual	7	0.3	85.7
Minor glands	336	14	46.4
Unknown	54	2.2	—

From Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol*. 1985;146:51-58.

Table 88-2

Relative Incidence of Malignant Salivary Gland Neoplasms

Histologic Type	Number	Percent
Mucoepidermoid	439	34
Adenoid cystic carcinoma	281	22
Adenocarcinoma NOS	225	18
Malignant mixed tumors	161	13
Acinic cell carcinoma	84	7
Squamous cell carcinoma	53	4
Other (anaplastic etc.)	35	3
TOTAL	1278	

From Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg*. 1986;8:177-184.

be secondary to obstruction by a salivary gland neoplasm; thus the latter must be considered in the evaluation of any salivary gland swelling with pain. Approximately 10% of parotid gland malignancies present with associated facial paralysis, and this portends a poor prognosis.[5,6]

Parotid Gland

The parotid glands are the largest of the major salivary glands and are unique in that they are the only salivary glands that contain intraglandular lymph nodes. Both parotid glands can be divided into a superficial "lobe" and a deep "lobe" by the plane in which the branches of the facial nerve course. These lobes are primarily defined for surgical treatment purposes, but anatomically they are also distinguished by the fact that the majority of the intraglandular lymph nodes are in the superficial lobe. The superficial lobe is the portion lateral to the plane of the facial nerve and contains approximately 10 to 20 lymph nodes on average. The deep lobe is medial to the plane of the facial nerve and extends into the parapharyngeal space.

A thorough examination of the parotid gland includes palpation of the gland itself and of the neck, assessment of the overlying skin, bimanual palpation of the buccal space, which includes Stensen's duct, examination of the oropharynx and nasopharynx, and a thorough evaluation of facial nerve function and symmetry. The parapharyngeal space can be divided into a prestyloid (or anterolateral) compartment and a poststyloid (or posterolateral) compartment by a fascial layer extending from the styloid process to the tensor veli palatini. Deep lobe parotid tumors can involve the prestyloid compartment of the parapharyngeal space and present as a submucosal bulging mass in the oropharynx and/or nasopharynx, distorting the soft palate or obstructing the Eustachian tube. If the tumor extends into the poststyloid compartment, there may be cranial nerve (CN) neuropathies, manifesting as a decreased gag reflex (CN IX, X), aspiration (CN IX, X), asymmetric palate elevation (CN X), hoarseness (CN X), dysphagia (CN X), weakness of the trapezius muscle (CN XI), or atrophy/paresis of the tongue (CN XII). If a parotid tumor extends posteromedially into the infratemporal fossa, there may also be associated trismus.

Submandibular Gland

The pair of submandibular glands, located in the submandibular triangle (level Ib) of the neck and extending to the medial aspect of the mandible, represents the second largest of the major salivary glands. These glands are intimately associated with the lingual nerve, hypoglossal nerve, facial artery and vein, and overlying marginal mandibular branch of the facial nerve. They drain into the floor of the mouth via Wharton's duct.

Bimanual (intraoral and external) palpation of any submandibular gland tumor should be performed to assess the extent of the tumor and to determine if there is fixation to adjacent structures such as the mandible or skin. A careful neurologic examination should also be performed to assess nerve involvement. In particular, worrisome signs of malignancy include numbness of the tongue (suggesting lingual nerve involvement), weakness of the tongue (suggesting hypoglossal nerve involvement), or weakness of the lower lip (suggesting facial nerve involvement). Careful examination of the neck is also important because 25% to 28% of submandibular malignancies will have metastases to regional lymph nodes.[1,7]

Sublingual Gland

The pair of sublingual glands is located in the floor of the mouth, one on each side of the frenulum, lateral to Wharton's duct in the submucosal compartment. The drainage of these glands is via Bartholin's ducts, which empty into Wharton's ducts. As with submandibular gland tumors, bimanual palpation of the floor of the mouth is important to assess the extent and possible fixation of sublingual gland tumors to the mandible. Because the sublingual gland is intimately associated with the lingual and hypoglossal nerves, a careful neurologic examination is important as previously stated. Although tumors in this area are usually painless, the vast majority (86%) of sublingual gland tumors are malignant.[1]

Minor Salivary Glands

Minor salivary gland tissue is plentiful with estimates between 500 and 1000 glands along the upper aerodigestive tract. Although they are located in the submucosa throughout the oral cavity, oropharynx, nasal cavities, paranasal sinuses, pharynx, and larynx, the majority of them are located in the oral cavity, with the highest concentration being in the submucosa of the hard palate. As such, the site most frequently involved with minor salivary gland malignancies is the hard palate.[8] Compared with the major salivary glands, minor salivary glands have minimal capsular tissue, making local invasion of tumors into surrounding tissue common. Patients with malignancies of the minor salivary glands most often present with a painless submucosal swelling, but there is frequently fixation of the overlying mucosa and ulceration. Approximately one quarter of patients will complain of local pain,[9] and pain or paresthesia/anesthesia is concerning for nerve invasion. Because minor salivary glands are distributed throughout the mucosalized surfaces of the head and neck, malignancies of these glands may present in diverse ways depending on the location. Symptoms may include nasal airway obstruction, sinusitis, eustachian tube dysfunction, or hoarseness. A thorough head and neck evaluation including fiberoptic examination and cross-sectional imaging should be performed in all cases.

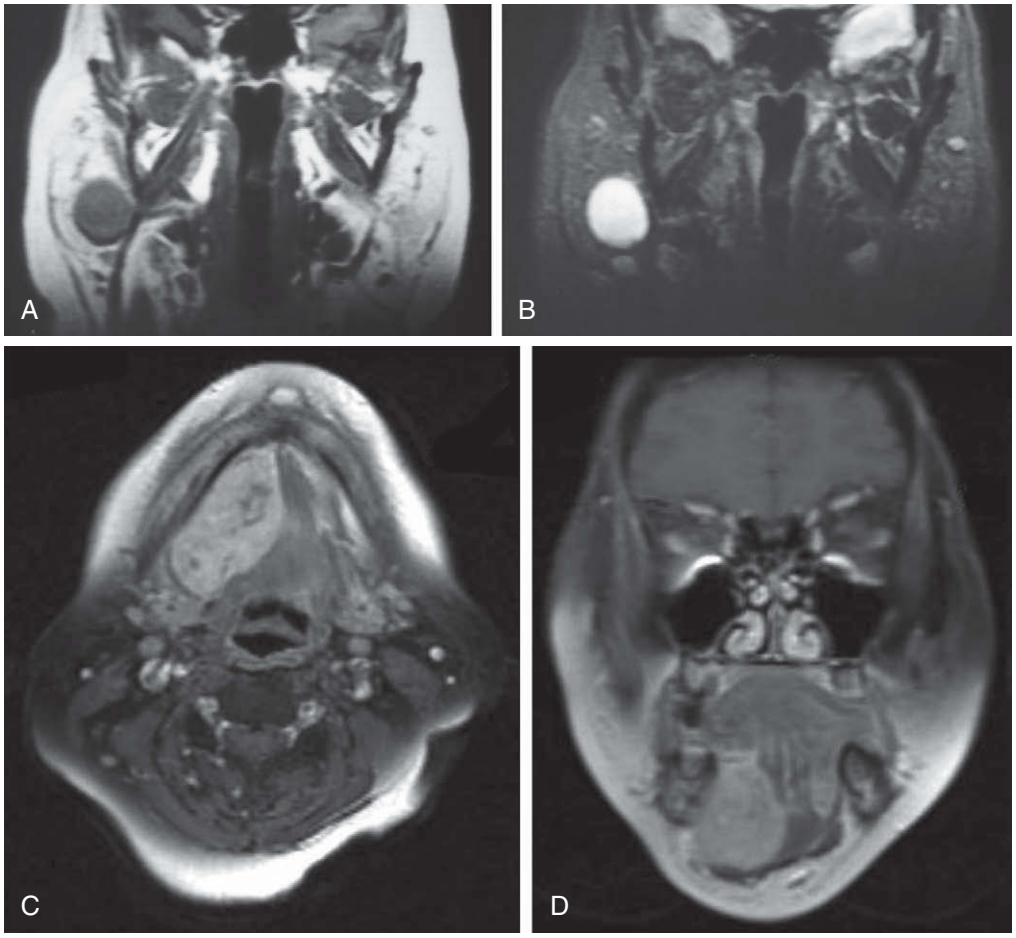

Figure 88-1. Magnetic resonance imaging of salivary gland neoplasms. **A,** T1-weighted image of a pleomorphic adenoma in the parotid gland. **B,** T2-weighted image of the same pleomorphic adenoma. **C,** Axial T1-weighted, postgadolinium, fat-saturated image of an adenoid cystic carcinoma of the right sublingual gland. **D,** Coronal T1-weighted, postgadolinium, fat-saturated image of the same tumor in **C.** *(**A** and **B** from Som PM and Curtain HD.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2002:2074, figure 39-102A and B).*

Radiologic Studies

Magnetic resonance imaging (MRI) is the radiologic modality most often recommended to assess salivary gland neoplasms if there are no contraindications. Benign and malignant neoplasms of the parotid gland are well visualized on T1-weighted images because they are easily distinguished from the fatty parenchyma of the gland, which appears hyperintense. In *general,* benign epithelial neoplasms (such as pleomorphic adenomas) and low-grade malignancies have low T1-weighted and high T2-weighted signal intensities (Fig. 88-1A and B). High-grade carcinomas tend to have low-to-intermediate signal intensities on both T1-weighted and T2-weighted imaging (discussed later). The use of contrast material such as gadolinium and fat saturation of T1-weighted imaging provides additional information regarding the extent of a salivary gland malignancy (Fig. 88-1C and D). This is particularly useful in terms of assessing bone involvement and perineural spread. Bone marrow and cortex appear hypointense on fat-saturated images, and infiltrating tumor tissue appears hyperintense when enhanced with gadolinium. Enlarged foramina at the skull base and the presence of hyperintense enhanced tumor tissue are suggestive of perineural spread.

Some have proposed that T2-weighted imaging is helpful in distinguishing benign from malignant salivary gland neoplasms. Som and Biller[10] examined 35 parotid tumors by MRI and made the following observations. Benign tumors and low-grade malignancies had low T1-weighted and high T2-weighted signal intensities, and they had clearly defined margins. High-grade malignancies, on the other hand, had low T1- and T2-weighted signal intensities and poorly defined margins. Freling and colleagues,[204] however, did not make the same observations. They examined 116 patients with parotid masses, 30 of which were malignant tumors, and found no correlation between malignancy and signal intensity, heterogeneity, or radiographic margins on MRI. Malignant lesions could be discriminated from benign ones only when there was infiltration into adjacent structures. Among the malignant lesions, there was no correlation between tumor grade and MRI features. Thus MRI provides useful information about the extent of the disease, but histopathologic diagnosis is still required to distinguish benign from malignant processes.

Computed tomography (CT) with intravenous contrast is also widely used in evaluating salivary gland masses primarily because of the speed with which images are acquired. CT is particularly useful for evaluating cortical bone erosion from adjacent tumors. CT is much better than MRI in visualizing small salivary duct calculi, and as such, it is particularly helpful in assessing salivary gland masses if sialolithiasis is considered to be a component of the etiology. Highly cellular tumors can be visualized in the parotid gland because the normal parotid tissue has a high fat content, which results in a lower radiodensity on CT imaging compared with neoplasms. However, in general, MRI is superior to CT for providing soft tissue detail and delineating the extent of salivary gland masses.

Biopsy

Pretreatment diagnosis has been made possible by the use of fine-needle aspiration (FNA) biopsies. This diagnostic tool was established in the mid-to-late 1960s[11-16] and has become a mainstay in the workup of salivary gland neoplasms. It is an extremely safe procedure that is well tolerated by patients and is considered to have no significant risk of tumor seeding to surrounding tissue.[17]

Although FNA biopsies of salivary neoplasms have proven to be extremely useful for preoperative planning, the interpretation of these biopsies can be difficult, resulting in diagnostic ambiguity and inaccuracy. A few entities have classic, pathognomonic features on needle aspiration. However, the variety of different tumor types and their widely overlapping histology usually necessitates the acquisition of biopsy or resection tissue for definitive diagnosis. Also, and most importantly, many malignant salivary gland tumors can only be diagnosable as such when the growth pattern (e.g., infiltration beyond the capsule into soft tissue, perineural invasion) is taken into consideration. In these cases, tumors can only be definitively diagnosed as malignant on surgical specimens, which adequately demonstrate the tumor architecture and its relationship to peripheral tissue. This is particularly true for low-grade malignant neoplasms such as polymorphous low-grade adenocarcinoma,[18] myoepithelial carcinoma,[19,20] and basal cell adenocarcinoma,[21] which usually have bland-looking tumor cells and lack necrosis or abundant mitoses. Among tumors of the head and neck, FNA biopsies of major salivary gland tumors are considered to have the highest rate of error.[22] By most reports, the sensitivity of FNA biopsies to diagnose a malignant neoplasm is much lower than the specificity.[22-26] In other words, it is more common to misdiagnose a malignant tumor as benign than the reverse. A 5-year review of data from 6249 participant responses from the College of American Pathologists Interlaboratory Comparison Program in nongynecologic cytology revealed that FNA biopsies had a 68% sensitivity for diagnosing a salivary gland neoplasm as malignant, with an overall false-negative rate of 32%.[27] The greatest number of false-negative diagnoses occurred in cases of lymphoma (false-negative rate = 57%), followed by acinic cell carcinoma (false-negative rate = 49%), low-grade mucoepidermoid carcinoma (false-negative rate = 43%), and adenoid cystic carcinoma (false-negative rate = 33%). In cases of benign neoplasms from the same study, the specificity of FNA biopsies was 91%, with an overall false-positive rate of 8%. The greatest false-positive rate was in cases of monomorphic adenoma (53%), which were most often diagnosed as adenoid cystic carcinoma. Pleomorphic adenomas, when diagnosed as malignant, were most often misinterpreted as adenoid cystic carcinoma, and Warthin's tumors as lymphoma.

Although the utility and ease of FNA biopsies have resulted in a decline in the use of frozen section analysis intraoperatively, there are still several indications for frozen section studies, as reviewed by Seethala and colleagues[28] and Westra.[22] These include assessing the extent of tumor spread to local/regional tissues such as the nerves and lymph nodes, assessing surgical margins, and confirming/establishing the diagnosis in cases where the preoperative FNA biopsy was not diagnostic or was equivocal.

Staging

Clinical staging of salivary gland cancers is important for prognosis and treatment decisions. The 2003 TNM staging classification for major salivary gland cancers established by the American Joint Committee on Cancer (AJCC) is the classification most commonly used in the United States (Tables 88-3A and B). Minor salivary gland carcinomas are staged according to the anatomic site of origin (e.g., oral cavity, sinus, larynx). The staging guidelines are applicable to all forms of carcinoma; any nonepithelial tumor type is excluded.

Table 88-3A

2003 AJCC TNM Staging for Major Salivary Gland Cancer

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor is ≤2 cm in greatest dimension without extraparenchymal extension*
T2	Tumor is >2 cm but not >4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor is >4 cm in greatest dimension and/or has extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.
AJCC, American Joint Committee on Cancer.
From Greene FL. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer-Verlag, 2002.

Histopathology

Because salivary gland malignancies are remarkably diverse and heterogeneous, their behavior and resulting clinical management are highly dependent on their histologic type and, quite often, their grade. Thus knowledge of the types of tumors and their pathologic classification is critical for the clinician in order to provide proper treatment. Table 88-4 lists most of the critical pathology-related issues that the clinician needs to consider. The following section is intended to provide a succinct, but sufficient, discussion of the pathology of these tumors.

First, it is important to consider the normal histology of the glands because most tumors differentiate into the same cell types that are present in the normal gland. Salivary glands contain acini composed of either serous or mucous cells or a mixture of both. Serous cells are rounded or polygonal in shape and characteristically have abundant blue cytoplasmic granules, which are periodic acid–Schiff (PAS) positive. Mucous cells consist almost entirely of lightly basophilic intracytoplasmic mucus. The fluid secreted by the parotid gland is almost exclusively serous, while that from the sublingual gland is almost exclusively mucous and that from the submandibular gland is a mixture of serous and mucous. The ducts have cuboidal to columnar lining cells with abundant eosinophilic cytoplasm. They form tubular structures within the glands (Fig. 88-2). Both the acini and ducts have supportive cells called myoepithelial cells along their periphery. The parotid glands normally contain, on average, 10 to 20 intraglandular lymph nodes, a feature of great importance because many parotid masses represent metastases to these lymph nodes from primary skin or other cancers of the head and neck. These nodes have an otherwise typical appearance to any other nodal tissue in the body. The submandibular (also referred to as submaxillary) and sublingual glands have no intraglandular lymph nodes.

Neoplasms of the salivary gland can be roughly classified on the basis of the type of normal salivary gland cell toward which they differentiate. Neoplasms can differentiate toward the acinar, ductal, or myoepithelial cells. Practically speaking, though, most of them have dual differentiation—specifically, most salivary gland neoplasms have

Table 88-3B

Stage Grouping for Major Salivary Gland Cancer

I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Table 88-4

Critical Pathologic Features for Assessing Malignant Salivary Gland Tumors

Tumor Type	Unique Pathologic Issue(s)
Mucoepidermoid carcinoma	Grade
Adenoid cystic carcinoma	Grade Dedifferentiation (Y/N)
Carcinoma ex pleomorphic adenoma	Specific histologic type of carcinoma Grade Degree of invasion
Myoepithelial carcinoma	Grade
Basal cell adenocarcinoma	Grade
Adenocarcinoma NOS	Grade
Acinic cell carcinoma	Grade Dedifferentiation (Y/N)
Small cell carcinoma	Primary vs. metastasis
Squamous cell carcinoma	Primary vs. metastasis
Lymphoma	De novo vs. secondary Grade (low vs. high) Necessity of tissue biopsy

some myoepithelial differentiation.[29] Also, most of the benign neoplasms have a malignant counterpart (e.g., pleomorphic adenoma and carcinoma ex pleomorphic adenoma, basal cell adenoma and basal cell adenocarcinoma, myoepithelioma and myoepithelial carcinoma). The number of different malignant epithelial tumors in the World Health Organization (WHO) classification has increased greatly over the past 50 years and now includes 24 entities.[21] Between 21% and 46%[3] of salivary gland tumors are malignant, including 15% to 32% of parotid, 41% to 45% of submandibular, 70% to 90% of sublingual, and 50% of minor salivary gland tumors.[21] It is important to note that the incidence of particular histologic types is dependent on the site. For example, polymorphous low-grade adenocarcinoma virtually never occurs in the major glands.[18,30]

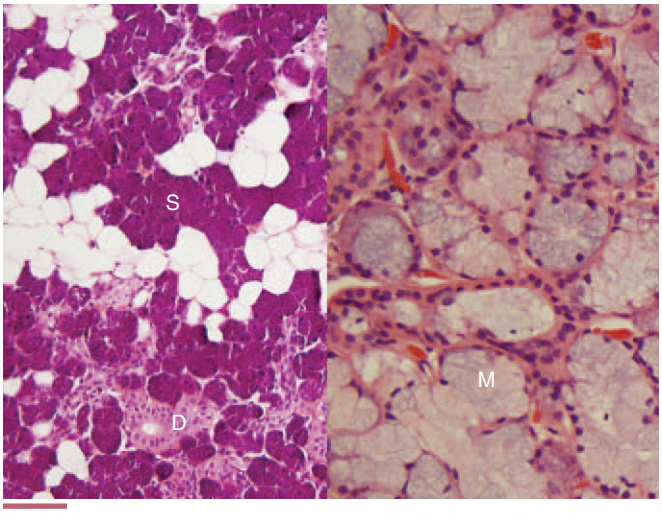

Figure 88-2. Normal major salivary gland histology. Serous acini (left; *S*) have blue-staining cytoplasmic granules; mucinous acini (right; *M*) have pale blue, homogeneous cytoplasm; and ducts (left; *D*) have a two-cell lining and cells with pale pink cytoplasm (400× for both).

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common salivary gland malignancy.[3,31-33] The majority of cases occur in the major salivary glands,[34] but mucoepidermoid carcinoma can also arise from minor salivary glands in the oral cavity, particularly in the hard palate, buccal mucosa, lip, and retromolar trigone.[35] Rarely, they can also arise intraosseously in the mandible and maxilla, but mucoepidermoid carcinomas of this location are considered odontogenic in origin and have a less aggressive clinical behavior.[36,37] Clinically, mucoepidermoid carcinomas are slightly more common in women and have a mean age of approximately 45 years, but they can also occur in children.[31] In fact, they are the most common pediatric salivary gland carcinoma.[38] Patients usually present with a painless, slow-growing mass. Intraoral tumors may mimic a mucocele or vascular lesion clinically by presenting as a blue-red superficial nodule.[3]

Grossly, these tumors are not distinct. They usually have both solid and cystic components, often with mucinous material within the cysts.[39] This is what sometimes imparts a bluish color to them, which can mimic the appearance of a mucocele in the oral cavity. Microscopically, their hallmark is the presence of three cell types: mucous, squamoid (or epidermoid), and intermediate (Fig. 88-3A). The architecture is usually a mixture of cystic (see Fig. 88-3B) and solid elements, the latter with sheets (see Fig. 88-3C), nests, or ductlike structures. The mucous cells have abundant, light blue mucin in their cytoplasm and nuclei displaced to the periphery. The mucin is usually obvious, but, in cases where it is scant, special stains such as PAS, mucicarmine, or Alcian blue can be used to highlight it. The squamoid cells are large with abundant pink cytoplasm, and, although they look somewhat squamous in appearance, true keratinization in mucoepidermoid carcinoma is rare.[40] Intermediate cells typically have more modest amounts of pink or clear cytoplasm. The proportion of cell types varies quite a bit among tumors. Intermediate cells usually predominate and mucous cells usually line cystic spaces. Cytologic atypia varies from minimal to quite prominent.[41-43] Immunohistochemistry is of limited to no utility in the diagnosis.[39]

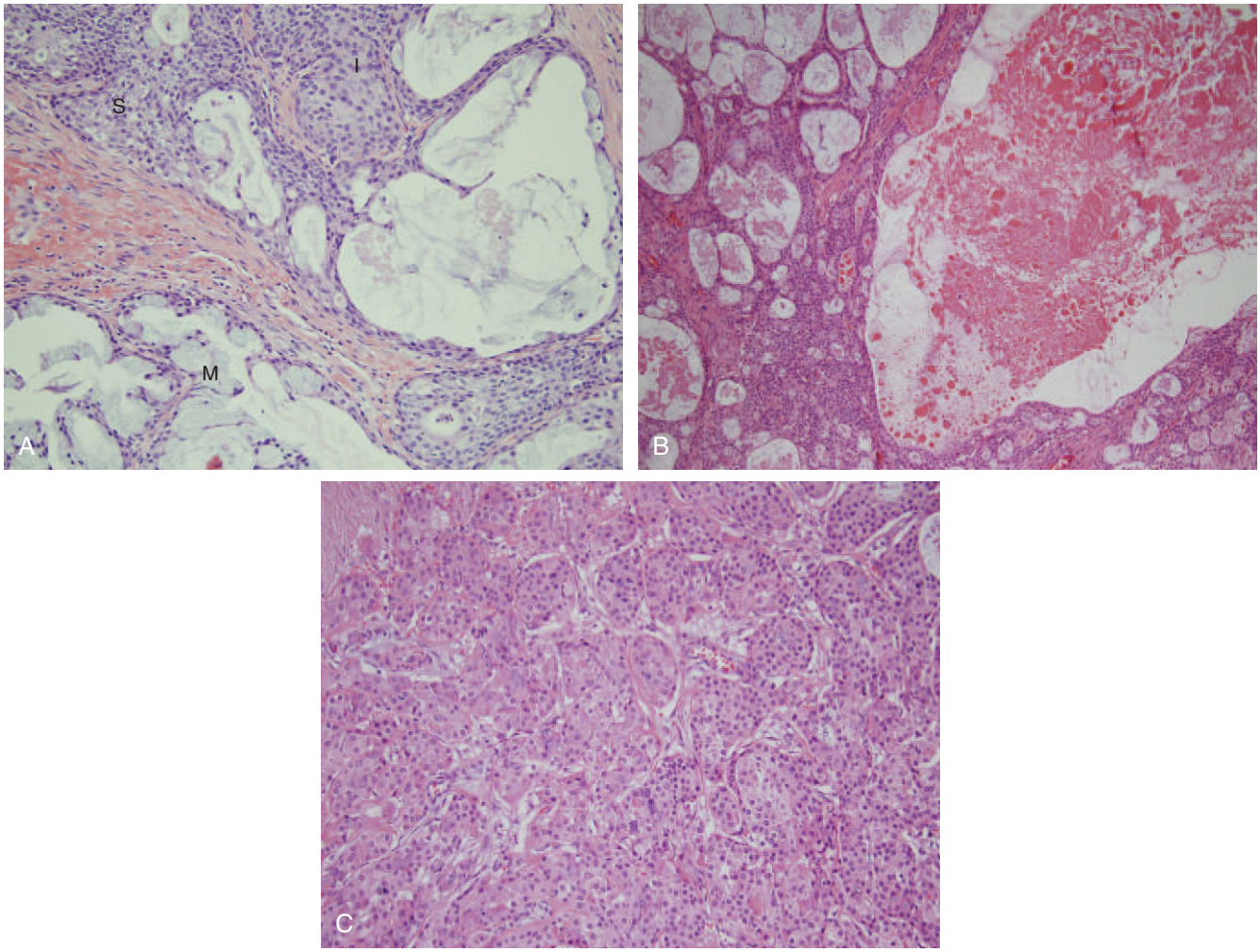

Figure 88-3. Mucoepidermoid carcinoma (MEC). **A,** Different cell types shown in this tumor with abundant intermediate cells *(I),* intermixed mucous cells *(M),* and also squamoid or epidermoid cells *(S)* with slightly more prominent, pink cytoplasm (200×). **B,** Tumor with extensive cystic change (100×). **C,** High-grade MEC with solid sheets of intermediate cells, minimal mucous differentiation, and no cystic change (200×).

FNA yields a mixture of cell types. At a minimum, both glandular and squamoid components must be present to make the diagnosis. The mucous cells have abundant vacuolated cytoplasm, intermediate cells are relatively round and small with little cytoplasm and nuclei with open chromatin, and the squamoid cells have moderate amounts of dense, homogeneous cytoplasm. These typically appear orange on Papanicolaou staining.

The differential diagnosis, particularly in tumors arising along mucosal sites, includes necrotizing sialometaplasia, an uncommon nonneoplastic lesion of the hard palate with reactive changes in minor salivary glands[44] and, more importantly, adenosquamous carcinoma, which is an aggressive variant of squamous cell carcinoma. Adenosquamous carcinomas are high grade, have definitive squamous differentiation usually with keratinization (unlike mucoepidermoid carcinoma), and often have surface mucosal squamous dysplasia, a feature that mucoepidermoid carcinoma does not have.[39]

Grading of mucoepidermoid carcinoma is important and correlates strongly with clinical behavior, although reproducibility and consistency are major issues, and no particular system has been universally accepted.[41-43,45] Clinical staging is as important as histologic grade, so the two should be considered in tandem. In general, low-grade lesions have a prominent cystic component and abundant well-differentiated mucous cells with little cytologic atypia and low mitotic activity. High-grade lesions are more solid with squamoid and intermediate cells predominating. They also have cytologic atypia, mitotic activity, necrosis, and infiltrative growth. A number of different grading schemes (well reviewed by Luna[39]) have been reported over the years. The most used grading system, originally designed by Auclair and colleagues,[41,43] uses a three-tiered score based on a number of histologic features (Table 88-5). The original grading system was initially criticized for a tendency to "under grade" the tumors when others demonstrated that a significant number of low-grade mucoepidermoid carcinomas developed progressive disease. The later modification by Brandwein and colleagues[42] (see Table 88-5) refined the grading system such that none of the tumors classified as low grade in their study went on to have progressive disease. Low-grade mucoepidermoid carcinoma, as strictly defined by their criteria, rarely ever metastasizes or results in death of the patient.[41-43]

In addition to grade, location of the primary tumor is potentially important in predicting clinical behavior. Several studies have shown that low-grade mucoepidermoid carcinomas of the submandibular gland recur and metastasize much more frequently than those of the parotid or minor salivary glands.[40,43] Whether or not this represents truly different biology, it merits the aggressive and thorough resection of any submandibular gland primary malignancy, especially for known mucoepidermoid carcinoma.[42]

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is one of the more common,[3,32,33] and certainly more recognizable salivary gland tumors, being notorious for its infiltrative growth and slowly progressive behavior with recurrences and spread over a protracted course of many years.[46] These tumors essentially occur with an even distribution among all salivary gland

Table 88-5

Grading Systems for Mucoepidermoid Carcinoma

Parameter (Auclair et al, 1992)	Point Value
Cystic component <20%	+2
Neural invasion	+2
4+ mitoses/10 HPF	+3
Necrosis	+3
Anaplasia	+4
Grade	**Point Score**
Low (I)	0-4
Intermediate (II)	5-6
High (III)	7 or more
Parameter (Brandwein et al, 2001)	**Point Value**
Cystic component <25%	+2
Tumor front invades in small nests and islands	+2
Pronounced nuclear atypia	+2
Lymphatic and/or vascular invasion	+3
Neural invasion	+3
Necrosis	+3
4+ mitoses/10 HPF	+3
Bony invasion	+3
Grade	**Point Score**
Low (I)	0
Intermediate (II)	2-3
High (III)	4 or more

From Auclair PL, Goode RK, Ellis GL. Mucoepidermoid of intraoral salivary glands. *Cancer.* 1992;69:2021-2030; Brandwein MS, Ivanov K, Wallace DI, et al. Mucoepidermoid carcinoma. A clinicopathologic study of 80 cases with special reference to histological grading. *Am J Surg Pathol.* 2001;25(7):835-845.

sites,[32] although the total number of minor salivary gland cases outnumber those of major salivary glands when all sites are considered together.[47-50] These malignancies occur with an equal incidence in men and women over a wide age range with the peak incidence between 50 and 60 years of age.[47-49,51]

Grossly, ACCs are solid, light tan, firm and well-circumscribed, but unencapsulated, tumors. Microscopically, there are three growth patterns: tubular, cribriform, and solid. The tubular form consists of small tubules sitting in a pink, hyalinized, and hypocellular stroma (Fig. 88-4A). The solid variant has only rounded lobules of tumor cells with no, or almost no, glandlike structures and without a defined architecture (see Fig. 88-4B). The classic and most easily recognized pattern, though, is the cribriform ("Swiss cheese"-appearing) variant. Nests of cells are arranged around glandlike spaces that consist of PAS-positive blue or pink material (see Fig. 88-4C). The central spaces look like glandular lumina but are actually extracellular cavities containing reduplicated basement membrane (or ground substance) material[52,53] and myxoid material that is produced by the tumor cells, rather than true epithelial mucin. The cells in ACC are markedly basaloid in appearance, with little cytoplasm and round-to-oval nuclei that are dark and hyperchromatic without nucleoli (see Fig. 88-4A).[48] They are quite uniform in size and show little mitotic activity, except for the solid type, where mitotic activity can range from barely to extremely prominent. A rim of inconspicuous myoepithelial cells with clear cytoplasm is also usually present.[29,54]

FNA frequently yields characteristic results in ACC. Aspirates have tumor cells with scant cytoplasm and round, regular nuclei in sheets and clusters. These features by themselves are not characteristic and actually are so bland that they might suggest a benign lesion. However, the finding of well-defined, round "cylinders" and/or spheres of acellular stroma accompanying these cells is typical, but not 100% specific, for ACC. The cells often "cling" to these rounded structures (see Fig. 88-4D).

Histologic grading has yielded conflicting results in the literature for predicting prognosis. Clinical stage, on the other hand, holds a great deal of prognostic information and, as such, should be considered as much or more than grade in clinical management.[51] Also, as with mucoepidermoid carcinoma, ACC of the submandibular gland has a much more aggressive clinical course than ACC of other sites.[49,51] The most accurate prognostic information has been garnered when tumors are not only graded by the predominant pattern (tubular, cribriform, or solid) but are more specifically graded as follows: tubular with or without some cribriform areas (grade I), cribriform with no tubular areas and with less than 30% solid areas (grade II), and cribriform with greater than 30% solid areas (grade III).[49,55] A frequent histologic feature of ACC is perineural invasion, which is identified in approximately 70% to 75% of cases.[49,56] Although somewhat inconsistent in the literature, many have correlated this finding with a worse prognosis, particularly when involving a major nerve trunk.[46,57-59]

The diagnosis of ACC is generally straightforward from routine hematoxylin and eosin examination. However, it can be difficult on small biopsies because one may not be able to appreciate the architecture and infiltrative growth. The differential diagnosis includes other salivary gland neoplasms (such as polymorphous low-grade adenocarcinoma or pleomorphic adenoma), basaloid squamous cell carcinoma, or high-grade neuroendocrine carcinoma.[54] Although beyond the scope of this text, immunohistochemistry is not usually necessary but can occasionally be helpful in differentiating among these tumor types.[60,61]

Polymorphous Low-Grade Adenocarcinoma

Polymorphous low-grade adenocarcinoma (PLGA) is a unique, low-grade neoplasm first recognized as a distinct entity in the mid 1980s.[62] PLGAs arise almost exclusively from the minor salivary glands and, in most series, are the second most common minor salivary gland carcinoma.[35,46] The most common site for these neoplasms is the palate,[63] particularly at the junction of the hard and soft palates. Other sites include the upper lip, buccal mucosa, and posterior third of the tongue.[18] There are only rare reports of PLGA arising in major salivary glands.[30] PLGA is twice as common in women and tends to present in the fourth to sixth decades as a slow-growing mass that may have been present for years.[18,63] They are often asymptomatic.[18] On gross examination, they are circumscribed, unencapsulated, pale yellow or tan masses that range from 1 to 3 cm. Microscopically, the architectural features of this tumor are quite variable, as the name would suggest. They are well circumscribed but unencapsulated and may appear as solid nests in lobules, cribriform glandlike structures, or ductlike arrangements. A common appearance within the tumor is concentric whorling of the nests around each other in a single-file arrangement. This has been termed the "eye of the storm" pattern (Fig. 88-5A). Stromal hyalinization with a slate-gray coloration is also characteristic.[18] Tumor cells are quite regular with moderate eosinophilic cytoplasm and characteristic round-to-oval, extremely regular nuclei with open chromatin (see Fig. 88-5B). There is little mitotic activity and no necrosis. The periphery of the tumor shows markedly infiltrative growth and most cases have perineural invasion (see Fig. 88-5C).[18,63,64]

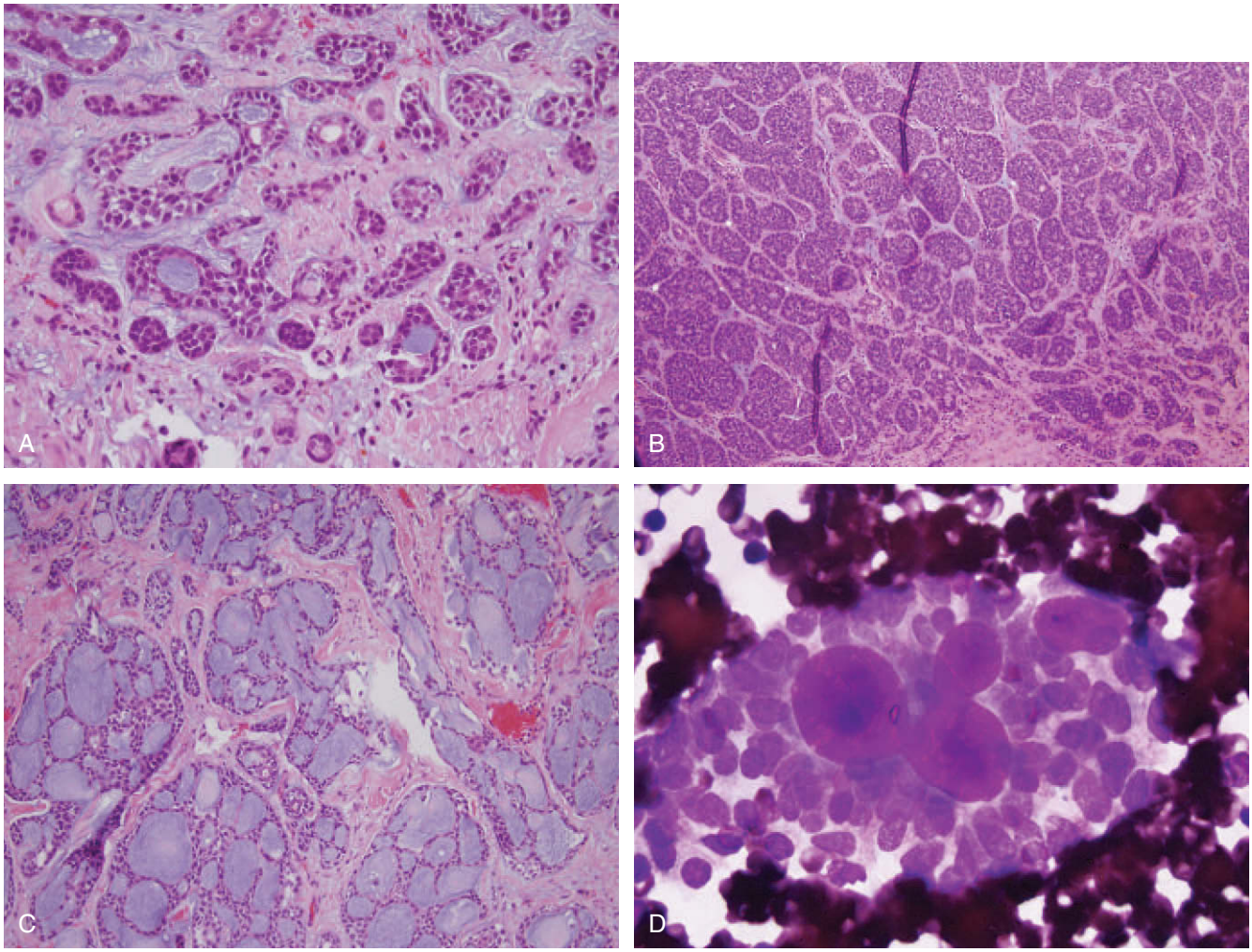

Figure 88-4. Adenoid cystic carcinoma (ACC). **A,** Tubular (grade I) ACC consisting of small tubule-like structures with an epithelial lining of small tumor cells with dark chromatin and with central blue ground substance-type material (400×). **B,** Solid (grade III) ACC with rounded nests of basaloid cells with very little to no ground substance or glandlike formations (100×). **C,** Cribriform (grade II) ACC with basaloid cells arranged around multiple rounded collections of central basophilic material giving a "Swiss-cheese" appearance (200×). **D,** Classic fine-needle aspiration finding of ACC with rounded "cylinders" of basement-membrane/ground substance material (Diff-Quik; 600×).

The differential diagnosis includes pleomorphic adenoma and ACC. The myxochondroid areas of pleomorphic adenoma are not seen in PLGA, and, although minor salivary gland pleomorphic adenomas are unencapsulated, they will not show the infiltrative growth pattern of PLGA and will not have perineural invasion. One particular immunostain that may be useful in difficult cases is worth mentioning here. Curiously, it has been recognized that almost all pleomorphic adenomas will be positive for glial fibrillary acidic protein (GFAP), whereas almost all PLGA are negative.[65-68] ACC is important to differentiate from PLGA. This is done primarily by cytologic features because ACCs have basaloid cells with dark chromatin and little cytoplasm, whereas PLGA cells have moderate eosinophilic cytoplasm and nuclei with open chromatin.

PLGA is a low-grade malignancy, and histologic grading is not applicable. Conservative resection is the treatment of choice. Local recurrence occurs in 10% to 15% of patients.[18,63,69] Because lymph node metastases are distinctly uncommon (literature rates of around 10% or less), neck dissection is only recommended with significant clinical adenopathy or needle-proven metastasis. This likely overestimates the occurrence, however. With strict histologic criteria for PLGA, nodal metastases are extremely rare.[18] Distant metastases are equally as uncommon,[70] and patients have an excellent long-term prognosis.[18,63,69] In fact, few patients have been documented to die from this tumor and only after prolonged periods.[18,63]

Acinic Cell Carcinoma

Acinic cell carcinoma, as the name implies, is a tumor with cells showing differentiation toward cells of the normal salivary gland acini (see Fig. 88-2). However, these tumors also show evidence of ductal and myoepithelial differentiation, an important feature to keep in mind. They are uncommon, comprising 1% to 3% of all tumors and approximately 10% of all malignant ones.[3,32,33,71] More than 90% occur in the parotid,[72,73] with the rest scattered among minor salivary gland sites and rarely the submandibular gland.[71,74] Occurring over a wide age range from children to the elderly, they are relatively evenly distributed in the second through seventh decades[75] with a peak in the third decade.[73] Of note, these tumors are the second most common childhood salivary gland malignancy. They present as a slowly growing mass, which is only occasionally painful and rarely associated with a facial palsy.[71,73]

Grossly, acinic cell carcinoma presents as a single, usually circumscribed, rubbery, solid mass with up to one third showing cystic degeneration.[75] Microscopically, they are highly variable, a feature of these tumors that has always led to angst in the diagnosing pathologist. The four principal histologic patterns are solid/lobular, microcystic, papillary-cystic, and follicular. Small tumors can be easily missed because the acinar cells are so well differentiated that they blend into the surrounding normal gland. Two features are classic, however. The first is the characteristic acinic cell, which has blue cytoplasm with abundant serous-type granules and a small, round, eccentrically placed nucleus (Fig. 88-6A).

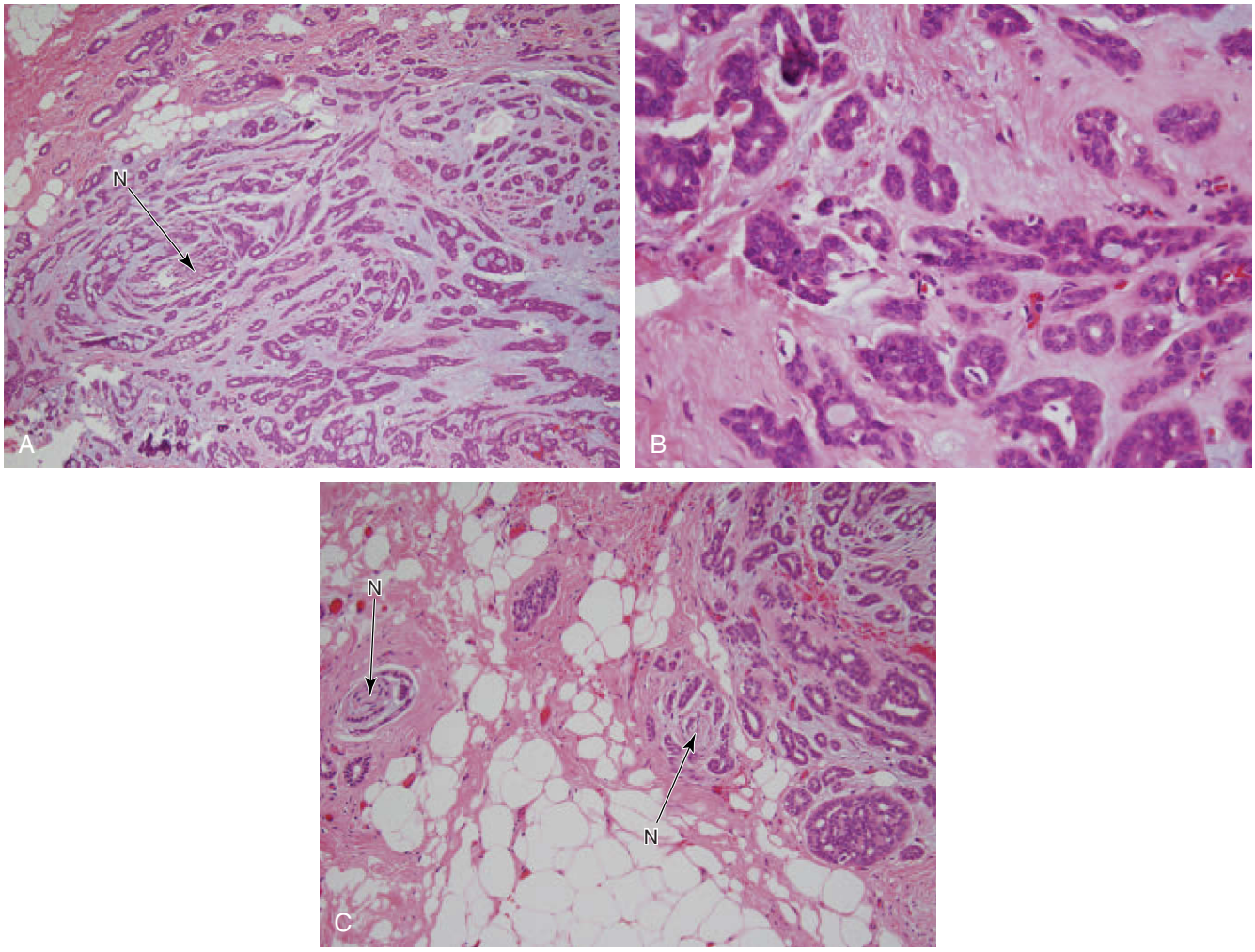

Figure 88-5. Polymorphous low-grade adenocarcinoma (PLGA). **A,** Hard palate PLGA showing an unencapsulated tumor with variable-sized tumor nests, different growth patterns from trabecular to tubular to cribriform, and infiltrating a myxoid and hyalinized stroma and growing around nerves *(N; arrow)* (100×). **B,** PLGA tumor cells with modest pink cytoplasm and oval nuclei with no significant variability in size or shape (400×). **C,** PLGA with infiltration of fat and foci of perineural invasion (200×).

PAS stains will be strongly positive in these cells. A number of other cell types are seen including pink, clear, and vacuolated cells, such that most tumors are a mixture of different cell types (see Fig. 88-6A). The second classic feature is a dense lymphoid infiltrate with germinal centers (see Fig. 88-6B). The periphery of the tumors may or may not be infiltrative but are often "pushing" in nature (see Fig. 88-6C). Although one would assume that lack of an infiltrative border might signal a benign or low-grade lesion, there is no benign equivalent for this lesion (i.e., there is no known benign acinic cell neoplasm). "Dedifferentiation" has been described in a small subset of acinic cell carcinomas. This consists of tumors with areas of classic, "conventional" acinic cell carcinoma and an intermixed undifferentiated carcinoma in sheets with large, pleomorphic cells, brisk mitotic activity, and often necrosis.[76-78]

The differential diagnosis includes normal parotid gland; however, acinic cell carcinoma will not have the exquisitely lobular architecture or the presence of ducts that normal salivary gland tissue will always have. For the pink and clear cell types, tumors such as oncocytic carcinoma or clear cell carcinoma not otherwise specified (NOS) must be considered, and the papillary variant of acinic cell carcinoma must be differentiated from cystadenocarcinoma. The finding of focal cells with blue, serous-type, cytoplasmic granules will confirm the diagnosis of acinic cell carcinoma. Immunohistochemistry has no significant utility in narrowing the differential diagnosis.

FNA biopsy of acinic cell carcinoma is fraught with difficulty because of the resemblance to normal tissue.[27] The diagnosis rests on finding a cellular specimen with sheets and clusters of large acinar cells with abundant granular cytoplasm and central round, regular nuclei. One should not see normal ductal epithelial cells or significant amounts of adipose tissue (both of these latter findings are from normal salivary gland tissue), but there is often a prominent background component of lymphocytes.

Surgical resection with negative margins is the most important therapy. These tumors will recur in approximately one third of cases.[71,73] Although classically regarded as low-grade malignancies, 10% to 15% of these tumors will metastasize locally to regional lymph nodes or distantly to the lung and bones. Acinic cell carcinomas are also notorious for recurrence and spread years beyond the primary presentation and for a protracted clinical course such that survival curves do not flatten out until after a decade.[79] Survival is approximately 80% at 5 years and 70% at 10 years.[71,75,79] Grading of these tumors has not correlated well with behavior, and there is not good agreement on histologic features within the proposed grading systems. Very bland, low-grade-appearing tumors can metastasize almost as frequently as tumors with more aggressive features. However, "dedifferentiation" (where there is a mixture of typical acinic cell carcinoma with a much higher-grade carcinoma) has consistently been associated with a poor outcome.[76-78]

Malignant Mixed Tumors

"Malignant mixed tumor" is the broad term that is used to encompass three different salivary gland malignancies: true malignant mixed tumor

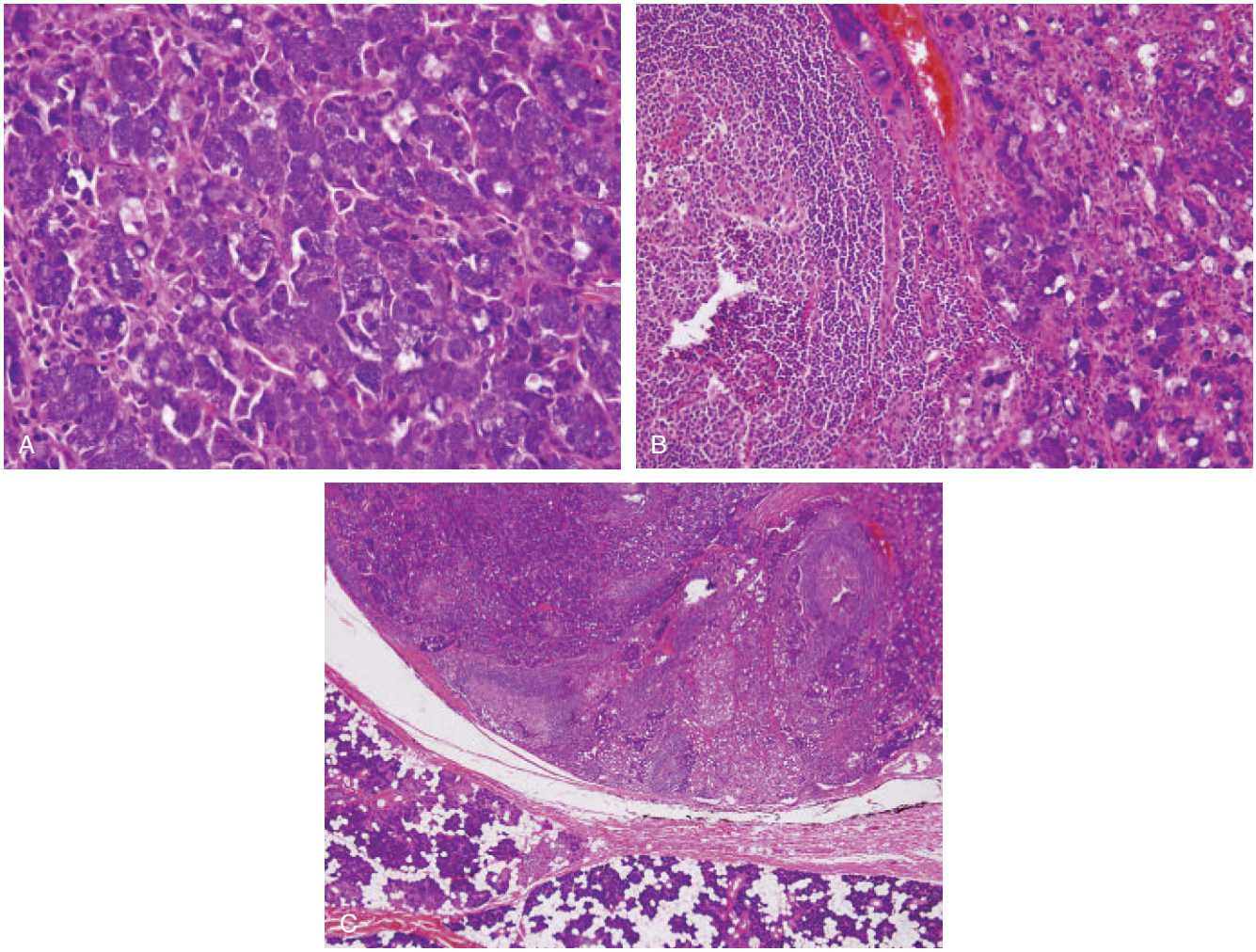

Figure 88-6. Acinic cell carcinoma. **A,** Typical acinic cell carcinoma with round cells having abundant granular, blue cytoplasm (400×). **B,** Dense lymphoid infiltrate (left side) in and around the tumor (200×). **C,** Acinic cell carcinoma with pushing border with adjacent normal salivary gland tissue (100×).

(or carcinosarcoma), carcinoma ex pleomorphic adenoma, and metastasizing mixed tumor. As a group, these account for approximately 3% to 5% of all salivary gland malignancies,[3,32] and carcinoma ex pleomorphic adenoma is by far the most common of these.

True Salivary Gland Malignant Mixed Tumor (or Carcinosarcoma)

True salivary gland malignant mixed tumor (or carcinosarcoma) is a malignant neoplasm that consists of distinct carcinomatous and sarcomatous components. These tumors are rare,[46] comprising approximately 1% of all salivary gland malignancies.[32,35] The mean age of presentation is 58 years. Two thirds of cases arise in the parotid gland, approximately 15% in the submandibular gland, and 15% in the palate.[80-84] Grossly, the findings are not distinct. The mass may be circumscribed or ill defined. It is commonly firm and tan-white with hemorrhage and necrosis and, on occasion, grittiness or calcification. Microscopically, there is an intimate admixture of the two components (carcinoma and sarcoma), but the amounts of each can vary widely. The carcinoma component can have any type of differentiation but typically takes the form of high-grade salivary duct carcinoma or undifferentiated carcinoma (Fig. 88-7A).[80] The sarcomatous component is usually a chondrosarcoma (see Fig. 88-7B) or osteosarcoma,[80] but fibrosarcoma, leiomyosarcoma,[83] or even liposarcoma[85] is possible. Treatment consists of wide local excision combined with radiotherapy. The tumors are aggressive with up to two thirds of patients dying of either local recurrence or, commonly, distant metastasis to the lungs or bone, usually within a period of 30 months.[80]

Carcinoma ex Pleomorphic Adenoma

Carcinoma ex pleomorphic adenoma is defined as a pleomorphic adenoma (or mixed tumor) in which, or with which, a carcinoma is present. It accounts for more than 95% of malignant mixed tumors but is still relatively uncommon. The critical thing to remember is that this term encompasses a heterogeneous group of tumors because the carcinoma component can be of any form, from very low grade to the highest grade types.[86] These tumors are most common in the parotid gland, followed by the submandibular gland, the minor salivary glands, and the sublingual gland.[87] Although there is a wide age range, most patients are in their sixth and seventh decades, approximately 1 decade later than the peak age for pleomorphic adenomas. The classic history is a patient with a longstanding mass that suddenly undergoes rapid growth over a period of several months.[87,88]

Grossly, these tumors can reach up to 25 cm and the average is more than twice that for pleomorphic adenomas.[86] They usually consist of a tan-yellow, firm mass with ill-defined, infiltrative borders, and there may be a component of nodular, translucent blue or gray tumor representing the preexisting pleomorphic adenoma.[88] Microscopically, the proportions of the two components vary quite a bit from tumor to tumor. The pleomorphic adenoma component has typical features with myxoid, blue stromal areas, a variable proliferation of epithelial elements, including ductlike structures and sheets of myoepithelial cells, and chondroid areas reminiscent of cartilage (Fig. 88-8A). This may be replaced by scarring or be overgrown by the malignant component. The malignant component is often distinguished by its collagenous stromal hyalinization (see Fig. 88-8B). It most commonly takes the form of

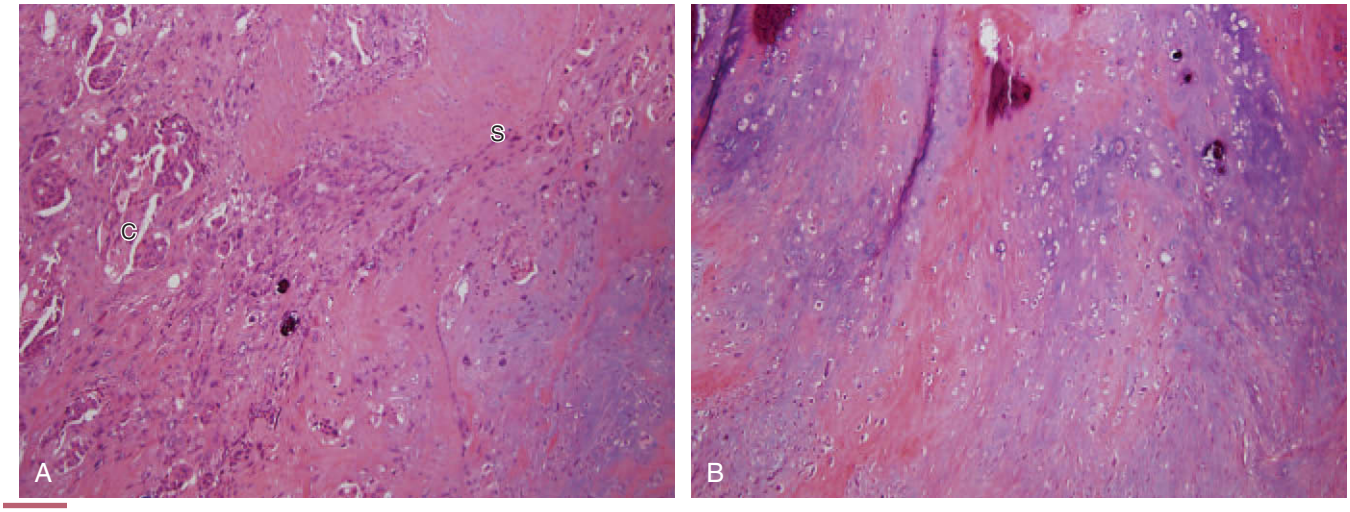

Figure 88-7. True malignant mixed tumor (carcinosarcoma). **A,** Biphasic tumor with a mixture of nests of poorly differentiated carcinoma *(C)* and a malignant spindle cell sarcoma in a myxoid stroma *(S)* (100×). **B,** Other areas of the same tumor show differentiation into chondrosarcoma with cells sitting in lacunae and a more blue, chondroid stroma (100×).

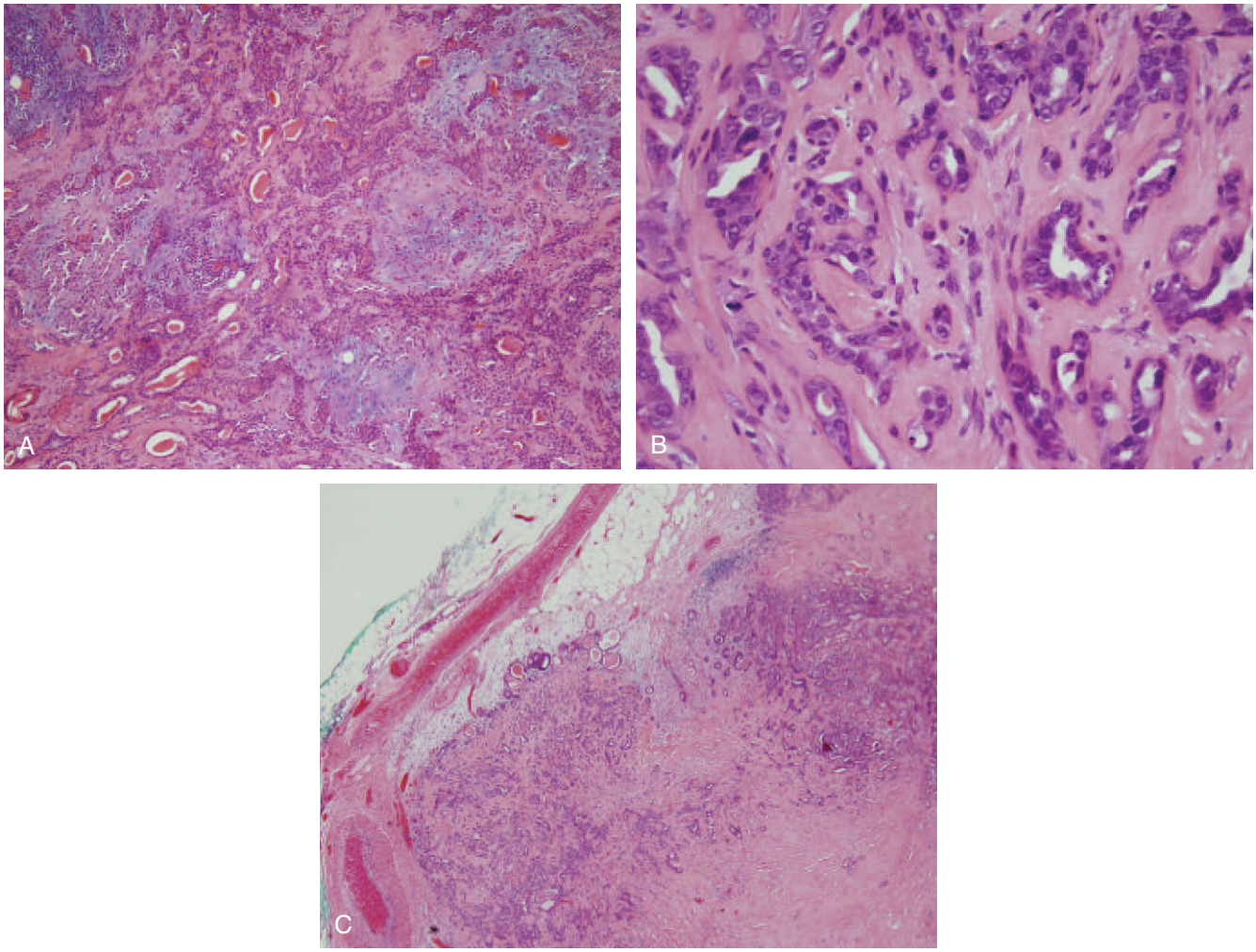

Figure 88-8. Carcinoma ex pleomorphic adenoma. **A,** Areas of otherwise typical pleomorphic adenoma in a carcinoma ex pleomorphic adenoma (200×). **B,** Another area showing nests of tubules of very atypical cells with nuclear pleomorphism, as well as mitotic activity. The cells sit in a hyalinized, pink stroma (400×). **C,** Carcinoma areas of a tumor that approach the periphery of the lesion but do not penetrate beyond it (carcinoma in situ) (40×).

poorly differentiated adenocarcinoma NOS, salivary duct carcinoma, or undifferentiated carcinoma.[88] However, essentially any form of carcinoma can be found. As one can imagine, the prognosis and management are highly dependent on the type of carcinoma.[86]

The extent of invasion is a critical histologic feature for prognostication.[86,88-92] The malignant component should be classified as noninvasive (intracapsular), minimally invasive (≤1.5 mm beyond the capsule), or invasive (>1.5 mm). For those tumors where there is no invasion beyond the capsule/rounded edge of the tumor (so-called carcinoma ex pleomorphic adenoma "in-situ") (see Fig. 88-8C) or where there is less than 1.5 mm invasion beyond it, there is essentially no risk of recurrence or metastasis from a completely resected tumor such that the behavior approaches that of benign pleomorphic adenoma.[92] For invasive tumors, those with high-grade features do poorly, and those that are widely invasive have a survival ranging from 26% to 65% at 5 years and 0% to 38% at 20 years.[86,88,89] Wide resection with lymph node dissection and radiation therapy is the treatment of choice for widely invasive tumors or obvious cervical lymph node metastases.

Metastasizing Mixed Tumor/Pleomorphic Adenoma

This is the least common form of malignant mixed tumor. These are tumors having the exact, bland morphology of a pleomorphic adenoma with a mixture of myoepithelial and ductlike epithelial elements and myxoid and/or chondroid surrounding matrix (see Fig. 88-8A). They show no significant cytologic atypia or mitotic activity, but they metastasize either to local lymph nodes (30%) or to distant sites including bone (50%) and lung (30%).[93-95] Often, there is a prior protracted clinical course with recurrences at the primary site.[96] The mean time between presentation of the primary tumor and detection of metastatic disease is 12 years.[96] Although rare, metastasizing mixed tumor serves as an important reminder to treat pleomorphic adenomas properly at the time of initial therapy.

Salivary Duct Carcinoma

Salivary duct carcinoma is a relatively recently described tumor that was separated from the generic category of salivary adenocarcinoma.[97] It is one of the most aggressive primary salivary gland tumors and has a similar histologic appearance to high-grade ductal carcinoma of the breast.[97-99] It accounts for less than 10% of salivary gland tumors. Males are more commonly affected at a rate of 4:1.[98,100-105] Patients generally present in the sixth decade with a rapidly growing parotid mass; a significant minority have facial nerve involvement and occasional facial skin ulceration.[105] Between 70% and 90% of cases arise in the parotid, with the remaining few occurring in the submandibular gland and oral minor salivary glands.[98,101,104-106] Grossly, these tumors are ill defined, solid and white, with hemorrhage, necrosis, and occasionally cystic areas.[101,105] Infiltration of the surrounding tissue is usually quite obvious. Histologically, most salivary duct carcinomas have a large and prominent ductal carcinoma in-situ component with a cribriform pattern[101] similar to what is seen in breast ductal carcinomas (Fig. 88-9A). This

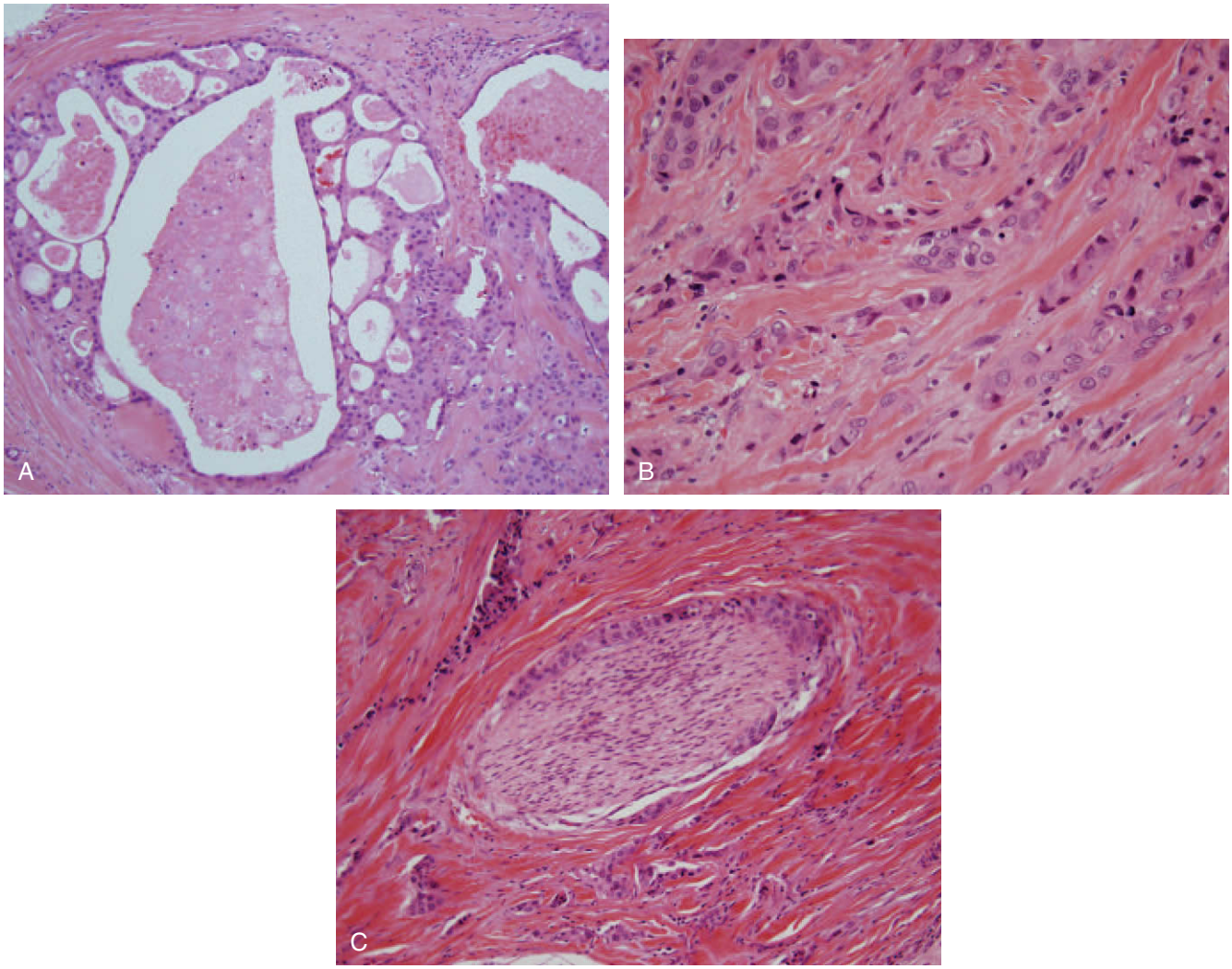

Figure 88-9. Salivary duct carcinoma (SDC). **A,** SDC showing cribriform carcinoma in situ in a large duct with large tumor cells with abundant pink cytoplasm (100×). **B,** Invasive component of SDC showing small nests and single cells with pink cytoplasm and large nuclei with pleomorphism and nucleoli (400×). **C,** Perineural invasion in SDC (200×).

is the classic histologic finding. There is often central comedo-type necrosis. The invasive component consists of small nests, cords, and single large cells with abundant pink cytoplasm and large, round nuclei with vesicular chromatin and prominent nucleoli (see Fig. 88-9B).[101,105] There is marked tissue infiltration with stromal desmoplasia and brisk mitotic activity. Vascular and perineural invasion (see Fig. 88-9C) are common.[101,105,106] Immunohistochemistry is not particularly useful for diagnosis, but salivary duct carcinomas are positive for low- and high-molecular-weight cytokeratins, carcinoembryogenic antigen (CEA), androgen receptors, and, in a significant minority, Her2/neu,[99,107,108] with distinct membrane staining for the latter. A minority of the tumors have actual amplification of the Her2/neu gene. Unlike the histologically similar breast carcinoma, almost all salivary duct carcinomas are negative for estrogen and progesterone receptors.[99] The differential diagnosis includes metastatic breast carcinoma, poorly differentiated squamous cell carcinoma, and mucoepidermoid carcinoma. Intraductal cribriform carcinoma is the most important feature that argues for a diagnosis of primary salivary duct carcinoma and rules out these other possible lesions.

Salivary duct carcinoma is high grade by definition. It is the most aggressive salivary gland carcinoma with 30% to 40% of patients developing local recurrence and between 50% and 75% developing distant metastases and dying of their disease, most within 4 years of diagnosis.[101,104,105] Wide local excision with neck dissection and postoperative radiotherapy is the treatment of choice.

Primary Squamous Cell Carcinoma

Squamous cell carcinomas are only rarely primary in the salivary gland, representing less than 1% of all malignancies in this site.[109] Metastases to intraparotid lymph nodes from primary skin cancers of the head and neck (particularly of the scalp, ear, and face) are much more common, as is direct invasion from adjacent tissues. Most patients are in their sixth through eighth decades, and sometimes there is a history of prior radiation therapy. By definition, the diagnosis of primary squamous cell carcinoma is restricted to the major salivary glands because those arising in the minor salivary glands cannot be distinguished from primary squamous carcinoma of the surrounding mucosa. Of these, 80% to 90% arise in the parotid gland, and 10% to 20% in the submandibular gland.[109,110] These tumors typically are high stage at the time of diagnosis.

Grossly, they appear as a firm, white, infiltrative, and nonencapsulated mass. Microscopically, they are identical to squamous cell carcinomas of the upper aerodigestive tract, although they tend to be better differentiated (most are moderately to well differentiated with abundant keratinization).[109-112] There is usually prominent desmoplasia and perineural invasion, with extension of the tumor into periglandular soft tissue.[109-112]

Primary squamous cell carcinomas are aggressive tumors, with a 5-year survival of approximately 20% to 50%.[112] Histologic tumor grade does not correlate well with behavior. Treatment involves radical surgery, neck dissection, and radiotherapy.

Primary Small Cell Carcinoma

Small cell carcinoma (or high-grade neuroendocrine carcinoma) can occur as a primary tumor in the salivary glands, but this is quite uncommon, representing approximately 2% of salivary gland malignancies.[113,114] The majority occur in major salivary glands, particularly the parotid.[113,114] They present as a painless mass of several months, typically in patients in their sixth and seventh decades, many with associated cervical lymphadenopathy and/or facial nerve palsy.

Grossly, they are not distinct, being poorly circumscribed, infiltrative masses that are white or tan with frequent necrosis.[114] Microscopically, they consist of large sheets or trabeculae of "small blue cells" (having moderate-sized nuclei and minimal cytoplasm). The nuclei characteristically have a punctate, granular ("salt and pepper") chromatin without nucleoli.[113,114] There is nuclear molding where nuclei look pressed against each other due to the minimal amount of cytoplasm (Fig. 88-10A). There is brisk mitotic activity, frequent apoptosis, and often areas of necrosis.

Immunohistochemistry shows staining for neuroendocrine markers such as synaptophysin, chromogranin-A, and CD56 (N-CAM).[113] There is typically punctate or "dotlike" staining for pan-cytokeratin. In addition, specific cytokeratin staining patterns have been described including positive staining for cytokeratin 20 (see Fig. 88-10B) and absence of staining for cytokeratins 34βE12 and 5/6.[61]

The differential diagnosis includes the solid variant of ACC and poorly differentiated squamous cell carcinoma, both of which can be ruled out by neuroendocrine marker staining (synaptophysin, chromogranin-A, neural cell adhesion molecule or N-CAM). Importantly, for both the pathologist and clinician, one must rule out metastases from primary lung small cell carcinoma or skin Merkel's cell carcinoma. Lung primary tumors should be detectable clinically and also would show positive staining for TTF-1 and lack of staining for cytokeratin 20. Metastatic Merkel's cell carcinoma, on the other hand, is virtually indistinguishable from primary salivary small cell carcinoma[113,115,116]; thus clinical findings are critical for these diagnoses.

The prognosis for small cell carcinomas is always relatively poor. However, for primary salivary small cell carcinoma, it may be slightly better than for pulmonary small cell, with reported 5-year survival rates between 13% and 50% and an average across studies of approximately

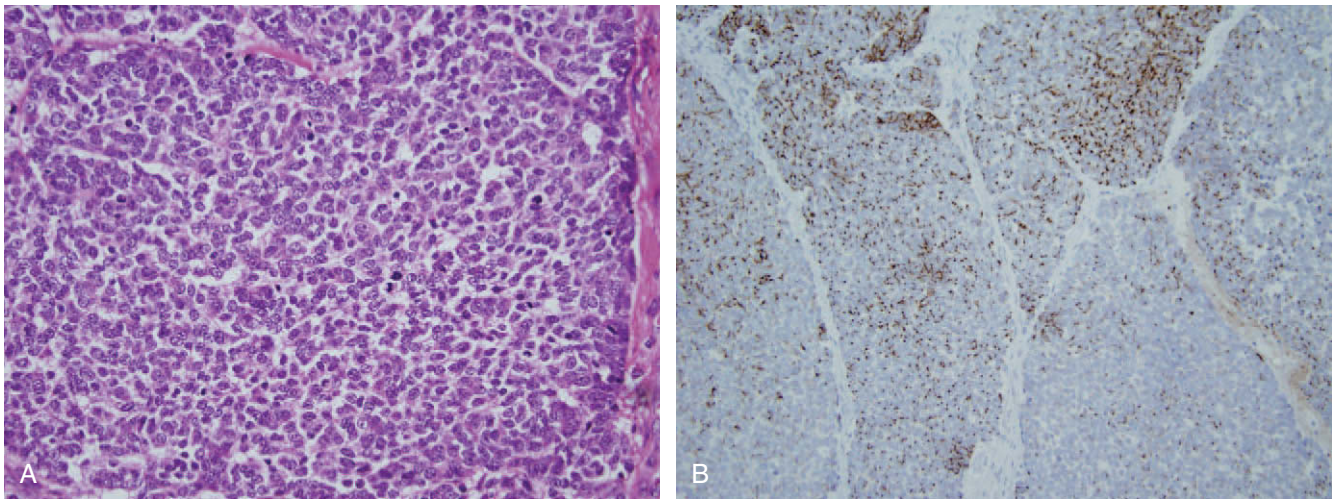

Figure 88-10. Small cell carcinoma. **A,** Typical small cell carcinoma with cells with granular, punctuate chromatin and only small amounts of cytoplasm (400×). **B,** Cytokeratin 20 staining in small cell carcinoma of the salivary gland. Keratin stains in this tumor typically have a dotlike or punctuate staining pattern as is seen here (200×).

30% to 40%.[113,114,117] Lymph node metastases are frequent, as are distant metastases to the liver, lung, brain, and bones.[113]

Other Malignant Tumors

The salivary glands are the primary site of a large number of additional (and heterogeneous) tumors, only a few of which are discussed here. Most of the additional carcinomas are low grade, with relatively frequent local recurrences, but uncommon or rare metastases. These include epithelial-myoepithelial carcinoma,[118] clear cell carcinoma, cystadenocarcinoma, basal cell adenocarcinoma,[119] and myoepithelial carcinoma,[19,20] although the latter is somewhat more aggressive.

Epithelial-myoepithelial carcinomas are low-grade tumors that account for approximately 0.5% to 1% of salivary gland neoplasms. They occur in older patients, predominantly in the parotid gland (80%), and rarely in the larynx or paranasal sinuses. Microscopically, they are usually well demarcated and partially encapsulated, but there is invasion of tumor into adjacent parenchyma. The classic appearance is of duct structures with eosinophilic lining cells (the "epithelial" component), immediately overlying and surrounded by prominent clear cells (the "myoepithelial" component). Classically, the stroma between the tumor nests is pink and hyalinized, and the individual tumor cells are bland with minimal mitotic activity. By immunohistochemistry, the ductal lining cells are positive for low-molecular-weight cytokeratins, and the outer cells are positive for calponin, smooth muscle actin, and p63 (all markers of myoepithelial differentiation). The differential diagnosis includes pleomorphic adenoma and the tubular variant (grade I) of ACC. Epithelial-myoepithelial carcinoma is a moderately aggressive tumor with a recurrence rate of 40%, metastases to lymph nodes, lung, and liver of 15%, and a survival of 80% at 5 years. Treatment is wide local excision with or without radiotherapy.

Basal cell adenocarcinoma is the rare, malignant counterpart to basal cell adenoma. The vast majority arises in the parotid gland[119] and has a typical morphology consisting of basaloid cells in tubular, trabecular, solid, or membranous patterns. The latter is called such because of the thick, hyalinized collagen that surrounds the nests of tumor cells. It is usually a low-grade carcinoma with histology showing a modest degree of cellular atypia and can only really be diagnosed as malignant on the basis of infiltrative growth into the surrounding tissue with or without perineural invasion.[119] Local recurrence occurs in a minority of patients, and metastases to regional lymph nodes in less than 10%. The prognosis is thus excellent.

Myoepithelial carcinoma is the uncommon malignant counterpart to myoepithelioma. About 60% occur in the parotid gland.[19] Like myoepitheliomas, these can have diverse cell types including epithelioid, spindled, plasmacytoid or hyaline, or clear cell. They have infiltrative peripheral borders, and one third of patients will die of metastatic disease, one third will have multiple local recurrences, and one third will be disease free after resection.

Adenocarcinoma NOS is a "salivary gland carcinoma that exhibits ductal differentiation but otherwise lacks the histologic features that define other types of salivary carcinoma." This should not be considered a "wastebasket" diagnosis; it is simply a gland-forming carcinoma outside of the usual "herd." There is an almost equal distribution between major and minor salivary glands.[120,121] They can range from bland but infiltrative tumors to pleomorphic and high-grade tumors with necrosis and wide infiltration. Thus given this heterogeneity, tumors should be graded into three categories: low grade, intermediate grade, and high grade.[121] In general, the prognosis for adenocarcinoma NOS is worse than for most other salivary gland carcinoma with reported 10-year survival rates of 55%[120] and 15-year survival rates of 41%, 34%, and 28% for low, intermediate, and high grade tumors, respectively.[121]

Metastases

Metastasis to the salivary glands or, more commonly, to intraglandular or periglandular lymph nodes, is a frequent occurrence. The parotid gland contains an average of 20 intraparenchymal lymph nodes, whereas the submandibular and sublingual glands do not contain any.[122] For this reason, the vast majority of metastases to the parotid gland are to intraparenchymal lymph nodes and thus from head and neck primaries,[123,124] while approximately 85% of those to the submandibular gland are from non–head and neck primaries. The parotid lymph nodes drain from the scalp, face, and ear skin and from the external auditory canal and tympanic membrane, so skin tumors such as squamous cell carcinoma and melanoma account for approximately 80% to 90% of metastases.[123,124] Merkel's cell carcinomas also spread to this area but are uncommon. The remaining are from non–head and neck primary tumors, most commonly kidney, lung, and breast carcinomas.[125] The opposite distribution is seen for the submandibular gland, with 85% of metastases coming from infraclavicular primary tumors, most commonly breast, kidney, and lung carcinomas (small cell carcinoma of the lung in particular).[125-128]

The histologic features of the tumors are identical to what is seen in the primary site lesions. In the parotid gland, when the tumors are smaller, they are seen as being "tropic" to the lymph nodes, a feature particularly important in identifying them as metastatic disease to the gland rather than emanating from it. They are focused within the lymph nodes, but they almost always have extracapsular extension with growth of the tumor into the adjacent normal salivary gland tissue. Many of them will obliterate the nodal tissue altogether (termed "soft tissue metastasis") and so may just be seen as a nodule within the salivary tissue composed entirely of tumor. In these cases the pathologist cannot always be sure that the tumor is not a primary lesion. This is particularly important for two tumors: squamous cell carcinoma and high-grade neuroendocrine carcinoma. Both are rare primary lesions. For squamous cell carcinoma, the distinction between primary versus metastasis must be clinically ascertained. For high-grade neuroendocrine carcinomas, the differential diagnosis includes primary parotid gland small cell carcinoma, metastatic pulmonary small cell carcinoma, and Merkel's cell carcinoma from the skin. As discussed earlier, immunohistochemistry can be helpful in this distinction.

Lymphoma

Primary lymphoma of the major salivary glands comprises approximately 5% of extranodal lymphomas and approximately 2% of all salivary gland tumors.[129,130] It is defined as arising in the salivary gland when there is absence of lymphoma in a noncontiguous site based on clinical evaluation.

Primary non-Hodgkin's lymphoma (NHL) occurs either as a de novo process unrelated to other diseases or as a secondary process related to lymphoepithelial sialadenitis. De novo NHL can be large B-cell lymphoma (35%), follicular lymphoma (35%), or another low-grade lymphoma (30%), with half of the latter being secondary forms of the extranodal marginal zone B cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type or just MALT lymphomas.[129,131] Most patients are older with the average age between 50 and 70[130] and present with a solitary, painless mass in de novo cases. In contrast, there is often a history of waxing and waning enlargement of several glands in the secondary forms.[132] Most cases of salivary gland Hodgkin's lymphoma occur in the parotid gland and probably just represent disease involvement of intraparotid lymph nodes.

Grossly, salivary glands involved with lymphoma usually have a tan-white to yellow-tan color and are diffusely and homogeneously involved (so-called "fish-flesh" appearance). The microscopic appearance depends a great deal on the type of lymphoma. Primary diffuse large B cell lymphoma consists of sheets of large lymphocytes diffusely effacing the normal gland and infiltrating (with little tissue reaction) into and around anything that is left (Fig. 88-11A). The cells have modest amounts of cytoplasm, round to oval nuclei with pale chromatin, one to three prominent nucleoli, and brisk mitotic activity (see Fig. 88-11B). Other primary lymphomas will have a similar growth pattern but with different cells depending on the type. MALT lymphomas occur in the setting of lymphoepithelial sialadenitis, with this being prominent in the background. There is a somewhat heterogeneous infiltrate of B cells with sheets of medium-sized lymphocytes with abundant pale cytoplasm, uniform nuclei, and distinct cell membranes. These form "halos" around the epithelial cell nests and extend away from them in broad strands (see Fig. 88-11C).[129] There is also a mixture of small cleaved lymphocytes, plasma cells, and lymphoplasmacytic cells that have cytologic features of both of the former two cell types

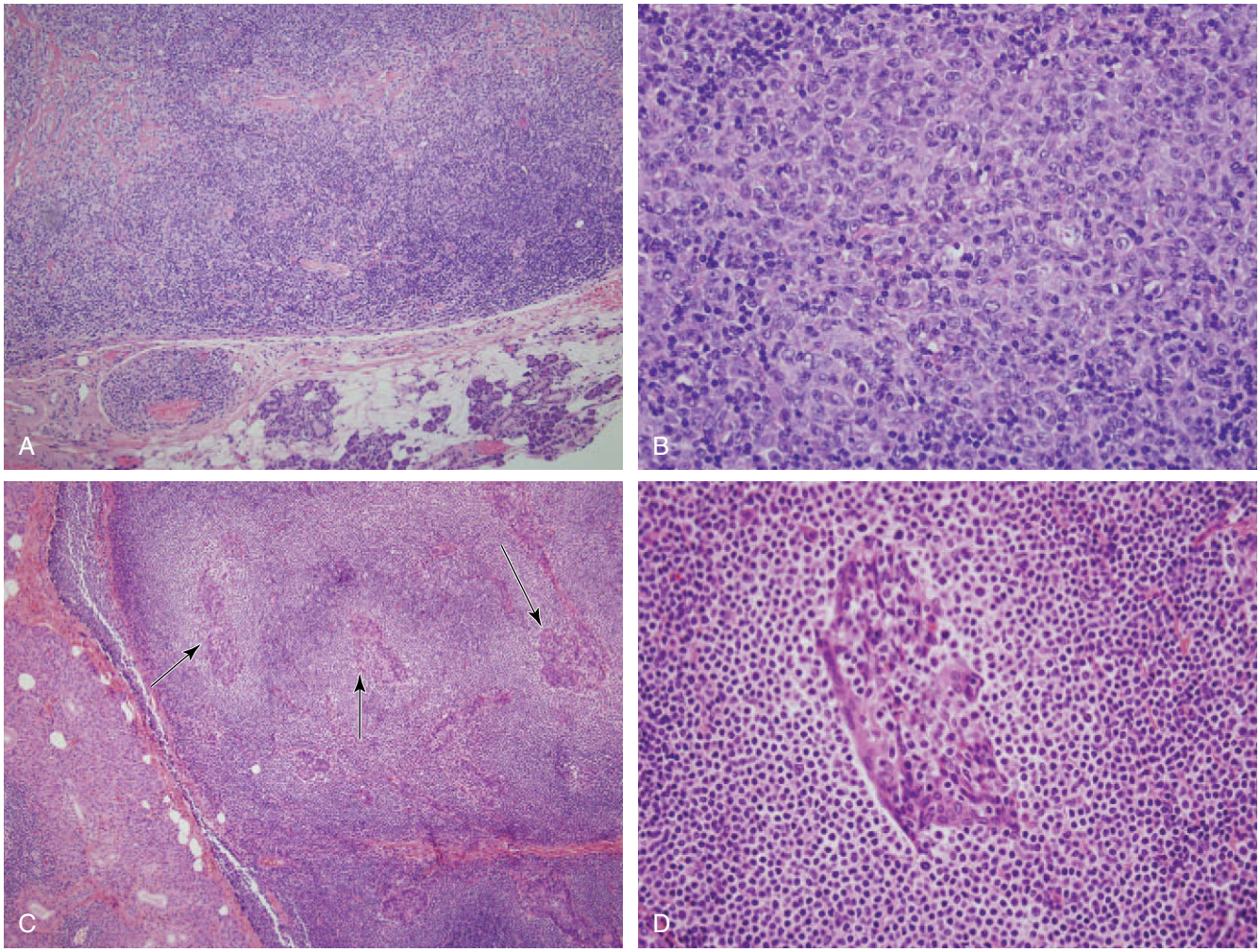

Figure 88-11. Salivary gland lymphoma. **A,** Large B-cell lymphoma growing as a sheet with infiltration of salivary gland tissue without any stromal reaction or fibrosis (100×). **B,** Cells of large B-cell lymphoma have modest amounts of pink cytoplasm and large nuclei with clumped chromatin and one to three prominent nucleoli (400×). **C,** Mucosa-associated lymphoid tissue lymphoma showing diffuse involvement of the parotid gland by sheets of lymphocytes, which manifests as clearing around the epimyoepithelial islands *(arrows)* from the plasmacytoid B cells with clear cytoplasm that are accumulating there (40×). **D,** Central epimyoepithelial island (residual inflamed duct epithelium) surrounded by sheets of plasmacytoid lymphocytes with round nuclei, clumped chromatin, and pale to clear cytoplasm (400×).

(see Fig. 88-11D). The lymphoma cells markedly expand the spaces between the epithelial islands and also infiltrate into these islands along with the non-neoplastic lymphocytes from the background non-neoplastic sialadenitis. FNA is quite useful for diagnosing salivary gland lymphoma with high sensitivity and specificity for the diagnosis, as well as for providing material for flow cytometry.[133]

Immunohistochemistry and molecular studies are critical to the diagnoses, particularly for MALT lymphoma, where the differential diagnosis includes inflammatory, non-neoplastic sialadenitis. In these cases, clonal immunoglobulin rearrangements by PCR combined with the light microscopic features makes the diagnosis of malignancy—both features are necessary.

Pediatric Salivary Gland Tumors

Pediatric salivary gland tumors are uncommon. The most common is the hemangioma followed by a long list of tumors, most of which are identical to adult forms such as mucoepidermoid carcinoma, acinic cell carcinoma, and ACC. Two are unique to the congenital period and bear mentioning here. Sialoblastoma is an extremely rare, potentially aggressive neoplasm that recapitulates the embryonic stage of salivary gland development and has been suggested to represent retained blastomatous cells. Local recurrence is relatively common, occurring in up to 30% of cases. Metastasis, however, is uncommon, and only one fatality has been reported. Salivary gland anlage tumor is a peculiar and unique hamartoma occurring in the perinatal period as a pedunculated mass attached to the wall of the nasopharynx.[134] These may obstruct the airway and, in this way, be clinically significant. Interestingly, they may be incidentally suctioned out of the newborn's airway or spontaneously expelled.

Prognostic Variables

The overall 10-year, disease-free survival rate of patients with salivary gland malignancies ranges from 47% to 74%.[4,32,135-139] Multiple studies have examined clinical, histologic, and molecular variables that may predict clinical outcome and survival. There is considerable variability in the results, and this is probably due to the fact that most of these studies have been of small numbers of patients. In addition, these data have been obtained entirely from retrospective studies; no prospective studies examining potentially prognostic variables have been reported. Nevertheless, some common themes can be gleaned from the available data (Table 88-6).

Clinical Variables

In general, several clinical characteristics of the primary tumor have been proposed to be predictive of outcome. Not surprisingly, advanced tumor (T) stage, which takes into account both tumor size and the

Table 88-6

Factors Associated with Occult Metastases and/or Poor Prognosis

Feature	Comment
Primary tumor site	Tumors of the submandibular and sublingual glands tend to metastasize more frequently than those of the parotid glands
Primary tumor size and extraglandular extension	T3 and T4 tumors tend to have a higher incidence of occult metastases and worse outcome
Age	Patients older than 50 years of age have a worse outcome
Presenting symptoms	Facial nerve paralysis and pain are associated with lymph node metastases
Histologic type/grade	Neoplasms with higher incidence of nodal metastases and poorer prognosis include high-grade mucoepidermoid carcinoma, undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma NOS, and salivary duct carcinoma
Local tissue invasion	Perineural invasion and local bone invasion portend a shorter disease-free and overall survival
Positive resection margins	Associated with worse locoregional control and lower survival rate
High Ki-67 and low p27 expression	Associated with shorter disease-free survival in adenoid cystic and mucoepidermoid carcinoma
HER-2/*neu* overexpression	Associated with shorter disease-free survival in salivary duct carcinoma and mucoepidermoid carcinoma

presence of extraglandular involvement, has been widely reported as being associated with the presence of metastases and poor survival.[138-146] The site of the primary tumor has also been proposed to have an association with poor survival. In particular, patients with malignant tumors of the submandibular and sublingual glands tend to have more frequent metastases and a worse outcome than patients with malignant tumors of the parotid gland.[1,145,147,148] The relationship between the presence of metastatic disease and the tumor's site and stage is reviewed later in "Surgery."

The age and gender of the patient have also been suggested to be associated with prognosis. In a multivariate analysis by Terhaard and colleagues,[138] more advanced age was an independent predictor of poor overall survival and male gender was associated with a 17% increased risk for distant metastasis. Hocwald and colleagues[142] also observed that patients older than the age of 50 years presented with more aggressive tumors and that men presented with higher T-stage tumors than women (53% vs. 26%). Similarly, O'Brien and colleagues[149] reported that patients 60 years or older had a significantly shorter survival but they did not find gender to be a significant factor for prognosis.

Presenting symptoms have also been examined for prognostic value. Specifically, facial nerve dysfunction and pain have been suggested in multiple studies to portend a poor prognosis. In the study by Terhaard and colleagues,[138] complete facial paralysis was an independent predictor of failed regional control, with a relative risk of 6.1. Likewise, in a multivariate analysis by North and colleagues,[150] facial nerve paresis was predictive of poor outcome with a 3-year, relapse-free survival of only 13%. In addition to its association with poor survival, facial nerve involvement has also been shown to be highly predictive of lymph node metastases.[146,151] Pain is another symptom that has been found to be associated with a poor clinical outcome in some studies[152]; however, due in part to its subjective measurement, pain has not always been highly predictive.[138]

Histologic Variables

It is generally accepted that certain histologic types of salivary gland malignancies can be placed into groups with either a favorable or poor clinical outcome. For example, patients with acinic cell carcinoma, low-grade mucoepidermoid carcinoma, PLGA, and basal cell adenocarcinoma tend to have better locoregional control rates and better disease-free survival following therapy compared with patients with other histologic types. Patients with high-grade mucoepidermoid carcinoma, undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma NOS, and salivary duct carcinoma tend to have a high incidence of nodal metastases and a poorer prognosis.

Tumor grade has been associated with prognosis for certain histologic types. Because the grading of salivary gland malignancies is subjective with variation between institutions and because there are many different histologic types, each with its own grading criteria, this variable has had mixed utility in predicting biologic behavior. Certain histologic types are inherently "high grade" or "low grade." For instance, salivary duct carcinoma is a "high-grade" cancer, whereas polymorphous low-grade adenocarcinoma, as the name implies, is "low grade" (for more discussion, see the specific tumor types in "Histopathology" earlier). It is important to note that "high grade" is used in the literature to refer to both high-grade histologic types (generally referred to as "*histologic grade*") and high-grade subtypes of certain specific malignancies, namely mucoepidermoid carcinoma and adenocarcinoma NOS.

When referring to *histologic grade,* high-grade malignant tumors are considered to include squamous cell carcinoma, undifferentiated carcinoma, high-grade mucoepidermoid carcinoma, and carcinoma ex-pleomorphic adenoma.[137,153] Low-grade malignancies include acinic cell carcinoma, low-grade mucoepidermoid carcinoma, low-grade adenocarcinoma (including basal cell and mucinous adenocarcinoma), and papillary cystadenocarcinoma. Intermediate-grade malignancies include adenoid cystic carcinoma and epithelial-myoepithelial carcinoma. In a multivariate analysis of 470 malignant tumors of the major salivary glands, Spiro and colleagues[137] found that histologic grade was an independent prognosticator of survival. This has been corroborated in another retrospective review by Chen and colleagues[139] of 207 patients with carcinomas of the major salivary glands that were treated with surgery alone. In this study, high histologic grade was also found to be an independent predictor of locoregional recurrence. Results such as these have led to the suggested role for postoperative radiation therapy in the treatment of high-grade salivary gland malignancies (discussed in "Radiation Therapy" later).

When considering a single histologic type of salivary gland malignancy, subtype grading of some malignancies is also highly correlated with clinical outcome. In general, grading seems to be most useful in predicting the clinical behavior of mucoepidermoid carcinoma and adenocarcinoma NOS.[1,154-157] In a review of 108 patients with mucoepidermoid carcinoma of the major and minor salivary glands by Guzzo and colleagues,[158] high-grade tumors were associated with a significantly reduced, 5-year, disease-free survival rate (22.5%) compared with low-grade tumors (97%, P <0.0001). Similarly, a recent review of 60 patients with mucoepidermoid carcinoma by Aro and colleagues[159] found patients with low-grade tumors to have a significantly better disease-free survival than those with either intermediate-grade or high-grade tumors. There was, however, no difference in disease-free survival between the intermediate and high-grade groups. Although adenoid cystic carcinoma has one of the more varied histologic phenotypes (tubular vs. cribriform vs. solid) allowing for easier grading classifica-

tion, there is controversy over the utility of tumor grade in predicting the prognosis of patients with this malignancy. Some have strongly advocated its utility,[160,161] but studies by Spiro and colleagues[1,47,51] did not find grade to be predictive of clinical outcome in patients with this tumor type.

Local tissue invasion, regardless of histologic type, appears to portend a worse clinical outcome. In particular, perineural invasion and spread has been found to be a predictor of a more aggressive tumor behavior. In the multivariate analysis by Terhaard and colleagues,[138] perineural invasion was an independent prognostic factor associated with the risk of distant metastasis (relative risk = 2.2). Similarly, Hocwald and colleagues[142] found perineural invasion to be an independent predictor of shorter disease-free survival in their multivariate analysis. Local bone invasion has also been shown to be independently associated with an increased risk of local recurrence and shorter overall survival.[138,162]

Not surprisingly, the presence of positive surgical margins has also been shown to be associated with a worse clinical outcome. Therkildsen and colleagues[135] found this variable to be independently associated with both worse locoregional control and lower survival rates. Terhaard and colleagues[138] also found the status of the resection margin to be independently associated with poor local control with a relative risk of 3.5. These observations are consistent with other studies in which poor local control was associated with positive resection margins.[56,163,164]

Molecular Markers

Markers of cell proliferation have been suggested to be prognostic for patients with salivary gland malignancy. Early studies looking at the proliferative fraction in salivary gland tumors using flow cytometry noted an association between proliferative activity and survival.[165] Two of the more commonly studied markers of proliferation are proliferating cell nuclear antigen (PCNA) and Ki-67. The expression of both PCNA and Ki-67 by tumor cells has been shown to correlate with higher-tumor grade and shorter, disease-free survival of patients with ACC and mucoepidermoid carcinoma.[166-171] In general Ki-67 is considered to be a more accurate marker of proliferating cells because it has a shorter half-life and hence more specific staining. In mucoepidermoid carcinoma, investigators have found that tumors with high expression of Ki-67 and low expression of p27 (a cyclin dependent kinase inhibitor, the action of which slows cell cycle progression) have a worse prognosis.[172,173]

Another potential indicator of prognosis is a specific translocation, t(11;19), which brings together the MECT1 and MAML1 genes. This translocation has been identified in up to 70% of mucoepidermoid carcinomas.[174] Tumors with this translocation were found to be better differentiated and were shown to have a better prognosis. Although provocative, this has not garnered enough attention nor proven useful enough to be instituted in practice in the management of patients with these tumors. Whether or not it adds information beyond grade and clinical stage is unclear.

Another marker that has been investigated as a potential prognosticator is a receptor tyrosine kinase of the ErbB family. HER-2/*neu* (also known as *ErbB2*) is frequently expressed in a subset of salivary gland malignancies, salivary duct carcinoma in particular, and expression correlates significantly with prognosis.[104,175] This oncogene is also overexpressed in approximately one third of mucoepidermoid carcinomas, and its overexpression appears to correlate with poorer prognosis.[176,177] Prognostic data such as these have become the basis for targeted therapy against HER-2/*neu*, as discussed later in "Chemotherapy."

Treatment

For the most part, salivary gland malignancies are primarily treated surgically when resectable. The following section is a general discussion of the surgical and nonsurgical management of salivary gland malignancies. Some aspects of the treatment for specific malignancies were also included earlier in "Histopathology".

Surgery

Parotidectomy

The parotid gland can be divided into a superficial (or lateral) and a deep "lobe" by a sagittal plane defined by branches of the facial nerve. The main trunk of the facial nerve, after it exits the stylomastoid foramen, gives off branches to the posterior belly of the digastric muscle and then runs through the parenchyma of the parotid tissue. It divides into an upper temporofacial division and a lower cervicofacial division at the pes anserinus, which is located approximately 1 to 2 cm from the stylomastoid foramen. The upper division divides further into the temporal, zygomatic, and buccal branches (Fig. 88-12). The lower division divides into the marginal mandibular and cervical branches. It is important to note that the parotid gland is actually unilobular and that the plane created by the fanning branches of the facial nerve is not a true anatomic separation of the gland into two discrete lobes. That being said, it is useful from a surgical standpoint to use the facial nerve as a plane of dissection.

When treating a salivary gland malignancy located in the lateral lobe, a superficial parotidectomy is generally adequate treatment for a small low-grade tumor that is well encapsulated, such as an acinic cell carcinoma. If the tumor is larger, a partial deep lobe resection can be performed to include an adequate margin of normal parotid tissue. A

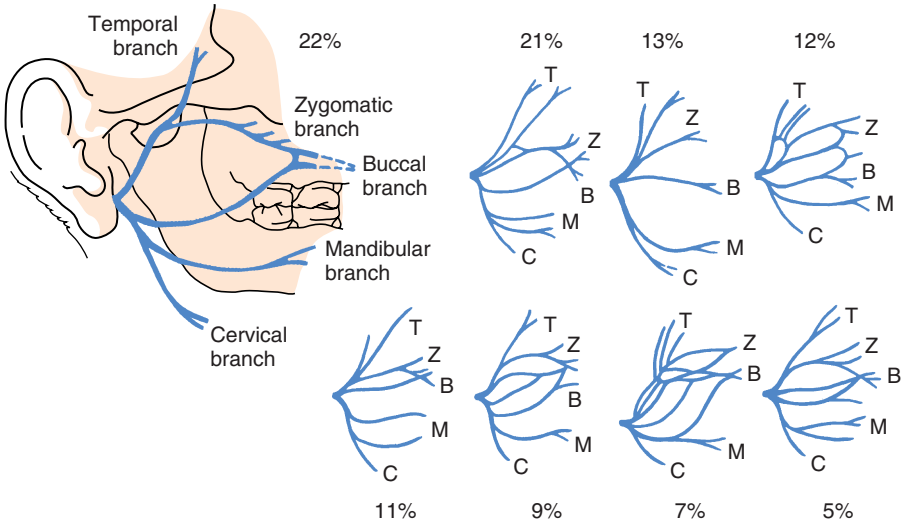

Figure 88-12. Branches of the facial nerve. Variations of the facial nerve branching in the parotid gland are depicted. *(Adapted from Davis RA, Anson BJ, Budinger JM, et al. Surgical anatomy of the facial nerve and parotid gland based upon a study of 350 cervicofacial halves.* Surg Gynecol Obstet. *1956;102:385-412).*

Figure 88-13. Modified Blair incision for parotidectomy operations.

total parotidectomy, removing all of the lateral and deep tissue, is indicated for (1) high-grade malignant tumors with a high risk for metastasis, (2) any parotid malignancy with an indication of having metastasized to intraglandular or cervical lymph nodes, and (3) any primary malignancy originating within the deep lobe itself.

When performing a parotidectomy, one begins by making a modified version of the Blair incision typically used in rhytidectomies (Fig. 88-13). It begins at the root of the helix and extends inferiorly in the preauricular crease, curving posteriorly just below the lobule and then extending inferiorly and anteriorly to lie in a skin crease approximately two fingerbreadths below the inferior border of the mandible at the level of the hyoid bone. The inferior part of the incision can be extended to provide exposure for a lymph node dissection should one be indicated. An anteriorly based skin flap is then elevated in the subcutaneous plan immediately over the superficial musculoaponeurotic system (SMAS) layer. The greater auricular nerve is identified and traced inferiorly. It is divided superiorly and reflected inferiorly, preserving as much length as possible in the event that the facial nerve is resected and a cable graft is required. The tail of the parotid is elevated off of the sternocleidomastoid muscle, and the posterior belly of the digastric muscle is identified. The parotid gland tissue is then elevated off of the anterior aspect of the tragal cartilage, and the dissection is carried into the deeper aspects of the gland. The main trunk of the facial nerve is identified approximately 1 cm medial to the tragal pointer (Fig. 88-14). The nerve exits the stylomastoid foramen immediately posterior to the styloid process and enters the parotid gland immediately anterior to the insertion of the digastric muscle into the mastoid tip. In this region the posterior auricular artery coming from the external carotid artery is typically encountered and should be ligated once the facial nerve is identified. The main trunk of the nerve is traced anteriorly to the pes anserinus, and the branches of the upper and lower divisions are then followed, separating the lateral lobe of the gland from the nerve. Deep to the lower branches of the facial nerve, the retromandibular (posterior facial) vein may be encountered and should be ligated if a deep lobe parotidectomy is to be performed. If the location of the tumor prevents the identification of the main trunk of the facial nerve, one can identify a distal branch and trace the branch in a retrograde fashion back to the main trunk. The marginal mandibular branch is often used for this and can be found by following the posterior facial vein superiorly (Fig. 88-15).

While performing a deep lobe parotidectomy, multiple intraglandular and periglandular vessels will be encountered. Specifically, branches of the external carotid artery must be identified and controlled, taking great care to identify and preserve the internal carotid artery. The external carotid artery is found just superior to the digastric muscle, and it should be controlled and/or ligated just before it enters the parotid gland. As mentioned earlier, the retromandibular (posterior facial) vein will often also need to be ligated to obtain access to the

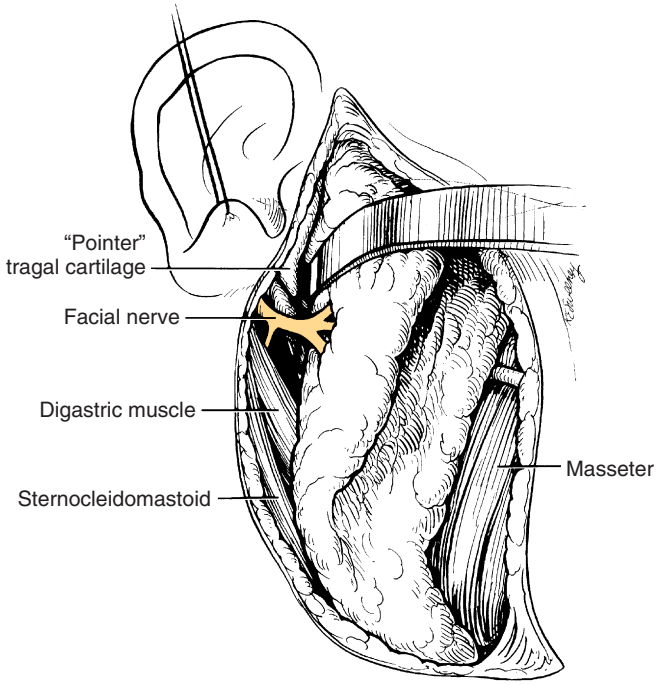

Figure 88-14. Identification of the main trunk of the facial nerve during a parotidectomy operation. The facial nerve exits the stylomastoid foramen and can be found approximately 1 cm medial and anteroinferior to the tragal pointer.

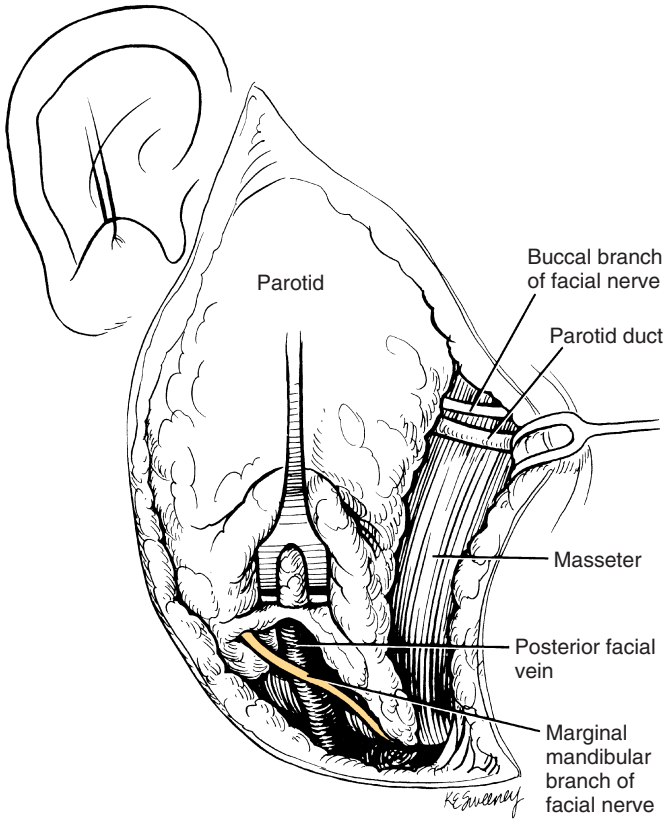

Figure 88-15. Identification of the marginal mandibular branch of the facial nerve. This branch can be found by carefully dissecting superiorly along the posterior facial vein. This can be useful when the location of the parotid tumor makes it difficult to identify the facial nerve at its main trunk. The marginal mandibular branch can be traced retrograde to the main trunk in these situations.

Figure 88-16. Dissection and removal of a deep lobe parotid tumor from the parapharyngeal space. The facial nerve has been dissected and mobilized over the tumor.

deep lobe. Once these vessels are controlled, the main trunk and branches of the facial nerve should be carefully elevated off of the deep lobe tumor (Fig. 88-16). Once this is accomplished, the gland can be dissected off of the deep musculature, mandible, and temporal bone. Intraglandular branches of the external carotid that will be encountered include the transverse facial artery and the internal maxillary artery. These should be ligated at the anterior aspect of the gland, at the posterior border of the mandibular ramus. If the tumor extends into the parapharyngeal space, it is dissected free using blunt dissection. Occasionally, the stylomandibular ligament will need to be divided so that the mandible can be retracted anteriorly to provide better access.

If the facial nerve is involved with tumor, it should be resected to negative margins. In general, if the preoperative facial nerve function is fully intact, the nerve is most likely not invaded, and all attempts should be made to preserve it. However, if the preoperative evaluation reveals a paretic or paralyzed facial nerve, it is likely invaded by the tumor and should be resected. The extent of the resection is dictated by intraoperative frozen section biopsies and should proceed until proximal and distal margins are deemed to be negative. This may require tracing the nerve into the mastoid region of the temporal bone by performing a mastoidectomy. The nerve is then reconstructed by primary neurorrhaphy or by placing an interposition graft, using either a segment of the greater auricular nerve or the sural nerve. Nerve mobilization after a mastoidectomy is often required in order to minimize tension on any reconstruction anastomosis. Facial nerve repair and facial paralysis rehabilitation is discussed in greater detail in another chapter within this textbook.

Advance parotid tumors may extend to adjacent structures including muscle (masseter, sternocleidomastoid, and pterygoid muscles), bone (mandible and mastoid tip), pharyngeal mucosa, and the overlying skin. In these situations the surgeon should be prepared to perform the type of operation that is necessary for complete extirpation of the tumor. This may require a partial mandibulectomy, a lateral or partial temporal bone resection, an extended resection of pharyngeal mucosa, or a resection of facial skin. Careful preoperative assessment of the extent of the tumor is essential to plan the extent of extirpation and reconstruction of the resulting defect.

Submandibular Gland Excision

For malignancies of the submandibular gland, excision of the gland along with the level Ib lymph node–bearing tissue is recommended. With the neck extended, a transverse incision is made approximately two fingerbreadths below the inferior border of the mandible within a neck skin crease, at the cranio-caudad level of the hyoid bone. This level is chosen to avoid injury to the marginal mandibular branch of the facial nerve. A superior skin flap is raised in the subplatysmal plane, looking for the nerve during this dissection. The nerve runs from the angle of the mandible, curving anteriorly and caudally to parallel the mandible. It passes over the posterior facial vein and curves cranially toward the commissure of the mouth. Once identified and isolated, the nerve is reflected superiorly to preserve it. The facial vein can be ligated, and the proximal stump can be retracted superiorly to help keep the nerve out of the field of active dissection.

The fatty lymph node–bearing tissue in level Ib is then separated from the inferior and medial aspect of the mandible. This is kept in continuity with the submandibular gland itself. The facial artery and vein are identified and ligated. Deep to the gland, the digastric muscle is identified and the dissection is carried anteriorly to the mylohyoid muscle. The mylohyoid muscle is retracted anteriorly, exposing the lingual nerve, the submandibular ganglion, and Wharton's duct. Deep to the duct and the anterior belly of the digastric muscle is the hypoglossal nerve, which should be identified and preserved unless grossly involved by the tumor. The submandibular ganglion and Wharton's duct are divided and ligated. Next, the specimen is separated from the digastric muscle. If a supraomohyoid neck dissection is planned, the digastric muscle fascia is separated from the muscle and the specimen is kept in continuity with levels II and III.

Sublingual Gland Excision

The pair of sublingual glands is located in the anterior floor of the mouth just deep to the mucosa. Treatment of sublingual gland malignancies involves a wide local excision and a level I neck dissection. In order to excise a tumor with an adequate margin, the excision often involves partial resection of adjacent structures, such as tongue musculature, mylohyoid muscle, mandible periosteum, mandibular bone, and lingual nerve. The excision is usually accomplished by a combined transoral and transcervical approach. For more advanced tumors, a lip-split incision and a posteriorly based cheek flap approach may be necessary to perform a composite resection that may include a marginal mandibulectomy, floor of mouth resection, and partial glossectomy. For tumors that have invaded the marrow space of the mandible, a segmental mandibulectomy may be required. Reconstruction of these defects may require a split-thickness skin graft, myocutaneous free or regional flap, and/or a free osteomyocutaneous free flap. The reconstruction of oral cavity defects following tumor extirpation is discussed in more detail in other portions of this textbook.

Minor Salivary Glands

The surgical management of minor salivary gland malignancies is dictated by the site of the tumor. The most frequent location is the palate, and in these situations, transoral and transfacial approaches are used in conjunction with partial or total maxillectomy for extensive lesions. Because minor salivary gland malignancies may arise in a wide variety of locations in addition to the palate (e.g., oropharynx, nasal cavities, paranasal sinuses, pharynx, larynx), the surgical approaches are not discussed here. Site-specific surgical approaches are discussed in detail in other chapters of this text.

Management of the N0 Neck

The decision of whether or not to treat a clinically N0 neck is controversial. Although some have advocated elective treatment of the neck in all patients with salivary gland malignancies, the majority have recommended that treatment of the neck be performed only in selected patients with tumors having poor prognostic features for metastasis (see Table 88-6).

The site of the primary tumor appears to be associated with the frequency of occult nodal involvement. Armstrong and colleagues[145] reviewed 474 cases of patients with major salivary gland malignancies

in order to define the indications for elective neck dissections. Of the cases, 407 (86%) had clinically N0 necks, and of these, an elective neck dissection was performed in 90 of the 407 (22%) patients. Occult metastases were discovered on histopathologic analysis in 34 of the 90 (38%) of the patients undergoing neck dissections. Albeit, these cases tended to be higher grade and more advanced. Tumors of the submandibular gland had a significantly higher incidence of occult metastasis to the cervical lymph nodes (21%) than those of the parotid gland (9%). These findings are corroborated by other studies. Spiro and colleagues[1] reviewed 2807 patients with salivary malignancies and also found that submandibular cancers had a higher incidence of lymph node metastases (28%) compared with parotid (18%) and minor salivary gland malignancies (15%). Yu and Ma[147] also found that submandibular and sublingual cancers tended to metastasize more frequently than cancers of other sites. Thus the site of the primary malignancy appears to be an important feature when considering treatment of the N0 neck.

The size of the primary tumor and the presence of extraglandular extension have also been correlated with risk of metastases. Armstrong and colleagues[145] demonstrated that tumors greater than or equal to 4 cm in size had a 20% risk of occult metastases compared with a 4% risk associated with smaller tumors ($P < 0.00001$). In a multivariate analysis of risk factors associated with occult metastases from parotid malignancies, Frankenthaler and colleagues[146] found that extraparotid tumor extension was among the most predictive variables. The T stage, which takes into account both the size of the primary and the presence of extraglandular extension, has been shown in multiple other studies to be associated with the risk of metastatic disease.[143,144] Thus results such as these have led to the suggestion that patients with high T stage (T3 and T4) tumors should undergo routine neck dissections even if they do not have clinical evidence of cervical lymph node metastases.

Other features that have been associated with a higher risk of occult metastases are the histologic type and grade of the primary tumor.[145-147,151,178-180] In general, histologic types considered to be at higher risk for occult nodal involvement include undifferentiated carcinoma, squamous cell carcinoma, high-grade mucoepidermoid carcinoma, adenocarcinoma NOS, carcinoma ex pleomorphic adenoma, and salivary duct carcinoma. Histologic types that have been deemed of lower risk include acinic cell carcinoma, adenoid cystic carcinoma, and low-grade mucoepidermoid carcinoma. The grade of the primary tumor has been reported to correlate with the incidence of occult nodal disease. Armstrong and colleagues[145] found that high-grade tumors had a 49% risk of occult metastases compared with a 7% risk for intermediate- and low-grade tumors. Similarly, Bhattacharyya and Fried[151] reported that high grading conferred a 1.99 odds ratio (95% CI 1.64 to 2.40) of having occult nodal involvement. These authors concluded that elective treatment of the neck is indicated in patients with high-grade histologic types such as adenocarcinoma and squamous cell carcinoma and high-grade subtypes such as high-grade mucoepidermoid carcinoma.

In sharp contrast to the authors of the studies cited earlier, Stennert and colleagues[143] found a much higher incidence of occult cervical lymph node metastases in all salivary gland malignancies, regardless of histologic type or tumor stage. As such, they have strongly advocated the elective treatment of the neck in all patients, raising controversy in the management of N0 necks. Their study of 160 consecutive patients was unique in that they treated all patients with an ipsilateral neck dissection in a nondiscriminatory manner. They found that of the 139 patients who were initially staged as having an N0 neck, 45% had occult metastases. The rates of occult metastases were particularly high for undifferentiated carcinoma (75%), squamous cell carcinoma (64%), and adenocarcinoma NOS (58%). These authors also found occult metastases to be surprisingly frequent in what has traditionally been considered "lower-risk" histologic types: acinic cell carcinoma (44%) and adenoid cystic carcinoma (36%). In addition, whereas occult metastases have most often been reported with larger tumors, Stennert and colleagues[143] found that even T1 and T2 lesions had frequent metastases (29% and 54%, respectively). From these data, the authors concluded that an ipsilateral neck dissection should be performed on all patients with salivary gland malignancies, regardless of histologic type or stage.

Another area of controversy has to do with how the neck should be treated once it has been actually decided to do so. Some have advocated the use of radiation therapy to treat an N0 neck because many of the features associated with occult disease are the same features that indicate the need for postoperative radiation of the primary site.[181] Others have advocated surgery in order to spare patients with pathologically N0 necks the morbidity of radiation and to obtain accurate staging of the disease. The arguments in favor of surgery also state that, in most cases, the exposure for the neck dissection is already established and/or partially completed during the resection of the primary tumor.

When a neck dissection is performed in a patient with a clinically N0 neck, a selective neck dissection is considered the treatment of choice. The levels of the neck to be dissected are determined by the site of the primary tumor. For parotid tumors, Armstrong and colleagues[145] demonstrated that 3 out of 30 patients (10%) had metastases in level I, 8 of 30 (27%) in level II, 7 of 30 (23%) in level III, 6 of 30 (20%) in level IV, and 1 of 30 (3%) in level V. They show that dissection of levels I through IV would have detected all occult metastases. The one patient with a positive level V node also had node-positive disease in levels II through IV. As such, the dissection of at least levels I through IV for parotid malignancies has been recommended. For submandibular and sublingual malignancies, occult metastases can be detected in N0 necks addressing levels I through III alone.[145,182] If occult disease is detected in the first echelon dissection for either parotid or submandibular primary malignancies, however, a comprehensive neck dissection is recommended to treat possible additional disease in the other levels.

Management of the N+ Neck

A consensus regarding treatment of the clinically N+ neck is more established. It is well accepted that an ipsilateral neck dissection should be performed in patients with palpable or radiographically enlarged cervical lymph nodes.[182] In addition, the use of radiation therapy following a cervical lymphadenectomy has been shown to improve locoregional control and survival (discussed in detail later).[183,184] Because salivary gland malignancies that have metastasized to regional lymph nodes can involve any of the five levels in the neck and can skip levels,[145] it has been recommended to perform a comprehensive modified radical neck dissection in N+ necks. However, because the incidence of nodal involvement in the contralateral neck is low, only the ipsilateral side should be treated.[144]

Radiation Therapy

Adjuvant Radiation Therapy

In general, the use of postoperative radiation therapy appears to improve locoregional control rates following resection of salivary gland malignancies. In a recent multivariate analysis of 140 patients with ACC, Chen and colleagues[185] observed that the omission of postoperative radiation therapy was an independent predictor of local recurrence with a hazard ratio of 5.82 (95% CI 1.96-17.26, $P = 0.002$). Although the rationale for the use of postoperative radiation is based entirely on retrospective studies such as this one, a number of these studies have revealed certain features where postoperative radiation is particularly useful in controlling locoregional recurrence (Table 88-7). These features include advanced-stage tumors, the presence of positive margins following resection, high-grade tumors, neural involvement, and bone involvement.

Local control following surgical resection of *advanced* stage tumors has been shown to be better when postoperative radiation is given. This improved local control, however, is less clear for earlier-stage tumors. In one of the largest retrospective multivariate analyses, Terhaard and colleagues[138] examined the outcomes and prognostic variables of 565 patients treated for a heterogeneous mixture of salivary gland malignancies in centers of the Dutch Head and Neck Oncology Cooperative Group. They found that patients who were treated by surgery alone had a relative risk of local recurrence of 9.7 and a relative risk of regional recurrence of 2.3 when compared with patients treated with surgery followed by radiation therapy. The local control of T3 and T4 tumors

Table 88-7

Indications for Adjuvant Radiation Therapy to the Primary Site

Feature	Reference
Advanced stage	Terhaard et al.[138,183]; Armstrong et al.[184]
Positive margins following resection	Garden et al.[56,188]; Hosokawa et al.[189]; Silverman et al.[190]
High-grade histologic types: squamous cell carcinoma, undifferentiated carcinoma, high-grade mucoepidermoid carcinoma, carcinoma expleomorphic adenoma, salivary duct carcinoma	Matsuba et al.[187]; Renehan et al.[153]
Local tissue invasion: perineural or bone invasion	Terhaard et al.[183]

treated with surgery followed by radiation was 84% at 10 years, and this was significantly improved compared with cases treated with surgery alone (18% at 10 years, $P < 0.001$).[183] This improvement in local control was not observed for T1 tumors (95% for surgery plus radiation vs. 83% for surgery alone) or T2 tumors (91% for surgery plus radiation vs. 88% for surgery alone). Furthermore, there did not appear to be any influence of radiation therapy on the development of distant metastases or overall survival. In a study by Armstrong and colleagues,[184] a retrospective matched-pair analysis also found that postoperative radiation improved local control in patients with stage III and stage IV disease. The 5-year local control rate in patients treated with surgery and postoperative radiation was 51%, and that of patients treated with surgery alone was 17%. The corresponding 5-year determinate survival rates were 51.2% and 9.5%, respectively. In comparison, there was not much difference in the outcomes between the two treatment groups among patients with stage I and II disease. These recent studies are consistent with previous observations demonstrating advantages of combining surgery and radiation.[136,150,186,187] Thus for advanced salivary gland cancers, there appears to be improved locoregional control and possibly an improvement in survival in patients treated with a surgical resection followed by radiation therapy.

In cases with positive margins, there tend to be increased rates of local recurrences overall (as discussed earlier in "Prognostic Variables"), and therefore it is not surprising that the addition of radiation therapy, when surgical margins are positive, appears to result in better local control. Garden and colleagues[56] retrospectively reviewed 198 patients with adenoid cystic carcinoma of the head and neck, with a median follow-up period of 93 months, and found that 18% of patients with positive margins developed local recurrences. In contrast, only 9% with close or uncertain margins and 5% with negative margins developed local recurrences ($P = 0.02$). In a separate study, Garden and colleagues[188] reviewed 166 patients with malignancies of the parotid gland and found that there was a trend for patients with positive margins to have improved local control when treated with radiation doses greater than 60 Gy. Similarly, Hosokawa and colleagues[189] reviewed 61 cases of mucoepidermoid carcinoma treated with either surgery alone or surgery followed by radiation and found that the use of higher doses of radiation (>55 Gy) resulted in better local control despite positive margins. More recently, a review of 75 patients with adenoid cystic carcinoma by Silverman and colleagues[190] demonstrated a statistically significant improvement in locoregional control of cases with positive margins when radiation therapy is administered following surgery. Thus postoperative radiation therapy is indicated when there are positive margins following tumor resection.

High-grade salivary gland malignancies have a propensity for locoregional recurrence, and postoperative radiation appears to be beneficial as adjuvant therapy. A study of high-histologic-grade malignancies of the parotid gland by Matsuba and colleagues[187] demonstrated a significantly improved 5-year local control rate when postoperative radiation was given (70%) compared with that of surgery alone (20%). Likewise, a retrospective multivariate analysis of 103 parotid gland carcinoma patients by Renehan and colleagues[153] found that the addition of postoperative radiation significantly reduced locoregional recurrence (15%) compared with surgery alone (43%) at 10 years and that this improved survival was seen mainly in patients with high-grade tumors. In contrast, postoperative radiation of low-grade malignancies did not affect locoregional control. Thus postoperative radiation therapy is recommended in cases of high-histologic-grade malignancies of the salivary glands.

Postoperative radiation is also recommended in cases where there is invasion into local tissues. Both perineural invasion and bone invasion are unfavorable histologic features and are associated with a poor clinical outcome. In the Terhaard study of 565 patients treated in centers of the Dutch Head and Neck Oncology Cooperative Group, postoperative radiation significantly improved the 10-year local control rates of cases with perineural or bone invasion compared with outcomes of surgery alone.[183]

Radiation of the Neck

The addition of postoperative radiation therapy of the neck in cases where there are lymph nodes positive for metastases from salivary gland cancers has been shown to improve locoregional control and survival. In a study by Armstrong and colleagues[184] comparing 16 patients with lymph node metastases treated with surgery alone with 23 patients treated with surgery and radiation, there was an improvement in 5-year locoregional control from 40% to 69% ($P = 0.05$). The corresponding 5-year survival improved from 19% to 49% ($P = 0.015$). The utility of postoperative radiation of the neck has been corroborated by the Terhaard and colleagues study.[183] They observed an 83% regional neck node control rate at 10 years in patients ($n = 22$) with pathologic N1 disease treated with postoperative locoregional radiation. In contrast, the 10-year regional neck node control rate was 57% in patients ($n = 10$) treated with no or only local postoperative radiation to the primary site ($P = 0.04$). Thus radiation therapy following surgical ablation of node-positive disease appears to improve outcome.

The use of radiation in the management of N0 necks, however, is less clear. In the Terhaard study, no significant benefit to regional control of the pathologic N0 neck was seen with the addition of postoperative radiation.[183] In contrast, a more recent study by Chen and colleagues[205] examined 251 patients with clinically N0 carcinomas of the salivary glands that were treated with surgery and postoperative radiation therapy. Elective neck irradiation was employed in 131 patients (90 ipsilateral and 41 bilateral). There was a significant reduction in the 10-year nodal failure rate from 26% to 0% ($P = 0.0001$). Of note, in the patients who did not receive elective neck irradiation, the nodal relapse occurred in cases of the more high-grade histologic types: squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma NOS, and mucoepidermoid carcinoma. No nodal recurrence was seen in cases of adenoid cystic or acinic cell carcinoma.

Neutron Beam Radiotherapy

Fast neutrons deliver more energy and thus result in greater radiation damage than what is created by conventional photon/electron radiotherapy. Because salivary gland malignancies have traditionally been considered to be fairly radioresistant, fast neutron therapy was proposed, and subsequently shown, to be effective in these cancers. In the only prospective randomized trial of radiation therapy of salivary gland neoplasms, fast neutron radiotherapy was compared with conventional photon radiotherapy in the treatment of unresectable and/or recurrent tumors. This study conducted jointly by the Radiation Therapy Oncology Group (RTOG) of the United States and the Medical Research Council (MRC) of Great Britain demonstrated a significant improvement in locoregional control with fast neutron radiotherapy.[191,192] Overall survival, however, was not significantly

different between the two groups. In this and subsequent studies, it appeared that patients tended to succumb to distant metastases despite the improvement in locoregional control and that this pattern of failure was the reason for the lack of improved survival, especially in cases of ACC.[193-196]

Chemotherapy

The use of systemic chemotherapy in the treatment of salivary gland malignancies is currently limited to palliative treatment of locally advanced unresectable, recurrent, and metastatic disease. A variety of agents have been explored; however, the studies that have been reported are nonrandomized and of small numbers of patients, making it difficult to assess the efficacy of these drugs. In addition, many of the reports are case series and retrospective reviews of heterogeneous types of malignancies and treatments. In order to circumvent the limitations of the available data, Rizk and colleagues[197] recently reported a meta-analysis of data from 205 patients obtained from 17 phase II or phase III trial studies. The chemotherapeutic agents used in these studies included cisplatin, carboplatin, epirubicin, cyclophosphamide, doxorubicin hydrochloride (Adriamycin), mitoxantrone, paclitaxel, 5-fluorouracil, vinorelbine, methotrexate, and bleomycin. All patients were treated for cancer of the major or minor salivary glands with either single-agent or multi-agent first-line palliative chemotherapy. Using meta-analysis linear regression, the authors found that patients treated with either platinum- or anthracycline (e.g., mitoxantrone)-based chemotherapy had an increase in their median survival. When looking at the data using a multivariate analysis, only platinum-based chemotherapy was found to be significantly associated with increased survival, but there appeared to be a positive interaction between platinum agents and anthracycline. Thus although the field is in need of prospective randomized trials, the available data suggest that these two agents may have a useful role, not only in palliative treatment, but also in definitive multimodality treatment of salivary gland malignancies prone to distant metastases.

Recently, attention has been directed to the possible role for directed therapy against biologic targets expressed in these cancers. These targets include receptor tyrosine kinases such as c-KIT and members of the ErbB family (the epidermal growth factor receptor (EGFR), Her2/*neu*). Adenoid cystic carcinoma has been shown to overexpress c-KIT in more than 90% of cases, and expression of c-KIT has been correlated with tumor grade.[198,199] EGFR (also known as *ErbB1*) is expressed in 79% of all parotid malignancies,[199] leading to the investigation of directed therapy against this target. Her2/*neu* (also known as *ErbB2*) is frequently expressed in a subset of salivary gland malignancies, namely salivary duct carcinoma, and expression correlates significantly with prognosis.[104,175] Observations such as these have established the rationale for investigating strategies to target these kinases in multiple phase II trials.[200-202] Unfortunately, no objective response was found when using either small molecule inhibitors or antibodies as monotherapy in patients with unresectable, recurrent, or metastatic disease. However, the therapeutics did appear to stabilize the disease in a substantial number of the patients in these trials, suggesting that inhibition of these targets was having some effect on the biology of these tumors. Indeed, there are promising data indicating that targeted therapy in combination with conventional chemotherapy may have a synergistic effect.[203]

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CHAPTER EIGHTY-NINE

Physiology of the Oral Cavity

Joseph B. Travers

Susan P. Travers

James M. Christian

Key Points

- Somatosensory innervation of the oral cavity is provided by cranial nerves V (trigeminal), second and third divisions, and IX (glossopharyngeal): (1) V2—maxillary, hard, soft palates; oral mucosa of the maxillary vestibule; maxillary teeth, gingivae, and periodontal ligaments; (2) V3—mandibular, oral mucosa of the cheek and mandibular vestibule; anterior two thirds of tongue; mandibular teeth, gingivae, and periodontal ligaments; and (3) IX, posterior one third of tongue; oropharynx.
- Periodontal ligament (PDL—the ligament separating tooth from bone in healthy, functioning teeth) receptors initiate oral reflexes of jaw opening and salivation and, together with receptors in the temporomandibular joint, contribute to interdental force discrimination and oral stereognosis. Therefore, bite force is lessened with a corresponding decrease in these PDL receptors (i.e., with periodontal disease, tooth extraction, and consequent denture construction).
- Dental pain is mediated by C-fibers (dull, burning) and A-delta fibers (sharp, bright) located in the pulp chamber ("nerve" of a tooth) and extending a short distance into the dentinal tubules (A-delta only). When enamel is breached (by decay, fracture, wear), the fluid in the tubules responds to stimuli and activates these nerve endings ("hydrodynamic theory of dental pain").
- Chewing, swallowing, and breathing are produced by brainstem central pattern generators that control the fundamental rate and pattern of muscle contractions that define each function. Coordination of muscle activity occurs among functions, among motor groups, and within the muscles themselves and is affected by peripheral feedback mechanisms.
- The main function of the masticatory muscles is to break down solid food into amounts small enough to be swallowed. These are strong muscles—jaw openers and jaw closers—that generate significant forces across short distances and apply them via teeth (dentures). These forces must be controlled precisely and effectively—by cortical preprogrammed movement patterns, reflex stimulation, and peripheral input/feedback loops—to allow for smooth movements and successful deglutition.
- Recent molecular and functional data show that there is no specific tongue "map" for taste buds; responsiveness to the five tastes—sweet, sour, bitter, salty, and umami—is present in all areas of the tongue supplied with taste buds.
- Sweet taste sensations are associated with simple carbohydrates; sour taste is generated by weak organic acids; salty taste is stimulated mostly by NaCl (sodium ions); bitter taste arises from stimulation by plant alkaloids (potential toxins); and umami taste is associated with amino acids and peptides.
- The biology of taste perception, mediated by taste receptor cells in the taste buds and innervated by cranial nerves VII, IX and X, is complex, but there is no argument that the clinical recognition of taste affects our survival.

The oral cavity is a complex organ comprising muscle, glands, teeth, and specialized sensory receptors. For most animals, the orosensory and oromotor apparatus is critical for successful defense, reproduction, exploration, nutrition, and vocalization.[1] In humans, vocalization has evolved into complex speech production, but other human behaviors depend less on the mouth and tongue than on the eye and hand. In all animals, however, the mouth is essential for the ingestion of nutrients. The incorporation of nutrients by mastication and drinking involves a high degree of coordination within and between different oral motor systems. Chewing requires the reciprocal activation of antagonist trigeminal muscles to open and close the jaws and the tongue to position food between the teeth. A diverse array of highly specialized sensory systems guides these complex oromotor responses and initiates secretion of digestive enzymes. Mechanoreceptors in the tongue, palate, and periodontal ligament (PDL) all contribute to a three-dimensional (stereognostic) perception of the oral cavity.[2] The sense of taste serves in both food selection and protection from ingesting potentially toxic substances.

Recent reviews provide comprehensive coverage of specific aspects of oral function including mastication,* swallowing,[3,4] oral mechanoreception,[5,6] and the sense of taste.[7-10] In addition, several recent papers have reviewed oral pain[11,12] and taste dysfunction.[13]

This chapter provides a concise overview of orosensory and oromotor function. A brief synopsis of orosensory function describes the innervation and sensitivity of the oral cavity and a summary of central pathways. A section on sensorimotor function includes a discussion of masticatory, lingual, and autonomic reflexes followed by a discussion

*References 64, 68, 75, 273-275.

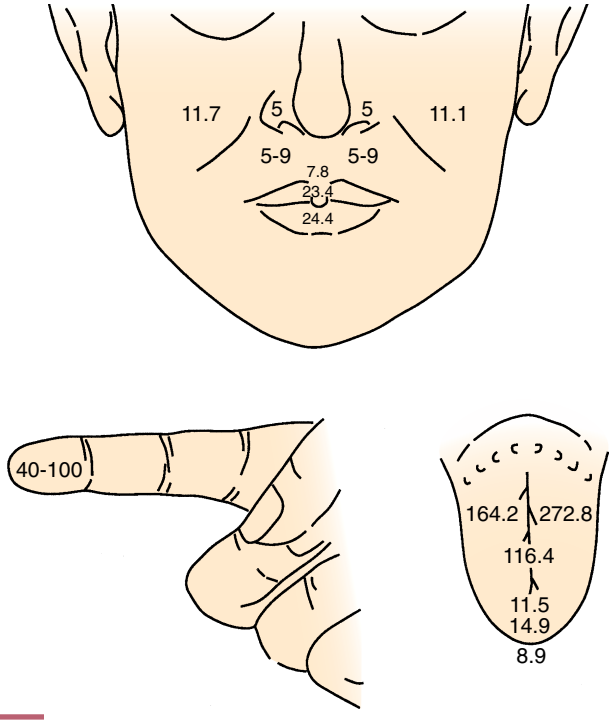

Figure 89-1. Spatial discrimination of tactile detection thresholds from a number of studies. Numbers represent mean threshold in milligrams weight. *(From Rath EM, Essick GK. Perioral somesthetic sensibility: do the skin of the lower face and the midface exhibit comparable sensitivity?* J Oral Maxillofac Surg. *1990;48:1181-1190.)*

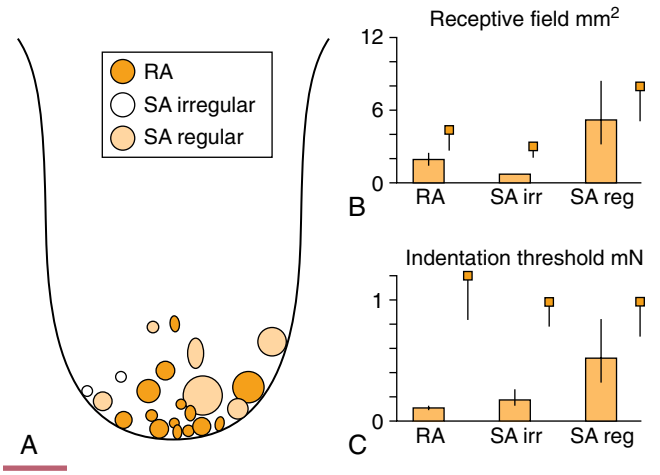

Figure 89-2. Receptive field properties of superficial mechanoreceptive afferents recorded from the human lingual nerve. **A,** Size and location of receptive fields of three types of mechanoreceptors: rapidly adapting (RA), slowly adapting (SA) regular, and slowly adapting irregular. **B,** Receptive field area. **C,** Receptive field threshold. Small squares indicate corresponding data from human median nerve.[70] Vertical bars indicate standard error. *(From Trulsson M, Essick GK. Low-threshold mechanoreceptive afferents in the human lingual nerve.* J Neurophysiol. *1997;77:737-748.)*

of mastication and the oral phase of deglutition. The sense of taste is treated separately.

Sensory Function

Oral Somesthesia

Somatosensory innervation of the oral cavity is provided by the maxillary and mandibular branches of the trigeminal nerve and by the glossopharyngeal nerve. The mandibular nerve branches to innervate the oral mucosa of the cheek, anterior two thirds of the tongue, mandibular dentition, PDL, gingiva, and anterior mandibular vestibule. Branches of the maxillary nerve innervate the hard and soft palates, the oral mucosa of the maxillary vestibule, and the maxillary dentition, gingiva, and PDL. Somatosensory innervation of the back of the tongue and oropharynx is provided by the glossopharyngeal nerve. Although the entire oral cavity is densely innervated with sensory fibers, considerable evidence indicates that the innervation is not uniform. Specialized oral tissues including the lips, teeth, PDL, tongue, and palate each display specific patterns of sensitivity. Although specific parts of the oral cavity rival the hand in terms of absolute psychophysical thresholds for tactile and thermal sensitivity, the structure/function of somesthetic correlations so painstakingly deduced for the hand have little predictive veracity in the mouth.

Overall, the anterior oral cavity displays greater tactile sensitivity than does the posterior oral structure.[1,14] The tip of the tongue is particularly sensitive, with a discriminative capability equivalent to that of the digits (Fig. 89-1). The midline of the palate and tongue are more sensitive than lateral regions. A similar pattern of sensitivity applies to the teeth.[15] Adults with complete dentition could detect a 1-g von Frey hair applied to the anterior (midline) teeth but require nearly 10 g to detect stimulation of the first molar. The sensitivity to warm and cold stimuli also varies widely across oral tissues. Sensitivity to warm stimuli is relatively high on the tip of tongue but not particularly so on either the palate or buccolabial surfaces.[16,17] In contrast, the sensitivity to a cool stimulus is less differentiated within the oral cavity, and the sensitivity of the tongue tip, palate, and buccolabial surfaces is essentially equal. In general, the sensitivity to cool stimuli is greater compared with warm stimuli.

Recording from single human lingual fibers innervating the anterior tongue[18] confirms the small receptive fields and high sensitivity to low-threshold forces observed psychophysically (Fig. 89-2). On the basis of their small receptive fields and low thresholds, lingual fibers could be divided into those innervating the superficial (mucosal) surface of the tongue and those innervating deeper muscle tissue. The majority of the superficial fibers were rapidly adapting—a characteristic in common with other highly sensitive structures used in exploratory activity (e.g., the hand). In contrast, the deeper receptors were all slowly adapting and may provide information about the position of the tongue.

Trigeminal endings mediating somesthetic and thermal sensitivity of the tongue and palate range from free nerve endings to an intermediate group of "semi-organized" endings[19] to more highly organized endings variously referred to as Krause end bulbs,[20] mucocutaneous end organs,[19] or coiled terminations.[21] All investigators agree that there are no Pacinian corpuscles in the oral mucosa. Based on ultrastructural criteria, Munger[22] refers to many highly organized oral mucosa endings as Meissner corpuscles, similar to those found in glabrous skin of the hand. However, despite all this variation in nomenclature, many of the illustrations of the specialized endings are quite similar and show "finely wound nonmyelinated fibers" without a clearly defined capsule.[19] Ultrastructural studies further reveal that some of these organized endings in the palate (but not the lingual epithelium) send axonal processes into the overlying epithelial pegs and are associated with Merkel cells.[22,23] In the hand, Merkel cells are correlated physiologically with slowly adapting mechanoreceptors; however, a similar correlation has not been made in the palate, and their apparent absence in the lingual epithelium does not preclude slowly adapting mechanoreceptors in this structure (see Fig. 89-2). Thus unlike the hand, a correlation between the morphology of oral receptor endings and their response properties as rapidly or slowly adapting has not been demonstrated.

Mechanoreceptors in the PDL have been studied in some detail (see reviews by Jacobs and Steenberghe[24] and Maeda and colleagues[25]). In addition to detecting forces directed against the teeth, PDL receptors initiate oral reflexes of jaw opening and salivation and, together with receptors in the temporomandibular joint, contribute to interdental discrimination and oral stereognosis.[2,24] As many as six varieties of receptor morphology are found in the PDL, ranging from complex Ruffini-like branched endings to free nerve endings.[26,27] The cell bodies for PDL receptors are located peripherally in the trigeminal ganglion

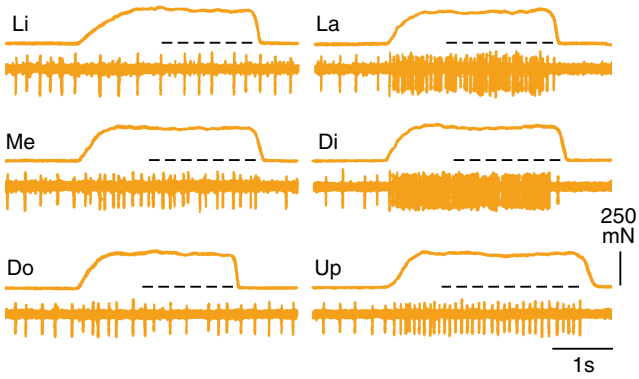

Figure 89-3. Responses of a single human periodontal afferent fiber to a force (≈250 mN) from various directions. The cell responded best to a force from the distal (Di) direction. Directions: lingual (Li), labial (La), mesial (Me), downward (Do), upward (Up). *(From Trulsson M, Johansson RS. Orofacial mechanoreceptors in humans: encoding characteristics and responses during natural orofacial behaviors.* Behav Brain Res. *2002;135:27-33.)*

and centrally in the mesencephalic trigeminal nucleus.[28] Mesencephalic trigeminal innervation of the PDL is primarily in the apical region near the root and consists mostly of small, myelinated, Ruffini-like endings.[29] Trigeminal ganglion innervation extends from the apical region to the more superficial region and includes small unmyelinated nerve endings.

Both rapidly and slowly adapting mechanoreceptors are found in the PDL, and it is likely that it is the location of the receptor in the ligament that determines its response characteristic. Because the tooth rotates about its fulcrum, forces directed laterally to the crown will translate to greater stretch at the root of the tooth compared with the fulcrum. Thus it is perhaps not surprising that lower-threshold fibers are found near the root and that they tend to be slowly adapting compared with receptors located near the fulcrum.[30] In addition, individual Ruffini endings are not uniformly distributed around the tooth and thus display directional sensitivity to the force required to activate them. Recordings from human nerves (microneurography) demonstrate the directional sensitivity of PDL receptors[31] (Fig. 89-3) and further indicate mechanical coupling between the teeth. Single fibers respond to stimulation of multiple (adjacent) teeth; however, there is no anatomic evidence that individual fibers innervate multiple teeth.[32]

The differential innervation of the PDL by the trigeminal ganglion and mesencephalic trigeminal nucleus has functional significance. Mesencephalic receptors are primarily medium and rapidly adapting receptor types, many with directional sensitivity. The central termination of these mesencephalic force detectors includes inhibitory connections to trigeminal jaw closer motoneurons via the supratrigeminal area.[33] Thus these receptors serve a protective role in preventing potentially damaging tooth contact during mastication. In contrast, trigeminal ganglion receptors include slowly adapting mechanoreceptors (position detectors) and high-threshold C fibers (nociceptors) in addition to rapidly adapting mechanoreceptors. Because these periodontal receptors from the trigeminal ganglion terminate centrally in the sensory trigeminal complex, the source for the ascending sensory pathway to the thalamus and cortex, they provide information about tooth displacement and dental pain to the forebrain.

Although mechanoreceptors in the PDL are not encapsulated, their response characteristics are influenced by the elastic properties of the ligament. When the attachment of the ligament is compromised (e.g., during periodontitis that loosens the connective attachments of the ligament), a corresponding loss in interdental force discrimination is observed.[34] Periodontal receptors also contribute to the regulation of bite force. Individuals with dentures could not bite as hard as normal dentulous subjects and could not perceive variations in their own bite force.[2,35] Similar results were obtained by anesthetizing the inferior alveolar nerve.[36] In contrast, anesthetizing the temporomandibular joint does not affect bite force discrimination but does impair jaw-positioning performance. Thus different populations of oral receptors may regulate sensing jaw position and controlling bite force during mastication.

Common Chemical Sense

Stimulation of the oral cavity with high concentrations of salts, acids, alkaloids, and other compounds elicits intense taste sensations but also evokes nontaste sensations ranging from stinging and burning to warm, cool, and painful. This sensitivity of the oral cavity, mediated by nonspecialized free nerve endings and shared by all mucosal membranes, is referred to as the common chemical sense or chemesthesis and should not be confused with taste. Although free nerve endings respond to many traditional gustatory stimuli, they typically display a much lower sensitivity. Electrophysiologic recordings from the lingual nerve, for example, indicate that single fibers require concentrations of sodium chloride (NaCl) 1000 times higher than those necessary to elicit a response from a gustatory fiber in the chorda tympani nerve (reviewed by Bryant and Silver[37]). Much lower concentrations of other types of chemical stimuli (e.g., menthol [10^{-4}]), however, are adequate to elicit a response in trigeminal nerve fibers. The types of chemical stimuli that elicit low-threshold responses in trigeminal fibers suggest that one function of the common chemical sense is to protect the oral cavity. Responses to common chemical stimuli include reflex salivation and coughing that function to diffuse and remove offending stimuli from the mouth. The common chemical sense is not purely protective, however. Spices such as horseradish, ginger, and red pepper are effective stimuli for trigeminal afferent fibers and contribute to the flavor of food. One of the receptors for chemesthetic stimulation was recently cloned.[38] A member of the TRP family of G-protein-coupled receptors, the vanilloid receptor termed "VR1" responds to both noxious heat and low concentrations of protons in addition to vanilloid compounds such as capsaicin, found in chili pepper. Stimulation of this receptor results in the opening of a cation channel, thus depolarizing the afferent fiber.

Dental Pain

Persons usually describe dental pain as either dull/burning or sharp.[39] Sensations of dull burning pain are associated with stimulation of C fibers terminating in the pulp chamber, whereas sharp "bright" dental pain is associated with A-delta fiber innervation that extends a short distance into the dentinal tubules matrix interposed between the pulp chamber and the enamel covering of the tooth (reviewed in Burgess and colleagues[40]). Unmyelinated C fibers constitute the majority of pulpal innervation (50% to 75%); however, endings within the pulp chamber may be unmyelinated terminals of A-delta (myelinated) afferent fibers. Polymodal C fibers innervating the pulp chamber respond to thermal stimuli and, in particular, to inflammatory mediators including histamine and bradykinin, endogenous factors associated with pulp pathology. C fibers innervating the pulp chamber contain neuropeptides such as substance P and calcitonin gene-related peptide.[41] The peripheral release of these neuropeptides on C fiber activation produces local vasodilation, thus increasing the pressure within the rigid pulp chamber and further augmenting C fiber activation (i.e., peripheral sensitization). The release of substance P in infected teeth has been directly measured in human patients using microdialysis, and patients with irreversible pulpitis had significantly higher levels of substance P in the pulp chamber compared with noninfected teeth.[42] Although the release of neuropeptides augments pain, there is evidence that it may also reduce inflammation and promote recovery. In experiments with animals, eliminating the afferent terminal release of neuropeptides by denervating the teeth reduced wound healing after lesions were experimentally induced.[43]

Sharp pain is mediated by A-delta fibers extending 0.2 to 0.3 mm into the dentinal tubules encasing the pulp chamber.[44] These nerve fibers respond to heat, mechanical, and osmotic stimuli applied to the distal end of the dentinal tubules that become exposed to environmental stimuli when the enamel layer is breached.[45] Because the dentinal tubules are filled with a fluid, the fluid transmits mechanical, thermal, and osmotic stimuli to the proximal end of the dentinal tubules where the nerve endings are located. This "hydrodynamic" theory of dental pain has gained anatomic, physiologic, and psychophysical support and further offers an explanation of dentinal hypersensitivity. When the

dentinal tubules are exposed by a cavity or other lesion, patients report sharp pain in response to innocuous stimuli such as mild temperature or osmotic stimuli (e.g., sweet compounds). However, the theory predicts that if the tubules are covered, thus limiting exposure to environmental stimuli, stimulated pain should be reduced. This had been experimentally assessed in human volunteers in whom a small cavity in a tooth was prepared (in a tooth scheduled for removal) and a conical chamber positioned over the cavity through which regulated air pressure could be delivered.[46] Creating a smear layer of amorphous tooth particles in the cavity, or dissolving it away with solvents, controlled the interface between the exposed dentinal tubules and the air pressure stimulus. When the smear layer was intact, covering the dentinal tubules, it took more air pressure to induce the perception of sharp pain than when the smear layer was dissolved.

Central Projections of Trigeminal System

Afferent fibers of the trigeminal nerve enter the brainstem in the pons, bifurcate, and terminate in either the principal sensory nucleus or descend to terminate in the spinal trigeminal complex in the medulla. The bifurcation of the trigeminal nerve at the level of the pons reflects a tendency toward a segregation of function.[47] In general, low-threshold mechanoreceptors predominate in the principal trigeminal sensory nucleus, indicative of a tactile discriminative function. In contrast, considerable evidence implicates the subnucleus caudalis in orofacial pain mechanisms, and many neurons in the subnucleus caudalis respond to noxious stimuli applied to the head and neck.[11] These neurons include those specifically activated by noxious stimuli (nociceptive-specific neurons) and wide-dynamic-range neurons, responsive to both low- and high-intensity stimulation.

Because the receptive fields for many nociceptive neurons in the subnucleus caudalis are large and include responses to nociceptive stimuli applied to the masticatory muscles, tooth pulp, and temporomandibular joint, a role for these neurons in referred pain has been suggested.[48] Anatomic studies confirm that afferent fibers innervating the oral cavity, tooth pulp, oropharynx, temporomandibular joint, masticatory muscles, and superficial skin all converge in the subnucleus caudalis.[49,50] In many patients, lesions in mandibular teeth have a high likelihood of producing referred pain to the maxillary region, the cheek, and the ear, in addition to the mandible itself.[51] Likewise, lesions in the maxillary teeth are often referred to the mandible, as well as the maxilla, temple, and orbital region.

In addition to subnucleus caudalis, other parts of the sensory trigeminal complex are also involved in trigeminal pain. Nociceptive responses have been obtained from extensive areas of the sensory trigeminal complex, and destruction of the subnucleus caudalis does not prevent all trigeminal pain function (reviewed in Sessle[52]). Case studies of patients who have undergone trigeminal tractotomy for intractable pain associated with cancer are completely analgesic on the face, but pulpal pain is intact.[52] Likewise, when the principal trigeminal nucleus and subnucleus oralis were damaged after a stroke, oral and perioral pain sensitivity was diminished, as well as normal tactile sensitivity from these structures.[53]

Neurons in both the rostral sensory trigeminal complex (subnucleus oralis) and the subnucleus caudalis may also form a substrate for "central sensitization" in which central neurons in the pain pathway have their response characteristics magnified as a result of peripheral stimulation.[54] These changes can last a variable amount of time and potentially contribute to both short-term hyperalgesia and long-term chronic pain. Fundamental to the concept of central sensitization is that neurons initially only responsive to high-threshold (nociceptor) input become responsive to low-threshold, non-nociceptive input. The increased responsiveness is thought to be mediated by A-β (non-nociceptive) input that only becomes functionally active after intense peripheral nociceptor input. One neural mechanism for the nascent response to non-nociceptive input has been studied in great detail. An intense afferent barrage of nociceptor input, following peripheral tissue damage or inflammation, "sensitizes" a central neuron via structural modification of an *N*-methyl-D-aspartate (NMDA) glutamate receptor. NMDA receptors are voltage sensitive and will not pass current, even in the presence of a ligand, unless the cell is sufficiently depolarized. The central release of a neuropeptide (e.g., substance P) by nociceptor afferents, however, may provide sufficient depolarization to modify NMDA glutamate receptors via intracellular signaling pathways, thereby allowing glutamate released by non-nociceptive (A-β) input to activate central neurons. A-β activation of a central nociceptor thus provides a neural mechanism for allodynia. Similar mechanisms have been demonstrated in the brainstem sensory trigeminal complex and may provide a substrate for chronic oral and facial pain.[11] Experimental studies demonstrate that neuropharmacologically blocking NMDA receptors prevents temporomandibular joint or tooth pulp afferents from inducing hyperactivity in central trigeminal neurons (i.e., central sensitization).[55,56]

Somatosensory information reaches the ventrobasal complex of the thalamus from all major subdivisions of the trigeminal sensory complex.[11] Many cells in the ventrobasal complex respond to low-intensity stimulation, indicative of a tactile discriminatory function; however, other neurons require high-intensity stimulation. The small receptive fields of both types of neurons suggest a role in localization. Other nuclei, including the posterior thalamic nuclei and the nucleus submedius, respond preferentially to high-intensity stimulation and may be involved in affective components of pain.[57] Both nociceptive and non-nociceptive trigeminally activated neurons from the thalamus project to the somatosensory cortex. Electrophysiologic mapping studies in primates indicate a complex, sometimes discontinuous somatotopic map of the facial and oral region.[58] In general, the face is represented medially on the cortical surface adjacent to the representation of the hand, with successively lateral representations of the teeth and tongue. Magnetic resonance imaging (MRI) in humans confirms this somatotopic representation.[59]

Motor Function

Oral motor functions include mastication, swallowing, respiration, and vocalization. This review will focus on mastication and the oral components of swallowing and respiration. One of the dominant concepts in oral motor physiology is central pattern generation. Chewing, swallowing, and breathing are each produced by brainstem central pattern generators that control the fundamental rate and pattern of muscle contractions that define each function. Although sensory pathways from the mouth play an intimate role in oral motor function, fundamental to the concept of central pattern generation is that afferent activity is not necessary to evoke rhythmic activity and does not provide the critical timing information for coordinated motor output.[60] Although organized in the brainstem, central pattern generators for chewing, swallowing, and respiration are influenced by descending inputs from virtually all major regions of the neuraxis. Detailed reviews of oromotor central pattern generation can be found in works by Nakamura and Katakura,[61] Rekling and Feldman,[62] and Jean.[3]

Fundamental to oral motor function is the complex interplay between behaviors competing for the same muscles. Chewing, swallowing, and respiration all require the coordinated activity of masticatory, lingual, facial, and infrahyoid muscles. Swallowing and respiration further depend on pharyngeal and abdominal muscles. Motor coordination takes place on multiple levels. At a behavioral or molar level, swallowing and respiration must be coordinated to prevent aspiration of food into the airway. How this coordination is achieved is only beginning to be understood but likely involves both interactions between central pattern generators and peripheral feedback. However, individual oral motor functions also require a high level of coordination. Bolus formation during mastication requires the coordinated activity of masticatory, lingual, and facial muscles, muscles innervated by motoneuron groups highly segregated in the brainstem. Although the jaws and tongue can function independently,[63] oftentimes the tongue and jaw appear inextricably "linked."[64,65] The nature of this linkage, and whether it relies on interactions between central pattern generators, reflex control, or peripheral mechanical linkage, represents a significant problem in oral motor control.

In addition to the complexity of coordination between functions and coordination between motor groups, another level of complexity in oral motor control can be found within the muscles themselves. Individual masticatory and lingual muscles are not homogeneously

functioning units; muscles are oftentimes composed of multiple compartments, with muscle fibers oriented in multiple directions. Thus different parts of a muscle can be more or less active during a given behavior.[66] Further adding to the complexity of oral musculature are the multiple isoforms of myosin heavy chain (MHC) proteins that form the contractile elements of the muscle fibers. The differential distribution of MHCs within different muscles and muscle compartments imparts additional degrees of freedom to motor output.

A myriad of "simpler" oral reflexes serve protective functions and contribute to complex rhythmic output. Muscle spindles in jaw-closer muscles, for example, may contribute to load regulation during chewing, and oral reflexes may assist coordination between the jaw and tongue. Autonomic oral reflexes modulate salivation and initiate digestive processes. Several recent reviews of oral reflex function are available.[63,67,68]

Muscles of Mastication and Reflex Control

The muscles of mastication can be divided into jaw openers and jaw closers. However, human jaw movement is more complex, even during stereotyped rhythmic mastication. During opening, the jaw translates forward; during closing it translates backward.[69,70] A given muscle is not isomorphic with a single movement. The masseter, temporalis, medial pterygoid, and superior head of the lateral pterygoid muscle have major jaw-closing (mandible elevation) functions, but contraction of the masseter and lateral pterygoid protrude the mandible, whereas contraction of the temporalis muscle retracts the mandible. Contraction of the anterior belly of the digastric opens retrudes the jaw; contraction of the inferior head of the lateral pterygoid lowers and laterally directs the mandible. Contraction of the mylohyoid muscle also depresses the mandible, as does contraction of the geniohyoid muscle, a muscle innervated by the hypoglossal nucleus.

Individual muscle fibers are physiologically classified as slow (S), fast fatigue resistant (FR), or fast fatigable (FF) and correlate to a high degree with specific isoforms of MHC contractile proteins.[71] Thus S fibers express the MHC-I isoform, FR units express the MHC-IIA isoform, and FF units express the MHC-IIB isoform. Individual fibers frequently contain more than one MHC isoform (i.e., hybrid isoforms),[72] and overall, masticatory muscles contain a larger proportion of hybrid isoforms compared with limb and trunk muscles.[73] Moreover, masticatory muscles express MHC isoforms not found in the limb and trunk, specifically MHC-fetal and MHC-cardiac-α. Thus muscle fibers in jaw-closing muscles (masseter, temporalis, and pterygoid) include numerous hybrids that expressed MHC-I combined with MHC-fetal and MHC-cardiac-α. Muscle fibers in jaw-opening muscles differ from their jaw-closing counterparts.[73] Overall, jaw-opening muscles have fewer hybrid fibers and a different distribution and relative weighting of the constitutive isoforms. In the anterior (and posterior) belly of the digastric, mylohyoid, and geniohyoid muscles, there were less MHC-I, MHC-fetal, and MHC-cardiac-α compared with jaw-closing muscles, but more MHC-IIA. The presence of both MHC-fetal and MHC-cardiac-α isoforms may reflect developmental factors, but functionally, hybrid isoforms confer intermediate contraction speeds and thus greater flexibility in motor output.[71]

Differences in MHC isoform reflect different motor demands on jaw-opening and jaw-closing muscles. The preponderance of slow and hybrid fiber isoforms in jaw-closing muscles reflects a muscle that contracts slowly and requires flexibility against a load during mastication. In contrast, jaw opening is more ballistic and does not normally work against a load. Even the relative distribution of MHC isoforms in different muscle compartments reflects functional specialization. Jaw-closing muscles that are particularly active during mastication (e.g., the anterior temporalis and the deep masseter muscles) have more MHC-I fibers than the posterior temporalis and the superficial masseter, which are less active. The cross-sectional size of individual masticatory motor units also imparts additional degrees of freedom in muscle control. Individual efferent axons from the motor trigeminal nucleus innervate a relatively small area of the target muscle, on the order of 5%, compared with innervation patterns of the limb and trunk, which are much greater.[71] Small cross-sectional innervation patterns allow specific areas of a muscle to be differentially controlled.

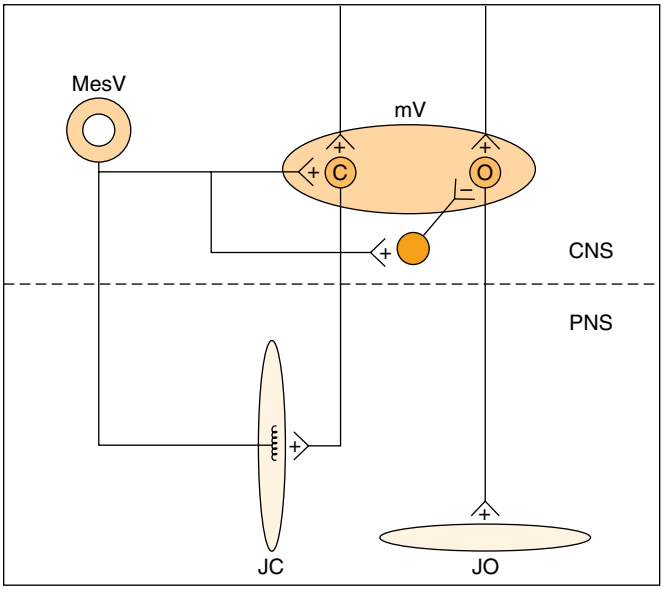

Figure 89-4. Circuit diagram for jaw-closing and unloading reflexes. Mesencephalic neurons innervate muscle spindles in jaw-closer neurons and monosynaptically excite jaw-closer motoneurons and interneurons with inhibitory connections to jaw-opener motoneurons. C, closer motoneuron; JC, jaw-closer muscle; JO, jaw-opener muscle; MesV, mesencephalic trigeminal nucleus; mV, motor trigeminal nucleus. *(From Orchardson R, Cadden SW. Mastication. In: Linden RWA, ed.* The Scientific Basis of Eating. *Basal, Switzerland: Karger; 1998.)*

Jaw-opener and jaw-closer muscles differ in their investment with muscle spindles, and hence reflex function. Muscle spindles, found only in jaw-closer muscles, are involved in multiple reflexes.[68,74,75] A "jaw-jerk" reflex that elevates the mandible (jaw-closing) can be elicited by a rapid depression of the mandible (i.e., tapping on the chin). This reflex, analogous to the patellar knee reflex, is mediated by muscle spindle afferents that respond to the rapid stretching of jaw-closing muscles and monosynaptically excite jaw-closing motoneurons. During mastication, these muscle spindle afferents potentially play an important role. During jaw closing against a food bolus, resistance to the load results in intrafusal fibers in the spindle that are (momentarily) shorter than the extrafusal motor fibers in which they are embedded. The consequent stretch of the spindle afferent adds excitatory drive to closer motoneurons, thus compensating for the load. This reflex action is termed the jaw-closing reflex.[75]

Muscle spindle afferents can also mediate a protective unloading reflex. When the jaws unexpectedly break through hard or brittle food, the rapid downward movement differentially shortens the extrafusal fibers compared with the intrafusal fibers, and muscle spindle afferent activity is decreased, thus producing a "silent period" in the jaw-closer muscle that limits excessive, potentially damaging forces directed against the teeth. These muscle spindle afferents can also indirectly potentiate jaw-opening during the unloading reflex through indirect, polysynaptic pathways. In addition to a monosynaptic excitatory synapse on jaw-closing motoneurons, these afferents can inhibit jaw-opening motoneurons through an inhibitory interneuron (Fig. 89-4). Thus during the jaw-closing phase of mastication, if there is concurrent excitation to jaw-opener motoneurons from a central pattern generator, jaw opening could be disinhibited by a lack of muscle spindle afferent input during unloading, thereby allowing the background excitation to dominate jaw-opener motoneuron activity. Damaging occlusal forces would thus be mitigated by a simultaneous lack of excitation to jaw closers and released excitation to jaw openers (see Fig. 89-4). The cell bodies for muscle spindle afferent fibers are located centrally in the mesencephalic trigeminal nucleus. Monosynaptic projections to jaw-closer motoneurons are well characterized; however, the location of inhibitory interneurons to jaw-opener motoneurons is more speculative.[76]

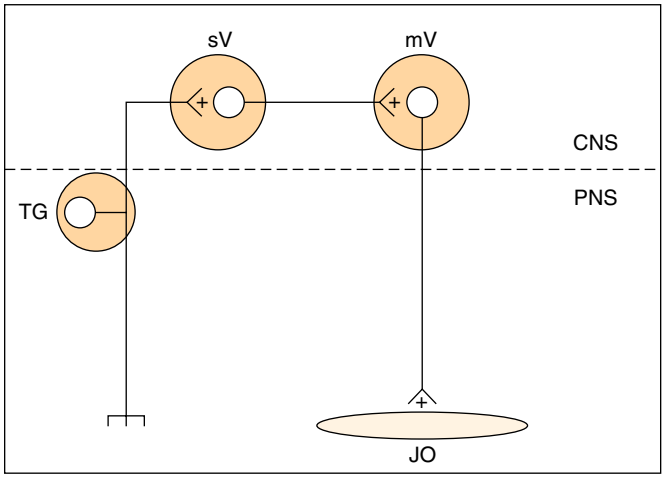

Figure 89-5. Circuit diagram for jaw-opening reflex. Nociceptor (and non-nociceptor) afferents in oral mucosa, muscle, and ligament terminate on interneurons in the sensory trigeminal complex to form a disynaptic pathway to jaw-opener motor trigeminal neurons. JO, jaw-opener muscle; mV, motor trigeminal nucleus; sV, sensory trigeminal nuclei; TG, trigeminal ganglion. *(From Orchardson R, Cadden SW. Mastication. In: Linden RWA, ed.* The Scientific Basis of Eating. *Basal, Switzerland: Karger; 1998.)*

Jaw-opening muscles do not have muscle spindles; thus during the jaw-closing phase of mastication, the corresponding lengthening of the jaw-opener muscles does not itself provide an afferent signal for a reciprocal reflex. However, stimulation of mechanoreceptors located in the PDL, tongue, and other soft tissues of the mouth can initiate reflexive jaw opening, at least in many nonprimate mammals.[68,74,75] The jaw-opening reflex is, at a minimum, disynaptic through neurons in the trigeminal sensory complex and may well involve additional interneurons (Fig. 89-5). Although the reflex can be elicited by non-noxious stimulation, it is generally thought to serve a protective function by protecting soft tissues (e.g., the tongue) against potentially damaging occlusal forces. The existence of a jaw-opening reflex in humans is still in doubt. Although it cannot be as readily demonstrated with sensory stimuli sufficient to produce it in experimental animals, robust electrical stimulation delivered to the upper lip produces electromyographic (EMG) activity in the anterior digastric muscle of humans.[76] It is of long latency, consistent with a polysynaptic substrate as suggested by animal studies.

Lingual Muscles and Reflexes

The tongue is composed of both intrinsic and extrinsic muscles innervated by the hypoglossal nerve (reviewed in Travers[77]). Extrinsic lingual muscles include the major tongue protruder muscle, genioglossus, major tongue retractor muscles, styloglossus and hyoglossus, as well as palatoglossus muscle. Intrinsic muscles of the tongue consist of the vertical, transverse, superior, and inferior longitudinal muscles. The geniohyoid often functions with the lingual muscles during tongue protrusion.[78,79] Most lingual movements involve both extrinsic and intrinsic muscles. The hydrostatic model of lingual function, in which the tongue is modeled as a closed bag, postulates that during tongue protrusion by contraction of the extrinsic genioglossus and geniohyoid muscles, the tongue is further lengthened by the simultaneous contraction of the intrinsic vertical and horizontal intrinsic muscles.[80] Likewise, shortening of the tongue during retraction is augmented by contraction of the longitudinal muscles together with the extrinsic hyoglossus and styloglossus muscles. Coactivation of different combinations of intrinsic muscles can curl or deviate the tongue.

Expression of different MHC isoforms varies across different human lingual muscles.[73,81,82] Intrinsic muscles of the anterior tongue have a large proportion of type MHC-IIA fast fibers in contrast to the posterior tongue, in which MHC-I (slow) and hybrid MHCs predominate. The geniohyoid, as with other suprahyoid muscles, has a large proportion of MHC-I fibers. The distribution of type II (fast) fibers in the anterior tongue is consistent with a role in fast, flexible movements compared with posterior tongue activity.

Although lingual muscles contain muscle spindles,[63,83,84] it is unclear whether there are any monosynaptic inputs from sensory afferents onto hypoglossal motoneurons (reviewed in Travers[77]). Rather, muscle spindle afferents travel in the ansa cervicalis and hypoglossal nerve and terminate in either the sensory trigeminal complex or the nucleus of the solitary tract. Electrical stimulation of the hypoglossal nerve elicits synaptic responses in hypoglossal motoneurons, as well as facial[85] and trigeminal motoneurons.[86] Lingual reflexes can also be elicited by stimulation of virtually any of the afferent nerves innervating the oral cavity. Depending on the site of stimulation, either a protrusive or retractive movement of the tongue is produced. An overview by Lowe[87] on the clinical significance of lingual reflexes emphasizes a protective role, either for the tongue itself during mastication or for the airway during swallowing.

Compounding the complexity of interpreting lingual reflexes are observations that reflex excitation of the tongue rarely influences a single lingual muscle, and contraction of a single lingual muscle can move the tongue in more than one plane.[88] For example, although a primarily retrusive movement of the tongue is produced by electrical stimulation of the lingual nerve, both protruder and retractor hypoglossal motoneurons are excited. Electrical stimulation of the glossopharyngeal nerve that innervates mechanoreceptors on the posterior aspect of the tongue and oropharynx also elicits tongue movement. Similar to the lingual nerve, stimulation of the glossopharyngeal nerve excites both protruder and retractor motoneurons, and the movement of the tongue is primarily retrusive. The simultaneous activation of the glossopharyngeal nerve afferent fibers by electrical stimulation, however, may mask a more complex reflex organization. Lowe has suggested that stimulation of lingual receptors innervated by the glossopharyngeal nerve elicits a primarily retrusive movement of the tongue, in contrast to the lingual protrusion produced by stimulating pharyngeal regions innervated by the glossopharyngeal nerve.[63] Thus both lingual and glossopharyngeal reflexes may protect the tongue during the occlusal phase of mastication with a retrusive movement.

In contrast, electrical stimulation of the superior laryngeal nerve that innervates laryngeal mechanoreceptors depolarizes protruder motoneurons and produces a protrusive action of the tongue. Thus mechanoreceptors in the oropharynx and larynx innervated by the superior laryngeal and the glossopharyngeal nerve may preserve airway patency during a swallow with a protrusive tongue movement. Lingual reflexes also play a protective role in respiration. When normal respiration is impeded by hypoxia, a normal breathing pattern, eupnoea, is replaced by gasps.[88,89] Gasps are associated with the coactivation of lingual protruder and retractor muscles that enlarge the upper airway.[90-92]

Jaw-Tongue Reflexes

Oromotor reflexes can involve multiple motor systems. Electrical stimulation of either the masseteric or anterior digastric nerves, for example, suppresses genioglossus activity, suggesting that proprioceptive or nociceptive signals from the trigeminal musculature inhibit lingual protrusion.[93] In contrast, passively depressing the mandible (in cats) excites the genioglossus muscle, suggesting that lingual protrusion may be reflexively assisted during jaw opening when the tongue is not subject to occlusal force.[94] Further evidence that masticatory muscle proprioceptive afferents influence hypoglossal motoneuron activity comes from experimental lesions of Probst's tract. Ishiwata and colleagues[95] showed that such lesions, which destroy descending mesencephalic projections, suppressed hypoglossal activity induced by passive jaw opening but left intact hypoglossal activity induced by stimulating a cutaneous oral sensory nerve. A jaw-tongue reflex in humans may also be mediated by masticatory muscle proprioceptive afferents.[96] Stimulation of the hypoglossal nerve, which contains some afferent fibers, inhibited the masseteric (jaw-closing) reflex.[86]

Autonomic Reflexes

In addition to somatomotor reflexes, stimulation of the oral cavity elicits numerous autonomic responses. Gustatory and mechanical

stimuli are highly effective in eliciting the flow of saliva during mastication.[97] The stimulation of receptors in the PDL may be one source for reflex salivation. In both rabbits and humans, there is a high correlation between parotid flow and mandibular movement, especially on the working, ipsilateral side. In humans, selective anesthetization of the nerves innervating the PDL significantly reduced the amount of saliva elicited from crushing a food stimulus held between the teeth.[98]

Both location and stimulus modality influence the release of saliva.[97,99] Stimulating the anterior part of the tongue is most effective for evoking salivation from the sublingual and submandibular glands, but posterior tongue stimulation is more effective for producing parotid gland flow. Aversive gustatory stimuli such as (sour) acids or (bitter) quinine hydrochloride are more effective for eliciting saliva than stimulation with weak salt or sucrose solutions. In animal experiments, sweet stimuli were the most effective stimuli for the release of the enzyme amylase from the parotid gland.[100]

Mechanical and chemical stimulation of the oral cavity also initiate the release of digestive enzymes. These cephalic phase responses include the release of gastric acid, insulin, glucagon, and pancreatic polypeptide.[101,102] An increase in gastric motility and emptying of the gallbladder also occurs. Although cephalic phase insulin release (CPIR) is a highly variable response not occurring in all individuals, insulin levels rise, on average, 25% above baseline within 2 minutes of oral stimulation. This release is neurally mediated because it does not occur in the absence of an intact vagus nerve.[103] In animal studies, sweet stimuli—particularly glucose—are most effective in triggering CPIR,[104,105] but are somewhat less effective in humans (discussed by Teff[102]). Rather, "palatable" stimuli appear more effective in general. Although cephalic phase insulin release accounts for perhaps only 1% of the total insulin release associated with a meal, this amount underestimates its potential importance in glucose metabolism. Experimental studies in which CPIR is bypassed by intragastric infusions can result in both hyperinsulinemia and hyperglycemia.[106,107] One possible mechanism for this is that vagally mediated insulin release acts as a signal on hepatic receptors to further regulate glucose metabolism; that is, it is acting as a signal to initiate metabolic events rather than simply to convert glucose.[102] Other cephalic phase responses represent larger fractions of total meal responses. In humans, cephalic phase gastric acid secretion can reach 50% of total meal release, antral motor activity can reach 70% of that achieved during a meal, and gallbladder emptying can reach 50%.[101]

Although cognitive factors and other sensory stimuli such as sight and sound can elicit cephalic phase responses, oral stimuli are usually the most effective. Oral stimuli signals carried by the gustatory and trigeminal nerves influence preganglionic parasympathetic vagal neurons located in the dorsal motor nucleus of the vagus.[108] Oropharyngeal receptors innervated by the superior laryngeal nerve may also influence digestive functions.[108] There is increased diuresis in response to drinking a saline solution as compared with the intragastric infusion of the same volume of fluid.[109]

Mastication

The orosensory apparatus of the mouth and perioral region is an integral part of the regulation of food and fluid intake. In general, the sensory receptors in the mouth are specialized for the consummatory phase of ingestion and play an important role in the sensory evaluation of food and in the sensory control of mastication and deglutition.

Food consumption through the oral cavity can be characterized as a series of stages or phases (Fig. 89-6). Different stages of ingestion have been defined by placing small metal markers in the jaws, hyoid, and tongue. These markers can be detected with high-speed cinefluorographic techniques, allowing the movements of the internal oral apparatus to be monitored during the entire ingestive sequence of the awake preparation. The division of feeding into five dynamic stages by Hiiemae and Crompton[64] is indicated on the second tier of Figure 89-6. The first stage of putting food into the mouth (ingestion) is followed by intraoral transport and the positioning of food between the molars (second stage) for mastication (third stage). Intraoral transport to the back of the tongue (fourth stage) initiates deglutition (fifth stage). The duration of each stage of feeding is highly species specific and variable, depending on what is being ingested. Fluid consumption does not require mechanical breakdown by mastication and thus has only three stages. In humans, drinking uses the same muscles as mastication, but the coupling among the facial, trigeminal, and lingual muscles is different. The orbicularis oris muscle contracts to form a tight seal during human drinking (sucking) but relaxes during mastication.

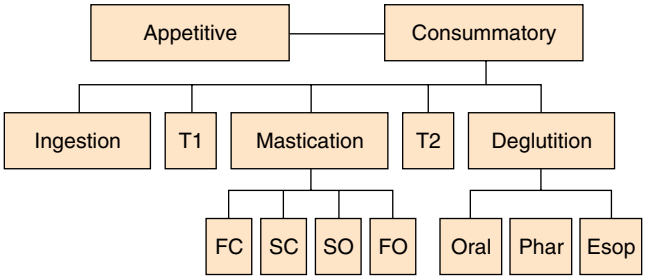

Figure 89-6. Schematic representation of different stages and substages of ingestive sequence. T1 and T2, first and second intraoral transfer; FC, fast closure; SC, slow closure; SO, slow open; FO, fast open.

The movements of mastication can be further subdivided. Kinematic measurements during mastication indicate that rhythmic masticatory movements of solid food typically involve several distinct components.[110,111] Beginning the masticatory cycle with an open mandible, the jaw closes rapidly and then more slowly. The transition from fast closure to slow closure occurs when the teeth make contact with solid food and is thought to involve sensory feedback from the PDL. More detailed analysis of the opening phase of mastication indicates additional complexity. After the slow-closure phase, when the teeth make maximal intercuspation, the masticatory cycle continues with a slow-opening phase followed by a fast-opening phase.

Feeding sequences analyzed using combined sirognathography and electromyography or video-fluorography present a modified picture of the human ingestive sequence.[112,113] Human jaw movements associated with eating natural foods do not show obvious changes in the rate of opening and closing during rhythmic mastication. Thus the stages of fast closing, slow closing, and slow opening were not evident as in animal studies. Nevertheless, the ingestive sequence could be divided into three stages, beginning with biting and transport of the bolus to the molars, chewing, and "clearance" (swallowing). A distinct stage from chewing to bolus formation for swallowing was not obvious, and swallowing occurred during mastication and as a terminal event.

Although mastication involves coordinated activity of the jaws, hyoid apparatus, and tongue,[64] the majority of electromyographic studies of mastication have focused on the jaw musculature. Jaw opening during mastication is associated with activity in the anterior digastric muscles and the inferior head of the lateral pterygoid muscle.[111,114] The closing phase of mastication begins with contraction of the masseter muscle, followed by the temporalis, medial pterygoid, and superior head of the pterygoid, which are recruited during the power stroke (slow closure). Food is typically chewed unilaterally. Although the trigeminal musculature is bilaterally activated during mastication, the ipsilateral (working) side is active earlier.

Food consistency is one factor affecting the masticatory rhythm. In a study of the effects of hardness on chewing, Plesh and colleagues[115] observed that most subjects chewed hard gum at a slightly slower rate than soft gum. The decreased frequency of chewing was associated with significantly longer opening and occlusal phases of chewing rather than with the closing phase, despite the significantly greater EMG activity in the masseter muscle. Age is another factor that affects the masticatory rhythm.[116] Older subjects chewed at the same frequency as younger subjects (approximately 1.4 Hz), but the structure of the rhythm was different. The older subjects opened and closed their mouths at a slower velocity but achieved the same overall chewing rate by not opening their mouths as far. Movement irregularities during chewing were also observed during the jaw-opening and jaw-closing phases of mastication in patients diagnosed with temporomandibular pain.[117] Unlike the smooth, uninterrupted alteration between opening and closing seen in

healthy persons, patients with temporomandibular pain frequently started reopening their mouths during the closing phase of mastication or reclosed during the opening phase.

Experimental studies indicate that the masticatory rhythm is centrally programmed; that is, a peripheral stimulus is not necessary to initiate the masticatory rhythm, nor is feedback from the active muscles necessary to sustain the response.[114] Fictive mastication evoked by central stimulation in a paralyzed experimental preparation indicates that neither the afferent limb of the jaw-opening reflex nor that of the jaw-closing reflex is necessary to generate the masticatory rhythm. Thus the alternating activation of a jaw-opening reflex followed by a jaw-closing reflex does not explain the origins of the masticatory rhythm.

Nevertheless, both the jaw-opening and jaw-closing reflexes are functionally entwined in rhythmic oral behavior, and the excitability of these reflexes varies as a function of jaw position during rhythmic opening and closing.[118] In general, the jaw-opening reflex is attenuated during rhythmic masticatory movements as compared with a stationary mandible. In particular, low-threshold mechanical stimuli are less effective than high-threshold stimuli in producing a jaw-opening reflex when applied during rhythmic masticatory movements. Thus during the occlusal phase of mastication, a protective jaw-opening reflex can be initiated in the presence of unexpected mechanical forces directed against the teeth or soft tissues, but innocuous mechanical stimulation associated with chewing will not interrupt the masticatory rhythm.

Transection studies relying on electrical stimulation to induce fictive jaw movements localized the central pattern generator for mastication to the medial core of the reticular formation. More recent studies using reversible pharmacologic lesion techniques in awake, freely moving (feeding) animal preparations indicate that a necessary substrate for rhythmic lingual/masticatory movements is in the lateral reticular formation in a region overlapping with substantial populations of preoromotor interneurons.[119,120] This region of the brainstem reticular formation is also the target of descending projections from metabolic integrative substrates in the hypothalamus and from the motor cortex.[61,121]

Although the basic neural circuitry necessary for the rhythmic alternating contraction of jaw-opening and jaw-closing muscles does not require sensory input, intraoral sensory receptors are critical for regulating bite force during mastication. Efficient eating requires that food be reduced in size for swallowing. This requires determining both the hardness and size of the food and correctly positioning food between the occlusal surfaces of teeth. Psychophysical studies in humans indicate that receptors in both the PDL and the temporomandibular joint contribute to the interdental discrimination required during eating.[2] The loss of PDL receptors associated with complete dentures results in impaired interdental discrimination, as does anesthetization of the dentition in individuals with natural teeth. Receptors in the temporomandibular joint also contribute to size discrimination in the mouth. When the temporomandibular joint is anesthetized, interdental discrimination decreases.

Oral Phase of Deglutition

After mastication and the intraoral transport of food to the back of the tongue, deglutition is initiated. The oral phase of deglutition consists of an upward movement of the tongue against the soft palate to force the bolus in the direction of the pharynx.[3,4] The precise nature of the stimulus that triggers the pharyngeal stage of deglutition is unknown. Both the volume and the rate of bolus accumulation interact to trigger swallows in experimental animals.[122] When the rate of licking (intraoral transport) increased in response to increased stimulus delivery, the volume per swallow also increased. Moreover, the physical nature of the bolus can influence the sequence and recruitment of individual muscles involved in the buccal phase of swallowing. In monkeys, the masseter muscle was recruited with the suprahyoid muscles (the anterior digastric, geniohyoid, and mylohyoid) during swallows of solid food, in contrast to fluid swallows.[123] Similarly, there is individual variation in the activation sequence of the suprahyoid muscles and the genioglossus muscle during voluntary swallows in humans.[124] In summary, the overall movement of a bolus from the dorsal surface of the posterior tongue to the pharynx characterizes the oral phase of swallowing. The precise motor sequence of individual muscles during the oral phase of deglutition can vary, depending on both the individual and sensory characteristics of the bolus. Contact of the bolus with sensory receptors in the oropharynx triggers peristaltic contractions of the pharyngeal musculature.

Like mastication, swallowing can be evoked from electrical stimulation of central structures in the absence of peripheral (muscular) feedback and is thus thought to be controlled by a central pattern generator.[3,4] The location of the central pattern generator for swallowing involves the caudal region of the nucleus of the solitary tract and the medullary reticular formation adjacent to the nucleus ambiguus. Cortical pathways that reach these medullary regions through descending pathways mediate voluntary swallowing.

Swallowing takes precedence over both respiration and mastication, causing a brief disruption of rhythm. Respiratory apnea associated with swallowing shows considerable variation across individuals, in one study ranging from 0.61 to 3.83 seconds.[125] For some individuals, the apneic period increases with the volume swallowed; for others it decreases. Spontaneous swallows tend to be associated with a shorter apneic period.[126] Swallows do not occur randomly throughout respiration. Rather, the majority of swallows occur during expiration or late inspiration and subsequently reset the respiratory rhythm (i.e., there is no modification of the postswallow rhythm to compensate for the swallow-induced apnea).[126] Sensory information from the oropharynx could reach the central pattern generator for respiration via the nucleus of the solitary tract to mediate adaptability of the respiratory rhythm to bolus size.[125] Alternatively, oropharyngeal afferents could influence the central deglutition substrate to modify respiration[126]; that is, there could be an interaction between central pattern generators for respiration and swallowing.[127]

Although swallowing affects the masticatory and licking rhythm in animals, it has only a minimal effect on human mastication.[128,129] Swallows most often occur during the early jaw opening phase of mastication and significantly prolong the masticatory cycle. In rodents, the prolonged lick cycle associated with a swallow equals the increased duration of tongue protrudor and retractor muscle contractions; that is, the increased cycle duration was used to accommodate the participation of the tongue in swallowing.[79] In addition to interactions between swallowing and mastication, there are also interactions between respiration and mastication. In general, mastication increases respiratory rate while at the same time decreases inspiratory and expiratory time.[129] In addition to possible metabolic demands of mastication on respiration (i.e., physical exertion), mastication can increase upper airway resistance by more closely apposing the tongue with the palate. In humans, there is a small but significant tendency for inspiration to occur during masticatory jaw opening.[128]

Specialized Sensory Systems: Taste

Gustatory Sensitivity

In contrast to the common chemical sense, taste sensations are evoked by relatively low concentrations of chemical stimuli when applied to the specialized gustatory receptor cells. Most investigators agree that there are a discrete number of taste sensations; the most common and easily recognizable are sweet, salty, sour, and bitter. Some contend that there is a fifth taste, umami (heavenly), associated with the taste of monosodium glutamate.[130] The sensations of flavor while eating are more diverse than those of pure taste and result from the interaction of taste with the smell and texture of food. The confusion between taste and flavor is well documented in taste and smell clinics. Self-reports of chemosensory dysfunction are highly unreliable; on testing, many individuals reporting loss of taste are frequently found to have impaired olfactory function with no loss in taste sensitivity.[131]

In addition to a sensory-quality dimension with four distinct tastes, taste stimuli can be categorized on a hedonic dimension with stimuli divided into those that are preferred and those that are disliked. The hedonic attribute of taste is concentration dependent and spans the different submodalities of sweet, sour, salty, and bitter. Low and medium concentrations of salt are preferred, but salt becomes aversive at high concentrations. Although there is a strong genetic component

to the hedonic values associated with gustatory stimuli, taste preferences are clearly modifiable by experience.[132] Human neonates find bitter solutions strongly aversive, but adults learn to enjoy coffee, alcohol, and other bitter-tasting substances. The hedonic attributes of taste are also subject to metabolic state.

Gustatory Structures

Approximately 7900 gustatory receptors in the human mouth are grouped into distinct subpopulations, defined by their intraoral location, gross morphology, and innervation.[133] Gustatory subpopulations differ in sensitivity to chemical stimuli; however, the overall morphology of the taste bud structure within each subpopulation is similar. Each taste bud contains 50 to 150 neuroepithelial cells arranged in spindle-like clusters. Some of the cells within the taste bud extend microvilli into a nonkeratinized "pore" region on the apical surface of the bud. Taste bud cells without microvilli occur both on the periphery of the bud (these are termed *marginal cells*) and at the base of the taste bud (designated basal cells).[134] Receptor cells die and are replaced over a 10- to 14-day period.[135] Marginal and basal cells may constitute replacement cells, but the lineage of replacement receptor cells within the taste bud remains controversial. Because taste cells undergo continuous differentiation, disruption of cell division by radiation or other agents can disrupt the sense of taste.

The chorda tympani branch of the facial nerve innervates two to five taste buds on each of approximately 400 fungiform papillae on the anterior aspect of the tongue.[136] Fungiform papillae density is greatest at the tip of the tongue and decreases along the dorsal and dorsolateral edges of the tongue. No fungiform papillae are found along the midline. Taste buds on the posterior aspect of the tongue are innervated by the glossopharyngeal nerve and located either in tightly packed clusters distributed along the walls of the trenches surrounding 7 to 10 circumvallate papillae or in the inner folds of the foliate papillae located along the lateral edges of the posterior part of the tongue. The 2400 taste buds in the circumvallate papillae and the 1300 taste buds in the foliate papillae constitute the largest percentage in the human oral cavity. A third large subpopulation of gustatory receptors located in the pharynx and larynx numbers approximately 2400 in humans. These taste buds are not associated with distinct papillae; however, the bud morphology is similar to that found on the tongue. Taste buds of the pharynx are innervated by the glossopharyngeal nerve, and the superior laryngeal nerve branch of the vagus innervates those in the larynx. A smaller subpopulation of taste buds (approximately 400 in humans) is found on the soft palate. These taste receptors, also not associated with distinct papillae, are innervated by the greater superficial petrosal nerve branch of the facial nerve. In rodent species, small populations of taste buds are also found on the buccal wall and the sublingual organ, but these have yet to be characterized in humans.[137]

The specific pattern of innervation of taste buds by a peripheral nerve has been characterized for the fungiform papillae on the front of the tongue. Single fibers of the chorda tympani nerve synapse on multiple receptor cells within a single taste bud and on receptor cells in adjacent taste buds.[138] Likewise, each receptor cell is innervated by more than one fiber of the chorda tympani nerve. Each fiber of the chorda tympani thus receives input from multiple receptor cells, and each bud is innervated by more than one fiber. This pattern of convergence of multiple receptor cells from adjacent taste buds onto a single afferent fiber provides an anatomic substrate for spatial interactions between adjacent taste buds. Successively lower perceptual thresholds in humans can be reached by stimulating multiple adjacent papillae with gustatory stimuli.[139]

Gustatory Physiology

A common observation in neurophysiologic studies of the gustatory system is that individual neural elements are usually sensitive to a variety of chemical stimuli. Receptor cells, afferent nerve fibers, and central neurons are often responsive to diverse chemical stimuli that elicit qualitatively different sensations in humans. The central issue in gustatory coding has been to determine how broadly responsive neurons code for such distinct sensations as sweet, salty, sour, and bitter. Recent work has focused on organizing gustatory neurons at different levels of the sensory pathway into neuron types.[99] Although many neurons are multiply sensitive to different-tasting stimuli, these sensitivities are not random. Neurons are not specifically tuned to a single stimulus, but typically respond best to one of the stimuli representing the four basic taste qualities. The representation (coding) of quality is thought to be mediated by comparison of activity across these classes of neurons.[140]

Gustatory Transduction

Discoveries made over the past 20 years and, in particular, in the brief time that has elapsed since the beginning of the 21st century, have shed remarkable light on the process by which chemical energy inherent in gustatory stimuli is transformed into cellular changes in the taste receptor cell. These studies on gustatory transduction have been the topic of several recent reviews.[8,141-144] Highlights and outstanding issues are emphasized here. Until the mid-1980s, hypotheses regarding gustatory transduction revolved around ill-defined interactions of taste stimuli with membrane-bound receptors. Molecular biologic studies of the past few years have revealed the chromosomal location and specific genetic sequence of receptors that transduce information about carbohydrates, artificial sweeteners, amino acids, and the diverse array of chemicals that humans describe as "bitter." All these receptors can be classified as G-protein-coupled receptors. Discoveries about these seven-transmembrane segment-spanning proteins have occurred rapidly, and though conforming in some ways to previous ideas, have revealed surprises and ignited controversies. However, well before molecular biologic investigations transformed the field, classic physiologic techniques revealed that one important ionic stimulus, Na^+, was transduced in part by transmembrane transport of the stimulus into the cell,[145] an event that would be expected to lead directly to depolarization.

The discovery of this mechanism was in conflict with prevailing ideas of stimulus-membrane interactions and the presumed impermeability of the receptor cell to its ligand.[146] Nevertheless, on the basis of the suppression of the peripheral nerve response to sodium salts after lingual application of amiloride across a variety of species, ranging from rodents (rat, gerbil, some mice) to primates (rhesus monkey, chimpanzee), a significant portion of the gustatory response to sodium salts appears to be due to entry of the sodium ions through amiloride-sensitive sodium channels located on the apical microvilli of taste receptor cells (reviewed by Halpern[147]). These sodium channels, which are epithelial Na^+ channels (EnaCs), resemble those found in a number of sodium-transporting epithelia such as kidney, lung, and colon (reviewed in Halpern[147] and Gilbertson and Margolskee.[8] In rodents, gustatory sodium transduction via ENaCs is reflected in the responses of particular subsets of primary afferent neurons, cells with relatively specific responses to sodium salts, as opposed to those cells with a broader sensitivity that extends to nonsodium salts and acids.[148]

In the rat, the amiloride-sensitive sodium channel has been demonstrated to be essential for behavioral discrimination of sodium from other salts,[149-151] but in the human, the significance of this transduction mechanism is not as clear. Although the overall intensity of NaCl is reduced by amiloride,[152] when subjects are asked to ascribe intensity ratings of NaCl to particular qualities, the main reductions in intensity are not in the "salty" taste per se but rather in the weaker "sour" taste that this stimulus elicits.[153,154] Thus although the ENaC channel is almost certainly present and operational in humans, it may have a more general function in detecting ionic stimuli than in rodents. Indeed, although sodium transduction via the amiloride-sensitive channel is widespread phylogenetically, in addition to the human there are other notable exceptions in which this mechanism appears less important (some mouse strains) or specific (dog).[96]

Further, although transduction via amiloride-sensitive channels plays an important role, not all sodium responsiveness, even in rodents, relies on this mechanism. A significant portion of the response to NaCl remains after blockade with amiloride, and therefore different transduction mechanisms must mediate the residual, amiloride-insensitive response. However, these mechanisms are not as well understood. Interaction with other apically located cation channels, as well as transport through the tight junctions of the taste bud to interact with basolateral ion channels, has been proposed. Importantly, the amiloride-insensitive mechanism(s) for sodium transduction is (are) not as specific for the

sodium cation as transduction via ENaC channels and thus is (are) generally believed to also explain responsiveness to nonsodium salts such as ammonium and potassium chloride (reviewed in Gilbertson and Margolskee[8]).

Transduction of the class of stimuli that taste sour to humans, namely organic and inorganic acids, is also not as well understood as the amiloride-sensitive mechanism for sodium. A variety of channels that exhibit responsiveness to or modulation by acids have been characterized and are suspected to have some function in taste tissue including members of the ENaC/degenerin superfamily, the acid-sensing channels, the mammalian degenerin-1 channel, and a group of hyperpolarization-activated channels that can be gated by cyclic nucleotides (HCN1 and HCN4) (reviewed in Gilbertson and Margolskee[8]). However, the contribution that these channels make to the transduction of acid stimuli in the taste system is not clear. An intriguing hypothesis regarding the "proximate" stimulus for acid transduction, however, has recently emerged. It has been proposed that taste cell responses to acids are a result of changes in intracellular pH caused directly by the entry of the acid stimulus into the receptor cell. Measurements of intracellular pH after stimulation with acids show systematic changes in intracellular pH that track concentration for a given acid. These changes are small, serving to keep the cell at a physiologic pH, but are highly reliable and explain a perplexing aspect of the perceptual characteristics of acids. Low pH is clearly the chemical feature that sour stimuli have in common and, for a given acid, sourness is a positive function of concentration and therefore pH. However, it has long been puzzling that, across acids, sourness is not correlated with pH. Rather, at a given pH, organic acids are much sourer. However, the intracellular measurements seem to solve this puzzle: sourness (and the magnitude of the chorda tympani response) is directly correlated with the intracellular drop in pH elicited by different acids. In the case of inorganic acids, hydrogen ions are proposed to enter the cell via ion channels, but organic acids enter the cells as electroneutral molecules by diffusing across the lipid bilayer and then are broken down by intracellular mechanisms.[155,156]

In contrast to simple ionic stimuli and acids, transduction of carbohydrates, amino acids, and bitter-tasting chemicals occurs via interactions of stimuli with distinct classes of G-protein-coupled receptors. In parallel with the diverse chemical substances that evoke the bitter quality, which include "… amino acids and peptides, flavonoids and terpenes, methylxanthines (caffeine), sulfimides (saccharin), ureas and thioureas (PTC, PROP), and organic and inorganic salts"[7] (referencing Rouseff[157]), transduction of bitter stimuli involves interaction with a large family of receptors, called T2Rs.[158,159] The identification of these receptors was aided by the sequencing of the human genome and genetic linkage studies in humans that localized variations in the threshold for a particular bitter substance, propylthiouracil, to a locus in chromosome 5.[160] The region identified by the linkage studies was screened, and this resulted in the identification of a family of candidate genes, arranged in groups in chromosome 5 and also in chromosomes 7 and 12, that encoded novel G-protein-coupled receptors. Homologous genes were identified in rodents. Additional investigation revealed that these genes showed a distant resemblance to chemosensory G-protein-coupled receptors found in the vomeronasal organ, as well as metabotropic receptors for the neurotransmitter, glutamate. Significantly, they are expressed specifically in taste buds.[158] Furthermore, the various T2R genes colocalized with each other and with a specific G-protein, "gustducin,"[158] which was already known to contribute to the ability of rodents to sense bitter stimuli.[161] The identification of naturally occurring variations in one T2R family member that correlated with the ability of different mouse strains to taste the bitter stimulus cycloheximide, along with heterologous expression experiments that conferred bitter responsiveness, provided compelling evidence that these genes code bitter receptors.[159] The large size of the gene family, the colocalization of the genes, and the specificity of responsiveness when heterologously expressed, prompted a hypothesis about the peripheral neural coding of the bitter quality—namely, the wide array of stimuli that humans perceive as bitter are likewise detected by a large number of distinct bitter receptors, each specifically tuned to particular substances but activating the same set of receptor cells.[159] However, fast on the heels of this proposal, a physiologic study using calcium imaging demonstrated that many individual taste receptor cells showed a high degree of specificity for particular bitter stimuli, suggesting that this simple hypothesis might not be adequate.[162]

Sweet stimuli and L-amino acids also are detected by a group of G-protein coupled receptors, termed T1Rs, although fewer distinct receptors appear to be involved. Both naturally sweet carbohydrates (i.e., mono- and disaccharides) and artificial sweeteners can be detected by a single receptor, a G-protein-coupled dimer of the subunits T1R2 and T1R3.[163] Interestingly, one mechanism for sensing amino acids involves one of these same subunits, T1R3, paired with a different one, T1R1.[164] A second amino acid taste receptor is a variant of the metabotropic glutamate receptor.[165,166] All of these receptors have been shown to be specifically localized to taste buds and to respond to appropriate ligands in heterologous expression systems, providing strong evidence for their gustatory function.

These discoveries about the molecular basis of taste transduction are all exciting, but the definition of receptors for amino acid stimuli may have a special significance for understanding taste function in mammals. Although it is widely agreed that the salty, sour, sweet, and bitter sensations represent distinct, fundamental gustatory qualities, the status of the amino acid taste has been more uncertain. Some have proposed that the taste evoked by certain amino acids, namely glutamate, especially in combination with nucleotide compounds like inosine monophosphate (IMP), evoke a unique umami sensation,[130] whereas others have considered the taste of amino acids to be a complex amalgam of the other qualities. The discovery of receptors for these stimuli has reawakened interest in this debate and led to more widespread acceptance of a "fifth basic quality."[83,164,167] However, it should be noted that even though specific receptors may detect such stimuli, this does not assure their independent status at higher levels of the gustatory system or as a perceptual quality. This issue is discussed later in "Central Gustatory Pathways and Function."

Although the T1, T2, and metabotropic glutamate receptors cover a broad spectrum of gustatory responsiveness, it is entirely possible that other receptors for bitter, sweet, and amino acid stimuli are yet to be discovered. There are currently no genetic knockouts for any of these receptors, which could assess the degree of their contribution to gustatory perception. In fact, other mechanisms have been proposed to contribute to bitter transduction. For example, quinine can directly block K^+ channels in taste receptor cells.[168] In addition, discrepancies between recent molecular findings and the much larger body of physiologic studies make it obvious that some of the seductively simple hypotheses about peripheral taste processing are probably not adequate. Questions about bitter processing were mentioned earlier. In addition, in situ hybridization studies demonstrate that T1 and T2 receptors are not colocalized within individual receptor cells (Fig. 89-7). These molecular findings suggest that entirely separate "labeled-lines" code for sweet, bitter, and amino acid stimuli at the most peripheral level of the taste system.[163] In contrast, physiologic studies of taste receptor cells using intracellular (reviewed by Herness[169]) and patch-clamp recording[170] or Ca^{2+} imaging[162] all suggest that, although individual taste bud cells are not equivalently responsive across taste qualities, they do exhibit at least some degree of broad tuning; in other words, they respond to more than a single quality (Fig. 89-8). The reason for the inconsistencies between the molecular biologic and the physiologic investigations is unclear, but the two types of studies give different pictures of taste quality coding by the most peripheral elements of the taste system.

Part of what complicates the interpretation of data on taste bud cells is how little is understood about processing within the bud itself. Aside from the obvious requirement that these cells must exhibit some degree of differential responsiveness across qualities, they also differ in several other characteristics. Importantly, only a fraction of the receptor cells have classic synapses onto the primary afferent nerve (reviewed by Witt and colleagues[134]). Because cells in the taste bud, like other epithelial cells, are in a constant state of turnover, it might be thought that the small number of cells with synapses merely reflect a small number of mature cells in the bud (i.e., cells without synapses are in the process of differentiating and thus can neither respond to taste

stimuli nor transmit information centrally). However, this simple explanation appears not to be true. None of the cells that express gustducin, a known element in bitter transduction, have classic synapses.[171] Thus the mechanism by which information from gustducin-containing, bitter-responsive cells reaches primary afferent neurons is mysterious. Perhaps these receptor cells communicate directly with primary afferent neurons using nonclassical synapses or first send information to other cells in the taste bud, which in turn, synapse with the primary afferent neuron. The possibility of intra-bud communication is bolstered by recent observations that taste bud cells contain and respond to a variety of neurotransmitters and peptides.[172,173] A recent molecular study[174] suggests that after receptor binding, downstream signaling events for bitter, sweet, and amino acid transduction all require the opening of a specific type of ion channel, the TRP channel. Animals in which the TRPm5 gene has been deleted show no evidence of responses to sweet, bitter, or amino acid stimuli, based either on recordings from the primary afferent nerves or behavioral responses to these stimuli.[174] These results are surprising because many other studies suggest that the downstream signaling events are much more heterogeneous (reviewed by Gilbertson and Margolskee[8]) and provide only limited evidence of TRP-mediated currents in response to taste stimuli in taste receptor cells.[175] A true appreciation of the logic of taste coding at the level of the receptor cell will clearly require a better understanding of the reasons for the discrepancies between the physiologic and molecular work and the nature of integrative processing in the taste bud–primary afferent nerve circuit.

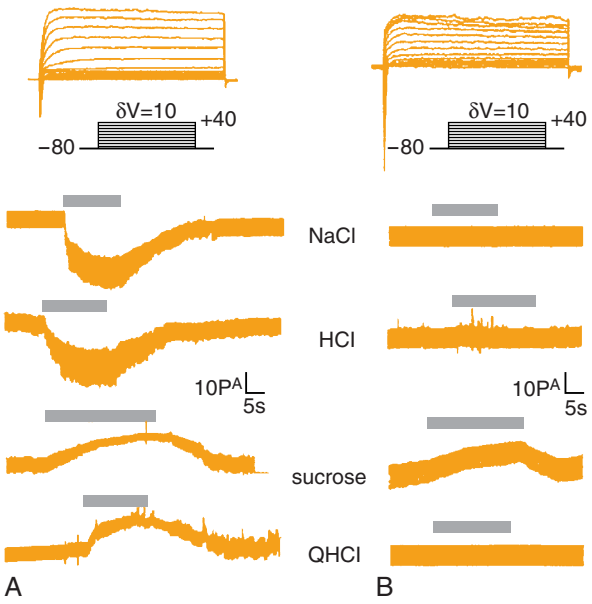

Figure 89-7. Patch-clamp recordings from two taste cells stimulated with four qualitatively different stimuli. The cell on the right **(B)** responds to just a single stimulus, but the cell on the left **(A)** responds to all four stimuli. The molecular data such as those presented in Figure 89-8, would not predict the coexistence of responses to sucrose (sweet) and QHCl (bitter) within a single cell. *(From Gilbertson TA, Boughter JD Jr, Zhang H, Smith DV. Distribution of gustatory sensitivities in rat taste cells: whole-cell responses to apical chemical stimulation.* J Neurosci. *2001;21:4931-4941.)*

Peripheral Sensitivity

REGIONAL DIFFERENCES. Regardless of the controversy surrounding the specificity of responsiveness of individual receptor cells in experimental animals, it is notable that single human fungiform papillae are broadly tuned across taste qualities. In humans, single fungiform papillae have an average of only about four taste buds,[139,176] and thus although there is certainly more than a single receptor cell in a given papillae, at the same time there is quite a limited number. Initial observations that single fungiform papillae were sensitive to a single taste quality resulted from stimulus concentrations that were too low.[177] In taste, as in other sensory systems, there is a trade-off between the area stimulated and the threshold concentration. The lingual threshold for a given gustatory stimulus requires progressively higher concentrations for progressively smaller areas. In one study, when single papillae were stimulated with sufficiently high concentrations, the majority of fungiform papillae mediated multiple taste sensations. Sixty-six percent of the fungiform papillae tested elicited recognition of at least three of the four standard taste qualities.[177] Similar results have been obtained by other investigators.[178,179]

Gustatory receptors sample food or fluid as it is ingested, masticated, and transported to the back of the mouth for swallowing. Receptor densities appear greatest at critical junctures of the ingestive sequence, which are outlined in Figure 89-6. Gustatory receptors at the tip of the tongue are contacted immediately as food enters the mouth and are optimally situated to determine whether to continue or abort the ingestive sequence. A second population on the back and sides of

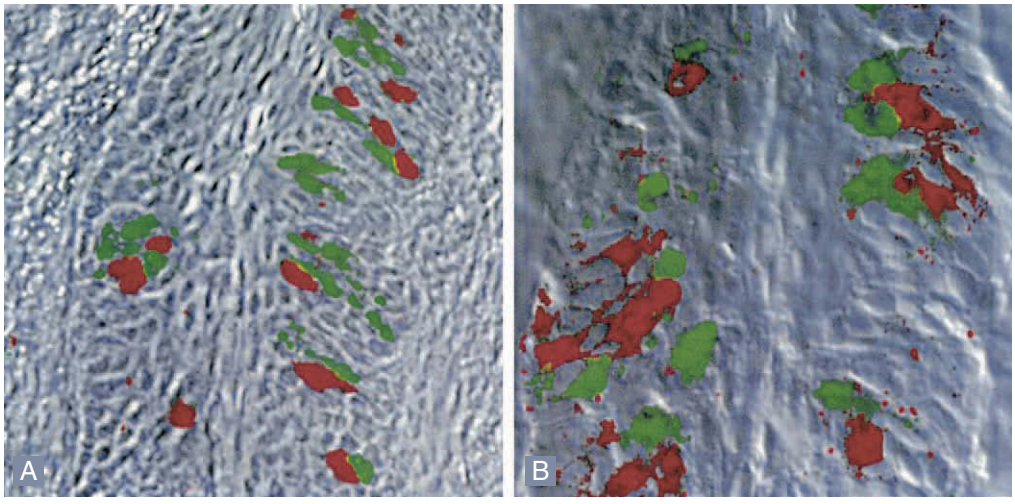

Figure 89-8. Photomicrographs of in situ labeling of taste receptor cells in the circumvallate **(A)** and foliate **(B)** papillae. The red labeling denotes staining with probes for the T2R class of receptors which transduce bitter stimuli; green with the T1R class that transduces sweet or amino acid stimuli. Note the lack of overlap of these classes of receptors within individual cells. These data are in some conflict with physiologic data, such as that shown in Figure 89-7. *(From Nelson G, Hoon MA, Chandrashekar J, et al. Mammalian sweet taste receptors.* Cell. *2001;106:381-390.)*

the tongue and on the opposing palate is probably stimulated during mastication when food is crushed between the molars. In addition to differences in location, the varied sensitivity of the various subpopulations of gustatory receptors to chemical stimuli suggests a differential contribution to gustatory function. However, it needs to be kept in mind that sensitivity differences are relative and not always related in a simple manner to variations in function.

The chorda tympani nerve in many animal species is highly sensitive to a variety of salts (e.g., NaCl). This sensitivity is consistent with human psychophysical studies that show a low threshold to NaCl on the anterior aspect of the tongue.[180] Studies in rats indicate that many individual chorda tympani fibers are sensitive to both NaCl and hydrochloric acid (which tastes sour to humans) but that a subset of peripheral nerve fibers are responsive exclusively to sodium salts.[148] When the sodium channel blocker amiloride was applied to the surface of the tongue, only the sodium-specific fibers lost their responsiveness to NaCl. Those chorda tympani fibers sensitive to both salts and hydrochloric acid maintained their sensitivity to NaCl stimuli in the presence of amiloride, implying that the sodium-specific neurons are particularly important for coding the salty quality of NaCl. Moreover, the recognition of NaCl decreases after chorda tympani nerve section in rats, further indicating a specialized role for this nerve in sodium recognition.[181]

Many mammals including humans have a high sensitivity to sugars and other sweet-tasting compounds on the anterior tongue. A common subject in gustatory research, the rat seems to be an exception because of its poor anterior tongue sensitivity to sweet stimuli. However, even in this species, a robust responsiveness to sweet stimuli is apparent in the anterior oral cavity, specifically in the nasoincisor ducts on the hard palate that lie in apposition to the anterior tongue.[182] The greater superficial petrosal branch of the facial nerve innervates the nasoincisor duct and soft palate receptors. In fact, the soft palate is also highly responsive to sweet stimuli.[183,184] Another rodent, the hamster, also exhibits a relatively greater responsiveness to sweet stimuli applied to the palate vs the tongue, but the hamster tongue also responds well to sweet stimuli.[185] Whether other mammals including humans are relatively more responsive to sweet stimuli applied to the palate is an open question. However, in humans, taste buds have only been described on the soft[186] but not the hard palate. Across a variety of species (e.g., rat,[187] sheep,[188] gerbil,[189] mouse,[190] monkey[191]), gustatory receptors on the posterior tongue are relatively more responsive to aversive, particularly bitter, stimuli than are receptors in the anterior oral cavity. Stimulation of taste receptors with bitter tastants initiates powerful rejection responses.[192-194] Consistent with this differential sensitivity, sectioning the glossopharyngeal nerves in rats attenuates the rejection response to quinine monohydrochloride to a greater degree than does sectioning the chorda tympani nerves.[195,196] However, surprisingly, section of the chorda tympani nerve actually has a greater effect on quinine discrimination.[197] These consequences of lesions and other considerations have led to the suggestion that the anterior oral cavity is more important in gustatory discrimination per se (regardless of quality), whereas the posterior oral cavity is more important in providing input for gustatory-guided reflexes.[187,197]

A specific function is particularly apparent for the superior laryngeal nerve. Chemoresponsive fibers in the superior laryngeal branch of the vagus nerve differ greatly from facial and glossopharyngeal nerve sensitivities. In general, superior laryngeal nerve fibers are insensitive to NaCl and sucrose but respond well to stimulation with potassium chloride, ammonium chloride, acids, and interestingly, water.[198,199] In fact, individual nerve fibers in the superior laryngeal nerve are not divisible into groups on the basis of their optimal sensitivity, as are fibers in the chorda tympani and glossopharyngeal nerves, but rather compose a single broadly responsive group.[200] The location of superior laryngeal nerve-innervated taste buds in the larynx and on the epiglottis indicates a protective-reflex role for these receptors, rather than contributing to gustatory quality perception. The superior laryngeal nerve is a particularly low-threshold nerve for eliciting swallows that could protect the airway.[201]

In addition to these neurophysiologic studies in animals, human psychophysical studies show clear regional variation in the recognition threshold to different gustatory stimuli.[180] The front of the tongue had the lowest threshold for both salty and sweet stimuli; sour stimuli had the lowest threshold when applied to the foliate papillae. Although the front of the tongue also had the lowest threshold for bitter stimuli such as quinine, stimulation of the circumvallate papillae produced a steeper intensity function than obtained by stimulating the front of the tongue. The psychophysical scaling results for quinine monohydrochloride are consistent with the frequent observation that bitter sensations are more intense in the back of the mouth. With the exception of the high sensitivity to sour stimuli on the sides of the tongue, the gradient for threshold to chemical stimuli on the tongue follows the gradient for thresholds to mechanical stimuli, with the anterior region the most sensitive.

Despite these regional variations in threshold and concentration response functions, sensations of sweet, sour, salty, and bitter can be elicited from each oral region where taste buds are present. Moreover, the loss of a single gustatory nerve may not be apparent to the individual and can often be ascertained only by specific psychophysical procedures.[202] In general, the high degree of specialization among the different gustatory nerves of experimental animals is not as obvious in humans. Destruction of the chorda tympani from middle ear surgery destroys taste sensitivity from the front of the tongue,[203,204] but there have been no reports of a disruption of salt intake. However, following third molar surgery, which has the potential to damage the chorda tympani nerve, patients incorrectly identified the taste of NaCl slightly more frequently after surgery.[205] It is also interesting to note that humans with laryngectomies reported thirst less often and were less able to localize thirst compared with a control group, suggestive of a role for the superior laryngeal nerve.[206] Although deficits after damage of single taste nerves are neither profound nor impressively specific, these data need to be interpreted cautiously due to their limited nature. Thus only a few studies of taste responsivity after chorda tympani damage have been carried out; no studies of the gustatory consequences of glossopharyngeal damage have been reported. In addition, perceptual testing has been limited and may not have detected subtle but significant effects on gustatory discrimination. Nevertheless, the regional intraoral variation of taste sensitivity of humans may represent only a vestigial form of reflex organization, superseded by a wider distribution of gustatory sensitivities within the oral cavity and by an increase in the voluntary neural control of ingestion.

INDIVIDUAL DIFFERENCES. Although there are regional differences in taste sensitivity within an individual, an equally salient feature of human gustatory perception is wide variation from person to person. Several studies have demonstrated as much as a 100-fold variation in detection threshold for both sucrose and NaCl across a wide age span.[207] The longest studied and perhaps clearest example of individual differences is the variation in both threshold and responsiveness to the chemically related compounds propothiouracil (PROP) and phenylthiocarbamide (PTC). Decades before anything was known of the molecular basis of bitter transduction, a fortuitous discovery by a chemist synthesizing PTC revealed that some persons found relatively low concentrations of this substance intensely bitter, whereas others found it nearly tasteless.[208] Genetic studies have found this variability to be a heritable trait, but there is still disagreement on the mode of inheritance.[209] Although thresholds for PTC and PROP show a bimodal distribution, there is a continuum of sensitivity in the middle range, suggesting that PTC/PROP sensitivity is not transmitted as a simple Mendelian dominant trait. Rather, partial dominance or multilocus models appear more appropriate.[209] In a recent study, Reed and colleagues[160,209] found a strong linkage to chromosome 5 and a suggestion of a linkage on chromosome 7 near sites where the molecular studies have identified G-protein-coupled receptors for bitter stimuli. Thus it might be tempting to speculate that PROP sensitivity is a consequence of phenotypic variation in the inheritance of partially dominant bitter receptors strongly responsive to PROP and related compounds. However, in some studies, persons who exhibit high or low responsiveness to PROP show similar differences to other stimuli including other bitter-[210,211] and sweet-tasting[211] compounds, as well as differences in responsiveness to a nongustatory stimulus, capsaicin, which produces a burning sensation.[211] Thus it seems possible that some of the variabil-

ity in PROP sensitivity reflects a more general variation in oral sensory sensitivity.

Indeed, differences in the number of fungiform papillae and pores have been identified in groups of people with high, moderate, and low sensitivity to PROP. "Supertasters" have the most fungiform papillae and highest sensitivity, "nontasters" have the fewest fungiform papillae and lowest sensitivity, and "medium-tasters" are in between on both measures.[212] Other studies have demonstrated a similar relationship between papillae number and sensitivity to gustatory stimuli including sucrose, NaCl, and PROP.[176] However, the relationship between fungiform papillae number and taste sensitivity, whether to PROP or other compounds, exhibits a high degree of variability, such that individuals assigned to various groups often overlap in their anatomic characteristics.[176,210,212] Thus the factors underlying individual differences in taste sensitivity are undoubtedly multifactorial and include not only multiple genetic factors (some yet to be discovered), but environmental factors such as nerve damage caused by otitis media,[213] as well as a decline in taste sensitivity with age.[214,215]

Whatever the underlying basis, it is interesting that a number of studies have made the suggestion that variation in taste sensitivity has the potential to affect health. Thus although there is not universal agreement, several studies have reported that people with a high PROP sensitivity claim less preference for certain vegetables (reviewed by Drewnowski[7]), and this appears to affect their intake.[216] Preliminary evidence suggests that these preferences could affect gastrointestinal health. A recent abstract[217] reported a positive relationship between colon polyps and PROP taster status. A relationship between oral health and PROP status has also been claimed, with individuals sensitive to PROP having fewer dental caries.[218-220] It has been speculated that this is due to a greater sensitivity to sweet, as well as bitter, substances, so highly sensitive individuals can consume lower amounts of sugar to achieve the same amount of satisfaction. However, given the lack of unanimous agreement on the positive relationship between PROP and general gustatory sensitivity, as well as the lack of any direct evidence regarding dietary habits in these individuals, more work is necessary to validate these claims and to understand their basis.

Central Gustatory Pathways and Function

Afferent gustatory fibers in the facial, glossopharyngeal, and vagus nerves synapse in the nucleus of the solitary tract (NST) of the medulla with a rostral to caudal organization.[221,222] In primates, taste information projects directly to the gustatory thalamus, which is situated medial to the oral somatosensory representation in the ventroposteromedial nucleus.[223] From the thalamus, taste information projects to the insular-opercular region of the cortex,[224] which comprises the primary gustatory cortex and then to a secondary gustatory cortical area located immediately anterior in the caudolateral orbitofrontal cortex.[225] The secondary gustatory cortex projects to several regions of the ventral forebrain including the hypothalamus and amygdala.[10] Positron emission tomography and functional MRI studies in humans have demonstrated that cortical regions analogous to those demonstrated on the basis of anatomic and physiologic studies in nonhuman primates most likely also comprise the primary and secondary gustatory cortical areas in people (Fig. 89-9).[226]

The gustatory pathway in rodents is organized somewhat differently. Taste information from the NST reaches an analogous thalamic relay in the ventro-posteromedial nucleus, but only after an additional synapse in the parabrachial nucleus of the pons.[227,228] The region identified as the primary gustatory cortex in rodents is also the insular cortex,[229,230] but a secondary taste cortex has not yet been identified. Instead, in rodents, taste information reaches limbic areas more directly, via a projection from the parabrachial nucleus.[231] However, regardless of species and the route the information takes, it has been hypothesized that the thalamocortical pathway can be specialized for perceptual/discriminative gustatory functions; the limbic projections may be more involved in the hedonic/motivational attributes of taste.[232] Local brainstem gustatory pathways, however, have the capacity to mediate basic gustatory discriminative functions. Decerebrate animals[233] and anencephalic human infants[193] discriminate palatable from unpalatable gustatory stimuli.

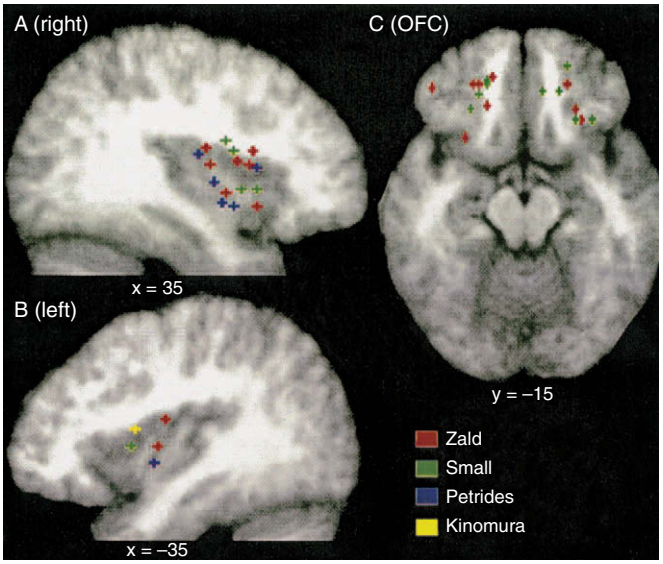

Figure 89-9. Human magnetic resonance images in the parasagittal (**A** and **B**) and horizontal **(C)** planes denoting the location of primary gustatory cortex in the insular-opercular region (**A** and **B**) and secondary gustatory, orbitofrontal **(C)** cortex. The different-colored symbols denote data from various laboratories. *(From Small DM, Zald DH, Jones-Gotman M, et al. Human cortical gustatory areas: a review of functional neuroimaging data.* Neuroreport. *1999;10:7-14.)*

Gustatory pathways are in close anatomic proximity with central pathways controlling the autonomic nervous system function. This proximity provides a substrate for interactions between gustatory and autonomic afferent information,[234] as do the numerous connections between limbic structures and the nuclei in the taste pathway.[140] In rodents, an early study demonstrated changes in the firing pattern of gustatory-responsive neurons in the nucleus of the solitary tract in response to gut distension that were indicative of interaction between the autonomic and gustatory systems.[235] More recent studies have extended these findings to the parabrachial nucleus. Indeed, not only does gut distention affect parabrachial taste neurons,[236] but another manipulation that mimics satiety, intraduodenal lipid infusion, also affects gustatory firing rates.[237] Specifically, lipid infusions depress taste responses, and furthermore this occurs mainly for responses to normally preferred gustatory stimuli. Thus lipid infusions most profoundly depress responses in neurons preferentially responsive to NaCl, and especially those responsive to sucrose. This is in contrast to a lack of effect on responses evoked by HCl and QHCl, stimuli that animals do not normally voluntarily ingest.[237] These effects of gastric and duodenal stimuli suggest a simple mechanism for the reduction in intake that occurs with the visceral sequelae of intake—namely, that neurons responsive to preferred taste stimuli, which normally drive ingestion, reduce their input into feeding circuits when the animal is satiated. Other changes in body state that affect ingestion have also been shown to have effects on early stages of taste processing in rodents. Both sodium deprivation and conditioned taste aversion have stimulus-specific effects in the NST.[238-240] In fact, different levels of dietary sodium even affect responses at the level of the peripheral nerve.[241,242] However, the nature of these neural changes induced by sodium appetite or conditioned taste aversion can be rather complex, and taken together they are not correlated in a straightforward way with the behavioral changes these state changes produce.[240] It is also of interest that these modulations observed at the early stages of gustatory processing in rodents appear only to occur at higher stages of processing in primates, although this has been evaluated only after inducing a state of satiety. In monkeys, recordings from the NST from awake, behaving animals showed that gustatory responses did not change as the animal was fed to a state of satiety.[243] In fact, taste responses were likewise stable in the primary insular-opercular cortex, regardless of whether the animal was

hungry or sated.[244] However, in secondary, orbitofrontal gustatory cortex,[245] as well as in the hypothalamus[246] and amygdala,[247] taste responses become progressively reduced during the course of feeding. A particularly interesting aspect of the primate phenomena is that the effect on taste responses exhibits what is known as "sensory-specific" satiety. That is, even within the realm of preferred stimuli, taste responses are most reduced for the stimulus that actually produces the satiety. For example, neurons responsive to both glucose and a complex stimulus, black currant juice, mainly exhibited reduced glucose responses if glucose was used to feed the monkey until he refused this stimulus. Neural and behavioral responsiveness to black currant juice, however, were relatively unaltered.[10]

Analogous to these effects demonstrated in experimental animals, changes in body state also affect perception of taste stimuli in humans. Such a phenomenon is readily demonstrated in short-term experiments, when subjects rate the pleasantness of a sweet taste before and after the induction of satiety. A classic study by Cabanac and colleagues[248] showed that ratings of the pleasantness of sucrose declined over time when subjects ingested the samples, drank an equivalent quantity of sucrose as a bolus, or received intragastric sucrose. Interestingly, ratings were unaffected by simple gastric distention, infusion of hypertonic saline, or intravenous glucose infusion. Later studies found similar effects.[9] Further, similar to the primate experiments just discussed, these changes in pleasantness exhibit sensory-specific satiety[249] and, accordingly, people will eat larger meals when the meals are composed of more varied foods.[250]

It has been more difficult to document preference of differences among populations of persons with different chronic conditions. For example, preferences for sweet stimuli in obese versus nonobese persons have been reported to be enhanced in some studies, but in other studies have been reported to be depressed or the same.[9] It seems likely that these equivocal results reflect the heterogeneity of the obese population in terms of etiology, chronicity, and dietary status, as well as the complexities involved in obtaining accurate preference ratings, particularly in a population of people who may feel self-conscious about their eating habits. Studies of diabetic patients are more consistent in reporting elevated psychophysical thresholds to glucose.[251,252] Loss of gustatory sensitivity in diabetics may result from a systemic lack of glucose receptors and from general neuropathy. However, even diabetes can be associated with multiple effects. An animal model of this disease, performed with the db/db mouse, shows elevated peripheral nerve responses to sugars.[253] Thus conditions that affect carbohydrate metabolism and body weight obviously have the potential to influence taste responsiveness, but the relationship is complicated and requires further study.

Recordings from the gustatory cortex of awake, behaving monkeys are relevant to current issues raised on the basis of cellular and molecular studies of taste transduction. One question is whether monosodium glutamate and related compounds evoke a unique gustatory quality, umami, with a status that is as distinct as the four classical taste qualities: sweet, salty, sour, and bitter. A related question is whether the gustatory world extends to fatty stimuli. Both questions have fundamental implications for understanding the functional organization of the taste system because they seek to expand the array of qualities that the system must represent and, furthermore, the qualities in question represent basic food groups important to human nutrition.

With regard to umami taste, evidence from cortex is in some disagreement. An initial study[254] suggested a unique status for this quality. Recordings from primary and secondary gustatory cortex demonstrated that the prototypic umami stimulus, monosodium glutamate (MSG), was just as effective as four standard gustatory stimuli—glucose (sweet), NaCl (salty), HCl (sour), and QHCl (bitter)—measured either by average firing rates or with regard to the number of neurons that responded optimally to a given stimulus. Furthermore, the neural representation of MSG relative to the other stimuli was just as distinct as the above four stimuli were from each other on the basis of correlations between responses to the stimuli evoked across the populations of neurons. Although the stimulus array used in that study was limited and did not allow a ready comparison between stimuli that are known to be the same and those known to be different, in a follow-up study with the four standard taste stimuli plus two umami stimuli,[255] it was indeed shown that the representation of MSG and the other umami stimulus, IMP, was more similar than any other stimulus pair. However, these data are not entirely compelling because the correlation between MSG and IMP (0.77) was actually only nominally greater than the correlation between MSG and the sour stimulus, HCl (0.71). Furthermore, in another study that used a large array of amino acids, MSG was not shown to be distinctly represented relative to the four standard qualities but was instead highly correlated with NaCl,[256] an observation that has been made frequently at lower levels of the rodent gustatory system.[257] Thus although amino acid stimuli activate a special set of gustatory receptors and are effective for stimulating taste neurons throughout the neuraxis, whether or not they represent a unique taste or a complex conglomerate of the classic four is still unresolved.

The neural representation of dietary fats has long been a mystery. Although the presumption had been that fat stimuli were represented not on the basis of their ability to stimulate the gustatory system but rather due to their olfactory and somatosensory properties, interest in a possible gustatory efficacy was reawakened by the discovery that certain free fatty acids were capable of stimulating taste receptor cells.[258] This neural representation of fat has recently been studied in the monkey orbitofrontal cortex.[259,260] This is a particularly appropriate brain region in which to study these stimuli because it receives not only gustatory but also olfactory and somatosensory inputs. Fatty stimuli (e.g., cream) were shown to activate a small subset of neurons in the orbitofrontal cortex. Occasionally, neurons were observed that responded to fat stimuli but not to standard taste stimuli, but more frequently fat-responsive cells were also taste responsive. There was not an obvious relationship between the gustatory sensitivity spectrum of a neuron and whether it responded to fat stimuli. Significantly, the chemical properties of the fats were not important in their effectiveness because nonfat stimuli including silicone and mineral oil were just as effective as dietary fats such as cream and vegetable oil. Thus at least in this sample of neurons, neither the olfactory nor the gustatory properties of the fats appeared to be responsible for driving the cells. Furthermore, the free-fatty acids specifically shown to stimulate taste receptor cells, linoleic and lauric, were poor stimuli for these cells, being no more effective than water. Indeed, this was true even though coconut oil, which contains high amounts of these fatty acids, was a highly effective stimulus. Thus it was concluded that the somatosensory properties of the fats were the determining factor. Interestingly, a parametric investigation of the responses of these cells to viscosity revealed that the responses of only a subset of these cells to fat could be predicted by their responses to viscosity. Thus a different, unidentified somatosensory property must be a critical variable in determining the effectiveness of fats as a stimulus.

Interaction between Saliva and Taste

The presence of saliva in the mouth continually stimulates gustatory receptors with low levels of salt ions. Correspondingly, recognition thresholds for NaCl are somewhat raised when the tongue is adapted with a solution containing salivary levels of sodium (4.3 mm compared with recognition thresholds using distilled water rinses, 0.14 mm).[261] By implication, the presence of other salivary constituents as a result of either disease or medication may affect gustatory sensitivity.[262] Salivary concentrations of pirmenol in patients being treated for ventricular arrhythmias, for example, can produce the bitter taste reported by these patients.[263] Increased salivary levels of glucose in diabetic patients provide one mechanism for the increased detection thresholds for glucose in this patient population.[252]

Saliva can also exert a trophic influence on gustatory receptors. Patients suffering long-term salivary loss as a result of Sjögren's syndrome had increased detection and recognition threshold to many gustatory stimuli.[264] Biopsy specimens of the circumvallate papillae from a subset of these patients indicated a profound loss of taste buds. The effects of desalivation on both taste bud morphology and gustatory sensitivity have also been explored in animals.[265,266] Surgically removing the salivary glands was associated with increased keratosis of the lingual epithelium and shrinking of the circumvallate papillae. Correlated with these morphologic changes was the increased consumption of nonpre-

ferred gustatory stimuli, indicative of a loss of gustatory sensitivity. Electron microscopic observation of the circumvallate papillae showed the infiltration of bacteria, suggesting that the loss of antibacterial agents in saliva permitted degenerative microbial action. Lack of salivation by acute pharmacologic manipulations in experimental human studies, however, had relatively little effect on gustatory sensitivity.[267]

The loss of taste acuity in humans after radiotherapy to the head and neck could result directly from the destruction of taste buds and indirectly from reduced salivary flow.[268] Direct irradiation of gustatory structures in experimental animals produced a loss of taste buds.[269] Radiotherapy can also influence the gustatory system through the formation of conditioned taste aversions.[270,271] Clinical observations of hedonic changes in taste may result, in part, from the pairing of a conditioned stimulus (food) with an unconditioned stimulus, the gastrointestinal distress resulting from either chemotherapy or abdominal radiation. Animal experiments indicate that such pairings can have a profound impact on gustatory preferences.[272] Animal studies also indicate that the formation of a conditioned taste aversion is a central phenomenon that requires an intact forebrain.

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CHAPTER NINETY

Mechanisms of Normal and Abnormal Swallowing

Jeri A. Logemann

Key Points

- Knowledge of normal swallow physiology is the basis for identification of dysphagia.
- Evaluation of oropharyngeal dysphagia requires careful and detailed assessment of all physiologic aspects of the oropharynx, usually with videofluoroscopy or videoendoscopy.
- Treatment of oropharyngeal dysphagia is directed to each patient's specific abnormality.
- Treatment for oropharyngeal dysphagia is largely behavioral and may involve posture change, exercises, sensory stimulation, application of voluntary control of swallowing, and diet change.
- All types of treatment for oropharyngeal cancer can cause various abnormalities in oropharyngeal swallow.

Stages of Normal Deglutition

Swallowing is a complex neuromuscular function involving structures in the oral cavity, pharynx, larynx, and esophagus. Various researchers have divided normal swallowing into four stages: the oral preparatory stage, the oral stage, the pharyngeal stage, and the esophageal stage.[1-5] The first two stages, the oral preparatory and the oral, are under voluntary control, whereas the second two stages, the pharyngeal and esophageal, are involuntary, being under reflexive control.[6,7] The oral stage of swallow is under voluntary control, whereas the pharyngeal swallow is no longer considered a reflex but rather a programmed activity; the motor program varies with the characteristics of the food being swallowed (i.e., the bolus), voluntary control, and other as yet undefined parameters.

Voluntary Stages of the Swallow

Oral Preparatory Stage

The oral preparatory aspect of deglutition, which prepares food for the swallow, involves the coordination of (1) lip closure to hold food in the mouth anteriorly, (2) tension in the labial and buccal musculature to close the anterior and lateral sulci, (3) rotary motion of the jaw for chewing, (4) lateral rolling motion of the tongue to position food on the teeth during mastication, and (5) bulging forward of the soft palate to seal the oral cavity posteriorly and widen the nasal airway.[4] The forward position of the soft palate is not present during active chewing, and premature spillage while chewing is common and normal in people of all ages. Much of this coordination requires cerebellar input.[8] The oral phase of deglutition is mechanical in that it involves the reduction of solid food to a pulverized consistency that may be easily swallowed. The most important neuromuscular function involved in the oral preparatory phase is the lateral rolling motion of the tongue.[9] Without normal range-of-tongue motion, the manipulation and mastication of food during the oral preparatory phase would be impossible. At the termination of the oral preparatory phase, the tongue pulls the food together into a ball or bolus and holds it in a cohesive fashion on the floor of the mouth or against the hard palate (Fig. 90-1) in preparation for the beginning of the oral phase of the swallow.[4,7,10-13]

Oral Stage

The oral stage of the swallow is also a mechanical, voluntary stage and is designed to move food from the front of the oral cavity to the pharynx, wherein the pharyngeal stage of swallow is initiated. Again, tongue motion is the most critical element in this phase of the swallow because the tongue shapes, lifts, and squeezes the bolus upward and backward along the hard palate until the food reaches the pharynx.[14-17] During this posterior propulsion by the midline of the tongue, the lateral margins of the tongue are sealed against the alveolar ridge, providing resistance against which the midline of the tongue propels the bolus.[15] Tension in the buccal musculature is also thought to contribute to propelling the bolus backward, but to a much lesser degree than tongue movements.[18] When the head or leading edge of the mandible crosses the tongue base, the pharyngeal swallow should be triggered in healthy people of all ages (Fig. 90-2). The pharyngeal swallow is usually triggered by the glossopharyngeal nerve (C9). In healthy people, the oral stage lasts no more than 1 to 1.5 seconds and is slightly prolonged with increasing age and with increasing viscosity of the bolus swallowed.[5,19]

In animal studies and in healthy humans, the pharyngeal swallow has been found to be triggered not only from C9 but also from the superior laryngeal nerve at the inlet of the larynx.[20-25] Normal swallowing does not use this secondary mechanism for triggering the pharyngeal swallow because food would have almost entered the airway by the time the pharyngeal swallow was triggered. Thus when videofluoroscopic examination of a patient shows that the pharyngeal swallow triggers late, as food is about to enter the airway or after the bolus has come to rest in the valleculae or pyriform sinuses, the patient is said to have a disorder of swallowing called a *delayed triggering of the pharyngeal swallow.*

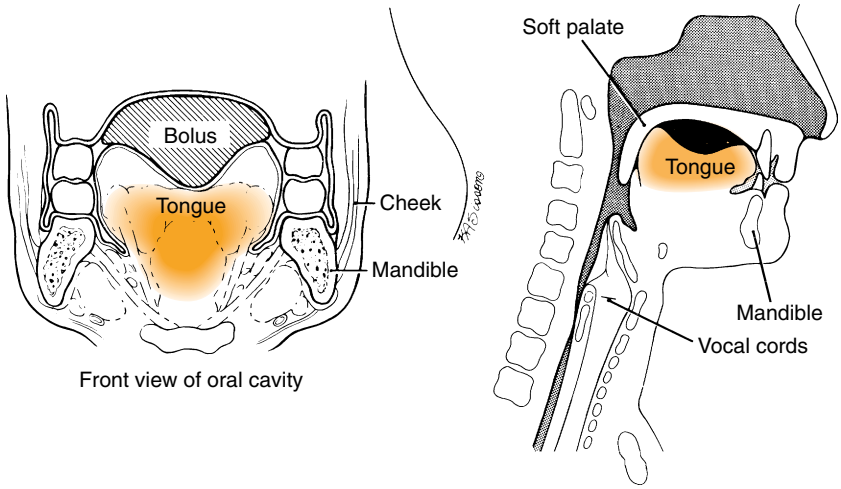

Figure 90-1. The anterior and lateral views of tongue position in holding bolus immediately before initiating oral stage of swallow.

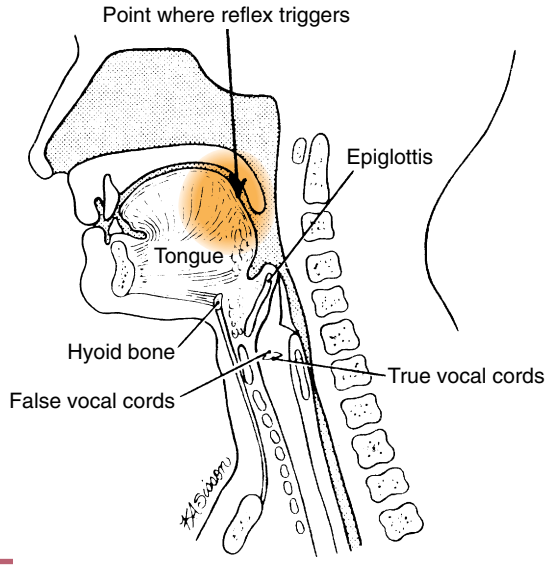

Figure 90-2. The lateral view of the head and neck illustrating the normal point at which swallowing reflex triggers.

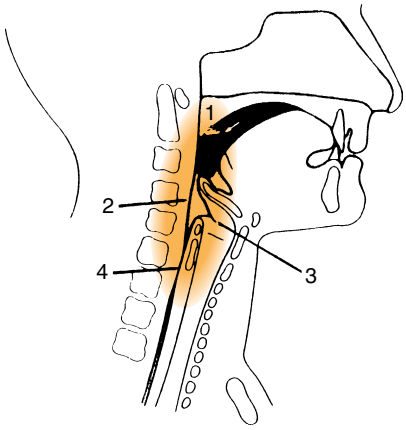

Figure 90-3. The lateral view of the head and neck, showing four neuromuscular components triggered by swallowing reflex: (1) closure of soft palate, (2) peristaltic action, (3) elevation and closure of larynx, and (4) relaxation of cricopharyngeal muscle.

Programmed Stages of the Swallow

Pharyngeal Stage

The pharyngeal stage of the swallow is the more physiologically important one because airway protection occurs during this stage in healthy people. The oral preparatory and oral stages of the swallow may be bypassed by reducing the consistency of food to liquid, by syringing food into the back of the mouth, or by positioning the head back so that gravity carries the food into the pharynx. The pharyngeal stage of the swallow cannot be bypassed.

The pharyngeal swallow is mediated in the lower brainstem (the medulla) in the reticular formation immediately adjacent to the respiratory center. Coordination exists between these two centers because respiration ceases for a fraction of a second when the airway closes during the pharyngeal swallow. There is also cortical input to the triggering of the pharyngeal swallow through the tongue movement patterns in the oral phase of the swallow.[20] The exact neurologic substrate for this cortical input is not clearly understood.[26]

Neuromuscular Activities Characteristic of the Pharyngeal Swallow

When the swallowing reflex is triggered, the brainstem swallowing center programs five neuromuscular activities to occur (Fig. 90-3). If triggering of the pharyngeal swallow is delayed, none of these neuromuscular activities occurs until pharyngeal swallow triggers (1) velopharyngeal closure to prevent backflow of material up the nose; (2) tongue base retraction to propel the bolus through the pharynx; (3) pharyngeal contraction to clear residue through the pharynx; (4) airway protection, which involves both elevation and closure of the larynx; and (5) cricopharyngeal or upper esophageal sphincter (UES) opening to allow the bolus to pass into the esophagus.[1,2,27-33]

Velopharyngeal closure and hyoid and laryngeal elevation occur as the first response to triggering the pharyngeal swallow. Then laryngeal closure occurs, followed closely by opening of the cricopharyngeal sphincter. These neuromuscular functions also overlap but do not all last for the entire pharyngeal stage of the swallow. Instead, each lasts only as long as the bolus is passing that part of the pharynx. When the bolus has reached the middle to lower pharynx, the soft palate lowers. At that time, the larynx is closed and elevated and the upper esophageal sphincter is open, preventing the passing bolus from entering the airway and allowing it to enter the esophagus. The duration of the pharyngeal stage of the swallow normally lasts a maximum of 1 second and does not vary dramatically with the consistency of food or age or gender of the patient.[5,19]

Airway Protection

Airway protection, as noted previously, involves two dimensions: elevation and closure. Elevation is created by contraction of strap muscula-

ture, which positions the larynx upward and forward under the tongue base as it is retracted at the end of the oral phase of the swallow. The larynx is pulled up and out of the way of the passage of the food bolus over the base of the tongue. Closure of the larynx involves three sphincters: the epiglottis and aryepiglottic folds, the false vocal folds and airway entrance, and the true vocal folds.[27,28,34-36] The relative importance of each of the three sphincters has been debated in the literature.[35,37,38] Most authors agree that the epiglottis and aryepiglottic folds play a relatively minor role in protecting the airway; their purpose is to divert food around the airway. The most important level of closure, airway entrance closure, is maintained only for the fraction of a second that the bolus is passing the airway.

Cricopharyngeal (Upper Esophageal Sphincter) Opening

The cricopharyngeus muscle acts in opposition to the function of the constrictor mechanism of the pharynx. At rest the constrictors are relaxed, and the cricopharyngeus muscle or upper esophageal sphincter is in tonic contraction to prevent air intake into the esophagus concurrent with inhalation into the lungs. Also, the contracted cricopharyngeus muscle prevents backflow from the esophagus into the pharynx.[1] During the swallow, as the constrictor mechanism is contracting, the cricopharyngeus muscle relaxes at the appropriate moment. The anterior superior movement of the larynx opens the UES, and the bolus passes into the esophagus. The duration of UES opening and airway closure increases as bolus volume increases.[39]

Pharyngeal Pressure Generation: Tongue Base Retraction and Pharyngeal Contraction

When the tail of the bolus reaches the tongue base, the tongue base moves rapidly backward like a piston, increasing pressure in the pharynx. As the tongue base moves backward, the lateral and posterior pharyngeal walls at the tongue base level move inward. The tongue base and pharyngeal walls should make complete contact. Electromyographic and radiographic studies have shown that pharyngeal contraction, or the squeezing action of the constrictor mechanism to move the bolus through the pharynx, occurs sequentially, beginning in the superior constrictor muscle and moving through the medial to the inferior constrictor muscle.[29,40]

Pharyngeal contraction is responsible for clearing material from the pharyngeal walls and pyriform sinuses. When residue or material remains in the valleculae after the swallow, it is interpreted as a symptom of reduced tongue base movement.[41] Tongue base movement occurs later as bolus volume increases.

Esophageal Stage

When the bolus has passed through the UES, the esophageal phase of swallow begins. The esophageal stage has greater variability in duration than the other stages of the swallow. Normal esophageal transit may vary from 8 to 20 seconds.[4] The upper third of the esophagus is composed of mixed voluntary and involuntary muscle, and the lower two thirds is composed entirely of involuntary muscle. The lower esophageal sphincter acts as a valve to the stomach, which must open in time to allow the bolus to pass from the esophagus into the stomach.

In summary, the pharyngeal stage of the swallow is responsible for transit of material into the esophagus and for airway protection, probably the most important aspect of deglutition.

Figure 90-4 illustrates the progression of the bolus through the pharynx. If an anatomic or neuromuscular disorder affects the pharyngeal stage of the swallow, aspiration may result.

Signs and Symptoms of Abnormal Swallow

Aspiration (Coughing, Choking)

Aspiration is the entry of material into the airway below the true vocal folds. The effect of chronic aspiration in adults is not well understood, but in the long term it may result in pneumonia or pulmonary changes. Patients who are observed to aspirate on a radiographic study of swallowing are at significantly greater risk of pneumonia developing than patients who do not show aspiration on such a study. Many patients with head and neck cancer who have chronic aspiration do not survive long enough to experience the long-term effects of their aspiration. Aspiration may occur before, during, or after the pharyngeal swallow.[4] Aspiration that occurs before the pharyngeal swallow may result from one of two disorders: reduced tongue control or a delayed or absent pharyngeal swallow. When tongue control is reduced during the oral preparatory or oral stages of the swallow, bits and pieces of food may fall into the pharynx and the open airway as the patient chews. Importantly, the airway is normally open during the oral preparatory and oral stages of the swallow. The airway is closed only for a fraction of a second during the pharyngeal swallow. Aspiration before the swallow can also occur because of a delayed or absent pharyngeal swallow. In these patients, the food is propelled out of the oral cavity by the tongue and falls into the pharynx, wherein it may come to rest in the valleculae, the pyriform sinus, or the airway before the pharyngeal swallow is triggered. The entry of food into the airway does not always trigger a cough, particularly in neurologically impaired patients and some patients with head and neck cancer in whom sensory input is damaged.[41,42]

Aspiration during the swallow takes place when airway closure is inadequate to prevent material from entering the airway during the pharyngeal swallow. Aspiration after the swallow occurs for a number of reasons including reduced laryngeal elevation, reduced tongue base retraction, reduced pharyngeal contraction, unilateral pharyngeal damage, or cricopharyngeal dysfunction. In all of these instances, residue remains in the pharynx after the swallow. When the patient opens the larynx to inhale as is normal after a swallow, some of this residue is sucked or falls into the airway. Determination of the cause of aspiration is critical for efficient treatment. Aspiration is only a symptom of a disorder. Evaluation of swallow is designed to identify the anatomic or physiologic cause of the aspiration. Treatment is designed to eliminate the reason for the aspiration. Each of the disorders noted previously as potential causes of aspiration is treated differently.

Inefficient Swallowing

Inefficient swallowing (i.e., inability to propel food or liquid into the stomach) at each meal can cause malnutrition, dehydration, and/or weight loss. Many different anatomic or physiologic swallowing disorders may cause these complications. As with aspiration, treatment is directed at the anatomic or physiologic disorder causing these complications.

Screening for Swallowing Disorders

Screening involves quickly reviewing patient characteristics to see whether they indicate the possible presence of a swallowing disorder and the need for a more in-depth examination. To screen a patient, the clinician may do a chart review, briefly talk with the patient, and/or observe him or her eating a meal.

Evaluation of Swallowing

Because inefficient swallowing or aspiration occurs in many patients without visible external symptoms such as coughing, a careful evaluation of swallowing is imperative for patients who have been temporarily removed from oral feeding because of surgery or a neurologic incident such as a cerebrovascular accident or closed head trauma. The currently available procedures to examine swallowing include fluoroscopy, manometry, ultrasonography, and endoscopy.

Bedside Evaluation

Bedside evaluation is the next step after screening a patient and includes assessment of facial, lip, tongue, pharyngeal, laryngeal, and respiratory control, as well as the patient's ability to follow directions. The bedside evaluation also includes an oropharyngeal structural examination. It ends with a recommendation as to whether the patient needs an instrumental assessment such as fluoroscopy or endoscopy. An instrumental assessment is necessary if the clinician suspects that the patient may have a pharyngeal stage abnormality that is invisible on bedside evaluation.

Videofluoroscopy

Videofluoroscopy is the only available procedure that allows direct observation of the upper aerodigestive tract during all four stages of

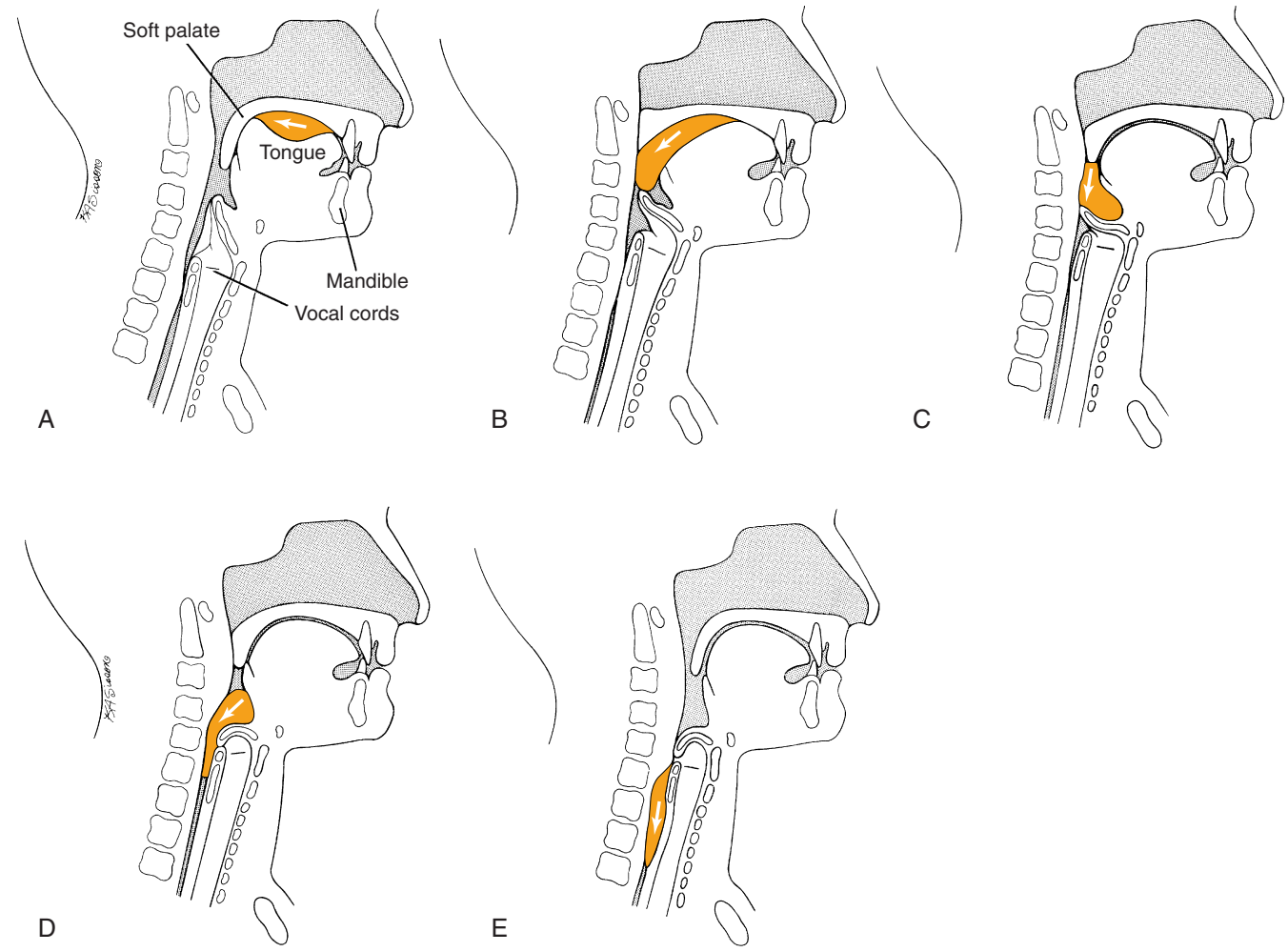

Figure 90-4. **A** through **E,** Lateral views of the head and neck illustrating progression of bolus through the pharynx.

deglutition, beginning with the oral preparatory phase and terminating with the esophageal phase. The standard barium swallow or "upper gastrointestinal (GI)" procedure is inappropriate for head and neck surgical patients or neurologic patients who have severe problems swallowing because of severe risk for aspiration.

In the usual barium swallow procedure, the patient is given a cup of barium and asked to swallow repeatedly. This procedure is designed to examine anatomy and motility in the esophagus, which is a collapsed tube that must be filled with barium to be viewed. For accurate evaluation of esophageal peristalsis without the effect of gravity, the patient lies in a supine position and usually viewed in the anteroposterior plane.

The modified barium swallow (MBS) technique is used to examine the oral cavity and pharynx radiographically, which presents different problems from those encountered when examining the esophagus. By definition, the oral cavity and pharynx are cavities. When they are filled with large amounts of material, visualization of their structure and function is obliterated rather than enhanced. In addition, the patient with an oral or pharyngeal swallowing disorder has greater difficulty handling a large bolus and is at much higher risk of aspiration. Thus modification of the barium swallow technique is necessary when assessing patients with oral and pharyngeal swallowing disorders. Only measured amounts of material are used because patients may exhibit difficulty in swallowing liquids as volume increases but not in swallowing heavier foods or vice versa.

During the MBS, the patient is seated upright in a normal eating position. In dysphagic patients, the physiology of the oral cavity and pharynx in the normal eating position must be established first. Then, if desired, the patient's position can be changed to note the postural effects on food flow during swallowing. In the modified barium swallow procedure, the patient is initially viewed in the lateral plane with the fluoroscopy tube focused on the lips anteriorly and the seventh cervical vertebra inferiorly as shown in Figure 90-5. This allows complete assessment of oral and pharyngeal motility and of aspiration during the pharyngeal aspect of the swallow. In the anteroposterior view, the trachea overlies the esophagus, making assessment of aspiration difficult.

The major purposes of the modified barium swallow are to (1) define the immediate oral and pharyngeal motility disorders during the swallow; (2) identify the presence of aspiration during swallow of any food consistency; (3) assess the speed of the swallow (compared with normal); and (4) assess the effects of therapy strategies such as postural changes, heightened sensory input, and therapy procedures including swallowing maneuvers.[16,36,41,43-50] If the patient aspirates or has a highly inefficient swallow, treatment procedures are introduced during the videofluoroscopic study to improve the swallow and allow the patient to continue to eat orally or return to oral intake as quickly as possible. The purpose of the test is to restore oral intake—not to stop the patient from eating.

Endoscopy

Endoscopy by way of transnasal placement of a flexible fiberoptic scope has been used to evaluate some selected aspects of the swallow.[50-53] The oral stages cannot be viewed, and during the swallow the image disappears as the pharynx contracts and closes against the scope. Any residual food in the pharynx after the swallow may be identified, as may any aspiration of the residue after the swallow.

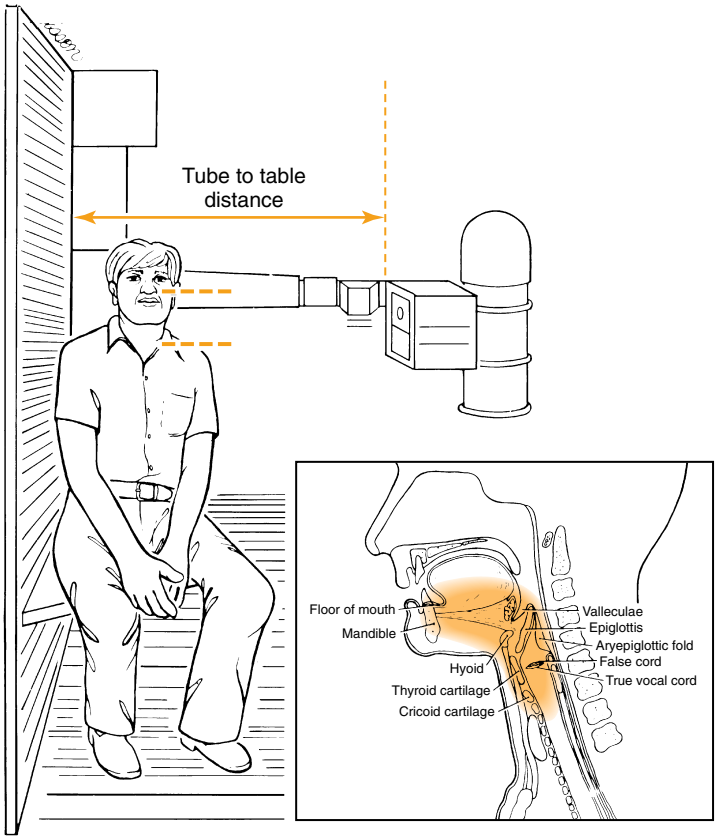

Figure 90-5. Positioning of patient during modified barium swallow. The structures to be examined in this lateral view are shown in lower right corner.

Manometry

Manometry is usually used to examine esophageal peristalsis and the adequacy of functioning of the upper and lower esophageal sphincters.[3,54,55] The patient swallows a soft tube containing pressure sensors. These sensors are positioned so that one registers the pressure in the UES, the second registers pressure changes in the body of the esophagus, and the third registers pressure in the lower esophageal sphincter. The gauges also may be positioned to register pressure in the pharynx, cricopharyngeal sphincter, and the body of the esophagus, thus permitting observation of the temporal relationship between pharyngeal contraction and opening of the cricopharyngeal sphincter.

Ultrasonography

Ultrasonography is used to assess the anatomy and physiology of the tongue during swallowing, but it currently cannot be used to examine the pharynx or larynx because of skeletal interference.[12] Thus it is limited to the study of the oral stage of deglutition.

Swallowing Disorders Resulting from Treatment for Head and Neck Cancer

Radiotherapy

Radiotherapy for the oral cavity and pharynx, in addition to reducing salivary flow and causing short-term oral or pharyngeal edema, may lead to difficulties with triggering of the pharyngeal swallow, laryngeal elevation, and pharyngeal contraction that may begin immediately or months after the therapy is completed.[4,56] Presumably, the problem with laryngeal elevation and pharyngeal contraction relates to increased fibrosis after radiation. The symptoms vary in duration and severity and may appear 6 months or more after completion of a full course of radiotherapy. The long-term effects of radiotherapy on swallowing deserve greater attention and more thorough study.

Chemoradiation

In recent years, treatment protocols that use high-dose concurrent chemoradiation have been increasingly used. Some of the patients undergoing these protocols develop severe swallowing problems, generally including a delayed triggering of the pharyngeal swallow, reduced laryngeal elevation, and reduced pharyngeal contraction, and must take nutrition nonorally. Over time (3 to 12 months), these disorders may reduce in severity so that some of these patients can return to oral intake. A great deal more research is necessary on measurement and treatment of these swallowing disorders after chemoradiation.

Surgical Treatment

The effects of surgical treatment for patients with head and neck cancer on swallowing depend on the site and extent of the resection and the nature of reconstruction.[4,57,58] Some data indicate that the reconstruction determines the swallowing pattern of the patient postoperatively, particularly when smaller amounts of tissue are resected.

Tongue

Within the oral cavity, the tongue is the most important organ for maintaining normal food intake. The tongue is responsible for oral manipulation and chewing to prepare food for the swallow and is responsible for the oral initiation of the swallow. Every effort should be made to permit as much range and coordination of tongue motion as possible. Use of the tongue in surgical closure may dramatically reduce the patient's ability to handle a normal diet.[16]

Posterior Oral Cavity

When a tumor invades the posterior oral cavity, a number of swallowing actions may be affected[59] including tongue mobility during oral preparation and the oral initiation of the swallow, triggering of the pharyngeal swallow, velopharyngeal closure, tongue base retraction, and pharyngeal contraction. Surgery at the tonsil and base of the tongue

directly invades the sensory area where the pharyngeal swallow is usually triggered and also damages the attachments of the pharyngeal constrictors into the base of the tongue, thus reducing tongue base retraction and pharyngeal contraction. Reconstruction of this area with a thick and bulky flap interferes with functioning of the pharynx, tongue, and remaining healthy tissues.[60]

Pharynx

Surgical involvement of the pharyngeal wall itself may dramatically impair pharyngeal contraction. If the surgical resection involves only one side of the pharynx, the patient may turn his or her head to the operated side to assist swallowing on the unoperated and less damaged side, thus directing food down the more normal side.[43] Alternately, the patient may tilt his or her head toward the more normal side to assist gravitational drainage of food down the stronger side. As in the oral cavity, the nature of the reconstruction may interfere with function on the unoperated side so that even with a change in head position the patient is permanently unable to handle food thicker than liquid and may even have difficulty with liquid. Greater pharyngeal peristalsis is required to move heavier and thicker food than is required for liquid.

Larynx

Resection of a part of the larynx, as occurs in hemilaryngectomy or supraglottic laryngectomy, may interfere with three aspects of the swallow: laryngeal elevation, laryngeal closure, and tongue base retraction.

After hemilaryngectomy, laryngeal closure is the greatest problem.[4] Depending again on the nature of the reconstruction and on the nature and amount of tissue positioned on the resected side, many patients regain normal swallowing in a relatively short time (1 month) after hemilaryngectomy with swallowing retraining, which usually involves laryngeal adduction exercises.[61]

Patients who have undergone supraglottic laryngectomy often have multiple problems with swallowing, which may include reduction in laryngeal elevation, laryngeal entrance closure, and tongue base retraction.[62] During the supraglottic laryngectomy procedure, portions or all of the hyoid bone are removed, and thus laryngeal suspension from the hyoid is disturbed.[63,64] Resultant residue at the top of the larynx may be aspirated after the swallow when the patients open the larynx and inhale. Airway protection in these patients is achieved by retraction of the tongue base to contact the anteriorly tilting arytenoid cartilages.[65] Any damage to the tongue base or the arytenoid cartilages or their function in adduction and anterior tilting results in inability to protect the airway and aspiration after the swallow.

Post-treatment Complications

In addition to the disorders that result from various treatment procedures, post-treatment complications that worsen swallowing may occur. For example, after radiotherapy, osteoradionecrosis of the mandible may affect chewing. After surgical procedures, scar tissue may form or a fistula that results in additional scar tissue may develop, further interfering with normal swallowing.

Summary

Dysphagia or swallowing difficulty and aspiration are generic terms for problems that have a number of specific anatomic or physiologic causes. Treatment of aspiration in head and neck surgical patients requires accurate identification of the reason for the aspiration. Each of the known causes of aspiration (e.g., reduced tongue control, delayed triggering of the pharyngeal swallow, reduced laryngeal closure, reduced laryngeal elevation, reduced tongue base retraction, reduced pharyngeal contraction) requires a different treatment procedure. The best available procedures should be used to assess the patient's swallowing physiology, and the findings should be compared with normal data. Currently, a videofluoroscopic procedure, the modified barium swallow, gives the most valid results for the evaluation of swallowing physiology and the assessment of aspiration and its cause. The other techniques for assessment of swallowing including bedside evaluation, manometry, ultrasonography, and endoscopy cannot accurately assess all aspects of oropharyngeal swallow physiology, the causes of aspiration, and the effectiveness of treatments.

Studies have shown that the bedside evaluation of aspiration may be as much as 40% in error in identifying patients who are aspirating[50] and cannot identify the underlying causes so that effective management may be planned. Optimum treatment of a patient with a swallowing disorder involves videofluoroscopic evaluation of swallowing at the time oral feeding is to be reinitiated so that appropriate swallowing therapy may be planned, the patient may be quickly advanced to as normal a diet as possible, and potential complications from chronic aspiration, malnutrition, or dehydration may be avoided.

A swallowing therapist should be involved in the patient's treatment from the time that head and neck cancer is diagnosed so that timely evaluation and management of swallowing disorders may be initiated and as much normal function as possible may be restored in the shortest postoperative time.

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CHAPTER NINETY-ONE

Oral Mucosal Lesions

James J. Sciubba

Key Points

- Appreciate that leukoplakia carries a small but significant risk of malignant transformation, and that the proliferative verrucous form has a far greater incidence of recurrence, multifocality, and absence of the usual risk factors and transformation rates than typical leukoplakia.
- At the moment there is no effective chemoprevention strategy for the management of leukoplakia.
- The risk of malignant transformation in cases of oral lichen planus and oral mucosal lichenoid lesions must be considered in the long-term aspect of patient follow-up.
- The role of areca (betel) nut in the pathogenesis of oral submucous fibrosis in India and many other countries forms the basis for the high rate of oral squamous cell carcinoma reported in those locations.
- Appreciate the various forms of oral candidiasis and the management options.
- Identify the specific antigenic target in pemphigus vulgaris as a member of the cadherin family of intercellular adhesion molecules.
- Appreciate the differences between pemphigus vulgaris and mucous membrane (mucosal) pemphigoid in terms of antigenic targeting and their anatomic localization.
- Aphthous ulceration may present in three forms with a variable approach to management ranging from observation only to the use of systemic agents.
- Recurrent herpes virus activation may form the basis for the development of recurrent erythema multiforme. Thus consideration is to be given for the use of prophylactic viral suppression treatment.
- The differential diagnosis of oral mucosal pigmentation includes the range of entities from innocuous to life-threatening. Thus the index of suspicion of such lesions is an important clinical consideration.

Red/White Lesions

Leukoedema

Definition

Leukoedema presents as a diffuse and generalized mild surface opacification that chiefly involves the buccal mucosa. It essentially represents a normal variation of surface mucosal texture and characteristics and can be identified in large numbers within the population; however, it is most marked in those possessing higher levels of cutaneous and mucosal pigmentation, being present in the majority of black adults and in nearly half of black children.

Etiology and Pathogenesis

No clear cause of this condition has yet been established. Factors that may have a role in the manifestation of this condition include smoking, alcohol ingestion, bacterial infections, electrochemical interactions, and possibly inflammatory salivary disorders, although no specific, reproducible, or definitive cause has been proven to date. Many authorities indicate that this hardly represents a disease entity but rather may be considered a variation of what is normal. Similar edematous alterations of mucosa may also be seen in the vagina and larynx, further supporting the notion that this is indeed a normal variant of mucosal surface appearance. The incidence of leukoedema increases with age up to 40 to 49 years, followed by a decline.[1]

Clinical Features

Leukoedema is asymptomatic in nature and is usually discovered incidentally during routine examination or by the patient. The distribution tends to be symmetric and involves the buccal mucosa and, to a lesser extent, the labial mucosa. The appearance may be that of a diffuse filmy grayish surface with white streaks, wrinkles, or milky alteration (Fig. 91-1). At rest the tissue may appear opaque, whereas when stretched, the opaque alteration dissipates to the point where it is barely visible.

Simply stretching the mucosa will cause the altered area to essentially disappear; however, leukoplakia or hyperkeratotic conditions will not demonstrate similar attenuation, thus allowing separation of this condition from leukoplakia. Other conditions that should be clinically separated from leukoedema include white sponge nevus, reactive keratosis caused by chronic low-grade trauma, the homogeneous form of lichen planus, and hereditary benign intraepithelial dyskeratosis.

Histopathologic Features

The surface of the epithelium is usually parakeratinized, whereas the epithelial ridges are broad and elongated with occasional spike-type morphology. Dominating the histomorphology is marked intracellular edema within the prickle cell or spinous cell layer, where individual cells will appear enlarged and optically clear or vacuolated, with peripherally displaced pyknotic nuclei and an overall bland appearance in association with a volumetric increase in the thickness of the epithelial layer (Fig. 91-2).

Figure 91-1. Leukoedema is characterized by a milky, translucent, and diffuse alteration of the buccal mucosa.

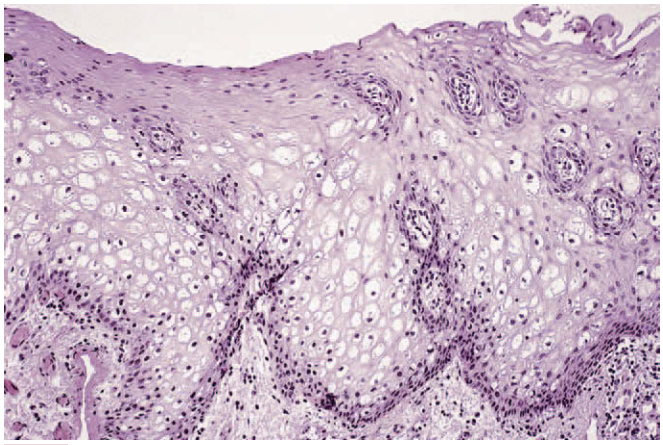

Figure 91-2. Leukoedema demonstrates large, pale epithelial cells with peripherally displaced pyknotic nuclei and broad epithelial ridges.

Management

This particular mucosal alteration does not require treatment because it is totally benign. There have been no reported cases of dysplastic alteration or transformation to carcinoma. The major concern relative to this condition is separating such from leukoplakia.

Oral Leukoplakia

Definition

Oral leukoplakia can be defined as a white patch or plaque that cannot be otherwise characterized clinically as representing any other disease entity. This de facto removes the concept of leukoplakia from the histopathology laboratory to the clinician in terms of definition and utility. From a historical perspective, albeit erroneous, many pathologists and clinicians use the term *leukoplakia* synonymously with *microscopic alteration,* in particular that of degrees of epithelial dysplasia or in situ carcinoma. The exclusionary diagnosis of leukoplakia will therefore eliminate more easily recognizable conditions including leukoedema, lichen planus, candidiasis, and white sponge nevus.

Experts commonly agree that leukoplakia represents the most common premalignant oral mucosal lesion; however, most cases are benign and remain so over time. The concept of malignant transformation is essentially related to the development of cancer or preinvasive cancer that is further characterized by variable degrees of epithelial dysplasia. The possibility of carcinoma and dysplasia must be carefully considered, with the percentages of leukoplakia showing microscopic evidence of dysplasia ranging from 3.7%[2] to 28.7%.[3] A more recent review[4] pointed out that the malignant transformation potential of leukoplakia was noted by Sir James Paget in 1851, when he provided the essential description of what we currently consider to be representative of leukoplakia. The entity of oral leukoplakia was initially and specifically described in the latter half of the 19th century by the Hungarian dermatologist Schwimmer. Since the late 18th century and into the 19th century, oral leukoplakia has been recognized and fully established as a definitive precancerous lesion, often serving as a harbinger for the development of oral cancer. The major clinical factor of importance in this lesion resides in its relationship to the general morbidity and relatively high overall mortality associated with invasive squamous cell carcinoma.

Conceptually, therefore, the definition of a premalignant lesion may be that of a morphologically altered tissue within which cancer is more likely to develop when compared with its apparently normal counterpart. In a more contemporary sense, the work of Waldron and Schafer (1975)[5] and Bouquot and Gorlin (1986)[6] established the clinical and microscopic correlation of leukoplakia in a large number of persons within the United States. In those studies the presence of dysplasia, carcinoma in situ, and invasive carcinoma in relation to oral leukoplakia from all sites ranged from 17% to 25%.

Figure 91-3. Lower lip vermilion surface affected with leukoplakia interspersed with patchy melanotic pigmentation.

Etiology

Although the cause of oral leukoplakia is unknown, several associated habits or behaviors are associated with the presence of this clinical lesion. Most closely associated with leukoplakia is the use of tobacco in its many forms including smoking and several forms of smokeless tobacco use. In other cultures the use of areca (betel) nut preparations with or without tobacco forms an additional source for this condition in patients.

By far, the most common cause of oral white lesions is trauma that includes frictionally related keratosis; however, this is not a true leukoplakia in that it represents a response to trauma in the form of hyperkeratosis, with reversal of such on elimination of the traumatic influence. A common site for frictionally induced hyperkeratosis is along the buccal mucosa at the occlusal line. At this location the formation of a linea alba is noted, whereas over the labial mucosa, a lip-biting habit can produce a slightly granular hyperkeratotic surface alteration, or so-called *morsicatio.* No evidence suggests that chronic frictional trauma transforms into dysplastic or frankly malignant disease.

Along the lower lip vermilion surface, patches of leukoplakia may develop in response to chronic sun exposure (actinic cheilitis), demonstrating close correlation with cumulative exposure and the level of cutaneous pigmentation (Fig. 91-3).

A recently described form of keratosis has been attributed to the use of mouthwash preparations and toothpaste containing an herbal

root extract, sanguinaria (Viadent). Characteristically, the lesion develops along the labial alveolar mucosa of the maxilla as an often translucent to slightly opaque white patch with well-defined margins and generally smooth surface features (Fig. 91-4). The relationship to development of dysplasia or malignant transformation in association with this entity remains controversial, with reversal of lesions often noted on withdrawal of sanguinaria-containing products.[7,8]

Figure 91-4. Viadent-related leukoplakia involves a portion of the maxillary alveolar mucosa as a well-defined thin keratotic surface alteration.

Clinical Features

A widely variable clinical pattern characterizes leukoplakia. In general the appearance can range from a thin grayish surface alteration demonstrating a white translucent quality with ill-defined margins (Fig. 91-5A) and generally smooth surface qualities to discrete, sharply marginated, thick and opaque plaques. In general terms such lesions may be homogeneous and smooth, focal or diffuse, or heterogeneous and multifocal with variable textures (see Fig. 91-5B and C). Surface textural alterations can range from a fine granularity to a slightly papillary outline. In addition, leukoplakia can appear ulcerative, erosive, speckled, nodular, or verrucous to the naked eye. Importantly, the various forms of leukoplakia often transition from one to another; however, this change of clinical appearance may not necessarily correspond to a shift in biologic behavior.[9,10] In cases where there is a clinical shift in

Figure 91-5. Leukoplakia. **A,** A homogeneous, slightly opaque alteration that is well marginated superiorly but merges with the gingival mucosa inferiorly. **B,** Hard palatal leukoplakia with a minimally elevated surface crossing the palatal midline. **C,** A thick, sharply marginated focal leukoplakia of the ventral/lateral tongue with a uniform erythematous periphery. **D,** Speckled or heterogeneous leukoplakia where the leukoplakia element is set on an erythroplakia. **E,** A diffuse thin leukoplakia of the ventral tongue surface with very homogeneous qualities and slightly diffuse peripheral margins.

appearance from homogeneous leukoplakia to a heterogeneous, speckled, or nodular form, a rebiopsy is mandatory (see Fig. 91-5D) because of the well-established correlation between increasing levels and frequencies of dysplasia and an increase in the level of regional heterogeneity or speckled quality.[11]

The term *thin leukoplakia* (see Fig. 91-5E) has been used to describe early leukoplakia formation. Such lesions generally progress over time from a macular to a slightly elevated translucent plaque with blending margins into normal-appearing mucosa, to later developing a more thickened appearance lending a more opaque white color to the lesion. Likewise, textural features may develop with increasing duration, which may be furrowed, leathery, or wrinkled in appearance. Similarly, lesions can become exophytic or verruciform in quality and might project above the surface. Although many lesions may remain for extended periods as homogeneous or more textured, thickened alterations, some lesions may disappear over time.

A recently described, uncommon variant of leukoplakia, *proliferative verrucous leukoplakia,* requires separate designation in that it is often noted in individuals without the usual risk factors for leukoplakia development, with lesion development noted in areas less commonly affected by oral squamous cell carcinoma. Behavior of this variant of leukoplakia is characteristically aggressive with changing histopathologic features, a more relentless behavior pattern, and greater tendency to develop into squamous cell carcinoma.[12] No linkage to human papillomavirus has been demonstrated in comparison with other forms of oral leukoplakia.[13] It is characteristically multifocal and persistent and tends to occur more often in women. An evolution from a thin, flat, white patch to a leathery, thickened, and ultimately papillary to verrucous stage characterizes this lesion over time (Fig. 91-6). When the lesion is microscopically evaluated at the papillary or verrucous stage, the diagnosis can vary from that of a benign or atypical verrucous hyperplasia to verrucous carcinoma or squamous cell carcinoma with papillary features. Likewise, characterizing this entity is persistence, a high recurrence rate, and development of squamous cell carcinoma in up to 74% of cases.[14,15] Gaining a better understanding of the behavioral qualities and variation across the spectrum of oral leukoplakia involves several factors including clinical appearance, location, and the presence and degree of dysplasia. Recent studies have demonstrated an association between progression of oral mucosal premalignancy and a loss of heterozygosity (LOH).[16] An essential step in the initiation of escape from normal epithelial proliferation and differentiation involves LOH at 3p and 9p where a modest 3.8-fold relative risk for oral cancer development has been noted. However, in cases where additional losses (4p, 8p, 11q, or 17p) existed, there was a 33-fold increase in relative risk for cancer development.[17] Lending a risk-targeting or prognostic strategy to this concept has been controversial, with earlier work concerning ploidy analysis being discredited and more recent studies refuting this claim.[18] No single or specific molecular pathway has been identified as the primary factor in the progression of epithelial dysplasia to squamous cell carcinoma. Continuing studies have revealed a range of molecular and genetic changes associated with oral squamous cell carcinoma tumorigenesis including mitochondrial alteration and several epigenetic changes, with continued ongoing investigation including those of altered methylation patterns and early carcinogenesis.[19] Finally, the relationship between the site of leukoplakia and the presence and risk of dysplasia or carcinoma must be considered. Earlier and more recent studies have underscored this relationship with the floor of the mouth, ventrolateral tongue, and retromolar trigone/soft palate complex carrying risk levels greater than other oral sites.[5,20]

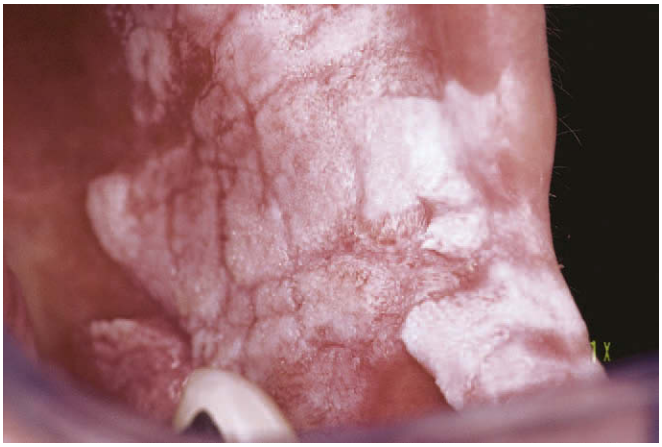

Figure 91-6. Developing proliferative verrucous leukoplakia with a thickened, elevated surface outline and coarsely granular to minimally warty surface qualities.

Histopathologic Features

A spectrum of histologic alterations characterizes idiopathic or true leukoplakia that ranges from hyperkeratosis and acanthosis to variable degrees of dysplasia or carcinoma in situ and ultimately invasive squamous cell carcinoma (Fig. 91-7). Cellular atypia, a component of dysplasia, refers to abnormal cellular features, whereas dysplasia refers to disordered cell growth and architectural distortion. With dysplasia, a grading system of mild, moderate, or severe is the convention; the level is determined subjectively in an attempt to convey tissue alteration to the level of intraepithelial localization or non-neoplastic or noninvasive quality.

Specific microscopic features of dysplasia include drop-shaped epithelial ridges, basal cell hyperplasia, irregular stratification and cellular maturation sequence, increased levels and abnormal quality of mitotic activity, individual cell or group level keratinization between the suprabasal and surface layers, cellular pleomorphism, altered nuclear-cytoplasmic ratio, reduced intercellular adhesion, and loss of basal layer polarity with "streaming" of spinous layer cells toward the surface.

An extension of these microscopic alterations to involve the entire epithelial compartment (i.e., "top-to-bottom effect") allows use of the carcinoma in situ designation. Alternatively, the term can also be used to designate particularly severe epithelial dysplasia that may not be fully developed from basal through the surface layers.

Treatment

Management of idiopathic leukoplakia will depend on the nature of the associated histologic findings obtained by incisional biopsy because the clinically defined term of leukoplakia requires microscopic characterization. With extensive lesions, multiple biopsies may be required to preclude errors of sampling, with the most clinically suspicious areas such as erythematous, granular, ulcerated, and indurated areas included.

Once defined as benign, premalignant, or malignant, a treatment plan can be formulated. In the case of benign or minimally dysplastic lesions, periodic simple observation or excision is an elective option, whereas premalignant lesions of moderate dysplasia or worse demand removal. The issue of how to manage mildly dysplastic lesions may concern itself with careful follow-up and observation or removal, if clinician and patient are committed to such. Complete removal of these lesions can be accomplished by a wide array of modalities including scalpel excision, laser ablation, electrocautery, or cryoablation.

The role of chemoprevention strategies in cases of mild dysplasia or treated dysplasia remains an active and important area of research, though there is no proven and effective prevention strategy regarding malignant transformation. Retinoids, antioxidants, and cyclooxygenase (COX)-2 inhibitors hold promise as management alternatives within the area of chemoprevention, though no effective strategy has yet been proven by randomized clinical trials. In general there is no effective treatment in preventing malignant transformation of leukoplakia.[21] On balance and regardless of location, the dynamic nature of oral leukoplakia and its cancer-related potential should be appreciated and understood. The key to limiting the likelihood of late-stage disease evolving from such lesions concerns itself with an appreciation of the potential of this group of mucosal alterations coupled with the establishment of early diagnosis, intervention, and follow-up.

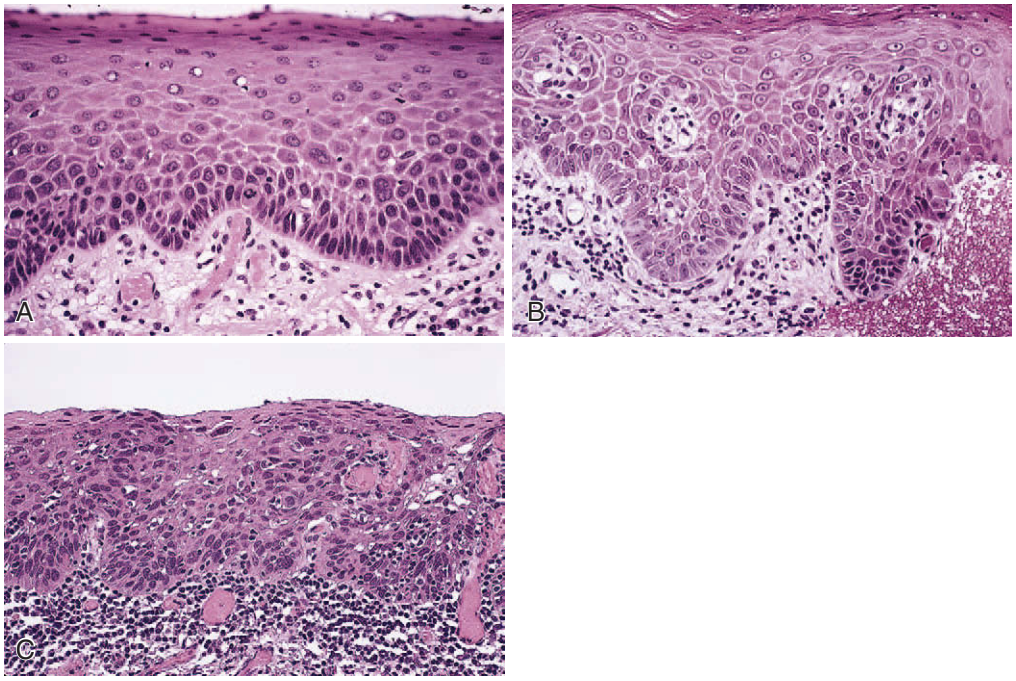

Figure 91-7. Epithelial dysplasia. **A,** Mild epithelial dysplasia with cytologic atypia confined to the lower epithelial strata. **B,** Moderate epithelial dysplasia contains several layers of atypical cells; however, the upper half of the epithelial thickness remains with a normal-appearing maturational sequence. **C,** Severe epithelial dysplasia with essentially full-thickness epithelial cell atypia, without evidence of invasion.

Figure 91-8. Oral hairy leukoplakia along the lateral tongue margin is characterized by vertically corrugated keratotic ridges.

Figure 91-9. A low-power view of oral hairy leukoplakia shows a thick parakeratotic surface layer and a characteristic pale subsurface layer above the spinous layer.

Oral Hairy Leukoplakia

Definition

A distinctive asymptomatic white lesion of the oral mucosa, oral hairy leukoplakia has been defined both clinically and microscopically with a distinct relationship in the vast majority of cases with systemic immunosuppression. The Epstein-Barr virus is considered the etiologic agent of this lesion that characteristically arises along the lateral tongue margins bilaterally, ranging from subtle white keratotic vertical streaks to thick corrugated and then to shaggy surface alterations (Fig. 91-8).[22] Early lesions may be more smoothly textured and macular in presentation. Less common sites include the dorsum of the tongue, buccal mucosa, and floor of the mouth.

Diagnosis by routine microscopy and in situ hybridization to demonstrate the presence of the Epstein-Barr virus is essential in that the confirmed diagnosis almost always correlates with systemic immunosuppression. The microscopic features suggesting this diagnosis include hyperkeratosis and irregular surface projections and irregularities (Fig. 91-9). Ballooning degeneration of the subsurface layers with nuclear alterations consisting of clearing and chromatin displacement by viral replication occurs along the inner aspect of the nuclear membrane in the form of "beading." Confirmation of the impression of a viral process can be achieved by in situ hybridization, Southern blot procedure, polymerase chain reaction, or ultrastructural demonstration of virus.

Management of hairy leukoplakia is not necessary in that establishment of the diagnosis remains the crucial task. In patients with proven association of HIV-AIDS, disappearance of the lesion usually accompanies antiretroviral therapy.

Oral Lichen Planus

Oral lichen planus is a relatively common mucocutaneous disease of immunologic origin that is mediated by a T-cell lymphocytic reaction

to antigenic components within the surface epithelial layer. The overall frequency of this condition is between 0.2% and 2% of the population. Characteristically over the oral mucosa, lichen planus typically presents as white striaform lesions that are bilaterally symmetric in their distribution, which, in this particular state, are relatively asymptomatic. However, other variants, in particular the erosive and ulcerative forms, will often be quite painful and may be what directs patients to seek care. In addition to its relative frequency, the importance of this particular entity concerns itself with the overall differential diagnosis, its similarity to other mucosal disorders, and its not infrequent symptomatic behavior.

Although the general etiology of lichen planus is unknown, it is generally thought to represent a T-cell-mediated or immunologically driven chronic inflammatory process in the absence of any consistent serologic changes. Immunologic studies have demonstrated that the lymphocyte subpopulations involve cells of mixed $CD4^+$ and $CD8^+$ types that express α-1 integrin molecules. The majority of the T cells present are activated $CD8^+$ cells.[23] Existing data suggest a complex nonspecific mechanism might be involved in pathogenesis including major histocompatibility complex (MHC) class 1- and MHC class 2-restricted antigen presentation by lesional keratinocytes, activation of antigen-specific $CD4^+$-positive helper T cells and $CD8^+$-positive cytotoxic T cells, clonal expansion of antigen-specific T cells, and keratinocyte apoptosis triggered by antigen-specific $CD8^+$-positive cytotoxic T cells. More recent studies, however, have discussed the monoclonal nature of lesional T cells in oral lichen planus.[24] Antigen-specific mechanisms therefore include antigen processing by resident dendritic cells and antigen-specific keratinocyte killing by $CD8^+$-positive cytotoxic T cells. A host of nonspecific mechanisms also seem to be involved in pathogenesis including activation of matrix metalloproteinases, mast cell degranulation, alterations in the epithelial basement membrane region, and elaboration of an array of proinflammatory cytokines including RANTES, which play a vital role in inflammatory cell recruitment into the area of the affected skin or mucosa.

An additional important factor in pathogenesis concerns basal and parabasal layer keratinocytes expressing MHC class 2 molecules, which they present to cells bearing $CD4^+$-associated T-cell receptors. The above-stated basement membrane alterations result in deposition of large amounts of fibrinogen in this region, which proves valuable within the context of the direct immunofluorescence testing and helps in establishing a diagnosis. In the process of basement membrane damage, up-regulation of additional molecules occurs including laminin, fibronectin, and types 4 and 7 collagen.

As a result of lymphocyte adhesion along the inner aspect of superficial vessels within the lamina propria of the mucosa, they soon exit the vasculature to traverse the basement membrane and migrate into the overlying epithelium secondary to the up-regulation of chemoattractants by keratinocytes.[25]

Clinical Features

Oral mucosal lesions of reticular lichen planus are most commonly seen in the middle-aged population with a characteristic distribution over the buccal mucosa in a symmetric bilateral manner. The surface of the mucosa is characterized by delicate white keratotic striae that intersect and arborize over a mucosal surface that may be diffusely erythematous to normal in quality (Fig. 91-10). Striae may be preceded by keratotic papules, which fuse and ultimately form the striae. The pattern is generally lacy to annular in configuration with extension over the buccal mucosa and often inferiorly into the mucobuccal folds. Striae may also appear over the dorsum and lateral portion of the tongue and less frequently over the attached gingiva and vermilion portion of the lip. Of note is the general freedom from symptoms related to this form or variant of oral lichen planus.

Other forms of oral lichen planus include the plaque form, atrophic or erythematous form, and erosive form. Characterizing the erosive form is a typically multifocal pattern of distribution, usually over the lateral and ventral tongue and buccal mucosa. Plaques can be smooth and macular to slightly elevated and minimally fissured. Although this form may be noted as the only presentation of oral lichen planus, it can also develop in late stages or previous areas of erosive lichen planus that had been successfully treated.

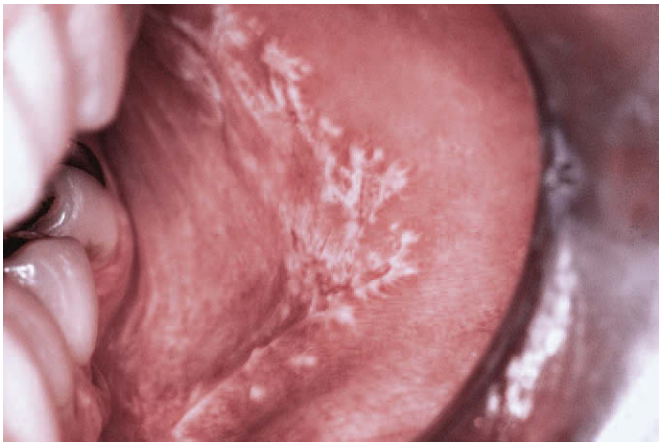

Figure 91-10. Reticular-type lichen planus with delicate striae over the posterior buccal mucosa.

Figure 91-11. Atrophic lichen planus with characteristic erythema and edema, loss of surface keratinization, and an overall glassy appearance.

Atrophic or erythematous lichen planus demonstrates only faint white striae, being dominated by thinned, reddened mucosa, often noted concomitantly with reticular or erosive forms of this disease. The attached gingiva is most likely to be involved by this type of lichen planus where there is a loss of the usual pink, stippled quality of the tissue surface (Fig. 91-11). In its place is a glossy, edematous, and erythematous alteration that is tender and bleeds easily, leading indirectly to the accumulation of large amounts of dental bacterial plaque. This usually results from the inability of patients to maintain their usual levels of dental hygiene given the friability and tenderness of the gingiva, which bleeds with the slightest provocation. Bacterial antigens and toxins in turn elicit the formation of inflammatory cytokines locally that further enhance the immunologically driven process within the lichen planus.[26]

Erosive lichen planus is characterized by central ulceration that can be deep and painful but is usually superficial in nature (Fig. 91-12). The ulcer is surfaced by a pseudomembrane or firmly adherent fibrinous plaque, which is usually sharply demarcated. Often it is possible to identify peripherally localized white striae, which gradually transition to an erythematous, nonstriaform region as the ulcerated area is approached. As the erosions heal, new areas will break down into ulcerations with variable patterns of change noted over time.

Rarely encountered is the bullous variant of oral lichen planus, with bullae ranging in size from a few millimeters to greater than 1 cm.

Figure 91-12. Erosive lichen planus of the buccal mucosa demonstrates irregularly marginated, intense erythema with patchy superficial erosions.

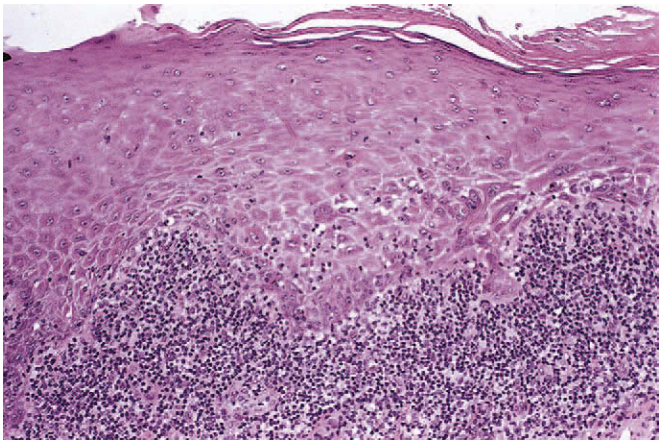

Figure 91-13. A characteristic intense lymphocytic infiltrate abuts the basal layer in mucosal lichen planus. Lymphocytes track into the epithelium, and intercellular edema is noted in the lower spinous layer with focal basal layer edema.

As with most oral bullae, they are transient and, on rupturing, painful ulceration results, with most lesions noted over the inferior and posterior aspects of the buccal mucosa. Identification of more typical forms of oral lichen planus likely to be present elsewhere in the mouth in association with this variant makes the clinical diagnosis less difficult.

Clinical Differential Diagnosis

The multifocal, bilateral nature of oral lichen planus will usually help exclude certain mucosal abnormalities such as traumatic keratosis and leukoplakia. Included, however, are lupus erythematosus, lichenoid drug reactions, graft-versus-host disease, candidiasis, and oral hairy leukoplakia. Plaque-type lesions can be confused with squamous cell carcinoma and leukoplakia; however, bilaterality and additional lichenoid alterations elsewhere will usually help separate these entities. With erosive/atrophic lichen planus involving the gingiva, consideration must be given to mucous membrane pemphigoid, pemphigus vulgaris, contact hypersensitivity, chronic atrophic candidiasis, lupus erythematosus, and erythema multiforme.

Association with Systemic Diseases

Oral lichen planus has been reported in conjunction with primary sclerosing cholangitis, lupus erythematosus, primary biliary cirrhosis, and Sjögren's syndrome.[27,28] Although controversial in certain geographic areas, within the United States there appears to be a lesser association between oral lichen planus and many systemic diseases, in particular hepatitis B and C, in comparison with patients with oral lichen planus in Italy and Japan, thus suggesting genetic susceptibility or predisposition.

Histopathologic Features

At the free surface of the epithelium, hyperkeratosis/parahyperkeratosis will be present. A slightly thinned to atrophic spinous layer overlies the basal and parabasal layers, which are often degenerate and vacuolated (Fig. 91-13). Over time, the epithelium becomes thin and may assume a sawtooth pattern on occasion. Scattered throughout the epithelium are increased numbers of dendritic cells that have been reported to function as antigen processing units, delivering prepared antigen to the subjacent lymphocyte population, which morphologically forms a dense bandlike pattern at the epithelial connective tissue junction.[29] At this junctional zone, occasional ovoid, anucleate eosinophilic droplets with hyaline features are noted. These represent apoptotic keratinocytes termed colloid or Civatte bodies.[30] Although nonspecific and nondiagnostic of lichen planus, they are highly suggestive of such when correlating other pathologic and clinical findings.

Reflective of the altered basement membrane region is the nonspecific deposition of fibrin that can be demonstrated by direct immunofluorescence studies as a uniform linear deposition along the basement membrane (Fig. 91-14). This pattern can be noted in up to 90% to 100% of cases.

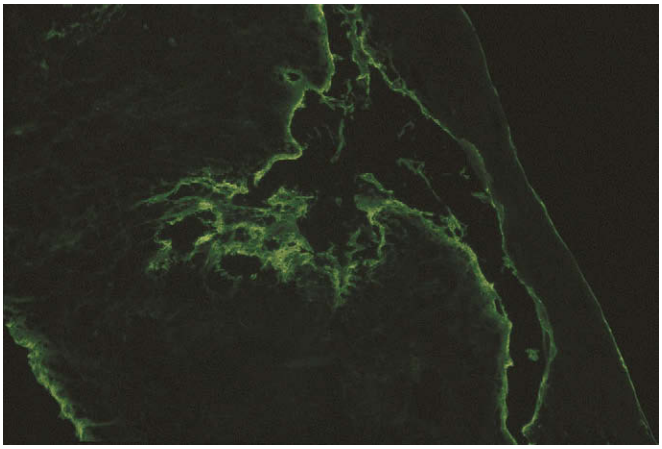

Figure 91-14. Fibrinogen reactivity at the basement membrane zone characterizes the direct immunofluorescence findings in lichen planus.

Treatment

Important in communicating the therapeutic end point to the patient is the notion that the goal of management is relief of symptoms because immediate cure is not to be achieved. Topically applied agents, usually corticosteroids, are the mainstay of management in most forms of oral lichen planus that are symptomatic in nature. The specific form or choice of corticosteroid will relate to the potency of such, with moderate to ultra-potent agents considered the modality of choice. More recently, the nonsteroidal topical agents tacrolimus and pimecrolimus have been shown to be effective in the management of symptomatic or lichen planus without the usual adverse effects related to topical steroid use, most commonly oral candidiasis.[31]

Management of recalcitrant focal areas of isolated lichen planus can be accomplished through the use of intralesional injections of corticosteroids such as triamcinolone suspension (10 or 40 mg/mL).

Systemic management of lichen planus can be used in cases of severe involvement using corticosteroids for a brief time until clinically obvious improvement is noted. Subsequently and for the longer term, topical management strategies can be used as noted earlier. Alternatives to systemic corticosteroids include hydroxychloroquine, azathioprine, and systemic retinoids.

Relationship to Oral Squamous Cell Carcinoma

A considerable degree of controversy exists as to whether a small percentage of lichen planus cases are capable of transforming into oral squamous cell carcinoma. Microscopic confusion, with epithelial dysplasia having an overall lichenoid quality, further adds to the controversy. There does, however, appear to be a small but bona fide risk of carcinoma evolving from proven oral lichen planus. Also important to understand is that when such transformation develops, it is far more likely to be seen in conjunction with the atrophic or erosive form of the disease rather than the far more common reticular or striaform type. This emphasizes the need for long-term follow-up, given the chronic nature of the disease process and the therapies employed for such.

The notion of lichenoid dysplasia versus dysplasia developing in lichen planus may not be readily settled. However, studies suggest a significant degree of allelic loss in dysplastic oral lichenoid lesions. Reports stating a degree of dysplasia in association with lichenoid features should alert the clinician to either remove the balance of the altered mucosa or follow the patient carefully.[32] Mattsson and colleagues[33] support the relationship between oral lichen planus and oral squamous cell carcinoma, yet they dispute, on an economic and practical basis, the need for continuous recall of these patients in specialists' offices and clinics.

Finally, the issue of an "oral lichenoid lesion" versus oral lichen planus has been discussed within the context of malignant transformation. Stated is the possibility of an increased risk of transformation within the context of lichenoid lesions, whereas true lichen planus may be less of a transformation risk.[34]

Submucous Fibrosis

Definition

Submucous fibrosis represents a multifactorial disorder with the considered chief etiologic factor being the consistent and habitual use of areca (betel) nut, either in the form of chewing or simply placing a quid of material (paan masala) in the buccal or labial sulcus several time per day, or in a packaged powdered form with other components (guthka), over many years. Submucous fibrosis is considered a premalignant condition, with transformation rates as high as 7.6% reported from India over a 17-year period.[35] Other researchers have reported 2.54% of cases demonstrating epithelial dysplasia.[36]

Etiology and Pathogenesis

Some experts believe the basic process is a failure of collagen remodeling and that altered epithelial-mesenchymal interactions result in formation of collagenous bands and aggregates within the submucosa and lamina propria. A diminished level of functional collagenase levels has been postulated as another mechanism to explain increased collagen accumulation.[37]

Clinical Features

Initial mucosal alterations characteristic of oral submucous fibrosis include erythema with or without vesiculation. The former reaction (erythema) is believed to be related to increased levels of inducible nitric oxide synthetase.[38] This is followed by slow diminishment of erythema and a progressive decrease in the degree of oral opening and tongue mobility reflective of the altered collagen metabolism. Pallor of the normally pink mucosa becomes evident as the underlying chronic inflammation recedes and fibrosis and hyalinization progress. Scar bands may become evident deep within the buccal soft tissues, further limiting jaw opening and function.

Development of squamous cell carcinoma is characterized by a gradual thickening of the epithelial surface with hyperplastic to verrucous surface qualities becoming evident.

Histologic/Diagnostic Features

Dominating the histopathology is a juxtaposition of atrophic epithelium surfacing a subjacent fibrosis. Early connective tissue alterations are characterized by delicate and loosely arranged collagen fibers with progressive degrees of hyalinization until, in the late stages, there is complete hyalinization of the supportive connective tissue. Variable degrees of chronic inflammation occur in the form of lymphocytes and plasma cells. Variable levels of dysplasia have been noted. In one study, mild dysplasia was present in 46% of cases, moderate dysplasia in 52%, and severe dysplasia in 2%.[39]

Treatment

Management of oral submucous fibrosis is problematic, particularly in advanced cases and when the use of areca-containing products remains in place. Surgical release procedures of scar bands have been only modestly successful. More recently collagenase and pentoxifylline administration in separate studies has been proposed.[37,40]

Verruciform Xanthoma

Definition

Verruciform xanthoma represents an uncommon benign oral mucosal lesion that also has a cutaneous counterpart where such lesions arise, particularly on the genitalia.

Etiology and Pathogenesis

The cause is unknown. The cellular lineage of the proliferative xanthoma cells is that of monocyte/macrophage type. They are noted chiefly in the fifth decade and have been classified into three types according to their microscopic surface qualities. These include the verrucous, papillary, and flat types.[41]

Clinical Features

As noted, three growth types have been identified. They are further characterized by being well circumscribed and with minimally to obviously granular surfaces. A wide size range has been reported, ranging from 0.2 cm to 2 cm. The surface may be depressed or flat, as well as elevated, and variably granular in texture.

Histopathologic/Diagnostic Features

Variable levels of surface hyperkeratosis cover a papillary or verrucous configuration with deeply invaginated crypts alternating with papillary extensions. Epithelial ridges composed of normal keratinocytes are elongated and extend uniformly into the lamina propria, which is engorged with numerous xanthoma cells containing characteristic foamy to flocculent cytoplasm. PAS-positive and diastase-resistant granules are present within the cytoplasm of these cells, as well as lipoid droplets, and are macrophages in nature.[42]

Treatment

Conservative surgical excision is the treatment of choice, with no recurrence potential noted.

Candidiasis

Definition

Candidiasis is a common opportunistic infection of the oral cavity, oropharynx, and corners of the mouth. Several clinical forms of this condition are noted—the easily recognized pseudomembranous form (thrush) in addition to erythematous, atrophic, and hyperplastic forms.

Etiology and Pathogenesis

Candida albicans represents the most common candidal species, whereas *Candida tropicalis, Candida krusei,* and *Candida glabrata* among others are less commonly involved. In immunosuppressed and neutropenic patients, however, these latter species are more often present. Of note is the essential shift from a commensal state to that of a "pathologic" state, in which former asymptomatic carriers of the organism now suffer from its overgrowth. Risk factors for development of candidiasis may include local and systemic factors (Tables 91-1 and 91-2). Commonly, systemic conditions such as poorly controlled diabetes mellitus and immunosuppression are associated with oropharyngeal candidiasis. Local effects or altered ecology of the region by topically delivered drugs (corticosteroids), xerostomia (with loss or diminution of saliva's protective function), heavy smoking, and denture appliances favor development of candidal overgrowth.[43-46]

Table 91-1

Oropharyngeal Candidiasis: Risk Factors

Local factors (mucosal barrier function)	Heavy smoking Foreign bodies (dentures, nasogastric tubes) Radiation-induced mucositis Inhalational and topical corticosteroid use Xerostomia Mucosal tumors
Systemic factors	Immunosuppression, age, viral-retroviral, chemotherapy, corticosteroid use Diabetes mellitus Intrinsic immunodeficiency Myelodysplasia/leukemia Antibiotic administration

Table 91-2

Clinical Forms of Oral/Oropharyngeal Candidiasis

Acute candidiasis	Pseudomembranous (thrush) Erythematous/atrophic
Chronic candidiasis	Hyperplastic (candidal leukoplakia) Denture-related (chronic erythematous/atrophic) Median rhomboid glossitis
Angular cheilitis	

From Akban A, Morgan R. Oral candidiasis. *Postgrad Med J.* 2002;78:455-459.

Figure 91-15. Acute erythematous candidiasis over the hard palate mucosa developed subsequent to a course of broad-spectrum antibiotics.

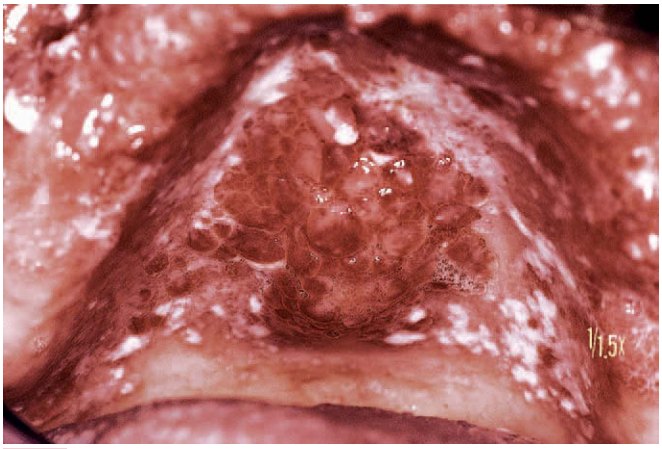

Figure 91-16. Pseudomembranous candidiasis (thrush) in a poorly controlled diabetic denture wearer.

Figure 91-17. Angular cheilitis caused by a lip-licking habit extending to perilabial skin.

Crucial to the establishment of infection, which implies a shift from commensalism, is fungal adhesion to mucosal surfaces and subsequent replication. Yeast adherence to several ligands is complex. It is aided by intrinsic candidal adhesion that in turn binds to salivary proteins that are absorbed onto cell surfaces.[47,48] Such binding, one measure of virulence, is a covalently mediated bonding in part related to fungal synthesis of this hyphae-associated proline-rich surface protein.

Clinical Features

Symptoms of oral/oropharyngeal candidiasis range from none or minimal ones to those that may include burning, dysgeusia, sensitivity, and generalized discomfort. Odynophagia may be noted in association with pharyngeal/hypopharyngeal involvement.

Of the clinical forms, the erythematous, atrophic, and pseudomembranous types are most likely to produce symptoms (Fig. 91-15). So-called denture sore mouth (chronic erythematous/atrophic candidiasis) is generally minimally to completely asymptomatic, whereas the acute forms are uniformly problematic. Deeply invasive candidal infection in immunosuppressed persons may present as an ulcerative lesion. Of note is the tendency of the various clinical forms to cycle from a bland, asymptomatic state to a symptomatic one in relation to general host factors or degree of medical compromise. Acute pseudomembranous candidiasis (thrush) with characteristic soft, white, and superficial colonies of organisms may be widespread and often asymptomatic (Fig. 91-16).

Angular cheilitis (Fig. 91-17) is generally considered to be a candida-related condition, although supervening or coinfection with staphylococcal species may be noted. In such instances the labial commissures can appear fissured, macerated, or erythematous, often with extension onto the adjacent skin.

Figure 91-18. So-called *candidal leukoplakia* may represent a hyperplastic response to long-term, asymptomatic oral candidiasis.

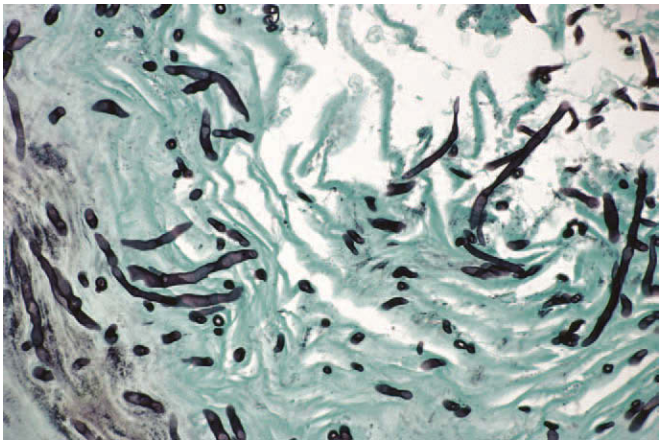

Figure 91-19. Fungal colonization of the oral mucosal surface with characteristic septate hyphae (methenamine silver stain).

Hyperplastic candidiasis, or leukoplakic-type hyperkeratosis, appears as asymptomatic keratotic plaques, often placed posterior to the labial commissures along the occlusal line. A triangular pattern of hyperkeratosis is noted with the apex directed posteriorly (Fig. 91-18). Less commonly, similar lesions may be present on the cheeks, palate, and lateral tongue surfaces. Because idiopathic leukoplakia may become secondarily colonized by candidal organisms, confusion may arise, often demanding a tissue biopsy to confirm the nature of the clinical lesion.

Differential Diagnosis

The manifold presentation of oral/oropharyngeal lesions permits a broad differential diagnosis. Of these entities, erythroplakia, speckled or nodular leukoplakia, and papular, erosive/atrophic lichen planus are to be considered. Squamous cell carcinoma, vitamin deficiency/malnutrition, hereditary dyskeratotic syndromes, and white sponge nevus can also be considered.

Histopathologic/Diagnostic Features

Clinical presentation of the diagnosis is often sufficient to allow for a diagnosis. The finding of atrophic red patches or white curdlike surface colonies with or without angular cheilitis in relation to discomfort in the more acute forms of the disease is usually compelling. The denture-related form of chronic erythematous candidiasis with restriction to the area covered by the appliance likewise forms the basis of a confident clinical diagnosis.

Confirmation of the diagnosis can be obtained by scraping the mucosal surface followed by smear preparation and placement of potassium hydroxide over the smear or use of a tissue stain such as periodic acid-Schiff (PAS) or methenamine silver preparations (Fig. 91-19). Finally, culture on Sabouraud medium may be considered and results of this test should be coupled with clinical findings. Of note is the fact that approximately 50% of adults (normal carriers) will have culture tests positive for intraoral candidal organisms; thus the clinicopathologic correlation becomes an important consideration.

Treatment

A wide spectrum of topical and systemic agents is available for several clinical classes. These include the topical polyene compound, nystatin, while the azole/triazole group of both topical and systemmic agents forms a larger treatment alternative. The nonabsorbable polyene compound in liquid or cream form may be useful for most mild to moderate infections, whereas the partially absorbed clotrimazole may be useful both topically and to a lesser extent systemically.[49] Systemically administered triazoles including fluconazole and itraconazole, as well as ketoconazole, are effective in eradicating more severe forms of this disease.[50,51]

Vesiculobullous/Ulcerative Lesions

Pemphigus Vulgaris

Definition

The term pemphigus relates to a group of autoimmune mucocutaneous diseases that may be life threatening and are characterized by intraepithelial cleavage or clefting with approximately 0.1 to 0.5 patients per 100,000 of the population per year affected by the most common form of this condition.[52,53] Despite the relative frequency in the population, otolaryngologists should be aware of this disease and its presentation; of note, at least 70% of patients with pemphigus vulgaris present with lesions in the upper aerodigestive tract as the initial manifestation, oftentimes heralding or preceding skin lesions by months to years.

In an effort to fully understand the pathophysiology or etiopathogenesis of this disease, one must understand that the mucosal lining of the nasal cavity, nasopharynx, oropharynx, oral cavity, and larynx is similar to that of the skin but differs in several important ways, not the least of which concerns the desmosomal components. Adhesion molecules desmogleins 1 and 3 (Dsg1 and Dsg3) are both expressed in the skin; however, mucosal epithelium expresses only Dsg3.[54] This particular desmoglein carries a 130-kilodalton molecular weight and resides in the extracellular space predominantly, although there is an intracellular domain that is bonded to an 85-kilodalton fraction, plakoglobin. Desmogleins as a group represent transmembrane glycoproteins and are members of the cadherin family of adhesion molecules. Dsg3 in particular is considered to represent the pemphigus antigen in the oral and oropharyngeal mucosa, is the specific target of the immune system in pemphigus vulgaris, and is targeted by immunoglobulins of the immunoglobulin (Ig) G class in the vast majority of cases; however, the IgA antibodies can also be the targeting antibody.

Several variants within the pemphigus group, the most common of which is pemphigus vulgaris, frequently involve the mouth, with its main importance being that this lesion or disease tends to run a chronic course. Before the introduction of corticosteroids, it was often fatal, secondary to complicating infections of the skin that ultimately led to sepsis, electrolyte imbalance, and fluid loss. In cases of pemphigus vulgaris in which only mucosal involvement is present, all antibodies are directed against the Dsg3 entity; however, when skin is involved, the antibodies to Dsg1 will also be present. In instances where antibodies to Dsg1 only are being synthesized, the condition pemphigus foliaceus develops with no evidence of disease in the upper aerodigestive tract because Dsg1 is not expressed in these locations.

A recently discovered form of pemphigus, paraneoplastic pemphigus, is usually associated with lymphoproliferative disease, although other types of malignancy may supervene. This entity was originally described by Anhalt and others[55] with numerous intraepithelial and

basement membrane antigens targeted simultaneously by a wide array of autoantibodies.

Etiology/Pathogenesis

As noted, autoantibodies directed against Dsg3 are the driving force in the development of mucosal dominant pemphigus vulgaris. The specific initiating factor or triggering event, as with any autoimmune disease, is unclear. However there is, in many instances, a genetic basis for the development of this disease. The latter is noted in particular within individuals demonstrating specific human leukocyte antigen (HLA) class 2 allele associations. These include rare haplotypes HLA-DR4 (DRBI *0402, DRw14, DRBI *1041).[52,56] The role of the HLA class 2 alleles appears to be important relative to recognition of Dsg3 peptides by the T lymphocytes, which are affecting the recognition response before the generation of specific antibodies by B lymphocytes.

In this disease there is a deposition of antibodies of the IgG class within the intercellular space that produces direct damage to the desmosomes, in particular the extracellular domain of the Dsg3 adhesion molecule.[57]

The specific mechanisms of epithelial cell dysfunction or acantholysis subsequent to immunoglobulin binding to the Dsg3 over the cell surfaces are being intensively studied. Several mechanisms being evaluated include down-regulation of desmoglein binding within the intercellular space, antibody-related altered transmembrane signaling, and possibly increased epithelial cell surface plasminogen activation that degrades nondesmoglein adhesion molecules.[57,58] Antigens other than desmogleins have been proposed as possibly contributing to the acantholysis process including a novel α-9 acetylcholine receptor that regulates keratinocyte adhesion, a keratinocyte annexin-like molecule, pemphaxin, and catenin.[59-61] The latter area of investigation remains controversial at the moment, with most authorities agreeing that the major antigen subset attacked in pemphigus vulgaris involving mucosal sites is Dsg3. The main effect of the process of antibody binding to target antigens within the epithelial intracellular space is epithelial cell dysadhesion or separation (acantholysis). This microscopic lesion results in the clinical evolution of vesicles and bullae.

Clinical Presentation

Oral and oropharyngeal lesions of pemphigus vulgaris are rarely seen in children and are usually noted in the fifth decade and beyond. The early oral manifestations tend to run a chronic course producing erosions, blisters, and ulcerations with the initial vesiculobullous lesions being short-lived; ease of rupture is followed by development of new vesicles as the older lesions collapse, and immediately after there is ulceration and pain.[62] The major clinical manifestations early on, therefore, are painful erosions and ulcerations seen predominantly in the oropharynx, soft palate, buccal mucosa, and labial mucosa (Fig. 91-20).

Figure 91-20. Pemphigus vulgaris of the buccal mucosa with patchy and irregular superficial ulcerations and surface slough representing collapsed bullae.

In contrast to mucous membrane pemphigoid, the mucosal ulcerations of pemphigus vulgaris heal relatively quickly and without scarring or complication. Healing is quickly followed, however, by formation of new lesions that run a similar clinical course. If the gingiva is involved, a desquamative process is evident as intensely erythematous, very friable surface qualities, with the slightest provocation producing tearing of the surface epithelial layer away from the deeper layers and resulting in transient bleeding (Fig. 91-21). Lesions will extend from the gingival margins to the alveolar mucosa, whereas the oropharyngeal lesions will favor the lateral aspects of the soft palate with extension to the lateral pharyngeal wall and inferiorly toward the vallecula.

Clinical Differential Diagnosis

To be considered along with pemphigus vulgaris in a clinical differential diagnosis are mucous membrane or cicatricial pemphigoid, lesions of lupus erythematosus, erythema multiforme and erosive lichen planus/bullous lichen planus, and paraneoplastic pemphigus.

Histopathologic Features

The dominant histopathologic feature of diagnostic importance represents separation or cleavage of the suprabasal layer from the basal layer of the overlying epithelium (Fig. 91-22). The basal cells will remain attached to the lamina propria, sometimes forming a so-called tombstone-like effect. Nonadherent spinous cells will separate and float freely

Figure 91-21. Subtle desquamative, tender lesions of pemphigus vulgaris involving the mandibular attached gingiva and alveolar mucosa.

Figure 91-22. A low-power view of clinically intact mucosa adjacent to ulcerated lesions of pemphigus vulgaris showing a discrete, uniform separation of the parabasal and superficial epithelium from the basal layer, which remains adherent to the basement membrane.

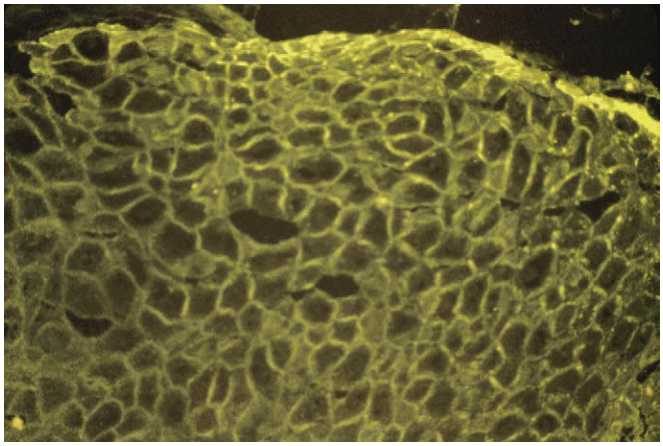

Figure 91-23. Fluorescence of the intercellular space regions with labeled anti-IgG antibody is diagnostic for pemphigus vulgaris.

Figure 91-24. Mucous membrane (cicatricial) pemphigoid with characteristic intact vesicles of the attached gingiva.

within the blister fluid (Tzanck cells), often becoming spherical in shape and demonstrating a somewhat eosinophilic quality.

Direct immunofluorescence examination is crucial in substantiating and formalizing the diagnosis, and results are positive in all cases of pemphigus vulgaris. Here one notes the presence of IgG localized to the intracellular spaces of the epithelium (Fig. 91-23), while C3 is localized to the intracellular spaces in approximately 80% of cases. Finally, indirect immunofluorescence will have positive results in nearly 80% of cases. Correlating the indirect immunofluorescence titers, as obtained by serial serum dilution, with the corresponding level of clinical severity will often be used to help determine treatment efficacy.

The diagnosis therefore becomes related to the nature of the clinical appearance, the mucosal manifestations, as well as the routine histologic investigation and the direct and indirect immunofluorescence study results.

Treatment

The mainstay of treatment concerns itself with systemic immunosuppression, using prednisone and nonsteroidal agents. Generally speaking, the initial attempt at management involves prednisone administration, 1 mg/kg, supplemented with either azathioprine or mycophenolate mofetil. Cyclophosphamide can be used, sometimes in conjunction with plasmapheresis, where severe disease is present, requiring rapid antibody reduction. For recalcitrant cases or for those unable to tolerate more routine immunosuppressive regimens, IV IgG may be appropriate. In cases of initially severe disease, plasmapheresis coupled with systemic immunosuppressive agents may be necessary.

The prognosis of pemphigus vulgaris remains guarded on the basis of the managing strategies necessary to suppress the disease and the risk of systemic infection, as well as treatment-related adverse effects. There is a 5% mortality rate due to long-term systemic corticosteroid use as a recognized treatment-related complication.

Mucous Membrane (Cicatricial) Pemphigoid

Definition

Mucous membrane, or cicatricial pemphigoid (MMP), is a heterogeneous cluster of autoimmune subepithelial vesiculobullous diseases immunologically characterized by a linear deposition of IgG and C_3 at the mucosal basement membrane zone. This group of conditions is disparate in terms of disease severity and the specific location of lesional activity at the microscopic or molecular level. Sites of mucosal involvement within the head and neck region include ocular, nasopharyngeal, oral, laryngeal, nasal, and esophageal areas.

Etiology and Pathogenesis

Mediation of this group of conditions involves the formation of autoantibodies directed against an increasing number of recently discovered

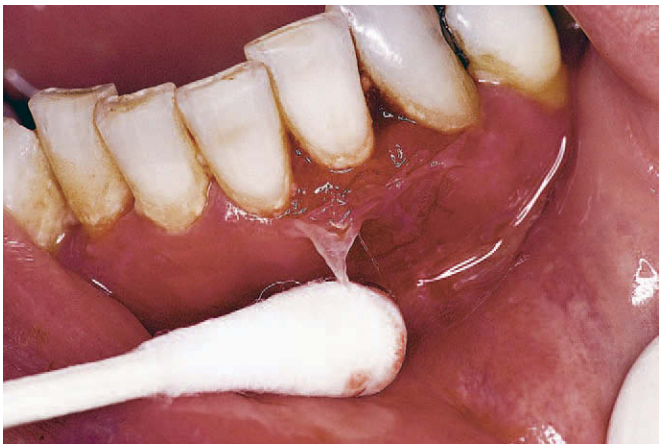

Figure 91-25. Stripping away the full thickness of gingival epithelium in mucous membrane pemphigoid with a dry cotton swab is helpful in identifying a cleavage disorder of the mucosa.

molecular components of the basement membrane zone. Most members of this group carry sequelae of scarring and loss of function, except for some cases in which exclusive oral mucosal involvement is present.[13] Pathogenic factors include antibodies to bullous pemphigoid antigen 2, laminin 5, β_4 integrin subunit, and bullous pemphigoid hemidesmosomal antigen 180.[63-65] To date, no specific correlation has been made between a target-specific autoantibody and a specific clinical form or subtype within this group.

In contrast to pemphigus vulgaris, a limited immunogenetic relationship has been noted, that being an increased occurrence of the HLA-DQB1 *0301 allele in patients with MMP.[66] Future studies investigating specific relationships between cell surface HLA-DQ molecules over antigen-presenting cells to T cells and specific autoantigens are necessary to better understand further details concerning the role of HLA-DQ alleles in this antigen-recognition process.

Clinical Features

The oral mucosa is the most commonly involved head and neck site in MMP, followed by ocular, nasal, and nasopharyngeal locations (Figs. 91-24 to 91-26). Oral and nasal sites will demonstrate erythematous features with patchy distribution of vesicles and bullae. At the site of a recently collapsed bulla, a pseudomembrane will surface an underlying ulcer. The most common location for this type of lesion is the keratinized tissue investing the palatal and attached gingival sites. Less commonly, the buccal mucosa and conjunctiva will be involved. Although

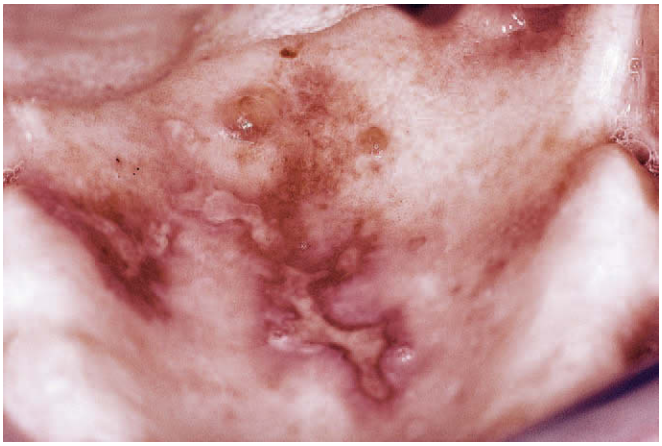

Figure 91-26. Intact vesicles and serpentine ulceration of the soft palate in mucosal pemphigoid are characteristic.

Figure 91-27. Ocular scarring (symblepharon) with bridging of the palpebral and bulbar conjunctiva in mucosal (cicatricial) pemphigoid.

intraoral scarring is not always present, ocular scarring is frequent with resultant complications that include symblepharon, ankyloblepharon, corneal opacification, entropion, and trichiasis. Scarring within the larynx and esophagus,[67] as well as within the trachea, may occur (Fig. 91-27).

Clinical Differential Diagnosis

As with pemphigus vulgaris, the differential diagnosis is a relatively broad one. Categories of inclusion would be those that are immunologically mediated, those related to aphthous ulcerations and Behçet's disease, and the group represented by reactions to drugs and other chemicals.[68] A summary of diagnostic considerations is seen in Table 91-3.

Histopathologic Features

On routine laboratory processing of formalin-fixed and hematoxylin-eosin stained tissue, a suggested diagnosis of mucous membrane pemphigoid could be made by virtue of demonstrating a separation of the mucosal epithelium from the underlying lamina propria in the absence of significant inflammation (Fig. 91-28). The site of tissue procurement should be an area adjacent to an inflamed, erosive, or bullous lesion, given the friable nature of clinically altered tissue. Thus a putative diagnosis of pemphigoid can be established, with a more definitive diagnosis related to performance of direct immunofluorescence testing. Perilesional mucosa will show linear immune deposits at the epithelial basement membrane zone composed of any one or combination of IgG, IgA, and C_3 in a continuous and homogeneous pattern (Fig. 91-29).

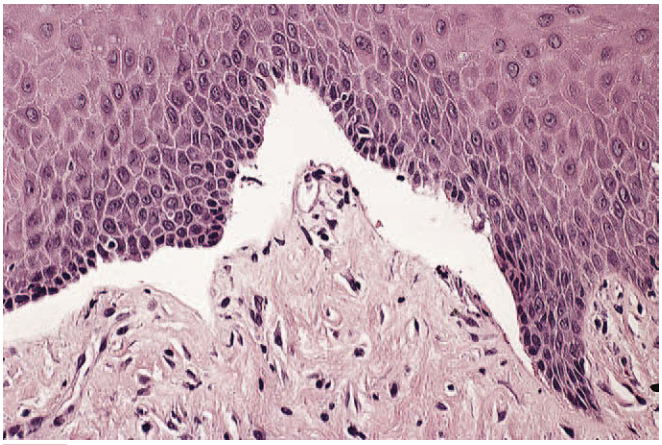

Figure 91-28. A sharply defined subepithelial cleft in the absence of significant inflammation is characteristic of mucous membrane pemphigoid but not completely diagnostic.

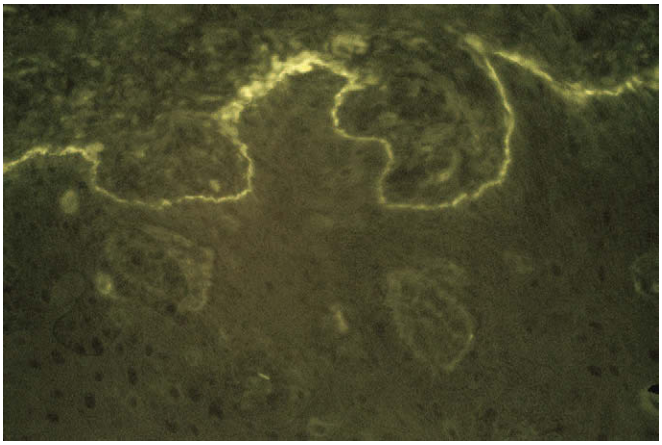

Figure 91-29. Mucous membrane pemphigoid (direct immunofluorescence) with linear IgG fluorescence along the basement membrane.

Table 91-3

Differential Diagnosis: Mucous Membrane Pemphigoid

Drug/substance/food reaction	
Viral (herpetic) infection	Primary herpes simplex Recurrent intraoral herpes simplex Intraoral varicelliform eruptions
Erosive lichen planus	
Epidermolysis bullosa acquisita	
Pemphigus vulgaris	
Paraneoplastic pemphigus	
Stevens-Johnson syndrome	
Erythema multiforme	
Linear IgA disease	

This pattern of fluorescence will allow separation of mucous membrane pemphigoid from other mucosal vesiculo-erosive diseases such as lichen planus, pemphigus vulgaris, erythema multiforme, and drug-induced lesions. Incorporation of clinical findings remains the final integrative step in finalizing this diagnosis.

Treatment

Factored into treatment must be the specific site of involvement, as well as the severity of involvement. With rapidly progressive disease that includes ocular mucosa, larynx, and esophagus, systemic prednisone and cyclophosphamide should be considered.[69,70] In cases of mild disease at several mucosal sites, initial treatment with Dapsone for 12 weeks can be used.[70] In cases in which only oral mucosa is involved, topical corticosteroids (moderate to high potency) could be the initial agents used. With gingival involvement, the use of soft acrylic removable carrier appliances can be helpful. Systemic tetracycline/nicotinamide has been used effectively as a nonsteroid-based approach in some studies.[71,72] Severe or unresponsive oral disease, however, may require oral prednisone with or without an additional immunosuppressive, steroid-sparing agent.[73]

Herpes Simplex Virus

Primary Herpes Simplex Infection

DEFINITION. Oral and oropharyngeal lesions caused by the human herpes simplex virus (HHV-1) are the most common virally induced oral/oropharyngeal ulcerative conditions, affecting from 60% to 90% of the population.[74,75] Each year in the United States, approximately 600,000 new cases of primary herpes simplex infection develop in the young, and less commonly in adults, without primary immunity. Spread of primary herpes simplex infection is usually through direct contact with an individual with active primary or recurrent disease. Additionally, asymptomatic shedding of HHV within the saliva of recovering or distantly infected persons serves as a source of infection.

ETIOLOGY AND PATHOGENESIS. HHV consists of a DNA core surrounded by a protein capsule assuming the three-dimensional form of an icosahedron enclosed within a protein envelope structure, measuring approximately 200 nm, and is subclassified into various subtypes on the basis of the level of virulence demonstrated within tissue culture. HHV-1 and -2 fall within the so-called α group of virulence classification, whereas more aggressive viral types fall within the β or γ groups.

The mode of oral infection involving HHV-1 (and rarely, HHV-2) relates to initial specific binding of virus to cell surface or plasma membrane receptors, specifically to envelope proteins on the virion surface. The viruses bind to keratinocytes, as well as neurons, and subsequently enter the cytoplasm of the cells by an endocytosis process. The viruses ultimately migrate through the nuclear pores and into the nucleoplasm, where propagation, virus core assembly, and release occur; in the process a nucleocapsid structure is acquired. Mature viral particles are then transported into the cytoplasm and ultimately are released through the cell membrane into the extracellular space whereupon they move ahead to infect adjacent cells. As a consequence of the replication and propagation of the virus within the nuclei of keratinocytes, there are terminal changes evident within the nuclei and plasma membrane to the point where plasma membrane leakage occurs and intracellular metabolic activity ceases. Ultimately, the cell becomes necrotic and releases large numbers of viral particles into the surrounding extracellular space. The lytic infectious process spreads from cell to cell, finally producing a clinically visible lesion in the form of a vesicle.

Also occurring during this time is the probable entry of virus into adjacent neurons, again by surface receptor engagement and endocytosis. This, in fact, represents the initial phase of latency development where virus reaches the trigeminal ganglion and, less commonly, other neuronal ganglia such as the nodose (vagal), dorsal root, and sympathetic ganglia.[75] Replication occurs within a minority of neurons between 2 and 10 days after provocation of recurrent infection, as noted in animal experiments.

CLINICAL FEATURES. The primary oral herpes simplex infection develops approximately 5 to 7 days subsequent to contact with an infected person. A prodrome lasting up to 48 hours can be characterized by focal mucosal tenderness and erythema, quickly followed by evidence of a group of small vesicles over the oral mucosa. Such vesicles are thin-walled, delicate, and short-lived. An inflammatory periphery surrounds each vesicle, followed by the development of shallow, painful, and discrete superficial ulcerations. In the primary phase of this disease, oral mucosal surfaces can be affected in both the keratinized and nonkeratinized regions. The presence of gingival lesions in the primary infection represents a key clinical diagnostic criterion in which the gingiva appears erythematous, boggy, and tender, with the free margin of gingiva discretely and distinctly involved by this process (Fig. 91-30). In this location, clusters of small superficial ulcerations are present in concert with lesions of similar quality elsewhere in the oral cavity. The infection can extend into the oropharynx and occasionally into the perioral skin region. The duration of the entire process ranges from 7 to 14 days with a generally self-limiting course. There is the potential that viral synthesis and presence within the oral cavity may continue for several weeks after clinical resolution (viral shedding), resulting in a continued ability to infect others lacking primary immunity.

Figure 91-30. Primary herpetic gingivostomatitis with tender, widespread vesicles and ulceration.

DIFFERENTIAL DIAGNOSIS. Clinical entities that may require separation from and that may resemble primary HHV-1 infection include herpangina (Coxsackie viruses A2, 4-6, 8-10), hand-foot-mouth disease (Coxsackie virus A16), chicken pox (varicella), measles (paramyxovirus), and erythema infectiosum ("fifth disease").

DIAGNOSIS. The establishment of a diagnosis of primary HHV-1 infection is made by virtue of the clinical presentation where the symptoms of prodrome are further characterized by the development of vesicular lesions that are quickly followed by ulceration and marginal gingivitis. It is generally not necessary to use laboratory methodologies to establish the diagnosis beyond the clinical recognition and affirmation; however, techniques including viral isolation and culture, cytologic analysis of vesicle content, and serum antibody titers as infection progresses are all valid techniques to verify and confirm the diagnosis.

TREATMENT. The management of primary intraoral HHV infection is generally considered to be symptomatic and supportive in nature as the patient develops antibodies to the infectious agent.

Recurrent Herpes Simplex Infection

DEFINITION. Recurrent HHV-1 infection ("secondary HHV-1") represents a recrudescent viral infection that occurs in a person previously infected with HHV-1. Underlying the recurrence is a formerly established latency state and abrogation of this former state of homeostasis between dormant virus and host immunity.

ETIOLOGY AND PATHOGENESIS. Escape or release from latency of virus from the dermatome-associated ganglionic neurons begins the process of recurrent disease progression. HHV-1 enters the neuron with sufficient DNA copies available to affect replication; however, the immune system suppresses such replication and α gene expression. A viral reservoir is necessary for maintenance of latency within infected

Figure 91-31. Recurrent herpes labialis with clustered intact vesicles at the skin-vermilion junction.

Figure 91-32. Recurrent intraoral herpes simplex in an adult with numerous, widely scattered vesicles and ulcers in association with pain, tenderness, and fever.

neuronal cells. Laboratory studies have shown that latency-infected neuronal cells range from 4% to 35% within the ganglion affected, on the basis of demonstrated virally directed RNA synthesis.[76]

Recurrences, as reflective of latency escape or viral activation, occur predominantly in the form of herpes labialis; however, intraoral recurrent disease also occurs, almost always within the keratinized epithelium of the hard palate and attached gingiva, and less commonly over the dorsal tongue surface. In such cases, multiple, shallow, closely cropped, tender erosions and ulcerations are noted. When on the hard palate, lesions often occur along the distribution of the greater palatine nerve, in particular in the first molar and premolar areas. The distribution is usually unilateral and involves the gingiva but does not cross the midline. When involving the mandibular-attached gingiva, the molar and premolar area is the site of predilection, as is the case in the maxilla.

Herpes simplex labialis represents the most common clinical form of HHV-1 recurrent disease, with a significant prevalence of HHV-1 primary immunity in the United States ranging from 40% to 60%.[77] The frequency of recurrent episodes ranges from 5% to 23% in some, whereas 58% to 61% suffer recurrences every 1 to 4 months.[78]

CLINICAL FEATURES. Characterizing recurrent herpes labialis is the initial prodrome period, which may be described as a focal area of altered sensation often described as painful, tingling, or burning with the subsequent development of vesicles at the prodrome site. The site most commonly involved occurs over the vermilion portion of the lip with overlap and extension to the skin surface immediately adjacent to this junction (Fig. 91-31). This site of involvement is generally repetitive or consistent from one recurrent episode to another. As vesicles form, they are initially pinhead in size and clustered, occur over an erythematous and edematous background, and often coalesce before rupturing with formation of tender ulcerations and ultimately crusting. Vesicles can remain intact for approximately 24 to 48 hours, and the crusting phase may persist for 5 to 7 days before healing without scarring, although in immunosuppressed individuals, in whom lesions tend to be larger and of longer duration, scarring can be observed.

Of note is the unusual presentation of widespread intraoral recurrent disease in adults with vesicle/ulcer distribution and corresponding pain and dysfunction (Figs. 91-32 and 91-33).

DIFFERENTIAL DIAGNOSIS. In the case of recurrent herpes labialis, a narrow clinical differential diagnosis exists. Contact sensitivity, angular cheilosis, traumatized perioral dermatitis, primary syphilis, and erythema multiforme can mimic this condition. However, the history, appearance, and distribution of the above-mentioned lesions will aid in their separation from herpes labialis.

HISTOPATHOLOGY. In cases in which recurrent herpetic lesions are biopsied, the usual circumstance is that of a recurrent intraoral vesicular lesion. In such instances, an intraepithelial vesicle forms in association with intense focal mixed inflammatory infiltrate (Fig. 91-34).

Figure 91-33. Typical recurrent intraoral herpes simplex infection along the course of the greater palatine nerve.

Infected keratinocytes will be enlarged with multilobulated viral inclusions (Tzanck cells), which will also be evident on a smear preparation obtained by unroofing an intact vesicle, removing the vesicular fluid for viral culture studies, and scraping the vesicle floor, followed by spreading the contents of the scraped cellular elements on a slide for a Tzanck prep and subsequent pathologic evaluation for the presence of viral cytopathic effect (Fig. 91-35).

TREATMENT. The management of recurrent herpetic infection in immunocompetent adults generally does not require the use of systemic antiviral agents. However, for the common labial recurrences, new topically delivered agents, docosanol cream and penciclovir cream, are available. Both agents target the viral replication process. At the intracellular level, in the case of penciclovir, the agent inhibits replication by way of inhibiting HHV-1 DNA polymerase formation. Docosanol, a saturated 22-carbon primary alcohol compound, prevents the initial fusion interaction between the viral envelope and keratinocyte plasma membrane, thus preventing access to the intracellular environment.[79]

Recurrent Aphthous Stomatitis

Definition

Recurrent aphthous stomatitis (recurrent aphthous ulcerations) represents the most common nontraumatic form of oral ulceration with an incidence range between 20% and 40% of the population. This remains an incompletely understood mucosal disease, chiefly affecting the oral and oropharyngeal mucosa, and less commonly, the genital mucosa. Of

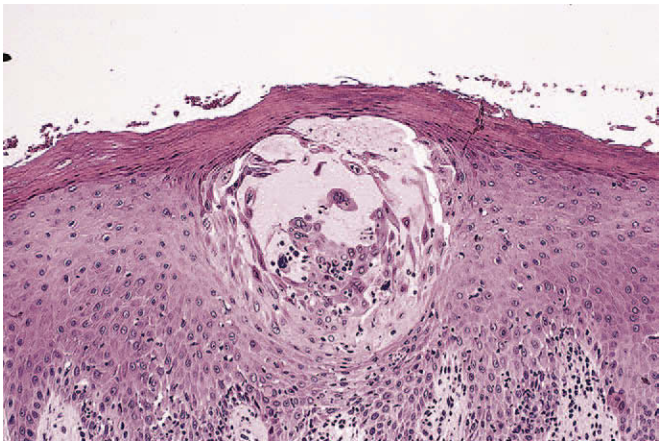

Figure 91-34. An intact vesicle of a herpes simplex lesion is intraepithelial in location and filled with serum and free-floating, virally infected keratinocytes and inflammatory cells.

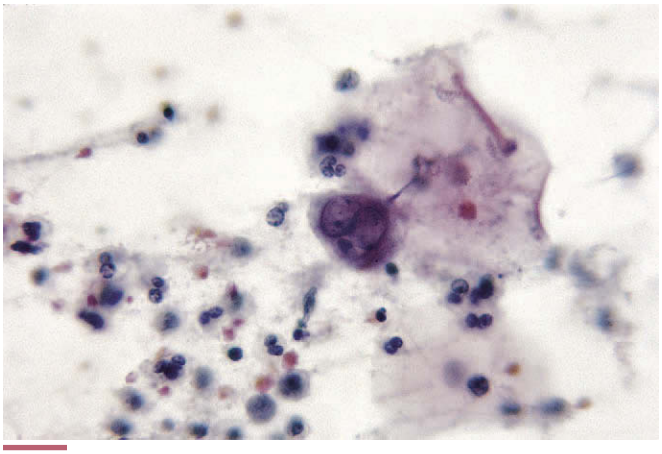

Figure 91-35. A Tzanck preparation from the floor of an unroofed herpetic vesicle showing virally induced cytopathic effect.

Table 91-4

Trigger Factors: Aphthous Stomatitis

Psychological stress	
Traumatic/iatrogenic injury	
Associated systemic diseases/conditions/syndromes	Crohn's disease/ulcerative colitis Behçet's disease Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome Malabsorption/gluten-sensitive enteropathy Human immunodeficiency virus disease Hematinic and other deficiency states Sweet's syndrome (acute neutrophilic dermatosis)
Foods	Chocolate Tomatoes Walnuts, hazelnuts, Brazil nuts
Menstrual cycle	

note are data indicating a greater prevalence among those in professional groups,[80] those of higher socioeconomic status, and nonsmokers.

Etiology and Pathogenesis

The specific etiopathogenesis of this entity is not known, although it is generally understood that there is a range of apparently disparate states or conditions with oral aphthous ulceration as a common feature. Included in this are Crohn's disease, Behçet's syndrome, gluten-sensitive enteropathy or celiac disease/nontropical sprue, and food hypersensitivity (e.g., nuts, spices, chocolate) (Table 91-4).

The ingestion of certain drugs including nonsteroidal anti-inflammatory agents, β-blockers,[81] and potassium-channel blockers[82] has also been associated with aphthous-type oral ulcerations. Withdrawal or avoidance of these agents in those affected will eliminate future recurrences, thus helping separate such lesions from true idiopathic aphthous ulcers.

Finally, two other systemic conditions, Sweet's syndrome (acute febrile neutrophilic dermatosis) and PFAPA syndrome (periodic fever, aphthous ulcers, pharyngitis, and adenitis), will demonstrate true aphthous ulcers as a component of the disease complex.[83,84]

A correlation or association with the presence of the HLA-B51 genotype[85] has been made in an attempt to explain familial clustering of this condition. Elaboration or up-regulation of the powerful cytokine TNF-α and other cytokines and chemokines of keratinocyte and lymphocyte origin, in association with up-regulation of adhesion molecule synthesis, results in keratinocyte lysis. Both T-cell–mediated and antibody-mediated processes are present, although the specific antigen remains unidentified.

An appreciation of the immunopathogenesis in the early phase of lesion formation, where a lymphocytic infiltrate at the site of the future ulcer is noted, is responsible for the clinical preulcerative phase of this process. This is quickly followed by the formation of a tense and tender focal tissue alteration characterized by a circumferential area of erythema that indicates a localized vascular engorgement and dilation along with a mild vasculitis. Within 24 hours, the papular tender area breaks down, forming the typical ulceration. Importantly, there is no sign of vesicle formation or blistering, versus primary or recurrent HHV infection, with a distribution of the lesions over the nonkeratinizing mucosal surfaces (labial, buccal, ventral and lateral tongue, floor of the mouth, soft palate, tonsillar pillars).

The complexity of lesion initiation and progression is emphasized by the likely multifactorial etiology with triggering and predisposing factors at play.[86] The latter include local physical trauma, psychic stress, the aforementioned hormonal influences, and a negative association in tobacco smokers and users of smokeless tobacco.[87,88]

Clinical Features

The traditional view concerning the clinical forms and presentations of recurrent aphthous stomatitis states the minor, major, and herpetiform types, with ulcer size being the major differentiating feature. More recent studies[86] have divided aphthous ulcers into three classes on the basis of their clinical presentation. Considered are the duration of the ulceration, their frequency/chronicity, and the level of symptomatology. From a practical standpoint, this form of lesional or disease classification can be more readily integrated with the type and intensity of treatment.

Minor aphthous ulceration accounts for up to 85% of all aphthous ulcers. Ulcers range up to 10 mm in diameter and are located over nonkeratinized mucosa, usually in the anterior portion of the oral cavity. The duration of ulcerative episodes ranges from 7 to 10 days, followed by healing without scarring (Fig. 91-36).

Major aphthous ulcers account for approximately 10% of aphthous ulcers.[89] They are large (>1 cm), occur typically in the posterior aspect of the oral cavity and oropharynx, may be associated with odynophagia, and are deeply cratered, sharply marginated, and painful

Figure 91-36. **A** and **B,** Minor aphthous ulcers of the labial mucosa and ventral tongue show a yellow fibrinous base, sharply marginated periphery, and erythematous periphery.

Figure 91-37. A solitary major aphthous ulcer at the posterior margin of the soft palate.

(Fig. 91-37). The duration of each episode may be up to 6 weeks but may persist for longer periods in the immunocompromised host, in whom they tend to be more severe, deeper, and more painful than minor-type aphthous ulcers, and they may serve as a marker for HIV disease progression.[90,91]

Herpetiform-type aphthous ulcers represent the least common variant of aphthous ulcers, with most cases affecting the moveable or nonkeratinized surface tissue, although there may be lesions of keratinized areas affected on occasion. Presentation occurs as multiple pin-

Figure 91-38. Herpetiform aphthous ulcerations of the lower labial and alveolar mucosa are pinhead in size, numerous, and of shallow depth.

Table 91-5

Recurrent (Two-Degree) HHV versus RAS (minor)

	HHV	RAS
Etiology	Herpes simplex I/II	Varied/immune dysfunction
Location	Keratinized tissue; mucosa	Moveable/ nonkeratinized
Vesicle phase	Yes	No
Duration	7-14 days	Varies (usually 7-10 days)
Management	Topical (docosanol, penciclovir), oral antivirals	Severity-related, usually topically-based steroids
Prodrome	Often	Uncommonly
Triggers	Stress, trauma	Stress, ultraviolet light, foods
Biopsy findings	Viral cytopathic effect	Nonspecific

HHV, human herpes virus; RAS, recurrent aphthous stomatitis.

head-sized to 2-mm shallow craterform ulcers with a widespread distribution (Fig. 91-38). Clinical resemblance to the lesions of primary HHV infection is noteworthy—hence their designation as herpetiform. To contrast these lesions with those of herpes simplex, one will note the absence of a vesicular phase before ulcer formation, and adult onset and pain levels are disproportionately greater than the extent of lesion development.

Differential Diagnosis

Separation of aphthous ulceration from the ulcers of intraoral HHV infection and traumatic ulcers remains the major differential diagnosis. Paramount in the separation of these conditions is an understanding of the general differences in location and the presence (herpetic infection) or absence of a vesicular phase (aphthous ulcer) in addition to other factors noted in Table 91-5.

Histopathologic Features

An absence of any pathognomonic features characterizes all forms of aphthous ulcers. An early central zone of keratinocyte necrosis/ulceration is evident. Ulcers are surfaced by a thin fibrinous plaque, whereas deep to the surface a mixed inflammatory infiltrate in association with an increased number of engorged, dilated vascular elements is present. Perivascular aggregates of lymphocytes and histiocytes are present in the absence of vasculitis.

Treatment

Mild and infrequent episodes of minor aphthous ulcers generally require little more than symptomatic management. When treatment is necessary, the general mainstay is the use of topical steroids. When lesions are severe or occur as a continuous series of outbreaks, short-term administration of systemic corticosteroids is effective. Intralesional steroid delivery can be useful in cases of larger (major) aphthae or those less than fully responsive to other forms of treatment.

Erythema Multiforme

Definition

Erythema multiforme (EM) represents a self-limiting, usually acute, mucocutaneous hypersensitivity reaction characterized by cutaneous or oral ulcerations. A less severe chronic or persistent form of this condition also exists, in which lesions of the skin, lips, and mouth may be noted concurrently or asynchronously. The condition may range from a self-limited, mild, exanthematous process with skin and minimal oral involvement (EM minor) to a more fulminant, progressive process with epithelial necrosis of skin and mucosa—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[92] It may be prudent to view EM, SJS, and TEN as an overlapping spectrum of the same process with varying degrees of severity.

Etiology and Pathogenesis

Controversy exists concerning the initiation event of this reactive disease process; however, it is clear that numerous triggers have been associated with this condition including photosensitivity, medications, and viral infections including Epstein-Barr virus, chronic hepatitis C, HHV-1, and parvovirus B19, with recurrent HHV-1 the most common trigger.[93-97] Although approximately 50% of cases can be associated with triggering agents or events (infections, drugs),[98] the latter group of cases (drug-induced EM) are most commonly identified as being associated with antiseizure medications such as carbamazepine and phenytoin, as well as sulfonamides, other antibiotics, and some analgesics. The strongest association, however, is between recurrent HHV-1 infection and EM; in two series, respectively, 79% to 100% of EM cases followed such an infection.[99,100] Controversies of etiology aside, it is clear that in a high percentage of EM cases, preceding recurrent HHV infection or another infectious process (e.g., viral, mycoplasma) or drug ingestion serves as the major etiologic factor. Also reported is the frequency of circulating immune complexes in the serum of patients with EM.[101]

At the tissue level, antigen-antibody complexes diffuse from local vasculature to initiate activation of the complement cascade followed by development of local vasculitis and a directed movement of neutrophils and macrophages into the epithelium and lamina propria. Keratinocyte necrosis follows with formation of oral and cutaneous ulceration.

Clinical Features

An acute and self-limiting reaction, EM involves mucosa and skin with bullae or ulceration in a symmetric distribution. Classic target or iris lesions develop over the skin and are characterized by concentric circles or annular configurations of slightly erythematous to pigmented quality (Fig. 91-39). At the center, bullae or vesicles may develop. The oral mucosa and vermilion portion of the lips may demonstrate aphthous-like ulcers and erosions, and on occasion vesicles or bullae may be present. Mucosal ulcers are symmetrically distributed, irregular in size and shape, tender, and covered with a fibrinous plaque (Fig. 91-40). Crusted, hemorrhagic plaques over the vermilion portion of the lips with edema, fissure formation, and extreme tenderness are characteristic (Fig. 91-41). Oral and oropharyngeal dysfunction includes sialorrhea, pain, odynophagia, and dysarthritic-type speech. Hydration and food intake may be impossible due to pain and the inability to chew and swallow. Severe EM (EM major/SJS) may best characterize this latter constellation of signs and symptoms along with involvement of other mucosal sites including eyes, genitalia, and uncommonly the esophagus and pulmonary tract. Of note is the occasional finding of antibodies to desmoplakin I and II in some patients with EM, suggesting a possible humoral mechanism at play, as well in the pathogenesis of the major form of this condition.[102]

Figure 91-39. Numerous "iris" or "target" lesions of erythema multiforme over the thenar eminence in a patient with oral and oropharyngeal involvement by this condition.

Figure 91-40. Intraoral ulcerations of erythema multiforme showing thick pseudomembranous lesions over the ventral tongue surface and floor of the mouth.

Differential Diagnosis

Other mucocutaneous diseases to be ruled out in the absence of iris or target lesions include severe aphthous ulceration, pemphigus vulgaris, mucosal (cicatricial) pemphigoid, and erosive lichen planus. The clinical diagnosis of EM is often one of exclusion, however, with a biopsy occasionally being necessary to exclude these conditions.

Histopathologic Features

Routine histopathology will, on perilesional or nonulcerated mucosa, show spongiosis, apoptotic basal and parabasal cells, intense lymphohistiocytic infiltration (often in a perivascular distribution), and edema, with extension of this process from the submucosa into the superficial lamina propria. Preulcerative areas will show keratinocyte necrosis,

Figure 91-41. Exudative, tender lesions of the lower labial vermilion surface and mucosa of erythema multiforme.

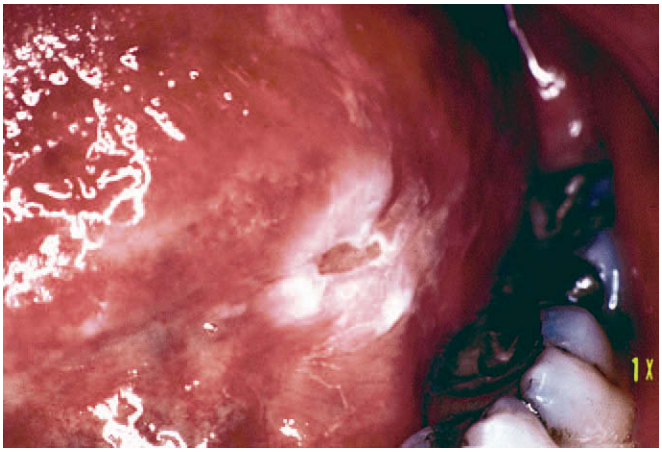

Figure 91-42. A so-called traumatic (eosinophilic) granuloma presents as a chronic, sharply marginated ulcer, often with a variable level of peripheral hyperkeratosis.

edema within the lamina propria, intercellular and intracellular edema, and vacuolar degeneration at the basement membrane zone.

Although the direct immunofluorescence findings are not pathognomonic, there will be an absence of antibody binding within the epithelium. However, blood vessel walls will contain fibrin, C_3, and IgM.

Treatment

Specifics and philosophy of managing EM are on one hand controversial and on the other related to the level of severity. Whereas prior HHV-1 (recurrent herpes labialis) infection was noted, dosing with antiviral drugs at less than full therapeutic doses has reduced further episodes of EM.[95] When only oral lesions are present (EM minor), management may be symptomatic only or with a short course of conservative corticosteroid administration. Details of symptomatic management will include use of oral hygiene aids, bland mouth rinses or compounded rinses containing combinations of topical steroids, and antifungal and local anesthetic agents. Analgesics may be useful in an effort to manage odynophagia, thus allowing adequate levels of hydration and caloric intake.

Traumatic (Eosinophilic) Granuloma

Definition

The traumatic or eosinophilic granuloma is a benign, usually large, and self-limiting chronic oral ulcer that is often of long duration. It is usually seen in association with a putative deep mucosal injury.

Etiology

In spite of its designation as "traumatic," it is unusual for affected individuals to isolate a prior traumatic event in relation. Most feel that the origin of the process is unknown.

Clinical Features

Presentation generally occurs in the fifth through seventh decades of life as a painful ulcer of rapid onset, with the majority of lesions developing along the lateral and ventral tongue surface. On occasion, dorsal tongue surface lesions may be seen. The average diameter ranges from 1 to 2 cm with a craterform center, sharply marginated periphery, and firm, indurated peripheral qualities (Fig. 91-42). Duration is usually several weeks but may persist for several months. Often, the peripheral or bordering epithelial surface is milky white to opaque/white in appearance over the indurated margin.

Differential Diagnosis

The location, texture, appearance, and chronic duration may suggest squamous cell carcinoma. Major aphthous ulceration, oral ulcers of Crohn's disease, syphilis, granulomatous diseases, and lymphoma may also be considerations at the clinical level.

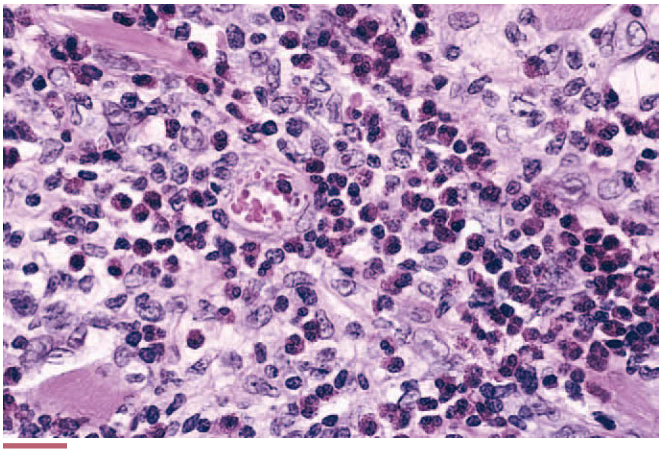

Figure 91-43. An intense chronic inflammatory infiltrate containing numerous scattered eosinophils between skeletal muscle bundles is characteristic of the traumatic granuloma.

Histopathologic Features

Deep ulceration extending into underlying skeletal muscle dominates the pattern, with an intense diffuse and polymorphous inflammatory infiltrate evident. The latter is characterized by the presence of large numbers of histiocytes, endothelial cells, and eosinophils (Fig. 91-43). Muscle bundles are often separated by the chronic inflammatory/granulomatous process. Myofibroblastic cells have also been identified within the stroma, although experts believe these cells are a reactive component.[103]

Immunohistochemical studies have demonstrated an unclear and complex array of staining results. Prominent are CD30 (Ki-1)-positive cells, which are found in Hodgkin's disease and benign reactive conditions. One study demonstrated highly active T cells, CD68-positive cells, and dendrites cells (CD1a+) suggesting a possible relationship to cutaneous CD30-positive lymphoproliferative disorders.[104] Histologic and behavioral similarities have been noted with the atypical histiocytic granuloma, implying the likelihood that this entity may form a subset or a histologic variant of the traumatic eosinophilic ulcer.[105]

Treatment

Because these lesions are self-limiting but often chronic, the clinician may choose a tactic of observation only. Use of topical or intralesional corticosteroids may hasten resolution. Excision is a consideration if the clinical presentation is in question.

Figure 91-44. Discrete, uniformly pigmented macules of the lower labial vermilion surface characterize the melanotic macule.

Figure 91-45. Focal melanosis ("smoker's melanosis") is characteristic over the buccal mucosa as scattered, macular, evenly pigmented patches.

Pigmented Lesions

Oral mucosal pigmentation of melanocytic type includes a wide variety of conditions including racial and physiologic types, nevi, and benign melanocytic proliferation to preinvasive and invasive melanoma. The variety of oral mucosal melanoma (<1% of all cases of all melanoma) has made a comprehensive analysis of this entity impossible; however, it is clear that melanoma can occur at any mucosal site with subtype variation similar to that seen at cutaneous sites.[106] Crucial for clinicians to appreciate as far as the overall poor prognosis for oral mucosal melanoma in general is a delay in recognition of early disease and a corresponding delay in diagnosis by physicians. Often noted is the lack of recognition or appreciation of oral melanotic or pigmented macules and plaques that can represent the radial growth phase of melanoma evolution.[107] In an effort to further define oral pigmented lesions of potential significance, the initial step is a determination of whether the pigmentation is intrinsic (e.g., melanocytic, inflammatory, non-melanin–containing) or extrinsic (e.g., amalgam tattoo, medication-related, traumatic implantation of exogenous material).[108]

Melanotic Macules

Definition

An often troubling pigmented lesion of the vermilion portion of the lower lip (30%), gingiva and alveolar mucosa (23%), and buccal (16%) labial mucosa (9%) is the melanotic mucosal macule.[109] Studies to date have identified a distinct female predilection with site (lower lip), sex (female, 2:1), and racial (white) predominance (Fig. 91-44).

Etiology and Pathogenesis

Mucosal melanotic macules can be idiopathic (ephelis), postinflammatory, syndrome-associated (Peutz-Jeghers, Laugier-Hunziker), or related to systemic disease (Addison's disease) (see Table 91-6 for a more complete listing). Melanocytic lesions derive from the neural crest–derived melanocyte. Melanocytic proliferation is common to mucosal melanocytic nevi that arise from intraepithelial melanocytes, while the submucosal/"dermal" melanocyte gives rise to the blue nevus. Other benign melanocyte-derived processes, the ephelides and melanotic macules, are representative of excess melanin production rather than melanocytic overgrowth/hyperplasia. Melanoma and its precursors (superficial spreading melanoma) relate to the malignant quality of melanocyte proliferation with markedly altered morphology, distribution, and behavior relative to typical melanocytes and nevus cells.

Clinical Features

MUCOSAL MELANOTIC MACULE. As the name mucosal melanotic macule indicates, a macular zone of hyperpigmentation, generally less than 10 mm in diameter with even, well-defined margins, and homogeneous pigment distribution characterize these benign hypermelanotic lesions (Fig. 91-45).

MUCOSAL MELANOCYTIC NEVI. Mucosal melanocytic nevi, on the other hand, as a result of nevus cell (altered melanocyte) proliferation, can appear in the young or at birth as focal macular to papular hyperpigmented lesions and may persist throughout childhood. Oral melanocytic nevi may be nonpigmented in up to 20% of cases, with the palate being the most common site affected, followed by the buccal/labial mucosa, gingiva, and alveolar ridge.

Table 91-6

Oral Mucosal Pigmented Diseases and Conditions

Etiology	Disease/Agent
Idiopathic-melanocytic	Ephelis (focal) Nevi (junctional, compound, intramucosal, blue, focal) Melanoma and melanoma precursors
Postinflammatory (diffuse)	
Syndromic (association)	Peutz-Jeghers (focal) Laugier-Hunziker (focal) McCune-Albright (diffuse) Neurofibromatosis (diffuse) Cushing's (diffuse) Addison's (focal and diffuse)
Medication-related (all diffuse)	Minocycline Clofazimine Chloroquine, antimalarials Azidothymidine Chlorpromazine Heavy metal–containing drugs Quinidine Cyclophosphamide
Extrinsic	Amalgam tattoo Traumatic implantation

Melanoma

Oral mucosal melanoma is a rare neoplasm with a racial predilection for Asians and blacks. Although a preexisting melanosis may be a precursor, this, when present, likely represents lateral spread or superficial spreading melanoma. Although oral melanomas do not fit neatly into the well-defined cutaneous melanoma categories, these are parallels to acral lentiginous and nodular melanomas.[110] Those melanomas evolving from an earlier or precursor lateral spreading or superficial spreading form are almost always found in adults. Early melanoma of this type is flat, irregularly marginated, and heterogeneously pigmented. With progress, the degree of pigmentation increases, as does the surface area, with a deeper brown to variegated gray-brown color noted. Most oral melanomas derive from the macular form; however, some arise ab initio as a rapidly growing nodule (nodular melanoma).

Most oral mucosal melanomas (40%) occur on the hard or soft palate, whereas gingival melanomas (Figs. 91-46 and 91-47) comprise approximately one third of melanomas.[109] Most intraoral lesions (85%) are invasive at initial discovery or show both invasive and in situ features. This site distribution is at odds with that of Pliskin,[111] who found 57% of cases originating in gingival soft tissue in his series.

Differential Diagnosis

A relatively narrow field of entities may be considered as clinical diagnostic alternatives within the spectrum of oral pigmented lesions. Melanotic mucosal macules must be separated from superficial spreading melanoma, Kaposi's sarcoma, and exogenous pigmentation such as amalgam tattoo. Nodular melanoma and intramucosal nevi can show clinical overlap, as can venous/vascular mucosal varicosities.

Histopathologic Features

The ephelides and melanotic macules are characterized by accumulation of melanin pigment within the basal layer of the mucosal epithelium, often with variable degrees of melanin incontinence into the superficial lamina propria (Fig. 91-48).

Mucosal melanocytic nevi, depending on specific type, are characterized by altered melanocyte ("nevus cell") accumulation within the epithelium exclusively, often in aggregates or as so-called "theques" in junctional nevi. In compound nevi, aggregates of nevus cells are present concurrently within the epithelium and lamina propria. When nevus cells are exclusively located in the lamina propria and superficial submucosa only, an intramucosal nevus is present. Finally, proliferation of the deeply located submucosal melanocyte forms epithelioid and spindle-shaped cells, often highly pigmented, in the blue nevus.

At early stages, melanoma histomorphology will show aggregation of atypical melanocytes at the epithelial-connective tissue junction, with extension toward the epithelial surface often noted. Later lesions will demonstrate melanocytic extension into the lamina propria and deeper structure as the vertical phase of growth establishes itself (Fig. 91-49).

Melanomas, as the great imitator, can assume a wide array of patterns and can demonstrate numerous cell morphologies including epithelioid, spindle (Fig. 91-50), stellate, and plasmacytoid forms.

Figure 91-46. Melanoma of the hard palate with uneven pigmentation, diffuse margins, and widespread distribution.

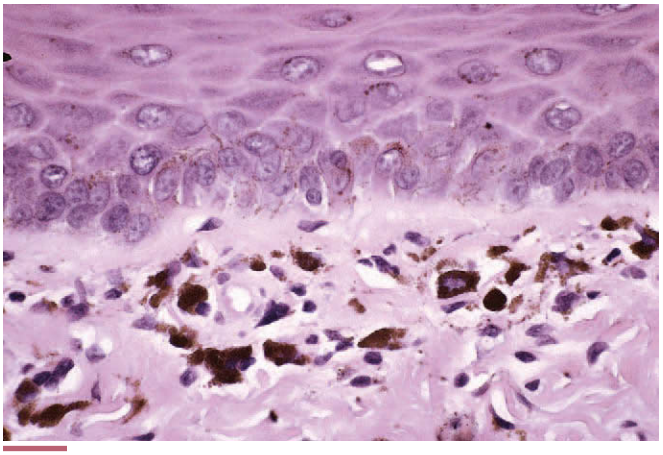

Figure 91-48. A focal melanotic macule with barely discernible dendritic processes of melanocytes within the epithelium in association with clusters of melanophages and free melanin in the lamina propria.

Figure 91-47. Gingival melanoma. This lesion arose as a slightly nodular pigmented surface alteration with more macular or superficial spreading qualities at the free gingival margin.

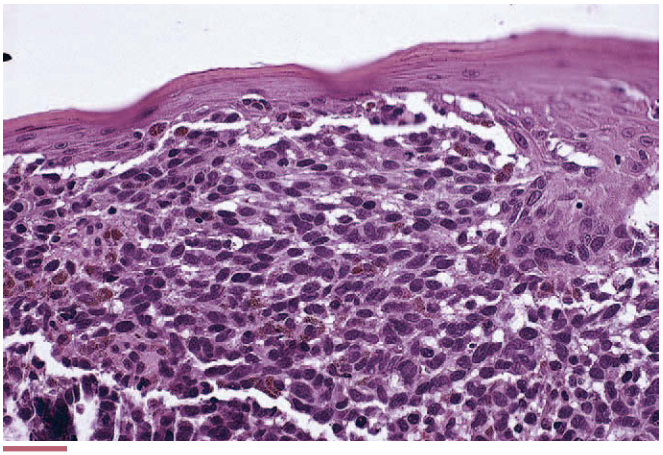

Figure 91-49. Melanoma of the palate with epithelioid and spindle-shaped melanocytes invading the epithelium and extending deeper into the lamina propria.

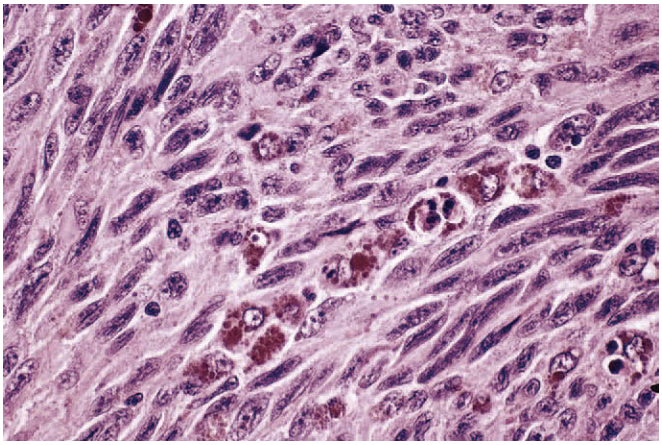

Figure 91-50. Melanin-laden melanoma cells of polyhedral shape within a prominent spindle cell population of melanoma cells.

Figure 91-51. An amalgam tattoo of the labial mucosa with a characteristic gray-black color, macular surface, and slightly diffuse margins.

Patterns formed may be likewise variable, including organoid clusters, sheets, spindle-neurotropic, alveolar, and desmoplastic variants. In cases of amelanotic melanoma or other variants, it may be necessary to use immunohistochemical techniques such as S-100, HMB-45, and melan-A expression to identify melanocyte lineage.

Treatment

Benign melanocytic lesions (e.g., macules, ephelides, melanocytic nevi) can be conservatively excised as the excisional biopsy during the diagnostic phase of investigation.

Superficial spreading and invasive and nodular melanoma remains, with surgery, the prime treatment modality. Depth, surface coverage of lesion, and location will determine the extent of excision.

Prognosis remains quite poor, independent of the site within the oral cavity. As with cutaneous melanoma, thickness of tumor and clinical stage are correlated with overall survival. Excellent sources discussing prognostic factors in head and neck melanomas are those of Batsakis and colleagues[112] and the consensus statement from the WESTOP Banff workshop[110] on oral mucosal melanomas. The overall 5-year survival for all oral mucosal melanomas is 15%, and there is a median survival time of 46 months in the absence of lymph node involvement versus an 18-month survival in the face of positive lymph node findings.[109]

Amalgam Tattoo

Definition

The amalgam tattoo is an extrinsically derived mucosal pigmentation that results from traumatic implantation or chronic low-grade frictional transfer of dental silver amalgam into adjacent oral mucosa.

Etiology

Subsequent to silver particles entering the lamina propria/submucosa, a minimal chronic inflammatory infiltrate becomes established. Macrophages, and less commonly, multinucleated giant cells ingest the material, thus allowing dispersal into the immediate vicinity. The migration of these phagocytic cells into regional lymph nodes may, as in the case of decorative tattoos, deposit particulate silver amalgam in regional draining lymph nodes, thus mimicking metastatic melanoma.[113]

Clinical Features

Usually well-defined, macular grayish-black focal macular mucosal discoloration characterizes the amalgam tattoo. These tattoos are noted characteristically on the mandibular-attached gingiva, mucobuccal fold, and alveolar gingiva or buccal mucosa (Fig. 91-51). On occasion, they may be evident on routine dental radiographs when traumatic implantation of sufficient material occurs. They range in size from 1 mm to 1.5 cm, with most being 0.4 cm or smaller.[114]

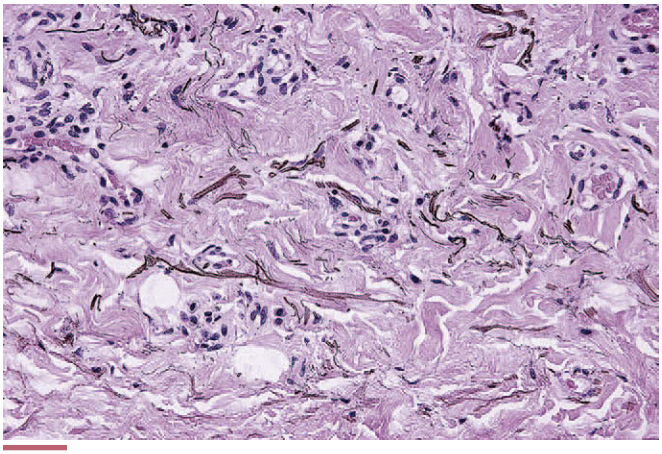

Figure 91-52. Fine particles of amalgam within this amalgam tattoo are distributed along collagen bundles within the submucosa.

Differential Diagnosis

A wide range of conditions may be considered at the clinical level within the context of the amalgam tattoo. These include melanoma; vascular malformations; melanotic lesions such as blue nevus, intramucosal, and other melanocytic nevi; and other traumatic implantations such as graphite.[115]

Histopathologic Features

Black (reduced) foreign metallic material will be located within the lamina propria and submucosa. Older lesions will contain collections of finely granular silver-containing deposits along the basement membranes of vasculature, nerves, and epithelium, as well as along collagen bundles (Fig. 91-52). Multinucleated giant cells, though not invariably present, will contain ingested material, as will macrophages. Energy-dispersive x-ray analysis has been used to demonstrate the presence of silver and copper in these tissues.[116]

Treatment

Management may relate to establishing a clinicopathologic correlation and observation only. Often a biopsy procedure will simply confirm the clinical diagnosis; however, once identified, removal is elective. Specific treatment strategies include simple surgical excision or, as has been reported, with use of a Q-switched ruby laser.[117]

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CHAPTER NINETY-TWO

Oral Manifestations of Systemic Diseases

Jonathan A. Ship

Michael D. Turner

Key Points

- Recent epidemiologic studies have demonstrated an association, but not a causal relationship, between heart disease and dental/periodontal diseases because of periodontal pathogens and certain serologic proteins found in the gingival sulcus that cause systemic inflammation.
- Antibiotic prophylaxis before certain dental procedures is recommended for persons with cardiac valvular abnormalities at risk for developing subacute bacterial endocarditis. Recent modification of the antibiotic recommendations simplified and clarified the regimen to reduce overuse of antibiotics, potential adverse effects, and drug resistance. Dental procedures for which endocarditis prophylaxis is reasonable are events that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.
- Patients on cardiovascular medications can have hyposalivation, which is deleterious to oral and pharyngeal health and function. Specific etiologies include classes of medications such as diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors.
- Early detection of oral cancer is critical because patients with early-stage tumors have considerably better survival rates than those with late-stage cancers that have already spread to regional tissues and the lymphatic system.
- Head and neck cancer patients must undergo preoperative dental evaluation and treatment before definitive therapy so as to remove oral pathology (e.g., dental caries, periodontal disease, nonrestorable teeth) before developing the common oral sequelae of surgery, chemotherapy, and radiotherapy.
- The motor, sensory, and cognitive alterations that accompany cerebrovascular diseases have deleterious effects on oral health and function. A cerebrovascular accident (CVA, or stroke) can cause permanent oral sensory and motor deficits, resulting in poor tongue function and lip seal, difficulty eating and drinking, impaired use of dentures, and visuospatial problems with adverse social and psychologic consequences.
- Most patients on anticoagulation requiring simple oral surgical procedures, if local hemostatic and conservative surgical techniques are used, do not need to discontinue their anticoagulation regimen.
- Patients who control their diabetes have fewer oral health problems than those with poorly controlled diabetes. There is an association between severe periodontitis and an increased risk of poor glycemic control.
- Sjögren's syndrome (SS), a systemic autoimmune disorder associated with inflammation of epithelial tissues, is the most common medical disorder associated with xerostomia and salivary dysfunction.
- Herpes simplex virus (HSV-1) and varicella-zoster virus (VZV) are the most common viral infections in the oral-facial region. They can present as herpes labialis or primary herpetic gingivostomatitis (HSV-1) or acute, painful, oral-facial lesions (VZV).
- The most frequent oral fungal infection is caused by *Candida albicans.* The overgrowth of *C. albicans* in the oral-pharyngeal region has many etiologies: endocrine disorders (e.g., diabetes), immunosuppression, nutritional deficiencies, medications (particularly antibiotics and long-term immunosuppressants), salivary gland hypofunction, removable dental prostheses, and poor oral and denture hygiene.
- Lichen planus is a chronic, mucocutaneous, autoimmune disorder that can be precipitated by a number of conditions such as genetic predisposition, emotional stress, or drug, food, or dental material hypersensitivity.

The oral cavity plays a major role in physiology. Three critical functions are performed by the oral cavity: the intake of foods and beverages, communication, and the protection of the host from noxious substances. Multiple head, neck, and oral tissues have evolved to carry out these vital functions including the following: muscles of facial expression, mastication, and deglutition (including the tongue); oral mucosal, dental, and periodontal tissues; salivary glands; and taste and smell receptors. These tissues continually work together to keep a person hydrated and nutritionally healthy, to protect the upper aerodigestive tract, and to provide chemosensory information about foods, beverages, and potentially dangerous substances. Many of these processes and tissues can remain remarkably intact throughout the course of a person's life, yet numerous systemic diseases and their treatment (e.g., medications, surgery, head and neck radiation, chemotherapy) can cause significant impairments to oral health. These problems can subsequently lead to malnutrition, infection, impaired communication, pain, and an impaired quality of life.

The oral cavity has been frequently referred to as a window into a person's body. Several systemic diseases manifest initially through oral manifestations, which can be readily examined via noninvasive techniques. Saliva and crevicular fluid (exudate from the periodontal ligament) may replace certain serologic tests in the future, and buccal epithelial cells may provide diagnoses for systemic diseases. Recognition of normal and unusual oral conditions will help improve the prevention, diagnosis, dissemination, and management of many systemic diseases. Systemic conditions may require modifications of oral treatments (Table 92-1), and drugs can affect oral health (Table 92-2). This clearly requires a multidisciplinary approach to health care involving numerous specialties from medicine and dentistry.

The purpose of this chapter is to provide an overview of the oral manifestations of the most prevalent medical conditions and their treatments. Recognition and treatment of many systemic conditions can help prevent the development of certain oral diseases. Conversely, diagnosis and management of numerous head, neck, and oral diseases can help minimize the progression and severity of several systemic diseases.

Diseases of the Heart

Diseases of the heart such as ischemic heart disease, myocardial infarction, and hypertension have remained the number one cause of death for the past 5 decades. Given that these diseases are common chronic ailments affecting the elderly, any oral manifestations of the conditions, as well as their treatments, will become more common in the future with the expansion of the older population.

Some cardiovascular conditions and their subsequent treatment have oral-facial signs and symptoms and therefore have oral treatment considerations. Anginal pain can appear as referred pain to the neck, clavicle, and mandible, and it can be localized to the mandible and teeth. A comprehensive differential diagnosis must include consideration of dental-alveolar origin (e.g., caries, periodontal disease), temporomandibular joint (TMJ) disease, referred musculoskeletal pain, central or peripheral nervous system pain, and myocardial infarction.

Table 92-1

Oral Treatment Considerations Due To Systemic Conditions

Systemic Condition	Cause	Oral Considerations	Treatment Considerations
Coagulation disorders	Anticoagulation therapy Chemotherapy Liver cirrhosis Renal disease	Increased bleeding risk	Alter anticoagulation therapy Limit dental-alveolar surgery Use topical anticoagulation methods
Immunosuppression	Alcoholic cirrhosis Chemotherapy Diabetes Medications Organ transplant therapy Renal disease	Microbial infections	Appropriate antimicrobial medications
Joint replacements	Accidents Osteoarthritis Rheumatoid arthritis	Increased risk for late prosthetic joint infections	Antibiotic prophylaxis
Radiation sequelae	Head and neck radiation	Salivary hypofunction Mucositis Osteoradionecrosis Increased caries risk Dysphagia Dysgeusia Difficulty with mastication Microbial infections Impaired denture retention	Regular fluoride use Salivary substitutes and stimulants Aggressive oral hygiene and recall Pain management
Steroid therapy	Autoimmune diseases Organ transplant therapy	Microbial infections Increased risk for adrenal insufficiency	Appropriate antimicrobial medications Steroid supplementation for dental procedures
Valvular damage/heart murmur	Acquired heart defects Congenital heart defects Valvular transplants	Increased risk for developing subacute bacterial endocarditis	Antibiotic prophylaxis

Table 92-2

Overview of Oral Sequelae of Medication Intake for Systemic Diseases

Drug Category	Drug	Oral Problem
Analgesics	Aspirin	Hemorrhage, erythema multiforme
	NSAIDs	Hemorrhage
	Barbiturates, codeine	Erythema multiforme
Anesthetics (local)	Benzocaine, procaine HCl, lidocaine	Taste disorders
Antiarrhythmics	Procainamide	Lupus-like reaction
	Quinidine	Lichenoid mucosal reaction
Antiarthritic, antipyretic, anti-inflammatory	Allopurinol, auranofin, colchicine, dexamethasone, hydrocortisone, levamisole, D-penicillamine, phenylbutazone, salicylates, 5-thiopyridoxine	Taste disorders
	Gold salts	Taste disorders, lichenoid reaction, oral pigmentation, vesiculo-ulcerative stomatitis
Antibiotics	All	Oral candidiasis
	Erythromycin	Hypersensitivity reaction, vesiculo-ulcerative stomatitis
	Penicillin	Hypersensitivity reaction, erythema multiforme, vesiculo-ulcerative stomatitis
	Chloramphenicol, ciprofloxacin, clindamycin, dapsone, isoniazid, sulfa antibiotics, tetracyclines	Erythema multiforme
	Minocycline	Melanosis
	Chlorhexidine	Brown pigmentation of teeth & tongue
	Ampicillin, cefamandole, ethambutol, hydrogen chloride, griseofulvin, lincomycin, metronidazole, niridazole, sulfasalazine, tetracyclines	Taste disorders
Anticoagulants	All	Hemorrhage
Anticonvulsants	Carbamazepine	Erythema multiforme, taste disorders
	Phenytoin	Erythema multiforme, gingival enlargement, taste disorders
Antidiarrheal agents	Bismuth	Dark pigmentation of tongue
Antihistamines	All	Salivary dysfunction
	Chlorpheniramine maleate	Taste disorders
Antihypertensives	All	Salivary dysfunction
	Calcium-channel blockers	Gingival enlargement
	Angiotensin-converting enzyme inhibitors	Vesiculo-ulcerative stomatitis, pemphigus vulgaris
	Chloramphenicol	Vesiculo-ulcerative stomatitis
	Hydralazine	Lupus-like reaction, erythema multiforme
	Methyldopa	Lupus-like reaction and lichenoid mucosal reaction
	Thiazide diuretics	Lichenoid mucosal reaction
	Minoxidil, verapamil	Erythema multiforme
	Acetazolamide, amiloride, captopril, diazoxide, diltiazem, enalapril, ethacrynic acid, nifedipine	Taste disorders
Antilipidemics	Cholestyramine, clofibrate	Taste disorders
Antimycotics	Griseofulvin	Erythema multiforme, black pigmentation of the tongue
	Amphotericin B	Taste disorders
Antineoplastics	All	Oral candidiasis, oral hemorrhage, recurrent oral viral infections, aphthous stomatitis, vesiculo-ulcerative stomatitis
Anti-parkinsonian	All	Salivary dysfunction
	Levodopa	Taste disorders

Continued

Table 92-2

Overview of Oral Sequelae of Medication Intake for Systemic Diseases—cont'd

Drug Category	Drug	Oral Problem
Antireflux agents	All Cimetidine	Salivary dysfunction Erythema multiforme
Antithyroids	Carbimazole, methimazole, methylthiouracil, propylthiouracil, thiouracil	Taste disorders
Antioxidants	Octyl gallate	Allergic ulcerations
Anxiolytics	Benzodiazepines	Salivary dysfunction
Chelating agents	Penicillamine	Ulcers and pemphigus vulgaris
Corticosteroids, immunosuppressants, antiproliferatives	All Azathioprine, bleomycin, carmustine, doxorubicin, 5-fluorouracil, methotrexate, vincristine sulfate Cyclosporin	Oral candidiasis, recurrent oral viral, infections, vesiculo-ulcerative stomatitis Taste disorders Gingival enlargement
Hypoglycemics	Sulfonylurea agents Glipizide, phenformin and derivatives	Erythema multiforme Taste disorders
Muscle relaxants	All Baclofen, chlorzoxazone	Salivary dysfunction Taste disorders
Others	Etidronate, germine monoacetate, idoxuridine, iron sorbitex, vitamin D	Taste disorders
Psychotherapeutics	All Glutethimide, meprobamate Phenothiazines Lithium carbonate Trifluoperazine HCl	Salivary dysfunction Erythema multiforme Oral pigmentation, tardive dyskinesia Erythema multiforme, taste disorders Taste disorders
Sympathomimetics	Amphetamines, amrinone	Taste disorders
Vasodilators	Bamifylline hydrogen chloride, dipyridamole, nitroglycerin patch, oxyfedrine	Taste disorders

HCl, hydrogen chloride; NSAIDs, nonsteroidal anti-inflammatory drugs.

Several recent epidemiologic studies have demonstrated an association, but not a causal relationship, between heart disease and dental/periodontal diseases.[1-5] Periodontal pathogens and certain serologic proteins found in the gingival sulcus (particularly C-reactive proteins) have been found in carotid atheromas and shown to induce platelet aggregation. However, the role of periodontal infection as a risk factor for cardiovascular disease requires further scientific validation. Recent data have further demonstrated a possible link between periodontal conditions and systemic measures of inflammation. Intensive periodontal treatment resulted in acute, short-term systemic inflammation (increased levels of C-reactive protein, interleukin-6, and the endothelial-activation markers soluble E-selectin and von Willebrand factor), as well as mild endothelial dysfunction. However, importantly, 6 months after therapy, without any adverse events, marked benefits in periodontal health were statistically associated with improvement in endothelial function.[6]

The treatment of cardiovascular diseases with drugs also has deleterious oral consequences. For example, antihypertensive medications have been shown to cause salivary dysfunction (as in the cases of diuretics, calcium channel blockers, β-blockers), gingival enlargement (calcium channel blockers), lichenoid mucosal reactions (thiazide diuretics), and disturbances in taste (ACE inhibitors, calcium channel blockers). Higher salt detection thresholds have also been observed in persons with hypertension.[7] Consideration of possible alteration of drug regimens is appropriate.

Persons who have undergone cardiac transplantation and are receiving postoperative immunosuppressive pharmacologic regimens must be evaluated for potential oral complications. Immunosuppressive therapy increases the prevalence of oral opportunistic infections such as reactivation of herpes simplex virus and overgrowth of *C. albicans.* Cyclosporine, a frequently used antirejection drug, has been reported to cause gingival enlargement in up to 13% to 85% of patients.[8]

Consideration must be given to cardiac conditions before dental treatment is undertaken. Patients receiving anticoagulation therapy may present with hemorrhagic lesions of oral mucosal tissues (see "Cerebrovascular Diseases" later). Antibiotic prophylaxis is recommended for persons with cardiac valvular abnormalities at risk for developing subacute bacterial endocarditis (Table 92-3). Recent modification of the antibiotic recommendations simplified and clarified the regimen to reduce overuse of antibiotics, potential adverse effects, and drug resistance.[9] Dental procedures for which endocarditis prophylaxis is reasonable (see Table 92-3) are events that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. The regimen for antibiotic prophylaxis is provided in Table 92-4.

Table 92-3

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous IE
- Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.
From Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. *J Am Dent Assoc.* 2007;138(4):458-474; and Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *J Am Dent Assoc.* 2007;138(6):739-745, 747-760.

Although the dental office environment and dental treatment can increase heart rates and blood pressures, treatment can be safely rendered to patients with ischemic heart disease with adequate anxiety and pain control.[10] The use of local anesthetics with epinephrine can be a concern in the treatment of cardiac patients because of the effect of increased heart rate, stroke volume, and cardiac output. However, at low doses, epinephrine has been found to have few of these systemic effects and in stable cardiovascular patients it can be safely used. For patients with a questionable cardiac history, 0.04 mg of epinephrine should be the maximum dose given (≈two 1.8-mL carpules of local anesthetic with 1:100,000 epinephrine), whereas unstable cardiac patients should receive epinephrine only for emergency dental treatment.

Malignant Neoplasms

Oropharyngeal cancer involves the soft palate, tonsil, base of the tongue, and vallecula and is diagnosed in nearly 9000 men and women in the United States annually.[11] Cancers of the oral cavity and pharynx, which represent 2.1% of all neoplasms in the United States, have a direct and frequently permanent deleterious effect on oral health and function. Although men experienced a much greater likelihood of developing oral-pharyngeal cancer in the past, the male-female ratio is now 2:1. The prevalence and mortality of oral cancers increase with age, and the major preventable risk factors are tobacco use and excessive alcohol consumption.

Common signs include nonhealing crusting and ulcerated leukoplakic and erythemic lesions. Pain is not necessarily a symptom of oral cancers, and patients should be advised to see their dentists or physicians for definitive diagnosis if a lesion or swelling has not resolved within a 2- to 3-week period.

Most of the remaining 10% of head and neck tumors are salivary gland tumors or lymphomas; further, approximately 1% of all tumors originate below the clavicles and metastasize to the head and neck.[12] Accordingly, visual inspection and palpation of the head and neck region must include lymph nodes, muscles of mastication and facial expression, and salivary glands. Furthermore, a histopathologic examination is required of all nonhealing head, neck, and oral lesions.

Early detection of oral cancer is critical because patients with early-stage tumors have considerably better survival rates than those with late-stage cancers that have already spread to regional tissues and

Table 92-4

Antibiotic Regimens for a Dental Procedure as Recommended in Table 92-3

Situation	Agent	Regimen—Single Dose 30-60 Minutes before Procedure	
Oral	Amoxicillin	Adults 2 g	Children 50 mg/kg
Unable to take oral medication	Ampicillin or Cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin Oral	Cephalexin* or Clindamycin Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 m/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† Clindamycin phosphate	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM, intramuscular; IV, intravenous.
From Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. *J Am Dent Assoc.* 2007;138(4):458-474; and Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *J Am Dent Assoc.* 2007;138(6):739-745, 747-760.

the lymphatic system. For example, 5-year survival rates for small and localized tongue cancers (stage I and II) and those tongue cancers with lymph node involvement and possible metastasis (stage III and IV) are 67% and 30%, respectively. Accordingly, since 1980, the American Cancer Society has recommended a cancer-related checkup every 3 years for persons aged 20 to 39 years and annually for individuals 40 years and older.[13] This is particularly relevant for the elderly population, which sees their dental practitioner less frequently than their younger counterparts, and in particular, older edentulous adults.

The treatment of most cancers will indirectly or directly affect oral health and function. Chemotherapy causes reversible mucositis, stomatitis, salivary hypofunction, smell and taste dysfunction, diminished appetite, and increased susceptibility to oral microbial infections. Clinically significant nutritional deficiencies and dehydration can occur in the presence of severe oral and pharyngeal mucositis and recurrent microbial infections. Because of the significant morbidity and mortality of antineoplastic therapies, these patients require frequent and long-term follow-up by dental professionals.

Treatment for oral-pharyngeal neoplasms includes surgery, radiation therapy, and chemotherapy, depending on the tumor stage and extent of regional spread.[14] Extensive removal of the cancerous growth and affected lymph nodes can result in significant facial disfiguration, dysphagia, altered speech and mastication, trismus, facial and oral paresthesia, salivary gland dysfunction, and diminished neck and shoulder mobility. Head and neck radiation is frequently used after surgery for the treatment of residual and microscopic disease; however, it also has significant adverse effects. These sequelae include mucositis, stomatitis, dysphagia, permanent salivary gland dysfunction, smell and taste dysfunction, oral microbial infections (e.g., reactivation of herpes simplex and varicella zoster viruses, *C. albicans* infections), and increased risk of developing osteoradionecrosis.[14]

Importantly, these patients must undergo preoperative dental evaluation and treatment before definitive therapy so as to remove oral pathology (e.g., dental caries, periodontal disease, nonrestorable teeth) before developing the common oral sequelae of surgery, chemotherapy, and radiotherapy. Both dentate and edentate postoperative patients must continue to perform scrupulous oral hygiene and maintain a regular recall schedule with their oral health professionals to reduce the risk of developing osteoradionecrosis, oral microbial infections, and other oral pathologies.

Recent findings of osteonecrosis of the maxilla and mandible have been associated with the bisphosphonate class of antiosteoclastic medications. A majority of the reported cases were found in patients being treated for osteometastatic breast carcinoma or multiple myeloma. The pathophysiology of the disease has not yet been determined.[15]

Cerebrovascular Diseases

The motor, sensory, and cognitive alterations that accompany cerebrovascular diseases have deleterious effects on oral health and function. A cerebrovascular accident (CVA) can cause permanent oral sensory and motor deficits, resulting in poor tongue function and lip seal, difficulty eating and drinking, impaired use of dentures, and visuospatial problems with adverse social and psychologic consequences.[16] Nutritional deficiencies and diminished quality of life can result from impaired food and fluid intake.

The location of the CVA determines the oral-facial deficits. Left cerebral cortex lesions cause right-sided paralysis and difficulty with auditory memory, speech, language, and the oral phase of swallowing. Right cortex lesions cause left-sided paralysis with subsequent neglect of affected sites, pharyngeal dysfunction with potential for aspiration, and difficulty with memory and performing certain tasks (such as tooth brushing). Oral-facial motor and sensory impairments can lead to improper dental and denture hygiene and food accumulation or pocketing around teeth, in the buccal vestibules, and underneath the tongue. Ultimately, this can lead to dental and periodontal diseases and oral microbial infections that can become exacerbated by the lack of sensory detection by the patient. Some patients experience problems with communication, judgment, and memory, which inhibit accurate solicitation of the patient's pertinent medical history, chief complaint, and compliance with home care instructions.

Anticoagulation therapy, the standard preventive treatment after a stroke, will produce hemorrhage, petechiae, ecchymoses, and purpura of all oral mucosal tissues. Dental treatment can be safely performed if the prothrombin time is within twice the normal range or if the international normalized ratio (INR) is less than 3.[17] However, if excessive dental-alveolar surgery is planned, conversion to low-molecular-weight heparin or heparinization in a hospital setting is recommended. Aspirin use is popular in adults at risk for cardiovascular thrombotic events, and low-dose aspirin is an excellent preventive agent; however, its antiplatelet properties have contributed to a perceived increased risk for bleeding after dental extractions. For most patients requiring simple oral surgical procedures, if local hemostatic and conservative surgical techniques are used, discontinuation of aspirin may not be necessary.[17]

Head and neck radiographic findings and oral/periodontal status may aid in identification of persons at risk of CVAs. Carotid calcifications of atherosclerotic plaques have been found on 4% of panoramic radiographs of asymptomatic persons older than 55 years.[18] In addition, periodontal disease and tooth loss are associated with increased risk of stroke.[19,20] It is hypothesized that the infectious burden of oral disease can initiate proliferation of inflammatory cells and clotting factors resulting in atherogenesis and thromboembolic events.[20] In addition, periodontal bacteria have been isolated from the atheromatous plaques after a CVA. The evidence to support a CVA-periodontal disease relationship is stronger than that found in investigations of cardiovascular and oral diseases.

Pulmonary Diseases

A common link between pulmonary diseases (COPD; bronchitis, asthma, and emphysema) and oral health is smoking. Smoking, one of the two preventable causes of oral cancer (see "Malignant Neoplasms" earlier), is also associated with benign oral mucosal pathology (nicotinic stomatitis, oral fungal infections). Little is known regarding the direct effects of COPD on oral health, yet it is well established that a common treatment modality of COPD (corticosteroids) has many oral consequences.[21] Chronic use of corticosteroids suppresses the hypothalamic-pituitary-adrenal axis that can result in acute adrenal insufficiency during stress. Therefore steroid replacement therapy is sometimes required for extensive dental and surgical procedures.[21] Many patients use steroid inhalers that should be brought to all dental appointments for use if necessary to ensure protection of a patent airway. Chronic use of systemic and inhaled corticosteroids also predisposes patients to oral fungal infections. Finally, nitrous oxide use is contraindicated in persons with severe COPD, secondary to oxygen-driven respiratory function.

Aspiration pneumonia, a common condition, particularly in hospitalized and older adults with compromised host defense mechanisms, is caused by the aspiration of gastric or oropharyngeal secretions. Oropharyngeal swallowing dysfunction, a consequence of neuromuscular and cerebrovascular diseases, debilitation, salivary hypofunction, and medications, is a frequent risk factor for aspiration pneumonia.[22] Colonization of the oropharynx with gram-negative bacilli predisposes to bacillary pneumonia.[23] A major source of anaerobe infection is the gingival crevice. Furthermore, the prevalence of bacterial colonization increases with poor oral hygiene and periodontal disease. Therefore patients at risk should receive routine dental examinations and treatment, and they may benefit from daily antimicrobial rinses.[24] Broad-spectrum antibiotics are the standard treatment regimen for pneumonia. Extended antibiotic use increases the risk of developing oral fungal infections and antibiotic resistance.

Tuberculosis, a major global health problem caused by the spread of *Mycobacterium tuberculosis,* manifests infrequently in the oral cavity. The classic oral mucosal lesion is a painful, deep, irregular ulcer on the dorsum of the tongue, with additional sites including the palate, lips, buccal mucosa, and gingival.[25] *M. tuberculosis* can also infect the cervical and submandibular lymph nodes (referred to as *scrofula*) and rarely affects the salivary glands.[26]

Oral tuberculosis lesions require diagnosis and appropriate antimicrobial management, as well as education on possible transmission via infected oral sites. A recent investigation reported positive oral cultures of *M. tuberculosis* from samples of saliva, dental plaque, caries

lesions, and denture plaque collected from tuberculosis patients, demonstrating the possibility of oral infectivity of these patients.[27] Interestingly, detection rates from these oral sites using polymerase chain reaction techniques were considerably higher (between 89% and 100% detection rates) than traditional culture methods (0% to 17%).[28] With the growing rate of human immunodeficiency virus/acquired immunodeficiency syndrome in the world, a disease that frequently manifests with tuberculosis, clinicians must be familiar with infection control procedures to protect workers against exposure to pathologic and possibly aerosolized microorganisms.

Endocrine and Exocrine Disorders

Diabetes Mellitus

The presence or absence of diabetes and the degree of glucose metabolic control in patients significantly influence the level and severity of diabetes-related oral diseases. Patients who control their diabetes have fewer oral health problems than those with poorly controlled diabetes,[29] and some data suggest that persons with controlled diabetes have the same incidence of oral disease as the general population.[30] Alternatively, poorly controlled diabetes is associated with a plethora of oral health problems. The most common oral disease seen in persons with diabetes and in greater prevalence than persons without diabetes is periodontal disease.[29,31] Many studies have shown that poor glycemic control precedes the incidence and progression of periodontitis. Furthermore, there is an association between severe periodontitis and an increased risk of poor glycemic control.[16,29,32]

Several mechanisms have been proposed to explain the increased susceptibility of persons with diabetes to periodontal diseases including alterations in host response, subgingival microflora, collagen metabolism, vascularity, gingival crevicular fluid, and heredity patterns.[32] Multiple pathophysiologic mechanisms (e.g., compromised neutrophil function; decreased phagocytosis and leukotaxis) have also been implicated in the increased alveolar bone loss found in persons with diabetes,[29,30] increased tendency for more active carious lesions and missing teeth,[33] and increased susceptibility to oral infections and mucosal lesions.[34] Autoimmune phenomena have been suggested as the cause of the increased prevalence of oral lichen planus in persons with diabetes.[35]

Diabetes predisposes an individual to sensory and peripheral neuropathies, which inhibit pain perception and may produce chemosensory deficits such as impaired taste function and decreased smell sensitivity.[30] This sensory dysfunction can inhibit the ability to maintain a proper diet, which leads to poor glycemic regulation. Persons with diabetes also have reported increased complaints of glossodynia and stomatopyrosis (burning mouth syndrome), as well as increased complaints of dry mouth (xerostomia). There is no consensus demonstrating a relationship between glycemic control and salivary gland dysfunction. However, the xerostomic complaints may be due to a variety of reasons including salivary gland basement membrane changes and diabetes-associated thirst.

Adrenal Diseases

Oral manifestations of Addison's disease, caused by primary adrenal insufficiency or hypoadrenalism, include diffuse, cutaneous pigmentation of the skin and mucous membranes. However, this presentation is not found in persons with secondary adrenal insufficiency, the result of chronic corticosteroid administration.

Persons diagnosed with hyperadrenalism or Cushing's disease (caused by an adrenal disorder or long-term, high-dose administration of corticosteroids) often present with characteristic moon-shaped faces. Oral symptoms include an increased susceptibility to oral infections (such as candidiasis) and muscle weakness manifested as difficulty with speaking, eating, and swallowing.

Pituitary Diseases

The chronic hypersecretion of growth hormone in acromegaly results in significant orofacial changes from the bony and soft tissue overgrowth. Tooth separation and malocclusion can be a consequence of alveolar enlargement of the maxilla and mandible. Extraoral facial features include frontal bossing, nasal bone hypertrophy, mandibular prognathism, and enlargement of the paranasal sinuses. Soft tissue overgrowth can present in the oral mucosal and salivary gland tissues, tongue, and lips. As a result of these structural changes, speech abnormalities and myofascial pain have been reported.

Thyroid Diseases

Macroglossia is the primary oral manifestation of hypothyroidism, which is often caused by chronic autoimmune thyroiditis (Hashimoto's thyroiditis) or is secondarily acquired (e.g., induced by surgery, radiation, or medication). Infants with undiagnosed congenital hypothyroidism may develop macroglossia, pronounced lips, and delayed tooth eruption with subsequent malocclusion.

Hyperthyroidism, or thyrotoxicosis, is commonly caused by an autoimmune disorder termed Graves' disease. Facial and skin manifestations include upper eyelid retraction with exophthalmos and hyperpigmentation and erythema of the skin. Young children can present with early loss of primary teeth with subsequent rapid eruption of permanent teeth. The hyperplasia of lymph tissue commonly found in Graves' disease can manifest in the tonsillar and oral pharynx region.

Parathyroid Diseases

Bone demineralization with subsequent fibrous-tissue replacement can produce well-defined cystic radiographic radiolucencies characteristic of hyperparathyroidism. Tooth mobility, loss of lamina dura, and a radiographic osteoporotic appearance may also be found.

Idiopathic hypoparathyroidism is an acquired autoimmune disease associated with polyendocrine glandular deficiency and with mucocutaneous candidiasis and pernicious anemia. Pseudohypoparathyroidism is an inherited disorder characterized by end-organ unresponsiveness to parathyroid hormone effects, a moon face, and brachymetacarpalism. These signs may appear together with trophic changes of the skin and nails, dryness of the mucous membranes, angular cheilitis, and enamel hypoplasia caused by chronic hypocalcemia.

Collagen-Vascular and Granulomatous Disorders

Sjögren's Syndrome

Sjögren's syndrome (SS), a systemic autoimmune disorder associated with inflammation of epithelial tissues, is the most common medical disorder associated with xerostomia and salivary dysfunction. SS was reclassified in 2002[36] and occurs in primary and secondary forms. Primary SS involves salivary and lacrimal gland disorders with associated decreased production of saliva and tears. In secondary SS, the disorder occurs with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, polymyositis, and polyarteritis nodosa.[37]

Focal, periductal, mononuclear cell infiltrates in exocrine tissues and autoantibodies (particularly anti-Ro/SSA, anti-La/SSB, and rheumatoid factor) are the hallmarks of SS. The salivary and lacrimal infiltrates consist predominantly of T cells ($CD4^+$ T helper cells), with fewer B cells, macrophages, and mast cells.[38] Clinical manifestations of the ensuing salivary hypofunction include cracked and ulcerated lips, desiccated oral mucosal tissues, fungal infections, new and recurrent dental caries, gingivitis, dysphagia, impaired use of removable prostheses (dentures), and difficulty speaking without the use of fluids. There is a reported 44-fold increase in the frequency of B-cell lymphomas among patients with SS[39]; accordingly, oral, head, and neck examinations must be performed on these patients on a regular basis.

Treatment for SS must address all organ systems affected by the disease.[27] Dry mouth and its associated oral sequelae require constant dental evaluations to reduce the risk of developing dental caries, oral microbial infections, dysphagia, dysgeusia, impaired eating, and wearing removable dentures.

Systemic Lupus Erythematosus

Approximately one quarter of SLE patients have oral lesions, which are usually superficial ulcers with surrounding erythema.[28] These lesions can occur on the lips and all oral mucosal surfaces and can be indistin-

guishable from those of lichen planus or leukoplakia, therefore requiring histopathologic diagnosis. Direct and indirect immunofluorescence of these lesions shows staining of the basement membrane of the dermal-epidermal junction with immunoglobulins and complement, similar to what is seen in the skin lesions. Other manifestations of SLE include periodontal diseases,[33] xerostomia, and hyposalivation that can occur independent of SS or can be associated with secondary SS. Patients with SLE (particularly those with long-standing disease) should undergo cardiac evaluation to determine whether they are candidates for antibiotic prophylaxis for dental treatment likely to result in bacteremia and bleeding.[24]

Scleroderma

The oral manifestations of this disease result from deposits of collagen in the tissues or as a result of collagen deposition around nerves and vessels. Difficulty opening the mouth occurs due to fibrosis of masticatory muscles, and immobility of the tongue and disorders in deglutition are also possible. The oral manifestations most commonly recognized are wide periodontal ligament spaces and occasional gingivitis.[40] Scleroderma can also be associated with SS and CREST (*c*alcinosis cutis, *R*aynaud's phenomena, *e*sophageal dysfunction, *s*clerodactyly, and *t*elangiectasia) syndrome,[40] and these patients can complain of accompanying xerostomia.

Dermatomyositis-Polymyositis

Dermatomyositis-polymyositis is an immunologic disease of muscle that can also involve the tongue and the upper portion of the esophagus. Patients can have difficulty with phonation, chewing, and deglutition, and they can also develop stomatitis.[41] Due to problems with swallowing, aspiration pneumonia is also a possible sequela. As part of secondary SS, patients can exhibit xerostomia and salivary hypofunction.

Sarcoidosis

Sarcoidosis, a systemic granulomatous disease, can appear with masses on the tongue, lips, mandible, and maxilla.[41] Biopsy results demonstrate characteristic noncaseating granulomas consistent with extraoral manifestations. The differential diagnosis includes other granulomatous diseases (e.g., infectious granuloma, Wegener's granulomatosis, lethal midline granuloma), infectious granulomatous diseases (e.g., histoplasmosis, blastomycosis), or even lymphoma.

Wegener's Granulomatosis

Wegener's granulomatosis is a rare disorder that is histologically characterized by granulomatous inflammation and vasculitis. The destructive granulomatous inflammation also occurs in the oral cavity as red to purple hyperplastic gingival lesions with petechiae.[31] In addition, patients can have tooth mobility leading to removal of teeth and failure of oral wounds to heal. The disease may remain localized and restricted to the oral cavity for a long period before multiorgan involvement occurs. Oral biopsy is critically important to establish an early diagnosis and to prevent destruction caused by this progressive disease.

Infectious Diseases

Viral Diseases

Herpes simplex virus (HSV-1) and varicella-zoster virus (VZV) are the most common viral infections in the oral-facial region. They can present as herpes labialis or primary herpetic gingivostomatitis (HSV-1) or acute, painful, oral-facial lesions (VZV).[42] Initial infection usually occurs in childhood. However, the dormant virus located in the sensory ganglia can be reactivated secondary to immunosuppression, trauma, stress, sunlight, gastrointestinal disturbances, and concurrent infection. After a prodrome, the HSV-1 fluid-filled vesicles will rupture, crust, and resolve in 1 to 2 weeks. Reactivation of childhood VZV infection appears as vesicles on skin and mucous membranes usually following a unilateral distribution of the ophthalmic, maxillary, or mandibular divisions of the trigeminal sensory nerves. Blindness, facial paralysis, auditory deficits, and vertigo are also potential sequelae of postherpetic neuralgia.[43]

Immediate treatment is required for HSV-1 lesions, ideally as soon as prodromal symptoms develop. Antiviral drugs, either topical and/or systemic, are required depending on the patient's immunologic status. Treatment of VZV infection in the oral-facial region may require several concomitant drugs: antivirals to suppress viral replication, analgesics and anxiolytics for pain relief, and immunosuppressive drugs to control virally caused inflammation.

Oral complications and manifestations of HIV disease and AIDS are numerous due to the immunocompromised state experienced by these patients.[44] Some of the most commonly presenting oral conditions in persons with AIDS (e.g., candidiasis, Kaposi's sarcoma, hairy leukoplakia) can be indicative of the level of immune suppression. Other common lesions affecting persons with HIV disease and AIDS include aphthous stomatitis, HIV periodontal disease (linear gingival erythema and necrotizing ulcerative periodontitis), salivary gland disease, non-Hodgkin's lymphoma, and lymphadenopathy.[45] Coinfection with cytomegalovirus, occurring in 90% of persons with HIV, can cause oral ulcerations, esophagitis, and retinitis. Hairy leukoplakia, a corrugated white lesion occurring on the lateral or ventral surfaces of the tongue, is caused by reactivation of Epstein-Barr virus in HIV-infected persons.

Hepatitis has oral-facial manifestations, especially during the icteric phase of the disease. Clinical findings include a yellow-brown hue to the oral mucosa, eyes, and skin.[46] Persons with chronic hepatitis C infection can develop lichen planus and lymphocytic sialadenitis caused by autoantibody production.[37]

Fungal Diseases

The most frequent oral fungal infection is caused by *C. albicans.* The overgrowth of *C. albicans* in the oral-pharyngeal region has many etiologies: endocrine disorders (e.g., diabetes), immunosuppression, nutritional deficiencies, medications (particularly antibiotics and long-term immunosuppressants), salivary gland hypofunction, removable dental prostheses, and poor oral and denture hygiene. Many varieties of oral manifestations of candidiasis exist including pseudomembranous (white, easily removable patches), acute erythemic or atrophic (erythemic or erosive lesions), chronic hyperplastic/denture stomatitis (hyperplastic lesions usually found underneath dentures), and angular cheilitis (erythematous, cracked, or fissured lesions located at commissures of lips).[47] Angular cheilitis is often caused by a loss of vertical dimension secondary to edentulism and drooling resulting from a stroke or other neuromuscular disorder.[35]

Bacterial Diseases

The oral cavity is host to numerous species of bacteria responsible for causing oral and pharyngeal infections. *Porphyromonas gingivalis* and *Treponema denticola* are often implicated in the development of periodontal disease, whereas *Staphylococcus aureus* and *Streptococcus viridans* are known to cause salivary gland infections. *Streptococcus mutans* and *Lactobacillus* sp are the common causes of new and recurrent dental caries. Dental infection that spreads through the teeth into underlying bone can result in a dentoalveolar abscess. The oral and facial swelling and asymmetry that develop as the infection progresses through the alveolar bone can become life threatening (e.g., Ludwig's angina). *M. tuberculosis* infections are uncommon in healthy persons and are primarily seen in immunocompromised patients (see "Pulmonary Diseases" earlier).

Sexually transmitted diseases caused by *Neisseria gonorrhoeae* and *Treponema pallidum* can also cause oral disorders.[41] *N. gonorrhoeae* infections are associated with submandibular lymphadenopathy, gonococcal stomatitis (ulcerations and erythema of mucosal tissues), and pharyngeal gonococcal infection (mild sore throat). In syphilis, the stage of the disease determines the oral manifestations. Primary syphilis causes a lip chancre, whereas secondary syphilis is associated with papular lesions, erythematous or grayish-white erosions, pharyngitis, lymphadenopathy, and parotid enlargement. Mucosal and skin lesions during this phase are highly infectious. Congenital syphilis causes dental abnormalities such as Hutchinson's incisors and mulberry molars.

Arthritides and Bone Disorders

Rheumatoid Arthritis

Rheumatoid arthritis (RA) causes progressive destruction of articular and periarticular structures including the temporomandibular joint (TMJ).[48] Multiple signs and symptoms of TMJ pathology occur in these patients including clicking, locking, crepitus, tenderness to palpation in the preauricular area, pain during mandibular movement, swelling (infrequent), and shifts in the relationship between the maxilla and mandible caused by erosion of the condylar heads. In addition, these progressive problems can cause considerable pain during mastication that could affect nutrition. RA is also frequently associated with other autoimmune connective tissue diseases such as Sjögren's syndrome.

The pharmacologic management of RA and other arthritic conditions can have serious adverse sequelae affecting oral health and the delivery of dental treatment.[49] Gold compounds, penicillamine, methotrexate, and other high-dose/chronic immunosuppressive drugs have been associated with acute stomatitis and recurrent microbial infections (e.g., oral candidiasis, recurrent HSV infections).[1,44] Newer anti-inflammatory biologic agents will also increase the tendency for patients to develop oral microbial infections. Surgical replacement of hips, knees, and other degenerated joints with prostheses requires antibiotic prophylaxis before dental procedures for 2 years after joint replacement and for a lifetime in patients at potential increased risk for hematogenous total joint infection (Table 92-5).[50] The antimicrobial guidelines are provided in Table 92-6 for dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

Other drugs used for RA such as high doses of nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, and immunosuppressive medications can increase the risk of excessive bleeding during or after dental-alveolar surgery.[24,49] The use of long-term immunosuppressive therapy causes adrenal insufficiency, and glucocorticoid supplementation is necessary before extensive dental procedures.[21]

Management of the arthritic-associated TMJ symptoms is frequently palliative (e.g., soft diets, pain/anti-inflammatory medications) but can also involve construction of hard acrylic intraoral orthotic devices, physical therapy, and TMJ surgery.[51] Arthritic deformities will ultimately impede mobility and dexterity that are required for daily oral hygiene and regular visits to the dental office. Daily assistance with oral hygiene may be necessary to maintain oral health.[52]

Osteoarthritis

Most forms of osteoarthritis (OA) have fewer serious systemic complications than RA, yet many of the concerns discussed for the RA patient are relevant for this population as well.[48] Patients may have greater problems performing oral hygiene, difficulty tolerating long dental treatments or placement in the supine position, and signs and symptoms of TMJ and related disorders. Adults with OA may have prosthetic joints and consequently require antibiotic prophylaxis before dental treatment.[50] Medical management with drugs (see "Rheumatoid Arthritis" earlier) may necessitate appropriate precautions before dental treatment or stomatologic follow-up for adverse effects.

Reiter's Syndrome

Reiter's syndrome is a recurrent arthritic condition characterized by conjunctivitis, asymmetric lower extremity arthritis, nongonococcal urethritis, circinate balanitis, and keratoderma blennorrhagia. Oral lesions appear as papules and ulcerations on the buccal mucosa, gingiva, and lips. Lesions on the tongue resemble geographic tongue.

Paget's Disease

Paget's disease is an acquired disorder of excessive bone resorption with variable attempts at repair. The skull and maxilla are frequently involved. Extensive enlargement and deformation of the maxilla occurs, with spacing and mobility of the teeth. These clinical findings are confirmed radiographically, with the presence of multiple radiolucent-radiopaque lesions of the affected bones.

Ewing's Sarcoma

Ewing's sarcoma is a rare tumor of bone, occasionally involving the mandible. Clinical presentation may include chin and lip paresthesias, which must be diagnosed after radiographic and nuclear images and biopsy specimens are obtained. Differential diagnosis includes granulomatous diseases, Paget's disease, Langerhans cell histiocytosis, and hyperparathyroidism.

Dermatologic Conditions

Lichen Planus

Lichen planus is a chronic, mucocutaneous, autoimmune disorder that can be precipitated by a number of conditions such as genetic predisposition, emotional stress, or drug, food, or dental material hypersensitivity.[53] It has a variety of clinical appearances: plaquelike, bullous, atrophic, reticular (lacy white lines known as Wickham's striae), and erosive (ulcerative lesions accompanied by peripheral striae). The lesions most often occur on buccal mucosa, gingiva, and tongue but

Table 92-5

Patients at Potential Increased Risk of Hematogenous Total Joint Infection

Immunocompromised/Immunosuppressed Patients
Inflammatory arthropathies: rheumatoid arthritis, systemic lupus erythematosus
Disease, drug, or radiation-induced immunosuppression
Other Patients
Insulin-dependent (type 1) diabetes
First 2 years following joint placement
Previous prosthetic joint infections
Malnourishment
Hemophilia

From American Dental Association. Advisory statement. Antibiotic prophylaxis for dental patients with total joint replacements. American Dental Association; American Academy of Orthopaedic Surgeons. *J Am Dent Assoc.* 1997;128(7):1004-1008.

Table 92-6

Suggested Antibiotic Prophylaxis Regimens for Orthopedic Joint Patients

Patients not allergic to penicillin	Cephalexin, cephradine, or amoxicillin, 2 g orally 1 hour before dental procedure
Patients not allergic to penicillin and unable to take oral medications	Cefazolin 1 g or ampicillin 2 g IM or IV 1 hour before the procedure
Patients allergic to penicillin	Clindamycin 600 mg orally 1 hour before the dental procedure
Patients allergic to penicillin and unable to take oral medications	Clindamycin 600 mg IV 1 hour before the procedure

From American Dental Association. Advisory statement. Antibiotic prophylaxis for dental patients with total joint replacements. American Dental Association; American Academy of Orthopaedic Surgeons. *J Am Dent Assoc.* 1997;128(7):1004-1008.

can also be found on the lips and palate.[53] Histopathologic samples are required for diagnosis to differentiate lichen planus from other common mucocutaneous oral lesions (e.g., aphthous stomatitis, pemphigus, pemphigoid, lupus). The goal in the treatment of many of these autoimmune mucocutaneous oral mucosal conditions is to reduce oral discomfort and inflammation. Depending on the extent of oral lesions, topical immunosuppressants (most commonly, glucocorticosteroids in the forms of ointments and gels) may be sufficient for patient comfort and prevention of exacerbation of lesions. If topical therapy is insufficient in controlling lesions, then systemic immunosuppressant therapy should be considered. Some evidence suggests that lichen planus lesions are predisposed to malignant transformation[53]; therefore lesions, particularly those with ulcerations, must be re-evaluated on a regular basis.

Pemphigus Vulgaris

Pemphigus vulgaris is an autoimmune disease caused by antibodies created against desmoglein 3, causing a disassociation of the epithelium at the suprabasal layer with acantholysis. Clinical presentation includes bullous lesions developing into vesicles that rupture, resulting in painful, bleeding ulcerations. The lesions can occur on oral and ocular mucosa and skin and resolve after 2 weeks with treatment. The oral mucosa of the palate, gingiva buccal mucosa, and tongue are the most common locations.[54] The diagnosis can be made with the production of a positive Nikolsky's sign, whereby a new lesion develops after slight pressure is applied to the asymptomatic oral mucosa. Histopathology and direct immunofluorescence tests are required as well.[55] Treatment strategies for pemphigus vulgaris are similar to those employed for lichen planus. However, due to the possible widespread extent of lesions, systemic steroids and immunosuppressants may be more likely to be used to prevent secondary complications such as recurrent infections, electrolyte imbalance, and dysphagia caused by lesion spread into the pharynx, larynx, and esophagus. A variant of pemphigus vulgaris, paraneoplastic pemphigus, is an autoimmune blistering disease that occurs in association with underlying neoplasms and requires carefully monitored multidisciplinary care.[38,56]

Mucous Membrane Pemphigoid

Antigens located at the base of the epithelium cause subepidermal detachment and subepithelial bullae formation in the mucous membrane pemphigoid.[55,57] Similar to pemphigus, the initially presenting erythemic and vesicular oral lesions rupture, resulting in pseudomembranous ulcerations. Intraorally, these lesions often occur on the gingival tissue, causing desquamative gingivitis and subsequent scarring.[58] Blindness is a complication of ocular lesions causing corneal damage and conjunctival mucosal scarring. Therefore definitive diagnosis is critically important, with subsequent management involving a multidisciplinary health care team.

Erythema Multiforme

Erythema multiforme is an acute, recurrent, self-limiting autoimmune disease commonly causing blistering oral and skin lesions.[59] It is believed to be precipitated by a type III hypersensitivity reaction, drug allergy, or herpetic infection. Presentation includes acute development of vesicles with subsequent rupture causing painful ulcers of the buccal mucosa, lips, palate, and tongue. Cutaneous lesions often present as a characteristic target or bull's-eye, and lips can become swollen, bleeding, and crusted. With corticosteroid and antiviral therapy or drug withdrawal, complete resolution occurs after 14 days. A more severe form of the disease, known as *Stevens-Johnson syndrome,* is usually triggered by a drug rather than an infection and involves oral and other cutaneous and mucosal surfaces.[11]

Gastrointestinal Disorders

Crohn's Disease and Ulcerative Colitis

Patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis can develop oral recurrent aphthous ulcers.[60] With ulcerative colitis, the aphthous ulcers are frequently associated with other mucous membrane involvement, iritis, arthritis, and erythema nodosum. Ulcerative colitis may also manifest with pyostomatitis, a progressive necrotic and inflammatory involvement of all oral mucosal tissues. In addition to oral aphthous ulcers, Crohn's disease is associated with nodular swellings, a cobblestone appearance of the mucosa, and deep granulomatous-appearing ulcers.

Behçet's Syndrome

Behçet's syndrome is an idiopathic condition that consists of recurrent oral and genital ulcers, arthritis, and inflammatory disease of the eyes and gastrointestinal tract. Oral ulcers appear as recurrent aphthous ulcers, which occur in the vast majority of patients and typically precede other sites of involvement.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease manifests in the oral cavity as mucosal and gingival erosions and inflammation thought to be caused by acid. When reflux continues for a long time, erosion of tooth enamel can occur.

Malabsorption Diseases

A plethora of gastrointestinal conditions lead to malabsorption of vitamins and nutrients, causing oral pathologies to occur. Gluten-sensitive enteropathy or celiac disease can manifest with recurrent aphthous ulcers. Vitamin A deficiency produces dyskeratotic changes of the skin and mucous membranes, angular cheilitis (fungal infection of the labial commisures), and defects in the dentin and enamel of developing teeth. Vitamin B_2 (or riboflavin) deficiency is associated with angular cheilitis and burning pain in the lips, mouth, and tongue. Deficiencies in vitamin B_{12}, as well as folate, can also produce recurrent aphthous ulcers. Niacin deficiency (pellagra) can involve the tongue and other oral mucosal tissues by causing the tongue to become swollen and press against the dentition.

Scurvy, or vitamin C deficiency, is associated with perifollicular hemorrhages and petechiae in the mouth caused by vascular integrity compromise, gingival hyperplasia, and stomatitis. The teeth may become loose, and involved gingival tissues can be the source of halitosis. Vitamin D deficiency will complicate calcium metabolism because vitamin D is required for calcium absorption. Calcium deficiency can contribute to mandibular osteopenia or osteoporosis (particularly in edentulous mandibles), as well as enamel hypoplasia caused by chronic hypocalcemia. Vitamin K deficiency leads to a hemorrhagic diathesis that often presents with oral hemorrhagic bullae. Folate and iron deficiencies produce atrophic glossitis caused by the atrophy of the filiform papillae, angular cheilitis, and occasionally hyperkeratotic lesions in the oral mucosa. Zinc deficiency has been associated with taste changes, which could result in a significant change in dietary intake of fluids and beverages.

Neurologic Diseases

Dementias Including Alzheimer's Disease

The progression of dementia is accompanied by a gradual inability to perform self-care including adequate oral hygiene because of self-neglect and a loss of cognitive and motor skills,[61] and these problems have been found to increase with the severity of dementia.[62] Persons with Alzheimer's disease, the most common form of dementia, have impaired oral health as a result of poor oral hygiene.[35] They have a greater prevalence of dental plaque, gingival bleeding, and calculus compared with age- and sex-matched adults,[44] and evidence of salivary gland hypofunction, even when not taking medications.[63]

Older adults with cognitive impairment have significantly older dentures and dentures that are less clean compared with individuals without dementia.[64] Another sequelae of poor oral hygiene is a trend toward increased coronal and root caries, which is observed with increasing dementia severity.[35] Many of these oral disorders are the result of the pharmaceutical treatment of dementing illnesses. Medications with anticholinergic side effects, such as antidepressants, are frequently used for dementia and are the cause of salivary dysfunction, which is ultimately the source of multiple oral and pharyngeal disorders.[65] Many of these patients do not have intact oral sensory or cogni-

tive function, and are unable to report symptoms of oral pain, infection, or pathology. Therefore, it is imperative that they undergo more frequent oral health exams as the disease progresses. Furthermore, as the level of dementia worsens, caregivers become critically important in providing daily oral hygiene, identifying stomatologic diseases, and facilitating dental treatments.[66]

Parkinson's Disease

Increased amounts of acetylcholine present in the brain in persons with Parkinson's disease can produce esophageal dysmotility and dysphagia. The ability to form a lip seal is impaired, resulting in drooling, and ultimately leading to a fungal infection of the lip commissures (referred to as angular cheilitis). Anticholinergic medications commonly used to help parkinsonian symptoms (e.g., levodopa, selegiline) cause salivary hypofunction and xerostomia. An adverse effect of long-term levodopa therapy is tardive dyskinesia, which is characterized by involuntary orofacial movements including lip smacking, grimacing, and tongue flittering.[67] Loss of facial expression, difficulty with mastication, slow speech, and tremors of the head, lips, and tongue are commonly found symptoms that increase with the severity of the disease.[68]

Myasthenia Gravis

Myasthenia gravis, an autoimmune disorder caused by loss or dysfunction of acetylcholine receptors, results in episodic muscle weakness. Orofacial symptoms include dysphagia with subsequent choking, nasal regurgitation, and alteration in voice.

Bell's Palsy

Unilateral facial paralysis, known as Bell's palsy, occurs due to a defect of cranial nerve VII. Facial appearance is distorted due to the lack of control of the muscles of facial expression. Functional ability of the lips and cheek is lost on the affected side; this can produce decreased natural cleansing and unilateral dental decay if appropriate oral hygiene is not maintained.

Multiple Sclerosis

The loss of muscle coordination resulting from the demyelination of long nerves in multiple sclerosis can severely impair oral care. Weakness of the tongue and loss of upper extremity use impairs dental and denture hygiene, as does wearing dental prostheses. Trigeminal neuralgia is common in these patients; it is characterized by excruciating unilateral pain of the lips, gingiva, or chin that can be triggered by contact with certain areas of the face, lips, or tongue.

Myotonic Muscular Dystrophy

The muscular weakness and subsequent wasting of myotonic muscular dystrophy severely compromise oral function and health. The inability to relax muscles after contraction results in difficulty chewing, pursing the lips, and turning the head. Facial muscle involvement inhibits the ability to wear dentures. Medications used to treat myotonic muscular dystrophy (quinine) are known to cause xerostomia and oral mucosal edema. Flared anterior teeth and mouth breathing are commonly seen due to weakness of the facial muscles and the enlargement of the tongue caused by fatty deposits.

Renal Diseases

Renal insufficiency or renal failure ultimately require peritoneal or hemodialysis. These patients are susceptible to numerous oral diseases, including salivary hypofunction, impaired wound healing, recurrent oral mucosal infections, dental caries, gingivitis, and periodontitis.[69,70] These problems, particularly those associated with microbial infections, are enhanced in patients taking long-term corticosteroids and other immunosuppressants. Uremic stomatitis is a condition unique to patients receiving dialysis that typically presents as an erythemic thickening of the buccal mucosa with a pseudomembranous covering, ulcerative lesions, gingival and mucosal hemorrhage, and ecchymoses.[71] Appearance of these lesions often corresponds to an acute increase in blood urea nitrogen levels, and they heal spontaneously after resolution of the uremic state.[71]

Bleeding from oral mucosal surfaces is also due to altered platelet aggregation and decreased platelet factor III, and hemodialysis patients experience increased bleeding due to platelet destruction. The oral manifestations of bleeding problems are petechiae and ecchymoses.

Bony changes commonly observed in renal failure include loss of lamina dura, demineralized bone, localized radiolucent jaw lesions (central giant cell granulomas with subsequent tooth displacement), and widened trabeculations.[71] These lytic bone lesions are the result of hyperparathyroidism. Smell and taste changes have been observed in patients with renal failure, and there is some evidence that chemosensory function improves after dialysis and renal transplantation.[72] Since heparin is administered during dialysis to prevent blood coagulation, dental procedures should be performed on alternate days of dialysis, and precautions should be taken to avoid excessive hemorrhage. Evaluation and management of potential anemic or hypertensive conditions are required when dental treatment is provided.

Renal transplantation is a treatment option for patients with severe renal failure. After transplantation, patients are administered long-term immunosuppressants that have multiple oral sequelae (e.g., cyclosporine-induced gingival hyperplasia, steroid-induced oral fungal infections). Renal transplant recipients have been reported to have a greater prevalence of oral lesions such as candidiasis, leukoplakia, dysplasia, and cancer of the lip.[73,74] These patients require pretransplantation oral evaluations and treatment, and close follow-up after transplantation to help maintain oral health and function and to diminish the likelihood of developing oral infections that may disseminate to the systemic circulation in an immunosuppressed person.

Peritoneal dialysis presents no additional problems in dental management, yet patients receiving hemodialysis are potentially at risk for developing infective endocarditis.[24] Approximately 10% to 17% of infective endocarditis cases in patients receiving hemodialysis are caused by organisms that can arise from the oral cavity (e.g., *S. viridans, Lactobacillus* sp).[75] Therefore it has been suggested that prophylactic antibiotics are prudent for hemodialysis patients with arteriovenous shunts/grafts when invasive dental procedures are performed.[24]

Chronic Liver Diseases and Cirrhosis

Poor oral hygiene and neglect resulting in dental caries, and periodontal diseases are frequent oral disorders in patients with chronic alcoholism.[24] However, even moderate consumption of alcohol has been reported to increase the risk of developing periodontal disease, perhaps due to alcohol's deleterious effect on neutrophil, macrophage, and T-cell function.[76] Nutritional disorders due to alcoholism and oral diseases can produce glossitis and loss of tongue papillae, as well as recurrent oral fungal infections of the oral mucosal surfaces and the labial commissures (angular cheilitis). Excessive alcohol intake and tobacco use are major risk factors for oral cancer (see "Malignant Neoplasms" earlier). Accordingly, oral examinations in these alcoholic patients must include scrutiny of high-risk sites such as the anterior floor of the mouth, the lateral border of the tongue, and the posterior oral-pharynx.[77]

Oral microbial infections and impaired wound healing are the most common oral complications of patients with cirrhosis, resulting from alcohol-induced immunosuppression.[41] Susceptibility to oral infections increases when patients require liver transplants and the requisite postoperative immunosuppressive regimens. These patients must receive close monitoring from their dentists to reduce their risk of developing stomatologic diseases. Diminished smell and taste function that can inhibit nutritional intake and parotid gland hypertrophy leading to reversible salivary gland dysfunction have been reported in patients with liver cirrhosis.

Coagulation disorders are a concern for patients with liver dysfunction, and accordingly persons are at risk for developing hemorrhage after undergoing oral surgical procedures. Mucosal petechiae and ecchymoses and spontaneous gingival bleeding can also result from coagulation abnormalities.[17] Presurgical coagulation tests are required before gingival, periodontal, and alveolar bone surgery, and special steps may be required to ensure adequate thrombus formation.[17]

Hematologic Disorders

Bleeding Disorders

Anticoagulation therapy for stroke and atrial thrombosis prevention predisposes patients to bleeding disorders. Anticoagulants (e.g., heparin, warfarin, vitamin K antagonists, direct thrombin inhibitors), antiplatelets (aspirin, adenosine diphosphate, or adenosine diphosphate receptor blockers), and thrombolytic or fibrinolytic drugs (e.g., first generation—streptokinase, second generation—alteplase; third generation—reteplase) can cause hemorrhagic oral mucosal lesions such as petechiae, ecchymoses, and purpura.[17]

Bleeding problems can also result from congenital platelet disorders and coagulopathies. Von Willebrand's disease, the most common hereditary bleeding disorder, is caused by the deficiency of secondary factor VIII (vWF), resulting in poor platelet adhesion. In mild cases, normal bleeding occurs after surgery or trauma; however, in more severe disease, spontaneous oral mucosal bleeding can occur, resembling hemophilia A disorder. Hemophilia A, a congenital coagulation disease, is caused by a deficiency or defect in factor VIII. The frequency and severity of bleeding problems in hemophilia A is directly associated with the blood levels of factor VIII. In severe cases, spontaneous and excessive bleeding in the oral cavity, lips, and joints can be initiated readily. The immunodeficiency produced in the X-linked recessive inherited disease, Wiskott-Aldrich syndrome, can result in recurrent infections, eczema, and chronic thrombocytopenia (with manifestations of hemorrhage and purpura of the skin and oral mucosa).

A decreased number of platelets due to deficiency, destruction, or consumption results in thrombocytopenic purpura. Primary idiopathic thrombocytopenia is thought to be an autoimmune process, whereas secondary thrombocytopenia can be caused by medications or systemic diseases such as leukemia. Oral manifestations include petechiae and hemorrhagic bullae of the oral mucosa.

White Blood Cell Disorders

Leukemias and their treatments have a profound effect on the oral cavity. Oral mucosal changes such as bleeding and ulceration, petechiae, and gingival hyperplasia may be the initial sign of leukemia.[78] Due to their immunocompromised state, patients are at risk for development of bacterial, fungal, and viral infections. Chemotherapy can cause mucositis and mucosal ulcerations.[79] Poor oral hygiene results in gingival inflammation and bleeding, mucosal ulcerations, and periodontal disease; however, these oral sequelae can be reduced by adequate oral hygiene, frequent dental visits for cleanings, and antimicrobial therapy. Graft-versus-host disease, the reaction of host antigen against donor cells, is a common occurrence after bone marrow transplant. Oral sequelae include mucosal ulcerations, mucositis, xerostomia, and dysphagia.[80]

The acute reduction in leukocytes produced in agranulocytosis can be precipitated by chemotherapeutic agents or immunologic diseases. Oral manifestations include necrotic and ulcerative lesions of the mucosa, pharynx, and skin. Recurrent bacterial infections, oral ulcerations, and periodontal disease are common oral manifestations of Chédiak-Higashi syndrome. Persons with this hereditary disease of the lysosomal membrane of granulocytes also often develop non-Hodgkin's lymphoma.

Oral manifestations of persons with anemia are associated with the cause of the reduction in the oxygen-carrying capacity of the blood. Pale oral mucosa, loss of tongue papillae (with associated soreness), and angular cheilitis are characteristic of vitamin B_{12}- and iron-deficiency anemia.[24] Severe iron-deficiency anemia can progress to Plummer-Vinson syndrome, resulting in oral soreness, dysphagia, and an increased risk for oral and pharyngeal carcinoma. The tissues of persons with sickle cell anemia may appear jaundiced, whereas radiographic bone findings include osteoporosis and trabecular changes. Delayed eruption and dental hypoplasia can also be found.

Hemoglobin Problems

Thalassemia is an inherited disorder of hemoglobin production causing chronic anemia and bone marrow overexpansion. Oral manifestations of this bony overgrowth can include a prominent maxilla with associated malocclusion, rarefaction of the alveolar bone, cranial nerve palsies, and tooth discoloration due to high iron deposition.[41] Porphyrias are disorders caused by defective metabolic assembly of the heme portion of the hemoglobin molecule. Reddish discoloration of the teeth (erythrodontia) can be found in congenital porphyria due to the deposition of porphyrin in the dentition.

Women's Oral Health and Disease

Many of the oral manifestations that are unique or typically found in women are thought to be precipitated or exacerbated by hormonal changes. These hormonal modulations throughout a woman's life span result in varying oral lesions that are often particular to a specific life stage (e.g., puberty, menses, pregnancy, menopause).

Puberty

Intraoral microfloral changes and increased inflammatory and hyperplastic gingival reactions to food debris and plaque have been reported to develop during puberty.[81] Eating disorders may initially be identified during this developmental stage from oral findings. Self-induced vomiting and chronic regurgitation of gastric contents observed in bulimia nervosa and anorexia nervosa can cause erosion of the lingual enamel of the teeth, most commonly in the maxillary anterior region. Other oral manifestations of these disorders include traumatized oral and pharyngeal mucosal tissue, angular cheilitis, dehydration, and parotid gland enlargement.[81]

Menses

Some oral changes are only associated with particular times within the menstrual cycle. These symptoms include swollen and erythematous gingival tissues, development of aphthous ulcers, activation of herpes labialis, prolonged hemorrhage following oral surgery, and swollen salivary glands.[81] Intake of oral contraceptives can cause oral changes such as gingival inflammation, intraoral microbial alterations, and increased risk for osteitis after third molar extraction.

Pregnancy

Pregnancy gingivitis, which is characterized by erythematous gingival and interproximal tissues, is the most common periodontal condition developing in approximately two thirds of all pregnancies. These symptoms usually appear during the first trimester and continue throughout the pregnancy. Inflammatory gingival hyperplasia, which is initiated by an increased reaction to local irritants, can develop into a mucosal condition known as a *pyogenic granuloma* (also called *pregnancy tumor, epulis gravidarum,* or *pregnancy granuloma*). It occurs in less than 10% of pregnancies, but can be found as a single tumor-like growth on interproximal tissues in the maxillary anterior region. Surgical excision is usually required for complete resolution.

Maternal periodontal disease has been identified as a possible risk factor for preeclampsia, preterm birth, and growth restriction.[82,83] A recent study demonstrated that treatment of periodontitis in pregnant women improves periodontal disease and is safe but does not significantly alter rates of preterm birth, low birth weight, or fetal growth restriction.[84] Therefore there are few contraindications for pregnant women to undergo active treatment for periodontal diseases.

Menopause and Postmenopause

Menopause has been associated with oral complaints (e.g., stomatodynia, stomatopyrosis or burning mouth syndrome, xerostomia), but the etiopathogenesis has not been clearly elucidated.[81] Burning mouth syndrome requires an extensive evaluation to rule out oral microbial, salivary, dental-alveolar diseases, nutritional deficiencies, and metabolic disorders before treatment with low-dose antidepressants is recommended.[45,85] Perimenopausal and postmenopausal oral mucosal changes include menopausal gingivostomatitis, which is characterized as pale, dry, shiny, and easily bleeding gingival tissues. Some studies have demonstrated a relationship between residual ridge resorption and osteoporosis. However, it is unknown whether systemic bone loss affects the severity of periodontal disease or contributes to alveolar bone

resorption and subsequent tooth loss. Some evidence indicates that hormone replacement and bisphosphonate therapy can contribute to decreased alveolar bone and tooth loss, but further clinical trials are required.[34] Oral bisphosphonates rarely contribute to unusual alveolar problem, termed *bisphonate-induced osteon ecrosis of the jaws* (BIONS), although IV bisphosphonates for oncologic purposes are most commonly the cause of this disorder of osteoclasts in the mandible and maxilla.[15]

Inherited and Congenital Disorders

Numerous congenital malformations have head, neck, and oral manifestations. Only the most common are discussed in this review; the reader is referred to specialized textbooks for details on all disorders.[11,41,86,87]

Several disorders affect the dentition,[88] one of the most common being stained or mottled teeth caused by ingestion of tetracycline or excessive fluoride during permanent tooth development. Congenital syphilis is associated with abnormalities on the incisors (notched edges; Hutchinson's teeth) and molars (dome-shaped or mulberry molars). In osteogenesis imperfecta (brittle bone disease), alveolar bone and dentin are affected. Teeth are opalescent and mobile, and pathologic bony fractures can occur in the facial bones as well. Dentinogenesis imperfecta manifests itself in a defective junction between enamel and dentin, resulting in teeth highly susceptible to fracture and dental caries. Malformed and supernumerary teeth are found in other skeletal system diseases such as cleidocranial dysostosis.

Abnormalities in the palate are evident in Turner's syndrome (a high palatal vault), Marfan's syndrome (high-arched soft palate as well as dental crowding), and the relatively more common cleft lip and palate disorders (see Chapter 186, Cleft Lip and Palate). Oral-facial-digital syndrome, or orodigitofacial dysostosis, is characterized by a short upper lip, hypertrophy of the frenula of the lips and tongue, and clefts of the hard and soft palates. Macroglossia and a cleft or high-arched palate may be observed in Down syndrome (trisomy 21) with a hypoplastic maxilla, as well as hypodontia or anodontia. These patients are more susceptible to early necrotizing gingivostomatitis and periodontitis.

Unusual oral mucosal pigmentations are the result of many disorders. Mucous membranes may show multiple angiomas and port-wine staining of the facial skin and oral mucosa in a unilateral trigeminal distribution in Sturge-Weber syndrome (encephalofacial angiomatosis). Telangiectasias of lip and oral mucosa surfaces appear during childhood and increase with age in several diseases: Rendu-Osler-Weber syndrome, hereditary hemorrhagic telangiectasia, and Fabry's disease (angiokeratoma corporis diffusum universale) have telangiectasias of the tongue, oral cavity, and nasal mucosa, which become apparent at puberty and increase as the patient ages. Melanosis of the gingiva can occur as a normal variant in the black population but also occurs in hemochromatosis, an autosomal dominant disorder of increased iron absorption from the gastrointestinal tract. Albright's disease (polyostotic fibrous dysplasia) demonstrates melanosis of the gingival tissues, café-au-lait spots on facial skin ("coast of Maine spots"), and migration and mobility of teeth caused by jaw involvement with the fibrous dysplasia. Melanosis of the perioral skin and gingival tissues is also present in Peutz-Jeghers syndrome. Tangier's disease, a disorder of lipoprotein metabolism, is associated with pathognomonic xanthomas that appear as yellow tonsils or yellowish-white to gray spots in the soft palate.

Fibromas of the maxilla, mandible, or tongue have been connected with at least five systemic syndromes[9]: Congenital von Recklinghausen's disease is an autosomal dominant disease with multiple neurofibromas of the skin and bone, café-au-lait spots on the skin, and oral melanosis.[53] Multiple endocrine adenomatosis type 3 is associated with neurofibromas of the tongue and lips.[38] Cowden's disease is dominantly inherited and is characterized by warty papules on the face, arms, and mucous membrane of the mouth.[56] Tuberous sclerosis, a neurocutaneous syndrome, also has café-au-lait spots and intraoral fibromas.[69] Melkersson-Rosenthal syndrome is a developmental abnormality with unilateral facial paralysis, edema of the periorbital skin, and a fissured tongue with papillary projections that reveal fibromas at biopsy.

Several congenital disorders develop bony lesions of the maxilla and mandible. Langerhans cell histiocytosis, Letterer-Siwe disease, Langerhans' cell eosinophilic granuloma, and Hand-Schüller-Christian disease all are associated with infiltrative-destructive lesions of the bone caused by overgrowth with histiocytes and may appear as a gingival epulis, loose teeth, or mucosal erosions. Gaucher's disease is characterized by a reduction in normal cerebroside breakdown with resultant accumulation of lipid-laden histiocytes; this results in radiolucent lesions in the jaw. Osteopetrosis has mandibular and maxillary hyperostosis, similar to that seen in Paget's disease, fibrous dysplasia, histiocytosis X, and acromegaly.

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CHAPTER NINETY-THREE

Odontogenesis, Odontogenic Cysts, and Odontogenic Tumors

John W. Hellstein

Key Points

- Odontogenesis is a complicated intermingling of processes with many levels of induction. There are many interactions between mesenchymal and epithelial tissues. Of particular interest is the embryology of Rathke's pouch as well as the normal distribution of dental laminae in the alveolar arches. In addition, portions of the enamel organ are the origin of most of the commonly known odontogenic cysts and tumors.
- The nomenclature of odontogenic and nonodontogenic cysts of the oral region is varied. Though many of these cysts are not directly covered in the Key Points, it may be beneficial for the reader to review Box 93-1 as an aid in formulating differential diagnosis lists.
- The keratinizing odontogenic cyst is specifically separated from the odontogenic keratocyst due to its much more innocuous presentation. The odontogenic keratocyst has also recently been renamed as keratocystic odontogenic tumor.
- The term primordial cyst continues to be used by some authors. However, its use often differs depending on the background of the author. Of most concern is that the term primordial cyst in many European publications is used synonymously with what it now termed the keratocystic odontogenic tumor (odontogenic keratocyst). In this chapter we will use the term *odontogenic cyst of undetermined origin* to describe those lesions that appear histologically identical to a dentigerous cyst or radicular cyst but are not anatomically related to any particular tooth.
- The odontogenic keratocyst has also been known as the parakeratinizing odontogenic keratocyst, and the WHO has recently renamed it the keratocystic odontogenic tumor. In addition, this cystic neoplasm is associated with basal cell nevus syndrome.
- The botryoid odontogenic cyst radiographically presents as a multilocular lesion and may recur. Histologically the lining is identical to the lateral periodontal cyst.
- The problem with the glandular odontogenic cyst diagnosis is that it is becoming overused due to lack of calibration and variability in its histologic definiton.
- For odontogenic tumors, in general readers are encouraged to always look over the general treatment considerations for each patient's situation. Specifically there is some concern about the evidence-based nature of treatment recommendations related to many of the odontogenic tumors. In the case of the calcifying epithelial odontogenic tumor, older texts and even modern texts often recommend rather aggressive therapy, although there is little evidence-based literature to support initial aggressive therapy in some tumors. With the exception of the ameloblastoma, there are only sparse reports of any of the benign odontogenic tumors "getting away" from the surgeon even if a recurrence does happen.

Odontogenic tumors are often intricate admixes of neoplastic and non-neoplastic lesions. Even the "simple" odontogenic lesions have their origin traced back to odontogenesis. But odontogenesis is far from simple. By understanding odontogenesis, the reader's appreciation for these lesions should be enhanced. In fact, it is the unique interaction of ectomesenchymal tissues with epithelial tissues during odontogenesis that make these cysts and tumors unique. These interactions of the mesenchyme and epithelium occur across short distances and within the confined volume of the jaws. Complications in histologic interpretation include artifacts caused by demineralization, sampling errors, separation of hard and soft tissues at the grossing bench, and general difficulties in sectioning disparate tissue types. Separation of disparate tissue at the grossing bench can make it impossible to analyze the relationship of tissues later under the microscope. Even when these background problems are not encountered, the result is often still a histopathologic hodgepodge. In the end, odontogenic lesions that contain both epithelial and mesenchymal components are often difficult to assess histologically.

A basic understanding of odontogenesis by the surgeon/clinician may help to predict behavior, enlighten the clinician on what information to give the pathologist, and guide proper treatment. Thus odontogenesis and the jaws' unique status within the body create a wide set of possibilities for clinical, radiographic, and histopathologic differential diagnosis lists. It is the goal of this chapter to review odontogenesis, as well as odontogenic cysts and tumors. It is hoped by the end of this chapter that a better understanding of odontogenic cysts and tumors will lead to a more thorough appreciation of this intricate and complicated set of diseases.

Background

Odontogenesis begins within generally well-defined areas of the stomodeum, then by maturational extension the oral cavity and alveolar

processes of the jaws. Unfortunately, simply knowing the location does not necessarily allow the clinician to always positively ascertain a lesion as being odontogenic in origin. Confounding elements include the embryologic nature of Rathke's pouch, extension of large odontogenic lesions outside the confines of the alveolar processes, and the propensity of products of odontogenesis to "wander." Thus reports of sinonasal ameloblastomas and craniopharyngiomas of the sella should not be surprising and still be considered odontogenic in origin. Simply put, the only prerequisite is that all odontogenic cysts and tumors must be derived from elements of stomodeal origin.

Histologically the rather unique epithelial portions of odontogenesis often remain distinct enough in cysts and tumors to allow for proper determination of origin. Unfortunately, the mesenchymal components of the dental papilla (as seen in myxomas) and cemental components (as seen in odontogenic fibromas) are impossible to definitively identify histologically as being of odontogenic origin. The only hope in identifying these as odontogenic is if they occur in association with other odontogenic epithelial elements. But generally, these mesenchymal lesions are identified as odontogenic on the basis of their location in the jaws.

Though this section focuses only on odontogenesis, remember that the oral and maxillofacial region is also associated with developmental remnants of salivary glands, seromucous glands, sinonasal epithelium, nasopalatine duct epithelium, and dermal epithelia. Due to these nearby, possibly confounding embryologic tissues, the true origin of any given lesion may be cloudy at best. However, by knowing the specific location, history, and histopathologic features and being additionally armed with knowledge of odontogenesis, the proper designation for any given lesion can almost always be filtered to arrive at a relatively short differential diagnosis list.

The enamel organ is generally divided into the bud stage, cap stage, and bell stage. The bud stage begins as a proliferation of the basilar cells of the stomodeum. This proliferation occurs along the area of the future alveolar mucosa apical to and separated from the vestibular mucosa. In this early stage the ectoderm of the stomodeum is lined by two to three cells. It is during the sixth week that the ectoderm in the region of the future alveolar processes begins to proliferate and form two somewhat horseshoe-shaped epithelial bands. Before being differentiated into the epithelial surfaces of the alveolar processes, each band is called a *dental lamina.* These dental laminae will eventually form the 20 separate proliferations necessary for the deciduous teeth. These 20 areas of proliferation are each called *tooth buds.* Each tooth bud then proliferates apically into the underlying ectomesenchymal tissue. Eventually at the bell stage the connection between the overlying stomodeum and the enamel organ will become separated. But the actual process of bud proliferation varies by arch, as well as by tooth type (i.e., deciduous central incisor, deciduous lateral incisor, deciduous canine, deciduous first molar and deciduous second molar). By the end of the eighth week all 20 buds have been produced.

During all phases of morphodifferentiation, histodifferentiation, and apposition the features of the enamel organ and the physiologic support of the enamel organ are changing. But with apposition of the dentin and vascularization near the outer enamel epithelium the enamel organ is further defined with a fourth cell layer termed the *stratum intermedium.* The cells of the stratum intermedium occupy an ill-defined area of flattened cells between the inner enamel epithelium and the stellate reticulum. Though the area of phenotypic change that defines the stratum intermedium must be present before enamel can be laid down, actually identifying these cells individually is extremely subjective.

Root Development

In the tooth root, the dentin forms the huge majority of the root volume, which is then sheathed in a layer of cementum instead of enamel. But the odontoblasts still cannot lay down dentin without induction by epithelium derived from the enamel organ. To accomplish this feat as the reduced enamel epithelium reaches the cemento-enamel junction, it becomes reduced to back-to-back inner and outer epithelial cells. This produces a collar of cells that separate from the reduced enamel epithelium. This separated collar is known as *Hertwig's epithelial root sheath.* Hertwig's root sheath as it moves apically to guide root formation will "leave behind" epithelial rests known as *rests of Malassez.* These rests will reside in the region of the periodontal ligament and provide a basis for several potential odontogenic cysts and tumors.

The periodontal ligament is actually a joint known as a *gomphosis joint.* Though the cementum cannot be distinguished except by location, the body, for instance, during orthodontic movement will resorb the bone on the lamina dura side of the periodontal ligament and not the cementum on the tooth side of the ligament. The tooth with the periodontal ligament will retain a certain amount of mobility within the joint. The reader is again referred to various texts for a more in-depth coverage of odontogenesis.[1-5,5a]

Summary

There are a number of odontogenic epithelial stages and each may provide a basis for odontogenic cysts or tumors. The four main stages considered are (1) dental lamina, (2) enamel organ, (3) reduced enamel epithelium, and (4) Hertwig's epithelial root sheath. The rests of Serres and Malassez are considered along with their respective progenitors of the dental lamina and Hertwig's root sheath. In addition, the stomodeal epithelium gives rise to Rathke's pouch, which retains odontogenic potential. Shafer and colleagues[6] suggest the original basal epithelium of the stomodeum also retains potential. In the adult this basal epithelium is represented by the gingival and alveolar mucosal surfaces.[6] This concept seems to be supported when peripheral ameloblastomas appear to develop directly from overlying gingival epithelium. With that said, most clinicians would consider the adult basal epithelium to be a rare source of odontogenic neoplasia. The rests of Malassez are common sources of inflammatory odontogenic cysts but retain little neoplastic potential. The rests of Serres, the enamel organ, and reduced enamel epithelium are generally considered the stages most likely to become neoplastic. All stages have the potential to form cysts but to variable degrees. Dentigerous cysts with their origin from the reduced enamel epithelium and radicular cysts from rests of Malassez make up the overwhelming majority of odontogenic cysts.

Odontogenic Cysts

Classification

When reading various sources it becomes quickly clear that what a cyst "is" varies by author and that the classification schemata are in disarray as well. The modified classification scheme seen in Box 93-1 is my attempt at organization. The odontogenic cyst of undetermined origin is a new, admittedly descriptive "diagnosis" used by some oral pathologists. Unfortunately the descriptive nature of that term will not be available to look up in other texts or journals. However, it replaces the diagnosis of primordial cyst. The need to use a descriptive term instead of primordial cyst is due to the ambiguous use of primordial cyst both as an odontogenic keratocyst (OKC) and a simple nonkeratinizing cyst that cannot be classified in relation to the tooth. The descriptive role is to provide a pigeonhole in which to place lesions that are histologically ambiguous, not directly associated with a tooth but located in the alveolus and thus presumably odontogenic in origin.

Several classification schemata for odontogenic cysts and oral and maxillofacial cysts exist.[7-9] The classification scheme seen here is modified from that of the World Health Organization (WHO). In 1992 WHO published the second edition of *Histological Typing of Odontogenic Tumors.*[10] Unfortunately the most recent WHO treatise on odontogenic tumors is contained within the *Pathology and Genetics of Head and Neck Tumors.*[11] In this change odontogenic cysts are no longer covered within the text. Box 93-1 also contains selected non-odontogenic cysts for completeness and comparison.

By definition a cyst is considered a "pathologic cavity at least partially lined by epithelium." To be an odontogenic cyst the epithelial lining must be derived from odontogenic epithelium. The best advice to the reader is that all classification schemata are artificial to some extent. The key is to organize them the way that is most useful to you. This modification in Box 93-1 is an attempt at self-

Box 93-1

Classification of Odontogenic with Other Selected Maxillofacial Cysts

Odontogenic cysts
- Developmental cysts
  - Dental lamina cyst (gingival cyst of newborn)
  - Odontogenic keratocyst (called keratocystic odontogenic tumor by WHO)*
  - Dentigerous cyst (follicular cyst)
  - Eruption cyst
  - Lateral periodontal cyst
    - Botryoid odontogenic cyst
  - Gingival cyst of adults
  - Keratinizing odontogenic cyst
  - Glandular odontogenic cyst
- Calcifying odontogenic cyst (Gorlin cyst)
- Odontogenic cyst of undetermined origin (replaces the term *primordial cyst*, which has been irretrievably confused in the literature. This new descriptor also serves as a useful designation for some lesions that do not classify well.)
- Inflammatory cysts
  - Periradicular cysts
    - Periapical cyst (apical periodontal cyst)
    - Lateralized periradicular cyst
  - Residual cyst
    - Dentigerous origin
    - Periapical origin
  - Paradental cyst
    - Mandibular infected buccal bifurcation cyst
  - Inflammatory collateral cyst

Nonodontogenic cysts
- Nasopalatine duct cyst (incisive canal cyst)
- Cyst of the incisive papilla
- Nasolabial cyst (nasoalveolar cyst)
- Palatal cysts of infants
  - Epstein's pearls (midline of hard palate)
  - Bohn's nodules (scattered on palates especially at junction of hard and soft)
- Lymphoepithelial cysts
- Oral lymphoepithelial cyst
- Cervical lymphoepithelial cyst (branchial cleft cyst)
- Gastric heterotopic cyst
- Thyroglossal duct cyst
- Salivary duct cyst
- Maxillary antrum associated
  - Surgical ciliated cyst
- Soft tissue cysts
  - Epidermoid cyst
  - Thymic cyst
  - Bronchogenic cyst
  - Trichilemmal cyst (pilar cyst)
- Pseudocysts
  - Idiopathic bone cavity (e.g., traumatic bone cavity, traumatic bone cyst, simple bone cyst, hemorrhagic bone cyst)
  - Aneurysmal bone cyst
  - Mucus-retention phenomenon (mucous-retention cyst)
  - Mucocele of the sinus
  - Cystic hygroma
- Miscellaneous
  - Dermoid cyst
  - Polycystic disease of the parotid
  - HIV-associated lymphoepithelial lesion

Nonexistent/spurious cysts

The following cysts are generally considered embryologically impossible or have been reclassified in previous descriptions of cysts.
- Globulomaxillary cyst (dismissed on the basis of embryology)
- Median mandibular cyst (dismissed on the basis of embryology)
- Median maxillary alveolar cyst (subcategory of nasopalatine duct cyst)

*Primordial cyst specifically *not* used synonymously.
HIV, human immunodeficiency virus; WHO, World Health Organization.

clarification and will hopefully be useful for others in either its pure or modified form.

Pathogenesis

Many odontogenic cysts are surfaced by nonkeratinized epithelium. Histologically the following nonkeratinizing cysts can look identical and cannot be separated except by clinical, historical, and/or radiographic means. These include dentigerous cyst (follicular cyst), eruption cyst, odontogenic cyst of undetermined origin, periapical cyst (apical periodontal cyst), lateralized periradicular cyst, residual cyst, and paradental cyst.

These cysts make up the majority of odontogenic cysts. As a group they are known as the *common odontogenic cysts.* For proper diagnosis of these common odontogenic cysts the clinician must provide sufficient information for the diagnosis to be made. The reader is urged to closely note the necessary or significant features when each of these cysts is specifically discussed later in this section.

The other odontogenic cysts will display histologic features to allow for the proper diagnosis, though history and communication are of course always appropriate and often essential. It is important to note that the presence of a specific type of keratin is not pathognomonic for an OKC and may be seen with other odontogenic cysts.

Cyst expansion occurs because of numerous factors including accumulation of inflammatory cells, fibrin, serum, and desquamated epithelial cells. As these products enter the cystic cavity, it is the accumulation of the intraluminal products that spurs the cystic expansion of the wall.[12-14] Alternatively, cyst expansion may be spurred on by the inherent mitotic activity of the cyst wall itself. If this mitotic activity is the major component of the cyst expansion, it may be better to consider the lesion a cystic neoplasm rather than a simple cyst.[14-20] This debate lies at the center of how to classify the OKC, as well as the calcifying odontogenic cyst.[21] In the case of the OKC, WHO has renamed it the *keratocystic odontogenic tumor.* Discussion of this entity is in the odontogenic cyst section. In the case of the calcifying odontogenic cyst (the tumor version), the reader is referred to more detailed articles on the epithelial odontogenic ghost cell tumor.

Multilocularity may in itself be a signal that the lesional growth is mitotically or multifocally driven rather than hydraulically driven.[22-25] For this reason the potentially multilocular odontogenic cysts, such as the botryoid odontogenic and glandular odontogenic cyst, may arguably have a neoplastic potential as well.[22,26-30] However, in the case of the botryoid cyst the possibility of multifocality cannot be ignored. Cell regulation protein studies to determine cell inhibition and division activities may be helpful in future classifications.[31,32] In addition, the ability of epithelia to break down elements of the connective tissue wall could be important.[33-37]

However, even simple cysts like the periradicular cyst derived from rests of Malassez must possess some mitotic activation, or growth would be impossible. Activation is thought to occur as a result of inflammatory production within the periodontal membrane.[13,38] In the skin and gingiva it has been shown that inflammation leads to release of inhibitors, which then allow the renewal of mitotic activity.[15] Once a solid epithelial sphere has been formed, it is thought that it eventually outgrows its vascular nourishment and the central area degenerates to form a lumen.[15,16] Following the formation of the central lumen, transepithelial flow of fluid is sustained by osmotic forces. Thus hydrostatic pressure plays a role in the development of the classic unilocular appearance of most cysts. How the pressure results to produce osteoclastic resorption is less clear.[17,39-41]

Cysts that are derived from the more neoplastic dental lamina, or are in themselves "cystic neoplasms," probably occur as a result of self-sustained or unregulated mitotic activity.[42] Even in neoplastic cysts, luminal expansion may occur through degenerative effects, debris accumulation, and hydraulic and mitotic activity.[43-45]

Periapical Cyst (Radicular Cyst, Periradicular Cyst)

The periapical cyst must be associated with a nonvital tooth. The tooth may be rendered nonvital by trauma, caries, or periodontal space extension. As such, these cysts may be seen at any age, although permanent teeth are more likely to be involved than deciduous teeth.[46] They are thought to be derived from rests of Malassez.

Figure 93-1. Occlusal radiograph of large periapical cyst associated with two endodontically treated maxillary incisors.

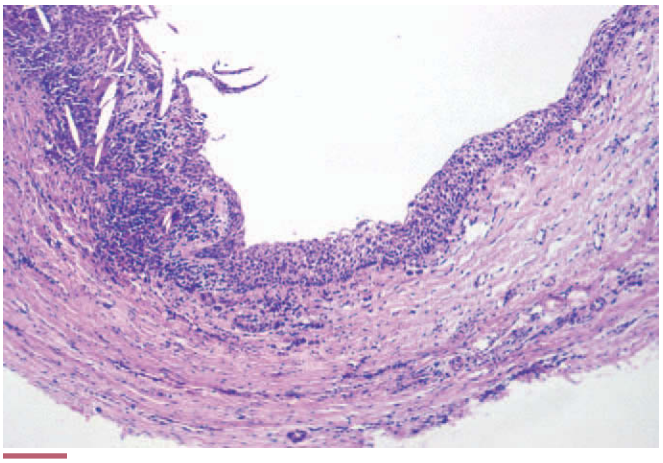

Figure 93-2. Photomicrograph of periapical cyst showing nonkeratinizing stratified squamous epithelium with inflammation. Cholesterol slits are seen toward the left side of the luminal surface and appear as empty white clefts.

Radiographic Features

Periapical cysts present as a unilocular radiolucency at the apical portion of the tooth. Though well defined, the border varies from corticated to sclerotic to merely well defined. Variations depend on the amount of inflammation present. Long-standing, neglected lesions can get quite large, though most are less than 1 cm in diameter (Fig. 93-1).

Microscopic Features

This is the classic inflamed "common odontogenic cyst" and as such the luminal lining will consist of nonkeratinized stratified squamous epithelium. This is an inflammatory cyst and inflammation is invariably present if sufficient sampling is performed (Fig. 93-2). Rests of Malassez are possible in the connective tissue. However, odontogenic rests are rarely seen in the cyst wall even though these rests are thought to be the source of the epithelial proliferation. Cholesterol slits, foreign body giant cells, and hemosiderin deposits are common findings. As in all "common odontogenic cysts," squamous odontogenic tumor-like" proliferations may be seen in long-standing lesions. These epithelial islands will be cytopathologically benign without evidence of dysplasia. If squamous odontogenic cystlike proliferations are noted, they should essentially be ignored and are of no prognostic significance. In endodontically treated teeth, foreign bodies secondary to endodontic therapy are common.[47] Bacterial colonies may also be seen in these cysts. Though actinomycetes colonies may portend a tendency for being slow

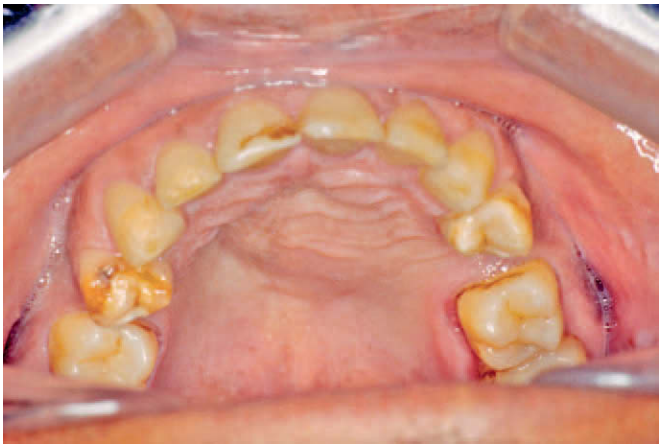

Figure 93-3. Clinical photograph of cyst seen in Figure 93-1 before enucleation.

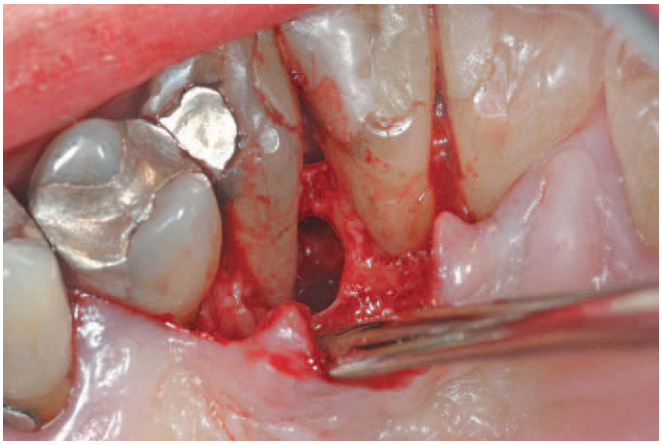

Figure 93-4. Intraoperative photograph of an inflammatory collateral cyst. Tooth is vital with periodontal pocket leading to intrabony cystic area.

to resolve, their presence should not result in a diagnosis of osteomyelitis. Such colonies are more commonly an incidental rather than a significant finding. Thus, for multiple reasons, the proper diagnosis of periapical cyst requires radiographic or clinical corroboration.

Treatment

This cyst is treated with simple enucleation (Fig. 93-3). Enucleation is often accomplished at the time of tooth extraction. Uncounted numbers of these cysts are probably adequately resolved with endodontic therapy. If a radiolucency persists longer than 6 months following endodontic therapy, enucleation and histopathologic review are necessary.[48-50]

Lateralized Radicular Cyst (Lateral Radicular Cyst, Lateral Periapical Cyst)

This cyst is simply a variant of the periapical cyst. It is associated with a nonvital tooth, but instead of being at the apex of the tooth the cyst is located lateral to the tooth root(s). This happens because the root canal system of teeth sometimes has exits on the lateral aspect of the root, not just at the apex. Therefore if the path of least resistance is out one of these lateral canals the lesion will be present laterally. Otherwise, the clinical, microscopic, radiographic, and histologic features are identical to the periapical cyst.

Residual Cyst

The majority of these cysts will be the result of leaving a periapical cyst "behind" following tooth extraction. All of these cysts are inflammatory cysts. Occasionally an inflamed dentigerous cyst is incompletely removed and could also be the source of a residual cyst. The clinical, microscopic, radiographic, and histologic features are identical to the periapical cyst.[48,49,51,52]

Inflammatory Collateral Cyst

This may or may not be considered by some to be a true cyst. However, because it is an occasionally used diagnosis, a quick summary is included here. This lesion is associated with periodontal disease of a vital tooth. Uncommonly, a deep intrabony periodontal pocket may be sufficiently isolated to allow for hydraulic expansion of the bone (Fig. 93-4). As such, radiographically there will be a radiolucent periradicular lesion (Fig. 93-5). There will also be a periodontal pocket associated with that radiolucency. This diagnosis should be limited to those cases where the clinician indicates the diagnosis as the most likely choice. Otherwise, the clinical, microscopic, radiographic, and histologic features are identical to the periapical cyst.[53]

Dentigerous Cyst (Follicular Cyst)

The dentigerous cyst by definition must be associated with the crown of an unerupted tooth, developing tooth, or odontoma. The eruption

Figure 93-5. Radiograph of inflammatory collateral cyst.

cyst is essentially a subtype of dentigerous cyst that is confined just by the overlying alveolar mucosa. Dentigerous cysts form when fluid accumulates between reduced enamel epithelium and tooth crown.[14] As alluded to earlier, the accumulation of fluid may be partially or largely surrounded by connective tissue and epithelium.[54,55] Because the third molars and maxillary canines are the teeth most frequently impacted, they are also the most likely to be associated with dentigerous cysts. However, any impacted tooth has an increased risk. There also may be inherent differences in impacted tooth development and how the reduced enamel epithelium is transformed/resorbed.[56] They are generally found in the teenage years and early adulthood.[57] However, the longer a tooth is impacted, the greater the chance a dentigerous cyst will develop.[58]

Figure 93-6. Radiograph of large dentigerous cyst associated with molar crown.

Figure 93-7. Clinical photograph of device used for cyst decompression. Note two holes to allow for proper irrigation (*arrows*). The device is constructed from acrylic resin with a central "waist" and blunderbuss ends. To keep it in place, nonresorbable sutures may be necessary for 2 to 3 weeks.

Radiographic Features

A dentigerous cyst presents as a unilocular radiolucency, which is associated with an unerupted tooth (Fig. 93-6). Dentigerous cysts may also involve odontomas that, by nature, also have "tooth crowns." The radiolucency is generally well demarcated and well corticated. The border may become sclerotic or display rarifying osteitis if secondary infection is present. Even large cysts that have pushed the associated tooth considerable distances will display evidence of origin from the cementoenamel junction if the film angle is adequate. In large lesions the origin from the cementoenamel junction is best visualized as an area of cortication at the cementoenamel junction. There is considerable overlap between the appearance of small dentigerous cysts and hyperplastic follicles.[56]

Microscopic Features

The specimen will present primarily as variably dense fibrocollagenous connective tissue with some areas being loose and myxomatous. Odontogenic epithelial rests are usually scattered within the connective tissue and are most common near the epithelial lining. The luminal lining consists of nonkeratinized stratified squamous epithelium. The presence of mucous prosoplasia within the lumen is not uncommon. Care should be taken to not overinterpret the mucus prosoplasia. Cholesterol slits and their associated multinucleated giant cells may be present in inflamed cysts and are generally associated with the connective tissue wall.[47] As mentioned earlier, the lumen may be partially or mostly lined by connective tissue.[14] If present in the specimen, crevicular epithelium may make microscopic separation of an inflamed dentigerous cyst from pericoronitis impossible. Thus proper diagnosis requires radiographic or clinical corroboration.

Neoplastic Potential

Dentigerous cysts appear to retain the ability to transform into true neoplasms. One study reported that 17% of ameloblastomas were associated with an existing dentigerous cyst.[59] This figure varies by study, however.[60-62] Both squamous cell carcinomas and mucoepidermoid carcinomas have been reported.[63-67]

Treatment

Dentigerous cysts are usually easily enucleated at the time of tooth extraction. In large lesions decompression with subsequent enucleation may be appropriate (Fig. 93-7).

Eruption Cyst

The eruption cyst is a form of dentigerous cyst that is found in the soft tissue overlying an erupting tooth. Because by definition it must be associated with an erupting tooth, eruption cysts occur only during the ages of tooth development.[7] They may be seen with erupting deciduous or permanent teeth, but the majority of lesions are seen in the first decade.[68] The lesion will present as a soft tissue swelling of the alveolar ridge overlying an area of age-appropriate tooth development. Some eruption cysts will have a slightly blue hue color, though the normal coral pink color of the surrounding mucosa is common (Fig. 93-8). Unlike dentigerous cysts, it is not uncommon for an eruption cyst to be associated with deciduous teeth. Eruption cysts may be seen in newborns with an incidence of 2 per 1000 births reported.[69] Clinical follow-up may also serve to confirm the diagnosis because the tooth will erupt within several weeks to months through the cystic expansion.[70-74]

Figure 93-8. Clinical photograph of maxillary eruption cyst found incidentally in an infant.

Treatment

The eruption cyst almost always resolves without intervention. In uncommon cases eruption of the underlying tooth may be impeded or delayed. In such cases a "deroofing" will allow eruption.

Paradental Cyst

The paradental cyst is considered by some to be a variant of the dentigerous cyst. This is because the various forms of paradental cyst all originate from the cementoenamel junction just like the dentigerous cyst. However, the paradental cysts are almost uniformly inflamed, so they are generally classified as inflammatory cysts rather than as developmental cysts. Paradental cysts occur on the buccal or distal aspect of

an erupted mandibular molar. Though the mesial aspect of a mandibular tooth may rarely be involved, there have been no reported occurrences to the lingual. Craig[75] reported the occasional presence of developmental enamel projections near the furcation of some teeth. This is particularly true of the subcomponent of paradental cysts known as *infected buccal bifurcation cysts.* How big a role these projections play in pathogenesis remains debatable.[76-81] In one series the paradental cyst accounted for 3% of all odontogenic cysts.[82]

Radiographic Features

The lesion will present as a well-defined radiolucency associated with but not surrounding the coronal area of a partially erupted tooth.[81]

Odontogenic Cyst of Undetermined Origin

It is with great regret that another diagnosis is added to the list of odontogenic cysts, but there appears to be no good alternative. On occasion the clinician and pathologist may come upon a lesion that is not classifiable by histologic, radiographic, or clinical features. As mentioned earlier, several odontogenic cysts have identical microscopic features. Odontogenic cysts with identical or potentially identical histologic features are referred to as the *common odontogenic cysts.* These "common" cysts are separated on the basis of clinical features alone.

The problem in diagnosis comes when a cyst is not associated with the crown of a tooth, residually or with the root of a nonvital tooth. Additionally, the cyst is not consistent with a fissural cyst but is at least partially located in the alveolar process. Historically, any cyst that occurred in an area where a tooth should have developed, or where supernumerary teeth could occur, were originally called primordial cysts.[83] This term was used to allude to development from the tooth primordium. Unfortunately, this was proposed in 1945 before delineation of the features defining the OKC and a large percentage of these "primordial" cysts had features of what would now be diagnosed as an OKC. When the OKC was defined in the 1950s, some pathologists had already recognized those histologic features in what they termed primordial cysts and thus they began to use the term interchangeably with OKCs. International journals, especially, came to use the term *primordial cyst* as a synonym of the OKC.[45,84] Americans often avoided the term *primordial* or left the moniker of primordial cyst for those lesions without features of a keratocyst.

The term primordial cyst is avoided to eliminate any confusion between the histopathologist and the clinician. This is intended to ensure that aggressive treatment of an OKC is *not* performed for this innocuous lesion.

Definition of the Odontogenic Cyst of Undetermined Origin

An odontogenic cyst of undetermined origin is a unilocular radiolucent cyst of the jaws with histologic features of common odontogenic cysts but lacking the clinical, histologic, and radiographic features of any defined common odontogenic cyst (Fig. 93-9).

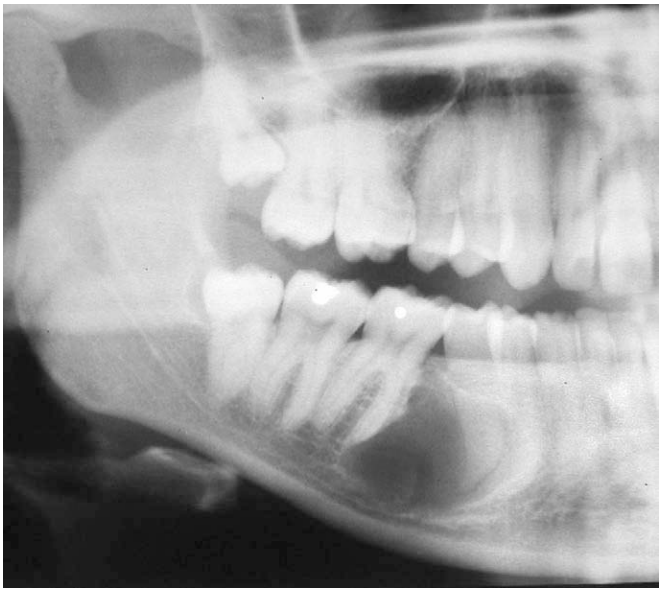

Figure 93-9. Radiograph of an odontogenic cyst of undetermined origin.

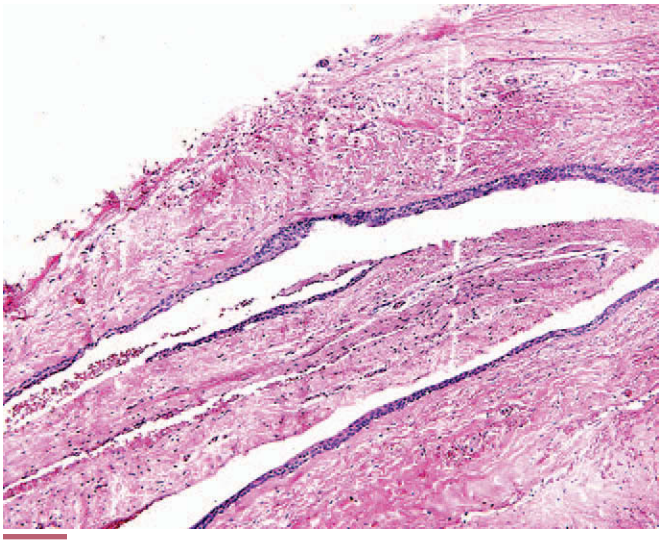

Figure 93-10. Photomicrograph of generally thin cyst lining typical of the lateral periodontal cyst.

Lateral Periodontal Cyst

These cysts are thought to be derived from the dental lamina and are thus thought to retain some limited neoplastic growth potential. This limited neoplastic potential is best displayed by the associated lesion known as a *botryoid odontogenic cyst.* Lateral periodontal cysts are located on the lateral surface of a vital tooth.[85,86] This assumes that the tooth has not been rendered nonvital by dental caries or trauma unrelated to cyst formation. The most common location is the mandibular premolar/canine area. If present in the maxilla, the lateral incisor area is the most common location. However, the lateral periodontal cyst may be seen in any area of the alveolar processes. This cyst is seen in the interproximal area between tooth roots and is usually an incidental radiographic finding.[87,88] Demographically the cyst is most common in males by a 2:1 ratio with a peak incidence in the fifth and sixth decades.[89] The gingival cyst of the adult and the botryoid odontogenic cysts are essentially subtypes of lateral periodontal cysts. Other cysts, especially the OKC, odontogenic cyst of undetermined origin, and the lateralized periapical cyst, also present interproximally. Histopathologic features and tooth vitality are important diagnostic considerations to separate these lesions. All of these lesions can be separated histologically and the lateralized periradicular cyst will be associated with a nonvital tooth.

Radiographic Features

The lesion presents as a unilocular radiolucency of the alveolus that is usually well corticated. Larger lesions may result in diverged roots.[90] Multilocular lesions are a special subset and are classified as botryoid odontogenic cysts (see "Botryoid Odontogenic Cyst" later).[27]

Microscopic Features

The cyst lining is composed of nonkeratinized simple to stratified squamous epithelium. The lining is most notable for being only a few cells in thickness (Fig. 93-10). Intermixed within this otherwise thin epithelial lining are nodular epithelial thickenings or plaques. The plaques may display somewhat whorled epithelial cell aggregates. The central cells in the aggregate may display cytoplasmic clearing. The clear

cells contain glycogen, which can be digested with diastase. Scattered mucous cells may be seen in some lesions but should not be a dominant feature.[90,91] The diagnosis of lateral periodontal cyst must be reserved for lesions displaying the thin epithelium described earlier. The plaque-like thickenings are helpful microscopic features but are not always found. The connective tissue wall may contain dental lamina rests, but they are not required for diagnosis.

Treatment

These cysts are treated with simple enucleation, though the surgeon is reminded to look for intraoperative multilocularity, which may not have been evident radiographically. If multilocularity is present, the lesion is probably a botryoid odontogenic cyst. In such cases light curettage of the surrounding bone wall is advised. Recurrence of the simple lateral periodontal cyst is not a problem and even the recurrences of botryoid cysts are usually easy to manage.

Botryoid Odontogenic Cyst

The botryoid odontogenic cyst will usually present as a multilocular lesion and is a special variant of the lateral periodontal cyst. Botryoid refers to the fact that these lesions may appear like grapelike clusters, both histologically and usually radiographically as well.[23,25,27]

Radiographic Features

Radiographically the botryoid odontogenic cyst presents in the same preferred alveolar process locations as the lateral periodontal cyst. Small locules may not be seen on radiographs.[23]

Treatment

Like the lateral periodontal cyst, treatment consists of enucleation with bony curettage. The multilocular nature may make this difficult, especially if teeth are to be spared. With full enucleation, light bone curettage recurrence should be uncommon. The slow growth of these lesions suggests that a 10-year radiographics is reasonable, though the small sample size makes this a suggestion at best.

Gingival Cyst of the Adult

Clinical Features

This lesion is essentially the soft tissue equivalent of the lateral periodontal cyst. As with the lateral periodontal cyst, it derives from dental lamina or rests of Serres.[92-94] These lesions generally present as an asymptomatic bluish nodule on the facial aspect of the gingiva. The sessile elevation will be centered in the attached gingiva, though extension below the mucogingival line is possible. Unlike the lateral periodontal cyst, there may be a slightly increased incidence in women.[95] The mandibular gingiva is most commonly involved and the peak incidence occurs in the fifth and sixth decades.[9,96] Other odontogenic cysts may also occur in the gingiva. Histologically distinctive odontogenic cysts that are appropriately diagnosed histopathologically should not be descriptively called *gingival cysts.* The possibility of some cysts of the gingivae arising from traumatically implanted surface epithelium does exist. Whether it is best to call these histologically different cysts *epithelial inclusion cysts* is debatable.[95] The term *gingival cyst of the adult* must be reserved for those lesions with histologically distinct microscopic criteria.

Radiographic Features

The lesion may sometimes display superficial cupping of the cortical bone. This cupping is usually only detected intraoperatively.

Gingival Cyst of the Newborn (Dental Lamina Cyst, Alveolar Cyst of the Newborn)

These cysts occur on the alveolar ridge of newborns. They are generally only a few millimeters in diameter and seen only in the first few months of life. Though studies are appropriately devoid of histologic sampling data, some clinical reports estimate these cysts occur in up to 50% of all newborns. The cysts are sessile and vary from normal in color to yellow or white. Similar-appearing inclusion cysts of the palatal midline (Epstein's pearls) or at the junction of the hard and soft palates (Bohn's nodules) are differentiated by location. The gingival cyst of the newborn is a soft tissue cyst and does not have an intrabony component (Fig. 93-11).[97]

Figure 93-11. Clinical photograph of possible gingival cyst of the newborn. Light color favors dental lamina cyst rather than eruption cyst. Cyst spontaneously resolved.

Microscopic Features

These cysts should generally never appear for pathologic review.

Treatment

These cysts almost always spontaneously rupture and require *no* therapy whatsoever. Occasionally a cyst will be large enough to interfere with nursing or persist to 6 or more months of age. In these rare cases, simple enucleation or even deroofing is sufficient.

Keratinizing Odontogenic Cyst (Orthokeratinizing Odontogenic Cyst, Orthokeratinizing Odontogenic Keratocyst)

Recognition of the keratinizing odontogenic cyst is a rather recent phenomenon. When the OKC was first defined, the definition did not separate these lesions. Over time several reviewers noted and separated keratinizing cysts that did not seem to otherwise conform with the microscopic criteria of the OKC.[98-100] The most notable difference in these cysts was the presence of orthokeratin rather than parakeratin, though other features such as lack of tombstoning, corrugation, and hyperchromatism are more important criteria. Wright[101] was the first to formally separate this group of cysts and proposed the name of OKC, orthokeratinizing variant. He noted the different histopathologic features and ably reported the lack of recurrences associated with these orthokeratinized cysts. However, the nomenclature of including the term *keratocyst* has created quite a bit of confusion, at least anecdotally. Historically, older texts and articles described keratinization of various odontogenic cysts and recognized the difference of these cysts from OKCs.[47,100]

The designation as *orthokeratinized OKC* (OKC, orthokeratinized variant) has evolved since first being described. Current nomenclature has evolved to avoid confusion with the "standard" OKC. It is also worth noting that some OKCs can contain orthokeratin, and the original series of "orthokeratinizing OKCs" described by Wright included 7 of 60 cysts with parakeratin.[101] Thus classification based solely on the type of keratin alone is unwise.

The separation of the keratinizing odontogenic cyst is clinically important because the reported recurrence rate of the keratinizing odontogenic cyst is only 2%. The peak incidence of keratinizing odontogenic cysts is in the third, fourth, and fifth decades, with about three fourths of them being in a dentigerous cyst relationship. Other locations are possible, in various relationships to the teeth. Most cysts are asymptomatic, though pain and swelling was reported respectively in 22% and 13% of cases.[98,99] The keratinizing odontogenic cyst is *not* associated with basal cell nevus syndrome (Gorlin-Goltz syndrome).

Figure 93-12. Radiograph associated with crown of impacted mandibular canine. Note that the tooth is the left canine, which has translocated across the arch.

Radiographic Features

The cyst presents as a well-defined unilocular radiolucency with the border generally being well corticated. If it is in a dentigerous cyst position, a cyst may be large (Fig. 93-12).

Microscopic Features

The epithelial lining will most often be thin with keratinization. However, the thickness will be somewhat variable. Keratin production varies and may only occur on a portion of the cyst wall. Orthokeratin is characteristic but *not* pathognomonic.[102] Most notable are the features that are not present. The features defining an OKC are absent.

Glandular Odontogenic Cyst (Sialo-odontogenic Cyst)

Clinical Features

Controversy encompasses this lesion and undoubtedly further delineation of features will evolve. The glandular odontogenic cyst is usually asymptomatic and involves the mandible more often than the maxilla.[29,103] Large cysts may be destructive and expansile.[104,105] The glandular odontogenic cyst involves adults and its pathogenesis is not yet understood.[106] This cyst may be either multilocular or unilocular. The cyst is generally well defined and often well corticated.

Radiographic Features

The lesion is radiolucent and may be unilocular, but it is more commonly multilocular. The radiographic margins are well defined and usually display a sclerotic rim.[107]

Microscopic Features

This cyst is lined by cuboidal epithelium of varying thickness, which may display cilia. Unfortunately, separating this particular microscopic feature from "normal" (and insignificant) mucus prosoplasia is sometimes difficult. The following features are more important in establishing the diagnosis. The cyst lining will be mucicarmine positive. The mucin detected by mucicarmine collects in small pools. Characteristically there are cuboidal cells near the surface, which give a slightly papillary appearance to the lumen.[103] The epithelium will also contain spheroid aggregates of cells.[108,109] The presence of mucous cells in other odontogenic cysts is *not* diagnostic for this lesion. This lesion, in this author's opinion, is "overcalled" and second opinion is often necessary. Standard "common odontogenic cysts" with mucus prosoplasia are often "upgraded" to glandular odontogenic cysts (Fig. 93-13). Glandular odontogenic cysts may be "upgraded" to central mucoepidermoid carcinoma. Great care to properly designate these lesions is necessary to ensure proper patient care.

Treatment

Recurrence after enucleation has been reported.[103] As in any multilocular lesion, nucleation and curettage of bone is recommended. Few cases are available to draw further treatment conclusions, but the overall prognosis is good.[30] Suggestions to treat this cyst aggressively appear to be misguided.

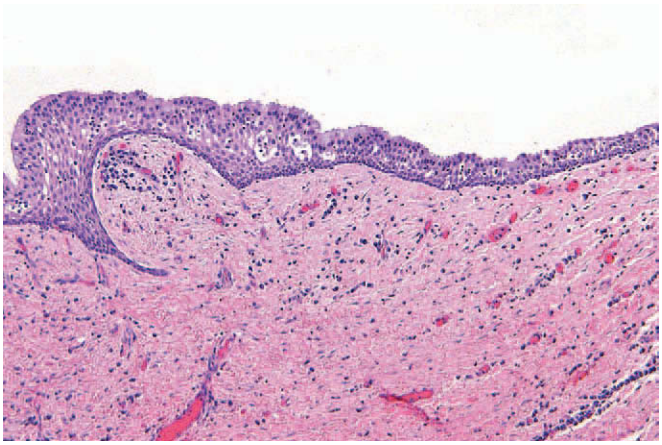

Figure 93-13. Photomicrograph showing mucus cells and spherical aggregate of glandular cells. **Note:** A single focus of such changes is not sufficient to make the diagnosis of glandular odontogenic cyst.

Odontogenic Keratocyst (Parakeratinizing Odontogenic Keratocyst, Keratocystic Odontogenic Tumor)

The OKC remains an enigma for the clinician and researcher, although knowledge gains in recent years have allowed for an improved understanding of this interesting lesion. The lesion was first described by Philipsen in 1956, but even 5 decades later the debate continues over the pathogenesis, behavior, treatment, and classification of this cystic neoplasm.[18-20] One major dilemma is whether to classify it as a cyst or a neoplasm. The current World Health Organization (WHO) nomenclature stresses the neoplastic nature and uses the term *keratocystic odontogenic tumor.*

Soft tissue extension, extension into adjacent bones, and expansion with associated bony destruction have been reported. These reports have prompted clinicians to question what the most appropriate method of treatment really is. Scharfferter and colleagues[110] documented increased mitotic activity within the epithelial lining of the OKC, which seems to support its neoplastic nature.

OKCs occur over a large age range. Lesions are often found during and slightly after odontogenesis of the permanent teeth. Peak incidence is in the second and third decades but may occur at any age. The mandible is more often involved than the maxilla, but treatment of maxillary lesions is often more problematic. OKCs are most common in the mandibular third molar area, but any area of the jaw may be involved. Patients are often symptomatic with swelling, pain, trismus, sensory deficits, and infection being the most common complaints. However, the lesion may also present as an incidental radiographic finding.

Of particular interest to the clinician is the biologic behavior of the OKC. Recurrence rates of up to 62.5% have been reported with enucleation alone. However, modern reports have a much lower recurrence rate when enucleation and careful curettage are performed. Most modern recurrence rates are less than 10%.[111,112] Reasons to explain the recurrence rate include daughter or satellite cyst formation[113]; incomplete removal of the epithelial lining, leaving satellite cysts left behind; collagenase activity of the cyst[114]; dental lamina rests left in the cyst wall or overlying mucosa; prostaglandin-induced bone resorption[115]; and increased mitotic activity. A handful of articles have demonstrated that the OKC can proliferate within muscle, and death from intracranial extension of mandibular OKCs has been reported by Jackson and colleagues.[84,116,117] Though these case reports should be remembered, the need to aggressively treat *all* OKCs should be resisted.

Radiographic Features

OKCs may be unilocular or multilocular, multiple, or single. OKCs with calcifications within a cyst wall have been reported, but calcification is rare and OKCs are considered radiolucent lesions. OKCs are highly variable in size (Fig. 93-14). They can appear pericoronally,

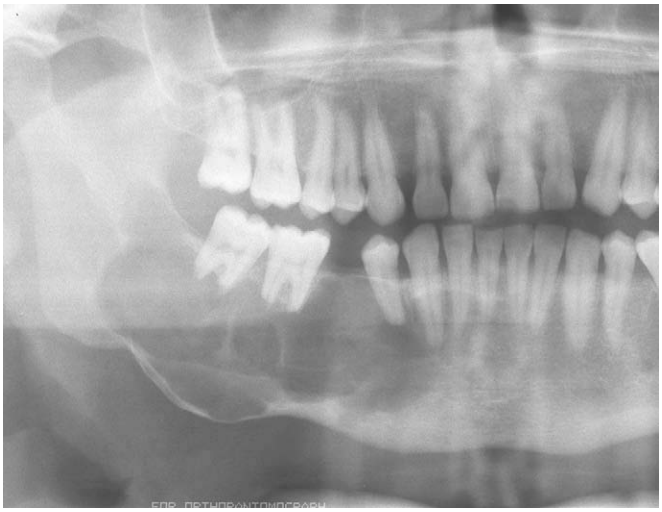

Figure 93-14. Radiograph of odontogenic keratocyst with bowing of inferior border and scalloping.

periradicularly, interradicularly, apically, and even peripherally. In summary, OKCs may occur in all areas of odontogenesis and they may extend significant distances.[97] The borders are well defined and often corticated.[98,118] Patients involved with Gorlin syndrome are more likely to present with metachronous or synchronous cysts. CT scans may be helpful in assessing large lesions and CTs are often essential in assessing maxillary lesions.[119-121]

Microscopic Features

The OKC has a specific microscopic appearance and the mere presence of a keratin lining or keratin within the cyst lumen is not sufficient to assure a diagnosis of OKC. The other features unique to the OKC must also be seen. The stratified squamous epithelium is generally 4 to 10 cells thick. The basal cell nuclei are particularly hyperchromatic, but even the parabasalar cells are more hyperchromatic than the spinous cells seen in other odontogenic cysts. The basal layer consists of cuboidal to columnar cells with a palisaded or "tombstone" appearance. Corrugated surface changes are often seen at the surface. Of perhaps least diagnostic help is the finding that OKCs are surfaced by parakeratinizing stratified squamous epithelium. Again, parakeratin is not pathognomonic for an OKC.

Treatment

A handful of reports with significant complications have led some clinicians to perform aggressive surgical procedures on *all* lesions. Debate persists about how to best manage OKC lesions in general. Treatment should center on decreasing the recurrence rate to a rate expected of the modern era and one that reduces patient morbidity. The reader is referred to other articles. After reading many treatises, the following is my opinion.[111,112,122-130]

Close radiographic follow-up is perhaps the most important modality to prevent complications secondary to recurrence. Recurrences, which often occur in the first 5 years, can take many years to present. Recently at this institution, my colleagues and I saw a recurrence 40 years after initial treatment, though the possibility of a new occurrence could not be eliminated. Establishing a diagnosis is important. Adequate material must be sent to be histologically diagnosed. Common problems are that the inner "layer" of keratin within the lumen is sampled and the diagnostic lining and wall are not submitted. Additionally, the diagnostic histologic features can be lost when inflammation is present.

If the patient has more than one cyst, the possibility of basal cell nevus syndrome is elevated. All cysts should still be examined histopathologically to confirm diagnosis. Clinical work-up to assess for syndrome is always prudent when multiple concurrent or sequential OKCs are diagnosed. Even when OKCs are in teenagers or younger patients are diagnosed with a single lesion, at least a cursory family history and gross clinical assessment for the syndrome should be performed. Some investigators have claimed good success with decompression and subsequent enucleation, while others advocate enucleation, excision of overlying mucosa, peripheral osteotomy, and chemical curettage.[125,129]

The use of Carnoy's solution is controversial. Carnoy first reported use of his fixative for the study of nematodes in 1887.[131] His goal was to fix the tissue and preserve nuclear detail for microscopic examination. However, fixation of the tissue intraoperatively for future microscopic exam is not really the effect that surgeons desire. Surgeons desire the chemical cauterization effect that the solution produces.

Regardless of the technique, the cyst lining must be entirely removed including satellite cysts and dental lamina rests. Thus careful enucleation is followed by some bone removal. Generally this is removal of daughter cysts and rests accomplished through curettage, peripheral ostectomy with rotary bur, or excision of one anatomic boundary such as periosteum (when bone penetration has occurred).

Recurrent OKCs may need to be treated more aggressively than primary lesions, but in syndrome patients "recurrences" should be considered new occurrences rather than recurrences. Large lesions may leave no other option than resection. However, one should consider decompression to shrink the lesion, followed by enucleation and curettage. In this manner a discontinuity defect or damage to vital structures is reduced or eliminated. If cortical perforation is encountered, frozen sections to assess margins may be necessary. Regardless, patients must be followed on a regular basis for many years following treatment of an OKC. As with most odontogenic lesions, surgery should be dictated by the destruction already caused by the lesion at hand, rather than simply on the histologic diagnosis.

Basal Cell Nevus Syndrome (Gorlin Syndrome, Gorlin-Goltz Syndrome, Nevoid Basal Cell Carcinoma Syndrome)

This complex syndrome is called by many names, and the nomenclature often depends on what portions of the syndrome (e.g., bifid ribs, OKC) are present. In the Gorlin and colleagues[132-134] description, no fewer than 37 anomalies have been associated with this syndrome. The reader is referred to the original sources.

OKCs are often the first diagnosis of the syndrome to present in childhood and often aid in establishing a diagnosis. This is especially true in cases in which there are new mutations with no prior familial history.[135] Up to 40% of cases may be new mutations, though genetic testing is advancing and there may be large variations in expression in this autosomal dominant disease.[134] One patient's first cyst occurred in the seventh decade. For this reason the syndrome should not be ruled out even in a middle-aged patient, and family history and phenotype may help in all age groups.

Treatment

The key to management of these patients is to at least phenotypically evaluate any patient that has an OKC for the syndrome. The assessment may be as simple as screening the patient for clinical evidence of any anomalies. In syndromic patients, "recurrences" should be presumed new occurrences rather than recurrences. Decompression is highly desirable in large lesions, and teeth should generally be saved rather than extracted if possible. Undoubtedly some teeth will need to be removed for access, but canines, incisors, and first molars should be heavily favored for retention. Each case is highly variable. As a medical advisor for this syndrome's support group I invite all providers to contact www.bccns.org for information.

Calcifying Odontogenic Cyst (Gorlin Cyst)

The calcifying odontogenic cyst (COC) is an unusual odontogenic lesion. As with the OKC, experts debate whether to classify the COC as a cyst or neoplasm. In this chapter the primarily cystic lesion with ghost cells is considered first, and the more solid epithelial odontogenic ghost cell tumor is considered later. The cyst was described by Gorlin and colleagues[136,137] in 1962. It is worthy of delineation because of its unusual clinical and histopathologic features. The COC occurs both

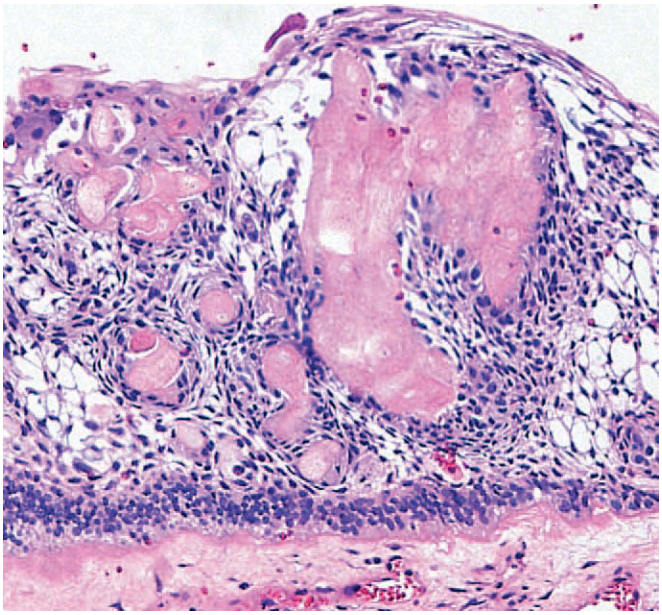

Figure 93-15. Photomicrograph showing ghost cells, odontogenic epithelium, and stellate reticulum-like areas.

within the bone and peripherally in the gingiva. COCs are often associated with odontomas or active products of odontogenesis.[138]

The separation of the cystic lesions from the solid lesions is appropriate. The solid/neoplastic version is considered briefly in the odontogenic tumor section under epithelial odontogenic ghost cell tumor.[139] The occurrence of the COC compared with the epithelial odontogenic ghost cell tumor may approach 40:1. Subclassification of the cysts is more of a histologic exercise than of prognostic or therapeutic importance. The reader is directed to articles by Praetorius and colleagues and Hong and colleagues for subclassification schemata.[140,141]

The origin of the COC is probably the early dental lamina. This may be best supported by the fact that craniopharyngiomas of the pituitary region often mimic the COC. COCs occur over a large age range. Though the mean age at occurrence is in the fourth decade, the peak incidence is in the second and third decades. Lesions in young adults are often associated with odontomas. The anterior portion of the jaws is more commonly involved than posterior regions, though any area can be involved. There is essentially equal distribution between females and males when all types are considered. There may be a slight maxillary predominance over the mandible.[139] Peripheral COCs will be centered in the attached gingiva.

Radiographic Features

The radiographic appearance is highly variable. As with the OKC, it may be either unilocular or multilocular, though unilocular lesions are more common. This is one of the odontogenic lesions that is classically considered to be mixed radiolucent radiopaque, though most lesions are purely radiolucent in the absence of an associated odontoma. If mineralization occurs in COCs without an odontoma, the radiopacities are often peripherally located. This appearance has been compared to "snowdrifting."[142]

Microscopic Features

Ghost cells are the classic cells seen in the COC. Ghost cells are *not* pathognomonic of COCs. In fact, ghost cells may be seen with other lesions such as odontomas, ameloblastic fibro-odontomas, and ameloblastomas. Of more significance is the presence of odontogenic epithelium with hyperchromic nuclei and somewhat of a palisaded basilar layer (Fig. 93-15). The thickness of the cyst wall is fairly thin and generally less than 10 cells thick. However, the thickness varies along the luminal wall and plexiform connections are often present, which creates a multicystic appearance in more complicated cysts.

Treatment

Treatment of the COC is simple enucleation of unilocular lesions. As in any multilocular lesion, enucleation with bony curettage is adequate therapy for the central lesions. The peripheral lesions require simple excision.[143] Recurrence is not expected, though radiographic follow-up is prudent.

Conclusion, Odontogenic Cysts

This chapter does not address every cyst that can affect the jaws. However, the intent by the author was to provide an overview of odontogenic cysts from the standpoint of behavior. Most cysts involving the jaws can be treated adequately with enucleation with or without curettage. In general multilocular cyst or cysts with scalloped borders need enucleation with bony curettage. Unilocular cysts can be simply enucleated. However, some cysts such as the OKC or certain variants of the calcifying odontogenic cyst, due to their neoplastic nature, may require additional surgical treatment, with enucleation and bony curettage advisable in all lesions. As stressed repeatedly, the treatment is often dictated more by the behavior (destruction the lesion has already caused) than by the histologic diagnosis.

Malignant Odontogenic Tumors and Malignancies Arising in Odontogenic Cysts or Tumors

Malignant transformation of odontogenic cysts is fortunately a rare occurrence but nonetheless occurs.[144-146] Many malignant transformations are considered to arise from residual cysts and occur in an edentulous area.[147,148] Transformation from an associated dentigerous cyst is seen in 25% of the reported cases.[146] Some OKCs have shown dysplastic features with few actually undergoing malignant transformation.[149,150] In summary, any cyst can undergo malignant transformation but such lesions are rare. Malignant lesions are likely to present with pain and swelling, but dysthesia is a foreboding symptom. Gardner reviewed the literature from 1889 to 1967 and found 25 acceptable examples of carcinoma arising from an odontogenic cyst.[151] A MEDLINE search for this chapter yields more than 100 additional examples.

Central mucoepidermoid carcinomas are thought to arise directly from prosoplastic cells of odontogenic cyst linings.[67,152-154] However, almost all types of salivary gland malignancy have been reported centrally in the jaw and the possibility of entrapped salivary tissue cannot be totally excluded. Bruner and Batsakis[153,155-157] reviewed a total of 66 reported cases of central mucoepidermoid carcinomas of the jaws, which indicates they may be more commonly reported than central squamous cell carcinoma malignancies.

Elzay[156] offered a classification for primary intraosseous carcinomas of the jaw in 1982. A scheme of classification is offered in Box 93-2 with modifications from that of Elzay to allow for salivary malignancies (especially mucoepidermoid carcinomas), origin from odontogenic tumors (other than ameloblastoma), and inclusion of sarcomas.

Verifying carcinomas arising de novo is difficult, but de novo cancers may be assumed if confined to intra-alveolar bone without a soft tissue component. Cysts appear to be a more common site of origin than odontogenic tumors. But nearly all odontogenic tumors have been reported to have malignant counterparts. The age at occurrence is in the sixth or seventh decade with some reports of a 2:1 male predominance, but full-ranging reviews are lacking.[157] And even if such reviews were available for all lesions seen in Box 93-2, their wildly variable characters would most likely be as appropriate as comparing apples with oranges.

Microscopic Features

All malignant lesions are based on histopathologic criteria.

Treatment

Significant treatment and prognostic differences exist between central squamous cell lesions and central mucoepidermoid lesions.[158] Treatment is based on size, histologic type, and histologic grade.

Box 93-2

Classification of Malignant Odontogenic Tumors with Other Selected Malignancies

Type I Arising ex odontogenic cyst
- a. Squamous cell carcinoma
- b. Mucoepidermoid carcinoma

Type II Odontogenic carcinomas
- a. Ameloblastoma derived
  - 1) Malignant ameloblastoma ("normal" ameloblastoma found as a metastatic lesion)
  - 2) Ameloblastic carcinoma (cytologically malignant)
- b. Clear cell odontogenic carcinoma
- c. Malignant epithelial odontogenic ghost cell tumor
- d. Malignant calcifying epithelial odontogenic tumor

Type III Arising de novo (presumed from odontogenic epithelium)
- a. Squamous cell carcinoma
  - 1) Nonkeratinizing
  - 2) Keratinizing
- b. Mucoepidermoid carcinoma
  - 1) Low-grade
  - 2) High-grade
- c. Most salivary gland malignancies have been reported centrally in the jaws

Type IV Sarcomas of possible odontogenic origin or with mesenchymal component
- a. Ameloblastic fibrosarcoma
- b. Fibrosarcoma
- c. Myoepithelial carcinoma

Box 93-3

Classification of Odontogenic Tumors

Epithelial odontogenic neoplasms
- Ameloblastoma
- Adenomatoid odontogenic tumor—Case 2
- Calcifying epithelial odontogenic tumor
- Squamous odontogenic tumor
- Keratocystic odontogenic tumor
- Epithelial odontogenic ghost cell tumor

Mixed epithelial and mesenchymal odontogenic neoplasms
- Ameloblastic fibroma
- Ameloblastic fibrosarcoma
- Ameloblastic fibro-odontoma
- Odontoma
  - Complex odontoma
  - Compound odontoma
- Odontoameloblastoma

Mesenchymal odontogenic neoplasms
- Odontogenic myxoma
- Cementoblastoma
- Ossifying fibroma

Odontogenic Tumors

The odontogenic tumors are a heterogeneous group of tumors that are generally separated in classification schemes by what components of odontogenesis are present within the tumor. Box 93-3 shows the classifications used in this chapter. When reviewing the treatment of these tumors, multiple considerations must be accounted for. When many articles are reviewed it becomes clear that there is a great desire for a "cookie cutter" type of recipe approach for every lesion based on diagnosis alone. Unfortunately, this just is not a realistic approach and in this author's opinion has resulted in gross overtreatment in a number of patients. As with the odontogenic cysts, the presence of scalloping and particularly multilocularity makes curettage following enucleation necessary. Although scalloping and multilocularity may be seen on planar films, intraoperatively the surgeon is in an ideal position to assess for these features in three dimensions. If scalloping or multiple locules are noted intraoperatively, curettage is appropriate at the time of biopsy to avoid having to reoperate.

The maxillofacial community has, in general, been a poor steward in defining criteria, measuring outcomes, reporting postoperative morbidities, and analyzing methods in relation to benign odontogenic tumors. This poor stewardship is true in both arches but is especially problematic when attempts are made in assigning therapeutic modalities indiscriminately to both the mandible and maxilla. In actuality the anatomic problems in each jaw differ dramatically and surgical differences abound.

In the mandible more emphasis needs to be paid to inferior and posterior cortical bone relationships to the tumor to potentially avoid discontinuity resections of these benign lesions. With the exception of ameloblastoma, there are only a handful of reports of mandibular benign odontogenic tumors "getting away" from the surgeon into soft tissues or nearby bones. Yet a cookie cutter approach is often applied. Ameloblastoma-like therapeutic models are applied to many benign odontogenic tumors. I am not aware of any studies on the morbidities associated with nonameloblastoma recurrences in the modern world of imaging. Likewise, despite studies associated with the jaw resections and obturators (generally in cancer therapy),[159-168] there are no studies on quality-of-life issues associated with benign odontogenic tumor therapy. Evidence to support recommended treatment margins is usually based on comparing recurrence rate with ameloblastomas, not the biologic behavior of the tumor. In addition, the 1-, 1.5-, and 2-cm margins recommended are often unclear. Regarding benign odontogenic lesions other than ameloblastomas, studies that have actually controlled for confirmed resection margins, pathologically and radiographically before and after surgery, are terribly lacking. For ameloblastomas Carlson and Marx[169] do a credible job in advocating resection. They also account for frozen sections, biologic barriers, and utilization of intraoperative radiographs (Fig. 93-16). However, they fail to recognize the simple fact that the actual goals are to ensure *and* confirm tumor removal, not to have a one-size-fits-all guideline. They also discuss confusion about solid and nonunicystic cystic ameloblastomas. More discussion of this problem is provided later. Gardner does an excellent job on the problems of doing retrospective analysis of the literature on ameloblastomas.[170]

In the maxilla, 1-cm bony margins are sometimes recommended in the proximal-distal direction. However, the anatomy of the sinuses, nasal cavity, orbit ethmoids, and pterygoid plates in many instances makes the use of anatomic boundaries more appropriate. In general, one or two anatomic boundaries are sufficient to ensure excision. In all lesions, even the ameloblastoma, the periosteum is thought to be an effective tumor barrier.[171] The interested lifetime/evidence-based learner is invited to perform a MEDLINE search of actual invasive benign odontogenic tumors. A 4-decade review by Leibovitch and colleagues[172] found only 11 reported cases of ameloblastomas with orbital involvement. A MEDLINE search for this chapter revealed about the same amount of reports (using search terms of ameloblastoma combined sequentially with "invasi," "extension," and "involve") revealed, in a cursory review of abstracts, approximately 25 to 40 cases/reports with the majority being from an original maxillary lesion. Without a doubt, soft tissue extension of recurrent ameloblastomas is a real problem, with Sampson and Pogrel documenting a high percentage of ameloblastomas involving soft tissues in a series of 26 cases.[173] But the ameloblastoma is a special case and is covered more thoroughly later. The following section discusses general principles concerning the other odontogenic tumors. With the exception of malignant variants, the reports of other odontogenic tumors extending, involving, or invading other adjacent structures are extremely rare.

Figure 93-16. Intraoperative radiograph. Note that the posterior margin is closer than the desired 1-cm margin. Such intraoperative radiographs help obviate the inability to perform frozen sections on bony tissue.

In assessing the benign odontogenic tumors, it is essential to critically read reports on how margin measurements were defined and how those margin measurements were confirmed both intraoperatively and postoperatively. I know of no adequately described prospective report. For example, I believe such measurements are in relation to the medullary bone and do not necessarily imply cortical bone. Surgically and restoratively, the loss of thin cortical bone on the buccal, lingual, and alveolar aspects is different from losing the inferior border of the mandibular body, the posterior border of the ascending ramus, or for that matter the condylar head or condylar neck. In all cases, it is this author's plea to always ask first, "Is there any realistic chance of this mandibular benign tumor getting away from me, if it recurs?" Second, ask, "Has the tumor already destroyed any of the critical structural elements of the mandible?" Third, ask, "Is there a reasonable chance of radiographic and patient follow-up?" I believe the first question will result in the surgeon realizing that loss of critical bony structures is unnecessary in most cases and the cookie cutter approach can be modified for the patient at hand. In the second question, if the lesion has not already destroyed critical structures, there are probable criteria *not* to iatrogenically destroy them. A huge caveat to this is that the lesion must be far enough away from these important structural elements to allow for a radiographically clear margin on the resected specimen. The clear margin will also then need to be confirmed histopathologically. If critical structures have already been destroyed by the lesion, the surgical decisions are straightforward. In the third question there are probably as many reasons or more to follow a person with history of tumor, a segmental resection, and a graft as compared with patients at risk of a recurrence alone. There are no reports of recurrence rates dropping to 0% after segmental resection. The surgeon is urged to review the literature with an eye to evidence-based data.

The maxillary lesions are more problematic due to the short distance needed to involve areas difficult to operate in and oblate the tumor. Such areas include but are not limited to the pterygoid plates, orbital floor, and pterygopalatine fissure. The head and neck surgeon realizes that in some areas any benign tumor is difficult to access and completely remove. Thus persistence of tumors in these areas is more a problem of location than of the inherent invasive potential of the tumor. Carlson and Marx[169] do a good job of discussing biologic barriers in their article.

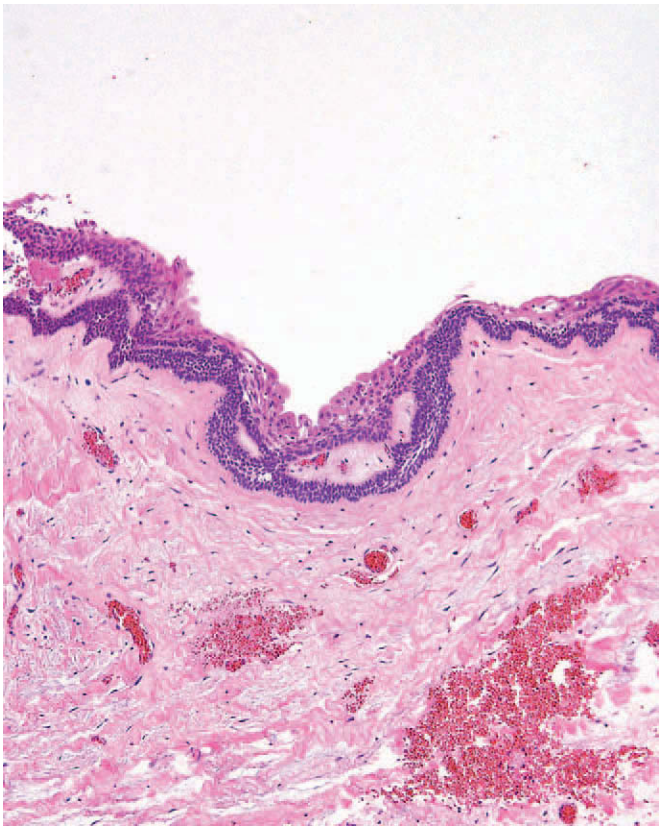

Figure 93-17. Photomicrograph of unicystic ameloblastoma with typical ameloblastomatous changes.

Unicystic Ameloblastoma

Unicystic ameloblastomas account for approximately 15% of all ameloblastomas. Unicystic ameloblastomas may be found in any odontogenic tissue–bearing area. Most unicystic ameloblastomas are found in the posterior mandible. Unicystic ameloblastomas most often occur in the second and third decades, a somewhat younger population than reported for the solid ameloblastoma. As with other odontogenic cysts and tumors, unicystic ameloblastomas are usually asymptomatic unless secondarily inflamed.[97]

Radiographic Features

Unicystic ameloblastomas present as radiolucent, unilocular lesions, with well-demarcated, corticated borders, indistinguishable from most odontogenic cysts or tumors. Many unicystic ameloblastomas appear to be dentigerous cysts both on radiographic and gross examination. However, they may be found in any location.

Microscopic Features

The microscopic features known as *Vickers and Gorlin criteria* define the unicystic ameloblastoma. These features are (1) columnar basilar cells, (2) palisading of basilar cells, (3) polarization of basilar layer nuclei away from the basement membrane, (4) hyperchromatism of basal cell nuclei in the epithelial lining, and (5) subnuclear vacuolization of the cytoplasm of the basal cells. Above the basal layer, loosely aggregated stellate cells resembling the stratum spinosum of a developing tooth are noted (Fig. 93-17).[174] It is important to realize that some portions of unicystic ameloblastomas may not show all these features. A variation of unicystic ameloblastoma described by Gardner allows for a plexiform variant. Inflammation may disrupt the diagnostic features of unicystic ameloblastoma.[175-177]

As in all odontogenic cysts and tumors of the jaws, the entire specimen needs to be embedded because the treatment depends on the presence or absence of ameloblastomatous epithelium in the fibrous wall.

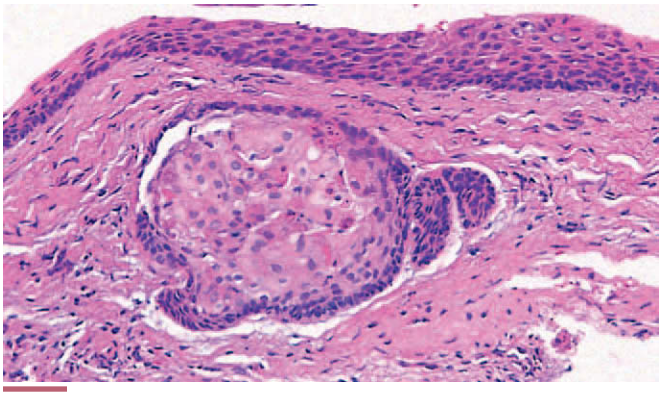

Figure 93-18. Area in a generally cystic ameloblastoma where the tumor has invaded the connective tissue wall. This portends an increased risk of incomplete removal and thus recurrence.

Definitions, Clarifications, and Treatment Recommendations

A unicystic ameloblastoma must be unilocular, as well as unicystic, and display the pathologic features of an ameloblastoma lining the lumen but not invade the connective tissue (Fig. 93-18). From the beginning, criteria have varied and caused confusion, but this definition applies in the following discussion.

The unicystic ameloblastoma was separated from the "standard" ameloblastoma by Robinson and Martinez in 1977.[178] The subtitle of that seminal paper was "a prognostically distinct entity." Since that time the application of their original definition has been problematic, with others often further muddying the picture. A number of authors have attempted to provide evidence of predicted behavior for different types of unicystic ameloblastomas.[178-183]

The first premise in this chapter's coverage of the unicystic ameloblastoma is that the only reason to separate the unicystic ameloblastoma is for therapeutic planning and expected clinical behavior. Ever since the original paper, it has been regrettable that multilocularity and connective tissue invasion were sometimes allowed within the diagnostic criteria. Ackermann and colleagues[183] have analyzed unicystic ameloblastomas with connective tissue invasion as "type 3." They found that they often recur if only enucleation is performed as therapy. For this reason, though, they should be more thoroughly studied and managed like a standard ameloblastoma. And thus separation as a "unicystic" ameloblastoma is spurious at best. Likewise, Philipsen and Reichart[182] found that multicystic or multilocular cystic ameloblastomas recurred with simple enucleation. Again, this should make it clear that they should not be grouped under the designation of unicystic ameloblastoma. These features are seen in "regular" ameloblastomas, and determining where to draw the line of what is too much multilocularity or too much connective tissue proliferations is totally subjective and unwise unless future studies define a method to separate lesions. Until such studies, unicystic ameloblastomas should be considered as such only if they are unicystic and unilocular and display no connective tissue invasion.

Some additional background information may also be helpful. Eversole and colleagues[184] found recurrences more common (actually all four recurrences) in lesions larger than 2 cm. Unfortunately they did not stratify their data to state whether these larger lesions were multilocular or how the connective tissue wall was invaded.[184] But this report implies that large or expansile lesions may recur even if the ameloblastoma is cystic. Likewise, a review of the original paper by Vickers and Gorlin,[174] which defined the features of ameloblastomas, reveals that all their cases were recurrences of what today would have been diagnosed as unicystic ameloblastomas.

Unicystic does not mean unilocular. Some authors allow for a multilocular radiographic appearance.[185] These authors often use terms such as *cystic* or *cystogenic* instead of unicystic. Regardless, the intent is to attempt to group these lesions with the unicystic ameloblastoma. Some purport that histologically the multilocular lesion was unicystic (how they confirm three dimensionally how a single cyst can make multiple locules and remain unicystic has never been adequately explained in my opinion). However, in my review of the literature, multilocularity increases the chance of recurrence and multilocular lesions should be at least enucleated and curetted rather than just enucleated. In my institution, multilocular and multicystic lesions would be signed out simply as ameloblastoma and presumed to be treated as such. Unilocular lesions may be histologically multicystic. Multicystic lesions are *not* unicystic lesions, so they should be considered standard ameloblastomas and treated as such.

In their review of 193 "unicystic" ameloblastomas, Philipsen and Reichert[182] found wide variations in definitions, nomenclature, and what lesions were included under the heading "unicystic" ameloblastoma. Simply put, the literature is horrible. Even separation of terms such as luminal, intraluminal, and mural varies among authors.

As proposed originally by Robinson and Martinez,[178] the reason for the diagnosis of "unicystic ameloblastoma" was to separate "a prognostically distinct entity." Even in their report, Robinson and Martinez had a recurrence rate of about 20%. But they allowed for connective tissue nests, multilocularity, and large cysts. Two of their three lesions described as "large dentigerous cysts" recurred. Eversole and colleagues[184] later used 2 cm as a cutoff for size because they found that larger "cystogenic" ameloblastomas had a propensity to recur with simple enucleation. Robinson and Martinez[178] did not separate lesions by connective tissue involvement. But authors including Philipsen, Reichart, and Ackerman and colleagues (in various publications) have shown that connective tissue involvement is an important predictor of recurrence with simple enucleation. They designate these as what they call type 3 unicystic ameloblastomas and state that they tend to recur (i.e., behave like "standard" ameloblastomas if only enucleation is performed). Current wisdom is that the 20% recurrence rate of Robinson and Martinez may have been due to large size or connective tissue proliferations.

Needless to say, inconsistencies have led to confusion. A goal of this chapter is to emphasize that the reason for the unicystic designation is to use the minimal amount of surgical intervention while minimizing the chance of recurrence. The literature is fairly clear that a subset of unicystic ameloblastomas can be managed with enucleation alone (or perhaps combined with minimal bony curettage). In this analysis the subset is the definition of unicystic ameloblastoma used.

Simple Unicystic Ameloblastoma

A unicystic ameloblastoma (referred to here as a "simple unicystic ameloblastoma") requiring enucleation *only* must have the following characteristics:

1. Histologic features conform to criteria established by Vickers and Gorlin for the diagnosis of an ameloblastoma.

2. Radiographic evidence of a singular unilocular radiolucency exists. Definitive septation requires exclusion, so evidence of peripheral scalloping (except between tooth roots) may eliminate the possibility of a lesion being considered unilocular.

3. Intraoperative confirmation of unilocularity, *any* multilocular/multicystic characteristic, and cortical perforation or soft tissue involvement preclude interpretation of the lesion as unicystic.

4. Histologic features display only luminal or intraluminal involvement. Proliferation of the ameloblastoma into the fibrous connective tissue wall, whether plexiform or follicular, precludes diagnosis of the lesion as unicystic.

5. Size of the lesion must be less than 2 cm.

I can only hope that further studies continue to define and separate the unicystic ameloblastomas, as well as delineate the line of when to designate a lesion as simply an ameloblastoma. Experience is available to justify the separation, and hopefully the science will follow.

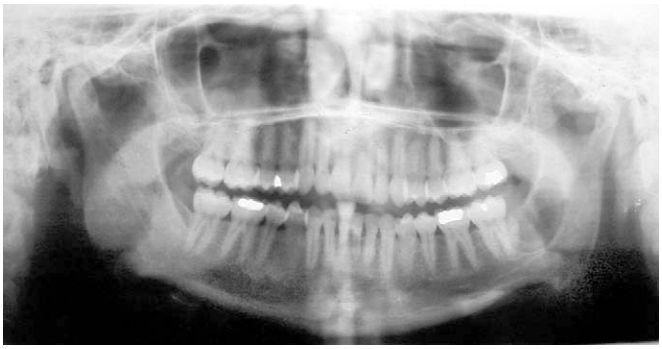

Figure 93-19. Pantomograph with ameloblastoma in area where a third molar was extracted several years previously.

Ameloblastoma, Intraosseous Type*

Definition

The ameloblastoma is a neoplasm of the enamel organ that recapitulates the cells necessary for tooth crown development. Intraosseous ameloblastomas arise from the lining of an odontogenic cyst, reduced enamel epithelium, or odontogenic rests. In the soft tissues of the oral cavity, specifically the gingiva or alveolar mucosa, they may arise from the basal cell layer. Those that arise from the overlying soft tissue are called *peripheral ameloblastomas* and are covered separately. In this chapter the three clinical types of ameloblastoma are unicystic ameloblastoma, peripheral ameloblastoma, and ameloblastoma. Here the modifiers of multicystic or solid are not used. They are not separated here because they are treated the same. Of these three, unicystic and peripheral have a much better clinical outcome after a conservative removal and assured margins. For clarification, I use the term *intraosseous ameloblastoma* to clarify that the lesion discussed is *not* peripheral.

Intraosseous ameloblastomas occur in the mandible and maxilla with the mandible accounting for about 80% of all cases. In the maxillae, ameloblastomas may evolve in the maxillary sinonasal region, as well as during the alveolar process. The location of the tumor is an important factor in the long-term prognosis. Tumors that are in the anterior maxilla or body of the mandible or are confined to the mandible are less likely to cause significant problems. Conversely, those penetrating the mandible in the posterior ramus region and those of the posterior maxilla can extend into areas difficult to manage.[186]

Radiographic Findings

Small ameloblastomas appear as a unilocular radiolucency with well-demarcated and at least partially corticated borders. These radiolucent lesions are indistinguishable from other cysts or benign tumors of the jaws (Fig. 93-19). Larger lesions may be easier to recognize radiographically. The classic description of larger lesions is a "soap bubble" or honeycomb appearance. Roots of adjacent teeth may show resorption in long-standing lesions. An ameloblastoma commonly displaces unerupted or erupted teeth. These radiographic features describe all histologic variants except for some desmoplastic ameloblastomas. In desmoplastic ameloblastomas of sufficient duration, a mixed radiolucent radiopaque lesion rather than a pure radiolucency may be seen. Additionally, the desmoplastic ameloblastoma is more common in the maxilla and anterior portion of the jaws.[97]

Microscopic Features

Multiple microscopic subtypes of ameloblastoma exist. Although they are of importance to the pathologist, these histologic subtypes are not of therapeutic or prognostic importance. But in summary, histologic subtypes include follicular, plexiform, granular cell, acanthomatous, desmoplastic, basal cell, and keratinizing. The classic features of ameloblastoma were described by Vickers and Gorlin.[174] These features are columnar basilar cells, palisading of basilar cells, polarization of basilar layer nuclei away from the basement membrane, hyperchromatism of basal cell nuclei in the epithelial lining, and subnuclear vacuolization of the cytoplasm of the basal cells. Above the basal layer, loosely aggregated stellate cells resemble the stratum spinosum of a developing tooth (Fig. 93-20).

*Includes solid types and all ameloblastomas that, although being cystic, do not conform to criteria within the unicystic ameloblastoma section.

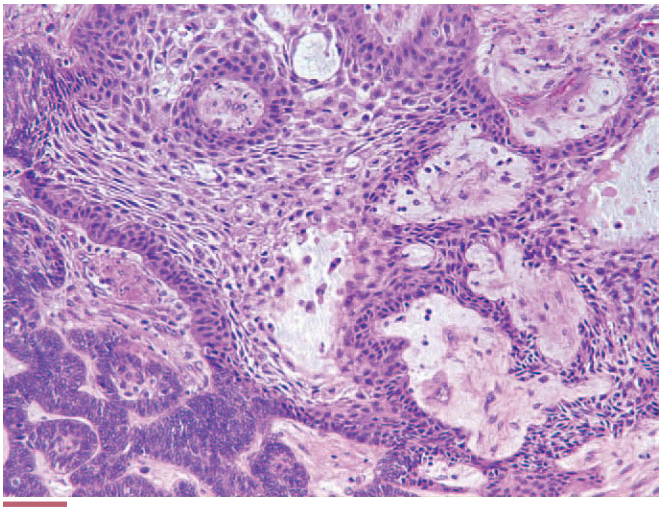

Figure 93-20. Photomicrograph of plexiform ameloblastoma with typical Vickers and Gorlin features. Stellate reticulum is also somewhat acanthomatous.

Natural History and Treatment

Gardner pointed out two main factors that explain the behavior of ameloblastomas: (1) their ability to infiltrate medullary bone and a relative inability to infiltrate compact bone; (2) the location of the tumor. As noted earlier, tumors near vital structures such as the orbit or cranial base are much more difficult to control and pose greater clinical problems. Free margins of excision are difficult to obtain in ameloblastomas arising in the posterior maxilla. Dense compact bone such as that of the inferior border of the mandible or ramus acts as the first-line barrier.[187] The outer periosteum appears to serve as a backup barrier to prevent tumor spread, but once it is broken, access to vital structures may occur.[171] In the maxilla, only a thin cortical plate exists between contiguous bones and is generally thought of as a poor barrier to prevent the spread of ameloblastomas.[169] Tumors of the posterior maxilla involving the orbit are the most difficult to treat and manage. Undoubtedly such lesions will present with unique and specific problems related to the individual case.[188]

Simple enucleation of ameloblastomas is not considered standard care in the United States. Even when it is combined with curettage, ameloblastomas are known to recur. Yet successful results with enucleation and curettage have been reported.[189,190] The recurrence rate is thought to be due to the fact that ameloblastoma infiltrates the trabeculae of cancellous bone. The reported success with curettage (or peripheral ostectomy with rotary bur) is probably due to relatively efficient/aggressive medullary bone removal. It is generally considered a fact that tumor infiltration frequently extends beyond the apparent radiographic margin. Ensuring even amounts of bone removal with enucleation and curettage can be difficult. Small bits of tumor may remain within the bone without the ability to assess margins grossly or histologically. It is thought that resection with adequate margin is the most predictable method to assure that the tumor will not recur. A resected specimen allows for intraoperative radiographic assessment of adequate margins and postoperative histologic confirmation of margins.

Histologically simply clear margins are acceptable. How pathologists deal with resected bone specimens in the pathology laboratory is inconsistent. The surgeon should explicitly request that the *entire* bony specimen be demineralized and margins fully assessed. The surgeon should mark surfaces that are not margins such as the vestibule, gingiva, alveolar mucosa, and sinus mucosa. As a pathologist, I know how much

work such requests entail. Although I dread these specimens coming into the laboratory, I believe this is the only way to assess therapy and plan for future reconstruction.

What an adequate radiographic margin should be is more controversial and probably varies by case. Even after en bloc resections, reportedly well past radiographic evidence of tumor, recurrence rates of 10% to 15% have been reported. Although some surgeons advocate larger margins, the general consensus is that resection should be 1 cm past the radiographic limits of the tumor. Unfortunately, there are no well-controlled studies of radiographs of the resected specimen compared with postsurgical defects to actually confirm what margins were achieved. Likewise, although there are anecdotal reports, there are no controlled studies of resected specimens correlated with radiographs to assess how far the tumor actually extended histologically past that radiographic evidence. Carlson and Marx have made initial attempts to accumulate such data, but a well-documented study has not yet been performed.[169] Due to the lack of reliable data, the following discussion is yet another anecdotal opinion on how to manage ameloblastomas.

Management of Mandibular Ameloblastomas

One-centimeter medullary bone margins, referring to the proximal and distal directions, are preferred. Lingual and buccal cortical bone is sacrificed, but 1-cm margins do *not* imply inclusion of soft tissue outside the periosteum. In the mandibular body and in the anterior ramus overlying mucoperiosteum, teeth, gingiva, and mucosa are submitted with the resected specimen. In essence, portions of the bone resection specimen without muscle attachments will have overlying mucosal soft tissue included in the specimen. In the depth of the lingual and buccal vestibules, as well as the ascending ramus where muscle attachments begin, the periosteum will remain with the resection specimen. These periosteal surfaces will represent the surgical margins of the specimen. If the coronoid process is more than minimally undermined, it is also sacrificed (following detachment from the temporalis muscle) and included or separate from the main resection specimen. If extension is suspected past any periosteal surface, frozen tissue margin protocols should be applied and specimens should be handled separately.

Management of Maxillary Ameloblastomas

Assessing bone margins in maxillary bone resection specimens is even more important. Some authors recommend 1- to 2-cm margins in the maxillae. The larger end of the range is probably unnecessary in the anterior region and difficult to obtain when lesions approach the orbit or pterygoids, or both. Again, such margin recommendations pertain to attempted bony margins and not to soft tissues. Soft tissue margins must be assessed by frozen section or on properly oriented permanent sections. Treatment of maxillary lesions varies greatly and depends on both CT and MRI interpretation. Follow-up of maxillary lesions is extremely important and it is assumed that attempts to spare vision and vital structures of the region may alter initial treatment plans. Excision to extend two biologic barriers past the tumor serves as a rule of thumb. The en bloc specimen should be examined intraoperatively from multiple radiographic views. Final margin assessment occurs after demineralization. Though not often recommended, radiotherapy may occasionally play a role in unresectable tumors.[191] Similar to the mandibular tumors, the periosteum above the level of muscle attachment is the surgical margin. Overlying mucoperiosteum, teeth, gingiva, and mucosa are submitted with the resected specimen.

Summary

In summary, the ameloblastoma is the most aggressive of the benign odontogenic tumors. Numerous reports on treatment are available, but well-controlled prospective studies are necessary to answer many questions.[126,173,187,189,192-208]

Peripheral Ameloblastoma (Extraosseous Ameloblastoma)

Peripheral ameloblastomas present as mucosal masses and arise from the gingiva or alveolar mucosa. The actual proliferation may come from dental lamina rests or basal cells of the overlying mucosa. Histopathologically the lesions appear as any of the previously mentioned variants, though the basal cell variant is the classic subtype. By definition these tumors do not infiltrate the underlying bone. If there is an intraosseous component, the lesion is *not* a peripheral ameloblastoma. If there is bone involvement, the lesion is treated as an intraosseous ameloblastoma. Peripheral ameloblastoma may become quite large. Lesions may be imaged with MRI or CT. Treatment is to assure excision with histopathologically confirmed margins.[209-218]

Malignant Ameloblastoma

Malignant ameloblastomas are lesions that have any of the classic benign histopathologic features of ameloblastoma but metastasize to a distant location. In many cases the metastases are long delayed and may occur years after the initial tumor was treated. The lung is the most common site for metastases. Cervical lymph node involvement has also been reported. Treatment varies by degree and site of involvement. Though excision is preferred, radiotherapy may be the only practical option.[219-224]

Ameloblastic Carcinoma

Ameloblastic carcinoma, in contrast to malignant ameloblastoma, shows cytopathologic features associated with malignancy (e.g., increased mitotic activity, increased nuclear and cytoplasmic ratio, nuclear pleomorphism, hyperchromatism). The cytopathologic/histopathologic features allow for this being diagnosed in the primary location. The tumor may or may not metastasize, but like the primary tumor the cytopathologic features display the anaplastic features of malignancy. These are rare lesions.[225-234]

Ameloblastic Fibroma

The ameloblastic fibroma is a benign odontogenic neoplasm characterized by proliferation of immature mesenchymal and ameloblastic cells, both of which are characteristic of a developing tooth. Unlike the ameloblastic fibro-odontoma or the odontoma (complex and compound), the ameloblastic fibroma does not have the capacity of producing enamel, dentin, or cementum. The tumor can be found in any tooth-bearing site. However, the tumor is most often seen in the premolar-molar region of the posterior mandible. There is no gender predilection, but the lesion is usually identified in a bimodal age distribution. The majority of lesions are diagnosed before age 20, though another smaller group of lesions is seen in middle age. As with other odontogenic neoplasms, the lesion is slow growing and asymptomatic unless secondarily inflamed. A firm expansion of the buccal cortical plate of the mandible or maxilla is the most common clinical finding. The lesions are most often small and unilocular. It is thought that an early version of odontoma necessarily goes through a stage that is histopathologically indistinguishable from an ameloblastic fibroma. Separating these early odontomas from a "real" ameloblastic fibroma is impossible. However, there are reports of large and destructive ameloblastic fibromas that clearly require the ameloblastic fibroma to be classified as a neoplasm rather than a hamartoma. The tumors that become large and destructive are perhaps more likely to be seen in older patients.[235-239]

Radiographic Features

The ameloblastic fibroma usually presents as a well-defined radiolucency. The border is often corticated though sclerotic changes may also be seen. Small lesions are usually unilocular, whereas larger, more aggressive tumors are usually multilocular. The majority of lesions are seen in association with the crown of an unerupted tooth.

Microscopic Findings

The histopathologic features of an ameloblastic fibroma are characterized by the proliferation of both epithelial and mesenchymal elements. The mesenchymal component presents as a relatively cellular-young, basophilic, fibromyxoid tissue suggestive of a developing tooth pulp or dental papillae. The fibroblastic cells vary from stellate to spindled. Admixed within the mesenchymal background are islands, cords, or nests of odontogenic epithelium. The outer epithelial cells near the basement membrane become cuboidal and occasionally columnar, at

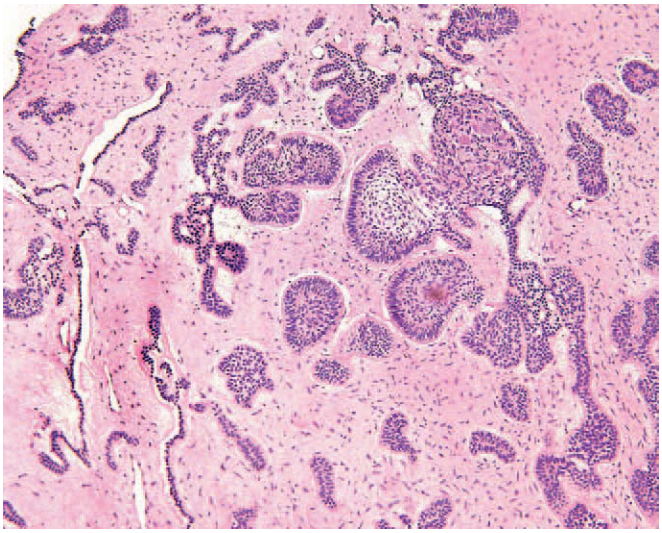

Figure 93-21. Photomicrograph of follicles that are essentially identical to an ameloblastoma, but the background stroma is consistent with dental papilla. Eosinophilic induction effect is seen around a few epithelial islands.

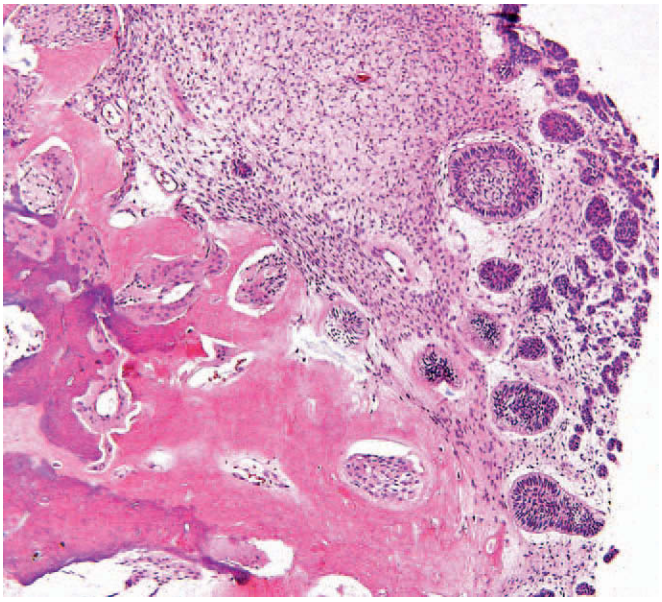

Figure 93-22. Photomicrograph in which an area identical to an ameloblastic fibroma dominates the right side of the image, but mineralized products dominate the left side and confirm the diagnosis as an ameloblastic fibro-odontoma.

least focally. These islands are essentially identical to islands seen in follicular ameloblastomas. By definition, ameloblastic fibromas will have no areas of mineralization. If mineralization is seen, the lesion is actually an ameloblastic fibro-odontoma (Fig. 93-21).[97]

Treatment

Conservative surgical enucleation of the tumor is the treatment of choice for all small, unilocular lesions. The tumor does not have the infiltrative margins characteristic of an ameloblastoma and therefore recurrence rates are low. With early detection and removal, the long-term prognosis is favorable. However, larger multilocular lesions may be destructive and reports of recurrence up to 40% were reported in a 1972 article from a series of cases at the Armed Forces Institute of Pathology.[239] Segmental resection is not indicated in any tumor except those that have essentially already destroyed the integrity of the jaw involved.

Ameloblastic Fibro-odontoma

The ameloblastic fibro-odontoma is a rare odontogenic tumor. The lesion has had some controversy in the literature in regard to its appropriate classification. Similar to the ameloblastic fibroma, it is thought that a maturing odontoma necessarily goes through a stage that is histopathologically indistinguishable from an ameloblastic fibro-odontoma. However, reports of large and destructive ameloblastic fibro-odontomas clearly confirm its ability to act as a neoplasm rather than a hamartoma. The majority of patients with ameloblastic fibro-odontoma are young, with a mean age of 10 years. Whether these data are skewed from improper inclusion of maturing odontomas is difficult to assess. Undiscovered tumors can cause significant cortical plate expansion. Most are discovered during other radiographic studies or when a tooth has failed to erupt. Occasionally the tumor can persist or recur. It is probably most prudent to assess the individual tumor and patient in its context. If the tumor is large and destructive, it is more likely to be acting neoplastically. Multilocular tumors should be assumed to be neoplastic.[97,240,241]

Radiographic Findings

The tumor is a well-circumscribed, unilocular or multilocular lesion.[242] Though evidence of mineralization must be present histopathologically to make the diagnosis, the mineralizations will not always be evident radiographically. Therefore early lesions may be radiolucent. The amount of mineralization varies widely.

Microscopic Findings

The histopathologic features of an ameloblastic fibro-odontoma are characterized by the proliferation of both epithelial and mesenchymal elements. The mesenchymal component presents as a relatively cellular-young, basophilic, fibromyxoid tissue suggestive of a developing tooth pulp or dental papillae. Admixed in the fibromyxoid tissue are mineralized and premineralized elements including enamel, enamel matrix, dentinoid, dentin, cementoid, and cementum. Admixed within the mesenchymal background are islands, cords, or nests of odontogenic epithelium. These scattered epithelial components are identical to those seen in the ameloblastic fibroma (Fig. 93-22).[243-246]

Treatment

Small ameloblastic fibro-odontomas are generally treated with simple enucleation. Multilocular lesions should be additionally treated with curettage/peripheral ostectomy with a rotary instrument. Unerupted teeth associated with the tumor may be retained. Depending on the amount of displacement and root development, they may or may not need orthodontic intervention to ensure eruption. Very large, inherently destructive lesions require complete but conservative surgical removal. Recurrences have been reported but are extremely rare. Segmental resection is not indicated in any tumors except those that have essentially already destroyed the integrity of the jaw involved.[247,248]

Epithelial Odontogenic Ghost Cell Tumor (Dentinogenic Ghost Cell Tumor, Odontogenic Ghost Cell Tumor)

In conjunction with this brief section, please refer to the earlier discussion on the calcifying odontogenic cyst. The epithelial odontogenic ghost cell tumor is an unusual jaw lesion that consists of a complex (at least focally), solid, tumor-like mass, though a cystic area is usually present as well. As with other odontogenic neoplasms and cysts, the lesion can occur in any tooth-bearing site. Most reports indicate that the lesion occurs most often in the posterior mandible. Most lesions arise centrally within bone; however, lesions may be identified as arising peripherally within the gingiva. Extensive data on these tumors is scarce but is assumed to have a similar age distribution as the calcifying odontogenic cyst. Terms such as *malignant* and *aggressive* have been appended to this diagnosis. Personally the malignant appendage should only be

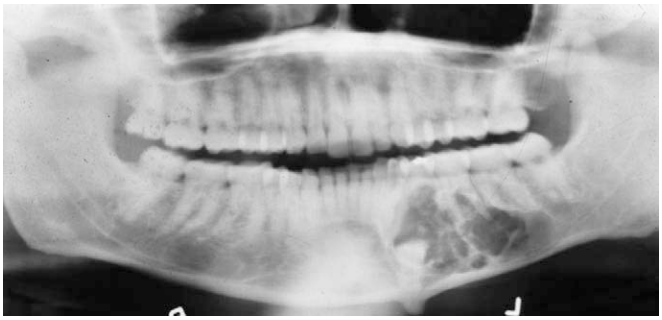

Figure 93-23. Radiograph of a large calcifying epithelial odontogenic tumor displacing a premolar and having a mixed radiographic appearance.

Figure 93-24. Gross specimen showing the gelatinous nature of an odontogenic myxoma.

used in cases where cytomorphologic characteristics of malignancy are noted. "Aggressive" lesions are identified by inherent destructive behavior or recurrence. Central bony lesions usually present as a firm, expansile mass of the buccal cortical plate. The lesions are asymptomatic unless secondarily inflamed. Gingival lesions appear as a firm, smooth, sessile, soft tissue enlargement involving the attached gingiva or edentulous alveolar ridge. These peripheral masses may present on either the buccal or lingual aspect.[139,140,249-261]

Review of the International Collaborative Study on Ghost Cell Tumours is a must-read when one of these lesions is encountered.[139] A pathologist well versed with all forms of this tumor should be consulted for proper classification.

Calcifying Epithelial Odontogenic Tumor (Pindborg Tumor)

The calcifying epithelial odontogenic tumor is an unusual odontogenic neoplasm characterized by sheets of hyperchromatic, pleomorphic cells with foci of amyloid and mineralization. Calcifying epithelial odontogenic tumors occur more often in the mandible than the maxilla with a ratio of about 2:1. Within the arch, they are often located in the molar-premolar region. As with other odontogenic tumors, they may or may not be associated with unerupted tooth crowns. Those seen in the second decade are often associated with an unerupted tooth. The tumors are rare but have been reported more often in males. The tumor most often occurs in the third through fifth decades.[97] This tumor is rarely seen peripherally as a gingival mass or alveolar ridge mass.[262,263]

Radiographic Findings

The tumor is usually well circumscribed with a multilocular appearance being more common than a unilocular lesion. Though evidence of mineralization is often present histopathologically, radiographically the mineralizations will sometimes not be evident. However, this is one of the classic mixed radiolucent-radiopaque lesions of the jaws. The amount of mineralization varies widely with some lesions having minimal evidence of radiopacity (Fig. 93-23). The peripheral lesions may produce a cupping effect of the underlying bone. In these instances the cupping is thought to be secondary to pressure resorption.

Microscopic Findings

The tumor is characterized by islands and sheets of epithelial cells dispersed throughout a nonspecific fibrous stroma. In many instances the polygonal, epithelial cells show remarkable pleomorphism and nuclear hyperchromasia. Borders of the epithelial cells are well defined and prominent intracellular bridges are characteristic. The cytoplasm is often strikingly eosinophilic, but tumors may display a prominent clear cell component.[264,265] Foci of homogeneous eosinophilic amyloid may be present.

Treatment

Conservative surgical excision is the treatment of choice for the extraosseous variant. Small unilocular and multilocular lesions are generally treated with simple enucleation and curettage. Very large or inherently destructive lesions require complete but conservative surgical removal. Recurrences have been reported. Segmental resection is not indicated in any tumors except those that have essentially already destroyed the integrity of the jaw involved.

Tumors with clear cell changes may be more clinically aggressive than standard tumors. Tumors with cytopathologically malignant features should be considered separately.[266]

Odontogenic Myxoma

The odontogenic myxoma is a relatively uncommon, benign neoplasm apparently arising from the mesenchymal portion of the tooth-forming unit known as the *dental papillae/dental sac.* Odontogenic myxomas have been identified most often in the posterior tooth-bearing areas of the dental arches and present in both upper and lower jaws. The mandible is more commonly involved than the maxilla. Most tumors are identified during the second or third decades of life. No gender predilection has been identified. As with other odontogenic neoplasms, clinical findings usually consist of a smooth, bony, hard expansion of the alveolus. The primary process of the odontogenic myxoma is to infiltrate through medullary spaces. Intraoperatively the myxoma is seen as gelatinous material (Fig. 93-24). Judging where the gelatinous material ends intraoperatively and especially radiographically may be difficult. In some instances odontogenic myxomas do penetrate the cortex. They have also been reported as forming outside the body of the mandible, in which case they would present as a smooth-surfaced gingival enlargement.[97,267-271]

Radiographic Findings

As with many other odontogenic neoplasms, an odontogenic myxoma may present as either a unilocular or multilocular radiolucency. Most lesions show radiolucency with variable cortication. When the cortical bone is penetrated, a periosteal reaction may result in apparent osseous production. Residual or reactive bone may also be seen intraosseously[272] and give a somewhat mixed radiopaque/radiolucent appearance. Cone beam CT may be helpful.[273] When residual bone is somewhat organized, the appearance has been described as similar to either a honeycomb or tennis strings.[274]

Microscopic Findings

Odontogenic myxomas are characterized by a relatively acellular myxoid tissue. Occasional strands and cords of odontogenic epithelium may be noted, but these rests are not seen in all neoplasms. Tumors may be somewhat collagenous/fibromatous, but the myxomatous features should dominate the histopathologic picture.

Treatment and Prognosis

Due to the loose, gelatinous nature of the tumor, surgical enucleation can be difficult to judge. However, the odontogenic myxoma is another lesion where the tumor has not been reported to "get away" from the surgeon on recurrence. The goal of treatment should center on removal of medullary bone well past the radiographic borders. Recommenda-

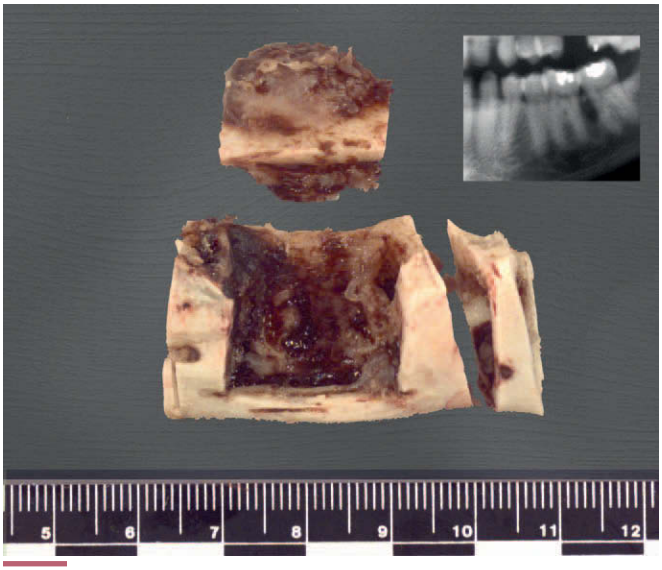

Figure 93-25. Although originally apparently small, intraoperatively gelatinous material was at resected margins, which necessitated successive removal of additional bone. Gelatinous material is not well seen on these fixed specimens.

tions of how much medullary bone to remove vary,[271,275] but 0.5 to 1 cm of medullary bone removal appears to be prudent. Removal of cortical bone in areas of penetration is also recommended. Recurrence rates can vary significantly from case to case and often show a direct correlation with the size of the lesion at initial diagnosis. Large and clinically aggressive tumors may necessitate segmental resection. In such cases the surgery is derived not from the diagnosis but by the nature of the lesion at hand. Intraoperative radiographs as described in treatment of ameloblastomas are also appropriate. Confirmation of margins histopathologically is also essential before reconstruction. Grossly the gelatinous material may also be easily seen at resected margins intraoperatively (Fig. 93-25).

Adenomatoid Odontogenic Tumor

The adenomatoid odontogenic tumor is a relatively infrequent odontogenic tumor that has vague histologic similarities to ameloblastoma. Unfortunately the histologic similarity led to past nomenclature as adenoameloblastoma or ameloblastic adenomatoid tumor. The vague microscopic similarity is this tumor's only similarity with that more aggressive tumor. Clinically the adenomatoid odontogenic tumor is by far the most innocuous odontogenic tumor, at least if the odontoma is considered a hamartoma. It appears that the tumor derives from the enamel organ epithelium but may arise from dental lamina rests. Though the actual ratio varies slightly by report, the adenomatoid odontogenic tumor is often known as the *two-thirds tumor* because it occurs two thirds of the time in females and two thirds of the time in the maxilla. Two thirds of the time this tumor is associated with impacted teeth (especially the canine), and two thirds of these tumors are found in teenagers. It is unusual in patients older than 30 years of age. Occasionally an adenomatoid odontogenic tumor arises peripherally within the gingiva. It is most often discovered radiographically when exploring the reason that a canine has not erupted long after its contralateral partner.[97,276-279]

Radiographic Features

The adenomatoid odontogenic tumor usually presents as a unilocular radiolucency with a sharp, circumscribed border. The border is well corticated to sclerotic. It is often associated with an uninterrupted tooth. The radiographic feature of the tumor blending with a follicle can sometimes be confused radiographically with a dentigerous cyst. Although purely radiolucent lesions are most common, this is another one of the classic radiolucent/radiopaque lesions of the jaws.

Microscopic Features

The tumor consists predominantly of spindle-shaped epithelial cells that form whorled masses or rosettes in a scant fibrous stroma. Ductlike structures lined by cuboidal or columnar epithelial cells are the classic histopathologic feature. Foci of amyloid, if present, are usually seen in the rosette/adenomatoid arrears. Other mineralized material may also be seen. These mineralizations are usually not well organized but may resemble dentin, cementum, or aborted attempts at enamel production.[280-282] Cystic spaces are also common. Some may be true luminal surfaces, though the largest surface lumen is probably adjacent to the tooth crown.

Treatment

These lesions are very well encapsulated and therefore easily enucleated. Aggressive behavior is never anticipated and recurrence is not a problem, though large lesions have been reported.[276] The lesion can be enucleated and the tooth can be left in place for eventual eruption or orthodontic therapy.

Odontomas

Odontomas are the most commonly diagnosed odontogenic tumors. They are considered by many to be a hamartoma rather than a true neoplasm. Odontomas are subdivided into two subtypes: complex and compound odontomas. Complex odontomas, when fully developed, consist almost entirely of intermingled aggregates of enamel, enamel matrix, dentin, and cementum arranged in a haphazard manner. Compound odontomas consist of enamel matrix, dentin, and cementum. Unlike the complex odontoma, the mineralized elements are organized with the overall appearance suggestive of multiple small, malformed, but easily identifiable teeth. These toothlike elements can easily be seen at the grossing table. Some epithelial elements may be seen peripherally. These epithelial cells represent the reduced enamel epithelium from which the hard tissues were formed. Odontogenic rests are also seen peripherally. Just as with an unerupted tooth, these epithelial linings and rests may lead to formation of dentigerous cysts. Likewise, any odontogenic cyst or tumor may also develop in association with an odontoma. Complex and compound odontomas occur with equal frequency and some lesions show features of both subtypes. Depending on size and location, they may deform adjacent teeth or delay eruption.[97,283,284]

Radiographic Findings

Both complex and compound odontomas show a well-demarcated radiolucency with a uniform corticated border delineating the lesion from surrounding bone. This has been described as a well-defined central radiopacity(s) surrounded by a thin radiolucent line surrounded by a thin radiopaque line. This is exactly the description of an erupting tooth. Centrally, there are differing brightness values associated with the radiopacities. The variation is due to the fact that enamel is more radiopaque than the dentin and cementum. Dentin and cementum cannot be differentiated radiographically. Compound odontomas will be a "sack of teeth," and complex odontomas will be a disorganized aggregate.

Microscopic Findings

Complex odontomas, when mature, consist almost entirely of a conglomeration of dentin, cementum, and enamel matrix. Following demineralization, the areas of mature enamel are lost and appear as empty spaces. In complex odontomas only scant amounts of reduced enamel epithelium remain. Peripherally, follicular tissue and odontogenic rests are common. During the demineralization process necessary for routine microscopic sectioning, the enamel portion of the specimen will be reduced to a retracted and fragmented, homogeneous, basophilic material. Less than 1% of the enamel is organic, and only this 1% is observed following demineralization procedures.

Treatment

Complex and compound odontomas are treated with simple enucleation and avoidance of damage to adjacent structures and teeth. If the term *never* can be used in health science, then odontomas never recur.

Squamous Odontogenic Tumor

This tumor is mentioned briefly because it is extremely rare with fewer than 100 ever reported. The lesions are generally small and usually present as "inverted" periodontal bone loss. Gingival tumors have also been described.[285,286] That is, in periodontal disease the triangular base is toward the cementoenamel juntion. In the squamous odontogenic tumor the base is toward the tooth apex. Familial and multifocal cases have been reported. Any portion of the tooth-bearing area may be involved, and the paucity of cases does not allow for much demographic analysis. The importance of the tumor is that the squamous epithelial islands seen microscopically may be misinterpreted. The squamous islands are cytopathologically totally benign. Yet their presence deep in connective tissue may be misinterpreted as invasion. The invasive appearance may lead to misdiagnosis as either an acanthomatous ameloblastoma or, worse, a squamous cell carcinoma. Tumors are easily treated with enucleation and simple conservative curettage.[286-289] Squamous, odontogenic, tumor-like proliferations are well known as being occasionally associated with inflammatory odontogenic cysts. These proliferations are inconsequential and do not warrant additional treatment or diagnostic proclamation.[290-292]

Odontoameloblastoma

Controversy surrounds the definition of odontoameloblastoma, and several lesions have likely been described under this designation. One subset of lesions given the moniker of odontoameloblastoma most likely represents an ameloblastoma arising from the epithelial elements of an odontoma. Other reports describe aggressive, large tumors that would be difficult to separate histologically from an "aggressive" ameloblastic fibro-odontoma.[293-295] One report of dentinoid production with an ameloblastoma could be an additional subset.[296] LaBriola and colleagues[297] also reviewed the difficulties associated with this diagnosis and reported one case, as did other researchers.[298,299] Generally these tumors define themselves by their destructive and/or recurrent behavior. Because of difficulties in histologic criteria, the diagnosis should always be made in consultation with a pathologist well versed in head and neck/oral pathology.

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CHAPTER NINETY-FOUR

Temporomandibular Joint Disorders

Bruce E. Rotter

Key Points

- Temporomandibular disorders is a collective term describing both intracapsular disorders and muscular disorders, or myofascial pain dysfunction.
- The general presenting complaints of temporomandibular disorders include facial pain, earache, and headache.
- The temporomandibular joint (TMJ) is a diarthrotic joint, with each joint incapable of independent movement.
- The TMJ is a ginglymoarthrodial joint, capable of both translational and rotational movement.
- TMJ dislocation occurs when a hypermobile joint translates anterior to the articular eminence and becomes locked in that position.
- The primary intracapsular disorders of the TMJ are (1) anteriorly displaced disk with reduction, (2) anteriorly displaced disk without reduction, and (3) degenerative disease.
- Anteriorly displaced disks (ADDs) are typically caused by frequent episodes of microtrauma such as clenching or grinding the teeth.
- ADDs with reduction are typically characterized by clicking or popping sounds on mouth opening. ADDs without reduction are typically characterized by a closed lock.
- Degenerative joint disease (DJD) is the most frequent abnormal condition affecting the TMJ.
- Absolute indications for TMJ surgery include treatment of neoplasms, growth abnormalities, and ankylosis of the joint.
- Relative indication for TMJ surgery is treatment of pain and dysfunction, which is refractory to nonsurgical therapy where there is confirmatory imaging evidence of pathology.
- Myofascial pain dysfunction (MPD) syndrome is a muscular disease that is believed to be induced by stress and muscular hyperactivity from parafunctional habits.

Temporomandibular disorders, or TMDs, is a collective term that has been used traditionally to describe multiple disorders. These include both intracapsular disorders, or true abnormalities of the temporomandibular joint (TMJ), and muscular disorders, or myofascial pain dysfunction syndrome (MPD). Additionally, some disorders have not been considered under the umbrella of TMD but either directly or indirectly affect the structures of the TMJ. Examples of these disorders are congenital and developmental deformities, trauma, and neoplastic disease.

The general presenting complaints of the temporomandibular disorders include facial pain, earache, and headache. Therefore it is important for otolaryngologists to be familiar with the diagnosis and treatment of these various conditions. Much of the difficulty encountered in the treatment of TMDs relates to the failure to distinguish between these disorders and other causes of head and facial pain because of the similarity of the signs and symptoms with which they present. The emphasis in this chapter is on the diagnosis of TMDs, with a subsequent discussion of what is known about the etiology of the various conditions, forming the basis for a rational approach to therapy.

Anatomy

The anatomy and function of the TMJ are unique in several ways. The TMJ is a diarthrotic joint. Because the mandible is hinged at both ends, each joint is incapable of independent movement. This is clinically important because dysfunction in one joint can adversely affect the function of the contralateral joint, producing bilateral symptoms.

Each individual joint consists of the condylar process of the mandible, which is housed within the glenoid fossa of the squamous portion of the temporal bone. The anterior wall of the glenoid fossa is formed by the articular eminence, which is the articulating counterpart to the condylar process. The articulating surfaces are lined with fibrous connective tissue and are enclosed by a fibrous capsule.

Interposed between the articulating surfaces of the TMJ is the articular disk. The disk is a unique structure that is concavo-convex on its superior surface and concave on its inferior surface, where it contacts the convex condylar head. The presence of the articular disk divides the joint into two distinct compartments and contributes to the dual action of this ginglymoarthrodial joint. The inferior compartment, or inferior joint space, allows for purely anterior and posterior rotational movement between the condyle and disk. The superior joint

space allows for translational movement between the disk and the glenoid fossa and articular eminence. In addition to assisting movement within the joint, the disk acts to compensate for any incongruencies between the articular surfaces and acts as a shock absorber within the joint.[1]

The degree of condylar movement is governed by the limiting actions of the joint capsule, the articular disk, and the joint ligaments. The primary ligaments of the TMJ are the lateral, sphenomandibular, and stylomandibular ligaments. The relationship of the articulating components of the joints is also influenced by the presence of the teeth. When the mouth is in an open position, the degree and direction of movement of the joints are influenced by the components discussed earlier. However, when the teeth come into contact, this occlusal relationship determines the final position of the condyle with respect to the rest of the joint. This factor becomes increasingly important in individuals who exhibit occlusal disharmony or parafunctional habits.

Diseases and Disorders

The TMJ is susceptible to the same conditions that affect other joints in the body such as congenital and developmental anomalies, traumatic injuries, dislocations, internal derangements of the articular disk, ankylosis, various arthritic conditions, and, rarely, neoplastic diseases (Table 94-1). Although many of these conditions are treated in the same manner as in other joints, the previously described anatomic and functional differences of the TMJ often require some variations of therapy.

Congenital and Developmental Anomalies

Because the condyle has an important role in mandibular growth, congenital and developmental anomalies such as condylar agenesis, condylar hypoplasia, or condylar hyperplasia can produce severe facial deformity. It is important to diagnose and treat these conditions early in order to limit the degree of mandibular, as well as compensating, facial deformity. However, examination of the current concepts regarding the diagnosis, preparatory treatment, and surgical therapy of the dentofacial deformities is beyond the scope of the current discussion. The reader is encouraged to explore the many good publications that thoroughly discuss orthognathic surgery.[2-10]

Trauma

The condyloid process and, more specifically, the condylar neck is one of the most frequent sites of fracture after trauma to the mandible. Condylar or subcondylar fractures will usually produce preauricular pain and tenderness, difficulty in opening the mouth, and malocclusion. Unilateral fracture will produce jaw deviation to the affected side on attempted mouth opening. Bilateral fractures frequently produce an anterior open bite due to loss of structural support in the ascending ramus.

Treatment of condylar and subcondylar fractures varies on the basis of multiple factors. Nondisplaced fractures with minimal dysfunction may be treated with soft diet and guiding elastics. Moderate changes in occlusion or function may require short-term maxillomandibular fixation. In situations where the malposed segment is significantly displaced or interferes with jaw function, there are no occluding teeth on the involved side, or the condyloid processes are fractured bilaterally and grossly displaced, open reduction should be performed.[11] Additional considerations for open reduction are the inability to perform maxillomandibular fixation and the presence of concomitant fractures in the mandible, maxilla, or midface.

Dislocation

Dislocation occurs when the hypermobile mandible becomes fixed in an open position with no or only the most posterior teeth contacting. Acute dislocation occurs when the condyle translates anterior to the articular eminence and becomes locked in that position. It is treated with manual reduction by applying downward pressure on the posterior mandible while placing upward and backward pressure on the chin. This manipulation is supplemented by the use of local anesthesia, intravenous sedation, or general anesthesia. Postreduction, the patient should restrict mandibular opening for 2 to 4 weeks. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed for control of pain and inflammation.

Dislocation that is chronic can be treated by injection of a sclerosing agent into the TMJ capsule and lateral ligament to produce scarring of the stretched tissues,[12] capsulorrhaphy, lateral pterygoid myotomy, temporal myotomy, or condylectomy.[13] Decision as to the appropriate surgical procedure is based on the etiology, severity, and persistence of the dislocation.

Neoplasms

Primary neoplasms originating in the TMJ are extremely rare. Chondroma, osteochondroma, and osteoma are examples of benign tumors affecting the TMJ. Malignant tumors, which are even more uncommon, include fibrosarcoma, chondrosarcoma, and multiple myeloma. Direct extension of neoplasms from adjoining tissues and metastasis from distant neoplasms have been reported.

Tumors of the TMJ cause joint pain, restriction of opening, and malocclusion. Radiographic examination may demonstrate radiolucent, radiopaque or mixed lesions. Biopsy is necessary to establish a definitive diagnosis. Surgery is the treatment of choice for both benign and malignant neoplasms. Most malignant neoplasms that affect the TMJ are not radiosensitive, so radiotherapy is generally not considered.

Intracapsular Disorders

Intracapsular disorders of the TMJ include the following: (1) anterior disk displacement with reduction on opening the mouth, (2) anterior disk displacement without reduction, and (3) degenerative joint disease.

Anterior disk displacement is typically caused by trauma. This may be a single, macrotraumatic event or, more likely, frequent episodes of microtrauma that occur over a prolonged period. The majority of microtraumatic events are the parafunctional habits such as tooth clenching or grinding, which is also known as bruxism.[14]

Anterior Disk Displacement with Reduction

Anterior disk displacement *with* reduction is typically characterized by clicking or popping sounds on mouth opening (Fig. 94-1). Reciprocal or closing clicks are not consistently present. Patients who present with anterior disk displacement with reduction generally exhibit a normal range of mandibular motion. There may or may not be pain associated with mandibular movement. Multiple studies have shown that asymptomatic anterior displacement with reduction is common and often persists for years without signs of progression.[14-16] It is believed that these asymptomatic, nonprogressive cases represent physiologic accommodation of the joint.[17] They require no treatment. When pain is present, it is the general determinant of any functional limitation that exists. Treatment of these painful joints consists of soft diet, self-limitation of opening, NSAIDS, splint therapy, and physical therapy. Patients refractive to these conservative modes of therapy may be candidates for more invasive procedures such as arthrocentesis, arthroscopy, or open joint surgery.

Anterior Disk Displacement without Reduction

Anterior disk displacement *without* reduction is characterized by a closed lock (Fig. 94-2). In the nonreducing joint, forward translation of the condyle on mouth opening forces the disk anteriorly, causing it to become a physical impediment to further opening. The maximum interincisal opening (MIO) is generally only 25 to 30 mm, and the mandible deviates toward the affected joint. Lateral excursive movements of the mandible are generally restricted to the contralateral side but not to the ipsilateral side. Pain is a common symptom, particularly on forced opening (beyond the MIO).

Acutely displaced disks without reduction can often be successfully treated by manual manipulation of the mandible with coincident reduction of the disk. In chronic conditions, manual reduction is much less likely to lead to satisfactory reduction of the disk. This is generally due to loss of disk morphology. Patients who exhibit a chronically nonreducing disk should be initially treated with a stabilization splint in order to reduce the pressure on the retrodiskal tissues produced by

Table 94-1

Differential Diagnosis of Temporomandibular Joint Disorders

Disorder	Pain	Limitation	Diagnostic Features
Agenesis	No	Yes	Congenital; usually unilateral; mandible deviates to the affected side; unaffected side long and flat; severe malocclusion; often ear abnormalities; radiograph shows condylar deficiency
Condylar hypoplasia	No	No	Congenital or acquired; affected side has a short mandibular body and ramus, fullness of face, deviation of the chin; body of the mandible elongated and face flat on the unaffected side; malocclusion; radiograph shows condylar deformity, antegonial notching
Condylar hyperplasia	No	No	Facial asymmetry with deviation of chin to the unaffected side; cross-bite malocclusion; prognathic appearance; lower border of the mandible often convex on the affected side; radiograph shows symmetric enlargement of condyle
Neoplasia	Possible	Yes	Mandible may deviate to the affected side; radiographs show enlarged, regularly shaped condyle or bone destruction depending on the type of tumor; unilateral condition
Infectious arthritis	Yes	No	Signs of infection; may be part of systemic disease; radiographs may be negative early, but later can show bone destruction; fluctuance may be present; pus may be obtained on aspiration; usually unilateral
Rheumatoid arthritis	Yes	Yes	Signs of inflammation; findings in other joints (e.g., hands, wrists, feet, elbows, ankles); positive laboratory tests; retarded mandibular growth in children; anterior open bite in adults; radiograph shows bone destruction; usually bilateral
Traumatic arthritis	Yes	Yes	History of trauma; radiograph negative except for a possible widening of joint space; local tenderness; usually unilateral
Degenerative arthritis	Yes	Yes	Unilateral joint tenderness; often crepitus; temporomandibular joint may be the only joint involved; radiograph may be negative or show condylar flattening, lipping, spurring, or erosion
Ankylosis	No	Yes	Usually unilateral but can be bilateral; history of trauma may exist; young patient may show retarded mandibular growth; radiographs show a loss of normal joint architecture
Internal disk derangement	Yes	Yes	Pain exacerbated by function; clicking on opening, or opening limited derangement to under 35 mm with no click; positive arthrographic or magnetic resonance imaging findings; history of trauma may exist; usually unilateral

From Laskin DM, Block S. Diagnosis and treatment of myofascial pain-dysfunction [MPD] syndrome. *J Prosthet Dent.* 1986;56:75.

masticatory and parafunctional forces. When pain is a significant component of this disorder, more aggressive or invasive procedures may be indicated.

Degenerative Joint Disease

Degenerative joint disease or degenerative arthritis is the most frequent abnormal condition affecting the TMJ. Primary degenerative arthritis is seen in older persons and is associated with normal aging. Symptoms are generally mild and rarely require treatment other than patient education and conservative homecare measures. Secondary degenerative arthritis is usually initiated by either macrotrauma or microtrauma. In the case of macrotrauma, the initial findings may be consistent with that of hemarthrosis and are initially characterized by TMJ pain, tenderness, and limitation of jaw movement. The radiograph may be negative or may show widening of the joint space caused by intra-articular edema or hemorrhage. Concomitantly, the teeth may exhibit a posterior open bite on the affected side. Degenerative arthritis caused by microtrauma is more common and is often the product of unresolved, nonreduced, anteriorly displaced disks. It produces more severe symptoms of pain and tenderness, clicking or crepitation, and limitation of jaw movement. The radiograph frequently will show flattening, lipping, osteophyte formation, or erosion of the articular surface of the condyle.

Treatment of degenerative joint disease includes administration of NSAIDs, soft diet, limited jaw movement, and use of a stabilizing bite splint to help reduce the effects of chronic clenching or bruxism. When nonsurgical management fails to relieve the symptoms, and when there is radiographic evidence of bony change on the articular surface of the condyle, surgical intervention may be indicated. This should involve removal of only the minimal amount of bone necessary to produce a smooth articular surface. Unnecessary removal of the entire cortical plate, as occurs with the so-called condylar shave or condylotomy, can lead to continued resorptive changes in some instances and should be avoided if possible.

Infectious arthritis is rare in the TMJ. It can be associated with a systemic disease or as an extension of a local infection. Clinically, there are typically signs of systemic disease and local signs of inflammation and limited jaw movement. Radiographic findings are initially negative

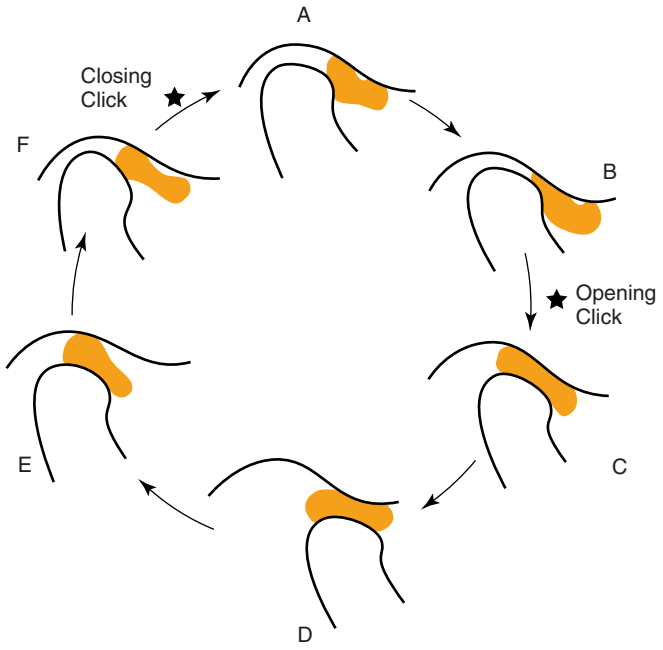

Figure 94-1. Anterior displacement of the intra-articular disk with reduction. Jaw closed; condyle seated in fossa with disk anteriorly displaced (*A*). Condyle beginning translation (*B*). Opening of the mouth (*C*). A clicking or popping sound occurs as the disk returns to its normal position in relation to the condyle. Condyle fully translated; disk in normal position (*D*). During closure, the disk again becomes anteriorly displaced, sometimes accompanied by a second sound (reciprocal click) (*E, F*). *(Modified with permission from McCarty W. Diagnosis and treatment of internal derangements of the articular disc and mandibular condyle. In: Solberg WK, Clark GT, eds.* Temporomandibular Joint Problems: Biologic Diagnosis and Treatment. *Chicago: Quintessence; 1980.)*

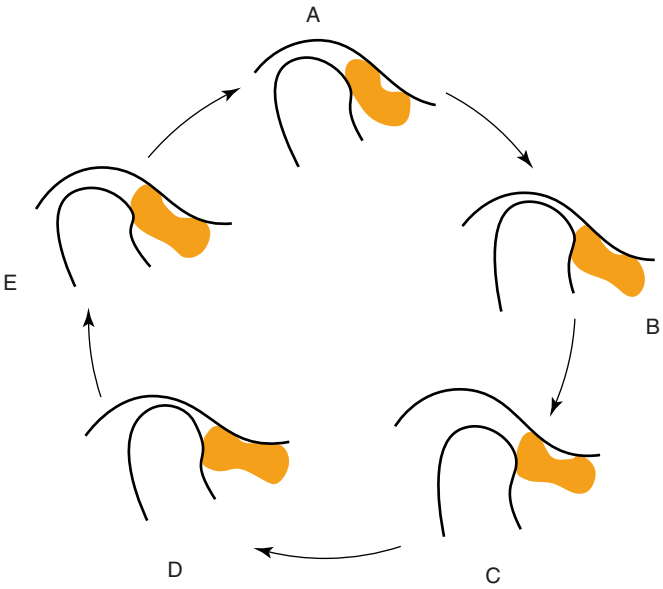

Figure 94-2. Anterior displacement of the intra-articular disk without reduction. Jaw closed; condyle seated in fossa with disk anteriorly displaced (*A*). Condyle beginning translation (*B*). Attempted mouth opening (*C*). The displaced disk acts as a barrier and prevents full translation of the condyle. Jaw closure; condyle returns to seated position in fossa (*D, E*). *(Modified with permission from McCarty W. Diagnosis and treatment of internal derangements of the articular disc and mandibular condyle. In: Solberg WK, Clark GT, eds.* Temporomandibular Joint Problems: Biologic Diagnosis and Treatment. *Chicago: Quintessence; 1980.)*

but may show extensive bone destruction later in the disease process. Treatment includes antibiotics, proper hydration, control of pain, and restriction of jaw movement. Suppurative infections may require drainage or sequestrectomy.

Rheumatoid arthritis occasionally can occur in the TMJ. It generally produces bilateral pain, tenderness and swelling, and limitation of jaw motion. In the early stages, the disease may not be radiographically evident, but with progression of the disease the articular surface of the condyle is destroyed and the joint space is obliterated. As a result, an anterior open bite can occur. There is a possibility for ankylosis of the joints to occur.

Treatment of rheumatoid arthritis in the TMJ is similar to that in other joints.[18] Anti-inflammatory drugs are used during the acute phases, and mild jaw exercises are used to prevent excessive loss of motion when the acute symptoms subside. In patients with severe cases, drugs such as steroids, disease-modifying antirheumatic drugs (DMARDs), immunosuppressants, interleukin-1 receptor antagonists, T cell inactivating drugs, and B cell inhibitors are also used to control the pain and inflammation. Surgery may be necessary if ankylosis develops.

Ankylosis

The most common causes of TMJ ankylosis are rheumatoid arthritis and traumatic injuries, although it also may result from congenital abnormalities, infection, or neoplasia. It is important to distinguish between true intracapsular ankylosis, which produces an abnormal condyle and fossa relationship, and false ankylosis, which involves extra-articular conditions such as enlargement of the coronoid process, depressed fracture of the zygomatic arch, or scarring from surgery or irradiation. In intracapsular ankylosis, radiographs usually show condylar deformity and either a narrowing or irregularity of the joint space.

In the surgical treatment of ankylosis, a cut is made through the condylar neck at the highest possible point on the ramus to maintain maximum ramal height and to minimize postoperative shift of the mandible. An interpositional material is placed in the newly created gap to prevent fusion of the bone ends. Patients must undergo long-term, aggressive physical therapy postsurgically in order to maintain the functionality of the newly formed joint.[19]

Temporomandibular Joint Surgery

As with many disorders, there are both absolute and relative indications for TMJ surgery. Absolute indications include treatment of neoplasms, growth abnormalities, and ankylosis of the joint. Relative indications for TMJ surgery tend to be nonspecific and lacking objective criteria. Experts generally agree that TMJ surgery is indicated to treat pain and dysfunction that is refractory to nonsurgical therapy where there is confirmatory imaging evidence of pathology.

Dolwick established criteria to guide the surgeon in determining the need and appropriateness of TMJ surgery[20]:

1. The more localized the dysfunction and pain are to the joint, the better the surgical prognosis. Localized, continuous TMJ pain that worsens with function or progresses through the day is an indication for surgical intervention. Patients who have pain that arises from a muscular source (myofascial pain dysfunction or MPD) or other nonintracapsular sources are not surgical candidates.

2. Surgery is indicated when TMJ pain or dysfunction is refractory to nonsurgical therapy. This nonsurgical therapy includes patient education, anti-inflammatory medication, physical therapy, occlusal therapy, and counseling. deBont and colleagues[21] suggest that surgical correction of intracapsular disorders should be considered only after reasonable nonsurgical efforts have failed and only when quality of life is significantly compromised. It should be noted that surgical correction of TMJ disorders is rarely performed in isolation; rather, it is supported by both presurgical and postsurgical therapy.

3. Imaging evidence should support the clinical findings. Imaging should not be used alone in diagnosis or as the primary determinant for surgical intervention.

Arthrocentesis

Arthrocentesis is the simplest and least invasive of the TMJ surgical procedures.[20] It is generally performed as an office-based procedure under intravenous sedation and local anesthesia. Arthrocentesis allows the surgeon to perform (1) TMJ lysis and lavage; (2) placement of anti-inflammatory medications into the superior joint space, although the benefit of injecting medication into the joint is still unproven; and (3) examination of the joint for range of motion under anesthesia.

The procedure is accomplished by inserting two 18-gauge needles into the superior joint space. The first needle serves as the injection port and the second as the outflow port. Injection of lactated Ringer's solution through this system provides lavage of the superior joint space, while blockage of the outflow port allows lysis of adhesions through distention of the superior joint space when coupled with concomitant mandibular manipulation.

Postoperative care consists of a nonchew diet for several days, range-of-motion exercises, and analgesics as needed. Multiple retrospective studies have indicated that arthrocentesis produces a 70% to 90% success rate in reducing TMJ pain and improving mandibular range of motion.[22-27] Arthrocentesis is not associated with any significant postoperative complications. Most patients note a temporary swelling and soreness in the TMJ region and exhibit mild posterior open bite, which is typically resolved within 24 hours.

Arthroscopy

Arthroscopy, like arthrocentesis, is a minimally invasive surgical procedure. Unlike arthrocentesis, it is generally accomplished in a surgical suite under general anesthesia. The procedure requires placement of a small surgical telescope into the superior joint space. A second access port is inserted anterior to the telescope. It acts primarily as an outflow port but can be used for instrument access to the superior joint space. The primary advantage that arthroscopy exhibits over arthrocentesis is the ability to visualize the anatomy and pathology of the superior joint space. Although more sophisticated operative procedures can be performed using the surgical telescope, most surgeons limit the use of arthroscopy to visualization of the superior joint space, lysis, and lavage.

Postoperative care is similar to that described for arthrocentesis. Multiple retrospective studies have indicated that the success rate for arthroscopic lysis and lavage approaches 80% to 90%.[28-33] In fact, Murakami and colleagues,[34,35] in both a 5-year and a 10-year follow-up, showed that lysis and lavage procedures were equally successful to open joint surgeries for all stages of internal derangement. Because the results of arthrocentesis parallel those achieved with arthroscopy and because it is a less invasive procedure, it has been suggested that arthrocentesis be attempted initially.[20]

Arthrotomy

Arthrotomy, or open joint surgery, encompasses a range of surgical procedures including débridement, disk repositioning or plication, diskectomy, arthroplasty, and joint replacement. Joints indicated for open joint surgery are those that exhibit an internal derangement or osteoarthritis that produces extensive mechanical interference with function or that have failed to respond to less invasive procedures.

The postoperative sequelae to arthrotomy are generally swelling at the surgical site, moderate discomfort, limitation of opening, and occlusal changes. These sequelae are transient and generally subside within 2 weeks of surgery. Patients often note preauricular numbness that may last 6 to 8 weeks. The most significant postoperative complication to arthrotomy is damage to the facial nerve. This occurs in only about 5% of surgical cases and most commonly affects the temporal branch of the nerve. In most instances this injury is self-limiting, but it has been shown to produce permanent deficit in less than 1% of cases.[20]

Variable success rates following open joint surgery have been reported in the literature, with many reports indicating a 80% to 95% success rate in reducing pain and restoring function to the joint.[36-42] It should be noted, however, that repeat surgeries show rapidly declining success rates.

Myofascial Pain Dysfunction Syndrome

MPD syndrome is a muscular disease that is believed to be multifactorial in origin.[43] It is generally accepted that centrally induced muscle tension from stress and anxiety combined with parafunctional habits such as clenching or grinding of the teeth results in abnormal muscle function and hyperactivity. This leads to fatigue and spasm of the muscles that ultimately produces pain and dysfunction. The pain stimulates muscle fibers to react, leading to further muscular dysfunction and spasm. Thus one can appreciate the cyclic nature of this disorder. Similar symptoms can also occasionally result from muscular overextension, muscle overcontraction, or trauma (Fig. 94-3).

MPD syndrome most frequently affects females in the 20- to 40-year age group. Men are much less affected, with a ratio of approximately 1:4. Children are rarely affected.

MPD syndrome is characterized by diffuse, poorly localized pain that ranges from complaint of preauricular pain to generalized pain throughout the muscles of mastication. The pain is often described as dull, aching, radiating pain that may be more severe in the morning. Patients also complain of pain and limitation of opening during function. The condition generally involves only one side of the face, and on examination, tenderness can usually be elicited in one or more of the muscles of mastication or their tendinous attachments.[44] Headache is frequently mentioned as a symptom. Ciancaglini and Radaelli[45] report a significant increase in headache in patients with TMD symptoms (27.4% vs. 15.2%). The only type of headache that is functionally related to MPD syndrome, however, is the tension-type headache, with other types being coincidental findings. The same is true for multiple complaints noted by MPD patients such as decreased hearing, tinnitus, burning tongue, and neuralgic pains. MPD syndrome that is left untreated can ultimately lead to organic changes in the TMJ and the masticatory muscles and may even cause alterations in the dentition.

The cardinal signs and symptoms of MPD syndrome are similar to those produced by intracapsular disorders, as well as by a variety nonarticular conditions (Tables 94-2 and 94-3). A careful history and thorough clinical evaluation should be performed to rule out these other clinical entities. Screening radiographs, particularly intraoral periapical films and a panoramic film delineating the structures of the jaws and the TMJ, can be helpful. If the screening views of the TMJ show some abnormality, tomographic views or CT scans are useful in further evaluating bony abnormalities. Magnetic resonance

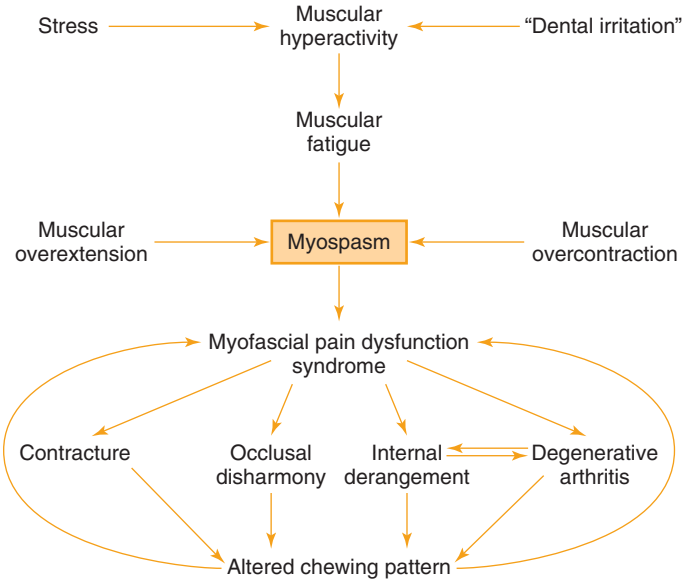

Figure 94-3. Etiology of the myofascial pain dysfunction syndrome. *(Modified from Laskin DM. Etiology of the pain-dysfunction syndrome.* J Am Dent Assoc. *1969;79:147.)*

Table 94-2

Differential Diagnosis of Nonarticular Conditions Mimicking Pain of Myofascial Pain Dysfunction Syndrome

Disorder	Limitation	Muscle Tenderness	Diagnostic Features
Pulpitis	No	No	Mild to severe ache or throbbing; intermittent or constant; aggravated by thermal changes; eliminated by dental anesthesia; positive radiograph findings
Pericoronitis	Yes	Possible	Persistent mild to severe ache; difficulty swallowing; possible fever; local inflammation; relieved with dental anesthesia
Otitis media	No	No	Moderate to severe earache; pain constant; fever; history of upper respiratory infection usually present; no relief with dental anesthesia
Parotitis	Yes	No	Constant aching pain, worse when eating; pressure feeling; absent salivary flow; ear lobe elevated; ductal suppuration
Sinusitis	No	No	Constant aching or throbbing; worse when head position changes; nasal discharge; often molar pain not relieved by dental anesthesia
Trigeminal neuralgia	No	No	Sharp stabbing pain of short duration; trigger zone; pain follows nerve pathway; older age group; often relieved by dental anesthesia
Atypical (vascular) neuralgia	No	No	Diffuse throbbing or burning pain of long duration; often associated autonomic symptoms; no relief with dental anesthesia
Temporal arteritis	No	No	Constant throbbing preauricular pain; artery prominent and tender; low-grade fever; possible visual problems; elevated sedimentation rate
Trotter's syndrome (nasopharyngeal carcinoma)	Yes	No	Aching pain in ear, side of face, lower jaw; deafness; nasal obstruction; cervical lymphadenopathy
Eagle's syndrome (elongated styloid process)	No	No	Mild to sharp stabbing pain in the ear, throat, or retromandible; provoked by swallowing, turning head, carotid compression; usually post-tonsillectomy; styloid process longer than 2.5 cm

From Laskin DM, Block S. Diagnosis and treatment of myofascial pain-dysfunction (MPD) syndrome. *J Prosthet Dent.* 1986;56:75.

imaging is valuable in evaluating soft tissue structures particularly when an internal derangement of the TMJ is suspected. In addition, certain laboratory tests may be helpful in some patients. These tests include a complete blood cell count if an infection is suspected; serum calcium, phosphorus, and alkaline phosphatase measurements for possible bone disease; serum uric acid determination for gout; serum creatinine and creatine phosphokinase levels as indicators of muscle disease; and erythrocyte sedimentation rate, rheumatoid factor, latex fixation, and antinuclear antibody tests for suspected rheumatoid arthritis. In patients suspected primarily of MPD syndrome, muscular function may be evaluated through electromyography. Many clinicians recommend psychologic evaluation, primarily to help determine patient compliance and to predict anticipated treatment outcomes.

Treatment

Laskin and Block[46] have delineated a treatment regimen for MPD syndrome and have divided it into four appropriate stages of therapy (Fig. 94-4). Their regimen remains an appropriate and timely course of therapy for MPD syndrome patients today and is as follows:

1. Once a definitive diagnosis is made, stage 1 therapy is started. This initially involves providing the patient with some understanding of the problem. Because patients often have difficulty accepting a psychophysiologic explanation for their condition, the discussion should deal with the issue of muscle fatigue and spasm as the cause of the pain and dysfunction, delaying consideration of the role of stress and psychologic factors until the symptoms have improved and the patient's confidence has been gained. Relating the symptoms to the specific masticatory muscles from which they originate helps the patient understand the reason for the type and location of the pain; for example, headache from the temporalis muscle, jaw ache from the masseter muscle, discomfort when swallowing and stuffiness in the ear from the medial pterygoid muscle, and earache and pain behind the eye from the lateral pterygoid muscle.

   In addition to the initial explanation, the patient is counseled regarding home therapy. Counseling includes recommendations about avoidance of clenching and grinding of the teeth; eating a soft, nonchew diet; use of moist heat on, and massage of, the masticatory muscles; and limitation of jaw motion. Because the patient has muscle spasm and pain, a muscle relaxant and an NSAID are prescribed. Diazepam and ibuprofen are commonly used.

2. About 50% of the patients will have a resolution of their symptoms within 2 to 4 weeks with stage 1 therapy. For those whose symptoms persist, stage 2 therapy is initiated. Home therapy and medications

Table 94-3

Differential Diagnosis of Nonarticular Conditions Producing Limitation of Mandibular Movement

Disorder	Pain	Muscle Tenderness	Diagnostic Features
Odontogenic infection	Yes	Yes	Fever; swelling; positive radiographic findings; tooth tender to percussion; pain relieved and movement improved with dental anesthesia
Nonodontogenic infection	Yes	Yes	Fever; swelling; negative dental findings on radiograph; dental anesthesia may not relieve pain or improve jaw movement
Myositis	Yes	Yes	Sudden onset; movement associated with pain; areas of muscle tenderness; usually no fever
Myositis ossificans	No	No	Palpable nodules seen as radiopaque areas on radiograph; involvement of nonmasticatory muscles
Neoplasia	Possible	Possible	Palpable mass; regional nodes may be enlarged; possible paresthesia; radiograph may show bone involvement
Scleroderma	No	No	Skin hard and atrophic; masklike facies; paresthesias; arthritic joint pain; widening of periodontal ligament
Hysteria	No	No	Sudden onset after psychologic trauma; no physical findings; jaw opens easily during general anesthesia
Tetanus	Yes	No	Recent wound; stiffness of neck; difficulty swallowing; spasm of the facial muscles; headache
Extrapyramidal reaction	No	No	Patient taking antipsychotic drug or phenothiazine tranquilizer; hypertonic movement; lip smacking; spontaneous chewing motions
Depressed zygomatic arch	Possible	No	History of trauma; facial depression; positive radiographic findings
Osteochondroma coronoid process	No	No	Gradual limitation; jaw may deviate to the unaffected side; possible clicking sound on jaw movement; positive radiographic findings

From Laskin DM, Block S. Diagnosis and treatment of myofascial pain-dysfunction (MPD) syndrome. *J Prosthet Dent.* 1986;56:75.

are continued, but at this point, a bite appliance is made for the patient. Although numerous types have been used, the Hawley-type maxillary appliance is probably most effective because it prevents contact of the posterior teeth and thereby also prevents most forms of parafunctional activity. Generally, the appliance is worn at night, but it can be worn for 5 to 6 hours during the day if necessary. It should not be worn continuously because the posterior teeth may supraerupt in some patients.

With stage 2 therapy, another 20% to 25% of patients will become free of symptoms in 2 to 4 weeks. The medications are stopped first, and wearing the bite appliance is discontinued next. If the patient has a return of symptoms when the appliance is not worn at night, its use can be continued indefinitely.

3. Patients who do not respond to the use of a bite appliance are entered into stage 3 of treatment for 4 to 6 weeks. In this phase, either physical therapy (e.g., ultrasound, electrogalvanic stimulation) or relaxation therapy (e.g., electromyographic biofeedback, conditioned relaxation) are added to the regimen. There is no evidence to show that one form of treatment is better than the other, and either can be used first. If one is not successful, the other can be tried. Stage 3 therapy usually helps another 10% to 15% of patients.

4. If all of the previous approaches fail and if there is no question about the correctness of the diagnosis, psychologic counseling is recommended. This involves helping patients identify possible stresses in their lives and cope with such situations. If there is doubt about the diagnosis, the patient should first be referred for appropriate dental and neurologic consultation and evaluation. Another alternative is to refer patients with recalcitrant MPD syndrome to a TMJ center or pain clinic because such patients generally require a multidisciplinary approach for successful treatment.

Summary

The successful treatment of patients with TMDs depends on establishing an accurate diagnosis. The clinician must distinguish among muscular disorders (MPD), true intracapsular TMJ disorders, and those disorders that are often not included under the TMD "umbrella," but which either directly or indirectly affect the structures of the temporomandibular joint. Only then can proper therapy, based on an understanding of the cause of the condition, be instituted. Of particular importance is understanding that not all TMD patients are surgical candidates. MPD syndrome patients do not benefit from surgical intervention and should not be considered for surgery. Even in those patients in whom surgical intervention is an acceptable alternative, many of the commonly encountered conditions such as arthritis and internal disk derangement respond well to nonsurgical or minimally invasive therapy. This type of treatment should be attempted before more aggressive surgical therapy is considered.

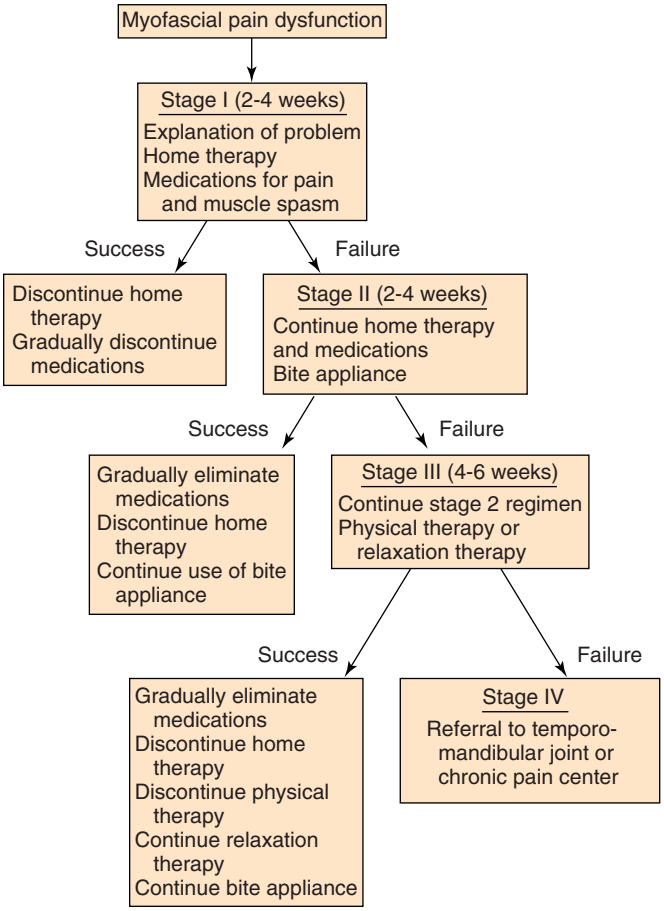

Figure 94-4. Management of myofascial pain dysfunction syndrome.

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CHAPTER NINETY-FIVE

Benign Tumors and Tumor-Like Lesions of the Oral Cavity

Timothy S. Lian

Key Points

- Benign neoplasms of the oral cavity are typically best treated with complete surgical excision. Generally, recurrence is rare, as is malignant transformation.
- Treatment for tumor-like lesions involves either conservative medical management or surgical excision depending on the particular clinical entity.
- Development of aphthous ulcerations occur in up to 60% of the population of the United States. Ulcerations that persist beyond 2 weeks should be biopsied.
- Necrotizing sialometaplasia is a benign inflammatory condition of the minor salivary glands that has an appearance similar to that of malignancy. Biopsy is necessary to establish the correct diagnosis.

A plethora of conditions manifest themselves as tumor or tumor-like conditions that involve the oral cavity and oral pharynx. Conditions that more commonly appear and should be familiar to the otolaryngologist head and neck surgeon are presented in this chapter. For convenience, these nonmalignant entities are grouped into congenital, inflammatory/traumatic, and neoplastic conditions when formulating differential diagnoses.

Congenital Conditions

Torus

Torus palatinus and torus mandibularis represent developmental anomalies that usually present in the second decade of life and continue to grow slowly throughout life.[1] Tori present as mucosally covered bony outgrowths of the palate and mandible. Tori of the oral cavity occur in 3% to 56% of adults and are more common in women.[2,3] The tori of the palate are found only in the midline of the hard palate, whereas mandibular tori are found to involve only the lingual surface of the anterior mandible, primarily in the premolar region.[1,4] Tori are typically pedunculated or multilobulated, broadly based, smooth, bony masses (Fig. 95-1). They consist of dense lamellar bone with relatively small marrow spaces that do not involve the deeper cancellous bones of the mandible or palate. Patients with tori are usually asymptomatic, unless the torus interferes with denture placement or is repeatedly traumatized when the patient eats. In symptomatic patients, the tori can be treated by removing them from the underlying cortex with osteotomes or cutting burs. Recurrence is occasionally seen; however, malignant transformation has not been reported.

Lingual Thyroid

Approximately 90% of all ectopic thyroid tissue is associated with the dorsum of the tongue.[5] Presence of the lingual thyroid reflects the lack of descent of thyroid tissue during development. The lingual thyroid is found in the midline in the area of foramen cecum. The true incidence of lingual thyroid may never be known because this entity does not always result in clinical manifestations; however, studies involving neonatal screening for hypothyroidism revealed that approximately 1/18,000 to 1/100,000 live births were associated with ectopic thyroid tissue involving the tongue.[6,7] Although usually asymptomatic, the presence of lingual thyroid can be associated with hypothyroidism. Studies have shown that up to 70% of patients with a lingual thyroid also have hypothyroidism.[8] Other symptoms might also be related to the mass effect of the lingual thyroid and might cause airway obstruction and/or difficulties with swallowing. Patients may complain of dysphagia or the sensation of a lump in their throat. Less common complaints include dysphonia or bleeding. Symptoms may occur at times of increased metabolic demands such as growth spurts during adolescence or during pregnancy.[9] Malignant transformation is rare.[10] Treatment for hypothyroid patients involves thyroid replacement therapy, which may also reduce the size of the lingual thyroid and, in turn, reduce any obstructive symptoms. Treatment for symptomatic euthyroid patients typically involves surgical excision. A number of different approaches for surgical excision of lingual thyroid have been described and include transcervical routes by means of lateral pharyngotomy or transhyoid pharyngotomy, as well as transoral excision with use of the CO_2 laser.[11] One must be prepared to administer postoperative exogenous thyroid hormone replacement therapy because approximately 70% of patients will have the lingual thyroid as the only functioning thyroid tissue.[8]

Developmental Cysts

Congenital cystic conditions of the oral cavity and oropharynx are relatively rare. These usually include dermoid cyst, duplication cysts, and nasoalveolar cysts. Dermoid cysts are cystic masses found along embryonic fusion lines and form from epithelial rests.[12] Histologically, dermoid cysts are lined by squamous epithelium of the keratinizing variety. They contain elements of epidermal appendages including hair follicles, sweat glands, and connective tissue. Approximately 7% of

Figure 95-1. Torus palatinus.

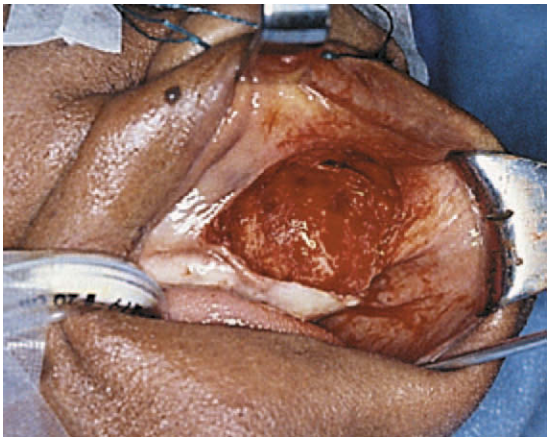

Figure 95-3. Remodeling of the maxilla associated with a nasoalveolar cyst.

Figure 95-2. Duplication cyst involving the tongue.

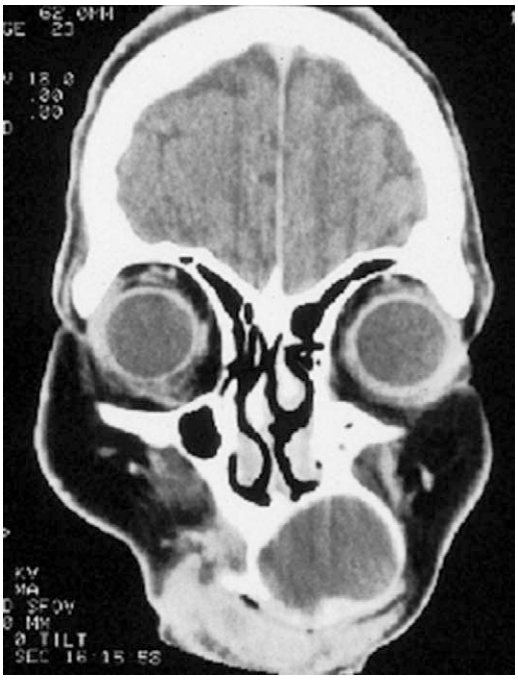

Figure 95-4. Sublabial approach to a nasoalveolar cyst.

dermoid cysts are found in the head and neck. Of these, 6.5% to 23% are found in the floor of the mouth.[13] Enteric duplication cysts are considered choristomas that contain elements of gastrointestinal mucosa.[14] The cysts are lined with stratified squamous and columnar epithelium. They are found anywhere along the digestive tract including the tongue and floor of the mouth. In the oral cavity, duplication cysts present at birth as an asymptomatic swelling involving the tongue and/or the floor of mouth (Fig. 95-2). As dermoid cysts and duplication cysts of the oral cavity enlarge, functional problems such as difficulties with deglutition, speech, and respiration can be expected to occur. Treatment for both dermoid cysts and duplication cysts requires complete excision of the cyst to include all epithelial components.

Nasoalveolar cysts are thought to originate from trapped nasal epithelium between the developing lateral and medial maxillary nasal processes. The manifestations of nasoalveolar cysts usually occur in adulthood as the cyst increases in size.[15] Patients typically present with swelling in the nasolabial area, which causes unilateral elevation of the nasal ala. Intraorally, a smooth, mucosal, covered mass in the gingival labial sulcus is seen. Remodeling of the anterior maxilla is also seen (Fig. 95-3). Treatment of nasoalveolar cysts involves complete excision, usually by a sublabial approach (Fig. 95-4). Care should be taken to repair any disrupted nasal mucosa such that the risk of postoperative oronasal fistula is diminished.

Inflammatory/Traumatic Conditions

Fibroma

Irritation fibroma is a common tumor-like condition of the oral cavity and oropharynx. It represents an inflammatory and fibrous hyperplastic response to chronic irritation or trauma. This entity should not be confused with true fibromatous neoplastic conditions such as fibrous histiocytoma, which is uncommon in the oral cavity and oropharynx. It is found in 1.2% of adults and has a 66% female predilection.[16] Although this condition can occur at any age, it usually becomes apparent during or after the fourth decade of life. The fibromas are usually solitary and seldom are larger than 1.5 cm. They characteristically present as an asymptomatic, sessile or pedunculated, firm mass involving typically the buccal mucosa and less commonly the labial, or tongue mucosa (Fig. 95-5). Histologically, fibromas are composed of dense and minimally cellular fascicles of collagen fibers and have a relatively avas-

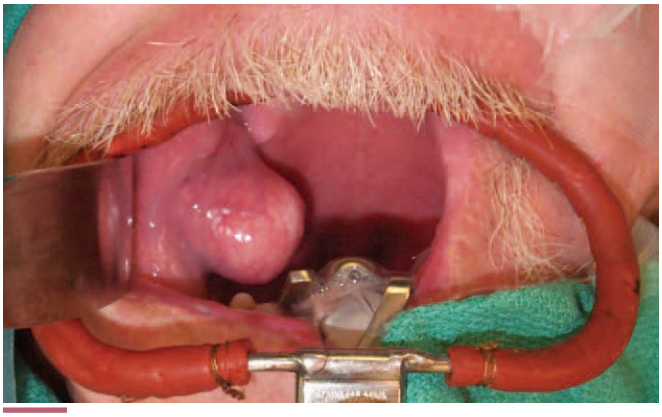

Figure 95-5. Fibroma involving the buccal mucosa.

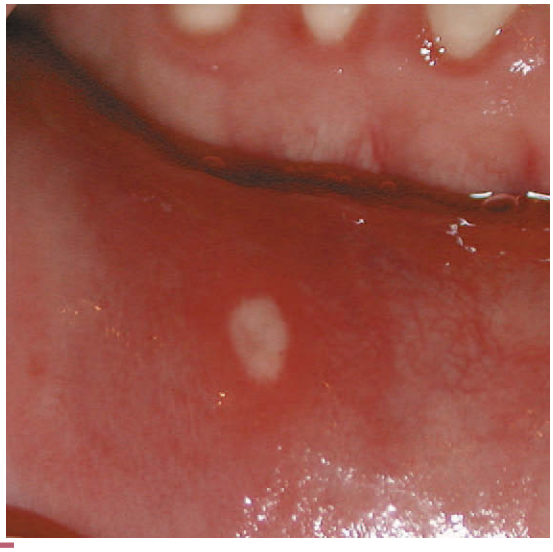

Figure 95-6. Aphthous ulcer with the characteristic erythematous halo surrounding a saucerized ulcer bed of fibrinoid necrotic debris.

cular appearance. Treatment is with conservative excision, and recurrence is unlikely, unless the precipitating trauma is continued or repeated.

Mucosal Ulcerations

Benign mucosal ulcerations can have the appearance similar to malignant lesions. Numerous local and systemic conditions can manifest themselves, in part, with benign mucosal ulcerations such as recurrent aphthous stomatitis, Crohn's disease, Behçet's syndrome, hematinic deficiency, or immunoincompetence. Likely the most common cause for benign ulcerations of the oral cavity and the oropharynx is recurrent aphthous stomatitis. Aphthae represent inflammatory mucosal ulcerations that occur in 20% to 60% of the U.S. population.[16] Development of aphthous stomatitis is thought to be related to cell-mediated mechanisms; however, the precise immunopathogenesis is unknown. Stress, local trauma, and/or allergy may play a contributory role in the development of aphthous ulcers. Characteristic features are a painful ulceration surrounded by an erythematous halo with a thin line of coagulation necrosis separating the halo from the saucerized ulcer bed of fibrinoid necrotic debris (Fig. 95-6). Immunoincompetent conditions do not produce the surrounding erythematous ring. Most aphthous ulcerations resolve without therapy within 10 days. Further workup for ulcerations that persist beyond 10 to 14 days should include tissue analysis. Further information pertaining to aphthous stomatitis can be found elsewhere in this text.

Figure 95-7. Pyogenic granuloma of the lateral tongue.

Pyogenic Granuloma

Pyogenic granulomas of the oral cavity and oropharynx can occur on any mucosal surface subject to acute or chronic trauma or infection.[17] Variants also arise in association with special events such as pregnancy or recent tooth extraction, resulting in epulis gravidarum and epulis granulomatosa, respectively. Most pyogenic granulomas involve the gingiva; however, other common sites include the labial mucosa, the buccal mucosa, and the tongue (Fig. 95-7). They typically present as raised or pedunculated lesions that remain less than 2.5 cm in size. They may bleed with minor trauma. Histologically, pyogenic granulomas consist of a rich profusion of anastomosing vascular channels in an edematous inflammatory and fibrosis stromal background. Lesions usually persist indefinitely, except for those associated with pregnancy. Treatment is by excision and removal of potential traumatic or infective factors.

Necrotizing Sialometaplasia

Necrotizing sialometaplasia is a self-healing, ulcerative, inflammatory reaction of unknown etiology. It has been postulated that it may be precipitated by local trauma that results in vascular compromise.[18] This entity typically arises from minor salivary glands and in 77% of cases involves the palate.[18] Most cases present with a painful ulceration and surrounding area of swelling that clinically stimulates a malignancy such as squamous cell carcinoma or mucoepidermoid carcinoma. Lesions are typically less than 2 cm. Histologic analysis is required to make the appropriate diagnosis. Light microscopy reveals lobar necrosis and sialadenitis mixed with squamous metaplasia of excretory ducts and acini. Pseudoepitheliomatous hyperplasia is usually seen in the associated surface epithelium, which may, due to sampling error, result in a pathologist reporting squamous cell carcinoma. Once definitively diagnosed, treatment is with supportive care because these lesions are self-limiting. Healing takes place within 3 to 6 weeks. Close follow-up during the healing process is necessary because necrotizing sialometaplasia can be found in conjunction with a malignancy.

Amyloidosis

Amyloidosis is a disorder that involves abnormal deposition of extracellular fibril proteins into tissues. Twenty-three different proteins have been identified in amyloidosis with each protein related to a particular clinical setting such as dialysis-associated amyloidosis (β_2-microglobulin), plasma cell disorders, (immunoglobulin light chains), or familial amyloidosis (transthyretin). The most common head and neck manifestation of amyloidosis is macroglossia (Fig. 95-8). Amyloid deposition can be such that the function of the tongue becomes limited, resulting in difficulties with speech and swallowing. The diagnosis is made by biopsy, which classically reveals intense green fluorescence also known as *apple green birefringence* with use of polarized light after Congo red staining. Treatment includes addressing the underlying cause of amyloid deposition if possible, as well as local excision in the case of

Figure 95-8. Amyloidosis of the tongue. Note the marked crusting and dryness of the exposed dorsum of the tongue.

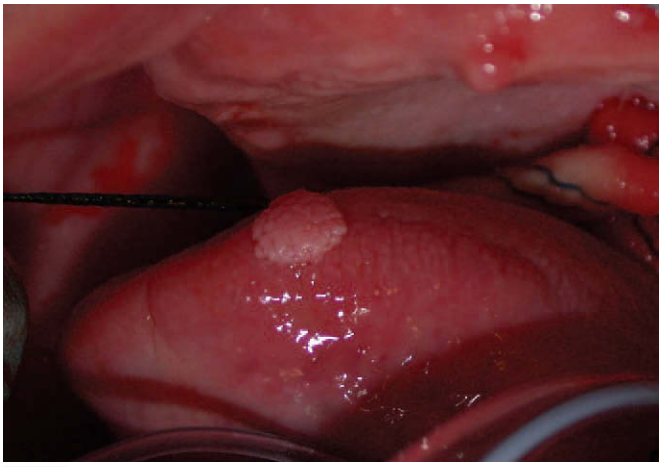

Figure 95-9. Squamous papilloma of the tongue.

macroglossia to include tongue reduction. Recurrences can be treated with further conservative resection.

Benign Neoplasms

Papilloma

Various unique squamous-derived entities of the oral cavity and oropharynx exist; however, one of the most frequently occurring conditions is squamous papilloma.[19] Approximately 4 out of 1000 adults in the United States have this condition of the oral cavity or oropharynx.[16] Squamous papillomas are most commonly associated with HPV-6 and HPV-11 virus subtypes.[19] Lesions typically present in adults and generally have a lower recurrence rate, are singular, and are less proliferative than squamous papillomas of other sites of the head and neck such as the larynx.[20] Development of precancerous proliferative verrucous leukoplakia within squamous papillomas is rare. Sites of occurrence typically involve the lingual, buccal, and labial mucosa, as well as the tongue (Fig. 95-9). Squamous papillomas typically present as a single, asymptomatic, soft, pedunculated mass with numerous finger-like projections at the surface. Histologically, the projections have fibrovascular cores and demonstrate a relatively narrow base. Treatment involves surgical excision or ablation with use of a CO_2 laser. Recurrence in the oral cavity or oropharynx is unlikely.

Figure 95-10. Granular cell tumor of the lingual dorsum.

Figure 95-11. Congenital epulis involving the maxillary gingiva.

Granular Cell Tumor

Granular cell tumors are commonly thought to be neural in origin. Granular cell tumors are usually diagnosed during or after the third decade of life. Although this entity can be found throughout the body, more than half of all cases occur in the oral cavity. Greater than a third of granular cell tumors involve the dorsum of the tongue. Other sites of occurrence include the soft palate, uvula, and labial mucosa.[16] Up to 15% of patients will have synchronous lesions. Granular cell tumors typically present as firm, painless, relatively immobile, sessile, nodular-appearing lesions less than 1.5 cm in greatest dimension (Fig. 95-10). Histologically, granular cell tumors show large polygonal, oval, or bipolar cells with abundant granular eosinophilic cytoplasm. Cells often appear in a ribbon pattern and extend to the surface epithelium and demonstrate pseudoepitheliomatous hyperplasia. The malignant variety of granular cell tumors represents approximately 1% of all cases. Surgical excision is the treatment of choice. Recurrence is less than 10%, even with a microscopically positive margin. Congenital epulis is the neonatal form of granular cell tumors. The congenital epulis is evident at birth and characteristically involves the maxillary gingiva (Fig. 95-11). Typically these unifocal growths measure no more than 2 cm, but they may interfere with feeding. Similar to the adult variant, treatment involves surgical excision, which can usually be performed at the bedside. Recurrence is rare.

Neurofibroma

Neurofibroma is the most common of the peripheral nerve neoplasms. The lesion is derived from a mixture of Schwann cells and perineural fibroblasts. Neurofibroma of the oral cavity and oropharynx is typically diagnosed in adolescents and young adults. The finding of multiple neurofibromas may be associated with von Recklinghausen's neurofi-

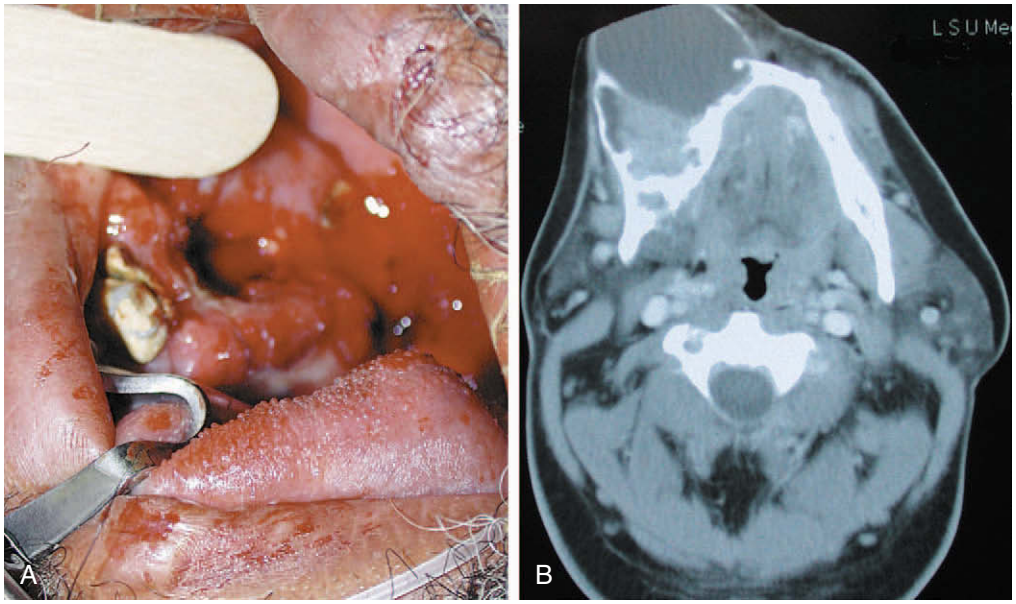

Figure 95-12. **A,** Ameloblastoma of the molar and ramus of the mandible. **B,** Bony infiltration and remodeling of the mandible as the result of ameloblastoma.

bromatosis (NF1). Approximately 70% of all cases of von Recklinghausen's neurofibromatosis involve the oral cavity, primarily the tongue. Solitary neurofibromas of the oral cavity usually involve the tongue, buccal, or labial mucosa[16] and present as soft, painless, slow-growing masses, but tender to pressure or palpation. Treatment ideally involves complete surgical excision. Solitary neurofibroma can be excised with relatively little risk of recurrence. Solitary neurofibromas rarely undergo malignant transformation into sarcoma; however, up to 15% of those with von Recklinghausen's neurofibromatosis develop a malignancy.

Lipoma

Lipoma is a relatively uncommon neoplasm of the oral cavity and oropharynx. Lipomas of the oral cavity and oropharynx usually occur after the third decade of life and present as a soft, slowly enlarging, mucosal-covered, smooth, painless mass. Lipoma is typically found in the buccal, lingual, or floor of mouth areas. Histologically, lipomas consist of mature adipocytes that are encapsulated and are typically clearly demarcated from surrounding tissues, although those that involve muscle can have an infiltrative appearance. Treatment of lipoma is surgical excision.

Hemangioma

Hemangioma of the head and neck is relatively common. Hemangioma of the oral cavity represents 14% of all hemangiomas.[16] Although usually present at birth with a rapid proliferative phase, they may become clinically evident later in life. They may be associated with a number of conditions including Sturge-Weber-Dimitri syndrome and von Hippel-Lindau syndrome. The lip is the most frequent site of hemangioma involving the oral cavity.[16] A mucosal hemangioma will present as a soft, painless mass that is red or blue. Hemangiomas are typically less than 2 cm in greatest dimension; however, they can become quite extensive to involve significant portions of the oral cavity and oropharynx to include the tongue. Hemangiomas tend to spontaneously regress over the years; however, there may be incomplete involution or associated fibrosis.[21] Hemangiomas that limit the form and function of the oral cavity and oropharynx are usually treated with conservative surgical excision. Recurrence or persistence is not unusual. Intralesional sclerosing agents, interferons, laser treatment, local and systemic steroids, and radiation have been reported as primary or adjunctive treatment with varying success.[21,22]

Ameloblastoma

Conditions of odontogenic origin can present as tumors or tumor-like conditions of the oral cavity. Ameloblastoma is the most common neoplasm of odontogenic origin. Ameloblastomas are thought to arise from rests of primitive dental lamina related to the enamel organ in alveolar bone. Patients are typically seen in the third decade of life with a painless mass involving the maxilla or mandible (Fig. 95-12A). In approximately 85% of cases, the mandible is involved, usually at the molar/ramus area.[23] Plain radiographic imaging usually reveals a unilocular or multilocular radiolucency. Cortical bone expansion can be seen (see Fig. 95-12B). Histologically, ameloblastomas are solid infiltrating tumors with a follicular or plexiform pattern, which exhibit an element of cystic change. Treatment for ameloblastoma is en bloc resection with at least 1-cm margins of normal-appearing tissue. The overall recurrence rate is 22%, with nearly half of all recurrences occurring within 5 years.[24] Lifelong follow-up is recommended. Malignant transformation can occur but is rare. Further information regarding ameloblastoma and odontogenic conditions can be found elsewhere in this text.

Pleomorphic Adenoma

Minor salivary glands are unencapsulated seromucinous glands located immediately beneath the mucosa throughout the oral cavity and oropharynx. Less than 10% of salivary gland tumors arise from minor salivary glands. Approximately 40% of tumors arising from minor salivary glands are benign.[25] Pleomorphic adenoma is the most frequently encountered benign tumor of minor salivary glands.[26] Other benign minor salivary gland tumors include canalicular adenoma, papillary cystadenoma, oncocytoma, and myoepithelioma. The most commonly occurring site of pleomorphic adenoma in the oral cavity is the hard palate (Fig. 95-13). Other presenting sites include the lip, buccal mucosa, alveolar ridge, floor of mouth, and tongue in decreasing order of frequency. Pleomorphic adenomas of the oral cavity tend to appear smooth and are relatively slow growing.

Treatment of pleomorphic adenomas of the oral cavity involves complete surgical excision. Unlike pleomorphic adenomas involving the parapharyngeal space, oral cavity pleomorphic adenomas are excised transorally. Because pleomorphic adenomas are encapsulated, complete excision makes recurrences rare. Excision typically involves both blunt and sharp dissection, although using the CO_2 laser as a cutting tool is also efficacious. Given their location in the oral cavity, intra-oral pleo-

Figure 95-13. Minor salivary gland pleomorphic adenoma of the retromolar trigone.

morphic adenomas can be identified before obtaining a relatively large size. Thus the resulting defect after excision can typically be addressed with local tissue rearrangement.

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CHAPTER NINETY-SIX

Malignant Neoplasms of the Oral Cavity

Richard O. Wein

James P. Malone

Randal S. Weber

Key Points

- Early detection of oral cancer directly results in improved survival after treatment.
- Tobacco use and habitual alcohol consumption synergistically increase the risk of developing oral carcinoma.
- For most presentations of cancer of the oral cavity, the risk of occult spread to the regional lymphatics exceeds 20% and warrants elective treatment of the regional lymphatics.
- Functional recovery after a significant oral cavity resection depends on adequate mobility and bulk of the soft tissue components and frequently requires free tissue reconstructive techniques.
- For patients with advanced-stage oral cavity carcinomas (overall stage III or IV), combined modality treatment with surgical resection of the primary, neck dissection to address the regional lymphatics, and postoperative radiation (or chemoradiation) therapy is the treatment of choice.

The topic of malignant neoplasms of the oral cavity is synonymous with a discussion of oral squamous cell carcinoma. The oral cavity is unique in that, unlike other anatomic regions of the upper aerodigestive tract, the routine detection of early-stage lesions is possible. However, given the relatively common presentation of other benign pathology within the oral cavity such as aphthous ulceration, delay in diagnosis can occur.

Perhaps more so than in other sites within the head and neck, primary surgical management represents the treatment of choice for oral cavity malignancies. In assessing the treatment strategy, the surgeon attempts to maximize locoregional control of the tumor while respecting the potential functional impact of a procedure on speech and swallowing. The appropriate selection of reconstructive techniques that assist appropriate wound healing while maximizing the patient's capacity for oral rehabilitation requires a broad knowledge and experience with the options available.

Etiology

Tobacco and alcohol consumption are considered the most common preventable risk factors associated with the development of oral cavity squamous cell carcinoma. In addition, this relationship is synergistic, with alcohol serving as a promoter for the carcinogenic effects of tobacco. When compared with nonsmokers, smoking confers a 1.9-fold risk to males and 3-fold risk to females for development of head and neck squamous cell carcinoma. The risk is directly proportional to the years spent smoking and the number of cigarettes smoked per day. Alcohol alone confers a 1.7-fold risk to males drinking 1 to 2 drinks per day compared with nondrinkers. This risk rises to more than 3-fold for heavy drinkers. Individuals who both smoke (two packs per day) and drink (four units of alcohol per day) are 35 times more likely to develop cancer when compared with controls.[1] The reported incident rates of developing head and neck cancer based on smoking status are higher in males than females, respectively (nonsmokers 24.4:4.8, former smokers 36.9:17.2, and current smokers 147.3:75.7); however, hazard ratios suggest smoking leads to a higher proportion of females (12.96 for females, 5.45 for males) eventually developing head and neck cancer with the same risk exposure.[2] Users of smokeless tobacco have a 4-fold increased risk of oral cavity carcinoma compared with nonusers.[3]

Tobacco is the leading preventable cause of death in the United States and is responsible for one out of every five deaths.[4] As of 1999, approximately one quarter of U.S. adults used tobacco products (25.7% of males and 21.5% of females).[5] The evidence supporting the benefit for head and neck cancer patients to cease smoking is compelling. In a study by Moore, 40% of patients who continued to smoke after definitive treatment for an oral cavity malignancy went on to recur or develop a second head and neck malignancy. For patients who stopped smoking after treatment, only 6% went on to develop a recurrence.[6] Induction of specific p53 mutations within upper aerodigestive tract tumors has been noted in patients with a history of tobacco and alcohol use.[7]

When smoking status in patients with head and neck squamous cell carcinoma is assessed, differences exist between the two populations (smoker vs. nonsmoker). Koch and colleagues noted that nonsmokers were represented by a disproportionate number of women and were more frequently at the extremes of age (younger than 30 or older than 85 years of age). Tumors from nonsmokers presented more frequently in the oral cavity, specifically within the oral tongue, buccal mucosa,

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Figure 96-1. Extensive floor of mouth squamous cell carcinoma extending to the mandible anteriorly.

Figure 96-2. Lower lip ulcerative squamous cell carcinoma extending toward the gingivobuccal sulcus.

and alveolar ridge. Smokers presented more frequently with tumors of the larynx, hypopharynx, and floor of the mouth (Fig. 96-1). Common genetic alterations such as loss of heterozygosity at 3p, 4q, and 11q13 and the overall number of chromosomal microsatellite (repeated base sequences) losses were significantly more likely in the tumors of smokers. In addition, the rate of p53 mutations was markedly increased in this group of patients.[8] Smoking and habitual use of alcohol have also been associated with p15 gene methylation.[9] Former smokers, defined as those individuals who had quit more than 10 years earlier, demonstrate a genetic profile more consistent with nonsmokers.[8] Additionally, multiple mesenchyme-associated, stroma-specific, genetic alterations may have a significant role in the development and progression of smoking-related head and neck cancers.[10]

In India and Southeast Asia, the product of the Areca catechu tree, known as a *betel nut,* is chewed in a habitual manner and acts as a mild stimulant similar to that of coffee. The nut is chewed in combination with lime and cured tobacco as a mixture known as a *quid.* The long-term use of the betel nut quid can be destructive to oral mucosa and dentition and has been demonstrated to be highly carcinogenic.[11] Another habit associated with oral malignancy is that of reverse smoking, where the lighted portion of the tobacco product is within the mouth during inhalation. The risk of hard palate carcinoma is 47 times greater in reverse smokers compared with nonsmokers.[12]

The human papillomavirus (HPV) is an epitheliotropic virus detected to varying degrees within samples of oral cavity squamous cell carcinoma. Infection alone is not considered sufficient for malignant conversion; however, results of multiple studies suggest a role of HPV in a subset of head and neck squamous cell carcinoma.[13]

Environmental ultraviolet light exposure has been associated with the development of lip cancer. The projection of the lower lip, as it relates to this solar exposure, has been implicated in the pathogenesis of squamous cell carcinomas arising on the vermilion border of the lower lip (Fig. 96-2).[14] Pipe smoking has also been associated with the development of lip carcinoma. Mechanical irritation, thermal injury, and chemical exposure are suspected etiologic factors contributing to lower lip cancer development in pipe-smoking patients.[15]

Other entities associated with oral malignancy include Plummer-Vinson syndrome (achlorhydria, iron deficiency anemia, and mucosal atrophy of the mouth, pharynx, and esophagus); chronic infection with syphilis; ill-fitting dentures; and long-term immunosuppression (30-fold increase with renal transplant). Although evidence linking HIV infection to squamous cell carcinoma of the head and neck is lacking, Kaposi's sarcoma may arise in the oral cavity.[16]

Molecular Biology

Tumor development represents the loss of multiple signaling mechanisms regulating the control of cell growth. After malignant transformation, the processes of replication (mitosis), programmed cell death (apoptosis), and the interaction of a cell with its surrounding environment are altered. Advances in molecular biology have allowed for the identification of many of the mutations associated with this transformation. Contemporary molecular analysis of tumors is providing insight into the processes of malignant transformation and tumor progression.

H-ras, a member of the ras gene family, encodes a plasma protein (p21), which has a role in the transduction of mitogenic signals to the intracellular environment. A synergism between H-ras and HPV is believed to play a role in the induction of squamous cell carcinoma. In human studies, 22% of oral squamous cell carcinomas expressed H-ras, whereas 11% expressed H-ras and HPV. All specimens of oral verrucous carcinoma that expressed H-ras (25%) demonstrated evidence of HPV DNA.[17]

HPV is a mucosotropic virus that has been closely associated with cervical carcinoma in women, such that HPV 16 and 18 are considered carcinogenic. In oral cavity specimens, variable detection has been reported with rates ranging from 19% to 78%.[18,19] Findings of HPV 16 within normal tissue at the margins of tumor specimens have suggested that infection is not a sole event preceding malignant transformation. Rather, it has been postulated that HPV may play a role in the early events of carcinogenesis. HPV oncoproteins E6 and E7 have the ability to bind and degrade tumor suppressor gene products of p53 and pRB, respectively. This binding can impair the capacity of the cell cycle to arrest for the repair of DNA damage and results in an accumulation of genetic changes assisting transformation.[13]

Smith and colleagues detected a significant increase in the presence of HPV DNA within oral cavity carcinoma samples (15%) compared with controls (5%). In addition, they noted that HPV (odds ratio [OR]-3.7) was a risk factor for carcinoma, independent of tobacco (OR-2.63) and alcohol use (OR-2.57).[20] Maden and coworkers noted an increased risk for oral cavity carcinoma with the presence of HPV 6 and HPV 16. Similar to Smith and colleagues, they also demonstrated HPV infection to be a risk factor, independent of age and tobacco and alcohol use.[21]

Costa and colleagues examined resectable oral cavity carcinomas for biomarkers predictive of chemosensitivity before primary surgical treatment. They found that tumors negative for glutathione S-transferase (GST-π) were more responsive to cisplatin and 5-fluorouracil than tumors that were GST-π-positive. They also noted that lack of bcl-2 expression was consistent with an improved 3-year disease-free survival. No relationship between p53 activity and chemotherapeutic response was observed.[22]

Overexpression of mutant p53 has been associated with carcinogenesis at multiple sites. Point mutations in p53 have been reported in up to 45% of head and neck carcinomas. Brennan and colleagues have evaluated the concept of primary site margin assessment of specimens on the basis of p53 staining to guide the need for further treatment.[23,24] Koch and others have noted that p53 mutation is a key event in the malignant transformation of greater than 50% of head and neck squamous cell carcinomas in smokers.[8]

Her2-Neu overexpression has been demonstrated in a subset of squamous cell carcinomas.[25] Expression of Her2-Neu and heat shock protein (HSP)-27 have been associated with regional treatment recurrence in patients with oral cavity and oropharyngeal carcinomas treated with primary radiotherapy.[26]

Koch's tumor progression model has demonstrated that 3p is a site of early loss of heterozygosity, 4q is a late event, and 11q13 is the site of the cyclin D1 gene. Reviews of the head and neck literature have suggested the role for p53, EGFR, TGF-α, and cyclin D1 in predicting clinical outcome for patients with squamous cell carcinoma.[27]

The Akt receptor has been correlated with the histologic progression of oral premalignant lesions to oral carcinoma. Massarelli and colleagues[28] demonstrated that phosphylated-Akt, when highly expressed, is associated with recurrence and shorter disease-free survival independent of a patient's overall staging.

Epidemiology

Oral cavity malignancies (excluding lip lesions) account for 14% of all head and neck cancers.[29] In a review (1985-1996) of the National Cancer Data Base (NCDB), patients diagnosed with an oral cavity cancer had a mean age at presentation of 64 years with a male predominance (60%). Squamous cell carcinoma (SCC) represented the majority of lesions (86.3%), and adenocarcinoma (5.9%), verrucous carcinoma (2.0%), lymphoma (1.5%), and Kaposi's sarcoma (1.5%) accounted for the remainder. At the time of diagnosis, 55% of patients had early-stage lesions (stage I-II). Patients 35 years old or younger were more likely to present with oral tongue SCC than older patients (76.1% vs. 33%) and less likely to present with a floor-of-mouth SCC (10.5% vs. 35.9%). Of note, the NCDB data did not reveal a poorer overall prognosis for those patients diagnosed at a younger age. In fact, younger patients demonstrated a better 5-year survival (63.7%) than older stage-matched patients (51% for 36 to 65 years of age and 47.6% for older than 65 years of age). Blacks and lower income patients more frequently presented with advanced-stage lesions. Five-year survival was found to be worse for males, blacks, and older patients (older than 65 years). Adenocarcinoma presented more commonly in women than men and was most frequently diagnosed on the hard palate.[30]

A study by Schantz and Yu[31] noted that the incidence for oral tongue carcinoma in patients younger than 40 years of age increased 60% from 1973 to 1984 and has since stabilized. During this same timeframe the incidence of carcinoma at all other oral cavity subsites remained constant or decreased.[32] The rise was related to patients born during the years 1938 to 1948. Despite this increase, the 5-year determinant survival of these patients was better than that for older individuals. Although the exact cause for the increase was considered unclear, etiologies of increased smokeless tobacco and marijuana use and human papillomavirus (HPV) infection were considered possible factors.[19]

Anatomy

Because of the pivotal role the oral anatomy has on articulation and deglutition, treatment of an oral malignancy can have a significant impact on a patient's quality of life. An understanding of the complex anatomic relationships among the salivary glands, maxilla, mandible, tongue function, and dentition are paramount to achieving satisfactory oncologic and functional results. The oral cavity extends from the vermilion border of the lip, posterosuperiorly to the hard palate–soft palate junction, inferiorly to circumvallate papillae (linea terminalis), and laterally to the anterior tonsillar pillars. It is divided into seven specific subsites. These subsites are the lips, dentoalveolar ridges, oral tongue, retromolar trigone, floor of mouth, buccal mucosa, and hard palate (Fig. 96-3).

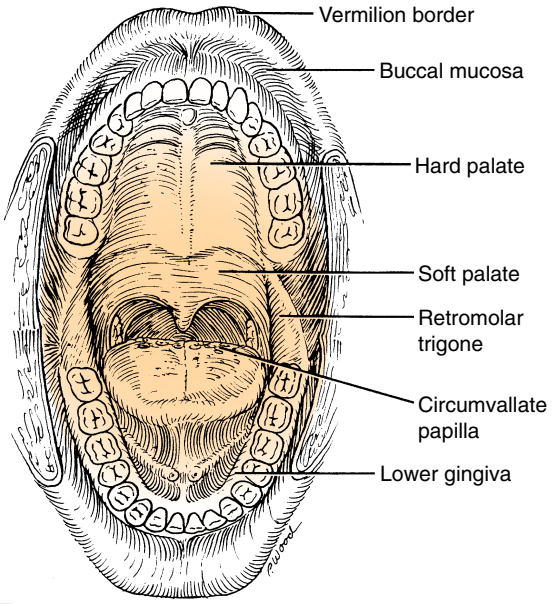

Figure 96-3. Overview of the oral cavity demonstrating the posterior boundary at the hard palate–soft palate junction and the location of the retromolar trigone relative to the inferior alveolar ridge.

The local, regional, and distant spread of oral cavity malignancies is dependent on the course of the neurovascular anatomy, lymphatic pathways, and the fascial planes of the head and neck. The latter serves as a barrier to the direct spread of tumor and can influence the pattern of local and regional lymphatic spread. In addition, perineural and angioinvasion can act as a conduit for the spread of head and neck malignancies. When present, these histologic findings can have a profound impact on the patient's prognosis and long-term survival.[33,34] Patients previously treated with either surgery or radiation for an oral malignancy may demonstrate atypical patterns of local invasion and regional spread of tumor.[35] A brief discussion of the vascular and lymphatic anatomy pertinent to the oral cavity while reviewing the unique attributes of the oral cavity subsites is necessary before considering diagnostic and treatment options.

Arteriovenous Anatomy

The arterial supply to the oral cavity includes multiple contributions from the external carotid artery. The lingual artery provides the majority of the vascular supply to the oral tongue and tongue base. Identification of the artery within the neck requires the exposure of the floor of the submandibular region. The artery is found deep to the hyoglossus muscle and requires the division of the muscle for maximal exposure. Superficial to the hyoglossus and deep to the mylohyoid muscle is the hypoglossal nerve and lingual veins (Fig. 96-4). An understanding of this relationship can aid in the localization of the artery when necessary for microvascular reconstruction or selective ligation. The vein, which closely approximates the nerve in this region, is prone to injury during dissection and necessitates care when attempting to obtain hemostasis if hypoglossal nerve injury is to be avoided.

The hard palate blood supply is derived from the greater palatine and the superior alveolar arteries. After branching off the descending palatine artery at the greater palatine foramen, in the region medial to the second maxillary molar, the artery runs anteromedially within the

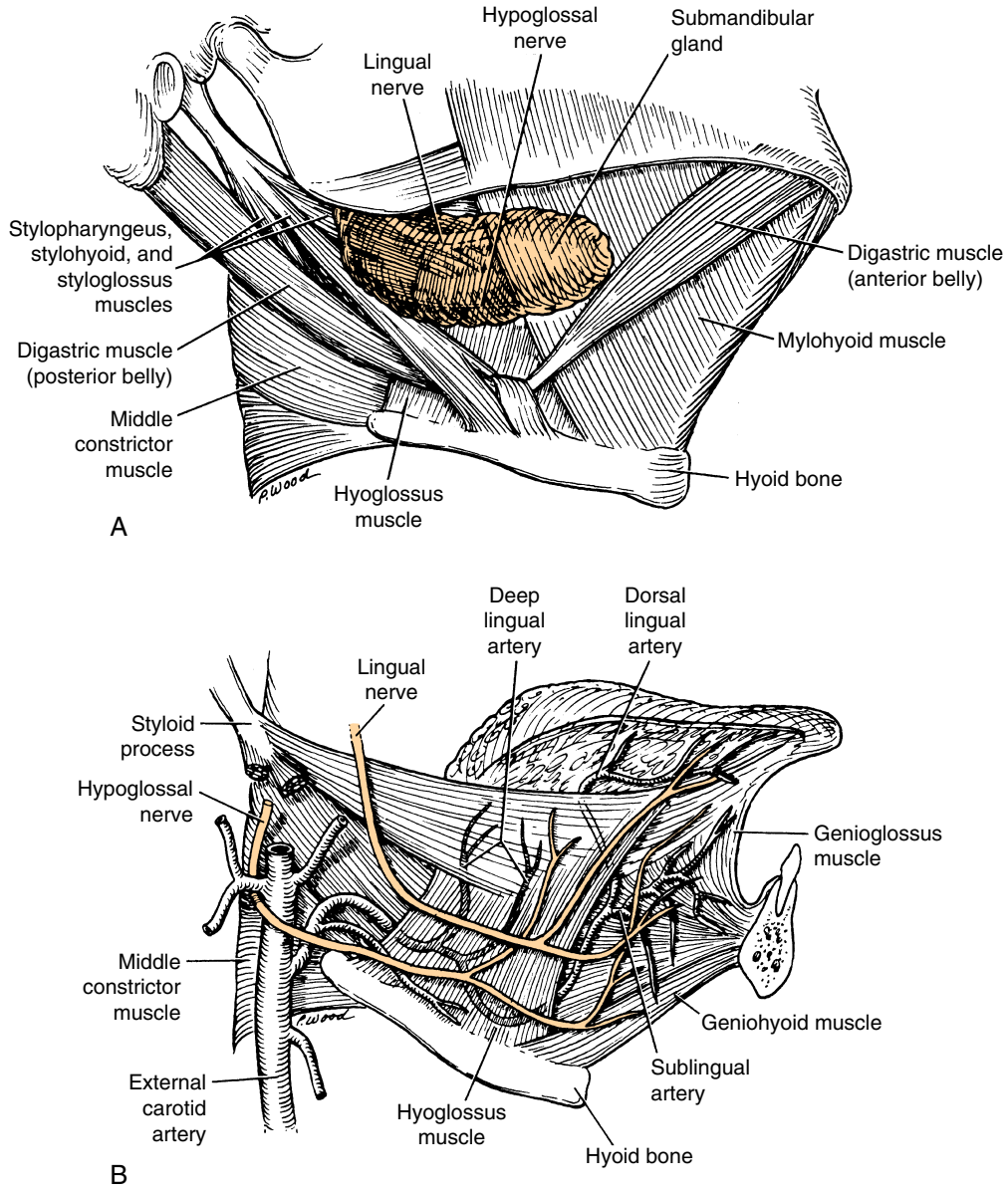

Figure 96-4. **A,** Musculature of the submandibular region and relationship of the lingual and hypoglossal nerves to the submandibular gland. **B,** Deeper anatomy of the submandibular fossa. The hypoglossal nerve runs deep to the mylohyoid muscle and superficial to the hyoglossus muscle. The lingual artery runs deep to the hyoglossus muscle and ascends to divide into deep and dorsal lingual arteries and the sublingual artery.

soft tissue of the hard palate (Fig. 96-5). The venous drainage is to the pterygoid plexus and subsequently to the internal jugular venous system. The superior alveolar arteries (anterior, middle, posterior) arise as terminal branches after the transition of the internal maxillary artery to sphenopalatine artery at the pterygopalatine fossa. These arteries provide blood supply to the maxillary gingiva, alveolar ridge, and dentition.

The facial artery crosses over the lateral aspect of the mandible approximately 1 cm anterior to the ascending ramus and courses toward the oral commissure where it gives rise to the labial arteries. These paired vessels are readily apparent during lip-splitting procedures and anastomose in the midline to create a vascular ring.

The primary vascular supply to the mandible and the lower dentition is from the inferior alveolar artery. Blood supply from the mandibular periosteum becomes more important with advancing age. The inferior alveolar artery, vein, and nerve enter the mandibular foramen along the medial aspect of the ramus of the mandible. Before their entry into the foramen, both the nerve and artery send off branches that extend anteriorly to supply the mylohyoid muscle.

The posterior floor of the mouth and retromolar trigone have an arterial supply and venous drainage similar to that of the anterior tonsillar region. The ascending pharyngeal and lesser palatine vessels contribute to the vascularity that may be encountered with surgical procedures at this site.

Subsites of the Oral Cavity

Lips

The lips represent a transition from external skin to internal mucous membrane that occurs at the vermilion border. The underlying musculature of the orbicularis oris, innervated by the facial nerve, creates a circumferential ring that allows the mouth to have a sphincter-like function. The sensation for the upper lip is supplied by the infraorbital nerve (CN V_2), whereas the lower lip is provided by the mental nerve

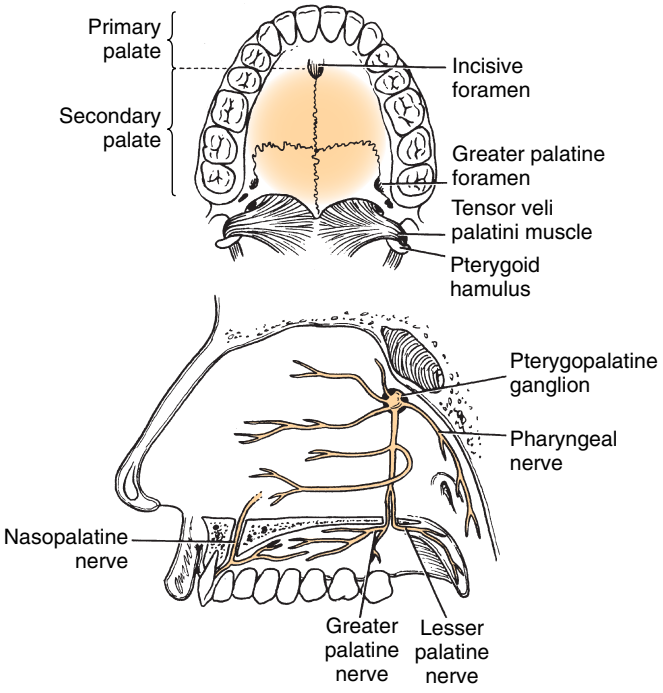

Figure 96-5. Primary and secondary portions of the hard palate. The relationship of the hard palate to the course of palatine nerves is important to consider when perineural invasion is suspected with squamous cell carcinomas or minor salivary gland malignancies in this region.

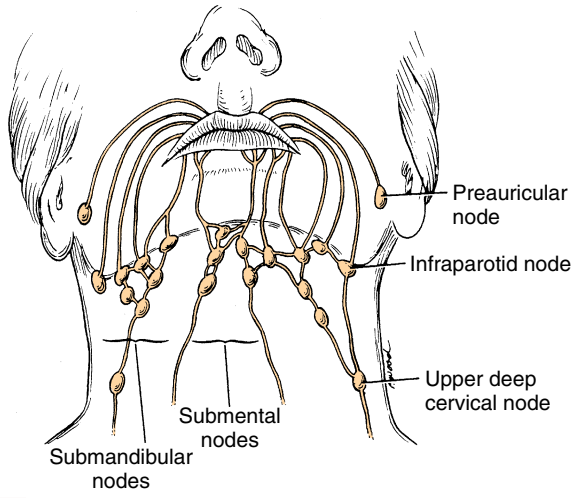

Figure 96-6. Lymphatic drainage pattern for the upper and lower lips.

(CN V_3). Lymphatics from both the upper and lower lips drain primarily to the submandibular lymph nodes, yet midline lower lip lesions may present with submental lymphatic spread. In addition, the upper lip may drain to preauricular, infraparotid, and perifacial lymph nodes (Fig. 96-6).

Alveolar Ridge

The lateral aspect of each alveolar ridge is represented by the mucosal sulcus created by the transition of tissue to buccal mucosa. On the lower alveolus, the medial margin is marked by the transition to the floor of the mouth and, on the upper alveolus, the transition is the horizontal orientation to the hard palate. The posterior margin of the lower alveolus is the ascending portion of the ramus of the mandible; whereas it is the superior aspect of the pterygopalatine arch for the upper alveolus. The close approximation of mucosa to underlying bone assists early bone invasion for malignant tumors in this region.

Oral Tongue

The oral cavity portion of the tongue is defined as that portion anterior to the linea terminalis. The tongue is composed of four intrinsic and four extrinsic muscles separated at the midline by the median fibrous lingual septum. The extrinsic muscles originate outside the substance of the tongue and include the genioglossus, hyoglossus, styloglossus, and palatoglossus. Of these, the genioglossus, which functions to depress and protrude, provides the majority of the bulk to the tongue. The paired intrinsic muscles of the tongue (superior-inferior longitudinal, transverse, and vertical) lie superficial to the genioglossus and function to alter the overall shape of the tongue. These muscles run with the tongue in three different orientations. This lack of distinct planes between muscles can allow for a diffusely infiltrating pattern of tumor growth. All of the musculature of the tongue derives its innervation via the hypoglossal nerve with the exception of the palatoglossus, which is supplied by a pharyngeal branch of the vagus nerve. The general sensory innervation of the anterior two thirds of the tongue is provided by the lingual nerve. It arises deep to the lateral pterygoid muscle, spirals from lateral to medial around the submandibular duct, and divides into several branches that lie in the submucosa of the oral tongue. The special sensory innervation of the oral tongue for taste is provided by the chorda tympani nerve (CN VII) that travels to the anterior tongue along with the lingual nerve. In contrast, both functions are performed by the glossopharyngeal nerve for the base of tongue.

The lymphatic drainage of the oral tongue varies by the region within the tongue. The tip drains preferentially to submental nodes, whereas the lateral tongue drains primarily to the levels I and II (Fig. 96-7). However, it is important to note that a defined lymphatic pathway from the lateral tongue does exist and drains directly to the level III/IV nodal group. The base of the tongue drains to the upper cervical lymphatics. The lack of anastomoses between the anterior tongue lymphatics results in lateralized oral tongue lesions tending to drain ipsilaterally. This is not the case with base-of-tongue lesions where crossover and bilateral cervical lymphatic spread may readily occur.

Retromolar Trigone

This region is represented by the mucosa overlying the ascending ramus of the mandible toward the coronoid process. It is continuous with the buccal mucosa laterally and the anterior tonsillar pillar medially. The superior extent is the maxillary tuberosity and the anterior margin is the posterior aspect of the second mandibular molar. The same considerations that were true for alveolar lesions exist for this anatomic site, given the close approximation of mucosa to the underlying mandible. Lower lip paresthesia may be an indication of perineural invasion at the level of the mandibular foramen with these lesions. The sensation to this region is provided by the lesser palatine nerve and branches of the glossopharyngeal nerve. It is the presence of CN IX that causes patients with lesions within this area to present with referred otalgia. The primary lymphatic drainage for this region is to the upper cervical-jugulodigastric nodal group (Fig. 96-8).

Floor of Mouth

The floor of mouth is a mucosal surface bordered by the oral tongue and alveolar ridge laterally and anteriorly. The posterior margin is the anterior tonsillar pillar. The lingual frenulum divides the region into two oval spaces. The mylohyoid and hyoglossus muscles provide the structural support for contents of the space. The significance of the floor of mouth comes from the anatomy that the region overlies. Hypoglossal or lingual nerve dysfunction may be the presenting complaint for patients with lesions in this portion of the oral cavity. The sublingual gland is vulnerable to direct invasion from lesions in this region. A branch of the lingual nerve provides sensation for the floor of mouth. The lymphatic drainage of the anterior aspect of this space may cross to contralateral submental-submandibular nodes, whereas

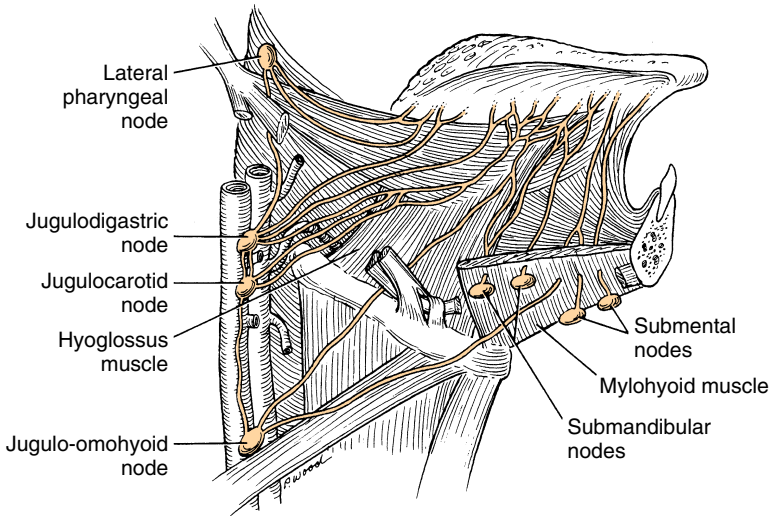

Figure 96-7. Lymphatic drainage pattern of the oral tongue, base of tongue, and floor of mouth.

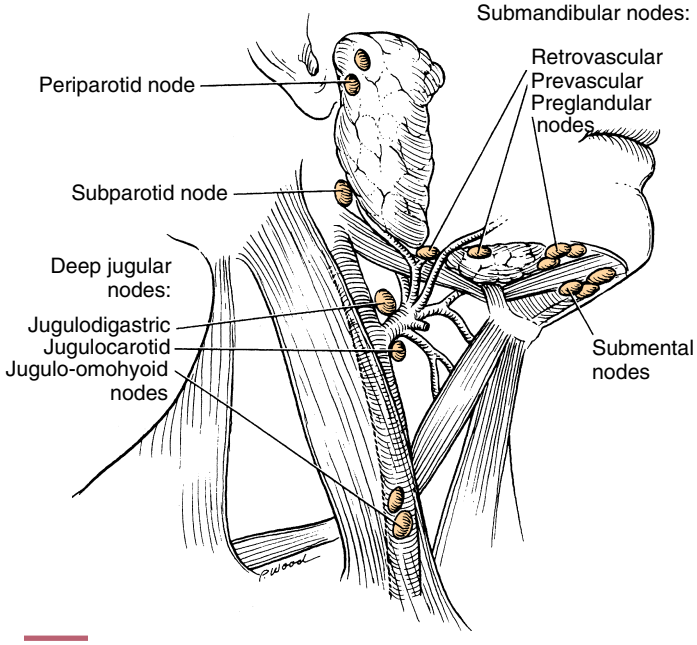

Figure 96-8. Lymphatic regions of the upper neck.

the posterior portion of the space tends to drain to ipsilateral upper cervical lymph nodes.

Buccal Mucosa

This surface extends from the posterior aspect of the lip to the alveolar ridges medially and the pterygomandibular raphe posteriorly. The parotid duct orifice is located next to the second maxillary molar after it exits the parotid and pierces the buccinator muscle. The sensation is provided by branches of the trigeminal nerve (CN V_2 and CN V_3). The lymphatics of this region drain preferentially to submental and submandibular lymph nodes.

Hard Palate

The hard palate has the maxillary alveolar ridges as anterior and lateral margins and the soft palate as a posterior border. Invasion through the hard palate results in extension of tumor into the nasal cavity or maxillary sinus. Infrastructure maxillectomy is frequently required for invasive lesions. A prosthetic obturator or flap reconstruction is necessary to re-establish oral competence and avoid hypernasal speech. The nasopalatine nerve (CN V_2) provides sensation to the region. Most of the lymphatic drainage from this site is to the upper cervical lymphatics or lateral retropharyngeal nodes.

Pathology

Certain histopathologic findings have significant implications on treatment. Tumor thickness, in particular with oral tongue carcinoma, has been the subject of many reports. Tumor thickness has been shown to have a direct relationship to the incidence of regional metastatic spread and survivorship.[36] The degree of differentiation and the presence of vascular or perineural invasion have important prognostic implications and may warrant the use of postoperative radiation therapy.

Premalignant Lesions

A discussion of the premalignant lesions of the oral cavity requires a review of the definitions commonly used in describing the gross and histologic appearance of these growths.

Leukoplakia is white, mucosal-based keratotic plaque that cannot be wiped free from the underlying tissue. This is a clinical term without a definitive histologic definition. Leukoplakic lesions may demonstrate parakeratosis, hyperkeratosis, and acanthosis on histologic examination. Paradoxically, an increased risk of malignant transformation of leukoplakic lesions is seen more commonly in nonsmokers compared with smokers. If a leukoplakic lesion is associated with an area of dysplasia (in 1% to 3% of all lesions), the risk of progression to malignancy increases seven-fold. Banoczy followed 670 patients with leukoplakic lesions for 3 years and noted that 31% of lesions disappeared, 30% improved, 25% experienced no change, and 7.5% demonstrated local spread. Only 6% of lesions demonstrated eventual progression to squamous cell carcinoma.[37] Syphilitic leukoplakias seen in tertiary syphilis have a higher reported rate of malignant transformation.[38]

Erythroplakia is a red mucosal plaque that does not arise from any obvious mechanical or inflammatory cause and persists after removal of possible etiologic factors. The associated risk for progression to carcinoma is significantly greater than that for leukoplakic lesions. Shafer and Waldron[39] resected erythroplakic lesions in 58 patients and found that 91% had evidence of invasive, carcinoma in situ, or severe dysplasia within specimens.

Submucosal fibrosis, most frequently encountered in individuals who chew betel nut, is associated with poor oral hygiene, advanced periodontitis, and oral carcinoma. The buccal mucosa becomes thickened and the entire cheek becomes fibrotic, resulting in trismus. Resection of tumors arising in the buccal mucosa in patients with submucosal fibrosis can be challenging and reconstruction can be complicated by wound breakdown and poor healing.

Lichen planus, in particular the erosive subtype, has also been associated with the development of oral carcinoma. The etiology of

lichen planus is unknown. T-cell lymphocyte infiltration is noted in this lesion, yet the development of lichen planus is not typically associated with immunologic disorders. The typical patient is a female in the fourth decade of life. Lesions demonstrate a lacy pattern of white striae. Atrophic lesions are red and smooth, whereas erosive lesions have depressed margins and are covered by a layer of fibrinous exudate. An estimated 1% risk of malignant change over 10 years has been reported.[38]

Dysplasia is the abnormal maturation and differentiation of mucosal epithelium with features of an increased nuclear-to-cytoplasmic ratio, loss of polarity, increased mitoses, and loss of intercellular adherence. Dysplasia is graded as mild, moderate, and severe.

Verrucous hyperplasia is a histologic finding that appears similar to verrucous carcinoma yet differs from the malignant form in that it does not invade the lamina propria.

Necrotizing sialometaplasia, although appearing clinically ominous, is benign. The typical feature is a butterfly-shaped area of ulceration at the junction of the hard and soft palate in the region of the palatine foramen. The etiology of this clinical lesion is necrosis of minor salivary acini usually secondary to localized pressure injury. This may be seen in the scenario of a poorly fitting or overused denture.

Squamous Cell Carcinoma and Variants

Several variants of squamous cell carcinoma exist and may be encountered in the oral cavity.

Sarcomatoid squamous cell carcinoma demonstrates a heterogeneous appearance with spindle-shaped cells interwoven with squamous cells. The cytologic behavior of this variant is considered aggressive with a reported metastatic rate of 37%.[40] Basaloid carcinoma is also considered a high-grade variant with reported 64% incidence of regional metastases and 44% incidence of distant metastases, and it is associated with 38% mortality at 17 months.[41] However, one report notes that when clinical T and N staging are matched, the 5-year disease-free survival associated with oral basaloid carcinoma is similar to that of poorly differentiated and moderately differentiated oral carcinomas.[42]

A thick zone of nonproliferating and nonkeratinizing cells distinguishes verrucous carcinoma histologically. The typical presentation is on the buccal mucosa (50%). It is considered a low-grade variant of squamous cell carcinoma and is exophytic in appearance. It has the capacity to invade locally yet carries a low risk of regional spread. Traditionally, this lesion has been considered to be "radioresistant" and surgical excision has been the treatment of choice.

Other Pathologies

Additional pathologies to consider in the differential diagnosis of oral cavity lesions include pyogenic granuloma, pseudoepitheliomatous hyperplasia, lymphoma, minor salivary gland tumors, and sarcomas.

The most common minor salivary gland malignancies are adenoid cystic carcinoma, mucoepidermoid carcinoma (low and high grade), polymorphous low-grade adenocarcinoma, and adenocarcinoma. They may present as a painless, slow-growing, submucosal mass at the junction of the hard and soft palate. Adenoid cystic carcinoma can present with perineural invasion that can extend within the greater palatine nerve to the pterygopalatine ganglion and ascend to the skull base.

Sarcomas of the oral cavity usually arise in the mandible or hard palate and include osteosarcoma (Fig. 96-9), chondrosarcoma, malignant fibrous histiosarcoma, rhabdomyosarcoma, and liposarcoma. Patel and colleagues demonstrated a 5-year local control rate for head and neck osteosarcoma of 78% and overall survival of 70%. Patients presented with osteosarcoma within the maxilla and mandible with approximately equal frequency, 45% to 41%, respectively. Surgery was performed in all patients, and neoadjuvant chemotherapy was used in 68% of patients. Positive surgical margins were found to be the only significant negative predictor with respect to disease-specific survival.[43]

Kaposi's sarcoma (KS) is the most common HIV-associated malignancy. The head and neck is the site for 63% of all presentations. KS may present as a mucosal or cutaneous lesion with a nodular or macular appearance and most commonly occurs on the hard palate. Despite being considered an incurable disorder, a variety of treatment options that may offer remission for limited disease are available. Local therapies include radiation, intralesional injection of chemotherapy, cryotherapy, alitretinoin gel, laser therapy, and surgical excision. Systemic chemotherapy is reserved for advanced disease.[16]

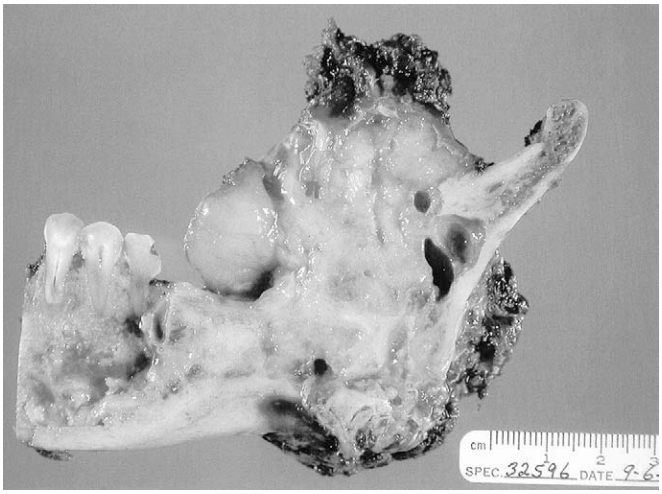

Figure 96-9. Osteosarcoma specimen of the right hemimandible.

Desmoplastic neurotrophic melanoma is a nonpigmented lesion of the lower lip that presents as an ulceration and has a high incidence for perineural invasion. Mucosal melanoma typically presents as a pigmented lesion of the oral cavity that may be associated with preexisting melanosis. Pigmented lesions of the oral cavity should be considered for biopsy to exclude this diagnosis.[44]

Diagnostic Evaluation

History and Physical Examination

A detailed history and physical examination are critical to the comprehensive evaluation of all head and neck cancer patients. When evaluating a patient for an oral lesion, inquiries into changes in the fit of a preexisting denture, otalgia, trismus, oral-dental pain, bleeding, halitosis, weight loss, dysphagia, odynophagia, dysarthria, and facial numbness should be made.

Patients should be questioned about specific medications, allergies, medical diagnoses, and previous surgical interventions. This information can be critical when formulating a treatment plan tailored to a patient's comorbidities. In addition, a detailed history of the patient's tobacco and alcohol use should be obtained.

The head and neck physical examination should allow for accurate staging of the tumor, assess the patient's functional capacity before treatment, and include a careful search for synchronous upper aerodigestive tract cancers. The physician should evaluate the dimensions of the index lesion and the potential anatomy involved by direct spread of tumor (Fig. 96-10). The lesion should be palpated to assess for fixation to the underlying periosteum suggesting potential mandibular or maxillary involvement. Determination of midline extension, regional lymphatic spread, and the need for reconstruction should be considered. The appropriateness of specific donor sites for free and/or pedicled flap reconstruction should also be assessed.

At the initial evaluation, if tissue pathology has not been previously obtained, a punch biopsy of the perimeter of the primary tumor and/or FNA (potentially ultrasound-guided) of suspected regional metastases should be performed. If the patient underwent biopsy at an outlying site before consultation, the specimen should be obtained and reviewed with the pathologist at the surgeon's facility to confirm the tissue diagnosis.

For patients with imaging already performed, films are reviewed for the extent of the primary disease and regional lymphadenopathy. Film quality, date of imaging, and need for supplemental imaging should be assessed. Before initiating treatment, the patient should be presented at a multidisciplinary tumor conference with representation

Figure 96-10. Tongue deviation to the right with atrophy suggestive of cranial nerve XII involvement by a floor-of-mouth cancer with right submandibular lymphadenopathy noted at pretreatment evaluation.

by surgeons, radiation oncologists, medical oncologists, and reconstructive surgeons for a discussion of available treatment options.

Future screening for oral cancer may be possible with outpatient biomarker laboratory assays. St. John and colleagues[45] have described the use of an assay for salivary interleukin (IL)-8 and serum IL-6 with promising results in patients with oral cavity and oropharyngeal carcinoma.

Preoperative Assessment

Obtaining information that either confirms or alters the strategy of the operative intervention and assesses the patient's overall readiness for surgery is necessary. Preoperative evaluation depends on the patient's age and comorbidities. In most instances an electrocardiogram, chest x-ray, and basic laboratory profile should be obtained. Patients with a history of alcohol abuse should have a liver profile performed. For patients with significant comorbidities, the patient's primary care physician or cardiologist should be included in the preoperative risk assessment.

Imaging to assess the primary extent of tumor and cervical lymph nodes includes either computed tomography (CT) or magnetic resonance imaging (MRI). CT is best for demonstrating cortical bone erosion and lymph node metastases. MRI is favored for demonstrating soft tissue invasion by tumor and extension into medullary bone. A Panorex may be obtained preoperatively in patients with suspected mandibular invasion and can assist dental evaluation. Dentascan imaging, using a dental CT-based software program, can be helpful in assessing the likelihood of mandibular invasion, with a reported sensitivity of 95%.[46] Goerres and colleagues noted the assessment of cortical invasion of the mandible was best assessed by conventional contrast-enhanced CT (as well as the CT component of PET-CT) with a sensitivity of 100% and accuracy of 97%.[47] The extent of imaging is frequently driven by physician preference and the complexity of the presenting lesion. Patients with T_1 lesions, without clinical lymphadenopathy, may not require extensive imaging to aid operative decision making.

Newer imaging modalities such as positron emission tomography (PET), PET-CT, single photon emission computed tomography (SPECT) scanning have been used to stage patients with head and neck cancer, but their role in preoperative assessment is not uniform and continues to evolve. Assessment for distant metastases may be performed using one of these modalities or via CT of the chest with contrast. Suspicion of distant metastases may require CT-guided biopsy for confirmation. Patients with distant metastases are not typically considered optimal candidates for curative treatment and may be better served by exploring palliative care options while preserving maximal quality of life.

Preoperative Interventions

Anticipating the nutritional needs of patients may prevent an extended need for hospitalization or treatment breaks during postoperative radiation. Malnutrition in the perioperative period can predispose patients to wound complications. Preoperative consultation for gastrostomy tube placement should be considered for those patients in which the ability to take oral nutrition is compromised before surgery or anticipated to extend for a prolonged period of time postoperatively. For those requiring postoperative radiation therapy, mucositis can result in a delay in the normal resumption of oral intake for several weeks to months.

In addition, dental evaluation is essential for patients with poor dentition and those who may require radiation as part of their treatment. Prosthodontic evaluation is indicated for those who will undergo maxillectomy and require a surgical obturator.

For patients with the potential for significant speech and swallowing impairment postoperatively, consultation and counseling with a speech-language pathologist can aid in long-term rehabilitation.

Endoscopy

Panendoscopy including bronchoscopy, esophagoscopy, and direct laryngoscopy has been advocated for the preoperative assessment of head and neck cancer patients. Given that the reported risk of harboring synchronous second lesion is between 5% and 10% in newly diagnosed patients, some consider panendoscopy necessary. Others advocate direct laryngoscopy but reserve performing esophagoscopy and bronchoscopy in symptomatic patients (with pretreatment dysphagia, odynophagia, cough, and/or hemoptysis) or if the preoperative thoracic imaging (chest x-ray or CT) is abnormal. If a percutaneous endoscopic gastrostomy tube placement is planned before definitive surgery, evaluation of the esophagus can be deferred to that procedure. Alternatively, a preoperative barium swallow can serve as a screening tool to exclude a second primary tumor; however, false-negative findings associated with the technique can occur. The extent of investigations for excluding second primary tumors is individualized according to physician preferences and the needs of an individualized patient.

Staging

Staging for oral cavity malignancies is defined by the American Joint Committee on Cancer (AJCC)[48] and follows TNM (primary Tumor, regional Nodal metastases, distant Metastasis) staging format (Table 96-1).

Histopathologic findings have been shown to have prognostic significance. Tumor characteristics such as keratin production, level of differentiation, nuclear appearance, mitoses, and host factors such as inflammation, desmoplastic reaction, patterns of invasion, and vascular invasion have been examined as an adjunct to clinical staging for predicting outcome. Nevertheless, staging remains based on clinical examination and diagnostic imaging.

Prognosis

Several studies examining the prognostic implications of primary tumor pathology that have been published are briefly reviewed.

Patients with tumors that display "pushing" margins (when the peripheral invasive margin is assessed as it relates to the surrounding soft tissue) as opposed to "infiltrative" growth patterns have better outcomes.[49] In addition, the depth of invasion of oral squamous cell carcinoma and its relationship to the risk of regional metastasis and 5-year survival has been examined. For lesions with a depth of invasion less than 2 mm, 13% of patients demonstrated regional metastases and a 95% 5-year survival was noted. For lesions with a 2- to 9-mm depth of invasion, 46% of patients had regional metastases and the 5-year survival rate decreased to 85%. When depth of invasion increased to

Table 96-1

American Joint Committee on Cancer Staging

Primary tumor

T_X	Unable to assess primary tumor
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_1	Tumor <2 cm in greatest dimension
T_2	Tumor >2 cm and <4 cm in greatest dimension
T_3	Tumor >4 cm in greatest dimension
T_4 (lip)	Primary tumor invading cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (e.g., nose, chin)
T_{4a} (oral)	Tumor invades adjacent structures (e.g., cortical bone, into deep tongue musculature, maxillary sinus) or skin of face
T_{4b} (oral)	Tumor invades masticator space, pterygoid plates, or skull base or encases the internal carotid artery

Regional lymphadenopathy

N_X	Unable to assess regional lymph nodes
N_0	No evidence of regional metastasis
N_1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N_{2a}	Metastasis in single ipsilateral lymph node, >3 cm and <6 cm
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, all nodes <6 cm
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, all nodes <6 cm
N_3	Metastasis in a lymph node >6 cm in greatest dimension

Distant metastases

M_X	Unable to assess for distant metastases
M_0	No distant metastases
M_1	Distant metastases

TNM staging

Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
Stage IVa	T_{4a}	N_0	M_0
	T_{4a}	N_1	M_0
	T_{1-4a}	N_2	M_0
Stage IVb	Any T	N_3	M_0
	T_{4b}	Any N	M_0
Stage IVc	Any T	Any N	M_1

From American Joint Committee on Cancer. *American Joint Committee on Cancer Staging Manual.* 6th ed. Chicago: AJCC; 2002.

Table 96-2

Observed Survival by Year per Stage for Oral Cavity Carcinoma, 1985-1991

Observed % Survival by Stage	Year Postdiagnosis 1	2	3	4	5
I	91.6	80.6	72.0	66.1	59.8
II	87.0	69.6	59.7	53.0	46.3
III	76.7	58.1	48.7	41.6	36.3
IV	60.2	38.4	30.9	26.5	23.3

Modified from Greene FL, ed. *American Joint Committee on Cancer Staging Manual.* 6th ed. New York: Springer Verlag; 2002.

greater than 9 mm, the risk of lymph node metastasis increased to 65% and the 5-year survival decreased to 65%.[50]

Loss of cadherin expression (E-cad and P-cad) as it relates to oral cavity squamous carcinoma correlates with the invasive potential of a cancer and locoregional disease recurrence. In particular, P-cad expression is considered an independent prognostic marker.[51] Marcus and colleagues[52] demonstrated that monocyte chemoattractant protein 1 was up-regulated in oral cavity carcinoma and the resultant increase in macrophage content was statistically associated with regional metastasis, extracapsular spread, and advanced-stage disease. Tissue inhibitor of metalloproteinase 1 and collagen type 11 alpha-1 have also been demonstrated to be increased in expression in oral cavity and oropharyngeal cancers that are metastatic.[53]

Laimer and colleagues[54] noted that a high STAT1 activation (>35%) in oral cavity carcinoma specimens was associated with a negative lymph node status and a better prognosis in patients receiving adjuvant chemotherapy when compared with nonexpressing counterparts. Xie and colleagues[55] noted that patients with higher numeric aberrations of chromosome X and 11 had shorter disease-specific survival. Podoplanin, a glycoprotein important in lymphangiogenesis, is expressed preferentially in oral tongue carcinoma. High levels of podoplanin have been shown to be predictive of lymph node metastasis and shortened disease-specific survival.[56] Additionally, intratumoral lymphangiogenesis in patients with early-stage oral carcinoma has been correlated with locoregional recurrence.[57]

The 5-year distant metastatic rate in patients with oral carcinoma after treatment is approximately 10%. This rate increases from 6.6% in patients with locoregional control to 21.4% in patients who develop a locoregional recurrence. Additional risk factors noted at the time of initial treatment associated with the development of distant metastasis in the two groups were greater than or equal to five positive lymph nodes, extracapsular spread, poor differentiation, and advanced pathologic stage (III or IV).[58]

In a study examining whether oral tongue carcinoma was associated with a worse prognosis when compared with other oral cavity subsites, Bell and colleagues demonstrated no significant difference in disease-free survival between the groups. Risk factors that were found to statistically affect overall and disease-specific survival were tumor grade and overall staging.[59]

Table 96-2 demonstrates the 5-year observed survival rates for patients with oral cavity squamous cell carcinoma stratified by stage as reported by the AJCC for 1985 to 1991.

Second Primary Tumors

Patients with smoking-related head and neck cancer are at risk for the development of a second primary tumor. A second primary tumor detected simultaneously or within 6 months of the initial primary tumor is defined as a *synchronous lesion.* Emergence of a second primary lesion more than 6 months after discovery of the index tumor is referred

to as *metachronous.* The incidence and site of subsequent primaries vary depending on the site of the initial primary lesion.

The overall incidence for synchronous and metachronous lesions for patients diagnosed with a primary head and neck malignancy is approximately 14%. Of these malignancies, 80% are metachronous cancers with 50% of cases presenting within the first 2 years of initial treatment of the primary tumor. For patients with oral cavity and oropharyngeal malignancies, the site of a second malignancy is most frequently in the cervical esophagus. New symptoms of dysphagia or odynophagia in this patient population should prompt a diagnostic evaluation with barium swallow or esophagoscopy.[60] There appears to be a bimodal pattern for second primary tumors in the esophagus, with an early group developing tumors within 2 years of treatment of the index primary tumor and a later group that develops esophageal cancer greater than 5 years after primary treatment.[61]

Treatment Considerations

The precise assessment of the tumor stage for oral cancers is necessary in order to develop an appropriate treatment approach. The general physical and psychologic condition of a patient should also be taken into consideration. Key questions that must be answered are: Is the patient medically fit for an extensive procedure? Can the patient's health status be optimized? Does the patient comprehend the treatment options and possible sequelae?

Perioperative antibiotics, in cases with aerodigestive tract exposure to the operative field, can decrease infectious complications associated with surgical intervention. Prophylactic antibiotics are most effective when administered immediately before surgery and for up to 24 hours postoperatively. Extended use of antibiotics in postsurgical patients has not been shown to decrease the risk of infectious complications or fistula formation. The inappropriate use of antibiotics increases the risk for pseudomembranous colitis and the emergence of resistant organisms. Selection of a prophylactic antibiotic for clean-contaminated head and neck surgery should provide adequate gram-positive in addition to anaerobic coverage.[62]

Multiple general statements can be made concerning the surgical management of oral cancer as a whole. A detailed discussion of the treatment of each oral cavity subsite follows within this chapter. For early-stage lesions of the oral cavity (T_1/T_2), transoral resection tends to be possible with complete tumor removal and adequate margin control. Primary closure, healing by secondary intention, or placement of a split-thickness skin graft may be used for reconstruction of small defects. Larger and more posteriorly located lesions may require a pull-through or mandibulotomy-based technique to aid exposure for resection and reconstruction. When the tumor closely approximates the mandible, marginal versus segmental mandibulectomy needs to be considered. Reconstructive options for advanced T-stage lesions include microvascular free tissue or pedicled flap reconstruction. Traditionally, T4b lesions have been considered inoperable. Liao and colleagues demonstrated equivalent results with T4a and selected T4b lesions (without carotid encasement and skull base extension) when aggressive surgical management of the primary site and regional lymphatics with postoperative radiation or chemoradiation therapy was performed. Free tissue reconstruction was necessary in 95% of patients. Local control, disease-free, and overall survival numbers were similar.[63]

When considering options for repairing larger soft tissue defects, one must consider the impact on speech, swallowing, and airway. Patients may require temporary tracheostomy and feeding tube placement in the perioperative period until adequate healing has occurred. The cosmetic implications of composite resection in advanced lesions also need to be weighed with the individual patient's expectation; however, the goal of treatment should remain an oncologic approach to achieve the best opportunity for long-term survival while maintaining quality of life.

Surgery—Treatment of the Primary Lesion

Operative Approaches

The surgical approach to the oral cavity primary site is dictated by the size, location, and associated involved anatomy relative to the tumor's presentation. Resection of limited (T1, small T2s) primary lesions can typically be performed transorally. Using transtumoral cuts, larger lesions can also be excised to a negative margin using the transoral approach. Advanced-stage oral tongue lesions, in particular those with posterior extension, may require a mandibulotomy-based approach to allow adequate access for the resection of the posterior margin of the tumor and allow for reconstruction. Advanced-staged tumors of the anterior oral tongue and floor of mouth, in particular those that involve the genioglossus and mylohyoid musculature (without mandibular involvement), can be efficiently managed with a visor or degloving approach. This approach can allow for excellent visualization enabling wide resection of the deeply invasive primary lesion while sparing the patient from a mandibulotomy and a possible postoperative nonunion. Specific considerations relative to the resection of various types of presentations at the different oral cavity sites are discussed as follows.

Lip

The majority of neoplastic lesions that affect this subsite present on the lower (88% to 95%) as opposed to the upper lip (2% to 7%) or the commissure (1%) (Fig. 96-11). For the lower lip, squamous cell carcinoma predominates, whereas basal cell carcinoma disproportionately arises on the upper lip. In addition to basal and squamous cell carcinoma, the differential diagnosis of a lip lesion includes keratoacanthoma, minor salivary gland tumors, malignant melanoma, and tumors of mesenchymal origin (malignant fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, angiosarcoma, and rhabdomyosarcoma).

The typical patient with a squamous cell carcinoma of the lip is a male 50 to 70 years of age. Risk factors include prolonged exposure to sunlight, fair complexion, immunosuppression, and tobacco use.

Clinical findings in lip cancer usually include an ulcerated lesion on the vermilion or cutaneous surface or, less commonly, on the mucosal surface. The majority of patients present with early-stage lesions and without evidence of neck metastases.[64] A nodular or sclerotic lesion may infiltrate into the deeper tissues, and careful palpation is important for determining the actual size of the lesion. Minor salivary gland tumors present as a submucosal nodule on the inner surface of the lower lip. The presence of paresthesias or dysesthesias in the area adjacent to the lesion indicates possible mental nerve involvement.[65]

Figure 96-11. Squamous cell carcinoma of the lip at the oral commissure.

Neck metastases are an infrequent finding with lower lip squamous cell carcinomas and occur in only 10% of cases. Lower lip lesions may metastasize bilaterally because of the communicating pattern of the lymphatics. An increased risk of regional metastasis is associated with commissure and upper lip lesions. Adverse prognostic features of lip primaries include perineural invasion, bony involvement, cancer arising on the upper lip or commissure, regional lymphatic metastasis, and age younger than 40 years at onset.[66] Lip cancer results in fewer than 200 patient deaths annually and is stage dependent. Diagnosed early and with adequate treatment, cure rates are high. Obtaining an adequate cosmetic result and functional outcome without microstomia can be challenging with advanced-staged lesions.

The surgeon should consider several factors when planning a resection and reconstruction for a patient with a lip carcinoma (Fig. 96-12). The typical lip length is 6 to 8 cm. Reconstructive algorithms are based on the proportion of lip resected. Realignment of the vermilion border during the reconstruction and preservation of the oral commissure (when possible) are important principles in attempting to attain an acceptable cosmetic and functional result.

Small primary lesions may be treated with surgery or radiation with equal success and acceptable cosmetic results. However, surgical excision with histologic confirmation of tumor-free margins is the preferred modality. The reconstruction of lip defects after tumor excision requires innovative techniques to provide oral competence, maintenance of dynamic function, and acceptable cosmesis. With small lesions, defects up to one third of the lip's length, simple excision with primary closure is possible. When lesions require resection of up to one third to two thirds of a lip's length, reconstructive options include a lip-switch (Abbe-Estlander) (Fig. 96-13) or a Johansson stepladder flap.[67] For tumors requiring resection of more than two thirds of the lip, the reconstructive options are the Gilles fan flap, bilateral advancement flaps, Karapandzic, or a free radial forearm with palmaris longus tendon. The Karapandzic flap (Fig. 96-14) is a sensate, neuromuscular flap that includes the remaining orbicularis oris muscle. The blood supply for this flap is the corresponding branches of the labial artery. Microstomia is a potential complication with these methods of lip

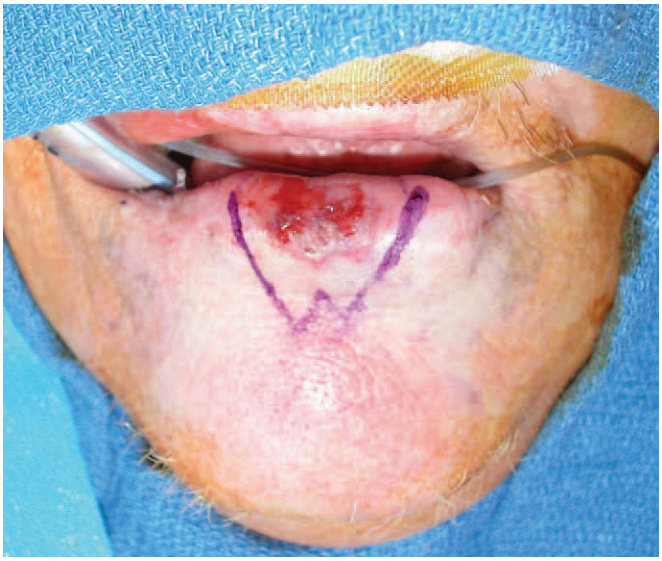

Figure 96-12. Midline lower lip squamous cell carcinoma noted with ulceration extending to the vermilion border. Wedge resection with primary closure is planned.

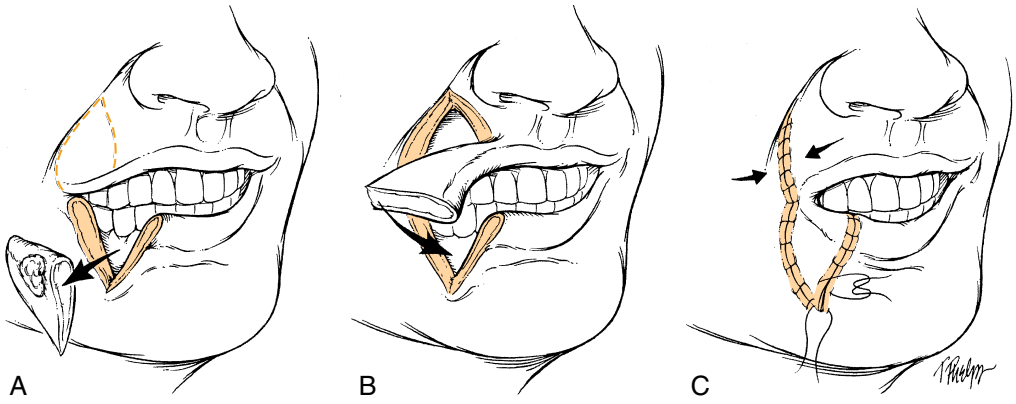

Figure 96-13. Abbe-Estlander flap for a left lower lip resection extending to the oral commissure. **A,** Wedge resection of lateral lower lip carcinoma. **B,** Initial mobilization of upper lip tissue preserving the commissure consistent with Abbe-Estlander flap reconstruction. **C,** Final inset of flap, *arrows* mark site of advancement and tension with closure. *(Adapted from Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

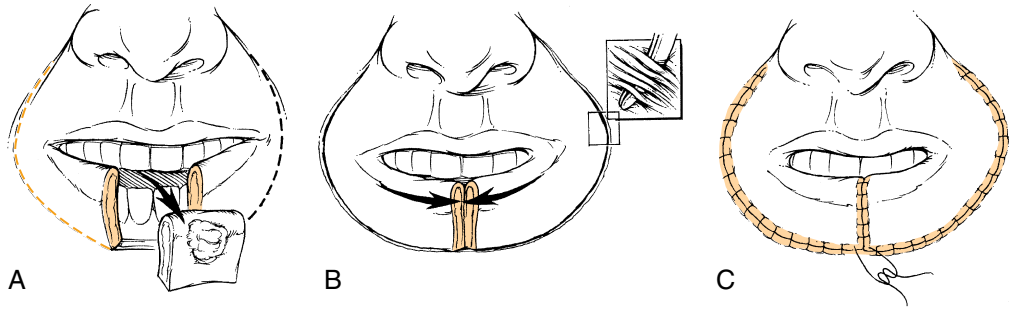

Figure 96-14. Karapandzic fan flap for midline lower lip defect. **A,** Rectangular-shaped full-thickness resection of lower lip carcinoma. **B,** Initial mobilization of circumoral advancement flaps, the neurovascular pedicle (inset on **B**) is preserved bilaterally. **C,** Final inset of reconstruction. *(Adapted from Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

reconstruction.[68] For large defects, Webster or Bernard procedures using lateral nasolabial flaps with buccal advancement have been described.[69] In addition, for aggressive and advanced-staged lesions, an evaluation for perineural spread should be performed at the time of resection. Potential biopsy of the mental nerve with a retrograde dissection in an attempt to obtain a negative margin should be considered. With extensive perineural invasion, a drill-out of the mental nerve or hemimandibulectomy may be required.

The primary echelon of nodes at risk for metastatic spread is the submandibular and submental region. Diagnostic evaluation for potential nodal spread includes fine-needle aspiration with or without ultrasound or CT guidance. In the presence of clinically evident neck metastasis, therapeutic neck dissection is indicated. Unnecessary sacrifice of both facial arteries (when bilateral neck dissections are required) could have implications on the vascularity of facial structures used for a complex lip reconstruction. Elective neck dissection is not typically advocated for lip carcinoma because the incidence of occult metastases is low.

The 5-year survival for stage I and II lesions is 90%. For patients with cervical metastases, the survival decreases by 50%.[67] Patients with oral commissure and upper lip carcinomas have a worse overall prognosis when compared with similar tumors of the lower lip. Postoperative radiation therapy is considered for patients with close or positive margins, lymph node metastases, or perineural invasion.

Alveolar Ridge

Squamous cell carcinoma of the mandibular and maxillary alveolar ridges represents approximately 10% of all oral cavity cancers. Lower alveolar ridge carcinomas present more frequently than upper lesions.

In a review of 155 patients with lower alveolar ridge carcinoma, the mean age at presentation was 66.7 years. In this group, 63% of tumors were located over the mandibular body and 25% arose over the symphysis. More than half of all lesions were diagnosed in edentulous patients. The majority of patients (67%) were noted to have early-stage lesions (T_1/T_2).[70]

Given that the mucosa closely approximates the underlying bone of the alveolus, osseous erosion and/or invasion at presentation is common. Tumors extending within adjacent dental sockets are associated with a higher likelihood of bone invasion. In this situation, preoperative radiographic evaluation can significantly aid in treatment planning. Close and colleagues[71] noted that the CT scan was more sensitive and specific than the bone scan and Panorex in predicting mandibular invasion. The need to address periosteal and bone invasion may be seen in up to 50% of patients. With mandibular invasion, the inferior alveolar nerve may become secondarily involved by perineural invasion. Treatment options of marginal versus segmental mandibulectomy are dependent on whether the tumor invades the periosteum, cortical, or medullary bone (Fig. 96-15). When tumors approach but do not invade the periosteum, a subperiosteal resection with mandibular preservation is possible with primary closure or split-thickness skin graft reconstruction. When the periosteum is invaded, marginal mandibulectomy is indicated. Marginal resection may be performed in two planes. The classic "rim" or coronal marginal mandibulectomy removes the superior aspect of the involved mandible, whereas a lingual sagittal marginal mandibulectomy removes the lingual cortex of the mandible contacting the tumor (Fig. 96-16). With lesions surrounding intact dentition, extraction and alveolar resection are required to obtain an adequate margin. When the tumor extends down the tooth socket into the medullary bone, segmental mandibulectomy is frequently necessary. With segmental mandibular defects of the symphysis, reconstruction with vascularized free tissue transfer with an osseous flap remains the standard of care. For lateral mandibular defects, the options are more varied and may include primary closure, pedicled and/or vascularized free flap soft tissue reconstruction, or vascularized osseous free tissue transfer.

When extensive maxillary alveolar ridge cancers are encountered, potential extension into the nasal cavity and paranasal sinuses should be anticipated.

General guidelines for neck dissection with oral cavity malignancies in the N_0 patient include treatment of the neck when the risk of occult metastatic spread to the regional lymphatics exceeds 20%. Upper alveolar ridge tumors tend to regionally metastasize to jugulodigastric lymph nodes, whereas lower alveolar ridge tumors drain to submandibular lymphatics. Among patients with clinical evidence of lymphadenopathy (N^+), regional treatment typically requires a modified radical neck dissection (levels I-V). Eicher and colleagues noted that levels IV and V harbored metastases in 20.9% of patients with inferior alveolar ridge cancer undergoing therapeutic neck dissection for clinically evident adenopathy. Patients undergoing elective dissection demonstrated occult metastases in levels I (53.3%), II (40%), and III (6.7%). Presence of an advanced T-stage (T_3, T_4) lesion and bony mandibular invasion have been correlated with the development of regional metastases. As such, elective neck dissection removing levels I to III is advocated for all advanced-staged primaries (T_3, T_4) and T_1-T_2 lesions at the mandibular symphysis or for tumors with moderate to poorly differentiated tissue pathology.[70] The overall risk of metastases with alveolar ridge carcinoma is 25%.[70,72] In patients with a clinically N_0 neck, occult metastases have been noted in 15% of operative specimens. The 2- and 5-year survival for patients with occult metastases who underwent END is better than for patients who underwent therapeutic neck dissection after the eventual development of metastatic adenopathy.[70]

The 5-year survival ranges from 85% (T_1, T_2) to 65% (T_3, T_4) for patients without metastatic spread. Among patients with regional or distant metastases, the 5-year survival has been reported to range from

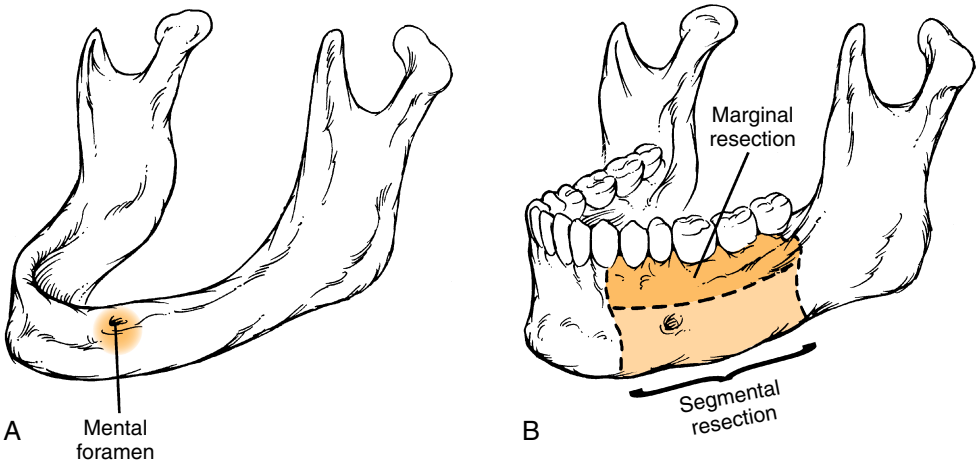

Figure 96-15. **A,** Atrophic appearance of an edentulous mandible. This demonstrates why marginal mandibulectomy is difficult to perform without iatrogenic fracture in these patients. **B,** Examples comparing a marginal versus segmental mandibulectomy. *(Adapted from Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

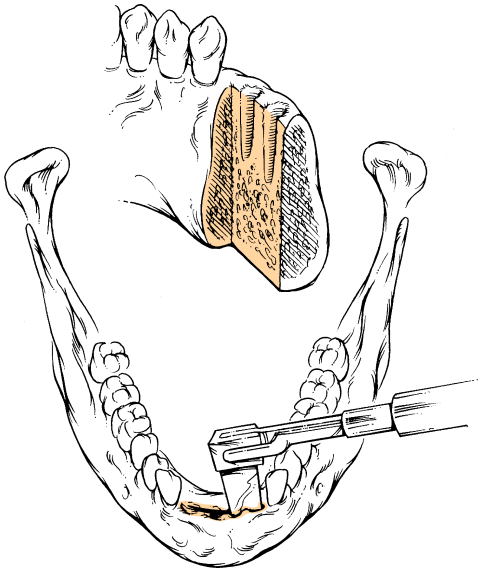

Figure 96-16. Cuts for a sagittal lingual marginal mandibulectomy at the symphysis. *(Adapted from Donald PJ.* Head and Neck Cancer: Management of the Difficult Case. *Philadelphia: WB Saunders; 1984.)*

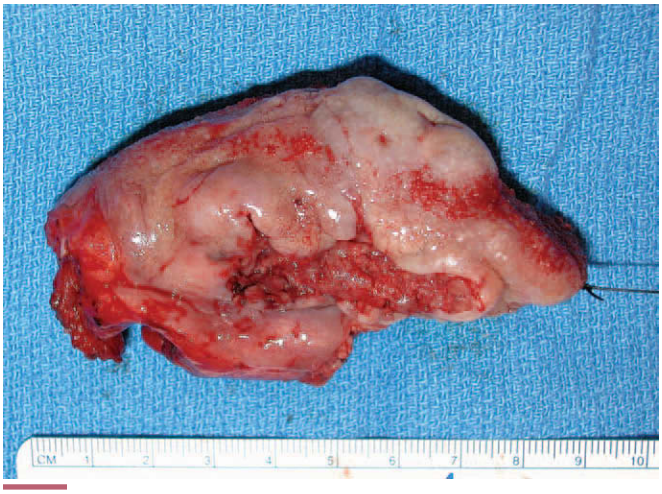

Figure 96-17. Hemiglossectomy specimen demonstrating an ulcer along the lateral edge from a tumor invading toward the floor of mouth.

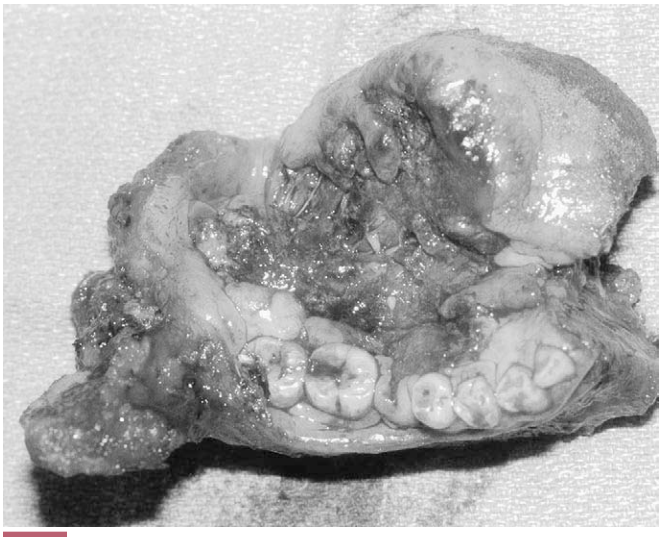

Figure 96-18. Composite resection specimen of ulcerative tongue carcinoma with lateral extension into the floor of mouth and mandible. Posterior extent of resection includes the retromolar trigone and anterior tonsillar pillar.

35% to 59%.[73,74] Decreased local control rates are seen with lesions greater than 3 cm and positive surgical margins. Significant prognostic factors include advanced T stage (T_3, T_4), margin status, mandibular invasion, and the presence of regional metastases. Neither local control nor survival are affected by the extent of mandibular resection, dental intervention near the site of the primary, perineural invasion, or histologic grade of the tumor.[72] Postoperative radiation therapy is advocated for patients with T_4 tumors, positive margins, perineural invasion, and regional metastasis.[70,72]

Oral Tongue

The oral tongue is a muscular structure with overlying nonkeratinizing squamous epithelium. The posterior limit of the oral tongue is the circumvallate papillae, whereas the ventral portion is contiguous with the anterior floor of mouth. Subsites include the lateral tongue, the anterior tip, the ventral tongue, and the dorsal oral tongue. Carcinomas of the tongue arise in the epithelium and invade into the deeper musculature. The most common presentation is that of a painful ulcerated or exophytic mass (Fig. 96-17).

Oral tongue carcinoma typically presents in males with a history of tobacco and alcohol use in their sixth or seventh decade of life. The majority is squamous cell carcinoma and approximately 75% occur on the posterolateral aspect of the oral tongue. The second most common site (20% of lesions) is the anterolateral and ventral surface of the tongue. The direct contact of carcinogens from tobacco or other agents is considered causative in the development of cancer at this site. Tumors may present on the dorsal surface of the tongue; however, this represents a minority of lesions (3% to 5%). The differential diagnosis for dorsal lesions of the tongue is broad and should include amyloidosis, median rhomboid glossitis, granular cell myoblastoma, and erosive lichen planus. Because of the rarity of carcinomas of the dorsal tongue, a delay in diagnosis is not infrequent.[75] The differential diagnosis of submucosal oral tongue tumors is those derived from mesenchymal tissues including leiomyomas, leiomyosarcoma, rhabdomyosarcoma, and neurofibromas.

Local invasion by tongue carcinoma may progress by various routes depending on the site of origin. A tumor of the anterolateral tongue may spread medially across the central raphe to the contralateral side, posteriorly to the tongue base, and inferiorly into the suprahyoid muscles and the muscular "root" of the tongue. Lateral spread to involve a significant portion of the floor of mouth is not uncommon. The lingual and hypoglossal nerves may be invaded directly by tumors. Their involvement produces the clinical findings of loss of sensation of the dorsal tongue surface and deviation on tongue protrusion, fasciculations, and atrophy. In addition, the patient may complain of referred otalgia. The extreme of lateral tumor extension, beyond floor of mouth, includes direct invasion of the mandible, requiring composite resection (Figs. 96-18, 96-19, and 96-20).

At the time of diagnosis, the majority of oral tongue carcinomas (75%) are T_2 or smaller. The surgical treatment for limited, small (T_1 to T_2) primary tumors is transoral wide local excision. Frozen section confirmation of the margin status is necessary before pursuing reconstruction. Advanced-stage lesions that approach the mandible or invade into the deep musculature are best accessed via a pull-through or mandibulotomy technique. When a segmental resection is warranted, access to the oral cavity through the mandibulotomy cuts provides wide access to the primary tumor.

A partial glossectomy, which may remove a significant portion of the lateral oral tongue, can still permit reasonably effective postoperative function. However, treatment of larger tumors that invade deeply within the tongue can result in a significant functional impairment. With resection of approximately one quarter to one third of the oral tongue, healing by secondary intention is an acceptable option. If a

limited portion of the floor of mouth is resected, reconstruction with a split-thickness skin graft should be used to prevent tongue tethering. Resection of approximately one half of the tongue results in loss of tongue bulk and scar contracture if limited reconstructive options are pursued. Lingual contact with the palate, lip, and teeth is decreased and can result in impaired articulation. Posterior propulsion of the food bolus and liquids may also be affected. The use of soft pliable fasciocutaneous free flaps such as a radial forearm or anterolateral thigh free flap can provide intraoral bulk and preservation of existing tongue mobility. A palatal augmentation prosthesis allows for contact between the remaining tongue tissue and the palate and may improve speech and swallowing function. For patients undergoing a partial glossectomy with a significant resection of the floor of mouth, free flap reconstruction to maintain tongue mobility is indicated.

Kurokawa and colleagues[76] noted that in patients with moderately differentiated squamous cell carcinoma of the oral tongue, tumor depth of invasion equal to or greater than 4 mm was associated with occult cervical lymph node metastases. Spiro and colleagues[77] demonstrated that increasing tumor thickness, and not T stage, correlated with treatment failure and survival. Disease-related death was uncommon for patients with depth of invasion less than 2 mm. The depth of invasion can be used to guide the necessity for elective neck dissection in N_0 patients with early-stage lesions.

At initial presentation, 40% of patients with oral tongue carcinoma demonstrate evidence of cervical metastases. For patients with T_1 and T_2 tumors with clinically N_0 neck examination, 20% to 30% of elective neck dissection specimens are pathologically positive. Byers and colleagues noted that 15.8% of lateral tongue carcinoma patients demonstrated "skip" metastases to lymph nodes, bypassing levels I and II, and presenting with level III or IV metastatic disease. They concluded that elective supraomohyoid neck dissection was inadequate for the control of regional lymphatics of oral tongue carcinoma patients and advocated for levels I to IV neck dissection in this situation.[78] When lesions approach the midline, the likelihood for bilateral regional metastasis is high and requires bilateral lymphadenectomy.

Patients with advanced-stage lesions (III or IV) require surgery and postoperative radiation therapy to achieve the best locoregional control rates. Franceschi and colleagues noted an increase in locoregional control for stage III and IV patients from 57% to 71% with the addition of postoperative radiotherapy. In this study the only factor predictive of locoregional recurrence was a positive surgical margin. The majority of patients (78%) recurred within 2 years.[79] Among patients developing a local recurrence, attempts at surgical salvage to control disease are frequently unsuccessful.

The 5-year survival for stage I or II tumors is 75% and less than 40% for stage III or IV tumors.[79,80]

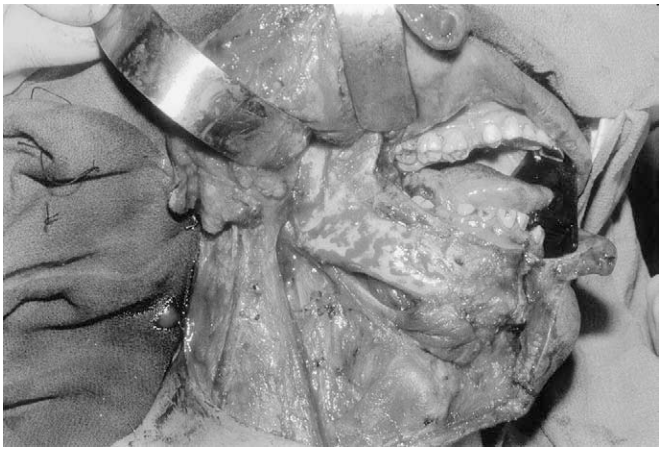

Figure 96-19. Approach for a composite resection for a T_4 tongue squamous cell carcinoma invading the lateral mandible.

Retromolar Trigone

The majority of patients with retromolar trigone carcinomas tend to present with advanced disease. At the time of presentation, up to 50% of patients present with regional metastatic disease. Mandible involvement is common given the thin layer of soft tissue separating these tumors from the ascending ramus. Trismus suggests involvement of the medial pterygoid muscle. As tumors progress in this location, extension to the faucial arch, tonsillar fossa, and the base of the tongue is common. In addition to squamous cell carcinoma, the differential diagnosis of lesions in this region includes minor salivary gland neoplasms, osteosarcoma, and soft tissue sarcomas.

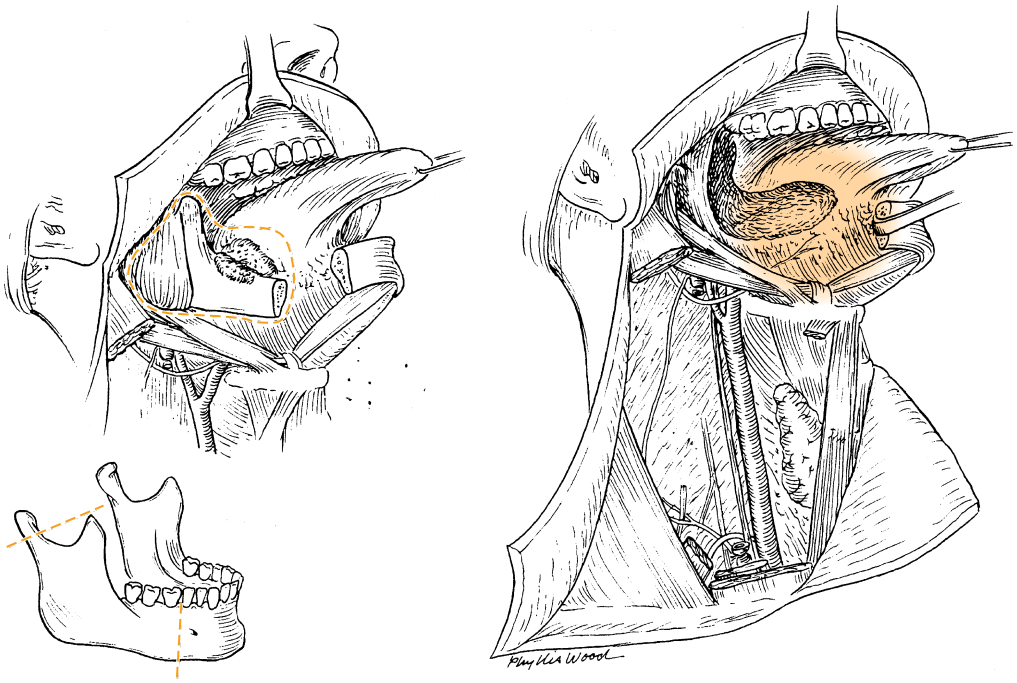

Figure 96-20. Hemimandibulectomy for posterior floor of mouth–lateral tongue tumor with associated modified radical neck dissection (type 1). Reconstruction options include soft tissue reconstruction of the deficit or osseous free tissue transfer.

Figure 96-21. Postresection appearance after L-shaped marginal mandibulectomy for a posterior alveolar ridge–retromolar trigone squamous carcinoma.

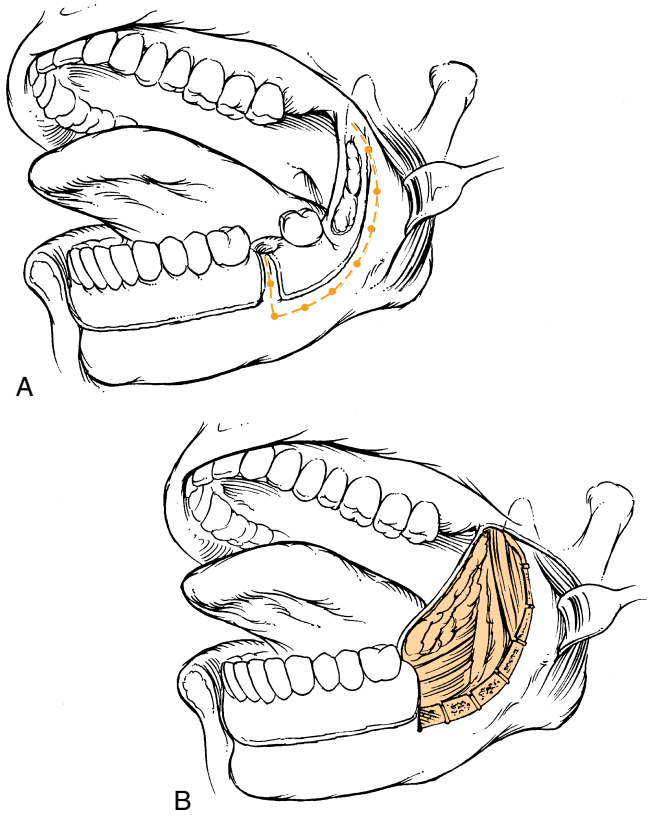

Figure 96-22. L-shaped marginal mandibulectomy for a retromolar trigone tumor. A generous portion of cortical bone remains at the posterior body-angle-ramus of the mandible such that the defect requires only soft tissue reconstruction. **A,** Planned approach for marginal mandibulotomy with wide local incision for retromolar carcinoma without gross bony invasion. **B,** Appearance after surgical resection of tumor prior to reconstruction revealing medial pterygoid and deep tongue musculature. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

Given the proximity of the mucosa to the underlying ramus of the mandible, surgical resection of early-stage retromolar trigone lesions may require a resection of a portion of the mandible. Treatment options include an L-shaped coronal marginal mandibulectomy, segmental mandibulectomy, and hemimandibulectomy. With the L-shaped marginal mandibulectomy, the superior aspect of the body—extending toward the angle and ascending the ramus—is resected (Figs. 96-21 and 96-22). Segmental mandibulectomy is performed for more extensive lesions with gross bone destruction.

Huang and colleagues demonstrated a 5-year, disease-free survival for T_1 lesions of 76%, which declined to 54% for T_4 disease. Patients with N_0 disease had a 5-year survival of 69%. Survival fell to 56% for those who were N_1 and to 26% for patients with N_2 disease. The recurrence rate for patients treated with radiation therapy alone was 44% compared with 23% for patients undergoing surgical resection with postoperative radiation therapy. Complications reported in patients undergoing treatment with radiation included osteoradionecrosis, soft tissue necrosis, or severe trismus.[81]

Floor of Mouth

Carcinomas of the floor of mouth typically present in males in their sixth decade of life. Approximately 35% of these patients present with an advanced T-stage (T_3, T_4) lesion on initial diagnosis.[50] The floor of mouth musculature plays an important role in the modes of tumor spread. The floor of mouth is composed of the slinglike genioglossus, mylohyoid, and the hyoglossus muscles, which serve as a barrier to the spread of disease. Invasion into these muscles can lead to tongue hypomobility and dysarthria. In addition, tumors of the anterior floor of mouth may extend posteriorly into the ventral aspect or "root" of the tongue, causing fixation.

Deep invasion into the intrinsic musculature of the tongue causes fixation and mandates a partial glossectomy in conjunction with resection of the floor of mouth. Lesions in the anterior floor of mouth may directly invade the sublingual salivary gland or submandibular duct and require in-continuity resection with the primary lesion. Direct extension of tumors through the sublingual space into the submaxillary space indicates the need for an in-continuity resection of the primary tumor and neck.

Anterior or lateral extension to the lingual aspect of the mandible is of primary importance in preoperative treatment planning for these lesions. Imaging studies of the mandible including CT, MRI, and Panorex are useful in conjunction with careful clinical evaluation by bimanual palpation to ascertain adherence to the mandible. The absence of fixation of the lesion to the inner mandibular cortex indicates mandible-preserving techniques are feasible.

The treatment of choice for early-stage lesions, not involving the mandible, is transoral resection. For more extensive anterior and lateral floor of mouth cancers without mandibular involvement, a pull-through technique can spare the need to perform a mandibulotomy. Paramedian or lateral mandibulotomy is seldom necessary except for some posterior floor of mouth tumors. The resection of larger tumors of the floor of mouth usually requires immediate reconstruction. The goals of reconstruction are to obtain a watertight closure to avoid salivary fistula and preserve tongue mobility. For extensive mucosal and soft-tissue deficits, the radial forearm free flap offers the best reconstructive option to accomplish these goals. Additional reconstructive options include the nasolabial, platysma, and pectoralis major flaps. The platysmal flap can be used for small lateral defects, whereas the pectoralis major myocutaneous flap can be used for larger soft tissue defects, preferably when the posterolateral mandible is resected.

For lesions without evidence of bony invasion but demonstrating involvement with the lingual periosteum, a coronal partial mandibulectomy may be required (Fig. 96-23). For massive lesions associated with

mandibular destruction, composite resection with segmental mandibulectomy is necessary (Fig. 96-24).

Cervical metastases are noted in approximately 50% of patients with floor of mouth carcinoma. The submandibular lymph nodes (level IB) are most frequently involved.[50] Bilateral metastases are common with lesions of the anterior floor of mouth.

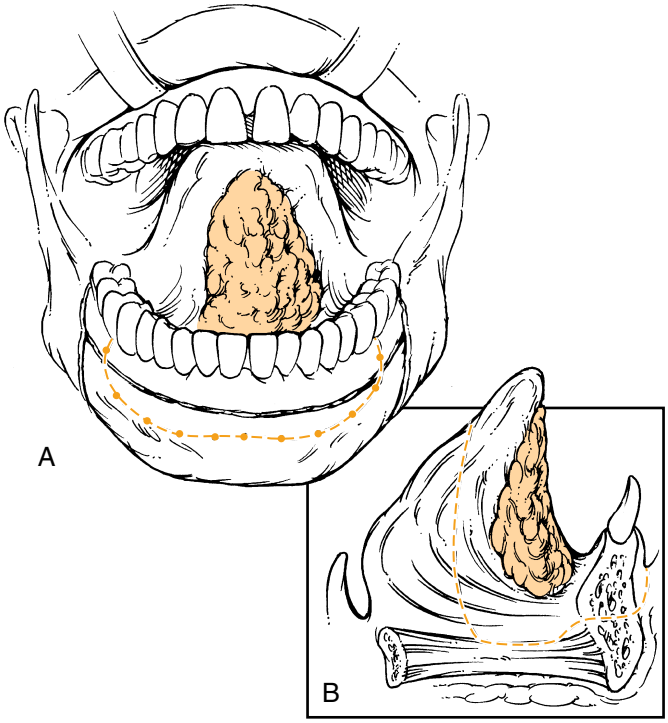

Figure 96-23. Anterior floor of mouth carcinoma treated with a marginal mandibulectomy with a visor flap approach. Teeth are extracted at the sites of the osteotomy cuts. **A,** Anterior view of marginal mandibulectomy approach with wide local excision for floor of mouth carcinoma. **B,** Sagittal view demonstrating bone and soft tissue cuts superficial to the geniohyoid and mylohyoid muscles. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

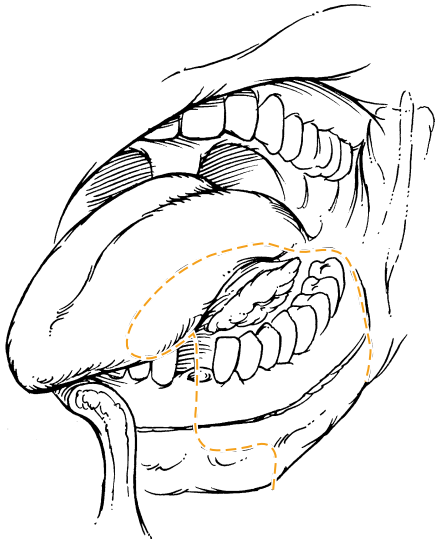

Figure 96-24. Composite resection of floor of mouth carcinoma with segmental mandibulectomy. To obtain wide surgical margins, a significant portion of lateral oral tongue is resected with the specimen. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

The 5-year survival for carcinomas of the floor of mouth are 90% for stage I, 80% for stage II, 65% for stage III, and 30% for stage IV disease.[50,82]

Buccal Mucosa

Carcinomas of the buccal mucosa represent 5% to 10% of all oral cavity malignancies (Fig. 96-25). There is a 4:1 male predominance and the typical patient is in the sixth decade of life. An association between smokeless tobacco use and buccal carcinomas has been noted. An increased incidence of these tumors is seen in the Southeastern U.S. population. In India, betel nut use is associated with a high incidence of buccal carcinoma.

Verrucous carcinoma usually arises on the buccal mucosa and is considered a low-grade malignancy. Poor oral hygiene, tobacco use, and viral infection have all been suggested as potential etiologies. Although considered low grade, foci of invasive carcinoma and areas of dedifferentiation may be found within an individual specimen. Surgical resection is the treatment of choice.[83] Elective treatment of the regional lymphatics is not necessary given the low likelihood of regional metastasis. The differential diagnosis for epithelial-based lesions presenting in the buccal mucosa should also include squamous papilloma and pseudoepitheliomatous hyperplasia. Minor salivary gland tumors may also present as a submucosal mass within this region.

The site of the buccal mucosa where squamous carcinomas are most frequently noted is adjacent to the third mandibular molar. Patients with advanced-staged disease may present with trismus as a result of direct invasion of the tumor into the muscles of mastication. Parotid duct involvement may produce obstructive sialoadenitis. Anterior lesions metastasize regionally to submandibular nodes, whereas posterior buccal lesions metastasize to upper jugulodigastric lymph nodes.

Small lesions can be excised transorally. Intermediate-staged primary tumors may be resected transorally or through a lip-splitting incision. With the exception of superficial lesions, the buccinator muscle should be resected in continuity, thus providing an adequate deep margin. Although primary closure or healing by secondary intention is acceptable for small primary tumors, larger defects should be repaired with a fasciocutaneous flap to avoid scar contracture and trismus, which are frequent sequelae of skin grafting. Local intraoral spread may necessitate resection of the alveolar ridge of the mandible or maxilla. For invasive squamous cell carcinomas and minor salivary gland tumors, the buccinator muscle should be included with the

Figure 96-25. Ulcerated buccal mucosal lesion in a patient with oral pain and trismus noted to be squamous cell carcinoma at biopsy.

Figure 96-26. Medial aspect of the extensive buccal carcinoma requiring partial maxillectomy and hemimandibulectomy. Crater from the ulcerative lesion extends anterior to the oral commissure and posteriorly to the retromolar trigone.

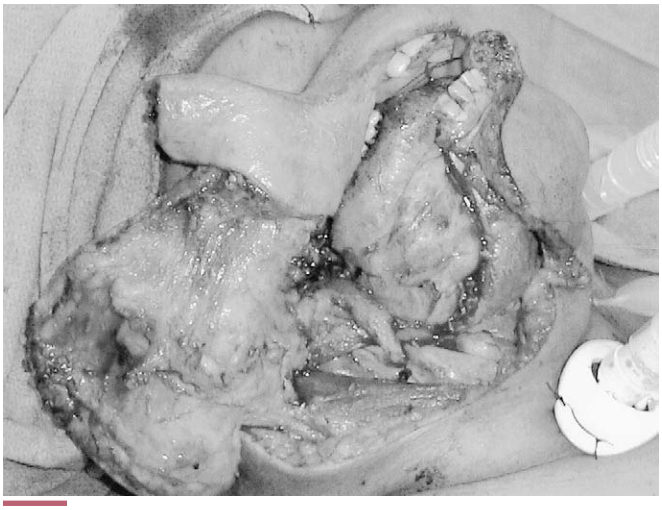

Figure 96-27. Lip-splitting approach extended into neck dissection incision for access to perform a hemimandibulectomy for a T_4 buccal carcinoma.

specimen at the time of resection. Deep invasion into the cheek may require through-and-through resection (Figs. 96-26, 96-27, and 96-28). Ideal reconstruction to provide both internal and external lining is best accomplished with a folded fasciocutaneous free flap. Surgery as a primary modality is advocated for buccal carcinoma, whereas combination therapy is advised for advanced lesions. As with most lesions of the oral cavity, tumor thickness has a direct correlation to prognosis. In T_1/T_2 N_0 tumors, depth of invasion greater than 5.17 mm at the primary site has been correlated with a risk of ipsilateral regional lymphatic spread.[84]

Diaz and colleagues reviewed a series of 119 (previously untreated) patients with buccal carcinoma undergoing treatment at the MD Anderson Cancer Center. Primary tumors were staged as follows: T_1—21%, T_2—38%, T_3—23%, and T_4—15%. The majority of patients (72%) were N_0 at presentation. The majority of patients were treated exclusively with surgery (71%). No patients were treated with radiation therapy alone, and postoperative radiation therapy (dosage 50 to 60 Gy) was used for patients with extracapsular nodal spread or positive margins. Transoral excision was performed in the majority of patients

Figure 96-28. Closure of "through-and-through" buccal carcinoma accomplished with a cervicofacial advancement flap and pectoralis major flap. A portion of the pectoralis major flap lines the oral cavity, a portion is desquamated to transition externally, and a portion is external at the oral commissure extending to the advancement flap.

with only 27% of patients requiring a lip-splitting incision and cheek flap for resection. Modified radical neck dissection was performed for patients with N_+ necks, and supraomohyoid neck dissection was used for those with N_0 necks. The 5-year survival for all patients within the series was 63%. Five-year survival declined from 70% for N_0 patients to 49% for patients with metastatic lymphadenopathy. Within the series of patients, 45% experienced recurrence (23% local, 11% regional, 9% local and regional) and salvage therapy was successful in only 22%. Stensen's duct involvement and buccinator muscle invasion had no effect on locoregional recurrence.[85]

Reported 5-year survival is 75% to 78% for stage I, 65% to 66% for stage II, 30% to 62% for stage III, and 20% to 50% for stage IV disease.[82,85,86]

For patients who are not considered appropriate candidates for extensive surgical resection and reconstruction, primary radiation or chemoradiation is a viable treatment option. The reported results on the use of primary radiation therapy in patients with locally advanced disease demonstrate high recurrence rates (45%) and compromised overall survival (38%) after treatment.[87]

Hard Palate

Squamous cell carcinoma is the most common malignancy of the palate (Fig. 96-29). A close second in frequency are minor salivary gland tumors that include adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and polymorphous low-grade adenocarcinoma.[88] Mucosal melanoma most commonly arises on the hard palate and the maxillary gingiva and presents as a nonulcerated, pigmented plaque. The typical patient is 40 to 50 years of age, and the prognosis is poor because of the locoregional aggressiveness of the tumor and propensity for distant metastases. Kaposi's sarcoma of the palate is the most common intraoral site for this tumor.[89] Chronic irritation from ill-fitting dentures may also play a causal role in the development of dysplasia. Inflammatory lesions arising on the palate may mimic malignancy and can be differentiated by biopsy. Necrotizing sialometaplasia appears on the palate as a butterfly-shaped ulcer and resembles a

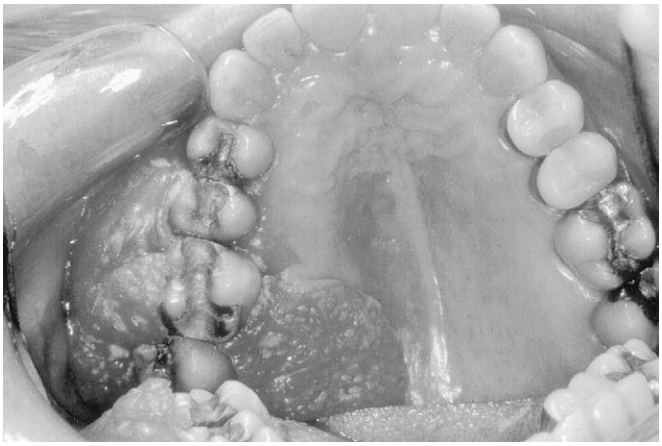

Figure 96-29. Hard palate squamous cell carcinoma extending over the upper alveolar ridge to the gingivobuccal sulcus. Margin control for this tumor would extend to the soft palate posterior and require an infrastructure maxillectomy. Retrograde spread along the greater palatine nerve could result in skull base extension.

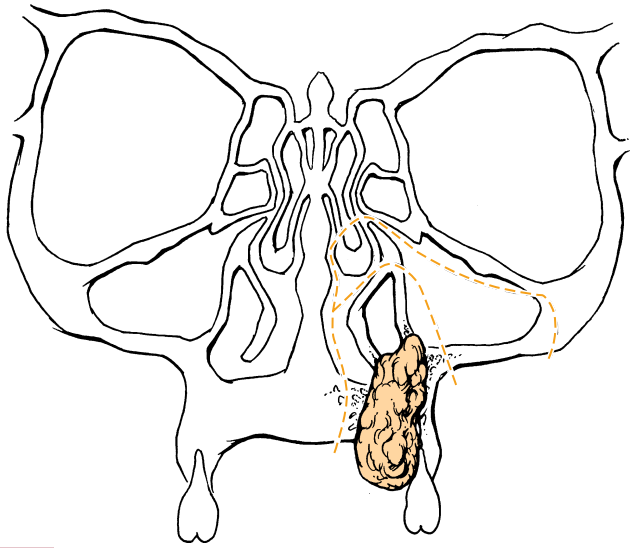

Figure 96-30. Bone cuts on an infrastructure maxillectomy for a hard palate malignancy. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

malignancy. Treatment is symptomatic and biopsy confirms its benign nature. Torus palatini are exostoses or bony outgrowths of the midline palate and maxillary bone that do not require surgical treatment unless patients are symptomatic.

The typical patient with a carcinoma of the hard palate is an elderly male with a history of tobacco use. A high incidence of hard palate carcinoma is seen in countries where reverse smoking is practiced.

Minor salivary gland tumors typically present as a submucosal nodule. Ulceration is rare unless a biopsy has been previously performed. Minor salivary gland tumors tend to arise at the junction of the hard and soft palate. Direct infiltration of bone may lead to extension into the floor of the nose or the maxillary antrum. Neurotropic spread along the greater palatine nerve may result in extension to the foramen rotundum or CN V ganglion.

Squamous carcinoma of the hard palate is treated surgically. Small lesions may be treated with transoral wide local excision. The resection may be performed to the level of the bony portion of the hard palate with anticipated re-epithelialization. Because the periosteum of the palatal bone acts as a barrier to spread, excision with bony preservation is adequate for small lesions. Involvement of the periosteum requires removal of a portion of the bony palate. Partial or subtotal maxillectomy is required for larger lesions or those involving the maxillary antrum (Fig. 96-30). For malignancies extending along the greater palatine nerve, biopsy of this nerve is important for identifying neurotropic spread. Small- to medium-sized defects may be reconstructed with the aid of local advancement flaps or a buccal fat pad flap. Oronasal postresection fistulas of the palate require a dental prosthesis for rehabilitation of speech and swallowing. For lesions resulting in a palatal defect after resection, prosthetic rehabilitation can offer the patient an excellent functional result. In this circumstance a maxillofacial prosthodontist may construct a splint preoperatively for use at the time of resection. A split-thickness skin graft is used to cover edges of bone from osteotomy and replace sites within the sinuses where mucosa was removed as part of the resection. The cavity is then packed with petroleum gauze, and a lag screw can be used to secure the prosthesis to the maxilla, providing support to the underlying repair (Figs. 96-31, 96-32, and 96-33). The temporary prosthesis is removed approximately 1 week later and the packing is evacuated. An interim prosthesis is worn until a more permanent option can be tailored to the resultant defect.[90] Adjuvant radiation is indicated for advanced staged tumors, perineural invasion, and positive margins.

Primary radiotherapy has been investigated as a therapy for hard palate carcinomas with an 80% 5-year local control rate reported for T_1 and T_2 tumors; however, this control rate falls to 24% for T_3 and

Figure 96-31. Hard palate squamous cell carcinoma before resection.

T_4 lesions. Nevertheless, surgery is the favored primary modality for carcinoma of the hard palate. In this study, 5-year survival was 48% for squamous cell carcinomas and 63% for minor salivary gland carcinomas.[91]

For patients with hard palate malignancies, 10% to 25% present with cervical metastases, most frequently to the submandibular and upper jugular cervical nodes.[92] Given the low incidence of occult metastases, elective neck dissection is not indicated in most cases.

The reported 5-year survival for patients ranges from 40% to 60%.[92,93]

Surgery—Treatment of the Mandible

The management of the mandible as it applies to oral cavity malignancies has evolved over time. Initially, squamous cell carcinoma of the oral cavity was believed to invade the mandible through the adjacent lymphatics. Direct invasion is now recognized as the most common pathway. In a paper by Marchetta and colleagues in 1971,[94] it was demonstrated that tumors involve the mandible by first invading the periosteum. When the periosteum was free of direct tumor invasion, a mandible-sparing operation was considered feasible.

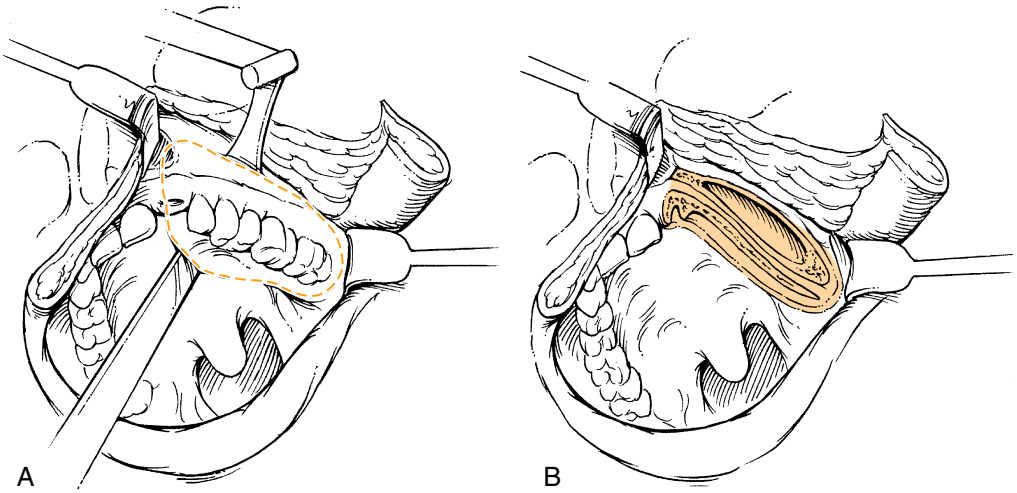

Figure 96-32. Approach to resection of a hard palate tumor. Weber-Ferguson incision with lip-split is shown for superoanterior exposure. Resection exposes the inferior aspect of the nasal cavity and maxillary sinus to the oral cavity. **A,** Planned cuts for resection of lateral maxillary alveolus and palate. **B,** Post-resection defect prior to reconstruction demonstrating communication with the lower aspect of the maxillary sinus. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

Figure 96-33. Obturator in place after infrastructure maxillectomy. Split-thickness skin graft covers the osteotomy margins and relines the maxillary sinus cavity and is held in place by petroleum gauze supported by the obturator.

Mandible-sparing procedures including vertical and horizontal marginal mandibulectomy (Fig. 96-34) and pull-through techniques have gained popularity as organ conservation philosophies have emerged within the field (Figs. 96-35 and 96-36). In addition, pull-through techniques offer the advantage of avoiding a lip-splitting incision and allow adequate exposure for free tissue reconstruction. A pull-through is contraindicated in patients with gross mandibular destruction but may be performed in continuity with resection of the lingual plate of the mandible.

Mandibulotomy for access in oncologic resection and reconstruction of oral cavity malignancies is typically reserved for advanced-stage primaries with extensive oropharyngeal spread. Placement of the osteotomy in the midline or paramedian locations (with mental nerve preservation) is the preferred site. The paramedian mandibulotomy offers the advantage of ipsilateral geniohyoid and genioglossus muscle preservation, whereas midline osteotomy requires transection of these muscles. At times, sacrifice of a mandibular incisor or canine tooth may be required to perform an osteotomy. Creation of a mild to moderate malocclusion, independent of technique, has been shown to be a common finding.[95] With the bone cut for the mandibulotomy, loss of a fine column of cortical bone occurs. This can be lessened by partially sawing through the lingual cortex and greenstick fracturing the posterior table with an osteotome. Placement of a titanium plate before actual osteotomy is a strategy that will allow for retention of the patient's normal occlusion when the mandible is reapproximated at the end of the procedure. The placement of drill holes for the plate at the inferior aspect of the mandible in patients with intact dentition avoids iatrogenic tooth root injury. If a lag screw technique is used, care needs to be exercised to avoid overcorrection with fixation of the mandibulotomy ends and creation of a malocclusion. Lateral mandibulotomy, at the level of the body or ramus, should be avoided because of poor healing at the osteotomy site and the interruption of the inferior alveolar artery and nerve at the time of osteotomy.

Complications from mandibulotomy have been extensively reported in the literature and range from 23.2% to 47.6%.[96,97] These include plate exposure, lip contracture, ankyloglossia, cellulitis-abscess, temporomandibular joint dysfunction, nonunion, and osteoradionecrosis. When mandibulotomy is performed in the setting of a marginal mandibulectomy, the risk of nonunion and infection associated with devascularization of the involved mandible has led some surgeons to abandon combining the two techniques.[96] Eisen and colleagues examined the morbidity of midline mandibulotomy in patients requiring postoperative radiation therapy. They found a complication rate of 11% in patients whose mandibulotomy site was included in the radiation field.[98]

Assessing the need for segmental mandibulectomy can be a difficult treatment decision to make (Table 96-3). Although gross mandibular invasion clearly mandates a segmental mandibulectomy, situations in which periosteal adherence and subtle cortical invasion are suggested (by clinical examination or radiographic imaging) require the experience and judgment of the surgeon as to whether to proceed with a marginal mandibulectomy versus segmental mandibular resection. Marginal resection in the setting of alveolar ridge carcinoma has been advocated by some authors when radiographically detected bony erosion fails to extend below the level of the mandibular canal.[99]

Segmental resections of the anterior mandible (including the symphyseal and parasymphyseal regions) mandate reconstruction with vascularized bone and soft tissue. Posterior segmental mandibular defects, in particular in edentulous patients or individuals with comorbidities limiting the ability for free tissue bony reconstruction, may be adequately repaired with soft tissue reconstruction only. Although the resection without bony reconstruction of the lateral mandible leaves patients with a J-shaped mandibular "swing," speech and swallowing function are generally good and patients are capable of decannulating if tracheostomy is performed at the time of procedure. Cosmetic

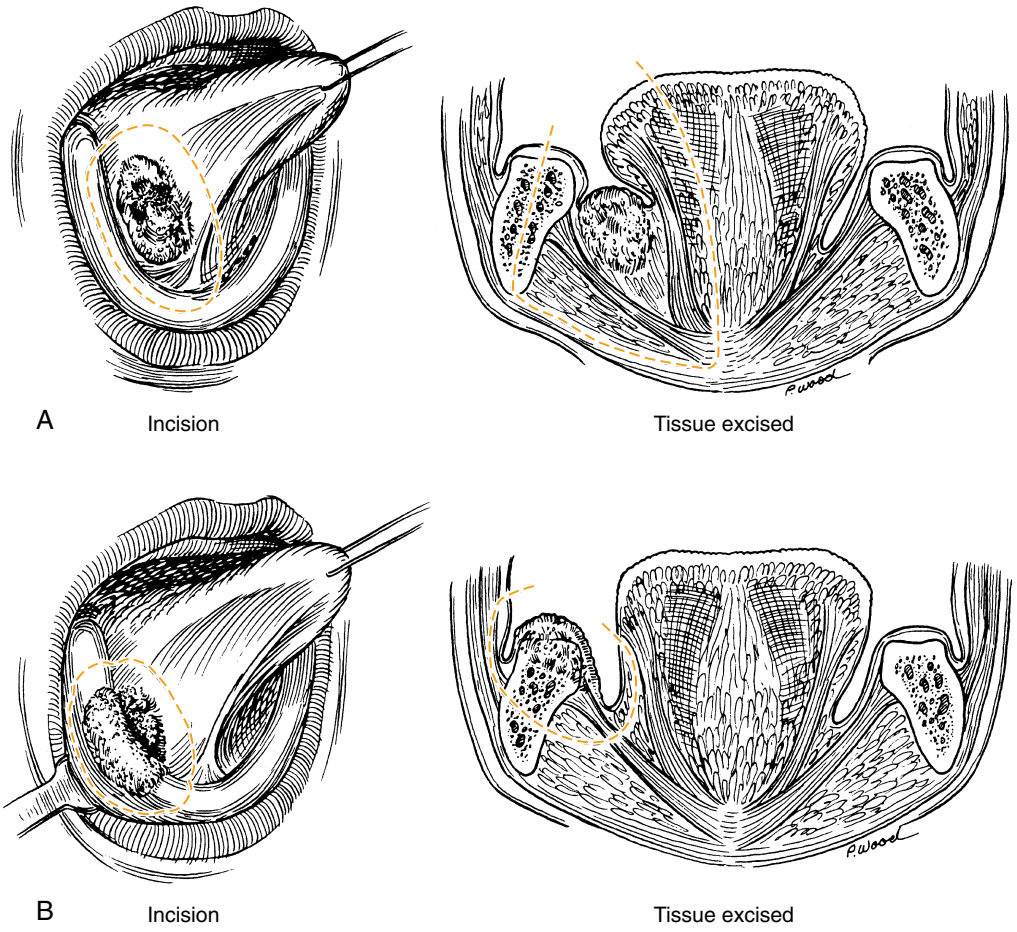

Figure 96-34. **A,** Floor of mouth tumor removed with a lingual sagittal marginal mandibulectomy. **B,** Floor of mouth–alveolar ridge tumor removed with a coronal "rim" marginal mandibulectomy.

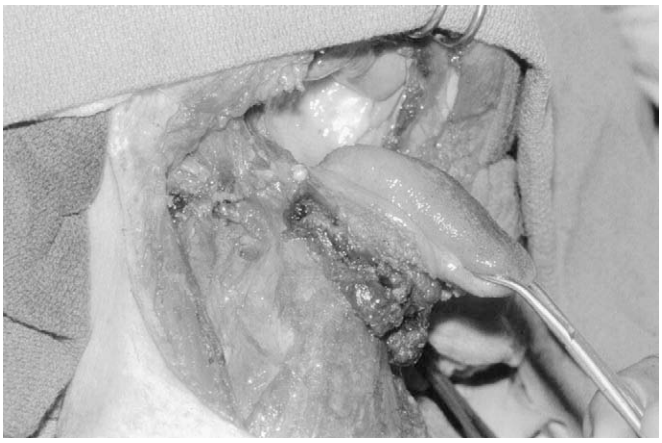

Figure 96-35. Pull-through technique for extensive floor of mouth carcinoma extending into the oral tongue.

Table 96-3

Indications for Surgical Treatment of the Mandible

Type of Presentation	Intervention Required
Mucosal lesion with mandibular approximation, freely mobile	Wide local excision with removal of adjacent periosteum
Mucosal lesion with isolated adherence to the mandible, lingual aspect	Lingual-sagittal marginal mandibulectomy
Mucosal lesion with isolated adherence to mandible, gingival aspect	"Rim"-coronal marginal mandibulectomy
Gross cortical invasion, inferior alveolar nerve involvement	Segmental mandibulectomy

asymmetry consistent with a concavity in the region of the mandibular ramus is notable. Chin drift may occur without the opposing aspect of mandible but can be reduced if a bulky soft tissue flap (e.g., pectoralis major) is used for reconstruction of the posterior mandibular site. Alternatively, the lateral mandibulectomy defect can be spanned with a titanium mandibular reconstruction plate to maintain the continuity of the mandible, maintain occlusion, and avoid the chin drift observed from allowing the mandible to "swing." This type of reconstruction should be done in combination with intraoral soft tissue reconstruction using a pedicled musculocutaneous flap (e.g., pectoralis major flap).

Surgery—Treatment of the Neck

Patterns of spread from primary tumor sites in the head and neck to cervical lymphatics are well described. The location and incidence of

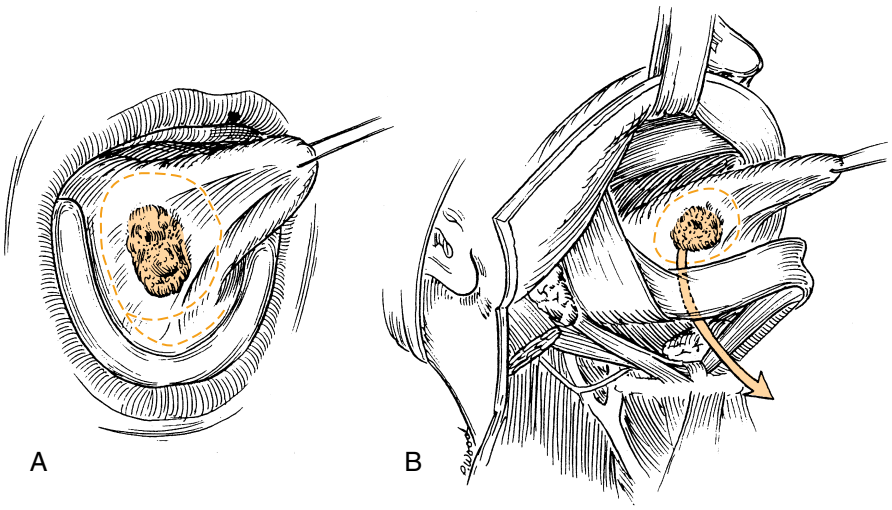

Figure 96-36. **A,** Floor of mouth tumor. **B,** Proposed pull-through approach. After raising the apron flap superiorly, the mylohyoid and anterior belly of the digastric are detached, allowing the delivery of the tumor for resection to a cervical location and sparing the need for mandibulotomy for selected lesions.

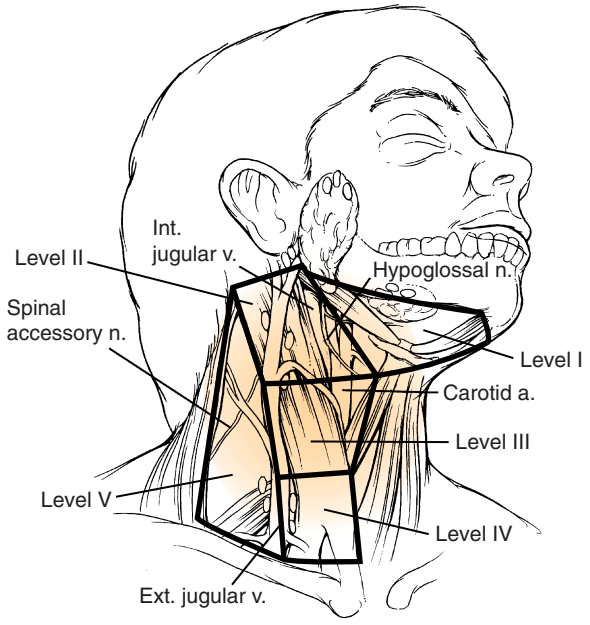

Figure 96-37. Levels of the regional lymphatics of the neck. *(Adapted from Silver CE, Rubin JS. Atlas of Head and Neck Surgery. 2nd ed. New York: Churchill Livingstone; 1999.)*

metastasis vary according to the primary site. Primary tumors within the oral cavity and lip typically metastasize to the nodes in levels I, II, and III (Fig. 96-37).

The need to perform a neck dissection in the N_0 patient has undergone considerable investigation. Lymphoscintigraphy with sentinel node biopsy in the setting of the N_0 oral carcinoma patient has been reported to have a negative predictive value of 100%.[100] Even in previously treated oral carcinoma patients, sentinel node biopsy has a high reported negative predictive value (91%).[101] Although initial results appear promising, most reported series reflect the experience of only a limited number of patients. Sentinel node biopsy is not currently considered standard of care for oral cavity carcinoma. Myo and colleagues reported on the use of cyclin D1 gene numeric aberrations assessed on FNA samples in stage I and II oral cancer patients. Cluster-type amplification of the cyclin D1 gene correlated with future regional recurrence in patients when the neck was not treated electively.[102]

For a patient with an oral cavity malignancy who is clinically and radiographically N_0, with a risk of occult metastases exceeding 20%, many consider elective treatment to the regional lymphatics necessary. Options for treatment of the regional lymphatics include elective neck irradiation versus neck dissection.[103,104] With time, modifications of neck dissection have evolved from radical neck dissection through modified radical neck dissection to selective neck dissection. Surgeons have traditionally treated the N_0 neck with surgery.[105] Selective neck dissection can serve as a staging procedure to determine the need for postoperative adjuvant radiotherapy. For the clinically N^+ neck, the surgical treatment of choice has traditionally been modified radical neck dissection (MRND) or radical neck dissection (RND), although some authors advocate selective neck dissection (SND) for the treatment of limited N_1 disease.[106] Kuntz and Weymuller examined quality-of-life data for patients undergoing RND, MRND, and SND. Shoulder disability at 6 months was the least for SND patients and similar for SND and MRND patients at 12 months. Additionally, MRND and SND patients were noted to have fewer problems with pain than RND patients.[107]

The most common selective neck dissection performed for the management of the regional lymphatics in patients with oral cavity cancers is the supraomohyoid neck dissection (SOHND), which includes removal of lymph node levels I, II, and III. The reported incidence of regional recurrence after elective SOHND is as low as 3%.[108] Inclusion of level IIb nodes within the neck dissection is advocated for oral cavity primaries because of a reported 10% incidence of spread to this region[109]; however, some authors disagree that the inclusion of level IIb is necessary in the setting of elective neck dissection.[110] The occurrence of skip metastases with oral tongue lesions makes possible the involvement of nodes in levels III or IV without involvement of higher echelons of levels I or II. Byers and colleagues[78] noted that patients with lateralized oral tongue squamous cell carcinoma with an ipsilateral N_0 neck had a 15.8% rate of "skip metastases." As a result, Byers and colleagues advocated a level I to IV neck dissection rather than a standard supraomohyoid neck dissection for patients with oral tongue carcinoma and an N_0 neck. Level V nodes are involved in some cases and are seen with concomitant involvement of higher echelon nodes.[111] Midline lesions have a high incidence of bilateral spread to cervical lymphatics and treatment of both necks is indicated in these scenarios. When considering the routes of spread, extensive hard palate lesions must be viewed with concern. Given the predilection for retropharyngeal spread of soft palate tumors, hard palate lesions with posterior extension should be considered for postoperative radiation therapy to address this region that might otherwise go untreated with standard neck dissection. For all sites, the actual presence of cervical

metastasis has a negative impact on survival and, as such, aggressive preoperative investigation and close follow-up for head and neck cancer patients is necessary.[112]

Sentinel node biopsy, as it is currently applied for skin malignancies, has been explored for early-stage (T_{1}-$_{2}N_{0}$) lesions of the oral cavity through the American College of Surgeons Oncology Group (ACOSOG). With the exception of floor of mouth tumors, promising initial results (with negative predictive values >95%) have been reported. Additional investigation of the technique will be required before it is considered standard of care for this clinical scenario.

The decision for surgery versus radiation therapy for treatment of the neck is determined by the modality of treatment chosen for the primary tumor. If the primary tumor is treated with surgery, the neck is generally managed surgically. If the primary tumor is treated with radiation, then the neck is treated similarly.[105] For advanced cervical lymphatic disease (N_2, N_3) or metastasis with extracapsular spread, surgical management of the neck alone is inadequate and postoperative adjuvant radiation therapy is necessary.

Surgically debulking of metastatic disease does not improve survival and is not advocated. Surgical salvage for recurrent neck disease after comprehensive neck dissection or radiation is associated with poor survival.[112]

Figure 96-38. Brachytherapy catheters in place for oral tongue carcinoma resected with narrow surgical margin on final pathology after radial forearm free flap reconstruction.

Radiation

Role of External Beam Radiation

Indications for radiation therapy with oral cavity malignancies include those common in other regions of the head and neck and are stratified by pathologic findings at the primary site and the neck. When indications at either site exist for postoperative radiation, the primary site and both sides of the neck are treated comprehensively. Indications include multiple pathologically positive nodes in the neck, perineural invasion, angiolymphatic invasion, extracapsular spread, close margins (<5 mm) at the primary site, tumor thickness of 10 mm or larger, and advanced T stage.

Of note, two of the indications for postoperative radiation therapy, perineural invasion and vascular invasion, may be identified less frequently than is actually present with standard hematoxylin and eosin staining. Kurtz and colleagues[113] demonstrated an increase in the identification of these pathologic findings when immunohistochemical staining with S-100 (for perineural invasion) and CD31 (for vascular invasion) was used.

Conventional dosing is 1.8 to 2 gray (Gy) per fraction, once a day, 5 days a week, to a dose of 62 to 70 Gy. For locally advanced head and neck cancer, radiation delivered in hyperfractionation and accelerated fractionation with concomitant boost protocols has been demonstrated to provide better locoregional control than conventional radiation dosing.[114]

The most common complication of radiation therapy to the oral cavity is xerostomia. A less common but more serious complication is osteoradionecrosis (ORN). Factors predisposing to ORN include poor dentition, inadequate soft tissue coverage of bony structures, mandibular tori, and mucosal trauma. Aggressive dental care in these patients by a dentist skilled in managing patients requiring radiation therapy is essential. To prepare the patient for radiation, pretreatment dental extraction, removal of tori, and meticulous closure of mucosa are necessary. For patients with preserved dentition, long-term fluoride treatments may prevent progressive caries and subsequent ORN.

Package Time

Rosenthal and colleagues[115] examined treatment package time, defined as the length of time from surgery to completion of radiation therapy, as it related to outcome for patients with locally advanced squamous cell carcinoma of the head and neck. Their findings supported the concept that a total treatment package time of less than 100 days was associated with improved locoregional control and survival. These findings emphasize the importance of developing a surgical treatment plan that minimizes the risks of complications that would delay the onset of radiation therapy and using a radiation protocol that minimizes the need for treatment breaks.

Brachytherapy

Brachytherapy catheter placement for localized radiation boost has a limited role in the treatment of oral malignancies. Brachytherapy has been used for oral tongue and floor of mouth cancers surgically resected with close surgical margins on final histopathologic interpretation. Intraoperative placement is necessary and tracheostomy may not be required (Fig. 96-38). Loading of the catheters occurs within a hospital setting in a protected room after placement. The use of brachytherapy does require a prolonged hospital stay compared with standard surgical treatment requirements. Brachytherapy as a primary treatment has not been advocated because of the creation of post-treatment fibrosis limiting monitoring for recurrence of disease, as well as the risk of post-treatment ORN.

Adjunctive Chemotherapy

Induction chemotherapy has been advocated to decrease the magnitude of resection; however, clinical trials supporting this approach are lacking. Induction (neoadjuvant) chemotherapy is not currently considered standard of care and potentially delays the timing of the definitive therapeutic procedure. Robbins and colleagues have reported on the use of a neoadjuvant RADPLAT protocol (intra-arterial infusion of cisplatin and intravenous infusion of sodium thiosulfate with concurrent radiation therapy to 50 Gy) in the setting of T_2 and T_3 oral carcinomas with varying levels of N staging. Surgery was described as a tumor nidusectomy performed after 8 weeks of therapy. Completed response was noted in 80% of the primary sites and 79% of the regional lymphatic fields. Five-year disease-specific survival rate was 64%, with a locoregional control rate of 74%.[116]

Increased survival with postoperative methotrexate and 5-fluorouracil (5-FU) has been demonstrated in patients with extracapsular nodal spread.[117,118] Evidence suggests a response to chemotherapy is predictive of the likelihood of response to radiation therapy.[119,120]

Cooper and colleagues examined patients at high risk for locoregional recurrence that would benefit from the concurrent addition of cisplatin to postoperative radiation. High-risk patients were identified as having two or more metastatic lymph nodes, presence of extracapsular nodal spread, or positive surgical margins. In reviewing trial data from the Radiation Therapy Oncology Group (RTOG) #85-03 and RTOG #88-24, a benefit in locoregional control was suggested in the concomitant chemoradiation patients defined as "high risk" as opposed to those who received postoperative radiation alone. A difference in survival benefit was not seen between the two groups; however, factors

such as lack of adequate randomization, limited group size, and length of follow-up were sited as reasons necessitating additional study.[120]

The role of induction polychemotherapy followed by radiotherapy or chemoradiotherapy for advanced-stage squamous cell cancer of the oral cavity, oropharynx, hypopharynx, or larynx has recently been reported in two randomized, phase three clinical trials. The European study (EORTC 24971/TAX 323) compared docetaxel, cisplatin, and fluorouracil (TPF) to cisplatin and fluorouracil (PF) as induction chemotherapy followed by radiation therapy for patients with previously untreated, unresectable squamous cell carcinoma.[121] Patients in the TPF group demonstrated a significant improvement in progression-free and overall survival as compared with patients in the PF group. A similar study by Posner and colleagues[122] (TAX 324) compared induction chemotherapy with TPF or PF followed by concomitant chemoradiotherapy with weekly carboplatin. The study population included previously untreated patients with either unresectable disease or advanced-stage disease where organ preservation therapy was being considered. The results were similar to the TAX 323 study, with patients receiving TPF demonstrating a significant improvement in progression-free and overall survival. Unfortunately, neither study included a control group of chemoradiotherapy alone for comparison to the induction chemotherapy group.

Additional Therapies

Photodynamic Therapy

Photodynamic therapy (PDT) may have a potential role in the treatment of widespread premalignant and superficial oral carcinoma. Use for residual tumor at positive resection margins has also been considered.[123] This modality has been used for palliative treatment of gastrointestinal tract, bladder, and lung cancers. Photofrin, a light-activated dye, which theoretically localizes to tumor tissue, is activated by exposure to a 620-nm light and produces oxidizing free radicals. Through disruption of the vasculature, tumor necrosis occurs.[124] Ideally, PDT should preferentially affect tumor tissue; however, histologic examination of post-PDT specimens have demonstrated the resultant tissue damage is not absolutely tumor-specific because tissues separate from the tumor also show evidence of necrosis.[125] Advantages of PDT include the potential for multiple treatments with favorable functional and cosmetic results. A disadvantage of PDT includes the prolonged skin photosensitivity that may last up to 6 weeks. Newer generations of photosensitizers may be more specific for neoplastic tissue and result in less long-term photosensitization.

In a review of the use of PDT for the treatment of carcinoma in situ (CIS) and early-stage lesions of the head and neck, Biel examined the response of CIS and T1 recurrent squamous carcinomas of the oral cavity.[123] A complete response to therapy was noted after one treatment in the 29 patients; however, 5 patients developed recurrences within a follow-up period of 70 months.[126] Intraoperative adjuvant treatment with PDT for advanced-stage and recurrent tumors at the tumor's primary site or regional lymphatic bed has also been advocated.[123]

Organ Preservation Protocols

An organ preservation approach to oral cavity carcinoma similar to laryngeal preservation treatment has been explored. Chemoradiation protocols have demonstrated effective organ preservation for advanced cancers and would be an attractive alternative for patients facing the need for total glossectomy if bony involvement is absent. Attempts at intra-arterial chemotherapy for advanced disease have demonstrated promising results; however, the toxicity and technical ability to perform this therapy remain obstacles to widespread utilization.[127]

Chemoprevention

The concept of chemoprevention has been investigated in clinical studies. The goals of treatment are to reverse oral premalignancy and prevent emergence of second primary tumors. Several agents have been used including peroxisome proliferator-activated receptor (PPAR), isotretinoin, and COX-2 inhibitors.[128] Because of the side effects associated with some agents (in particular with retinoids) and lack of proven efficacy, general application in the clinical setting has not occurred. Investigation into the use of a "biofilm" created with a mucosal adhesive film to allow for topical administration of tretinoin has been demonstrated to be safe in the animal model and has the potential to decrease the toxicities associated with conventional use of the medication.[129]

In animal models, lyophilized black raspberries and vitamins C and E can reduce the number of dimethylbenz(a)anthracene (DMBA)-induced tumors within a hamster cheek pouch and may prove to have a role in chemoprevention.[130,131] However, in a randomized controlled trial, research examining the potential protective effects of vitamin E and beta-carotene supplementation failed to demonstrate a protective effect on the development of oral cancers in male smokers.[132] Studies have also suggested the Bowman-Birk protease inhibitor may be an agent of interest for treating premalignancy. A response was noted in approximately one third of patients treated for leukoplakia with low associated toxicity.[133]

Regular use of aspirin has been shown in a case-control study to decrease the risk of developing head and neck cancer. The effect was noted to be more significant in women and low to moderate users of alcohol and tobacco products. Heavy smokers and users of alcohol failed to demonstrate a chemoprotective benefit from regular aspirin use.[134]

Reconstruction

For a successful reconstruction after oncologic resection, several important principles must be taken into consideration. These include maximizing mobility of the remaining tongue, reconstructing adequate bulk, obtaining adequate access to inset tissue for reconstruction, performing a watertight closure, and reconstructing the appropriate sulci such that prosthetic rehabilitation is not hindered.

The method chosen for reconstruction depends on the nature of the defect and the patient's comorbidities. Options, after the resection of small lesions, include allowing the wound to heal by secondary intention, primary closure, and split-thickness skin or dermal grafting. Depending on the size and location of the defect, various advancement and rotation flaps serve as reconstructive options. Use of buccal fat, temporoparietal fascia, or pectoralis major flaps each offer unique options for soft tissue reconstruction. Reconstruction of the mandible is a more significant challenge. Anterior mandibular defects mandate osseous reconstruction (Fig. 96-39). The expanded reconstructive armamentarium provided by free-tissue transfer affords a one-stage method for restoring form and function in patients with complex defects. Reliability of free-tissue transfer is greater than 95% at experienced centers.[135] The possibility of distraction osteogenesis to address

Figure 96-39. Postresection of a T_4 floor of mouth squamous cell carcinoma requiring composite resection extending from mandibular angle-to-angle. Note the extent of the soft tissue defect around the inferior aspect of the tongue. Osseous free tissue reconstruction was required.

smaller mandibular defects is currently under investigation and may provide an alternative to free-tissue transfer in selected patients.[136]

Indications for Free Flap Reconstruction

Pectoralis major pedicled flaps and microvascular soft tissue reconstruction allow for the correction of the mucosal and soft tissue defects associated with tumor resection. For full-thickness buccal defects and extensive glossectomy defects, the pectoralis major flap can be partially de-epithelialized or rotated back on itself to provide resurfacing of the oral cavity components and the external lower one third of the face. However, the optimal treatment for many of these complex defects often requires microvascular free tissue reconstruction. The radial forearm free flap allows for a reconstruction that is tailored in shape to the oral defect without the burden of excessive bulk; offers the option for neural anastomosis, thus providing sensate reconstruction; and is associated with a limited donor site morbidity. When additional soft tissue is required, the anterolateral thigh,[137] rectus, and parascapular-scapular flaps may be harvested with larger skin paddles and associated muscle for additional bulk.

As discussed earlier in this chapter, reconstruction of the mandible depends on the location of the defect. In a review of their experience, Urken and colleagues reported on 210 cases requiring mandibular reconstruction. The need for segmental mandibulectomy was necessary for the treatment of benign and malignant tumors of the oral cavity and in the management of stage III osteoradionecrosis. They compared four groups of patients that included those reconstructed with iliac crest, patients who were not reconstructed (lateral defects), normal denture wearers, and normal dentate patients. The study demonstrated that speech and swallowing function were determined by the soft tissue reconstruction. Bite force was best if osteointegrated implants were achieved in patients with bony reconstructions. In addition, oral competence was improved with reconstructed patients.[135]

Indications for a fibula osteocutaneous free flap reconstruction include total-subtotal mandibular reconstruction, reconstruction of "bone-only" defects (osteoradionecrosis), reconstruction of the atrophic mandible, pediatric mandibular reconstruction, and secondary reconstruction of the subcondylar-condylar complex (Fig. 96-40).[135]

Patients with advanced-staged complex primary lesions often present reconstructive dilemmas. For defects requiring additional soft tissue reconstruction, double free-tissue transfer with a soft tissue flap and an osseous flap have been advocated.[135] A scapular composite flap offers the advantage of multiple skin paddles with bone.[138] In addition, the presence of a musculoskeletal abnormality of the lower extremities may preclude a fibular free tissue transfer. Use of two microvascular free flaps, the fibula free flap combined with radial forearm free flap, has also been described to accomplish a reconstruction consistent with the needs of the specific defect. When external skin resurfacing is necessary, a cervicofacial advancement flap is a desirable option to consider in combination with a separate intraoral reconstructive technique.

Reconstructive options for composite resections of the oral cavity are dependent on location and the functional status of patients. An anterior mandibular defect in a healthy young patient is viewed differently than a lateral mandibular defect in a deconditioned elderly patient with poor dentition. Despite technical feasibility, not every patient requires free flap reconstruction to attain the postoperative goals of adequate speech and effective swallowing. An understanding of a patient's expectations and an understanding of the attainable reconstructive results, while using the support of prosthodontists and speech and swallowing therapists, can create an atmosphere for successful rehabilitation.

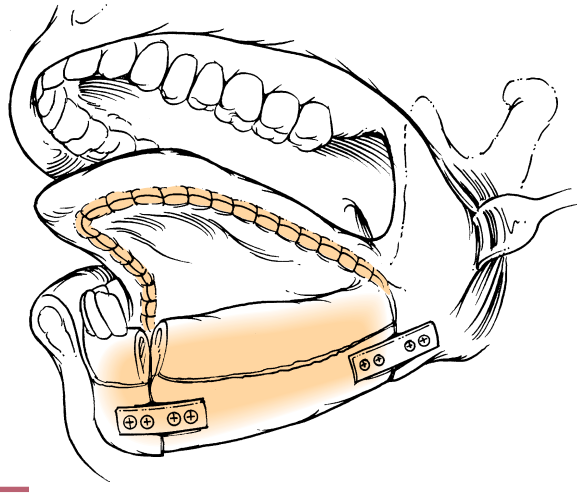

Figure 96-40. Fibular free flap reconstruction of the segmental mandibular defect and of the soft tissue defect of the floor of mouth and tongue. Vessel anastomosis is noted in the neck. *(Adapted from Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. New York: Churchill Livingstone; 1999.)*

Long-Term Management and Rehabilitation

Speech and Swallowing

To achieve the optimal functional outcome, it is important that the speech and swallowing therapist evaluates the patient before treatment. Preoperative consultation will provide an assessment of the patient's pretreatment functional status and allow counseling concerning the potential functional outcome after treatment. The educated patient has more realistic expectations with respect to dysphagia, nutritional supplementation, xerostomia, and mucositis that may occur with treatment. A successful speech and swallowing outcome requires a high degree of patient motivation and cooperation.

As a rule, the more limited the surgical resection, the less likely a patient is to experience significant functional impact on speech and swallowing. Patients requiring wide surgical resections of the retromolar trigone or procedures that extend deep within the tongue base experience the most significant impact on swallowing. Floor of mouth resections are associated with a detrimental effect on chewing.[139] Radiation, alone or in combination with surgery, has a side effect profile including problems such as xerostomia, lymphedema, and fibrosis with scar contracture. Postoperatively, the speech and swallowing therapist will assess the patient's ability to progress to normal oral intake. Prevention of aspiration pneumonia in these patients is vital. An early postoperative evaluation of swallowing function with a flexible laryngoscope (with a fiberoptic endoscopic evaluation of swallowing protocol) or modified barium swallow can guide the direction of swallowing rehabilitation.

Pain Management

Patients undergoing treatment of oral cavity malignancies, in particular those having extensive surgical procedures with reconstruction, require a comprehensive pain management plan. Initial postoperative pain management is accomplished by the use of patient-controlled analgesia (PCA). A transition from intravenous analgesia to oral administration is important as the patient progresses to discharge. A visual analog pain scale will aid the physician and patient in adjusting the amount of analgesia required. A balance must be struck between providing adequate pain control and excessive sedation, which delays ambulation and rehabilitation. The importance of physical therapy for patients recovering from extensive surgical and reconstructive procedures is significant. Finally, for patients whose pain management is difficult, consultation by the pain management service is helpful for tailoring the analgesia regimen.

Palliative Care

Palliative care options should be considered for patients with unresectable disease or when recurrence precludes curative therapy. Palliative chemotherapy and radiation can provide symptom relief when pain and tumor growth adversely affect quality of life. Decisions to place a tracheostomy and gastrostomy tube are individualized and may provide significant comfort without unnecessarily prolonging life. Hospice consultation is important for aiding the patient and family with making end-of-life decisions.

Table 96-4

American Head and Neck Society Guidelines for Cancer Surveillance

Year Post-Treatment	Interval (Mo)
1st	1-3
2nd	2-4
3rd	3-6
4th and 5th	4-6
After 5th	Every 12

From Deschler DG, Hayden RE. The optimum method for reconstruction of complex lateral oromandibular-cutaneous defects. *Head Neck*. 2000;22:674-679.

Follow-up

Follow-up occurs in two phases for patients undergoing surgery and radiation for oral malignancies. In the initial phase, when the patient is recovering from surgery or radiation therapy, weekly follow-up may be necessary to assess nutritional status and monitor rehabilitation goals. The second phase is cancer surveillance. See Table 96-4 for the American Head and Neck Society guidelines for cancer surveillance.[140]

In addition to monitoring for locoregional recurrence, an annual chest radiograph, liver function tests, and comprehensive head and neck examination are important for detecting metachronous lesions. A biannual thyroid-stimulating hormone (TSH) determination is necessary for patients after neck irradiation, as are frequent dental evaluations for dentate patients.

Long-term survival in the face of disease recurrence is limited. Argiris reported on the experience of 399 patients in Eastern Cooperative Oncology Group trials (ECOG 1393 and 1395) receiving palliative chemotherapy in the setting of locoregionally recurrent or metastatic disease. At 1 year, the overall survival was 32%. At 2 years, 49 patients (12%) were alive. Only 6 patients lived to 5 years after the diagnosis of recurrence.[141]

Complications

Postoperative complications are common after extensive head and neck surgical procedures. In the immediate postoperative period the patient is at greatest risk for pulmonary embolism, gastric ulceration, hemorrhage, delirium tremens, and aspiration pneumonia. Vigilance for symptoms indicative of these adverse events may permit early detection and life-saving interventions.

A late complication after radiation therapy is osteoradionecrosis. Early treatment may prevent substantial bone loss and includes hyperbaric oxygen therapy, antibiotics, and sequestrectomy. When mandibular loss occurs, microvascular reconstruction has been successful in salvaging the remaining healthy tissue while reconstructing the necrotic tissue lost.

Delayed pathologic fracture may occur after marginal mandibulectomy when inadequate mandible remains. After bony reconstruction, a nonunion may occur and lead to infection, mobility, or fistula formation.

Summary

The oral cavity is a unique site within the head and neck in that the accessibility of the region readily allows for the identification of premalignant and early-staged lesions. The preferred primary treatment modality for oral cavity malignancies is surgical. Given that speech and swallowing function are profoundly affected by the treatment of oral tumors, oncologic resection and reconstruction require careful preoperative planning. For advanced-staged lesions, the use of combination therapy—surgery followed by postoperative radiation therapy—remains the optimal treatment option. Management by a multidisciplinary team is critical to provide the patient with the best chance for control of cancer while achieving the best functional outcomes.

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CHAPTER NINETY-SEVEN

Reconstruction of the Mandible

Brian Nussenbaum

Key Points

- Advances in surgical techniques and improved hardware options enabled the development of successful methods used today for mandibular reconstruction.
- Most mandible defects are caused by resection of neoplasms, most of which are malignant. The effectiveness of associated soft tissue reconstruction, especially if it involves the oral tongue, is frequently the major determinant in functional recovery.
- Marginal mandibulectomy involves excising a rim of mandible but with maintenance of the mandibular arch. These defects should be made in a curvilinear manner, and at least 1 cm of mandibular height should be retained.
- Segmental mandibulectomy involves resection of a full-thickness segment of bone, which creates a discontinuity defect. Lack of reconstruction causes significant functional and cosmetic morbidity.
- Segmental anterior defects should be corrected by reconstruction with osseous free tissue transfer in combination with a locking reconstruction plate. Lateral defects are generally corrected by reconstruction with either osseous or soft tissue flaps in combination with a locking reconstruction plate. The best long-term stable, successful reconstructions are with osseous free flaps.
- A soft tissue flap is less often used than a bone flap for lateral mandibulectomy defects because of extrusion (within 1 year of surgery) or fracture (within 2 years) of the plate in this setting.
- Patients who require segmental mandibulectomy because of malignancy have a poor prognosis, which sometimes influences the choice of the method of reconstruction.
- Fibular free-flap reconstructions for oromandibular defects are durable, lasting at least 10 years, and this vascularized bone graft does not undergo significant resorption, even in the setting of postoperative radiation.

Major advances in patient care generally occur through paradigm shifts (Fig. 97-1). For reconstruction of the mandible and maxilla, the first major paradigm shift occurred with the development of reliable free tissue transfer options along with advances in hardware devices. Before these advances, techniques involving nonvascularized bone grafts, vascularized pedicled bone grafts, and alloplastic materials were not reliably successful for primary reconstruction, especially in the typical defects that were caused by tumor-ablative surgery.[1,2] Both advances in surgical techniques and improved hardware options were crucial for this first paradigm shift, which occurred circa 1990 for mandibular reconstruction and circa 2000 for maxillary reconstruction. Although current options have proved to be reliably successful for single-stage primary reconstruction in the mandible and maxilla, these procedures remain highly complex and challenging, and donor sites are still required. In addition, it is difficult to restore the intricate three-dimensional structure precisely in many defects with bone from distant sites because of differences between the size and shape of the bone graft and the defect configuration. Advances in biotechnology, specifically in the field of tissue engineering, will probably have an effect on mandibular and maxillary reconstruction and will cause another paradigm shift within the foreseeable future.[3]

Anatomy, Physiology, and Pathophysiology

The mandible is the strongest facial bone.[4] It is a U-shaped bone with a horizontal portion (body), which carries an alveolar process with teeth, and two vertical portions (rami), which, through the temporomandibular joints, articulate with the skull bilaterally (Fig. 97-2). The mandible is attached to other facial bones by ligaments and muscles, and it articulates with the maxilla through occlusion of the teeth.

The body of the mandible has a dense cortical structure on the lateral and medial surfaces with a small core of spongiosa that contains nerves, blood vessels, and lymphatic vessels. The lower portion of the body contains heavy, thick bone that changes very little throughout life. The upper portion of the body, called the *alveolar process,* contains the dental sockets that support the teeth. Changes in the alveolar process occur throughout adult life, especially after dental extractions, which cause subsequent atrophy of this bony segment (Fig. 97-3). The mental foramen is midway between the inferior border and upper edge of the alveolar process, at the level of the second premolar tooth. The mental nerve branch of the inferior alveolar nerve and the associated vessels pass through this foramen. In an edentulous mandible, the mental foramen drifts to the upper border of the bone as a result of atrophy of the alveolar process (see Fig. 97-3).

The rami, the two vertical portions of the mandible, are composed of broad, thin plates of dense bone. Each ramus joins with the body to form the angle of the mandible. Each ramus ends anteriorly in the coronoid process and posteriorly in the condylar process. The coronoid and condylar processes are joined by a concave ridge called the *mandibular notch.* The condylar process is composed of the condyle and condylar neck. The superior surface of the condyle articulates with the temporomandibular joint.

The mandible is traversed by the alveolar canal, which begins on the inner surface of each ramus at the mandibular foramen and extends toward the symphysis to open on the lateral surface at the mental

foramen. The inferior alveolar nerve passes through this canal to provide sensation to the teeth roots and to the soft tissue of the lower lip and chin through the mental branch, which exits the mandible through the mental foramen.

The movement of the mandible is dependent primarily on two groups of muscles. The depressor-retractor group, which is anterior, is the weaker of the two groups and is composed of the geniohyoid and digastric muscles. These muscles insert into the inferior inner aspect of the symphyseal region and exert downward posterior force. The elevator group, which is posterior, is composed of the masseter, medial pterygoid, and temporalis muscles. The masseter muscle inserts along the outer aspect of the inferior edge of the angle. The medial pterygoid muscle inserts on the inner surface at the mandible angle, thus producing the masseteric-pterygoid sling. The masseter and medial pterygoid muscles always act simultaneously and hold each other in balance, but the angulation of the attachments at the angle is more favorable for the medial pterygoid. Thus, although the medial pterygoid muscle is weaker than the masseter in the intact mandible, it usually overpowers the masseter in segmental defects as a result of this more favorable angulation; this accounts for the typical displacement patterns that occur. Other muscles with more minor influence on the movements of the mandible include the lateral pterygoid and mylohyoid muscles. The lateral pterygoid muscle inserts mostly on the anterior inner aspect of the condylar neck and pulls primarily the neck medially and anteriorly. The mylohyoid muscle has minimal influence on movements of the intact mandible, inasmuch as most of its bundles insert into the muscle's midline raphe rather than onto the mandible.[4]

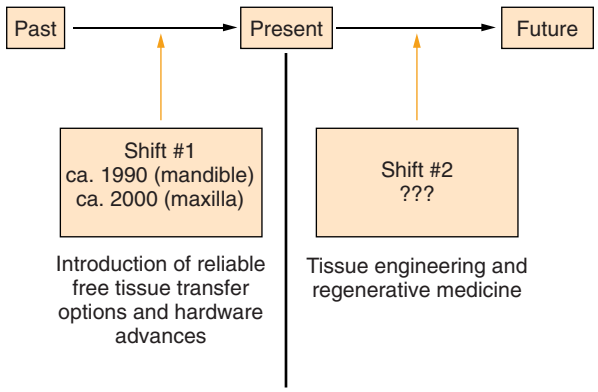

Figure 97-1. Advances in mandibular reconstruction.

The damage to the oral cavity after tumor extirpation was described by Conley in 1962.[5] Options for bone or soft tissue reconstruction were limited at that time, but the serious effects of extirpative surgery on function and cosmesis were clearly recognized. Functions of the oral cavity structures include mastication, swallowing, maintenance of oral competence, articulation, taste, oral hygiene, and airway protection.[6] Effective reconstruction of the oral cavity soft tissue components is crucial for functional restoration, especially in preserving mobility, position, and shape of the tongue, which is probably most critical for functional rehabilitation.[6]

There are two types of mandibulectomies: marginal and segmental (Fig. 97-4). In a marginal mandibulectomy, a rim of bone is resected, but continuity of the mandibular arch is maintained. When this type of mandibulectomy is performed, a curvilinear excision configuration must be used, and a minimal 1 cm height of inferior bone must be preserved, in order to avoid iatrogenic fracture.[7,8] The bone defect in a marginal mandibulectomy does not necessitate any specific reconstruction except for soft tissue coverage, usually with a soft tissue flap or skin graft.[9] The reconstructive plan in this setting is directed by the characteristics of the soft tissue defect and influenced mostly by the extent of soft tissue loss and whether the tissue has been previously irradiated.

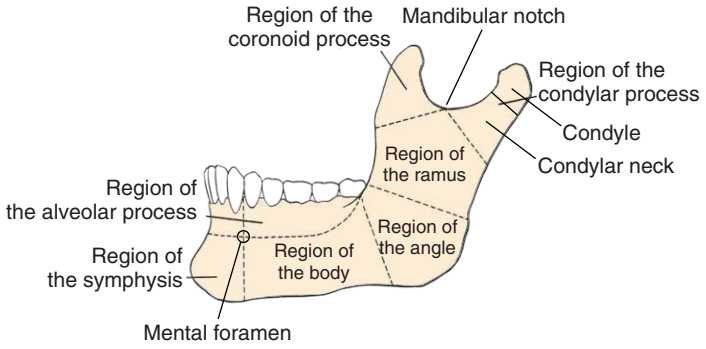

Figure 97-2. Anatomic regions of the mandible. *(From Dingman RO, Natvig P.* Surgery of Facial Fractures. *Philadelphia: WB Saunders; 1964.)*

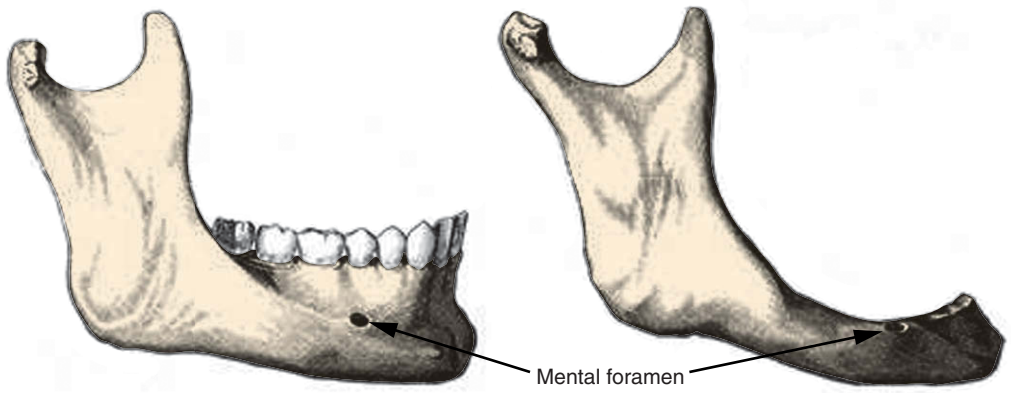

Figure 97-3. Comparison of the anatomy of a dentulous mandible (*left*) with an edentulous mandible (*right*). *(From Dingman RO, Natvig P.* Surgery of Facial Fractures. *Philadelphia: WB Saunders; 1964.)*

Segmental mandibulectomy involves resection of a full thickness of bone, which creates a discontinuity defect (see Fig. 97-4). Significant cosmetic and functional morbidity are associated with segmental defects. For defects involving the anterior mandible (between both mental foramina), the lateral segments act independently, and the displacement pattern is influenced by the remaining attached muscles (Fig. 97-5).[10,11] The medial pterygoid muscle overpowers the masseter and pulls the segments upward, posteriorly, and medially. This movement brings the teeth out of alignment and disrupts mastication. There is complete loss of projection of the lower midline third of the face, which causes an overhanging upper jaw, the so-called Andy Gump appearance. The tongue loses anterior support, thus becoming malpositioned with posterior displacement. The oral sulci become obliterated. The upward movement of the larynx is lost with swallowing as a result of detachment of the suprahyoid musculature. The lower lip is numb as a result of resection of the mental nerves. All these changes lead to a cosmetically and functionally disabling situation for the patient. For defects involving the lateral mandible (posterior to the mental foramina), the remaining bone deviates toward the defect through the action of the remaining muscles of mastication, primarily the medial and lateral pterygoid muscles (Fig. 97-6).[10,11] This causes malalignment of the teeth, which affects mastication. The deformity is accentuated by opening the mouth or chewing.

Most mandibular segmental bone defects are caused by ablative surgery for benign or malignant neoplastic tumors; the majority of affected patients have oral cancer. An associated loss of oral soft tissues also occurs in most of these patients, which causes an oromandibular defect. An important consideration for these patients is whether they have a history of treatment with radiation or whether postoperative irradiation will be required. Fewer patients have a segmental defect caused by trauma, osteoradionecrosis, bisphosphonate-induced osteonecrosis, or osteomyelitis.

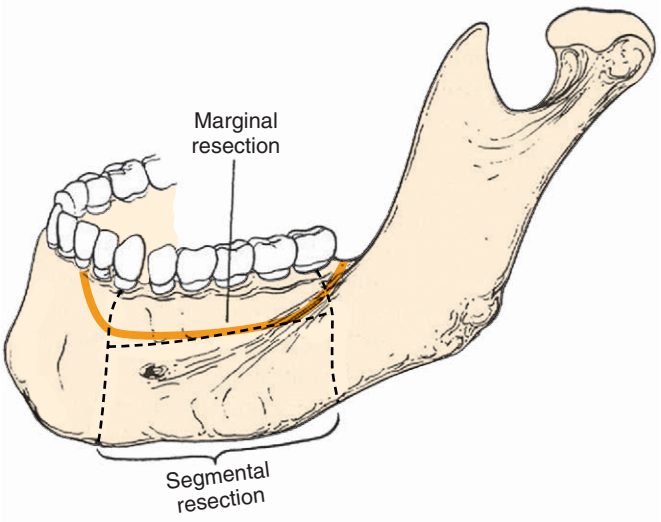

Figure 97-4. Techniques of mandibulectomy: marginal and segmental. *(From Silver CE, Rubin JS.* Atlas of Head and Neck Surgery. *2nd ed. London: Churchill Livingstone; 2002.)*

Classification of Defects

A combination of the extent of bone and soft tissue loss determines the reconstructive method. Classification systems that account for this fact are useful. Various classification schemes that have been described for segmental mandibulectomy defects can be used for documenting the defect components, which helps with planning the reconstruction (Fig. 97-7). In Boyd and colleagues'[12] classification, *H* defects are lateral defects of any length up to the midline that include the condyle; *L* defects are lateral defects that exclude the condyle; and *C* defects involve the central segment containing the four incisors and two canines. The three lowercase letters in this classification system describe the associated soft tissue components: *o* (no skin or mucosal component), *s* (skin), *m* (mucosa), and *sm* (skin plus mucosa). Boyd and colleagues recognized the reconstructive and functional problems posed by the absence of the condyle and mentum; thus, their system is similar to Pavlov's classification system, described before the era of free tissue transfer.[12] With loss of the condyle, reconstruction of an articular surface is difficult. Loss of the central segment poses problems with restoration of stomal competence, restoration of an anterior gingivo-

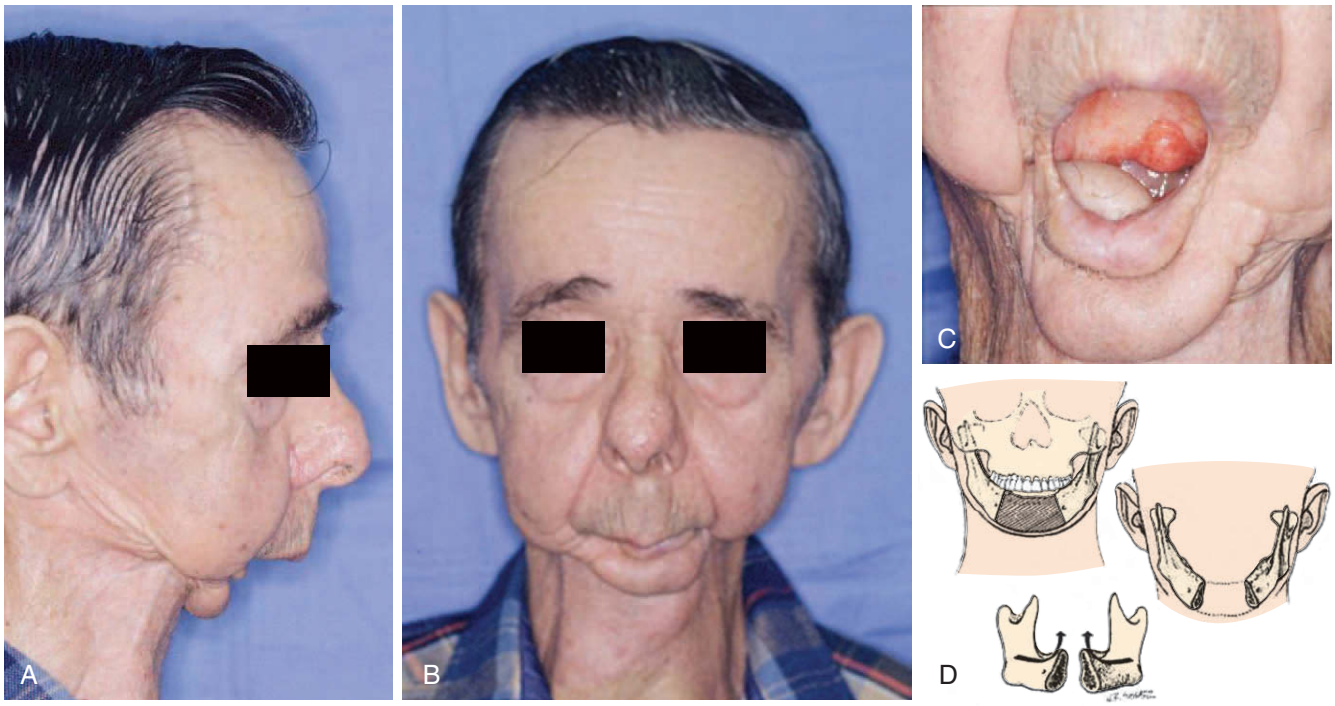

Figure 97-5. Anterior mandible defect without reconstruction. **A, B,** and **C,** Typical "Andy Gump" deformity. **D,** Displacement of the remaining mandible segments. *(**D,** From Cohen M, Schultz RC. Mandibular reconstruction.* Clin Plast Surg. *1985;12:411-422.)*

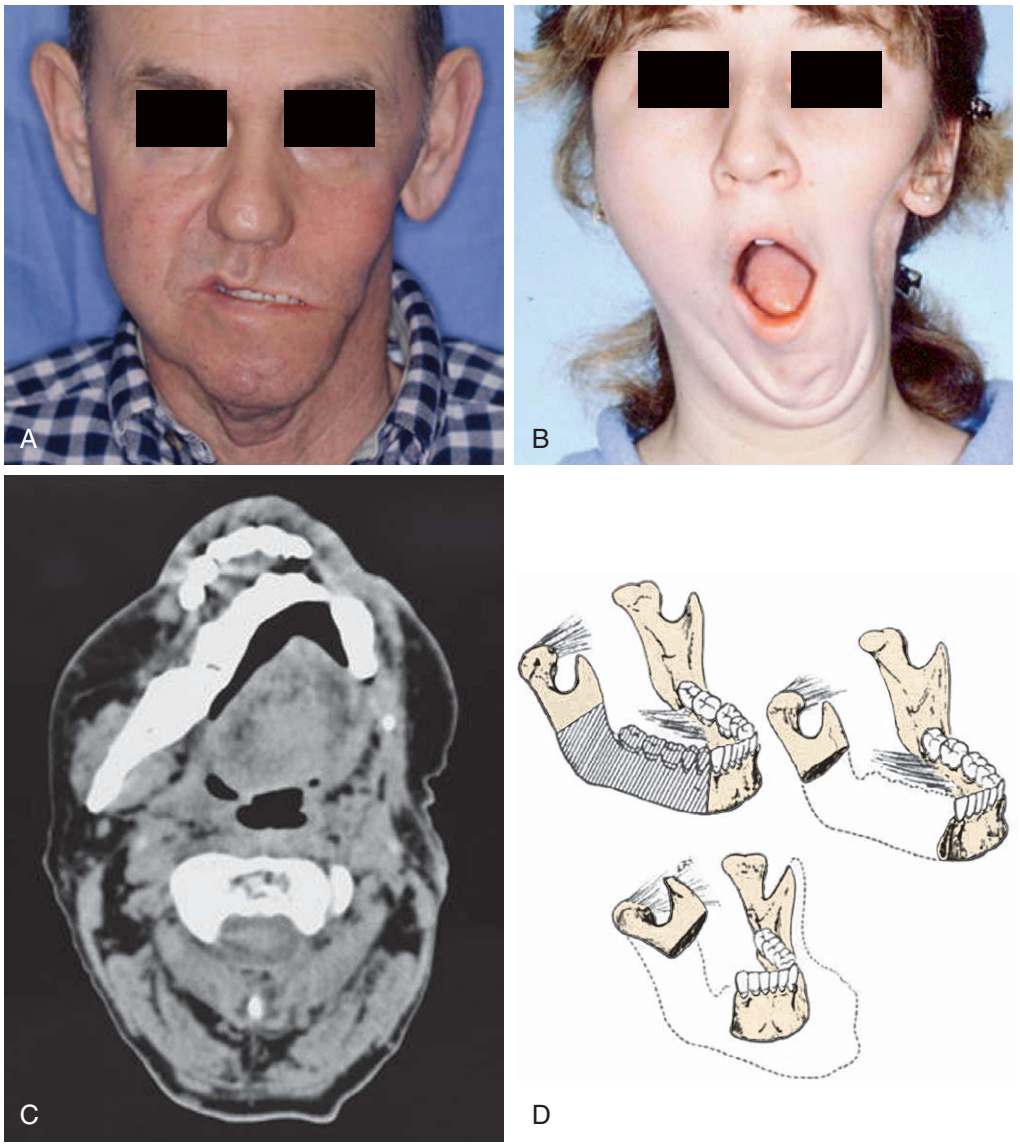

Figure 97-6. Lateral mandible defect without reconstruction. **A,** Typical defect with loss of symmetry on lower third of face and malocclusion. **B,** Accentuation of the defect with oral opening. **C,** Computed tomography scan of the patient in **A,** showing the malalignment of the upper and lower jaws. **D,** Diagram of displacement of the remaining mandible segments. *(**D,** From Cohen M, Schultz RC. Mandibular reconstruction.* Clin Plast Surg. *1985;12:411-422.)*

labial sulcus to fit prosthetics for dental rehabilitation, and restoring the lip height for cosmesis.

Another classification scheme, described by Urken and associates,[13] is similarly based on functional considerations caused by the detachment of different muscle groups and difficulties with cosmetic restoration. This reconstruction scheme has similar anatomic designations, including separate components of the condyle (*C*), ramus (*R*), body (*B*), total symphysis (*S*), hemisymphysis (S^{H}), and palate (*P*). Urken and associates' classification system also includes a detailed description of soft tissue and neurologic deficits.

Neither of these two classification systems describes the absolute length of the defect. Before the use of free tissue transfer, the chance of healing and bony union depended more significantly on size when nonvascularized bone grafts were used. When osseous free flaps are used, outcomes are less dependent on the length of the graft required to bridge the defect.[12]

Goals of Mandibular Reconstruction

The primary objective of tumor resections that necessitate mandibulectomy is cure, but the functional and cosmetic rehabilitation are crucial for the physiologic and psychologic well-being of patients. The ideal reconstruction for a segmental mandibulectomy (1) restores oral competency, (2) maintains occlusal relationships with remaining teeth, (3) allows for prosthetic dental restoration, (4) restores bone continuity, and (5) restores facial symmetry and contour to the lower third of the face.[14] In addition, wound closure should be immediate and complete in order to maximize early functional recovery, avoid orocutaneous fistula, avoid infection, create a safe wound that can undergo postoperative radiation 6 weeks later, and facilitate early hospital discharge. To achieve these goals, basic principles of reconstructive surgery dictate that the simplest method to achieve the desired results should be chosen for each individual patient.

Background and History

Before the development of advances in surgical techniques and improvements in hardware, reconstructive options were limited and yielded disappointing results. The available options for bone replacement at that time included nonvascularized autogenous bone grafts, allogeneic bone grafts, and vascularized pedicled bone grafts.[11] The failure rate of vascularized pedicled bone grafts was as high as 50%.[1] Nonvascularized

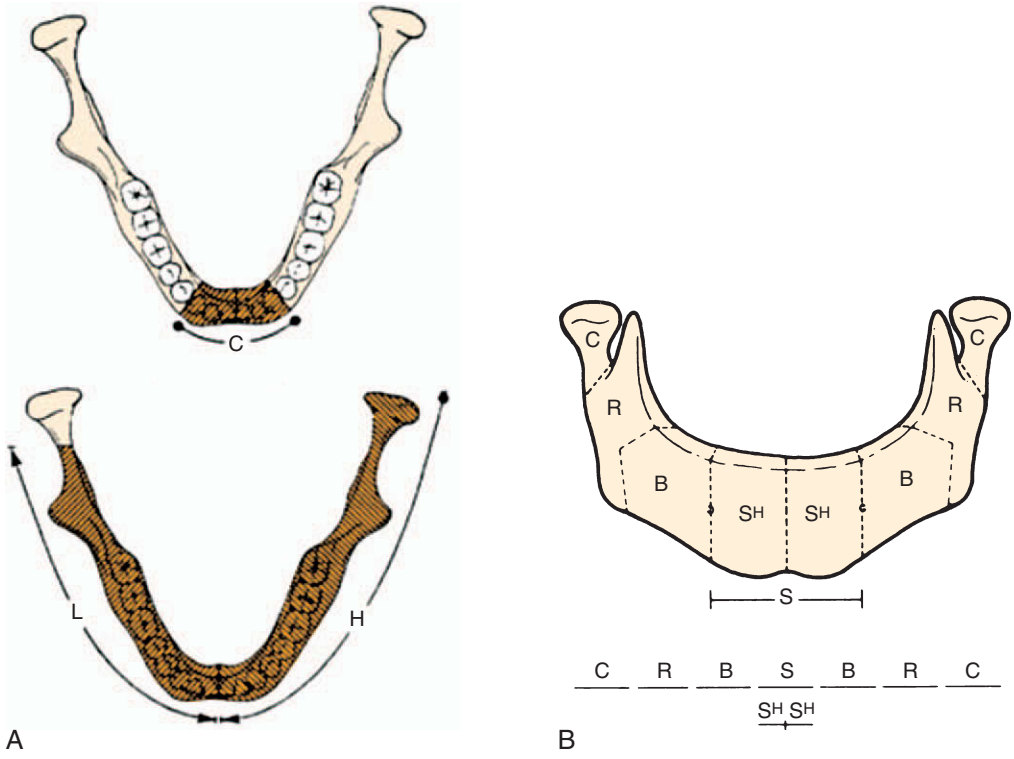

Figure 97-7. Systems of classification of mandible defects described by Boyd and colleagues[12] **(A)** and Urken and associates[13] **(B).** *(**A,** From Boyd JB, Gullane PJ, Rotstein LE, et al. Classification of mandibular defects.* Plast Reconstr Surg. *1993;92:1266-1275.* ***B,*** *From Urken ML, Weinberg H, Vickery C, et al. Oromandibular reconstruction using microvascular composite free flaps. Report of 71 cases and a new classification scheme for bony, soft tissue and neurologic defects.* Arch Otolaryngol Head Neck Surg. *1991;117:733-744.)*

bone grafts, which rely on neovascularization, were found to be prone to infection, extrusion, or resorption when placed into defects in which the oral mucosa was violated or in the setting of perioperative irradiation. Hardware options included alloplastic materials such as trays, prostheses, and Kirschner wires. These devices were designed to prevent displacement of the remaining mandibular segments, support the surrounding soft tissue, and minimize wound contracture.[15] Unfortunately, these devices yielded disappointing results because of loosening, migration, exposure, and fracture.

Many studies, including those published by Adamo and Szal,[2] Lawson and Biller,[1] and Komisar,[16] consistently revealed poor results of mandibular reconstruction with the available approaches and technologies. Mandible reconstruction usually proceeded in multiple stages fraught with complications. The management of these complications increased the number of hospitalizations by an average of three per patient.[16] These complications sometimes delayed the postoperative treatment with radiation, which affected the ability to cure the cancer. Primary reconstruction yielded the best results but had the highest rate of complications. Secondary reconstruction produced fewer complications but suboptimal results.[1,2,16,17] In the secondary setting, soft tissue contracture and fibrosis caused by prior irradiation would fixate the remaining bone segments in a malpositioned orientation, and the fibrosis of the remaining muscles of mastication accentuated this problem.

Even with the successful reconstructions, although most patients demonstrated cosmetic improvement, few experienced significant functional benefits.[15-17] The functional limitations resulted from misalignment of the mandible, trismus caused by fibrosis, soft tissue losses, and failure of a bony segment capable of supporting a dental prosthesis. Gullane[15] reported that the functional outcomes for patients with primarily lateral defects were more dependent on the soft tissue loss than on the bone reconstruction. At this point, the decision to perform reconstruction needed to be weighed against the overall poor results, increased complications, increased morbidity, and possibility of introducing delays in receiving postoperative radiation treatment. Although the outcomes were suboptimal, many important factors for success that were learned during this era are still basic tenets for mandible reconstruction: (1) stable immobilization of the mandible segments to minimize distortion and maintain occlusal relationships, (2) performance of as much primary reconstruction as possible, (3) importance of soft tissue reconstruction for functional restoration and minimizing hardware complications, and (4) importance of good wound bed vascularity. These early efforts were also important strides toward the development of reliable, one-stage primary reconstructive techniques that are frequently used today.

The paradigm shift toward current reconstructive options occurred with advances in surgical techniques involving free tissue transfer and with the introduction of improved hardware options with mandibular reconstruction plates that replaced Kirschner wires and metal trays. Successful transplantation of autologous vascularized composite tissue was the most important innovation that allowed for this paradigm shift. Although improvements in bone fixation methods were also important, their importance was secondary to the reliability and adequacy of bone and soft tissue healing, which were provided with free flaps.

In 1976, Panje and coworkers[18] introduced successful reconstruction for large oral soft tissue defects after tumor-ablative surgery. A free groin flap was used for reconstruction in four patients, and these tissue transfers were successful despite preoperative or postoperative irradiation and oral bacterial contamination. Inclusion of bone with a skin flap was a natural extension of the free flap concept for repairing composite oromandibular defects. Pioneering experimental and anatomic studies proved the feasibility of using composite flaps consisting of bone and soft tissue that were based on a single vascular pedicle.[19-22] Subsequently, successful reconstruction for large oromandibular defects with bone from the ilium was described.[23-25] The transfer of vascularized fibular bone, which was initially described for complicated extremity reconstruction, was subsequently described for oromandibular reconstruction.[26,27] In the majority of medical centers, the fibular osteocuta-

neous flap is now the most common free tissue transfer used for oromandibular reconstruction.

Hardware for use in the mandible was initially composed of Vitallium (an alloy containing cobalt, chromium, and molybdenum), but because of poor malleability, the metal was subsequently changed to stainless steel and then to titanium for better tissue compatibility.[15] In a study of 60 patients treated from 1974 to 1986, Klotch[28] described the effectiveness of reconstruction plates for bridging the defect and providing stabilization of the remaining mandibular segments. These plates could be placed rapidly, were well tolerated by tissue, were structurally rigid, and could be readily shaped to the contour of the defect. Hardware problems, however, still occurred frequently with these plates until the development of more reliable methods of soft tissue reconstruction with pedicled and distant flaps.[15,28-30] The initial combination of well-vascularized soft tissue reconstruction with reconstruction plates significantly improved the short-term results of primary reconstruction; however, because of continued problems with plate extrusion, plate fracture, and screw loosening, this combination did not provide long-term stability.[31] Without bone reconstruction for the defect, the hardware still tended to fail as a result of metal fatigue, leveraged forces with mastication (especially for patients who still had teeth), and volume losses.[32] Using this technique anterior mandibulectomy defects continued to have a particularly high rate of extrusion, and affected patients were not considered good candidates for this approach.[29,33] The subsequent development and application of osseous free flaps in combination with plates further improved the reliability (short- and long-term) and outcomes of one-stage primary reconstruction for both anterior and lateral mandible defects.[34]

Current Methods

Three options for reconstructive treatment of segmental mandibulectomy defects are available: (1) reconstruction plate alone, (2) reconstruction plate combined with an osseous free tissue transfer, and (3) reconstruction plate combined with a soft tissue flap. Decision making can be quite complex, being influenced by the patient's age, performance status, comorbid conditions, tumor characteristics, prognosis, dental status, patient's anatomy, patient's preferences, surgeon's comfort level, and characteristics of the defect components. Use of a reconstruction plate alone should be considered as only a temporizing short-term method because of the high risk of hardware complications. This technique should be considered only for patients with small lateral defects, minimal associated soft tissue defects, severe medical comorbid conditions, and poor cancer prognosis.

Reconstruction plate combined with an osseous free tissue transfer is the preferred reconstructive method for anterior defects because other methods have a high rate of hardware extrusion and because of the significant morbidity associated with not performing reconstruction for the defect.[29,33] For lateral defects, this approach has several advantages: (1) restoration of the bone continuity of the mandible, (2) facilitation of dental restoration, (3) the most consistent long-term outcomes and stability of the reconstruction with minimal hardware complications. The disadvantages of this approach include (1) donor site morbidity, (2) technical difficulty of complicated tissue inset in accurately reconstituting the three-dimensional shape of the resected bone, and (3) the possibility that the associated soft tissue defect is not suitable for reconstruction with the soft tissue available with the bone flap, which would then necessitate two flaps. Figure 97-8 depicts typical harvested fibular and scapular osseous free flaps, and Figure 97-9 depicts the scapular flap inset into an anterior mandibulectomy defect. Table 97-1 summarizes and compares the major characteristics of each of the bone donor sites commonly used for oromandibular reconstruction.[35-46] The decision of which flap to use is complex and dependent on the defect characteristics, the patient's characteristics and preferences, and plans for dental restoration.

Osseous free flap reconstruction for an oromandibular defect can be divided into three steps: planning, harvest, and inset. The considerations for planning include the anticipated bone defect (height, length, and location) and the anticipated soft tissue defect (surface area, volume, and subunits involved). If a single flap cannot provide both the soft tissue and bone needed for the reconstructive needs

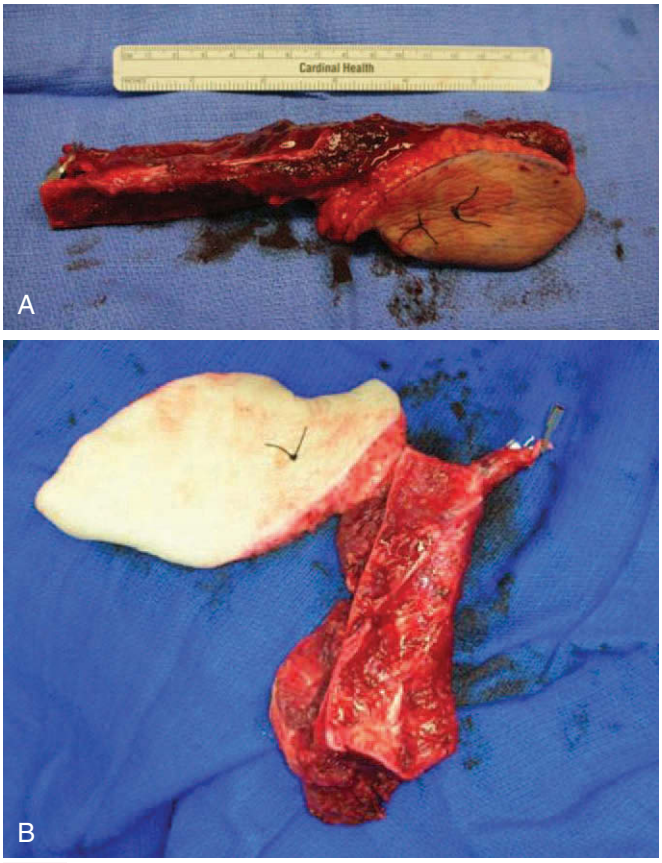

Figure 97-8. Vascularized flaps commonly used for oromandibular reconstruction. **A,** Fibular. **B,** Scapular.

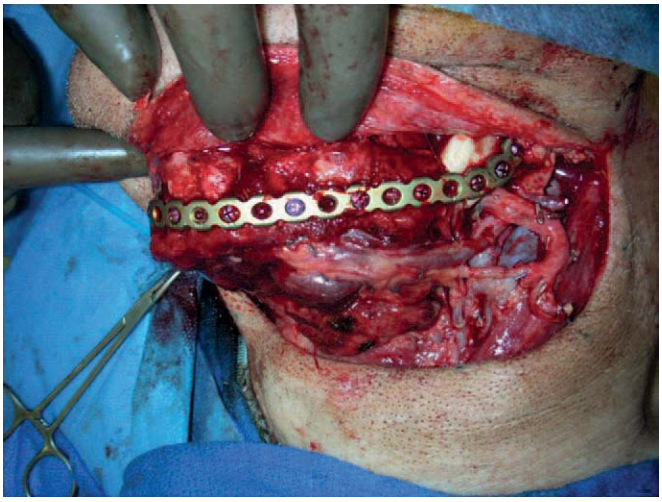

Figure 97-9. Scapular osteocutaneous free flap inset into anterior mandibulectomy defect.

of the defect, then two flaps must be considered, versus using a flap-plate option. In this alternative approach a reconstruction bar is used alone to maintain mandibular continuity, and a soft tissue flap is used to reconstruct the soft tissue components in the defect. Surgical planning also involves positioning of the patient for flap harvest. The scapular osteocutaneous flap needs to be harvested with the patient in at least a 30-degree lateral decubitus position, whereas the other options can be harvested with the patient in a supine position, which facilitates two-team surgery. Planning the side of the flap harvest

Table 97-1

Different Osseous Free Tissue Transfer Options for Mandible Defects

Feature	Fibula	Iliac Crest	Scapula	Radius
Ease of harvest	++	+/–	–	+
Bone characteristics	20-25 cm in length Bicortical Thick Short (1½ cm)	10-15 cm in length Tall and thick	10-12 cm in length Short and thin	Maximum 10 cm in length Very thin Blood supply is tenuous
Soft tissue characteristics	Thin, pliable skin paddle with large surface area Some difficulty with orientation changes in relation to bone Usually good reliability	Thin broad muscle Thick skin relatively fixated to bone	Thicker skin paddle that is independent from bone Possibility of independent skin paddles Possibility for "mega flap" when combined with latissimus flap	Thin, pliable skin paddle with large surface area Fixed to orientation of bone
Donor site morbidity	Favorable	Unfavorable (hernias, chronic pain)	Variable (shoulder function)	Favorable (plate can be used to prevent radial bone fractures)
Dental restoration	+	++	+/–	–

Symbols: ++, Excellent; +, adequate; +/–, mixed; –, inadequate.

is also an important consideration. For fibular flaps, preoperative vascular imaging is recommended because anatomic variations in the vascular blood supply to the foot and atherosclerotic disease might preclude the use of the flap. With conventional angiography, the test results help determine which side to use in up to 25% of patients.[47] Other methods described for preoperative evaluation before fibular flap harvest include magnetic resonance angiography, computed tomography–angiography, and color-flow Doppler imaging.[48-50] Preoperative evaluation before a radial forearm osteocutaneous flap consists of Allen's test.[46] For flaps from the scapula and iliac crest, preoperative imaging or tests are not necessary to determine which side to use to harvest the flap.

The hardware used during inset is usually a locking reconstruction plate, although the alternative use of miniplates has been described.[51] The plate should be bent to the preexisting mandible contour before resection. At the same time, holes should be drilled for fixation screws to ensure that the plate can be reapplied after mandibulectomy, with the bone fragments maintaining anatomic alignment. In general, the reconstruction bar is placed on the lower border of the mandible to avoid tooth roots, maintain optimal aesthetic facial contour, and to lessen chances for intraoral exposure.[32] In fibular flaps, however, this can make restoration with osseointegrated implants problematic because of the short bone height in comparison with a dentulous mandible.[52] In these cases, several options should be considered: placing the reconstruction plate 1 cm above the inferior mandible border, using a double-barrel fibular flap construct, or choosing an alternative donor site with more bone height, such as an iliac crest flap.

During inset, the bone must be contoured to the reconstruction plate, and the surgical team must be aware of how bone inset affects the geometry of the soft tissue component and the vascular pedicle. This portion of the inset is complex and crucial for the success of the tissue transfer. For fibular flaps, closing wedge ostectomies are performed to provide the proper bone shaping, whereas opening osteotomies are performed for the other bone flap options.

Reconstruction plate combined with a soft tissue flap is generally an option only for lateral defects; when this approach is used for anterior defects, the rate of hardware complications is high. There are several advantages to using this approach as an alternative to osseous free flaps in reconstruction for lateral defects: (1) Application is easy and quick, (2) rigid fixation of the remaining mandible segments is provided, (3) morbidity of bone donor site is avoided, (4) cosmetic restoration is adequate, and (5) the range of flap choices is wider for optimal reconstruction in the soft tissue defect, which can have a more significant effect on functional recovery. Screw loosening is not a problem with locking plates, because the stability of the fixation is not dependent on the screw-bone interface. One consideration with this approach, however, is the overall poor rate of survival that has been consistently reported from multiple institutions; thus, a reconstructive technique that maximizes functional restoration and minimizes operative risk is favored.[16,53-56] Because of this and other disadvantages, including subacute and long-term hardware complications (extrusion and fracture) and the difficulty with dental restoration, this approach is not widely favored.

An example of plate extrusion is shown in Figure 97-10A. Reconstruction plate extrusion usually occurs extraorally, and the mean time from surgery to exposure is approximately 10 months.[54,57] The pathophysiologic development of plate exposure is postulated to be related to plate characteristics and the size of the defect. The extrusion rates for stainless steel and titanium plates are not significantly different, but the use of low-profile plates has decreased the extrusion rate from 29% to 7%.[56-58] The volume of the bone and soft tissue deficit has also been shown to be predictive of exposure.[31,32] Without replacing bone within the defect, wound contracture medial to the plate can occur during wound healing as a result of inadequate volume replacement; the contracture causes a slow but steady pressure of the plate on the overlying skin, thus resulting in extrusion. A volume-based approach with "over-reconstructing" the soft tissue defect medial to the plate can be used to avoid a dead space in this area; this approach has been shown to decrease the exposure rate from 38% to 8% (Fig. 97-11).[54]

An example of plate fracture is depicted in Figure 97-10B. The average time from surgery to plate fracture is 21 months.[54] Plate fractures occur primarily because of metal fatigue. This is accentuated by the forces involved in mastication, especially in dentulous patients. Although reconstruction plates can fracture in any patient, those with teeth are at particularly high (up to 26%) risk.[30,54] Therefore, dentulous patients who require reconstruction for lateral mandible defects should be considered better candidates for osseous free flaps than for soft tissue flaps, especially when the associated soft tissue defect

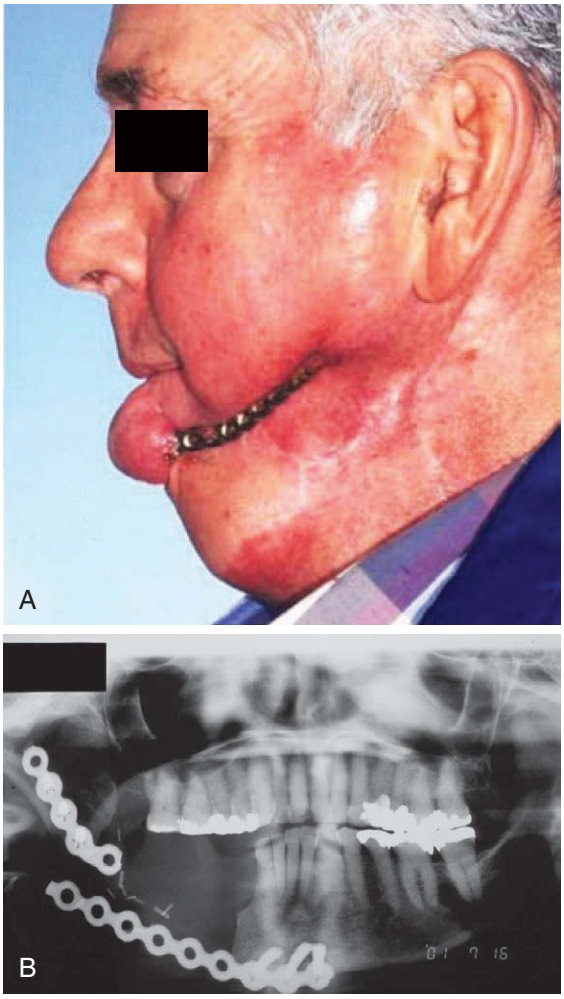

Figure 97-10. Plate complications. **A,** Extrusion. **B,** Fracture.

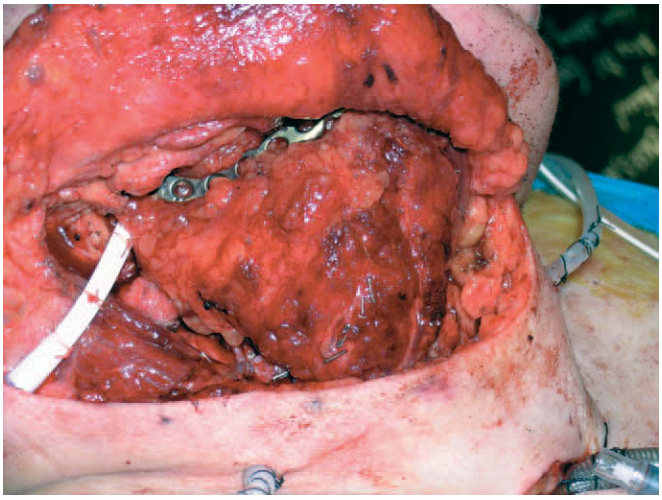

Figure 97-11. Lateral mandible defect that was corrected by volume-based reconstruction with an anterolateral thigh free flap and a locking reconstruction plate.

is not complex. In addition, dentulous cancer survivors who undergo reconstruction with a plate combined with a soft tissue flap are at particularly high risk for subsequent plate fracture; to avoid this complication, planned secondary bone reconstruction should be considered for these patients.[59]

Outcomes

Cordeiro and colleagues[60] reported on short-term results of oromandibular reconstruction in which osseous free flaps were used in 150 consecutive patients during a 10-year period. Of these flaps, 90% were fibular, and testing was performed at least 6 months after surgery. Swallowing, speech, and aesthetic results were all favorable. Of the patients, 45% tolerated an unrestricted diet and 45% were on a soft food diet. Only 9% had unintelligible speech, and only 14% were considered to have poor aesthetic results. Hidalgo and Pusic[39] subsequently reported long-term outcomes of oromandibular reconstruction after a follow-up period of at least 10 years. Of the 82 patients who had undergone osseous free flap reconstruction for oromandibular defects from 1987 to 1990, only 32 were still alive in 2002, and 20 agreed to participate in the study. The mean bone defect length was 13 cm, and 75% of defects were associated with radiation exposure either before (n = 2) or after surgery (n = 13). The aesthetic result was judged to be excellent for 55% of patients and good for 20%. Seventy percent of patients tolerated a regular diet, and the rest were on soft-food diets. Speech was easily intelligible in 85%. There were no cases of fracture or osteoradionecrosis of the transferred bone. This study demonstrated that the favorable functional and aesthetic results remain stable over time.

The value of mandible reconstruction has also been measured through objective testing and patient questionnaires. Urken and associates[61] studied multiple different functional and aesthetic outcome measures in a group of patients who underwent placement of an iliac crest free flap with dental implant, in comparison with patients with similar defects who underwent no bone reconstruction. Patients were also compared to normal denture wearers and normal dentulous patients. Overall, patients with bone free flap reconstruction had better oral competence, mastication, and cosmesis. In Wilson and coworkers' study,[62] patients who had undergone hemimandibulectomy were surveyed with regard to whether mandible reconstruction was performed. Mandible reconstruction was associated with a better appearance, better eating ability, and a better overall quality of life.

Long-term follow-up has revealed that the bone transferred with fibular flaps maintains bone mass and height, even in the presence of postoperative radiation.[39,63] On average, bone height decreased between 4% and 7%. The retention of bone height is not affected by site of reconstruction, patient's age, length of follow-up, adjuvant irradiation, or osseointegrated implants.

Developments

For osseous free flap reconstructions, establishing proper contour of the reconstruction plate is crucial for obtaining correct alignment of the temporomandibular joints, reestablishing normal occlusion, and providing an aesthetically appropriate shape to the mandible.[52] Ideally, the plate is contoured to the native mandible shape before the bone cuts for the mandibulectomy are made. This technique is not possible when the tumor extends through the buccal-labial cortex of the mandible or if the tumor margin might be violated in attempts to expose the outer cortex of the mandible. In addition, secondary mandibular reconstruction in the presence of preexisting occlusal problems is a challenge to contouring a reconstruction plate accurately. Previous techniques to overcome these challenges have included placing the patient in temporary maxillomandibular fixation to align the mandibular fragments before or after tumor resection and then contouring the plate "free hand" with a best estimation to ensure tandem movement of the temporomandibular joints and correct positioning of the occlusion.

For these challenging cases, techniques are now commercially available for using stereolithographic modeling of patients' anatomy for surgical planning and accurately contouring the reconstruction plate. These models can be made from acrylic, cellulose, or plaster. They are constructed in a computer-assisted process based on computed tomography imaging. The models are accurate to within 1 mm. The computer-assisted design process can be used to manipulate the three-dimensional image and mirror normal anatomy in order to create a "perfected" mandible for which a model can be made, and then the reconstruction plate is contoured to the model during surgery. An example of the effective use of this technique is shown in Figure 97-12. Advantages of this approach for selective cases include providing an

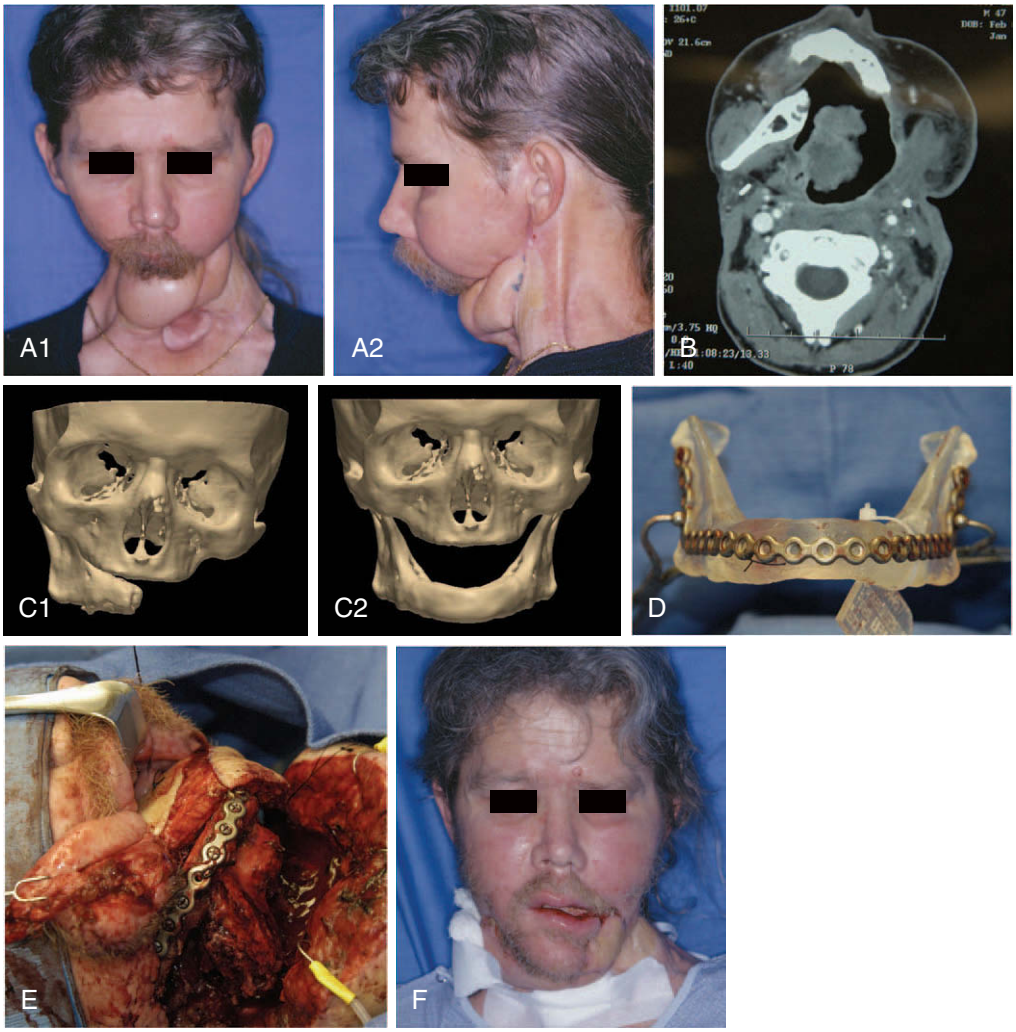

Figure 97-12. Example of using medical models as an adjunct to accurate reconstruction. The patient had an Andy Gump deformity 5 years after undergoing curative treatment for an oral carcinoma (**A**). **B,** A 1-mm cut, helical computed tomography scan of the neck is obtained. **C,** Computer-assisted design is then used to make a three-dimensional representation of the patient's existing anatomy and then to make a "perfected" mandible that is based on a mirror image from the existing anatomy. **D,** Computer-assisted manufacturing is then used to make a stereolithographic model, which in turn is used to contour the reconstruction plate for implantation at the time of the fibular flap reconstruction (**E, F**).

accurate template for contouring the reconstruction plate, saving time during the operation by bending the reconstruction plate preoperatively, allowing for surgical simulation, improving treatment planning, and assisting with preoperative counseling. The disadvantages are the necessity for additional time to make the model (usually can be done in less than 1 week) and the high cost (up to $3000). D'Urso and colleagues[64] prospectively studied the use of medical models in 45 patients with various sites of disease in the craniofacial region. Use of models decreased operating room time by 18%, improved planning, and improved measurement accuracy. In addition, patients found the education provided for informed consent helpful.

Future Approaches

Although current methods of reconstruction for mandibular defects are effective, limitations are still significant. These limitations include measurable donor site morbidity, increased surgical time for harvesting the flap, possible complications from flap harvest, difficulty of tissue inset, and unavailability of autologous bone grafts that truly reflect the three-dimensional shape of the resected bone. Therefore, advancements in tissue engineering are starting to be applied for mandible reconstruction. *Tissue engineering* can be defined as the regeneration or repair of new tissues through the use of biologic mediators and matrices. This regeneration occurs through the recapitulation of key events that occur during tissue formation and growth, which includes cellular migration, proliferation and apoptosis, differentiation, inductive and inhibitory interactions, and tissue patterning and morphogenesis. Signaling molecules, cells, and a scaffold are required for most tissue engineering approaches in order to reproduce this developmental sequence of events.[3]

Most tissue engineering strategies for mandible reconstruction have been based on bone morphogenetic proteins (BMPs). BMPs were discovered by Urist[65] in 1965 as the osteoinductive component of demineralized bone matrix, and these proteins were subsequently isolated, cloned, and purified in the 1980s.[66] BMPs are a large subgroup within the transforming growth factor β (TGF-β) family of growth and differentiation proteins.[67] The human genome encodes 20 known BMPs; BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9 have demonstrated osteoinductive activity. Human recombinant BMP-2 and BMP-7 are now commercially available, and human recombinant BMP-2 was approved by the U.S. Food and Drug Administration in March 2007 for specific orodental applications (sinus floor augmentation, localized alveolar ridge augmentation for extraction socket defects).

Preclinical data regarding the use of osteoinductive BMP therapies for healing mandibular and calvarial defects in animal models (mice, rats, rabbits, dogs, pigs, and nonhuman primates) are extensive. More

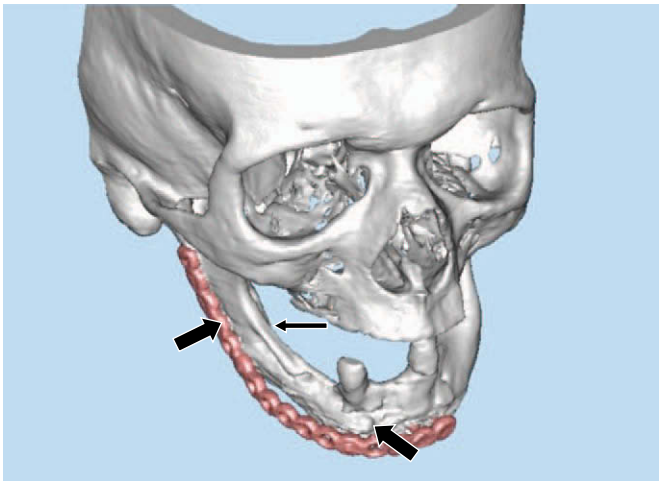

Figure 97-13. Three-dimensional computed tomography scan of a mandible reconstruction in which bone morphogenetic protein 2 (BMP-2) was used. The 6-cm lateral defect involving the body (between *the large arrows*) was caused by débridement of a sequestrum from a nonunion fracture. The *small arrow* points to an area of bone remodeling to the form of a neo-alveolus. A technetium-99m bone scan performed 9 months postoperatively demonstrated appropriate metabolic uptake in the regenerated bone. *(From Nussenbaum B, Krebsbach PH. The role of gene therapy for craniofacial and dental tissue engineering.* Adv Drug Deliv Rev. *2006;58:577-591.)*

recently, case reports and small case series have documented the use of BMPs for reconstruction for segmental mandibulectomy defects in humans.[68-70] An example is shown in Figure 97-13. In the cases so far described, BMPs have been used in defects caused by resection of benign neoplasms or caused by trauma. Use of BMPs is currently contraindicated in wounds caused by tumor-ablative surgery because the effects of these growth factors on the cancer cells are unknown. Also, their use in previously irradiated wounds or wounds that will receive postoperative radiation is not currently advisable.[71,72] At the time this chapter was written, use of BMPs for mandible reconstruction was recommended only in clinical trials in carefully selected patients because the ultimate success of this technique was unknown, although very promising.

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CHAPTER NINETY-EIGHT

Prosthetic Management of Head and Neck Defects

Jeffery C. Markt

Thomas J. Salinas

William Donald Gay

Key Points

- Dentoalveolar evaluations should be accomplished prior to radiation therapy in the interest of establishing lifelong prognoses for those teeth to be included in potential radiation therapy fields. Those teeth not enjoying good prognoses should be extracted before radiation therapy, preferably at the time of a surgical ablation if a surgical ablation is endeavored.
- The risk of osteoradionecrosis secondary to invasive dentoalveolar procedures is substantial in areas that have received more than 5000 cGy of radiation.
- The Marx hyperbaric oxygen regimen is used to diminish the risk of osteoradionecrosis when invasive dentoalveolar procedures must be done in areas that received more than 5000 cGy of radiation.
- Xerostomia-induced carious lesions are common among patients whose major salivary glands are included in radiation therapy fields. Topical fluoride gel and meticulous oral hygiene are paramount for the prevention of carious lesions for patients who have been rendered xerostomic secondary to radiation therapy.
- Maxillofacial prosthodontists can offer radiation oncologists a host of devices to lend assistance to the delivery of radiation therapy. These include shielding and positioning devices, tissue equivalency devices, and brachytherapy devices.
- Maxillofacial prosthodontists can offer assistance in evaluating the relative safety associated with invasive dentoalveolar procedures following radiation therapy by way of evaluating dose distributions, simulation radiography, and computed tomography.
- Maxillofacial prosthodontists are uniquely positioned to mitigate palatopharyngeal insufficiency or palatopharyngeal incompetence through the fabrication of palatal lift prostheses, speech aid prostheses, and obturator prostheses.
- Maxillofacial prosthodontists routinely offer mandibular resection prostheses for patients with discontinuity defects or defects that have been reconstructed with microvascular free flap procedures.
- Endosseous titanium implants are often necessary for the rehabilitation of patients with congenital or acquired intraoral and extraoral dentoalveolar and maxillofacial defects. Endosseous titanium implants are often placed in grafted microvascular osseous tissues, as well as native maxillary or mandibular bone.
- Maxillofacial prosthodontists work closely with speech language pathologists to prosthetically mitigate dysfunctional articulation and dysphagia.
- Orbital, ocular, nasal, and auricular prostheses constitute the most common extraoral prostheses provided by maxillofacial prosthodontists.
- The construction of facial prostheses requires impression making, wax or clay sculpting, fabrication of molds, casting of pigmented elastomers such as silicone, and painting surface skin tones.

Maxillofacial prosthetics comprises a subspecialty of prosthodontics directed toward the prosthetic habilitation of patients with congenital maxillofacial defects, the prosthetic rehabilitation of patients with acquired maxillofacial defects, and the medical management of patients undertaking treatment for essentially any maxillofacial pathosis. Maxillofacial prosthodontists are often involved in hospital-based multidisciplinary craniofacial and cleft lip and palate teams and head and neck oncology teams either as institutional staff members or participating private practitioners. The maxillofacial prosthodontist's role in patient care often begins with an otolaryngology or oral and maxillofacial surgery referral at the onset of a diagnosis because the prosthodontist's contribution early in the course of a patient's care can foster the prosthetic management necessitated by either the patient's condition or the treatment of the condition. This is true for patients affected by congenital anomalies or trauma-related anatomic deficits, as well as oncologic patients treated primarily by ablative surgery, radiation therapy alone, or combinations of surgery, radiation therapy, and chemotherapy.

Because the treatment of head and neck cancer has evolved into a complex multidisciplinary approach, the maxillofacial prosthodon-

tist's participation in the tumor boards of centers actively treating oncology patients can be quite meaningful. Prosthetic care may address common issues relating to routine dental health and occlusal rehabilitation, as well as matters as diverse as dysphonia, dysphagia, and facial cosmesis, so the prosthodontist's diagnostic input before a surgical ablation can assist the reconstructive phase of virtually all head and neck oncology patients regardless of the primary tumor site. Additionally, the maxillofacial prosthodontist's diagnostic contribution for patients who have or will be treated with radiation therapy can aid in the prevention of osteoradionecrosis and obtund or prevent mucosal or dental disease in patients suffering from early or late effects of radiation therapy. The maxillofacial prosthodontist's role in evaluating dose distributions to assist safe oral surgical care when it is necessary after radiation therapy is also paramount.

This chapter reviews some of the duties of maxillofacial prosthodontists associated with multidisciplinary head and neck oncology teams from the perspective of three staff maxillofacial prosthodontists in different tertiary care settings. Although the chapter principally relates to an oncology population, the sections pertaining to intraoral and extraoral prosthetic rehabilitation correspond quite readily to patients whose defects are traumatically acquired or congenital.

Maxillofacial Prosthetics and the Radiation Oncology Patient

Given that the treatment of head and neck neoplasms often involves radiation therapy alone or in combination with surgical ablation or chemotherapy, it is useful for the maxillofacial prosthodontist to become involved in patient care during the diagnostic phase of any proposed intervention. Because the risk for osteoradionecrosis is increased when a poor dentition is allowed to remain within irradiated maxillary or mandibular alveolar bone, a thorough evaluation of the dentition and periodontium is extremely useful in establishing dental prognoses before the initiation of radiation therapy. Additionally, because the xerostomia induced by a majority of head and neck radiation fields requires an increased diligence respecting home care and follow-up during and after radiation therapy, the maxillofacial prosthodontist's early consultation can help prevent dental disease that could later contribute to added debility, possibly including osteoradionecrosis.

Because many head and neck cancers are treated by surgical ablation followed by radiation therapy, the maxillofacial prosthodontist's diagnostic efforts should be performed preoperatively so that any necessary oral surgical interventions can be accomplished in conjunction with the otolaryngologist's surgical encounter. This allows a sufficient amount of time for mucosal and alveolar bone healing before the initiation of radiation therapy, which usually occurs 6 weeks later. Patients whose dentoalveolar evaluations are accomplished after ablative surgeries are sometimes fast approaching a juncture in their care when radiation therapy should expeditiously commence in the interest of controlling local and regional oncologic disease, and delays associated with healing oral surgical wounds may be unacceptable. Likewise, the maxillofacial prosthodontist must consider similar delays in the initiation of radiation therapy when treatment plans call for primary radiation therapy or radiation therapy to be delivered concurrently with chemotherapy in the absence of an ablative surgical encounter.

Dental Diagnoses and Oral Surgical Management Preceding Radiation Therapy

Any dentoalveolar evaluation in preparation for radiation therapy should include a thorough assessment of the periodontium, as well as the dentition, and should be done with the intent of establishing lifelong prognoses for those teeth likely to be included in radiation therapy fields anticipated to receive doses in excess of 5000 cGy.

Extractions are indicated for teeth with poor prognoses meeting the criteria listed in Box 98-1.[1-13] Although the assessment is accomplished in the interest of preventing osteoradionecrosis, it is also done considering the potential for any prosthetic rehabilitation that may become necessary. Because this assessment requires consideration of primary tumor size and location, as well as regional lymph node status, diagnostic information gleaned through participation in multidisciplinary head and neck tumor board conferences supplements decisions made in the dental clinical setting where medical imaging is limited and endoscopy is not typically available.

Box 98-1

Clinical Presentations Leading to the Assignment of Questionable or Poor Lifelong Prognoses

- 5-mm periodontal pockets
- Class I, II, or III furcation involvement
- Active endodontic or periapical pathosis
- Mobile primary teeth
- Nonrestorable teeth
- Nonfunctional or unopposed teeth
- Impactions

In addition to an evaluation of the dentoalveolar structures, the maxillofacial prosthetic assessment includes intraoral and extraoral palpation and visualization of hard and soft head and neck tissues, panoramic radiography, and intraoral radiography of those teeth thought to be sound enough to retain vis-à-vis imminent radiation therapy. Although the intraoral radiography generally includes routine bitewing and periapical exposures, occlusal radiographs are sometimes helpful for primary tumor staging by affirming bony erosion associated with oral cavity lesions affecting gingivae, buccal or palatal mucosa, or the floor of mouth.

With respect to the periodontium, teeth with periodontal sulci equal to or greater than 5 mm in depth may be assigned poor prognoses and should be considered candidates for extraction before radiation therapy. Likewise, teeth with mucogingival defects or furcation involvement should be given similar prognoses and should be considered for extraction. Although prior successful endodontic treatment should not necessarily condemn a tooth for extraction, the unpredictability of endodontically treating active periapical or pulpal pathoses in the usually limited time available before radiation therapy should give rise to enough caution that the extraction of endodontically involved teeth should be strongly considered. Although gingival recession is not in itself a definite indication for exodontia in the absence of deep periodontal sulci, consideration must be given to the maintenance of radicular surfaces exposed to the xerostomic oral environment as a result of recession, because cementum is more prone to the development of inoperable carious lesions than is the more mineralized coronal enamel.

With regard to the dentition, mobile primary teeth should be extracted from alveolar bone to be irradiated, as should any unrestorable teeth. If no plan is or can be made to restore the occlusion of unopposed posterior teeth that will be irradiated, consideration should be given to their extraction, because subsequent supraeruption can contribute to expansive gingival embrasures that are difficult to maintain free of plaque and food debris, possibly resulting in localized periodontitis or radicular carious lesions that are difficult or even impossible to repair. Although extracting impacted teeth from alveolar bone soon to be irradiated is meritorious, consideration should be given to the length of healing time often required of associated surgical sites. This is particularly true of impacted third molars that carry an increased risk for developing acute alveolar osteitis. When deciding whether an impacted tooth should be extracted before radiation therapy, the impacted tooth's likelihood of erupting enough to gain exposure to the oral environment should be considered. If a bony impacted tooth is unlikely to erupt permucosally, the relative risk of it contributing to a future osteoradionecrosis should be judged low and the tooth should be allowed to remain in situ, unless of course there is a pathosis associated with the tooth that overrides a conservative approach. Conversely, an impacted tooth within a proposed radiation field whose anatomic position suggests a potential for intraoral eruption should be deemed a candidate for extraction before radiation therapy.

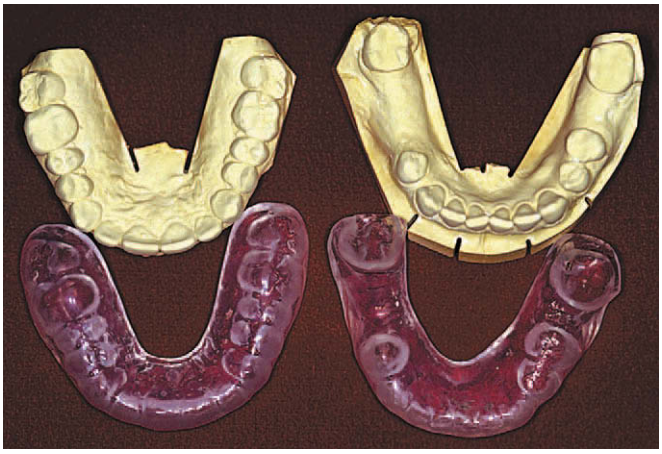

Figure 98-1. Thermoplastic vinyl fluoride gel carriers and the models on which the gel carriers are made.

The presenting or oftentimes soon to be rendered edentulous or partially edentulous condition of many newly diagnosed head and neck cancer patients also demands evaluation of maxillary or mandibular exostoses, tori, and tuberosities primarily in preparation for removable, but sometimes fixed, prosthodontic rehabilitation after the completion of oncologic care. Preprosthetic surgery to include the removal of tori and exostoses and the reduction of tuberosities that could prove obtrusive relative to future prosthetic considerations should coincide with any necessary exodontia as far in advance of radiation therapy as possible. The reduction of these anatomic structures can improve prosthetic-bearing areas and reduce the risk of prosthetic-induced mucosal violations that could contribute to the development of osteoradionecrosis. Although the completion of such preprosthetic surgery before radiation therapy is paramount for those structures lying within proposed radiation fields, the extended mucogingival flaps required for removing bony prominences require consideration for the removal of such prominences even if their juxtaposition to the primary field does not lend to an anticipated dose exceeding 5000 cGy.

Patients using removable prostheses should be advised to minimize prosthetic use during and immediately after radiation therapy to diminish the risk of exacerbating mucositis underlying intaglio prosthetic surfaces, particularly when prostheses are ill fitting and radiation therapy fields directly encompass the oral cavity. Even small prosthesis-related mucosal ulcerations could result in the exposure of alveolar bone and the initiation of osteoradionecrosis. When oral cavity mucositis is anticipated, restorative dental care of high priority should be expeditiously undertaken considering the fact that compromised patient comfort will make restorative dental care difficult or impossible after as little as 1000 to 2000 cGy of radiation. Routine dental prophylaxes should also be sought before head and neck radiation therapy because the relative attenuation of plaque and calculus could diminish the severity of gingival mucositis induced by direct oral cavity irradiation and could decrease the potential for cariogenic dental colonization associated with xerostomia. Additionally, a hiatus in orthodontic care could be considered for those whose radiation therapy coincides with orthodontia because the removal of bands, brackets, and wires could lend to a diminution of trauma to inflamed mucosal surfaces.

For patients retaining a full or partial natural dentition whose head and neck radiation therapy will induce xerostomia, it is important to institute a daily and lifelong regimen of topical fluoride gel use to concur with the initiation of radiation therapy.[1-7,9,12,14-18] This is true for patients whose retained dentition is or is not encompassed by radiation therapy fields. Dental casts generated from clinical impressions recorded before radiation therapy but subsequent to any oral surgical procedures in preparation for radiation therapy should be used to fashion thermoplastic vinyl fluoride gel carriers (Fig. 98-1) into which topical fluoride gel can be applied. After routine brushing and flossing, patients should be instructed to place pharmacy-prescribed 1.1% neutral sodium fluoride or 0.4% stannous fluoride gel into the dental aspects of the fluoride gel carriers for 5 to 10 minutes every day indefinitely before applying them to their dentition. The topical fluoride gel application should be followed by expectoration of excess gel and a period of 30 minutes during which the patient is encouraged not to rinse, eat, or drink.

Prosthodontic Support of the Radiation Oncologist

The maxillofacial prosthodontist may be called on to lend support to the radiation oncology team in their efforts to manage dosimetry by way of patient posturing,[19-22] anatomic displacement or shielding,[3,6,19,23,24] fabrication of brachytherapy appliances,[3,25] or construction of devices capable of mimicking normal tissues.[3,19,24] Although the devices should be constructed following any oral surgical procedures that are done in preparation for radiation therapy, they must be manufactured before radiation therapy simulation appointments in that they must be positioned at the time of simulation.

The undulating topography of head and neck cutaneous structures makes the uniform delivery of radiation difficult at best without the use of boluses constructed of materials considered more or less to be tissue equivalent in terms of their relative resistance to photon or electron penetrance. Consequently, the radiation oncologist may call on the maxillofacial prosthodontic team to assist with facial moulage recording and bolus fabrication when evaluating the physics associated with treating malignant head and neck skin lesions. A facial moulage cast with a gypseous dental stone can aid the radiation oncology team's delineation of a proposed treatment field and prescription of an appropriate bolus thickness before a bolus is constructed of dental baseplate wax or polymethylmethacrylate. Boluses can be particularly useful for providing more even dose distributions for nasal (Fig. 98-2) or orbital malignancies.

Although Aquaplast masks are routinely used to immobilize patients throughout the course of head and neck radiation therapy,[19] customized intraoral devices can be used to provide a stable maxillomandibular relationship when attempts are made to precisely localize an external photon or electron beam relative to oral cavity anatomy. The use of intraoral positioning devices is particularly useful when there is a desire to shield all or part of the maxilla or the mandible from radiation when the opposing jaw is to be included in an external beam field. By positioning the mandible in a prescribed open position with the use of a polymethylmethacrylate appliance that prevents deviation from an arranged spatial relationship to the maxilla, the radiation oncology team can make shielding possible by way of replicable daily positioning of patients from the time of simulation to the completion of radiation therapy. This strategy is helpful when mandibular structures are to be spared from sinonasal or maxillary radiation or when maxillary structures are to be excluded from fields involving the floor of mouth, oral tongue, or other sites encompassing the mandible. In addition to stabilizing the maxillomandibular relationship, the incorporation of radiopaque materials such as orthodontic wire, ball bearings, or gutta percha into such devices can lend support to the radiation oncology team's efforts to identify structures for inclusion in proposed radiation fields at the time of simulation (Fig. 98-3).

Furthermore, intraoral polymethylmethacrylate appliances can be constructed that harbor Lipowitz's alloy.[19,21,26] Being the same metal used by radiation oncology teams to create the portals and shields suspended from frames situated between patients and linear accelerator collimators that fashion conventional three-dimensional (3D) conformal radiation therapy fields, Lipowitz's alloy, a low-fusing combination of lead, bismuth, tin, and cadmium, can suitably shield intraoral anatomy when electron beam therapy is indicated. These devices typically serve the dual purposes of shielding and maxillomandibular positioning because their interocclusal construction also stabilizes the maxillomandibular relationship. These alloy-containing intraoral appliances are often fabricated for lip (Fig. 98-4) and ipsilateral parotid gland (Fig. 98-5) fields. The protective intent of these appliances is supplemented when they are constructed in such a fashion as to physically displace soft tissues away from the source of an electron beam. When

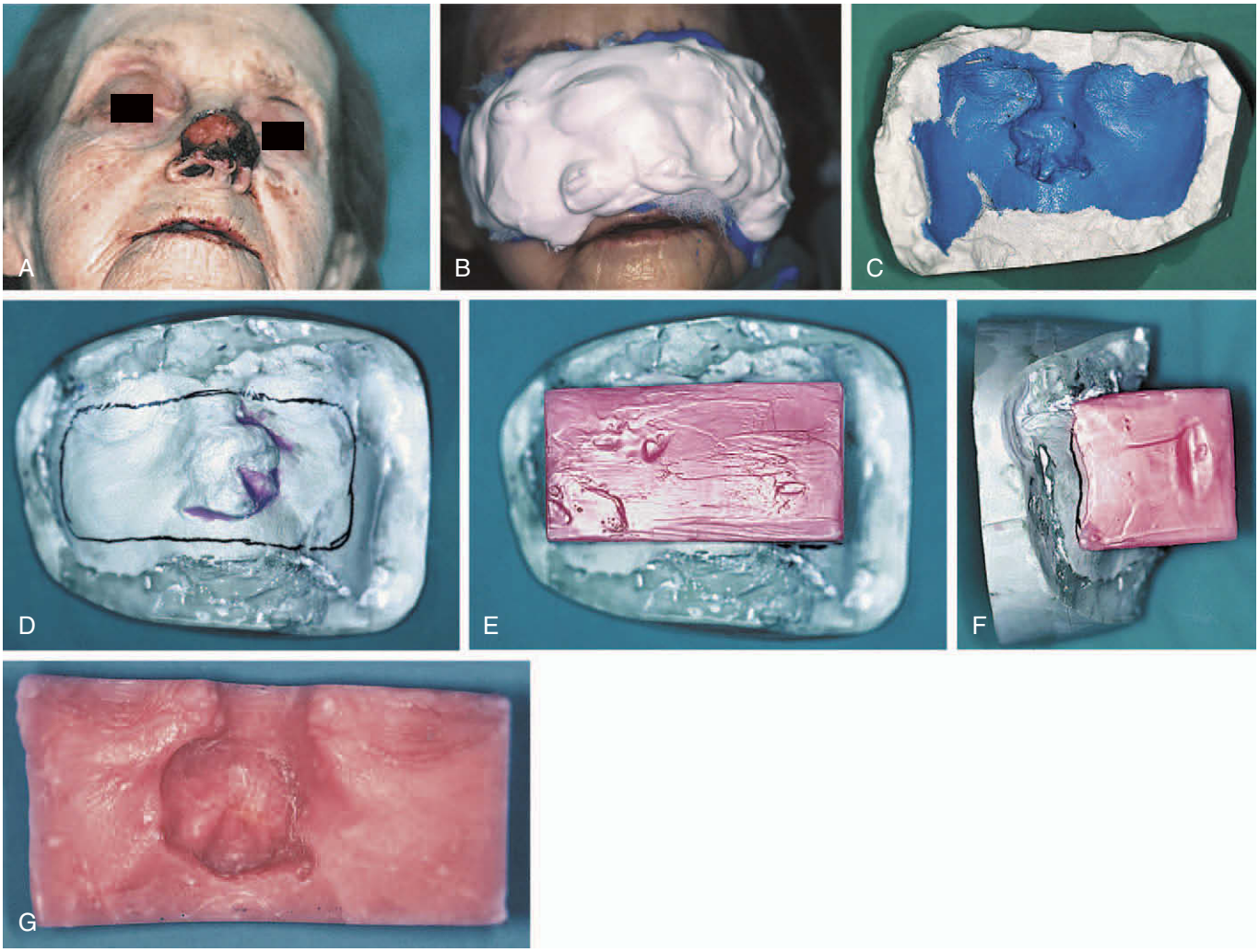

Figure 98-2. **A,** Basal cell carcinoma of the nasal bulb to be treated with external electron beam radiation therapy. **B,** Facial moulage being recorded. **C,** Facial moulage prepared for casting. **D,** Model on which the wax bolus was fabricated. **E,** Frontal view of the bolus. **F,** Lateral view of the bolus. **G,** Intaglio surface view of the bolus.

parotid gland shielding devices are used, patients are instructed to position the tongue anteriorly during treatment. Doing this while occluding on the interocclusal appliance forces the bulk of the tongue into a contralateral position where less radiation is encountered. When parotid gland malignancies are treated with a combination of photons and electrons, radiation oncologists sometimes find it helpful to use two appliances, one with Lipowitz's alloy and one lacking metal. The use of the appliance devoid of alloy during the delivery of photons offers the advantages of consistent day-to-day maxillomandibular positioning and soft tissue displacement without the electron backscatter potentially associated with an appliance that harbors a large volume of metal.

The radiation oncologist's desire for tissue equivalence is not limited to the application of surface boluses because postoperative tissue voids can give rise to an uneven distribution of radiation resulting in suboptimal dosing or overdosing of tissue peripheral to cavernous surgical defects such as those resulting from a maxillectomy. Unfortunately, however, the rigidity of wax and polymethylmethacrylate does not solely allow the dependable use of these materials as intracavitary tissue mimicking materials by virtue of soft tissue and bony undercuts usually associated with these defects. Consequently, filling an intracavitary void with tissue-equivalent material in the interest of improving radiation therapy dose distribution often requires the use of pliable materials that assist daily insertion and removal without unduly traumatizing surrounding tissue. The combination of an inflexible customized intraoral device that stabilizes the maxillomandibular relationship with a pliable material that fills an intracavitary void can, however, overcome the limitations posed by the complex nature of a maxillectomy defect. This combination can be achieved by constructing an intraoral positioning device that incorporates a shelf of polymethylmethacrylate immediately inferior to the maxillectomy defect. The device is capable of supporting a balloon that can be inflated with a tissue-equivalent mixture of radiopaque liquid and water before radiation therapy simulation and each fraction (Fig. 98-6).

Although the maxillofacial prosthodontist is not likely to lend assistance in the clinical application of interstitial brachytherapy, the management of intracavitary brachytherapy often requires the combined efforts of the radiation oncology and maxillofacial prosthetic teams. The orbit and nasopharynx comprise the most common intracavitary head and neck brachytherapy sites, and the stents used for these sites are typically constructed of polymethylmethacrylate that surrounds catheters into which radioisotopic seeds are inserted. The radiation oncologist or physicist, in accord with an intended dose distribution specific for the radioisotope proposed for use, prescribes the catheter positions in consultation with the maxillofacial prosthodontic team after the generation of a master cast from an impression of the site to be treated. When the stents are positioned, they are retained for the duration of treatment by anatomic soft tissue undercuts (Fig. 98-7) or dentoalveolar structures.

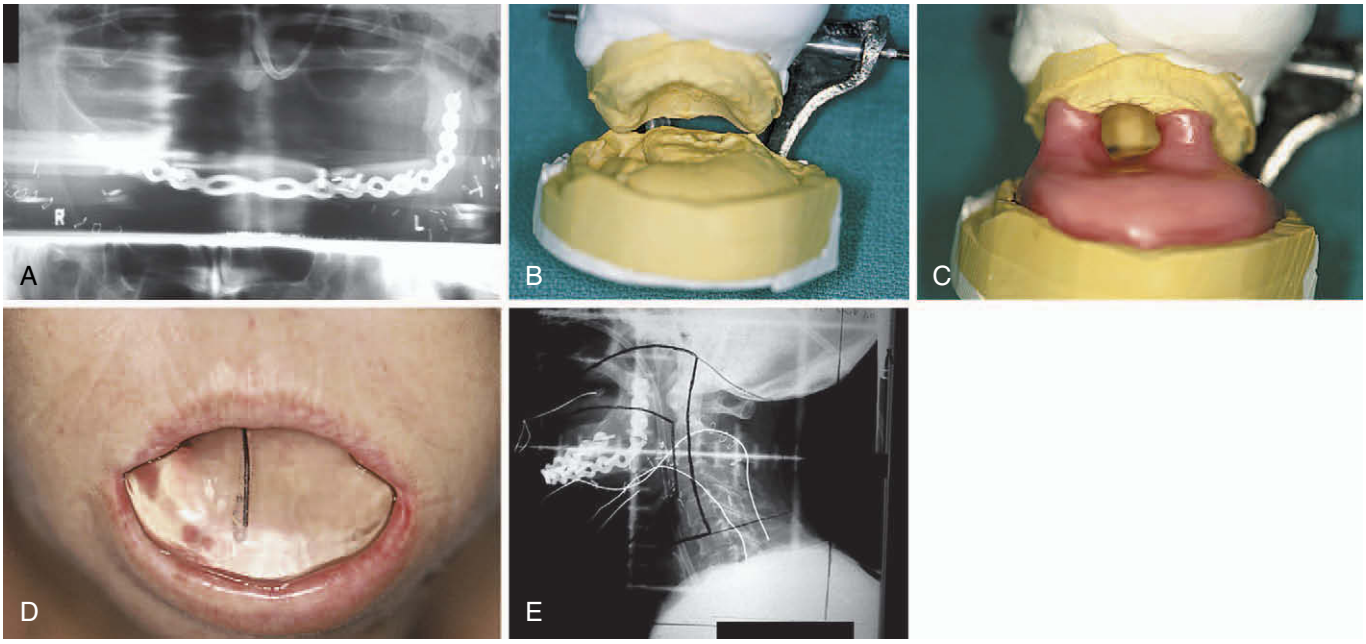

Figure 98-3. **A,** Panoramic radiograph of a patient's status after segmental mandibulectomy, total glossectomy, floor of mouth resection, and microvascular fibula free flap reconstruction for a squamous cell carcinoma. **B,** Models of the maxillary and neomandibular structures articulated in relation to one another. **C,** Wax pattern of the proposed positioning device before its completion. The wax pattern covers the microvascular free flap tissues in the area of the floor of mouth once occupied by the oral tongue. Bilateral pillars engage the maxillary model to maintain a consistent maxillomandibular relationship during each radiation therapy fraction. **D,** Clinical view of the anterior aspect of the polymethylmethacrylate positioning device. A segment of orthodontic wire placed within the midsagittal plane of the positioning device identifies the dorsum of the microvascular free flap structures during radiation oncology simulation and ensures its inclusion in proposed radiation therapy fields. **E,** Simulation radiograph exposed with the positioning device positioned intraorally.

Dental Management during Radiation Therapy

Recalling patients every 2 to 3 weeks during radiation therapy is beneficial from the standpoint of identifying dental, periodontal, and mucosal pathoses that may coincidentally appear or arise secondary to radiation therapy. Such a follow-up interval is also meritorious for reinforcing the import of increased hygiene vigilance and the use of topical fluoride gel. It is not uncommon for patients with newly diagnosed life-threatening neoplasms to forget virtually everything that was discussed during an initial maxillofacial prosthodontic evaluation that may have coincided with appointments in otolaryngology, radiation oncology, diagnostic radiology, nuclear medicine, medical oncology, anesthesia, internal medicine, and oral surgery. The overwhelming nature of patients' initial oncologic experience lends to a necessary redundancy with respect to patient communication and education.

Although restorative dental care can be accomplished during radiation therapy, procedures that potentially exacerbate mucositis should be avoided. However, particularly in cases involving oral cavity radiation, patients may reach a point—usually after 2 to 3 weeks of fractionation—where mucositis is severe enough that they do not want to be subject to dental restorative procedures. Regardless of the need for restorative dental care, a readily concocted mouthrinse to obtund mucositis consists of mixing 1 teaspoon of baking soda and 1 teaspoon of salt in a quart of water that is warmed before use. Alternatively, a compounded solution of tetracycline, diphenhydramine, nystatin, and hydrocortisone termed "magic mouthwash" can be obtained from a pharmacy. Two teaspoons of magic mouthwash swished and gargled thrice daily before swallowing serves to mollify radiation-induced stomatitis and pharyngitis.

Dental Management after Radiation Therapy

Follow-up examinations should be arranged every 4 to 8 weeks after the completion of radiation therapy with patients returning to a standard interval thereafter as long as they comply with hygiene and daily topical fluoride gel regimens. Patients can be considered routine patients in terms of their candidacy for restorative dental care after head and neck radiation therapy; however, they must understand that they should not undertake bone-exposing oral surgery within anatomic areas that received more than 5000 cGy of radiation. Such exposures could prompt the development of osteoradionecrosis that could precipitate a pathologic fracture or necessitate a bony resection.[2,6,7,9,12,27-34] Therefore when patients complete their radiation therapy, they should be asked to inform the maxillofacial prosthodontist of any future oral treatment proposal to include a tooth extraction, the surgical placement of an endosseous titanium implant, or periodontal or endodontic flap surgery in advance so that an estimation of dosimetry can be provided to the surgeon. When these estimates indicate that a bone-exposing violation of mucosa could occur in an area that received more than 5000 cGy of radiation, the Marx hyperbaric oxygen protocol should be considered as an adjunct to the surgical procedure.[3,6,7,9,12,27,28,32] Marx's hyperbaric oxygen regimen involves 90-minute dives at a barometric pressure of 2.4 atmospheres while breathing 100% oxygen. Twenty dives are undertaken preoperatively, and 10 dives are completed postoperatively in the interest of stimulating an angioneogenesis that partially and irreversibly[32] counteracts the hypovascularity caused by radiation therapy that is responsible for the increased risk of osteoradionecrosis.

Because dosimetry is highly variable depending on primary tumor sites, regional metastases, radiation oncology philosophy, and available technology, patients and their dental caregivers cannot be expected to routinely know whether it is safe to go forward with bone-exposing oral surgical interventions after radiation therapy. Consequently, it is incumbent on the maxillofacial prosthodontist to assist this determination whether the prosthodontist personally accepts this responsibility or shares it with radiation oncology personnel. When patients have been treated with conventional 3D conformal radiation therapy, possession of simulation and portal radiographs, as well as radiation oncology records, sometimes allows the prosthodontist to establish a relative risk for surgically precipitated osteoradionecrosis without the assistance of a physician or a physicist. On the other hand, when intensity-

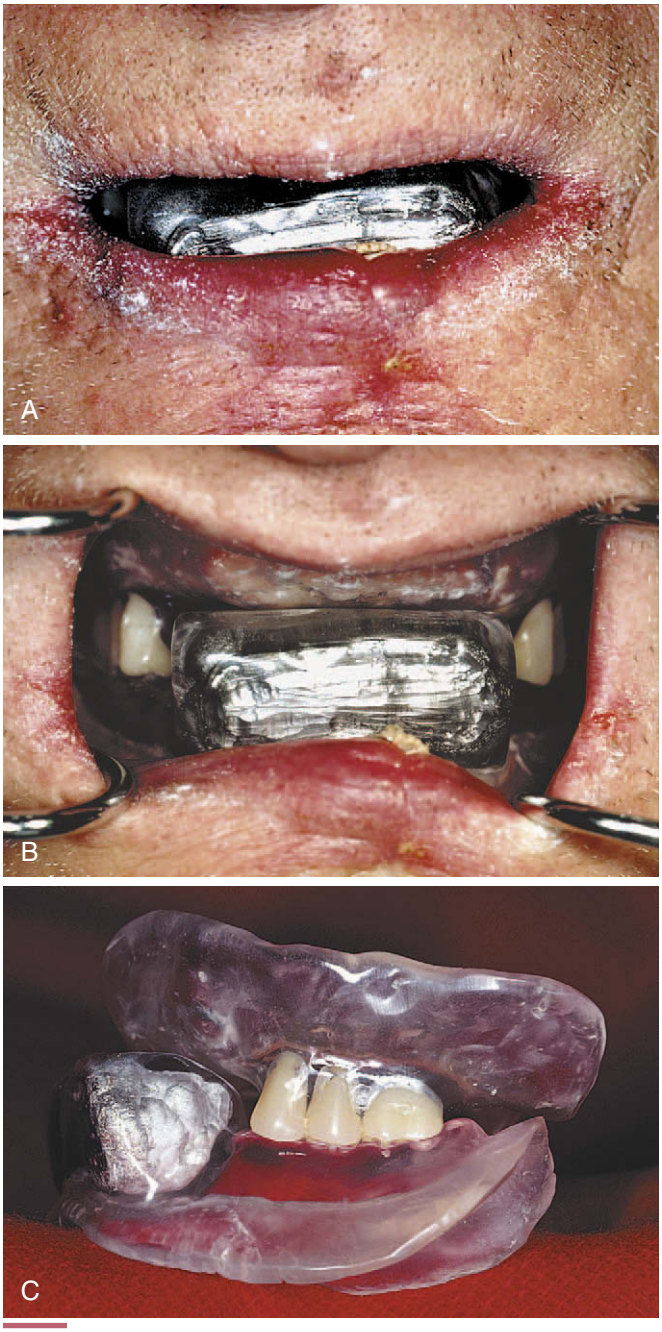

Figure 98-4. **A,** Clinical frontal view of a Lipowitz alloy-containing shielding device used during external electron beam radiation therapy for a squamous cell carcinoma of the lower lip. The device was held in its interocclusal position during fractionation and served not only to shield normal anatomy but also to anteriorly displace the labial tissues being treated from posterior structures to be spared of radiation. **B,** Clinical frontal view of a Lipowitz alloy-containing shielding device with the patient's lips retracted. **C,** Extraoral view of the shielding device.

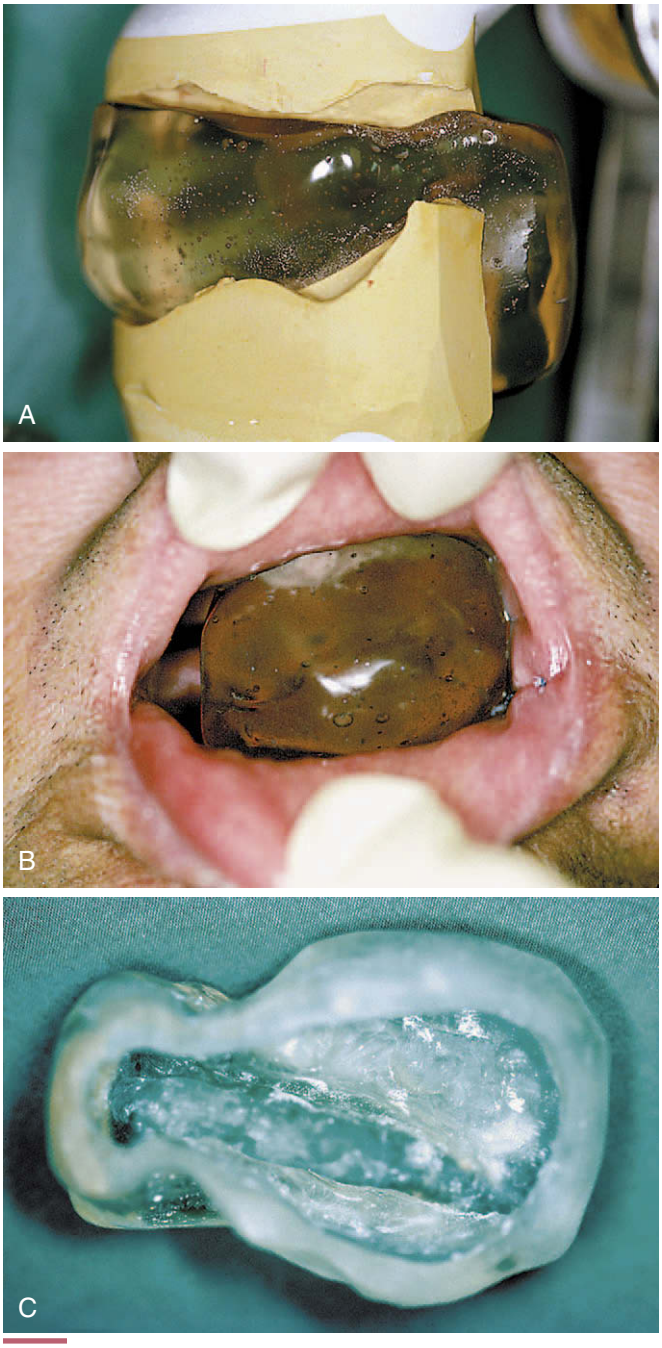

Figure 98-5. **A,** Shielding device positioned on the articulated models on which it was constructed. The device was fashioned for use during radiation therapy for a left parotid gland adenoid cystic carcinoma. The device extends as far into the oropharynx as the patient will allow without gagging. Lateral view demonstrates that portion of the polymethylmethacrylate intended to displace buccal tissues in an ipsilateral direction to further separate tissues to be treated from those that should not be treated. **B,** Clinical verification of the fit of the device before it is filled with Lipowitz's alloy. **C,** The device is hollowed from the medial side before being loaded with Lipowitz's alloy.

modulated radiation therapy, the latest 3D conformal radiation modality, is used, a greater reliance on the radiation oncologist or radiation physicist, or both, may be necessary.

Oral surgical planning after conventional 3D conformal radiation therapy first involves the acquisition of simulation and portal radiographs, as well as a complete description of the radiation oncologist's dosimetric and clinical assessments.[3,6,19] Although the possession of simulation and portal radiographs provides the dental team a mere 2D perception of the fields prescribed by the radiation oncologist, their value in determining whether dentoalveolar structures of interest lie within or without treatment fields allows for surgical treatment planning often without the need for further conference with radiation oncology personnel. When parallel opposed field simulation and portal radiographs are shown to encompass dentoalveolar structures, the dental team must take for granted the fact that an invasive procedure within that field will place the patient at risk for osteoradionecrosis if

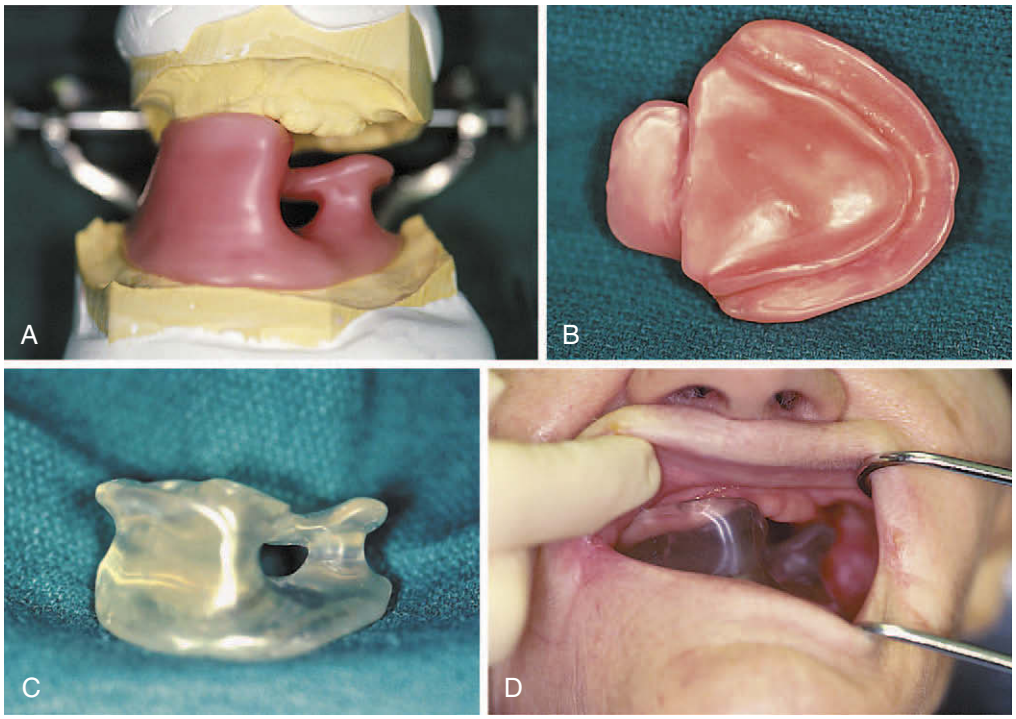

Figure 98-6. **A,** Anterior view of articulated maxillary and mandibular models and the wax pattern used to generate an intraoral device that serves to repetitively position the mandible and oral tongue and support a diaphragm to be filled with water during radiation fractionation. The water-containing diaphragm thus occludes maxillectomy defects and serves as a tissue-equivalent material. **B,** Inferior view of the wax pattern demonstrating an axial shelf to inferiorly confine and exclude the oral tongue from the radiation fields. **C,** Anterior view of the finished intraoral device. **D,** Anterior view of the positioned intraoral device demonstrating the diaphragm-supporting shelf situated immediately inferior to the maxillectomy defect.

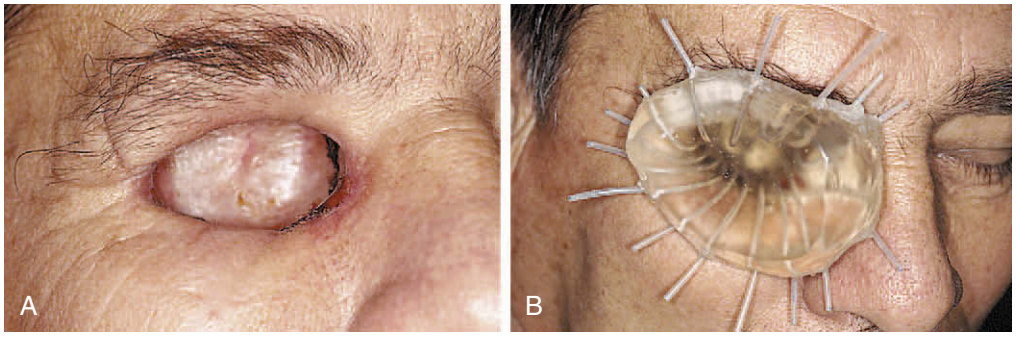

Figure 98-7. **A,** Orbital exenteration site for a patient whose positive melanoma margins necessitated postoperative brachytherapy. **B,** Brachytherapy device in position demonstrating accessibility to catheters for radioisotopic seeding and treatment.

the prescribed dose to that field surpassed 5000 cGy. However, as is frequently the case in head and neck radiation oncology, the exclusion of dentoalveolar structures anterior, superior, or inferior to a field boundary allows surgical intervention in the excluded area without risking osteoradionecrosis (Fig. 98-8) because osteoradionecrosis by definition comprises a volume of necrotic bone within a radiation therapy field.[30] Uncertainty can arise, however, when treatment field borders bisect or tangentially appose dentoalveolar structures to be included in a proposed surgical intervention. Although dosages at the borders of conventional 3D conformal radiation therapy fields approximate only 50% of the prescribed dose, patient positioning can vary by as much as 5 mm in any given dimension despite exceptional efforts on the part of radiation oncology teams to reproducibly orient their patients on a daily basis. Considering the possibility of positioning errors during the course of daily radiation therapy sessions, such scenarios warrant erring on the side of caution with the assumption that affected field border areas could become osteoradionecrotic after a surgical insult.

Likewise, when ipsilateral dentoalveolar structures are found within unilateral treatment fields where photon doses exceeded 5000 cGy, it can be assumed that ipsilateral oral surgical procedures within that field would place a patient at great risk for osteoradionecrosis. Conversely, the risk for contralateral, oral, surgically induced osteoradionecrosis can be relatively low for such a patient considering the fact that only about one third of a conventionally prescribed photon dose would reach contralateral dentoalveolar structures. However, because the use of electron beams; uniform, oblique, or wedged pair multiple fields; or appositional fields can complicate dosimetric deductions made with the use of simulation and portal radiographs and a medical record narrative, it is always reasonable to confer with the radiation oncologist or physicist when questions arise before invasive oral surgical procedures. The potential debility associated with the precipitation of osteoradionecrosis merits such caution.

In contrast to conventional 3D conformal radiation therapy, in which gantry positions are limited and static, intensity-modulated radiation therapy can be delivered by way of a mobile collimator. The

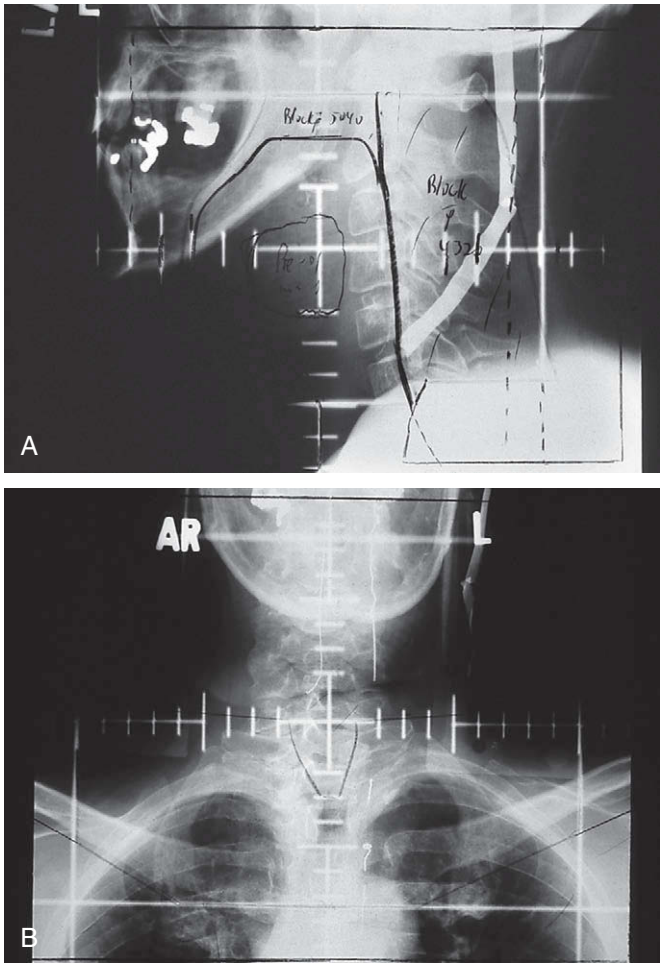

Figure 98-8. **A,** Bilateral parallel opposed simulation radiograph for a patient who undertook radiation therapy after a total laryngectomy for a squamous cell carcinoma. The exclusion of dentoalveolar structures anterior to the field boundaries allowed for the safe extraction of the remaining carious dentition without adjuvant hyperbaric oxygen therapy. The patient's treatment plan includes the placement of endosseous titanium implants in the parasymphyseal mandible to enhance removable prosthetic retention. **B,** Appositional anteroposterior simulation radiograph delineating the supraclavicular field associated with the patient's radiation therapy.

collimator arcs across several swaths of parallel appositional fields while two rows of tungsten leaves within the collimator (Fig. 98-9) concentrically open and close to strategically deliver radiation to targeted tissues while sparing normal structures of the highest radiation burdens.[22,35-38] In another technique that has come to be known as *step and shoot intensity-modulated radiation therapy,* radiation is directed from multiple stationary gantry positions that are each uniquely and statically collimated through the use of multiple layers of tungsten leaves capable of converging from the periphery of the linear accelerator's nonadjustable port to fashion customized portal shapes in accord with the radiation oncologist's or physicist's treatment prescription (Fig. 98-10). In either scenario, intensity-modulated radiation therapy simulation is based on an interface between computed tomography imaging and dosimetric treatment planning software such as the CORVUS system. As such, intensity-modulated radiation therapy simulation and portal radiographs offer limited or no value for establishing surgically induced osteoradionecrosis risks after radiation therapy, and intensity-modulated radiation therapy dosimetry must be evaluated using software that is at this time almost universally unavailable to any dental team. This software, however, offers an evaluation of each computer-generated tomographic slice that is so detailed in its resolution that

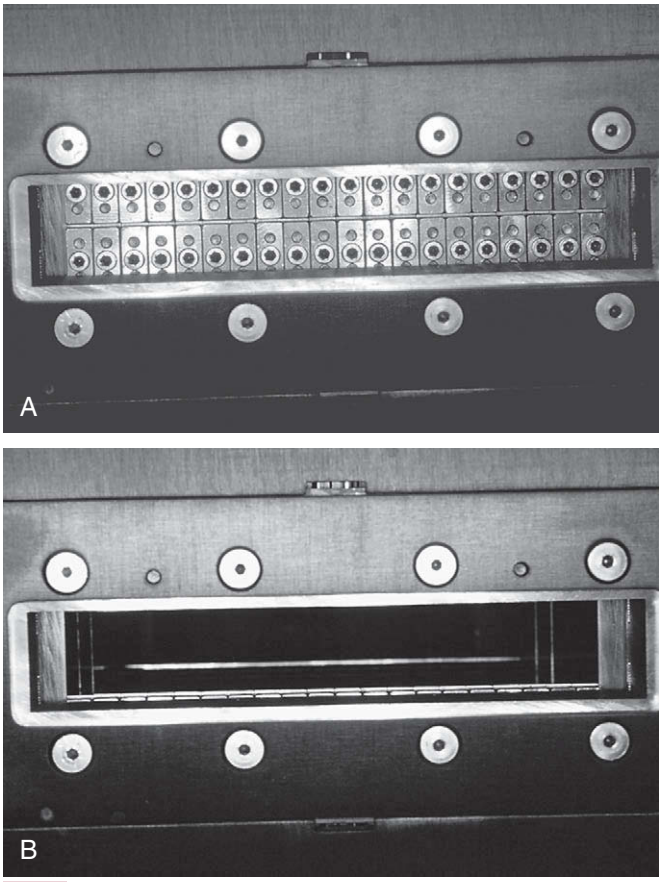

Figure 98-9. **A,** MIMiC collimator showing two rows of tungsten leaves in their closed positions. **B,** MIMiC collimator showing the tungsten leaves in their opened positions.

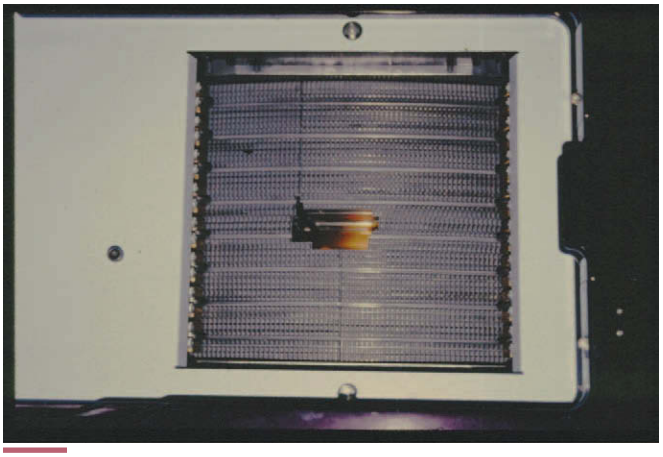

Figure 98-10. Step and shoot intensity-modulated radiation therapy collimator.

anatomic structures as small as individual tooth roots can be identified and dosages can be estimated at the pinpoint level of a computer mouse cursor superimposed over the area of dosimetric interest. Because CORVUS and other intensity-modulated radiation therapy software firms offer axial, sagittal, and coronal tomography sections, a comprehensive 3D depiction of dosimetry can be achieved by means of a review of computer records. This can be done without the need for assessing multiple simulation and portal radiographs that may be geometrically confusing, tattered from age, untidily drawn, of poor radiographic quality, or entirely lost or discarded.

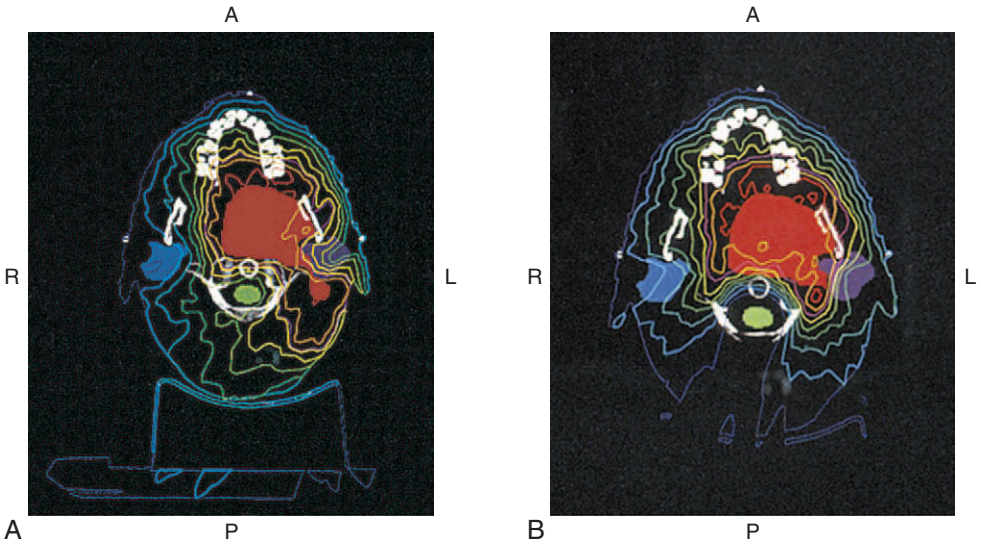

Figure 98-11. **A,** Computed tomography illustration of intensity-modulated radiation therapy isodose lines for a patient treated for a left tonsillar squamous cell carcinoma. The development of a second primary squamous cell carcinoma in the area of the right maxillary palatal mucosa after intensity-modulated radiation therapy necessitated a right inferior maxillectomy. The subsequent development of osteoradionecrosis in the area of the maxillectomy is substantiated by the cumulative dose of radiation in the area of the posterior right maxilla. The axial image demonstrates dosages delivered to the dentoalveolar structures at a level midway between the crestal alveolar bone and the periapices of the right maxillary molars. **B,** The patient's left tonsillar tumor bed was boosted during the administration of intensity-modulated radiation therapy. The computed tomography axial image delineates the additional dosages that were received during the boost in the area of the right posterior maxilla. The collective dose to the right posterior maxilla in the area of subsequent postoperative osteoradionecrosis approximated 7000 cGy and warranted a hyperbaric oxygen therapy regimen that indeed mitigated the osteoradionecrosis.

Although intensity-modulated radiation therapy dosimetric evaluations performed in the interest of establishing the relative safety of proposed dental interventions are readily achieved by way of the dental team's access to computer records when maxillofacial prosthodontic support is found in the facility in which a patient's therapy was delivered, communicative problems can arise between dental and radiation oncology personnel when they are separated geographically. Radiation oncology personnel are not always familiar with dental anatomy and terminology or oral surgical procedures, and dental personnel are not generally knowledgeable of intensity-modulated radiation therapy computer simulation packages or the general delivery of intensity-modulated radiation therapy. It can thus benefit dental practitioners routinely involved in invasive oral procedures to personally meet a radiation oncology team involved in the delivery of intensity-modulated radiation therapy before encountering their first head and neck intensity-modulated radiation therapy patient. Conversely, dental personnel can share an oral surgical treatment plan with a patient's radiation oncology team face-to-face when they first encounter a patient treated by way of intensity-modulated radiation therapy. Either way, an initial interdisciplinary conference at the intensity-modulated radiation therapy facility could lend clarification to each team's needs and concerns when future patients are shared and fiscal, travel, and time constraints make it impractical or impossible to convene personally. Once dental and intensity-modulated radiation therapy providers possess a working knowledge of one another's methodology and concerns, distant communication can be assisted. The most convenient means by which to request dosimetric data from a remote intensity-modulated radiation therapy center involves obtaining printed colorized serial computed tomograms displaying isodose information that is superimposed over imaged anatomy (Fig. 98-11). These images are generated by all intensity-modulated radiation therapy computer packages and offer a reasonable representation of dosages delivered in three dimensions. A common impediment to dental teams' treatment planning efforts involves their receipt of black-and-white photocopied computerized tomography isodose images that are essentially illegible by virtue of the fact that intensity-modulated radiation therapy computer packages routinely rely on the use of color for the assignment of dosimetric values.

Overview of Maxillofacial Prosthodontic and Radiation Oncology Interactions

The maxillofacial prosthodontic team's involvement in the care of head and neck cancer patients who will receive radiation therapy is initially focused on treatment planning in the interest of preventing osteoradionecrosis and the preparation for any prosthetic rehabilitation necessitated by that treatment planning or a patient's comprehensive oncologic management. The maxillofacial prosthodontist also participates in decision making intended to diminish the risk of osteoradionecrosis for patients obliged to undertake oral or maxillofacial surgical procedures after radiation therapy. Because these efforts are usually multidisciplinary to the extent that decisions made by any of those involved in the treatment of an oncology patient could affect the maxillofacial prosthodontic team's treatment options, participation in multidisciplinary head and neck tumor board conferences is constructive. Additionally, with support from the general dental and oral hygiene communities, the maxillofacial prosthodontist contributes to preventive dental health education and care from the outset of the oncologic experience through what should become a lifelong follow-up relationship. Furthermore, maxillofacial prosthodontic personnel can assist the radiation oncology team with intraoral and extraoral devices that repeatedly position and shield anatomy, serve as tissue-equivalent material to allow a more even dose distribution of external radiation beams, or situate radioisotopic sources for intracavitary brachytherapy. Finally, the participation of maxillofacial prosthodontic team members at the commencement of any head and neck oncologic treatment is meritorious in that the often complex intraoral and extraoral rehabilitation of anatomic deficits acquired before, during, or after that treatment is germane to the traditional role of maxillofacial prosthodontists.

Intraoral Rehabilitation of Tumor-Ablative Surgical Defects

The incidence of oral cancer approaches about 5% of all new cancers diagnosed in the general population of the United States.[21] A significant number of head and neck oncology patients are treated for neoplasms of the lip, tongue, oropharynx, mandible, maxilla, soft palate, larynx, external ear, orbit, and external nose. The highest incidence of onco-

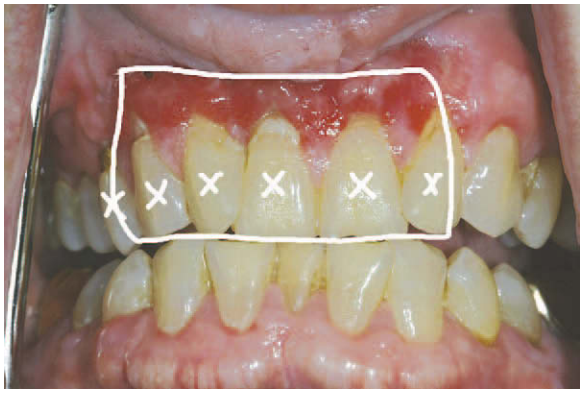

Figure 98-12. Preoperative assessment of patient with squamous cell carcinoma of the anterior maxilla. The maxillectomy was planned to include removal of six teeth with split-thickness skin graft to buccal aspect of cheek flap and defect.

Figure 98-13. Panoramic radiograph of patient with mucoepidermoid carcinoma of the left posterior maxilla. Anterior osteotomy site is to be made through socket of the upper left first premolar. Note the impacted third molar, left side.

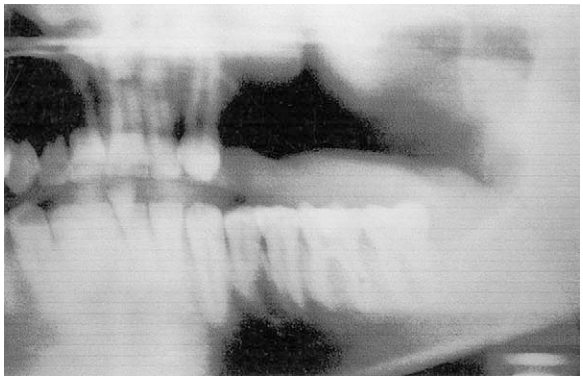

Figure 98-14. Postoperative panoramic radiograph of patient in Figure 98-13. Note removal of maxillary segment and impacted lower third molar with ample healing time before radiation therapy.

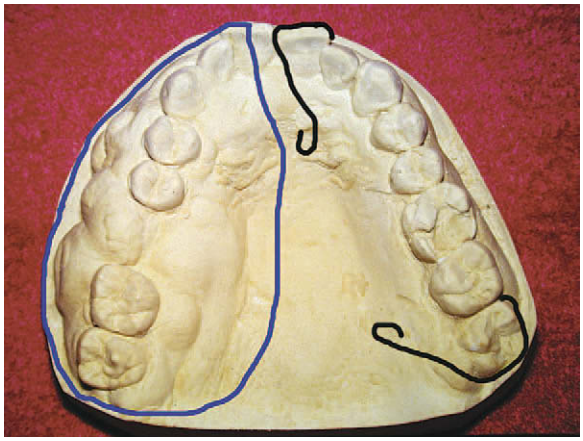

Figure 98-15. Diagnostic cast made from a patient to undergo maxillectomy. Blue area to be included in resection and black wire diagrams denote abutment teeth to be used for surgical prosthesis.

logic disease afflicts those persons with significant risk factors such as an excessive use of alcohol and tobacco or exposure to ultraviolet light and human papillomaviruses. To successfully eradicate disease, these tumors are treated with multimodal therapy including tumor-ablative surgery, radiotherapy, and chemotherapy. Patients treated for tumor-ablative surgery of the oral and pharyngeal areas may have significant anatomic deficits compromising speech, swallowing, and mastication.

Prosthetic Maxillary Obturation

The maxilla may require resection for tumor control that may create a host of problems related to speech, swallowing, and aesthetics. Traditional resection of the maxilla involves an infrastructure, medial, or total maxillectomy to include the infraorbital rim. The maxillectomy procedure used to control incipient disease of the oral cavity has been classified by Aramany[39] on the basis of frequency of occurrence. As with other anatomic defects, tumor surveillance dictates keeping these areas clearly visible to detect recurrences, should they arise. Obviously, the more teeth, bone, and soft tissue available, the more easily prosthetic rehabilitation can be achieved. However, edentulous and some partially dentate patients requiring a maxillectomy may have significant difficulty in obtaining stability with prostheses, and in these cases a consideration for the use of dental implants may be warranted.

Surgical Obturation

Resection of maxillary tumors that involve the oral cavity is dedicated to total eradication of disease. Similarly, preservation of anatomy conducive to prosthetic rehabilitation should be considered. Preoperative assessment of the patient by the maxillofacial prosthodontist is integral to overall treatment success by the head and neck treatment team (Fig. 98-12). Clinical examination with panoramic radiography may assist with decisions to extract diseased teeth at the time of surgical resection (Fig. 98-13). In this way, if adjunctive radiotherapy is necessary, a 4- to 6-week healing time offers a distinct advantage (Fig. 98-14). Preoperative assessment also aids to plan osteotomy planes through the existing tooth sockets in dentate patients to preserve the support of adjacent teeth.[40] These teeth, also called *abutments,* may be strategic for retention of a prosthesis. In fact, the more arch curvature formed by remaining teeth, the more favorable retention may be for a prosthesis of this type.

Arches planned for maxillectomy should be approached with the thought of disease eradication. As a secondary thought, preservation of structures vital for support should be kept in mind for maximum potential of successful rehabilitation. The first of these preserves as much of the hard palate as possible, which is the primary stabilizing structure of a maxillary prosthesis. Second is grafting of the cheek flap with epidermis or split-thickness skin (discussed further later). Third comes removal of the inferior conchae, which, if not eliminated, frequently obstruct proper obturation. This is most evident with posterior and some lateral resections that involve the oral cavity. Finally, the sinus walls should be grafted, if possible. Again, split-thickness skin will limit polypoid tissue formation and keep mucus formation to a minimum.[41] The roof of a sinus grafted with skin will allow its use as a supporting wall for the prosthesis.

Impressions can be made before surgery to provide diagnostic casts (Fig. 98-15). These casts will aid in fabrication of a prosthesis to be inserted at the time of surgery. These prostheses are usually made from polymethylmethacrylate resin and can be made with or without pros-

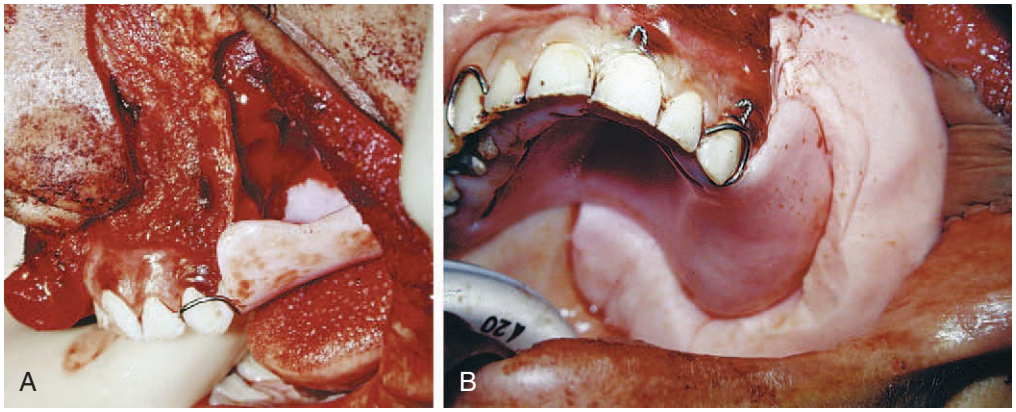

Figure 98-16. **A,** Surgical prosthesis is tried for proper fit. **B,** A surgical bolster is added with xeroform gauze, denture-conditioning material, and stainless steel ligatures securing in place for 5 to 7 days. Note split-thickness skin graft sewn in lateral cheek flap. *(Surgery performed by Gary Clayman, DDS, MS.)*

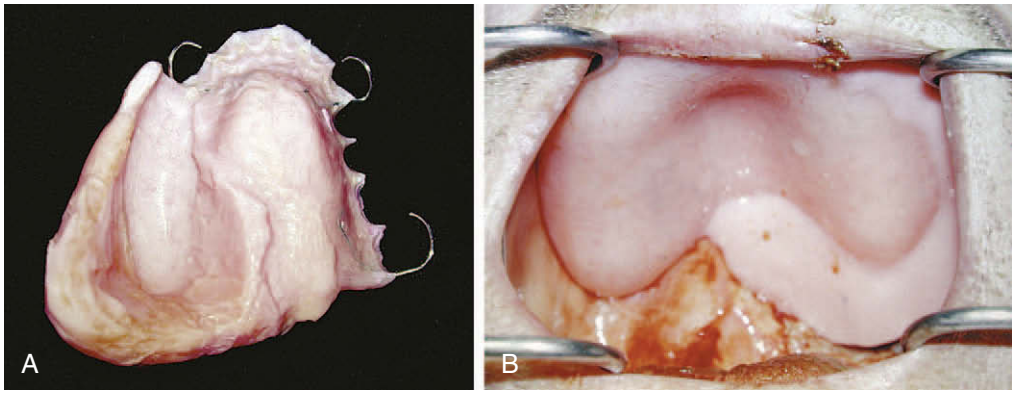

Figure 98-17. **A,** At pack removal, interim obturators made from modification of surgical prosthesis. **B,** Photograph of an edentulous patient's interim obturator. Patients are instructed on defect hygiene and placement/removal of prosthesis.

thetic teeth. The advantage of having no functioning dental components to these prostheses is that occlusal forces are left off the wound to allow for efficient healing. A surgical prosthesis offers advantages relating to speech, swallowing, and psychological well-being. Also, the prosthesis is helpful in securing a surgical bolster and aids the patient in acclimating to wearing a removable prosthesis. Because respiratory epithelium may remain within a sinus defect, prosthetic loading of this area can be problematic. The ability to clean the defect also becomes a concern, with hardened mucus being a particular obstacle for placement of a prosthesis. Grafting of the defect with split-thickness skin can create a more comfortable surface with fewer mucus secretions. As with any skin graft, positive pressure with a surgical bolster can aid with providing this type of surface. Perforating the graft with dispersed small incisions can minimize the likelihood of hematoma formation, thus improving take of the skin graft. In partially dentate patients, securing the prosthesis can be accomplished by incorporating stainless steel wrought wires in the prosthesis that encircle the most terminal teeth (also called *abutments*) (Fig. 98-16). In addition, the prosthesis can be wired to the abutment tooth closest to the defect using 25-gauge stainless steel wires. In edentulous patients, the prosthesis can be held in place using sutures, circum-zygomatic wiring, or several titanium screws (2.7, 10 mm) into the remaining hard palate. Care should be taken to ensure that the screws are placed in an angled fashion so as to allow screwdriver insertion at pack removal. In most cases the surgical prosthesis should be kept in place between 5 and 7 days.

After this time, removal of the packing material and prosthesis should ideally be undertaken by the surgeon and prosthodontist. Removal of the packing material can precipitate a hemorrhage, and preparations with oxidized cellulose, gelatin foam, or microfibrillar collagen can be invaluable. At this time, transitioning the prosthesis by addition of tissue-conditioning material assists patients in becoming accustomed to placement and removal (Fig. 98-17). The patient is also instructed on how to cleanse the defect twice daily with a dilute solution of baking soda and salt. This can best be accomplished using an irrigation syringe and a dispersion attachment head. The patient returns weekly during the following month for changing of the material on the prosthesis as the defect continues to change shape.

Interim Obturation

At the time of pack removal, it is beneficial to have the patient place and remove the prosthesis so that the defect can be lavaged and allowed to heal appropriately. The patient should be seen weekly for the first month after resection. Maximum changes will occur during this time and may be accommodated in the shape of the defect portion of the prosthesis. The original acrylic resin portion of the prosthesis can still be used at this stage to provide a stable anchorage for the changing defect. Other soft acrylic resins can be attached to it and can be changed to a solid acrylic resin prosthesis before radiation therapy, if indicated. If necessary, prolonged use of the interim obturator can assist further surgery or other significant modification. Occasionally, a new impression procedure shortly after packing removal will obtain an improved adaptation of the interim prosthesis. During times of radiation to the area of the defect, it is desirable to have a solid acrylic resin structure that is more resistant to the effect of opportunistic *Candida* colonization.

Definitive Obturation

After an extended period of healing (i.e., 6 weeks) following surgery and/or radiation therapy fabrication of a definitive prosthesis may take

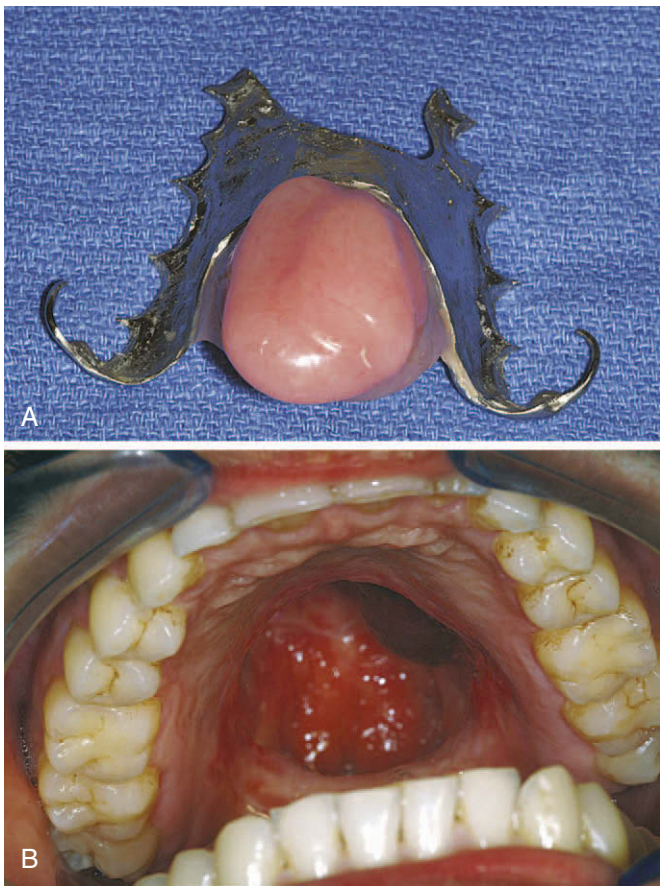

Figure 98-18. Definitive obturator made with cast chrome base **(A)** for resection defect of pleomorphic adenoma **(B).**

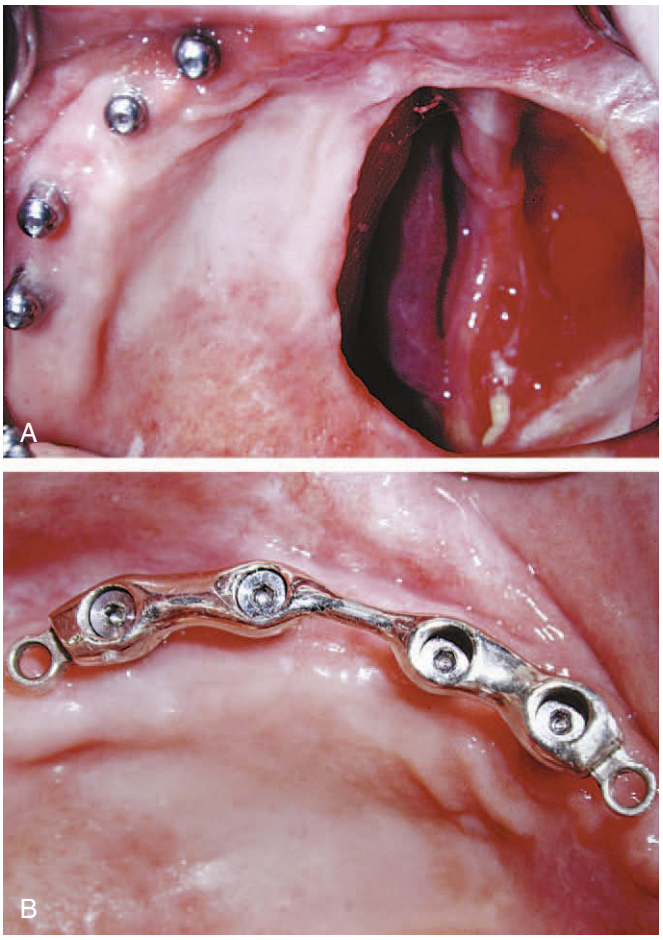

Figure 98-19. **A,** Implant-retained obturator with sinus augmentation and, **B,** stress-breaking bar attachment of nondefect side.

place. For dentate patients, this prosthesis can be made of either acrylic resin and stainless steel wrought wire clasps or a cast chromium framework that supports a bulb extension made of polymethylmethacrylate (Fig. 98-18). Specific recommendations for design have been well published.[26] Prostheses with masses of less than 45 g may remain solid, but prostheses of greater masses should be hollowed.[16,42] Edentulous patients are treated with prostheses made entirely of acrylic resin, the bulbs of which can be hollowed similarly. Teeth placed in the area of the defect serve as aesthetic replacements and prevent opposing tooth supraeruption but are of limited functional value.

Many edentulous or partially edentulous patients have difficulty with retention and, in some cases, difficulty with support as well. In these cases, osseointegrated implants can anchor and support the obturator prosthesis. Although long-term follow-up studies of patients possessing implants in irradiated bone warrants their cautious use, implants remain potentially advantageous.[43] Because maxillary sinuses may be extensively pneumatized following tooth extractions, installation of implants into this area can be problematic unless bone is grafted into the sinuses. This use of sinus augmentation has been well documented and deemed to be successful with the use of implants.[44] This technique can be used on a nondefect side where a unilateral or posterolateral defect of the opposite side is present. Splinting of approximately four to five implants with a stress-breaking bar is generally suggested and provides the patient with a retentive, stable prosthesis that may offer improved support as well (Fig. 98-19). Recently, the use of zygomatic implants (extended length) has been suggested as an alternative to sinus augmentation.[20,45] The implant protocol for zygomatic implants mandates bilateral placement, and preservation of the infraorbital rim on the defect side may improve surgical stability. Both techniques require a screw-retained bar attachment to be made with the obturator (Fig. 98-20).[46] Remote anchorage sites have been suggested as a means of stabilizing prostheses rehabilitating maxillary defects.[46,47]

Mandibular Resection Prostheses

Resection of a portion of the mandible may be necessary to control disease and may or may not create a discontinuity defect. Because the mandible is so integral to oral and respiratory physiology, it is desirable to preserve function as much as possible.

If a marginal mandibulectomy is performed, a general guideline is to surgically preserve about 1 cm of vertical mandibular height for integrity. Subsequently, the remaining mandible can be rehabilitated with a split-thickness skin graft and removable tissue-borne prostheses, or alternatively it can be reconstructed with osseointegrated dental implants. In the dentate patient, preservation of the inferior alveolar nerve in the posterior mandible may preclude placement of implants if there is minimal bone available above the canal position to stabilize implants. In these cases, either nerve transposition[48] (Fig. 98-21) or onlay bone grafting can serve to provide an osseointegrated rehabilitation (Fig. 98-22).

In edentulous patients, placement of either conventional prosthetics or implant supported/retained prosthetics may be desirable. Often, prosthetics can rely on select placement of implants in the anterior mandible with specified posterior occlusal cantilevering (Fig. 98-23). This procedure is well documented, with recent evidence indicating immediate functionality when implants are placed in the native mandible.[49,50]

Discontinuity Defects

If a discontinuity defect is created by composite resection, it may be feasible to collapse the defect and not reconstruct mandibular continuity. This becomes more feasible if the patient is edentulous because

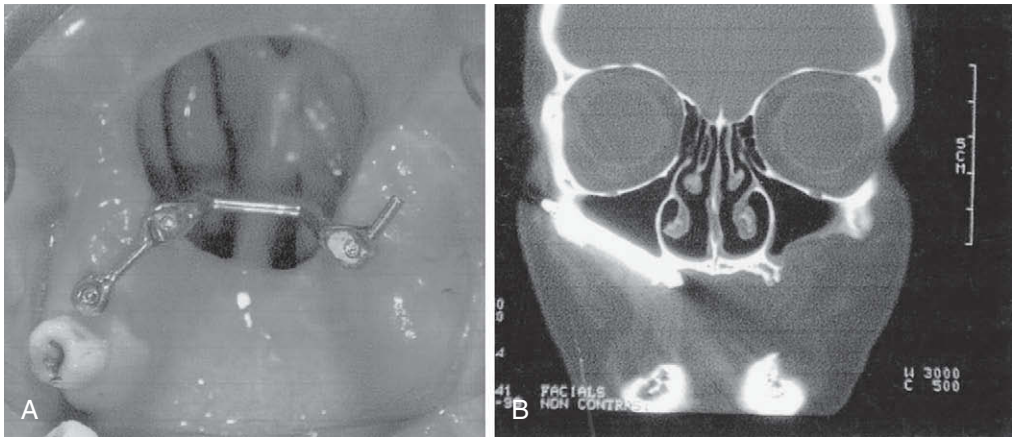

Figure 98-20. Use of extended-length implants **(A)** that traverse lateral aspect of maxillary sinus and engage dense zygoma **(B)**. Such implants obviate the necessity for sinus augmentation for installation of conventional endosseous implants. *(Courtesy of Samuel Zwectchenbaum, DDS.)*

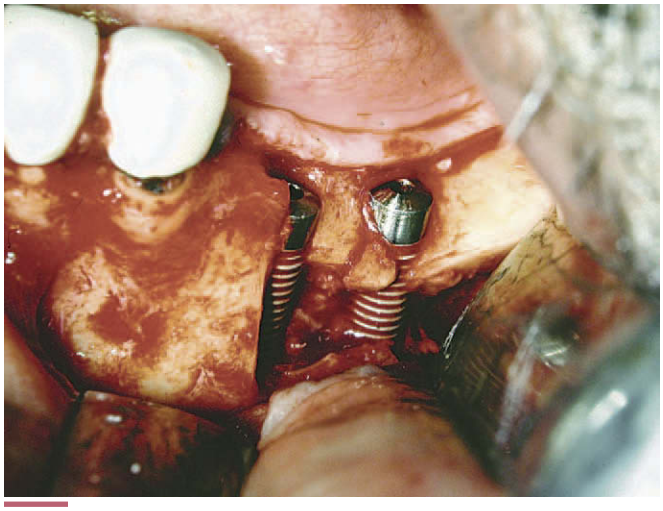

Figure 98-21. Implant placement performed with mandibular inferior alveolar nerve repositioning.

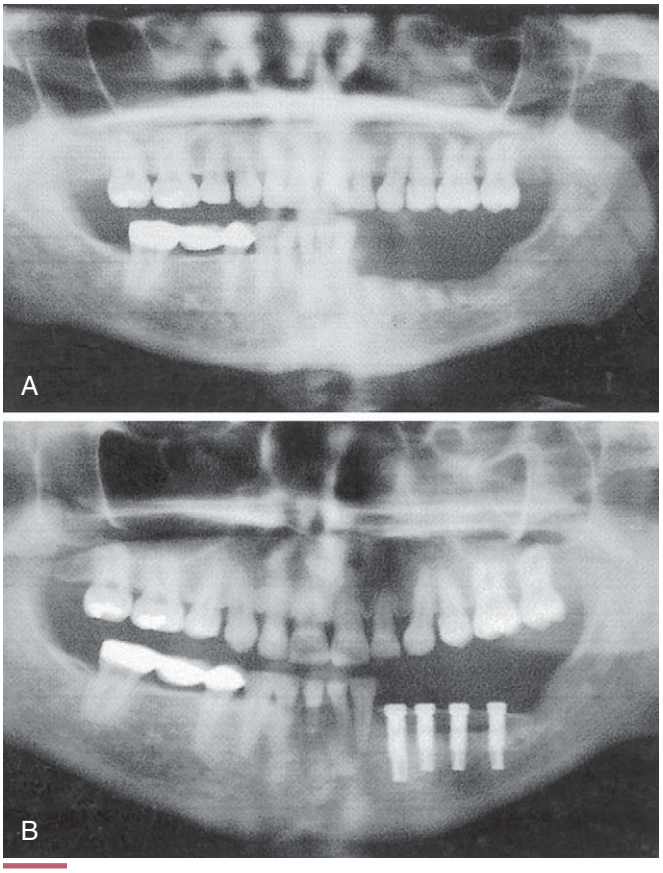

Figure 98-22. **A,** Patient with squamous cell carcinoma resected at left alveolar ridge. **B,** Onlay bone grafting with iliac crest and endosseous implants. *(Courtesy of Michael Miloro, DMD, MD.)*

dentate patients will have significant occlusal discrepancies that make postoperative rehabilitation difficult to impossible. In these cases a significant cosmetic deformity may result because the lower third of the face is asymmetric (Fig. 98-24). Also, disability of the tongue usually results because portions of the tongue may be used to close the wound, making swallowing problems inevitable. Additional consideration is given to the fate of the proximal resection segment of the mandible after the resection. Reconstruction bars may create additional backscatter radiation if adjunctive radiation is used for tumor control (Fig. 98-25).

The key to functioning in these cases lies with preservation of the ramus, for which attachment of the muscles of mastication is preserved. Through removal of the ramus, less function is evident without balance of contralateral pull of pterygoid, temporal, and masseter muscles. If more of the ramus is retained and not maintained in its preoperative position, it may collapse on the maxillary buccal vestibule and obstruct maxillary dental hygiene procedures or the fabrication of a maxillary prosthesis. Furthermore, the ramal segment could be sequestered into the oral cavity. Reconstruction in these cases is the wiser choice and does not advocate joining the plate to small condylar remnants.[51] If mandibular continuity is not preserved after resection, it may be desirable to reconstruct the area with an autogenous or alloplastic graft. Location of the resection may be indicative of the relative success of the reconstruction. Anterior reconstructions that cross the midline with a plate system alone may be less successful than those with an osseous reconstruction as well.[52] Cosmetic and functional deformities are also more of a consideration in the anterior mandibular areas. This is perhaps due to the influence of the suprahyoid musculature on swallowing and respiration. Concurrently, it is considerably difficult to conform an osseous graft to an arch form in this area. Posterior or lateral resections appear to be less debilitating and problematic because a linear replacement of bone is frequently sufficient to reconstruct this area. A reconstruction with pedicled soft tissue may serve to deviate the remaining mandibular segments to the affected side. Osteomyocutaneous flaps are superior in reconstructing mandibular discontinuity to avoid this deviation and preserve maxillomandibular relationships vital to rehabilitation.

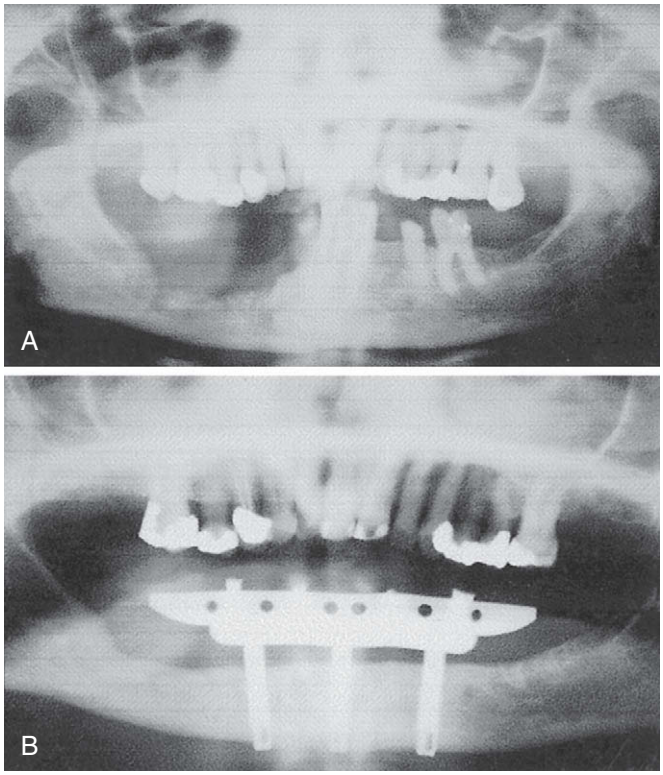

Figure 98-23. **A,** Patient with squamous cell carcinoma resected by marginal mandibulectomy. Remaining decimated dentition insufficient to support prosthesis. **B,** Placement of implant supported by prosthesis 2 months after resection. Note remodeling of alveolus in comparison with postoperative Panorex. *(Courtesy of William Lydiatt, MD, and Michael Miloro, DMD, MD.)*

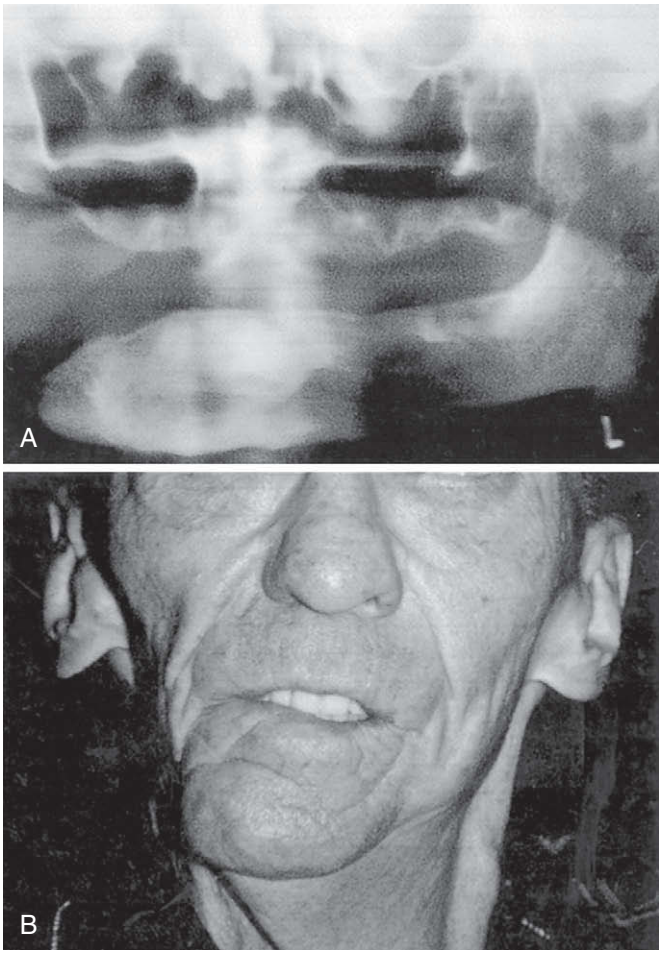

Figure 98-24. **A,** Mandibular composite resection without reconstruction resulting in, **B,** significant mandibular deviation.

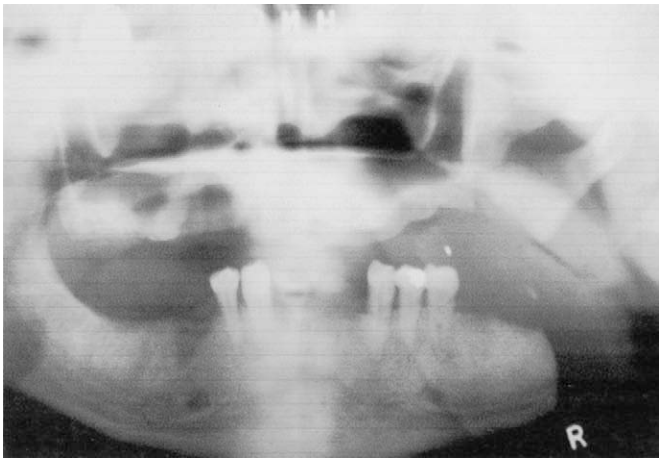

Figure 98-25. Proximal segment without reconstruction results in deviation and displacement against maxillary posterior ridge.

In some cases, autologous grafts offer a greater volume of viable bone with progenitor cells capable of creating a more favorable environment for osseointegration.[36] Nonvascularized or vascularized osteomyocutaneous flaps can also be used for reconstruction. It may be preferable to use vascularized flaps in previous operative beds or in areas that have been or will be irradiated, because the provision of a blood supply may offer a more predictable opportunity for the graft to remain viable. Vascularized iliac crest has been used with some degree of success for mandibular defects and some maxillary defects. Introduced by Hidalgo,[53,54] the use of vascularized fibular grafts has also shown a promising degree of success in the reconstruction of these complex mandibular defects.[55] Being a non-weight-bearing bone, the fibula is of reasonable dimension to functionally and cosmetically reconstruct the mandible. Additional phases of rehabilitation with titanium implants have been demonstrated to be uniquely applicable to these cases. Bicortical stability is typically well obtained at surgical installation, and long-term success has been favorable (Fig. 98-26). The choice of using either a sectional overdenture design or a screw-retained fixed prosthesis may be predicated on the amount of tissue missing, the function of the tongue, perioral scarring, and adjacent/opposing occlusion (Fig. 98-27). Frequently, the restoration to implant height ratio is seen to be greater than 1:1. Passive splinting of these implants is crucial to their long-term success, and close attention should be paid to the development of the occlusal scheme. Occasionally, it may be necessary to perform soft tissue revision procedures if the skin pedicle is thick or if a greater vestibular depth is necessary. This ensures soft tissue health and visibility for hygiene procedures.

Tongue Resection

Resection of the oral or pharyngeal tongue is occasionally necessary to control disease. Integral to swallowing, speech, and mastication, the tongue is often treated aggressively for tumor control. Centrally located malignant lesions have a propensity to metastasize bilaterally to the neck and may require extensive resection for tumor control. As a result of large resections of tongue muscle, wound closure becomes a concern for postoperative healing. Vascularized myocutaneous or fasciocutaneous flaps may be a valuable adjunct for reconstruction of these resections. However, these flaps are generally insensate and do not provide tissue conducive for normal swallowing and speech production. Physiology of swallowing has been described and is divided into three main

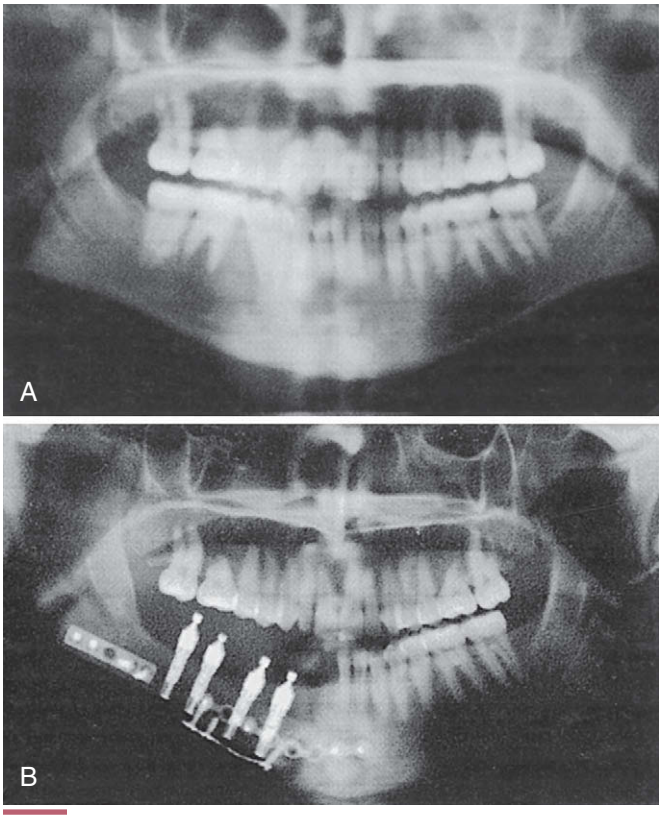

Figure 98-26. Osteosarcoma of mandible resected and reconstructed with vascularized fibula and end endosseous implants. *(Courtesy of William Lydiatt, MD, and Perry Johnson, MD.)*

Figure 98-27. Screw-retained ceramometal prosthesis used for patient in Figure 98-26.

phases: oral, pharyngeal, and esophageal. The voluntary oral phase can be further subdivided into two phases of oral preparatory and mastication.

The competency of the lips is mandatory for the oral phase to function effectively because a lip seal will create a boundary for bolus transportation. Mastication is an independent function of the tongue for tougher-consistency foods, and efficiency is also dependent on dental status of the patient. The time taken for the bolus to be transported to the posterior oral cavity past the anterior faucial arch demarcates the oral transit time. In healthy adults, the oral transit time can be about 1 to 2 seconds. After tumor-ablative surgery of the tongue or mandible, the range of motion needed for swallowing and speech production may not be sufficient. In these cases the height of the palatal vault may not allow appositional contact of the remaining tongue tissue to propel the bolus of food or liquid into the pharyngeal area where the involuntary phase of the swallowing reflex is initiated. Consequently, lowering of the palatal surface prosthetically can aid in providing a surface that approximates the extent of the tongue's range of motion postsurgically. This prosthesis, known as a *palatal augmentation prosthesis,* can be used in dentate or edentulous patients (Fig. 98-28).[56,57] In patients with dysphagia, palatal augmentation prostheses have been shown to decrease oral transit times, thereby increasing swallowing efficiency.[58]

Articulatory speech debility is dependent on the area(s) of the tongue that are resected. For instance, resection of the anterior or tip of the tongue may not allow articulation of linguoalveolar sounds such as /t/, /d/, /n/, or /s/. In other cases the base or sides of the tongue may be resected to create deficiencies in /g/, /ng/, /k/, or /c/. In these cases a prosthesis may serve to better aid production of these sounds. Because the shape needed for swallowing may be markedly different from that which is necessary for speech production, a prosthesis with interchangeable surfaces being incorporated into a palatal augmentation or a mandibular "tongue" prosthesis has been advocated. Each respective surface is used specifically for speech or swallowing.[51,59] Regardless of the type of prosthesis being constructed, involvement of a speech pathologist can be quite instructive to patients and the maxillofacial prosthodontist.

Soft Palate Resection

As a component of Waldeyer's ring, the soft palate is occasionally included in resection of tumors of squamous cell origin. Because of its dynamic nature, the soft palate, like the tongue, is integral to swallowing and speech. The anterior faucial arch serves as a landmark for the involuntary phase of swallowing and, if included in resection, can predispose the patient to aspiration. An anatomic deficit of the soft palate can also create velopharyngeal insufficiency, which may result in nasal regurgitation of swallowed matter and nasal speech production. Replacement of velar function with pharyngeal flaps is reserved for conservative soft palatal defects that may be acquired or congenital. A prosthesis (known as a *speech aid*) replacing soft palate function should obturate the pharyngeal recess at the level of the first cervical vertebra or Passavant's pad, frequently seen as a conglomeration of muscular tissue in the superior pharyngeal constrictor (Fig. 98-29). At this level, the extension of the prosthesis should serve to partially fill the pharyngeal recess while providing room for the dynamic nature of the pharyngeal and tongue musculature. A stable reference for the prosthesis starts with assessment of the oral cavity. Anchorage for the prosthesis can be tooth borne or partially or completely tissue borne. For tooth-borne prostheses, anchorage with molar teeth becomes advantageous because anchorage closer to the vectors of dislodging forces discourages premature loosening with function.

Soft palate function can also be affected by cerebrovascular accidents, demyelination diseases, or surgical procedures. The anatomic structures, in these cases, may be incompetent in performing velopha-

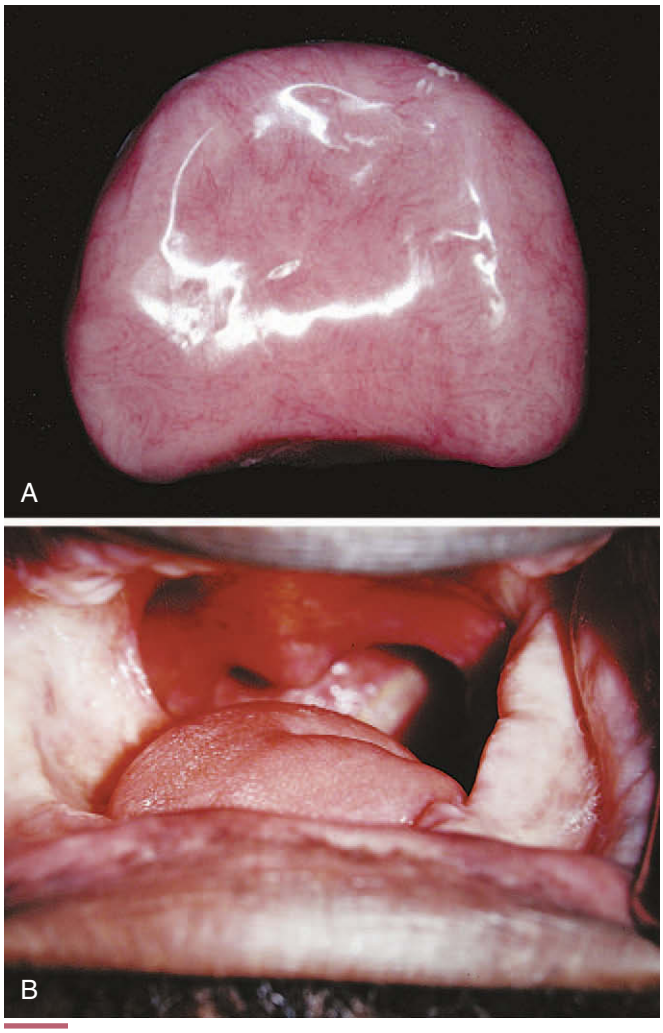

Figure 98-28. Palatal augmentation prosthesis **(A)** used for improved patterns of swallowing and speech in this patient **(B)**, who undertook the resection of a base of tongue squamous cell carcinoma.

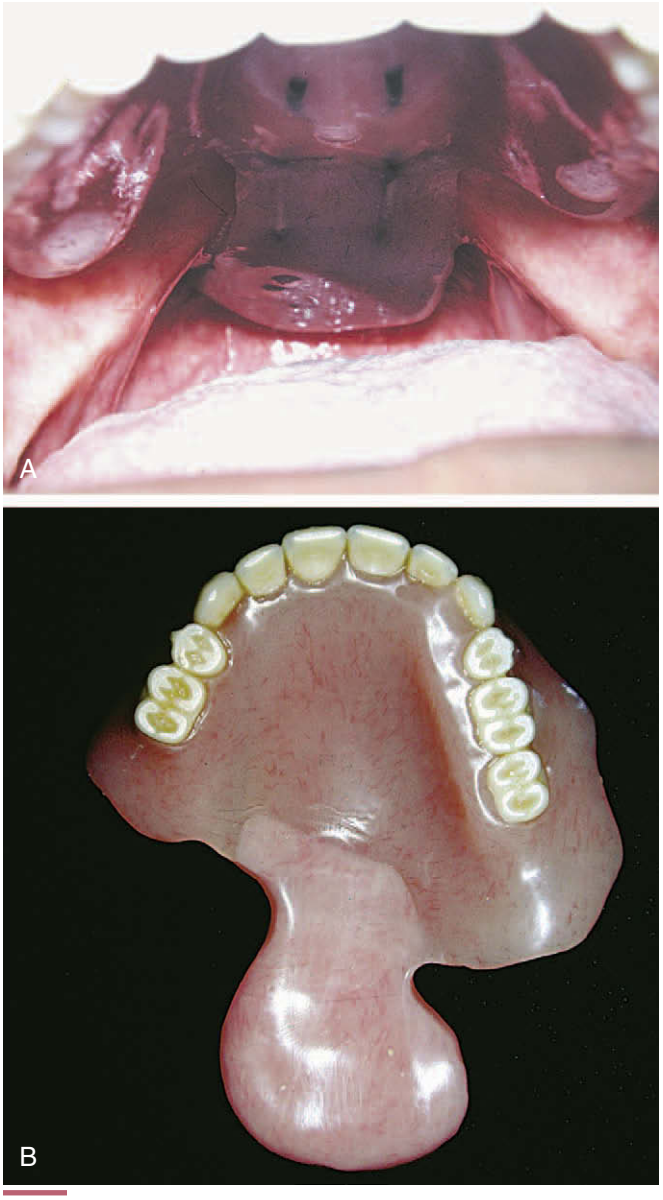

Figure 98-29. Patient with soft palate resection restored with speech aid **(A)** or pharyngeal obturator prosthesis **(B)**.

ryngeal closure. A palatal lift prosthesis may serve to provide the patient also with better speech production and improved swallowing patterns and it may stimulate the musculature to perform at increased functional levels.[60-62] For the palatal lift prosthesis to be effective, some pharyngeal muscular movement must be present. To effectively evaluate the closure of the soft palate, a nasal endoscope can aid in directly identifying deficiencies.

Intraoral rehabilitation of congenital and acquired defects has historical roots in traditional restorative dentistry. It is within this literature that restoring a patient's preoperative level of function has proved essential. Quality-of-life and clinical outcome studies have been shown to validate these goals and objectives. These achievements have been taken to a higher level with our knowledge of osseointegration, tissue physiology, and technology. Continued developments in tissue engineering and other related technology will continually explore and improve outcomes in this complex area of clinical treatment.

Prosthetic Management of Acquired Facial Defects

Facial defects acquired from trauma or surgery can be devastating and among the most socially crippling for the patient. There is a tremendous emphasis on perfection and beauty in today's society. The prosthetic restoration of patients who are not surgical reconstruction candidates can lead to their return to active, productive lives and complete social acceptance.

The decision of whether to manage a facial defect surgically or prosthetically is often a difficult one. Most patients would rather have surgical reconstruction. However, the advantages and disadvantages of each method must be considered as the decision is made. The patient's functional status and overall health are concerns. Radiation treatment to the defect area results in a reduced blood supply and can prevent some surgical procedures. The texture, contour, and color of the surrounding tissue must also be considered, as well as the need to examine the surgical area for an extended period after the original intervention. Achieving the correct shape to restore contour can be difficult with living tissue, and large defects may require staged procedures. If all of these factors can be managed positively and there are no other contraindications, the patient and surgeon may opt for surgical reconstruction. If the defect can be successfully managed with the patient's own tissues in an aesthetically acceptable fashion, this may be the first choice. Otherwise, a prosthesis is required.

Prosthetic management of facial defects has its disadvantages as well. Although excellent contour and color are attainable, the prosthetic materials used have fairly limited life spans—usually 18 to 24 months. The prosthesis may have to be retinted during that time, depending on

Table 98-1

Prosthetic Management of Facial Defects

	Advantages	Disadvantages	Ideal Defect
Nasal	Postoperative inspection; color; contour	Longevity; daily removal; retention without implants; hygiene dependent	Total rhinectomy including nasal bones; central location; nasolabial fold intact; STSG in anterior floor, implants
Orbital			
Scleral shell	Postoperative inspection; longevity; color, contour, no surgical equivalent	Daily removal; small space, thin; hygiene dependent	Scleral contents removed; implant
Custom ocular	Postoperative inspection; longevity; color, contour, no surgical equivalent	Periodic removal; hygiene dependent	Total globe removal; implant posteriorly
Oculofacial	Postoperative inspection; color, contour; no surgical equivalent	Longevity; daily removal; retention without implants; hygiene dependent	Confined to orbit; no irregular margins; brow in normal location; STSG, implants
Auricular	Postoperative inspection; color, contour	Longevity, retention without implants; hygiene dependent	Total removal; minimal extension, implants; tragus intact

STSG, split-thickness skin graft.

its environment. Craniofacial implants or adhesives must be used to retain the prosthesis, and it should be removed for a few hours regularly each day to maintain the underlying tissues in a healthy state. Various masking techniques such as large-framed glasses or cosmetics are often used to hide margins. Some patients develop chronic mechanical tissue irritation from wearing prostheses, and allergic responses, though not common, may affect prosthesis use. Despite this, excellent cosmetic results and patient acceptance are obtainable in the vast majority of cases (Table 98-1).

Prosthesis retention can be managed in several ways. Where possible, tissue undercuts should be used. Tissue "pockets," particularly those that have been lined with split-thickness skin grafts, can be effective as retentive aids. The most common of the retentive aids used are the skin adhesives. These have been effective, and there are several kinds in use. Mechanical aids such as glasses frames, double-faced tape, or straps are also used where appropriate. Craniofacial implants can be used and have several distinct advantages over the other types of retention. With several strategically placed implants, connecting bars can be used, with corresponding clips or other types of attachments that are bonded to the tissue side of the prosthesis. These hold the prosthesis securely, adding a measure of confidence for the patient and allowing him or her to accurately place it without the sometimes irritating effects of an adhesive. Where possible, this is the retention of choice, particularly for large facial prostheses.

Previously irradiated patients may not be good candidates for craniofacial implants due to compromised blood supply to the supporting bone. However, implant placement within the first 3 months after radiation is possible due to the delayed tissue response. Use of hyperbaric oxygen treatments in irradiated patients also improves the bone and soft tissue response to implant placement. Patients with facial prostheses must have good manual dexterity and the ability to keep the prosthesis and defect clean.

A psychosocial support system of family or friends helps to ensure success in dealing with a facial prosthesis, especially for older patients. Those without this support and the dexterity required may have difficulty and cease wearing the prosthesis. The patient's willingness to accept the defect and cope with it, as well as having reasonable expectations, are of paramount importance. The most cosmetic and retentive prosthesis is still a failure if the patient cannot deal with it. Interdisciplinary discussions between the surgeon and the maxillofacial prosthodontist before or during surgery will be helpful in the management of the primary disease and the postoperative rehabilitation of the patient.

Although the eradication of disease and the preservation of the patient's life are the first priority, there are intraoperative procedures the surgeon can complete that will greatly enhance the tissues surrounding the defect for support and retention of a prosthesis. These procedures are best discussed according to the type of facial defect involved. The most common types of facial surgical defects are the nasal, auricular, and orbital.

Nasal Defects

Many variations of acquired defects are caused by ablative surgery involving the nose. Where there is a relatively small, isolated defect, a split- or full-thickness skin graft can be used if primary closure is not feasible. In these cases, prosthetic management need not be considered unless the surgeon wishes to observe the defect for an extended period of time. Defects involving greater areas including not only skin but bone, subcutaneous tissues, and mucosal lining can be reconstructed using various flap procedures with or without autogenous support. If more than half the nose is resected, a complete rhinectomy should be considered. Alar tabs or unsupported tissue surrounding the defect do nothing for prosthetic support and, in fact, hinder the fabrication of a cosmetic prosthesis. Although it may be possible for the patient to wear a prosthesis, more margins will be visible, thus compromising the aesthetic value. Centrally located defects, leaving the nasolabial folds intact with surrounding supported tissue, provide the best base for restoration (Fig. 98-30). Those defects that extend beyond the nose laterally or toward the upper lip are more difficult to restore due to greater tissue mobility in these areas; they therefore require greater exposure of margins. Placement of split-thickness skin grafts, particularly at those margins extending toward the lip, will be beneficial in preventing scar contraction of the lip and will provide a firm, immobile base for the inferior margin of the prosthesis. Craniofacial implants are useful in the retention of a nasal prosthesis and should be placed in the anterior floor of the nose where there is sufficient bony support. They are best used in conjunction with split-thickness skin grafts, and their position should be such that the abutments will extend into the greatest thickness of the subsequent nasal prosthesis (Fig. 98-31).

Auricular Defects

As with nasal defects, flexible remnants of the ear such as the lobe and helix should be removed unless surgical reconstruction of the ear is anticipated. The tragus, however, should be retained because part of

Figure 98-30. Small, centrally located nasal defect with nasolabial folds intact and no involvement of the upper lip.

Figure 98-32. Auriculectomy defect with split-thickness skin graft in place and a bar splint supported by craniofacial implants. Notice the presence of the tragus.

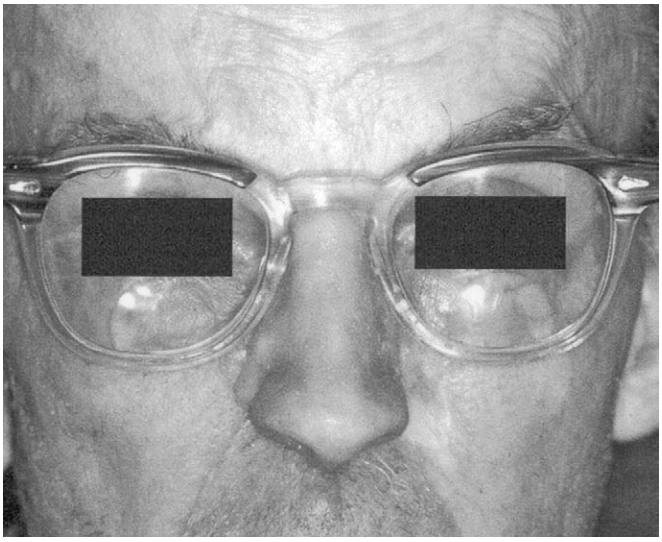

Figure 98-31. Nasal defect restored with a prosthetic nose.

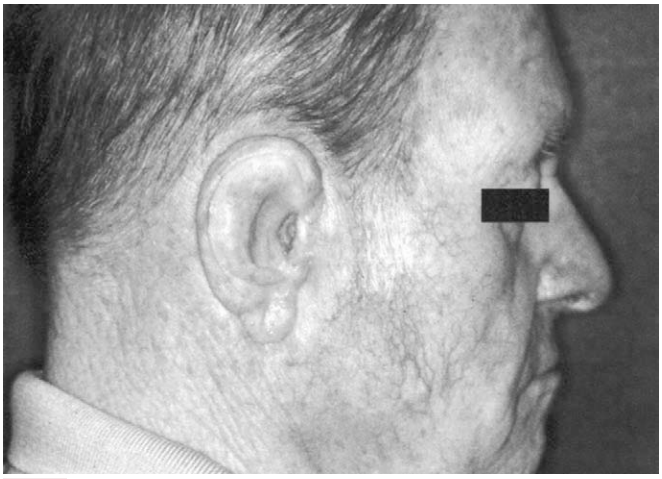

Figure 98-33. Prosthetic ear in place with the tragus masking the anterior margin.

the anterior margin of the prosthesis can be hidden behind it. A defect that results from a partial resection is much more difficult to restore prosthetically than that of a total auriculectomy. If an attempt at surgical reconstruction has been made and has failed, the tissue should be completely removed (Fig. 98-32). A split-thickness skin graft will provide a firm, immobile tissue bed for the prosthesis. Full-thickness or hair-bearing skin grafts should not be used. It should be remembered that prosthesis margins that must overlay the condylar area can loosen during function if they rely on adhesive for retention. If implants can be placed in a position such that they will be in the thickest part of the auricular prosthesis, usually close to the helix, they will provide maximum retention and patient confidence.

The auricular prosthesis has two major advantages over the nasal or midface prosthesis; the viewer cannot focus on both ears at the same time because they are located laterally, and the patient's hair can be used to hide a portion of the margin (Fig. 98-33).

Ocular Defects

Evisceration, enucleation, or exenteration of the eye requires, more than any other, the combined efforts of the surgeon and maxillofacial prosthodontist for a successful restoration. After evisceration, or removal of the global contents, a spherical implant is placed within the scleral space. A thin, custom ocular prosthesis or scleral shell is fabricated to fit over the implanted sclera and reproduce the contour and aesthetics of the original eye. Because the muscles controlling globe movement are left intact, movement of the prosthesis should be relatively good. This prosthesis must be thin to keep the eye from appearing exophthalmic and to accommodate the potential movement.

Enucleation is the total removal of the eye after severing the optic nerve and detaching the ocular muscles. The space provided by the procedure, along with placement of an implant in the posterior wall associated with the muscles, makes it possible to provide an aesthetic, mobile, custom ocular prosthesis.

The aesthetic and functional restoration of the orbital exenteration defect, where all the contents of the orbit are removed, is a difficult one. Its success usually depends on the amount of tissue that must be removed beyond the orbit. It is unique among the types of facial prostheses in that the eye within the prosthesis has no movement and the normal eye presents itself for easy comparison, unlike the ears (which are located laterally) or the nose (which has no basis for comparison on the face). During socialization, the eyes are usually focal points. In defects that extend beyond the orbit

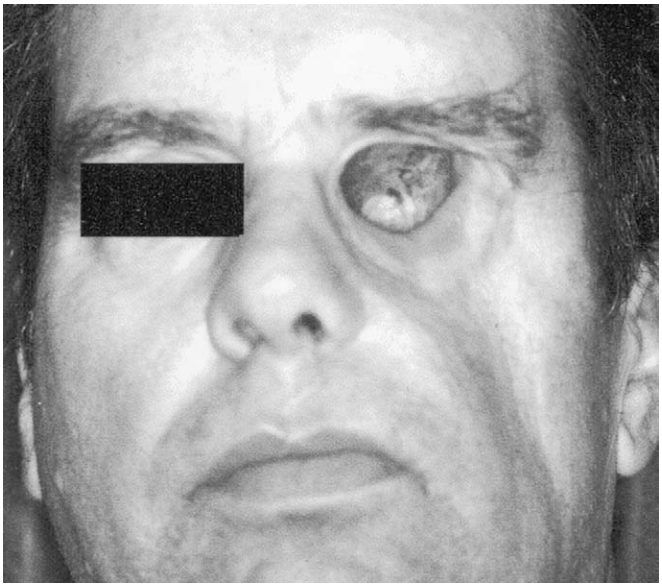

Figure 98-34. Orbital exenteration defect lined with a split-thickness skin graft that does not extend beyond the orbital rim.

into the more mobile tissues of the face, the margin of the prosthesis can loosen during facial expressions if it relies solely on adhesive to retain it.

An ideal defect is one that is within the orbital boundaries with no marginal irregularities, lined with a split-thickness skin graft, and having sufficient depth to recreate normal anatomy with the oculofacial prosthesis (Fig. 98-34). Without the skin graft, the tissues are much more sensitive and difficult to manage hygienically. If the eyebrow cannot be kept in normal position, it is best to remove it and include it in the area of the skin graft. Where possible, placement of implants in the lateral or superior orbital rims is a great advantage for retention of the prosthesis. As with placement for other types of facial prostheses, location of the implants and their angulation should be such that they will be in the thickest portion of the prosthesis. If these requirements can be met without compromising the patient's cure, it will be possible to provide a defect that the patient can manage hygienically and one for which the most aesthetically pleasing and retentive prosthesis can be made (Fig. 98-35).

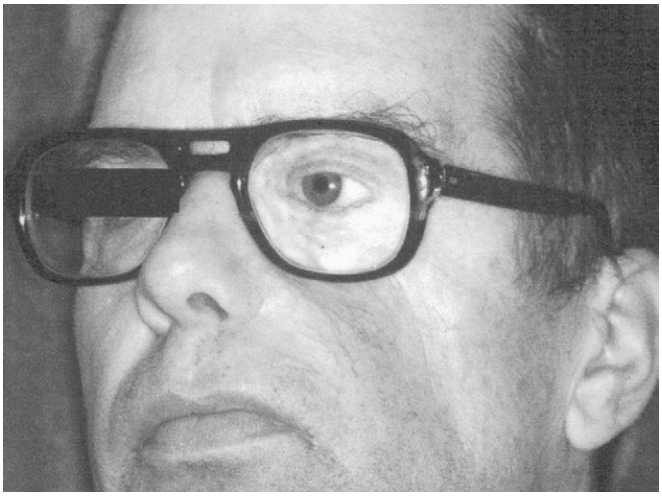

Figure 98-35. Oculofacial prosthesis in place with margins masked by glasses.

SUGGESTED READINGS

Readers interested in the discipline of maxillofacial prosthetics should be abreast of current literature associated with the many disciplines with which maxillofacial prosthodontists interact. Several recent textbooks offer a comprehensive overview of the topic.

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CHAPTER NINETY-NINE

Benign and Malignant Tumors of the Nasopharynx

Luke Tan

Thomas Loh

Key Points

- A large number of different tumors can arise in the nasopharynx (NP) (see Table 99-1).
- Juvenile angiofibroma (JNA) is the commonest tumor in the male adolescent and can extend into the paranasal sinuses, infratemporal fossa, and skull base, as well as intracranially.
- The mainstay of JNA management is surgical and the endoscopic route is being used more frequently.
- Recurrence rates can be up to 33%.
- Nasopharyngeal carcinoma (NPC) is the commonest malignancy in the NP. It has strong correlation to (1) ethnicity, (2) Epstein-Barr virus infection, and (3) dietary habits.
- NPC presents with nodal metastasis in more than half of cases at presentation.
- Early-stage NPC is treated by radiation. Stages 3 and 4 are treated with chemoradiation.
- Surgery is reserved for salvage. A radical neck dissection is the preferred mode of treatment. At the primary site, surgical approach depends on the extent of tumor. Endoscopic resection is reserved for small, localized lesions.

The nasopharynx (NP) is an embryologic confluence of the end of the nasal structures and the beginning of the pharynx. It is also bounded superiorly by the ectodermal origins of the cranial base and upper cervical spines posteriorly. For this reason, a large range of pathologies occur in this small confine (Table 99-1). Because of the NP capacity for tumor growth and expansion, the symptoms in general arise late. Thus they can reach significant sizes before presentation because of the diagnostic inaccessibility of the NP area.

The learning points in this chapter are (1) to know the range of tumors (benign and malignant) that can occur in this region and (2) to have a comprehensive understanding of the most common benign and malignant tumors in the NP, which are juvenile angiofibroma (JNA) and nasopharyngeal carcinoma (NPC).

Diagnostic Approach for Nasopharyngeal Masses

The presentation of an NP tumor is variable ranging from ear, nasal, and throat symptoms to neck masses and cranial nerves palsies. The age and sex of the patient is important in the differential diagnosis of an NP mass. Although it is usually due to adenoidal hypertrophy in the pediatric age group, JNA should be strongly considered in teenage males having a NP mass. In adults, NP malignancy should be the default diagnosis for masses in this area as adenoid hypertrophy would have usually regressed. In certain regions of the United States (California, Alaska) and in several Asian regions (Singapore, Hong Kong, Guangzhou province of China) NP malignancy is common and usually of the Epstein-Barr virus–related, undifferentiated type of carcinoma.

As a diagnostic approach, it is reasonable to proceed to imaging studies before biopsy of the mass. Both computed tomography (CT) and magnetic resonance imaging (MRI) have their benefits. Radiologic studies in cases where extension from an intracranial lesion is suspected are particularly important. Outpatient clinic–based transnasal biopsy for patients with suspected malignancy is commonly practiced in areas where NPC is endemic. However, in patients where JNA is suspected, this should be done under conditions where hemostasis of significant bleeding is available, usually in the operating suite.

The histology of the NP mass dictates the management. For benign lesions, surgical removal is commonly required. The most common benign lesion is JNA, which is discussed in detail in this chapter. NP malignancy is usually treated with radiation and chemotherapy.

Thornwaldt's Cyst/Bursa

This is the commonest epithelial growth next to adenoidal hypertrophy in the NP. The cyst is a result of cleavage line between the nasal and pharyngeal embryologic processes (Rathke's pouch). This lesion is usually asymptomatic, although some patients may present with post-nasal drip due to the extrusion of the contents of the cyst occasionally. The diagnosis of this mass is usually incidental as part of a nasal endoscopic examination. The findings are that of a smooth, usually centrally located mass with a yellow hue due to the cystic contents. The differential diagnosis here should include a meningocele or meningoencephalocele. Occasionally, the lesion can be darker colored due to a hemorrhage or hemosiderin content. In such a situation the lesion should be removed or at least biopsied to exclude a melanoma. However,

Table 99-1

Benign and Malignant Tumors of the Nasopharynx

- Benign Tumors
  - Developmental
    - Thornwaldt's cyst
    - Hairy polyp
    - Teratomas (varied origin)
  - Ectodermal
    - Papilloma
    - Adenomatous polyps
  - Mesodermal
    - Juvenile angiofibroma
    - Fibromyxomatous polyps
    - Choanal polyps
    - Osteomas
    - Fibrous dysplasia
    - Craniopharyngioma
    - Solitary fibrous tumor
    - Desmoid fibromatosis
    - Schwannoma
  - Benign Salivary Gland Tumors
    - Pleomorphic adenoma
    - Monomorphic adenoma
- Malignant Tumors
  - Epithelial
    - Nasopharyngeal cancer (NPC)
    - Undifferentiated carcinoma
    - Squamous cell carcinoma
  - Embryonal
    - Chordoma
  - Lymphoid
    - Lymphoma
  - Mesodermal
    - Hemangiopericytoma
    - Malignant fibrous histiocytoma
    - Rhabdomyosarcoma
  - Malignant Salivary Gland Tumors
    - Adenoid cystic carcinoma
    - Mucoepidermoid carcinoma
    - Acinic cell carcinoma
    - Adenocarcinoma
  - Metastatic Tumors
    - Adenocarcinoma
    - Papillary carcinoma

in general, Thornwaldt's cyst need not be removed or biopsied if the diagnosis is apparent. The root of the cyst can be adherent to the underlining prevertebral fascial and complete exenteration would best be done under general anesthesia. The wound after resection heals well, as in a case of adenoidectomy.

Squamous Papilloma

This benign epithelial tumor is common in the anterior and posterior nasal space. The epithelial changes of such a tumor may be inverting at the basal membrane, whence they are termed "Schneiderian" or "inverting" papilloma. The presentation is unusually incidental for lesions of the nasopharynx (which is not common), and diagnosis should be done with a biopsy. The base of the lesion should be completely removed with a margin of normal tissue. The use of powered instrumentation is helpful in difficult recesses of the nasopharynx. Further detail on the management of inverting papilloma of the nose and paranasal sinuses is available in Chapters 49 and 99.

Craniopharyngioma

Craniopharyngiomas are histologically benign tumors that arise developmentally from Rathke's pouch. They usually present with symptoms similar to pituitary tumors (endocrine and visual disturbances), but occasionally they may present with nasal symptoms such as nasal obstruction due to extension into the nasopharynx. In children, these lesions have been known to mimic presentation similar to adenoidal hypertrophy.[14] Treatment is surgical excision with or without radiation therapy. The gamma knife has been used as the primary treatment.

Angiofibroma

Angiofibroma usually occurs in adolescent males and is thus commonly called JNA. It accounts for less than 1% of all head and neck tumors. The peculiar vascular nature of this mass and difficulty in accessing the deep-seated tumor mass for diagnosis provide the basis for abundant published literature regarding this disease.

Growth Patterns

The tumor mass is locally infiltrative and usually has a wide-based attachment to the NP and to its surrounding related anatomy. JNA is a slow-growing vascular tumor arising in the area of the sphenopalatine foramen at the root of the pterygoid process on the lateral nasal wall. The tumor expands laterally via the pterygopalatine fossa to the infratemporal fossa but has no resistance to growth into the NP and choanal space and thereby may expand into the anterior nasal cavity and all the related sinuses. It can have intracranial extensions into the middle and anterior cranial fossae, although this is uncommon. It can also extend bilaterally to the maxillary sinuses and superiorly to the cranial skull base. Because JNA commonly occurs in young males, this has prompted studies related to the androgen receptor (AR) and estrogen receptor (ER) in the tumor tissue. A recent study suggests a stronger relationship to ER positivity, which may provide a platform for ER modulators in the management of JNA.[1]

Pathologic Features

The gross pathology usually shows a sessile, lobulated, rubbery dark red to tan gray mass that can be large in size. Mucosal ulceration is uncommonly seen and the tumor is unencapsulated and composed of an admixture of vascular tissue and fibrous stroma. The vessel walls lack elastic fibers and have incomplete or absent smooth muscle that will account for their tendency to bleed.[2]

Clinical Features

Although JNA is typically diagnosed between the ages of 10 and 25 in males, many case reports exist for female patients and also in patients who are in the later decades of life. JNA patients present with nasal obstruction (usually unilateral), epistaxis, blood-stained sputum, and serous otitis media. Less common symptoms include nasal discharge, facial swelling, proptosis, sinusitis, and anosmia. The duration of symptoms is usually long and often mild and innocuous. JNA cases occurring in sites other than the NP have been reported. The next commonest site, the maxillary sinuses, is associated with a greater proportion of females.[3]

Diagnosis

On endoscopic examination, JNA presents as a rubbery vascular mass protruding into the anterior nasal space and may have excessive bleeding on contact. A CT scan with contrast will show an enhancing soft tissue mass arising from the NP or lateral wall of the nose. Although the pterygopalatine fossa may be widened by the tumor (Fig. 99-1), bone erosion is not present in general. MRI will show a vascular tumor with flow voids within the mass and enhances on gadolinium. MR angiography will be the least invasive form of vascular imaging that will show the feeding vessels arising from the branches of the external carotid system. The authors have found the MRI with contrast to be more useful for follow-up evaluation (Fig. 99-2). The use of ^{99m}Tc-RBC single photon emission computed tomography has been suggested to

Figure 99-1. Computed tomography showing the widening of the left sphenopalatine foramen from a juvenile angiofibroma.

Figure 99-2. Magnetic resonance imaging showing the follow-up of the same JNA patient with no recurrence at 3 years.

be accurate in the diagnosis of JNA.[4] However, final proof of diagnosis is histologic.

Staging

In 1984 Chandler and colleagues[5] proposed a staging system (Table 99-2) on the basis of clinical and CT assessment. This staging system is logical and easy to understand and it is useful for reporting. Due to the large anatomic region of stage 3, Sessions and Radkowshi have suggested refining stage 3. However, none of the systems has been used extensively for comparing outcomes because published case series have usually been of small numbers.

Chandler's Staging of JNA

Stage 1 Tumor confined to nasopharynx

Stage 2 Tumor extends into nasal cavity or sphenoid

Table 99-2

The 2002 UICC TNM Staging of Nasopharyngeal Carcinoma

T Classification	
Tx	Primary tumor unable to be assessed
T0	No evidence of tumor
T1	Confined to nasopharynx
T2a	Extends to nasal cavity, oropharynx
T2b	Tumor extends to parapharyngeal space
T3	Tumor involves sinuses, orbit, skull base, hypopharynx
T4	Intracranial or infratemporal involvement
N Classification	
N0	No nodal involvement
N1	Ipsilateral lymph nodes < 6 cm
N2	Bilateral lymph nodes < 6 cm
N3	Lymph node > 6 cm; supraclavicular node
M Classification	
M0	No distant metastasis
M1	Distant metastasis (includes mediastinal nodes)
Stage Classification	
Stage I	T1N0M0
Stage II	T1N1M0, T2N0M0, T2N1M0
Stage III	T3N0-2M0, T1-2N2M0
Stage IVa	T4, any NM0
Stage IVb	any TN3M0
Stage IVc	any T, any N, M1

TNM, tumor node metastasis; UICC, Union Internationale Contre Cancre.

Stage 3 Tumor involves the maxillary, ethmoids, infratemporal fossa, orbit, cheek, and cavernous sinus

Stage 4 Tumor is intracranial

Management

The primary treatment is surgical extirpation. Due to the infrequency of the disease, most of the experience for managing this disease is limited to case series based on institutional practice gleaned over a period of time. For the patient diagnosed with histologically proven JNA, the initial relevance would be to assess for fitness for surgery. Although this is usually not an issue with young adult males, intracranial lesions can be associated with long surgeries and comorbidities. With intracranial masses, a team of skull base surgeons (head and neck and neurosurgeon) would be necessary for joint management.

Although the traditional method of surgery has been the open approach, recent interest surrounds the use of the exclusively endoscopic techniques for removal of such vascular tumors. The open approach, however, remains an important method for tumors that may not be fully accessible endoscopically. For small lesions, an intraoral transpalatal approach allows for access to the nasopharynx. This approach will likely be replaced by the endoscopic route. The more commonly employed medial maxillectomy approach can be done via a lateral rhinotomy or preferably a midfacial degloving incision, which affords reasonably good access to the NP and eliminates facial scars.

For extension outside the NP into the paranasal sinuses, a Le Fort type 1 osteotomy will allow an inferior approach to the maxillary and ethmoid sinuses as well as the pterygopalatine canal. For lesions involving the infratemporal fossa or large lesions involving the majority of the sinuses, a facial translocation approach affords a large window of access. The facial translocation involves the rotation of the facial cheek flap as a single osteoplastic unit with the underlying maxilla rotated

laterally after osteotomies to the maxillary nasal, orbital maxillary, and zygomatic arches. The senior author has also incorporated the entire nose and cheek as a single rotation based laterally. This allows for excellent access to the infratemporal fossa and hemostatic options in the event of bleeding. A lateral infratemporal fossa approach has been recently used as reported by Tyagi and colleagues.[6]

Endoscopic sinus surgery techniques have advanced significantly over the past 2 decades and have allowed the intranasal access and nasal anatomy to be approached in an extremely competent fashion. Several authors have published their experience of successful endoscopic resection of such tumors. Several reports of endoscopic resection have reasonable follow-up durations (13 patients in 23 months) and low recurrence rates (8%).[7] Combination approaches of type 3 JNA with open and endoscopic approaches have also reported good success but of shorter-term results.[8] For larger lesions such as stage 3A disease, Hofmann and colleagues have reported successful endoscopic resection with long-term results (52 months) in a series of 21 patients and have reported that extension to the medial aspect of infratemporal fossa and retromaxillary space was not a contraindication to an endonasal endoscopic approach.

Preoperative embolization of the tumor mass is used by some to reduce intraoperative bleeding. However, the risk of recurrence has been highlighted with the use of preoperative embolization.[9] In extensive tumors where the feeding vessels come from the internal carotid system, a laser-assisted extracranial-intracranial bypass has been used before the definite surgery in order to prevent neurologic deficits.[10]

Recurrence rates have been reported to be as high as 35% depending on the length of follow-up. For patients with recurrent disease, the options remain for observation alone, revision surgery, or radiation. Radiation has been used for treatment of JNA, especially those that recur after surgery and those with intracranial extension where clearance of margins may be difficult. Cummings and colleagues[11] reported a series of 56 patients treated with 3000 cGY. However, issues of impact on growth centers, cataract formation, and osteoradionecrosis have been reported, as have cases of malignant transformation.[12] For these various reasons, observation, sometimes followed by involution with aging or repeat surgery, is an option in the presence of recurrence. In patients who cannot undergo surgery, recalcitrant cases of tumor recurrence despite several repeat resections and inaccessible recurrences may be considered for radiation therapy with full disclosure of possible long-term, late effects (e.g., radiation-induced malignancy, carotid artery damage). Park[13] recently reported using the gamma knife with good success for a case of recurrent intraorbital JNA.

Chordoma

Chordoma is a locally aggressive malignancy that may arise from bone of the basisphenoid and erode through the bony skull base to appear through the sphenoid and into the nasopharynx. These tumors arise from notochord remnants and can present with cranial nerve deficits including hoarseness, swallowing difficulties, or diplopia. They may also present in asymptomatic patients when identified incidentally by CT or MRI of the head and neck. The definitive diagnosis of these tumors may be accomplished by transnasal endoscopic biopsy, but it is also frequently made at the time of surgery, which will require a team effort including a neurosurgeon and skull base surgeon. An anterior midline subfrontal approach, or more recently an expanded endonasal approach, may be employed for exposure. Cranial nerve deficits and even long tract deficits may ensue after surgery due to the need to work around the brainstem and vertebrobasilar system of vessels on the dorsal extent of these tumors. The use of postoperative radiotherapy is necessary in patients who do not have complete removal of these lesions due to the complicated anatomy and risk of neurologic or vascular trauma. Proton beam therapy is recommended.

Adenoid Cystic Carcinoma of the Nasopharynx

Adenocystic carcinoma of the sinonasal tract constitutes 20% of all adenoid cystic carcinomas of the head and neck. They, along with other tumors of salivary gland origin, arise from the minor salivary glands in this region. Those of the NP are not common but can be insidious and slow growing.[14] The lesion can extend from the nasopharynx into the anterior skull base and can present as bilateral nasal lesions. In the latter, there is a need to differentiate this from simple bilateral nasal polyps. Patients with either condition may present with simple nasal obstruction with hyposmia. Other accompanying symptoms do not usually occur, unless palpable neck metastasis is detectable at presentation. Otitis media with effusion may exist if the eustachian tube is involved. These tumors have the propensity for perineural spread and thus MR imaging is important in the pretreatment evaluation. The primary treatment of such lesions is surgical resection. However, proximity of the nasopharynx to the sphenoid, and, hence, the internal carotid arteries and intracranial structures, plus their propensity for centrifugal spread along nerves, may preclude complete removal. Postoperative radiotherapy is important in local control of such lesions.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is unique in its epidemiologic pattern. It is common in certain ethnic groups, with the highest incidence in southern China, Hong Kong, and southeast Asia. The majority of patients with NPC are diagnosed with advanced disease. However, over the past 20 years, the survivals of these patients have improved.[15] This has been attributed to the combined use of chemotherapy and radiation to treat the patients with advanced disease.[16] Furthermore, with the advent of improved techniques in radiation, the side effects, which plagued long-term survivors in the past, may be reduced.[17,18] The strategy in the management of NPC is to find novel methods of early detection and develop improved techniques of effective primary treatment with the focus on reducing morbidity from the treatment. In this chapter we describe the epidemiology, etiology, pathology, clinical features, staging, treatment, and prognosis of NPC.

Epidemiology

The highest incidence of NPC is recorded in Guangzhou, China, where the age-adjusted incidence rate is reported to be more than 30 per 100,000.[19] Hong Kong has a rate of 20.2 per 100,000 in males and 7.8 per 100,000 in females.[15] Patients who are affected by NPC are ethnic Chinese with an ancestry from the southern part of China. In southern China the two main ethnic subgroups are the Cantonese and the Fujians. In Hong Kong the vast majority of the population is Cantonese. In Singapore the overall incidence in males from 1998 to 2002 was 10.8 per 100,000.[20] This lower rate may be in part accounted for by the demographics of Singapore, which unlike China, Hong Kong, and Taiwan, has a more heterogeneous population. The population in Singapore is approximately 70% Chinese, with the remaining major ethnic groups being Malays and Indians. The majority of the NPC patients in Singapore are Chinese (Fujians and Cantonese).[21] The incidence of NPC in Singaporean male Chinese is 12.5 per 100,000. These incidence rates in southern China, Hong Kong, and southeast Asia are among the highest in the world and have remained stable for many years. However, in the most recent review of the latest trend in the incidence of NPC, both Singapore and Hong Kong have reported a significant decrease for the first time after many years of stable rates.[15] Why there was a fall in incidence is unclear, but one theory advanced to account for this is the change in dietary habits.[22,23] Other ethnic groups, with rates that are reported to be intermediate to high, include the Eskimos,[24,25] Polynesians, and indigenous Mediterranean population.[26] NPC is not common in whites. In North America the highest incidences are seen in the ethnic Chinese who are first-generation immigrants.[23] Subsequent-generation immigrants have a lower incidence, although it is still higher than the other ethnic groups. Overall, these incidence rates are lower than those in southern China and southeast Asia. This pattern of decreasing incidence rates seen in emigrant Chinese is a well-known phenomenon. It is likely that with migration, there is over time a greater variation in the gene pool arising from factors such as intermarriage, although the adoption of different dietary habits cannot be discounted. The epidemiologic pattern indicates that NPC occurs commonly in Chinese. This will suggest the possibility of a genetic link or a shared habit such as dietary intake.

Etiology

Three main factors are believed to be associated with the development of NPC.[27] These are genetic and environmental factors, as well as EBV. The knowledge relating to these factors that are associated with NPC has been advanced over the past 20 years. However, we are still unable to assimilate the information in an orderly fashion to translate the knowledge into prevention, early detection, or markedly improved survivals. Nevertheless, the current school of thought among those involved in NPC research believes that this cancer is probably a result of interaction among the three main factors.

Genetic Factors and Nasopharyngeal Carcinoma

A large body of evidence indicates that genetic factors play a significant role in NPC. Family clusters with NPC are not uncommon. Ung and colleagues[28] had reported that the risk of NPC in a first-degree family member could be as high as eight times. Reports from Hong Kong and Guangzhou have also estimated this risk to be as high as 20 times when compared with the general population. We had reported that 15.5% of all NPC patients have had a first-degree relative with NPC.[29] The majority of first-degree family members who are affected are usually siblings (70%) rather than parents and children (30%).[29] The mean duration between two siblings who are affected within a family is 5.3 years, whereas that between a parent and child is 25 years.[29] Experts also believe that the risk for a first-degree relative also developing NPC is higher if the index NPC patient is diagnosed at age younger than 40 years.[30] The presence of such family clusters may indeed be due to common genetic factors, but it can also be argued that shared environmental factors may play a role.

The association of HLA alleles with NPC was established in 1975.[31] These alleles are the HLA class I alleles belonging to the HLA A, B, and D groups in chromosome 6. HLA A2, Bw46, B 17, Bw58, DR3, and DR9 have been consistently found to be significantly more prevalent in NPC patients in contrast to the general population.[31-35] These haplotypes are associated with increased risks for NPC. Further refinements in establishing these haplotypes have been reported with the highest risks established consistently for patients with the haplotypes A2 and B46.[34,36] It has also been found that multiple alleles confer protective effects. The evidence suggests it is likely that the tumor susceptibility gene has a recessive mode of inheritance because an NPC-linked gene with a dominant mode will not be associated with such wide allelic variations in protective effects.[37] It has also been established that most Chinese patients with NPC have the HLA-A0207 haplotype in contrast to the HLA-A0201 found in whites.[38] Microsatellite instability in the nearby region of the HLA loci has been described, suggesting the possibility of tumor susceptibility factors.[39] NPC patients may have alleles in these loci that may contain genes that contribute to the oncogenesis of normal nasopharynx cells. However, linkage analysis has shown that the tumor susceptibility gene is not likely to be at the position of the high-risk A2 B46 haplotypes.

Chromosome changes that have been described include deletions in chromosomes 3, 9, and 11.[40-43] The significance of these chromosomal changes is the implied loss of function of known specific factors: for example, chromosome 9p21 region codes for known cell cycle regulators such as p15 and p16. The protein p16 has been reported to be inactivated in NPC patients.[44,45] Other chromosomal changes have been sporadically reported. Each of these genetic deletions has also been associated with an implied tumor suppressor gene. Novel markers have also been reported to suggest the possibility of other tumor suppressor gene candidates.[46] Despite this wealth of information, it is difficult to determine if these changes are downstream events rather than early changes. What will be helpful will be genome-wide scans of NPC tumor samples and normal tissues, as well as using techniques such as comparative genomic hybridization to narrow in on the true early changes.

Environmental Factors and Nasopharyngeal Carcinoma

The most common environmental factor associated with NPC is diet. It has been suggested that certain diets high in preservatives are associated with NPC. These include salted fish, eggs, and vegetables.[47-51] The origin of these associations is traced to the epidemiologic studies performed on a group of high-incidence NPC patients, the "boat people" of Hong Kong. These people had originated from a common region in China many years ago and had settled into a life based largely on living in boats. The diets are necessarily based on preserving the food from the sea (e.g., salted fish). Subsequently large epidemiologic studies have suggested similar findings, too.[52] It is believed that the risk is associated with early exposure or during weaning period.[50,53] The carcinogen believed to be the inciting factor is nitrosamines. Other environmental causes that have been thought to be associated include chemical fumes and wood dust.[54] Smoking is not an associated factor unlike squamous cell carcinoma of the aerodigestive tract. However, it is always difficult to attribute food alone as the factor that leads to oncogenesis because many confounding factors are also often present.

Epstein-Barr Virus and Nasopharyngeal Carcinoma

EBV is a ubiquitous virus. The vast majority of the population in the world have been infected with EBV. It is a herpes virus, with a central core of DNA and an envelope known as the *capsid.* Infection with the virus occurs in early childhood or as young adolescents. Those infected in early childhood tend to be asymptomatic, whereas young adolescents will be symptomatic, often resulting in a clinical syndrome that is consistent with infectious mononucleosis. Once a person is infected with EBV, he or she develops immunity. However, EBV is present for the remaining life of the person within specific circulating B lymphocytes or shed through saliva. The latter route is believed to account for the horizontal transmission typical of this infection.

The IgM and IgG class of antibodies to antigens on the EBV are raised in acute and convalescent phases of infection. The antigens on the EBV are either the nuclear core early antigen (Ea) or the viral capsid antigen (VCA). Hence in the majority of any population, the IgG VCA and Ea will be raised. In NPC, however, the IgA VCA and Ea are raised.[55] This is used as a marker, with laboratories using immunofluorescence to detect these antibodies. The sensitivity and specificity of these two antibodies are high.

EBV antigens are also found on NPC cells. EBV expresses both lytic and nuclear antigens. Lytic antigens include latent membrane proteins 1, 2, and 3 (LMP-1, -2, -3). Nuclear antigens include the Epstein-Barr nuclear antigens 1 to 6 (EBNA-1 to 6). In NPC, EBNA-1 is always expressed, whereas LMP-1 is consistently expressed in significant levels. Both of these are latent proteins. EBNA-1 is believed to be responsible for maintaining the viral episomes in the tumor cells. LMP-1 has been shown to induce cellular growth by inducing epithelial hyperplasia and altered keratin gene expression.[56,57] It reduces cytokeratin expression and inhibits squamous cell differentiation. It has been shown to up-regulate epidermal growth factor receptors. NPC also expresses Epstein-Barr encoded ribonucleic acids (EBERs) within the cytoplasm. These EBV antigens and EBERs are not present in normal nasopharynx cells.

The vast majority of the people infected with EBV do not develop NPC. In addition, the expression of latent proteins EBNA-1 and LMP-1 are not seen in normal nasopharynx cells. Therefore it is believed that EBV is not the initiating event in NPC and that its role in the development of NPC is a result of latent infection of the genetically susceptible and environmentally transformed epithelial cells of the nasopharynx.

Clinical Presentation

Virtually all NPC patients are symptomatic at the time of diagnosis. Less than 1% of NPC patients are asymptomatic and diagnosed incidentally. This may occur because of imaging performed for some other indications or an abnormal EBV serology is detected because of health screening. Three quarters of NPC patients are males. More than 80% are diagnosed between 30 and 60 years of age with more than 50% diagnosed between 30 and 50 years. The proportion of NPC patients diagnosed at a relatively young age has a significant socioeconomic impact on these patients and their families. Approximately 15% to 20% of NPC patients will also report a first-degree relative who was similarly affected.[29]

The most common presentation in NPC is the presence of a neck lump (Fig. 99-3). About 60% of our patients presented with a neck lump. These neck lumps are due to metastatic disease in the cervical

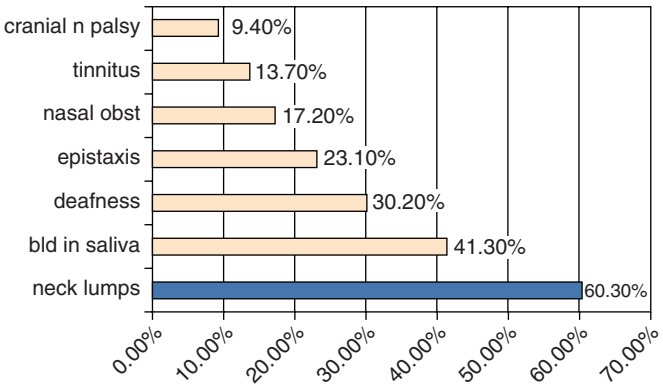

Figure 99-3. Clinical presentation of nasopharyngeal carcinoma patients.

Figure 99-4. Bulky bilateral cervical lymph nodes in levels II, III, IV, and V.

lymph nodes. It is not uncommon for the enlarged nodes to be matted. The nodal metastasis is usually located in the superior aspect of the neck (Fig. 99-4), corresponding to high level V and level II. The first echelon of nodal metastasis is in the retropharyngeal nodes. These retropharyngeal nodes may be so bulky that they can be visualized on physical examination as nodular swellings in the posterior pharyngeal wall. Occasionally NPC patients may present with enlarged level III nodes (Fig. 99-5) and less commonly level IV. Enlarged submental lymph nodes at the time of diagnosis are rare and not encountered in our series. Some patients may present with a parotid swelling due to metastatic parotid lymph nodes, although these are also uncommon. Metastatic NPC nodes are usually firm. If left for a significant duration of time, a node may enlarge to such an extent that central necrosis occurs, followed by abscess formation. In endemic regions such as China, Hong Kong, and Singapore, a Chinese adult male presenting with large bulky bilateral nodes is usually either NPC or lymphoma. Although 60% of NPC patients present with a neck lump due to nodal metastasis, at least 80% of NPC will be classified as N1. This is because even in the NPC patients without palpable nodes, imaging will show metastatic nodes in at least another 20%.

The next most common presenting symptom or sign is that of blood-stained saliva or sputum (41.3%). The patient usually reports a persistent production of blood in the saliva without any other symptom. Epistaxis is not common in NPC because the tumor is located in the postnasal space. The natural tendency is for blood from the tumor to gravitate and hence mix with saliva or sputum. Indeed, epistaxis was reported in only 23.1% of our patients. Frank epistaxis, however, is not typical of NPC. Deafness was more commonly reported (30.2%). This is due to otitis media with effusion, which is believed to be secondary to eustachian tube dysfunction. The hearing loss is therefore conductive in nature and impedance tympanometry corresponds to the type b pattern. Other presenting complaints include nasal obstruction and

Figure 99-5. Right level III nodes in nasopharyngeal carcinoma.

unilateral tinnitus. Persistent headaches are also common in patients with intracranial extension or clival erosion. Cranial nerve palsies are encountered in about 10% of the patients. The most common nerves affected in descending order of frequency are the sixth, fifth, twelfth, and ninth/tenth nerves. In the endemic regions, isolated sixth nerve palsy, caused by cephalad extension through the foramen lacerum, is an indication to have the nasopharynx examined and the skull base imaged for possible NPC. Some of these patients with cranial nerve palsies at the time of diagnosis may show resolution following treatment with radiation. The most likely explanation for this is that the tumor had caused surrounding edema near the cranial nerves, resulting in deficits such as diplopia. Also, some syndromes are associated with NPC. Patients with dermatomyositis are at high risk for developing this cancer and should be screened regularly because approximately 10% of these patients can be at risk for developing the cancer.

Examination of the nasopharynx in NPC patients usually reveals an exophytic mass that may occupy the whole postnasal space (Fig. 99-6). This may be ulcerated and contact bleeding is usually encountered. However, in about 10% of NPC patients the lesion is submucosal. In these cases the mucosal surface of the nasopharynx is normal in appearance. Occasionally, only a slight irregular mucosa is detected. This may consist of a small area of heaped-up mucosa or just an erythematous change, both of which could be passed off as normal. The significance of submucosal NPC in a patient is unclear, although a review of our patients suggested that this group might have more aggressive disease.

In the endemic regions the axioms are that a Chinese adult male presenting with a neck lump needs to be investigated for NPC and that a Chinese adult male presenting with a neck lump, blood-stained sputum, and unilateral deafness has NPC until proven otherwise.

Diagnosis of Nasopharyngeal Carcinoma

The gold standard in the diagnosis of NPC is histologic confirmation by nasopharynx biopsy. This is performed transnasally under local anesthesia using rigid endoscopy. The biopsy of the tumor is thereby performed under direct visualization. In rare instances patients suspected of NPC will have the biopsy performed under general anesthesia. An example of such a situation is when the fine-needle aspirate cytology of a metastatic node confirms undifferentiated carcinoma but the nasopharyngeal biopsies remain negative for malignancy. In these patients a deep nasopharynx biopsy under general anesthesia including Rosenmüller's fossa and the vault of the nasopharynx is indicated. A nasopharyngeal biopsy may also be performed under general anesthesia if previous biopsies in a patient highly suspected of having NPC were negative and a diagnosis is imperative before treatment is instituted.

The classification of NPC[58,59] is shown in Table 99-3. The vast majority of patients with NPC—at least 90%—in the endemic region

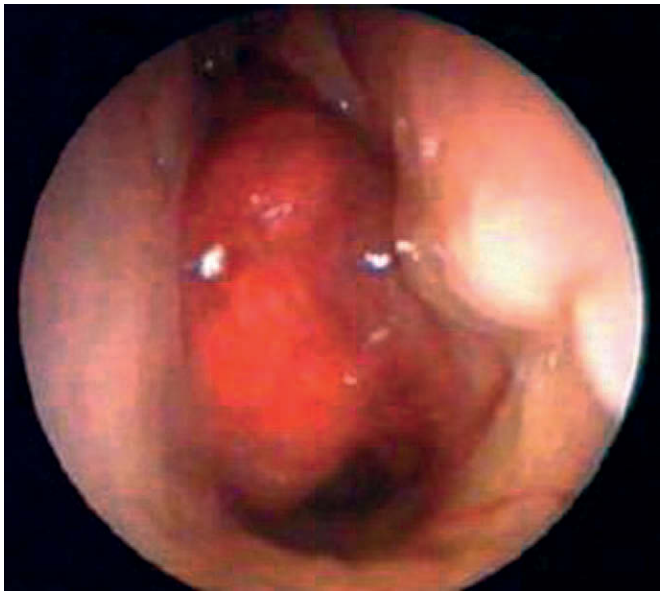

Figure 99-6. Nasopharyngeal mass occupying the whole of the post-nasal space.

Table 99-3

World Health Organization (WHO) Classification of Nasopharyngeal Carcinoma

Type 1 (I)	Squamous cell carcinoma
Type 2a (II)	Keratinizing undifferentiated carcinoma
Type 2b (III)	Nonkeratinizing undifferentiated carcinoma

Types 1, 2a, and 2b correspond to WHO types I, II, and III, respectively, and are used interchangeably.

have a histologic pattern termed as *nonkeratinizing undifferentiated carcinoma (type 2b or type III).* Squamous cell carcinoma is uncommon in endemic regions.

Staging of Nasopharyngeal Carcinoma

The TNM staging system is shown in Table 99-2. This staging system is based on clinical and radiologic examination. In general, two thirds of NPC patients are classified as stage III or IV at the time of diagnosis. Only about 10% of newly diagnosed NPC patients have stage I disease.

Computed Tomography Scan/Magnetic Resonance Imaging

CT scan had been for many years the essential staging investigation for assessing the primary tumor, as well as regional disease. The soft tissue of the nasopharynx is shown well and CT is particularly useful in delineating clival and skull base erosion.[60] It has been the cornerstone of radiologic staging of NPC for many years. However, MRI has been used increasingly in many centers. This is because of the superior definition afforded by MRI in detecting soft tissue changes and intracranial involvement. It is not uncommon for MRI to show features consistent with disease that is not shown on a CT scan.[61]

Other Staging Investigations

These include chest radiograph, ultrasound of liver, and bone scans. Alternatively, CT scans of the lungs and liver may be performed. The main purpose is to locate distant metastasis. Of these the highest pick-up rate appears to be the bone scan. This is consistent with the skeleton being the most common distant site of metastasis in NPC. In the past 5 years, PET scans have come into more prominent use. Much of the information in the literature on the use of PET CT in NPC is with regard to detecting local and regional recurrences or residual disease, as well as in the detection of distant metastasis.[62] It is a useful imaging tool for patients with indeterminate CT or MRI abnormalities that may represent local, regional, or distant recurrences. Enhancement will suggest a higher possibility of recurrences in such indeterminate imaging abnormalities. However, caution has to be advised in the interpretation of current data on PET CT, especially as a tool for staging newly diagnosed NPC patients. The main criticisms of these reports have been the lack of a standardized methodology to determine the histopathology of the tissues that have high uptake of agents like 18-fluoro-2-deoxyglucose (FDG). Oftentimes these reports will include any form of enhancement on PET CT to represent metastasis without confirmation of the pathology. Inflammatory reactions and radiation necrosis, without malignancy, can lead to high uptake.[63] Literature on the efficacy and cost-effectiveness of using PET CT as a staging tool in newly diagnosed NPC patients to assess the primary tumor and regional metastasis is scant.

Other Investigations

An audiogram and tympanogram are performed to obtain a baseline level. This is crucial as the patient undergoes radiation that might worsen the hearing. Indeed, with increasing use of combined chemotherapy and radiation, certain chemotherapy agents like cisplatin might give rise to idiosyncratic sensorineural hearing loss.

EBV serology titers are performed. These include IgA VCA (viral capsid antigen) and IgA Ea. The former is highly sensitive and the latter specific. The main usefulness of this test is in assisting diagnosis of new NPC patients. In particular, a negative IgA Ea likely will indicate that the patient has no NPC. It has to be emphasized that the diagnosis of NPC is histologic proof on biopsy of the nasopharynx, therefore, these titers are not a substitute for diagnosis.

Treatment of Nasopharyngeal Carcinoma

Pretreatment Planning

The treatment of a newly diagnosed NPC patient is best served by a multidisciplinary team of head and neck surgeon, radiation oncologist, medical oncologist, pathologist, and radiologist. This includes audiological investigations and dental clearance. In addition, if chemotherapy is part of the treatment, hematologic and biochemical investigations are performed including creatinine clearance. Dental clearance involves ensuring that oral hygiene is maintained because the oral cavity will inevitably be in the radiation field. The decaying, unhealthy tooth is extracted to prevent osteomyelitis from setting in during the postradiation period. However, there is no evidence that prophylactic extraction will reduce osteoradionecrosis in patients undergoing radiation of the head and neck.[64,65] Allowing such prophylactic extractions will potentially delay treatment and increase costs for the patient.

Treatment

NPC is treated by radiation. In general, patients with stage I and II NPC are treated by radiation only, whereas stage III and stage IV patients are treated by concurrent chemotherapy and radiation. In addition, there is evidence that patients diagnosed with stage IV NPC with locally advanced disease may be better controlled by neoadjuvant cisplatin followed by chemoradiation.[66] Radiation is administered by linear accelerator, and the dose reaches 60 to 70 Gy in the nasopharynx and both necks. This is given daily at up to 2 Gy in 35 to 40 fractions. The main side effects include mucositis and xerostomia. The former may take up to 3 months after the last day of treatment to heal. Xerostomia affects every patient and can be permanent, although the younger patients show much better improvement with time. Other side effects include sinusitis, crusting, and blood-stained nasal discharge. Otitis media with effusion can develop or be worsened with radiation. Sensorineural hearing loss has been attributed to radiation, although the cochlea is resistant and it has been shown that this may be due to other causes such as infiltration by tumor cells.[67] Trismus is particularly more

severe in those treated for skull base involvement. It may take several years for trismus to develop. Late side effects include cranial nerve palsies, which may give rise to difficulties in distinguishing trismus from recurrent disease. The most common cranial nerve to be affected post-radiation, other than the cochlear-vestibular nerve, is the hypoglossal nerve. In the past 5 to 10 years, data have emerged to confirm the efficacy of using intensity-modulated radiation therapy (IMRT) to treat NPC patients. This has resulted in control rates similar to conventional radiation.[68] It has also resulted in better treatment outcomes, especially xerostomia[17] and skin burns.

The use of concurrent chemotherapy and radiation to effectively treat local and regionally advanced NPC patients was reported by Al-Sarraf.[69] There is compelling evidence for using concurrent chemotherapy and radiation in advanced stage NPC.[70] The concurrent chemotherapy regimen includes cisplatin and 5-fluorouracil (5-FU). We had found this to give good local and regional control, but it increases both acute and late toxicities. Two of the significant toxicities associated with cisplatin are idiosyncratic sensorineural hearing loss and peripheral neuropathy. To avoid these toxicities, other agents such as Taxol combined with 5-FU and hydroxyurea are alternatives that can be considered.[71]

Surgery is reserved for recurrent local and regional disease. Although recurrent local disease may be treated by brachytherapy, localized recurrent tumor may be considered for resection. The three contraindicating factors are internal carotid artery involvement, skull base erosion, and intracranial involvement. The surgical approaches use either one or a combination of transnasal, transmaxillary, midfacial degloving, or transpalatal approach. Regional disease in general is dealt with by neck dissection. This will usually take the form of a radical neck dissection or a modified neck dissection. Usually the spinal accessory nerve and the sternocleidomastoid muscle are not spared and the internal jugular vein is not commonly preserved. If brachytherapy is considered, a pectoralis major myocutaneous flap is harvested to reduce the likelihood of cutaneous necrosis and to protect the carotid artery. A second course of radiation to treat regional recurrences may be considered, albeit with its attendant risks.

Surgical Treatment of Nasopharyngeal Carcinoma

The indications for surgical treatment of NPC are currently for local and regional recurrences.

Surgical Treatment of Local Recurrences

Approximately 5% to 10% of all newly diagnosed NPC patients will develop local recurrences. Up to 50% of these patients will be amenable to salvage by surgery. The remaining 50% are usually too far advanced for surgical intervention. This may be due to intracranial invasion or carotid artery encasement. In some patients this may be due to concomitant distant metastasis. The surgical treatment of locally recurrent or residual NPC is nasopharyngectomy. In those who can be salvaged surgically, the recurrent T (rT) classification is often rT1 to rT3.[72] The success of surgical intervention in recurrent NPC is strongly correlated with T classification. The best results are obtained with rT1 patients. Patients with rT3 recurrences are considered by some to be not salvageable. In particular if there is clival erosion, some surgeons consider this to be a situation in which complete tumor extirpation is not possible. Hence careful and diligent follow-up coupled with biopsies of any suspicious areas of the nasopharynx are crucial factors that allow for early detection of recurrences or residual tumor.

The local recurrences may be dealt with by either another course of radiation or by surgery. Treatment by a second dose of radiation will carry with it the risk of complications such as transverse myelitis, leading to weakness and numbness of the limbs. The risks of temporal lobe necrosis, severe trismus, severe sensorineural hearing loss, choanal stenosis, palatal dysfunction, and lower cranial nerve palsies are increased by a second course of radiation. These effects may be reduced by the use of IMRT. Radiation is generally reserved for patients with a large recurrence such as when there is skull base erosion or intracranial extension or when tumor tissue surrounds the carotid arteries.

All patients with local recurrences are assessed with a CT scan or MRI. The thorax, liver, and bones are also assessed for possible metastasis. In the past 3 years, the use of PET scan has been found to be a useful tool for staging recurrent patients. The depth of invasion of the local recurrences can be assessed by a PET CT and allows us to plan our resection approaches.

Figure 99-7. Magnetic resonance imaging showing a small recurrence on the left side of the nasopharynx.

When faced with a local recurrence that can be salvaged, the head and neck surgeon will have to decide the surgical approach. The factors that govern the chosen approach and access to tumor resection are usually the surgeon's preference and expertise, as well as the extent of the tumor recurrence. Many surgical approaches have been reported. This is a testament to the difficult access to the nasopharynx. The anterior-posterior distance from the nasal vestibule to the nasopharynx is about 10 cm, and open approaches mean that the surgeon is operating through a narrow and deep window. In addition, the internal carotid artery lies just posterior and lateral to the eustachian tube cushion. These considerations, as well as possible intracranial extension and operating in a previously radiated or chemoradiated field, are the main issues in nasopharyngectomy. All the approaches give adequate visualization.

Endoscopic Approach

This approach is clearly possible for small recurrences.[73] It is best limited to recurrences that are centrally placed on the posterior wall of the nasopharynx (Fig. 99-7). Recurrences that extend out to the pterygopalatine fossa, the soft palate, and beyond may be too large for endoscopic nasopharyngectomy, although experienced endoscopic skull base surgeons may not necessarily consider this an absolute contraindication. The success of this approach lies in being able to choose the patients well. Besides proper instruments, the key to being able to have excellent visualization and control of the surgical approach lies in resection of the posterior nasal septum. Depending on the site and size of the recurrences, the medial maxillary wall may have to be resected. It is also important to remember to resect adequately the roof of the nasopharynx and drilling down the vomer. The depth of resection should include at least the prevertebral muscles. Once the resection and frozen sections are completed, the wound in the resected nasopharynx is packed with antiseptic gauze and left for at least 1 week.

Lateral Rhinotomy and Medial Maxillectomy Approach

This approach can be used for tumors slightly larger than those indicated for endoscopic approach. It may be used for recurrent or residual tumors limited to the nasopharynx or with extension out to the pterygopalatine fossa. It may also be combined with a transoral approach to resect tumors with oropharyngeal extension. Alternatively it may be extended for tumors that invade the orbit. After completion of the lateral rhinotomy, the medial wall of the maxilla is removed as far out laterally as possible while preserving the infraorbital nerve. The naso-

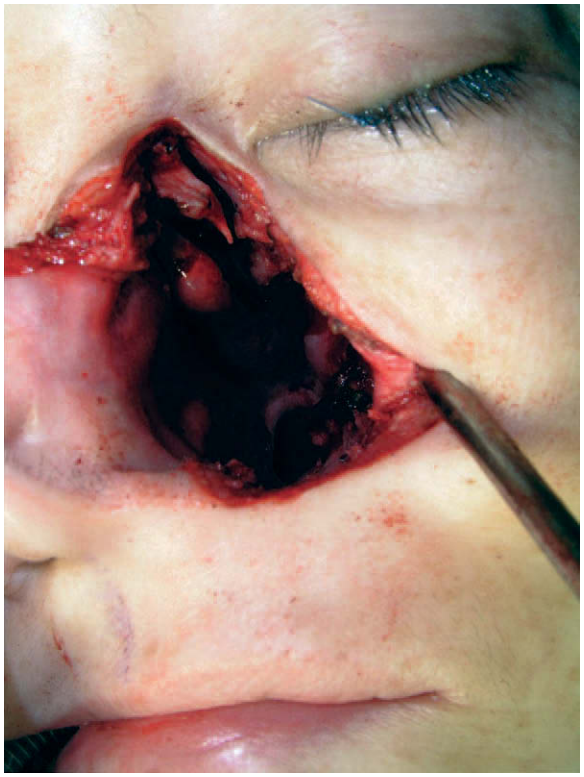

Figure 99-8. Lateral rhinotomy approach with resection of medial maxilla and posterior nasal septum completed, exposing the whole nasopharynx.

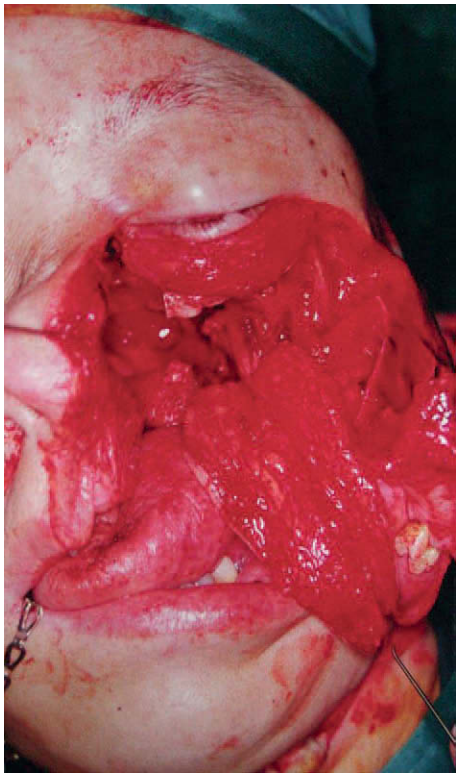

Figure 99-9. Left maxillary swing approach. The skin, subcutaneous tissue, left maxilla, and hard palate are rotated laterally en bloc to expose the nasopharynx.

lacrimal duct is marsupialized. Resecting the inferior half of the middle turbinate will also help with surgical access. The key to visualizing the entire nasopharynx well is in resecting the posterior nasal septum (Fig. 99-8). The surgical access is adequate but not as wide as the view afforded by the maxillary swing approach. It does not require any palatal split. The wound almost always heals well and cosmetically it is not an issue with the patient. Trismus is uncommon and palatal fistula does not exist. However, postoperatively these patients often complain of headaches, which usually take about a month to settle. The problem is the prolonged period of nasal clearance required to rid the crusts that develop. Exposed bone may lead to localized osteoradionecrosis.

Maxillary Swing

This is an elegant operation described by Wei in 1991.[74] It provides a wide access for resecting nasopharyngeal tumors. The procedure involves a Weber-Ferguson incision. The maxilla is exposed, and osteotomies are made such that the maxilla will be rotated laterally but the skin and subcutaneous tissues continue to provide the blood supply to the maxilla because it is not dissected off the anterior wall of the bone (Fig. 99-9). The medial maxillary wall is removed. This is an approach that provides excellent access to remove tumors that have infiltrated the pterygopalatine space. It is also argued that the internal carotid artery may be controlled should there be tumor extension laterally. It does, however, require a palatal split and this can lead to palatal fistulas.

Other Surgical Approaches

Lateral infratemporal and Le Fort 1 drop-down approaches have been described. These are not common approaches used to perform nasopharyngectomy for recurrent NPC and are used by surgeons familiar and comfortable with the respective surgical approaches.

Surgical Treatment of Regional Recurrences

Regional recurrences or residual regional disease occur in about 10% of patients. These patients commonly also have local disease or distant metastasis. Which factors are associated with regional recurrences is unclear. It is also difficult to detect regional recurrences because it may be difficult to elicit signs on palpation of the fibrotic neck after radiation. In fact, it is not uncommon to be able to palpate an obvious mass in the neck and yet the fine-needle aspirate cytology to be negative. A CT scan or MRI of the neck is useful. Once regional recurrence is detected, metastatic workup should be performed and the primary site should be cleared before setting off on a treatment plan for the patient.

The treatment of regional recurrence and residual regional disease is by neck dissection (Fig. 99-10). The evidence clearly indicates that a radical neck dissection should be performed.[75] This is because regional disease is often along the chain of nodes of the upper internal jugular vein, as well as the accessory nerve. Furthermore, the metastatic node, unlike similar nodes in squamous cell carcinoma of the head and neck, tends to have a propensity for extracapsular spread. Hence the internal jugular vein, accessory nerve, and sternocleidomastoid muscle should be sacrificed. In fact, it is not uncommon to perform an extended radical neck dissection involving resection of the skin. Levels I to V nodes are removed. Although retropharyngeal nodes are said to be the first echelon of nodes in NPC, these do not need to be removed because oftentimes the radiation will have encompassed the retropharyngeal nodes. The main problems with performing a radical neck dissection for recurrent NPC are related to bleeding and wound infection, because a good proportion of these patients will have had radiation with or without chemotherapy. The risk of carotid blowout is higher if the wound breaks down and the carotids are exposed. This may be prevented by the use of a pedicled flap such as the pectoralis major (see Fig. 99-10) or latissimus dorsi flap. The effectiveness of the treatment is good, with overall survival after radical neck dissection reaching above 50%.[76] Regional control is often achieved and further recurrences are often at distant sites.

Prognosis

The poor prognostic factor in NPC is stage IV disease. In particular, N3 disease is associated with poorer survival and higher rates of distant metastasis. Patients with stage III or IV disease who have had concur-

Figure 99-10. Left radical neck dissection and left myocutaneous pedicled pectoralis major flap to cover skin defect, as well as protect the carotid artery.

rent chemoradiation have a 5-year overall survival rate of about 70%.[77] Stage I and II NPC patients treated by radiation alone have 5-year overall survival rates of 80% and higher. The use of chemoradiation for stage III and IV patients has seen improvements in local and regional control, but distant metastasis remains the main failure leading to death in NPC patients.[78]

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CHAPTER ONE HUNDRED

Malignant Neoplasms of the Oropharynx

Uli Harréus

Key Points

- About 10% to 12% of all head and neck malignancies are oropharyngeal tumors, more than 90% of which are histopathologically squamous cell carcinoma (SCC).
- On the basis of different diagnostic, therapeutic, and outcome characteristics, the oropharynx should be subdivided into soft palate, tonsillar fossae, base of tongue, and oropharyngeal wall.
- The invasive cell grading system by Bryne and colleagues is a significant predictor for the outcome and survival of cancer patients using degree of keratinization, nuclear polymorphism, number of mitoses, pattern of invasion, and lymphoplasmacytic infiltration.
- In addition to SCC, the most frequent malignancies of the oropharynx are lymphoepithelial carcinoma, salivary gland tumors (adenoid cystic carcinoma, mucoepidermoid carcinoma), soft tissue tumors, hematolymphoid tumors, and mucosal malignant melanoma.
- Diagnostic evaluation includes thorough history taking, physical examination, imaging (e.g., ultrasound, MRI, CT, PET-CT), endoscopy, and biopsy of the tumor.
- Therapeutic management of oropharyngeal cancer depends on staging, tumor location, post-treatment function, and the patient's preference after thorough information.
- Endoscopic or transoral laser surgery has become an important tool in the surgical treatment of oropharyngeal cancers with good functional and prognostic outcome.
- Early-stage lesions can be treated surgically with or without postoperative radiation.
- Advanced-stage lesions can be treated surgically with or without reconstructive surgery and postoperative chemoradiation therapy or with definitive chemoradiation therapy in case of inoperability.
- Most oropharyngeal cancers can be approached transorally. However, lateral and transhyoid pharyngotomy, as well as mandibular swing approaches, can be necessary for selected tumors on the basis of location and tumor size.
- As for other malignancies of the head and neck region, a thorough follow-up enables early detection of possible recurrence and timely intervention for improved disease control.
- In addition to locoregional control and patient survival, quality of life is a key factor in the judgment of therapeutic success. The International Classification of Functioning, Disability and Health (ICF) core set by the World Health Organization enables standardized quality-of-life assessments for head and neck cancer patients.

About 10% to 12% of all malignancies of the upper aerodigestive tract occur in the oropharynx. Approximately 130,000 new cases were detected worldwide in 2002.[1] Histopathologically, most malignancies found in the oropharynx (>90%) are squamous cell carcinomas (SCCs) with an incidence of 1 to 3/100,000 in the United States and Europe per year. Although the male population has a higher prevalence of oropharyngeal cancer, future counts will depend on tobacco and alcohol consumption behavior, which is the major risk factor for oropharyngeal carcinoma, followed by occupational and environmental pollutants and endogenous risks.

The prognostic outcome for patients with oropharyngeal malignancies strongly depends on the primary location within the oropharynx and the initial staging and grading of the disease. Survival is based on locoregional recurrence, its prevention, early detection, and treatment. Moreover, all head and neck cancer patients are at risk for second malignancies of the upper aerodigestive tract. However, one has to consider persisting mortality counts despite improved therapeutic options in recent years. Therefore intensive knowledge of existing treatment plans is required, and new treatment strategies based on latest studies and research must be aimed for in the future.

Anatomy of the Oropharynx

The structure of the oropharynx is complex and can be subdivided into the soft palate, tonsils, and base of tongue respecting different site-specific characteristics. The oropharyngeal borders are the soft palate superiorly and the hyoid bone and the vallecula inferiorly. The ventral border is the base of tongue, which ends at the circumvallate papilla. Laterally and dorsally the oropharynx contains the tonsillar region and

the lateral and dorsal pharyngeal wall, respectively. In the following sections, the anatomic sites are described separately, accounting for their specific characteristics (Fig. 100-1).

Soft Palate

The soft palate incompletely separates the nasopharynx and oral cavity from the oropharynx. It is built by the palatopharyngeal arch and the uvula containing the levator and tensor muscle of the palate, the uvular muscle, and laterally the palatopharyngeal and constrictor muscles. Small salivary glands exist within the soft palate tissue. The blood supply is based on the palatine arteries accompanied by palatine sensory nerves.

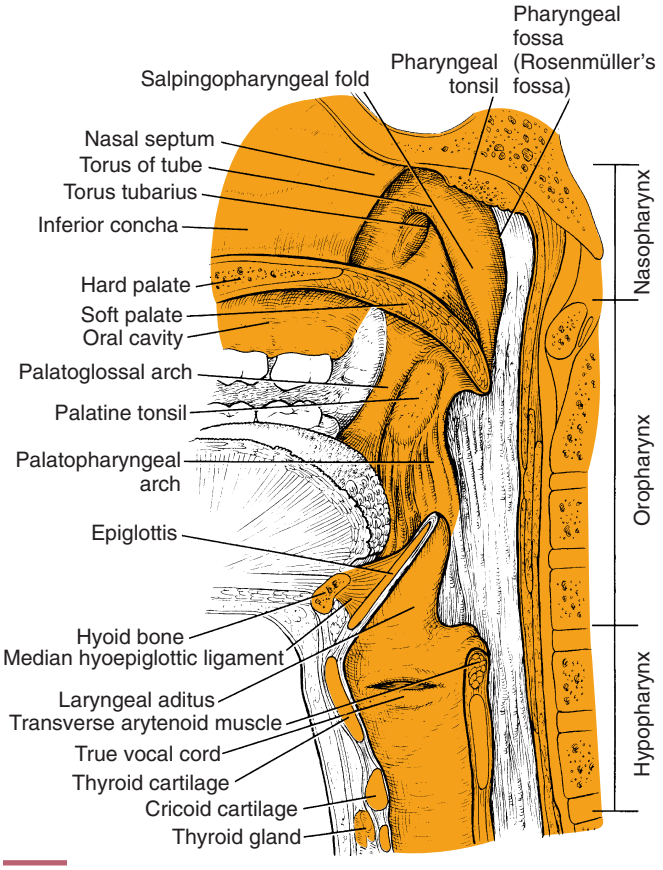

Figure 100-1. Surface anatomy of the oropharynx.

Tonsillar Fossae

The tonsillar region contains the lymphoid tissue of the palatine tonsil, located on the lateral pharyngeal wall. The vascular supply of the palatine tonsils is covered by posterior branches of the lingual artery, the ascending pharyngeal artery, branches of the facial artery, and palatine branches of the internal maxillary artery. The tonsils are embedded in the anterior and posterior pillar, formed by the palatoglossus and the palatopharyngeal muscle, respectively.

Base of Tongue

The base of tongue reaches from the circumvallate papilla to the vallecula and to the glossopalatine sulci laterally. The tongue base is rich in lymphatics and contains part of Waldeyer's ring. The blood supply is covered by the lingual arteries. Innervation of the tongue musculature is provided by the hypoglossal nerve (Fig. 100-2).

Oropharyngeal Wall

The posterior pharyngeal wall of the oropharynx reaches from the region of the soft palate to the epiglottis and borders the tonsillar fossae and the lateral aspect of the piriform sinuses laterally. The wall is composed of superior constrictor muscle and the buccopharyngeal and pharyngobasilar fascia covered by the pharyngeal mucosa (Fig. 100-3).

Lymphatics

The lymphatic pattern of the oropharynx is complex, and lymphatic spread from malignant lesions depends on size and location of the primary malignancy. Its understanding is of high importance for the outcome of surgical and/or radiotherapy treatment of oropharyngeal lesions. A number of previous studies have defined the routes of lymphatic spread in the head and neck.[2-4] The clinical neck levels are defined by levels I to VI with subdivisions A and B for levels I, II, and V (Fig. 100-4).[5]

Oropharyngeal carcinoma is predisposed to drain to levels II, III, and IV with possible further spread to other regions in extensive disease.[6] However, primary drainage is to the jugulodigastric nodes in the upper deep jugular chain (level II) and to the retropharyngeal and parapharyngeal nodes in the retropharyngeal and parapharyngeal space, respectively. Other metastatic spread may involve midcervical (level III) and lower cervical nodes (level IV). Skip metastases to other clinical levels are extremely rare. Shah described in a retrospective study of 1119 radical neck dissection specimens that tumors of the oropharynx characteristically metastasized to lymph node levels II to IV. There was no positive node involvement of level V when levels II to IV were negative.[7]

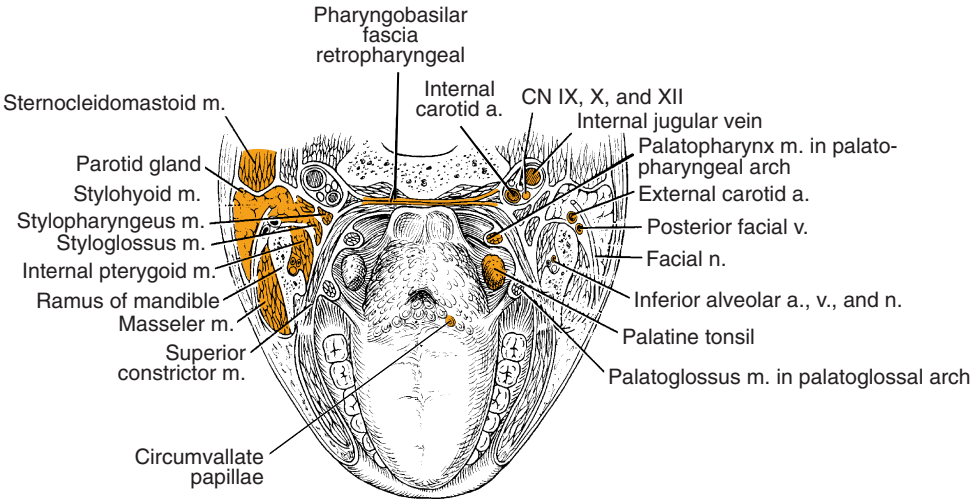

Figure 100-2. Cross-sectional anatomy of the oropharynx.

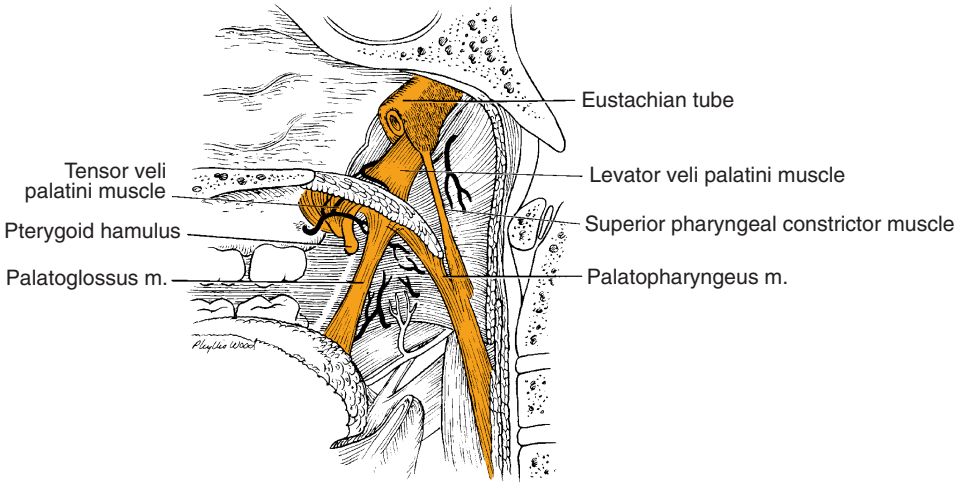

Figure 100-3. Deep anatomy of the oropharyngeal muscles, nerves, and blood vessels.

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Figure 100-4. Lymph node chains of the neck that may be involved with cervical metastatic spread from oropharyngeal tumors. **A,** Superficial cervical and facial nodes. **B,** Deep cervical and intraparotid lymph nodes.

Attention should be spent on the location of the primary malignancy near the midline. Tumors of the base of tongue, the soft palate, and the posterior pharyngeal wall have a higher incidence of bilateral lymphadenopathy. These considerations should influence therapeutic planning to optimize therapy and minimize patient morbidity (Figs. 100-5 and 100-6, Table 100-1).

Pathology

SCC is the most common malignancy of the oropharynx, comprising more than 90% of all malignant tumors of that origin. Other malignant transformations are lymphomas, lymphoepithelial carcinoma, minor salivary gland tumors, malignant melanomas, and other rare malignancies. The World Health Organization Classification of Tumours outlines the presently known malignancies of the oropharynx (Table 100-2).[8]

Epithelial Precursor Lesions

In general, precursor lesions of the oropharynx clinically present as white patches (leukoplakia) (Fig. 100-7) or red patches (erythroplakia). Some lesions appear as mixed variants with white and red components. Most white lesions do not show dysplastic cells and relate to hyperplasia. However, erythroplakia or mixed lesions frequently display dysplasia. Whereas leukoplakia rarely undergoes malignant transformation and may even regress after elimination of underlying etiologic factors, erythroplakia can often lead to malignancy.

Hyperplasia describes increased cell counts in the spinous layer (acanthosis) or in the basal/parabasal layers. The cells are free of atypia and tissue architecture is regular.

In case of changes in architecture and in the presence of atypia in cells, we speak of dysplasia. Dysplasia is considered a range and it is somewhat challenging to divide the dysplastic spectrum into mild, moderate, and severe.

Mild dysplasia is described as mild cell atypia with architectural changes limited to the lower third of the epithelium.

Moderate dysplasia shows architectural changes up to the middle third of the epithelium and cytologic atypia.

Severe dysplasia begins with architectural changes over two thirds of the epithelium and atypic cells. Again, there is no definite division

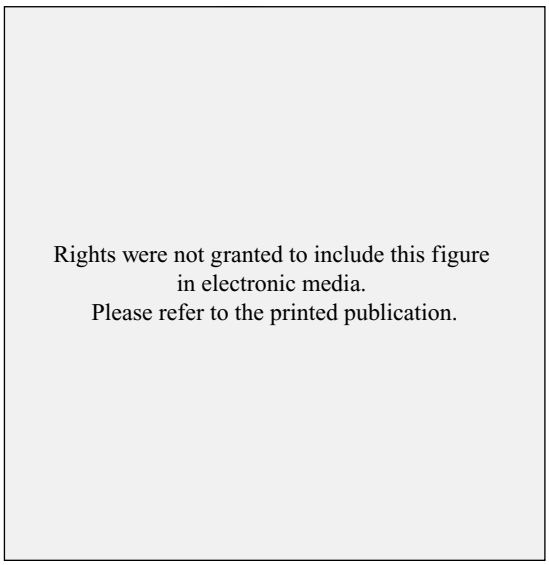

Figure 100-5. Lymphatics of the base of the tongue, with jugulodigastric node involved first.

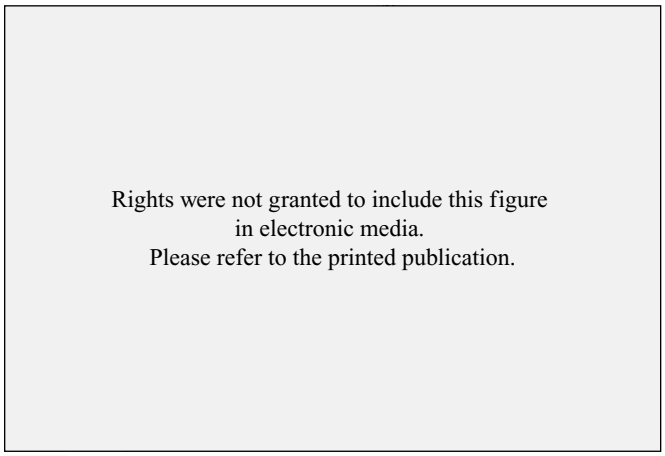

Figure 100-6. Bilateral base of tongue lymphatic drainage.

of dysplastic variants and, depending on the degree of cell atypia, upgrading of dysplasia categories might have to be considered.

Carcinoma in situ is described as malignant transformation without invasion, which is difficult to distinguish morphologically. WHO experts recommend that CIS be diagnosed when full-thickness architectural abnormality and severe cytologic atypia is found.[9]

Squamous Cell Carcinoma

SCC is defined as an invasive epithelial neoplasm with varying degrees of squamous differentiation and a propensity to early and extensive lymph node metastases, occurring predominantly in alcohol- and tobacco-using adults in the fifth and sixth decades of life.[10] The clinical appearance varies and presents as exophytic, flat, ulcerated, verrucoid, or papillary in growth (Fig. 100-8). Independent from the gross appearance, histopathologic patterns of invasion demonstrate multiple variations as well. SCC can vary from keratinizing to nonkeratinizing and well differentiated to poorly differentiated. Severe dysplasia and CIS are common elements found in association with invasive SCC. Invasive carcinoma eliminates the regular architecture and can include lymphovascular space invasion, neurotropism, and infiltration of other tissue components such as muscle or cartilage, demonstrating aggressive behavior of the tumor.

Table 100-1

Percentage Incidence of Cervical Lymph Node Metastasis as Determined by Clinical Examination

Location and Tumor Stage	Node Stage N_0	N_1	N_2
Oropharyngeal wall			
T_1	75	0	25
T_2	70	10	20
T_3	33	23	45
T_4	24	24	52
Soft palate			
T_1	92	0	8
T_2	64	12	25
T_3	35	26	39
T_4	33	11	56
Tonsillar fossa			
T_1	30	41	30
T_2	33	14	54
T_3	30	18	52
T_4	11	13	77
Base of tongue			
T_1	30	15	55
T_2	29	15	57
T_3	26	23	52
T_4	16	9	76

From Lindberg R: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer.* 1972;29:1446. By permission of the American Cancer Society.

Most invasive SCC can easily be identified by experienced pathologists. However, early clinical stages might significantly complicate the diagnosis of invasive patterns. Inflammation can make detailed analysis of the deep epithelial layers and the lamina propria difficult. Presence of cytologic atypia and mitotic features can lead to the correct diagnosis, although they cannot be found in all cases of early SCC pathology. Borderline cases without unambiguous evidence of invasion might still be called early invasive carcinoma after communication between clinician and pathologist.

Malignancy grading can be a prognostic marker, although different grading systems have been proposed with diverse impact on prognosis. Broders suggested a four-tiered grading system for carcinoma of the lip in 1929.[11] His grading system allows assessment of tumor differentiation with some predictability of prognosis because poorly differentiated tumors are more likely to recur.[12,13] However, the grading system has also been shown to lack consistent prediction of prognosis using multivariate analyses.[14,15] A subsequent multivariate analysis on 77 patients with oropharyngeal cancer unveiled only the invasive pattern of the tumor to be an independent predictor for patients' survival.[16] Anneroth and colleagues[17] proposed that grading should include six morphologic features: degree of keratinization, nuclear polymorphism, number of mitoses, pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration. Bryne and colleagues[18] revised this grading method, applying Anneroth's criteria to the most anaplastic fields in the areas of highest infiltration. This invasive cell grading was demonstrated to be a highly significant predictor for oral SCC patients' outcome and survival.[18-20] Table 100-3 summarizes the invasive cell grading system (ICG) by Bryne and colleagues.

Table 100-2

World Health Organization Classification of Malignant Tumors of the Oropharynx

- Malignant epithelial tumors
  - Squamous cell carcinoma
    - Verrucous carcinoma
    - Basaloid squamous cell carcinoma
    - Papillary squamous cell carcinoma
    - Spindle cell carcinoma
    - Acantholytic squamous cell carcinoma
    - Adenosquamous cell carcinoma
    - Carcinoma cuniculatum
  - Lymphoepithelial carcinoma
- Salivary gland tumors
  - Salivary gland carcinoma
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
    - Polymorphous low-grade adenocarcinoma
    - Basal cell adenocarcinoma
    - Epithelial-myoepithelial carcinoma
    - Clear cell carcinoma, not otherwise specified
    - Cystadenocarcinoma
    - Mucinous adenocarcinoma
    - Oncocytic carcinoma
    - Salivary duct carcinoma
- Myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Soft tissue tumor
  - Kaposi's sarcoma
- Hematolymphoid tumors
  - Diffuse large B-cell lymphoma (DLBCL)
  - Mantle cell lymphoma
  - Follicular lymphoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Burkitt's lymphoma
  - T-cell lymphoma
  - Extramedullary plasmocytoma
  - Langerhans cell histiocytosis
  - Extramedullary myeloid sarcoma
  - Follicular dendritic cell sarcoma/tumor
- Mucosal malignant melanoma
- Secondary tumors

The present WHO grading system has been recommended for histopathologic typing of oropharyngeal cancers by the American Joint Committee on Cancer (AJCC).[21] This grading system is based on Broders' system and includes three grades, which are described in Table 100-4.

Lymphoepithelial Carcinoma

The lymphoepithelial carcinoma is defined as a poorly differentiated SCC or undifferentiated carcinoma, accompanied by a prominent reactive lymphoplasmacytic infiltration. The lymphoepithelial carcinoma is rare and diagnosed in 0.8% to 2% of all oral and oropharyngeal malignancies.[22] More than 90% of all lymphoepithelial carcinoma in the oral and oropharyngeal region is found in the tonsils and the base of tongue. Some are found in the buccal mucosa and the palate.

The histopathologic pattern is described as invasive, comprising syncytial sheets and clusters of carcinoma cells with prominent nucleoli, ill-defined cell borders, and often intact surface. The tumor sites are accompanied by rich lymphoplasmacytic infiltrate. These tumors are radiosensitive and local control can be achieved in a high percentage of cases.[23]

Figure 100-7. Leukoplakia of the tongue.

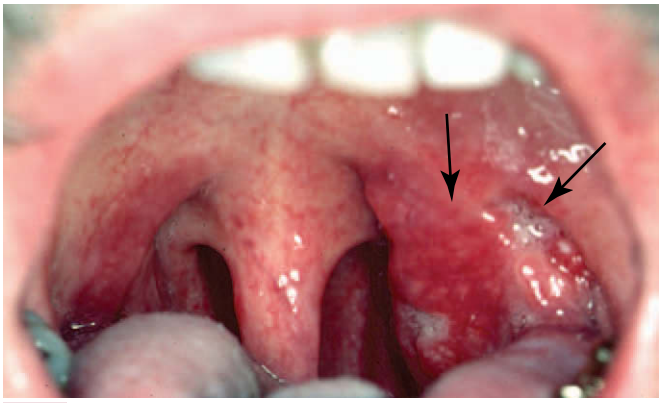

Figure 100-8. Squamous cell carcinoma of the left tonsil (*arrows*).

Salivary Gland Tumors

Among malignant salivary gland tumors, 9% to 23% are found in the oral cavity and oropharynx.[24-26] Nearly half of the salivary gland tumors in the oral cavity and oropharynx are malignant.[24] However, most neoplasms of minor salivary glands arise in the oral cavity. The most common oropharyngeal sites are the (soft) palate, the tonsillar fossa, and base of tongue. Oropharyngeal salivary gland tumors are rare with only 1.1% to 3.3% of all minor salivary gland tumors.[24,25,27] All malignant salivary gland tumors that can possibly arise in the oropharynx are listed in Table 100-2. Among those, adenoid cystic carcinoma and the mucoepidermoid carcinoma are most frequent.

The *adenoid cystic carcinoma* is relatively common in minor salivary glands. A large series describes 42.5% of this lesion to be found in minor glands and 20.5% of minor salivary gland adenoid cystic carcinoma in the oral/oropharyngeal space.[28] They usually present as slow-growing masses, sometimes with ulceration of the palate. Symptoms like pain, signaling nerve invasion, suggest progressive disease. The histopathologic pattern is cylindromatous or cribriform, although some can show tubular areas or appear solid.[29] Cribriform lesions have a more favorable prognosis than solid tumors. The spread of adenoid-cystic lesions is commonly hematogenous, typically in the lung and bones, and lymph node involvement is rather rare. Therefore neck dissection is generally reserved for patients with palpable disease.[30] In case of radiation therapy for these rather moderately radiosensitive

Table 100-3

Invasive Cell Grading System (ICG)

Morphologic Feature	1	2	3	4
Degree of keratinization	Highly keratinized (>50% of cells)	Moderately keratinized (20-50% of cells)	Minimal keratinized (5-20% of cells)	No keratinization (0-5% of cells)
Nuclear polymorphism	Little nuclear polymorphism (>75% mature cells)	Moderately abundant nuclear polymorphism (50-75% mature cells)	Abundant nuclear polymorphism (25-50% mature cells)	Extreme nuclear polymorphism (0-25% mature cells)
Number of mitoses (high-power field)	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well-delineated infiltrating borders	Infiltrating solid cords/bands/strands	Small groups/cords of infiltrating cells	Marked and widespread cellular dissociation in small groups or in single cells (n <15)
Lymphoplasmacytic infiltration	Marked	Moderate	Slight	None

From Bryne M, Koppang HS, Lilleng R, et al. New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. *J Oral Pathol Med.* 1989;18:432-437.

Table 100-4

World Health Organization Grading System for Oral Squamous Cell Carcinoma

Grade	Description
1	Well differentiated. Histologic and cytologic features closely resemble those of the squamous epithelial lining of the oral mucosa. There are varying proportions of basal and squamous cells with intercellular bridges; keratinization is a prominent feature; few mitotic figures are seen and atypical mitoses or multinucleated epithelial cells are extremely rare; nuclear and cellular polymorphism is minimal.
2	Moderately differentiated. This is a neoplasm with features intermediate between well differentiated and poorly differentiated. Compared with well-differentiated squamous cell carcinoma, these tumors have less keratinization and more nuclear and cellular pleomorphism; there are mitotic figures and some are abnormal in form; intercellular bridges are less conspicuous.
3	Poorly differentiated. Histologically and cytologically there is only a slight resemblance to the normal stratified squamous epithelium of the oral mucosa. Keratinization is rarely present, and intercellular bridges are extremely scarce; mitotic activity is frequent and atypical mitoses can readily be found; cellular and nuclear pleomorphism are obvious and multinucleated cells may be frequent.

From Pindborg JJ, Reichert PA, Smith CJ, et al, eds. *Histological Typing of Cancer and Precancer of the Oral Mucosa.* 2nd ed. Berlin: Springer-Verlag; 1997:11. By permission of the publisher.

tumors, neutron beam radiation is recommended.[31] Prognosis is negatively influenced by minor salivary gland as origin, tumor size greater than 4 cm, osseous invasion, advanced stage, and local recurrence.[32,33]

Mucoepidermoid carcinoma is the most common salivary gland malignancy and accounts for 9.5% to 23% of all minor salivary gland tumors.[25,34,35] Half of the often asymptomatic cases arise in the palate, whereas the base of tongue and other oropharyngeal locations are rare.[36] They are commonly well differentiated and appear as a bluish swelling. Some show granulation or a papillary surface. Oropharyngeal tumors can cause symptoms of dysphagia. Histopathologically, a mixture of epidermal epithelium and mucous membrane-producing cells is found. Treatment usually includes wide surgical excision, and neck dissection appears to be beneficial in patients with suspected or clinically obvious metastases. Olsen and colleagues reported on a series of oropharyngeal mucoepidermoid carcinoma at Mayo Clinic. Based on a follow-up of at least 10 years, recurrence rate was significantly reduced after wide local excision, including bone if necessary compared with simple excision with closer margins. Of the patients in the series, 24% presented with positive lymph nodes.[37] Patients treated with primary radiation or postoperative radiation did not profit in terms of local control or survival in this evaluation; however, numbers might be too small to draw final conclusions and radiotherapy might be beneficial in case of adverse effects in those patients.

Soft Tissue Tumors

Kaposi's sarcoma is a locally aggressive growing neoplasm, which might present as cutaneous but also as mucosal lesion, showing multiple patches and nodules (Fig. 100-9). It can also affect lymph nodes and visceral organs. It rarely metastasizes and is a member of intermediate-type vascular tumors. It is associated with human herpes virus 8 (HHV 8) infections. Kaposi's sarcoma occurs as an indolent variant in elderly men in the Mediterranean and Eastern Europe, as endemic disease in equatorial Africa, and in immunosuppressed patients after organ transplantation or in case of human immunodeficiency virus (HIV) infection.[38]

Oral Kaposi's sarcoma is found predominantly on the palate, the gingiva, and the tongue. It clinically presents as reddish blue or brown nodules or plaques with possible ulceration. The AIDS-related form of Kaposi's sarcoma is the most aggressive form. There are three histopathologic stages of Kaposi's sarcoma: the patch stage in early lesions, the plaque stage, and the nodular stage. Stages can be considered a spectrum and they blend into another. Early lesions are uncharacteris-

Figure 100-9. Kaposi's sarcoma of the palate.

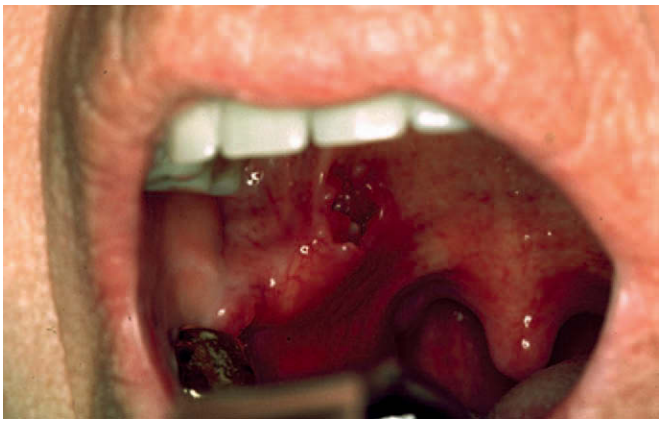

Figure 100-10. Non-Hodgkin's lymphoma of the palate with submucosal swelling and ulceration.

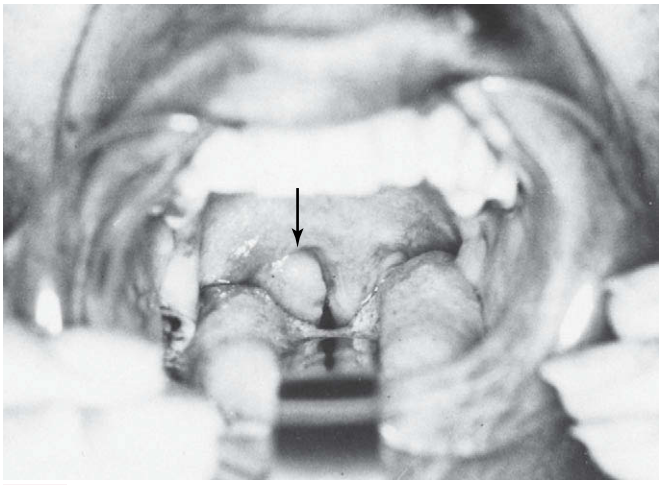

Figure 100-11. Lymphoma of the tonsil *(arrow)*.

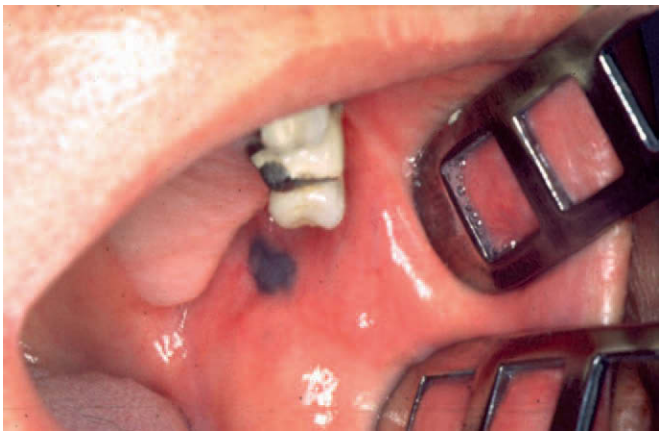

Figure 100-12. Malignant melanoma of the retromolar trigone.

tic, showing vascular proliferation, collagen fibers, hyaline globules, endothelial cell lining, and cells with some atypia and infiltration of inflammatory cells as they grow.

Patients might be treated with surgery, radiation, and chemotherapy, depending on the epidemiology of the disease. The incidence and course of the disease has improved with antiretroviral therapy in HIV-infected patients.[38]

Hematolymphoid Tumors

On the basis of the complex and widespread lymphatic tissue in the oropharynx, lymphoid malignancies often occur in this area. *Non-Hodgkin's lymphomas* (NHLs) are found in the palatine tonsils, palate, base of tongue, and other oropharyngeal sites. Etiologic factors are yet unknown in most patients, although some lymphoma patients might suffer from an immunodeficiency. Clinical symptoms can be fullness of the throat, dysphagia, snoring, and pain. Systemic symptoms are rare.[39] The lesions present as exophytic mass, submucosal swelling, and sometimes ulcerations (Figs. 100-10 and 100-11).

Most NHLs in the oropharynx are B-cell lymphomas, with diffuse large B-cell lymphoma being the predominant type. Histopathologically the stroma is densely infiltrated with lymphoma cells, which vary depending on the histologic type. Treatment is based on radiotherapy and/or chemotherapy depending on the histologic type and stage. Studies have demonstrated a benefit for adjuvant chemotherapy along with radiation compared with radiation treatment only.[40,41] The 5-year survival rate for localized disease has been reported from 50% to more than 80%.[41-45]

Mucosal Malignant Melanoma

Although malignant melanoma (MM) most commonly manifests as skin lesions, it may also arise from melanocytes in the mucosa, but only 1.3% of all melanomas are mucosal melanomas (Figs. 100-12 and 100-13). Of those, 55.4% are mucosal MMs of the head and neck.[46] They are characterized as malignant transformed melanocytes at the epithelial–connective tissue interface with migration into the epithelium and the connective tissue, respectively. Oropharyngeal mucosal melanoma is exceedingly rare, with more mucosal MM of the head and neck occurring in the oral cavity (50%).[46,47]

No known etiologic factors exist for mucosal MM of the head and neck. Clinically they can present as black, gray, or reddish, and they are rarely amelanotic. They typically consist of widespread, multiple, pigmented lesions with or without nodules. Ulcerations and bone infiltration are common and oral bleeding, dysphagia, and sensations of pain can be symptoms before diagnosis. Mucosal MM is usually diagnosed in an advanced stage with most tumors showing invasive character. However, 20% are in situ lesions.[47] Aggressive surgical resection is still the primary treatment of choice, although many adjuvant modalities including different chemotherapy regimens and radiotherapy have been applied. Despite surgically achieved possible local control, 5-year survival of pharyngeal melanoma is only 13%.[46,48,49] Developments for improved treatment options are limited because mucosal MM is a rare disease lacking clinical treatment trials. By early detection, melanoma

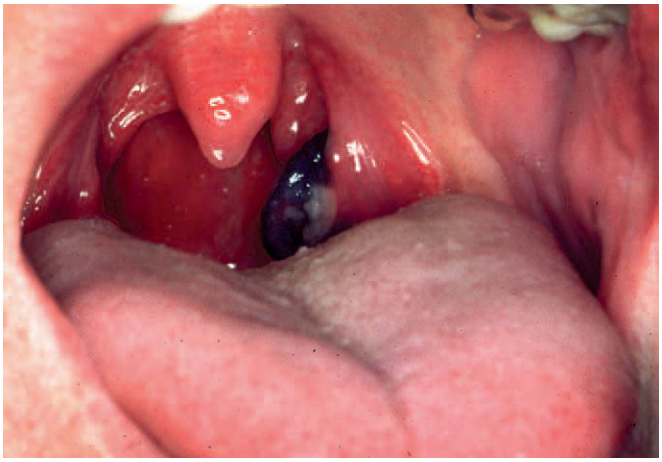

Figure 100-13. Malignant melanoma of the left tonsillar fossa.

patients have the best chance for cure and physician's threshold for biopsy of a suspected lesion should be low.

Squamous Cell Carcinoma

Etiology

Predominant and synergistic acting risk factors for SCC of the oropharynx are tobacco and alcohol consumption.[50] These factors account for about 75% of oral and oropharyngeal carcinoma in Western countries.[50,51] For the highest consumption levels, relative risks from 70 to 100 have been reported compared with lowest consumption levels. A super-multiplicative effect in case of contact with tobacco and alcohol substances has been shown for oral and oropharyngeal cancers in case-control studies.[52]

Tobacco chewing is a common habit, particularly in India, parts of Southeast Asia, the Middle East, China, and Taiwan. Tobacco is often consumed in betel quids containing areca nut, which has been classified as human carcinogen by the IARC in 2003. Smokeless tobacco is a major risk factor for oropharyngeal cancer in these parts of the world.[53] In India about 50% of oropharyngeal cancers in male and 90% in female are caused by chewing.[54]

Human papillomavirus (HPV) infection is another well-established cancer risk factor. Genotypes HPV 16 and 18, known causes for uterine cervix and skin cancer, are found in 50% of tonsillar and oropharyngeal SCC, and studies suggest that up to 40% of oropharyngeal cancer cases may be due to HPV infection.[55] The incidence of HPV-associated oropharyngeal primaries is rising according to recent reports—up to 70% of all presenting cases in some series. The cohort of patients harboring this form of the disease is younger by approximately 10 years and has a distinctly favorable prognosis. Epidemiologic studies propose that having multiple sexual partners is significantly associated with HPV-related tumors.[1]

In addition to exogenic risk factors, multiple endogenic risks have been identified and associated with head and neck cancer.[56] DNA repair, differences in mutagen sensitivity, and alteration of genes such as epidermal growth factor receptor (EGFR) have shown their impact on head and neck cancer and influenced modern therapy and prevention strategies.

Clinical Presentation, Patterns of Spread

Patients with SCC of the oropharynx often present at advanced stages III and IV. Despite psychologic and social factors, late symptoms might cause prolonged und undiscovered tumor growth. First symptoms may be dysphagia, pain, feel of throat mass, oral bleeding, otalgia (involvement of cranial nerves IX and X), or presentation of a neck mass. Oropharyngeal regions can vary in clinical presentation and pattern of spread, causing different considerations for diagnostics and treatment.

Cancers of the *soft palate* present almost always on the anterior oropharyngeal portion. They are well detectable and can in most cases be biopsied in the office. Primary lymphatics involved are commonly level II nodes, with other levels involved depending on the clinical stage. Whereas midline and paramedian lesions have a tendency for bilateral lymphatic spread, this becomes more unlikely the more lateral the tumor growth is located.

The most frequent location for oropharyngeal tumors is the *tonsillar fossa,* with the palatine tonsil and the anterior tonsillar pillar. They commonly present as foreign body, dysphagia, otalgia, or impeded jaw mobility caused by infiltration of the periosteum or bone of the mandible or the pterygoid muscles in extended cases. Physical examination can show exophytic or ulcerated lesions, dysplasia, and/or inflammation reaction. Extension into the base of tongue inferiorly and the soft palate superiorly is common, with 55% and 60% in a study by Perez and colleagues, respectively.[57] Lymphatic drainage is directed primarily to level II nodes but can involve level III parapharyngeal and retropharyngeal nodes level I, IV, and V, depending on stage of presentation.[58-60] Lindberg described nodal metastasis for cancer of the tonsil in 76% of cases compared with 45% in patients with cancer of the tonsillar pillar, with most common node involvement in level II for both locations. Contralateral nodal disease was found in 11% of patients with cancer of the tonsil and 5% with primary malignancy of the pillar.[61] However, in these studies no mention is given of proximity to the midline, which is the most frequent reason a lateralized tumor epicenter in the oropharynx would present with "contralateral" neck metastasis. Differences might be based on higher-staged groups with tonsillar lesions, and likelihood of contralateral lymphatic spread is less than 5% for T1 and T2 cancers.

Cancer of the *base of tongue* is particularly difficult to detect and often becomes clinically evident in an advanced stage. This is due to relatively late clinical symptoms because the base of tongue is nearly without pain fibers. Moreover, the assessment of the base of tongue can be more difficult during physical examination due to prominent lingual tonsils or submucosal location, and deep basal areas might not completely present even using operative endoscopy. As in the palatine tonsil, occult carcinoma with clinically prominent metastatic disease, typically in neck level II, is often found in the base of tongue and is often the presenting feature of this disease. As with neck metastases primarily clerived from tonsils, some of these neck masses can be misdiagnosed as branchial cleft cysts or, on biopsy, as branchiogenic carcinomas.[62] To rule out such findings, meticulous microendoscopic examination (see Fig. 100-12) and biopsy of suspected lesions are mandatory. Base of tongue cancer has a higher frequency of bilateral metastases (up to 20%), which is mainly due to proximity to the midline but enhanced by a rich lymphatic drainage of the base of tongue and tendency to late clinical presentation with upstaging. Ipsilateral node involvement can be detected in more than 70% of cases.[63]

Prolonged diagnosis is also common in *oropharyngeal wall* tumors. Symptoms can be pain, dysphagia, and bleeding. Infiltration of the prevertebral fascia posteriorly and deep cervical structures and vessels laterally negatively affect therapeutic options and prognosis. Lymphatic spread is found in about 25% of T1 and in 75% or more of T4 cancers. Most pharyngeal wall tumors come close or past the midline with frequent bilateral lymphatic spread. Microscopic parapharyngeal and retropharyngeal lymphatic spread has to be considered even in small lesions without palpable cervical nodes.

Diagnostic Evaluation

Anamnesis

A thorough anamnesis is part of any comprehensive evaluation of head and neck cancer patients. Symptoms at first presentation of oropharyngeal cancer patients are commonly dysphagia and/or odynophagia, oral bleeding, otalgia, or changes in speech. In addition to the history of risk factors such as alcohol and tobacco consumption, xenobiotic exposure at working places and in the environment should be evaluated. Dietary and social habits are also worthwhile to evaluate. Knowing about possible risk factors for head and neck cancer in individual patients enables for future elimination and enlarges the chances for prevention of recurrent disease. Also, better results and improved treatment tolerance are obtained for patients who quit smoking.[64] Other

factors such as social aspects, family support, and general health status have great impacts on treatment and outcome and should therefore be consequently evaluated.

Physical Examination

Physical examination is one of the initial keys for cancer diagnosis, selection of further diagnostics, and treatment plan. In case of suspicion for oropharyngeal cancer, patients should carefully be investigated with focus on the tongue (appearance and movement), tonsillar fossae, retromolar trigone, soft palate (appearance and mobility), base of tongue, vallecula, and pharyngeal walls. Inspection should include a close endoscopy (flexible or rigid) and palpation, especially of the tongue base and sensate testing. Examination can unveil local tumor extension and nerve infiltration. Video endoscopy and documentation of findings are helpful tools for teaching reasons and future comparisons.

All cancer patients need to undergo a complete head and neck investigation to exclude secondary cancers. Bimanual palpation of the neck is mandatory in order to assess lymph node status and possible regional tumor spread.

Imaging

For most head and neck malignancies, imaging is an important and recommended tool for diagnostics and clinical staging. Oropharyngeal malignancies, especially with their close anatomic relationship to important soft tissue and bony structures, require further imaging studies for precise evaluation and treatment plans.

Gray-scale and Doppler ultrasonography of the neck have proven to be valuable methods to evaluate lymphadenopathy of the neck. Using ultrasound for cervical assessment has advantages. It is a relatively inexpensive procedure with real-time imaging and can be frequently performed without radiation exposure. However, there is limitation to ultrasonography in patients with head and neck malignancies. Retropharyngeal nodes and deep structures are not accessible using ultrasound. Furthermore, ultrasound has deficits describing extracapsular spread and infiltration of soft tissue and bone. Moreover, the oropharyngeal primary usually cannot be detected using ultrasonography.[65]

Most oropharyngeal malignancies today are evaluated using computed tomography (CT) or magnetic resonance imaging (MRI). Sometimes the imaging technique preferred simply depends on its availability. Each has its advantages and disadvantages. Some oropharyngeal malignancies involve bony structures such as the maxilla, mandible, cervical spine, and skull base, and a CT scan might be helpful in interpretation of bone infiltration, although modern MRI precisely demonstrates infiltration of the periosseous membrane and allows for exact interpretation of bone involvement. In some cases panoramic x-ray views of the mandible can support identification of mandibular infiltration. Especially in deep invasive malignancies, MRI is helpful, although it can lead to false-negative results regarding superficial lesions. Although magnetic resonance scanning is generally the most recommended imaging method for the evaluation of the oropharynx and the neck, both CT and MRI have been used in such determinations.[66] Positron emission tomography (PET)/CT plays an increasing role for the management of head and neck SCC. It can unveil unknown primary tumor sites and synchronous primary tumors, regional lymph node metastases, and distant metastases. It plays a lesser role for T-staging of a known primary based on decreased anatomic definition compared with MRI and contrast-enhanced CT.[67] Its reliability may be limited by previous surgical or radiation therapy. Recent studies suggest that PET/CT is more accurate 2 to 3 months after completion of radiation therapy.[68-70] Whereas a negative PET/CT is found to be highly reliable, positive results must be correlated with findings in physical examination and cross-sectional imaging modalities because nonspecific inflammation may cause false-positive results.[71]

In addition to evaluation of locoregional tumor spread, imaging systems are used to screen for distant metastatic spread in organs such as the lung, liver, skeletal system, and brain. On the basis of the primary malignancy and the accompanying likelihood of distant metastases, regular chest radiographs and ultrasonography of the abdomen might be sufficient staging methods. In many cases, CT scanning of the lung and CT and/or MRI for the abdomen are recommended. In recent years, FDG PET/CT showed growing importance for the detection of distant metastatic spread.[71]

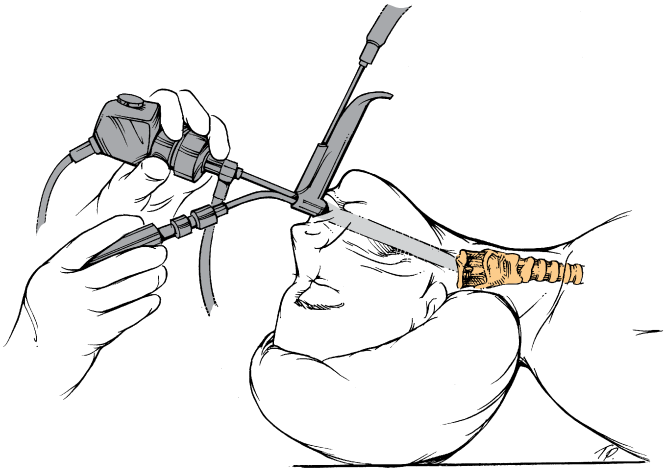

Figure 100-14. Microendoscopic setting. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Endoscopy, Biopsy, and Frozen Section

To further diagnose oropharyngeal lesions, a biopsy and histopathologic examination must be performed. Biopsies of oropharyngeal tumors might be taken under local anesthesia. Lymphadenopathy without perceptible primary lesion can be evaluated using fine-needle aspiration (FNA). Best diagnostic results are found for FNA using ultrasound of the neck.[72]

Some oropharyngeal lesions are not sufficiently accessible in the office setting and may require general anesthesia to biopsy an adequate-sized specimen. Occasionally small oropharyngeal malignancies can be difficult to detect in physical examination, as well as in imaging systems, and demand further diagnostics (e.g., using endoscopes with or without microscopic assistance) (Fig. 100-14). Microscopic evaluation is a sensitive procedure for the identification of unknown primary lesions, which can often be detected in the base of tongue or tonsillar fossa, respectively. The panendoscopy in general anesthesia is an important tool not only to detect and biopsy such lesions and to define tumor extension but also to rule out any secondary malignancy, which can be found in head and neck cancer patients and includes endoscopy of the bronchi and esophagus.

Frozen sections as confirmation of a suspected malignancy and as criteria for tumor-free margins have been critically evaluated in the past.[73] The reliability of frozen sections depends on the experience and technique of the pathologist and requires close interdisciplinary communication. The accuracy of frozen sections is close to the final diagnosis (>90%).[74] Considering the possibility of false-positive results, depending on the examiner's expertise, frozen sections cannot be generally recommended as a basis for final treatment, however. The final treatment should be based on standard histopathology.

Staging

The Union Internationale Contre Cancer (UICC) and the American Joint Committee on Cancer (AJCC) in its *Cancer Staging Manual* (sixth edition) have defined the current staging system for oropharyngeal cancer.[75,76] Both classifications correspond exactly. Tables 100-5 and 100-6 present an overview of the present oropharyngeal staging system.

Experts have debated and evaluated the clinical use of the staging system.[77] The fifth edition of the tumor node metastasis (TNM) classification divided stage IV tumors into three subcategories (IVA, IVB, and IVC), which already caused relevant changes to the fourth edition.[78] The sixth edition of the TNM classification introduced a subdivision of advanced tumors of group T4 into T4a (lower risk) and T4b (higher risk), which describes the risk of uncontrolled disease in patients with

Table 100-5

Definition of the Tumor Node Metastasis Staging System

Primary Tumor (T)

T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
Oropharynx	
T_1	Tumor ≤ 2 cm in greatest dimension
T_2	Tumor > 2 cm but ≤ 4 cm in greatest dimension
T_3	Tumor > 4 cm in greatest dimension
T_{4a}	Tumor invades the larynx, deep or extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T_{4b}	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional Lymph Nodes (N)

Oropharynx and Hypopharynx	
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension
N_2	Metastasis in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N_{2a}	Metastasis in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N_3	Metastasis in a lymph node > 6 cm in greatest dimension

Distant Metastasis (M)

M_X	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago. The original source for this material is the *AJCC Cancer Staging Manual,* 6th ed. (2002) published by Springer-Verlag New York, www.springer-ny.com.

Table 100-6

Stage Grouping for Oropharymgeal and Hypopharymgeal Cancers

Stage	Group		
0	T_{is}	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_1	M_0
IVA	T_{4a}	N_0	M_0
	T_{4a}	N_1	M_0
	T_1	N_2	M_0
	T_2	N_2	M_0
	T_3	N_2	M_0
	T_{4a}	N_2	M_0
IVB	T_{4b}	Any N	M_0
	Any T	N_3	M_0
IVC	Any T	Any N	M_1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago. The original source for this material is the *AJCC Cancer Staging Manual,* 6th ed. (2002) published by Springer-Verlag New York, www.springer-ny.com.

tumor extension beyond the site of origin. T4a disease describes tumors with reasonable opportunity for disease control on the basis of the resectability of structures involved such as larynx, deep/extrinsic muscles of the tongue, medial pterygoid, mandible, and hard palate. T4b describes tumors with certainty of poor outcome showing involvement of the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or carotid artery. O'Sullivan and Shah[79] suggested invasion of the prevertebral fascia to be classified as high risk and therefore included into subgroup T4b. T4a and T4b in combination with categories for N (regional lymph node disease) and M (distant metastasis) assist the classification of the advanced tumor stage IV into the subgroups with advanced lower-risk stage IVA (potentially curable), advanced higher-risk IVB (of dubious curability), and stage IVC with distant metastatic disease (undoubtedly incurable). Despite some suggested additions, the sixth edition of TNM classification offers valuable assistance in clinical management and research. Changes in the staging system over the past decades and improvements of staging tools such as modern imaging systems must be taken into consideration when former clinical studies about outcome and prognosis are evaluated.

Despite the importance of therapeutic management, outcome, and prognosis, clinical staging remains strongly dependent on the examiner's skills, the imaging system and its quality, and the excellence of surgical and pathologic assessment.

Oropharyngeal cancer is usually amenable to direct or endoscopic visualization and palpation, which in combination with imaging assessment enables a thorough clinical evaluation. Reasons for misjudgment remain. The examiner's evaluation does not unveil microscopic and deep infiltration. Using MRI and CT scanning for further information results might be limited when examining superficial smaller lesions.[62] Additionally, poor demarcation and accompanying inflammatory tissue reaction may affect interpretation of the images. Tumor size can be overestimated or underestimated by these factors and misjudged, and it can strongly influence therapeutic planning. Not only clinical but also postoperative staging might be affected (e.g., by shrinkage of the specimen and lack of clinical and surgical information). Moreover, large tumor extension might lead to difficulties about classification of the site of origin (e.g., whether a lesion derived from the oropharynx, hypopharynx, or supraglottic region). Because those tumor extensions commonly accompany high staging and comparably worse prognosis, there is less influence concerning management strategies but concerning scientific studies and statistical evaluation. Nevertheless, correspondence between the clinician and the pathologist is the key for best postoperative staging.

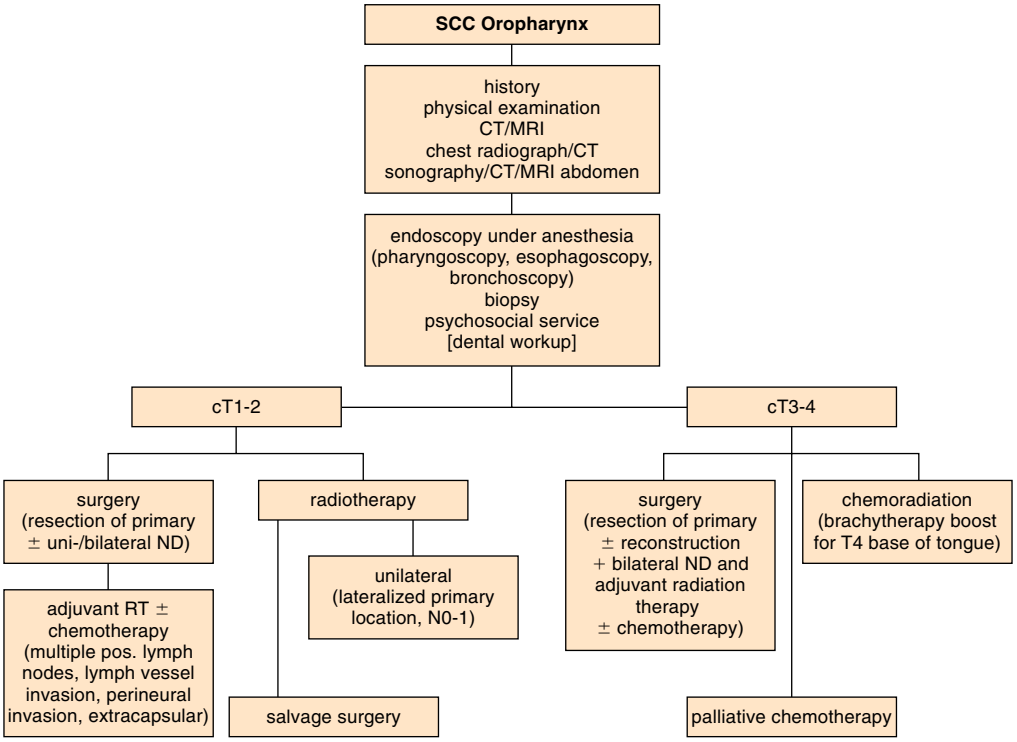

Figure 100-15. Management algorithm for squamous cell carcinoma of the oropharynx.

Therapeutic Management and Outcome

The main criterion for a successful treatment is locoregional control of the primary tumor. The choice of treatment modality depends on the location of the primary and the ability to control the primary and the regional node involvement. Figure 100-15 presents an informing algorithm for oropharyngeal cancer treatment. With improvements in locoregional control, distant metastases are a growing issue in the treatment of oropharyngeal cancers. To achieve this goal, surgery, radiotherapy, and chemotherapy can be administered alone or in combinations. In case of an early tumor stage, surgery and radiation therapy can be used for primary treatment. In later stages of oropharyngeal cancer, combinations of surgery, radiation therapy, and chemotherapy are recommended in most cases. The impact of additional therapies such as immunotherapy/biotherapy (e.g., epidermal growth factor receptor [EGFR] inhibitor) is currently investigated and their significance has yet to be evaluated. The decision-making process for treatment modality should include information from the latest review of the Cochrane Collaboration on the treatment on oral and oropharyngeal cancer. Only one study by Robertson (1998) compared surgery plus adjuvant radiotherapy and radiotherapy alone, fitting their criteria and therefore being included. The trial was prematurely stopped because of the unacceptably high number of deaths in the radiotherapy arm.[80,81] However, in addition to outcome, post-therapeutic function associated with the patient's quality of life must be considered in the decision about treatment.

With the use of modern free tissue transfer techniques, patients' quality of life and functions like speech and swallowing have considerably improved after surgery with ablative defects.[82] Patients should be thoroughly informed about possible treatment options to be included in the decision-making process. Complications and long-term effects possibly arising from surgical interventions or toxicity of chemoradiation therapy must be clearly assessed. As for all head and neck cancers, the clinician's experience, the options given by the institution, and the patient's individual reliability should be accounted for in order to achieve the optimal cancer treatment.

Soft Palate

Early disease of the soft palate (Fig. 100-16) shows favorable results for local control using surgery and using radiation therapy. Considering possible long-term side effects caused by radiation therapy and good reconstructive options with positive functional outcome, surgery (conventional or laser surgery) might be preferred. Some studies have been performed using radiation in combination with brachytherapy (Iridium-192 implant), without any proof of significant benefit.[83-86]

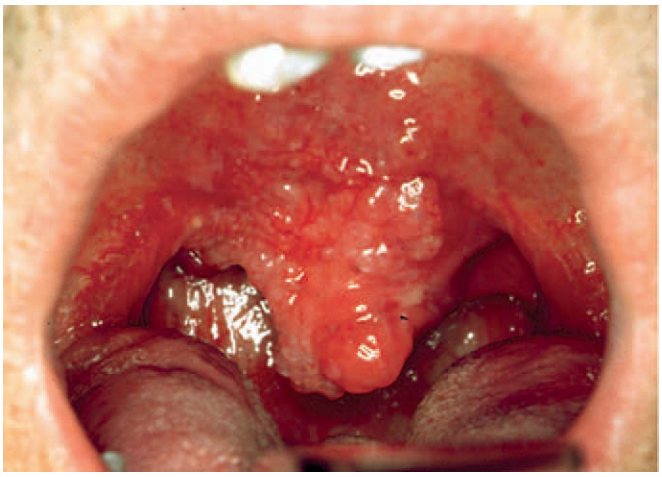

Figure 100-16. Squamous cell carcinoma of the uvula.

Advanced disease is commonly treated with surgery and adjuvant radiotherapy with or without chemotherapy. Radiation therapy did not demonstrate convincing results.[87] However, Calais and colleagues[88] showed more favorable results using radiation therapy with concomitant chemotherapy compared with radiation therapy alone as an alternative therapeutic modality for stage III and IV cancers.

The decision for performing a *neck dissection* is led by the propensity of soft palate cancers to metastasize even in early stages. Har-El and colleagues[89] showed that more than 48% of patients with soft palate cancers present with clinical evidence of neck disease, and even in patients with no palpable or radiographic proof, more than 40% of

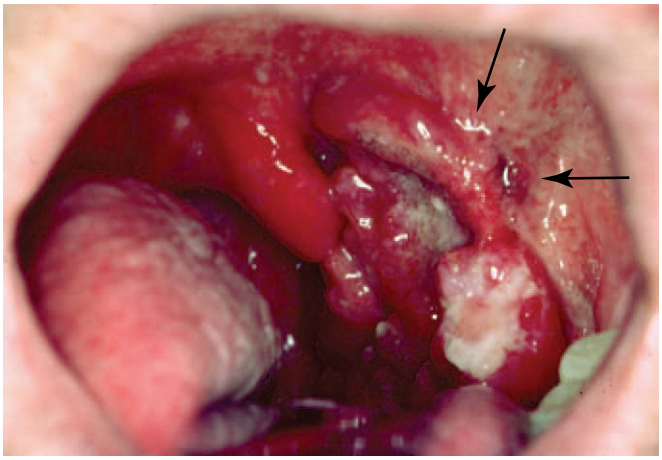

Figure 100-17. Advanced squamous cell carcinoma of the tonsil.

their patients eventually had neck disease. As a consequence, patients with positive nodes should be treated with neck dissection (e.g., followed by radiation therapy). Also, patients with clinically negative neck should either receive elective neck dissection or radiation therapy. Some authors describe radiation therapy followed by neck dissection in clinically positive nodes as well.[81] Yet higher complication rates have been found for neck dissection following radiation therapy in several studies, suggesting surgery as primary treatment.[90] The closer the lesion is positioned toward the midline, the higher the likelihood for bilateral lymphatic spread and the necessity to perform bilateral neck dissection.[91]

Tonsillar Fossae

Early lesions of the tonsillar region can be treated with surgery or radiation. Both modalities offer good outcome and functional results. In most cases modern surgical techniques and instruments allow good transoral access to the tumor site without comorbidity worth mentioning. Procedures including mandibulotomy are rarely necessary and used only in some cases of extensive disease and reconstruction. Also, laser techniques add to the advancements of surgical precision and reduced morbidity.[92,93] Local control rates up to 90% after surgery have been described.[94,95] Comparing external radiation beam therapy (EBRT) with surgery, no differences in locoregional control or overall survival have been unveiled. However, complications based on high dosage for primary treatment and the effect on the patient's quality of life must be considered and compared with those resulting from surgery.

Advanced lesions (Fig. 100-17) are commonly treated with surgery and postoperative radiotherapy ± chemotherapy). One study was performed using single-modality (surgery vs. radiotherapy) treatments for stage III and IV cancers, with significantly better 5-year survival rates using surgery, even though more patients were stage IV in the radiated group.[96] Foote and colleagues evaluated advanced cases treated with surgery ± adjuvant radiotherapy. After surgery with postoperative radiation, their overall survival rate was found to be 100% for stage III and 78% for stage IV cases, whereas patients who underwent solely surgery showed 56% and 43% survival, respectively.[97] Another study from the Memorial Sloan-Kettering Cancer Center demonstrated favorable local control rates (T3 94%, T4 75%) and 64% disease-free survival. In case of positive or close surgical margins, 60 Gy or higher was administered and followed by a 93% local control rate.[98]

Spiro and Spiro compared radiation therapy and combined therapy with surgery followed by radiation retrospectively from 1969 until 1983. They found 3-year local control rates comparable with other investigators but for stage IV disease, although possibly biased against the combined treatment by preselection of high-staged cases.[99] Recently, concomitant chemoradiation following surgery compared with postoperative radiation was investigated for head and neck cancers in Europe and the United States in two multicenter studies. For oropharyngeal tumors, the evidence for a benefit using concomitant chemoradiation therapy remains somewhat weak, although much stronger in patients with additional features such as extracapsular spread of lymph nodes.[100,101] Parsons and colleagues presented a review of several studies comparing surgery ± radiation therapy with radiation ± neck dissection for tonsillar carcinoma. Despite comparable counts for 5-year survival and locoregional control, they criticize higher complication rates in the surgery group, although the data indicate that almost all fatal complications resulted in studies with radiation therapy performed before the surgery.[102] Salvage surgery in the tonsillar region after primary radiation is accompanied by high mortality and low 5-year survival rates. One investigation by Gehanno and colleagues[103] showed a 5-year survival of 24% and a mortality rate as high as 8% in 120 patients. Two investigations support the idea of brachytherapy salvage in this area with 5-year survival rate of 64% and a 2-year survival rate of 42%, respectively.[104,105]

In general, the clinically negative neck should be treated in case of an incidence of occult metastasis of 20% or higher.[106] In patients with carcinoma of the tonsillar region, ipsilateral elective *neck dissection* is commonly performed even for small lesions and clinically negative necks. The latest considerations about neck dissections in clinically negative necks and the more selective surgery (e.g., sparing level IIb) have significantly reduced comorbidity and improved patients' outcome.[107] Postoperative radiation is often recommended in case of positive nodes, although prospective randomized trials exploring the role of radiation therapy after selective neck dissection are necessary.[107] On the basis of the size and location of the primary metastasis and the ongoing higher likelihood of bilateral metastases, bilateral neck dissection or radiation treatment should be considered. This is true for T3 and T4 lesions, involvement of the tongue base, and neck findings greater than or equal to cN2. However, patients with T1-2 lesions and N0/N1 might be adequately treated with ipsilateral surgery/radiation.

Base of Tongue

As with other locations of the oropharynx, *early lesions* might be treated with surgery and/or radiation therapy according to the literature. Published study results show that local control and survival do not significantly differ between the two modalities. Again, the functional outcome is an important factor to be considered in the decision-making process. Modern surgical applications such as transoral laser surgery have significantly improved surgical treatment and reduced morbidity.[108] Latest investigations demonstrate highly effective surgical treatments with good functional outcome using transoral laser techniques. Grant and colleagues treated 59 patients with primary cancer of the base of tongue, among whom 11 had stage I and II disease. Their locoregional control for the entire patient collective was as high as 88%, and their recurrence-free survival was 84% with excellent postoperative function results measured.[109] Steiner and colleagues reviewed 48 patients, 94% of whom were in stage III and IVA. The Kaplan-Meier 5-year recurrence rate was 20% and overall survival was 52% for T3 and T4 lesions. For T1 and T2 lesions, however, there was no local recurrence after 5 years and overall survival was 73%.[110] New operative systems with even further chances of improvement like the transoral robotic surgery have been shown to be suitable and are under further evaluation.[111] More extensive surgical procedures like transhyoid pharyngotomy or mandibulotomy are commonly reserved for patients with larger lesions. Radiation therapy is often performed as combination of external beam radiation therapy and brachytherapy with an interstitial 192-Iridium implant.[63] Primary radiation therapy ± neck dissection without brachytherapy implant showed varying local control rates between 78% and 96% for T1 and 47% and 88% for T2 lesions.[112-115] Others used external beam radiation in combination with brachytherapy implants and reported local control rates between 71% and 100% for T1 and T2 lesions.[116-118] Houssett and colleagues compared surgery plus adjuvant radiation therapy, external beam radiation therapy plus 192-Iridium implant, and external beam radiation alone on stage T1 and T2 base of tongue carcinoma. They found comparable results for surgery plus adjuvant radiation and external beam radiation plus implant, although external beam radiation therapy alone showed an unacceptable failure rate twice as high as in the other two groups.[113]

Advanced disease of the base of tongue can be managed with two therapeutic strategies, one of which is resection with adjuvant radiation ± concomitant chemotherapy. Advances in oropharyngeal reconstruction in the past 2 decades can ensure good function and improved quality of life even when ending up with large defects of the tongue base and surrounding tissues.[119] Zelefsky and colleagues performed a 7-year follow-up on 51 patients with carcinoma of the tongue base who received surgery and postoperative radiation therapy, most of those with T3 and T4 cancers. Their local control rate was as high as 94% and 75% in patients with T3 and T4 lesions, respectively. The disease-free survival for all patients was 64% after 7 years and the likelihood for distant metastases was 30%.[117,120] Concurrent chemoradiation therapy has been shown to significantly improve local control and disease-free (59% vs. 41%) and overall survival (65% vs. 49%) compared with conventional radiation in a study by the European Organization for the Research and Treatment of Cancer (EORTC) reported by Bernier and colleagues in 2001. Acute toxicity (e.g., mucositis) was higher in the chemoradiation group, although chronic toxicity was comparable.[101] In case of persistent or recurrent disease, surgical and radiotherapeutic modalities were evaluated. One study from 1980 performed by Pradhan and colleagues[121] reported unsatisfying results after aggressive salvage surgery in most cases. However, on the basis of when the study was performed, this investigation contains many negatively affecting components that must be considered. Encouraging results were published by Grant and colleagues in 2006. They investigated patients with recurrent and residual disease showing local control rates of 75% and an overall survival of 54% after 2 years.[122] Other groups have performed after-loading techniques with Iridium-192 in patients treated with radiation therapy ± surgery earlier. One group achieved local control in 59% and actuarial survival of 48%,[123] and others achieved local control of 61% in base of tongue cancer patients.[124] However, residual or recurrent disease of the tongue base remains a demanding therapeutic problem.

As for tonsillar carcinoma, tongue base lesions should be treated with elective, selective, modified radical, or radical *neck dissection,* depending on their clinical stage due to the high propensity of such cancers to lymphatic spread. Clinically negative necks should be treated less extensively to achieve reduced morbidity. Levels considered are II to V for base of tongue SCC. In case of primary chemoradiation therapy the neck is included in the planning, depending on the neck stage. In N2 to N3 disease some authors discuss planned neck dissection after surgery on the basis of the risk for residual occult disease.[125] Cupino and colleagues favored neck dissection before definite primary chemoradiation in stage IV oropharyngeal cancer patients. Their small population of 25 patients had an actuarial locoregional control rate of 88% and an actuarial overall survival rate of 92% after 3 years.[126] Independent from the modality used, the high incidence for bilateral occult or evident lymphatic disease commonly demands bilateral neck treatment.

Oropharyngeal Wall

Early lesions of the oropharyngeal wall can be treated with surgery and/or radiation therapy. Transoral conventional or laser surgery ± radiation therapy has shown to be a valid therapeutic option with low morbidity to the patients. In case of positive nodes surgery is commonly followed by radiation therapy ± chemotherapy. However, definitive radiation therapy is also sometimes used for small oropharyngeal lesions. An early analysis performed at M. D. Anderson Cancer Center showed survival rates of 71% (T1) and 73% (T2) using radiation therapy.[127] In another early study from 1978, Marks and colleagues[128] compared results for patients treated with radiation followed by surgery and those treated with definite radiation alone and found discouraging 17% survival for both groups and high complication rates for the group receiving surgery after radiation.

Most *advanced lesions* of the oropharyngeal wall are treated with surgical resection of the primary, bilateral neck dissection, and postoperative radiation therapy ± chemotherapy. Using modern reconstructive options, acceptable function often can be achieved. A retrospective analysis of posterior pharyngeal wall cancers by Spiro and colleagues[129] showed 5-year survival rates ranging from 15% to 44% depending on tumor staging after surgical treatment with or without radiation therapy. However, in some cases resectability is not given and definitive chemoradiation therapy is applied. Some might use definitive radiation with addition of neck dissection. For posterior wall lesions the close proximity to the spinal cord is challenging for radiation planning and application.[63]

In oropharyngeal wall cancers, lymphatic distribution and spread of disease is of particular concern for the treating physician. Retropharyngeal and parapharyngeal nodes can be difficult to access and likelihood of bilateral spread is high. Therefore in those cancers adjuvant radiation therapy after bilateral *neck dissection* is often indicated. As with all oropharyngeal cancers, the neck should be addressed by neck dissection bilaterally in case of clinically evident disease. In case of a high propensity of contralateral lymphatic spread and clinically negative nodes on this side, radiation therapy without surgery can be considered.

Surgical Approaches

The choice of the adequate surgical approach depends on the location and size of the lesion to be resected. Whereas most oropharyngeal lesions can be approached transorally using adequate surgical devices, some larger lesions or tumors located close to the supraglottic and hypopharyngeal area might require wider exposure using lateral or transhyoid pharyngotomy, mandibula swing, or split approaches. Especially large cancer resections with following flap reconstruction might call for open approaches. In case of neck dissection, the approach selected must be considered when planning the neck incision. However, the surgical approach chosen also depends on the surgeon's experience and preference.

Transoral Approach

Most oropharyngeal lesions can be removed transorally. This is a minimally invasive approach, suitable for most small- and medium-sized lesions and even larger lesions in the upper part of the oropharynx. Necessary exposure can be achieved using the Stierlen (Fig. 100-18), McIver, Kastenbauer (Fig. 100-19), or Dingman mouth gag or endoscopes such as the Kleinsasser or Steiner for laser surgery of tongue base or deeply located lesions (Fig. 100-20).

The laser surgical approach either via microendoscopy or using a laser hand device is an excellent tool for oropharyngeal cancer resection

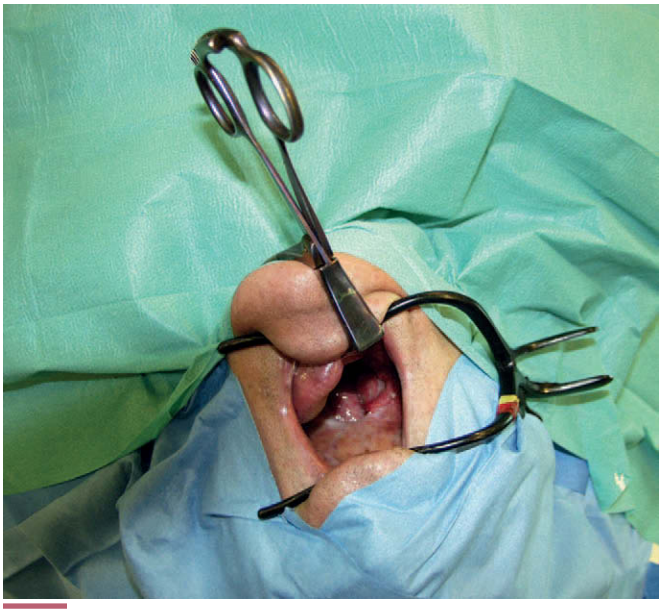

Figure 100-18. Exposure of a recurrent carcinoma of the left soft palate and tonsil using the *Stierlen* mouth gag. Tumor resection was performed, as well as implantation of a radial forearm flap for reconstruction, via this access.

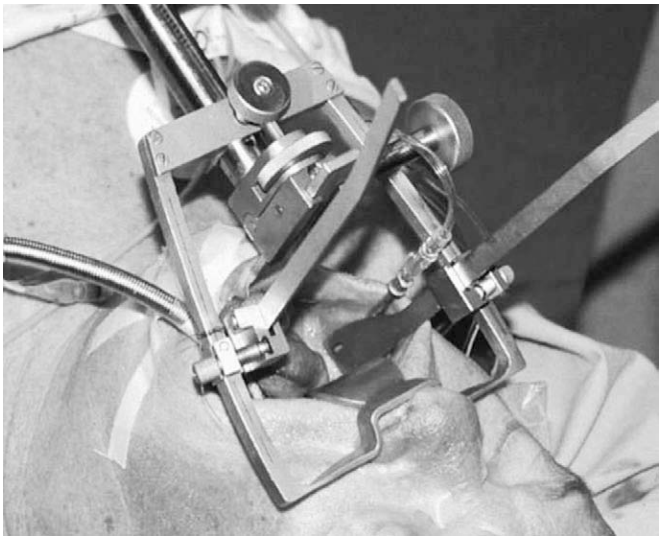

Figure 100-19. Transoral exposure using the *Kastenbauer* mouth gag.

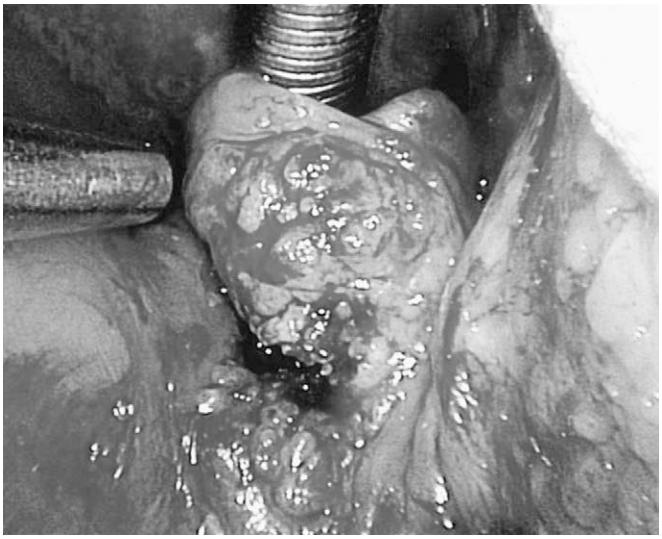

Figure 100-20. Transoral laser resection of a tongue base and epiglottic tumor.

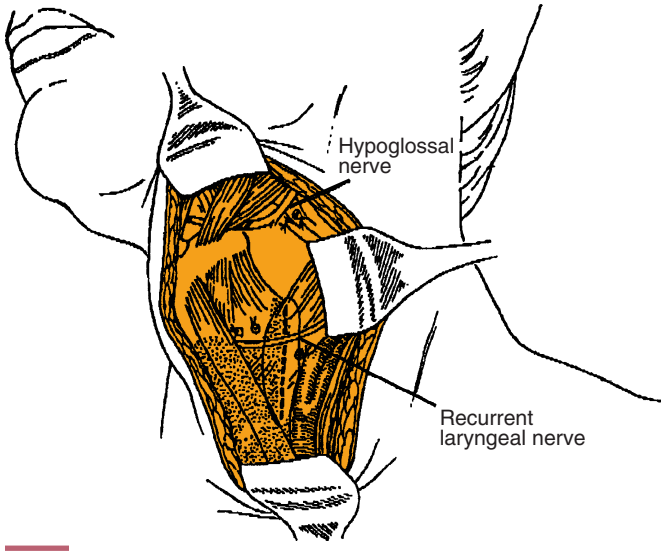

Figure 100-21. The epiglottis and tongue base are exposed through a lateral pharyngotomy approach. *(From Carrau RS. Lateral pharyngotomy. In: Myers EN, ed.* Operative Otolaryngology: Head and Neck Surgery. *Philadelphia: WB Saunders; 1997:242. Used with permission.)*

with minimized morbidity to the patient.[130] Other adequate options are electrocautery and cold knife or scissor. Using the CO_2 laser, lesions of the soft palate, tonsil, pharyngeal wall, and tongue base can be resected (see Fig. 100-20). Depending on the individual skills of each surgeon, larger lesions involving more than one subsite can be resected with the laser. In case of involvement of the lateral pharyngeal wall/tonsillar fossa, depending on the depth of tumor growth, neck dissection should be addressed first. The medial portion of vessels such as the carotid can be easily protected with sponges before transoral laser resection. Laser surgery requirements such as adequate surgical training and local precautions in the entire operating room must be met. Today's laser procedures enable minimal invasive access, reduced blood loss and morbidity, rapid secondary wound healing, and rehabilitation. Yet using electrocautery and scissors might be more suitable in selected cases.

Outcomes using the transoral laser microsurgical approach, both oncologic and functional, have proven to be excellent, even for advanced stage III and IV disease. Haughey and Rich (personal communication) have analyzed a large prospectively registered and followed group of patients (N = 84) presenting at their institution with stage III and IV oropharyngeal cancer. They found 95% locoregional control, 86% disease-free survival at 5 years (with a minimum follow-up of 2 years), and a mean functional outcome swallowing score of 1.4 (0 [best] to 5 [worst]). Feeding tubes were necessary in only six cases, five of which were introduced during postoperative adjuvant radiotherapy.

Lateral and Transhyoid Pharyngotomy

Some inferior lesions might not be accessible transorally or the patient's neck mobility might not allow for reflexion and adequate vision of the lesion. In such cases lateral or transhyoid pharyngotomy can be performed. Those approaches can be combined and variations depend on the location and size of the tumor to be resected. The conventional lateral approach would leave the hypoglossal nerve cranially and the superior laryngeal bundle inferiorly (Fig. 100-21). Attention has to be spent on where to enter the pharynx in order not to cut into tumor tissue. In those cases, preliminary endoscopy can be recommended.

Transhyoid pharyngotomy is achieved by freeing the hyoid from supraglottic musculature and entering the vallecula medially (Fig. 100-22). Again, tumor location has to be considered before entering the pharynx. The lesion is then visualized and thorough resection with adequate distance to the tumor can be performed. Separation of muscle structures like the stylohyoid or digastric muscle can further improve access to the surgical field. Using these approaches, there is no additional skin incision than that for the neck dissection and proper exposure in most cases in avoidance of lip and mandibular splitting. Yet the pharyngotomy can result in fistulas and closure of the pharynx has to be performed thoroughly inverting the mucosa using absorbable sutures.

Mandibular Swing Approach

The mandibular swing approach is commonly reserved for extensive lesions, which also often require reconstructive surgery. The incision of the skin is usually performed through the midline of the lip, followed by a zigzag-shaped line down to the mental fold, around the mentum, and continuing into the neck incision submentally (Fig. 100-23).

The soft tissue and gingiva, as well as the periosteum, are cut and the latter released from the bone only in the area of the mandibular split. Tissue must be handled carefully and later closure of the oral vestibule must be considered. A plate must be prepared to fit the contour of the mandible, and holes should be drilled and sized before mandibular splitting. The course of the dental roots must be considered before positioning the plate. The osteotomy is performed in the midline using an electric saw, although the cranial part of the mandible should be handled with an osteotomy in order of preservation of the roots of

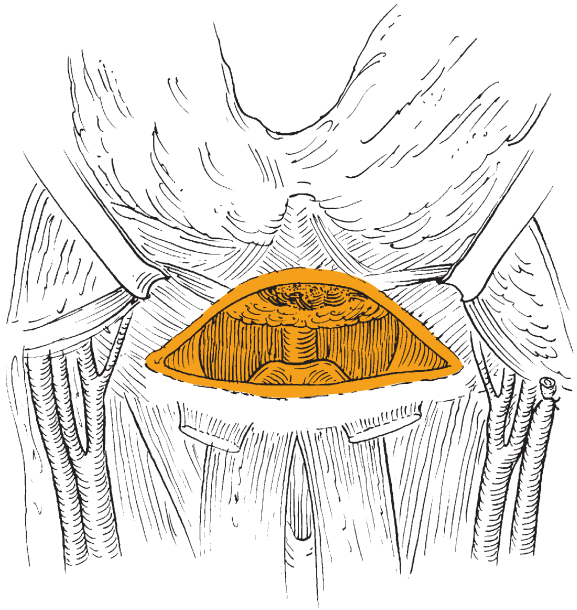

Figure 100-22. The suprahyoid musculature is released from the hyoid bone, and the vallecula is entered.

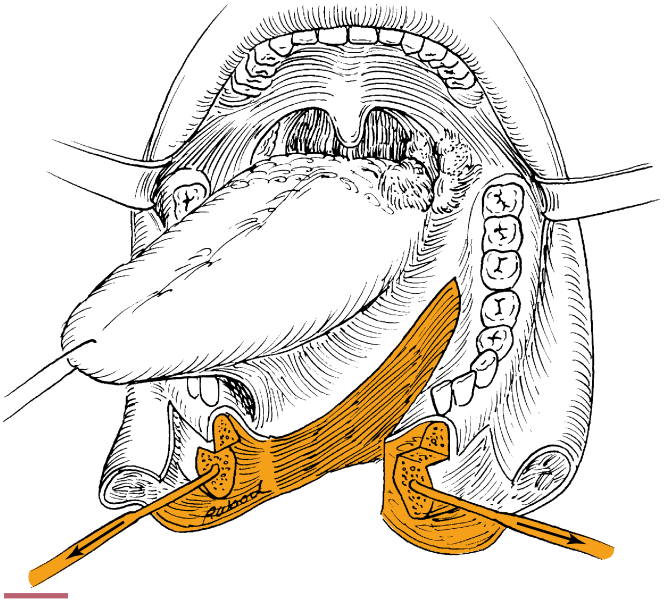

Figure 100-24. Anterior mandibulotomy may be used to expose the oropharynx. Incision along the medial aspect of the mandible is made to obtain posterior exposure. Arrows indicate direction of tissue retraction.

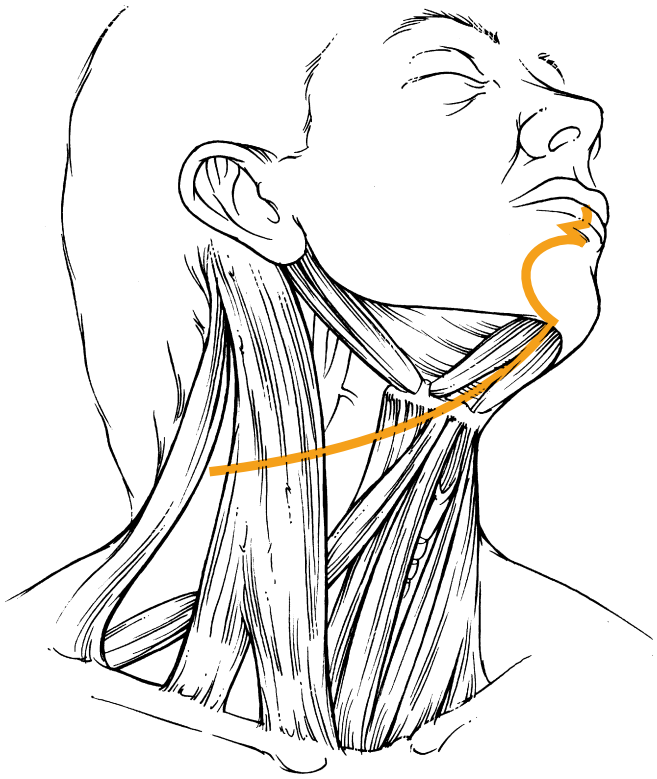

Figure 100-23. Skin incision for mandibular swing approach. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

incisor teeth. The osteotomy can also be performed in a stair-step-like fashion. Then the floor-of-mouth soft tissues are divided and enough tissue must be left laterally toward the mandible for sufficient soft tissue closure with or without tissue transfer for reconstruction (Fig. 100-24). This approach allows the widest access to the oropharynx, although it is the most invasive. However, it might be necessary for extensive tumors and adequate exposure for resection and reconstruction. Other procedures for oropharyngeal access without mandibulotomy via the floor of mouth have been described, although indication seems limited and transoral approach might have been sufficient in the cases described.[131]

Follow-up

As with other head and neck tumors, the impact of follow-up on survival is controversial. However, it seems obvious that thorough follow-up enables early detection of possible recurrence and timely intervention with chances of further disease control. Figure 100-25 presents a suggested concept for the follow-up of oropharyngeal cancer patients. Follow-up schedules should always include the treating physician's judgment about each individual patient's compliance.

Special Treatment Considerations

Data on oropharyngeal cancer treatment remain controversial. The Scottish Intercollegiate Guidelines Network (SIGN) found that randomized controlled trials comparing surgery versus radiotherapy ± chemotherapy for the treatment of primary lesions were unavailable for both early and advanced lesions. This is also true for the treatment of the neck.[132] Although more studies were included in their analysis, the Cochrane Collaboration also criticized the lack of valid evidence for one modality or the other.[77] The assessment of existing literature must include the time frame of the investigation because many surgical and radiotherapeutic, as well as chemotherapeutic applications, have been tremendously modified in the past.

Quality of life has been hardly addressed in the Cochrane literature despite being one of the most important factors for decision making concerning therapy.[77] Selective studies offer quality-of-life assessments, yet scaling systems differ significantly and results are not comparable. Moreover, upcoming investigations should include adverse events and morbidity caused by the applied therapy. It is recommended to clearly separate studies on therapy and outcome on the basis of the exact tumor location respecting the complexity of the different head and neck subsites. Finally, treatment regimen might also be influenced by socioeconomic factors; thus elements such as length of hospital stay and costs should, ideally, be integrated in future studies.

Complications

Complications related to *surgery* may be divided into perioperative and postoperative. Possible perioperative complications include damage to blood vessels and nerves (e.g., cranial nerves V, VII, IX, X, XI, XII). Complications after surgery include fistulas, trismus, aspiration, mus-

Years after treatment	1				2				3		4		5	
Months after treatment	1–3	6	9	12	15	18	12	24	30	36	42	48	54	60
History Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasound of neck		X		X		X		X	X	X		X		X
(PET) CT/MRI		X				X			X					
Chest radiograph/CT		X				X			X		X		X	
Panendoscopy Biopsy	X clinically indicated													

Figure 100-25. Recommended follow-up of oropharyngeal cancer patients.

cular dysfunction (e.g., shoulder mobility), bleeding, pain, dysphagia, and dysarthria, as well as flap loss after reconstruction. Using modern surgical approaches for the primary malignancy, employing laser techniques for selected cases and current free tissue transfer techniques for reconstruction, complications could be strongly reduced compared with earlier studies.

Complications of *radiation therapy* can be acute or chronic in nature and are influenced by concomitant therapy such as surgery and/or chemotherapy, fraction size, and way of fractionation and total dose applied. Acute side effects are commonly mucositis, dysphagia, xerostomia, loss of taste, dental impairment such as caries, pain, skin affections, hair loss, and loss of sebaceous gland functions. Additional late complications may include osteoradionecrosis and affected ability of wound healing in radiated fields. Modern applications such as intensity-modulated radiation therapy (IMRT) and improved technique resulted in reduced complications after radiation, although patients are frequently affected by lasting dysphagia, xerostomia, and altered sense of taste or recurrent mucositis, especially after doses exceeding 60 Gy for definitive treatment.

Prognostic Factors

TNM status, general performance, and gender are known influential factors for prognosis in oropharyngeal cancer patients.[91,133] Aebersold and colleagues[134] found intratumoral microvessel distribution to effect local control and overall survival using definitive radiation therapy with unfavorable high microvessel density. In case of proliferating cell nuclear antigen (PCNA) and vascular endothelial growth factor (VEGF) receptor, no predictive effect was investigated in patients with oropharyngeal cancer independent from the treatment modality used. A high Ki-67 labeling index was found to be linked to a reduced time interval until relapse of disease after surgery and adjuvant radiation.[134-136] Several studies have analyzed the negative impact of anemia on radiation therapy.[133,137] Also, hypoxia measured in lymph node metastases from head and neck cancers reduced the response rate for radiation and chemoradiation therapy.[138-140] Many other molecular markers such as EGFR and DNA-repair enzymes are currently under investigation. Regardless of these tested markers, one of the most important predictive factors seems to be the exposure to exogenous risk factors such as tobacco and alcohol, before and following treatment. Patient compliance must also be considered for future outcome. Different reviews have been performed to explore the effect of delay in commencing postoperative radiotherapy on patient's outcome. Although it remains vague whether outcome is significantly impaired by a delayed postoperative radiotherapy, there is some evidence supporting time intervals between surgery and radiotherapy not to exceed 6 to 8 weeks.[141,142] However, such prognostic factors are important for the evaluation of the ideal treatment modality and must be taken into account in the judgment of outcome in existing clinical studies.

Quality of Life

Quality of life is the major key for judgment of therapeutic success besides evaluation of locoregional control and survival. As mentioned earlier, multiple variants for life quality assessment exist and comparability is low. However, the importance of the issue has tremendously grown for head and neck cancer patients in the past and studies including objective criteria are necessary in order to compare the impact of different treatment modalities on patients' quality of life. In acknowledgement of the problem, the International Classification of Functioning, Disability and Health (ICF) supported by the World Health Organization in 2007 initiated an international consensus meeting on head and neck cancer and developed a core set for this patient group. In future studies, this core set will enable a standardized quality of life assessment for head and neck cancer patients.[143]

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CHAPTER ONE HUNDRED AND ONE

Reconstruction of the Oropharynx

S. Mark Taylor

Bruce H. Haughey

Key Points

- Oropharyngeal reconstruction is complex, but an organized systematic approach using the reconstructive ladder aids the surgeon in the decision-making process. The simplest reconstruction that results in the highest level of function should be chosen.
- The size and location of the oropharyngeal defect combined with patient-related factors such as age and comorbid status determine the reconstructive technique appropriate for each patient.
- Extensive defects of the oropharynx are best reconstructed with a free tissue transfer. The neurotized radial forearm flap remains the flap of choice for these defects.
- Oropharyngeal defects involving 50% or more of the soft palate will result in velopharyngeal insufficiency. The reconstruction should address this by narrowing the caliber of the velopharyngeal aperture.

The complexity of the human upper aerodigestive tract renders oropharyngeal reconstruction one of the most challenging tasks in the field of head and neck surgery. Successful reconstruction requires detailed knowledge of the normal anatomic and physiologic mechanisms of swallowing and velopharyngeal competence that exist in this area, in combination with the surgical expertise and insight to execute various techniques for a multitude of defects. This chapter discusses the various options for reconstruction of oropharyngeal defects and the decision-making process the surgeon must go through when encountering specific defects in this area.

Oropharyngeal reconstruction has gone through several stages in the past 25 years. Reconstruction of this area before the advent of the pectoralis major flap proved difficult and was commonly complicated by wound infection and breakdown. First described in 1979 by Ariyan[1] and Baek,[2] the pectoralis major myocutaneous flap revolutionized head and neck reconstruction at that time and added a new dimension to our reconstructive capability. This was soon followed by the introduction of free tissue transfer with the belief that reconstructions that rendered the patient functionally and esthetically superior could now be performed. These effective reconstructions are even more important as the prognosis for advanced oropharyngeal cancer has improved.[3]

Several factors influence reconstructive decision making. First, one must consider the overall medical condition of the patient, with particular emphasis on comorbidities such as peripheral vascular disease, diabetes, previous radiotherapy, and nutritional insufficiency, because these conditions may adversely affect postoperative wound healing. A detailed medical history should be obtained to determine the patient's ability to tolerate extensive surgery. Severe coronary artery disease, chronic obstructive pulmonary disease, or poor overall functional status or prognosis may preclude a complicated time-consuming reconstruction. Instead, a reliable and more expedient reconstructive technique should be considered. The reconstructive surgeon should have a detailed preoperative discussion with the patient to determine which donor site would be most appropriate given the patient's lifestyle and expectations.

Careful three-dimensional (3D) analysis of the defect is critical at the conclusion of the ablative portion of the case. The size of the primary tumor, specifically the T stage, has been shown to directly correlate with the functional status of the patient in the postoperative period.[4,5] The soft tissue and the bony defect should be determined. The purpose of the soft-tissue reconstruction is to re-establish bulk, sensation, and a re-epithelialized passageway for respiration and deglutination. The dimensions of the defect should be measured with a ruler, or a template of the defect can be fabricated with Esmarch (Microtek Medical, The Netherlands). The subsites of the oropharynx involved should be determined. Although this chapter focuses on oropharyngeal reconstruction, these defects do not exist in isolation. Factors such as laryngeal and mandibular arch preservation must be taken into account before determining the reconstruction of choice. For example, a base of tongue defect in combination with a supraglottic laryngectomy may be best reconstructed with a sensate fasciocutaneous free flap, as opposed to a musculocutaneous flap that cannot be reinnervated. Also, surgeon and hospital factors come into play in the decision-making process. A surgeon will decide on a reconstructive technique on the basis of his or her experience and level of training. Hospital factors include the availability of an intensive care unit experienced in monitoring head and neck patients with free flaps, microsurgical instrumentation, and appropriate paramedical staff for rehabilitation.

Cost has also become a factor in recent times. Managed care has affected most American centers, and more cost-effective methods of reconstruction are often stressed elsewhere. The use of free tissue transfer for oropharyngeal reconstruction has been compared with pedicled soft tissue transfer. These studies have demonstrated that the operative costs are higher in the free flap group; however, the overall costs are lower compared with the pectoralis major flap.[6,7] A more recent study, however, showed no evidence that cost or morbidity differed in the two groups.[8] In other areas where universal health care systems are in place, operative time and long waiting lists may dictate which form of reconstruction is used. All things being equal, however, the most important determining factor should be the resultant quality of life for the patient. The method of reconstruction chosen must give the patient the best chance of re-establishing an oral diet, intelligible speech, and a stable airway without cannulation. It has been shown that quality of life and

functional status can be restored at 6 months after microvascular reconstruction for advanced (T3, T4) oropharyngeal cancers, and most have improved post-treatment scores at 1 year.[9]

Options for Reconstruction

Various reconstructive options are available for defects of the oropharynx. It is helpful for the surgeon to consider the reconstructive ladder and to work through the possible techniques for a given defect (e.g., soft palate versus base of tongue, starting with the simplest and progressing to the more complicated) (Fig. 101-1). The simplest method of reconstruction that achieves the highest level of function should be chosen.

No reconstruction by tissue graft or transfer, i.e., healing by secondary intention, is the simplest form of reconstruction. This is not commonly used for open approaches, given the size and complexity of most oropharyngeal defects; however, both authors have used this as their method of first choice after transoral laser resections of the tonsil and base of tongue, as well as smaller soft palate defects. It is successful even for deep resections extending into the parapharyngeal space. Healing by secondary intention can be used for small defects typically less than 4 to 5 cm, although it is not advisable when the oropharyngeal wound communicates with the neck. The advantage of this method is in its simplicity and the tendency of the granulating bed to mimic the native tissue when fully healed. The main disadvantages are the contracture and tethering that can occur when unopposed surfaces heal. This can be particularly a problem when used for larger resections of the tonsil that are taken down to the parapharyngeal fat pad, and/or forward into the retromolar trigone, mainly because of anterior displacement of the soft palate, resulting in velopharyngeal incompetence. Healing by secondary intention can also be supplemented by the use of a prosthesis for obturating defects of the palate.

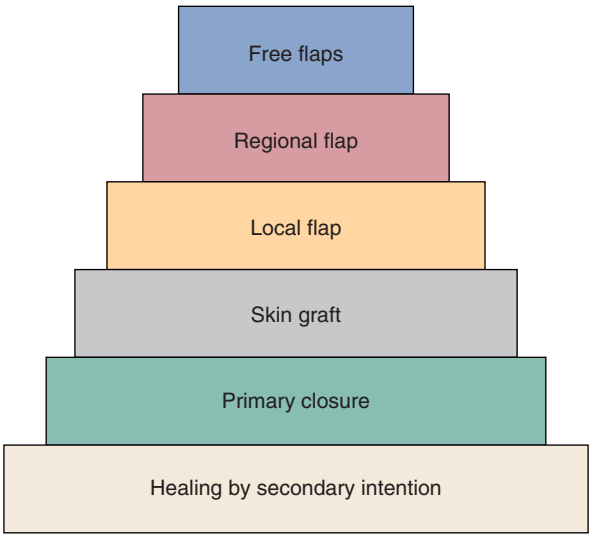

Figure 101-1. A reconstructive ladder is an organized method of working through the various options of reconstructing a defect starting with the simplest and working through to the most sophisticated. Routine use of the ladder will ensure that no possible reconstructive modalities are overlooked.

Primary closure is sometimes possible after surgical ablation of an oropharyngeal tumor. It should only be considered when a tension-free closure is obtained without distortion of the normal anatomy of the region. A prospective case-comparison study by McConnel and colleagues challenged the idea of free and pedicled flap reconstruction of the oral cavity and base of tongue. They concluded that speech and swallowing are superior with primary closure for defects of 60% or less of the tongue base.[10] Although there are inherent flaws in the study and the defects addressed were small, their findings bring to light the need for objective research on reconstructive efforts of the oropharynx and its effect on speech and swallowing.

Skin grafts can be used effectively for small defects of the posterior pharyngeal wall that are not amenable to primary closure. A bolster dressing is used to decrease shearing forces on the graft, and a tracheotomy should usually be performed in conjunction with this. Skin grafting can also be used in combination with healing by secondary intention. The graft is used in critical areas such as the glossotonsillar sulcus to decrease contracture formation and to maintain tongue mobility.

Local Flaps

Local flaps have not gained popularity for oropharyngeal reconstruction. Tongue flaps are of historical interest and are mentioned here only to be discouraged. The flap is performed by dividing the anterior tongue and then rotating it posteriorly into the surgical defect. It is clear that the use of this flap leads to restriction in the mobility of the remaining tongue and leads to impaired oral and oropharyngeal function.[11,12]

By comparison, the palatal island flap does have a role in oropharyngeal reconstruction.[13] The flap is composed of hard palatal mucoperiosteum and is based on a single greater palatine artery (Fig. 101-2). It is performed by sharply incising the mucoperiosteum of the hard palate approximately 1 cm medial to the maxillary alveolus. A periosteal

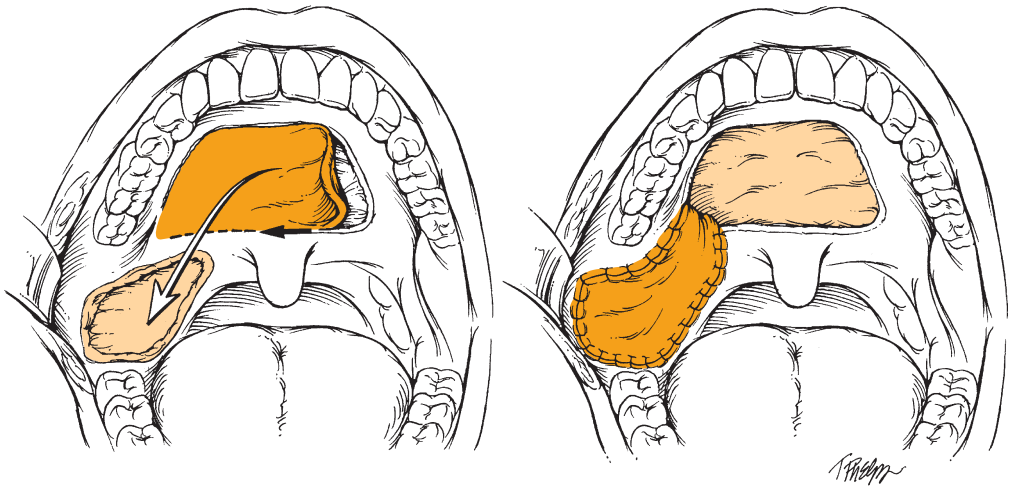

Figure 101-2. The palatal island flap consists of hard palatal mucoperiosteum pedicled on a single greater palatine pedicle. It is ideal for reconstructing limited defects of the soft palate, tonsil, and retromolar trigone. *(Adapted from Gullane PJ, Arena S. Palatal island flap for reconstruction of oral defects.* Arch Otolaryngol. *1977;103:598.)*

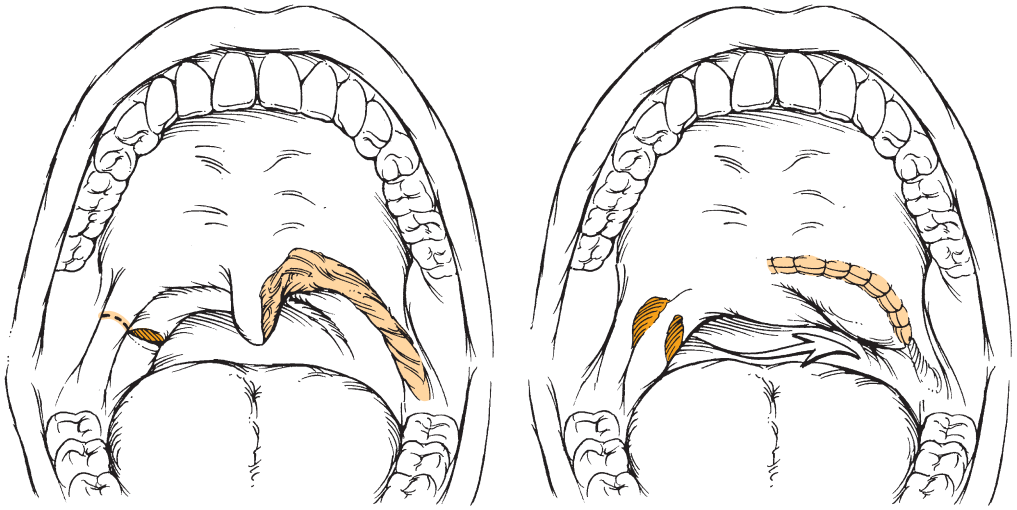

Figure 101-3. Uvulopalatal flap. Lateral defects of the soft palate are amenable to reconstruction with this technique. The flap consists of the uvular remnant that is transposed into the defect after a releasing incision is made in the contralateral tonsillar pillars. Most of the uvula and the contralateral soft palate must be intact for this flap to be used. *(Adapted from Gillespie MR, Eisele DW. The uvulopalatal flap for reconstruction of the soft palate.* Laryngoscope. *2000;110:613.)*

elevator is then used to elevate the flap, and the base is narrowed accordingly. The hard palate is left to remucosalize. The flap provides thin but relatively nonpliable tissue for reconstruction.

The uvulopalatal flap can be used for limited lateral soft palatal defects.[14] Most of the uvula and the contralateral soft palate must be intact for this flap to be used. The uvula is denuded of its mucosa and is then rotated into the defect (Fig. 101-3). A releasing incision is made in the contralateral anterior and posterior tonsillar pillars to increase the arc of rotation. Other local flaps such as inferior and superior pharyngeal flaps, the superior-constrictor advancement-rotation flap (SCARF), and the buccinator myomucosal flap, should also be considered as local flap options for palatal defects,[15,16] but all must be measured against the gold standard procedure for through-and-through defects, which is the folded radial forearm flap.

Regional Flaps

Before the advent of free tissue transfer, oropharyngeal reconstruction was most commonly performed with regional flaps. Currently, these flaps remain an excellent option for selected defects of the oropharynx because they are reliable and relatively easy to harvest. The pectoralis major flap has served as the workhorse of head and neck reconstruction for more than 2 decades (Fig. 101-4). The flap is based on the thoracoacromial artery, which originates from the second part of the axillary artery. It passes medial to the pectoralis minor and courses on the undersurface of the pectoralis major muscle. The lateral thoracic artery may contribute to the blood supply of the flap as well.[17] The flap can be used as a myocutaneous or a myofascial transfer.[18] The bulk of the flap can make it difficult to fold into a complex oropharyngeal defect, and this flap is therefore not the technique of choice at most centers.

The platysma myocutaneous flap was initially proposed for oropharyngeal reconstruction in 1978.[19] The flap has not gained wide acceptance in the literature, and many believe it is an underused technique for head and neck reconstruction (Fig. 101-5). Koch[20] reported on 34 patients who had this flap performed for head and neck defects. Postoperative fistula formation was noted in five patients (15%), and flap desquamation was seen in six cases (18%). Donor site complications were rare, with two cases developing distal skin loss at the closure site. Complications were not related to previous radiation. The platysma myocutaneous flap is based on the submental branch of the facial artery. Ligation of the facial artery during neck dissection does not compromise the blood supply to the flap.[12,21] The flap can be harvested in 20 to 30 minutes and can be done with or without a neck dissection. It provides a thin, pliable skin paddle that is ideal for oropharyngeal reconstruction. The main disadvantage cited in the literature is the

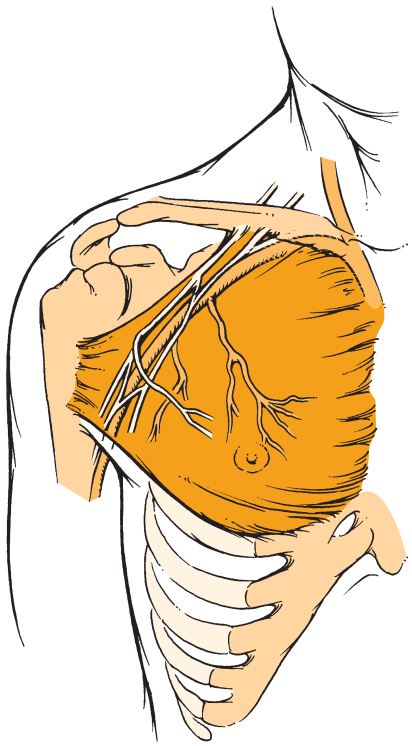

Figure 101-4. Pectoralis major flap. This flap is supplied mainly by the thoracoacromial artery, but the lateral thoracic artery also contributes to the blood supply. The lateral and medial pectoral nerves provide motor supply to the muscle. The flap has been described as the "workhorse" flap in head and neck reconstruction because of its reliability, hardiness, and versatility. *(Adapted from Urken ML, Cheney ML, Sullivan MJ, et al.* Atlas of Regional and Free Flaps for Head and Neck Reconstruction. *New York: Raven Press; 1995:16.)*

reliability of the flap because flap-related complication rates have been reported to be as high as 40%.[22]

The temporal area provides two regional flaps for oropharyngeal reconstruction. The temporoparietal fascial flap provides thin, highly vascular tissue for reconstruction.[23] Its blood supply is based on the superficial temporal artery and vein. It can be used either as a pedicled

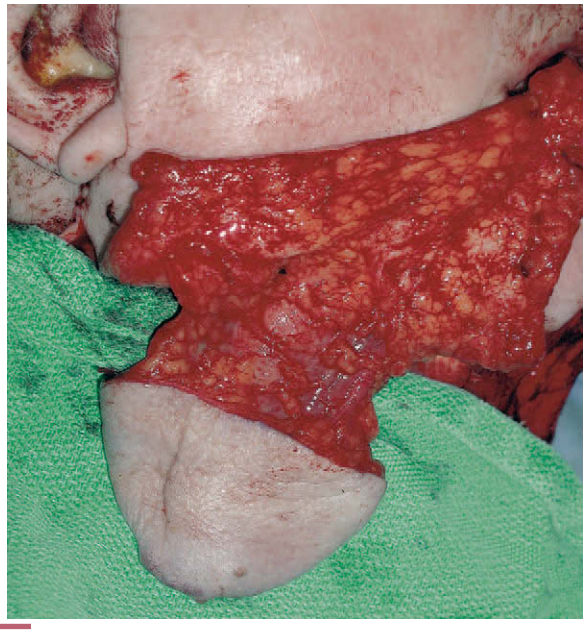

Figure 101-5. Elevation of a platysma myocutaneous flap. Note the presence of subcutaneous fat on the anterior surface of the platysma muscle in keeping with meticulous elevation of a subdermal/supraplatysmal superior skin flap. This is done along with a standard subplatysmal dissection to free the muscle and allow transposition into the defect.

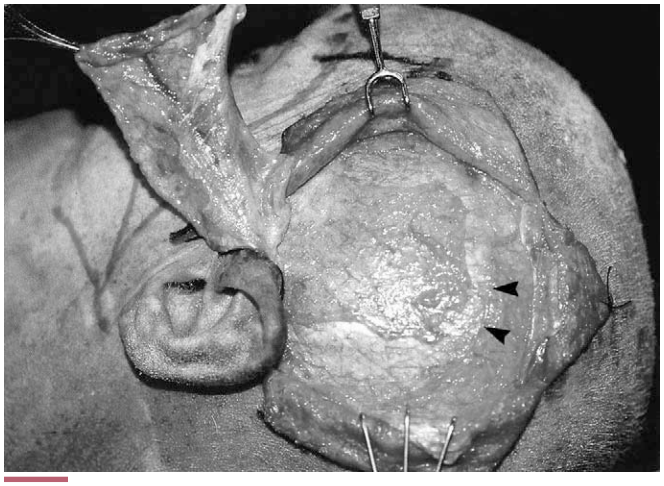

Figure 101-6. Temporoparietal flap. This flap provides thin highly vascularized tissue for reconstruction of defects of the superior oropharynx. The harvest may be extended to the vertex of the scalp or carried to the contralateral side if needed to increase flap length. It may also be used as a free tissue transfer if required. *(From Urken ML, Cheney ML, Sullivan MI, et al.* Atlas of Regional and Free Flaps for Head and Neck Reconstruction. *New York: Raven Press; 1995:207).*

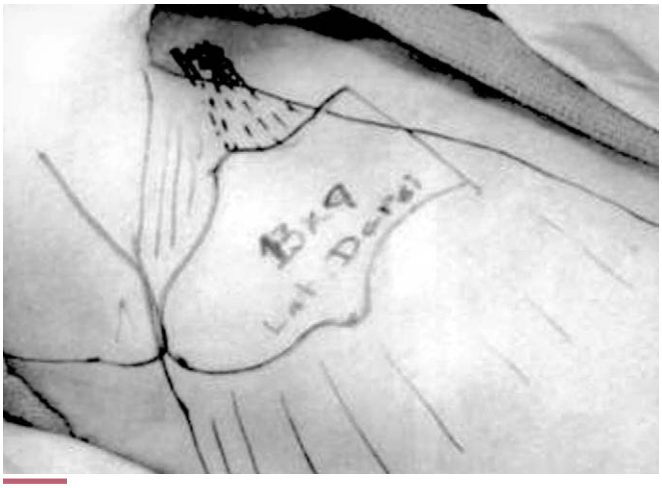

Figure 101-7. The anatomy of the latissimus dorsi muscle is shown in this patient who is in the right lateral decubitus position. The anterior limit of the muscle extends from the midaxillary line to the anterior superior iliac spine, whereas the posterior limit extends approximately 2 cm above the scapular tip. The neurovascular pedicle is shown and is usually located 8 to 10 cm from the midaxilla along the anterior border of the muscle. The skin paddle depicted demonstrates our flap design for total glossectomy defects where the skin paddle is oriented transverse to the underlying muscle. *(From Haughey B. Tongue reconstruction: concepts and practice.* Laryngoscope. *1993;103:1133.)*

or free tissue transfer if this is required to enhance inset of the flap. An outer table calvarial bone graft superior to the temporal line may also be harvested with the flap.[24] Identification of the vascular pedicle by Doppler ultrasonography is done at the initiation of the harvest. A preauricular incision is then made and is carried superiorly through the temporal scalp and can be extended to or above the vertex if necessary (Fig. 101-6). The dissection is begun superiorly just deep to the hair follicles. Care must be taken when dissecting the anterior branch of the artery because this is accompanied by the frontal branch of the facial nerve. The fascia is then divided by carrying the dissection to the level of the superficial layer of the deep temporal fascia. It is then narrowed inferiorly; at this point the anterior branch of the artery is divided close to the origin of the posterior branch of the superficial temporal artery, being aware of the facial nerve. The flap is then tunneled into the oropharynx and is sutured into the defect. A skin graft may be used on the flap but is not necessary because the surface of the flap will remucosalize. Similarly, the temporalis muscle can be tunneled into the oropharynx after removal of the zygomatic arch, which is later replaced. It is less commonly used than the temporoparietal flap because of its added bulk, limited arc of rotation, and difficult tunneling into the defect, although in experienced hands and with a fascial extension it has proved useful in soft palate and pharyngeal wall defects.[25]

The latissimus dorsi musculocutaneous flap is another viable option for reconstructing oropharyngeal defects.[26,27] It can be used either as a pedicled or free flap, especially for total glossectomy defects (Fig. 101-7). The flap is based on the thoracodorsal artery, which is a branch of the subscapular system of vessels. The subscapular artery arises from the third part of the axillary artery. The latissimus muscle arises from the thoracolumbar fascia, the lower six thoracic vertebrae, and the iliac crest and inserts onto the medial surface of the humerus. Several musculocutaneous perforators supply the overlying skin and are more abundant in the upper two thirds of the muscle. The flap is harvested by first incising the lateral aspect of the skin paddle and then extending this superiorly following the lateral border of the muscle into an axillary crease. The pedicle is found along the lateral border of the muscle 8 to 10 cm from the midpoint of the axilla. The medial skin paddle incision is next fashioned, and tacking sutures are placed between the skin and underlying muscle. The muscle is then divided distally and medially, and the pedicle is traced into the axilla after identifying and dividing the branch to the serratus anterior. Finally, the superior muscle cut is made protecting the vascular pedicle. If the flap is to be used as a pedicled transfer, a tunnel is made above or below the pectoralis major muscle. We have had success with a tunnel above the muscle in combination with a partial-thickness myotomy of the lateral aspect of the pectoralis major.

Less commonly, the trapezius musculocutaneous flap may be used. It is generally not a good option because trapezius muscle sacrifice leads to significant shoulder dysfunction and chronic pain. Other factors that make it an unpopular choice are the flap's limited arc of rotation and

Figure 101-8. The forearm flap is the most commonly used free flap for oropharyngeal reconstruction. The flap provides thin pliable tissue that is ideal for this purpose. We harvest the flap with a cuff of soft tissue around the pedicle to prevent kinking and also routinely incorporate the deep and superficial venous systems by preserving the communicating branch between the two.

need for patient repositioning in the lateral decubitus position. By comparison, the longus colli muscle flap can be used to reconstruct defects of the lateral and posterior pharyngeal wall.[28] There have been reports on 13 patients who had pharyngeal reconstruction with this regional technique with no postoperative fistulas. The flap is reported to have minimal, if any, donor site complications; however, three patients had postoperative Horner's syndrome, and there is a question as to whether this was related to the ablation of high pharyngeal wall tumors as opposed to a flap-related problem. Experience with the longus colli flap is limited, and more evidence is necessary before the flap can be championed for oropharyngeal reconstruction.

Free Tissue Transfer

The introduction of free tissue transfer has been the greatest advance in the area of oropharyngeal reconstruction. This technique is available at most tertiary care centers. As stated previously, reconstructive advances have not changed the prognosis for oropharyngeal cancer.[3] Quality of life and postoperative function are then paramount when deciding on reconstructive efforts. Free flap reconstruction has been found to be superior from a functional standpoint in both prospective and retrospective studies.[7,9] In the following sections, commonly used free flaps from their respective donor tissues are outlined, and details of their use are addressed.

Fasciocutaneous

The radial forearm flap is the most commonly used free flap for oropharyngeal reconstruction (Fig. 101-8). The flap was initially described in the Chinese literature. The flap is based on the radial artery and the accompanying paired venae comitantes. The cephalic vein is also routinely incorporated into the flap and serves as the superficial venous drainage system. The lateral antebrachial cutaneous nerve provides sensation to the forearm skin, and the flap can be successfully neurotized to improve pharyngeal sensation.[29] Sensory recovery is also present in most patients even when a neural anastomosis is not performed, and more commonly occurs in fasciocutaneous flaps than musculocutaneous flaps.[30] This reinnervation is, however, often incomplete and unpredictable, and it is not valid to rely on spontaneous sensory recovery of free flaps in oral and oropharyngeal reconstruction.[31] The skin paddle of the forearm flap is thin and pliable and thus makes it ideal for a variety of oropharyngeal defects. In fact, because of its thinness it can be used for reconstruction of large defects after transoral resections, inset through the mouth albeit with greater technical difficulty. It can be elevated either deep or superficial to the investing fascia of the forearm, depending on the bulk required. A preoperative Allen test should be performed on all patients. The flap is elevated under tourniquet control. The skin paddle is incised along its ulnar, distal, and radial aspect. The flap is then elevated at the desired level, preserving the sensory branches of the radial nerve. The level of dissection is taken to the subfascial level as the pedicle is approached. The pedicle is then identified between the medial head of the brachioradialis and the flexor carpi radialis and is then divided. A lazy S-shaped incision is fashioned into the antecubital fossa, and the cephalic vein is incorporated into the flap, leaving a generous cuff of fat and fascia to prevent kinking. An external skin monitor can be incorporated into the flap proximally if the main skin paddle is not visible for evaluation.[32] The radial artery is dissected to its origin and is divided distal to the radial recurrent artery. We routinely incorporate the deep and superficial venous systems and generally have two veins for performing venous anastomoses. The donor site is covered with a split-thickness skin graft, and a bolster and cast is left in place for 1 week.

The lateral thigh free flap is another commonly used fasciocutaneous flap for oropharyngeal reconstruction. It was first described by Baek[33] in 1983 and has since been used extensively in the head and neck with excellent results. Hayden[34] reported a 98% success rate in 43 pharyngeal reconstructions, of which 11 were used in the oropharynx. The flap is usually based on the third perforator of the profunda femoris artery, which terminates in the intermuscular septum between the long head of the biceps femoris and the vastus lateralis. Occasionally, the second or fourth perforator will serve as the dominant blood supply to the flap. The lateral femoral cutaneous nerve provides sensation to the skin of the lateral thigh and may be incorporated into the flap. The flap is typically harvested as an ellipse of skin whose epicenter is based on the midpoint of the intermuscular septum between the greater trochanter and the lateral epicondyle of the femur. The dominant perforator is identified in the subcutaneous plane and is then traced through the biceps femoris to the main pedicle. Release of the adductor magnus from the linea aspera assists dissection of the main pedicle, which is divided distal to the origin of the dominant perforator and is then dissected proximally, where its diameter is usually 2 to 5 mm. Paired venae comitantes serve as the venous drainage of the flap. These veins typically converge before entering the deep femoral vein, and this vein ranges in size from 3 to 5 mm. The advantages of this flap are the ability to close the donor site primarily and the relative separation between the ablative site and the donor site, which tends to assist a simultaneous harvest. The disadvantages of the flap are the prevalence of atherosclerosis in the donor artery and the variability of the donor perforators to the skin paddle.

The anterolateral thigh flap has gained recent popularity in head and neck reconstruction and is now more commonly used than the lateral thigh flap. It was first described by Song and colleagues in 1984 and has been used extensively in Asia ever since.[35] The flap is most often supplied by perforating vessels arising from the descending branch of the lateral circumflex femoral artery. This artery courses in the intramuscular space between the vastus lateralis and rectus femoris muscles and provides musculocutaneous and septocutaneous perforators to the overlying skin of the anterolateral thigh. The flap can be harvested as a subcutaneous, fasciocutaneous, myocutaneous (a portion of the vastus lateralis muscle may be incorporated for ease of harvest or to increase bulk), or adipofascial flap, giving this flap the required versatility for reconstructing a variety of head and neck defects.[36] The advantages of this flap are its versatility, as mentioned previously, a potentially long vascular pedicle (16 cm) of excellent caliber (2 to 3 mm), low donor site morbidity, and the ability to harvest the flap simultaneously with an ablative team. The main disadvantage relates to the variations in the vascular pedicle, which may exist at the time of harvest.[36] Also, with the incidence of obesity in Western countries the flap donor is bulkier; thus the flap has not gained widespread use in North America[37] and is usually too thick for base of tongue or palatal reconstruction. Wei and colleagues reported on their experience with 475 anterolateral thigh free flaps used for defects of the head and neck.[38] The overall flap survival rate was approximately 95%. The authors concluded that the thigh flap has potential in many Asian patients because it is as thin as the forearm flap and has essentially replaced the forearm flap at their center.

The lateral arm flap was described by Song in 1982 and was specifically applied to head and neck reconstruction by Sullivan 1 decade later.[39,40] Civantos[41] reported on the use of this flap in 28 head and neck defects, of which 14 encompassed the oropharynx. The flap success rate in this series was 100%. The authors concluded that this

flap is ideal for oropharyngeal reconstruction because it incorporates thin skin from the proximal forearm, which is ideal for reconstructing the pharyngeal wall, and thick skin from the upper arm, which can be used in the tongue base where additional bulk is sometimes required. The flap is supplied by the posterior radial collateral artery, which is a terminal branch of the profunda brachi artery. It courses in the lateral intermuscular septum between the triceps posteriorly and the brachialis and brachioradialis anteriorly. Sensation to the flap is provided by the posterior cutaneous nerve of the arm. The flap is harvested from the nondominant arm without the use of a tourniquet. The desired skin paddle is based on the lateral intermuscular septum that topographically is located between the lateral epicondyle and the V-shaped insertion of the deltoid on the humerus. The flap can also be extended distally over the upper forearm to achieve additional pedicle length. The pedicle is identified between the previously described muscles and is divided distally. The radial nerve is identified along the anterior aspect of the pedicle and is preserved, dissecting free the posterior cutaneous nerve of the arm. The deltoid is released, and the radial nerve and pedicle are followed into the spiral groove. The pedicle is then divided at this point. Wide undermining of the skin is performed, allowing for primary closure of the donor site in most cases. The main advantage of this flap is that the feeding vessels are terminal and nonessential for perfusion of the arm. Also, the donor site may be closed primarily and may be more aesthetically pleasing than the forearm flap. The disadvantages of the lateral arm flap are the risk to the radial nerve and the relatively small caliber of the donor vessels.

Visceral Tissue Free Flaps

Jejunum, gastric wall, and colon are sources of free tissue that have been described in oropharyngeal reconstruction. The jejunum and colon segments are split along their antimesenteric borders to form a flat patch. Examples of split jejunum used for palatal reconstruction are seen in Figures 101-9 and 101-10.

Musculocutaneous Flaps

The latissimus dorsi myocutaneous free flap is our flap of choice in this category. The anatomy of the flap and the technique of harvest have been described previously in the regional flap section. The authors have found this flap most useful after total glossectomy. One of the authors (BHH) has described a useful technique of using an innervated latissimus myocutaneous free flap for reconstructing total glossectomy defects.[42] The skin paddle is designed at a right angle to the course of the underlying muscle (see Fig. 101-7). The muscle is inset as a transverse sling on the undersurface of the mandible by suturing it to the remnant of the pterygoid, masseter, or superior constrictor, depending on what is available. The thoracodorsal nerve is then anastomosed to a suitable hypoglossal nerve, usually ipsilateral to the microvascular anastomoses. This gives the reconstructed tongue the ability to elevate superiorly toward the palate, thus enhancing the swallowing mechanism.

The rectus abdominis free flap is another viable option for selected defects of the oropharynx. It, too, has been used extensively for total glossectomy defects,[43-45] although it lacks the potential for convenient motor reinnervation. The flap is based on the deep inferior epigastric artery and vein, which provide several myocutaneous perforators that traverse the rectus muscle and terminate in the periumbilical skin. The skin paddle is designed with its epicenter above and lateral to the umbilicus because myocutaneous perforators are more abundant in this area. The superior portion of the skin paddle is incised, and the dissection is taken through the anterior rectus sheath to the underlying muscle. The fascia is then split vertically above the skin paddle to the costal margin. The lateral and inferior portions of the skin paddle are next incised, and the dissection is once again taken to the fascial level. A small cuff of anterior rectus fascia is preserved medially and laterally, taking care not to disrupt the cutaneous perforators. The fascia is then split vertically down to the pubic region. The rectus muscle is divided superiorly, taking care to ligate the superior pedicle. The muscle is then dissected free from the posterior rectus sheath, and the dissection is then taken below the arcuate line, noting that the posterior rectus sheath is absent below this level. The vascular pedicle is identified below the arcuate line along the lateral deep aspect of the muscle. The inferior portion of the muscle is divided after a tunnel is made between the pedicle and the overlying muscle. The pedicle is then dissected inferiorly to its origin off the external iliac system. The anterior rectus sheath is reconstructed with a patch of Gore-Tex or Mersilene mesh, whereas the cutaneous defect is closed primarily after wide undermining of the abdominal skin. The flap is highly reliable in the head and neck. A review of 73 flaps used in the head and neck revealed only one flap failure.[46] The vascular pedicle is long and of excellent caliber. The flap can be easily harvested and can be performed simultaneously with the ablative team. The main disadvantage of this flap is the donor site morbidity, progressive flap muscle atrophy, and the chance of abdominal wall herniation.

Osteocutaneous

Free osteocutaneous flaps are not generally used in isolated defects of the oropharynx. However, as stated previously, these defects often accompany other sites in the head and neck. These flaps are commonly used for extensive mandibular defects that extend to the central segment of the mandible or that portion anterior to the mental foramen. Our flap of choice for anterior mandibular defects has been the fibular osteocutaneous flap. Other widely used flaps for this purpose are the iliac crest and scapular flap. These defects are not addressed in this chapter. Lateral mandibular defects, however, are commonly found in combination with oropharyngeal defects, particularly in the case of retromolar trigone primary tumors. These mandibular defects are effectively reconstructed with a soft tissue flap with or without a mandibular reconstruction plate. A recent study at the M. D. Anderson Cancer Center specifically addressed posterior mandibular defects reconstructed with vascularized bone compared with those reconstructed with a free soft-tissue flap.[47] They report that vascularized bony reconstruction of posterior mandibular defects results in superior speech, diet, and midline symmetry. The rectus abdominis free flap was used in 75% of the soft tissue reconstructions, which may have provided too

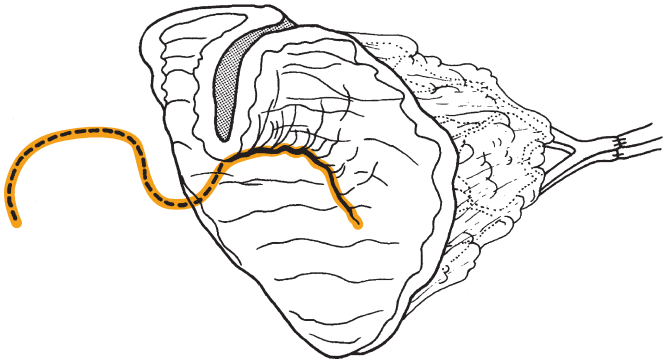

Figure 101-9. Split jejunal flap plicated to form oropharyngeal patch for posterior wall, left lateral wall, and left hemipalate. (From Haughey BH. The jejunal free flap in oral cavity and pharyngeal reconstruction. *Otolaryngol Clin North Am.* 1994;27:1159-1170.)

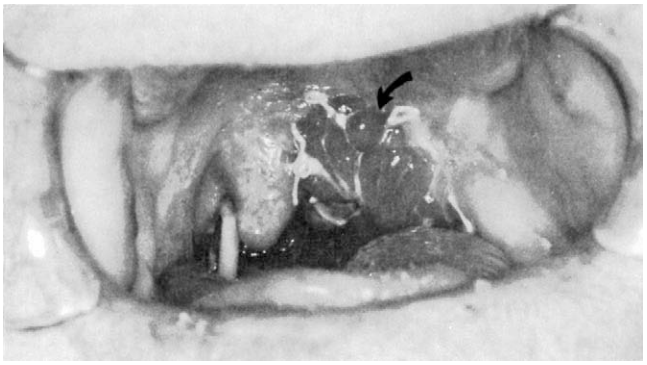

Figure 101-10. Palate and pharyngeal wall reconstruction 2 days postoperatively. *Arrow* depicts jejunal tissue. (From Haughey BH. The jejunal free flap in oral cavity and pharyngeal reconstruction. *Otolaryngol Clin North Am.* 1994;27:1159-1170.)

much bulk for adequate function. Also, the group failed to perform detailed analysis of the oropharyngeal portion of the defect and the radiation protocols used on the cohort of patients. The authors' preference has been to reconstruct all defects of the pharynx with a single flap.[48] Several others, however, recommend using a free bone flap for mandibular reconstruction in combination with a soft tissue flap for reconstructing the remainder of the defect.

Site-Specific Defects

Soft Palate

The soft palate is critical for velopharyngeal competence because it serves as a dynamic muscular structure to effectively separate the oral and nasal passageways. Ablative surgery to the area may result in hypernasal speech, with obvious air escape or nasal regurgitation of food with swallowing. These problems can be greatly improved with functional palatal reconstruction. The goals of palatal reconstruction are to recreate a functional myomucosal velum and to establish closure of the oronasal communication.[49] Several options are available for palatal reconstruction including the use of local, regional, and free flaps. Also, more conservative methods such as the use of a palatal prosthesis may be considered. Primary closure and healing by secondary intention are rarely indicated but may be considered when a marginal resection of the soft palate is performed and the muscular raphe of the palate is not violated. Skin grafting of soft palatal defects is of little use because it does not adequately reestablish the bulk necessary for through-and-through palatal defects, therefore leading to contracture and palatal dysfunction. We suggest referring to the reconstructive ladder for all defects of the oropharynx.

Prosthetic obturation is the traditional means of reconstructing palatal defects. It is available at most academic centers and is usually performed by a maxillofacial prosthodontist. It remains the method of choice for defects of the hard palate.[50] A prosthesis can also be used effectively to obturate a combined defect of the hard and soft palate or a total soft palate defect. Isolated defects of the soft palate, however, are among the most difficult to treat with a prosthesis.[51] Prosthetic rehabilitation of soft palatal defects is often functionally inferior because the prosthesis lacks the dynamic capability of the native palate.[52] Also, the prosthesis may irritate the remnant palate and result in patient discomfort and the need for multiple adjustments. Yoshida and colleagues[53] compared surgical and prosthetic reconstruction for speech disorders after ablative surgery of the soft palate. All surgical reconstructions were performed with a free radial forearm flap. They concluded that defects extending into the posterior edge of the soft palate are best reconstructed surgically because they believe patients achieve better restoration of speech and function. In cases in which a posterior band of soft palate remained, half of the patients reconstructed with an obturator had excellent restoration as tested by a standard speech intelligibility score.

If the decision is made to obturate a defect, preoperative impressions of the palate are made and the initial obturator is fabricated on the basis of the planned area of resection. The obturator is positioned in the operating room with the patient under general anesthesia after frozen section analysis of the margins has been completed, and negative margins are confirmed. The obturator can be fixated to existing teeth if available. Edentulous patients can have an upper denture made with a palatal extension to fill the defect. Patients can resume an oral diet immediately after surgery, and hospital stay is generally short. Often a subsequent interim prosthesis and finally a permanent prosthesis must be made to maximize function as the wound contracts.

Local flaps are an excellent option for reconstructing soft palatal defects in cases in which less than 50% of the palate has been resected. The uvulopalatal flap has been used successfully for marginal defects of the posterior soft palate. The uvula and contralateral soft palate must be intact for this flap to be used (see Fig. 101-3). Zohar and colleagues[49] first reported on the use of this flap in five patients to close small to moderate defects of the lateral soft palate. None of the patients had evidence of velopharyngeal insufficiency postoperatively. Zohar and colleagues concluded that the uvulopalatal flap is a technically simple technique without significant donor site morbidity and satisfies the two goals of soft palatal reconstruction. More recently, Gillespie and Eisele[14] reported on 18 patients in whom the uvulopalatal flap was used for soft palatal reconstruction. A total of 11 patients had the flap used alone, whereas the flap was used in combination with a free radial forearm flap, pectoralis major flap, and a skin graft in four, two, and one patients, respectively. All flaps survived. One flap partially dehisced but healed uneventfully. Of the 11 patients who had reconstructions with the flap alone, nine had normal speech, whereas two had mild hypernasal speech. All patients with T1 tumors had normal speech (six of six). The remaining five patients had T2 lesions. By comparison, all six patients with T1 tumors had no evidence of dysphagia, whereas 40% (two of five) of the patients with T2 tumors had dysphagia requiring G-tube alimentation. The authors concluded that postoperative speech and swallowing function depends on initial tumor stage and the extent of the resection and that the uvulopalatal flap is an effective method of soft palate reconstruction either alone or in combination with other methods of reconstruction for selected oropharyngeal defects. We have used the uvulopalatal flap successfully in our practices. One of the authors (SMT) has used this flap in combination with the platysmal myocutaneous flap for tumors of the retromolar trigone. The uvulopalatal flap is used for the soft palatal defect, and the platysmal flap is used for the lateral pharyngeal and retromolar trigone reconstruction.

The buccinator musculomucosal flap is another option for limited defects of the soft palate. Originally used in cleft palate repair and for closure of septal perforations, the buccinator musculomucosal flap has been relatively overlooked in the otolaryngologic literature. The flap was originally described by Bozola and colleagues,[54] and the vascularity of the flap was defined. The maximal flap size available is 7 cm in length by 4 cm in width. The flap is elevated in an anterior to posterior direction. Care is taken to stay 3 to 5 mm below the opening of Stensen's duct and 1 cm posterior to the oral commissure. The buccal mucosa and the buccinator muscle are incised, and the dissection is taken to the level of the buccopharyngeal fascia. Posteriorly the buccal artery, which serves as the feeding vessel, and buccinator nerve are identified and preserved (Fig. 101-11). The flap is transposed into the defect, and the donor site is closed primarily. A recent article reported on eight patients who had this flap used for reconstructing defects of the soft palate, retromolar trigone, and oral cavity.[15] The distal 3 mm of one flap underwent necrosis; however, this patient had had previous surgery at the site and was treated with radiotherapy after the initial surgery. The wound was débrided and healed uneventfully by secondary intention. Two of the eight patients had soft palatal reconstructions, and

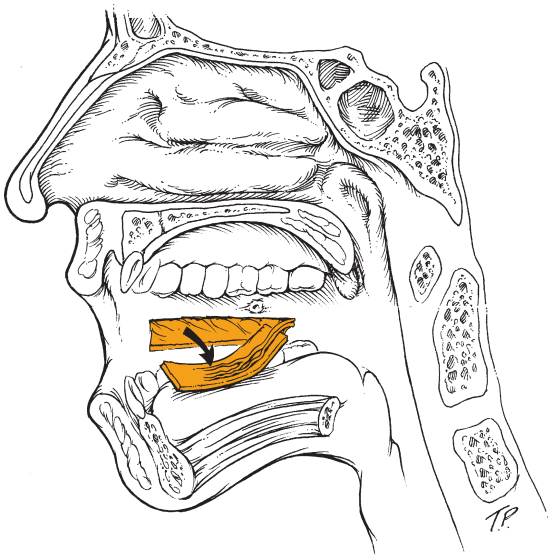

Figure 101-11. Buccinator musculomucosal flap. This demonstrates the design and anatomy of the flap. Note the proximity of the flap to the parotid duct and the oral commissure. *(Adapted from Licameli GR, Dolan R. Buccinator musculomucosal flap: applications in intraoral reconstruction.* Arch Otolaryngol Head Neck Surg. *1998;124:72.)*

both were staged as T1 tumors. The two patients had no problems with swallowing. Speech results were not reported. All patients reported light single-point touch sensation over the flap 2 weeks after surgery. The authors concluded that the flap is dependable, sensate, and has a well-defined neurovascular pedicle, which can be readily used for intraoral reconstructions. Our experience with this flap has been limited, and further studies are necessary to determine the usefulness of the flap for palatal reconstruction. A sound anatomic basis for the flap has been demonstrated by Licameli and Dolan,[15] which makes the flap somewhat promising. The main problem with the flap, however, is the limited amount of tissue available for transfer and the thinness of the flap. The main advantage of the flap is the defined sensory nerve supply to the flap, which may aid in oropharyngeal rehabilitation. Also, the flap is relatively easy and quick to harvest, with minimal donor site morbidity, and eliminates the need for extraoral reconstructions when a transoral resection has been performed.

The Superior Constrictor Advancement-Rotation Flap (SCARF) is another local flap that has been used for semisoft palate defects. The basic approach of flap design and use was initially described by Strong and colleagues[55] and Healy and colleagues.[56] More recently, Zeitels and Kim[16] have reported on the use of this flap to reconstruct defects of 35% to 65% of the soft palate. They state that the use of this flap achieves circumferential closure of the velopharynx, which reestablishes its valvular sphincteric function. The flap was used to reconstruct 10 patients with transmural defects from the paramidline posterior pharyngeal wall to the soft palate. Two cases had temporalis flaps transposed into the lateral pharyngeal wall defect in combination with the SCARF. The SCARF reestablished velopharyngeal competence in all 10 patients. Two patients required secondary procedures because of partial dehiscence of the flap. Both subsequently healed uneventfully. All patients were able to resume a normal oral diet without significant nasopharyngeal regurgitation. Three patients had evidence of mild hypernasality, but these patients were not dissatisfied with their voice quality.

The SCARF is elevated by first transecting the anterior and posterior tonsillar pillars of the residual soft palate as low as possible without violating the tongue. The lateral oropharyngeal musculature is transected as the dissection is carried toward the mandibular ramus, therefore dividing the palatoglossus, the palatopharyngeus, and the superior constrictor. A stab incision is then made in the remnant of the soft palate just medial to the pterygoid hamulus. Dissection is performed bluntly with a Kelly clamp or a hemostat deep to the superior constrictor, and finger dissection is then used posteriorly until the cervical spine is palpable and the retropharynx is reached. These maneuvers effectively mobilize the soft palate, and the cut surface of the soft palate can then be rotated superolaterally and sutured to the exposed superior constrictor on the posterior pharyngeal wall (Fig. 101-12). The remainder of the wound including the stab incision on the soft palate is left open to heal by secondary intention. A pedicled muscle flap can be used to augment the lateral pharyngeal wall if necessary. Patients are started on an oral diet in approximately 7 days. The neovelopharyngeal aperture is narrow initially but widens as the lateral pharyngeal wall heals by secondary intention. Also, the neovelopharynx is sensate and has dynamic capability. This reconstructive approach may be feasible in cases in which the resection has been performed by way of a transoral technique and no communication with the neck exists. However, it necessitates surgical interruption of adjacent, normal palate and pharynx. The authors have had limited experience with this method of reconstruction and have favored the use of free fasciocutaneous flaps to reconstruct large defects of the soft palate, tonsil, and lateral pharyngeal wall.

The palatal island mucosal flap may be considered for lateral defects of the soft palate in combination with tonsillar and retromolar trigone defects. The authors address this local flap option in "Tonsil and Pharyngeal Wall" later. Similarly, the authors would not recommend regional flap reconstruction of isolated soft palate defects, but these often occur in combination with defects of the tonsil and pharyngeal wall that are amenable to regional flap reconstruction. Because of this, they, too, are addressed later in "Tonsil and Pharyngeal Wall."

Free flap reconstruction of the soft palate has become the most common method of reconstruction at our institutions (Halifax, Nova Scotia, Canada, and St. Louis). The authors most commonly encounter these defects after extensive resections of the oropharynx for tonsillar carcinomas. The radial forearm flap has become our flap of choice for this, although other flaps that may be considered are the anterolateral thigh and lateral arm free flap. The anatomy and technique of harvest for the radial forearm flap was described earlier in the chapter. The palatal defect is measured from the nasopharyngeal resection margin to the proposed neopalatal margin and is then doubled to take into account our folding technique. The flap is designed with the distal aspect of the forearm flap used for the palatal reconstruction. The width of the distal flap is determined by the preceding measurement, and the remainder of the flap is planned accordingly. The distal portion of the flap is inset first, with the distal midpoint of the flap sutured to the inferior remnant of the soft palate (Fig. 101-13). The nasopharyngeal surface is then reconstituted by folding the flap on itself. The oral surface of the palate is then reconstructed. The authors do not routinely perform a pharyngoplasty to create an adhesion between the flap and the posterior pharyngeal wall but consider this in cases where greater than 50% of the soft palate has been resected. This method nicely reestablishes the velopharynx, but it does lack dynamic capability.

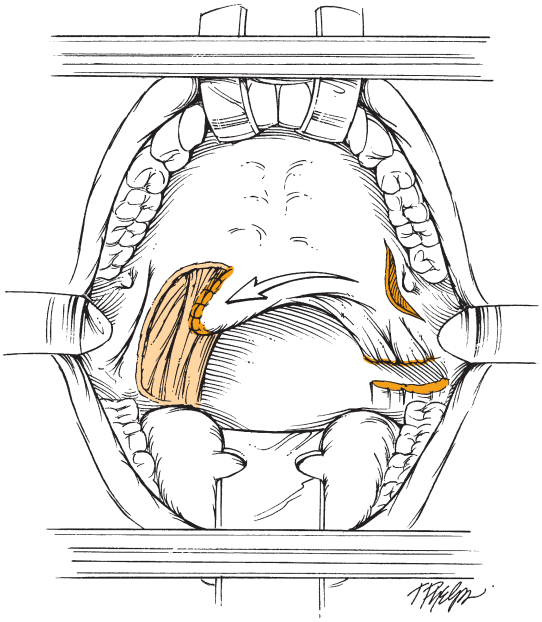

Figure 101-12. The superior constrictor advancement rotation flap is used for soft palatal reconstruction and leaves the pharyngeal wall defect to heal secondarily. Releasing incisions are made low on the contralateral tonsillar pillars and are carried through the underlying superior constrictor. A stab incision is then made just medial to the pterygoid hamulus, and further mobilization of the superior constrictor is performed through this incision. The superior constrictor is then advanced and sutured to the transected edge of the soft palate. *(Adapted from Zeitels SM, Kim J. Soft-palate reconstruction with a "SCARF" superior-constrictor advancement-rotation flap.* Laryngoscope. *1998;108:1138.)*

Another option is to use the Gehanno method in combination with a free tissue transfer as suggested by Kimata and colleagues.[57] In the Gehanno method the lateral and posterior pharyngeal wall is mobilized, and this advancement flap is turned inside out and sutured to the posterior surface of the remaining soft palate, thus reconstituting a mobile neovelopharynx.[58] The free flap is then used to patch the anterior aspect of the soft palate and lateral pharyngeal wall. Kimata recommends the use of the Gehanno method in combination with a free flap (they used the rectus abdominis musculocutaneous flap in 26 of 40 reconstructions) for defects that extend to the contralateral soft palate because velopharyngeal function is superior due to a decreased incidence of wound dehiscence.[57]

Lacombe and Blackwell[59] have reported their results with a folding technique similar to ours with a radial forearm flap. However, they

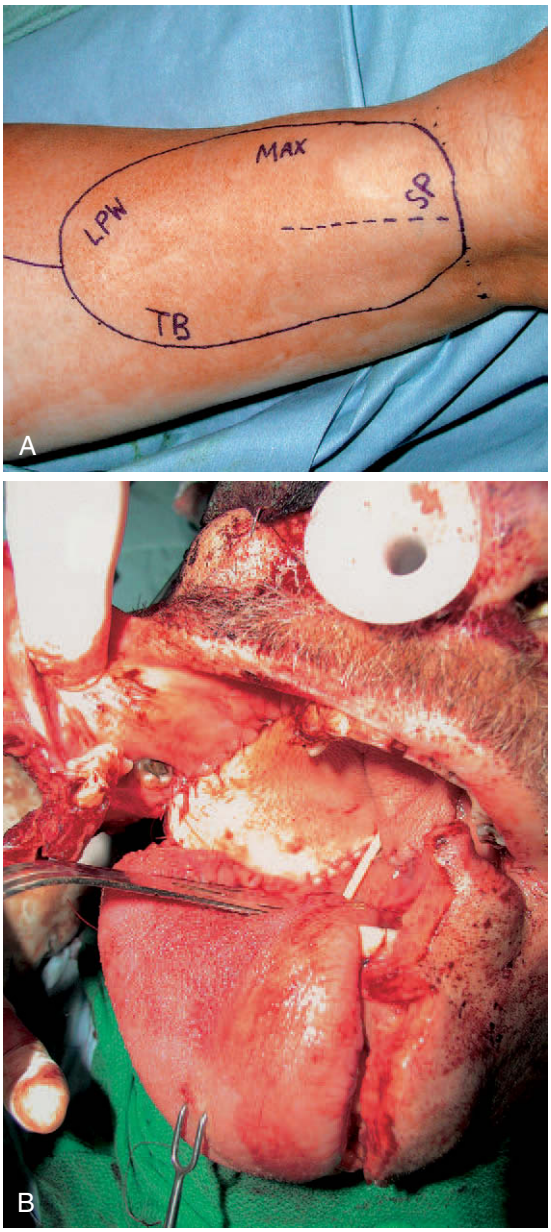

Figure 101-13. These photographs demonstrate our design for folding the forearm flap into the soft palatal defect. In **A**, note the distal aspect of the flap is used for this purpose, and the proximal flap is used for the pharyngeal and tongue base component if present. The flap was used in this case to reconstruct a 70% defect of the soft palate, as shown in **B**.

routinely perform a midline adhesion in cases in which more than one third of the soft palate is reconstructed. They accomplish this by deepithelializing a portion of the forearm flap and suturing it to a denuded area on the posterior pharyngeal wall. Red rubber catheters (16 F) are used to establish lateral ports, essentially converting the result to look and function like a pharyngeal flap. Their study reviewed 15 patients who had soft palatal reconstruction with the free radial forearm flap. Thirteen of 15 patients achieved an oral diet, whereas two were dependent on enteral feeding. Similarly, 13 patients were reported as having good velopharyngeal function without revision surgery or use of a prosthesis. One patient required a palatal-lift prosthesis for nasal regurgitation, and another patient had a secondary pharyngeal flap to decrease the size of one lateral velopharyngeal port. As with pharyngeal flaps, judgment of the size of the velopharyngeal ports needs to be correct in order to avoid nasal obstruction and sleep apnea.

Several other groups have reported on their experience with soft palate reconstruction with a free radial forearm flap. Two used a forearm flap in conjunction with a superiorly based pharyngeal flap. Brown and colleagues[60] and Penfold and collegues[61] used this approach in 11 and 3 patients, respectively. They noted good functional results for swallowing, speech intelligibility, and velopharyngeal sufficiency. The larger of the two studies done by Brown used objective measures of function such as videofluoroscopy, voice intelligibility recordings, and functional outcome evaluation by means of a questionnaire. We would caution the use of the pharyngeal flap in cases in which a significant volume of the pharynx has already been resected, and further sacrifice with the pharyngeal flap may further compromise swallowing.

Speech function after palatal reconstruction was specifically addressed by Yoshida and colleagues,[53] who reported on five patients who had soft palate reconstructions with a free radial forearm flap. Three of the five patients reconstructed with forearm flaps had a speech intelligibility score greater than 70%. The other two patients had scores of 40.8% and 57.8%. Two patients had a slight improvement of their intelligibility scores with placement of a special prosthesis. Eighty percent (four of five) of the patients were endoscopically and aerodynamically shown to have evidence of velopharyngeal incompetence. McCombe[62] reported on velopharyngeal function in patients following reconstruction of defects between 50% and 100% of the soft palate. All patients were reconstructed with a free radial forearm flap. Results were disappointing and the authors recommend a reduction of the velopharyngeal aperture to compensate for the lack of mobility in the soft tissue reconstruction. This had been scientifically previously shown by Seikaly and colleagues,[63] who found that patients with 50% or more of the soft palate resected and reconstructed with a radial forearm flap had significantly higher nasalance values and velopharyngeal orifice areas. Another recent report by Sinha and colleagues[64] on 16 folded forearm flap reconstructions for soft palatal defects found that all patients had intelligible speech and 14 of the 16 patients were able to tolerate a normal or soft diet within 6 weeks. Figure 101-14 presents an algorithm for reconstruction of defects of the soft palate.

Tonsil and Pharyngeal Wall

The extent of tonsillar and pharyngeal wall defects encountered is dependent on the approach to the primary tumor. In centers where radiotherapy is used as the primary modality of treatment, the reconstructive surgeon will be faced with extensive defects of the region because of the aggressive nature of the resection required for surgical salvage. These defects generally require a free or pedicled flap reconstruction because of the size of the defect and the compromised blood supply of the local tissue as a result of radiation. By comparison, centers that treat these tumors with primary surgery will be faced with a multitude of defects that may be reconstructed in a variety of ways, depending of the location and stage of the tumor. The same issue arises for tumors located in the tongue base.

Early tonsillar cancers can be easily resected transorally with the use of the carbon dioxide laser and the wound left to heal by secondary intention.[65] The authors have used this technique for T1 lesions of the tonsil and lateral pharyngeal wall, thereby leaving defects of up to 4 cm. The resection is taken down through the superior constrictor to the parapharyngeal fat pad. It is important to leave the fat undisturbed if possible because this serves to protect the carotid artery from intraoral contents. Patients can be started on an oral diet the same day of surgery. The authors have found that this technique is well tolerated, and patients heal well with little if any distortion of native tissue. Close examination of the healed defect usually reveals slight inferior displacement of the soft palate on the side of the resection, but velopharyngeal insufficiency is rare. This has been exemplified in cases reconstructed with the SCARF because the entire basis of its use is to reconstruct the soft palate with local tissue while allowing the lateral pharyngeal wall to heal secondarily. Healing by secondary intention is also possible for posterior pharyngeal wall defects. This is usually accomplished by suturing the margins of the defect to the prevertebral fascia and allowing the defect to remucosalize over the exposed fascia.

Primary closure is another option for reconstructing defects of the tonsil or pharyngeal wall. No specific guidelines apply for defects that

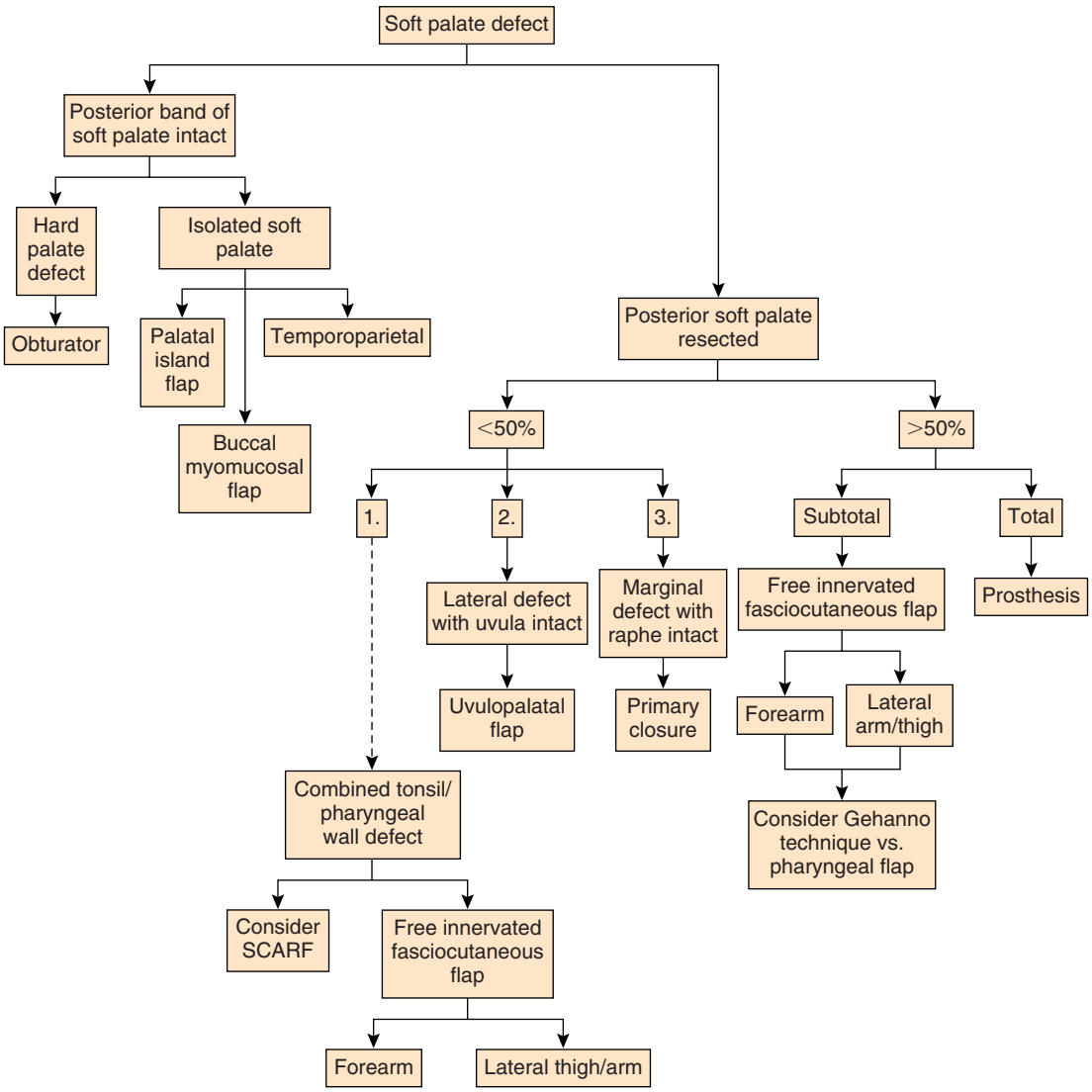

Figure 101-14. An algorithm for reconstructing defects of the soft palate.

are amenable to primary closure. The general principles include the absence of tension on the pharyngeal wound closure and lack of distortion of the normal anatomy of the region. As stated previously, this technique must be used with caution in patients who have been previously radiated. McConnel and colleagues[66] studied the functional results of primary closure versus flap reconstruction of the oropharynx. This was a prospective case-comparison study drawing from a database of 284 patients treated at four head and neck cancer institutions. Patients were matched for tumor location and the extent of resection. Speech and swallowing function was assessed preoperatively and 3 months after healing. They report that patients who had primary closure had less pharyngeal residue, were more efficient at swallowing liquids, and had higher conversational intelligibility than patients who had reconstruction with a distal flap. The primary closure patients had a longer oral transit time than the distal flap group. Compared with the free flap cohort, the primary closure patients had more efficient swallowing of liquids, less pharyngeal residual, and shorter pharyngeal delay times with paste. The authors did not find any difference in speech and swallowing function between the distal myocutaneous flap and the free flap groups. They conclude that primary closure results are equal or better in function than the use of flap reconstruction. This article is particularly controversial because it goes against most of our current trends in oropharyngeal reconstruction. Several questions have been raised about this study, and the authors of this chapter suggest reviewing the letter to the editor submitted by Reece and colleagues[67] with regard to this. A more recent study by Zuydam and colleagues showed improved speech and swallowing in patients closed primarily as compared with those reconstructed with free flaps.[68] Other published studies, however, support the use of primary closure for selected defects of the tonsil, pharyngeal wall, and tongue base.[11,69] These studies do highlight the importance of considering this modality for selected cases and the need to objectively study speech and swallowing results achieved with the various means of reconstruction.

Skin grafting of tonsil/pharyngeal wall defects is another uncomplicated method of reconstruction available to the surgeon. Pauloski and colleagues[69] described this technique in 14 patients with tonsillar defects in combination with varying defects of the tongue base and soft palate. The study specifically addressed variables affecting speech in patients with oral and oropharyngeal cancer including methods of reconstruction. Results were favorable for those reconstructed with a skin graft because they had more limited defects than the flap reconstruction group. Skin grafting may also be used to reconstruct defects of the posterior pharyngeal wall. The skin graft is sutured to the margins of the defect, and a bolster dressing is used to decrease the shearing forces on the graft. This technique can be used after a transoral or transcervical approach. A tracheotomy is recommended for airway protection in cases in which a skin graft is used.

Local flap reconstruction of tonsil and pharyngeal wall defects is uncommon. The longus coli muscle flap has been reported to be useful for defects of the lateral pharyngeal wall.[28] The longus colli muscles

arise from the anterior tubercles and transverse processes of the vertebral column from the arch of the atlas to the third thoracic vertebra and lie deep to the prevertebral fascia but anterior to the ligaments of the cervical spine. The muscle extends inferiorly to the level of the cervical esophagus. Innervation is from the cervical plexus (C2-C7), whereas the blood supply arises from muscular perforators of the vertebral artery. The muscle is thicker laterally, measuring approximately 0.5 to 1 cm in thickness. The flap is mobilized by dissecting free the lateral border of the muscle and then bluntly dissecting dorsal to the muscle. The muscle is rotated anteriorly into the defect without transecting it. Collins[28] reports that up to 4 to 5 cm of flap width is available for use, and the procedure takes from 5 to 10 minutes. She reported on 16 patients who were reconstructed with this flap. A total of 13 had primary tumors of the pharyngeal wall. Eighty-eight percent of patients had stage 3 or 4 disease, and 50% had T3 or T4 primary tumors. She reports that there were no wound infections or fistulas, although one of two previously radiated patients had a transient wound-healing problem. Two thirds of patients achieved an oral diet, and 58% (7 of 12) of patients who had laryngeal preservation procedures were decannulated. The author concludes that the longus colli muscle flap is useful for defects of the lateral pharyngeal wall on the basis of the reliability of wound healing and the absence of a negative impact on oncologic and functional results.

The palatal island flap is another local flap option appropriate for limited defects of the tonsil and pharyngeal wall. The entire hard palate mucoperiosteum based on a single greater palatine neurovascular pedicle is available to be transferred with this technique (see Fig. 101-2). The flap is ideal for defects less than 5 cm involving the upper tonsil/pharyngeal wall and retromolar trigone. Gullane and Arena[13] reported a 5% failure rate in a series of 53 palatal island flaps. They caution the use of this flap after irradiation, previous palatal surgery, or ligation of the external carotid or internal maxillary artery. Care must be taken to inset the flap without tension. The donor site is left open, and remucosalization occurs rapidly with little morbidity.

Regional flap reconstruction of the tonsil and pharyngeal wall remains a common reconstructive technique. The pectoralis major flap is without question the most commonly used regional flap for this purpose. This flap was first described by Ariyan[1] in 1979 for head and neck reconstruction and revolutionized the field. It can be used as a musculocutaneous, myofascial, or myogenous transfer and may be tailored to fit almost any defect of the head and neck. The anatomy of the flap has been outlined previously with the pectoral branch of the thoracoacromial artery serving as the flap's main blood supply. The flap is simple to harvest, and some surgeons prefer to do this through a deltopectoral-sparing incision starting in the axilla and coursing along the lateral border of the muscle inferiorly. If a cutaneous paddle is to be included, the lateral component is first incised, confirming correct planning of the skin paddle over the distal muscle. An avascular plane exists between the pectoralis major and the underlying pectoralis minor. The muscle is divided medially and laterally from its sternal and humeral attachments, respectively, after completing incision of the skin paddle. The skin paddle is then sutured to the underlying muscle to prevent shearing on the musculocutaneous perforators. The pedicle is identified medial and anterior to the pectoralis minor, and the flap can be narrowed superiorly or completely skeletonized on the pedicle alone, as the clavicle is approached. This assists tunneling into the neck.

Baek[2] first reported on the use of the pectoralis major flap for oropharyngeal reconstruction. Since then, several groups have reported their experience with this flap. The largest study to date was a series of 371 patients who had pectoralis major myocutaneous flaps performed for head and neck defects. The overall complication rate was 36% with a 2.4% incidence of total flap necrosis.[70] Koh has also recently reported on the use of this flap for oropharyngeal reconstruction and concluded that the pectoralis major flap is not only an alternative to a free flap but in fact may be a better choice for patients because the complication rates at their institution were lower in the pectoralis cohort compared with the free flap group.[71] One of the limiting factors of the flap for pharyngeal wall reconstruction is its excessive bulk. For this reason, we have preferred to use this flap as a myofascial transfer because it can be easily molded to the pharyngeal defect and the accompanying fascia is useful for suture placement.[72] Righi and colleagues[73] reported a flap complication rate of 22% with their series of myofascial flaps. We have used this flap primarily in tonsillar/pharyngeal wall defects in combination with lateral oromandibular defects in patients believed to be poor candidates for free tissue transfer (Fig. 101-15).

Figure 101-15. A pectoralis major myofascial flap was used to reconstruct the lateral pharyngeal wall in combination with a posterior mandibular defect. The patient had significant comorbidities and was felt to be a poor candidate for a free tissue transfer. Despite this, he was decannulated and is tolerating a normal diet.

The platysmal myocutaneous flap is another viable option for tonsillar/pharyngeal wall reconstruction. It is ideal for this purpose because of the thinness and pliability of the flap. It can be harvested in 20 to 30 minutes with little, if any, donor site morbidity. No special skills or equipment is necessary. The flap is designed low in the neck, with the skin paddle planned over the midportion of the platysma muscle. The upper skin paddle incision is made first, and a subcutaneous flap is raised to the level of the mandible. Next, the inferior portion of the skin paddle is incised and carried through the platysma. A subplatysmal flap is then elevated to the level of the mandible, which essentially frees the muscle and the overlying skin paddle (see Fig. 101-5). The flap has been used mostly for intraoral reconstruction; however, most series include patients in whom the flap has been used in the oropharynx. Ruark and colleagues[21] reported on 13 of a total of 41 patients who had primary tumors of the oropharynx reconstructed with this technique. This is the largest series of platysmal flaps reported in the literature for oropharyngeal reconstruction. They did not specifically analyze the subsites reconstructed, but the flap was used for tonsil, lateral pharyngeal wall, and soft palate defects. Other than this report, a total of 29 myocutaneous oropharyngeal reconstructions are reported in the literature.[19-22] Twelve were used for tonsil/pharyngeal wall reconstruction, whereas 17 were used in the tongue base. The complication rate for the tonsil/pharyngeal wall reconstructions was 67% (8 of 12). A more recent study by Jackel[74] reported on six patients reconstructed with a platysmal myofascial flap. These patients had tonsillar primaries resected with transoral laser microsurgery and all were free of complications.

The sternocleidomastoid myocutaneous flap may also be used for tonsil/pharyngeal wall reconstruction. The flap can be used either as a superiorly or inferiorly based flap based, respectively, on the occipital and transverse cervical arteries. The superior thyroid artery supplies the midportion of the muscle. Ariyan[75] reported on 31 consecutive reconstructions using this flap, of which 6 were used for the tonsil or pharyngeal wall. The remainder were used for defects of the oral cavity. Superiorly based flaps were used in two thirds of the cases. Fourteen patients had previous radiotherapy, and 17 had concomitant modified neck dissections. The complication rate in his series was 52%. Thirteen of 31 had partial loss of the skin paddle develop, whereas one was lost completely. Two patients had fistulas develop, despite no loss of the

skin paddle. All healed without additional surgery. There was no difference in complication rates for patients who had neck dissections or previous radiation. The location of the blood supply (inferior vs. superior) was not found to be significant. Significant concerns exist with regard to the use of this flap. First, the reliability of the skin paddle is questionable on the basis of the preceding and other studies. The vascularity of the skin paddle may be enhanced by preserving the superior thyroid pedicle.[76] One other major criticism of the use of this flap is its intimate relationship with potential nodal metastasis in the neck. The largest published study in the literature addresses these two issues. Sebastian and colleagues[77] reported on 121 superiorly based flaps for oral reconstruction in patients with clinically N0 necks. Total flap loss occurred in 7% of cases, whereas superficial skin loss was seen in 23%. The fistula rate in the series was 12%. Radiation was found to increase the incidence of flap complications. Pathologically N0 necks had a recurrence rate of 6% compared with 17% in necks that were pathologically positive.

The temporal system of flaps may be useful for reconstructing tonsil/pharyngeal wall defects as well. The techniques of harvesting the temporalis and the temporoparietal fascia flap have been outlined previously in "Regional Flaps." The flap's ease of harvest and proximity to the defect make it a viable option. It may be particularly useful in cases in which the coronoid process of the mandible has been resected, leaving the muscle functionless. We have tended not to use this flap routinely for oropharyngeal defects given its bulk, difficulty of inset, and donor site morbidity. We previously discussed the use of this flap in conjunction with the SCARF, where the flap was used to augment the lateral pharyngeal wall defect in two cases.[16] Huttenbrink[78] reported on the use of this flap specifically for oropharyngeal reconstruction, and this represents the only dedicated article to this in the English literature. The transfer used by Huttenbrink consisted of muscle, fascia, and periosteum. He stresses the importance of subperiosteal dissection along the deep aspect of the flap to protect the deep temporal vascular pedicle. A total of 11 patients with oropharyngeal defects were reconstructed with the temporalis flap. One flap developed partial necrosis of the fascial layer, but the muscle healed uneventfully. There were no problems with the other 10 flaps. No fistulas or flap dehiscence occurred. The author was nonspecific with reporting of functional outcomes and simply reported that nearly all patients could swallow and speak without restraint. A subsequent article by Huttenbrink in the German literature expanded on his experience and reported on 26 patients in whom the flap was used.[79] A more recent study by Smith and colleagues[80] reported on 26 temporalis flaps used for oropharyngeal and nasopharyngeal reconstruction. They reported two cases of minor flap loss and two cases of transient frontal nerve weakness. More than 50% of patients were able to tolerate a normal diet, and 8% were G-tube dependent.

The temporoparietal fascial flap may be used in a similar fashion. The thinness, pliability, and vascularity make it ideal for this purpose. Flap harvest is relatively simple and was described in detail previously in this chapter. Donor site morbidity is rare, with frontal nerve injury and alopecia being the most significant. Cheney and colleagues[23] have nicely outlined the application of this flap in head and neck reconstruction. They report on the variety of defects that can be reconstructed with this flap including the pharyngeal wall. The flap can be used either as a pedicled or free tissue transfer. Most defects of the pharyngeal wall should be amenable to pedicled flap reconstruction because of the proximity of the donor site and the thinness of the flap to be tunneled into the defect. Objective measures of functional outcomes that use this method of reconstruction are lacking.

Free flap reconstruction is now the gold standard reconstructive modality for extensive defects of the tonsil and pharyngeal wall. Usually, these defects occur in combination with defects of the soft palate and tongue base, and we focus on these two subsites in this section because published data on free flap reconstruction for isolated defects of the pharyngeal wall are scant. The radial forearm flap is the "workhorse" free flap in this area and has gained widespread popularity because of its thinness and pliability, ease of harvest, and minimal donor site morbidity. The forearm flap has become the most common free flap used in oral and pharyngeal reconstruction. Compared with the jejunum and gastro-omental free flaps for this purpose, there was no difference in speech, swallowing, or control of saliva between the different reconstructive modalities.[81] The gastro-omental cohort, however, was found to have a higher complication rate. The authors make no reference as to whether the forearm flaps were neurotized at the time of surgery. We prefer the use of the forearm flap over the jejunum and gastro-omental flaps because the forearm flap may be reinnervated, which may improve pharyngeal sensation, thus preventing aspiration. Also, the forearm flap avoids the laparotomy required for harvest of the other two flaps.

A recent Finnish study addressed free flap reconstruction in the management of oral and pharyngeal cancer.[82] Of the 50 patients included in the study, seven had defects of the tonsil and pharyngeal wall. All seven patients were reconstructed with a free radial forearm flap. Twenty percent of the flaps required reexploration, and the overall flap success rate was 96%. Patients who had primary tumors of the tonsil had the best 3- and 5-year survival rates at 85% and 57%, respectively. This point stresses the need for functional reconstruction because prognosis at this subsite tends to be good compared with the hypopharynx and oral cavity. Schwager[83] reported the use of the forearm flap in reconstructing 62 patients with pharyngeal carcinoma. A regular diet was achieved an average of 14 days postoperatively. All patients had a tracheotomy performed at the time of surgery, and 90% were decannulated at 1 year. Another European article by Barzan[84] reported on four patients with isolated posterior pharyngeal wall defects. All patients were reconstructed with a free radial forearm flap. No flap problems, fistulas, or donor site morbidity was noted. Speech and swallowing function was not noted.

Combined defects of the lateral and superior (soft palate) pharyngeal wall have been addressed by Kimata and colleagues.[57] All 40 patients had extensive defects of the lateral pharyngeal wall combined with varying defects of the soft palate. They classified the defects as follows: type 1, localized in the lateral pharyngeal wall and including palatopharyngeal, palatoglossal, and superior pharyngeal muscles; type 2, extending to the soft palate and including the tensor veli palatini and levator palatini muscles; and type 3, extending to the contralateral soft palate. Free flap reconstructions were performed on all patients. The rectus abdominis flap was used in 26 patients, an anterolateral thigh flap in 7 patients, and a forearm flap in 5 patients. Jejunum and superior iliac crest flaps were used in one patient each. Six flaps underwent partial necrosis, and 34 survived completely. The authors describe four different methods of reconstructing these defects, namely the patch, jump, denude, and Gehanno methods (Fig. 101-16). Wound dehiscence between the remnant soft palate and flap developed in 7 of the 40 patients. This occurred in 4 of 8 (50%) patients treated with the denude method and 3 of 10 (30%) patients treated with the Jump method. Of the seven patients with wound dehiscence, five had a wide fissure develop between the flap and the soft palate that resulted in postoperative hypernasality. As expected, patients with type 1 defects had the best overall velopharyngeal function. All 10 patients in this group had satisfactory postoperative function. Sixteen patients had type 2 defects. The authors report that most of these patients showed satisfactory function. Five of these patients had mild or severe nasal emission during soft blowing, and seven had mild nasal regurgitation with eating. Fourteen patients had type 3 pharyngeal defects. Of these, five patients had satisfactory function without nasal emission with soft blowing. The five patients who had flap dehiscence had severe velopharyngeal incompetence. The remaining four patients initially had intact velopharynges, but as the rectus free flap atrophied, they had progressive incompetence develop. Overall, patients with type 3 defects had low speech intelligibility scores, and 9 of 14 patients had evidence of hypernasality. The authors conclude that flap dehiscence was directly correlated to poor speech intelligibility, hypernasality, and nasal emission. The rates of wound dehiscence were lower with the patch and Gehanno methods. They suggest the use of the Gehanno method for extensive defects of the oropharynx and for all type 3 defects of the soft palate.

The lateral arm and thigh free flaps are other options for reconstructing defects of the tonsil and pharyngeal wall. Civantos[41] reported on 28 patients who had the lateral arm flap used in head and neck

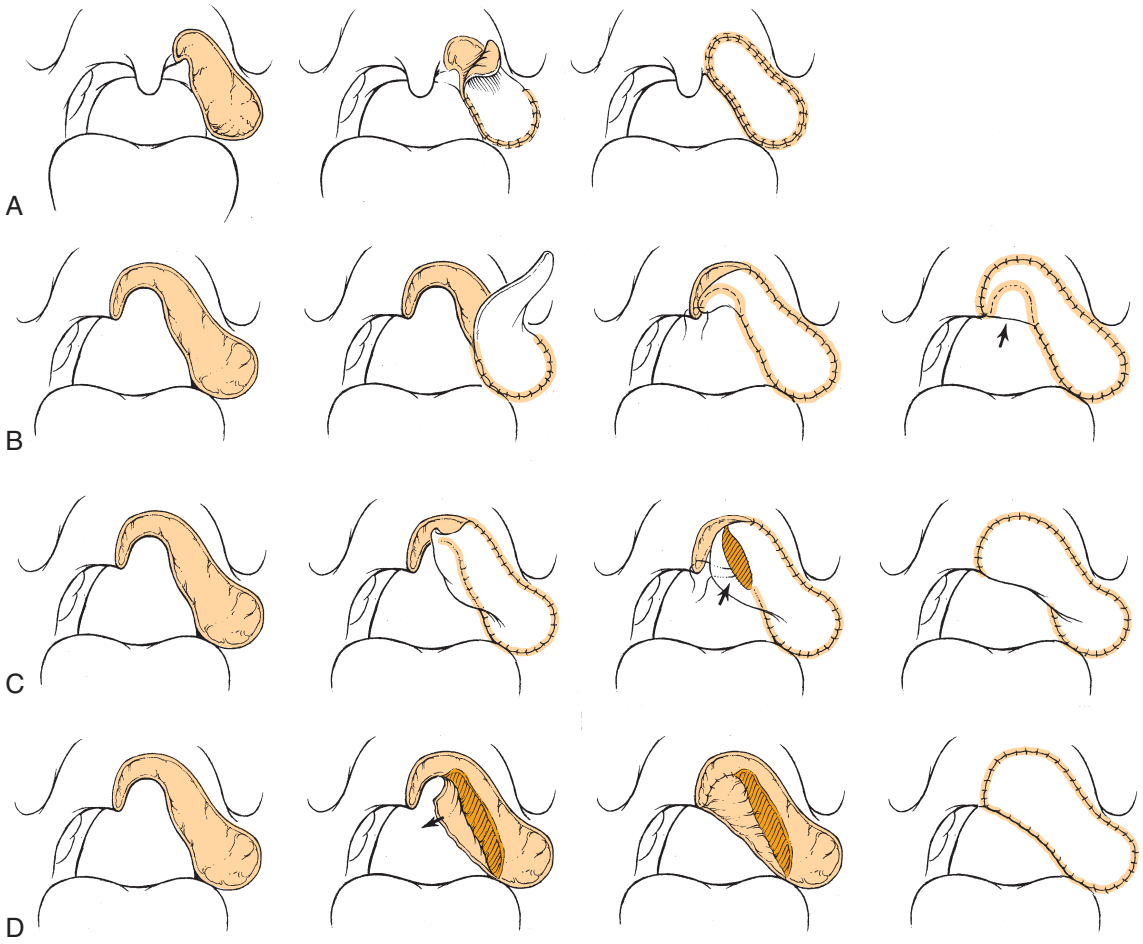

Figure 101-16. **A,** Patch method: The flap is simply sutured into the defect. **B,** Jump method: The inferior portion of the free flap is left unsutured to the posterior pharyngeal wall and soft palate, therefore jumping directly to the anterior soft palate. **C,** Denude method: The flap is used to reconstitute the posterior pharyngeal wall, and the portion of the flap adjacent to the cut end of the soft palate is deepithelialized and sutured to the remaining soft palate. **D,** Gehanno method: The posterior and lateral pharyngeal wall is advanced and sutured to the posterior surface of the soft palate remnant. The flap is then used as a patch for the anterior portion of the defect. *(Adapted from Kimata Y, Uchiyama K, Sakuraba M, et al. Velopharyngeal function after microsurgical reconstruction of lateral and superior oropharyngeal defects.* Laryngoscope. *2002;112:1037-1042.)*

reconstruction. Of these, 14 patients had large oropharyngeal defects, four of which involved the tonsil and pharyngeal wall. Eight of the 14 patients resumed early oral feeding, and all eventually were able to obtain nutrition orally. Swallowing was compared with a simultaneous control group that was reconstructed with pectoralis major flaps. The swallowing ability of the lateral arm cohort was found to be superior to the group reconstructed with the pectoralis flaps. The authors concluded that the lateral arm free flap is ideal for oropharyngeal reconstruction because the flap incorporates thin skin from the proximal forearm and thicker skin from the upper arm. They suggest that the thin forearm skin may be used in the lateral pharyngeal wall, whereas the thicker upper arm skin may be used to reconstruct the tongue base. Also, the flap is amenable to neurotization. Hayden and Deschler[34] make similar recommendations with regard to the use of the free lateral thigh flap. They reported their experience with the lateral thigh flap in 58 cases. Most flaps were used for pharyngoesophageal reconstruction, but two involved the pharyngeal wall. The authors of this chapter have used the lateral thigh flap in the past as their second line flap but now prefer the anterolateral thigh flap in patients who are not candidates for radial forearm flap reconstruction or have very thin lower extremities. Figure 101-17 reviews an algorithmic approach to defects of the tonsil and pharyngeal wall.

Tongue Base

Reconstruction of the tongue base is challenging because of its proximity to the larynx and the resultant risk of aspiration. These defects may occur as an isolated entity but also may occur in combination with defects of the anterior tongue, with the extreme being the total glossectomy defect with or without laryngeal preservation. The goals of tongue base reconstruction in order of importance are (1) maintenance of the airway; (2) swallowing; and (3) articulation. The tongue base is critical for the first and second goals, with the anterior tongue being more significant with regard to articulation. The ideal tongue base reconstruction provides the necessary bulk to create a shelf above the laryngeal inlet. This serves to better direct the oral bolus down the posterior pharyngeal wall and away from the larynx. The form of reconstruction chosen should provide pliable tissue that has dynamic capability, which is required for adequate speech and swallowing. Last, reinnervation of the flap from both a sensory and motor standpoint would be ideal because this would improve pharyngeal sensation, thus decreasing the risk of aspiration, whereas motor function would enhance tongue and laryngeal elevation, resulting in a more physiologic swallow. These factors are critical in cases in which partial laryngectomy is performed because the risk of aspiration is increased.[84]

With the growing popularity of minimally invasive techniques, endoscopic resection of tongue base tumors with the use of the CO_2 laser has emerged in selected centers. We have performed endoscopic resections of T1 to T3 carcinomas of the tongue base, leaving up to 6 cm to heal by secondary intention. With time, the surgical bed granulates in and forms a neotongue that closely resembles and functions like the native tongue base. This form of reconstruction is simple and reliable in the nonirradiated patient, although it may also be used as a

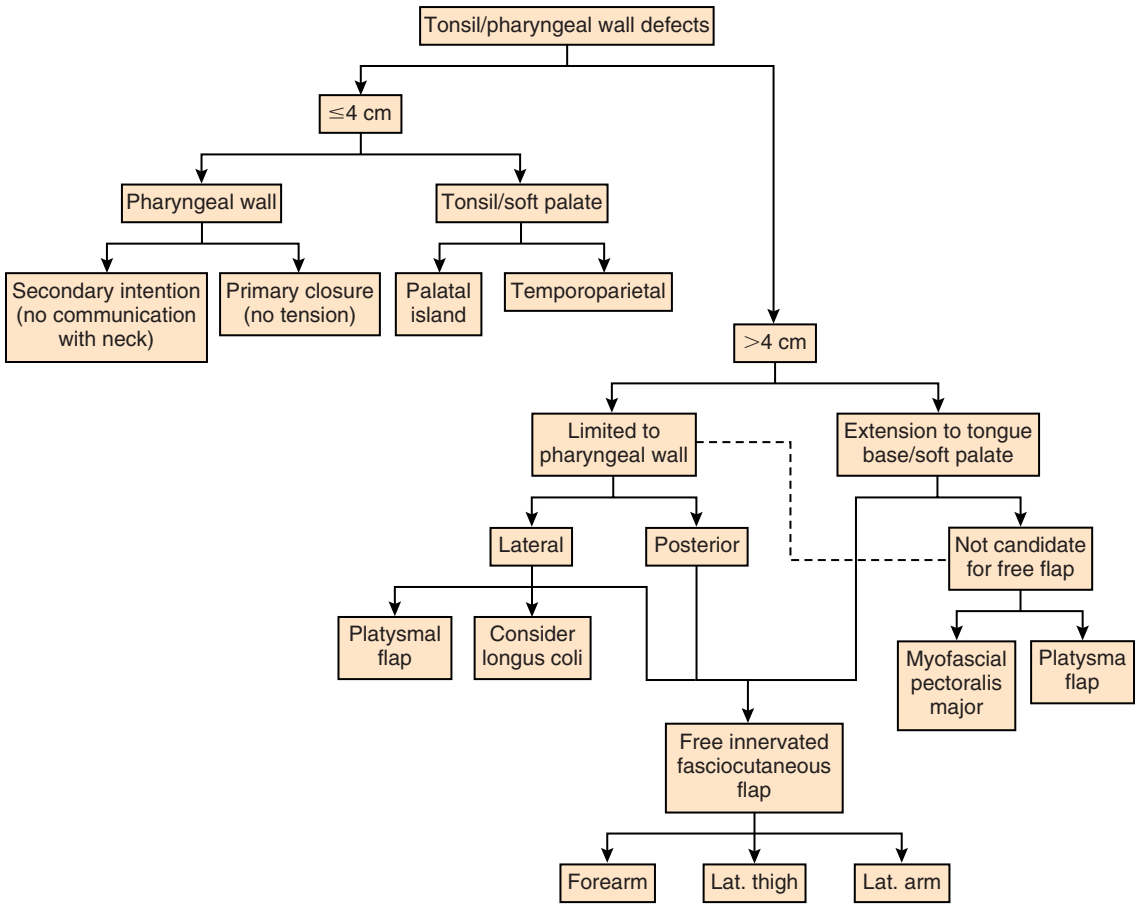

Figure 101-17. Reconstructive algorithm for the tonsil and pharyngeal wall.

salvage technique, with healing and local control being less predictable. Overall patient functioning is generally directly related to the extent of the resection performed.[69] Primary closure is an excellent option for reconstructing selected defects of the tongue base. This approach has been championed by McConnel and colleagues.[10,66] We have previously addressed this study in detail in "Tonsil and Pharyngeal Wall." Tongue base defects of up to 60% were closed primarily, and these were matched against similar defects reconstructed with free and pedicled flaps. They report that there is no significant improvement in swallowing efficiency between patients having flaps and patients with primary closure. Conversely, patients with primary closure had better swallowing efficiency than both the free flap and pedicled flap groups. This report is controversial because it represents a paradigm shift in conventional reconstructive ideals. Currently, most would recommend flap reconstruction for defects involving far less than 60%, with one group suggesting flaps are necessary in cases where more than 20% of the tongue base is resected.[67] Clearly, there are no definite guidelines to follow, and much is based on surgeon preference and experience. As a general rule, we have tended to use free tissue transfer in cases in which a mandibulotomy was performed for exposure, while reserving consideration of primary closure for transoral, transhyoid, or pharyngotomy approaches. Basic principles still apply for the use of primary closure because the wound must be free of tension, and there should be minimal or no distortion of the native anatomy. We have used primary closure for tongue base defects of 30% or less and favor the use of free flaps for more extensive defects.

Skin grafting and local flaps are not recommended in isolation for reconstructing defects of the tongue base. Local flaps are mentioned only for completeness sake and are not appropriate in the tongue base because of the resultant deformation and tethering of the tongue that occurs. Similarly, we have not used skin grafting alone for defects of the base of tongue because immobilization of the skin graft is difficult and lacks the volume of tissue required for adequate reconstruction. A skin graft may be considered in combination with other forms of reconstruction, particularly in key areas such as the glossotonsillar sulcus, if insufficient flap is available to fully cover the wound.

Regional flap reconstruction of the base of tongue remains an option. The pectoralis major myocutaneous flap is the tried, tested, and true regional flap used for this purpose. Soon after the description of this flap, Conley and colleagues[86] reported their experience with reinnervated pectoralis myocutaneous flaps for reconstructing total glossectomy defects. The pectoral nerves were anastomosed to the stump of the hypoglossal nerve in all cases. Electromyographic recordings confirmed that reinnervation had occurred. Although flap atrophy was prevented with the reinnervation of the muscle, coordinated contraction and movement of the neotongue was not observed. Even if muscular contraction had been observed, this would result in inferior movement of the flap, which is opposite to the desired upward movement seen in normal swallowing. Sultan and Coleman[87] reported on a group of 11 patients who were reconstructed with pedicled pectoralis flaps. They proposed that delayed sagging of the flap leads to decreased laryngeal mobility. There is a scarcity of functional outcomes reported with this form of reconstruction. Weber and colleagues[88] reported on swallowing results in 27 patients who had subtotal or total glossectomies with laryngeal preservation. All patients were reconstructed with a pectoralis major flap. Of the 27 patients, 18 (67%) were able to obtain an oral diet; however, with time, this number decreased to 12 (45%), thus confirming the subjective observations of Sultan and Coleman. Gehanno[85] reported his experience with 80 patients with advanced carcinoma of the tongue who were treated with total glossectomy. Reconstruction was performed with a pedicled musculocutaneous flap in 75 patients (64 pectoralis major, 8 trapezius, and 3 latissimus) and a gastro-omental free flap in 5 patients. Twenty-six (32%) patients had a pharyngocutaneous fistula develop, and half of these patients required

further surgery. Half of the patients were decannulated within 30 days of their initial surgery. At 3 months, 41 (53%) patients were able to eat soft food, and speech was intelligible in 49 (63%) patients. Five-year survival of the study patients was a dismal 12%.

Another regional musculocutaneous flap that may be used for total and subtotal glossectomy defects is the latissimus dorsi. This is our flap of choice for this defect. However, we have abandoned its use as a pedicled transfer and use it solely as a free flap for this purpose. Haughey[42] has reported his initial experience with this flap as a pedicled transfer in tongue reconstruction. Of his first four latissimus flaps for tongue reconstruction, three were used as pedicled transaxillary transfers. Two of these three flaps failed, and both were salvaged with pectoralis major myocutaneous flaps. We have abandoned the pedicled transfer for tongue reconstruction because of the unreliability of the flap for this purpose and the potential limitations of neotongue mobility caused by pedicle tethering.

The platysmal myocutaneous flap has recently been reported to be appropriate for use in the tongue base. Koch[20] reported on nine patients with base of tongue defects that were reconstructed with the platysma flap. Despite the high rate of complications reported with this flap by some, all nine flaps survived entirely. One patient had a pharyngocutaneous fistula develop that healed uneventfully with conservative measures. Eight of the nine patients were able to achieve an oral diet. The one patient unable to do so had a resection of a T3 tumor of the tongue base after failure of radiation and chemotherapy. None of the patients had evidence of aspiration. The flap was used for tongue base primary tumors in approximately 25% of the reported cases (9 of 34) in this series. A review of other published data on the platysma flap revealed only eight other cases in which this flap was used for tongue base reconstruction.[12,22,89] Seven of the eight flaps survived entirely, and one flap developed partial necrosis of the skin paddle. Functional results for these patients are not apparent. The overall flap survival rate for the platysmal flap for tongue base reconstruction is 94% (17 of 18). The advantages of this flap for tongue base reconstruction are the flap's simplicity and proximity to the defect, thus allowing a tension-free closure. Disadvantages of this technique are the lack of flap bulk and sensory potential.

Free tissue transfer has become the "go to" method of reconstruction for defects of the tongue base. Fasciocutaneous and musculocutaneous flaps are most commonly used for this purpose. Sensory recovery has been documented with fasciocutaneous flaps in tongue reconstruction.[90] Seventeen patients who underwent reconstruction of glossectomy defects with reinnervated forearm flaps were studied 8 months after surgery. Sensory recovery occurred in all 17 patients. The free flap reconstructions had superior sensation compared with the contralateral forearm donor site and approached that of the native tongue. Despite this, no direct link between sensory recovery and functional recovery has been conclusively shown.[90,91] We also published our experience with fasciocutaneous flaps for tongue and floor of mouth reconstruction.[92] Forty-three reconstructions were performed, of which 13 were centered in the tongue base and did not extend into the oral tongue or floor of mouth for more than 2 cm. The defects were reconstructed with a planar inset of a forearm flap between the hyoid inferiorly and the oral tongue superiorly. No patients had a supraglottic laryngectomy or a delayed total laryngectomy for aspiration. In the presence of a contiguous pharyngeal wall defect, the flap was folded 90 degrees from the plane of the tongue base to provide coverage of the pharyngeal component. One lingual artery and hypoglossal nerve were preserved in all cases. Laryngeal suspensions were performed in all cases. All patients were decannulated at an average of 14.6 days. The Functional Outcomes Swallowing Score was used to assess swallowing outcomes.[93] The tongue base cohort had a mean score of 1.6, which was superior to the oral tongue group at 2.4, but this was not statistically significant. Finally, speech intelligibility was greater than 90% in all patients, with a mean score of 98%. We believe this was partially due to the flap's allowing for excellent anterior tongue remnant mobility.

Urken[94] contended for the importance of reconstructing isolated base of tongue defects with tissue that provides both bulk and sensation. His flap of choice for this defect is also the radial forearm flap because it can be harvested with large amounts of additional vascularized subcutaneous fat to impart the necessary bulk while also providing sensation. He has described a tripartite subcutaneous extension from the body of the flap to reconstruct these defects. The bulk that is provided with these extensions does not diminish as is seen in vascularized muscle. All forearm flaps were sensate in his series. The earliest signs of sensation were noted after 4 months in most patients. The degree of discrimination did not seem to be age dependent. Improvements that suggested a role for sensory recovery were a reduction or disappearance in coughing and decreased use of adaptive techniques for aspiration during the time when sensation returned in the neotongue. However, no swallowing measures or quality of life instruments were used to support the contention that bulk or sensation was helpful, and the absence of a control group further confuses the reinnervation issue.[11] Rieger and colleagues[95] reported on their functional results on 32 patients following reconstruction of the base of tongue with a free radial forearm flap. Speech intelligibility was above 90% for most patients. Only five patients required a feeding tube at some point over the year of postoperative evaluation, and one patient used a tube as the primary source of nutrition. These results contrast with those of Borggreven,[5] which found that patients with advanced tumors (T3-T4 vs. T2) and combined base of tongue and soft palate reconstructions were associated with profound swallowing problems. Despite giving details of sensory reinnervation, swallowing and rates of decannulation were not reported. Urken[96] expanded the use of the sensate forearm flap and has described its use in combination with the iliac crest free flap for reconstruction of significant glossectomy-mandibulectomy defects.

The lateral arm free flap may also be used for base of tongue defects. Civantos[41] reported on 17 patients who underwent major oropharyngeal resections, of whom 12 had more than half of the tongue base removed. Thirteen of these patients had reinnervation of their lateral arm flaps. Three patients had a total laryngectomy for oncologic reasons, and all were able to swallow. Of the remaining 14 patients, 12 could be evaluated between 6 months and 1 year postoperatively. Eight patients (67%) were able to swallow within 2 months, and 11 patients (92%) were able to feed orally by 8 months. All surviving patients were eventually able to achieve an oral diet. Salibian and colleagues[97] reported on seven patients who had ulnar forearm flaps for reconstruction of subtotal glossectomy defects. All patients were able to feed orally. Four patients were able to resume a normal diet, whereas the remaining three were tolerating a soft diet.

Total or subtotal glossectomy defects are a particularly challenging problem for the reconstructive surgeon. The complexity of the reconstruction is due to the multitude of functions provided by the native tongue. These functions are possible because of the array of intrinsic and extrinsic musculature along with the strategic position of the tongue above the larynx. Our flap of choice when faced with these defects is the innervated free latissimus dorsi musculocutaneous flap. Haughey[42] has reported on a design for latissimus dorsi flaps in tongue reconstruction. The flap is designed in such a fashion that the skin paddle is oriented perpendicular to the underlying muscle. The dimensions of the skin paddle are obtained by measuring the distance from the mandibular symphysis to the inferior extent of the resection in the base of tongue, vallecula, or supraglottic larynx. Allowance is made dorsally so that the flap will contact the palate once inset, and lateral wings are added to the skin paddle if a tonsillar defect is present. Also, a triangular wedge of anterior skin is deepithelialized, imbricated, and repaired to create a "cupula," which rises from the anterior neotongue. An allowance is then required anteriorly in the skin paddle design to provide sufficient tissue for this maneuver. The key to this technique is in the inset of the flap. The flap is inset from an inferior to superior direction. If the epiglottis is preserved, the flap is sutured as close to its base as possible. The flap is then suspended from the skull base bilaterally to form a sling under the mandible. This is performed by suturing the latissimus muscle to the pharyngeal constrictors, medial pterygoids, or the masseter if the mandibular ramus was resected (Fig. 101-18). The thoracodorsal nerve was anastomosed to the hypoglossal nerve in all free flap cases. Postoperative superior movement of the flap was observed presumably from reinnervation of the latissimus muscle and was documented by video-oropharyngography in two patients. Fifteen cases were included in the study including three pedicled flaps and one

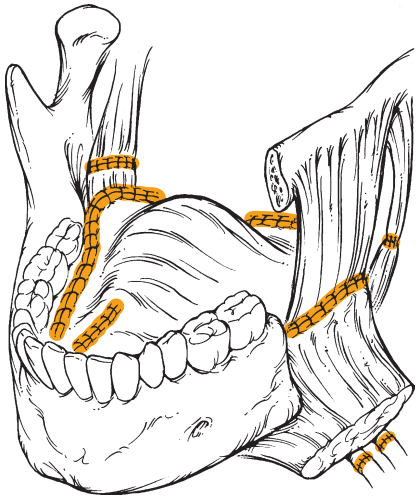

Figure 101-18. Inset of the latissimus dorsi flap for reconstruction of total glossectomy defects. Note the transverse sling created along the undersurface of the mandible by suturing the muscle to the medial pterygoid *(left)* and the masseter *(right),* as well as the neural anastomosis. *(Adapted from Haughey B. Tongue reconstruction: concepts and practice.* Laryngoscope. *1993;103:1136.)*

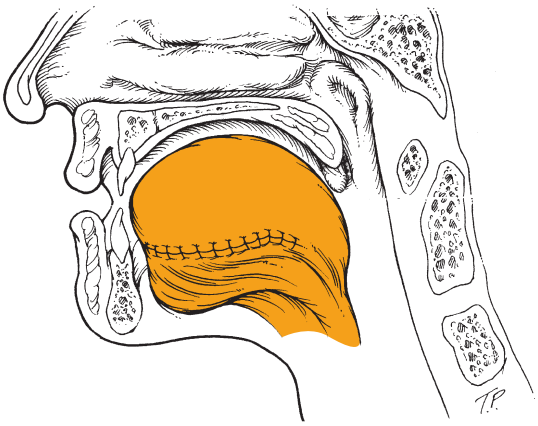

Figure 101-19. Schematic of a tongue reconstructed with a money pouch–like technique using a free rectus flap. Note the position of the neotongue high against the hard palate. *(Adapted from Kiyokawa K, Tai Y, Inoue Y, et al. Functional reconstruction of swallowing and articulation after total glossectomy without laryngectomy: money pouch-like reconstruction method using rectus abdominis myocutaneous flap.* Plast Reconstr Surg. *1999;104:2016.)*

free innervated radial forearm flap. Two of the three pedicled flaps and one of the 12 free flaps failed. Pedicled flap reconstruction with this technique is no longer recommended by the author. Four patients underwent a laryngectomy or laryngeal closure, and one died perioperatively. Of the 10 remaining patients, 8 were decannulated at a median interval of 3.2 weeks. An oral diet was obtained in 10 patients. Two patients in the series were G-tube dependent including one patient whose flap failed and was salvaged with a pectoralis major flap. Three patients who had died did not have swallowing results available. Speech intelligibility was not formally studied but was estimated by a speech language pathologist to be in the range of 85% to 90% on the basis of observations made in three patients. Videos of active, voluntary movement in the flap initiated by the patient are available from the author (BHH) upon request.

Kimata and colleagues[43] reported on functional results and complications after total glossectomy with microvascular reconstruction. Thirty patients were included in the study, all of whom had a total glossectomy with laryngeal preservation. The rectus abdominis musculocutaneous flap was the authors' flap of choice, and this was used in 23 patients. Other flaps used include combinations of the latissimus dorsi, serratus anterior, anterolateral thigh, and radial forearm flaps. Flaps were designed as wide and thick as possible while still allowing for primary closure of the donor site. The flaps were inset from an inferior to superior fashion, with slight anterior and superior traction in an attempt to elevate the larynx. A formal laryngeal suspension to the mandible was performed on four patients. There was one flap failure, and marginal necrosis occurred in five flaps. Orocutaneous fistulas developed in nine patients (27%), and two of these required additional surgery. Of the 30 patients in the study, 21 (70%) were decannulated with laryngeal preservation, and all of these patients were able to achieve an oral diet. In 9 of 30 patients, laryngeal function could not be preserved. Preoperative cerebral dysfunction, resection of the epiglottis, and postoperative orocutaneous fistulas were found to be statistically significant with regard to failure of laryngeal preservation. Speech was judged to be intelligible in 16 of 19 patients evaluated. At the conclusion of follow-up at a mean duration of 29 months, 10 patients were alive without disease. Similarly, Lyos and colleagues[45] reported their experience with the rectus abdominis flap for tongue reconstruction. This was a retrospective outcomes analysis of 14 patients who had a minimum of 75% of the tongue resected with preservation of the mandible and larynx. Eight patients had a total glossectomy, whereas six had subtotal resections. Decannulation was possible in 12 patients (86%) at an average interval of 3.5 months postoperatively. One patient required a laryngectomy for intractable aspiration, and three patients required G-tubes for severe dysphagia. Eleven of 14 patients (81%) were able to tolerate an oral diet of some variety. A palatal augmentation device was found to be of benefit in eight patients because of insufficient vertical height of the free flap reconstruction. This is due to the atrophy of the rectus muscle and subsequent displacement of the skin paddle inferiorly. Speech was judged as being acceptable in nine patients (64%).

A money pouch–like reconstructive method after total glossectomy without laryngectomy has been described with a free rectus abdominis myocutaneous flap.[44] With this technique, the authors established a money pouch–like neotongue by harvesting a skin paddle that is 20% larger than the defect in both width and length. When the skin paddle is sutured to the defect, the excess skin and fat fold into the shape of a money pouch, thus establishing the vertical height needed for successful tongue reconstruction (Fig. 101-19). They report on only three patients in this study; however, a normal swallow was achieved in all patients by 6 weeks with the assistance of oral ingestion training. Speech intelligibility was about 50% to 60% in the patients. Although this seems to be a novel technique, other descriptions of the rectus flap for tongue reconstruction have attempted to overcorrect to achieve this vertical height of the reconstruction.[43] The rectus flap may also be inset as a sling under the mandible to support the overlying position of the skin paddle. Urken[46] has preferred the use of the rectus flap over the latissimus for this purpose because of the tendinous inscriptions, which are able to hold sutures. He also advocates the use of drill holes in the mandible for suspension of the rectus flap. Atrophy of the rectus is inevitable, but this may be reduced by reinnervating the muscle with a hypoglossal nerve stump, although meaningful movement of the muscle has not been documented.[94]

Hayden[34] reported on the use of the lateral thigh flap for reconstructing nine patients with total or near-total glossectomy defects. All flaps survived completely, and no patients had postoperative fistulas develop. Functional results in this cohort of patients are not reported. The author states that the flap is ideal for this purpose (in selected cases with appropriately fat thighs) because the distal portion of the flap can be deepithelialized and used as a platform under the mandible, while the proximal thicker portion of the flap is used for reconstruction of the neotongue.[34] The free anterolateral thigh flap has been reported for total and near-total glossectomy defects. The flap is useful for this purpose because it provides significant bulk and also the possibility of sensory reinnervation. Yu[98] reported on 13 patients

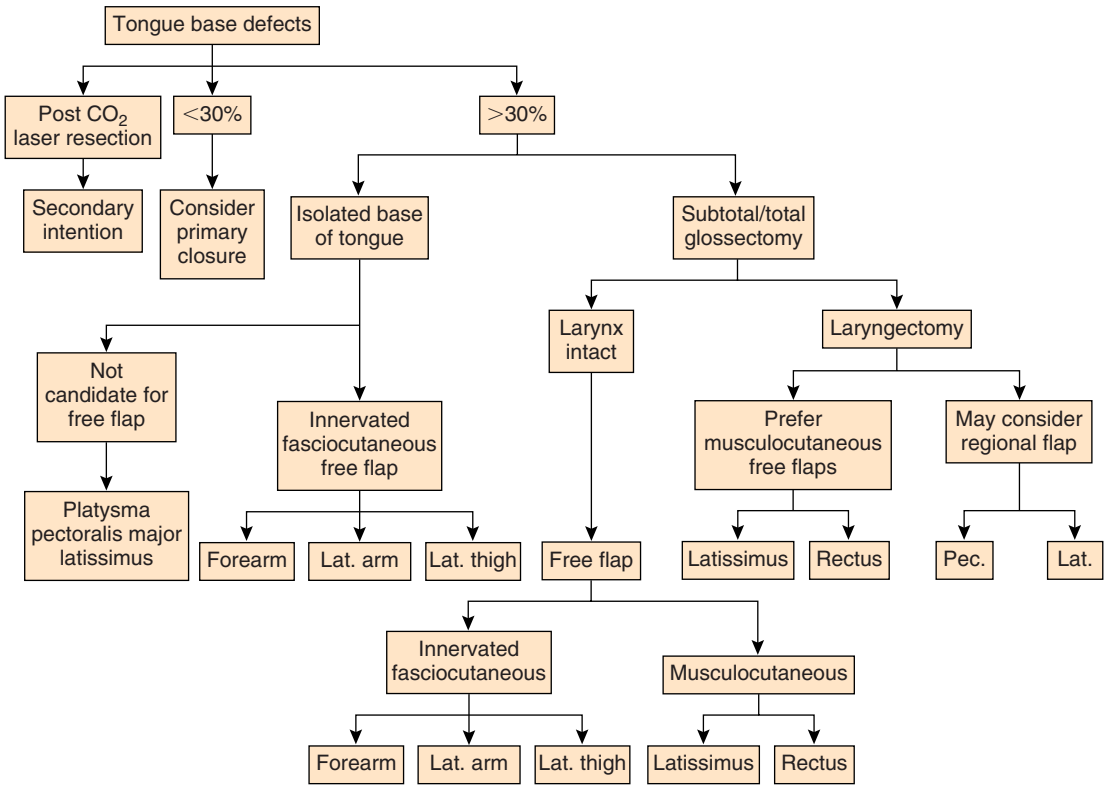

Figure 101-20. Algorithm for tongue base reconstruction.

reconstructed with this flap, 8 of which were reinnervated. Innervated flaps were found to have superior sensory recovery, which resulted in improved swallowing function and patient satisfaction. Figure 101-20 presents an algorithm for reconstructing defects of the tongue base.

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CHAPTER ONE HUNDRED AND TWO

Diagnostic Imaging of the Pharynx and Esophagus

Barton F. Branstetter, IV

Key Points

- Esophagram (sometimes called *barium swallow*) should be used to evaluate pharyngeal mucosa, whereas modified barium swallow should be used to assess deglutition.
- PET/CT has become an essential modality for the staging, monitoring, and surveillance of pharyngeal and esophageal carcinomas.
- Although endoscopy has replaced fluoroscopy for many pharyngoesophageal diagnoses, diseases of peristalsis, fistulas, and diverticula are still best evaluated radiographically.
- Nasopharyngeal carcinoma is best staged with a combination of MRI and PET/CT.
- Esophageal carcinoma is best staged with a combination of endoscopic ultrasound and PET/CT.
- Oropharyngeal and hypopharyngeal carcinoma is best staged with endoscopy and PET/CT.

As the diversity of radiologic examinations continues to grow, it is increasingly important for referring clinicians to understand the arsenal of tests offered by radiologists. The improved quality and availability of cross-sectional imaging, along with advances in endoscopic techniques, have contributed to a decline in fluoroscopy. However, many disorders of the pharynx and esophagus still are best evaluated with fluoroscopic techniques. In particular, patients who have pain, trismus, a hyperactive gag reflex, or bulky disease are often not optimally evaluated with direct inspection or endoscopy, and mucosal lesions may not be evident on cross-sectional modalities. This chapter discusses the basics of radiographic technique and anatomy, with a focus on the appropriate choice of imaging modality for evaluation of the pharynx and esophagus. The radiographic appearance of specific disorders is then discussed.

Techniques

Conventional Radiography

Conventional radiographs (plain films) of the neck are economical and readily available. They are particularly useful in pediatric patients with airway distress. The lateral projection provides the most information, and it will often be obtained without the frontal projection (Fig. 102-1). If the examination is performed to evaluate a radiopaque foreign body, the frontal projection should be included. Patients are instructed to say the letter "e" during exposure to bring the tongue forward and better demonstrate the oropharynx.[1] If a hypopharyngeal lesion is being evaluated, the patient should blow through compressed lips to distend the hypopharynx. In children, the lateral radiograph should be obtained during peak inspiration to prevent redundancy of the prevertebral soft tissues that may simulate pathology.

Chest radiographs occasionally reveal advanced esophageal abnormalities or pneumomediastinum, but fluoroscopy and cross-sectional imaging are preferred for evaluation of the thoracic esophagus.

Computed radiography and digital radiography are the modern counterparts to screen-film techniques. Instead of exposing a piece of film, the technologist captures an image on a reusable array of digital elements and reads the image directly into a computer. One advantage of these techniques is the ability to emphasize subtle soft tissue differences, even in suboptimally exposed images.[2]

Xeroradiography is a historical technique that clearly delineated the soft tissues of the neck.[3] However, xeroradiography had a narrow range of applications, and it is no longer available at most institutions.

Linear and complex-motion tomography improve on conventional radiographs by blurring the soft tissues that obscure the pharyngeal walls. Small mucosal lesions can sometimes be distinguished, but conventional tomography has been replaced almost universally by computed tomography (CT).

Fluoroscopy

Motion capture techniques with intraluminal contrast are invaluable when studying the functional dynamics of the pharynx and esophagus. Although endoscopy provides direct visualization of the mucosa, radiographic techniques provide a more physiologic examination. Both cineradiography (high-resolution images obtained at a low frame rate) and video capture (low-resolution images obtained at a high frame rate) are used in each examination. Cineradiography provides better spatial resolution for mucosal detail, whereas video capture allows more dynamic evaluation with less radiation. At most institutions, the video capture is not permanently stored, so it may be cumbersome or impossible to review these data after the examination is completed.

On traditional film, radiodense elements appear whiter than radiolucent elements. This convention has not persisted in the age of digital imaging; some aspects of anatomy and pathology are visualized better when the image is inverted. The images in this chapter follow the traditional convention.

The term "esophagram" is slowly replacing the ambiguous term "barium swallow." Note that an esophagram, which is designed to evaluate the pharyngeal and esophageal mucosa, is distinct from a "modified barium swallow," which evaluates laryngotracheal aspiration and is usually performed in conjunction with a speech pathologist. At some institutions, an esophagram includes a complete evaluation of the pharynx, but at other institutions, a "cervical esophagram," "pharyngoesophagram," or "pharyngography" must be specifically requested. Note that the nasopharynx is not evaluated with fluoroscopic techniques; cross-sectional imaging is required.

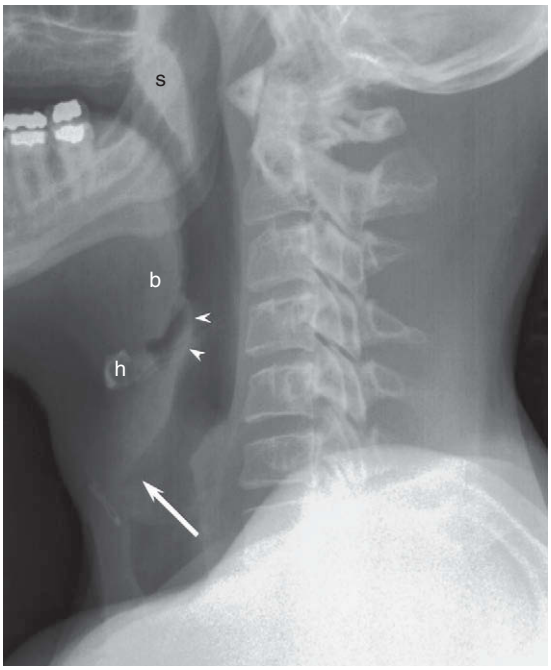

Figure 102-1. Lateral radiograph of the neck emphasizing soft tissues. The soft palate *(s),* tongue base *(b),* hyoid bone *(h),* and epiglottis *(arrowheads)* are marked. The laryngeal ventricle is barely visible as a dark wedge *(arrow).*

Pharyngoesophagram

A complete esophagram has three phases: full-column (single contrast), air-contrast (double contrast), and mucosal relief.[4] To obtain full-column images, the patient is given a thin suspension of barium by mouth. The pharynx is best imaged in the standing position, with rapid cineradiography (four to six images per second) in several projections (Fig. 102-2). In the frontal projection, the patient's neck is extended to prevent the jaw from obscuring the pharynx. When digitally displayed, cine images reveal much of the swallowing dynamics. Video capture is still useful, however, to evaluate equivocal filling defects.

Full-column images of the esophagus (Fig. 102-3) are obtained in a prone oblique position, with the patient drinking barium suspension from a straw. There are two objectives to this portion of the examination: evaluate esophageal peristalsis and maximally dilate the esophagus to identify contour abnormalities. Peristalsis is evaluated with videotaped single swallows. Maximum dilatation is achieved with rapid swallows followed by a Valsalva maneuver. The prone position eliminates gravity as a factor in peristalsis.

Air-contrast images of the esophagus (see Fig. 102-3) are obtained with the patient upright and in slightly left anterior obliquity. An effervescent agent is first administered, followed by a thick barium suspension. The barium coats the mucosal surface, whereas the gas from the effervescent agent distends the lumen. This provides exquisite mucosal detail and is most useful for the evaluation of small plaquelike mucosal tumors and the mucosal irregularities of esophagitis.[5] If the patient is unable to undergo the air-contrast portion of the thoracic esophagram, prone full-column imaging should be obtained in two orthogonal planes as an alternative.

Air-contrast images of the pharynx are not always necessary because this region is amenable to direct inspection. However, in some cases, such as tumors arising in the hypopharynx, air-contrast images are of use. After the administration of thick barium suspension, phonation and a modified Valsalva maneuver are used to distend the pharynx (Fig. 102-4).

Mucosal-relief images of the esophagus (Fig. 102-5) are obtained after the administration of thick barium suspension, but without air distention. Esophageal varices and some mucosal lesions are best seen with mucosal relief. Only the distal esophagus and gastroesophageal junction need to be imaged in this phase of the examination.

At the conclusion of an esophagram, after the esophagus has completely cleared all contrast, Valsalva and modified Valsalva maneuvers should be performed to document gastroesophageal reflux. It is important to realize, however, that these maneuvers are insensitive for the diagnosis of intermittent gastroesophageal reflux.

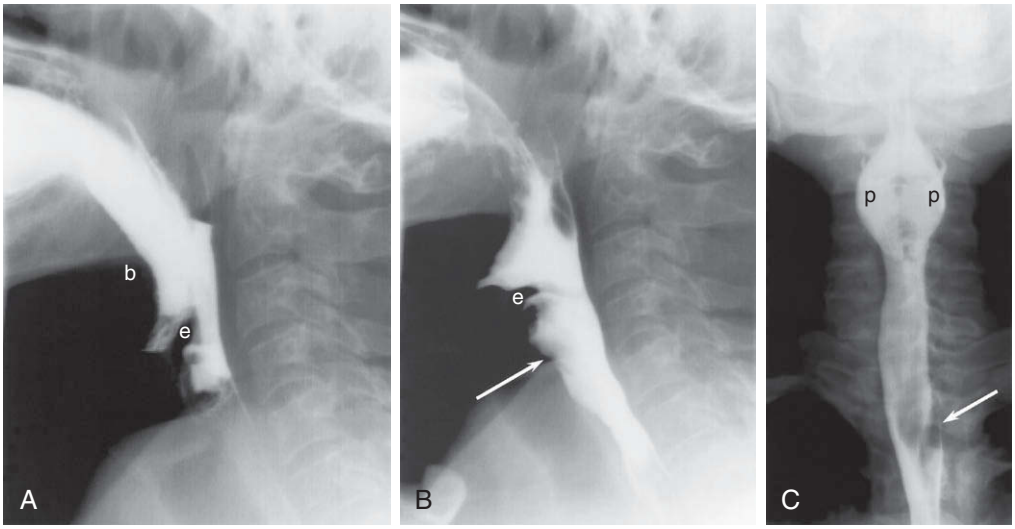

Figure 102-2. Normal pharyngogram. **A,** Lateral projection, early phase. The epiglottis *(e)* is upright, and the base of tongue *(b)* is well evaluated. **B,** Lateral projection, late phase. The epiglottis *(e)* has inverted. Note the normal anterior venous plexus *(arrow),* which mimics a mucosal lesion. **C,** Frontal projection, late phase. The pyriform sinuses *(p)* are well seen. Dynamic flow *(arrow)* can mimic a filling defect.

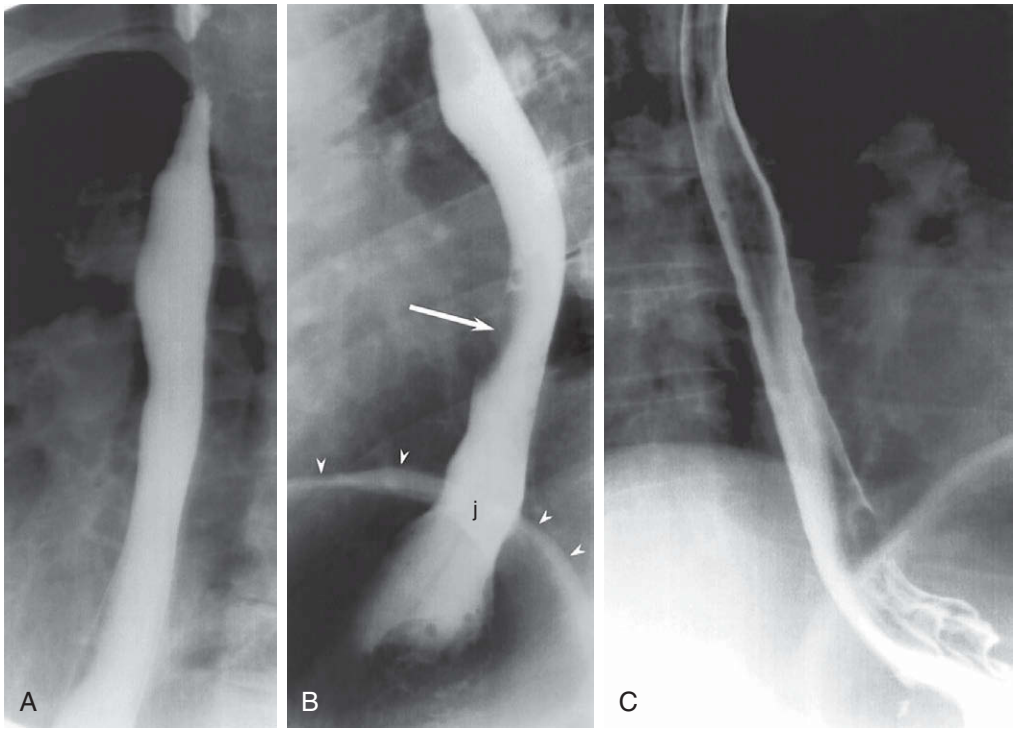

Figure 102-3. Normal esophagram. **A,** Full-column prone oblique image of the upper thoracic esophagus. Note the featureless mucosa. **B,** Full-column prone oblique image of the distal esophagus. Contrast spills past the gastroesophageal junction *(j)* into the air-filled stomach. The diaphragm is marked by *arrowheads.* An air bubble *(arrow)* can be distinguished from a true lesion because the air bubble moves during the examination. **C,** Normal air-contrast upright oblique image of the distal esophagus.

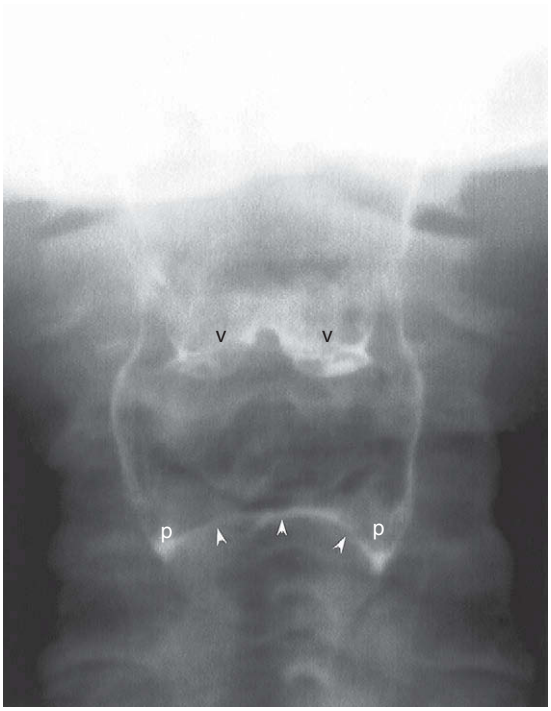

Figure 102-4. Normal air-contrast pharyngogram, frontal projection. Barium outlines the valleculae *(v)* and pyriform sinuses *(p).* The pyriform sinuses are connected by the smooth, arcuate postcricoid line *(arrowheads).*

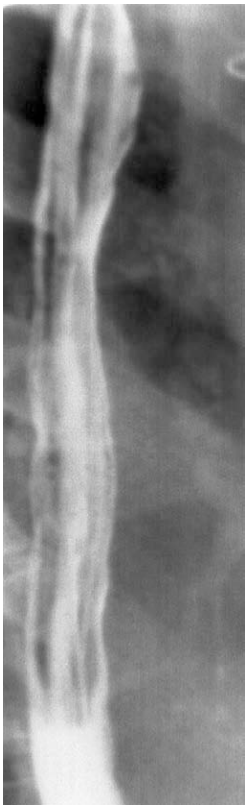

Figure 102-5. Normal mucosal-relief esophagram, oblique projection. Thick barium coats the undistended midthoracic esophagus. The normal longitudinal mucosal folds are easily identified.

Modified Barium Swallow

A modified barium swallow evaluates the coordination of the swallow reflex. It is most often used to determine a cause for, and evaluate the severity of, tracheal aspiration. The speech pathologist, using appropriate radiation safety precautions, administers barium suspensions of varying thickness while the radiologist observes fluoroscopically in the lateral projection. The entire examination is videotaped.[6,7]

The patient is given barium suspension of several consistencies (e.g., thin liquid, thick liquid, nectar, paste, solid). The various barium suspensions are intended to mimic different food consistencies and provide a more complete assessment of aspiration risk. If tracheal aspiration or laryngeal penetration is identified with the head in a neutral position, the speech pathologist may direct the patient to perform protective maneuvers during deglutition. Such maneuvers include varying the head position (chin tuck) and postprandial forced cough. The examination can be supplemented with images in the frontal projection to evaluate symmetry of the pyriform sinuses.

Oral Contrast Agents

Barium suspension is the best-known fluoroscopic contrast agent, but some patients are not appropriate candidates for oral barium administration. Patients who may have a perforated pharynx or esophagus are at risk for barium extravasation into the soft tissues of the neck or chest. Extravasated barium may incite an inflammatory reaction or may become inspissated and fail to resorb.[8] Water-soluble contrast agents (such as those used for intravenous CT contrast) may be used as an alternative. Unfortunately, water-soluble agents are not as dense as the barium suspension, so they are less sensitive to small leaks. If no leak is detected after the administration of a water-soluble agent, the examination should be repeated with barium.[9]

Ionic contrast agents have another disadvantage: if they are aspirated into the lungs, they may cause a chemical pneumonitis and pulmonary edema.[10] Nonionic water-soluble agents are presumed to be safer and thus should be used if there is a risk of aspiration or tracheoesophageal fistula.

Oil-based contrast agents for the evaluation of the larynx and pharynx are of historical interest only.

Computed Tomography

At most institutions, CT is the modality of choice for evaluating masses in the neck and chest. Two recent advances have dramatically changed the quality of CT imaging: multidetector scanners and helical acquisition. Multidetector scanners have several rows of photoreceptors, allowing the simultaneous acquisition of several slices. Helical techniques allow patients to move continuously through the scanner instead of stopping for each slice. These advances have dramatically decreased scan times and radiation doses while improving spatial resolution.[11] This improved resolution allows multiplanar and three-dimensional reconstructions that rival magnetic resonance (MR) for clarity and diagnostic accuracy. The rapid scan times permit dynamic CT imaging, which can assess vascularity and other physiologic properties.[12]

CT is readily available and provides critical information about the extent and character of mass lesions. In known tumors, CT is used to determine the degree of invasion into surrounding deep tissues, the relationship of the neoplasm to critical structures such as the vocal cords and arteries, and the involvement of regional lymph nodes.[13] CT is comparable to magnetic resonance imaging (MRI) for the evaluation of bone invasion,[14] but MRI is preferred for the evaluation of soft tissue extent, particularly at the skull base.[15] Disadvantages of CT include artifacts from dental amalgam and from patient body habitus, particularly at the shoulders.

Intravenous contrast is of particular importance in the neck because enlarged lymph nodes may be difficult to distinguish from unenhanced vessels. Allergies to contrast material and renal dysfunction are relative contraindications to intravenous contrast. Some practitioners avoid intravenous contrast in patients who may require radioablation of thyroid neoplasms because the contrast can impede iodine uptake for an indeterminate amount of time after the examination.

Ionic contrast media are more prone to allergic reactions than the more expensive nonionic media. For this reason, some institutions have abandoned ionic contrast media. Ionic contrast should be avoided in patients with airway pathology because a mild allergic reaction could precipitate severe airway compromise.

Helical neck CT should be performed with a maximum slice thickness of 3 mm. Thinner slices may be required to delineate the extent of pathology, particularly in tumors near the larynx. A contrast bolus of 75 to 125 mL is used, with a delay of 30 to 60 seconds.[16] Faster scanners require longer contrast delays, so revised protocols are required when equipment is upgraded. CT of the chest is performed with a thickness of 5 to 7 mm; additional intravenous contrast is usually not required. CT of the neck and chest should not be performed as a continuous acquisition because the arms are positioned differently for the two scans.

Magnetic Resonance Imaging

Unlike CT, which relies on ionizing radiation to create images, MRI uses a strong magnetic field and radiofrequency pulses to interrogate the patient's tissues. It is particularly useful for evaluating tumors of the pharynx and larynx, but it is less useful in the thorax, where motion artifact and field distortions prevent a thorough evaluation of the mediastinum.[17]

MRI has the substantial advantage of multiple pulse sequences, which allows more precise characterization of pathologic tissue. The most frequently used sequences are T1-weighted and T2-weighted sequences. Postcontrast images are exclusively T1 weighted. T1-weighted images demonstrate anatomic relationships, whereas T2-weighted images are sensitive for pathology. Many additional sequences and modifications (e.g., inversion recovery, fat suppression, magnetization transfer, and diffusion weighting) can more precisely determine tissue characteristics and extent of pathology.

Advantages of MRI include reduced artifacts from dental amalgam and body habitus, as well as the ability to directly image in any plane including oblique planes. The gadolinium-based intravenous contrast agents used in MRI have a substantially lower risk of allergic reaction than CT agents do.[18] Disadvantages of MRI include the long duration of MRI studies, which sometimes results in motion artifact, especially in debilitated patients or patients with respiratory compromise. The small bore of the MRI magnet often induces claustrophobia. Many patients cannot go near the MRI magnet because of metallic or electronic implants that might be displaced or triggered by the rapid changes in the magnetic field.[19] In particular, cardiac pacemakers/defibrillators, cochlear implants, and ferromagnetic aneurysm clips are relative contraindications to MRI.[20] Metallic foreign bodies may also be of concern, depending on their location.[21]

Different receiving coils are available for MRI, with characteristics tailored to different body parts. It is critical for head and neck patients to be imaged with a surface coil, which allows for improved spatial resolution and higher signal-to-noise ratios. Low-field "open" MRI magnets do not have the spatial resolution or signal-to-noise characteristics to evaluate the intricate anatomy of the skull base or larynx and are not recommended for imaging of the head and neck.

Ultrasound

Transcutaneous sonographic evaluation of the neck[22] has undergone a resurgence in popularity in patients with thyroid cancer and for guidance in interventional procedures. Although ultrasound can be used to evaluate superficial lymph nodes in the neck, it may overlook deep nodes and cannot be relied on for a complete evaluation of cervical tissues. Transesophageal echosonography provides information that is complimentary to CT and invaluable for the evaluation of the extent of esophageal lesions across tissue planes.[23] All sonographic techniques are highly operator dependent, so experienced technologists and appropriately trained physicians are necessary to produce diagnostic-quality examinations.

Positron Emission Tomography-Computed Tomography

Combined 18F-fluorodeoxyglucose positron emission tomography and CT scanning (PET/CT) has revolutionized the care of head and neck cancer patients.[24] PET is a functional imaging technique that relies on the increased metabolic uptake of glucose in tumors to identify

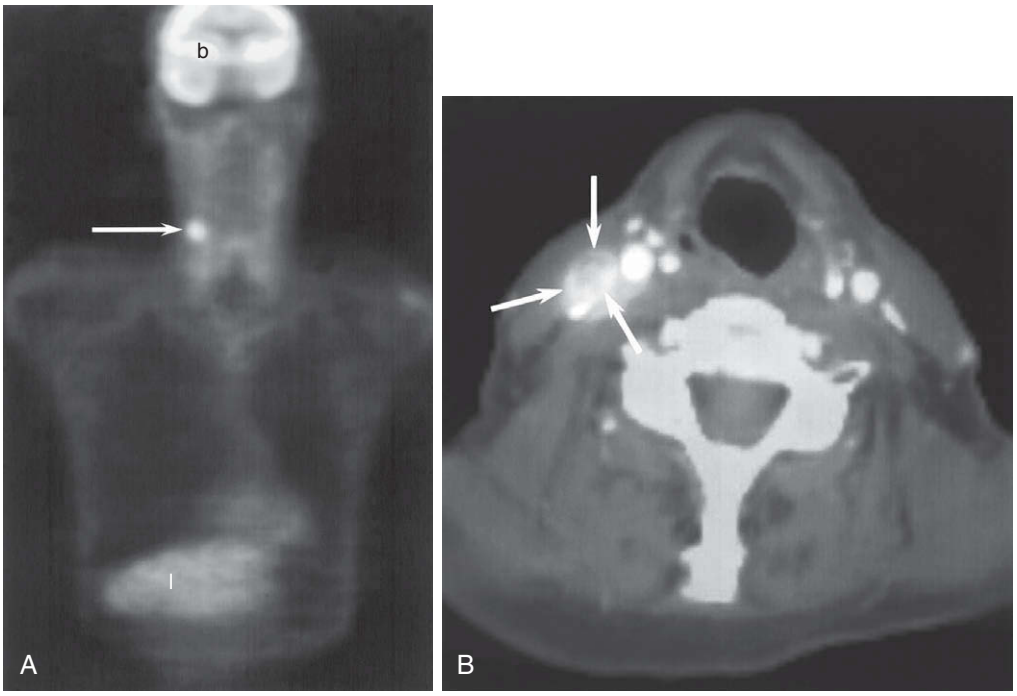

Figure 102-6. Positron emission tomography (PET)-computed tomography identifies a metastatic cervical node. **A,** Coronal PET image shows focal uptake in the lower neck *(arrow),* but the precise anatomic location is uncertain. Brain *(b)* and liver *(l)* are marked. **B,** Fused axial image localizes the uptake to a level III lymph node.

unknown primary tumors, stage malignancies, search for metastatic disease, and evaluate recurrences.[25,26] The major limitation of PET imaging is its poor spatial resolution, which is particularly significant in the head and neck. Combined PET/CT scanners use the high spatial resolution of CT with the functional information of PET to produce fused images that overcome this difficulty (Fig. 102-6). For the evaluation of head and neck cancers, PET/CT is superior to either PET or CT alone.[27]

PET/CT is used in the staging of cancer, the monitoring of treatment response, and the surveillance of treated patients.[28] Optimal monitoring and surveillance schemata have not yet been established, but it is known that PET/CT should not be performed until at least 8 weeks after the conclusion of therapy to avoid both false-positive and false-negative results.[29] Surveillance with PET/CT is particularly useful because of the low rate of false-negative studies.

The analysis of PET/CT scans is complicated and requires a radiologist with experience in both PET/CT and head and neck imaging. Physiologic uptake of FDG is prevalent in the head and neck, especially during contraction of muscles (e.g., neck and thyroarytenoid muscles), and may therefore be confused with tumor uptake.[30] Inflammation, either postoperative or from infectious sources such as the teeth, palatine, or lingual tonsils, may also obscure the interpretation, resulting in false-positive reads and unnecessary clinic evaluations and biopsies.

Future trends in PET/CT will likely include combined PET-MR scanners, the development of novel ligands to supplement or replace fluorodeoxyglucose, and guidance for optimizing the utilization of this relatively new modality.

Other Nuclear Medicine

Although PET/CT is the most commonly used nuclear medicine examination in the head and neck, other nuclear medicine tests are sometimes of use. Esophageal transit, gastroesophageal reflux, and gastric emptying can be studied with conventional nuclear medicine techniques.[31,32] These studies are more sensitive than fluoroscopy for the presence of reflux, but the quantitative degree of reflux does not correlate well with symptoms. Radionuclide swallowing studies are used predominantly in the pediatric population.

Radiographic Anatomy

Pharynx

The radiographic anatomy of the pharyngeal lumen is best visualized with air-contrast fluoroscopic images (see Fig. 102-4). The mucosal surfaces of the epiglottis, vallecula, and pyriform sinuses are easily identified. Normal asymmetry of the lingual tonsils should not be confused with a vallecular mass. The epiglottis is best evaluated in the lateral projection, where its thickness can be directly assessed. The pyriform sinuses may be asymmetric, but a complete lack of filling is suspicious for tumor. Barium pooled between the posterior margin of the larynx and the posterior wall of the hypopharynx forms the postcricoid line (see Fig. 102-4). Disruption or irregularity of this line is a sign of tumor invasion. The cricopharyngeus muscle lies anterior to the sixth cervical vertebra. It may be seen as a slight indentation on the posterior wall of the hypopharynx, but it is often not visualized in normal individuals. The normal cross-sectional anatomy of the upper aerodigestive tract is demonstrated in Figures 102-7 and 102-8.[33]

Esophagus

The esophagus begins at the level of the sixth cervical vertebra. The cervical esophagus lies posterior to, and slightly to the left of, the trachea (see Fig. 102-7). Surrounding structures that may affect the cervical esophagus include the trachea, cervical spine, thyroid and parathyroid gland, and cervical lymph nodes. On CT, the anteroposterior diameter of the collapsed cervical esophagus should not exceed 16 mm, and its lateral dimension should not exceed 24 mm, except at the esophageal verge, where it may be more prominent.[34] On full-column lateral projections, there is a normal mucosal irregularity of the anterior esophagus just below the cricoid cartilage (see Fig. 102-2). This is caused by lax mucosal folds overlying the ventral submucosal venous plexus, and it should not be mistaken for tumor invasion or a web.[35] Unlike webs and tumors, the venous plexus changes shape during swallowing.

The thoracic esophagus lies anterior to the spine, anteromedial to the descending aorta (see Fig. 102-7). The phrenic ampulla, which is a normal widening of the esophageal lumen, is seen just above the gastroesophageal junction (Fig. 102-9). There are three normal inden-

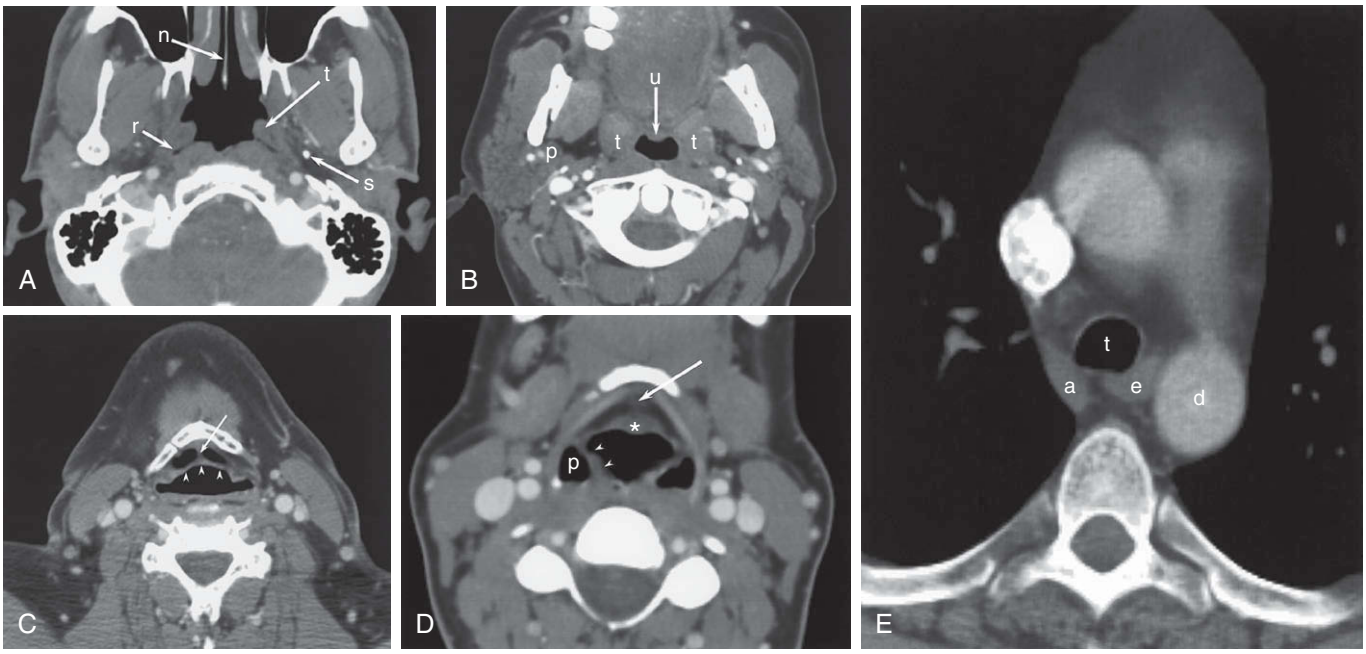

Figure 102-7. Normal computed tomography anatomy. **A,** Nasopharynx. The torus tubarius *(t),* fossa of Rosenmüller *(r),* nasal septum *(n),* and styloid process *(s)* are marked. **B,** Oropharynx. Tonsillar pillars *(t),* deep lobe of the parotid *(p),* and uvula *(u)* are marked. **C,** Supraglottis. The epiglottis *(arrowheads)* and the hyoepiglottic ligament *(arrow)* form the borders of the vallecula. **D,** Hypopharynx. The petiole of the epiglottis *(*)* should not be confused with tumor invading the pre-epiglottic fat *(arrow).* The aryepiglottic fold *(arrowheads)* forms the medial border of the pyriform sinus *(p).* **E,** Thorax. The esophagus *(e)* lies posterior and to the left of the trachea *(t).* Surrounding structures include the azygous vein *(a)* and the descending aorta *(d).*

tations on the anterolateral esophagus: aortic arch, left mainstem bronchus, and left atrium (see Fig. 102-3). Other nearby structures include the descending aorta, aortic arch and great vessels, carina, mediastinal lymph nodes, and spine.

When the esophagus is filled with contrast, it is a featureless tube. When the esophagus is collapsed, longitudinal mucosal folds appear along the entire length of the organ. Occasional transverse folds are normal.

Motility Disorders

Pharynx

The modified barium swallow is the most appropriate radiologic test to evaluate swallowing dysfunction.[7] Although an esophagram provides some information about deglutition, the modified swallow uses barium of several different consistencies, which provides a more detailed evaluation. Functional endoscopic evaluation of swallowing, with or without sensory testing, has been proposed as an alternative to the modified swallow.[36] However, the modified swallow provides a more physiologic environment because there is no endoscope to interfere with motility. During a modified swallow, patients can use protective maneuvers such as chin tuck and forced cough, which are not available during endoscopy. Furthermore, the modified swallow evaluates the upper phases of swallowing in more detail.[37] Endoscopy and modified swallow are considered complementary examinations at most institutions.

The modified barium swallow can evaluate all phases of the swallow reflex.[1,6,38] The tongue forms the oral bolus and then transports it from the oral cavity to the oropharynx. The soft palate elevates and approximates the posterior pharynx to prevent velopharyngeal reflux. The entire larynx elevates, followed by a peristaltic wave through the pharynx. The epiglottis inverts to deflect the bolus into the pyriform sinuses and protect the laryngeal vestibule. At the bottom of the hypopharynx, the cricopharyngeus muscle relaxes to permit the passage of the food bolus.

Velopharyngeal occlusion can be observed directly. Elevation of the larynx is best visualized by observing the hyoid bone. Epiglottic inversion is fast, and confirmation of this event may require review of the video images. Brief episodes of contrast penetration may be seen in the laryngeal vestibule. If the contrast clears rapidly and without cough, this finding does not indicate a risk of tracheal aspiration. A small amount of barium may pool in the valleculae or the pyriform sinuses in normal patients, but the peristaltic wave should strip the contrast from the remainder of the pharynx. The cricopharyngeus muscle lies at the level of the C6 vertebral body, and it is not normally visualized.

Abnormal Deglutition

Aspiration can occur in any phase of deglutition. During the oral phase, incomplete control of the oral bolus allows contrast to spill over the base of the tongue into the vallecula. In severe cases, the vallecula will fill completely, and contrast will spill over the epiglottis into the larynx. During peristalsis, failure of epiglottic inversion allows contrast to enter the larynx. After the swallow, incomplete clearance of contrast leads to postprandial aspiration when the patient resumes breathing.

Abnormal pharyngeal motility is caused by disorders of the brainstem, cranial nerves IX and X, the myoneural junction, or the pharyngeal musculature. Myasthenia gravis is a disorder of the myoneural junction that produces hesitancy in swallow initiation, nasopharyngeal reflux, enlargement of the pharynx, tracheal aspiration, and incomplete clearance. The findings worsen over consecutive swallows and improve after neostigmine administration. Diseases that affect the pharyngeal muscles such as dermatomyositis, systemic lupus erythematosus, myotonic dystrophy, systemic sclerosis, and oculopharyngeal myopathy produce weakened pharyngeal contractility with incomplete clearance.

Unilateral pharyngeal palsy causes an asymmetry in the pyriform sinuses because the contrast is thrown to the palsied side by the functioning pharyngeal constrictors.[39] This asymmetry should not be misinterpreted as a filling defect from carcinoma in the unaffected side. A careful dynamic examination of several swallows may be necessary to prevent this diagnostic error.

Cricopharyngeal Dysfunction

Unlike the other muscles of pharyngeal constriction, the cricopharyngeus remains contracted between swallows, acting as an upper esophageal sphincter. It normally relaxes during deglutition to allow the

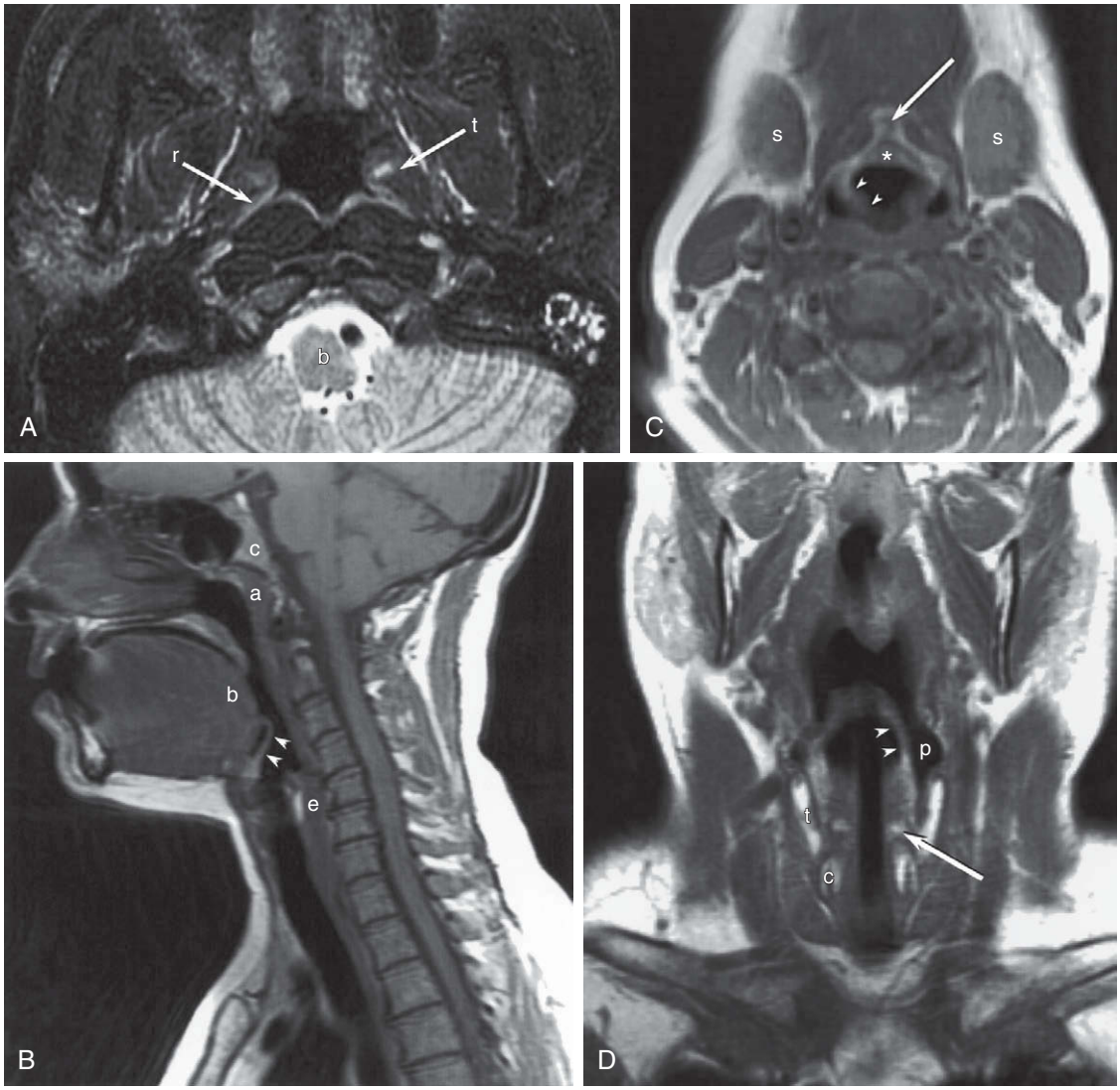

Figure 102-8. Normal magnetic resonance anatomy. **A,** T2-weighted axial image through the nasopharynx. Brainstem *(b),* torus tubarius *(t),* and fossa of Rosenmüller *(r)* are marked. **B,** Sagittal T1-weighted image through the neck and face. Adenoids *(a),* tongue base *(b),* clivus *(c),* epiglottis *(arrowheads),* and cervical esophagus *(e)* are marked. **C,** Axial T1-weighted image through the hypopharynx. The petiole of the epiglottis *(*),* the pre-epiglottic fat *(arrow),* the aryepiglottic fold *(arrowheads),* and the submandibular glands *(s)* are marked. Compare with Figure 102-7, **D. D,** T1-weighted coronal image of the neck. The aryepiglottic fold *(arrowheads)* forms the medial border of the pyriform sinus *(p).* Invasion of the thyroid *(t)* and cricoid *(c)* cartilages from hypopharyngeal tumors can be assessed in this plane. The arytenoid cartilages *(arrow)* are also seen.

passage of the food bolus. When the muscle fails to completely relax (cricopharyngeal achalasia), there is a smooth posterior impression on the hypopharynx at the level of the C6 vertebra (Fig. 102-10). Unlike most retropharyngeal masses, the cricopharyngeus does not exceed 1 cm in vertical dimension. The most frequent cause of cricopharyngeal achalasia is cerebrovascular disease. Other causes include pseudobulbar palsy, nasopharyngeal carcinoma, poliomyelitis, thyroid myopathy, cervical vagotomy, polymyositis, dermatomyositis, oculopharyngeal syndrome, amyotrophic lateral sclerosis, and hiatus hernia, but many cases are idiopathic. Cricopharyngeal achalasia has been implicated in the development of Zenker's diverticula.[40]

Incompetence of the upper esophageal sphincter is called cricopharyngeal chalasia. It manifests radiographically as a lack of cricopharyngeal impression between swallows. Cricopharyngeal chalasia is specific for myotonic dystrophy, although most patients with myotonic dystrophy have cricopharyngeal achalasia instead.[41]

Delayed opening of the cricopharyngeus, seen in familial dysautonomia, results in aspiration and recurrent pulmonary infections. This disorder is distinct from cricopharyngeal achalasia in that the muscle relaxes completely after a delay.

Esophagus

Manometry is considered the reference standard for evaluation of esophageal dysmotility. The relative sensitivity of fluoroscopy, radionuclide scans, and manometry is controversial.[31,32,42,43] However, radiographic techniques are less invasive and elicit less patient discomfort. Fluoroscopy has the additional advantage of identifying structural abnormalities.

A normal (primary) peristaltic wave is initiated by a swallow. The wave passes uninterrupted to the lower esophageal sphincter (LES). The contrast bolus should remain intact during a primary wave; contrast that escapes proximally is the earliest sign of weakened peristalsis. Secondary peristaltic waves are initiated in the midesophagus by local irritation such as from gastroesophageal reflux or retained food. Tertiary contractions are nonperistaltic local contractions, a contributing factor in dysmotility.

Diminished Peristalsis

Achalasia is a neuromuscular disorder caused by degeneration of Auerbach's plexus.[44] Peristalsis fails, but the LES remains tight, so the esophagus progressively dilates. In severe cases a dilated esophagus with

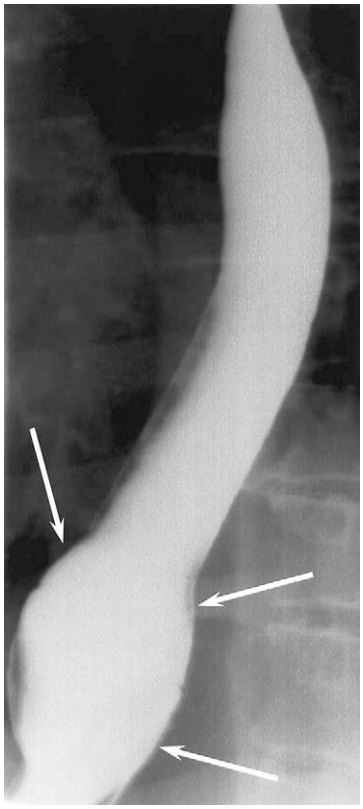

Figure 102-9. The phrenic ampulla is a normal widening of the distal esophagus just above the diaphragm.

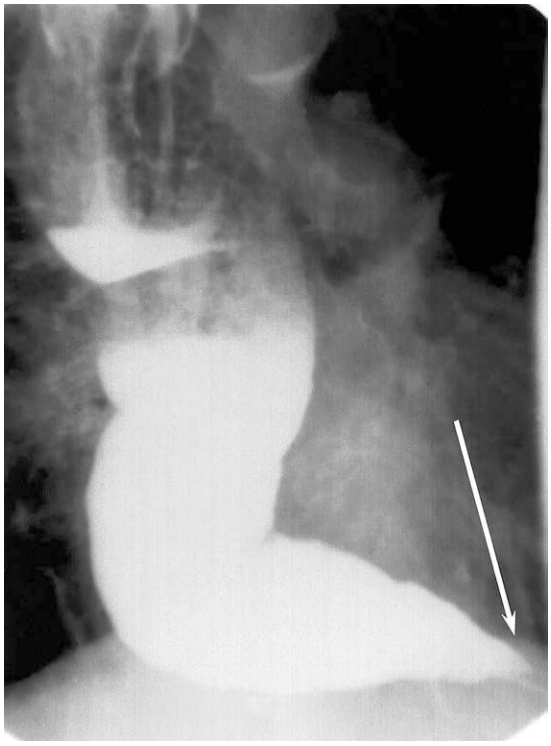

Figure 102-11. Achalasia. Oblique image of the lower mediastinum reveals a patulous esophagus with beaking of the gastroesophageal junction *(arrow)*.

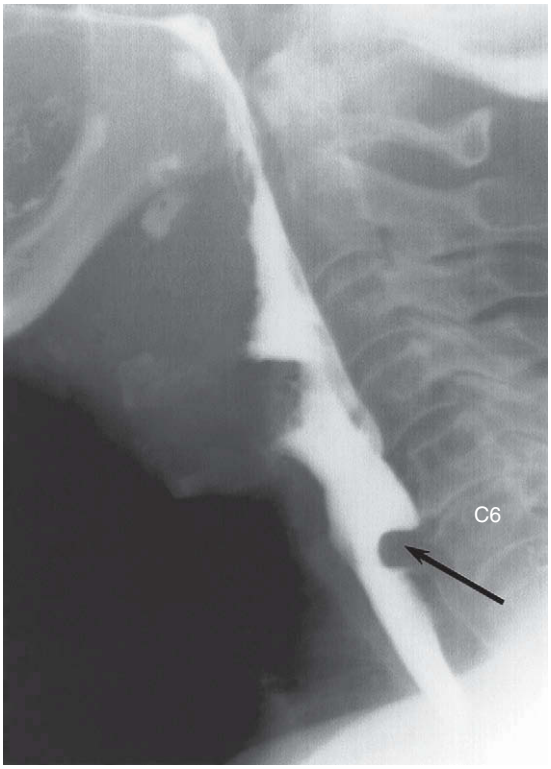

Figure 102-10. Cricopharyngeal achalasia. Lateral view from an esophagram reveals a smooth, rounded impression *(arrow)* on the posterior esophagus at the level of the sixth cervical vertebra *(C6)*.

retained food can be appreciated on a chest film. On fluoroscopy, the distal esophagus has a conical (beaked) shape (Fig. 102-11). In early stages of the disease, the esophagus may be only minimally dilated, with dominant tertiary contractions. This is called vigorous achalasia, and it may mimic esophageal spasm (Fig. 102-12).[45] Patients with achalasia are at increased risk of esophageal carcinoma, and radiographic screening may be indicated.[46,47]

Impairment of the LES is a constant feature of achalasia, but it is not pathognomonic. Patients with diffuse esophageal spasm, presbyesophagus, or connective tissue diseases may also have impaired relaxation of the LES. Carcinoma of the distal esophagus or gastric cardia can mimic achalasia.[48] Chagas' disease, in which the parasite *Trypanosoma cruzi* affects the ganglion cells of the esophagus, may appear identical to achalasia on an esophagram.[49] Other mimics of achalasia include central and peripheral neuropathies such as stroke, diabetes mellitus, and amyloidosis, and strictures from reflux esophagitis.[40]

Presbyesophagus is a failure of peristalsis associated with aging. It is frequently observed in older patients with dysphagia, but the relationships among reflux esophagitis, presbyesophagus, and dysphagia remain unclear.[50] Presbyesophagus manifests as failure of the primary peristaltic wave with intermittent tertiary contractions.

Many other diseases can cause diminished peristalsis including severe esophagitis, diabetes, alcoholism, hyperthyroidism, anticholinergic medications, and surgical vagotomy.[40]

Connective Tissue Diseases

Scleroderma is the prototype for a connective tissue disease with esophageal manifestations. Peristalsis is absent in the distal two thirds of the esophagus (the portion with smooth muscle rather than striated muscle). This usually results in mild dilation of the distal esophagus. In contrast to achalasia, the LES becomes incompetent, allowing reflux (Fig. 102-13). Scleroderma has been associated with hiatus hernia, *Candida* esophagitis,[51] aspiration pneumonia, esophageal adenocarcinoma,[52] and reflux esophagitis with Barrett's esophagus.[53]

Systemic lupus erythematosus, rheumatoid arthritis, and polymyositis have radiographic manifestations similar to scleroderma. Der-

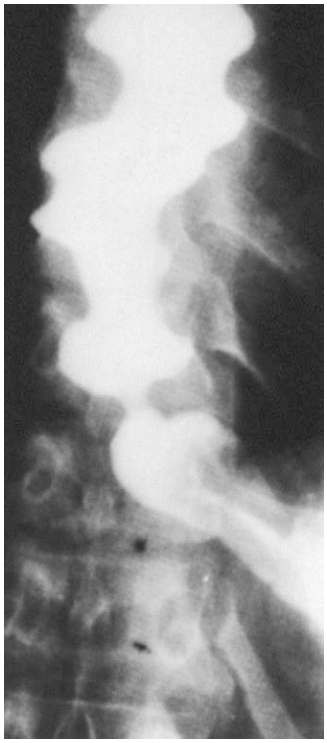

Figure 102-12. Vigorous achalasia. Barium esophagram shows dilation of the esophagus with multiple nonperistaltic contractions.

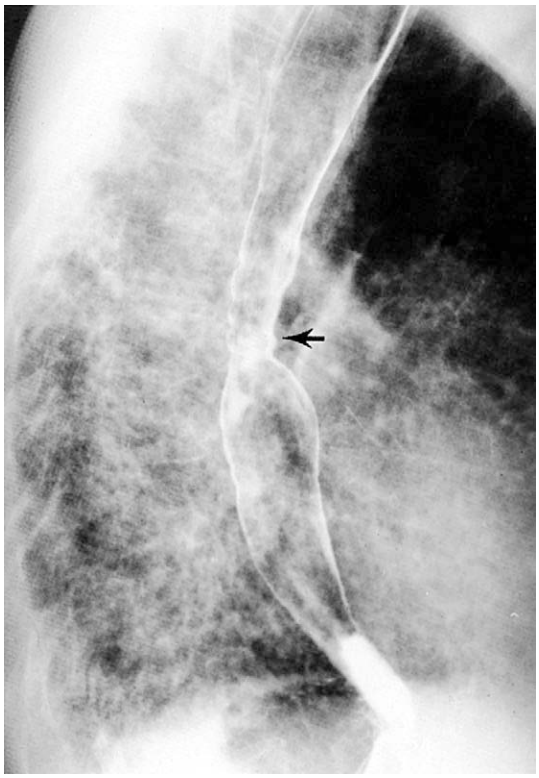

Figure 102-13. Scleroderma. Midesophageal stricture *(arrow)* secondary to reflux esophagitis in a patient with scleroderma. Note the interstitial lung disease.

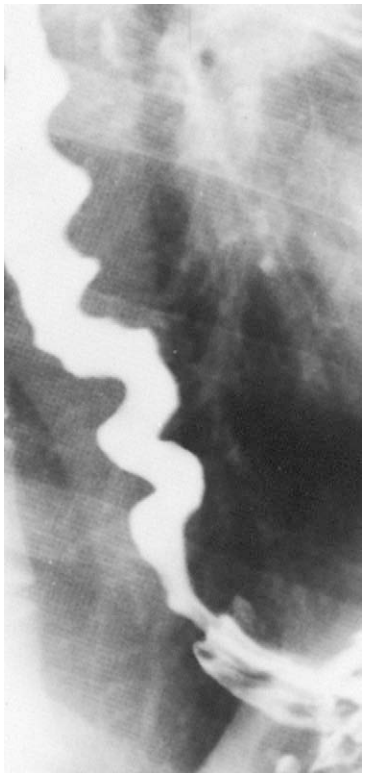

Figure 102-14. Diffuse esophageal spasm. Barium esophagram demonstrates a corkscrew appearance of the esophagus produced by nonperistaltic contractions in a patient with chest pain.

matomyositis, in contrast, predominantly affects the striated muscle of the pharynx and upper esophagus.[40] Fluoroscopy and manometry are more useful than endoscopy in the evaluation of connective tissue disorders.[54]

Esophageal Spasm

Patients with diffuse esophageal spasm have normal peristalsis in the proximal third of the esophagus, but contractions in the distal two thirds are uncoordinated and nonperistaltic. Possible radiographic manifestations include the corkscrew esophagus (a spiral column of contrast, Fig. 102-14), the rosary or shish-kebob (pouches separated by tight contractions), and diffuse narrowing. The diagnosis of diffuse esophageal spasm is made only when these radiographic findings are accompanied by substernal chest pain.

Nutcracker esophagus, also known as symptomatic esophageal spasm or hypertensive peristaltic esophagus, is characterized by high-contractility peristaltic waves causing chest pain. The esophagram is usually normal; this diagnosis is made with manometry.[55,56]

Diverticula

Zenker's Diverticula

Zenker's diverticulum is the most prevalent of the pharyngeal diverticula. It is a true diverticulum of the posterior pharyngeal wall, arising through Killian's dehiscence just above the cricopharyngeus muscle. Patients generally present with halitosis and food regurgitation. Zenker's diverticulum is best imaged fluoroscopically in the lateral projection (Fig. 102-15). Contrast is seen filling the diverticulum during swallowing, with variable retention between swallows. Large diverticula may compress the hypopharynx. Fluoroscopy is useful to delineate the size of the pouch and the diameter of its neck.

Pharyngeal Pouches

The pharyngeal wall may protrude out of its normal contour at the levels of the tonsillar pillar or thyrohyoid membrane. This "pharyngeal

Figure 102-15. Zenker's diverticulum. Oblique image from an esophagram shows a barium-filled pouch extending posteriorly from the hypopharynx, displacing and compressing the upper esophagus. The neck of the diverticulum is denoted by *arrowheads.*

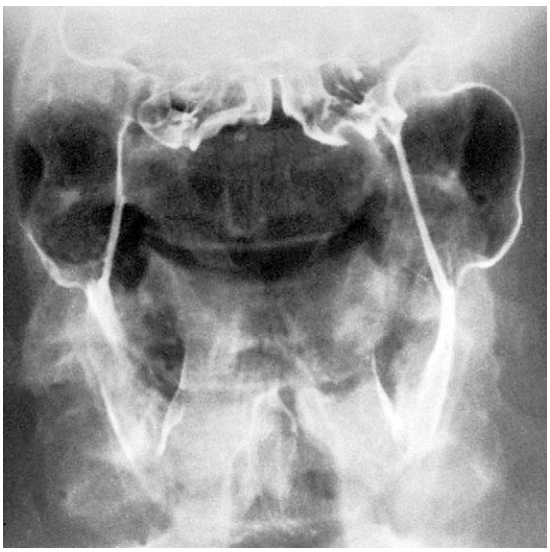

Figure 102-16. Lateral pharyngeal pouches. Frontal view from an air-contrast pharyngogram shows bilateral bulging of the lateral pharyngeal walls as the patient performs a modified Valsalva maneuver. These pouches are not true diverticula.

pouch" is usually asymptomatic, but patients may complain of dysphagia or regurgitation of food in severe cases. Pharyngeal pouches are best viewed in frontal projection, where they fill transiently (Fig. 102-16). Pouches should be distinguished from true pharyngeal diverticula, which present as persistent outpouchings of pharyngeal mucosa

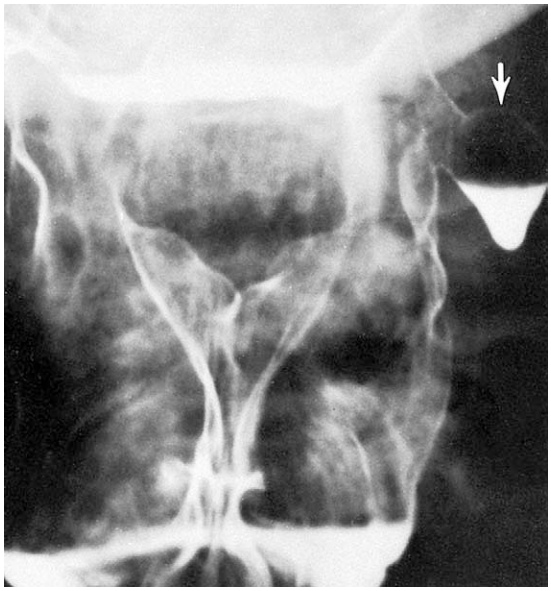

Figure 102-17. Acquired lateral pharyngeal diverticulum. Frontal view from an air-contrast pharyngogram shows persistent focal outpouching *(arrow)* of the lateral pharyngeal wall. This outpouching represents protrusion of the hypopharyngeal mucosa through the thyrohyoid membrane.

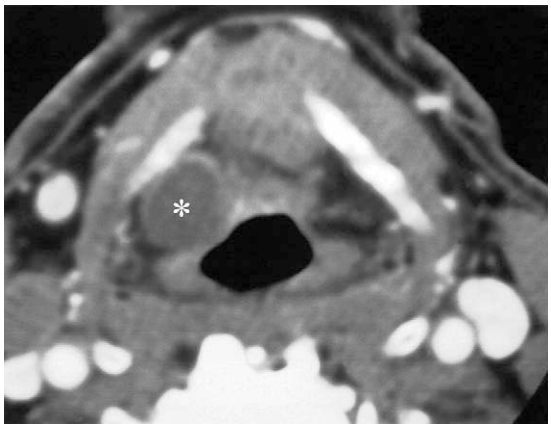

Figure 102-18. Intrinsic laryngocele. Enhanced computed tomography of the larynx reveals a fluid-filled mass *(*)* in the paraglottic fat. Laryngoceles may be filled with air or fluid.

(Fig. 102-17).[57] Pharyngeal diverticula are seen with chronically increased pharyngeal pressure, as in trumpet players and glass blowers.

Laryngoceles

A laryngocele is a diverticulum of the saccule of the laryngeal ventricle. Laryngoceles are classified as internal, external, or mixed, depending on whether they traverse the thyrohyoid membrane. Esophagram is usually normal, but the aryepiglottic folds may be displaced by the underlying mass. Laryngocele is best evaluated with CT or MR, where it appears as a well-defined, air-filled or fluid-filled mass in or around the larynx (Fig. 102-18).[58] The density or signal of the mass varies with the degree of proteinaceous debris.

Midesophageal Diverticula

Esophageal diverticula arise at the level of the carina or in the epiphrenic region. They are formed by pulsion rather than traction.[59] Fluoroscopically, esophageal diverticula present as smooth outpouchings that expand and contract with peristalsis (Fig. 102-19). These diverticula are usually seen in the setting of esophageal dysmotility.

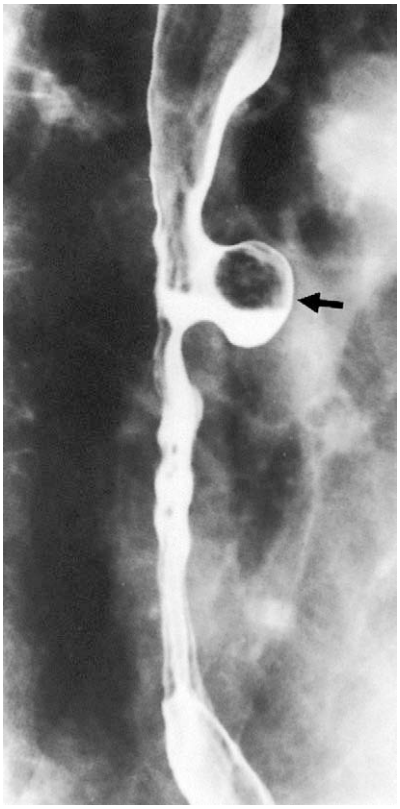

Figure 102-19. Midesophageal diverticulum. Air-contrast esophagram shows a smooth, round diverticulum *(arrow)* at the subcarinal level in a partially collapsed esophagus.

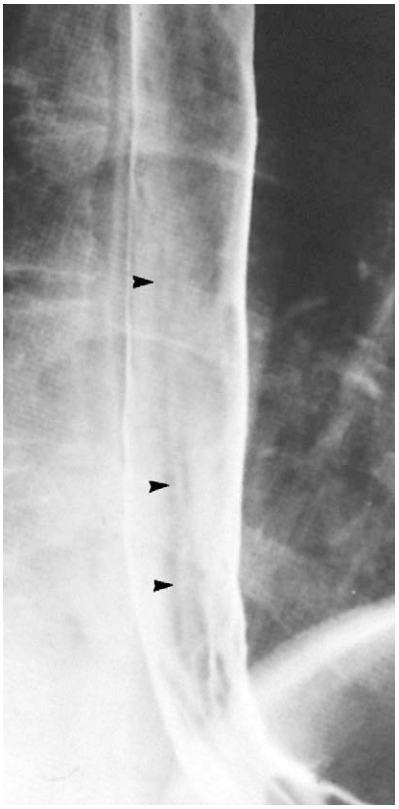

Figure 102-20. Reflux esophagitis. Air-contrast esophagram demonstrates several linear ulcerations *(arrowheads)* in a patient with reflux esophagitis.

Infection/Inflammation

The radiographic hallmark of esophageal inflammation is an altered mucosal pattern. The mucosa is best evaluated fluoroscopically by use of both full-column and air-contrast techniques.[60] Thickening of the esophageal folds and a lack of normal distensibility can be seen in all forms of esophagitis. The abnormal folds may have a transverse orientation and are often fixed during peristalsis. A variety of chemical, physical, and infectious agents cause esophageal inflammation, but gastroesophageal reflux is by far the most prevalent.

Reflux Esophagitis

The radiologist uses a variety of evocative maneuvers to elicit gastroesophageal reflux (GER) during an esophagram. These include coughing, Valsalva maneuver, leg raising, Trendelenburg position, epigastric compression, and the water-siphon test, in which the patient swallows water when contrast is already in the stomach. Despite these maneuvers, radiographic evidence of GER is present in only half the patients who have endoscopic evidence of reflux esophagitis.[61] Endoscopy itself is insensitive for the diagnosis of GER, and 24-hour pH monitoring remains the best diagnostic test.[62]

The earliest radiographic manifestations of GER are subtle: diminished contractility of the distal esophagus, granular mucosa, and tiny superficial erosions. As the disease progresses, frank ulcerations can appear, with either linear or round configurations (Fig. 102-20). Advanced GER results in deep ulceration (Fig. 102-21). These ulcerations heal with a variable degree of scarring, and strictures may result (Fig. 102-22). Although most patients with GER have a hiatus hernia, the relationship between these diagnoses is not completely understood.[63]

The esophagus is normally covered by squamous epithelium and the stomach by columnar epithelium. Patients with severe GER may transform the normal squamous epithelium of the distal esophagus into a columnar epithelium, thus changing the location of the squamoco-

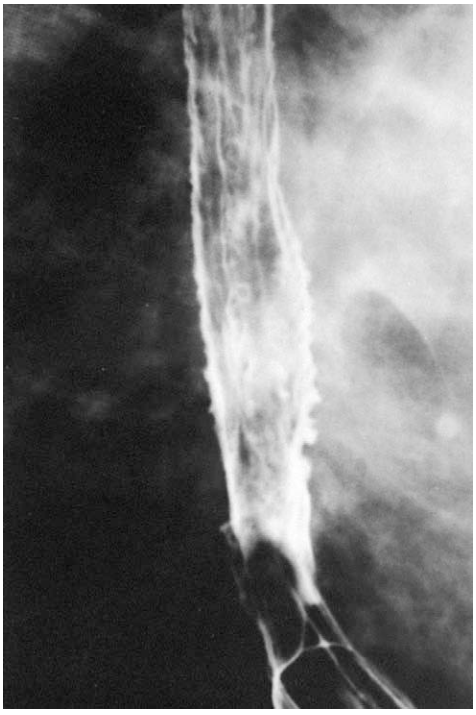

Figure 102-21. Severe reflux esophagitis. Air-contrast esophagram shows marked irregularity of the mucosa with multiple ulcerations.

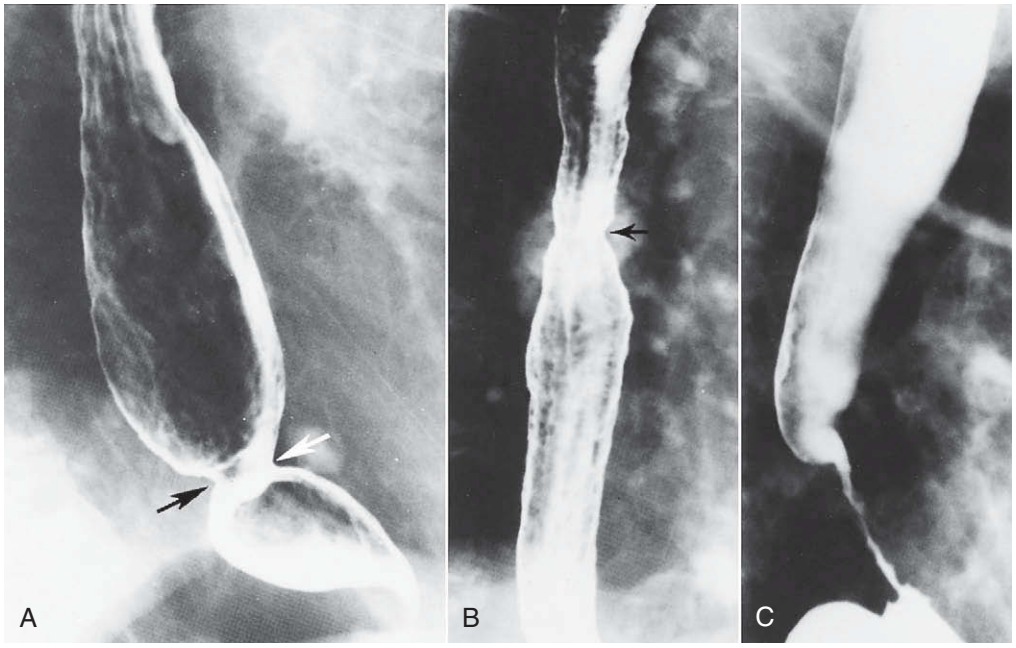

Figure 102-22. Peptic strictures. **A,** Smooth symmetric focal stricture of the distal esophagus *(arrows)* secondary to reflux esophagitis. **B,** Mildly irregular midesophageal stricture *(arrow)* in a patient with severe reflux esophagitis. Note the irregularity of the esophageal mucosa. **C,** Long narrow stricture of the distal esophagus with irregular margins secondary to severe reflux esophagitis.

lumnar junction. This is called Barrett's esophagus. Patients with Barrett's esophagus have a dramatically increased risk of esophageal carcinoma (incidence of 0.5% per year).[64]

There are no radiographic findings specific to Barrett's esophagus, but strictures or ulcers in the mid to upper esophagus suggest the diagnosis (Fig. 102-23). A fine reticular pattern in the mucosa adjacent to a stricture is also suggestive.[63] However, endoscopy with biopsy is preferable to fluoroscopy for the diagnosis and surveillance of Barrett's esophagus.[64]

Infectious Esophagitis

Infectious esophagitis is seen predominantly in immunosuppressed patients such as those with AIDS, cancer, diabetes mellitus, or organ transplants. Long segments of esophagus are usually involved. Odynophagia is the most frequent presentation. The radiographic findings in early esophagitis are easily overlooked on single-contrast examinations; air-contrast techniques are recommended.[65]

Candida albicans is the most frequent organism to cause esophagitis. It is seen not only in immunocompromised patients but also in the setting of esophageal stasis (e.g., achalasia or stricture).[66] Radiographic findings in early disease include abnormal motility and longitudinal mucosal plaques. As the disease progresses, these plaques coalesce and the mucosa acquires a "shaggy" appearance (Fig. 102-24). The mucosal abnormalities resolve after treatment.

Herpes simplex virus is the second most common organism to cause esophagitis. Fluoroscopy reveals discrete ulcers in the midesophagus (Fig. 102-25). Strictures and giant ulcers are less frequently seen.[67] The mucosal vesicles seen endoscopically precede the ulcerations visible on fluoroscopy. Cytomegalovirus, another member of the herpes family, can have radiographic manifestations that mimic *Candida* esophagitis, herpes esophagitis, or reflux esophagitis.[65]

Esophagitis has been reported from bacteria, fungi, mycobacteria, and from HIV itself.[68-71]

Caustic Esophagitis

Caustic esophagitis is the result of ingestion of corrosive materials. The most common caustic agent seen in the United States is lye (sodium hydroxide), which is commercially available in drain cleaners. The radiographic appearance of caustic esophagitis depends on the corrosive agent. For example, acids cause coagulation necrosis, which limits their penetration, whereas alkali causes liquefaction necrosis and penetrates deeply.[72] Endoscopy has become the predominant modality for evaluation and treatment of caustic injuries,[73] but radiology provides useful information in both the acute and chronic stages of the disease.[74]

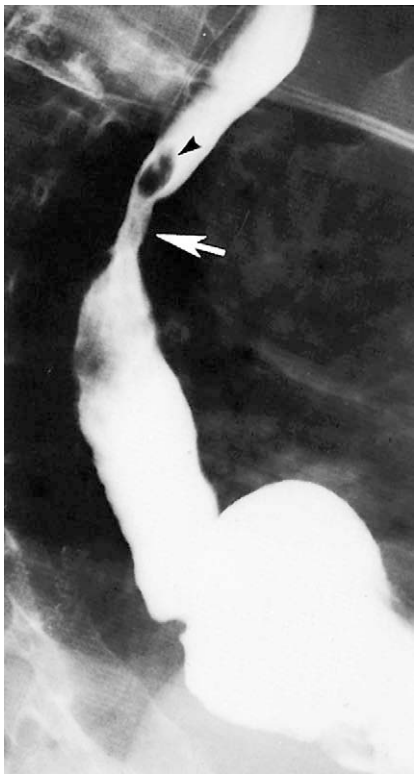

Figure 102-23. Barrett's esophagus with stricture. Left posterior oblique view from an upper gastrointestinal examination demonstrates a midesophageal stricture *(arrow)* in a patient with chronic gastroesophageal reflux. Note the pill *(arrowhead)* lodged above the stricture.

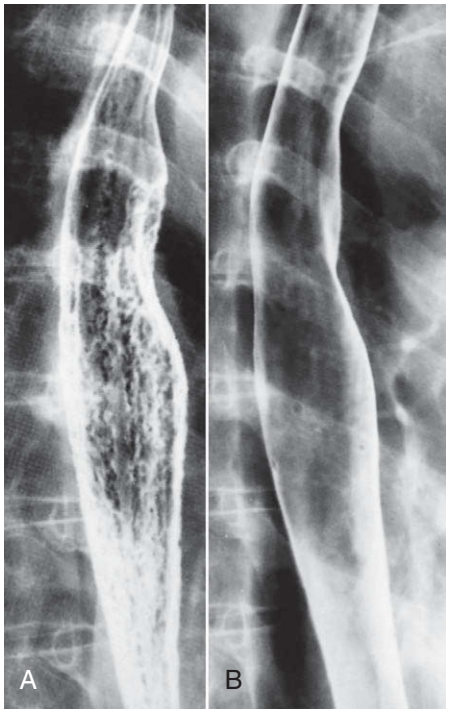

Figure 102-24. *Candida* esophagitis. **A,** Air-contrast esophagram demonstrates shaggy mucosa with irregular, longitudinal plaquelike filling defects involving most of esophagus. **B,** Repeat air-contrast esophagram after treatment with amphotericin-B shows complete resolution of the esophagitis. *(Courtesy of Dr. Marvin Lindell, Houston.)*

Figure 102-26. Lye stricture. Barium esophagram shows a long, smooth midesophageal narrowing in a patient who had ingested lye many years previously.

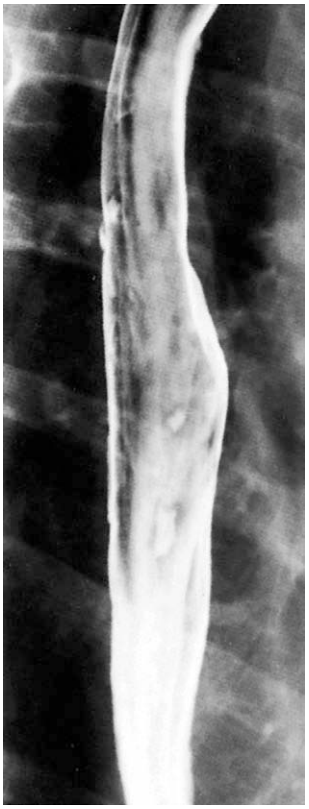

Figure 102-25. Herpes esophagitis. Air-contrast esophagram demonstrates multiple discrete mucosal ulcerations characteristic of viral esophagitis.

In the acute stage, there is mucosal irregularity, ulceration, fold thickening, and weakened peristalsis. Sloughed mucosa may produce filling defects. Thickening of the esophageal wall may result in luminal narrowing.[75] Lye ingestion may result in esophageal perforation, so patients should be given water-soluble agents before barium is administered.

Esophageal strictures develop 1 to 3 months after the injury. These appear as long segments of esophageal narrowing (Fig. 102-26). The strictures usually have smooth contours, but submucosal fibrosis occasionally causes nodular defects or scalloping. Concomitant gastric injuries occur in 25% of patients with lye ingestion, so a complete upper gastrointestinal series is warranted in these patients.[75]

Patients with caustic strictures are at risk for esophageal carcinoma approximately 30 years after the initial injury.[76] Nodularity or ulceration in the region of a previously smooth stricture suggests malignant transformation.

Although caustic ingestion most commonly affects the esophagus, pharyngeal strictures and gastric injury are also seen.[75,77]

Granulomatous Esophagitides

Tuberculous esophagitis is usually caused by direct extension from adjacent lymph nodes. Swallowed sputum is causative only when there is an underlying structural abnormality of the esophagus.[65] Immunocompromised patients are more prone to tuberculous esophagitis.[78] The radiographic findings are nonspecific and include stricture, fistula, and mucosal irregularity.[79]

Crohn's disease may affect the esophagus. The earliest finding is aphthous ulcers, which increase in size and number as the disease advances. Cobblestoning, fistulas, and strictures are late findings.[80] Early Crohn's disease may be mistaken for drug-induced esophagitis.

Behçet's disease is a multisystem disorder that may show ulcerations on esophagram. Histoplasmosis is a granulomatous infection that may cause ulcers or fistulas.

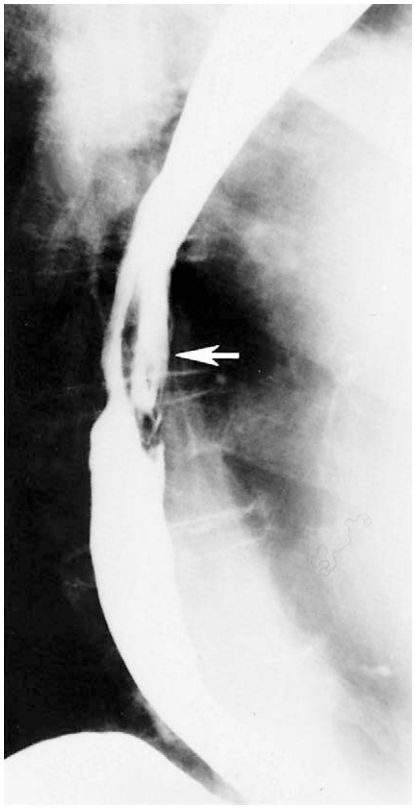

Figure 102-27. Drug-induced esophagitis. Left posterior oblique view from a barium esophagram demonstrates a large ulcer *(arrow)* in the midesophagus caused by potassium tablets in a patient with massive cardiomegaly. Note the posterior displacement of the esophagus by enlarged heart.

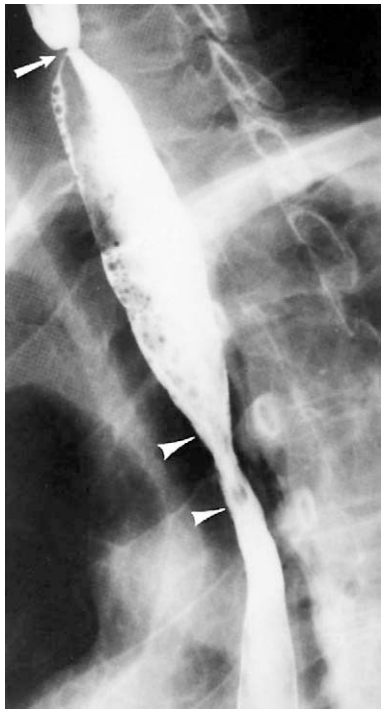

Figure 102-28. Epidermolysis bullosa. Esophagram demonstrates cervical esophageal web *(arrow)* and midesophageal stricture *(arrowheads)*.

Other Esophagitides

Many medications can irritate the esophagus with prolonged contact. Antibiotics such as tetracycline and doxycycline, quinidine, potassium chloride, iron sulfate, and vitamin C are among the offending agents.[40] Most patients do not have underlying esophageal pathology, but bedtime dosing, a tortuous esophagus, and medication taken with no water can predispose to drug-induced esophagitis. Radiographic abnormalities include a solitary ulcer (or small cluster of ulcers) in the midesophagus, with or without focal esophageal spasm (Fig. 102-27). These abnormalities generally resolve within 2 weeks of medication withdrawal. The major differential consideration is herpes esophagitis.[81]

Radiation esophagitis manifests as superficial ulcerations in the mucosa 7 to 10 days after radiation therapy. Another appearance is granular mucosa with spasm. After several months, dysmotility with normal morphology is the most common presentation, but smooth strictures or longstanding ulcers may also be seen.[82]

Severe peptic esophagitis may develop in patients with prolonged nasogastric intubation because the LES is rendered incompetent. Strictures in these patients tend to be long and tapered.

Epidermolysis bullosa is a hereditary skin disorder with recurrent blisters that rupture and scar. Only the recessive form, epidermolysis bullosa dystrophica, has esophageal manifestations.[83] Early disease presents as ulcers, dysmotility, spasm, or edema. Small, nodular filling defects represent bullae.[84] Extensive bulla formation leads to a serrated or spiculated mucosa. Advanced disease has scarring or stricture in the upper thoracic esophagus (Fig. 102-28). Radiography plays an important role in the assessment of patients with epidermolysis bullosa because the esophageal mucosa is prone to injury from endoscopy.

Pemphigoid is another disorder of the skin and mucous membranes with chronic bulla formation and rupture. Early disease is manifested by edema, spasm, and ulceration.[85] The bullae themselves are rarely visualized. Late disease has strictures and webs in the upper thoracic esophagus. Early radiographic diagnosis of esophageal involvement is important because adhesions can be lysed before strictures form.[86]

Intramural pseudodiverticulosis is ectasia of the esophageal mucous ducts. It is associated with many types of esophagitis, and *C. albicans* is frequently cultured from affected patients, but no definite cause has been established. The radiographic appearance is dramatic, with innumerable small outpouchings in linear rows (Fig. 102-29). Strictures are frequently identified in association with the pseudodiverticula. Radiographic studies are more sensitive than endoscopy for the diagnosis of intramural pseudodiverticulosis.[87]

Alcohol-induced esophagitis, graft-versus-host disease, and eosinophilic esophagitis all share the nonspecific radiographic finding of mucosal irregularity. In these diseases the diagnosis is suggested by the clinical history.[81]

Epiglottitis

Epiglottitis is a fulminant infection of the supraglottis that usually affects children 3 to 6 years old. *Haemophilus influenzae* is the most frequent infectious agent. The clinical presentation of drooling, fever, and sore throat is similar to that of viral laryngotracheobronchitis (croup) or retropharyngeal abscess; lateral radiographs of the neck help to distinguish these entities.

The typical plain film findings in epiglottitis are thickening of the epiglottis (thumb sign) and thickening of the aryepiglottic folds (Fig. 102-30).[88,89] The hypopharynx may distend as airway compromise progresses. Diseases such as angioneurotic edema, caustic burns, and radiation therapy have the same radiographic appearance, but they can be distinguished clinically. It is important to recognize the involvement of the aryepiglottic folds because this may distinguish epiglottitis from epiglottic abscess, cyst, or hematoma. The term "supraglottitis" has begun to replace "epiglottitis" to emphasize the involvement of the aryepiglottic folds.

Although thickening of the supraglottic tissues can be easily appreciated on CT, and CT can more completely evaluate differential possibilities such as retropharyngeal abscess, patients with epiglottitis have a tenuous airway, and the recumbent positioning of CT may provoke abrupt airway occlusion. Thus conventional radiographs are preferred for the initial evaluation.

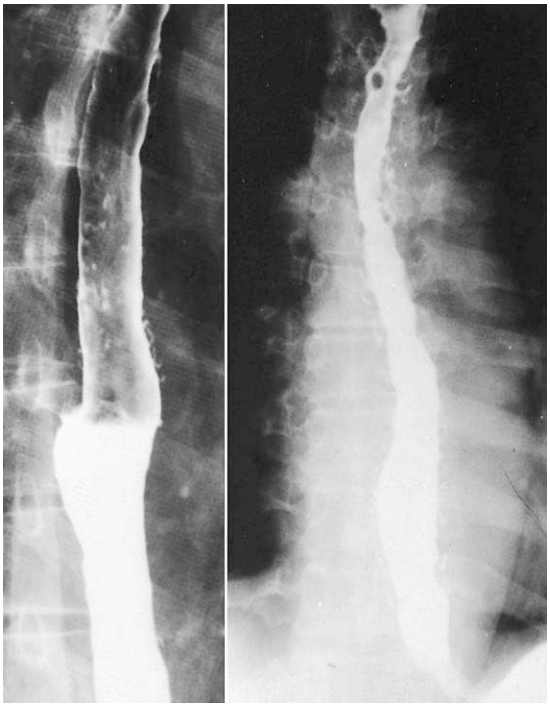

Figure 102-29. Intramural pseudodiverticulosis. Esophagrams from two patients show multiple irregular linear collections of barium outside the esophageal lumen, representing dilated excretory ducts of mucous glands.

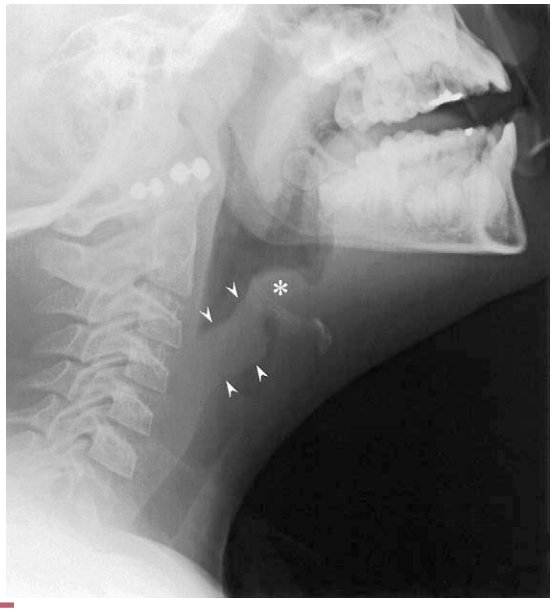

Figure 102-30. Epiglottitis. Lateral plain film of the neck reveals thickening of the epiglottis *(*)* and the aryepiglottic folds *(arrowheads)*. The pharynx is expanded.

Patients with epiglottitis can have rapid clinical deterioration with airway obstruction. If epiglottitis is suspected clinically, personnel experienced with emergent intubation should accompany the patient to the radiology suite.[90]

Abscess

Common sources of neck infection include the teeth, salivary glands, and palatine tonsils. However, a definite source of infection is found in only 50% of neck infections.[91]

Figure 102-31. Peritonsillar abscess. Enhanced computed tomography through the upper neck reveals a low-density mass *(*)* with a thick, enhancing rim, in the expected location of the tonsillar pillar. The oropharynx and tongue are displaced.

An abscess is a drainable collection of infected fluid, whereas a phlegmon is infected, edematous tissue. The differentiation between phlegmon and abscess is critical for surgical planning. The usual CT appearance of an abscess is a fluid-attenuation mass with a rim of enhancing tissue (Fig. 102-31). This rim of enhancement is initially thick and irregular but progresses to a well-defined thin rim over several days.[91] Phlegmon appears as a low-density region of soft tissue with a poorly defined margin and little surrounding enhancement. Unfortunately, these findings lack specificity and phlegmon is difficult to reliably distinguish from abscess on cross-sectional imaging.[92] Surgeons should expect a high false-positive rate for the diagnosis of neck abscess on CT.

CT and MR are excellent at determining the extent of neck infections. Retropharyngeal and peritonsillar abscesses frequently extend into the parapharyngeal space. Patients with retropharyngeal disease are at risk for spread into the mediastinum by way of the danger space, so imaging of patients with retropharyngeal infection should include the thorax.[33]

Esophageal Narrowing

Webs

A pharyngoesophageal web is a thin membrane extending horizontally from the anterior mucosal surface, usually within 2 cm of the pharyngoesophageal junction (Fig. 102-32). Circumferential webs are unusual. Webs are covered with normal mucosa and will often reduce with a large bolus of barium. Thus they are identified less frequently on radiographic studies than on autopsy series.[93] Webs in the pharynx and cervical esophagus are usually idiopathic and asymptomatic, but a fixed stenosis of less than 13 mm can result in dysphagia.

Webs will occasionally arise from longstanding inflammation (epidermolysis bullosa, pemphigoid, reflux esophagitis), but most are incidental findings. Pharyngoesophageal webs are best visualized fluoroscopically in the lateral projection (see Fig. 102-32). Webs are not generally seen on cross-sectional imaging.

Strictures

Inflammatory strictures are the end result of many forms of esophagitis. Iatrogenic strictures form after surgical resection, usually at the site of an anastomosis. Therapeutic radiation may also result in alimentary strictures.

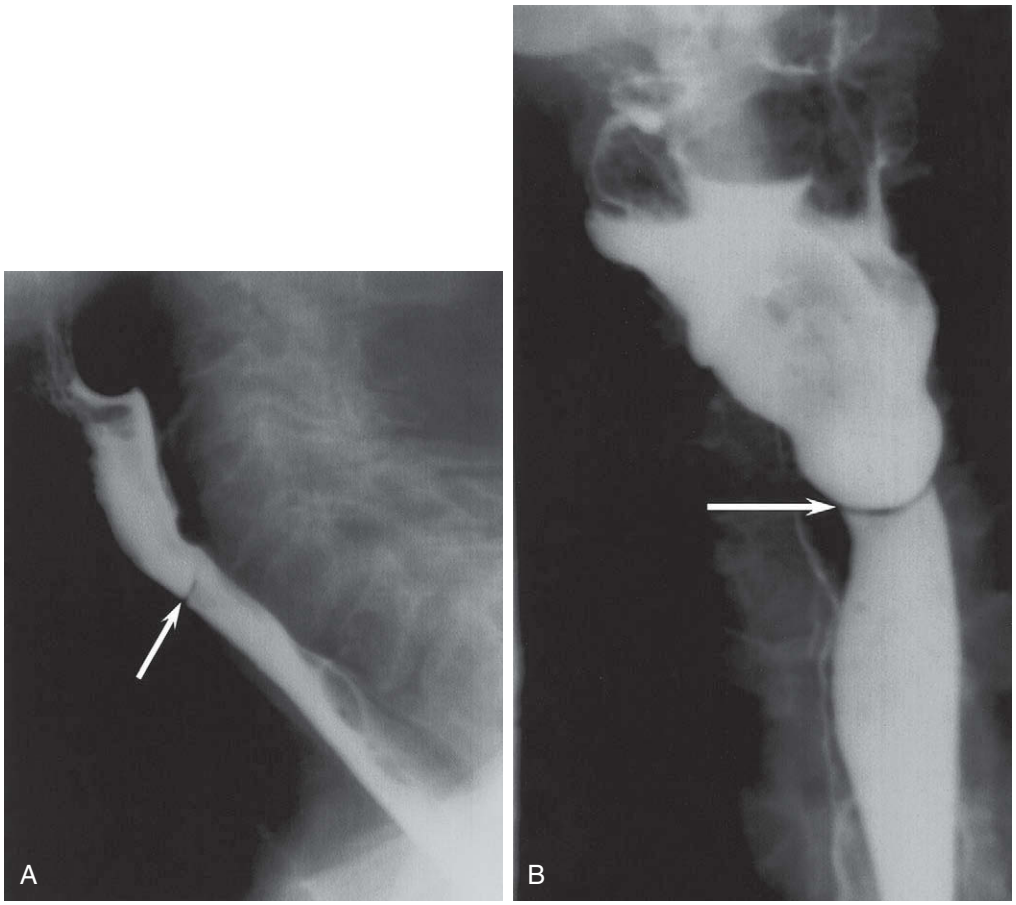

Figure 102-32. Esophageal web. Lateral **(A)** and frontal **(B)** projections show a thin filling defect (*arrows*) extending from the anterior esophageal wall.

In the setting of an esophageal stricture, the most important determination is whether the lesion represents a cancer or is the result of a benign process. In general, malignancies produce a discrete area of irregular mucosa with overhanging borders (Fig. 102-33). The esophagus may be fixed to surrounding structures at the level of a malignant stricture. Asymmetry favors a malignant process. Absence of these findings, however, is not sufficient to exclude malignancy. In the setting of a stricture without a definite benign etiology, endoscopy with biopsy is indicated. CT is often useful to exclude a surrounding mass.

Extrinsic Compression

The most frequent source of external compression of the pharynx and esophagus is degenerative disease of the spine. Anterior vertebral osteophytes create an undulating posterior impression on fluoroscopy (Fig. 102-34). In severe cases, cervical osteophytes may cause dysphagia or may interfere with inversion of the epiglottis and cause aspiration.[94,95]

Infection is another frequent cause of extrinsic compression. A peritonsillar or retropharyngeal abscess can displace or compress the oropharynx and hypopharynx (see Fig. 102-31). Although retropharyngeal soft tissue swelling can be seen on lateral plain films of the neck, CT is the preferred modality to evaluate the extent of disease and to distinguish abscess from phlegmon.[91]

Foregut duplication cysts are an unusual cause of esophageal compression. Three types of duplication cyst exist: esophageal cyst, bronchogenic cyst, and neurenteric cyst. All three present as well-defined cervical or mediastinal masses. The three types are distinguished by location. On cross-sectional imaging, foregut duplication cysts usually mimic water (Fig. 102-35), but inspissated secretions can change the CT and MR characteristics.[96] On fluoroscopy, foregut duplication cysts can mildly displace or compress the esophagus. When an esophageal cyst communicates with the true esophagus, it is called an esophageal duplication, and it appears as a double-barreled esophagus (Fig.

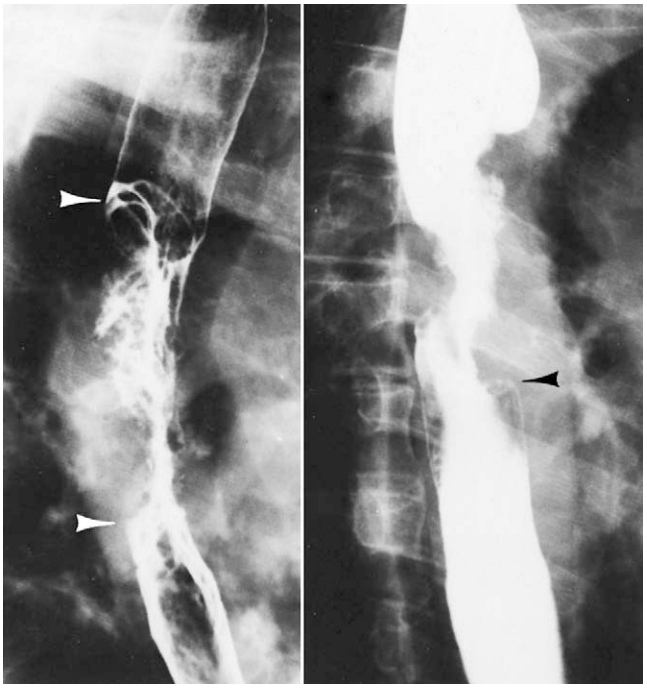

Figure 102-33. Esophageal carcinoma. Two examples of squamous cell carcinoma producing irregular segmental constriction of the esophageal lumen by large ulcerated masses. Note the sharp overhanging edges produced by the mass in each case *(arrowheads)*.

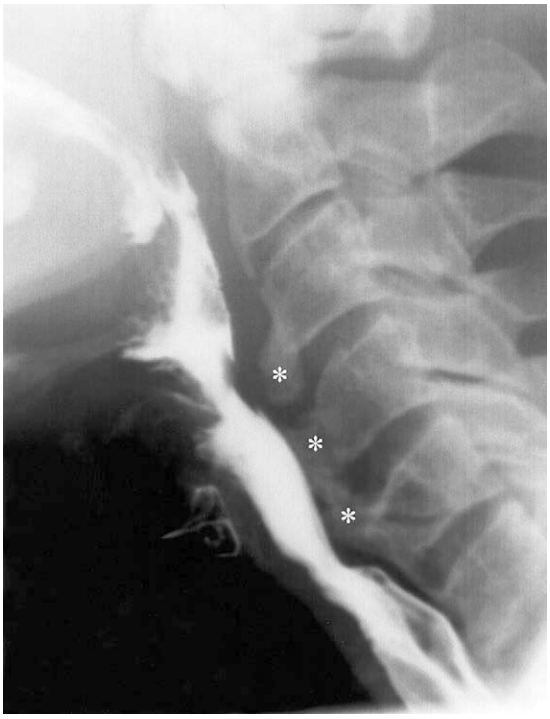

Figure 102-34. Vertebral osteophytes. Lateral esophagram shows large bridging osteophytes *(*)* creating an undulating impression on the posterior hypopharynx.

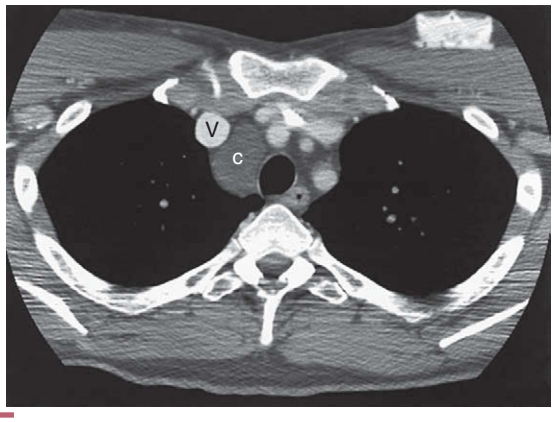

Figure 102-35. Bronchogenic duplication cyst. Computed tomography through the upper thorax reveals a cystic mass *(c)* between the trachea and the right brachiocephalic vein *(v)*. This is a frequent location for bronchogenic duplication cysts.

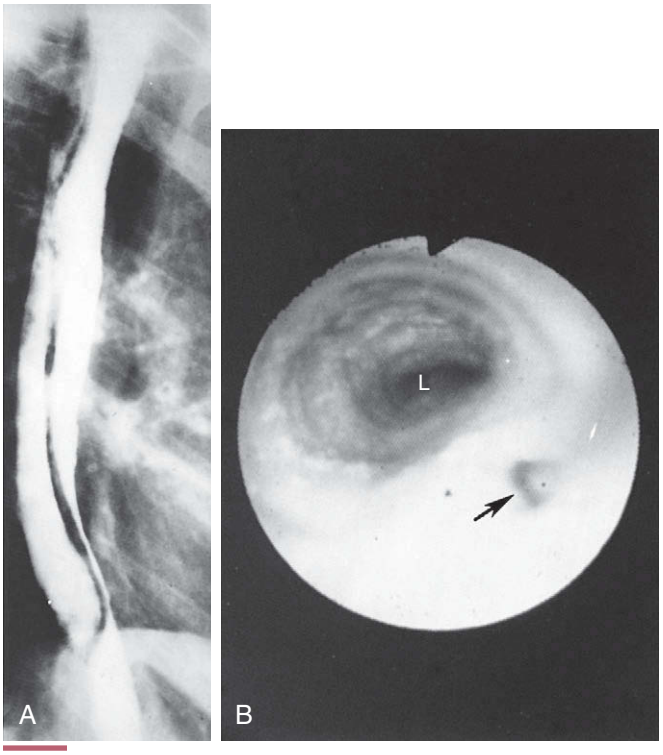

Figure 102-36. Communicating esophageal duplication. **A,** Barium esophagram demonstrates near-complete esophageal duplication communicating with the esophageal lumen. **B,** Photograph taken during endoscopy shows the duplication cyst *(arrow)* communicating with esophageal lumen *(L)*.

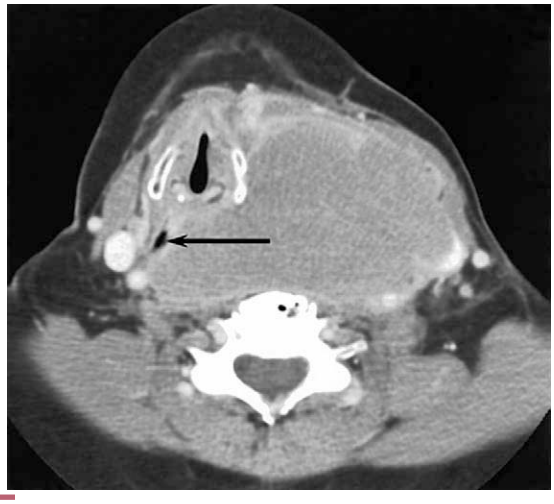

Figure 102-37. Thyroid goiter. Enhanced computed tomography through the larynx. A large mass replaces the left thyroid gland, displacing the larynx and esophagus *(arrow)*.

102-36).[40] If solid elements are identified in conjunction with a duplication cyst, metastatic degeneration should be considered.[97]

Vascular abnormalities that compress the esophagus include left atrial enlargement, aortic ectasia, aberrant subclavian artery, pulmonary sling, and double aortic arch.[98] Benign or malignant masses may displace the esophagus and pharynx; thyroid goiter is the most familiar example (Fig. 102-37). In the setting of trauma, hematoma may displace the tissues of the neck. If displacement is noted on an esophagram, the patient should undergo CT to identify any adjacent mass and evaluate the extent of disease.

Retraction of the esophagus in the setting of pleural, pulmonary, or mediastinal scarring can be mistaken for esophageal deviation from a mass. This is an important distinction because retraction is generally benign and requires only a chest x-ray to confirm the presence of scar. Displacement, on the other hand, requires CT evaluation. On fluoroscopy, a retracted esophagus is widened, whereas a displaced esophagus is narrowed.[98]

Fistulas

Congenital

Tracheoesophageal Fistula

Tracheoesophageal fistula (TEF) results from an incomplete separation of the trachea and alimentary tract. Among the four classes of TEF,

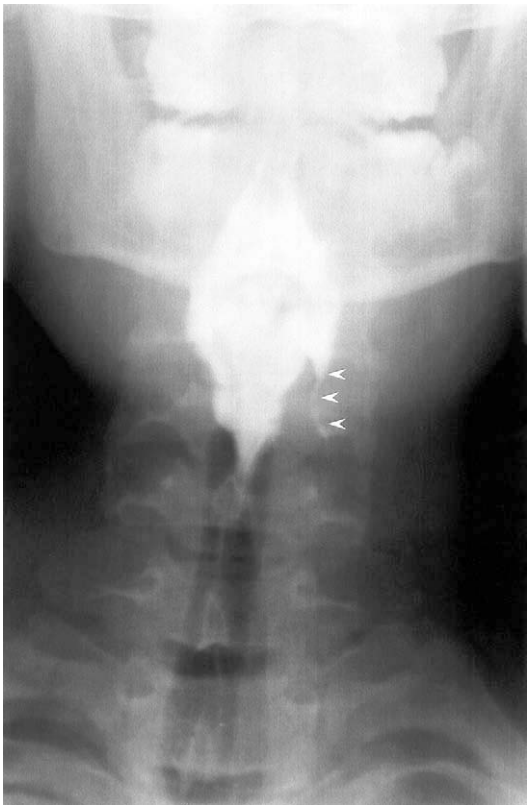

Figure 102-38. Fourth branchial cleft fistula. Frontal esophagram shows a thin line of barium (*arrowheads*) extending from the apex of the left pyriform sinus. On later images, contrast continued to the skin surface.

type 3 (esophageal atresia with distal fistula) is by far the most common. The diagnosis of type 3 fistula is usually clinical. If fluoroscopic confirmation is necessary, contrast should be introduced through a catheter so that the radiologist can control the amount of contrast and remove the contrast after the procedure.[40] Clinically, type 1 TEF (esophageal atresia without fistula) is difficult to distinguish from type 3 TEF (esophageal atresia with fistula). An abdominal plain film helps; if there is gas in the stomach, a fistula is present, so the anomaly must be type 3.

Type 2 TEF (esophageal atresia with proximal fistula) is diagnosed when oral contrast enters the bronchial tree, and the abdomen is gasless. Type 4 TEF has two subtypes: H-type TEF (fistula without atresia) and atresia with proximal and distal fistulae. It may be difficult to demonstrate an H-type fistula radiographically because the fistula slopes upward from the esophagus to the trachea. Prone positioning helps to delineate the abnormality.

Branchial Cleft Anomaly

Branchial cleft anomalies are remnants of the fetal communication between the alimentary tract and the skin of the lateral neck.[99] The most frequent remnant is a branchial cleft cyst, but sinuses and fistulae may also remain. Although a branchial cleft cyst is best imaged with CT or MRI, a branchial cleft sinus or fistula is best imaged fluoroscopically. CT performed after infusion of a contrast agent into the fistula provides more precise delineation of the path of the fistula.[100] A thin line of contrast extending from the pyriform sinus is the classic appearance for a third or fourth branchial cleft fistula (Fig. 102-38).

Perforation

Iatrogenic trauma, as from intubation, endoscopy, or dilation, is the most frequent cause of esophageal perforation.[59] Other causes include blunt trauma, penetrating trauma, and foreign body penetration. Prompt diagnosis is essential because complications such as fasciitis and mediastinitis can be fatal.

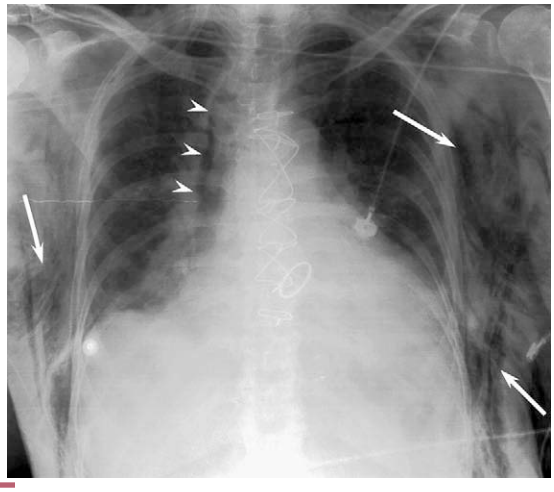

Figure 102-39. Pneumomediastinum. Chest x-ray reveals extensive gas in the subcutaneous tissues *(arrows)* and outlining the mediastinal structures *(arrowheads).*

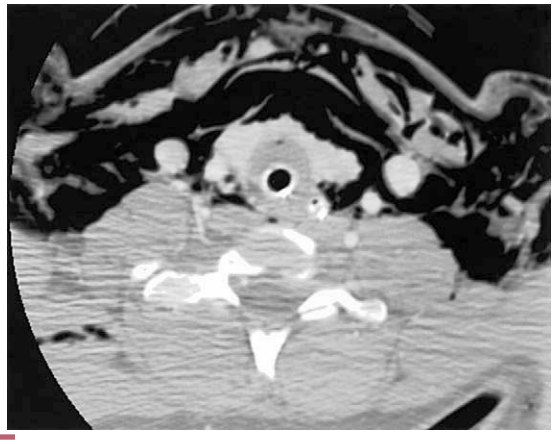

Figure 102-40. Subcutaneous emphysema of the neck. Enhanced computed tomography through the thyroid bed reveals extensive gas within the deep fascial planes of the neck, the result of pharyngeal perforation.

Plain films of the neck and chest are appropriate screening tools to assess for cervical emphysema or pneumomediastinum (Fig. 102-39). However, only half of patients with esophageal rupture will demonstrate abnormalities on conventional radiographs.[101]

Esophagography should be performed first with water-soluble contrast material to avoid inspissation of extravasated barium. If no leak is identified with water-soluble agents, the examination should be repeated with barium, which is more sensitive for small leaks.[9] If a nasogastric tube is already in place, an esophagram may be performed with the patient in the recumbent position by slowly retracting the tube while infusing contrast. The contrast bolus will extend superior to the tip of the nasogastric tube, and leaks may be identified before the tip of the tube reaches the site of perforation. This technique is useful in patients who are unable to cooperate with standard esophagography.

CT may also be used to evaluate perforation in patients who are unable to cooperate with esophagography. Extravasated oral contrast and gas within the soft tissues are indicators of alimentary perforation (Fig. 102-40).[101] Gas is also seen in the soft tissues with laryngeal or tracheal injuries or as an extension of pneumomediastinum.

Mallory-Weiss syndrome is a mucosal tear of the distal esophagus, usually caused by forceful vomiting. Esophagography is insensitive for this diagnosis; endoscopy is the preferred examination. Although many

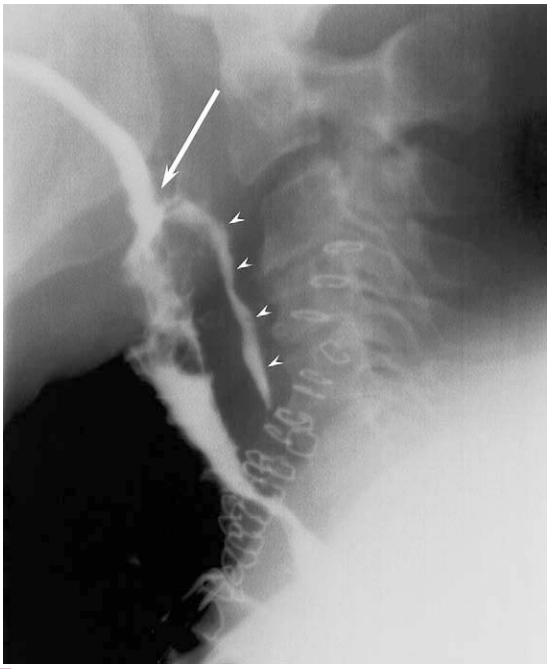

Figure 102-41. Postoperative pharyngeal leak. Two days after total laryngectomy, lateral esophagram reveals barium extravasating from the posterior pharynx. The point of origin is marked with an *arrow,* and the sinus tract is marked with *arrowheads.*

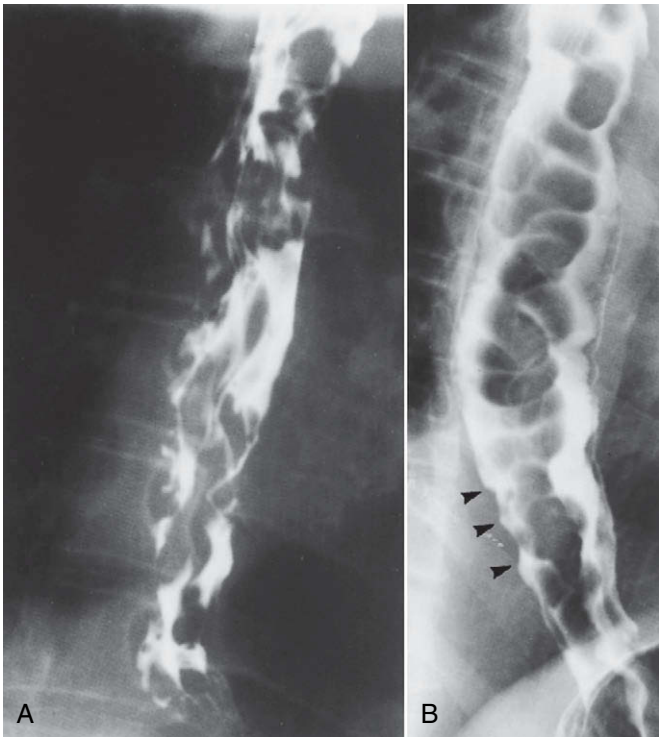

Figure 102-42. Varices. **A,** Mucosal relief radiograph of the esophagus demonstrates multiple serpiginous filling defects. **B,** Full-column esophagram from another patient shows multiple ovoid filling defects with scalloping of the distal esophageal contour *(arrowheads).*

patients with Mallory-Weiss syndrome may be treated conservatively, persistent bleeding can be addressed with angiographic infusion of vasospastics or catheter embolization.[102]

Patients who are at risk for perforation are also at risk for esophageal hematoma. On an esophagram, an esophageal hematoma usually appears as a broad submucosal mass and may be indistinguishable from benign masses, such as leiomyomas.[98]

Other Fistulas

After pharyngoesophageal surgery, a fistula may form between the alimentary tract and the skin surface, or a sinus tract may form within the deep soft tissues of the neck. These complications are best evaluated with a pharyngoesophagram (Fig. 102-41). Fistulous communication between the esophagus and the trachea, pericardium, aorta, or pleura is usually iatrogenic, but trauma, infection, and tumor erosion should also be considered.

Varices

Esophageal varices are enlarged veins in the submucosa of the esophagus. "Uphill" varices have cephalad flow, are located in the lower esophagus, and are usually the result of portal hypertension. "Downhill" varices have caudal flow, are located in the upper esophagus, and are usually the result of superior vena cava obstruction. Endoscopy is the most appropriate test for screening and treatment of esophageal varices.[103] Emergent transhepatic portosystemic shunt placement is the preferred treatment for patients who have acute variceal bleeding when endoscopic treatment fails.[104]

On esophagogram, varices are best visualized with mucosal relief techniques.[105] Varices appear as thickened longitudinal folds or serpentine filling defects (Fig. 102-42). Respiration, peristalsis, and Valsalva maneuvers change the size and configuration of the varices. Most varices are seen best when the patient is recumbent, but some are better visualized when the patient is upright. Both positions should be used. Anticholinergic agents can be used to prevent the varices from collapsing during esophageal peristalsis. Varices can be distinguished from tumors and extrinsic masses because the varices change configuration during the examination.

Foreign Body

Pieces of food, such as small bones or an unchewed bolus of meat, are the most frequent source of impacted foreign bodies in the pharynx and esophagus. The initial evaluation is frontal and lateral plain films of the neck with a technique that emphasizes soft tissues instead of the vertebral bodies (Fig. 102-43). Plain films are particularly useful for depicting the three-dimensional structure of the foreign body. However, CT better identifies foreign bodies that are near soft tissue density, so CT should be used if plain films are negative. An esophagram will show bulky foreign bodies as filling defects but may fail to identify smaller foreign bodies such as bones. Because foreign body impaction carries a risk of perforation, initial esophagography should be performed with water-soluble media. Secondary signs of perforation (pneumomediastinum, prevertebral swelling, and gas within the fascial planes of the neck) should be sought on conventional radiographs or cross-sectional imaging.

Spicules of bone most commonly lodge in the inferior tonsil, tongue base, or vallecula. Larger objects get stuck at pathologic strictures (Fig. 102-44) or areas of anatomic narrowing: the cricopharyngeus muscle, the thoracic inlet, the aortic arch, or the diaphragmatic hiatus. Because many foreign bodies lodge below the level of the larynx, cross-sectional imaging should include the entire neck and chest.

Ossification of the laryngeal cartilages can be confused with radiopaque foreign bodies.[106] The cricoid cartilage, in particular, ossifies along the posterior margin and superior tip, which can mimic a swallowed bone. The posterior lamina and inferior horn of the thyroid cartilage can also ossify in a manner suggestive of a foreign body. Postinflammatory tonsillar calcifications have a characteristic appearance on CT (Fig. 102-45); they should not be mistaken for foreign bodies.[107]

Up to 20% of ingested foreign bodies require intervention. Although balloon and magnet techniques have been used by radiologists to extract foreign bodies, endoscopy has become the treatment of choice at most institutions.[108]

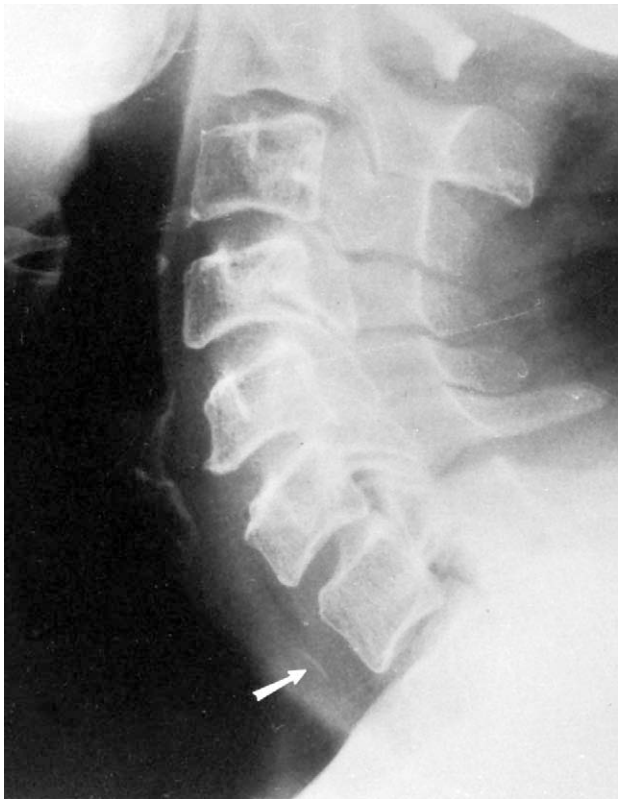

Figure 102-43. Foreign body. Lateral soft-tissue radiography of the neck shows a chicken bone *(arrow)* lodged near the pharyngoesophageal junction.

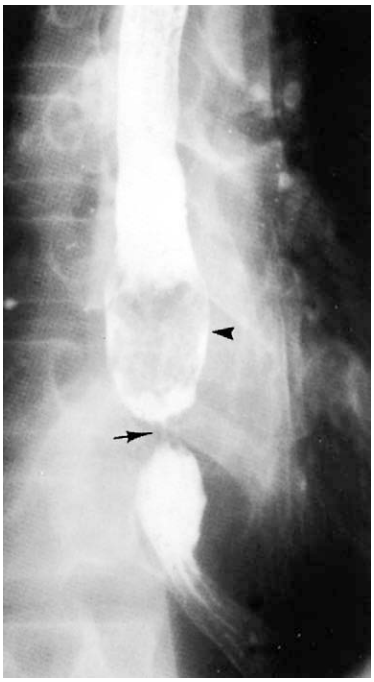

Figure 102-44. Foreign body. Barium esophagram shows a large piece of meat *(arrowhead)* lodged above a focal peptic stricture *(arrow)*.

Mass Lesions

Pharyngoesophageal filling defects are categorized as mucosal, submucosal, or extrinsic on the basis of their radiographic appearance.[59] Mucosal lesions are irregular, with abrupt, well-delineated borders. Submucosal lesions are broad based with smooth borders. Extrinsic masses displace the esophagus. These distinctions drastically shorten the differential diagnosis of pharyngoesophageal lesions. Mucosal lesions are usually sarcomas or carcinomas, whereas submucosal lesions are almost always benign. Extrinsic masses are usually not of esophageal origin.

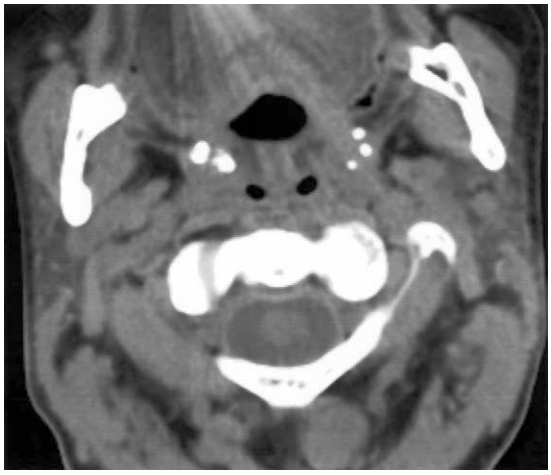

Figure 102-45. Tonsillar calcifications. Unenhanced computed tomography demonstrates coarse calcifications in both tonsillar pillars. These benign calcifications are the result of chronic inflammation.

Malignant Neoplasms

Squamous cell carcinoma accounts for most tumors in the pharynx and esophagus. Although most patients are initially seen with advanced disease, the radiologist must give particular attention to the tonsillar pillars, tongue base, nasopharynx, and pyriform sinuses to avoid overlooking early tumors in these frequently affected areas. Furthermore, patients with cancer of the head and neck are prone to second primary tumors, which are often discovered by the radiologist.

Esophagography is used to exclude carcinoma in patients who have dysphagia. Although esophagography has a low yield in this setting, it is relatively inexpensive and may provide an alternate explanation for the dysphagia. Precise evaluation of a lesion's mucosal extent is usually left to endoscopy. CT, MR, or PET/CT is necessary to assess the submucosal extent of a carcinoma and to stage the tumor.

No imaging findings reliably distinguish squamous cell carcinoma from the less common malignancies of the pharynx and esophagus, but there are some features that may be suggestive. Adenoid cystic carcinoma and lymphoma are prone to perineural invasion, which may be evident only on MRI. Esophageal adenocarcinomas arise primarily in the distal esophagus, often in the setting of Barrett's esophagus. Esophageal carcinosarcomas and spindle cell sarcomas are frequently polypoid.[109]

Nasopharynx

Nasopharyngeal carcinomas are mostly squamous cell carcinomas, lymphomas, and lymphoepitheliomas. Imaging is used to define the extent of disease, particularly in the skull base (Fig. 102-46). MRI is the preferred modality for the evaluation of skull base invasion and perineural spread, whereas PET/CT is preferred to identify nodal and distant disease.[110,111] Common pathways of intracranial spread include direct invasion through the clivus and extension into the foramen lacerum. In either case, the tumor may spread to the cavernous sinus and Meckel's cave. The clivus, jugular foramen, and hypoglossal canal should be carefully evaluated, especially in patients with cranial nerve dysfunction. The dural extent of disease is best identified on coronal postcontrast images. Invasion of the brain parenchyma is seen as edema on T2 and fluid attenuated inversion recovery images.

Evaluation of nasopharyngeal tumors must include evaluation of the neck because 90% of patients have nodal spread at diagnosis.[110] Retropharyngeal lymphadenopathy, in particular, may be clinically occult. PET/CT is the most sensitive modality for this evaluation.

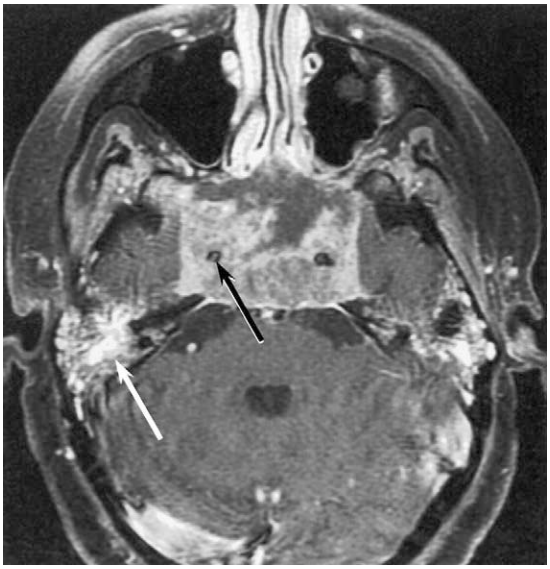

Figure 102-46. Nasopharyngeal carcinoma. Enhanced, fat-suppressed, T1-weighted axial magnetic resonance imaging demonstrates a large, partially necrotic mass replacing the clivus and surrounding structures. The internal carotid arteries *(black arrow)* are encased. Mastoiditis *(white arrow)* can be the earliest radiographic sign of nasopharyngeal carcinoma.

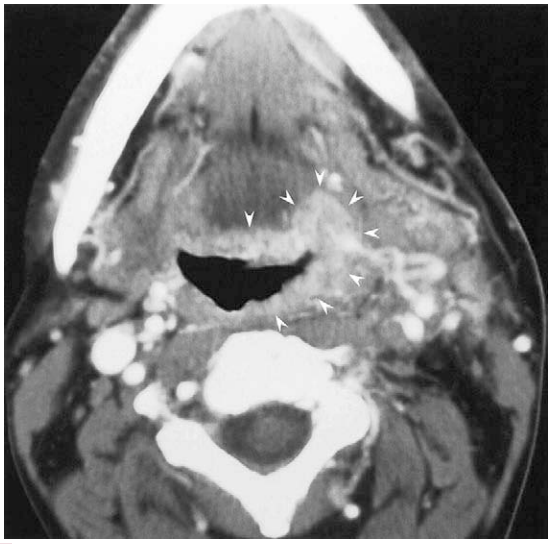

Figure 102-47. Oropharyngeal squamous cell carcinoma. Enhanced computed tomography reveals submucosal spread of tumor *(arrowheads)* from the inferior tonsil to the tongue base and posterior oropharynx.

All patients with incidentally noted mastoid effusions should be carefully evaluated for small tumors in the nasopharynx that have obstructed the eustachian tube.

Oropharynx

Oropharyngeal carcinomas most frequently arise in the tonsillar pillars, soft palate, or tongue base. They may be clinically occult and present with nodal metastases, usually in level 2. Cross-sectional imaging is useful in the search for a primary lesion, but small cancers are often indistinguishable from the surrounding gland and soft tissues. Even PET/CT has difficulty distinguishing tumor uptake from uptake in an asymmetrically hyperplastic gland.[112] Tonsillectomy is often necessary to exclude a primary tumor in this location.

Either CT or MRI may be used to assess the local extent of oropharyngeal carcinomas. MRI may be advantageous in patients with extensive dental amalgam that would obscure CT images. The extent of disease from the palatine tonsils into the tongue base, oral floor, parapharyngeal space, and mandible can be evaluated with CT or MRI (Fig. 102-47).[113]

Mandibular invasion is of particular importance in the preoperative planning of advanced oropharyngeal carcinomas. Although MRI is more sensitive for mandibular invasion, it is less specific than CT. Recent advances in CT techniques have improved the sensitivity, so CT is the preferred modality at many institutions.[14] A dental CT scan, in which thin axial images are reconstructed into a curved paracoronal plane, may be particularly useful.

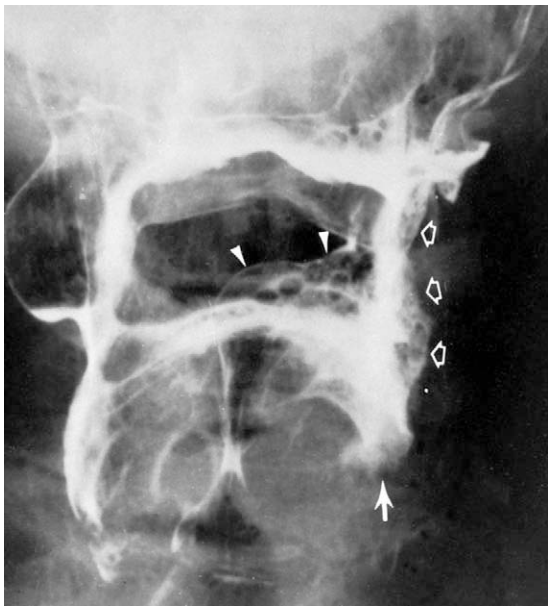

Figure 102-48. Left pyriform sinus carcinoma. Frontal view from air-contrast pharyngography shows a mass *(arrowheads)* arising from the left pyriform sinus, causing irregularity and amputation of the pyriform sinus *(arrow)* and loss of the normal contour of the lateral pyriform sinus wall *(open arrows)*.

Hypopharynx

Hypopharyngeal carcinomas may arise in the pyriform sinus, posterior pharyngeal wall, or postcricoid region.[114] Because the pyriform sinus is often collapsed during cross-sectional imaging and the apex can be difficult to evaluate endoscopically, barium studies are particularly useful for pyriform sinus tumors. Findings include filling defects, rigidity of the sinus walls, mucosal irregularity, and elevation of the postcricoid line. Involvement of the apex can usually be demonstrated or excluded (Fig. 102-48).[114] Lesions arising in the medial pyriform sinus can usually be distinguished from lesions arising within the larynx on cross-sectional imaging.

Tumors of the posterior hypopharyngeal wall extend predominantly along the mucosa, but posterior spread to the prevertebral tissues has a dramatic effect on prognosis and treatment. Invasion of the prevertebral tissues is best assessed with an esophagram because the radiologist can evaluate motion of the larynx relative to the vertebral column during deglutition. Decreased motion suggests invasion.[114]

Postcricoid hypopharyngeal tumors are rare. They can be difficult to demonstrate radiographically. The most frequent appearance is stricture or contour abnormality on full-column esophagography.

Cross-sectional imaging (CT or MRI) is necessary in all patients with hypopharyngeal tumors to assess the extent of tumor into surrounding structures such as the larynx, supraglottis, esophagus, and thyroid gland, as well as to evaluate nodal metastases (Fig. 102-49).[115]

Esophagus

Both fluoroscopy and CT have traditionally played important roles in the diagnosis of esophageal carcinoma, but PET/CT and endoscopic ultrasound now represent the standard of care for staging of this disease. Fluoroscopy or endoscopy may be used for detection; endoscopic ultrasound and PET/CT are used for staging.[116,117] MRI has limited usefulness in the chest, but it is sometimes used to precisely define local spread of tumor.

Esophageal carcinoma has a varied appearance on fluoroscopy. Early disease may be only a flat plaque, whereas advanced disease can present as an annular mass, a large ulceration, an irregular segmental narrowing, or an exophytic mass (see Fig. 102-33). Submucosal spread of tumor may simulate varices (Fig. 102-50).[118]

On CT, esophageal carcinoma appears as focal enlargement of the esophagus. The collapsed cervical esophagus should not exceed 16 mm by 24 mm, and the collapsed thoracic esophagus should be of constant diameter.[34] PET/CT provides valuable information about the local extent of tumor to aorta or lung; nodal metastases in the thorax and upper abdomen (Fig. 102-51); and distant metastases to the liver, lung, or adrenal glands.

Figure 102-49. Hypopharyngeal squamous cell carcinoma. The tumor involves all walls of the right pyriform sinus *(*).*

Lymphadenopathy

CT and MRI are more sensitive than physical examination for cervical lymph node metastases.[119] The radiologic classification of lymph nodes in the neck mirrors the American Academy of Otolaryngology–Head and Neck Surgery classification system, with radiologic landmarks substituted for surgical landmarks.[120,121] The hyoid bone separates levels II and III; the inferior cricoid cartilage separates levels III and IV; and the posterior margin of the sternocleidomastoid muscle is the anterior boundary of level V. Cross-sectional imaging is particularly important for identifying retropharyngeal nodes (Fig. 102-52), which are not included in the classification system and are not readily assessed clinically.

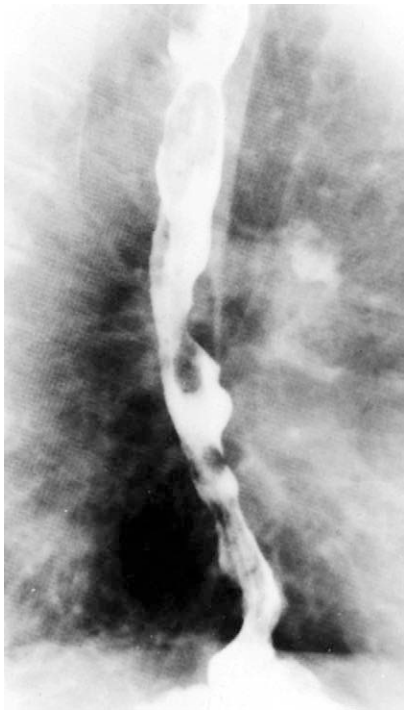

Figure 102-50. Varicoid carcinoma of esophagus. Barium esophagram demonstrates multiple, smooth, elongated filling defects in the esophagus, simulating varices.

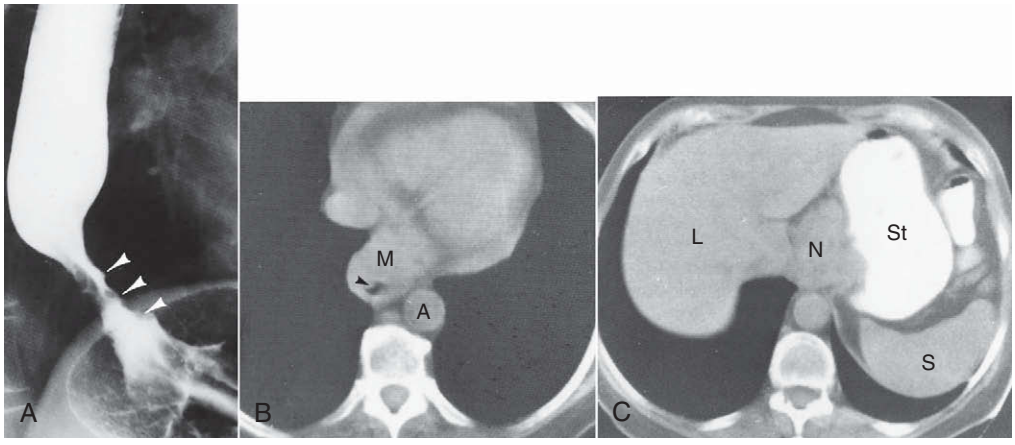

Figure 102-51. Computed tomography (CT) staging of esophageal carcinoma. **A,** Radiograph from an upper gastrointestinal examination shows irregular narrowing of the distal esophagus *(arrowheads),* consistent with esophageal carcinoma. However, the barium study gives no information about local spread of disease. **B,** CT scan demonstrates distal esophageal mass (*M*) with an eccentric narrowed lumen (*arrowhead*). **C,** CT scan at a more caudal level shows a large lymph node mass *(N)* in the region of the gastrohepatic ligament, making carcinoma unresectable for cure. A, aorta; L, liver; St, stomach; S, spleen. *(From Mauro MA, Lee JK, Heiken JP, Balfe DM. Radiologic staging of gastrointestinal neoplasms.* Surg Clin North Am. *1984;64:67.)*

The radiologic diagnosis of lymphadenopathy is based on the size, shape, enhancement, and homogeneity of the nodes. No single feature is sufficient to confidently diagnose or exclude metastatic disease; the diagnosis is based on a combination of the preceding criteria. Lymph nodes greater than1 cm (>1.5 cm for the jugulodigastric node) are considered abnormal. Nodes with central hypodensity or fluid signal are necrotic, unless the central hypodensity represents the fatty hilum of the node. Reniform or oval nodes are usually normal or hyperplastic, whereas spherical nodes are more likely malignant (Fig. 102-53). Ill-defined nodal margins and obliteration of surrounding fat planes are suggestive of extracapsular spread of tumor.

CT and MRI are useful for detecting vascular invasion from malignant lymph nodes.[122] Nodes that are adjacent to the carotid greater than 4 cm in length or approximately 270 degrees of circumference are likely invading. Nodes that are adjacent for less than 180 degrees are likely not invading. When carotid sacrifice is contemplated, balloon catheter occlusion with brain perfusion imaging can predict postoperative morbidity.[123]

In the chest, CT is insensitive for the spread of esophageal carcinoma to periesophageal nodes because unenlarged nodes often contain tumor. PET/CT is a more sensitive means of evaluating these lymph nodes.[124,125]

MRI and CT have comparable sensitivity for the detection of cervical lymph node metastases.[126] Recent advances in MR imaging such as T1-rho and magnetization transfer may provide additional benefit but are as yet unproven in large clinical trials.[127] PET/CT, however, is superior to either CT or MRI in the evaluation of nodal and distant metastatic disease.

Benign Neoplasms

Benign esophageal neoplasms present as submucosal masses (Fig. 102-54). They are usually asymptomatic and incidental. Leiomyomas are the

Figure 102-52. Retropharyngeal lymphadenopathy. Even large retropharyngeal lymph nodes *(*)* may not be clinically evident.

Figure 102-53. Reactive lymph nodes. Size alone does not indicate the presence of tumor. Enhanced axial computed tomography demonstrates a 28-mm jugulodigastric node *(*)* that retains its reniform configuration, suggesting a benign etiology. The patient had a peritonsillar abscess.

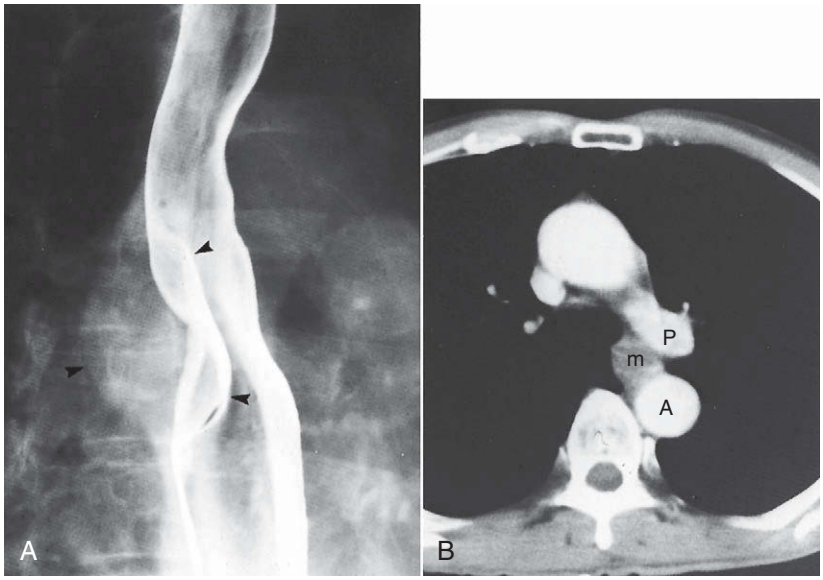

Figure 102-54. Esophageal leiomyoma. **A,** Air-contrast esophagram demonstrates a smooth soft tissue mass *(arrowheads)* arising in the wall of esophagus. **B,** Computed tomography scan shows a round soft tissue attenuation mass *(m)* between the descending aorta *(A)* and the left pulmonary artery *(P)*.

Figure 102-55. Vallecular cyst. Enhanced computed tomography reveals a large cystic mass filling the left vallecula, displacing the epiglottis to the right and compromising the airway.

Figure 102-56. Tornwaldt cyst. Enhanced computed tomography reveals a complex cystic mass in the midline of the upper nasopharynx.

most common benign esophageal neoplasm, but lipomas, neurofibromas, hemangiomas, fibromas, and granular cell tumors have been reported.

Papillomas appear as sessile mucosal masses that may extend into the larynx. Adenomas are mucosal masses that should be surgically removed because of their malignant potential. Benign extra-alimentary tumors such as schwannomas and hemangiomas may become large enough to displace the pharynx or esophagus.

Non-neoplastic Mucosal Masses

A retention cyst, the result of a single obstructed mucous duct, can be seen anywhere in the pharynx or esophagus. The most familiar locations are the adenoids, vallecula, lingual tonsil, and distal esophagus. Retention cysts appear as submucosal masses on fluoroscopy. On cross-sectional imaging, retention cysts are usually fluid-filled, but longstanding cysts may become dense on CT and have high signal on T1-weighted MRI (Fig. 102-55).

A Tornwaldt cyst is an embryologic remnant found in the midline of the nasopharynx (Fig. 102-56). It is indistinguishable from a retention cyst, except by location. Fibrovascular polyps are pedunculated masses projecting into the lumen of the cervical esophagus. Inflammatory esophageal polyps are actually rugal folds, enlarged by reflux disease, extending into the distal esophagus.

A tortuous internal carotid artery may simulate a submucosal or extrinsic mass behind the pharynx. A definitive diagnosis can be made with contrast-enhanced CT (Fig. 102-57).

Esophageal hematoma may appear as a mucosal or submucosal mass; the history is usually suggestive.

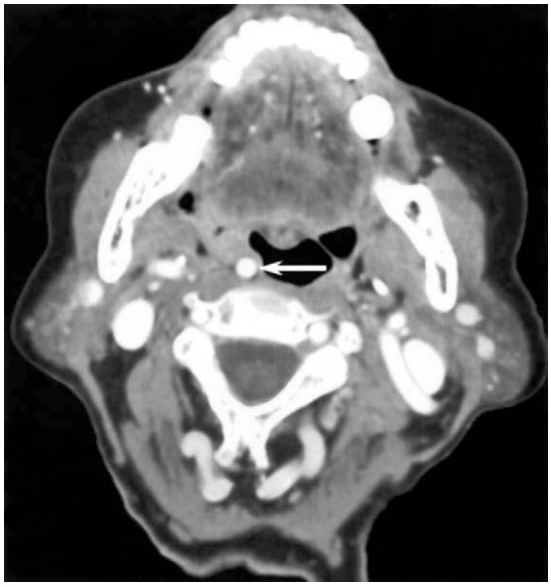

Figure 102-57. Retropharyngeal carotid artery. Enhanced computed tomography reveals a tortuous right internal carotid artery *(arrow),* which may simulate a submucosal mass.

Post-treatment Appearance

Total Laryngectomy

The postlaryngectomy neopharynx looks like a featureless tube on esophagography (Fig. 102-58). It is normal for a small pouch to form along the anterior surgical bed. The ridge of tissue between the anterior pouch and the neopharynx is called a *pseudoepiglottis* because of its fluoroscopic appearance (Fig. 102-59). Residual cricopharyngeal fibers, although they lack an anterior attachment, may form a smooth posterior impression on the esophagus, similar in appearance to cricopharyngeal achalasia.

Benign strictures can have one of two configurations: a focal stricture at the distal surgical closure or a long tapered stricture throughout the neopharynx.[128] These strictures, as well as fistulas and leaks, are best assessed with esophagography.

Recurrent tumor may be seen on an esophagram as mucosal irregularity, a mass displacing the neopharynx, or circumferential narrowing (Fig. 102-60). Nonmucosal recurrences are frequently not evident on an esophagram, so cross-sectional imaging (CT, MRI, or preferably PET/CT) should be used for surveillance. Esophagography is reserved for patients with delayed postoperative dysphagia.

Laryngopharyngectomy

Patients who undergo laryngopharyngectomy may be reconstructed with a primary closure, a jejunal interposition, or various flaps. These reconstructions have different radiographic appearances. Flap reconstructions and primary closures result in a smooth, tubular neopharynx with only mild surrounding soft tissue on CT. Jejunal interpositions have a more confusing appearance.

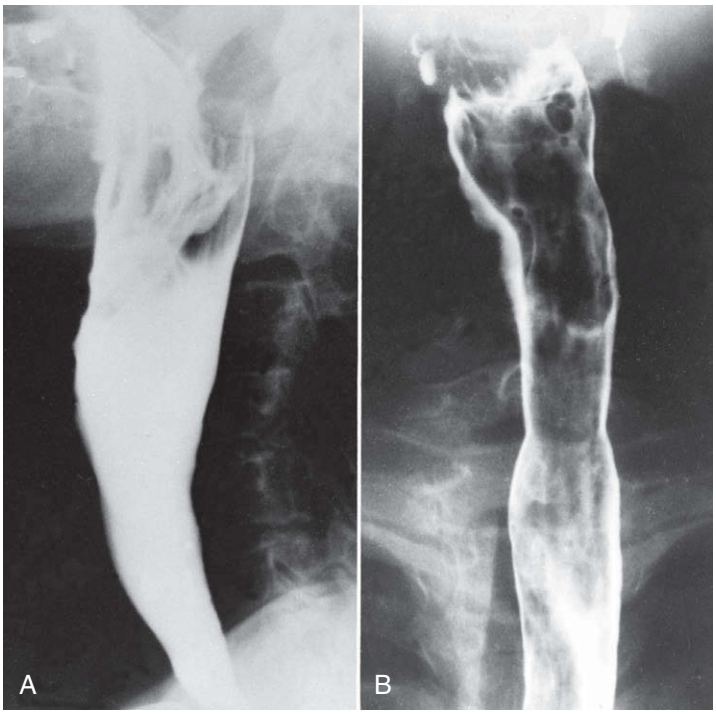

Figure 102-58. Normal postlaryngectomy pharyngoesophagography. **A,** Frontal projection. **B,** Lateral projection. The neopharynx is essentially a featureless tube.

Figure 102-59. Pseudoepiglottis. Lateral esophagram in a laryngectomy patient demonstrates a ridge of tissue mimicking the epiglottis. This is a normal postoperative appearance.

Figure 102-60. Tumor recurrence after total laryngectomy. Frontal view from an esophagram shows a 3-cm mass indenting the right side of the neopharynx *(arrows).*

On CT, the jejunal mucosa enhances briskly and may simulate recurrent tumor (Fig. 102-61). The interposed jejunum may have a tortuous course within the neck, further complicating the radiographic evaluation.[129] On an esophagram, the plicae circulares of the jejunum have a characteristic appearance (Fig. 102-62). Longstanding jejunal grafts may show evidence of peristalsis. Because jejunal peristalsis is much slower than normal pharyngeal peristalsis, these patients may present with dysphagia.

All laryngopharyngectomy reconstructions share characteristic sites of stenosis. Short-segment strictures most frequently involve the proximal or distal anastomosis. Long, tapered strictures affect the midneopharynx, particularly in patients who undergo radiation therapy.

Radiotherapy

Motility disorders are often identified in patients who have received therapeutic radiation to the neck. The most common dysfunction is failure of epiglottic inversion,[130] but hypocontractility, tracheal aspiration, and failure of cricopharyngeal relaxation are also seen.

On cross-sectional imaging, prior radiation therapy is evidenced by stranding of the cervical fat, thickening of the platysma muscle, increased density of the salivary glands, and persistent edema of the laryngeal mucosa (Fig. 102-63). This mucosal swelling is less pronounced, and less persistent, in the pharynx.

Monitoring and Surveillance

Combined PET/CT scanning has dramatically changed the assessment of recurrent tumor in the head and neck.[131,132] Traditional surveillance with CT or MRI relies on morphologic changes over the course of many months to distinguish postoperative scar from recurrent or residual tumor. PET/CT can detect residual disease as soon as 8 weeks after therapy and may be useful during chemoradiation to assess response to therapy (Fig. 102-64). Appropriate screening regimens for postoperative surveillance with PET/CT have yet to be established.[133]

PET/CT is also able to detect second primary tumors, either in the head and neck or elsewhere in the body (Fig. 102-65). This is particularly important because of the high rate of synchronous and metachronous tumors in patients with carcinomas of the pharynx and esophagus.

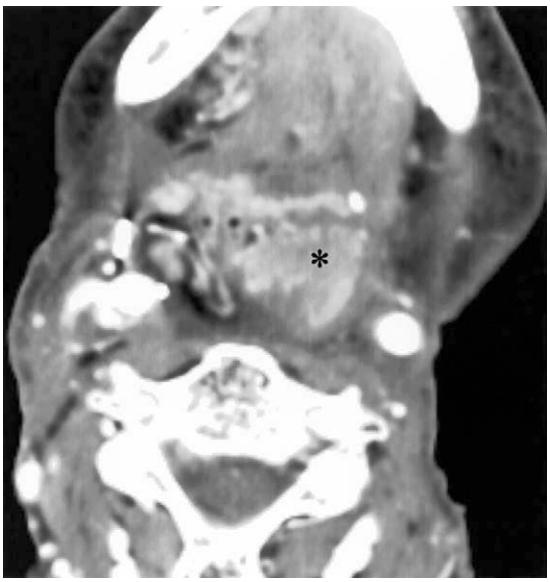

Figure 102-61. Jejunal interposition graft. Enhanced CT reveals an irregular, enhancing mass *(*)* in the surgical bed. This is the normal appearance of the transposed jejunum and should not be confused with tumor recurrence.

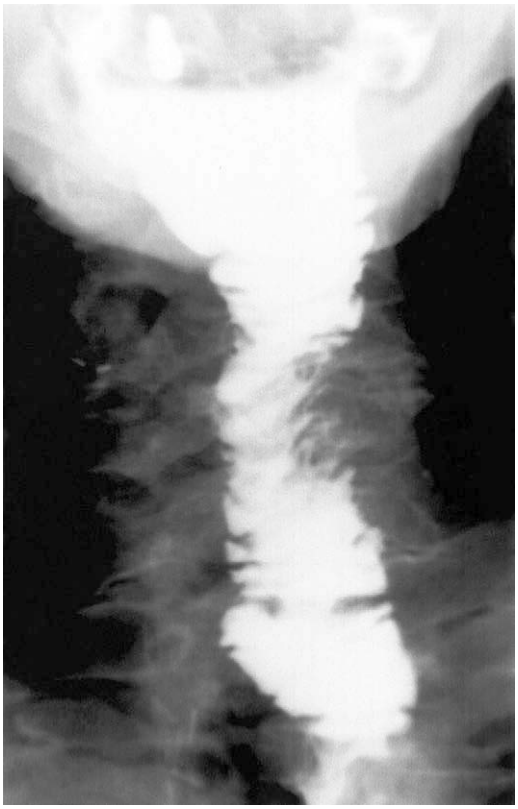

Figure 102-62. Jejunal interposition graft. Frontal esophagram demonstrates normal jejunal folds in the neopharynx.

Figure 102-63. Effects of radiotherapy. Enhanced computed tomography reveals extensive edema *(*)* lining the larynx. The submandibular glands *(g)* are dense. The platysma muscle *(arrow)* is thickened.

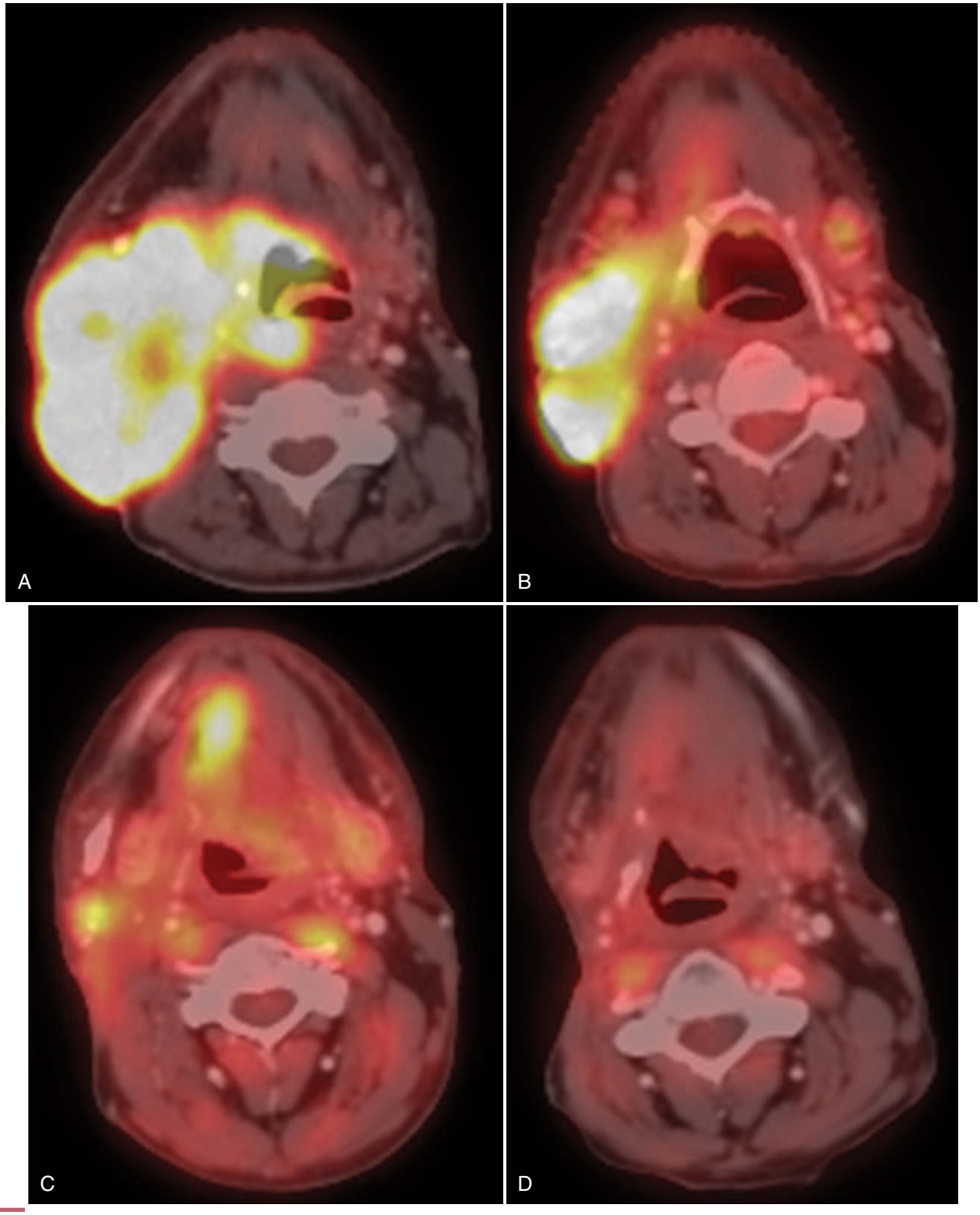

Figure 102-64. Monitoring tumor response with positron emission tomography-computed tomography. Sequential fused axial images through the oropharynx show large tumor at presentation **(A),** improved after 2 months of therapy **(B),** further regressed 4 months later **(C),** and completely resolved 3 months later **(D).**

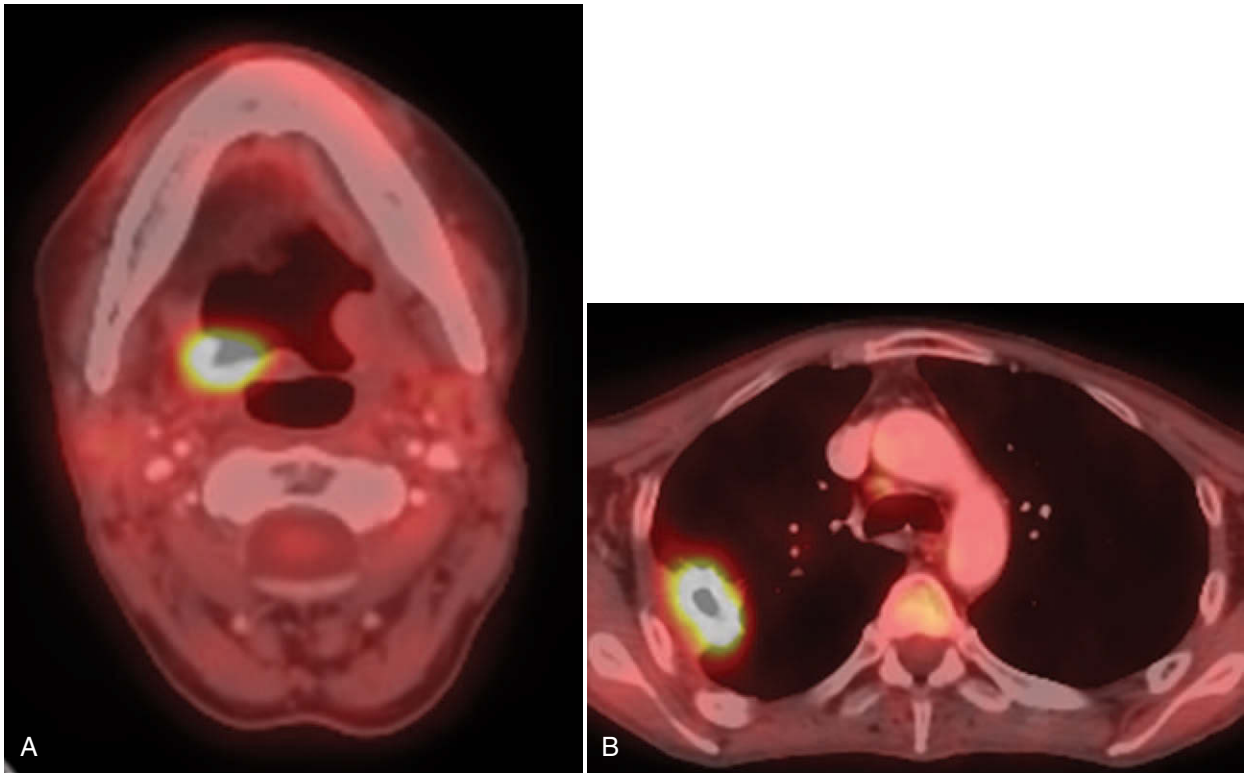

Figure 102-65. Detecting second primary tumors with positron emission tomography-computed tomography (PET/CT). **A,** Fused axial PET/CT image through the oral cavity demonstrates recurrent squamous cell carcinoma in the right tonsillar pillar and soft palate. **B,** On the same scan, an unsuspected second primary lung cancer is revealed.

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CHAPTER ONE HUNDRED AND THREE

Neoplasms of the Hypopharynx and Cervical Esophagus

Ravindra Uppaluri

John B. Sunwoo

Key Points

- Of all subsites of head and neck squamous cell carcinoma, patients with hypopharyngeal carcinomas as a group fare the worst in terms of oncologic outcome.
- Hypopharyngeal carcinomas tend to have significant submucosal extent, especially inferiorly, but according to one study, this does not worsen locoregional recurrence nor does it affect 5-year survival.
- Organ-preserving therapy for hypopharyngeal lesions includes nonsurgical concurrent or induction chemotherapy and radiation or surgical options including transoral laser microsurgery and supracricoid hemilaryngopharyngectomy.
- Combined chemotherapy and radiotherapy for hypopharyngeal carcinomas leads to a higher rate of stricture and gastrostomy tube dependence compared with other subsites of the head and neck.
- Advanced hypopharyngeal tumors requiring surgery routinely involve reconstruction with either microvascular free flaps (fasciocutaneous or jejunum interposition) or gastric pull-ups.

Neoplasms of the hypopharynx and cervical esophagus are some of the most challenging diseases managed by the head and neck surgeon. Pathologically the vast majority of these lesions are squamous cell carcinomas, which usually present at an advanced stage and thus pose several challenges to the managing physician. As with all advanced head and neck cancers, a multidisciplinary approach involving head and neck surgeons, radiation therapists, and medical oncologists is used in formulating a treatment plan. Unfortunately, the available modalities of treatment yield a similar poor prognosis for patients with hypopharyngeal and cervical esophageal cancer. When primary surgical-based approaches are used, a careful assessment of the tumor extent is critical because hypopharyngeal tumors often have significant submucosal extension, which can significantly affect the planned resection. Furthermore, the surgeon must consider the reconstructive challenges of the surgical defect, which affects swallowing, speech, and respiration. When radiation and chemotherapy are used as initial modalities of therapy, great care must be taken to follow patients because the ability to surgically salvage treatment failures is an integral part of the therapeutic regimen. The goal of this chapter is to provide a comprehensive review of cancers of the hypopharynx and cervical esophagus that have such devastating effects on the patients who develop them.

Anatomy of the Hypopharynx and Cervical Esophagus

The hypopharynx is the region of the pharynx that extends from the oropharynx superiorly to the cervical esophagus inferiorly. The cervical esophagus is that portion of the esophagus that extends to the thoracic inlet. The superior extent of the hypopharynx is approximately at the level of the hyoid bone or at the level of the pharyngoepiglottic folds. Inferiorly, the hypopharynx tapers to the esophageal introitus at the cricopharyngeus muscle. It is bordered anteriorly by the larynx and posteriorly by the retropharyngeal space. It is subdivided into three regions: the pyriform sinuses, the postcricoid region, and the posterior pharyngeal wall (Fig. 103-1).

The pyriform sinuses (one on each side) are composed of anterior, medial, and lateral walls that form an inverted pyramid with the base of the pyramid at the level of the pharyngoepiglottic fold and the apex extending to just below the cricoid cartilage. This lower region is lateral to the aryepiglottic folds and medial to the thyroid lamina. Because of this close relationship, tumors of the hypopharynx often extend to invade the larynx.[1] The medial pyriform mucosa forms the posterior wall of the paraglottic space and is separated from the endolarynx by the aryepiglottic folds and the lateral cricoarytenoid muscles. Hypopharyngeal tumors extending medially from the medial wall of the pyriform sinus can, therefore, invade into the larynx.

The postcricoid region is the anterior wall of the hypopharynx, extending from just below the posterior aspect of the arytenoid cartilages to the esophageal introitus. Postcricoid tumors commonly invade the cricoid cartilage and the posterior cricoarytenoid muscle. Because the postcricoid region lies just medial to the tracheoesophageal groove, tumors arising from this area can involve the recurrent laryngeal nerve, paratracheal nodes, and thyroid gland.

The third region of the hypopharynx, the posterior hypopharyngeal wall, is separated from the vertebral and paravertebral structures by the potential retropharyngeal space. Tumors can easily cross this space to invade prevertebral tissues. The posterior wall extends from the level of the hyoid bone to the superior aspect of the cricopharyngeus muscle.

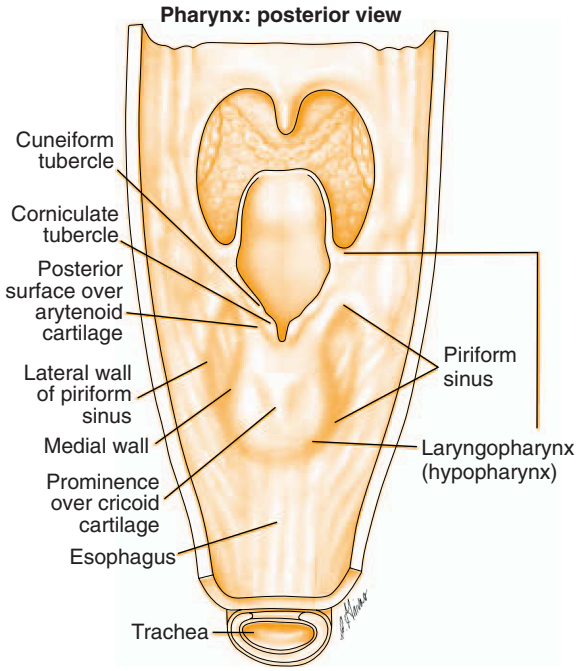

Figure 103-1. Anatomic regions of the hypopharynx.

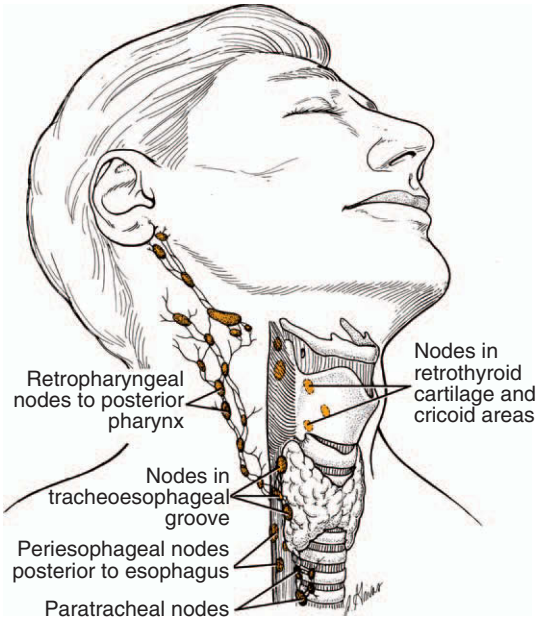

Figure 103-2. Hypopharyngeal carcinomas metastasize primarily to the superior jugular and midjugular nodes. However, metastasis to the retropharyngeal nodes, paratracheal nodes, paraesophageal nodes, and parapharyngeal space nodes may be present.

The aryepiglottic folds separate the endolarynx from the medial wall of the pyriform sinus bilaterally and form what has been termed the "marginal area." Although the aryepiglottic folds are actually part of the supraglottic larynx, tumors arising at this site behave aggressively like hypopharyngeal cancers and not supraglottic carcinomas.[2]

The cross-sectional anatomy of the hypopharynx reveals that it is composed of four layers: a mucosal lining formed by stratified squamous epithelium over loose stroma; a fibrous layer formed by the pharyngeal aponeurosis; a muscular layer; and a fascial layer arising from the buccopharyngeal fascia. The muscular layer is composed of the posterior cricoarytenoid muscles anteriorly and the middle/inferior constrictor muscles posteriorly. The inferior constrictor condenses into the cricopharyngeus muscle distally, and just superior to this junction is a potential area of weakness, known as *Killian's triangle,* through which posterior pharyngeal wall tumors can extend outside the hypopharynx. Just inferior to the hyoid bone at the thyrohyoid membrane, there is another potential area of weakness through which hypopharyngeal tumors may extend laterally along the vascular pedicle and the superior laryngeal nerve.

The arterial blood supply to the hypopharynx is primarily through the superior thyroid arteries. Branches from the lingual and ascending pharyngeal arteries also form collaterals supplying this area. The venous drainage mirrors the arterial blood supply.

Sensory innervation from the hypopharynx that assists in swallowing passes through the glossopharyngeal (cranial nerve IX) and the vagus (cranial nerve X) nerves to the nucleus solitarius in the brainstem. The sensory input is connected to the nearby cranial nerve motor nuclei by interneurons and assists in the coordination of deglutition. The internal branch of the superior laryngeal nerve passes through the superior portion of the lateral wall of the pyriform sinus and through the thyrohyoid membrane to join the vagus nerve. These sensory fibers then synapse in the jugular ganglion within the jugular foramen along with sensory fibers of Arnold's nerve from the external auditory canal. This juxtaposition accounts for the referred otalgia that is often experienced by patients with tumors of the pyriform sinus.

Lymphatic drainage from the pyriform sinuses passes through the thyrohyoid membrane primarily to the jugulodigastric lymph node and to the midjugular and spinal accessory chains (Fig. 103-2). Lymphatic vessels from the inferior portion of the hypopharynx and from the postcricoid region also drain to the paratracheal and paraesophageal nodes and to nodes in the supraclavicular fossa. Lymphatic drainage from the posterior hypopharyngeal wall is to the retropharyngeal nodes and to the midjugular chain. The retropharyngeal nodes are divided into a medial and lateral group. Lateral retropharyngeal nodes, also known as the *nodes of Rouvière,* are present at the level of the skull base.

The cricopharyngeus muscle represents the transition between the hypopharynx and cervical esophagus. The cervical esophagus is also a muscular tube that has a squamous epithelial layer, a submucosa rich in lymphatics, a muscular layer, and an adventitial layer. The muscular layer is divided into an inner circular and outer longitudinal layer. The trachea and thyroid are anterior to the cervical esophagus with the lobes of the thyroid also extending laterally. The retroesophageal space is contiguous with the retropharyngeal space above and the posterior mediastinum below. The lymphatics of the cervical esophagus are almost coincident with the hypopharyngeal lymphatics and include drainage to the recurrent laryngeal, paratracheal, and jugular chain nodes. The only difference in lymphatic drainage may involve some drainage of the cervical esophagus to the superior mediastinal lymph nodes. The vascular supply is derived from the inferior thyroid arteries with some contribution from the high thoracic vasculature. Finally, innervation to the cervical esophagus is provided by sympathetics, parasympathetics, and cranial nerves IX, X, and XI (the spinal accessory nerve). The recurrent laryngeal nerve and the pharyngeal plexus provide innervation to the cricopharyngeus.

Incidence

The incidence of cancer of the hypopharynx varies depending on worldwide geographic location. In addition, the incidence of cancer arising from specific subsites within the hypopharynx may also vary by geographic location. In the United States, three large database reviews shed light on the epidemiology of hypopharyngeal carcinoma. Neoplasms specific to the cervical esophagus are not mentioned in the first two of these three studies. Canto and Devesa[3] analyzed data from 1975 to 1988 in nine registries of the Surveillance, Epidemiology, and End Results (SEER) database. Although these data are not a random sample because each registry is from a specific geographic location, they represent approximately 10% of the U.S. population. The rates of cancer per 100,000 person-years vary with race and sex. It is also not clear from this study why the sites are listed separately as hypopharynx and pyriform. Whether there is overlap in these numbers is not stated in

this study. For white males the rate is 0.4 and 0.9 for the hypopharynx and pyriform sinus, respectively. For African American males the rate is 0.8 and 2.3 for the hypopharynx and pyriform sinus, respectively. For white females the rate is 0.2 for both the hypopharynx and pyriform sinus. For African American females the rate is 0.2 and 0.5 for the hypopharynx and pyriform sinus, respectively.

Hoffman and colleagues[4] conducted a second major database review of the National Cancer Data Base (NCDB) report, which is a comprehensive hospital-based registry of all cancer cases encountered. The data cover the years 1985 to 1994 and reveal that hypopharyngeal malignancy comprised 4.3% of all head and neck cancers, which included salivary gland and thyroid tumors in this study. Ninety-five percent of the hypopharyngeal tumors were squamous cell carcinomas with the remainder being adenocarcinomas, lymphoma, and other pathologies. Stage III and IV tumors comprised 77.3% of cancers, demonstrating the advanced stage of hypopharyngeal tumors at presentation. The survival data in this study were noteworthy in that hypopharyngeal cancers had the worst 5-year survival compared with any other primary site in the head and neck. The 5-year disease-specific survival was 31.4%.

Finally, Davies and Welch[5] analyzed the updated SEER database for the years 1999 to 2001 and found an average of 75,000 new cases of head and neck cancer. Interestingly, compared with the average 1975 statistics, this study found that incidence and mortality rates for hypopharyngeal and cervical esophageal cancer were decreasing. The one caveat to consider in saying that this trend was a definitive finding is that the rates of these tumors were below 1 per 100,000. Notwithstanding this statistic, this study shows a continued significant incidence of these deadly cancers within all head and neck squamous cell carcinomas.

The statistics outside of the United States reveal similar epidemiologic data. Wahlberg and colleagues[6] analyzed the comprehensive Swedish databases, covering 1960 to 1989, and found rates of 1.22/100,000 for men and 0.45/100,000 for women, similar to rates described by Canto and Devesa.[3] During this time the rates for men increased, but the rates for women decreased. The authors suggest that this may reflect a decrease in Plummer-Vinson syndrome, the sideropenic anemia common in Northern Sweden that predisposes to development of postcricoid carcinoma.

The data on cervical esophageal carcinoma are much more limited. Esophageal carcinoma causes approximately 12,000 deaths per year in the United States.[7,8] In one series, cervical esophageal carcinoma represented only 5.3% (9/168 patients) of all esophageal cancers.[9] Given this low frequency, the data are limited on the incidence and optimal treatment of this cancer. Additionally, these tumors are often included in statistics regarding all esophageal cancers.

Clinical Evaluation

PATIENT SYMPTOMS. Patients with lesions in the hypopharynx and cervical esophagus usually present at an advanced stage of disease. Lesions in this area can grow unabated to a size larger than most other head and neck sites because the anatomic boundaries of neighboring structures are not as limiting as for other sites (e.g., the larynx). Thus a disturbance of function is not seen until the disease is advanced. Because this area also has a rich lymphatic drainage, a neck mass is not an uncommon finding, especially in the advanced-stage disease. Hoffman and colleagues[10] analyzed presenting symptoms in 2939 cases from the Patient Care Evaluation study of the American College of Surgeons Commission on Cancer (Table 103-1). For stage I/II disease, gastroesophageal reflux, a common and nonspecific symptom, was most common (30.5%) followed closely by sore throat (28.1%). Importantly, 37.3% of patients with early-stage disease were asymptomatic at presentation. For stage III/IV disease, the most common symptom was a neck mass (92.3%) followed by shortness of breath (87.9%). Dysphagia occurred in 21.6% of early-stage and 78.4% of advanced-stage lesions. Additionally, referred otalgia was present in 25.1% of early-stage and 74.9% of advanced-stage lesions.

PHYSICAL FINDINGS. The overall appearance of these patients will likely reveal a malnourished individual. A complete examination of the head and neck should be performed with a focus on the mucosa of the upper aerodigestive tract to evaluate the extent of the primary tumor and to assess for second primaries. Synchronous tumors were present in a significant proportion of asymptomatic stage I/II patients in the Hoffman and colleagues' study.[10] In the same study a significant portion of patients presented with a neck mass; thus clinical staging of the neck to define the nodal stage is also critical. In the clinic, fiberoptic laryngoscopy should be used to evaluate the airway because impending airway distress is a possibility with advanced tumors. Immobility of the vocal cord(s) may reveal whether the larynx has been invaded.

In defining the options for managing a patient with hypopharyngeal and cervical esophageal cancer, the following must be addressed. The extent of tumor and lymph node involvement must be defined by office examination, operative endoscopy, and imaging. For tumors involving the posterior pharyngeal wall, invasion of the prevertebral fascia needs to be assessed clinically and radiographically to ensure an adequate surgical margin. Because distant metastases in certain series are the highest for hypopharyngeal cancers,[11] a metastatic workup by imaging and laboratory testing should also be completed. Comorbidities of the patient are also a significant contributing factor in managing these patients. For example, if a conservation surgical procedure is planned, the pulmonary function status of the patient needs to be evaluated because these patients are at significant risk for aspiration and must have adequate pulmonary reserve.

Table 103-1

Presenting Symptoms of Lesions

Symptoms*	All Cases	Clinical Stage I/II	Clinical Stage III/IV
Dysphagia	48.0	21.6	78.4
Neck mass	45.1	7.7	92.3
Sore throat	43.0	28.1	71.9
Hoarseness	35.6	18.7	81.3
Otalgia	17.5	25.1	74.9
Shortness of breath	11.8	12.1	87.9
Hemoptysis	8.1	18.0	82.0
Gastroesophageal reflux	3.0	30.5	69.5
Asymptomatic	1.9	37.3	62.7

*Numbers are percentages. Note the columns do not total 100% because single patients may have had more than one symptom. Adapted from Hoffman HT, Karnell LH, Shah JP. Hypopharyngeal cancer patient care evaluation. *Laryngoscope.* 1997;107:1005-1017.

Imaging

In the treatment of hypopharyngeal malignancies, the role of imaging involves the pretreatment evaluation of the extent of the primary tumor and possible metastases, as well as the evaluation of the patient following treatment. Hypopharyngeal tumors have a propensity for submucosal spread that may be undetectable on clinical or radiographic examination.[12] Causes for surgical failure include submucosal extension, involvement of the thyroid gland, and metastasis to paratracheal and upper mediastinal lymph nodes.[13] Thus imaging is essential to assess tumor extent or recurrence.

Although the barium swallow has been historically used to identify malignancies in this region,[14] its use is now more limited. Some centers continue to use the swallow to evaluate for second primaries in the esophagus. In the case of a cervical esophageal cancer where an endoscope cannot be passed distally, the barium swallow can be used for

Figure 103-3. Axial computed tomography scan of a patient with a left pyriform squamous cell carcinoma invading the arytenoids cartilage and the thyroid lamina.

imaging the distal extent of disease. Another use of the barium swallow study is in the postoperative setting to examine the deglutition process or to identify anastomotic problems such as stricture or fistula.

The primary imaging modality for pretreatment evaluation of the hypopharynx is cross-sectional imaging with computed tomography (CT) or magnetic resonance (MRI). In multiple studies examining the impact of cross-sectional imaging on the staging of hypopharyngeal and/or esophageal cancer, the clinical tumor stage was upstaged in up to 90% of patients.[15] Accuracy of tumor staging, determined by comparison to pathologic findings, is 58% for clinical examination, 80% for CT, and 85% for MRI.[16] CT is often preferred to MRI to assess cartilage invasion; however, an experienced radiologist looking for an increased T2 and decreased T1 signal intensity on MRI, which indicates cartilage involvement, can achieve a high degree of sensitivity (89% to 100%).[15] The specificity of MRI for cartilage invasion, however, is inferior to CT (62% vs. 84%).[17] A wide variability in specificity reflects the variability in ossification and the degree of inflammation, edema, and/or fibrosis at the tumor site. The specificity for cartilage invasion is lowest for the thyroid cartilage (57%), highest for the arytenoid cartilages (95%), and intermediate for the cricoid cartilage (87%).[16] Figure 103-3 demonstrates a T4 left pyriform sinus squamous cell cancer that has invaded the arytenoid cartilage and the thyroid lamina. The incidence of a second neoplasm of the aerodigestive tract, either synchronous or metachronous to an index tumor of the hypopharynx, has been reported to be 16% to 18%[11]; therefore a thorough radiographic evaluation of the entire aerodigestive tract including the esophagus is necessary.[18,19]

There are no available data supporting the routine use of imaging with CT or MRI in the post-treatment period to follow disease-free status. Typically patient symptoms or clinical endoscopic findings will dictate the utilization of specific imaging. The role of positron emission tomography (PET) has been explored as a modality to assist in the detection of locoregional recurrence and/or persistent disease. Several studies have reported on the improved sensitivity of PET over MRI in the evaluation of response to therapy.[20,21] Although this modality appears to have an increased sensitivity (86%) for recurrence over CT/MRI (57%), there is a lower measured specificity with PET (75% vs. 92% for CT/MRI).[21] An improvement in specificity with PET may be achieved as newer tracers are studied. For example, Chesnay and colleagues[22] described the successful use of ^{11}C-methionine to follow post-chemotherapy tumor response. The combination of PET and CT scans (PET/CT) provides significant advantages due to the ability to correlate fluorodeoxyglucose (FDG) avid lesions with anatomic findings and is increasingly used in all phases of hypopharyngeal tumor management.[23] Figure 103-4 illustrates the use of PET/CT in a patient with an advanced left pyriform sinus squamous cell carcinoma with cervical lymphadenopathy. The fused scan not only shows the primary FDG avid lesion but also highlights the left cervical lymph node with obvious tumor involvement. Thus the combination of CT, MRI, and PET scanning can be used in all phases of the management of hypopharyngeal and cervical esophageal carcinoma.

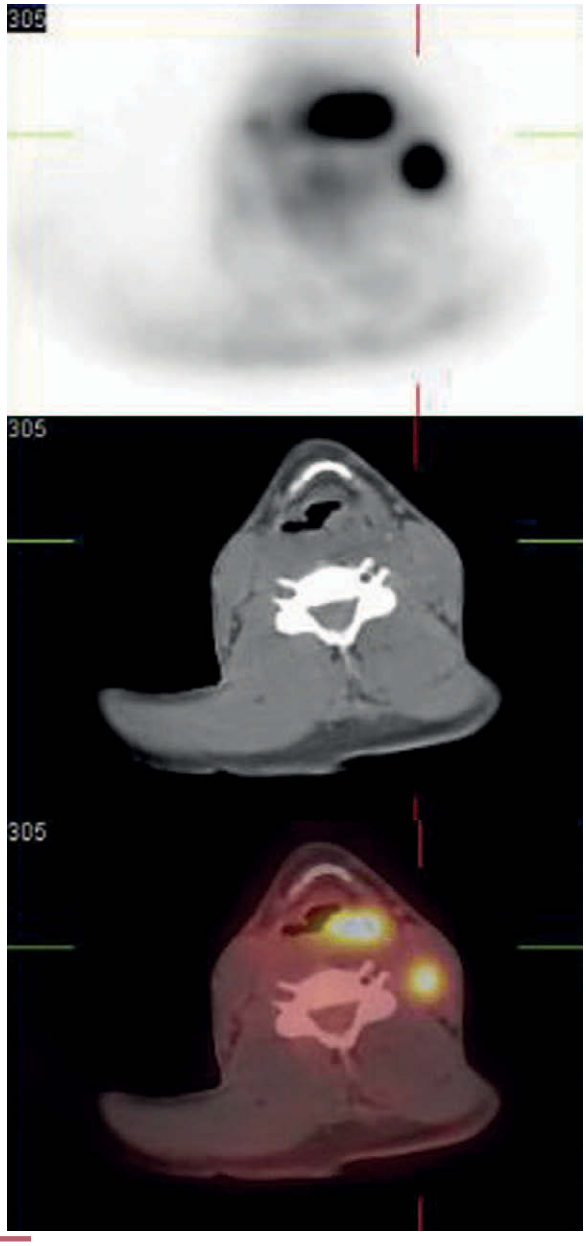

Figure 103-4. The bottom panel shows the positron emission tomography/computed tomography (PET/CT) fused image of a left pyriform sinus carcinoma with regional lymph node metastasis. The top panel shows the PET image alone, and the middle panel shows the CT alone.

Pathology

Although the vast majority (95% in the Hoffman and colleagues' study[10]) of neoplasms of the hypopharynx and cervical esophagus are squamous cell carcinomas, other rare pathologic entities have been described (Fig. 103-5). In addition, variants of squamous cell carcinoma have also been described.

Unusual malignant lesions include lymphomas, which can present in the hypopharynx as the primary site or can secondarily involve the hypopharynx and cervical esophagus after systemic presentation. Some of the subtypes include angiocentric T cell lymphomas, non-Hodgkin's extranodal lymphomas, and mucosa-associated lymphoid tissue (MALT) lymphomas.[24] A high index of suspicion for lymphoma should

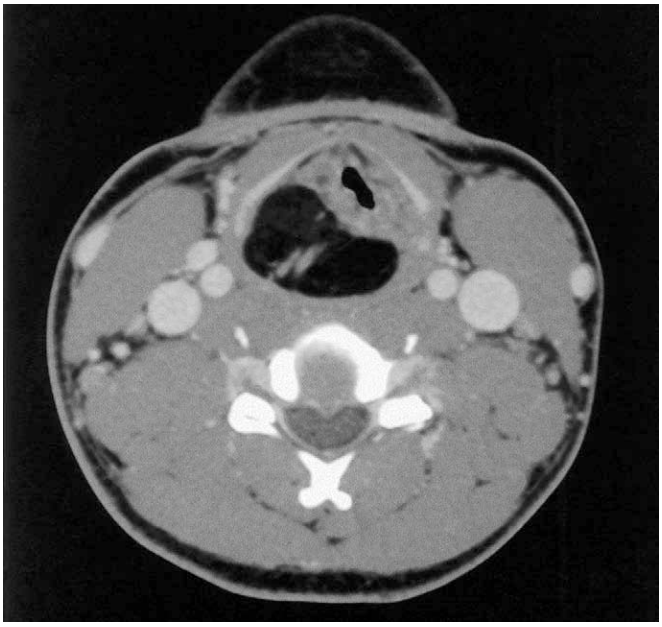

Figure 103-5. Axial computed tomography scan of a patient with a hypopharyngeal lipoma displacing the larynx.

be maintained in patients with AIDS and a hypopharyngeal mass.[25] Lymphomas need to be extensively staged and, depending on subtype, are treated with a combination of radiation and/or chemotherapy. The neuroendocrine tumors of the larynx and hypopharynx are a diverse subset of small cell tumors.[26] Depending on the histologic subtype, treatment varies from chemotherapy and radiation to surgical therapy.

Adenocarcinomas are another rare malignant entity seen in the hypopharynx and cervical esophagus. These lesions may initiate in the minor salivary glands within the hypopharynx or ectopic gastric mucosa in the cervical esophagus. The outgrowth of adenocarcinomas from ectopic gastric mucosa is a rare event.[27] Thyroid malignancies may secondarily involve the hypopharynx or cervical esophagus via direct invasion.[28] Other extremely rare malignancies include sarcomas[29] such as liposarcomas,[30] angiosarcomas,[31] and synovial sarcomas.[32]

Of the squamous cell cancers, there are three histologic subtypes that deserve special attention. First is basaloid squamous cell carcinoma,[33] which is a bimorphic variant of squamous cell carcinoma that has distinct pathologic features. Clinically, these lesions appear primarily in the supraglottis, pyriform sinus, and tongue base and have a distinctly more aggressive clinical course.[34] Second, lymphoepitheliomas are the hypopharyngeal counterpart of nasopharyngeal cancers.[35,36] These tumors are treated with radiation and chemotherapy, similar to nasopharyngeal carcinoma. Finally, the adenosquamous carcinoma is another rare variant, which also behaves clinically in an aggressive manner.[37]

Location of Tumors and Patterns of Spread

An understanding of the site of initiation and patterns of spread of hypopharyngeal carcinoma is critical in the management of these tumors. Substantial data exist regarding the origin of the carcinoma within specific subsites of the hypopharynx. Kirchner[1] described experience at the Yale University hospitals in managing hypopharyngeal carcinoma. In their patient population, 152 (86%) carcinomas arose in the pyriform sinus, 17 (10%) were in the posterior pharyngeal wall, and 8 (4%) were located in the postcricoid region. In the series of Carpenter and colleagues,[38] 117 (72%) carcinomas arose in the pyriform sinus, 37 (23%) in the posterior pharyngeal wall, and 8 (5%) were located in the postcricoid region. Saleh and colleagues[39] described their series of patients from Egypt and found that postcricoid cancers were the majority of presenting lesions (50.1%) followed by pyriform sinus (26.5%) and finally posterior pharyngeal wall tumors (23.4%). A European cancer registry review[40] demonstrated highest rates of pyriform sinus cancer in France (78%) and lowest rates in Sweden (5%). Although difficult to identify the precise reason for these subsite differences, one explanation is the possibility that an assignment of the exact origin of these tumors may be difficult except in the earliest stages.

Regarding the histologic spread of tumor, Kirchner[1] performed whole organ serial sections on 51 surgically resected pyriform sinus carcinoma specimens and described several interesting findings. Tumors were able to infiltrate the larynx and behave as transglottic cancers. They may invade the lateral and posterior pharyngeal walls and they may spread into the supraglottis and base of tongue. Invasion inferiorly into the cervical esophagus was not a common finding in these specimens. Twenty-two specimens invaded the thyroid cartilage at its posterior border, and all were found to have lateral pharyngeal wall involvement. Kirchner demonstrated in this study that the exclusion of tumors with pyriform apex involvement from conservation surgery was indeed appropriate because all of these tumors had laryngeal framework invasion.

A distinct feature of hypopharyngeal carcinoma that was noted early in the surgical treatment of this disease was its tendency to spread in a submucosal fashion.[13,41] This is an often-cited feature of hypopharyngeal cancer, especially in discussing its poor prognosis. Ho and colleagues[12] performed a detailed analysis of submucosal extension by serial sectioning of 57 specimens of hypopharyngeal cancer. Three classes of submucosal extension were identified: type 1 was a direct submucosal extension visible on gross inspection as elevated mucosa, type 2 was direct submucosal extension that was only visible on histologic examination, and type 3 was a true "skip" lesion with no connection to the primary. Only 1 of 57 specimens had type 3 extension; however, 33 (58%) patients did have submucosal extension of some type. In contradiction to the findings of Harrison,[13] significant inferior extension toward the cervical esophagus was observed. Patients treated with preoperative radiotherapy had significantly increased amounts of type 2 extension. Interestingly, in comparing overall 5-year survival, no differences were found between the group that had submucosal extension and the one that did not. Additionally, submucosal extension was not associated with increased locoregional recurrences. Thus although it is true that submucosal extension occurs in a significant number of patients with hypopharyngeal cancer, most of it is detectable clinically and a poorer prognosis is not seen in patients with submucosal extension of tumor.

Included in the data from serial sectioning by Ho and colleagues and Wei[12,42] was the finding that submucosal extension was greatest in the inferior direction, followed by lateral extension, and finally superior extension. On the basis of these data, they recommended that resection margins should be 3 cm inferiorly, 2 cm laterally, and 1.5 cm superiorly in patients who have not received previous radiation. For those with previous radiation, these margins were recommended to be 4 cm, 3 cm, and 2 cm, respectively. The deep margin was recommended to be greater than 1 mm in all patients.[43]

Etiology and Biology

The causal relationships among alcohol and tobacco intake, genetic predisposition, diet, and socioeconomic conditions in the development of squamous cell cancers of the head and neck apply as well to hypopharyngeal cancer.[44-46] In examining these factors, two specific components appear to be more closely associated with hypopharyngeal cancer. The first is alcohol intake, which appears to be more common in patients with hypopharyngeal cancer, at least when compared with laryngeal cancer.[10,47-49] What the specific effect of alcohol may be in hypopharyngeal cancer development is unclear. Alcohol may have direct carcinogenic effects, may be more of a promoter of tobacco's carcinogenic effects, or may have both functions. Two recent studies found that specific chewing tobacco products or exposure to wood smoke were associated with hypopharyngeal cancers in India.[50,51]

A condition specifically associated with postcricoid carcinoma is the Plummer-Vinson or Paterson-Brown-Kelly syndrome, which primarily affects women (85% of the cases).[52] This syndrome represents the combination of dysphagia, iron deficiency anemia, and hypopharyngeal and esophageal webs. It is hypothesized that chronic irritation results in the hypopharyngeal webs that then progress to carcinoma.

The syndrome is also geographically biased in that patients are predominantly located in the United States, Wales, and Sweden. The etiology is believed to be due to nutritional deficiency and since these issues have been addressed, the incidence of postcricoid carcinomas has declined in Sweden.[6]

The elucidation of the molecular genetic events underlying the development of squamous cell carcinoma of the head and neck has progressed rapidly over the past decade. A separate chapter in this text reviews the relevant molecular biology in detail.

Staging

The TNM system continues to be the standard by which the morphologic extent of the tumor is described. The American Joint Commission on Cancer updated the TNM staging in 2002, and the relevant hypopharyngeal and cervical esophageal system is listed in Tables 103-2 and 103-3.[53] The TNM system's major advantages are that it allows for comparing end results, communicating about patients, determining prognosis, and selecting treatments.[54] However, it is also acknowledged to have deficiencies due to inconsistencies; inaccuracies; observer variability; problems with various T, N, and M classification criteria; and exclusion of host factors. Piccirillo and colleagues from our institution have examined the role of host factors including patient symptom severity and comorbidities on outcomes of treatment. Piccirillo and colleagues[55,56] demonstrated that comorbidities are an independent prognostic factor in outcomes of patients with head and neck cancer. The most recent AJCC Cancer Staging Manual[53] recommends comorbidity assessment but does not yet incorporate these factors into staging.

Available Modalities for Management

The evolution of the management of hypopharyngeal and cervical esophageal carcinoma has paralleled that of management of cancer of other sites within the head and neck. From the early part of the century through the 1980s, the standard therapy focused on radical surgery followed by radiation or radiation alone. More conservative procedures for early lesions became possible with the introduction of conservation laryngeal procedures in the 1960s. There is no standard of care for these lesions because some institutions use combination chemotherapy and radiation protocols as primary treatment, whereas others continue to use surgery followed by radiation alone or with chemotherapy as the primary modality.

Therapeutic Modalities—Surgical Options Including Techniques

An understanding of the technical aspects of surgical management is amplified in the context of the historical experience. In addition, an appreciation of the pathologic behavior in the context of the anatomic boundaries of a hypopharyngeal or cervical esophageal carcinoma allows one to appreciate the extent and limitations of these procedures.

Cheever[57] first described the lateral pharyngotomy in combination with a mandibulotomy approach in 1878. Resection of a large tonsil tumor and a node plucking were performed; however, the patient recurred with local and regional metastases. With no anesthesia, attempts at control of the local recurrence were made with 18 applications of white-hot irons. Not surprisingly, the patient's tumor continued to grow. Other highlights in the development of hypopharyngeal cancer treatment include Sebileau's (1904) description of the lateral retrothyroid pharyngectomy; Trotter's (1913) development of the lateral pharyngectomy; the supracricoid hemilaryngopharyngectomy (SCHLP) described by Andre, Pinel, and Laccourreye (1962); and Ogura's (1965) development of the extended supraglottic laryngectomy. Many other surgeons contributed to the development of other techniques including Orton, Alonso, and Harrison.

The available surgical options can be divided among the organ-preservation procedures and more radical operations (Table 103-4). The conservation surgical procedures are limited to T1, T2, or highly selected T3 lesions, except for the endoscopic approach used by Steiner and colleagues.[58] The more radical operations typically require extensive reconstruction of the alimentary tract. The options and the algorithm for deciding on a specific reconstruction are discussed in a separate section.

Table 103-2

Tumor and Lymph Node Staging

Primary Tumor (T)	
Hypopharynx	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to one subsite of hypopharynx and ≤ 2 cm in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures > 2 cm but not > 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor > 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue (including prelaryngeal strap muscles and subcutaneous fat)
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
Cervical Esophagus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
Regional Lymph Nodes (N)	
Hypopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node > 3 cm but not > 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N3	Metastasis in a lymph node > 6 cm in greatest dimension
Cervical Esophagus	
NX	Regional lymph nodes cannot be assessed
N1	No regional lymph node metastasis
N2	Regional lymph node metastasis
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

PARTIAL PHARYNGECTOMY. This option is considered when tumors are staged as T1 or T2 and are limited to the posterior or the lateral wall of the pyriform sinus. Contraindications to this technique include extension of the tumor to more than one wall of the pyriform, extension to the pyriform apex, and involvement of the larynx in any fashion. Four surgical approaches can be taken to approach these lesions to perform a partial pharyngectomy.

The first technique is a standard *lateral pharyngotomy* and involves a collar incision, which can be extended to address the cervical lymphat-

Table 103-3

Stage Groupings

Hypopharynx

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Cervical Esophagus

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2,T3	N0	M0
IIB	T1,T2	N1	M0
III	T3	N1	M0
	T4	Any N	M0
IV	Any T	Any N	M1

ics. A neck dissection is first performed if indicated for the lesion. A tracheotomy is a standard part of the operation because significant pharyngeal edema may compromise the airway postoperatively. After this the carotid sheath and its contents are identified and gently dissected away from the posterior thyroid ala. This maneuver exposes the inferior constrictor muscle and the superior thyroid neurovascular pedicle. Transection of the inferior constrictor muscle identifies the pyriform sinus mucosa, which is then sharply divided, ideally at a resection margin, to enter the hypopharynx. The tumor in the posterior or lateral wall is then extirpated. After tumor removal, the defect is examined and a reconstruction plan is devised. If adequate mucosa is present, a two-layer primary closure can be performed. However, a skin graft or flap patch may be necessary (see reconstruction section later).

A tumor that more extensively involves the lateral hypopharyngeal wall needs to be addressed by wider margin. This can be accomplished with a *lateral transthyroid pharyngotomy* (Fig. 103-6) by a wider resection that involves the posterior portions of the thyroid cartilage and the hyoid bone.[59] In this variation, instead of approaching the tumor through the pyriform, an entry through the vallecula is chosen. Once the neck dissection is completed, a medial and inferiorly based perichondrial flap is elevated off the thyroid cartilage. The hyoid bone is exposed from lesser cornu extending laterally. The hyoid bone is then cut through the lesser cornu, and cartilage cuts are made in a vertical fashion at the junction of the anterior two thirds and posterior one third of the thyroid cartilage. The hypopharynx is then visualized by entering through the vallecula. A blunt retractor placed into the vallecula assists entry. The incision is then carried laterally and inferiorly through the cartilage cuts. As these cuts are made, visualization through the initial incision ensures a safe margin around the tumor. The lesion is reflected laterally and the other required circumferential cuts are completed. Frozen sections for control of the margins are obtained. Reapproximating the mucosa and suturing the perichondrial flap as a second layer closes the defect.

With both these approaches, complications include pharyngocutaneous fistula with wound breakdown and dysphagia. Fistula problems are addressed by attempting to decrease or divert salivary contamination, meticulous wound care, and the possibility of secondary flap closure. A cricopharyngeal myotomy performed intraoperatively is one prophylactic measure to address possible dysphagia, although one study has shown no benefit of this maneuver in head and neck cancer patients.[60]

The *anterior transhyoid pharyngotomy* (Fig. 103-7) is another approach for lesions that primarily involve the posterior pharyngeal wall. Thus T1 or T2 lesions are good candidates for this approach. A tracheotomy is first performed. Again, a collar incision is used to identify the hyoid bone. The hyoid may be resected or the approach may be above or below the hyoid. The vallecula is identified, and sharp dissection through this mucosa with subsequent tongue base retraction

Table 103-4

Surgical Options

Procedure	T Stage	Reconstruction
Partial pharyngectomy	T1, T2	Primary closure
Partial laryngopharyngectomy	T1, T2, T3	Regional or free flap
Supracricoid hemilaryngectomy	T1, T2, T3	Primary closure
Endoscopic CO_2 laser resection	T1, T2 (possible T3, T4)	Secondary intention
Total laryngectomy with partial/total pharyngectomy	T3, T4	Primary closure vs. regional or free flap
Total pharyngo-laryngo-esophagectomy	T4	Gastric pull-up

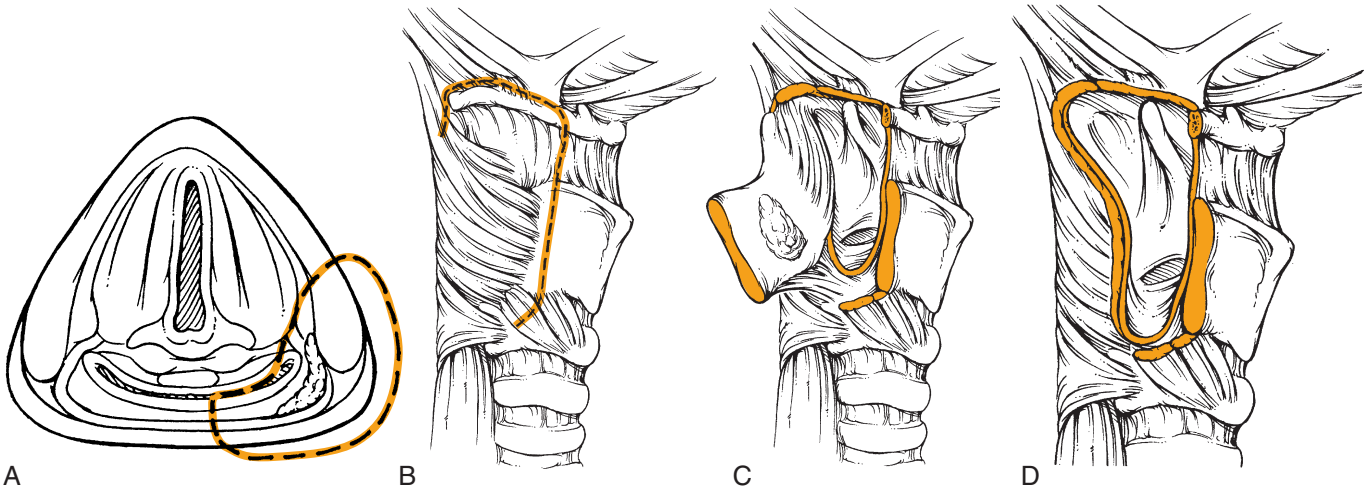

Figure 103-6. Partial pharyngectomy via the lateral pharyngotomy. **A,** Area removed, including the posterolateral hypopharyngeal wall and a portion of the thyroid ala. **B,** *Dotted lines* show cuts on the thyroid cartilage, hyoid, and vallecula. **C,** After entry into the hypopharynx, the specimen is reflected laterally and final cuts are made. **D,** Defect following excision of the posterolateral hypopharyngeal tumor.

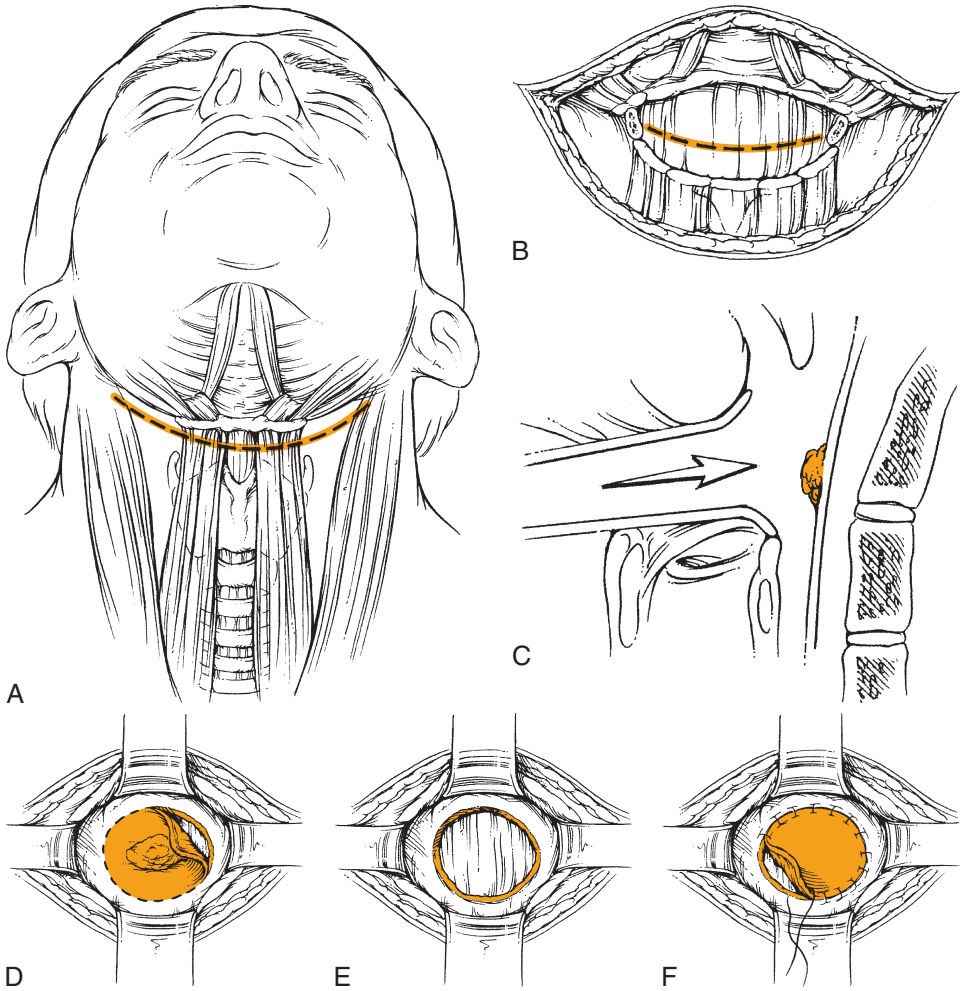

Figure 103-7. **A,** The anterior transhyoid approach is begun by transecting the musculature above (as shown) or below the hyoid bone. **B,** After removal of the hyoid, the vallecular incision is made to enter the pharynx. **C,** Inferior retraction of the pharynx and superior retraction of the base of the tongue exposes the posterior pharyngeal wall tumor. **D** and **E,** Tumor resection margin and defect. **F,** A skin graft is sutured to the posterior pharyngeal wall.

provides access to the posterior hypopharyngeal wall. The tumor is removed with the prevertebral fascia as the deep margin. After all margins are assessed by frozen section, a split-thickness skin graft can be used to cover the defect. The wound is closed by reapproximating the vallecular mucosa. The primary limitation to this procedure is that there is limited visualization of the full hypopharynx. Thus choosing the appropriate tumor for this approach is critical. Complications of this approach include pharyngocutaneous fistula and dysphagia.

The *median labiomandibular glossotomy* can be used to treat limited T1 and T2 lesions of the posterior hypopharyngeal wall. The procedure uses a mandible and tongue-splitting approach to gain access to the hypopharynx. The procedure is begun by creating a lip-splitting incision that is designed to prevent scar contracture over the chin. The incision is carried down to the mandible and inferiorly to the level of the hyoid. Holes for a reconstruction plate are drilled into the mandible and then a bone cut is made in the midline. The tongue is then split in the avascular midline plane and each segment is retracted laterally. Once the tumor is identified and resected in the posterior wall of the hypopharynx, a skin graft can be sutured onto the prevertebral fascia. The tongue is then reapproximated in several layers, and finally the mandible is reduced using the predrilled holes. Meticulous closure of the skin is the final step. Its major advantage is the wide exposure that can be achieved. This has to be balanced with the possible morbidity of the procedure, which includes malunion of the mandible, contracture in the chin skin incision, and dysphagia.

PARTIAL LARYNGOPHARYNGECTOMY. This operation combines the classic hemilaryngectomy operation with a partial pharyngectomy.[61] In certain cases the laryngeal remnant is still able to maintain speech, swallowing, and airway protection. The tumor must fit strict criteria including involvement of the medial pyriform sinus. The lesion may be a marginal aryepiglottic fold tumor. Extension into the base of tongue, lateral pyriform sinus, and vallecula can potentially be included in the resected specimen. Contraindications include (1) involvement of the pyriform apex, (2) extension to the postcricoid region, (3) ipsilateral true vocal cord paralysis, or (4) encroachment into the cricopharyngeus.

The procedure (Fig. 103-8) is begun after the completion of the tracheotomy and the neck dissection(s). For a lesion involving the medial wall of the pyriform sinus, minimal extension onto the epiglottis, and encroachment onto the arytenoid, the final resected specimen will contain the tumor on the medial wall, a portion of the epiglottis, the ipsilateral arytenoid, the ipsilateral half of the hyoid bone and the superior two thirds of the ipsilateral thyroid cartilage. After transection of the suprahyoid musculature, a superiorly based perichondrial flap is elevated off the thyroid cartilage. The thyroid cartilage is cut in the midline in an incision extending approximately two thirds of its height. This cut is then extended horizontally to the posterior border of the cartilage. The ipsilateral hyoid is freed and the vallecula is entered. Extension of this incision along with visualization of the epiglottis allows better exposure. At this point the epiglottis is grasped and retracted, providing visualization of the tumor. The epiglottis is then divided with a safe margin around the tumor and this cut is brought to, but does not include, the anterior commissure. One blade of the scissors is placed into the ventricle, and the other blade approximates the horizontal thyroid cartilage cut. This incision is made to the arytenoid, which is spared only if there is no involvement; however, it has to be sacrificed with tumor involvement. The vallecular incision is extended inferiorly with a good margin around the tumor. This is where a portion of the lateral pyriform/pharyngeal wall can be included in the resection if involved with tumor. The medial and lateral cuts meet at the arytenoid. If tumor involves more of the supraglottic area, a standard supraglottic laryngectomy can be performed to resect the entire epiglottis, pre-epiglottic space, and/or a portion of the base of tongue.

After clear margins are obtained on frozen section, closure of the wound is completed. With resection of the arytenoid, the ipsilateral true vocal cord must be sutured in the midline to the cricoid to prevent aspiration. A cricopharyngeal myotomy is performed, and for small lesions primary closure may be possible. However, myocutaneous flap closure or a microvascular free flap should be considered to avoid postoperative complications of wound breakdown. The complications include fistula formation and the possibility of aspiration. Meticulous postoperative care followed by eventual decannulation and attempts at oral feeding follow.

SUPRACRICOID HEMILARYNGOPHARYNGECTOMY. The major proponent of this technique is the French group of Laccourreye.[62-65] This procedure extends the partial laryngopharyngectomy procedure to include the entire ipsilateral supracricoid hemilarynx along with the pyriform sinus. Thus contraindications to this approach include involvement of the pyriform apex, ipsilateral cord fixation, postcricoid involvement, or posterior pharyngeal wall invasion.

The technique begins with appropriate neck dissections followed by a hemithyroidectomy and node dissection of the recurrent laryngeal nerve groups. The posterior border of the strap muscles is retracted to identify the posterior thyroid cartilage border. A musculoperichondrial flap is then elevated off the cartilage just past the midline. The ipsilateral half of the hyoid bone can be resected by cutting it at the lesser cornu. At this point the cricothyroid joint is identified and disarticulated. The airway access is then converted to a tracheotomy. The entrance into the hypopharynx is begun by incising the cricothyroid membrane vertically in the midline and connecting this to the midline vertical thyrotomy. The incision is extended superiorly through the epiglottis and the pre-epiglottic fat, where the contralateral fat is incorporated into the resection, and finally this incision ends in the vallecula. The specimen is then rotated open visualizing the tumor within the hypopharynx. A horizontal incision, on the superior surface of the cricoid from the midline extending to the cricoarytenoid joint, is then completed. The incision from the vallecula is then brought down inferiorly and connected to the interarytenoid incision, releasing the entire specimen. After clear margins are obtained, the contralateral arytenoid is covered with surrounding mucosa. A buttress using any remaining ipsilateral true vocal cord needs to be created for good apposition of the remaining functional vocal cord. The musculoperichondrial flap is then closed to the lateral pharyngeal wall.

Postoperatively, because these patients are at significant risk for aspiration, aggressive pulmonary toilet is critical and highlights the need for careful preoperative selection of patients with adequate pulmonary function. Fistula formation is a theoretic possibility but is not seen in Laccourreye's series.

ENDOSCOPIC CO_2 LASER RESECTION. The discussion of the endoscopic approach to management of hypopharyngeal tumors represents a transition from conservation laryngeal procedures to more radical extirpations. For more than 3 decades, Steiner and colleagues have been performing transoral laser microsurgery (TLM), which is an endoscopic resection of carcinomas of the upper aerodigestive tract. The cited advantages to this procedure are that (1) no tracheotomy is required, (2) the preservation of the suprahyoid musculature allows more normal swallowing, (3) not reconstructing is often the rule, and (4) hospital stay is decreased with patients returning to an oral diet as early as postoperative day 1. This approach has yielded remarkable results for all areas in which it has been applied. Certainly the full validation of these results awaits a prospective trial, but anecdotal experience at our own institution has been excellent (B.H. Haughey, personal communication, September, 2008).

The technique for all tumors involves use of a bivalved laryngopharyngoscope, an operating microscope, and a CO_2 laser as the dissecting instrument. As opposed to conventional open procedures, the tumor is often cut through during endoscopic approaches to provide a direct view of tumor depth and/or to assess cartilage invasion. Under microscopic vision, tumor margins are taken up to 10 mm and in this fashion the entire tumor is removed. The specimen is usually resected in multiple pieces, which are all oriented appropriately by the surgeon. A typical sequence of resection for a pyriform sinus primary is an initial cut through medial tumor, transverse to the plane of the aryepiglottic fold to assess extent of laryngeal extension, followed by posterior ± arytenoid, anterior, inferior posterolateral, and then superior posterolateral excisions. Margins are checked by frozen sections and a step serial technique.[66] Cartilage may be exposed or resected during the surgery and to avoid perichondritis antibiotics are given prophylactically. The wound bed is allowed to heal by secondary intention. In Steiner's management, delayed neck dissections are performed as indi-

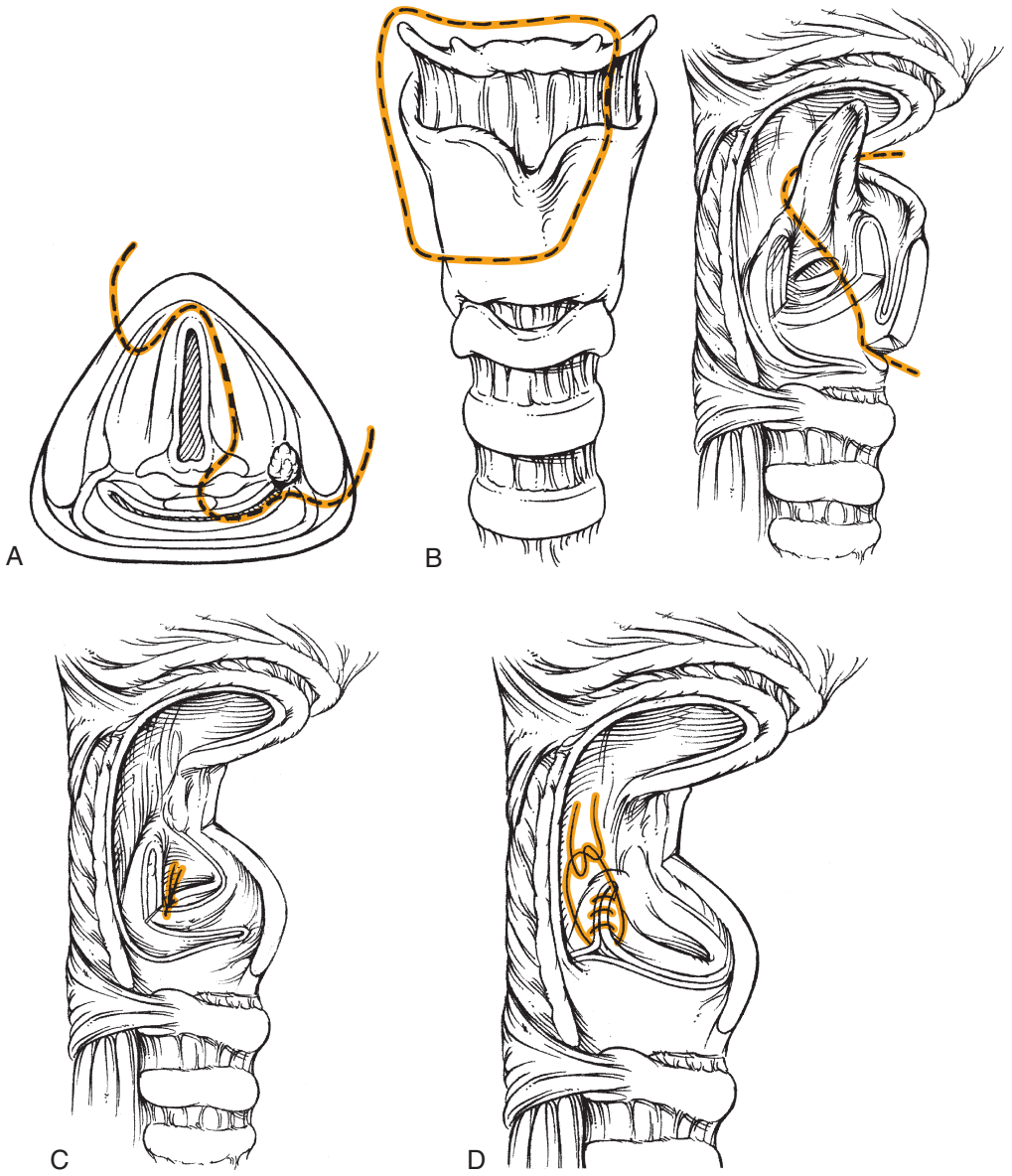

Figure 103-8. **A,** The resection margin after a partial laryngopharyngectomy for a medial pyriform tumor is shown in the superior view. **B,** This view demonstrates the bone and cartilage cuts for a partial laryngopharyngectomy. **C,** The completed resection of the medial pyriform tumor is shown. The epiglottis may be divided (as described in the text) or removed completely as shown here. **D,** With resection of the arytenoid, the ipsilateral true vocal cord must be sutured in the midline to the cricoid to prevent aspiration. The laryngeal mucosa is reapproximated as much as possible as shown.

cated by the tumor size, location, and lymph node status. Postoperatively the patients are started on an oral diet, as early as day 1, unless extensive resections are undertaken.

TOTAL LARYNGECTOMY WITH PARTIAL/TOTAL PHARYNGECTOMY. For T3 (those that are judged inappropriate for conservation therapy) and T4 lesions of the hypopharynx, combining a standard laryngectomy with excision of the involved pyriform walls completes this operation. In addition, total laryngopharyngectomy (TLP) is increasingly used as a salvage procedure for failures of chemoradiation protocols. Figure 103-9 shows a TLP of the patient whose PET/CT is shown in Figure 103-4 after failed chemoradiation. Reconstruction of these defects with primary closure can be accomplished if an adequate remnant of pharyngeal mucosa remains. Myocutaneous or free flap coverage may be required. Postoperative complications can include pharyngocutaneous fistulas with rates as high as 40% in patients previously treated with chemotherapy and/or radiation.[67]

Tumors with significant inferior extension may require a circumferential resection of the hypopharynx. This resection in addition to the laryngectomy encompasses this operation. The remaining defect will require re-establishment of the continuity between the oropharynx and the cervical esophagus. Again, some of the complications include fistula and dysphagia.

TOTAL PHARYNGO-LARYNGO-ESOPHAGECTOMY. This procedure is indicated for patients with involvement of the cervical esophagus due to either primary involvement or regional extension from the hypopharyngeal subsites. As for the TLP, this procedure is also used in cases of chemoradiation failure. Harrison recommended this operation for patients with postcricoid carcinoma because of the possibility of skip lesions.[68]

The procedure is begun after completion of bilateral neck dissections including paratracheal lymph node dissections and a total thyroidectomy with parathyroid autotransplantation. A total laryngopharyngectomy is performed as described earlier. A transhiatal pull-through esophagectomy is then performed to complete the inferior resection. Reconstruction is performed with the gastric pull-up technique as described later. The morbidity (20% to 60%) and mortality

(5% to 20%) rates are significant with this combined procedure.[69] Larynx-sparing esophagectomy has been described in certain case reports for lesions limited to the cervical esophagus.[70,71]

Therapeutic Modalities—Options for Reconstruction

Although briefly mentioned earlier, the spectrum of reconstructive options available for hypopharyngeal reconstruction is discussed here. The only situation where closure is not routinely performed is with the endoscopic excision of hypopharyngeal carcinoma, where healing by secondary intention is the rule. In addition to the brief discussion here, a separate chapter in this text discusses reconstruction of the pharynx and esophagus.

The principles of reconstruction that are used for hypopharyngeal reconstruction are the same as elsewhere in the head and neck region. These include the restoration of form and function with minimal donor site morbidity. In addition, to be able to achieve these goals in a single setting without need for secondary procedures is ideal. For the conservation procedures, a primary closure can be performed so long as there is no compromise of the pharyngeal lumen that could result in significant dysphagia. Primary closure can be performed safely when the pharyngeal lumen measures between 28 and 32 French. Skin grafts are the next available alternatives and are primarily used in the posterior pharyngeal wall resections. In addition, mucosal and dermal grafts, local rotation flaps, and tongue flaps have been described for closure.[72] Regional flaps that have been described include the platysma, deltopectoral, and latissimus dorsi flaps.[73] These flaps are typically used in the event of failure of the more popular options discussed later.

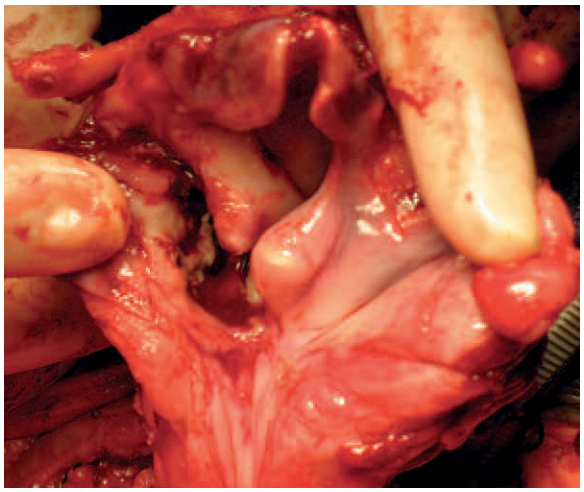

Figure 103-9. Total laryngopharyngectomy of a pyriform sinus carcinoma after failed chemotherapy and radiation. The ulcer crater in the left pyriform sinus is visible.

Ideally the head and neck/reconstructive surgeon has the full armamentarium of available surgical techniques for more extensive surgical defects. This not only provides the surgeon with multiple options for any given defect, but also ultimately provides the patient with the best possible functional outcome. In practice, the surgeon's level of comfort with a particular technique dictates the reconstructive option that is chosen. This bias is reflected in the literature where multiple case series from various groups describe their particular technique and its functional outcomes. For these reasons and also because of the limitation in number of extensive hypopharyngeal defects, no prospective, randomized studies exist comparing various reconstructive techniques.

PECTORALIS MYOCUTANEOUS FLAP. The pectoralis major myocutaneous flap has been the "work-horse" pedicled flap for head and neck reconstruction since its introduction by Ariyan in 1979.[74] The advantages of its use to close partial defects of the hypopharynx include its reliability and ease of harvest (Fig. 103-10). Disadvantages include the bulky nature of the flap, which can lead to postoperative stenosis, fistula problems, dysphagia, and difficulties of harvest in women with pendulous breasts. Partial defects are best closed with this flap when there is a strip of pharyngeal mucosa available for direct suturing. Although possible, tubing of this flap is not facile and should be avoided. Fabian described use of this flap for repair of partial defects[73,75] and others have extended his earlier reports.[76,77]

CIRCUMFERENTIAL DEFECTS. The reconstruction of circumferential defects of the hypopharynx and cervical esophagus is a controversial topic because a single flap has not been identified that necessarily gives the best functional outcome with the least morbidity. The choice of reconstruction is also limited by the surgeon's experience and availability of options at a particular institution. The literature on reconstruction in the 1980s and 1990s primarily focused on the jejunal free flap or the gastric pull-up as viable options. More recently, fasciocutaneous flaps that are tubed around a salivary stent have gained favor.[78-80]

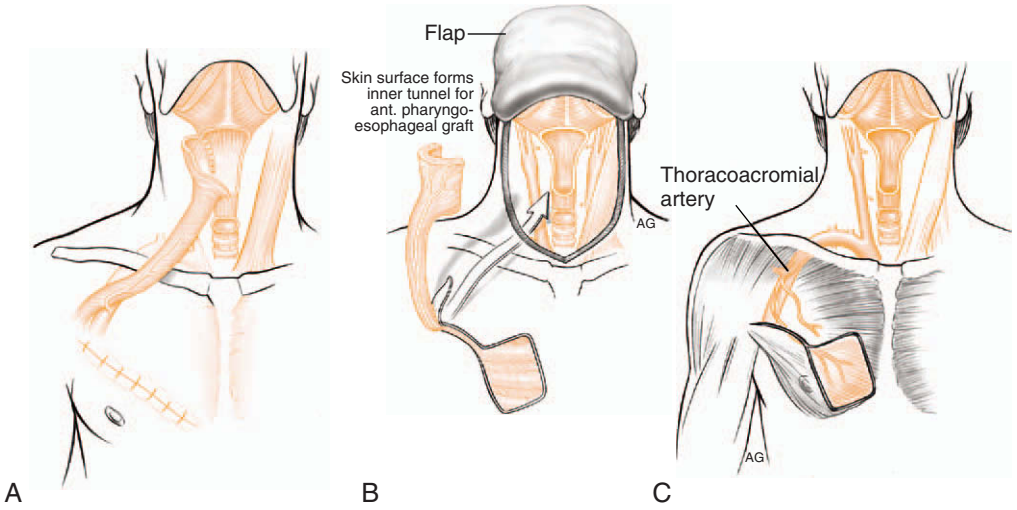

Figure 103-10. **A,** Rolling of the pectoralis major mucocutaneous flap to reconstruct the hypopharynx. The lower anastomosis should be carefully performed to reduce the likelihood of stricture. **B,** In this pectoralis major mucocutaneous flap, an 8-cm × 10-cm skin paddle is outlined and raised on the long axis of the pectoral branch of the thoracoacromial artery. **C,** Outline of the skin paddle over the pectoralis major for hypopharyngeal reconstruction. When soft tissue is excessive, a split-thickness skin graft can be applied directly to the muscle to reduce the bulk of the flap.

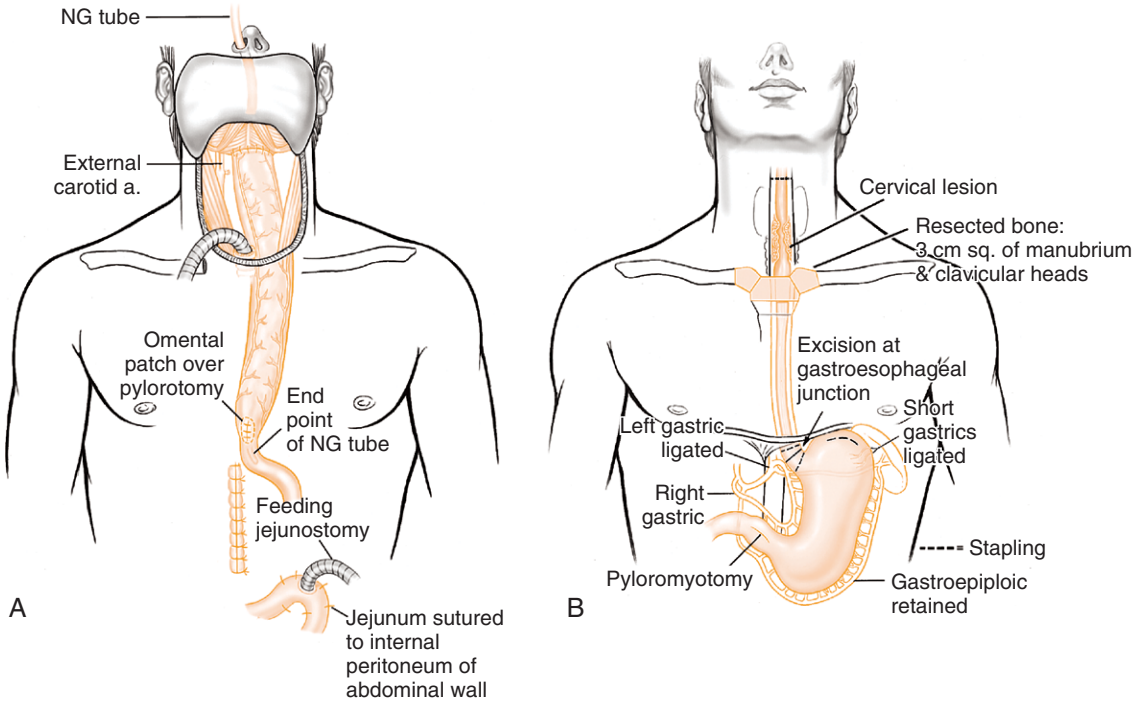

Figure 103-11. **A,** Gastric transposition. The stomach is passed through the posterior mediastinum. Pyloromyotomy enhances food passage. A jejunostomy will be used for decompression and for temporary feeding. Jejunostomy may be retained when postoperative radiation is planned. **B,** The advantage of the gastric pull-up procedure is no anastomosis within the abdomen or mediastinum. The single anastomosis occurs near the thoracic inlet. Ligation of the short gastric vessels and left gastric artery permits rotation of the greater curvature of the stomach upward through the funnel created at the time of resection of the esophagus. The stomach is placed in a plastic bag, which allows gentle passage through the posterior mediastinum to the neck.

Reconstruction options for circumferential defects that result after TPL include a regional flap, jejunal interposition, a tubed fasciocutaneous flap, a gastro-omental flap, and a gastric pull-up. A gastric pull-up or colon interposition can be used for total pharyngo-laryngo-esophagectomy defects. The regional flap as described earlier is the pectoralis myocutaneous flap.

GASTRIC PULL-UP. This option can be used when the inferior margin of tumor ablation extends past the cervical-thoracic junction of the esophagus or when a safe margin requires total esophagectomy. One school of thought advocates a complete esophagectomy along with the hypopharyngeal resection to address possible second primary malignancies for all hypopharyngeal cancer. Harrison, who originally advocated this concept, stated: "Total removal of the esophagus not only ensures complete resection of the lower limits of the tumor but also areas of potential malignancy and unexpected, undiagnosed second tumors."[68] He based these comments on whole-organ serial sections, which showed second primaries in the esophagus consistent with the field cancerization idea of Slaughter and coworkers.[81] Most recently, Martins made a similar case for total laryngo-pharyngo-esophagectomy in patients with advanced-stage hypopharyngeal cancer.[82]

Turner originally described this operation for esophagectomy using stomach as the reconstruction (Fig. 103-11).[83] However, it was Ong and Lee[84] who popularized this reconstructive method for laryngo-pharyngo-esophagectomy defects. The operation is carried across three compartments: neck, thorax, and abdomen. After completion of the laryngo-pharyngo-esophagectomy, the stomach is mobilized on the basis of the right gastric and right gastroepiploic artery. A pyloromyotomy is performed, and the stomach is then passed to the neck through the posterior mediastinum. A pharyngogastric anastomosis is then completed. As described earlier, the combination of total laryngo-pharyngo-esophagectomy with gastric pull-up is associated with high morbidity and mortality.[69]

JEJUNAL FREE FLAP. Seidenberg and colleagues first described the jejunal free flap in 1959 (Fig. 103-12).[85] The advantages to this procedure are that a large segment can be harvested for anastomosis as high as the nasopharynx. Concomitantly with the harvest, the primary tumor resection can be performed in the neck. Additionally, the intrinsic mucus production of the jejunum is hypothesized to assist in swallowing. The disadvantages are poor donor vessels, a short ischemia time, dysphagia from the intrinsic peristalsis of the jejunum,[86] poor vocal rehabilitation using a tracheoesophageal puncture, and morbidity from the abdominal surgery. Despite these potential problems, the jejunal free flap is a popular method of reconstruction for these defects.

While tumor resection is being performed in the neck, a second team performs the harvest. A segment of jejunum is harvested with associated vessels. Typically the second vascular arcade of vessels after the ligament of Treitz has a caliber that matches those of donor vessels in the neck. An exteriorized segment can be used to monitor flap viability. The jejunum usually matches the lumen on the side of the cervical esophagus. The flap is oriented such that isoperistaltic contraction will aid normal swallowing. At the proximal anatomosis, cutting the antimesenteric border to provide a better match with the oropharynx or nasopharynx expands the jejunum. A jejunostomy distal to the bowel anastomosis is then placed. The major disadvantage to this procedure is the requirement for a laparotomy, which can lead to complications in the debilitated and malnutritioned cancer patient. Recent efforts with minimally invasive laparoscopic harvest may revitalize the interest of surgeons who may have turned away from this option.[87,88] Two studies described successful harvest of the required jejunal segment. Gherardini and colleagues[87] performed the bowel anastomosis via a mini-laparotomy, whereas all patients in the study by Wadsworth and colleagues[88] underwent laparoscopic bowel anastomosis. The laparoscopic approach avoids the complications of postoperative ileus and other abdominal complications.

Although early case series using this technique reported poor results,[89,90] more recent and larger series have shown flap success rates between 95% and 97%.[91-93] Complications included flap failure, fistula, stricture, and abdominal complications. Detailed description of these complications is described by Reece and colleagues,[92] who found that flap failure caused by arterial thrombosis occurred in 7 of 93 patients.

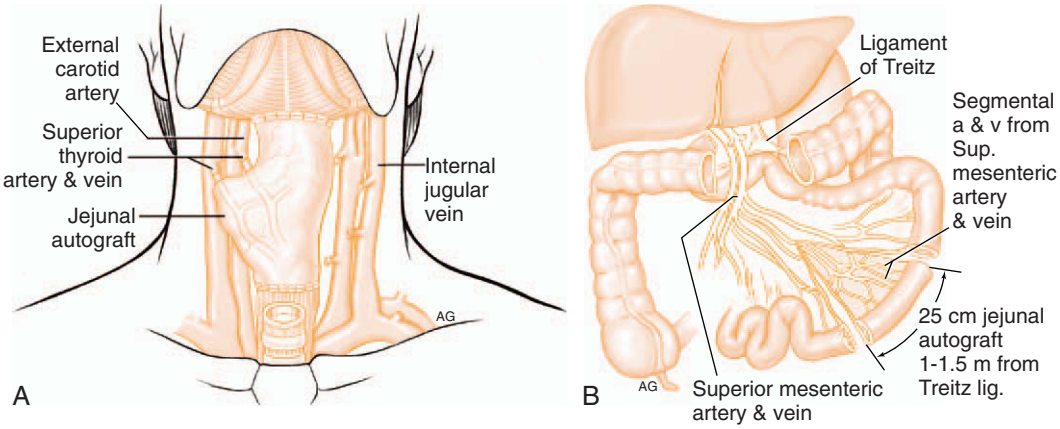

Figure 103-12. **A,** Free jejunal segment reconstruction. The mesenteric artery is anastomosed to the superior thyroid or external carotid artery. Vein anastomosis to the facial thyroid or end-to-side to the jugular vein is another option. Preservation of a jugular vein is required. Vein is anastomosed to the superior thyroid (facial). **B,** A segment of jejunum is isolated with complete arcade and an adequate length of the mesenteric artery and vein.

Postoperative fistulas, which delay oral alimentation and initiation of adjuvant therapy, have been reported to be high for jejunal flaps. Fistula rates were reported as 10% by Disa and colleagues[94] and 19% by Reece and colleagues.[92] Strictures as a cause of dysphagia were reported to occur in 4% to 15% of patients. Donor site morbidity consisting of dehiscence, small bowel obstruction, and infection occurred in only 1 of 90 patients in the Memorial Sloan-Kettering series and in 9 of 93 patients in the M.D. Anderson group of patients. Postoperative oral alimentation began between 11 and 14 days after surgery in two large case series. An unrestricted diet was tolerated between 53% and 92% of patients in three large case series.[91-93]

Although animal studies suggested that the jejunal autograft was poorly tolerant of radiation,[89] patients with jejunal grafts have tolerated postoperative radiation with minimal complications.[94-97] Wei and colleagues[97] performed biopsies at defined intervals over a 2-year period on either cohorts of patients receiving radiation or controls who did not receive radiation after jejunal free tissue transfer. Although microscopic changes were identified, no clinically significant symptoms or signs were observed consistent with previous observations.

Vocal rehabilitation using a TEP in these patients has been described as worse compared with patients who have undergone total laryngectomy alone.[98] The patients are described as having a "wet" voice. Most patients in the study by Reece and colleagues used an electrolarynx for communication with only 12 of 93 patients using a TEP.

FASCIOCUTANEOUS FREE FLAPS. Although the literature regarding hypopharyngeal reconstruction primarily discusses the jejunal free flap or gastric pull-up techniques, fasciocutaneous free flap techniques are being used more frequently. The popularity of these flaps has increased within the past decade.[78] This method was first described by Harii and associates in 1985 as an alternative reconstructive option; however, the early experience with fasciocutaneous flaps showed fistula rates as high as 67%.[99-101] One possible reason for strictures is that granulation tissue that forms at the fistula site ultimately may lead to stenosis at the anastomosis. However, more recent studies with modified techniques have shown more positive results.

Varvares and colleagues[80] and Scharpf and Esclamado[79] reported on their series of 20 and 25 patients, respectively, who underwent radial forearm free flap reconstruction of pharyngoesophageal defects. Both authors used surgical modifications to attempt improvements on past reported data on fistulae and stenosis. In seven patients of the Varvares series, the flap was completely tubed around a Montgomery salivary bypass tube and one patient developed a fistula. In Esclamado's report a "lock and key" design at the distal anastomotic site, a slightly larger flap than the actual defect (to allow for contraction) and minimal stretching prior to inset yielded a 28% (7/25) total fistula rate and a 36% (9/25) stenosis rate. Of the fistulas, five occurred greater than 4 weeks after surgery and all healed spontaneously. The stenosis was treated satisfactorily in 5/9 patients. Recently, Rosenthal and colleagues[102] reviewed their experience with 104 patients who underwent radial forearm free flap reconstruction for hypopharyngeal reconstruction. Similar to other studies, a fistula rate of 28.8% was noted in this series, which was associated with longer hospital stays and other complications. The anterolateral thigh is another effective donor site for circumferential defects and results in acceptable postoperative speech and swallowing.[103,104]

Therapeutic Modalities—Radiation Therapy

Although these modalities are discussed briefly here, a separate chapter in this text discusses in further detail chemotherapy, radiation therapy, and concurrent chemoradiation. The use of radiation as a single-modality therapy for hypopharyngeal carcinoma is limited to early lesions such as T1 cancers and selected T2 lesions. Favorable lesions are considered to be those that are exophytic in appearance and those lesions limited to the medial wall of the pyriform. The neck is included in the radiation field, although surgical salvage for bulky neck disease may be required.[105] Additional contexts in which this modality may be used are for elderly, debilitated patients; patients with advanced lesions who refuse surgical treatment; or palliative treatment. Complications associated with radiation include mucositis, stricture, airway compromise caused by laryngeal edema, chondronecrosis, and dysphagia.

In addition to the standard delivery of the radiation dose, altered fractionation schemes have been shown to achieve improved locoregional control in patients with head and neck cancer.[106] This was demonstrated in the large Radiation Therapy Oncology Group (RTOG) trial, in which different schemes were used in a randomized trial.[107] Two general types of altered fractionation schemes exist. The first is hyperfractionation, which results in a higher total dose by delivering smaller fractions more frequently (typically twice a day) without causing more late complications. The second is accelerated fractionation, which shortens the overall treatment time and attempts to achieve the same overall dose as standard fractionation. In the study by Fu and colleagues,[107] both hyperfractionation and accelerated fractionation with a concomitant boost showed significantly improved locoregional control but showed no difference in overall survival compared with standard treatment. Depending on the arm, between 11% and 15% of the patients in this trial had hypopharyngeal primary tumors. Acute reactions were increased in all accelerated fractionation schemes. Thus incorporation of these techniques in the use of radiation for cure or as postoperative treatment is a further advance for treating head and neck cancer patients.

Therapeutic Modalities—Chemotherapy

Chemotherapy is not used to treat hypopharyngeal and cervical esophageal carcinoma as single-modality treatment except in palliative treat-

ment cases. For all squamous cell carcinomas of the head and neck, the best responses are to platinum-based compounds such as cisplatin or carboplatin. In addition, 5-fluorouracil (5-FU), methotrexate, leukovorin, mitomycin C, and the taxanes have been used.[108] Some of the major complications of the commonly used 5-FU and cisplatin include hearing loss, mucositis, myelosuppression, and peripheral neuropathy.

LeFebvre and colleagues[109] published the first prospective, randomized study evaluating laryngeal preservation for hypopharynx carcinoma. Their protocol involved infusional chemotherapy consisting of cisplatin and 5-FU followed by endoscopy to assess tumor response. After two or three cycles, complete responders went on to receive definitive radiation and the remaining patients underwent conventional surgery.

Therapeutic Modalities—Concomitant Chemoradiotherapy

This combination modality attempts to combine the toxic effects of both agents on cancer cells to achieve therapeutic benefit. Concurrent chemotherapy also potentially radiosensitizes tumor cells in addition to direct toxic effects. These approaches use various combinations of cisplatin, 5-FU, taxanes/taxol, or hydroxyurea in conjunction with radiation. Obviously, one untoward effect of concurrent therapy is a significant increase in toxicity to patients. These toxicities are the same as those seen in patients being treated with the individual modality alone but are much more severe. Again, these include neutropenia, thrombocytopenia, mucositis, nausea, dysphagia with the need for a feeding tube, renal failure, cutaneous reactions, chondronecrosis, airway compromise, and death. Lee and colleagues[110] found that hypopharyngeal or upper esophageal strictures occurred in 21% of patients (41/222) undergoing concurrent chemoradiation and that a hypopharyngeal primary was a significant risk factor for developing this complication. A separate chapter in this text provides further details on chemoradiotherapy for hypopharyngeal and cervical esophageal malignancies.

Management of the Neck

The control of regional metastasis is a critical component of the management of hypopharyngeal and cervical esophageal tumors. Although this statement can be generalized to all other head and neck tumor sites, it is particularly important in this region due to the rich lymphatic drainage and the high percentage of tumors that have regionally metastatic disease (see Fig. 103-2). As for other sites, the discussion of neck management can be divided between elective neck dissection (for N0 stage necks) and therapeutic neck dissection (for N+ necks). For necks with positive nodes, the current management is to treat both necks, either with radiation followed by salvage surgery if necessary or surgery followed by radiation. For the ipsilateral neck that is staged N0, there is compelling evidence to treat both necks for all but the very early lesions where a unilateral neck dissection alone may be adequate. The types of neck dissections are discussed in a separate chapter in this text.

Many studies demonstrate the prognostic significance of lymph node metastasis in hypopharyngeal carcinoma. We focus on two early studies that demonstrate this finding. Shah and colleagues[111] observed that positive neck node(s) were a poor prognostic indicator in patients with hypopharyngeal carcinoma. In their series of 104 patients who were N0 at presentation, 61 underwent radical neck dissection and 36 did not. Nodes were positive in 25 (41%) patients who underwent neck dissection. In comparing survival with those patients whose nodes were negative after neck dissection, the 5-year survival was significantly better in the pathologically N0 group (50% vs. 32%). It is unclear whether the tumor stage was controlled for these groups (i.e., it is possible that the node-negative group involved early stages, whereas the node-positive group involved advanced stages). However, it is apparent from this overall study that positive nodes in hypopharyngeal cancer do not indicate a good prognosis. LeFebvre and colleagues[112] confirmed these data by examining lymph node status in a large series of patients treated at the Centre Oscar Lambret from 1974 to 1983. Almost 70% of these patients presented with palpable cervical metastasis. Again, a significant correlation between prognosis and lymph node status (N0 vs. N+) was established.

Given this prognostic significance, what are the draining lymph node basins for hypopharyngeal carcinoma? To understand the drainage patterns, Shah[113] reviewed the records of 1081 patients, 126 of whom had hypopharyngeal primaries, who underwent radical neck dissections. All the occult positive nodes in this study were in levels II and III. Interestingly, in the therapeutic neck dissection group, all five levels were found to have lymph nodes involved with tumor. On the basis of these studies, Shah recommended levels II, III, and IV neck dissection for N0 patients and comprehensive levels I to V neck dissection for node-positive patients. Shah and colleagues[114] confirmed these findings on a larger group of hypopharyngeal cancer patients and again came to the conclusion that N0 necks should be treated electively removing levels II to IV and N+ necks should undergo comprehensive neck dissection.

These studies provide support for the prognostic value of neck dissections and detail the nodal basins that need to be addressed. We next address the rates of lymphatic metastasis in patients with N0 necks to describe a rationale for ipsilateral neck treatment. Multiple studies demonstrate that patients of stage N0 will have occult lymph node metastasis. In some of these studies a comparison of N0 necks in T1/T2 tumors to N0 necks in T3/T4 tumors was not performed. Clearly, one problem in attempting this comparison is the relatively few T1/T2 tumors that are encountered compared with T3/T4 tumors. Byers and colleagues[115] reported on the occurrence of occult metastasis in elective neck dissections from patients with cancers at various sites in the head and neck. There were only three N0 patients with T1/T2 pyriform sinus tumors and two of these had occult metastasis. The T3/T4 group had 16 of 29 (55.2%) patients with occult metastasis. Buckley and MacLennan[116] prospectively examined 16 neck dissection specimens that were N0 from primary hypopharyngeal tumors with a careful sampling technique of all nodal levels. This subset of tumors was part of a larger series of cancers examined similarly. They found 9 of 16 (56%) of the hypopharyngeal neck dissection specimens to harbor occult metastatic deposits, although the T stages were not specifically given for the positive necks. Some of these occult tumor deposits were in nodes as small as 3 mm. Both the Byers and Buckley studies illustrate the high occult metastatic rate of hypopharyngeal carcinoma. These studies in combination with the studies of Shah and colleagues support the idea of selective level II/III/IV dissections in patients with N0 neck stage.

The retropharyngeal and paratracheal level VI nodes also form part of the draining echelon of nodes for these tumors. The studies discussed earlier do not discuss these nodal basins in detail. The removal of these nodes in conjunction with the jugular chain nodes is supported by the following studies. The study of Buckley and MacLennan[116] mentions that there were positive nodes in N0 necks in level VI, but no detail is given as to what primaries are or what tumor stage yielded these nodes. Harrison[117] performed serial sections of laryngopharyngectomy specimens and showed that lymphatic channels pierce through the cricothyroid membrane and drain into the paratracheal lymph nodes. Thus he argued that a total thyroidectomy with paratracheal node dissection was critical in the management of these tumors. Weber and colleagues[118] analyzed 141 patients from the M.D. Anderson Cancer Center who underwent paratracheal lymph node dissections for laryngeal, hypopharyngeal, or cervical esophageal cancer. Of the patients with a cervical esophageal primary, 10 of 14 (71.4%) had metastases in these nodes and 3 of 36 (8.3%) of hypopharynx primaries had positive nodes. Survival was significantly reduced in patients with positive paratracheal nodes. On the basis of these findings, the authors recommend paratracheal node dissection in all patients with primaries in these locations.

The retropharyngeal lymph nodes are not commonly addressed in hypopharyngeal and cervical esophageal squamous cell cancers and few studies have discussed management of these nodes. McLaughlin and colleagues[119] analyzed pretreatment CTs or MRIs for retropharyngeal adenopathy in patients with head and neck cancers. Pharyngeal wall tumors had 19% incidence of adenopathy in this area. As a group, rates of regional relapse were highest in those patients with retropharyngeal adenopathy. Hasegawa and Matsuura[120] found that 8 of 13 (62%) hypopharynx cancer patients had retropharyngeal lymphatic metastasis.

Amatsu and colleagues[121] performed retropharyngeal node dissections in 82 patients with hypopharyngeal and cervical esophageal carcinoma. Twenty percent (16/82) of patients had positive lymph nodes identified in the retropharynx. Thus these authors recommend bilateral retropharyngeal node dissection in all patients with hypopharyngeal and cervical esophageal cancer. Despite this data, the standard approach does not include dissection of these nodes. A recent case report highlights the involvement of retropharyngeal lymph nodes in hypopharyngeal cancer and the use of fused PET/CT in the pretreatment evaluation.[122]

The treatment of the N0 contralateral neck in hypopharyngeal carcinoma has been addressed by few studies. Marks and colleagues[122a] studied this question in a diverse group of head and neck cancer patients. Their conclusions were that (1) the risk of developing contralateral metastasis was unrelated to the size of the tumor, (2) the contralateral metastasis existed or developed in 13% of pyriform sinus tumors, and (3) the risk of contralateral metastasis was higher in patients with ipsilateral palpable disease. However, Johnson and colleagues[123] compared regional nodal metastases in medial versus lateral pyriform wall tumors and found significantly higher rates of contralateral metastases in the medially based tumors. These authors recommend bilateral neck dissections for medial pyriform wall tumors and unilateral neck dissections for lateral pyriform wall tumors.[123] Buckley and MacLennan[116] further examined this question in their study. For N+ necks, 3 of 3 patients had positive nodes in contralateral necks. Interestingly, in the N0 cases, 7 of 15 (47%) contralateral necks were positive for occult carcinoma in the lymph nodes. The disease was always in levels II to IV or VI, and never in level I or V. Except for these studies, there are limited other data on the treatment of the contralateral neck in hypopharyngeal carcinoma. The choice to treat the contralateral neck in the majority of cases will be straightforward because so many patients present with advanced disease. Postoperative radiation is routinely administered to treat the necks if there is extracapsular spread or if more than one lymph node is involved.

Therapeutic Outcomes

There are currently no prospective, randomized reports comparing the modalities available for the management of cervical esophageal or hypopharyngeal squamous cell carcinoma. Thus no clear evidence exists for the superiority of one strategy versus the next. It appears in reviewing the literature that individual preference of the physician in charge of the patient's care directs the therapeutic modality that is chosen. In summary, options for tumors that are staged T1 or select T2 tumors include surgery followed by radiation or radiation followed by salvage neck surgery for residual nodal disease. For any other lesions radical surgery followed by postoperative radiation is the standard practice. Laryngeal preservation, using induction chemotherapy followed by radiation, is supported by the study of Lefebvre and coworkers.[109] This protocol requires an understanding by the patient that surgical salvage is part of the protocol. Also, it is incumbent on the treating physician to closely follow the patient's tumor because prompt surgical salvage will ensure survival similar to conventional treatment.

A review of the literature reveals multiple series with various algorithms for management of this disease. These studies are confounded by several factors, which make comparing separate series difficult, including that they (1) are retrospective, (2) are nonrandomized, (3) represent a heterogeneous population of patients, (4) use techniques that evolved over the course of a study, (5) in some instances used preoperative radiation, (6) used different staging systems, (7) failed to include comorbidities, and (8) used different statistical techniques. However, despite these caveats some conclusions can be drawn from them and these are presented in the following sections. In this section we first discuss the results of large reviews of databases that reveal overall survival when analyzed retrospectively, without regard to actual surgical techniques or heterogeneity in radiation treatment. Then, we review the studies that use different modalities with a view to presenting a comprehensive picture of the current management of hypopharyngeal and cervical esophageal carcinoma.

Pingree and colleagues[124] completed a review of 1362 cases of hypopharyngeal cancer contained in the Rocky Mountain database that covered the periods 1973 to 1983. Of these, 239 (17.5%) were stage I and II and 966 (71%) were stage III and IV. Of the advanced stages 231 (23.9%) had distant metastatic disease at presentation. The hypopharyngeal tumors were predominantly located in the pyriform sinus. On the basis of treatment data, 695 of these patients who were followed for 5 years were available for analysis. The therapeutic modalities used were radiation alone, surgery alone, or combined surgery and radiation. The overall survival for all groups of patients was 25% at 5 years. The authors provide further data on stage-specific survival and therapeutic modality specific survival for all stages. Surprisingly, for all stages examined, the surgery alone or the combined modality groups had equivalent survival at 1-, 3-, and 5-year points and these were always better than radiation alone. The 5-year survival of the radiation-only group was 11.5% versus 39% for surgery only and 31.8% for combined therapy. Clearly, these data confirm that hypopharyngeal cancer has a poor prognosis. However, there are several confounding aspects of this retrospective review that must be appreciated in examining the data. First, the results against radiation in advanced-stage tumors is likely subject to selection bias because the radiation-only group likely had a significant number of advanced, inoperable patients, whereas the surgery or combined-modality therapy groups likely had patients felt to be operative candidates. Other uncontrolled or unclear variables in these analyses are what types of surgery were used, the doses of radiation, and the cause of death.

A decade later Hoffman and colleagues[10] published their retrospective review of the Patient Care Evaluation (PCE) study of the American College of Surgeons. This database was subdivided between two periods, 1980 to 1985 and 1990 to 1992. There were 1317 cases in the first set of years and 1622 in the second set. Again, the majority of these were located in the pyriform sinus (64.4%) and the advanced stages (III and IV) comprised approximately 75% of the cases in both situations. A stage migration effect was clearly seen as the pathologic stage advanced a significant number of patients to stage IV disease. As 5-year survival was available only for the 1980 to 1985 cohort, an analysis of outcomes for this group was presented. Overall, disease-specific survival was 69.6% at 1 year, 39% at 3 years, and 33.4% at 5 years. Analysis of stage-specific survival revealed a gradual decrease as stage increased from 63.1% for stage I to 22% for stage IV. When analyzed for therapeutic modality, a conclusion similar to that of Pingree and colleagues[124] was reached. Those patients who had surgery alone had a 50.4% five-year survival, those with combined modality had a 48% survival, and the radiation-alone group had a 14.9% survival. However, Hoffman and colleagues went on to correct for possible selection bias by matching tumors with the TNM classification and found the same pattern. The greatest difference was noted in the T3/T4N0M0 groups, in which surgery alone produced a 34.6% five-year survival and radiation alone had a 3.2% five-year survival. This would suggest that for advanced tumors radiation alone is not an adequate modality.

Wahlberg and colleagues[6] addressed overall survival of patients with hypopharyngeal tumors in a retrospective review of a 30-year (1960-1989) experience. Data were analyzed from the Swedish Cancer Registry, which is a compilation with a completeness of more than 95% of all tumors in Sweden. There were 2012 total cases that not only included squamous cell carcinomas but also adenocarcinomas, malignant salivary gland tumors, and other rare tumors (these accounted for 5% to 10% of all the tumors). This study primarily examined overall survival rates, but no data describing tumor stage, actual cause of death, details of therapy, recurrences, second primaries, or status of neck disease were presented. The treatment of these patients was heterogeneous, but in general in the early years radiation was used primarily and in the 1980 to 1989 period evolved to include combined surgery followed by radiation. Incidence of cancer decreased in women at an average of 2% per year, and although not clear, may be explained by better treatment of Plummer-Vinson syndrome. The 2-year and 5-year overall survival rates were 25% and 13%, respectively. The overall survival for nonsquamous cell cancers was slightly better at 5 years.

Thus in these large retrospective reviews, it is clear that carcinoma of the hypopharynx has a poor outcome relative to other sites in the head and neck. These studies have their deficits as discussed earlier, but they allow physicians to discuss the outcomes of overall therapy with their patients. No surveys addressing cervical esophageal carcinoma

alone have been reported likely due to the limited numbers of primaries in this region and variation in reporting these cancers. In the following sections, we focus further on specific modalities as used at different institutions and their respective outcomes.

Therapeutic Outcomes—Primary Radiation Therapy

Although outcomes of radiation are discussed in brief here, Jean Louis LeFebvre describes more extensively the use of radiation therapy in a separate chapter. The best evidence for the use of therapeutic radiation as the primary modality is for T1 and selected T2 cancers. Overall, these lesions constitute a low number of cancers from the hypopharynx. These favorable lesions are exophytic in nature, are high in the pyriform (i.e., not involving the apex), and have a low volume by CT scan measurement.[125] Multiple groups have shown that actuarial survival using radiation followed by neck dissection for bulky neck disease is equivalent to conservation surgery with postoperative radiation for T1 and select T2 tumors.

The M.D. Anderson experience was first described by El-Badawi and colleagues[126] and later expanded by Garden and colleagues.[105] In a 1996 report, Garden and colleagues retrospectively reviewed 82 patients with T1 (19 patients) and T2 (63 patients) tumors of the hypopharynx who were treated between 1976 and 1992 with definitive radiation.[105] Fifty-two percent (43/82) were node positive at the start of radiation, and of these 23 of 43 had a neck dissection performed after radiation. Radiation itself was given in a single daily dose or in divided daily doses to 40 and 42 patients, respectively. The 2- and 5-year actuarial survival rates were 72% and 52%, respectively, and overall the altered fractionation scheme gave better results. The preference of this group is to use single-modality therapy whenever possible. Thus for early tumors, the M.D. Anderson experience has been to radiate and then perform neck dissections only on those patients who still have cervical lymphadenopathy. This strategy spares a subset of patients from having surgery. Other studies that used radiation as the primary modality include the Institut Gustave-Roussy,[127] which noted a 40% five-year survival of selected T1 and T2 tumors. All other tumor stages in their study of radiation as the primary modality did poorly at 5 years.

The experience of Mendenhall and colleagues at the University of Florida has been described in several reports.[128-130] As opposed to the other available studies on radiation as primary treatment, Mendenhall and colleagues analyzed their data using overall stages rather than tumor stage (i.e., T1 or T2). Patients either received twice-daily fractionated therapy or daily treatments. The overall absolute and cause-specific survival rates at 5 years were 43% and 58%, respectively. A stage-specific analysis showed that the probability of cause-specific survival was 100% for stages I and II, 62% for stage III, 43% for stage IVA, and 25% for stage IVB. Acute complications occurred in two patients and included severe mucositis and hospitalization for dehydration. Complications included chondronecrosis leading to total laryngectomy in one patient. Six others had aspiration, dysphagia, or laryngeal edema leading to tracheostomy. Five of 10 patients who had to undergo total laryngectomy had significant postoperative complications including wound breakdown with fatal carotid rupture, a separate death, and fistulas.

In summary, although the caveats listed earlier apply to all these studies, the basic premise from all of them is that early lesions can be treated with radiation as the primary modality. The data on survival are similar to that achieved with conservation surgery from other studies. As a reminder, again, this subset of patients is a small portion of all hypopharynx carcinoma patients. Despite this limitation, a future prospective trial designed to randomize patients to radiation with surgery if necessary or conservation surgery with postoperative radiation may ultimately answer the question of superiority of either approach. Until then, clinical practice will be dictated by the treating physician's preferences in the context of these retrospective studies.

Several groups have described radiation as primary therapy for cervical esophageal carcinoma. Mendenhall and colleagues[131] described 34 patients treated in this fashion and reported a 14% five-year overall survival. Jones and colleagues[132] reported on a series of 12 patients who underwent radical radiation therapy and 14 patients treated with surgery. The overall 3-year survival was 18%. Although it is difficult to draw a definitive conclusion from these small series, radiation as primary therapy appears to achieve poor control of cervical esophageal carcinoma.

Therapeutic Outcomes—Primary Surgical Therapy

Conservation surgery for hypopharyngeal cancer became possible because of contributions from Trotter, Orton, and Alonso. In the 1960s, Ogura and associates applied lessons learned from conservation laryngeal surgery to hypopharyngeal cancers. They reported on the development of the partial laryngopharyngectomy operation and described the results of this operation.[61,133] *Preoperative* radiation was routinely administered during this period. A summary of the major surgically oriented studies reported in the literature is shown in Table 103-5.

Holsinger and coworkers reviewed the experience of the Laccourreye group for patients with T1 or T2 lateral wall pyriform tumors that were resected using a lateral pharyngectomy with primary closure.[134] A subset of these patients was treated with preoperative chemotherapy and some patients received postoperative radiation. Three postoperative deaths occurred (one related to surgery), but all patients were eventually decannulated. Surprisingly for these small tumors, this series found that the 5-year survival rate was 23.3% with four patients (13%) having local recurrences.

In addition to the lateral pharyngectomy, Laccourreye and colleagues[63] used the supracricoid hemilaryngopharyngectomy (SCHLP) to treat cancers primarily of T1 to T3 staging (one patient who was a T4 was included in the series). In their retrospective review, 240 patients were treated with an ipsilateral neck dissection and the SCHLP. Deglutition was recovered in 204 of 233 patients with a 17-day average time to removal of the nasogastric tube, although the authors state that "recovery of satisfactory deglutition may take up to 1 year." A thorough evaluation of survival data on all 192 patients was not discussed in this study. A detailed analysis of 34 selected T2 pyriform cancers was published in 1993.[65] Prior to operation, most patients received chemotherapy consisting of either bleomycin (7 patients); vincristine, methotrexate, and bleomycin (14 patients); or cisplatin and 5-FU (10 patients). Postoperatively 31 of 34 patients received radiation. Of the 34 patients, 33 were decannulated and 31 of 34 patients were able to swallow after 1 month (range 13 to 26 days). Aspiration pneumonia occurred in 7 of 34 patients (20%). A completion laryngectomy was eventually performed in 3 of 34 patients due to intractable aspiration. Voice quality was initially judged as good to satisfactory in 32 of 34 patients. The 5-year actuarial survival rate was 55.8% with only one patient developing a local recurrence and two patients (one was the same, who developed local recurrence) developing neck recurrences. Cause of death was intercurrent disease in 7 of 34, second primary in 6 of 34, nodal recurrences in 1 of 34 and primary recurrence in 1 of 34. One patient died from chondroradionecrosis of the larynx, and two deaths were from unknown causes. Compared with the results with radiotherapy alone or other conservation surgical methods, these data produce similar actuarial results but appear to have a significant associated complication rate including aspiration pneumonia. However, of the several confounding factors cautioning against direct comparisons with other methods is the routine use of preoperative chemotherapy. It is unclear whether this treatment predisposed patients to the various complications described. In addition, the chemotherapy itself was given in three different regimens. An updated review of this group's experience with SCHLP on 147 patients has been reported[62,64] and demonstrates actuarial 5-year survival rates of 96.2% for T1, 91.1% for T2, 92.9% for T3, and 62.6% for T4 lesions. These rates and the functional outcomes described compare favorably with other organ-preserving approaches.

Steiner and colleagues have been strong proponents of the TLM CO_2 laser endoscopic approach to excision of tumors of pharyngeal, supraglottic, glottic, and hypopharyngeal origin. The postoperative course and survival data of their group of patients are impressive and are briefly reviewed.[58] Between 1981 and 1996, 129 cases of hypopharyngeal cancer underwent endoscopic excision and can be subdivided as follows: pT1:24, pT2:74, pT3:17, and pT4:14. Of these patients 68% were node positive and 75% were stage III/IV. Surgery as sole modality was used in 42% of patients, and the remainder had surgery followed by radiation. The overall survival rates were 71% and 47%

Table 103-5

Selected Surgical Studies

Reference	Yr	Patients	Disease Burden*	Survival (5 yr except where indicated)	Technique(+)	EBM Grade #
Laccourreye et al.[65]	1993	34	All T2	55.8%	SCHLP + C ± RT	C
Steiner et al.[58]	2001	129	T1 = 24, T2 = 74, T3 = 17, T4 = 14	Stage I/II = 71% and stage III/IV = 47%	CO_2 ± RT	C
Rudert and Hoft[135]	2003	29	T1/T2 = 27, T3 = 1, T4 = 1	Stage I/II = 78% and stage III/IV = 35%	CO_2 ± RT	C
El-Badawi et al.[126]	1982	328	T1 = 22, T2 = 49, T3 = 156, T4 = 191	S = 25% S + RT = 40%	Surg or Surg/RT	C
Vandenbrouck et al.[127]	1987	199	T1 = 27, T2 = 6, T3 = 156, T4 = 10	33%	Surg or Surg/RT	C
Kraus et al.[138]	1997	132	Advanced = 78%	Overall = 30% Disease-specific = 41%	Surg ± RT	C
Elias et al.[139]	1995	101	Stage II = 23, stage III = 30, stage IV = 48	Overall = 27% Disease-specific = 37%	RT, Surg or Surg/RT	C
Spector et al.[2]	1995	408	1 wall, 2 wall, 3 wall	1 Wall (lat) = 73% 1 wall (med) = 63% 2/3 wall= 49%	Surg ± RT (preop or post)	C
Harrison and Thompson[141]	1986	101	Advanced	58% Actuarial	PLE/pull-up	C
Wei[69]	1998	317 total, 69 (1986-1996)	Advanced	24.5% Actuarial	PLE/pull-up	C
Triboulet et al.[142]	2001	209	Advanced	24% Actuarial	PLE/pull-up	C
Bova et al.[143]	2005	180	Stage I/II—9%, stage III/IV—91%	DSS—52%, OS—33%	TLP with jejunum First 82 patients received induction chemo	C
Holsinger et al.[134]	2006	30	T1 or T2 lateral pyriform tumors	23.3% actuarial	Lateral pharyngectomy	C
Kania et al.[62]	2005	147	Stage I—12, stage 2—39, stage 3—41, Stage Iva—43, stage IVb—12	T1/2 = 96.2-91.1% T3/T4 = 92.9-62.6%	SCHLP + C ± RT	C
Wang et al.[144]	2006	41	Advanced	Overall = 31.5%	PLE/pull-up + RT	C
Martin et al.[136]	2008	172	Stage I/II—15%, stage III/IVa—85%	Stage I/II—73%, stage III—59%, stage IVa—49%	TLM ± RT	C

*Disease burden was determined as described by the authors. Comparisons across studies are not possible because various American Joint Commission for Cancer criteria were used.

CO_2, carbon dioxide laser; PLE/pull-up, total pharyngo-laryngo-esophagectomy with gastric pull-up reconstruction; RT, radiation therapy; SCHLP +C, supracricoid hemilaryngopharyngectomy with chemotherapy; Surg., surgery; EBM grade # (evidence-based medicine grade) based on the definitions from the Centre for Evidence Based Medicine (as described in Sackett DL, Straus SE, Richardson SW, et al. *Evidence-Based Medicine: How to Practice and Teach EBM.* 2nd ed. Edinburgh: Churchill Livingstone; 2000). All studies are grade C because they are retrospective reviews without internal control groups.

for stages I/II and III/IV, respectively. These data compare favorably with outcomes using conventional treatment of these tumors. The most impressive aspect, however, of this technique is the perioperative management. Only 5 of 129 cases underwent tracheotomy during surgery and 1 required tracheotomy postoperatively due to hemorrhage. Thirty-five patients were taking an oral diet on the first postoperative day and all but two patients eventually achieved oral feeding. Only one patient developed a hypopharyngeal stenosis and was dependent on gastrostomy tube feeding. Thus although technically challenging, this procedure appears to be oncologically sound and has the significant added advantage of no tracheotomy, no reconstruction, voice preservation, and a quick return to an oral diet. For advanced-stage tumors, a defini-

tion of the inferior extent of the tumor is required because extension into the cervical esophagus would clearly limit the ability of the endoscopic surgeon.

Rudert and Hoft[135] described their experience managing 29 patients with hypopharyngeal carcinoma using the endoscopic approach. Except for two patients (one T3 and one T4), the remaining 27 patients had T1 and T2 tumors. Of these patients, 9 were stage I/II and 20 were stage III/IV. No patients underwent tracheotomy at operation; however, the authors do not report on whether any required it in the postoperative period. Functionally, no surviving patients had speech or swallowing problems at 5-year follow-up. The 5-year survival rates for stage I/II were 78% and 35% for stage III/IV. Not surprisingly, node status was a significant predictor of outcome with N0 patients having 74% and node-positive patients having 34% overall survival. Locoregional recurrences occurred in 8 of 29 (27.6%) patients each. Interestingly, 7 of 8 of the local recurrences occurred below an arbitrary line drawn at the interarytenoid line. Distant metastases and second primaries occurred in 8 of 29 (27.6%) and 12 of 29 (41%) patients, respectively. These authors found the best local control with tumors of the pharyngeal walls.

Recently, Steiner and colleagues[136] reported the outcomes analysis of 172 patients with hypopharyngeal tumors treated with TLM. Although the relationship between this cohort and the one reported previously is not clear from the publication, the time period of the two cohorts shows some overlap. The 5-year recurrence-free survival in this study was reported to be 73% for stages I and II, 59% for stage III, and 49% for stage IVa. These numbers compare favorably with other modalities with the major reported benefits as described earlier. Again, the outcomes of this technique need broader evaluation but deserve closer attention because of the apparent superior functional outcome and our patients' demands of more minimally invasive techniques to handle even advanced cancers.

ADVANCED LARYNGOPHARYNGEAL CANCER. Multiple groups have published their retrospective series of patients treated with partial laryngopharyngectomy, total laryngopharyngectomy, or laryngo-pharyngo-esophagectomy. In this section we review a select set of the series with large groups of patients with adequate follow-up.

Goepfert and colleagues[126] reported the M.D. Anderson experience in treating squamous cell carcinoma of the pyriform sinus from 1949 to 1976. An evolution in techniques affected the specific procedures used to treat patients, but the majority of lesions were treated with surgery and postoperative radiation. This factor clearly affects the analysis of the outcomes data. The major subdivisions in the treatment groups were between those patients who underwent surgery alone and those who underwent surgery and planned postoperative radiation.[31] Each group had approximately equivalent numbers of patients in each T category but the nodal status was not described for each individual group. Locoregional control was superior in the combined therapy group (39% vs. 11% in the surgery-only group). The 5-year survival (not adjusted for any other factors) was 25% for the surgery-only group and 40% for the combined-therapy group. Thus as opposed to the study of Pingree and colleagues[124] and Hoffman and colleagues,[10] Goepfert and colleagues found that combined therapy was superior to surgery alone.

Vandenbrouck and colleagues[127] described the Institut Gustave-Roussy's experience with radical surgery followed by radiotherapy in 181 cases from 1968 to 1978. The overall 5-year survival in these patients was 39% and was not broken down by further staging or node status. Consistent with all other head and neck sites, node positivity and extracapsular spread resulted in poorer outcome. The distant metastatic rate was 27.6% and was the most common cause of failure.

Kraus and colleagues described the Memorial Sloan-Kettering experience[138] in managing 132 patients with hypopharyngeal squamous cell carcinoma. Of these patients, most (78%) had advanced disease; however, none had distant metastasis at presentation. These patients were all treated by surgery and 80% then received postoperative radiation. Radiation in 76 of 106 patients was given at various outside institutions due to logistical considerations, which may be one variable in understanding the outcomes. Surgery consisted of partial laryngo-pharyngectomy, total laryngectomy with partial pharyngectomy, or total laryngopharyngectomy. The 5-year overall survival was 30% and disease-specific survival was 41%. Although T stage was not significant in outcome, the following factors were all significant: N0/N1 was better than N2/N3, stages I/II/III did better than stage IV, patients who underwent laryngectomy did worse than those who did not need one, and finally positive margins portended a poor prognosis.

Elias and colleagues[139] reported their analysis of 101 patients with pyriform sinus cancer. Over a 20-year period, treatment evolved from radiation as primary therapy to surgery with postoperative radiation therapy. They reported a 5-year overall survival of 27% and a 5-year disease-free survival of 37%. Survival correlated with stage of the patient, and disease-free survival was significantly better in the combined surgery and radiation group.

Spector and colleagues[140] reported a 30-year experience from our institution on 408 patients with pyriform sinus cancers. These patients were treated with a heterogeneous group of modalities: 95 patients were treated with a single modality (either radiation or surgery) and 302 were treated with preoperative radiation and then surgery or surgery followed by postoperative radiation. Survival was described by grouping these lesions into specific anatomic locations in the hypopharynx. At 5-year follow-up, survival for one-wall lesions was 73%; medial-wall lesions, 63%; and 2- or 3-wall lesions, 49%. Distant metastasis and second primary tumors occurred in 17.7% and 6.2% of patients, respectively. Interpretation of these data is complicated by the fact that there was such a diversity in therapeutic modalities. The broad experience at Washington University does, however, give an overview of survival rates in these patients.

Harrison and Thompson[141]reported on their series of 101 patients who underwent total pharyngolaryngectomy and esophagectomy from 1965 to 1983. They reported an 11% mortality rate and a 33% morbidity rate. The morbidities included 15 patients with pneumonia and 2 with abdominal dehiscence. Actuarial survival of 58% was achieved at a 5-year follow-up. Second primaries or distant metastasis accounted for 18 of 101 (15%) patient deaths. Harrison clearly acknowledged the contribution of comorbidities in these patients as he stated, "In comparing the relative success of the various operations … one must consider not only the intrinsic risks of the actual procedure but the age and general condition of the patients."

Triboulet and colleagues[142] performed a retrospective review of 209 patients treated from 1982 to 1999 who underwent total laryngo-pharyngectomy that in some cases included a cervical or total esophagectomy followed by reconstruction with either jejunal free flap (77 patients), gastric pull-up,[92] or pharyngocolic anastamosis.[121] Nearly all of these patients presented at an advanced stage or had multiple small tumors distributed between the hypopharynx and cervical esophagus, thus requiring a more radical operation. Forty-two patients were failures of preoperative treatment consisting of chemotherapy, radiation, or both. At 3- and 5-year follow-up, the overall actuarial survival rates were 32% and 24%, respectively. Survival was unrelated to the reconstruction technique used, but negative factors included positive margins, advanced primary tumor in the cervical esophagus, and not receiving postoperative radiation therapy. The mortality rate was 4.8% and the morbidity rate was 38.3%. Interestingly, patients who underwent free jejunal transfer had more complications including flap necrosis and fistulas, leading to delayed feeding. Thus these authors favor gastric pull-up over jejunum for reconstruction of the alimentary tube. Two more recent studies[143,144] show similar low 5-year survival rates of approximately 30% using TLP with esophagectomy.

The group of William Wei at the University of Hong Kong has extensive experience in managing these difficult tumors.[69,145] Wei and colleagues[69] analyzed outcomes of 317 patients treated at the University of Hong Kong from 1966-1995. The goal of their 1998 study was to compare a group of 69 patients undergoing operations from 1986 to 1995 with earlier groups they had treated to evaluate changes in survival and morbidity and mortality of treatments. These authors exclusively used a total laryngopharyngectomy and esophagectomy for advanced tumors of the hypopharynx and cervical esophagus. In their earlier experience, this operation was also applied to advanced tumors of the larynx but was not used for these tumors from 1986 to 1995. The hospital mortality for this operation declined from 31% to 9% over 3

decades. The 5-year actuarial survival rate improved from 18% in the 1970s to 24.5% for the subset of patients from 1986 to 1995.

Data on the outcomes of cervical esophageal cancer are more limited due to the lack of experience at most centers and due to clustering of these lesions with the esophagus as a whole.

Laterza and colleagues[146] reported their 20-year experience with the surgical management of carcinoma involving the cervical esophagus. Of 167 patients, 37 had primary cervical esophageal involvement with the others extending superiorly to involve the hypopharynx or inferiorly to involve the thoracic esophagus. The overall 5-year survival rate was only 16.6% with a mortality rate of 8.8%. Kelley and colleagues[147] examined the management of 67 patients seen at the Memorial Sloan-Kettering Cancer Center from 1980 to 1993. A diverse set of protocols was used to manage these patients. Of these, 22 patients were treated with surgery with curative intent and other subsets were treated with radiation or chemotherapy in various combinations. Survival was poor in all groups (mean survival for entire group was 17 months and cumulative 5-year survival was 12%), although the surgery group had the best outcome. It is difficult in this study to compare specific treatments because of heterogeneity in therapy and the small numbers. However, Kelley and colleagues concluded that surgical therapy provided the best outcome.

THE ROLE OF CHEMOTHERAPY. Chemotherapy regimens for advanced unresectable head and neck cancers were begun in the 1970s. In the 1980s it was described that cisplatin and 5-FU were able to produce a significant number of partial and complete responders.[148] These data were augmented by the interesting description of Ensley and colleagues[149] that chemosensitivity was a predictor of radiosensitivity. Ultimately, this led to the landmark Veterans Affairs study on laryngeal preservation.[150]

In the meta-analysis reported by Pignon and colleagues[151] a significant benefit of concomitant chemoradiation was observed; however, a significant confounding factor was the heterogeneity between the trials. Multiple phase III trials have attempted to use concomitant chemoradiation in the treatment of locally advanced head and neck cancers.[108,152] Typically the hypopharyngeal and cervical esophageal cancers have been grouped with other subsites.[153,154] In addition to concurrent protocols, some investigators have expanded on induction chemotherapy protocols for advanced head and neck cancers.[155] These findings now form some of the key bases for combined chemotherapy and radiotherapy protocols for hypopharyngeal cancers. Again, the data on concomitant chemoradiotherapy application in advanced head and neck cancers are discussed in a separate chapter.

QUALITY OF LIFE STUDIES. Although survival is a critical measure of the success of therapy for all head and neck cancers, the patient's perception of his or her quality of life (QOL) after therapy is also an important measure. As chemotherapy, radiation, and reconstructive options have advanced the management of these diseases, the question of patient perception of their lives post-treatment is one that is addressed by QOL studies. Several validated measurement tools exist for the evaluation of quality of life.[156] Studies limited to QOL in patients with hypopharyngeal or cervical esophageal carcinomas are not available. However, several studies have reported QOL in patients with advanced head and neck cancers, subsets of which include hypopharyngeal carcinomas.[157-159] The major limitation in these studies is the patient numbers that impede extrapolation. For example, in a large prospective evaluation of all sites for QOL, Weymuller and colleagues[160] had 14 patients pretreatment and 4 post-treatment with primaries in the hypopharynx. They concluded that it is difficult to perform these types of studies from a single institution because statistical significance cannot be reached on the basis of limited numbers and because there is selection bias.[160,161]

Studies on QOL in laryngeal cancer patients treated with organ-sparing protocols yielded results that may be applicable to hypopharyngeal cancer patients. Terrell and colleagues[162] evaluated QOL in surviving patients from the Veterans Affairs Laryngeal Cancer Study. Four different measures were used to examine patients from the surgery/radiation group or the chemotherapy/radiation group. The differences identified include better scores for the chemoradiation group in the bodily pain scores and in the mental health domain. All other scores were equivalent. Surprisingly, comparing speech domain scores in patients who underwent laryngectomy versus those with intact larynges demonstrated no significant differences and Weymuller and colleagues and Deleyiannis and colleagues[161,163] confirmed these data and reported that the functional limitation imposed by a laryngectomy did not affect overall quality of life. Thus although organ-sparing protocols may appear intuitively to be superior in terms of patient QOL, these data indicate that overall QOL may not be affected by laryngectomy.

Although the frequency of QOL studies has increased in the past few years, reflecting an acknowledgement of the importance of this component of postmanagement patient care, no broad studies have emerged specifically dealing with hypopharyngeal or cervical esophageal carcinoma. Incorporating QOL instruments in future prospective trials in patients either treated with conventional therapy or organ-preservation therapy is necessary.

Conclusion

Taken together, this chapter summarizes the complexities in the management of patients with hypopharyngeal and cervical esophageal neoplasms. Clearly, the survival of these patients is poor compared with all other sites in the head and neck. However, with advances in reconstructive techniques and organ-preservation protocols, improved options are available for patients. Ultimately, prospective, multi-institutional trials together with biomarkers are necessary to delineate the "best" therapy for individual patients. Progress in outcomes research will continue to add data on tumor staging and yield a better understanding of QOL and survival figures. These studies in combination with novel molecular approaches for treating head and neck malignancies will ultimately improve on the current poor prognosis of patients with hypopharyngeal and cervical esophageal malignancies.

Acknowledgments

We apologize in advance if we have not mentioned specific studies either due to oversight or space limitations. We thank B.H. Haughey, B.N. Nussenbaum, and R.C. Paniello for insightful comments during the preparation of this chapter.

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CHAPTER ONE HUNDRED AND FOUR

Radiotherapy and Chemotherapy of Squamous Cell Carcinomas of the Hypopharynx and Esophagus

Jean-Louis Lefebvre

Antoine Adenis

Key Points

- Hypopharynx cancers occur in heavy drinkers and long-term smokers. As a result, most of the time hypopharynx patients present with notable comorbid illness.
- Hypopharynx cancers carry a particular high risk to metastasizing to the neck or distant sites.
- The vast majority of hypopharynx cancers are diagnosed at an advanced stage, often at a metastatic stage.
- The overall prognosis remains poor because of local, regional, and distant failures and undercurrent diseases as well.
- Early diseases may be treated by partial surgery or irradiation, or both.
- Advanced diseases, as long as there is no extension to the esopharyngeal junction or to the soft tissues of the neck, may be treated by chemotherapy/radiotherapy-based larynx preservation protocols.
- More intensive chemoradiation regimens including taxanes, sequential chemoradiation, concurrent chemoradiation, as well as molecular targeted therapies (in particular targeting the epidermal growth factor receptor [EGFR] pathway), are under evaluation.

The treatment of squamous cell carcinomas (SCCs) of hypopharyngeal and esophageal malignancies remains a real challenge. These tumors are most often diagnosed at advanced stages in rather debilitated patients. They have high locoregional aggressiveness, as well as a high metastatic propensity. Treatment planning must take into account both the locoregional extension and the frequent comorbid illnesses and is too often considered with palliative intent. Surgery with postoperative irradiation has long been the only one treatment performed with curative intent. This surgery was in the vast majority of the cases rather mutilating and had, in particular for esophageal cancer, a notable morbidity. The development of the use of a combination of irradiation and chemotherapy has somewhat modified these therapeutic approaches. If globally, the outcome in terms of disease control and survival has not been tremendously improved, the organ-preserving strategies have allowed, in selected cases, to improve the quality of life without jeopardizing survival. A multidisciplinary decision-making approach that includes the surgeon, medical oncologist, radiation therapist, imaging specialist, and general practitioner is mandatory to better treat these patients.

Hypopharynx Cancers

Background

The hypopharynx is most certainly the worst primary site when considering the different cancers of the upper aerodigestive tract. This was clearly seen in two studies from Centre Oscar Lambret.

The first study was a prospective epidemiologic analysis carried out on 339 new successive hypopharynx patients. This population consisted of 329 males (97%) with a mean age of 57 years and 10 females (3%) with a mean age of 55 years. Of the patients, 114 (34%) lived alone at time of diagnosis. Only 95 patients (28%) were employed, 38% were retired, 20% were disabled, 13% were unemployed, and 1% (all females) had never had any occupation. Of the patients, 330 (97%) acknowledged they had both used tobacco and abused alcohol. The mean lifelong consumption of tobacco was 317 kg of tobacco smoked before diagnosis, ranging between 13 and 998 kg. The mean lifelong consumption of alcohol was as high as 1654 kg of equivalent of pure ethanol, ranging between 55 and 6074 kg. Such impressive data explained why more than half the patients presented with comorbid illnesses.

The second study was a retrospective review of the clinical charts of 652 new successive hypopharynx patients. Again, 97% of patients were males. All tumors were SCC. Of the patients, 346 had at least one comorbid illness (e.g., liver cirrhosis in 11% of the patients). Stage I included only 4% of the cases, with a similar figure (3%) for stage II, while stages III and IV made up 40% and 53%, respectively. Metastatic cervical lymph nodes were found on either palpation or computed tomography (CT) scan in 78% of patients.

Conventional Treatment Modalities

Surgery, combined with postoperative irradiation, and definitive irradiation (with surgery in reserve for salvage in case of local failure) have long been the only two options for treatment of hypopharyngeal cancers. As for larynx cancers, no randomized comparison of both approaches has been carried out. Comparison of these two approaches

is particularly inappropriate for hypopharynx cancers. As most of the patients present with locoregionally advanced diseases and notable comorbidities, surgical series are assessed on the basis of selected cases (resectable diseases in operable patients); however, radiotherapeutic series include cases that are expected to conclude with much more unfavorable results.

Early Diseases

Partial surgery of the hypopharynx has been proposed for early diseases. This surgery may consist of partial lateral or posterior hypopharyngectomy or of supraglottic hemilaryngopharyngectomy. The indication of such a surgery is rare because it requires a thorough assessment of patients' local extension and performance status. When indicated, this surgery is given a local control as high as 90%.[1,2] Laser CO_2 surgery has also been advocated with similar results.[3] This surgery may generate laryngopharyngeal dyssynergia with frequent aspirations, particularly when postoperative irradiation is delivered or when a cricoid resection has been necessary. Adjuvant irradiation is most often required because of the risk of submucosal spread and the frequent nodal involvement. The reported 5-year survival rates range around 50%.

Definitive radiation therapy has also been proposed. Several series have shown similar results, with probably slightly better functional results,[4-6] but, in case of failure in about all resectable local recurrences, salvage surgery resulted in a total laryngectomy.

No straightforward rule exists for selection of either partial surgery or irradiation. In general radiation is proposed for exophytic tumors located in the "membranous part" of the hypopharynx (i.e., behind the thyrohyoid membrane). For more infiltrating tumors and tumors located in the "cartilaginous part" of the hypopharynx (i.e., behind the thyroid ala), surgery is the preferable treatment. When irradiation is proposed, a radical neck dissection followed by radiotherapy to the primary tumor and to the neck seemed to improve the outcome in case of T_1T_2 with enlarged metastatic lymph nodes.[7]

Advanced Diseases

The majority of hypopharynx cancers, when resectable, are only able to endure a total laryngectomy with a partial pharyngectomy performed with a radical neck dissection. Postoperative irradiation improves the results of surgery.[8] This surgery is able to control 85% of the cancers above the clavicles in French series.[9-11] Despite this advantageous local control rate, the 5-year survival rate does not exceed 35%, most of deaths being attributed to distant metastases, intercurrent diseases, or, to a lesser extent, second primary tumors. In addition, a major structural and functional alteration to the patient's upper aerodigestive tract is incurred. All previously untreated patients must receive postoperative irradiation to the surgical bed and both sides of the neck. Comparison between preoperative and postoperative irradiation showed that the postoperative results were superior.[12]

Endoscopic laser CO_2 surgery has also been advocated by some teams for advanced diseases of the hypopharynx. A recent retrospective study reported (5-year local control as high as 75% for pT3 and 57% for pT4a, while 5-year recurrence-free survival was of 59% for stage III and 47% for stage IVa.[13] This surgery is indicated for selected cases, although its application widens in the hands of experienced surgeons.

Conventional irradiation often gives poor results in T_3 and T_4 diseases both in terms of local control and survival far under the locoregional control rates seen after surgery and postoperative irradiation.[4,5,14]

New Modalities

For a long time, chemotherapy was used primarily for palliative purposes because of its poor outcomes in the treatment of cancer of the head and neck. A new era in the management of cancer of the head and neck was initiated in the early 1980s with the introduction of platinum-based chemotherapeutic regimens. Actually, clinical studies using cisplatin as a single agent or more often in combination with other drugs have demonstrated partial response rates of 40% to 50% and complete response rates of 26% to 50%, for an overall response rate ranging between 78% and 94%.[15,16] In the early 1990s it appeared obvious that this approach had not provided any improvement in survival benefit for most patients. This was clearly demonstrated by the major meta-analysis carried out at the Institute Gustave Roussy (MACH-NC analysis)[17] including more than 10,000 patients enrolled in randomized trials comparing conventional treatment with the same treatment with chemotherapy (either adjuvant or induction or concomitant chemotherapy). The conclusion of this meta-analysis was that adjuvant chemotherapy, as well as induction chemotherapy (4%), produced an insignificant increase in survival (1%). But when induction chemotherapy consisted of cisplatin and fluorouracil, a significant 5% benefit in survival was achieved. On the contrary, concomitant chemoradiotherapy resulted in a significant increase in survival to 8%, but this group had a mixture of definitive and postoperative radiation trials. However, additional trials of chemoradiation as the first line of treatment, which were published after this meta-analysis, confirmed the trend toward an improved outcome.[18-20] This meta-analysis was updated in 2007[21] including 16,665 patients and confirmed that concurrent chemoradiation provided the highest benefit in survival (hazard ratio: 0.81), particularly for platinum-based chemotherapy (hazard ratio: 0.75), but the effects of chemotherapy decreased with increasing age. It must be underscored that these trials did not address hypopharynx cancers specifically. As a result, chemoradiation remains an important treatment that is still under evaluation for this primary site.

Radiation therapy has also been subject to intensive clinical research, particularly regarding fractionation and overall treatment time (discussed later in this chapter).

Chemotherapy to Improve the Outcome after Total Laryngectomy

In an attempt to improve the results of radical surgery with postoperative irradiation, chemotherapy has been evaluated. In 1990 the European Organization for Research and Treatment of Cancer (EORTC) Head and Neck Group reported a randomized trial[22] comparing this approach with the same treatment preceded by one course of vincristine with bleomycin and methotrexate. No difference was shown for locoregional control, distant metastases, and metachronous cancers. In 1996 the Institute Gustave Roussy[23] reported on perioperative chemotherapy in which patients received three cycles of cisplatin-fluorouracil before surgery and two additional cycles between surgery and postoperative irradiation without any improvement in outcome when compared with historical controls without chemotherapy.

A French trial[24] assessed the role of induction chemotherapy consisting of three cycles of the conventional regimen cisplatinum-fluorouracil. In one arm this chemotherapy was followed—whatever the response to chemotherapy—by a total laryngectomy with a radical neck dissection and postoperative irradiation. The other arm consisted of the same chemotherapy protocol followed again—whatever the response—by definitive irradiation, keeping the surgery in reserve for salvage. The aim of this trial, to evaluate a larynx preservation approach, is discussed later in this chapter, but the "surgical" arm may be analyzed separately in regard to the impact of chemotherapy. In this arm the 5-year survival was 37%. The fact that induction chemotherapy has not tremendously improved survival has been often underscored, whatever the primary site.

Another way to try to improve the results of radio-surgical protocols is to deliver postoperative concurrent chemotherapy and irradiation[25-28] in high-risk patients (e.g., positive margins, extracapsular spread, multiple nodal involvement, perineural invasion). One of these situations is often encountered after hypopharynx resection. Two recent randomized trials (RTOG 95-01 and EORTC 22-981) have explored the same protocol consisting of conventional 70 Gy external beam irradiation with cisplatin on days 1, 22, and 43 at a dosage of 100 mg/m^2. Randomized or not, none of these studies have focused on hypopharynx cancer only.

The Radiation Therapy Oncology Group RTOG 95-01 trial[29] randomized patients with two or more positive lymph nodes or extracapsular spread or positive margins. This trial failed to find a significant difference. A trend appeared for a slight difference in 2-year estimates for locoregional control in the experimental arm (79% vs. 74%, $P = 0.16$) and in 2-year estimates for overall survival (63% vs. 57%, $P = 0.51$), while a borderline significant difference appeared for

disease-free survival (54% vs. 43%, $P = 0.049$). The EORTC 22-951 trial[30] included many more clinical situations (stage III and IV or two or more positive lymph nodes or extracapsular spread or positive margins or vascular embolisms or perineural invasion or positive lymph nodes in levels 4 or 5). The interim analysis demonstrated a significant increase in 3-year estimates for disease-free survival (59% vs. 41%, $P = 0.0096$), for overall survival (65% vs. 49%, $P = 0.0057$), for time to progression (56% vs. 44%, $P = 0.0016$), and for local control (83% vs. 64%). Longer-term results and detailed comparison of both trials should help in the future understanding of this discrepancy.

Radiation Therapy

Altered fractionation has been explored in advanced head and neck cancers. The largest randomized trial was a four-arm trial[31] carried out by the RTOG (RTOG 90-03) that compared (1) conventional irradiation with (2) a split course accelerated fractionation with (3) a delayed concomitant boost and with (4) a hyperfractionated irradiation. Previously untreated advanced head and neck carcinomas were eligible for this study. Of the 1073 patients enrolled in the study, 13% had hypopharyngeal cancers. Both hyperfractionated irradiation and concomitant boost showed significantly better locoregional control, disease-free survival, disease-specific survival, and overall survival, but also a higher rate of acute and, to a lesser extent, late toxicities. No data specifically studying the hypopharynx have been published. Another large meta-analysis[32] pooled together updated individual patient data from randomized trials comparing conventional irradiation with unconventional radiotherapy schedules (hyperfractionation, acceleration, acceleration with dose reduction). A total of 6515 patients had been randomized in 15 trials. With a median follow-up of 6 years there was a significant survival benefit with altered fractionated radiotherapy (+3.4% survival at 5 years); the highest benefit (+8% at 5 years) was achieved with hyperfractionated irradiation. Again, few patients had hypopharyngeal diseases.

Combined Chemotherapy and Irradiation for Larynx Preservation

Induction Chemotherapy

As discussed earlier in this chapter, induction chemotherapy using cisplatin and fluorouracil provided impressive response rates.[33] Chemosensitive tumors' radiosensitivity was confirmed in a number of cases and suggested the ability of induction chemotherapy to predict radiosensitivity.[34] This led some teams to use a scheme of induction chemotherapy as a selective test for two groups of patients: good responders are candidates for subsequent radiation therapy and poor responders are still candidates for subsequent surgery. The larynx has been the most investigated primary site for this new approach, most often in noncontrolled trials using historical comparisons with surgical series.

Many published series have assessed in a nonrandomized fashion the reliability of induction chemotherapy–based protocols. They usually reported small series of cases mixing laryngeal, hypopharyngeal, and oropharyngeal tumors or tumors amenable to partial surgery and to radical surgery. In addition, the concept of organ preservation or preservation of function was unclear. Finally, larynx preservation rates were presented under different forms: for the overall population at a precise follow-up time, in survivors at that time, or according to a median follow-up. All in all, larynx preservation could be achieved in one third to one half of patients according to the patient selection.

Only two randomized trials focused on cancer of the hypopharynx. The first trial was conducted by the EORTC[35] on cancer of the hypopharynx eligible for total laryngectomy with partial pharyngectomy. In this study 202 patients were enrolled in which the standard treatment (surgery and postoperative radiation) was compared with two or three cycles of chemotherapy, followed in clinically complete responders at the primary site by irradiation, or, for other patients, by the conventional treatment. A notable difference appeared in the median survival, favoring the experimental arm (44 months) when compared with the surgery arm (25 months). This difference in median survival was only explained by the fact that distant metastases appeared later after chemotherapy, leading to a better survival at 3 years, which was not shown at 5 years. There was no significant difference in locoregional control or in second primaries' appearance. However, at 3 and 5 years, half the survivors in the chemotherapy arm had retained their larynx.

The second trial[24] compared 92 patients with resectable cancer of the hypopharynx (only amenable to total laryngectomy-pharyngectomy) with the outcome of patients randomly assigned to receive induction chemotherapy. In one arm, chemotherapy was followed by surgery and postoperative radiation therapy. In the other arm, chemotherapy was followed by radiation, with surgery reserved for salvage. In this trial chemosensitivity was not taken into consideration for deciding a subsequent treatment. With a median follow-up of 92 months, researchers observed a better 5-year survival (37%) and a better local control (63%) in the surgery arm when compared with the radiotherapy arm (19% and 39%, respectively). The comparison of this trial with the EORTC trial suggests that the cancer's sensitivity to chemotherapy must be taken into account before deciding a subsequent radiation therapy instead of surgery.

In 2000 the previously mentioned meta-analysis[17] assessed separately three randomized trials on larynx preservation based on induction chemotherapy. There was an insignificant 6% better survival in the surgical arm, but it was balanced by a 56% larynx preservation rate in the induction arm.

Induction chemotherapy has once again gained interest after the publication of two randomized trials comparing the conventional cisplatin 5-fluorouracil regimen with a triplet mixing cisplatin, fluorouracil, and docetaxel either in nonresectable diseases followed by irradiation alone[36] or in resectable/nonresectable diseases followed by concurrent chemoradiotherapy.[37] In both trials the triplet arm achieved significantly better overall and progression-free survivals.

In 2009 the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC)[38] published the results of their induction chemotherapy–based larynx preservation trial for larynx and hypopharynx cancer candidates for a total laryngectomy. Eligible patients were randomly assigned to receive either three cycles of cisplatin and fluorouracil in one arm or, in the other arm, three cycles of cisplatin with 5-fluorouracil and docetaxel. In both arms, following this induction chemotherapy, responders over 50% went to radiation therapy while other patients went to radical surgery and postoperative irradiation. The larynx preservation rate was significantly higher in the triplet chemotherapy arm but without significant difference in survival.

Concurrent Chemoradiotherapy

As discussed earlier in this chapter, there are promising data on concurrent chemoradiation. The questions are (1) how many patients in daily community practice are able to undergo such toxic treatments? (2) what is the largest disease stage amenable to larynx-preserving strategies? (are clinically defined T_4 or large necrotic lymph nodes acceptable?) (3) what are the most appropriate tools used to detect as soon as possible residual diseases to be treated by salvage surgery? and (4) what would be the postoperative morbidity of this salvage surgery? These concerns are of the utmost importance if the cancer is initially operable.

As far as cancer of the hypopharynx is concerned, it must be underscored that (1) this site is rarely studied separately; (2) in case of mixed sites, the hypopharynx represents just a few cases; (3) little is known about the selection of patients with cancer of the hypopharynx (detailed locoregional extension, performance status); and (4) no information is provided about the possibilities of surgical salvage.

The first randomized trial issuing larynx preservation with concurrent chemoradiotherapy to be published was the RTOG 91-11 trial.[39] But it concerned only laryngeal sites. Preliminary results suggested that concurrent chemotherapy was able to significantly increase the rate of larynx preservation when compared with induction chemotherapy and with radiotherapy alone. However, there was no difference in survival (the 5-year, disease-free survival was 39%) and, in particular, there was no difference in laryngectomy-free survival, which was 46% at 5 years.[40]

In 2007 the EORTC head and neck and radiotherapy groups published the second trial on larynx preservation comparing larynx and hypopharynx cancers candidates for radical surgery including a total

laryngectomy. This trial compared the sequential administration of induction chemotherapy and irradiation versus their alternating administration (EORTC 24954 trial).[41] No significant difference was found between both arms for either the primary end point survival with a functional larynx in place) or the secondary end points (overall survival, progression-free survival, and larynx preservation) whatever the primary site (larynx or hypopharynx).

Finally a randomized trial[42] compared radiotherapy with radiotherapy and cetuximab, a monoclonal antibody binding the extracellular receptor of the epidermal growth factor, in advanced, previously untreated head and neck cancer. Both locoregional control and overall survival were significantly higher in the cetuximab arm. In the subset of patients with larynx and hypopharynx cancers, the larynx preservation rate was also higher in the cetuximab arm.[43]

The next step could be to mix both approaches with induction chemotherapy followed, in case of chemosensitivity, by concurrent chemoradiotherapy. The potential role of the adjunct of targeted therapies (e.g., EGFR, angiogenesis, cyclin D1) must also be taken into account. A randomized phase II is currently ongoing in France under the responsibility of the GORTEC-Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) groups. After three cycles of induction chemotherapy (cisplatin, fluorouracil, and docetaxel), responders with at least 50% reduction of tumor volume and larynx mobility recovery are randomized between concurrent administration of radiotherapy and, at a 3-week interval, cisplatin versus radiotherapy and weekly cetuximab.

Localized Squamous Cell Carcinoma of the Esophagus

In most countries the standard of care for limited esophageal cancer (AJCC stage I and II) is surgery alone. Because most of the patients have local and distant recurrences, many cancer centers worldwide have favored a multimodality preoperative approach, although the evidence supporting this practice is inconsistent with no survival advantage seen in randomized studies. For patients who are not suitable candidates for surgery (AJCC stage III) or who refuse it, the current standard of care is radiotherapy in conjunction with chemotherapy.

Postoperative Therapy

A total of 8 randomized trials have examined the role of post-operative radiotherapy[43-47] or postoperative chemotherapy.[49-51] None of these studies has observed a survival benefit for patients receiving adjuvant treatment,[44-51] although Japanese investigators showed that disease-free survival for adjuvant chemotherapy was superior to surgery alone.[50]

Preoperative Therapy

Based on the five existing trials, there is no clear evidence that preoperative radiotherapy improves the survival of patients with potentially resectable SCC.[52-56] Results from clinical trials have been confirmed on 1147 patients by a meta-analysis on updated individual patient data that showed an insignificant reduction in the risk of death of 11%.[57]

Until recently, published studies that have examined the role of preoperative chemotherapy have failed to demonstrate any improvement in overall or relapse-free survival.[56,58-66] Moreover, some data suggested a reduced resectability rate[51,60] and a higher treatment-related mortality rate.[60,66] All these negative studies but one[63,64] involved a small number of patients. Conversely, a survival benefit was noted in two studies.[67,68] One small trial, published in an abstract form,[67] reported a significant increase in median survival in favor of a preoperative regimen with cisplatin and etoposide. The European OE02 study included a majority of adenocarcinomas and showed a significant improvement in survival and disease-free survival favoring the preoperative chemotherapy. A microscopically complete resection was significantly more often achieved in the preoperative chemotherapy arm (60% vs. 53%, $P < 0.0001$). In that trial, 802 patients (SCC: 31%, adenocarcinoma: 66%) were randomly assigned to surgery alone or two cycles of cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2) daily for 4 days every 3 weeks followed by surgical resection.[68] In a large Japanese study reported at the 2008 Gastrointestinal Oncology symposium, 330 patients with clinical stage II/III (excluding T4) SCC of the thoracic esophagus were randomized to two courses of chemotherapy (cisplatin, fluorouracil) followed by surgery and surgery followed by two courses of chemotherapy. With a median follow-up time of 22.6 months, this study did not reach its primary end point to detect a difference in terms of disease-free survival. Surprisingly, the Japanese investigators showed a significant survival benefit favoring preoperative chemotherapy over postoperative chemotherapy (hazard ratio: 0.64, two-sided $P = 0.014$).[69] More mature and detailed results are awaited before considering neoadjuvant chemotherapy as a new standard of care for resectable, localized SCC of the thoracic esophagus. Finally, Thirion and colleagues[70] showed, with an individual patient data-based meta-analysis (9 trials, 2102 patients), a statistically significant survival benefit favoring preoperative chemotherapy (hazard ratio: 0.87, $P = 0.003$) over surgery alone. This 13% relative survival benefit translated into a 5-year absolute survival increase of 4% (from 16% to 20%).[70]

Ten randomized trials have compared chemoradiation and surgery with surgery alone in operable SCC of the esophagus (Table 104-1).[56-79] Two of these trials contained a substantial number of adenocarcinomas.[72,76] All these studies but two, only published as abstracts,[75,78] have failed to show any survival advantage favoring the neoadjuvant approach. However, some of these studies,[72-74,76] as well as retrospective studies,[80,81] have reported the prognostic value of pathologic complete response on overall survival. In fact, most of these trials recruited a small number of patients and were not statistically powered to detect any realistic difference between the different strategies. One of the largest studies has been conducted by the French Foundation of Digestive Cancer (FFCD) and the EORTC.[74] A total of 282 patients with resectable (stages I and II) SCC were randomized to preoperative chemoradiation versus surgery alone. The chemoradiation regimen consisted of a sequential perfusion of cisplatin (80 mg/m^2, 0 to 2 days) followed by an unusual split-course radiation therapy (3.5 Gy × 5, then a 2-week rest and another 3.5 Gy × 5). With a median follow-up of 55 months, patients who were allocated to the multimodality regimen had a significant greater 3-year, disease-free survival (40% vs. 28%, $P = 0.003$) and a higher rate of microscopically complete resection (81% vs. 69%, $P = 0.02$). It is worth noting that these patients also had a higher rate of postoperative death (12% vs. 4%, $P = 0.02$) along with a lack of advantage in terms of survival (median survival: 19 months).[74] A more recent trial with protracted radiation therapy (35 Gy/15 fractions over 3 weeks) combined with a single course of chemotherapy (cisplatin 80 mg/m^2 on day 1 followed by fluorouracil 800 mg/m^2/day on days 1 to 4) also failed to detect a better outcome for patients with resectable esophageal cancer.[76] Even subgroup analysis showed that patients with SCC had better progression-free survival with chemoradiotherapy followed by surgery than with surgery alone (hazard ratio: 0.47 $P = 0.014$). In addition, the trimodality group had more complete resections than did the surgery-only group (R0 resection: 80% vs. 29%, $P = 0.0002$).[76] Two trials have reported a survival benefit from neoadjuvant chemoradiotherapy.[75,78] Walsh and colleagues[75] showed on a small series of 98 SCCs of the esophagus a better median survival for patients treated by chemoradiotherapy followed by surgery (12 m vs. 8 m, $P < 0.02$). These results have to be tempered by the unusually high rate of operative mortality (>17% in both therapeutic arms). Five hundred patients were targeted for enrollment in the Cancer and Leukemia Group B 9781 trial.[78] However, this trial was closed due to poor accrual after a total of 56 patients had entered the study over a 2.5-year period.[78] In this underpowered study the statistical difference, favoring the trimodality therapy group (54 m vs. 22 m, $P = 0.02$) reported by Tepper and colleagues,[78] applied to differences between median survival and was not based on the areas between the two survival curves. Finally, a recent meta-analysis (1209 patients, nine trials) suggested a survival benefit of 19% (OR: 0.81; 95% CI: 0.7-0.93; $P = 0.002$) for concomitant chemoradiotherapy followed by surgery compared with surgery alone. The hazard ratio for death by any cause was 0.84 ($P = 0.04$) for patients with SCC.[82]

Finally, on the basis of the fully published and adequately powered randomized trial, there is little evidence that preoperative chemoradiation may improve survival. On the other hand, preoperative chemoradiation improves resectability (R0 resection) and locoregional control,

Table 104-1

Randomized Trials of Surgery versus Preoperative Chemoradiotherapy in Esophageal Cancer

Reference	SCC	Evaluable Patients	CT	XRT Gy/f/d	Resectability	Operative Mortality	Median Survival	2-Yr Survival	5-Yr Survival	*P* Value
Nygaard 1992	100% 	53 58	CDDP/BLEO	35/20/28	66% 69%	24% 13%	 	23% 13%	 	ns
Apinop 1994	100% 	35 34	CDDP-FU	40/–/–	74% 100%	14% 15%	10 m 7 m	30% 23%	24% 10%	ns
LePrise 1994	100% 	41 45	CDDP-FU	20/10/12	85% 84%	9% 7%	10 m 10 m	 	 	ns
Bosset 1997	100% 	143 139	CDDP	37/10/28	>80% >80%	13% 4%	19 m 19 m	47% 42%	25% 25%	ns
Walsh 2000a	100% 	46 52	CDDP-FU	40/15/21	 	19.5% 13.5%	12 m 8 m	 	36% 11%	*P* = .017
Urba 2001	25% 	50 50	CDDP-FU-VLB	45/15/21	100% 94%	4% 2%	17.6 m 16.9 m	≈35% ≈40%	≈13% ≈20%	ns
Lee 2004	100% 	51 50	CDDP-FU	45.6/38/28	94% 96%	0.5% 0.5%	28.2 m 27.3 m	55% 57%	≈48% ≈40%	ns
Burmeister 2005	37% 	128 128	CDDP-FU	35/15/21	82% 86%	4% 5%	22.5 m 19.3 m	 	 	ns
Tepper 2006a	25% 	30 26	CDDP-FU	50.4/28/35	 	0% 7.5%	54 m 22 m	 	39% 16%	*P* = .02

a, abstract; BLEO, bleomycine; CDDP, cisplatin; CT, chemotherapy; FU, 5-fluorouracil; nb, resectability applies both to curative and palliative resection; ns, nonsignificant; SCC, squamous cell carcinoma; VLB, vinblastine; XRT, radiation therapy.

well-conducted meta-analysis supports improved survival, and neoadjuvant chemoradiation is a commonly used therapeutic approach worldwide. Therefore chemoradiation followed by surgery may be a reasonable alternative to surgery alone in the management of resectable esophageal cancer.

Definitive Chemoradiation

Because several uncontrolled studies on primary unresectable cancer have shown promising activity with chemoradiation with or without subsequent surgery, this procedure has been applied to potentially curable tumors without surgical resection. Seven randomized trials have compared definitive radiation therapy alone with definitive chemoradiation for operable or inoperable esophageal cancer (Table 104-2).[83-91] The RTOG 85-01 study was the only trial realistically designed to deliver adequate doses of systemic chemotherapy (fluorouracil: 1000 mg/m^2 as a continuous infusion × 4 days + cisplatin: 75 mg/m^2 at day 1, every 3 weeks, 4 cycles) with concurrent radiation therapy (50 Gy, 2 Gy/day).[83] At the 5-year follow-up, the latter trial showed a clear survival advantage favoring the combined therapy (26% vs. 0%, $P < 0.001$).[85] These long-term survival data have been confirmed in a subsequent study by the RTOG.[92] Therefore this RTOG 85-01 chemoradiation regimen is currently considered the standard of care for the nonsurgical management of esophageal cancer. However, it is also associated with increased morbidity rates. Compared with radiation therapy alone, patients who received combined modality therapy had a higher incidence of severe toxic events (23% vs. 66%), and chemotherapy could not be completed in more than 40% of the patients.[83,84] A trial from the Eastern Cooperative Oncology Group confirmed this survival benefit when chemotherapy was added to radiotherapy (median survival: 9 m vs. 14.9 m for radiation and chemoradiation, respectively; $P = 0.03$).[89] Because patients were treated according to their physicians' choices (surgery or continued radiation ± chemotherapy) after 40 Gy (± chemotherapy), the results of that pragmatic study are somewhat difficult to interpret. The EORTC trial included 221 patients. Any patients considered inoperable because of general physic condition or because they refused surgery and who fulfilled other classic eligibility criteria including localized SCC entered the study.[91] The chemoradiation regimen consisted of a perfusion of cisplatin (100 mg/m^2) followed 3 or 4 days later by a split-course radiation therapy (4 Gy × 5, then a 2-week rest and another 4 Gy × 5). After a post hoc stratification for clinical stage at entry, the investigators reported a significant difference favoring the combination arm for progression-free survival ($P = 0.048$) and overall survival ($P = 0.028$).[91] On the basis of the available randomized studies and results favoring chemoradiation over radiation therapy alone, it is not surprising that a recent meta-analysis confirmed that chemoradiation over radiation alone provided a significant reduction in local recurrence rate and in mortality (hazard ratio: 0.73).[93] The combined treatment was also associated with a significant risk of severe and life-threatening toxicities.[93]

Investigators have also addressed questions on the intensification of radiation dose (50.4 Gy vs. 64.8 Gy),[92] the scheme of radiation regimen (protracted vs. split),[94] and the optimal chemotherapy regimen (fluorouracil and cisplatin vs. fluorouracil, folinic acid, and oxiliplatin).[95] The RTOG 01-22 (Table 104-3) showed that increasing radiation dose (64.8 Gy vs. 50.4 Gy) with concurrent chemotherapy did not translate into enhanced survival or local control but increased morbidity and mortality rates.[92] The randomized study ($n = 202$ inoperable stage I to III SCC) by Jacob and colleagues[94] reported a significantly better 2-year, disease-free survival with conventional protracted radiation over split-course radiation scheme. Conroy and colleagues[95] investigated the role of a new chemoradiotherapy regimen that includes protracted standard radiation therapy (50 Gy, 25 fractions, 5 weeks)

Table 104-2

Randomized Trials of Definitive Chemoradiotherapy versus Radiotherapy in Esophageal Cancer

Reference	Staging (TNM 1978)	Evaluable Patients	CT	XRT Gy/f/d	Median Survival	2-Yr Survival	5-Yr Survival	*P* Value
Earle 1980	Inoperable	40 37	BLEO	40-60/30/42 40-60/30/42	6.2 m 6.4 m	≈15% ≈10%		ns
Roussel 1989	Inoperable	75 69	MTX	56/25/35 56/25/35	9 m 8 m	≈14% ≈14%		ns
Araujo 1991	T1-2Nx	28 31	MMC/FU/BLEO	50/25/35 50/25/35	≈16 m ≈15 m	38% 22%	16% 6%	ns
Herskovic 1992*	T1-3N0-1	61 62	CDDP/FU	50/25/35 64/32/46	14.1 m 9.3 m	36% 10%	26% 0%	*P* < .001†
Smith 1998†	T1-2Nx	59 60	MMC/FU	40/22/32 or 60/36/46 40/22/32 or 60/36/46	14.6 m 9.2 m	27% 12%		*P* = .04†
Wobbes 2001	T1-3N0-1 inoperable	110 111	CDDP	40/8/28§ 40/8/28§	9.6 m 7.9 m	20% 15%		*P* = .048†
Slabber 1998	T3Nx	34 36	CDDP/FU	40/10/28 40/10/28	≈5.8 m ≈4.8 m	≈5% ≈5%		ns

*See also Al Sarraf and associates[84] and Cooper and colleagues.[85]
†After 40 Gy (± CT), patients were treated according to physicians' choice (surgery or RT ± CT).
‡Log-rank analysis.
§Split course.
BLEO, bleomycin; CDDP, cisplatin; CT, chemotherapy; FU, 5-fluorouracil; MMC, mitomycin; MTX, methotrexate; ns, nonsignificant; XRT, radiotherapy.

Table 104-3

Randomized Comparison between Definitive Chemoradiotherapy Schemes in Esophageal Cancer

Reference	Staging	Evaluable Patients	SCC %	CT	XRT Gy/f/d	Endoscopic Complete Response	Median Time to Progression	Median Survival	2-Yr Survival	*P* Value
Minsky 2002	Stage I-III	109 109	83%	CDDP/FU CDDP/FU	50.4/28/35 64.8/36/45	— —	≈13 m ≈13 m	18.1 m 13 m	40% 31%	ns
Conroy 2007	Inoperable stage I-IVa	44 53	82%	CDDP/FU lohp/FU/FAA	50/25/35 50/25/35	12/40 (30%) 21/47 (45%)	9.4 m 15.2 m	14.9 m 22.7 m	≈30% ≈45%	nd

CDDP, cisplatin; CT, chemotherapy; FA, folinic acid; FU, 5-fluorouracil; lohp, oxiliplatin; nd, not done (randomized phase II); ns, nonsignificant; SCC, squamous cell carcinoma; XRT, radiotherapy.

combined with concurrent and sequential fluorouracil, folinic acid, and oxiliplatin courses (Folfox 4 regimen) (see Table 104-3). The primary end point of this trial was to assess the feasibility and the complete endoscopic response rate of the Folfox 4/radiation combination. Ninety-seven patients with inoperable esophageal cancer (82% of SCC) were randomized to receive either the experimental therapy or the standard treatment, which was the RTOG 85-01 schedule (fluorouracil, cisplatin, and radiation therapy). Definitive chemoradiotherapy with Folfox 4 was found feasible because 75% of the patients completed the planned treatment, whereas 70% of the patients completed the RTOG 85-01 schedule. Of 47 patients, 21 (45%, 95% CI: 30% to 60%) achieved an endoscopic complete response with Folfox 4 compared with 12 of 20 patients (30%, 95% CI: 17% to 46%) with the fluorouracil-cisplatin regimen. Median survival was 22.7 and 14.9 months for the Folfox 4 and the RTOG 85-01 groups, respectively.[95]

Is surgery necessary as part of local therapy in patients with locally advanced esophageal carcinoma?

A series of randomized trials,[75,78,85] as well as uncontrolled studies[96,97] and meta-analyses,[93,98] have confirmed that chemoradiation allows a certain proportion of complete clinical and pathologic responses and long-term survival. These features led researchers to investigate whether surgery is necessary after neoadjuvant chemoradiation.[99,100] The FFCD 9102 trial[99] (Table 104-4) compared chemoradiation alone with chemoradiation followed by surgery in patients with operable T3N0-1M0 thoracic esophageal cancer who responded to a first course of chemoradiation. Four hundred and fifty-five patients (SCC: 89%) received radiation therapy (either conventional 46 Gy in 4.5 weeks or

Table 104-4

Is Surgery Necessary As Part of Local Therapy in Patients with Locally Advanced Esophageal Carcinoma? Randomized Studies

Reference	Patients	Evaluable Patients	Sequential CT	Concurrent CT	XRT	Surgery	2-Yr Relapse-free Survival	Median Survival	2-Year Survival
Stahl 2005	Operable T3-4N0-1M0	86 86	CDDP/FU/AF/VP16 CDDP/FU/AF/VP16	CDDP/VP16 CDDP/VP16	50-65 Gy over 5-6 weeks, plus a boost (HF-EBRT or HDR-B)	No Yes	64.3%† 40.7%†	16.4 m 14.9 m	35% 40%
Bedenne 2007	Operable T3N0-1M0	130* 129*		CDDP/FU	20 Gy over 2 weeks or 1-week course of 15 Gy	No Yes	40% 43%	≈19 m ≈18 m	40% 34%

*A first cohort of 444 eligible patients has been treated with chemoradiation (either conventional 46 Gy in 4.5 weeks or split-course 15 Gy × 2, days 1 to 5 and days 22 to 26, in conjunction with two courses of FU and CDDP). Patients with response (n = 259) were randomly assessed to surgery or continuation of chemoradiation.
†Local 2-year relapse-free survival.
CDDP, cisplatin; CT, chemotherapy; FA, folinic acid; FU, 5-fluorouracil; HDR-AL, high-dose rate brachytherapy; HF-EBRT, hyperfractionated external-beam XRT; VP16, etoposide; XRT, radiotherapy.

split-course 15 Gy × 2, days 1 to 5 and days 22 to 26) in conjunction with two cycles of fluorouracil and cisplatin. The 259 responding and still operable patients were randomly assigned to surgery or continuation of chemoradiation (conventional or split-course radiation) with three further courses of chemotherapy. The 2-year local control rate was 66.4% in the surgery arm compared with 57% in the chemoradiation arm. A 2 years the survival rate was 34% for the surgery arm versus 40% for the chemoradiation arm.[99] The quality-of-life study did not show any difference between the two arms.[101] Indeed, hospital stay was shorter in the chemoradiation arm. Conversely, patients in the surgery arm had fewer needs in esophageal stenting (13% vs. 27%, P = 0.005).[99] According to the authors, chemoradiation with or without surgery resulted in similar survival rates for locally advanced thoracic esophageal cancer patients responding to chemoradiation.[99] One hundred and seventy-seven patients with locally advanced SCC (T3-4, N0-1, M0) have been randomized in a German study[100] (see Table 104-4) in order to compare sequential and concurrent chemoradiation only with sequential and concurrent chemoradiation followed by surgery. The chemoradiation-only group of patients received three courses of sequential fluorouracil, folinic acid, cisplatin, and etoposide followed by one course of cisplatin and etoposide combined with radiation (50 to 65 Gy, 2 Gy per fraction, 5 to 6 weeks, plus a boost with either bifractioned external-beam radiation or high-dose rate brachytherapy). In another group, patients received the same neoadjuvant chemotherapy, followed by one course of cisplatin and etoposide with concurrent radiation (40 Gy, 2 Gy per fraction, 4 weeks), followed by surgery. Two toxic deaths in each arm were attributed to chemotherapy, but no fatalities related to chemoradiation occurred. Postoperative deaths occurred in 62 patients who underwent surgery. Despite improved local control (2-year freedom from local progression: 64% vs. 41%, P = 0.003), surgery after radiotherapy and sequential and concurrent chemotherapy resulted in equivalent survival (intent-to-treat analysis) compared with chemoradiation alone. Median survival was 16 and 15 months for the multimodality treatment and chemoradiation alone, respectively. Cox regression analysis revealed that response to induction chemotherapy was the single independent prognostic factor (hazard ratio: 0.30, P < 0.0001), regardless of the group of treatment.[100] From these results[100] and those from the FFCD[99] group, there is now a body of evidence suggesting that in patients with locally advanced SCC there is no survival benefit for adding surgery to chemoradiation. However, local control still represents an issue; persistent local disease is present in about 40% of the patients treated with chemoradiation only,[83,84] and median time to locoregional recurrence after sequential and concurrent chemoradiotherapy is about 14 months.[100] Whether or not salvage surgery should be offered to nonresponding patients is still a matter of clinical research.

Metastatic Squamous Cell Carcinoma of the Esophagus

The amount of chemotherapeutic agents with activity against advanced squamous cell esophageal cancer is rather limited, but responses have been documented using cisplatin, fluorouracil, vindesine, mitomycin, irinotecan, oxiliplatin, paclitaxel, and vinorelbine. Various combinations of these molecules were shown to be associated with higher response rates but also higher morbidity and in some cases with 10% to 14% of toxic deaths. Among the available regimens, the cisplatin-vinorelbine combination seems to fit the best therapeutic ratio in metastatic SCC.[102] However, we still do not know if chemotherapy provides any benefit in terms of survival versus best supportive care.[103] One randomized trial from the EORTC gastrointestinal group has examined the activity of cisplatin (100 mg/m^2, q 3 weeks) versus cisplatin (same dosage) plus fluorouracil (1000 mg/m^2 as a continuous infusion from day 1 to day 5, q 3 weeks) in 88 evaluable patients with advanced SCC. Although greater activity was demonstrated for the cisplatin-fluorouracil combination (response rate: 35% vs. 19%, median survival: 33 vs. 28 weeks), this was achieved at the expense of substantially increased toxicity. The randomized phase II study concluded that neither arm could be recommended as the standard chemotherapy for patients with advanced SCC.[104] Another randomized study compared cisplatin-fluorouracil with no chemotherapy in 156 patients. Again, there was no difference in survival but an increase of adverse events in the chemotherapy arm, which resulted in toxic deaths in 6% of this frail population.[105]

SUGGESTED READINGS

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CHAPTER ONE HUNDRED AND FIVE

Reconstruction of the Hypopharynx and Esophagus

Douglas B. Chepeha

Key Points

- To obtain the best outcome for the patient, perform pharyngoesophageal reconstruction as part of a knowledgeable multidisciplinary team.
- Hypopharyngeal defects are associated with the highest surgical complication rates in the head and neck.
- Careful monitoring of thyroid-stimulating hormone and optimization of nutritional status improve wound healing outcomes.
- Use of the salivary bypass tube reduces the incidence of stenosis and helps reduce the impact of fistula.
- Careful defect assessment before surgery is important for planning the appropriate reconstructive approach.
- In patients with a history of chemoradiation therapy, vascularized tissue is useful for reducing complications even if a primary pharyngeal closure is performed.
- If a fistula develops and the great vessels are exposed, creation of a controlled fistula is the best way to make the wound safe.
- A pedicle monitoring plan should be integrated into revascularized free tissue transfer for reconstruction of pharyngeal defects.

Many technical advances in conservation surgery of the larynx and pharynx have occurred, and new treatment protocols for organ preservation with chemotherapy and radiation have developed. Current management of advanced-stage laryngopharyngeal and esophageal cancers generally involves multiple modalities to optimize outcomes. At present, there is a trend toward reserving surgery as a salvage procedure after failure of other modalities for advanced laryngeal and hypopharyngeal cancers (Fig. 105-1).[1-5] The adverse effects of radiation therapy on wound healing have been well documented.[6] Salvage surgery in patients exposed to previous radiotherapy and/or chemotherapy is associated with a higher incidence of wound complications, with overall complication rates ranging from 37% to 100%.[7] For example, postoperative salivary fistula rates as high as 50% have been reported after surgical salvage for persistent disease after chemoradiation therapy.[8] Therefore prior treatment must be taken into consideration when choosing a reconstructive method for patients who undergo salvage surgery. Given the high complication rate with surgical salvage, treatment selection may be a better choice to reduce the incidence of surgical complications.[9] Treatment selection makes use of induction chemotherapy to determine the responsiveness of a tumor. If the tumor responds (shrinks) by more than 50% to one or two doses of chemotherapy, then the patient undergoes chemoradiation therapy. If the tumor does not respond, the patient undergoes surgery followed by radiation therapy (Fig. 105-2). The possible advantage of treatment section is customization of therapy and avoidance of surgical salvage with its attendant complications. Reconstruction of the hypopharynx and esophagus is largely being shaped by the current trend toward primary concurrent chemoradiation therapy. The surgeon is most commonly involved in salvage of treatment failure, which is resulting in new approaches that attempt to reduce complications and improve function in this compromised patient group.

Patient Population at Presentation

Most patients who require reconstruction of the hypopharynx and esophagus harbor a malignancy at those sites. At the University of Michigan, patients present for reconstruction of their hypopharynx or cervical esophagus after failure of chemoradiation for advanced-stage squamous cell carcinoma of the larynx, pharynx, or trachea. Primary resection is reserved for patients who present with laryngeal cartilage invasion or those who do not respond to induction chemotherapy. Patients who undergo surgical resection and pharyngeal reconstruction have the highest postsurgical complication rate when compared with any other site in the upper aerodigestive tract.[10] Carcinomas of the larynx tend to be less aggressive than carcinomas of the hypopharynx. Hypopharyngeal carcinomas are known to demonstrate aggressive behavior, with a high incidence of submucosal spread, satellite lesions, and subsequent invasion of adjacent structures. Careful assessment of the lungs is also important. A solitary focus of disease in the lung can be resected, but more extensive metastatic disease or mediastinal disease would make the patient incurable and a palliative approach would be taken. This patient population has a high prevalence of tobacco and alcohol abuse and often has related comorbidities such as cardiovascular disease, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, and nutritional deficiency. Because of these underlying comorbidities and the disease process, treatment of this patient population is more difficult. Trauma from explosive devices or accidents, previous radiation or chemoradiation resulting in stenosis, or chemicals (e.g., lye ingestion injury) is another possible cause for reconstruction of the hypopharynx and esophagus.

Perioperative Counseling

Nursing, social work, speech pathology, dentistry, cessation counseling, nutrition, and appointment scheduling are all part of the pretreatment

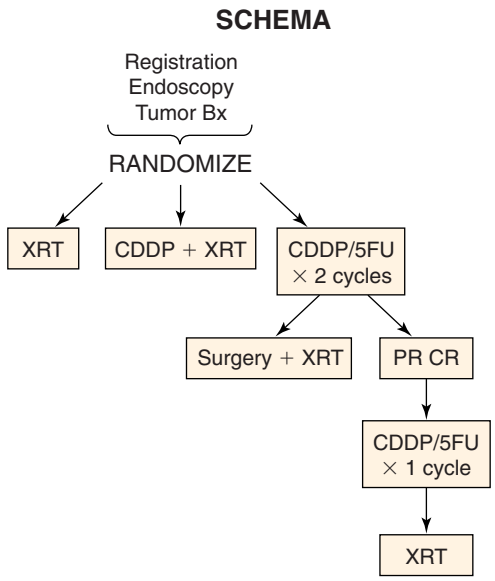

Figure 105-1. Schema of 91-11, 3-arm, randomized, multi-institutional phase III trial for the treatment of advanced laryngeal cancer. The 5-year overall survival of the chemoradiation arm was the best. As the trial progresses through 5- to 10-year follow-up, the treatment selection arm has, nonstatistically significant, better overall survival than the chemoradiation arm. If laryngeal resection can be performed before chemoradiation, the surgical reconstruction will be more straightforward. Note that this trial excluded patients with cartilage invasion. Bx, biopsy; CDDP, cisplatinum; CR, complete response; 5FU, 5 fluorouracil; PR, partial response; XRT, external beam radiation therapy.

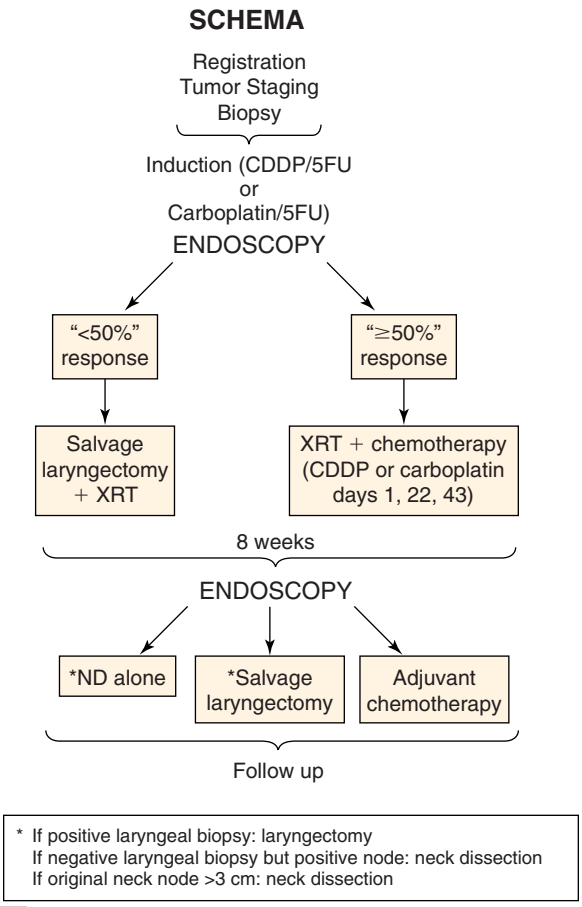

Figure 105-2. Schema of UMMC 9520, single-arm, single institution, phase II selection trial for the treament of stage III to IV laryngeal cancer. The 5-year survival was better than any arm in the 91-11 study. The selection arm in 9520 used concomitant chemoradiation therapy for responders and surgery with radiation therapy for nonresponders. The goal was to customize therapy and avoid surgical salvage after chemoradiation therapy. Note that the trial included patients with cartilage invasion. CDDP, cisplatinum; 5FU, 5 flourouracil; ND, neck dissection; XRT, external beam radiation therapy.

workup. Because of the many disciplines involved, the treatment and rehabilitation experience can be bewildering for the patient. This has put the nurse clinical coordinator at the core of the patient care experience. It is not uncommon for these patients to have a poor predisease diet that, when coupled with a painful obstructive disease process involving the upper aerodigestive tract, can lead to significant malnutrition. Preoperative counseling with the speech pathologist is an essential part of patient education and shaping expectations. The speech pathologist is often regarded by the patient as the individual who will restore function post treatment. The greatest counseling challenge in this patient group is overcoming poor coping skills.[11] The speech pathologist must contend with the patient's coping mechanisms in order to assist rehabilitation. Psychosocial counseling, which speech pathologists often do on an "ad hoc" basis, has been shown to benefit head and neck cancer patients when compared with controls.[12] The speech pathologist must describe the expected long-term functional outcomes, identify the communicative and swallowing strategies that will be necessary, and indicate his or her interest in supporting the patient throughout treatment and rehabilitation. An addicted patient is unlikely to be effectively rehabilitated. Smoking is highly correlated with alcohol intake and depression. Smoking cessation interventions, particularly those that take into consideration alcohol intake and depression, have been shown to be efficacious for this patient population.[13] The patient must understand that continuation of addictive behaviors represents the greatest risk to survival and future functioning. It is important to emphasize that there are many different ways to quit smoking, that alcohol is a facilitator, and that nicotine is not a carcinogen. Use of patient volunteers who have completed treatment are an important resource. They provide education and experience with regard to post-treatment recuperation and long-term quality of life to patients who are preparing for treatment.

For rehabilitation to be effective, the patient's social, psychologic, and addictive behaviors must be assessed and treated. Many of these patients have addictions to tobacco and alcohol at presentation and may lack social support. All these issues should be comprehensively addressed, and in so doing, providers and patients are often rewarded by the productive role the patients assume for themselves, for their families, and in the workplace.

Preoperative Evaluation

A thorough preoperative evaluation including endoscopy and radiographic studies must be performed to assess the extent of the primary tumor and to detect the presence of regional or distant metastasis. Particular attention must be given to a complete esophagoscopy. The degree of involvement of the cervical esophagus should be assessed carefully, keeping in mind the propensity for submucosal spread and skip lesions. The presence of a tumor in the esophagus must be ruled out because it may necessitate a total esophagectomy. It is generally not possible to preserve the larynx with advanced lesions, although laryngeal-sparing surgery may be an option for a select few patients. Partial laryngeal procedures and the associated reconstructive approaches are discussed in another chapter. The ideal margin for hypopharyngeal lesions is still controversial. Some authors advocate distal margins of up to 3 to 6 cm as long as there is no evidence of disease in the remaining esophagus.[14-17] Although routine total esophagectomy had been recommended in the past for management of carcinoma involving the hypopharynx, this approach is no longer the standard of care.[18] The esophagus is removed only for adequate margin or direct involvement. If the patient has been previously treated with chemotherapy and radiation therapy, the quality of the cervical skin can be poor. The skin may need to be replaced as part of the reconstructive procedure. It is also

important to assess thyroid function preoperatively because the patient can be hypothyroid due to prior radiation. Hypothyroidism causes delayed healing and contributes to postoperative wound complications.

Goals and Principles of Reconstruction

The goals of reconstruction are a healed wound with protection of the great vessels, restoration of a pharyngeal conduit, protection of the airway, and rehabilitation of the voice. The principles of pharyngeal reconstruction are (1) if the area has undergone prior chemoradiation therapy, vascularized tissue from outside of the radiation field should be used to close or re-enforce the pharyngeal closure; (2) if the pharyngeal reconstruction needs to be tubed, the thickness of the tissue should be less than or equal to 2 cm; (3) if aspiration pneumonia is affecting the patient's quality of life, the trachea has to be separated from the aerodigestive tract; (4) if the patient is going to be fitted with a tracheoesophageal speech prosthesis, a cricopharyngeal myotomy needs to be performed; (5) if there is risk for stenosis after reconstruction, then a salivary bypass tube needs to be inserted; and (6) if there is concern about pharyngocutaneous fistula, then a salivary bypass tube should be inserted.

Defect Classification

Pharyngoesophageal defects are classified according to the amount of pharyngeal (partial, near total, and total), oropharyngeal (base of tongue, lateral pharyngeal wall, posterior pharyngeal wall, soft palate), esophageal, and skin involvement. Partial pharyngeal defects are those arising from the extirpation of a larynx that may include some pharyngeal mucosa and can be closed primarily without stenosis or require a small graft to reconstruct less than 50% of the circumference of the pharynx. Near-total pharyngeal defects are defects in which only a thin strip of pharynx (≈1 cm) remains and requires a graft to reconstruct more than 50% of the circumference of the pharynx. Total pharyngeal defects are those in which there is complete absence of a segment of the pharynx. For the purposes of this chapter, we do not discuss partial laryngeal defects or reconstruction of hypopharyngeal defects with an intact larynx because this topic is covered elsewhere. Anecdotally, there have been numerous attempts to reconstruct hypopharyngeal defects with an intact larynx. Interestingly, there are no published case series. Drawing from the author's experience and discussions with colleagues, there does not seem to be a reliable and reproducible technique. This reconstructive issue needs more investigation. Defects that extend into the oropharynx may need additional reconstructive planning. Particularly those defects that involve the soft palate will require a pharyngoplasty and additional tissue to resurface the palate and tonsil.[19] Defects of the tonsil can generally be closed primarily. Associated defects of the tongue base can be partial or total. Partial defects that involve up to 50% of the tongue base do not require reconstruction. Primary closure of these defects is achieved by advancing the tongue base across the defect and suturing it to the resected edge of the oropharynx. This approach results in a sensate, functional tongue base reconstruction. Defects of the entire tongue base are more concerning and may require reconstruction with a graft, particularly if the patient has a near total or total pharyngeal defect and is post chemoradiation therapy. Although it has been suggested that patients who have undergone hemilaryngectomy do not require reconstruction of the base of the tongue, loss of the entire tongue base diminishes the ability of the patient to propel the bolus through the pharyngeal segment and can limit dietary intake to thin liquids. If the resection of the pharynx extends into the mediastinum and a reliable distal anatomosis cannot be sutured, then a visceral transposition is the reconstruction of choice. For a visceral transposition, the patient will undergo a complete esophagectomy, dissection of the mediastinum, and an open abdominal approach. The cervical skin needs to be assessed for tumor involvement and viability. A cervical skin defect in combination with a pharyngeal defect significantly affects reconstructive decision making.

Reconstructive Decision Making

Reconstruction of the hypopharynx and cervical esophagus is associated with a high risk of morbidity and mortality. A wound at this site can expose the carotid and internal jugular vein, which can lead to life-threatening hemorrhages. Wound breakdown of the common wall between the trachea and esophagus usually results in aspiration pneumonia and is associated with a high mortality rate. Hypopharyngeal reconstruction should be designed to make a wound safe and provide a pharyngeal conduit that assists swallowing and speech. If the only priority of the reconstructive surgeon was a safe wound, then exteriorization of the upper aerodigestive tract with a pharyngostome, esophagostome, and tracheostome would ameliorate nearly all of the associated wound complications. The patient is interested in more than a safe wound and wants to return to pretreatment levels of social interaction and occupation. For this reason, reconstructive surgeons reconstruct the pharynx despite the attendant risk and measurable mortality. Fortunately, there are many reconstructive options for hypopharyngeal reconstruction (Fig. 105-3A and B). These options include local and regional cervical skin flaps, deltopectoral flap, pectoralis flap, latissimus flap, gastric transposition, colonic interposition, revascularized fascial flaps, and the gastro-omental flap. The following factors must be considered when choosing a reconstructive option:

1. The condition of the local tissue, which includes the pharynx and the overlying cervical skin. If the local tissue is compromised by chemoradiation therapy or the patient has radiation chondritis, then nonradiated vascularized tissue should be used in the wound.[20,21]

2. The likelihood of a total versus a partial versus a primary hypopharyngeal closure.

3. The likelihood of extension into the esophagus.

4. The likelihood of oropharyngeal extension.

5. The vascular access in the cervical region.

6. The overall comorbid status of the patient.

7. The thickness of the donor site. Patients who present for hypopharyngeal reconstruction are rarely obese, but if they are, adjustments in donor site choice must be made. Thick cutaneous tissue will not make a good tube. If the patient does not have a good cutaneous donor site, the jejunum can be considered if there are not other comorbid conditions.

Voice rehabilitation also needs to be addressed with respect to primary versus secondary tracheoesophageal puncture (TEP). If the patient is high risk or the reconstructive plan was not appropriate given the intraoperative findings, the patient can be closed with a pharyngostomy, an esophagostomy, and a tracheostomy. This is a safe, staged approach.

Local and Regional Skin Flaps

From 1877 through 1904 Czerny, Mikulicz, and Trotter[22,23,24] described the first techniques to restore continuity to the pharynx. These procedures were multiple-stage procedures that used cervical skin flaps for reconstruction. In the 1940s Wookey improved on these techniques when he used a two-stage repair for pharyngoesophageal defects with a laterally based rectangular cervical flap. In the first stage the cervical skin was redraped over the prevertebral fascia and was interposed between the pharyngeal and cervical esophageal stomas to create the posterior wall of the pharyngeal reconstruction.[25,26] The approach exteriorized salivary and gastric secretion, protected the vascular sheath, and controlled infection. The continuity of the pharynx and cervical esophagus was returned at a second stage, usually 2 or 3 months later. Rectangular skin flaps with a base along the reconstructed posterior pharyngeal wall were fashioned from the cervical skin, on the right and left sides. These flaps were tubed and closed vertically in the midline to create a skin-lined pharyngoesophageal segment. A skin graft was placed on the reconstructed pharynx and the donor sites of the rotated cervical flaps. All these methods that used local skin flaps required multiple steps and were associated with a high frequency of complications. Although this approach created a safe wound, the functional outcomes of speech and swallowing were compromised because of the

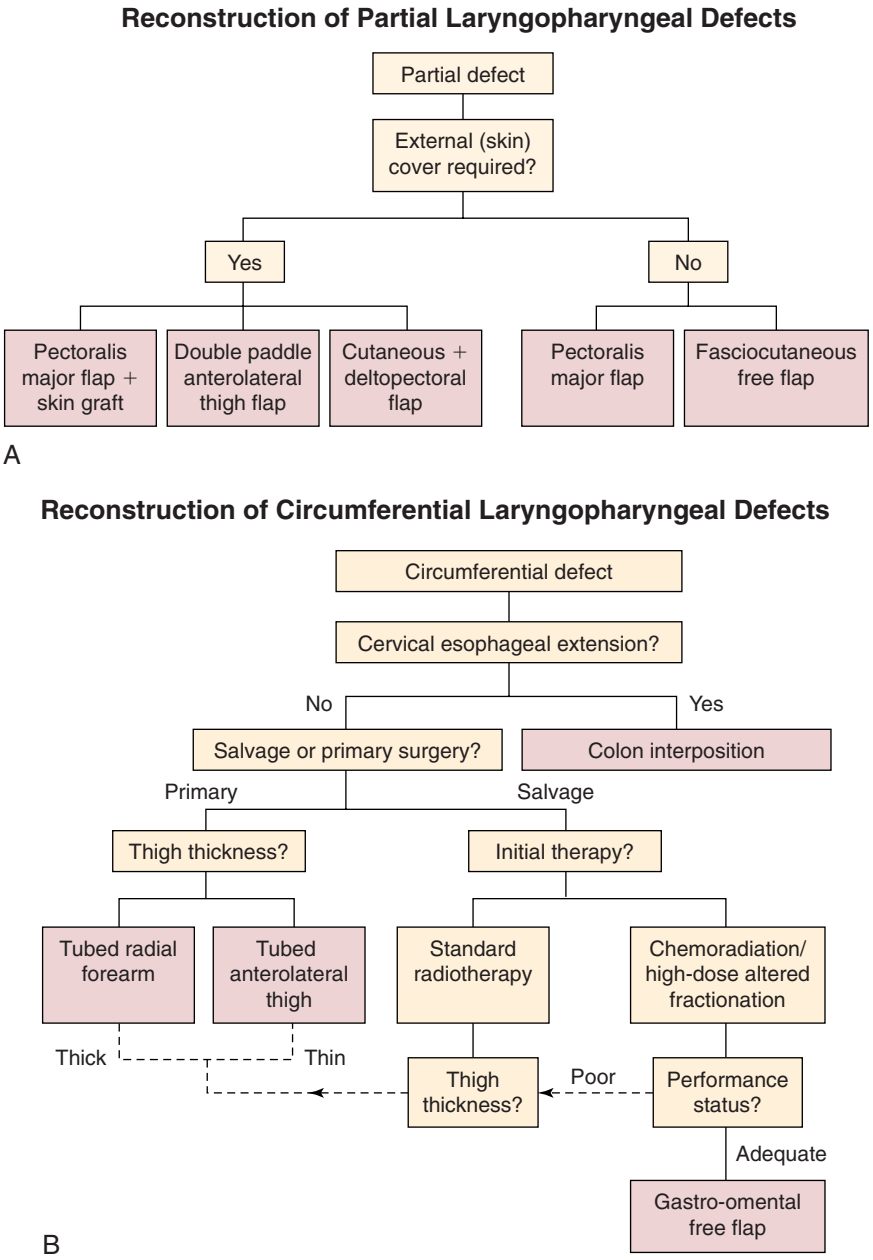

Figure 105-3. **A,** Decision tree for partial pharyngeal defects. Note that the decision tree does not include a decision point for patients who have salvage surgery after chemoradiation therapy and undergo primary closure of the pharynx. For these patients, a vascularized pharyngeal interposition graft is suggested to support the primary pharyngeal closure. **B,** Decision tree for total pharyngeal defects. *(**A** and **B** adapted from Clark JR, Gilbert R, Irish J, et al. Morbidity after flap reconstruction of hypopharyngeal defects.* Laryngoscope. *2006;116(2):173-181.)*

difficulty of reconstructing a pharynx that would not fistulize or stenose. The use of radiation increases the complication rate of this reconstructive approach. Although it is important to be aware of this approach, it is largely of historical interest. The concept of a two-layer closure, one for the pharynx and one for neck cervical skin, using local flaps for mature pharyngocutaneous fistula has its conceptual roots in this approach. To improve the success rate of pharyngeal closure, nonradiated tissue with an axial blood supply was necessary.

The description of the deltopectoral flap by Bakamjian in 1965 represented a significant advance over previous methods.[27] Unlike local flaps that rely on a random blood supply, this regional chest skin flap is based on a more reliable axial-pattern blood supply through the perforating branches of the internal mammary artery. It provides well-vascularized tissue from a donor site that lies outside of the typical radiation fields used for head and neck cancer. The deltopectoral flap has a consistent vascular supply and can be reliably used without the need for surgical delay of the flap if limited to the area medial to the deltopectoral groove. This donor site continues to evolve. New approaches involve mobilizing the internal mammary artery by removing the costochondral junction to improve the mobility and transposability of the flap.

Like the Wookey approach, the deltopectoral flap is a multistage procedure requiring the initial creation of a controlled fistula. In the case of the deltopectoral flap, it is used to form the pharyngeal tube and the cervical skin is draped over the deltopectoral inset. At the first stage, a medially based skin flap is elevated and tubed to the superior cut edge of the pharyngeal resection. The posterior wall of the inferior cut edge was sutured to the deltopectoral flap, and a controlled fistula was fashioned with the anterior wall of the inferior edge of pharyngeal resection. The flap pedicle was divided at least 6 weeks later, along with closure of the fistula and skin grafting to the donor site. The deltopectoral flap was an improvement, but there remained an unacceptably

Figure 105-4. A right deltopectoral flap rotated into ipsilateral neck as a second-layer closure for repair of a pharyngeal cutaneous fistula, which occurred after a total laryngectomy. The stoma seen in the photo is the tracheostoma, and the deltopectoral flap is shown after transposition and inset into the recipient bed.

high rate of fistula formation, flap necrosis, and stenosis. Given these limitations, this approach is not commonly used, although these techniques may still occasionally be useful in certain patients who have failed or are unable to undergo alternative reconstructive approaches. At present, this donor site is most commonly used for the closure of a fistula after hypopharyngeal reconstruction (Fig. 105-4).

Myocutaneous Flaps

The development of regional myocutaneous flaps such as the pectoralis flap and the latissimus flap decreased surgical complications, improved outcomes, and introduced single-stage reconstruction of hypopharyngeal defects. The myocutaneous flaps were described for head and neck reconstruction in the early 1970s by Ariyan, Baek, and other researchers. The use of these flaps for hypopharyngeal reconstruction became the treatment of choice by the 1980s. The pectoralis and latissimus myocutaneous flap allows immediate, single-stage reconstruction of hypopharyngeal defects that would previously have required multiple stages and an extended wound healing period. However, these myocutaneous flaps are thick and are difficult to form into a tube. This characteristic makes them a good alternative for partial pharyngeal defects but not as effective an alternative for total or near total hypopharyngeal defects. The myocutaneous flaps made hypopharyngeal reconstruction less difficult for the surgeon and the patient. They reduced wound complications, but the wound healing and functional results were not satisfactory in total and near total defects.

The pectoralis major muscle primary blood supply derives from the perforating vessels from the pectoral branch of the thoracoacromial artery, with secondary contributions from the lateral thoracic artery and parasternal perforators from the internal mammary artery. A skin paddle of sufficient size to close the pharyngeal defect is designed over the inferior medial portion of the muscle. The pectoralis major muscle with its investing fascia is elevated, and the flap is then transposed over the clavicle into the neck through a widely undermined subcutaneous tunnel. Closure of the donor site can often be accomplished primarily, although a skin graft may be required for larger defects. An inframammary incision with a lateral approach will reduce deformity and preserve the deltopectoral flap. A lateral approach allows for identification of the lateral edge of the pectoral muscle. A subpectoral pocket can be fashioned similar to the approach for placement of breast implants. Once a subpectoral pocket is created, the origin of pectoral muscle can be directly visualized and the skin paddle can be positioned in an optimal location to maximize vascularity. The pectoralis myocutaneous flap had adequate pedicle length to rotate into pharyngeal and adjacent tonsil and base of tongue defects. It is important to cut the lateral pectoral nerve, which is adjacent to the pedicle, and the medial pectoral nerve, which is more lateral and closer to the humeral insertion. The maneuver prevents volitional contraction of the muscle once it has been positioned in the defect.

The latissimus dorsi myocutaneous flap is a larger, thinner, more reliable flap than the pectoralis myocutaneous flap. It is used less frequently because it is located laterally on the thoracic cage, requires semi-decubitus patient positioning on the operative bed, and requires pedicle dissection. The same vessel dissection is performed for the elevation of the rotational flap and the free revascularized transfer. When rotating a latissimus flap, the following advice can prevent kinking or traction, or both, of the pedicle.

1. The pedicle needs to be dissected to the axillary artery and vein.
2. The subscapular artery and vein need to be ligated.
3. The tunnel needs to be deep to the sternal head of the pectoralis muscle.
4. The tunnel goes through the superior aspect of the clavicular head of the pectoralis muscle.
5. The pedicle needs to have a gentle curve as it branches from the axillary vessels.
6. The branches of the pedicle need to be ligated with suture to minimize the likelihood of a hemorrhage from the pedicle in the tunnel because Ligaclips can be torn or cause kinking of the pedicle in the tunnel.
7. The flap should be placed in a plastic bag used for visceral transposition to assist with transposition through the tunnel.
8. The latissimus muscle in the flap should not be innervated once the flap has been interposed.
9. The humeral head should be sutured to the clavicle to prevent excessive traction on the pedicle during inset.
10. Postoperatively, the patient's arm should be elevated on a pillow to prevent compression of the pedicle.

The primary use of the myocutaneous flap is for reconstruction of partial pharyngoesophageal defects. A strip of pharyngeal mucosa is left so that a complete tubing of the myocutaneous flap may be avoided.[28] However, it may be the only option for patients with poor cardiopulmonary status who cannot tolerate prolonged surgery or the combined violation of thoracic and abdominal cavities. It is also a good option for those who do not have suitable recipient vessels for free tissue transfer because of previous radical surgery. The pectoralis flap may be most useful as a salvage flap for extra soft tissue, for carotid protection as a myofascial flap, or as a reinforcing layer in previously irradiated patients to minimize the chance of fistula formation.[29] Voice can be successfully restored in patients reconstructed with pectoralis myocutaneous flaps.[30]

Many modifications have been proposed to maximize the usefulness of the pectoralis myocutaneous flap for near total or total pharyngoesophageal reconstruction. Due to newer reconstructive techniques, these modifications have less clinical utility. However, they are important to know as alternatives to conventional reconstructive approaches. These modifications include harvest of the flap as a myofascial flap, thereby avoiding the often excessively bulky subcutaneous tissue that makes tubing of the myocutaneous flap difficult. The difficulty with this approach is stenosis. To our knowledge this approach is no longer used. Alternately, the pectoralis flap can be partially tubed 270 degrees around and closed to prevertebral fascia that has been grafted.[31] When the pectoralis flap is used for reconstruction of circumferential defects, it is associated with stricture formation at the distal anatomosis. Stricture formation after pharyngoesophageal reconstruction with the pectoralis flap has been reported in 35% of patients.

Some surgeons have suggested that a disadvantage of myocutaneous flaps is a relatively high rate of fistula formation. Fistula formation in hypopharyngeal reconstruction is more likely to be related to the history of prior chemoradiation therapy or use of the myocutaneous flap in a defect that is too large for the primary angiosome. Myocutaneous flaps are ideal for defects limited to the hypopharynx. It can also be useful if there is a combined cervical defect because the muscle can be skin grafted to resurface the cervical skin and the cutaneous portion of the flap can be used to resurface the hypopharynx.[32] The pectoralis flap is also useful in chemoradiation patients for the reinforcement of the primary closure to reduce fistula formation. A pectoralis flap is often inadequate at closing a defect extending into the superior-lateral oropharynx or nasopharynx. Other potential disadvantages of the pectoralis flap include the risk of shoulder dysfunction, particularly in patients who have undergone neck dissection.

Visceral Transposition

Visceral transposition is reserved for the reconstruction of lesions that extend past the cervical esophagus. Because of morbidity and mortality associated with laparotomy, dissection of the mediastinum, and resection of the esophagus, these procedures are only performed when necessary. Colon transposition has likely surpassed gastric transposition as the most frequently performed visceral transposition procedure for lesions extending into the thoracic esophagus. Because these procedures are infrequently performed, there is limited reporting on current treatment paradigms. Colon interposition is a more desirable technique because it is reliable and leaves the stomach in its anatomic position, which reduces regurgitation and eliminates gastric dumping. Both the colon and stomach are patulous, which leads to difficulty with restoration of voice with a tracheal esophageal puncture prosthesis. In this patient group an artificial electric larynx is more frequently necessary for effective voice production.

Gastric Transposition

In 1960 Ong and Lee[33] were the first to describe gastric transposition with pharyngogastric reconstruction. They used a transthoracic approach for the single-stage reconstruction after pharyngoesophagectomy. At present, the "gastric pull-up" technique is performed without thoracotomy in favor of blunt esophageal dissection to reduce the high morbidity and mortality associated with simultaneous violation of the thorax and abdomen.

Gastric transposition offers many of the ideal elements for pharyngoesophageal reconstruction: It provides a reliable, single-stage restoration of alimentary continuity by use of well-vascularized tissue from a donor site that is remote from the field of radiation. Significantly, it allows complete removal of the esophagus, thereby eliminating the dangers of unappreciated submucosal extension or a synchronous tumor in the distal esophagus. There is only one visceral anastomosis, which is generally located in the neck, thereby decreasing the possibility of stricture, fistula, and postoperative mediastinitis. Before the mastery of microvascular techniques, gastric transposition was regarded as the procedure of choice for hypopharyngeal lesions because it was a relatively simple and reliable technique that allowed most patients to swallow with timely healing and reasonable morbidity.

Gastric transposition (gastric "pull-up") is performed with a two-team approach. The stomach is approached through an upper midline laparotomy incision. Blood supply to the stomach is maintained through the right gastric artery and its gastroepiploic arcade. A pyloroplasty and a vagotomy are also often performed to promote gastric emptying postoperatively. The entire esophagus is then mobilized by blunt bimanual dissection. Great care must be taken to avoid injuring the posterior membranous tracheal wall during this maneuver. Next, the proximal stomach is transposed into the neck through the posterior mediastinum. The pharyngogastric anastomosis is sutured in a two-layered fashion. A feeding jejunostomy tube is commonly placed to allow for enteric alimentation until oral feeding can be started. Oral intake can usually begin within 10 to 14 days.

The major disadvantage to gastric transposition is the relatively high rate of morbidity and mortality associated with a procedure that involves three surgical fields. Wei and colleagues[17] recently reviewed the trends in gastric transposition surgery in their series of 317 patients operated on over a 30-year period. There was a significant reduction in their perioperative mortality from 31% to 9%, as well as a decrease in fistula rates from 23% to 9%. Their review of the literature demonstrated a 16% overall mortality rate in studies reporting on series of 10 or more patients. They also reported an overall complication rate of approximately 50%, of which most were minor. Pulmonary complications are common including pulmonary effusion, pneumothorax, and pneumonia. Permanent hypoparathyroidism is often unavoidable, necessitating chronic calcium replacement. Previous gastric surgery, peptic ulcer disease, significant cardiopulmonary disease, and cirrhosis are contraindications to this technique. Occasionally, the stomach cannot be mobilized sufficiently to bridge a defect extending superiorly into the oropharynx or nasopharynx.

Other disadvantages to gastric pull-up include frequent abdominal discomfort and dysfunction in the immediate postoperative period including regurgitation of bile and/or food, distention, and diarrhea. Both gastric dumping and gastric outlet obstruction have also been observed. Many of these symptoms will subside over time; regurgitation can be minimized if the patient eats small, frequent meals in an upright position.

Successful voice rehabilitation has been reported in patients with pharyngogastric repair after pharyngolaryngoesophagectomy. Voice quality after gastric pull-up tends to have a wet or gurgling quality.

Colonic Transposition

Goligher and Robin[34] detailed their use of a pedicled segment of colon to reconstruct a defect after pharyngolaryngectomy and cervical esophagectomy in 1954. This technique provides a single-stage method of reconstruction with a smooth, mucosa-lined tube. A section of colon is mobilized in the abdomen, and this can be performed at the same time as the resection in the head and neck. The colon is pedicled on the inferior mesenteric artery. After a section of colon has been mobilized, the remaining colon is closed primarily. The colon is transposed and one end is anastomosed to the fundus of the stomach, while the other end is anastomosed to the remnant of the upper aerodigestive tract. The colon is brought from the abdominal cavity to the upper aerodigestive tract along the path of the esophagus. The esophagus is dissected bluntly just as with the esophagectomy performed for a gastric transposition. By using this technique, a thoracotomy is avoided. If the colon appears to be poorly vascularized when it is transposed into the neck, the associated artery and vein can be anastomosed to a recipient artery and vein in the neck, which is rarely necessary.

The advantages of the colon are its ability to extend easily to the oropharynx, which reduces tension on the anastomosis (Fig. 105-5). The result is a lower rate of dehiscence when compared with the gastric transposition. When the colon is transposed, distal anastomosis is performed to the fundus of the stomach. This leaves the stomach in situ, which resolves the issues of regurgitation and gastric dumping. The colon is able to tolerate radiation therapy as with other visceral grafts. The colon is also an ideal reconstruction for patients who have severe stenosis of the pharynx and esophagus after caustic ingestion.[35] If the pharynx and larynx have been spared, the colonic anastomosis can be performed at the level of the cricopharyngeus, thus preserving the larynx. With this approach, the risks for recurrent laryngeal nerve paralysis and future aspiration are high. But if the larynx can be preserved, the risks of these complications are worthwhile.

As with other procedures that require a laparotomy, colonic grafts have a risk of possible abdominal complications, as well as graft necrosis and fistula formation at the cervical anastomosis. At present, colon transposition is more reliable and flexible than gastric transposition. The symptoms of regurgitation and gastric dumping associated with gastric transposition are so distressing to patients that colon transposition is the reconstruction of choice for total pharyngoesophagectomy. The patients are still challenged with speech and swallowing. The peristaltic movements of the colon do not impair swallowing or speech, but due to the colon's patulous anatomy, any solid oral intake needs copious liquid wash to move the food bolus into the stomach. With respect to voice, many patients use an electric artificial larynx because the colon can lack a vibratory segment to generate voice.

Revascularized Free Tissue Transplantation

Microvascular free tissue transfer surgery has advanced hypopharyngeal reconstruction, particularly for patients with near total and total hypopharyngeal defects. Autogenous tissue transplantation represented an improvement because the donor tissue was not radiated, the reconstruction could be performed in a single stage, circumferential defects could be addressed, and the complication rate was lower when compared with alternative approaches. Revascularized free tissue transfer is the most reliable reconstructive technique in the head and neck.[16] When revascularized free tissue transfer replaced other approaches, the pectoralis myocutaneous flap was the most common approach for partial, near-total, and full-thickness defects including the cervical skin. For total pharyngeal defects, gastric transposition was the reconstruction of choice. At present, the pectoralis myocutaneous flap remains a reasonable option for partial pharyngeal reconstruction. Visceral transposition (colon and gastric transposition) is now limited to defects that include the thoracic esophagus.

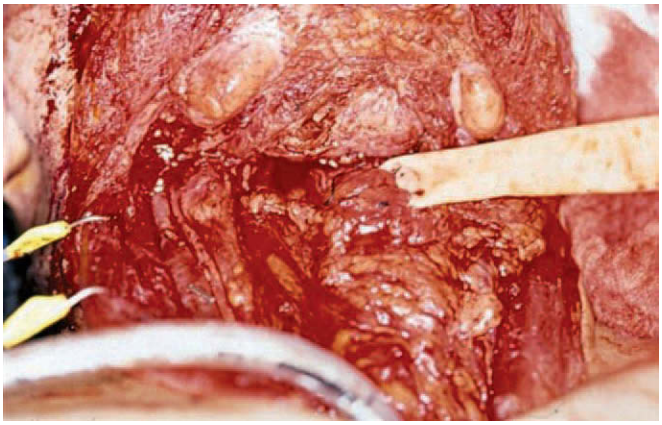

Figure 105-5. A colon interposition in place after a total laryngopharyngectomy and esophagectomy. The patient's head is to the upper part of the figure and the thorax is to the lower part. The colon is shown reconstructing the pharyngeal segment. The patient presented with a leiomyosarcoma of the cricopharyngeus, which was treated with radiation, chemotherapy, and surgical excision. The patient consumed a normal diet, which was taken in many small meals each day, and used an artificial electronic larynx for communication.

The jejunum was the first revascularized free tissue transfer used for hypopharyngeal and cervical esophageal reconstruction. This flap was reliable and well suited to defects that were near total, were total, and/or included the skin. This approach was slowly replaced by fasciocutaneous revascularized free tissue transfer primarily because an abdominal incision was avoided, and speech and swallowing were improved.[36,37] Revascularized free tissue transfer is the current approach of choice for the reconstruction of pharyngoesophageal defects that do not extend below the thoracic inlet. Distal anastomosis of the revascularized free tissue transfer in the mediastinum is not recommended because wound breakdown is likely to result in a life-threatening infection.

An additional level of complexity with revascularized free tissue transfer is the location of appropriate recipient vessels in the head and neck, particularly if the patient has undergone prior laryngectomy and bilateral neck dissection. For patients who have had a bilateral neck dissection, a preoperative computed tomography (CT) scan is useful to determine the patency of the internal jugular veins. A CT angio can be performed simultaneously and is useful for guiding the dissection for the recipient artery. If the patient has poor vascular access, a latissimus rotation flap with staging or a colon interposition is an alternative. The right internal mammary artery can also be flipped in to the neck after removing the second or third distal rib, or both. Monitoring of the transplant also merits consideration when the reconstruction is covered by the cervical skin. Monitoring can be customized to the individual patient in several ways. A monitoring segment can be left externally.[38] This could be a small skin paddle in patients who have undergone transplant of a radial forearm or an anterolateral thigh flap. A monitoring segment could also be a piece of jejunum or a portion of omentum that is left externally from a jejunum or a gastro-omental revascularized free tissue transfer. Monitoring can also be performed with oxygen saturation sensors placed around the venous anastomosis. Monitoring can be performed with Doppler scanning after appropriate planning in the operating room. The cervical skin must be scanned separately to ensure that the Doppler signal is not from the overlying skin. Next, the pedicle of the tissue transfer can be placed in a midline position, which is away from the carotids. The midline Doppler site can be a reliable monitoring option if these steps are followed (Fig. 105-6A).

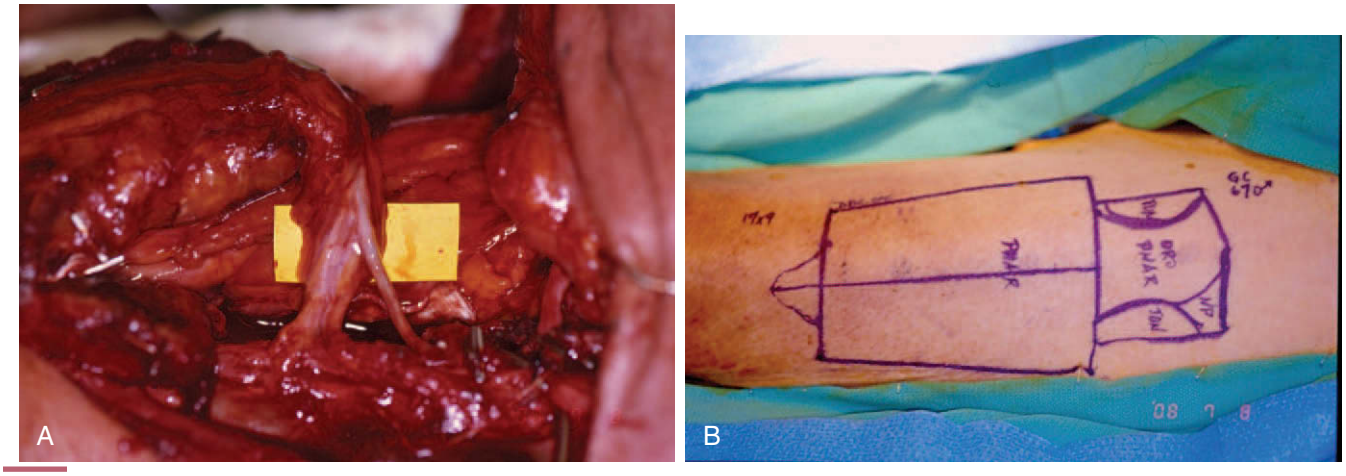

Figure 105-6. **A,** The donor artery and vein are shown crossing the yellow background, which was placed for emphasis of the pedicle but will be removed before closure. The patient is in a supine position with the head on the right side of the figure and the thorax on the left. The figure shows the pedicle in a paramedian position that allows for Doppler monitoring without an external skin paddle. **B,** The template for the same patient is shown before elevation. The donor site is the left anterolateral thigh. The donor site skin is thin, which makes it desirable for a total pharyngeal reconstruction. The pelvis is to the right of the figure and the foot is to the left. The reconstruction will be sutured into a tube along the long axis of the template. The distal or inferior aspect of the template shows a tab that will be inset into the esophagus to reduce the likelihood of stricture. The proximal or superior aspect of the template shows a large square tab that was added to reconstruct a large oropharyngeal extension of the defect.

Fasciocutaneous Transplantation

Radial Forearm Donor Site

The radial forearm flap was introduced into the Chinese literature in China by Yang in 1981 and has since become the commonly used free flap for soft tissue defects in the head and neck because of its versatility and dependability. Harii and colleagues[39] first described the use of a tubed fasciocutaneous radial forearm free flap for pharyngoesophageal reconstruction in 1985. It is currently used to reconstruct partial, subtotal, and total pharyngoesophageal defects. It is also useful for reconstruction of persistent fistula and hypopharyngeal stenosis. It is important to perform a workup for recurrence, which should include tissue biopsy and CT imaging of the neck and chest to ensure the stenosis or persistent fistula is not secondary to a tumor recurrence. The major functional advantage of the radial forearm is speech quality after total laryngopharyngectomy reconstruction.[37,40]

The major disadvantage of the radial forearm flap is the high fistula rate (42% to 59%), particularly when used for total pharyngeal defects.[32,39] Creation of a controlled fistula or use of a salivary bypass stent can decrease fistulization and stricture.[41]

The primary angiosome of the radial forearm site is approximately 150 to 250 cm^2, which is thin, pliable, and well suited for single-stage reconstruction of the pharynx and cervical esophagus. Harvest is straightforward because the pedicle is anatomically consistent, the anatomy is superficial, and the pedicle is large. Blood supply to this flap derives from the radial artery and its fascial plexus. Venous drainage is through paired venae comitantes and the superficial system of subcutaneous veins. There are usually numerous connections between the deep and superficial venous systems, providing excellent drainage of the flap. Preoperative confirmation of adequate collateral ulnar circulation to the hand is essential to avoid postoperative ischemia. Allen's test is the most commonly used and consists of digital occlusion of the radial artery for assessment of blood flow through the palmar arches to the thumb. This is a simple and reliable indicator of postharvest blood flow. Due to the superficial nature of the dissection, the donor site morbidity is low. Donor site morbidity can include injury of the superficial sensory branch of the radial nerve. Overly tight closure of the wound or placement of tight dressings can lead to a compartment syndrome. The hand needs to be monitored along with the transplant to prevent complications secondary to limb ischemia. Closure of the donor site defect requires a split-thickness skin graft. Functional loss of the hand is limited to minor loss of grip strength.

The location of the forearm relative to the head and neck allows for two surgical teams to operate simultaneously. Several points should be considered when designing the template for a total pharyngeal defect. The inferior aspect of the reconstruction should include a small triangle of skin, approximately 2 × 2 cm. This triangle is interdigitated into a 2-cm longitudinal incision into the esophagus, which is placed at a right angle to the edge of the esophagus. This approach was first taught by Hayden and is universally used to reduce the likelihood of distal anastomotic stricture (Fig. 105-6B).[39,40] A monitoring segment can be designed from the skin of the proximal aspect of the flap (i.e., separated from the skin paddle by a subcutaneous fascial segment).[42] The monitoring segment is exteriorized by incorporating the skin island into the closure of the neck flaps and is an indicator of the viability of the buried flap. The flap can be fashioned into a tube while still vascularized in the forearm, which saves additional time with an approach that involves two surgical teams. Successful oral intake is seen in 75% to 88% of patients.[39,43]

Anterolateral Thigh Donor Site

The anterolateral thigh has become the fasciocutaneous flap of choice for thin patients who have near-total and total pharyngeal defects including those defects involving skin. This flap is harvested as an ellipse on the anterolateral thigh. The advantages of this flap are ample skin, primary closure, opportunity to harvest a distal monitoring segment, and new reports of lower fistula rate when compared with the forearm site.[32] The disadvantages are the variable blood supply that may require harvesting a portion of the vastus lateralis and the thickness of the flap, particularly in North American patients.[44]

The anterolateral thigh flap receives its blood supply from the descending branch of the lateral femoral circumflex artery and the associated venae comitantes. The pedicle can pass in between the rectus femoris and the vastus lateralis, or it can pass through the vastus lateralis muscle. The pedicle is situated at the midpoint of a line drawn from the anterior superior iliac spine to the lateral aspect of the patella. It is best to position the template over the middle third of this line. Due to the variability of the pedicle anatomy, the medial incision can be made first, the perforators located, and the flap designed depending on the perforator location. It is important to place the medial incision in a near-midline location to ensure incorporation of the pedicle. The principles of inset described earlier for the radial forearm site are similar for all fasciocutaneous flap types and can be applied to the anterolateral thigh flap. A monitoring segment or a paddle for cutaneous reconstruction can be designed on a distal perforator that is found at the junction of the middle and distal third of the line from the anterior superior iliac spine to the lateral aspect of the patella. Approximately 300 cm^2 are available for reconstruction. The available skin at this site makes the anterolateral thigh a good choice for defects that extend to the tonsil or base of tongue or include the cervical skin.

Other Fasciocutaneous Donor Sites

The lateral thigh was used by Western Hemisphere surgeons before the anterolateral thigh flap because the anterolateral thigh had not been published and Western surgeons lacked experience with this site. The lateral thigh had many similar reconstructive advantages, particularly for total pharyngeal defects. The lateral thigh was used by select surgeons with extensive reconstructive experience because the pedicle was short and its harvest was difficult. The pedicle of the anterolateral thigh is much longer and the harvest is much more straightforward. Hayden described the use of the lateral thigh site for total pharyngoesophageal reconstruction.[45] This flap is harvested as an elliptically shaped skin paddle over the lateral aspect of the thigh. Its blood supply comes primarily from the third cutaneous perforator off the profunda femoris artery. Two venae comitantes accompany the arterial perforator, joining proximally and entering the profunda femoris vein.

The advantages to the lateral thigh flap are minimal donor site morbidity and thin, pliable tissue. Usually the donor site can be closed primarily, which avoids the need for a skin graft, yielding a more cosmetic scar. Like other fasciocutaneous flaps, the skin can be easily tubed for total pharyngeal defects. Unlike enteric flaps, no laparotomy incision is necessary. Dissection of the lateral thigh flap can be difficult, however, which may explain its less common use compared with the anterolateral thigh site or the radial forearm site. It is not advised for use in obese individuals or in those with previous surgery or trauma to the thigh. Excessive hair growth on the thigh may also be a relative contraindication to this flap.

The lateral arm and scapular flaps have also been described for pharyngoesophageal reconstruction. They have disadvantages including a limited amount of available tissue (lateral arm) and the need for patient repositioning for flap harvest, which results in a longer operative time (scapula). In addition, these flaps are usually not as thin as the radial forearm or the anterolateral thigh sites. Use of the ulnar flap has also been reported, with similar advantages and disadvantages as the radial forearm flap.[43]

Enteric Transplantation

Jejunal Donor Site

Seidenberg was the first to report successful transfer of a free vascularized segment of jejunum in 1959.[46] Microvascular techniques were not yet perfected at that time, but as microvascular techniques improved, interest in the free jejunal autograft was reinvigorated.

The major advantage of the jejunal free flap is that it provides a moist, mucosa-lined tube for single-stage reconstruction of pharyngoesophageal defects. The jejunum is a good size match for the cervical esophagus and is ideally suited for circumferential defects. Because it is already a tube, there are only two anastomotic suture lines in the neck,

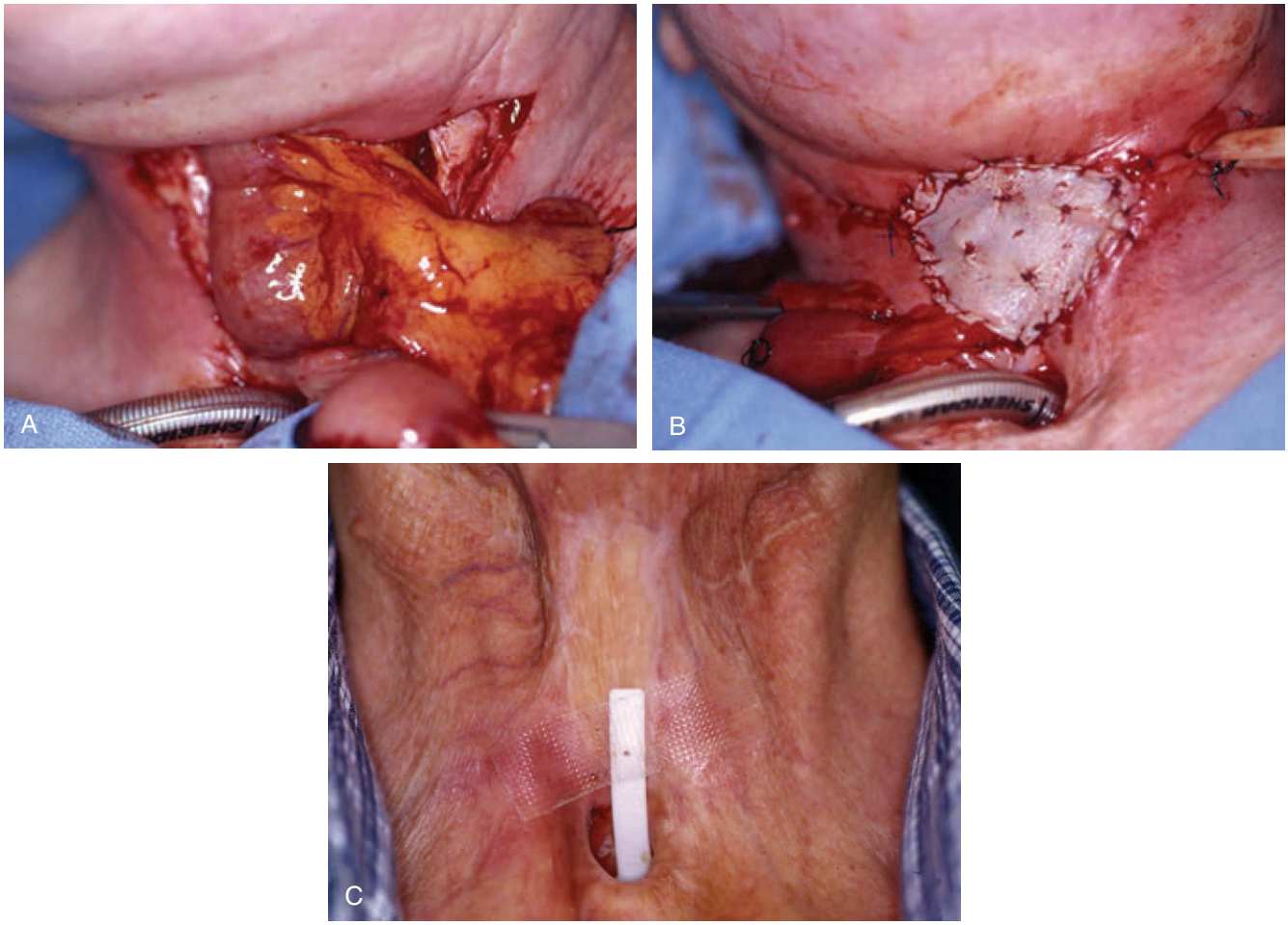

Figure 105-7. **A,** The jejunum is shown reconstructing a total pharyngeal defect. The patient's head is at the top of the figure, and the tracheal stoma can be seen at the inferior aspect of the figure with an endotracheal tube in place. The mesentery is seen to the right of the figure and will be used for the external, cutaneous reconstruction. This patient had a laryngectomy many years before this procedure and developed pharyngeal stenosis. The patient was referred following a dilation, which resulted in necrosis of the cervical skin and the anterior aspect of the pharynx. **B,** The patient is in the same orientation. The figure shows the patient after the mesentery has been draped over the jejunum and a skin graft has been applied as an epithelial reconstruction. On the left of the figure a small segment of jejunum is shown. It was used as an external monitoring segment. **C,** The patient is shown approximately 1 year after treatment. The tracheal stoma is shown with an indwelling tracheal-esophageal speech prosthesis. The skin graft is well healed just above the stoma and the patient is eating and phonating well. The reconstruction has been stable without further intervention for the past 9 years.

which potentially decreases fistula and stricture formation. The vascular arcade supplies a longer segment of jejunum than is required for pharyngeal reconstruction. The additional mesentery can be used to reconstruct an associated cervical skin defect (Fig. 105-7A). The jejunum is also easily used as a patch graft for subtotal defects. If the jejunum is opened, it is important to open the jejunum along its antimesenteric border. A free jejunal segment can be tailored to fit defects of varying lengths. In addition, the jejunum tolerates radical doses of radiotherapy.[47]

Jejunal reconstruction of the pharyngoesophagus requires a two-team approach. An appropriately sized segment of jejunum is harvested after the abdomen has been entered by way of a standard laparotomy incision. The jejunal segment is usually selected from the bowel distal to the ligament of Treitz on the basis of the second jejunal branch of the superior mesenteric artery. An intestinal segment of up to 20 cm can be harvested. Transillumination of the bowel is performed to allow identification of the best arteriovenous pedicle, which is confirmed by palpation of the vessels through the mesentery. An extra length of jejunum based on the same mesenteric arcade as the graft can be harvested to serve as an external monitoring loop (Fig. 105-7B). The additional mesentery can also be used to reconstruct the cervical skin (Fig. 105-7C). The proximal end of the graft should be marked with a suture to ensure isoperistaltic insetting of the jejunum into the pharyngoesophageal defect. The jejunum has to be inset under moderate tension. A kink or loop will functionally obstruct, making postoperative speech and swallowing more difficult. A feeding jejunostomy tube is placed after harvest of the graft. Revascularization of the jejunum does not need to be performed before insetting, but the ischemia time should be minimized. Both pharyngeal and esophageal anastomoses should be hand-sutured in a two-layered closure because a higher rate of stenosis formation has been reported with stapling.[28,48] The external monitor loop can be excised on postoperative day 7.

Reconstruction with the jejunal free flap does have several potential disadvantages. Laparotomy, with its accompanying abdominal complications, is cause for morbidity in these patients. Recent advances in laparoscopic harvest of the jejunal segment have helped to decrease donor site morbidity.[49] Ascites and Crohn's disease are absolute contraindications to the jejunal flap. Previous abdominal surgery may be a relative contraindication, as is a debilitated patient either from other medical comorbidities or age.

The key disadvantage of the jejunum relates to postoperative speech and swallowing function. This is the key reason that it is not commonly used. The intrinsic peristalsis of the jejunum remains after transplantation and often causes significant early postoperative dys-

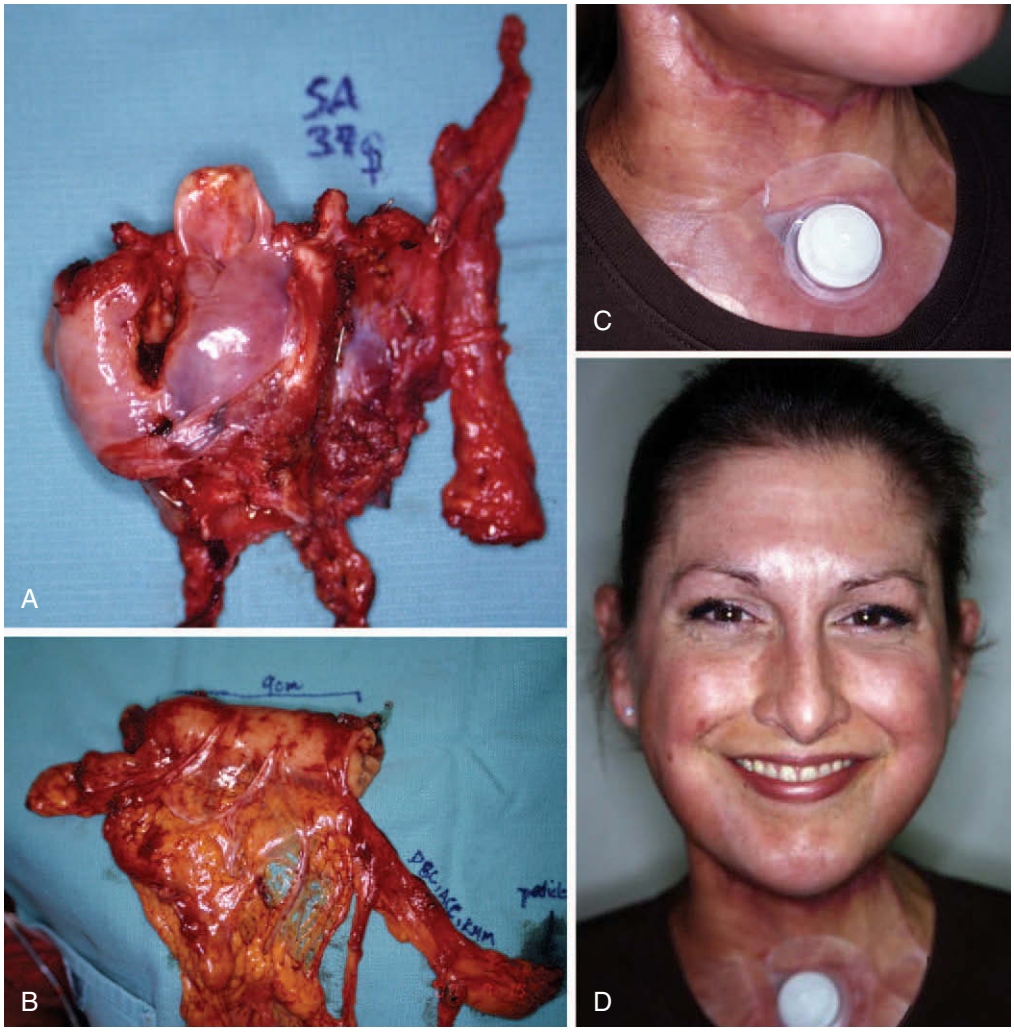

Figure 105-8. **A,** Laryngopharyngectomy specimen with the pharynx bisected to assist a view of the postcricoid and pyriform sinus sites. The posterior surface of the larynx is shown facing toward the camera with the epiglottis facing superiorly. The patient was referred with a recurrent piriform sinus cancer, seen on the left side of the figure, that underwent prior treatment with laser excision, ipsilateral neck dissection chemotherapy, and radiation therapy. **B,** A gastro-omental flap is shown after elevation. The stomach tube is shown in the upper part of the figure, and the omentum is shown in the lower part of the figure. The pedicle can be seen on the right side of the figure. The stomach tube is sized with two 30-French chest tubes along the greater curvature, taking care to preserve the gastric antrum. Note the rugae seen on the right side of the figure running along the length of the gastric tube. A portion of the omentum is harvested and can easily cover all the dissected areas of the wound. **C,** Close-up of the cervical skin of the same patient 3 months following the operation. The skin was not closed primarily in this case. Omentum was left exposed in the open wound, covered with Iodoform-Vaseline gauze as a bolster, in a defect that was 60 cm^2. The patient had a methicillin-resistent *Staphylococcus* wound infection postoperatively, which required intravenous antibiotics. No skin grafting or further reconstruction was required. **D,** A hands-free stoma cover is in place for this patient, who is communicating with tracheal esophageal speech, consuming a soft, solid diet, and working.

phagia because jejunal peristalsis is not coordinated with the pharyngeal swallow. In addition, mucous production by the jejunal mucosa can impair speech intelligibility and cause a coarse vocal quality in patients who undergo speech rehabilitation with a tracheoesophageal puncture and voice prosthesis after jejunal flap reconstruction.

Gastro-omental Donor Site

The first successful transfer of a segment of gastric antrum for reconstruction of the pharyngoesophagus was reported by Hiebert and Cummings in 1961.[50] The gastric mucosa is smooth and flexible tissue, similar in texture to the rest of the alimentary tract. This may assist the transit of food through this adynamic segment and possibly be a better vibratory segment for voice when compared with a reconstruction that uses skin. The gastro-omental graft may also be advantageous in hirsute patients, although hair on a cutaneous flap rarely causes problems by trapping food. The omentum is thin and well vascularized, offering excellent coverage of the great vessels. It can also be used to fill soft tissue defects of varying sizes and shapes because of its plasticity. The omentum also has the unique ability to form adhesions to tissues that are inflamed, ischemic, or necrotic, thereby encapsulating them and separating them from the surrounding tissues. The rich vascularity of the omentum is beneficial for healing in surgical fields that have poor tissue quality. These qualities make the gastro-omental flap a good choice for complicated wounds that are prone to infection developing or for closure of persistent fistulae. At present, the most common indication for total laryngopharyngectomy is treatment failure after chemoradiation therapy (Fig. 105-8A). The fistula and wound complication rate is higher in this patient group, and the gastro-omental flap is an ideal choice to ameliorate some of these wound-healing complications. The research challenge will be determining whether the complications resulting from a laparotomy will offset the reduction of wound complications and improvement of functional results in the head and neck.

The greater omentum is a double-layer of peritoneum attached to the greater curvature of the stomach and the transverse colon. The

gastro-omental free flap consists of a segment of gastric antrum that is harvested in continuity with its attached omentum (Fig. 105-8B). A laparotomy incision is used, allowing simultaneous harvest with the ablative procedure. The blood supply for the omentum and greater curvature of the stomach arises from the right and left gastroepiploic arteries. The right gastroepiploic artery is used for the anastomosis because it is usually the dominant vessel. The gastric segment is harvested with an enteric stapler that both separates the flap and closes the remaining stomach. Depending on the patient, the mucosal graft can either be tubed to reconstruct a circumferential defect or used as a patch graft in a partial pharyngeal defect. The omentum is used to cover the great vessels and envelop the reconstruction, which should reduce the complication rate. If there is a large cervical soft tissue defect, the omentum can be easily contoured to fill the defect and can also be skin grafted in a second stage. The option to easily reconstruct a cervical defect adds great value to a salvage reconstruction for a patient who has failed chemoradiation (Fig. 105-8C). In many chemoradiated patients, the skin is stiff, edematous, and contracted. At the completion of the pharyngeal reconstruction, primary closure of the skin can be difficult. Because of the condition of the skin, it tolerates a closure with tension poorly. To reduce tissue tension with the cervical closure, it is valuable to be able to interpose tissue above the tracheal stoma. If this reconstructive approach is taken, then there is no additional design required for the gastro-omental flap because the omentum is well suited to reconstruct above the tracheal stoma (Fig. 105-8D).

Disadvantages to the gastro-omental flap largely stem from the potential abdominal complications. These include possible gastric leak with subsequent peritonitis or abscess formation, gastric outlet obstruction, or volvulus. Peptic ulcer disease or a history of gastric outlet obstruction precludes the use of a gastro-omental flap. In addition, previous abdominal surgery or infection may be a relative contraindication to its use. Also, a history of a gastric tube may make the harvest of the gastro-omental flap more difficult.

Only small series of gastro-omental reconstructions of pharyngoesophageal defects have been reported in the literature. Guedon and colleagues[51] demonstrated successful oral intake in 18 patients reconstructed with either a patch graft (10 patients) or with a tubed gastro-omental flap (8 patients). Fistulae occurred in three patients (17%), but all resolved spontaneously. Genden and colleagues[52] illustrated the usefulness of the gastro-omental flap in patients previously exposed to multimodality therapy, who are at a high risk of fistulae and other complications developing. They reported on five patients reconstructed with a tubed gastro-omental flap; there were no fistulae or flap complications. Three patients had strictures develop that were successfully treated with dilation, and 80% ultimately achieved oral intake.

Management of Postsurgical Complications

Historically, complications of hypopharyngeal reconstruction are more frequent and more serious than other sites in the upper aerodigestive tract.[10] A number of strategies have reduced the incidence of wound complications. The salivary bypass tube seems to reduce the incidence and severity of pharyngocutaneous fistula.[41] The combination of salivary bypass tube and anterolateral thigh flap has reduced the overall complication rate at this site.[53] Should a fistula arise, determine if the carotid needs to be protected from salivary contamination. Check the thyroid-stimulating hormone (TSH) and free T4 to ensure that the patient does not have iatrogenic hypothyroidism. If the carotid is not at risk and there is nonradiated, vascularized tissue around the pharyngeal reconstruction, then these cases can be managed with regular wound irrigation, antibiotics, and thyroid replacement. If the carotid is at risk, it may need to be covered with vascularized tissue from outside the radiation field such as the pectoralis or latissimus muscle. A revascularized free tissue transfer can also be used to repair a fistula and protect the great vessels.[54] Should the patient not be able to undergo flap surgery at the time of fistula, then the fistula can be exteriorized. Exteriorization of the pharynx is effective, creates a safe wound, and involves the least tissue dissection when compared with any other approach. If the pharynx is intact, a pharyngostomy can be fashioned in the midline of the neck (Fig. 105-9). If there is no pharynx, exteriorization is accomplished by creating a pharyngostomy and an esophagostomy. The pharyngostomy is fashioned by making a transverse incision in the neck skin at the cervical-mental angle approximately 5 cm long. The superior aspect of the incision is sutured to the base of the tongue, and the inferior aspect of the incision is sutured to the posterior pharyngeal wall. The esophagus is sutured to the left of the tracheostoma. The neck skin is draped over the deep cervical fascia and carotid sheath. With the saliva diverted, the carotid is safe and the patient can undergo a secondary reconstruction in the future.

Calcium levels need to be monitored in the perioperative period. Extension of pharyngeal resection, dissection of the mediastinum, paratracheal node dissection, and use of a jejunostomy tube can all increase the likelihood of postoperative hypocalcemia.[32] The more dissection that occurs around the parathyroid gland, the more likely the parathyroid glands are to be partially or completely devascularized. If a parathyroid is detached, it should be morselized and reimplanted into muscle. Before reimplantation, it should be confirmed that it is parathyroid tissue with a frozen section histology. Feeding through a jejunostomy can exacerbate calcium absorption issues if the parathyroids are unable to produce large amounts of parathyroid hormone. The exposure of calcium to the acidic pH of the stomach assists absorption. If the enteral feeding regimen is bypassing the stomach, intravenous calcium may be a better route. Whenever hypocalcemia is noted in this patient group, administering both dihydroxy vitamin D and calcium is advisable.

Stenosis is a common postoperative problem. It typically presents with increased difficulty eating solid foods. It can present with increased difficulty producing speech. Careful attention to changes in swallowing function and patient education can assist early intervention. Stenosis rates are higher in patients who have undergone fasciocutaneous reconstruction versus visceral reconstruction. The stenosis rate is reduced substantially by the insertion of the salivary bypass tube at the time of initial surgery.[41] The effectiveness of the salivary bypass for reducing stenosis is one of the reasons that fasciocutaneous flaps have become more popular. Stenosis had been one of the major limitations to using these flaps. If a patient does develop stenosis, dilation is required.

Stenosis can present as soon as 6 weeks postoperatively despite prophylaxis. Cancer recurrence should always be considered and ruled out. Dysphagia secondary to malignancy tends to be associated with otalgia and odynophagia. If the patient is pain free, it is less likely that the dysphagia is secondary to recurrence. In this case a swallow study can be helpful to differentiate a cicatricial stenosis versus a functional stenosis secondary to cricopharyngeal spasm. Cicatricial stenosis is treated with dilation, which can be difficult due to inability to extend the neck. For these cases, dilation over a guidewire is advisable. If there is concern about distal placement of the guidewire, a small flexible scope such as a choledochoscope can be inserted over the guidewire to verify distal placement. Patients who suffer from functional stenosis secondary to spasm of the cricopharyngeus can be helped with dilation with the first occurrence. At the same time, or with second occurrence, the cricopharyngeal spasm should be treated with botulinum toxin injection. The injection can be performed endoscopically or percutaneously.

A subset of patients require frequent dilations. Awake, self-dilation is an option. After several teaching sessions, self-dilation can be a favored option for patients. For the first several awake dilations, the patient should have the oropharynx anesthetized with a topical spray to reduce the involuntary gag reflex. The patient should also swallow a small quantity of 4% lidocaine based on body weight for topical anesthesia of the dilation site. This increases the comfort of the dilation. With each session, the patient can perform more of the procedure until he or she becomes adept and self-sufficient.

Voice Rehabilitation

After laryngopharyngectomy the patient has a tracheostoma in the lower neck and a separated digestive tract. The stoma requires management to prevent stomal stenosis and prevent stomal trauma. The lungs require humidification and control of tracheal crusting. Various products prevent tracheostomal stenosis, protect the stoma from digital trauma, and enhance pulmonary humidification. Many of these tra-

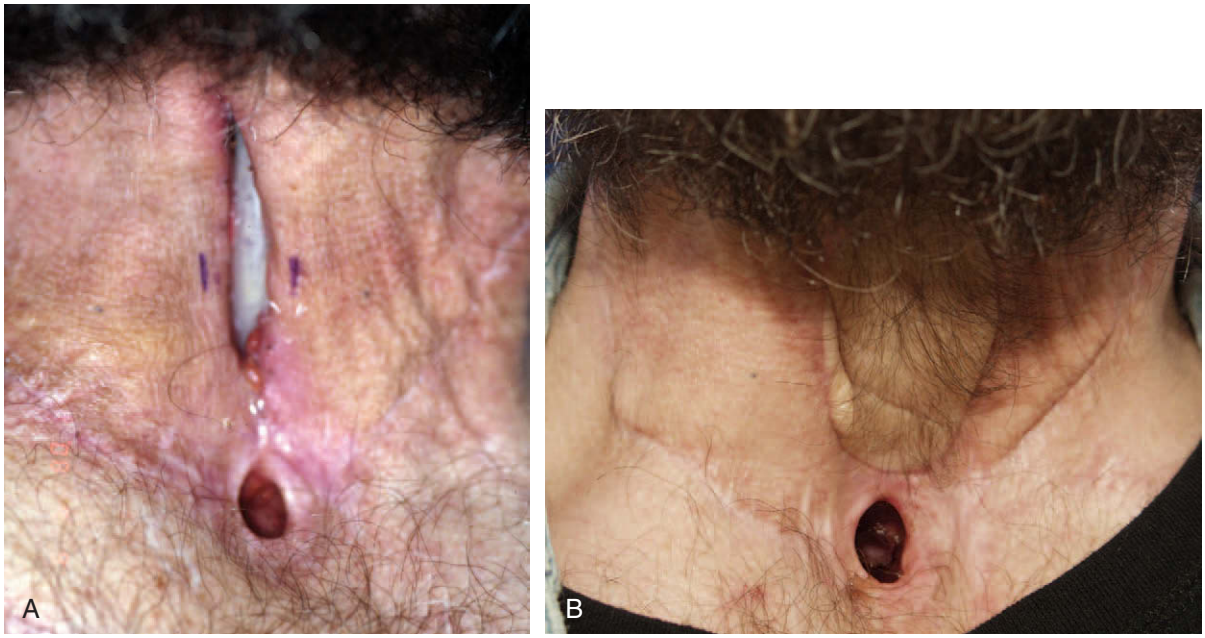

Figure 105-9. **A,** Midline pharyngostomy. The patient had an intact pharynx. The head is at the top of the figure and the tracheostoma is at the bottom of the figure. A salivary bypass tube that is in the pharynx can be seen through the pharyngostoma. The patient was treated with radiation therapy, failed, was treated with a laryngectomy and bilateral neck dissection, developed a fistula involving the carotid, and underwent a pectoralis flap, which failed to separate the fistula from the carotid. The patient was referred for definitive management and a controlled fistula was created as a first stage. **B,** A radial forearm revascularized transplant forming the external layer of a two-layer closure of the controlled pharyngostomy. The inner layer was reconstructed with advancement rotation flaps, which were pedicled on the pharyngostomy. The patient is communicating with tracheoesophageal speech, consuming a normal diet, and working.

cheal stomal prosthetics are designed to be used with or without tracheoesophageal prostheses.

Rehabilitation of speech after laryngopharyngectomy has improved with the use of tracheoesophageal prosthetic devices. Options for speech rehabilitation after laryngectomy include tracheoesophageal voice, voice generated by an artificial larynx, and esophageal voice. Use of tracheoesophageal voice has become the gold standard for voice rehabilitation after total laryngectomy. A surgical tract needs to be made for the tracheoesophageal voice prosthesis. The tract is called a *tracheoesophageal fistula* or *puncture.* The tracheoesophageal puncture can be created at the time of the resection or as a secondary procedure. If a laryngectomy with a partial pharyngectomy has been performed and wound healing problems are not expected, then a puncture with placement of a red rubber tube at the time of surgery is a common approach. If a total laryngopharyngectomy has been performed, then it may be a good idea to perform the puncture as a second procedure approximately 4 weeks after the resection. The reason for delay of the puncture is to maximize the healing of the pharyngeal reconstruction before any additional surgical wounding. A cricopharyngeal myotomy should be performed at the time of the pharyngeal resection. This will decrease the likelihood of cricopharyngeal spasm, which could impair sound production. Placement of secondary tracheoesophageal puncture can be difficult if the head does not extend. One option is to insert an endotracheal tube into the pharynx while the patient is under general anesthesia. The tip of the tube is inserted to the planned tracheoesophageal puncture site. A fiberoptic scope is inserted into the endotracheal tube so that the puncture site can be visualized from the esophageal lumen. Under direct endoscopic vision, a needle from a central line kit can be inserted through the common tracheal wall approximately 1.5 cm distal to the stomal opening. The needle should be visualized in the esophageal lumen. A guidewire is passed and the central line is inserted. The patient can be dilated over a guidewire in 2 weeks in the clinic, and a prosthesis can be placed.

The challenge with prosthetic rehabilitation is a customized solution because "one size does not fit all." An experienced speech pathologist is essential for long-term patient compliance. The electric artificial larynx may be used as a long-term means of alaryngeal communication in a selected number of patients. Additionally, it is often used during postoperative recovery until functional tracheoesophageal voice is achieved. Another alaryngeal speech option is esophageal speech, which does not use devices or implants. It involves trapping air in the pharynx distal to the cricopharyngeus with subsequent controlled release of air to produce a voice. Learning esophageal speech is time intensive and can take up to a year to achieve a functional result, whereas voice production with a tracheoesophageal voice prosthesis, in many instances, can be achieved on the day of insertion. As a result, esophageal speech is not commonly used.

As with swallowing, cricopharyngeal spasm can affect fluency of alaryngeal voice production. Botulinum toxin can be beneficial in improving fluency. Before the decision to inject botulinum toxin, the patient can undergo local infiltration of 1% lidocaine in the peristomal region in the area of the cricopharyngeus to determine if voice fluency can be improved. This approach also helps determine the most effective location for percutaneous injection of botulinum toxin.

Post-treatment Speech and Swallowing Outcomes

There is a wide variation in the reported speech and swallowing outcomes in head and neck cancer patients who have undergone partial or total pharyngeal reconstruction. Most reports have focused on reconstructive approach to reduce complication rate and maintain an open conduit from the oropharynx to the distal aerodigestive tract. The data are difficult to interpret because of survivor bias, historical bias, the changes in cancer treatment approaches, the lack of sample size to compare two different approaches, the variety of reconstructions, the variation of measurement, the availability of a trained rehabilitation team, the variety of options for postoperative speech, and particularly the motivation of the patient. More outcome data exist for patients who have undergone laryngectomy, but relatively less on patients who have undergone pharyngolaryngectomy. Risk factors for poor outcomes after pharyngolaryngectomy are total pharyngectomy, preoperative

radiation therapy, preoperative chemoradiation therapy, history of fistula, and resection of oropharyngeal structures. Factors that affect swallowing outcomes are the caliber of the pharyngeal lumen, propulsive force of the base of the tongue, and lubrication of the reconstructed segment and the closure of the velopharynx. Factors that affect speech outcomes are a poor vibratory segment, cricopharyngeal spasm, and accumulated secretions, which give the voice a wet quality. A way to understand this is to think of the oropharynx creating a seal and a propulsive force to push food through the pharynx. A patient will swallow well if the base of the tongue is of adequate volume and has good innervation, if the pharynx is large, and if the palate can seal well. For a patient to speak well, there must be a vibratory segment. The patient is more likely to have a good vibratory segment if he or she has some native pharyngeal mucosa. For speech, the pharynx cannot be obstructed with a stenosis or cricopharyngeal spasm, but it must be small enough to have a vibratory segment. Most patients can swallow and speak, but the degree to which they are successful depends on the factors discussed earlier. Specific outcome data with respect to these issues are sparse. At the University of California, San Francisco, a small group of laryngectomized patients was evaluated and compared with patients who underwent pharyngolaryngectomy, which was reconstructed with a vascularized forearm flap. Although the range of pitch was slightly greater in the laryngectomized patients, both groups were rated as "good" or "excellent" by untrained listeners.[55]

Summary

Hypopharyngeal and esophageal reconstruction is most commonly performed in patients who have failed prior radiation or chemoradiation therapy. If treatment selection protocols are used, primary surgery or alternative treatment approaches may reduce the frequency of salvage surgery. This patient population frequently has advanced disease and comorbid conditions, which require workup before surgery. To obtain a good postsurgical result, a team approach that includes nursing, speech pathology, dietician, cessation counseling, and social work is necessary. Presurgical assessment is important for appropriate reconstructive planning. Assessment of the distal resection margin is necessary to appropriately plan for esophagectomy. It is important to determine if the defect will include a total versus partial pharyngectomy, resection of components of the oropharynx, and resection of cervical skin. Also of importance is vascular access for free tissue transfer and the quality of the local tissues.

The goals of hypopharyngeal and esophageal reconstruction are protection of the great vessels, restoration of a pharyngeal conduit, protection of the airway, and rehabilitation of the voice. Pharyngoesophageal defects are classified as partial, near total, and total, whether the oropharynx, esophagus, or cervical skin is included. When making reconstructive decisions it is important for the surgeon to be aware of the high complication rate associated with hypopharyngeal reconstruction and to develop a plan that maximizes the safety of the wound.

Patients who have undergone prior chemoradiation therapy benefit from reinforcement of primary hypopharyngeal closure with vascularized tissue. Patients with partial pharyngeal defects can be reconstructed with rotational flaps such as pectoralis or latissimus dorsi flaps. Near-total, total, and extended hypopharyngeal defects are reconstructed with revascularized free tissue transfer. Fasciocutaneous free tissue transfer, particularly anterolateral thigh flap, has become the most commonly used flap due to the area of available donor skin, minimal donor site morbidity, reliability, two-team surgery, and good functional results with respect to speech and swallowing. The pharyngeal bypass tube is a critical part of the success of fasciocutaneous reconstruction as it reduces the incidence of stenosis. Visceral transposition is reserved for defects that include the esophagus. Colon interposition has become the reconstruction of choice due to lower rates of distal necrosis and better swallowing results. Gastric transposition is being evaluated for reduction of complications in patients who have failed chemoradiation therapy and require a laryngopharyngectomy. This approach may also result in improved speech and swallowing results.

Should a fistula occur after reconstruction, protection of the great vessels is the most important wound care issue. A controlled fistula is one of the best approaches available to create a safe wound. TSH levels should be checked to ensure that there is metabolic support for wound healing. After initial wound healing, difficulty with voice or difficulty swallowing can mean functional or cicatricial stenosis. Recurrence must be ruled out and the stenotic segment treated. Tracheal esophageal speech prostheses and stomal prostheses have undergone many improvements and are effective for most patients. Overall, pharyngoesophageal reconstruction can be effectively performed with careful preoperative planning, defect assessment, control of complications, and an effective multidisciplinary rehabilitative team.

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CHAPTER ONE HUNDRED AND SIX

Diagnostic Imaging of the Larynx

Franz J. Wippold, II

Key Points

- CT and MRI have become the procedures of choice for defining mass lesions and traumatic abnormalities and supplement the findings at laryngoscopy when additional diagnostic information is required to plan treatment.
- Appreciation of normal anatomy is essential when analyzing cross-sectional images.
- Diagnosis and extent of involvement of inflammatory lesions such as croup, epiglottitis, and retropharyngeal abscess can be confirmed with imaging.
- Cross-sectional imaging is extremely useful in evaluating the patient with vocal cord paralysis.
- In the laryngeal carcinoma patient, cross-sectional imaging provides crucial information about involvement of deep structures such as the paraglottic space, cartilage, and lymph nodes.
- MR scanning is now preferred for post-therapy evaluation. Additionally, combined PET/CT can be used for more confident diagnosis of recurrent tumor and for biopsy.
- In laryngeal trauma, cross-sectional imaging permits easy and rapid evaluation of the extent of cartilaginous injury, adjacent soft tissue changes, and the degree of airway compromise.
- Plain film and CT are useful in localizing foreign bodies within the larynx, trachea, and esophagus.

The radiologist plays an important role in the evaluation of upper airway disorders in children and adults by providing unique and useful diagnostic information directly affecting the treatment of the patient.[1,2] In the past, evaluation of the airway included plain-film radiography, barium studies, and fluoroscopy. Now computed tomography (CT) and magnetic resonance imaging (MRI) have become the procedures of choice for defining mass lesions and traumatic abnormalities. These procedures can supplement the findings at laryngoscopy when additional diagnostic information is required to plan treatment.

Normal Airway

Technique

Plain films remain an effective and inexpensive screening examination for acute airway obstruction. Except in rare circumstances, plain-film examination of the airway should include anteroposterior and lateral radiography of the pharynx and laryngotracheal air column. In cooperative patients, these films should be exposed during inspiration with the patient upright because acute respiratory obstruction may be exacerbated in the recumbent position. Although conventional soft tissue techniques are often adequate, high kilovoltage magnification technique with selective filtration better visualizes the airway with improved air/soft tissue interfaces.[3-5] Xeroradiography has been abandoned in clinical practice.[6,7] When plain films are inconclusive, fluoroscopy and barium studies of the esophagus may be required for diagnosis. Abnormal vocal cord motion or swallowing mechanisms, vascular impressions, mass lesions, or nonopaque foreign bodies are best evaluated by these methods. Cross-sectional imaging may also be helpful in chronic airway disease.

Anatomy

Lateral radiography is excellent for identifying the tongue, adenoids, tonsils, epiglottis, aryepiglottic folds, pyriform sinuses, laryngeal ventricle, and subglottic trachea (Fig. 106-1A). The anteroposterior airway is superb for examining the glottic and subglottic areas (see Fig. 106-1B). During quiet inspiration, the vocal cords are abducted and the width of the upper airway almost equals that of the trachea. During phonation of the vowel "e," the vocal cords adduct, resulting in narrowing of the glottic area. However, narrowing of the subglottic area should be considered abnormal.

The airway may show considerable variability in children, unlike in adults. Therefore knowledge of the normal airway anatomy is essential before attempting to recognize pathology. This requires that the patient be properly positioned for the study. Lateral airway radiography should be obtained as much as possible in full inspiration with the neck extended. If the study is performed during expiration or with forward flexion of the neck, the retropharyngeal soft tissue in children bulges anteriorly and may simulate a retropharyngeal mass (Fig. 106-2).[8]

The size of the adenoids and tonsils in children and irregular cartilage ossification in adults can present significant problems in evaluation of the airway. In newborns and infants, the tonsils and adenoids are normally sparse; lymphoid tissue can be identified radiographically in all children at 6 months of age.[9] After age 6 months, the tonsils and adenoids vary considerably in size and may encroach on the nasopharynx or oropharynx, suggesting a pathologic soft tissue mass. In most cases these structures, even when large, are normal and are frequently noted as incidental findings on plain-film radiography or cross-sectional imaging scout views or sagittal views. Occasionally, however, they can

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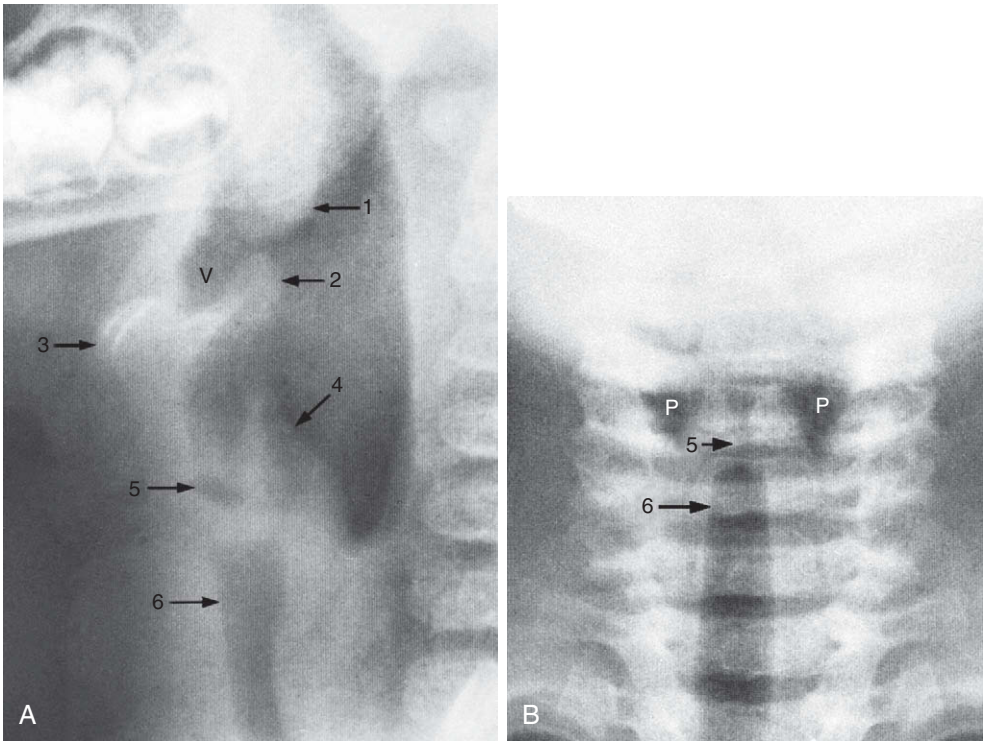

Figure 106-1. **A** and **B,** A healthy upper airway in a 20-month-old child. The following structures are well visualized: palatine tonsils *(1)*, epiglottis *(2)*, body of the hyoid bone *(3)*, aryepiglottic folds *(4)*, laryngeal ventricle *(5)*, subglottic airway *(6)*, vallecula *(V)*, and pyriform sinus *(P)*.

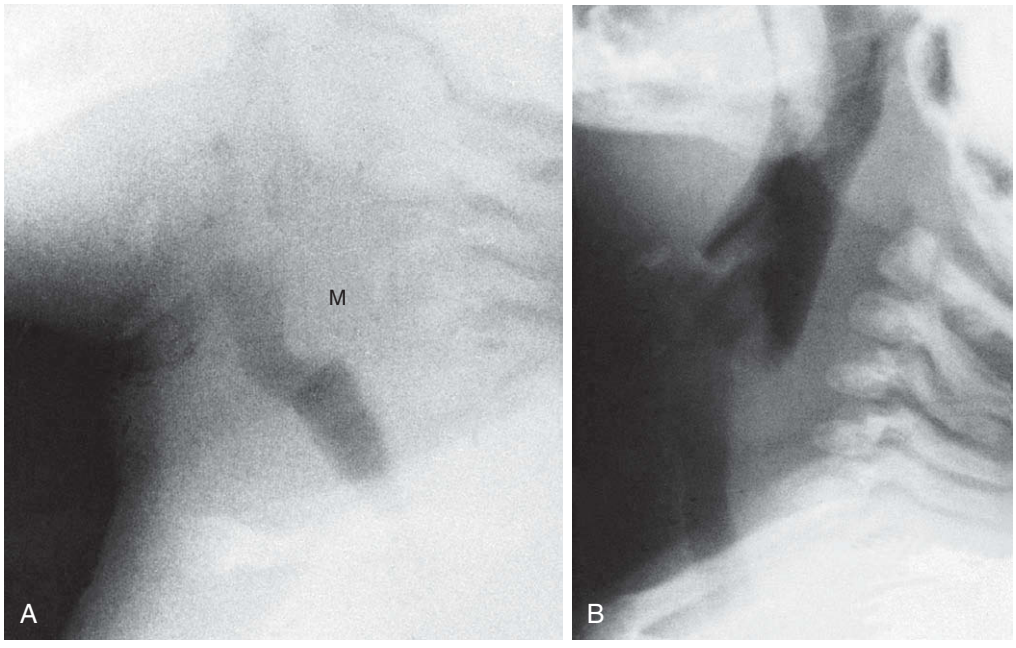

Figure 106-2. Pseudoretropharyngeal mass. **A,** A retropharyngeal mass *(M)* is suggested in this child, who was examined with the neck flexed and the airway only partially distended. **B,** Healthy retropharyngeal soft tissue is seen when the examination is repeated during inspiration with the neck extended.

be associated with airway obstruction (Fig. 106-3).[10,11] The adenoids are largest at 7 years to 10 years of age and then decline by the seventh decade.[12] In most instances, adenoidal size can be evaluated subjectively, but objective methods of assessing adenoidal size using an adenoidal-to-nasopharyngeal ratio have been described.[12,13] The final decision as to whether adenoid or tonsillar tissue is of symptomatic importance is clinical, not radiographic.

Cartilage of the neck may pose another problem because in certain adults, normal thyroid and cricoid calcifications can be irregular and incomplete, thereby simulating a foreign body or neoplastic destruction.[14] These normal calcifications can be seen occasionally in older children, but as a rule the only cartilage calcified routinely in the younger child is the hyoid bone. Any other radiopaque structure is usually abnormal.

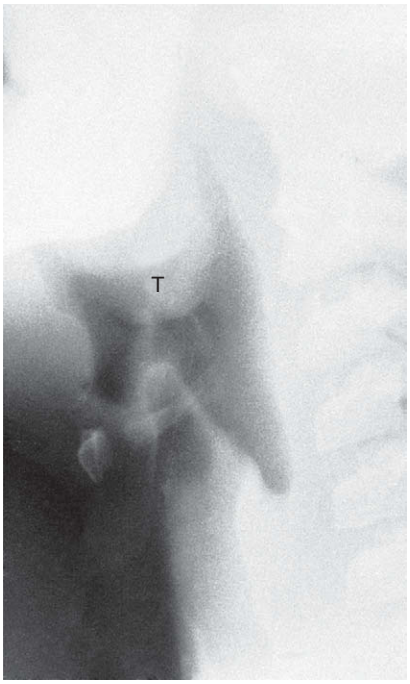

Figure 106-3. Tonsillitis. Lateral view shows enlarged palatine tonsils *(T)*.

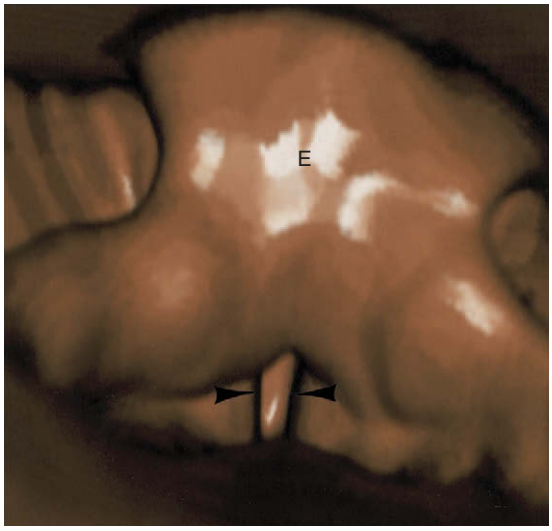

Figure 106-4. Volume-rendered three-dimensional image of the normal epiglottis (*E*) and normal vocal cords *(arrowheads)* derived from multirow detector spiral CT data. *(Case courtesy of Dr. Elizabeth McFarland.)*

Cross-sectional imaging also adequately shows the airway. Configuration of the airway on axial or transverse images varies depending on the level of the image. At the level of the epiglottis and aryepiglottic folds, the airway is elliptic. Approaching the false cords, the airway narrows and assumes a tear-drop shape. The airway becomes elliptic at the true cords. The term *rima glottidis* refers to the airway at the level of the true vocal cords. The intermembranous portion of the rima glottidis (glottis vocalis) consists of the ventral 60% of the cords, and the dorsal intercartilaginous portion (glottis respiratoria) consists of the portion between the arytenoid cartilages.[15] Below the cricoid cartilage, the airway appears circular. The posterior membrane of the trachea may posteriorly flatten, and the normal esophagus occasionally indents the airway silhouette.[16] Nodular projections into the airway or asymmetric tracheal wall thickening should be viewed suspiciously as subglottic tumor involvement. Multirow detector CT imaging has recently allowed computer-generated, three-dimensional visualization of the airway lumen and contiguous structures by reconstructing two-dimensional data. Named "virtual laryngoscopy," this technique offers noninvasive interactive evaluation of the tracheal lumen that correlates well with conventional rigid endoscopy (Fig. 106-4).[17,18]

Inflammatory Disease of the Larynx

Epiglottitis

Epiglottitis is an inflammation of the epiglottis caused by the bacteria *Haemophilus influenzae.* The entire supraglottic airway may be involved, but the epiglottis and aryepiglottic folds are most extensively involved. These normally well-defined thin structures become edematous, enlarged, and unsharp, resulting in a rounded, thumblike density in place of the epiglottis. The edema often encroaches on the vallecula and rarely may extend to the posterior pharyngeal wall. In addition, the hypopharynx and pyriform sinuses are usually mildly to moderately overdistended.[19-22] The remainder of the airway is fairly normal, although at least 25% of children with epiglottitis have subglottic narrowing.[23]

The changes of epiglottitis are shown best on lateral radiography (Fig. 106-5). Extensive manipulation of the patient should be avoided because of the possibility of inducing glottic spasm. Cross-sectional imaging is unnecessary.

Figure 106-5. Epiglottitis. Marked thickening of the epiglottis *(arrow)* and aryepiglottic folds *(arrowheads)* is seen. Mild hypopharyngeal overdistention is also present.

Enlargement of the epiglottis may result from various other disorders including irritation from a foreign body or burn, tumors such as epiglottic cysts or neoplasms (e.g., lymphoma), granulomatous disease (e.g., sarcoidosis, tuberculosis, Wegener's granulomatosis), and angioneurotic edema.[24,25] The radiographic findings should therefore be correlated with the patient's clinical history (Fig. 106-6). On occasion, an omega epiglottis—a normal anatomic variant in children in which the epiglottis is floppy, vertically positioned, and resembles the capital Greek letter "omega"—may be misdiagnosed as epiglottitis.[26] An important distinguishing feature is the absence of thickened aryepiglottic folds or other edematous changes.

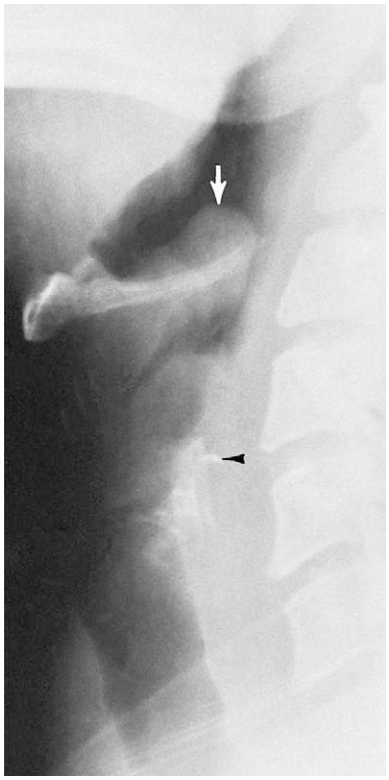

Figure 106-6. Sarcoidosis. Marked enlargement of the epiglottis *(arrow)* is present. *Arrowhead* points to normal calcification in the posterosuperior aspect of the cricoid cartilage.

Croup

Croup is an inflammation of the subglottic larynx usually caused by parainfluenza virus type 1. It typically occurs in young children. Radiographic studies are not indicated or obtained routinely in patients with croup but are useful in confusing cases, primarily to exclude other causes of stridor. The radiographic changes are the result of inflammatory edema affecting the larynx and subglottic tissue. Radiographically, the frontal view is most helpful in the diagnosis (Fig. 106-7). Symmetric subglottic airway narrowing or "penciling" of the airway is the major radiographic finding.[19-22] In contrast to congenital subglottic stenosis, narrowing of the subglottic portion of the trachea is not fixed and may improve on expiration.[27] The lateral view of the neck appears less helpful, although the narrowing may be noted. This projection shows hypopharyngeal airway distention, but more importantly it establishes that the epiglottis and aryepiglottic folds are normal.

Membranous or bacterial croup and viral croup may present with similar symptoms; however, membranous croup is characterized by diffuse inflammation of the larynx, trachea, and bronchi with adherent exudate and mucus on the surface of the upper tracheal mucosa.[28] Radiography shows subglottic narrowing and multiple tracheal soft tissue excrescences (Fig. 106-8). These intraluminal lesions can be mistaken for foreign bodies, so clinical correlation is required for diagnosis.

Retropharyngeal Abscess

The retropharyngeal space lies posterior to the larynx between the middle and deep layers of the deep cervical fascia. It extends from the base of the skull to the mediastinum and frequently serves as a conduit for spread of disease from the neck into the chest.[29,30] Retropharyngeal abscess results from suppuration of retropharyngeal lymph nodes in patients with upper respiratory tract infection or from perforation of the pharynx or upper esophagus by a foreign body. If the abscess compresses the larynx and upper trachea, symptoms of upper airway obstruction develop.

Lateral soft tissue radiography of the neck will show fixed thickening of the retropharyngeal soft tissues, anterior displacement of the

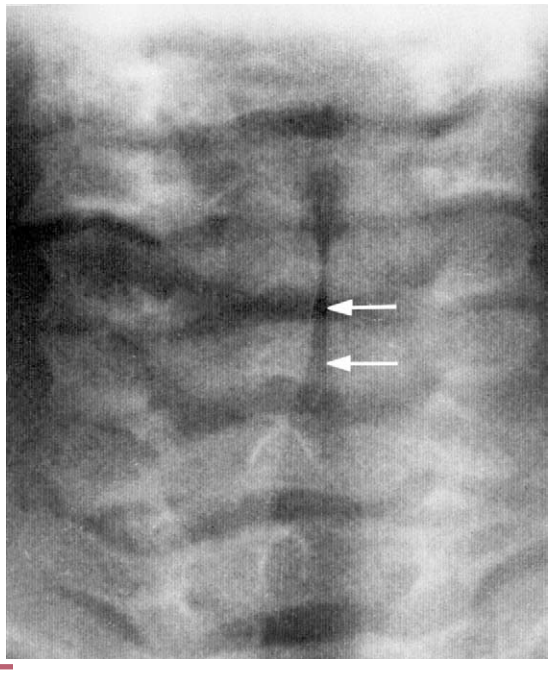

Figure 106-7. Croup. Frontal view shows typical funnel-shaped subglottic narrowing *(arrows)*.

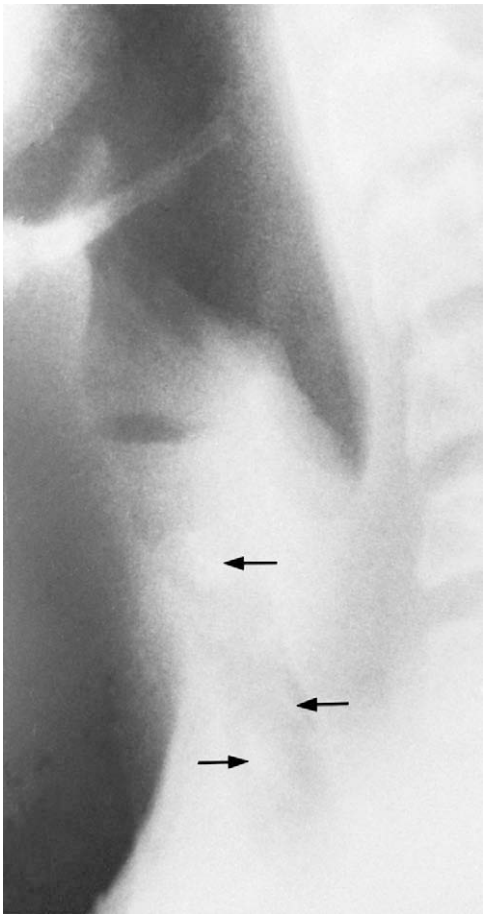

Figure 106-8. Membranous croup. Multiple irregular membranes *(arrows)* are present in the subglottic airway.

airway, reversal of normal cervical lordosis, and occasionally gas bubbles within the abscess (Fig. 106-9).[19,21,27] The retropharyngeal space should not exceed 7 mm as measured from the most anterior aspect of C2 to the posterior pharyngeal wall. At C6, the thickness of the retropharyngeal tissues should not be greater than 14 mm in children and 22 mm in adults.[31] Fluoroscopy or barium esophagography may be necessary to confirm that the radiographic changes did not occur with expiration or with the head in a flexed position.

Figure 106-9. Retropharyngeal abscess secondary to foreign body perforation of the esophagus. The prevertebral soft tissues are markedly swollen, and the trachea is displaced anteriorly *(small arrows)*. *Large arrow* points to a metallic foreign body.

CT and MRI superbly evaluate the retropharyngeal space. Suppurative adenopathy is usually limited to the suprahyoid region of this space and spares the midline. As infection becomes extranodal, the entire width of the retropharyngeal space frequently becomes thickened. Inflammation can then easily track into the infrahyoid region. The full extent of the process can be imaged by CT or MRI before therapy.[29] Abscess will appear hypodense on CT, hypointense on T1-weighted, and hyperintense on T2-weighted magnetic resonance (MR) images, reflecting the presence of liquefaction (Fig. 106-10). Ring enhancement may be seen following administration of intravenous contrast. Differentiation between retropharyngeal abscess and adenitis is difficult on CT because both processes cause hypodense regions within the inflammatory mass. Some authors advocate the use of ultrasound in this evaluation.[32] If air bubbles or a foreign body is present within the mass, the diagnosis of a retropharyngeal abscess is more likely.

Thickening of the retropharyngeal soft tissues also can occur secondary to bleeding and edema from cervical spine trauma, lymphadenopathy (e.g., lymphoma, tuberculosis), or retropharyngeal tumors (e.g., cystic hygroma, neuroblastoma, hemangioma, retropharyngeal goiter, cancer).[27,33-35] The imaging findings should therefore be correlated with the clinical history.

Laryngomalacia

Laryngomalacia or congenital flaccid larynx is one of the most common causes of inspiratory stridor in the neonate and infant.[21] Laryngoscopy shows flaccidity of the epiglottis, aryepiglottic folds, or the entire larynx, which collapses during inspiration. The corresponding radiographic findings are best shown with fluoroscopy. Hypopharyngeal overdistention with associated collapse of the aryepiglottic folds and epiglottis is observed on inspiration. Paradoxic narrowing of the subglottic portion of the airway may also be seen as the patient inspires. The primary reasons for laryngoscopy and radiography are to exclude other causes of congenital stridor (e.g., cysts, webs, tumors, stenoses). In most children, the symptoms disappear by 1 year of age.

Vocal Cord Paralysis

Paralysis of the vocal cord may be caused by any process involving the vagus nerve or its recurrent laryngeal branch between the jugular foramen and its entrance into the larynx. Almost 75% of patients have unilateral paralysis.[36] Almost 90% of paralyses are caused by lesions that

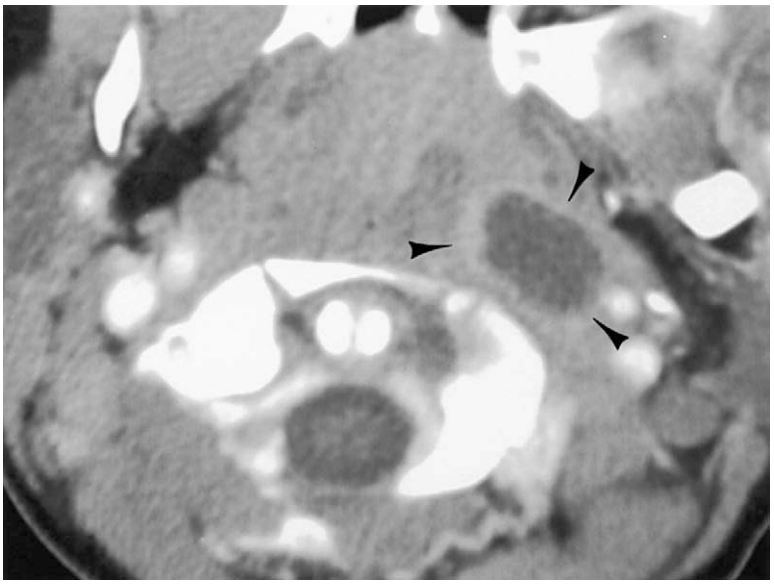

Figure 106-10. Retropharyngeal abscess. Enhanced CT image of the neck demonstrates a fluid collection in the left retropharyngeal space (*arrowheads*).

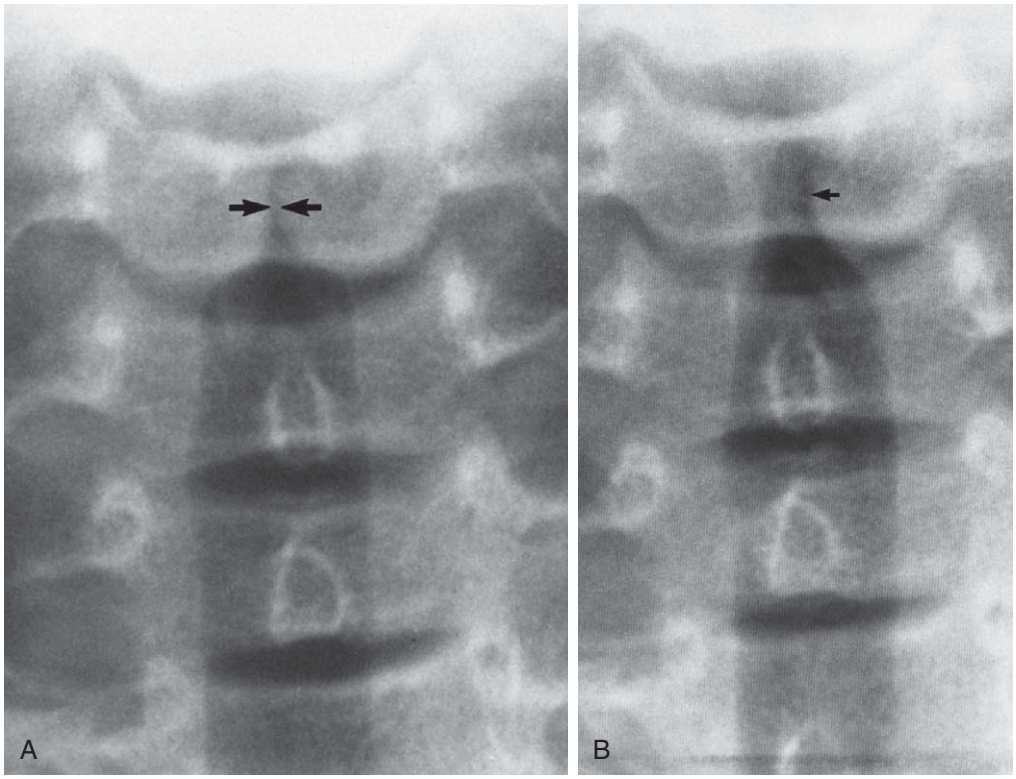

Figure 106-11. Left true vocal cord paralysis. **A,** During phonation, both vocal cords are in a paramedian location *(arrows)*. **B,** During inspiration, the left true vocal cord remains in a paramedian position *(arrow)*, whereas there is abduction of the normal right true vocal cord.

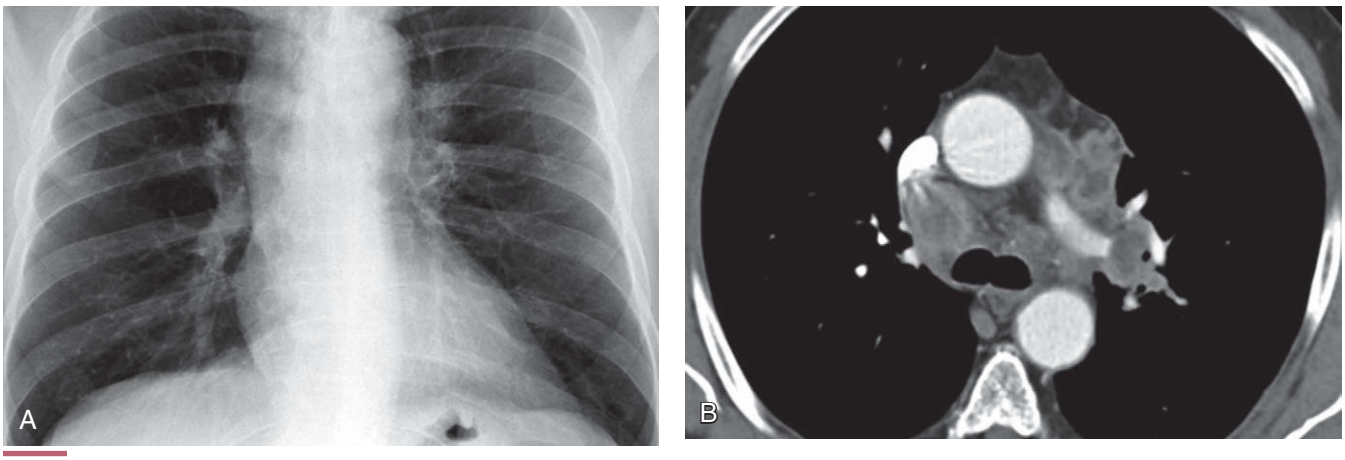

Figure 106-12. True vocal cord paralysis secondary to squamous cell carcinoma. **A,** Chest radiography shows massive mediastinal and bilateral hilar lymphadenopathy. **B,** Computed tomography confirms the presence of multiple necrotic lymph nodes throughout the mediastinum.

compress the nerve along peripherally located segments, and only 10% originate in the central nervous system or before the nerve exits the jugular foramen; central paralyses are accompanied by other cranial neuropathies.[37] The peripheral location of most lesions reflects the long and redundant routes of the recurrent laryngeal nerves. Specific causes include neoplasm (36%); postoperative complications, such as from parathyroid and thyroid surgery (25%); and inflammation (13%). Some cases are idiopathic.[36] Congenital central nervous system anomalies are often associated with childhood vocal cord paralysis.[38] Although laryngeal cancers can paralyze the cord by direct invasion of the thyroarytenoid muscle, infiltration of the recurrent or superior laryngeal nerves by local tumor is rare.[39]

Although plain-film radiography, fluoroscopy, and CT can evaluate vocal cord mobility, abnormal vocal cord motion is generally diagnosed by laryngoscopy (Fig. 106-11).[40,41] However, in patients with vocal cord paralysis secondary to neoplasm, imaging helps show the extent of neoplasm and its relationship to the adjacent cartilaginous structures.[42,43] Radiologic evaluation of the isolated paralyzed cord should entail imaging of the entire vagus nerve from the skull base to the pulmonary hila. CT is excellent for evaluating the neck and chest; MRI is superior for the skull base (Fig. 106-12).[36,44,45,] Imaging signs of cord paralysis include paramedian position of the cords, displaced arytenoid cartilage, ipsilateral dilation of the pyriform sinus, tilting of the thyroid cartilage, and prominent laryngeal ventricle.[37] Dynamic MRI using an open-bore configuration, with the patient seated, has recently been explored as a technique for evaluating swallowing and other laryngeal and pharyngeal functions.[46]

Figure 106-13. Subglottic hemangioma. Lateral view shows a soft tissue mass *(arrows)* in the posterior portion of the subglottic airway.

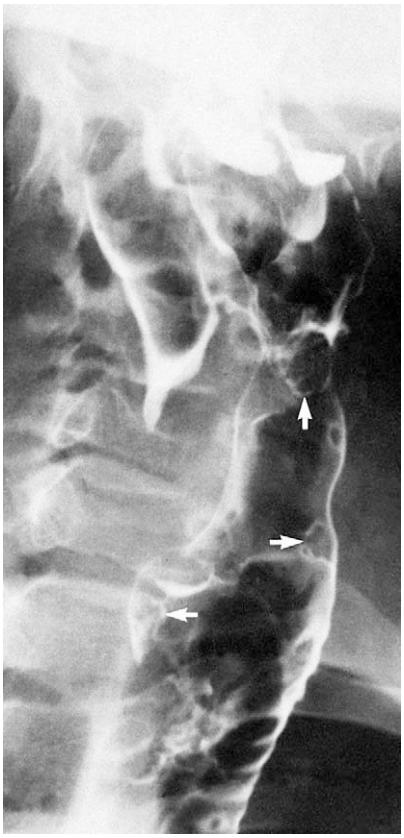

Figure 106-14. Laryngotracheal papillomatosis. Oblique view from a bronchogram shows multiple nodules *(arrows)* of varying sizes in the glottic and subglottic airway.

Benign Laryngeal Masses

Benign neoplasms can cause respiratory obstruction. Symptoms and imaging features depend on tumor distribution and extent. CT is the preferred screening method because of its widespread availability and superior information.

Although rare in adults, subglottic hemangioma is the most common laryngeal and upper tracheal neoplasm in the newborn and infant. The lesion typically appears as a well-defined mass in the posterior or lateral portion of the subglottic airway (Fig. 106-13).[25,47] The subglottic narrowing is usually eccentric; however, circumferential narrowing suggestive of croup may also be seen. Additional hemangiomas may occur on the skin or elsewhere in the body.

Squamous papillomas, the most frequent laryngeal tumors in children, have also been reported in adults.[48,49] The imaging appearance of papillomatosis is contingent on the size and location of the lesions. Generally single or multiple intraluminal soft tissue nodules are seen in the glottis or in the tracheal air column (Fig. 106-14). Because papillomas may extend to the bronchial tree or pulmonary parenchyma, chest CT is extremely important in defining the extent of disease. Localized areas of atelectasis, air trapping, or pneumonia have been reported. Papillomas also may appear as well-defined discrete pulmonary nodules that eventually cavitate, forming multiple thin-walled cystic lesions.[50,51]

A laryngocele is an abnormal elongation and expansion of the saccule of the laryngeal ventricle and represents more than 20% of submucosal lesions of the larynx.[52,53] Almost 25% are bilateral.[54] Although laryngoceles are usually asymptomatic, large lesions may be associated with airway obstruction and vocal cord paralysis.[55] Laryngoceles within the paraglottic space and confined by the thyroid lamina are termed *internal*. These lesions may present on laryngoscopy as soft, localized bulges of the aryepiglottic fold and may be mistaken clinically for submucosal neoplasms.[56-58] Lesions that pierce the thyrohyoid membrane to present in the lateral neck are termed *external*. Most cases are a combination of external and internal lesions and are referred to as *mixed*. Regardless of position, laryngoceles are usually visualized as sharply defined air-containing structures on imaging (Fig. 106-15).[59] A modified Valsalva's maneuver occasionally improves visualization of these lesions. Laryngeal mucocele is a fluid-filled laryngocele caused by obstruction of the ostium of laryngeal saccule and may appear as a soft tissue mass. These lesions are overwhelmingly benign; however, up to 15% may be associated with a small ventricular cancer.[57,60,61] Rarely, cystic lesions such as cystadenomas can mimic a laryngeal mucocele.[62]

CT can be helpful in showing fluid-containing and air-containing laryngoceles (Figs. 106-16 and 106-17).[56] If the mass is of soft tissue density because it contains either mucoid or purulent material, the distinction from neoplasm may be more difficult. However, its location and smooth surface in conjunction with a healthy mucosa on laryngoscopy should suggest a laryngocele. CT may also help show the external component of a laryngocele that is not apparent on physical examination. An enhancing wall usually indicates infection. The endolaryngeal origin of this lesion differentiates it from a lateral thyroglossal duct cyst.[57]

Congenital cysts of the larynx are rare causes of respiratory obstruction in infants. They most commonly arise in the region of the epiglottis or aryepiglottic fold. Plain-film examination of the airway will disclose a soft tissue mass of varying size, encroaching on and displacing the healthy airway.

Laryngeal Carcinoma

Nearly all mucosal tumors are diagnosed by direct inspection and biopsy; imaging provides crucial information about involvement of deep structures such as the paraglottic space, cartilage, and lymph nodes. CT is a proven imaging technique for evaluating patients with laryngeal carcinoma.[63-67] In most patients, CT shows more extensive disease than is initially appreciated by laryngoscopy. The cross-sectional

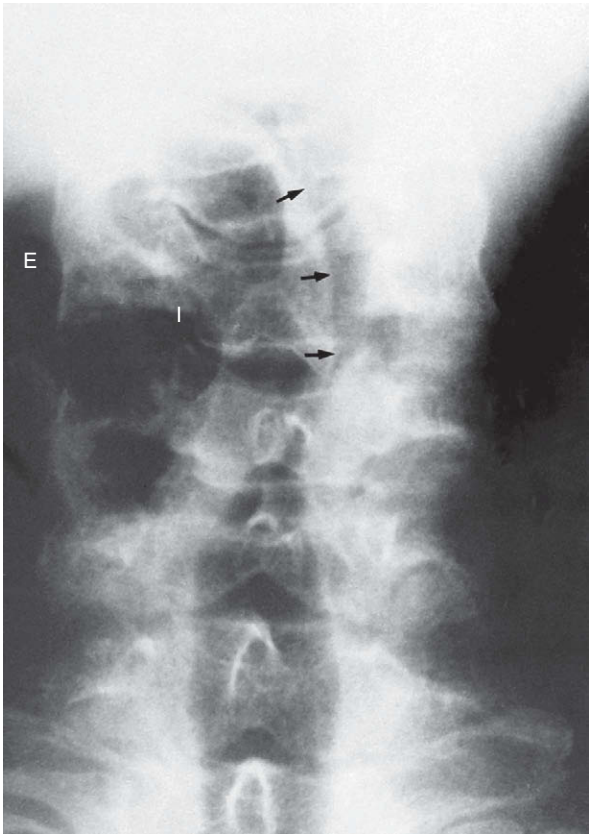

Figure 106-15. Mixed laryngocele. Frontal view shows the large internal *(I)* and external *(E)* components of the laryngocele with compression of the supraglottic airway *(arrows)*.

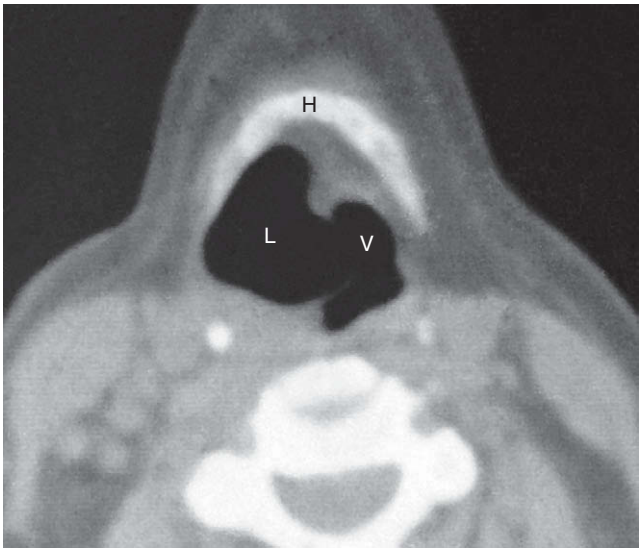

Figure 106-16. Internal laryngocele. Computed tomography shows the air-filled laryngocele *(L)* filling the right paraglottic space and compressing the laryngeal vestibule *(V)*. The hyoid bone *(H)* is also seen.

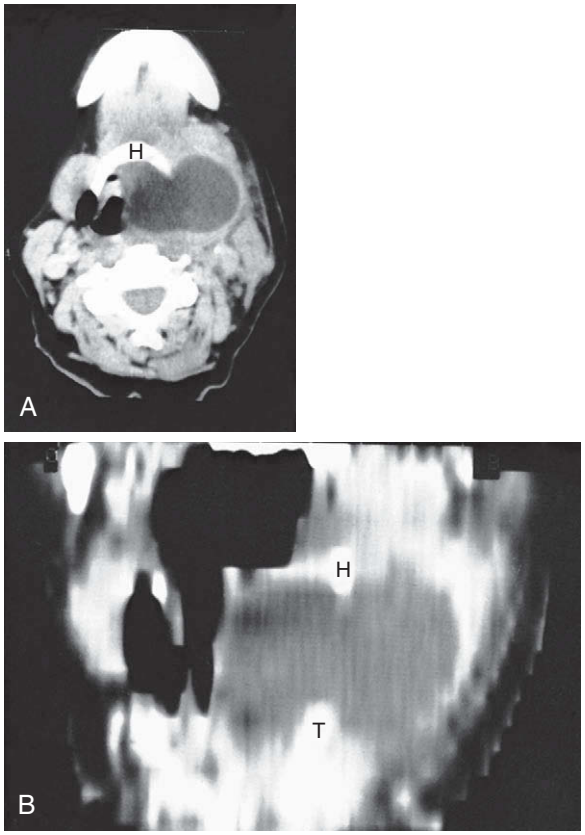

Figure 106-17. Bilateral mixed laryngoceles. **A,** Computed tomography (CT) shows a fluid-filled, dumbbell-shaped cyst with intralaryngeal and extralaryngeal components on the left. Smaller air-filled laryngocele is seen on the right. **B**, Reformatted coronal CT shows both laryngoceles herniating through the thyrohyoid membrane. The hyoid bone *(H)* and thyroid cartilage *(T)* are also seen.

imaging provided by CT allows evaluation of the intrinsic and deep soft tissues of the larynx and the cartilaginous skeleton.

MRI provides anatomic information on the neck that compares favorably with CT.[68-72] Advantages of MRI include its excellent soft tissue contrast, which is superior to CT. Multiplanar display enables coronal, transverse, and sagittal anatomic formatting, whereas CT is usually limited to the transverse plane. Newer multirow detector CT scanners allow for multiplanar reconstructions; however, these views are derived from data obtained in the transverse plane. MRI uses no ionizing radiation and is not plagued by artifacts caused by beam hardening, dental amalgam, or poor beam penetration of the shoulders. MRI does have limitations, however. It is slower than CT, and therefore motion artifacts from breathing, carotid artery pulsations, and swallowing may degrade images.[73-75] This should be considered when choosing a modality in laryngeal cancer patients, who are often elderly and may have other medical debilities (e.g., chronic obstructive pulmonary disease).[74] MRI does not image cortical bone or calcifications well. Furthermore, MRI is contraindicated in patients with cardiac pacemakers, metallic cochlear implants, and cerebral aneurysm clips.[76-79]

The decision for selecting radiotherapy, conservation surgery, or total laryngectomy depends on an accurate delineation of tumor extent.[80,81] CT and MRI are excellent noninvasive methods capable of three-dimensional (3D) anatomic display of portions of the larynx that are not well examined by laryngoscopy. Submucosal extension of tumor and cartilaginous destruction that are not suspected clinically can be assessed. Because imaging modalities have different strengths and weaknesses, the choice of CT or MRI should be tailored to the patient. Furthermore, imaging is not a substitute for but is complementary to laryngoscopy. Although imaging may show advanced mucosal abnormalities, minor mucosal abnormalities and abnormalities of intrinsic motion are best studied by laryngoscopy.[82]

Neoplasm is identifiable on CT as an area of increased soft tissue density that alters the normal symmetric laryngeal anatomy. Similarly, the hallmark of an abnormal larynx on MRI is asymmetry. The superb soft tissue contrast provides additional information. On T1-weighted images, fat signal is hyperintense and differs significantly from the mucosa and muscles in appearance. Signals from lymph nodes and

infiltrating tumor, which are less intense than fat, are well visualized on T1-weighted images. On T2-weighted images, muscle signal is less intense than mucosa, fat, and many tumors. Carcinomas within the mucosa and muscles can be well delineated.[83] Neither CT nor MRI findings are histologically specific, and similar appearances can be produced with hemorrhage, edema, inflammation, or fibrosis. Therefore, examination should be correlated with the clinical history and should be performed before laryngeal biopsy or at least 48 hours after biopsy to avoid confusion with postbiopsy edema and hemorrhage.

Technique

Spiral (helical) CT using multidetector technology and volumetric data sets has largely replaced conventional dynamic CT (slice-by-slice acquisition) in most medical centers.[69,84] Spiral CT permits rapid scanning of large volumes of tissues during quiet respiration.[85] Spiral images are less susceptible to patient motion than conventional CT, although image noise is slightly increased.[86,87] Thin sections can provide information about specific regions, such as the anterior commissure.[88] Moreover, volumetric spiral data permit multiplanar and 3D reconstructions.[87,89,90] The amount of intravenous contrast may be reduced compared with dynamic CT.[91] Iodinated contrast is administered intravenously to distinguish nonenhancing lymph nodes from enhancing vessels. Images are obtained during slow inspiration. If the images are performed during suspended inspiration, adduction of the true vocal cords may cause the airway to appear falsely narrowed. Scans are occasionally obtained during phonation or during modified Valsalva's maneuver to distend the pyriform sinuses and improve visualization of the aryepiglottic folds.

3D CT is currently being used for radiotherapy planning. Slices are obtained in the conventional axial orientation. Using special computer software, selected anatomic structures are then traced and reformatted into a 3D wire diagram depicting the tumor and key adjacent tissues that can then be manipulated to reveal the optimal radiation port. This technique limits extraneous collateral radiation to other organs such as the salivary glands.[92,93] CT is also useful for guiding percutaneous biopsies.[94-97]

MR techniques may vary depending on scanner type and available hardware and software. Surface coils are essential to adequately image the larynx.[42,98] Sagittal, transverse, and coronal T1-weighted images best display anatomic relationships. T1-weighted and T2-weighted transverse images further define the signal characteristics of the tissues. Sections are usually 3 to 5 mm thick. Gradient moment nulling, flow compensation, cardiac gating, and presaturation pulses minimize motion artifacts.[74] Fast spin-echo T2-weighted technique has replaced conventional spin-echo technique and offers relatively short acquisition times.[99-102]

Gadolinium-enhanced images improve delineation of margins in many lesions,[103-107] although lesions embedded in fat may be obscured.[108,109] Another potential pitfall is that healthy aerodigestive mucosa enhances, therefore possibly obscuring small mucosal tumor volumes.[54] Fat-suppression techniques improve conspicuity of soft tissue lesions embedded in fat by selectively diminishing the hyperintensity of fat on T1-weighted images.[108,110] Gadolinium-enhanced, fat-suppressed T1-weighted images are especially useful in staging nodal disease.[111] Agents are typically well-tolerated.[104,112] Newer agents such as gadobenate dimeglumine are improving lesion conspicuity compared with equivalent doses of older agents. A word of caution is necessary, however. Recently, several cases of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD) have been reported in patients with renal failure receiving gadolinium compounds, especially in high doses. (It is worth noting that the use of double and triple doses of contrast, sometimes valuable in intracranial disease, has little value in neck imaging.[113]) NSF/NFD, a rare and somewhat mysterious complication, causes a progressive sclerosis of the skin and connective tissue and may lead to death. Currently, recommendations include calculating a glomerular filtration rate for patients with renal insufficiency or frank failure and avoiding the use of contrast agents in the impaired patient.

Fat suppression may produce several annoying artifacts, however, such as signal loss at bone-air interfaces, inhomogeneous suppression at the base of skull compared with the infrahyoid regions, and frank failure of suppression at fat-air interfaces producing aberrant hyperintense signal.[114] Moreover, some techniques may be misleading because nonfatty tissue with T1 values similar to fat (e.g., proteinaceous fluid, methemoglobin, intensely enhancing soft tissue) may also be suppressed.[115]

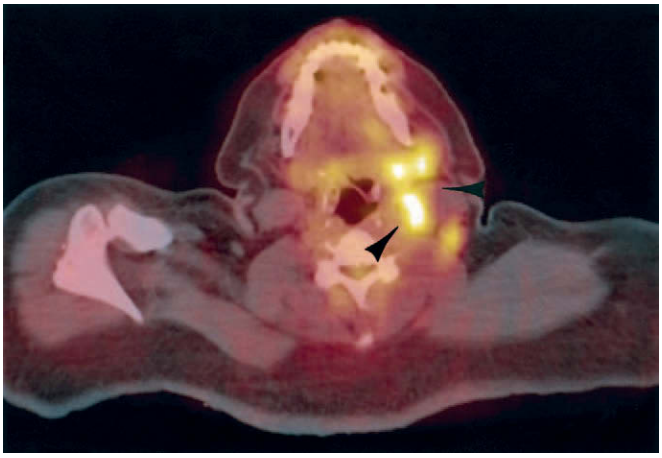

Figure 106-18. Combined positron emission tomography/computed tomography (PET/CT) image of the neck demonstrating increased PET activity *(arrowhead)* superimposed on the corresponding CT image. The increased PET activity indicates hypermetabolic tumor. The CT image allows accurate anatomic localization of this tumor.

MR techniques and applications such as magnetization transfer improves the contrast between lesions and background tissue.[116-120] Reconstruction algorithms permit simultaneous 3D depiction of the tumor volume embedded within the surrounding soft tissues. This display assists the transformation of two-dimensional information into a 3D format and allows the examiner to "dissect" the display to a desired tissue depth.[121,122] Diffusion-weighted MRI, nanoparticle-enhanced MRI, and perfusion MRI are also currently being explored.[123]

Open-bore units are being used to guide biopsies.[124,125] These units are useful for the claustrophobic patient, who would otherwise be unable to tolerate the confining space of conventional magnets. Unfortunately, many of these scanners lack sufficient magnet strength to optimally display difficult or complex anatomic relationships.

Special applications such as MR spectroscopy have been evaluated for certain head and neck tumors.[126] MR spectroscopy measures and graphically displays tissue metabolites.[127] Choline (Cho), a precursor to phosphatidylcholine, is involved in membrane turnover. An elevation of the Cho spectral peak within tissue implies cellular turnover and may serve as a potential tumor marker.[128,129] MR spectroscopy may prove useful by using metabolic data to map tumors and complement anatomic data from conventional imaging.[130] Although MR spectroscopy has advanced rapidly on the intracranial application front, initial enthusiasm for head and neck lesions has dampened. Formidable technical issues such as artifacts from paranasal sinuses, airway, neck fat, and blood vessels have made consistently reliable spectra difficult. Therefore widespread use in head and neck awaits significant refinement.

Combined positron emission tomography (PET) CT is a new technique in which near simultaneously acquired PET and CT information is superimposed. This image fusion has the advantage of comparing superior sensitive functional PET data with the superior anatomic data offered by CT (Fig. 106-18). Promising applications include evaluation of post-therapy patients for evidence of recurrent tumor, analysis of ambiguous lymph nodes and soft tissue masses, and verification of biopsy sites.[123,131,132]

Normal Anatomy

Accurate interpretation of scans of the larynx necessitates understanding of normal laryngeal anatomy as depicted on CT or MR images (Figs. 106-19 through 106-26).[133] Some degree of normally occurring

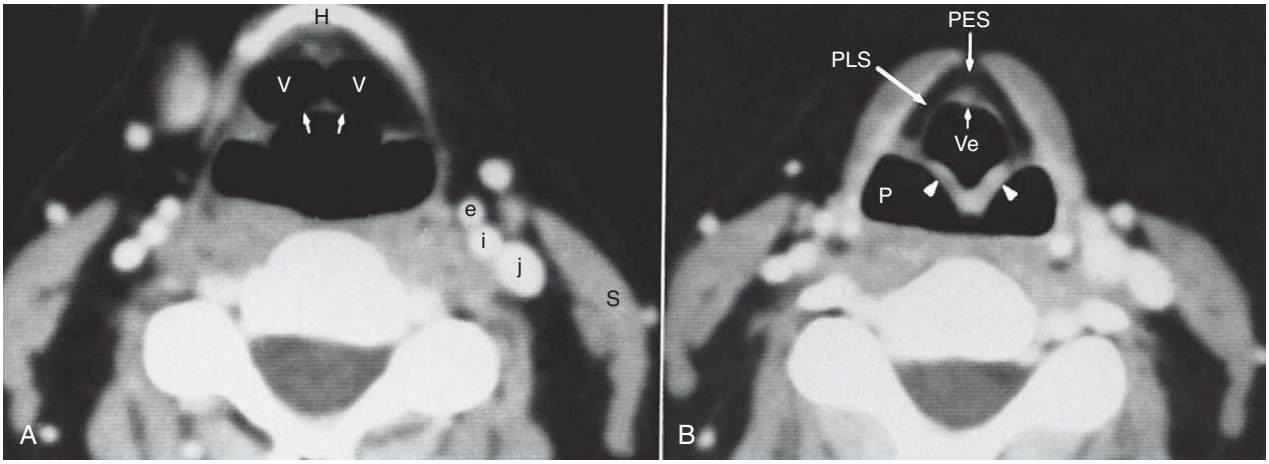

Figure 106-19. Normal anatomy on computed tomography showing supraglottic larynx after intravenous contrast injection. **A,** The two air-filled valleculae *(V)* separated by the median glossoepiglottic fold are seen anterior to the epiglottis *(arrows)*. The jugular vein *(j)*, internal carotid artery *(i)*, external carotid artery *(e)*, sternocleidomastoid muscle *(S)*, and hyoid bone *(H)* are also seen. **B,** Eight millimeters inferiorly, a fat-containing pre-epiglottic space *(PES)* anteriorly contrasts with the soft tissue density of the epiglottis *(arrow)*. The fat in the pre-epiglottic space extends posterolaterally into the paralaryngeal (paraglottic) space *(PLS)*. The aryepiglottic folds *(arrowheads)* separate the air-containing pyriform sinuses *(P)* and the laryngeal vestibule *(Ve)*.

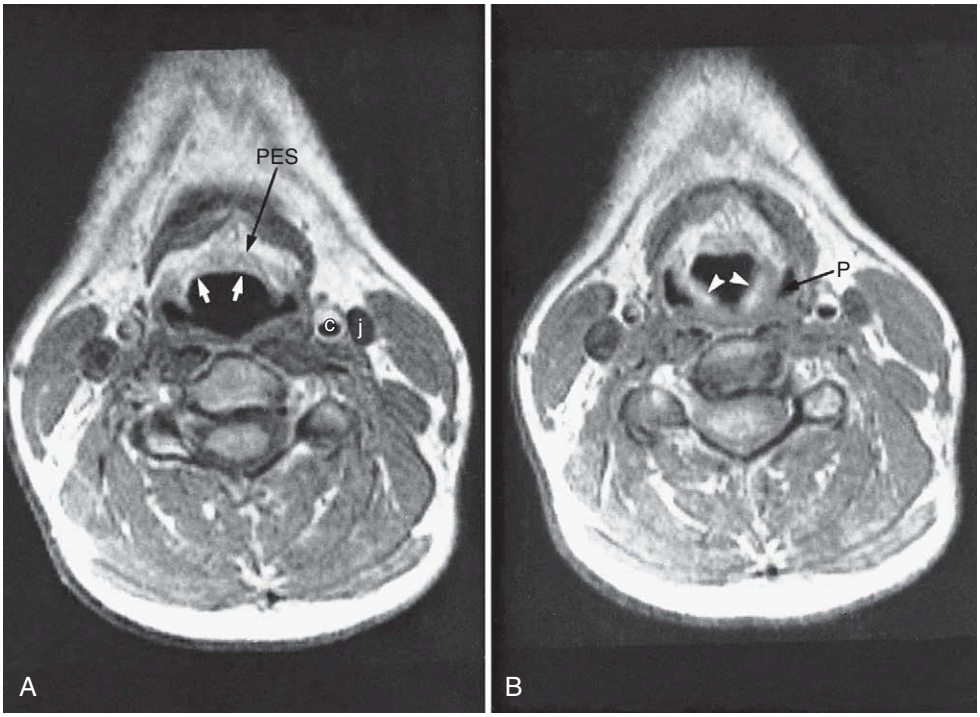

Figure 106-20. Normal anatomy of the supraglottic larynx on magnetic resonance imaging. **A**, A fat-filled pre-epiglottic space *(PES)* is anterior to the epiglottis *(arrows)*. The internal carotid artery *(c)* and internal jugular vein *(j)* are also seen. Fat on this sequence is higher in signal intensity than the epiglottis or muscle. **B,** Five millimeters inferiorly, the pyriform sinuses *(P)* are lateral to the aryepiglottic folds *(arrowheads)*.

asymmetry should be recognized in patients with suspected laryngeal abnormalities to avoid misinterpretation of scans.

The laryngeal skeleton consists of the epiglottic, thyroid, arytenoid, and cricoid cartilages. The hyoid bone is considered part of the lingual apparatus, but relationships with the larynx are important. The unique appearance of the hyoid bone and laryngeal cartilages allows for easy orientation on CT. The degree of cartilaginous mineralization varies considerably. In particular, calcification of the thyroid cartilage may be irregular and incomplete, simulating neoplastic invasion. The calcified or ossified portions of the laryngeal skeleton are hypointense on MR scans and may be more difficult to identify than on CT. Non-calcified cartilage such as the epiglottis is intermediate in signal intensity. Fat within medullary spaces is hyperintense on T1-weighted sequences.

The intrinsic soft tissue structures of the larynx include the aryepiglottic folds, true vocal cords, and false vocal cords. The aryepiglottic folds, which form the medial walls of the pyriform sinuses, extend obliquely from the top of the epiglottis toward the false cords inferiorly (see Figs. 106-19 and 106-20). Although the aryepiglottic folds may be asymmetric during inspiration, distention of the pyriform sinuses during modified Valsalva's maneuver or phonation results in a more symmetric appearance.

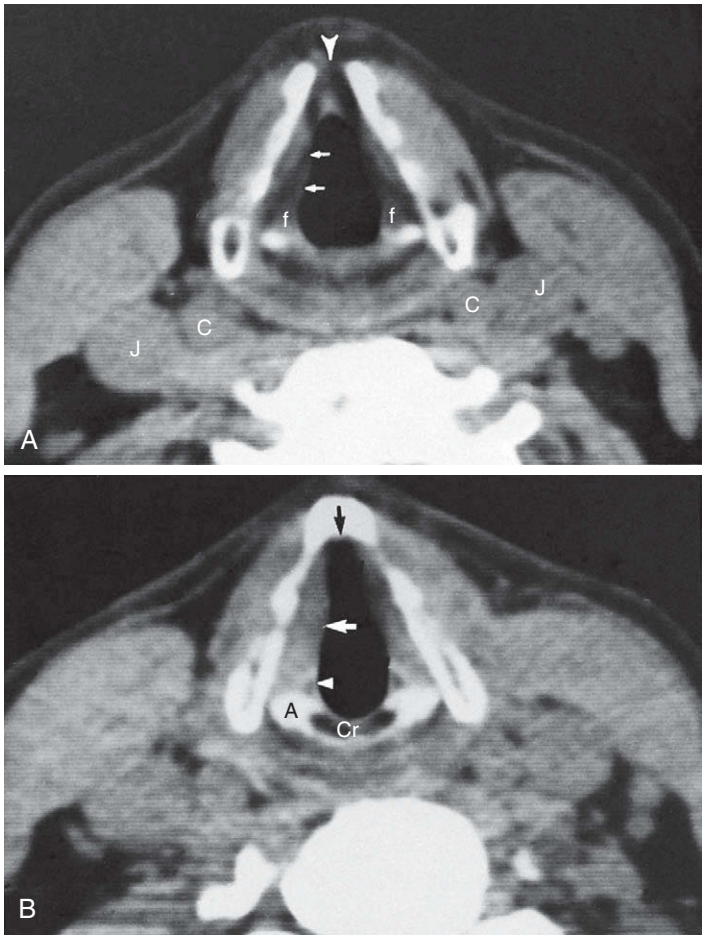

Figure 106-21. Normal anatomy of the false and true vocal cords on computed tomography. **A,** The false vocal cords *(arrows)*, medial to the fat-containing paraglottic space, lie at the level of the foot processes *(f)* of the arytenoid cartilages. The superior thyroid notch *(arrowhead)* is noted anteriorly between the thyroid laminae. The thyroid cartilage is incompletely calcified, which is a normal variation that should not be mistaken for cartilage destruction. The jugular vein *(J)* and carotid artery *(C)* are also seen. **B,** Four millimeters inferiorly, the true vocal cords *(white arrow)* are seen at the level of the vocal processes *(arrowhead)* of the arytenoid cartilages *(A)*, located superolateral to the upper posterior border of the cricoid cartilage *(Cr)*. Thyroid lamina join anteriorly to form the laryngeal prominence. The soft tissues at the anterior commissure *(black arrow)* are normally less than 2 mm in thickness.

Figure 106-22. Normal anatomy of the true vocal cords on magnetic resonance imaging. The true cords *(arrowheads)* are of soft tissue intensity. The arytenoids *(small arrows)* and thyroid lamina *(curved arrow)* are seen as high signal intensity on this sequence because of fatty marrow. The superior portion of the cricoid is also shown *(arrow)*.

The pyriform sinuses are bilateral air-containing structures bulging into the laterally positioned paraglottic spaces (see Figs. 106-19 and 106-20). They are partially collapsed during quiet breathing but distend during modified Valsalva's maneuver or phonation. The pyriform sinuses are frequently asymmetric on scans, both in their size and their caudal extent.

The true vocal cords are visualized in an abducted position during slow inspiration (see Figs. 106-21 and 106-22). They are triangular in shape and wider posteriorly, measuring about 9 mm in thickness. The posterior commissure is located in this area between the vocal processes of the arytenoids. At the anterior commissure, where the true vocal cords meet and attach to the thyroid cartilage, the thickness tapers to 1 mm. Only minimal soft tissue thickening (≤1 to 2 mm) should be seen in the anterior or posterior commissure. If the cords are adducted, the soft tissues in the anterior and posterior commissures may appear falsely thickened. The rapid scanning times with spiral CT permit study of vocal cord motion and verification of questionable abnormalities detected with dynamic CT.

The false vocal cords appear as a thicker band of soft tissue at the level where the foot processes of the arytenoids are present (see Fig. 106-21). In contrast to the region of the anterior commissure and true vocal cords, normally appreciable soft tissue thickening occurs anteriorly behind the thyroid lamina, in part because of insertion of the

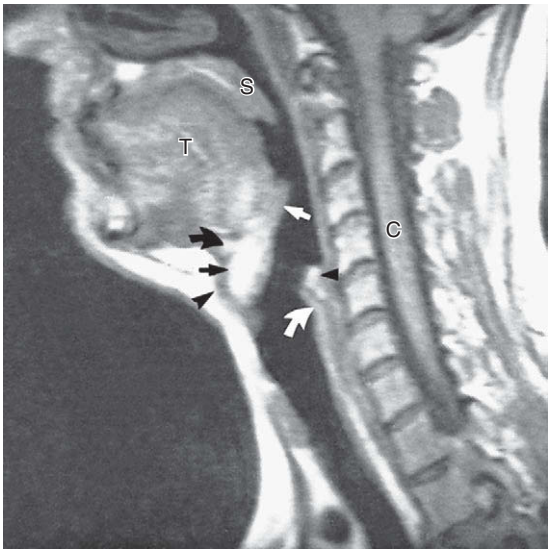

Figure 106-23. Normal anatomy of the midsagittal plane on magnetic resonance imaging. Epiglottis *(white arrow)*, fat-containing pre-epiglottic space *(black arrow)*, extrinsic strap muscles *(black arrowhead)*, arytenoid cartilages and muscles *(small black arrowhead)*, hyoid bone *(curved black arrow)*, and cricoid cartilage *(curved white arrow)* are shown. The soft palate *(S)*, tongue *(T)*, and spinal cord *(C)* are also seen.

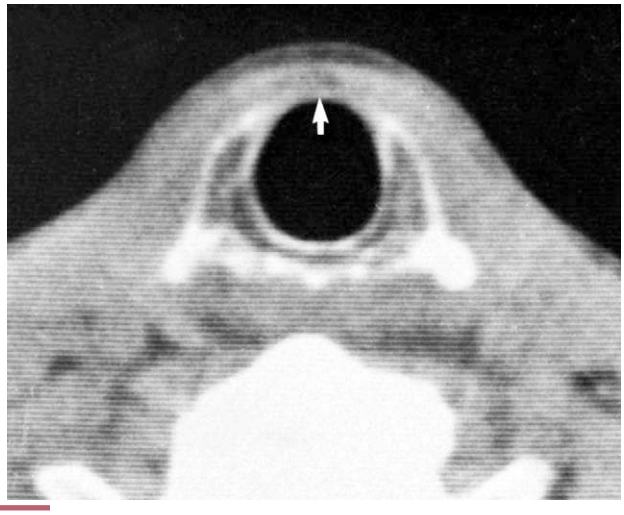

Figure 106-24. Normal anatomy of the subglottic level on computed tomography. The cricoid ring is almost complete, except in the area of the cricothyroid membrane anteriorly *(arrow)*. Note that the circular subglottic airway is in close apposition to the cricoid cartilage.

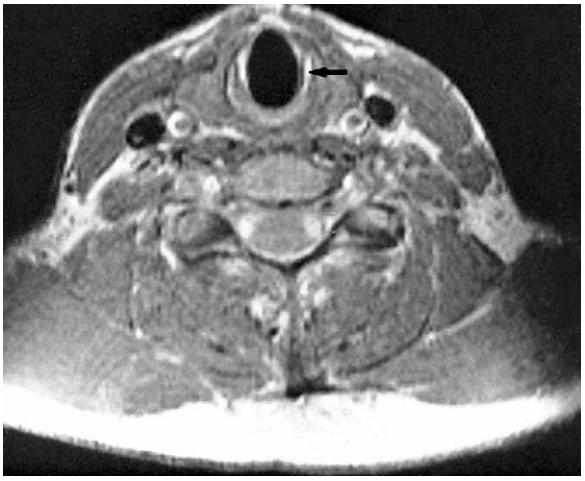

Figure 106-25. Normal anatomy of the subglottic level on magnetic resonance imaging. Fat-containing cricoid surrounds the airway *(arrow)*.

Figure 106-26. Normal anatomy of the coronal plane on magnetic resonance imaging. Cricoid cartilage *(large black arrowhead)*, thyroid cartilage *(small black arrowhead)*, true cords *(white arrowhead)*, and aryepiglottic folds *(white arrow)* are shown.

thyroepiglottic ligament. The laryngeal ventricle separating the true and false vocal cords is visualized only in 10% of patients scanned in the axial plane because of partial volume averaging. On MR imaging, the ventricle is best identified in the coronal plane. The use of a reverse "e" maneuver may improve visualization of the laryngeal ventricle.

The soft tissue (pre-epiglottic and paraglottic spaces) deep to the endolarynx is well visualized on CT because it is composed primarily of fat. Consequently it is more hypodense than the true vocal cords or neoplasm (see Fig. 106-19). On MR imaging, these spaces display relative hyperintensity on T1-weighted images, reflecting the fat composition. Sagittal MR images are especially useful in evaluating the preepiglottic space (see Figs. 106-20 and 106-23).[134,135]

The laryngeal airway has different shapes at different levels. The laryngeal vestibule or supraglottic portion of the airway is elliptic with a long lateral axis. The anterior-posterior dimension of the airway increases at the level of the true vocal cords. The subglottic region has a circular configuration with a flat posterior border at the level of the trachea. The cricoid ring indicates the level of the subglottic space. In this area, soft tissue should not be detectable on CT or MR scans between the inner surface of the cricoid cartilage and the airway (see Figs. 106-24 through 106-26).

The jugular veins and carotid arteries can be clearly visualized posterolateral to the thyroid laminae. The right jugular vein, which is usually larger than the left, may be confused with lymphadenopathy on imaging and physical examination. In such cases, CT performed after administration of intravenous contrast improves identification of the normal vascular structures. Rapidly flowing blood within the jugular vein and carotid arteries is devoid of signal on MR imaging and

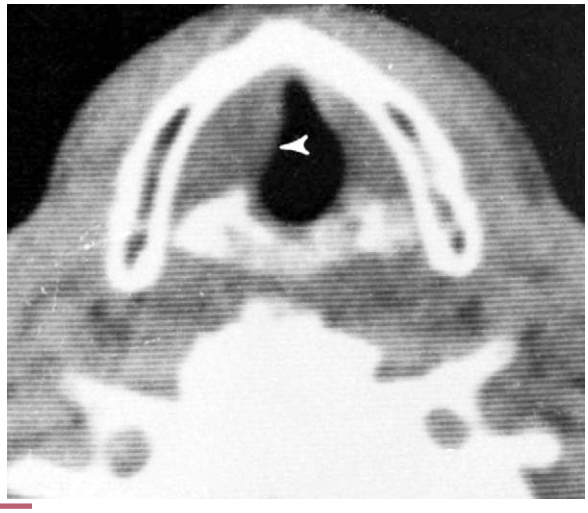

Figure 106-27. Localized true vocal cord carcinoma on computed tomography. A neoplasm diffusely thickens the right true vocal cord *(arrowhead)*. CT more inferiorly showed no subglottic extension.

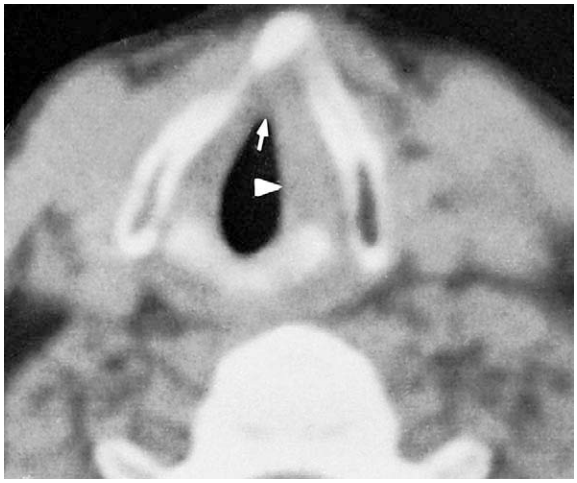

Figure 106-28. True vocal cord carcinoma with involvement of anterior commissure on computed tomography. Tumor of the left true vocal cord *(arrowhead)* extends anteriorly to involve the anterior commissure *(arrow)*.

therefore can be easily separated from soft tissue structures; however, turbulence of flow may require careful image analysis.[136]

Glottic Tumors

Carcinomas confined to a normally mobile true vocal cord may be treated with radiotherapy, laser, cordectomy, or partial laryngectomy.[81,82] In these cases, imaging may be normal or show nonspecific focal or diffuse vocal cord thickening (Fig. 106-27). If the true cord is fixed in the midline, imaging shows deep infiltration of tumor before surgery.[43] CT cannot distinguish whether the cord is paramedian in position because of paralysis or direct involvement with tumor. MR imaging is helpful in this determination because of its superior soft tissue contrast. Nevertheless, signal characteristics are often nonspecific. CT occasionally shows that vocal cord fixation or a laryngeal mass is secondary to prior occult trauma and that the laryngeal neoplasm is less extensive than suspected clinically.

Glottic tumors spread anteriorly, posteriorly, inferiorly, or laterally into the paraglottic space. The primary role of imaging true vocal cord neoplasms is evaluation of the anterior and posterior commissures, the paraglottic and subglottic spaces, and the thyroid and cricoid cartilages. CT and MR imaging reliably show tumor involvement at these sites. If involvement is greater than 30% of the contralateral true vocal cord, thyroid cartilage invasion is evident, or subglottic extension of tumor is demonstrated, partial laryngectomy is generally contraindicated.[81,82]

Tumors can extend anteriorly to the anterior commissure and posteriorly to the arytenoid cartilage, posterior commissure, and cricoarytenoid joint (Fig. 106-28). Identification of air abutting the thyroid cartilage at the anterior commissure on transverse images indicates tumor absence in this area. If soft tissue thickening of the anterior commissure is greater than 1 mm on imaging, tumor invasion is implied.[71,89,137] Tumor that has reached the anterior commissure can grow into the thyroid cartilage, pre-epiglottic space, opposite vocal cord, or subglottic space.[138] Care should be taken to avoid misdiagnosis of anterior tumor spread caused by various cord configurations that occur in different phases of respiration. Tumor that has reached the posterior commissure results in soft tissue thickening over the arytenoid cartilages; rotation or displacement of the arytenoid cartilages may also occur.

Subglottic tumor is diagnosed on imaging by determining the relationship of the tumor mass to the level of the true cords (Fig. 106-29). Exophytic tumor will distort the tracheal air column (Fig. 106-30). If the extent of tumor caudad from the inferior margin of true vocal cords is greater than 1 cm anteriorly and 6 mm posteriorly, total laryngectomy may be indicated.[81,138] However, the relationship between the subglottic tumor and the cricoid cartilage is more important than a standard measurement because the cricoid cartilage supports the larynx. On CT and MR scans, no measurable soft tissue thickness should be observed between the cricoid cartilage and the airway. MR imaging also can image the coronal plane, which allows tracing of tumor extension below the level of the conus elasticus.[68]

Imaging also shows spread of laryngeal carcinoma into the paraglottic space. Although a thin line of fat density may be seen medial to the thyroid cartilage at the level of the true vocal cords, the paraglottic space is wider in the area of the false vocal cord.[139] Therefore extension into the paraglottic area is easier to show at this level. CT, however, may not be able to determine extension into the false vocal cord itself; this is better evaluated by laryngoscopy. Coronal MR images help document paraglottic extension.

CT and MR imaging are excellent methods for showing cartilaginous invasion by laryngeal carcinoma, although limitations exist.[15,73,140-143] Because the thyroid cartilage normally may have an irregular pattern of calcification and ossification, neoplastic involvement can be confidently diagnosed only when advanced. Frank destruction of the cartilage by an adjacent mass or demonstration of intramedullary cancer are the most reliable imaging signs of cartilage invasion. On CT, marked destruction of the cartilage appears as fragmentation of the cartilage with lateral extension of soft tissue tumor (Fig. 106-31). Cartilage involvement may also be suggested by abnormal bowing of the thyroid cartilage. Because of its symmetry, sclerosis or destruction of the cricoid is easier to appreciate on CT than on MR scans.[137]

Ossified portions of cartilage are at higher risk for invasion possibly because of vascular channel penetration, whereas intact perichondrium surrounding avascular unossified cartilage resists tumor encroachment.[144-148] Almost 50% of pathologically sclerotic cartilages associated with a mass show invasion at surgery.[145,149] Nonmalignant causes of thyroid cartilage sclerosis include rheumatoid arthritis and polychondritis; however, these conditions can usually be differentiated from cancer by the presence of sore throat, difficult inspiration, subluxation of the arytenoid cartilages, and the absence of a mass.[145]

Many investigators contend that MR images detect cartilage invasion better than CT.[72,73,126,150-153] On MR scans, cortical bone and dense calcification have no signal on T1- or T2-weighted sequences. However, medullary fat is hyperintense on T1-weighted images. Invasion of fat lowers this signal and can be further differentiated from nonossified cartilage on T1-weighted and T2-weighted images because of the hyperintensity displayed by tumor (Fig. 106-32).[42,72,109,142,146,154,155] Almost 10% of healthy thyroid cartilage may have focal areas of signal intensity; however, an associated mass increases confidence in the diagnosis, especially if the mass exceeds 5 cm^3 in volume.[42,156] If the imaging

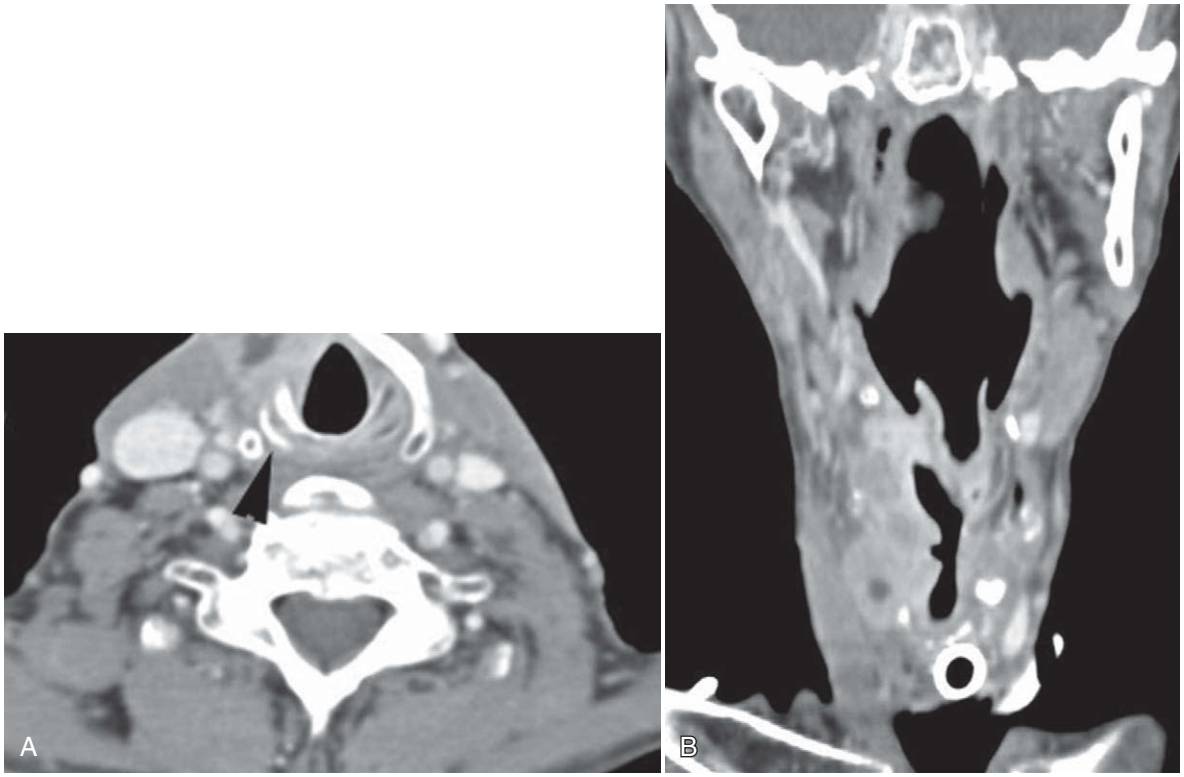

Figure 106-29. Massive transglottic carcinoma on computed tomography. **A,** Necrotic tumor has destroyed the right thyroid cartilage lamina. The right portion of the cricoid cartilage is sclerotic *(arrowhead),* indicating involvement with tumor. The mucosal thickening adjacent to the cricoid and extending inferiorly (slices not shown) suggests subglottic extension. **B,** Reformatted coronal scan nicely demonstrates the cranio-caudal extent of the tumor. Spiral scanning technology permits superb multiplanar reformations.

Figure 106-30. Magnetic resonance imaging of subglottic extension of carcinoma shows high signal in an extensive neck mass *(arrow).* Subglottic extension *(arrowheads)* compresses the tracheal air column.

findings are equivocal, biopsy of the cartilage confirms the need for radical surgery.

Supraglottic Tumors

Imaging is extremely useful in staging supraglottic carcinoma and may discover more advanced disease than clinically suspected in up to 20% of patients.[157] Carcinoma of the epiglottis is seen on imaging as thickening of one of the margins of the epiglottis or as a large soft tissue mass (Figs. 106-33 and 106-34). Localized carcinoma of the epiglottis may be managed with radiotherapy or a supraglottic laryngectomy.[158] However, if there is invasion of the pre-epiglottic space, radiotherapy alone is considered inadequate.[159] Extension of epiglottic carcinoma to the pre-epiglottic space is frequently difficult to show clinically. CT and MR imaging help evaluate the pre-epiglottic and paraglottic spaces because infiltrating tumors usually obliterate the normal appearance of fat in these areas (Figs. 106-35 and 106-36).[68,109,160] T1-weighted sagittal MR imaging is especially useful for examining pre-epiglottic tumor invasion.[146,161] Transversely oriented CT or MR images are helpful when the vocal cords and the space immediately superior to the cords are normal. Similarly, transverse slices are useful when the cords are unequivocally involved. In patients with supraglottic disease that approaches the ventricles but in whom transverse imaging does not clearly depict the ventricle, a coronal MR scan is the best study.[68] CT and MR scans can also show deep spread of tumor into the region of the anterior commissure. Spread of tumor into the base of the tongue is best evaluated by sagittal MR images.

Carcinoma of the aryepiglottic fold is recognizable by thickening of the aryepiglottic fold and is often better seen on scans obtained during phonation or a modified Valsalva's maneuver (Fig. 106-37). The rapid scanning speed of spiral CT is ideally suited for such functional imaging. CT obtained during phonation shows distention of the pyriform sinuses and thinning of the healthy aryepiglottic fold, allowing for easier CT demonstration of tumor. If the tumor extends anteriorly across the midline, imaging studies may not determine whether the tumor originates in the aryepiglottic fold or in the epiglottis.

Neoplasms of the pyriform sinus generally are more aggressive than lesions of the endolarynx and have a high incidence of thyroid cartilage invasion. They may also spread to the true and false vocal cords, aryepiglottic folds, and pre-epiglottic space. CT or MR images can show tumor spread outside of the larynx between the thyroid and

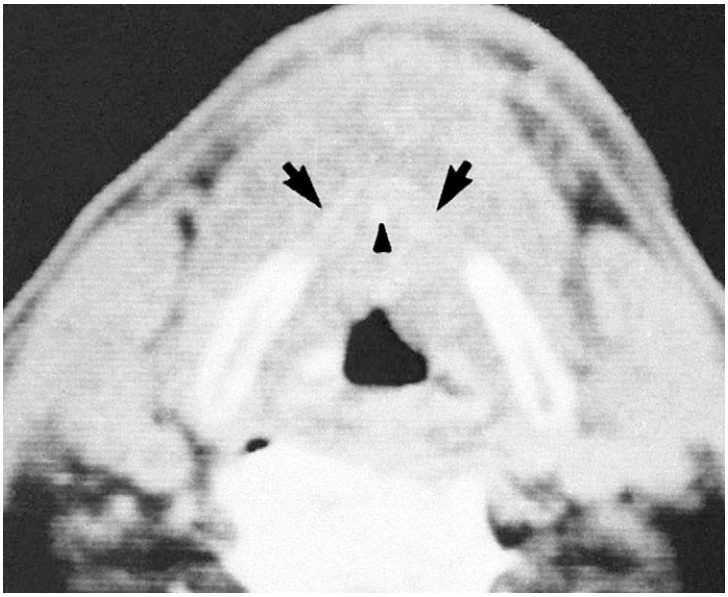

Figure 106-31. Thyroid cartilage destruction on computed tomography. A large neoplasm involving the anterior commissure destroys both thyroid alae anteriorly *(arrows)* and extends into the adjacent soft tissues. A small bony fragment can be seen within the tumor *(arrowhead)*.

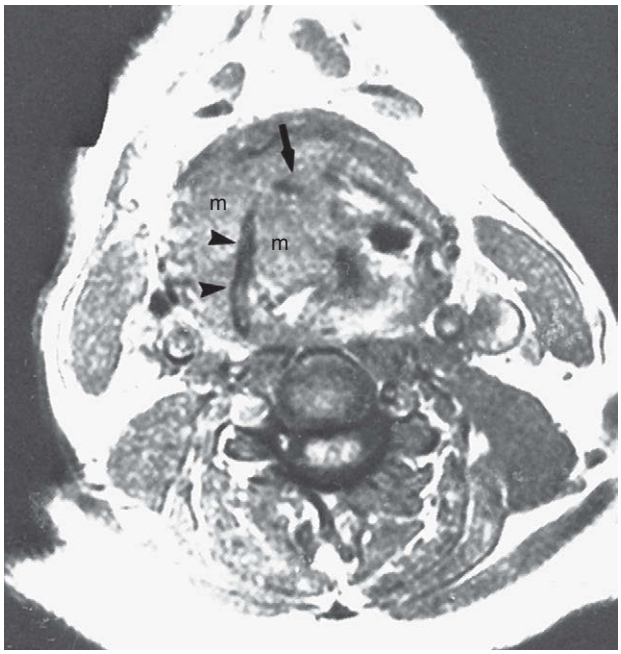

Figure 106-32. T1-weighted magnetic resonance imaging shows thyroid cartilage destruction. An extensive carcinoma *(m)* envelopes the thyroid cartilage destroying anterior portions *(arrow)*. The invaded lateral cartilage has lost its hyperintensity because of tumor replacement *(arrowheads)*.

cricoid cartilages. This appearance usually is seen only with pyriform sinus tumors (Fig. 106-38).[162]

In addition to using imaging appearances to evaluate stage of disease, quantitative methods may prove valuable. Calculated pretreatment tumor volumes using CT may predict local control following radiation or surgery.[163,164]

Transglottic Tumors

Transglottic tumors extend across the laryngeal ventricle to involve the supraglottic, glottic, and often the subglottic portions of the larynx (see Fig. 106-38).[137,165] This extension of tumor may be mucosal or submucosal. Transglottic tumors have a high incidence of thyroid cartilage destruction and extralaryngeal spread that may not be apparent clinically. Coronal MR scans may better show spread of tumor than axial images. MR imaging is also effective, demonstrating tumor involvement of the prevertebral space.[166]

Lymph Nodes

Most enlarged lymph nodes identified on CT are clinically palpable, but occasionally CT may show enlarged lymph nodes that cannot be felt on physical examination.[167] MR imaging and ultrasonography are also effective methods for evaluating lymph nodes.[123,168,169] Imaging also helps show the relationship of enlarged lymph nodes or tumor extension to adjacent vessels (Fig. 106-39). Surgical salvage is less likely if the neoplasm totally encases or invades vascular structures. Knowledge of the vessels of the neck is crucial in order to avoid mistakenly identifying a vein as a lymph node.[136]

Post-Therapy Larynx

Physical examination of patients who have undergone prior irradiation or surgery may be difficult because of altered normal laryngeal anatomy and swelling of the adjacent soft tissues. Although CT can define the anatomy of the postoperative larynx and assist laryngoscopy in the detection of recurrent neoplasm (Fig. 106-40),[170-173] MR scanning is now preferred for post-therapy evaluation.[174]

In patients with previous vertical hemilaryngectomy, recurrent intralaryngeal cancer is suggested by increased width of the contralateral true vocal cord, convexity of the postsurgical pseudocord at the glottic level, mass in the subglottic region, or masses in the extralaryngeal neck.[171] In patients with supraglottic subtotal laryngectomy, recurrence is usually heralded by mass effect on the pharyngeal or laryngeal air column, obliteration of the adjacent soft tissue planes, destruction of cartilage, or development of lymphadenopathy.[172] Imaging signs of recurrence in patients who have undergone total laryngectomy include masses involving the internal jugular lymph node chain adjacent to the neopharynx or neurovascular bundle, masses within the mediastinum, thickening of the tracheal wall, or thickening of the soft tissues surrounding the tracheostomy.[170] Nodular masses at the site of radical neck dissection are unusual and should prompt evaluation for tumor.[173] Care should be taken in radiographically evaluating the postoperative patient because abscess or granulation tissue can mimic recurrent tumor.[171]

Regardless of the surgical procedure, hemorrhage and edema are usually evident on imaging during the early postoperative period and persist for 4 to 6 weeks. A baseline scan is therefore best postponed for

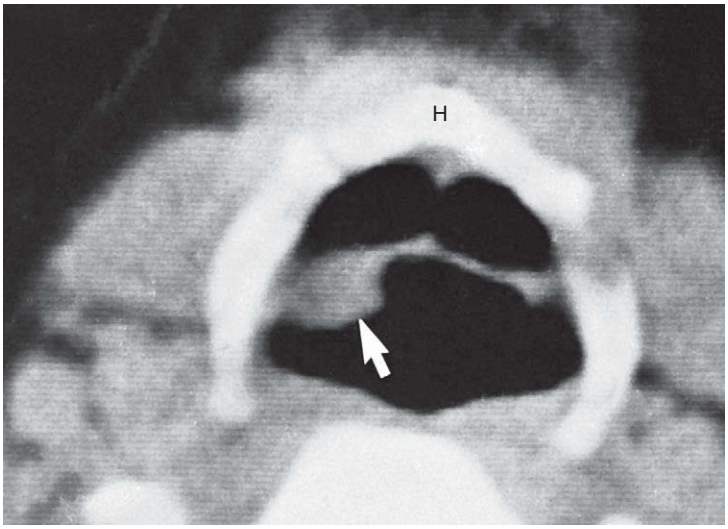

Figure 106-33. Epiglottic carcinoma on computed tomography. A tumor produces thickening of the right side of the epiglottis *(arrow)* at the level of the hyoid bone *(H)*.

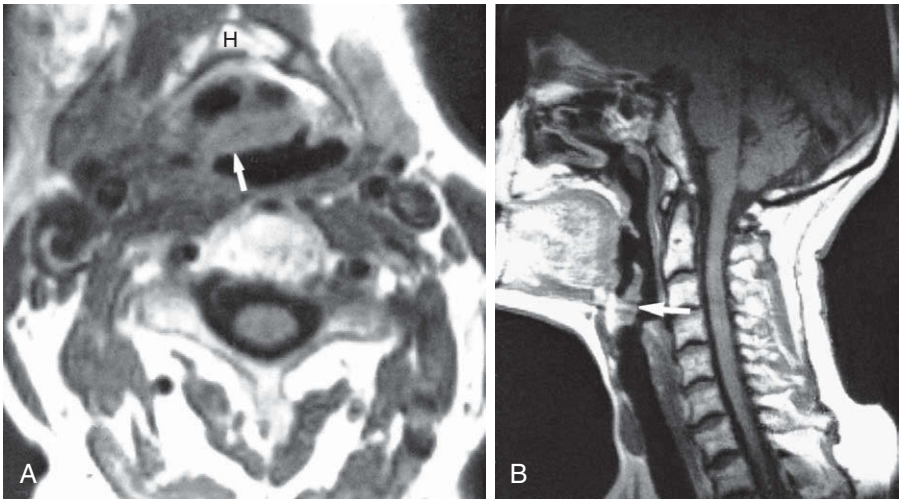

Figure 106-34. Magnetic resonance imaging of epiglottic carcinoma. **A,** Tumor thickens the right side of the epiglottis *(arrow)* at the level of hyoid *(H)*. **B,** Sagittal view shows nodular thickening of the epiglottis caused by tumor *(white arrow)*.

Figure 106-35. Epiglottic carcinoma on computed tomography. A large epiglottic tumor *(T)* infiltrates the pre-epiglottic space.

Figure 106-36. Magnetic resonance imaging of supraglottic carcinoma. Large mass *(T)* markedly thickens the epiglottis and invades the pre-epiglottic space.

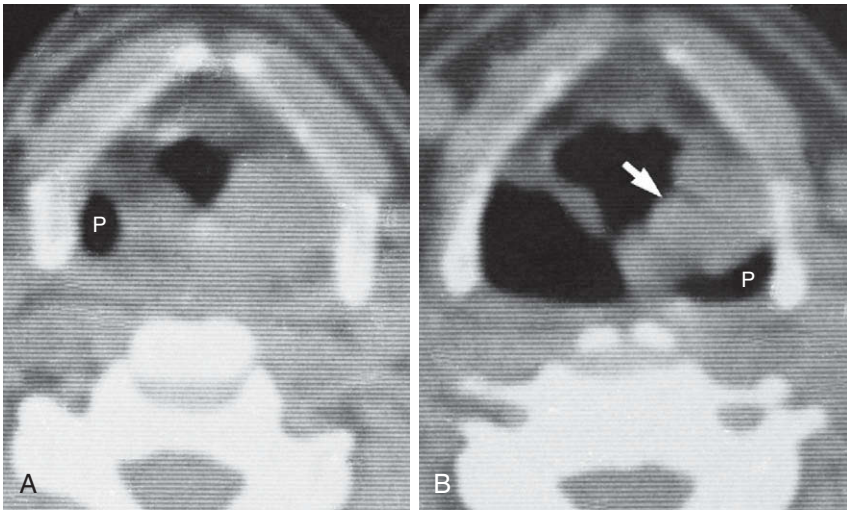

Figure 106-37. Aryepiglottic fold carcinoma on computed tomography (CT). **A,** The left aryepiglottic fold and pyriform sinus are not well visualized. The right pyriform sinus is shown *(P)*. **B,** CT performed during a modified Valsalva's maneuver more clearly shows a tumor involving the left aryepiglottic fold *(arrow)* and compressing the left pyriform sinus *(P)*.

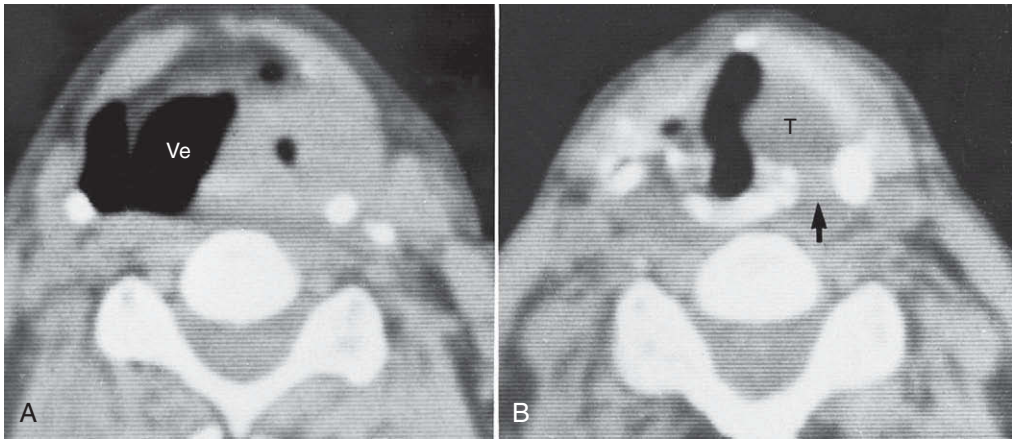

Figure 106-38. Transglottic pyriform sinus carcinoma on computed tomography. **A,** A large tumor is seen arising in the left pyriform sinus and displacing the laryngeal vestibule *(Ve)* to the right. **B,** Tumor extends inferiorly to involve the left true vocal cord *(T)* and widen the distance *(arrow)* between the left thyroid lamina and the arytenoid cartilage.

at least 1 month and preferably for 6 to 8 weeks to avoid potentially confusing soft tissue masses.[82] Scanning every 4 to 6 months for the first 3 years is recommended.[175,176] Examinations are then performed yearly unless an ominous change in clinical status prompts a more timely scan.[176]

Typically, cancer recurrence within the first 2 months after surgery is unusual if the specimen margins were free of tumor.[176] With time, tissue planes become more defined but remain somewhat obscured compared with the preoperative images. Scar tends to be less dense on CT but may be difficult to differentiate from fibrous tissue without biopsy. MR images usually cannot reliably distinguish recurrent tumor from edema, radiation necrosis, or inflammatory lesions.[146] Fibrosis tends to be hypointense on T2-weighted images, whereas recurrent tumor is hyperintense.[175] Growth of any soft tissue density on imaging is another sign of recurrence, whereas scar remains stable or diminishes with time.[176]

Radiotherapy can also change the appearance of the neck on imaging.[177] The major and minor salivary glands are especially sensitive to radiation, and 1000 to 2000 cGy causes mucositis.[178] On CT, the major salivary glands enhance and eventually atrophy.[179] 3D Radiation port planning shields the parotid glands and ameliorates post-therapy xerostomia.[92] The subcutaneous fat becomes thickened and streaked with linear soft tissue densities at 6500 to 7000 cGy.[137,179] The skin also may become thickened. With doses approaching 7000 cGy, skin ulceration becomes increasingly likely.[178] At doses greater than 7000 cGy, the pharyngeal walls and aryepiglottic folds become thickened as the paraglottic and pre-epiglottic spaces increase in CT density.[161,178] Higher doses of radiation weaken membranes and cartilage and may contribute to chondronecrosis and cartilage collapse.[137] Chondronecrosis is difficult to differentiate from recurrent tumor on CT. The soft tissues are thickened, and cartilages may be distorted or fragmented.[82] Radiated cartilage is also more prone to infection and may develop perichondritis if biopsied.[180]

Other organs may be affected by neck radiation. The adjacent skeleton may show hyperintense marrow signal on T1-weighted images because of post-therapy marrow fat infiltration, the mandible may succumb to osteoradionecrosis, and rarely, the radiated bone may give rise to sarcomas.[178] Osteoradionecrosis involves the devitalization of radiated bone and is caused by vascular damage and direct injury to osteoblasts augmented by xerostomia and resultant dental caries. The involved bone has focal demineralization, disorganized trabeculae, cortical thickening, patchy sclerosis, and occasionally pathologic

fractures.[178] Periosteal reaction is unusual and should prompt consideration of infection.

Carotid rupture or "blow out" is a life-threatening complication with a high morbidity and mortality. Catheter angiography with endovascular therapy effectively diagnoses and treats many of these lesions.[181]

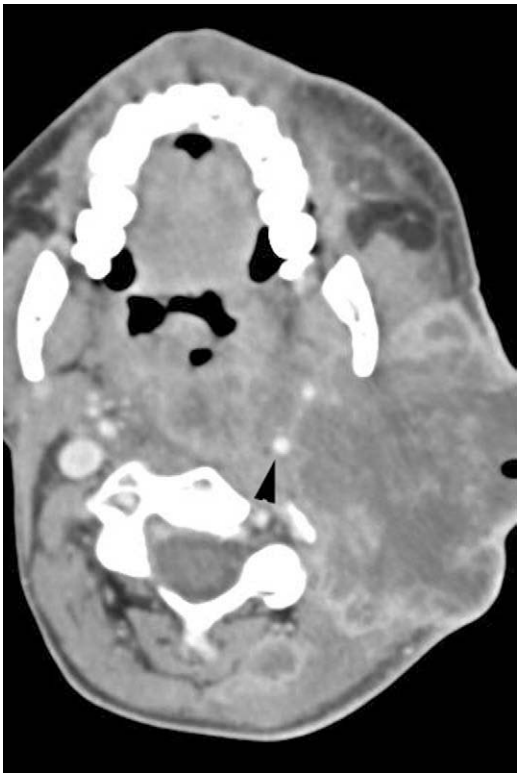

Figure 106-39. Laryngeal carcinoma with lymph node metastases on computed tomography. Massive necrotic cervical and retropharyngeal lymph node metastases are seen encasing the left internal carotid arteries *(arrowhead)*.

Differentiating postradiation changes from recurrent tumor is difficult on imaging studies.[182] Intralaryngeal edema may be symmetric or asymmetric and therefore offers no definitive criteria for tumor recurrence.[82,161,178] Residual tumor usually maintains a high signal intensity on MR scans, and the signal intensity of successfully managed tumor tends to diminish with development of fibrosis.[183] However, similar nonspecific and occasionally confusing signal intensities can also be produced by edema, hyperplastic lymphadenopathy, infection, and hemorrhage.[174,178,183,184] Differentiation between fibrosis and early recurrent tumor often requires laryngoscopic biopsy. Complete or near complete resolution of the primary lesion on imaging is one of the best criteria for a successful radiation response. Residual mass greater than 50% of the original tumor volume usually indicates therapy failure.[185] Finally, growth of associated soft tissue mass suggests tumor recurrence. The appearance of new focal masses and ulcerations on barium pharyngography supports the clinical diagnosis of recurrence.[186] Other modalities such as PET or single photon emission CT (SPECT) with fluorodeoxyglucose may be more useful than conventional cross-sectional imaging.[73,161] Combined PET/CT merges PET and CT data into a single scan that couples functional metabolic information with precise anatomic localization. This information can be used for more confident diagnosis of recurrent tumor and for biopsy.[131]

Postradiation sarcomas are rare and usually appear after a latent period lasting decades. Because of the age of the typical neck cancer patient, the associated multisystem debilities from chronic smoking, and the unfortunately high rate of recurrent tumor, sarcomas are usually not seen.

Laryngeal Trauma

Laryngeal trauma usually results from direct blunt injury to the anterior neck. The usual mechanism for the observed damage is the forceful impact of larynx against the cervical spine. The thyroid cartilage may be fractured in almost 50% of cases. The cricoarytenoid joint may also be dislocated. The ring-shaped cricoid cartilage may also fracture. Because of its configuration, usually two or more sites are involved. Rarely, the epiglottis may be disrupted.[187] Hemorrhage and edema may spread into the paraglottic and pre-epiglottic spaces.[188] Nondisplaced fractures may be managed conservatively; however, displaced and comminuted fractures require surgery.[189-191]

Cross-sectional imaging permits easy and rapid evaluation of the extent of cartilaginous injury, adjacent soft tissue changes (e.g., edema, hemorrhage), and the degree of airway compromise (Figs. 106-41 and

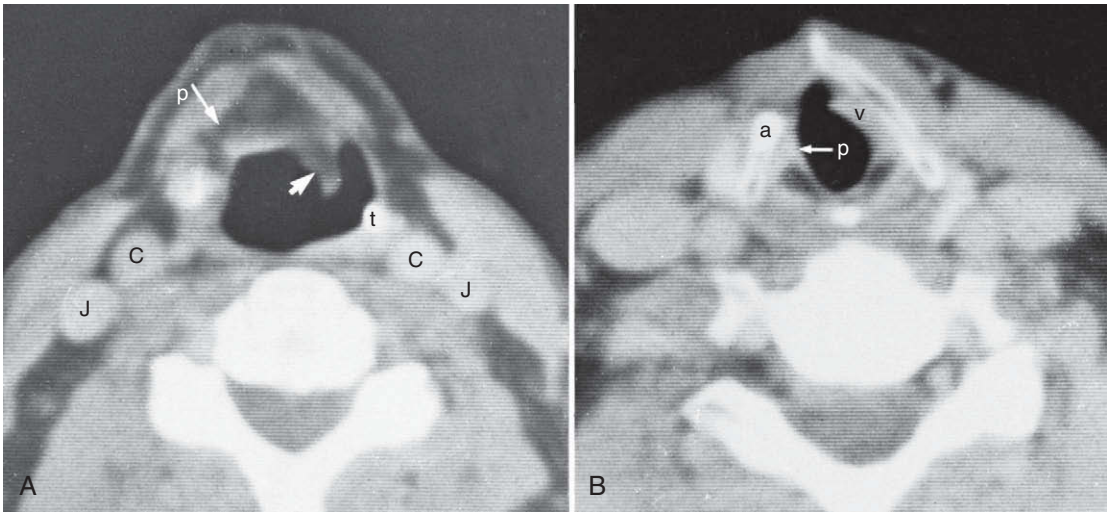

Figure 106-40. Computed tomography of normal anatomy after right vertical hemilaryngectomy. **A,** Level of superior cornua of the thyroid cartilage. *Arrow* points to residual aryepiglottic fold on the nonoperated side. The superior cornu of thyroid cartilage *(t)*, pre-epiglottic space with diminution of fat content *(p)*, carotid artery *(C)*, and internal jugular vein *(J)* are also seen. **B,** Level of glottis. Note the normal tilt of the airway to the right. The residual right thyroid ala *(a)*, surgically created pseudocord *(p)*, and residual left true vocal cord *(v)* are also seen.

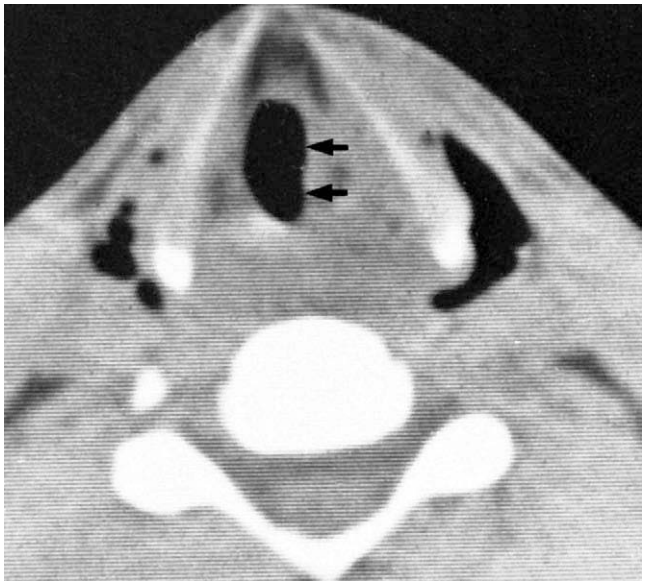

Figure 106-41. Soft tissue swelling with intact cartilage on computed tomography. Marked soft tissue thickening of the right paraglottic space is seen with compression of the airway *(arrows)*. Both thyroid alae are intact. Subcutaneous emphysema is secondary to a mucosal tear from an emergency tracheotomy.

Figure 106-42. Computed tomography shows multiple fractures of the thyroid cartilage. Extensive hemorrhage and edema almost totally obliterate the airway *(arrow)*.

106-42). Although conventional frontal and lateral radiography can provide useful information about the injured larynx, CT is preferred in the acutely injured patient because of its speed and ability to define calcified cartilages and soft tissue damage.[191-193] Spiral techniques are well suited for this situation. A complete examination of the neck can be acquired within seconds. With the addition of intravenous contrast, the raw CT data can be used to reconstruct 3D images of the carotid and vertebral arteries in a technique known as *CT angiography* (CTA). CT also is useful in patients with marked supraglottic swelling that prevents adequate laryngoscopic evaluation. CT can accurately identify

Figure 106-43. Foreign body. A straight pin *(arrow)* is lodged in the vallecula.

transverse or vertical fractures of the thyroid or cricoid cartilage, dislocation of the arytenoid cartilages at the cricoarytenoid joint, disruption of the cricothyroid joint, and extensive hemorrhage obliterating the airway. On occasion, the thyroid notch may be mistaken for a fracture, although contiguous sections usually provide the correct diagnosis. MR scans do not image calcified cartilage well and are therefore of no use in the initial evaluation of acute laryngeal trauma. Following patient stabilization, MR imaging may be useful in evaluating adjacent soft tissue damage or spinal injury.

Pharyngeal perforation is a rare but known complication of endotracheal intubation.[194,195] Traumatic intubation may also cause severe soft tissue damage, soft tissue emphysema, and arytenoid cartilage dislocation. Radiography of the area often shows air within the retropharyngeal soft tissues or in the anterior mediastinum. Oral contrast studies of the esophagus may define the problems related to perforation including subsequent development of a pseudodiverticulum.

Foreign Bodies

Foreign bodies in the larynx, trachea, or esophagus should be considered in patients, particularly children, with symptoms of acute or recurrent airway disease.[196,197] The radiopaque objects are readily diagnosed (Fig. 106-43). With plain-film techniques including high kilovoltage radiography, nonopaque foreign bodies also may be identified at times. The radiographic findings of aspirated foreign bodies vary directly with the location and extent of obstruction. On occasion, calcification of a laryngeal cartilage or of the stylohyoid ligaments may be confused with aspirated foreign bodies, although oblique projections usually permit separation (Fig. 106-44).[14]

In patients with suspected aspiration of a foreign body and a normal examination of the upper airway, inspiratory-expiratory plain chest radiography or decubitus chest radiography should be performed. These may show regional obstructive emphysema resulting from aspirated foreign bodies in the bronchi.[19,198] In uncooperative patients, fluoroscopic examination of diaphragmatic and mediastinal excursions may help determine if air trapping is present.

Figure 106-44. Stylohyoid ligament. Ossification of the stylohyoid ligament *(arrows)* can simulate a foreign body.

Figure 106-45. Esophageal foreign body in a child with stridor. Lateral view from a barium esophagram discloses a piece of meat *(large arrows)* in the upper esophagus compressing the posterior wall of the trachea *(small arrows).*

Swallowed foreign bodies in the upper esophagus may produce airway obstruction by compressing the posterior wall of the larynx and trachea. Tracheal compression, appreciated best on lateral radiography, is the expected radiographic finding. A barium esophagram is the definitive procedure in disclosing the occult esophageal foreign body, although CT may prove a useful adjunct method (Fig. 106-45).[197] If the object erodes through the esophageal wall, a retropharyngeal abscess may form with resulting compression of the adjacent airway.

Various synthetic materials may be inserted into the larynx and neck. Teflon injected into the paraglottic space adds bulk to a paralyzed or reconstructed vocal cord. Stents ensure patent airway in patients with laryngeal stenosis. Speaking tubes and valves help the laryngectomy patient use the esophagus when speaking. Tracheostomy tubes are inserted into the midcervical region in the patient with laryngeal stenosis, acutely compromised airway, or laryngectomy.[180] Some of these materials may be incidentally noted on scans in patients who have failed to mention past surgical procedures; these materials should not be misinterpreted as masses or traumatic foreign bodies.

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CHAPTER ONE HUNDRED AND SEVEN

Malignant Tumors of the Larynx

William B. Armstrong

David E. Vokes

Robert H. Maisel

Key Points

- Squamous cell carcinoma (SCC) accounts for 85% to 95% of malignant laryngeal tumors.
- Tobacco and alcohol are the two most important risk factors for the development of laryngeal SCC.
- In the United States, laryngeal SCC occurs in the glottis more frequently than in the supraglottis. Subglottic SCC is rare.
- Laryngeal preservation may be achieved in properly selected cases by the use of conservation laryngeal surgery (partial laryngectomy), radiotherapy, or chemoradiotherapy.
- Early laryngeal SCC (stage I, II) is generally treated with single-modality therapy: either surgery or radiotherapy.
- Advanced laryngeal SCC (stage III, IV) is generally treated with combined-modality therapy.
- Endoscopic partial laryngectomy (transoral laser microsurgery) has similar oncologic outcomes to open partial laryngectomy with less functional morbidity.
- Total laryngectomy is the gold standard surgical procedure for the treatment of advanced laryngeal SCC.
- Concurrent chemoradiotherapy in a properly executed organ preservation protocol is the most effective nonsurgical treatment for advanced laryngeal SCC.
- The stage of disease is the most important factor predictive of prognosis, with N (nodal) stage more significant than T (tumor) stage.

Cancer of the larynx is the second most common malignancy of the upper aerodigestive tract (UADT), with over 11,000 cases annually in the United States alone.[1] Although a large variety of malignancies may occur in the larynx, 85% to 95% of laryngeal malignancies are squamous cell carcinoma (SCC), arising from the epithelial lining of the larynx.[2] The successful management of laryngeal malignancy requires accurate diagnosis, staging, assessment of patient wishes, and the selection of the most appropriate treatment for the individual patient, with close post-treatment surveillance. Treatment options have expanded and become more complex as new surgical procedures have been developed, advanced radiation therapy (RT) modalities have evolved, and new chemotherapeutic drugs have become available. These treatments still have significant morbidity and pose risks of adverse impact on voice quality, airway integrity, and swallowing. In recent decades, major efforts have been made to develop therapeutic strategies to preserve the larynx anatomically and functionally using RT, conservation laryngeal surgery, and chemoradiotherapy (CRT). These techniques are now important tools in the armamentarium of the head and neck oncologist. This chapter focuses on the principles of the diagnosis, evaluation, and treatment of SCC of the larynx. Non–squamous cell malignancies form a small but important subset of laryngeal malignancies and are also covered in detail. More specific details of surgical techniques are discussed in subsequent chapters.

Anatomy and Embryology

A detailed understanding of laryngeal embryology and anatomy is necessary to understand patterns of spread of laryngeal cancer and help understand its clinical behavior. The pattern of spread of tumors within the larynx is guided by the ligaments, connective tissue membranes, and major cartilages of the larynx that contain the spread of tumors, as well as by the soft tissue spaces within the larynx that act as pathways for the spread of tumors within and outside of the larynx. The lymphatic drainage of the three regions of the larynx differs, and therefore the risk of metastasis to regional lymph nodes, the likelihood for contralateral metastasis, and the first echelon nodes vary according to the site of the primary tumor. This characteristic of tumor behavior can be explained by the embryologic development of the larynx.

Embryology

The embryologic development of the larynx determines the pattern of metastatic spread of laryngeal cancer. The supraglottic larynx is derived from the buccopharyngeal primordium, which develops from the third and fourth branchial arches. The glottis and subglottis are derived from the tracheobronchial primordium from the sixth branchial arch and are formed by the union of lateral furrows that develop on each side of the tracheobronchial primordium. Therefore the larynx has a dual blood supply and lymphatic drainage. The supraglottis is supplied by the superior laryngeal arteries, and its lymphatic drainage follows these vessels to the carotid sheath to drain into deep cervical chain nodes in levels II and III. The glottis and subglottis are supplied by the inferior laryngeal arteries, and similarly, lymphatic drainage from these two regions follows these arteries to drain into prelaryngeal and pretracheal nodes (Level VI), before reaching the deep cervical chain nodes in level IV.[3]

The glottic region is formed by paired structures that fuse in the midline. The lymphatics drain unilaterally. The vocal folds have sparse

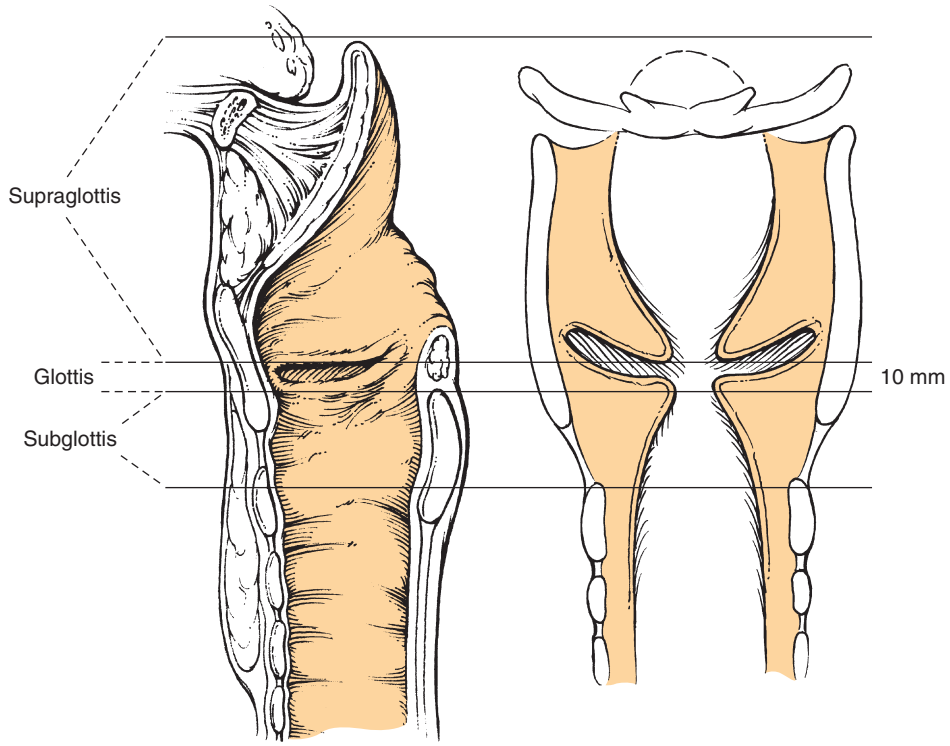

Figure 107-1. Classification of laryngeal lesions by the anatomic site involved. *(Adapted from Ogura JH, Biller HF. Partial and total laryngectomy and radical neck dissection. In: Maloney WH, ed.* Otolaryngology. *Vol 4. New York: Harper & Row; 1971.)*

lymphatics. Therefore, glottic cancers must invade deeply before getting access to lymphatic channels. These factors explain the lower incidence of lymphatic metastasis in glottic SCC, as well as the propensity for unilateral metastases. Because the supraglottis is formed without a midline union, its lymphatics drain bilaterally and the increased likelihood of bilateral lymphatic metastases from supraglottic carcinoma is ascribed to this embryologic factor, as described by Frazer in 1909.[4] Pressman and colleagues[5] noted that the inferior extent of supraglottic injection was the inferior false vocal cord, with the ventricle defining an anatomic barrier and halting further inferior flow of the dye.

Anatomy

A complete description of the anatomy of the larynx is beyond the scope of this chapter, so the following discussion is limited to a description of the boundaries of the larynx, its compartments, and its lymphatic drainage. The laryngeal framework is formed by three unpaired cartilages (epiglottis, thyroid, cricoid) and the paired arytenoid cartilages. The superior boundary of the larynx consists of the superior surface of the epiglottis and the superior edge of the aryepiglottic folds. The anterosuperior limit is formed by the lingual surface of the suprahyoid epiglottis and the hyoepiglottic ligament, which forms the superior boundary of the pre-epiglottic space. The anterior boundary of the larynx is formed by the thyrohyoid membrane and thyroid cartilage in the supraglottis, thyroid cartilage in the glottis, and cricothyroid membrane and anterior arch of the cricoid cartilage in the subglottis. The inferior limit of the larynx is defined by the horizontal plane, which passes through the inferior edge of the cricoid cartilage.[6] The posterior and lateral borders of the larynx are composed of the laryngeal surface of the aryepiglottic folds, arytenoid cartilages, interarytenoid space, and posterior surface of the subglottic space (which is defined as the mucosa covering the surface of the cricoid cartilage).

The larynx is divided into three regions or sites: the supraglottis, the glottis, and the subglottis (Fig. 107-1). This division reflects the embryologic structure of the larynx and the anatomic barriers to spread of laryngeal cancer outlined earlier. The TNM staging system further subdivides the supraglottis and glottis of the larynx into multiple subsites, used to define the T stage (Table 107-1).[6]

Table 107-1

Anatomic Sites and Subsites of the Larynx

Site	Subsite
Supraglottis	Suprahyoid epiglottis Infrahyoid epiglottis Aryepiglottic folds, right and left (laryngeal surfaces) Arytenoids, right and left Ventricular bands, right and left
Glottis	True vocal cords, right and left (including the anterior and posterior commissures)
Subglottis	No separate subsites defined

From Greene F, Page D, Fleming I, et al. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.

The supraglottis is composed of the suprahyoid and infrahyoid epiglottis (both the lingual and the laryngeal surfaces), aryepiglottic folds (laryngeal surfaces only), arytenoids, and ventricular bands (false vocal cords). The boundary between the suprahyoid and infrahyoid epiglottis is a horizontal plane passing through the hyoid bone. The inferior limit of the supraglottis is a horizontal plane through the lateral margin of the ventricle at its junction with the superior surface of the true vocal cord. The glottis is composed of the true vocal cords (both the superior and inferior surfaces) and includes the anterior and posterior commissures. The inferior boundary of the glottis is a horizontal plane 1 cm inferior to the inferior limit of the supraglottis (defined as the lateral margin of the ventricle at its junction with the superior surface of the vocal cord). The subglottis extends from the inferior limit

of the glottis to the inferior edge of the cricoid cartilage. It is not divided further into any subsites.[6]

The mucosal lining of the larynx differs in the three regions. The epithelium of the supraglottis is predominantly of the pseudostratified columnar type, except at the edges of the aryepiglottic folds and the lateral borders of the epiglottis, which are stratified squamous epithelium. The supraglottic mucosa has an abundance of mucus glands and lymphatic vessels. The true vocal cords have a unique structure: stratified squamous epithelium covers a three-layered lamina propria (composed of superficial, intermediate, and deep layers). The intermediate and deep layers of the lamina propria make up the vocal ligament, which forms the superior border of the conus elasticus and interdigitates with the vocalis muscle. The true vocal cords (and thus the glottis) have few lymphatic vessels. The subglottis is lined by pseudostratified columnar epithelium, which is in close approximation to the cricoid cartilage and cricothyroid membrane.[7]

The laryngeal cartilages, hyoepiglottic ligament, thyrohyoid membrane, quadrangular membrane, conus elasticus, anterior commissure, and cricothyroid membrane form natural barriers to the spread of tumor. Within the larynx, the pre-epiglottic space (PES) and the paraglottic space (PGS) provide pathways for spread of laryngeal tumors (Fig. 107-2). The boundaries of the PES are: *anteriorly,* the thyroid cartilage and thyrohyoid membrane; *superiorly,* the hyoid bone, hyoepiglottic ligament, and valleculae; *posteriorly,* the anterior surface of the epiglottic cartilage and the thyroepiglottic ligament; and *laterally,* the PES is open and continuous with each of the two PGSs. The PES contains fat and areolar tissue[7] and is frequently invaded by tumors because the cartilage of the epiglottis has multiple small fenestrations through which cancers arising from the infrahyoid epiglottis may pass. Superiorly, the hyoepiglottic ligament provides a barrier to spread of tumor to the tongue base (Fig. 107-3). The lymphatics of the PES drain through the thyrohyoid membrane, spreading to lymph nodes on both sides of the neck, primarily in zones II and III (Fig. 107-4).[5] Supraglottic tumors with PES involvement are staged as T3 lesions.

The PGS lies lateral to the true and false vocal folds and extends laterally to the thyroid cartilage (Fig. 107-5). The boundaries of each PGS are: *medially* (from superior to inferior), the quadrangular membrane, laryngeal ventricle, and conus elasticus; *laterally,* the thyroid cartilage (anteriorly) and the mucosa of the medial wall of the pyriform sinus (posteriorly); and *inferolaterally,* the cricothyroid membrane.[8] Anteriorly, each PGS is continuous with the PES, and tumors may spread along this pathway (see Fig. 107-2). Paraglottic space involvement in either a glottic or supraglottic tumor is staged as T3 and is significant because the extent of the PGS means that tumors in this

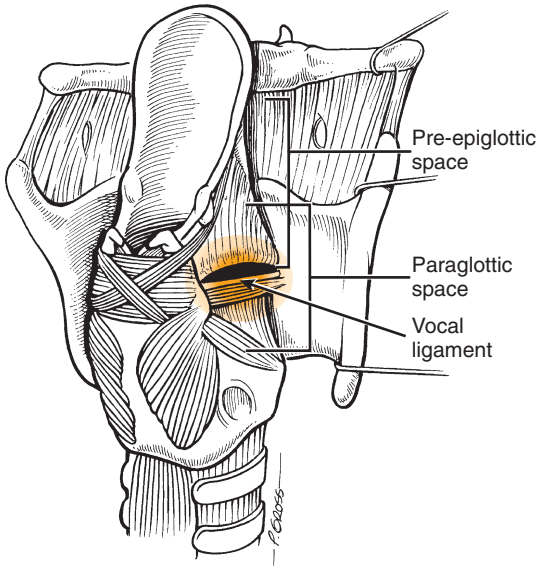

Figure 107-2. Posterior oblique view of larynx showing confluence of pre-epiglottic and paraglottic spaces. *(Reprinted with permission from Myers EN, Suen JY, Myers JN, Hanna EYN.* Cancer of the Head and Neck. *4th ed. Philadelphia: WB Saunders; 2003, Fig. 15-21.)*

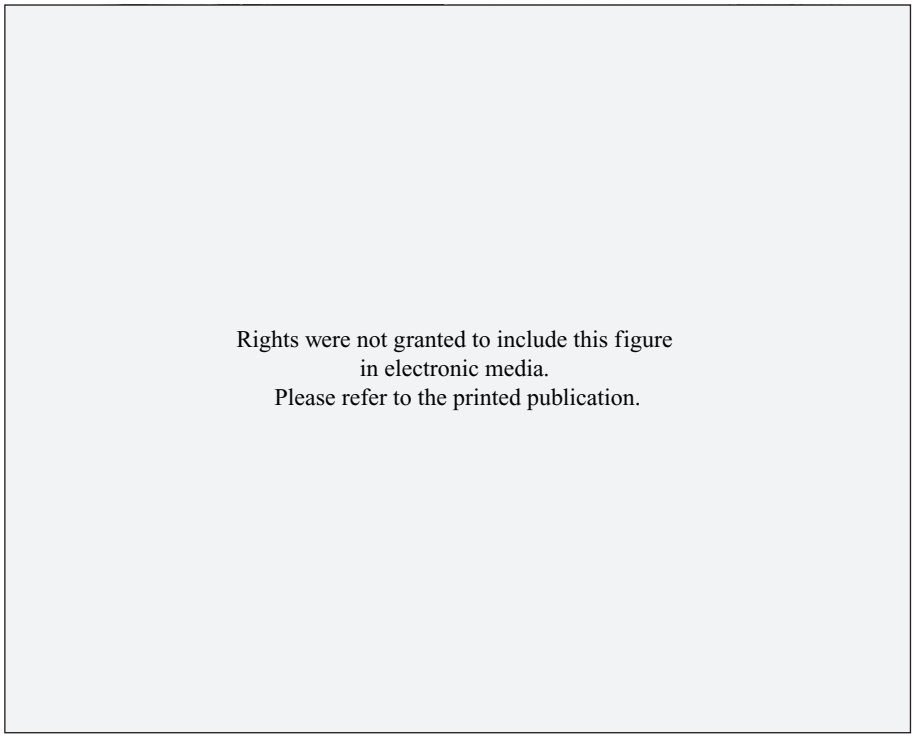

Figure 107-3. A, Total laryngectomy specimen with a deeply invasive supraglotttic carcinoma arising from the false vocal cord. **B,** Sagittal section shows cancer filling the paraglottic space without penetrating the hyoepiglottic ligament *(arrows). (From Zeitels SM, Kirchner JA. Hyoepiglottic ligament in supraglottic cancer.* Ann Otol Rhinol Laryngol. *1995;104:770.)*

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Figure 107-4. Histologic sections. **A,** Carcinoma on the laryngeal surface of the epiglottis growing through a normal epiglottic fenestration *(light arrows)* into the pre-epiglottic space. A typical fibroelastic pseudocapsule has formed *(heavy arrows)* around advancing carcinoma (hematoxylin-eosin; original magnification ×40). **B,** Atypical example of squamous cell carcinoma of the epiglottis located below the hyoepiglottic ligament did not grow through the epiglottic foramina into the pre-epiglottic space *(arrow)* (hematoxylin-eosin; original magnification ×10). **C,** Squamous cell carcinoma arising on the laryngeal surface of the epiglottis *(light arrow)* demonstrating classic pattern of invasion through foramina in epiglottic cartilage with pre-epiglottic space extension *(heavy arrow)* (hematoxylin-eosin; original magnification ×1). *(From Zeitels SM, Vaughan CW. Endoscopic management of early supraglottic cancer.* Ann Otol Rhinol Laryngol. *1990;99:951.)*

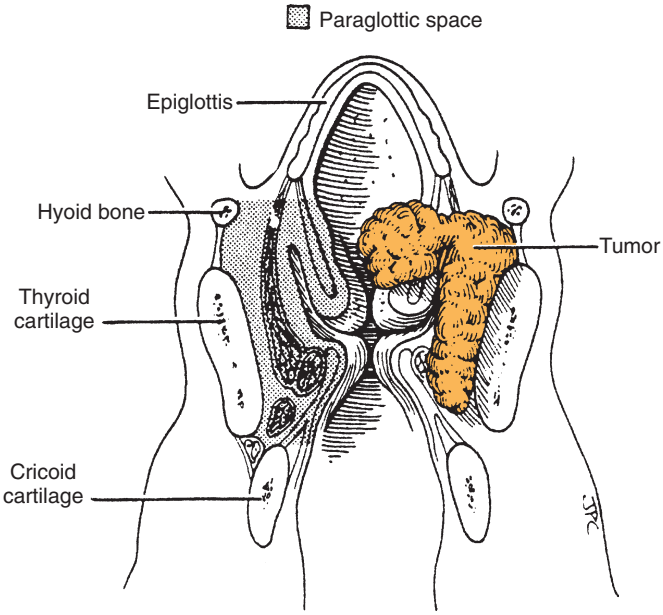

Figure 107-5. Dimensions of the paraglottic space located between the mucosa of the larynx and its cartilaginous framework. *(Reprinted with permission from the American Academy of Otolaryngology—Head and Neck Surgery; from Myers EN, Alvi A. Management of carcinoma of the supraglottic larynx: evolution, current concepts, and future trends.* Laryngoscope. *1996;106:561.)*

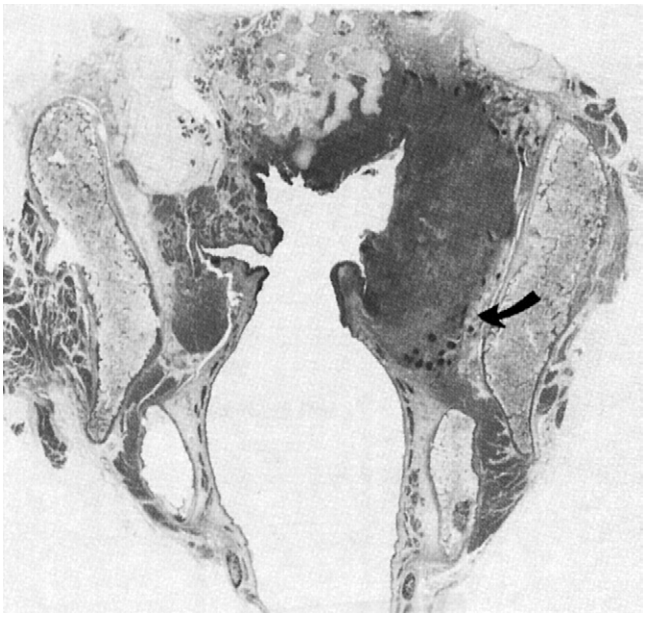

Figure 107-6. A T3 supraglottic carcinoma extending to the glottis through the paraglottic space. Note the extension below the floor of the ventricle *(arrow)* with widening of the paraglottic space (hematoxylin-eosin, gross coronal section). *(From Weinstein GS, Laccourreye O, Brasnu D, Tucker J, Montone K. Reconsidering a paradigm: the spread of supraglottic carcinoma to the glottis.* Laryngoscope. *1995;105:1131.)*

space may spread to involve any or all of the three regions of the larynx (Fig. 107-6).

Conservation laryngeal surgery is undertaken on the basis of the theory of compartmentalization of the larynx, which evolved from the work of Frazer,[4] Pressman and colleagues,[5] and Tucker and Smith.[9] Pressman and colleagues found that this separate embryologic derivation explains why supraglottic tumors of substantial bulk do not spread across the laryngeal ventricle to the vocal cord. In experiments using submucosal vital dyes and radioisotopes, Pressman also noted that the inferior extent of supraglottic injection was the inferior false vocal cord. The ventricle was an anatomic barrier to the inferior flow of the dye and thus was confirmed as a barrier to tumor spread. Using animals, cadavers, and whole organ serial sections of human tumor specimens, Tucker and Smith confirmed that elastic tissue barriers within the larynx explained the findings of the dye studies. Although these studies confirm compartmentalization of the larynx and clinically supraglottic tumors are observed to invade the glottis (and vice versa) uncommonly, there is no true anatomic barrier separating the supraglottis from the glottis.

Transglottic Cancer

Transglottic tumors are an important subset of laryngeal tumors with aggressive behavior and high risk of lymphatic metastasis. The term *transglottic* was first used by McGavran and associates in 1961.[10] It is not used in the American Joint Commission and associates for Cancer (AJCC) staging system and is defined by Kirchner and colleagues and colleagues as a tumor that crosses the ventricle in a vertical direction.[11] LeRoux-Robert probably first described this type of cancer, proposing that the site of origin was the ventricle and was the only tumor that invaded supraglottic and subglottic areas.[12] Kirchner and colleagues[11] have shown that transglottic tumors do not necessarily arise from the ventricle. Tumors can become transglottic in four ways: by crossing the ventricle directly; by crossing at the anterior commissure; by spreading through the paraglottic space; and by spreading along the arytenoid cartilage posterior to the ventricle.[11,13] The latter form of spread does not predict deep invasion: in Kirchner's series of 50 transgottic tumors studied in whole organ preparations, none of the 8 tumors with transglottic spread along the arytenoid demonstrated laryngeal cartilage invasion. In the same series, invasion of the laryngeal framework was seen in over half of transglottic tumors over 2 cm. Cervical metastases were seen in 30% of cases; and in primary tumors greater than 4 cm in dimension, 55% of tumors had nodal metastases.[11]

Anterior Commissure

The anterior commissure is the part of the glottis in which the true vocal cords meet anteriorly. The anterior commissure tendon is a band of fibrous tissue 1 mm wide and 10 mm in length extending from the vocal ligaments to the midline of the inner surface of the thyroid cartilage. At this insertion, the thyroid cartilage is devoid of perichondrium.[14] In this area the true vocal cords are therefore in close approximation to the thyroid cartilage. Kirchner has studied factors associated with spread of tumors along the anterior commissure.[15] The anterior commissure tendon forms a strong barrier to spread of cancer. Tumors crossing from one true vocal cord to the opposite cord do not necessarily have deep invasion. Thyroid cartilage invasion or extralaryngeal spread of cancer at the anterior commissure requires significant supraglottic or infraglottic extension. Superiorly, tumors have access to the petiole of the epiglottis and pre-epiglottic space, while inferiorly they have access to subglottic lymphatics, the thyroid cartilage, and the cricothyroid membrane. Inferiorly, the thyroid cartilage is more likely to be ossified, and ossified cartilage is not as strong a barrier to invasion as cartilage.[16]

Classification of Malignant Tumors of the Larynx

Although the vast majority of malignant tumors of the larynx originate from squamous epithelium, a small number arise from other tissues within the larynx. Because of the differing clinical behavior of these tumors, an accurate histologic diagnosis is crucial. Recognizing the importance of this issue and the need for standardization in the histologic nomenclature of laryngeal tumors, the World Health Organization (WHO) has published a histologic classification of laryngeal tumors.[17] This classification system is outlined in Table 107-2. Non–squamous cell laryngeal malignancies are described individually later in the chapter.

Staging

For the staging of malignant tumors, the AJCC and the International Union against Cancer (UICC) use the TNM classification system, which was developed by Pierre Denoix in 1943.[6,18] The TNM system takes into account the extent of the primary tumor (T), the absence or presence and extent of regional lymph node metastasis (N), and the absence or presence of distant metastases (M). The 2002 AJCC/UICC TNM definitions for epithelial laryngeal malignancies are given in Table 107-3. Using this system, tumors with varying combinations of T, N, and M are grouped into stages, which are described in Table 107-4. A tumor may be classified clinically, designated cTNM or simply TNM, or pathologically, designated pTNM. The clinical classification is based on evaluation of the patient before treatment is commenced and includes information obtained from physical examination, radiologic imaging, endoscopy, and biopsy.

The TNM classification system for the larynx is used for epithelial malignancies of the larynx only—nonepithelial tumors such as those of lymphoid tissue, soft tissue, cartilage, or bone are not included, although such lesions may be staged according to the system relevant to their histopathology (e.g., lymphomas of the larynx are staged according to the TNM system for lymphoid neoplasms).

An additional comment regarding the T staging of glottic tumors should be made. The T2 classification for glottic tumors encompasses a wide variety of lesions including those with normal and impaired vocal cord mobility (vocal cord fixation denotes a T3 tumor). Because the local control rate of RT for T2 glottic tumors with impaired vocal cord mobility has been observed to be lower than that of T2 tumors with normal vocal cord mobility, many authors distinguish between these two subsets of the T2 group by using T2a to denote those tumors with normal vocal cord mobility and T2b for those with impaired mobility.[19] This division of the T2 stage has not been incorporated into the AJCC/UICC TNM system.

Premalignant Laryngeal Lesions and Carcinoma in Situ

The World Health Organization (WHO) classifies premalignant laryngeal lesions as hyperplasia; keratosis; mild, moderate, or severe dysplasia; and carcinoma in situ (CIS).[17] Very early lesions may demonstrate hyperkeratosis or parakeratosis without cellular atypia or dysplasia. Squamous cell dysplasia is a premalignant lesion of squamous epithelium characterized by cellular atypia and loss of normal maturation and stratification short of CIS. The cellular abnormalities of mild dysplasia are minor and are limited to the basal one third of the epithelium; moderate dysplasia displays more marked cellular abnormalities involving up to two thirds of the epithelial thickness; and severe dysplasia has cellular abnormalities involving more than two thirds of the epithelial thickness. Carcinoma in situ is an intraepithelial neoplasm in which the full thickness of the squamous epithelium shows the cellular features of carcinoma without violation of the basement membrane and stromal invasion (Fig. 107-7).[17] Severe dysplasia and CIS are classified as different lesions, but clinically they behave in a similar fashion and may be considered as one.[20] There is widespread variability in pathologic interpretation and diagnosis, which is inherently subjective.[21,22]

Malignant transformation of mild dysplasia has been reported to be as high as 11%.[23] The malignant transformation rates for severe dysplasia and CIS show significant variability (up to 45%), but 30% is the generally accepted figure. A recent review noted that 30% of patients with dysplastic lesions that progressed to invasive cancer eventually underwent total laryngectomy.[23] The likelihood of progression is related to the extent of disease, and at least one series observed that almost all diffuse lesions showing CIS developed invasive cancer.[24] Because some lesions showing mild dysplasia and even those without dysplasia may progress to invasive cancer, long-term follow-up of all premalignant laryngeal lesions is warranted. Malignant transformation is a multistep process that takes many years. Blackwell and colleagues[25] observed a 3.9-year interval between initial biopsy to progression to invasive cancer. In a large series of over 1000 keratotic larynx lesions, the mean time interval to malignant transformation was 3.1 years.[26] The latency was longer for earlier lesions, and 7% of lesions transformed to invasive carcinoma more than 10 years after the initial biopsy.

The visual appearance of a premalignant laryngeal lesion does not predict its histologic nature. Nor does laryngeal videostroboscopy reliably differentiate premalignant from malignant lesions.[27] Biopsy is the gold standard for diagnosis, and adequate sampling is important because an insufficient biopsy will result in sampling error.

Adjunctive techniques have been developed to improve the clinician's ability to characterize these lesions and to guide biopsies. The use of vital dyes including toluidine blue and methylene blue as a diagnostic aid have been explored.[28,29] Lundgren and coworkers used toluidine blue to detect dysplasia or malignant changes and noted 91%

Table 107-2

Differential Diagnosis of a Laryngeal Mass/Lesion

Non-Neoplastic Lesions
- Mucus retention cyst
- Laryngocele/saccular cyst
- Heterotopic thyroid tissue
- Vocal fold polyp
- Vocal process granuloma
- Infections
  - Tuberculosis
  - Candidiasis
  - Histoplasmosis
- Inflammatory
  - Wegener's granulomatosis
  - Foreign body granuloma (e.g., Teflon)
  - Relapsing polychondritis
- Pseudoepitheliomatous hyperplasia
- Squamous cell hyperplasia
- Keratosis
- Necrotizing sialometaplasia
- Chondrometaplasia
- Amyloidosis
- Langerhans' cell histiocytosis
- Rosai-Dorfman disease

Benign Neoplasms
- Epithelial
  - Papilloma
  - Pleomorphic adenoma
- Oncocytic papillary cystadenoma
  - Nonepithelial
  - Soft tissue
    - Lipoma
    - Schwannoma
    - Neurofibroma
    - Leiomyoma
    - Rhabdomyoma
    - Hemangioma
    - Lymphangioma
    - Granular cell tumor
    - Paraganglioma
- Inflammatory myofibroblastic tumor
  - Bone and cartilage
    - Chondroma
    - Giant cell tumor

Premalignant Lesions
- Squamous cell dysplasia
- Carcinoma in situ

Primary Laryngeal Malignancies

Epithelial
- Squamous cell carcinoma (SCC)
  - Verrucous SCC
  - Spindle cell carcinoma
  - Adenoid SCC
  - Basaloid SCC
  - Clear cell carcinoma
  - Adenosquamous carcinoma
  - Giant cell carcinoma
  - Lymphoepithelial carcinoma

Malignant salivary gland tumors
- Adenocarcinoma
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Carcinoma ex pleomorphic adenoma
- Epithelial-myoepithelial cell carcinoma
- Salivary duct carcinoma

Neuroendocrine tumors
- Carcinoid tumor
- Atypical carcinoid tumor
- Small cell carcinoma
- Malignant paraganglioma

Malignant soft tissue tumors
- Fibrosarcoma
- Malignant fibrous histiocytoma
- Liposarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Angiosarcoma
- Kaposi's sarcoma
- Malignant hemangiopericytoma
- Malignant nerve sheath tumor
- Alveolar soft part sarcoma
- Synovial sarcoma
- Ewing's sarcoma

Malignant tumors of bone and cartilage
- Chondrosarcoma
- Osteosarcoma

Hematolymphoid tumors
- Lymphoma
- Extamedullary plasmacytoma

Secondary Laryngeal Malignancies

Contiguous primary site
- Hypopharynx
- Oropharynx
- Thyroid

Distant primary site
- Kidney
- Skin (melanoma)
- Breast
- Lung
- Prostate
- Gastrointestinal tract

Table 107-3

Tumor Node Metastasis System for the Larynx (Epithelial Malignancies)[6]

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx, (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node, >6 cm in greatest dimension
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

From Greene F, Page D, Fleming I, et al. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.

sensitivity, but only 52% specificity.[29] Contact endoscopy provides magnification of 60 to 50× and, with methylene blue staining, provides histologic information and an assessment of vascular patterns.[30] However, subsurface visualization is limited to 150 to 200 microns and is inadequate for characterizing thicker lesions. Widespread adoption of this technique has been hindered by the need for extensive experience to interpret the findings and for special equipment.

Human tissue has many compounds that fluoresce when exposed to blue light. The differing fluorescence of abnormal tissues has been exploited as a diagnostic aid for laryngeal malignancy. With experience, this technique can be useful. Limitations include false-positive and false-negative examinations in scarring, hyperkeratotic lesions, and inflammation.[31] Induced autofluorescence using 5-aminolevulinic acid (5-ALA) also shows potential diagnostic utility. 5-ALA selectively induces accumulation of protoporphyrin IX fluorescence in tumors. Using a nebulizer, it is topically applied 1 to 2 hours before the examination and a light source emitting short wavelength visible light (375 to 440 nm) is used to induce fluorescence. Protoporphyrin IX fluorescence appears red during imaging. A series of 16 patients with suspected or proven laryngeal malignancy subjected to 5-ALA–induced

fluorescence endoscopy demonstrated a sensitivity of 95% and a specificity of 80%.[28]

A prospective evaluation of autofluorescence and 5-ALA–induced fluorescence in 56 patients demonstrated that the two techniques have similar sensitivities (94% and 97%) and specificities (82% and 64%) to distinguish hyperplasia or mild dysplasia from moderate dysplasia, severe dysplasia, CIS, and invasive SCC.[32] Autofluorescence was unreliable when scarring was present, whereas 5-ALA–induced fluorescence resulted in false-positive findings in inflamed lesions.

The combined use of autofluorescence and contact endoscopy ("compact endoscopy") has also been explored. A pilot study by Arens and colleagues of 83 patients with hyperkeratotic, dysplastic, and invasive laryngeal lesions found correlation with histology in 88% of cases.[33] Inflammation and scarring resulted in overestimation of disease, whereas underestimation of disease was seen in hyperkeratotic lesions.

Current noninvasive diagnostic modalities do not reliably distinguish premalignant lesions from invasive SCC. Optical and microscopic imaging is limited by the inability to see below the first few layers of epithelial cells to evaluate the submucosal architecture. Infrared light has increased tissue penetrance and can provide diagnostic information about subsurface tissues. Optical coherence tomography (OCT) is a new diagnostic modality under investigation to examine the epithelial and subepithelial architecture that uses near-infrared light waves to produce cross-sectional images of tissue in vivo, with a resolution approaching that of histology.[34,35] In the larynx, OCT clearly identifies basement membrane violation from laryngeal cancer and is able to identify transition zones at the margins of the cancer (Fig. 107-8).[36] OCT has been used to assess the larynx intraoperatively to guide the extent of transoral laser resections for laryngeal cancer to ensure that excision is complete.[37] The primary disadvantage of OCT is the limited depth of penetration (<2 mm), which limits its utility in bulky lesions. However, OCT has potential as a useful tool in the management of laryngeal cancer: for the diagnosis of smaller epithelial lesions, for guiding surgical biopsies and resections, and for monitoring larynges post treatment.[36,37]

Table 107-4

Tumor Node Metastasis Stage Groupings

Stage	Primary Tumor	Regional Lymph Nodes	Distant Metastasis
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3 T1-3	N0 N1	M0 M0
IVA	T4a T1-4	N0-1 N2	M0 M0
IVB	T4b Any T	Any N N3	M0 M0
IVC	Any T	Any N	M1

From Greene F, Page D, Fleming I, et al. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.

Treatment of Premalignant Lesions

The treatment of a premalignant lesion should aim to eradicate the lesion while preserving voice quality and laryngeal function. Accurate diagnosis is critical for proper decision making, and a number of factors related to the characteristics of the lesion, as well as patient factors, affect the treatment decision-making process (Table 107-5).

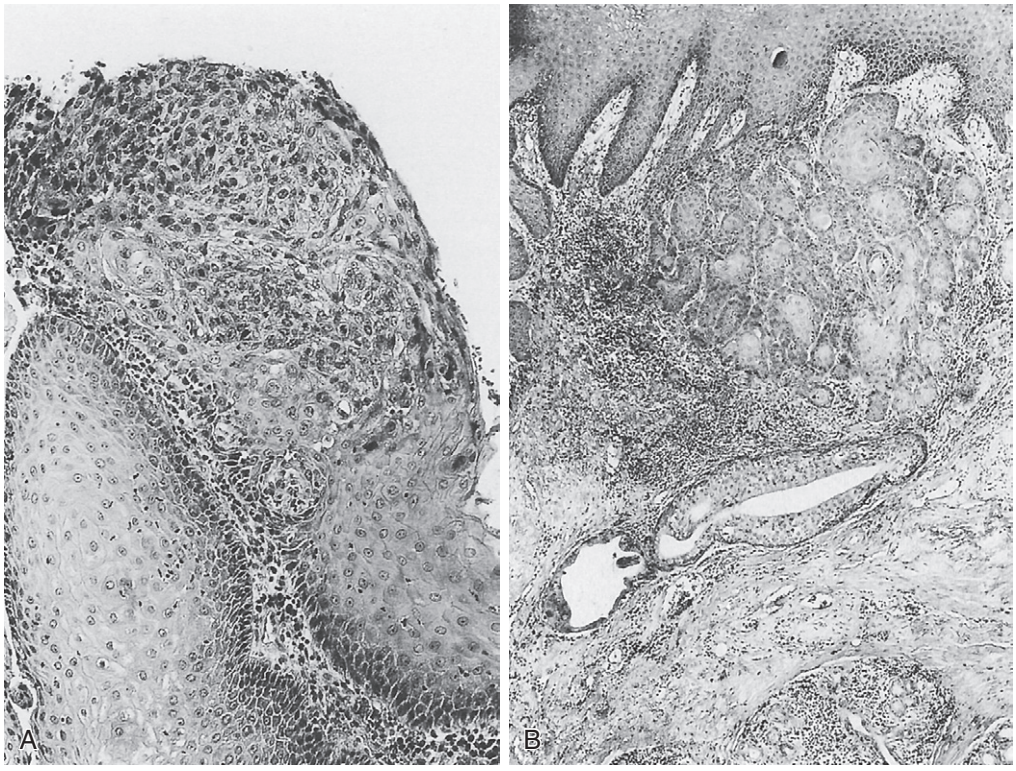

Figure 107-7. A, Carcinoma in situ. **B,** Microinvasive carcinoma. In the early phase of invasion, irregular nests of well-differentiated squamous cells infiltrate the lamina propria and evoke an inflammatory response. A gland with squamous metaplasia is present near deeper carcinomatous cells. *(From Ferlito A, Carbone A, Rinaldo A, et al.* Ann Otolaryngol. *1996;105:245.)*

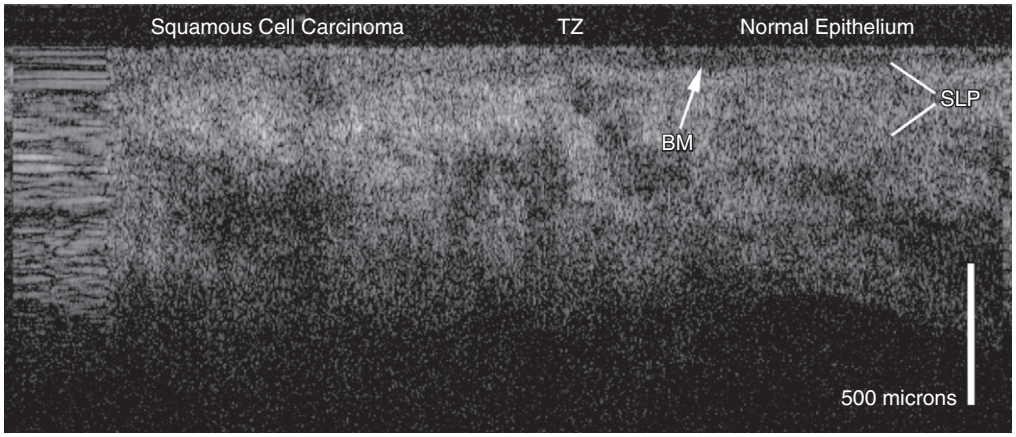

Figure 107-8. Optical coherence tomography image of a recurrent T2 glottic squamous cell carcinoma (SCC) following radiation therapy. Normal epithelium is present on the right, and a transition zone (TZ) between normal epithelium and squamous cell carcinoma is seen in the middle of the image. The basement membrane (BM) is not visualized on the left side, corresponding to the region of invasive SCC. SLP, superficial lamina propria.

Table 107-5

Factors to Consider in Treatment of Premalignant Laryngeal Lesions

Patient Factors	Tumor Factors
General health/comorbidities	Extent of lesion Unilateral vs. bilateral Anterior commissure involvement Extension beyond the glottis Focal vs. diffuse lesion
Vocal demands (e.g., professional singer)	Previous treatment Prior surgical excision Prior radiation therapy
Compliance with Tobacco cessation Alcohol cessation Reflux treatment	
Patient choice	

Hyperplastic and dysplastic lesions are excised with microlaryngoscopic techniques to remove the visible lesion. Close follow-up is required due to the risk of recurrence of the lesion and possible malignant transformation. Carcinoma in situ may be treated with either surgery or RT. Surgical management is microlaryngoscopic excision. Critical to this is high-power magnification, fine microsurgical instruments, and meticulous surgical technique to remove the entire lesion and preserve underlying lamina propria. The carbon dioxide (CO_2) laser is useful for precise excision, although thermal injury to the underlying lamina propria may result. Vocal cord stripping is the removal of the mucosa of the vocal fold including the lesion from the vocal process up to, but not across, the anterior commissure. It has significant risk of producing scarring and has been superseded by the more controlled microsurgical excision. Surgery provides tissue for pathologic analysis and can be repeated as often as needed. Voice quality is preserved in most cases. The recurrence rate for CIS treated with surgery is greater than those treated with RT and is reported to be approximately 20% after initial excision.[23] With repeated surgical excision the ultimate local control rate is excellent and is at least equivalent to that of RT.[38,39] Surgical treatment is preferred for focal lesions in patients who are reliable and will attend routine follow-up.

Radiation therapy is also an effective treatment for CIS: a recent review of 16 studies of CIS treated with RT determined that the local control rate was 93.5%.[23] Radiation therapy is particularly useful for multiple recurrences following surgical excision; for diffuse lesions extending beyond the vocal cords that cannot be excised without inducing significant morbidity; for patients who are unlikely or unable to attend follow-up; and for medically infirm patients unfit for general anesthesia. Voice quality is well preserved following RT.[40,41] The primary disadvantage of RT is that it cannot be repeated if there is a recurrence or second tumor in the irradiated field. The successful management of premalignant laryngeal lesions also requires implementation of tobacco and alcohol cessation strategies and treatment of laryngopharyngeal reflux when present.

In-Office Treatment of Premalignant Lesions

In recent years, in-office management of laryngeal pathology has become more common. This includes the treatment of premalignant lesions using photodynamic therapy (PDT) and fiber-based laser systems such as the pulsed dye laser (PDL) and the pulsed KTP laser.

The 585nm PDL and 532nm pulsed KTP lasers are the two most widely used lasers for the in-office treatment of laryngeal epithelial lesions including leukoplakia, keratosis, and dysplasia. In a pilot study, Franco and colleagues[42] used PDL for the treatment of dysplasia in the operating room under general anesthesia. In most cases the treated lesions were then excised and sent for histologic examination. This treatment was effective: 81% of patients had greater than 70% regression of their lesions. The authors also noted that regression occurred in treated lesions that were not excised. A subsequent report from the same group demonstrated the efficacy of PDL delivered via a flexible endoscope in the office for the treatment of dysplasia.[43] Koufman and colleagues found that 64% (16/25) of their patients with dysplasia required no further treatment during the follow-up period of their study.[44] Franco[45] has also described favorable experience with the use of PDL for dysplasia. Zeitels and colleagues[46] have subsequently adopted the pulsed KTP laser for in-office use, citing smaller fiber diameter, greater reliability, improved intralesional energy absorption, and improved hemostasis as advantages of the pulsed KTP system over PDL.

The energy from these lasers is preferentially absorbed by oxyhemoglobin, with the absorption of energy from the pulsed KTP being superior to that of PDL, causing photoangiolysis of the sublesional blood vessels.[46] Preferential destruction of intraepithelial desmosome junctions and separation of the treated epithelial cells from the basement membrane have also been observed microscopically.[47] Apart from the obvious advantages of in-office procedures (avoidance of general anesthesia, lower cost, improved efficiency, and patient preference), these lasers have minimal effect on the surrounding tissue and the scarring is uncommon. The bilateral simultaneous treatment of lesions in

and around the anterior commissure is possible, with minimal risk of web formation.[44]

One of the major criticisms of in-office procedures for the treatment of laryngeal lesions, especially dysplasia, is that there is no specimen obtained for pathologic examination, and therefore a definitive assessment of the tumor extent and margin status is not possible. In the reports published to date, all patients have been biopsied before the commencement of treatment.[44,46] A biopsy may be obtained in the operating room and initial treatment with the laser given at this time, or it may be taken in the office via the endoscope. Potential complications of in-office treatment include poor exposure of the lesion or poor patient tolerance of the procedure; however, these issues only arise in a small minority of cases.[44] Further studies with long-term follow-up are awaited to ensure that this novel technology has similar outcomes for patients with dysplastic laryngeal lesions.

Photodynamic therapy uses nontoxic chemicals that are taken up preferentially by dysplastic or malignant cells. These photoreactive chemicals are activated by light of a specific frequency range unique to the compound used. The light activation of tissues at the target site in the presence of oxygen results in cell death that is confined to the cells that have selectively accumulated the chemical.[48] Several agents have been used in the head and neck including 5-ALA, Photofrin, hematoporphyrin derivative, and Foscan. In the United States several photosenstitizers have been approved for use by the Food and Drug Administration, but treatment of head and neck malignancies is an off-label use at the present time. In the European Union, Foscan has been approved for treatment of early head and neck cancer. At present, data are available for approximately 1500 subjects treated with PDT for head and neck SCC. Biel[48] reported on 115 patients with Tis to T2 larynx SCC treated with Photofrin PDT. With a mean follow-up of 91 months, the 5-year cure was 91%. All recurrences were salvaged successfully.

Photodynamic therapy has several useful characteristics: it is performed in an outpatient setting and is repeatable. The effects on voice quality are minimal, and scarring of the vocal folds has not been observed.[48] Careful light-avoiding precautions are required because light sensitivity lasts up to 4 weeks. There is no pathologic specimen, and care must be taken to accurately assess tumor depth. PDT may have a particularly useful role for diffuse dysplasia or CIS. Schweitzer[49] reported 80% local control with PDT in 10 cases of diffuse laryngeal CIS previously treated with RT. Published reports show promise for this modality, but currently it is used by a small number of practitioners and is not widely available.

Chemoprevention of Laryngeal Cancer

Carcinogenesis is a multistep accumulation of genetic damage, the end result of which is the development of cancer.[50,51] The early arrest or reversal of carcinogenesis offers the opportunity to make a meaningful impact on cancer in the premalignant disease state, or before development of a second tumor.[52,53] Chemoprevention is the use of specific chemical agents to reverse, suppress, or prevent carcinogenesis before invasive cancer develops.[54] In numerous studies a low -fat diet and an increase in the consumption of fruits, vegetables, and fiber were associated with a protective effect against a number of cancers.[55,56]

13-cis-retinoic acid (13-cRA) has been studied extensively in oral leukoplakia.[57,58] In randomized placebo-controlled trials, 13-cRA showed encouraging results against oral premalignant lesions. In the first major human trial of 13-cRA completed in 1986, Hong and colleagues[58] observed a 67% response rate of oral leukoplakia in the treatment arm versus a 10% response rate for the placebo group. Significant side effects were seen and, unfortunately, mucosal lesions recurred in half of the patients receiving 13-cRA within 3 months following discontinuation of 13-cRA. In an effort to improve effectiveness and decrease toxicity, a multiagent trial using 13-cRA, alpha tocopherol, and interferon-α was conducted at the same institution. A complete remission was observed in 50% (7/14) of laryngeal lesions at 12 months. Subsequent analysis of biomarkers found the laryngeal lesions tended to have a lower level of chromosomal polysomy, and the level of chromosomal polysomy correlated with higher response rates to the three agents. There was also a trend toward a better response rate in cases without abnormal p53 accumulation, presumably reflecting less advanced disease.

A number of other agents show potential as chemopreventive agents for head and neck cancers including green tea polyphenols, sulindac, COX II inhibitors, curcumin, and protease inhibitors.[54] None have undergone the same level of study as the retinoids, and considerable effort will be required to determine the ultimate potential of promising agents.

Squamous Cell Carcinoma of the Larynx

Squamous cell carcinoma is the most common malignant tumor of the larynx, responsible for between 85% and 95% of all laryngeal malignancies.[2,59] This tumor arises from stratified squamous epithelium or from respiratory epithelium that has undergone squamous metaplasia. The incidence of SCC in each of the three regions of the larynx—the supraglottis, glottis, and subglottis—varies according to the patient population. In the United States, Canada, England, and Sweden, glottic SCC is more common than supraglottic SCC, whereas the reverse is true in France, Italy, Spain, Finland, and the Netherlands. In Japan, glottic and supraglottic SCC have a similar incidence. Primary subglottic SCC is rare in all populations.[2] In a large review of nearly 160,000 cases of laryngeal SCC in the United States, the glottis was the site of origin in 51%, the supraglottis in 33%, and the subglottis in 2% (with 14% of lesions unable to be categorized accurately).[60]

Epidemiology

In the United States, approximately 11,300 cases of laryngeal cancer were diagnosed in 2007 and there will be approximately 3660 deaths. The male-to-female incidence ratio is 3.8:1.[1] The epidemiology and risk factors for laryngeal cancer largely parallel those for head and neck cancer overall. Over 90% of cancers occur in those older than 40 years of age, and 85% to 95% of these are SCC. The higher incidence in males is due to an increased exposure to risk factors rather than an inherent gender predilection, and therefore as the number of females smoking has increased over the past 60 years, the gap has narrowed from over 15:1 to approximately 4:1. There does not appear to be a racial predilection to laryngeal cancer.[61]

Risk Factors

Tobacco and Alcohol

Tobacco and alcohol use are the two primary risk factors for cancer of the larynx. The International Agency for Research on Cancer (IARC) has concluded that there is enough evidence to state that there is a causal link between tobacco use and alcohol use with development of head and neck cancer. The risk is proportional to the intensity and duration of tobacco or alcohol consumption, and the risk decreases slowly after cessation but does not return to the baseline rate for at least 20 years. There are variations in risk with the type of tobacco exposure (e.g., cigar vs. cigarette, filtered vs. nonfiltered cigarettes), but the most important factors are the amount of tobacco consumed and the duration of exposure. Tobacco and alcohol act synergistically to increase the risk of cancer.[62-64] The relative contribution of alcohol and tobacco varies by site. Alcohol consumption is a more important risk factor for supraglottic carcinoma, whereas tobacco use is strongly associated with glottic carcinoma.

Laryngopharyngeal Reflux

Chronic irritation of the larynx has been proposed as a risk factor for laryngeal cancer and may be a contributing factor for those who do not smoke or drink. Concern that laryngopharyngeal reflux (LPR) of acid could cause cancer was raised in the 1980s.[65,66] It is difficult to determine if the relationship is causal or merely an association. A large case-control study of U.S. veterans concluded that there is a moderately increased risk for laryngeal or pharyngeal cancer associated with LPR independent of tobacco and alcohol use.[67] A critical review of the literature indicates that the relationship between LPR and larynx cancer is unknown. LPR could be an associated factor, a cocarcinogen, or possibly an independent risk factor.[68] Alkaline bile reflux may also be a causative factor. One study identified a significantly higher incidence

of laryngeal carcinoma in patients who underwent gastrectomy compared with controls.[69] The significance of asbestos exposure is controversial. A meta-analysis published in 1999 concluded there was a weak association between asbestos exposure and laryngeal cancer.[70]

Other Toxins

Occupational exposure to toxins is another risk factor for laryngeal cancer. The incidence of laryngeal cancer is higher in unskilled manual workers who have both a high alcohol and tobacco intake and are exposed to disproportionate levels of potential toxins.[71-73] Numerous agents including diesel exhaust, asbestos, organic solvents, sulfuric acid, mustard gas, certain mineral oils, metal dust, asphalt, wood dust, stone dust, mineral wool, and cement dust have been implicated as risk factors for laryngeal cancer. Establishing a link between any one toxin and larynx cancer has been difficult because the studies have been underpowered and plagued with confounding variables.[74]

Human Papillomavirus

Human papillomavirus (HPV) has been recognized as a causative factor for cervical cancer. The role of HPV in cervical cancer is well studied, and several HPV vaccines are undergoing evaluation for prevention of cervical cancer. The link between HPV and head and neck SCC was first suggested in the early 1980s.[75] Further studies have brought to light that HPV is a significant and increasing risk factor for head and neck cancer, particularly in the oropharynx. HPV is an independent risk factor for head and neck SCC.[76] The association of sexual practices and risk of head and neck cancer has become clear over the past decade, and a recent study has emphasized the role of HPV on a subset of head and neck cancer patients.[77] Vaccination against HPV has been shown to be highly effective at preventing cervical HPV infection.[78] If the vaccine can also prevent oropharyngeal infection, then the vaccination of children has the potential for significantly reducing the risk of oropharyngeal cancer and possibly cancer at other sites in the head and neck. The mechanism for carcinogenesis is believed to be the E6 and E7 viral protein-mediated degradation of p53, which is involved in maintaining genomic integrity, controlling cellular proliferation, and apoptosis. A recent review shows a site-specific link between HPV and head and neck cancer: the magnitude of the association is strongest for the tonsil (Odds Ratio [OR] 15.1), intermediate for other subsites in the oropharynx (OR 4.3), and weakest for the oral cavity (OR 2.0) and the larynx (OR 3.0, 95%, confidence interval [CI] 1 to 4.2).[79] The influence of HPV as a risk factor for larynx cancer is lower than for the oropharynx. Nevertheless, in one series, HPV was isolated in 36% of laryngeal cancers.[80] Evidence suggests that the presence of HPV in a head and neck SCC is associated with a better prognosis.[81] This observation is supported by a recent meta-analysis of the effect of HPV on head and neck cancer survival, but the effect is limited to oropharyngeal SCC.[82]

Genetic Susceptibility

Most smokers will die prematurely as a result of tobacco use, but only a minority will develop cancer. Genetic susceptibility to cancer clearly plays a role in risk for development of head and neck, as well as other cancers, but the risks are not clearly delineated. Epidemiologic studies can stratify risk for developing head and neck cancer and other cancers, and biomarkers are under development to identify molecular changes associated with cancer development. These assays provide markers for genetic susceptibility to cancer (e.g., mutagen sensitivity) and have the potential to provide prognostic information about response to treatment.[83] Polymorphisms of phase I and phase II detoxifying enzymes are also associated with risk of developing head and neck cancer, as well as polymorphisms of DNA repair enzymes. These studies are useful for understanding the pathogenesis of cancer but currently do not provide assistance to guide the clinician managing individual patients.

The discovery of familial cancer syndromes drew attention to the role of genetic susceptibility to developing cancer.[84] Only a small proportion of head and neck cancers arise from familial syndromes (e.g., xeroderma pigmentosum); however, studies of head and neck cancer demonstrate an elevated risk of head and neck cancer in family members. Copper and colleagues found a relative risk (RR) of 14.6 for respiratory tract cancers in the siblings of cancer patients and an overall RR of 3.5 for first-degree relatives.[85] The host ability to tolerate exposure to carcinogens is highly variable and is related to the ability to prevent activation of procarcinogens, inactivate active carcinogens, repair deoxyribonucleic acid (DNA) damage, and maintain immune surveillance. These factors are highly variable among individuals and are still poorly understood.

Diet

There is evidence linking dietary factors to the risk of head and neck cancer.[86,87] An increased intake of fruit and vegetables and a decreased intake of meat and fat have a protective effect and are associated with a reduced incidence of head and neck cancer, as well as colon cancer and cardiovascular disease. However, these benefits may take 20 years or longer to accrue, and at present these epidemiologic observations have not led to the successful development of a cancer reduction program.[88,89]

Second Primary Tumors

The single greatest risk factor for head and neck SCC is prior head and neck SCC. The annual risk of a second primary tumor (SPT) following an index head and neck SCC is 1% to 7%, with the risk persisting for at least 10 years.[57,90-92] The cumulative risk of developing an SPT is at least 20% and is greater for those who continue to use tobacco and alcohol. An individual with stage I or II head and neck SCC is more likely to die from an SPT than from the index tumor. The majority of SPTs develop in the head and neck, but a significant proportion occur in the esophagus or lung. Second primary tumors may be synchronous (identified within 6 months of the index tumor) or metachronous (diagnosed more than 6 months after the index tumor). In a study of 875 patients with SCC of the head and neck, 207 had SPTs develop within 5 years of their index tumor.[93] Of these patients, 31% had a third primary malignancy develop and 10% had a fourth primary malignancy develop. For laryngeal cancer, the lung is a significant site for synchronous and metachronous SPTs. An isolated lung malignancy in a patient with larynx cancer is more likely to be an SPT than a metastasis from the laryngeal cancer. Therefore an isolated pulmonary nodule should be considered an SPT until proven otherwise.[92] Prior RT is associated with SPTs in a small number of cases.[74] Slaughter and associates[94] examined clinically normal tissue adjacent to head and neck cancers and identified many histologic changes seen in the malignant cells in the adjacent normal appearing tissue, leading him to propose the concept of "field cancerization." Improved understanding of head and neck carcinogenesis has provided a molecular explanation for Slaughter's observations.[50,95] Bedi and colleagues examined X-chromosome inactivation and performed microsatellite analysis to evaluate allelic loss at chromosomes 3p and 9p in females with multiple primary head and neck cancers. Both the original cancer and the second malignancy arose from a single clone.[95] Califano and coworkers similarly observed that tissues adjacent to malignant and premalignant lesions shared common genetic changes.[50] Multiple tumors generally do not arise from multiple transforming events, but instead a single transforming event produces a cell with growth advantage that spreads throughout the mucosal surface. The tumor may accumulate further genetic damage, resulting ultimately in additional malignancies that are geographically distinct but genetically related to the original cancer.[95]

Molecular Biology

The molecular biology of laryngeal SCC is similar to that of SCC in other sites of the head and neck. Carcinogenesis is a long process occurring over many years preceding the development of cancer. Disruption of multiple genes is required to induce malignant transformation, with 6 to 12 distinct mutations generally necessary to produce malignancy. Understanding the molecular biology of head and neck cancer is useful to predict who is likely to develop cancer, to measure response to preventive agents, to identify novel targets for treatment, and to predict a patient's response to RT or chemotherapy. The molecular biology of head and neck cancer is discussed in Chapter 76.

Pathology

Squamous differentiation is the hallmark of SCC, which is characterized by the formation of keratin and/or the presence of intercellular

bridges.[17] SCC is graded by its histologic appearance into three categories: well, moderately, and poorly differentiated. Well-differentiated SCC resembles normal squamous epithelium and contains basal-type cells and squamous cells with keratinization and intercellular bridges. The nuclei are hyperchromatic and irregular in size and shape (pleomorphic), and the nuclear-cytoplasmic ratio is reduced. Atypical mitoses are rare. Moderately differentiated SCC has less keratinization, more atypical mitoses, and more nuclear pleomorphism. Intercellular bridges are present. Poorly differentiated SCC has minimal (if any) keratinization, minimal intercellular bridges, and numerous atypical mitoses.[17,59] The histologic grade has been reported as having prognostic value; however, grading is subjective, and sampling error may influence the grade assigned.

SCC breaches the basement membrane of the epithelium to invade the underlying tissue. The interface between the tumor and the adjacent normal tissue varies according to the pattern of invasion, which may be expansive, characterized by well-defined pushing margins, or infiltrative, characterized by poorly defined margins with occasional cells or tongues of tumor found in the tissue adjacent to the tumor. The latter pattern of invasion is associated with a worse prognosis.[96] A lesion in which the entire thickness of the epithelium shows the cellular features of carcinoma without invasion of the underlying stroma is termed *SCC in situ.* Microinvasive SCC refers to SCC in which limited tumor invasion is confined to the area just deep to the basement membrane.[17]

SCC expresses epithelial markers such as cytokeratin and epithelial membrane antigen.[59] These markers are detected by immunohistochemistry, which is used to differentiate between malignant tumors of similar histologic appearance.

The pathologic diagnosis of SCC is usually straightforward; however, two entities in particular can be difficult to distinguish from SCC. Pseudoepitheliomatous hyperplasia (PEH) is characterized by an overgrowth of squamous epithelium that histologically mimics carcinoma. It can be a primary process or a secondary histologic finding associated with chronic irritation, trauma, infection, or giant cell tumor. The epithelium does not demonstrate cytologic evidence of malignancy; however, elongation of the rete ridges may simulate invasion when specimens are cut tangentially. Properly oriented specimens and careful examination will usually distinguish PEH from SCC, but immunostaining may aid differentiation of the two entities.[17,97]

Necrotizing sialometaplasia is thought to be the result of infarction of salivary tissue. It is extremely uncommon in the larynx, but a few cases have been reported.[98] It may develop in the larynx after ischemia or trauma and is characterized by squamous metaplasia of the ducts and acini of seromucinous glands, which may be confused with SCC or mucoepidermoid carcinoma. This lesion resolves spontaneously. Immunohistochemistry may be required to differentiate necrotizing sialometaplasia from SCC and certain nonsquamous malignancies such as mucoepidermoid carcinoma, neuroendocrine carcinoma, malignant melanoma, or lymphoma, which may have a similar appearance when examined histologically.[17,99]

Clinical Presentation

The symptoms of laryngeal SCC depend on the site from which the primary tumor originates. The cardinal symptom of glottic SCC is dysphonia, which develops early in the natural history of the disease as the normal vibratory characteristics of the vocal cord are altered by even a small lesion. Therefore patients with glottic SCC usually present with earlier stages of disease, although if the early symptoms are ignored or attributed to other diagnoses, symptoms of advanced disease such as dyspnea and stridor may arise. Glottic tumors remain localized in the glottis for prolonged periods, owing to the natural barriers to tumor spread (ligaments, membranes, and cartilages) and to the relative paucity of glottic lymphatics. Supraglottic tumors may cause dysphonia (often an alteration in vocal resonance), dysphagia, odynophagia, otalgia, stridor, dyspnea, or hemoptysis. Patients with supraglottic SCC may also present with metastatic cervical adenopathy, without obvious laryngeal symptoms, because the supraglottic larynx has a rich lymphatic drainage network. SCC of the subglottis often presents with advanced-stage disease. Dyspnea and stridor are the most common symptoms of subglottic SCC. Because their onset is usually gradual and insidious, subglottic SCC may be misdiagnosed as asthma or other pulmonary diseases.[100,101]

On examination of the larynx, SCC may appear as an ulcerative, exophytic, sessile, or polypoid lesion. However, in cases of ventriculosaccular SCC (which is uncommon), an epithelial lesion may not be seen in the early stages because the carcinoma arises from the ventriculosaccular system, which lies within the paraglottic space.[102] Fullness of the vestibular fold may be the only obvious examination finding. In this scenario, deep biopsies of the vestibular fold are necessary to confirm or exclude the diagnosis of malignancy. A second clinical presentation, in which occult laryngeal SCC may be the underlying etiology, is that of the laryngocele. An association between laryngoceles and SCC has been recognized for some time.[103] In patients with laryngoceles, direct laryngoscopy with careful inspection of the ventricle using angled endoscopes is mandated to exclude an SCC of the ventricle.

Cervical Nodal Metastases

The incidence of cervical metastases from SCC of the larynx, as well as the nodal groups involved, vary according to the site of the primary tumor (Fig. 107-9). Due to its rich network of lymphatics, supraglottic SCC has the highest incidence of regional metastases—both clinically apparent and occult metastases. Cervical metastasis has been confirmed pathologically in 10% of T1 supraglottic lesions, 29% of T2, 38% of T3, and 57% of T4.[104] The incidence of occult metastases (cN0, pN+) in supraglottic SCC varies from 12% to 40% for all T stages.[105-108] The incidence of occult metastases is greater in tumors with a higher T stage: T1 0% to 14%, T2 20% to 21%, T3 28% to 35%, and T4 40% to

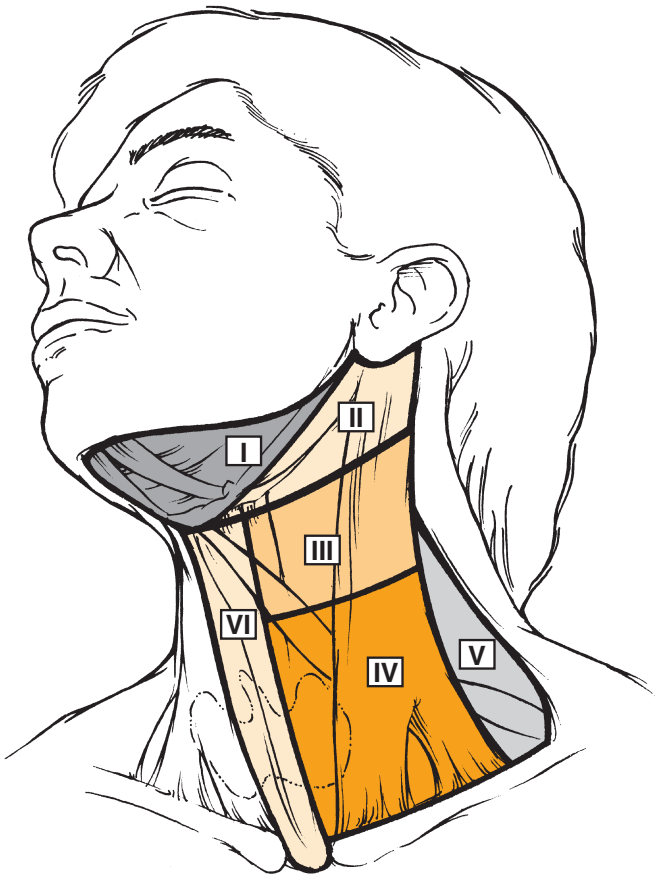

Figure 107-9. The six nodal levels of the neck. *(Redrawn from Robbins KT, Clayman G, Levine PA et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology–Head and Neck Surgery.* Arch Otolaryngol-Head Neck Surg. *2002;128:751-758, Figure 1*).

75%.[106,109] Supraglottic SCC usually metastasizes to levels II, III, and IV. Levels I and V are involved by metastases rarely and only when other nodal levels are also involved.[110,111] Bilateral metastases (palpable and occult) occur frequently in supraglottic SCC and are more common in midline or bilateral tumors.[104,112] Therefore, in cases of supraglottic SCC, surgical treatment of the N0 and N1 neck is usually with a bilateral selective neck dissection (levels II-IV). For N2 or N3 disease, a comprehensive neck dissection (levels I-V) is indicated.

Glottic SCC has a low risk of cervical metastasis: in a series of 910 patients, the overall incidence of pathologically confirmed nodal metastasis was 5.9%, with an incidence of occult metastasis of 18%.[113] Similar to supraglottic SCC, the incidence of regional metastasis correlates with T stage. In the same series, nodal metastases were found in 0.1% of T1 tumors (one patient only), 5% of T2, 18% of T3, and 32% of T4.[113] The nodes at risk of metastasis from glottic SCC are those in levels II, II, and IV, as well as level VI (prelaryngeal, pretracheal, and paratracheal nodes). Bilateral or contralateral metastases are rare.

Primary subglottic carcinoma is rare, and descriptions of the clinical behavior of these tumors are based on a small number of patients. The paratracheal nodes (level VI) are most frequently involved with metastases, including contralateral or bilateral metastases. Metastases to levels III, IV and V are uncommon. Although these tumors are aggressive and have a poor prognosis, the incidence of cervical metastasis is generally reported to be low, with a range of 4% to 27%.[101,114] However, Harrison[115] detected metastatic tumor in approximately 50% of serially sectioned paratracheal nodes. Metastases to mediastinal lymph nodes are common (up to 46%), but they are classified as distant metastases.[116]

Distant Metastases

Distant metastases from laryngeal SCC include not only hematogenous metastases to distant organs, but also lymphatic metastases to nodal groups outside the neck.[59] The most common site for distant hematogenous metastases is the lung. The liver and skeletal system (ribs, vertebrae, and skull) are affected less often. The mediastinum is the most common site for distant lymphatic metastases.[117] Distant metastases are uncommon at initial presentation. Patients who develop distant metastases have almost always had regional metastases diagnosed at some stage in the course of their disease. The incidence of distant metastasis varies according to the site of the primary tumor: 3.1% to 8.8% in glottic SCC, and 3.7% to 15% in supraglottic SCC.[117-121] Supraglottic SCC usually has a higher incidence of distant metastases compared with glottic SCC. The frequency of distant metastases from subglottic SCC is less certain because primary tumors in this site are rare; however, Spector and colleagues[117] observed that 14.3% of subglottic SCCs developed distant metastases. Clinical and pathologic factors associated with an increased risk of distant metastases include advanced stage of primary tumor (especially T4 stage); presence of cervical metastases (especially N2 and N3 disease); duration, level, and extracapsular spread of cervical metastases; and locoregional recurrence.[117,121,122] Lymphatic metastasis to the skin is also a sign of advanced disease and, similar to distant metastases, has a grave prognosis.[123]

Diagnosis and Evaluation

A clinical diagnosis of SCC can usually be made on the basis of the appearance of the larynx on examination. Confirmation of the diagnosis and staging of the tumor are achieved with a thorough evaluation, which includes physical examination, flexible laryngosocopy, endoscopic examination under general anesthesia, biopsy, and imaging.

History and Physical Examination

A history of the presenting symptoms and any associated UADT symptoms should be elicited, with particular attention paid to symptoms suggesting impending airway obstruction such as stridor and dyspnea. Additional information that should be gathered includes exposure to risk factors for laryngeal cancer (primarily tobacco and alcohol), medications, and medical comorbidities such as cardiovascular, pulmonary, or renal disease that may affect the type of treatment that can be offered.

A complete head and neck examination is performed for suspected laryngeal cancer. Initial assessment should determine whether urgent intervention is required, for example, to secure an airway for a patient with a large obstructing lesion. Subsequent assessment is directed at assessing the location and extent of the primary tumor, palpating for neck nodes, and examining the rest of the upper aerodigestive tract for synchronous tumors.

Indirect laryngoscopy (IDL) using a mirror may provide an excellent three-dimensional view of the larynx and any lesions. However, images are not recorded, the hypopharynx is not adequately visualized, and in patients who do not tolerate IDL, the larynx cannot be evaluated completely. Flexible fiberoptic laryngoscopy permits photographic and video documentation, as well as examination during dynamic maneuvers (e.g., Valsalva's maneuver, coughing, swallowing). Laryngeal videostroboscopy is useful for the documentation of small lesions on the vocal fold and assessment of the mucosal wave before and after treatment. However, videostroboscopy cannot reliably distinguish intraepithelial neoplasia from invasive carcinoma, nor is it reliable for determining the depth of invasion of vocal cord carcinoma.[124]

In the patient with laryngeal cancer, specific examination findings that should be noted include the site of the primary tumor; the subsites involved; extension to adjacent structures; vocal cord mobility (normal vs. impaired vs. fixed); and patency of the airway. A biopsy may be taken in the office via a transoral approach or via the working channel of the flexible laryngoscope, although this is usually performed in the operating room under general anesthesia, unless there are concerns regarding a patient's fitness for anesthesia. The base of tongue and the laryngeal skeleton are palpated to assess for extralaryngeal spread, and the neck is palpated to assess the nodal status.

Imaging

Radiologic imaging is a critical part of the evaluation of a patient with a suspected laryngeal malignancy.[125] When feasible, imaging is performed before operative endoscopy and biopsy to obtain images before potential edema and distortion from biopsy and manipulation of the larynx. Information obtained with imaging can be integrated with endoscopic findings and, in some cases, can guide the surgeon to focus attention on deeper areas not normally visible on endoscopy requiring a biopsy. Cross-sectional imaging, using either computed tomography (CT) scanning or magnetic resonance imaging (MRI), yields the most useful information in the evaluation of tumors of the larynx.

Computed tomography is the most commonly used radiologic investigation in the evaluation of laryngeal cancer, although MRI is superior in some situations. CT is superior to MRI for imaging bony structures (such as ossified cartilages) and calcifications.[125] MRI is superior for detecting cartilage invasion and has enhanced ability to discriminate soft tissues. The disadvantages of MRI of the larynx compared with CT include increased imaging time (resulting in motion artifact), decreased spatial resolution, inferior ability to detect bone invasion, and increased cost.[126] MRI is also contraindicated for patients with pacemakers or other ferromagnetic foreign bodies, and false-positive findings are common because MRI is often unable to distinguish clearly between reactive inflammatory changes and tumor.[127]

Evaluation with CT includes a standard neck scan to evaluate extralaryngeal structures and lymph nodes, and finely cut images (≈1 mm) through the larynx to avoid partial volume averaging of the vocal folds, and allow multiplanar reconstruction.[128] The axial images should be aligned parallel to the true vocal cords to allow correct interpretation of tumor location and size.[125] Intravenous contrast is especially important because the primary tumor usually enhances with contrast, improving its visualization, and because the contrast will differentiate between nodal disease and blood vessels in the neck. Contrast (gadolinium)-enhanced, T1-weighted MRI images improve the definition of pathologic tissue, although some authors have found the use of contrast adds no information when assessing laryngeal tumors.[129,130] Special MRI series such as fat suppression are often helpful, especially when assessing the paraglottic and pre-epiglottic spaces.[125]

Positron emission tomography (PET), using radiolabeled glucose (18 F-fluorodeoxyglucose, FDG), is able to distinguish between malignancy and other pathologic processes such as inflammation.[131] PET is

particularly useful in the head and neck when performed in conjunction with CT (PET/CT), giving superior anatomic localization of suspicious areas.[132] PET has several potential uses: the staging of malignant tumors (especially for the detection of regional and distant metastases); the diagnosis of the unknown primary; the detection of synchronous lesions in addition to the index malignancy; and in the diagnosis of residual or recurrent cancer, which is particularly challenging in the irradiated larynx (see later).[133] PET is being used more commonly in the head and neck as our understanding of its abilities and applications improves.

Radiology plays an important role in the staging of laryngeal SCC because deep invasion by the primary tumor is assessed poorly by clinical and endoscopic examination. Several characteristics of the primary tumor used for staging cannot be determined without imaging including invasion of the PES, the PGS, the thyroid or cricoid cartilage, the extralaryngeal tissues, the prevertebral space, mediastinal structures, and encasement of the carotid.[6]

Invasion of the PES is diagnosed on CT by a loss of fat in the PES and replacement with a moderately enhancing mass.[128] On MRI, tumor has a low to intermediate signal on T1-weighted images, with a high signal on T2, and enhances with contrast on T1.[128] MRI is highly sensitive in the diagnosis of PES and base of tongue invasion and is superior to CT.[134] The radiologic appearance of the thyroid and cricoid cartilages depends on the degree of ossification. Although CT is superior to MRI for imaging bone and calcium, MRI is superior to CT in the detection of laryngeal cartilage invasion.[126,127,135] MRI is highly sensitive for cartilage invasion and has a high negative predictive value; however, it is not good at distinguishing between reactive inflammation and tumor, resulting in a lower specificity and a positive predictive value of approximately 70%.[126,127,135] CT is less sensitive than MRI in the diagnosis of cartilage invasion. Findings on CT such as extralaryngeal spread, sclerosis, erosion, and lysis suggest cartilage invasion.[136] MRI is also better than CT at detecting cricoid invasion in subglottic tumors.[137] The accurate diagnosis of cartilage invasion is important because it will upstage a carcinoma to T3 or T4a and is associated with a worse response to radiotherapy, poorer local control, and an increased risk of chondroradionecrosis.[126,138]

Imaging is also important to stage the neck accurately and detect distant metastases. In one series, CT and MRI were equivalent in the detection of cervical metastases in larynx cancer and superior to clinical examination and ultrasound. However, ultrasound-guided FNA and PET were the most accurate.[139] PET has not been used extensively in the pretreatment evaluation of laryngeal cancer because standard PET lacks anatomic detail. However, fused PET/CT scanning addresses this issue and in all likelihood will become more widely used for this indication.[140]

The lungs are the most common site of metastasis for lung cancer, and second primary tumors commonly occur in the lungs as well. A chest radiograph or a chest CT should be obtained to exclude pulmonary lesions. In patients with advanced primary tumors and low cervical metastases, PET/CT is useful for identifying distant metastases or SPTs that would alter patient management.[140]

Operative Endoscopic Examination

Unless there are medical contraindications, all patients with suspected laryngeal cancer should undergo an endoscopic examination under general anesthesia. Direct laryngoscopy allows the clinician to examine the larynx in greater detail, palpate the larynx, and obtain a biopsy for histologic analysis. Angled endoscopes are useful to evaluate the laryngeal surface of the epiglottis, anterior commissure, ventricles, and undersurface of the true vocal cords. If vocal cord mobility is noted to be abnormal on preoperative examination, palpation of the vocal cord and arytenoid cartilage will differentiate arytenoid fixation from vocalis muscle invasion causing cord immobility. Invasion of adjacent sites in the oropharynx or hypopharynx is assessed with direct pharyngoscopy and palpation of the tongue base. The neck may be palpated under general anesthetic to assess nodal status. The complete examination should be documented with photos, video, and a diagram of the extent of the primary tumor. Esophagoscopy is performed to exclude an SPT in the esophagus. Bronchoscopy is not required routinely if the preoperative chest imaging is normal.[141] Biopsies of the primary tumor and any suspicious areas are taken to confirm the histologic diagnosis and to determine the extent of tumor.

Caution should be exercised when performing direct laryngoscopy for patients presenting with laryngeal tumors obstructing the airway. Maintenance of a secure airway at all times is the paramount concern, and for severely compromised airways a tracheostomy under local anesthetic may be necessary. However, if possible, debulking of the obstructing tumor (using either cup forceps, a microdebrider, or the CO_2 laser) is the preferred technique to avoid a tracheostomy and to maintain the airway so that thorough evaluation and staging can be performed before selection of the definitive treatment.[142] If a tracheostomy is necessary, a high tracheostomy is performed so that any subsequent resection allows preservation of as much of the trachea as is oncologically possible. Surgical treatment is usually required for patients requiring tracheostomy because significant destruction of the larynx is usually present. The traditional treatment of an obstructing laryngeal SCC requiring a tracheostomy was an emergency laryngectomy (after a biopsy and frozen section biopsy had confirmed the diagnosis). However, emergency laryngectomy does not offer a survival advantage over tracheostomy with delayed laryngectomy and does not allow the patient to be counseled and prepared both psychologically and nutritionally before such radical laryngeal surgery.[142,143] Tracheostomy has not been found to increase the risk of peristomal recurrence, which is more strongly associated with advanced local disease, especially subglottic tumor extension.[143-146]

Differential Diagnosis

The differential diagnosis of laryngeal SCC includes non-neoplastic conditions, benign tumors, premalignant squamous cell lesions, and non–squamous cell malignant tumors (see Table 107-2).

Treatment of Squamous Cell Carcinoma

The goals in the treatment of laryngeal cancer are (1) to cure the patient; (2) to preserve the larynx or, more correctly, to preserve the function of the larynx; and (3) to minimize the morbidity of the treatment. A functional larynx should allow the patient to communicate with an intelligible voice; to swallow adequate nutrition without aspiration; and to breathe through the nose or mouth without the need for a stoma or a tracheostomy tube.

The most important information required for therapeutic decision making are (1) the histologic diagnosis of the tumor; (2) the site of origin of the tumor; and (3) the stage of disease (T, N, and M stage). The importance of accurate staging cannot be underestimated, and therefore a thorough evaluation of the patient is crucial.

A number of treatment options are available for patients with laryngeal cancer. Surgery and RT have long been the two most important treatment modalities. In the past 30 years, further therapeutic options have become available with the introduction of new surgical techniques for conservation laryngeal surgery (partial laryngectomy) and of chemotherapy combined with RT (CRT), which may be used in a neoadjuvant, concurrent, or adjuvant role. In general, early laryngeal cancer (stage I or II) is treated with single-modality therapy, either surgery or RT. Advanced laryngeal cancer (stage III or IV) is treated with combined-modality therapy, either primary surgery followed by RT or CRT, or primary CRT or RT with surgery for salvage. The selection of which modality to use, or (in advanced laryngeal cancer) which modality to use initially, should be made after careful consideration of a number of factors, which can be grouped into patient factors, disease factors, and institution factors (Table 107-6). For early-stage disease, voice quality, swallowing function, the duration of therapy, and patient preference are the major factors considered when selecting treatment.

The following general discussion of the therapeutic options available emphasizes decision making and treatment selection. Subsequent chapters will describe the specifics of the treatment of early glottic cancer (Chapter 108), transoral laser microsurgery (Chapter 109), conservation laryngeal surgery (Chapter 110), total laryngectomy (Chapter 111), radiation therapy (Chapter 112), and vocal rehabilitation following total laryngectomy (Chapter 113).

Table 107-6

Prognostic Factors in Treatment of Laryngeal Cancer

Patient Factors	Tumor Factors	Institution Factors
Age	Histologic diagnosis	Surgical expertise & experience
Comorbidities & general health	Site of primary tumor	Oncologic expertise & experience
Performance status	Stage (T,N,M)	
Occupation	Histologic features:	
Vocal demands	• Adequacy of resection margins	
Compliance & reliability (for treatment & follow-up)	• Extracapsular spread	
Smoking status	• Perineural invasion	
Nutritional status	• Lymphovascular invasion	
Distance from the treatment center		
Patient preference		

Treatment of Glottic Squamous Cell Carcinoma

Treatment of the Early Primary Tumor in Glottic Squamous Cell Carcinoma

Early glottic SCC (defined as stage I or II disease, i.e., T1-2N0) may be treated with either RT or surgery, without the need for elective treatment of the neck.[147] Primary RT for T1 glottic SCC provides 5-year local control rates of 81% to 90% and laryngeal preservation in 90% to 98% of patients.[148-150] For T2 tumors with normal vocal cord mobility, RT achieves local control in 64% to 87%, with laryngeal preservation rates of 75% to 87%.[148,151,152] The effectiveness of RT may be overestimated due to complete excision of the tumor at the time of the initial biopsy. In 12 of 60 patients undergoing partial laryngectomy for early glottic SCC, Stutsman and McGavran found that there was no tumor in the pathologic specimen.[153,154]

Surgical treatment of early glottic SCC also aims to preserve the larynx and is referred to as *conservation laryngeal surgery* or *partial laryngectomy.* Traditionally, these limited laryngeal resections were performed via an external approach: Cordectomy and vertical hemilaryngectomy (VHL) are the two classic open procedures for the treatment of early glottic carcinoma. Cordectomy is the removal of the diseased true vocal cord via a laryngofissure. Vertical hemilaryngectomy removes the ipsilateral true and false vocal cords, extending laterally to the perichondrium of the thyroid cartilage. The lamina of the thyroid may be removed to allow the soft tissues adjacent to the larynx to collapse medially to reconstitute the glottis for phonation, or it may be preserved, with transposition of soft tissue (such as a strap muscle) medial to the lamina to recreate the glottis. Variations of the VHL (extended VHL) have been described to include the resection of the anterior commissure, contralateral true vocal cord, arytenoid, and supraglottic or subglottic tumor extension. Open surgical treatment oncologic results are reported as having 90% to 98% local control rates and 93% to 98% larynx preservation rates.[155,156]

In the past 30 years, endoscopic approaches analogous to the open procedures have been developed to accomplish the same resection without disruption of the supporting structures of the larynx. The oncologic results for transoral laser microsurgery (TLM) have been reviewed by Ambrosch.[157] For Tis-T2 tumors, local control rates are 80% to 94% with a greater than 94% laryngeal preservation rate.[158] In the hands of experienced surgeons, local control and laryngeal preservation rates following TLM equal those following open surgical techniques.[158] In comparison with open surgical techniques, TLM avoids a tracheostomy, the hospital stay is shorter, the cost is reduced, and there is a lower incidence of dysphagia postoperatively.[157]

Lesions of the middle third of the true vocal cord have the best local control rates and may be treated by either TLM, open cordectomy or RT; local control approaches 100% after surgical excision, whereas RT achieves a 95% local control rate.[159] Radiation failures may be caused by unrecognized deep invasion. Following surgical excision, repeat surgery or RT may be used to treat residual or recurrent tumor. Although RT alone has excellent results, a second course of radiation for a recurrence or for a second tumor cannot be offered. Recurrent tumors may not be amenable to conservation surgery after previous RT.

T2 glottic lesions with impaired vocal cord mobility warrant special consideration. Although classified as T2 lesions by the TNM system, glottic tumors with impaired vocal cord mobility have a worse prognosis than tumors that are classified as T2 on the basis of supraglottic or infraglottic invasion. Impaired vocal cord mobility is usually secondary to either tumor bulk or deep invasion. Radiotherapy is less effective in controlling these lesions, and this is probably often due to tumor volume. Dickens and colleagues[148,160] noted that 4% of tumors less than 15 mm recurred after radiotherapy, whereas 26% of larger lesions of a similar stage recurred, even when only one true vocal cord was involved. T2 tumors managed by primary RT showed a 30% local failure rate, which, when surgically salvaged, improved to 94%.[19,161] Harwood and DeBoer[19] observed that impaired vocal cord mobility resulted in lower control rates in T2 lesions, and they suggested the classification be divided into T2a and T2b on the basis of mobility. In this analysis, a 70% local control rate was noted for the former category versus 51% in the latter. McLaughlin and colleagues[162] noted recurrence rates of 11% and 26% for T2a and T2b tumors, respectively.

Voice quality following either surgery or RT is influenced by the extent of tumor and depth of invasion. Small superficial tumors will have excellent voice quality with either surgery or RT. Deeper tumors with muscular invasion will have inferior voice outcomes with either treatment modality. Furthermore, the control rate with RT will be lower. Surgical treatment provides a better assessment of tumor extent and in some cases may result in upstaging of the tumor. For small superficial tumors, voice quality with surgery or RT is generally good with comparable voice results.[163]

Early Glottic Squamous Cell Carcinoma and the Anterior Commissure

Anterior commissure involvement has been associated with decreased local control rates with surgery and RT.[164,165] The topic has been controversial, and several explanations for the poorer control rates have been offered. One hypothesis for the decreased effectiveness of RT has been underdosage with supervoltage RT at the tumor-air interface. Increased dose fractions (to >2 Gy) are believed to have solved this problem. The anterior commissure is also a difficult region to assess, and deep invasion may not be recognized, resulting in understaging and thus undertreatment. The lack of perichondrium at the insertion of the anterior commissure tendon was thought to increase the risk of cartilage invasion. Kirchner and Carter[166] examined laryngeal carcinoma with anterior commissure invasion using whole organ sections of the larynx and discovered that the anterior commissure tendon is a strong barrier to cancer spread. Deep invasion was seen only in cases where the tumor had invaded the supraglottis superiorly or the subglottis inferiorly. Spread of tumor across the anterior commissure did not increase the risk of deep invasion. Kirchner concluded that supraglottic

spread provides access to the PES and that subglottic spread provides access to the thyroid cartilage and the cricothyroid membrane.

Frontolateral VHL obtains local control rates of 80% to 90% for T1 carcinomas involving the anterior commissure.[167,168] Supracricoid partial laryngectomy (SCPL) is a more extensive procedure that removes the anterior commissure and the anterior two thirds of the vocal folds. Laccourreye and colleagues have reported a 5-year local control rate of 98% for T1 and T2 glottic tumors with anterior commissure involvement.[169] Bron and colleagues[170] reported local control of 94.5% for 45 previously untreated laryngeal SCCs involving the anterior commissure treated with SCPL. Although oncologically effective, voice quality is significantly impaired following this technique.

Early reports of TLM for glottic carcinoma considered anterior commissure involvement to be a contraindication. Krespi and colleagues noted a high rate of failure at the anterior commissure.[171] This region may be difficult to visualize at the time of surgical resection. With improved understanding of the anatomy, instrumentation, and technique, excellent control rates have been obtained.[172,173] Pearson and Salassa[165] reported their initial experience of 39 patients with anterior commissure involvement. They had no local failures among 17 pT1 and pT2a tumors. The majority (19/22) of advanced tumors with anterior commissure involvement (pT2b, pT3-4) tumors were controlled with endoscopic surgery. Steiner and colleagues[158] reported results on 263 patients with early glottic tumors treated over a 10-year period and observed a modest decrease in local control and laryngeal preservation rates, with equivalent 5-year survival. For T1a tumors, local control was 90% when the anterior commissure was not involved and 84% with anterior commissure involvement. The corresponding laryngeal preservation rates were 99% versus 93%. Similar findings were seen with T1b and T2a tumors.

Treatment of the Advanced Primary Tumor in Glottic Squamous Cell Carcinoma

Advanced glottic SCC (stage III or IV disease) is associated with vocal cord fixation, cartilage invasion, transglottic spread of tumor, subglottic extension, laryngeal framework invasion, extralaryngeal spread, lymph node metastases, and distant metastases. These features portend worse prognosis. The treatment of choice for T3 and T4 glottic tumors remains controversial because of the heterogeneity of the tumors and lack of reliable studies comparing surgery and radiotherapy for T3 and T4 carcinoma of the larynx.[174] T3 and T4 glottic tumors are discussed separately in this chapter. T3 glottic carcinomas are unusual because despite their advanced T stage, in general they have a low risk of nodal metastasis. Furthermore, the spectrum of disease with T3 lesions is variable, ranging from low-volume tumors invading the vocalis muscle to cause fixation to very large transglottic tumors. Tumor volume and transglottic spread of T3 tumors predict increased aggressiveness, increased rate of lymph node metastasis, and poorer response to treatment. Tumors larger than 1.5 cm, subglottic extension, and lymph node metastasis laterally or to paratracheal or anterior pretracheal nodes predict failure above the clavicle.[175,176]

Traditionally, T3 tumors have been treated with total laryngectomy as single-modality therapy. Open VHL and more extensive partial laryngectomies are used in carefully selected cases. Kirchner and Som[177] reported a 2-year survival rate of 60% following open partial laryngectomy and noted that failures occurred when there was inferior tumor extension in the larynx. Biller and Lawson reported a 73% absolute 2-year, tumor-free control rate following partial laryngectomy (with resection extended to include a portion of the cricoid cartilage when there was >5 mm of subglottic extension).[178] Pearson and coworkers have published extensive experience of near-total laryngectomy (NTL) for patients with tumors not suitable for other conservation procedures.[179] This procedure preserves one arytenoid and a portion of the cricoid cartilage to create a diversionary voice shunt from the trachea. Patients remain tracheotomy dependent for breathing and use the shunt to produce speech.

Radiation therapy has a local control rate of approximately 50% for T3 tumors, which is lower than that of surgery.[180] For T3 tumors, the return of vocal cord mobility following RT predicts a good response. In a small series of 14 patients with T2b-3 laryngeal carcinomas, all five patients who did not have return of cord mobility and none of nine patients who had return of vocal cord mobility developed recurrent cancer.[181] Tumor volume may predict the response to irradiation, with poor results in larger tumors.[182] For small T3 tumors that would be amenable to partial laryngectomy, primary RT could be considered in those not wishing to pursue surgical option, although surgical resection generally has higher local control.[183,184] Intensified RT regimens including twice-daily treatments and the use of intensity-modulated radiotherapy (IMRT) may improve local control.[185] Further discussion on RT can be found in Chapter 112. Total laryngectomy or CRT is recommended for bulky T3 tumors or tumors not suitable for conservation laryngeal surgery.

In general, T4 glottic carcinoma is not considered amenable to conservative laryngeal resection. Options for T4 glottic carcinoma include total laryngectomy (usually with postoperative RT or CRT), near-total laryngectomy, or primary CRT in selected low-volume disease with limited cartilage destruction to preserve the larynx. Near-total laryngectomy may be considered in selected cases with limited subglottic extension and no interarytenoid involvement.[186] Recent encouraging results for TLM for T3-4 laryngeal cancer support its use in carefully selected cases by experienced surgeons for organ preservation.[187]

Primary RT for T4 glottic carcinoma has poor local control rates. A historical review of primary RT for laryngeal SCC found that only 2 of 25 T4N0 glottic carcinomas treated with primary RT survived 5 years.[188] In patients unable or unwilling to undergo concurrent CRT and unwilling to have a total laryngectomy, primary RT may provide a chance of local control. In some patients, the addition of newer agents such as cetuximab may increase the effectiveness of RT with acceptable risk of increased toxicity.[189]

Although attempts to avoid total laryngectomy are worthwhile, RT may result in significant local tissue destruction, scarring, and persistent edema. Thus the larynx may be preserved, but the patient may be left with a severely compromised organ with a restricted airway, a poor voice, dysphagia, and/or aspiration. If RT is selected for primary management, close follow-up is required as the success of this approach relies on the early detection of residual or recurrent disease, which may be challenging in a larynx scarred from irradiation. A total laryngectomy is usually required for salvage if recurrent disease is diagnosed. The successful salvage rate for recurrences after RT is approximately 60%. Persistent postradiation edema predicts persistent disease: 45% of patients with edema persisting for longer than 6 months after RT had a deep recurrence.[190] In these situations close follow-up with endoscopy and imaging is vital.[191] Distinguishing between recurrence and chondroradionecrosis of the larynx can be challenging. Deep biopsies required to obtain an accurate diagnosis can induce or exacerbate chondroradionecrosis. Positron emission tomography (PET) scanning has been helpful to resolve this dilemma and assists surveillance for tumor recurrence.[192]

Selected T4a tumors may be considered for nonsurgical organ preservation trials (see "Nonsurgical Organ Preservation" later). The success of organ-preservation protocols for bulky T4a tumors is lower than for T3 tumors because cartilage destruction predicts poor response to organ preservation protocols. These patients were excluded from the RTOG 91-11 trial comparing concurrent CRT, induction chemotherapy followed by RT, and RT alone.[193]

When total laryngectomy is undertaken for T4 disease, hemithyroidectomy or subtotal thyroidectomy is recommended for cases of palpable abnormality, subglottic tumors, or glottic tumors with greater than 1 cm of subglottic extension.[194] Thyroid gland invasion may be predicted if a positive Delphian node or cartilage destruction is present. Cancer is found in 3% to 8% of thyroid specimens.

Treatment of the Neck in Glottic Squamous Cell Carcinoma

The incidence of nodal metastasis for glottic SCC is lower than either supraglottic or subglottic SCC. Because the true vocal cords are nearly devoid of lymphatics, tumors limited to the glottis rarely metastasize to regional nodes. When metastasis does occur, the nodes at risk are the prelaryngeal, pretracheal, and paratracheal nodes, as well as the upper, mid, and lower deep cervical chain nodes (levels II, III, and IV).

Occult metastases from T1-2 glottic SCCs are uncommon, and elective treatment of the N0 neck is not required.[195] T3 glottic SCC is more controversial. In general, occult nodal metastases are uncommon from T3 glottic carcinomas unless there is transglottic spread of the tumor, which has a higher rate of occult metastasis.[196] A national survey of otolaryngologists published in 2003 reported that 87% of respondents treated the neck of patients with T3N0 glottic SCC, and 90% treated the neck of those with T4N0 glottic SCC.[197] T4 glottic carcinomas have a higher risk of occult metastases, approximately 20%, and treatment of the neck is recommended. If the primary tumor is being treated surgically, an ipsilateral selective neck dissection is recommended. For glottic carcinoma, the paratracheal nodes and levels II-IV are dissected. Adjuvant treatment with RT or CRT is used depending on pathologic findings in the neck dissection specimen.[198,199] If RT is used to treat the primary tumor, the central compartment and ipsilateral lateral neck are included in the field.

For all T stages, clinically evident nodal disease (N+) warrants aggressive treatment, the choice of which depends on the management of the primary tumor. If surgery is used for the primary tumor, an ipsilateral comprehensive neck dissection is indicated for N+ disease. Adjuvant treatment may be indicated depending on pathologic findings.

Postoperative RT is recommended when multiple nodes, extracapsular spread, extralaryngeal invasion, and perineural or lymphovascular invasion is present. Recently, two large studies have demonstrated improved locoregional control with use of platinum-based chemotherapy given concurrently with RT.[200,201] Cooper and colleagues[200] found a 10% increase in the 2-year locoregional control rate (82% vs. 72%), although there was an associated 43% increase in acute grade III or higher toxicity (34% vs. 77%). Similarly, Bernier and associates observed an 11% increase in 5-year progression-free survival, which was also associated with a higher rate of acute toxicity.[201] A comparative analysis of the combined results of these two studies found that extracapsular spread and microscopically positive surgical margins were the only risk factors for which adjuvant chemotherapy enhanced the efficacy of RT in both studies.[202] Other variables trended toward statistical significance, but patients who had two or more positive lymph nodes (without extracapsular spread) as their only risk factor did not seem to benefit from the addition of chemotherapy.

Improved locoregional control rate with primary concurrent CRT has led to the addition of chemotherapy to RT as an adjuvant treatment for patients with adverse pathologic findings in the surgical specimen. The decision to use chemotherapy in this setting requires careful consideration of the ability of the patient to tolerate the treatment. The success of this therapy is dependent on completion of the treatment regimen without significant breaks.[203-206] Encouragingly, a recent analysis of the tolerability of concurrent CRT in patients older than 70 years of age demonstrated high compliance with a regimen of concurrent carboplatin and RT.[207]

Treatment of Supraglottic Squamous Cell Carcinoma

SCC of the supraglottis metastasizes to the cervical lymph nodes more frequently than glottic SCC. Therefore management of the cervical lymphatics plays a prominent role in treatment planning of supraglottic SCC. Similar to head and neck SCC in other sites, the regional nodal status (N stage) of a patient with supraglottic SCC is the most important predictor of survival. A number of therapeutic options are available for supraglottic SCC, especially for early primary tumors (T1 and T2). Early-stage disease (stage I and II) is generally treated with single modality therapy, whereas advanced disease (stage III and IV) is generally treated with combined modality therapy.

Sessions and colleagues[208] reported the results of 653 patients with supraglottic SCC treated with a number of modalities (except chemotherapy). Overall 5-year, disease-specific survival for all stages was 66%, with rates of 77%, 74%, 64% and 50% for stages I, II, III, and IV, respectively. No treatment modality was found to result in superior survival. The larynx was preserved in 86% of patients treated with open partial laryngectomy, and in 73% of RT patients. In another large series of patients (n = 903) treated with conservation surgery, the 5-year uncorrected actuarial survival for stage I, II, III, and IV disease was 84%, 81%, 76%, and 55%, respectively.[209]

An important point to highlight is that survival from laryngeal SCC has diminished over the past 20 to 30 years in the United States. A review of the National Cancer Database by Hoffman and colleagues[60] found that 5-year relative survival from supraglottic SCC has decreased from 52.2% in 1985-1987 to 47.3% in 1994-1996. The greatest decline in survival for patients with supraglottic SCC occurred in those with T1N0 and T2N0 tumors, with a lesser but still significant decline in survival for T3N0 tumors. The authors noted that the frequency of use of the various treatment modalities has changed during this period, with an increase in RT and CRT, and hypothesized that the decreased survival observed in early supraglottic cancer could be explained by less aggressive surgical treatment of the primary and of the neck.

Treatment of the Early Primary Tumor in Supraglottic Squamous Cell Carcinoma

For early supraglottic cancer, the two most frequently used treatment options are supraglottic partial laryngectomy (SGL) or RT. SGL for early supraglottic SCC (as well as some T3 tumors) is achieved by an open supraglottic laryngectomy (OSGL) or by the more recently described TLM.

The traditional OSGL was first described by Alonso in 1947 and subsequently refined by Ogura and Som.[210-212] The oncologic validity of OSGL as a treatment for supraglottic SCC comes from the principle that the supraglottis is embryologically separate from the glottis and subglottis, and for this reason, supraglottic SCC remains localized to the supraglottis in most cases, despite the lack of an anatomic structure preventing invasion of the glottis.[213] OSGL removes all laryngeal structures superior to the floor of the ventricle, preserving both true vocal cords, both arytenoids, the base of tongue, and the hyoid bone (Fig. 107-10). Indications for OSGL are T1, T2, or selected T3 supraglottic tumors. T3 tumors with PES and no transglottic spread and/or vocal

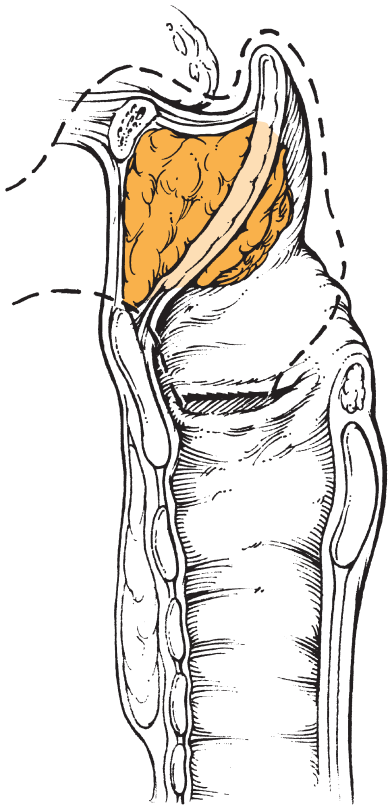

Figure 107-10. Outline of resection for open supraglottic laryngectomy. Note inclusion of entire pre-epiglottic space. *(Redrawn from Som ML. Conservation surgery for carcinoma of the supraglottis.* J Laryngol Otol. *1970;84:657.)*

cord impairment are amenable to OSGL. Contraindications to OSGL include poor general physical condition (e.g., advanced age, lung disease, neurologic disease, preexisting dysphagia or aspiration), glottic involvement, impaired mobility or fixation of the vocal cord, thyroid or cricoid cartilage invasion, involvement of the base of tongue to within 1 cm of the circumvallate papilla, or involvement of the deep muscles of the tongue.[214] The functional morbidity of OSGL is significant, and almost all patients will experience some aspiration postoperatively. Therefore careful patient selection is crucial to the overall success of this procedure: Candidates for OSGL must have good pulmonary function to tolerate the expected aspiration. An OSGL is referred to as an extended OSGL when a more extensive resection is carried out for the treatment of SCC involving the lingual surface of the epiglottis, the base of tongue, or one of the arytenoids.[214]

The functional and oncologic outcomes of OSGL are well documented. Because OSGL disrupts the pharyngeal muscles, the strap muscles, and the sensory innervation of the pharynx and larynx, swallowing is markedly impaired, especially in the early postoperative period. A tracheostomy is required in all patients to provide a safe airway and to protect the lower airway from aspiration. Suarez and colleagues[215] reported that 10% of patients in their series required a completion total laryngectomy for chronic aspiration. Advanced age (older than 65 years) was the major risk factor for intractable aspiration. A further 24% of subjects required permanent tracheostomy. Bron and colleagues[216] noted approximately one quarter of their patients aspirated in the early postoperative period. The median duration until normal oral feeding was established was 16 days, and the median duration until decannulation was 17 days.

OSGL yields excellent local control in the treatment of early supraglottic cancer in the range of 80% to 100%.[217-222] In patients treated with OSGL for T1-3 supraglottic SCC, Bron and colleagues[216] reported 5-year local control, locoregional control, and overall survival rates of 92.5%, 90%, and 92%, respectively. Adjuvant RT was given in 30% for positive surgical margins or adverse pathologic findings in the lymph nodes. Local control and survival were poor when cartilage invasion was present or when there was extralaryngeal extension of disease (i.e., pT4). Suarez and colleagues[222] treated 193 patients with supraglottic SCC with OSGL and ND. Nearly half of the subjects received adjuvant RT. Local control was 98% for T1 tumors and 91% for T2 tumors. No improvement in overall survival was noted with the addition of RT. In Bocca's series of 537 patients with supraglottic cancer (predominantly T2), local control was 94% for stage I and 82% for stage II. Overall 5-year survival was 78%.[218]

Robbins and colleagues[220] treated 139 T2 and T3 supraglottic SCCs with OSGL if technically possible, or with total laryngectomy or radiotherapy if not. Local control at 3 years was 100% for the OSGL group and 91% for the total laryngectomy group. Those subjects treated with primary RT had a 69% local control rate, which improved to 85% with salvage total laryngectomy. Five-year survival was 89% for those subjects treated with OSGL primarily, 78% with TL, and 70% with RT.

Transoral laser microsurgery for supraglottic carcinoma, first described by Vaughan in 1978, has become an accepted alternative to OSGL for supraglottic SCC.[223] The indications for TLM are similar to those for OSGL (i.e., T1-2 and selected T3 tumors), although some institutions will use TLM for more advanced lesions such as T4.[224,225] Few contraindications to TLM exist: incomplete exposure of the tumor; tumor involving the great vessels of the neck; and tumor location and/or bulk requiring an extensive resection that would place the patient at high risk of aspiration (e.g., extensive tongue base involvement).[225] The indications for neck dissection are not changed with TLM, and both sides of the neck may be dissected at the same time the primary is resected, or more commonly performed in a staged fashion several weeks after the initial TLM.[226] The local control rates of TLM are similar to those of OSGL; however, the functional morbidity is much less following TLM because the extrinsic muscles of the larynx, pharyngeal muscles, cartilaginous framework of the larynx, and superior laryngeal nerves are left intact.[227] The functional advantages of TLM include the possible avoidance of a temporary or permanent tracheostomy; less impairment of swallowing postoperatively including less aspiration; and a lower incidence of pharyngocutaneous fistulae.[224,228]

Steiner's group reported their experience with TLM for early supraglottic carcinoma in 1998.[224] Only 4% of subjects were treated with adjuvant RT—96% underwent TLM only. No tracheostomies were performed at the time of the resection, although one patient required a temporary tracheostomy to manage aspiration. The average duration of nasogastric tube feeding was 6 days, and overall swallowing was excellent postoperatively. The oncologic results were equivalent to OSGL: 5-year local control rates were 100% for pT1 and 89% for pT2 tumors, which were salvaged with either a second TLM or with OSGL to give an ultimate local control rate of 97%. Overall 5-year survival was 76%.

Iro and colleagues[229] reported the results of TLM in a series of 141 supraglottic cancers, which were predominantly T1-2. Half of the subjects also had neck dissections, and 45% received adjuvant RT. Tracheostomies were required in 13% of subjects during the course of treatment and were permanent in 9%. All but one of the subjects requiring a permanent tracheostomy were staged as pT4 and underwent extensive resection of the tongue base. Five-year local control rates were 86%, 75%, 75%, and 78% for stages I, II, III, and IV, respectively. Five-year, disease-free survival was reported as 66% (75% for stages I and II, 56% for stages III and IV).

Motta and colleagues[230] performed TLM on 124 subjects with T1-3N0 supraglottic carcinoma and observed local control rates of 82%, 63%, and 77% for T1, T2, and T3 lesions. Laryngeal preservation rates were 89%, 85%, and 95%. Overall survival rates were 91%, 88%, and 81%. Advanced supraglottic tumors were also included in a series of TLM reported by Rudert and associates.[231] The majority of patients (24 of 34) received RT and nearly 20% required tracheostomies. Local control was 100%, 75%, 78%, and 37% for T1, T2, T3, and T4 tumors; overall survival was 71% for stages I and II and 50% for stages III and IV tumors.

The functional outcomes of patients who underwent either TLM or OSGL for predominantly T1-2 supraglottic SCC were compared by Peretti and colleagues.[227] A temporary tracheostomy was required in 14% of TLM patients for an average of 4.5 days compared with 100% of OSGL patients who were decannulated after an average of 35 days. No permanent tracheostomies were required in either group. A feeding tube was used in 21% of the TLM patients for an average of 5 days, compared with 100% of OSGL patients, for an average of 19 days. No permanent feeding tubes were placed in either group. The average period of hospitalization was 11 days for the TLM group versus 26 days for the OSGL group. No significant difference in voice quality between the two groups occurred.

The role of adjuvant RT in TLM has been unclear, with up to 94% of subjects receiving adjuvant RT after TLM in some series.[232]

Zeitels and colleagues[233] concluded that small T1-2 supraglottic lesions in subsites amenable to endoscopic resection (suprahyoid epiglottis, aryepiglottic fold, vestibular fold) could be treated successfully with TLM without RT but recommended that RT should be given after endoscopic resections of larger lesions (T2-3) in less favorable sites (e.g., infrahyoid epiglottis). In this series there was a high rate of local failure after RT in those patients in whom negative margins were not achieved at TLM, suggesting that RT was unable to control residual disease at the primary site. Davis and coworkers described the concept of TLM as a neoadjuvant treatment to remove all carcinoma at the primary site (with negative margins), followed by RT to treat any residual microscopic disease and treat the neck.[234] Using this approach for T2 supraglottic SCC, TLM (and neck dissections for N+ subjects) was performed, with 83% of subjects receiving adjuvant RT. Over one third of subjects were staged as pT3 secondary to PES invasion. Local control was 100% in the surgery-only group and 97% in the combined-modality group. Regional control was 96% in the N0 subjects who received RT to the necks and 91% in the N+ subjects who received surgery and RT to the necks. Overall survival was low at 63% for the TLM/RT group and 50% for the TLM-only group due to a high rate of non–cancer-related deaths. A permanent feeding tube was required in 3%, but there were no permanent tracheostomies. The average time until normal swallowing was established was less than 14 days.

Because RT generally has an inferior local control rate compared with surgery, especially for bulky lesions, Agrawal and colleagues[232] proposed that a TLM procedure to debulk the primary tumor may improve the oncologic outcome. In a prospective trial of TLM with adjuvant RT for T1-2N0-1 supraglottic SCC, the 3-year local control rate was 97%, with one recurrence that was salvaged by TL. The overall survival rate was 88%. The functional results were not as good as in other TLM series, and this was probably due to the addition of the adjuvant RT: 21% of subjects experienced a prolonged period of dysphagia (3 to 10 months), and 9% required a permanent gastrostomy tube. Subject accrual for this trial became difficult as some coinvestigators were reluctant to use RT for all patients because they became increasingly comfortable in the use of surgery as single-modality treatment for these patients.

Radiation therapy plays an important role in the treatment of patients whose tumors are not amenable to partial laryngectomy, who are medically unfit for surgery, or who prefer to avoid surgery. In general, surgical excision has a higher local control rate for early supraglottic tumors than RT.[235] Radiation therapy alone is also less effective than surgery (with adjuvant RT) or CRT in patients with advanced laryngeal carcinoma; however, it may be used to treat patients who are not eligible for CRT protocols but wish to attempt to preserve their larynx. However, RT is not without complications including dysphagia, aspiration, laryngeal edema, and chondronecrosis, which may require tracheostomy or total laryngectomy.[235]

Harwood reported initial local control rates with RT of 70% for T1N0 tumors, 68% for T2N0, and 54% for T3-4N0.[236] Mendenhall and colleagues[235] treated 209 supraglottic carcinomas with primary RT and obtained initial local control rates of 100%, 85%, 64%, and 36% for T1, T2, T3, and T4 lesions. Patients with recurrent disease were salvaged with either a total laryngectomy or, if possible, an OSGL, to give an ultimate local control rate of 100%, 88%, 81%, and 57%. The cause-specific survival for the series was 100%, 92%, 75%, 47%, and 32% for stages I, II, III, Iva, and IVb. Tumor volume ($<6\,cm^3$) and vocal cord mobility were significant predictors of local control. Hinerman and coworkers[237] reported on 274 patients with supraglottic SCC treated with RT with or without neck dissection. The 5-year local control rate after RT was 100%, 86%, 62%, and 62% for T1, T2, T3, and T4 tumors. The 5-year cause-specific survival was 100%, 93%, 81%, 50%, and 49% for stages I, II, III, Iva, and IVb.

Primary RT was compared with partial laryngectomy (and neck dissection) by Spriano and colleagues[238] for the treatment of 166 stage I and II supraglottic SCC. The surgical group had a superior 5-year, disease-free survival rate of 88% versus 76% for the RT group. Salvage surgery was effective in 66% of the partial laryngectomy failures and in 50% of the RT failures. Altered fractionation regimens have also been used to treat supraglottic SCC, and several reports have suggested improved local control rates with twice-daily hyperfractionated RT compared with once-daily RT.[239-241]

Treatment of the Advanced Primary Tumor in Supraglottic Squamous Cell Carcinoma

Advanced primary supraglottic tumors (i.e., T3 or T4) have traditionally been treated with total laryngectomy, bilateral neck dissections, and postoperative RT. However, laryngeal preservation has become an important aim in the treatment of laryngeal cancer in an attempt to improve the quality of life of patients.[242] The therapeutic options for these advanced lesions currently include surgical excision (total laryngectomy or partial laryngectomy in selected cases) with bilateral neck dissections, followed by adjuvant RT (or concurrent CRT); primary RT with surgical salvage (usually total laryngectomy); or concurrent CRT with surgical salvage.[243]

The Department of Veterans Affairs (VA) Laryngeal Cancer Study, published in 1991, was a landmark trial in the development of nonsurgical organ preservation and chemotherapy for the treatment of advanced laryngeal cancer.[244] Nearly two thirds of the subjects (208 of 332) had supraglottic SCC, with the majority of tumors classified as T3. The section on nonsurgical organ preservation later in this chapter describes the design and results of the important studies of nonsurgical treatment of advanced laryngeal cancer.

A second important trial investigating the nonsurgical treatment of advanced laryngeal SCC, the Head and Neck Intergroup Study (RTOG 91-11), was reported in 2003.[193] Over two thirds of the subjects (356 of 518) had supraglottic tumors. Large-volume T4 tumors that extended into the tongue base by more than 1 cm or penetrated through cartilage were excluded. The concurrent CRT group had statistically significant higher rates of locoregional control (78%) and laryngeal preservation (88%) compared with the induction chemotherapy– and radiation therapy–alone arms. The findings of this study have led to concurrent CRT becoming the standard nonsurgical organ preservation protocol for advanced laryngeal cancers with T2, T3, and low-volume T4 tumors (without gross cartilage destruction). Further information on nonsurgical preservation is discussed later.

The surgical excision of advanced primary tumors has traditionally been achieved by total laryngectomy, and although this remains the most commonly used procedure, conservative laryngeal resections such as OSGL, extended OSGL, supracricoid partial laryngectomy (SCPL), or TLM may be used for selected cases. Supracricoid partial laryngectomy, first described in 1959 by Majer and Rieder, is an organ-preserving surgical technique in which the aim is to preserve function without the need for a stoma of any kind.[245] It may be used as a primary treatment or as a salvage procedure after RT.[246] This procedure resects both true vocal cords, both false vocal cords, both paraglottic spaces, the entire thyroid cartilage, and the epiglottis. The hyoid bone and the cricoid cartilage are preserved. One of the arytenoids may also be included in the resection, but at least one intact cricoarytenoid unit must be preserved for postoperative function.[245] Following the resection of a supraglottic cancer, the surgical defect is closed by tightly apposing the hyoid bone and base of the tongue to the cricoid cartilage, termed *cricohyoidopexy* (CHP). A SCPL (with CHP) is used for selected T2, T3, and T4 supraglottic and transglottic tumors: T2 tumors not amenable to OSGL because of involvement of the true vocal cords or anterior commissure, extension to the floor of the ventricle, and/or impaired motion of the true vocal cord; T3 transglottic and supraglottic tumors with true vocal cord fixation and/or pre-epiglottic space invasion; and T4 transglottic and supraglottic tumors with limited invasion of the thyroid cartilage without extension to the outer thyroid perichondrium, or extralaryngeal spread.[245] Contraindications to SCPL include poor general health, poor pulmonary function, invasion of the cricoarytenoid joint, invasion of the cricoid cartilage, involvement of the posterior commissure, extension to the subglottis, invasion of the hyoid bone, extension of tumor to the outer perichondrium of the thyroid cartilage, or extralaryngeal spread.[214,247]

The oncologic results of SCPL with CHP are excellent, with 5-year survival rates of 67% to 95% and local control rates of 88% to 95%.[245,248] Total laryngectomy is the recommended salvage procedure for recurrent disease. In general, laryngeal function is good after SCPL. A tracheostomy and feeding tube are required for all patients initially but are temporary in most.[246,249] A completion total laryngectomy may be required on occasion for intractable aspiration.[170,246] The major disadvantage of SCPL is poor voice quality.[245]

In summary, for T3 or T4a supraglottic tumors without extensive base of tongue involvement or cartilage destruction, either nonsurgical organ preservation (using concurrent CRT) or, in selected cases, conservative laryngeal surgery (with adjuvant RT) may be used primarily in an effort to preserve a functional larynx. Adjuvant RT or concurrent CRT may be required after primary surgical treatment, and total laryngectomy may be required as a salvage procedure after either nonsurgical or surgical organ preservation treatment. For extensive T4 tumors with gross cartilage destruction and/or extralaryngeal spread, total laryngectomy is the preferred initial treatment.

Treatment of the Neck in Supraglottic Squamous Cell Carcinoma

Supraglottic SCC has a high incidence of clinically apparent and occult regional metastases. Supraglottic SCC usually metastasizes to levels II, III, and IV. Bilateral metastases occur frequently in supraglottic SCC. Elective treatment of the clinically negative neck is indicated in all supraglottic SCCs except T1 lesions. The choice of either surgery or RT for the neck will vary according to how the primary tumor is to be

treated. For early-stage tumors (T1-2), either surgery or RT may be used as a single modality to treat both the primary site and the neck. The indications for neck dissection do not alter when the primary tumor is treated with a partial laryngeal resection. For advanced primary lesions (T3-4), combined modality therapy is usually indicated. Often, nonsurgical organ preservation such as CRT or RT is used initially, with surgery to the primary and/or neck for salvage. Alpert and colleagues[250] investigated the use of RT for the treatment of clinically negative necks in SCC: for patients staged N0, both necks were treated with RT; and for patients with ipsilateral nodal metastases, the ipsilateral neck was treated with surgery and the contralateral neck was treated with RT. RT was effective in this role because failure was observed in only 3% of node-negative necks.

The standard surgical treatment of the neck in N0 supraglottic SCC is bilateral selective neck dissection of levels II to IV. Several studies have observed that levels I and V are rarely involved by metastases when clinically apparent metastases are present in levels II-IV and are never involved when occult metastases are present in the lateral neck.[104,251,252] A selective neck dissection (levels II to IV) is as effective as a comprehensive neck dissection (levels I to V) for N0 (and N1) disease.[253] Further studies of N0 supraglottic (and glottic) SCC have observed that metastases are not common in sublevel IIb and level IV, and therefore Ferlito and colleagues have suggested that a more targeted selective neck dissection of sublevel IIa and level III may be adequate for the elective surgical treatment of the neck in these cases.[111] An exception to these findings was a study that found occult metastases were present in level I in 82% of supraglottic SCC staged cN0.[108]

Treatment of the N+ neck is less controversial. If surgery is the primary treatment modality, a selective neck dissection (levels II to IV) is as effective as a comprehensive neck dissection for N1 disease, but for more extensive nodal disease (N2-3), a comprehensive neck dissection should be undertaken.[253,254] Bilateral neck dissection has been found to decrease the regional failure rate of the surgical treatment of supraglottic SCC from 20% of cases (in which the contralateral undissected neck was the most common site for recurrence) to 8%.[255] Adjuvant RT is indicated for neck dissections showing unfavorable pathologic findings including multiple involved nodes, extracapsular spread, or soft tissue extension of tumor.[209,218,256]

In summary, for supraglottic SCC, surgical treatment of the N0 and N1 neck is usually with a bilateral selective neck dissection (levels II to IV). For N2 or N3 disease, a comprehensive neck dissection (levels I to V) is indicated for the N+ neck, with a contralateral selective neck dissection (II to IV) if the contralateral neck is N0. Primary nonsurgical treatment should include RT to both necks.

Subglottic Squamous Cell Carcinoma

The treatment of subglottic SCC usually requires total laryngectomy and postoperative RT. Total laryngectomy is necessary because laryngeal framework invasion is frequent, and because of the difficulty of laryngeal reconstruction when a portion of the cricoid cartilage is resected in a partial laryngectomy. Ipsilateral thyroidectomy and paratracheal node dissection is also required (Fig. 107-11). Distal tracheal spread may occur, requiring a low tracheal resection and manubrial removal, and posterior extension into the cervical esophagus may be encountered. For patients with nodal metastases or extralaryngeal invasion, adjuvant RT (including the superior mediastinum) or concurrent CRT is used to decrease the likelihood of stomal recurrence.[101]

Despite such extensive treatment, survival is poor. Vermund reported 36% survival in pooled reports of subglottic SCC treated with primary RT compared with 42% for those treated surgically.[188] Stell and Tobin reported 44% cancer mortality in their series.[257] More recently, Garas and McGuirt reported a 25% three-year survival rate in 15 patients, the majority of whom presented with advanced disease.[101] Radiation therapy can be considered for early-stage lesions, but there are limited data to guide management.

Nonsurgical Organ Preservation Treatment

A number of studies in the 1980s found that the addition of chemotherapy before RT for surgery for advanced head and neck cancer resulted in high rates of complete tumor regression associated with prolonged survival.[258-260] Response to chemotherapy predicted tumor radiosensitivity. However, this improved response did not translate into increased survival.[261]

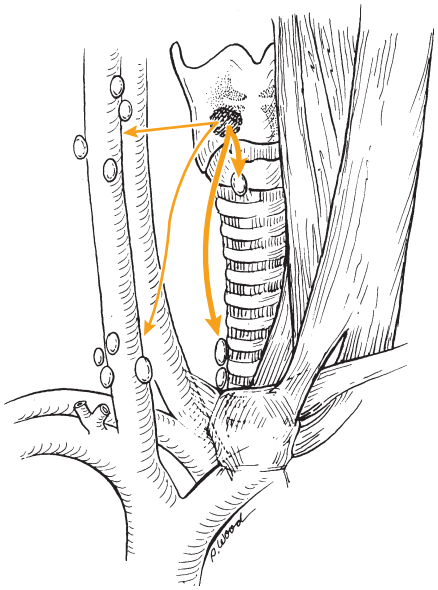

Figure 107-11. Pathways of nodal metastasis from primary subglottic tumors. Spread occurs along submucosal lymphatics to paratracheal nodes and along lower and midjugular chains.

These early studies provided the rationale for the VA laryngeal cancer study reported in 1991.[244] This was the first large prospective randomized study to demonstrate the effectiveness of the use of chemotherapy to define the more favorable patients and avoid laryngectomy in responders. This multi-institutional study reported on 332 patients with stage III or IV previously untreated laryngeal SCC. Subjects were randomized to receive either induction chemotherapy (IC) followed by RT, or surgery (total laryngectomy) and RT (Fig. 107-12). Two cycles of IC were given to the first group: nonresponders to the IC underwent immediate total laryngectomy, whereas responders received a third cycle of chemotherapy followed by RT (with salvage total laryngectomy for residual disease) (see Fig. 107-12). The laryngeal preservation rate was 64% for patients assigned to the IC/RT group, although only 39% had a fully functioning larynx. The 2-year survival for both groups was 68%. In a follow-up study, a further 10% decrease in the number of those with a functioning larynx was noted at 5 years, and there were no statistically significant differences in survival between the two groups.[262]

In an effort to determine the relative contributions of chemotherapy and RT to laryngeal preservation, as well as to determine whether concurrent chemotherapy as a radiosensitizer would improve the likelihood of organ preservation, the Head and Neck Intergroup conducted a prospective randomized study that included 518 patients randomly assigned to three arms (Fig. 107-13).[193] Subjects received either IC followed by RT, concurrent CRT, or RT alone. Previously untreated stage III and IV glottic or supraglottic carcinomas requiring total laryngectomy for surgical treatment were eligible. This study excluded subjects with T1 tumors and bulky T4 tumors with laryngeal cartilage destruction, invasion through the laryngeal cartilages, or extensive tongue base invasion. At 2 years, the larynx was preserved in 88% of patients in the concurrent CRT group, compared with 75% and 70% in the IC/RT- and RT-only groups. The overall survival rate for all three groups was similar (5-year survival 54% to 56%). The high rate of laryngeal preservation in the concurrent CRT group was associated with an 82% incidence of high-grade toxicity compared with an incidence of 81% and 62% in the IC/RT and RT groups, respectively. In those who failed nonsurgical organ preservation therapy, total laryngectomy salvaged approximately three quarters of the patients.

Adelstein and associates compared RT with concurrent CRT for stages III and IV laryngeal cancer and observed a significant difference in the recurrence-free interval (51% vs. 62%).[263] The 5-year overall survival was similar for the two groups (48% vs. 50%), which the authors believed was due to the efficacy of salvage surgery and non–cancer-related deaths. Most other studies of concurrent CRT in the head and neck do not address the larynx specifically and do not have large numbers of laryngeal cancer patients.[243] The utility of IC has been re-examined in a recent report by Urba and colleagues,[264] in which a single cycle of chemotherapy was used to select patients with advanced laryngeal cancer for treatment with concurrent CRT. The 3-year, cause-specific survival and overall survival rates were 87% and 85%, respectively, with a laryngeal preservation rate of 70%.

Despite the encouraging results, nonsurgical organ preservation is not without disadvantages, especially with regard to its toxicity, which must be taken into consideration when deciding on treatment. In the RTOG 91-11 study, acute toxicity was more common and severe with concurrent CRT when compared with the other two groups and included chemotherapy-related side effects (e.g., neutropenia, nausea, vomiting) and increased rates of severe radiation induced mucositis.[193] The total rate of severe toxic effects, acute and late, was 82% in the concurrent CRT group. There was no difference between the three groups with regard to speech, with 3% to 8% reporting moderate or worse speech impairment at 2 years. However, the incidence of dysphagia was high: 26% of patients treated with concurrent CRT had problems swallowing at 1-year post treatment. At 2 years, there was no significant difference between the groups, with 15% of the concurrent CRT group reporting ongoing dysphagia. Previous RT and CRT may also pose problems for both the patient and the surgeon if surgery (usually total laryngectomy) is required after nonsurgical organ preservation for residual or recurrent disease, chondronecrosis, or intractable aspiration. In a subsequent report on the RTOG 91-11 trial, Weber and colleagues[265] concluded that the morbidity of TL after organ preservation was acceptable but observed that up to 30% of patients developed a pharyngocutaneous fistula. The incidence was highest in the concurrent CRT group, but this difference was not statistically significant.

Therefore two important principles must be adhered to when nonsurgical larynx preservation treatment protocols are undertaken. First, if neoadjuvant chemotherapy or concurrent CRT is used, total laryngectomy must be performed for salvage in patients who fail to respond if survival is not to be compromised.[266] Second, the success of CRT is dependent on the completion of the treatment protocol. The efficacy of RT is significantly diminished if treatment breaks are taken due to toxicity.[267] Because nonsurgical larynx preservation therapy has significant toxicity (and mortality of 2% to 4%), patients with comorbidities and poor social support to help them through this challenging treatment regimen are less likely to complete the treatment and thus benefit from the addition of chemotherapy.

The success of nonsurgical larynx preservation treatment outside closely supervised clinical trials has also been questioned. Hoffman and colleagues[60] observed a concerning decrease in larynx cancer survival between 1985 and 2001, in patients with advanced glottic cancer, early supraglottic cancer, and T3N0M0 supraglottic cancer. During this same period there was a marked increase in use of nonsurgical larynx preservation treatment. Recently Chen and colleagues[268] analyzed 7019 larynx cancer cases from the National Cancer Database and observed that total laryngectomy was associated with a statistically significant increase in survival compared with CRT for stage IV laryngeal cancer.

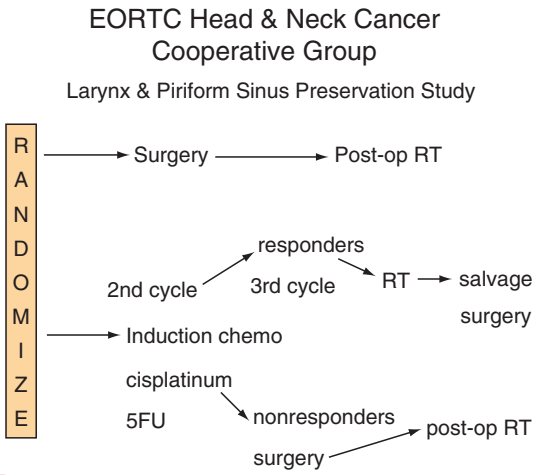

Figure 107-12. Schematic of the Department of Veterans Affairs Laryngeal Cancer Study.

Management of the Neck after Nonsurgical Organ Preservation Treatment

In all nonsurgical larynx preservation protocols, management of the neck and primary site must be considered both individually and together. Experts do not uniformly agree on the management of the neck in patients when there has been a complete response to treatment at both the primary site and in the neck. Traditionally, if any residual disease is detected in the neck after completion of RT or CRT, either by clinical examination or by radiographic evaluation, dissection of the neck is indicated.[244] In the initial VA study of the 106 patients who underwent IC and RT, 46 had N2 or N3 disease. A complete response to treatment was obtained in 18 of 46 patients (39%) with advanced neck disease and a partial response in 16 of 46 patients (35%). There

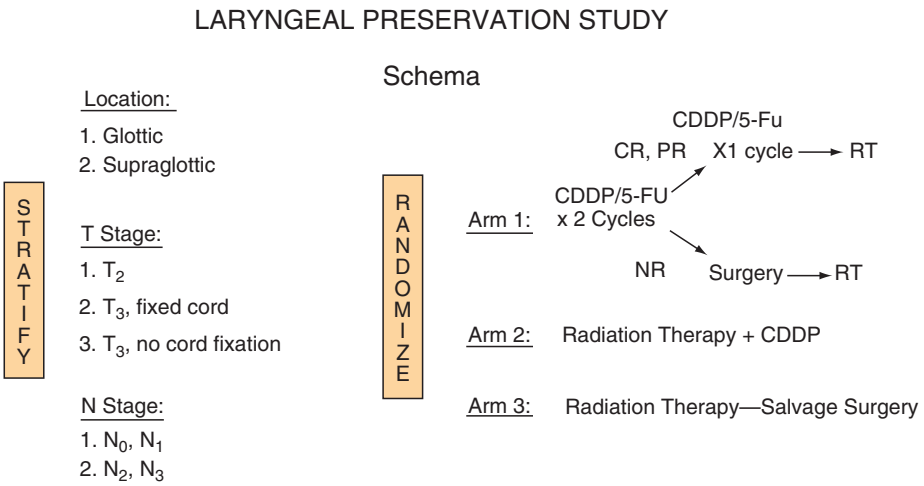

Figure 107-13. Schematic of the National Cancer Institute Intergroup Laryngeal Cancer Study.

was no response in 12 patients (26%). Fifty percent of the complete responders had N2 disease, and 33% had N3 disease. These data demonstrate that there is not a direct correlation between initial node size and response. Of the 18 patients who obtained a complete response in the neck, 5 eventually required a neck dissection. Of the 28 patients who had less than a complete response, 19 underwent neck dissection. When there was a delayed recurrence in the neck, survival was poor—less than 30%. When a poor response was obtained in the neck to the combined therapy, salvage by surgery still resulted in a poor outcome.

Further experience with CRT protocols for laryngeal preservation has focused attention on the cervical metastases, and a paradox has been identified. When routine neck dissection is performed after CRT, various series have reported a 14% to 39% incidence of positive findings in patients who had a complete clinical response to CRT.[269] In patients with less than a complete response, the majority of specimens did not demonstrate pathologic evidence of tumor.[270,271] Furthermore, in studies in which no neck dissection had been performed following CRT, the rate of recurrence in the neck was low at 0% to 6%.[272] It is hypothesized that in many patients with pathologic findings of tumor in the neck specimen, the cells are not viable but have not yet been cleared by the body. In a study of patients with persistent tumor after completion of treatment for nasopharyngeal cancer, serial biopsies every 2 weeks following treatment determined that positive biopsies showing tumor were seen for up to 12 weeks in patients who ultimately had complete response.[273] Increasingly, a PET scan 3 months after the completion of treatment is used to assess the effectiveness of treatment. A negative PET scan at 3 months reliably indicates the absence of persistent disease. For patients with N1-2 disease, the use of PET shows promise for predicting which patients can avoid a neck dissection post treatment.

Treatment of Recurrent Squamous Cell Carcinoma

Recurrent laryngeal SCC can be salvaged in approximately two thirds of cases, making close follow-up and the thorough investigation of any potential recurrence critical. Radiation therapy or CRT failures may be salvaged with surgery, whereas surgical failures may be salvaged with either further surgery or, in some cases, RT or CRT.

The detection of recurrent (or residual) disease is challenging and has become particularly important since the advent or nonsurgical organ preservation therapies. The status of the larynx may be difficult to assess following RT or CRT due to inflammation, edema, fibrosis and/or scarring, which develop as the result of the treatment. The symptoms of recurrence may vary according to the site of the original primary tumor and the nature of the recurrence. Signs of local recurrence include increasing edema, thickening of the true vocal cords, impairment of true vocal cord mobility, vocal cord fixation, leukoplakia, a mass lesion, and/or ulceration.[274] Recurrent cancer may be submucosal, and deep biopsies may be required because superficial biopsies of the epithelium may fail to diagnose recurrent tumor. A deep biopsy should be undertaken with caution in the irradiated larynx because it may cause infection, perichondritis, or chondroradionecrosis.[275] Recurrent disease must be differentiated from radiation-induced edema, perichondritis, or chondronecrosis because the clinical presentation of these entities may be similar, and a biopsy remains the gold standard for the diagnosis of recurrent disease.

PET scanning has been used successfully to distinguish between chondronecrosis and residual or recurrent tumor in the larynx following organ preservation therapy and helps to avoid unnecessary biopsies.[192,276] The sensitivity and specificity of PET for the diagnosis of residual or recurrent carcinoma in the larynx was found to be 80% and 81%, respectively, compared with 58% and 100% for CT.[277] In another report, the accuracy of PET for the diagnosis of recurrent cancer was superior to CT and clinical examination: 79% versus 61% versus 43%, respectively.[278] The utility of PET for the diagnosis of recurrent disease is still being evaluated, and a prospective trial comparing PET (followed by a direct laryngoscopy and biopsy if the PET scan is positive) and direct laryngoscopy (and biopsy) has been proposed.[279]

Almost half of the patients diagnosed with recurrent SCC have transglottic rT3 or rT4 tumors.[280] The standard treatment for recurrent laryngeal SCC is total laryngectomy. However, partial laryngectomy has been used to treat recurrent SCC for several decades and is particularly useful for early tumors that have failed RT. Som reported the use of an open approach (laryngofissure) for the salvage of radiation failures in the 1950s.[281] In 1970 Biller and colleagues[282] proposed criteria that would preclude the use of partial laryngectomy as surgical salvage, which included subglottic extension greater than 5 mm, cartilage invasion, contralateral vocal cord involvement, arytenoid involvement (except the vocal process), vocal cord fixation, and recurrence that did not correlate with the original primary lesion. In Ballantyne and Fletcher's series of 78 early glottic cancers that recurred following RT, 75% could be salvaged. Total laryngectomy was performed in 85% of cases and partial laryngectomy in the remainder.[274] A more recent report from the same institution observed that even though a greater variety of conservation laryngeal surgical procedures (such as TLM and SCPL) are available as treatment options, total laryngectomy is still required in approximately 70% of recurrences of early-stage (T1-2) glottic cancer.[283]

Therefore, in the minority of cases of early-stage recurrent disease, conservation laryngeal surgery may be possible. The results of open partial laryngectomy have been reported by several authors over the past 50 years.[281,282,284,285] The more recently described procedure of SCPL has good oncologic results in the small numbers of subjects reported to date.[246,286,287] Transoral laser microsurgery is effective for early-stage recurrences and, in the hands of experienced surgeons, for selected advanced stage recurrences.[283,288-290]

Nonsurgical organ-preservation therapies have become increasingly commonplace as a primary treatment modality for laryngeal SCC.[60] However, surgery still plays an important role and may be indicated for the salvage of residual or recurrent disease at the primary site, for residual or recurrent disease in the neck, for chondroradionecrosis, or for functional problems such as intractable aspiration, laryngeal stenosis, or pharyngoesophageal stenosis. These functional problems result from the adverse effects of RT on the soft tissue of the larynx, particularly decreased tissue vascularity and fibrosis.[291,292] Although it improves the oncologic efficacy of treatment, the addition of chemotherapy to RT also appears to increase the incidence and severity of these adverse soft tissue effects and there is a high risk of postoperative complications when surgery is required for these patients following RT or CRT.[193,265] Poor wound healing and high rates of pharyngocutaneous fistula formation were observed in patients in the RTOG 91-11 trial undergoing salvage surgery by Weber and colleagues.[265] Although a greater proportion of patients in the concurrent CRT group developed a fistula (30%), this was not statistically significant. There was no correlation between the timing of surgery and the incidence of complications.

Davidson and colleagues reported a series of 88 patients undergoing salvage surgery after RT without chemotherapy.[293] The 5-year survival rate was 35%, which did not correlate with the TNM stage of the original tumor or with the timing of the diagnosis of the recurrence. As expected, the highest rate of surgical complications occurred in patients undergoing pharyngectomy (48%), with pharyngocutaneous fistulae occurring in 27% of the subjects. Sassler and colleagues[294] studied patients undergoing surgery after nonsurgical organ preservation protocols and noted an overall complication rate of 61%. The rate of complications was 77% when surgery was performed within 1 year of treatment and only 20% when performed after 1 year. This was in contrast to the Davidson study. In this study (and in the literature in general), the risk of surgical complications was greatly increased when the pharynx was entered. Neck dissection alone (without entry into the UADT) has a much lower complication rate. Sassler observed a pharyngocutaneous fistula rate of 50%, with a mean time until closure of 7.7 months. The liberal use of free tissue transfer for reconstruction following total laryngectomy or laryngopharyngectomy for the treatment of RT or CRT failures decreases the incidence of pharyngocutaneous fistulae, decreases the duration of any fistulae that do occur, and decreases the rate of stricture formation and dependence on feeding tubes.[295,296]

In patients undergoing surgery following nonsurgical organ-preservation therapy, wound infection, delayed healing, and fistula formation cannot always be attributed to the RT or CRT alone and may be the result of malnutrition, metabolic abnormalities, or other comorbidities. Therefore, when surgery is indicated for this group of patients, their nutrition, thyroid status, and general health should be optimized beforehand.

Stomal Recurrence

After total laryngectomy, recurrence of SCC around the stoma is a grave sign. Stomal recurrence is often insidious and only discovered after the disease has become extensive. Recurrent disease may be secondary to paratracheal node involvement, invasion of the thyroid gland, intraoperative tumor spill with implantation of cells in the stoma, or incomplete excision of tracheal invasion by subglottic spread. Subglottic SCC is most frequently associated with stomal recurrence.[297,298]

The treatment of stomal recurrence is morbid and often unsuccessful, so prevention of stomal recurrence is paramount. When the risk of stomal recurrence is great (i.e., in primary subglottic SCC, glottic SCC with greater than 1 cm of subglottic extension, or T4 glottic tumors), the ipsilateral thyroid lobe is removed together with the larynx and bilateral paratracheal node dissections are performed. Adjuvant RT is also given, and the treatment field should include the upper mediastinum. In a large series reported by Rubin and colleagues,[146] the majority of stomal recurrences (12 of 15) were from primary subglottic tumors.

Dissection of the mediastinum and wide local resection for stomal recurrence was pioneered by Sisson, who proposed a four-category classification system (Fig. 107-14).[299] Significant morbidity and mortality are associated with the surgical treatment of stomal recurrence including injury to the great vessels, mediastinitis, hypocalcemia, and fistula formation. Aggressive treatment of stage III and IV stomal recurrence is usually not indicated because the prognosis for these patients is poor.[300] Sisson concluded that mediastinal failure was an important factor in advanced head and neck cancer and should be considered for T4 glottic and subglottic tumors in which mediastinoscopy was positive for nodes.[299]

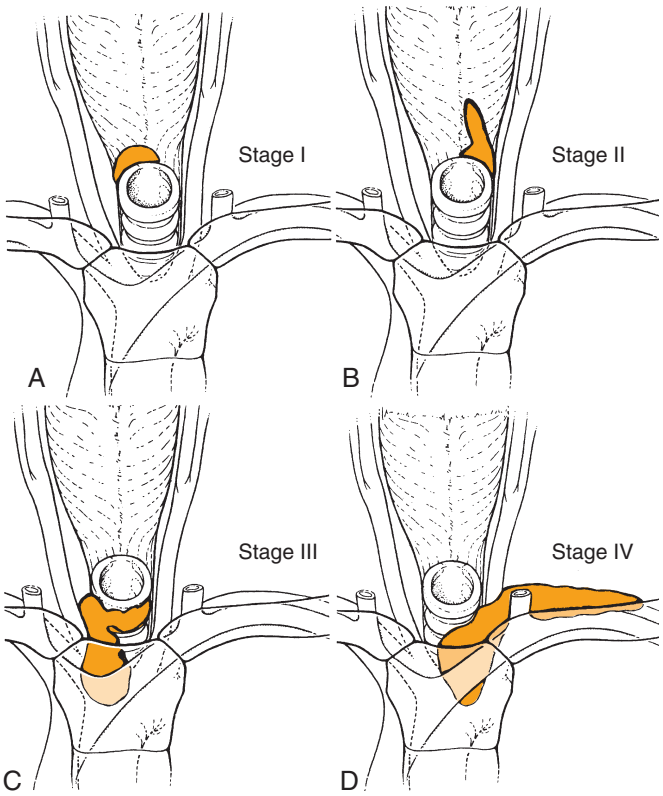

Figure 107-14. Stomal recurrence. **A,** Stage I. **B,** Stage II. **C,** Stage III. **D,** Stage IV. *(From Sisson GA Sr. Ogura memorial lecture: mediastinal dissection.* Laryngoscope. *1989;99:1264.)*

Prognosis and Prognostic Predictors

The 5-year relative survival rate for laryngeal SCC is 64%.[60] The 5-year relative survival rates for the individual sites are 47% for supraglottic SCC, 79% for glottic SCC, and 30% to 50% for subglottic SCC.[60,114] The prognosis for patients with laryngeal SCC depends on many variables, which may be classified as either disease factors or patient factors.

Disease Factors

Clinical Features

The most important predictor of prognosis for patients with laryngeal cancer is the clinical stage: An increase in T stage or in N stage is associated with a decrease in survival.[301,302] However, the N stage is more important than the T stage in predicting survival.[303] Overall survival is significantly better for patients who are N0 compared with patients who are N+.[302] In patients with cervical metastases, the presence of extracapsular spread (ECS) on histologic examination is an unfavorable prognostic sign and is associated with a significant further reduction in survival.[304,305] The prognosis for patients with distant metastases is poor, with a 5-year survival of less than 10%.[117] The site of the primary tumor is the second most important predictor of prognosis. Glottic SCC has the best prognosis, and subglottic SCC has the worst.[60,114]

Local control of laryngeal SCC with RT is worse with tumors of larger volume.[306,307] Fixation of the vocal cord upstages an SCC to T3; however, impaired vocal cord mobility is also an important clinical sign. Having observed lower local control rates after RT for T2 tumors with impaired vocal cord mobility, Harwood and DeBoer[19] proposed that the classification for T2 tumors be divided into T2a (normal vocal cord mobility) and T2b (impaired vocal cord mobility). A recent study reported that the failure of return of vocal cord movement in a small series ($n = 14$) of T2b and T3 tumors treated with RT plus or minus chemotherapy was associated with locoregional recurrence in all cases, while none of the patients with return of vocal cord mobility had a recurrence.[181]

Radiologic Characteristics

Several reports have examined whether characteristics of the primary tumor observed on imaging can predict the outcome of treatment, particularly RT or CRT. Using CT or MRI, involvement of particular regions or structures of the larynx by tumor such as the anterior commissure, the PES, the laryngeal cartilages, or even having tumor adjacent to the thyroid cartilage has been found to be a predictor of local control.[308-312] Tumor volume measured by CT, MRI, or even PET is also a reliable predictor of local control, although this is not always an independent factor.[312-315] PET is the most accurate modality for determining tumor volume, which may be overestimated by CT or MRI.[316] Another potential prognostic indicator determined by PET has recently been described: A high pretreatment standard uptake value of FDG by the primary tumor was associated with poorer local control and disease-free survival.[317,318] At present there are no standardized criteria to predict local control or failure on the basis of CT, MRI, or PET.[125]

Histopathologic Characteristics

Several histologic features have been reported to be predictive of prognosis. The most important is the extracapsular spread of metastatic tumor in cervical nodes, which is associated with a significant decrease in survival in SCC of the head and neck including the larynx.[304,305] The histologic type of tumor is also important. There are several variants of SCC, some of which have a different biologic behavior to conventional SCC. Verrucous carcinoma is less aggressive and has a better prognosis than conventional SCC, whereas the opposite is observed in cases of adenosquamous carcinoma. These variants are discussed in more detail in a subsequent section of this chapter.

The histologic grade of the tumor (well vs. moderately vs. poorly differentiated),[319,320] the pattern of invasion (a pushing vs. infiltrative

interface between the tumor and the normal tissue),[96,321] and the presence of perineural and/or vascular invasion[322] may also influence local control and survival.

The risk of local recurrence in the larynx is increased if the excision margins of the primary tumor are positive after open partial laryngectomy.[323,324] Although complete excision of the primary tumor remains the most important principle of oncologic surgery, excision margins may be close without compromising local control, as reports of endoscopic laser resections have demonstrated.[325]

The prognostic usefulness of DNA ploidy is controversial. DNA ploidy status has been shown to be a marker for nodal metastases in laryngeal carcinoma and predictive of overall survival following RT.[326] Aneuploid tumors have an increased risk of local recurrence after RT.[327] However, some authors have not found DNA ploidy to be a significant prognostic factor.[328]

Patient Factors

Several factors independent of the stage or histologic characteristics of the tumor may affect the outcome of laryngeal SCC. Patient variables that have consistently been found to be important predictive factors include comorbidity (general health), age, and performance status. Comorbidity may be measured using one of several validated scales such as the Washington University Head and Neck Comorbidity Index (developed specifically for head and neck cancer patients)[319] and is an independent prognostic factor for patients with laryngeal cancer.[329,330] Advanced age (older than 65 years) is associated with a worse prognosis for SCC of the head and neck including laryngeal carcinoma.[302,319] Patients with a higher performance status, as measured by scales such as the Karnofsky Performance Status, have a more favorable outcome.[331,332] The significance of gender as a prognostic factor is controversial, with some reports finding no difference[319,331] and others reporting a worse prognosis for women with laryngeal cancer.[333,334] For patients undergoing RT for laryngeal SCC, a normal hemoglobin level is associated with increased overall survival.[335]

Molecular Markers of Prognosis

Clinicians and researchers alike are searching for molecular markers that will allow the identification of patients with laryngeal cancer who have adverse prognostic features so that more aggressive and successful treatment may be offered. The most commonly mutated gene in human cancer including laryngeal cancer is p53; however, its prognostic value in laryngeal cancer is uncertain.[336-338] Epidermal growth factor receptor (EGFR) overexpression has been found to be a marker for aggressiveness, nodal metastasis, and survival.[338,339] EGFR overexpression is also associated with radioresistance and poor local control of laryngeal cancer,[340] and therefore a tumor's EGFR status may be used to predict radiosensitivity and chemosensitivity.[338] Vascular endothelial growth factor (VEGF) positivity is associated with increased overall survival in patients irradiated for laryngeal SCC.[341] Cyclin D1 and cyclin D3 overexpression are reported to be significant predictors of disease-free survival, and determining the cyclin D1/D3 coexpression status of laryngeal carcinomas has allowed stratification of patients into prognostic groups, with patients overexpressing both cyclins having the worst prognosis.[342] Markers of epithelial differentiation such as type 2 cyclooxygenase (Cox-2) and galectin-3, may also have predictive value. Low expression of Cox-2 in laryngeal SCC is associated with aggressive biologic behavior (including invasion), whereas galectin-3 expression is associated with improved overall survival.[338] At present, much of the data regarding molecular markers are conflicting and no reliable prognostic molecular markers exist for clinical use.

Follow-Up

Follow-up after treatment for laryngeal cancer has several goals: (1) to detect recurrent disease; (2) to detect second primary tumors; (3) to assist in the ongoing rehabilitation of speech and swallowing; (4) to ensure that adequate nutrition is being maintained; and (5) to treat any other problems that may arise as a side effect of treatment such as chronic pain. The first two goals are probably less important than the other goals. In a study of the utility of follow-up after treatment (with curative intent) for laryngeal cancer, Ritoe and colleagues[343] reported that an asymptomatic tumor recurrence was found in only 2% of all routine visits and that no survival benefit came from the detection of these asymptomatic recurrences as part of the follow-up regimen. In a second study from the same institution, Ritoe and colleagues[344] also observed that screening (with a chest radiograph) to detect lung cancer in asymptomatic patients after curative treatment for laryngeal SCC did not improve survival for those who were diagnosed with lung cancer.

The National Comprehensive Cancer Network (NCCN) suggests a physical examination every 1 to 3 months for the first year after treatment, every 2 to 4 months in the second year, every 4 to 6 months in the third, fourth, and fifth years, and every 6 to 12 months thereafter.[345] Thyroid function tests should be checked every 6 to 12 months because thyroid function is reduced after larynx cancer treatment that includes radiotherapy or extensive laryngeal and thyroid surgery. Hypothyroidism may develop years after treatment, and symptoms are often vague and nonspecific—the patient who seems depressed and lethargic after treatment may be hypothyroid. The risk of hypothyroidism is 20% after RT, 50% after laryngectomy and ipsilateral thyroid lobectomy, and greater than 65% if both RT and surgery are used (see Table 107-6).[346]

Variants of Squamous Cell Carcinoma

Verrucous Carcinoma

Verrucous carcinoma (VC) is a variant of SCC characterized by a predominantly exophytic growth of well-differentiated keratinizing epithelium with pushing margins. These tumors are slow growing; however, they can cause extensive local destruction.[17] The larynx is the second most common site in the head and neck for VC, with most VC occurring on the true vocal cords.[347] HPV, particularly HPV 16 and 18, is associated with some but not all of these tumors, but the significance of this relationship is uncertain.[348]

Histologic examination of VC reveals thickened papillary projections and bulbous invaginations of well-differentiated squamous epithelium, with marked keratinization and thin fibrovascular cores (Fig. 107-15). The squamous epithelium lacks the cytologic criteria for malignancy, which distinguishes it from conventional SCC.[349] The margins of the tumor are pushing rather than infiltrating. Superficial biopsies may miss the histologic features of VC, and often patients are diagnosed only after multiple biopsies. There is often marked peritumoral inflammation, and patients may present with reactive lymphadenopathy, but pure VC does not metastasize.[350] A hybrid form of VC, which contains foci of conventional SCC, may metastasize to the cervical nodes.[351]

The preferred treatment is conservative surgical excision because VC is less radiosensitive than conventional SCC.[352] The risk of residual

Figure 107-15. A photomicrograph of verrucous carcinoma of the larynx shows hyperkeratosis, papillomatosis, and club-shaped rete ridges (hematoxylin-eosin; original magnification ×25). *(From Fliss DM, Noble-Topham SE, McLachlin M, et al. Laryngeal verrucous carcinoma: a clinicopathologic study and detection of human papillomavirus using polymerase chain reaction.* Laryngoscope. *1994;104:147.)*

or recurrent disease is higher with RT than surgery, but RT is indicated for extensive lesions, for which the only surgical treatment possible is total laryngectomy, or for patients who are poor surgical risks.[347,350,353] In one large series of VC, surgical salvage was universally successful.[352] Previously there were concerns that irradiated VC may undergo anaplastic transformation, but reviews have concluded that these cases were hybrid tumors misdiagnosed as VC.[349,351] Neck dissection is not indicated, as pure VC does not metastasize.[350] The hybrid form of VC, which may metastasize, should be treated in the same manner as conventional SCC. Overall, the prognosis for VC is excellent, with 5-year survival approximately 90%.[347,354]

Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma (BSCC) is a rare and highly malignant variant of SCC. The supraglottic larynx and pyriform sinus are the most common sites for BSCC.[355] BSCC is a bimorphic tumor with both basaloid and squamous cell components.[17] The basaloid component is more prominent and consists of small cells with hyperchromatic nuclei and scanty neoplasm arranged in lobules.[356] Presence of the squamous component, which may be in situ or invasive carcinoma, differentiates BSCC from adenoid cystic carcinoma.[17] Stromal hyalinization and cystic spaces in the tumor (which may contain mucoid material) help to distinguish BSCC from conventional SCC.[357]

Patients with BSCC often present at a late stage, and both cervical and distant metastases are common.[355] Aggressive treatment with radical surgery (including neck dissection) and postoperative RT or CRT is indicated.[355,358] Basaloid SCC is generally considered to be more aggressive than conventional SCC and to be associated with a worse prognosis, although there is some disagreement in the literature regarding this.[355,358-360]

Spindle Cell Carcinoma

Spindle cell carcinoma (SPCC), also referred to as *sarcomatoid carcinoma, carcinosarcoma,* or *pseudosarcoma,* is a biphasic tumor composed of a surface squamous cell lesion (either CIS or invasive SCC) and an underlying malignant spindle cell component (which is predominant).[17,361] The histogenesis of SPCC has been debated, but current evidence suggests that it is a neoplasm of epithelial origin with mesenchymal differentiation.[362] This is an uncommon lesion, which has been reported following RT, although radiation is not thought to be a major etiologic factor. However, like conventional SCC, SPCC is strongly associated with tobacco and alcohol abuse.[361] The majority of SPCC occurs as a polypoid lesion in the glottis. Cervical metastases are common (25%) and distant metastases less so (5% to 15%).[362] The diagnosis of SPCC may be difficult, especially if the squamous component is small, or if the biopsy fails to sample that part of the tumor. SPCC may be misdiagnosed as a sarcoma such as a fibrosarcoma or MFH or as a reactive or benign proliferation of spindle cells such as nodular fasciitis.[361,362]

Surgery is the recommended primary treatment modality for SPCC because RT alone is not effective. The extent of surgery (partial vs. total laryngectomy, and neck dissection) for SPCC is similar to that required for conventional SCC at the same site and stage, and RT is often given postoperatively.[361,363,364] The clinical behavior of SPCC is similar to that of SCC, with site and stage the most important prognostic factors. The 5-year survival rate for SPCC is 63% to 94%.[361]

Adenosquamous Carcinoma

Adenosquamous carcinoma (ASC) is a rare neoplasm with histologic features of both SCC and adenocarcinoma.[17] The larynx is the most common site for this tumor in the UADT.[365] ASC arises from the basal cells of the surface epithelium that are capable of divergent differentiation.[366] The two distinct histologic components of ASC are distinct from one another. The squamous cell component, which arises from the surface epithelium, is predominant and may be either severe dysplasia, CIS, or invasive SCC. The second component, adenocarcinoma, is found deeper in the tumor.[365] ASC may be misdiagnosed as mucoepidermoid carcinoma; however, the latter tumor lacks a mucosal component.[366]

ASC is a highly malignant tumor, which is more aggressive than conventional SCC. Nearly two thirds of patients develop cervical metastases, and 23% develop distal metastases.[367] Radical laryngeal surgery with dissection of the neck is recommended; however, the prognosis is poor. Nearly half of patients experience a local recurrence, and their 5-year survival rate is 15% to 25%.[366-368]

Acantholytic Squamous Cell Carcinoma

Acantholytic SCC (ASCC), also referred to as *adenoid SCC,* is another uncommon variant of SCC and is characterized by pseudoglandular spaces or lumina resulting from the acantholysis of tumor cells.[17] Neither true glandular differentiation nor mucin production is observed in these tumors.[369] In the head and neck, ASCC arises most often in sun-exposed skin and is only rarely diagnosed in the supraglottic larynx.[370,371] Immunohistochemistry and mucin staining are important in the diagnosis of ASCC, which may be confused with adenosquamous SCC, angiosarcoma, and minor salivary gland–type tumors such as adenoid cystic carcinoma and mucoepidermoid carcinoma.[369] The treatment of ASCC is similar to that of conventional SCC. The prognosis of ASCC is similar to SCC, although some authors report that ASCC is a more aggressive tumor.[369,370,372]

Papillary Squamous Cell Carcinoma

Papillary SCC (PSCC) is an uncommon variant of SCC, which may occur as either an in situ lesion or an invasive tumor.[373] PSCC is characterized by an exophytic papillary growth pattern, composed of cores of fibrovascular stroma covered by squamous epithelium with severe atypia, increased mitotic activity, and loss of normal stratification.[17] The markedly abnormal cytologic changes observed in PSCC help to differentiate it from verrucous carcinoma in which the cytologic features of malignancy are either absent or minimal. The differential diagnoses of PSCC also include squamous papilloma and exophytic SCC. A full-thickness biopsy is crucial to allow a definitive diagnosis of PSCC.[373] Similar to conventional SCC, tobacco and alcohol are important risk factors for these tumors. PSCC may arise from squamous cell papilloma, although the true role of HPV in the pathogenesis is uncertain because the prevalence of HPV in these tumors is less than 50%.[374,375] PSCC arises from the supraglottis more commonly than from the glottis or subglottis.[373,376] PSCC may metastasize to the cervical nodes, but distant metastases are rare.[373] PSCC is treated in a similar fashion to conventional SCC and has been reported to have a better prognosis,[375-377] although some authors disagree.[378]

Uncommon Malignant Laryngeal Tumors

Although most laryngeal malignant tumors are SCCs, a wide variety of malignant tumors of other histologic types may occur in the larynx, as either a primary or a secondary tumor. For many of these tumors, the numbers reported in the literature are small. Therefore recommendations regarding treatment are often made on the basis of case reports and/or case series.

Malignant Salivary Gland Type Tumors

The larynx contains many minor salivary glands, which are submucosal and concentrated in the saccule, supraglottis (vestibular folds, aryepiglottic folds, and caudal epiglottis), and anterior subglottis.[379] Salivary gland–type tumors in the larynx are rare and constitute less than 1% of laryngeal tumors.[380] The majority of salivary gland type tumors are malignant, and the majority of these are either mucoepidermoid carcinoma or adenoid cystic carcinoma.[381] Because these lesions are submucosal, they tend to present late as large tumors.[382] The clinical features of salivary gland–type tumors does not differ significantly from those of SCC.[380] Recommendations for treatment cannot be regarded as definitive because the number of cases treated is small.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is a malignant epithelial tumor composed of a mixture of squamous cells, mucin-secreting cells, and cells of intermediate type.[17] This rare tumor, which accounts for one third of malignant salivary gland type tumors, is thought to arise from the intercalated ducts of seromucinous glands.[383,384] MECs are classified as either low- or high-grade carcinomas, and the histologic grade

correlates significantly with survival.[380] High-grade tumors may be difficult to distinguish from SCC on standard hematoxylin and eosin preparations. Staining for mucin may be required to confirm the diagnosis. Men are affected much more often than women.[381] These tumors are most commonly discovered in the supraglottis (especially the epiglottis).[380] Nearly half of patients with MEC present with, or eventually develop, cervical metastases.[381]

Surgery (either partial or total laryngectomy) is the primary modality for the treatment of malignant salivary gland–type tumors including MEC.[382,383,385,386] Neck dissection is indicated for N+ disease; however, there is some disagreement about the indications for neck dissection in the N0 neck: some authors have recommended an elective neck dissection in cases of high-grade MEC only,[386,387] whereas others have suggested that all patients with MEC should undergo surgical treatment of the neck given the high rate of regional metastases.[383] The use of adjuvant treatment is also uncertain. Indications for postoperative RT include close surgical excision margins, pathologically confirmed cervical metastases, and high-grade MEC.[383,386,387] Locoregional control and survival in MEC depend on the stage of the disease and histologic grade of the primary tumor.[380] Low-grade MEC has been reported to have a 5-year survival rate of greater than 95% compared with less than 30% for high-grade MEC.[388]

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a distinctive type of adenocarcinoma composed mainly of small, uniform basaloid cells forming tubules, cords and/or compact masses, surrounded and intersected by cylinders of hyaline or mucoid material, giving a cribriform or lacelike pattern.[17] Like MEC, ACC is rare and accounts for one third of malignant salivary gland–type tumors.[381] ACC is thought to originate from the intercalated duct reserve cells of the terminal tubule complex.[380] Three subtypes of ACC have been described according to their histologic appearance: cribriform, tubular, and solid.[380] ACC has a propensity for perineural invasion, and for this reason pain may be a prominent symptom in ACC.[386]

In contrast with most other malignant laryngeal tumors, women and men are affected in equal numbers by ACC.[380] The majority of these tumors occur in the subglottis (60%) and the supraglottis (35%), with only occasional glottic tumors reported.[381] The mucosa overlying ACCs, which are predominantly submucosal, is usually ulcerated.[380] ACCs demonstrate distinctive biologic behavior: an infiltrative growth pattern, a propensity for perineural invasion, and a tendency for hematogenous spread.[380] Cervical lymph node metastases are uncommon; however, late recurrence with distant metastases is a common clinical scenario.[382]

Surgery is the primary modality for the treatment of ACC. Partial laryngectomy is possible, although caution should be exercised because ACC has an infiltrative submucosal growth pattern and conservative surgery may result in incomplete excision with positive margins. For this reason, some authors have recommended total laryngectomy as the standard treatment for ACC,[386] whereas others have suggested that partial laryngectomy can be used to treat patients with small, well-defined tumors amenable to complete excision with negative surgical margins.[382] Another treatment philosophy for ACC is that radical surgery should be avoided where possible because it will have no effect on the distant metastatic disease, which often develops many years after initial treatment.[383] A neck dissection is indicated only for the clinically positive neck because the risk of regional metastasis is low.[382,389]

ACC is a relatively radioresistant tumor; however, postoperative RT has been used for pathologically confirmed cervical metastases and for close surgical margins.[386,390,391] Fast neutron RT may be more effective in the treatment of ACC; however, its use is limited by the side effects on normal tissue, which is of particular importance in the larynx.[392] ACC has a tendency for late recurrence, most often with distant metastases.[382]

Neuroendocrine Tumors

After SCCs, neuroendocrine tumors of the larynx (NTL) are the second most commonly diagnosed malignancies of the larynx.[393] NTL are a group of heterogeneous neoplasms that vary from benign to highly malignant in their biologic behavior and clinical course. The WHO has classified NTL into the following types: typical carcinoid; atypical carcinoid; small cell carcinoma, neuroendocrine type; and paraganglioma.[394] Atypical carcinoid is the most common of the NTL (54%), followed by small cell carcinoma, neuroendocrine type (28%), paraganglioma (12%), and typical carcinoid (7%).[393] The larynx contains neuroendocrine cells in the epithelium of the ventricle and the subglottis, which are thought to be the cells of origin of typical carcinoids, atypical carcinoids and small cell carcinomas, neuroendocrine type.[395] However, some authors disagree, suggesting that these tumors may instead arise from pluripotential stem cells in seromucinous glands and in the squamous epithelium.[396] Paragangliomas of the larynx arise from the paraganglia of the larynx.

The clinical presentation of NTL does not differ significantly from that of SCC of the larynx and depends on the site of the primary tumor. However, several reports have described paraneoplastic syndromes associated with typical carcinoid tumors, atypical carcinoid tumors, and small cell carcinomas.[393]

Typical Carcinoid

Typical carcinoid (TC) (commonly called carcinoid) of the larynx is an epithelial tumor of low-grade malignancy composed of round to spindle cells with evidence of neuroendocrine differentiation.[394] This lesion is the least common of the NTL. Males are affected more commonly than women.[394] TCs are usually submucosal or polypoid masses found in the supraglottis.[397]

Neither RT nor chemotherapy is effective against TCs.[393] For smaller primary tumors, complete but conservative surgical excision is recommended. Total laryngectomy is reserved for extensive lesions. Elective neck dissection is not indicated because the risk of cervical metastasis is low.[393]

Although TCs are regarded as a low-grade malignancy, approximately one third of patients develop distant metastases.[398,399] The 5-year survival rate for laryngeal TCs has been reported as 48%,[400] although this may be less than expected due to the inclusion of cases of atypical carcinoids, misdiagnosed as typical carcinoids.[393]

Atypical Carcinoid

Atypical carcinoid (AC) is the most common neuroendocrine neoplasm in the larynx. Histologically, ACs are differentiated from TCs by having larger cells, more mitoses, necrosis, cellular atypia and pleomorphism, and angiolymphatic invasion.[394] ACs share some characteristics with TCs: Both tumors are more common in males, present as a submucosal or polypoid mass, and are usually found in the supraglottis.[401] Immunohistochemistry is important for the correct diagnosis of AC, which may be mistaken for a TC, paraganglioma, malignant melanoma, or medullary thyroid cancer.[394] ACs are aggressive tumors with propensity for regional and distant metastases. In one large series 43% of patients developed cervical metastases, while two thirds were found to have distant metastases.[402] A full metastatic workup is important in the management of AC and should include a complete skin examination because this tumor often metastasizes to the skin and subcutaneous tissues.[393]

Surgery is the recommended treatment. Partial or total laryngectomy is performed depending on the size and location of the primary tumor, together with bilateral neck dissections (including patients staged as N0).[393,403] Partial laryngeal resections may be performed via an open approach or endoscopically.[404] AC is regarded as a radioresistant neoplasm; however, a recent report observed a response to adjuvant RT or CRT and suggested that adjuvant RT be given for local extension, multiple nodal metastases, and extracapsular spread.[405] The prognosis for AC is poor: In one series, the 5- and 10-year survival rates were 48% and 30%, respectively,[402] while a subsequent report observed a 5-year survival rate of 46%.[400]

Small Cell Carcinoma, Neuroendocrine Type

The most malignant and second most common of the NTL is small cell carcinoma, neuroendocrine type (SCCNET).[401] Similar to the typical and atypical carcinoids, SCCNET is more common in males and usually arises in the supraglottis.[394] At presentation approximately

half of patients with SCCNET have cervical metastases, and up to 90% develop distant metastases.[406] The prognosis for SCCNET is grave, with 2- and 5-year survival rates of 16% and 5%, respectively, observed in one series[407] and a 5-year survival rate of 7.7% in a second series.[398] Due to the high incidence of disseminated metastatic disease, surgery is rarely indicated.[393] Instead, RT in conjunction with multiple-drug chemotherapy is the preferred treatment, using protocols similar to those for small cell carcinoma of the lung.[393,407]

Paraganglioma

Paragangliomas of the larynx are neuroendocrine neoplasms arising from either the superior or inferior laryngeal paraganglia.[401] These tumors are benign (with the exception of a single case of a metastasizing laryngeal paraganglioma[408]) but are included in this section to complete the discussion on laryngeal neuroendocrine tumors.

Laryngeal paragangliomas are the third most common NTL. They are three times more common in women and may be associated with paragangliomas in other sites (familial paragangliomas).[408,409] The majority of paragangliomas are found in the supraglottis, especially in the aryepiglottic fold, and are thought to arise from the superior paraganglia.[401] They appear as a well-circumscribed tan, brown, or red submucosal mass.[408] Excessive hemorrhage may result from an attempt to biopsy a paraganglioma, and if possible the diagnosis should be made preoperatively on the basis of the findings of a CT or (preferably) an MRI scan, in conjunction with an octreotide scan, to avoid a biopsy.[410]

Surgical excision with laryngeal preservation is the preferred treatment for paragangliomas. An open approach, via a lateral pharyngotomy, lateral thyrotomy, or laryngofissure, has been recommended, to allow vascular control before excision of the tumor.[410,411] Successful transoral CO_2 laser resection of a supraglottic paraganglioma has been described, but most authors advise against this technique because of difficulties with hemostasis and an increased risk or recurrence.[409,412] Subglottic paragangliomas may be excised using conservation techniques such as a cricoid split; however, total laryngectomy may be required.[409,413] A neck dissection is not indicated because paragangliomas do not metastasize to the cervical nodes.[409] If a neck mass is detected in conjunction with a laryngeal paraganglioma, there should be a high index of suspicion that either the neck mass is a carotid body paraganglioma or that the laryngeal primary tumor is another type of neuroendocrine tumor such as an atypical carcinoid.[393] Paragangliomas respond to RT, but do so incompletely.[414] The prognosis for laryngeal paragangliomas is excellent.[408]

Malignant Tumors of Soft Tissue, Bone, and Cartilage (Sarcomas)

Malignant neoplasms may arise from the connective tissue of the larynx. Fibrosarcomas were previously regarded as the most common laryngeal sarcoma, but modern pathologic techniques, especially immunohistochemistry, have demonstrated that most of these tumors were diagnosed as fibrosarcomas incorrectly and are in fact other types of malignancies, especially spindle cell carcinoma, a variant of SCC.[415,416] Fibrosarcomas may occur as a complication of RT.[417]

Chondrosarcoma

Chondrosarcomas of the larynx are rare but are the most frequent nonepithelial laryngeal neoplasm, accounting for 0.1% to 1% of all laryngeal tumors.[418] These lesions occur in adults between the ages of 50 and 80 years. Males develop this disease more commonly than females by a ratio of 3 to 4:1.[418] Chondrosarcomas usually arise in ossified hyaline cartilage, and the cricoid cartilage is the most common site for chondrosarcomas in the larynx, especially the posterior or posterolateral region of the cricoid, because these regions ossify first.[419] The thyroid cartilage is a much less common site, and epiglottic chondrosarcomas are rare indeed.[420] Chondrosarcomas are composed of neoplastic hyaline cartilage and are graded as low-, intermediate-, or high-grade lesions. A dedifferentiated variant of chondrosarcoma has also been described.[421] Most chondrosarcomas are low grade, grow slowly, and follow an indolent clinical course. High-grade and dedifferentiated chondrosarcomas have a high risk of metastases and are associated with a poorer prognosis.[419]

Patients with chondrosarcomas may present with dyspnea, stridor, dysphonia, or dysphagia. They may notice a palpable mass in the neck. These symptoms usually develop insidiously. Examination findings may include a submucosal mass, narrowing of the subglottic airway, vocal fold immobility, or arytenoid hypertelorism.[422] CT scanning is the most useful radiologic investigation in the evaluation of chondrosarcomas, but MRI can give supplementary information.[423] For histologic diagnosis a biopsy is obtained via direct laryngoscopy. The CO_2 laser may be helpful in ensuring that an adequate sample has been obtained.[424] Despite a thorough evaluation, it may still be difficult to distinguish between a chondroma and a chondrosarcoma—clinically, radiologically, or histologically. Recent reports have suggested that many chondromas have been misdiagnosed and are in fact low-grade chondrosarcomas.[421,424] In the largest published series of laryngeal chondrosarcomas, the majority were associated with chondromas on histologic examination, suggesting that chondrosarcomas may develop from chondromas that undergo malignant transformation.[419]

The treatment for chondrosarcomas is surgery: partial laryngectomy is indicated for low-grade lesions and total laryngectomy for high-grade or dedifferentiated lesions. Conservation laryngeal surgery for cricoid chondrosarcomas is challenging due to the functional sequelae of resection of part or all of the cricoid; however, both open and endoscopic approaches have been described: hemicricoidectomy,[425] total cricoid resection,[426] and TLM.[424] Reconstruction of the larynx may be achieved using grafts, local flaps, thyrotracheal anastomosis,[426] and free flaps.[427] Radiation therapy has been used to treat only a small number of cases, with long-term follow-up reported in only two patients.[428,429] Chemotherapy is not effective.[418] Chondrosarcomas have a good prognosis with a 90% survival rate at 5 years.[424] Local recurrence may be treated with a total laryngectomy or, more conservatively, with intermittent endoscopic debulking.[424,430]

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma in general. However, it is extremely rare in the larynx.[416] Prior RT has been implicated in the pathogenesis of some cases of MFH.[431,432] Macroscopically these tumors may be sessile or polypoid, and they are usually found in the glottis.[433] A spindle cell carcinoma may be mistaken for an MFH on histology, so the diagnosis of MFH should only be made after the appropriate immunohistochemistry has been performed.[415] Radiation therapy is not effective against MFH, which is treated surgically.[415,433-435] A neck dissection is indicated only when there is evidence of nodal disease.[436] The prognosis of MFH is variable, although this tumor usually demonstrates aggressive biologic behavior.

Liposarcoma

Primary liposarcomas of the larynx (LSL) are extremely rare. LSLs most commonly occur in males older than the age of 40 years, who often present with airway obstruction.[416] These tumors have a predilection for the supraglottis and have never been found in the subglottis.[437] The majority are low-grade tumors and follow an indolent course. For these reasons they may be misdiagnosed as lipomas initially, and the diagnosis of liposarcoma may be made only after several recurrences.[438] CT and MRI are useful in differentiating between lipomas and liposarcomas.[437] Wide local excision is the treatment of choice because simple endoscopic excision has a high recurrence rate when compared with more extensive surgery such as an open partial laryngectomy via a lateral pharyngotomy.[439] A neck dissection is not required because LSLs do not metastasize to cervical nodes.[415] The usefulness of RT and chemotherapy for these tumors is not known. The prognosis for patients with LSL is excellent, with a 5-year survival of 90%.[416]

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a vascular endothelial cell neoplasm of uncertain origin.[440] However, some have hypothesized that KS is a reactive phenomenon, with vascular proliferation stimulated by angiogenic factors released by $CD4^+$ lymphocytes or by viruses.[441] KS is classified

into three subtypes, which affect different populations: classic (older Mediterranean or Jewish men), endemic (men in equatorial Africa), and epidemic (immunocompromised patients such as those with AIDS). KS of the larynx is exceedingly rare.[440] The supraglottis (particularly the epiglottis) is the most common site for laryngeal KS.[415] Macroscopically, the tumors may be macular, nodular, or pedunculated and are a red-purple color.[440] A wide variety of treatments, both medical and surgical, have been used for KS. Local treatments include surgical excision (including TLM),[440] RT,[442] and intralesional injection of vinblastine.[443] Systemic chemotherapy[440] and immunotherapy (with interferon-α)[444] have also been reported. Often a combination of these treatments is used. Although airway obstruction may occur and require specific treatment such as a tracheotomy, KS of the larynx is usually not life threatening, and therefore the goal of treatment is the relief of symptoms such as pain, bleeding, dyspnea, dysphonia, and dysphagia.[440,441]

Malignant Hematolymphoid Neoplasms

Hematolymphoid neoplasms of the larynx are uncommon, either as primary tumors, or in association with disseminated disease.[445] Extramedullary plasmacytomas affect the larynx more often than lymphomas.[446]

Extramedullary Plasmacytoma

Plasma cell neoplasms (antibody forming B cells) usually involve the bone marrow diffusely, (multiple myeloma), but they may also occur as single lesions localized to bone marrow, a medullary plasmacytoma; to bone, a solitary plasmacytoma of bone; or to soft tissue without bone marrow involvement, an extramedullary plasmacytoma (EMP).[447] By definition, patients with EMP do not have multiple myeloma. The finding of an extramedullary plasmacytoma necessitates referral to a hematologist for a workup to exclude multiple myeloma. EMPs comprise less than 5% of plasma cell neoplasms, but more than 80% occur in the head and neck region, with approximately 5% in the larynx.[421] By 1996, approximately 90 cases had been reported.[448] Laryngeal EMP is more common in males by a ratio of 3:1 and has a peak incidence between 50 and 70 years of age.

Patients usually present with hoarseness, dyspnea, or a foreign body sensation.[449,450] Dysphagia, stridor, and pain are late symptoms associated with aggressive lesions.[448] Laryngeal EMPs are polypoid or sessile submucosal masses and occur most frequently in the supraglottis (especially in the epiglottis),[447] with vocal fold[449] and subglottic[450] EMPs less common. An adequate biopsy is crucial in the diagnosis of EMP. Because the lesion is usually submucosal, a deep biopsy must be performed to ensure that pathologic tissue has been obtained,[451] and the specimen must be sent fresh to allow the appropriate investigations to be undertaken. Immunohistochemistry, flow cytometry, and immunophenotyping are necessary to establish the diagnosis of EMP. Amyloidosis is an important differential diagnosis because amyloidosis is associated with plasma cell infiltrates (polyclonal on immunohistochemistry) and up to 40% of EMPs have evidence of amyloid on biopsy.[447]

Options for the treatment of laryngeal EMPs include surgery alone, surgery combined with RT, and RT alone.[447] Conservative surgical treatment such as TLM has been suggested for small lesions in easily accessible locations (such as the epiglottis),[452,453] but because EMPs are radiosensitive, the majority have been treated with RT.[447,450] The cervical nodes should be included in the RT fields to decrease the risk of regional failure.[450] The prognosis for patients with EMPs is good, with a local failure rate of less than 10%.[447] However, 16% to 32% of patients with EMPs later develop multiple myeloma; therefore long-term follow-up is important.[450]

Lymphoma

Primary non-Hodgkin's lymphoma (NHL) of the larynx is also rare with fewer than 100 cases reported in the literature.[454] Secondary involvement of the larynx by lymphomas from regional lymph nodes is more common.[421] Most primary laryngeal NHLs are B-cell lymphomas, most commonly diffuse large B-cell lymphoma and extranodal marginal zone B-cell lymphoma of MALT type.[455-457]

Patients with laryngeal lymphomas usually present with dysphonia, a foreign body sensation, or airway obstruction.[456] Laryngeal lymphomas are usually submucosal masses (because they arise from submucosal aggregates of lymphoid cells) without mucosal ulceration and are most commonly found in the supraglottis (especially in the aryepiglottic folds). An adequate biopsy is also critical in the diagnosis of lymphoma. Because the lesion is usually submucosal, a deep biopsy must be performed to ensure that tumor has been sampled. The specimen must be sent fresh. Immunohistochemistry, flow cytometry, and immunophenotyping are necessary to establish the diagnosis and determine the type of NHL. Once the diagnosis of lymphoma has been confirmed, a hematologic consultation should be sought. A thorough evaluation including blood work, a bone marrow biopsy, and imaging is performed for staging. Most patients with primary laryngeal NHL present with early-stage disease (Ann Arbor stage IE or IIE).[455-457]

Treatment of laryngeal lymphoma usually involves RT or chemotherapy, or a combination of the two, and the appropriate treatment regimen is selected on the basis of histologic typing. Localized RT has been the most common treatment for laryngeal NHL.[456,457] Chemotherapy with the RCHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) has also been used successfully, particularly for diffuse large B-cell lymphoma.[455,458]

Mucosal Malignant Melanoma of the Larynx

In the head and neck, most melanomas are of cutaneous origin. Mucosal malignant melanomas of the UADT constitute 0.5% to 3% of melanomas from all sites, and only 4% to 7% of these arise in the larynx. Therefore primary mucosal malignant melanoma of the larynx (PMMML) is extremely rare. The majority of these tumors affect men, and the peak incidence is in the sixth and seventh decades. Most PMMMLs occur in Caucasians, but African Americans may also be affected.[459]

PMMMLs may arise from the malignant degeneration of intralaryngeal melanocytes or intralaryngeal melanocytic lesions (e.g., melanosis, nevi, lentigo).[460,461] Intralaryngeal melanocytes are located either in the basal cell layer of the epithelium, stroma of the submucosa, or minor salivary glands in the submucosa. The etiology of PMMML is uncertain, although smoking has been implicated in its pathogenesis.[462]

The supraglottis is the most common site for PMMML. A subglottic PMMML has never been reported.[459] The tumors have a variable appearance and may be nodular, sessile, or polypoid. Their color may also vary significantly, ranging from black, brown, or red-pink, to tan-gray or white.[461] Immunohistochemistry is key to the diagnosis: Immunoreactivity to S100 and HMB45 in a pleomorphic, epithelioid, or spindle cell neoplasm is diagnostic of melanoma.[463] However, histologically, PMMMLs are identical to primary cutaneous melanomas, which are the most common malignancy to metastasize to the larynx. Therefore it is vital to determine whether a melanoma in the larynx represents a metastasis from a cutaneous site, by performing a full cutaneous examination to look for a primary lesion, and by imaging the neck, chest, abdomen, and pelvis to look for metastatic disease.[461]

The recommended treatment for PMMML is wide local excision, which may be achieved using either partial or total laryngectomy, with a neck dissection for patients with nodal disease.[464,465] Adjuvant RT has been used, with a higher dose per fraction recommended.[463,464] The prognosis for patients with PMMML is poor, with a 5-year survival of less than 20%.[461,462] The incidence of local recurrence is low, although there is a high rate of regional and distant metastases to account for this.[466] Prognostic criteria used in cutaneous melanomas, such as depth of invasion, tumor thickness, and ulceration are not useful in PMMML.[459]

Neoplasms of Uncertain Behavior

Two unusual neoplasms warrant special consideration because they are classified as "borderline" lesions of uncertain behavior: inflammatory myofibroblastic tumor (IMT) and giant cell tumor (GCT).

The nature and etiology of IMT is controversial. It was orginally described as a benign, non-neoplastic proliferative lesion that could be

treated with conservative surgery and steroids.[467,468] However, subsequent genetic studies have suggested that IMT is a neoplasm, which usually behaves in a benign fashion.[469,470] The larynx (primarily the glottis) is the most common site in the head and neck for these tumors, which are composed of myofibroblastic cells with inflammatory cells and collagen. These lesions are not typically aggressive, although metastases from visceral IMTs have been reported. Conservative surgical excision is the treatment of choice.[469,470]

Giant cell tumor is a rare neoplasm composed of large multinucleated osteoclast-like giant cells and mononuclear cells; it arises from the thyroid cartilage, cricoid cartilage, or epiglottis.[471] This tumor is aggressive and locally destructive but has not been reported to metastasize. Complete surgical excision is the recommended treatment, either by partial or total laryngectomy.[472] Note that GCT is a different entity from giant cell carcinoma, which is an extremely rare undifferentiated carcinoma with a poor prognosis. The histogenesis of giant cell carcinoma is uncertain.[473]

Secondary Tumors of the Larynx

Secondary tumors of the larynx are tumors that originate in another site in the body and then spread from that site to involve the larynx. These tumors may spread from a site contiguous with the larynx by direct invasion (e.g., thyroid, oropharynx, hypopharynx, cervical esophagus, trachea) or they may spread hematogenously from a distant site, in which case the secondary laryngeal tumor is a true metastasis.

Laryngeal Involvement by Tumors from Contiguous Sites

The larynx may be invaded by malignant neoplasms arising from any of the adjacent structures. Involvement of the larynx carries a worse prognosis, which is reflected in the advanced T stage assigned to tumors of the oropharynx (laryngeal invasion = T4a), the hypopharynx (laryngeal hemifixation = T3, thyroid or cricoid cartilage invasion = T4a), the cervical esophagus (laryngeal invasion = T4), and the thyroid (laryngeal invasion = T4a). Treatment of the primary aerodigestive tract tumors is discussed in the relevant chapters of this volume.

The treatment of thyroid cancer with laryngeal invasion is discussed briefly because there has been some controversy regarding its optimal management. Well-differentiated thyroid cancers such as papillary thyroid cancer, the most common histologic type of thyroid cancer, invade the larynx in approximately 1% to 2% of cases,[474,475] and involvement of the endolarynx is associated with a worse prognosis.[475] Anaplastic thyroid cancers invade the larynx more often, but the prognosis for patients with these tumors is poor and therefore treatment is usually palliative.

For well-differentiated thyroid cancer, surgery is the primary treatment modality and plays a particularly important role in the management of extrathyroidal disease. It is generally accepted that leaving gross residual disease is associated with a poorer prognosis,[475,476] and therefore complete resection of macroscopic disease is the goal. In cases in which there is aerodigestive tract invasion, there is debate regarding how extensive surgery should be. The surgical options for laryngeal invasion include shave excision, partial laryngectomy, or total laryngectomy. Shave excision may be used if there is limited invasion of the larynx; however, if there is intraluminal tumor, a shave excision will leave macroscopic tumor.[476] McCaffrey and Lipton[477] and McCaffrey[475] have recommended a shave excision for partial-thickness cartilage invasion and complete resections for full-thickness cartilage involvement or intraluminal tumor: a cricotracheal resection when less than half of the cricoid is involved; a total laryngectomy for more extensive cricoid involvement; and a partial laryngectomy (such as a vertical hemilaryngectomy) for unilateral thyroid cartilage or paraglottic space invasion. Postoperatively, radioactive iodine and/or RT are recommended as adjuvant treatment for extrathyroidal spread in well-differentiated thyroid cancers.[478]

Metastases to the Larynx

Metastases to the larynx are rare and represent only 0.09% to 0.4% of laryngeal tumors.[445,479] Ferlito[445] reviewed 134 cases of metastases to the larynx in 1993. The majority of these tumors were either cutaneous malignant melanomas or carcinomas. The primary tumors responsible for these metastases to the larynx were (in descending order of incidence) cutaneous malignant melanoma (34%), renal cell carcinoma (16%), and cancer of the breast, lung, prostate, colon, stomach, and ovary (each <10% of the total). The metastases spread to the larynx hematogenously, via the systemic circulation or via the paravertebral venous plexus. Metastasis to the larynx is rare because the larynx itself is a small organ at the terminal part of the circulatory system and does not receive a high volume of blood flow.[479] The supraglottis is most frequently affected (in 35% to 40% of cases) because it has the richest blood supply. The subglottis (10% to 20%) and glottis (5% to 10%) are less commonly involved, but metastases in multiple subsites are common.[421]

Kleinsasser[480] has observed two types of metastases: submucosal soft tissue metastases, usually affecting the vestibular and aryepiglottic folds, and metastases to the cartilaginous framework, most often the cricoid and thyroid cartilages. When cartilage is involved, it is usually the marrow space of the ossified portion of the cartilage. Metastatic melanoma and renal carcinoma metastasize to the soft tissues, whereas breast and lung cancer metastasize to the cartilages.

Metastasis to the larynx generally reflects widespread disseminated disease, and the prognosis is grim. Treatment is almost always palliative, and supportive measures such as a tracheostomy are the most appropriate. However, if the laryngeal metastasis is solitary, then surgical treatment should be considered, depending on the biologic behavior of the primary tumor, the symptoms from the laryngeal lesion, and the patient's overall condition.[445] Prolonged survival has been reported in such cases.[481,482] Surgical options include both partial laryngeal surgery (open or endoscopic[483]), as well as total laryngectomy.[445]

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CHAPTER ONE HUNDRED AND EIGHT

Management of Early Glottic Cancer

Henry T. Hoffman

Tim A. Iseli

Lucy H. Karnell

Timothy M. McCulloch

John M. Buatti

Gerry F. Funk

Key Points

- The glottis represents the site where approximately 50% of laryngeal cancers arise, and 95% of laryngeal malignancies are squamous cell carcinoma.
- Five-year relative survival is approximately 90% for T_1N_0 tumors and 75% for T_2N_0 tumors.
- Second primary tumors (lung followed by head and neck) are the most common cause of death in patients with early glottic cancer.
- Staging is based on cord mobility (T_1 normal, T_2 impaired) and spread outside the glottis (T_{1a} one cord, T_{1b} both cords, T_2 supraglottis or subglottis).
- Leukoplakia followed for 3 years will develop invasive cancer in approximately 4% without dysplasia, 10% with mild/moderate dysplasia, and 18% with severe dysplasia/carcinoma in situ.
- Diagnosis is by laryngoscopy and biopsy. Staging often includes a CT of the larynx for cartilage invasion and paraglottic space assessment and increasingly PET scan for second primaries.
- Radiotherapy is an effective treatment modality and is the most commonly used modality in North America.
- Most likely, radiotherapy has the best final voice quality in patients retaining their larynx. Failures most commonly require total laryngectomy; however, some centers are increasingly using laryngeal conservation surgery for salvage.
- Larynx-preserving alternatives to radiotherapy include transoral laser microsurgery and open laryngeal conservation surgery.
- Surgery has the advantages of having a higher rate of final laryngeal preservation, particularly in T_2 tumors, and repeatability for recurrence or second primary tumors.

> ... at the start of the 21st century, the oncologist and patient are presented with a bewildering array of choices for laryngeal cancer therapy.
>
> —Ferlito and colleagues[1]

Background

Statistics from the National Cancer Database (NCDB) provide insight into contemporary demographics and management of laryngeal cancer in the United States.[2] The most common site for laryngeal squamous cell carcinoma is the glottic larynx (Fig. 108-1). The role for surgery as single-modality therapy for advanced laryngeal cancer is diminishing as combined chemoradiation has become more common in the initial management (Fig. 108-2). Five-year relative survival was best for early-stage (stages 0, I, and II) glottic cancer (Fig. 108-3).

Analysis of this dataset demonstrated that squamous cell carcinoma is the dominant histologic type of laryngeal cancer in the United States, representing approximately 95% of cases (Fig. 108-4). Unless indicated otherwise, the remainder of the discussion in this chapter focuses on squamous cell carcinoma.[3,4]

Etiology

Squamous cell carcinoma of the larynx is strongly associated with the use of tobacco and alcohol. An increase in the prevalence of cigarette use among females in the past has been linked to a proportionate increase in the number of female patients with laryngeal cancer. Other factors implicated in the development of laryngeal cancer include

passive smoking, chronic laryngeal irritation from gastroesophageal reflux, and viral infection.[5-9]

Since 1979 gastric acid reflux has been identified as a risk factor for laryngeal and pharyngeal cancer.[10,11] Alkaline reflux has more recently been identified as a laryngeal carcinogen by Galli and colleagues.[12] These investigators identified a higher than expected number of patients with pharyngolaryngeal cancer associated with achlorhydria and presumed alkaline reflux after gastric resection. They concluded that periodic endoscopy of the upper aerodigestive tract should be performed on gastrectomized patients because of their higher risk for pharyngolaryngeal disorders in general and cancer in particular. These investigators also identified that, among patients with laryngeal squamous cell carcinoma with an intact gastric acid secreting mechanism, 81% showed abnormal acid reflux on 24-hour pH testing.

Human papillomavirus (most notably the oncogenic type 16) has been associated with head and neck cancer.[13-15] The role for human papillomavirus (HPV) infection in laryngeal oncogenesis has been supported by previous study but does not have as strong an association as has been identified with cancer of the oropharynx and oral cavity.[16,17] Initial study suggests that a difference exists in behavior between HPV and non–HPV-related squamous cell carcinoma of the upper aerodigestive tract, with a better prognosis afforded the HPV-positive cases.[18]

Differences in exposure to carcinogens or genetic susceptibility may explain the differences in the predominant types of laryngeal cancer throughout the world. Glottic cancers predominate over supraglottic cancers in the United States at a ratio of 2:1. In France the opposite occurs, where the number of supraglottic cancers exceeds that of glottic cancers at a ratio of 2:1.[19] In Finland the incidence of supraglottic cancer decreased and the incidence of glottic cancers increased between the decades 1976 to 1985 and 1986 to 1995.[20] Supraglottic cancers were more common than glottic cancers in the earlier decade (ratio of 1.4:1). Glottic cancers predominated in the later decade at a ratio of 2:1. The reason for this change in distribution of laryngeal cancers in Finland is not clear. A low exposure to alcohol and a high availability of medical services were factors Brenner and colleagues identified as important determinants to the characteristics of laryngeal cancer in Israel. These investigators linked these factors to the high proportion of laryngeal cancers treated at an early stage with an overall better outcome when compared with other countries.[21]

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Figure 108-1. Cancers isolated to the glottic larynx account for approximately one half of all laryngeal cancer cases in the United States. *(From Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival.* Laryngoscope. *2006;116[9 Pt 2 Suppl 111]:1-13.)*

Staging

The most widely accepted system for classifying cancer in the United States, as is currently promoted by the American Joint Committee on Cancer (AJCC), had its beginning in 1959 with the organization of the American Joint Committee for Cancer Staging and End-Results Reporting (AJC).[22] This staging system was first published in 1977 in the *Manual for Staging of Cancer.*[23] The staging system has evolved to its current form as it is codified in the *AJCC Staging Manual, Sixth Edition* published in May of 2002 and implemented as of January 1, 2003.[24] Major revisions made to the fifth edition in the head and neck section were directed primarily to the advanced-stage cases. Although

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Figure 108-2. General treatment type by year for laryngeal squamous cell carcinoma. *(From Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival.* Laryngoscope. *2006;116[Suppl 111]:1-13.)*

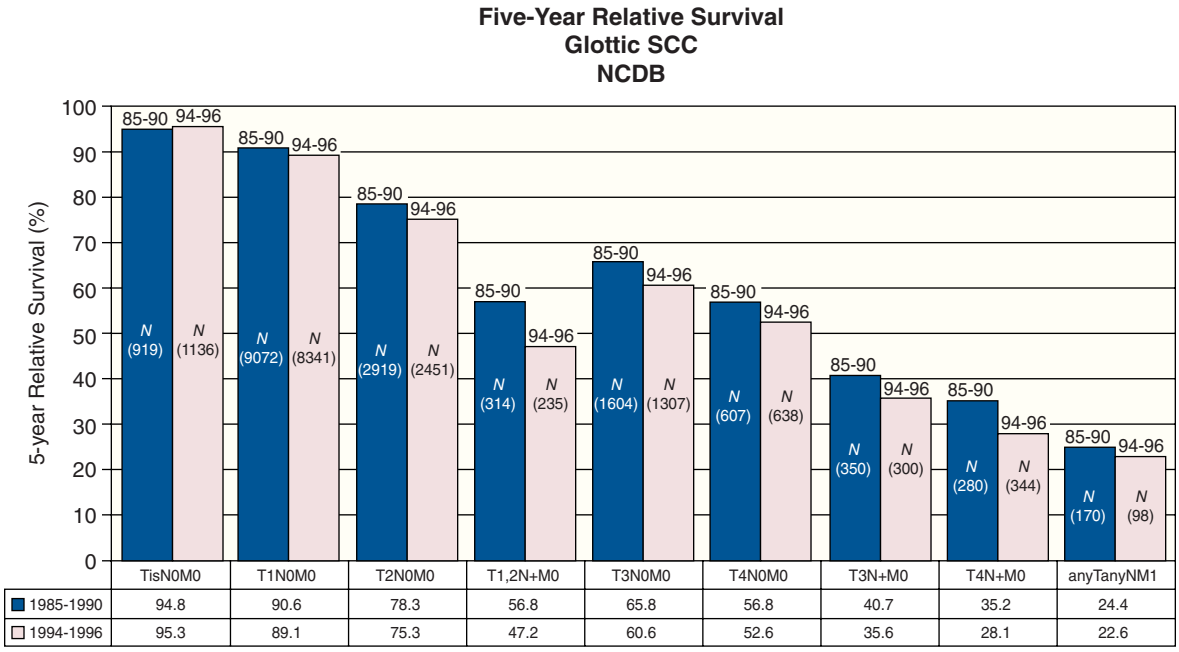

Figure 108-3. Five-year relative survival calculated between the early (1985-1990) period and later period (1994-1996) for glottic cancer. The number of cases *(N)* was lowest for the classification *"anyTanyNM+"* for the later period (*N* = 98) and largest for the classification *"T1N0M0"* for the earlier period (*N* = 9072). *(From Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival.* Laryngoscope. *2006;116[Suppl 111]:1-13.)*

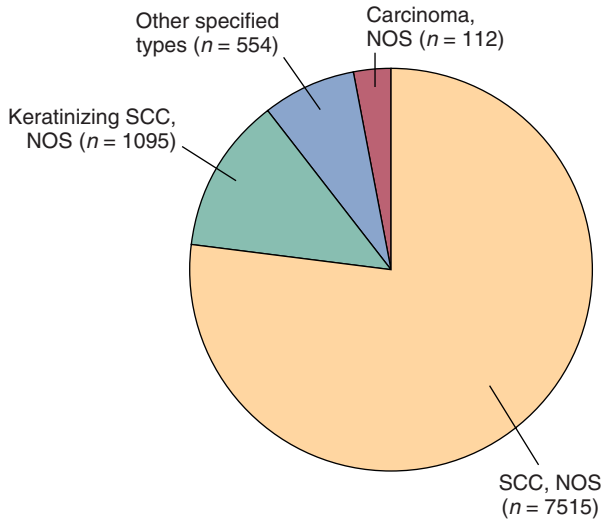

Figure 108-4. Histology of laryngeal cancer cases diagnosed in 2000 national cancer database. (From National Cancer Database Benchmark Report: Histology of Laryngeal Cancer in the U.S. in 2000. © *Commission on Cancer, American College of Surgeons. NCDB Benchmark Reports, v1.1. Chicago, 2002. [The content reproduced from the applications remains the full and exclusive copyrighted property of the American College of Surgeons. The American College of Surgeons is not responsible for any ancillary or derivative works based on the original text, tables, or figures.])*

the definitions for stages 0, I, and II laryngeal cancers remained unchanged, alterations to the T_3 definitions in the sixth edition have impacted on the interpretation of T_1 and T_2 classification.

The anatomic definitions and boundaries between sites, as published in the *AJCC Staging Manual,* have remained constant across the multiple editions. The glottis has been defined as the true vocal cords including the anterior and posterior commissures. Unfortunately, the definition of the posterior commissure remains vague. It is difficult to discriminate among the glottis, the adjacent supraglottis (arytenoids), and the hypopharynx (postcricoid region) in the region of the posterior commissure.[25] The superior border of the glottis is more clearly defined by a horizontal plane passing through the apex of the ventricle. The inferior limit of the glottis is defined by a line parallel to and 1 cm inferior to this plane.

Glottic cancers are staged primarily by clinical assessment of degree of vocal cord mobility (Table 108-1).[24] Cancers confined to the glottis with normal mobility are staged T_1. Subdivision of T_1 vocal cord cancers is based on extension to involve the opposite cord. A tumor limited to one vocal cord is T_{1a}. A horseshoe lesion that extends around the anterior commissure to involve both vocal cords without impairing mobility is T_{1b}. Despite consistency across all previous editions of AJCC staging manuals indicating that T_4 status is based on "tumor invasion through the thyroid cartilage … ," it has been common clinical practice to consider any extent of thyroid cartilage invasion from a glottic cancer to be cause for T_4 classification. Clinically apparent stage I glottic cancers ($T_1N_0M_0$) were reassigned stage IV status ($T_4N_0M_0$) when "microscopic invasion of adjacent cartilage" was identified.[26] Revision to the *AJCC Staging Manual, Sixth Edition* identifies that minor cartilage erosion (e.g., inner cortex) should be classified as T_3 rather than T_4.

Glottic cancers continue to be classified T_2 on the basis of two separate criteria: impaired vocal cord motion or transglottic spread beyond the glottis to involve either the supraglottis or subglottis. Although the AJCC does not discriminate between these two criteria, some investigators distinguish T_{2a} from T_{2b} cancers. T_{2a} vocal cord cancers do not impair mobility but are a higher stage than T_1 cancers by virtue of transglottic spread to involve the supraglottis or subglottis. T_{2b} cancers are sufficiently invasive to impair vocal cord mobility without causing complete fixation. Revision to the sixth edition identifies that T_3 classification results from vocal cord fixation or invasion of the paraglottic space. This clarification is helpful to resolve controversy in the interpretation of subtle differences between impaired vocal cord motion and fixation. If the arytenoid remains mobile but the membranous vocal cord is tethered by deep infiltration to the paraglottic space, the cancer is considered a T_3.

Still further clarification is necessary to address inconsistencies that persist among publications describing the paraglottic space.[12,27-29]

Table 108-1

Primary Tumor (T) Classification of Glottic Cancer

T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T_{1a}	Tumor limited to one vocal cord
T_{1b}	Tumor involves both vocal cords
T_2	Tumor extends to supraglottis or subglottis, or with impaired vocal cord mobility
T_3	Tumor limited to the larynx with vocal cord fixation or invades paraglottic space, or minor thyroid cartilage erosion (e.g., inner cortex)
T_{4a}	Tumor invades through the thyroid cartilage or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T_{4b}	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

From Greene F, Page D, Fleming I, et al. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer Verlag; 2002.

Berman defined the borders of the paraglottic space as they have been commonly reported by others:

- Anterolateral: the thyroid cartilage.
- Inferomedial: the conus elasticus.
- Medial: the ventricle and the quadrangular membrane.
- Posterior: the pyriform sinus.[12]

This definition fails to address the controversy as to whether all, part, or none of the thyroarytenoid muscle is part of the paraglottic space.[30] An assessment by Weinstein and colleagues[31] defines the medial border of the paraglottic space as the tissue lateral to the conus elasticus at the glottic level and lateral to the quadrangular membrane at the supraglottic level. By this convention, the thyroarytenoid muscle is considered part of the paraglottic space. Others define the glottic portion of the paraglottic space as the fat deep to the intrinsic laryngeal musculature. For the purposes of T classification according to the revised AJCC criteria, it is reasonable to consider that paraglottic space invasion (T_3) occurs when the fat compartment deep to the intrinsic laryngeal musculature is involved with tumor. Impaired vocal cord mobility (T_2) (without paraglottic space involvement) may be considered when the thyroarytenoid or lateral cricoarytenoid muscles are infiltrated but not fully transgressed.

Carcinoma in situ is classified as T_{is}. Accuracy in classifying premalignant changes affecting the laryngeal epithelium is compromised by the subjective nature of the assessment and by a lack of uniformity in terminology. Some pathologists discriminate between severe dysplasia and carcinoma in situ, whereas others group them together as type III intraepithelial neoplasia.[32-34] The grading of laryngeal dysplasia as mild, moderate, and severe or as carcinoma in situ originated from a similar classification of preneoplastic diseases of the uterine cervix. Keratinizing dysplastic lesions of the upper airway are more common than in the cervix and are also more difficult to categorize. The differences that exist in the behavior of carcinoma in situ originating at these two distinctly different anatomic sites has also undermined the transfer of concepts governing uterine cervical carcinoma in situ to laryngeal carcinoma in situ.[35] Despite the clearly stated pathologic principle that high-grade dysplasia and carcinoma in situ are equivalent terms in describing abnormal laryngeal squamous epithelium, clinical management is generally less aggressive for high-grade dysplasia than for carcinoma in situ.

Table 108-2

Stage Grouping of Laryngeal Cancer

Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_3	N_0	M_0
T_1, T_2, or T_3	N_1	M_0	
Stage IV a	T_{4a}	N_0, N_1, N_2	M_0
T_1, T_2, T_3, or T_{4a}	N_2	M_0	
Stage IV b	T_{4b}	Any N	M_0
Any T	N_3	M_0	
Stage IV c	Any T	Any N	M_0

From Greene F, Page D, Fleming I, et al. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer Verlag; 2002.

The stage grouping of primary tumor, regional lymph nodes, distant metastatic (TNM) classifications for laryngeal cancer is the same as for other head and neck mucosal sites (Table 108-2). Although the stage groupings have been revised—with the sixth edition introducing the division of stage IV into IV a, IV b, and IV c—the staging of early glottic cancer has remained constant (stages 0, I, and II).

Definitions: Early Glottic Cancer

The appropriate definition of the term *early* as it applies to laryngeal cancer has been debated. Some investigators have loosely used the term to describe laryngeal cancer in the context of management options. By this convention, a laryngeal cancer is considered early if it can be treated by partial laryngeal (conservative) surgery without a neck dissection, by endoscopic excision, or by radiotherapy alone.[36] Others apply the term *early* to stage 0, I, or II tumors and *late* to stage III or IV tumors. This definition of *early* may be inappropriate. Because the extent of disease—not the rate of growth—determines staging, the term *localized* is more accurate than the term *early.*[37] Similarly, the term *advanced* may be more appropriate than the term *late.*[38] The most accurate grouping uses the terms *localized* for any-TN_0M_0 disease, *regionally spread* or *vicinally spread* for any-$TN+M_0$ disease, and *widely disseminated* for any-T-any-NM_1 disease.[39] Convention and tradition dictate that this chapter continue to use the terms *early* to refer to lower stage (0, I, and II) and *late* to refer to higher stage (III and IV).

Diagnosis

Endoscopic Imaging

The initial evaluation of a patient with an early glottic lesion requires inspection of the larynx. The common use of flexible fiberoptic laryngoscopy to supplement indirect mirror examination now permits visualization of the majority of laryngeal cancers in a clinical setting. Videoendoscopy and videostroboscopy offer further refinement in

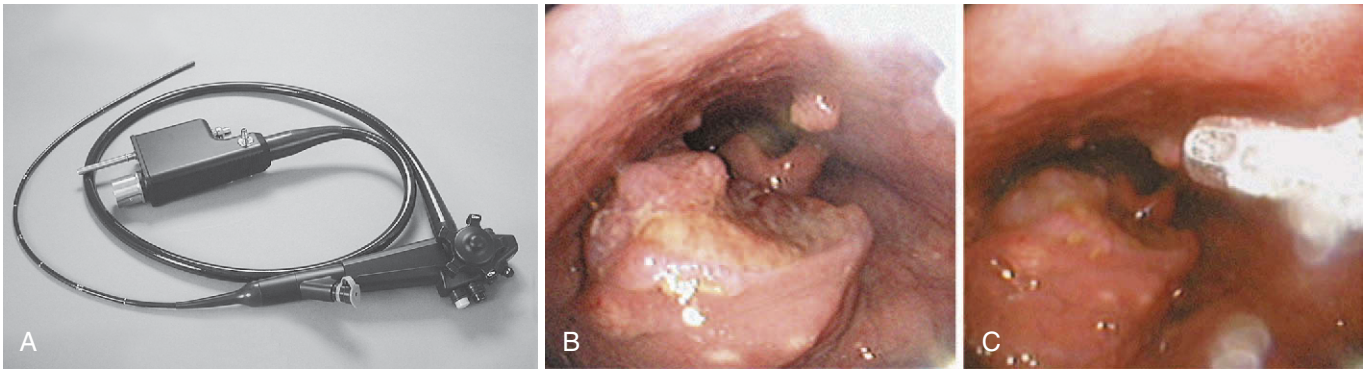

Figure 108-5. **A,** Transnasal esophagoscope (TNE) (Pentax). **B,** View of oropharynx and hypopharynx through TNE. **C,** Biopsy forceps prepared to remove posterior pharyngeal wall lesion.

assessing glottic lesions. It has become standard practice in many institutions to permanently record the appearance of all laryngeal cancers through video recording, using rigid or fiberoptic endoscopy. The capacity to refer to these permanent records documenting the extent of the original lesion often improves long-term patient care.

The development of flexible fiberoptic endoscopes designed for transnasal endoscopy has also permitted use of these instruments to evaluate the larynx and trachea.[40-43] The improved optics of these instruments—coupled with the presence of a side port that permits the use of suction, placement of biopsy instruments, and instillation of topical anesthetics—has expanded the capacity to perform in-office laryngeal evaluations (Fig. 108-5A). Although direct laryngoscopy remains the most appropriate approach to evaluate and biopsy the majority of lesions suspected of being malignant, in selected cases biopsy can be effected in the clinic (see Fig. 108-5B and C).

When videostroboscopy was introduced as a common clinical tool, enthusiasm was high for its potential to help discriminate invasive cancer from epithelial atypia on the basis of the stroboscopic appearance of the vocal fold epithelial pliability.[44,45] Subsequent experience of Colden and colleagues[46] has identified that laryngeal stroboscopy is neither reliable in distinguishing vocal fold atypia from invasive cancer nor useful in determining the depth of invasion of vocal fold cancer. These investigators did suggest that the stroboscopic appearance of a relatively normal mucosal wave indicates that a lesion is superficial and does not extensively involve the underlying vocal ligament.

Advances in technology, coupling physical and biologic analysis to endoscopy, have identified several adjuncts to complement standard imaging of the larynx at the time of direct laryngoscopy. Lugol's solution, as well as toluidine blue, have been used to stain laryngeal tissue in an effort to discriminate normal tissue from tumor.[47,48] These approaches have not met with uniform success and therefore have not been widely adopted. Fluorescent tumor markers such as tetracyclines and hematoporphyrin derivatives are preferentially absorbed by tumor cells and can be used to discriminate tumor from adjacent normal tissue by the red fluorescence they emit when exposed to ultraviolet light.[49] Additional cost and operating time, as well as problems with skin photosensitivity, have limited the usefulness of this technique. A more promising approach employing autofluorescence laryngoscopy has been reported. Zargi and colleagues[50] have employed the lung imaging fluorescence endoscope (LIFE) system to evaluate laryngeal lesions. Their preliminary work identified differences in the intensity of autofluorescence between normal and tumor tissue when exposed to blue or violet light. They also identified shortcomings in the use of the LIFE system for this purpose, noting that further technical advances are necessary to make this endeavor a useful clinical tool.

Stone and colleagues[51] reported that the fluorescence of biologic tissue actually may impede the use of Raman spectroscopic analysis to discriminate normal from malignant laryngeal lesions. These investigators have developed strategies that negate the impact of the natural biologic fluorescence to permit evaluation of the distinctive spectral signatures of tissues elicited when exposed to monochromatic laser excitation. This strategy may develop into a noninvasive tool in the early detection of cancerous and precancerous lesions.

Radiology

Chest X-Ray

A chest radiograph is necessary in the evaluation of patients with glottic cancers to assess for concurrent pulmonary disease and to screen for second primary lung cancers. The incidence of distant metastatic spread of an early glottic cancer to the lung is sufficiently rare that a preoperative chest radiograph is not generally intended to survey for that specific purpose. Annual chest x-rays should be obtained in the course of clinic follow-up examinations primarily because of the high incidence of second primary lung cancers in patients managed for laryngeal cancer.[52]

Magnetic Resonance Imaging and Computed Tomography

In our institution most early laryngeal cancers will be assessed clinically and with a fine cut computed tomography (CT) to determine invasion into or through the thyroid cartilage and to assess for spread into the paraglottic space. The appropriate role for magnetic resonance imaging (MRI) and CT in early glottic cancers is still being defined.[53] These advanced imaging studies are of questionable value in the assessment of most superficial T_1 lesions of the vocal cords. Selected T_1 lesions with anterior commissure involvement may benefit from MRI or CT imaging if extension of the tumor superiorly into the preepiglottic space or anteriorly into the thyroid cartilage is detected. The more routine use of MRI or CT is advocated in the evaluation of T_2 lesions not only to help determine tumor extent (and hence T classification) but also tumor volume. Some authors have suggested that CT or MRI of T_2 lesions may help determine radiocurability by assessing tumor volume. Other investigators have not found the size of the tumor to be useful for predicting radiocurability.[54]

Wenig and colleagues[55] contend that surgical treatment of laryngeal cancer with less than a total laryngectomy mandates preoperative MRI in almost all cases. These investigators identify that tumor involvement of the entire vocal cord or the anterior commissure, as well as the presence of vocal fold paresis, is considered an indication for the use of MRI. They relate that only the most superficial T_1 lesions of the mobile portion of the vocal cord need not be imaged because MRI will not detect the extent of these lesions. This philosophy is distinctly opposite from that of Steiner and Ambrosch,[56] who relate that advanced imaging of laryngeal cancer is fraught with artifact. Steiner and Ambrosch find little value in preoperative imaging of laryngeal cancers and relate that the most accurate assessment of tumor extent comes at the time of endoscopic laser microsurgical resection.

Debate continues as to whether CT or MRI offers the most useful information when imaging the larynx.[57] Advances in the speed with which CTs can now be done offer an advantage to this technique. In 2002 Stadler and colleagues[58] reported that use of rapid imaging spiral CTs of the larynx permits complete evaluation during the course of a

Table 108-3

Selected Surgical Procedures for Glottic Cancer

Procedure	Indications	Study
Microlaryngoscopy partial cordectomy with or without carbon dioxide laser (excisional biopsy)	T_1 midcord leukoplakia, T_{is}/microinvasion	Strong and Jako (1972) Kleinsasser (1990) Shapshay, Hybels, and Bohigian (1990)
Cordectomy complete with or without carbon dioxide laser (endoscopy)	T_1 midcord	Strong (1975) Annyas et al (1990) Shapsay, Hybels, and Bohigian (1990) Eckel and Thumfart (1992)
Cordectomy (laryngofissure)	T_1 midcord	DeSanto et al (1977) Bailey (1985)
Frontolateral partial laryngectomy	T_1 with extension to anterior commissure	Leroux-Robert (1975)
Hemilaryngectomy and extended hemilaryngectomy	T_1/T_2 with extension to arytenoid, without anterior commissure fixation (minimal)	Norris (1958) Som (1975) Mohr et al (1983)
Anterior partial laryngectomy with epiglottoplasty or with keel	T_1/T_2 with extension to anterior commissure (without arytenoid)	Tucker et al (1979) Som and Silver (1968)
Subtotal laryngectomy with cricohyoidoepiglottopexy	T_{1b}/T_2 bilateral anterior involvement; may include removal of one arytenoid	Laccourreye et al (1990) Charlin et al (1988)

single maneuver. This rapid imaging of the larynx may be accomplished as the patient performs either a modified Valsalva maneuver or phonation of the utterance "E." This functional imaging (done during the maneuver) was compared with nonfunctional imaging (done with quiet breathing) and correlated with postsurgical pathology assessments and findings at microlaryngoscopy. Although the numbers in their study were small, Stadler and colleagues conclude that functional CT imaging appears to be more accurate in determining tumor extent than nonfunctional imaging.

Positron Emission Tomography

The role for positron emission tomography (PET) is continuing to expand. Although distant metastases from early laryngeal cancers are rare, the most common cause of death in patients with early laryngeal cancer is second primary tumor.[59,60] The most common second primary tumors are lung followed by other head and neck primaries, which are more easily detected clinically and with endoscopy. It has become standard practice in our institution to order a PET scan in all but the earliest T1 laryngeal cancers.

F-18-fluoro-deoxy-glucose (FDG) PET scanning has been reported as useful in detecting subclinical recurrent or persistent cancer at a stage when it is highly curable.[61] Terhaard and colleagues[62] propose an algorithm for the follow-up of patients treated for laryngeal or hypopharyngeal cancers that emphasizes the use of PET imaging. Through a prospective study of 109 PET scans done on 75 patients with either laryngeal or hypopharyngeal cancer, these investigators concluded that an FDG PET scan should be the first diagnostic step when a recurrence is suspected after treatment with irradiation. As a result of this study, in which the majority of cases were glottic and classified as either T_1 or T_2, these investigators suggested that no biopsy is necessary if the scan is negative. In the face of a positive scan and a negative biopsy, a follow-up scan showing decreased FDG uptake would indicate that a recurrence is unlikely. Caution should be exercised in following these guidelines if other clinical indicators support the need for a biopsy. At this point in our experience, endoscopy with a biopsy to sample tissue suspicious in appearance for cancer remains the most critical means by which recurrence is evaluated.

Shortcomings of PET imaging have been noted. Most investigators suggest waiting at least 3 months after treatment to perform PET imaging because false-positive results are common if the imaging is done soon after radiotherapy is completed.[63] False positives may also result from infection, radionecrosis, or accumulation of saliva in the vallecula.[64,65] Some of these shortcomings of PET imaging are being addressed by use of pharmaceuticals other than FDG. The presence of viable tumor has been identified through PET imaging with 1-[1-^{11}C]-tyrosine (TYR). TYR PET imaging analyzes protein synthesis activity and has been reported to be successful in detecting recurrent squamous cell carcinoma of the larynx.[66] Further progress with PET imaging is anticipated with the introduction of other pharmaceuticals.

Treatment

The ideal initial management of an early glottic cancer is the one that is most likely to result in cure and to preserve a normal voice without impaired swallowing or breathing while leaving all modalities of treatment available for recurrence or second primary cancers. It is not often possible to meet all of these goals. A compromise is generally required, wherein the choice of therapy is based on the desires of an informed patient who understands the shortcomings of the alternatives. The surgeon should be aware of the options to make an informed recommendation to the patient. Ideally the patient will meet with both the surgeon and a radiation oncologist to permit identification of the full spectrum of treatment options from differing perspectives.

The following discussion focuses on specific surgical and radiotherapy techniques and concludes with a review of general management principles, focusing on the impact of management on the voice.

Surgery

Physicians' views vary on the indications for use of a specific procedure or radiotherapy technique. General guidelines for selection of an approach based on the extent of a lesion are listed in Table 108-3 and depicted in Fig. 108-6. The choice of therapeutic approach for a patient requires consideration of many other variables in addition to the anatomic extent of the cancer. Overall cure rates and laryngeal preservation

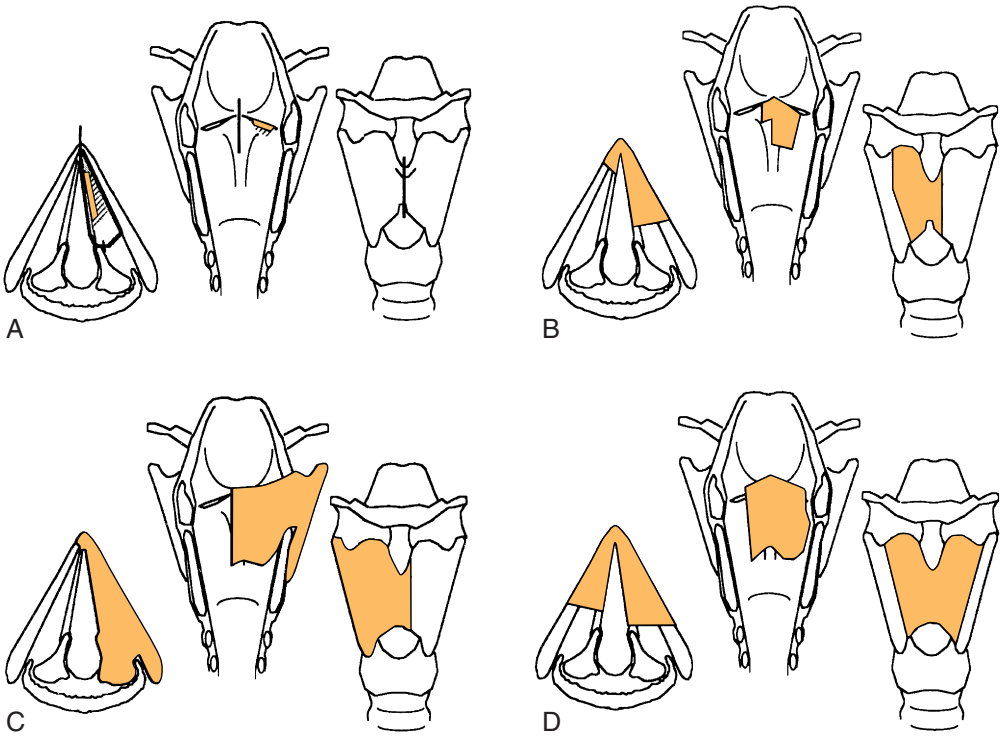

Figure 108-6. **A** through **D,** Diagrams of vertical partial laryngectomy.

figures are high for the surgical management of early glottic squamous cell carcinoma (Table 108-4).

Endoscopic Excision

The histopathologic correlate of a superficial T_1 primary cancer may reveal a lesion without deep extension beyond the superficial layer of the lamina propria.[67] Endoscopic surgical excision of such a lesion may allow for resection with a clear margin without damaging the underlying vocal ligament or vocalis muscle (Fig. 108-7).[68] However, not all T_1 glottic cancers are amenable to superficial conservative resection. Up to 20% of T_1 cancers will show normal mobility despite invasion of the vocal ligament.[69] Carcinoma in situ, which by definition does not invade past the basement membrane, is most amenable to complete excision without disruption of the underlying vocal ligament. The importance of achieving clear surgical margins at the first attempt at resection is highlighted by a review of 1467 patients treated with laser microsurgery. Patients with residual tumor at re-resection had significantly worse locoregional control regardless of clear margins at the second surgery.[70]

Biopsy

In general, discrete lesions of the vocal cords are better sampled through excisional biopsy than through small, piecemeal, random biopsies. The opportunity to effect a cure exists through excisional biopsy if the pathologic assessment shows carcinoma in situ or a minimally invasive cancer. Excisional biopsies also avoid any sampling error wherein small areas of invasive cancer may be missed within a larger field of dysplastic epithelium. Judgment should be exercised in determining the extent of dissection in performing a biopsy on patients who are candidates for irradiation. Smaller biopsies that are sufficient to confirm the diagnosis of invasive cancer impair the posttreatment voice to a lesser degree than larger excisions if irradiation is used as definitive treatment. It is useful to discuss the decision making with the patient in weighing the benefits and risks to approaching the biopsy conservatively or aggressively.

Laser Excision

Endoscopic laser excision is addressed in Chapter 109, and is not discussed here.

Open Partial Laryngectomy

The topic of open partial laryngectomy is covered well in Chapter 110 and is not addressed here.

Voice Considerations

There are two central issues when discussing voice outcomes of various treatment options for early laryngeal cancer: absolute quality of voice, which generally favors radiotherapy; and final laryngeal preservation, which generally favors surgery.[71]

Cragle and Brandenburg[72] reported that surgical treatment of early glottic cancers may produce a vocal result that is equivalent to that following irradiation. These investigators evaluated voice profiles in 11 patients treated with laser cordectomy and 20 patients treated with irradiation. Both groups had similar voice profiles, characterized by decreased maximum phonation times and increased jitter, shimmer, and signal-to-noise ratios.

Most investigators contend that, in cases of early glottic cancers, a better voice more reliably follows treatment with radiotherapy rather than with surgery.[73-77] Unlike surgery, radiotherapy does not require removal of adjacent healthy tissue to provide a clear margin around a cancer. However, vocal deterioration may result from radiotherapy and may be significant if loss of vocal cord bulk results from tumor necrosis or if fibrosis develops.

Ton-Van and colleagues[78] evaluated 356 patients with early glottic cancer and determined that the quality of voice after treatment with radiotherapy is "indisputably superior to that after conservation surgery." However, these investigators pointed out that a functional larynx was preserved in 92% of patients treated surgically compared with 81% initially treated with radiotherapy. The investigators acknowledged that these results could have been biased by management, which generally used total laryngectomy for surgical salvage. As a result of these findings, Ton-Van and colleagues[78] advocate the use of surgery as a primary mode of therapy in patients capable of safely undergoing an anesthetic. Exceptions include patients who are willing to accept a greater risk of total loss of the larynx in the effort to preserve the highest-quality voice.

For most patients with laryngeal cancer, the absolute quality of their voice may not be as important a consideration in selecting

treatment as is their general ability to communicate. For these patients, speech intelligibility may be more meaningful as a criterion to assess results rather than acoustic and aerodynamic measurements. Schuller and colleagues[80] used interviews and questionnaires to evaluate 75 patients treated surgically for early laryngeal cancers. They found that 88% of the respondents were content with the postoperative voice.

The vocal behaviors of most patients after partial laryngectomy are similar to those of patients with glottic incompetence caused by vocal cord paralysis. Leeper and colleagues[81] evaluated six patients who had undergone vertical hemilaryngectomy operations. They found that, whereas large variability was noted, the general tendencies for patients after hemilaryngectomy were (1) incomplete glottic closure; (2) vibratory action of the supraglottic structures (ventricular folds, arytenoids); and (3) high average transglottal airflow with reduced maximum phonation time.

The ability of the vocal tract to regain normal appearance and function is determined by the extent of tumor damage and by the extent of surgical resection. Benninger and colleagues[82] evaluated factors associated with recurrence and voice quality after radiotherapy for early glottic carcinomas. They identified that large excisional biopsies before irradiation increased the risk of poor voice quality.

Radiotherapy

Radiotherapy is considered effective treatment for early glottic cancer (Table 108-5). Broad comparisons between outcomes after initial treatment with either irradiation or surgery are often made without addressing the differences in the various approaches to the administration of radiotherapy or different techniques in performing the surgery.[83] Variables in the application of radiotherapy that affect tumor control include fraction size, total dose of radiation delivered, treatment duration, field size, energy of the x-rays, and method of delivery.[84-87] Rudoltz and colleagues[85] identified duration of treatment as a significant variable in predicting local control and survival in the management of early glottic cancer. Patients completing treatment within 46 days had better local control than those treated over a longer period (Fig. 108-8). Treatment applied through fractions of at least 200 cGy for the standard once-a-day, 5-day-a-week dosing also improved control rates relative to treatment with less than 200 cGy per day.[84,88] Ricciardelli and colleagues[89] also supported the use of higher per-dose fractions through a clinical study and in an in vivo tumor model. In 1993 Rudoltz and colleagues[85] reported that accelerated regimens employing higher-dose fractions were of value primarily because they allowed for shorter treatment duration.

The benefit derived from accelerated fractionation needs to be balanced against the additional morbidity induced. In a phase III study Hliniak and colleagues[90] compared an accelerated regimen (AF) of 66 Gy given in 33 fractions during 38 days (2 fractions every Thursday) with conventional regimen (CF) of 66 Gy given in 33 fractions during 45 days. A total of 395 patients with $T_{1-3}N_0$ glottic and supraglottic cancer treated between 1995 and 1998 were evaluated. More acute morbidity (acute mucositis with pain and dysphagia) was seen in the AF arm at 1 and 2 months. At 4 months after treatment all types of toxicity except skin telangiectasia were similar in both arms. Although there was no difference in the disease-free survival between the two arms, these investigators calculated that shortening of the overall treatment time by 1 week resulted in a 3% to 5% therapeutic gain ($P = 0.37$). They suggest that further shortening of the treatment time could be done within the limits of acceptable morbidity, especially if the volume of the irradiated tissue was small (as for T_1 and T_2 tumors).

Another important consideration in the radiotherapeutic management of early glottic cancer is the technique used for planning and delivery. The treatment target for an early cancer is the lesion itself

Table 108-4

Results of Surgical Management of Early Glottic Cancer*

Study	Patients (*n*)	Stage	Type of Management	Lesions Controlled (%)			Survival (%)	
				Initially	Ultimately	After Laryngeal Preservation	2-yr	5-yr
Ton-Van et al[78]	170	T_{1a}		94				
	36	T_{1b}	Cordectomy	78	98	92	*87*	*84*
	24	T_2		75				
Rothfield and Johnson (1990)	54	T_1	Hemilaryngectomy	98	98	98	98	—
	31	T_2	Hemilaryngectomy	67	90	67	84	—
Laccourreye and Weinstein (1991)	308	T_1	Cordectomy	87	—	—	—	—
	107	T_2	Vertical hemilaryngectomy	78				
Daniilidis and Nikolaou (1990)	94	T_1	Cordectomy	90	93	84	—	93
Rothfield and Myers (1991)	20	T_{is}-T_{mi}	Microscopic direct laryngoscopy	95	80	95	100	100
Casiano et al[73]	37	T_1	Carbon dioxide laser	62	97	91	—	97
	16	T_1†		51	100	69	—	100
Ambrosch et al (1998)	29	T_{is}	Carbon dioxide laser		100		97	
	96	T_1		98	100	99	—	87
	34	T_2‡		100			78	
Fagan and Myers (1994)	50	T_1	Carbon dioxide laser	92	100	100	100	
Olsen and Thomas (1993)	159	T_1	Laryngofissure approach	92	100	94	91	84

*Italicized numbers are mean figures for entire patient group.
†Radiation failure patients.
‡T_2 with mobile cords.

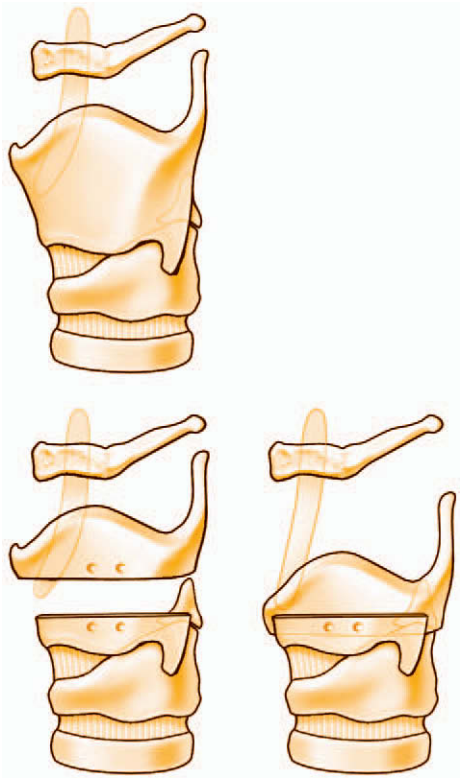

Figure 108-7. Diagram demonstrating removal of a horizontal strip of thyroid cartilage permitting imbrication of the ipsilateral false cord to the glottic level to restore glottic competence.

without the need to address the rare occult metastasis. Conventional techniques initially depended on the physical examination with the placement of a square open field that generally ranged from 44 cm up to 66 cm for larger T_2 lesions. Most of the published experience is based on utilization of either cobalt −60 or linear accelerators of 4 meV or less. The treatment field was traditionally defined by positioning a light field to cover the midthyroid notch superiorly to the inferior cricoid inferiorly. The posterior border of the treatment field was defined by the physician's estimate of the posterior border of the tumor. Anteriorly, the field was extended to completely cover over the anterior skin with additional margin. Careful attention to the daily placement of the field based on external anatomic landmarks was a key to accurate targeting. Treatment simulation employed plain radiographs with confirmation of appropriate targeting of the field based on portal films to check the position of the cartilaginous anatomy that is well visualized on lateral radiographs.

Despite this simple and common sense approach to treatment setup, dosimetric misses occurring because of field misplacement, as well as dose calculation considerations in the small air-filled and irregular cavity of the larynx, were problematic. Reports using higher (6 meV) energy beams (which today are more commonly available than lower energy beams) were initially associated with higher failure rates because of a lack of adequate dosimetric considerations.[91,92] With the advent of virtual simulation it has become possible to better account for the 3D anatomic considerations within the glottis. More sophisticated corrections for the air interfaces can also now be made. These advances permit better estimation of the optimal wedge used to shape the beam profile. Multiple field techniques can now be employed to assure homogeneous and accurate doses. These new techniques improve success but still depend on verification for accurate daily reproducibility and dosimetry.[93,94]

Most radiation failures of early glottic cancer represent local recurrences rather than regional or distant metastasis.[95] The ability to salvage radiation failures with partial laryngectomy or endoscopic laser resection contributes to the overall success of radiotherapy for initial treatment modality (Table 108-6).[96-101] The extent to which conservation laryngeal surgery (partial laryngectomy) rather than total laryngectomy is used to salvage irradiation failures of T_1 and T_2 glottic squamous cell carcinoma depends on multiple factors: the intensity of follow-up (designed to identify persistent tumor at an early stage), the desires of the patient, the presence of comorbidity, and the management philosophy of the treating physicians. Differing philosophies likely contribute to the variable success reported with salvage partial laryngectomy.

Toma and colleagues[102] expanded on their initial criteria to permit partial laryngectomy salvage of early glottic irradiation failures unless the tumor invaded:

- the arytenoid cartilage (except the vocal process)
- beyond the anterior half of the contralateral vocal cord
- subglottically more than 10 mm in the anterior half or 5 mm in the posterior half of the larynx
- into the thyroid or cricoid cartilage

Application of these criteria to 19 recurrent T_1 and T_2 glottic cancers treated with primary radiotherapy at their institution between 1989 and 1998 yielded three failures (recurrences), which were each successfully salvaged with total laryngectomy. These criteria may be considered as general guidelines but should not be applied to all cases for several reasons. Consideration as to anatomic differences in laryngeal size should allow a more subjective assessment of resectability than afforded by the absolute measurement of 10 mm of anterior subglottic extension as a contraindication. A large male larynx will differ from a small female larynx in applying these criteria.

Additionally, Toma and colleagues did not address the role that supracricoid laryngectomy may play in salvaging irradiation failures. Laccourreye and colleagues[103] reported successful use of supracricoid laryngectomy as a salvage procedure with a laryngeal preservation rate among 12 patients who had failed radiotherapy. The major contraindications they pointed to in use of supracricoid laryngectomy were fixation of the ipsilateral arytenoid cartilage, cricoid cartilage invasion, extralaryngeal spread of tumor, and infraglottic spread to the cricoid cartilage.

Chemotherapy

Because early glottic cancers are highly curable with conventional surgery or radiotherapy, the addition of chemotherapy to most treatment algorithms has not been strongly supported. In addition, past dogma has dictated that invasive squamous cell carcinoma of the upper aerodigestive tract is not curable with chemotherapy alone.[104] Laccourreye and colleagues reported that some of the patients with early glottic squamous carcinoma that they treated with an induction chemotherapy regimen (platinum based) had a complete response clinically and chose to forgo the further treatment that was suggested.[105] Although local recurrence was noted in almost one third of these patients, none of the patients who had local recurrence ultimately died from their disease or lost their larynx. This finding has prompted further interest in the use of chemotherapy for early laryngeal cancer to the point that prospective trials evaluating this modality are now under way.

Choosing a Treatment Modality

Carcinoma in Situ

Isenberg and colleagues[106] reviewed 2188 biopsies for leukoplakia revealing no dysplasia (53.6%), mild-moderate dysplasia (33.5%), and severe dysplasia or carcinoma in situ (15.2%). Followed for 3 years, 3.7% of patients with no dysplasia, 10.1% with mild/moderate dysplasia, and 18.1% with severe dysplasia or carcinoma in situ developed invasive squamous cell carcinoma.

Close interaction between the clinician and pathologist is necessary to manage optimally carcinoma in situ ($T_{is}N_0M_0$). Depending on the bias among several pathologists evaluating a biopsy, the same lesion may be reported as grade III intraepithelial neoplasia, high-grade dys-

Table 108-5

Results of Radiotherapy for Early Glottic Cancer*

Study	Patients (*n*)	Stage	Dose Mean (Range)	Lesions Controlled (%)			Survival (%)	
				Initially	Ultimately	After Laryngeal Preservation	2-yr	5-yr
Howell-Burke and Peters (1990)	114	T_2	70 Gy† (65-78 Gy)	68	96	74	—	92‡ 70
Kersh and Kelly (1990)	95 53	T_1 T_2	60 Gy	94 76	100 86	*91*	100 86	—
Johansen and Overgaard (1990)	295 63	T_{1a} T_{1b}	—	81	94	—	— —	94
Ton-Van et al[78]	68 39 19	T_{1a} T_{1b} T_2	60 Gy (50-65 Gy)	*70*	*94*	79	—	67
Pellitteri and Kennedy (1991)	113 48	T_1 T_2	60 Gy 64-70 Gy	93 78	98 92	95 79	—	87 79
Terhaard et al (1991)	194	T_1	66 Gy (58-68 Gy)	91	97	92	97	—
Small et al[86]	103	T_1	64 Gy (54-70 Gy)	89	97	89	—	97
Rudoltz, Benammar, and Mohiuddin[85]	91	T_1	64 Gy (59-70 Gy)	80	95	84	—	92
Fein et al (1993)	19	T_{is}	56 Gy§ (56-60 Gy)	93	100	93	100	—
Smitt and Goffinet[77]	29	T_{is}	62 Gy (53-66.5 Gy)	92	96	96	—	82

*Italicized numbers are mean figures for entire patient group.
†Ten patients managed twice daily with 1.2 Gy.
‡Disease specific.
§Median dose.

plasia, or $T_{is}N_0M_0$.[107] Despite the often stated pathologic principle that high-grade dysplasia and $T_{is}N_0M_0$ are equivalent terms in describing abnormal squamous epithelium, the clinical management is generally less aggressive for high-grade dysplasia than for $T_{is}N_0M_0$. Whereas radiotherapy has commonly been supported as a reasonable treatment alternative for $T_{is}N_0M_0$, it is not recommended in the management of high-grade dysplasia.

Difficulty in discriminating between reactive processes and carcinoma in situ is underscored by a study evaluating imprecision in histopathologic diagnoses. Westra and colleagues[108] reported three cases of laryngeal $T_{is}N_0M_0$ submitted from outside hospitals that were, on review with a second opinion at their hospital, considered to be reactive atypia.

Controversy persists regarding the role for radiotherapy in the management of $T_{is}N_0M_0$. A common management approach has been to address laryngeal $T_{is}N_0M_0$ surgically when conservative endoscopic removal is possible.[109] Persistence after multiple resections or the presence of extensive involvement of multiple sites has been used as an indication for irradiating $T_{is}N_0M_0$.[110] Factors such as the anticipated need for multiple endoscopic resections, cost of treatment, voice considerations, reliability of the patient for follow-up, patient's age, and presence of comorbidities are all factors that may influence initial definitive treatment with irradiation.[111]

Issues regarding the appropriate management of $T_{is}N_0M_0$ are unresolved. Local excision and radiotherapy are effective management options.[112] Either approach requires close follow-up.

Invasive Squamous Cell Carcinoma

Selection of an appropriate treatment modality for early glottic cancers ($T_1N_0M_0$, $T_2N_0M_0$) is made difficult by the many opinions that support conflicting approaches. The simplest conceptual approach is offered by Hinerman and colleagues,[113] who identified that, in the past at the University of Florida, "Radiation therapy has been the treatment of choice for all previously untreated T_1 and T_2 vocal cord cancers." These investigators later amended this practice to prefer transoral laser excision over radiotherapy for the small subset of patients with limited T_1 midthird vocal cord lesions for whom surgical excision is expected to preserve voice quality.

Although the NCDB survey of laryngeal cancer indicates that in the United States radiotherapy is used most commonly in the management of T_1 and T_2 cancers, there are well-considered arguments for a more liberal use of surgery as the initial management.[114] Morris and colleagues,[115] through an intensive literature review, identified an overall 8.6% failure rate at the primary site for T_1 glottic cancers managed surgically (cordectomy) compared with a 16.7% failure rate among similarly staged cancers managed with radiotherapy.[116] Stronger support

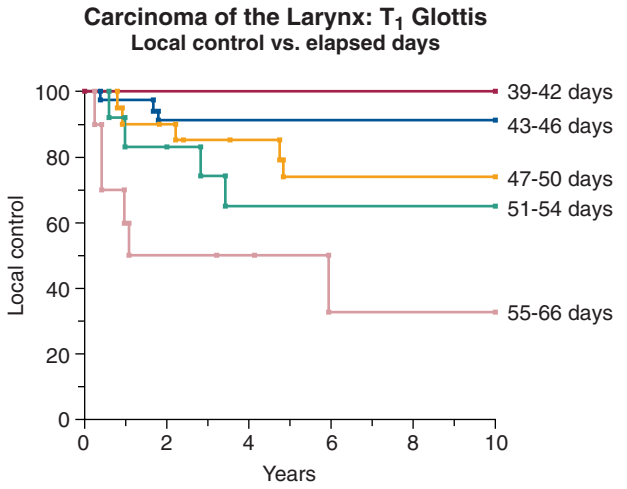

Figure 108-8. T_1 glottic carcinoma of the larynx: local control versus radiotherapy elapsed time. Local control is a function of elapsed days for patients managed with radiotherapy for T_1 squamous cell carcinoma of the glottis. *(From Rudoltz MS, Benammar A, Mohiuddin M. Prognostic factors for local control and survival in in T1 squamous cell carcinoma of the glottis.* Int J Radiat Oncol Biol Phys. *1993;26:768.)*

comes for use of surgery as the primary treatment for T_2 glottic cancers. In 1990 Howell-Burke and colleagues reported from MD Anderson that, among patients treated with primary irradiation for T_2 glottic cancers, only 74% maintained a functional larynx.[117] Some investigators contend that T_2 glottic cancers initially treated with irradiation have a higher risk that laryngeal function will be lost than when conservation surgery is the initial treatment.[118]

Further support for this concept comes from review of published recurrence rates following initial treatment of early-stage laryngeal cancer (see Tables 108-6 and 108-7). A review of these same rates identifies that the great majority of early laryngeal cancers that recur are ultimately treated with total laryngectomy. A problem leading to this need for total laryngectomy may be identified as difficulty in surveillance permitting early detection. Suzuki and colleagues[119] reported in 1994 that 60% of patients initially identified with an early laryngeal cancer are identified with an increased stage at the time of recurrence.

Barthel and Esclamado[120] reviewed management of 45 patients with early glottic cancer who were treated with primary irradiation at the Cleveland Clinic between 1986 and 1994. These investigators reported that their local control rates of 87.5% for T_1 and 75% for T_2 lesions were consistent with prior published series. Among the nine recurrences that developed, six had tumors that were (retrospectively) considered to be amenable to treatment with a partial laryngectomy. Among these six cases (all treated with irradiation), only one was successfully salvaged with conservation laryngeal surgery. These investigators concluded that patients with T_2 glottic tumors may be better treated primarily with surgery because T_2 glottic cancers have a high recurrence rate after irradiation and surgical salvage with less than a total laryngectomy was unlikely to be successful. Valuable insight is provided by a report by Jorgenson and colleagues that addresses 1005 Danish patients treated at a single referral center between 1965 and 1998.[121] The philosophy of treating all but those who had previous treatment with irradiation resulted in remarkably little selection bias regarding treatment choice, with 99% of patients receiving initial management with radiotherapy. Jorgenson and colleagues[121] identify that the presence of a stable patient base within a cachement area of 1.33 million people, coupled with excellent follow-up (only three patients were lost to follow-up), lends further credibility to this study. Among 312 T_1 glottic cancers treated with irradiation, 5-year locoregional control was 88%, which, coupled with surgical salvage, resulted in a 99% 5-year disease-specific survival. Among 233 T_2 glottic cancers treated with irradiation, 5-year locoregional control was 67.4%, which, when coupled with surgical salvage, resulted in an 88.4% 5-year disease-specific survival. These investigators identify that this high recurrence rate (one out of three) for T_2 glottic cancers resulted in an overall laryngeal preservation of 80%, which is substantially lower than the 95% organ preservation reported by Chevalier and colleagues when supracricoid laryngectomy was used as the initial treatment.[122] Based on these data, Jorgensen and colleagues raised the logical question: Why not introduce supracricoid partial laryngectomy as primary standard treatment of T_2 glottic cancer? Jorgenson and colleagues argued that part of the excellent results reported by Chevalier and colleagues reflected a selection bias that favoring surgical results by reserving supracricoid laryngectomy for the more favorable cases. Jorgensen and colleagues additionally pointed out that the voice quality is better after irradiation than after supracricoid laryngectomy. For these reasons, they have not altered their standard approach to managing T_2 glottic cancers with irradiation. They also observed that improved radiotherapy techniques, as well as the capacity to salvage irradiation failures with

Table 108-6

Recurrence Rates of Early Stage Laryngeal Cancer Following Initial Treatment with Irradiation*

Study	T1 Recurrence (%)	T2 Recurrence (%)
Jose et al, *J Surg Oncol*. 1984	T_1, 18	T_2, 18
(summarized 8 reports before 1984)	T_1, 15	T_2, 31
Fisher et al, *Arch Otolaryngol Head Neck Surg*. 1986	T_1, 8	T_2, 36
Strauss, *Laryngoscope*. 1988	T_1, 11	T_2, 23
Maipang et al, *J Surg Oncol*. 1989	T_1, 20	T_2, 36
Foote et al, *Mayo Clin Proc*. 1992	T_1, 16	T_2, 16
Suzuki et al, *Acta Otolaryngol*. 1994	T_1, 7	T_2, 82
Parsons et al, *Int J Radiat Oncol Biol Phys*. 1995	T_1, 4	T_2, 15
McLaughlin et al, *Head Neck*. 1996	T_1, 6	T_2, 16
Nibu et al, *Head Neck*. 1997	—	T_2, 11-73
Mendenhall, *J Clin Oncol*. 2001	T_1, 7	T_2, 28
Warde et al, *Int J Radiat Oncol Biol Phys*. 1998	T_1, 9-18	T_2, 31
Wang et al, 1997	T_1, 7	T_2, 29
Garden, *Int J Radiat Oncol Biol Phys*. 2003	—	T_2, 28

*T_1 approximately 10%; T_2 approximately 30%.
Modified from Mendenhall WM, Werning JW, Hinerman RW, et al. Management of T1-T2 glottic carcinomas. *Cancer.* 2004;100:1786-1792.

Table 108-7

Percentage of T1/T2 Laryngeal Cancers with Recurrence Requiring Total Laryngectomy

Study	Recurrence (%)
Jose et al, *J Surg Oncol.* 1984	95
Fisher et al, *Arch Otolaryngol Head Neck Surg.* 1986	100
Maipang et al, *J Surg Oncol.* 1989	100
Nichols and Mickelson, *Ann Otol Rhinol Laryngol.* 1991	>30
Suzuki et al, *Acta Otolaryngol.* 1994	91
Parsons et al, *Int J Radiat Oncol Biol Phys.* 1995	>40
McLaughlin et al, *Head Neck.* 1996	83
Stoeckli et al, *Arch Otolaryngol Head Neck Surg.* 2000	92

supracricoid laryngectomy, will likely decrease the ultimate need for total laryngectomy further.[103]

Motamed and colleagues[123] reviewed all series of laryngeal preserving surgical salvage following localized radiotherapy failure for early laryngeal cancer. They estimated that one third of recurrences following radiotherapy are amenable to localized treatment. In this highly select group of patients the average laryngeal conservation rate was 77% following open conservation surgery and 65% following the endolaryngeal laser microsurgery. The trend favoring surgery over radiotherapy with regards to final laryngeal preservation may therefore be due to differing salvage philosophies, as well as submucosal or diffuse recurrence patterns and the difficulties in early detection of recurrence due to edema and tissue changes following radiotherapy.

The preceding studies have focused on AJCC (or the International Union Against Cancer) TNM classification as the factor determining treatment. Others have identified specific features of early glottic cancers separate from this classification system that may be helpful in assessing the likelihood of cure with radiotherapy.[124] It is useful to individually evaluate these characteristics that are either not included in the TNM staging (anterior commissure extension and large tumor bulk) or are used to discriminate T_2 from T_1 lesions (impaired vocal cord mobility and subglottic extension). Many investigators support surgery as the preferred initial treatment for patients who have such characteristics.[125]

In general, the survival outcomes for early laryngeal cancer are very good regardless of treatment modality. In a series of 410 patients treated with primary radiotherapy, Franchin and colleagues[59] showed that second primary tumors were the major cause of death. Patients who developed a second primary (most commonly lung followed by head and neck) had a 32% 10 year survival compared with 77% 10-year survival for those without a second primary tumor. In a series of 240 early-stage laryngeal cancers treated with radiotherapy followed for a median 6 years, Holland and colleagues[60] showed that 28% developed second primary tumors (6% in the head and neck) with median survival 14 months.

Laryngeal-preserving surgery, whether endoscopic or open, is repeatable, whereas radiotherapy, in general, can only be used once. Although radiotherapy is more commonly used, surgical techniques reserve the capability of using radiotherapy in treatment of more deadly second primary tumors of the head and neck, which may be more advanced at presentation or be in sites where surgical treatment is more morbid and less of an equally suitable alternative than the larynx.

The anterior commissure has been, in a contradictory fashion, either considered as a barrier to tumor spread or as an early pathway for cancer extension into the laryngeal framework.[126] Shvero and colleagues[127] related that surgical treatment is preferred for cancers arising in this region because of a higher local recurrence rate after radiotherapy with an increased risk for distant metastasis. They contend that the behavior of small cancers in this location is much different from that of other early glottic cancers.[79] Other investigators have attributed the higher rates of failure after radiotherapy for anterior commissure lesions to problems with adequate dosing.[128,129] The distance from the anterior commissure to the skin varies greatly among patients. This variability and the thick overlying thyroid cartilage have been cited as impediments to consistent dosing of radiation to this region.

Insight into poor outcomes after irradiation of cancer affecting the anterior commissure is offered through a retrospective review by Maheshwar and Gaffney of 53 patients with T_1 glottic cancer treated between 1989 and 1996 with a minimum dose of 63 Gy in 30 fractions during 6 weeks with parallel opposed fields.[130] These investigators reported an overall 20.8% locoregional recurrence rate. The recurrence rate (57.1%) with anterior commissure involvement was much higher than the recurrence rate (15.8%) when the anterior vocal cord was involved but did not include the anterior commissure. They hypothesized that a lack of pretreatment CT imaging may have contributed to their poor results. Without this advanced imaging, they may have understaged the group of anterior commissure cancers, which have a high chance of cartilage involvement and hidden tumor bulk. Although some investigators relate that modern radiotherapy techniques with improved dosimetry have adequately addressed these concerns, Maheshwar and Gaffney[130] report in their study that they had addressed the potential to underdose the anterior commissure by adding wax bolus to the region during treatment.

T_{2b} cancers and those with subglottic extension generally have a larger tumor volume that may contribute to the lower cure rates with radiotherapy.[131,132] Many contend that surgery as a single modality is more effective than radiotherapy for managing these larger "early" glottic lesions. Questions persist about the capacity of a management plan that uses definitive radiotherapy coupled with salvage by partial laryngectomy to provide equivalent rates of laryngeal preservation.[69]

One final factor weighing against radiotherapy is the absence of definitive histologic specimen. From the early days of laryngeal conservation surgery it has been known that up to 20% of biopsy proven cases will have no residual cancer found on definitive resection.[133] Such cases improve results in both radiotherapy and surgical outcome studies and would not require radiotherapy to the unaffected residual tissues.

A systematic review of the world's literature (including the Cochrane Controlled Trials Register, as well as MEDLINE, EMBASE, CINAHL, and Cancer Lit, up to October 2000) identified three randomized clinical trials (RCTs) comparing treatment of patients with stages I and II glottic cancer with either irradiation or surgery.[134] One trial was excluded because of insufficient numbers of patients[135] and another because of the combination of suboptimal radiotherapy dosimetry, small numbers of patients with glottic cancer, and improper randomization.[136]

The most relevant RCT was an Eastern European multicenter trial to which 234 patients with early laryngeal cancer were randomly assigned, starting in 1979. They were treated with open surgery, radiotherapy, or a combination of radiotherapy and chemotherapy (prospodine) after stratification by anatomical site (glottis or supraglottis) and by tumor stage (T_1 or T_2).[137] The published results (which did not report the number of events or patients at risk in each treatment arm) identified 5-year survival rates of 100% after surgery and 91.7% after radiotherapy for T_1 tumors. For T_2 tumors the 5-year survival rates were 97.4% after surgery and 88.8% after radiotherapy. Although these higher survival rates for patients receiving surgery were not statistically significant, the 5-year disease-free survival rates of 78.7% for surgery and 60.1% for radiotherapy were significant ($P = 0.036$). In subsequent review, Dey and colleagues[134] questioned the validity of these results because they believed the patients in the study were inadequately staged

before being randomly assigned, that the radiotherapy may have been suboptimal, and that the follow-up was poor. Dey and colleagues concluded from their systematic review that uncertainty remains as to the comparative benefits and societal costs of these different treatment modalities.

A large survey employing Canadian and American data sets to assess outcome as a function of differing management philosophies acknowledged that "current practice is based on reports from individual institutions recommending differing treatment policies."[138] These investigators opine that a clear advantage to one approach will be difficult to identify because randomized trials comparing surgical and nonsurgical treatment of glottic cancer will never be conducted because of entrenched beliefs. Although it is clear from the review by Dey and colleagues that RCTs have been done addressing early laryngeal cancer, none has yet compared the effectiveness of endolaryngeal resection with either radiotherapy or open surgery.

Summary

Selection of a treatment modality for early glottic cancers should be determined after a careful discussion of options with the patient. Ideally patients should have a discussion with both a radiation oncologist and a surgeon experienced in laryngeal conservation surgery (open or laser). Radiotherapy and careful follow-up employing surgical salvage offers a similar chance for a cure as that provided by treatment with surgery and most likely provides the best voice quality in patients retaining their larynx. The major shortcomings of radiotherapy include the need for prolonged treatment, the higher risk of requiring a total laryngectomy for salvage, and limitation in repeatability in the event of a second primary head and neck tumor. Second primary tumors are the most common cause of death in early laryngeal cancer. T1 cancers with anterior commissure involvement or large tumor bulk and T2 cancers most likely have higher final laryngeal preservation following initial surgical treatment rather than irradiation. The major shortcomings of surgery include exposure to a general anesthetic and most likely worse voice quality, although with higher final laryngeal preservation. Potential swallowing impairment, as well as other comorbidities, should be considered when recommending an approach. Close follow-up is important to detect second primary tumors and treat selected early recurrence using laryngeal-preserving techniques.

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CHAPTER ONE HUNDRED AND NINE

Transoral Laser Microresection of Advanced Laryngeal Tumors

Michael L. Hinni

John R. Salassa

Bruce W. Pearson

Key Points

- Transoral laser microsurgery (TLM) permits both small and large laryngeal tumors to be resected. The limits of resectability are based on access and functional consequences and not on extent or T stage.
- Piecemeal resection of cancer permits precise tumor mapping and may improve local control over traditional "en bloc" resections. It further permits larger tumors to be removed through endoscopes that could otherwise not accommodate the physical volume.
- TLM offers numerous functional advantages including fewer tracheostomies, no fistulas, earlier swallowing, and sensation.
- TLM can replace traditional conservation laryngeal operations.
- TLM can fit well into multimodality therapy strategies.

Terms and Definitions

Transoral laser microsurgery (TLM) is a surgical treatment strategy for primary cancers of the mouth, pharynx, and larynx. In TLM, the instrument of excision is a carbon dioxide (CO_2) laser beam, an operating microscope imparts the perspective, and the natural passageways of the upper aerodigestive system provide the access.

Two features distinguish TLM from open surgery[1]: healing is allowed to occur by secondary intention[2] and the tumor block can be subdivided into manageable units by the laser (in situ).

TLM is clearly a conservation strategy, but it is not a reconstructive one. "Piecemeal" removal is a distinguishing feature of TLM—and a key source of controversy. Tumor transection endows important diagnostic dimensions to TLM, and magnification exploits the difference in visual appearance between normal tissue and cancer.

Safe TLM requires two conditions: adequate exposure through the mouth and a tangible specimen.

TLM is an excision, not vaporization. A specimen is the basis of meaningful frozen section margins. Individual specimens may be small, but, in aggregate, the resected tissue volume parallels that of an open operation.

In many ways, TLM is a misleading name. Transoral laser microsurgery is not totally transoral—open surgery is still required for nodes in the neck. TLM is not entirely laser, either—it depends on endoscopic cautery, vascular clipping, and occasionally blunt and sharp dissection. Finally, TLM is not exclusively surgical—radiotherapy may be offered (for neck indications, but never to finesse margins).

The aim of TLM is to improve cure and function through patient selection and technical excellence. The goal is the cure rate of open surgery and the functional promise of a tissue-conserving treatment like radiotherapy, all of this with less morbidity, at lower cost.

"Advanced" (as in "advanced laryngeal tumors") is a confusing term. In the context of laser surgery, it once meant any tumor larger than T1a glottic. In traditional discussions, it used to mean cancer with a fixed cord. The staging system suggests a different connotation—positive neck nodes. What is clear is that laryngeal cancer is not one disease. It is many different diseases. And unless we digress and clarify the descriptors of the different laryngeal cancers, all discussions of treatment are ambiguous. The answer to the question, "Does an advanced case qualify for TLM?" is "It depends. What do you mean by advanced?" Let's look at the classifications.

Is it cancer? Laser surgery manages everything along the histologic spectrum, but this chapter only relates to the worst actor, invasive squamous cell carcinoma. The Ljubljana taxonomy[3] is probably the closest thing we have to an internationally accepted classification of epithelial hyperplastic laryngeal lesions (EHLL). For the most benign, "simple hyperplasia," acanthosis predominates. "Abnormal hyperplasia" is next, and basal proliferation is the hallmark. "Atypical hyperplasia" features dysplasia and atypia. Fourth is carcinoma in situ (CIS), cytologic neoplasia on an intact basement membrane. All these can be laser resected, but TLM is a higher strategy for a higher challenge, group five, neoplasia with subepithelial penetration (i.e., invasive squamous cell cancer).

Is it TLM? An excellent classification for laser cordectomies has been developed by the European Laryngological Society.[4] It names five types: subepithelial, subligamental, transmuscular, total, and extended cordectomy. The first three are elegant one-piece excisional biopsies, and a laser may be used on them. TLM (and the strategy of depth determination) comes into play for the last two.

What site? Before "multidisciplinary" committees imposed a theoretic anatomic classification (glottic, supraglottic, and subglottic) on

laryngeal cancer, surgeons included clinical behavior in the sorting system. For 50 years, laryngeal cancer was "intrinsic" or "extrinsic."[5] Intrinsic was "interior region" cancer, primarily glottic in origin, and slow growing, and its nodes were generally late.[6] TLM treats most of these, but not all. Extrinsic cancer was more supraglottic, originating around the laryngeal opening or its pharyngeal surface. It had a higher rate of metastases and was more lethal. TLM treats the local disease, but not the metastases.

Now the official categories are glottic, supraglottic, and subglottic, whereas "transglottic" is used to describe tumors that span the ventricle. However, in the anterior larynx, glottic and subglottic cancers behave similarly.[7] Subglottic cancer often turns out to be glottic, with descent. The height of the glottis is controversial (5 mm high, 10 mm high), or excluded posteriorly (sparing the posterior commissure). None of the sites is off limits to TLM.

In discussing local extent, clinicians often reduce their spoken references to "early" and "advanced" laryngeal cancer, the traditional dividing line being vocal cord motion. In these terms, TLM is primarily an "early" cancer treatment, as opposed to the "advanced" group.

The tumor, node, metastasis (TNM) staging system[8] uses T_X, T_{is}, T_1 (a and b in the glottis), T_2, T_3, T_{4a}, and T_{4b} to define a local tumor, expanding 3 regions to 18 "extents." And this is just for the local disease (T). Nodes multiply the possibilities by 7. Metastases multiply the possibilities by 3, for more than 300 possibilities. Some are suitable for TLM. Some are not. No one knows where we should place the dividing line, or where "advanced" should start (or end). The staging system does encourage a summary format, stage 1, stage 2, stage 3, and stage 4, but the neck dominates this classification. If the neck is positive, everything is stage 3 or 4 (advanced), even if the primary is miniscule.

The staging of laryngeal cancer is not linked to any particular therapy and has significant limitations. TNM staging leaves out historic factors (age, previous treatments, habits, work, duration of and number of symptoms, literacy, religious beliefs, distance from treatment facility, etc.) and leaves out comorbidities. Both symptom severity scores and comorbidity scales have been shown to improve the accuracy of TLM.[9] TNM also ignores complex patient factors (e.g., exophytic vs. endophytic, keratinized vs. ulcerated, stridor, obesity vs. cachexia, forced expiratory volume, ejection fraction, hemoglobin, protein levels, blood sugar, liver function tests). These and other limitations of TNM staging pose challenges to the treating physician.

This leaves the doctor with the problem of how to interpret the term "advanced" in the context of TLM. It makes little sense to link advanced to a higher TNM stage (3 or 4) if patients with T_1 and T_2 local cancers will be included (all that is required to make a T2 cancer "stage 3" is for someone to feel a node in the neck). For example, the 2002 American Joint Committee on Cancer (AJCC) TNM staging of larynx cancer states that stage III includes T_1, T_2, or T_3 N_1(or T_3 N_0), where N_1 is a single node smaller than 3 cm. The AJCC also lists stage IVA to include T_1, T_2, T_3, or T_{4a} N_2 (or T_{4a} N_1 or N_2), where N_{2a} is a node between 3 and 6 cm in size, on the same side; N_{2b} is multiple nodes smaller than 6 cm, on the same side; and N_{2c} is bilateral or contralateral nodes smaller than 6 cm in size.

This chapter is primarily about the treatment of the local diseases by TLM. Therefore we need to classify local diseases and to help distinguish those for whom TLM is an option and those for whom it is not.

Five Types of Local Laryngeal Cancer

From the surgeon's standpoint, local laryngeal cancer comes in five different "flavors," each one more damaging (to function) and more difficult to cure. Severity relates to what stock local excision would be required for complete removal. What would that impose on the patient, in terms of voice, swallow, and nasal breathing? This does not indicate the treatment is surgery. It does ensure that the appropriate local option for surgery is identified, especially to the patient, when the selection among various modalities is made. Each flavor can thus be defined by one of five classic excisions, which ascend in severity from laryngoscopic biopsy to total laryngectomy. Each excision removes a customary block, from one nodule to the whole larynx and its coverings, and each has a formal technique. We have a published record for each of local control rates from 98% to 80%. The expected functional outcome ranges from normal voice, swallow, and breathing down to tracheoesophageal puncture (TEP) voice and stomal breathing. Each of these five categories can be named as follows: very early, early, intermediate, advanced, and very advanced.

1. Very Early
   Exophytic midcordal T_{1a} carcinoma. Encompassed by transoral excisional biopsy removal. Includes one-piece subepithelial cordectomy (stripping), subligamental[4] partial cordectomy, and midcordal transmuscular cordectomy.

2. Early
   Two subtypes, glottic and supraglottic.
   a. Early Glottic
      T_{1a}, T_{1b}, and T_{2a} true cord carcinoma whose formal external excision would be a vertical partial laryngectomy,[10,11] or hemilaryngectomy.[12,13] The European Laryngological Society's total cordectomy and extended cordectomy[10] concepts probably fit here.
   b. Early Supraglottic
      T1 supraglottic carcinoma fitting within a supraglottic laryngectomy block.[1,14,15]

3. Intermediate
   Laryngeal cancer that fits within a supracricoid partial laryngectomy block.[16,17] Thus T_2 glottic carcinoma (T_2 by spread to the supraglottis), T_3 glottic (T_3 by thyroid cartilage erosion from the anterior commissure—mobility is preserved), T_2 supraglottic (T_2 by descent to involve the vocal cords), or T_3 supraglottic cancer (if T_3 by involvement of the preepiglottic space PES).[18-20]

4. Advanced
   T_3 glottic carcinoma (T_3 by unilateral cord fixation and invasion of the paraglottic space or the thyroid ala) is the prototype because it is lateralized and fits within a near-total laryngectomy.[21] Lateralized invasive T_{2b} glottic carcinoma qualifies if the T_{2b} is by impaired mobility of one vocal cord. Also, advanced glottic carcinoma includes T_2 supraglottic carcinoma, where T_2 means involvement of the vallecula or the medial pyriform wall, and T_3 supraglottic carcinoma, where T_3 means unilateral cord fixation with invasion of the paraglottic space or the thyroid ala.

5. Very Advanced
   Bilateral anterior T_3 glottic carcinoma invading both ventricles, bilateral posterior T_3 supraglottic cancer invading the postcricoid region, or T_{4a} glottic or supraglottic carcinoma, which means the cancer has invaded into adjacent structures outside the larynx—the strap muscles, the thyroid gland, the tongue beyond the immediate base, the trachea, or the esophagus. The minimum excision these cancers would require is at least a wide field total laryngectomy (T_{4b} is incurable by surgery). T_{4b} means gross distant extension. But this is virtually unheard of in cancers with no prior treatment. Examples include direct extension into the prevertebral space or the mediastinal structures or encasing the carotid.

Now we can examine TLM in the context of the clinical severity of the local disease. Others can judge the use and validity of the approximate term *locally advanced.*

Acronyms

CHEP Cricohyoidoepiglottopexy.[22] Reconstruction for supracricoid partial laryngectomy (SCPL).

CHP Cricohyoidopexy.[23,24] Reconstruction for SCPL.

HSL Horizontal supraglottic laryngectomy.

NTL Near-total laryngectomy.[25,26] Frontoanterior VPL with epiglottoplasty, SCPL, and NTL have at various times all been called *subtotal laryngectomies.*[27-30]

PES Preepiglottic space.

SCPL Supracricoid partial laryngectomy. Frontoanterior VPL with epiglottoplasty, SCPL, and NTL have at various times all been called *subtotal laryngectomies.*[27-29]

TLM Transoral laser microsurgery.

TEP Tracheoesophageal puncture, tracheoesophageal prosthesis.[31,32]

VPL Vertical partial laryngectomy. Includes the vertical frontoanterior and frontolateral[10,11,33,34] partial laryngectomies, and hemilaryngectomy.

Laser Surgery and Transoral Laser Microsurgery in the Treatment of Early, Intermediate, and Advanced Cancers

Laser surgery is not new in larynx cancer. Davis and colleagues[35]; Jako and colleagues[36]; Strong[37]; and Vaughan and assessites[38] all treated selected tumors during the 1970s and early 1980s.

Through the 1980s and 1990s, Motta and others[39] and Steiner[40,41] pioneered a new concept: tumor transection in situ. Consider the implications. If infiltrative cancer could be safely resected in pieces, tumor depth could be determined in situ. Incremental resection would become possible—as in Mohs' chemosurgery.[42] (Mohs treated cancer successfully in more sites than just the skin.) One could "follow the tumor" (i.e., custom tailor the excision to each individual patient). If tumors could be subdivided into manageable subunits, early, intermediate, and even some advanced laryngeal cancers might be candidates.

Of course, transoral cordectomy provided outstanding results long before the laser was added. Suspension[43-46] and the microscope were the keys, not a laser. What the laser added was questionable—costs for new equipment, time to set up, regulations in the operating room, thermal injury hazards, maintenance issues, anesthesia issues, more suction, filters, retraining requirements, and new credentialing. And what the laser gave up was considerable—the tactile feedback of cold steel microinstruments, the ability to cut around corners, the plume-free operating site, the char-free pathology specimen, operating room space, an unencumbered microscope, and the precision of a cut path versus a vaporization path.

But in the 1980s and 1990s, a sustained experience of endoscopic laser surgery for larger than T_{1a} glottic cancers was growing in Germany.[40,41,47-51] This raised additional questions among traditionalists. They had concerns about exposure, hemostasis, reconstruction, margins, and wound healing. The greatest concern, however, was tumor transection. Steiner cut right through laryngeal cancer—in situ—through a laryngoscope! The claimed advantage was visualization and confirmation of tumor depth. How did the skeptics respond? First, they were asked to compromise access and work through smoke with an endoscope, with no convincing evidence this was meaningful. Then they were asked to give up orientation and violate the principle of en bloc resection—with no laboratory evidence this was safe!

Other concerns fueled the discussion. After a laser supraglottic resection, there was no reconstruction! Open supraglottic laryngectomy always led to aspiration if one failed to repair the gap between the glottic unit and the tongue base.[15,52,53] After laser SCPL, there was no cricohyoidopexy. Yet this was essential in open SCPL.[19,24] There were so many additional issues a laser did not address (e.g., bleeders over 2 mm, ossified cartilage, neck nodes).

Furthermore, the obvious problems of access were troubling. Big tongues, small mandibles, capped teeth, mild trismus, and other challenges all lay in waiting, even for the most resourceful of operators. Very early midcordal T_{1a} carcinomas may have been fine. But early cancers would require greater exposure, intermediates more, and so on. Some would be too big to extract through an endoscope. A growing plethora of "laser laryngoscopes" raised suspicion that the problem of access remained unsolved.

Another challenge would be quality control from the pathology department. In cancer operations, negative margins are compulsory. If laser specimens were vaporized, the pathologist would have no margins to read. If they were excised with a laser, margins would at best be charred. If they were excised in several pieces, positive margins would be meaningless!

In North American practices, these considerations delayed TLM. This occurred despite much of the pioneering work originating in North America—the entire organ serial section studies from New Haven,[54] Philadelphia,[55] and Toronto[56,57]; the development of the CO_2 laser itself at American Optical Corporation by Strong[58] and associates in 1965; and the pioneering clinical laryngology of Strong[37]; Jako,[36] Vaughan,[38] Davis,[35] and Ossoff[59] and their coworkers; and Shapshay.[60] But the German centers were leaders in the collaborative development of all the ancillary laryngologic instrumentation needed to capitalize on the technique. They pushed their experience well beyond the concerns recited earlier, tracked their results, and continue to report on their experience.[41]

In 1996 the authors of this chapter began to study this body of work more closely, and subsequently we took numerous steps to incorporate TLM into our practices. This effort provided new perspectives on laryngeal cancer management and the initial selection of therapy. Now we seek to share what we have learned.

Theoretic Basis of Transoral Laser Microsurgery

TLM does violate a time-honored dictum of surgical oncology—en bloc resection. A typical glottic or supraglottic cancer (above T_1) is likely to be extracted in three to six separate pieces!

En bloc has always been a prudent tactic to avoid unseen physical dispersion of viable malignant cells in a wound. When a scalpel penetrates cancer, the cells exposed will be alive. Viable cancer cells may adhere to the blade. Nothing prevents the surgeon from inadvertently transferring unseen cancer to an adjacent site in the wound. If unseen cell transplantation does occur during open surgery, and then we close the wound, how could tumor not recur? In open traditional surgery, this is why we isolate cancer in an unbroken package of normal surrounding tissue—to prevent contact between cancer and a scalpel or a scissor. This way, maybe we can avoid transplanting living malignant cells from the cancer back into the patient.

Rethinking this chain of events in laser microresections raises a new question. What would be the apparatus of physical transplantation? Cancer cells do not adhere to a beam of light. There is no physical carrier to transplant the tumor. Then again, grasping forceps and the suction cautery tips are used in TLM. They could do it. But assuming no tearing of the specimen, how would exposed cancer cells be viable? Cells revealed by laser energy are thermocoagulated, not viable. Finally, in the TLM paradigm, we do not close the wound. An unseen cancer cell falls on a thin layer of coagulum, not a healthy tissue surface. This layer is gradually sloughed, not incubated.

These are theoretic reasons we postulate that laser surgery permits local cancer ablation without en bloc resection. Is there any laboratory or clinical data? Werner and colleagues showed (for CO_2 laser incisions) that the lymphatic vessels of the wound margin are sealed immediately, and lymphatic vessels remain sealed for about 10 days after laser surgery.[61] And we also have 20 years of European clinical data.[62-65] Steiner and colleagues[41,64-67] have been performing TLM since the early 1980s. He and his colleagues have observed a low local recurrence rate (2% to 10%), a high survival rate, and a low rate of complications.[66,67] They have not seen an increase in late neck or distant metastases during follow-up of more than 10 years. The incidence of cure by TLM is the same as the best results reported for open conservation surgery. Put another way, open surgery follows the principle of block resection but produces no more local cures than TLM! TLM allows laser tumor subdivision, but local failure occurs with the same low incidence as in traditional open conservation surgery.

If tumor transection can be safely accomplished (it is not automatic, care is still important), we have an attractive new technique to determine the depth of cancer invasion before we commit to the plane of excision. If we misjudge and cleave too close to the tumor, this is

just another form of tumor transection. We can extend the excision, incrementally. All we have lost is some time.

If tumors can be divided in situ, the tumor itself ceases to be a factor in obstructing our vision. Complete removal always requires that we expose the entire mucosal margin of the tumor. Now we can achieve that goal in a mosaic of views, unrestricted by the bulk of the disease.

If tumors can be extracted in pieces, the internal diameter of the laryngoscope does not set the limit on how large a tumor we can resect. The limit becomes the exposure for each step and our disciplined attention to specimen orientation. Mohs[42] transected cancers in situ successfully, and his attention to orientation was uncompromising.

Later in this chapter we summarize our TLM results, as well as those of others.[67] We have documented a low incidence of failure at the primary site and also reported the ultimate causes of death. Our conclusion is that ultraradical treatment of the primary is not justifiable in a disease for which the main causes of death are advanced neck recurrences, distant metastases, second primaries, and serious general diseases. In modern times, quality of life is increasingly salient. In related diseases like hypopharyngeal cancer (TLM treats pyriform cancer, too[68]), 5-year survival rates have stood between 15% and 30% for decades. Aggressive combined therapy (chemotherapy, radiotherapy, and radical surgery) have not improved the poor prognosis. Again, if we can effect local control with conservation laser surgery, the argument in favor of radical ablation clearly declines.

Transoral Laser Microsurgery Compared with Open Conservation Surgery

Open operations approach intralaryngeal carcinoma from its "blind side." The surgeon cannot see the primary cancer until he or she has opened the neck, divided the fascia, separated the strap muscles, opened the framework, and penetrated the lumen at a critical point, determined by the local anatomy. Once exposed, field margins are oozy, not laser cut. Structures within the field relocate with the surgery, instead of maintaining a fixed position. The tumor margins are diminutive, not magnified, and the headlamp is illuminated, not microscope superilluminated. For safety and reproducibility, open operations closely replicate a named excision block, chosen without the benefit of intraoperative depth information. For example, supraglottic laryngectomy removes the superstructures above the cords, which produces a predictable wound, requires a characteristic reconstruction, and can be repeated for numerous supraglottic cancer patients, despite the fact each has unique anatomy, distinctive preoperative findings, and slightly different tumor characteristics. Because the neck will be opened, the timing of a node dissection is determined. The neck dissection is continuous with the primary wound, so steps must be taken to prevent a fistula. Because the framework is elevated to the tongue base and both swell, airway safety demands a temporary tracheotomy. Supraglottic laryngectomy supports the principle of en bloc resection, but this was necessitated by the scalpel, not the cancer. It assists teaching, but for gross anatomy, not for the microanatomy and micropathology. Open supraglottic laryngectomy provides the access needed for reconstruction, but the open surgery necessitated the reconstruction.

By approaching laryngeal carcinoma through the mouth, TLM requires no disassembly for access. The laryngeal framework continues to support the airway. A tracheotomy is usually superfluous in a supraglottic TLM. The strap muscles retain their swallowing contribution. Through the endoscope, the operator confronts the authentic primary right from the beginning of the resection, with no disassembly of the patient just to reach the cancer. The laryngoscope stabilizes the field. The magnification and brilliant illumination unveil important subtleties (e.g., dysplasia at a margin). With no disturbance of the neck, and no connection of a neck wound with a laryngeal wound, pharyngocutaneous fistulae disappear from the list of potential complications.

During TLM, diagnosis continues.[69] Wherever the local tumor extends, the microscope and the laser try to follow. Magnified tissue appearances acquire new significance. Some tumors change the vascular patterns in the mucosa. Deeper in, invasive cancer tends to appear pale and dysmorphic. Tissues give up subtle information about their consistency as they are retracted. Cancer is stiff or soft (soft can progress to friability and bleeding). Beyond the tumor, the expected microarchitecture is striated muscle, fat, seromucinous glands, fibrous perichondrium, (ossified) cartilage, or bone. Fat looks yellow and lobulated; mucous glands are pale and lobulated but more noticeably vascular. Muscle is striated. Fibrous tissue is white and dry. Ossified cartilage and bone carbonize to a dominoes-like appearance. The undersurface of the strap muscles is loose and areolar.

TLM is a natural ally of combined treatment. Once the tumor is out, the locoregional microvasculature is still undisturbed—the best milieu for postoperative radiotherapy. And complete three-dimensional resection under the microscope has minimized the chances of a positive margin.

During the weeks after TLM, the endolaryngeal wound heals by secondary intention (in many ways similar to a tonsil bed). The framework resists stenosis because it remains intact. The thermal damage from laser resection is superficial (after electrocautery, it is deeper). No local flaps are mobilized or transposed, so there is no chance to bury residual tumor. "Second look" endoscopies become a meaningful way to revisit the primary site.

Months later, persistent granulation may signal the need for endoscopic removal, to improve voice. Follow-up laryngoscopy also allows the removal of small, ossified cartilage sequestra, which sometimes develop after laser resection has been carried down to the framework. Reepithelialization seems to forecast recovery but does not completely eliminate all risk of recurrence. Not even a negative second look excludes later recurrence. An overhanging anterior glottic scar may hide an unsuspected nubbin of residual tumor—still a salvageable circumstance, by simple laser resection, if discovered in time by this tactic. Before recommending TLM, discuss the willingness of the patient to return for a "second look."

Instrumentation and Techniques of Transoral Laser Microsurgery

Instruments

We use a floor-model CO_2 laser console that can generate an output beam of 1 to 50 W or a hand-held hollow CO_2 fiber (Omni-Guide). The latter device permits some cutting at angles. Two modes, pulsed and continuous, are possible. Pulsed mode produces the fastest vaporization and the least adjacent thermal injury—the least char, hence the best clear recognition of the texture at the cut surface. But any vessel larger than an arteriole will bleed, and the bleeding must be arrested with electrocautery. Pulsed mode at low power (2-3 W) is ideal for glottic mucosa. One can maintain control over the cut (working slowly), avoid collateral heat (especially unintended thermal injury to the anterior commissure), and also avoid a "hole" of unintended depth (by pausing). For most normal laryngeal incisions, we use continuous mode at around 6 W of power. This setting provides excellent hemostasis but not enough char to upset the pathologists. Most mucosa bleeds too much in pulsed mode. Continuous mode results in a little more coagulation (about 50 to 100 µm).

The overall spectrum of power in laryngeal work is wide—1 W (focused, pulsed mode, for fine cutting of cordal mucosa), to 20 W (defocused, continuous mode, to vaporize friable semi necrotic centers inside bulky cancer, one of the few justifications for vaporization).

Besides mode and power, four more variables influence the effect:

- Speed: How quickly one moves the beam. Thermal transmission takes some time.
- Focus: Defocus the beam to create a superficial cautery effect but turn up the power, especially for broad forward advancement. Defocusing reduces the density of the power.
- Target tissue: Normal tissue (moist, not running wet) cuts best. Wet tissue (fluid is visible) cuts slowly, with a lot of thermal artifact from the boiling that has to take place first.

- Bleeding: Flowing blood stops laser surgery cold. It has to be ended (with electrocautery) before the excision can continue. Bleeding tissue just takes refuge under an expanding black char ball. Paradoxically, a beam set for the least char may impose the greatest char, by requiring the use of electrocautery.

An articulated arm brings the laser beam to the microscope body. From here we direct it with the joystick on a Sharplan Acuspot 712 micromanipulator. The frame of the micromanipulator bears a gimbaled half-silvered mirror through which we see the target and with which we manipulate the laser beam. The narrowness of the micromanipulator frame is important. Anything wider than the microscope body will conflict with the introduction of instruments (22 to 23 cm long). Unimpeded maneuvering and hemostasis at the primary site demand a clear path alongside the microscope for the grasping forceps and suction cautery tubes.

If the hollow Omni-Guide CO_2 fiber is preferred, the micromanipulator can be removed from the microscope granting greater visibility and increasing the working space. The company can provide both straight and angled introducing fiber carriers. Occasionally we use both the micromanipulator (for precise tremor-free work) and the fiber.

The CO_2 cutting beam is invisible, at 10,600 nm (far infrared). The wavelength of visible light is 400 nm (violet) to 700 nm (red). The surgeon observes a red spot on the target produced by an integral red Helium Neon (HeNe) beam at 632.8 nm (visible red). A video camera is mounted on the microscope as in otologic microsurgery. A monitor displays the operative field, so the operating room nurses can anticipate and assist.

More than anything else, laser microresection requires sophisticated skills in direct laryngoscopy. Much of this is experience, but part of it is an understanding of the laryngoscopes. Narrow tubular endoscopes (i.e., narrow side-to-side) overcome difficult exposure best. The tongue is incompressible (a fluid) and confined by the arch of the mandible. It can only be distorted. Wherever the scope contacts the tongue, it employs strong pressure and deforms it such that a straight path to the anterior commissure results. The narrower an endoscope, the more it can sink into the tongue, and the more the tongue can squeeze around the sides.

A narrow vertically oval instrument like the Hollinger anterior commissure laryngoscope is the optimal tool to overcome difficult anterior visualization. But a narrow monocular laryngoscope is too narrow to accommodate the side-by-side dual optical pathways of an operating microscope. A Dedo anterior commissure laryngoscope overcomes this limitation. It provides just barely enough width to accommodate a microscope. The Zeitels Endocraft laryngoscope[70] maintains this advantage and adds a useful tip enhancement for glottic work—less bevel. A blunt tip is better for holding aside the false cords. Regular tips actually cover the anterior commissure by the time the rest of the barrel reaches distal enough to lateralize the false cords. Zeitels' scope also features proximal slots along the sides to improve access for the instruments. Special modifications load both the Dedo and the Zeitels instruments with extra light and need extra suctions carriers. Laser plume is the most troublesome limitation to clear vision during TLM, so the optimum allocation of suctions is important.

Storz and colleagues[66,67] have developed a specific assortment of laryngoscopes for TLM. Their standard adult laser laryngoscope (8661 CN) has a dome-shaped cross-section, a lip at the tip (anterior commissure), and an unobtrusive suction channel incorporated into the upper wall of the blade and the handle. For larger tumors, distending laryngoscopes are the best. Two we have considered indispensable are the Weerda distending operating laryngoscope (8588 L) and the Weerda/Rudert distending supraglottiscope (8588 E). These instruments are wider, independently adjustable, and fitted with great suction tubes. The upper blade features flare at the side to help hold the tongue out of the way. The lower blade mounts on a strong left proximal C arch (8588 L) or a strong ring (8588 E) to provide minimal encroachment on instrument access.

The best vallecular laryngoscope is probably the Lindholm instrument (8587 A). The essential laser laryngoscopes for difficult access and subglottic access are the Steiner models. These are long and thin. The "half dome" subglottiscope (8661 DN) sinks into a large tongue the best, and the suction channel is incorporated into the handle. The flat-bodied subglottiscope (8661 E) gets past prominent incisor teeth the best, and a separate suction can be clipped.

We protect the incisors by fashioning a custom splint of heated Aquaplast (PS-1685), a thermoplastic substance that sets to a hard stable cap and diffuses the pressure over five or six teeth (WFR/Aquaplast Corp., Wyckoff, N.J.). Sometimes we provide external counterpressure to the larynx with a band of tape across the table to provide downward pressure to the larynx.

You can never have too much suction for plume evacuation—suction tubes on the laryngoscopes, suction tubes on the grasping instruments, suction in the insulated cautery, and plain dedicated suction tubes. Support each one with a separate suction line. Then add special suction tubes for blood. We prefer plain suction tubes for cleanup and gentle tissue manipulation and insulated suction-cautery tubes for flowing blood (two of each). Insulated (model 8606) suction cauteries come in various diameters—the insulation is necessary to prevent them from sparking out to the endoscope. Prevent suction trauma (and worse, sticking to a friable specimen and tearing it) with a small relief hole in the tubing or at the sucker tip. We recommend at least three separate suction lines per case.

Larger vessels sometimes require something more targeted than suction cautery. Insulated model 8663 alligator forceps will pick up a small bleeder around a corner for electrocoagulation. Control the lateral vascular pedicles coming into the supraglottis with insulated MicroFrance CE 0459 bipolar cautery-forceps (specify 22.5-cm length). Place titanium clips on named arteries such as the superior laryngeal and the anterior cricothyroid arteries. Delayed secondary hemorrhage would be a formidable complication in a patient with no tracheotomy. Stop this problem before it arises by using laryngeal vascular clip applicators (model 8665 works well).

Bouchayer fenestrated forceps (8662 R or L) are excellent grasping instruments for small cordal specimens. But to secure the grip we need on the larger specimens we manipulate in TLM, normal laryngeal microinstruments are too delicate. Saw-tooth grasping forceps meet the need. Use one (model 8662 EL, FL, GL, or HL) to maintain a stable grip on tumor subunits. Use two to advance by double grasping. The L denotes a suction channel.

Controlled resection is only as certain as the stability we create for the micromanipulator. A rock-steady microscope stand, like a Universal S3, serves our Zeiss OPMI 111 well. Reduce the wrist and finger movements you transmit to the system with adjustable armrest stabilizers on a pneumatic chair (like the Möller-Wedel Combisit E). Adjust the microscope and the patient to a comfortable position for you (as in otologic microsurgery) instead of the other way around.

During TLM, operating laryngoscopes require frequent redirection. This is why a rack-and-pinion chest table (like the Storz Göttingen model) is worthwhile. It permits efficient breakdown and redirection of the suspension system, which affords the operator the opportunity to quickly re-establish a different stable vantage point several times per case. Coupled with table-height and tilt adjustment (controlled from the head end of the table too), the operator can repeatedly re-establish the optimal line of sight.

Techniques

To enhance endoscopic exposure of the anterior commissure, one can laser-transect the ventricular bands (i.e., the inferior free margin of the false cord or upper lip of the ventricle) from their anterior anchorage on the framework of the larynx. But this diminishes the contribution undisturbed false cord tissues might have made to voice (exposure of the anterior commissure for lasering presupposes that the anterior glottic contribution to voice will be lost).

Do not rely completely on the pathologist. Study the mucosal margin around the tumor yourself. The operator enjoys the advantage over the pathologist when it comes to dodging a falsely negative margin reading. The pathologist will only see some of the margin—a rolled edge, with its telltale vascular network empty and collapsed. The surgeon gets to view the living margin under brilliant illumination, extended by traction, and further described by its vascular patterning.

Once beneath the mucosa, follow the cancer in an orderly way. Use your knowledge of cross-sectional anatomy. Use the telescopes to inspect beyond the tumor. Use the power of laser surgery to resect one piece at a time and maintain constant orientation. Replace finger palpation with instrument palpation. Pull the tumor into the field with grasping forceps. Finish an area before changing the tension and exposure in favor of another.

For laryngeal cancers that we choose to remove in sections, the plan of TLM is to complete each subresection a block (or view) at a time. Use transection at the edge of the field to find the healthy tissue plane and deliver all the cancer that will be taken in that established view. Tumor transection defines the plane of separation from the rest of the cancer. Consider marking it with ink. This surface will be the plane we need to place within the next view we "capture," to maintain a continuous resection. Like a Rubik's cube, as each new tumor subcomponent is delivered, an adjacent component becomes more accessible.

As each subunit is resected, three obligations are paramount:

1. Maintain continuous orientation to the cancer. Recognize what has been completed and what next to expose. Know what remains to be done.

2. Orient the resected specimen for the pathologist. The deep margin is the margin of interest, not the margin released from the rest of the tumor, which is known to be cancerous. It usually remains unmarked or bears the specific color we use to designate tumor transection surfaces.

3. Ink the deep surface margins and the peripheral margins, which are expected to be negative, with the previously agreed on study color (usually blue).

Any time TLM is applied to intermediate or advanced cancer, some patients will present with significant disease in the subglottic larynx. This can be a challenging location for exposure. Among the most helpful ploys are a small endotracheal tube, proper choice of the endoscopes, top-to-bottom sequencing of the resection, and special positioning of the larynx. Tip the larynx up by elevating the thyroid cartilage with the laryngoscope blade and depress the cricoid with cross-table taping. Most patients with subglottic cancer have glottic cancer. Excise the glottic component first and exposure is automatically improved for the subglottic disease. When cancer descends to the inferior margin of the thyroid cartilage, include the cartilage margin itself in the resection. It is possible to encounter (and recognize) the Delphian node when laser resections extend forward through the lower margin of the thyroid cartilage. Resection with the cricothyroid soft tissues provides an opportune method to identify an important mode of extralaryngeal nodal spread, a finding that usually calls for further treatment of the nodes in the neck.[70] Laser resection and histopathologic study of the Delphian node should probably be a routine part of any significant subglottic resection.

TLM is not just a simple combination of already familiar techniques. It forces us to reconsider the detailed anatomy of the larynx—to learn it "inside out." Otolaryngologists introducing TLM into their practice should watch someone do it. Take a course. Be prepared to train an assistant and a scrub nurse too. If facilities permit, fresh frozen cadaver dissection has merit. Some of the goals would be to distinguish the greater horn of the hyoid versus the upper edge and cornu of thyroid cartilage, the preepiglottic fat versus the glands around the ventricle, the distribution of the superior laryngeal artery and its main branches,[26] the form and attachments of the conus elasticus, and other parts of the neck.

If you biopsy a cancer at a separate sitting, use this opportunity to evaluate your preparedness and equipment for TLM. Determine whether your exposure will be adequate. When it comes to making the transition from study and observation to practice and application, start with small cancers and edentulous patients, the easiest to expose. Then work your way up.

Pathology Issues

TLM tends to be a "one-surgeon" operation. But it is by no means a one-doctor operation. An interested, enthusiastic, and involved frozen-section pathologist is an essential partner. Multiple specimen blocks require mutual understanding and clear communication. The step-section technique works nicely for a single block (like a T1a glottic specimen). It is not appropriate for the usual multiblock TLM case.[2]

When a tumor has been subdivided in situ, as already noted in this chapter, not all raw borders are margins. We have outlined one way to ink the margin in question on the specimen (Davidson Marking System). Another is to cut separate margin specimens from the wound. You may be surprised at how easily a specimen becomes disoriented. Orientation is often lost by the time the specimen reaches the lips! If you want the pathologist to work from the primary specimen itself, ink the margin in situ before the specimen is detached. In complex resections, ink the site of detachment, too, so that the subsequent readings will be easier to track. If you prefer, cut specific separate margin specimens from the wound. Then all the pathologist has to do is evaluate the entire submitted specimen. Is it yes or no? Is tumor present or not? The surgeon's responsibility is to avoid three errors—errors of sampling, errors of communication, and errors of identification. Sampling is the art of providing a dead specimen and getting the pathologist to tell you what will happen with the adjacent living tissue still present in the patient. Communication means providing the pathologist with key information, like whether the patient was irradiated before. Identification means keeping track of the sites of the sources of the biopsies. Use hemo clips, maps, lists, and inks of different colors. Number the specimens and link them to a map or a color. Make sure you and the cytopathologist share the same site names.

Transoral Laser Microsurgery in Relation to Each of the Five Clinical Categories of Laryngeal Cancer

Very Early Laryngeal Cancer

Very early laryngeal cancers provide a good initiation to laser laryngology, but the laser is just a "stand-in" for microforceps and cautery with little tangible advantage. Expert laryngologists commonly cure midcordal T1a glottic lesions by transoral laser excision. But all they perform is a simple excisional biopsy. Suspension microlaryngoscopy is a key asset. But the secret to the high cure rate in "very early" cancer is patient selection, skillful laryngoscopic exposure, careful en bloc excision, and negative margins. The advantage lies not with a laser, but with the nature of the disease. Very early glottic cancers are an exceptional neoplasm, being small, localized, and off the anterior commissure. No new principles were really required and no old principles were really challenged.

Early Laryngeal Cancer

"Early" laryngeal cancer comprises two groups, loosely similar to previously untreated T1B and T2A glottic cancer and previously untreated T1 supraglottic cancer: (1) glottic cases falling within the purview of an open vertical partial laryngectomy and (2) supraglottic cases falling within the boundaries of a supraglottic laryngectomy.

Transoral laser microresection clearly meets or exceeds expectations in early laryngeal cancer:

- The cure rate matches the open operations (vertical partials and supraglottics) while the morbidity and functional losses decline.[67]

- TLM does not require a temporary tracheotomy to treat early cancer. Hospital time contracts to 3 days[72] and costs fall.[73]

- Radiotherapy may outperform open VPL for voice in early glottic cancer, but only if cure is obtained. TLM provides the same high cure rate of VPL, but a better voice than VPL.[74] The major advantages of TLM relate to the efficiency of cure (obtained with only one treatment) and speed of completion (treatment is finished at the

same direct laryngoscopy and biopsy the patient would require to start radiation treatment).

- Radiotherapy may surpass open supraglottic laryngectomy (HSL) in resisting aspiration (but it loses on cure and efficiency). TLM preserves better swallowing[75] than HSL and, unlike radiotherapy, requires no diminution of lubrication or taste.

- Over a lifetime, up to 25% of laryngeal cancer patients develop a second cancer.[76] Half involve the upper aerodigestive system. Patients who opted for TLM retain every possible option for the second cancer (including radiotherapy and laser surgery). Patients who accepted radiotherapy—and even prevailed—have narrowed their de facto future options to surgery in an irradiated field.

The conduct of TLM in early laryngeal cancer proceeds as follows. Intubate for general anesthesia with a small laser-approved endotracheal tube. (To minimize trauma, consider doing it yourself.) Our tubes have two balloons filled with water. Set up the laser for parfocal operation, for the smallest microspot (0.25 mm), and for continuous mode. Ask for 3 W power if you are a beginning laser surgeon, more as you learn to work faster. Establish the initial laryngoscopic exposure and the video image. Protect the face with a wet towel.

For early glottic cancer, use the laser, retract with suction, and outline the tumor margins. Then subdivide the lesion into a "middle plus anterior" and a "posterior" subunit.[66] Identify the depth of infiltration into the thyroarytenoid muscle and the extent onto the arytenoid. Laser-resect the posterior block. Resuspend the laryngoscope and transect the remaining tumor between the "middle" and "anterior" block. Laser-resect the middle block so that all that remains is the front. Reconfirm the depth by frozen section. Finally, reposition the laryngoscope and resect the anterior block. Traction with Bouchayer forceps works well to clarify the resection line at the anterior commissure.

In anterior commissure cancer, the voice is usually bad due to the disease. Voice after TLM for anterior commissure cancer is usually no worse.[72] However, the mechanism is different. Extensive resection of anterior commissure/anterior glottic cancers changes the glottis to a keyhole shape. It also bares the inner aspect of the thyroid cartilage. Healing on the inner aspect of cartilage will produce thin mucosa on a solid base, cartilage or fibrous scar with tethered restriction points. Thus we obtain stiffness. And stiffness produces hoarseness. Also, the intact thyroid cartilage will brace open the defect to produce an anterior glottic gap. And a gap produces breathiness.

In some cases, breathiness can be reduced with phonosurgery (e.g., cartilage implantation[77]) to reduce the anterior glottic gap. The correction of hoarseness caused by stiffness awaits future advances. The principal strategy now is the intelligent preservation of uninvolved tissues and the avoidance of unnecessary desiccation of the normal tissues left behind (TLM preserves glandular elements better than radiotherapy).

For early supraglottic cancer (confined to the supraglottis—the glottis and both arytenoids are free), split the suprahyoid epiglottis[78,79] vertically in the midline (even if this transects cancer crossing the midline). Identify the hyoid bone. Cut the vallecula and expose more hyoid to each side. Pass down the thyrohyoid membrane and clearly identify the upper margin of the thyroid cartilage. Plan to capture the bilateral supraglottic vascular pedicles with insulated grasping forceps or the bipolar cautery forceps. In most cases, it is prudent to clip (with two or three hemoclips) the internal branch of the superior laryngeal artery. Resect suprahyoid tissues before infrahyoid tissues, in planned subsections, proximal to distal. Above the plane of the thyroid alar margin, you will not harm the glottis. Below this plane, improve your access and vision by having resected all of the suprahyoid tissues on both sides. When resecting the false cords, take advantage of the angled suction protectors (model 8596) to shield the vocal cords. Insert the "baffle" into the ventricle or above the anterior commissure. In every supraglottic case, the surgeon should work to resect all of the preepiglottic space.

Intermediate Laryngeal Cancer

Earlier we defined "intermediate" laryngeal cancer to be one that would require SCPL to be encompassed by an open operation. Most "intermediate" glottic or supraglottic cancers can be treated by laser microresection, open SCPL, or radiation with surgical salvage. The problem with radiation and salvage is that intermediate cancers that fail radiotherapy are not cured by conservation operations. SCPL has a better record of local control,[24,80] but patient selection and surgical execution require tremendous sophistication. SCPL pushes function to the limit—it is probably the most extensive open resection one can do and still restore swallowing and an internalized airway (i.e., the tracheotomy is temporary).

Experience refutes the allegation that TLM cannot encompass intermediate cancers. When an anterior commissure lesion is too big for a vertical partial (but too mobile for a near total or total laryngectomy),[72] TLM provides a logical resection. TLM clearly rivals open SCPL for functional results. The morbidity is more than we see after TLM for early cancer, but clearly less than we expect after open SCPL for intermediate cancer.[81] Case selection may be more forgiving than it is for open SCPL because of the intraoperative diagnostic advantage of TLM.

Full exposure of intermediate cancer is only slightly more difficult than for early cancer. The larger challenge is continuity and orientation. Start with early cases to master exposure. Then progress to intermediate cases and the greater manipulative and directional tests they offer. Intermediate anterior glottic cancers typically involve the thyroid cartilage but spare the arytenoids. Of course, anterior laryngeal resections can include large pieces of the thyroid cartilage and the subglottis. Ossified framework can be devitalized with heat and outlined for endoscopic resection with Jackson laryngeal scissors (Pilling).

If motion on one side of the anterior glottis is at all impaired (T2b), look for extraconical cancer during TLM. And bear in mind that once external to the conus, the tumor descends to escape outside the larynx (through the cricothyroid triangle).[82] Borders of the cricothyroid triangle are the inferior margin of the thyroid cartilage, the lateral edge of the cricothyroid ligament, and the medial border of the cricothyroid muscle. An "intermediate" cancer found to extend outside the larynx can be managed by TLM. However, early in one's experience it might be better to open the neck and permit the formal resection of, say, a near-total laryngectomy, which includes strap muscles and the thyroid isthmus and lobe.[83] The price is the permanent stoma that accompanies NTL, but this is better than recurrent cancer.

TLM can also treat T_2 supraglottic cancers if the reason for "T_2" is invasion of the glottis or the medial pyriform wall. Once, a total laryngectomy was rationalized in these cases (by the notion that the tumor exceeded the limits of a supraglottic laryngectomy). That was why SCPL was a real advance. When TLM is feasible for T_2 supraglottic cancer, TLM becomes the next advance. Note that the patient undergoing TLM for intermediate cancer reaps the additional benefit of continuing diagnosis. Under brilliant magnification and stable exposure, little extensions of unexpected cancer[84] are likely to be recognized and removed. So are erythroplasia and keratosis, future sites of origin of the next cancer. When TLM cannot be done for intermediate cancer, the attempt to perform a laser excision may demonstrate why transoral laser and open SCPL are both unsafe (in that patient).

Intermediate TLM risks glottic stenosis. The maximum safe preservation of intralaryngeal mucosa and cricoid cartilage resists it. Preemptive suppression of reflux with antacid medical regimens also makes sense. If you anticipate losing an arytenoid at TLM, do a tracheotomy at the time of the laser surgery. Take advantage of the view (no endotracheal tube) and protect (to the degree possible) the patient against initial aspiration with a cuff.

TLM may generate the most logical resection for intermediate cancer, but the wound is still left to granulate and contract by itself. Open SCPL calls for a strong cricohyoidopexy.[85] The return of swallowing after TLM implies cricoarytenoid elevation is accomplished by other means. Perhaps this is preservation of the strap muscles—no suprahyoid dissection, no circumhyoid suturing.

The risk of a fistula after TLM for intermediate laryngeal cancer is nil because the neck dissection never connects to the primary site.

Advanced Laryngeal Cancer

"Advanced" laryngeal cancers are glottic, supraglottic, transglottic, aryepiglottic, or even medial pyriform cancers distinguished by two

fundamental features: (1) permeation of the paraglottic space (therefore advanced cancers impair the motion on one side) and (2) a clearly lateralized disposition (advanced cancers seem to permeate the "hemilarynx").

The block to encompass such a cancer corresponds to a near-total laryngectomy.[83] NTL is a complete supraglottic laryngectomy plus an extended hemilaryngectomy, combined to include all of one paraglottic space and all of its contiguous neighbors (i.e., thyroid lobe and isthmus, hemicricoid, arytenoids, pyriform, anterior commissure and subglottis). However, much contralateral anterior glottis is necessary to encompass the cancer. Patients undergoing NTL retain a lung-powered voice—a prosthesis-free tracheopharyngeal fistula voice—but their stoma is permanent.

What saves these patients from being classified as "very advanced" are the following characteristics.

1. Most of the subglottic mucosa within the cricoid, certainly all of it on the "good" side, is free of cancer.

2. The contralateral ventricle is clear of cancer.

3. The contralateral vocal cord is only involved in the superficial mucosa and the most anterior glottic musculature.

4. The posterior commissure and postcricoid regions are completely clear.

To recognize patients with "advanced" laryngeal cancer, we have to be able to identify and exclude the "very advanced" cancers, for which near-total laryngectomy would not be safe. "Very advanced" means the only dependable ablative option is total laryngectomy and the preferred voice strategy is TEP. Typical "very advanced" laryngeal cancers are midline and bilateral, not lateralized. For example:

1. Massive "horseshoe" glottic/subglottic cancers (both ventricles and both muscular vocal cords are cancerous).

2. Significant subglottic cancers (generally involve the cricoid bilaterally and often present with airway obstruction).

3. Posterior commissure/postcricoid cancers (both arytenoid complexes are involved).

Near-total laryngectomy is the most logical open "block" for advanced cancers. But NTL requires a specialized lateral laryngotomy. The challenge is to enter the lumen without encountering cancer and without compromising the future speaking shunt. In many candidates, it would be easier to outline the block from within the lumen of the larynx. And the laser would be the ideal tool. More subglottic mucosa could be saved (which improves the tapered capacity of the inferior shunt—the tracheocricoid entry into the speaking shunt). More interarytenoid soft tissue could be saved (which contributes to the shunt's voicing and valving capacities). Occasionally, it might be recognized that both arytenoids were actually clear. That is, the cancer was "intermediate," not "advanced," and a logical laser supracricoid operation could be performed. This would confer an important advantage for the patient—no permanent tracheotomy.

Generally, we find "advanced" cases cannot be treated by TLM because reconstruction is required. The value of TLM lies not in complete excision, but in prereleasing the crucial tissue that really needs to be excised—this can define whether the cancer actually rises to the level of a near-total laryngectomy. Prerelease occurs with visible direction from familiar endolaryngeal landmarks, and it avoids the cancer itself. Then the surgeon can perform open delivery through the neck. No concerns about the site of entry, where the true margins lie, or where unseen submucosal cancer might extend. Perhaps the pharyngeal augmentation flap (to be turned down from the ipsilateral side to participate in the shunt[83]) can be precut with the laser as well. Voice shunt reconstruction would then be a simplified assembly with precut margins, no mucosal bleeding, and the least chance of cautery damage

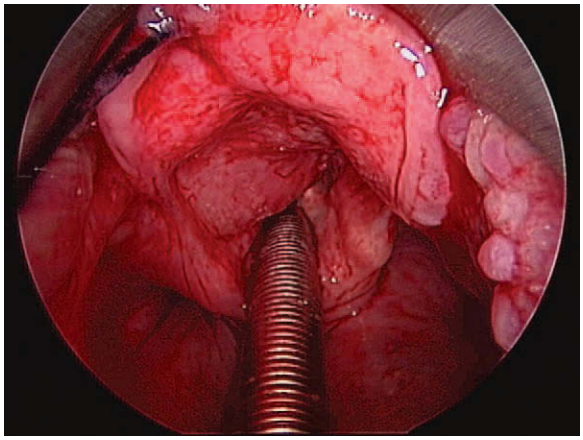

Figure 109-1. Preoperative T_4 transglottic squamous cell carcinoma (cartilage penetration).

to the nerve supply or the muscular components of the shunt. The exception is when both arytenoids and cricoarytenoid joints—or at least the posterior half of the arytenoids can be preserved. In this situation, complete tumor excision is possible via TLM, generally with acceptable functional consequences (Figs. 109-1 through 109-3).

Very Advanced Laryngeal Cancer

TLM has no apparent application in the "very advanced" category of laryngeal cancer. The exception might be the emergency treatment of neglected cancer with airway obstruction.[86]

Total Laser Microresection and Neck Dissection

The neck nodes are treated by open surgery or postoperative radiotherapy. We can carry out a neck dissection at the same sitting as TLM on the primary, but laser endoscopic surgery cancels the argument to perform a node dissection now because "the neck is already violated" (to access the primary). A better time might be weeks later. One unproven hypothesis suggests later is better because the micrometastases "in transit" at the time of the TLM will have had time to lodge in the nodes. A more practical reason would be to wait until a patient with serious comorbidities has recovered from the primary resection, or until after an elderly patient has regained swallowing after a laser supraglottic laryngectomy, or until after we know exactly what the pathologist has to say about the invasive nature of the primary cancer. Because a "second look" is possible after TLM, this might be a suitable time to operate on the deferred neck. With respect to the patient with a very low tolerance for complications, we have already mentioned that staging the primary and the neck surgery at separate sittings reduces the chance of a pharyngocutaneous fistula to zero.

Total Laser Microresection and Radiotherapy

TLM undoubtedly works best as a primary treatment. But surgeons who can offer TLM are not always consulted when the initial therapy is being selected. About half of our anterior commissure patients had already received previous treatment by the time we were called on to consider laser surgery.[72] Therefore surgeons will be confronted with patients who seek TLM for radio recurrent disease.

Prior radiotherapy complicates the planning of TLM and increases the morbidity attributable to delayed wound healing. It diminishes the accuracy of clinical judgment and the specificity of preoperative imaging. Radio recurrent cancer is often submucosal and sometimes discontinuous.[87] These factors complicate the decision to even attempt TLM. If TLM is undertaken, magnification does help disclose atypical patterns of spread. But magnification comes with its own danger—the temptation to cut normal-looking margins too close.

In our anterior commissure series,[72] 5 of 16 patients with intermediate laryngeal cancers received postoperative radiotherapy. The

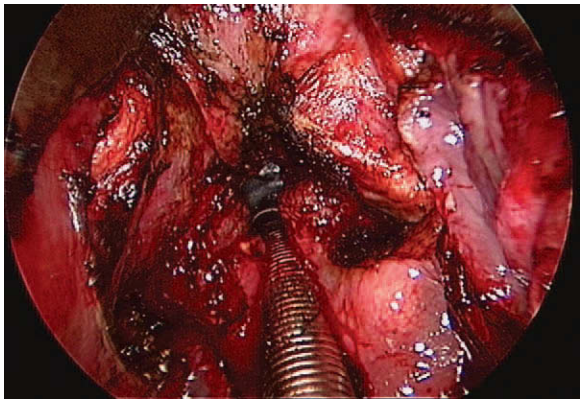

Figure 109-2. Extensive TLM resection removing left and anterior thyroid cartilage, both true vocal cords, supraglottic structures and preepiglottic space, and some strap muscle, but preserving cricoid ring and both posterior arytenoids.

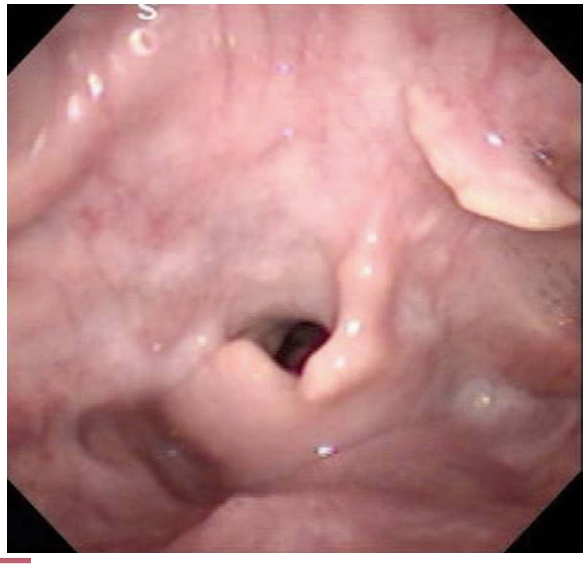

Figure 109-3. One year post-transoral laser microresection (and radiotherapy). Feeding tube has been removed and there was no tracheostomy.

indication was suspected disease in the neck, never a positive margin at the primary site. A positive margin at the laser site is an indication for further surgery, not radiotherapy.

TLM gives us a way to remove the primary without first disturbing the neck. After TLM, postoperative radiation faces the novel circumstance that no one has first disturbed the microcirculation with an open operation. Maybe the obligation to include the primary site in the radiotherapy fields is more questionable after TLM, when margins were clear and radiotherapy is being given for neck indications. TLM patients tend to heal as quickly as patients with open surgery. But more importantly, the risk of a complication (necrosis, a fistula, an infection in the neck) is diminished. Therefore TLM may be a more logical choice for the excisional component of combined therapy. Indicated radiotherapy will not likely be delayed by the prior performance of a TLM.

Complications of Transoral Laser Microresection

The complications of stray laser light include unwanted burns. Tiny pinpoint burns to normal laryngeal or pharyngeal mucosa are not rare, as the beam can easily pop the endotracheal cuff. Burns to facial skin, or worse, to the eyes or the airway are extremely rare but potentially devastating. We use small, wet precut toweling strips to cover fields beyond the target site, and angled suction protectors shield the cords. Cover the face and eyes of the patient with wet toweling after you position the laryngoscope. The microscope itself will save the operator's eyes from harm, but all other personnel need protective eyewear in the operating suite. Give the laser pedal to the surgeon (only) and the cautery pedal to the assistant (only). Control the concentration of oxygen in the airway (below 30% FiO_2), and use a double-cuffed laser endotracheal tube with saline in each cuff to maintain the seal confining the oxygen to the distal trachea.

Prolonged endoscopic displacement of the tongue causes obvious, sometimes severe, lingual contusion, swelling, and subsequent dysphagia, with or without long-term lingual dysesthesia. Chipped or loosened teeth follow difficult intubations or forceful endoscopic suspension in the dentulous patient. Sponges used to protect mucosa easily drift out of sight to be left behind when an endoscope is repositioned. Arteries can bleed voluminously into the wound in the larynx, particularly in the patient recently taking platelet inhibitors. All of these complications threaten the airway—with swelling, foreign bodies, or blood.

Many patients undergoing TLM require no tracheotomy. However, every consideration should be given to one in the intermediate and advanced cases where the role of a tracheotomy may be different. Here are some potential indications:

- To bypass expected edema from prolonged pressure on the tongue base in a lengthy case with difficult exposure.
- To bypass the specter of serious hemorrhage in the supraglottic region in the absence of airway protection.
- To avoid the impediment to exposure an endotracheal tube can pose, especially in the subglottis.
- To allow cuffed resistance to laryngotracheal aspiration in a patient with susceptible lungs.

Sudden secondary bleeding—without a tracheotomy—is probably the most dangerous risk.[88] The best treatment is avoidance: never trust the cautery to provide sustained control of a named artery (like the superior laryngeal), clip named arteries, and never trust the standard mouth guards to protect the teeth. Also, cover the upper incisors with thermosetting plastic and cool it with ice water. We use the small square of double-folded Aquaplast, the same material used to fashion rhinoplasty splints. As much as possible, the surgeon should pick up the tempo of the TLM to avoid prolonged tongue pressure. Do not be slowed down by inadequate plume suction, a weak laser beam, or a medium power beam weakened by defocusing. Learn to adjust the power and focus to the optimal settings for pace. Lengthy surgery risks tissue stasis and deep vein thromboembolism. Consider timed repositioning and apply antiembolism devices to all but the "very early" cases.

TLM imposes obvious limitations on reconstruction, but, in practice, the fact that the wound must heal by secondary intention is usually an advantage. The surface we will eventually be following in the office will be recovered by indigenous mucosa, not a skin graft, regional flap, or irradiated mucosa. This should improve our ability to monitor for local recurrence. Secondary intention healing involves contraction and granulation tissue, of course, but the preserved laryngeal framework does a surprisingly good job resisting contraction and stenosis is not common. Beware the patient with reflux. Reflux slows healing, which encourages fibrous stenosis. Be prepared to give proton-pump inhibiting medications on minimal evidence. Leaving the wound unreconstructed may yield two additional benefits: free cancer cells (if any) will fall on a slightly more inhospitable surface than the one we "bury" by reconstruction in open operations; and, at a future date, not having buried that surface, we preserve the possibility of a second chance through the discovery of persistent cancer at a "second look."

Whenever the inner surface of the cartilage is exposed by TLM, a sizeable granuloma is almost inevitable. Small osseocartilaginous sequestrae will perpetuate a granuloma until they are removed. At the anterior commissure, extensive resection leads to a rounded open anterior glottic defect. The opening produces breathiness. The walls consist of thin new mucosa, directly applied to the cartilage. The stiffness begets hoarseness. Prevention involves the optimal preservation of laryngeal mucosa,[89] plus the recognition and removal of any cartilage that undergoes laser thermal devitalization. Treatment of the breathiness draws on one's phonosurgical experience.[77] The stiffness is so far resistant to intervention.

TLM incurs new expenses. The institution incurs new costs, for training and equipment, and increased demands are made on the cytotechnicians and frozen-section pathologists. Some patients require a "second look" laryngoscopy (a few patients require more than one "second look"). Other patients will seek phonosurgical procedures (Fig. 109-4A and B). Some patients will receive postoperative radiotherapy (but their indications will be the same as in open surgery, so this cannot be considered an extra cost). TLM requires more travel for some patients because of its limited availability in the United States (although travel for radiotherapy is also common, and the time required away is considerably longer). Despite these extra costs, TLM reduces costs considerably.[72,73] Unfortunately, in practice, many patients do not receive TLM until after they have already incurred the expense of a previous therapy (that has failed). If TLM gains broader acceptance as an initial option, the potential for expense reduction may further improve.

TLM is a more difficult skill to transfer to the residents than is open surgery. The subtleties of orientation defer the assignment of part to the resident, part to the consultant. TLM tends to be a one-person, start-to-finish operation. There is not the usual sharing of duties possible with open surgery or the formal laboratory experience familiar to ear surgeons who prepared themselves on the temporal bone. TLM requires new judgment from laryngeal surgeons with respect to case selection and more advanced skills in laryngeal endoscopy because of the challenges of proper exposure. There are additional procedures to master including second-look direct laryngoscopies, new phonosurgical procedures, and the artful management of the complications noted earlier.

Contraindications to Transoral Laser Microresection

Extensive tumor spread to the neck (e.g., great vessels, esophagus, thyroid gland) is an absolute contraindication to TLM. So is inability to expose (with caveats if the upper teeth are the only impediment). The patient might consider the extraction of (carious) teeth, especially if it might save an open approach and a separate dental charge. Radiotherapists advise patients who have cancer to have pretreatment extractions. Preparation would include receiving patient consent and the taking of a dental impression.

TLM should not be advised for unresectable cancer, advanced cancer needing reconstruction, patients with functional disorders after extensive partial resections (like severe persistent aspiration or secondary stenosis), or the patient with overwhelming comorbidities. TLM is not very successful in any palliative role. It will usually prove unhelpful at the primary site in a patient with an N_3 neck or distant metastasis. A fixed (not impaired) cord is a relative contraindication to TLM, as is recurrent cancer in an irradiated "bed."

TLM has the potential to attract more patients with unrealistic expectations (e.g., those with advanced or very advanced laryngeal cancer after chemoradiation failure) or patients with major systemic comorbidities hoping to avoid a needed open operation for cancers that are advanced or very advanced. Sometimes a patient seeking TLM has built up too much faith in "the laser myth" while denying the realities of his or her predicament. TLM cannot repair tissues or functions already lost to cancer, radiotherapy, or previous surgery. It cannot restore tissues currently compromised by cancer. TLM cannot bring back lubrication, it will not reverse soft tissue or chondro-osseous necrosis, and it does not improve edema or painful soft tissue induration after radiotherapy.

Results of Transoral Laser Microresection

After an open operation or radiotherapy, laryngeal cancer reappearing at the original site is properly designated as "local persistence" or "recurrence." Local recurrence is disease that reappears after the initial treatment program has been completed. In TLM a "second look" is often a planned second phase of treatment. The discovery of residual cancer

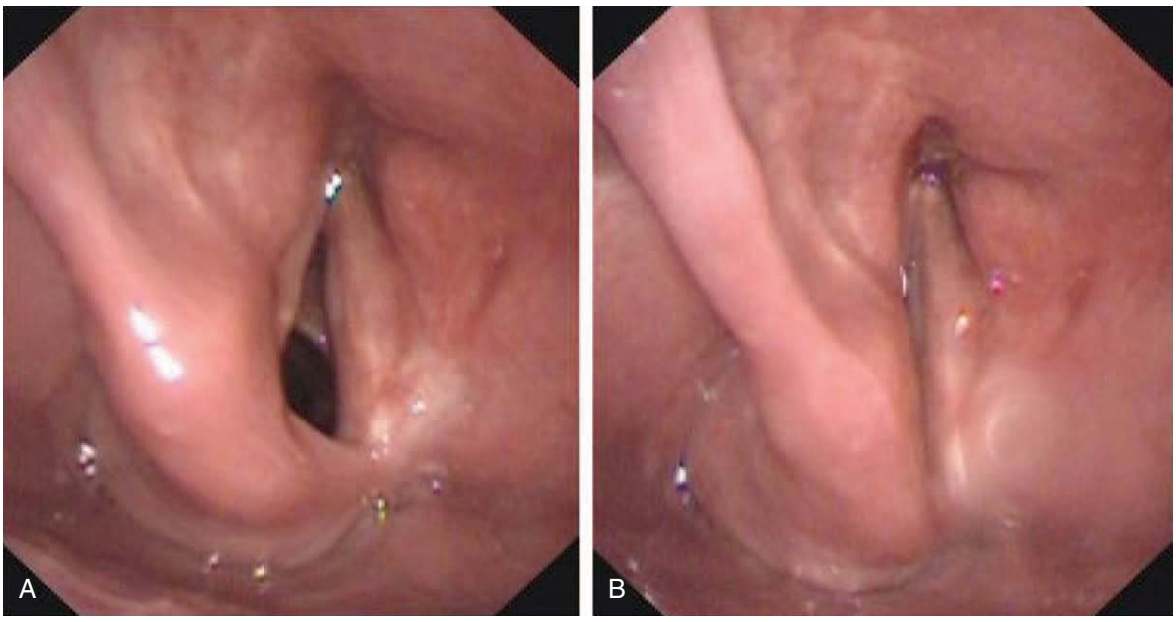

Figure 109-4. **A,** Open view of post-transoral laser microresection larynx for T_3 (fixed R true vocal cord requiring removal of right arytenoid) after open phonosurgical reconstruction (Gortex). **B,** Closed view. Patient does not use a feeding tube.

amenable to cure by laser resection at the time of the second look should not be listed as "local persistence" or "recurrence." These are diagnoses one would logically withhold until after a second-look strategy has been completed (or after one has been refused). This convention would be similar to the standard for chemotherapy, where persistent cancer at the primary site is not considered a failure if only the first cycle has been given.

In our recent publication on TLM for advanced laryngeal cancer the results of 117 patients were presented. These results were compared with the chemotherapy and concurrent radiotherapy and the radiotherapy-only arms of the RTOG 91-11 study.[90] The overall and T stages were similar with fewer T2s in the TLM group (8% vs. 12%). In the TLM series, at 2 years the percentage of patients with an intact larynx after treatment was 92%. The 2-year local control and locoregional control rates were 82% and 77%, respectively. The 2-year disease-free and overall survival rates were 68% and 75%, respectively. The 5-year Kaplan-Meier estimates were local control, 74%; locoregional control, 68%; disease-free survival, 58%; and overall survival, 55%. Most patients in our series did not receive adjuvant radiotherapy. These results compare favorably with those published in the RTOG 91-11 trial.[91] We concluded that TLM with or without adjuvant radiotherapy is a valid treatment for select advanced staged laryngeal cancers.

Göttingen Group Results

After first observing TLM by Wolfgang Steiner and Petra Ambrosch in 1996, and later by Heinrich Rudert in Kiel, Germany, the authors attempted to emulate these techniques in their own practices. Around that time, a comprehensive report on the results of TLM was given by Steiner and his colleagues at the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) in Budapest. Because many North American laryngologists remain unfamiliar with this important presentation and, because our own combined experience in more than 900 TLM patients seems congruent with this original work, we have tried to summarize Steiner's data here.

His reports were based on 606 patients treated from 1979 to 1986 in Erlangen-Nurnberg or 1986 to 1993 in Göttingen. The last Erlangen entry was in January 1994, and the last Göttingen entry was in December 1995. The only exclusions were patients with simultaneous second primary cancers, thus not treatable for cure. Of the patients, 360 had early glottic cancer, 43 had early supraglottic disease, 147 had late glottic carcinoma, and 56 had late supraglottic cancer. The T distributions were pT_{is}; 45 patients, pT_1; 228 patients, pT_2; 231 patients, pT3; 69 patients and pT4; 33 patients. As might be expected, the T_{is} and T_{1a} cases did extremely well and will receive no further comment.

Attempting to reclassify all of Steiner's glottic cases as "very early" (pT_{is} or pT_{1a} for 236 patients) and "early" (pT_{1b} pT_{2a} for 124 patients), there were 18 recurrences (15%) in the 124 "early" cases. Among the 26 pT_{1b} glottic cancer patients, 5 local tumors recurred. Of the 98 patients with pT_{2a} glottic cancers, 13 experienced recurrences. Combining the very early and early patients, there were 35 recurrent cancers among 360 TLMs. Of these 35 recurrences, 5 occurred more than 5 years after initial treatment (thus possibly were second primaries).

Of the 35 patients, 27 were salvaged by functional surgery, mainly by transoral laser microreresection. Eight patients proceeded to laryngectomy. Of the 360 (0.5%), 2 died from the glottic cancer. Six developed neck metastases, three with their primary controlled and three with recurrent cancer at the primary site. During the course of their follow-up, 23 patients (6.4%) developed second primaries and 16 (5%) died of their second primary. The commonest cause of death in the whole group was intercurrent disease—64 patients (17.5%). The 5-year Kaplan-Meier survivals were 87% for the "very early" glottic group and 83% for the "early" cases. TLM preserved voice in 352 of the 360 patients (98%) and was judged to be of satisfactory quality in 90%. One patient bled. No one needed a tracheotomy.

Steiner reported 43 previously untreated patients with supraglottic cancers. Of these, 18 (42%) underwent TLM to the primary only. Of the 43 patients, 23 (53%) also had open surgery on their neck. Two (5%) received postoperative radiotherapy. Again, trying to apply our clinical definitions to Steiner's supraglottic cases, we judged none to be "very early," 10 to be "early," and 33 to be "intermediate." Only four (9.5%) developed a local recurrence (or second primary) within 5 years, and three of these were salvaged by functional operations (one open supraglottic laryngectomy and two transoral laser reresections). No patients lost their larynx. Five (12%) died from their supraglottic cancer—one who refused treatment of a local recurrence, one who was never controlled in the neck, and three with distant metastases. In addition, five (11.3%) developed second primaries, two (5%) ultimately fatal. Six supraglottic patients (14%) died of intercurrent disease, while in one patient the cause of death was unknown. As in the glottic cancer patients, intercurrent disease placed ahead of laryngeal cancer as a cause of death. The 5-year Kaplan-Meier overall survival was 73%.

Of the 43 patients undergoing laser supraglottic resection, 36 (84%) required a feeding tube. One received a tracheotomy at the time of the laser surgery, and one needed a tracheotomy postoperatively. Two patients with dyspnea (5%) required assistance, including one of the temporary tracheotomies. The other was managed by lasering. Two with aspiration required treatment, one by tracheotomy to allow a cuffed tube and the other by conservative means. Two patients (5%) had bleeding, and one of these had to be returned to surgery for cautery under general anesthesia.

TLM was used for glottic cancer staged T_{2b} and above in 147 patients in Steiner's report. There were 93 pT_{2b} glottic cancers, 40 pT_3, and 14 pT_4. Using our clinical classification, this was about 93 early or intermediate and 54 intermediate or advanced. Ninety (61%) were TNM stage 2, 38 (26%) stage 3, and 19 (13%) stage 4. Ninety-five (65%) of the 147 glottic patients received laser treatment of the primary (only). Thirty-two (22%) were treated with TLM at the primary site plus open surgery in the neck. Four more (3%) underwent TLM and radiotherapy. Eight (5%) had laser microresection, neck surgery, and postoperative radiotherapy. All in all, 40 patients (27% of the "T_{2b} and above" glottic cancer patients) underwent neck dissections, mainly selective dissections of levels 2 and 3. Twenty patients (14%) received radiotherapy after surgery.

Among the 147 patients treated by TLM for early/intermediate/advanced glottic cancer, there were 45 local recurrences (including possible second primaries). The 5-year Kaplan-Meier survival overall was 59%. During 40 months, the recurrence rates broken out by clinical stage ran as follows: 28 of the 93 patients with early and intermediate glottic cancer and 17 of the 54 intermediate to advanced. Seven patients developed neck metastases in addition to their recurrence at the primary site. One grew nodal disease without a primary recurrence. Three (2%) patients acquired distant metastases.

In the entire 147 patients undergoing TLM for T_{1b} early or T_2 intermediate or T_3 advanced glottic cancer, 45 developed local recurrences. In 21, this led to a total laryngectomy, 8 of whom also received postoperative radiotherapy. Four patients received open vertical partial laryngectomies. Ten were salvaged by TLM, and six more were salvaged by TLM and radiotherapy. Four of the patients who developed local recurrences received palliative care only. Thirteen of the 93 early/intermediate cases and 12 of the 54 patients with intermediate/advanced cancer died from their glottic disease. Thus 25 of the 147 patients (17%) with larger tumors died. Only 11 of the 25 died of local/locoregional recurrence. One died from regional recurrence alone, and 13 died from distant metastases. The number of second primaries was 14 (9.5%), with only 1 in the head and neck. Ten patients (7%) died of a second primary and 29 (20%) died of intercurrent disease. Once again, intercurrent disease beat glottic cancer treated by TLM as the cause of death in these patients.

Steiner's report to EUFOS included 56 patients with higher TNM stage supraglottic cancer. One had pT_1 local disease, 7 had pT_2, 29 had pT_3, and 19 had pT_4. Therefore 48 of 56 patients had pT_3 or pT_4 supraglottic cancer. Eight (14%) underwent only TLM. One (2%) had TLM and radiotherapy. Of the 56 supraglottic TLM patients, 47 (84%) also received neck surgery, mainly of selective dissection of levels II and III. Twenty six (46%) had neck surgery only; 21 (37.5%) had postoperative radiotherapy as well. In the whole group of 56

patients with higher-stage supraglottic cancer, 22 (39%) had radiotherapy after surgery. Of the 56, 11 (19.5%) developed local recurrences (or second primaries). Eleven patients developed neck metastases, five with their primary controlled and six with recurrence at the primary site (locoregional recurrence). Of these, three also developed distant metastases.

No local recurrence was salvaged with an open partial laryngectomy. Three were salvaged with radiotherapy and six patients required a total laryngectomy. Two also received postoperative radiotherapy. Two patients with recurrence received palliative treatment only. The overall 5-year Kaplan-Meier survival for these patients with higher-stage supraglottic cancer (where the primary was treated by TLM) was 50%.

In Steiner's 1996 series, 48 patients had pT_3 or pT_4 supraglottic cancers. Complications in this group included three patients with early stenosis. One was lasered. Two required a permanent tracheostomy. Five patients suffered significant aspiration, leading to total laryngectomy in three. One responded to a temporary cuffed tracheotomy, and one accepted a gastrostomy tube. Four patients experienced bleeding that required endoscopic coagulation under general anesthesia.

In the pT_3/pT_4 supraglottic cancer group, 11 recurrences (or second primaries) (23%) appeared. Six patients with recurrence (12.5%) were laryngectomized (two with postoperative radiotherapy). Nine second primaries (16%) arose, four in the head and neck. Of these patients, seven (12.5%) died from their second primary. Six patients (11%) died of intercurrent disease. Of the 13 (23%) patients who died from supraglottic cancer, 4 died from local recurrence, 5 of regional recurrence, and 4 from distant metastasis. Notice that if TLM failed locally in pT_3 or pT_4 supraglottic cancer, half the patients required a laryngectomy (6 of 11 or 55%). And again, intercurrent disease and second primary cancers combined to cause death as often as locally advanced supraglottic cancer treated primarily with TLM.

For interested readers, Steiner also reported his TLM results for pyriform cancer to EUFOS.[68] Of 103 previously untreated patients with hypopharyngeal cancer, mainly pyriform, 63 patients had pT_2 cancers and 14 had pT_3. Sixty percent had proven neck disease. Steiner excluded patients with simultaneous second primaries, very advanced neck disease (N3), or distant metastases (i.e., not treatable for cure). All patients underwent TLM, but 75% also had neck surgery and 50% had postoperative radiotherapy. Of these 103 patients, 93 were controlled locally—there were only 10 local recurrences during a 44-month mean follow-up period. The 5-year Kaplan-Meier survivals mirrored supraglottic cancer (69.2% for combined stage I and II, 52.5% for stage III and IV), validating Krishaber's classic differentiation of "intrinsic" versus "extrinsic" disease. More laser surgery, open surgery, and radiotherapy were used to address failure. Eighteen patients (17%) died from pyriform cancer. Nearly as common (as causes of death) were intercurrent disease (16, or 15%) and second primaries (13 deaths among 16 second primaries or 13% of the total group).

Conclusions

TLM is not cancer surgery through a keyhole. In fact, it has oncologic advantages. The diagnostic component supports accurate verification of the tumor extent. The patient receives not the largest resection, but the most logical resection. The strategy of "follow the tumor" reduces the risk of undertreatment. Tissues adjacent to the resection site do not require dissection, which ensures preservation of the local microcirculation—the optimum precondition for adjuvant radiotherapy. And TLM leaves behind an open resection site—no chance to bury residual cancer cells, and all the better in follow-up.

TLM offers meaningful functional advantages—fewer tracheotomies, no fistulae, less disfigurement, less pain (nurse's observations), earlier swallowing, and a lower risk of overtreatment. It also carries certain socioeconomic advantages—reduced treatment costs from the shorter length of stay and the low rate of retreatment (for local control). TLM is a repeatable treatment (radiotherapy is not). And TLM anticipates the real problem of second primaries. After TLM, all treatment options remain.

Some things have changed with the introduction of TLM and some have not (e.g., time spent in the operating room—it takes us just as long to perform a transoral resection as an open one). More time is spent on the resection and the frozen sections, while less time is spent on open approaches and closures. The indications for and performance of neck dissection remain the same. The only variation is the greater opportunity to stage the neck. The indications for adjunctive radiotherapy remain the same, and, of course, so does the need for expert anesthesia and skilled postoperative care.

In the United States, opinions once held that TLM should never be done because it contravened oncologic principles—transected cancer, burned specimen margins, and replaced brilliant reconstructive techniques with healing by secondary intention. Now TLM is receiving more and more attention. Block excision can be seen as just a tactic to spill no viable cancer in the wound, and TLM as a strategy that supports this goal, but with a different tactic. It turns out that pathologists can read laser microresection specimens well. There are more specimens to study, and the surface coagulation is only several cells deep—less than what electrocoagulation will sometimes produce in an open surgery specimen. Secondary intention healing is no longer seen as a disadvantage because TLM selects patients for whom secondary intention healing provides excellent results.

Of course, not all change is progress. Predictions that laser surgery would (or should) produce miracles because laser technology was new, easier, faster, and bloodless were clearly exaggerations. TLM is a demanding endoscopic intervention and a complex resection, with no savings in time and its own special set of challenges. Bleeding does occur, and it can stop the laser in its tracks. Cautery and hemoclips remain entirely necessary. Laser surgery does require us to invest in new equipment and accept new safety regulations. Laboratory evidence of oncologic efficacy still lags, but it may be a bit late for animal evidence, given the excellent cure rates reported in actual human application.[66,67,78] Detailed documentation of quality-of-life outcomes is starting to become available. The TNM system retains its due respect as a reporting system, but we feel we have better concepts to guide initial treatment selection. Some will claim long-term multi-institutional cooperative trials have supported other modalities in the United States[92,93] and not TLM, but our own experience suggests that properly selected patients with advanced lesions can be managed by TLM with equal or superior rates of control and function. TLM does not rule out chemotherapy or radiation whenever they can add to the outcome. Radiotherapy cannot be used until a direct laryngoscopy and biopsy have been done, and this is usually a perfect opportunity for laser microresection.

Cartilage involvement and subglottic extension were once thought to constitute contraindications to TLM, but this turns out not to be so. Margins are not unobtainable just because the thyroid cartilage is involved. Laser microresection of the arytenoid was predicted to cause inevitable intolerable aspiration, but, again, this proves to be an overstatement. Subglottic resection is challenging, but now special techniques and special endoscopes[70,94] are available to overcome the limits on exposure.

TLM is eminently suited to the treatment of laryngeal cancer because squamous carcinoma starts in the epithelium and the epithelium is accessible through the mouth. The tumor needs to be accessible to endoscopy, but it does not need to be completely exposed in a single field of view. The cancer will need to be completely resected, with negative margins, but it will not need to be removed in one single piece. The resection site will need to have the time and conditions to heal by secondary intention and the support to resist stenosis—but it will not require primary closure. T stage in and of itself does not rule out TLM as worthy of consideration. In a series of laryngeal cancers involving the anterior commissure,[72] transoral laser excision was valid in selected carcinomas staged pT_2b, and a small number of pT_3 and pT_4 anterior commissure cancers were also treated successfully. This led to our focused study on advanced laryngeal cancer.[91]

In patients with very early laryngeal cancer, suspension microlaryngoscopies and laser excisional biopsies might best be considered "beginners TLM." When possible, it avoids 6 weeks of radiotherapy.

In early glottic cancer, TLM virtually replaces conventional VPL and hemilaryngectomy in our practice. We have experienced the same for early supraglottic cancer. TLM basically puts conventional HSL out

of business. (The minimum prerequisite is at least one mobile arytenoid cartilage.)

TLM challenges supracricoid laryngectomy, and it replaces partial laryngeo-pharyngectomy (Ogura's "PLP"[71]). Laryngeal cancer extension outside the framework contraindicates TLM, but in cases of doubt this decision can be made during treatment because endoscopic surgery can always be converted to open surgery. The need for reconstruction is considered a relative contraindication to TLM. But the vertical closures familiar in HSL and SCPL have not proven necessary in patients treated by TLM.

TLM now also has a role to play in advanced laryngeal cancers, but the arytenoid complex must be preserved bilaterally in part or in total to resist aspiration.

TLM has no role in very advanced laryngeal cancer, except possible palliative relief of airway obstruction until definitive open laryngectomy.

Transoral laser microsurgery is clearly one of the important treatment options for squamous cell cancer of the larynx. Advantage is taken of the operating microscope, laser micromanipulators and the new CO_2 fiber, and advanced laryngoscopic instrumentation to provide the most logical tumor resection, the least loss of normal tissue, and the best opportunity to follow tumor extension beyond what was visible in the office and to the scanners. With fewer tracheotomies, shorter hospitalizations, and no limitation on additional treatment, laser resection seems to combine the promise of the "light scalpel" with endoscopic advances and the realities of laryngeal cancer. For many patients, transoral laser microresection can provide the optimum combination of cure and quality of life.

Appendix on the Clinical Classification Used in This Chapter

"Early" and "advanced" were ancient designations intended to differentiate whether the cord was fixed. Fixation meant advanced, which meant total laryngectomy. Early glottic cancer had two operations: resection via direct laryngoscopy or laryngofissure and cordectomy. Early meant a low volume of cancer and a reasonable prospect of cure by radiotherapy. Advanced meant radiation usually failed, and surgery would usually be required. But sometimes radiotherapy worked and avoided a total laryngectomy.

Some early cancers were so favorable that they could be cured by a biopsy. This could falsely inflate treatment results—irradiation after an excisional biopsy would invariably produce a "cure." Therefore this subgroup was given its own category, namely "very early."

Conservation surgeons recognized that some cases with a fixed cord could have less than a total laryngectomy. These types of cancers kept the name advanced, but those cancers that everyone agreed had no chance with anything less than a total laryngectomy came to be called "very advanced."

A clinical classification of local laryngeal cancer thus evolved. There were four categories, very early, early, advanced, and very advanced. Early could be handled by classic conservation operations like the vertical and horizontal partials. Advanced was defined as lateralized cancer pervading one paraglottic space and sparing enough mobile innervated glottic tissue on the contralateral side to make a voicing shunt. The cord was fixed, but advanced could be controlled by a near-total laryngectomy.

Naturally, some laryngeal cancers fell in between a supraglottic laryngectomy and a near-total laryngectomy. We called them "intermediate" (between early and advanced). As it happens, these cancers fit the supracricoid partial laryngectomy block quite nicely.

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CHAPTER ONE HUNDRED AND TEN

Conservation Laryngeal Surgery

Gregory S. Weinstein

Ollivier Laccourreye

Christopher H. Rassekh

Ralph P. Tufano

Niels Kokot

Key Points

- Four principles of organ-preservation surgery help provide consistent oncologic and functional outcomes: local control; accurate assessment of the 3D extent of tumor; cricoarytenoid unit as the basic functional unit of the larynx; and resection of normal tissue to achieve an expected functional outcome.
- Indirect laryngoscopy and staging operative endoscopy are critical to planning conservation laryngeal surgery. Vocal fold fixation must be distinguished from arytenoid fixation, which implies cricoarytenoid joint invasion and is a contraindication to conservation laryngeal surgery.
- The overall health of the patient must be assessed. Patients must tolerate some degree of aspiration in the postoperative period. Pulmonary function tests are rarely used. Instead, if a patient is active in daily life and can walk up two flights of stairs without being winded, he or she may be a candidate for a conservation laryngeal procedure.
- Open organ-preservation options for glottic carcinomas include vertical partial laryngectomy (VPL) and supracricoid partial laryngectomy with cricohyoido-epiglottopexy (SCPL-CHEP).
- The classic VPL and its extensions all share a common approach, which includes a vertical transaction through the thyroid cartilage and paraglottic space, as well as a "blind" entry into the larynx through a narrow exposure.
- Functional results with VPL are variable depending on the extent of resection and the type of reconstruction, which varies from imbrication laryngoplasty, to strap muscle flap, to epiglottic laryngoplasty.
- Oncologic results for VPL are excellent with T_1 glottic carcinomas, but VPL should be avoided with advanced T_2 lesions and all T_3 and T_4 glottic lesions.
- The main use for SCPL-CHEP has been in selected T_2 and T_3 glottic carcinomas, with local control rates greater than 90%. The SCPL-CHEP does not resect the entire supraglottis, so for transglottic tumors, the supracricoid partial laryngectomy with cricohyoidopexy is preferred.
- Functional results with SCPL-CHEP are predictable due to the identical resection and reconstruction in all cases. Long-term dysphagia is rare.
- Organ-preservation options for supraglottic carcinomas include the supraglottic laryngectomy and the supracricoid partial laryngectomy with cricohyoidopexy (SCPL-CHP).
- Supraglottic laryngectomy has produced excellent oncologic results for T_1 and T_2 supraglottic carcinomas with local control rates greater than 90%, but outcomes are extremely variable with advanced lesions.
- Voice results for supraglottic laryngectomy are typically excellent, although a certain degree of temporary dysphagia is to be expected, with more severe dysphagia expected with extended procedures.
- SCPL-CHP is indicated for supraglottic carcinomas in which there is glottic level involvement, pre-epiglottic space involvement, decreased vocal fold mobility, or limited thyroid cartilage invasion.
- The oncologic success of the SCPL-CHP is attributed to the en bloc resection of bilateral paraglottic spaces, the preepiglottic space, and the entire thyroid cartilage.
- Contraindications to the SCPL include (1) subglottic extension greater than 10 mm anteriorly and 5 mm posteriorly; (2) arytenoid fixation; (3) massive preepiglottic space involvement with involvement of the vallecula; (4) extension to the pharyngeal wall, vallecula, base of tongue, postcricoid region, and interarytenoid region; and (5) cricoid cartilage invasion.
- Transoral Robotic Surgery (TORS) is a new technique that offers an alternative to open and transoral laser approaches for the treatment of glottic and supraglottic carcinomas.

A variety of open surgical approaches are available. When applied for the appropriate indications, they have an excellent ability to control laryngeal cancer while conserving laryngeal function. Conservation laryngeal procedures are historically the original "organ-preservation" techniques; the first hemilaryngectomy for malignancy was performed by Billroth in 1874.[1] Long before nonsurgical approaches were available to attempt to preserve the entire structure of the larynx, innovative surgical techniques were being used to remove enough of the larynx to allow for local control of the malignancy while preserving adequate structure to allow the larynx to function.[2] There exists a spectrum of laryngeal malignancies for which there is a complementary spectrum of conservation laryngeal procedures available. This chapter reviews the open conservation laryngeal procedures in the organ-preservation surgical paradigm available for managing the spectrum of selected glottic, transglottic, and supraglottic carcinomas. These techniques allow for the maintenance of physiologic speech and swallowing without the need for a permanent tracheostoma. The modern head and neck surgeon must have a comprehensive understanding of both surgical and nonsurgical organ-preservation strategies to allow for the most comprehensive care in the treatment of the patient with laryngeal cancer.

Although the origins of conservation surgery of the larynx are more than a century old, during the second half of the past century, the conservative options were limited to vertical hemilaryngectomy and supraglottic laryngectomy. The inherent limitations of these procedures in terms of indications led to these procedures losing favor among many physicians with experimental approaches, with chemotherapy and radiation dominating the management of advanced laryngeal cancer. Then, in the last decade of the 20th century in the United States, the introduction of supracricoid partial laryngectomies, as well as the introduction of endoscopic laser resections, created a renaissance in surgical organ preservation for laryngeal cancer. At present, this surgical renaissance in organ-preservation surgery for laryngeal cancer has evolved into an acceptable standard of care for the 21st century.

The common thread in the history of conservation laryngeal surgery is that these procedures were first developed outside the United States and then imported to its shores. Improvements in antibiotics and anesthetic techniques fostered the development of conservation laryngeal surgery.[3] Vertical hemilaryngectomy, which was first described by Billroth[1] in Germany and popularized in Europe by Leroux-Robert and Portmann,[4] was refined in the United States by Som,[5] Norris,[6] and Conley.[7] A French surgeon named Huet described a procedure in which a portion of the supraglottis was excised without the upper portion of the thyroid cartilage in 1938.[8] Later, a Uruguayan surgeon named Alonso extended this procedure to resect the upper portion of the thyroid cartilage together with the supraglottic structures, thereby defining the supraglottic laryngectomy.[9,10] The supraglottic laryngectomy was popularized in Europe by Bocca[11] and in the United States by Ogura,[12] Som,[5] and Kirchner.[13] The supracricoid laryngectomies originally were described in 1959 by the Austrian surgeons Majer and Reider[14] approximately one decade after Alonso had described the supraglottic laryngectomy.[9] The supracricoid laryngectomies were later promoted in Europe by Labayle[15] and Piquet and associates[16] and were imported to numerous institutions in the United States during the 1990s.[17]

The first of two major classes of techniques that developed was the vertical partial laryngectomy, in which entry into the endolarynx is through a vertical thyrotomy, the most notable example of which is the vertical hemilaryngectomy. The second major class of techniques is the horizontal partial laryngectomy, in which endolaryngeal entry is made through a transverse or horizontal thyrotomy (i.e., supraglottic partial laryngectomy). During the 1960s through the 1980s, innovative surgeons[18-23] reported numerous small series of patients in which the indications and extent of resection of these basic techniques were extended in an attempt to manage larger lesions. The commonalities among these series were (1) the relatively small numbers of patients; (2) variable local control rates compared with the strict previous indications for the procedure that was being extended; and (3) complex reconstructions requiring cartilage and mucosa rotation flaps with variable functional results.[18-25] These variable results made it difficult for other surgeons to use these extended procedures in the treatment of larynx cancer. Despite these innovations of the pioneers of conservation laryngeal surgery, the techniques that most surgeons became facile with, as reflected by the large numbers of series in the literature, were the standard vertical hemilaryngectomy and standard supraglottic laryngectomy. A common surgical solution in the United States for lesions considered too large for these standard conservation laryngeal procedures was total laryngectomy, with the innovations being in the area of alaryngeal speech and speech shunt development.[26,27]

In many European countries, laryngectomy, with its concomitant permanent stoma, was considered an anathema to be avoided when possible, and a different approach evolved. In 1959 in Austria, Majer and Reider[14] reported on a new horizontal partial laryngectomy technique in which the entire thyroid cartilage, true cords, false cords, and all or a portion of the epiglottis and preepiglottic space were resected. The reconstruction was with a pexy either between the cricoid and hyoid (cricohyoidopexy) or between the cricoid and the remaining epiglottis and hyoid (cricohyoidoepiglottopexy). This procedure, known as the supracricoid partial laryngectomy, allowed for a complete resection of the preepiglottic and paraglottic spaces and of the surrounding cartilage and soft tissue, resulting in higher local control in glottic, supraglottic, and transglottic cancers that equaled total laryngectomy, resulting in speech and swallowing without a permanent tracheostomy. Unlike the plethora of extensions of the vertical partial laryngectomy and the supraglottic laryngectomy, the supracricoid laryngectomies were repeated in many patients by numerous European centers during the 1970s through the 1990s with consistently excellent local control and functional results.[16,28-37]

Conservation Laryngeal Surgery Today

Although conservation surgery of the larynx had its origins in the 19th century, the standard of care in the 21st century dictates that when vertical partial laryngectomy, supraglottic laryngectomy, or supracricoid laryngectomy are alternatives for a given patient, these options should be discussed with the patient. In most cases, it is the general otolaryngologist–head and neck surgeon who makes the diagnosis of laryngeal cancer, and therefore these are frequently the physicians who first counsel the patients concerning their treatment options. Standard of care dictates that a discussion based on the literature be given to the patient concerning both surgical and nonsurgical approaches to organ preservation. In our opinion, one scenario might be that a physician might rationalize that because "I don't do these procedures," he or she might send the patient to the radiation therapist—but this may not be in the best interest of the patient. Alternatively, in our opinion the physician diagnosing a laryngeal cancer that does not have the expertise to offer all surgical and nonsurgical options could refer the patient to a multidisciplinary center that can triage patients to either surgery or nonsurgery on the basis of the needs and desires of the patient.

An analogy can be made with free tissue reconstruction surgery. If a patient has a large jaw carcinoma and the superior option from the oncologic and functional perspective is a free flap, we would not offer him or her a lesser surgical procedure or chemotherapy and radiation. The patient would be sent to a surgeon with a special expertise in free flap surgery. This is possible because, in the past 20 years, a cadre of head and neck subspecialists have cropped up that have a particular interest and expertise in performing free flap surgery. In fact, over the past decade we have witnessed a similar phenomenon in the United States in the area of organ-preservation surgery for laryngeal cancer. In our opinion, a similiar situation exists in which some head and neck surgeons have special expertise in open and endoscopic approaches for laryngeal organ preservation in the face of laryngeal cancer.

The focus of this chapter is to provide the general otolaryngologist–head and neck surgeon with an introduction to these techniques. This information is important because it is the responsibility of the general otolaryngologist–head and neck surgeon to understand the indications for the full spectrum of open and endoscopic organ-preservation surgical approaches and either gain the expertise to perform these procedures or refer the patient to surgeons who have this special expertise.[38]

During the 1970s and 1980s, the functional and oncologic results after supraglottic laryngectomy were reported in numerous series in

the United States, defining the role of this technique among the plethora of surgical and nonsurgical options available for supraglottic carcinoma.[39-41] During the same period and into the 1990s, the role of vertical partial laryngectomy for glottic carcinoma has been re-examined because of advances in nonsurgical and laser endoscopic approaches to similarly staged disease.[3,42] In the 1990s the supracricoid laryngectomies were imported to numerous institutions in the United States, and the European functional results have been reproduced.[17,43,44] The supracricoid laryngectomies have broadened the spectrum of reliable techniques available to the conservation laryngeal surgeon.[3]

At present, a renaissance is occurring in the United States in the area of conservation laryngeal surgery. Many factors have fostered the rekindled interest in conservation laryngeal surgery, including (1) a clearer understanding of the three-dimensional extent of laryngeal carcinoma, which has stemmed from numerous clinicopathologic studies and from advances in radiologic techniques; (2) numerous long-term studies of outcome after the application of a broad spectrum of techniques; and (3) the introduction of new techniques during the past 2 decades. Today, there are a variety of techniques available for selected laryngeal malignancies, with predictable functional and oncologic outcome based on analyses in the literature of many patients. The full spectrum of surgical techniques allows the surgeon to consistently offer patients, with selected lesions, excellent local control that will result in speech and swallowing without the need for a permanent tracheostoma. This may provide the patient with an alternative to nonsurgical organ-preservation modalities. There are organ-preservation principles to which the surgeon must adhere to maximize both oncologic and functional outcome. Conservation laryngeal surgery is precision surgery,[45] and to achieve successful oncologic and functional results, the conservation laryngeal surgeon should have a firm grasp on the clinical assessment of laryngeal cancer and a complete understanding of the surgical techniques. The art of correctly staging the lesion as one appropriate for a conservation laryngeal procedure requires an in-depth knowledge of both the static and dynamic anatomy of the larynx and how the tumor relates to it.

Anatomy, Physiology, and Tumor Spread

In 1966 Bocca elegantly stated that, "often cancer seems to have limits, while the surgeon seems to have none. We should make efforts to force upon our knife the same limits as those which surrounding tissues or structures force upon cancer and its spread."[11] Bocca's eloquent statement underscores that successful outcome in conservation laryngeal surgery is predicated on a thorough knowledge of the pertinent surgical anatomy and on an understanding of the behavior of the malignancy in a particular anatomic site. Much of what is known concerning the three-dimensional spread of malignancy through the larynx has been derived from clinicopathologic studies in which the entire larynx was sectioned. These whole organ section studies are the basic science foundation for clinicians performing conservation laryngeal surgery.

The surgical anatomy of the larynx can be understood in terms of the skeleton and connective tissue barriers, the spaces delineated by these structures, and the soft tissue structures, which include the fat, musculature, vessels, nerves, and adnexa that fill these spaces. The skeleton of the larynx (Fig. 110-1) is dominated by the thyroid cartilage, which articulates posteriorly and inferiorly through the inferior cornua with synovial joints on the posterolateral aspects of the cricoid cartilage. A thick tendon originates from the superior cornua and attaches to the lateralmost aspect of the "crown" of the larynx, the hyoid bone. Anteriorly there is a notch, and the lateral aspect of the laminae is traversed by the oblique line, which is the point of attachment of the strap musculature. The extension of cancer into the thyroid cartilage tends to occur in areas of ossification of the cartilage.[46] The mode of invasion into the ossified bone has been attributed to osteoclast formation,[47] extension along collagen bundles,[48] or through areas of high vascularity.[49] The most common site of invasion of the thyroid cartilage was at the angle,[50] although other sites of predilection for carcinoma invasion are the points of attachment of the cricothyroid membrane and the anterior origin of the thyroarytenoid musculature.[48] The perichondrium provides an excellent barrier to invasion, and once the carcinoma is within the cartilage, the cancer can extend throughout the cartilage behind an intact perichondrium, precluding surgical cuts through the cartilage, as is done in some partial laryngectomies.[51] Nakayama and colleagues[52] noted that a large proportion of patients staged clinically as T_3 actually had thyroid cartilage invasion when the specimens were analyzed by whole organ sectioning, and they noted that in these patients with T_3 glottic cancers, any combination of two factors including significant degree of calcification of the cartilage, tumor length greater than 2 cm, and anterior commissure involvement resulted in a higher incidence of cartilage invasion (71% to 92%).

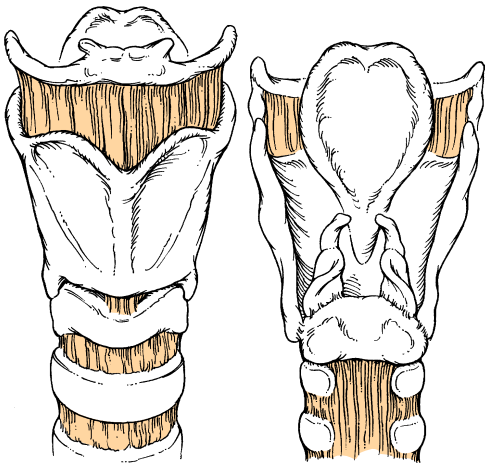

Figure 110-1. Skeletal structure of the larynx.

The cricoid cartilage is the only circumferential ring in the airway, and preservation or reconstruction of its ring-shaped structure allows for decannulation after conservation laryngeal surgery. The arytenoid cartilages sit atop the cricoid, to which they are attached by a synovial joint. The two muscular processes of the arytenoid cartilages are oriented posteriorly and laterally, and the vocal cord tendon originates from the tip of the vocal process and spans anteriorly to the thyroid cartilage. The most common site of cricoid cartilage invasion by carcinoma is at its posterior superior border, and the most common site of arytenoid invasion is at the points of attachment of the joint capsule.[53]

The epiglottis, with its numerous fenestrations, originates from the tendinous attachment on the thyroid cartilage, fanning out from its most inferior point known as the petiole to a widened superior aspect above the hyoid. The carcinoma on the infrahyoid surface of the epiglottis readily extends through the fenestrations of the epiglottic cartilage through blood vessels[49] and the ducts of the seromucinous glands.[54] The hyoid bone is almost never involved by supraglottic carcinoma. Kirchner[55] noted no cases of hyoid bone invasion in 55 supraglottic carcinomas evaluated by whole organ section, although in Kirchner's series,[55] two patients had cancer up to the periosteum, one of which could be palpated at the level of the thyrohyoid membrane and one which had vallecula mucosa involvement. Among 172 patients with supraglottic carcinoma reported by Timon and colleagues,[56] only four patients had hyoid bone invasion, and a common feature of all of these patients was vallecula mucosal involvement. Preservation of the hyoid bone helps with swallowing postoperatively. Understanding this concept is essential and makes it possible to perform supracricoid laryngectomy with cricohyoidopexy in selected transglottic tumors. These authors concluded that it is sound to preserve the hyoid bone in cases without palpable submucosal vallecula carcinoma or vallecula mucosal involvement.[55,56]

There are numerous condensations of fibrous tissue that traverse the three-dimensional anatomy of the larynx. Some of the modern knowledge of these structures comes from the pioneering work of Tucker and Kirchner, both of whom studied whole organ sections of larynges and analyzed this anatomy.[57-59] The conus elasticus (Fig. 110-2) spans from each vocal cord down laterally to the cricoid cartilage. The conus elasticus provides a temporary barrier for the spread of early glottic carcinoma, but ultimately, for larger cancers, it serves as

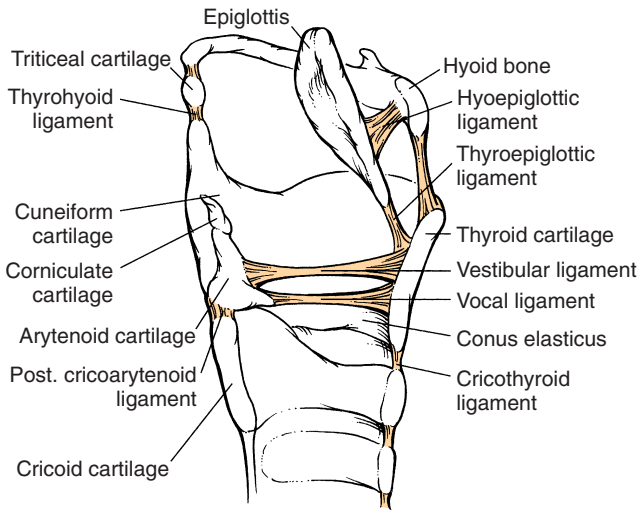

Figure 110-2. Conus elasticus.

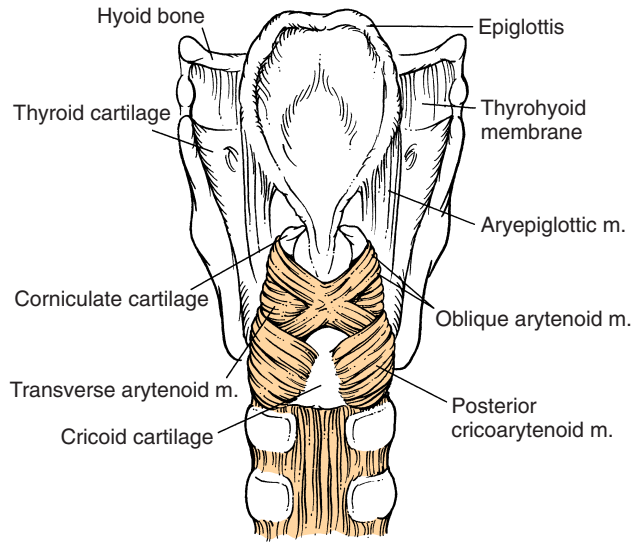

Figure 110-3. The thyrohyoid membrane.

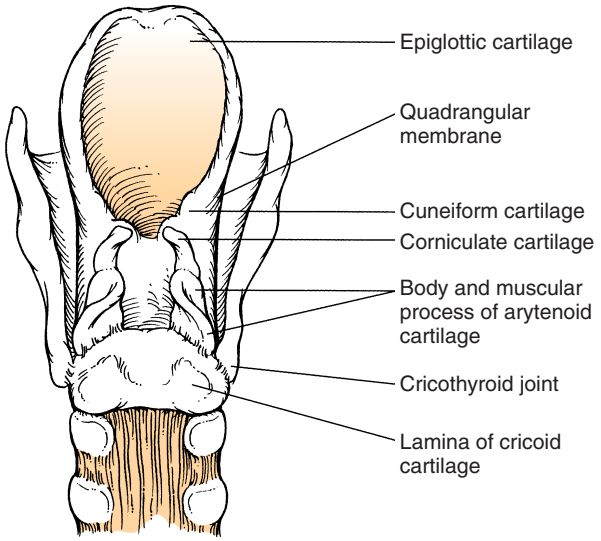

Figure 110-4. The quadrangular membrane.

the gateway to the subglottic and extralaryngeal spread of carcinoma.[60] Posteriorly, it is also attached to the arytenoid, providing stability to the arytenoid and the vocal tendon. The vocal tendon, which essentially is a medial condensation of the conus elasticus, attaches anteriorly to the thyroid cartilage at the Broyles ligament or the anterior commissure tendon.[61] Although the anterior commissure tendon is devoid of perichondrium, the ligament constitutes a dense fibrous attachment to the cartilage and sends slips of fibrous tissue superiorly to the thyroepiglottic ligament. Kirchner and Carter[60] have noted that the anterior commissure tendon is a point of dense adhesion of fibrous tissue, and it is rare for an early glottic cancer with anterior commissure involvement to erode into the thyroid cartilage here. However, the anterior commissure tendon provides access to cartilage invasion for larger cancers, which spread superiorly or inferiorly.[60] Anteriorly, there is a superior inferior condensation of the conus elasticus called the cricothyroid ligament, which is a central structure and does not spread out laterally to provide a connective tissue barrier along the circumference of the cricoid.[50] This is different than its superior counterpart, the thyrohyoid membrane. The thyrohyoid membrane drapes along the entire circumference of the thyroid cartilage superiorly and spreads upward to the hyoid bone (Fig. 110-3). Extension out of the larynx through the thyrohyoid membrane alone is rare and is typically seen when cancer exits the larynx through the upper portion of the thyroid cartilage.[50] The quadrangular membrane (Fig. 110-4) originates from the top of the arytenoid posteriorly and from the lateral aspect of the epiglottis anteriorly and then extends inferiorly like a curtain to an inferior condensation of fibrous tissue, which spans between the inferior aspect of the arytenoid posteriorly and the petiole of the epiglottis anteriorly. The hyoepiglottic ligament was recently elegantly described by Zeitels and Kirchner,[62] who showed this structure to be a resilient barrier to malignant spread from the supraglottis to the tongue base when the cancer is confined to the laryngeal membranes and does not clinically invade the suprahyoid epiglottis.

The skeleton and fibrous tissue barriers demarcate a number of spaces within the larynx. The superiormost space is the preepiglottic space (Fig. 110-5), which is filled with fat and traversed by blood and lymphatic vessels.[63] Kirchner and Carter[60] noted that carcinoma tends to invade within the preepiglottic space with a "pushing edge," which is almost "encapsulated" after it reaches the elastic tissue membranes in the preepiglottic space, contributing to the oncologic safety in saving the hyoid bone during supraglottic surgery. The boundaries of this space are the vallecula mucosa and the hyoid superiorly, the thyrohyoid membrane and the thyroid cartilage anteriorly, and the epiglottis posteriorly. Posterolaterally, on either side, the preepiglottic space is bounded by the superior portions of the paraglottic space.[64]

There is a paraglottic space on either side of the larynx (Fig. 110-6). Superiorly, the medial boundary is the quadrangular membrane, whereas inferiorly, the medial margin is the conus elasticus. It originates superiorly within the aryepiglottic fold, where it fades to a peak. The paraglottic space makes up the substance of the true and false cords and within it are the thyroarytenoid musculature and the mucosa-lined, air-filled space known as the *ventricle* and its superior extension, the *saccule.* Inferiorly, it follows the conus elasticus down to the top of the cricoid cartilage. Anteriorly, it abuts the preepiglottic space and the anterior third of the thyroid cartilage, and the posterolateral boundary is the mucosa of the medial aspect of the pyriform sinus. The paraglottic space traverses the supraglottis, glottis, and subglottis laterally within the larynx. Rather than having a distinct barrier to superior-inferior spread, cancer seems to be impeded in its course through the paraglottic space to varying degrees by the hourglass shape of the space, which is made by the indentation of the ventricle and saccule.[65] One additional space is Reinke's space, which actually is a potential space under the true vocal cord mucosa and provides no barrier to invasion.

The behavior of carcinoma in the supraglottis is modified by the soft tissue, connective tissue barriers, and the skeleton of the larynx (Fig. 110-7). Kirchner[57] showed, in an analysis of whole organ sections, that supraglottic carcinomas that overlie the epiglottic cartilage have a

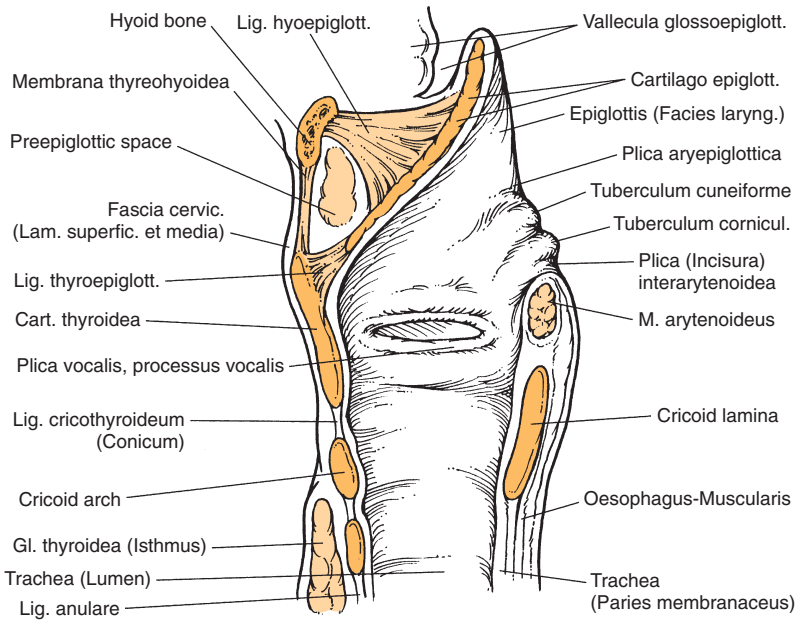

Figure 110-5. The preepiglottic space.

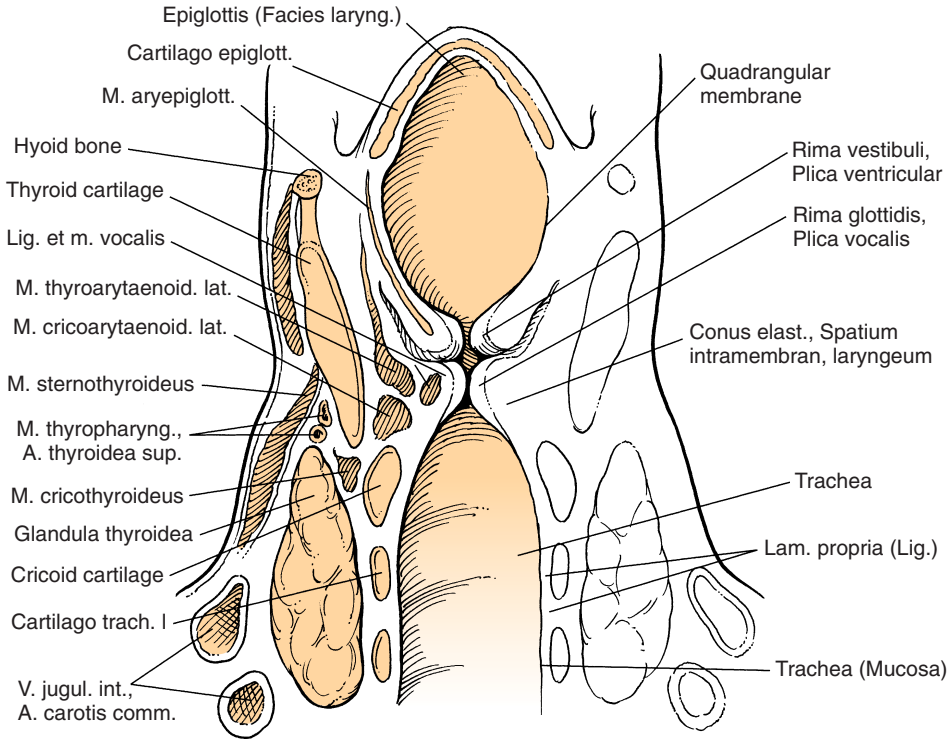

Figure 110-6. The paraglottic space.

tendency (9 of 10 cases) to extend into the preepiglottic space, at least microscopically, through the fenestrations in the epiglottic cartilage. In addition, Bridger,[54] working with the whole organ section collection at Johns Hopkins, showed that seromucinous tubuloalveolar glands extend through the fenestrations and provide a route of spread of cancer into the preepiglottic space. Although it had been suggested in the past that embryologic fusion planes somehow provide protection against inferior spread of carcinoma from the supraglottis to the glottis, a recent study that evaluated all of the series of whole organ sections in the literature revealed that the incidence of spread of supraglottic carcinoma to the glottic level is between 20% and 54%.[65] This study indicated that there was a statistically significant relationship between the presence of abnormal cord mobility or involvement of carcinoma below the false cord and glottic level extension, most commonly through the paraglottic space.[65]

Carcinomas at the glottic level tend to begin at the junction of the anterior one third and posterior two thirds of the vocal cord. They readily pass through Reinke's space to the tissues below. Early studies by Pressman,[66] with submucosally injected dyes and radioisotopes, indicated that barriers existed between the two sides of the glottis and the supraglottis. Welsh and colleagues[53] demonstrated that as dye concentration increases, these barriers become less effective. For early lesions,

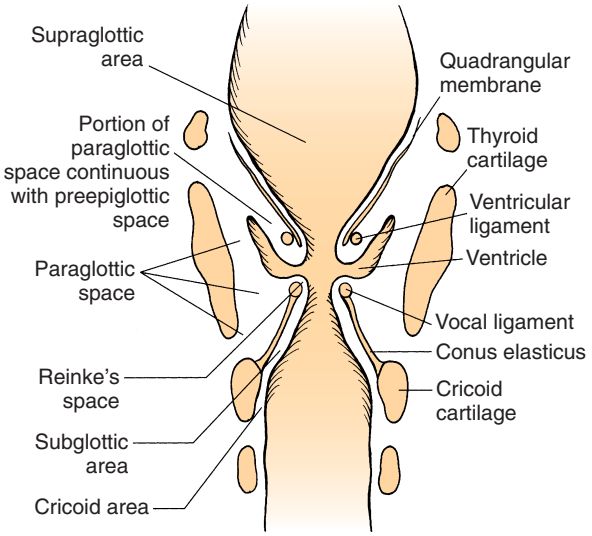

Figure 110-7. Connective tissue barriers within the larynx.

the conus elasticus provides a barrier to extension; as the lesion enlarges, this barrier becomes less pertinent.[67]

The sensation to the supraglottis is supplied by the superior laryngeal nerves, whereas the glottis and subglottis are innervated by the recurrent laryngeal nerve. The neural structures play an important role in timely postoperative functional rehabilitation.[68] Whenever possible, the main trunks of the superior and recurrent laryngeal nerves and the hypoglossal nerves, bilaterally, should be preserved during conservation laryngeal surgery.

Certain aspects of physiology of the larynx are pertinent to successful application of conservation laryngeal surgery. Hirano and colleagues,[69] in a whole organ analysis of the normal larynx, noted that 50% to 65% of the entire adult airway is located posterior to the tips of the vocal processes and concluded that the posterior larynx is the respiratory airway and the anterior portion is the phonatory airway. This is because all of the musculature that opens and closes the glottic chink, the lateral cricoarytenoid musculature, changes the position of the vocal processes during speech and swallowing. The arytenoids are responsible for opening the airway for breathing and for closing during swallowing and speaking. The vocal cords provide vocal quality during phonation; therefore loss of one or both vocal cords results in hoarseness, but preservation of at least one arytenoid and an intact circumferential ring at the level of the cricoid is sufficient for speech and swallowing without a tracheostomy.[70-75]

Principles of Organ-Preservation Surgery

The otolaryngologist–head and neck surgeon must adhere to certain key principles to determine a patient's eligibility for a conservation laryngeal surgery. The advent of the supracricoid laryngectomy makes us direct our focus away from the vocal fold and concentrate on the cricoarytenoid unit as the essential functional unit of the larynx. The organ-preservation principles are formulated to help provide consistent oncologic and functional outcomes.[76] These can then be compared with current nonsurgical organ-preservation options to allow the patient and physician to make educated decisions regarding treatment. Adopting these principles will enable the surgeon to maximize oncologic and functional outcomes for a number of glottic, supraglottic, and transglottic malignancies.

First Principle: Local Control

Local control is the most important principle. Survival from the index cancer is compromised if there is a local failure after radiation therapy or surgery to the supraglottis and glottis.[77] Early detection of the primary site recurrence may be difficult for a number of reasons. Medical and surgical organ-preservation modalities alter the topography of the larynx and make definitive evaluation of recurrent cancer difficult. Symptoms may be attributed to the treatment intervention or recurrent tumor, although increasing pain, persistent ear pain, and dysphagia are ominous signs. Repeat endoscopy and biopsy of the original primary site is warranted. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) may also be helpful in explaining recurrent or persistent cancer. Organ-preservation laryngeal procedures should be used only when resection of the tumor can be accomplished comfortably with local control rates approximating those of total laryngectomy.

Second Principle: Accurate Assessment of the Three-Dimensional Extent of Tumor

The second principle of organ-preservation surgery is to be able to confidently predict the extent of tumor. A comprehensive appreciation of laryngeal anatomy and function is necessary. The inability to accurately predict the extent of tumor in a conservation laryngeal procedure may lead to total laryngectomy when another organ-sparing approach may have been possible.

Third Principle: Cricoarytenoid Unit Is the Basic Functional Unit of the Larynx

The cricoarytenoid unit is the basic functional unit of the larynx. The cricoarytenoid unit consists of an arytenoid cartilage, the cricoid cartilage, the associated musculature, and the superior and recurrent laryngeal nerves for that unit. Preservation of at least one functional cricoarytenoid unit makes it possible to consider an organ-preservation procedure. This is a foreign concept to most surgeons who perform vertical partial laryngectomy and supraglottic laryngectomy. The surgeons, along with the T-staging system for laryngeal cancer, focus on the vocal fold rather than on the cricoarytenoid unit. The paradigm shift from the vocal fold to the cricoarytenoid unit is essential for the head and neck surgeon to be able to use the full spectrum of organ-preservation surgeries. It is the cricoarytenoid unit, not the vocal folds, that allows for physiologic speech and swallowing without the permanent need for a tracheostoma after supracricoid laryngectomy.

Fourth Principle: Resection of Normal Tissue to Achieve an Expected Functional Outcome

This principle may seem counterintuitive because we are talking about "conservation laryngeal surgery." What we are conserving is the function of the larynx, not necessarily all the regions of the larynx that are uninvolved with cancer. This resection of normal tissue is necessary to achieve consistent functional outcomes in terms of speech and swallowing. A reliable reconstruction for each organ-preservation surgical choice that is proven with regard to speech and swallowing outcome should make the surgeon feel more at ease when comparing nonsurgical and surgical organ-preservation results for a patient. Reconstructions based on the extent of tumor resection for clear margins alone often result in novel reconstructions and the surgeon's trepidation regarding functional outcome. A better approach is to perform a standard resection where a consistent functional outcome is known.

Preoperative Evaluation

The preoperative evaluation includes an oncologic assessment of the primary site, regional nodes, and distant sites. In addition, it includes an assessment of the patient's ability to medically undergo the surgery and postoperative treatment. Finally, patient and family insight, emotional state, and ability and willingness to undergo the postoperative rehabilitation should be considered.

Clinical Evaluation of the Primary Site

Before examining the larynx, the physician should listen to the patient speak and breathe. The degree of airway impairment and the voice quality should be assessed. Glottic carcinomas that affect the phonatory structures tend to cause hoarseness; supraglottic cancers frequently are above the cords and cause a muffled "hot potato" voice as they enlarge. Hoarseness from a supraglottic carcinoma may indicate impairment of cord mobility as a result of arytenoid involvement or glottic level involvement. Next, both sides of the neck should be palpated for nodal disease. The thyroid cartilage itself should be palpated for irregularities,

as should the areas directly above and below the thyroid cartilage. A bulge or mass at the level of the thyrohyoid membrane may indicate massive preepiglottic space invasion. A mass at the level of the cricothyroid ligament may indicate a Delphian lymph node, which indicates subglottic extension of the malignancy.[78] Indirect mirror or fiberoptic laryngoscopy is used to assess the larynx and surrounding structures. The important gross pathologic characteristics that need to be evaluated are airway impairment, endophytic versus exophytic, superficial spread versus deep invasion, mucosal structures involved, arytenoid and vocal cord mobility, and extensions out of the endolarynx.

The clinical assessment of laryngeal mobilities provides excellent insight into the three-dimensional extension of carcinoma within the larynx. Mobility of the vocal cord itself, without attention to arytenoid mobility, is adequate when planning for management that is directed to the entire organ such as total laryngectomy or radiotherapy. Biller and Lawson[79] and Ogura's team[80] have noted that assessment of arytenoid mobility and cord mobility is important in the preoperative planning for conservation laryngeal surgery, particularly when the vocal cord itself is fixed. Assessment of vocal cord mobility is best clinically assessed during indirect laryngoscopy by having the patient speak or breathe deeply, whereas arytenoid mobility is best assessed by having the patient cough gently.

Cancers involving the glottis and supraglottis have different effects on vocal cord mobility and arytenoid mobility. Impaired mobility from glottic carcinoma may be a result of superficial thyroarytenoid invasion or bulk on the surface of the cord in an exophytic lesion.[67] Hirano and others[81] assessed the degree of thyroarytenoid muscle invasion in glottic carcinoma and found fixed cords had deeper invasion into the musculature than impaired cords. Numerous studies have demonstrated that glottic carcinoma associated with a fixed vocal cord most commonly results from extensive invasion of the thyroarytenoid muscle.[81-83] In some patients, subglottic extension with fixation to the cricoid cartilage and lateral extension with adherence to the thyroid cartilage resulted in fixation of the cord[82] and invasion of the lateral cricoarytenoid musculature and the cricoarytenoid joint.[83] At the supraglottic level, cancer invasion into the thyroarytenoid musculature at the glottic level is less likely, and the most common cause of cord fixation, noted by Hirano and others,[81] was deep arytenoid cartilage invasion superiorly. Montgomery[84] and Ogura[85] assessed vocal cord and arytenoid mobility, independently, in preparation for conservation laryngeal surgery of the supraglottis. Brasnu and colleagues,[86] in a whole organ section series, noted two types of impairment in arytenoid mobility—namely the "weight impact" of the tumor—in which the arytenoid motion seems impaired superiorly causing "pseudofixation" versus actual fixation from the malignant involvement of the intrinsic laryngeal musculature, the cricoarytenoid joint, or both (Fig. 110-8). They are distinguished by careful evaluation of the vocal fold; if any motion of the cord is noted in the presence of what seems to be arytenoid fixation from a supraglottic cancer, this is "pseudofixation."[86] This information is valuable to the conservation laryngeal surgeon because it is unlikely that a larynx with a "pseudofixed" arytenoid has cricoarytenoid joint and musculature involved, whereas these areas are involved in more than two thirds of patients when "true fixation" of the arytenoid is present. We have found that the fiberoptic scope has use in the assessment of vocal cord mobility in the presence of exophytic supraglottic carcinomas because the tip of the scope can be manipulated past the lesion to look at the structures below. The clinical implication is that careful assessment of the vocal cord and arytenoid mobilities is essential when planning for conservation laryngeal surgery to attempt to understand which deep structures are invaded and which in turn may improve the likelihood of applying the appropriate surgical technique.

Figure 110-8. Entire section through the cricoarytenoid joint with fixation of the true cord and the arytenoid revealing cricoarytenoid joint invasion.

The final aspect of the physical examination of the primary site is performed during direct laryngoscopy during general anesthesia. The direct laryngoscopy allows for biopsy of the lesion to be performed and for a thorough visual evaluation of the larynx and surrounding structures with the routine use of the operating microscope or rigid endoscopes. Palpation of the lesion and surrounding structures with endoscopic instrumentation can yield valuable information concerning submucosal extent of disease. Palpation of the vallecula with a finger and of the posterior floor of mouth provides a critical assessment of submucosal extent of disease in these areas from supraglottic carcinoma.

After this clinical assessment, the conservation laryngeal surgeon should have a clear understanding of the extent of the lesion and have in mind which surgical or nonsurgical options are optimal for the patient.

Radiologic Evaluation of the Primary Site

Although imaging studies are frequently available before the clinical evaluation of the primary site, the best role of these studies is to corroborate the clinical findings noted on indirect and direct laryngoscopy and to corroborate clinical evidence of deep growth of lesions. This is because although there are specific findings that are particularly useful to assess with imaging studies, there are limitations to the value of these studies, and they may either overpredict or underpredict tumor in certain situations. One caveat is that when evaluating particularly small lesions or the superficial extension of a large lesion, CT[87] or MRI may demonstrate little abnormality. This is because these modalities are insensitive to superficial mucosal masses. Another pitfall is seen in those with large exophytic lesions. When lesions have large extensions into the airway, they may sit up against adjacent mucosal sites such as the pyriform sinus, tongue base, floor of mouth, lateral pharyngeal wall, or ventricle or saccule. Although the point of the attachment of the cancer may be small and discrete, the scan may deceptively indicate that all mucosal surfaces are involved. In these patients the endoscopist has a better view of the lesion, and the clinical examination takes precedence over the radiologic evaluation. Valsalva maneuver performed during the CT scan may be useful if these issues cannot be resolved at endoscopy.[88] Occasionally, tumors may be isodense (CT) or isointense (MRI) with the surrounding tissues, which at times may overestimate or underestimate the size of the lesion noted on the clinical examination.[89] In these patients the radiologist and surgeon should work together to find the true extent of tumor.

Laryngeal imaging studies have been useful in a number of areas. Occasionally, the bulk of the lesion extends submucosally into the subglottis. In these patients, MRI more so than CT can be useful to demonstrate the direct invasion or secondary thickening or asymmetry caused by the lesion in this area. Coronal T_1-weighted MRI scans are particularly elegant in demonstrating submucosal transglottic spread. The cricoarytenoid area is best evaluated with axial scans, and sclerotic changes on CT are indications of perichondrial or direct arytenoid cartilage involvement.[88,90] Sagittal MRI has been shown to be a sensitive and specific test for varying degrees of preepiglottic space invasion.[91] Because the cartilages of the larynx calcify starting in the second decade in an inhomogeneous fashion, loss of calcification of the cartilage on CT is an unreliable indicator of tumor extension.[92] MRI has been shown to be highly sensitive to cartilage invasion, particularly if fat-suppressed and postgadolinium scans are performed. Enhancement

into cartilage on postgadolinium fat-suppressed scans is highly sensitive to invasion, but it suffers from reduced specificity because inflammation and chondronecrosis will show similar findings. Kirchner[93] noted that the most common site of thyroid ala invasion from glottic carcinoma is the lower edge, and questionable isolated involvement of the superior aspect of the thyroid cartilage may represent random calcification patterns within the cartilage. We agree with Kikinis and colleagues[94] that MRI has been more useful for evaluating tumor extension into or through laryngeal cartilages. Fluorodeoxyglucose (FDG) PET has gained popularity among physicians in the staging and surveillance of head and neck cancer.[95] Its most promising role in larynx cancer appears to be in the delineation of posttreatment effect (medical organ-preservation strategies) from recurrent tumor. The role of FDG PET in organ preservation for the larynx paradigm is currently being assessed in a prospective study.

T Stage

The larynx by convention is divided into three discrete parts for the purpose of T staging. The supraglottis begins inferiorly at the lateral angle of the ventricle. Although the supraglottis extends superiorly up to the tip of the epiglottis, the vallecula mucosa is part of the oropharynx. The glottis begins at the lateral angle of the ventricle, and it extends 1 cm inferiorly at the midcord level. The subglottis begins at the inferior aspect of the glottic level and extends to the inferior aspect of the cricoid cartilage. Although this partitioning of the larynx is somewhat artificial, it allows for a staging system that, despite its shortcomings, allows for comparison of treatment modalities and prognostication.[96] Although the T-staging system is useful when comparing modalities that encompass the entire larynx such as radiotherapy or total laryngectomy, it lacks the precision necessary to determine whether conservation laryngeal surgery may be performed at all and, if so, which particular procedure is indicated. Within each of the four T stages, at each site there is a spectrum of lesions for which a variety of conservation laryngeal procedures may be used with successful outcome. When planning for conservation laryngeal surgery, numerous factors that go beyond the level of detail required in the T-staging system should be evaluated. The factors that are clinically important include the precise extent of mucosal involvement, the depth of invasion of the malignancy, and the vocal cord and arytenoid mobilities. Although it has frequently been stated that millimeter margins are adequate for conservation laryngeal surgery, the caveat to this axiom is that for any given conservation laryngeal technique, millimeters of tumor extension within the larynx may preclude performing that technique and may result in intraoperative conversion to total laryngectomy. The conservation laryngeal surgeon should describe the lesion in more detail than the T-staging system to allow for application of the appropriate conservative laryngeal technique.

Overall Clinical Assessment

The primary medical issues important to the conservation laryngeal surgeon are the patient's ability to successfully tolerate the general anesthesia required to perform the procedure, the patient's lack of severe systemic medical problems that may dramatically impair wound healing, and the patient's pulmonary reserve to tolerate the postoperative course. The standard criteria are available for assessing anesthesia-related risks before surgery and should be used. Systemic illnesses that may predispose to poor wound healing include severe nutritional depletion, medications associated with organ transplantation, diabetes mellitus, and gastroesophageal reflux.

The degree to which the severity of pulmonary disease is used in the decision to proceed with conservation laryngeal surgery remains controversial in the literature. The real question is how well the patient will tolerate some degree of aspiration during the early postoperative period.[97] The amount of postoperative aspiration varies with the type of surgery contemplated. Vertical hemilaryngectomy sparing arytenoid typically causes little impact on swallowing function, whereas extensions of standard or extended supraglottic laryngectomy may result in increased dysphagia and aspiration risk.[98] Some authors advocate pulmonary function tests routinely for all patients,[99] whereas others use clinical evaluation such as walking up two flights of stairs without getting short of breath.[1,97] The percutaneous gastrostomy tube has been useful for patients who require long periods of no nutrition by mouth.[100] The literature actually leaves a fair amount of leeway for the clinician in terms of the pulmonary workup and in terms of how to use this information in clinical decision making. We rarely use pulmonary function testing preoperatively, unless requested by a medical consultant or anesthesiologist in preparation for a general anesthetic. If the patient has chronic obstructive lung disease but can walk up two flights of stairs without being winded and is active in his or her daily life, then the risks, benefits, and alternatives of conservation laryngeal surgery are discussed with the patient. If the pulmonary status indicates severe impairment of activity and a likelihood of morbidity or mortality after the procedure, we do not recommend conservation laryngeal surgery for that particular patient. In actual practice, each surgeon should know, over time, the limitations of a particular surgical technique in "their hands." Using this approach, there rarely will be patients who need functional laryngectomy for intractable aspiration, although there will also be many patients who have had their larynges spared with conservation laryngeal surgery.

An important factor in patient selection is the patient's insight into the problem and the ability of the patient to play an active role in his or her rehabilitation. The issue of age has been discussed often in the literature. Some authors have strict age criteria for performing partial laryngeal surgery.[101] Others have stated that it is the biologic age and the patient's overall constitution that is more important than the chronologic age.[1,100,102] In addition, conservation laryngeal surgery is a "team endeavor," and if the patient and family prefer to "sit on the sidelines" rather than be actively involved in the rehabilitation process, it is our experience that the patient will likely have a protracted course with increased morbidity. In our institutions, the assessment of the patient's willingness and ability to be rehabilitated is a joint decision among the speech pathologist, otolaryngologist, patient, and family. Although we do not obtain preoperative modified barium swallow, all patients are assessed by a speech pathologist, and the rehabilitation is discussed with the patient. The sine qua non for a cooperative and functional patient postoperatively is extensive preoperative counseling by the surgeon and speech pathologist. The patient and family should understand that much work is required on their part for rehabilitation. Some patients may choose alternative nonsurgical approaches to their problem or even total laryngectomy to avoid the swallowing rehabilitation required for some conservation laryngeal procedures.

The literature is replete with nonsurgical strategies for the preservation of the larynx for all stages of laryngeal carcinoma. All surgical and nonsurgical therapies have expected sequelae, risks, and complications, which are balanced by the ability of a given technique to control the malignancy. The two central issues of great importance to the patient, his or her family, and the physician are (1) the quality of life and (2) cancer control. The clinician weighs each factor carefully in advising a patient on which modality is preferred in a particular case. It is tempting for clinicians to apply their value system to what is good for a patient, although when making recommendations, it is clinicians' ethical and legal responsibility to offer patients the risks, benefits, and alternatives to the variety of treatment options that are available for their cancer.

Surgical Techniques

The next section reviews the various conservation laryngeal techniques available for the management of the spectrum of laryngeal carcinomas. The discussion is limited to open surgical approaches in which the functional goal is speech and swallowing without a permanent tracheostomy. The main category of surgical technique is introduced with a review of the literature analyzing the oncologic results, basic surgical technique, key surgical points, extensions of the procedure, expected functional outcome, and complications.

Indications and Contraindications

The indications for particular surgical techniques, presented in the literature, have varied over time. Indications frequently vary, depending

on the stage of development of the technique. When a technique is first introduced, most surgeons advocate conservatism in its application.[2,9] Later, pioneering surgeons attempt to cautiously extend the use of techniques, frequently on the basis of applications of their surgical skills combined with their knowledge of surgical anatomy and by necessity without the benefit of long-term oncologic follow-up evaluation.[103,104] The final stage in the development of a technique, according to Daly,[105] is reevaluation followed by acceptance of the technique on the basis of reported results. Before the last stage of development, the indications for a particular technique are usually parochial and based on the anecdotal experiences at a particular institution or the pronouncement of a pundit in the field. Reliance on the literature for indications and contraindications is, therefore, frequently not helpful because surgeons usually attempt to use techniques for a large spectrum of tumor stages. To address this problem, we have provided, for each technique, a thorough literature review in terms of oncologic results, functional outcome, and complications. The surgeon can use this information when advising patients concerning the risks, benefits, and alternatives for a particular surgical procedure.

Conservation Laryngeal Surgery for the Lesions Originating in the Glottic Level

Vertical Partial Laryngectomies

All vertical partial laryngectomies share a common approach, which includes a vertical transection through the thyroid cartilage and paraglottic space. The extent of resection is decided on the basis of the preoperative and intraoperative assessment of the tumor extent. Although this vertical approach provides useful and expeditious access to the endolarynx, they all share a common characteristic, which is "blind" entry into the larynx through a narrow exposure.[106] Depending on the extent of the primary lesion, the initial vertical cut may be close to or distant from the cancer. This point should be considered when these procedures are used.

Vertical Hemilaryngectomy

ONCOLOGIC RESULTS. Among the series in the English language literature in which local control has been reported in terms of the T stage, the local recurrence rates for T_1 lesions ranged from 0% to 11%, with five of six series having a local control of greater than 90% (Table 110-1). In one large series of 248 patients, the local control was 93% (104 of 112) for patients with malignancy confined to the true cords without anterior commissure involvement.[106] In that same series, patients with anterior commissure involvement without impaired mobility or extension beyond the glottis had local failure rate of 25% (8 of 32). When the anterior commissure is involved, the most common site of recurrence is the subglottis, as demonstrated in a series in which 14% (8 of 58) of patients with anterior commissure involvement had vertical hemilaryngectomy failure; in 7 of 8 of these patients, the recurrence was in the subglottis.[107] When the anterior commissure is involved by cancer, a wide surgical margin is indicated in the subglottis. Another factor that portends poor local control is extension beyond the confines of the glottis or impaired mobility.

Mohr and others[108] reported the highest local control in the literature for T_2 glottic carcinoma after extended vertical hemilaryngectomy, but they included only T_2 lesions with impaired mobility and excluded lesions that extended beyond the midventricle (only five patients) or beyond 5 mm into the subglottis because of the known high local failure rate for these lesions.[108] Subglottic extension has been associated with cricoid cartilage invasion, which is not resected in the standard vertical hemilaryngectomy.[109] Extension into the supraglottis through the ventricle should alert one to the possibility of thyroid cartilage invasion, which may account for the higher local recurrence in this patient group.[108] The difficulty in managing T_2 glottic carcinoma with vertical hemilaryngectomy was noted in a number of series that had local failure greater than 20%,[41,106,110] and six of the eight series in the English language literature that correlated local recurrence with T stage reported a local recurrence rate of greater than 14% (Table 110-2). One cause for impaired cord mobility is varying degrees of thyroarytenoid muscle invasion within the paraglottic space, which, in our opinion, may account for the higher local failure rates in vertical hemilaryngectomy in which the paraglottic space is routinely transected.[67]

The local control after the management of T_3 glottic carcinoma with vertical partial laryngectomy has yielded variable local failure rates ranging from 0% to 46%, with four of the eight series reporting local failure rates of greater than 36% (Table 110-3). This finding may be related to the fact that many cases may be understaged[52] and may have thyroid cartilage invasion, which is routinely partially resected during vertical hemilaryngectomy.

Our analysis reveals that consistently excellent oncologic results can be expected for T_1 glottic carcinomas involving the mobile membranous vocal cord, although once the anterior commissure is involved or if there is extension beyond the glottis or impaired cord mobility, vertical hemilaryngectomy should be used cautiously. On the basis of

Table 110-1

Local Recurrence after Vertical Hemilaryngectomy for T_1 Glottic Carcinoma

Author	Yr	T_1	LR	LR (%)
Thomas et al	1994	94	8	9
Lui, Ward, and Pleet	1986	24	1	4
Bailey and Calcaterra	1971	9	0	0
Mohr, Quenelle, and Shumrick	1983	25	2	8
Laccourreye et al	1991	146	16	11
Rothfield et al	1989	54	2	4

LR, local recurrence.

Table 110-2

Recurrence after Vertical Hemilaryngectomy for T_2 Glottic Carcinoma

Author	Yr	T_2	LR	LR (%)
Lui, Ward, and Pleet	1986	14	2	14
Bailey and Calcaterra	1971	18	3	17
Mohr, Quenelle, and Shumrick	1983	27	1	4
Kirchner and Som	1975	58	8	14
Som	1975	104	25	24
Biller, Ogura, and Pratt	1971	58	3	5
Laccourreye et al	1991	102	26	26
Johnson et al	1993	31	7	23

LR, local recurrence.

Table 110-3

Local Recurrence after Vertical Hemilaryngectomy for T_3 Glottic Carcinoma

Author	Yr	T_3	LR	LR (%)
Lesinski, Bauer, and Ogura	1976	18	3	17
Bailey and Calcaterra	1971	4	0	0
Biller and Lawson	1986	11	4	36
Mohr et al	1983	5	0	0
Som	1975	26	11	42
Kessler et al	1987	27	3	11
Mendenhall et al	1984	13	6	46
Kirchner and Som	1971	22	9	41

LR, local recurrence.

our review of the oncologic results in the literature, they do not recommend vertical hemilaryngectomy for those with advanced T_2 lesions or any T_3 or T_4 glottic carcinomas.

SURGICAL TECHNIQUE. A tracheostomy routinely is performed. A horizontal skin incision is used that is separate from the tracheostomy site. The midline raphe between the strap muscles is dissected from the cricoid cartilage to just above the superior aspect of the thyroid cartilage. When feasible, we prefer to resect the window of thyroid cartilage adjacent to the vocal cord, allowing reconstruction through imbrication laryngoplasty.[111] The external thyroid perichondrium is scored in the midline with a blade, and the perichondrium is elevated as a single flap in continuity with the strap musculature. This is done with an elevator such as a Freer and by cutting the perichondrium sharply with a knife at its superior and inferior attachments to the thyroid cartilage. A variety of techniques have been described in which varying amounts of ipsilateral thyroid cartilage is excised, ranging from no cartilage[112] to the entire ipsilateral ala.[41] We use the technique described by Pleet and colleagues,[111] in which a window of cartilage is outlined with a marker lateral to the level of the true vocal cord. The inferior aspect of the resected cartilage begins approximately 5 mm above the inferior aspect of the thyroid cartilage, and the resected portion is approximately 1.5 cm in height.[113] It extends from the midline to the posterior aspect of the thyroid cartilage. At this point the midline thyrotomy and other cuts are made with a knife, drill, or saw, depending on the degree of calcification of the thyroid cartilage and the preference of the surgeon. A No. 15 blade is used to make a midline vertical cricothyrotomy.

At this point the patient is paralyzed, the cords are held apart from below with a mosquito clamp, and a No. 12 blade is used to gently transect the anterior commissure, as in laryngofissure and cordectomy. The true and false cords are separated sharply up to the level of the petiole of the epiglottis. The cancer is visualized. The soft tissue resection is accomplished with a No. 15 blade for the anterior and posterior cuts. A right-angled Beaver blade or small right-angled scissors are useful for the posterior cut.

A variety of reconstructive options exist including no replacement of the glottic level allowing healing to occur by secondary intention, strap muscle flap with thyroid cartilage preservation,[112] and skin flaps.[7] In imbrication laryngoplasty,[111] we elevate a composite flap that includes the superior portion of the thyroid cartilage and the undermined false cord (Fig. 110-9).[113] This flap of vascularized, innervated false vocal cord is stabilized by the imbrication of the cartilage. It allows

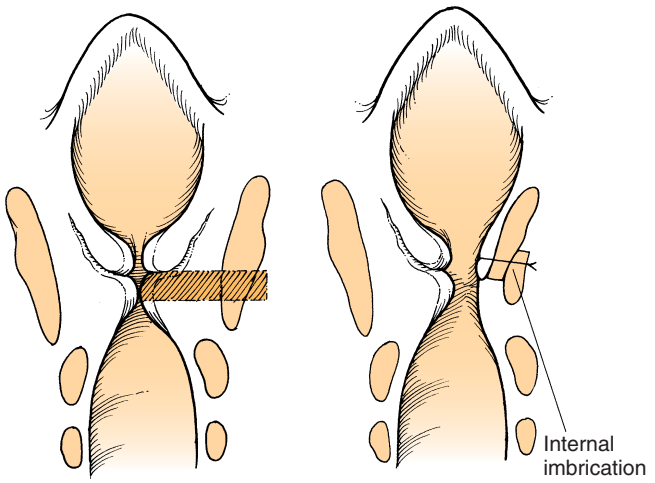

Figure 110-9. Imbrication laryngoplasty—reconstructive technique.

for soft tissue coverage from the false cord, but the inset of the superior thyroid cartilage on the inferior remnant also ensures medialization of the mucosal surface, which may improve phonation when compared with no reconstruction.[113]

EXTENDED PROCEDURES. A number of extensions of the standard procedure have been described.

FRONTOLATERAL VERTICAL HEMILARYNGECTOMY. Frontolateral vertical hemilaryngectomy has been used for lesions that approach or involve the anterior commissure or opposite true vocal cord anteriorly.[6] In this case the vertical thyrotomy is made through the thyroid lamina of the less involved side, allowing for removal of the anterior angle of the thyroid cartilage, anterior commissure, and a portion of the contralateral true vocal cord.

POSTEROLATERAL VERTICAL HEMILARYNGECTOMY. Posterolateral vertical hemilaryngectomy is used for cancers that extend posteriorly to involve the ipsilateral arytenoid mucosa.[5] The thyrotomy approach is the same as the standard operation, and the modification lies in the posterior extension of the resection to encompass part or all of the ipsilateral arytenoid cartilage and mucosa.

EXTENDED VERTICAL HEMILARYNGECTOMY. A number of procedures have been described in which extensive resection is accomplished through a vertical approach. Common characteristics include resection of the entire ipsilateral hemilarynx with the option of resecting the superior aspect of the cricoid cartilage. A variety of reconstructions have been proposed for these radical resections including sparing a posterior strip of the ipsilateral thyroid cartilage and fashioning a new hemilarynx, strap muscle reconstruction,[112] or pyriform sinus mucosal flap advancement into the hemilaryx.[108]

FUNCTIONAL OUTCOME. The functional outcome after the standard vertical hemilaryngectomy is some degree of permanent hoarseness, which varies with the reconstructive technique. A more impaired voice tends to accompany no reconstruction, whereas the best voice was associated with replacement of the glottis with an adjacent false cord flap.[113] Hirano and colleagues[114] compared the vocal function after a variety of reconstructions and noted that poor outcome was least often associated with free mucosal grafts, although this report did not evaluate the imbrication technique. Blaugrund and colleagues[115] noted that the supraglottic structures were responsible for voicing postoperatively predominantly in patients in whom one arytenoid was resected but also in patients in whom both arytenoids were spared. The supraglottic voicing was rougher and associated with a lower fundamental frequency than glottic voicing. Chronic dysphagia is not associated with the standard vertical hemilaryngectomy with or without resection of the vocal process, and 92% (11 of 12) of patients resumed a normal postoperative diet within 1 month.[98] It is not clear from the literature how extended vertical hemilaryngectomy affects function in terms of speech and swallowing.

KEY SURGICAL POINTS.

1. As in cordectomy, always tack the petiole of the epiglottis back into position with a 3-0 Vicryl stitch so that the epiglottis will not prolapse posteriorly postoperatively, obscuring the view of the glottis.

2. Also as in cordectomy, suture the anterior commissure on the noninvolved side anteriorly at the external thyroid perichondrium with a 4-0 Vicryl stitch so that the cord will be in normal position and the vocal tendon will have proper tension.

COMPLICATIONS. Uncommonly, wound complications such as seroma or hematoma might occur. Again, as in cordectomy, fistula is uncommon. In extended procedures, there is a higher incidence of complications including delay in decannulation, stenosis, and long-term dysphagia.[79] Persistent airway edema can be managed expectantly or with laser laryngoscopy.

Epiglottic Laryngoplasty

ONCOLOGIC RESULTS. Epiglottic laryngoplasty was first described by the Czechoslovakian surgeon Sedlacek,[116] then reported by Kambic and colleagues[117] in Yugoslavia, and later popularized in the United States by Tucker and associates.[118] The history of the development of this technique is classic for conservation laryngeal surgery in general; it was first developed in Europe and later imported and popularized in the United States. The term *epiglottic laryngoplasty* refers to the reconstruction, which is done by undermining the epiglottis and advancing it inferiorly and laterally to reconstruct the larynx after vertical hemilaryngectomy or anteroinferiorly to reconstruct after a bilateral vertical partial laryngectomy. The entrance into the larynx, like in all vertical partial laryngectomies, is through two vertical thyrotomies: one just anterior to the posterior aspect of the thyroid cartilage on the more involved side, and the other can be anywhere from a midline thyrotomy when the reconstruction is applied to the standard vertical hemilaryngectomy or symmetrically placed on the opposite thyroid ala for extensive bilateral lesions. In the most extensive resection, both cords, true cords, and one arytenoid may be resected. Tucker and colleagues[74] reported on a series of patients who underwent the procedure with a minimum follow-up period of 2 years and in which there were no local recurrences among four T_{1a}, 8 T_{1b}, and 11 T_3 cancers and one recurrence in eight (12.5%) T_2 cancers. Tucker[119] noted a 50% local recurrence rate for lesions with greater than 6 mm of subglottic extension anteriorly.

SURGICAL TECHNIQUE.[118] A tracheostomy is performed. We describe the procedure in which both thyroid ala are resected to manage a bilateral lesion. The midline raphe of the strap muscles is identified. The thyroid perichondrium is incised in the midline. The perichondrium is elevated in continuity with the overlying strap musculature. The vertical thyrotomies are made 3 to 4 mm anterior to the posterior aspect of the thyroid cartilage on the more involved side and placed more anteriorly on the less involved side. A transverse cricothyrotomy is performed. Right-angled scissors are used to transect the soft tissue of the paraglottic space on the less involved side through the previously made thyrotomy. The resection on the involved side can resect the arytenoid, taking care to preserve the posterior arytenoid mucosa. The epiglottis is undermined to the level of the vallecula, which is not transgressed (Fig. 110-10). It is advanced inferiorly and sutured to the cricothyroid membrane or cricoid cartilage and laterally to the thyroid cartilage remnants. The external thyroid perichondrial flap and strap muscles are then sewn across the midline.

KEY SURGICAL POINTS.

1. At least one functional arytenoid should be saved, and care should be taken not to damage the cricoarytenoid joint during the resection.

2. The preepiglottic space is dissected away from the anterior surface of the epiglottic cartilage, and this dissection should be brought up through the median hyoepiglottic ligament to allow for the epiglottis to be advanced far enough inferiorly.

3. No internal mucosal stitches are necessary, although the inferior suture line should be under no tension to prevent dehiscence.

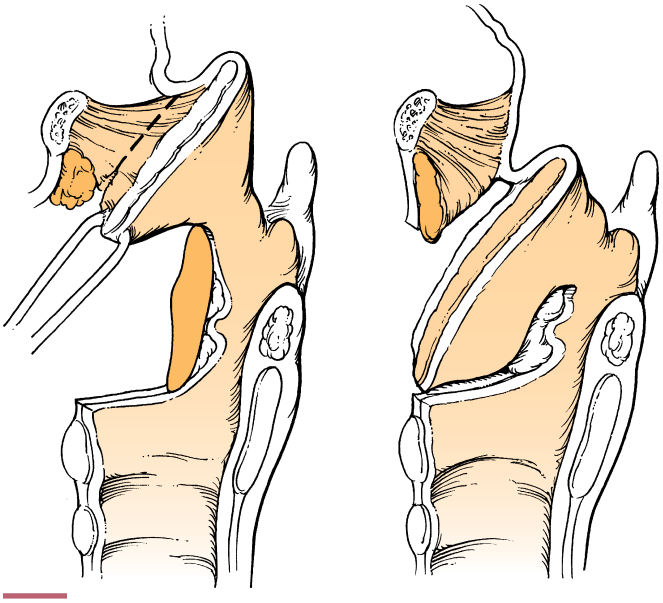

Figure 110-10. Epiglottic laryngoplasty—undermining of the epiglottis in the preepiglottic space before closure.

EXTENDED PROCEDURES. One extension of the epiglottic laryngoplasty has combined the procedure of the supracricoid partial laryngectomy with cricohyoidoepiglottopexy as described by Guerrier and colleagues,[29] in which an epiglottic advancement flap and pexy of the cricoid and the hyoid are performed.

FUNCTIONAL OUTCOME. In Tucker and associates'[118] original description, all patients were taking food by mouth from 1 to 18 days after decannulation, although as in all conservation laryngeal procedures in which one arytenoid is resected, some degree of temporary dysphagia is to be expected. Other authors have encountered increased degrees of postoperative aspiration and an extremely breathy voice, which they attributed to the wide anterior posterior dimension of the airway that prevents appropriate sphincteric function of the posterior glottis.[120] Nong and others[121] have responded to this problem by modifying the procedure by use of a number of endolaryngeal flaps to reconstruct the neolarynx to decrease aspiration and breathiness while preserving respiration.

COMPLICATIONS. Reported complications have included delayed decannulation from postoperative aspiration and mild upper airway obstruction.[118]

Horizontal Partial Laryngectomies

Horizontal partial laryngectomies are so called because the initial entry into the laryngeal lumen is through a transverse or horizontal cut. This incision is distant from the cancer, which allows for safe entry into the endolarynx followed by inspection of the lesion before making additional incisions. Although in the past the term *horizontal partial laryngectomy* has been used by some authors interchangeably with supraglottic partial laryngectomy, this is one type of horizontal technique that is used for supraglottic carcinomas. During the past 2 decades, the supracricoid partial laryngectomy with cricohyoidoepiglottopexy, another horizontal technique with use for managing selected glottic carcinomas, has been developed.

Supracricoid Partial Laryngectomy with Cricohyoido-Epiglottopexy

ONCOLOGIC RESULTS. The supracricoid partial laryngectomy with cricohyoido-epiglottopexy allows for resection of both true cords, both false cords, the entire thyroid cartilage, both paraglottic spaces bilaterally, and a maximum of one arytenoid. Speech and swallowing without a permanent tracheostomy are achieved. The technique's main use has been for the management of selected T_2 and T_3 carcinomas of the glottis, although it has been reported that it was used for T_{1b} and

selected T_4 glottic carcinomas. There were no local recurrences among nine patients with T_1 glottic carcinomas (one T_{1a} and eight T_{1b}).[72] The local control for T_2 lesions is 4.5% (3 of 67).[122] The local recurrence for selected T_3 glottic carcinomas was 10% (2 of 20).[123] Piquet and Chevalier[47] reported the local recurrence for a group of 104 (T_1, 12; T_2, 77; T_3, 15) previously untreated patients to be 5%, although local recurrence was not reported by T stage in this series. One of the reasons for the consistently low local recurrence rates may be the complete resection of the entire thyroid cartilage and the bilateral en bloc resection of the paraglottic spaces.

Transglottic lesions have been defined as carcinomas that extend across the laryngeal ventricle, involving the true and false cords.[124] Although the exact origin of these cancers is frequently unclear, the origin is attributed to the site in which the epicenter of the tumor resides. In carcinomas with transglottic extension, the local recurrence after conservation approaches that use extended vertical hemilaryngectomy or extended supraglottic laryngectomy has yielded a local failure rate of 23% (7 of 30).[125] One caveat is that the supracricoid laryngectomy with cricohyoidoepiglottopexy does not result in a complete resection of the supraglottis, and therefore we prefer to perform supracricoid laryngectomy with cricohyoidopexy for transglottic extension.

SURGICAL TECHNIQUE.[72] After the creation of a U-shaped incision in line with the tracheostomy site, which will be placed later in the procedure, the superior flap is elevated to approximately 2 cm above the hyoid bone, exposing the underlying strap muscles. Next, the sternothyroid and the thyrohyoid muscles are transected individually, from medial to lateral, along the superior aspect of the thyroid cartilage. The sternohyoid muscle is elevated inferiorly, allowing for the exposure of the sternothyroid muscle. Typically, there is a blood vessel that pierces the deep strap musculature to the more superficial layer that should be ligated at this point bilaterally. The sternothyroid muscle is then carefully transected along the inferior edge of the thyroid cartilage. Care is taken at this point not to cut the underlying thyroid gland. The constrictor muscles are then transected along the posterior and superior-lateral aspect of the thyroid cartilage, and the pyriform sinus mucosa is elevated off of the internal surface of the thyroid cartilage bilaterally, as is done in a total laryngectomy. A Freer elevator is used to disarticulate the cricoarytenoid joint bilaterally, taking care to protect the recurrent laryngeal nerves. The recurrent laryngeal nerves are never actually visualized. The isthmus of the thyroid gland is transected and ligated. At this point, a blunt finger dissection of the cervicomediastinal trachea is done to the level of the carina, as is done in a tracheal resection and anastomosis, to close the tracheal defect. A transverse cricothyrotomy is performed just above the cricoid cartilage, and the endotracheal tube is removed from above and placed into the cricothyrotomy. The larynx is then entered through a transverse transepiglottic laryngotomy. The scissors are oriented obliquely and inferiorly to allow transection of the epiglottis at the level of the petiole, if the lesion is amenable to such an approach, and to allow for entry just above the false cords and preservation of as much epiglottis as possible.

The endolaryngeal excision is now performed on the non–tumor-bearing side first, and the incision is brought down in the sagittal plane with a scissors at the junction between the false cord and arytenoid. The transection is carried inferiorly just posterior to the ventricle and then through the vocal process of the arytenoid. Special care is taken to avoid entering the cricoarytenoid joint with the scissors. Just above the cricoid cartilage, the orientation of the scissors changes to allow connection of this incision, through the cricothyroid muscle, to the previously made cricothyrotomy. The larynx is opened up on its anterior spine like a book (Fig. 110-11). The cut on the tumor-bearing side may be made through just posterior to the ventricle again or may transect all or part of the arytenoid cartilage. This incision can be done by cutting the subglottic mucosa with a No. 15 blade and following posteriorly and superiorly to the level of the arytenoid. Nonetheless, the posterior arytenoid mucosa should be spared so that it can be used in the endolaryngeal reconstruction to cover the cricoarytenoid joint area on the cricoid. This forms a cushion, postoperatively, against which the remaining arytenoid will abut to allow for closure of the larynx.

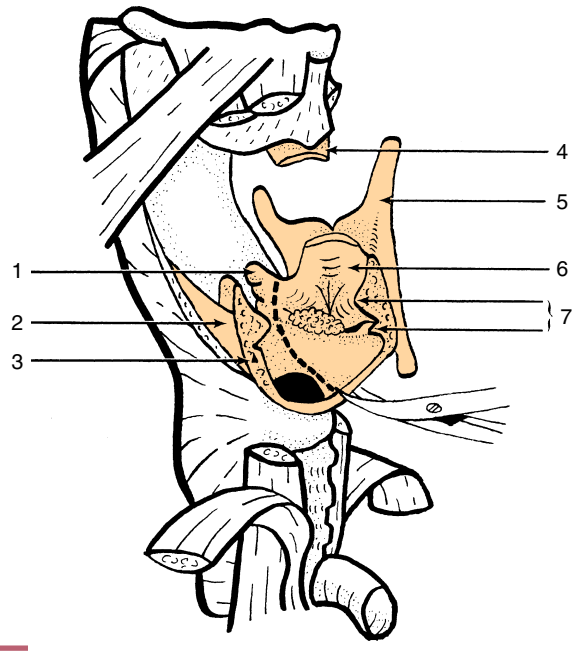

Figure 110-11. Supracricoid partial laryngectomy with cricohyoidoepiglottopexy—exposure of malignancy. *1,* arytenoid; *2,* internal thyroid perichondrium; *3,* vocal process; *4,* inferior aspect of transected epiglottis; *5,* thyroid cartilage; *6,* petiole of the epiglottis; *7,* false and true vocal cords.

The reconstruction is begun by pulling the arytenoid cartilages forward with 3-0 Vicryl suture material by placing a stitch just at or just above the vocal process and sewing them (or the posterior arytenoid mucosa in the case of unilateral arytenoid resection) anterolaterally to the cricoid cartilage. In this way, the arytenoid will not prolapse backward postoperatively. Impaction of the cricoid to the hyoid is performed with three centrally placed 2-0 Vicryl sutures on a 65-mm round needle. The first stitch is placed circumferentially, submucosally around the cricoid cartilage, in the midline. The stitch is then passed through a few millimeters of inferior epiglottic cartilage, submucosally, so that when the stitch is tied down, the epiglottic mucosa will be approximated to the cricoid mucosa. Next, the same first stitch is passed back into the preepiglottic fat and up around the hyoid bone and deep into the tongue base. This large needle allows the suture to be passed deeply into the tongue base, submucosally, while it is carefully palpated with a finger on the tongue base mucosa to pull it back and have a bulge of tongue-base tissue over the airway postoperatively (Fig. 110-12). Before tightening the sutures, the two lateral sutures are pulled taut, which places the trachea in its postoperative position, and the tracheostomy is performed in line with the skin incision. With the two lateral cricohyoidoepiglottopexy sutures under tension, the central pexy stitch is tied, followed by the two lateral stitches. The strap muscles are closed as a second layer closure with 3-0 Vicryl. A cuffed tracheostomy tube is put into place. The skin wound is closed in two layers, taking special care to separate the tracheostomy site from the remainder of the wound with a subcutaneous stitch placed between the skin and the underlying strap muscles above the tracheostomy site.

Key Surgical Points

1. During the exposure, elevate the skin flaps to approximately 2 cm above the hyoid bone to prevent tethering of the skin in the closure postoperatively.

2. When disarticulating the cricoarytenoid joint, be careful not to injure the recurrent laryngeal nerve.

3. When making the vertical prearytenoid incision just posterior to the ventricle, be careful not to enter the cricoarytenoid joint.

4. Always save the posterior arytenoid mucosa in the case of a transected arytenoid cartilage, and sew this mucosa anteriorly to the cricoid cartilage during the closure.

5. The three tongue base sutures should be placed precisely 1 cm apart and arched up deeply into the tongue base. We use a 2-0 Vicryl on a 65-mm needle.

6. Perfect alignment between the cricoid cartilage and the hyoid bone should be created to reduce the risk of dysphagia postoperatively.

7. Submucosal stitches in the inferior aspect of the epiglottic remnant should be performed to avoid posterior rotation of the epiglottis that may cause airway compromise postoperatively.

8. Gentle internal palpation of the upper esophageal sphincter with a finger will allow for assessment of hypertonia, which should prompt the consideration of cricopharyngeal myotomy except in the presence of gastroesophageal reflux.

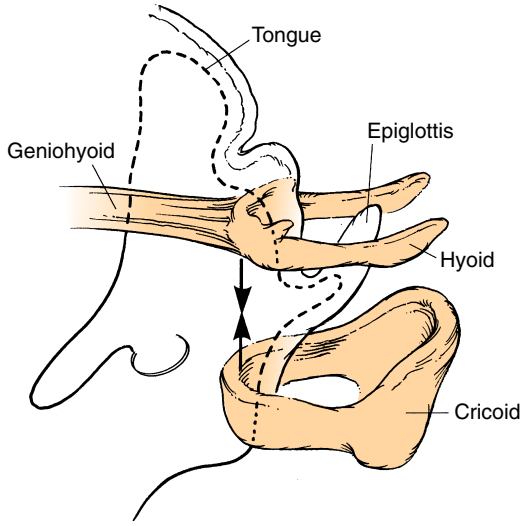

Figure 110-12. Supracricoid partial laryngectomy with cricohyoidoepiglottopexy—laryngoplasty using circumferential cricoid, hyoid, epiglottic, and tongue base sutures.

9. The dissected inner thyroid perichondrium should be gently sewn anteriorly with one 3-0 Vicryl stitch after the creation of the cricohyoidoepiglottopexy to reposition the pyriform sinus in a closer approximation to normal.

10. Always put the tracheostomy in line with the main incision, and always pull up the trachea before placing the tracheostomy so that it will be in line with the incision postoperatively.

EXTENDED PROCEDURES. Extensions of the basic technique include resection of one arytenoid. Anterior subglottic extension may be managed with resection of the anterior arch of the cricoid,[126] which is closed with a pexy between the first two tracheal rings and the hyoid or a tracheohyoidoepiglottopexy.

FUNCTIONAL OUTCOME. Temporary dysphagia immediately postoperatively is to be expected, but long-term dysphagia is rare. Review of the functional results in the world literature revealed a range of days to removal of nasogastric tube postoperatively from 9 to 50 days (Table 110-4). The need for removal of the larynx for intractable aspiration was low and ranged from 0% in 4% of seven studies and ranged from 1% to 4% in the remaining three studies (see Table 110-4). These results compare favorably with the functional laryngectomy rate for aspiration noted after supraglottic laryngectomy (Table 110-5). The vocal quality after supracricoid partial laryngectomy has been studied in a prospective fashion, and by the sixth month, speech parameters of phrase grouping and number of words per minute were similar to normal speakers, although the mean fundamental frequency was lower and wider than normal, suggesting some voice instability postoperatively.[127] In addition, we found that the degree of voicelessness parameters increased, suggesting difficulties in achieving consistent neoglottic closure during speech.[127]

COMPLICATIONS. In one series, the only complication was progressive hyoid necrosis, resulting from underlying severe vasculitis.[72] Three patients in Piquet's series had neolaryngeal stenosis develop requiring placement of a Montgomery T-tube for 3 months.[47]

Conservation Laryngeal Surgery for Lesion Originating in the Supraglottic Level

The management scheme at most institutions managing supraglottic carcinoma has included surgical and nonsurgical approaches. Table 110-6 categorizes patients with supraglottic carcinoma, from a number of large series, treated in the United States by various approaches including partial laryngectomy, total laryngectomy, or radiotherapy alone.[40,97,128,129] The range of percentages of patients undergoing primary surgical management varied from 47% to 90%. When the authors analyzed the number of patients undergoing total laryngectomy

Table 110-4

Functional Outcome after Supracricoid Laryngectomy with Cricohyoido-epiglottopexy

Author	Patients (*n*)	Duration NG	Func Laryn	Func Laryn (%)
Guerrier et al	58	9-50	1	1.7
Vigneau et al	52	19*	2	3.8
Traissac and Verhulst	97	10-33	1	1.0
Piquet and Chevalier	104	21-45	0	0
Laccourreye et al	67	11-40	0	0
Piquet	46	10-90	0	0
Pech	17	10-40	0	0

*Average duration.
Func laryn, functional laryngectomy for aspiration; NG, nasogastric tube.

Table 110-5

Adverse Results after Supraglottic Laryngectomy*

Author	Series Includes Extended Procedures	SGL	Permanent Gastrostomy (%)	Death from Pneumonia (%)	Functional Laryngectomy (%)
Herranz-Gonzales[102]	N	110	0 (0.00)	0 (0.00)	1 (0.91)
Soo et al[148]		78	0 (0.00)	0 (0.00)	0 (0.00)
Hirano et al[139]	Y	38	0 (0.00)	0 (0.00)	3 (7.89)
Burstein and Calcaterra[133]		40	0 (0.00)	0 (0.00)	1 (2.50)
Flores et al[100]		46	4 (8.70)	2 (4.35)	5 (10.87)
Lee et al[40]		60	1 (1.67)	1 (1.67)	3 (5.00)
Beckhardt et al[99]		49	2 (4.08)	1 (2.04)	4 (8.16)
Spaulding et al[135]		33	0 (0.00)	0 (0.00)	1 (3.03)

This table includes series that reported functional results.
*Includes all laryngectomies done for chronic aspiration.

Table 110-6

Therapeutic Management of Supraglottic Carcinoma

Author	Period	Patients Surgery (*n*)	Patients Partial (*n*)	Patients Total (*n*)	Patients Primary RT (*n*)	Surgery (%)	Total (%)
Zamora et al[129]	1952-1985	445	258	187	75	0.86	0.42
DeSanto[39]	1971-1980	227	103	124	24	0.90	0.55
Lee et al[40]	1974-1987	190	65	125	211	0.47	0.66
Lutz et al[97]	1975-1986	202	72	130	99	0.67	0.64

Table 110-7

Local Recurrence after Surgical Management of Supraglottic Carcinoma

Author	Patients Partial (*n*)	LR Partial	Patients Total (*n*)	LR Total	Overall LR
DeSanto[39]	103	3	124	6	0.04
Coates et al[130]	40	1	117	4	0.03
Lee et al[40]	65	0	125	—	0.00
Lutz C et al[97]	72	1	130	3	0.02

LR, local recurrence.

in these series, they noted that the range was from 42% to 66%. Although numerous surgical series have had overall local recurrence rates including all T stages of less than 5%[39,40,97,130,131] in most series (Table 110-7), most patients undergoing primary surgical treatment of the supraglottis underwent total removal of the larynx (see Table 110-6). The conservative surgical option among the patients in Table 110-7 (with the exception of five patients in the Mayo series who were treated with transoral epiglottectomy) was standard or extended supraglottic partial laryngectomy. The main use of the standard supraglottic laryngectomy is for those with selected T_1 and T_2 supraglottic carcinomas,[5] whereas its extensions are used for those with highly selected T_3 and T_4 cancer.[132]

Table 110-8

Local Recurrence vs. T Stage after Supraglottic Laryngectomy

Author	T_1	LR T_1	LR T_1 (%)	T_2	LR T_2	LRT_2 (%)	T_3	LR T_3	LRT_3 (%)	T_4	LR T_4	LRT_4 (%)
Bocca et al[132]	59	5	9	296	38	13	46	8	17	28	7	25
Burstein and Calcaterra[133]	3	0	0	20	3	15	16	1	6	1	0	0
Lee et al[40]	3	0	0	32	0	0	21	0	0	4	0	0
Alonso[9]	167	16	10				42	19	45	22	13	59
Spaulding et al[135]	4	0	0	16	0	0	4	3	75	9	6	67
Herranz-Gonzales et al[102]	37	3	8	55	2	4	8	0	0	10	1	10

LR, local recurrence.

Horizontal Partial Laryngectomies

Supraglottic Laryngectomy

ONCOLOGIC RESULTS. When series of supraglottic laryngectomy from the United States were analyzed, it was noted that the local recurrence varied from 0% to 12.8%, with seven of eight of the large series having a local control of 90% or higher.[5,39,40,97,130,133-135] When local recurrence after supraglottic laryngectomy was analyzed by T stage, one saw consistently high local control for selected T_1 and T_2 lesions but an extremely variable success rate for those with T_3 and T_4 lesions, with local recurrence rates as high as 75% for the former and 66.7% for the latter (Table 110-8). It is not clear from the literature which patients with specific T_3 or T_4 lesions were at highest risk for recurrence; therefore until this is evaluated further in the literature, supraglottic laryngectomy should be performed with caution for those with highly selected T_3 and T_4 lesions of the supraglottis. Lee and colleagues[40] noted improved local control among intermediate-sized supraglottic carcinomas with the addition of postoperative radiotherapy after supraglottic laryngectomy, although the tradeoff for local control seemed to be decreased functional results after extended supraglottic laryngectomy and radiotherapy in that series. Nonetheless, supraglottic laryngectomy provides consistently excellent oncologic results among patients with selected T_1 and T_2 lesions. Our recent analysis of the extension of supraglottic carcinoma to the glottic level revealed a statistically significant increase in glottic involvement for those with lesions with impairment of the vocal cord or involvement of the ventricle.[65] These findings support the contentions that extension below the false cord and impaired cord mobility are contraindications for supraglottic laryngectomy.[84]

SURGICAL TECHNIQUE. We perform an apron incision, in line with the tracheostomy, and routinely perform bilateral modified neck dissection. The main trunk of the superior laryngeal nerve should be spared bilaterally in the nonextended supraglottic laryngectomy. The fascia between the strap muscles at the level of the superior aspect of the thyroid cartilage is divided. In addition, the fascia between the strap muscles is divided inferiorly, and the thyroid isthmus is transected and ligated routinely. The intervening fascia between the strap muscles is left intact. The sternohyoid and the thyrohyoid muscles at the superior border of the thyroid cartilage are divided, with care taken laterally to avoid damaging the superior laryngeal nerves. The constrictor muscles are sharply cut at the posterior and superior edge of the thyroid cartilage laterally all the way to the top of the superior cornua. The superior edge of the thyroid cartilage is scored with a knife, and a Freer elevator is used to elevate the periosteum off of the thyroid cartilage. The external thyroid cartilage perichondrium is elevated halfway down the cartilage from the superior edge to allow for the transverse thyrotomy to be made at the level just above the anterior commissure. The pyriform sinuses are then freed up bilaterally for endolaryngeal tumors, as is done in total laryngectomy, and unilaterally for tumors that involve the pyriform sinus. A tracheostomy is then performed. The next step in the procedure depends on whether the tumor involves the endolarynx alone or is in the vallecula.

The following is the standard technique for T_1 and T_2 endolaryngeal supraglottic carcinomas. If the tumor has not involved the vallecular mucosa and if it was not palpable beneath the vallecula mucosa in the pre-epiglottic space, then it is oncologically sound to spare the hyoid bone, and it is skeletonized from below with an electrocautery. The horizontal thyrotomy is made through the thyroid cartilage at the appropriate level with a sagittal saw. The vallecula is entered, and the epiglottis is pulled externally with an Allis clamp. The resection is done close to the epiglottis, sparing both arytenoids. The cut is made anterior to the arytenoid cartilage bilaterally in a superior-to-inferior direction with one scissor blade in the laryngeal lumen and one scissor blade between the thyroid cartilage and the previously elevated internal thyroid perichondrium (Fig. 110-13). This will allow sparing of the pyriform sinuses bilaterally. The cut is brought down to the level of the ventricle, at which point the transection is made through the ventricle at right angles to the previously made transection in front of the arytenoid. The specimen is then removed for frozen section analysis.

The reconstruction is accomplished by first sewing either the remnant of false cord mucosa or the lateral aspect of the floor of the ventricle to the external perichondrium at the corresponding level of the remaining thyroid cartilage. The stitch should be placed to reposition the anterior commissure into normal position if necessary. There have been numerous reports in the literature on various techniques for closure and laryngoplasty after supraglottic laryngectomy.[55,136,137] The technique we use is similar to the closure used in supracricoid laryngectomy. The concept is to provide mucosa-to-mucosa closure while creating a prominence of tongue-base tissue right over the central aspect of the larynx and the laryngeal inlet. This is done by passing stitches submucosally deep into the tongue base. Three 1-0 Vicryl stitches are used as in supracricoid laryngectomy (Fig. 110-14). The first stitch is placed circumferentially around the remnant of the thyroid cartilage, taking care to remain submucosal and to not damage the anterior commissure. The stitch is then arched high up around the hyoid and submucosally deep into the tongue base, using the entire circumference of the needle. Two additional stitches are placed 1 cm lateral; again, care is taken to pass the stitches around the entire circumference of the remaining inferior thyroid ala, subperichondrially on the internal surface of the thyroid cartilage, so that the thyroarytenoid musculature is not tethered by the stitch. Each of these stitches is passed around the hyoid bone, if it is present, and submucosally deep into the tongue base. The two lateral stitches are held tight by the assistant while the central stitch is tied down. The two lateral stitches are then tied. The periosteum with the overlying inferior strap muscle flap is sewn superiorly to the suprahyoid musculature. The skin flaps are closed, with special care to separate the tracheostomy site from the remainder of the neck wound with a semicircular running 3-0 Vicryl stitch placed sub-

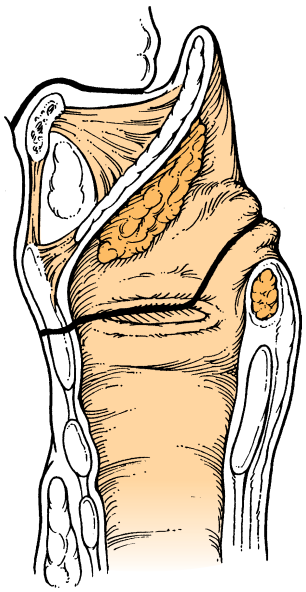

Figure 110-13. Supraglottic laryngectomy—superior to inferior of the false cord, to the level of the ventricle, anterior to the arytenoids.

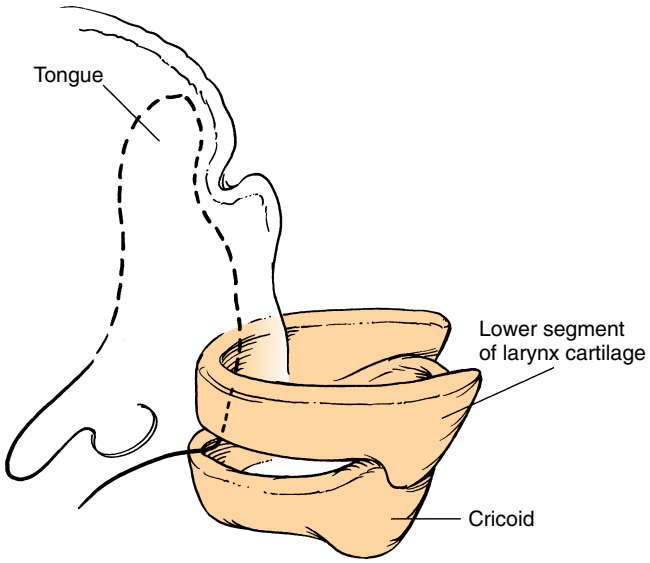

Figure 110-14. Supraglottic laryngectomy—laryngoplasty performed with three closure stitches circumferentially around the inferior half of the thyroid cartilage and submucosally into the tongue base, as is done in the supracricoid partial laryngectomies.

cutaneously in the upper flap to the strap muscles above the tracheostomy site.

Key Surgical Points

1. We locate the main trunk of the internal and external branches of the superior laryngeal nerve routinely at the time of bilateral modified neck dissection (Fig. 110-15). This is accomplished by dissection of the fat pad, which is anterior to the carotid artery, inferior to the hypoglossal nerve, and lateral to the superior laryngeal nerves. The superior thyroid artery runs through this fat pad and is transected proximally and distally to perform this dissection. This procedure also requires removal of the lymphatics, which travel adjacent to the larynx, allowing the main trunk of the superior laryngeal nerves to be spared bilaterally.

Figure 110-15. Superior laryngeal lymph node dissection—exposure of the superior laryngeal nerve at the time of modified neck dissection. *A,* internal jugular vein; *B,* omohyoid muscle; *C,* sternocleidomastoid muscle. *1,* hypoglossal nerve; *2,* carotid artery; *3,* superior laryngeal nerve; *4,* transected proximal and distal ends of the superior thyroid artery.

2. The superior aspects of the pyriform sinus are dissected from the inner aspect of thyroid cartilage when they are not involved by the malignancy.

3. The superior aspects of the arytenoid are spared, unless the malignancy is directly involving this area.

4. The hyoid bone is not spared when the malignancy involves the vallecula or tongue base.

5. The greater cornua of the hyoid is resected in those with marginal lesions.

6. The tongue base sutures are placed in the midline and 1 cm off of the midline, avoiding damaging the hypoglossal nerves and the lingual arteries.

EXTENDED PROCEDURES. There are two basic extensions of the supraglottic laryngectomy: (1) resection of one arytenoid or the upper part of the pyriform sinus and (2) resection of a portion of the tongue base.[32] Modifications of the standard procedures can be accomplished systematically by the following two approaches.

ARYTENOID, ARYEPIGLOTTIC FOLD, OR SUPERIOR MEDIAL PYRIFORM INVOLVEMENT FROM SUPRAGLOTTIC CARCINOMA. Skeletonize the hyoid bone, and free up the lateral cornua of the hyoid if it is to be resected. Only free up the internal thyroid perichondrium on the uninvolved side. Enter the endolarynx through the vallecula on the uninvolved side or through the thyrotomy inferiorly if the vallecula is involved. Cut anterior to the uninvolved arytenoid and through the false cord. Bring the resection around the upper pyriform on the involved side, which is transected at the level of the ipsilateral true vocal

cord. When the pharyngoepiglottic fold is involved, resect a generous margin of the posterior tonsillar pillar and a portion of the ipsilateral tongue base. If the posterior tonsillar pillar and tongue base have been unilaterally resected, close this portion of the defect separately, taking care to advance the tongue base posteriorly. Close the tongue base with three large stitches.

BASE OF TONGUE EXTENSION FROM SUPRAGLOTTIC CARCINOMA. Enter inferiorly through the thyrotomy. Do not skeletonize the hyoid bone. If necessary, free up the twelfth nerves and move them out of the line of resection. Cut above the hyoid bone and do not skeletonize. Make the tongue base resection under direct visualization from below with a 2-cm margin. The resection should leave at least 1 cm of tongue base posterior to the circumvallate papillae to allow for adequate function postoperatively. The closure is with the submucosal tongue base sutures.

FUNCTIONAL OUTCOME. Although there is some variability in vocal quality after supraglottic laryngectomy combined with radiotherapy, among patients who have undergone decannulation within the first 3 postoperative weeks, microstrobolaryngoscopic findings reveal normal vibration of the cords and normal vibration amplitudes, and results of sonographic evaluations are normal, with some abnormalities related to removal of the resonance space above the cords.[68] One study, which assessed the subjective voice qualities, found that 87% of patients had normal-to-mild breathiness and that 67% had mild or no evidence of hoarseness.[138]

The stages of wound healing and stabilization may take months, although a reasonable measure of progression of swallowing rehabilitation, in the literature, has been the point at which the patient no longer relies on tube feedings for nutrition. Hirano and colleagues[139] noted that 84% (32 of 38) of patients had removal of the nasogastric tube within 30 days postoperatively, whereas some patients required tube feeding for 3 months. Padovan and Oreskovic[68] noted that complete rehabilitation takes at least 3 months, and this may be prolonged in irradiated patients. The factors that Hirano and colleagues[139] found to be significantly related to duration of nasogastric intubation were extent of removal of the arytenoid and asymmetric removal of the false cords, whereas resection of the hyoid and tongue base was not related to swallowing outcome. Flores and colleagues[100] also noted that arytenoid resection was associated with failure to attain swallowing function and that resection of the hyoid and tongue base did not worsen swallowing outcome. Although Flores and others[100] could not find a significant correlation between transection of one versus two superior laryngeal nerves and swallowing outcome, it is interesting to note that all nine patients who failed to swallow had at least one superior laryngeal nerve resected, and there were no patients in this series with the nerves spared bilaterally with which to make a comparison. Although Padovan also agreed that arytenoid preservation is important in swallowing outcome, his group stressed the importance of bilateral preservation of the superior laryngeal nerve to achieve timely swallowing function.[68] This nerve can be visualized after modified neck dissection, and when the pyriform sinus is not involved by the malignancy, the main trunks of the internal and external branches of the superior laryngeal nerve frequently can be spared bilaterally. Staple and Ogura,[140] in a cineradiographic study of 36 patients who had undergone supraglottic laryngectomy, emphasized the association of impaired neuromotor function of the tongue through the hypoglossal nerves and significant degrees of aspiration.

Impaired swallowing function has been associated with extended supraglottic laryngectomy.[40,98,100] The literature was reviewed, and the results from series that assessed the extreme adverse outcomes of permanent gastrostomy, functional laryngectomy, and death resulting from aspiration pneumonia were tabulated in Table 110-5. The series of patients undergoing supraglottic laryngectomy without extended procedures[5,102] seem to be less likely to undergo functional laryngectomy compared with the series that included extended procedures.

COMPLICATIONS. The reported fistula rate after supraglottic laryngectomy has been 0% to 12.5%.[133] Other reported complications, reported in large series, include aspiration pneumonia (0% to 10.8%),[99,141] inability to decannulate the tracheostomy (0% to 5.5%),[102,133] and tracheocutaneous fistula.[5]

Supracricoid Laryngectomy with Cricohyoidopexy

ONCOLOGIC RESULTS. Supraglottic carcinomas that are not amenable to supraglottic laryngectomy because of glottic level involvement either through the anterior commissure or the ventricle, preepiglottic space invasion, decreased cord mobility, or limited thyroid cartilage invasion frequently will be resectable with supracricoid laryngectomy with cricohyoidopexy. These lesions are not rare, and in one study, the incidence of spread of supraglottic carcinoma to the glottic level was between 20% and 54% in the literature.[65] Glottic level invasion should be suspected when there is either impaired cord mobility or extension of carcinoma to the ventricle.[65] In a series of selected supraglottic carcinomas, Laccourreye and colleagues[72] found there were no local recurrences in 68 patients (T_1, 1; T_2, 40; T_3, 26; and T_4, 1) with a minimum follow-up period of 18 months. Laccourreye and colleagues[142] later reported on 19 patients with gross pathologic invasion of the preepiglottic space, with a minimum follow-up period of 5 years, and noted a local control of 94.4% (18 of 19). Chevalier and Piquet[143] reported on their series of 61 consecutive cases of supraglottic carcinoma managed with supracricoid laryngectomy with cricohyoidopexy and noted a local recurrence rate of 3.3% (2 of 61). They attributed the oncologic success to the en bloc resection of the bilateral paraglottic spaces, the preepiglottic space, and the entire thyroid cartilage. Contraindications to the procedure include (1) subglottic extension greater than 10 mm anteriorly and 5 mm posteriorly because of the potential for cricoid cartilage involvement; (2) arytenoid fixation; (3) massive preepiglottic space invasion with involvement of the vallecula; (4) extension to the pharyngeal wall, vallecula, base of tongue, postcricoid region, and interarytenoid region; and (5) cricoid cartilage invasion.[72]

SURGICAL TECHNIQUE.[72] The approach and many of the steps are the same as in supracricoid laryngectomy with cricohyoidoepiglottopexy, although in this procedure, the entire epiglottis and preepiglottic space is resected. A U-shaped incision is made in line with the tracheostomy site, which will be placed later in the case, and the superior flap is elevated to approximately 2 cm above the hyoid bone, exposing the underlying strap muscles. The incision is made up to the mastoid tip to accommodate the bilateral modified neck dissections that are done in the case of supraglottic carcinoma. The sternothyroid and the thyrohyoid muscles are transected individually from medial to lateral, along the superior aspect of the thyroid cartilage. The thyrohyoid muscle is elevated inferiorly, allowing for the exposure of the thyroid muscle. As in supracricoid laryngectomy with cricohyoidoepiglottopexy, there is a blood vessel that pierces the deep strap musculature to the more superficial layer, which needs to be ligated bilaterally. The sternothyroid muscle is then carefully transected along the inferior edge of the thyroid cartilage. Care is taken not to cut the underlying thyroid gland, which will cause undue bleeding and obscure the surgical field. The constrictor muscles are then transected along the posterior and superior-lateral aspect of the thyroid cartilage, and the pyriform sinus mucosa is elevated off of the internal surface of the thyroid cartilage bilaterally, as is done in total laryngectomy. A Freer elevator is used to disarticulate the cricoarytenoid joint bilaterally, taking care to protect the recurrent laryngeal nerves. The recurrent laryngeal nerves are never actually visualized, although the area posterior and lateral to the inferior cornua of the thyroid cartilage is respected and avoided. The isthmus of the thyroid gland is transected and ligated. A blunt finger dissection of the cervicomediastinal trachea is done to the level of the carina, as is done in a tracheal resection and anastomosis to close the tracheal defect. A transverse cricothyrotomy is performed just above the cricoid cartilage, and the endotracheal tube is removed from above and placed into the cricothyrotomy. Now, rather than entering the larynx through a transverse transepiglottic laryngotomy and transecting the epiglottis as is done in supracricoid laryngectomy with cricohyoidoepiglottopexy, we resect the entire epiglottis and preepiglottic space. To do this, the superior aspect of the transected sternothyroid and sternohyoid muscles are elevated off of the thyrohyoid membrane. The upper aspect of the preepiglottic space is dissected off of the inferior aspect of the hyoid bone with an electrocautery unit. The dissection is done medially to create an opening in the vallecula just large enough to allow the epiglottis to be pulled externally and grasped with an Allis

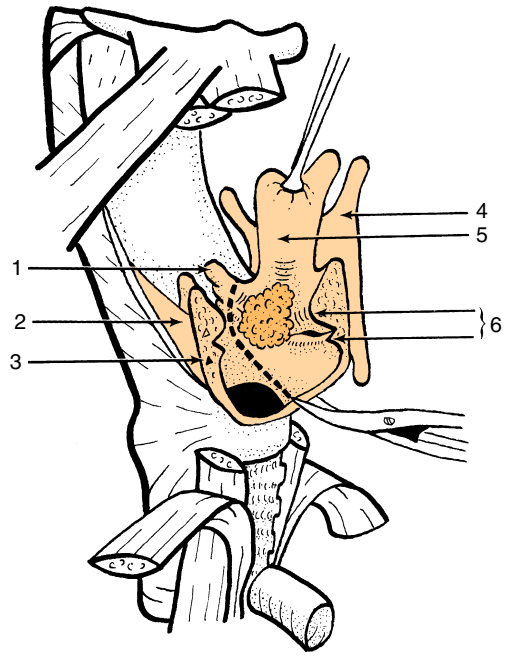

Figure 110-16. Supracricoid partial laryngectomy with cricohyoidopexy—exposure of malignancy. *1,* arytenoid; *2,* external thyroid perichondrium; *3,* vocal process; *4,* thyroid cartilage; *5,* epiglottis; *6,* false and true cord.

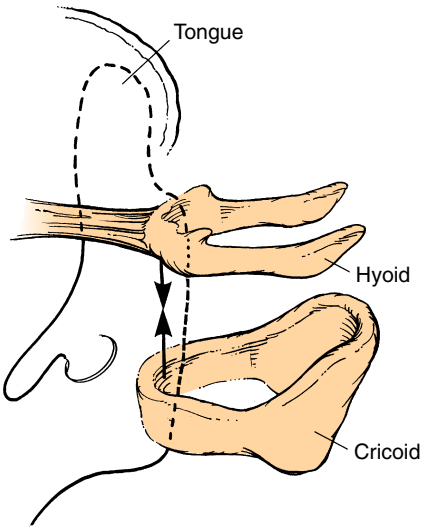

Figure 110-17. Supracricoid partial laryngectomy with cricohyoidopexy—laryngoplasty using three circumferential cricoid, hyoid, and tongue base stitches.

clamp. One scissor blade is placed in the endolaryngeal lumen, and one blade is placed externally. The cut is made in a superior-to-inferior direction to allow for resection of the entire preepiglottic space, although the cut is made medial to the main trunk of the internal branch of the superior laryngeal nerve to keep this intact. The scissors are advanced with one blade in the lumen and the other between the elevated internal thyroid perichondrium and the thyroid cartilage. This cut is made anterior to the pyriform sinus, which remains intact posteriorly.

The endolaryngeal excision now is performed on the non–tumor-bearing side first, in the same fashion as in supracricoid laryngectomy with cricohyoidoepiglottopexy. The incision is brought down, in the sagittal plane, with a scissor blade at the junction between the false cord and arytenoid. The transection is carried inferiorly just posterior to the ventricle and then through the vocal process of the arytenoid. Special care is taken to avoid entering the cricoarytenoid joint with the scissors, avoiding cricoarytenoid ankylosis. Just above the cricoid cartilage, the orientation of the scissors changes to allow connection of this incision, through the cricothyroid muscle, to the previously made cricothyrotomy. The larynx is opened up on its anterior spine like a book, which allows for direct visualization of the lesion (Fig. 110-16). The cut on the tumor-bearing side may be made just posterior to the ventricle or may transect all or part of the arytenoid cartilage. This can be done by cutting the subglottic mucosa with a No. 15 blade and following posteriorly and superiorly to the level of the arytenoid. The posterior arytenoid mucosa should be spared to be used in the endolaryngeal reconstruction and to cover the cricoarytenoid joint area on the cricoid. This forms a cushion, postoperatively, against which the remaining arytenoid will abut to allow for closure of the larynx. The patient will have severe swallowing impairment postoperatively unless this posterior arytenoid mucosa is spared.

The reconstruction is begun by pulling the arytenoid cartilages forward with 3-0 Vicryl suture material by placing a stitch just at or just above the vocal process and sewing them (or the posterior arytenoid mucosa in unilateral arytenoid resection) anterolaterally to the cricoid cartilage. In this way, the arytenoid will not prolapse backward postoperatively. The impaction of the cricoid to the hyoid is performed with three centrally placed 2-0 Vicryl sutures on a 65-mm round needle. The first stitch is placed circumferentially, submucosally around the cricoid cartilage, in the midline. The stitch is placed submucosally in the subglottis. Next, the same first stitch is passed up around the hyoid bone and deep into the tongue base. This large needle allows the suture to be passed deeply into the tongue base, submucosally, while it is carefully palpated with a finger on the tongue base mucosa, to pull it back and have a bulge of tongue base tissue over the airway postoperatively (Fig. 110-17). A self-release needle should not be used because it may become embedded in the tongue base musculature. Before tightening the sutures, the two lateral sutures are pulled taut, which places the trachea in its postoperative position, and the tracheostomy is performed in line with the skin incision. With the two lateral cricohyoidoepiglottopexy sutures under tension, the central pexy stitch is tied, followed by the two lateral stitches. The strap muscles are closed as a second layer closure with 3-0 Vicryl. A cuffed tracheostomy tube is put into place. The skin wound is closed in two layers, taking special care to separate the tracheostomy site from the remainder of the wound, with a subcutaneous stitch placed between the skin and the underlying strap muscles above the tracheostomy site.

KEY SURGICAL POINTS. The key surgical points are the same as those in supracricoid laryngectomy with cricohyoidoepiglottopexy.

EXTENDED PROCEDURES. The extension of the basic technique, as in supracricoid laryngectomy with cricohyoidoepiglottopexy, is the resection of one arytenoid.[72]

FUNCTIONAL OUTCOME. When the world literature is analyzed, variability was noted in the duration of tube feedings with a range from 13 days[142] to 365 days (Table 110-9).[28] The percent of patients undergoing functional laryngectomy for intractable aspiration varied from 0% to 10.8% (see Table 110-9). In the large series, with more than 65 patients analyzed, the need for functional laryngectomy remained less than 5%, which may indicate that experience is of value in achieving successful functional results.[31,35,72] Dysphagia is more common after supracricoid laryngectomy with cricohyoidopexy when one arytenoid is resected.[73,143] Success in postoperative swallowing results has been attributed to careful attention to preoperative patient selection, intraoperative technique, and postoperative rehabilitation.[144]

The duration and frequency characteristics of normal speakers was compared with 14 patients who had undergone supracricoid laryngectomy with cricohyoidopexy.[145] The findings in that study revealed that although the average F_0 among the supracricoid laryngectomy group was within normal range, the operated group was significantly less efficient in jitter, shimmer, maximum phonation time, and phase

Table 110-9

Functional Outcome after Supracricoid Laryngectomy with Cricohyoidopexy

Author	Patients	Duration NG	Func Laryn	Func Laryn (%)
Labayle and Dahan[31]	101	?	3	3.0
Piquet et al[16]	72	?	3	4.2
Alajmo et al[101]	17	?	1	5.9
Botazzi[28]	21	20-365	2	9.5
Pech et al[34]	32	33*	2	6.3
Prades et al[36]	29	30*	1	3.4
Marandas et al[32]	57	34*	4	7.0
Junien-Lavillauroy et al[30]	37	33*	4	10.8
Laccourreye et al[123]	68	13-70	0	0.0
Traissac and Verhulst[156]	25	20-56	3	12.0
Laccourreye et al[144]	19	13-29	0	0.0
Maurice et al[33]	43	17-120	1	2.3

*Average duration.
Func laryn, functional laryngectomy for aspiration; NG, nasogastric tube.

grouping.[145] The authors attributed these findings to the instability of the neoglottis, resulting from the wide surgical resection and the fact that the neoglottis allows for air escape during phonation.

COMPLICATIONS. Among the extremely rare complications reported in the literature are rupture of the cricohyoidopexy,[146] pneumonia caused by severe gastroesophageal reflux,[115] chondroradionecrosis,[142] and glottic stenosis.[142]

Organ-Preservation Surgery Spectrum for Glottic and Supraglottic Cancer

Organ laryngeal preservation surgery is based on three fundamental keys. The surgeon needs to be able make an accurate assessment of the patient as a surgical candidate, be able to accurately assess the origin and extent of the lesion, and have a thorough understanding of the available surgical techniques and preoperative issues. Figures 110-18 and 110-19 are schematic representations of the surgical disease spectrum of glottic and supraglottic carcinomas, respectively.[76] Below the schematics are a number of possible variables. These are important clinical factors that have a bearing on the application of organ-preservation surgery of the larynx. There are representative examples of carcinomas from the smallest on the left to the largest on the right. Every other schematic is blank, enabling the surgeon to consider placement of a lesion in its appropriate space, designating the appropriate organ-preservation surgeries available. This schematic allows the surgeon to formulate an organ-preservation surgical plan by comparing the tumor to known lesions while accounting for certain key organ-preservation variables. It is meant to be used as a helpful teaching aid in learning the concepts of organ-preservation surgery for larynx cancer.

Intraoperative Conversion to Total Laryngectomy

Accurate preoperative staging is critical to avoid intraoperative conversion to total laryngectomy including an accurate prediction of the surface extension and the depth of invasion. In general, the problem occurs when there are close margins intraoperatively that necessitate resection of structures that are necessary for the postoperative functional reconstruction. Whole organ section studies reveal that deep and superficial lesions are commonly surrounded by a penumbra of microinvasion carcinoma, carcinoma in situ, and dysplasia.[109] Deep invasion is best appreciated preoperatively during the clinical evaluation, which includes visualization of mobility, palpation during direct laryngoscopy, and radiologic studies. The surface invasion is best evaluated by indirect and direct endoscopy. The penumbra of surface changes surrounding the deeply invasive carcinoma may be particularly difficult to assess clinically because of natural tendency to focus on the obvious cancer during endoscopy and because of the difficulty in assessing subtle mucosal changes on a mucosal surface, which is tangential to direct vision with the naked eye or the microscope. If either subtle granularity or erythema is noted in a critical area on the mucosal surface that would obviate the conservation technique that is contemplated, it should undergo microscopic biopsy at the time of endoscopy. We do not perform random microscopic biopsies of normal-appearing mucosa because the excoriations of these sites may lead to confusion at the time of the definitive resection.

One area that results in conversion to total laryngectomy when dealing with supraglottic laryngectomy is extension to the glottic level. In the past, it has been suggested that supraglottic carcinoma rarely, if ever, extended to the glottic level. A recent analysis of whole organ sections of laryngeal carcinoma and a literature review have revealed that the true incidence of glottic level extension from the supraglottis is between 20% and 54%.[65] The most common route of extension is the paraglottic space. Surgeons relying on the previously held assumption that the carcinoma is unlikely to extend to the glottis, regardless of the proximity of the cancer to the glottis, may need to convert to total laryngectomy in 25% of patients.[13]

The area in glottic carcinoma for which involvement may result in intraoperative conversion to total laryngectomy is invasion of the cricoarytenoid joint. Fixation of the joint is an indication that the joint capsule, the joint itself, or the surrounding musculature is involved by carcinoma.[147] This should be fully assessed, and the joint involvement should be predicted to avoid the necessity of intraoperative conversion to total laryngectomy when performing either vertical partial laryngectomy or supracricoid laryngectomy.

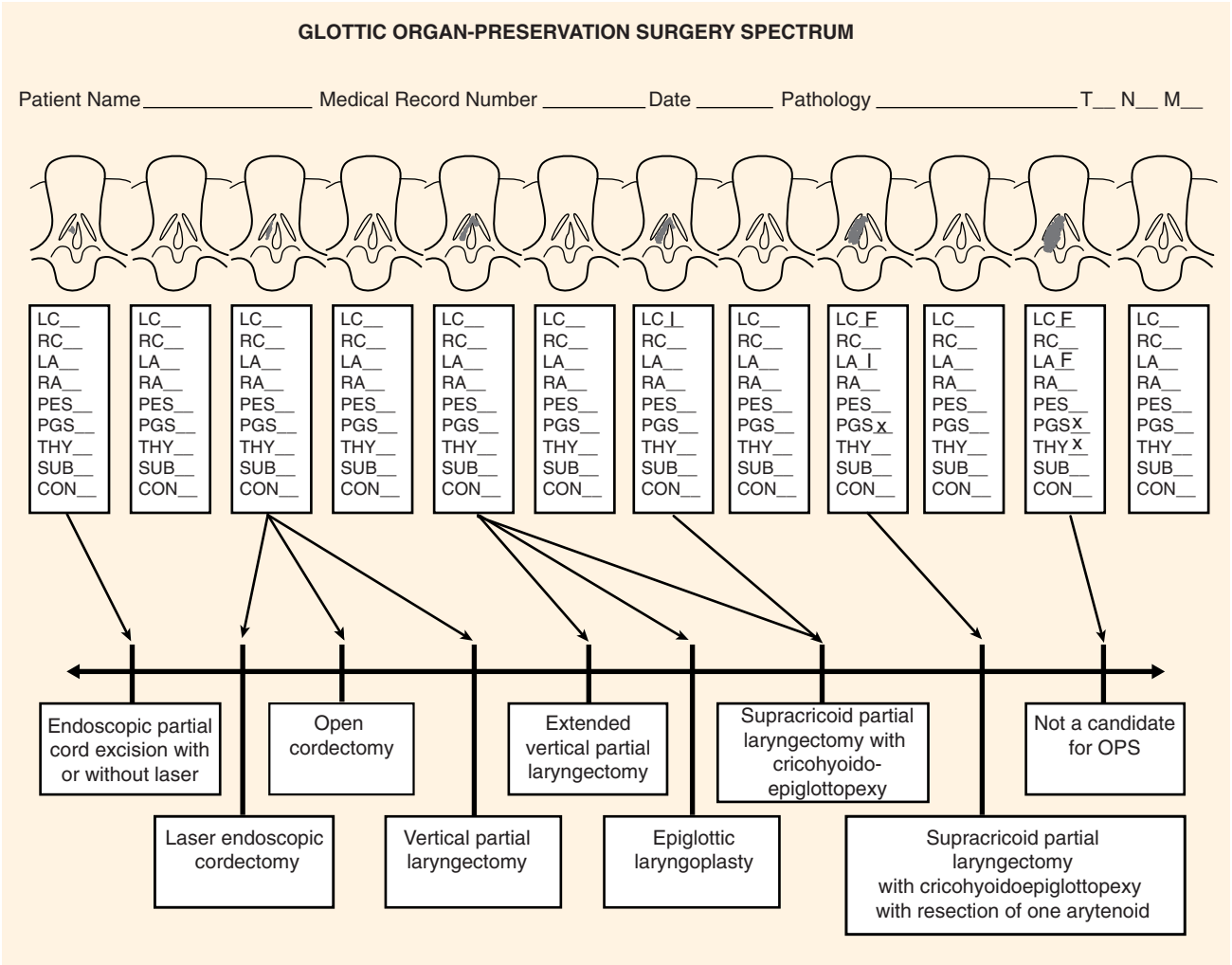

Figure 110-18. Glottic organ-preservation surgery spectrum. *LC,* left vocal cord mobility; *RC,* right vocal cord mobility; *LA,* left arytenoid mobility; *RA,* right arytenoid mobility; *PES,* preepiglottic space involvement; *PGS,* paraglottic space invasion; *THY,* early radiologic evidence of thyroid cartilage invasion; *SUB,* subglottic extension greater than 1 cm at midcord, or greater than 0.5 cm at posterior cord level; CON tumor and non-tumor contraindications. At the top of the form is a series of schematic diagrams of the larynx with additional descriptors in the text box below. At the bottom of the form is the spectrum of organ-preservation surgeries that are applicable. Representative cancers are shown in a spectrum from least extensive on the left through most extensive on the right. The mucosal extent is documented on the schematic. Mobility is documented with either a "blank" for normal mobility, "i" for impaired mobility, and "f" for fixation. An "x" documents involvement of the preepiglottic space, paraglottic space, thyroid cartilage, and a tumor- or non-tumor–related contraindication. This form may be used in surgical planning by drawing the lesion into a blank laryngeal schematic, in the appropriate place on the spectrum. *(From Weinstein GS, Laccourreye O, Brasnu D, et al.* Organ Preservation Surgery for Laryngeal Cancer. *San Diego: Singular Publishing Group; 2000.)*

The best approach to avoid intraoperative conversion to total laryngectomy is preoperative planning. The surgeon has a wide spectrum of conservative techniques available with consistent functional and oncologic outcome in the literature. We do not advocate conversion from one type of conservation laryngeal surgery intraoperatively to another to avoid total laryngectomy. In our opinion, this conversion will lead to poor oncologic and functional outcome. Rather, to avoid intraoperative conversion to total laryngectomy, the procedure of choice should be decided on preoperatively, and this should be the technique that affords the safest oncologic margins for that particular lesion. Nonetheless, the surgeon always should obtain consent from the patient for the possibility of intraoperative conversion to total laryngectomy, with the understanding that in rare instances, removal of the entire larynx may be necessary. The patient who cannot accept this option is not a good candidate for conservation laryngeal surgery.

All patients undergoing attempts at conservation laryngeal surgery must give their consent for possible total laryngectomy. Careful preoperative planning can help to reduce the incidence of conversion to total laryngectomy. If the patient cannot accept this possibility or if the surgeon feels that there is a distinct possibility for total laryngectomy, the patient should be encouraged to pursue an organ-preservation medical strategy if appropriate.

Current Organ-Preservation Paradigm for Laryngeal Cancer

The trial conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group 1991 compared induction chemotherapy (cisplatin plus fluorouracil) followed by radiation versus surgery (total laryngectomy) and radiation for advanced laryngeal cancer.[148] The conclusion from this study was that induction chemotherapy followed by radiation was able to preserve the larynx while not affecting survival. This provided an alternative to total laryngectomy for these patients with advanced laryngeal cancer. Recently, the Radiation Therapy Oncology Group (RTOG) Trial 91-11 was performed to examine the contributions of chemotherapy and radiation therapy to medical larynx-preserv-

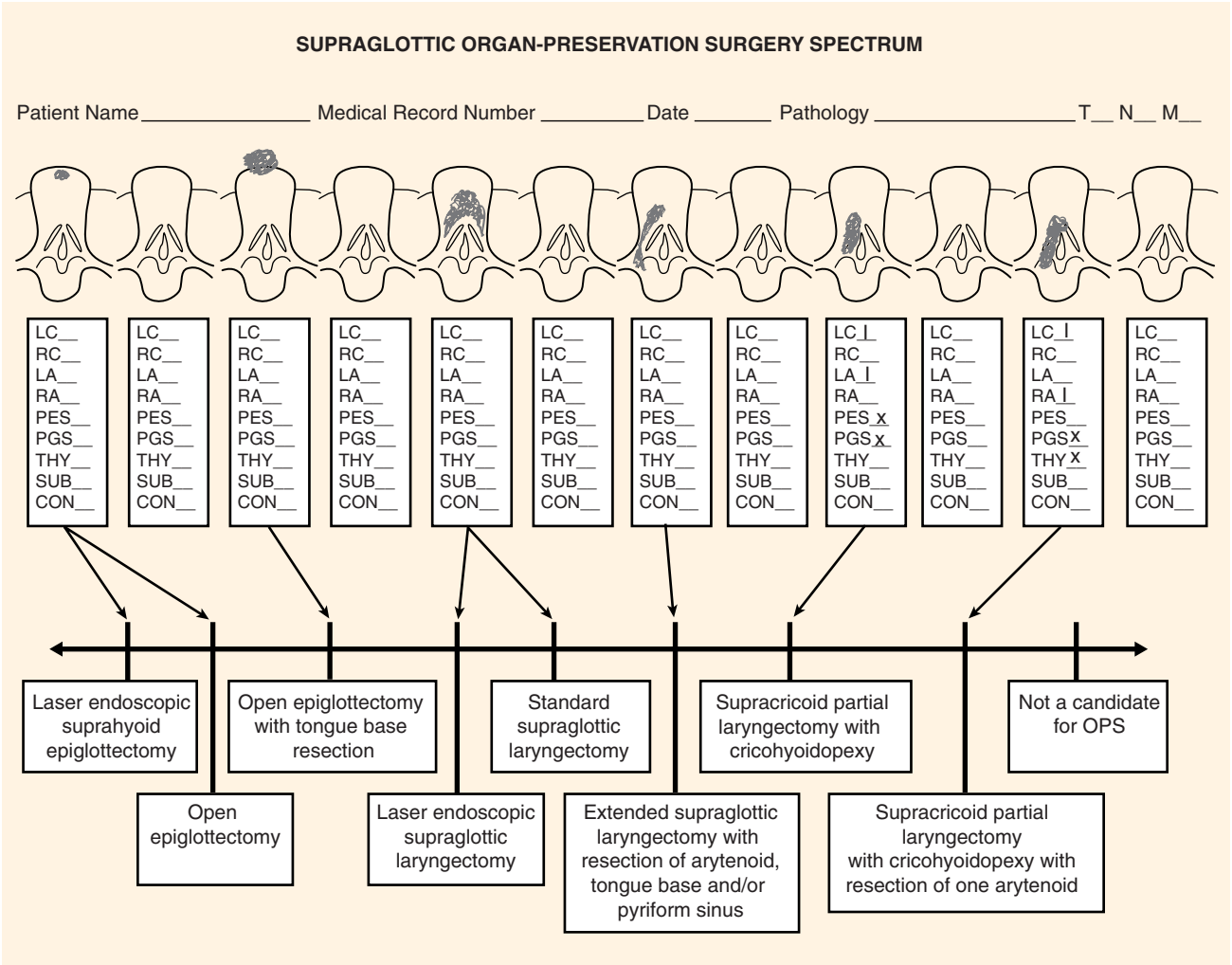

Figure 110-19. Supraglottic organ-preservation surgery spectrum. *LC,* left vocal cord mobility; *RC,* right vocal cord mobility; *LA,* left arytenoid mobility; *RA,* right arytenoid mobility; *PES,* preepiglottic space involvement; *PGS,* paraglottic space invasion; *THY,* early radiologic evidence of thyroid cartilage invasion; *SUB,* subglottic extension greater than 1 cm at midcord, or greater than 0.5 cm posterior cord level; *CON,* tumor and non-tumor contraindications. At the top of the form is a series of schematic diagrams of the larynx with additional descriptors in the text box below. At the bottom of the form is the spectrum of organ-preservation surgeries that are applicable. Representative cancers are shown in a spectrum from least extensive on the left through most extensive on the right. The mucosal extent is documented on the schematic. Mobility is documented with either a "blank" for normal mobility, "i" for impaired mobility, and "f" for fixation. An "x" documents involvement of the preepiglottic space, paraglottic space, thyroid cartilage, and a tumor- or non-tumor–related contraindication. This form may be used in surgical planning by drawing the lesion into a blank laryngeal schematic, in the appropiate place on the spectrum. *(From Weinstein GS, Laccourreye O, Brasnu D, et al.* Organ Preservation Surgery for Laryngeal Cancer. *San Diego: Singular Publishing Group; 2000.)*

ing regimens.[149] The conclusion from this study was that concurrent chemotherapy and radiation was superior to both induction chemotherapy followed by radiation and radiation alone for larynx preservation in patients with stage III and stage IV disease (T_2, T_3, or T_4 not extending to tongue base or through cartilage). The study states that radiation with concurrent cisplatin should be the standard of care for the previously staged patients.

The study fails to recognize that organ-preservation surgical strategies for laryngeal cancer have gained widespread acceptance throughout the past decade.[150-155] These strategies offer an alternative to concurrent cisplatin and radiation for similarly staged lesions (T_2, T_3, and selected T_4). The majority of the patients in the RTOG 91-11 trial were staged as T_3 tumors. Previously, the only surgical option available to most of these patients was a total laryngectomy. With the worldwide acceptance of organ-preservation surgical approaches (in particular, supracricoid laryngectomy), these patients now have an established surgical alternative to concurrent cisplatin and radiation with defined oncologic and functional outcomes.[38,156-161]

It is incumbent on all physicians caring for patients with laryngeal cancer to understand all of the available options for treatment. Correct staging is absolutely essential to this and requires an interpretation of dynamic laryngeal function that at present can only be made by direct examination of the larynx. This mandates the need for a head and neck surgeon's examination and interpretation of the larynx. The discussion held before treatment must include all organ-preservation approaches available for that patient's particular tumor. The ability of the patient to choose from these options allows for a tailoring of treatment that best suits the patient's needs and wishes. These options should be to the benefit of the patient with larynx cancer and should not be preferentially excluded.

Conservation Laryngeal Surgery and Radiotherapy

Essential differences exist between nonsurgical organ-sparing modalities versus conservation laryngeal surgery. In nonsurgical approaches the clinician accepts that when treating those with larger lesions within the spectrum of malignancy that more patients will have local

recurrence and rely on surgical salvage when possible, which frequently is total laryngectomy.[77] The advantage to this approach is that for the patients without local recurrence, the entire larynx is spared, and it is inferred that for those patients, the functional outcome is maximized. The approach of the conservation laryngeal surgeon is the opposite. When managing progressively larger lesions within the spectrum of malignancies, the procedure is chosen from the spectrum of conservation laryngeal procedures that then maximize local control while progressively removing more laryngeal tissue. The loss of functional anatomy usually manifests as permanent hoarseness when the glottis is resected and as temporary dysphagia when the supraglottis is resected. Long-term severe dysphagia for conservation laryngeal surgery is rare (see Tables 110-4, 110-5, and 110-9). The conservation laryngeal approach to organ preservation accepts decreased laryngeal function for the entire population of patients to decrease the morbidity and mortality associated with local recurrence. The nonsurgical approach to organ preservation accepts the sequelae of local recurrence in an effort to preserve anatomic structure for selected patients.

Although functional outcome after conservation laryngeal surgery is well documented in the literature, this has not been the case of the nonsurgical organ-sparing regimens for intermediate-stage to high-stage lesions. Outcomes in terms of vocal quality, long-term dysphagia, reliance on long-term enteral feeding, and need for tracheostomy need to be evaluated in future studies for the nonsurgical approaches to verify that preservation of anatomic structure ensures improved functional outcome.

Surgical salvage with conservation laryngeal surgery has been well documented in the literature. Early diagnosis of failure after radiotherapy for laryngeal carcinoma is often difficult because of posttherapeutic edema, erythema, and changes in laryngeal mobilities.[162] This often leads to late discovery of the recurrence, leaving most patients who are eligible for surgical salvage needing to undergo total laryngectomy.[131,163] Patients with failure at the glottic level who were amenable to vertical hemilaryngectomy in the preradiation period and in whom the tumor has not enlarged may undergo the procedure and expect a local control rate of 83.3% (15 of 18).[164] Although in the DeSanto and colleagues[131] series, 80% (24 of 30) of patients with supraglottic carcinoma who underwent radiotherapy and failed would have been theoretically amenable to supraglottic laryngectomy before radiotherapy, only 30% (9 of 30) underwent conservation laryngeal surgery for postradiation failure. Sorensen and colleagues[165] reported poor oncologic and functional results after supraglottic laryngectomy for radiation failure and advocated total laryngectomy in these patients. Lavey and Calcaterra[166] have stated, after a review of the literature, that vertical hemilaryngectomy should be contraindicated in the radiation failure case if (1) the tumor involves the arytenoid; (2) there is greater than 10 mm of subglottic extension anteriorly and greater than 5 mm posteriorly; and (3) cartilage invasion into the thyroid or the cricoid is present. Shaw[167] stated that supraglottic laryngectomy is contraindicated in the postradiation failure setting unless (1) the primary tumor is small; (2) the recurrence is located anteriorly; and (3) the carcinoma has never involved the anterior commissure. One alternative for larger lesions is to use either supracricoid laryngectomy with cricohyoidopexy or cricohyoidoepiglottopexy as the salvage procedure, which has a reported local control of 83.3% (10 of 12).[168]

It seems that supracricoid laryngectomy may be ideally suited to treat early (T_1 and T_2) glottic radiation failures. The en bloc resection of the entire thyroid cartilage and its contents along with a significant portion of the anterior subglottic mucosa makes it particularly attractive in those with anterior commissure recurrences. Often, the only salvage modality offered to these patients is total laryngectomy. The role of supracricoid laryngectomy in salvage of glottic radiation failures will be explained as more institutions use the technique.

Management of metachronous primary tumors is an important consideration. Roberts and colleagues[169] reported that the average annual risk for a second malignant neoplasm developing after a glottic carcinoma was 3.1% a year over the ensuing 10 years. Seventy-one percent of these second lesions occurred in the upper aerodigestive tract or in the lungs.[169] The physician should also consider the future management of second primary malignancies when planning treatment for the patient with primary cancer.

Postoperative Management Issues

Although postsurgical management varies from institution to institution, the central issues generally center on the timing of tracheal decannulation and on the approach to swallowing rehabilitation. In this section we discuss our approach to these management issues. We deflate the tracheotomy tube as early as possible postoperatively. In the absence of contraindications such as ventilator dependence, we drop the tracheostomy cuff on day one. Second, we remove the tracheostomy early, and our first attempts at decannulation are between days 3 and 5. The tracheostomy should be kept in for prolonged periods if there is laryngeal edema or salivary stasis. As a rule, patients undergoing vertical partial laryngectomies or supracricoid laryngectomies can be decannulated sooner than those undergoing supraglottic laryngectomies. Swallowing rehabilitation is not begun until the tracheostomy is removed, the stoma is closed, and the patient is swallowing his or her saliva. The larynx should always be visualized with indirect laryngoscopy before decannulation. If there are any ensuing airway problems, the tracheotomy tube should be immediately replaced. Although stridor is the sentinel sign of laryngeal airway impairment, other signs such as sweating or agitation should be carefully evaluated even in the absence of audible stridor. Finally, the speech pathologist is central to the speech and swallowing rehabilitation and is consulted early postoperatively.

Future Developments

In addition to open surgical approaches, endoscopic transoral laser microsurgery (TLM) has become widely accepted as a means of conservation laryngeal surgery. Results of TLM for glottic and supraglottic carcinoma have been widely reported, and proponents of this technique cite its advantages including organ and function preservation, avoidance of a tracheostomy, low morbidity, and shorter periods of hospitalization.[170-172] However, TLM may be limited by line of site visualization of the operative field, which may lead to the inability to obtain adequate exposure for resection of laryngeal carcinomas. This is because laryngoscopes are used to expose the operative field in conjunction with operating microscopes, which are positioned outside the oral cavity, allowing the surgeon to visualize a limited operative field that is in line with the microscope.

In an effort to overcome these limitations, preclinical transoral experiments with the *da Vinci* Robotic Surgical System (Intuitive Surgical, Inc., Sunnyvale, Calif.) in mannequin and cadaver models revealed that exposure of the laryngopharynx might be possible using mouthgags rather than laryngoscopes, with the prediction that this may also apply in the human clinical setting.[173,174] The *da Vinci* Robotic Surgical System consists of a robotic cart next to the patient with three arms, two placed laterally for the instruments and the middle one for the endoscopic camera. The surgeon controls the instruments through a separate console, which provides the surgeon with a three-dimensional view and translates the movements of the surgeons hands at the console to the robotic arms positioned in the patient's oral cavity. The robotic arms employ "wristed" instruments that allow 7 degrees of freedom and 90 degrees of articulation, providing the surgeon with improved dexterity and precision for transoral approaches. In addition, 0-degree and 30-degree endoscopes are available to allow visualization that cannot be obtained with the line-of-site view obtained with operating microscopes. Weinstein and colleagues[175-177] have reported the efficacy of transoral robotic surgery (TORS) for performing supraglottic laryngectomy and glottic microsurgery in the canine model, as well as a supraglottic partial laryngectomy in three human patients. They noted excellent visualization, minimal blood loss, and shorter operating times than traditional laser resection. Negative surgical margins, avoidance of tracheostomy, and a normal diet were achieved in all patients.

Multiplaner transection with monopolar cautery, using instruments that mimic normal hand movements including caudal to cranial transection, was seen to be advantageous over traditional laser excision, which is limited by "line-of-site" resection with carbon dioxide laser, no caudal to cranial resection possible, and no axial plane resection possible. As clinical experience has expanded, TORS for supraglottic and glottic resections has continued to have the advantages of improved visualization, shorter operating times, minimal blood loss, and excellent functional outcomes. With continued experience, TORS has the potential to be an integral part of the armamentarium for the conservation laryngeal surgeon.

Summary

In 2003 Forastiere and colleagues in their landmark report of a prospective trial comparing concurrent chemotherapy and radiation to other nonsurgical treatment for advanced laryngeal carcinoma concluded: "Radiotherapy with concurrent cisplatin should be considered standard care for patients desiring laryngeal preservation whose cancer is within the categories of disease studied in this trial, and laryngectomy should be performed only as salvage therapy. We believe that in most patients with laryngeal cancer, the disease can be managed without a primary surgical approach."[149] In a letter to the editors of the New England Journal of Medicine, Weinstein, Myers, and Shapsay responded to Forastiere and colleagues with this statement: "When patients with early or advanced laryngeal cancer are candidates for surgical approaches that preserve the larynx, it is the standard of care to discuss the surgical and nonsurgical organ-preserving options with the patient and allow the patient to participate in the choice of appropriate treatment."[178] Although the latter statement concerning the role of organ-preservation surgery was made by surgeons, this opinion has been expressed by nonsurgeons as well. In 2006 the practice guidelines for laryngeal preservation of the American Society of Clinical Oncologist (ASCO) were created by a multidisciplinary group, which included radiation oncologists, head and neck surgeons, and medical oncologists.[179] This ASCO multidisciplinary panel concluded that for both early and advanced laryngeal cancer surgical and nonsurgical options should be considered as standard options.[179] We agree with the contention of the ASCO laryngeal cancer practice guidelines, and the purpose of this chapter has been to provide an overview to clinicians involved in the diagnosis and treatment of laryngeal cancer to fully understand the surgical organ-preservation options.

A spectrum of conservation laryngeal procedures that allow for management of the broad spectrum of laryngeal carcinomas is available. The vertical partial laryngectomy, supraglottic laryngectomy, and supracricoid laryngectomy are accepted worldwide with established oncologic and functional outcomes. No single surgical approach is a panacea, and a conservation laryngeal surgeon may only perform a few of each technique to manage a large number of laryngeal carcinomas. Accurate understanding of the anatomy and physiology of the larynx and the behavior of neoplasm in a particular site is necessary to assess the three-dimensional extent of the malignancy preoperatively. A thorough understanding of the whole organ section literature is paramount for success in conservation laryngeal surgery. The conservation laryngeal surgeon uses a variety of surgical approaches to allow for the preservation of a functional larynx. The functional goals of conservation laryngeal surgery are speech and swallowing without a permanent tracheostomy. The acute functional sequelae vary but typically include temporary dysphagia and a tracheostomy. Among the procedures that have gained acceptance in multiple centers, including vertical hemilaryngectomy, supraglottic laryngectomy, and supracricoid laryngectomy, the rate of severe dysphagia requiring functional laryngectomy for aspiration has been low. The most common long-term functional sequela of conservation laryngeal surgery is hoarseness. If the choice of surgical procedure is based on sound principles gleaned from large series of patients reported in the literature, successful oncologic results in terms of local control are attainable. Open surgical approaches for laryngeal preservation afford the surgeon the opportunity to perform laryngoplasty to maximize functional outcome.

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CHAPTER ONE HUNDRED AND ELEVEN

Total Laryngectomy and Laryngopharyngectomy

Christopher H. Rassekh

Bruce H. Haughey

Key Points

- Total laryngectomy remains as the standard by which other forms of treatment for advanced primary laryngeal carcinoma are evaluated. It should still be considered as a primary treatment modality for selected patients.
- Total laryngectomy is also occasionally indicated for advanced thyroid cancers or tumors of the oropharynx and/or neck that invade the larynx.
- The special subset of patients with laryngeal cancer who require a total laryngectomy instead of organ preservation therapy present management issues that are particularly complex.
- Higher complication rates can be expected in the setting of preoperative radiotherapy and chemoradiotherapy with longer and more complex salvage procedures. Pharyngocutaneous fistula is much less common in nonirradiated patients. Closure of the pharynx should be done in a meticulous fashion.
- Other factors that may predispose to complications include positive margins, technical errors, diabetes mellitus, hypothyroidism, and poor nutritional status.
- Total laryngectomy is also important for management of chronic aspiration as a result of diseases that render the larynx incompetent.
- Rehabilitation of swallowing and voice with tracheoesophageal speech allows a reasonably good quality of life after total laryngectomy for most patients.
- The tracheal stoma is the hallmark of total laryngectomy. Effective ways to create and manage an adequate stoma are available.
- Total laryngopharyngectomy is used for more advanced laryngeal and pharyngoesophageal carcinomas.
- Prognosis with hypopharyngeal carcinoma is poor compared with laryngeal carcinoma, but functional organ preservation rates are also poor, and although controversial, surgery incorporating adequate reconstruction for swallowing and voice is the best choice for many patients.
- The key to successful management of total pharyngeal defects following laryngopharyngectomy is free flap reconstruction. Fasciocutaneous flaps have significant advantages over visceral flaps.

Total Laryngectomy

Historical Development

Although Patrick Watson of Edinburgh often is credited with performing the first total laryngectomy in 1866, there is no recorded proof that the operation actually was done by him. Research into Watson's own article[1] apparently answers this question; Watson stated he performed only a tracheotomy while the patient was alive and then did a postmortem laryngectomy of the syphilitic larynx. Billroth of Vienna, on December 31, 1873, carried out the first total laryngectomy for a patient with laryngeal cancer. One month earlier, he had performed a vertical cricothyrotomy and local intralaryngeal excision of this patient's lesion. Gross pathologic recurrence necessitated further radical ablation,[2] but the total laryngectomy was punctuated by considerable bleeding, coughing, and arousal from the anesthetic. The patient died 7 months after surgery,[3] but Bottini of Turin in 1875 performed a total laryngectomy on a patient who survived for 10 years. In 1880 the operative or early postoperative mortality rates were approximately 50%.

This high mortality rate led Gluck of Germany to develop a two-stage procedure in which the tracheal separation was performed first, such that a healed tracheocutaneous stoma was present when the laryngectomy and pharyngeal closure were performed 2 weeks later. In the 1890s, with his pupil Sorenson, he then developed a successful single-stage operation, similar to contemporary techniques, in which the larynx was removed from above downward. Solis-Cohen, advancing from partial laryngectomies in the 1860s, reported at the 1892 Philadelphia County Medical Society Meeting carrying out a total laryngectomy by use of similar Gluck-Sorenson techniques, although Frederick Lange of New York apparently reported performing the first total laryngectomy in the United States in 1879.[3,4] Radiation therapy was popular for treatment of patients with laryngeal cancer during the first half of the twentieth century, although with improvements in surgical and anesthetic technique and a recognition of radiation therapy's

limitations, surgery (including total laryngectomy) still maintained a prominent role in the second half of the century. In the past two decades, there has been an increased focus on organ preservation. For intermediate and advanced-stage tumors, concurrent chemotherapy and radiotherapy have become part of the standard of care,[5] particularly for those patients who are in some way unsuitable for organ preservation surgery such as transoral laser or robotic excision. However, total laryngectomy as a primary treatment modality is still relevant for many patients. The attention on chemoradiation has resulted in an increase in salvage total laryngectomy and laryngopharyngectomy procedures, complicated by a greater potential for complications due to the tissue damage following chemoradiotherapy.

Indications for Total Laryngectomy

Malignant Disease

With the spectrum of organ preservation surgery that is now available,[6] the need for total laryngectomy as the only surgical option for those with laryngeal cancer has decreased. Organ preservation surgery includes specific procedures for supraglottic and glottic cancer. There are two major organ preservation surgical strategies, transoral (endoscopic) and open. Transoral procedures range from the very limited endoscopic resections that most head and neck surgeons can accomplish to extensive laser procedures that require greater surgical experience and specialized instrumentation,[7,8] covered in Chapter 109. Open procedures include the more conventional vertical partial laryngectomy group of procedures and horizontal supraglottic partial laryngectomy group. In the early 1990s, a group of open operations called the supracricoid partial laryngectomies became more popular. The supracricoid partial laryngectomy with cricohyoidopexy (SCPL-CHP) for selected supraglottic carcinomas and the supracricoid partial laryngectomy with cricohyoidoepiglottopexy (SCPL-CHEP) for selected glottic carcinomas have extended the spectrum of tumors that can be managed surgically while avoiding total laryngectomy.[9] More information about organ preservation surgery and nonsurgical organ preservation are covered in Chapters 110 and 112. In addition to the increased number and success of open procedures for organ preservation, even in the setting of prior radiotherapy, the continually improving instrumentation and experience of endoscopic transoral resections continues to improve, which reduces the need for total laryngectomy.[10-14] Organ preservation surgery can safely be used after radiotherapy but with a higher complication rate.[15]

Another operation that avoids total laryngectomy is the "near-total laryngectomy."[16] This procedure is not strictly an organ preservation operation because it does not maintain an airway without a tracheostome. Essentially, it can be viewed as a total laryngectomy with an epithelialized voice fistula.[17] Nonsurgical treatment for patients with laryngeal malignancy also is established as primary treatment in some centers. Management includes definitive radiation alone with surgery for salvage for patients with primary lesions up to T3 or neoadjuvant chemotherapy and radiotherapy, with total laryngectomy reserved for those with unresponsive tumors. The frequently cited Veterans Affairs study[18,19] randomly assigned patients with advanced laryngeal cancer to chemotherapy and radiotherapy or total laryngectomy. Although present, the increased survival in the surgical arm was not significant. Criticisms of the study prompted a head and neck intergroup trial that randomly assigned patients to three groups and compared radiation alone versus concurrent versus sequential chemotherapy with radiotherapy. This study has recently been published and demonstrates that concurrent chemotherapy with radiotherapy is superior to sequential chemotherapy followed by radiotherapy or radiation alone in terms of local control and organ preservation.[20] However, there was no surgical arm to this study, thereby falling short of establishing a new standard of care. Furthermore, using primary concurrent chemoradiation therapy, the 5-year results for both disease-free survival (39%) and laryngectomy-free survival (46%) show that this method leaves the majority of patients either dead or absent their larynx at 5 years.[21] Therefore, this leaves much room for improvement in treatment of laryngeal cancer. Other studies have shown that if nonsurgical organ preservation is to be used, concurrent chemotherapy with hyperfractionated radiotherapy is more effective than radiotherapy alone[22] and that hyperfractionated radiotherapy is more effective than standard radiation alone.[23] Newer trials are investigating the impact of induction chemotherapy to assess tumor response. A complete (or near complete) response to chemotherapy then selects the patients for concurrent chemotherapy and radiotherapy.[24] No biologic marker yet identified can reliably predict which patients are better treated surgically. This is also the topic of investigations in concurrent studies.[25] Because the survival of the two treatment strategies is equivalent, quality-of-life issues are of paramount importance. Recently, a study demonstrated that in the intergroup trial, patients who had total laryngectomy after radiotherapy had a high complication rate including a risk of pharyngocutaneous fistula of up to 30%, highest in the concurrent chemotherapy group.[26] Studies that have evaluated the quality of life after nonsurgical management of advanced laryngeal cancer do suggest that organ preservation is associated with improved quality of life.[27,28] Although the details of such studies are beyond the scope of this chapter, the results indicate that more extensive analysis of the quality of life is important. These studies are difficult to accomplish because many patients are not available after the study, and the quality of life of the survivors might be significantly different than those of the patients who have died, particularly if they died of local complications related to uncontrolled primary site disease. Total laryngectomy still remains a viable option as the primary surgery for advanced cancer or as salvage surgery after radiotherapy and finally for a group of less common conditions. Overlap between these indications occurs. For example, a patient with radionecrosis of the larynx may be found to have residual tumor on permanent sections and, as such, the surgery was salvage in hindsight. Similarly, a tumor that fails radiotherapy may also be causing chronic aspiration and may be too large to allow for any sort of organ preservation surgery. This sort of patient has three (or more) of the following indications for undergoing the procedure.

Indications

1. Advanced tumors with cartilage destruction and anterior extralaryngeal spread; particularly presenting initially with laryngeal dysfunction (including vocal cord paralysis), airway obstruction, or severe aspiration (these patients are not good candidates for "organ preservation" because the organ already has been damaged and will not likely function even if preserved anatomically).[29]

2. Posterior commissure or bilateral arytenoid/cricoarytenoid joint tumor involvement, as is sometimes seen in advanced supraglottic tumors.

3. Circumferential submucosal disease with or without bilateral vocal cord paralysis.

4. Subglottic extension with extensive invasion of the cricoid cartilage.

5. Radiotherapy or chemoradiation failures including those who have also had partial laryngectomy failure.

6. Completion laryngectomy for failed conservation or extensive endoscopic surgery.

7. Hypopharyngeal tumor originating at or spreading to the postcricoid mucosa.

8. Massive neck metastases or thyroid tumors (usually recurrent) invading both sides of the larynx from outside the laryngeal skeleton.

9. Advanced tumors of certain histologic types that are incurable by endoscopic resection, chemotherapy, or radiotherapy (e.g., adenocarcinoma, spindle cell carcinoma, soft tissue sarcomas, minor salivary gland tumors, large cell neuroendocrine tumors); chondrosarcomas of the thyroid cartilage.

10. Extensive pharyngeal or tongue base resections in patients who are at high risk for aspiration problems.

11. Radiation necrosis of the larynx, despite tumor control, unresponsive to adequate antibiotic and hyperbaric oxygen management. This condition can be painful and also predispose patients to aspiration, and often tumor is found when total laryngectomy is performed.

12. Severe irreversible aspiration, with the laryngectomy used for complete separation of the air and food passages. This indication should be rare, considering the variety of other separation or closure procedures available.

Patient Selection and Workup

The following patient requirements should be met before a total laryngectomy is performed.

1. Candidate for general anesthesia; consider severe comorbid conditions as a relative contraindication.

2. Informed consent including realistic understanding of total laryngectomy state and lifestyle after surgery (including the risk of drowning and the need to avoid swimming and certain risky activities and the lack of sense of smell in the event of fire, smoke, or toxic fume exposure).

3. Sufficient performance status, especially dexterity, to allow basic self-care of stoma.

The workup required for a total laryngectomy includes the anesthetic-related assessment of general health (not elaborated here) and specific tests relevant to the larynx. Assuming the patient has a laryngeal carcinoma, the following are required:

1. History (especially details of any previous radiation) and physical examination.

2. A comprehensive head and neck examination, especially the neck, for detection of cervical metastasis.

3. Biopsy proof of malignancy and careful endoscopic assessment of tumor location; use of both microscopic and telescopic endoscopy can help determine the need for total laryngectomy and can also help determine which patients are likely to have extensive subglottic extension or submucosal extension in the hypopharynx.

4. Synchronous primary tumor screening including bronchoscopy, esophagoscopy, and/or barium swallow, chest radiography, and chest computed tomography (CT) in selected cases.

5. Metastatic screen when indicated.

6. Neck CT for assessment of cartilage or pre-epiglottic space invasion in those with advanced or radiation-recurrent lesions and for assessment of radiologically detectable neck metastasis. PET and MR scan may also be useful.

7. In the laboratory evaluation, diabetes and hypothyroidism should be evaluated and managed appropriately because they increase the risk of complications. A nutritional screen is also indicated. Evaluation for the potential for postoperative alcohol withdrawal is also important.

The role of metastatic workup is detailed in other chapters, as are indications for different imaging studies.

Surgical Technique (see Key Indicator Video on website)

Resection

Proper patient positioning provides access to the anterior part of the neck for the surgeon and the assistant. Positioning is best achieved by placing the patient on a table fitted with a head holder, allowing the head to be cantilevered out but remain well supported. This also assists bilateral neck dissection, which is often performed "in-continuity" and allows surgeons to position themselves all the way around the head. The table is turned 180 degrees from the anesthesiology team to further assist access to the patient. Before the operation day, airway management is planned with the anesthesiologist so that an agreement is reached regarding timing of tracheotomy and intubation. In the unobstructed larynx the anesthesiologist may pass an orotracheal tube with anesthetic induction, which may be removed at subsequent tracheotomy or left in situ until tracheal transection is performed at the end of the laryngectomy. With an obstructed airway or in a case in which intubation may displace malignant tissue into the lower airway, a preliminary tracheotomy with the patient under local anesthesia is performed. The tracheotomy skin incision is made at the intended site of the final stoma. The stoma can be placed in the line of the incision (long flap) or 2 to 3 cm inferior to the incision (Fig. 111-1, A and B). The advantage of the former is that creation of the stoma is more

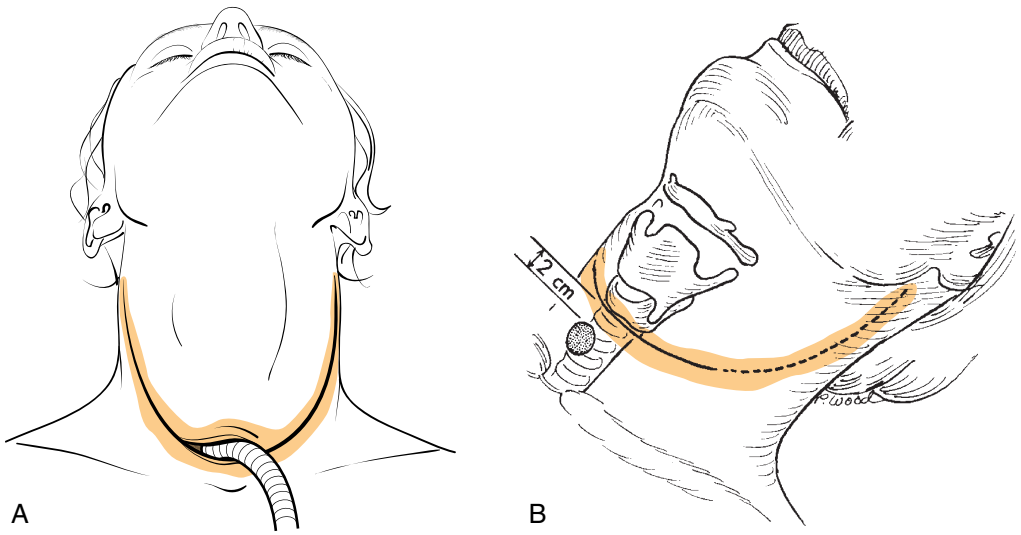

Figure 111-1. Incision options for total laryngectomy and total laryngopharyngectomy. **A,** Long apron flap without separate incision for tracheostomy from mastoid tip to mastoid tip intersecting the midline at approximately the level of the cricoid cartilage, usually about 2 cm above the sternal notch in the midline. **B,** Short apron flap with separate tracheostome incision 2 to 3 cm inferior to the flap incision. A U-shaped incision (not shown) is rarely used, but feasible when neck dissection is not performed.

reliable and avoids a bipedicled bridge of skin between the flap incision and the tracheostomy incision, which can result in stenosis of the stoma. The advantage of the latter is that in the event of pharyngocutaneous fistula, which requires diversion, the stoma is less likely to be involved in the resulting wound. The latter consideration is perhaps more important in previously irradiated patients because the risk of fistula in primary total laryngectomy is low. This configuration also avoids the technical nuances of bilateral, three-point closures at the stoma necessitated by exteriorizing the lower cut tracheal end through the laryngectomy skin incision. In the long flap approach, the three-point closure is performed after the inferior aspect of the stoma is completed, elongating it with the technique shown in Fig. 111-6. This is somewhat more difficult to accomplish with the stoma created 2 to 3 cm into the inferior flap because the trachea is not anchored to the lateral aspect of the dissection. Ultimately, the comfort level of the surgeon determines the choice of incision.

Every attempt should be made to enter the trachea with a horizontal cut at the ultimate level intended for tracheal transection, but in the event that a tracheotomy already is in place, the tracheal transection will be 2 cm inferior to the existing tracheotomy site (if possible). A precurved or flexible reinforced cuffed tube then is passed into the trachea, and adequate ventilation is confirmed. The cuff of the tube is prepped into the field so that the tube can be removed intermittently for suture placement during creation of the stoma.

For access to the larynx itself, a curved, horizontal neck skin incision is preferred because of its minimal intersection with the pharyngeal closure and its potential for extension laterally into a neck dissection incision. Once the incision is deepened through, but not beyond, the platysma, flaps are elevated superiorly and inferiorly in the subplatysmal plane until there is exposure above to the upper border of the hyoid bone and below to the cervical trachea. The anterior jugular veins and the prelaryngeal Delphian node are left undisturbed on the specimen, as are the strap muscles. The sternocleidomastoid muscle then is identified along its anterior border on each side. The investing layer of cervical fascia is incised longitudinally from the hyoid above to the clavicle below. The omohyoid then is divided, which allows entry to the loose areolar compartment bounded laterally by the sternomastoid muscle and carotid sheath and medially by the pharynx and larynx contained in the visceral compartment of the neck. Appropriate neck dissections are performed. The extent of neck dissection is beyond the scope of this chapter, but a few points merit mention. For supraglottic carcinoma, the minimal neck dissection to be performed is selective neck dissection, stations II and III bilaterally. It is extended to level IV and possibly IB and V if lymphadenopathy indicates the need. For advanced glottic carcinoma with supraglottic involvement, the same procedure is recommended. Unilateral (ipsilateral) neck dissection can be considered for T3 glottic carcinoma. For patients who have previously been irradiated, evidence still supports selective neck dissection.[30,31] In general, both neck dissections can be pedicled at the thyrohyoid membrane area and the resection can easily be done en bloc.

The strap muscles then are divided inferiorly from their sternal origins and elevated to expose the thyroid gland (Fig. 111-2, A). Controversy exists with regard to thyroidectomy as part of a total laryngectomy. Studies note that involvement of the thyroid gland is rare.[32] However, when there is nodal disease in the jugular chain from glottic or subglottic cancer, the thyroid is at high risk because of the paratracheal and parapharyngeal lymphatics associated with the thyroid. Also, in patients who have invasion of the thyroid or cricoid cartilage in close proximity to the thyroid gland, the gland may become directly involved by the tumor. The risk to the thyroid is highest with transglottic cancers that extend more than 1 cm subglottic.[32-34] In some cases, both lobes of the thyroid should be removed because of these risk factors. When the lobe of the thyroid is to be removed, the superior and inferior thyroid vascular pedicles are therefore ligated and divided, as is the middle thyroid vein. The lobe(s) to be preserved then is (are) dissected off the laryngotracheal skeleton from medial to lateral, thereby preserving blood supply to the remaining thyroid and parathyroid parenchyma by way of inferior thyroid vessels (the superior thyroid artery can be preserved also if oncologically sound, but this is not necessary). An effort should be made to preserve the vascularity to the parathyroid glands, but if a parathyroid gland is noted that is poorly vascularized after the procedure, this can be reimplanted into the neck musculature as is done for parathyroidectomy in thyroid cancer. Next, after dividing and ligating the upper and lower extent of the anterior jugular veins, the superior aspect of the hyoid bone is skeletonized by detaching the mylohyoid, geniohyoid, digastric sling, and hyoglossus in sequence from medial to lateral (see Fig. 111-2, B). "Cold" knife dissection should be used lateral to the lesser cornu, avoiding excess electrical stimulation or direct damage to the hypoglossal nerve. Caution is advised for supraglottic cancers that involve the aryepiglottic fold, pyriform sinus, or vallecula because too much skeletonization of the hyoid bone and thyrohyoid membrane area may put the surgeon in close proximity to the deep extent of the tumor, which might result in a close or positive margin histologically. This is not a concern with completely endolaryngeal cancers. The sternohyoid and thyrohyoid muscle attachments on the lower border of the hyoid bone remain undisturbed. Further laryngeal cartilage skeletonization now is performed if the tumor does not extend outside the pyriform fossa. The posterior border of the thyroid cartilage lamina is rotated anteriorly by upward traction, allowing sharp release of the constrictor muscles from the inferior to the superior cornu (see Fig. 111-2, C). Above the superior cornu, the laryngeal branch of the superior thyroid artery should be identified, ligated, and divided before it penetrates the thyrohyoid membrane.

The pharyngotomy incisions and definitive laryngeal removal now are performed. To avoid contact with the neoplasm or cutting through its submucosal extensions, the pharynx is entered contralateral to the tumor. If superior extension to the tongue base is present, lateral pharyngotomy behind the thyroid cartilage is performed, and by use of a headlamp, the extent of tumor is inspected. A safe 2-cm margin of normal-looking mucosa then is preserved with further cuts from below, progressing superiorly behind the thyrohyoid membrane, around the hyoid bone, and then transversely across the vallecula or tongue base. By contrast, if the disease is confined below the level of the hyoid, entry by way of the vallecula is feasible with a direct anteroposterior approach (Fig. 111-3) in the horizontal plane of the upper hyoid border. Strict maintenance of this plane, avoiding excessive inferior traction on the hyoid itself, precludes violation of the pre-epiglottic space. Once the mucosa is breached, the epiglottis' tip is identified, grasped with an Allis forceps if tumor free, and gently pulled anteriorly out of the pharyngotomy. A view of the endolarynx and pharynx now is possible to assess tumor extent and to plan appropriate mucosal cuts (see Fig. 111-2, D).

With a Mayo scissors, bilateral, inferiorly direct cuts are made, releasing the lateral pharynx from the larynx. The inside scissors blade is on mucosa, and the outside blade is on constrictor musculature. As these vallecula-to-pyriform sinus incisions are made, the larynx is further angled anteriorly out of the wound until it is released to the apices of the pyriform sinuses. The postcricoid mucosa is exposed and incised sharply in the transverse direction connecting the inferior extent of both lateral incisions across the lower half of the cricoid lamina. A plane of blunt dissection initially behind the posterior cricoarytenoid muscle, but from there down between the trachea and longitudinal esophageal muscle, is then opened until the desired level of tracheal transection is reached. Optimum exposure of the trachea at this stage is achieved by further lateralization of the preserved thyroid lobe and then followed by knife transection of the trachea itself. This cut is bevelled upward from anterior to posterior (see Fig. 111-6, A), with special care not to encroach on any subglottic tumor extension. If the latter is present, a 1.5- to 2-cm margin of healthy-appearing trachea should be resected in continuity with the larynx to avoid stomal recurrence.[35] If a preliminary tracheotomy had not been performed, the oral endotracheal tube is next withdrawn from the tracheal stump and a new, cuffed, flexible tube is inserted for connection to new anesthesia tubing. As an alternative, the steps can be altered slightly as indicated by the pathology. As long as there is not extensive subglottic spread, preliminary tracheotomy assists the resection greatly. This is performed after dissection of the thyroid gland and skeletonization of the thyroid cartilage. The trachea is entered 2 cm below the inferior extent of tumor, and careful inspection is performed on entry. The endotracheal tube is withdrawn, and the trachea is further incised laterally with a

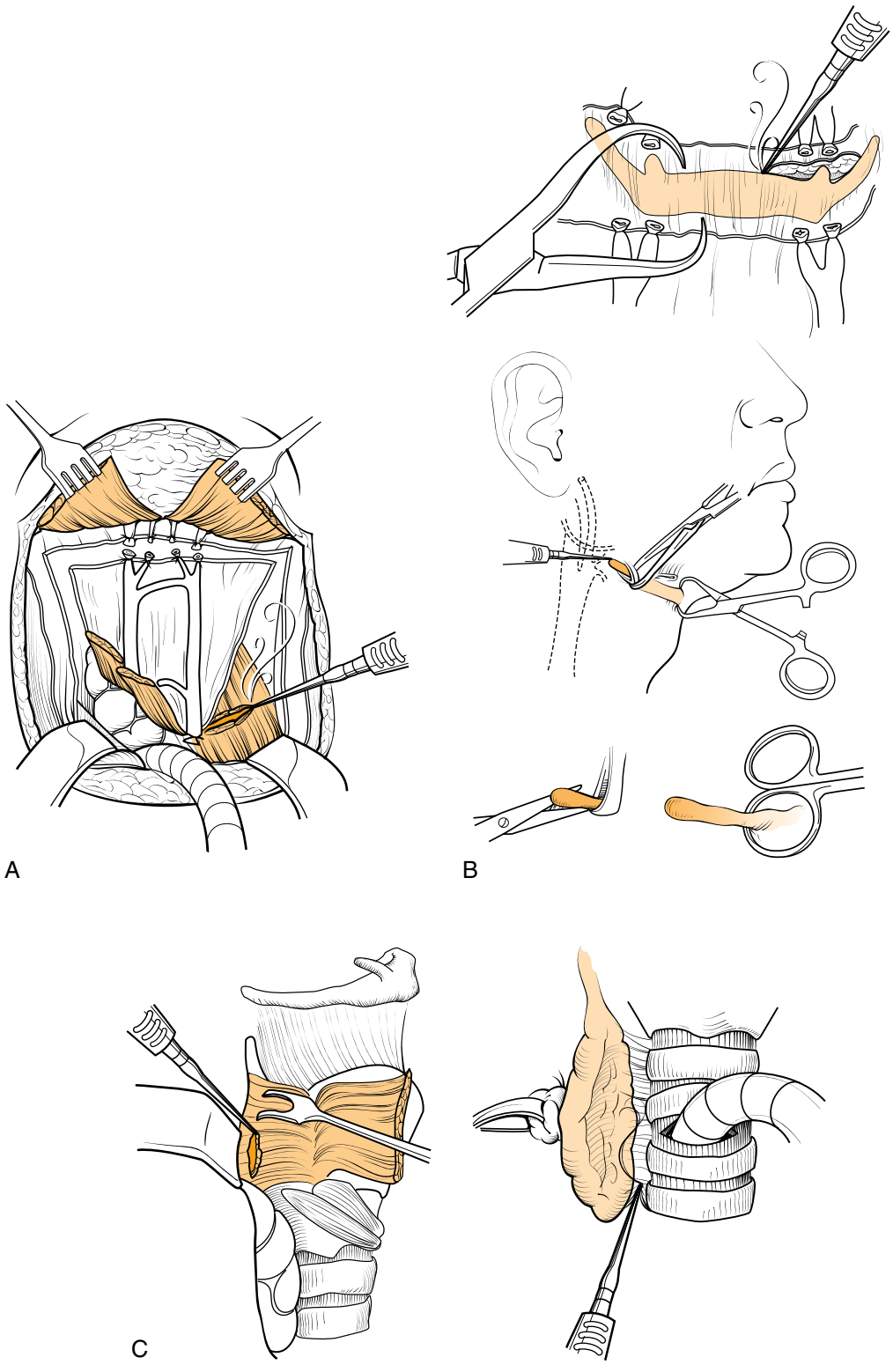

Figure 111-2. Skeletonization of the larynx. **A,** Division of the strap musculature after elevation of a subplatysmal flap. The omohyoid is divided inferiorly, usually during the neck dissection. The sternothyroid and sternohyoid muscles are divided inferiorly to expose the thyroid gland and trachea. **B,** Division of suprahyoid musculature. This is performed staying close to the superior aspect of the hyoid bone. Cautery is avoided lateral to the lesser cornu to avoid injury to the hypoglossal nerve. In this area the hyoid is retracted in such a way as to distract the greater cornu inferiorly, and a scissor is used to release the cornu staying right on the bone. **C,** Division of constrictor musculature along the lateral aspect of the thyroid cartilage and dissection of the thyroid. If the thyroid is to be resected, it is elevated and the dissection proceeds directly to the tracheoesophageal groove. If the thyroid is to be preserved, the lobe is dissected away from the tracheoesophageal groove after division of the isthmus. Electrocautery dissection is useful to minimize bleeding in this area. The degree of skeletonization depends on tumor extent. Once the thyroid cartilage is skeletonized, the superior laryngeal neurovascular bundle can be divided to decrease bleeding during the resection.

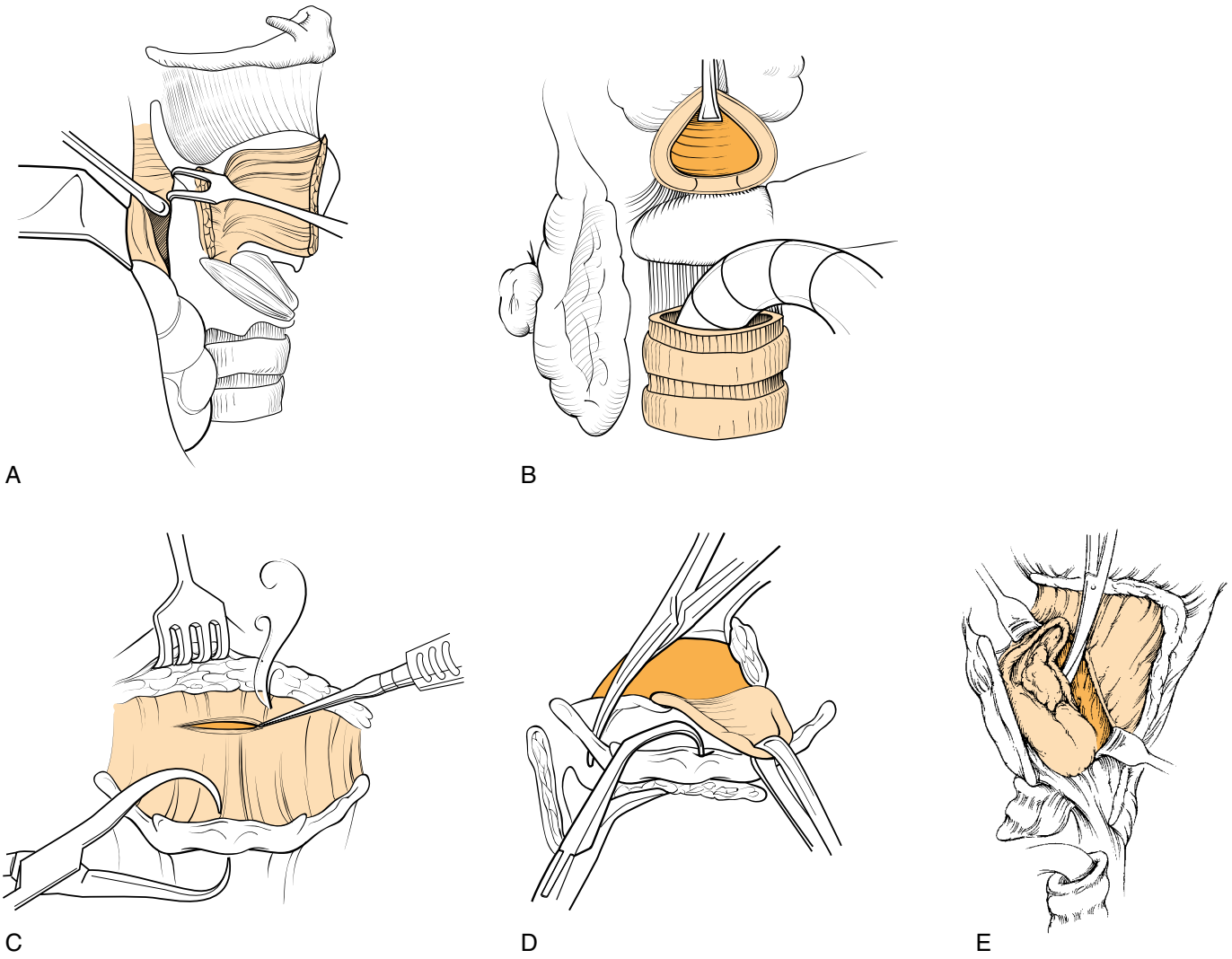

Figure 111-3. Entry into larynx. **A,** Use of a Freer elevator to mobilize the pyriform sinus and internal perichondrium from the thyroid cartilage. This should not be performed if the pyriform sinus is likely to be involved by the tumor. **B,** The trachea is transected, and the ligamentous attachments are divided permitting dissection of the trachea away from the upper esophagus up to the level of the posterior cricoarytenoid musculature. This cut is beveled as shown in Figure 111-6. This step is delayed if there is concern about significant subglottic extension. **C,** Dissection follows the hyoepiglottic ligament to the epiglottis and vallecula to avoid entry into the pre-epiglottic space. **D,** If clinically uninvolved, the vallecula is entered on the nontumor side, and if it is not involved, the tip of the epiglottis is grasped. **E,** The pharyngoepiglottic fold cuts are extended. If uninvolved, the previously preserved pyriform sinus mucosa is preserved by transecting the mucosa close to the aryepiglottic fold. This is accomplished by placing one scissor blade in the lumen and the other between the previously released internal perichondrium and the thyroid cartilage. This leaves the larynx pedicled only on the mucosa of the anterior esophageal inlet, which can be transected under direct vision preserving as much mucosa as is oncologically sound. If the trachea was not previously transected, it is done at this time to release the specimen.

beveled cut (see Fig. 111-6, A). A reinforced tube is placed and a sterile connector passed through the drapes to connect to the circuit. The trachea is then transected by making a notched incision in the posterior wall. This is taken down to the esophageal musculature. Once the ligamentous attachments and the recurrent laryngeal nerve are divided, blunt dissection can be performed up to the level of the posterior cricoarytenoid musculature. Then, when the surgeon enters the larynx and completes the mucosal cuts from superiorly along the aryepiglottic folds, the specimen is pedicled on the postcricoid mucosa only, and this assists the final transection, which can reduce the blood loss. The surgeon places a pack in the pharynx and neck while inspecting the specimen for orientation and margin assessment (Fig. 111-4). After the specimen is passed from the table, it is carefully inspected for adequacy of resection, and a pathologist's frozen section study of the patient's entire cut margins including trachea, tongue, and pharyngeal mucosa is requested. The tracheal margin is critical because there are patients in whom submucosal occult microscopic disease spreads down the trachea, despite relatively normal-looking mucosa. Excising all disease helps prevent stomal recurrence. The wound is thoroughly irrigated, all clots are removed, and hemostasis is achieved.

If a primary tracheoesophageal puncture is to be performed, creating the tracheostome before pharyngeal repair may be considered because it enables definitive positioning of the trachea relative to the esophagus and skin before a puncture site is selected. A pair of right-angled forceps then is passed into the esophagus, with the tip elevating the posterior tracheal wall at the intended puncture site (see Fig. 111-7). A tracheoesophageal stab incision is made, exposing the forceps tip, and with these, a catheter is grasped, pulled into the pharynx, and then fed down the esophagus. This is secured to the anterior chest wall skin with an op-site and suture. The previously described resection technique clearly needs to be modified according to the extent of tumor spread. A common variation is the "wide-field" laryngectomy, in which overlying neck skin is resected in continuity with the larynx and thyroid gland (see Fig. 111-8). This method is sometimes prudent for tumors that

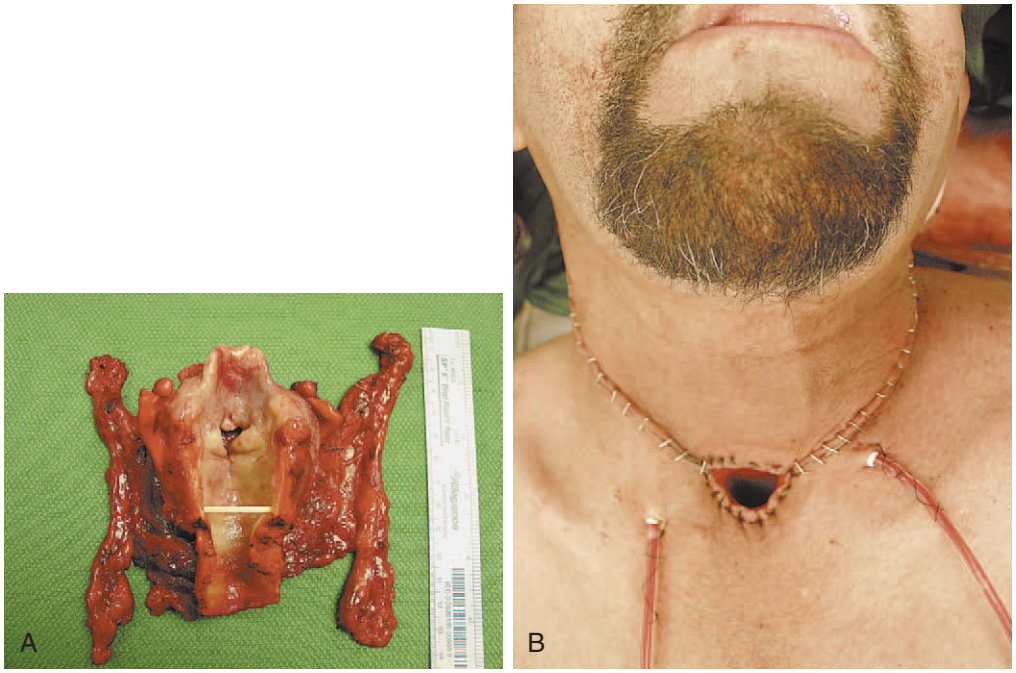

Figure 111-4. Specimen and resulting wound. **A,** Total laryngectomy specimen in continuity with bilateral selective neck dissections. **B,** Final closure with stoma in long flap approach.

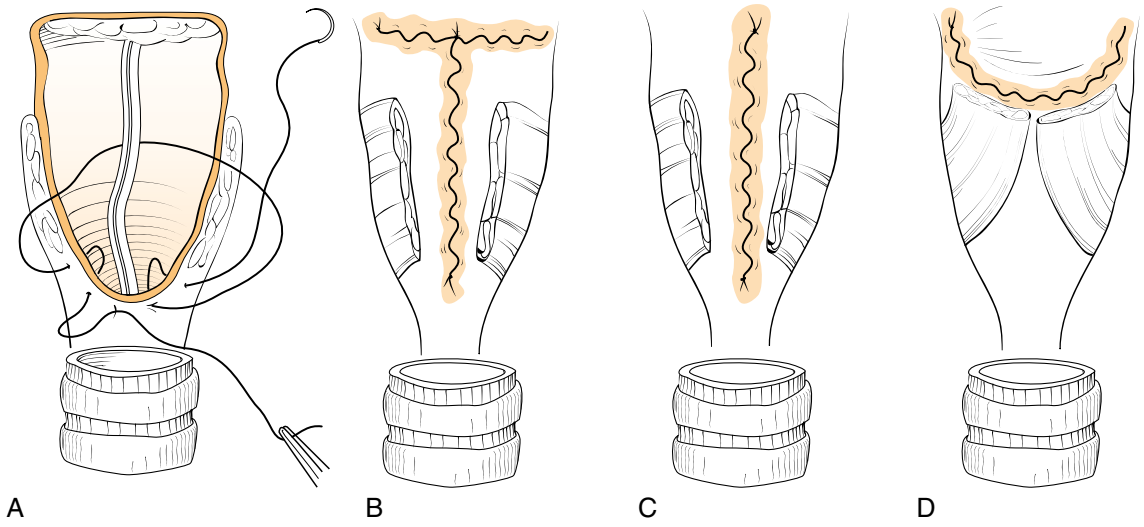

Figure 111-5. **A,** Closure of pharynx with detail of suturing technique. **B,** T-closure. **C,** Vertical closure. **D,** Horizontal closure.

have invaded soft tissue outside the laryngeal skeleton but usually requires pedicles of free flap to close the neck and create a stoma.

Repair and Reconstruction

Pharynx

Pharyngeal reconstruction is currently performed by direct closure or flap augmentation. Configurations for a direct repair are T shaped or linear (horizontal or longitudinal) (see Fig. 111-5). Selection of closure type is based on an assessment of the shape and size of the pharyngeal defect, elasticity of remaining tissue, and simulated wound approximation before suturing. The least-tensioned apposition of wound edges is the best; it is usually T shaped and results in minimal or no horizontal pharyngeal shelf formation.[36] However, a straight closure is less prone to technical failure in patients with abundant pharyngeal mucosa for closure.

The pharyngeal wall is closed in a single layer. A running or interrupted closure, according to the surgeon's preference, is used with particular attention to inversion of the mucosal edges into the pharynx. This inversion is achieved with an absorbable stitch that runs horizontally through the submucosa, without penetration of the mucosal surface. A longer retained material such as polyglycolic acid (3-0) is used and is adequate for irradiated tissue. Large series of stapled closures have also been reported.[37] Although some advocate closure of the pharyngeal muscle, this is not necessary. Reinforcement of the suture line with muscle sutures may be performed in selected cases where the mucosa has been compromised by radiation, but it is not a substitute for good mucosal closure. One study[38] has shown that a mucosal closure alone is sufficient for sound healing. Closure of muscle can lead to difficulty with tracheoesophageal speech.[39] and dysphagia. Some surgeons recommend a closure of the muscle over the suture line with a constrictor myotomy performed laterally and myotomy inferiorly along

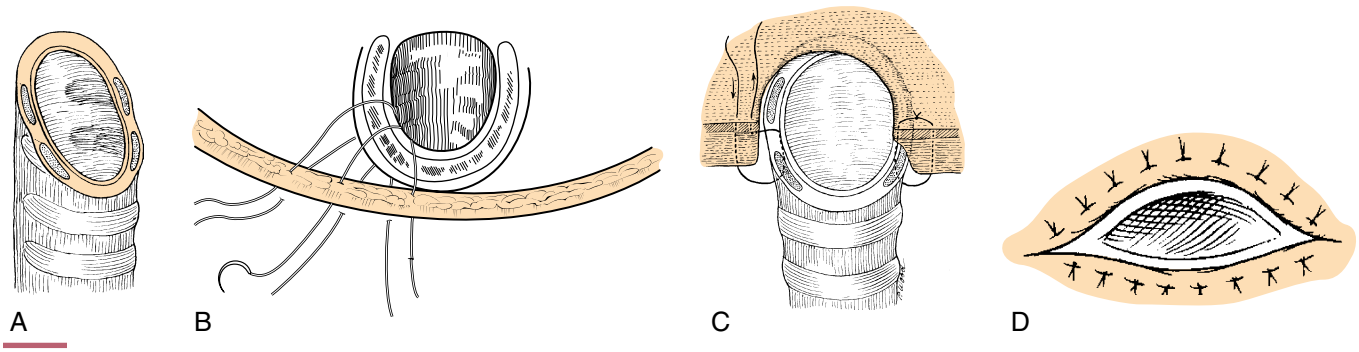

Figure 111-6. Steps to avoid stenosis in creation of tracheostoma (long flap incision). **A,** Bevel the tracheal cut such that more posterior wall is preserved. This is done by curving a scissor upward as the anterior tracheostomy is extended laterally. The posterior wall is transected with a V-shaped incision in the mucosa to lengthen it and prevent scar contracture. **B,** Elongate the anterior edge of the stoma by placing sutures from midline outward, proceeding farther along the skin than the trachea and by continuing this well onto the lateral portion of the trachea. **C,** Bury the exposed tracheal cartilage with a half-buried vertical mattress suture from far on the skin around the tracheal cartilage and then back through the near edge of the skin tying the suture on the skin. To minimize granulation tissue, an effort should be made to place these sutures submucosally. Absorbable sutures are preferred. 2-0 Vicryl is advisable for the central suture, and 3-0 Vicryl is used for the remainder. **D,** Final closure including appearance of stoma using long-flap approach and the stoma technique described in **A** through **C.** Note the quite ample diameter of the stoma that results from suture placement in the manner described.

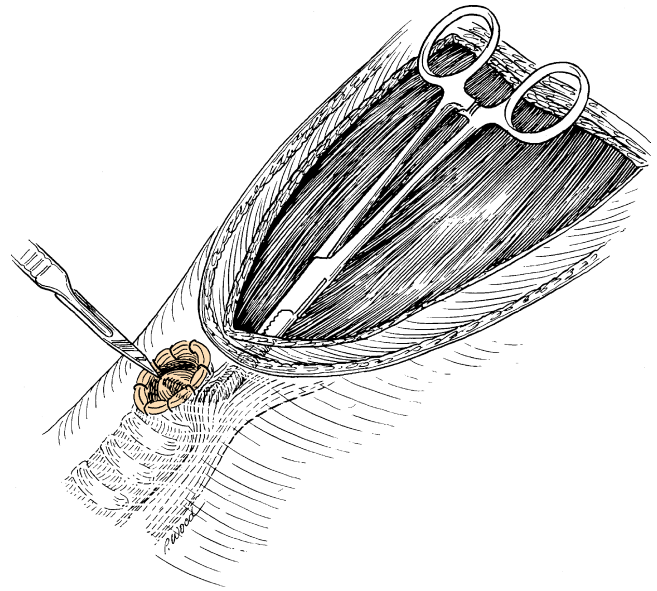

Figure 111-7. Technique of tracheoesophageal puncture. See text for description of technique.

the lateral aspect of the esophagus, sometimes called a cricopharyngeal myotomy (somewhat of a misnomer given that the cricoid has been removed). This technique reinforces the closure with a second layer but avoids the circumferential effect of the muscle closure.

If there is insufficient pharyngeal wall to close over a 36-French (F) dilator, a flap repair should be considered to increase the circumferential dimension of the neopharynx. Hui and colleagues[40] addressed the question of the width of the pharyngeal wall remnant relative to postoperative dysphagia and concluded that a remnant as small as 1.5-cm wide was sufficient to avoid dysphagia, although the study included only one patient with a remnant as small as 1.5 cm. Reconstructive options include a myocutaneous flap, a muscle flap, or a microvascular free flap. In extremely difficult patients, a controlled salivary fistula can be created to avoid catastrophic wound problems. In such patients, the flap will allow a vascularized bed that will ultimately allow removal of the conduit that is placed.

Tracheal Stoma

For the long flap approach, the stoma is inserted into the center of the lower flap with a central suture of 2-0 Vicryl excising an ellipse of skin if needed. In the short flap, the permanent end-tracheal stoma is created by excising a shield-shaped skin island from the lower neck flap in the midline, just above the sternal notch. Any excess adipose tissue or bulky sternomastoid muscle or tendon is excised deep to the skin flap to minimize tracheostenosis. The central suture is then secured to the lower aspect of the shield-shaped defect. The circumferential suture line should provide support for the trachea and accurate skin-mucosa apposition without cartilage exposure. These sutures should be placed beginning in the center and each subsequent suture placed lateral to the prior one. For each suture, the surgeon proceeds farther along the skin edge than the mucosal edge, which serves to pull the trachea outward. In addition, the trachea is not sewn in a circular fashion. By bringing the lateral trachea down to the inferior flap, the inferior aspect of the stoma is elongated, producing a more horizontally based trapezoid (shield) shape that avoids the circumferential stenosis or slitlike vertical stomas, which may result in a need for revision. This is best achieved by a modified ("half-buried") vertical mattress suture that traverses (1) skin (peripherally); (2) cartilaginous tracheal wall (extramucosally); and (3) skin (centrally).

So, to summarize, we have Figure 111-6, which demonstrates that the three ways to maximize stoma size are (1) "bevel the trachea"; (2) "elongate the base"; and (3) "cover the cartilage." A 2-0 Vicryl is used for the central suture and a 3-0 Vicryl for the remaining inferior sutures. A trifurcating suture can be used (either 3-0 or 4-0 Vicryl) where the superior flap comes into contact with the lateral aspect of the stoma bilaterally (in the long flap approach). Absorbable sutures are preferable because suture removal is undesirable in the stoma region.

Postoperative Management and Complications

Apart from routine postsurgical care, the specific treatment of early postlaryngectomy patients includes the following monitoring: systemic vital signs, fluid balance, oxygenation, wound drain vacuum retention and output, and neck flap viability. Postoperative treatment includes ventilator assistance, as per respiratory status; tracheostomy tube care (cleaning, cuff pressure checks); airway humidification; bronchodilator treatments or chest physical therapy; suture line care three times daily; and nasogastric or tracheoesophageal fistula tube feeding once bowel sounds are present. Drains are removed when output is less than 25 mL/day for 2 consecutive days, and oral feeding is normally begun 7 days after surgery in the nonirradiated patient. Laryngectomees previously radiated are fed 12 to 14 days in most cases because edema precludes earlier assessment of the safety of the wound. Timing of feeding in total laryngectomy can be individualized depending on individual patient considerations.

Figure 111-8. Wide-field laryngectomy defect for radiation recurrent tumor including anterior neck skin, thyroid, sternomastoid, and selective neck node resection.

Early Complications

Early complications usually occur during the patient's postoperative hospitalization.

Drain Failure

Drains unable to hold a vacuum represent a serious threat to the wound. Usually there is either a leak in the pharynx or the skin and stoma closure that needs to be promptly detected and sealed.

Hematoma

Although rare, a hematoma requires prompt intervention to avoid pressure separation of the pharyngeal repair and compression of the upper trachea. The patient is returned to the operating room; the clot is evacuated, and any detectable bleeding is controlled. New drains are inserted because blockage of the original ones with clot is inevitable.

Infection

A subcutaneous infection after total laryngectomy is recognized by increasing erythema and edema of the skin flaps 3 to 5 days after surgery. Associated odor, fever, and elevated leukocyte count occur. If an infected collection is present, the wound is opened during sterile conditions and the pus is evacuated and cultured. Dead space between the neopharynx and skin flap is managed with repeated antiseptic gauze packing until healed. Antibiotic coverage is modified according to culture results, and a pharyngocutaneous fistula is suspected if wound discharge continues or increases. A chyle fistula should be ruled out if neck dissection was performed.

Pharyngocutaneous Fistula

Patients with poor preoperative nutritional status and positive surgical margins and those with diabetes are at high risk for fistula development.[41] Early studies[35,42] did not show a significantly increased fistula rate in patients who have had preoperative radiotherapy, but subsequent studies seem to refute this.[26,41,43-45] A fistula begins as a major accumulating salivary leak from the pharyngeal closure into the subcutaneous space beneath the skin flaps and may be encouraged by a tight distal hypopharyngeal closure. Its existence often is heralded by increased turbid drain output and by erythema and edema around part of the wound closure, which, on opening, drains purulent material and saliva.

Such fistulas may occur 1 to 6 weeks postoperatively, depending on the presence or absence of previous radiation, and communication from the skin to the pharynx is confirmed by a methylene blue swallowing test or a Gastrografin swallow radiograph. Persistent or recurrent tumor always should be ruled out.

Initial management is by regular, antiseptic gauze fistula-track packing, dressings, and antibiotic therapy, as well as by giving the patient nothing by mouth. An active drain can often be converted to a passive drain to allow diversion of the saliva and prevention of salivary collection. A pressure dressing is sometimes useful. Conservative therapy attempts to allow the fistula to close from the inside toward the skin. A useful adjunct is to "sterilize" the fistula from within by administering 10 mL of 0.25% acetic acid by mouth or an antibiotic or other antiseptic preparation, three to four times daily. If the previously described measures are unsuccessful in sealing off the pharynx from the neck, operative closure should be considered. Although spontaneous closure may occur up to 6 weeks after onset, most patients prefer a more rapid resolution so that oral feeding may begin.

An excellent option for fistula closure before complete epithelialization is a pedicled muscle flap (pectoralis, trapezius, or latissimus dorsi) slipped between the pharyngeal and skin defects. Such flaps endow excellent blood flow and antibacterial benefits to an avascular, infected bed.[46] A control pharyngostome catheter suction system, as described in the discussion of surgical technique, also may be used to direct saliva away from the carotids. Further surgery at this stage also should correct any benign pharyngeal stricture distal to the fistula. Another option is a salivary bypass tube, which allows saliva to pass by the pharyngeal defect. This can be used in conjunction with a flap. Control of esophageal reflux is also an important aspect of preventing and managing pharyngocutaneous fistula.

Wound Dehiscence

Wound dehiscence may accompany a tensioned skin closure, the postradiation state, wound infection, fistula, or poorly designed ischemic neck flaps. Local wound care should suffice for healing by secondary intention, but if the carotid becomes persistently exposed, vascularized muscle flap coverage is advisable.

Late Complications

Stomal Stenosis

If the stoma is created as described earlier, this complication is uncommon. This approach can be used in revision as well. In patients with small tracheas or a propensity for stenosis, women have a higher likelihood of fistula.[47] Revision, when necessary, can be done with V-Y advancement flaps, Z-plastys, and a "fish-mouth" stomaplasty. Excision of cartilage remnants is preferable to radical excision and laryngectomy tube placement, but in some cases prolonged use of a laryngectomy tube will be required.

Pharyngoesophageal Stenosis and Stricture

Tumor recurrence should be suspected, but once excluded by endoscopy and biopsy, outpatient dilation is usually effective. An adequate lumen (36 F) is necessary not only for swallowing and nutrition but also for tracheoesophageal speech production. If dilatation is unsuccessful, flap reconstruction is preferable.

The high incidence of wound complications as a result of salvage laryngectomy has prompted some surgeons to transfer vascularized tissue to help minimize short-term and long-term problems. The results from these series suggest that it is possible to decrease the incidence of complications, but the rate of fistula is still high.[48,49] Unfortunately, the same patients that are at the highest risk for severe and chronic wound complications are often those who are not ideal candidates for free tissue transfer. Although the rate of fistula may be as high as 50% in some patients who have undergone intensive chemoradiation, this policy would result in unnecessary flap reconstructions in some patients if applied to all salvage cases.

Hypothyroidism

Preoperative or postoperative radiotherapy plus hemithyroidectomy is usually sufficient to induce a low thyroid state.[50-52] Thyroid function tests every 1 to 2 months after completion of all treatment indicate when supplemental thyroid medication is required.

Rehabilitation

Swallowing

Oral intake usually is commenced 7 days after surgery, although waiting until after 14 days is advisable if the patient has had preoperative radiotherapy. In a Brazilian study, 625 laryngectomees were fed 3 days after surgery and showed no increase in complications. They were able to avoid use of a nasogastric tube altogether.[53] Further study has replicated this finding,[54] but in reality, feeding patients this early is not always feasible because of postoperative edema. Because of this, length of hospital stay was found not to be significantly affected by early oral feeding in one study.[55] In general, once the patient can swallow saliva, it seems reasonable to consider oral feeding. The literature shows that most pharyngocutaneous fistulas occur at or just after postoperative day 7. In uncomplicated cases with minimal edema, it may be possible to be certain there is no fistula sooner than that. Our experience has been that we do tend to feed people who have previously been irradiated later and more carefully. Because of this, the recognition of the fistula has sometimes been delayed well beyond a week. It is our experience that fistula is more common after radiotherapy. Regardless of the timing of oral feeding, the key is recognition of the fistula if it does occur. A higher index of suspicion of pharyngocutaneous fistula should be maintained in patients with edema or prior radiotherapy or in patients with comorbid conditions such as diabetes mellitus, renal insufficiency, or on immunosuppressive agents. Every effort should be undertaken to avoid positive margins not only for cancer control but also because the presence of tumor can result in fistula. A gastrostomy may be of benefit in likely to have a pharyngocutaneous fistula or dysphagia postoperatively. Once a soft diet is tolerated, the patient may advance to normal intake, but edentulous patients should be especially cautious about solid food.

If dysphagia prevents adequate caloric or fluid intake, pharyngeal stricture, tumor recurrence, stenosis, or tongue weakness may be responsible. A modified barium swallow test[56] or manofluorography[57] helps diagnose which component or components of the swallowing tract or mechanism are faulty. Radiation fibrosis of the neck, causing pharyngeal stenosis some months or years after completion of treatment, should be counteracted by regular dilatation. Neuromuscular paralysis or weakness may be either preexisting or iatrogenic from radiotherapy or from surgical damage to the hypoglossal nerve. In these patients, except those with radiation neuritis, time and speech therapy exercises assist recovery.

Occasionally, circumferential spasm of the pharyngoesophageal segment may be sufficient to cause dysphagia, in which case Botox A injections or myotomy may be helpful.[58,59]

Voice

Electro-Mechanical Devices

These devices are useful in the early, postoperative phase, before it is safe for the healing pharyngeal wall to be insufflated. Some patients also use them for permanent communication. Their major disadvantages are the monotonous, mechanical sound production; poor intelligibility; and the need for a cumbersome external device.

Esophageal Speech

Although esophageal speech is mastered only by a few patients,[60] a good esophageal speaker eventually may undertake public speaking engagements. Air charging is achieved by thrusting the tongue back and forcing a bolus through the cricopharyngeus. The air bolus then is regurgitated through the pharyngoesophageal segment, which vibrates to produce sound. Spasm of the pharyngoesophageal musculature or fixed stricture may prevent acquisition of this technique, as may poor patient motivation. The former may be managed by botulinum toxin injection.[56]

Tracheoesophageal Speech

This method is the most commonly employed technique of voice restoration following total laryngectomy. The principle behind tracheoesophageal speech is diversion of exhaled air into the pharynx by way of a permanent, surgically constructed tracheoesophageal fistula. The pharyngoesophageal segment above the fistula vibrates, producing a neovoice. Singer and Blom[61] and Panje[62] have developed prosthetic devices that allow airflow to the pharyngoesophagus and prevent salivary leak into the trachea. Tracheostomal occlusion is either digital or by wearing a valved stoma button that flaps shut with forceful exhalation. The tracheoesophageal puncture (TEP) may either be done primarily at the time of laryngectomy or as a secondary procedure when wound healing is complete. Primary TEP has been shown to be more effective overall and it has been demonstrated that it can be done safely even in the setting of prior radiotherapy.[63] Many surgeons place the appropriate diameter tube through the TEP site for early postoperative nutrition. Our experience has shown that primary TEP in nonirradiated patients is preferred if the patient has a good understanding of the process and is counseled appropriately. Some patients cannot grasp this complexity at the time of primary total laryngectomy. Other patients who have received high doses of radiotherapy and are at increased risk for wound problems are probably best allowed to heal before performing TEP. Also, patients who have primary total laryngectomy for subglottic cancer will require high-dose postoperative radiotherapy to the stoma and are probably best allowed to heal the stoma before placing any foreign body. Manipulation of peristomal tissue and vibratory excursion of pharyngoesophageal mucosa ensues once phonation training begins. Both may cause excessive edema, unless thorough tissue recovery from radiation has occurred. A stoma at least 1 cm in diameter is required. Refer to Chapter 113 for further details of tracheoesophageal speech and prosthesis management. We perform both primary and secondary tracheoesophageal puncture by incising over a Crawford clamp and then passing a catheter under direct vision. Recently, transnasal esophagoscopy has made it possible to do tracheoesophageal puncture in the clinic under local anesthesia.[64] Tracheoesophageal speech is a major factor in improving quality of life in laryngectomy patients and is the preferred method for rehabilitation.[65]

Nevertheless, long-term problems with the puncture site do occur. Leakage and granulation tissue can be troublesome, as can yeast infection. Leakage can be treated by increasing the diameter of the prosthesis, but in some cases it requires closing the tract.

Ultravoice

A speaking device built into a denture is another option for patients who are unable to acquire tracheoesophageal speech.[66]

Total Laryngopharyngectomy

Total laryngopharyngectomy includes associated circumferential pharyngectomy. The vertical extent of the pharyngectomy may be from the nasopharynx above to the cervical esophagus below, depending on tumor location and spread. Advanced squamous carcinoma of the hypopharynx or cervical esophagus with pharyngeal extension is the most common clinical entity requiring this operation (Fig. 111-9).

Historical Development

Total laryngopharyngectomy was a logical extension of total laryngectomy. Thus after Billroth's landmark total laryngectomy in 1873, von Langenbeck removed a larynx plus much of the pharynx and cervical esophagus in 1875. Czerny, who had assisted Billroth in the first total laryngectomy, performed the first total laryngopharyngectomy in 1877.[67] According to Macbeth,[67] little had been done to reconstitute the pharynx until the 1920s, when Trotter introduced the concept of skin flaps turned in from the neck to form a posterior pharyngeal wall at stage 1, followed by circumferential tubing for stage 2. Gluck, operating in the late 19th century, also is credited with discovering this concept,[69] in which bilateral, laterally based neck skin flaps were used.

Once the complications of sepsis and perioperative mortality had been minimized, attention turned to better reconstruction. Wookey[70] in Toronto published a series of total laryngopharyngectomies followed by a unilaterally based skin flap reconstruction. Since then, advances have centered on more sophisticated forms of single-stage reconstruction, with the resectional techniques for the larynx and pharynx remaining standard.

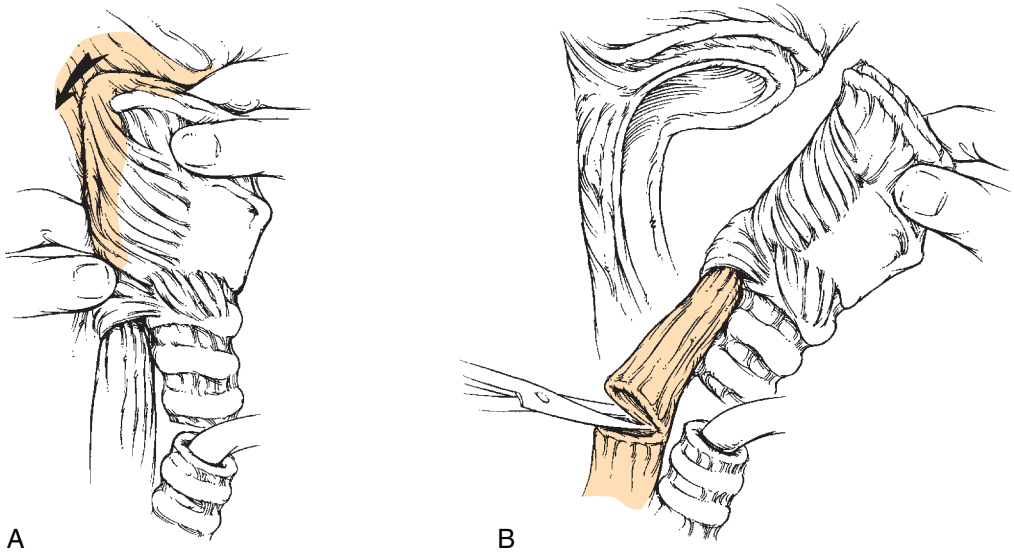

Figure 111-9. Total laryngopharyngectomy. **A,** The retropharyngeal dissection has been performed. **B,** Now superior and inferior cuts that are cirumferential will complete the resection.

Indications

Assuming surgery is advised, patients with advanced tumors of the hypopharynx with the following features require total laryngopharyngectomy.

Pyriform Sinus Carcinoma

Posterior pharyngeal spread of the tumor across the postcricoid region beyond the midline posteriorly or extension into the esophageal inlet necessitates circumferential pharyngectomy. The larynx, even if not directly involved, is sometimes sacrificed because it loses its dynamic pharyngeal support for swallowing or it becomes denervated. Total pharyngeal resection and reconstruction with laryngeal preservation have been described but require superb patient performance status. This result is the exception rather than the norm in the hypopharyngeal cancer population. Laryngeal spread, especially if it involves the posterior cricoarytenoid muscle to cause abductor paralysis, as indicated previously, nearly always necessitates total laryngectomy.

Again, some patients may be suitable candidates for near-total laryngectomy,[17] but these patients also usually require flap reconstruction of the pharynx. Alternatively, supracricoid hemilaryngopharyngectomy[71] has been advocated for select patients with carcinoma of the pyriform sinus. More recently, Steiner's group has reported on a series of endoscopically excised hypopharyngeal tumors with creditable survivorship.[72] The goal of treatment of any patient requiring surgery of the laryngopharynx is to achieve cancer control and restore airway, swallowing, and speech. The authors believe this goal is achievable with appropriate reconstruction even in patients undergoing total laryngopharyngectomy.[73]

Organ preservation rates are lower in hypopharyngeal carcinoma than in laryngeal carcinoma with a chemoradiation strategy.

Carcinoma of Posterior Hypopharyngeal Wall

When carcinoma of the posterior hypopharyngeal wall extends anteriorly into the pyriform sinuses or inferiorly below the level of the arytenoids, total laryngopharyngectomy is necessary.

Postcricoid Carcinoma

Postcricoid carcinoma usually is seen late, after spread downward into the esophageal inlet has occurred. In these patients, total laryngopharyngectomy is required, especially if there is vocal cord paralysis caused by infiltration of the posterior cricoarytenoid muscles or cricoarytenoid joints.

Patient Selection and Workup

The same general patient considerations apply as outlined for total laryngectomy. Special features of the preoperative workup of patients with hypopharyngeal cancer include nutritional assessment and supplementation, careful scan staging of local and distant disease extent, and endoscopy with mapping biopsies. Then an assessment of resectability is made (carotid artery, vertebral column, and extensive neck metastatic involvement is common), followed by complete evaluation of potential donor sites for pharyngoesophageal reconstruction. Preoperative calcium and thyroid hormone levels are assessed as a baseline for postoperative management.

Surgical Technique

Resection

Patient positioning and anesthetic considerations are the same as for those undergoing total laryngectomy with the addition of donor sites such as the forearm, lateral thigh, or abdomen prepared for flap harvest or, in patients with gastric pull-up, stomach mobilization. The neck dissection usually is performed first; the specimen is pedicled medially on the pharyngeal wall from the hyoid level down to the cricopharyngeus. Suitable arterial stumps (lingual, facial, superior thyroid, transverse cervical) are preserved, provided no oncologic compromise results, to allow a microvascular free tissue transfer. Similarly, the external jugular, anterior jugular, internal jugular tributaries, or transverse cervical vein may be kept, unless a classic radical neck dissection is necessary. If esophageal resection well inferior to the thoracic inlet is required to obtain clear margins, a total esophagectomy and visceral transposition may be the best reconstruction, obviating the need for recipient vessel preservation and avoiding the potential leakage of saliva or refluxate into a suture line near the great vessels. In such cases a mediastinal tracheostomy may also be necessary to assist tracheal resection.

The initial dissection steps for laryngopharyngectomy are the same as for total laryngectomy, except that mobilization of the larynx, pharynx, and cervical esophagus as a unit is performed by extending the lateral dissection into the retropharyngeal and retroesophageal space. This actually makes this operation much simpler because the pyriform mucosa is not dissected free. The skeletonization of the larynx is not performed laterally, so the dissection can be done bluntly once the deep cervical fascia is divided medial to the carotid artery along the prevertebral fascia adjacent to the lateral masses of the vertebral bodies. Careful observation is maintained for spread beyond the buccopharyngeal and prevertebral fasciae into the prevertebral muscles or vertebral

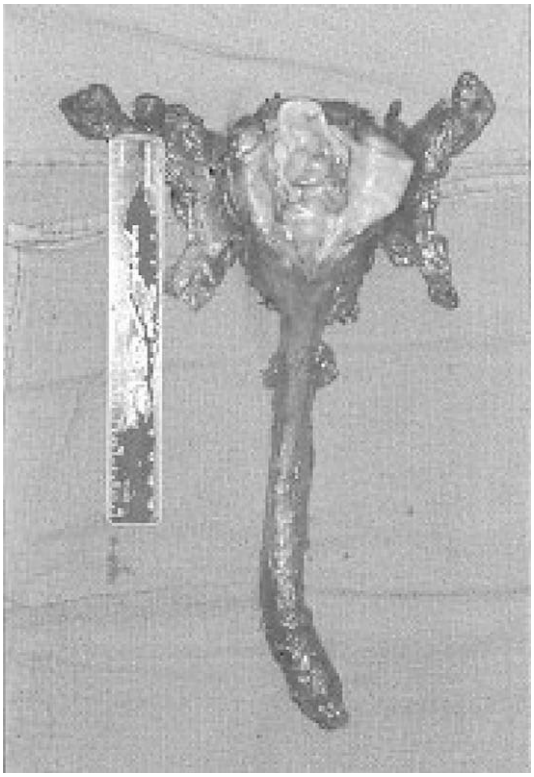

Figure 111-10. Total laryngopharyngoesophagectomy specimen en bloc with bilateral neck dissections and thyroidectomy. This patient had one hypopharyngeal tumor and a second, distal esophageal tumor.

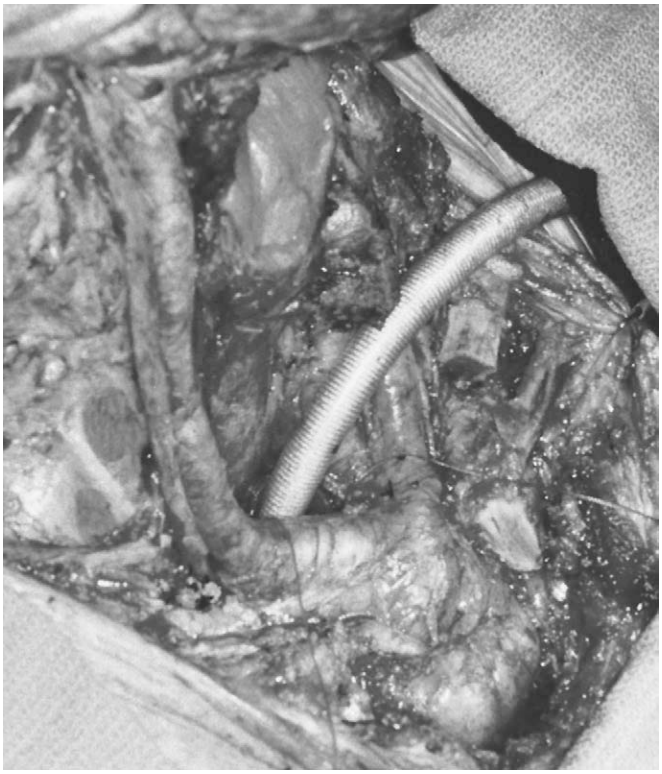

Figure 111-11. Superior mediastinal resection defect including heads of clavicles and sternal manubrium. All node-bearing tissue is excised, preserving brachiocephalic and common carotid arteries. Ventilation tube enters cut tracheal stump.

bodies. The prevertebral fascia itself is a moderately resistant barrier to tumor spread, but it is resected in continuity with the specimen if necessary. Some surgeons would discontinue resection once prevertebral fascia involvement was proven.[74]

Once the pharynx, larynx, and upper cervical esophagus are circumferentially mobilized, the thyroid gland should be dissected free from its vascular pedicles to be removed with the specimen. The parathyroid glands contralateral to the tumor's epicenter often may be preserved but may have to be removed to ensure clearance of the surrounding paratracheal nodes. If there is no oncologic risk, parathyroid reimplantation into a muscle bed is effective to avoid long-term hypocalcemia.

The pharynx is entered above the hyoid contralateral to the site with the most superior spread. Piriform sinus tumors may extend superiorly into the base of the tongue, thereby requiring a wide margin of resection during direct observation. In such patients, performing a contralateral lateral pharyngotomy improves the view without inhibiting a subsequent total laryngopharyngectomy if deemed necessary. Then pharyngeal mucosal cuts are continued horizontally around and onto the posterior pharyngeal wall at least 2 cm above the highest extent of the lesion, such that the entire upper pharynx and larynx are free. Then the trachea is transected, followed by the cervical esophagus at a level appropriate to the tumor extent. The operation can be summarized in three steps: (1) mobilizing a large tube that includes the larynx and pharynx; (2) cutting the superior end of the tube (base of tongue and pharyngeal walls); and (3) cutting the inferior end (esophagus). If total esophagectomy is to be performed, blunt dissection of the esophagus continues from above downward until the inferior esophageal dissection from the abdomen is encountered (Fig. 111-10). Superior mediastinal adenopathy is dealt with by use of a manubrial resection approach (Fig. 111-11).

Reconstruction

An extensive history and voluminous surgical literature deals with reconstruction of circumferential pharyngeal defects. We prefer to use a tubed skin flap such as the radial forearm flap (Figs. 111-12 and 111-13),[75] but a jejunal free transfer is an alternative. If the esophageal resection extends well below the thoracic inlet, a visceral transposition (gastric pull-up) is used, thus avoiding anastomoses in the mediastinum. Quality of life after high pharyngogastric anastomosis is poor in our experience. With adequate access created by sternectomy, a tubed free skin flap reconstruction endows other major advantages such as avoiding thoracoabdominal transgression. Further details of hypopharyngeal reconstruction are given in Chapter 105.

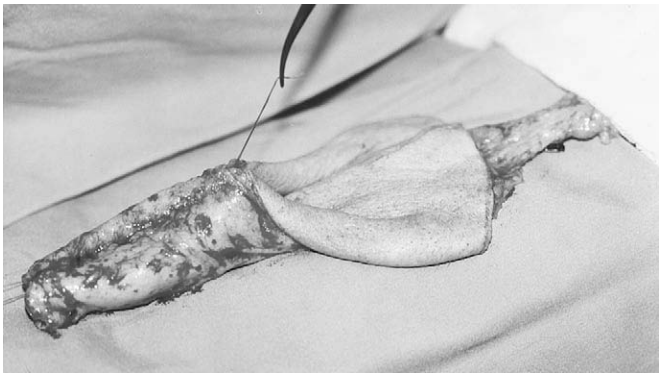

Figure 111-12. Radial forearm flap pretubed on the forearm before transfer to the neck. Note proximal skin paddle to be folded through 180 degrees, separated by a de-epithelialized transverse strip and inset in one stage to provide neck coverage.

Postoperative Management and Complications

Postoperative Management

The same management applies as that described for total laryngectomy, although one or more neck dissections and abdominal or extremity

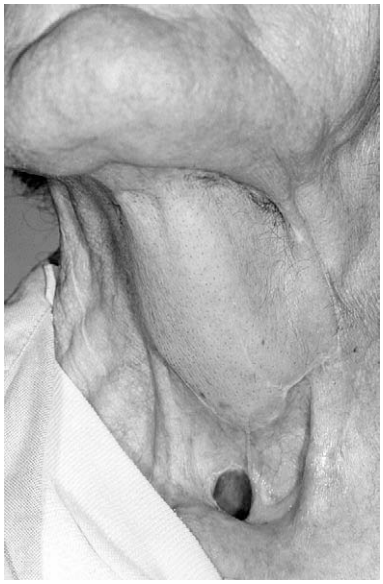

Figure 111-13. Postoperative result at 2 years. Patient maintains normal diet, and skin paddle pliability assists neck movement. Contour of tubed neopharyngeal component is visible deep to radial skin paddle.

donor sites frequently are used, and this greater magnitude of surgery necessitates special attention to pulmonary function, fluid nutritional balance, and local wound conditions in the neck, thorax, and donor site. Regular postoperative checks of calcium, magnesium, and phosphorus levels are necessary, and supplementation with calcium, magnesium, and 1, 25-dihydroxycholecalciferol usually is required.

Early Complications

Early fistula formation is more common than in patients undergoing total laryngectomy alone and needs especially aggressive management because of the mediastinitis risk. When a fistula or infection in the neck is detected, the wound is opened widely and left open with the track packed and is directed to pass away from the carotids and microvascular pedicle. A tight, distal closure of the pharyngoesophageal reconstruction is a prime cause of early fistula formation. Leaking pharyngeal or esophageal anastomoses, especially if secreting gastric or jejunal tissue has been used for reconstruction, may need to be controlled with pharyngostome formation and, if healing is poor, should be reinforced with fresh, vascularized, nonirradiated flap tissue (e.g., pectoralis or trapezius muscle flaps).

Late Complications

Stricture

Strictures are more common at the inferior, esophageal end of the pharyngeal reconstruction than superiorly, where the recipient lumen of the pharynx is wider. A stricture causing dysphagia may develop some weeks or months after surgery or after radiotherapy is complete.

Whether the reconstruction is skin or viscera, the principles of stricture management are the same as for patients after total laryngectomy alone: repeated, outpatient dilatation once tumor recurrence is excluded by endoscopy and biopsy, progressing to surgical revision if the latter is unsuccessful or poorly tolerated.

During this decade, a strategy that uses a salivary bypass tube in combination with a radial forearm free flap has been reported to be encouraging in pharyngoesophageal reconstruction. Another innovation that has been reported is the topical application of mitomycin C just after dilation.[76]

Functional Swallowing Problems

The jejunal free flap frequently maintains its contractility after transposition to the neck. This has been shown to cause functional dysphagia in some patients if the food bolus is delivered simultaneously with circumferential contractions.[56] Regurgitation of food is a recognized complication of the gastric transposition procedure, and it usually is caused by loss of the gastric reservoir or narrowing at the pylorus rather than anastomotic stricture and may be variable in its severity.

Frequent, mechanically blenderized meals eaten slowly usually are sufficient to maintain nutrition. It is possible that a passive segment of a tubed skin flap is superior for swallowing, although no prospective comparison studies have been performed.

Rehabilitation

The considerations in swallowing are the same as those noted previously in the discussion of functional swallowing problems after total laryngectomy.

Voice

Despite the interposition of circumferential visceral, skin, or myocutaneous tissue, voice may be attained with a tracheoneodigestive tract fistula technique. The stomach,[77] the jejunum, and skin or myocutaneous flaps are capable of sufficient vibration to produce intelligible speech.[71] Detailed analysis of voice characteristics after radial forearm flap reconstruction has been documented.[78] A tracheoesophageal puncture procedure may be safely performed as a primary procedure if the fistula tract does not communicate with the main resection site. In some patients, a strip of mucosa can be preserved and a pedicled or free flap can be sutured to the edges. If it is not oncologically sound to preserve a strip of mucosa, and the flap is too bulky to make a complete tube, then the skin of a myocutaneous flap can be sutured to the prevertebral fascia and this can allow for a watertight closure. An example is when a free flap fails and a salvage flap such as a pectoralis major myocutaneous flap modification is used. The flap is sutured to the mucosa or the fascia in these two situations in a "horseshoe" fashion.[79] Although such a procedure is difficult in obese patients, thinner patients can be successfully reconstructed in this way. In all of these situations rehabilitation of voice is feasible with tracheoesophageal speech.

Summary

A review of contemporary indications, techniques, and rehabilitation for patients undergoing total laryngectomy or total laryngopharyngectomy is presented. Total laryngectomy is the most cost-effective treatment option for advanced laryngeal cancer.[80] Total laryngopharyngectomy is the most effective treatment for hypopharyngeal carcinoma today.[81] Most patients requiring these operations have head and neck cancer, and the scope of the chapter is limited to the relevant clinical details of operative and perioperative events. Readers are referred elsewhere to consider the effectiveness of these operations in cancer control.

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CHAPTER ONE HUNDRED AND TWELVE

Radiation Therapy for Cancer of the Larynx and Hypopharynx

Alice Cheuk

Parvesh Kumar

Key Points

Laryngeal Cancer

Early-Stage Glottic Cancer (T_1-T_2 Lesions)

- Definitive radiation therapy offers several advantages over a primary surgical option, including superior quality of voice outcome and the ability to treat subclinical lymphatic nodal disease without the need for a neck dissection with equivalent outcomes to surgery. Initial and ultimate local control outcomes for T_1 and T_2 disease are noted in Tables 112-1 and 112-2, respectively.
- Prognostic factors predicting outcome with radiation therapy include impaired vocal cord mobility,[7] anterior commissure involvement, total dose/dose per fractions/and overall treatment time,[8] tumor bulk,[6] pretreatment and post-treatment hemoglobin levels,[9] p53 and p21 molecular markers,[10-11] and concurrent smoking.[12]
- The rate of chronic long-term complications with definitive radiation therapy is very low (<5%).

Advanced-Stage Glottic Cancer (T_3-T_4 Lesions, N+)

- Primary surgical treatment is recommended for large bulky tumors in which concurrent chemoradiation therapy is unlikely to achieve local control of disease, or for those patients with a poor presenting quality of voice outcome or a destroyed epiglottis, resulting in an irreversibly compromised swallowing function with a high probability of aspiration (outcomes noted in Table 112-3).
- For organ preservation therapy, definitive concurrent chemoradiation therapy is recommended for nonbulky tumors for which local control can be achieved with a nonsurgical approach.

Supraglottic Cancer

- Treatment principles for early and advanced stage supraglottic cancers are the same as for glottic cancers, except that lymphatic nodal stations should be included in the radiation volume even for early stage disease. Outcomes after treatment are noted in Tables 112-6 and 112-7.

Subglottic Cancer

- Subglottic cancers are extremely rare. Early-stage lesions can be definitively treated with radiotherapy alone (66-70 Gy at 2.0 Gy/fx), whereas advanced stage tumors should be treated with surgery followed by radiation therapy with or without chemotherapy.

Hypopharyngeal Cancer

Early-Stage Hypopharyngeal Cancer

- Treatment principles for early-stage lesions are the same as for glottic cancers, except that lymphatic nodal stations should be included in the radiation volume. For T_1 lesions, ultimate local control rates are 87%-95% (Table 112-9). For T_2 tumors, ultimate local control rates are 74%-91% (Table 112-9).

Advanced-Stage Hypopharyngeal Cancer

- Low volume disease should be managed with definitive radiation therapy (with or without chemotherapy) to avoid sacrificing the larynx associated with a primary surgical approach.
- Treatment principles involving surgical and organ preservation approaches are similar to advanced-stage glottic cancer.
- The 5-year local control rates range from 20%-50%, whereas overall survival varies from 20%-35%.

Overview

Of the millions of species on planet Earth, none has the ability to communicate as effectively as Homo sapiens. Of course, central to this ability to communicate is the larynx. Besides directly assisting the human voice, the larynx is indirectly involved in other critical functions such as swallowing. Hence it is not surprising that cancer of the larynx is a devastating diagnosis for a patient not only because of its potentially life-threatening implications but also due to the numerous implications on the individual's quality of life. The American Cancer Society estimated that 12,250 cases of laryngeal cancer were diagnosed in 2008 and that 3670 deaths resulted from this disease.[1] Cancer of the hypopharynx, though rare with 2500 new cases estimated every year, has similar implications on the individual patient's well-being and quality of life.

Treatment of the larynx and hypopharynx should achieve two major goals: cure of the cancer and preservation of organ function to maintain quality of life. In one extreme, an aggressive surgical approach that would leave the patient with gross deformities and functional impairment is not optimal; on the other hand, advocating chemoradiation therapy for a patient with a larynx that is not worth preserving is equally futile. Cure can usually be achieved in early-stage larynx and hypopharynx cancers, but the prognosis is still relatively poor for advanced-stage disease, with 5-year overall survival ranging from 15% to 50%. For these reasons, the involvement and coordination of a multidisciplinary team including ear, nose, and throat surgeons; radiation oncologists; medical oncologists; and appropriate supportive staff (i.e., nurses, dieticians, social workers, speech and swallowing therapists) is vital to determining the best management for each patient, in order to maximize cure and preserve quality of life.

In determining the most optimal therapy for an individual patient, careful attention should be paid to patient-related factors (e.g., baseline quality of voice and swallowing function, weight loss, comorbidities, duration of symptoms to gauge the "tempo" of the cancer, age, performance status, hemoglobin levels, family support system, patient's motivation to complete the proposed treatment); tumor-related factors (e.g., volume and extent of disease, nodal disease, tumor grade); and treatment-related factors (e.g., the likely acute/chronic toxicities of the therapy and their impact on the quality of life, duration of treatment). A careful "holistic" approach that takes into account these factors is necessary for the optimal treatment of each patient's cancer.

In order to achieve succinctness and clarity, this chapter is organized as follows:

1. Review of pertinent anatomy
2. Key points in initial evaluation and workup of patients
3. Overview of treatment options and radiation techniques
4. Innovations and future direction in treatment

Anatomic Considerations

A fundamental knowledge of laryngeal and hypopharyngeal anatomy is necessary to allow the clinician to understand how (1) a particular cancer affects function to produce signs and symptoms; (2) patterns of local invasion and lymphatic and distant spread differ for individual cancers of the larynx and hypopharynx; and (3) the extent of tumor within the larynx and hypopharynx determines treatment selection. For the radiation oncologist, knowing the relation of the laryngeal and hypopharyngeal structures to bony landmarks is critical in radiation treatment planning.

The hypopharynx extends from the superior aspect of the hyoid bone, which corresponds to the level of the vallecular floor, to the inferior border of the cricoid cartilage. The three subsites of the hypopharynx are (1) the paired pyriform sinuses, (2) the postcricoid area, and (3) the posterior and lateral hypopharyngeal walls.

The larynx is intimately related to the hypopharynx; it is situated anteriorly to the hypopharynx, at approximately the same cervical levels. Anatomically, the larynx extends from the tip of the epiglottis at the level of the lower border of the C3 vertebra to the distal extent of the cricoid cartilage at the level of the C6 vertebra. The larynx is subdivided into three anatomic regions: the supraglottis, the glottis, and subglottis regions. The supraglottic region includes (1) the epiglottis, (2) the aryepiglottic folds, (3) the arytenoids, (4) the false vocal cords, and (5) the ventricle. The glottis consists of the true vocal cords and the anterior and posterior commissures. Importantly, the anterior commissure is usually within 1 cm of the skin surface, an important consideration for radiation treatment planning. The lower boundary of the glottis extends 5 mm below the free margin of the vocal cords, or to the horizontal plane 1 cm below the apex of the ventricle. The vocal cords attach to the thyroid cartilage at what is visualized to be the "figure-of-eight" on a lateral plain film. The subglottis extends from the lower boundary of the glottis to the inferior margin of the cricoid cartilage. These anatomic boundaries are readily visualized on plain lateral x-ray films (Fig. 112-1).

Figure 112-1. Plain simulation film.

From a radiographic perspective, it is important to note that the thyroid, cricoid, and most of the arytenoid cartilages are composed of hyaline cartilage, which begins to ossify when a person is about 20 years old. The epiglottis, corniculate, and cuneiform cartilages and the apex and vocal process of the arytenoids are made up of elastic cartilage, which does not ossify and therefore is not radiopaque.

Lymphatic Drainage

Knowledge of the lymph node levels in the neck in relation to bony landmarks, as well as surgical landmarks, is important for the radiation oncologist when planning radiation portals. Level I nodes are above the hyoid bone, below the mylohyoid muscle and anterior to the back portion of the submandibular gland. This corresponds to the submental and submandibular triangles. Level II nodes are located from the skull base to the lower body of the hyoid bone inferiorly, posterior to the back of the submandibular gland, and anterior to the posterior extent of the sternocleidomastoid muscle. The jugular chain lymph nodes, which run from the mandible down to the carotid bifurcation, are included in this level. Level III nodes extend from the lower body of the hyoid to the inferior margin of the cricoid, also anterior to the

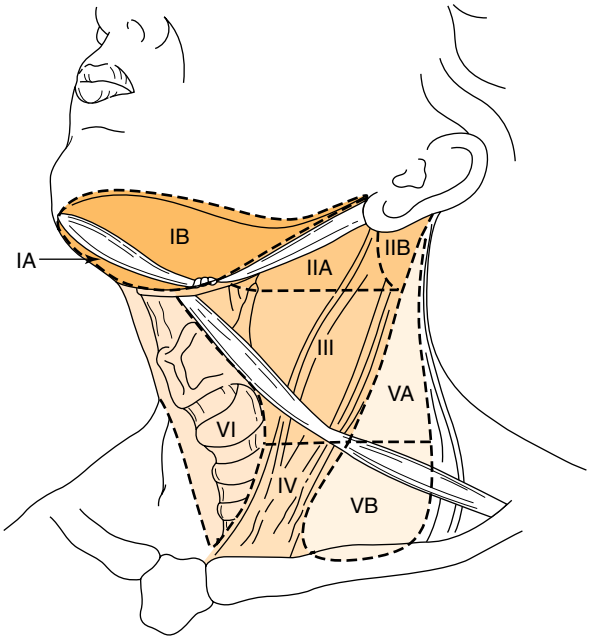

Figure 112-2. Lymph node levels of the neck. *(Adapted from Harish K. Neck dissections: radical to conservative.* World J Surg Oncol. *2005;3:21.)*

posterior margin of the sternocleidomastoid muscle, corresponding to the region from the carotid bifurcation to the omohyoid muscle. Level IV lymph nodes are bordered superiorly by the lower border of the cricoid cartilage and inferiorly by the clavicles and are anterior to the posterior margin of the sternocleidomastoid muscle, which corresponds to the region from the omohyoid muscle to the clavicle. Level V lymph nodes run from the skull base to the level of the clavicle in the region posterior to the sternocleidomastoid muscle; this area is the posterior triangle bounded by the SCM anteriorly, the trapezius posteriorly, and the omohyoid inferiorly. Level VI lymph nodes are between the lower body of the hyoid bone and the suprasternal notch, otherwise known as the anterior compartment between the carotid arteries (Fig. 112-2).

Clinical Presentation and Evaluation

Clinical Presentation

Larynx

SUPRAGLOTTIS. The most common presenting symptoms of carcinoma of the supraglottis are sore throat and odynophagia. Often a neck mass may be the first sign of carcinoma of the supraglottis because of the high incidence of lymph nodal metastases. Unilateral otalgia occurs because of referred pain from the involvement of the vagus nerve and the auricular nerve of Arnold (a branch of cranial nerve X). Hoarseness is usually not an initial symptom, and it occurs with invasion of the vocal cords. Weight loss, dyspnea, foul breath, and aspiration occur with advanced disease.

GLOTTIS. The most typical presenting symptom of early-stage vocal cord cancer is hoarseness. The symptoms of advanced disease include sore throat, localized pain as a result of cartilage invasion, otalgia, and dyspnea as a result of airway compromise.

SUBGLOTTIS. Carcinoma of the subglottis is relatively asymptomatic during early stages. With advanced-stage disease, dyspnea becomes the predominant symptom as a result of narrowing of the airway; other less common symptoms include hoarseness, odynophagia, and hemoptysis.

Hypopharynx

Secondary to anatomic location, patients with hypopharyngeal cancers often present at more advanced stages than other head and neck cancers. Typical presenting symptoms include hoarseness, odynophagia and/or dysphagia, a sore throat, otalgia, weight loss (20%), and neck masses. In more advanced stages, patients may also complain of hemoptysis and stridor as the airway becomes involved.

Diagnostic Evaluation/Workup

The diagnostic evaluation of a patient who is suspected of having cancer of the larynx should begin with a mandatory history and physical examination. The mainstay of the physical examination is the flexible fiberoptic endoscope, which allows for excellent visualization of the infrahyoid epiglottis and anterior commissure; these regions may be difficult to see with indirect laryngoscopy. Several key clinical pearls should be remembered when performing the examination. In addition to determining the tumor extent, assessment of the mobility of the vocal cords is absolutely critical because this determines staging and is an important factor when deciding between treatment modalities. For lesions in the supraglottis, careful palpation and an examination of the base of tongue should be performed to determine involvement. Because hypopharyngeal carcinomas can often present as skip lesions with disease distant from the primary site, a thorough examination is imperative to localize all areas of disease. The neck should be carefully palpated to determine the size, number, pliability (mobile, partially mobile vs. fixed), and location (ipsilateral, bilateral, or contralateral) of lymph node metastasis. Fixed lymph nodes may warrant preoperative radiation therapy (RT) versus preoperative chemoradiation therapy in order to make surgical resection more feasible.

Routine laboratory tests include a complete blood count and liver function tests. If the liver function tests or serum alkaline phosphatase are abnormal, further studies (e.g., computed tomography [CT] of the abdomen, bone scans) may be indicated.

Imaging studies include a chest radiograph (a CT scan should be considered for patients at high risk of metastasis to the chest) and a CT scan with contrast enhancement of the head and neck region. The CT scan should be performed before the biopsy whenever possible because postbiopsy edema may overestimate tumor extent. CT slices 3-mm thick should be obtained at 3-mm intervals throughout the larynx. The relative usefulness of CT scanning versus magnetic resonance imaging (MRI) remains controversial. MRI is more useful for delineating the soft-tissue extent of the primary tumor and cartilage invasion, whereas CT scanning is better for evaluating early bone invasion and the remainder of the laryngeal anatomy. The disadvantages of MRI are longer scanning time and motion artifact. For patients who are at moderate to high risk for harboring distant metastases, fluorodeoxyglucose positron emission tomography scan is recommended. This is particularly important for patients with hypopharyngeal cancer and for laryngeal cancer associated with bulky (N2-3) nodal disease.

Examination under anesthesia with direct laryngoscopy and biopsy of the tumor is the most important step in the diagnosis of carcinoma of the larynx and hypopharynx. In advanced-stage disease, a panendoscopy (bronchoscopy and esophagoscopy) should be performed to rule out synchronous tumors, if suspected.

If RT is considered, patients should be referred for a thorough dental evaluation and extractions, if necessary, before treatment. This is imperative because xerostomia, which frequently results from radiation, predisposes patients to dental carries, particularly those with poor oral hygiene initially. In addition, if dental work needs to be performed, especially tooth extractions, it should be done before treatment because healing of the mandible is impaired after radiation, leading to increased chances of infection and osteoradionecrosis.

Staging

Laryngeal and hypopharyngeal cancers are staged according to the American Joint Commission for Cancer Tumor Node Metastasis system. The sixth and most recent version of the staging system published in 2002 can be found in other chapters. In contrast to staging in other sites, the staging for tumors in the larynx is based on involvement of anatomic structures and not on the size of the lesion. Staging in the hypopharynx is based on size and subsite involvement in early stages. Note that in both the larynx and hypopharynx, fixation of either

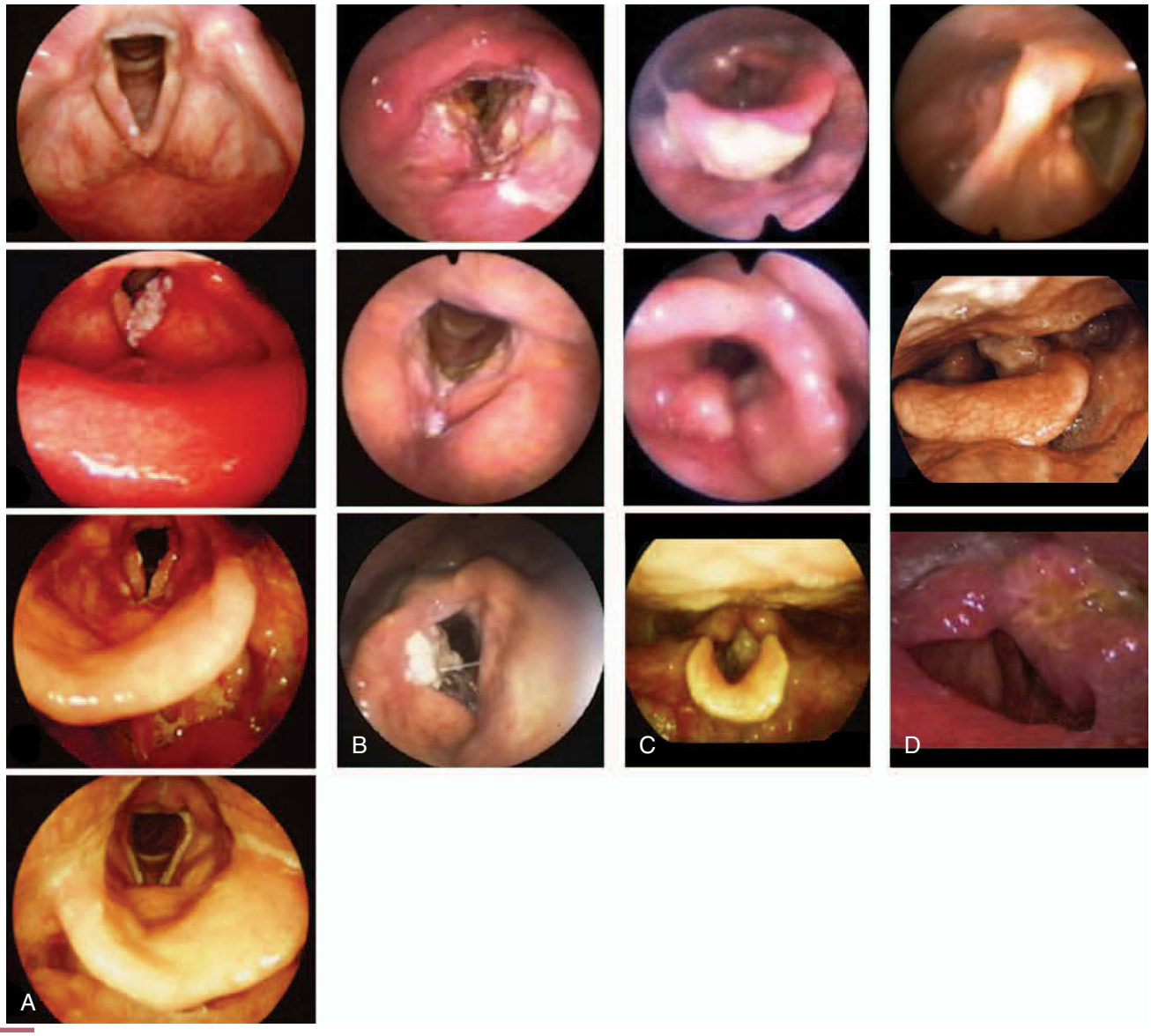

Figure 112-3. **A,** T_1 Glottis. **B,** T_2 Glottis. **C,** T_1 Supraglottis. **D,** T_1 Hypopharynx. *(From* Foote RL. Radiotherapy alone for early-stage squamous cell carcinoma of the larynx and hypopharynx. Int J Radiat Oncol Biol Phys. *2007;69(2 Suppl):S31-S36.)*

vocal cord automatically stages the tumor as a T3, regardless of the tumor bulk. T4 disease is the same in all glottic subsites and hypopharynx, reflecting invasion outside of thyroid cartilage or beyond. Nodal staging is the same as that in other head and neck malignancies (with the exception of the nasopharynx). The ability to visualize the stage of the disease from an anatomic framework, rather than memorizing lines of description in text, is useful. Direct laryngoscopy images of early T-stage laryngeal and hypopharyngeal cancers are shown in Figures 112-3A-D.

Treatment Options, Radiotherapy Techniques, Dose-Fractionation Schemes, Outcome, Prognostic Factors, and Complications

Overall Management

Recognizing that management of patients with laryngeal and hypopharyngeal cancers involves a combined modality approach involving the radiation oncologist, the head and neck surgeon, and the medical oncologist, we also recommend consultation with other specialists such as the dentist for clearance before radiotherapy (especially if the mandible is likely to be in the radiation field), dietician, and speech and swallowing therapist to assist the patient's rehabilitation and recovery from the malignancy and treatment sequelae.

Management of the Neck

We do not devote much consideration to the management of the neck in this chapter because it is covered extensively elsewhere in this textbook. As a matter of principle, nonbulky nodal disease (i.e., ≤3 cm) can be generally managed with either RT alone or chemoradiation therapy with surgery reserved for salvage therapy. However, bulky nodal disease (i.e., >3 cm) generally requires a combined-modality approach involving either preoperative or postoperative RT, or definitive chemoradiation or radiotherapy alone followed by a planned (generally limited) neck dissection, especially if the patient still has palpable lymphadenopathy after full doses of irradiation. Hence when we speak of "early-" versus "advanced-" stage disease, we are usually referring to the "T-stage" versus "N-stage" disease.

Laryngeal Cancers

Early-Stage Glottic Cancer (T_1 or T_2)

Early-stage laryngeal cancer can often be cured with either RT or surgery. No randomized trials have directly compared surgery with RT,

but published series report similar local-regional control rates for both treatment approaches. Selection of a treatment modality for an individual patient depends on a number of factors including number of prior surgical procedures (e.g., "surgical stripping," laser excisions), quality of voice, and location of the lesion. For example, laser excision of a lesion in the region of the anterior commissure can result in permanent hoarseness as a sequela of surgery. On the other hand, the same laser excision of a mid-vocal-cord lesion often leaves patients with excellent quality of voice without the need for 6 to 7 weeks of daily radiotherapy treatments. Conversely, a patient who has already failed a number of prior surgical interventions (e.g., "surgical strippings," laser excisions) is unlikely to achieve the "same old" natural quality of voice when treated with definitive RT. Generally, the advantages of RT include the following:

1. Avoidance of surgical morbidity such as poor quality of voice (i.e., chronic hoarseness) and anesthesia risks
2. Maintaining surgery as a salvage treatment option
3. Treatment of subclinical lymphatic nodal spread without the need for a neck dissection

The main contraindication to definitive RT is the likelihood of noncompliance to daily treatments for 6 to 7 weeks because of decreased local control associated with radiotherapy treatment breaks.

Radiation Techniques and Dose-Fractionation Schemes

Multiple-dose fractionation schemes have been used to treat patients with T_1 and T_2 glottic carcinoma, with total dose equaling 66 to 70 Gy at 2.0 Gy/fraction (fx) per day, 63 Gy at 2.1 Gy/fx per day, or 60.75 Gy to 65.25 Gy at 2.25 Gy/fx per day, 5 days per week.[2-4] At the Department of Radiation Oncology, University of Southern California (USC) Keck School of Medicine (KSOM), patients with T_{cis}, T_1 (including verrucous carcinoma), and small T_2 lesions are treated to 66.0 Gy at 2.0 Gy/fx. Patients with T_2 lesions are treated to a total dose of 70 Gy at 2.0 Gy/fx. These dose-fractionation schemes are used at USC because of the ease of tolerability (i.e., rarity of treatment related interruptions) in our experience and excellent local control rates. Doses less than 2.0 Gy/fx should not be used to treat early-stage glottic tumors because of the extended interval of RT, which enhances tumor repopulation rates, leading to inferior local control rates.[5,6] Although altered-dose fractionation schemes (i.e., hyperfractionated or accelerated radiotherapy) can be used to treat patients with unfavorable early-stage glottic cancers (e.g., bulky T_2 lesion), the treating radiation oncologist should only embark on this path if he or she has experience in using these alternative-dose fractionation schemes.

At USC, a three-dimensional conformal RT (3-D CRT) approach is used to treat patients with early-stage laryngeal carcinoma. A planning CT scan is done with the patients in a supine treatment position, with the head hyperextended and immobilized with an individually made face mask. For T_1 and very early T_2 lesions, two small opposing lateral fields, usually measuring $5 \times 5\,cm^2$ to $6 \times 6\,cm^2$, are used (Fig. 112-4). The fields typically extend from the upper thyroid notch superiorly to the lower border of the C6 vertebral body inferiorly. The anterior border of the field should flash at least 1 cm in front of the skin surface at the level of the vocal cords (approximately C4). The posterior border of the field should include the anterior portion of the vertebral bodies. During fluoroscopic simulation (if possible) of the fields, the patients should be asked to swallow to monitor the superior extension of the glottis to ensure that it is still within the radiotherapy field because sometimes a patient may actually swallow during the radiation treatment. During treatment planning, radiation dose homogeneity, especially in the anterior commissure region, using wedges should be achieved to prevent overdosing or underdosing (Fig. 112-5). The lymph nodes are not treated in patients with T_{cis} and T_1 disease because of the virtually nonexistent incidence of lymphatic nodal metastases. The incidence of lymphatic nodal involvement varies from 5% to 15% with T_2 disease. Generally, for T_2 lesions, we recommend treatment of at least the first-echelon lymph nodes (subdigastric and midjugular, or lower levels II and III), especially in a patient with bulky disease.

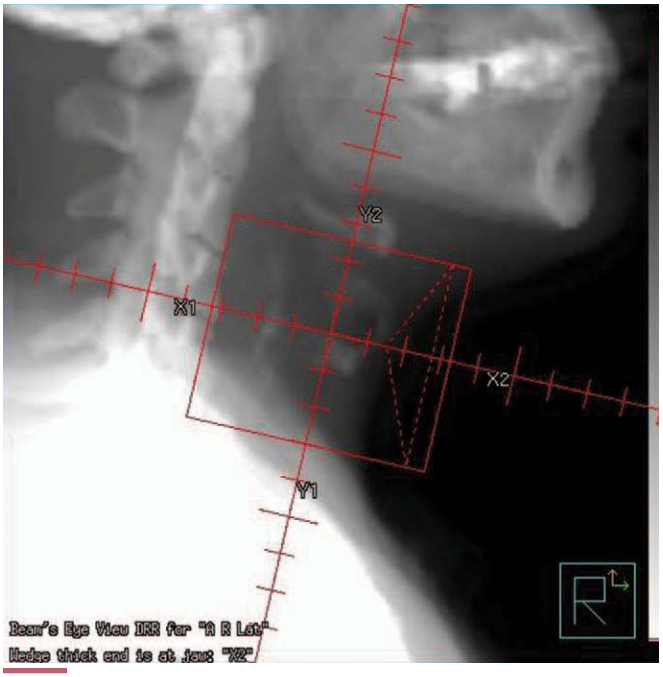

Figure 112-4. Simulation film of a T_1 glottis cancer.

Outcome and Prognostic Factors

For T_{cis} and T_1 lesions, local tumor control rates vary between approximately 85% and 95% at 5 years (Table 112-1). With surgical salvage, ultimate local control rates between 95% and 99% at 5 years can be achieved. For T_1 verrucous carcinoma, similar high local control rates have been reported with definitive RT. For T_2 glottic lesions, initial local control rates vary between 70% and 90% at 5 years with RT alone (Table 112-2). Following surgical salvage of radiotherapy failures, ultimate local control rates between 80% and 96% at 5 years can be achieved for T_2 lesions.

Various prognostic factors have been identified for early-stage glottic cancers including the following:

1. Impaired vocal cord mobility[7]
2. Anterior commissure involvement presumably due to underdosing of this region during treatment in the non-3-D CRT era
3. Total dose/dose per fraction/overall treatment time[8]
4. Tumor bulk (visible lesions as opposed to subclinical)[6]
5. Pretreatment and post-treatment hemoglobin levels[9]
6. p53[10] and p21 molecular markers[11]
7. Concurrent smoking[12]

Anterior commissure involvement has been shown in older studies to be associated with lower tumor local control rates. However, in the era of 3-D CRT with computer treatment planning, which can detect and thus limit underdosing of the anterior commissure region, this prognostic factor is no longer significant. Fraction sizes of less than 2.0 Gy result in inferior local control rates and therefore should not be used. Studies have also shown that extending treatment times beyond approximately 42 days results in inferior outcomes secondary to accelerated repopulation by tumor cells.[8] In a study of 91 patients with T_1N_0 squamous cell carcinoma of the glottis treated with definitive radio-

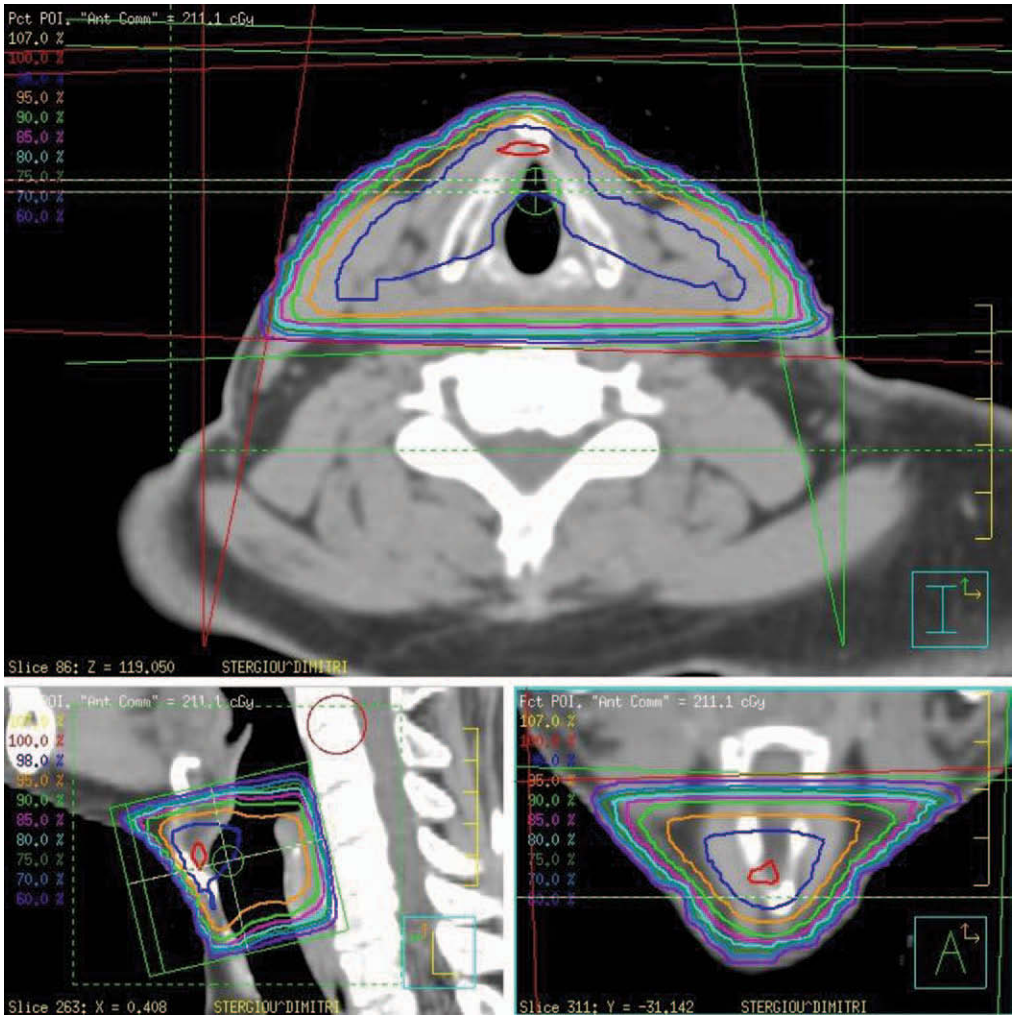

Figure 112-5. Axial CT image of early glottic cancer with isodose curves.

Table 112-1

Local Control of T_1 Carcinoma of the Glottis Treated with Definitive Radiotherapy and Surgical Salvage

Reference	Patients (*n*)	Initial Local Control	Ultimate Local Control
Elman et al (1979)[64]	T_{1a}, 210 T_{1b}, 61	T_{1a}, 94% T_{1b}, 93%	T_{1a}, 98% T_{1b}, 98%
Fletcher and Hamberger (1974)[65]	332	89%	98%
Mittal et al (1983)[66]	177	83%	96%
Amornmarn et al (1985)[67]	86	92%	99%
Wang (1990)[68]	723	90%	97%
Johansen et al (1990)[69]	358	83%	94%
Akine et al (1991)[70]	154	89%	94%
Le (1997)[71]	315	83%	97%
Mendenhall et al (2001)[72]	184	93%	97%
Lee (2002)[73]	85	81%	91%
Cellai et al (2005)[74]	831	83%	93%

Table 112-2

T_2 Carcinoma of the Glottis: Local Control with Radiotherapy and Surgical Salvage

Reference	Patients (*n*)	Initial Local Control	Ultimate Local Control
Elman et al (1979)[64]	T_{2a}, 146 T_{2b}, 82	T_{2a}, 80% T_{2b}, 72%	T_{2a}, 96% T_{2b}, 96%
Fletcher and Hamberger (1974)[65]	175	74%	94%
Mittal et al (1983)[66]	327	69%	—
Howell-Burke et al (1990)[75]	114	68%	76%
Amornmarn et al (1985)[67]	34	88%	94%
Karim et al (1987)[76]	156	81%	95%
Wang (1990)[68]	173	69%	86%
Le (1997)[71]	83	67%	—
Mendenhall et al (2001)[72]	120	75%	95%
Frata et al (2005)[77]	256	70%	85%

therapy, both overall treatment time (i.e., ≤42 days vs. > 42 days) and dose per fraction (i.e., <200 cGy vs. ≥200 cGy) predicted for local control. Typically, a loss of approximately 1.4% (0.4% to 2.5%) in local control occurs for every day of a treatment break or overall extension of treatment time. Multiple studies have shown an adverse effect of low pretreatment and/or post-treatment hemoglobin levels (Hgb) on outcome in early- and advanced-stage laryngeal cancer.[9] For example, in a study from Fox Chase Cancer Center that analyzed 109 patients with T_1 or T_2 glottic cancers treated with definitive RT, pretreatment Hgb levels less than or equal to 13 g/dL adversely affected both 2-year local control rates and overall survival (66% vs. 95% and 46% vs. 88%, respectively) on multivariate analysis.

Complications from Radiation Therapy

Because the treatment fields for early-stage glottic cancer are small, patients typically experience few side effects from RT. Common side effects include skin erythema and/or hyperpigmentation, desquamation, hoarseness, sore throat, and resultant dysphagia. These effects are self-limiting, manifesting approximately 2 to 4 weeks into therapy and usually resolving within 6 to 8 weeks after the completion of treatment. Hypothyroidism is also a possible consequence of radiation, and therefore patients should have thyroid function testing before treatment and every 6 to 12 months. Hypothyroidism rates as high as 30% to 40% have been reported in the literature after radiation.[13] Hormonal replacement can be given to replete thyroid hormone levels. More serious though rarer late sequelae from RT include laryngeal arytenoid edema and laryngeal arytenoid necrosis. In patients who have been irradiated for carcinoma of the glottis, the incidence of mild to moderate laryngeal edema persisting for more than 3 months after RT is about 15.4% to 25%.[14] The incidence of severe laryngeal edema is about 1.5% to 4.6%,[15-18] and this increases with greater total dose, field size, dose per fraction, and T stage of the lesion.[16,18,19] Initially these patients should be managed conservatively with voice rest, abstinence from alcohol and cigarettes, and careful, close follow-up examinations. Antibiotics and low-dose steroids (i.e., 2 mg po bid) may be used when there is suspicion of infection or when the edema is severe enough to significantly compromise the airway. However, if the edema is progressive and unresponsive to conservative measures and recurrent disease is strongly suspected, biopsies should be carried out to rule out malignancy as the underlying cause. Salvage surgery is performed if biopsies are positive. Late laryngeal arytenoid necrosis after RT is rare, with a reported incidence of about 0.5% to 1.8% for glottic cancer.[15,20,21]

Advanced-Stage Glottic Cancer (T_3 or T_4, Stage III or IV)

Overall Considerations: Balancing Cure, Organ Preservation, and Quality of Life

Historically, resectable locally advanced carcinoma of the glottic larynx (i.e., T_3 and T_4 and/or N_2 and N_3 disease) has been generally treated with combined surgery and postoperative RT. However, a primary surgical approach requiring a total laryngectomy has the disadvantage of loss of organ function such as voice and swallowing. Hence during the past several decades, various primary nonsurgical approaches have been explored to achieve cure of locally advanced disease and preserve the larynx so as to maintain organ function. These therapeutic approaches have consisted of radiotherapy alone or a combination of chemoradiation therapy. Currently, concurrent chemoradiation therapy has evolved to become the "standard of treatment" for patients with locally advanced laryngeal cancer who otherwise would require a total laryngectomy. For patients whose primary lesion is amenable to conservation laryngeal surgery, the choice is between chemoradiation and the former. The authors advise against the use of such a "generic" reflexive chemoradiation approach that does not individualize therapy for each patient. For example, a patient presenting with a large-volume laryngeal glottic carcinoma with significant epiglottic destruction and poor voice quality is unlikely to have reversal of these symptoms let alone eradication of local disease; hence a primary surgical approach consisting of a total laryngectomy followed by postoperative RT with or without chemotherapy would be more optimal for the patient in this setting.

Hence we recommend a primary surgical approach in the following settings:

1. Large, bulky tumors in which concurrent chemoradiation is unlikely to achieve local control of disease.

2. Poor presenting quality of voice, which is unlikely to reverse with a primary nonsurgical therapeutic approach.

Table 112-3

Postoperative Head and Neck/Glottic Trials with Chemoradiation

Study	High-Risk Population			Outcomes			
				LC	DFS	OS	
RTOG 9501[23]	1) + LN ≥ 2 2) + ECE 3) + margins	3-yr	RT CT/RT	72% 82%	36% 47%	47% 56%	(p = 0.9)
EORTC 22931[24]	1) pT_3 or pT_4 (except T_3N_0 larynx) 2) pT_1 or T_2 with N_2 or N_3 3) pT_1 or T_2 and N_0 or N_1 with any one: a) + margins b) + ECE c) + PNI d) + vascular emboli	5-yr	RT CT/RT	69% 82%	36% 47%	40% 53%	
German ARO 96-3[25]	1) + LN ≥ 3 2) + ECE 3) + margins	5-yr	RT CT/RT	72.2% 88.6%	50.1% (PFS) 62.4%	48.6% 58.1%	(p = 0.11)

3. A destroyed epiglottis resulting in an irreversibly compromised swallowing function with a high probability of aspiration.

Primary Surgical Approach: Adjuvant Therapy

At USC, we prefer to use postoperative versus preoperative radiotherapy in the setting of a primary surgical approach based on results of the Radiation Therapy Oncology Group (RTOG) 7303 and the "inherent" advantages of adjuvant treatment.[22] RTOG 7303 was a randomized trial comparing preoperative (50 Gy) versus postoperative (60 Gy) RT in advanced-stage, operable supraglottic larynx and hypopharynx cancers. The 10-year locoregional control was significantly improved in the postoperative versus the preoperative group (70% vs. 58%, respectively). Additionally, the rate of complications was much higher in the patients undergoing preoperative RT (9%) versus the postoperative group (5%). On the basis of the results of this RTOG study and the inherent advantage of having pathologic information after surgery, postoperative RT is preferred over preoperative RT. At USC, the role of preoperative RT is limited to shrinking locally advanced disease considered to be unresectable.

Although locoregional tumor control rates with total laryngectomy followed by postoperative RT are relatively high, some patients with high-risk disease features still do poorly with adjuvant radiotherapy alone. Hence several randomized trials have evaluated the role of adding concurrent chemotherapy to adjuvant RT following surgery for locally advanced head and neck cancer including primary laryngeal tumors. These studies include RTOG 9501, European Organization for the Research and Treatment of Cancer (EORTC) 22931, and the German ARO 96-3 study (Table 112-3).[23-26] All three of these randomized trials showed that adjuvant concurrent chemoradiation therapy is better than radiotherapy alone for local control and disease-free survival in patients with high-risk disease following surgery. In the RTOG 9501 trial, 459 patients with high-risk locally advanced head and neck cancer defined as any T-stage disease with two or more involved lymph nodes, positive extracapsular extension (ECE), and/or positive mucosal margins of resection were randomized to either RT alone (60 to 66 Gy at 2.0 Gy/fx) or the same RT with concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43). At 2 years, local control rates (82% vs. 72%, p = 0.01, respectively) and disease-free survival (35% vs. 25%, p = 0.04, respectively) were significantly better among those who underwent adjuvant chemoradiation therapy versus radiotherapy alone, respectively. However, there was no statistical difference in overall survival between the two arms (45% vs. 35%, p = 0.19, respectively). In the EORTC 22931 trial, high-risk disease was defined as any patient with a pT_3 or pT_4 tumor with any nodal stage, or a pT_1/pT_2 tumor with N_2 or N_3 disease, or pT_1/pT_2 and N_0 or N_1 disease with involved mucosal margins, positive ECE, perineural invasion, and/or vascular emboli. In the EORTC trial, 334 patients were randomized to RT alone (66 Gy at 2.0 Gy/fx) or the same RT with cisplatin (100 mg/m^2 on days 1, 22, and 43). At 5 years, local control rates (82% vs. 69%, p = 0.007, respectively) and progression-free survival (PFS) (47% vs. 36%, p = 0.02, respectively) and overall survival (53% vs. 40%, p = 0.04, respectively) were significantly better among those who underwent adjuvant chemoradiation therapy versus radiotherapy alone, respectively. The German ARO 96-3 trial included 440 high-risk patients with three or more involved lymph nodes, ECE and/or involved mucosal margins of resection who were randomized to either RT alone (66 Gy at 2.0 Gy/fx) or the same RT with concurrent cisplatin (20 mg/m^2 on days 1 to 5 and 29 to 33) with 5-fluoruracil (600 mg/m^2 on days 1 to 5 and 29 to 33). As with the other two trials, adjuvant concurrent chemoradiation therapy as compared with RT alone improved local control rates (72% vs. 89%, p = 0.00259, respectively) and PFS (50% vs. 62%, p = 0.024, respectively) at 5 years. However, there was no statistical difference in overall survival between the two arms (49% vs. 58%, p = 0.11, respectively) at 5 years.

Hence at USC, patients with locally advanced laryngeal cancer who are found to have low-risk disease (i.e., ≤1 involved lymph nodes, no extracapsular extension and/or negative mucosal margins of resection) after surgery are treated with adjuvant radiotherapy alone (66 Gy at 2.0 Gy/fx). Those patients with high-risk locally advanced head and neck cancer are treated with adjuvant concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43) and radiotherapy (at least 66 Gy at 2.0 Gy/fx). However, treating physicians should be forewarned that acute severe toxicity (e.g., mucositis, epidermatitis, dysphagia, odynophagia) associated with concurrent adjuvant chemoradiation therapy is usually twice that of using adjuvant radiotherapy alone. Hence patients undergoing concurrent adjuvant chemoradiation therapy require considerable nutritional (e.g., dietary consultation/intervention, PEG placement as needed) and rehabilitative support. Certain patients with high-risk disease (e.g., the very elderly, those with poor KPS and/or nutritional status) may not be good candidates for adjuvant concurrent chemoradiation therapy; in these cases, concurrent chemotherapy with adjuvant radiotherapy may not be possible. Therefore a more prudent approach

may be to proceed with adjuvant radiotherapy alone rather than risk not being able to complete the planned course of adjuvant chemoradiation therapy alone!

Organ Preservation Approaches: Combining Chemotherapy with Radiation Therapy

The main disadvantage of a primary surgical approach is the loss of organ function. Although progressive surgical reconstructive techniques such as tracheoesophageal punctures allow patients who undergo total laryngectomies to phonate, voice quality is suboptimal and patients often express dissatisfaction with the results. For example, in a study evaluating the significance of organ preservation, 20% of people would elect to maintain their voice at the expense of decreased survival.[27] Hence therapeutic options that would allow patients to preserve their larynx without compromising survival have been explored for the past several decades.

Because RT alone for the treatment of advanced laryngeal cancer provided poor results, focus has been turned to adding chemotherapy with radiation in attempts to preserve the larynx and maintain survival for the past several decades. The first randomized study to evaluate a surgical versus nonsurgical approach was the Veterans' Administration (VA) Laryngeal Preservation Trial.[28] This trial randomized 332 patients with stage III and IV (excluding T_1N_1 lesions) between surgery (total laryngectomy) followed by postoperative RT versus induction chemotherapy with fluorouracil and cisplatin, followed by definitive RT. At 2 years there was a 64% laryngeal preservation rate in the chemoradiation group, but no difference in overall survival (OS) at 68% between the two treatment arms; hence OS was equivalent with the chemoradiation arm but with almost two thirds of the patients retaining their larynx. However, one of the criticisms of the VA Laryngeal Preservation Trial was the lack of a radiotherapy-alone arm. So the Head and Neck InterGroup Laryngeal Preservation Trial (RTOG 9111) was designed. This was a three-arm phase III trial that randomized patients with stage III and IV laryngeal cancer to standard RT alone (70 Gy in 35 fractions) versus induction cisplatin (100 mg/m^2 on days 1 and 22) with 5-fluorouracil (FU) (1000 mg/m^2 daily continuous infusion for 5 days for two cycles) followed by the same standard RT, or concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43) with the same RT.[29] The primary end point of laryngeal preservation was 83.6% in the concurrent chemoradiation therapy arm, compared with 70.5% ($p = 0.0029$) in the induction chemotherapy arm and 65.75% ($p = 0.0018$) in the RT-alone arm at 5 years. The 5-year rates of local regional tumor control were also significantly improved in the concurrent chemoradiation therapy arm (68.8%) compared with the induction chemotherapy arm (54.9%, $p = 0.0018$) or the RT-alone group (51%, $p = 0.0005$). The 5-year overall survival was similar in all three groups (54.6% in the concurrent chemoradiation arm, 59.2% in the induction chemotherapy arm, and 53.5% in the RT-alone group). The laryngectomy-free survival (in which either a laryngectomy or death from any cause constituted a treatment failure) was also similar between the concurrent chemoradiation arm (46.6%) and the induction chemotherapy arm (44.6%), but both were better than the RT-alone group (33.9%).[30] Hence on the basis of the Head and Neck Intergroup Laryngeal Preservation trial, concurrent chemoradiation therapy is considered a viable alternative to a primary surgical approach for advanced laryngeal carcinoma. *However, the RTOG Intergroup trial did not typically include large bulky tumor or "advanced T4 lesions," so caution must be exercised in extrapolating the results from these trials to "blankety" recommending concurrent chemoradiation for advanced laryngeal cancers.*

Additionally, achieving better locoregional tumor control and larynx preservation with concurrent chemoradiation therapy comes with a price of increased toxicity; the rate of severe toxicity (acute and late effects) was significantly higher with concurrent chemoradiation therapy (82%) as compared with RT alone (61%).[29] Hence, as with adjuvant chemoradiation therapy, these patients require extensive nutritional and rehabilitative support.

Review of quality-of-life (QOL) factors comparing surgery against larynx-preserving treatment reveals that there is no statistically significant difference in overall QOL scores between the two groups.[31] There was a trend toward better social functioning in the chemoradiotherapy group, but significantly greater dissatisfaction with dry mouth. The surgery group had significantly greater problems with taste and smell, coughing, and use of painkillers. From a cost-effectiveness standpoint, the cost of total laryngectomy followed by RT is approximately $3000 less than organ-preserving chemoradiation strategies.[32]

Organ Preservation Approaches: Combining Targeted Biologic Agents with Radiation Therapy

Incorporation of targeted biologic agents into the multimodality treatment of advanced head and neck cancers remains investigational. Recently, a phase III multinational, randomized trial comparing RT alone using various dose-fractionation schemes (i.e., 70 Gy in 35 fractions, 72.0-76.8 Gy at 1.2 Gy/fx bid and 72 Gy in 42 fxs [concomitant boost technique]) or with same concurrent RT with cetuximab for stage III or IV nonmetastatic squamous cell carcinoma of the oropharynx, hypopharynx, and larynx was completed.[33] Cetuximab is a monoclonal antibody against the epidermal growth factor receptor that is abnormally overexpressed in head and neck squamous cell carcinomas. Chemotherapy was not used in this trial because concurrent chemoradiation had not become the standard of treatment at the time the trial was designed. This study revealed improved 2-year local control rates (41% vs. 50%, respectively) and 3-year overall survival (45% vs. 55%, respectively) with the cetuximab/RT arm. However, a few caveats need to be appreciated regarding this trial. The majority (60%) of patients enrolled in this trial had oropharyngeal primaries. The local control benefit was limited to patients with oropharyngeal primaries, and the overall survival benefit was limited to patients with oropharyngeal primaries treated with a concomitant boost technique (72 Gy in 42 fxs). Moreover, the role of targeted biologic agents in the setting of chemoradiation therapy is unknown. This role is currently being addressed in RTOG 0522, which randomizes patients with stage III and IV head and neck squamous cell carcinomas to RT (72 Gy in 42 fxs using an accelerated fractionation scheme with concomitant boost) and cisplatin with or without cetuximab. Therefore given the above caveats, results from randomized trials are necessary before targeted biologic agents can be incorporated into the chemoradiation therapy treatment of laryngeal cancer. Moreover, the authors caution against the substitution of targeted biologic agents for chemotherapy agents with radiotherapy in the absence of randomized data.

Most Optimal Radiotherapy Dose-Fraction Scheme

The most optimal radiation dose fractionation scheme to use concurrently with chemotherapy remains unknown. Hyperfractionated irradiation uses higher total doses of radiation in the same time interval as standard fractionated (once-daily) irradiation to achieve at least the same local control but theoretically with reduced late toxicity. Accelerated fractionated radiotherapy aims to deliver the same total dose of irradiation as standard fractionated (once-daily) radiotherapy but in a shorter time interval to improve local control with theoretically the same late toxicity. RTOG 0129, which was recently closed to accrual, randomized locally advanced head and neck cancer (larynx and nonlarynx sites) patients to standard radiotherapy (70 Gy in 35 fractions given once a day) or accelerated fractionated RT with concomitant boost ([AFX-C] 72 Gy in 42 fractions at 1.8 Gy/fx with a concomitant boost at 1.5 Gy/fx during the last 12 fractions) with concurrent cisplatin (100 mg/m^2 every 3 weeks × 3 on days 1, 22, and 43) in both arms. The basis for the AFX-C arm was RTOG 9003,[34] which was the largest randomized trial to evaluate various dose fractionation schemes for head and neck squamous cell carcinomas. This was a four-arm randomized trial that compared standard fractionated radiotherapy (70 Gy in 35 fractions at 2.0 Gy/fx given once a day) with hyperfractionation (81.6 Gy in 7 weeks at 1.2 Gy/fx given twice daily), accelerated fractionation (67.2 Gy in 6 weeks at 1.6 Gy/fx twice daily including a 2-week break after 38.4 Gy), or AFX-C scheme (72 Gy in 42 fxs at 1.8 Gy/fx with a concomitant boost at 1.5 Gy/fx during the last 12 fractions). The 2-year local regional control rate was the best in the AFX-C arm (54.5%) compared with the standard fractionation arm (46.0%), so it was chosen as the experimental arm for RTOG 0129.

However, the price for this greater local control in the AFX-C arm was higher grade ≥3 toxicity (58.8% vs. 35% for standard RT). Hence we recommend using standard fractionated radiotherapy (1.8 or 2.0 Gy/fx once daily) with or without chemotherapy until the results of RTOG 0219 show otherwise.

Radiation Therapy Techniques: General Principles

Recently, technical advances in the delivery of irradiation such as 3-D CRT and intensity modulated radiation therapy (IMRT) have allowed for better homogeneous delivery of radiation doses, more precise delivery of radiation dose to the tumor and normal tissues so as to minimize dose to the surrounding critical organs (e.g., spinal cord, salivary glands) and thus reduce late toxicity (e.g., xerostomia), and the escalation of radiation dose to improve local-regional control of tumor.[35-38] The choice of whether to use 3-D CRT, IMRT, or a combination of both depends on a number of factors including the extent of disease in the head and neck area and the experience of the radiation oncologist in using the specific technology. Typically, IMRT is used to deliver radical doses of irradiation to the primary tumor and involved lymph nodes with the aim of limiting high doses to the salivary glands and other critical organs. For example, in a patient with extensive bilateral pathologic neck disease including levels I-III, it would not be wise to use IMRT because salivary glands are unlikely to be spared the high doses of irradiation due to their proximity to the involved neck disease. In fact, a number of investigators have reported a high risk of neck recurrences following IMRT among patients who were probably not the most suitable patients for this type of highly precise delivery of irradiation.[39-41] Additionally, IMRT also presents with the further challenge of determining how "hot" to run your primary tumor dose and how "cold" to run your involved lymph nodes for the treating radiation oncologist.[42] Of note, there have been no phase III randomized trials that have compared 3-D CRT with IMRT in head and neck cancer. As a general principle, high doses of irradiation are delivered to the areas of gross and/or resected disease and the involved lymphatic nodal regions (i.e., ≥60 Gy at 2.0 Gy/fx), whereas lower doses (i.e., 50-54 Gy at 2.0 Gy/fx) are used for the next echelon of uninvolved lymph nodes and subclinical microscopic disease (Table 112-4).

At the University of Southern California, a 3-D CRT approach is used among patients who present with either pathologic or subclinical *extensive* neck disease in whom limiting dose to the salivary glands is considered to be too risky due to concern for marginal miss of disease. Occasionally, a combination of 3-D CRT may be employed initially for the treatment of gross and subclinical disease followed by an IMRT boost to the regions of gross and/or resected disease, which allows for dose escalation while sparing higher doses to the surrounding critical organs. At USC, daily amifostine (Ethyol) is used for salivary gland protection when a significant portion of the salivary gland(s) is to be irradiated.[43]

Radiation Therapy Techniques: Patient Setup and Dose-Fractionation Schemes

Patients are immobilized in the supine position with thermoplastic immobilization masks. For patients undergoing a 3-D CRT approach, irradiation of advanced laryngeal carcinoma is accomplished using opposed lateral shrinking fields that encompass the primary tumor and the upper cervical lymph nodes, which are matched with an anterior AP field (i.e., "three-field" technique) (Fig. 112-6A-E). Ideally, the upper and lower fields should be set up using a "half-beam" technique so that the potential overlap in the spinal cord region can be dosimetrically reduced. Therefore this setup uses one isocenter, which becomes the inferior border of the lateral fields and the superior border of the anterior low-neck field. Nonetheless, a safety spinal cord block should still be placed either in the inferior-posterior portion of the lateral upper neck fields or the upper midcenter position of the lower neck field so that any areas of gross disease are not blocked. Typically the superior border of the initial field should cover the level II lymph nodes as appropriate and indicated, which requires that the field extend to the base of skull. In cases where there is suspected cranial nerve involvement, a margin above the base of skull must be left to encompass the appropriate foramen. The lower border of the lateral fields should encompass the larynx, usually at or below the level of C5 (the bottom of the cricoid cartilage) depending on disease extent. The guiding principle is that all areas of gross disease with at least a 2.0-cm margin in the initial volume should be included in the lateral fields. A single anterior field is used to irradiate the lower neck. This also encompasses the supraclavicular and infraclavicular regions and should be wide enough to cover at least the medial two thirds of each clavicle. After a dose of 40 Gy (at 2.0 Gy/fx) is delivered to the upper neck/opposed lateral fields, the posterior border is moved to the midvertebral bodies and the posterior necks are supplemented with electrons to shield the spinal cord from higher doses of irradiation so as not to exceed dose tolerance. Usually, at a dose level of 50 to 54 Gy, additional blocking is added to the opposed lateral upper neck fields so that the "boost field #1" is treated to 60 Gy encompassing the areas of resected or gross disease with generally a 1.5-cm margin. After 60 Gy, the upper neck opposed lateral fields are further reduced with more blocking so that the final "boost field #2" is treated to 70 Gy encompassing areas of gross disease, positive mucosal margins, and/or extracapsular extension with a 1.0-cm margin. Sometimes, a final boost field #3 is also necessary for dose escalation to 74 to 76 Gy level. The lower neck AP field is treated to a dose of 50 Gy delivered to a depth of 3 cm to adequately treat the uninvolved lymph nodes. If an emergent tracheostomy was performed, then the stoma (which is usually encompassed in the lower neck AP field) needs to be treated to at least 56 Gy, which can be achieved by giving an extra *en face* electron boost dose of 6 Gy.

When there is extensive subglottic involvement and/or positive lymph nodes in the low neck or supraclavicular fossa, a mini-mantle field technique can be used. In this technique, matching anteroposterior and posteroanterior fields are used, with the patient in the hyperextended position to achieve homogeneous dose distribution and to prevent unnecessary irradiation to the lips and oral cavity. The mini-mantle field extends superiorly from the mastoid processes to the lower neck area to include the supraclavicular and infraclavicular fossae. Typically, the mini-mantle field is treated to 40 Gy, after which the patient is switched to a three-field plan as described earlier (i.e., two parallel opposed lateral fields that are half-beam junctioned with an AP anterior field) and a shrinking field technique is used to treat the patient to definitive radiation doses.

Table 112-4

Recommended Standard Radiation Dose-Fractionation Schemes

Region at Risk	Total Dose (Gy at 2.0 Gy/fx Once Daily)
Gross primary and/or gross lymphatic nodal disease	≥66-70
Resected primary and/or lymphatic nodal disease*	≥60-66
Next-echelon uninvolved lymphatic nodal station	50-54

*Positive margin and/or ECE.

Outcomes and Prognostic Factors

Typically, locoregional tumor control rates are influenced by the ability to control both the primary tumor and nodal adenopathy, whereas overall survival is mostly influenced by the extent of nodal disease, which is a predictor and harbinger of metastatic disease. Local control rates for T_3-T_4 lesions treated with definitive chemoradiation therapy vary between 70% and 80% (Table 112-5). Laryngeal preservation rates range from 50% to 75% using either RT alone or chemoradiation therapy. Local control rates for advanced glottic lesions treated with

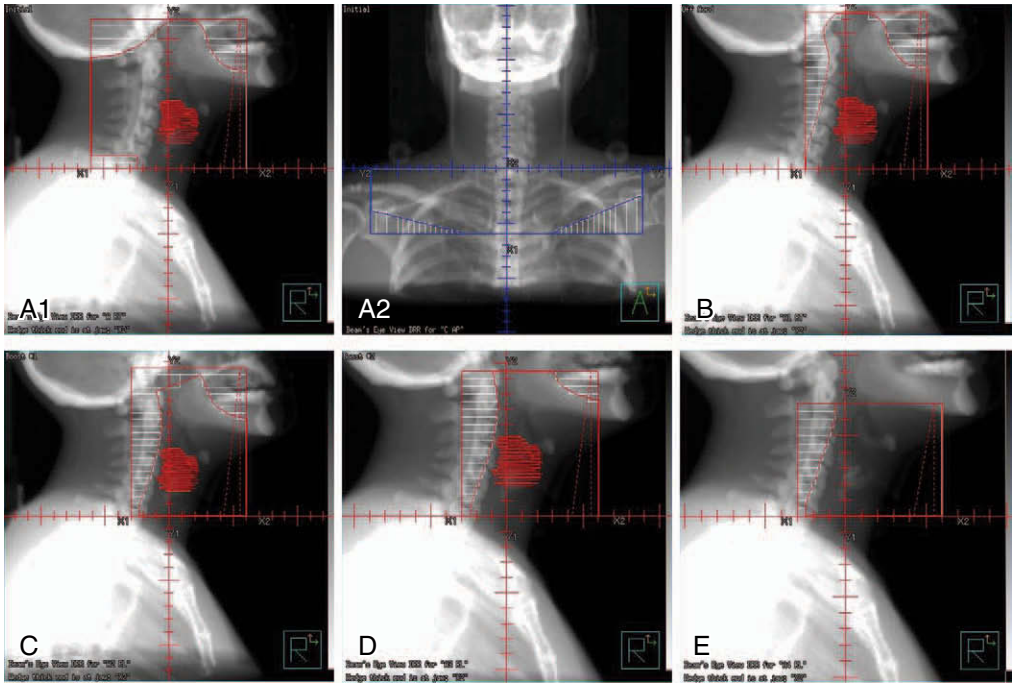

Figure 112-6. Simulation fields for advanced larynx cancer, showing the shrinking field technique. **A,** Simulation film with initial treatment field. **B,** Simulation film with off-cord field. **C,** Simulation film with boost field #1. **D,** Simulation film with boost field #2. **E,** Simulation film with boost field #3.

Table 112-5

Outcome with Definitive Chemoradiation Therapy for Locally Advanced Laryngeal Cancer

Trial	Primary Tumor Site	Patients (*n*)	Local Control	2-Yr Overall Survival	Larynx-Preservation Rate
Department of Veterans Affairs Laryngeal Cancer Study Group[28]	Larynx	332	Surgery, 93% Induction CT, 80%	68% in both arms	Surgery, N/A Induction CT, 64%
GETTEC[78]	Larynx (T_3)	68	Surgery, 87.5% Induction CT, 75%	Surgery, 84% Induction CT, 69%	N/A 42%
RTOG[29,30]	Larynx	547	RT, 56% CT→RT, 61% CT/RT, 78%	RT, 75% CT→RT, 76% CT/RT, 74%	RT, 70% CT→RT, 75% CT/RT, 88%
2006 ASCO Update		515	RT, 51% CT→RT, 54.9% CT/RT, 68.8%	RT, 53.5% (5-Yr) CT→RT, 59.2% CT/RT, 54.6%	RT, 65.7% CT→RT, 70.5% CT/RT, 83.6%

CT, chemotherapy; CT→RT, induction CT followed by RT; CT/RT, concurrent CT and RT; RT, radiation therapy.

total laryngectomy and postoperative radiation with or without chemotherapy range from 70% to 88%. Overall survival for stage III or IV disease ranges from 35% to 50% at 5 years. Recognizing that the majority of patients with advanced laryngeal carcinoma have other tobacco and/or alcohol related comorbidities, the significantly lower overall survival rate reflects deaths caused by other noncancerous-related conditions. A treatment algorithm for the management of glottic carcinomas is presented in Figure 112-7.

As with early-stage glottic cancer, the prognosis of patients with advanced laryngeal disease is affected by hemoglobin levels, extent of nodal disease, and elapsed treatment days. For example, in a retrospective review of 306 patients with stage III to IV glottic or supraglottic cancer, van Acht and colleagues[44] showed that both local control and overall survival were affected by pretreatment hemoglobin levels.

Complications from Radiation Therapy

Not unexpectedly, both the acute and late side effects are more frequent and severe with advanced-stage glottic cancer as compared with early-stage disease due to multiple factors including larger field sizes, higher total doses, and combined modality therapy including surgery and/or chemotherapy. For example, data from RTOG 9111 showed that 77% of patients in the concurrent chemoradiation arm experienced grade ≥3 acute toxicity compared with only 47% in the RT-alone group. Furthermore, both acute and late sequelae were determined to be 82% in

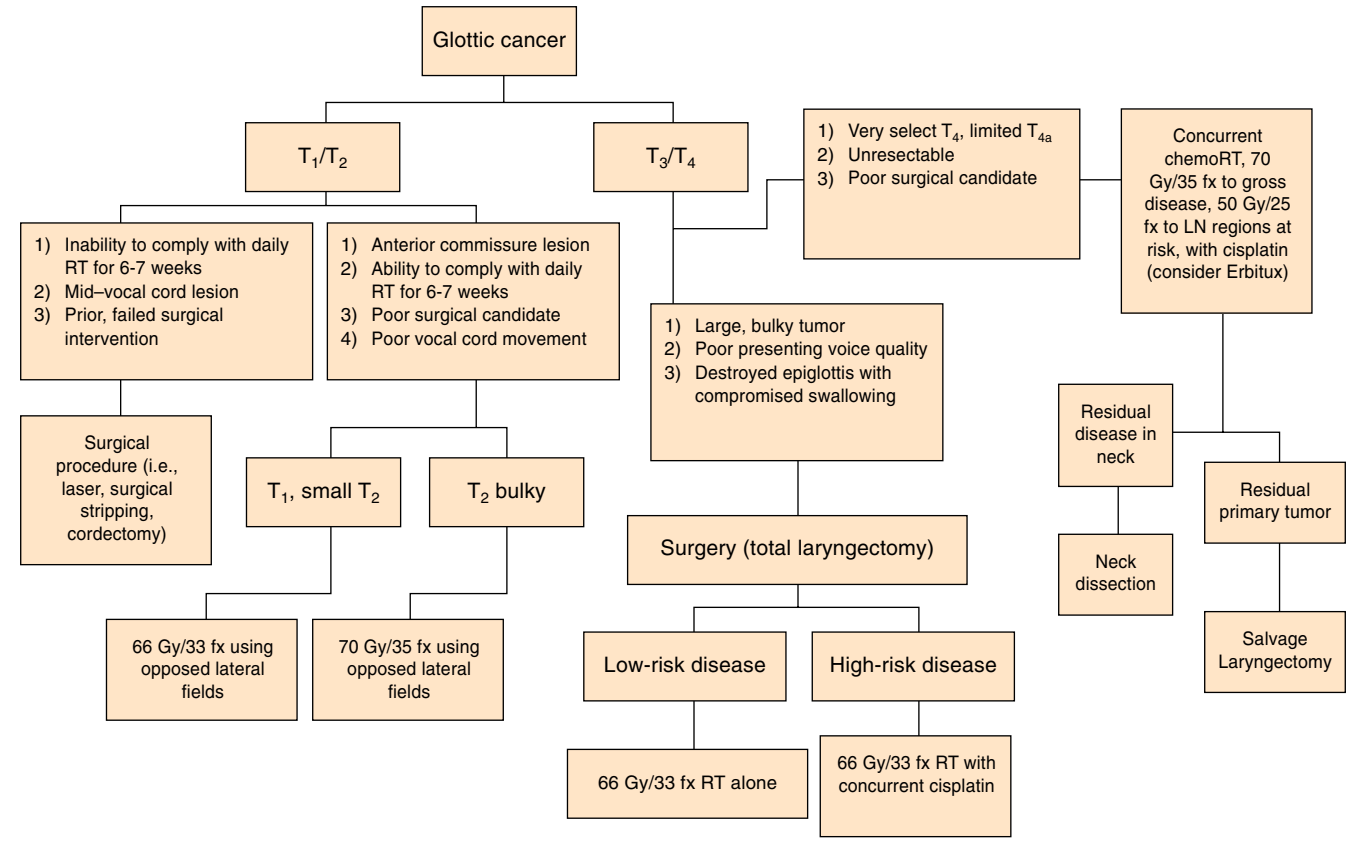

Figure 112-7. Treatment algorithm for glottic carcinomas.

the concurrent chemoradiation arm versus only 61% in the RT-alone group.[29]

Acute common side effects that are transient include skin erythema and desquamation, oral mucositis, and xerostomia with accompanying changes in taste. These acute side effects are self-limiting and need to be treated symptomatically with the aim of maintaining adequate liquid and nutritional intake so that radiotherapy treatments can be continued without significant interruptions. We do not recommend the prophylactic placement of a percutaneous esophagogastrectomy tube (PEG) unless the patient has already lost more than 10% of the baseline body weight or is unable to maintain nutritional intake by mouth due to the effects of the cancer or other reasons. In our experience the prophylactic placement of a PEG decreases the motivation for the patient to maintain oral intake during the radiotherapy treatment and quite often results in the patient becoming chronically PEG dependent. However, in order to support the patient during periods of decreased oral intake, we recommend aggressive intravenous fluids for up to three to five times per week. In addition, the use of radioprotectors such as amifostine also ameliorate the acute toxicity of radiotherapy such as mucositis and xerostomia.[43] Late sequelae from radiotherapy therapy include xerostomia and neck fibrosis, especially exacerbated by surgery. Rare late sequelae include mandibular osteoradionecrosis or arytenoid necrosis and chronic laryngeal edema.

Early-Stage Supraglottic Cancer

Many of the same general management principles used to treat early-stage glottic cancers also apply to the management of supraglottic lesions and are therefore not repeated in this section; however, the unique and salient features in the treatment of supraglottic cancers are highlighted. As with early-stage glottic cancers, early-stage $T_{1\text{-}2}$ supraglottic cancers can be treated with either radiotherapy alone or supraglottic laryngectomy, with excellent local control and preservation of voice. However, unlike T_1 glottic cancers, T_1 supraglottic lesions and certainly T_2 cancers require treatment of the next-echelon, uninvolved lymphatic nodal regions because of their propensity for subclinical metastases, and thus the risk of xerostomia is more significant in this setting and is a potential disadvantage to using radiotherapy. Conversely, not every patient with early-stage supraglottic disease is a candidate for supraglottic laryngectomy. From an anatomic standpoint, supraglottic laryngectomy is contraindicated under the following conditions:

1. More than minimal extension into the medial wall of the pyriform sinus
2. Involvement of the postcricoid region
3. Arytenoid fixation or bilateral arytenoid involvement
4. Impaired vocal cord mobility or fixation
5. Invasion of the thyroid or cricoid cartilage
6. Extension into the infrahyoid epiglottis or into the ventricle within 5 mm of the anterior commissure and/or the true vocal cord(s)
7. Extension into the base of the tongue to involve both lingual arteries and/or extension anterior to the circumvallate papillae

Of course, from a functional standpoint, elderly patients or those with poor lung function who may have difficulty swallowing and consequent complications of aspiration are also not good candidates for conservation surgery.

Radiation Techniques and Dose-Fractionation Schemes

The dose-fractionation schemes for early-stage supraglottic cancers are similar to those for early-stage glottic cancer as indicated earlier in the chapter. However, because of the propensity for lymphatic nodal

metastases for even T_1 and obviously T_2 lesions, the treatment volume should include any involved regional lymphatic nodes and the uninvolved next-echelon lymphatics.

At USC, we treat T_1 tumors with 66.0 Gy in 2.0 Gy/fx, again with a shrinking field technique with the final total dose delivered to the tumor with a 2.0-cm margin. The treatment volume should include the involved lymph nodes and the next-echelon uninvolved lymphatics. The involved lymph nodes should be treated with radical doses of radiation depending on the size of the disease (i.e., ≤1 cm with 60.0 to 66.0 Gy, >1 to 2 cm with 66 Gy and >2 cm with at least 70 Gy at 2.0 Gy/fx), and the uninvolved lymphatics should be treated with 50 Gy at 2.0 Gy/fx. For T_2 lesions, we recommend doses of at least 70 Gy at 2.0 Gy/fx. Several investigators have reported using alternative-dose fractionation schemes for T_2 lesions. Hinerman and colleagues[45] used a twice-daily hyperfractionated schedule for a total dose of 74.4 to 76.8 Gy at 1.2 Gy/fx with a minimum daily interfraction interval of 6 hours. Other investigators such as Wang and Montgomery[46] at the Massachusetts General Hospital have used an accelerated, fractionated radiotherapy schedule with a total dose of 67.2 Gy at 1.6 Gy/fx, twice a day, 5 days per week, with a 2-week rest after 38.4 Gy. We recommend caution using these alternative fractionation schedules unless the treating radiation oncologist has experience with these types of schemes because these patients require considerable support during their treatment because of acute toxicity.

The choice of treatment technique depends on multiple factors including the extent of the disease and the experience of the treating radiation oncologist. At USC, two parallel opposed fields using a 3-D CRT approach are used for T_1N_0 lesions, whereas a classic three-field technique (described previously) is used to treat $T_{1\text{-}2}$, N+ disease with successive shrinking fields.

Outcome and Prognostic Factors

Local control after RT for T_1 supraglottic carcinoma is excellent, ranging from 88% to 100%. For T_2 lesions, local control after RT varies from 73% to 89% (Table 112-6). Overall survival for stage I and II supraglottic cancers is 60% to 73%, comparable with the survival data for early-stage glottic tumors. Prognostic factors for glottic tumors also apply to supraglottic lesions.

Complications from Radiation Therapy

Compared with patients undergoing radiation for early-stage glottic tumors, patients undergoing radiation for early supraglottic lesions experienced more side effects from radiation secondary to the use of typically larger fields.

Advanced Supraglottic Cancer

The same principles used to select the optimal management for advanced glottic carcinoma also apply to advanced supraglottic cancers. *Hence we recommend a primary surgical approach for large, bulky tumors in which concurrent chemoradiation therapy is unlikely to achieve local control of disease; poor presenting voice quality that is unlikely to reverse with a primary nonsurgical therapeutic approach; or a destroyed epiglottis resulting in an irreversibly compromised swallowing function with a high probability of aspiration.* For T_3 lesions with mobile vocal cords, a supraglottic laryngectomy can be considered, with or without the addition postoperative RT depending on the risk status of the disease. However, as with glottic lesions, total laryngectomy is the preferred treatment for more advanced lesions with bilateral vocal cord involvement and compromised airway. When surgery is used as the primary definitive therapy, postoperative RT is added to reduce the risk of locoregional failure. Postoperative RT is indicated when there is tumor at or close to the surgical margins, cartilage invasion, involvement of the soft tissues of the neck, extensive subglottic infiltration, lymphatic nodal metastasis, extracapsular nodal extension, and perineural, lymphatic, or vascular invasion. Indications for adding chemotherapy to postoperative irradiation include other risk factors such as two or more involved lymph nodes, extracapsular extension, and/or positive surgical margins.

Concurrent chemoradiation therapy is a reasonable treatment option for patients with nonbulky, locally advanced supraglottic cancers. Typically, results with RT alone for locally advanced supraglottic cancers are suboptimal. Harwood and colleagues[47] and Karim and colleagues[48] reported local control rates of 56% (39 patients) and 63% (38 patients), respectively, with T_4 disease.

Table 112-6

Local Control after Radiotherapy for Early-Stage Supraglottic Carcinoma

Series	Stage	Patients (*n*)	Local Control
Fletcher et al (1980)[79]	T_1	24	88%
	T_2	56	79%
Ghossein et al (1974)[80]	T_1	17	94%
	T_2	64	73%
Wall et al (1985)[81]	T_1	38	89%
	T_2	132	74%
Wang and Montgomery (1991)[82]	T_1	23	89%
	T_2	79	89%
Nakfoor et al (1998)[83]	T_1	24	96%
	T_2	73	86%
Skyes et al (2000)[84]	T_1	65	92%
	T_2	136	81%
Hinerman et al (2002)[85]	T_1	22	100%
	T_2	125	86%
Johansen et al (2002)[86]	T_1	154	64%
	T_2	86	62%

Radiation Techniques and Dose-Fractionation Schemes

The same general techniques used to treat advanced glottic cancers also apply to advanced supraglottic cancers. The total dose used to treat T_3 to T_4 supraglottic tumors using standard, once-daily fractionated RT is at least 70 Gy at 2.0 Gy/fx. Higher total doses (up to 76 Gy) may be used for bulky or nonresponding disease with either IMRT or stereotactic radiosurgery techniques. Please refer to Table 112-4 regarding our recommendations for radiation doses. The treatment volume should include any gross or resected regions of disease, as well as any involved regional lymphatic nodes and the uninvolved, next-echelon lymphatics. Please refer to the section on advanced glottic cancer for general principles regarding dose-volume recommendations.

Outcome and Prognostic Factors

As discussed previously, locoregional tumor control rates are approximately 80% with concurrent chemoradiation therapy, 60% with induction chemotherapy followed by RT, and 55% with RT alone for stage III and IV disease.[28,29] For selected T_3 and T_4 lesions, local control rates with RT alone vary between 46% and 76% and 43% and 91%, respectively (Table 112-7), and approximately two thirds of the failures can be salvaged by surgery (Table 112-8). Overall survival rates range from 37% to 50%.

Subglottic Cancers

Primary carcinomas of the subglottis are rare. As a result, RT data about the management of subglottic carcinoma is sparse. Paisley and colleagues[49] reported their retrospective analysis of 43 patients with subglottic cancer who were treated with primary RT alone. Overall, the initial local control was 56% with RT alone, with an ultimate local control rate of 81.4% with surgical salvage. When analyzed by T stage,

the initial local control rates for T_1, T_2, T_3, and T_4 lesions with primary RT alone were 63.6%, 66.7%, 50%, and 41.7%, respectively. With surgical salvage, the ultimate local control rates for T_1, T_2, T_3, and T_4 lesions were improved to 91%, 100%, 75%, and 58.3%, respectively. Most subglottic lesions are relatively advanced at the time of diagnosis and are managed by primarily with surgery followed by postoperative RT. However, definitive RT offers a viable alternative to surgery for the management of subglottic carcinomas. Overall survival rates range from 45% to 60% for stage I and II subglottic tumors and 30% to 45% for stage III and IV lesions. Our recommendations for dose-fractionation-volume for early- and advanced-stage subglottic cancers are similar to those of glottic carcinoma.

Hypopharyngeal Cancers

Overall Management Considerations

Because of the unique "anatomic intimacy" between the hypopharynx and the larynx, a primary surgical approach for the management of the hypopharynx typically requires sacrifice of the larynx; hence hypopharyngeal carcinomas, especially early- and intermediate-stage "low-volume" lesions, should be managed with definitive radiotherapy with or without chemotherapy whenever possible.

Early-Stage Hypopharynx

Early-stage hypopharyngeal carcinoma can be effectively managed with RT alone and is generally the preferred treatment modality due to the advantage of laryngeal organ preservation.

Radiation Techniques and Dose-Fractionation Schemes

The dose-fractionation schemes for early-stage hypopharyngeal cancers are similar to those for early-stage glottic cancer as indicated earlier in the chapter and Table 112-4. However, because of the propensity for lymphatic nodal metastases for even T_1 and obviously T_2 lesions, the treatment volume should include any involved regional lymphatic nodes and the uninvolved next-echelon lymphatics. Bilateral upper and lower necks need to be treated even in early-stage disease. A three-field technique as described earlier for glottic cancers is used, but some subtle yet important differences exist between the field designs for the hypopharynx. The inferior border of the lateral fields (and hence the superior margin of the lower neck field because one isocenter is used) is placed as low as possible on the neck without passing through the shoulder in order to give a margin on the inferior extent of disease. For posterior pharyngeal wall lesions, the posterior extent of the off-cord field is placed at the posterior third of the vertebral bodies as opposed to splitting the vertebral bodies in half to ensure an adequate margin on the tumor.

As with glottic cancers, T_1 lesions should be treated to at least 66 Gy at 2.0 Gy/fx using a shrinking field technique. For T2 lesions, a minimum total dose of 70 Gy at 2.0 Gy/fx should be used.

Table 112-7

Local Control after Radiotherapy for Advanced-Stage Supraglottic Carcinoma

Series	Stage	Patients, *n*	Local Control
Fletcher et al (1980)[79]	T_3	29	62%
	T_4	17	47%
Ghossein et al (1974)[80]	T_3	35	46%*
	T_4	87	52%
Wall et al (1985)[81]	T_3	50	70%
	T_4	28	46%
Wang et al (1991)[82]†	T_3	95	71%
	T_4	12	91%
Nakfoor et al (1998)[83]	T_3	51	76%
	T_4	16	43%
Skyes et al (2000)[84]‡	T_3	83	67%
	T_4	47	73%
Hinerman et al (2002)[85]§	T_3	99	62%
	T_4	28	62%

*All had vocal cord fixation.
†Twice-daily treatment.
‡All were N_0, and some were salvaged with total laryngectomies.
§1998 American Joint Committee on Cancer staging.

Table 112-8

T_3,T_4 Carcinoma of the Glottis: Results of Definitive Radiotherapy and Surgical Salvage

Reference	Stage	Patients, *n*	Initial Local Control	Ultimate Local Control
Stewart et al (1975)[87]	T_3	67	57%	69%
Harwood et al (1980)[88]	T_3N_0	112	51%	77%
Lustig et al (1984)[89]	T_3	47	65%	NR
Lundgren et al (1988)[90]	T_3	141	44%	59%
Mendenhall et al (1988)[91]	T_3	47	62%	81%
Bryant et al (1995)[92]	T_3	55	55%	NR
Pameijer et al (1997)[93]	T_3	42	62%	NR
Hinerman (2007)[94]	T_3,T_4 [87, 22] (T_3N_0, T_3N_1, T_3N_{2b})	78%, 81%	88.5%	

NR, not reported.

Table 112-9

Local Control after Radiotherapy for Early-Stage Hypopharynx Cancer

Reference	Stage	Patients, *n*	Site	Initial Local Control	Ultimate Local Control
Mendenhall et al (1993)[51]	T_1	17	PS	88%	94%
	T_2	56	PS	79%	91%
Garden et al (1996)[50]	T_1	19	All	89% (2-yr)	NR
	T_2	63	All	77%	NR
Amdur et al (2001)[95]	T_1	19	PS	89%	95%
	T_2	67		82%	91%
Nakamura et al (2006)[96]	T_1	39	All	74%	87%
	T_2	76	All	58%	74%

Outcome and Prognostic Factors

In general, hypopharyngeal cancers carry a poorer prognosis when compared with laryngeal tumors. Local control rates range from 74% to 90% for T_1 disease and from 59% to 79% for T_2 disease (Table 112-9).[50-52] The use of hyperfractionated radiotherapy may improve local control rates for early-stage disease. Mendenhall and colleagues[51] reported local control of 94% in patients with T_2 pyriform sinus cancers treated with twice-a-day RT. Wang[52] reported a 5-year actuarial local control rate of 76% in patients with T_2 pyriform sinus cancer treated with split-course accelerated RT. Garden and colleagues[50] reported a local control rate of 89% for early-stage hypopharyngeal carcinoma. Overall survival is 30% to 35% for stage I and II hypopharyngeal carcinoma.

Complications

Because large fields are used to treat even early-stage disease, side effects experienced by patients undergoing radiation for early-stage hypopharyngeal tumors are similar to the effects experienced by advanced-stage laryngeal cancer patients.

Advanced-Stage Hypopharynx

As with laryngeal cancers, we recommend concurrent chemoradiation therapy only for those patients with low- or moderate-volume disease in whom speech and swallowing functions have not been already irreversibly compromised. Otherwise, we recommend a primary surgical approach followed by postoperative RT because of the high risk of local failure. An analysis by Frank and colleagues[53] found that patients with hypopharyngeal cancer who received postoperative irradiation had only a 14% rate of locoregional failure as compared with 57% in those treated with surgery only, despite the fact that patients treated with combined-modality therapy had more advanced disease. Indications for adding chemotherapy to postoperative irradiation typically include two or more involved lymph nodes, extracapsular extension, and/or positive surgical margins.

Voice-preserving strategies have been examined for this disease site as well. The European Organization for the Research and Treatment of Cancer (EORTC) conducted a voice-preservation study of patients with hypopharyngeal carcinomas, EORTC 24891, which revealed that an induction chemotherapy followed by radiation did not compromise survival and allowed laryngeal preservation in 35% of patients.[54] The details of this study are discussed later in "Outcome and Prognostic Factors." Hence combining chemotherapy with RT offers an alternative to patients with advanced-stage disease. However, based on the results of RTOG 9111 and other trials[55,56] we recommend concurrent chemoradiation therapy as compared with induction chemotherapy followed by definitive irradiation.

Radiation Techniques and Dose-Fractionation Schemes

The same general techniques used to treat advanced glottic cancers also apply to advanced supraglottic cancers. The total dose used to treat T_3 and T_4 hypopharyngeal cancer tumors using standard once-daily fractionated RT is at least 70 Gy at 2.0 Gy/fx. Higher total doses (up to 76 Gy) may be used for bulky or nonresponding disease with either IMRT or stereotactic radiosurgery techniques. Please refer to Table 112-4 regarding our recommendations for radiation doses. The same general techniques used to treat patients with early-stage hypopharyngeal cancers can be applied to treat patients with advanced-stage disease. Due to the typically large size of these lesions, maintenance of adequate margins around the gross tumor and areas of high-risk disease requires either a "mini-mantle" field arrangements as previously described or an IMRT technique.

Outcome and Prognostic Factors

As mentioned previously, hypopharyngeal cancer has the worst prognosis of any head and neck cancer. The 5-year local control rates range from 20% to 50% and overall survival rates from 18% to 35% for stage III and IV lesions. In the EORTC 24891, 202 patients were randomized to either immediate surgery followed by postoperative RT (50 to 70 Gy) or induction cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 daily on days 1 through 5) for three cycles followed by RT (70 Gy at 2.0 Gy/fx once daily). The locoregional failure rates were similar for both the surgery arm (31%) and the induction chemotherapy arm (40%). Survival rates were equivalent in the two treatment groups at 5 years (35% for the surgery arm vs. 30% for the induction chemotherapy arm), but patients in the chemotherapy group had a 5-year voice preservation rate of 35%. However, only 5% of the patients in this EORTC trial had T_4 disease. In combining chemotherapy with RT, we recommend a concurrent approach as the current "nonsurgical" standard of treatment.

The same factors that influence prognosis in laryngeal cancer affect outcome in hypopharyngeal tumors.[8,10,11,54,55] In addition, some data indicate that lesions in the postcricoid region have worse local control rates.[56]

Complications

Because similar fields are used to treat advanced hypopharyngeal tumors and laryngeal cancers, the same complications are experienced by this population of patients. Esophagitis leading to difficulty in maintaining oral intake and xerostomia are of particular concern when treating these patients.

Radiation Therapy for Recurrent Disease

The majority (80%) of the recurrences in head and neck cancer occur within the first 2 to 3 years after treatment, and prognosis of these patients is poor, with median survival of approximately 6 months.[57] Moreover, most of these recurrences are locoregional, so these patients still can be approached with a "curative" salvage therapy. In fact, up to 10% of patients with recurrence from their head and neck cancers can enjoy long-term control with aggressive therapy. Surgical salvage is preferred, but in many cases the recurrent disease is unresectable.

The management of patients with recurrent head and neck cancer is anything but "standard" and requires a thoughtful individualized approach for each patient on the basis of numerous factors including the following:

1. Time interval from the completion of prior curative therapy to the recurrence
2. Patient's performance status
3. "Surgical" versus "nonsurgical" disease and candidate

RTOG 9610 addressed the efficacy and safety of re-irradiation in patients for unresectable recurrence or secondary primaries in the head and neck within previously radiated fields. In this study, 86 patients were enrolled and treated with 4 weekly cycles of concurrent RT delivered in 1.5 Gy fractions twice daily, separated by at least 6 hours, to a total dose of 60 Gy, with concurrent 5-FU and hydroxyurea.[58] There was a week break between each weekly cycle. Estimated 2-year and 5-year overall survival was 15.2% and 3.8%, respectively. Grade IV toxicity was experienced by 17.7% of patients, and 7.6% experienced grade V toxicity (death). Three patients were alive at 5 years.

There is often the mistaken notion that patients with recurrent head and neck cancer should be treated "focally" with smaller fields to the areas of gross recurrent disease. However, quite often, the area of gross recurrent disease represents only the "tip of the iceberg" and "spot-welding" would only put the patient at risk for future recurrences in areas that are not irradiated. It is imperative to study the dosimetry from previous radiation and document doses to critical structures such as the spinal cord, mandible, and larynx (arytenoids, vocal cords). At the University of Southern California, patients with recurrent head and neck cancer are treated "comprehensively" using a continuous hyperfractionated radiotherapy scheme to 7700 cGy at 110 cGy/fx twice daily. The volume of irradiation includes the areas of recurrent gross disease and adjacent uninvolved lymphatic nodal regions. An "off-cord" three-field arrangement from the start of the re-treatment is typically used to keep the spinal cord dose below tolerance levels. IMRT is used in select situations to boost areas of gross disease in order to further limit dose to surrounding critical structures. In a recent report of our experience using this approach, we showed that comprehensive re-irradiation using a continuous hyperfractionated scheme is feasible and tolerable in the majority of patients.[59]

Future Strategies and Directions

Alternative Chemoradiation Therapy Strategies: The "RADPLAT" Approach

Another strategy for the treatment of advanced laryngeal and hypopharyngeal cancers involves the use of supradose intra-arterial cisplatin (100 mg/m^2 on days 1, 8, 15, and 22 with sodium thiosulfate rescue) and concurrent RT (68 to 74 Gy).[60] This strategy, termed "RADPLAT," has the advantage of "targeting" the chemotherapy to avoid the toxic systemic effects of intravenous chemotherapy while still sensitizing the effects of concurrent RT. The RADPLAT approach has been evaluated in locally advanced head and neck cancers including a multi-institutional trial of 67 patients with T4 disease.[61] In this RTOG trial (#9615), the RADPLAT approach was shown to be feasible in 87% of patients with a very high (80%) pathologic complete response rate and acceptable acute toxicity. Similar results were also shown in a study of 25 pyriform sinus cancer patients with stage III (24%) and stage IV (76%) disease who were also treated with the RADPLAT therapy.[62] Seventeen patients presented with bulky nodal disease, whereas 10 were diagnosed with T_4 lesions. At a median follow-up interval of 42 months, none of the 25 patients had experienced a local recurrence at the primary site, and only one patient relapsed regionally in the lymph nodes, which was subsequently salvaged with surgery. Moreover, the larynx preservation rate was 88%.

Emerging Technologies: CyberKnife Stereotactic Radiotherapy

In patients with head and neck cancer, local failure of disease not only adversely affects a patient's quality of life but also has a significant negative impact on overall survival. Escalation of radiotherapy doses represents one method of potentially reducing local failure rates and improving overall survival. However, escalation of radiotherapy doses beyond the "standard doses" (i.e., 70 to 76 Gy) using conformal radiotherapy techniques is not possible without causing significant increased acute and late sequelae. Additionally, not all patients with recurrent head and neck cancer are eligible to receive further re-irradiation for multiple reasons including maximal radiation dose to critical structures. One recent method of radiation dose escalation and re-treating recurrent head and neck cancer is CyberKnife (CK) stereotactic radiotherapy (SRT). The CK is a lightweight 6-MV photon linear accelerator mounted on a robotic arm that has the capability to deliver image-guided SRT with a "sharp" dosimetric dose profile. Since 2002, we have used CK SRT to treat more than 200 head and neck cancer cases for curative and palliative intent. Recently, we reported our results using CK SRT for management of recurrent head and neck carcinoma in the infratemporal fossa.[63] In this series, all patients with a prior history of chemoradiation therapy underwent further surgical debulking followed by CK SRT and cetuximab for their recurrent disease. CK SRT was well tolerated by all patients without any acute or late toxicity with moderate local control of recurrent disease.

SUGGESTED READINGS

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CHAPTER ONE HUNDRED AND THIRTEEN

Vocal and Speech Rehabilitation Following Laryngectomy

Frans J. M. Hilgers

Michiel W. M. van den Brekel

Key Points

- Surgical prosthetic voice restoration is the best possible option for patients to regain oral communication after total laryngectomy and is considered the "gold standard" for voice rehabilitation of laryngectomized individuals.
- Surgical prosthetic voice restoration, in essence, is always achievable in patients fit enough to tolerate total laryngectomy and motivated to regain optimal oral communication.
- Surgical prosthetic voice restoration requires a multidisciplinary team approach (physician, speech therapist, oncology nurse) in order to obtain optimal results.
- If a good prosthetic voice deteriorates, prompt clinical consultation is required. Patients should be instructed accordingly.
- The vast majority of problems in prosthetic voice restoration are relatively simple and immediately solvable by a trained physician, speech-language pathologist, or nurse.
- Reconstruction of the pharynx (e.g., with free revascularized or pedicled flaps) does not preclude surgical prosthetic voice restoration.

History of Alaryngeal Voice and Speech

Historically the start of postlaryngectomy voice rehabilitation was surgical and prosthetic. The patient who underwent the first total laryngectomy (TL) for cancer, by Billroth in 1873, used an artificial larynx in order to speak. As eloquently described by Billroth's colleague Gussenbauer in 1874, the patient could be understood from one side of the ward to the other.[1] Considering that patient wards in those days were huge, holding up to 40 beds, this must have been an impressive achievement. This first artificial larynx, essentially a tracheotomy tube with a pharyngeal extension (Fig. 113-1), allowed pulmonary-driven speech. It contained a valve mechanism to prevent aspiration, a special membrane to act as a heat and moisture exchanger, and a reed to act as a vibrating tone generator. The only futile component of the initial artificial larynx was the tone generator in the form of a reed. Apparently, in preparing this device before the operation, it was not anticipated that diverting pulmonary air into the pharynx could produce mucosal vibrations and thus sound, which actually could interfere with the monotonous tone of the reed, potentially leading to diplophonia. The main reasons for abandoning artificial larynges in those early decades were the many wound-healing complications with these bulky devices in an era without proper anesthesia and antibiotics.[2] The discovery that with air insufflation the pharynx can act as a tone generator has undoubtedly helped to stay away from surgical voice restoration options for a long period of time.[3]

Over the past three decades, voice rehabilitation after TL has changed considerably. Until the late 1970s, there were only three options for audible postlaryngectomy voicing (i.e., esophageal voice, electrolarynx voice, and a surgical shunt between the trachea and the neopharynx). Besides these three options, there were the barely audible but sometimes still quite intelligible options of buccal and whispered voicing.

In the late 1970s and early 1980s, surgical procedures (e.g., Asai's, Staffieri's, and Amatsu's techniques) to create a functional tracheoesophageal fistula and thus allow tracheoesophageal voicing were initially popular but have since declined.[4-6] After the first enthusiastic reports about the good voice that could be achieved, many head and neck specialists became disappointed about troublesome aspiration problems. In essence, one could say that if the patient had a good voice, he or she would aspirate, and when there was no aspiration, the patient had no or only a strained voice. Although in many countries these techniques were more or less completely abandoned, in others they led to a quest for solving the aspiration problem.[7-12] The solution was found in the development of presently available voice prostheses, which have in common a surgically created tracheoesophageal fistula and the containment of a one-way valve mechanism.[13] These prostheses keep the tracheoesophageal connection open, allow the passage of pulmonary air into the esophagus in order to produce pharyngeal vibrations and sound, and prevent aspiration by automatic closure of the valve when the pulmonary air pressure drops. These devices have proven to be both functional and reliable.[14]

Some historical reflections are important at this point. Although Singer and Blom have been credited with initiating modern voice prostheses development, the first paper on a useful prosthetic device (Fig. 113-2) actually originated in Poland, where Mozolewski (1917-2007) in 1972 published his results with 24 patients.[15] This publication in Polish with abstracts in Russian and English probably went unno-

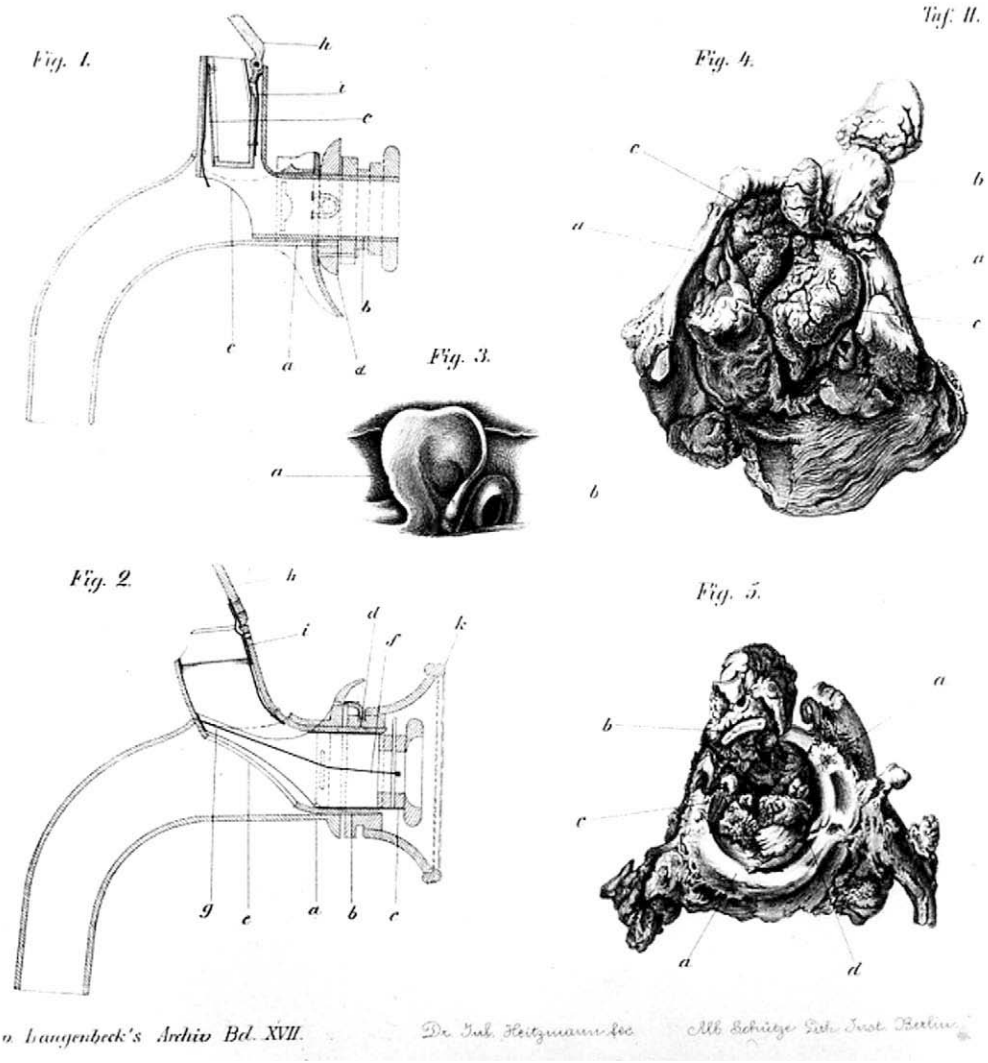

Figure 113-1. Drawings from the original paper by Gussenbauer. Note the almost complete obstruction of the subglottic space within the cricoid cartilage. On the left are the first and second versions of the artificial larynx. In the center the postoperative situation is depicted, with a pharyngostoma to hold the pharyngeal extension of the artificial larynx (note that the epiglottis was not removed). *(From Gussenbauer C. Ueber die erste durch Th. Billroth am Menschen ausgefuerte Kehlkopf-Extirpation und die Anwendung eines kuenstlichen Kehlkopfes.* Arch Klin Chir. *1874;17:343-356.)*

Figure 113-2. Photograph of the original hand-made indwelling Mozolewski voice prosthesis, which, unlike the present voice prostheses, was inserted in a pharyngocutaneous fistula just above the tracheostoma. *(Photograph courtesy of Prof. Dr. Czeslawa Tarnowska, Szczecin, Poland.)*

ticed. However, Mozolewski and colleagues[16] remained active and in 1975 published a report in *Laryngoscope* about a postlaryngectomy surgical arytenoid vocal shunt procedure as an alternative to the popular Asai procedure. Subsequently, they presented both their surgical and prosthetic methods at a conference in Boston in May 1978. After these initial reports, however, Blom and Singer have put prosthetic voice rehabilitation on the world map and diligently and tenaciously instructed and educated numerous clinicians. Since the introduction of the first Blom-Singer prosthesis in 1980, many other brands have been introduced and further developed: Panje, Groningen, Herrmann, Traissac, Algaba, Provox, Nijdam, and Voicemaster, many of which are still available.[7-12,17-19]

Physiology of Alaryngeal Voice and Speech

Prosthetic voice is pulmonary driven, as is laryngeal voicing. Sound is produced by comparable mucosal vibrations in the pharyngoesophageal segment.

For a good understanding of voice and speech rehabilitation after TL, the basic principles of normal laryngeal voice and speech production should be kept in mind. In order to be able to speak, it is necessary to have airflow, a sound source, and a cavity in which the sound will be

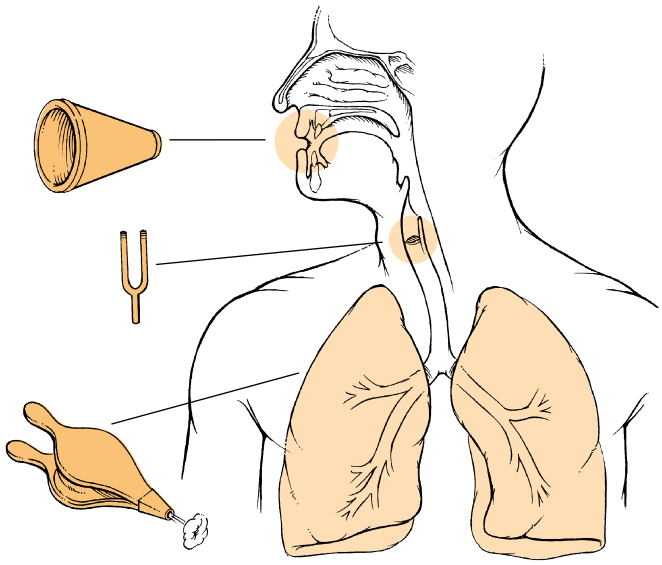

Figure 113-3. Necessary for normal speech are a bellows (i.e., pulmonary airflow), a sound source (i.e., vocal folds with vibrating mucosa), and a vocal tract, in which the articulators transform the laryngeal sound into intelligible speech. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

transformed into intelligible speech. Normally, the airflow is provided by pulmonary exhalation, which through the well-known Bernoulli effect causes vibrations of the mucosa in the voice box and thus a sound source. The sound thus produced will be transformed into intelligible speech in the mouth, nose, and throat cavities by articulation (e.g., by movements of the muscles present in that area, together forming the vocal tract, schematically shown in Fig. 113-3).

After TL the vocal tract is only slightly changed because the removal of the hyoid bone and the larynx alters the position of the tongue base, possibly influencing speech intelligibility. The most obvious change, however, is that the voice box as the natural sound source is replaced by the pharyngoesophageal (PE) segment, which has a significant impact on voice quality.[20] And without any additional measures, the disconnection of the airway and the PE segment makes the lungs unavailable as an air source.

Esophageal Voice and Speech

A potential source of air can be air injected into the esophagus and/or stomach. By expelling this air, it is possible to set the mucosa in the PE segment into vibration, which acts as a sound source. With the sound thus produced, intelligible speech can be formed in the intact vocal tract. This so-called esophageal speech is schematically depicted in Figure 113-4. A drawback of this method is that relatively little air is available (≈80 mL), in contrast to the liters of air in the lungs available before the operation. Therefore the phonation time is short, about 1 to 2 seconds compared with more than 20 seconds in laryngeal voicing. Additionally, for many patients this technique is difficult to acquire and rehabilitation often takes months. Success rates in the literature vary substantially, partly because of the lack of a good definition of voice quality. No more than 40% to 60% of the patients acquire reasonable speech and only 10% develop a really good voice.[21]

Electrolarynx Voice and Speech

Another method is the use of a tone generator, which consists mostly of an electrically driven instrument called an *electrolarynx*. These devices generate vibrations that pass through the skin toward the throat (schematically depicted in Fig. 113-5). Sound generated in this way is transformed in the vocal tract into intelligible speech. The advantage is that most patients acquire this speech rapidly, but the drawbacks are a monotonous, robot-like sound and the necessity to always have one hand occupied while using it.

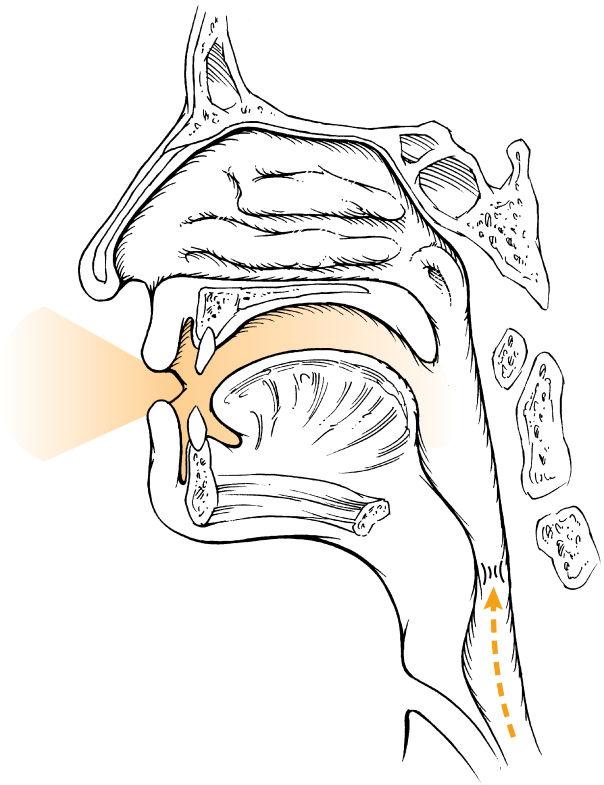

Figure 113-4. Esophageal speech. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

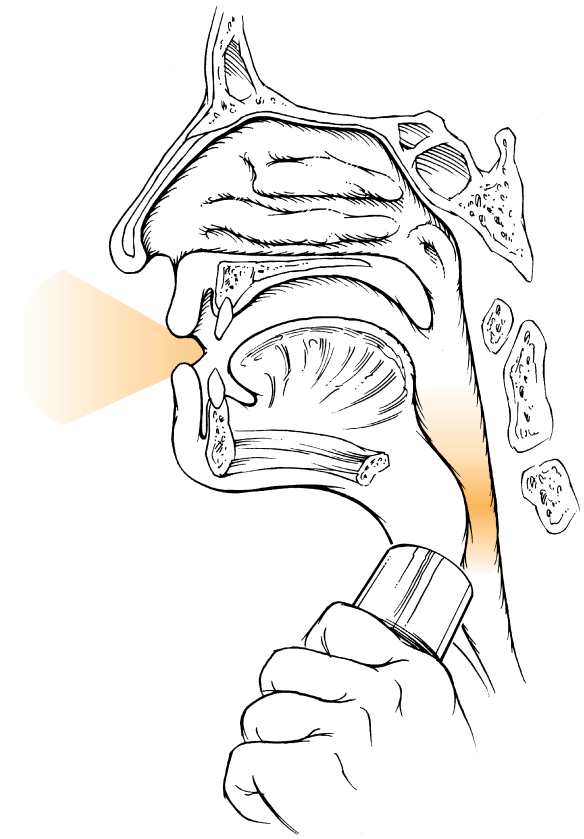

Figure 113-5. Electrolarynx speech. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

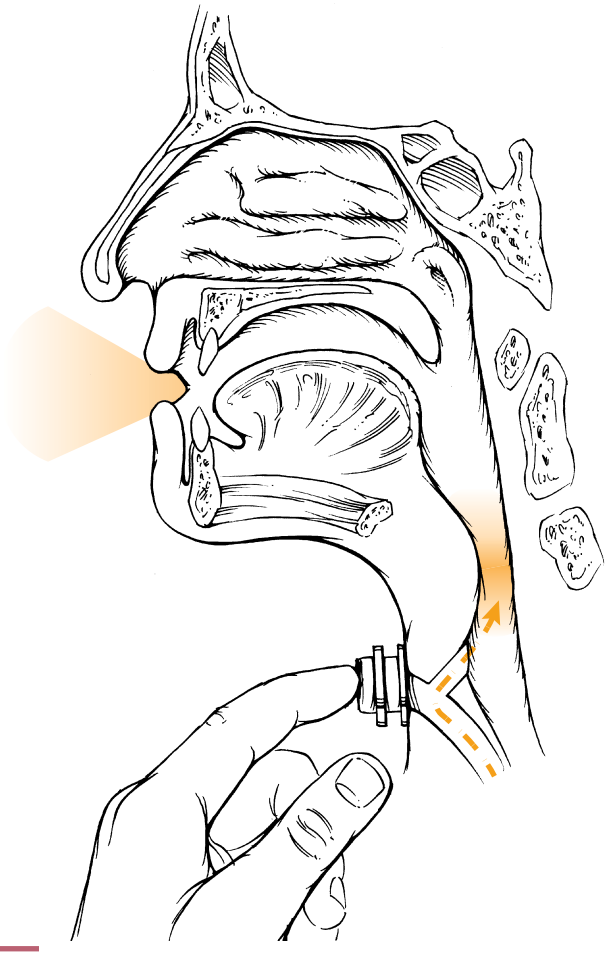

Figure 113-6. Prosthetic voice rehabilitation: The *dashed line* indicates the pulmonary air, by occlusion of the stoma through the prosthesis diverted into the pharyngoesophageal segment, where mucosal vibrations generate the sound for speech production in the vocal tract. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Tracheoesophageal Voice and Speech

The limitations of esophageal and electrolarynx speech outlined previously have initiated the development of the so-called voice prosthesis, essentially a one-way valve allowing air to pass from the trachea into the PE segment and preventing aspiration. Through a minor surgical procedure, either primarily at the time of the laryngectomy or secondarily at a later date, a tracheoesophageal fistula is created, allowing implantation of this device. After closure of the stoma, just like before the operation, air from the lungs creates vibration, in this case in the mucosa in the throat (schematically depicted in Fig. 113-6).[22-24] Even after extensive resections and reconstructions of the throat, this method is applicable, whereas esophageal speech in these cases is hardly ever successful.[25] The recovery of oral communication is so rapid (in most cases a useful voice develops within 2 weeks) and the success rate of the prosthetic method is so high (in the magnitude of 90%) that this rehabilitation technique has developed into the "gold standard" and recovery of speech after TL has become quite predictable.[26,27]

Tracheoesophageal speech, like normal laryngeal speech, is pulmonary driven and thus is closest to normal. The availability of the pulmonary air allows maximum phonation times (MPT) that in many patients are approaching normal values; mean MPTs of 16 to 17 seconds are no longer the exception.[28] Even in most COPD patients, pulmonary capacity is still sufficient to allow for good voicing.[29] As already mentioned, the sound is produced in the PE segment by mucosal vibrations generated by the pulmonary air.[22,24] An important issue to stress at this point is that there is no gender difference in postlaryngectomy anatomy and physiology of the new sound source.[23] This means that male and female voices do not differ in fundamental frequency, which is approximately 100 Hz. Thus female voices often sound too low, whereas male voices are fine.[24,30] This is one of the remaining issues to address in the future.[31] Although it may sound like a superfluous remark, one has to keep in mind that the pharynx also constitutes the alimentary tract, so after laryngectomy the PE segment has a dual function: a sound generator and a passageway for food. This should never be forgotten when problems occur with voice prostheses and when solutions are searched for: What could be beneficial to one function might be detrimental to the other one.

Types of Voice Prostheses

Indwelling and Nonindwelling Prostheses

In general, two types of TE voice prostheses can be distinguished: nonindwelling and indwelling devices. The first voice prostheses that became available in the United States were of the nonindwelling type (Blom-Singer duckbill and Panje prostheses),[11,12] whereas the first European prostheses were indwelling devices (Mozolewski and Groningen)[10,15] (Fig. 113-7).

The nonindwelling TE voice prostheses can be removed and replaced by the patient. The indwelling TE voice prostheses stay in place permanently and must be removed and replaced by a clinician experienced in the method. The need for prosthesis replacement occurs at the end of the device's life span, which is usually determined by leakage of fluids through the prosthesis into the airway or an increased airflow resistance of the prosthesis. Because indwelling devices may have a more robust construction, their life spans are generally longer than those of their nonindwelling counterparts. Furthermore, indwelling devices have the distinct advantage in that the patient's dexterity plays a lesser role in the daily maintenance of the device; this mainly consists of internal cleaning with a brush and/or a flushing device without the need of regularly replacing the prosthesis. Even with increasing age or decreasing general health status, or both, a useful (prosthetic) voice can be preserved.[14,32] The obvious disadvantages of indwelling prostheses are that patients need a clinician for the replacement and hospital or clinic visits remain necessary. However, nonindwelling devices can also cause problems, forcing the patients to consult their clinicians. Thus the difference in the need for clinical aftercare is far from "all or nothing." Furthermore, as with indwelling devices, a regular checkup of the fistula/stoma region is necessary because of the need for early detection of possible adverse side effects (e.g., hypertrophy, infection, widening of the TE fistula) and for oncologic follow-up, irrespective of the prosthesis used. Therefore from the beginning of the modern prosthetic rehabilitation era in most of Europe, there was a strong preference for indwelling devices.[9,10,32-34] Today's most widely used indwelling prostheses in Europe, the Provox® and Provox® 2 system, are shown in Figures 113-8 and 113-9, respectively.

The evolution of voice prosthetics in the United States has been somewhat different from that in most of Europe. The American development has been influenced by speech-language pathologists (SLPs), who from the beginning favored delaying the insertion of the prosthesis. Instead, the preference has been to create a tracheoesophageal fistula and stent it with a rubber (feeding) catheter either primarily or secondarily. The insertion of the voice prosthesis is done only after wound healing is completed. The disadvantage of this approach is the tendency for the fistula to have associated edema and irritation and not to have reached its final length when the prosthesis is fitted 10 to 12 days later. In contrast, when the insertion of the prosthesis is done at the time of laryngectomy, as was originally described by Annyas and colleagues,[35] a second fitting can be avoided and the estimate of the length of the prosthesis is more accurate (almost always 8 mm). Nonetheless, others prefer inserting a feeding tube through the fistula at the time of the laryngectomy, which has the advantage of avoiding an indwelling feeding tube attached to the nose. Usually, the patient is ready to take oral feeds when the tube is removed 10 to 12 days later for placement of the prosthesis. For patients who were treated previously with radiation therapy, this length of time for tube feeding is preferred. Although insertion of the prosthesis during the postoperative phase may be difficult for some patients, the majority of them tolerate this well.

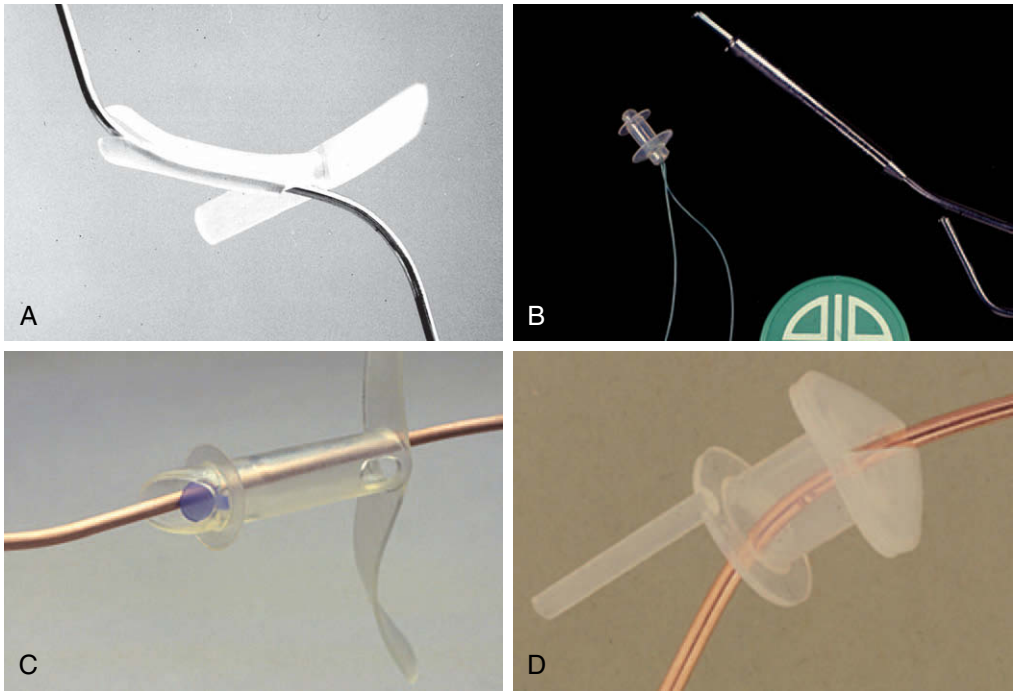

Figure 113-7. **A,** The original Blom-Singer duckbill prosthesis (1979/80) without a retention flange. **B,** The Panje prosthesis (1981), which had a retention flange, and a safety strap from the start. **C,** The later low-resistance version with a retention flange (1982). **D,** The indwelling Groningen prosthesis, which had a sturdy retention flange–valve combination, ensuring proper retention, even when inserted at the time of tracheoesophageal puncture (primarily or secondarily). For the Mozolewski prosthesis, see Figure 113-2.

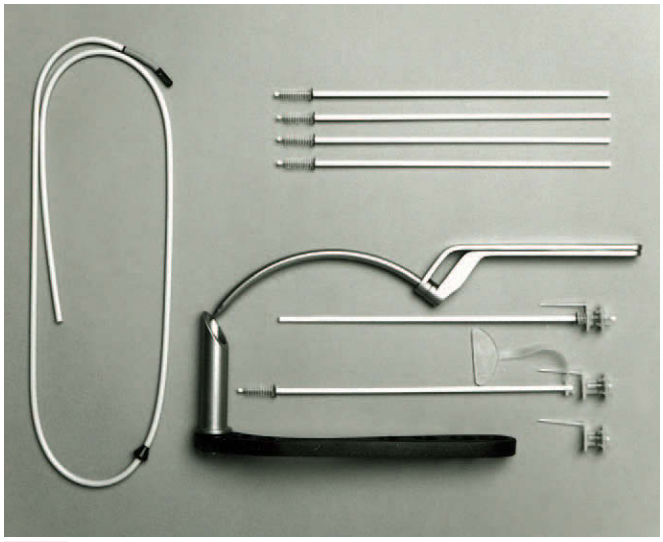

Figure 113-8. The Provox® voice rehabilitation system. From bottom to top, a pharynx protector for use during a primary TEP procedure, the voice prostheses in three sizes (6, 8, and 10 mm shaft length), a brush for internal cleaning, a plug for temporary occlusion of the prosthesis in case of leakage through the prosthesis, the trocar and cannula for primary and secondary TEP, and to the left a disposable guide wire for retrograde insertion during TEP procedure, or for prosthesis replacement (both Provox® and Provox® 2).

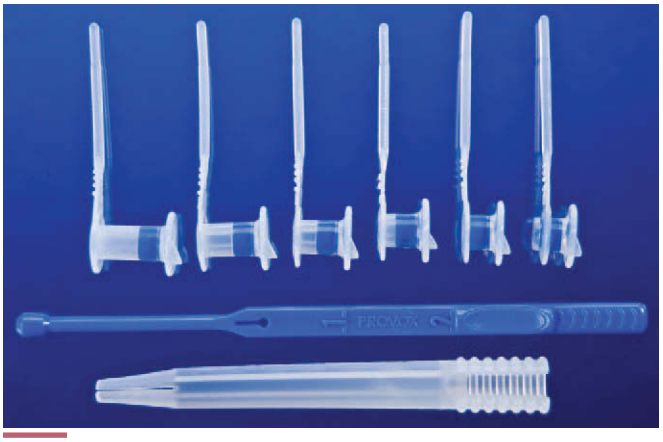

Figure 113-9. The Provox® 2 anterograde replacement system, with five different shaft lengths (4.5, 6, 8, 10, 12.5, and 15 mm) and the loading tube with inserter.

However, the alternate approach of inserting the prosthesis immediately at the time of the laryngectomy as described earlier has been reported to be quite satisfactory with a low complication rate.[9,32,35,38-41] Additionally, consideration should be given to the psychological advantage for patients to start voicing immediately after removal of the feeding tube. The recent trend by some centers to start oral intake soon after the laryngectomy in nonirradiated patients, within 24 to 48 hours, coordinates well with the early insertion philosophy.[42] Therefore it is not surprising that the immediate insertion method is gaining popularity in the United States, with SLPs still being the main responsible clinicians for the rehabilitation of postlaryngectomy voice and speech rehabilitation.

Surgical Aspects of Alaryngeal Voicing

Problem solving and prevention starts at the time of TL.

As with any other surgical technique and prosthetic appliance, problems and complications must be taken into account. Proper handling of the occasional problems is mandatory in order to maintain oral communication for the rest of the laryngectomy patient's life. Because the prognosis for many laryngectomized individuals is good, many of them have a long enough life expectancy and it is necessary for medical professionals to provide care specific for communication over the long

term. Hence investing in a good protocol to ensure optimal handling of adverse events is worthwhile for both patients and clinicians.

Standard Total Laryngectomy

For the indications and surgical aspects of TL, see Chapter 111. In the following section, specific aspects of surgical prosthetic voice rehabilitation are discussed.

Surgical Techniques and Refinements

Primary prosthetic voice restoration is presently the method of choice for optimally reestablishing postlaryngectomy oral communication.

Primary prosthetic voice restoration, meaning tracheoesophageal puncture (TEP) and immediate insertion of a voice prosthesis at the time of TL, is the method of choice for many experienced medical professionals (see Fig. 113-12, B; video clip available on website).[13,36] This enables the easiest and most comfortable voice rehabilitation because the patient is still under general anesthesia when the first prosthesis is inserted. No stenting of the fistula with a nasogastric feeding tube is necessary because the device itself is used to stabilize the puncture site.[37] The TEP can almost always can be done as a primary procedure, even when the circumference of the neopharynx has to be reconstructed, provided the esophagus is still present at the level of the trachea.[25] Only when the proximal esophagus is dissected off the trachea, as in the gastric pull-up procedure, is there a need to delay the TEP for 4 to 5 weeks.[25] In those cases, secondary TEP is performed after the completion of wound healing and before possible postoperative radiotherapy (see also discussion of the role of radiotherapy in the Prosthetic Voice Rehabilitation and Radiotherapy section).

With the currently available devices, voice prostheses (if available and affordable)[43-46] can be applied, irrespective of the method of closure of the pharyngeal mucosa and the extent of the pharyngeal constrictor muscle defect. However, with a few refinements in the surgery of TL, several postlaryngectomy problems such as hypertonicity of the pharyngoesophageal (PE) segment and a poor contour of the stoma can be avoided or diminished.

Refinements of standard TL techniques for optimizing prosthetic voice restoration results are:

1. A short myotomy of the upper esophageal sphincter to prevent hypertonicity of the PE segment
2. Suturing of the trachea in a separate fenestra in the inferior skin flap to create a stable stoma
3. Sectioning of the sternal heads of the sternocleidomastoid muscles to prevent a "deep" stoma
4. Pharyngeal mucosa closure without tension (T shape) to prevent pseudo-vallecula formation

1. Prevention of hypertonicity of the PE segment
Hypertonicity of the PE segment is the most frequent reason for failure to develop fluent prosthetic speech, as well as esophageal speech.[47,48] The cause is excess tone in the constrictor pharyngeus muscles forming the wall of the PE segment. In patients with this problem, this tonicity is exacerbated after inflation of air and thus blocks the flow of air through the PE segment, preventing mucosa vibrations and thus sound production. Although there are several surgical solutions described in the literature, we believe the best option to prevent this problem is to perform a short anterior positioned myotomy of the circular proximal upper esophageal sphincter (cricopharyngeus) muscle in every patient (Fig. 113-10; video clip available on website), unless palpation during surgery reveals that this muscle is completely relaxed.[49] After this myotomy and prosthesis insertion, the surgeon can still close the pharynx (mucosa and constrictor muscles) in the preferred manner.

2. Creation of an optimally contoured stoma
Ideally, the patient has a stable stoma with the same diameter as the trachea or only slightly narrower in order to have easy access to the voice prosthesis and to avoid a cannula to stent the stoma for adequate respiration. Reasons for stoma stenosis can be a dehiscence of the trachea from the skin because of infection and traction, sectioning of the last tracheal cartilage "ring" and diminishing its internal stability, or contraction of the tracheocutaneous suture. A reliable technique is to suture the trachea into a separate fenestra in the lower skin flap (Fig. 113-11).[50] This fenestra should have approximately the same size and diameter as the trachea, and the cranial trachea ring should remain intact. This latter aspect is the most important point of the creation of a stable stoma: the collagen fibers in the trachea cartilage are distributed in such a manner (dense and parallel on the outside and loose and intermingled on the inside) that the cartilage acts as a "spring" trying to widen the trachea.[51] If the cartilage is cut, these spring forces are lost and the trachea will collapse, resulting in a smaller stoma. Meticulous suturing of the skin to the trachea mucosa and optimally covering the bare trachea cartilage is important to prevent local infection and fibrosis. The small strip of skin (8 to 10 mm) cranially is surprisingly vital and only rarely breaks down, even in irradiated patients. The advantage of this technique is that trifurcations in the wound are avoided, which is not the case if the stoma is created in the TL skin incision itself. Obviously, in some cases in which the trachea has to be sectioned lower down, it is not long enough to be sutured in a separate fenestra and the entire inferior skin flap is necessary to be able to form a stoma. But even in these cases, with an intact last tracheal ring it should be possible to decannulate the patient following the procedure. The absence of a cannula results in less irritation of the trachea and stoma (i.e., less coughing and strain, improved wound healing).

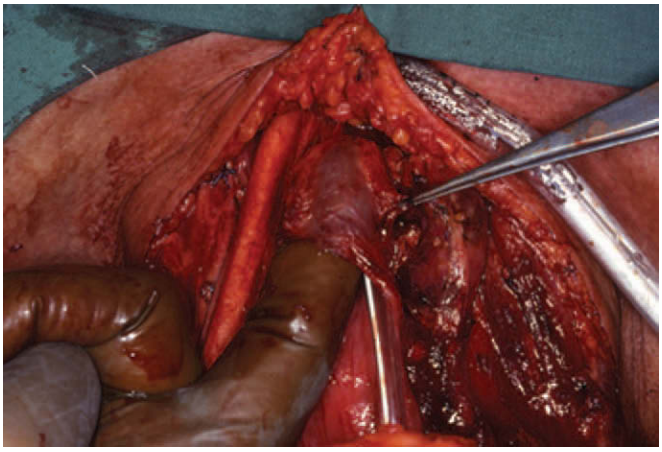

Figure 113-10. Myotomy of the cricopharyngeal muscle to prevent hypertonicity of the pharyngoesophageal segment (video clip available on website).

3. Prevention of an excessively deep stoma
A deep stoma is problematic for the later application of additional rehabilitation devices that potentially rely on peristomal attachment such as a heat and moisture exchanger (HME) or an automatic speaking valve (ASV). Sometimes a deep stoma is unavoidable (e.g., when more than 3 to 4 trachea rings are removed). However, most "deep" stomas are caused by the protrusion of the sternal heads of the sternocleidomastoid muscles (SCMMs) (Fig. 113-12; video clip available on website). Therefore the solution is to cut the sternal attachment of the SCMMs during the operation and before skin closure. This generally results in a flat peristomal area, making attachment of external devices considerably easier. Functional side effects from resected SCMMs have not been observed.

4. Pharyngeal mucosa closure
Meticulous closure of the pharyngeal mucosa is important to avoid unnecessary wound healing problems. Importantly, any undue tension on the suture line should be avoided. This means that purely

Figure 113-11. **A,** Creation of a stoma in a separate fenestra in the lower skin flap, with subsequent meticulous skin to mucosa suturing covering the intact tracheal cartilage. **B,** An immediate postoperative example of a primary tracheoesophageal puncture with immediate insertion of the voice prosthesis (in most cases an 8-mm long prosthesis is sufficiently long) (video clip available on website).

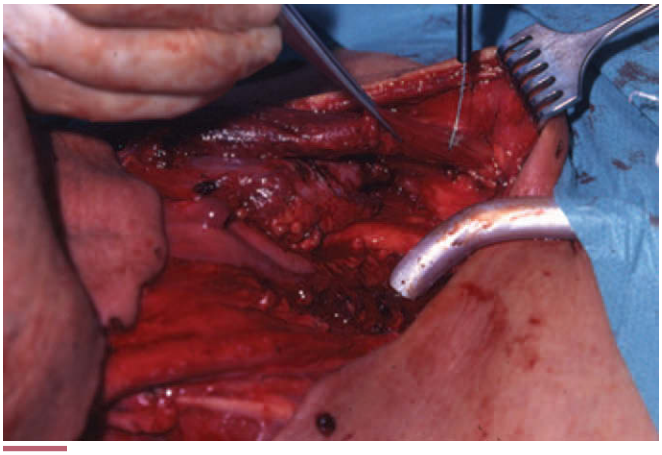

Figure 113-12. Cutting of the sternal attachment of sternocleidomastoid muscle on the left; the right side is already sectioned (video clip available on website).

vertical or horizontal closure of the pharyngeal defect seldom is possible. To avoid undue tension, the closure should be T shaped, with a variable length of the horizontal and vertical bar of the T (Fig. 113-13). If the trifurcation is reinforced with an extra submucosal stitch, there is no increased fistula formation. Most experts agree that this closure also avoids pseudo-vallecula formation, which seems to occur more frequently when a pure vertical closure is used as a standard.

Postoperative Management

Alimentary Care

Postoperative management initially involves nutritional intake through a feeding tube and stoma care. Early removal of the feeding tube, even as soon as the second postoperative day, and the commencement of a liquid oral diet seems feasible without an increased fistula rate.[42] After 8 days, mostly a soft, solid, normal diet can be resumed.

Pulmonary Care

Stomal care consists of the immediate postoperative application of an HME attached by a peristomal hydrocolloid adhesive and housing (Fig. 113-14). The early use of an HME avoids noisy external humidifiers while the patient easily adjusts to the breathing resistance of the HME, which is somewhat lower than the normal upper respiratory tract resistance.

Secondary Prosthetic Voice Rehabilitation

Secondary prosthetic voice rehabilitation is a simple endoscopic technique with antibiotic prophylaxis; in failed esophageal speakers hypertonicity is more likely to be present and might require secondary treatment (e.g., chemodenervation [Botox], myotomy).

In relation to prevention of problems with secondary tracheoesophageal puncture (TEP) and immediate prosthesis insertion (also in this case the method of choice; two video clips of standard and alternative methods are available on the website), there are several issues worth mentioning. If the patient is a failed esophageal speaker, there is a chance that the cause for this failure is hypertonicity of the PE segment.[48] This means that the medical professional and the patient have to anticipate further treatment before optimal fluent voicing can be achieved (see later for secondary hypertonicity treatment). With respect to the endoscopic technique when using a standard rigid esophagoscope, it is important to ensure the puncture is made high in the trachea (approximately 5 to 10 mm from the mucocutaneous border). This position makes the daily maintenance of the device by the patient (cleaning with a brush, or flushing, or both) and replacement by the medical professional in the outpatient clinic easiest. Further, the puncture should be done with a sharp trocar, preferably not with a scalpel incision or too wide of a fistula tract may result. As in primary TEP, the length of the prosthesis still can be mostly 8 mm, although slightly more often a longer prosthesis has to be used; the thickness of the party wall can be judged well through palpation through the stoma onto the esophagoscope. However, special measuring devices or prepuncture ultrasound can also be used. Because the prosthesis can be inserted immediately, patients can resume an oral diet almost immediately after the procedure and can begin voice and speech rehabilitation the same day. Finally, in order to prevent local infection, as in all "clean-contaminated" head and neck surgery, broad-spectrum antibiotic prophylaxis should be applied during TEP.

Prosthetic Voice Rehabilitation and Radiotherapy

Radiotherapy up to the normal doses of 70 Gy in 7 weeks and its equivalents, as well as planned postoperative radiotherapy, are not contraindications for TEP and immediate prosthesis insertion.

Many surgeons are reluctant to perform a TEP in patients needing a TL for a recurrence after chemoradiotherapy or in patients with advanced disease needing postoperative radiotherapy. In cases of radiation failure, the potential for an increased risk of complications, especially fistula development, may bias one to avoid creating a fistula. Nevertheless, there is enough evidence in the literature that this controlled fistula formation does not increase the incidence of wound complications and that, as such, TEP with immediate insertion of a voice prosthesis is a safe and reliable method.[14,32,39] The only warning is that after radiotherapy, one should wait 6 weeks to let the radiation side effects heal before performing a TEP (Box 113-1).

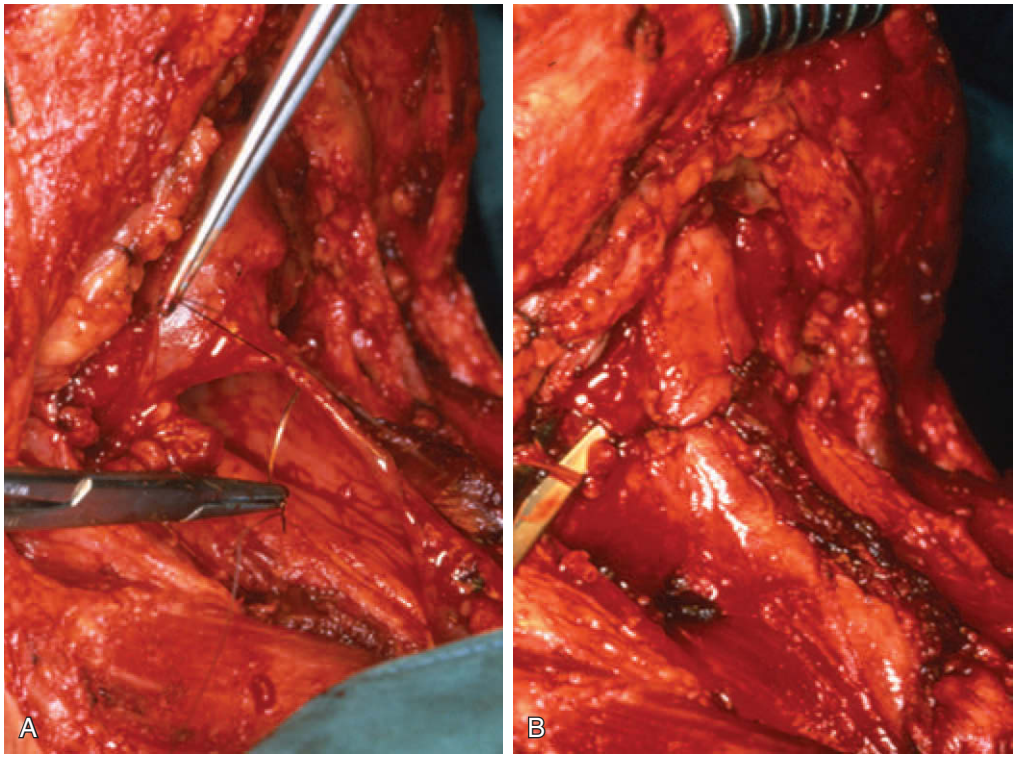

Figure 113-13. Mucosa and constrictor pharyngeus muscle closure in T shape to avoid pseudovallecula formation. **A,** Closure of the pharyngeal defect in a T-shaped manner. **B,** Pharynx after closure of the middle and inferior constrictor pharyngeus muscles. Suture these to the suprahyoid musculature. The instrument on the right side of the neck is identifying a plexus pharyngeus branch, which should be left intact.

Prosthesis Replacement and Maintenance

Indications

Voice prostheses are semipermanent implants with a limited life span. Leakage of fluids through the voice prosthesis is the most frequent reason for replacement of the device.

Silicon rubber voice prostheses, irrespective of the brand applied, are semipermanent devices that have a limited life span. The life span of prostheses shows considerable variation; in the literature mean device life spans of 4 to 5 months are found in the Western world, but much longer device life spans (10 to 18 months) are described in the Mediterranean and United States.[14,32,41,52-59] However, it is more important to look at the median device life span, which is a better reflection of the clinical practice, because the mean is often strongly influenced by a limited number of patients with long-lasting prostheses, sometimes up to 11.5 years.[14]

The main reason for replacement is leakage of fluids through the prosthesis, which signals incomplete closure of the valve. Although patients can temporarily apply a plug into the prosthesis to prevent aspiration, eventually replacement is necessary. For indwelling prostheses, this means an outpatient clinic procedure, which is easy because of the availability of anterograde replacement procedures.[34,60] The most common reason a valve starts to leak is because of growth of *Candida* species on the valve mechanism, which prevents its proper closure.[61] Measures to limit this *Candida* growth such as using antifungal drugs (e.g., Nystatin, Diflucan) are debated, but there is limited clinical evidence about their effectiveness.[62,63] A better option is to check the patient's diet and advise the consumption of probiotics such as certain yogurts that have proven effective in both in vitro and in vivo studies.[64-67]

A second reason for early prosthesis failure is the inadvertent opening of the valve due to a negative pressure created in the esophagus during deep breathing and swallowing. Especially during deep breathing, a negative pressure is created inside the thorax and thus also inside the esophagus. Normally this is of no consequence because the upper esophageal sphincter is preventing air from flowing into the esophagus. But with a voice prosthesis present under the level of the sphincter, the valve can open and air can be sucked in. Consequently, these patients often complain of disturbing aerophagia. The easier opening of the valve, perhaps in conjunction with a delayed closure, causes leakage to occur more readily. Increasing the airflow resistance of the valve could limit this problem but would create a voicing problem. Recently a special voice prosthesis (Provox ActiValve) that eliminates both the problem of *Candida* growth on the valve mechanism and the inadvertent opening by negative pressure became available.[68] This was accomplished by creating a valve mechanism made of Teflon-like material, insensitive to *Candida* growth, with built-in magnets to counteract the underpressure in the esophagus. This device appears to offer a good long-term solution for *Candida* and negative pressure–related short prosthetic life spans. In a group of patients who required an early replacement of their standard voice prosthesis after a median of 21 days, insertion of the modified device led to a median life span of 336 days.[69]

Internal blockage of the valve itself preventing proper voicing is a rare problem, and blockage is caused mostly by interference of the mucosa with the valve function. This issue and other indications for prosthesis replacement such as leakage around the device and local fistula problems are discussed as follows.

Replacement for Valve Incompetence—Transprosthetic Leakage

With any prosthesis replacement, the proper length of the device should be carefully checked even if there is "only" leakage through the prosthesis.

In case cleaning the valve with a brush or flushing device does not solve transprosthetic leakage, replacement of the device is required.[34,52,60] The preventive action to be taken in any replacement is carefully checking the length of the valve, even if there is no sign of periprosthetic leakage. By gently pulling at the tracheal flange with a hemostat, it is easy to assess whether the length is still good or the prosthesis has become too long in relation to the mostly gradually decreasing length of the fistula. The ability to move the device up to 2 to 3 mm in an anteroposterior

Figure 113-14. Use of a heat and moisture exchanger (HME) in a peristomal hydrocolloid adhesive **(A)** is safe for the healing incision, hygienic, and obviously less noisy than an external humidifier **(B).** And depending on the local health insurance system, it also may be a more cost-effective prevention and treatment of possible postoperative pulmonary sequels. Most HMEs are capable of retaining 60% of the extra water loss through a stoma, which in 24 hours is 500 mL more than in normal nasal breathing.

direction is not only tolerable but indicates that there is little or no pressure from the flanges on the mucosa. More than 3 mm in movement is an indication to downsize the prosthesis one level (e.g., from 8 to 6 mm). Care should be taken not to create a fit that is too tight, which may cause pressure of the flanges on the mucosa, leading to edema and further tightness or even tissue necrosis (see later discussion). In patients needing frequent replacements (weeks up to 2 months), one could consider the application of a Provox ActiValve, as described earlier.

Replacement for Valve Discrepancy—Periprosthetic Leakage—Too Long Prosthesis

Periprosthetic leakage is usually the result of subsiding postsurgical edema, for which downsizing of the device is recommended.

Valve-fistula discrepancy leads to periprosthetic leakage. In most instances this is a result of the natural gradual decrease of the thickness of the tracheoesophageal party wall. Subsiding surgical edema and tissue inflammation leads to a shorter fistula tract causing a once well-fitting prosthesis to become too long. This can result in piston-like movement of the prosthesis within the fistula tract, causing liquids to be squeezed around it. Because subsiding edema and inflammation are normal in the healing process, they are not considered to be complications and the solution is simply to insert a shorter prosthesis.[14] One should avoid downsizing more than one level at once in order to prevent excessive tightness, as previously described.

Box 113-1

Pros and Cons of Primary Indwelling Voice Prosthesis Insertion

The retrograde insertion technique, preferably using a special trocar, cannula, and guidewire, diminishes the risk of separation of the tracheoesophageal party wall. To some extent, the device stabilizes this wall.

The tracheal and esophageal flanges of the device give optimal protection of the TE fistula against leakage of saliva and gastric fluids.

There is less irritation of the tracheostoma and pressure on the fistula tract compared with a feeding tube taped to the skin of the neck.

There is no postoperative interference with a cannula or heat and moisture exchanger, or both.

Early postoperatively, patients can quickly become familiar with the care for their voice prosthesis as instructed by the nurses or other professionals (e.g., speech pathologists, surgeon).

There is no need for fitting the prosthesis in the early postoperative phase at a time when the stoma may still be sore from healing, and the patient's mental and physical status is not yet optimal.

Around the tenth postoperative day, there can be an immediate focus on voicing itself, which can give a tremendous psychologic boost to the patient.

Postoperative radiotherapy is not a contraindication and most patients develop a useful voice before the start of radiation treatment.

The first TEP prosthesis replacement is usually months later when wound healing is completed, surgical edema has subsided, and patients are generally in a better physical and mental state.

This approach allows the speech pathologist to maintain an active role in the multidisciplinary rehabilitation team.

The only disadvantages to the early insertion of voice prostheses are the necessity to use nasogastric feeding tube during the early postoperative period and the expectant but temporary deterioration of the voice during the postoperative radiotherapy phase. For the latter issue, the reassuring role of the speech pathologist is important because most patients retain a useful voice that will regain its original quality in the majority of individuals. The advantage of being able to communicate using the restored voice through this difficult period of treatment outweighs any disadvantage related to its quality.

Nonindwelling Voice Prostheses

With the exception of aspiration, the use of nonindwelling prostheses does not necessarily lead to other complications encountered with the indwelling types. Because of the more flimsy retention collars, nonindwelling prostheses are more prone to fall out of the tracheoesophageal fistula tract.[70] Because the majority of patients with nonindwelling devices can change the prostheses themselves, the advantage is self-management of problems with valve leakage. Consequently, if cleaning of the device fails to restore the valve, the prosthesis can be discarded and a new valve inserted. However, the spectrum of problems with the tracheoesophageal fistula can be encountered with nonindwelling prostheses, too, and patients should be instructed to consult their SLP or head and neck surgeon whenever their normal voice deteriorates. The solutions to address the problems are essentially the same as mentioned for the indwelling prostheses, as outlined next in the troubleshooting section.

Troubleshooting Prosthetic Voice

Adverse events occur in approximately one third of the patients, but such concerns require replacement of the prosthesis in only about 1 out of 10. Clinics supporting patients with voice prostheses should adopt a protocol for handling all known adverse events, and patients should be instructed to report their problems in a timely fashion.

As with any surgical and prosthetic method, complications and adverse events must be taken into account. However, most problems can be solved using routine diagnostic procedures and solutions. The occurrence is relatively common because one third of patients in a large series occasionally had problems.[14,71] Nonetheless only 10.7% of 318 patients followed for more than 5 years required prosthesis replacement because of an adverse event.[14] The complication rate is higher for patients who have had radiotherapy, but not to the extent that it would prohibit the use of voice prostheses. On the contrary, prosthetic voice rehabilitation is successful in the majority.

Patients with voice prosthesis problems, which often gradually develop, tend to postpone the visit to the clinic until "the last minute." Therefore it is important for any clinic dealing with TL patients to have a comprehensive straightforward protocol for dealing with all the known complications and adverse events. If this protocol is known by the clinicians in charge of this patient group, dealing with these occasional problems is hardly more time consuming than dealing with the regular replacement procedure needed for a leaking valve. Clinicians should instruct patients to seek clinical attention as soon as they notice a change in their voice. The sooner a problem is identified, the easier it can be corrected.

Atrophy of the Fistula/Party Wall or Too Wide of a Fistula

Atrophy of the party wall occurs in about 3% of the prosthesis replacements in 18% of the patients, ultimately leading to temporary fistula closure in 6% and to permanent closure in 1 of 318 patients.[14] Although many studies have revealed that radiotherapy does not significantly influence the outcome of prosthetic voice rehabilitation,[14,39,57,72-74] it is correlated with a higher incidence of complications during follow-up including atrophy.[14] Gradual thinning of the tracheoesophageal tissues is a naturally occurring process. Only in a minority of cases does it lead to such a short fistula tract that the shortest voice prosthesis (4 to 4.5 mm length) is still too long to ensure proper sealing of the fistula. The problem of atrophy becomes more difficult to handle if there is also a substantial widening of the fistula tract. A fistula tract that is too wide can also be caused by infection or (pressure) necrosis or making too long of an incision when creating the fistula tract. All of these causes can to some extent be avoided using a good technique and early intervention.

Algorithm to Solve Atrophy/Periprosthetic Leakage

An algorithm for periprosthetic leakage not solvable with a shorter device follows: 1a. Shrinkage; 1b. Washer; 2. Purse-string suture; 3. Augmentation; 4. Surgical closure.

If the party wall is thinner than 4 mm, there is a fair chance that a 4- or 4.5-mm prosthesis is not able to seal the fistula enough to prevent *periprosthetic* leakage. If this algorithm is followed, few patients will need the last option (i.e., closure of the TEP).

1a. Shrinkage: Although still a valid option, this is seldom applied today because it is cumbersome for the patient. Removal of the prosthesis and letting the fistula shrink for a few days is effective but requires a feeding tube and a cuffed cannula to prevent aspiration. Therefore the next option is preferred.

1b. Silicon washer: This is a thin silicon disk (we use a custom-made device: outer diameter 18 mm, inner diameter 7.5 mm, thickness 0.5 mm) punched out with a tailored punch. The washer can easily be moved behind the tracheal flange and around the shaft of the prosthesis with the help of two hemostats (like pulling a button through a buttonhole). The washer is not intended to compensate for a prosthesis that is too long but to adhere to the mucosa by surface tension; hence it should not be thicker than 0.5 mm (Fig. 113-15). This is a reliable and easy first solution for most of the "leakage around" cases, as shown in a 3-year clinical study of 32 patients.[75] Under optimal circumstances with a physician in the background, application of this washer probably can be carried out by a qualified SLP or oncology nurse as well. If the application of the washer fails to solve the periprosthetic leakage, the patient needs one of the next options.

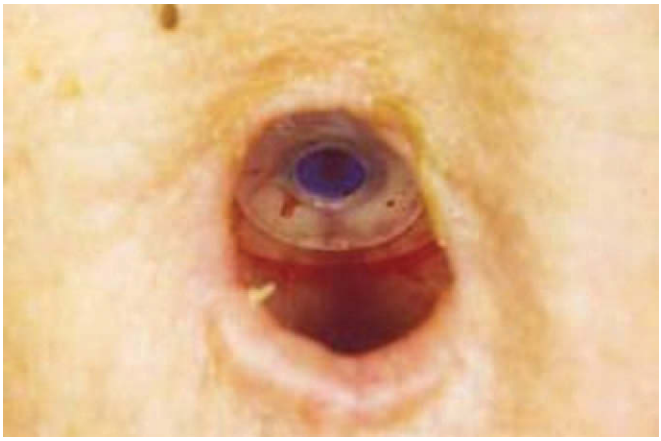

Figure 113-15. Example of a thin (0.5-mm thick) silicon washer behind the tracheal flange of the voice prosthesis blocking periprosthetic leakage in case of atrophy or scarification of the tracheoesophageal fistula.

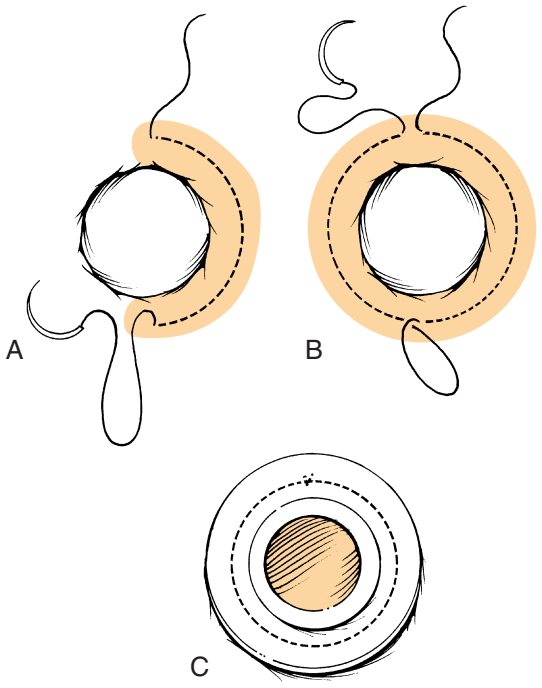

Figure 113-16. Purse-string suture: A 3-0 atraumatic Vicryl suture is inserted at 12 o'clock, curved submucosally to 6 o'clock **(A),** inserted again, and curved submucosally on the other side to 12 o'clock **(B).** After insertion of a new prosthesis, the suture is gently tightened pulling the tissues against the shaft of the prosthesis and preventing further leakage around the device **(C).** The suture should be left to degrade spontaneously, potentially enabling tissue augmentation. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

2. Purse-string suture: If the tissues are not too atrophic and the fistula is not too wide, a purse-string suture using 3-0 atraumatic vicryl is an effective and quick physician's solution. After removal of the prosthesis, the suture is started at 12 o'clock with the needle curving submucosally at a distance of 1 to 2 mm from the edge of the fistula

until 6 o'clock. Next, the needle is inserted at 6 o'clock and curved submucosally on the other side until 12 o'clock (Fig. 113-16). Sometimes three steps are easier to make (i.e., from 12 to 4, from 4 to 8, and from 8 to 12 o'clock). After placing the suture, a new prosthesis is inserted and the suture is gently tightened to pull the mucosa against the prosthesis. This procedure is always successful in the short term, and by letting the suture degrade spontaneously, it can have a tissue-augmenting effect, solving the problem also in the long term. However, if repeating this procedure once or twice does not have the intended permanent effect, the next step in the algorithm should be considered. Jacobs and colleagues[76] recently published a refinement of this method (they "buried" the suture knot submucosally, probably enhancing the efficiency of the method) and the positive long-term results that can be obtained.

3. Augmentation of party wall: Permanent augmentation of the party wall with a nondegradable product like bioplastic is highly successful and described in several papers.[77,78] The same effect can be achieved with injection of autologous fat or GAX collagen, but bioplastic probably gives the best permanent effect and is safe to use in everyday clinical practice.[79,80] Another option might be the use of granulocyte-macrophage colony-stimulating factor to induce a sterile inflammation to augment the fistula tract.[81]

4. Fistula closure and later secondary puncture: If all measures mentioned previously fail or in case there is a too wide of a fistula with a lack of tissue to be tightened around the prosthesis or augmented, fistula closure is unavoidable. Because most fistulas are completely epithelialized after 6 months, they must be dissected and closed in three tissue layers.[82] This can be best achieved by approaching the fistula from above, separating the esophagus and trachea until just caudally of the fistula, sectioning the fistula, closing the esophageal side in two layers and the tracheal side in one, and closing the skin in layers. If the tissues are fibrotic, one can consider swinging the sternal head of the SCMM in between the trachea and esophagus or using a fascia graft to enforce the esophageal and tracheal suture lines.[82] Generally, repuncture with immediate prosthesis insertion can be carried out after 6 weeks.

Sometimes larger fistulas cannot be closed in this way and tissue augmentation/addition must be performed by using a properly tailored pectoralis major muscle-fascia flap, occasionally using a split-skin graft, fixed with tissue glue, for coverage on the tracheal side. Unintended widening of the TE fistula is often related to unsuccessful local TE fistula closures via the tracheostoma. These cases can be difficult to treat. If the esophageal side cannot be closed primarily, the mucosa can be sutured to the fascia of the PM flap and that side of the defect will epithelialize secondarily. A skin island on the flap is often too bulky and is rarely necessary. Seldomly, more extensive surgery must be applied (e.g., free radial forearm flap, gastric pull-up). No standard procedure for these situations exists—a tailored approach is required.

Scarification of the Fistula

Scarification of the fistula is something seen mostly if the TEP is not punctured (e.g., with a trocar and cannula) but done through a vertical incision. This can result in an incompletely round fistula tract with a retraction on a certain spot. Patients then complain that the periprosthetic leakage always comes from the same spot (e.g., leakage at 11 o'clock). In this case the same algorithm as provided earlier is applicable: first a washer can be tried,[75] next a purse-string suture, and then tissue augmentation, with the latter method being used more readily because only the small retracted scar region has to be augmented. Permanent closure in these situations is therefore less common because mostly there is no clear atrophy of the fistula.

Infection of the Fistula

Infection of the fistula can be treated with a broad-spectrum antibiotic without removing the prosthesis; one should make sure that the device is long enough in the swollen fistula, and if needed a longer prosthesis should be inserted.

Local infection is occasionally seen in approximately 10% of the patients. Treatment is usually simple. Because local infection leads to swelling of the tissues, it is important to decrease the resulting pressure of the flanges onto the mucosa. If the prosthesis was originally fitted well, this means that in such a case the prosthesis must be replaced with a longer device. More often than not, one has to upsize at least two sizes (e.g., from 6 mm to 10 mm) to allow for a proper fitting in the infected fistula. In case of a local infection, temporary removal of the prosthesis should be avoided because that will most likely lead to a permanent closure of the TEP, leaving the patient unnecessarily speechless for a certain period. Broad-spectrum antibiotic treatment in most cases solves the infection. Subsiding of the swelling will eventually make the prosthesis too long and potentially prone to periprosthetic leakage, but this can take several months, and by that time the device likely has to be replaced for transprosthetic leakage anyway.

Hypertrophy of the Fistula

Two forms of hypertrophy of the fistula tissues exist:

1. Anterior hypertrophy.
   This consists of excessive fibromatous or granulating mucosa, potentially leading to complete overgrowth of the tracheal flange. Anterior hypertrophy is seen mainly in patients requiring a trachea cannula, which can exert pressure on the prosthesis, or in patients with prostheses that are too short and drawn inward. Obviously, the prosthesis should be of the correct size and the use of a cannula should be avoided. If this is not possible, a stoma plasty should be considered.[83] Sometimes it is necessary to remove the excessive tissue because it bulges too far forward into the trachea, decreasing the airway too much. For this, any form of electrocautery or (laser) resection can be used.

2. Posterior hypertrophy or esophageal pocket.

Posterior hypertrophy (i.e., formation of an esophageal pocket) leads to strained voicing and slight bleeding during brush cleaning; once diagnosed it is easily correctable by inserting a long prosthesis to "fistulize" the excess tissue of the pocket.

This phenomenon is sometimes incorrectly called a *separation of the party wall.* It forms an important problem in daily practice because it is not always obvious and its diagnosis is often delayed. These patients typically complain about a deterioration of their voice (more strained) and getting some blood at their brush while cleaning the inside. Often even an overt esophageal pocket is formed with eventually complete mucosa overgrowth on the backside of the prosthesis. Once suspected, it is easy to diagnose by careful inspection of the fistula with a thin (flexible) endoscope through the prosthesis, or after removal of the prosthesis it can often be seen directly. The solution is also simple: Inserting a longer prosthesis (at least two sizes longer), which encompasses the excess tissue in between the flanges, will immediately restore the patient's voice and lead to "fistulizing" the excess tissue. Anterograde insertion can be accomplished in most cases, but it is wise to overshoot the device (i.e., push the complete prosthesis into the esophagus and then pull the tracheal flange in situ with a hemostat to ensure the proper position of the esophageal flange on the backside) (Fig. 113-17). Seldomly, the traditional retrograde insertion method must be applied, and rarely this procedure must be carried out under general anesthesia (only if the fistula tract cannot be probed atraumatically).

Partial Prosthesis Extrusion

A prosthesis that is too short can cause pressure necrosis of the tracheoesophageal party wall, which should be avoided at all times. If a false passage develops, this can be solved by inserting a long enough prosthesis to bridge the defect and cover the false passage.

The riskiest complication is (partial) extrusion of the prosthesis. This adverse event has only been seen when a prosthesis that is too short has exerted too much pressure on the tissues, leading to local necrosis. This type of prosthesis can result from downsizing too rapidly or from a local infection. In any case, a prosthesis that is too short must be removed and replaced with a longer prosthesis to solve the problem. The new

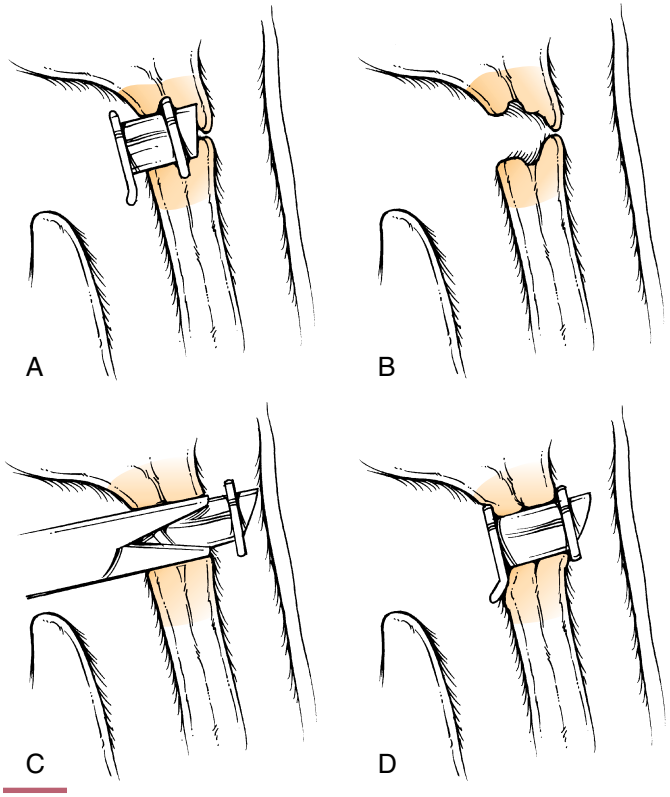

Figure 113-17. Esophageal pocket treatment: removal of the prosthesis and insertion of a sufficiently long prosthesis smoothing out the pocket. **A,** Prosthesis with esophageal flange retained in the esophageal pocket. **B,** Esophageal pocket after removal of the prosthesis. **C,** Overshooting the prosthesis into the esophagus to make sure that the esophageal flange will be in the esophageal lumen. **D,** The prosthesis correctly in place, "bridging" the extra tissue and smoothing out the pocket. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

prosthesis covers both the thickened fistula tract and the false passage. In all cases encountered, complete spontaneous healing has occurred. Sometimes excessive tissue must be removed to ensure proper fit of the new, longer prosthesis. A course of broad-spectrum antibiotics should be prescribed. Although this is potentially dangerous because of the risk of aspiration of the device "on its way out," pressure necrosis with partial prosthesis extrusion can usually be solved by replacing the too-short prosthesis with a longer device.

If the prosthesis is completely extruded and the patient cannot indicate its whereabouts, it is important to check whether the dislodgment has occurred toward the trachea or into the esophagus. In this situation a proper flexible endoscopy of the trachea and, if negative, radiologic examination (thorax and/or abdomen overview) must be conducted. If the prosthesis is trapped in the bronchial tree, it must be removed endoscopically. If the device is located in the alimentary tract, spontaneous passage can be expected in most cases.

Some Nonprosthesis-Related Problems

Hypertonicity of the Pharyngoesophageal Segment

Hypertonicity of the PE segment is the most important reason for failure to acquire fluent prosthetic speech, and chemodenervation with botulinum toxin type A (Botox) is the preferred treatment method.

Hypertonicity, although not a complication of prosthetic voicing, is still worth mentioning because it is the most important reason for failure to develop fluent speech. As already described, performing a short myotomy of the upper esophageal sphincter can be considered the most effective preventive measure to be taken during TL. However, if hypertonicity exists and intensive speech therapy is not capable of solving this, the condition warrants treatment. The easiest and least invasive option available is chemodenervation with botulinum toxin.[84,85] After proper identification of the hypertonic PE segment with videofluoroscopy, marking the segment on the skin, 100 MU of Botox (or for the alternative brand Dysport, 400 MU) is injected in the constrictor pharyngeus muscle area, preferably using a hollow electromyography needle. Interestingly, once a good result has been achieved, the effect is long lasting, in contrast to other clinical conditions in which Botox is used.[84,85] Apparently, once the patient has experienced fluent speech, through some kind of biofeedback, the effect is maintained. This phenomenon is sometimes even seen after the temporary denervation with Lidocaine injection, which should be used as a diagnostic procedure in all cases of hypertonicity. Since the availability of Botox, surgical myotomy is hardly ever necessary, although it is still an option. Care should be taken to perform a myotomy of the complete constrictor and cricopharyngeus muscle groups and to avoid fistula formation, especially in radiated patients.[86-88]

Hypotonicity of the Pharyngoesophageal Segment

Hypotonicity of the PE segment leads to a whispery and even aphonic voice and potentially can be treated surgically by creating an SCMM sling as an internal pressure band to prevent the excessive bulging of the distended PE segment.

Although not a complication of voice prostheses, hypotonicity of the PE segment can be a disturbing condition because the patient cannot produce a good sound and only has a whispering, aphonic voice. Mostly, there is no pitch detectable in the voice of patients with this condition. The sometimes extreme distension of the PE segment is caused by an inadvertent complete denervation of the constrictor muscles, which is why plexus pharyngeus neurectomy, once popular as a means to prevent hypertonicity of the PE segment,[89] should be considered with caution. Until recently, only through application of some external pressure (digital or with a special pressure band) could this problem be treated.[48] However, now an interesting surgical technique for treating hypotonicity exists (i.e., using an SCMM sling as an internal pressure band).[90] This results in clear improvement in the voice, especially because of an increase in the maximum phonation time and dynamic range.

Voice and Speech Therapy

Postlaryngectomy voice and speech rehabilitation in many countries is the domain of the SLP, but it should be stressed that optimal results are only achievable with good teamwork between the SLP and head and neck surgeon. Especially in situations where the rehabilitation process does not develop smoothly, a close collaboration among all team members leads to a quicker and better solution of the underlying problem. If clinical evaluation does not lead to a diagnosis and solution, videofluoroscopy is the best diagnostic method to analyze possible voicing problems (a video clip is available on the website).[24,49,91] For those who are interested in studying rehabilitation in head and neck cancer patients, especially TL patients, in more depth, the books by Doyle and Keith and Ward and van As-Brooks are recommended.[92,93] Some interesting reading about perceptual and acoustic research on postlaryngectomy voice and speech can be found in the publications of van As-Brooks and colleagues.[20,94]

Pulmonary Care and Rehabilitation

An HME should be an integral part of the rehabilitation protocol of laryngectomized individuals, not only in order to restore (in part) pulmonary physiology, but also to optimize prosthetic voicing.

Introduction

"Rehabilitation after TL requires more than improving voice alone",[95] and pulmonary rehabilitation is an essential and vital part of the comprehensive rehabilitation protocol after TL. Because of the short circuiting of the upper respiratory tract, TL significantly disrupts normal pulmonary physiology.[96] The disconnection of the upper and lower airways has repercussions for the conditioning—warming,

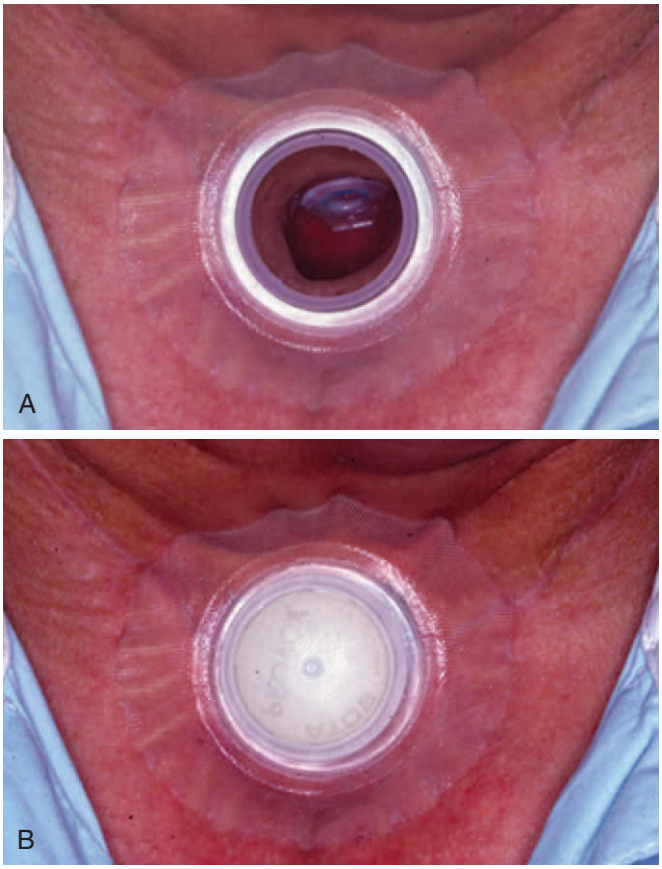

Figure 113-18. Pulmonary rehabilitation using a peristomal adhesive **(A)** with a heat and moisture exchanger **(B),** preferably applied 24/7 for optimal effectiveness, optimizing pulmonary climate.

humidifying, and filtering—of inhaled air, which is thereby precluded. There is also a loss of breathing resistance, which theoretically has a negative impact on pulmonary physiology, although less than has been postulated in the past.[97] Recent tracheal climate measurements have clearly shown that temperature and humidity decrease significantly after TL.[98-100] Especially at the end of the inspiration, both temperature (28° C instead of 32° C) and relative humidity (70% to 80% instead of 100%) are seriously below normal physiologic values. Consequently, many laryngectomized patients suffer from respiratory problems, of which involuntary coughing, excessive phlegm production, forced expectoration, and dyspnea are the most pronounced complaints.[101] These symptoms develop and tend to increase during the first 6 months postoperatively and probably well beyond that period, but later seem to stabilize. Frequently, there is an increase in respiratory symptoms during cold and wet seasonal periods. Moreover, these problems can have a serious impact on many aspects of daily life, including increased fatigue and sleeping problems, compromised voice quality, disrupted social contacts, and heightened psychological distress.[101]

Furthermore, an objective impairment of the pulmonary function of laryngectomized patients can be expected as well. The technique of pulmonary function assessment requires special attention: testing should not be performed with an intratracheal cuffed cannula, but with an extratracheal device (e.g., HME adhesive).[102] If an intratracheal cuffed cannula is used, the flow-volume loop is influenced by the internal diameter of the cannula, which is smaller than that of the trachea, resulting in lower (incorrect) values. This phenomenon does not play a role when using an external peristomal adhesive attachment. Pulmonary function studies have shown that the pulmonary function values of laryngectomized patients are significantly lower than the (age, sex, height, and race adjusted) predicted values.[29]

Heat and Moisture Exchangers

Treatment Aspects

In an attempt to restore some of the lost "nose" functions, HMEs have been introduced.[103] With these devices, placed over the stoma through special peristomal adhesives (Fig. 113-18), it appears possible to reduce the diurnal loss of water through the exhaled air (500 mL) by approximately 60%. In the aforementioned climate studies, both at standard (23° C) and cold (4° C) environmental conditions with a standard HME the intratracheal relative humidity appears to be restored to the physiologic level of 100%, although at a slightly lower temperature under room temperature conditions (under cold conditions there is a significant increase in intratracheal temperature).[98-100] In several studies the positive influence of an HME on respiratory problems (i.e., restoring intratracheal humidity) could be clinically established.[104-106] The results of the various clinical studies indicated that the regular use of an HME leads to significant improvement of the respiratory and the related psychosocial problems of laryngectomized patients. Significant reductions were found in the mean daily frequency of sputum production, stoma cleaning, and forced expectoration. Consequently several aspects of daily life (e.g., feelings of fatigue and malaise and sleeping problems) improved. Interestingly, in all studies carried out so far, the use of an HME also positively influenced voice quality. Positive HME effects also could be established objectively: A significant improvement over time in the inspiratory flow-volume values has been observed.[104]

Prevention Aspects

HMEs can prevent the development and reduce the severity of respiratory symptoms when used as soon as possible following TL, as was established in a study comparing pulmonary complaints in a regular user and a nonuser group at 3 and 6 months postoperatively.[107] Long-term use of HMEs also appears to prevent and significantly decrease pulmonary infection rates, as was demonstrated in a recent randomized study.[108] This coincides with the present clinical experience that severe tracheitis, which before the "HME era" was regularly encountered during winter, now seems to be a disease of the past. The few cases still seen are only in patients who are not compliant with HME use.

From these and other studies, it can be concluded that the only effective nonpharmaceutic treatment of pulmonary problems in laryngectomized patients is the regular use of an HME. Of vital importance is that all clinicians involved in the treatment of laryngectomized individuals—head and neck surgeon, SLP, and oncology nurse—are aware of the profound pulmonary physiologic changes TL brings about and of the necessity to prescribe HMEs for the prevention and treatment of the otherwise inevitable pulmonary problems patients will suffer from.

Compliance Aspects

The recent development of more specialized systems has reduced problems with peristomal attachment and airtight stoma closure necessary for voicing, which has resulted in an improved compliance rate.[109,110] An interesting side effect of these specialized devices is a reportedly better intelligibility of the prosthetic speech, which is brought about by a longer maximum phonation time and a wider dynamic loudness range.[28,109] However, still more development is necessary to optimize the peristomal or intrastomal attachment of these indispensable medical devices such as HMEs and automatic speaking valves (see later).

Early Postoperative Pulmonary Hygiene

Another step forward in recent years is that through the availability of colloid adhesives these HMEs can be used from the first postoperative day onwards, even with the stitches still in situ, as discussed earlier in the section on postoperative management and pulmonary care. Also as described earlier, it is virtually always possible to create a stable tracheostoma that does not need a cannula to be kept open, and this colloid adhesive can easily be glued to the peristomal skin (Fig. 113-19). Also, when patients still need a cannula to keep the stoma open, some systems allow the simultaneous application of an HME.[111] This makes external

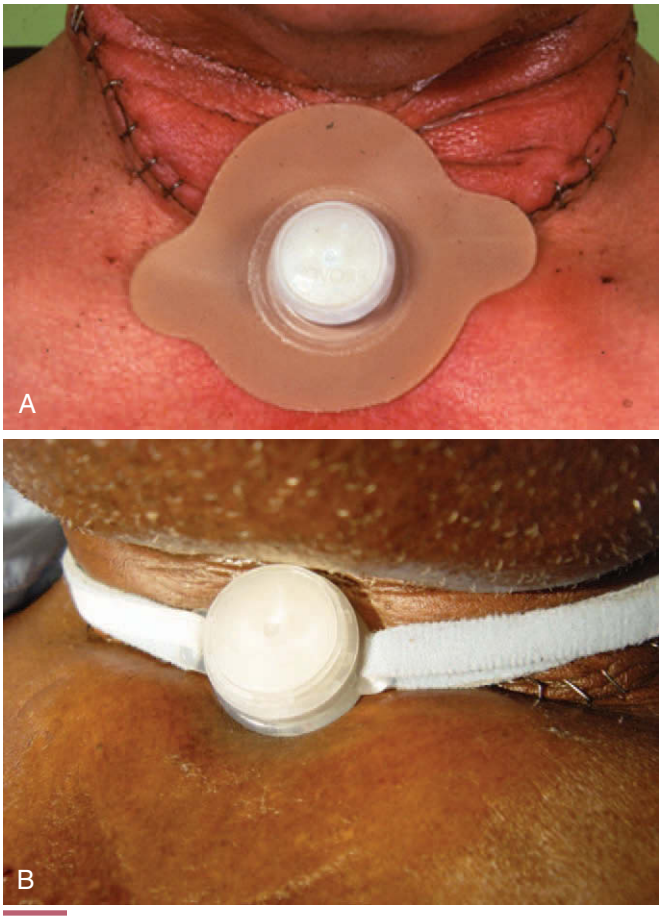

Figure 113-19. Early postoperative application of a heat and moisture exchanger using a colloid adhesive **(A)** or special cannula **(B).**

humidification superfluous, and depending on the local insurance situation, this mostly also appears to be cost-effective. This custom has several other definitive advantages: the patient has optimal stoma protection as early as possible, noisy external humidification is avoided, the patient gets used to the HME early (no problem with the airflow resistance of the device because this is lower than the preoperative upper airway resistance), the stoma has a well-cared appearance for the family and other visitors, and spreading of sputum during coughing is diminished.

Another advantage of using an HME immediately postoperatively concerns the early onset of voice rehabilitation. Often, patients are somewhat reluctant to start with speech therapy because it can be difficult to "digitally" close the not yet ideally healed stoma, which may still be sore. By applying an HME, the patient can start speech therapy and properly close the stoma digitally and hygienically, without undue pressure on the healing stoma.

Hands-Free Speech

A drawback of prosthetic speech is that the patient needs to occlude the stoma with a finger. Not only does this lead to the uncomfortable occupation of one hand, but also increases the "visibility" of the patient's handicap (i.e., being pointed at in conversation). This is still the case when the patient is using an HME. Applying an automatic speaking valve (all of which presently incorporate an HME) can solve this problem.[112-114] Although the success rate is still quite moderate with approximately 25% of daily users, with more modern and technically advanced devices (Fig. 113-20) it seems possible to increase the percentage of patients who can successfully apply an automatic speaking valve and HME as an additional rehabilitation tool for specific occasions such as shopping and social visits.[115]

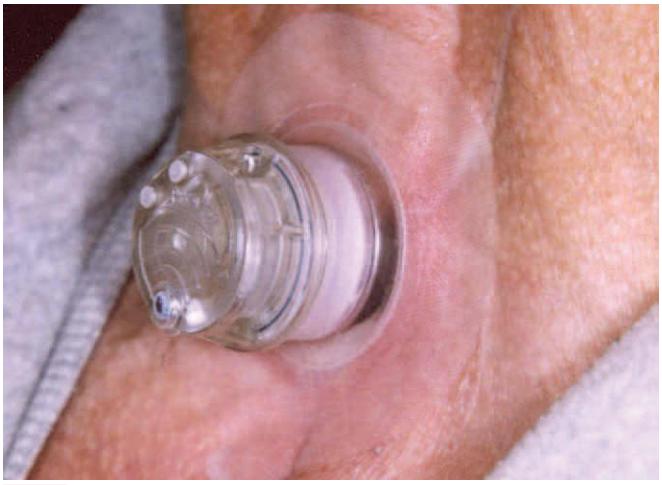

Figure 113-20. Patient with an automatic speaking valve to enable hands-free speech.

Conclusions of Pulmonary Rehabilitation

The use of an HME can effectively reduce the physical and psychosocial problems after TL. Continuous use of an HME, both day and night, is advisable to obtain an optimal pulmonary rehabilitation effect. With the availability of special colloid adhesives, early postoperative application is feasible and early pulmonary hygiene and voicing are improved. Early postoperative application also improves short- and long-term compliance with the use of HMEs because digital stoma occlusion is greatly assisted. Ideally, a combination of an HME and an automatic valve should used. It must be emphasized again that an HME is a medical device that should be prescribed with proper counseling of patients in order to obtain optimal results.

Olfaction Rehabilitation

Deterioration of the sense of smell seems an inevitable consequence of TL.[21] This bothering side effect of the operation is caused by disconnection of the upper and lower airways, which results in breathing through a tracheostoma in the neck, and thereby absence of nasal airflow. Therefore, odor molecules are no longer passively reaching the olfactory epithelium* and patients are effectively anosmic despite the fact that the olfactory system is essentially intact (Fig. 113-21). Over the years, several studies have established this problem, without finding a solution for this nuisance. Most patients actually seem to accept this problem, probably because of proper counseling before the surgery and the lack of an effective rehabilitation method.[21,116] The absence of complaints about this problem is surprising in view of the many patients visiting the otolaryngology practice when they experience a sudden or gradual loss of the sense of smell. In laryngeal patients this is apparently considered to be an unacceptable symptom of what is often suspected to be a sign of a serious underlying illness.[117]

In order to prove that the sense of smell is essentially intact if there would be a nasal airflow, the larynx bypass is a useful instrument.[118-120] This device consists of a mouthpiece, a tube, and an attachment possibility of that tube to the stoma (Fig. 113-22). By connecting the mouth with the stoma and subsequently breathing in through the nose, a nasal airflow is provoked. This allows odor testing, and it could be shown that in most laryngectomized individuals the sense of smell is

*Two types of smelling exist: passive and active. Passive smelling is a bonus of normal nasal breathing: During inhalation through the nose, odor molecules can reach the olfactory epithelium in the upper regions of the nasal cavity and provoke an olfactory stimulus. This often results in active smelling or sniffing in order to identify the odor and its source. After TL, passive smelling is mostly absent and only few patients have some spontaneous capability of active smelling.

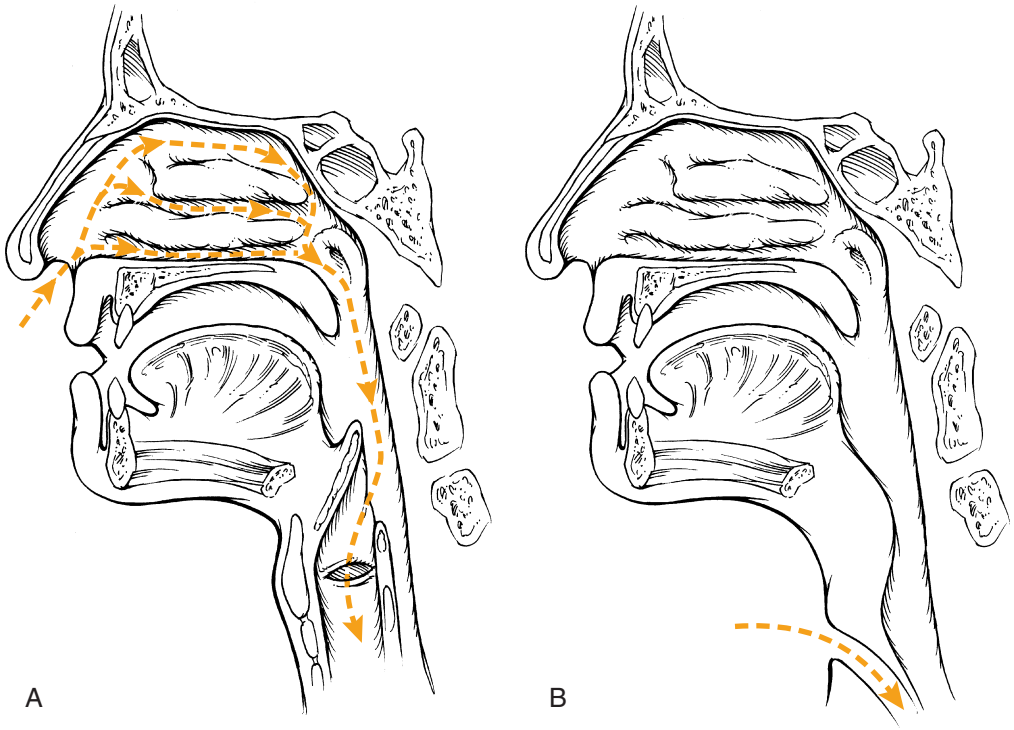

Figure 113-21. **A,** Normal nasal breathing and passive smelling. **B,** Stomal breathing without a nasal airflow, resulting in anosmia. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

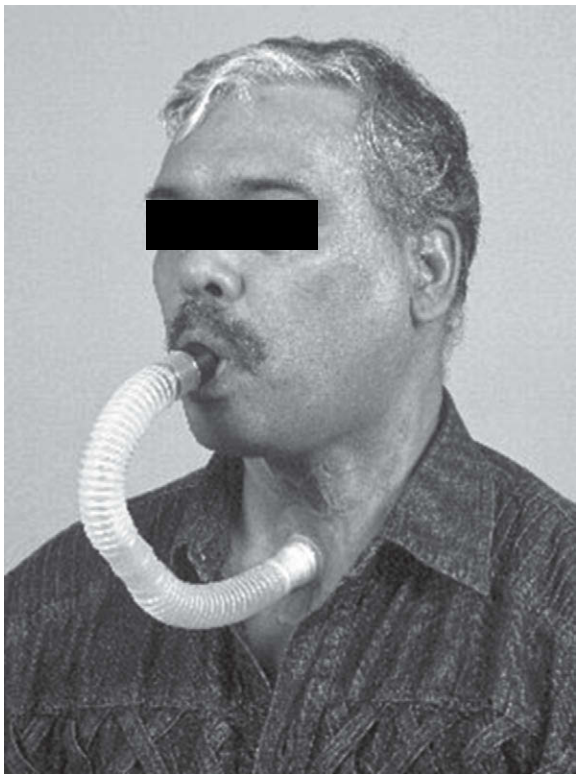

Figure 113-22. Larynx bypass, connecting the oral cavity with the stoma. Breathing through the nose results in nasal airflow and allows olfaction again.

intact. However, for obvious reasons, this is not a useful instrument to rehabilitate the olfactory acuity in everyday life.

Recently, this problem has been studied in depth, and again the magnitude of this problem was established.[116] On the basis of two odor tests and standardized questionnaires, it was found that more than two thirds of a cohort of 63 laryngectomized individuals were effectively anosmic (nonsmellers). Careful observation of the patients, who scored positive on one or both of the odor tests (smellers) revealed that they used their facial muscles more often. Furthermore, most of these patients were using their smell technique unconsciously and had discovered it all by themselves.

Analyzing the observed movements of the facial muscles, the conclusion was that some movements actually result in a nasal airflow, which allows the odor molecules to reach the olfactory epithelium again. Refining these observed movements led to the conception of a nasal airflow inducing maneuver (NAIM) or so-called "polite yawning" technique.[121] This technique induces a rapid increase in volume of the oral cavity while keeping the lips closed airtight. The potential vacuum, prompted by the expansion of the oral cavity, has to be filled. The result is an airflow through the nasal cavity (Fig. 113-23). By repeating this maneuver rapidly, a pumping effect is created and a sufficient airflow through the nose is established in order to smell again.

The effectiveness of the NAIM was established in an intervention study and subsequently confirmed in a follow-up study.[121,122] Approximately half of the patients were able to smell again after one half-hour training session. Also, 25% of the patients in this series, who were already able to smell with a personal technique, indicated an improvement. After instruction by the speech pathologist, they were much better able to initiate a nasal airflow and could much better smell at will. Recently, these results were confirmed and it also became clear that a longer and intensified rehabilitation period further increases long-term olfaction rehabilitation results.[123,124] A comprehensive book on olfaction rehabilitation was published recently, and this information is also available on the Internet (www.hoofdhals.nki.nl/olfaction/Start.aspx).[125]

Conclusions of Olfaction Rehabilitation

Olfaction rehabilitation in laryngectomized individuals should form an integral part of the rehabilitation program, deserving as much attention

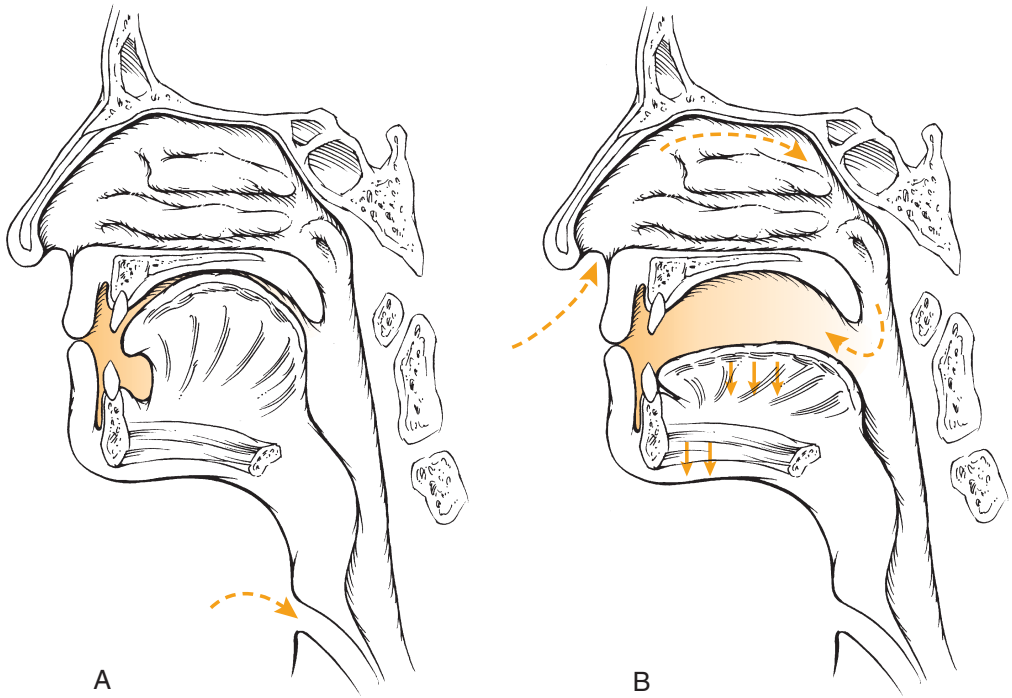

Figure 113-23. Schematic illustration of the nasal airflow inducing maneuver or "polite yawning" technique for olfaction rehabilitation after total laryngectomy. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

from the multidisciplinary team as the other two postlaryngectomy fields of interest (i.e., voice and speech rehabilitation and pulmonary rehabilitation). For head and neck surgeons it is important to know when counseling potential TL patients that this once seemingly insolvable problem now can be rehabilitated effectively by the SLP. The nasal airflow inducing maneuver or polite yawning technique forms an excellent instrument for the SLP to address this disturbing problem, resulting in a clear improvement not only in olfaction, but also in taste perception, and thus in an improved quality of life.

Quality of Life after Total Laryngectomy

With any oncologic treatment it is important not only to address the various (local, regional, and distant) control rates of the disease, but also to study the effects of the treatment on quality of life. Especially with an oncologic treatment as effective as TL, the long-term sequelae of the treatment are important to take into consideration when counseling patients. Clinicians are increasingly shying away from surgical, organ-sacrificing treatments like TL and favoring organ-preservation chemoradiotherapy treatments (CRTs). However, organ preservation is still not synonymous with function preservation and CRT has not always led to improved functional results, especially in advanced larynx cancer.[126,127] Data indicates that CRT has even decreased long-term cure rates.[128]

With all the postlaryngectomy rehabilitation options available, it is important to weigh the pros and cons of the various treatment options carefully. Wayne Koch[27] eloquently discussed quality-of-life issues in laryngectomized versus chemoradiated patients in a review, stating: "Tracheoesophageal puncture has made high-quality voice restoration readily available to most individuals who must undergo TL. Although none of these patients would voluntarily choose to undergo a TL if not faced with a life-threatening condition, at least some achieve better quality of life, including better vocal function, after treatment and rehabilitation (than chemoradiated patients). Although far from perfect, TL with tracheoesophageal puncture affords both quality and quantity of life to a group of individuals who currently have no alternative but to undergo debilitating surgery in an effort to extend their lives." Adding pulmonary and olfaction rehabilitation to this description, the present comprehensive postlaryngectomy rehabilitation possibilities to establish and maintain an acceptable quality of life are clear.

SUGGESTED READINGS

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CHAPTER ONE HUNDRED AND FOURTEEN

Diagnosis and Management of Tracheal Neoplasms

Chadrick Denlinger

G. Alexander Patterson

Key Points

- Ninety percent of primary tracheal tumors in adults are malignant.
- The incidence of tracheal squamous cell cancers and adenoid cystic tumors is equivalent, and together they account for 75% of all primary tracheal tumors.
- The 5-year survival for resectable squamous cell cancers is 45% and is influenced by the presence of positive mediastinal lymph nodes.
- The 5-year survival for adenoid cystic carcinoma is 55% and is not significantly affected by the presence of positive resection margins or pulmonary metastasis.
- Half of the trachea can be safely resected and anastomosed primarily.
- Unresectable tracheal tumors have a poor prognosis but can be palliated with several different types of bronchoscopic treatment modalities.

Overview

Primary tracheal tumors are relatively uncommon with an estimated annual incidence of two cases per 1 million people.[1,2] Therefore an understanding of these neoplasms is based predominantly on small case series from large referral centers. Tracheal tumors are categorized as either primary or secondary depending on whether they arise within the trachea or secondarily involve the trachea from metastatic disease or local invasion. Primary tracheal tumors are further subdivided into benign or malignant lesions. In adults 90% of primary tracheal tumors are malignant, but in children 80% are benign.[1] Primary tracheal tumors are most often treated with multimodality therapy including surgical resection and radiation.[3] Currently, the disease-specific and all-cause mortality for primary malignant tracheal tumors are 73% and 79%, respectively.[4]

Secondary tracheal tumors are, by definition, malignant and involve the trachea either by direct extension or hematogenous metastases. Direct extension occurs most commonly from cancers arising in the lungs, esophagus, thyroid, and mediastinum, in order of decreasing frequency. Distant metastases from renal cell carcinomas, sarcomas, breast cancer, colon cancer, and melanomas have been reported. Optimal management for this diverse group of tumors depends on their location, natural history of the primary, and patient comorbidities. Surgical resection offers a chance for cure for patients with lung or thyroid cancers that involve the trachea by direct extension. However, the vast majority of secondary tracheal tumors are treated with palliative intent.

Historical Review

Morgagni described the first primary tracheal neoplasm, a fibroma, in 1761. Over 100 years would pass before experimental attempts at tracheal resection with primary end-to-end reconstruction would be described.[6] Kuester performed the first human tracheal resection and primary reconstruction in 1884. Before the 1960s, it was generally believed that tracheal resection was limited to four tracheal rings, about 2 cm, because greater resections would place undue tension on the anastomosis and prevent adequate healing.[7] Because of the presumed limits of resection and primary anastomosis, efforts at prosthetic replacement of the trachea were undertaken. In 1950 Belsey[7] reported his initial attempt with tracheal reconstruction after resection of an adenoid cystic carcinoma using fascia lata reinforced with stainless wire. Pearson and colleagues[8] used heavy Marlex mesh for tracheal replacement in seven patients and reported excellent function of the airway in three patients for several years. Neville and colleagues[9] reported extensive experience with the use of a solid silicone tube to replace the trachea; others, however, have reported unacceptable morbidity and mortality with this nonporous material.[10] Over the past several decades, a variety of other foreign materials, nonviable tissue, autogenous tissue, tissue engineering, and transplantation techniques have been attempted, but successful tracheal replacement remains elusive.[11]

Fortunately, the development of techniques for tracheal mobilization[12-14] made it possible to perform extensive tracheal resections, involving 50% of the tracheal length, with primary reconstruction. Using these techniques, tracheal replacement is uncommon. For the rare occasion when primary anastomosis cannot be performed and replacement is necessary, promise lies with tracheal allotransplantation, but long-term immunosuppression requirements will obviously limit its potential uses.[15]

For secondary tumors involving the trachea and carina, surgical techniques have been developed to address those with the potential for

Table 114-1

Classification of Tracheal Tumors

Epithelial Neoplasms	Mesenchymal Neoplasms
Benign	**Benign**
Squamous cell papilloma	Fibroma
Papillomatosis	Hemangioma
Pleomorphic adenoma	Granular cell tumor
	Schwannoma
Malignant	Neurofibroma
Squamous cell carcinoma	Fibrous histiocytoma
Adenoid cystic carcinoma	Pseudosarcoma
Carcinoid	Hemangioendothelioma
Mucoepidermoid carcinoma	Leiomyoma
Adenocarcinoma	Chondroma
Small-cell undifferentiated carcinoma	Chondroblastoma
	Lipoma
Secondary Malignancies	**Malignant**
Invasion by adjacent malignancy	Leiomyosarcoma
Metastases	Chondrosarcoma
	Paraganglioma
	Spindle-cell sarcoma
Non-neoplastic Tumors	Lymphoma
Tracheobronchopathia osteochondroplastica	Malignant fibrous histiocytoma
Amyloidosis	Rhabdomyosarcoma
Inflammatory pseudotumor	Melanoma

From McCarthy MJ, Rosado-de-Christenson ML. Tumors of the trachea. *J Thorac Imag.* 1995;10:180.

cure (thyroid and bronchogenic). Advances in therapeutic bronchoscopy offer options for patients who are not candidates for surgical resection. Endoscopic débridement, laser treatment, photodynamic therapy (PDT), cryosurgery, brachytherapy, and tracheal stents can provide palliation for patients with incurable disease.

Primary Tracheal Tumors

Primary tumors of the trachea are uncommon, but a variety of benign and malignant neoplasms have been described (Table 114-1). In recent reports, men and women are equally affected by tracheal tumors, and the peak age of diagnosis is 50 to 59 years. Primary tumors can originate from any layer of the tracheal wall and histologically are classified as either epithelial or mesenchymal tumors. Although primary tumors can be found anywhere in the trachea, the proximal and distal thirds of the trachea are most frequently affected, as is the membranous wall. A few large surgical series of primary tracheal tumors have been reported (Table 114-2).[16-19]

Staging

Neither an American Joint Committee on Cancer nor a Union Internationale Centre le Cancer staging system currently exists for primary tracheal tumors. However, a tumor node metastasis (TNM) system has been proposed on the basis of a single institution's retrospective review of 99 patients with primary tracheal tumors. T1 and T2 tumors were defined as tumors confined within the trachea that are less than 2 cm or greater than 2 cm, respectively. T3 tumors extend beyond the trachea but do not involve any surrounding structure. T4 tumors extend into surrounding structures such as the esophagus or great vessels. In addition, patients are either N0 or N1 and M0 or M1 depending on the absence or presence of lymph node or distant metastasis, respectively.[20]

Benign Primary Tracheal Tumors

Uncommon in adults, benign primary tracheal tumors are usually well circumscribed, round, soft, and smaller than 2 cm. On chest computed tomography (CT) scanning, these lesions typically are seen as smooth, homogeneous tumors that do not extend through the tracheal wall. The presence of calcium within the lesion suggests a benign histology.[21]

Squamous Papilloma

Squamous cell papillomas are superficial, sessile, or papillary masses consisting of a connective tissue core covered by squamous epithelium. In children, squamous papillomas are the most common tracheal neoplasm. In adults, these lesions are rare and associated with heavy cigarette smoking. Although these lesions can be found throughout the respiratory tract, approximately 90% to 95% are isolated to the larynx.[12,22,23] Eleven percent of the patients had papillomatosis in the trachea in addition to the larynx, but only 1.2% had disease isolated to the trachea. Presence of the disease below the larynx has been linked to the presence of a tracheostomy.[22] Papillomatosis is caused by human papillomavirus (HPV) types 6 and 11,[23] transmitted from mother to fetus during childbirth.[24] Despite being a benign tumor, papillomatosis frequently recurs and is difficult to completely eradicate. Fortunately, it usually regresses spontaneously after puberty. Numerous therapies have been used including microdébridement, nebulized or intralesional injection of cidofovir, PDT, pulsed dye laser, and indole-3-carbinol.[25,26] Recently, the carbon dioxide laser has shown promise in the treatment of papillomatosis.[7] Adjuvant treatment with α-interferon has been used.[27]

Papillomas undergo malignant transformation to squamous cell carcinoma and verrucous carcinoma, a phenomenon apparently more commonly seen with HPV 11,[28] that occurs with an incidence of 1.6% to 4%.[25,29]

Granular Cell Tumor

Granular cell tumors were first described by Abrikosoff in 1926[30] as a myogenic tumor, but more currently these tumors are understood to be neurogenic in origin. There appears to be no gender predilection, but the majority of granular cell tumors occur in African Americans. They rarely are seen in children. Approximately 50% of granular cell tumors occur in the head and neck region and 10% appear in the larynx, but the cervical trachea is rarely affected.[31] Multicentric tumors occur in 20% of patients, and these tumors tend to be biologically more aggressive.[32] Granular cell tumors are not encapsulated and tend to invade locally, despite being benign. Seventy-three percent of these tumors are intraluminal, and the remainder are either extraluminal or mixed.[33] Malignant degeneration occurs in 1% to 2% of all granular cell tumors, but this has never been reported in children.[34,35] Bronchoscopic resection of tumors smaller than 8 mm has been recommended.[34] Granular cell tumors larger than 8 mm have a high likelihood of transmural involvement and recurrence following bronchoscopic resection, and these should be managed with segmental tracheal resection.

Chondroma

Chondromas are the most common benign mesenchymal tracheal tumors, occurring most often in older men.[17-19,36] These cartilaginous tumors are hard, broad-based, and covered by intact mucosa. The most common site of origin is the internal aspect of the posterior cricoid lamina,[37] but they are evenly distributed throughout the length of the

Table 114-2

Summary of Major Recent Surgical Series of Primary Tracheal Tumors

	Malignant Neoplasms					Benign Neoplasms					All	
	SCC	ACC	Carcin	ME	Misc	Pap	Chon	Leio	GCT	Misc	Total	HM
Pearson et al[18]	9	28	0	0	5	0	1	0	0	1	44	12.8%
Grillo and Mathisen[17]	70	80	11	4	11	5	2	2	2	11	198	5%
Perelman et al[71]	21	66	20	5	13	2	0	1	0	17	144	15%
Regnard et al[19]	94	65	9	5	8	2	5	5	3	12	208	10.5%
Refaely and Weissberg[43]	5	13	2	0	0	0	0	1	0	1	22	4.5%
Webb et al[4]	34	19	0	1	20	–	–	–	–	–	74	4.1%
Total	199	252	42	14	37	9	8	9	5	42		
% Total	32.3%	40.9%	6.8%	2.3%	6%	1.5%	1.3%	1.5%	0.8%	6.8%		

ACC, adenoid cystic carcinoma; Carcin, carcinoid; Chon, chondroma; GCT, granular cell tumor; HM, hospital mortality for surgical resection; Leio, leiomyoma; ME, mucoepidermoid tumors (low and high grade); Misc, miscellaneous; Pap, papilloma; SCC, squamous cell carcinoma.

trachea. Calcification is radiographically seen in 75% of patients, although this will not distinguish chondromas from malignant chondrosarcomas, into which chondromas may degenerate on the basis of anecdotal evidence.[38] Endoscopic resection may be used for palliation but leads to recurrence, and thus segmental tracheal resection is recommended.

Leiomyoma

Tracheal leiomyomas originate from the smooth muscle of the tracheal wall and most commonly arise from the membranous portion of the lower third of the trachea.[39] These tumors typically grow as smoothly contoured, broad-based polypoid masses. Intraluminal growth can cause symptomatic airway obstruction. Death from bleeding has been reported during bronchoscopic excision, and this treatment modality has been recommended only for patients with pedunculated tumors.[40] Segmental tracheal resection is recommended for leiomyomas in order to prevent local recurrence following incomplete resection.

Hemangioma

Hemangiomas of the airway occur in adults and children. In adults, cavernous hemangiomas develop in the larynx, whereas capillary hemangiomas originate in the subglottic trachea. Tracheal hemangiomas occur more often in young children and are actually the most common obstructive subglottic mass in this patient population.[32] These lesions are asymptomatic at birth, but most will cause stridor within the first 6 months of life. Cutaneous hemangiomas are present in half of the affected infants.

In the airway, capillary hemangiomas develop within the submucosa and are covered by normal respiratory epithelium. They are typically located on the posterolateral aspect of the subglottic trachea, are smooth, bluish in color, and project into the airway from a sessile base. Most of these spontaneously regress by 2 to 3 years of age and close observation is advocated when possible. In highly symptomatic patients, a tracheostomy may be required temporarily. Regression following treatment with steroids, interferon, or laser ablation has been reported, although surgical resection may be associated with less stricture formation.[41]

Miscellaneous Benign Primary Tumors

A variety of other benign tracheal tumors have been reported including adenomas, myoepithelial cell tumors, lipomas, fibromas, schwannomas, neurilemomas, hemangiomas, paragangliomas, fibrous histiocytomas, neurofibromas, chondroblastomas, benign mucoepidermoid tumors, angiofibromas, xanthomas, myoblastomas, hamartomas, glomus tumors, intratracheal goiters, and chemodectomas. All combined, these tumors represent less than 10% of all primary tracheal tumors. Treatment for these diverse tumors is generally surgical excision, although some may be successfully managed with endoscopic resection.[39]

Malignant Primary Tracheal Neoplasms

In adults, the majority of primary tracheal tumors are malignant. Typically, malignant lesions have a shorter duration of symptoms than benign lesions, are larger in size, and exhibit an irregular surface. In most series, approximately 75% of all primary malignant tracheal neoplasms are histologically either squamous cell carcinoma or adenoid cystic carcinoma.[3,18,19,42,43] Historically, malignant tumors were much more common in men than women and squamous cell histology was most prevalent. More recently, however, the incidence of tracheal squamous cell carcinomas has declined, while the incidence of adenoid cystic carcinomas has increased. At the same time, the distribution between genders has nearly equalized.[1,4,19] The most frequent presenting symptoms are cough (72%), dyspnea (66%), hemoptysis (39%), stridor (39%), and hoarseness (31%), but the presence or absence of these symptoms has no prognostic implication.[44]

Squamous Cell Carcinoma

Until the 1980s, squamous cell carcinomas were the most common primary malignancy of the trachea, but the incidence of this disease has decreased significantly since then (Fig. 114-1).[4,44,45] Men are twice as likely to develop this cancer than are women, and the mean age of patients is 60 years.[46] A history of cigarette smoking is found in 90%, and synchronous or metachronous respiratory tract malignancies occur in 30% of these patients.[46] These tumors demonstrate exophytic growth with ulceration. Sputum cytology results are positive for cancer in nearly one half of patients. The lateral tracheal wall is often involved by these tumors, although when a squamous cell carcinoma involving the membranous tracheal wall is found, invasion from a primary esophageal tumor should always be considered.

Squamous cell cancers of the trachea are lethal, biologically aggressive tumors that grow rapidly and metastasize early. In a large series of squamous cell and adenoid cystic tracheal tumors by Gaissert and colleagues,[42,46] 33% of patients had tumors that were unresectable at presentation, and this percentage declined over the past 4 decades. Of those with resected squamous cell tumors, 27% had positive mediastinal lymph nodes. Hospital mortality averaged 7% in the series reviewing a 4-decade experience but improved to 3% in the last decade.

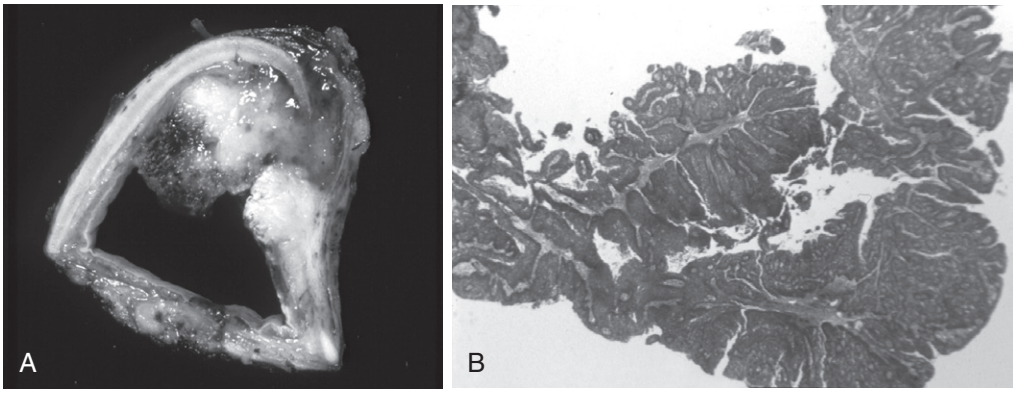

Figure 114-1. **A,** Cross section of trachea through a tracheal squamous cell carcinoma. The bulk of the mass is intraluminal, with focal growth through the tracheal cartilage and into the adventitial soft tissue. **B,** Histopathologic examination of tracheal squamous cell carcinoma showing a papillary growth pattern, with constituent atypical squamous cells (hematoxylin and eosin, ×40). *(Reprinted with permission from Patterson GA, Campbell DB. Clinical-pathologic conference in thoracic surgery: basaloid squamous carcinoma of the trachea.* J Thorac Cardiovasc Surg. *2000;120:187-193.)*

Median survival was 38 months for patients with resectable tumors but only 8.8 months for unresectable patients. The 5-year survival rates for these two groups were 39.1% and 7.3%, respectively. The presence of invasive carcinoma at the resection margins correlated with poorer prognosis, although the number of patients in this category was too small to reach statistical significance. Mediastinal lymph node involvement had the strongest prognostic implication following surgical resection in this review, but this finding was consistent among other case series. The 5-year survival for patients with negative mediastinal lymph nodes was 48.4% compared with 12.5% of patients with positive lymph nodes.[46] Conversely, a large French review found that the presence of positive lymph nodes had no impact on long-term survival, which had an overall 5-year survival rate of 47%.[19]

Radiation therapy has been used to palliate patients with unresectable squamous cell carcinomas. In a series by Grillo and Mathisen,[17] the median survival of patients with tracheal squamous cell carcinomas treated with radiation alone was 10 months, which was greater than survival among untreated patients. In addition, better survival has been observed in patients treated with surgery and radiation compared with either surgery alone or radiation with or without chemotherapy.[4] Similarly, Jeremic and colleagues[47] reported a series of tracheal squamous cell carcinomas treated with 60 Gy of radiation. The median survival was 24 months, and 5-year survival was 27%. The presence of metastasis in the mediastinal lymph nodes portended a poor survival.[47]

Adenoid Cystic Carcinoma

Adenoid cystic carcinomas, previously referred to as *cylindromas,* were first described by Billroth in 1859. These tumors can be seen in all age groups with equal distribution between men and women, but the peak incidence occurs in the fourth or fifth decade. They usually arise in the trachea or main bronchi and thus are frequently symptomatic, although many patients experience symptoms for more than a year before the diagnosis is secured. There is no association with sex, race, or cigarette smoking. Adenoid cystic carcinomas are nonencapsulated, slow-growing, low-grade malignant tumors that originate from the epithelium of the glands lining the mucosa of the respiratory tract. Adenoid cystic carcinomas are known to push mediastinal structures aside rather than invade them (Fig. 114-2). Despite growing slowly, these tumors unfortunately show a predilection for perineural, submucosal, and distant metastatic spread. Surgical resection margins are frequently microscopically positive well away from grossly apparent tumor. In these circumstances, adjuvant radiation therapy is used and commonly associated with long-term survival.[46,48] Lymphatic metastases are relatively uncommon (13% to 19%), but hematogenous metastases develop in 44%.

Treatment consists of surgical resection with preoperative radiation frequently given for large tumors. Surgical resection is possible in only 75% of patients at the time of their initial presentation due to extensive radial and longitudinal growth.[46] The indolent but persistent

Figure 114-2. Computed tomography cross-sectional image of a tracheal adenoid cystic carcinoma displacing mediastinal structures rather than invading them.

nature of adenoid cystic carcinomas conveys long-term survival rates of 33% and 10% at 5 and 10 years, respectively, in unresectable patients.[46] Survival is improved following surgery to 54% and 33% at 5 and 10 years.[46] Although controversial because of the prolonged survival seen even with unresectable disease, pulmonary metastases are not considered a contraindication to tracheal resection in otherwise operable patients. Mean survival in patients with pulmonary metastases was only 37 months.[19,48] Unfortunately, late local recurrences often occur, leading to death in patients thought to be completely resected. Overall mean and median survival rates as high as 85 and 60 months, respectively, have been reported.[48]

Adenoid cystic carcinomas are responsive to radiation therapy.[42] Radiation therapy usually commences approximately 4 weeks after surgical resection. Before initiating radiation, bronchoscopy is performed to assess adequacy of healing. Regnard and colleagues[19] reported adjuvant radiotherapy significantly improved survival in patients with an incomplete resection (positive margins).

Other Malignant Primary Tracheal Tumors

Besides adenoid cystic carcinoma and squamous cell carcinomas, a variety of other malignant tracheal tumors have been reported. All combined, these tumors represent approximately 25% of primary tracheal tumors.[3,18,19] In a recent large, single-institution review of all primary tracheal lesions, 90 of 357 patients had histology that was neither squamous cell nor adenoid cystic carcinoma.[3] Of this diverse

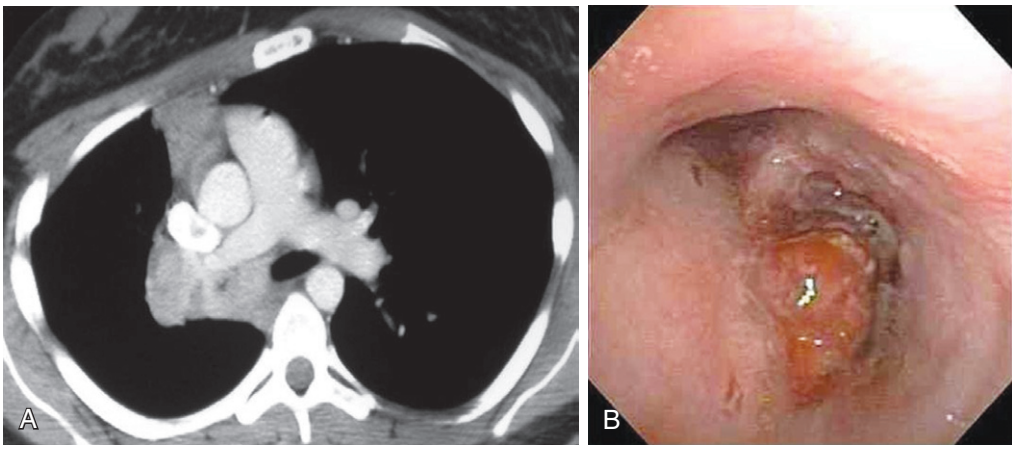

Figure 114-3. **A,** Computed tomography cross-sectional imaging of a carcinoid tumor involving the right mainstem bronchus. Note the enhancement with intravenous contrast administration. **B,** Bronchoscopic view of the same carcinoid tumor.

group, carcinoids and mucoepidermoid carcinomas are the most frequent. Less commonly seen malignant primary tracheal tumors are seen in Table 114-1. Survival at 10 years was 94% for benign tumors. Long-term survival is also frequently observed in patients with uncommon malignant tracheal tumors following resection. Gaissert and colleagues[3] reported a 10-year survival rate of 83% for carcinoid tumors and 5-year survival of 60% for bronchogenic tumors, 100% for mucoepidermoid tumors, and 78% for sarcomas.

Carcinoid Tumors

Carcinoid tumors develop from the argyrophilic Kulchitsky's cells that are present in the airway mucosa. Carcinoids are considered part of a spectrum of neuroendocrine tumors that include small cell lung cancers. These tumors have been subcategorized as neuroendocrine grade I (typical carcinoid), grade II (atypical carcinoid), and grade III (small or large cell undifferentiated neuroendocrine carcinoma).[49] Typical carcinoids, which occur 10 times more frequently than atypical carcinoids, grow slowly and infrequently metastasize.[3] Atypical carcinoids demonstrate aggressive biologic behavior and are characterized by malignant histologic features including nuclear abnormalities, mitotic activity, and necrosis. The majority of patients with atypical carcinoids have lymph node or distant metastases at the time of diagnosis. Small cell carcinoma of the trachea is rare and usually unresectable when diagnosed.

The diagnosis of carcinoid tumors depends on histologic confirmation that can often be obtained by bronchoscopic biopsy. These tumors tend to bleed profusely, so biopsy in the operating room using a rigid bronchoscope may be preferred. The typical bronchoscopic appearance has been described as "mulberry-like" (Fig. 114-3).

The treatment of choice for tracheal carcinoids without mediastinal lymph node involvement is surgical resection, which has been associated with an 83% 10-year survival rate.[4] Aggressive atypical carcinoids are often treated as small cell lung cancers, and responses to chemotherapy and radiation therapy have been seen. Small cell carcinoma of the trachea has an extremely poor prognosis despite management with combined chemotherapy and radiation.

Mucoepidermoid Carcinoma

At bronchoscopy, mucoepidermoid carcinomas of the trachea appear as pink, polypoid masses that can be confused with a carcinoid tumor. Mucoepidermoid carcinomas are derived from minor salivary gland tissue of the proximal tracheobronchial tree. On the basis of mitotic activity, level of necrosis, and nuclear pleomorphism, these tumors are classified as low or high grade. Low-grade tumors behave in a benign fashion, whereas high-grade mucoepidermoid carcinomas progress rapidly. Bronchoscopic biopsy provides the diagnosis and optimal treatment requires surgical resection. Long-term survival is common (100% 5-year survival) when these tumors are completely resected, but unresectable tumors have a poor prognosis with no patients surviving 5 years.[4] Adenosquamous carcinomas are pathologically similar to mucoepidermoid carcinomas and have an aggressive course.

Secondary Tracheal Tumors

Secondary tracheal tumors arise either from direct extension from the primary tumor or from metastatic spread to the airways. Direct tumor extension from adjacent organs is more frequent than metastatic spread and most commonly occurs from tumors of the lung, esophagus, thyroid, mediastinum, and head and neck. Of the tumors that involve the trachea by direct extension, only lung and thyroid have any chance for cure with surgical resection.[34,50] Optimal surgical management of thyroid tumors that secondarily involve the trachea remains controversial. Some favor shaving the tumor off the trachea at the time of a thyroidectomy given the relatively slow-growing nature of most thyroid malignancies and the availability of radiotherapy for local control.[12] Others have supported tracheal resection for thyroid tumor invasion, noting adherence to oncologic principles and the fact that these operations can be performed safely.[51-53] Grillo and Zannini[54] reported effective palliation and occasional cure with aggressive tracheal resection, particularly when the trachea is invaded by well-differentiated thyroid cancer. Complete resection has been associated with a 5-year survival of 78%, which compares favorably with incompletely resected patients who have a 44% 5-year survival rate. However, the results of this one particular study must be evaluated with the understanding that complete resections were attempted in all of these patients, and therefore incompletely resected tumors likely represented more aggressive disease.[55] Some have advocated cervicomediastinal exenteration when necessary, with resection of the involved trachea, larynx, and esophagus, esophageal replacement by colon or stomach, and formation of an end tracheostomy for cure.[56] Anaplastic thyroid cancer and lymphomas with extension to the trachea should not be treated by surgical resection.

Carcinoma of the lung invades the trachea either by proximal extension of a primary tumor within a mainstem bronchus or from involved paratracheal or subcarinal lymph nodes. Aggressive tracheal and carinal resections are warranted in patients without mediastinal lymph node involvement.

Invasion of the trachea by esophageal carcinomas, mediastinal malignant neoplasms, or head and neck cancers are not considered for surgical resection because they have not been shown to benefit from surgical intervention and their outcome is universally poor. Therapy for these tumors is palliative, and management options include radiotherapy, chemotherapy, stents, and other endoscopic techniques.

The most common metastatic tumors to the airway include renal cell carcinoma, sarcomas, breast cancer, and colon cancer. Melanomas can represent a primary tumor of the trachea or more commonly can be metastatic to the trachea. Rarely tumors of the uterus, testes, and

adrenal gland have reportedly metastasized to the trachea. Metastatic tumors involving the trachea can cause airway compromise by direct invasion and endoluminal obstruction or by extrinsic compression of the trachea. Determining the cause of the obstruction is crucial in directing treatment. Metastatic lesions to the trachea are incurable and treated palliatively.

Diagnosis

Symptoms, Signs, and Physical Examination

Tracheal masses are often not diagnosed until months or years after the onset of symptoms and are frequently large when discovered. Tracheal masses grow silently and do not produce symptoms until the lumen of the airway is narrowed by approximately 75%.[32] Adding to the typical delay in diagnosis is the fact that tracheal tumors are extremely uncommon, and the initial symptoms often mimic those of common disorders such as asthma or chronic bronchitis.

The most common symptom in a patient with a tracheal tumor with significant airway narrowing is exertional dyspnea. Other common symptoms of tracheal lesions include stridor, wheezing, cough, difficulty clearing secretions, recurrent pneumonia, hemoptysis, and hoarseness. Hoarseness is usually the result of reduced air flow across the vocal cords, although it can also indicate recurrent laryngeal nerve involvement. Systemic symptoms including weakness, weight loss, and dysphagia may be seen with metastatic tumors and are a poor prognostic sign.

Physical examination in a patient with a tracheal tumor may be unrevealing, but stridor, wheezing, bronchial breath sounds, increased accessory muscle use, signs of obstructive pneumonia, or subtle alteration in the timber of the voice may be present with significant narrowing of the airway. A clue that the symptoms are caused by a tracheal lesion rather than pulmonary disease is the inspiratory and often paradoxic nature of dyspnea, which is exacerbated by lying down. A history of another primary neoplasm in the setting of airway obstructive symptoms suggests direct extension or metastatic spread and should prompt evaluation.

Radiographic Evaluation

In general, the diagnosis of a tracheal tumor requires a high index of suspicion and appropriate confirmatory radiographic studies. A posteroanterior and lateral chest radiograph will identify an obstructing tracheal lesion in one quarter to one half of the cases.[32] Findings on a plain chest radiograph suggesting a tracheal tumor include the presence of a mass and narrowing, distortion, or disruption of the tracheal air column (Fig. 114-4). Direct extension from an adjacent primary may be detected.

Chest CT scans are an important part of the evaluation of a tracheal tumor. In addition to demonstrating the degree of luminal compromise, CT is excellent for assessing mediastinal tumor extension and nodal or metastatic disease (Fig. 114-5). Inspiratory and expiratory CT scans can help clarify dynamic states such as tracheomalacia, and spiral CT with three-dimensional reconstruction is useful in the evaluation and management planning of complex lesions involving the carina.

In many patients a CT scan can suggest the histologic type of the tumor. The presence of fat and calcification within a tracheal mass is virtually pathognomonic of a hamartoma.[32] Marked enhancement of a tracheal lesion after intravenous contrast administration suggests a carcinoid tumor.[57]

In other patients, CT scans may provide clues to the benign or malignant nature of a tracheal tumor. Features suggestive of a benign lesion by CT scan include an intraluminal tumor with limited spread along the tracheal wall, a well-circumscribed lesion with a smooth or lobulated appearance, and a size usually smaller than 2 cm.[58,59] Calcification suggests a cartilaginous lesion, but it does not rule out malignancy. Features suggestive of a malignant tracheal lesion include an irregular surface with extension over variable lengths of the trachea, extramural extension into the mediastinum, lesions larger than 2 cm, circumferential tracheal involvement, and enlarged mediastinal lymph nodes.[59]

CT scans are unreliable for delineating the submucosal spread of disease, and thus they will underestimate the longitudinal dimensions of a tumor. This is particularly true for adenoid cystic carcinoma, which has a propensity for submucosal spread well beyond the limits of the gross pathologic tumor. Furthermore, because adenoid cystic carcinomas tend to grow slowly and push mediastinal structures away rather than invade them, the CT finding of a loss of fat planes between the tumor and mediastinal structures is a poor predictor of actual invasion with this tumor.[32]

Figure 114-4. Careful examination of the tracheal air column seen in this standard posteroanterior chest radiograph demonstrates an oval mass nearly obstructing the trachea *(arrows)*.

Magnetic resonance imaging (MRI) has been used in the evaluation of tracheal tumors. Coronal, axial, and oblique sagittal planes can demonstrate the superior or inferior extent of a tumor and its relationship to adjacent mediastinal structures. One area in which MRI has shown promise recently has been in the detection of tracheal invasion by thyroid carcinoma.[60] MRI offers some advantage over CT when vascular or cardiac invasion is suspected and to determine whether a lesion has a pedicle or broad-based attachment.[59]

Pulmonary Function Testing

Pulmonary function tests can suggest an upper airway obstruction and occasionally can lead to the diagnosis of a tracheal lesion. Characteristic findings include a significant reduction in peak expiratory flow rate, FEV_1 and FEV_{25-75}, with relative preservation of vital capacity.[11] Significant improvement in symptoms, as well as pulmonary function test values, have been observed after tracheal and bronchial stent placement for stenosis.[11]

Bronchoscopy

Bronchoscopy represents the mainstay of diagnosis for tracheal tumors and is a necessary step in the examination of patients with these neoplasms. Capabilities for rigid bronchoscopy are essential, particularly in those with proximal tracheal tumors. Biopsy and manipulation of a tracheal tumor with flexible bronchoscopy are potentially hazardous because they may precipitate bleeding or total obstruction of an already compromised airway. The combination of flexible and rigid bronchoscopy allows biopsy of the tumor, precise measurement of tracheal length, identification of tumor extension, and determination of the proximity of the tumor to the larynx or carina. Mucosal extension of the tumor may be suggested by evidence of inflammation or erythema above or below the lesion.

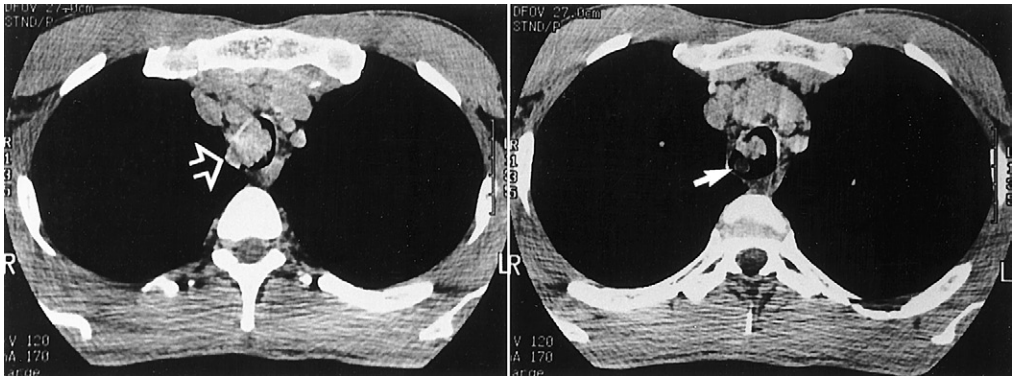

Figure 114-5. Two images from the computed tomography scan of a patient with what proved to be a tracheal hamartoma demonstrate the degree of tracheal luminal obstruction by the tumor and its attachment to the right lateral tracheal wall. Although the right lateral tracheal wall is deformed by the tumor *(open arrow),* there is no invasion beyond the wall. Fat *(closed arrow)* within the tumor suggests the diagnosis of hamartoma.

Our preference for initial evaluation is transnasal or transoral flexible fiberoptic bronchoscopy using topical anesthesia and intravenous sedation. Patients with nonobstructing distal tracheal tumors can be intubated after the induction of general anesthesia and then can undergo biopsy and evaluation with the flexible bronchoscope. Patients with large proximal tracheal tumors are best treated by the induction of general anesthesia with inhalational agents and intravenous sedatives followed by the evaluation of the airway with a rigid bronchoscope. Rigid bronchoscopy is preferred when tracheal tumors are causing subtotal obstruction because ventilation can be maintained through the bronchoscope. In addition to maintaining ventilation, the rigid bronchoscope can be used to dilate and core out the malignant lesion, providing stabilization of the airway. Tumor bleeding, although a concern, is rarely a problem with rigid bronchoscopy because the bronchoscope can be used to apply pressure to the site; alternatively, cautery or laser treatment can be used to control bleeding.

Treatment

Appropriate treatment of a tracheal tumor begins with a careful assessment of the overall situation. Coexistent medical disorders, especially cardiopulmonary disease, should be evaluated and optimized. Pneumonia should be cleared, and the airway should be stabilized, if necessary, with rigid and flexible bronchoscopic techniques. Importantly, tracheal tumors once symptomatic can rapidly progress to critical airway obstruction. Tracheal luminal diameters less than 10 mm are typically asymptomatic, even with activities, although exertional dyspnea usually manifests at a tracheal diameter of 8 mm and worsens rapidly with any further decrease in diameter. Stridor is present at rest when the tracheal diameter is narrowed to 5 mm or smaller. Acute decompensation can occur with minimal edema or secretions.

Primary Malignant Tracheal Tumors

The majority of adult tracheal tumors are malignant, and when feasible, surgical excision with circumferential tracheal resection and primary end-to-end reconstruction represents the best therapy. Limitations to resectability include the invasion of critical mediastinal structures and involvement of such an extensive length of trachea that reconstruction would be impossible. Patients with tracheal squamous cell carcinoma who are potential candidates for resection require mediastinoscopy. If metastatic disease is detected in superior mediastinal nodes, the likelihood of complete resection and long-term survival is remote. In these patients, resection should not be undertaken. These patients are treated better with combination chemoradiotherapy. If the results of the mediastinoscopy are negative, resection should proceed immediately. Anterior mobilization of the lower cervical and entire thoracic trachea will already have been accomplished by the mediastinoscopy. In contrast, the presence of metastatic disease in regional mediastinal nodes in patients with adenoid cystic carcinoma does not have a clear impact on survival rate and should not preclude resection. Furthermore, Pearson and colleagues[18] have noted that many patients with adenoid cystic carcinoma remain asymptomatic from pulmonary metastases for years, and thus patients with synchronous pulmonary metastases should not be considered inoperable.

Anesthetic Management

Patients with tracheal tumors present major challenges in airway management. Before surgical resection of tracheal tumors, flexible and rigid bronchoscope techniques are used to stabilize the airway, if necessary. Surgery should then be undertaken in a short time span to prevent the tumor from reobstructing the airway. A mixture of inhalational and intravenous sedation is used, allowing spontaneous ventilation while the airway is secured. Tracheostomy is unwarranted and detrimental in patients with tracheal tumors because stomal placement may interfere subsequently with ideal positioning of the tracheal anastomosis.

After intubation, the next challenge in airway management occurs during tracheal division and reconstruction. After transecting the trachea, ventilation can be maintained by one of three methods: (1) advance the endotracheal tube down into the distal trachea across the transected portion of the airway; (2) pass a small jet ventilation catheter either down the endotracheal tube or across the sterile field and into the distal airway; or (3) directly intubate the distal airway using a sterile, wire-reinforced endotracheal tube connected to sterile, corrugated plastic ventilator tubing brought across the field. For patients with distal tracheal lesions, it may be necessary to intubate the left or right mainstem bronchus individually, with intermittent inflation of the opposite lung if the oxygen saturation decreases as a result of persistent blood flow through the atelectatic lung (shunt). These patients require close monitoring with digital pulse oximetry and frequent arterial blood gases. Cardiopulmonary bypass is hazardous and unnecessary in nearly all patients.[51]

Surgical Management: Tracheal Resection and Primary Reconstruction

A low-collar incision provides access to the cervical and the upper two thirds of the intrathoracic trachea. If necessary, additional exposure can be obtained by adding a partial or complete sternotomy. Tumors of the distal third of the trachea are approached through a right posterolateral thoracotomy (usually at the fourth interspace). When the carina is involved, a median sternotomy may be preferable for exposure (Fig. 114-6).[13,18]

When using a cervical incision, the patient is positioned with the neck fully extended using an inflatable pad behind the shoulders. A transverse collar incision is made 1 to 2 cm above the clavicular heads, and subplatysmal skin flaps are created extending from the superior aspect of the thyroid cartilage to the clavicular heads. The strap muscles are separated in the midline, exposing the anterior trachea. The trachea is then mobilized and brought into the incision, and the site of resection can be determined by bronchoscopically visualizing a needle being

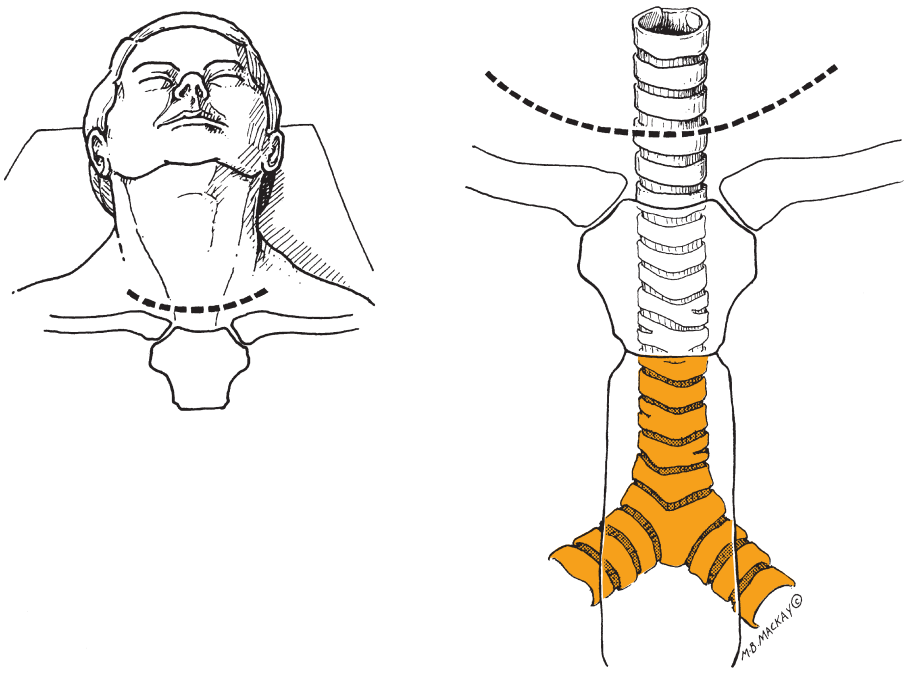

Figure 114-6. Location of cervical incision used for cervical and upper one half to two thirds of the mediastinal trachea *(unshaded area).* The distal trachea and carina *(shaded area)* requires either a median sternotomy or right posterolateral thoracotomy. *(Modified from Griffith Pearson F, Cooper JD, Deslauriers J, et al.* Thoracic Surgery. *New York: Churchill Livingstone; 2002:407.)*

passed through the anterior tracheal wall. During mobilization of the trachea, care is taken to preserve the blood supply, which enters laterally. In patients with benign tumors, the dissection is kept immediately adjacent to the trachea and no attempt is made to isolate or identify the recurrent laryngeal nerves. Resections for malignant tumors require identification and preservation of the recurrent laryngeal nerves, if possible. If one recurrent laryngeal nerve is involved with tumor, it should be sacrificed. Sacrifice of both recurrent laryngeal nerves requires concomitant tracheostomy and a subsequent vocal cord-lateralizing procedure. Paratracheal nodes are excised with malignant tumors to the extent possible without compromising the blood supply to the remaining trachea.

Care is taken during resection to prevent anastomotic tension. In optimal circumstances, approximately half the trachea can be resected and a primary anastomosis can still be performed without undue tension,[13] but advanced patient age and prior mediastinal radiation may impose restrictions on tracheal resections because of the loss of tissue resiliency. Before complete division and resection of the involved airway, stay sutures are placed in the remaining proximal and distal ends to assist alignment and to gauge tension. The proximal endotracheal tube is pulled back and the distal trachea is intubated for ventilation. Resection margins should be assessed by intraoperative frozen section. Unfortunately, it may not be possible to determine the necessary extent of resection until after the airway is open.

After completion of the tracheal resection, the patient's neck is flexed by deflating the pad behind the patient's shoulders and a primary anastomosis constructed using a continuous running absorbable suture on the posterior membranous portion and interrupted simple absorbable suture to close the anterior cartilaginous portion of the trachea (Fig. 114-7). After placement of the posterior membranous sutures, the patient's oral endotracheal tube is readvanced across the anastomosis and the distal endotracheal tube is removed. The anterior tracheal wall sutures are then placed. All intrathoracic anastomoses should be wrapped to interpose tissue between the suture line and adjacent pulmonary or systemic vessels. Frequently, either pedicled pleura or pericardial fat is used, although omentum is recommended when there has been previous mediastinal irradiation.[42] A drain is usually placed alongside the anastomosis and brought out through a separate stab incision in the neck. If there is any doubt about the viability of the anastomosis, a Montgomery T-tube can be placed across it. The incision is then closed by reapproximation of the strap muscles, the platysma, and the skin (see Fig. 114-7).

To reduce tension on the anastomosis, cervical flexion is maintained with a heavy (No. 2) monofilament "guardian" stitch between the chin and the anterior chest wall. It is left in place for approximately 7 days and is usually removed after confirmation of anastomotic healing by bronchoscopy (Fig. 114-8).

Preferably, and if deemed appropriate, the patient is extubated in the operating room. However, the presence of edema may preclude this, and an uncuffed endotracheal tube should be used in these situations. The patient is taken to the intensive care unit for postoperative management. Yearly follow-up bronchoscopy should be performed for life, particularly in patients with adenoid cystic carcinoma, because recurrences have been identified more than 25 years after tracheal resection.

Release Maneuvers

If it becomes apparent that the necessary amount of tracheal resection will place the anastomosis under tension, various mobilization and release techniques can be performed to provide additional tracheal length. For resections involving the cervical trachea, the easiest maneuver is simple neck flexion and dissection along the anterior trachea in the neck and mediastinum. An additional 2 to 3 cm of tracheal length can be obtained by performing either a suprathyroid[12] or suprahyoid[14] laryngeal release. These procedures allow the larynx to drop down, thus providing additional mobility and tracheal length. Of the two procedures, the suprahyoid is preferred because it involves a lower incidence of swallowing complications postoperatively. For thoracic tracheal and carinal resections, these release maneuvers are generally not useful. In these cases, dissection of the left main bronchus along its anterior surface (taking care to avoid lateral blood supply) will provide slightly more mobility and is easily performed. Intrapericardial hilar release maneuvers are also used and can be effective in obtaining an additional 2 cm of tracheal length by elevating the carina. The right hilar release is performed by making a U-shaped incision in the pericardium beneath the inferior pulmonary vein and incising the intrapericardial septum, which joins the lateral aspect of the atrium and inferior vena cava to the pericardium (Fig. 114-9). The performance of the maneuver on the

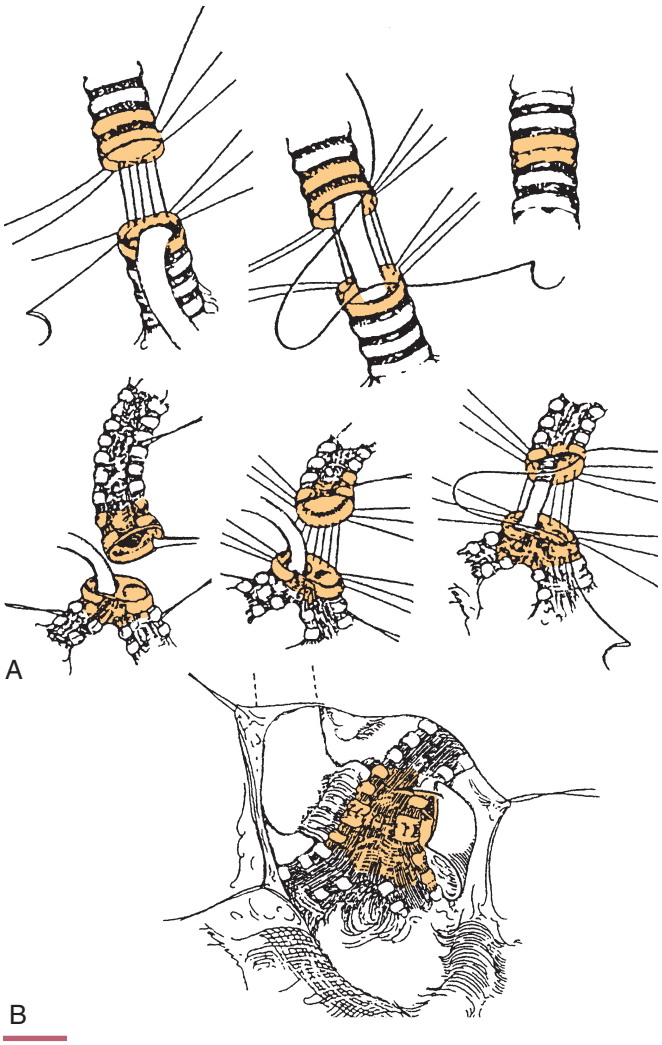

Figure 114-7. **A,** A tumor of the upper trachea has been excised, and the proximal and distal ends of the trachea are mobilized (although not circumferentially, as suggested in this diagram). Interrupted simple sutures are placed with the knots on the outside. Ventilation is accomplished initially across the field with intubation of the distal airway. Subsequently, as the anastomosis nears completion, the endotracheal tube is advanced across the anastomosis. **B,** A tumor of the distal trachea is excised, and ventilation is maintained by selective intubation of the left mainstem bronchus across the field. After suture placement, the endotracheal tube is advanced across the anastomosis and into the left mainstem bronchus. The completed anastomosis is wrapped with a pleural flap. *(Modified from Grillo HC. Reconstruction of the trachea. Experience in 100 consecutive cases.* Thorax. *1973;28:667.)*

left is basically the same, except there is no intrapericardial septum to divide and the ductus arteriosus should be transected. Although seldom necessary, an additional 2.7 cm of tracheal length can be obtained through division of the proximal left mainstem bronchus and reimplantation into the bronchus intermedius. Obviously, this increases the complexity and the potential morbidity of the operation. Even more mobility can be obtained by incising the pericardium around the hilar airway. While this release maneuver can be performed on the right, the left mainstem bronchus is relatively fixed by its relationship with the aortic arch.

Subglottal Resections

Tumors that involve the subglottal region require precise surgical intervention to prevent permanent recurrent laryngeal nerve damage and vocal cord injury. In selected patients, tumors of the subglottal airway can be managed by excision of the anterior cricoid arch and the posterior cricoid plate leaving its perichondrium in place. A primary thyrotracheal anastomosis is then performed, usually within 1 cm of the inferior border of the vocal cords with preservation of the recurrent laryngeal nerves (Fig. 114-10).[8] Resectional management of well-differentiated thyroid carcinomas invading the trachea may require complex reconstruction.[61]

Although rarely necessary, techniques for cervical exenteration have been described. Occasionally these techniques may be useful in the palliation of strangulating tumors. Rarely, this drastic technique can be curative.[42]

Carinal Resections

Tumors involving the carina present major technical challenges. Again, the need for a tension-free anastomosis is critical. In carinal resections, tumors involving more than 4 cm of tracheal length usually preclude resection. The complexities of carinal resection and the options for reconstruction were well reviewed by Grillo in 1982 (Fig. 114-11).[62] After carinal resection, the simplest technique for reconstruction involves approximating the medial walls of the right and left mainstem bronchi to fashion a new carina and then anastomosing this to the distal trachea (Fig. 114-12). This technique is applicable only with small tumors, which require limited tracheal resection. The fixation of the left mainstem bronchus by the aorta limits the ability to approximate the ends of the airway in most patients. More commonly, the trachea is anastomosed end-to-end to one of the mainstem bronchi, and the other mainstem bronchus is sutured into the lateral wall of the trachea above the first anastomosis (Fig. 114-13).

Benign Tracheal Tumors

Most benign tracheal tumors are readily managed with segmental tracheal resection and primary anastomosis. Patients with pedunculated or exophytic tumors or those with benign tumors in anatomic locations that might make resection difficult are potential candidates for endoscopic resection. Current methods of endoscopic resection include coring out and biting off the tumor with a rigid bronchoscope and biopsy forceps, cautery excision, cryoablation, and laser photocoagulation. Benign tumors most amenable to these techniques include lipomas, hamartomas, papillomas, fibromas, and small (≤8 mm) granular cell tumors. The base of the tumor should be ablated to reduce the incidence of recurrence, and patients with recurrence detected on a follow-up bronchoscopy should be considered for resection.

Palliative Treatment of Unresectable Malignant Tracheal Tumors

Therapeutic Bronchoscopy

Endoscopic procedures including dilation, mechanical débridement, laser vaporization, PDT, cryotherapy, brachytherapy, or stenting can provide palliation of unresectable tracheal tumors. For endotracheal lesions, the optimal choice of endoscopy technique depends on the individual tumor's characteristics, and often a combination offers the best approach.[63] Dilation of the narrowed segment, if caused by an endobronchial component, can be dilated by passage of rigid bronchoscopes of increasing size, use of bougies, or, alternatively, balloon dilation. Gentle passage of the rigid bronchoscope past the lesion should be performed to prevent creation of false passage. Dilation, although effective, is temporizing and rarely used as the sole treatment of unresectable endobronchial tumors. One can use the rigid bronchoscope to remove large pieces of an obstructing neoplasm by running the scope against the wall of the trachea and slicing off the tumor. This is referred to commonly as *coring out* of the tumor or *mechanical débridement*. Bleeding is controlled with compression by the rigid bronchoscope supplemented with epinephrine-soaked sponges if necessary. Laser vaporization has been used in combination with the rigid bronchoscope for lesions that are quite vascular such as metastatic renal cell carcinoma. Laser vaporization can be used alone as a treatment of unresectable tracheal neoplasms, but this is more time consuming. Besides being hemostatic, an additional advantage of laser vaporization is that it can

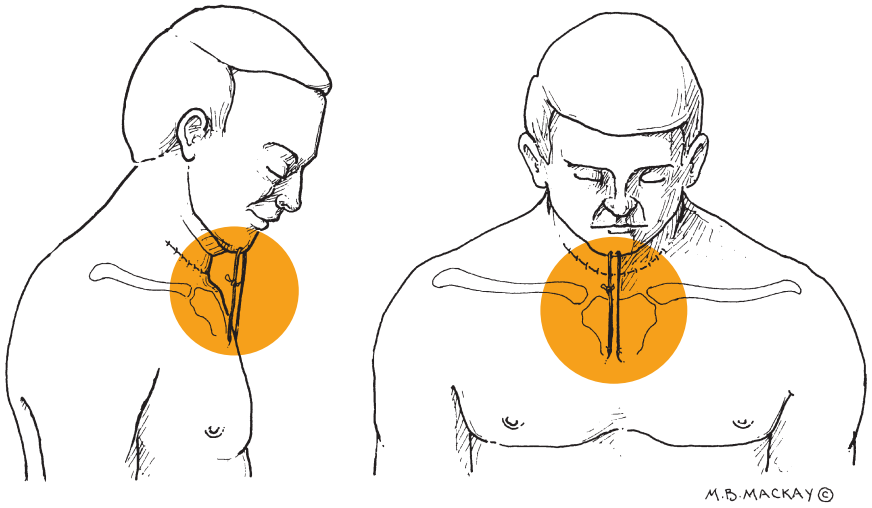

Figure 114-8. Guardian stitch is placed at the end of the operation to maintain neck flexion for the first postoperative week. *(Modified from Griffith Pearson F, Cooper JD, Deslauriers J, et al.* Thoracic Surgery. *New York: Churchill Livingstone; 2002:411.)*

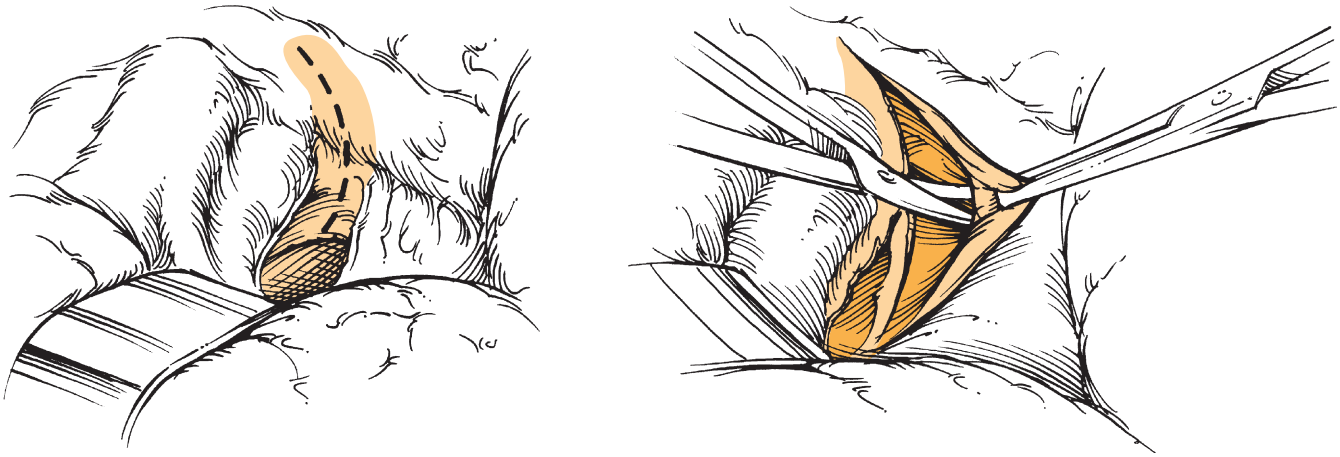

Figure 114-9. Right hilar release is accomplished by creating a U-shaped incision beneath the right inferior pulmonary vein and then incising the septum joining the lateral aspect of the atrium and inferior vena cava to the pericardium. *(Redrawn from Urschel HC Jr., Cooper JD.* Atlas of Thoracic Surgery. *New York: Churchill Livingstone; 1995.)*

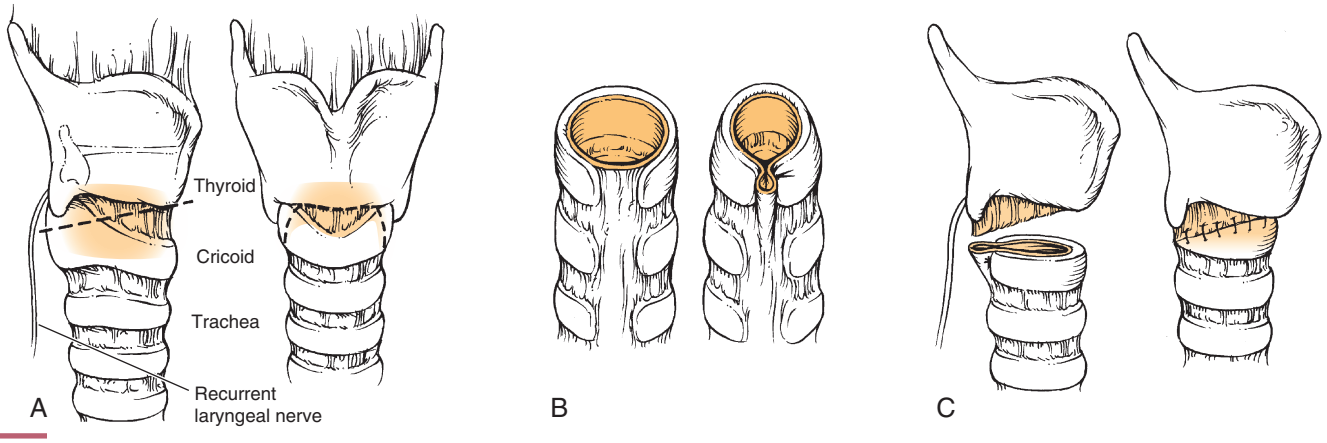

Figure 114-10. **A,** The oblique resection line across the cricoid. The line begins anteriorly at the inferior border of the thyroid cartilage and extends posteriorly through the lower border of the cricoid plate below the entry of the recurrent laryngeal nerve. **B,** Diagrammatic appearance of the distal tracheal resection line. The membranous trachea is plicated to approximate the ends of the uppermost tracheal ring and to produce a complete circle of cartilage to replace the resected cricoid ring. **C,** Completed thyrotracheal anastomosis with the distal trachea "telescoped" in front of the shell of residual cricoid cartilage. *(Modified from Pearson FG, Cooper JD, Nelems JM, Van Nostrand AW. Primary tracheal anastomosis after resection of the cricoid cartilage with preservation of recurrent laryngeal nerves.* J Thorac Cardiovasc Surg. *1975;70:806.)*

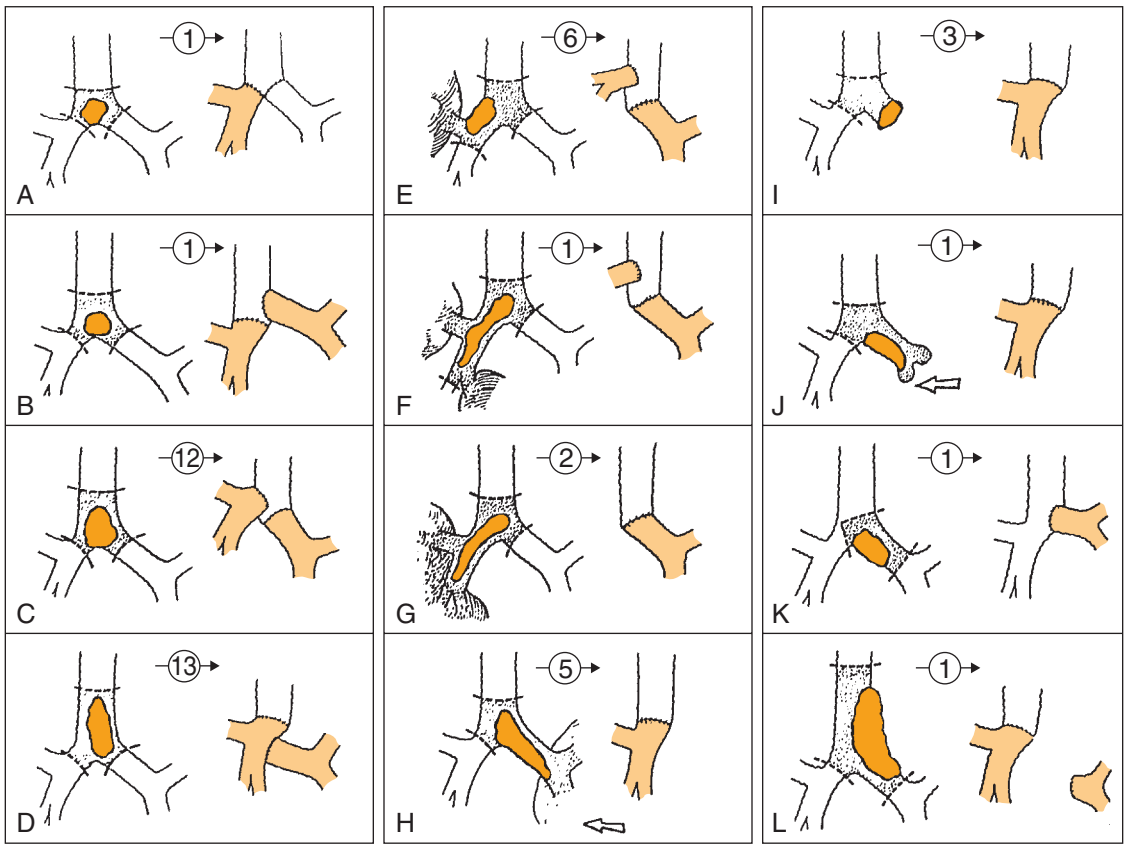

Figure 114-11. Alternatives for carinal resection and reconstruction. *Circled number* is number of patients. *Open arrows* indicate side of approach when not conventionally right-sided. **A,** Limited resection permits carinal restitution. **B,** Technique used in initial carinal resection; technique in **A** would now be used. **C,** More extensive resection. **D,** Greater length of trachea. Technique of Barclay and others. **E,** Involvement of right mainstem bronchus and right upper lobe bronchus requires right upper lobectomy. **F,** Middle lobe also removed. Right lower lobe bronchus may be anastomosed to left mainstem bronchus. **G,** Right carinal pneumonectomy. **H,** Left carinal pneumonectomy. **I,** Resection of carina after previous left pneumonectomy. **J,** Resection of carina with extra-long stump. **K,** Wedge removal of left mainstem bronchus from the right. **L,** Tracheocarinal resection with long segment of left mainstem bronchus. Exclusion of remaining left lung from the right. Left pneumonectomy also through bilateral thoracotomy. *(Modified from the Society of Thoracic Surgeons. Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results.* Ann Thorac Surg. *1990;49:69.)*

be performed through a flexible bronchoscope, thus avoiding general anesthesia. The most frequently used laser is the neodymium:yttrium-aluminum-garnet (Nd:YAG).[64] Complications with laser vaporization include airway perforation, bronchopulmonary artery fistulas, airway fires, and skin burns.

PDT is an option for endotracheal tumors, but because the mucosal edema may exacerbate airway stenosis, this therapy is not recommended for highly obstructive lesions. For PDT the patient is given a photosensitizer, dihematoporphyrin ether (DHE), intravenously, which is retained longer in tumor cells but is also taken up by normal cells. After 2 days the patient is treated with an argon dye laser system (630 nm). The DHE absorbs the light energy, radical oxygen species are produced, and the tumor cells necrose. PDT results in a wider radial extent of necrosis compared with mechanical débridement or laser vaporization and therefore results in a more durable palliation.[65-67] Bronchoscopies to remove necrotic mucosa are usually performed on days 1 and 3 following treatment. Subsequent treatments can be performed if residual tumor persists. PDT, like laser vaporization, is hemostatic and therefore can be used for highly vascular tumors. The disadvantages of PDT are photosensitivity of the patient for up to 8 weeks after DHE injection, scar and stricture formation with multiple treatments, and possibly fistula formation.[67]

Cryotherapy involves a probe placed with either rigid or flexible bronchoscopes to freeze tumor cells, resulting in necrosis. Thus cryotherapy is similar to PDT in that it does not provide immediate relief and can initially worsen the obstruction. Repeat bronchoscopy is necessary over the course of the next few days to débride the necrotic exudate. Also similar to PDT, cryotherapy provides extensive radial necrosis, and thus the number of repeat treatments may be lessened. Its major disadvantage lies in its complexity, time requirement, and a lack of familiarity with the procedure among most surgeons.

Brachytherapy delivers high amounts of localized radiation therapy to the tumor with endotracheal catheters that are placed with flexible bronchoscopy. Large, bulky lesions do not respond well to this treatment, but it has been used on unresectable tumors with a curative intent. It is frequently used in combination with mechanical core-out or laser therapy and provides better palliation than either used alone. Usually iridium-192 is used to deliver 2 Gy/min over several minutes to provide 7 to 15 Gy at a setting. A total of two to four fractions at 1-week intervals are delivered.[68] Brachytherapy has a few significant complications including radiation bronchitis (10%), stenosis (1% to 3%), and massive hemoptysis (5% to 20%).[68] One study found local failure, persistent malignancy, delivery of laser photocoagulation, and direct contact of the endobronchial brachytherapy applicator, and the tracheobronchial walls at the vicinity of the great vessels were the most indicative indicators of a massive hemoptysis.[69]

Tracheal tumors that cause airway obstruction by extrinsic compression are best palliated with endoluminal stents. Patients requiring palliation with tracheal stents typically have short life expectancies with a recent series showing a mean survival of 8 months after stent placement.[70] Stents have been used with adjuvant chemotherapy and radiation, and they have also been used in combination with other endoluminal treatment modalities. Two types of stents currently available are silicone and metal expandable stents. Silicone stents, which are

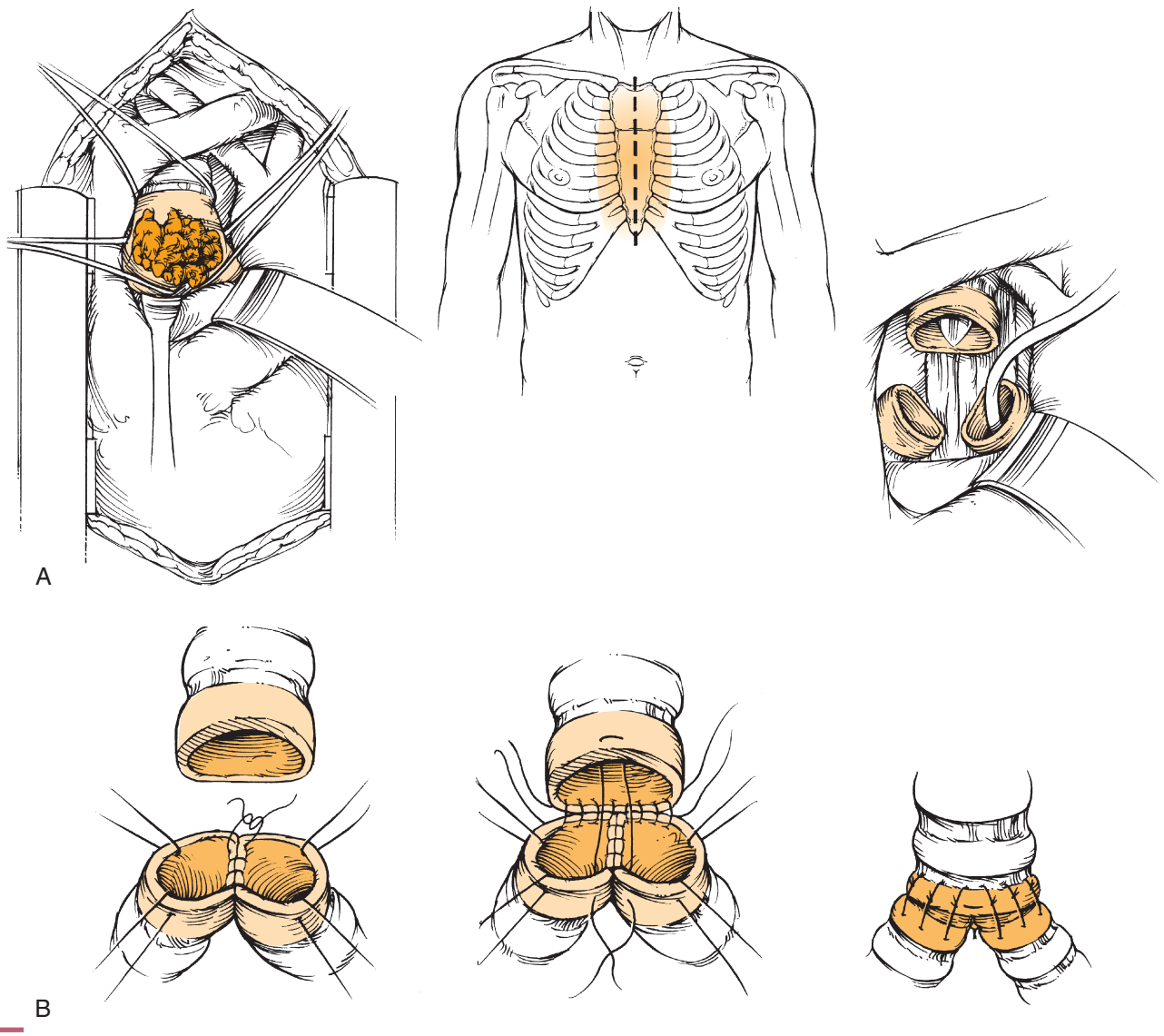

Figure 114-12. **A,** A tumor at the carina is excised. Ventilation is accomplished with a small jet ventilation catheter brought across the field and directed down the left mainstem bronchus. **B,** The medial walls of the right and left mainstem bronchi are anastomosed to form a new carina, which is then sutured to the distal trachea. *(Redrawn from Urschel HC Jr, Cooper JD.* Atlas of Thoracic Surgery. *New York: Churchill Livingstone; 1995.)*

available in cylindrical or bifurcated forms, are somewhat more difficult to place than expandable metal stents because they require rigid bronchoscopy. These stents are easy to remove or reposition because they do not incorporate into the surrounding tissues. Unfortunately, for the same reason, silicone tubes are known to spontaneously dislodge and migrate. Newer models of silicone stents are available with external studding to help reduce the risk of dislodgement. In comparison, expandable metal stents can be placed with a flexible bronchoscope. They incorporate firmly into tissues and thus are difficult to remove or reposition. Complications associated with airway stenting include stent migration, erosion, ingrowth of granulation tumor, and impaired secretions clearance.

Results

Hospital mortality rates for primary tracheal tumor resection have ranged from 5% to 15%.[18,19,42,71] Regnard and colleagues[19] reported morbidities of anastomotic failure (12%), pneumonia (6.3%), and aspiration (13.9%). The highest postoperative mortalities occurred in patients undergoing carinal resection and tracheal reconstruction attempts. Regnard and colleagues[19] reported 5- and 10-year survivals of 47% and 36%, respectively, for resected squamous cell carcinomas and 73% and 57% for resected adenoid cystic carcinoma, respectively.

Hospital mortality for patients who underwent tracheal resection for the invasion of a well-differentiated thyroid carcinoma in one series was 9%.[50] Of the 34 patients in this series treated with surgical resection, only 2 patients had airway recurrence, and 50% of patients remained alive for between 1 month and 14.5 years postoperatively (average, 5.3 years). In a series of 60 tracheal resections for thyroid cancer reported by Ishihara and colleagues,[55] complete resection was possible in 56.7% of patients. Complete resection was associated with improved long-term survival rate (78.1% at 5 years) compared with those who had an incomplete resection (40% at 5 years). Yang and colleagues[72] resected the tumors in eight patients with well-differentiated thyroid carcinoma invading the trachea, and at follow-up ranging from 14 to 183 months, five remained free of disease (three of these were followed up for more than 10 years).

Results for patients with primary lung cancer undergoing carinal resection reveal a 10% operative mortality and 5-year survival of 42%. Patients with no lymph nodes involved have a 51% 5-year survival, whereas those with positive results for mediastinal lymph node disease have only a 12% 5-year survival rate.[73]

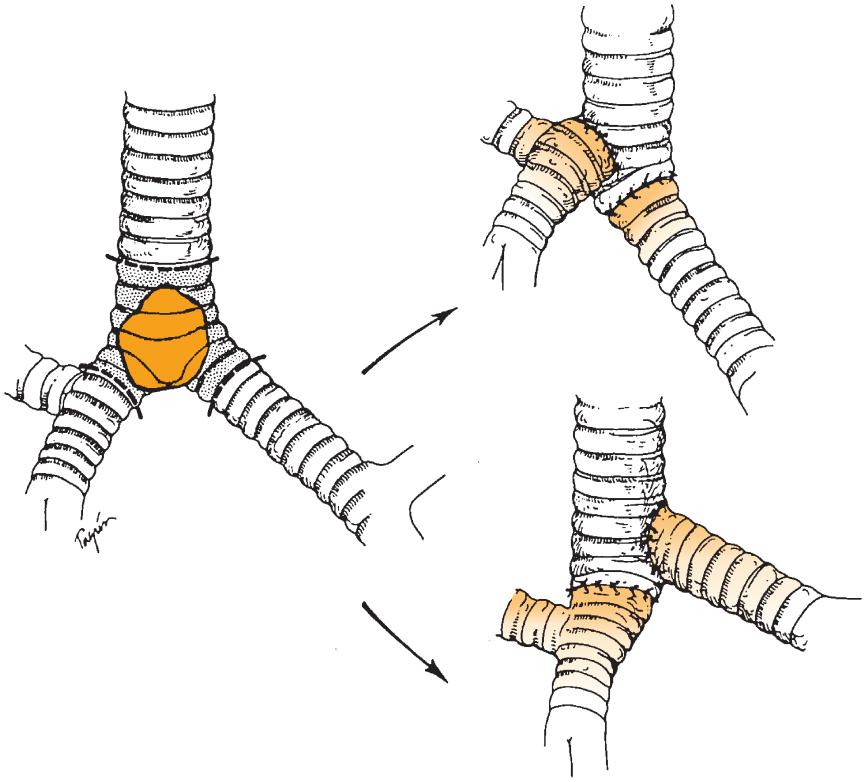

Figure 114-13. Carinal reconstruction after resection. The trachea is anastomosed end-to-end to either the left (most commonly) or the right mainstem bronchus, and the other bronchus is placed into the lateral wall of the trachea above the first anastomosis. *(Modified from Grillo HC. Tracheal tumors: surgical management.* Ann Thorac Surg. *26:112, 1978.)*

Complications

Regnard and colleagues[19] identified four factors that were significantly associated with the development of postoperative complications: an increasing length of resection, the need for laryngeal release, laryngotracheal or carinal resection as opposed to standard tracheal resection, and squamous cell histology.

Common problems after tracheal surgery include atelectasis, retained secretions, pneumonia, and swallowing dysfunction with aspiration. Aspiration is most likely to be a problem in patients with recurrent laryngeal nerve dysfunction and in those who underwent a release procedure of the upper airway (superior laryngeal or suprahyoid technique). In many patients, the problem resolves within a few weeks, either spontaneously or with swallowing modification techniques. Vocal cord dysfunction may be transient or permanent, depending on the nature of the injury to the recurrent laryngeal nerve. Dysfunction of one vocal cord usually produces hoarseness and an impaired cough. Bilateral cord dysfunction can cause airway obstruction requiring tracheostomy.

Wound infections, particularly in the cervical area, are rare. Prompt opening and complete drainage of the wound is essential. Intrathoracic infections are potentially much more serious, particularly when an anastomotic dehiscence produces an air leak or a space within the mediastinum. Urgent and wide drainage is critical to prevent the development of mediastinitis.

Anastomotic dehiscence usually occurs as a result of excessive tension or compromised tracheal blood supply. Excessive tension occurs with overzealous tracheal resection or inadequate mobilization. Ischemia is more likely to occur in patients with previous irradiation to the area and in those who undergo extensive nodal dissection or circumferential mobilization of the airway. Acute separation can be resutured if it occurs early and if there is no necrosis or ischemia.[54] Otherwise, a tracheostomy or T-tube can be inserted across the defect.

An uncommon but lethal complication of airway surgery is tracheal-innominate or tracheal-pulmonary artery fistula formation. Fistulas can result from pressure against the innominate artery by a postoperative tracheostomy tube or by direct abrasion of the anastomosis against the innominate or pulmonary artery. To protect against fistula formation at the airway anastomosis, dissection near the brachiocephalic artery should be performed on the trachea, leaving adjacent soft tissue undisturbed on the artery itself. This will prevent most fistulas. If the artery is bared, vascularized soft tissue such as a pedicled strap muscle should be interposed between the artery and the anastomosis. Within the thorax, soft tissue, like the thymus or pericardium, should be placed between the pulmonary artery and an airway suture line. Some patients will have a "herald" bleed, and prompt exploration with bronchoscopy and opening of the wound may save these patients. Unfortunately, most patients who develop this complication suffer a sudden, fatal hemorrhage into the airway.

Late complications include the development of granulation tissue or stenosis at the anastomosis. Exuberant granulation tissue can often be extracted endoscopically with a biopsy forceps. Occasionally, granulation is a result of infection or necrosis of underlying cartilage and can be a particular problem if it involves the cricoid. When the cricoid is involved, the infection can slowly progress over many months and definitive management often requires operative débridement. Anastomotic stenosis developed in 5% of patients who survived tracheal or carinal resection and reconstruction in the series by Grillo and Mathisen.[17] Symptomatic stenoses occurred in 14% of patients in the series reported by Regnard and colleagues,[19] and it occurred significantly more frequently among patients who had postoperative locoregional complications such as tracheal dehiscence or mediastinitis. Anastomotic stenoses can often be managed with endoscopic techniques including dilation and T-tube placement. Attempts at resection should be delayed for 4 to 6 months after the initial surgery to allow the acute inflammation to subside.[74] As noted by Grillo and colleagues,[74] the difficulties of tracheal reconstruction increase markedly with each attempt at repair, and thus conditions should be optimal. Every effort should be made at the time of the initial resection and

reconstruction to avoid complications that could lead to an anastomotic stenosis.

Summary

Primary tracheal tumors are rare, and in adults, most tumors are malignant. More than 80% of malignant tracheal tumors are either squamous cell carcinoma or adenoid cystic carcinoma. Tracheal tumors are best managed by resection with end-to-end anastomosis. Great care should be taken to avoid excessive tension on the anastomosis by limiting the extent of the resection and, in addition to cervical flexion, performing appropriate release procedures as needed. Anastomotic ischemia is avoided by limiting the area of circumferential dissection, carefully preserving the lateral blood supply, and being judicious in the extent of the paratracheal lymph node excision.

Adjuvant radiotherapy is probably of benefit after resection of squamous cell and adenoid cystic carcinoma, particularly in those with positive resection margins. Radiotherapy as primary management for malignant tracheal tumors is reserved for patients medically unfit for an operation, those with unresectable airway tumors, and those with metastatic disease. Overall, the 5-year survival rate for patient with adenoid cystic carcinoma (73%) is much greater than for those with squamous cell carcinoma (47%). Management for tumors involving the trachea secondarily is in general palliative, although aggressive tracheal resection for invasive thyroid carcinoma and bronchogenic carcinoma offers a chance for cure.

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CHAPTER ONE HUNDRED AND FIFTEEN

Penetrating and Blunt Trauma to the Neck

David B. Hom

Robert H. Maisel

Key Points

- With penetrating neck trauma, emergent surgical exploration is necessary for any immediate life-threatening signs or symptoms (expanding hematoma, nonexpanding hematoma in the presence of hemodynamic instability, hemomediastinum, hemothorax, hypovolemic shock).
- For the stable patient, the choice of treatment for penetrating neck trauma remains controversial. Classifying the neck zone involvement (zone I, II, or III), mechanism of injury, and velocity of the projectile are helpful in determining the risk of major injury. Zone I and zone III injuries usually require arteriography on all stable patients. Because hemorrhage is the leading cause of death for penetrating neck injuries, hemodynamic and neurologic status should always be monitored closely for at least 48 to 72 hours.
- In blunt neck trauma, symptoms can present with a delayed onset and be easily underdiagnosed. Thus careful observation should be made for individuals with significant blunt neck trauma in order to monitor for progressive signs and symptoms of injury.

As the incidence of violent trauma rises in our society, the rate of penetrating trauma to the head and neck also grows. Presently, penetrating neck injury comprises 5% to 10% of all trauma cases. All penetrating neck wounds are potentially dangerous and require emergency treatment.

In the neck, multiple vital structures are vulnerable to injury in a small anatomic area and are not protected by bone. Such vital structures of the neck can be divided into four groups: the air passages (trachea, larynx, pharynx, lung); vascular (carotid, jugular, subclavian, innominate, aortic arch vessels); gastrointestinal (pharynx, esophagus); and neurologic (spinal cord, brachial plexus, peripheral nerves, cranial nerves [CNs]). Signs or symptoms listed in Box 115-1 should alert the otolaryngologist that injury to any of these structures has occurred.

Physical Properties of Penetrating Objects

Knowledge of the physical properties and ballistics of the penetrating object can help determine a management plan and predict the risk of injury. The location of penetration also predicts risk and helps in planning for management.[1] The magnitude of injury is determined by the kinetic energy that is transferred from the projectile to the target tissue: $KE = \frac{1}{2}M(V_1 - V_2)^2$. *KE* is the kinetic energy of the projectile, *M* is the mass of the projectile, V_1 is the initial velocity on contact, and V_2 is the exit velocity. Thus differences of projectile velocity transform into kinetic energy by the second power.

Handgun

Civilian handgun injuries are traditionally from projectiles with low-muzzle velocity (90 meters per second [m/s]). An impact velocity of 50 m/s penetrates skin, and an impact velocity of 65 m/s will fracture bone. These slow-velocity projectiles have been known to push aside vital structures such as arteries. Penetrating wounds caused by small-caliber handguns have a less damaging effect than other projectiles of higher velocity.

Guns are classified by projectile type, speed, and caliber (diameter of muzzle bore). Bullets that travel greater than 610 m/s are considered high-velocity projectiles. Handguns or pistols (.22 caliber to .45 caliber) have muzzle velocities from 210 to 600 m/s. Caliber is a term interchangeable with the designation of the cartridge (i.e., .22-caliber pistol). Handguns can develop up to 1000-foot pounds of energy. A .44-caliber magnum, which has a large powder charge, can create even more hypervelocity. Thus injury from this gun can cause tissue destruction comparable with that caused by a rifle bullet, a larger projectile.

The yaw of the bullet describes the deflection of the projectile around the axis of travel. If the yaw is minimal (not tumbling), with the bullet entering perpendicular to the body surface, the bullet will pass through the tissues with little energy transmitted. A tumbling bullet causes injury in a wider path. The projectile can follow tissue planes and may not injure vital structures. A bullet also can deflect from bones of the mandible or cervical spine. Unfortunately, civilian gunshot wounds increasingly involve heavier projectiles with higher-velocity handguns. In all cases a full inspection of the entire naked body and palpation of the head is necessary to reveal all entrance and exit wounds. This information may be useful in predicting damage.

Low-velocity bullets are usually lead shielded and often leave a radiographic track. A diagnosis based on physical signs of injury, after full and careful organ system evaluation, is often sufficient for these injuries if all presentations are normal. Radiographic confirmation or surgical exploration should follow any uncertainty or deterioration of physical signs.

Box 115-1

Signs and Symptoms of Penetrating Neck Trauma

Airway
Reparatory distress
Stridor
Hemoptysis
Hoarseness
Tracheal deviation
Subcutaneous emphysema
Sucking wound

Vascular System
Hematoma
Persistent bleeding
Neurologic deficit
Absent pulse
Hypovolemic shock
Bruit
Thrill
Change of sensorium

Nervous System
Hemiplegia
Quadriplegia
Coma
Cranial nerve deficit
Change of sensorium
Hoarseness

Esophagus/Hypopharynx
Subcutaneous emphysema
Dysphagia
Odynophagia
Hematemesis
Hemoptysis
Tachycardia
Fever

From Stiernberg C, Jahrsdoerfer RA, Gillenwater A, et al. Gunshot wounds to the head and neck. *Arch Otolaryngol Head Neck Surg.* 1992;118:592.

Rifle

Most military rifles have a jacket of strong metal, usually copper, that surrounds a lead projectile. This permits smoother and longer flight because of less drag and less aerodynamic compression. Similarly, because of the lack of deformation, these military bullets create a clean hole with a through-and-through wound without a lead track to follow. The M16 military rifle has a bullet that is designed to tumble, and therefore it causes more tissue injury. It is against the terms of the Hague Convention of 1908 for military projectiles to include expanding bullets such as hollowpoint, softnose, or dumdum bullets. These soft-tip bullets expand on contact and cause greater soft-tissue injury. They create a large wound cavity, may not cause an exit wound, and may fragment, with partial projectiles causing injury far from the primary direct path. Hunting rifles use these expanding bullets, and therefore the civilian wounds caused by these projectiles can be more devastating than a comparable wound inflicted by a military weapon.

Most military rifles have a muzzle velocity of 760 m/s. High-velocity missiles (>610 m/s) not only tear tissue but transmit energy to surrounding tissue. A cavity of up to 30 times the size of the missile may be created and pulsate over 5 to 10 ms, with several waves of contraction and expansion of the tissue (Fig. 115-1).[2] This may explain the finding of a punctured viscus without direct penetration and should

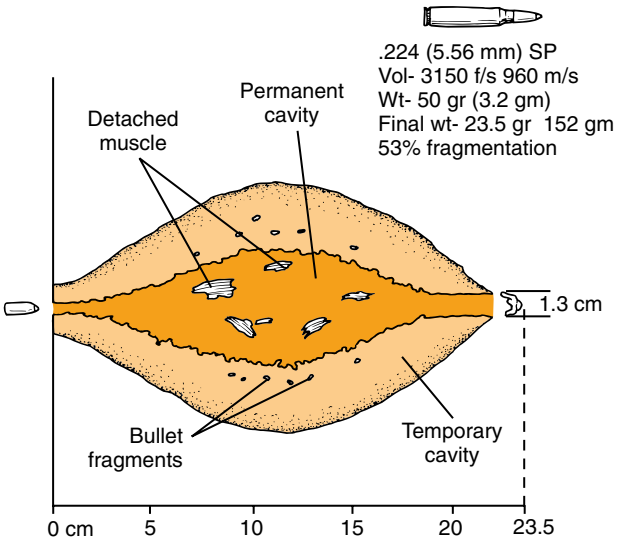

Figure 115-1. Characteristic wound profile of a high-velocity, soft-point rifle bullet. Note characteristic large temporary and permanent cavities with massive tissue disruption. The wound profile of a conventional copper-jacketed, high-velocity bullet would reveal a similar temporary cavity. *(From Fackler M, Bellamy R, Malinowski J. The wound profile: illustration of the middle-tissue interaction.* J Trauma. *1988;28(Suppl):21.)*

alert the surgeon to examine the trachea and esophagus, even when a bullet wound is 2 inches away (Fig. 115-2).

High-energy missiles are not easily deflected and cause significant destruction along their path because the energy is absorbed by the surrounding tissue. Deer rifles fire a projectile designed to mushroom on impact, causing a large amount of tissue destruction within a small area.

The mortality from all high-velocity rifle injuries inflicted directly on the neck is significant. These patients usually do not survive and are not available for study. In view of the expected severity of injury, all known victims of high-velocity rifle injuries who survive on reaching the hospital merit strong consideration for surgical exploration. For stable patients, angiograms should be considered before surgery. In helping to determine if mandatory surgical exploration or further preoperative diagnostic tests are necessary, knowledge of the size and velocity of the intruding missile is helpful.

Shotguns

The severity of shotgun wounds is largely dependent on the distance between the weapon and the victim, the type of weapon used, and the size of the projectile (shot). Pellets tend to scatter as they travel on the basis of the distance to impact and the interior muzzle diameter (choke) of the shotgun. At close range the entire charge can act like a single missile with a KE similar to a high-velocity bullet.[3] At further distances, birdshot pellets scatter and act as multiple individual missiles. With larger pellets such as buckshot, significant injuries can occur from individual pellets up to 150 yards away with a standard-length barrel. A sawed-off shotgun leads to early spraying of the shot. Shotguns are low-velocity weapons (muzzle velocity of 300 m/s).

Birdshots are pellets with a diameter less than or equal to 3.5 mm (0.13 inch) and are categorized as No. 4 shot or smaller. Buckshots have a diameter greater than 3.5 mm and have a greater range, causing significant injury up to 150 meters. This is in contrast to birdshots, which have a 12-m maximum range of serious injury (Tables 115-1 and 115-2). Each pellet injury from a buckshot blast is similar to a bullet injury from a handgun. Buckshot wounds are usually more serious than handgun bullet wounds because of the number of missiles involved.

The gauge of the gun determines how much shot can be included in a single shell. The actual shot varies from 00 buckshot (for deer hunting, which has eight and one half pellets per ounce with a larger

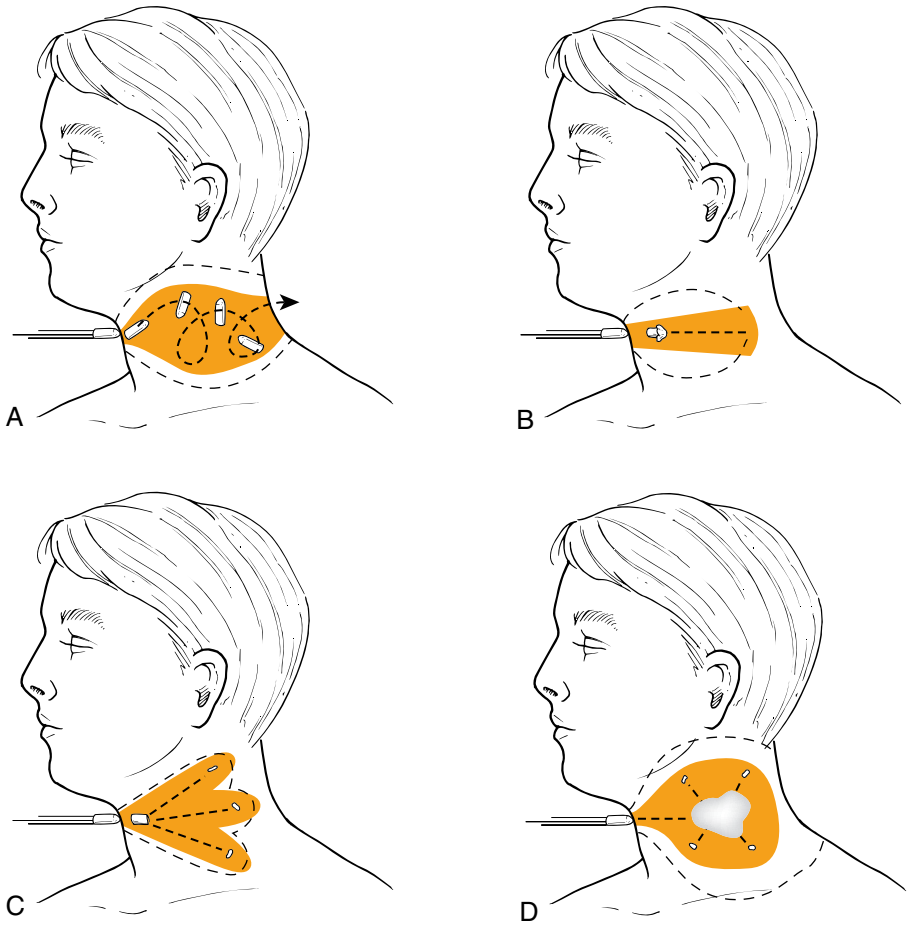

Figure 115-2. Types of injuries caused by different missiles. Both temporary cavity *(dotted line)* and permanent cavity *(stipple area)* are large. **A,** Tumbling missile. **B,** Expanding bullet. **C,** Fragmenting bullet. **D,** Self-exploding bullet. *(From Holt GR, Kostohryz G. Wound ballistics of gunshot injuries to the head and neck.* Arch Otolaryngol. *1983;109:313.Copyright 1983, American Medical Association.)*

tissue impact) up to 12 buckshot (which has 2400 pellets per ounce, has little destructive ability, and is used for target shooting). An 8 buckshot with 400 pellets per ounce is used for shooting small game such as rabbits and birds.

At close range, shotgun injuries cause as much damage as rifle injuries because of the massive blast effect to the tissues. When the distance between the shooter and the recipient is more than 6 m, the details of gauge, shot, powder load, and the choke of the gun become more important. Wadding from the shotgun blast also should be searched for and removed from the wound to prevent infection. Radiography is useful for revealing pellets in unexpected locations such as the intracranial, intrathoracic, or intraorbital cavities. Magnetic resonance imaging (MRI) may be even more valuable than computed tomography (CT) for the stable patient because metal scatter artifact does not occur.

Knife and Stab Injuries

Knife, ice-pick, cut-glass, or razor-blade injuries usually proceed along more predictable pathways. However, what appears to be a single-entry wound may be from multiple stab wounds. The history of the attack may be of some help to the physician in determining whether the blow was overhand or underhand, whether both the attacker and the recipient were standing, and other similar details. Compared with gunshot wounds to the neck, cervical stab wounds have a higher incidence of subclavian vessel laceration.[4] This is because stabbings to the neck often occur in a downward direction with the knife slipping over the clavicle and into the subclavian vessels.[5] In gunshot wounds the direction of the projectile is more perpendicular to the neck; thus the clavicle can protect the subclavian vessels. In regard to spinal injuries, neck stab wounds have a lower incidence than cervical bullet wounds.[5]

Mandatory versus Elective Exploration

Penetrating neck injuries should be differentiated into two basic presentations depending on whether or not they are immediately life threatening. The signs of immediate life-threatening injuries include massive bleeding, expanding hematoma, nonexpanding hematoma in the presence of hemodynamic instability, hemomediastinum, hemothorax, and hypovolemic shock. In all of these instances, immediate surgical exploration is mandatory. On the other hand, hemodynamically stable patients who present with non–life-threatening features can undergo thorough imaging investigations to determine the extent of injury.

For the stable patient, the choice of management remains controversial: either mandatory exploration for all penetrating neck wounds or selective exploration with observation. Retrospective studies have supported both mandatory surgical exploration and selective surgical exploration.[6,7] For the selective surgical approach, it is emphasized that the clinical status of the patient should be monitored closely by frequent observation and medical examination using diagnostic radiology and surgical endoscopy. In civilian injury this is often possible, but in times of war or civilian catastrophe, resources such as radiography and observation beds may not be available for large numbers of casualties.

Until World War II, the mortality of penetrating neck wounds ranged from 7% to 15%. By the end of the Vietnam War, it was reduced to 3% to 6% (Table 115-3).[7] However, mortality remains high if major vascular structures (carotid or subclavian arteries) or the cervical spinal cord is injured. During the Vietnam War, it was customary to explore all patients with penetrating neck wounds below the platysma layer under general anesthesia, regardless of preoperative findings. The idea of mandatory exploration was also advocated by Fogelman and Steward in 1956 for civilian injuries. This philosophy was followed until the mid-1980s by most general trauma centers in large cities in

Table 115-1

Shotgun Shells

Shot Size	Diameter (inches)	Maximum Range (yards)	Pellets per Ounce (n)
12-Gauge round ball	.645	1420	.75
16-Gauge round ball	.610	1340	1.0
10-Gauge round ball	.545	1200	1.25
410-Gauge round ball	.38	850	—
000 Buckshot	.36	—	6
00 Buckshot	.34	748	8
0 Buckshot	.32	704	9
1 Buckshot	.30	660	11
2 Buckshot	.27	—	15
3 Buckshot	.25	—	19
4 Buckshot	.24	—	21
#1 Shot	.16	352	73
#2 Shot	.15	330	90
#3 Shot	.14	308	109
#4 Shot	.13	286	135
#5 Shot	.12	264	170
#6 Shot	.11	242	225
#7 ½ Shot	.095	209	350
#8 Shot	.09	198	410
#9 Shot	.08	176	585
#12 Shot	.05	110	2385

From Ordog GJ: Missile wounds of the neck. In Ordog GJ, ed. *Management of Gunshot Wounds.* New York: Elsevier; 1988.

the United States. However, it was realized that in many instances significant injuries to major structures did not occur. This reasoning led some surgeons to follow a more selective approach for these injuries. However, advocates for mandatory exploration believe that exploration has time-proven success. Each of the proponents gives arguments that support their views, both medically and economically (Table 115-4).

Classification

Anatomically, the neck can be divided into three major zones in order to aid in the decision making for diagnostic tests and timing of surgery (Fig. 115-3).[1] Zone I is below the cricoid and represents a dangerous area because the vascular structures in this zone are in close proximity to the thorax. The bony thorax and clavicle act to protect zone I from injury, as do other bony structures at the base of the neck. This osseous shield also makes surgical exploration of the root of the neck difficult. In zone I, injuries to the right side are often approached through a median sternotomy, whereas injuries to the left side are often managed by a left anterior thoracotomy to control the hemorrhage. Zone I has a fairly high mortality rate of 12%.[8] Mandatory exploration is not usually recommended for zone I injuries; angiography is usually suggested to ensure that the great vessels are not injured.

Zone III is located above the angle of the mandible. This area is also protected by skeletal structures and is difficult to explore because of the skull base and the need to divide or displace the mandible. The necessity for craniotomy in exploration and control of high carotid injury in this location makes zone III treacherous. Recognizing injuries to many of the cranial nerves exiting the skull base in zone III is important because these injuries may be indicative of injuries to the great vessels due to their close proximity. An abnormal neurologic examination would suggest the need for angiography in the stable patient.

In view of the difficult surgical approaches to zone I and zone III, most authors agree that all patients with such injuries who are stable and without evidence of acute airway obstruction, significant bleeding, or expanding hematoma should be evaluated with angiography, with consideration of barium swallow. For zone III injuries, frequent intraoral examination should be performed to observe for edema or expanding hematoma within the parapharyngeal or retropharyngeal spaces.

Zone II penetration is the most frequently involved region (60% to 75%), and injury in this zone has created a great deal of controversy in the American literature over the past 25 years.[9] Experts are having an ongoing debate about the use of mandatory exploration versus selective exploration with serial examination, endoscopic tests, and angiography. In zone II, isolated venous injuries and isolated pharyngoesophageal injuries are the most common structures missed clinically in the preoperative evaluation. A substantial number of patients can be selectively managed depending on signs, symptoms, and direction of the trajectory. When patients are stable and lack physical signs of obvious major neck injury, they are evaluated by diagnostic radiologic

Table 115-2

Classification of Birdshot Shotgun Wounds

Type	Range*		Injury	Mortality (%)
	Standard Barrel	Sawed-off Shotgun		
0	Long >12 m	>4 m	Superficial—pellets in skin only	0
I	Long >12 m	>4 m	Penetrates only subcutaneous tissue	0-5
II	Close 5-12 m	2-4 m	Penetrates beyond deep fascia	15-20
III	Point blank <5 m	0-2 m	Extensive tissue damage	85-90

*The distance will vary with each type of shotgun and is significantly reduced for sawed-off shotguns.
From Ordog GJ: Missile wounds of the neck. In Ordog GJ, ed. *Management of Gunshot Wounds.* New York: Elsevier; 1988.

and endoscopic techniques. All patients are admitted for observation. A hospital with a comprehensive trauma service with experienced personnel doing careful and repeated physical examinations and with 24-hour availability of radiologic and endoscopic capability is necessary.[5] The leading cause of death from penetrating neck injuries is hemorrhage from vascular structures. In a study by Stone and Callahan, vascular injuries in the neck accounted for 50% of deaths.[10]

One article emphasizes the increased lethal potential of transcervical penetrating neck wounds when the projectile crosses the midline. In this study all 11 patients with transcervical gunshot and shotgun wounds sustained vascular or aerodigestive injuries and longer hospital stays (14 days) compared with patients with other gunshot wounds (6.6 days). We believe that transcervical injuries should be reported separately from zone I, II, and III injuries because they tend to be more severe.[11]

Initial Management

The initial care of patients with penetrating neck injuries should follow the basic tenants of trauma care. The emergent management of all penetrating neck trauma requires (1) airway establishment, (2) blood perfusion maintenance, and (3) clarification and classification of the severity of the wound. In the emergency department, satisfactory control of the airway is established by intubation, cricothyroidotomy, or tracheostomy. Direct transcervical tracheal intubation is safer than oral or nasal intubation when the oral cavity, pharynx, or larynx are traumatized and filled with blood. In the setting of a gunshot wound, it may be difficult to fully evaluate the cervical spine until the airway is controlled. Multiple blind intubation attempts will risk enlarging a lacerated piriform sinus wound and extending it iatrogenically into the mediastinum. Similarly, a tracheal tear may be exacerbated by extending the neck, which distracts the proximal and distal segments. The airway must be established and the hemodynamic status stabilized before transporting the patient to the angiography suite. Large-bore intravenous lines are placed, even when the patient is not hypotensive, so that fluids can be rapidly introduced if necessary. Particularly in zone II, hemorrhage or an expanding hematoma will respond to direct pressure and should not be managed by indiscriminate clamping through the wound. Under no circumstances should a penetrating neck wound be probed because clot dislodgement and uncontrollable bleeding can occur.

Every patient with significant neck trauma should have routine anterior and lateral neck and chest radiographs. When a pneumothorax is identified by a radiograph or physical examination, a chest tube should be inserted emergently. In the rare circumstance of an exsanguinating oral hemorrhage, a tracheostomy must be performed immediately and the pharynx must be packed. In high-volume trauma hospitals, the emergency department usually has an operating theater intended for emergent patients on whom control of a major vessel hemorrhage must be performed immediately. Physical findings of vascular injury are pulse deficit, active bleeding, expanding hematoma, bruit, murmur, neurologic deficit, or hypotension. Patients with acute injury to the spinal cord may present with hypotension without tachycardia (spinal shock). Cranial nerve injury is not common; however, when it is evident, documentation of the deficit is helpful in evaluating the direction of the projectile and possible injury to adjacent structures. For instance, if a hypoglossal nerve injury is present, one should be suspicious for a possible carotid artery injury. Horner's syndrome (pupil constriction, upper eyelid ptosis, skin flushing, and absence of sweating on the affected side) may indicate injury to the carotid artery or to structures along the sympathetic chain. Under controlled circumstances, the patient is taken to the operating room, where a wide-apron incision is made from the mastoid tip to the midline of the neck at the cricoid level for definitive exploration.

Table 115-3

Mortality of Penetrating Neck Trauma in Wartime and Current Civilian Practice

Incident	Injuries *(n)*	Mortality (%)
Civil War	4114	15
Spanish-American War	188	18
World War I	594	11
World War II	851	7
Current civilian practice	n/a	3-6

n/a, not available.
From McConnell D, Trunkey D. Management of penetrating trauma to the neck. *Adv Surg.* 1994;27:97.

Table 115-4

Mandatory versus Selective Management of Neck Wounds

Consideration	Mandatory	Selective
Diagnosis	Potential life-threatening injuries can be missed by the preoperative workup.	Most major injuries can be diagnosed preoperatively; routine exploration can miss some injuries.
Skill and resources	Selective management requires more skill, manpower, experience, and judgment; additional special diagnostic procedures are also required.	Selective care will reduce unnecessary explorations by a surgeon inexperienced with trauma.
Hospital stay	Length of stay is similar for observation and negative exploration.	No advantage of negative exploration.
Delay	If occult injuries are delayed, morbidity and mortality will increase.	Delay has not been shown to significantly increase morbidity and mortality of occult injuries.
Patient care	Active observation requires continuous availability of experienced trauma medical staff for monitoring the patient.	Selective management emphasizes the concept of collaboration among trauma team members and reduces unnecessary surgical exploration.

Adapted from Obeid F, Haddad GS, Horst HM, Bivins BA. A critical reappraisal of a mandatory exploration policy for penetrating wounds of the neck. *Surg Gynecol Obstet.* 1985;160:517.

Diagnostic Evaluation

When the patient's stability allows, an orderly history and physical examination including a full examination of the unclothed body to look for entrance or exit wounds should be performed. In the conscious patient a full neurologic examination should be done and a chest radiograph taken. The radiograph should be examined to rule out hemothorax, pneumothorax, or pneumomediastinum. The latter would suggest a punctured viscus and demands further evaluation. Subclavian vessel injury may be first recognized by an abnormal chest radiograph. All patients should be managed assuming potential cervical spine fractures until they undergo radiographic evaluation. On radiographs, all cutaneous wounds can be marked with radiopaque objects to aid in evaluating the site of the injury.

Most trauma centers suggest that personnel and equipment be available 24 hours a day for flexible endoscopy or arteriography, with accessibility for immediate neuroradiologic interpretation.

A hospital trauma team should include an otolaryngologist as part of the surgical team to help evaluate and repair the aerodigestive tract and explore the nerves and branches of the carotid artery in the neck. Patients with significant bleeding or an expanding hematoma need immediate attention with probable emergent exploration in the operating room.

Several series of cases have shown examples of injuries being misdiagnosed, both by angiography and during direct exploration.[12] False aneurysms, external carotid branch lacerations, arteriovenous fistulas, and viscus-vessel fistulas have all been described despite the presence of sophisticated personnel and experienced examiners. Approximately 30% of patients with carotid artery injury present with a neurologic deficit.[13] Arterial injury or propagation of a thrombus into the skull can lead to cerebral ischemia. One third of the population cannot tolerate complete unilateral carotid occlusion.

The debate over the merits of mandatory versus selective exploration continues. Meyer and colleagues[14] have reviewed their data and suggest that mandatory exploration is appropriate. Others have used similar data to suggest the advantages of selective exploration.[9,14] Among patients explored routinely, 50% to 70% have negative explorations with some morbidity and some cosmetic deformity.[15,16]

Several surgeons claim that mandatory exploratory operations are the gold standard against which all other procedures should be measured. The rare case of a patient under observation suffering from an underdiagnosed hemorrhage with complications is cited to encourage exploration. However, prospective studies have failed to prove that either choice is clearly better. Many level I trauma centers have become more encouraged by selective management (Figs. 115-4 and 115-5). Table 115-5 shows the accuracy of selective evaluation techniques with the caveat that using rigid and flexible esophagoscopy together can be more accurate than the use of either one alone.[17] In cases where the cervical spine has not been cleared, flexible endoscopy is helpful for evaluating injuries of the pharynx and esophagus. Contrast infusion CT scanning can aid in the surgical decision making for zone II penetrating neck injuries.[18]

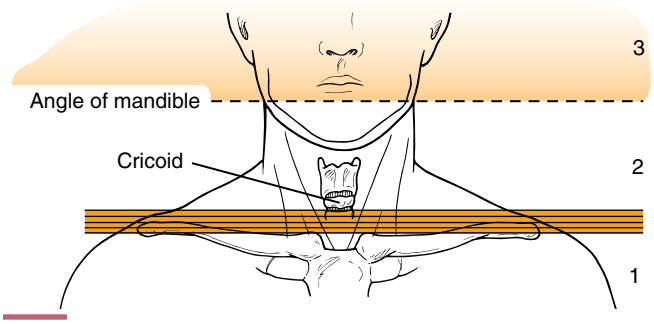

Figure 115-3. The three zones of the neck are seen on this frontal view. The *shaded area* represents the portion that some authors consider zone I but that others label zone II. *(From Carducci B, Lowe RA, Dalsey W. Penetrating neck trauma: consensus and controversies.* Ann Emerg Med. *1986;15:208.)*

Angiography

Angiography is the most urgently performed diagnostic technique because once the airway has been secured by intubation or tracheostomy, hemorrhage can be life threatening. A positive angiogram may mandate an immediate trip to the operating room, but evaluation of the upper digestive tract in the radiology suite may be useful if time and the patient's condition permit. Zone I and zone III injuries usually require routine preoperative arteriography on stable patients because their surgical approach is more difficult than zone II injuries. In addition, when wounds involve both sides of the neck with zone I and zone III injuries, four-vessel angiography (bilateral carotid and vertebral arteries) should be considered in stable but symptomatic patients.

Zone II wounds are usually easily accessible and a low risk for exploration. Zone II injuries may be evaluated by selective angiography or exploration. Certain indications for an angiogram in zone II injuries include a stable patient who has persistent hemorrhage or neurologic deficits compatible with adjacent vascular structure damage (Fig. 115-6).[19] An example of this is a Horner's syndrome indicative of sympathetic nerve plexus injury or hoarseness indicating a recurrent laryngeal nerve injury. This neurologic picture suggests that the carotid sheath has been violated, and vascular integrity needs confirmation by angiography, as well as frequent close observation to detect for a lacerated carotid artery, intimal tear, or pseudoaneurysm (Fig. 115-7).[20] Arteriography can be accurate diagnostically with good technique and with an experienced radiologist. Patients with negative arteriography

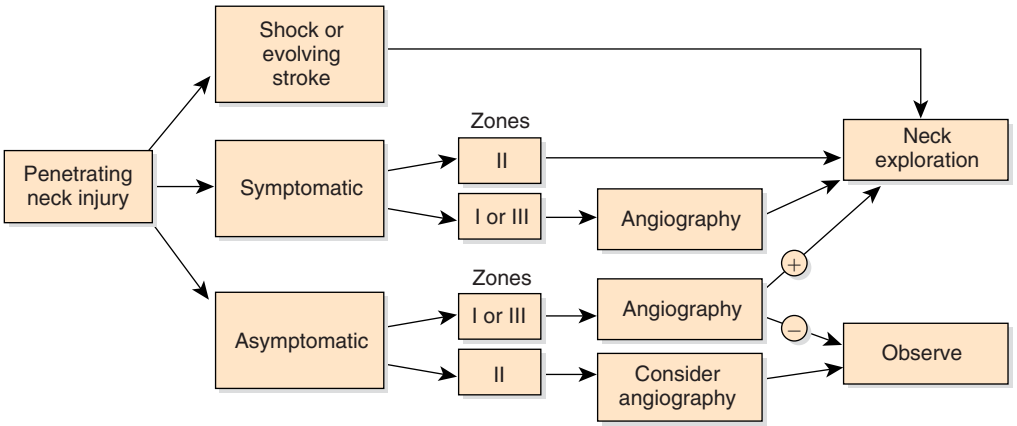

Figure 115-4. Selective management of penetrating neck injury. *(Adapted from McConnell D, Trunkey D. Management of penetrating trauma to the neck.* Adv Surg. *1994;27:97.)*

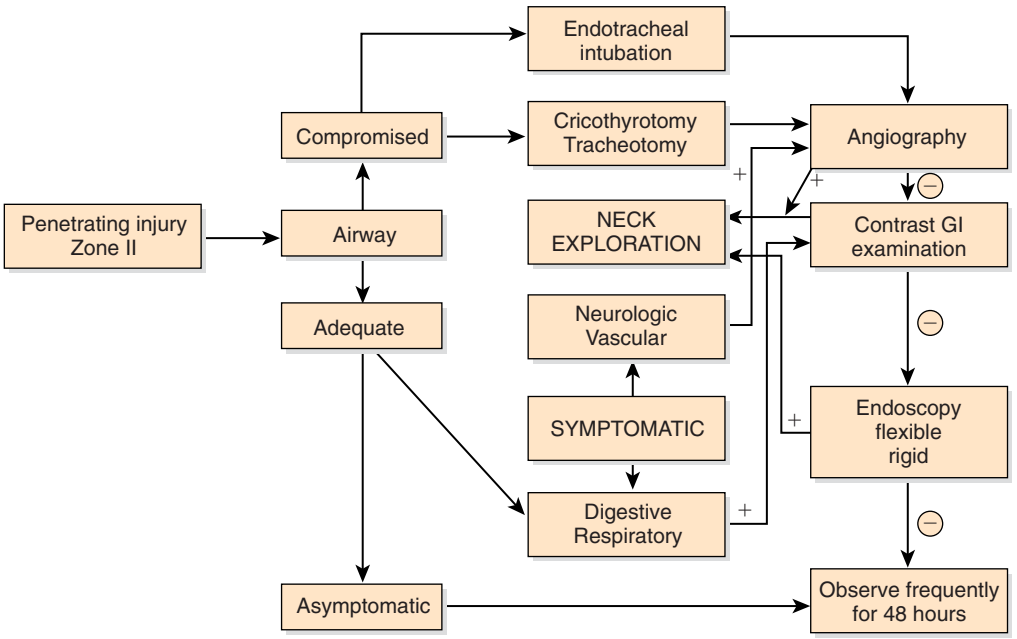

Figure 115-5. An algorithmic approach to penetrating neck wounds of zone II.

Table 115-5

Accuracy of Selective Evaluation Techniques

Procedure	Indications	Contraindications	Accuracy (%)
Angiography	Wounds near vessel in zone I or zone III	Expanding hematoma	98.5
		Profound shock	
		Uncontrolled bleeding	
Barium swallow	Hematemesis	Intubated	90.0
	Drooling	Saliva in wound	
	Dysphagia	Unstable patient	
	Vocal cord paralysis	—	
Esophagoscopy	Suspected but unconfirmed injury by barium swallow	None	86
	Intubated	—	
	Laryngeal or tracheal injury	—	
	Vascular injury in zone II or zone III	—	
Direct laryngoscopy and bronchoscopy	Vocal cord paralysis Hoarseness Tenderness or crepitance over larynx Subcutaneous emphysema Hemoptysis	None	100

From Miller RH, Duplechain JK. Penetrating wounds of the neck. *Otolaryngol Clin North Am.* 1991;24:15. Used with permission.

and positive physical signs still need exploration. If there is radiographic evidence that a bullet has changed location due to gravitational or positional change of the patient, removal of the bullet should be considered. This is because a migratory bullet can increase the risk of embolic phenomenon.[21]

For asymptomatic zone II penetrating neck injuries, the usefulness of angiography remains controversial. One study showed no statistically significant difference in sensitivities between a clinical examination and angiography for the detection of vascular injury. This study concluded that the clinical examination for zone II injuries may be sufficient to detect significant vascular lesions unless the trauma is in close proximity to the major vessels.[22] Other studies have supported the use of angiography for stable asymptomatic patients (Fig. 115-8).[23] Some have suggested the increasing role of computed tomographic angiography

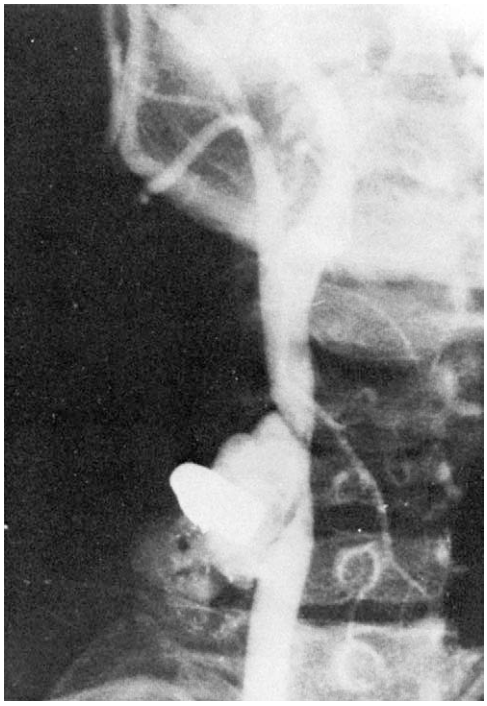

Figure 115-6. Arteriogram demonstrating common carotid artery injury in a 26-year-old man with small hematoma and normal neurologic examination. *(From Hiatt JR, Busuttil RW, Wilson SE. Impact of routine arteriography on management of penetrating neck injuries.* J Vasc Surg. *1984;1:860.)*

(CTA) as a fast, minimally invasive screening method to evaluate penetrating neck injuries in hemodynamically stable patients.[24]

Management of Vascular Penetration

Zone I vascular perforation requires thoracic surgery. Although a low cervical incision may result in sufficient exposure, a mediastinotomy extension or a formal lateral thoracotomy may be necessary.

Zone III injuries at the skull base can be temporized by pressure, but once delineated, access to the injury may require mandibulotomy in the midline similar to exposure for a parapharyngeal space tumor. A temporary arterial bypass of the carotid artery may be placed until the lacerated or aneurysmatic vessel can be approached safely.

For controlling distal bleeding from the internal carotid in zone III, Perry[26] has described passing a No. 4 Fogarty catheter through a Pruitt-Inahara shunt. By passing the Fogarty catheter beyond the injury and inflating the balloon to occlude the lumen, the shunt can then be advanced beyond the injury (Fig. 115-9).[25] After removing the Fogarty catheter, proximal shunt placement is performed. To evaluate patency and vascular flow of the artery repair, Doppler probe measurements are conducted with consideration for angiography.

All veins in the neck can be safely ligated to control hemorrhage; if both internal jugular veins are interrupted by the injury, an attempt to repair one is appropriate. All external carotid artery injuries are easily managed by suture ligation because collateral circulation is good. Common carotid or internal carotid injury in zone II is explored once the diagnosis is made by an approach along the anterior border of the sternocleidomastoid muscle. To find the carotid artery in cases where the vessel is no longer pulsating (i.e., hematoma injury or proximal interruption), the external carotid branches may be followed retrograde from the facial artery at the submandibular gland or from the superior thyroid artery at the superior cornu of the thyroid cartilage.

Techniques of lateral arteriorrhaphy for vascular repair (Fig. 115-10) have been suggested.[26] End-to-end anastomosis or autogenous grafting is recommended when stenosis is evident by arteriography.

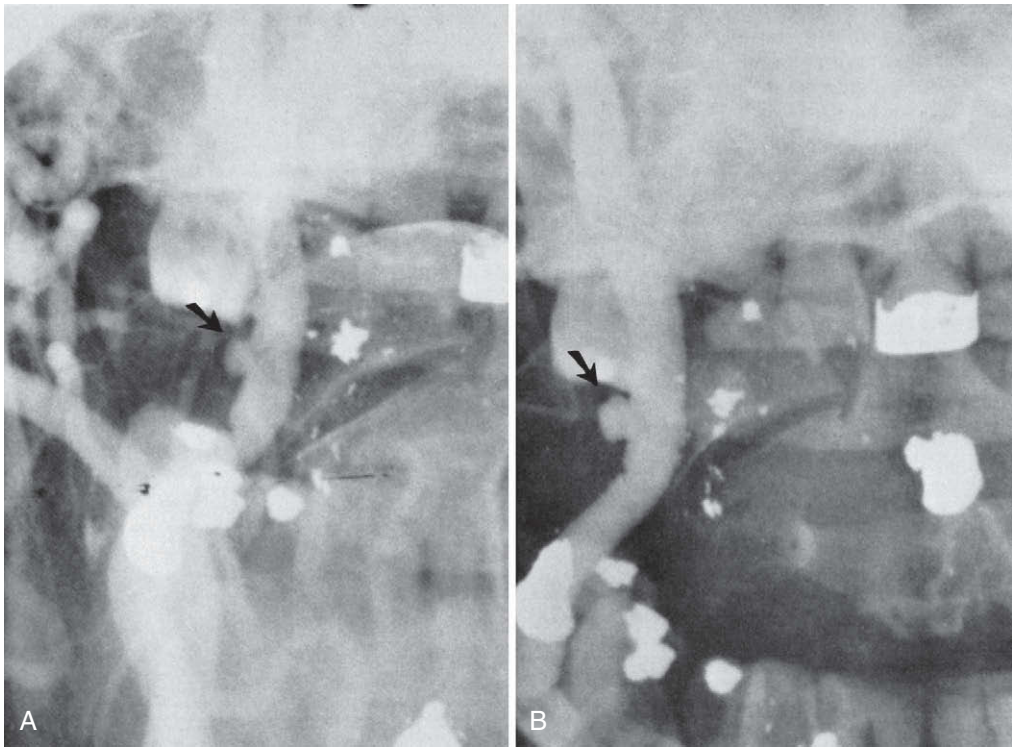

Figure 115-7. A, Anteroposterior view arteriogram of the right common carotid artery reveals a contained extravasation of the internal carotid artery near the base of the skull *(arrow)*. Cranial nerve deficits at the jugular foramen (X to XII) accompany this injury. **B,** A follow-up arteriogram of the internal carotid artery 1 week later shows enlargement of the pseudoaneurysm. *(From Scalfani S, Panetta T, Goldstein A, et al. The management of arterial injuries caused by penetration of zone II of the neck.* J Trauma. *1985;25:871.)*

Ligation of the common or internal carotid injuries is generally reserved for irreparable injuries and in patients who are in a profound coma state with bilateral fixed and dilated pupils. Delayed complications from unrepaired vascular injuries include aneurysm formation, dissecting aneurysm, and arteriovenous fistulas.

More recently, interventional radiologists have used angiographic techniques to treat vascular injury. In some instances, embolization procedures can help control arterial disruption.[27] For arterial injuries in zone III, transcatheter arterial embolization can be an effective modality to obtain hemostasis. Penetrating injuries in zone III have a higher incidence of multiple vascular injuries involving the internal carotid artery, internal maxillary artery, and external carotid artery.[27] In areas of difficult vascular access at the skull base, detachable balloons or steel coils can be placed for carotid occlusion.[28] Embolized bullets also can be retrieved by angiographic techniques. The possible complications of interventional angiography include blood vessel injury, inadvertent balloon detachment, ischemic events, pseudoaneurysm formation, and treatment failure.

Achieving hemorrhage control of penetrating vertebral artery injuries can be challenging given their anatomic relationship with the bony structure of the cervical spine and mandible. Because these vertebral artery injuries often result in both neurologic and hemodynamic sequelae, they are frequently associated with higher morbidity and mortality rates. Because their surgical management can be complex, endovascular treatment approaches have been promising.[29]

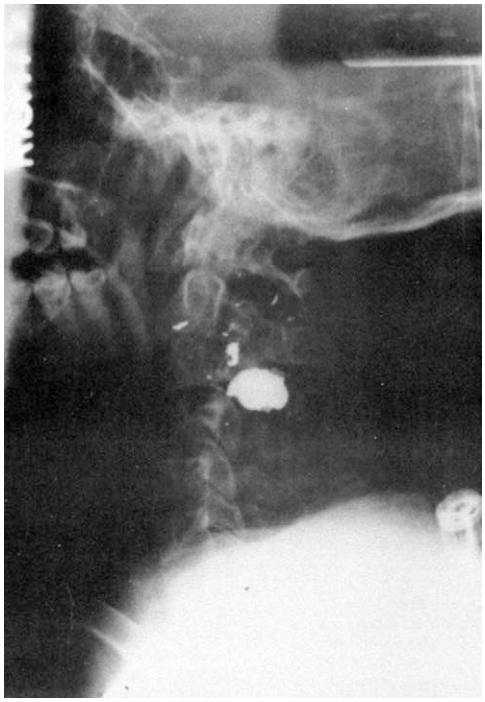

Figure 115-8. This patient had a high cervical cord resection with quadriplegia. No vascular injury was recognized. *(From Ordog GJ, Albin D, Wasserberger J, et al. 110 bullet wounds to the neck.* J Trauma. *1985;25:238.)*

Digestive Tract Evaluation

In the patient with a possible esophageal perforation, most radiologists recommend Gastrografin swallow as a first-order contrast study because barium extravasation radiographically distorts soft tissue planes for other studies and is more toxic. Reports in the literature are mixed[7,12] regarding which of these methods is more reliable in demonstrating a perforated esophagus or pharynx. A negative Gastrografin study should be followed by a barium swallow if suspicion remains high.[12]

Many studies report the use of flexible esophagoscopy to circumvent the need for general anesthesia during rigid endoscopy. However, several authors have reported a missed perforation near the cricopharyngeus, as well as the hypopharynx, where flexible endoscopy is least satisfactory due to mucosa redundancy. Missed esophageal tears (Fig. 115-11) represent most of the delayed injuries and, when they progress to mediastinitis, morbidity and mortality are considerable.[30] Meyer and colleagues[14] found a significant incidence of missed esophageal injury in their prospective endoscopic, contrast radiographs, and subsequent mandatory exploration studies. Some surgery services mandate neck exploration for patients who have air in the soft tissues of the neck despite yielding normal endoscopy results. At the time of exploration to rule out pharyngeal and esophageal injuries, a nasogastric tube can be gently pulled up to the level of the neck and methylene blue infused through the nasogastric tube to help localize the injury site. The combination of flexible endoscopy and rigid esophagoscopy to examine the entire cervical and upper thoracic esophagus has also been reported. No perforations were missed in those series using both techniques on all patients. If suspicion of a pharyngeal perforation remains unconfirmed by examination or even by exploration, the patient is given no food and is observed for several days. Fever, tachycardia, or widening of the mediastinum on serial chest radiographs requires that repeat endoscopy or neck exploration be considered. When an esophageal injury is found early, management involves a two-layer closure with wound irrigation, débridement, and adequate drainage. After repair of the mucosa perforation, a muscle flap may be interposed over the esophageal suture line for further protection.[31] One study showed the value of a muscle flap placed in the bed of a traumatic esophageal and tracheal wound to minimize the risk of a tracheoesophageal fistula (Fig. 115-12).[19] If an extensive esophageal injury is present,

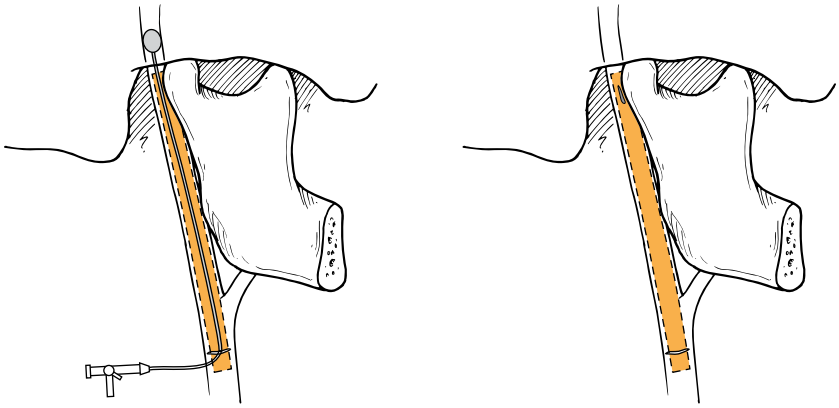

Figure 115-9. No. 4 Fogarty catheter method with shunt placement in an attempt to control bleeding of internal carotid artery near skull base. *(Modified from Perry M. Injuries of the carotid and vertebral arteries. In: Bongard FS, Wilson SE, Perry MO, eds.* Vascular Injuries in Surgical Practice. *Norwalk, Conn: Appleton & Lange; 1991.)*

it may necessitate a lateral cervical esophagostomy and later definitive repair.

Many surgeons perform direct laryngoscopy, bronchoscopy, and rigid esophagoscopy under anesthesia for penetrating injuries of the neck with air in the soft tissues, hemoptysis, hematemesis, or other suspicious clinical findings. Direct laryngoscopy and rigid bronchoscopy can be combined with flexible airway examination to recognize and stent a lacerated trachea temporarily. In the setting of a cervical spine fracture, rigid esophagoscopy may have to be omitted. Definitive management for any airway compromise is always essential.

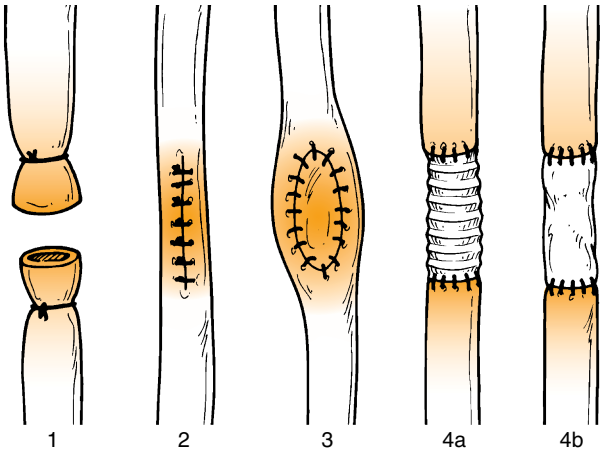

Figure 115-10. Types of vascular repairs: **1**, vessel ligation; **2**, vessel wall repair; **3**, vessel patch graft; **4a**, synthetic vessel graft; **4b**, autogenous vessel graft. *(From Dichtel WJ, Miller RH, Feliciano DV, et al. Lateral mandibulotomy: a technique of exposure for penetrating injuries of the internal carotid artery at the base of the skull.* Laryngoscope. *1984;94:1142.)*

If the clinical examination is benign, follow-up examination is done frequently (at least three times every 24-hour shift) by a physician recording his or her observations. Frequent monitoring of vital signs, as well as examination of the neck and the entry wounds by the nursing staff, is also crucial. A 48- to 72-hour observation period should be used to monitor for changes in physical findings or vital signs that mandate urgent attention. Most vascular injuries that need attention present within 48 hours. Careful appraisals show that the patient with a negative physical examination and normal radiograph and endoscopy will most likely have a negative neck exploration, and no significant injury will be discovered. Direct observation can thus be recommended.[9]

Management of Laryngotracheal Injury

Laryngeal mucosal lacerations from penetrating injury should be considered to be repaired early (within 24 hours) because the time that elapses before repair can affect airway scarring and voice.[32]

Significant glottic and supraglottic lacerations and displaced cartilage fractures need surgical approximation. Endoscopy and CT will differentiate between the patients who need only observation (small laceration, shallow laceration, nondisplaced fracture) and those that require a thyrotomy or open fracture reduction and mucosal approximation. A soft laryngeal stent may be necessary for badly macerated mucosa.

Simple tracheal lacerations that do not detach a tracheal ring or encroach on the airway can be repaired without a tracheostomy. More severe disruptions (gunshot wound directly to the trachea) imply more soft tissue injury and a 6-week tracheostomy either below or through the tracheal injury is the safest procedure. Later the stenosis may require sleeve resection, but if the stenosis is soft, it can often be managed by a T-tube tracheostomy tube.

Blunt Neck Trauma

Blunt neck injuries can occur from motor vehicle accidents and sports injuries. A blunt force may result in laryngeal, vascular, and digestive

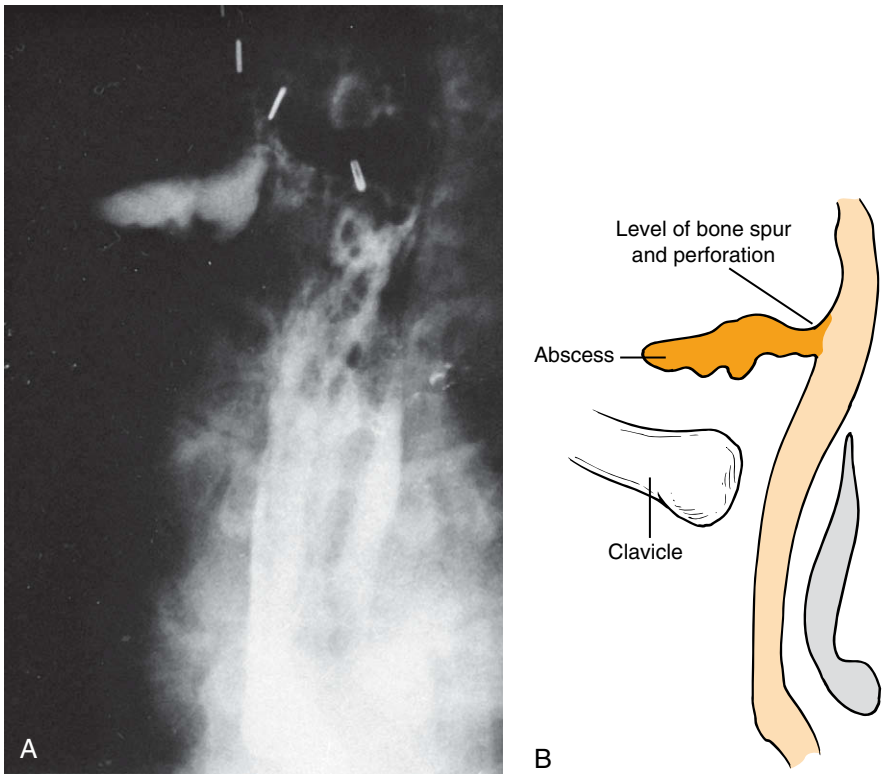

Figure 115-11. This perforation occurred from blunt trauma. Cervical esophageal perforation from flexion-hyperextension injury. **A,** Esophagogram showing perforation at the level of the C5-6 vertebrae. **B,** Level of bone spur and perforation. *(From Splener CW, Benfield JR. Esophageal disruption from blunt and penetrating external trauma.* Arch Surg. *1976;111:663-667. Copyright 1986, American Medical Association.)*

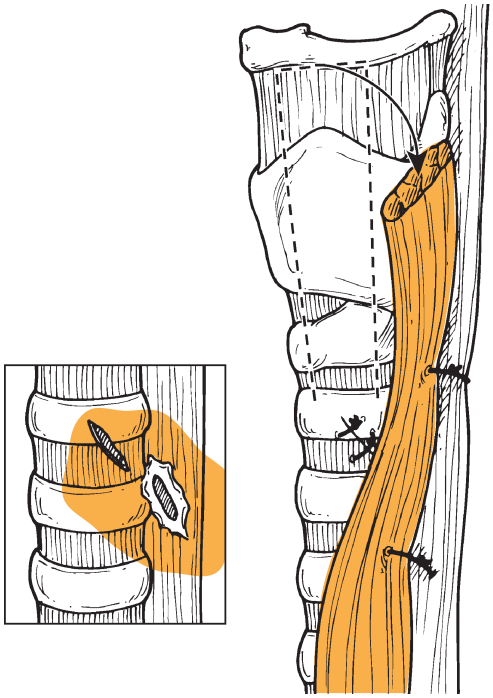

Figure 115-12. Interposition of strap muscle between esophageal and tracheal repair. *(From Miller RH.* The Surgical Atlas of Airway and Facial Trauma. *Philadelphia: WB Saunders; 1983.)*

injuries and be easily underdiagnosed because their onset can be delayed. In addition, occult cervical spine injury may be present with blunt neck trauma.[33]

For these reasons, careful observation should be made for individuals with blunt neck injury because their signs and symptoms may be delayed in onset involving the airway, vascular, digestive, and neurologic systems. This is especially apparent in patients who have multisystem trauma in which blunt laryngotracheal injuries can be frequently overlooked. Due to slow progression of airway edema from laryngotracheal trauma, airway obstruction may not occur until several hours after the injury. Thus monitoring for delayed signs and symptoms of airway injury should be carefully watched for as described in Box 115-1 in the beginning of this chapter. CT may be helpful to determine degrees of injury to the larynx and vessels.[34,35] Blunt injury to the cervical vessels can lead to thrombosis, intimal tears, dissection, and pseudoaneurysm. Treatment options for blunt artery injuries are based on the mechanism, type of injury, and location. Treatments for blunt artery injuries include surgery, anticoagulation, and observation. Surgical intervention for blunt vascular injuries includes ligation, resection, thrombectomy, and stent placement.

Summary

Emergent surgical exploration is indicated for any immediate life-threatening signs or symptoms from penetrating neck trauma (i.e., massive bleeding, expanding hematoma, nonexpanding hematoma in the presence of hemodynamic instability, hemomediastinum, hemothorax, hypovolemic shock).

For the stable patient, the choice of treatment remains controversial. Knowledge of the neck zone involvement (I, II, or III), mechanism of injury, and velocity of the projectile are helpful in determining the likelihood of vital structure injury. Presently, many trauma centers manage stable patients with non–life-threatening penetrating neck trauma with selective exploration; however, this must be supported by on-site angiography, flexible and rigid endoscopy, and closely monitored physical examinations. High-velocity missiles inflict a significantly greater amount of damage than low-velocity projectiles. Zone I and zone III injuries usually require arteriography on all stable patents. Stable patients with zone II injuries may require angiography. Because hemorrhage is the leading cause of death for penetrating neck injuries, hemodynamic and neurologic status should always be monitored closely for at least 48 to 72 hours.

In blunt neck trauma, injuries can involve the laryngeal, cervical, vascular, and digestive structures. Symptoms can present in a delayed fashion and be easily underdiagnosed. For these reasons, careful observation should be made for individuals with significant blunt neck trauma in order to monitor for progressive signs and symptoms of laryngeal, cervical, vascular, and digestive injury.

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CHAPTER ONE HUNDRED AND SIXTEEN

Differential Diagnosis of Neck Masses

Amy Chen

Kristen J. Otto

Key Points

- Neck masses are common in the general population and represent a wide array of pathologies.
- The likelihood for any given neck mass diagnosis is most closely related to the patient's age.
- Inflammatory neck masses are the most common neck masses in pediatric and young adult age groups.
- Congenital neck masses are rarely seen in older adults, and the possibility for malignancy must be thoroughly investigated in this group of patients.
- The unknown primary squamous cell carcinoma of the neck represents a special entity and diagnostic paradigm. A specific protocol must be followed when patients with unknown primary squamous cell carcinoma of the neck are being evaluated, with the main goal of locating the primary lesion in a mucosal site.

A mass in the neck is an extremely common clinical finding in patients of all age groups. Neck masses are often the result of inflammation caused by self-limited processes such as viral infections, although the differential diagnosis of a neck mass actually encompasses the entire spectrum of pathology from congenital to infectious to neoplastic. The list of all conditions associated with neck masses is too sizable to list in this chapter, but with a detailed understanding of the anatomy and what constitutes an abnormality, the evaluation of any neck mass can be approached systematically. This chapter focuses on the important examination findings, diagnostics, and workup of the most common etiologies associated with neck masses. Treatment of masses of the neck is not discussed in this chapter.

History and Physical Examination

Age is a crucial element of the history-taking when evaluating a patient with a neck mass. For the purposes of the workup, patients can be broken up into several age groups: pediatric (0 to 15 years old), young adult (16 to 40 years old), and older adult (older than the age of 40) (Fig. 116-1). The difference in relative probabilities of congenital versus inflammatory versus neoplastic neck masses within these groups makes their differentiation important. In the pediatric population inflammatory masses are more common than those of congenital origin, and congenital masses are more common than neoplastic neck masses. The same can be said for the young adult population, although, as the patient ages, the risk for a neck mass of congenital origin decreases as the risk for a neoplastic process increases. The major distinction can be made in the older adult population, where consideration for neoplasia should be highest on the differential diagnosis list.[1] With the exception of masses that occur in the thyroid, 80% of adult neck masses are neoplastic and 80% of those are malignant. In a child, however, more than 90% of neck masses are benign.[2,3] Other important elements of the history include the time course to presentation, risk factors for immunodeficiency, and prior trauma, travel, irradiation, or surgery. Associated symptoms are also important and can help differentiate neck mass etiology and origin. Of these, fever, dysphagia, weight loss, otalgia, hearing loss, and respiratory difficulty are just a few.

Physical examination is a key component to the workup of an unknown neck mass and should not be limited to palpation of the mass itself. The physician must remember to perform a full head and neck examination including evaluation of all mucosal surfaces of the head and neck. A key adjunct to visual inspection of the head and neck and aerodigestive tract mucosa is fiberoptic laryngoscopy, which should be used in most instances of evaluating an unknown neck mass. The clinician should remember that primary lesions may be submucosal in the head and neck. Thus palpation of mucosal sites such as the floor of mouth and tongue base are also important. Other adjunctive examination findings such as a bruit may point toward a vascular origin. The otolaryngologist must always make a point to evaluate the patient's airway status during fiberoptic examination. Airway evaluation will be crucial for eventual surgical planning and will also delineate the patient's need for emergency airway intervention.

Diagnostic Imaging of the Neck

The preferred imaging modality in the workup of a neck mass may differ on the basis of patient age, time course to presentation, and the clinical suspicion of the examiner (Table 116-1). In a child with suspected infectious adenopathy, ultrasound can be used to differentiate a fluid-filled abscess from a solid lymph node and help in the eventual treatment protocol.[3] Ultrasound imaging is helpful in the diagnosis of pediatric neck masses because it does not require the use of sedation or general anesthesia as do the more detailed imaging modalities such as computed tomography or magnetic resonance; it is inexpensive and allows the patient to avoid ionizing radiation. Ultrasound is useful for soft tissue imaging, the differentiation of cystic versus solid masses,

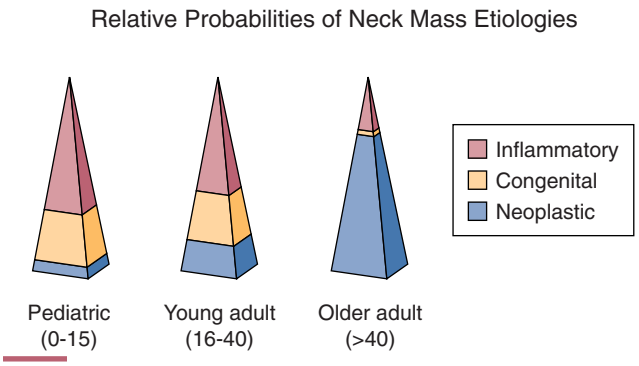

Figure 116-1. Breakdown of neck masses by age.

Table 116-1

Imaging of Neck Masses

Modality	Basic Indications
Ultrasound	Good for pediatric neck masses, thyroid masses. Differentiates cystic versus solid.
Computed tomography	Workhorse imaging modality for adult neck masses. Provides three-dimensional relationships, excellent detail of mucosal disease and involvement of adjacent bone.
Magnetic resonance imaging	Superior soft tissue delineation. Good for lesions of the salivary glands and tongue (where dental amalgam may obscure the view on a CT). Modality of choice for determining nerve enhancement. Consider for thyroid imaging in cases necessitating radioiodine.
Radionuclide scanning	Useful for midline lesions in children—differentiates functioning from nonfunctioning tissue.
Positron emission tomography	Useful for staging of head and neck malignancies. Can be used in cases of unknown primary malignant neck masses or treated neck disease.
Angiography/magnetic resonance angiography/computed tomography angiography	Useful for lesions encasing the carotid and vascular lesions. Conventional angiography should be considered for preoperative assessment in cases of potential carotid artery sacrifice or where embolization is required.
Plain radiograph	Generally should not be considered in the workup of a neck mass.

thyroid pathology, and salivary gland pathology,[4] but it is extremely limited in providing detail regarding soft tissue invasion and approximation to bone.

Computed tomography (CT) is the workhorse imaging modality for adult neck masses. CT provides excellent resolution of both soft tissue and bone and, when used in conjunction with iodinated intravenous contrast, allows for superior delineation of vascular lesions. Neck masses can be evaluated for invasion of surrounding soft tissue and bone, airway compression, and perineural and perivascular invasion. CT also allows for determination of jugular vein occlusion in the case of infectious neck masses. CT locates masses within or outside of glands or nodal chains and provides three-dimensional relationships.[4] In the workup of an adult with a suspected unknown primary metastatic neck node, CT gives excellent detail regarding head and neck mucosal sites.

Magnetic resonance imaging (MRI) is the most superior imaging modality for soft tissue detail, although it is less readily available and more expensive than the choices described previously. MRI is useful in pregnant women because it does not require radiation, and it is also a good choice for cases of well-differentiated thyroid malignancies where radioiodine therapy is to be used because iodinated contrast is not necessary.[4] MRI is the best choice of imaging when perineural spread is to be determined. CT and MRI are often complementary imaging tools for the workup of an adult with a suspected head and neck malignancy.[5]

Radionuclide scanning can be of help in the workup of an anterior or midline neck mass, particularly in the pediatric population. Radionuclide scanning gives the added benefit of differentiating functioning from nonfunctioning tissue and thus can be considered in the workup of a lingual thyroid or thyroglossal duct cyst, where the presence of normal functioning thyroid tissue must be determined before any consideration for surgical excision. Radionuclide imaging can also be considered in the workup of salivary gland pathology because lesions can be localized to within or outside of the major salivary glands.[3]

Positron emission tomography (PET) is a useful imaging adjunct in the workup of head and neck malignancies, but it should not be considered standard for first-line evaluation. PET can differentiate persistent disease from postradiation effects, particularly when it is used in conjunction with contrast-enhanced CT to evaluate treated nodal disease,[6] and can occasionally detect metastatic nodal disease equivocal on CT or MRI. PET is also helpful in the diagnosis of distant metastatic disease for patients with known head and neck malignancies.

In cases of suspected vascular lesions, arteriography can be helpful, both from diagnostic and therapeutic viewpoints. Arteriography can identify lesions with carotid infiltration and can help in differentiating the origin of paragangliomas. The use of arteriography in a preoperative setting can also allow for balloon occlusion testing in cases of possible carotid artery sacrifice or embolization of tumor feeding vessels. CT arteriography (CTA) and magnetic resonance arteriography (MRA) are also both readily available and allow for excellent vascular imaging clarity. They have the added benefit of reducing the risk of the invasiveness of arteriography. In general, these tests can be considered for basic imaging of vascular lesions, but when an intervention such as balloon occlusion or embolization is necessary, traditional arteriography is the gold standard.

Plain radiographs are of little use in the workup of a neck mass in any population and, in general, should not be considered in the face of the excellent imaging modalities discussed earlier. A plain radiograph of the chest (CXR), however, is an important tool for comprehensive staging in the case of a suspected malignancy of the head and neck. CXR should accompany the other diagnostic imaging modalities in these patients.

Initial Workup of the Unknown Neck Mass

The correct clinical management course of a neck mass will often be determined by information gleaned from the history and physical examination, as well as the imaging. The most important first step is making a diagnosis. In the pediatric and young adult populations, where inflammatory neck masses are common, an antibiotic trial is a reasonable starting point for patients with suspected infectious adenopathy. In general, antibiotics may be given for several weeks, after which time the differential diagnosis should be reconsidered and further workup may be necessary. Typically, unilateral, enlarging, or asymmetric masses; masses located in the supraclavicular fossae; masses associated with other worrisome symptoms; and masses not associated with prior infectious symptoms should be further investigated. If, during the

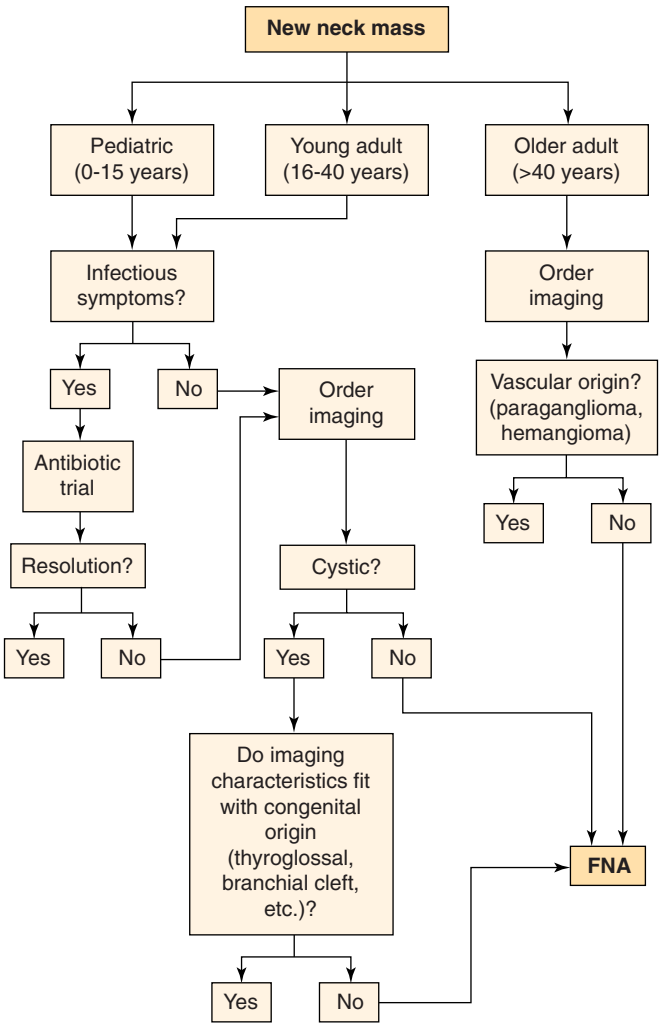

Figure 116-2. Diagnostic schema for a new neck mass.

antibiotic trial, the mass progresses or the patient develops new symptoms, the management paradigm should be reconsidered as well. Imaging of the neck mass is a good starting point to better define the mass and the structures it involves.

If a patient has failed an antibiotic trial, or in any case of an adult with a new neck mass, biopsy should always be considered as an essential step in making a diagnosis. The gold-standard biopsy modality in the workup of a neck mass is fine-needle aspiration (FNA) (Fig. 116-2). The sensitivity and specificity of FNA for both pediatric and adult head and neck masses have been reported to be approximately 97% when diagnostic material is obtained.[7-9] FNA should always be done before the consideration of any open procedures. FNA can be used for both cytology and culture (in cases in which a suspected infectious neck mass does not respond to conventional antibiotic therapy). If an FNA is unsuccessful or if sufficient information is not obtained from an initial FNA, the FNA should be repeated before open biopsy. Multiple aspirations using a thin needle (usually 25-gauge) are necessary. The FNA should be performed in the presence of an experienced cytopathologist to ensure ideal slide preparation and thus useful diagnostic information.[8,9] Studies comparing the sufficiency, accuracy, and diagnostic outcome of FNAs performed by cytopathologists versus those performed by clinicians have actually shown that cytopathologists' FNA attempts yield significantly more useful diagnostic information than those of clinicians.[8] Cells obtained by FNA can be analyzed for microbiologic, molecular, and cytogenetic properties if these techniques are useful in the diagnosis.[5,8,9] If an FNA has been unsuccessful or has failed to reveal useful results after several attempts, a core needle biopsy should be considered.[3,5,9] FNA may miss the true lesion in cases where a neck mass is especially bloody, necrotic, or fibrotic, and specific diagnostic information may be unattainable in lesions where complex tissue architecture is necessary.[7] Open biopsy of neck masses should only be considered as a last resort for diagnosis. In the case that squamous cell carcinoma is identified in the neck during open biopsy, the surgeon should be prepared to proceed with a comprehensive neck dissection. This possibility should be part of the patient's preoperative counseling.

Once the diagnosis is made, it will be necessary to determine whether the particular diagnosis warrants further investigations. The best example of this is the case of an unknown primary malignancy of the neck. A detailed diagnostic protocol must be adhered to in the workup of an unknown primary malignancy in the neck. A variety of pathologic entities can manifest with the primary presentation being an enlarged metastatic cervical lymph node. Among these, adenocarcinoma, thyroid malignancies, poorly differentiated carcinoma, and melanoma are seen on occasion, but squamous cell carcinoma is the most common.[3,5] The detailed workup required in the evaluation of the unknown primary squamous cell carcinoma of the neck is discussed later in this chapter.

Unknown Neck Mass: Differential Diagnosis

Inflammatory Neck Masses

Inflammatory neck masses represent the most common and ubiquitous neck masses across all age groups.

Lymphadenopathy/Lymphadenitis

Inflammatory lymphadenopathy can occur in response to any infectious or inflammatory process in the head and neck and is typically a self-limited process lasting days to weeks. Lymph nodes will enlarge and become tender in the face of infection or inflammation, then typically subside without treatment. Occasionally lymph nodes will become necrotic in the face of bacterial or viral infection, and an abscess forms. These nodes can be differentiated by ultrasound or CT. *Staphylococcus* and *Streptococcus* are the organisms most commonly cultured from neck abscesses.[3,4,10] Diffuse lymphadenopathy is common in patients with human immunodeficiency virus, but a growing or dominant mass should raise suspicion for lymphoma.[11]

Granulomatous Diseases

The clinician should keep a multitude of granulomatous processes in mind when evaluating a neck mass. Diagnosis of most of these will rely on associated signs and symptoms, history of exposure or travel, and, of course, FNA biopsy. These entities include tuberculosis, atypical mycobacterial infections, actinomycosis, cat-scratch disease, and syphilis. FNA is the preferred biopsy technique because open procedures may create nonhealing wounds.

Sialadenitis/Sialolithiasis

Inflammation, infection, and/or blockage of the parotid or submandibular glands or their ducts can produce neck masses. The infected parotid or submandibular gland will present as a warm, tender, enlarged gland. Systemic symptoms such as fevers and chills may be present. Often, the examiner will be able to express purulent material from the duct draining the gland. This diagnosis typically does not require imaging, and treatment is with antibiotics, hydration, warm compresses, massage, and sialagogues.

Patients with sialolithiasis will experience periodically enlarged and painful glands, often in association with eating. Ultrasound imaging will typically detect salivary stones either within the glands or the ducts. Chronic sialolithiasis can lead to salivary stasis and eventually sialadenitis. Treatment is with hydration, massage, and sialagogues.

Congenital Neck Masses

The list of congenital causes may be considered in the differential diagnosis both for children and adults with neck masses. Caution, however, should be exercised before assuming a cystic mass in a patient in the older adult population is of congenital origin. In these instances, malignancy must be considered first and foremost, and congenital

diagnoses entertained only once malignancy has been ruled out. A thorough description of the embryology and anatomy of the congenital masses of the neck is beyond the scope of this chapter but is crucial to guiding appropriate and accurate surgical therapy.

Thyroglossal Duct Cysts

Anomalies of the thyroglossal duct are seen commonly in the pediatric population; they are second in frequency only to lymphadenopathy. Remnants of the thyroglossal duct are actually found in approximately 7% of the population, but only a small number of these ever become symptomatic.[12] Because the thyroid begins as a diverticulum within the tongue musculature and descends caudally to finally situate itself low in the neck anterior to the larynx and trachea, it is possible to see remnants of the duct and thyroglossal duct cysts anywhere along this course. The tract of the thyroglossal duct can descend either anterior or posterior to the hyoid bone. Thyroglossal duct cysts usually become evident in childhood as a midline neck mass, often one that is fluid filled and elevates in the neck with tongue protrusion or swallowing. Occasionally, thyroglossal duct cysts present as an infected midline mass. Incision and drainage should generally be avoided in this circumstance because eventual surgical eradication is made more difficult. Needle aspiration, together with antibiotics, is the recommended treatment option for infected thyroglossal duct cysts. Patients should be taken for proper surgical excision once the infection is cleared.

Before consideration for surgical excision, patients must undergo a complete workup of thyroid function to rule out median ectopic thyroid. The workup should consist of thyroid function studies and either ultrasound (to confirm thyroid location) or radionuclide scanning. If a solid mass is discovered during excision of a thyroglossal duct cyst, the diagnosis of median ectopic thyroid should be entertained. If frozen section analysis confirms normal thyroid tissue, the surgeon should confirm the presence of thyroid tissue in the expected location before proceeding.

Performing the proper surgical treatment for thyroglossal duct cysts relies directly on knowledge of the embryologic pathway of the thyroid gland. The Sistrunk procedure, the preferred method of surgical excision, involves excision of the entire pathway of the thyroglossal duct. The patient is placed in the supine position with the neck extended. A horizontal neck incision is planned overlying the cyst. The cyst is dissected free from the surrounding soft tissue and is taken in continuity with the pyramidal lobe of the thyroid (if present) to ensure comprehensive inferior pathway removal. Dissection is then carried superiorly toward the hyoid bone. Often, a proximal tract can be identified. The tract is taken, with a cuff of soft tissue surrounding it. Once the dissection reaches the hyoid bone, the central portion of the bone is taken in continuity with the dissected soft tissue. The bone must be excised due to the inconsistent nature of the tract in relation to it. The final step of the procedure involves following the tract to the level of the tongue base and then amputating the entire tract with suture ligation.

If median ectopic thyroid is identified during thyroglossal duct cyst excision, the proper surgical management is debatable. If there is normal thyroid tissue present in the expected location, the Sistrunk procedure should be performed. If the ectopic focus is the only normal thyroid tissue, it should either be left alone or possibly repositioned laterally in the neck. Thyroid hormone suppression should be considered in these cases to control the size of the ectopic focus for either functional or cosmetic benefit.[12]

Branchial Cleft Anomalies

Approximately 30% of pediatric neck masses are the result of anomalies of branchial clefts; they can present as cysts, sinuses, or fistulae.[12] They are common both in the pediatric and young adult populations. The specific site in the neck where a branchial cleft anomaly occurs is dependent on the brachial arch from which it is derived. Anomalies of the second arch are by far the most common (representing 95% of all branchial cleft anomalies) and typically manifest as a lateral neck swelling associated with an upper respiratory tract infection.[4,12] When these lesions present as infected neck masses, it is important to manage the infection first, although attempts should be made to avoid incision and drainage as in the case of thyroglossal duct cysts.

Particular mention should be made of anomalies of the first branchial arch because these often present a diagnostic and treatment dilemma in the pediatric population. Despite the fact that these anomalies account for only 1% of branchial cleft anomalies,[12] their association with the facial nerve can make management difficult. First arch anomalies come in two types and typically present as cysts, sinuses, or fistulae located between the external auditory canal and the angle of the mandible. Type 1 first branchial cleft anomalies are duplications of the external auditory canal and often have attachments to the skin of the external auditory canal or to the tympanic membrane. These lesions contain ectodermal elements only and typically run lateral to the branches of the facial nerve. Type 2 first branchial cleft anomalies, however, contain ectoderm and mesoderm. These anomalies can often contain cartilage elements. Type 2 first branchial cleft anomalies often course deep to the facial nerve and its branches.

The proper surgical treatment for anomalies of the first branchial cleft includes excision of the entire cyst, fistula, or sinus tract, which often involves superficial parotidectomy and dissection of the facial nerve branches. Complete surgical excision of first branchial cleft anomalies associated with the ear canal requires resection of ear canal skin. If the tract of the anomaly courses medial to the tympanic membrane, a separate procedure is often required to remove the middle ear component.

The most common of the branchial cleft anomalies, accounting for greater than 95%, are those originating from the second arch.[12] Second arch anomalies present as swellings or draining tracts anterior to the sternocleidomastoid muscle. The course runs lateral to the internal carotid artery and enters the pharynx at the tonsillar fossa (the product of the second branchial pouch). Surgical excision is performed by a horizontal incision in the neck overlying the cyst or skin tract. In the case of sinuses and fistulae, skin excision is required to ensure complete eradication. The tract is then followed superiorly to the entry into the pharynx at the tonsillar fossa. Suture ligation occurs at this point. Often, a stair-step incision is required to follow the tract along its entire course.

Anomalies of the third and fourth branchial arches are extremely uncommon. Cysts of these arches can present with airway obstruction, especially if they become infected. The course of anomalies of the third arch is deep to the internal carotid artery. They pierce the thyrohyoid membrane with the superior laryngeal nerve and enter the pharynx at the pyriform sinus. Fourth branchial arch malformations are even rarer and have a variable course depending on the side where they occur. On the left, they course into the mediastinum and around the arch of the aorta, medial to the ligamentum arteriosum. On the right, they follow a tract around the subclavian artery. Fourth arch anomalies ascend into the neck deep to the internal carotid artery, can be intimately associated with the thyroid gland, and enter either the pyriform sinus or the cervical esophagus. Third and fourth branchial cleft malformations present as swellings or sinuses in the low neck anterior to the sternocleidomastoid muscle border, or they can even present as intrathyroid cysts. Excision of these anomalies is rarely necessary but requires excision of the entire course of the tract. Often, hemithyroidectomy is performed simultaneously. Pharyngoscopy and esophagoscopy can be helpful in pinpointing the pharyngeal communication point.

Dermoid Cysts

Dermoid cysts are the result of trapped rests of epithelial elements along the natural lines of embryonic fusion. These cysts contain both ectodermal and endodermal elements. They present as median or paramedian masses that slowly enlarge due to the accumulation of sebaceous contents. They are typically diagnosed before the age of 3.[4,12] Infection within dermoid cysts is rare.

Teratomas

Teratomas, on the other hand, contain elements from all three germ layers. Teratomas of the head and neck comprise less than 2% of all teratomas, but the common head and neck subsites are the neck and nasopharynx.[12] These lesions are usually diagnosed in the prenatal or

early neonatal period, as rapidly enlarging masses. They may present with polyhydramnios caused by esophageal obstruction, or they may cause airway compression. Some neonates will require immediate intubation.

Lymphangiomas

Lymphangiomas are benign hamartomatous lesions of lymphatic vessels and channels. They are soft, compressible masses located most commonly in the posterior triangle of the neck but are also seen in the oral cavity, axilla, and abdomen. Half of all lymphangiomas are present at birth, and 90% are present by the age of 2.[4] They can often enlarge with upper respiratory infections or with hemorrhage into the cystic spaces. Airway intervention is necessary on occasion. These lesions are often diagnosed by physical examination, but ultrasound or CT may be helpful in determining the extent of infiltration into surrounding tissues.

Hemangiomas

Hemangiomas represent congenital lesions of endothelial cells, which always present in the first few months of life. Hemangiomas commonly occur in the head and neck. They are soft, compressible, bluish-purple lesions associated with a bruit or thrill. There are three growth phases to hemangiomas, making their management predictable in most cases. A rapid expansion phase can last 6 to 12 months, followed by a stable phase in which minimal growth or change occurs. The final phase is one of involution, which usually begins by 24 months. Tumor regression is complete in 50% of children by age 5, and nearly all tumors regress by ages 10 to 12.[13]

Primary Neoplasms of the Neck

Unlike those lesions that manifest themselves as metastatic cervical lymph nodes, there are also several neoplastic processes that occur primarily in the neck.

Lymphoma

Lymphoma represents the only primary neoplasm seen in cervical lymph nodes and accounts for approximately 4% of new cancer diagnoses in the United States each year.[8] Lymphomas are the most common head and neck malignancies in the pediatric population and are the second most common overall head and neck malignancy, second only to squamous cell carcinoma.[2,3,14] Lymphoma can be classified as either Hodgkin's or non-Hodgkin's types. Eighty percent of patients with Hodgkin's disease have cervical nodal disease, whereas only about 33% of those with non-Hodgkin's disease have involved cervical lymph nodes. Non-Hodgkin's lymphoma, however, is approximately five times more common than Hodgkin's disease in the head and neck. Greater than 90% of non-Hodgkin's lymphomas are of B-cell origin, while the remainder are of T-cell origin. There is also a strong link between non-Hodgkin's disease and the human immunodeficiency virus.[11,14]

CT represents the best and most appropriate imaging modality for patients with lymphoma; both for the purposes of staging and follow-up. FNA can be helpful for identifying a clonal lymphocyte population in a neck mass, although frequently, nodal tissue is required, by open biopsy, to confirm a diagnosis by flow cytometry.[2] The clinician should pay attention to associated symptoms because these may raise clinical suspicion and assist in the ultimate diagnosis of lymphoma. The so-called "B" symptoms (those symptoms that, when found, upstage the patient) are unexplained fever, unexplained weight loss, and night sweats. These symptoms, when present, make the likelihood of systemic disease much greater.[14]

Thyroid Neoplasms

Thyroid neoplasms represent the most common neoplastic anterior neck masses in all age groups. The incidence of benign thyroid nodules increases with age so that approximately 40% of the population older than the age of 40 have at least one thyroid nodule detectable by ultrasound. Thyroid nodules are approximately four times more likely to occur in women. More than 90% of all thyroid nodules are benign, but the incidence of malignancy within a thyroid nodule increases with the extremes of age—either the very young or the very old. The incidence of malignancy is also increased in men with thyroid nodules.[15] In the pediatric population, a lateral neck mass (lymph node metastasis) is the most common presenting sign of well-differentiated thyroid carcinomas, whereas thyroid masses are the more common presenting sign in adults.[3] As with other neck masses, thyroid nodules should be evaluated with FNA biopsy. Ultrasound imaging is extremely useful for masses of the thyroid because it can provide detail about the thyroid gland itself, as well as the surrounding nodal chains.

Neoplasms of Salivary Glands

Salivary gland tumors represent 1% of all head and neck masses. Among salivary gland neoplasms, 80% arise primarily in the parotid glands, 15% arise in the submandibular glands, and the remainder arise in the sublingual and minor salivary glands. In adults, 80% of parotid lesions are benign; the majority of these are mixed tumors, or pleomorphic adenomas. The incidence of malignancy in salivary gland neoplasms increases as the lesions appear in the smaller glands, such that 50% of submandibular masses are malignant and greater than 75% of sublingual masses are malignant.[16] In children, salivary gland neoplasms are rare, but a greater percentage (35%) are malignant. Hemangiomas represent the most common benign lesions of the parotid glands in children.[3,16] Mucoepidermoid carcinomas are the most common salivary gland malignancies in all population groups.

Although diagnostic imaging is probably not essential for small lesions located in the major salivary glands, both CT and MRI can offer useful information regarding lesions of the salivary glands. Both CT and MRI can help to distinguish tumor invasion, associated adenopathy, and extension into the deep lobe of the parotid and to differentiate deep lobe lesions from tumors of the parapharyngeal space. MRI is the best imaging modality to pinpoint facial nerve enhancement.[17]

Because surgical excision is the management of choice for most salivary gland tumors, there is some debate regarding the necessity and utility of preoperative FNA. FNA can be used for all types of salivary gland tumors and has a sensitivity for distinguishing benign from malignant salivary gland tumors of approximately 95%. FNA is likely useful for preoperative counseling of patients and for assisting in determining the appropriate comprehensiveness of surgical resection.[18]

Neurogenic Neoplasms

Schwannoma is the most common solitary neurogenic tumor of the neck. These lesions occur in patients who are 20 to 50 years old, and 25% to 45% of extracranial schwannomas occur in the neck. The parapharyngeal space is a common cervical location for tumors of neurogenic origin, and for this reason the tumors may clinically mimic salivary gland lesions as they grow laterally. Schwannomas can occur in the cranial nerves, sympathetic trunk, or spinal nerve roots.[19] These lesions are best imaged by CT or MRI; they are enhancing and will often demonstrate areas of cystic degeneration.[19] When located in the carotid sheath, schwannomas will displace the internal and external carotid arteries anteriorly, a feature distinguishing them from carotid body tumors. These lesions can be difficult to diagnose by FNA because FNAs typically reveal bland spindle cell cytology and can be confused with other soft tissue tumors.[20] Schwannomas can manifest as cranial nerve deficits of the involved nerves and are typically painful on attempts at FNA biopsy.

Other neurogenic neoplasms of the neck include neurofibromas and malignant peripheral nerve sheath tumors. Neurofibromas should be considered in their association with von Recklinghausen's disease (NF-1). Most patients with NF-1 present with diffuse or plexiform neurofibromas. There is a 2% to 6% incidence of malignant degeneration into or de novo generation of malignant peripheral nerve tumors for patients with neurofibromas associated with NF-1.[19]

Neurogenic tumors can also present in the form of lesions of neuroblastic origin. The list of pathologies includes neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Neuroblastoma represents the most common extracranial solid tumor in children and causes 8% to 10% of all childhood malignancies. Although primary cervical neuroblastomas are seen rarely, cervical metastases from intra-abdominal neuroblastomas are the more common presentation in the head and neck.[19]

Another neural entity seen with relative frequency in the neck is the neuroma. Neuromas occur at sites of neuronal injury and represent an inflated response to the injury manifested histologically by fibrous tissue, regenerating axons, and Schwann cells, in a disorganized mass. Neuromas are encountered commonly in the neck at the cut end of the greater auricular nerve after neck dissection or parotidectomy.[3,19]

Paragangliomas

Paraganglia are collections of cells of neuroectoderm origin that secrete catecholamines. They have an important functional role during embryogenesis, when they serve as the major source of catecholamines. After birth, most paraganglia rests disappear, with the exception of the adrenal medulla and the sites around the autonomic nervous system. In the adult the function of the paraganglia is to help the autonomic nervous system respond to stressors such as hypercapnia, hypoxia, or decreasing pH.[21]

In the head and neck, tumors of the paraganglia and paragangliomas occur in three main locations: carotid body, jugulotympanic region, and vagus nerve. These are highly vascular, slow-growing, mostly benign lesions, with less than 10% thought to be malignant.[21] Although most are single and sporadic, approximately 10% occur in an inherited pattern (autosomal dominant) or are associated with a syndrome (multiple endocrine neoplasia IIA or IIB, or von Hippel–Lindau disease) and 10% occur as multicentric lesions in the same patient.[21]

Paragangliomas have differing presentations on the basis of their location in the head and neck. Carotid body tumors typically present as a painless, slowly enlarging neck mass. The classic diagnostic features are a mass that is mobile horizontally, but fixed vertically, and a mass with an associated bruit or vascular thrill.[3,21] As these lesions enlarge, they may also cause cranial nerve or sympathetic chain neuropathies. Vagal paragangliomas will have a similar presentation but may have an increased incidence of hoarseness, pharyngeal fullness, or dysphagia at presentation.[3,21] Paragangliomas of the jugulotympanic region tend to have otologic symptoms at presentation (hearing loss, pulsatile tinnitus, fullness), as well as lower cranial nerve deficits. These lesions do not usually present primarily as neck masses.[21]

The major distinction between carotid body tumors and vagal paragangliomas is that seen on angiography. The classic *lyre's sign* or splaying of the internal and external carotid arteries indicates a carotid body tumor. Vagal paragangliomas tend to displace both vessels anteriorly, rather than splaying them. Angiography can also be a useful tool when preoperative embolization is to be considered for larger lesions, especially those of the carotid body.

More commonly, MRI is used as an important diagnostic tool for lesions of the paraganglia. Paragangliomas have a distinct "salt and pepper" appearance on T1-weighted MR images due to their vascular flow-voids. They are hyperintense on T2 images. Often, the position of the lesions with respect to the internal and external carotid arteries can also be determined from MRI, so this is the imaging of choice for these lesions. CT can be helpful in determining bony skull base erosion and can thus assist in the diagnosis of those of jugulotympanic origin.[21-22] These lesions should be diagnosed by physical examination and imaging, and FNA should, in general, not be performed.

Lipomas

Lipomas represent the most common subcutaneous soft tissue tumor of adults. They commonly occur in the posterior neck but can occur throughout the neck and face. They are slow-growing, benign tumors composed of adipocytes, with a firm to rubbery consistency on palpation.

Special Consideration: Unknown Primary Squamous Cell Carcinoma of the Neck

As with any patient with a neck mass, the most important starting point in the workup of a patient with an unknown primary head and neck squamous cell carcinoma is a thorough physical examination (Table 116-2). This examination should consist of careful inspection and palpation of all mucosal subsites of the oral cavity and oropharynx, as well as fiberoptic endoscopy. During endoscopy, particular attention should be paid to the nasopharynx, tongue base and tonsillar fossae, and hypopharynx.

Table 116-2

Steps in the Workup of an Unknown Primary Squamous Cell Carcinoma of the Neck*

1. Complete physical examination (inspection and palpation) of all head and neck subsites	Oral cavity Oropharynx Thyroid Salivary glands Face/scalp/neck skin
2. Fiberoptic endoscopy examination	Nasal cavity Nasopharynx Oropharynx Hypopharynx Larynx
3. Fine-needle aspiration	
4. Primary imaging	Head and neck (computed tomography or magnetic resonance imaging) Chest (radiograph or computed tomography)
5. Secondary imaging	Positron emission tomography
6. Panendoscopy/mucosal site sampling	Include laryngoscopy, bronchoscopy, esophagoscopy, and ipsilateral tonsillectomy. Pay close attention to the tongue base and hypopharynx.

*Each step should be followed in order until a primary diagnosis is made.

Next, imaging of the head, neck, and chest must be obtained. The clinician should keep in mind that when patients present with metastatic adenopathy in the low neck or supraclavicular fossae, there is an increased risk that the primary lesion will be located below the clavicles. Prognosis is extremely poor for this group of patients.[5] Imaging of the head and neck should be in the form of CT or MRI. CT of the chest should be performed. Clinicians have been increasingly interested in using PET scans to detect unknown primary malignancies of the head and neck. Results show that PET might help to pinpoint specific areas of increased metabolic activity in a small subgroup of patients with unknown primaries, but PET is also fraught with a significant number of false-positive results.[23] PET can be considered an adjunct to the complete workup of patients with an unknown primary head and neck squamous cell carcinoma. It should be performed before panendoscopy and biopsy to potentially provide a site to target and also to prevent false-positive results that might be seen in the face of tissue that has been recently instrumented and biopsied.

Once a complete battery of imaging has been completed, the patient should undergo panendoscopy and directed biopsies under general anesthesia. The examination should also include thorough palpation of the oropharyngeal subsites including the tongue base, tonsillar fossae, and glossotonsillar sulci. An ipsilateral tonsillectomy should be performed in patients who have not had previous tonsillectomy or in those with adequate lymphoid tissue remaining. Directed biopsies of the nasopharynx, tongue base, and hypopharynx should also be performed. The ipsilateral tonsil has been found to harbor the occult primary in 20% to 40% of cases of unknown primary squamous cell

carcinoma of the neck as reported in several series in the literature. The next most common subsite is the base of tongue.[5,23]

If the primary tumor has still not been identified after the thorough workup discussed earlier, the patient should be referred for nonsurgical management of the unknown primary. If the primary lesion is identified in the workup, treatment of the neck mass will be given according to the principles of treatment of the primary site.

Summary

Neck masses are extremely common and represent a wide variety of both head and neck and systemic pathologic entities. The most important element in the workup of an unknown neck mass is the exclusion of malignancy. As such, malignancy will be much more common in the older adult with a neck mass, particularly one that is painless, enlarging, and asymmetric. A thorough head and neck examination is the mainstay in the diagnosis of most neoplastic neck masses. In the pediatric population, inflammatory masses will present most commonly, but one should always be aware of the potential for a congenital mass to mask itself as an infectious adenitis. In these patients multiple recurrent neck infections should increase one's clinical suspicion and prompt imaging of the neck.

Finally, the otolaryngologist should always be aware of the airway in patients presenting with neck masses. Although formal airway evaluation is not always essential, the potential for airway compromise should be kept in mind before any further investigations. In the case of any clinical suspicion or overt airway symptoms, fiberoptic endoscopy should be performed and one should be ready for immediate intervention.

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CHAPTER ONE HUNDRED AND SEVENTEEN

Ultrasound Imaging of the Neck

Mikhail Vaysberg

David L. Steward

Key Points

- High-resolution ultrasound is the best imaging modality for nodular thyroid disease.
- Sonographic features of thyroid nodules suggesting malignancy include microcalcifications, irregular borders, extrathyroidal extension, and increased vascularity.
- Thyroid nodules with suspicious sonographic features or greater than 1 to 1.5 cm in size should undergo ultrasound-guided, fine-needle biopsy.
- Ultrasound is the most sensitive tool for detection and localization of persistent or recurrent thyroid cancer in the neck.
- Repeat neck ultrasound to look for metastatic lymphadenopathy is indicated preoperatively in patients with cytologically diagnosed thyroid cancer.
- Ultrasound is a sensitive tool for parathyroid adenoma localization, providing greater anatomic detail than radionuclide imaging.
- Ultrasound is useful for submandibular and parotid salivary gland neoplasms, especially when combined with ultrasound-guided, fine-needle biopsy.
- Sonographic features suggestive of metastatic lymph nodes include absence of echogenic hilum, round shape, cystic component, irregular borders, and jugular vein indentation.
- Ultrasound-guided, fine-needle biopsy reduces sample error and nondiagnostic rates when compared with palpation alone.
- To assist sonographic imaging of the needle tip during fine-needle biopsy, the bevel of the needle should be facing up toward the ultrasound transducer.

Basics of Ultrasound

Over the past 30 years sonographic imaging technology has undergone tremendous change. As a result of excellent resolution and portability, it has gained popularity as an office-performed procedure adding another dimension to physical examination and going beyond physicians' proprioception. Understanding of anatomy and disease pathophysiology remains the key in any radiologic study, yet one is required to understand the principles and physics of ultrasound (US) technology in order to maximize the information provided.

Sonographic technology is based on the properties of the acoustical wave. The energy by a US transducer is transferred to molecules of a medium. The molecules vibrate in a series of rhythmic, mechanical compressions generating a number of longitudinal waves like a ripple in the water. Each wave has a particular number of cycles per second that determines its *frequency*. One cycle per second is equal to 1 Hz; 10^6 cycles/second is equal to 1 megahertz (MHz). Audible sound has a frequency between 20 and 20,000 Hz, whereas US has a frequency greater than 20,000 Hz.

The sonographic signal is generated at the level of the transducer that contains crystals with piezoelectric properties. These crystals are linearly arranged and their properties permit conversion of electrical energy into US energy and vice versa. As US waves propagate through tissue, a small percentage of the energy (echo) is reflected back to the transducer. The US image is formed by the returning wave, and the strength of the image is proportional to the strength of the returning wave. Substances with a greater density produce stronger "echoes." Structures of different densities are easier to distinguish from one another.

Multiple tissue interfaces emit various sonographic echoes and permit generation of readable images. High-frequency waves provide better images because of higher reflection, but they are restricted to the evaluation of the superficial structures caused by rapid energy loss. Because of the superficial location of most head and neck structures, clinical US uses fluctuating frequencies between 5 and 10 MHz or 7 and 12, 13, or 16 MHz. This range combines the penetration of lower frequencies and higher resolution of higher frequencies. The frequency of the sound changes when it is reflected from a moving object. The change in frequency is known as the *Doppler shift* and can be used to determine the flow of red blood cells as they course through vessels.

One should be familiar with terminology used in US imaging. *B-mode sonography* refers to a gray-scale mode, where *Doppler* sonography is used for assessment of blood flow and is color coded. *Echogenicity* defines the appearance of tissues on the US image relative to its ability to reflect the US wave. *Anechoic* means no return signal; it represents complete penetration of the energy through a structure, appearing black. An *isoechoic* object has similar echogenicity to surrounding tissue. *Hypoechoic* tissue has lower echogenicity than reference tissue, appearing darker. *Hyperechoic* tissue is brighter compared with the reference structure due to higher echogenicity.[1]

Utility and Limitations

The majority of structures and pathologies in the neck are located within 5 cm distance from the skin surface. With high-resolution sonographic technology, virtually all extracranial structures can be accurately assessed, though the primary utility is imaging of thyroid, parathyroid, and salivary glands, as well as lymph nodes. Magnetic resonance imaging (MRI) or computed tomography (CT) scans generally offer no additional information regarding size, margin, or malignant potential.[2] Being relatively inexpensive, office-based US technology is readily available, portable (size of laptop computer), quick and easy to perform, and harmless to the patient. It also allows real-time diagnostic imaging and image-guided fine-needle biopsy to be performed at the same visit. It does not involve ionizing radiation or require intravenous contrast.

Ultrasonography should be the first imaging modality for evaluation of thyroid nodular disease. The limitations of US include difficulty assessing deep soft tissue and bony invasions and inability to penetrate through bone or cartilage. It cannot reliably evaluate perineural spread, involvement of the skull base, or parapharyngeal/retropharyngeal/mediastinal nodes.[4]

Operator dependence is one of the major limitations of ultrasonography. Mastering office-based sonography by a surgeon who knows the anatomy, patient, and disease eliminates reliance on someone else's reporting, provides better real-time preoperative localization, assesses related lymphadenopathy, permits single operator consistent follow-ups with image-based documentation, assists more accurate specimen acquisition, and adds another dimension to physical examination.[3,5,6]

Brief Description of Technique

The patient is placed in a semi-reclined or fully reclined position with mild neck extension. The monitor is placed near and at the same level as the patient. The examiner should be able to view the monitor and perform the scan without undue stretching or twisting. Convention dictates the orientation of the transducer relative to the patient. Transducers have an embedded indicator that must be directed cephalad during scanning in the sagittal plane and directed toward the patient's right during scanning in the transverse plane. The examiner's hand is stabilized on the patient's skin, with the transducer held between the thumb and first two fingers. The transducer is advanced with constant skin contact with mild consistent pressure. For better acoustic coupling, the skin is covered with aqueous gel. Patient position should not be considered to be static; changes in position are often necessary to improve the quality of the image, to assess a particular structure, or to discriminate mobile from fixed reflectors. The dynamic examination is one of the advantages of real-time US imaging.

It is important to develop a readily replicated, systematic approach for the examination of neck structures. We prefer to use B-mode (gray-scale) scanning in the transverse/axial plane primarily. Starting inferiorly in the lateral neck, the probe is tilted inferiorly to visualize the subclavian vessels and then steadily advanced in superior direction with the carotid along the medial aspect of the field of view. The examination is then repeated on the contralateral side.[6,7]

For central compartment evaluation, one half of the trachea should be visible on the medial aspect of the screen and the great vessels visible laterally, proceeding inferiorly to superiorly. A light touch will minimize compression of the jugular vein. Longitudinal/sagittal imaging is less intuitive; thus it is mostly reserved for confirmation and sizing in the cranial-caudal dimension of selected pathology once it is identified. For subtle changes in position, the probe can be slightly tilted back and forth, which allows more precise movement than sliding the probe along the skin surface. Color Doppler imaging can be used to assess vascularity, though most vessels are readily distinguished in gray scale. Once an image is localized in real time, the image can be frozen, labeled, sized, saved, and printed for the patient's file (Fig. 117-1).[8]

Thyroid Ultrasound

Neck US is widely accepted as the optimal modality for evaluation of thyroid nodularity. The thyroid gland, one of the easiest neck structures to image with US, should be homogeneous and of intermediate gray scale. It is considered the reference echogenicity for comparison with other structures. Solid hyperfunctioning thyroid nodules tend to be mildly hyperechoic with respect to the surrounding gland. Fluid-filled or cystic nodules tend to be hypoechoic, similar to vascular structures. Cystic nodules can be differentiated from vessels as one scans from inferior to superior because nodules will appear and then disappear, whereas vessels will continue in one direction or another. Doppler imaging can be used to assess vascularity of the gland overall or a discrete nodule. Untreated Graves' patients demonstrate increased vascularity throughout a relatively homogeneous thyroid gland. In contrast, Hashimoto's thyroiditis usually appears heterogeneous with splotchy ill-defined hypoechoic areas; the micronodular pattern represents lymphocytic infiltrations. As the disease progresses, it results in generalized gland atrophy and fibrosis-induced hypoechoic lobulation that may mimic nodularity. The diseased gland is often associated with benign-appearing reactive lymph nodes frequently located inferior to the gland.

US provides the most accurate sizing of nodular disease for surveillance, and its sensitivity for detection of thyroid malignancy approaches 80% to 90% in experienced hands.[9,10]

In the setting of a multinodular thyroid, it is important to carefully evaluate each nodule individually and target which sonographic features increase the predictive value of fine-needle aspiration (FNA) for carcinoma. Although there is no single pathognomonic sonographic feature, the constellation of findings may suggest malignancy: microcalcifications, intranodular intrinsic vascularity, absent "halo sign," extraglandular extension, and irregular or microlobulated margins (Fig. 117-2, Box 117-1). Unless purely cystic, the presence of cystic component within a lesion does not diminish risk of carcinoma, and is common in papillary carcinomas. One should be aware of inspissated colloid as a common misinterpretation for microcalcifications. The presence of a comet-tail or ring-down artifact posterior to the echogenic foci is seen with colloid (Fig. 117-3). We still perform a biopsy of the largest nodule in spite of benign sonographic features, but will select other nodules for biopsy that appear suspicious independent of size alone.[11,12]

In addition to evaluation of the thyroid gland, cervical lymph nodes must be carefully examined, especially in patients suspected of having malignancy.[13] Sonographic identification of round, enlarged, hypoechoic, solid or cystic lymph nodes with microcalcifications and absent echogenic hilum should raise suspicion of papillary or medullary thyroid carcinoma (Fig. 117-4). They should undergo fine-needle biopsy. Lymphatic drainage accompanies vascular supply with levels III, IV, and VI being predominantly involved. Lymphadenopathy as high as cervical level II is not uncommon due to the pathway of superior thyroid vascular pedicle,[14] and level V due to transverse cervical vessels. Metastatic nodes are often seen posterior to the carotid along the inferior thyroid artery.

Ultrasonography can be used not only for initial preoperative localization of malignant thyroid disease, but can play an important role for determination of residual or recurrent disease. Neck US may be the most sensitive tool for detecting recurrent differentiated thyroid carcinoma, especially in combination with thyroglobulin measurement. Patients may be considered to be disease free when US evaluation of the neck is negative, TSH-stimulated thyroglobulin is undetectable, and antithyroglobulin antibodies are absent.[15]

Parathyroid Ultrasound

Hyperfunctioning parathyroid adenomas are responsible for approximately 90% of cases of primary hyperparathyroidism. Due to early recognition of disease with asymptomatic hypercalcemia noted on routine renal panels, many diagnoses are made while adenomas are relatively small. Surgical therapy remains the best treatment for this disease. Thus the localization of the pathologic gland constitutes the main challenge. With an experienced and motivated sonographer, high-resolution US can reliably localize solitary adenomas to correct side and location (right vs. left and superior vs. inferior) in about 90% of cases, which supersedes sensitivity of sestamibi scan and provides greater anatomic detail.

US techniques for localization of parathyroid adenomas deserve specific mentioning. Normal-sized parathyroid glands (<40 mg) are not

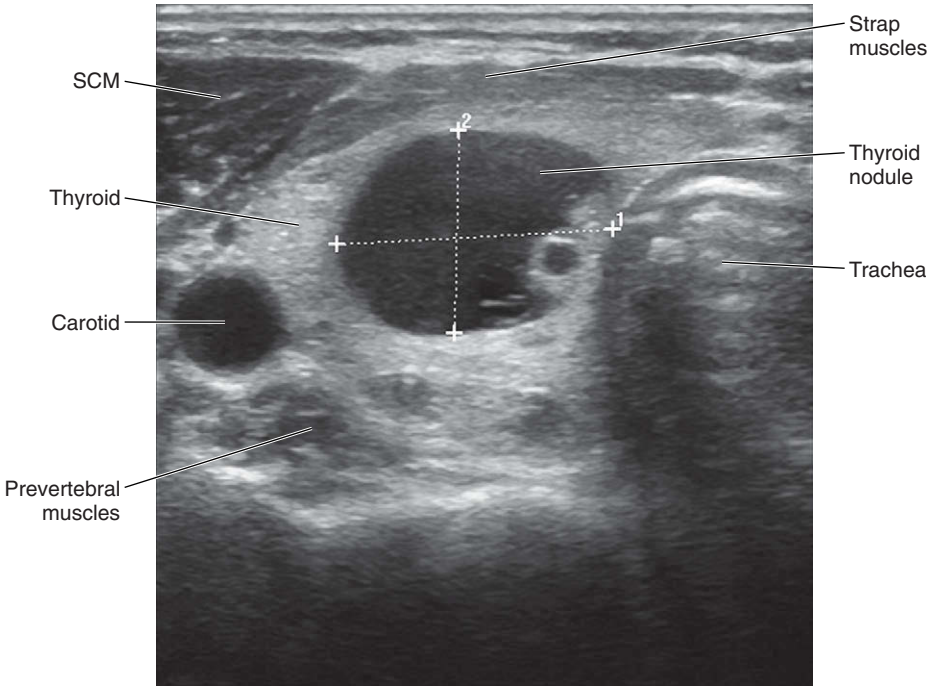

Figure 117-1. Transverse/axial image of a predominantly cystic thyroid nodule with a solid component along the medial aspect. SCM, sternocleidomastoid muscle.

usually distinguishable with currently available equipment for high-resolution ultrasonography (7 to 15 MHz). Localization of enlarged parathyroid glands (≥100 mg) requires a careful and deliberately slow transverse (axial) scanning technique. First, tilt the transducer inferiorly to examine the superior mediastinum. Then advance the transducer superiorly beyond the superior pole of the thyroid one side at a time. The initial focus is on the central neck region and expected parathyroidal orthotopic locations, but the entire anterior and lateral neck should be examined.[16,17]

Parathyroid adenomas are most often hypoechoic relative to the thyroid gland. They are rarely anechoic or cystic and occasionally nearly isoechoic relative to the thyroid. The inferior parathyroid adenomas are most often visualized just inferior to the inferior lobe of the thyroid, sometimes just posterior to the inferior lobe (Fig. 117-5). The superior parathyroid glands are almost always on the posterior aspect of the midportion of the thyroid gland, in a deeper plane than the inferior glands (Fig. 117-6). The distinction between superior and inferior parathyroid can at times be challenging, even during surgical exploration. The inferior parathyroid glands lie anterior to the plane of the recurrent laryngeal nerve, whereas the superior parathyroid glands lie posterior to this plane. Using the inferior thyroid artery or the posterior surface of the common carotid artery as a surrogate marker for the plane of the recurrent laryngeal nerve, adenomas located entirely deep to the posterior surface of the artery are most often superior parathyroid glands even if located in a somewhat more inferior location than typical (Fig. 117-7).[18]

If an enlarged parathyroid is not readily identified on either side, repeat the examination increasing the far field or overall gain in both transverse and longitudinal planes. The possibility of an ectopic location is raised. Ectopic superior parathyroid glands are located in a posterior plane from the hyoid to the posterior mediastinum, usually posterior to the carotid sheath, occasionally intrathyroid (most often posterior when "caught" by migration of the ultimobranchial body), and more commonly retropharyngeal/esophageal/tracheal. Scanning from a more lateral position will often avoid shadow artifact related to the carotid artery and trachea and reveal the hidden adenoma. Although the majority of ectopic adenomas can be localized, the posterior mediastinum cannot be visualized with US. Suspected intrathyroidal parathyroid adenomas can undergo US-guided, fine-needle biopsy with cytology to rule out thyroid malignancy and needle rinsing with 1 to 2 mL of saline for chemical identification of intact parathyroid hormone, which is better able to discriminate parathyroid from thyroid.[12] Ectopic inferior parathyroid glands are located in an anterior plane from the hyoid to the anterior mediastinum, with the majority being within or in close proximity to the thymus at the thoracic inlet or superior mediastinum. Such glands are often amenable to identification with US and resection through a cervical approach. Another common ectopic location is intrathyroidal within the posterior aspect of the inferior pole. Less commonly, the glands are within the carotid sheath.

Patients with thyroiditis often have hypoechoic reactive lymph nodes adjacent to the thyroid gland, which can be a source of false-positive localization and may be differentiated from parathyroid adenomas by their hyperechoic hilum and hilar rather than peripheral blood supply identified with color Doppler imaging. Frequently thyroid nodularity is incidentally noted and can be evaluated at the same time with US-guided, fine-needle biopsy, permitting appropriate surgical management if necessary.

Primary parathyroid hyperplasia presents a localization challenge. The glands tend to be smaller, and one gland can be predominantly larger than the others, giving the false impression of being an adenoma. In these cases, eliciting a family history of parathyroid disease can be helpful. Parathyroid hyperplasia seen in primary hyperthyroidism is more common in patients with a positive family history or multiple endocrine neoplasia (MEN) syndromes I and IIa, or both, and can often be localized with US. Sporadic primary hyperplasia should be considered in patients with negative cervical US and negative sestamibi scans because these glands, despite their collective hyperfunction, can remain too small for accurate localization. Hyperplastic parathyroid glands in secondary or tertiary hyperparathyroidism are usually easily identified on US if the hyperparathyroidism is severe enough to warrant surgical intervention.[19]

Ultrasonography of Salivary Glands

Salivary gland neoplastic disease constitutes less than 3% of the head and neck tumors, although sialadenitis is common. The clinical evaluation alone is often nonspecific. Imaging is frequently required to differentiate pathologies arising within salivary glands, as well as the ones stemming from neighboring structures. US is ideally suited for evaluation of the submandibular and parotid glands, though the

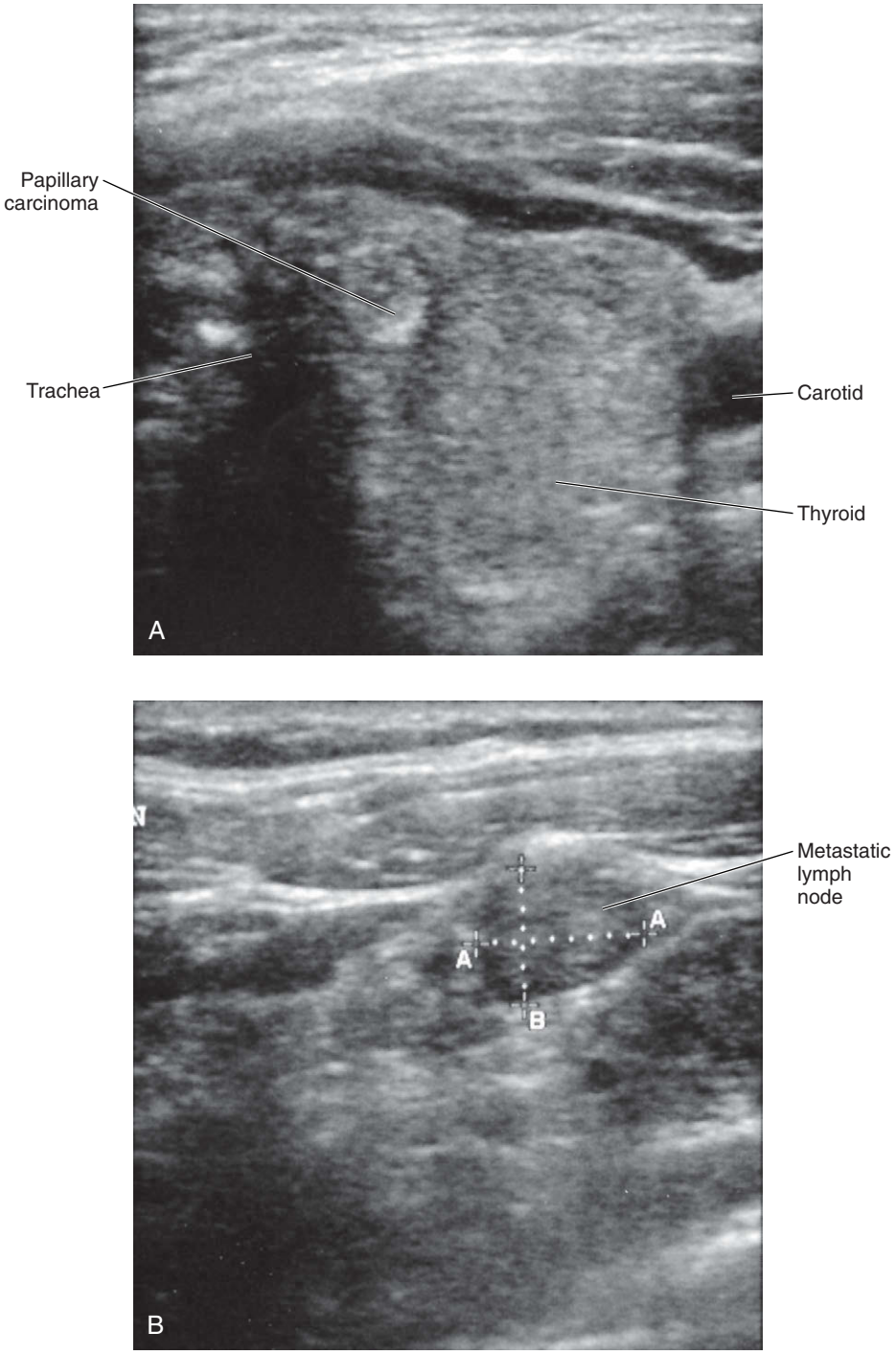

Figure 117-2. **A** and **B,** Papillary thyroid carcinoma with microcalcifications and nodal metastasis.

Box 117-1

Ultrasound Features Suggestive of Thyroid Nodule Malignancy

Microcalcifications
Absence of halo
Irregular border
Hypoechoic
Tall shape
Marked intranodular blood flow on color Doppler

mandible precludes reliable sonographic evaluation of the deep lobe and parapharyngeal space. US can differentiate between neoplastic and inflammatory process, but without US-guided fine-needle biopsy it cannot reliably differentiate benign from malignant neoplasms. Office US is incredibly useful in discriminating among submandibular lymphadenopathy, sialadenitis, and salivary neoplasm (Fig. 117-8). It is also helpful to differentiate parotid tail neoplasm from adenopathy and superficial neoplasm from sialadenosis or sialadenitis (Fig. 117-9).

In adult patients, salivary glands have a uniform parenchymal echo appearance that is more echogenic than surrounding musculature and similar in echogenicity to the thyroid. Multiple hyperechoic linear

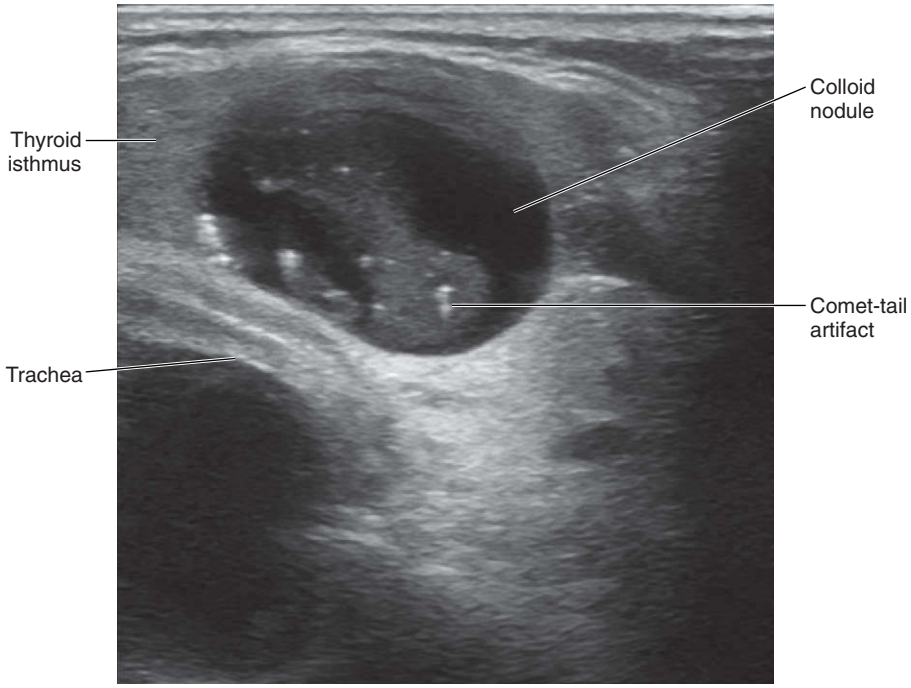

Figure 117-3. Transverse/axial image of a colloid nodule with comet-tail artifact.

streaks represent intraglandular ducts. Nondilated main ducts are usually invisible with standard probes, but dilated ducts are easily visualized in chronic sialadenitis with or without sialolithiasis. Chronic sialadenitis results in a more hypoechoic gland, similar to thyroiditis. The presence of germinal centers suggests Sjögren's syndrome.

Normal lymph nodes are usually small, ovoid hypoechoic lesions with presence of echogenic hilum and short axis equal to or less than 5 to 6 mm.[20] In the submandibular triangle, small lymph nodes are commonly seen superior and anterior to the submandibular gland. Jugulodigastric (Kuttner) lymph nodes reside just posterior to the submandibular gland. They are larger and more circular, with a prominent echogenic hilum.

The late embryogenesis (second trimester) of the parotid gland is responsible for subcapsular and intraparenchymal location of lymph nodes. These nodes may present a diagnostic challenge but can be differentiated from neoplasms by the presence of an echogenic hilum.

Intraglandular masses are often hypoechoic compared with the normal parenchyma. Solid lesions can be homogeneous or heterogeneous with or without a cystic component.[21] A solid appearance of a lesion does not predict the benign or malignant nature of the disease, but the diagnosis can be assisted by US-guided fine needle aspiration biopsy (see Fig. 117-9).

Although there are no pathognomonic features separating malignant from benign neoplasms, US can distinguish benign from malignant tumors up to 80% of the time. High-grade malignancies tend to demonstrate an irregular shape, a heterogeneous echostructure, extracapsular spread, and metastatic lymph nodes. They tend to show increased vascularity on Doppler imaging. Intraglandular metastases are usually multiple, round, and sharply demarcated. Lesions smaller than 2 cm and well-differentiated malignancies may not possess the previously mentioned features. Multiple pathologies can mimic tumors. US cannot distinguish among subtypes of malignant tumors. To make a diagnosis, cytologic assessment should be performed on all accessible lesions.

Several pathologies of salivary glands deserve specific mentioning.

Calculous lesions 2 mm and above are hyperechoic with acoustic shadowing behind a stone. Smaller calculi do not have a shadowing effect, but the obstruction can be inferred from dilated ducts (markedly hyperechoic lines). Sialogogues assist demonstration of the dilatation.

Sjögren's syndrome is a chronic autoimmune disorder associated with intense lymphocytic and plasma cell infiltration of the exocrine glands with or without connective tissue disorders. Sonographically, the gland is heterogeneous with scattered oval hypoechoic or anechoic areas or it has a reticulated appearance due to the presence of hyperechoic lines. Sonolucent areas are thought to represent dilated ductal structures and aggregates of lymphocytes, analogous to the pattern seen with the lymphocytic infiltrations found in Hashimoto's disease. It is associated with increased incidence of infections and less commonly with lymphoma. Sjögren's patients should be followed to detect changes signaling the development of lymphoma. No pathognomonic US features are associated with lymphoma, but a discrete mass lesion is worrisome. If suspicion for lymphoma has risen, US-guided core biopsy of the parotid gland is safe and accurate for diagnosis of disease.

Cystic salivary gland disease may result from salivary flow obstruction, vascular malformation, first branchial cleft cyst, Warthin's tumor, low-grade mucoepidermoid carcinoma, pleomorphic carcinoma, necrotic mass, neurogenic tumors, end-stage Sjögren's syndrome, lipoblastoma, and human immunodeficiency virus infection. Sonographically, simple cysts have anechoic content, well-defined margins, posterior acoustic enhancement, and no evidence of internal blood flow with color Doppler imaging. Any cystic lesions containing solid components dictate biopsy for final diagnosis.

Acute infections do not require imaging and can be inferred from the patient's presentation and help of serology or cultures. The sonogram is useful in cases of ductal obstruction or abscess formation, or both. In the presence of abscess, the typical clinical sign of fluctuation is absent due to lack of space between glandular parenchyma and thick fibrous capsule. Sonographically, abscess is seen as ill-defined hypoechoic avascular foci with posterior acoustic enhancement (created by increased reflection of ultrasonic waves at the fluid-solid interface). Hyperechoic air bubbles and moving debris can be visualized on careful examination.[22]

Ultrasonography in Head and Neck Cancer

Unfortunately, US cannot detect aerodigestive tract mucosal primary lesions. One of the main roles of office-based ultrasonography is detection, localization, and surveillance of cervical metastatic lymph nodes. Using well-established sonographic criteria for metastatic

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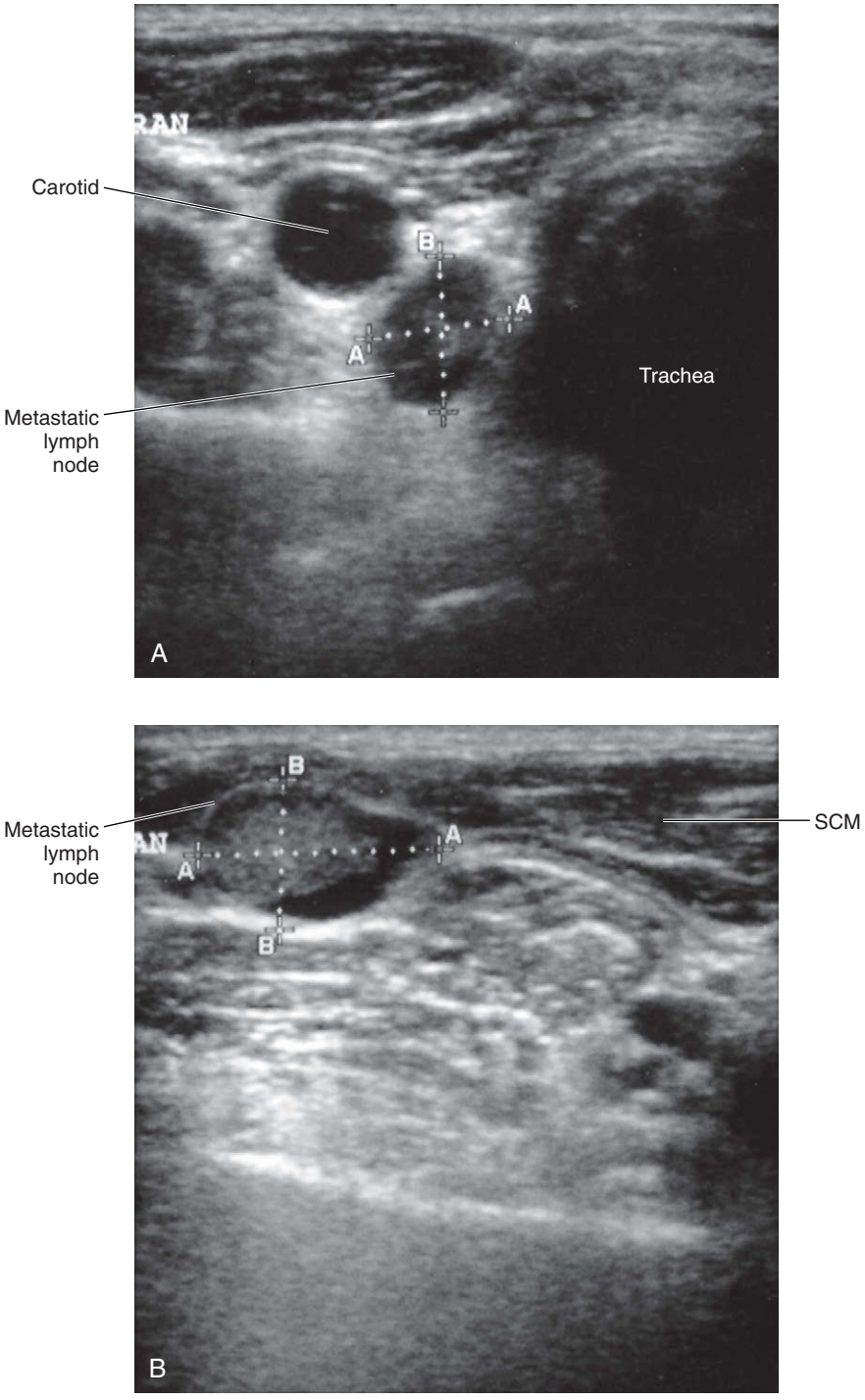

Figure 117-4. **A** to **D,** Metastatic papillary thyroid carcinoma within central and lateral lymph nodes. SCM, sternocleidomastoid muscle.

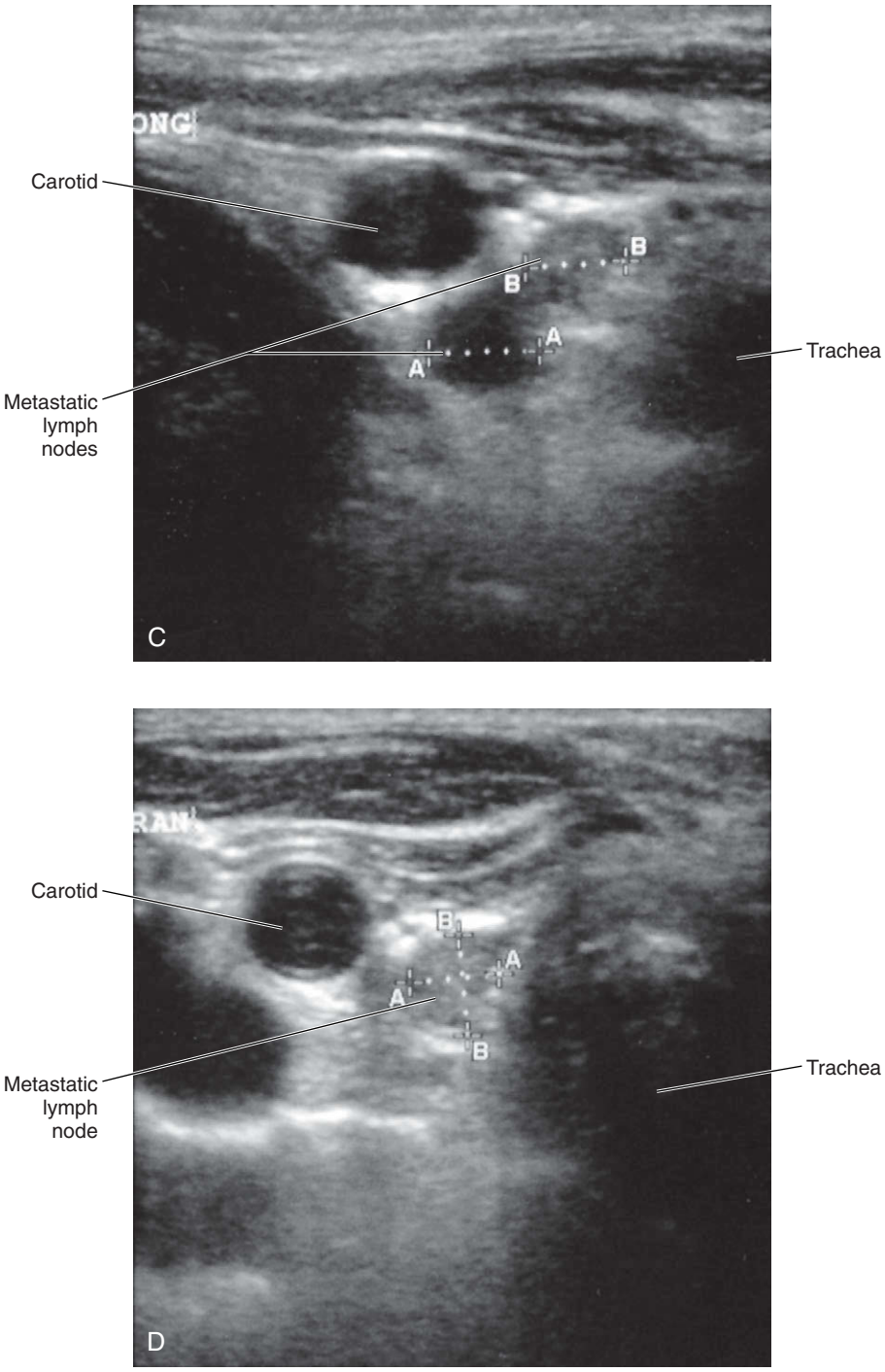

Figure 117-4, cont'd.

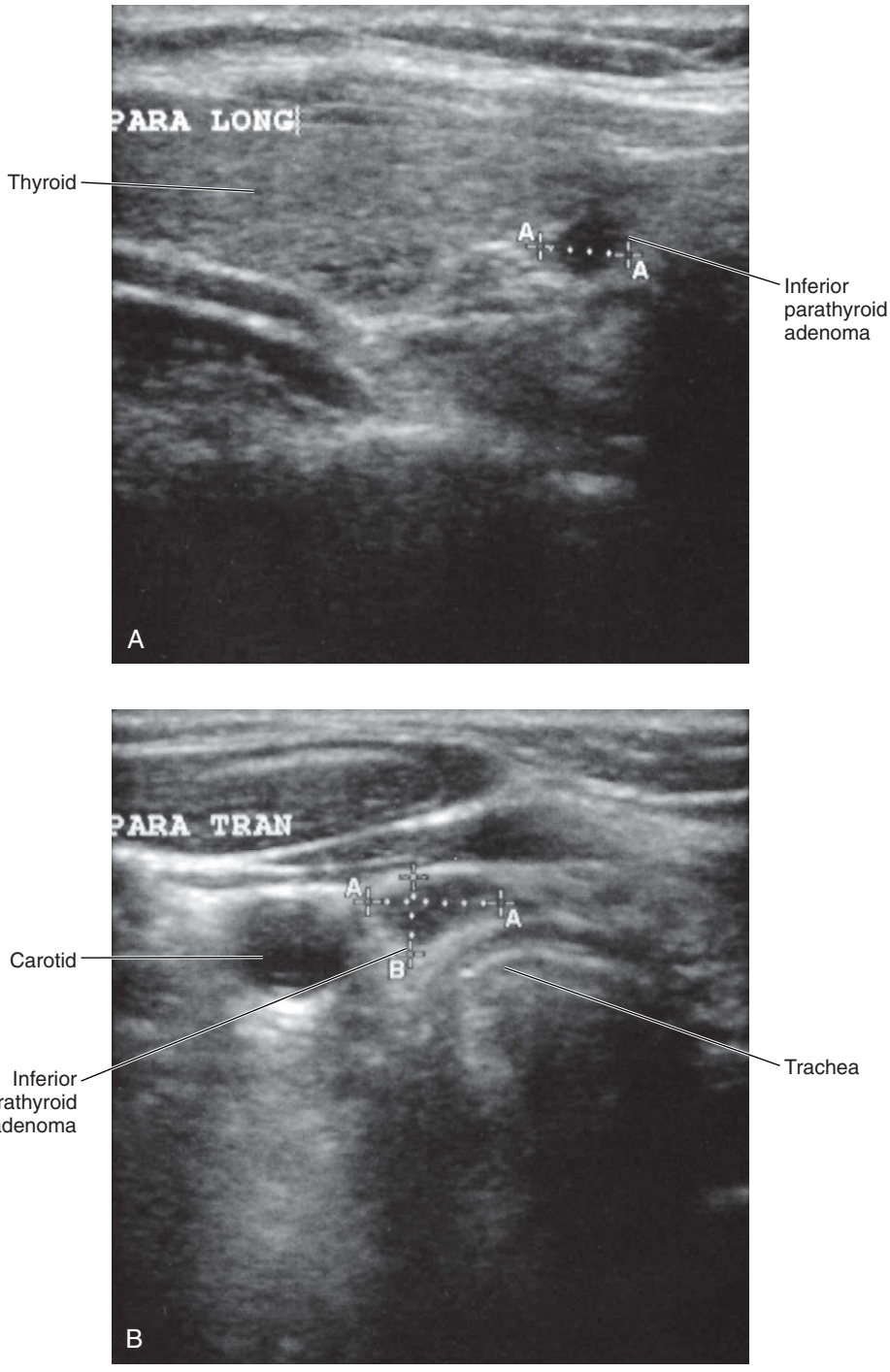

Figure 117-5. **A** and **B,** Inferior parathyroid adenoma, seen in longitudinal/sagittal and transverse/axial planes.

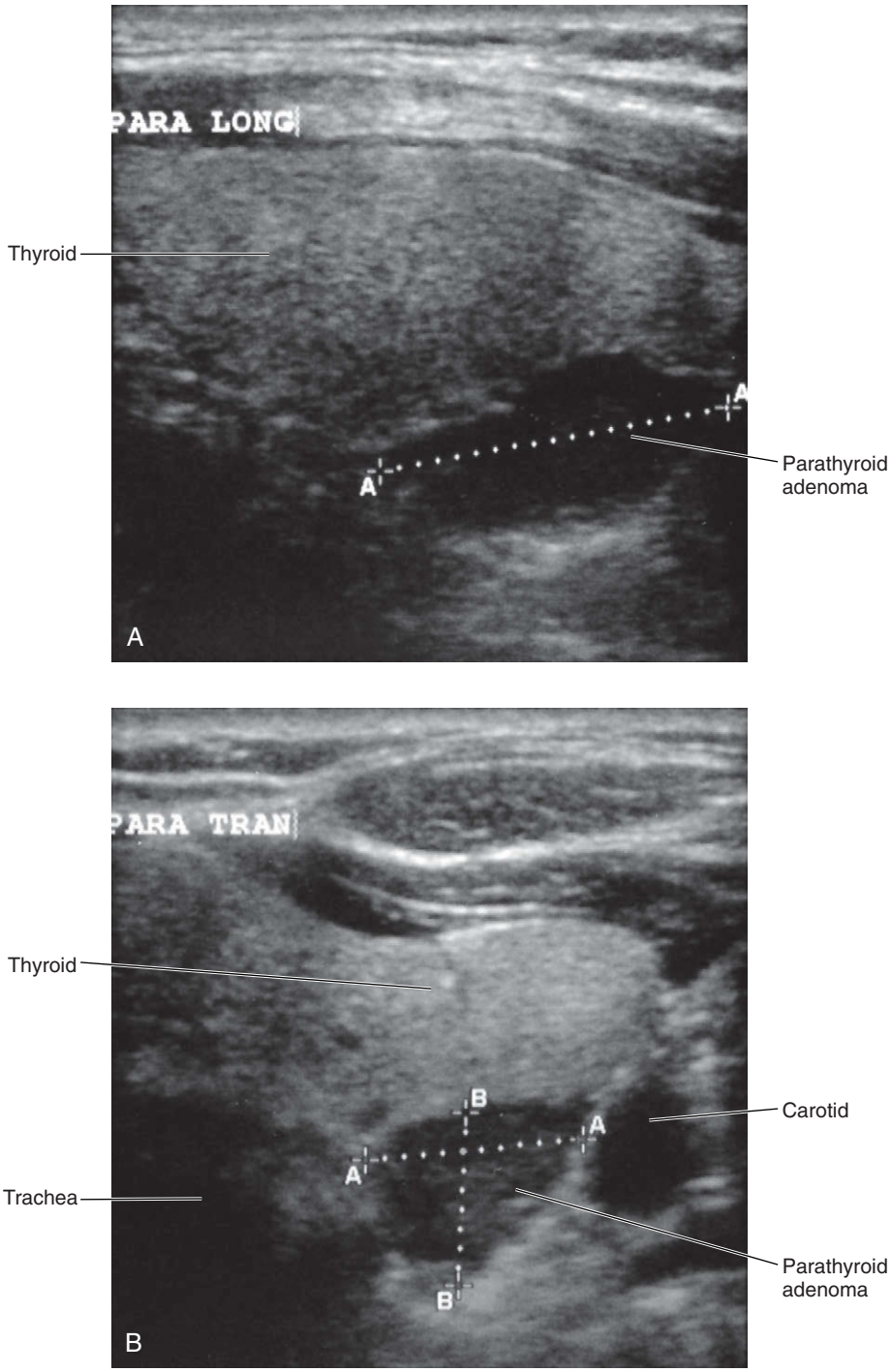

Figure 117-6. **A** and **B,** Superior parathyroid adenoma, seen in longitudinal/sagittal and transverse/axial planes.

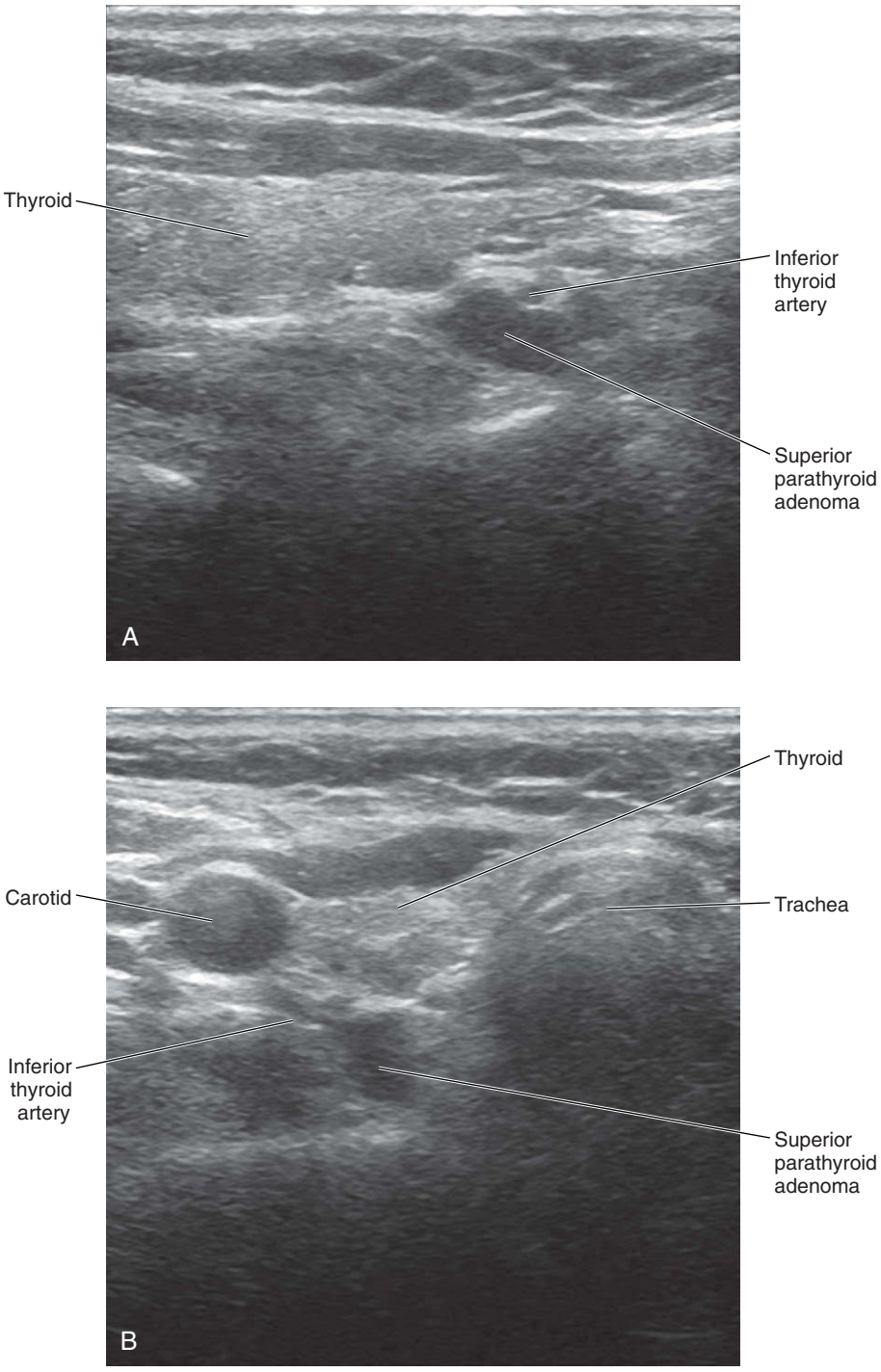

Figure 117-7. **A** and **B,** Superior parathyroid adenoma with inferior thyroid artery, seen in longitudinal/sagittal and transverse/axial planes.

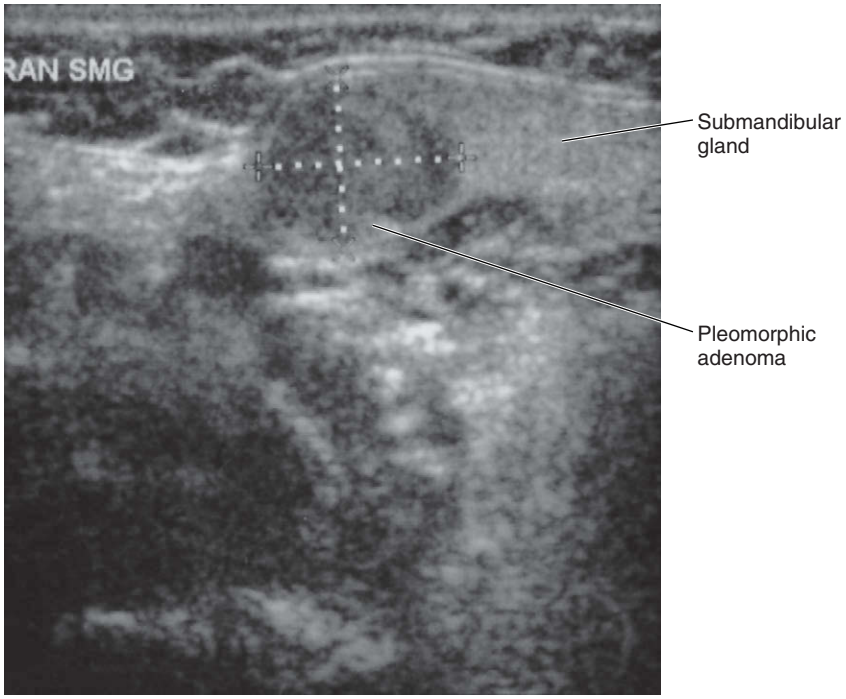

Figure 117-8. Submandibular pleomorphic adenoma.

lymphadenopathy, clinically occult metastatic disease can be diagnosed (tumor staging) and the extent of therapy can be determined. Sonographic features such as round shape, absence of echogenic hilum, hyper/hypoechogenicity, intranodal cystic degeneration, absence of planes and sharp borders, and adjacent soft tissue edema are highly suggestive of malignancy. Furthermore, US can detect malignancies in lymph nodes less than 1 cm not detected by CT or MRI. Reduction of the risk of occult cervical metastasis to around 10% permits expectant management of the N0 neck. With strict US follow-up of the N0 necks, the relapse and neck metastasis rates after successful early salvage surgery have been reported equivocal to prophylactic neck dissections. As a result, elective neck dissections can be avoided in a significant number of patients without negatively affecting their survival.[23] Preoperative neck US has been shown to influence surgical management of thyroid malignancy in 40% of patients.

Description of Diagnostic Ultrasound Fine-Needle Aspiration Technique

Ultrasonography renders most extracranial soft tissue masses in the head and neck region accessible to US-guided fine-needle aspiration biopsy (FNAB). US-guided FNA reduces sample error and false-negative results. It also significantly increases the diagnostic adequacy rate over palpation-guided FNA. On-site cytologic evaluation of the smears also reduces nondiagnostic aspirates but may be unnecessary with a US-guided approach.

The following technique of performing FNAB is based on personal experience that maintains a nondiagnostic aspiration rate around 7%. It is important to communicate with the cytopathologist regarding his or her preferences for specimen processing (air dried vs. fixed and glass slide vs. cell block) to optimize diagnostic utility. Detailed accurate labeling of the specimen source, as well as inclusion of relevant clinical information, is critical.

Once the lesion in question is localized, the transducer is stabilized and the mixture of local anesthetic with epinephrine is deposited subcutaneously using a 25- or 27-gauge needle. The needle is advanced in the direction of the long axis of the probe to visualize the entire shaft. The solution is deposited beneath the strap muscles and along the anticipated needle tract. The depth of the lesion and the proximity of the great vessels or airway, or both, may dictate the angle at which the needle is placed. We prefer to combine tissue acquisition via both capillary and aspiration techniques using a 22-gauge, 1½-inch needle. The capillary sampling is performed first. One should be warned that the image-acquiring surface of crystals with the transducer probe is about 1 mm (the thickness of a credit card). The FNAB needle is entered through the skin immediately next to the midportion of the long axis of the transducer at a 45-degree angle between the transducer and skin. The bevel of the needle is pointed toward the transducer to increase the echogenicity of the needle tip, which is critical to reduce sample error. On US imaging, the needle appears white (hyperechoic) (Fig. 117-10). Back-and-forth motion of a needle within the specimen during collection can be clearly visualized. With the capillary action technique, we use a free needle to shave the cells along the needle path within the lesion. Holding the needle in place for a short time is recommended to allow some time for capillary action. Microcores of the specimen can be shaved by rotating the needle within the specimen just before needle removal. With this capillary technique, the cell yield may be reduced but it tends to be less painful, the cellular architecture is better preserved, and contamination with blood is significantly less, making it ideal for glass slide smear preparation. The specimen is then deposited on a glass slide and smeared with another slide. Immediate fixation of the specimen is necessary to avoid the artifacts and cell disruption from desiccation. If submitting an air-dry smear, the cytologist needs to be notified because different stains are used. When aspirating cystic lesions, a syringe should be attached to avoid spillage of contents. The solid component of the cyst should be preferentially biopsied.The next two to three passes are performed using the suction aspiration technique. A 3-mL syringe with 1 mL of air is attached to a needle. The air will help expel the specimen into solution after aspiration into the needle hub. Once the needle is within a lesion, 2 mL of negative pressure is applied. Before changing the direction of the needle, several back-and-forth motions along the same path will shave cells and pack them into the shaft of the needle. The negative pressure should be released before withdrawal of the needle from the neck to avoid sucking the specimen into the syringe. The specimen is washed out into a container of fixative. Once a needle is irrigated with fixative, it must be discarded. A brand new needle is used for the next collection. The cells are retrieved by centrifuge, and red blood cells are lysed before specimen preparation. On completion of the procedure the patient should be instructed

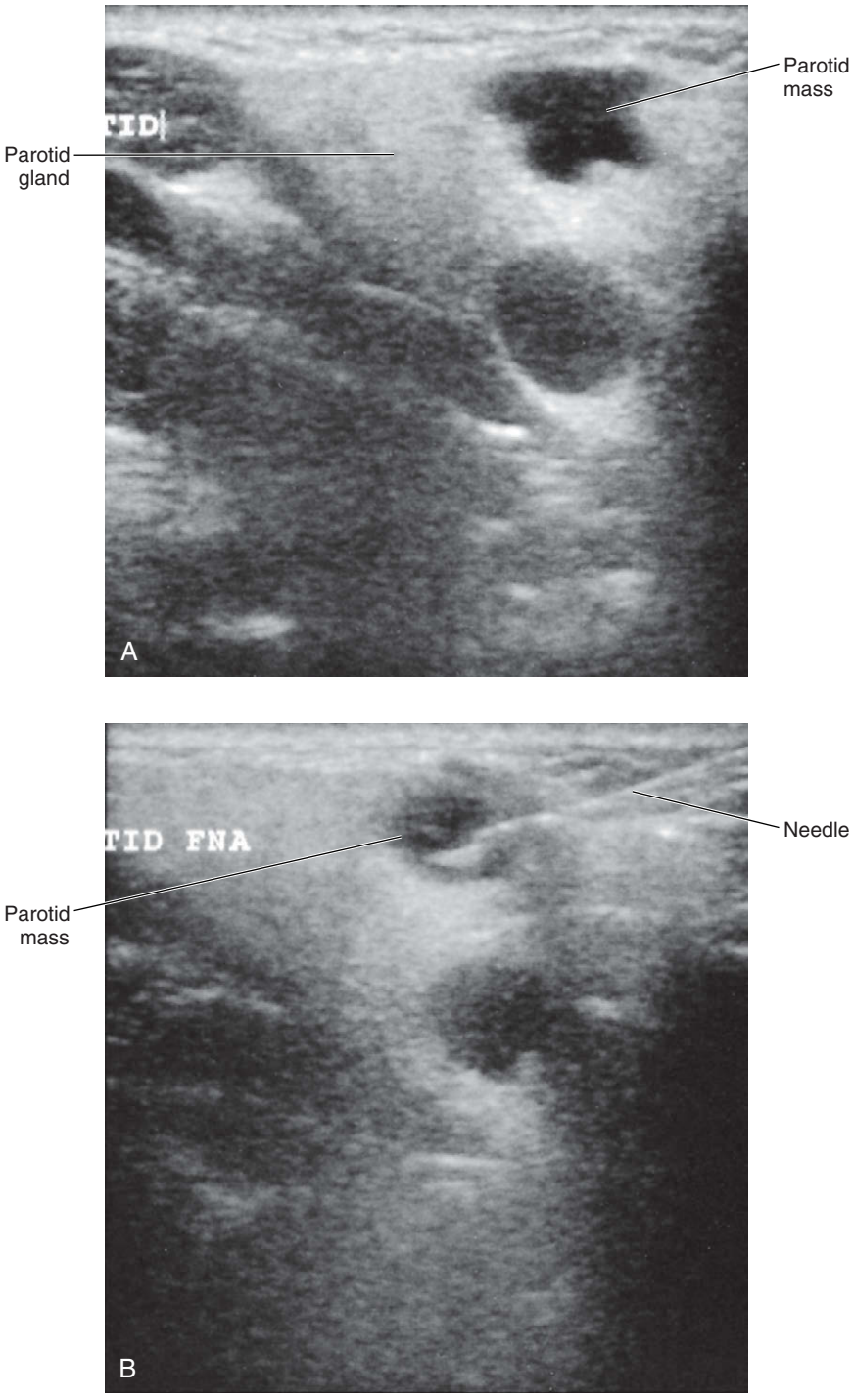

Figure 117-9. **A,** Parotid mass. **B,** Ultrasound-guided, fine-needle biopsy of parotid mass.

to use over-the-counter pain medications to control discomfort, which may last 24 to 72 hours.

To perform a biochemical analysis of metastatic or persistent/recurrent thyroid carcinoma within an abnormal lymph node, the FNAB specimen can be rinsed with 1 to 2 mL of normal saline, and the wash can be sent in a red-topped test tube to be tested for presence of high thyroglobulin level. Simultaneous serum thyroglobulin level should be obtained to avoid false-positive results due to blood contamination. If one suspects medullary carcinoma, one should request the use of calcitonin staining on the cell block and send a needle wash for calcitonin. To confirm intrathyroid parathyroid adenoma, one can submit a wash of tissue sample to test for the presence of parathyroid hormone. FNAB of lymph nodes tends to be more challenging due to the nodes' smaller size, proximity to great vessels, tendency to bounce off the needle, and lack of stability during specimen aspiration.

Conclusion

US imaging is a great tool in the armamentarium of an otolaryngologist. The sonographic images augment physical examination and, together with superior understanding of head and neck anatomy, lead to a faster and more accurate diagnosis. US imaging is a relatively inexpensive, quick, and simple-to-use technology. In some respects it is the best imaging modality that is available. As with any tool, it requires understanding of its strengths and limitations, mastering tech-

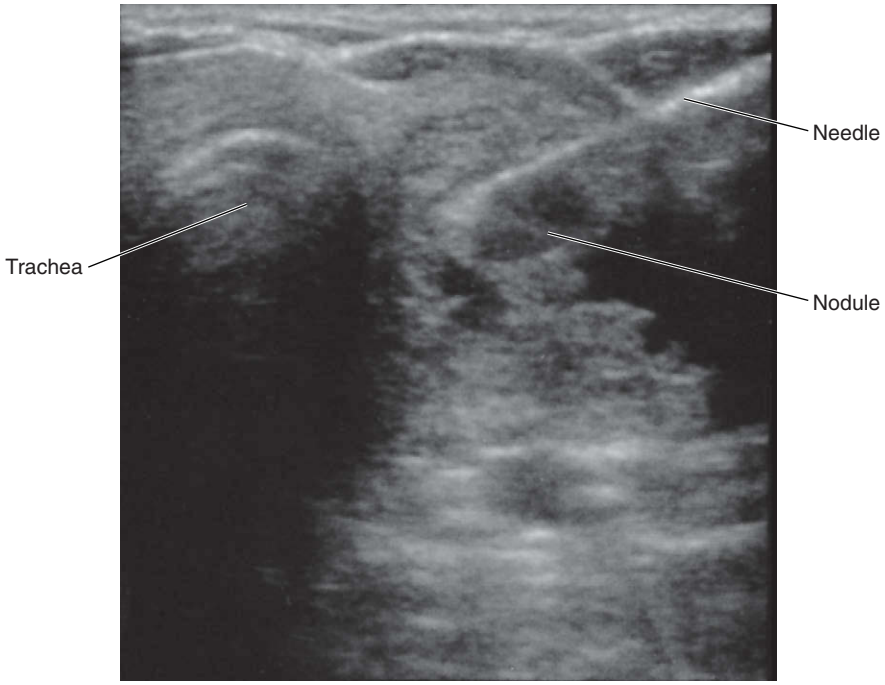

Figure 117-10. Ultrasound-guided, fine-needle biopsy of thyroid nodule.

niques, and proper application. Once a comfort level is achieved, US technology may greatly enhance patients' care and reduce health care costs.

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CHAPTER ONE HUNDRED AND EIGHTEEN

Neoplasms of the Neck

Terry A. Day

Luke Buchmann

Zoran Rumboldt

John K. Joe*

Key Points

- Neck masses represent a diverse group of pathologic processes and require a broad differential diagnosis.
- Both benign and malignant lesions can present as a mass in the neck, making a careful approach to these lesions important.
- A complete history and physical examination, as well as appropriate ancillary studies, are important to arriving at the correct diagnosis.
- Appropriate use of fine-needle aspiration biopsy and endoscopy are critical for determining the presence of an upper aerodigestive tract malignancy.
- Understanding the utility of different imaging modalities such as MRI, CT scanning, PET/CT imaging, and angiography can aid greatly in the evaluation and treatment of these differing pathologies.
- Treatment depends critically on determination of a correct diagnosis and can include surgery, radiation therapy, chemotherapy or a combination of these treatment modalities.

Neoplasms of the neck include those tumors that arise from, rather than metastasize to, lymphovascular structures of the neck, as well as those tumors originating from the soft tissues of the neck. These neoplasms may be either benign or malignant, and, although they are less commonly the etiology for a mass in the neck, one should always consider these tumors in the differential diagnosis of a neck mass. This chapter is divided into benign and malignant sections and provides the reader with a comprehensive review of neoplasms that may originate in the neck.

Diagnostic Evaluation

The diagnosis of neoplasms of the neck involves the standard practice of the complete history and physical examination. Importantly, the patient should be questioned regarding prior neoplasms, family history, and systemic signs and symptoms in addition to the risk factors for primary and metastatic lesions to this area. A comprehensive head and neck examination should include the ear and temporal bone, sinonasal cavity, nasopharynx, oropharynx, hypopharynx, and larynx including a full cranial nerve examination in addition to examination of the neck. Specific information collected from the physical examination of the neck should include the character of the mass, mobility, and pulsation in addition to accurate assessment of neck level. For instance, immobility of a pulsatile mass in the craniocaudal direction may point to the presence of a carotid body tumor. If the neck mass is not pulsatile or vascular in nature, a fine-needle aspiration (FNA) should be performed. Only when the FNA is nondiagnostic or inadequate should excisional biopsy be performed, and at that time the surgeon should be prepared to proceed with appropriate neck dissection with margin analysis if necessary.

Radiologic Studies

Both computed tomography (CT) and magnetic resonance imaging (MRI) may be useful in the evaluation of soft tissue tumors of the head and neck region with particular advantages of each technique varying by type of tumor, location, regional disease, and proximity to vital structures. Although radiographic findings may provide clues to the diagnosis within the broad and, in some cases, even specific differential, accurate diagnosis cannot be ascertained without histologic evaluation. CT scanning is particularly useful in evaluating bone detail in addition to calcification within the tumor, and the addition of contrast improves the diagnostic utility of the soft tissue examination. In addition, CT-directed biopsy of difficult-to-access tumors such as the parapharyngeal space may provide diagnostic tissue. MRI has surpassed CT in evaluating soft tissue extent and relationships in the head and neck region; however, image quality may be degraded by patient motion. It is generally recommended in the majority of soft tissue tumors or tumors adjacent to vital structures of this region, primarily for nasopharyngeal, sinonasal, parotid, and possibly oral cavity lesions.

Similar to CT, MRI should be performed with contrast enhancement using gadolinium agents. Fat suppression is helpful for postcontrast and T2-weighted sequences; however, nonenhanced T1-weighted images without fat suppression should always be obtained because they frequently provide the best delineation of the normal anatomic structures and the extent of pathologic processes.[1,2] Positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG),

*Deceased: A loving son, brother, husband, father, and physician who unselfishly gave himself to others every moment of his life. This chapter is dedicated to his brightest stars, Molly and Charlie.

primarily PET-CT scanning, has evolved as a well-established modality in the evaluation of the primary site, regional nodal disease, and the presence of distant tumor for staging information, particularly for squamous cell carcinoma and the detection of synchronous primary tumors such as lung and esophagus. PET-CT scans may allow for precise localization of the lesion and may decrease the number of false-positive and false-negative findings.[2,3] A controversial use of PET/CT imaging is in the clinical decision making of neck treatment following definitive chemoradiation therapy for advanced head and neck cancer. Several studies have addressed the use of PET scanning in the postirradiated neck. Porceddu and colleagues have shown that in patients with N2 and N3 neck disease a negative PET scan at 8 weeks allowed the observation of those patients with residual neck mass without compromising regional control. Of 27 patients observed by Porceddu with negative PET scans there were no failures in the neck. Yao and associates obtained similar results in a similar patient population. Optimal timing for post-therapy PET scanning appears to be at least 8 weeks, because scanning at 8 to 12 weeks significantly improved the negative predictive value over those who scanned earlier.[4-6] On the basis of these studies it may be a reasonable strategy to obtain a PET-CT scan 8 to 12 weeks following therapy to evaluate for residual disease and performing neck dissection on those with positive scans while observing those with negative scans whether a neck mass is present or not. It should be mentioned that the spatial resolution of PET (and PET-CT) allows for detection of lesions that are at least 8 mm in size.

Ultrasound imaging has become a valuable tool in the head and neck surgeons' diagnostic repertoire. It has the ability to allow the addition of imaging to the in-office examination of the neck as an adjunct to the physical examination. In addition, for the evaluation of the N0 neck it allows not only the characterization of lymph nodes in the neck but allows guided FNA biopsy of nodes of interest.[7] The ability for ultrasound to be used as a primary prognostic tool in the neck to help dictate whether elective neck dissection is necessary has been investigated but has not changed the treatment paradigm in the N0 head and neck patient.

Benign Neoplasms of the Neck

Benign neoplasms of the neck are often misdiagnosed as infectious in etiology (lymphadenitis) or congenital (branchial cleft cyst) on initial presentation. Thus, the diagnosis of all neck masses requires a vigilant approach using the history, physical examination, radiologic studies, and FNA biopsy. Because these tumors are uncommon, a review of the diagnostic approach is vital to the clinician's evaluation and management of each case. Benign primary neoplasms of the neck include vascular tumors such as paragangliomas, peripheral nerve neoplasms such as schwannomas or neurofibromas, lipomas, and salivary gland tumors. The following discussion of the more common benign neoplasms is categorized by tissue of origin.

Vascular Neoplasms

Paragangliomas comprise the most common class of benign vascular neoplasms of the neck. Paragangliomas arise from extra-adrenal paraganglionic cells derived from the neural crest.

Pathology

The paraganglion system denotes a collection of neuroectoderm-derived chromaffin cells in extra-adrenal sites. The system is vital as a source of catecholamines in fetal development, until the formation of the adrenal medulla.

Normal paraganglia contain two types of cells: type 1, chief cells or granular cells; and type 2, the supporting or sustentacular cells. Type 1 cells contain dense-core granules filled with catecholamines, a property that places them in the amine precursor and uptake decarboxylase (APUD) system. Type 2, or sustentacular cells, are elongated cells that closely resemble Schwann cells. Their function is not entirely clear. Tumors of paraganglia such as carotid body tumors contain both type 1 and 2 cells. Type 1 cells predominate and are arranged in an organized-nested pattern, known as *Zellballen,* surrounded by sustentacular cells in a fibrous stoma. These nests of Zellballen are illustrated in Figure 118-1. Type 1 chief cells tend to be polygonal shaped with abundant granular eosinophilic cytoplasm. They are peripherally surrounded by type 2 sustentacular cells that are difficult to identify by light microscopy and appear as spindle-shaped basophilic cells. Nuclear pleomorphism and cellular hyperchromatism are common in paragangliomas and should not be considered evidence of malignancy. Immunohistochemistry aids the diagnosis and differential diagnosis of these neoplasms. Type 1 cells stain positively with neuron-specific enolase, chromogranin A, and synaptophysin. Type 2 cells stain with S-100 and focally with glial fibrillary acidic protein.

Nomenclature

The controversy over the proper nomenclature of paragangliomas has been confusing. Historically they have been referred to as *glomus tumors, chemodectomas,* and *nonchromaffin tumors.* The correct terminology of paragangliomas is based on location (i.e., carotid paragangliomas, jugulotympanic paragangliomas, and vagal paragangliomas), although the terms *carotid body tumor, glomus tympanicum,* and *glomus jugulare* still persist.

Other terms such as *chemodectoma, glomus tumor,* and *nonchromaffin tumor* are less accurate terms and should be avoided. *Chemodectoma* is an inaccurate term to describe all paragangliomas of the head and neck because the carotid body is the only known paraganglia of the head and neck that behaves as a chemoreceptor. The term *glomus tumor* more accurately describes benign cutaneous tumors arising from neuromyoarterial cells surrounding arteriovenous anastomoses. Designation as nonchromaffin tumor relates to histologic staining characteristics. An early histologic staining technique employing the chromaffin reaction failed to show the presence of catecholamines; paragangliomas were therefore described as nonchromaffin tumors. Newer techniques however have detected catecholamines in small quantities.[8] The chromaffin reaction is a highly insensitive method on which to classify these tumors.[9]

Epidemiology

Approximately 90% of tumors arising from the paraganglion system are in the adrenal gland. These tumors are termed *pheochromocytoma.* The remaining 10% arise from extra-adrenal sites with 85% arising in the abdomen, 12% in the thorax, and the remaining 3% in the head and neck area.

The most common paraganglioma of the head and neck is the carotid body tumor, followed by jugulotympanic paragangliomas and vagal paragangliomas. Other sites include the larynx, nasal cavity, orbit, trachea, aortic body, lung, and mediastinum. It has been estimated that paragangliomas comprise 1 in 30,000 head and neck tumors.[10] However, the true incidence of paragangliomas may be unknown because previous reports have confused paragangliomas with neuroendocrine tumors.[11] Further complicating an accurate estimate is the multicentricity of these tumors, particularly in familial paragangliomas.

Carotid Paragangliomas

Carotid paragangliomas are the most common type of paragangliomas and serve as the template of discussion on the history, physiology, and etiologic factors relevant to paragangliomas.

History

The anatomist von Haller first described the carotid body in 1743; its function, however, was unknown at the time. Histologic studies of the carotid body revealed glandular acini, so the carotid body was renamed the *carotid gland.* Von Luschka first described a tumor of the carotid body in 1862. In 1880 Reigner performed the first resection of a carotid body tumor, but the patient did not survive. Six years later Maydl resected a carotid body tumor, and the patient survived but had postoperative hemiplegia and aphasia. In 1889 Albert was the first surgeon to resect successfully a carotid body without ligating the carotid vessels. The first successful removal of a carotid body tumor in the United States was reported by Scudder in 1903.[12] The term *paraganglion* was first used by histologist Kohn in 1903 to describe the carotid body.[13] This term was most appropriate because cells of the carotid body originate from the neural crest and migrate in close association with autonomic ganglion cells, hence the name "paraganglionic." In 1950

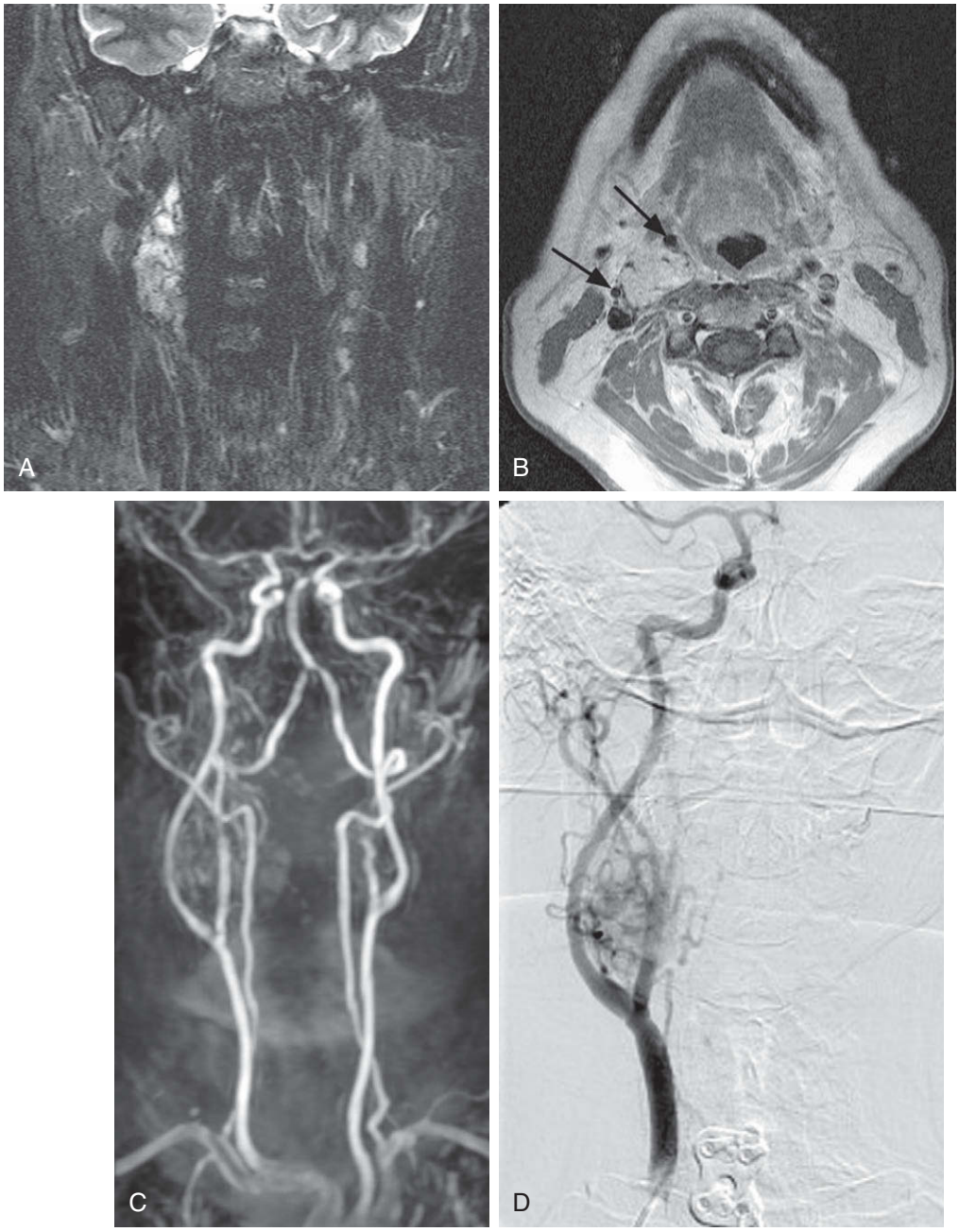

Figure 118-1. Carotid paraganglioma. **A**, Coronal T2-weighted magnetic resonance (MR) image with suppression of fat (short tau inversion recovery, STIR) shows a hyperintense mass in the right neck with prominent internal vessels (flow voids). **B**, Axial postcontrast T1-weighted MR image reveals avid enhancement of the mass, which splays apart the internal and external carotid arteries *(arrows).* Note that the internal flow voids are again visualized. **C**, Frontal projection MIP (maximum intensity projection) image from neck MR angiogram shows presence of vessels between internal and external carotid arteries on the right, which are splayed apart. **D**, DSA (digital subtraction angiogram) frontal projection image following right common carotid artery injection demonstrates the tumor vasculature to a better advantage.

Mulligan described in the dog neoplastic degeneration of the carotid body as chemodectoma because of the chemoreceptor function of the carotid body.[14]

Anatomy and Physiology

The carotid body is located in the adventitia of the posteromedial aspect of the bifurcation of the common carotid artery. The normal carotid body measures 3 to 5 mm in diameter but is often larger in persons living at higher altitudes. The average weight of the normal adult gland is 12 mg, with a wide range previously reported as 1 to 47 mg.[15] During surgical removal, the typical finding is a small, reddish-brown to tan, ovoid structure attached to the carotid vessels at the bifurcation by Mayer's ligament, through which the feeding vessels run, primarily from the external carotid artery. Blood flow and oxygen consumption of the carotid body, gram for gram, exceed those of the brain or thyroid gland.[16] Sensory innervation is from Hering's nerve, a branch of the glossopharyngeal nerve that originates approximately 1.5 cm distal to the jugular foramen.

The carotid body has a chemoreceptor role by modulating respiratory and cardiovascular function in response to fluctuations in arterial pH, oxygen, and carbon dioxide tension. Acidemia, hypoxia, or hypercapnia stimulate the carotid body to initiate an autonomic reflex, which leads to increased respiratory rate and depth, as well as increased heart rate, blood pressure, and cerebral cortical activity. It is this close association with respiratory drive and the sympathetic nervous system response that has prompted investigation of the carotid body's role in

disease processes such as obstructive sleep apnea (OSA) and sudden infant death syndrome (SIDS). Although no clear conclusions can be drawn at this time, the carotid body and its response to intermittent hypoxia appear to be related to the systemic hypertension seen in OSA. It has also been shown that some SIDS children had either small carotid bodies or a decreased ratio of mature type 1 cells to type 2 cells. It is hypothesized that this may attenuate the child's response to a hypoxic crisis.

Etiology

The etiology of paragangliomas appears to be multifactorial. Most paragangliomas are solitary. Multiple pheochromocytomas and paragangliomas are seen in familial syndromes, mainly multiple endocrine neoplasia types 2A and 2B. Other syndromes associated with paragangliomas are neurofibromatosis type 1 and von Hippel-Lindau disease, which is characterized by retinal angiomas and cerebellar hemangioblastomas. Carney's triad demonstrates the association of paraganglioma, pulmonary chondroma, and gastric leiomyosarcoma.[17]

In addition to these associations, a syndrome of familial paragangliomas characterized by multiple paragangliomas, especially in the head and neck region, has been described and occurs in at least 10% of cases. The familial nature of carotid body tumors was first suggested by Chase in 1933 in his description of two sisters with carotid body tumors.[18] Many developments have occurred recently in the characterization of the familial paraganglioma (PGL) syndromes including the genes and mutations involved and recommendations for the head and neck surgeon in managing these patients and their at-risk family members (Table 118-1). Genetic mutations responsible for the hereditary form of PGL have been identified in genes coding for succinate-dehydrogenase subunit D (SDHD), B (SDHB) and C (SDHC) genes, which map to chromosome 11, 1 and 1, respectively. Hereditary PGL syndrome has been classified genetically into four entities: PGL1, PGL2, PGL3, and PGL4. Germline mutations in SDHD, SDHB, and SDHC have been identified in PGL1, PGL4, and PGL3, respectively. The gene for PGL2 has not been identified.[19] Individuals with hereditary paraganglioma syndrome have early onset of tumors and a higher frequency of bilateral and/or multiple tumors than do those with sporadic disease. Past reports suggested familial paraganglioma to be rare, although recent literature challenges this assertion and suggests the association of paragangliomas with germline genetic mutations is likely to be significantly higher, representing 17% of sporadic patients in one study[19] and up to 28% to 40% in other studies.[20-22]

PGL1 is caused by mutations in the D subunit of the succinate dehydrogenase (SDH) gene and is the most common inherited genetic abnormality in families with a history of paragangliomas. All three syndromes follow an autosomal pattern of inheritance, but the inheritance pattern for PGL1 is autosomal dominant modified by genomic imprinting. Genomic imprinting in paragangliomas was described by van der Mey and colleagues after reviewing data from 15 large Dutch pedigrees.[23] The imprintable gene is transmitted in a mendelian manner, but the expression of the gene is determined by the sex of the transmitting parent. With paragangliomas, the gene results in the development of a tumor when it is paternally inherited. Offspring of male carriers were observed to demonstrate a 50% incidence of tumors, whereas children of female carriers never developed tumors. PGL1 is associated most commonly with head and neck tumors but also confers a risk for pheochromocytoma. It is estimated that 86% of individuals with a gene mutation will develop a tumor by age 50.[24] Gene mutations in SDHC are rare, with few families identified to date.

Of further interest is the development of a paraganglioma syndrome in head and neck patients due to the inheritance of mutations in the SDHB gene. Although the PGLs associated with mutations in SDHB are less common than their D subunit counterpart, mutations in this gene confer a higher risk for the development of extra-adrenal, catecholamine-secreting, and often malignant pheochromocytomas, making identification of these individuals crucial in management of the at-risk family members to ensure that proper screening for pheochromocytoma and other paragangliomas takes place. Several cases of renal cell carcinoma in carriers of these mutations have also been reported, and one case of papillary thyroid cancer has been documented in the literature.[24] The role of genetic counseling and testing in this population of patients cannot be overemphasized. Due to the apparent high rate of mutations in patients with a history consistent with sporadic paragangliomas, consideration of genetic counseling and testing should be given to every patient with a carotid body tumor or other paragangliomas.

Table 118-1

Screening Recommendations for Carriers of SDHB, SDHD, or SDHC Gene Mutations*

Annual physical examination and measurement of blood pressure
Annual levels of urinary catecholamines and metanephrines
Imaging of neck, thorax, abdomen and pelvis every 6-12 mo by computed tomography and/or magnetic resonance imaging

*Starts in early teens.
Succinate-dehydrogenase subunits D (SDHD), B (SDHB), and C (SDHC).
From Drucker AM, Houlden RL. A case of familial paraganglioma syndrome type 4 caused by a mutation in the SDHB gene. *Nat Clin Pract Endocrinol Metab.* 2006;2(12):706-712 and Isik C, Erem C, et al. Familial paraganglioma. *Eur Arch Otorhinolaryngol.* 2006;263(1):23-31.

Clinical Presentation and Diagnosis

The characteristic feature of carotid body tumors is slow growth rate, which is reflected clinically by the delay between the first symptoms and the diagnosis, which averages between 4 and 7 years. A carotid body tumor usually presents as a lateral cervical mass, which is mobile laterally but less mobile in the cranio-caudal direction because of its adherence to the carotid arteries. This physical finding has been called a *positive Fontaine sign.*[25] Alternatively, a carotid body tumor may present as a parapharyngeal mass. Many carotid body tumors are pulsatile by transmission from the carotid vessels or, less commonly, expand themselves, reflecting their extreme intrinsic vascularity. Sometimes a bruit may be heard by auscultation, but it can disappear with carotid compression. The consistency varies from soft and elastic to firm and these tumors are generally nontender. As they enlarge, progressive symptoms of dysphagia, odynophagia, hoarseness, and other cranial nerve (IX-XII) deficits appear. Carotid sinus syndrome syncope has been described in association with carotid body tumors.[26] The syndrome refers to a loss of consciousness accompanied with a reflex bradycardia and hypertension. Inciting stimuli include spontaneous movement of the head or following digital pressure applied to the tumor. Rarely, paraganglioma of the head and neck may present as a functional neuropeptide secreting tumor.

The capacity for catecholamine synthesis in head and neck paragangliomas, however, does not translate immediately to clinical findings. Although all paragangliomas have neurosecretory granules, only 1% to 3% are considered functional.[27] Glenner and coworkers first described a functional carotid body tumor secreting norepinephrine in 1962.[9] Patients should be asked about signs and symptoms indicating elevated catecholamines. Complaints of headaches, palpitations, flushing, and perspiration should be evaluated. In these patients a 24-hour urine collection is examined for norepinephrine and its metabolites including vanillylmandelic acid (VMA) and normetanephrine. Alternatively, plasma metanephrine may be assessed. Excess epinephrine or metanephrine should prompt suspicion of an adrenal pheochromocytoma because head and neck paraganglioma lack the enzyme to convert norepinephrine to epinephrine (phenylethanolamine-N-methyltransferase). An abdominal CT scan should be performed to rule out a concomitant adrenal pheochromocytoma. α- and β-Adrenergic blocking is undertaken if a tumor is found to be functional preopera-

tively. This decreases the risk from sudden catecholamine release that may occur with tumor manipulation in surgery. Routine screening for urinary metanephrines and VMA and serum catecholamines is only indicated for multiple or familial paragangliomas or in the presence of catecholamine-related symptoms.[28]

Multicentricity

The carotid body tumor is the most common paraganglioma in the head and neck, and the most frequent combination of multiple tumors is bilateral carotid body tumors. The overall incidence of multiple tumors is reported in the literature to be approximately 10%; some of these may be unrecognized familial genetic mutations. If a familial pattern is recognized, the incidence of multiple tumors is reported to be between 30% and 50%.

Malignancy

Cellular criteria for malignancy have not been established. Harrington and Dockerty[29] attempted to classify malignant tumors of the carotid body. Criteria for malignancy included mitoses with giant cells, nuclear pleomorphism, and capsular invasion. Using these criteria, 50% of the 20 tumors studied would be considered malignant. Batsakis[30] concurred that increased mitotic rate and capsular invasion should not be considered as determinants of malignancy. Other authors have hypothesized that all carotid body tumors demonstrate some degree of capsular invasion.[31] Malignancy is determined by metastasis, which must be proven with biopsy, because paragangliomas may exhibit multicentricity. There are no histologic criteria for malignancy. In fact, previous reports have described metastatic carotid body tumors without mitoses.[32] The diagnosis of malignancy should be made by evidence of spread to regional lymph nodes or distant sites[33,34] (most common being lung and bones).

Malignant paragangliomas have been reported in 6% of carotid body paragangliomas by Batsakis.[30] Accurate 5-year survival rates are not available because of the low malignancy rate of an uncommon tumor. Data from the National Cancer Data Base[35] suggest an overall 5-year survival rate of 60%. Distant metastases had a worse prognosis with a 5-year survival rate of 11.8%, while those with regional spread of disease fared much better with a 5-year survival rate of 78%.

Imaging Studies

Various diagnostic imaging modalities are available in the workup of carotid body tumors. Noninvasive duplex ultrasonography demonstrates a hypervascular mass and the tumor's relationship to the carotid artery. Ultrasonography may also delineate any intrinsic carotid artery disease.

Computed tomography (CT) scanning with intravenous contrast demonstrates a hypervascular mass with avid contrast enhancement, similar to normal vessels, at the carotid bifurcation, splaying the internal and external carotid arteries. CT angiography may be performed to demonstrate the relationship of the carotid vessels to the enhancing neck mass.

MRI with gadolinium may be the most useful imaging study for evaluating carotid body tumors (see Fig. 118-1A and B) because it offers superior soft tissue contrast without the need for ionizing radiation compared with CT scanning. MRI is sensitive for tumors as small as 0.8 cm.[36] Paragangliomas larger than 2 cm in diameter typically demonstrate on T2-weighted images internal flow voids, dark lines, and dots that correspond to vascular structures. This is, however, not always present with carotid paragangliomas. Carotid body tumors demonstrate a characteristic lyre sign characterized as a bowing and displacing of the internal and external carotid arteries as shown in Figure 118-1B and C. Radiographic evaluation should be sufficient to make the diagnosis of carotid body tumor.

Carotid angiography has been replaced by MRI (including MR angiography, see Fig. 118-1C), but catheter angiography remains useful when preoperative embolization is necessary (see Fig. 118-1D). The use of preoperative embolization is controversial, but many authors have recommended its use for large tumors to decrease blood loss.[37] Preoperative embolization may also be used in those rare instances where a malignant carotid body may be suspected. If preoperative embolization is planned, surgery should be performed 24 to 48 hours following in order to avoid revascularization, edema, or local inflammation. Additionally, angiography with temporary balloon occlusion using clinical and electroencephalographic monitoring, combined with brain CT perfusion scanning, can provide specificity as to the tolerance of collateral cerebral circulation across the circle of Willis in select cases.

The high density of somatostatin receptors in paragangliomas provides for newer functional nuclear medicine imaging techniques including metaiodobenzylguanidine (MIBG) scanning and octreotide scanning. MIBG scanning uses I-131 labeled tracer, which is concentrated in intracellular storage vesicles of paragangliomas.[38] Octreotide scanning uses Indium-111 labeled somatostatin analog octreotide to diagnose primary tumors of the APUD system, as well as their metastases.[39] These functional imaging studies have been recommended as a possible screening test for familial paragangliomas for patients at risk.[40] They also allow the detection of additional tumors when malignant paraganglioma is suspected.[41]

Classification

Although not universally adopted in the literature on carotid body tumors, a classification system has been previously proposed for carotid body tumors. In 1971, while a surgery resident at the Mayo Clinic, Shamblin and coworkers described a classification system used to grade the difficulty of resection in carotid body tumors.[42] Group I tumors were defined as localized, relatively small, and minimally attached to the carotid vessels. Surgical excision was described as carried out without difficulty in this group. Group II encompassed tumors adherent to or partially surrounding the vessels, with moderate arterial attachment. These tumors were described as amenable to careful surgical removal. Group III carotid body tumors completely encased the carotids. Shamblin and his colleagues recommended approaching these tumors with great care and with consideration for vessel replacement.

Management

Surgery remains the mainstay of treatment for carotid body tumors. Controversy persists in certain cases, particularly as it relates to multicentric tumors, or for patients with advanced disease or significant comorbidities.

Surgery

In a report from Memorial Sloan-Kettering Cancer Center, Lack and colleagues discussed 39 of 43 patients with carotid body tumors treated surgically; one patient received definitive radiation therapy; and 3 others were observed but not treated.[43] In this cohort of patients, 24 of 39 patients were free of disease following surgery, at an average follow-up interval of 12 years (6 months to 38 years). Local recurrence occurred in 4 of 39 patients (10%). Regional or distant metastases occurred in 4 of 39 patients (10%). All four of these patients were dead of disease within 6 years.

The incidence of permanent cranial nerve impairment as a complication of surgery has been reported in the literature to occur in approximately 20% of cases. In this report by Lack and colleagues,[43] cranial nerve sacrifice of the vagus or hypoglossal nerve was necessary in 15% (6 of 39) of patients. An additional patient developed Horner's syndrome postoperatively. Although not quantified, the superior laryngeal nerve supplying sensory innervation to the larynx and motor innervation to the cricothyroid muscle may be the most frequently injured nerve during carotid body resection. Paralysis of one superior laryngeal nerve may result in some degree of aspiration, although isolated palsy of one superior laryngeal nerve typically requires no additional rehabilitation. Furthermore, denervation of one cricothyroid muscle may result in pitch changes in singers, but changes in voice may not be perceptible. Injury to the cervical sympathetic chain will result in Horner's syndrome, with ipsilateral ptosis, miosis, and anhidrosis. Netterville and colleagues have described first bite syndrome resulting from injury to the cervical sympathetic chain, resulting in loss of sympathetic input to the parotid gland.[36] Patients with first bite syndrome complain of severe cramping in the parotid area when they take the first bite of food, particularly with the first meal of the day. The pain generally subsides over the next several bites but is more intense with strong

sialogogues such as tart or bitter foods. The physiologic mechanism behind first bite syndrome is likely due to denervation supersensitivity of the sympathetic receptors that control the myoepithelial cells in the parotid gland. With oral intake, parasympathetic neurotransmitters are released and cross-stimulation of the sympathetic receptors causes a supramaximal response of the myoepithelial cells. Treatment includes restriction to bland foods and oral carbamazepine (100 to 200 mg twice daily) for those with severe pain.

Anand and colleagues[44] reviewed 1181 published cases of carotid body tumors treated with surgical resection. Internal carotid artery injury was identified in 23% of cases (275 cases), with an overall occurrence of central nervous system (CNS) complications of 26%. This subcategory of internal carotid artery injury was further examined. In 23% of cases (62 cases), internal carotid artery repair was accomplished with simply suture or patch repair, with a CNS complication rate of 3%. The internal carotid artery was reconstructed in 45% (125 cases), with a CNS complication rate of 10% and a mortality rate of 2%. It was necessary to ligate the internal carotid artery in 32% (89 cases), resulting in a CNS complication rate of 66% and a mortality rate of 46%.

Minimizing surgical complications requires a multidisciplinary approach using head and neck surgeons familiar with cervical neurovascular anatomy for approaching the tumor and the vascular surgeon for assistance in resection and vascular repair if necessary. The keys to successful surgery are careful preoperative planning, proximal and distal control of the vasculature with vessel loops, careful identification and preservation of neural structures such as the vagus nerve and hypoglossal nerve, and dissection in the periadventitial plane with meticulous attention to hemostasis. Occasionally, ligation of the external carotid artery is necessary to resect the carotid body tumor; however, typically it can be preserved. Larger tumors may require bisection of the tumor to separate it from the internal and external carotid artery branches. The surgeon should be prepared for vascular reconstruction of the internal carotid artery if necessary, with suture repair, patch grafting, or interposition saphenous vein graft. Routine intraoperative shunting is not recommended and should be used only as needed in those rare instances where internal carotid artery resection and reconstruction is required in patients who do not tolerate preoperative balloon occlusion testing. Shunts may cause vascular complications including hemorrhage and thrombosis and are associated with a 6% incidence of CNS complications and 2% mortality rate.

Controversy over Surgery for Multicentric Tumors

In the patient with bilateral paraganglioma every effort must be made to save at least one vagus nerve and its laryngeal branches. Should a patient present with bilateral carotid body tumors, the case may be made to resect the smaller carotid body tumor first, with the intent of preserving the vagus and hypoglossal nerves on the less challenging side, before embarking on resecting the larger tumor on the other side. At a planned second stage, resection of the larger carotid body tumor may be undertaken. In the case of bilateral carotid body tumors with unilateral preexisting cranial nerve palsy, such as that affecting the vagus nerve (whether caused by surgery or the natural course of the tumor), the functional side should undergo tumor resection only if growth has been observed clinically or radiologically. In these cases, further bilateral cranial nerve damage must be prevented. In the case of an enlarging tumor, radiation therapy may be an option and some authors are advocating this therapy.

Another recently described and rarely recognized problem following bilateral carotid body excision is baroreflex failure syndrome.[36] The clinical manifestations are caused by bilateral denervation of the carotid sinus. The carotid sinus is situated in the adventitia of the carotid bulb and serves as a baroreceptor to decrease systemic blood pressure. Bilateral baroreceptor dysfunction causes unopposed sympathetic outflow, resulting in marked fluctuations in blood pressure and a sustained tachycardia postoperatively. Over time, compensation occurs, but it is variable and unpredictable. Compensation may occur by baroreceptor fibers in the aorta or through neural regrowth at the carotid sinus. Therapy consists of sodium nitroprusside in the early recovery phase to prevent excessive hypertension. Long-term control may be accomplished using oral antihypertensives such as clonidine or phenoxybenzamine. Clonidine is an α-2 agonist, resulting in decreased release of norepinephrine into synaptic clefts, and stimulation of parasympathetic outflow, slowing the heart rate. Phenoxybenzamine is an α-1 and α-2 antagonist that decreases peripheral resistance and increases cardiac output.

Radiation Therapy

Carotid body tumors were originally thought not to be radiosensitive because the effects of radiation therapy were cytostatic but not cytotoxic. Radiation therapy for paragangliomas will arrest growth but not shrink tumor size. Furthermore, potential tumor regrowth following radiation therapy remains a possibility. Risks associated with radiation therapy for paragangliomas include carotid atherosclerosis, the risk of radiation-induced malignancy, and associated morbidity including mucositis.

Radiation oncologists at the University of Florida have described effective local control of 23 carotid and vagal paragangliomas using definitive radiotherapy.[45] In their study, 15 patients with 23 carotid or vagal paragangliomas were treated with radiotherapy between 1981 and 1995. Nineteen tumors were treated with radiation therapy alone, and four were treated with surgery and postoperative radiation therapy. For benign tumors, total doses ranged from 35 to 48.5 Gy. The two malignant tumors received 64.8 and 70 Gy, respectively. Follow-up ranged from 1.5 to 10 years. Local control was achieved in 96% of tumors at 5 years. Five-year disease-specific survival was 89%, with one patient dead of locally recurrent disease 5 years after radiation therapy. This patient had been previously treated with surgery and radiation therapy before treatment by the authors. Another patient died of atherosclerotic disease 13.5 years after radiation therapy. There were no patients with regional or distant failure following treatment. Complications reported by these authors included one patient experiencing a delayed transient CNS syndrome. No other complications were reported.

Valdagni and Amichetti reported 7 patients with 13 carotid body tumors treated with radiation therapy between 1968 and 1987.[46] Treatment consisted of radiotherapy alone for 10 tumors and surgery plus radiation therapy for 3 tumors. Total doses ranged from 46 to 60 Gy at 1.8 to 2.5 Gy per fraction. Follow-up ranged from 1 to 19 years. Local control was achieved in all patients. Acute side effects were minimal. No short or long-term toxicities were reported.

Even proponents of radiation therapy for carotid body tumors concur with surgical resection as the preferred modality of treatment for most lesions.[47] Definitive radiation therapy may be reserved for patients who are poor surgical candidates due to a debilitated medical condition and for locally advanced tumors where anticipated postoperative morbidity may preclude consideration for surgical resection. Adjuvant radiation therapy may be considered following surgery for malignant carotid body tumors for locoregional control.

Observation

Using sequential radiologic imaging, Jansen and colleagues[48] have estimated the median tumor doubling time for 20 carotid body tumors to be 7.1 years including 12 cases without detectable growth. Farr has estimated a growth rate for carotid body tumors, plotting tumor size against years of symptom duration, of 2 cm in 5 years.[49] A scan-and-wait policy may be considered for those patients who are not suitable candidates for surgery or radiation therapy. This highly select group of patients includes those individuals whose medical condition is so poor that both surgery and radiation therapy are contraindicated, or those patients of such advanced age that the carotid body tumor may have minimal impact on their life expectancy or quality of life. This group may also include those patients with malignant carotid body tumors with distant metastases where locoregional treatment would be only palliative in intent.

Vagal Paragangliomas

Vagal paragangliomas are tumors derived from paraganglionic tissue associated with one of the ganglia of the vagus nerve.[50] Vagal paragangliomas most commonly arise from the inferior vagal ganglion, also referred to as the *nodose ganglion.* Tumors arising from the superior

vagal ganglion, or jugular ganglion, may be dumbbell-shaped and may extend from the neck intracranially through the jugular foramen.

Clinical Presentation and Diagnosis

Vagal paragangliomas, like carotid body tumors, may present as a palpable neck mass that is more mobile in a lateral direction than a craniocaudal orientation. Paralysis of the ipsilateral true vocal cord or Horner's syndrome, from involvement of the ipsilateral sympathetic chain, may be present as the tumor grows in size. True vocal cord paralysis may result in hoarseness with or without aspiration of liquids from glottic incompetence. Large tumors arising from the jugular ganglion may be associated with cranial neuropathies of IX, XI, and XII. Diagnostic imaging studies described previously in the chapter may demonstrate anterior displacement of the carotid artery from the tumor present in the posterior carotid sheath. Unlike carotid body tumors, the internal and external carotid arteries do not manifest a splayed configuration in vagal paragangliomas (Fig. 118-2).

Management

The treatment strategies employed for carotid paragangliomas described in the previous section apply to the management of vagal paragangliomas as well. Most are treated by surgical resection, and the discussion pertinent to preoperative embolization described earlier is germane to vagal paragangliomas as well. Patients should be counseled preoperatively as to the fact that complete resection of the vagal paraganglioma typically necessitates sacrifice of the vagus nerve. The resultant ipsilateral true vocal cord paralysis may be addressed in the postoperative period as needed on the basis of the patient's deficits. Vagal paragangliomas arising from the nodose ganglion are usually approached by a transcervical approach, whereas more superiorly located tumors of the jugular ganglion may require a combined transmastoid-transcervical approach, with possible craniotomy should there be intracranial extension. The necessity of carotid artery resection and repair is less common in vagal paragangliomas than their carotid artery counterparts. Indications for definitive radiation therapy or observation alone, which have been previously described for carotid paragangliomas, are applicable to vagal paragangliomas as well.

Arteriovenous Malformations of the Head and Neck

Arteriovenous malformations (AVMs) represent another form of benign vascular neoplasms that present in the head and neck. The most common site of head and neck AVMs are the cheek, ear, nose, forehead, and upper aerodigestive tract. These can be difficult neoplasms to manage. Both excision and interventional radiologic procedures have

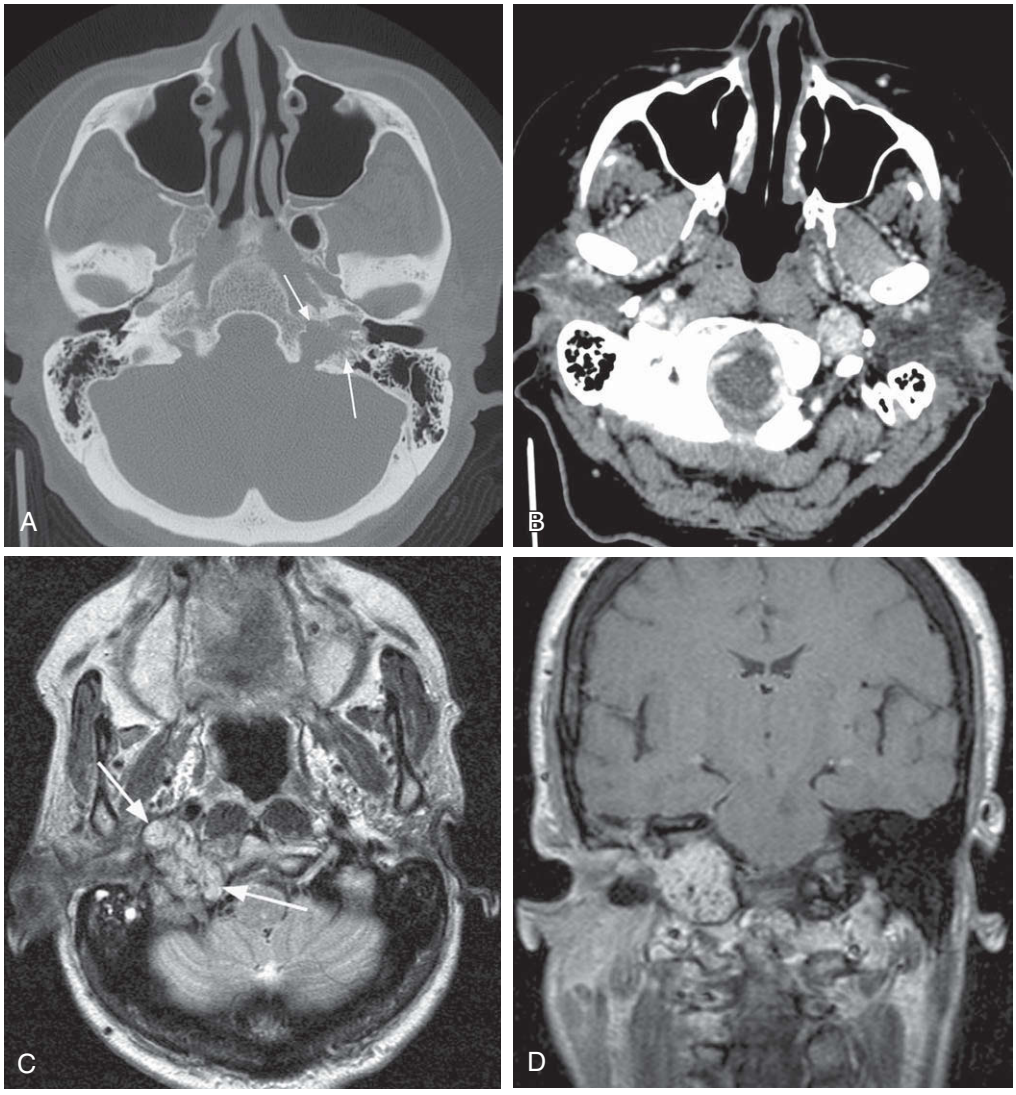

Figure 118-2. Jugular paraganglioma. **A**, Axial computed tomography (CT) image with bone algorithm and window shows subtle bony erosions and widening of the left jugular foramen *(arrows)*. **B**, Axial postcontrast CT image with soft tissue algorithm and window at a slightly lower level shows a densely enhancing mass just below the skull base on the left. **C**, Axial T2-weighted MR image in a different patient shows a hyperintense mass in the right jugular foramen *(arrows)* with internal flow voids. **D**, Coronal postcontrast T1-weighted magnetic resonance image shows enhancement of the mass with still noticeable internal vessels ("pepper").

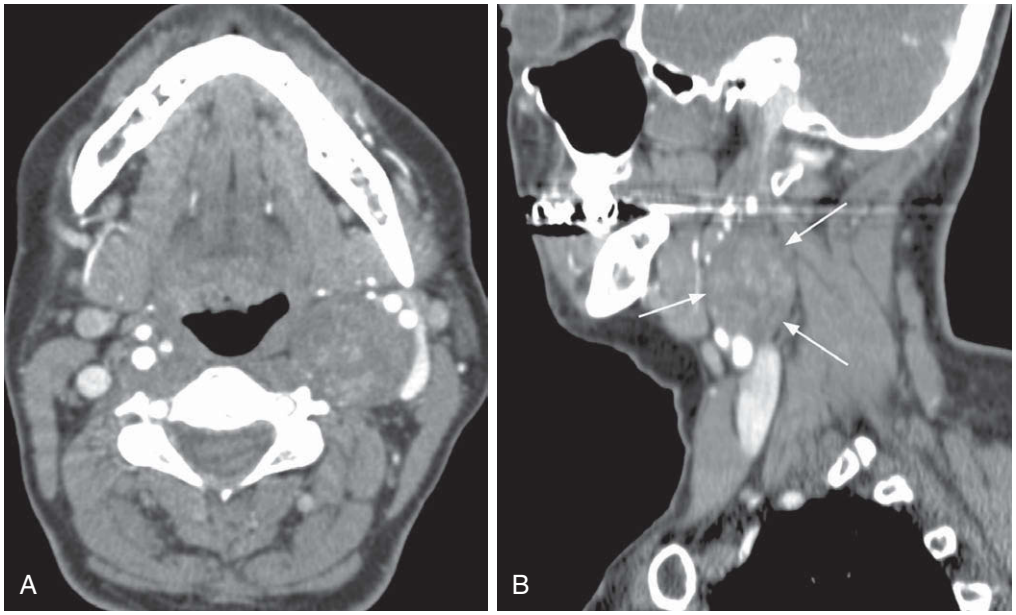

Figure 118-3. Carotid space schwannoma. **A**, Axial postcontrast computed tomography (CT) image shows a left carotid space mass with mild heterogeneous enhancement. Carotid arteries and jugular vein are displaced laterally. **B**, Reformatted sagittal postcontrast CT image demonstrates the craniocaudal extension of the tumor.

been used with some success. Kohout and colleagues[51] presented a large series of 81 patients with head and neck arteriovenous malformations in which patients were separated on the basis of the Schobinger classification and outcomes over a 20-year period were discussed. These authors found that lesions in stage I responded well to therapy and had a higher cure rate than those in stage II or III, although this did not meet statistical significance. They also found that the largest percentage of patients who did not undergo therapy were in stage I, leading to the conclusion that more potentially curable patients were left untreated. Their recommendations for intervention include early-stage lesions and rapidly progressive and painful lesions. Treatment options include both resection and embolization or a combination. Reconstructive considerations must also play a role in decision making with surgical intervention.

Peripheral Nerve Neoplasms

In addition to tumors of vascular origin, other primary tumors of the neck include those derived from peripheral nerves. Benign tumors of the head and neck arising from peripheral nerves include schwannomas and neurofibromas.

Schwannomas

Schwannomas, also called *neurilemomas,* are typically well-encapsulated, slowly growing tumors that arise from Schwann cells of peripheral nerves. These tumors are typically solitary but may occur in multiples, and up to half occur in the head and neck region.[52] Schwannomas may arise from cranial nerves such as VIII (acoustic neuromas) or X, the sympathetic chain, cervical nerve roots, or the brachial plexus. Clinically, schwannomas of the lateral neck may present as a painless neck mass. The clinical presentation of acoustic neuromas is covered elsewhere in this text (see Chapter 177). Radiologically, schwannomas typically present as a well-circumscribed mass that enhances on contrasted studies. They are usually heterogeneous and contain bright areas on T2-weighted images (Fig. 118-3A and B). Histologically, schwannomas demonstrate a characteristic cellular pattern of alternating regions containing compact spindle cells called *Antoni type A areas* and more loosely arranged, hypocellular zones called *Antoni type B areas.* Rows of nuclear palisading may be observed, and such arrangements are referred to as *Verocay bodies.* The treatment of choice of schwannomas of the neck typically involves surgical resection. Cranial neuropathies following surgical resection of head and neck schwannomas are common, and preoperative counseling of the patient as to predicted deficits is crucial in management. Preoperative speech and swallowing evaluation, as well as postoperative management, are critically important in voice and swallowing rehabilitation in these patients. Malignant transformation of schwannomas is rare.

Neurofibromas

Neurofibromas (Fig. 118-4) are benign nerve sheath tumors that may present either as a solitary neck mass or as multiple tumor nodules in association with the autosomal dominant disorder neurofibromatosis. In contrast to schwannomas, neurofibromas are unencapsulated and histologically demonstrate an interlacing bundle of spindle cells. Like schwannomas, solitary neurofibromas undergo malignant transformation uncommonly and are best treated by complete surgical resection. Neurofibromas associated with neurofibromatosis are more difficult to treat, in light of the multiple numbers of infiltrative tumors that are not well-defined. Surgery for neurofibromatosis is typically reserved for those lesions that are painful, that may cause compressive symptoms from their large size, or for lesions that are malignant. Malignant transformation of neurofibromatosis occurs more commonly than solitary neurofibromas.

Lipomas

Lipomas are benign tumors derived from adipose tissue. They are the most common soft tissue tumors of the neck and typically present as a soft, painless neck mass. Their histologic appearance is consistent with a lobular pattern of mature adipocytes. Lipomas are best treated by complete surgical resection for compressive or aesthetic reasons. The case may be made for observation of asymptomatic, small lipomas.

Benign Lesions of the Parapharyngeal Space

The parapharyngeal space is a pyramidal area bounded by the skull base superiorly, the hyoid bone inferiorly, the pterygomandibular raphe anteriorly, the vertebral fascia posteriorly, the medial pterygoid laterally, and the superior constrictor muscle medially. The space contains both the prestyloid and poststyloid compartments, and pathology in this area is based on these anatomic structures. Some tumors presented earlier in the chapter including paragangliomas and benign peripheral nerve tumors are also neoplasms of the parapharyngeal space. Salivary gland tumors are the most common tumors in the parapharyngeal

Figure 118-4. Neurofibromas in an NF-1 patient. Coronal T2-weighted magnetic resonance image with suppression of fat (short tau inversion recovery, STIR) reveals numerous bilateral masses, mostly extending along the cervical nerves.

space and are the main consideration in the differential diagnosis. A full description of both benign and malignant tumors of the salivary glands can be found elsewhere in this volume, in Chapters 87 and 88. The most common benign neoplasm of the parapharyngeal space is the pleomorphic adenoma followed by paragangliomas. Parapharyngeal space neoplasms can arise de novo or extend from surrounding structures. In the case of benign salivary gland tumors, it is hypothesized that they arise de novo from rests of salivary tissue in the parapharyngeal space. Both MRI and CT scanning are useful in assessing masses of the parapharyngeal space; however, MRI is superior in detailing the complicated neurovascular anatomy of the parapharyngeal space as illustrated in Figure 118-5A through D. Successful resection of the lesions can be accomplished by both a transparotid/transcervical approach or a strictly transcervical approach. Mandibulotomy is generally not necessary except in large tumors where wide exposure is necessary for the control of vessels. Warthin's tumors and other neurogenic tumors have been described in the parapharyngeal space but are much less common, as are salivary malignancies.[53,54]

Malignant Neoplasms of the Neck

Primary malignant neoplasms of the neck are rare entities. Few studies have elucidated the true incidence of primary malignancies of the neck because they are often described in case reports or small series or not reported at all. Thus our knowledge and data are based on these limited publications and reports on non–head- and neck-related soft tissue tumors. In the larger series of reports of these tumors of the entire head and neck region, only approximately 4 to 20 cases are listed per year.[55,56] The following discussion provides the reader with an overview of the differential diagnosis, evaluation, and management of malignant tumors of the neck.

Because malignant primary neoplasms of the neck are rare, it is imperative that consideration be given to the more common regional metastatic lesions that are often misdiagnosed before definite biopsy and treatment. Thus before addressing the "primary" tumors in this region, a brief discussion includes the unknown primary, metastatic lesions from the region and distant sites to provide the physician with the necessary foundation from which to then address primary malignancies of this complicated area.

Metastatic Lesions to the Neck

Unknown Primary

The "unknown primary" refers to a squamous cell carcinoma identified in the lymphatic structures of the neck without a known primary site. This tumor is usually identified by a mass in the neck and is typically diagnosed histologically by FNA biopsy. This diagnosis should lead the physician to repeat a thorough head and neck examination to include the entire upper aerodigestive tract, the most common site of these primary lesions. Occasionally, the unknown primary is diagnosed at the time of an excisional biopsy of a cervical lymph node. When this occurs, consideration should be given to intraoperative-directed biopsies of the most common sites harboring occult primaries (i.e., nasopharynx, base of tongue, tonsil and piriform sinus) and neck dissections. There are studies supporting both approaches (e.g., Mendenhall and Million, Robbins).

The location of the neck mass signals a clue regarding the primary site because of the well-known lymphatic drainage routes in the head and neck region and the updated classification system of neck lymph node levels. The location of the metastatic regional lymph node may direct the physician to the most common site of the primary lesion. Regional metastatic lesions from primary lesions of the oral cavity typically are found in levels 1, 2, and 3; from the oropharynx and hypopharynx, and larynx levels 2, 3, and 4; while level 5 metastases are more commonly associated with nasopharyngeal primaries. When the mass presents in the supraclavicular region, esophageal and pulmonary primary sites should be considered in addition to abdominal and pelvic locations.[57,58]

Usually, the primary site is identified during the head and neck examination or during operative endoscopy, at which time biopsies confirm the location and histology of the primary site. When the primary site cannot be identified, imaging techniques including CT, MRI, and/or PET scan have been used with varying degrees of success et al.[59,60] Fused PET/CT imaging has been helpful in determining the site of disease in unknown primary tumors of the neck. Fencl and associates found a sensitivity of 62% and a specificity of 81.9% in 190 patients with unknown primary lesions.[61] Figure 118-6 demonstrates the utility of this modality in detection of the primary site in a case of unknown primary in level 2 with detection of the primary site following PET/CT imaging. The treatment of unknown primary cancers of the neck continues to evolve, particularly related to consideration of directed biopsies, tonsillectomy, and extent of radiation therapy and neck dissection.

Metastatic Neoplasms to the Neck—Regional

Aside from the unknown primary and the far more common squamous cell carcinomas of the aerodigestive tract, it is important to not overlook the possibility of metastatic disease from other sites in the head and neck region. Common primary sites of metastatic disease include the skin of the ear, face, scalp, and neck, which often present with an enlarged lymph node in the parotid, cheek, submandibular, or cervical region. The major and minor salivary glands may present with a primary neoplasm that initially appears to be a metastatic lesion to the neck manifesting as a level 1 or level 2 neck mass. The surprising diagnosis of adenocarcinoma may lead one to an exhausting search for a primary site in the lower digestive tract only to surmise eventually that this is a primary salivary gland tumor. Another common primary site that may be diagnosed first as a primary neck neoplasm is the thyroid gland, which not uncommonly initially presents as a neck mass.[62]

Metastatic Neoplasms to the Neck—Distant

Any neck mass determined to be malignant should also be considered as originating at a distant site. Although hundreds of neoplasms have been described to metastasize to the neck, the more common distant sites include pulmonary, esophageal, renal, ovarian, cervical, and prostate.[63]

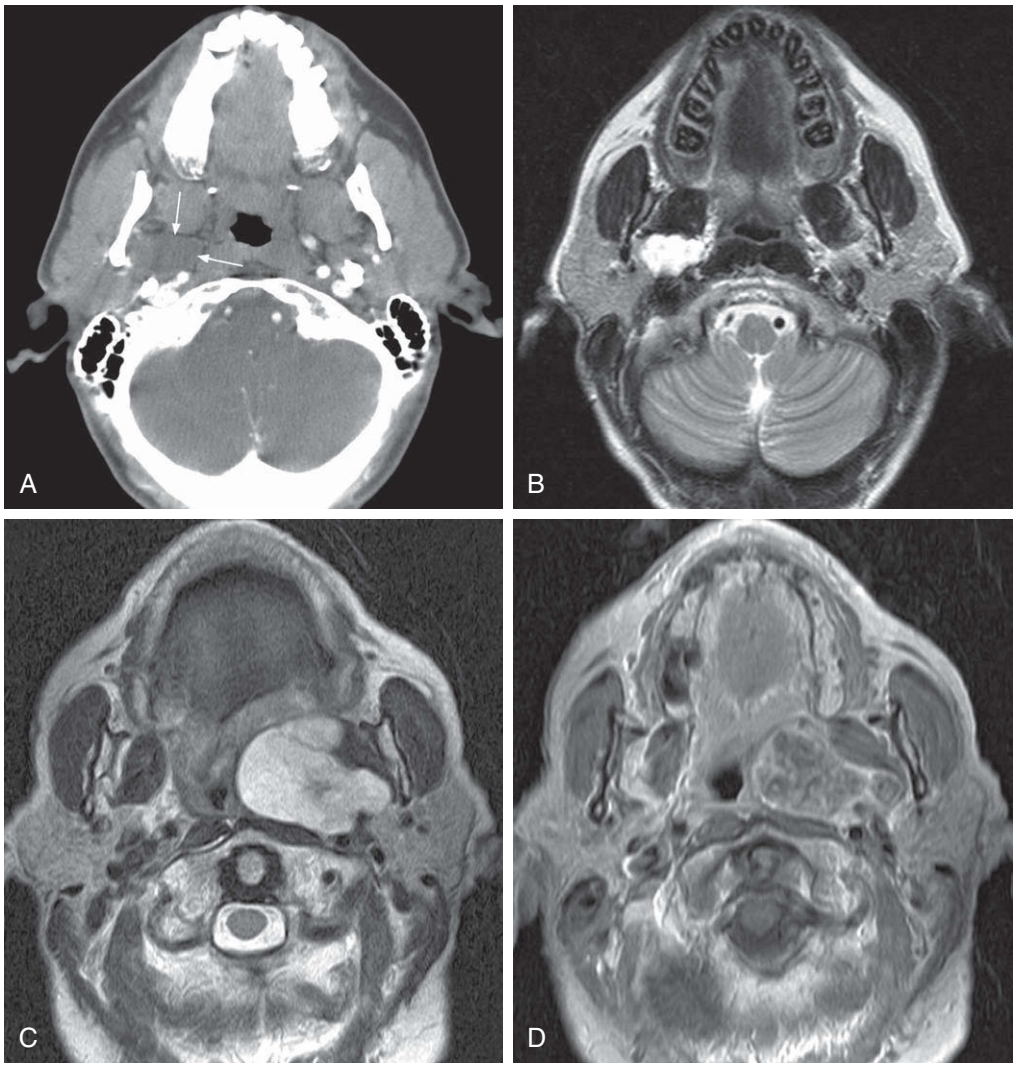

Figure 118-5. Parapharyngeal space pleomorphic adenoma. **A**, Axial postcontrast computed tomography image shows a left parapharyngeal space slightly hypodense mass *(arrows),* adjacent to the deep lobe of the parotid gland. **B**, Corresponding T2-weighted magnetic resonance (MR) image reveals characteristic brightness of the lesion comparable with the cerebrospinal fluid in the spinal canal. **C**, Axial T2-weighted MR image in a different patient shows a large well-delineated hyperintense mass in the left parapharyngeal space with prominent mass effect on the adjacent structures and displacement of the pharynx. **D**, Corresponding postcontrast T1-weighted MR image demonstrates a relatively typical heterogeneous contrast enhancement pattern of the tumor.

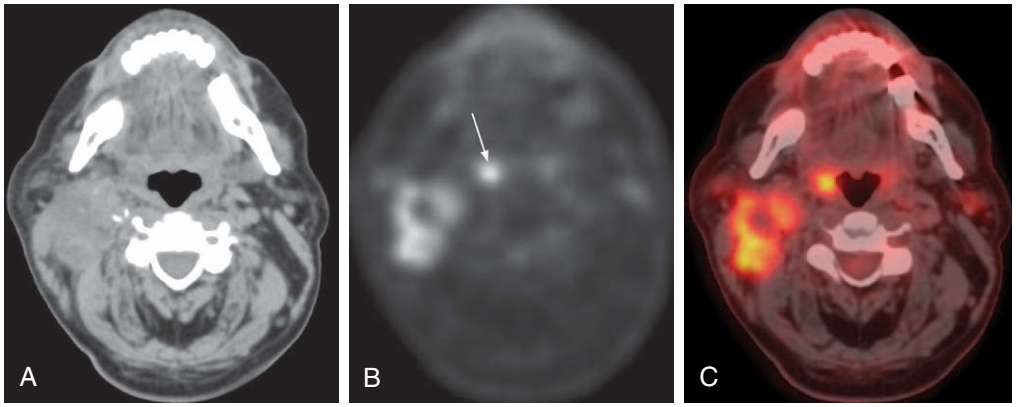

Figure 118-6. Unknown primary. **A**, Nonenhanced axial computed tomography (CT) image from positron emission tomography (PET)-CT study shows large heterogeneous level 2 lymph nodes. The palatine tonsils appear symmetric. **B**, Corresponding FDG (^{18}fluorodeoxyglucose)-PET image reveals increased metabolic activity in the nodes, as well as another focus of high FDG uptake *(arrow).* **C**, Fused PET-CT image clearly demonstrates high metabolic activity in the right palatine tonsil and metastatic nodes.

Table 118-2

Soft Tissue Sarcomas

Angiosarcoma
Epithelioid sarcoma
Extraskeletal chondrosarcoma
Extraskeletal osteosarcoma
Fibrosarcoma
Leiomyosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Malignant hemangiopericytoma
Malignant mesenchymoma
Malignant schwannoma
Rhabdomyosarcoma
Synovial sarcoma

Primary Malignant Tumors of the Neck

The following discussion includes those rare malignancies that arise in the neck region without known primary sites and are considered to be isolated primary malignancies. The following neoplasms are not all inclusive but include those that most practitioners should consider in the differential diagnosis of a malignant mass in this region.

Parapharyngeal Space Neoplasms

Numerous histologic types of primary malignancies of the PPS have been reported including malignant salivary gland tumors (mucoepidermoid carcinoma, adenocarcinoma, adenoid cystic carcinoma, carcinoma ex-pleomorphic adenoma, acinic cell carcinoma); malignant neurogenic tumors; lymphoma; liposarcoma; fibrosarcoma; and malignant meningioma.[53,64-67]

Sarcomas

The neck and parotid have been described as the most common head and neck sites involved by sarcomas, although they represent less than 1% of all head and neck malignancies.[68] In the United States fewer than 5000 cases of sarcomas of all sites are reported annually with approximately 80% diagnosed in adults. Of these, only 15% to 20% are identified in the head and neck region with soft tissues of the neck and paranasal sinus region the most common sites identified. Although the etiology has not been determined, these neoplasms arise from mesenchymal cells, which may include endothelial cells, muscle, cartilage, and supporting connective tissue. More than 80% of sarcomas are derived from soft tissue, and approximately 20% arise within bone.

When all anatomic sites are considered, the most common histologic type is malignant fibrous histiocytoma. In the head and neck the most common sarcoma in children is rhabdomyosarcoma (RMS); in adults, osteosarcoma, angiosarcoma, malignant fibrous histiocytoma, and fibrosarcoma are most common. RMS is the most common sarcoma in children and is also the most common sarcoma of the head and neck region. Overall, however, malignant fibrous histiocytoma is considered the most common type of sarcoma.

Classification and Staging

Sarcomas have generally been classified and named according to the tissue of origin rather than "site" of origin. Many "soft tissue" sarcomas such as malignant fibrous histiocytoma may be diagnosed within bone, but the diagnosis depends on the histologic material for confirmation. The newer American Joint Commission for Cancer (AJCC) staging system now takes into account differing histologies and separates bone and soft tissue. The listing of types of soft tissue sarcomas is provided in Table 118-2, and the approved 2003 AJCC staging system is shown in Table 118-3 for the soft tissue histologies. The listing of bone histologies can be found in Table 118-4, and the AJCC staging system in Table 118-5.

Table 118-3

American Joint Committee on Cancer Staging System for Soft Tissue Sarcomas (2003)

Stage	Definition
Primary Tumor	
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Tumor < 5 cm in greatest dimension (T_{1a}, superficial; T_{1b}, deep)
T_2	Tumor > 5 cm in greatest dimension (T_{2a}, superficial; T_{2b}, deep)
Regional Lymph Nodes	
N_x	Lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1*	Regional lymph node metastasis
Distant Metastases	
M_x	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis present
Histopathologic Grade	
G_x	Grade cannot be assessed
G_1	Well differentiated
G_2	Moderately differentiated
G_3	Poorly differentiated
G_4	Poorly differentiated or undifferentiated
Combined	
IA—G_{1-2}, T_{1a-b}, N_0, M_0	Low-grade, small, and superficial or deep tumor
IB—G_{1-2}, T_{2a}, N_0, M_0	Low-grade, large, and superficial tumor
IIA—G_{1-2}, T_{2b}, N_0, M_0	Low-grade, large, and deep tumor
IIB—G_{3-4}, T_{1a-b}, N_0, M_0	High-grade, small, and superficial or deep tumor
IIC—G_{3-4}, T_{2a}, N_0, M_0	High-grade, large, and superficial tumor
III—G_{3-4}, T_{2b}, N_0, M_0	High-grade, large, and deep tumor
IV—any G, any T, N_1, M_0	Any metastasis

The AJCC staging system for soft tissue sarcoma is shown in Table 118-3, although other staging systems have been described, particularly for various types of tumors. In addition, fibrosarcoma grade I (fibromatosis or desmoid tumor) and dermatofibrosarcoma are not listed under sarcoma staging. Other changes effective in 2003 include the addition of subdivisions of tumor (T) category into superficial (Ta) and deep (Tb) lesions. In general, the tumor should be described pathologically by grade as G1-G4 with tumor size less than 5 cm (T1) or greater than 5 cm (T2).

The AJCC staging system for bone sarcoma is shown in Table 118-5, although other staging systems have been described, particularly for various types of tumors. In addition, malignant lymphoma, leukemia, and multiple myeloma are not listed under bone sarcoma staging. Unlike the soft tissue sarcomas, the bone sites do not include subdivisions by depth of tumor as superficial or deep. Instead, T1 tumors are confined to within the cortex, whereas T2 tumors invade beyond the cortex.

Table 118-4

Bone Sarcomas

Osteosarcoma
Chondrosarcoma
Mesenchymal chondrosarcoma
Malignant giant cell tumor
Ewing's sarcoma

Table 118-5

American Joint Committee on Cancer (AJCC) Staging System for Bone Sarcomas (2003)

Stage	Definition
Primary Tumor	
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Tumor confined within the cortex
T_2	Tumor invades beyond the cortex
Regional Lymph Nodes	
N_x	Lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
Distant Metastases	
M_x	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis present
Histopathologic Grade	
G_x	Grade cannot be assessed
G_1	Well differentiated (low grade)
G_2	Moderately differentiated (low grade)
G_3	Poorly differentiated (high grade)
G_4*	Poorly differentiated or undifferentiated (high grade)

*Ewing's sarcoma, considered G_4.

Treatment

The treatment of sarcomas involving the head and neck region involves multidisciplinary evaluation and planning in order to provide optimal chance of cure and rehabilitation. The treatment should always include consultation with a head and neck surgeon, medical oncologist, and radiation oncologist in close cooperation with a head and neck pathologist and neuroradiologist familiar with these neoplasms. Other specialists often involved in the care of these patients include dental oncologists, maxillofacial prosthodontists, speech and swallowing therapists, and rehabilitation specialists. The histology, evaluation, and treatment of each histologic type of sarcoma and site of origin will vary and thus are discussed according to the cell of origin.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma in adults. Rarely, it involves the head and neck region including the soft tissues of the paranasal sinuses, neck, skull base, and parotid gland. Of 88 fibrous histiocytomas (benign and malignant) of the head and neck analyzed, the neck was the second most common site behind the sinonasal region.[69] Etiologic factors include prior radiation therapy and historical use of silica as injection material. The cell of origin has received much discussion, although consideration of fibroblastic or primitive mesenchymal cell has emerged as the leading theory.[70] Microscopically, these tumors tend to reveal histiocytes, fibroblasts, giant cells, spindle cells, and collagen with the storiform-pleomorphic form the most common. MFH is considered a high-grade sarcoma and is classified into numerous subtypes providing for a separation from the standard staging for sarcomas. There is evidence that the survival and course of the disease is related to the size and depth of these tumors.[71] The treatment is surgical with wide margins. Although elective treatment of the neck is not indicated due to the low incidence of cervical metastases, a possible exception may be the oral cavity where MFH has a higher metastatic potential to regional lymph nodes.[72,73] Local recurrence rates approach 30% with overall lymph node metastases near 10% and distant metastases approximately 35%, most of which occur within the first 2 years.[71] Recurrence seems to result in a lower surgical salvage rate for head and neck MFH than in extremities and overall survival is poorer for head and neck sites. Survival approaches 75% for patients without local recurrence following surgery and drops to 38% with local recurrence for an overall 5-year survival of approximately 51%.[74]

Rhabdomyosarcoma

RMS is a malignancy that is derived from mesenchymal cells associated with skeletal muscle differentiation. It represents the most common soft tissue sarcoma in children and accounts for 20% of sarcomas in all age groups. More than 45% of RMSs arise in the head and neck region with the highest incidence in the first decade and another peak occurring in the second and third decades. The most common sites in the head and neck from a recent series of 50 cases include the face, orbit, nasal cavity, neck, paranasal sinuses, and parameningeal sites.[75] MRI imaging provides detailed evaluation of the location and extension of disease, allowing a more precise approach to these tumors (Fig. 118-7A through D). Metastatic disease was present in 33% of cases with the most common sites being bone marrow, cerebrospinal fluid, peritoneal fluid, and lung.[75] Other reports reveal the neck soft tissue to be involved in almost 14% of adult head and neck RMSs.[76] These tumors are categorized by the Intergroup Rhabdomyosarcoma Study (IRS) into the following subtypes: embryonal, embryonal-botryoid variant, embryonal-spindle cell variant, alveolar-classic and solid variants, undifferentiated, and anaplastic. These are also commonly classified as embryonal, alveolar, pleomorphic, and mixed types. The embryonal type represents the most common RMS in both children and adults and microscopically, reveals small spindle cells with a central nucleus, although round cells often resembling lymphocytes may be seen. The botryoid variant grows in a polypoid, grapelike fashion and differs microscopically from the classic embryonal by a subepithelial condensation of tumor cells. The alveolar type occurs primarily in the teenage and young adult population and is identified histologically by an alveolar pattern of loosely arranged cells with hyperchromatic nuclei. The pleomorphic type represents approximately 17% of the adult RMS and less than 5% of pediatric cases. These lesions are found to have large, pleomorphic cells with eosinophilic cytoplasm. Immunohistochemistry has provided valuable diagnostic techniques to the histologic diagnosis of these lesions with antidesmin staining in 94%; 77% positive for desmin, 78% positive for muscle specific actin, and 30% for myoglobin.[77]

Treatment of RMS has continued to improve since the development of the IRS and now often involves combined modality treatment to include surgery, chemotherapy, and radiation therapy. Therapy has been based on the site category, which the IRS had delineated as (1) orbit, (2) parameningeal, and (3) other head and neck. Primary treatment often includes induction chemotherapy followed by radiation therapy, although concomitant therapy may be used. Surgery is typically reserved for debulking or for tumors that can be resected entirely without functional or cosmetic deformity. Neck dissection is warranted in obvious neck involvement or in clinically enlarged adenopathy. The survival rates for each of these sites were 92%, 69%, and 81%, respectively.[78-81] IRS III and IV analysis of nonorbital nonparameningeal patients does show an overall 83% five-year survival and a better prognosis in N0 patients than those with N1 disease.[82] Prognosis correlates with patient age, site of disease, histologic type, size of tumor, and

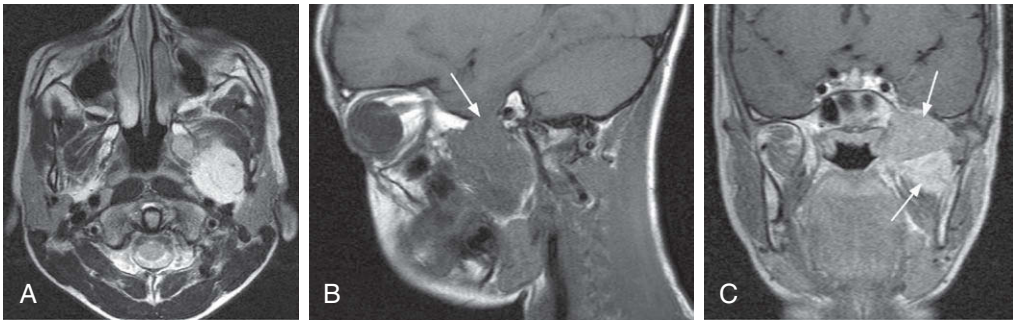

Figure 118-7. Rhabdomyosarcoma. **A**, Axial T2-weighted magnetic resonance (MR) image shows a hyperintense mass within the left masticator space. **B**, Sagittal T1-weighted MR image reveals extension of the mass through an expanded foramen ovale *(arrow)*. **C**, Coronal postcontrast T1-weighted image shows two different areas of enhancement *(arrows)* within the tumor, a relatively common finding with rhabdomyosarcomas.

metastases with botryoid and spindle associated with a better prognosis than the embryonal type, which is better than alveolar and pleomorphic.[83] Long-term follow-up has identified significant morbidity related to these treatments and long-term functional outcomes should be considered in addition to locoregional control and survival.[84] Lymphatic metastases are found to occur in 3% to 20% of RMS, although hematogenous spread may also occur.[85,86] Staging of RMS is commonly based on the IRS, which incorporates extent of disease with metastases and surgical results. It was also recommended by IRS that staging systems for this disease require ongoing analysis to confirm prognostic correlation with stage[77,85] (Table 118-6).

Osteosarcoma

Osteosarcoma of the head and neck primarily involves the mandible and maxilla with the mandible having a slightly higher incidence. The tumor rarely involves the soft tissues of the neck, although isolated regional metastases have been reported in addition to several reports involving the hyoid and larynx.[87,88] The treatment of these lesions has primarily included surgical resection with or without radiation therapy and chemotherapy. The incidence of cervical metastases is reported to be less than 10%, making routine neck dissection unwarranted.[89] The poor prognosis of soft tissue osteosarcomas of the larynx may encourage multimodality treatment for these sites in the future.

Fibrosarcoma

The neck is the second most common site of presentation of head and neck fibrosarcoma, following the paranasal sinus region. Although it can occur at any age, it is more common in adults between 40 and 70 years of age. There also exists a subset of children diagnosed before age 2. This neoplasm originates from the fibroblast and usually arises spontaneously but is known to arise in areas of prior burn scars and radiation therapy.[90,91] Histologically, they are identified by a malignant fibroblastic proliferation with variable amounts of collagen and reticulin forming a "herringbone" pattern. These lesions have a broad differential diagnosis and the well-differentiated types are commonly confused with fibromatosis and other benign processes. They typically present in the neck as a painless enlarging firm mass and have a low rate of lymphatic metastasis, thus making routine neck dissection unwarranted. There tends to be a high local recurrence rate up to 50% despite radical surgical excision with a survival of 50% to 75% and possibly higher in young children.[90,92-95] Adjuvant treatment should be based on size of the tumor, tumor grade, and status of surgical margins.[94] Review of the literature on these tumors should proceed with caution because of changes in histochemical diagnosis that may alter the inclusion of certain tumors previously classified as fibrosarcoma in earlier series.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma is a rare tumor that is stated to involve the head and neck region in approximately 25% of cases, although it represents less than 1% of all sarcomas. The exact differentiation of this tumor remains elusive; however, muscular and neural derivations are hypothesized. Recent work has failed to recognize the cell of origin in ASPS, but identification of the unbalanced translocation der(17) t(X:17)(p11;p25) leading to the fusion gene *ASPL-TFE3* has generated two important realizations. First, the presence of this fusion protein is causative in ASPS, and second, specific immunohistochemical stain for this fusion protein has led to improved accuracy in diagnosis.[96] The common sites affected in the head and neck include the tongue and orbit with the orbit having the best prognosis. ASPS rarely involves the neck and is reported to metastasize to the neck from head and neck primary sites in less than 10% of cases making elective neck dissection unwarranted. Distant metastatic disease does occur and may not present for years or decades after the primary site was treated. Surgery remains the mainstay of treatment, although local recurrence is common. More recent reports have shown success with multimodality treatment including chemotherapy. Overall survival is approximately 65% at 5 years but drops to 50% at 10 years.[97-103]

Angiosarcoma

Angiosarcoma is another rare sarcoma representing less than 1% of all sarcomas with up to half involving the head and neck. There remains consideration that this disease involves both vascular and lymphatic vessels—hence the differentiation from lymphangiosarcoma. The etiology remains unclear, although trauma, radiation, and lymphedema have been associated with some cases.

Treatment is primarily surgical using wide margins due to the multicentric nature of these tumors and local recurrence rate nearing 50%. Postoperative adjuvant radiation therapy is also generally recommended. There is limited experience using primary or adjuvant chemotherapy in these neoplasms. Metastatic disease commonly occurs in the lung and liver, whereas regional metastatic disease is common in lesions of the scalp. Elective neck dissection is recommended for clinically and radiographically evident disease and/or primary lesion involving the scalp. The 5-year survival remains low with most reporting less than 25%.[104-110]

Epithelioid Hemangioendothelioma

This tumor is extremely rare and is described to involve the head and neck region in only approximately 10% to 15% of the cases. These lesions are found to be derived from an epithelioid or histiocytoid type of endothelial cell.[111] It does manifest a wide spectrum of biologic behavior ranging from a benign form to an extremely aggressive form of the disease, although all are vascular in nature. Aggressiveness and eventual mortality seem to be related to location of the lesion with liver lesions having a worse prognosis than other sites including the head and neck.[112] There has recently been described a more "benign" variant without distant metastases.[113] Another form has been described as *spindle cell hemangioendothelioma* but is now thought to be a benign process. This variant is referred to as *spindle cell hemangioma for solitary lesions.*[114] Variants that are more aggressive and similar to angiosarcoma most often arise in the thyroid, submandibular, and neck soft tissues, although mucosal and skin sites have been described including the paranasal sinuses, larynx, and temporal bone.[115-117] Demonstration of endothelially derived cells is important in arriving at a correct diagno-

Table 118-6

Rhabdomyosarcoma Intergroup Staging System

Tumor Node Metastasis Pretreatment Staging System (IRSG)

Stage	Sites	T	Tumor Alae	N	M
I	Orbit	T_1 or T_2	a or b	N_0 or N_1 or N_2	M_0
	Head and neck (excluding parameningeal)			—	
	GU-Nonbladder/Nonprostate			—	
II	Bladder/Prostate	T_1 or T_2	a	N_0 or N_X	M_0
	Extremity			—	
	Head and neck parameningeal			—	
	Other (trunk, retroperitoneum, etc.)				
III	Bladder/Prostate	T_1 or T_2	a	N_1	M_0
	Extremity		b	N_0 or N_1 or N_X	
	Head and neck parameningeal			—	
	Other (trunk, retroperitoneum, etc.)			—	
IV	All	T_1 or T_2	a or b	N_0 or N_1	M_1

Definitions of T, N, and M Classifications in Pretreatment Staging

Classification	Description
Tumor	
T_1	Confined to anatomic size of origin
a	<5 cm in diameter
b	≥5 cm in diameter
T_2	Extension and/or fixation to surrounding tissue
a	<5 cm in diameter
b	≥5 cm in diameter
Regional Lymph Nodes	
N_0	Regional lymph nodes not clinically involved
N_1	Regional lymph nodes clinically involved by neoplasm
N_1	Clinical status of regional lymph nodes unknown (especially with sites that preclude lymph node evaluation)
Metastasis	
M_0	No distant metastasis
M_1	Metastasis present

Survival of IRS-II and IRS-III Patients by IRSG Pretreatment Stage

	Estimated 5-Yr Survival	
Pretreatment Stage	IRS-II	IRS-III
I	91%	09%
II	73%	06%
III	52%	69%
IV	23%	30%

GU, genitourinary; IRSG, Intergroup Rhabdomyosarcoma Study Group; IRS, Intergroup Rhabdomyosarcoma Study.

sis, and immunohistochemical studies for endothelial markers such as FVIII-Rag (factor VIII related antigen) and CD 34 have been found to be positive in a majority of cases.[112,118] Treatment has typically included surgical excision with possible radiation therapy. Recurrence and metastatic potential correlates with biologic aggressiveness with the more epithelioid lesions having a better prognosis, whereas the sarcomatous lesions have a higher metastatic potential and poorer prognosis.[119,120]

Chondrosarcoma

Although chondrosarcoma is typically found in the maxillary and mandibular region of the head and neck, presentation in the neck

or origin in soft tissues can occur.[121,122] Histologically, evidence of cartilage formation exists with varying degrees of differentiation and grade. These tumors are typically classified as osseous or extraosseous and may be subtyped into conventional, myxoid, and mesenchymal with mesenchymal being much more common in children and young adults. Prognosis does seem to be related to the subtype with myxoid having the worst prognosis followed by mesenchymal and conventional. There has been some controversy surrounding the histologic separation of osteoblastic chondrosarcoma from osteosarcoma. From the National Cancer Database (NCDB) report, the average age of patients with chondrosarcoma of the head and neck is 51, although more than 32% were younger than age 40. There is a slight male predominance and ethnicity reveals that non-Hispanic white constitutes more than 86% of cases. Only a small percentage of cases with regional or distant metastases at diagnosis with 5.6% and 6.7%, respectively, are found in the NCDB report.[122] Treatment includes wide surgical resection, although consideration of postoperative radiation may be entertained, particularly in high-grade tumors. Survival from the NCDB report reveals a surprisingly high survival of head and neck chondrosarcomas at 87.2% five-year and 70.6% ten-year survival, with 59.5% undergoing surgery alone and 21.0% having adjuvant radiation therapy.

Leiomyosarcoma

This is a neoplasm that generally affects older adults, although it can occur at any age. It represents 6% of all sarcomas, with 3% involving the head and neck region. The oral cavity followed by the sinonasal region and subcutaneous areas are the most common sites.[76] Although the scalp and face are the most common sites of occurrence of the subcutaneous lesions, there are reports involving the superficial and deep tissues of the cervical region.[123,124] The neoplasm develops from smooth muscle origin and histologically has a typical appearance of fascicles arranged in a perpendicular fashion with the cigar-shaped nuclei, eosinophilic cytoplasm, and paranuclear vacuoles. Most leiomyosarcomas also expresse muscle-specific actin, smooth muscle actin, and desmin.[125] These can be differentiated from fibrosarcoma by "cigar-shaped" nuclei rather than the "pointy" nuclei of fibrosarcoma. The most common presentation is a nodular dark blue or black lesion involving the dermis and epidermis, which may be tender to palpation. Those that arise in the subcutaneous tissues have a higher local recurrence, metastatic rate, and worse prognosis. Of those originating in the oral cavity, there is a high rate of local recurrence in addition to metastatic disease to the cervical nodes, lungs, and subcutaneous tissues.[76] Deep neck masses should also be considered in the differential even without skin involvement. The treatment includes wide resection with negative margins. Neck dissection may be indicated due to the potential for regional and distant metastases.[126,127] The prognosis varies greatly with site of origin and histologic variations, thus making accurate estimates of survival of each site difficult.

Liposarcoma

Although considered the most common soft tissue sarcoma of adults, constituting 12% to 18% of cases, involvement in the head and neck region is rare, occurring in an estimated 3% to 6% of cases.[76] A relationship to previous lipoma and traumatic events has been considered, yet there is insufficient evidence to confirm the relationship to the development of liposarcoma. In a review of head and neck liposarcomas, Barnes identified the larynx and hypopharynx to be the most common sites, followed closely by the neck. Others report the neck to be more commonly involved.[76,128] The prognosis appears to be dependent on site and classification with the well differentiated and myxoid having a better prognosis (75% to 100%) than the round cell and pleomorphic varieties (12% to 30%).[76,128-130] The liposarcoma is considered to occur primarily in deeper soft tissue locations than the lipoma or atypical lipoma. Although cervical metastases are rare, distant metastases have been reported primarily to the lung and liver.

Atypical Lipoma

Despite its benign behavior, the atypical lipoma or pleomorphic lipoma may be misdiagnosed as liposarcoma because of the histologic similarity. These are typically more superficial and radical treatment is not necessary if wide surgical margins are obtained. Similarly, the spindle cell lipoma has also been described and behaves in a similar fashion to the atypical lipoma. Both of these processes are more common in adult males.[131]

Malignant Hemangiopericytoma

Hemangiopericytoma (HPC) arises from the cells of Zimmerman, which occur around capillaries and postcapillary venules. The majority of HPCs of the head and neck are found in the paranasal sinuses; however, because of their cells of origin, nearly any tissue could be involved, including the neck.[132,133] The tumor primarily affects adults, although there is a subset of children from birth to 5 years of age who can be affected. The treatment is surgical because HPC has been shown to be relatively radioresistant, and the highly vascular nature of these tumors may require preoperative embolization. Adjuvant radiation therapy has been recommended for those with high-grade features and/or positive margins. Neck dissection is not necessary because lymphatic spread is rare. Varying reports of distant metastases seem to correlate HPCs with histologic pattern, mitotic figures, and proliferation indices.[134-136] The 5-year survival is near 70% and distant metastases usually portend recurrence at the primary site.

Malignant Peripheral Nerve Sheath Tumor

The malignant peripheral nerve sheath tumor (MPNST) refers to a type of neurosarcoma that represents nearly 10% of all sarcomas and behaves in an aggressive fashion with a poor prognosis. The tumor appears to have varying distribution by gender and is typically a disease of adults.[137,138] The tumor typically arises in the neck in up to half of the head and neck cases, although the sinonasal region, parapharyngeal space, parotid, and thyroid have been involved. These tumors are generally considered to occur in two settings: (1) spontaneous and (2) within the setting of a neurofibroma, particularly neurofibromatosis I (NF-1). Those arising in the latter typically occur at a younger age (fourth decade) and have a worse prognosis.[139] It is stated that for patients diagnosed with NF-1, the risk of developing an MPNST is 2%.[140] The typical presentation is of a progressive swelling with many presenting with pain in the region. Those with a history of NF-1 may describe a long history of a mass with a recent rapid enlargement. Associated neurogenic symptoms of weakness or paresthesias may be associated. Microscopically, they typically reveal atypical spindle cells similar to Schwann cells that are closely associated with a peripheral nerve. There remains significant controversy and variability in the histopathologic diagnostic criteria. The treatment includes wide resection with clear margins and postoperative radiation with margin status and tumor size correlating with survival.[139,141,142] The prognosis is poor despite aggressive treatment with more than 40% developing local recurrence. The presence of lymphatic metastases is rare.[138,141,143,144]

Synovial Sarcoma

Synovial sarcoma (SS) comprises 6% to 10% of all soft tissue sarcomas and 3% to 10% of all head and neck sarcomas. This neoplasm has been described to arise in the periarticular regions of the body, although the sites of the head and neck are not usually in these areas. This tumor typically arises in people aged 20 to 40 with the hypopharyngeal and retropharyngeal regions the most likely sites of the head and neck. It is thought to be derived from a pluripotential mesenchymal cell with both epithelioid and spindle differentiation. Microscopically, the tumor is found to have a predominant spindle cell component with cuboidal and columnar cells surrounding glandular areas and may have calcifications in up to 30% of cases.[145,146] Prognosis appears related to tumor size, mitotic indices, high grade, local recurrence, and tumor necrosis, although absence of calcifications and ploidy may also be related.[145,147] The symptoms on presentation are usually related to mass effect, although a painful mass may be identified. The treatment requires wide surgical resection. Chemotherapy may also be beneficial when used preoperatively.[148,149] Neck dissection is not necessary due to the absence of cervical metastases. The 5-year survival is 47% to 58% with up to 40% incidence of local recurrence.[76,146,150]

Malignant Giant Cell Tumor

The malignant giant cell tumor (MGCT) of the head and neck region is extremely rare and may be considered to be radiation induced after patients are treated for a benign giant cell tumor. MGCTs account for less than 10% of all GCTs. The sinonasal region and mandible are the most common sites in the head and neck.[151,152] The secondary MGCT appears more common than primary MGCTs, which arise de novo without prior evidence of a benign GCT. Overall 5-year survival of secondary MGCTs was 32%.[153] Metastatic lesions of GCT are usually identified in the lungs.[154]

Ewing's Sarcoma

Ewing's sarcoma represents a malignancy derived from primitive neuroectoderm and is the second most common bone tumor in children. Of 70 cases described at a single institution, only 5 (7.1%) occurred in the head and neck region.[155] These are separated into osseous and extraosseous types with approximately 75% occurring in the first 2 decades. Primitive neuroectodermal tumor (PNET) is a diagnosis that has many overlapping features with extraosseous Ewing's sarcoma and may be related.[89] PNET occurs in the paraspinous regions in approximately 50% of cases. The most common head and neck sites for Ewing's sarcoma include the mandible, maxilla, skull, and sinonasal region, although soft tissue sites have been described.[156] The incidence of lymphatic spread to the cervical nodes is uncommon. Treatment involves multimodality therapy including chemotherapy, whereas surgery may be necessary for complete control of the primary site and for reconstructive considerations. Radiation may be beneficial in combination with these other modalities.

Solitary Fibrous Tumor

There exists a wide range of benign and malignant fibrous tumors with varying degrees of local, regional, and metastatic growth potential. The one that deserves mention because of its frequency in the head and neck, particularly in children, is desmoid fibromatosis. These tumors have a wide range of behavior and very low mortality rate. Treatment includes wide resection because of the high local recurrence rate of 21% to 47%.[69,157,158]

Lymphoma

Lymphoma deserves mention because of the common presentation in enlarged cervical lymph nodes but is presented in detail in Chapter 119.

Melanoma

Although melanoma may arise or metastasize to the neck without a known primary site, a thorough evaluation should be undertaken to identify the primary site. A review of 300 cases of melanoma by Balm[159] revealed that 17 (5.7%) presented with a cervical lymph node without known primary. The treatment included surgery, and the 5-year disease-specific survival was 48% with a median of 36 months, which correlated with other patients with a stage II cutaneous melanoma.[159]

In a large series of head and neck melanomas, elective neck dissection and therapeutic neck dissection did not appear to improve survival over patients undergoing delayed neck dissection for regional metastases developing later than 3 months following primary treatment. There was, however, a higher incidence of distant metastatic disease in patients who did develop regional metastatic disease.[160]

Squamous Cell Carcinoma Arising in Branchial Cleft Cyst

Rarely, squamous cell carcinomas have been documented to arise within branchial cleft cysts of the neck. Cytopathologic diagnosis is difficult but should be considered in the differential diagnosis of a cystic neck mass. Final confirmation of the diagnosis should follow the criteria proposed in differentiating these tumors from cystic squamous cell carcinoma of cervical lymph nodes.[161]

Carcinoma Arising within Thyroglossal Duct Cyst

This extremely rare occurrence has been described, providing evidence for cytologic examination of thyroglossal duct cysts in suspicious cases.[162-165]

Although it is understood that many soft tissue tumors may metastasize or originate in the neck region, the most common remains squamous cell carcinoma of the head and neck aerodigestive tract. A broad differential is required when evaluating the neck mass, particularly in children, making a systematic approach essential to the diagnosis. Because of the limited number of prospective and retrospective studies of nonsquamous malignancies involving the neck, it is essential that the clinician remains updated on the optimal treatment and incorporates a multidisciplinary approach to these tumors.

Summary

Neoplasms of the neck are rare but must be considered in any neck mass allowing for optimal evaluation and management. The well-known diagnostic algorithm with FNA should be followed for any neck mass because the overwhelming majority of malignancies are regional metastases from skin and upper aerodigestive tract primaries. When atypical cells are identified on FNA biopsy or unusual findings on radiologic studies, a primary tumor of the neck region should be considered. The ultimate diagnosis often requires surgical resection, which may entail simultaneous wide resection with confirmed clear margins and neck dissection to afford the patient the best chance for cure. Review of the existing literature for rare tumors including sarcomas and consideration of clinical trials will allow for long-term improvement in locoregional response and survival.

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CHAPTER ONE HUNDRED AND NINETEEN

Lymphomas Presenting in the Head and Neck

Nancy L. Bartlett

Key Points

- Surgery does not play a role in the curative treatment of lymphomas.
- An adequate biopsy is critical for rendering an accurate diagnosis and classification of lymphoma. An excisional or incisional biopsy is the preferred procedure for confirming a new diagnosis of lymphoma.
- Specimens should be submitted to the pathologist in saline, along with the patient's clinical history and differential diagnosis, in order to perform appropriate testing such as flow cytometry.
- Highly aggressive lymphomas such as Burkitt's or lymphoblastic lymphoma should be referred to a medical oncologist emergently.
- Limited stage Hodgkin's lymphoma and diffuse large B-cell lymphoma presenting in the head and neck are highly curable with combined modality therapy including combination chemotherapy and involved-field radiotherapy.
- Mucosa-associated lymphoid tissue lymphomas of the thyroid and salivary glands are rarely life-threatening and should be treated with low-dose involved-field radiotherapy.
- Diffuse large B-cell lymphoma of the paranasal sinuses is associated with a high risk of central nervous system relapse.
- NK/T cell lymphoma nasal type has an aggressive clinical course and frequently causes marked tissue destruction and necrosis. Wide-field radiotherapy to a dose of at least 50 Gy is the most effective therapy.

Lymphomas are malignant neoplasms of lymphocytes and their precursor cells. Historically, lymphomas were classified merely by their histologic appearance, specifically cell size (e.g., small, large, mixed) and architecture (nodular or diffuse). The current classification system is the World Health Organization (WHO) system, which defines specific subcategories of lymphoma according to the immunologic and molecular characteristics of the lymphoma cells, as well as the morphology.[1] Most subtypes of lymphoma can potentially involve the head and neck, either as the only site of disease or as one of many sites of involvement. Because an enlarged cervical or supraclavicular lymph node is a common presentation of many lymphomas, otolaryngologists are often the first physicians to evaluate and biopsy these patients, as well as the first to inform patients of their diagnosis. Understanding the pathology, clinical features, treatment, and prognosis for each of the nodal and extranodal lymphoma subtypes that can present in the head and neck will allow for a more accurate and efficient evaluation. In addition, a brief discussion of the diagnosis and prognosis by the head and neck specialist is extremely valuable to patients and their families while they are awaiting an initial appointment with a medical oncologist.

Epidemiology

It is estimated that 74,300 new cases of lymphoma will be diagnosed in the United States in 2008, including 66,100 cases of non-Hodgkin's lymphoma (NHL) and 8200 cases of Hodgkin's lymphoma (HL).[2] The incidence of NHL rose dramatically between 1970 and 1995 but has stabilized over the past 14 years. The cause of this increase is incompletely understood. The human immunodeficiency virus (HIV) epidemic and the increase in NHL after solid-organ transplants account for only a minority of the new lymphomas. The incidence of NHL is slightly higher in men than women and increases exponentially with age. The most reproducible environmental risk factor includes exposure to certain pesticides or herbicides, and inconsistent associations have been reported with hair dyes, certain occupations, smoking, consuming foods high in animal fat, and receiving blood transfusions.[3] Infectious agents including Epstein-Barr virus (EBV), HIV, human T-cell leukemia virus (HTLV)-1, *Helicobacter pylori, Chlamydia psittaci,* hepatitis C, HHV8, and *Borrelia burgdorferi* have been proposed as etiologic agents in the pathogenesis of some cases of NHL.[4] Other factors associated with a significant increased risk of NHL include autoimmune disorders, most commonly Sjögren's syndrome and rheumatoid arthritis, although it is difficult to separate the effects of immunosuppressive drugs used to treat these diseases and the underlying autoimmune disease.

HL has a bimodal age distribution in developed countries, with the first peak occurring in the third decade of life and the second peak occurring after age 50 years. Men have a slightly higher incidence than women. There is an association between HL and factors that decrease exposure to infectious agents at an early age including advanced maternal education, early birth order, decreased number of siblings, and living in a single-family residence. A history of infectious mononucleosis increases the risk of HL twofold to threefold and suggests EBV as an etiologic agent.[5] There is a slightly increased risk of HL in patients infected with HIV and other conditions associated with chronic immunosuppression. An increased incidence among first-degree relatives, a significant concordance rate among identical but not fraternal twins, and linkage with certain HLA types suggest a genetic predisposition for

Figure 119-1. Neck computed tomography scan of a 23-year-old woman with classical Hodgkin's lymphoma showing a conglomeration of bulky, right supraclavicular lymph nodes adjacent to the right thyroid lobe.

HL.[6] The incidence of HL varies significantly with geography, suggesting either an environmental or a genetic association. HL is rare in Japan, but interestingly, the incidence increases in Japanese Americans, suggesting an important environmental component.[7]

Clinical Presentation of Lymphomas of the Head and Neck

Lymphoma should be included in the differential diagnosis of any patient with adenopathy, salivary gland enlargement, or a mass in Waldeyer's ring (WR), the nasal cavity, the paranasal sinuses, or the thyroid. Approximately 75% of lymphomas presenting in the head and neck are nodal and 25% extranodal. An accurate history and physical examination can provide important clues to the diagnosis.

Classical HL occurs most commonly in young adults and usually presents as painless lymphadenopathy in the cervical and/or supraclavicular regions. In contrast to NHL, HL spreads in a contiguous pattern and rarely involves the preauricular or occipital nodes or extranodal sites of the head and neck such as the tonsil or sinus. Infraclavicular involvement in patients with bulky supraclavicular nodes is common in HL but is rarely seen in NHL. Bulky, matted nodes are not uncommon (Fig. 119-1). Although staging studies reveal mediastinal adenopathy in more than 85% of patients with HL, symptoms of cough, chest pain, dyspnea, and superior vena cava (SVC) syndrome are uncommon, even in patients with bulky mediastinal disease. Systemic symptoms or "B" symptoms including fevers (temperature > 38° C), drenching night sweats, and weight loss occur in 30% to 40% of patients with stage III or IV disease, but in less than 10% of patients with stage I or II disease. A hallmark of HL, generalized, severe pruritus, occurs in approximately 25% of patients with HL, often precedes the diagnosis by months, can be a presenting symptom of both early and advanced-stage disease, and has no known prognostic significance. Alcohol-induced pain in involved lymph nodes is a rare symptom of HL (<1%). A rare subtype of HL, nodular lymphocyte-predominant HL (LPHL), usually presents as a solitary cervical, axillary, or inguinal lymph node. In LPHL the mediastinum is generally spared, and in contrast to the contiguous pattern of lymph node involvement in classic HL, there is no consistent pattern of spread.

Presenting symptoms of NHLs vary substantially depending on the pathologic subtype of NHL and the site(s) of disease. Indolent lymphomas such as follicular (FL) or small lymphocytic (SLL) lymphomas often present with painless, peripheral adenopathy. Multiple soft, mobile, bilateral cervical nodes ranging in size from 1 to 2 cm are common presentations of both FL and SLL (Fig. 119-2). Matted peripheral lymph nodes are uncommon. Isolated head and neck involvement is unusual with these subtypes of lymphoma, and examination of axillary and inguinal regions usually reveals additional enlarged nodes. SLL can involve the tonsillar regions. Because spontaneous regressions occur in up to 20% of patients with FL, the patient may describe a history of waxing and waning adenopathy, with nodes present for years in some cases. Most patients with indolent lymphoma feel well at presentation, and B symptoms including fevers, drenching night sweats, and weight loss are unusual. Patients with SLL frequently have involvement of the peripheral blood, and a complete blood count may reveal a lymphocytosis. Peripheral blood flow cytometry may provide a diagnosis and obviate the need for a tissue biopsy. Indolent lymphomas are uncommon before age 50.

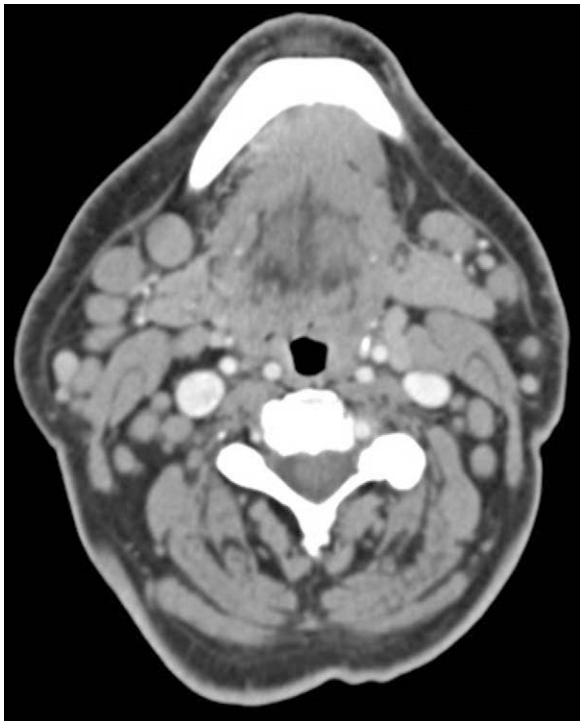

Figure 119-2. Neck computed tomography scan of an 81-year-old man with small lymphocytic lymphoma showing bilateral diffuse cervical lymphadenopathy.

Mucosa-associated lymphoid tissue (MALT) lymphomas, indolent lymphomas occurring in extranodal sites, can present as an isolated swelling in the thyroid or a salivary gland, most commonly the parotid gland. Bilateral parotid involvement can occur and occasionally a history of stable enlargement over months or years is elicited. Cases of MALT lymphoma have also been reported in the sinuses, oral cavity, and nasal cavity. MALT lymphomas of the head and neck are often associated with autoimmune disorders, such as Hashimoto's thyroiditis and Sjogren's syndrome, and occasionally precede the diagnosis of the autoimmune disorder.

Many aggressive lymphomas, the most common being diffuse large B-cell (DLBC), also often occur as painless cervical or supraclavicular adenopathy, without other associated symptoms. Fevers, night sweats, or weight loss occur in about 20% of patients with advanced-stage disease. Primary extranodal large cell lymphomas are common, accounting for 15% to 20% of all large cell lymphomas and can present in the tonsils, nasopharynx, oropharynx, thyroid, salivary glands, or sinuses. The presentation of extranodal lymphomas of the head and neck is discussed in more detail later in this chapter.

The very aggressive lymphomas, lymphoblastic and Burkitt's, are rare in the adult population, but can occur with acute symptoms and can be life threatening without rapid intervention. In adults, lymphoblastic lymphomas occur most commonly in young men, and frequently occur with acute respiratory compromise due to bulky mediastinal adenopathy, and pleural or pericardial effusions. Occasionally supraclavicular adenopathy is present and the otolaryngologist will be called upon to obtain diagnostic tissue emergently.

Biopsy Techniques and Specimen Handling

Because surgery does not play a role in the curative treatment of lymphomas, the goal of biopsy is to provide enough material for an accurate diagnosis, while minimizing the cosmetic effect of the biopsy. If the biopsy involves a nodal site, sample the largest node or any node

Table 119-1

Proposed World Health Organization Classification for NHL

- B-cell neoplasms
  - Precursor B-cell lymphoblastic leukemia/lymphoma*
  - Mature B-cell neoplasms
    - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
    - B-cell prolymphocytic leukemia
    - Lymphoplasmacytic lymphoma
    - Mantle-cell lymphoma
    - Follicular lymphoma†
    - Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
    - Nodal marginal zone lymphoma ± monocytoid B cells
    - Splenic marginal zone B-cell lymphoma
    - Hairy cell leukemia
    - Diffuse large B-cell lymphoma†
    - Subtypes: mediastinal (thymic), intravascular, primary effusion lymphoma
    - Burkitt's lymphoma
    - Plasmacytoma
    - Plasma cell myeloma
- T-cell neoplasms
  - Precursor T-cell lymphoblastic leukemia/lymphoma*
  - Mature T-cell and NK-cell neoplasms
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic leukemia
  - NK-cell leukemia
  - Extranodal NK/T-cell lymphoma, nasal-type
  - Mycosis fungoides†
  - Sézary syndrome
  - Angioimmunoblastic T-cell lymphoma
  - Peripheral T-cell lymphoma (unspecified)†
  - Adult T-cell leukemia/lymphoma (HTLV1$^+$)†
  - Systemic anaplastic large-cell lymphoma (T- and null-cell types)†
  - Primary cutaneous anaplastic large-cell lymphoma†
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Enteropathy-type intestinal T-cell lymphoma
  - Hepatosplenic γ/δ T-cell lymphoma

*The classification of acute lymphoid leukemias will expand on the classification of precursor B-cell and T-cell malignancies, incorporating both immunophenotypic and genetic features.
†Morphologic and/or clinical variants of these diseases are not listed, for the purpose of clarity and ease of presentation.
NHL, non-Hodgkin's lymphoma; NK, natural killer.

growing out of proportion to other nodes in order to rule out transformed lymphoma. Sampling a single site is usually adequate.

Tissue biopsy is essential in the diagnosis and management of patients with lymphomas. Recent advances in the immunology and molecular biology of lymphomas, as well as new diagnostic reagents and methods, have resulted in more precise diagnoses. The most recent WHO classification includes more than 25 subtypes of NHL, with B-cell neoplasms representing 80% to 90% of NHLs (Table 119-1). When the clinical history is suggestive of lymphoma, but initial histologic review and immunohistochemistry by flow cytometry or on paraffin-embedded tissue sections are nondiagnostic, molecular testing for T-cell receptor and immunoglobulin heavy-chain gene rearrangements should be considered. Cases in which the pathologic diagnosis seems inconsistent with the clinical history should be reviewed by an expert hematopathologist.

The proper handling of specimens for adjunctive diagnostic tests is critical whenever lymphoma is suspected. Specimens should not be transported on dry towels or surgical sponges; they should be submitted to the pathologist in saline along with the patient's clinical history and differential diagnosis. Specimens should not be held overnight or for extended periods before processing by the pathology laboratory. If there will be a delay in processing the specimen, preserve a portion of the specimen in formalin to maintain the architecture. Crushed specimens are extremely difficult to evaluate for lymphoma.

The pathologist usually reserves fresh cells or frozen tissue for immunophenotyping and molecular diagnostics as needed. Immunophenotyping is performed, either by flow cytometry or using immunohistochemical methods, on slides prepared from frozen tissue or paraffin-embedded fixed tissue, on nearly all new cases of NHL or HL. Flow cytometry requires a fresh cell suspension, but it offers the advantage of preservation of antigens. Although fewer antigens are preserved in fixed and embedded tissues, immunohistochemical staining of paraffin-embedded specimens allows analysis of archival specimens and offers the benefit of correlation with architectural and cellular details.

Application of the World Health Organization classification system requires the integration of clinical, morphologic, cytogenetic, molecular, and immunophenotypic features to accurately characterize lymphoproliferative disorders. Therefore it is essential that all available clinical and diagnostic information related to a specimen be made available to the hematopathologist including any prior diagnosis of lymphoma.

Fine-Needle Aspiration

Because of the improved diagnostic methods previously discussed, a less invasive procedure such as fine-needle aspiration (FNA) or core-needle biopsy may lead to a precise diagnosis without the need for surgery in some cases of lymphoma. Although FNA is a rapid and cost-effective method, it provides only cytologic material. Cytology alone is less useful for the initial diagnosis of lymphomas because the architectural pattern is often necessary for accurate subclassification. In addition, FNA often does not provide adequate tissue for immunophenotyping, especially when the lymphoma is associated with extensive fibrosis, limiting the ability to aspirate cells. However, if an adequate number of cells can be aspirated, many pathologists agree that FNA may be adequate in the setting of *relapsed* disease because it is often easier to confirm a previous diagnosis than to render an initial diagnosis on the basis of limited material.

Due to the lack of fibrosis and a unique cytologic appearance and immunophenotype, small lymphocytic lymphoma and lymphoblastic lymphoma can often be accurately diagnosed solely on the basis of a fine-needle biopsy. Lymphoblastic lymphoma (LL), a high-grade lymphoma, often presents with SVC syndrome or severe dyspnea and progresses extremely rapidly. The ability of pathologists to provide a preliminary diagnosis within hours on the basis of an FNA of a supraclavicular or mediastinal node may allow earlier initiation of therapy. In one report of eight children with LL, FNA was employed as the initial diagnostic procedure.[8] Immunophenotyping established the T cell derivation in all cases, and treatment was initiated only on the basis of FNA results in six cases. Two patients had subsequent surgical biopsies that confirmed the FNA diagnosis of LL. In a separate retrospective study, nine out of nine cases of lymphoblastic lymphoma were correctly identified on the basis of specimens obtained by FNA.[9]

Stewart and colleagues[10] reported that FNA of *palpable* lymph nodes correctly identified 61 of 67 (91%) malignant lymphomas, with 27% of the cases representing recurrent lymphomas. However, in a more recent study, Hehn and colleagues[11] found that a specific and complete histologic diagnosis of lymphoma was obtained in only 27 of 93 FNA attempts (29%) at initial diagnosis, and in only 9 of 22 FNA attempts (41%) done in the setting of recurrent disease. Importantly, these 115 needle aspirations were interpreted by 70 different pathologists in the community setting and only 43% had concurrent ancillary studies such as flow cytometry. Howlett and colleagues[12] reported results of an audit of 276 patients who underwent FNA and subsequent surgery for evaluation of a "neck lump" at one of five hospitals in the Sussex cancer network in the United Kingdom during 2004. Of the

276 aspirations, 105 (38%) were nondiagnostic, 54 of 104 (52%) in the neck node group, 23 of 54 (43%) in the salivary gland group, and 28 of 118 (24%) in the thyroid group. Only patients in the thyroid group had ultrasound guidance for the procedure. Interestingly, 15 of the 54 nondiagnostic FNAs in the neck node group were NHL at surgery, as well as 3 of the 23 cases in the salivary gland group and 1 of the 28 thyroid cases. Additionally, 2 of 12 neck node aspirations and 2 of 24 salivary gland aspirations diagnosed as benign revealed NHL at surgery.

An accurate diagnosis of lymphoma by FNA requires an experienced sampling team, an expert cytopathologist, and the facilities to perform and interpret appropriate ancillary tests. The continued identification of unique immunophenotypic and molecular changes associated with many subtypes of lymphoma is likely to make this procedure more promising as the sole method of diagnosis in the future.

Core-Needle Biopsy

The use of percutaneous core-needle biopsies can sometimes overcome the limitations of FNA by retaining the architecture of the tissue and providing serial sections for histochemical and immunocytochemical stains. If a core-needle biopsy is technically feasible, use the largest-gauge needle possible (12 to 16 gauge) and obtain multiple cores. In general, both the peripheral and central portion of the mass should be sampled to avoid obtaining only necrotic tissue.

Several studies evaluating core-needle biopsy for lymphoma diagnosis have been published.[13-16] In one study, 241 patients with lymphoma underwent core-needle biopsy as their initial biopsy.[13] Overall, an 82.5% success rate was observed. Several studies included both patients undergoing initial evaluation, as well as patients with suspected relapse or progressive disease.[14-16] Core-needle biopsy procedures yielded sufficient material for formulation of a treatment plan in 83% to 93% of patients. A recent report of 88 patients undergoing ultrasound-guided core-needle biopsy for head and neck masses included 16 patients with a final diagnosis of lymphoma.[17] In 3 of 16 patients inadequate tissue was obtained by core-needle biopsy, and the patients had subsequent excisional biopsies. In 12 of 13 with "adequate" tissue to make a diagnosis of lymphoma, full subclassification of the lymphoma was possible and treatment initiated on the basis of the core-needle biopsy. Importantly, these 12 patients did not have an open biopsy to confirm the results of the needle biopsy. Gong and colleagues[18] compared results of FNA and core-needle biopsy in 74 patients with lymphoma. FNA with flow cytometry was insufficient in 47% of patients and core-needle biopsy was insufficient in 28% of patients.

Open Biopsy

Despite encouraging results with limited needle biopsies, both oncologists and hematopathologists prefer an excisional or incisional biopsy as initial diagnostic tissue in nearly all cases of lymphoma. Because head and neck masses can usually be biopsied with less invasive procedures than intrathoracic or intra-abdominal lymph nodes, there should be no reason to potentially compromise the diagnosis due to limited material.

Prebiopsy Corticosteroids

Historical teaching dictates that patients with suspected lymphoma should not receive corticosteroids before biopsy because of the theoretic risk of obscured results because of rapid tumor response. In reality, except in the rare case of lymphoblastic lymphoma, steroids are unlikely to have a significant detrimental effect if tissue is obtained within 24 to 48 hours of the first dose. In one study of 86 children with mediastinal lymphoma, 23 received prebiopsy corticosteroids. In five (22%) an adverse effect on the pathologic diagnosis was observed, one patient with HL and four with probable lymphoblastic lymphoma.[19] However, the only indication for prebiopsy steroids should be severe, life-threatening airway compromise. Although patients with SVC syndrome can be quite symptomatic, these symptoms are not life threatening over the short term and steroids should not be administered until diagnostic tissue is obtained. If lymphoblastic lymphoma is suspected, every effort should be made to obtain tissue within 1 day of presentation and before administration of steroids.

Nodal Lymphomas of the Head and Neck

Hodgkin's Lymphoma

As described earlier, most patients with HL present with asymptomatic peripheral adenopathy, most commonly cervical and supraclavicular. The incidence peaks between 15 and 40 years of age. Severe, generalized pruritus is common in HL, rare in NHL, and often precedes the diagnosis by months. Systemic symptoms including fever of greater than 38° C for 3 consecutive days, drenching night sweats, or unexplained weight loss of more than 10% of body weight in the preceding 6 months occur in about 25% of patients with HL, but they are uncommon in early-stage disease.[20] Pruritus, systemic symptoms, and many of the laboratory abnormalities seen in HL are probably a result of cytokine production by Reed-Sternberg cells.

HL is a neoplastic proliferation of Reed-Sternberg (R-S) cells or R-S variants, large cells with abundant cytoplasm and multiple or multilobed nuclei. R-S cells are surrounded by host inflammatory cells including lymphocytes, plasma cells, neutrophils, and eosinophils. R-S cells are derived, in most cases, from germinal center B cells.[21] The World Health Organization classifies HL as either "classic" HL or nodular LPHL. LPHL and classic HL have different natural histories, prognoses, and treatments.[21] Immunohistochemical studies accurately distinguish LPHL from classical HL and should be performed if histology is equivocal. In classical HL, the large atypical cells generally express CD15 and CD30, whereas other T- and B-cell–associated antigens are usually negative. In contrast, the tumor cells of LPHL are $CD20^+$ (a pan-B-cell antigen), $CD45^+$ (leukocyte common antigen), $CD15^-$, and variably reactive for CD30, an immunophenotype often seen in B-cell NHL. Flow cytometry is nondiagnostic in HL.

Staging

The Ann Arbor staging system for HL and NHL is detailed in Table 119-2. The designation E applies to extranodal involvement, which is limited in extent and contiguous with lymph node disease. Extranodal involvement of HL of head and neck sites is extremely rare. Proper staging requires computed tomography (CT) scans of the chest, abdomen, and pelvis. CT scans of the neck are optional and probably add little to a thorough physical examination but may aid in designing radiotherapy portals if radiotherapy is planned. The mediastinal mass ratio (MMR), defined as the ratio of the maximal transverse diameter of the mediastinal mass to the maximal transverse intrathoracic diameter, is an important prognostic factor and should be calculated in all patients with significant mediastinal adenopathy. An MMR greater than 0.33 by chest radiograph (CXR) or 0.35 by CT portends a worse prognosis and may influence treatment recommendations. Positron emission tomography (PET)/CT upstages and potentially alters treatment in 10% to 20% of patients with HL compared with CT alone and should be considered in the initial staging of patients with early-stage disease.[22,23]

Treatment and Prognosis

The treatment of HL has been a true success story, with nearly 80% of all patients having durable remissions including 90% to 95% of patients with nonbulky stage I to II disease, 80% of patients with bulky stage I to II disease, and 70% of patients with stage III to IV disease. Current efforts are aimed at minimizing therapy for low-risk patients in an effort to avoid both short- and long-term complications and developing new therapies for the small subset of high-risk patients.

Early-stage HL is usually considered "favorable" or low risk if there are no B symptoms and no sites of bulky disease, with bulk commonly defined as an MMR greater than 0.33 or a nodal mass greater than 10 cm. Extended-field RT is no longer appropriate therapy for these patients due to long-term complications. Debate continues regarding the best approach to treatment. Several trials demonstrate equivalent survivals for chemotherapy alone versus chemotherapy followed by involved-field radiotherapy (IFRT).[24,25] In most studies, chemotherapy alone is associated with a slightly inferior event-free survival (EFS) compared with combined modality therapy (CMT). However, many investigators agree that this modest increase in relapses will be counterbalanced by a significant reduction in fatal radiation-

Table 119-2

Ann Arbor Staging System for Lymphoma*

Stage I	Involvement of a single lymph node region or lymphoid structure, or involvement of a single extralymphatic site (I_E)
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm, which may be accompanied by localized contiguous involvement of an extralymphatic site or organ (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by involvement of the spleen (III_S) or by localized contiguous involvement of an extralymphatic site or organ (III_E)
Stage IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues, with or without lymph node involvement

*The absence or presence of fever (>38° C), unexplained weight loss (>10% body weight), or night sweats should be denoted by the suffix letters A or B, respectively.

induced complications during long-term follow-up. Both approaches are acceptable alternatives while we await mature results of randomized trials. Chemotherapy alone is particularly appealing in women aged 15 to 30 years, a subgroup particularly susceptible to second breast cancers after mediastinal and axillary radiation; smokers due to a marked increase risk of lung cancer after mediastinal RT; and patients with a strong family history of cardiovascular disease. Trials also are ongoing to determine if lower doses of radiation (20 Gy) in combination with chemotherapy are equivalent to currently prescribed doses of 35 to 40 Gy.[26] The impact of these changes on the frequency of serious long-term complications will not be realized for at least 2 decades. Another approach being studied is the use of early-restaging PET/CT scans following one or two cycles of chemotherapy. Patients with an early negative PET scan have an excellent prognosis, and eliminating RT in that subset may be reasonable. In a joint report from the Italian Intergruppo Linformi and the Danish Lymphoma Group that included 260 newly diagnosed patients with HL, the 2-year progression-free survival (PFS) for patients with a positive PET following two cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was 12.8%, compared with 95% for patients with a negative interim PET scan.[27] Patients with clinical stage I or II disease and a bulky mediastinal mass have a worse prognosis compared with other early-stage patients. Because of high relapse rates in this subset of patients when they are treated with either chemotherapy or RT alone, CMT is recommended.

Approximately 70% of patients with advanced-stage HL can be cured with six cycles of ABVD chemotherapy, the current standard of care. The International Prognostic Factors Project on Advanced HL identified seven independent prognostic factors in patients with advanced-stage HL including serum albumin less than 4 g/dL, hemoglobin less than 10.5 g/dL, male sex, age 45 years or older, stage IV disease, leukocytosis (WBC > 15,000/mm^3), and lymphocytopenia (lymphocyte count < 600/mm^3 and/or lymphocyte count < 8% of the WBC).[28] The HL prognostic score showed that patients at the lowest risk with zero to two high-risk features had a 67% to 84% freedom from progression (FFP) at 5 years, whereas those at highest risk with four to seven adverse risk factors had a 42% to 51% FFP. The German Hodgkin's Study Group also reported encouraging results of a more intense regimen, dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine, procarbazine, and prednisone) for patients with advanced-stage HL. In a randomized trial, dose-escalated BEACOPP resulted in a 2-year FFS rate of 89% compared with 70% for standard chemotherapy.[29] Compared with ABVD, dose-escalated BEACOPP results in sterility in nearly all patients and is associated with a higher incidence of secondary acute leukemia. These added toxicities may be acceptable in the highest-risk patients if improved cure rates can be confirmed.

Complications of Treatment

Treatment advances have dramatically improved the survival of patients with HL. Unfortunately, long-term survival frequently goes hand in hand with late-term treatment complications. Consideration of latent side effects should play an integral role in the choice of treatments for this highly curable malignancy. Investigators at Stanford University performed a retrospective analysis of 2498 patients with HL treated between 1960 and 1995 to determine latent complications of therapy and causes of mortality.[30] At 15 years, risk of death from HL was 17%, with only a slight increase thereafter. Risk of death from other causes was also 17% at 15 years; however, there was a sharp increase after 15 years. Similar results have also been reported from other centers, with a consistent association between increased doses of mediastinal radiation and delayed cardiopulmonary toxicities and secondary neoplasms.

The increased incidence of second malignancies following treatment for HL has been reported in numerous studies and is thought to be due primarily to the RT.[31,32] In a large study of more than 32,000 patients pooled from 16 cancer registries, a 21.9% risk of solid tumors was observed at 25 years.[31] Frequent among these second malignancies are primary cancers of the head and neck. In patients receiving RT to the neck for HL, the relative risk (observed/expected) of thyroid cancer is 4 to 5; esophagus 2 to 2.5; tongue, mouth, and pharynx 2.8 to 3.4; and salivary gland 6.[31,32] Treatment of these second cancers is often complicated by the previous radiation. Thyroid diseases are common after neck irradiation, with an actuarial risk of 67% at 26 years after therapy.[33] In most of these patients, hypothyroidism develops, but the risk of Graves' disease is also 7 to 20 times that for normal subjects.

Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL)

DLBCL is the most common subtype of NHL and frequently presents with cervical or supraclavicular adenopathy. As described later in this chapter, it is also the most common NHL to occur as a primary extranodal lymphoma in the head and neck including thyroid, sinus, WR, or a salivary gland. Additional workup after a diagnostic biopsy includes a history and physical examination with documentation of adenopathy, hepatosplenomegaly, performance status, the presence of B symptoms, laboratory evaluations, radiographic studies, and in most cases, a bone marrow biopsy. Necessary laboratory tests include a complete blood cell count, liver-function tests, calcium, creatinine, and lactate dehydrogenase. The Ann Arbor staging system, initially developed for HL, is also used to stage NHL (see Table 119-2). Alternative staging systems have been proposed but never adopted. Proper staging requires CT scans of the chest, abdomen, and pelvis, as well as bilateral bone marrow biopsies. PET and PET/CT scans have improved the accuracy of initial staging and response assessment in patients with DLBCL. As initial staging, they are most useful in patients with equivocal CT findings and in patients who appear to have localized disease at presentation, where finding additional sites of involvement could potentially alter management.

Treatment and Prognosis

Historically, the standard approach for stage I or II DLBCL was CMT. A prospective, randomized, multi-institutional study established the superiority of CMT over chemotherapy alone in this setting. Four hundred patients received either three cycles of CHOP (cyclophosphamide, doxorubicin, Oncovin, and prednisone) chemotherapy followed by IFRT or eight cycles of CHOP alone.[34] RT doses ranged from 40 to 55 Gy. Patients treated with CMT had significantly better 5-year FFP (77% vs. 64%) and overall survival (OS) (82% vs. 72%) rates compared with patients treated with chemotherapy alone. A phase II study of three cycles of rituximab (R)-CHOP chemotherapy followed by IFRT for limited-stage nonbulky large cell lymphoma showed 2-year

PFS and OS rates of 93% and 95%, respectively.[35] In contrast to previous studies, a large randomized trial published by the GELA in 2007 showed no advantage to four cycles of CHOP plus RT over four cycles of CHOP alone for the treatment of low-risk localized large cell lymphoma in patients older than 60 years.[36] Interestingly, in the subgroup of patients older than 70 years, the 5-year OS was higher in patients treated with chemotherapy alone (69% vs. 58%, $P = 0.2$). Avoiding RT in patients with head and neck sites is an appealing approach because the short- and long-term complications of dry mouth and altered taste often have a significant impact on quality of life. In patients with a negative early restaging PET scan (after one or two cycles of chemotherapy), four to six cycles of R-CHOP alone should be considered.

Patients with advanced-stage DLCBL are treated with six cycles of R-CHOP. Several randomized trials demonstrated a survival benefit when patients received R-CHOP versus CHOP as their initial therapy for large cell lymphoma.[37-39] The GELA reported 5-year OS rates of 58% and 45% and FFP rates of 54% and 30% for the R-CHOP and CHOP groups, respectively.[37] A population-based study from British Columbia confirmed the benefit of adding rituximab to standard chemotherapy.[38] Two-year PFS was 69% in the post-rituximab era and 51% in the pre-rituximab era.

Indolent Non-Hodgkin's Lymphoma

Indolent lymphomas, specifically follicular and small lymphocytic lymphoma, commonly involve the cervical and supraclavicular nodes and are often the presenting sign, even when widespread adenopathy is present. Multiple, bilateral, mobile nodes are often present and SLL may involve the tonsils. In some patients the nodes may wax and wane or remain stable over months or years, so a long history of enlarged nodes should not preclude a biopsy. Patients with FL and SLL are at risk for transformation to large cell lymphoma. Occasionally transformation is discovered at initial presentation. Signs of possible transformation include the presence of B symptoms, elevated LDH or calcium, necrosis of the node noted on CT scans, and discordant growth, with one node growing rapidly in the presence of other stable nodes. If lymphoma is suspected, an effort should be made to excise the largest node possible or any node that shows necrosis on CT scan. It is helpful to sample a non-necrotic node simultaneously because occasionally there are no viable cells for diagnosis in a necrotic node.

Treatment and Prognosis

The approach to patients with indolent lymphomas has changed significantly in the past 5 years, due to the publication of several randomized trials showing a significant improvement in remission duration and survival with the combination of rituximab (a chimeric anti-CD20 antibody specific for B lymphocytes) and chemotherapy compared with chemotherapy alone. Despite the marked improvement in outcomes, there is still no plateau in the EFS curves with the use of chemoimmunotherapy and "cures" are unlikely. The Follicular Lymphoma International Prognostic Index (FLIPI) includes five independent poor prognostic factors, age 60 years and older, stage III or IV, greater than four involved nodal areas, elevated serum LDH, and hemoglobin less than 12 gm/dL.[40] The 10-year overall survival rate for patients with three or more risk factors according to the FLIPI is 35% compared with 70% for patients with none or one high-risk feature.

Given the improved sensitivity of staging studies including CT scans, PET scans, and the use of flow cytometry to evaluate bone marrow specimens, the diagnosis of limited-stage indolent lymphoma is uncommon. Observation, IFRT, single-agent rituximab, a combination of rituximab and chemotherapy, and CMT with rituximab plus or minus chemotherapy with IFRT are all options for patients with this unusual presentation. No randomized trials have compared these approaches and treatment decisions should be based on the site and bulk of disease and patient age with the more aggressive approaches being preferred for younger patients and those with bulky stage I to II disease.

The current standard of care for patients with stage III to IV indolent lymphomas requiring therapy is a combination of rituximab and chemotherapy. Following the improvement in outcomes with chemoimmunotherapy, the role of observation or "watch and wait" has been questioned. However, despite many effective but to-date "noncurative" therapies, there has never been any objective evidence that early intervention improves overall survival in asymptomatic patients.[41] There remains a subset of patients with indolent lymphomas that have no indications for therapy more than 15 years after diagnosis. Asymptomatic, older patients with low-volume disease may still be best served by close observation until progression.

Several randomized trials show a significant improvement in EFS and overall survival with the addition of rituximab to combination chemotherapy.[42-44] Three- to five-year EFS rates range from 50% to 77% in recent series of combination therapy. There is no clear advantage of one chemotherapy regimen over another and excellent results have been reported with R-CVP (cyclophosphamide, vincristine, prednisone), R-CHOP, R-FND (fludarabine, mitoxantrone, dexamethasone) and R-Fludarabine. Currently the choice of regimen should be based on patient age and comorbid conditions. Non–anthracycline-based approaches should be considered in patients older than 65 and those with underlying cardiac disease. Fludarabine-based regimens are associated with an increased risk of opportunistic infections, particularly varicella zoster, due to a marked, prolonged decrease in the $CD4^+$ count.[45] Investigators testing R-FND in patients with newly diagnosed follicular lymphoma reported an alarming 4% incidence of myelodysplasia and acute myeloid leukemia.[46]

The question of maintenance rituximab following first-line chemoimmunotherapy is under investigation. Two large studies have shown a significant improvement in remission duration and overall survival with maintenance rituximab following chemoimmunotherapy for relapsed follicular lymphoma.[47,48] No data are available on continuing maintenance rituximab beyond 2 years. There are no known long-term effects of prolonged rituximab therapy.

An alternative approach for patients with low-volume disease, older patients, and patients with serious comorbid conditions is single-agent rituximab. Toxicities of rituximab are mild and are limited primarily to infusion-related reactions such as fevers, chills, myalgias, transient hypotension, and rarely bronchospasm. Maintenance rituximab following an initial course of four weekly doses improves remission durations but does not improve survival or increase the time to requiring chemotherapy compared with retreatment with rituximab at relapse.[49,50]

Studies of mAbs conjugated with radioisotopes are promising. Response rates of approximately 80% have been reported with both the [^{131}I]-anti-CD20 mAb, Bexxar, and the [yttrium-90]-anti-CD20 mAb, Zevalin. Side effects are modest and self-limited. The current Food and Drug Administration approval is for patients with relapsed indolent lymphomas; however, encouraging results have been reported incorporating Bexxar into front-line therapy, either as a single agent or as consolidation following chemotherapy. Kaminski and colleagues[51] reported a 95% response rate, 75% complete response rate, and 6-year PFS in 76 patients with previously untreated indolent lymphoma following a single dose of Bexxar. Press and colleagues[52] reported a 67% 5-year PFS rate for CHOP followed by Bexxar as initial therapy of follicular lymphoma. Larger series with longer follow-up are required before approaches incorporating radioimmunotherapy become the standard of care.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) occurs most frequently in men older than age 60 and has a variable presentation ranging from adenopathy in an asymptomatic patient to a leukemic presentation with extensive blood and bone marrow involvement. Involvement of neck nodes and tonsils is not uncommon. MCL has also been reported in most extranodal sites of the head and neck.

Treatment and Prognosis

More aggressive approaches such as those used for acute leukemia and Burkitt's lymphoma have resulted in improved outcomes for patients with MCL. Although remissions and survivals are substantially longer with intensive therapy, no study has yet reported a plateau in the PFS rate with more than 5 years of follow-up. In addition, the improved results are likely biased by patient selection, with aggressive regimens

most feasible for younger patients without significant comorbidities. Historical series of standard chemotherapy regimens such as CVP or CHOP include substantial numbers of older patients. Investigators at the M. D. Anderson Cancer Center reported 3-year failure-free survival and OS rates of 64% and 82%, respectively, with R-hyperCVAD (rituximab, high-dose cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and ara-C.[53] The role of consolidative autologous stem cell transplant in first remission is unproven, but this approach is widely used.

Highly Aggressive Lymphomas

Both Burkitt's lymphoma and lymphoblastic lymphoma can present with cervical or supraclavicular adenopathy. If a biopsy reveals either of these lymphoma subtypes, the surgeon should request an emergent medical oncology consult. These highly aggressive lymphomas occur most commonly in children and young adults. Lymphoblastic lymphoma is diagnosed twice as often in men than women. The majority of patients with lymphoblastic lymphoma present with a large mediastinal mass. Rapid growth of the tumor occasionally causes acute respiratory compromise because of tracheal compression and SVC syndrome and is the most likely NHL to present as a medical emergency. Pleural effusions occur in up to 70% of patients, and thoracentesis may be the quickest and least morbid diagnostic procedure. Pericardial effusions are also common.

Treatment and Prognosis

Treatment for these rare, highly aggressive lymphomas must include intensive combination chemotherapy and central nervous system (CNS) prophylaxis, similar to regimens currently used for acute leukemia. All stages of disease are approached similarly. CNS prophylaxis with intrathecal methotrexate and ara-C is an essential component of therapy. Five-year survival rates are approximately 50% for patients with advanced stage disease and 80% for the small subset of patients who present with stage I or II disease.[54,55] Tumor responses in lymphoblastic lymphoma and Burkitt's lymphoma are extremely rapid, often with complete normalization of radiographic studies within a few days. Patients are at high risk for tumor lysis syndrome and should receive their first dose of chemotherapy as an inpatient with vigorous hydration and prophylactic allopurinol or rasburicase. As discussed previously, patients suspected of having lymphoblastic lymphoma on clinical grounds should not receive corticosteroids before a diagnostic biopsy or thoracentesis.

Extranodal Lymphomas of the Head and Neck

Thyroid Lymphomas

Primary thyroid lymphomas comprise less than 5% of all thyroid malignancies and occur most commonly in middle- and older-aged women in the setting of lymphocytic thyroiditis.[56,57] Chronic thyroiditis increases the risk of primary lymphoma of the thyroid by 70- to 80-fold.[58] In one series, evidence of lymphocytic thyroiditis was present in 94% of specimens from primary thyroid lymphomas.[59] Two distinct subtypes comprise nearly all cases of primary thyroid lymphoma, diffuse large B-cell lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma, also referred to as *extranodal marginal cell* or *marginal zone lymphoma.* Approximately one third of cases are pure MALT lymphomas, one third are de novo DLBCL, and one third have features of both MALT lymphoma and DLBCL consistent with transformation of the indolent MALT lymphoma to an aggressive DLBCL.[59] The clinical presentation depends on the histology with MALT lymphoma usually presenting as a slowly enlarging thyroid mass and DLBCL presenting as a rapidly growing mass. One third of patients have symptoms of compression of surrounding structures including dyspnea, dysphagia, stridor, hoarseness, choking, and coughing.[59,60]

MALT lymphoma is difficult to diagnose on needle biopsy. Because one third of cases of primary thyroid lymphoma will have evidence of both MALT lymphoma and DLBCL, an open biopsy is still the preferred method of diagnosis. The morphologic features of MALT lymphomas include lymphoepithelial lesions, follicular colonization, and presence of plasma cells and Dutcher's bodies. The lymphoma cells resemble small lymphocytes with round or slightly irregular nuclei that center on reactive follicles with a marginal zone-type distribution. A characteristic phenotype includes the presence of the pan-B cell antigen CD20 and lack of the CD5 and CD10 antigens, which is unique among indolent lymphomas.[1]

Staging

Most cases of MALT lymphoma of the thyroid present with stage IE or IIE disease. Rarely, initial staging with CT scans of the neck, chest, abdomen, and pelvis reveals nodal involvement beyond the neck and mediastinum or involvement of another extranodal site, most commonly lung, stomach, or orbit. PET scans have a high false-negative rate in MALT lymphomas and should not be used as initial staging.[61]

In patients with DLBCL without associated MALT lymphoma, approximately half will have evidence of disseminated lymphoma at staging, raising the question of the lymphoma being primary or secondary from another involved site.[62] PET/CT scan is the most sensitive staging method for DLBCL. Serum LDH and performance status are important prognostic factors in DLBCL and should be documented before initiating therapy.

Treatment and Prognosis

Patients with DLBCL of the thyroid, with or without a component of MALT lymphoma, should receive the same therapy as patients with DLBCL of nodal sites. As described earlier, six cycles of R-CHOP chemotherapy is standard of care for stage III to IV disease.[37] CMT should be considered for most patients with stage I to IIE disease including three to six cycles of R-CHOP followed by IFRT.[35] RT is especially important in patients with a component of MALT lymphoma because this subtype is not thought to be curable with chemotherapy alone. There is no role for surgery in the treatment of DLBCL of the thyroid. The prognosis depends on the absence or presence of high-risk features including stage III to IV, age older than 60 years, abnormal LDH, performance status greater than 1, and involvement of more than one extranodal site. Patients younger than 60 with early-stage disease have approximately a 90% 4-yr PFS, whereas those with advanced-stage disease have a 55% to 80% 4-year PFS, depending on other risk factors.[63]

Stage I and IIE MALT lymphomas of the thyroid have an excellent prognosis, with PFS and OS of 95% to 100% in most series.[56,59,64] IFRT is highly effective therapy and doses of 30 Gy are often sufficient. Systemic therapy (chemotherapy and or immunotherapy) is not indicated unless advanced-stage or relapsed disease are present. Tsang and colleagues[65] reported on 85 patients with stage I to IIE MALT lymphoma treated with IFRT only. The median RT dose was 30 Gy and the local control rate with RT was 95%. None of the 13 patients with a primary MALT lymphoma of the thyroid had a recurrence. In patients where MALT lymphoma is discovered following a partial or total thyroidectomy, the need for postoperative RT is unclear. If there is disease extending to the margin of the specimen, IFRT is recommended. Following what appears to be a complete resection, IFRT or observation are both acceptable options.

Salivary Gland Lymphomas

Lymphoma of the salivary glands is uncommon, representing less than 2% of salivary malignancies, and usually presents as an enlarging mass.[66] The parotid gland is involved most frequently, followed by the submandibular, minor salivary, and sublingual glands.[66,67] The most common histologies are MALT lymphoma in 60% to 70% and diffuse large cell lymphoma in 20% to 30%. There are rare reports of nearly every other NHL subtype involving the salivary glands. Involvement of cervical nodes is uncommon with MALT lymphoma but present in more than half of patients with other histologies.[67] At least one third of patients with MALT histology have involvement of multiple salivary glands at the time of diagnosis.[67] Involvement of other nonsalivary extranodal sites such as stomach is reported, and some authors recommend upper endoscopy in addition to CT scans as initial staging.[68] At least half of patients with salivary gland MALT lymphomas have an

associated autoimmune disorder, most commonly Sjögren's syndrome. In one series, 7 of 33 (21%) patients with MALT lymphoma of the salivary gland had hepatitis C virus (HCV), a common risk factor for marginal cell lymphomas of the spleen.[69] Approximately 25% of patients have an associated monoclonal protein and cryoglobulinemia is common, especially in patients with Sjögren's or HCV.

Treatment and Prognosis

Aggressive histologies such as DLBCL presenting in the salivary glands are treated like their nodal counterpart as discussed in detail earlier. They also have a prognosis similar to nodal DLBCL with similar prognostic features. Limited-stage disease is treated with chemoimmunotherapy (R-CHOP) and IFRT, and advanced-stage disease with chemoimmunotherapy alone.

Salivary gland MALT lymphomas presenting as stage I to IIE disease are effectively treated with IFRT with RT doses of 30 Gy with 5-year OS and exhibit 5-year cause-specific survival rates of 85% and 94%.[69] In contrast to gastric and thyroid MALT lymphomas, relapses occur in at least one third of patients with salivary gland MALT lymphomas.[69,70] In one series of 32 patients with extranodal MALT lymphoma, the median time to first recurrence was 47 months with a range of 14 to 307 months.[70] The high incidence of late relapses warrants lifelong follow-up of these patients. Local relapses in a nonirradiated site can often be radiated, resulting in many cases in a second long remission. For patients with disease not amenable to IFRT, mild chemoimmunotherapy regimens such as R-CVP (cyclophosphamide, vincristine, prednisone), oral cyclophosphamide, or single-agent rituximab are effective.[69,71]

Paranasal Sinus and Nasal Cavity Lymphomas

Lymphomas of the paranasal sinuses and nasal cavity are uncommon and are pathologically and clinically heterogeneous.[72] In Asian and South American populations, nasal lymphomas are more common and are predominantly the NK/T cell subtype, whereas in Western populations the sinonasal lymphomas are usually diffuse large B-cell type.[73] These two histologic entities have distinct natural histories and prognoses and require different therapeutic approaches.

DLBCL occurs most commonly in middle-aged to older adults, has a male predilection, usually involves the sinuses without nasal involvement, is commonly associated with orbital invasion and ocular symptoms, and is rarely associated with EBV except in the case of HIV-associated lymphomas.[74] The majority of tumors confined to a paranasal sinus involve the maxillary sinus.[72] Approximately two thirds of cases present as stage I to IIE.[74]

NK/T nasal lymphoma, previously referred to as *lethal midline granuloma* or *angiocentric lymphoma,* affects young to middle-aged adults, has a male predilection in most series, and commonly presents with a nasal mass or obstruction, epistaxis, palatal destruction, and erythema and swelling of the face.[74,75] Infiltration of the tumor cells is frequently perivascular and vascular occlusion with massive necrosis of the tissue is one of the presenting features.[76] Because of tissue necrosis, it is sometimes difficult to make a diagnosis and multiple biopsies are often necessary. Virtually all cases of NK/T cell lymphoma are associated with EBV and in situ hybridization with EBER 1/2 may aid in the histologic diagnosis of nasal lymphomas.[75] Immunohistochemical stains for $CD56^+$ should also be done in any patient with a suspected diagnosis of nasal lymphoma. $CD56^+$ and EBV^+ lymphocytes are rarely observed in normal or inflammatory nasal mucosa.[76] More than 80% of patients present with stage I to IIE disease.[77]

Therapy and Prognosis

The treatment of DLBCL of the paranasal sinuses is similar to nodal or other extranodal presentations of DLBCL. Patients with stage I to IIE should receive three to six cycles of R-CHOP and IFRT.[78] Historically, poor results were reported with RT alone.[72,73] Chemotherapy alone has not been tested with modern regimens such as R-CHOP. Due to the proximity of the CNS, leptomeningeal spread and CNS relapse are more frequent than other presentations of DLBCL.[79] CNS prophylaxis is recommended and usually includes three to six doses of intrathecal methotrexate or cytarabine. Prognosis is similar to that for other presentations of DLBCL, with the majority of early-stage patients being cured.[63]

Radiotherapy is the mainstay of therapy for NK/T cell nasal lymphoma. Li and colleagues[80] reviewed 105 cases of stage I to IIE nasal NK lymphoma. Of 65 patients, 54 (83%) treated with initial RT achieved a complete response compared with only 8 of 40 (20%) of patients treated initially with chemotherapy. Five-year PFS and OS rates were similar for patients treated with RT alone and those treated with CMT. Isobe and colleagues[81] reported the importance of radiotherapeutic parameters in the outcome of patients with NK/T cell nasal lymphoma. Patients treated with greater than or equal to 50 Gy and a field that included all sites of potential contiguous spread (paranasal sinuses, palate, nasopharynx) had significantly better local control than those treated with less than 50 Gy and a field that included only macroscopic disease with wide margins. The International Prognostic Index for NHL has predictive power in NK/T cell lymphoma.[63] However, models including B symptoms, stage, LDH, regional node involvement, and local tumor invasiveness defined as bony invasion or destruction or tumor invasion of the skin improve prognostic discrimination.[82,83] In most series, 40% to 50% of patients are alive and disease free 5 years after diagnosis.

Waldeyer's Ring Lymphomas

More than half of all extranodal lymphomas of the head and neck occur in WR with the tonsil representing the most common site, followed by the nasopharynx.[84] Lymphomas of the base of tongue and soft palate are less frequent. There is controversy about whether WR should be considered nodal or extranodal.[84,85] In one series of 130 adult patients with localized lymphoma of WR, 84% were DLBCL and the remainder were equally divided among six additional histologies including both indolent and aggressive.[84] Lymph node involvement, if present, is usually regional and spleen and bone marrow involvement is uncommon.[86] In a series of 77 patients with primary WR lymphoma, no synchronous involvement of the gastrointestinal tract was found at diagnosis; however, involvement of the gastrointestinal tract at recurrence was relatively common.[86]

Treatment and Prognosis

With the use of CMT, most series show outcomes similar to those reported for stage I to II nodal lymphomas.[34,78,84,85,87] In a report of 382 patients from one center with DLBCL, 58% were nodal, 11% WR, and 31% other extranodal sites.[87] WR lymphomas showed the best 5-year OS (77%) compared with nodal (49%) and other extranodal (59%) sites. However, when the analysis was corrected for the International Prognostic Index, there was no difference according to the site of presentation. Several series show an advantage to CMT over RT or chemotherapy alone.[84,85] As previously discussed, these reports do not use current chemoimmunotherapy strategies such as R-CHOP. It is not clear whether CMT will continue to show an advantage when more effective chemotherapy regimens are used.

Summary

Lymphomas commonly present in the head and neck, either as cervical or supraclavicular adenopathy or as a primary extranodal lymphoma of the thyroid, salivary gland, paranasal sinus, nasal cavity, or WR. Most lymphomas are highly treatable and often curable with chemotherapy or radiotherapy. Otolaryngologists play a critical role in obtaining adequate tissue for accurate lymphoma classification.

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CHAPTER ONE HUNDRED AND TWENTY

Radiation Therapy and Management of the Cervical Lymph Nodes and Malignant Skull Base Tumors

Vincent Grégoire

Nancy Lee

Key Points

- In the previously untreated neck, lymph node infiltration follows a predictable pattern.
- Except for nasopharyngeal carcinoma, selective irradiation can be proposed for patients with N0-N1 neck.
- Three-dimensional delineation of the node levels should be performed on thin contrast-enhanced CT sections following the consensus guidelines.
- High control rate of the node-negative neck (>90%) is achieved with a prophylactic (≈50 Gy) dose of ionizing radiation.
- For the node-positive neck, a higher dose of ionizing radiation (≈70 Gy) is required.
- After node-positive neck treatment with radiotherapy, neck dissection should be restricted to those patients who did not achieve a complete response.
- Postoperative irradiation is required for a pathologic node-positive neck (>pN1).
- Postoperative concomitant chemoradiotherapy is required for patients with extracapsular rupture.
- Proton beam irradiation can be designed to yield a uniform dose across the target and deliver virtually zero dose deep to the target, as well as lower dose proximal to the target.
- Cyberknife is a frameless robotic radiosurgical device that has been developed mainly to treat extracranial lesions.
- Intensity-modulated radiation therapy is a refinement of three-dimensional (3D) conformal radiotherapy that has the ability to treat an irregularly shaped target regardless of size while minimizing the dose delivered to the surrounding normal tissues.
- Treatment of esthesioneuroblastoma typically consists of combination therapy: either surgery followed by radiotherapy with or without chemotherapy or concurrent chemotherapy and radiation therapy followed by surgery for salvage.
- Sinonasal undifferentiated carcinoma portends a poor prognosis owing to its high rates of locoregional failures, as well as distant metastases.
- The preferred radiation technique for chordomas is proton therapy.
- High rates of locoregional control can be achieved using intensity-modulated radiation therapy for nasopharyngeal carcinoma.
- Distant failure is the predominant cause of failure in patients with nasopharyngeal carcinoma.
- The preferred treatment approach for sinonasal cancer is complete surgical resection followed by postoperative radiation therapy.

Radiation Therapy and Management of Cervical Lymph Nodes

Assessment and treatment of regional lymph nodes (LNs) in the neck are of utmost importance in the management of patients with head and neck squamous cell carcinoma (SCC). The philosophy of treatment of the neck has evolved over the past decades. Radiation oncologists and head and neck surgeons progressively realized that extensive treatments were associated with more morbidity but not always with a better oncologic outcome than less extensive procedures. Today, a comprehensive approach of the treatment of the neck needs to be multidisciplinary, taking into account the quality of life of the patients but without jeopardizing cure and survival. A better understanding of the patterns of LN metastasis promoted the use of not only selective dis-

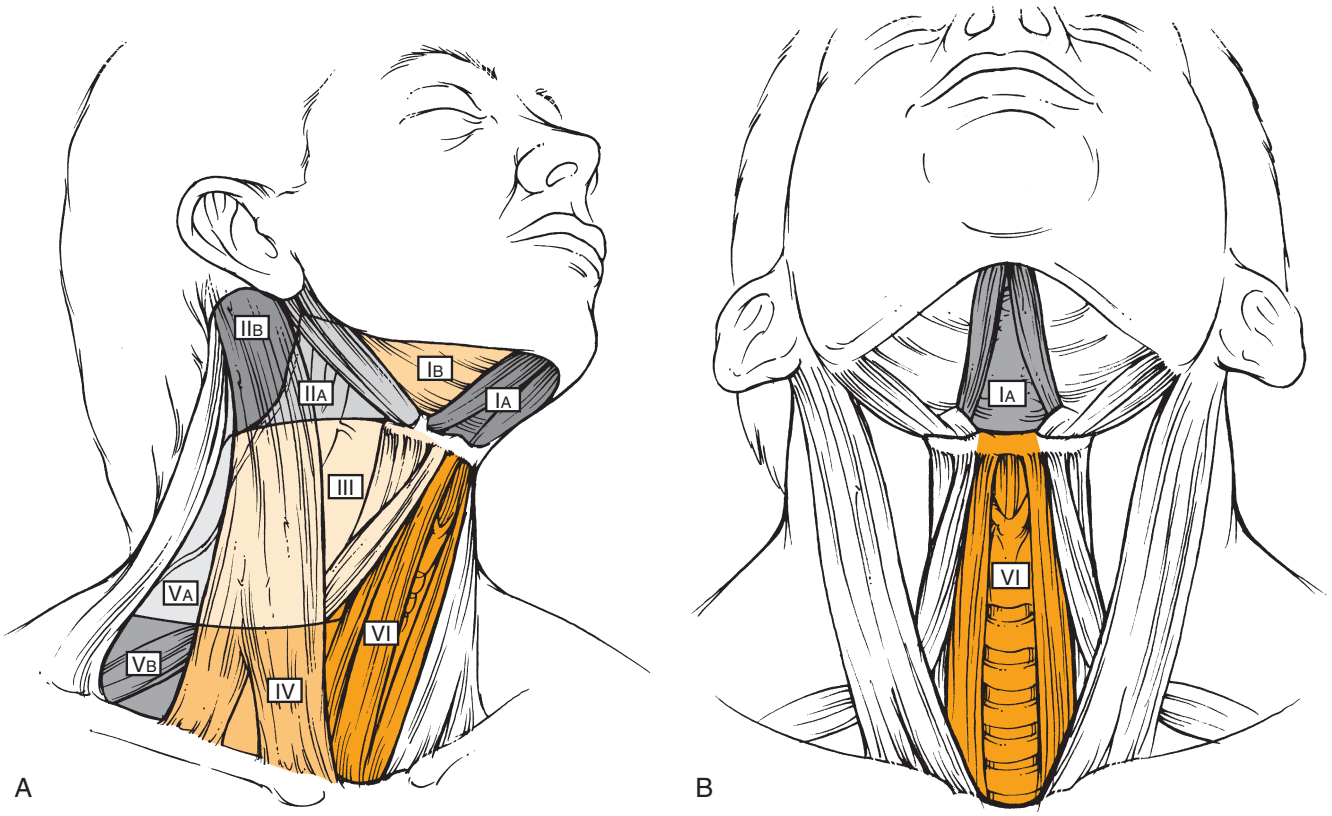

Figure 120-1. Schematic representation of the various neck node groups (**A**, lateral view; **B**, frontal view): *IA,* submental; *IB,* submandibular; *II,* upper jugular; *III,* middle jugular; *IV,* lower jugular; *V,* posterior triangle; *VI,* anterior compartment. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

section but also selective irradiation in subgroups of patients. Concepts are still evolving (e.g., with the sentinel lymph node biopsy for which the exact role is under evaluation).

In this chapter, only the management of the neck for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal SCCs is discussed. The specific management of the neck for thyroid, nasal cavities, paranasal sinuses, and skin cancers is covered in the respective chapters dealing with these anatomic sites.

Lymphatic System of the Neck

The head and neck region has a rich network of lymphatic vessels draining from the base of the skull through the jugular nodes, the spinal accessory nodes, and the transverse cervical nodes to the venous jugulosubclavian confluent or the thoracic duct on the left side and the lymphatic duct on the right side.[1,2] The whole lymphatic system of the neck is contained in the celluloadipose tissue delineated by aponeurosis enveloping the muscles, vessels, and nerves. The lymphatic drainage is mainly ipsilateral, but structures like the soft palate, tonsils, base of the tongue, posterior pharyngeal wall, and especially the nasopharynx have bilateral drainage. On the other hand, sites such as the true vocal cord, paranasal sinuses, and middle ear have few or no lymphatic vessels at all.

The nomenclature of head and neck lymph nodes has been complicated by various confusing synonyms that are still in use in major textbooks and articles. More recently, several expert bodies have proposed the adoption of systematic classifications aimed at standardizing the terminology. Following the description by Rouvière, the Tumor Node Metastasis atlas proposed a terminology, dividing the head and neck lymph nodes into 12 groups.[3] In parallel to this classification, the Committee for Head and Neck Surgery and Oncology of the American Academy for Otolaryngology–Head and Neck Surgery has been working on a classification (the so-called *Robbins classification*), dividing the neck into six levels including eight node groups (Fig. 120-1).[4] This classification is based on the description of a level system, which has been used for a long time by the Head and Neck Service at the Memorial Sloan-Kettering Cancer Center.[5] Because one of the objectives of the Robbins classification was to develop a standardized system of terminology for neck dissection procedures, only the lymph node groups routinely removed during neck dissection were considered. The terminology proposed by Robbins was recommended by the Union Internationale Contre Cancer (UICC).[6] A comparison between the TNM and the Robbins terminology is shown in Table 120-1. The major advantage of the Robbins classification over the TNM terminology is the definition of the boundaries of the node levels. The delineation of these boundaries is based on anatomic structures such as major blood vessels, muscles, nerves, bones, and cartilage that are easily identifiable by the surgeon during neck dissection procedures. It is beyond the scope of this chapter to go into a detailed description of the node levels. The reader is referred to a recent review article outlining the anatomic basis of the neck node classification.[7]

Staging of Neck Node Metastasis

The sixth edition (2002) of the American Joint Committee on Cancer (AJCC) staging for neck node metastasis is presented in Table 120-2.[8] This classification does not apply to nasopharyngeal carcinoma, thyroid, or skin cancers. In comparison with the fourth (1987) or fifth (1998) edition, the only modification is the possibility to use a descriptor for nodal metastasis located below (L) or above (U) the lower border of the cricoid cartilage. The use of this descriptor will not influence the nodal staging. The classification for nodal staging does apply irrespective of the modality used for the neck assessment (i.e., clinical examination or imaging). However, the routine use of computed tomography (CT) or magnetic resonance imaging (MRI) and, in expert hands, ultrasonography, is recommended, especially to assess nodes not clini-

Table 120-1

Comparison between the Tumor Node Metastasis (TNM) Atlas and the Robbins' Classification of the Lymph Nodes of the Neck

TNM Atlas for Lymph Nodes of the Neck		Robbins' Classification	
Group Number	Terminology	Level	Terminology
1	Submental nodes	Ia	Submental group
2	Submandibular nodes	Ib	Submandibular group
3	Cranial jugular nodes	II	Upper jugular group
4	Medial jugular nodes	III	Middle jugular group
5	Caudal jugular nodes	IV	Lower jugular group
6	Dorsal cervical nodes along the spinal accessory nerve	Va	Posterior triangle group
7	Supraclavicular nodes	Vb	Posterior triangle group
8	Prelaryngeal and paratracheal nodes	VI	Anterior compartment group
9	Retropharyngeal nodes	—	—
10	Parotid nodes	—	—
11	Buccal nodes	—	—
12	Retroauricular and occipital nodes	—	—

Table 120-2

Sixth Edition (2002) of the American Joint Committee on Cancer (AJCC) Staging for Neck Node Metastasis

Stage	Definition
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, ≤3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node, >3 cm but ≤6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral nodes, ≤6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral nodes, ≤6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension

cally identifiable (e.g., retropharyngeal, intraparotid, or superior mediastinal nodes) or in patients for whom clinical palpation of the neck is less sensitive (e.g., thick or small neck).[9] Last, it should be emphasized that the Nx classification only applies when the neck was not assessed or could not be assessed.

Incidence and Distribution of Neck Node Metastasis

Incidence and Distribution of Lymph Node Metastasis from Clinical and Radiologic Assessment

The metastatic spread of head and neck tumors into the cervical lymph nodes is rather consistent and follows predictable pathways, at least in the neck, which has not been violated by previous surgery or radiotherapy. In Figures 120-2 to 120-6, the frequency of metastatic lymph nodes is expressed as a percentage of node-positive patients.[10,11]

The frequency of neck node metastases and the distribution of clinically involved nodes depend to a major extent on the primary tumor site. Typically, hypopharyngeal tumors have the highest propensity for nodal involvement, which occurs in 70% of cases. Cranial and anterior tumors (e.g., oral cavity tumors) mainly drain into levels I, II, and III, whereas more caudally located tumors (i.e., laryngeal tumors) mainly drain into levels II and III, and to a lesser extent into levels IV and V. Contralateral nodes are rarely involved except for midline tumors or tumors in those sites where bilateral lymphatic drainage has been reported (e.g., soft palate, base of the tongue, pharyngeal wall). Even in these tumors, the incidence of contralateral involvement is much lower, reaching, for example, in base of the tongue tumors with clinically positive nodes 31% in contralateral level II compared with 73% in ipsilateral level II (data not shown). Interestingly, node distribution follows the same pattern in the contralateral neck as in the ipsilateral neck. Except for nasopharyngeal tumors, involvement of ipsilateral level V is a rather rare event, occurring in less than 1% of all oral cavity tumors, in less than 10% of all oropharyngeal and laryngeal tumors, and in about 15% of all hypopharyngeal tumors. It almost never occurs in contralateral level V. Nasopharyngeal tumors behave differently than other head and neck tumors. These highly lymphophilic tumors carry almost the same risk of nodal involvement in the ipsilateral and contralateral neck, with the preferential involvement of level V in almost one third of patients. On the other hand, the incidence of level I infiltration is much lower.

Metastatic lymph node involvement in the neck depends on the size of the primary tumor, increasing with the T stage. In the series

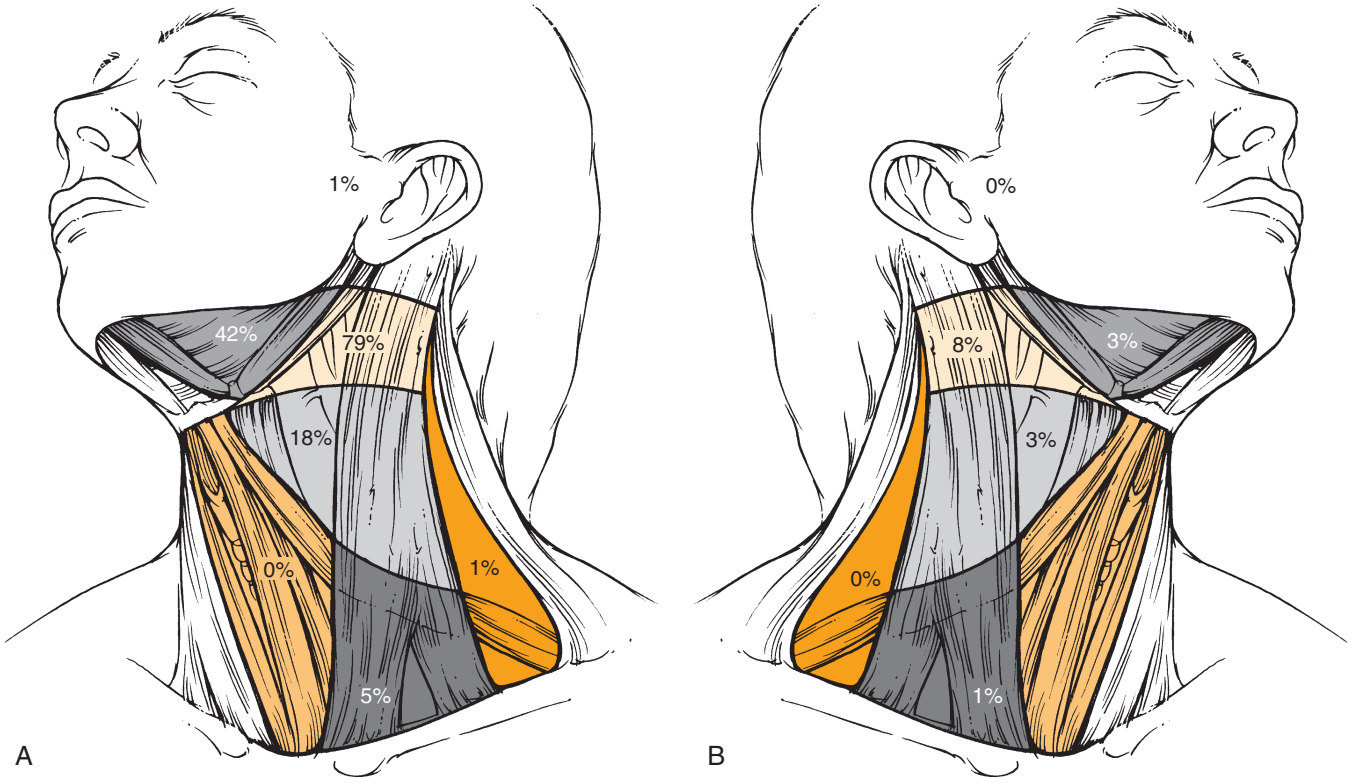

Figure 120-2. Clinical incidence of metastatic lymph nodes in the neck of patients (n = 787) with squamous cell carcinoma of the oral cavity (**A,** ipsilateral neck; **B,** contralateral neck). Data are expressed as a percentage of node-positive patients. *(From Bataini JP, Bernier J, Brugere J, et al. Natural history of neck disease in patients with squamous cell carcinoma of the oropharynx and pharyngolarynx.* Radiother Oncol. *1985;3:245-255 and from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer. *1972;29:1446-1449.)*

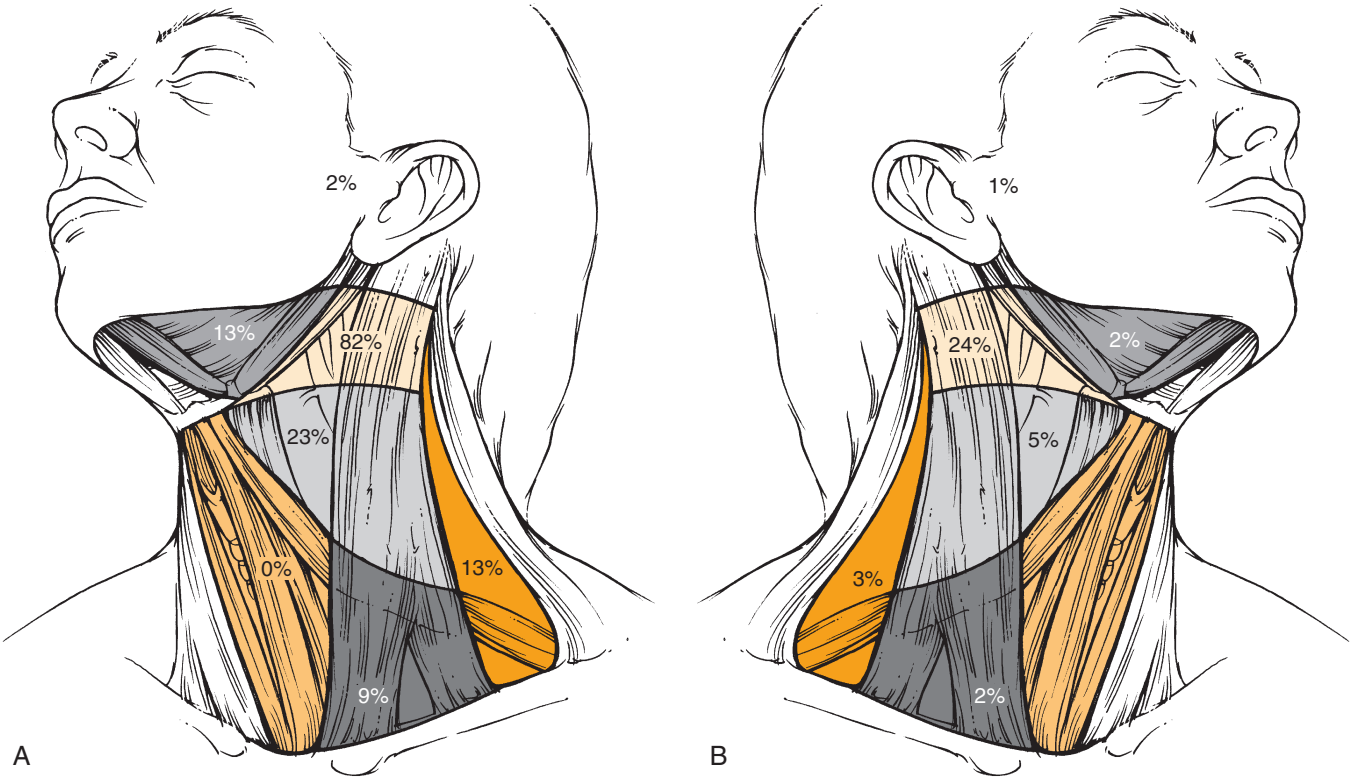

Figure 120-3. Clinical incidence of metastatic lymph nodes in the neck of patients (n = 1479) with squamous cell carcinoma of the oropharynx (**A,** ipsilateral neck; **B,** contralateral neck). Data are expressed as a percentage of node-positive patients. *(From Bataini JP, Bernier J, Brugere J, et al. Natural history of neck disease in patients with squamous cell carcinoma of the oropharynx and pharyngolarynx.* Radiother Oncol. *1985;3:245-255 and from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer. *1972;29:1446-1449.)*

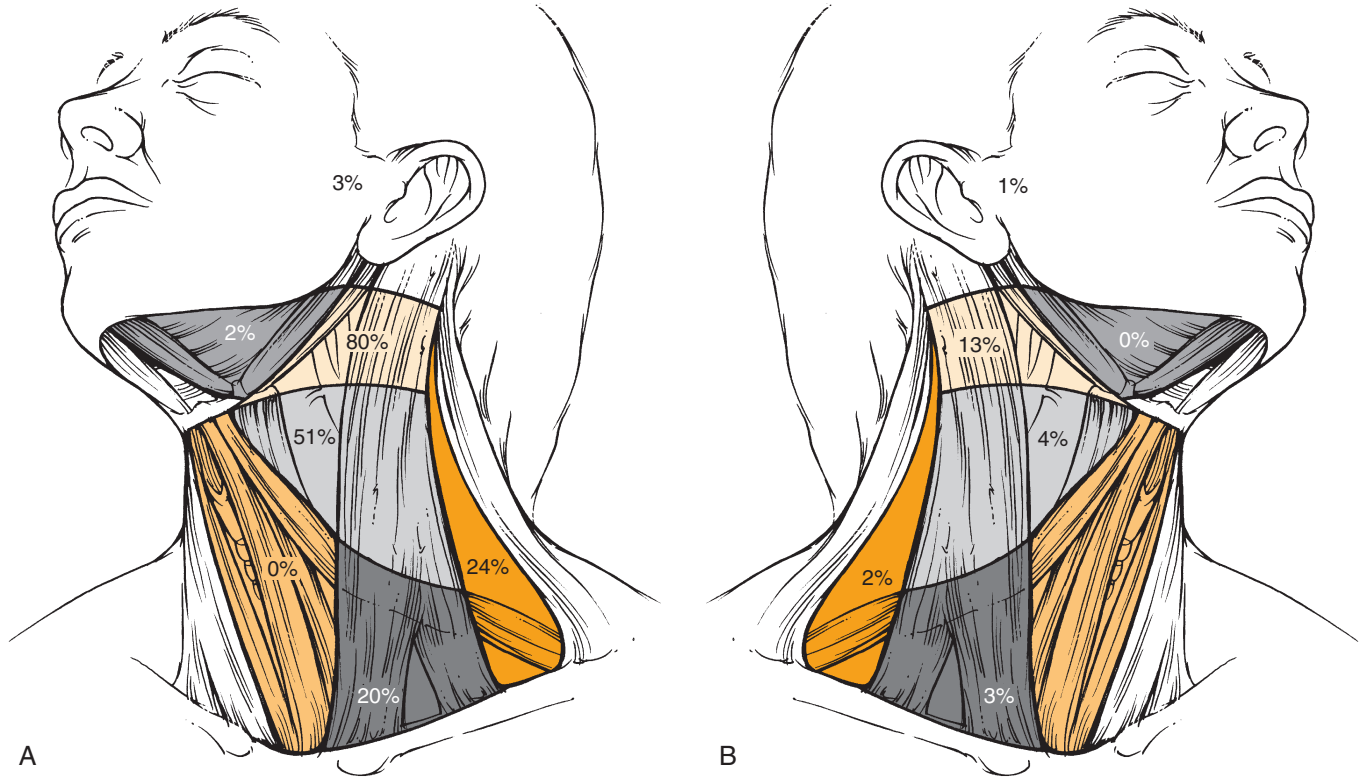

Figure 120-4. Clinical incidence of metastatic lymph nodes in the neck of patients (n = 847) with squamous cell carcinoma of the hypopharynx (**A,** ipsilateral neck; **B,** contralateral neck). Data are expressed as a percentage of node-positive patients. *(From Bataini JP, Bernier J, Brugere J, et al. Natural history of neck disease in patients with squamous cell carcinoma of the oropharynx and pharyngolarynx.* Radiother Oncol. *1985;3:245-255 and from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer. *1972;29:1446-1449.)*

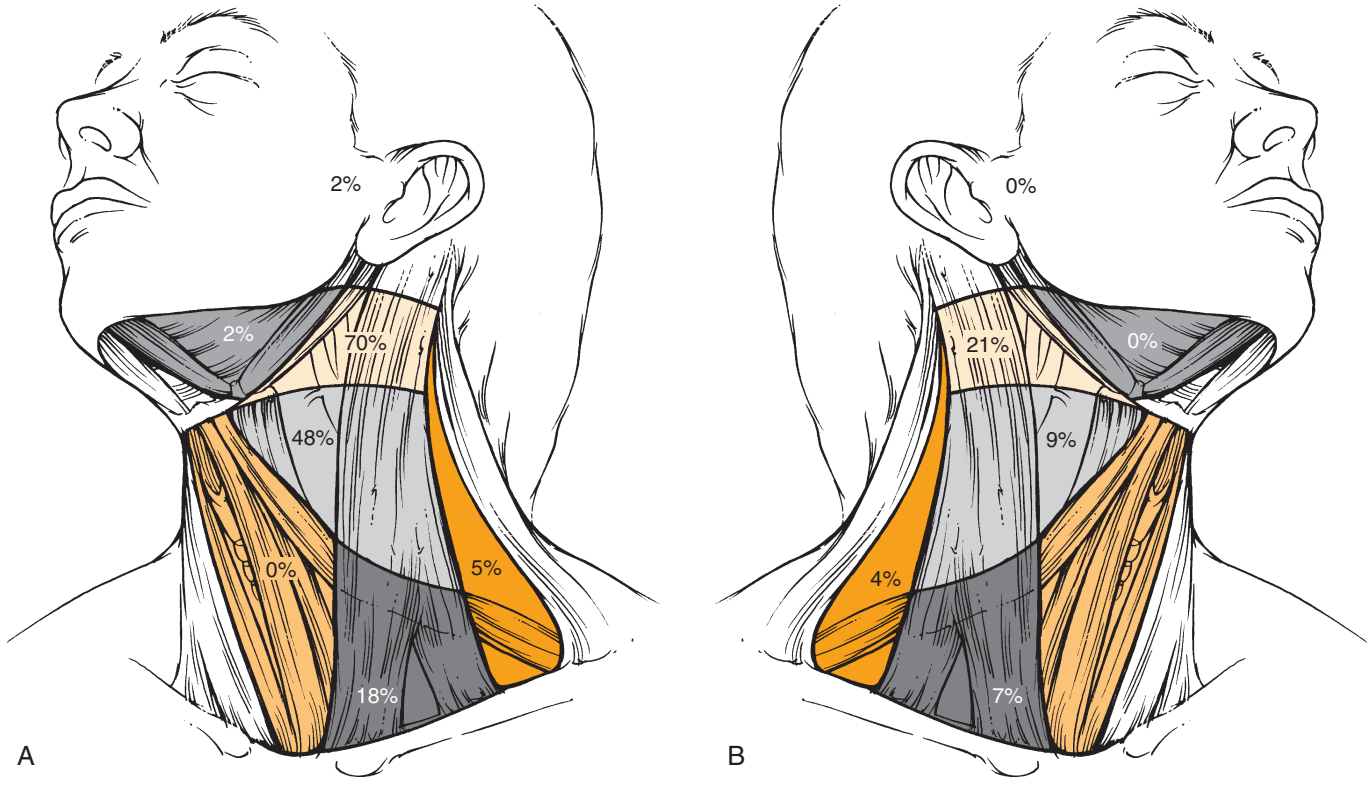

Figure 120-5. Clinical incidence of metastatic lymph nodes in the neck of patients (n = 428) with squamous cell carcinoma of the supraglottic larynx (**A,** ipsilateral neck; **B,** contralateral neck). Data are expressed as a percentage of node-positive patients. *(From Bataini JP, Bernier J, Brugere J, et al. Natural history of neck disease in patients with squamous cell carcinoma of the oropharynx and pharyngolarynx.* Radiother Oncol. *1985;3:245-255 and from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer. *1972;29:1446-1449.)*

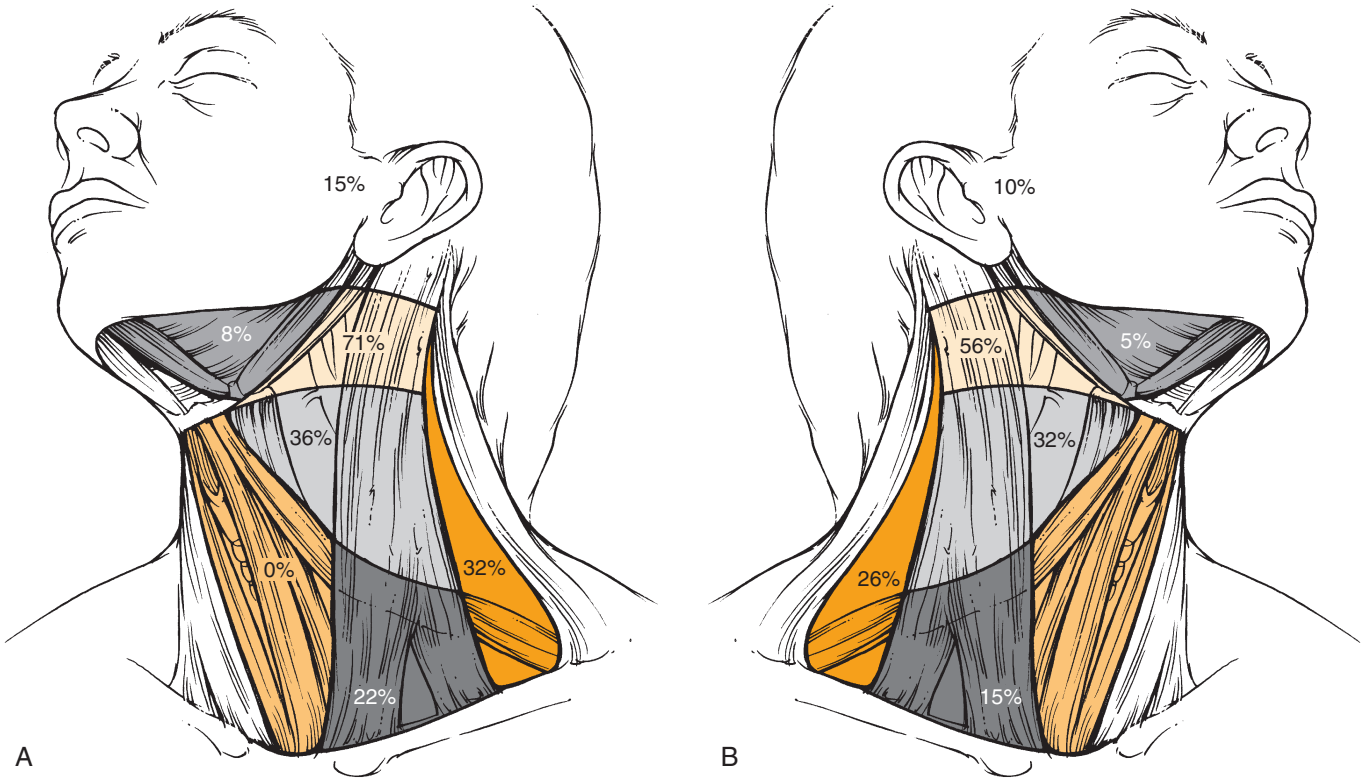

Figure 120-6. Clinical incidence of metastatic lymph nodes in the neck of patients (n = 440) with carcinoma of the nasopharynx (**A,** ipsilateral neck; **B,** contralateral neck). Data are expressed as a percentage of node-positive patients. *(From Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer. *1972;29:1446-1449; Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity.* Cancer. *1990a;66:109-113; and Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract.* Am J Surg. *1990b;160:405-409.)*

reported by Bataini,[10] 44% of patients with a T1 tumor had clinical lymph node involvement; this increased to 70% for patients with T4 lesions. There are, however, no data suggesting that the relative distribution of involved neck levels varies with the T stage.

Retropharyngeal lymph nodes represent a special entity inasmuch as they are usually not clinically detectable. The incidence of retropharyngeal lymph node involvement can thus only be estimated from series in which CT or MRI of the retropharynx has been systematically performed as part of the diagnostic procedure. Retropharyngeal node involvement occurs in primary tumors arising from (or invading) the mucosa of the occipital and cervical somites (e.g., of the nasopharynx, pharyngeal wall, and soft palate). Interestingly, the incidence of retropharyngeal lymph nodes is higher in patients in whom involvement of other neck node levels has also been documented. However, in clinically N0 patients with nasopharyngeal tumors, and to a lesser extent in patients with pharyngeal wall tumors, the incidence of retropharyngeal nodes is still significant (i.e., between 16% and 40%). Also, as already described for the other lymph node levels, involvement depends on the T stage and is typically lower for T1 tumors. Accurate figures are, however, not available.

Incidence and Distribution of Pathologic Lymph Node Metastasis

The distribution of pathologic lymph node metastasis in patients with primaries of the oral cavity, oropharynx, hypopharynx, and larynx can be derived from retrospective series in which a systematic radical neck node dissection was proposed as part of the initial treatment procedures.[12-15] In essence, retrospective series are biased regarding patient and treatment selection, but these series from the Head and Neck Department at Memorial Sloan-Kettering Cancer Center are the largest and most consistent data ever published on that matter. The results of these retrospective studies are shown in Table 120-3. The data are presented in terms of the number of neck dissections with positive lymph nodes over the total neck dissection procedures and expressed as a percentage. The vast majority of patients (>99% for the N0 neck patients and 95% for the N+ neck patients) only had unilateral treatment, and no distinction between the ipsilateral and contralateral neck was made.

Overall, metastatic disease was detected in 33% of the elective neck dissections and in 82% of the therapeutic neck dissections. As already observed with the pattern of clinical metastatic lymph nodes, the distribution of pathologically confirmed metastatic lymph nodes depended on the primary tumor site. Typically, in clinically N0 patients, metastatic lymph nodes were observed in levels I to III for oral cavity tumors, and in levels II to IV for oropharyngeal, hypopharyngeal, and laryngeal tumors. This pattern of node distribution is similar to that determined from the clinical palpation of the neck. It should be noted that the T-stage distribution was different in the various groups. Of patients with laryngeal tumors, 54% (42/79) had T3-T4 tumors (mainly supraglottic) compared with 27% (52/192), 25% (6/24), and 17% (8/47) in patients with oral cavity, hypopharyngeal, and oropharyngeal tumors, respectively. Such a difference in T stage presumably explains the high incidence of microscopic node metastases in the larynx group.

When considering the patients who underwent therapeutic neck dissection, the pattern of metastatic node distribution was similar to that observed in clinically N0 patients, with the difference that significant pathologic infiltration of an additional nodal level was typically observed (i.e., level IV for oral cavity tumors and levels I and V for oropharyngeal, hypopharyngeal, and to a lesser extent laryngeal tumors). Overall, this observation illustrates the gradual infiltration of node levels in the neck.

Table 120-3

Incidence of Pathologic Lymph Node Metastasis in Squamous Cell Carcinomas of the Oral Cavity, Oropharynx, Hypopharynx, and Larynx

	Distribution of Metastatic Lymph Nodes per Level (percentage of the neck dissection procedures)											
	Elective RND						Therapeutic (immediate or subsequent) RND					
Tumor Site	No. of RND	I	II	III	IV	V	No. of RND	I	II	III	IV	V
Oral cavity	192	20%	17%	9%	3%	1%	323	46%	44%	32%	16%	3%
Oropharynx	48	2%	25%	19%	8%	2%	165	15%	71%	42%	27%	9%
Hypopharynx	24	0%	12%	12%	0%	0%	104	10%	75%	72%	45%	11%
Larynx	79	5%	19%	20%	9%	3%	183	7%	57%	59%	30%	4%

RND, radical neck dissection.

Incidence and Pattern of Node Distribution in the Contralateral Neck

Few data are available on the pattern of pathologic node distribution in the contralateral neck. Bilateral neck dissection was only performed when the surgeon considered that there was a high risk of contralateral node involvement (e.g., tumors of the oral cavity or the oropharynx reaching or extending beyond the midline, hypopharyngeal and supraglottic tumors). Obviously, in such cases bilateral radical neck dissection was never performed, so an accurate estimate of the pattern of node involvement in levels I to V of the contralateral neck is not possible. Furthermore, in almost every study, data on both sides of the neck were pooled for presentation. Kowalski presented data on 90 patients who underwent bilateral supraomohyoid neck dissection, and in whom the pattern of node distribution in each side of the neck was reported separately.[16]

The majority of these patients had SCC of the lip or oral cavity. In the ipsilateral neck, pathologic infiltration in levels I, II, and III reached 20%, 15%, and 15%, respectively. In the contralateral neck, corresponding values reached 13%, 11%, and 0%, respectively. These figures are in good agreement with data on clinical node distribution showing that both sides of the neck exhibited a similar pattern of node distribution, but with a lower incidence in the contralateral neck. Foote[17] reported the rate of contralateral neck failure in a limited series of 46 clinically N0 patients with base of the tongue tumors treated by some form of glossectomy and ipsilateral neck dissection. None of these patients received postoperative radiotherapy. Ten patients (22%) had contralateral neck recurrence, and the most common sites were in levels II, III, or IV. It appears that in two of these patients, recurrence was also observed at the primary site. The development of delayed contralateral neck metastases was not related to the clinical or pathologic extent of the base of the tongue tumor. O'Sullivan[18] reported a retrospective series of 228 patients with tonsillar carcinoma who were treated on the primary tumor and the ipsilateral neck only with radiotherapy. The vast majority of these patients had T1-T2 and N0-N1 disease. Contralateral recurrence in the neck was only observed in eight patients (2%) including five patients with local recurrence as well. No contralateral neck recurrence was observed in the 133 N0 patients. Although not significant due to the small number of events, involvement of midline structure (i.e., soft palate and base of tongue) appeared to be a prognostic factor for contralateral neck recurrence. Similar results were reported in a series of 101 node-negative tonsil carcinoma (mainly T1-T3) treated unilaterally.[19] Only two neck recurrences were observed in the contralateral neck.

Recommendations for the Selection of the Target Volumes in the Neck

The data presented in the previous sections indicate that metastatic lymph node involvement of primary SCC of the oral cavity, pharynx, and larynx typically follows a predictive pattern. Both data on clinical and pathological neck node distribution and on neck recurrence after selective dissection procedures support the concept that not all the neck node levels should be treated as part of the initial management strategy of head and neck primaries of squamous cell origin.[20,21] One should bear in mind, however, that the data on which such a concept is based have come from retrospective series, and thus may include possible bias (e.g., patient selection, series from pre-imaging area) that could limit its validity.

Tables 120-4 to 120-7 present recommendations for the selection of the target volumes in the neck for pharyngolaryngeal SCCs. These guidelines can be applied irrespective of the treatment modality (i.e., surgery or radiotherapy). The discussion of the choice between these two modalities is beyond the objective of this chapter but should be considered relative to the neck stage, the treatment option for the primary tumor, the performance status of the patient, and the institutional policy agreed on by a multidisciplinary head and neck tumor board.

For clinically N0 patients with head and neck SCC of the oral cavity, oropharynx, hypopharynx and larynx, selective treatment of the neck is appropriate.[21-23] Typically, levels I to III should be treated for oral cavity tumors, and levels II to IV for oropharyngeal, hypopharyngeal, and laryngeal tumors. Robbins has suggested that elective treatment of level IIb is probably not necessary for N0 patients with a primary tumor of the oral cavity, larynx, or hypopharynx.[24] On the other hand, Byers suggested that level IV be included in the treatment of the mobile tongue due to the high incidence (10%) of skip metastases.[25] Retropharyngeal nodes should be treated in tumors of the posterior pharyngeal wall. For subglottic tumors, tumors with subglottic or transglottic extension, or hypopharyngeal tumors with esophageal extension, level VI nodes should also be included in the treatment volume.

As proposed by Byers, similar guidelines could also be recommended for N1 patients without radiologic evidence of extracapsular infiltration.[22] However, when an involved lymph node is located at the boundary with a level, which has not been selected in the target volume, it has been recently recommended to extend the selection to include the adjacent level.[26] Typically, this will only apply for oropharyngeal tumors with a single lymph node in level II at the boundary with level Ib or for an oral cavity tumor with a N1 node in level III at the boundary with level IV.

For patients with multiple nodes (N2b), the available data suggest that adequate treatment should include levels I to V. Level I could, however, be omitted for laryngeal tumors, and level V for oral cavity tumors with neck involvement limited to levels I to III. Elective treatment of the retropharyngeal nodes should be systematically performed for oropharyngeal and hypopharyngeal tumors. As for N0 patients, level VI nodes should also be treated for subglottic tumors, tumors with

Table 120-4

Recommendations for the Selection of the Target Volume in the Neck for Oral Cavity Tumors

	Selected Levels	
Nodal Stage (AJCC 2002)	**Ipsilateral Neck**	**Contralateral Neck**
N0-N1 (in levels I, II, or III)	I, II*, III + IV†	I, II*, III + IV†
N2a-N2b	I, II, III, IV, V‡	I, II*, III + IV for anterior tongue tumor
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V ± adjacent structures according to clinical and radiologic data	I, II*, III + IV for anterior tongue tumor

*Level IIb could be omitted for N0 patients.
†For anterior tongue tumor and for any tumor with extension to the oropharynx (e.g., anterior tonsillar pillar, tonsillar fossae, base of tongue).
‡Level V could be omitted if only levels I through III are involved.
AJCC, American Joint Committee on Cancer.

Table 120-5

Recommendations for the Selection of the Target Volume in the Neck for Oropharyngeal Tumors

	Selected Levels	
Nodal Stage (AJCC 2002)	**Ipsilateral Neck**	**Contralateral Neck**
N0-N1 (in levels II, III, or IV)	(Ib)*-II-III-IV + RP for posterior pharyngeal wall tumor	II-III-IV + RP for posterior pharyngeal wall tumor
N2a-N2b	Ib, II, III, IV, V + RP	II-III-IV + RP for posterior pharyngeal wall tumor
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V + RP ± adjacent structures according to clinical and radiologic data	II-III-IV + RP for posterior pharyngeal wall tumor

*Any tumor with extension to the oral cavity (e.g., retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsillar pillar).
AJCC, American Joint Committee on Cancer; RP, retropharyngeal nodes.

Table 120-6

Recommendations for the Selection of the Target Volume in the Neck for Hypopharyngeal Tumors

	Selected Levels	
Nodal Stage (AJCC 2002)	**Ipsilateral Neck**	**Contralateral Neck**
N0	II*-III-IV + RP for posterior pharyngeal wall tumor + VI for apex of piriform sinus or esophageal extension	II*-III-IV + RP for posterior pharyngeal wall tumor + VI for esophageal extension
N1-N2a-N2b	Ib, II, III, IV, V + RP + VI for piriform sinus or esophageal extension	II*-III-IV + RP for posterior pharyngeal wall tumor + VI for esophageal extension
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	I, II, III, IV, V + RP + VI piriform sinus or for esophageal extension ± adjacent structures according to clinical and radiologic data	II*-III-IV + RP for posterior pharyngeal wall tumor + VI for esophageal extension

*Level IIb could be omitted for N0 patients.
AJCC, American Joint Committee on Cancer; RP, retropharyngeal nodes.

Table 120-7

Recommendations for the Selection of the Target Volume in the Neck for Laryngeal Tumors (T1N0 Glottic Carcinoma Excluded)

	Selected Levels	
Nodal Stage (AJCC 2002)	Ipsilateral Neck	Contralateral Neck
N0-N1 (in levels II, III, or IV)	II*-III-IV + VI for transglottis or subglottis extension	II*-III-IV + VI for transglottis or subglottis extension
N2a-N2b	II, III, IV, V + VI for transglottis or subglottis extension	II*-III-IV + VI for transglottis or subglottis extension
N2c	According to N stage on each side of the neck	According to N stage on each side of the neck
N3	Ib, II, III, IV, V + VI for transglottis or subglottis extension ± adjacent structures according to clinical and radiologic data	II*-III-IV + VI for transglottis or subglottis extension

*Level IIb could be omitted for N0 patients.
AJCC, American Joint Committee on Cancer.

subglottic or transglottic extension, or hypopharyngeal tumors with esophageal extension. Recently, for patients with nodes in the upper neck (i.e., upper level II) it has been proposed to extend the upper limit of the target volume to include the retrostyloid space.[26] Similarly, the subclavicular fossae should also be included in the target volume in case of lower neck involvement (i.e., level IV or Vb nodes).[26]

No data on the distribution of pathologic metastatic neck nodes in patients presenting with a single ipsilateral large node (N2a or N3) or with bilateral or contralateral nodes (N2c) are available. For patients with a single large node, in absence of data, it appears safe not to recommend selective treatment. For N3 patients, the type of treatment of the neck is likely to be also dictated by the local extension of the node into the adjacent structures (e.g., paraspinal muscles, parotid gland, blood vessels). For N2c patients, one proposal is to consider each side of the neck separately (e.g., selective treatment in both sides for a small single node in each side, selective treatment for a small single node in one side, and more extensive treatment in the other side in the case of multiple nodes).

Elective treatment of the contralateral N0 neck is still in the gray zone and is likely to be based on clinical judgment rather than on strong scientific evidence. Typically, patients with midline tumors or tumors originating from or extending to a site that has bilateral lymphatic drainage (e.g., base of the tongue, vallecula, posterior pharyngeal wall) are thought to benefit from bilateral neck treatment, whereas well-lateralized tumors (e.g., the lateral border of the tongue, retromolar trigone, tonsillar fossa) can be spared contralateral treatment. It has also been reported in tumors of the pharynx and larynx that the risk of contralateral neck metastases increased with involvement of the ipsilateral neck.[27] Putting all these data together, one could recommend restricting the treatment to the ipsilateral neck for tumors of the lower gum (not approaching the midline); lateral floor of the mouth; lateral border of the mobile tongue; upper gum; cheek; retromolar trigone; tonsillar fossa (without extension to the base of the tongue, soft palate, or posterior pillar); and lateral wall of the piriform sinus. In the other situations, where elective contralateral neck treatment is recommended, the selection of the node levels to be treated should follow similar rules to those for the ipsilateral neck.

Because of the lymphophilicity of nasopharyngeal carcinoma tumors, bilateral treatment of levels II to V and retropharyngeal nodes is recommended even for patients with a node-negative neck (Table 120-8). For patients with node-positive necks, additional treatment of level Ib might be considered.

In principle, a similar approach should apply for the definition of the node levels to be irradiated postoperatively. However, if one agrees on the selection criteria for postoperative radiotherapy (i.e., capsular rupture, patients with a metastatic node >3 cm in diameter or with more than one metastatic node), irradiation of levels I to V are typically performed. As for primary radiotherapy, the retrostyloid space and the subclavicular fossae should be included in the target volume depending on the location of the metastatic nodes.[26] For laryngeal tumors, level I could be omitted. For oral cavity tumors, postoperative irradiation of level V could be omitted in the case of metastatic nodes located in level I and/or II only. Retropharyngeal and paratracheal nodes should be treated as mentioned earlier.

Table 120-8

Recommendations for the Selection of the Target Volume in the Neck for Nasopharyngeal Carcinoma

	Selected Levels	
Nodal Stage (AJCC 1997)	Ipsilateral Neck*	Contralateral Neck*
N0-N2	(Ib)†-II-III-IV-V + RP†	(Ib)†-II-III-IV-V + RP
N3	(Ib)†-II-III-IV-V + RP ± adjacent structures according to clinical and radiologic data	(Ib)†-II-III-IV-V + RP

*In case of lymph node involvement in levels IV and Vb, inclusion of supraclavicular nodes may be required,
†Level Ib may be considered for node-positive patients.
AJCC, American Joint Committee on Cancer; RP, retropharyngeal nodes.

Neck Node Delineation and Irradiation Techniques

Delineation of the Clinical Target Volume

Since the late 1990s, several authors have proposed recommendations for the delineation of the neck node levels.[28-32] In the radiation oncology community, however, the so-called Brussels and Rotterdam guidelines have emerged as the most widely used.[28-30] A critical review of the two proposals was undertaken in 2003 in collaboration with representatives of the major European and North American clinical cooperative groups to generate an international set of guidelines for the delineation of the neck node levels in the node-negative neck.[33] The correspondence between these guidelines and neck dissection proce-

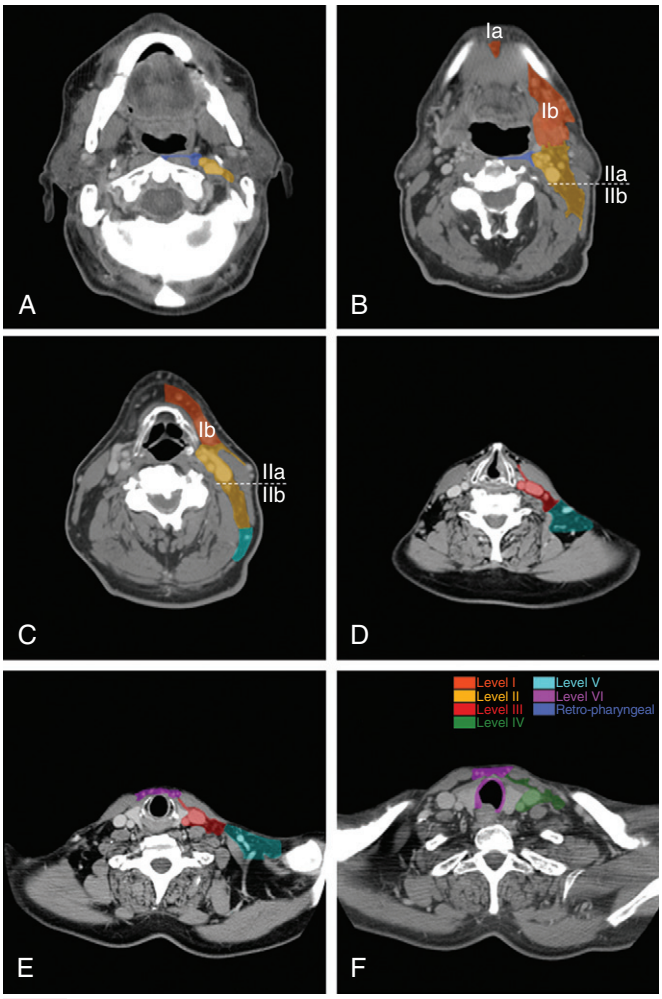

Figure 120-7. Computed tomography (CT) imaging of a patient with a T1N0M0 glottic SCC (see tumor in **D**). The examination was performed on a dual-detector spiral CT (Elscint Twin, Haifa, Israel) using a slice thickness of 2.7 mm, an interval reconstruction of 2 mm, and a pitch of 0.7. Contrast medium was injected intravenously at a rate of 2 mL/s with a total amount of 100 mL. Sections were taken at the level of the bottom edge of C1 **(A),** the upper edge of C3 **(B),** mid C4 **(C),** the bottom edge of C6 **(D),** the bottom edge of C7 **(E),** and mid D1 **(F).** Neck node levels were drawn on each CT slice using the consensus guidelines. Each node level corresponds to the clinical target volume, and thus does not include any security margin for organ motion or setup inaccuracy.

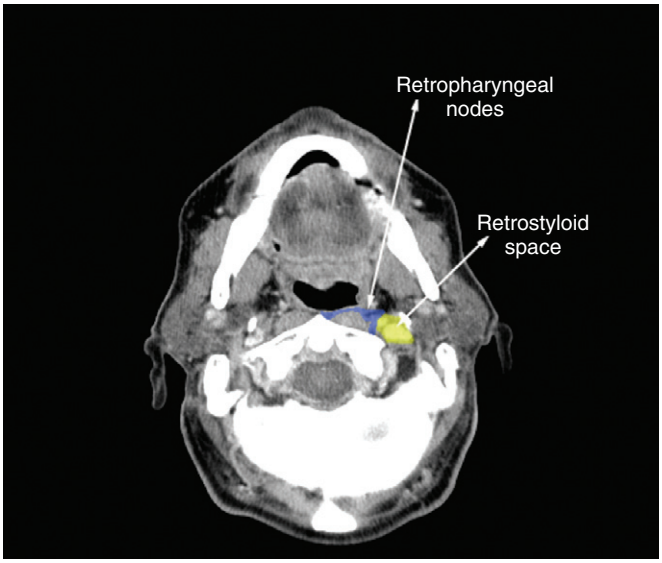

Figure 120-8. Computed tomography section at the level of the base of skull. The image was acquired as explained in Figure 120-7. The delineated areas correspond to the clinical target volume and thus do not include any security margin for organ motion or setup inaccuracy.

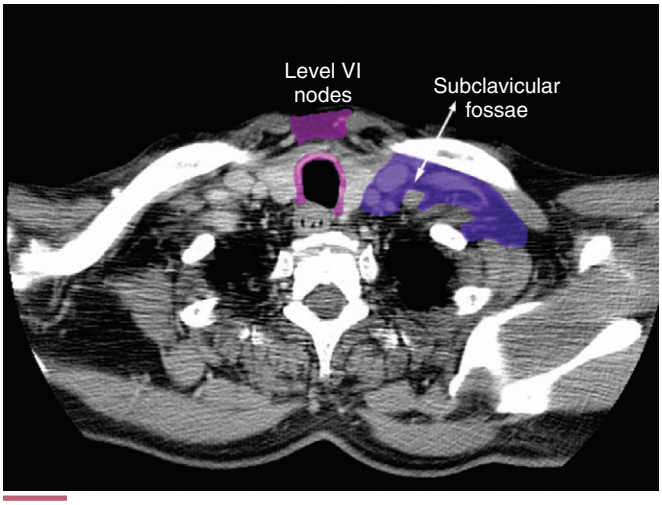

Figure 120-9. Computed tomography section at the level of the subclavicular area, 18 mm above the sterno-clavicular joint. The image was acquired as explained in Figure 120-7. The delineated areas correspond to the clinical target volume and thus do not include any security margin for organ motion or setup inaccuracy.

dures was further validated by a recent clip study.[34] Last, few amendments were recently proposed to take into account the specific situation of the node-positive and postoperative neck.[26,35] In short, this later proposal recommended the delineation of extranodal structures in case of muscular infiltration, the inclusion of the retrostyloid space in case of infiltration of level II, and the inclusion of the subclavicular fossae in case of infiltration of level IV and/or Vb.

It is beyond the scope of this chapter to present an in-depth discussion of the boundaries of the various levels. Interested readers are invited to refer to the original publications or to visit public Web sites, where atlases of neck node delineation have been posted (http://groups.eortc.be/radio/N0HEADNECKCTV.htm; http://www.rtog.org/atlases/hnatlas/main.html).[26,33] Figures 120-7 to 120-9 present several CT cuts of the neck with selected levels.

Irradiation Techniques

With the use of three-dimensional (3D) conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT), there is no standard recipe anymore on how to set up the field sizes and borders according to bony landmarks. Instead, the irradiation technique should be selected and adapted so that the entire planning target volume (PTV) receives the prescribed dose within the adopted dose-volume constraints and in full respect of the International Commission on Radiation Units and Measurements recommendations.

The dose prescription depends on various factors (e.g., elective vs. therapeutic irradiation, the use of combined modality treatment, planned neck node dissection, postoperative irradiation), which are beyond the scope of this section for comprehensive review. Typically, for primary radiotherapy, an elective dose on the order of 50 Gy in about 2 Gy per faction over 5 weeks and a therapeutic dose on the order of 70 Gy in about 2 Gy per fraction over 7 weeks will be prescribed. For postoperative irradiation, depending on the risk factors, doses will range from 60 to 64 to 66 Gy, in 2 Gy fraction over 6 to 6.5 weeks. A typical example of neck irradiation is presented in Figure 120-10.

Control of the N0 Neck

It is generally recommended to perform elective treatment of the neck in patients with primary head and neck SCC clinically staged N0 but having 20% or greater probability of occult lymph node metastases.[36] Elective neck dissection and elective neck irradiation are equally effective in controlling the N0 neck. The choice between these two procedures thus generally depends on the treatment modality chosen for the primary tumor, which in turn mainly depends on the institutional policy. However, the basic rule that should govern the choice between surgery and radiotherapy is to favor the use of a single-modality treatment if possible and thus avoid overtreatment. For example, for a T1 or a T2-N0 supraglottic larynx, typically, a supraglottic laryngectomy with a selective neck node dissection or a primary radiotherapy on the larynx and the neck are equally effective therapeutic options. For such stage disease, the need for postoperative radiotherapy is indeed quite low. Conversely, for a T3-N0 supraglottic larynx, a conservative treatment approach with primary radiotherapy or concomitant chemoradiotherapy should be favored because of the necessity of postlaryngectomy radiotherapy and the nonsuperiority of the surgical approach.

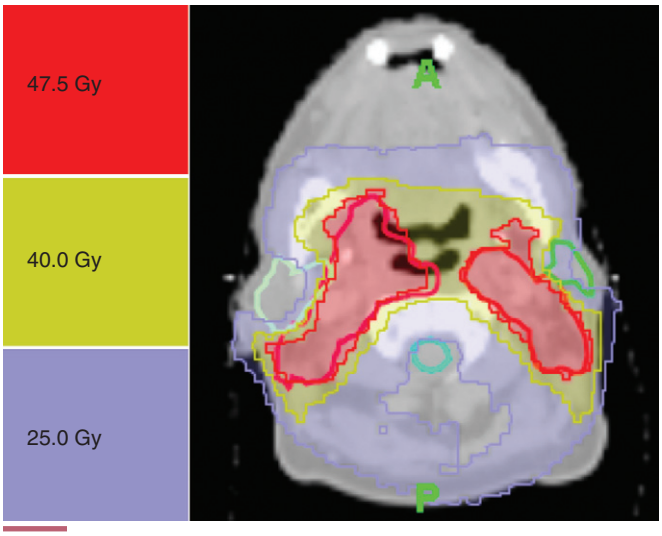

Figure 120-10. Computed tomography section at the level of C2 with dose distribution from an intensity-modulated radiation therapy plan for a hypopharyngeal T4-N0-M0 squamous cell carcinoma treated by concomitant chemoradiation. An elective dose of 50 Gy was prescribed to levels II to IV on both sides of the neck. A total dose of 70 Gy was prescribed to the right piriform sinus. Three courses of cisplatin (100 mg/m^2) were given in weeks 1, 4, and 7. The target volumes are delineated in red *(bold line).* The left parotid gland is delineated in green. The right parotid is delineated in light green. The spinal cord is delineated in blue. The color scale for the dose areas is depicted on the left. Sharp dose gradients are created between the target volumes and the normal tissues. A mean dose of 20.0 Gy was delivered to both parotids. The maximum dose to the spinal cord did not exceed 25 Gy.

Table 120-9 presents the percentage of neck recurrences in large retrospective series of pharyngolaryngeal SCC treated with conventional fractionated radiotherapy.[37-39] Some of the patients reported in those series were treated in the late 1950s, and thus the data must be interpreted with caution because of the likelihood of large uncertainties on the absolute dose calculation and dose distribution. Altogether, the neck control reached more than 92% after radiotherapy. After salvage surgery, the ultimate neck control reached a range of 94% to 100%. As expected, because of the high probability of regional control obtained with standard fractionation regimens, altered fractionation regimens or combined chemoradiotherapy do not improve the neck control.[40,41] All these studies were performed using two-dimensional (2D) irradiation techniques (i.e., with target volumes extending typically from the base of skull to the clavicles).

With the introduction of 3D-CRT and IMRT, as well as selective neck irradiation, one important issue is the potential risk of geographic miss outside of the irradiated volumes. Eisbruch reported a series of 135 patients treated bilaterally from 1994 to 2002 with 3D-CRT or IMRT for primary tumors mainly located in the oropharynx ($n = 80$) and without node metastasis on the contralateral neck.[42] On the contralateral neck, the clinical target volume (CTV) included typically level II to IV and the retropharyngeal lymph nodes. For the contralateral level II, the upper limit was set at the junction between the posterior belly of the digastric muscle and the jugular vein. The median elective dose was 50.4 Gy with a fraction of 1.8 to 2 Gy. With a median follow-up of 30 months (range: 6 to 105), 15 patients had a regional recurrence (of whom 6 also had a primary tumor recurrence), 11 on the ipsilateral side and 4 on the contralateral side. Only 1 of the 15 patients presented a retropharyngeal node recurrence marginal to the CTV. Using a similar treatment philosophy, Bussels and colleagues[43] did not report any recurrence on the ipsilateral N0 neck treated with parotid sparing 3D-CRT in a series of 72 patients with oral cavity and pharyngo-laryngeal SCC. Chao and colleagues[44] also looked at the pattern of recurrence in a series of 126 patients treated postoperatively ($n = 74$) or primarily ($n = 52$) by IMRT for head and neck SCC from 1997 to 2000. In this series the lower neck (below the thyroid notch) was treated with a "traditional" anterior field. With a median follow-up of 26 months, 17 (13%) recurrences were observed. Six of these patients recurred outside of the target volumes, of which only one was in the lower neck of a N0 patient.

Control of the N1-N3 Neck

Neck Control after Primary Radiotherapy

The lower probability of regional control of the positive neck with radiotherapy has been already documented by several retrospective series.[37,39,45] In a series of 1646 patients with SCC of the oropharynx

Table 120-9

Neck Failure after Primary Radiotherapy for Node-Negative Patients

Authors	Primary Tumor Site	Number of Patients (Study Period)	Dose/Overall Treatment Time	Control of the Neck	
				After Radiotherapy	After Salvage Surgery
Bernier[37]	Oral cavity, hypopharynx, larynx	611 (1958-1974)	45-55 Gy/4.5-5.5 wk	93%	Not stated
Johansen[39]	Oral cavity, hypopharynx, larynx	1324 (1963-1991)	57-72 Gy/6-9 wk*	92% at 10 yr	94% at 10 yr
Alpert[38]	Supraglottic larynx	98 (1971-1998)	50 Gy/5 wk	96.7%	100%

*Including 28% of patients with a split course.

and pharyngo-larynx from the Institut Curie in Paris, the 3-year regional control probability was 98%, 90%, 88%, and 71% for N0, N1, N2, and N3 (AJCC 1976 classification), respectively.[37] The nodal size was an even more discriminating factor with nodal failure of 6%, 14%, and 39% for nodes below 3 cm, between 4 and 7 cm, and more than 7 cm, respectively.[45] In this series, 75% of the neck nodes were, however, treated by a form of concomitant boost approach with total dose in the range of 70 to 85 Gy in 5 to 6 weeks. In the series of 458 node-positive patients with SCC of the larynx and pharynx treated at Aarhus University hospital from 1963 to 1991, the 5-year neck node control reached 68%, 68%, and 56% for N1, N2, and N3 UICC 1982 stage, respectively.[39]

A key issue in the management of the positive neck by radiotherapy is whether these rather poor results are improved by hyperfractionated or accelerated regimens, or by concomitant chemoradiotherapy. In randomized studies comparing a standard fractionated regimen with an altered fractionated regimen, no improvement was observed between the two arms (Table 120-10).[46-48] In the European Organization for Research and Treatment of Cancer (EORTC) 22791 trial, only N0 or N1 neck patients were included, and because of the excellent control of the neck in the standard arm, it was not surprising that the hyperfractionated regimen did not bring any benefit.[46] In the Danish Head and Neck Cancer (DAHANCA) 6 and 7 trials, no significant regional improvement was observed with the accelerated regimen in the node-positive patients.[47] Similarly, despite a benefit in overall survival, the Toronto trial did not observe any increase in the control of the neck with an accelerated hyperfractionated regimen.[48] Contrary to results achieved with altered fractionation regimens, concomitant chemoradiotherapy regimens appear to affect the control of the neck (Table 120-11).[49,50] In the study of Calais, all neck stages were analyzed together. However, because 75% of patients were node positive, it is unlikely that the 12% improvement results only from a beneficial effect on the N0 patients. In the study of Lavertu, which included fewer patients, the improvement in node control was observed for all positive neck stages.

Indications for Postoperative Irradiation/Postoperative Chemoirradiation

The benefit of postoperative radiotherapy in head and neck SCC has progressively emerged in the 1970s and 1980s as a standard of care for patients at high risk of locoregional relapse after surgery.[51-54] Prognostic indicators for locoregional relapse after surgery have been progressively identified, including the primary disease site, surgical margins at the primary site, presence of perineural invasion, number of metastatic lymph nodes, and presence of extracapsular rupture.[55,56] On the basis of the clustering of these pathologic factors, the M. D. Anderson Cancer Center proposed to stratify the patients into three risk categories conditioning the need for postoperative irradiation (Table 120-12).[57] In the absence of any risk factor, the need for postoperative radiotherapy could not be demonstrated. Patients with extracapsular rupture or a combination of two or more risk factors were identified as being at high risk of locoregional relapse, and for those patients, a randomized study demonstrated the benefit of a radiation dose of 63 Gy (in 35 fractions) compared with 57.6 Gy (in 32 fractions). For patients with only one risk factor other than extracapsular rupture, a dose of 57.6 Gy was demonstrated as optimal. A subsequent study from the same group

Table 120-10

Probability of Neck Node Control after Altered Fractionated Regimens

				Control in the Neck	
Authors	**Primary Tumor Site**	**Stage**	**Treatment Schedule**	**Std Arm**	**Exp Arm**
Horiot[46] EORTC 22791 (*n* = 325)	Oropharynx	T2-T3, N0-N1, M0	Std: 70 Gy/35f/7 wk Exp: 80.5 Gy/70f/7 wk	N0: 93% at 5 yr N1: 90% at 5 yr	N0: 93% at 5 yr N1: 90% at 5 yr
Overgaard[47] DAHANCA 6&7 (*n* = 1476)	Oral cavity, pharynx, supraglottic larynx	Stage I-IV	Std: 62-68 Gy/6-7 wk Exp: 62-68 Gy/5-6 wk	N^-: 68% N^+: 44%	N^-: 77%*† N^+: 52%‡
Cummings[48] (*n*= 331)	Larynx, oral cavity, hypopharynx	Stage III-IV	Std: 51 Gy/20f/4 wk Exp: 58 Gy/40f/4 wk	All stage: 71% at 5 yr	All stage: 68%§ at 5 yr

*Locoregional control.
†Odds ratio (95% CI): 0.65 (0.50-0.85).
‡Odds ratio (95% CI): 0.72 (0.49-1.05).
§*P* value: .80.
Exp, experimental; f, fraction; Std, standard.

Table 120-11

Probability of Neck Node Control after Concomitant Chemoradiotherapy

				Control in the Neck	
Authors	**Primary Tumor Site**	**Stage**	**Treatment Schedule**	**Std Arm**	**Exp Arm**
Calais[49] (*n* = 222)	Oropharynx	Stage III-IV*	Std: 70 Gy/7 wk Exp: 70 Gy/7 wk + carbo-5Fu ×3	All stage: 69%	All stage: 81%
Lavertu[50] (*n* = 100)	Oral cavity, larynx, pharynx	Stage III-IV†	Std: 65-72 Gy/7 wk Exp: 65-72 Gy/7 wk + cddp-5Fu ×2	N1: 6/10 (60%) N2-3: 13/27 (48%)	N1: 8/8 (100%) N2-3: 17/26 (65%)

*75% of patients were node positive.
†71% of patients were node positive.
carbo, carboplatin; CDDP, cisplatin; Exp, experimental; 5FU, fluorouracil; Std, standard.

further validated the use of these categories of risk factors and also individualized the time between surgery and the start of postoperative radiotherapy, as well as the total treatment time (from surgery to the end of radiotherapy) as additional risk factors.[58] In this latter study, it was also demonstrated that patients with high risk of relapse benefited from an accelerated treatment (63 Gy in 5 weeks vs. 63 Gy in 7 weeks) both in terms of locoregional control and survival.

With the need to further improve the locoregional control after surgery and postoperative radiotherapy, few trials combining postoperative concomitant chemotherapy and radiotherapy have been reported in the 1990s.[59,60] Although positive in favor of the combined approach, these studies did not really influence the pattern of care of patients primarily treated with surgery. More recently, the EORTC and the Radiation Therapy Oncology Group (RTOG) conducted similarly designed studies aiming at assessing the benefit of postoperative radiotherapy (60 to 66 Gy) combined with *cis*-platinum (100 mg/m^2) given on days 1, 22, and 43 for patients with a variety of risk factors, but slightly different between the two trials.[61,62] In the EORTC study, a highly statistically significant benefit in favor of the combined treatment was observed for both loco-regional control and overall survival (Table 120-13). In the RTOG study, the benefit in locoregional control probability did not translate into a statistically significant difference in survival. Combined modality treatment did not decrease the incidence of distant metastasis in any of these studies. In both studies, the concomitant use of chemotherapy significantly enhanced the acute local toxicity of radiotherapy and only half the patients could actually receive the full treatment as planned. A meta-analysis of these two studies was recently performed and demonstrated a statistically significant benefit of combined chemoradiotherapy, but only in patients presenting with positive surgical margins and/or extracapsular spread (i.e., patients with the highest risk of relapse after surgery).[63] For the other patients, radiotherapy alone can still be considered as a standard of care.

Table 120-12

Prognostic Factors for Locoregional Relapse after Surgery

Moderate Risk	High Risk
Positive margin at the primary (R1) or close margin (<5 mm)	Extracapsular spread (ECS)
Primary tumor in the oral cavity	A combination of two or more of the moderate risk factors
Perineural invasion	
Two or more invaded lymph nodes	
Two or more invaded node levels	
Invaded node(s) >3 cm in diameter	
More than 6 wk between surgery and start of radiation therapy	

Indications for Postradiotherapy Neck Node Dissection

Recent advances in (chemo)radiotherapy for advanced head and neck carcinoma have demonstrated that organ preservation is feasible without compromising disease-free survival and overall survival.[64,65] This strategy has led to controversial issues concerning the role of node dissection following radiotherapy or chemoradiation for patients with N2-N3 disease at initial diagnosis. Residual neck mass may be present in up to 30% to 50% of patients after completion of chemoradiotherapy. For those patients, irrespective of the neck stage, there seems to be a consensus in the literature favoring an immediate neck node dissection because of the low probability of achieving a neck control with salvage surgery when recurrence develops.[66] Should a neck dissection be proposed to all patients with N2-N3 disease at diagnosis or only to those with a no complete response, is still a matter of debate.[67-70] This controversy seems to be fueled by the difficulty of assessing the residual neck disease after organ-preservation protocol. In this respect, the use of FDG-PET scanning has gained some interest. In a 2004 study including 41 patients treated with definite radiotherapy (with or without concomitant chemotherapy), a negative postradiotherapy PET was highly correlated with a negative pathologic finding after neck node dissection or fine-needle aspiration, or with the absence of neck relapse (negative predictive value of 100% for a maximum standardized uptake value < 3.0).[71] In another study including 24 patients staged with FDG-PET after induction chemotherapy followed by chemoradiotherapy, the negative predictive value of PET, however, only reached 73%.[72] Further prospective studies are thus necessary to validate the use of PET to assess the need for post (chemo)radiotherapy neck node dissection. In the meantime, balancing the benefit with the increased morbidity of postchemoradiotherapy surgery, evidence suggests that neck node dissection be restricted to those patients with a noncomplete response after organ-preservation protocol.

Late Complications after Neck Irradiation

In the following section, only specific complications arising in the soft tissues of the neck are reviewed. It mainly concerns subcutaneous

Table 120-13

Efficacy of Postoperative and Concomitant Chemotherapy Radiotherapy

			LR Control		Overall Survival	
Author	Site	Regimen	RT	RT-CH	RT	RT-CH
Bernier[61] (*n* = 334)	Oral cavity, oropharynx, hypopharynx, larynx	66 Gy (6.5w) vs. 66 Gy (6.5w) + CDDP (100 mg/m^2) days 1, 22, 43	69% at 5 yr	82% at 5 yr*	40% at 5 yr	53% at 5 yr†
Cooper[62] (*n* =416)	Oral cavity, oropharynx, hypopharynx, larynx	60-66 Gy (6-6.5w) vs. 60-66 Gy (6-6.5w) + CDDP (100 mg/m^2) days 1, 22, 43	72% at 2 yr	82% at 2 yr‡	56% at 2 yr	64% at 2 yr§

*P = .007 (Gray's test).
†P = .02 (log-rank test).
‡P = .01 (Gray's test).
§P = .19 (log-rank test).
CDDP, cisplatin.

fibrosis, thyroid dysfunction, and carotid artery stenosis. Typically, late-complication probability depends on the total dose, dose per faction, time interval between fractions, volume of normal tissue that received a high dose, and use of concomitant chemotherapy and/or biologic modifier.

The probability of grade 3 to 4 (RTOG late-morbidity scale) subcutaneous fibrosis in the neck is rather low after standard radiotherapy. From randomized studies performed in the 1990s, it can be estimated to be around 3%.[49,73-75] After accelerated or hyperfractionated treatments, no increase in grade 3 to 4 subcutaneous toxicity was observed, providing that enough time was left between fractions.[74] On the contrary, in an EORTC trial with only a 4-hour interfraction time, a 50% risk of fibrosis was documented at 5 years after treatment.[76] After concomitant chemoradiotherapy, randomized trials reported a substantial increase in late skin morbidity reaching figures around 10%.[49]

Clinically indolent hypothyroidism has been reported in patients irradiated on the lower neck with a frequency of up to 24%.[77,78] The majority of patients usually develop hypothyroidism within a year post treatment. Postoperative radiotherapy, especially after laryngeal surgery including partial thyroidectomy, has been shown to be a risk factor. Yearly thyroid function test (i.e., thyroid-stimulating hormone level) is advised in the follow-up of patients irradiated to the neck.

Carotid artery stenosis after neck irradiation has been reported by several authors, but few studies have investigated the incidence, disease patterns, and risk factors. Matched control Doppler ultrasound examinations have reported significant carotid stenosis in 30% to 50% of patients previously irradiated to the neck.[79] Compared with the general population, a relative risk of stroke of 5.6 has been reported in patients previously irradiated to the neck.[80] This relative risk was further increased for patients older than 60 years and with follow-up longer than 10 years. Increased attention to the clinical signs of carotid stenosis together with proper management of the other risk factors (e.g., diabetes, hypertension, hypercholesterolemia, smoking, obesity) should contribute to decrease the incidence of stroke and neurologic sequelae in this patient population.

All the published data on late complications are from the pre-IMRT area. With the use of modern radiotherapy technique, a major reduction in late complications is anticipated mainly through a reduction in the volume of normal tissue irradiated at high dose and a reduction of the "uncontrolled" hot spot within or outside of the PTV. The introduction of IMRT has, however, raised the controversial concern of an increased risk of radiation-induced secondary neoplasm because a larger volume of normal tissue might be irradiated at lower dose in comparison with standard 2D techniques. Also, the delivery of a specified dose to the isocenter from modulated fields requires a longer beam time compared with the same dose delivered with a nonmodulated field. The IMRT treatment plan then results in an increase in the number of monitor units by a factor of 2 to 3, increasing the dose outside the boundary of the primary collimator as a result of leakage and scattered radiation.[81] As a consequence, the total body dose received is substantially increased. It is estimated that an additional 0.5% of surviving patients will develop a secondary malignancy as a result of an increased volume of normal tissue receiving a small radiation dose. This number needs to be added to the 0.25% of surviving patients who subsequently develop a radiation-induced malignancy. In all, it is thus estimated that about 0.75% of surviving patients are expected to develop a secondary malignancy as a result of the switch to IMRT, which is approximately twofold greater than the incidence observed following more conventional radiotherapy.[82] Whatever the contribution of IMRT in the induction of secondary cancers may be, we should bear in mind that even if IMRT increases the probability of locoregional control and the potential for increased cause-specific survival, this group of patients will suffer from comorbidities and increased risk for a second primary associated with their lifestyle, which may decrease the relative importance of radiation-induced secondary malignancies.

Management of Recurrent Disease in the Neck

Whether treated by radiotherapy, surgery, or the combination of both, the prognosis of patients with recurrence in the neck remains abysmal. Recurrent neck disease is quite invariably associated with unfavorable prognostic factors. Extracapsular spread is almost always reported and multiple LNs levels are frequently involved.[83] Neck recurrences are often unresectable because of involvement of the wall of the common carotid artery or the internal carotid artery, the paraspinal muscles, and the cranial nerves. Even when salvage surgery is attempted, the inability to achieve a complete resection with clear margins is generally the rule.

Few studies have specifically addressed the problem of recurrent neck disease following curative treatment in head and neck SCC. Godden retrospectively reviewed the charts of 35 patients with recurrent neck disease.[83] More than 80% of patients had primary surgery and the remainder were treated with radiotherapy. Fifty percent of the patients treated with primary surgery had postoperative radiotherapy. Eighteen patients had a neck dissection at initial presentation. The recurrence was managed by neck dissection in 25 patients, and among them, 18 had postoperative radiotherapy. Ten (29%) were considered as inoperable. Of the 18 patients who had an initial neck dissection, 9 (50%) recurred in the level II, previously cleared. Neck recurrence seemed to be more related with residual disease after the first neck dissection. This surprisingly high rate of level II recurrence stresses the necessity of adequate training for surgeons performing neck dissection procedures. In this series the ultimate control of the neck was only obtained in 5 of the 35 patients and the 4-year overall survival did not exceed 20%.

The likelihood of successful salvage treatment in patients who experienced neck recurrence after primary radiotherapy is low. Bernier and colleagues[37] reviewed 116 patients with isolated nodal failure after radiotherapy alone for oropharyngeal, hypopharyngeal, and laryngeal carcinoma. Fourteen patients had salvage neck dissection and 18 were reirradiated on the neck. Only one patient (1%) was successfully salvaged. The University of Florida recently reviewed the medical records of 51 patients who experienced recurrent disease occurring in the neck only.[84] Only 18 patients (35%) underwent salvage treatment, chemotherapy alone in 4 patients, chemotherapy and neck dissection in 1 patient, neck dissection alone in 11 patients, and neck dissection with postoperative radiotherapy in 2 patients. After salvage treatment, all patients had relapse of disease (locally, regionally, or distantly). Control of the neck at 5 years was 9% for the group who underwent salvage treatment, which was similar to the rate of neck control for the whole population. For the whole group of patients, absolute and cause-specific survival reached 10% at 5 years for both end points. However, at 3 years, patients who received salvage treatment had absolute and cause-specific survival rates of 44%. In comparison, none of the 33 remaining patients was alive at 3 years. Few institutions have evaluated salvage treatment with aggressive combined modality approaches that include low-dose reirradiation (preoperation or postoperative with or without concurrent chemotherapy) combined with an attempt at gross resection plus intraoperative irradiation (IORT) with either electrons (IOERT) or high-dose-rate brachytherapy (HDR-IORT).[85] Although the series involve small numbers of patients, early results suggest potential improvements in both locoregional control and survival when compared with standard salvage approaches, and further evaluation is warranted.

In summary, the majority of patients with regional recurrence are unable to undergo salvage treatment, and when salvage treatment with standard approaches (surgical resection, external beam radiation) is attempted, control of the neck remains poor. Salvage neck dissection alone should be restricted to patients with limited recurrence in the neck.

Radiation Therapy and Malignant Skull Base Tumors

Tumors of the cranial base are rare and present with minimal symptoms. They account for less than 1% of all new cases of cancer.[86] Unless these tumors impinge on vital organs or extend from the maxillary sinus to the nasal cavity resulting subsequent epistaxis or obstruction, diagnosis is often delayed. Depending on the location and the histopathology, treatment using radiation therapy is either in the definitive, neoadjuvant, or adjuvant setting. Because multiple critical normal tissues are located within or near the skull base (e.g., optic chiasm, cranial nerves, orbits, brainstem), radiotherapy techniques are focused

on treating the tumor while minimizing toxicities and complications. In this section of the chapter, we discuss the indications of radiation and describe the different technical advances in radiotherapy and their applications in the treatment of more commonly seen skull base tumors.

The treatment of cranial base tumors presents a difficult and challenging task for the radiation oncologist. Because tumors are irregularly shaped and are near or at the cranial base, a pair of lateral-opposed fields often cannot adequately encompass the tumor without causing excessive toxicity to the surrounding normal tissues. Therefore with conventional techniques, the dose of radiation is often limited by the need to respect normal tissue tolerance to radiation. Thus multiple different methods have evolved in treating tumors of the cranial base. Stereotactic irradiation, linear accelerator (LINAC)-based or gamma knife unit, is one method used in radiation delivery. The radiation delivered has a sharp dose fall-off between the target and the surrounding tissue, thus allowing precise delivery of radiation to the tumor target while minimizing the dose of radiation delivered to the surrounding normal tissues. However, radiosurgery can be limited by the size and shape of the tumor. IMRT, an evolution of 3D-CRT, allows the delivery of radiation to larger volumes and even more irregularly shaped tumors. For this reason, IMRT has recently gained popularity in the treatment of head and neck cancer, especially in the treatment of skull base tumors. Lastly, other technical approaches such as proton beam radiotherapy (cyclotron) or the CyberKnife (photon beam), though not available in most radiotherapy clinics, are also used. Indeed, the advancement in technology allowing more precise targeting of the tumor has resulted in improved tumor control or improved palliation of tumor-related symptoms. This is especially true when these tumors are unresectable or are recurrent on presentation.[87-89]

Radiation Technical Advances

LINAC-Based and Gamma Knife Stereotactic Irradiation

Stereotactic irradiation is a procedure whereby radiation is delivered using stereotactic principles.[90] Stereotactic irradiation can be performed by using any one of the high-energy forms of radiation, whether radiographs, gamma rays, or charged-particle irradiation. This procedure requires a multidisciplinary team approach and is used to destroy or to induce a desired biologic effect in a predetermined target while minimizing radiation to the surrounding tissues without having to open the skull. The word *stereotaxis* is derived from two Greek words: stereos, which means "three-dimensional," and taxis, which means "orderly arrangement." The concept of stereotactic irradiation derived from the understanding and use of stereotactic neurosurgery. The main benefit of stereotactic irradiation is that a high dose of radiation can be delivered to a defined region, usually within a well-immobilized system that conforms closely to the 3D shape of the target volume, at the same time having a rapid dose fall-off to the surrounding normal tissues.

Stereotactic irradiation was first introduced in 1951 by Lars Leksell, who coupled a stereotactic device to an orthovoltage x-ray tube and used 280-kV x-rays to treat trigeminal neuralgia.[90,91] Dr. Leksell also used a linear accelerator using higher-megavoltage radiation beams. In 1968 Leksell began using cobalt sources for irradiation of the thalamus in two cases of intractable pain. Subsequently, 179 highly collimated cobalt-60 sources were used to treat a variety of human diseases such as cancer pain, acoustic neuromas, craniopharyngiomas, intracranial arteriovenous malformations, parkinsonism, and Cushing's disease. These multiple, small, radioactive cobalt sources produced focused gamma beams, which Leksell called *gamma knife–based radiosurgery.* During the same time period at the University of California-Berkeley Lawrence Laboratory, charged-particle beams were used to treat pituitary tumors stereotactically (i.e., with protons, helium ions, neutrons). In the 1970s and 1980s, many radiotherapy centers used the existing linear accelerator at their facilities and adapted it to produce narrow, collimated beams of high-energy photons or x-rays. This was a less expensive alternative to both the gamma knife and the heavy charged-particle units. These new techniques were all based on the concept of using stereotactic frames for lesion localization, treatment setup, and patient immobilization during treatment. It was also during this time that Lunsford at University of Pittsburgh used the first 201 cobalt-60 source gamma knife unit to treat brain lesions stereotactically in the United States. Special collimator helmets (4, 8, 14, and 18 mm) with small apertures of corresponding sizes ensure that the 201 gamma ray beams converge at the focal point. Studies have shown that the gamma unit is more successful at conforming to the highly irregular shapes of the tumor than conventional LINAC-based stereotactic irradiation. The accuracy has been on the order of plus or minus 1.2 to 1.3 mm.[92-94] With proper planning, education, and awareness, gamma knife unit can greatly increase the number of patients being treated with stereotactic irradiation and can be effective for control of skull base tumors. However, minimal complications can arise (e.g., involving the optic structures) in patients who undergo stereotactic irradiation. In general, complications can occur in less than 2% of cases when patients receive more than 8 Gy as a single dose to a short segment of the optic apparatus.[95]

Proton Beam

Proton beam radiotherapy has superior dose distribution of radiation compared with photons due to the physical characteristics of protons.[96,97] Protons can be designed to yield a uniform dose across the target and deliver virtually zero dose deep to the target, as well as lower dose proximal to the target. Another benefit of proton beam radiotherapy is that the integral dose (dose delivered to the entire body) is approximately one half that of photon beam radiotherapy. This applies to both single-field and multiple-field treatment plans. Currently, there are few available and active proton beam units in the United States (e.g., Massachusetts General Hospital, Loma Linda Medical Center, Florida Proton Therapy Institute in Jacksonville, M. D. Anderson Cancer Center), in Europe (e.g., Paul Scherrer Institute in Switzerland, Orsay in France) and in Japan (e.g., Chiba, National Cancer Center, Hyogo Ion Beam Medical Center, Proton Medical Radiation Center). Approximately 15 more units are being built or are in active planning throughout the world. Proton beam units are extremely costly (2.6 times that of photon beam units) and require a tremendous amount of physical space to implement.[98] The small but definite advantage that they offer over conventional photon radiotherapy may not justify their widespread use. However, clinical gains have been observed over conventional photon radiotherapy in the treatment of patients with uveal melanoma, chordoma, and chondrosarcoma.

CyberKnife

The CyberKnife is a frameless robotic radiosurgical device that has been developed to treat mainly extracranial lesions.[99] This is contrary to the frame-based stereotactic radiosurgery devices as seen with the gamma knife or the LINAC-based stereotactic irradiation. The advantages of the CyberKnife include the ability to deliver radiation without a frame, the feature of increased fractionation flexibility, and the ability to treat extracranial lesions. The accuracy of the first-generation CyberKnife reported by Murphy and Cox in 1996[100] is found to be comparable with that of the frame-based system, on the order of 1.6 mm. The advances in digital imaging, robotics, and high-speed computers have made the CyberKnife just as accurate as frames on the order of 1.1 mm. The robotic CyberKnife can change the target of the beam delivery instantaneously. Target coordinate can be racked with external markers or with the use of an old stereotactic technique: biplane teleradiography. This is a noninvasive alternative to conventional stereotactic techniques and also assists fractionated treatment. To correct for patient misalignment, the device provides both translational, as well as rotational, corrections. The CyberKnife depends on a co-registration of digitally reconstructed radiographs that are generated from CT images and x-ray projections that are captured during the treatment session.

Intensity-Modulated Radiation Therapy

IMRT is a refinement of 3D-CRT that relies on the modulation of radiation beams to deliver a high dose to the tumor target while significantly reducing the dose to the surrounding normal tissues.[101,102] The underlying principle of IMRT is that each broad radiation beam is divided into a number of smaller beams called *beamlets.* This is achieved with the use of an intensity-modulator (e.g., multileaf collimator) or the hardware of IMRT. The different beamlets, each with a

different intensity, are added to form a dose distribution that is tailored to the shape of the target at hand. IMRT can be divided into two broad categories: forward-planning and inverse-planning therapy. Forward planned multisegmented technique (FPMS), also called *simple IMRT* or *forward-planned IMRT* (FP-IMRT), can achieve similar dose distributions when compared with inverse-planned IMRT (IP-IMRT). The drawback with FPMS is that optimization is done using manual iteration (trial and error) by the planning dosimetrist or physicist. It is heavily dependent on the experience of the treatment planner, and it is quite time consuming. With proper placement and weighting of beam angles, the number of iterations can be significantly reduced. On the other hand, computer-optimized or IP-IMRT relies on a computer software program that has an optimization algorithm that can achieve an ideal dose distribution on the basis of thousands of iterations. Currently, different treatment software is available throughout the world. Most centers use commercially available software (e.g., Peacock, Corvus, Pinnacle). Some centers such as Memorial Sloan-Kettering Cancer Center use their own in-house computer software.

Head and neck cancers, particularly skull base tumors, are ideal tumors for IMRT application because the tumors often present in close proximity to multiple critical normal tissues such as the brainstem, optic chiasm, optic nerves, and spinal cord.[101,103] In addition, because there is a lack of organ motion in the head and neck region, daily patient setups can be reproduced appropriately, with adequate immobilization. Furthermore, because head and neck cancer often presents in a locally advanced stage, potential dose escalation to the primary tumor using IMRT may result in an improvement in local control. However, an important issue cannot be overlooked involving the use of IMRT. IMRT has a sharp dose fall-off gradient between the target and surrounding normal tissue, thus making adequate target volume delineation absolutely essential. The treatment planning system will not treat areas not drawn on the CT slices, and the algorithm will even "work hard" to spare regions that are not contoured. Precise target volume delineation is dependent on a thorough physical examination and adequate imaging studies such as MRI, especially near the skull base region. Given these factors, target volume delineation ideally should be done with a multidisciplinary team approach consisting of the involvement of a radiation oncologist, a neuroradiologist, and in the postoperative setting, a head and neck surgeon. The target volumes of each case are carefully and accurately defined jointly by the multidisciplinary team. Therefore to use this new technology properly and effectively, IMRT requires a dedicated team of physicians, physicists, dosimetrists, and therapists to work together.

Treatment of Malignant Cranial Base Tumors

The cranial base can be divided into three regions: the anterior, middle, and posterior skull base. The complex anatomy of this region requires a multidisciplinary approach to skull base neoplasms. Definitive and complete surgical resection with or without postoperative radiotherapy is in general the favored treatment approach, with the exception of nasopharyngeal cancer. At the time of initial diagnosis, there should be close communication between the surgeon and the pathologist to ensure adequate tissue for diagnosis and subsequent confirmatory studies when necessary. It is absolutely essential that the surgeon and the pathologist be in direct communication regarding sites of surgical margins of greatest concern, as well as the orientation of the resected specimens. In addition, placing surgical clips at the time of surgery in the areas of concern can also provide useful information for the treating radiation oncologist so that he or she will have a better understanding of where to focus the highest dose of radiation. The authors will discuss malignant tumors arising from the anterior and middle cranial base. Tumors of the posterior cranial base are typically benign and therefore discussed in a separate chapter.

Anterior Cranial Base

The anterior cranial base extends from the frontal bone, which contains the frontal sinus, to the anterior and superior edge of the greater wing of the sphenoid bone. The posterior wall of the frontal bone forms the anterior limit of the anterior cranial base. This anterior base is above the orbital roofs and contains the frontal poles of the brain. The roof of the ethmoid and sphenoid sinuses forms the floor of the anterior cranial base between the bilateral orbits. The olfactory nerves (cranial nerve I) exit through the foramina (cribriform plate) of the anterior skull base into the nasal cavity.[104]

Malignant tumor involvement of the anterior cranial base is the result of contiguous spread from the paranasal sinuses, nasal cavity, or nasopharynx. Tumors confined to the ethmoid sinus without any involvement of the surrounding structures and sinuses are extremely rare. Ethmoid sinus tumors with extension to the ipsilateral nasal cavity, maxillary sinus, orbit, sphenoid, anterior cranial fossa, frontal sinus, and nasopharynx are common. Tumors can also extend to the orbit via the lamina papyracea and superiorly into the anterior cranial fossa via the cribriform plate. If the dura is compressed but not involved with tumor, it does not portend a poor prognosis when compared with tumor extension with histologic involvement of the dura.

Benign lesions such as meningioma, juvenile angiofibroma, and fibroosseous lesions and malignant lesions such as esthesioneuroblastoma (ENB) and SCC can originate from the anterior skull base. For the purpose of this chapter, selected malignant tumors of the anterior skull base are discussed. The role of radiotherapy in the treatment of ENB is reviewed in this section, as is sinonasal undifferentiated carcinoma (SNUC).

Esthesioneuroblastoma

First described in 1924, ENB remains a relatively rare entity. It is also known as "olfactory neuroblastoma" and accounts for 1% to 6% of all intranasal cancers, which constitute less than 1% of all human malignancies.[105,106] The tumor arises from the olfactory mucosa at the cribriform plate and frequently invades the paranasal sinuses, orbits, and skull base. Patients present with symptoms of nasal obstruction, epistaxis, nasal discharge, sinus pain, visual changes, facial numbness, or a neck mass. Tumors are often locally advanced on presentation. Cervical nodal metastases have been reported in 17% to 27% of patients, whereas distant metastases have been on the order of 10% to 40%. Different staging systems have been used by different centers.[107] MRI in addition to CT is useful as part of the staging workup because it can better differentiate between tumor and secretions caused by sinusitis.

Prognostic factors include age, stage, sex, and grade.[108] Patients older than 50 years of age have a worse prognosis than females. Those who present with nodal disease have a lower survival than those with node-negative disease (29% vs. 64% at 5 years). Grade has also been reported to be an important prognostic factor. Hyams' grade[109] is based on defined histologic features such as lobular architecture, neurofibrillary background, rosettes, nuclear pleomorphism, mitosis, necrosis, and calcification of the tumor. Each of these features is assigned a numeric grade (the Hyams' grade). Patients who present with a high Hyams' grade did significantly worse in one series compared with those with a low Hyams' grade (36% vs. 81% 5-year overall survival).

Locoregional failure rates after definitive treatment of ENB have been reported in the range of 24% to 75%, and the 5-year overall survival rates ranged from 60% to 78% (Table 120-14). Patients treated with surgery and radiation had a 5-year local control rate of 87.4% versus 51.2% with radiation alone in one series. Patients who failed treatment locoregionally failed within the ethmoid sinus or the orbit. Patients can also fail distantly in the liver or the brain parenchyma.

There is little consensus in the literature regarding the different therapeutic approaches; however, combination therapy generally has demonstrated greater benefits than single-modality therapy. One series reported a recurrence-free rate of 92% in those who underwent surgery followed by adjuvant radiation versus 14% for surgery alone and 40% for radiation alone.[110] Radiation in addition to surgery has been shown to improve survival by as much as 20%.[107] Most authorities favor craniofacial resection followed by adjuvant radiation therapy for patients who present with Kadesh stage A (limited to tumors of the nasal fossa) and B (extension to the paranasal sinuses) disease. In those who present with stage C (extension beyond the paranasal sinuses) disease, chemotherapy such as cisplatin, cyclophosphamide, etoposide, doxorubicin, and vincristine is often added to surgery and radiation.

Table 120-14

Results of Treatment for Esthesioneuroblastoma

Author/Center	Follow-up Survival (yr)	Overall Survival (%) 5 yr	10 yr	15 yr	Disease-free (%) 5 yr	10 yr	Local Recurrence (%)
Eden[106]/UVa, *n* = 40	10.8	78	71	65	—	—	38 (1959-1991)
Dulguerov[107]/UCLA, *n* = 26	7.2	74	60	—	—	—	33 (1970-1990)
Simon[143]/Univ. Iowa, *n* = 13	6.3	61	24	—	56	42	31 (1978-1998)
Argiris[144]/Northwest, *n* = 16	4.3	60	—	—	33	—	75 (1981-2000)
Chao[145]/Mallinckrodt, *n* = 25	8.0	66	—	—	56	—	27 (1976-1996)
Foote[108]/Mayo Clinic, *n* = 51	6.0	61	—	—	55	—	27 (1951-1990)
Eich[146]/Univ. Cologne, *n* = 17	7.2	*	—	—	60	—	24 (1981-1998)

*Median survival of 7.8 years.

Chemotherapy (cisplatin and etoposide) in conjunction with proton beam radiotherapy (equivalent to 68 Gy of photon irradiation) has been used with success in a small series of nine patients. With a short median follow-up of 20.5 months, eight of nine patients have been controlled. Longer follow-up will be required to determine the long-term success rates. Chemotherapy has also been used as a palliative modality and was found to have modest efficacy in patients who present with intracranial metastases.[111] The median survival is poor at 10.5 months.[112]

The technique of radiation used to treat ENB has evolved over time from intracavitary radium implants, cobalt-60, and orthovoltage treatment to the current use of photon or proton beam irradiation. Conventional techniques require the use of three fields, one anterior and two lateral wedged fields, to encompass the target volume. Radiation dosages range from 50 to 65 Gy given postoperatively. Due to the proximity of the tumor target to multiple critical normal tissues such as the orbital structures, there is often a limitation of dose that can be safely delivered to the tumor or the operative bed. It is likely that with IMRT and with the use of stereotactically guided conformal radiotherapy, much higher doses of radiation can be delivered safely to control the tumor target without exceeding the normal tissue tolerance (Fig. 120-11). Ultimately, this may translate into an improvement in local control, as well as survival. Whereas most centers advocated surgery followed by postoperative radiotherapy in the treatment of esthesioneuroblastoma, some centers prefer preoperative radiotherapy-chemotherapy as a complement to radical craniofacial resection attempting to reduce the tumor burden before surgery.[106] Polin and colleagues[113] reported 34 consecutive patients with biopsy-proven esthesioneuroblastoma who underwent preoperative radiation therapy with or without chemotherapy followed by surgical resection. Patients received 50 Gy along with either single-agent cyclophosphamide, vincristine, or in combination with doxorubicin hydrochloride (Adriamycin). The overall 5- and 10-year survival rates were 81% and 54.5%, respectively. The results are impressive because 23 patients had Kadesh C disease. In light of all these promising results, a recent meta-analysis of results from different centers showed that the 5-year overall and disease-free survival averaged 45% versus 41%, respectively.

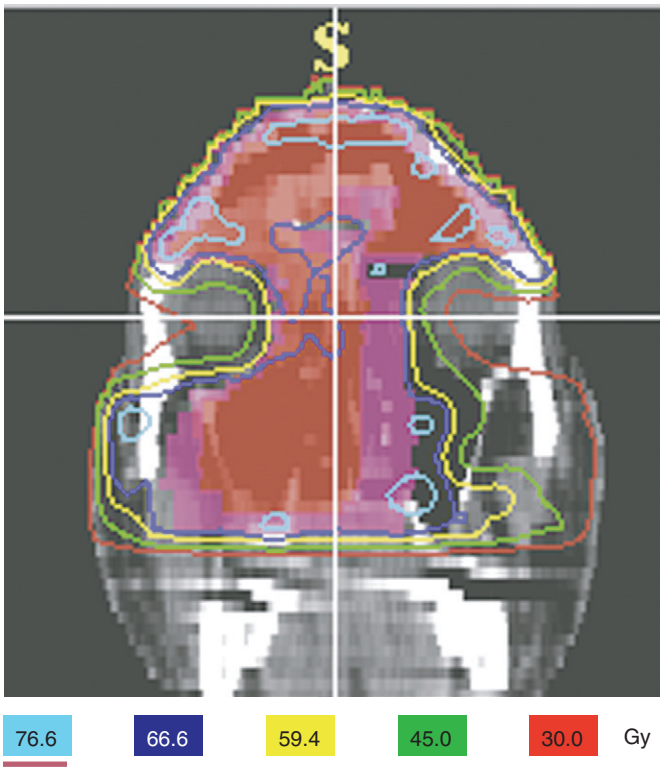

Figure 120-11. This patient presented with esthesioneuroblastoma extending intracranially and underwent complete surgical resection and postoperative intensity-modulated radiation therapy (IMRT) to the surgical bed. The red colorwash is the preoperative gross tumor volume and the magenta colorwash is the subclinical target volume. Notice that IMRT has the ability to tailor the prescription isodose lines around the target while sparing the critical surrounding orbital structures.

Sinonasal Undifferentiated Carcinoma

Primary sinonasal neuroendocrine tumors can be subdivided into four major histologic phenotypes: esthesioneuroblastoma (discussed earlier), sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinoma, and small cell undifferentiated carcinoma.[114] SNUC portends a poor prognosis because of its high rates of locoregional failures, as well as distant metastases.[115-117] An international collaborative study reporting on the results of craniofacial resection for malignant paranasal sinus tumors reported a 5-year overall survival rates of 0% for the undifferentiated tumors.[118] Investigators have suggested that the poor outcomes were due to the lack of the use of chemotherapy and/or the inclusion of small cell histologies because recent data are more promising.[114] Recently, Rischin and colleagues[119] reported promising results with chemoradiation for SNUC patients. In their study, 10 patients, 9 of

whom had T4 disease, underwent three cycles of induction platinum and 5-fluorouracil followed by concurrent chemotherapy using platinum. With a median follow-up of 43 months (range, 8 to 101 months), the 2-year progression-free, overall survival rates were 43% and 64%, respectively. Similarly, Rosenthal and colleagues[114] also reported a 5-year overall survival rate of 64.2% for patients with SNUC histology in their cohort of sinonasal neuroendocrine tumors.

Middle Cranial Base

The intracranial portion of the middle cranial base is composed of the greater wing and body of the sphenoid body, the petrous bone that is anterior to the petrous ridge, and the squamous portion of the temporal bone. The temporal lobes of the brain occupy most of the space. The sella turcica is below the optic chiasma and located behind the posterior wall of the sphenoid sinus. The pituitary gland resides within the sella. On either side of the sella turcica is the cavernous venous sinus, which is a common site for tumor involvement in the cranial base. The cavernous sinus houses cranial nerves III, IV, V1, V2, and VI. The extracranial surface of the middle cranial base comes in contact with the temporal fossa, infratemporal fossa, pterygopalatine fossa (space between the posterior wall of the maxillary sinus and pterygoid plates), and poststyloid space. The foramen ovale, through which V3 passes, and the foramen spinosum, which transmits the middle meningeal artery, are located within the infratemporal fossa. The eustachian tube exits the skull base just medial to the spine of the sphenoid at the junction of the infratemporal fossa and the poststyloid space. The pterygopalatine fossa contains the foramen rotundum through which the second division of the trigeminal nerve exits the skull base. The fossa also contains the vidian nerve, the nerve of the pterygoid canal. The poststyloid space contains the entrance to the carotid canal and the jugular foramen. Benign lesions such as meningioma, pituitary adenoma, chordoma, and craniopharyngioma and malignant lesions such as nasopharyngeal carcinoma (NPC), SCC with paranasal sinus extension, and adenoid cystic carcinoma all can arise within the middle cranial base. The role of radiotherapy in the treatment of chordoma and NPC are discussed.

Chordoma/Chondrosarcoma

Chordoma arises from the remnants of the primitive notochord. It occurs almost exclusively along the axial skeleton with 36% of the cases involving the base of skull with a slight male predominance. The average age at diagnosis is around 38 years of age when it involves the head and neck region.[120-122] These tumors are slow growing and the development of symptoms depends on the route of spread, intracranially, or inferiorly to involve the nasopharynx, maxillary sinus, or the nasal cavity. Symptoms may include headache, visual disturbances, diplopia, nasal obstruction, otalgia, and proptosis. Radiographically, it appears as an expansile, osteolytic lesion with areas of calcifications and is associated with a soft tissue mass. Local tumor control is essential for long-term survival because salvage treatment after local recurrence is often not successful. Definitive radiotherapy alone using 2D photon beams results in recurrences in more than 80% of the cases within 5 years of treatment and can be fatal within a time period from weeks to several decades.[121]

Treatment of skull base chordoma/chondrosarcoma is challenging and fairly complex because it often requires repeated, extensive surgical resections followed by high-dose postoperative radiotherapy. Due to the nearby critical neural and vascular structures, a total surgical resection is difficult and uncommon.[123-125] With modern high-precision, 3D treatment techniques, control rates have been reported that are superior to conventional radiotherapy techniques. Local control rates given postoperatively on the order of 82% at 2 years and 50% at 5 years have been reported when using CT- or MRI-based 3D planning to a median dose of 66.6 Gy.[126] With high-dose conformal radiotherapy to the skull base, radiation-induced damage to the hypothalamus and pituitary gland can occur.[127] Patients can have hyperprolactinemia followed by hypothyroidism, hypogonadism, and finally hypoadrenalism. Heavy-particle carbon ions and protons have also been used with more success than conventional photon radiotherapy, with a control rates up to 90%.[128-130] Further research is necessary to compare high-precision radiotherapy versus particle beam radiotherapy in terms of the efficacy and toxicity of each modality.

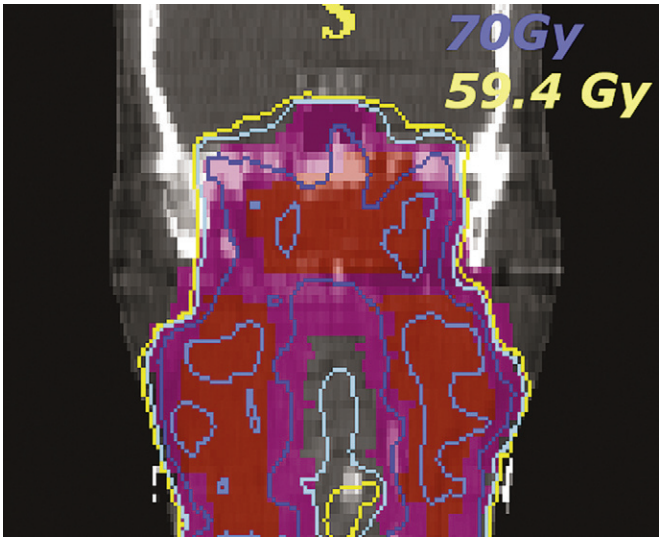

Figure 120-12. This is a patient with T4N2 nasopharyngeal carcinoma who underwent concurrent chemoradiotherapy using intensity-modulated radiation therapy: coronal view. The gross tumor volume is presented by the red colorwash, whereas the magenta colorwash depicts the subclinical region at risk for disease. The dark blue line is the 70-Gy isodose line and the light blue line is the 59.4-Gy isodose line. Notice the nice conformality of the isodose lines encompassing the respective target volumes while sparing the critical structures, specifically chiasm and brainstem. Notice that the parotid glands are outside the high dose regions with a mean dose of 28 Gy.

Nasopharyngeal Carcinoma

NPC is common among Asians, especially persons from Southern China, but it represents less than 1% of all cancers in the United States.[131] The standard treatment of patients with early-stage nasopharyngeal cancer is definitive radiotherapy, whereas those with locally advanced tumors are treated with a course of definitive chemoradiotherapy.[101] Historically, local control rates have ranged from 64% to 95% for stage T_1 and T_2 tumors, and for T_3 and T_4 diseases, the local control rate decreases to between 44% and 68%. The 5-year overall survival rate has been reported to be between 36% and 58%. IMRT has absolutely gained popularity in the treatment of head and neck cancer, especially nasopharyngeal cancer. The intensity of the radiation beams can be modulated so that a highly conformal dose of radiation can be delivered to the tumor target without causing excessive toxicity to the patient. IMRT is especially ideal in patients who present with locally advanced nasopharyngeal tumors in which it is nearly impossible to deliver a meaningful dose of radiation to the tumors without causing blindness, brainstem injury, or necrosis. Figure 120-12 is an example of a patient with locally advanced NPC treated with IMRT.

The longest experience of using IMRT in the treatment of NPC is the series from University of California–San Francisco (UCSF) Medical Center.[101] The local and locoregional progression-free rates have been 95% and 98%, respectively, for 89 patients. Approximately 60% of the patients in this series presented with T_3 and T_4 diseases. This is a marked improvement over the reported historical series. In addition, patients are complaining less of xerostomia. Because of the encouraging results, a national trial from the RTOG is currently under way to determine, at a multi-institutional level, the benefits of IMRT in the treatment of NPC. Several centers throughout the world (e.g., Hong Kong, Taiwan, China) are currently enrolling patients in their respective trials, and early results report similar encouraging results. Table 120-15 contains the local progression-free rates using IMRT in the treatment of nasopharyngeal carcinoma from different single insti-

Table 120-15

Results of Intensity-Modulated Radiation Therapy for Nasopharyngeal Carcinomas

Author	*N*	TNM Stage	Follow-up (mo)	Local-Progression Free (%)
Lee[101]	67	T1-T4	33	97
Wolden[147]	74	T1-T4	35	91
Kwong[148]	33	T1	24	100
Kam[149]	63	T1-T4	29	92

tutions. Although these results were excellent, the distant metastases rates reported in these series can be as high as 30%. Therefore the overall survival of NPC patients have not changed significantly in patients treated with IMRT versus conventional radiotherapy. Studies are under way to further decrease distant metastases rates with the incorporation of newer systemic agents.

Overexpression of vascular endothelial growth factor (VEGF) has correlated with higher recurrence and lower survival in NPC.[132] Studies have also shown that NPC patients are more likely to remain disease free when VEGF is decreased after treatment.[133] Bevacizumab, a monoclonal antibody that binds to VEGF-A, inhibits tumor neovascularization and improves chemotherapy delivery to tumors by normalizing the permeability of existing tumor vasculature.[134] Bevacizumab has shown improvement in overall survival in randomized trials when compared with standard chemotherapy, in metastatic colorectal, lung, and breast cancers. An ongoing national protocol is studying the treatment outcome in locoregionally advanced NPC patients with the addition of bevacizumab into the current standards of concurrent chemoradiotherapy followed by adjuvant chemotherapy. It is anticipated that the addition of bevacizumab, which targets VEGF expressed in NPC, will further minimize distant failures leading to improvement in patient overall survival.

Other Cranial Skull Base Tumors

It is beyond the scope of this chapter to discuss all tumors involving the cranial base. Several scattered case reports have described radiotherapy as a definitive treatment modality for tumors of the cranial base. Stereotactic irradiation has been used to treat various newly diagnosed or recurrent malignant tumors involving the skull base.[93] Tumor histologies included adenoid cystic carcinoma, basal cell carcinoma, osteogenic sarcoma, and SCC. Patients can experience symptomatic response to treatment with local control rates of 95% at 2 years and 78% at 3 years. Stereotactic irradiation can provide good local control and symptomatic relief in patients with recurrent salivary gland malignancies involving the skull base.[135]

Combination chemotherapy with high-dose radiotherapy using accelerated fractionation has also been used to manage unresectable malignant tumors of the skull base. The results are promising with a 2-year local progression-free survival of 94%, distant metastases-free survival of 57%, and overall survival of 80%. However, complications occurred in 20% and resulted in death of one patient in one series.[136] With advances in radiotherapy techniques, it is anticipated that the complications due to treatment will resolve over time. This has been supported by recent reports from centers using IMRT in the treatment of sinus cancer that involves the skull base.[137,138]

Complications after Skull Base Irradiation

For patients treated with radiation therapy for malignancies of the skull base, the high doses required to achieve local control have been historically associated with a high incidence of treatment-induced morbidity. In particular, the location of these tumors in relation to the optic structures, brainstem, spinal cord, and bony structures has raised concerns regarding the potential development of such complications as blindness, brain injury, and osteoradionecrosis. The majority of the publications on radiation-related complications have focused on patients treated using conventional nonconformal radiation techniques. Complications included radiation retinopathy, neovascular glaucoma, unilateral and bilateral blindness, and osteoradionecrosis.

Although recent studies have suggested the potential of IMRT to reduce complications, careful attention to dose constraints are necessary to minimize complications.[139-141] The UCSF series reported no patients experiencing complete loss of vision as a result of treatment with IMRT.[142] Similarly, the Memorial Sloan-Kettering Cancer Center experience did not report visual loss secondary to IMRT treatment for malignant tumors involving the skull base.[137] A longitudinal analysis of the UCSF experience showed that the incidence of grade 3 or higher late complications changed significantly for patients treated with conventional radiation therapy versus 3D-CRT and IMRT. For instance, 13% of patients treated with IMRT developed any grade 3 or higher late complication compared with 22% and 54%, respectively, of patients treated using 3D-CRT and conventional radiation therapy, respectively.[138]

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CHAPTER ONE HUNDRED AND TWENTY-ONE

Neck Dissection

K. Thomas Robbins

Sandeep Samant

Ohad Ronen

Key Points

- Neck dissection is a surgical procedure that is designed to remove metastatic cancer involving the cervical lymph nodes.
- The gold standard procedure is the radical neck dissection.
- Modifications of the radical neck dissection procedure include the modified radical neck dissection, which has been designed to reduce morbidity by sparing nonlymphatic structures, and selective neck dissection, which is used for treating early nodal disease by removing only the lymph node groups at greatest risk for harboring metastases.
- The lymph nodes in the neck are grouped into six major levels (I to VI) with additional division into two sublevels (A and B) of levels I, II, and V.
- Clear anatomic, radiologic, and surgical landmarks are used to define the borders between the different levels.
- The term *therapeutic neck dissection* is used when there is clinical evidence of metastatic cervical lymphadenopathy.
- The term *elective neck dissection* is used when the procedure is performed to remove lymph node groups that have an increased risk of harboring occult disease in the neck.
- A planned neck dissection, performed whenever there is a high risk of residual cancer, is typically done 6 to 8 weeks after other treatment to the neck has been completed, such as radiotherapy or chemoradiotherapy, regardless of the clinical response to the initial treatment.
- A "salvage" neck dissection is done when there is clinical evidence of metastatic disease in the neck after previous treatment. It can further be classified as early versus late depending on whether there is persistent versus recurrent neck metastases.
- Complications of a neck dissection include air leaks, bleeding, chylous fistula, facial or cerebral edema, blindness, carotid artery rupture, and damage to nerves such as the phrenic, vagus, brachial plexus and cutaneous nerves and the mandibular branch of the facial, hypoglossal, or lingual nerves.
- A neck dissection following chemoradiation therapy poses special challenges because the indications and the extent of the procedure remain controversial.

The terms *neck dissection* and *cervical lymphadenectomy* refer to the systematic removal of lymph nodes with their surrounding fibrofatty tissue from the various compartments of the neck. This procedure is used to eradicate metastases to the regional lymph nodes of the neck. In most patients, these metastases originate from primary lesions involving mucosal sites of the upper aerodigestive tract, particularly the oral cavity, pharynx, and larynx.

The propensity for spread to the regional lymph nodes by carcinomas of the upper aerodigestive tract is variable and is associated with several factors such as histology, T classification, and location of the primary tumor. For example, if the histology shows perineural invasion or invasion of the tumor's microcirculation, the risk is higher. In general, the more advanced the T classification, the higher the likelihood of nodal spread. Certain subsites such as the oral tongue, floor of the mouth, piriform sinus, and supraglottic larynx are associated with higher rates of lymphatic metastasis as compared with such subsites as the buccal mucosa, lip, nasal cavity, paranasal sinuses, and glottic larynx. Although the anatomic distribution of the surrounding lymphatic channels may explain some of this variation, inherent differences in the biologic behavior among these cancers are likely as well. Thus the indications for cervical lymphadenectomy depend not only on the presence of palpable disease but on factors that increase the risk of occult disease such as the size and characteristics of the primary tumor. The term *therapeutic neck dissection* applies to the former condition, whereas the term *elective neck dissection* applies to the latter situation. Other factors that are important when deciding whether cervical lymphadenectomy is indicated relate to the overall treatment plan. For example, if the treatment of choice for the primary tumor is radiation rather than surgery, it may also be preferable to radiate the regional nodes when the clinical staging of the nodal disease is N_0 or N_1. If surgical transgression of the regional lymphatics is required to resect the primary tumor, cervical lymphadenectomy should also be included.

Historical Perspective

In publications that came out before the 20th century, little attention was given to the indications or techniques for treating cervical lymph node metastases. The first conceptual approach for removing nodal metastases was made by Kocher in 1880[1]; he described the removal of

the lymph nodes located within the contents of the submandibular triangle to gain surgical access to a cancer of the tongue. Later, Kocher recommended that nodal metastases should be removed more widely through a Y-shaped incision, with the long arm extending from the mastoid to the level of the omohyoid at its junction with the anterior border of the sternocleidomastoid muscle. Around the same time, Packard supported the concept of removing the surrounding lymph nodes for lingual cancer.[2] The first description of the radical neck dissection was by Jawdynski, a Polish surgeon.[3] However, the individual credited the most for developing and reporting the efficacy of this procedure is George Crile.[4] Crile believed that distant (hematogenous) metastases were uncommon in head and neck cancer and that metastases more commonly occurred in the neck through the permeation of lymphatics. The descriptions by both of these surgeons of a block resection encompassing all of the cervical nodal groups from the level of the mandible above to the clavicle below became the basis for the radical neck dissection we know today. Relevant to the modifications of radical neck dissection that were subsequently made, Crile recommended preservation of the internal jugular vein and the sternocleidomastoid muscle for patients in whom there were no palpable nodes. In addition, his technique was to remove only the regional lymph nodes that were known to drain the field of the original focus of disease when metastases could not be seen. Also, it is interesting to note that, in the accompanying illustrations of the more radical en bloc resections, the spinal accessory nerve was preserved.

This philosophy of radical en bloc resection based on Crile's descriptions remained popular with the head and neck surgeons during the first half of the 20th century, in part because of the works of Blair and Brown[5] and Martin,[6] who were strong proponents of the radical en bloc technique of neck dissection in a manner similar to the radical surgery that had evolved for breast cancer. Martin, in particular, categorically insisted that the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle should be removed as part of all cervical lymphadenectomies. It may be useful to remember that, during this time, radiotherapy had not yet been developed as an effective adjuvant modality, and radical surgery represented the only hope for cure.

Associated with the procedure of the radical neck dissection was the presence of significant postoperative morbidity related to shoulder dysfunction; the operation also had limitations as a bilateral procedure.[7] In the 1950s Ward and Robben[8] reported that the neck dissection could be modified in some circumstances by sparing the spinal accessory nerve and thereby preventing postoperative shoulder drop. Later, Saunders, Hirata, and Jaques[9] compared the functional results of cases undergoing radical neck dissection with those in whom the spinal accessory nerve was spared; this demonstrated that shoulder symptoms were only mild or moderate in more than 80% of the patients who had the nerve preserved or cable grafted. The concept of conservation neck surgery was further popularized during the 1960s by Suarez[10] in Argentina and promoted by Bocca and Pignataro,[11] who independently described an operation that removed all of the lymph node groups while sparing the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. They emphasized that fascial compartments surrounding the lymphatic contents of the neck could be removed without sacrificing the nonlymphatic structures, as mentioned.

Other authors reported the sparsity of nodal disease within the posterior triangle for carcinoma of the oral cavity, pharynx, and larynx, thus setting the stage for modifications directed toward preserving lymph node groups.[12-15] These observations paved the way for another type of neck dissection modification: one in which there was selective preservation of one or more lymph node groups.[16-18] Some of the initial proponents of this concept were the surgeons at MD Anderson Cancer Center, who called the procedure "modified neck dissection."[19,20] Two of the variations of the modified neck dissection were also called "supraomohyoid" and "anterior" neck dissections.[16] However, the term *selective neck dissection* (SND) subsequently became associated with the concept of preserving lymph nodes in one or more of the neck levels through the American Academy of Otolaryngology's classification.[17,21] The lymph node groups removed are based on the pattern of metastases, which are predictable relative to the primary site of cancer.

Table 121-1

Types of Neck Dissection

Terminology	Definition
Radical	Removal of lymph node levels I to V, sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein.
Modified	Removal of lymph node levels I to V (as in radical neck dissection [ND]), but preservation of at least one of the nonlymphatic structures (sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein).
Selective	Preservation of one or more lymph node levels relative to a radical ND.
Extended	Removal of an additional lymph node level or group or a nonlymphatic structure relative to a radical ND (muscle, blood vessel, nerve). Examples of other lymph node groups are superior mediastinal, parapharyngeal, retropharyngeal, peri-parotid, postauricular, suboccipital, and buccinator. Examples of other nonlymphatic structures are external carotid artery, hypoglossal, and vagus nerves.

Terminology of Neck Dissection

The evolution of cervical lymphadenectomy procedures during the 20th century has provided the modern head and neck surgeon with a repertoire of surgical techniques for removing nodal metastases. Concurrent with this expansion has been the emergence of a multitude of terms used to describe these procedures. Originally proposed by authors without any uniformity of terminology, this lack of standardization unfortunately resulted in redundancy, misinterpretation, and even confusion among clinicians. Realizing the importance for standardizing the diverse nomenclature, the Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology–Head and Neck Surgery convened a special task force in 1988 to address the problems of terminology related to cervical lymphadenectomy. The specific objectives of the group were as follows: (1) to recommend terminology that adhered to more traditional terms such as "radical" and "modified radical" neck dissection, and to avoid the use of eponyms and acronyms; (2) to define which lymphatic structures and other nonlymphatic structures should be removed or preserved relative to the radical neck dissection; (3) to provide standard nomenclature for the lymph node groups and the nonlymphatic structures; (4) to define the boundaries of resection for lymph node groups; (5) to use terms for the neck dissection procedures that are basic and easy to understand; and (6) to develop a classification on the basis of the biology of the cervical metastases and the principles of oncologic surgery.[17]

Recently updated by the Committee for Neck Dissection Classification of the American Head and Neck Society (AHNS), the classification is outlined in Table 121-1).[9,22,23] The new versions included modifications of the original classification in an effort to remain contemporary and to follow the current philosophy of managing lymph node metastases.

Cervical Lymph Node Groups

The patterns of spread of cancer from various primary sites in the head and neck to the cervical lymph nodes have been documented by retrospective analyses of large series of patients undergoing neck dissection.[12,16,24] The nodal groups at risk for involvement are widespread throughout the neck, extending from the mandible and skull base

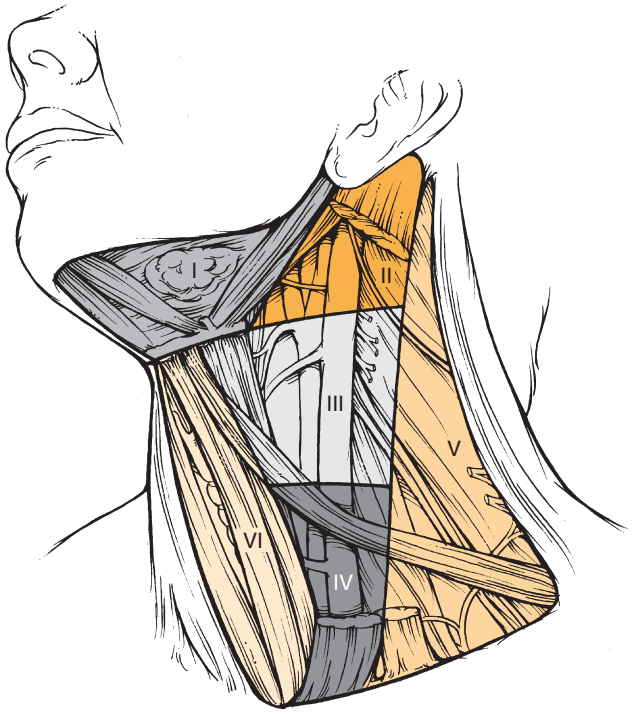


Figure 121-1. The six levels of the neck for describing the location of lymph nodes in the neck. *I,* submental and submandibular group; *II,* upper jugular group; *III,* middle jugular group; *IV,* lower jugular group; *V,* posterior triangle group; and *VI,* anterior compartment group. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

superiorly to the clavicle inferiorly and from the posterior triangle of the neck laterally to the midline viscera and to the contralateral side of the neck. It is now recommended that the lymph node groups in the neck be categorized according to the level system originally described by the Memorial Sloan-Kettering Group (Fig. 121-1).[19]

There are two important lymph node groups within level I: the submental group and the submandibular group. The submental nodes are defined as those that are contained within the boundaries of the submental triangle (i.e., the anterior belly of the digastric muscles and the hyoid bone). The submandibular lymph node group refers to the nodes lying within the boundaries of the submandibular triangle (i.e., the anterior and posterior bellies of the digastric muscle and the body of the mandible). Because many of these lymph node groups lie in close proximity to the submandibular gland, this structure is removed to ensure thorough exenteration of all of the lymph nodes within this triangle. Thus the boundaries of level I lymph nodes include the body of the mandible, the anterior belly of the contralateral digastric muscle, the posterior belly of the ipsilateral digastric muscle, and the stylohyoid muscle. It should be noted that the perifacial lymph nodes including the buccinator nodes are located outside of this triangle superior to the mandibular body. These nodes may contain metastatic disease when the primary site involved is the lip, buccal mucosa, anterior nasal cavity, or soft tissue of the cheek. Thus the neck dissection performed for nodal disease associated with primary lesions of these sites should be modified to encompass the perifacial nodes.

Level II is defined as the region containing the upper jugular lymph nodes. These are located around the upper third of the internal jugular vein and adjacent to the spinal accessory nerve, extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical landmark) inferiorly to the skull base superiorly. The lateral boundary is the posterior border of the sternocleidomastoid muscle, and the medial boundary is the stylohyoid muscle. Recently, the AHNS committee recommended that the perpendicular plane defined by the posterior aspect of the submandibular gland could serve as the radiologic landmark for this boundary.

Level III contains the middle jugular lymph node group. These nodes are located around the middle third of the internal jugular vein, extending from the carotid bifurcation superiorly (surgical landmark) or the level of the inferior aspect of the body of the hyoid bone (clinical and radiologic landmark) to the junction of the omohyoid muscle with the internal jugular vein (surgical landmark) or the lower border of the cricoid arch (clinical and radiologic landmark) inferiorly. The lateral boundary is the posterior border of the sternocleidomastoid muscle, and the medial boundary is the lateral border of the sternohyoid muscle. Recently, the AHNS committee recommended that the lateral border of the common carotid artery could serve as the radiologic landmark for the medial boundary.

Level IV contains the lower jugular lymph node group. These nodes surround the lower third of the internal jugular vein, extending from the omohyoid muscle (surgical landmark) or cricoid arch (clinical landmark) superiorly to the clavicle inferiorly. The lateral boundary is the posterior border of the sternocleidomastoid muscle, and the medial or anterior boundary is the lateral border of the sternohyoid muscle. As with level II, the lateral border of the common carotid artery could serve as the radiologic landmark for the medial boundary.

Level V encompasses all lymph nodes contained within the posterior triangle, and these are collectively referred to as the posterior triangle group. The boundaries include the anterior border of the trapezius muscle laterally, the posterior border of the sternocleidomastoid muscle medially, and the clavicle inferiorly. The nodes in this triangle comprise three predominant lymphatic pathways: nodes located along the spinal accessory nerve as it traverses the posterior triangle; nodes located along the transverse cervical artery as it courses along the lower third of the triangle; and the supraclavicular nodes located immediately above the clavicle. The supraclavicular nodes also extend below the level of the upper horizontal border of the clavicle to include one particular node of importance: the sentinel—or Virchow's—node.

Level VI encompasses the lymph nodes of the anterior compartment of the neck.[19,21] This group is made up of nodes that surround the midline visceral structures of the neck, extending from the level of the hyoid bone superiorly to the suprasternal notch inferiorly. On each side, the lateral boundary is formed by the medial border of the carotid sheath. Located within this compartment are the perithyroidal lymph nodes, paratracheal lymph nodes, lymph nodes along the recurrent laryngeal nerves, and precricoid (Delphian) lymph node. These lymph nodes and their connecting lymphatic channels represent pathways of spread from primary cancers originating in the thyroid gland, apex of the piriform sinus, subglottic larynx, cervical esophagus, and cervical trachea.

The superior mediastinal lymph nodes (optionally referred to as *level VII*) are bounded superiorly by the superior edge of the manubrium, inferiorly by the superior border of the arch of the aorta, and laterally by the common carotid artery on the left side and the innominate artery on the right.

Division of Neck Levels by Sublevels

The 2001 report of the American Head and Neck Society's Neck Dissection Committee recommended the use of sublevels for defining selected lymph node groups within levels I, II, and V on the basis of the biologic significance, independent of the larger zone in which they lay.[21] These are outlined in Figure 121-2 as sublevels IA (submental nodes), IB (submandibular nodes), IIA and IIB (together composing the upper jugular nodes), VA (spinal accessory nodes), and VB (transverse cervical and supraclavicular nodes). The boundaries for each of these sublevels are defined in Table 121-2.

The risk of nodal disease in sublevel IIB is greater for tumors arising in the oropharynx as compared with the oral cavity and larynx.[25-32] Thus in the absence of clinical nodal disease in sublevel IIA, it is likely not necessary to include sublevel IIB for tumors arising in these latter sites. The dissection of the node-bearing tissue of sublevel IIB (submuscular recess) creates a risk of morbidity. Adequate exposure necessitates significant manipulation of the spinal accessory nerve and may account for trapezius muscle dysfunction observed in a significant

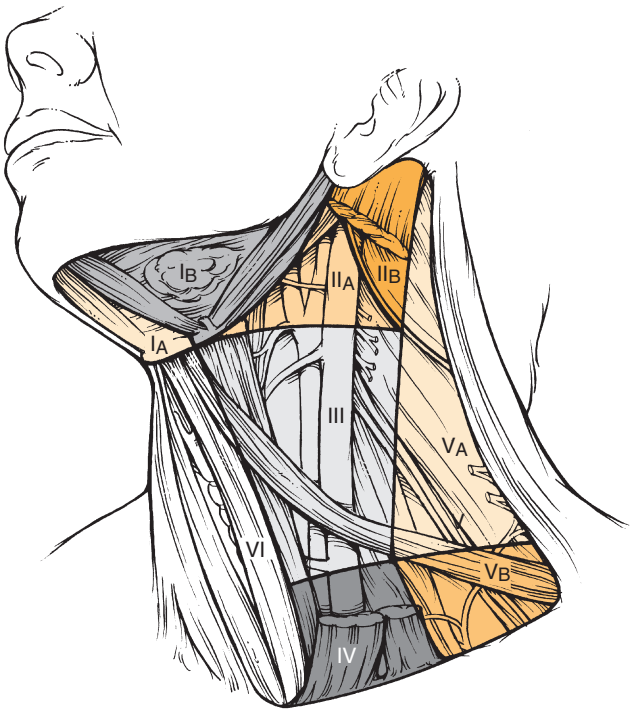


Figure 121-2. The six sublevels of the neck for describing the location of lymph nodes within levels I, II, and V. *IA,* submental group; *IB,* submandibular group; *IIA,* upper jugular nodes along the carotid sheath including the subdigastric group; *IIB,* upper jugular nodes in the submuscular recess; *VA,* spinal accessory nodes; and *VB,* the supraclavicular and transverse cervical nodes. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

minority of patients after an SND. Sublevel IA is a zone from which many surgeons do not remove lymph nodes unless the primary cancer involves the floor of the mouth, the lip, or structures of the anterior midface or there is obvious lymphadenopathy.

Level V is the third region that has been subdivided, into levels VA and VB. The superior component, level VA, primarily contains the spinal accessory lymph nodes, whereas level VB contains the transverse cervical nodes and the supraclavicular nodes, which carry a more ominous prognosis when positive in cases with upper aerodigestive tract malignancies.

Correlation of Neck Level Boundaries with Anatomic Markers Depicted Radiologically

Radiologists have now identified landmarks that more accurately identify the location of lymph nodes according to the level system (Table 121-3).[33,34] Using radiologic landmarks, level I includes all of the nodes above the level of the lower body of the hyoid bone, below the mylohyoid muscles, and anterior to a transverse line drawn on each axial image through the posterior edge of the submandibular gland. Level IA represents those nodes that lie between the medial margins of the anterior bellies of the digastric muscles, above the level of the lower body of the hyoid bone, and below the mylohyoid muscle (these were previously classified as submental nodes). Level IB represents the nodes that lie below the mylohyoid muscle, above the level of the lower body of the hyoid bone, posterior and lateral to the medial edge of the ipsilateral anterior belly of the digastric muscle, and anterior to a transverse line drawn on each axial image tangent to the posterior surface of the submandibular gland on each side of the neck (these are also referred to as *submandibular nodes*). Level II extends from the skull base at the lower level of the bony margin of the jugular fossa to the level of the lower body of the hyoid bone. Level II nodes lie anterior to a transverse line drawn on each axial image through the posterior edge of the sternocleidomastoid muscle, and they lie posterior to a transverse line drawn on each axial scan through the posterior edge of the submandibular gland. However, any nodes that lie medial to the internal carotid artery (ICA) are retropharyngeal and thus not level II.

Level III nodes lie between the level of the lower body of the hyoid bone and the level of the lower margin of the cricoid cartilage. These nodes lie anterior to a transverse line drawn on each axial image through the posterior edge of the sternocleidomastoid muscle. Level III nodes also lie lateral to the medial margin of either the common carotid artery or the ICA. On each side of the neck, the medial margin of these arteries separates level III nodes, which are lateral, from level VI nodes, which are medial.

Thus the revised classification uses the horizontal plane defined by the inferior border of the hyoid bone instead of the carotid bifurcation to delineate the boundary between levels II and III. Similarly, the revised classification uses the horizontal plane defined by the inferior border of the cricoid cartilage instead of the junction between the superior belly of the omohyoid muscle to delineate the boundary between levels III and IV. However, from a surgical perspective, it is important to note the significance of the anatomic relationship between the omohyoid muscle and the internal jugular vein because lymph nodes are usually located in this region. These nodes would be included in level III.

Neck Dissection Classification

The classification for neck dissection recommended by the American Head and Neck Society's committee is based on the following rationale: (1) that radical neck dissection is the standard basic procedure for cervical lymphadenectomy, and all other procedures represent one or more modifications of this procedures; (2) when the modification of the radical neck dissection involves the preservation of one or more nonlymphatic structures, the procedure is called *modified radical neck dissection;* (3) when the modification involves the preservation of one or more lymph node groups that are routinely removed in the radical neck dissection, the procedure is called *SND;* and (4) when the modification involves the removal of additional lymph node groups or nonlymphatic structures relative to the radical neck dissection, the procedure is called *extended radical neck dissection* (see Table 121-1).

A "planned" neck dissection is typically performed 6 to 8 weeks after the completion of radiotherapy or chemoradiotherapy when the chance of residual disease in the neck is high. Some centers use ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scan to further decide whether to perform a neck dissection. Because the reliability of a PET scan is questionable before 3 months have passed following completion of radiation or chemoradiation, a "planned" neck dissection based on the results of this investigation may have to be deferred until this time.

As opposed to a planned neck dissection, a "salvage" neck dissection is performed when metastatic disease in the neck occurs after it has been treated previously. The salvage neck dissection can be further classified as "early" procedure when it is done for persistent disease after chemo/radiation or "late" when it is done for recurrent disease.

Radical Neck Dissection

DEFINITION. This procedure includes the removal of all ipsilateral cervical lymph node groups extending from the body of the mandible superiorly to the clavicle inferiorly and from the lateral border of the sternohyoid muscle, hyoid bone, and contralateral anterior belly of the digastric muscle anteriorly to the anterior border of the trapezius muscle posteriorly.[22] Included are all lymph node groups from levels I through V, the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle (Fig. 121-3). It does not include the removal of the postauricular and suboccipital nodes, the periparotid nodes (except for a few nodes located in the tail of the parotid gland), the perifacial and buccinator nodes, the retropharyngeal nodes, and the paratracheal nodes.

INDICATIONS. The radical neck dissection is indicated for patients with extensive lymph node metastases with extension beyond the capsule of the node or nodes to involve the spinal accessory nerve and the internal jugular vein.

Table 121-2

Lymph Node Groups Found within the Six Neck Levels and the Six Sublevels

Lymph Node Group	Description
Submental (sublevel I_A)	Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone; these nodes are at the greatest risk of harboring metastases from cancers arising from the floor of the mouth, anterior oral tongue, anterior mandibular alveolar ridge, and lower lip (see Fig. 121-2).
Submandibular (sublevel I_B)	Lymph nodes within the boundaries of the anterior belly of the digastric muscle, the stylohyoid muscle, and the body of the mandible, including the preglandular and postglandular nodes and the prevascular and postvascular nodes. The submandibular gland is included in the specimen when the lymph nodes within this triangle are removed. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, the anterior nasal cavity, and the soft tissue structures of the midface and the submandibular gland (see Fig. 121-3).
Upper jugular (sublevels II_A and II_B)	Lymph nodes located around the upper third of the internal jugular vein and the adjacent spinal accessory nerve, extending from the level of the skull base above to the level of the inferior border of the hyoid bone below. The anterior (medial) boundary is the stylohyoid muscle (the radiologic correlate is the vertical plane defined by the posterior surface of the submandibular gland), and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. Sublevel II_A nodes are located anterior (medial) to the vertical plane defined by the spinal accessory nerve. Sublevel II_B nodes are located posterior (lateral) to the vertical plane defined by the spinal accessory nerve. The upper jugular nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, and parotid gland (see Fig. 121-3).
Middle jugular (level III)	Lymph nodes located around the middle third of the internal jugular vein, extending from the inferior border of the hyoid bone above to the inferior border of the cricoid cartilage below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx (see Fig. 121-3).
Lower jugular (level IV)	Lymph nodes located around the lower third of the internal jugular vein, extending from the inferior border of the cricoid cartilage above to the clavicle below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk of harboring metastases from cancers arising from the hypopharynx, thyroid, cervical esophagus, and larynx (see Fig. 121-3).
Posterior triangle (sublevels V_A and V_B)	This group is composed predominantly of the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in the posterior triangle group. The superior boundary is the apex formed by the convergence of the sternocleidomastoid and trapezius muscles; the inferior boundary is the clavicle, the anterior (medial) boundary is the posterior border of the sternocleidomastoid muscle, and the posterior (lateral) boundary is the anterior border of the trapezius muscle. Sublevel V_A is separated from sublevel V_B by a horizontal plane marking the inferior border of the anterior cricoid arch. Thus sublevel V_A includes the spinal accessory nodes, whereas sublevel V_B includes the nodes that follow the transverse cervical vessels and the supraclavicular nodes (with the exception of Virchow's node, which is located in level IV). The posterior triangle nodes are at greatest risk for harboring metastases from cancers arising from the nasopharynx, oropharynx, and cutaneous structures of the posterior scalp and neck (see Fig. 121-3).
Anterior compartment (level VI)	Lymph nodes in this compartment include the pretracheal and paratracheal nodes, the precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerves. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, and the lateral boundaries are the common carotid arteries. These nodes are at greatest risk for harboring metastases from cancers arising from the thyroid gland, glottic and subglottic larynx, apex of the piriform sinus, and cervical esophagus (see Fig. 121-2).
Superior mediastinum (optional—level VII)	These nodes represent an extension of the paratracheal lymph nodes chain extending inferiorly below the suprasternal notch along each side of the cervical trachea to the level of the innominate artery.

Table 121-3

Imaging-Based Classification of Location of Lymph Nodes

Level	Boundary	Clinical	Radiologic	Surgical
Level I				
Sublevel I_A (submental)	Superior	Symphysis of mandible	Geniohyoid muscle, plane tangent to inferior border of mandible	Symphysis of mandible
	Inferior	Body of hyoid	Body of hyoid	Body of hyoid
	Lateral (posterior)	N/A	Anterior belly of ipsilateral digastric muscle	Anterior belly of ipsilateral digastric muscle
	Medial	N/A	Anterior belly of contralateral digastric muscle	Anterior belly of contralateral digastric muscle
Sublevel I_B (submandibular)	Superior	Body of mandible	Mylohyoid muscle, body of mandible	Body of mandible
	Inferior	Plane through hyoid bone	Inferior edge of the hyoid bone	Digastric tendon attachment to hyoid bone
	Lateral (posterior)	Anterior border of SCM	Posterior edge of the submandibular gland	Posterior edge of the submandibular gland
	Medial	N/A	Anterior belly of digastric muscle	Anterior belly of digastric muscle
Level II (upper jugular)				
II_A	Superior	Mastoid process	Skull base, caudal edge of C1 lateral process	Skull base
	Inferior	Horizontal plane defined by the inferior border of the hyoid bone	Horizontal plane defined by the inferior border of the hyoid bone	Carotid bifurcation
	Lateral (posterior)	N/A	Posterior border of the internal jugular vein	Vertical plane defined by the spinal accessory (XI) nerve
	Medial	Anterior border of SCM	Posterior edge of the submandibular gland	Posterior edge of the submandibular gland
II_B (submuscular recess)	Superior	Mastoid process	Skull base, caudal edge of C1 lateral process	Skull base
	Inferior	Horizontal plane defined by the inferior border of the hyoid bone	Horizontal plane defined by the inferior border of the hyoid bone	Carotid bifurcation
	Lateral (posterior)	Lateral border of SCM	Lateral border of SCM	Lateral border of SCM
	Medial	N/A	Medial edge of internal carotid artery, paraspinal (levator scapulae) muscle	Vertical plane defined by the spinal accessory (XI) nerve
Level III (midjugular)				
	Superior	Horizontal plane defined by the inferior border of the hyoid bone	Horizontal plane defined by the inferior border of the hyoid bone	Carotid bifurcation
	Inferior	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage	Omohyoid muscle
	Lateral (posterior)	Lateral border of SCM	Lateral border of SCM	Sensory branches of the cervical plexus
	Medial	Medial border of SCM	Medial aspect of the common carotid artery, paraspinal (scalenus) muscle	Sternohyoid muscle

Continued

Table 121-3

Imaging-Based Classification of Location of Lymph Nodes—cont'd

Level	Boundary	Clinical	Radiologic	Surgical
Level IV				
	Superior	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage	Omohyoid muscle
	Inferior	Clavicle	2 cm cranial to sternoclavicular joint	Clavicle
	Lateral (posterior)	Lateral border of SCM	Lateral border of SCM	Sensory branches of the Cervical plexus
	Medial	Medial border of SCM	Medial aspect of the common carotid artery, paraspinal (scalenus) muscle	Sternohyoid muscle
Level V (posterior triangle)				
V_A	Superior	Apex of the convergence of the sternocleidomastoid and trapezius muscle	Apex of the convergence of the sternocleidomastoid and trapezius muscle	Apex of the convergence of the sternocleidomastoid and trapezius muscle
	Inferior	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage
	Lateral (posterior)	Anterior border of trapezius muscle	Anterior border of trapezius muscle	Anterior border of trapezius muscle
	Medial	Lateral border of SCM	Lateral border of SCM	Sensory branches of the Cervical plexus
V_B	Superior	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage	Horizontal plane defined by the inferior border of the cricoid cartilage
	Inferior	Clavicle	Clavicle	Clavicle
	Lateral (posterior)	Anterior border of trapezius muscle	Anterior border of trapezius muscle	Anterior border of trapezius muscle
	Medial	Lateral border of SCM	Lateral border of SCM	Sensory branches of the Cervical plexus
Level VI (anterior or central)				
	Superior	Hyoid bone	Hyoid bone	Hyoid bone
	Inferior	Superior edge of the manubrium sternum bone	Superior edge of the manubrium sternum bone	Superior edge of the manubrium sternum bone
	Lateral (posterior)	Common carotid artery	Medial aspect of the common carotid artery	Common carotid artery
	Medial	Common carotid artery	Medial aspect of the common carotid artery	Common carotid artery
Optional—Level VII (superior mediastinal)				
	Superior	Superior edge of the manubrium sternum bone	Superior edge of the manubrium sternum bone	Superior edge of the manubrium sternum bone
	Inferior	N/A	Innominate artery	Innominate artery
	Lateral (posterior)	N/A	Innominate artery and left common carotid artery	Innominate artery and left common carotid artery
	Medial	N/A	Innominate artery and left common carotid artery	Innominate artery and left common carotid artery

SCM, sternocleidomastoid.

Figure 121-3. Radical neck dissection; the boundaries of dissection are depicted by the heavy line. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

Technique

POSITIONING. The patient is positioned supine on the table with the shoulder roll placed to optimally extend the neck. The skin is prepped and draped to allow for full exposure of both sides of the neck with clear visualization of surrounding landmarks (e.g., the lower face including the mentum, both mastoid processes, earlobes) and the clavicles and suprasternal notch inferiorly. In this way the incision may be mapped in an accurate fashion, and throughout the procedure, overall orientation may be maintained.

INCISION PLANNING. The incision is planned for optimal exposure of all lymph node levels to be dissected (levels I to V) and to preserve as much blood supply as possible. The neck flaps raised should be broadly based, either superiorly or inferiorly, and preferably to avoid any trifurcations, particularly overlying the carotid sheath. Incisions that best fit these criteria are the hockey stick and boomerang patterns; the McFee incision; and, in patients undergoing bilateral neck dissection, the apron incision, which is a bilateral hockey stick incision (Fig. 121-4). Other incisions use trifurcations that overlie the carotid sheath, although modifications of the Schobinger incision include placing the trifurcation more laterally based. Although the boomerang incision may be somewhat less aesthetically pleasing, it is an excellent alternative to use in conjunction with oral cavity and oropharyngeal tumors wherein exposure of the primary site involves extending the incision through the lip for a mandibulotomy approach.

FLAP ELEVATION. The initial incision is carried through skin and platysma muscle, although the platysma is deficient in the midline and the lateral-most parts of the incision. This anatomic feature can be used to reapproximate the flaps at the time of closure because the platysmal muscle edges serve as "natural hash marks." The flap is raised in the subplatysmal plane so that the external jugular vein and the greater auricular nerves are not included in the flap (Fig. 121-5A). Although these structures will ultimately be sacrificed in the radical neck dissection, in SND procedures, they are routinely preserved. When there is gross pathologic evidence of tumor extension through the platysma muscle, with or without skin involvement, the area of disease involvement should also be removed and modifications of the skin flap may be required. Identification of the mandibular branch of the facial nerve is performed after complete elevation of the skin flaps superiorly and inferiorly to expose all of the lymph node levels of the neck. It is recommended that the anterior facial vein be ligated and retracted superiorly to protect this nerve only after the superior skin flap is raised. This allows proper assessment of the prevascular and postvascular lymph nodes in the submandibular triangle, which will need to be removed. Therefore it is best to incise the submandibular fascia at the lower border of the submandibular gland and to carefully raise this fascia off of the submandibular gland superiorly to the level of the lower border of the mandible as a separate flap. Usually the mandibular branch of the facial nerve may be seen as this fascia is raised (see Fig. 121-5B).

DISSECTION OF THE POSTERIOR TRIANGLE. The subsequent order of dissection is a matter of individual preference, although there is some oncologic rationale for dissecting from below upward rather than from above downward. Thus the next step is to expose the anterior border of the trapezius muscle from its superior aspect, where it converges with the posterior border of the sternocleidomastoid muscle, to its inferior aspect, where it approaches the clavicle (see Fig. 121-5C). The fibrofatty tissue is then incised along its anterior border beginning superiorly and working inferiorly to expose the muscular floor of the posterior triangle. In so doing, the spinal accessory nerve will be severed at the point at which it enters the trapezius muscle in the lower aspect of the posterior triangle. After this step has been completed, the floor of the posterior triangle at its inferior extent is next exposed by incising through the fibrofatty tissue immediately above the superior border of the clavicle. This requires incising through the inferior belly of the omohyoid muscle and the fibrofatty tissue overlying the brachial plexus. In this region, the transverse facial artery will be encountered immediately overlying the muscular floor of the triangle; this artery should be preserved unless there is gross disease involving the region. The fibrofatty contents of the posterior triangle are then mobilized anteriorly, lifting them away from the floor of the neck, which, in this region, is formed by the splenius capitis, levator scapulae, and scalene muscles. It is important to remain superficial to the prevertebral fascia during this step of the operation to prevent injury to the phrenic nerve and the brachial plexus. As the fibrofatty tissue is swept in a lateral-to-medial direction, the sensory branches of the cervical plexus will be encountered and divided.

ANTERIOR TRIANGLE DISSECTION. As the fibrofatty tissue is elevated medially toward the carotid sheath, it will be necessary to incise the mastoid attachment of the sternocleidomastoid muscle and the clavicular attachments (see Fig. 121-5D). The carotid sheath will be exposed, and identification of the common carotid artery and vagus nerve may be made. Attention should be given to preserving the cervical sympathetic chain, which is closely applied to the prevertebral fascia behind the carotid sheath. The plane of dissection will be carried between the vagus nerve and the carotid artery below and the internal jugular vein above. Thus the internal jugular vein may be mobilized from the skull base superiorly to its inferior aspect near the clavicle; ties may then be placed around the upper and lower ends of the internal jugular vein, thereby allowing ligation and complete mobilization. When incising the soft tissue contents of the lower medial aspect of the neck, lymphatic channels will be encountered, particularly on the left side. It is imperative to precisely identify these and ligate them immediately as they are encountered. The thoracic duct is located to the right of and behind the left common carotid artery and the vagus nerve. From here, it arches upward, forward, and laterally, passing behind the internal jugular vein and in front of the anterior scalene muscle and the phrenic nerve; it then opens into the internal jugular vein, subclavian vein, or angle formed by the junction of these two vessels. The duct is anterior to the thyrocervical trunk and the transverse cervical artery. To prevent a chyle leak, the surgeon should also remember that the thoracic duct may be multiple in its upper end and that, at the base of the neck, it usually receives the jugular trunk, a subclavian trunk, and maybe other minor lymphatic trunks that should be individually divided and ligated or clipped.

After ligation of the lower part of the internal jugular vein, the contents of the mobilized specimen are retracted superiorly and medi-

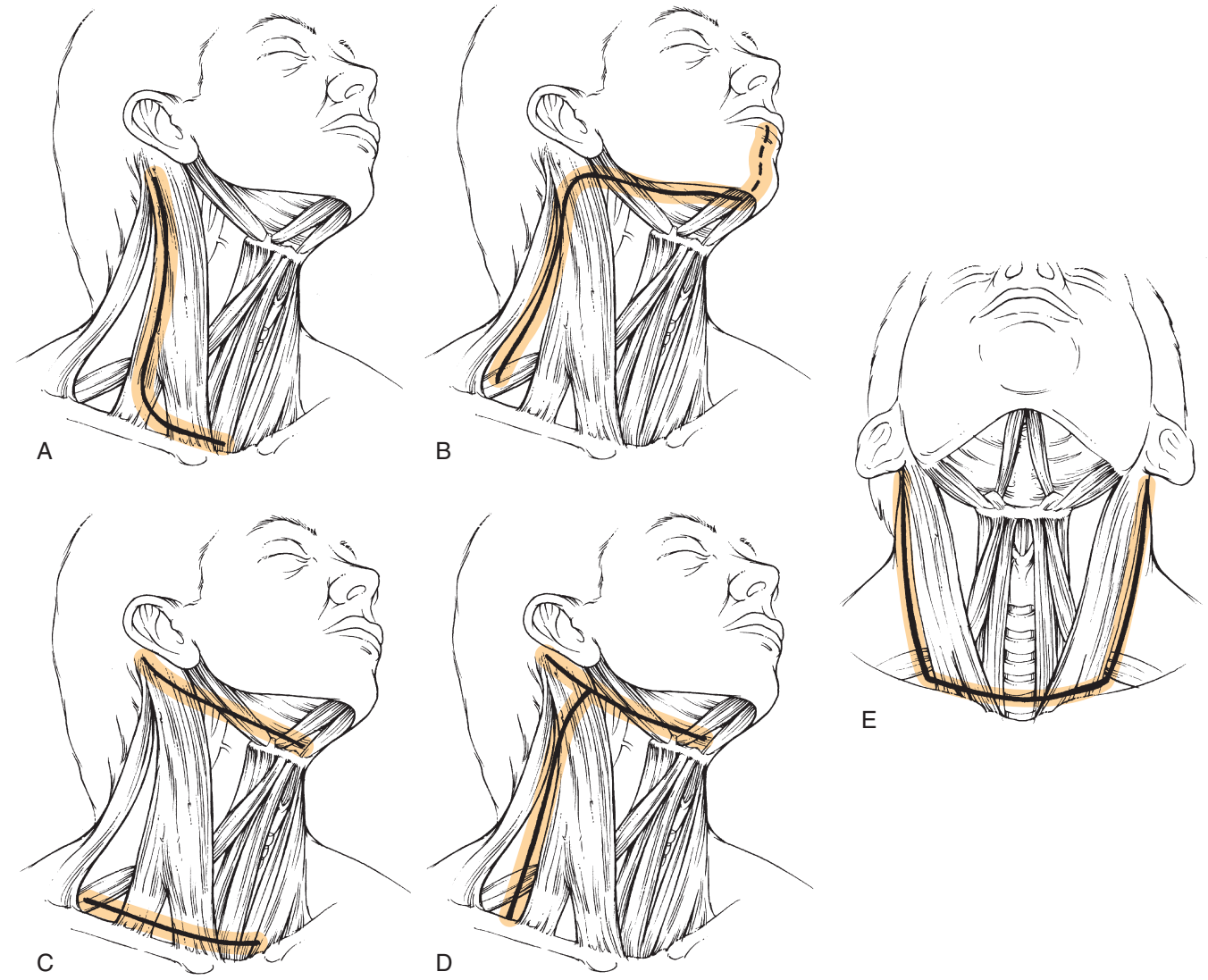


Figure 121-4. Incisions for radical and modified radical neck dissections. **A,** Hockey stick. **B,** Boomerang. **C,** McFee. **D,** Modified Schobinger. **E,** Apron or bilateral hockey stick. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

ally. Dissection is carried along the common carotid artery and medially as far as the sternohyoid muscle. Further elevation of the contents exposes the carotid bifurcation. As this is done, the branches of the internal jugular vein require identification and ligation. Specifically, these are the middle and superior thyroid veins and the retromandibular vein. Further superior elevation of the fibrofatty contents away from the upper part of the carotid sheath exposes the hypoglossal nerve lying lateral to the external carotid artery and the spinal accessory nerve extending from above downward.

At this point, the posterior belly of the digastric muscle is identified, and the soft tissue attachments of the neck contents lying superior to the muscle are divided, including the sternocleidomastoid muscle as it attaches to the mastoid process, vascular channels extending into the postauricular region and parotid gland, the tail of the parotid gland that extends downward inferior to the level of the digastric muscle, and soft tissue attachments to the angle of the mandible. After completion of this part of the dissection, all of the lower contents of the neck dissection specimen should be freely mobile, and the only remaining attachments are the upper end of the internal jugular vein and the undissected contents of the submandibular triangle and the submental triangle (see Fig. 121-5E).

DISSECTION OF THE UPPER NECK COMPARTMENTS. Excision of level I lymph nodes is begun by dividing the soft tissue overlying the body of the mandible including the facial artery and vein as they emerge above the submandibular gland and extend lateral to the body of the mandible. The anterior bellies of the ipsilateral and contralateral digastric muscles are skeletonized, thereby delineating the boundaries of the submental triangle. After the fibrofatty tissue has been removed from occupying this space, the fibrofatty contents of the anterior portion of the submandibular triangle are removed from the underlying mylohyoid muscle until its lateral border may be identified. The lateral border of the muscle is then retracted anteriorly, exposing the deep contents of the submandibular triangle. This allows for visualization of the lingual nerve, submandibular duct, and hypoglossal nerve. The submandibular duct is isolated, divided, and ligated. Next, the submandibular ganglion should be divided, thus allowing the lingual nerve to retract superiorly away from the area of dissection. Care is taken to not injure the hypoglossal nerve and its venae comitantes in the deep portion of the triangle. The last attachment of the contents of the submandibular triangle is the proximal end of the facial artery as it courses deep to the submandibular gland. It is important to remember that complete excision of all contents of the submandibular triangle within its muscular boundaries—and not just the submandibular gland—is required.

Variations in the approach to the radical neck dissection should be made, depending on the location of the disease and its degree of mobility. For example, it is best to mobilize the areas that are least involved with a tumor that is difficult to remove, which will enhance

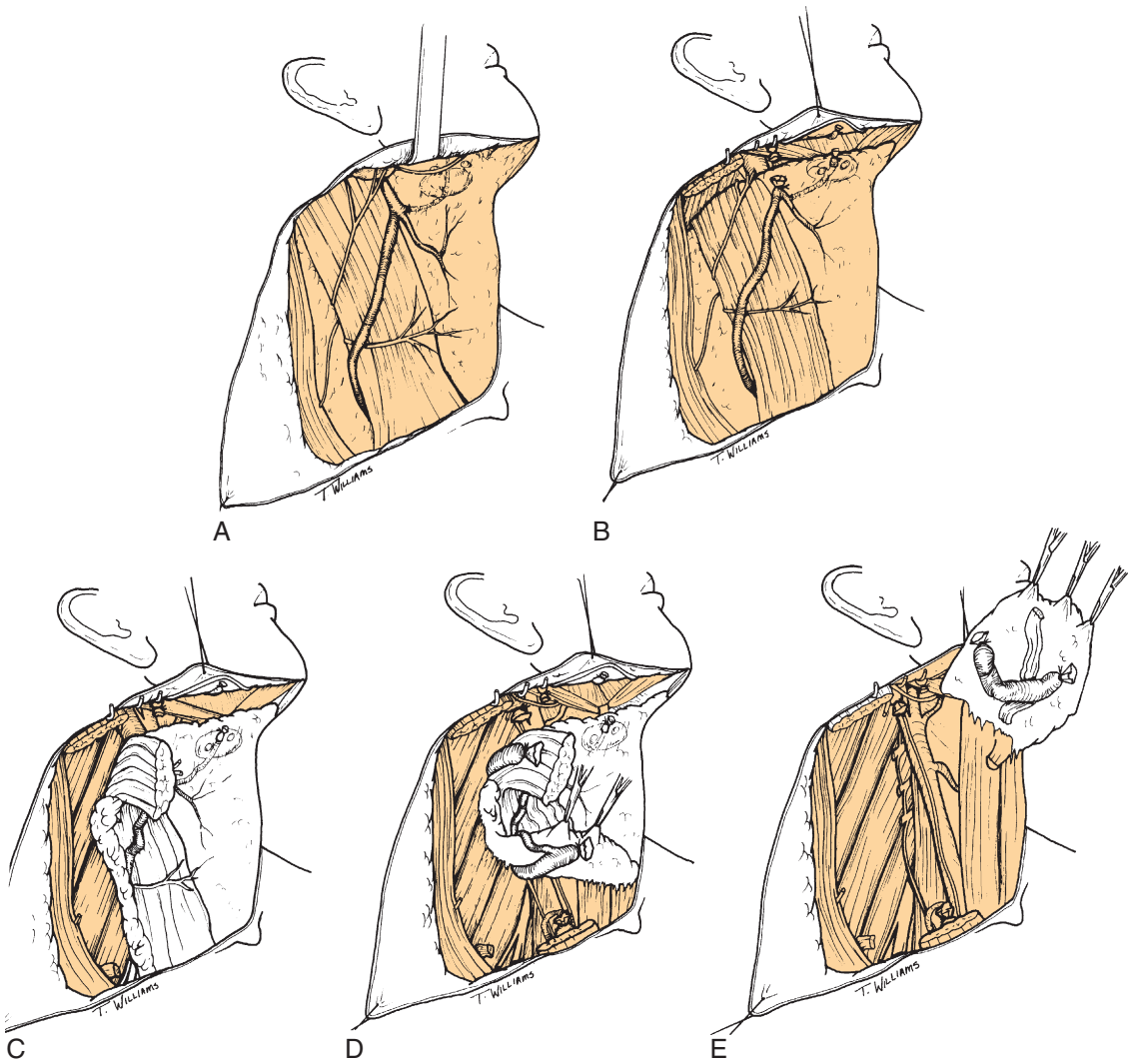


Figure 121-5. Steps of the radical neck dissection. (See text for discussion.)

the exposure of the anatomic structures that may be directly invaded by the disease itself.

Neck drains are inserted and brought through separate stab incisions through the most dependent areas of the dead space. Closure of the incisions are usually performed in two layers, including approximation of the platysma anteriorly and the subcutaneous tissue laterally and the second layer approximating the skin.

Modified Radical Neck Dissection

DEFINITION. A modified radical neck dissection is defined as the en bloc removal of lymph node–bearing tissue from one side of the neck (levels I to V). The dissection extends from the inferior border of the mandible above to the clavicle below and from the lateral border of the strap muscles medially to the anterior border of the trapezius muscle laterally. Unlike the radical neck dissection, there is preservation of one or more of the following structures in the modified radical dissection: spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle (Fig. 121-6). The major purpose of these modifications relates to the morbidity encountered when the spinal accessory nerve is removed. Although the degree of morbidity is less for removal of the sternocleidomastoid muscle and the internal jugular vein, this issue becomes far more important if bilateral neck dissections are required. Simultaneous sacrifice of both internal jugular veins may result in severe swelling of the face with increased intracranial pressure.

INDICATIONS. The major indication for a modified radical neck dissection is to remove grossly visible lymph node disease, particularly if there is involvement of several levels, that is not directly infiltrating or fixed to the nonlymphatic structures. It is difficult to justify the sacrifice of the spinal accessory nerve if it is not directly involved with disease when the hypoglossal nerve and the vagus nerve, which also lie in similar proximity to nodal disease, are spared.

TECHNIQUE. Knowledge of the surgical anatomy of the spinal accessory nerve is essential to preserve this structure. Below the jugular foramen, the spinal accessory nerve is located deep to the digastric and stylohyoid muscles and lateral or immediately posterior to the internal jugular vein; it then runs obliquely downward inferiorly and posteriorly to reach the medial surface of the sternocleidomastoid muscle near the junction of the superior and middle third. It traverses this muscle, giving off a major branch to it. The remaining part of the nerve then exits the posterior border of the sternocleidomastoid muscle near the area known as *Erb's point,* where the four superficial branches of the cervical plexus—the greater auricular, lesser occipital, transverse cervical, and supraclavicular nerves—emerge from behind the muscle. This point is located approximately at the junction of the upper and middle thirds of this muscle. From here, the spinal accessory nerve courses through the posterior triangle of the neck to enter the anterior border of the trapezius muscle at a point located approximately at the junction of the middle and lower thirds of the anterior border of this muscle.

The incisions and skin flaps are raised for modified radical neck dissection as similarly described for the radical neck dissection. The same procedure is followed to identify and protect the mandibular branch of the facial nerve in level I.

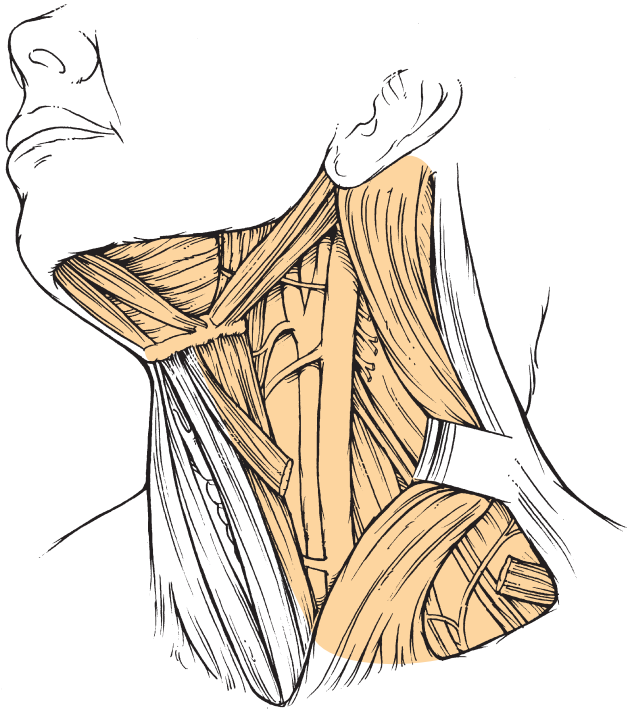


Figure 121-6. Boundaries of the modified radical neck dissection, in which there is preservation of the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

Unlike what is found in the radical neck dissection procedure, the next step is to identify the spinal accessory nerve. This is initially done in the posterior triangle from which the nerve exits at or around Erb's point (Fig. 121-7A). The nerve lies superficially in the fibrofatty contents of the posterior triangle and usually may be identified by careful spreading of the fibrofatty tissue; the use of a nerve stimulator may assist this process. Once located, the nerve is isolated and dissected away from the underlying fibrofatty contents from Erb's point medially to the point at which it enters the anterior border of the trapezius muscle laterally (see Fig. 121-7B). The nerve is next isolated in its superior third, which is done by incising the anterior border of the sternocleidomastoid muscle from its attachment superiorly at the mastoid to its lowermost attachment at the sternal head. The sternocleidomastoid muscle is retracted laterally as the fibrofatty soft tissue contents anterior to this muscle are dissected away from it, and the many arcades of small blood vessels coursing between the muscle and the soft tissue are divided. This part of the procedure mobilizes the anterior aspect of the sternocleidomastoid muscle along its full extent. As the muscle is retracted laterally in its upper portion, the spinal accessory nerve is seen entering its deep surface (see Fig. 121-7C). From this point, the nerve is traced superiorly by dividing the overlying fibrofatty contents until the posterior belly of the digastric muscle is identified. This muscle is retracted superiorly to gain exposure to the superior end of the internal jugular vein near the jugular foramen. The posterior border of the sternocleidomastoid muscle may be freed completely from the underlying fibrofatty contents all the way from its mastoid attachment above to its clavicular attachment below. Except for its course through this muscle, the spinal accessory nerve is now completely mobilized from its entry into the anterior border of the trapezius muscle below to its superior extent at the skull base above.

The fibrofatty tissue in the posterior triangle is separated from the entire anterior border of the trapezius muscle and is mobilized from a lateral to a medial direction. Tissue lying superficial to the spinal accessory nerve as it courses across the posterior triangle should be divided immediately above the spinal accessory nerve so that it may be passed along with its deep component beneath the nerve and the elevated sternocleidomastoid muscle (see Fig. 121-7D). After the fibrofatty contents have been dissected and swept over the carotid artery, vagus nerve, and internal jugular vein, the sternocleidomastoid muscle may be retracted laterally and the contents passed underneath the muscle for subsequent dissection of the anterior triangle of the neck (see Fig. 121-7E). Careful sharp dissection will allow for separation of these contents from the carotid artery and the jugular vein. This dissection is continued until the sternohyoid muscle, which is the medial boundary of anterior triangle contents in the lower neck, is reached. The branches of the internal jugular vein are usually ligated to allow a thorough clearance of the anterior triangle contents. Dissection is carried superiorly to remove the fibrofatty tissue attachments overlying the internal jugular vein at the level of the skull base. The retromandibular vein may be preserved, but the anterior facial vein needs to be ligated (see Fig. 121-7F). Subsequent dissection is then performed to remove the contents of the submandibular and submental triangles.

Sacrifice of one or two of the nonlymphatic structures of the neck (i.e., spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein) may become necessary as a result of gross involvement by cancer intraoperatively, although the operation continues to be called a modified radical neck dissection as long as at least one of these structures is preserved (Fig. 121-8).

Selective Neck Dissection (see Key Indicator Video on website)

DEFINITION. SND is performed for patients who are at risk for early lymph node metastases. The procedure consists of the en bloc removal of one or more lymph node groups that are at risk for harboring metastatic cancer, an assessment that is based on the location of the primary tumor. Thus the levels removed depend on the location of the primary lesion and its known pattern of spread.

RATIONALE. Although the concept of SND dates back to procedures used for treating lip cancer, its broader adoption to treat other cancers of the upper aerodigestive tract was popularized by surgeons at the MD Anderson Cancer Center.[20] It was based on removing lymph node groups that were at highest risk in patients with N_0 nodal disease. Studies have shown that this procedure has the same therapeutic value as more extensive neck dissections[16]; it is also intended to preserve functionally and cosmetically relevant structures as a secondary goal.

The topographic distribution of lymph node metastases appears to be predictable in patients with previously untreated squamous cell carcinoma of the head and neck, particularly in those with early disease. The basic anatomic studies of Rouviere[35] and Fisch and Sigel[36] showed that lymphatic drainage of the mucosal surfaces of the head and neck follow relatively constant and predictable routes. The clinical study by Lindberg in 1972[12] showed that the lymph node groups most frequently involved in patients with carcinoma of the oral cavity are the jugulodigastric and midjugular nodes. In addition, the nodes in the submandibular triangle are frequently involved in patients with carcinoma of the floor of the mouth, the anterior oral tongue, and the buccal mucosa. Lindberg also noted that tumors frequently metastasize to both sides of the neck and may skip the submandibular and jugulodigastric nodes, metastasizing first to the midjugular region. The Lindberg study showed that, in the absence of metastases to the first echelon nodes, tumors of the oral cavity and oropharynx rarely involve the lower jugular and posterior triangle nodes. Similar findings were reported by Skolnik in 1976,[14] who, in a study of radical neck dissection specimens, found no metastases in the nodes of the posterior triangle of the neck in radical neck dissections, regardless of the site of the primary tumor or the presence or absence of metastases in the jugular nodes. Further evidence subsequently has been provided by Shah[25] in a retrospective study of radical neck dissection specimens performed for patients with oral cavity and larynx or laryngopharyngeal metastases. Shah demonstrated that tumors of the oral cavity metastasize most frequently to neck nodes in levels I, II, and III, whereas carcinomas of the pharynx, hypopharynx, and larynx involve mainly the nodes in levels II, III, and IV. Whenever nodes were found in other areas, there was also positive disease in the areas of highest risk.

Some authorities believe that SND is, in essence, a procedure for staging the necks of patients whose tumors are amenable to treatment

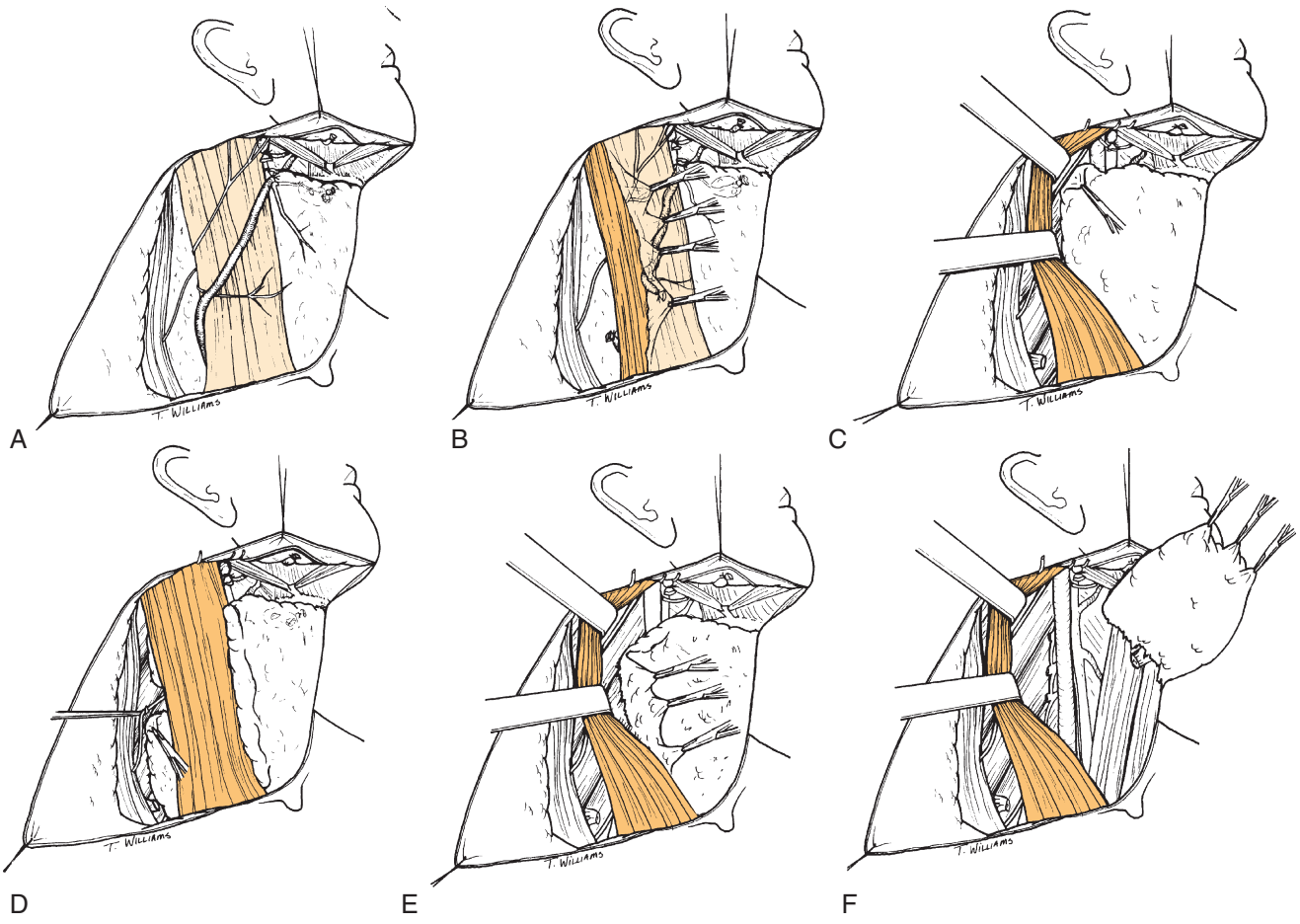


Figure 121-7. A-F, Steps of the modified radical neck dissection, in which there is preservation of the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle.

with surgery alone. In patients who have this procedure done in conjunction with the excision of the primary tumor, further information about the status of the nodal disease is provided. If there is evidence of multiple lymph node metastases or extracapsular spread in the neck dissection contents, then postoperative radiotherapy is indicated. Byers and colleagues[37] also reported a lower rate of regional recurrence among patients with N_1 disease if postoperative radiation therapy was administered. More intensive therapy may be used for patients who have more aggressive tumors.

Selective Neck Dissection for Oral Cavity Cancer

DEFINITION AND RATIONALE. The procedure of choice is SND (levels I to III) and is often called the supraomohyoid neck dissection. The procedure involves the removal of lymph nodes contained in the submental and submandibular triangles (level I), the upper jugular lymph nodes (level II), and the midjugular lymph nodes (level III). The cutaneous branches of the cervical plexus and the posterior border of the sternocleidomastoid muscle mark the posterior limit of the dissection. The inferior limit is the junction between the superior belly of the omohyoid muscle and the internal jugular vein.

SND is recommended for patients with oral cavity cancer who are at risk of harboring occult nodal disease (Fig. 121-9). Also, SND can be performed for patients with low-volume nodal disease (N_1) located in the upper neck provided that postoperative radiation therapy is part of the treatment plan. Tumors originating in this region, particularly in the subsites of the oral tongue and the floor of the mouth, have a high propensity to metastasize early, regardless of size and differentiation. Primary echelons for nodal spread include the submental, submandibular, upper jugular, and middle jugular groups. In patients with tongue cancer, the lower jugular lymph node groups (level IV) are also at risk.[38] Even when there is no clinical evidence of nodal disease, there is at least a 20% risk for occult disease associated with these lesions. Unless the management of choice for the primary lesion is radiotherapy, elective neck dissection with removal of levels I through III (level IV for those with tongue cancer) is the minimal recommended treatment for patients with squamous cell carcinoma of the oral cavity associated with N_0 nodal disease. For patients with palpable nodal disease, it is usually necessary to perform a modified radical neck dissection, but a selective removal of levels I through IV is an appropriate alternative when the nodal disease is confined to levels I and II. With the possible exception of a solitary metastatic node without extracapsular extension, postoperative radiation therapy is usually indicated for all patients undergoing SND who have positive pathologic nodes in the specimen.[37] Elective cervical lymphadenectomy of the contralateral neck is indicated for patients with primary lesions involving the floor of the mouth or the ventral surface or with midline involvement of the tongue, in whom ipsilateral neck dissection is planned and in whom there are no definite indications for postoperative radiotherapy. Contralateral therapeutic neck dissection is indicated for patients with clinically N_{2c} disease.

TECHNIQUE. When an ipsilateral supraomohyoid neck dissection is planned, a modified apron incision is made to provide adequate exposure of levels I through III (Fig. 121-10A). If bilateral neck dissection is necessary, the horizontal component of the apron incision is carried across the midline to the other side of the neck (bilateral apron incision; see Fig. 121-10B). The ipsilateral and bilateral apron incisions are also appropriate for exposure of the primary disease when a pull-through exposure is indicated. When it is necessary to split the lip for access to the primary tumor, the medial component of the ipsilateral apron incision may be extended for this purpose. If bilateral neck dis-

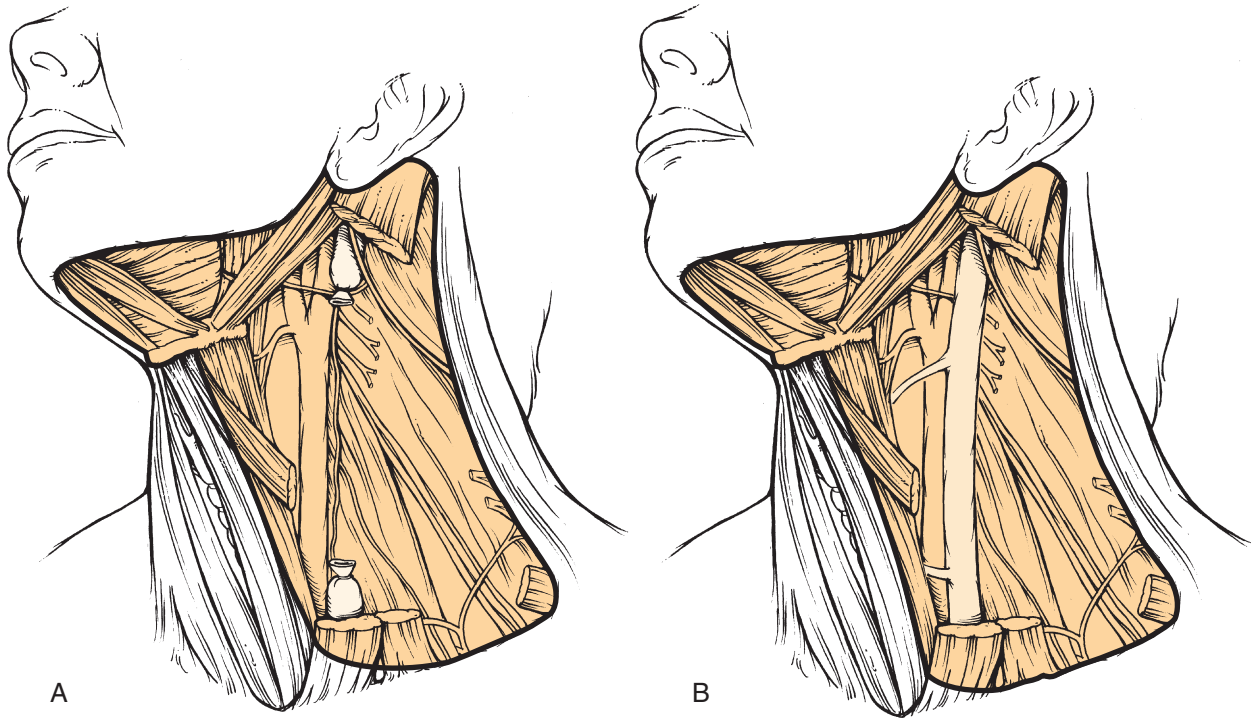


Figure 121-8. Modified radical neck dissection in which there is **A,** preservation of the spinal accessory nerve only, and **B,** preservation of the spinal accessory nerve and internal jugular vein. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

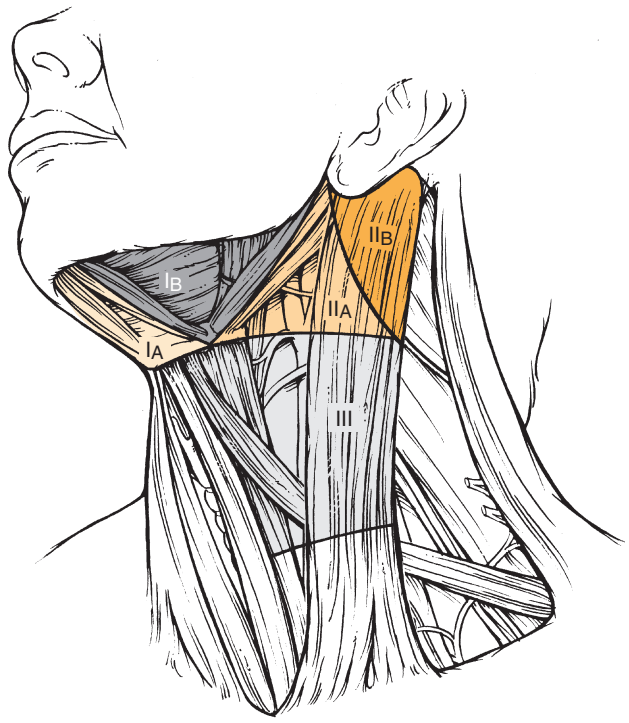


Figure 121-9. Boundaries of the selective neck dissection for oral cavity cancer, selective neck dissection (*I* to *III*) or supraomohyoid type. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

section is planned and a lip-splitting incision is also required, a bilateral boomerang incision is substituted for the bilateral apron incision (see Fig. 121-10C). This neck incision pattern is also preferred for those with more advanced nodal disease associated with oral cavity primaries in whom it is necessary to dissect all five levels of the ipsilateral neck. The boomerang incision is also preferred for patients with stage N_{2c} disease because it may be extended across the midline for exposure of all levels of the contralateral lymph nodes (see Fig. 121-10D).

For the removal of levels I through III, the modified apron skin flap is raised in the subplatysmal plane until there is exposure of the upper two thirds of the anterior border of the sternocleidomastoid muscle, mastoid process, body of the mandible, and mandibular symphysis (Fig. 121-11A and B). It is preferred not to raise the fascia off of the submandibular gland until the subplatysmal flap is first elevated to the level of the body of the mandible, which permits a more accurate assessment of the submandibular triangle for assessing tumor involvement of the superficial layer of the deep cervical fascia. After this possibility is excluded, the fascia overlying the submandibular gland is carefully raised as a separate flap to avoid injuring the mandibular branch of the facial nerve. This branch is often seen within the superficial layer of the deep cervical fascia, but, with careful dissection of this layer, the nerve may be protected and preserved.

Next, an incision is made in the investing layer of the deep fascia at the anterior border of the sternocleidomastoid muscle. Care is taken to not injure the external jugular vein and branches of the greater auricular nerve that lie lateral to the sternocleidomastoid muscle but posterior to the fascial incision being made. Because lymph nodes associated with the external jugular vein are almost never involved with aerodigestive tract carcinomas, these structures are left undisturbed. The fibrofatty contents of the anterior triangle are peeled away first from the anterior border and then from the medial aspect of the sternocleidomastoid muscle all the way from a point close to the mastoid process above down to the level of the omohyoid muscle below, stopping when the posterior border of the muscle is reached. Although the upper third of the sternocleidomastoid muscle is being separated, the spinal accessory nerve comes into view as it enters the muscle (see Fig. 121-11C). This nerve is dissected free of its surrounding fibrofatty

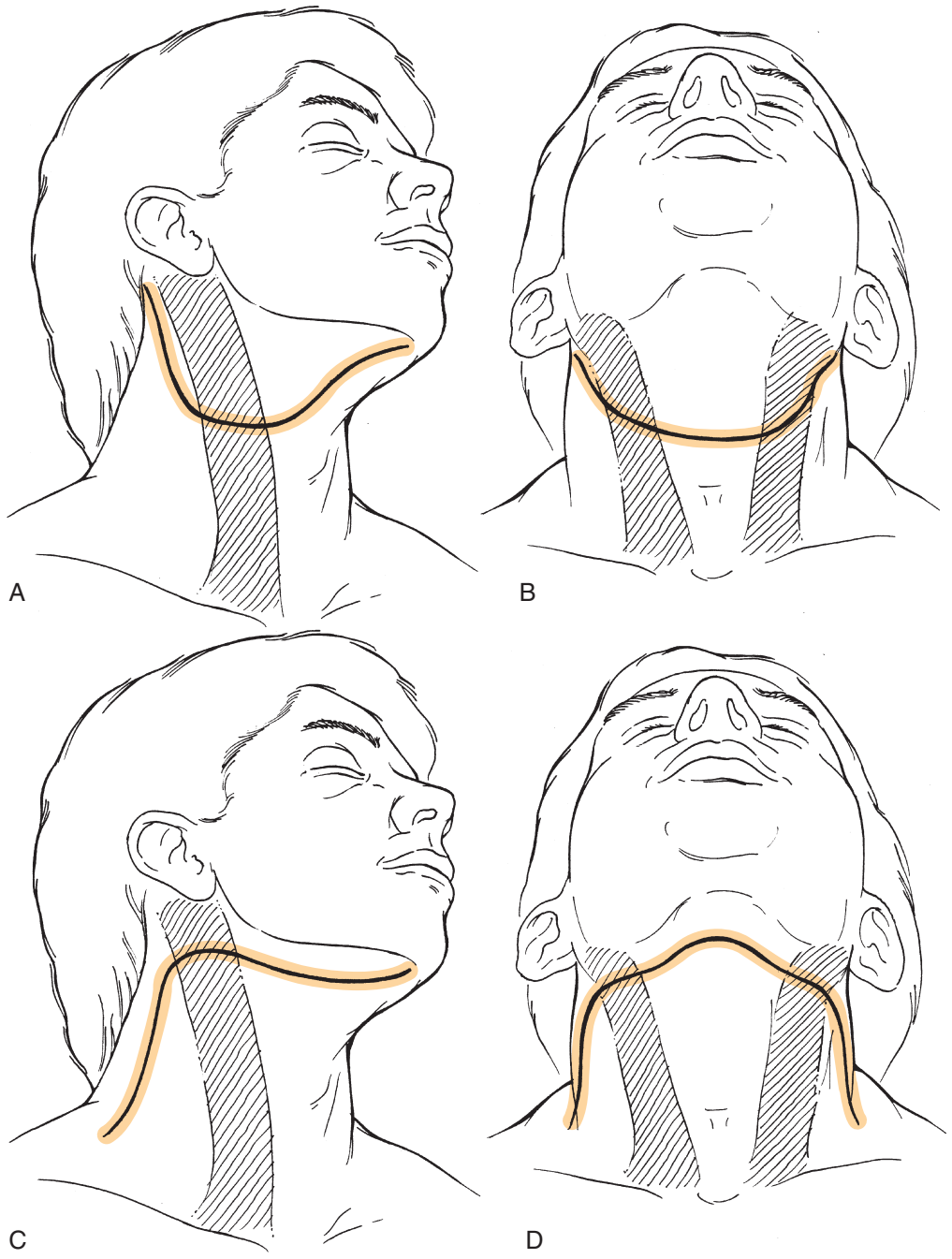


Figure 121-10. Incisions for selective neck dissection (*I* to *III*). **A,** Modified apron incision. **B,** Apron incision. **C,** Boomerang incision. **D,** Bilateral boomerang incision.

tissue from the level of the skull base adjacent to the internal jugular vein to its point of entry into the sternocleidomastoid muscle. It is necessary to dissect along the inferior border of the posterior belly of the digastric muscle and to retract it supralaterally to provide adequate exposure of the upper carotid sheath near the skull base. Fibrofatty tissue is also dissected away from the inferior border of the posterior belly of the digastric muscle as far posteriorly as the attachment of the mastoid process. This triangle formed by the digastric muscle, spinal accessory nerve, and sternocleidomastoid muscle outlines the triangular packet of tissue-bearing lymph nodes belonging to level II. It is important to separate this triangular packet from the underlying paraspinal muscles and to pass it under the spinal accessory nerve (see Fig. 121-11D). The dissection is continued inferiorly by incising along the fibrofatty tissue corresponding with the posterior border of the sternocleidomastoid muscle to the level of the omohyoid muscle. Care is taken to not cut across the sensory branches of the cervical plexus as the incision is carried down to the muscular floor. When the sensory branches of the cervical plexus are encountered, the fibrofatty tissue is dissected in a plane that is superficial to these nerves (see Fig. 121-11E). At this point in the procedure, it is important to carefully inspect and palpate the lower jugular chain and the posterior triangle for evidence of nodal disease. If found, the dissection of the lymph-node-bearing tissue would have to be extended to encompass level IV and the posterior triangle (level V), thus converting the operation to a modified radical neck dissection. For this purpose, a lower cervical flap would then be raised for adequate exposure of the clavicle and the anterior border of the trapezius.

After completion of the lateral boundary of dissection, the lymph node–bearing tissue is swept medially in a plane immediately above the fascia of the paraspinal muscles. The sensory branches of the cervical

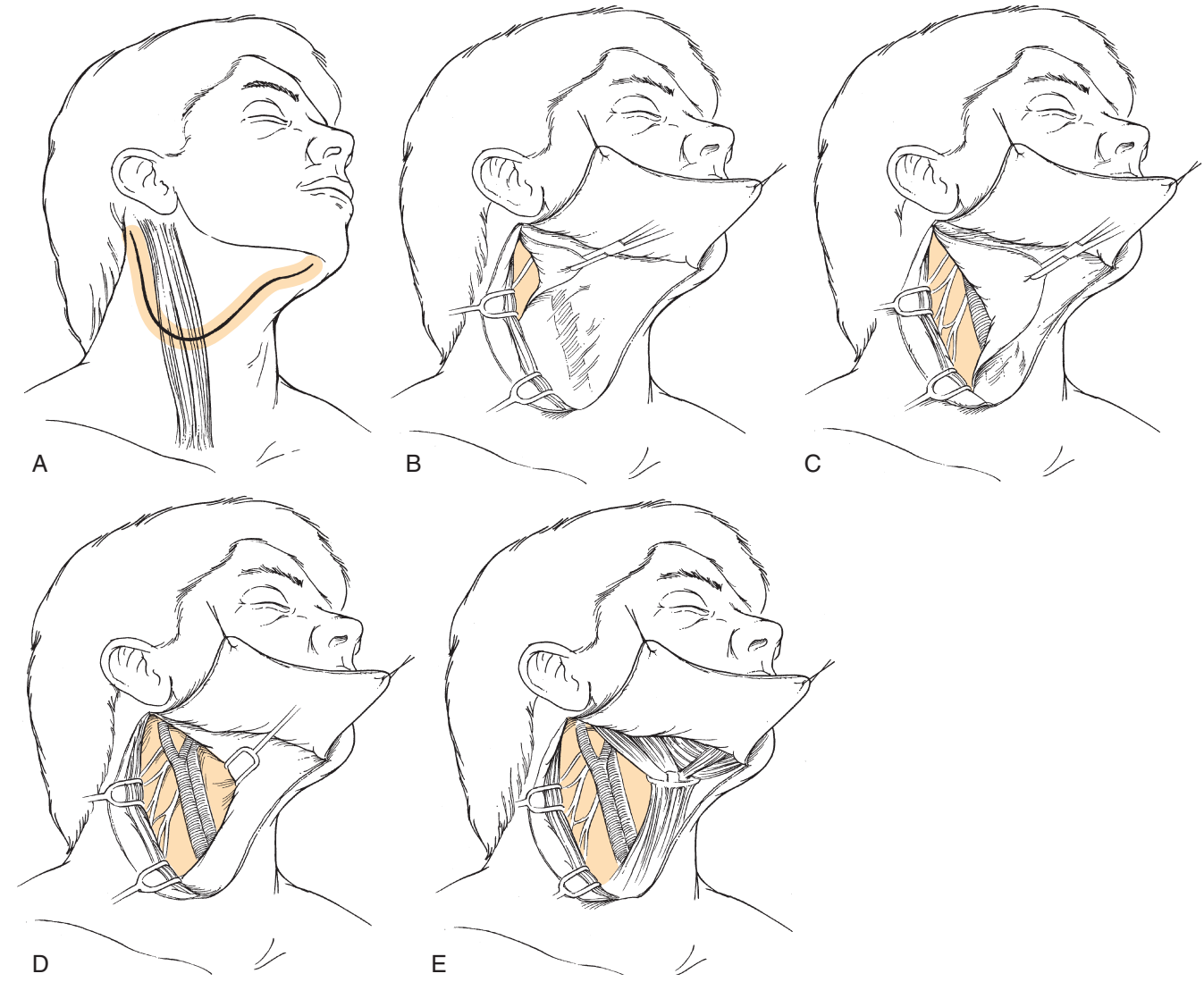


Figure 121-11. Steps of the selective neck dissection for oral cavity cancer (SND *I* to *III*). **A,** Modified apron incision. **B,** Flap raised in the subplatysmal plane to expose the upper two thirds of the carotid sheath and the submandibular and submental triangle; exposure of the upper third of the spinal accessory nerve and dissection of the submuscular recess (level IIB). **C,** Dissection of level III and preservation of the cervical plexus. **D,** Completion of the dissection of levels III and IIA. **E,** Dissection of level I.

plexus may be preserved only when level V dissection is not performed. This maneuver allows the lymph node–bearing tissue to be swept over the carotid sheath and permits exposure of its structures from the level of the clavicle or omohyoid muscle below to the skull base above. Sharp dissection is used to remove the fascia overlying the sheath, which usually includes preserving the internal jugular vein if a tissue plane can be readily identified. Next, the superior belly of the omohyoid muscle is skeletonized along its superior border to the level of the hyoid bone. The hyoid bone is also skeletonized medially, as is the anterior belly of the contralateral digastric muscle; this completes the medial boundary of dissection. The fibrofatty tissue is dissected from below at the level of the omohyoid muscle in a superior direction toward the submandibular triangle. After the lymph node–bearing tissue in the submental triangle has been cleared, the contents of the submandibular triangle are removed to complete the neck dissection (see Fig. 121-11). To ensure complete removal of all lymph nodes from this region, it is important to dissect along the fascial planes of the muscles within this triangle rather than enucleate the submandibular gland only, which includes dissecting the preglandular nodes underneath the anterior belly of the digastric muscle and the prevascular and postvascular nodes along the lower border of the body of the mandible. It is usually not necessary to remove the perifacial nodes lying lateral to the mandibular body, unless the primary cancer involves the buccal mucosa, upper gum, or upper lip. Dissection of this latter nodal group increases the risk of injury to the mandibular branch of the facial nerve. After completion of the dissection, the excised tissue is separated according to the level of the lymph node groups, each level being submitted separately for pathologic evaluation. Before closing the incisions, a single drain is placed in the surgical bed extending inferiorly from the digastric muscle above to a separate cutaneous puncture site made at the most dependent region below the skin incision. The drain is placed on continuous suction. A second drain is placed in the contralateral neck for bilateral procedures. The drain is usually removed 3 days after surgery, if the fluid collection is less than 20 mL/24 hours.

Selective Neck Dissection for Oropharyngeal, Hypopharyngeal, and Laryngeal Cancer

DEFINITION AND RATIONALE. The procedure of choice for these anatomic sites is SND (levels II to IV), and its boundaries are outlined in Figure 121-12; it is also called a *lateral neck dissection.* The procedure refers to the removal of the upper jugular lymph nodes (level II), the midjugular lymph nodes (level III), and the lower jugular lymph nodes (level IV). The superior limit of dissection is the skull base, and the inferior limit is the clavicle. The anterior (medial) limit is the lateral

border of the sternohyoid muscle and the stylohyoid muscle. The posterior (lateral) limit of the dissection is marked by the cutaneous branches of the cervical plexus and the posterior border of the sternocleidomastoid muscle. In the case of cancers involving the oropharynx and the hypopharynx, there is evidence indicating that the lateral retropharyngeal nodes are also at risk. Level IIB is at greater risk for metastases associated with oropharyngeal lesions relative to laryngeal and hypopharyngeal cancers. Thus if level IIB is excluded (as is sometimes done for N_0 laryngeal and hypopharyngeal cancers), the procedure would be designated SND (IIA, III, and IV). When the risk for lymphatic metastases is bilateral, the procedure of choice is a bilateral SND (II to IV). If the retropharyngeal lymph nodes are included, as in the case of cancers involving the pharyngeal wall, the procedure is designated SND (II to IV, retropharyngeal nodes). If the nodes in level VI are removed, as in the case of laryngeal and hypopharyngeal cancers extending below the level of the glottis, the procedure is designated SND (II to IV and VI).

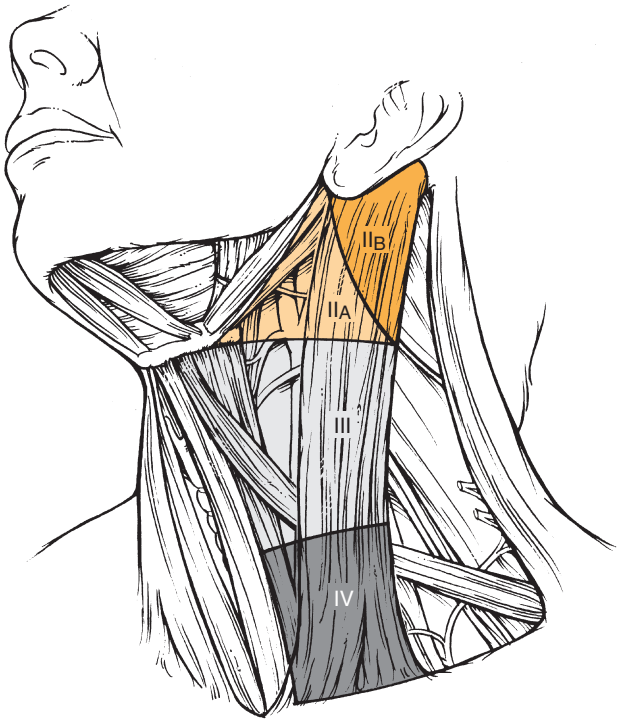


Figure 121-12. Boundaries of the selective neck dissection for oropharyngeal, laryngeal, and hypopharyngeal cancer, selective neck dissection (*II* to *IV*) or lateral type. (Redrawn from art provided courtesy of Douglas Denys, MD.)

It should be noted that there is a controversy over which selective neck dissection is indicated for an oropharyngeal cancer without known metastasis to the neck (N_0). Although the "classic" findings by Shah[25] and others[39-42] showed the pattern of lymph node to be involved is in levels II to IV, other studies have suggested that the levels at risk are I to III.[43,44] One possible explanation for this discrepancy could be the fact that it is easy to confuse nodes located posterior and deep to the submandibular gland with level IB, when in essence they are in level IIA. The same mistake could be done when dividing the specimen ex vivo into the different levels. Another possible explanation would be that an original oropharyngeal base of tongue cancer involves the oral tongue as well, thus putting level Ib at higher risk.

TECHNIQUE. The incision should allow for adequate exposure of levels II through IV and, should occult disease be found, exposure of level V as well. The hockey stick incision as described for radical and modified radical neck dissection is useful for this purpose; it may also be extended across the midline and carried along the contralateral neck as a broadly based apron flap or bilateral hockey stick incision (Fig. 121-13). After the neck flaps have been raised, the fibrofatty contents of the anterior triangle are removed en bloc, including the lymph nodes lying along the internal jugular vein from the skull base superiorly to the clavicle inferiorly. The dissection proceeds by incising along the anterior border of the sternocleidomastoid muscle and by separating it from its underlying attachments to the fibrofatty tissue. Care is taken to identify the spinal accessory nerve as it enters the anterior aspect of the sternocleidomastoid muscle. Then it is skeletonized from its entry point into the muscle inferiorly and into the skull base superiorly, wherein it lies deep to the posterior belly of the digastric muscle and lateral to the internal jugular vein. As described for the supraomohyoid neck dissection, the fibrofatty tissue deep to the sternocleidomastoid

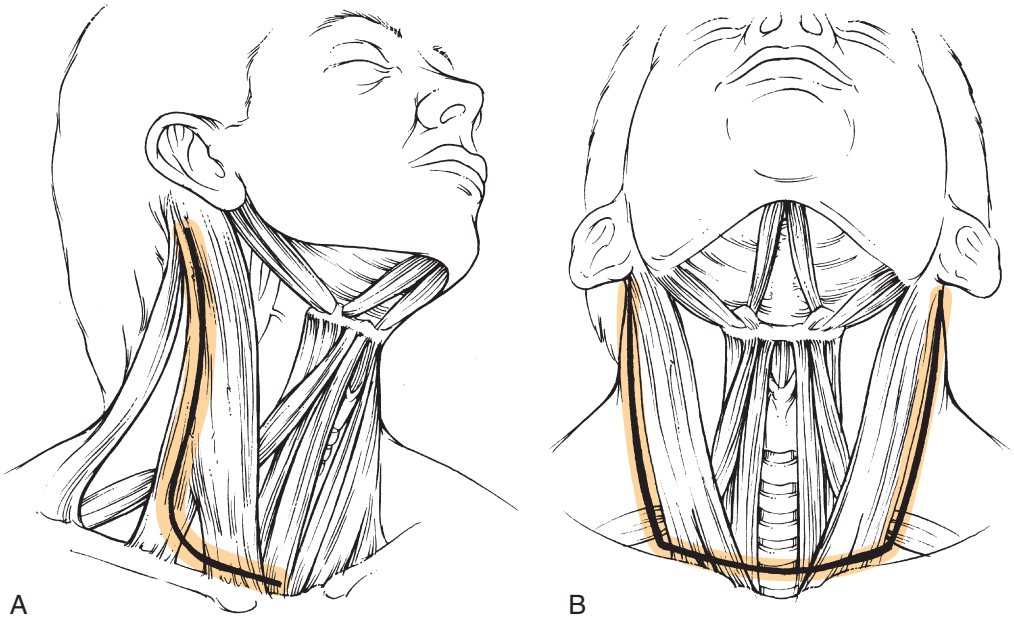


Figure 121-13. Incisions for selective neck dissection (*II* to *IV*). **A,** Hockey stick. **B,** Bilateral hockey stick. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

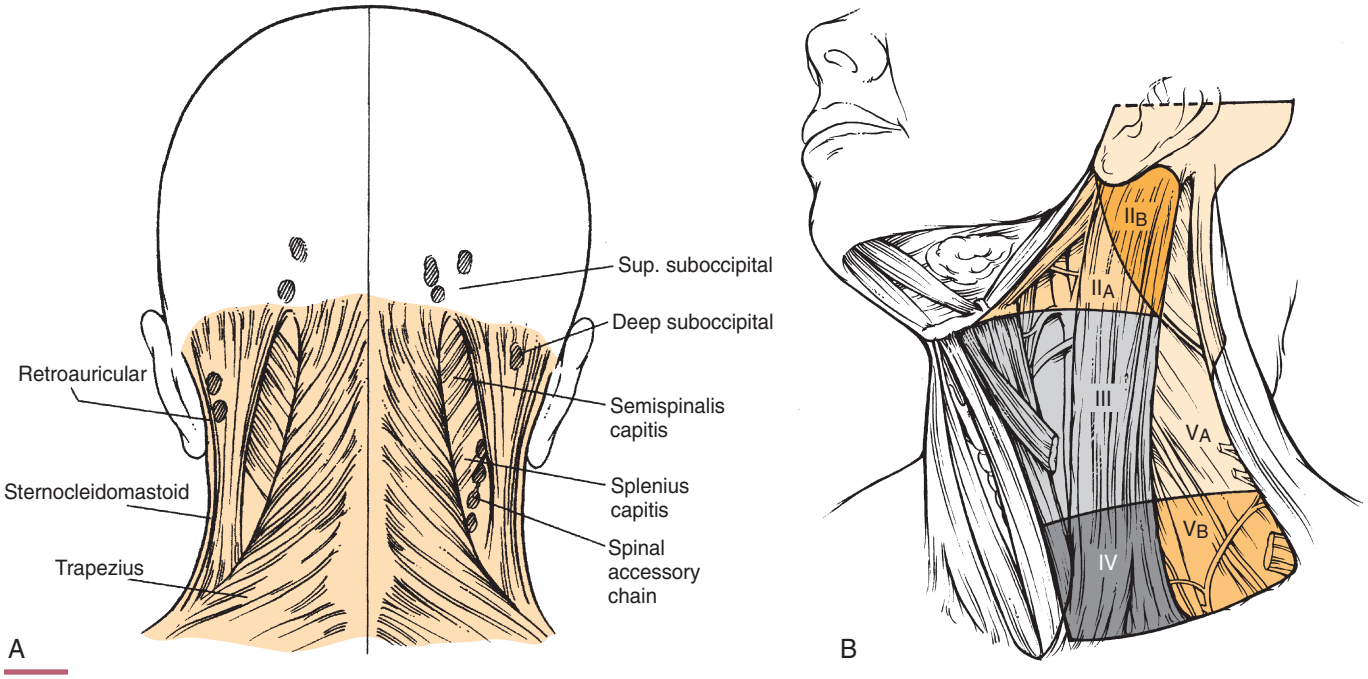


Figure 121-14. **A,** Localization of retroauricular and suboccipital lymph nodes. **B,** Selective neck dissection (SND) for posterior scalp and upper posterolateral cutaneous malignancies, SND (*II* to *V,* postauricular, suboccipital) or posterolateral neck dissection. *(**B,** Redrawn from art provided courtesy of Douglas Denys, MD.)*

muscle is incised and separated from the underlying splenius and levator muscles. The sensory branches of the cervical plexus may also be preserved by limiting the mobilization of fibrofatty tissue to the region superficial to these nerve branches. The contents are swept medially over the internal jugular vein, thereby exposing the full length of the vein from the skull base above to the clavicle below. At the lower end, care should be taken to meticulously identify and ligate any lymphatic channels encountered. On the left side, the thoracic duct will frequently be encountered; this structure must be carefully separated away from the fibrofatty tissue, avoiding any injury. If injury occurs, a repair must immediately be performed with fine, nonabsorbable suture material (e.g., silk, monofilament synthetic); occasionally this will necessitate ligation of the duct. After the internal jugular vein has been completely skeletonized, the remainder of the fibrofatty contents of the anterior triangle is mobilized by skeletonizing the medial border of the sternohyoid muscle and the stylohyoid muscle. The branches of the internal jugular vein in the neck may be sacrificed to assist this process, although the communicating branch to the anterior facial and retromandibular veins may be easily preserved.

Selective Neck Dissection for Cutaneous Malignancies

DEFINITION AND RATIONALE. The operation of choice depends on the location of the lesion and the adjacent lymph node groups, which are most likely to harbor metastatic disease. In the case of cancers involving the posterior scalp and upper neck, the procedure of choice is SND (II to V, postauricular, and suboccipital) (Fig. 121-14). This particular version is also called the posterolateral neck dissection; it is primarily used to eradicate nodal metastases associated with cutaneous malignancies and soft tissue sarcomas.[9]

It involves the removal of the suboccipital lymph nodes, retroauricular lymph nodes, upper jugular lymph nodes (level II), middle jugular lymph nodes (level III), lower jugular lymph nodes (level IV), and nodes of the posterior triangle of the neck (level V). The superior limit of dissection is the skull base anteriorly and the nuchal ridge posteriorly, and the inferior limit is the clavicle. The medial (anterior) limit is the lateral border of the sternohyoid muscle and the stylohyoid muscle; the lateral (posterior) limit is the anterior border of the trapezius muscle inferiorly and the midline of the neck superiorly. It is common to all sites that the lymphatic pathways for the seeding of tumor to the first and secondary echelon nodes involve the posterior auricular, occipital, posterior triangle, and jugular groups (see Fig. 121-14). Thus the dissection is designed to encompass the lymph node–bearing fibrofatty tissue of the posterior and lateral compartments of the neck. In addition, it is important to remove the intervening subdermal fat and underlying fascia between the lymph node groups and the primary disease, which ensures the removal of smaller nests of metastasizing tumor cells that are characteristic of malignancies originating in cutaneous soft tissue. For cutaneous malignancies arising on the preauricular, anterior scalp, and temporal regions, the elective neck dissection of choice is SND (parotid and facial nodes, levels IIA, IIB, III, and VA, and the external jugular nodes). For cutaneous malignancies arising on the anterior and lateral face, the elective neck dissection of choice is SND (parotid and facial nodes, levels IA, IB, II, and III). The development of techniques of lymphatic mapping may have a future role in specifically defining unpredictable lymphatic echelons of risk for cutaneous malignancies.

TECHNIQUE. The optimal incision for posterolateral neck dissection is one that allows exposure along the nuchal ridge to the occiput and the posterior triangle and exposure of the upper, middle, and lower jugular lymph node groups; this may usually be accomplished with a lazy S pattern or the combination of the hockey stick pattern with a horizontal extension from its upper aspect along the nuchal ridge. The patient should be placed in the lateral decubitus position to allow for adequate exposure of the posterior scalp and occiput. In patients with midline posterior scalp lesions, the procedure should encompass the nodal groups on both sides of the neck. In this latter situation, the patient should be placed in the prone position to allow access to both sides. The skin flaps are raised in the subplatysmal plane anteriorly and the subdermal plane posteriorly. The posterior auricular and suboccipital nodes are removed by incising the soft tissue overlying the fascia of the upper neck muscles that attach to the nuchal ridge and occiput. In addition, the upper part of the trapezius muscle that attaches to the skull base should be divided to allow for complete exposure of the suboccipital nodes; these nodes lie along the occipital artery as it courses laterally along the skull base. After completing this part of the dissection, the posterior triangle is cleared in the fashion that has already been described for the modified radical neck dissection. The spinal accessory nerve is routinely identified and preserved unless there is direct tumor

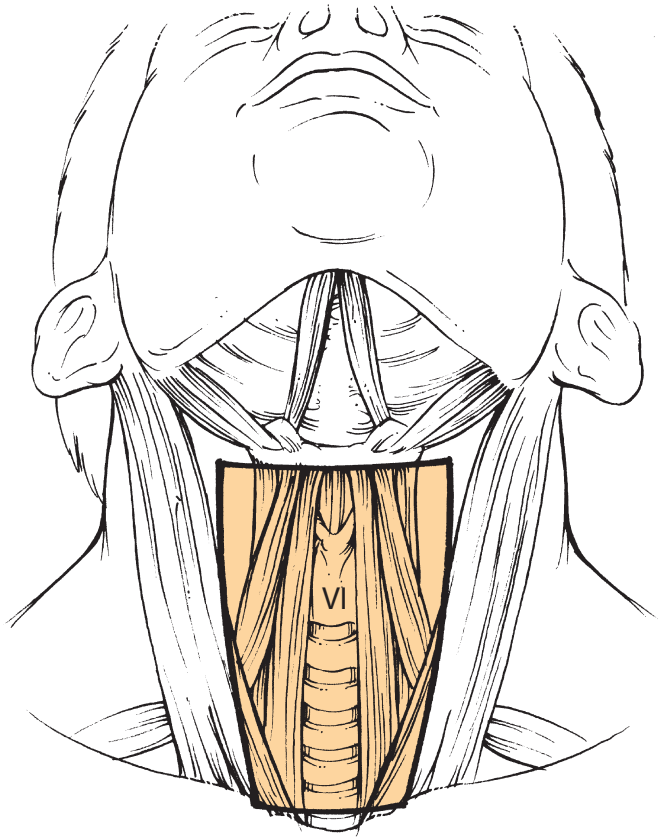


Figure 121-15. Boundaries of the selective neck dissection for thyroid cancer, selective neck dissection *(VI)* or anterior neck dissection. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

extension into the soft tissue surrounding it. The technique for locating and preserving the spinal accessory nerve has already been described. The remainder of the procedure involves mobilizing the fibrofatty contents of the anterior triangle, thereby removing the upper, middle, and lower jugular groups of lymph nodes. The technique for this procedure has already been described.

Selective Neck Dissection for Cancer of the Midline Structures of the Anterior Lower Neck

DEFINITION AND RATIONALE. The procedure of choice is SND (level VI) and is often called the *anterior neck dissection* or the *central compartment dissection* (Fig. 121-15). The procedure is most often indicated with or without dissection of other neck levels for thyroid cancer, advanced glottic and subglottic larynx cancer, advanced piriform sinus cancer, and cervical esophageal/tracheal cancer. This refers to the removal of the lymph nodes within the central compartment of the neck including the paratracheal, precricoid (Delphian), and perithyroidal nodes and the nodes located along the recurrent laryngeal nerves. The superior limit of dissection is the body of the hyoid bone, and the inferior limit is the suprasternal notch; the lateral limits are defined by the medial border of the carotid sheath (the common carotid artery). This neck dissection does not have a contralateral counterpart, and it assumes that the lymph nodes are removed on both sides of the trachea. In the case of metastases extending below the level of the suprasternal notch, dissection of the superior mediastinal nodes may be indicated, in which case the procedure is designated SND (VI, superior mediastinal nodes or the optional VII). Exposure of this latter region may require removing the manubrium and possibly one or both sternal heads of the clavicles.

In the case of thyroid cancer in which there is evidence of nodal metastases into level V, the procedure of choice would include the jugular nodes, as well as the posterior triangle nodes, and would be designated SND (II to V, VI).

In patients with unilateral laryngeal and hypopharyngeal lesions, the dissection of level VI may be confined to one side of the compartment, provided that there is no evidence of nodal metastases involving the contralateral side. In this way, the morbidity of disrupting the blood supply to the parathyroid glands or reimplanting them may be avoided.

TECHNIQUE. If there is an indication to dissect the lateral and posterior neck compartments, this procedure is done first. Then the strap muscles are either divided near the attachments at the sternum or mobilized and retracted laterally. The carotid artery is skeletonized along its medial border as far superiorly as the superior thyroid artery (Fig. 121-16A). The ipsilateral lobe of the thyroid gland is mobilized along its lateral border by dividing the fascia and its arterial and venous supply (see Fig. 121-16B). The recurrent laryngeal nerve is identified inferiorly as it courses the tracheoesophageal groove. If the larynx is to be removed, protection of the nerve is unnecessary. The fibrofatty contents of each side of the anterior compartment then may be removed by excising all of the loose areolar tissue located between the carotid artery laterally and the trachea medially (see Fig. 121-16C); the thyroid lobe also is removed as part of this en bloc resection (see Fig. 121-16D). The parathyroid glands should be identified and reimplanted into the sternocleidomastoid muscle. If it is necessary to completely remove nodal-bearing tissue from the entire anterior compartment, the procedure is completed on the contralateral side of the trachea. Thus a total thyroidectomy is performed, and all of the parathyroid glands are reimplanted. The dissection is carried superiorly as far as the hyoid bone and inferiorly as far as the suprasternal notch. If there is evidence of nodal disease at the lower end of the trachea, a more thorough cleanout of the superior mediastinum may be achieved by splitting the sternum or removing the manubrium and one or more clavicular heads.

Extended Neck Dissection

Any of the neck dissections described previously may be extended to remove either lymph node groups or vascular, neural, or muscular structures that are not routinely removed in a neck dissection. A neck dissection may be extended to remove the retropharyngeal lymph nodes on one or both sides when the primary tumor originates in the pharyngeal walls. Ballantyne[45] found a 44% incidence of retropharyngeal node involvement in a group of patients with carcinomas of the pharyngeal wall who were treated surgically. Tumors of the base of the tongue, the tonsil, the soft palate, and the retromolar trigone may also spread to these lymph nodes when they involve the lateral or posterior walls of the oropharynx. Adequate removal of a metastatic tumor in the neck may dictate the need to extend a neck dissection to resect structures such as the hypoglossal nerve, levator scapulae muscle, or carotid artery.

Controversy still exists about the advisability of resecting the common or the ICA (Fig. 121-17). Some surgeons believe that it is not justified to resect these arteries in patients with squamous cell carcinoma of the upper aerodigestive tract because of the associated morbidity and because the prognosis of patients with disease in the neck that is extensive enough to warrant such a resection is dismal.[46] For example, Moore and Baker[47] observed a mortality rate of 30% and a cerebral complication rate of 45% among patients who underwent carotid ligation; it should be noted that these figures included elective and emergency ligation. In a study of 28 patients who had tumors grossly excised by "peeling" them off of the carotid artery, Kennedy and colleagues[48] found that only 18% developed a recurrence in the neck without distant metastases; this observation led the authors to state that only this small group of patients may have benefitted from carotid resection. Goffinet and colleagues[49] reported encouraging results for patients with large cervical metastases attached to the carotid artery who were by the resection of the tumor and intraoperative iodine[125] seed suture implants over the remaining carotid artery. Tumor control was obtained in the neck in 77% of the patients, although only 15% of them were alive and free of disease after 1 year. There are surgeons who advocate resecting the common artery or the ICA when the extent of disease dictates it; they believe that current methods of assessing the adequacy of cerebral circulation on the basis of the contralateral carotid system allow for better preoperative patient selection.[50-52] These

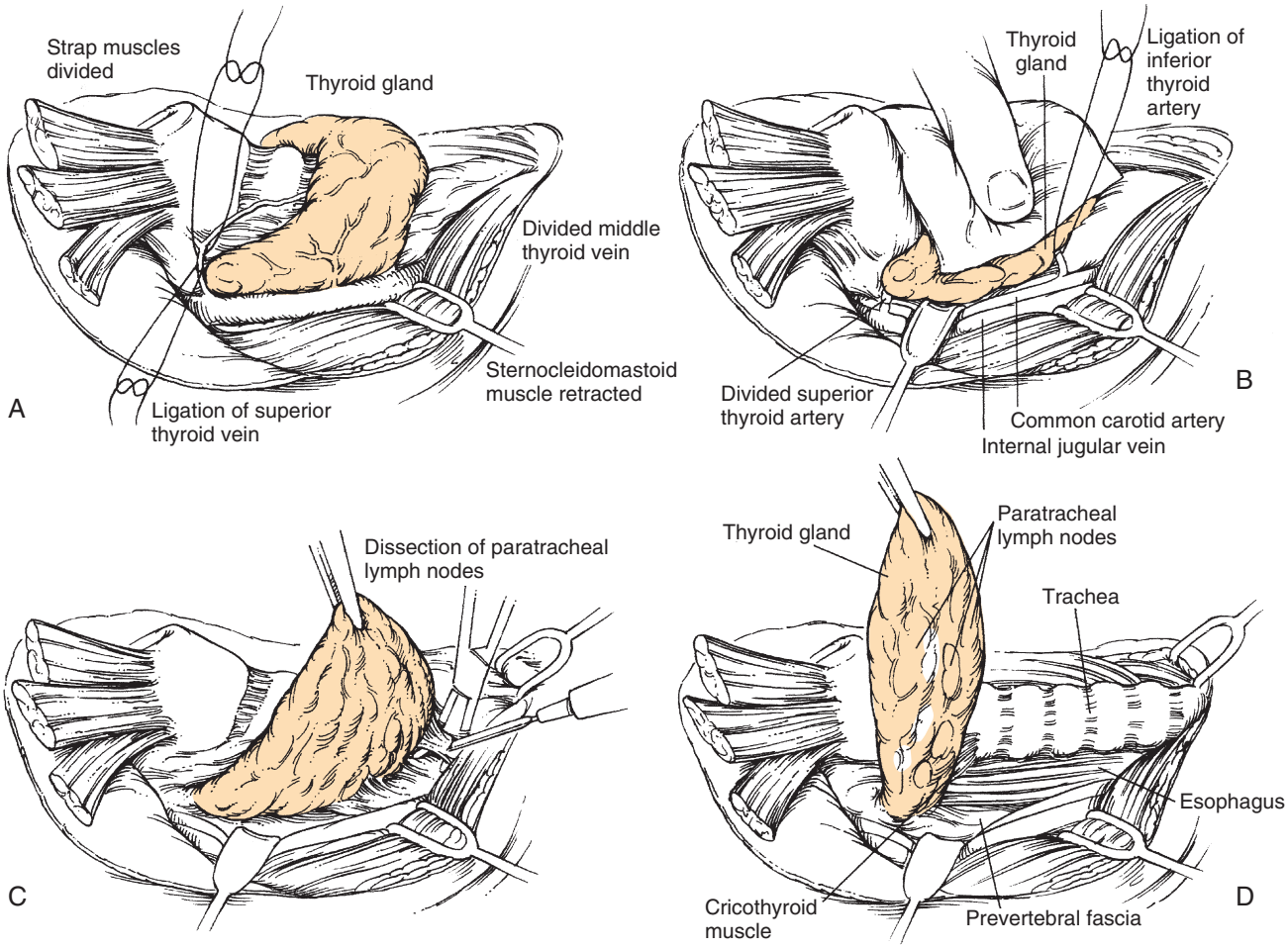


Figure 121-16. Steps of the selection neck dissection *(VI)*. See text for discussion.

Figure 121-17. Extended radical neck dissection, with resection of the common carotid artery. *(Redrawn from art provided courtesy of Douglas Denys, MD.)*

beliefs—coupled with improved techniques for vascular and soft-tissue reconstruction—have made it possible to resect the carotid artery with acceptable morbidity. McCready and colleagues[53] reported their observations in 16 patients who underwent carotid artery resection for the management of advanced carcinomas of the head and neck. Only two patients (12%) developed postoperative cerebrovascular complications, and seven patients (45%) were free of disease at 1 year. Others have reported similar results.[50,52] Patients with frank involvement of the carotid wall whose preoperative examination indicates intolerance of carotid ligation should have carotid resection and reconstruction. Saphenous vein grafts are preferred over prosthetic grafts for reconstruction, and, if the skin has been heavily radiated or a portion of the skin over the carotid is resected, a myocutaneous flap should be used to cover the graft.[54,55]

If carotid artery resection is considered preoperatively, then endovascular balloon occlusion of the ICA with physiologic assessment will strongly predict the potential for stroke and the need for revascularization.[56,57] An angiogram is performed, and an intravascular balloon placed in the ICA. The patient is heparinized, and the balloon is inflated to occlude the ICA. A second catheter in the contralateral carotid artery is used for an intracranial angiogram to assess the patency of collateral flow through the circle of Willis to the hemisphere in jeopardy. The demonstration of an excellent crossover flow through a patent anterior communicating artery, along with symmetric venous filling bilaterally, is predictive of a low probability of stroke if the ICA is sacrificed, and there is no indication for revascularization. If the angiogram is questionable, then occlusion may be maintained for 30 minutes, hypotension induced, and the patient observed clinically. Alternatively, a functional cerebral blood flow study such as intra-arterial xenon, xenon inhalation computed tomography scan, or single-photon emission computed tomography scan can be performed to

assess functional cerebral blood flow to the hemisphere in jeopardy. If studies suggest that the patient will not tolerate ICA sacrifice, then consideration should be given to surgery designed to salvage the ICA, or a revascularization procedure should be employed.

Revascularization procedures may be within the bed of the tumor resection if proximal and distal ends of the carotid artery and ICA remain. Artificial versus saphenous vein interposition grafts can be used, depending on previous or future radiation therapy and wound infection potential. ICA revascularization procedures continue to be practiced in select neurosurgical cases, particularly in those involving extracranial to intracranial bypass grafting, with good results seen at select centers.[56,57]

Patients with significant atheromatous disease pose an interesting dilemma with regard to planned cervical dissections. A history of any embolic symptoms will increase the risk of stroke with carotid vessel manipulation at surgery. If carotid salvage is planned as a part of the procedure, then preoperative stenting should be considered before cervical dissection, or endarterectomy should be performed at the time of surgery, if anatomy allows. Asymptomatic carotid bifurcation disease should be managed by careful intraoperative manipulation, with vessel preservation dictated by the surgical expectations.

Results of Neck Dissection

Radical Neck Dissection

Obviously the best results reported for patients undergoing radical neck dissection are those in whom the presence of histologically positive metastatic disease is not evident. In this scenario, 3% to 7% of patients will have disease recur in the ipsilateral neck.[58] When radical neck dissection is used as a therapeutic procedure, there is a range of regional control rates. An appropriate analysis of results should, therefore, involve the consideration of several factors related to the degree of nodal involvement and whether the primary tumor remains under control.

The presence of extracapsular spread is an important prognostic factor with regard to recurrence in the neck after neck dissection.[59,60] In addition, the degree of extracapsular involvement is also important. For example, Carter and colleagues[46] reported a 44% recurrence rate for macroscopic extracapsular spread versus a 25% rate for microscopic extracapsular spread. In addition, the number of lymph nodes involved by tumor has also been found to correlate with the rate of recurrence. Patients with four or more involved nodes had a dramatically worse 4-year survival rate than patients with only one involved node.[61] Strong also reported that the level of nodal involvement had prognostic importance, observing a recurrence rate in the neck of 36.5% in patients with positive nodes in one level versus 71% in patients with positive nodes in multiple levels.[62] Remember that the use of adjuvant radiotherapy is considered by most to improve the rate of control in the neck after neck dissection.[58,63]

Modified Radical Neck Dissection

The rate of recurrence in the neck after modified radical neck dissection depends on the amount of disease to which the procedure was applied. When used as an elective procedure for patients with clinically N_0 disease, the rate of recurrence varies between 4% and 7%. However, when this procedure is used therapeutically for patients with clinically positive disease, the recurrence rate in the dissected neck varies between 0% and 20%. In some of these reports, preoperative or postoperative radiation was also used. These results indicate that, in selected patients, modified radical neck dissection is an attractive alternative to radical neck dissection.[16,58]

Selective Neck Dissection

Data indicating the effectiveness of SND for the control of regional metastases related to upper aerodigestive tract carcinoma are available. For supraomohyoid neck dissection, Byers[16] reported a regional recurrence rate of 5.8% for 154 patients with pathologic N_0 disease, 24 of whom received postoperative radiotherapy. The rate of regional disease control for 80 patients with pathologic positive nodal disease was 15%; 62 of these patients had multiple positive nodes, and 61% had postoperative radiotherapy. In a later review of the MD Anderson experience, Medina and Byers[51] found the recurrence rate to be 5% among patients with pathologic N_0 disease, 10% when a single nodal metastases without extracapsular spread was found, and 24% when multiple positive nodes or extracapsular spread was found. Postoperative radiotherapy decreased the recurrence rate to 15% in the group with multiple nodes or extracapsular spread.

For patients undergoing lateral neck dissection, Byers[16] reported a regional recurrence rate of 3.9% among 256 patients with pathologic N_0 disease, 126 of whom received postoperative radiotherapy. Among the 41 patients with pathologic positive nodal disease, 37 of whom had postoperative radiotherapy, 7.3% had regional recurrences.

The data indicating relatively low regional recurrence rates for patients with clinical N_0 neck disease support the effectiveness of SND procedures for patients with upper aerodigestive tract carcinoma. Of greater controversy is whether the procedures are effective for patients with node-positive disease. Pelliteri and colleagues[64] found the regional recurrence rate for patients with pathologic positive nodal disease to be 11.1% among 27 patients undergoing a supraomohyoid neck dissection and 4.8% among 21 patients who had a lateral neck dissection. These results, along with those reported by Byers[16] and Medina and Byers,[51] indicate that the SND is feasible for a defined subset of patients with positive nodal disease. Postoperative radiotherapy is recommended for patients with multiple nodal disease or extracapsular spread. More recently, the efficacy of SND for clinically positive neck disease has been demonstrated by others.[65-67] In 2002 Andersen and colleagues[68] reported a 10-year, multi-institutional, retrospective review of pooled data from 106 previously untreated clinically and pathologically node-positive patients undergoing 129 SNDs and followed for a minimum of 2 years or until patient death. Overall, nine patients experienced disease recurrence in the neck, for a regional control rate of 94.3%. Six of these recurrences were in the areas of the neck that had been dissected during the SND. The authors concluded that these results support the use of SND in carefully selected patients with clinically positive nodal metastasis from head and neck squamous cell carcinoma (HNSCC). Regional control rates comparable with those achieved with the radical and modified radical neck dissections could be achieved in appropriately selected patients. The main advantages of the use of SND are that surgical time is shortened and morbidity—especially with regard to shoulder dysfunction—is decreased.

Among patients previously treated with radiotherapy or other types of neck surgery, most surgeons prefer to perform neck dissections that encompass all five neck levels when salvage surgery is feasible. However, emerging data support the use of SND as part of the planned treatment for patients with bulky neck disease whose primary tumor and regional nodes were initially treated with definitive radiation therapy or chemoradiation.[69,70] Nigauri and colleagues[71] failed to find evidence of skip metastases outside of levels II and III among 217 patients with squamous cell carcinoma of the oropharynx who were treated with radiation therapy. These authors recommended SND for patients with N_1 disease, whereas modified radical neck dissection or radical neck dissection was recommended for patients with N_2 or N_3 disease. Boyd and colleagues[72] analyzed 25 patients with squamous cell carcinoma of the oropharynx, nasopharynx, hypopharynx, and supraglottic larynx who had been treated with radiation therapy. Among the 28 necks dissected (all but one patient had N_2 or N_3 disease), only one had a tumor outside of levels II through IV. On the basis of this, SND was recommended for patients with disease in all pharyngeal sites who required salvage or planned neck surgery after radiation therapy. Efficacy of targeted chemoradiation and planned SND to control bulk nodal disease in advanced neck cancer has been reported by Robbins and colleagues.[73] In addition, Clayman and colleagues[74] have used SND after chemoradiotherapy for oropharyngeal cancer in patients with advanced nodal disease. Thus it may be that, in the future, SND will play a more definitive role in the overall management of patients with initial bulky neck node disease with head and neck cancer that has been treated with nonsurgical modalities; however, further evidence is necessary.

Lymphoscintigraphy-Directed Neck Dissection

A potentially powerful adjunct to surgical treatment of the neck is lymphoscintigraphy and sentinel lymph node biopsy. This technique,

which was pioneered by Morton and colleagues[7] for use in detecting the lymphatic spread of cutaneous melanoma, capitalizes on the ability of nuclear radiography to identify primary, secondary, and tertiary echelons of lymphatic drainage basins and to identify the index or "sentinel" lymph node associated with primary regions within the head and neck. It is minimally invasive, and it possesses the capacity to accurately stage the clinically occult neck in a number of different neoplasms.[75] Linking this diagnostic and staging modality to lymphadenectomy or other elective treatment of the neck in mucosal carcinomas represents an attractive concept that has recently been explored by Pitman and colleagues[76] at the University of Pittsburgh. These investigators examined the feasibility of identifying the sentinel lymph node in primary echelons of drainage from known primary neoplasms through lymphoscintigraphy and sentinel lymph node biopsy, thus enabling one to stage the N_0 neck in a minimally invasive manner and to direct elective neck therapy accordingly. On the basis of findings with both N_0 and N_+ patients, the investigators thought that lymphoscintigraphy and lymphatic mapping would offer the ability to stage neck disease and provide information about the presence of atypical basins of lymphatic flow from upper aerodigestive tract primary sites that would not typically be addressed by the more classic anatomic regions outlined for SND. Accordingly, patients undergoing this procedure would have lymphatic flow patterns uniquely defined according to neck anatomy and the effects of previous treatment. In addition, findings from the study suggested that lymphoscintigraphy in the N_+ or previously treated neck demonstrated the potential for defining unpredictable cervical nodal levels at risk for metastasis. Studies such as this indicate that the use of lymphatic mapping for the treatment of HNSCC may ultimately provide the surgeon with the ability to adequately stage the N_0 neck and direct elective therapy or assess the neck with recurrence in a minimally invasive manner to determine the extent of salvage required. The place of lymphatic mapping for avoiding a neck dissection remains inadequately defined at this time in terms of therapeutic efficacy, practical application, and health-related quality of life. Lymphatic mapping in HNSCC is probably best considered an investigational technique; as such, it has not yet achieved the status of "standard of care" for the treatment of head and neck carcinoma patients.[77]

Sequelae of Neck Dissection

The most notable sequela observed in patients who have undergone a radical neck dissection is related to the removal of the spinal accessory nerve. The resulting denervation of the trapezius muscle, which is one of the most important shoulder abductors, causes destabilization of the scapula, with progressive flaring of this bone at the vertebral border (drooping of the scapula and lateral and anterior rotation of it). The loss of the trapezius function decreases the patient's ability to abduct the shoulder above 30 degrees at the shoulder. These physical changes result in the recognized shoulder syndrome of pain, weakness, and deformity of the shoulder girdle that is commonly associated with radical neck dissection.

For the past few years, it has been debated in the literature whether there is a major difference in postoperative shoulder dysfunction after a radical neck dissection that preserves the spinal accessory nerve. Using patient questionnaires, Schuller and colleagues[78] compared symptomatology and the ability to return to preoperative employment of patients who underwent either a radical neck dissection or a modified radical neck dissection. Although they found no statistically significant difference between the two groups, Sterns and Shaheen[79] and others using similar methods found that the majority of patients who had a nerve-sparing procedure did not have postoperative pain or shoulder dysfunction.[80,81]

Only recently have objective data about shoulder dysfunction after neck dissection been gathered prospectively. Leipzig and colleagues[82] studied 109 patients who had undergone various types of neck dissections using preoperative and postoperative observations of shoulder movement made by the surgeons who rated the degree of shoulder dysfunction. The researchers concluded that any type of neck dissection may result in an impairment of function of the shoulder. They also noted that dysfunction occurred more frequently among those patients in whom the spinal accessory nerve was extensively dissected or resected.

In 1985 Sobol and colleagues[55] performed a prospective study in which preoperative and postoperative measures of shoulder range of motion were compared. In addition, postoperative electromyograms (EMGs) were obtained in some patients. Shoulder range of motion was better in patients who underwent a nerve-sparing procedure than in patients who had a radical neck dissection. In addition, the type of nerve-sparing procedure was found to have an influence on the degree of shoulder disability. Patients who had undergone a modified radical neck dissection, in which the entire length of the nerve was dissected, had no dramatic difference in shoulder range of motion as compared with those patients who had a radical neck dissection 16 weeks after surgery. Patients who underwent a supraomohyoid neck dissection, in which there was less-extensive dissection of the spinal accessory nerve, performed significantly better ($P > .05$) than either of the other groups in terms of shoulder range of motion and EMG findings for the trapezius muscle. Interestingly, 16 weeks after surgery, moderate to severe EMG abnormalities were noted in up to 65% of the patients in whom the spinal accessory nerve was dissected along its entire length (i.e., modified radical neck dissection). Although no severe abnormalities were noted in the group undergoing supraomohyoid neck dissection, 22% of these patients showed moderate abnormalities. Several patients from each group had repeat studies at approximately 1 year after surgery. Unlike patients who had a radical neck dissection, patients in whom the nerve was spared showed evidence of improvement in all parameters studied.

A prospective study by Remmler and colleagues[83] revealed that patients who had a nerve-sparing procedure had a serious but temporary spinal accessory nerve dysfunction. In this study, preoperative strength, range-of-motion measures, and EMG of the trapezius muscle were compared with postoperative measures obtained at 1, 3, 6, and 12 months. The groups studied consisted of patients undergoing nerve-sparing procedures and those who had the nerve resected. Most of the patients in the nerve-sparing group had supraomohyoid neck dissections. Patients who underwent radical neck dissections had a major decrease in trapezius muscle strength on EMG at 1 month; these parameters did not improve with time. Interestingly, patients in the nerve-sparing group had a small but significant reduction in trapezius muscle strength and evidence of trapezius muscle denervation at 1 and 3 months, which improved by 12 months. More recently, Kuntz and Weymuller[84] reported reduced quality-of-life scores among patients after neck dissection, with the worst scores being associated with radical neck dissection and the best scores with SND.

Hence the evidence indicates that even procedures involving minimal dissection of the spinal accessory nerve may result in shoulder dysfunction.[84] It is only appropriate, therefore, to make every effort to avoid undue stretch or trauma to the nerve when a nerve-sparing procedure is performed. In addition, it is imperative that every patient who undergoes a neck dissection be questioned about the function of the shoulder and be examined by a physical therapist early during the postoperative period. If any deficit is detected, the patient should be properly counseled and coached to ensure proper rehabilitation of the shoulder.

Complications of Neck Dissection

In addition to the various medical complications that may occur after any surgical procedure in the head and neck region, a number of surgical complications may be related solely or in part to the neck dissection. If the course of a patient who has undergone a neck dissection as part of the surgical treatment of cancer of the head and neck region is followed, several complications may arise. When a neck dissection is done after radiotherapy of more than 70 Gy, there might be a higher risk of complications.[48] However, adding chemotherapy to radiotherapy may not increase the complication rate.[17]

Air Leaks

Circulation of air through a wound drain is a common complication that is usually encountered 1 day after surgery. The point of entrance of air may be located somewhere along the skin incision, although, if

the drains are connected to suction in the operating room near the completion of the wound closure, such an air leak usually becomes apparent then and may be corrected. Other points of entrance may not become apparent until after surgery, when the position of the neck changes or when the patient begins to move. A typical example of this situation is the improperly secured suction drain that gets displaced, thereby exposing one or more of the drain vents. A similar situation occurs frequently when a lateral trapezius flap is used in conjunction with a neck dissection. The slightest movement of the shoulder may produce an air leak into the neck wound through the extensive donor defect, even after meticulous tacking of the skin edges to the underlying tissues and painstaking suturing of a skin graft. This problem may be prevented by using an adhesive vinyl drape applied over the defect and surrounding skin to seal any possible air leak instead of using the bolster of gauze that is traditionally used to immobilize the skin graft.

Air leaks with potentially more serious consequences are those that occur through a communication of the neck wound with the tracheostomy site or through a mucosal suture line. In these patients, it is likely that, in addition to air, contaminated secretions are circulated through the wound. Thus early identification of the site of leakage is desirable, although it may not be a simple task, and correcting it may require revision of the wound closure in the operating room.

Bleeding

Postoperative hemorrhage usually occurs immediately after surgery. External bleeding through the incision, without distortion of the skin flaps, often originates in a subcutaneous blood vessel. In most patients, this may be readily controlled by ligation or infiltration of the surrounding tissues with an anesthetic solution containing epinephrine. Pronounced swelling or ballooning of the skin flaps immediately after surgery, with or without external bleeding, should be attributed to a hematoma in the wound. If a hematoma is detected early, "milking" the drains occasionally may result in evacuation of the accumulated blood and the problem will resolve. If this is not accomplished immediately or if blood reaccumulates quickly, it is best to return the patient to the operating room, explore the wound under sterile conditions, evacuate the hematoma, and control the bleeding. Attempting to do this in the recovery room or at the bedside is ill advised because lighting and surgical equipment may be inadequate and sterile conditions may be precarious. Failure to recognize or manage a postoperative hematoma properly may predispose the patient to the development of a wound infection. Although bulky pressure dressings may be useful for curtailing postoperative edema and they do not prevent hematomas, they may delay their recognition as well.

Chylous Fistula

In a 1990 review of 823 neck dissections performed by the surgeons at Memorial Hospital in New York City that included the removal of the lymph nodes in level IV, Spiro and colleagues[63] found that 14 patients (1.9%) developed a chyle fistula. In this and other studies,[85] a chylous leakage was identified and apparently controlled intraoperatively in the majority of patients who developed the complication. These observations remind the surgeon to not only avoid injury to the thoracic duct proper but also to ligate or clip any visualized or potential lymphatic tributaries in the area of the thoracic duct. This may be accomplished with relative ease if the operative field is kept bloodless when dissecting in this area of the neck. In addition, as soon as the dissection of this area is completed and again before closing the wound, the area should be observed for 20 or 30 seconds while the anesthesiologist increases the intrathoracic pressure; even the smallest leak of chylous material should be pursued until it is arrested. Indiscriminate clamping and ligating may be difficult and sometimes counterproductive because of the fragility of the lymphatic vessels and the surrounding fatty tissue. Hemoclips are ideal to control a source of leakage that is clearly visualized; otherwise it is preferable to use suture ligatures with pliable material, such as no. 5-0 silk, which are tied over a piece of hemostatic sponge to avoid tearing.

Despite the surgeon's best efforts to avoid it, a postoperative chylous fistula occurs after 1% to 2% of neck dissections. Management of this complication depends on the time of onset of the leak, the amount of chyle drainage in a 24-hour period, and the physician's ability to prevent accumulation of chyle under the skin flaps. When the daily output of chyle exceeds 600 mL (especially when the chyle fistula becomes apparent immediately after surgery), conservative closed wound management is not likely to succeed. In such patients, early surgical exploration is preferred, before the tissues exposed to the chyle become markedly inflamed and before the fibrinous material that coats these tissues becomes adherent, thus obscuring and jeopardizing important structures such as the phrenic and vagus nerves.

Chylous fistulas that become apparent only after enteral feedings are resumed and, particularly those that drain less than 600 mL of chyle per day, are initially managed conservatively with closed wound drainage, pressure dressings, and low-fat nutritional support. Parenteral alimentation through a central line can further reduce chylous output and may be considered for high-output or intractable fistulas.

Facial/Cerebral Edema

Synchronous bilateral radical neck dissections, in which both internal jugular veins are ligated, may result in the development of facial edema, cerebral edema, or both. The facial edema, which sometimes may be dramatically severe, appears to be caused by an inadequacy of venous drainage, which usually resolves to a variable extent with time as collateral circulation is established. Facial edema appears to be more common and more severe in patients who had previous radiation to the head and neck and in those patients in whom the resection includes large segments of the lateral and posterior pharyngeal walls. Massive facial edema may be prevented by preserving at least one external jugular vein whenever a bilateral radical neck dissection is anticipated. The external jugular is usually separated from the tumor in the neck by the sternocleidomastoid muscle and may be dissected free between the tail of the parotid and subclavian veins.

The development of cerebral edema may be at the root of the impaired neurologic function and even coma that may occur after bilateral radical neck dissection. Ligation of the internal jugular veins leads to increased intracranial pressure.[86,87] It has been shown experimentally that the increased cerebral venous pressure that occurs as a result of ligating both internal jugular veins in dogs is associated with inappropriate secretion of antidiuretic hormone.[88] It may then be speculated that the resulting expansion of extracellular fluids and dilutional hyponatremia aggravate the cerebral edema and create a vicious cycle. In practice, these observations behoove the surgeon and the anesthesiologist to curtail the administration of fluids during and after bilateral radical neck dissections.[89] In addition, perioperative management of fluid and electrolytes in these patients should not be guided solely by their urine output but rather by the monitoring of central venous pressure, cardiac output, and serum and urine osmolarity.

Blindness

Visual loss after bilateral neck dissection is a rare but catastrophic complication. To date, there have been five cases reported in the literature.[90] In one report, histologic examination revealed intraorbital optic nerve infarction, which suggests intraoperative hypotension and severe venous distension as possible etiologic factors.[61]

Carotid Artery Rupture

The most feared and the most commonly lethal complication after surgery of the neck is the exposure and rupture of the carotid artery; therefore every effort should be made to prevent it. If the skin incisions have been designed properly, seldom does the carotid artery become exposed in the absence of a salivary fistula. Fistula formation and flap breakdown are more likely to occur in the presence of malnutrition, diabetes, infection, and previous radiotherapy, which impair healing capacity and compromise vascular supply. Faced with any of these risk factors, the surgeon should use flawless surgical techniques in the closure of oral and pharyngeal defects. The use of free and pedicled vascularized flaps (which provide skin for the closure of mucosal defects) has rendered nearly obsolete the use of "protective" measures such as dermal grafts, levator scapulae muscle flaps, and controlled pharyngostomies.

Management of the exposed carotid artery depends on the likelihood of rupture based on the length of the exposed segment, condition

of the surrounding tissues, and size of the oropharyngocutaneous fistula. Large cutaneous defects or large, high-output fistulas in previously irradiated patients are not likely to heal by secondary intention in a timely manner. The likelihood of rupture of the carotid artery in these patients is extremely high. Therefore an attempt should be made to repair the defect and to cover the carotid using well-vascularized tissue before the vessel has been irreversibly damaged. Whenever the carotid is exposed, it is advisable to take "carotid precautions," which include warning and instructing nursing personnel and house staff about the possibility of a carotid rupture, the site of potential rupture, and the steps to be taken in the event of bleeding, having compatible blood available, and keeping appropriate surgical instruments at the bedside.

When a carotid artery rupture occurs, it is usually possible to stop the bleeding with manual pressure while blood and fluids are administered to restore and maintain the patient's blood pressure; only then is the patient taken to surgery. Attempts to repair the area of rupture are futile. Introduction of Fogarty catheters through the area of rupture is helpful for controlling the bleeding temporarily while the artery is exposed and ligated proximally and distally to the area of rupture.

Neck Dissection after Treatment with Chemoradiation

One of the treatment options for advanced local or regional squamous cell carcinoma of the head and neck is chemoradiation. This method of treatment may allow for preservation of one or more upper aerodigestive organs with comparable or even better local and regional control rates compared with radiation alone.[91-93] The neck following treatment with chemoradiation is hard to evaluate both clinically and with the use of imaging techniques. As newer, more effective chemotherapy agents are developed, further innovations in the way radiotherapy is administered, and as diagnostic tool are improved, constant assessment of the recommended approaches to evaluate and treat the neck post chemoradiation therapy is necessary. The current assessment approach relies on the initial tumor stage and the clinical and imaging assessment before and after treatment.

When there is a disease failure at the primary site without evidence of nodal disease, following chemoradiation, a neck dissection should be considered if the primary site is to be salvaged surgically. A salvage neck dissection is necessary in a situation where there is an evidence of nodal disease after chemoradiation treatment to the neck. The salvage neck dissection can be further divided into an "early" procedure when there is persistent disease following chemoradiation. A "late" salvage neck dissection is done for recurrent disease. Recurrent disease in the neck following chemoradiation has a worse prognosis than a neck dissection done for persistant disease.[94] The assessment of the regional response to chemoradiation treatment is done 6 to 8 weeks after completion of treatment and is based on clinical examination and imaging (a computer tomography/magnetic resonance imaging [CT/MRI] and or PET scans).[73,95-98]

For patients with nodal disease of stage N_0 or N_1 who have a complete response after radiation alone or chemoradiation, a neck dissection is indicated only if there is evidence of persistance regional disease.[73,96,98-101] It is controversial to perform a neck dissection for patients with stage N_2 and N_3 nodal disease who achieve complete response after chemoradiation on the basis of clinical examination and imaging. Some support performing a planned radical or modified neck dissection 6 to 8 weeks after completion of chemoradiation therapy,[72,95,100,102,103] whereas others have found that this can be avoided in certain cases[49,73,98,104,105] or, if done, a selective neck dissection can be appropriate.[72-74,98,106,107]

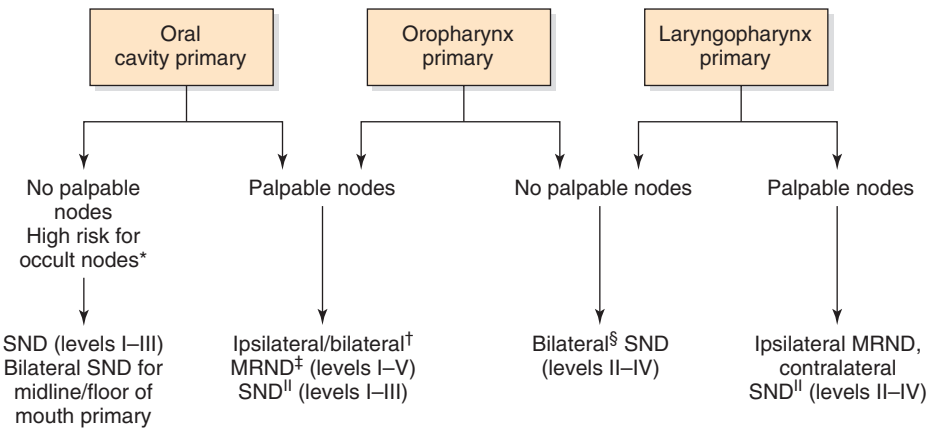
Differences in approaches might be related to different chemoradiation protocols used and different treatment response assessment methods.[108]

The major advantage of avoiding a neck neck dissection under such conditions is the avoidance of the potential morbidity.[84,109,110]

When a neck dissection is considered, it should be done when wound healing is optimal, PET-CT scans false-positive rates are minimal, and patients have recovered from the toxicities associated from the chemotherapy and radiotherapy. The typical timing is 6 to 8 weeks following radiation therapy, but it may be as long as 12 weeks.[111-114] The delay is based on reported inaccuracy of FDG PET scans for detecting residual neck disease in the early postchemoradiation therapy setting.[115]

Summary

Neck dissection is an operative procedure that is designed to remove metastases involving the regional cervical lymph nodes. The gold standard procedure is the radical neck dissection, which, for most patients, is too extensive and results in excessive morbidity. Modifications of the radical neck dissection procedure, which have been designed to reduce morbidity by sparing nonlymphatic structures (modified radical neck dissection) and to treat early nodal disease by removing only the lymph node groups at greatest risk for harboring metastases (SND), have now evolved. To help the reader determine which type of neck dissection is most appropriate for the management of nodal disease associated with the three major sites of the upper aerodigestive tract, an algorithm is provided (Fig. 121-18).



*T_1–T_4 oral tongue; $T_{2–4}$ other sites; perineural/lymphatic invasion.
†Bilateral neck dissection for N_{2c} disease.
‡RND if gross tumor invasion of nonlymphatic structures.
§Ipsilateral neck dissection for oropharyngeal primaries if postoperative radiotherapy is planned.
II SND for nodes confined to one level.

Figure 121-18. Algorithm for cervical lymphadenectomy options in patients with carcinomas of the upper aerodigestive tract, assuming that cervical lymphadenectomy is the treatment of choice for these regional lymph nodes. *MRND,* modified radical neck dissection; *RND,* radical neck dissection; *SND,* selective neck dissection.

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CHAPTER ONE HUNDRED AND TWENTY-TWO

Complications of Neck Surgery

Frederick C. Roediger

David W. Eisele

Key Points

- Complications of neck surgery have evolved over time with the introduction of new procedures and philosophies in the management of patients with head and neck cancer.
- Comprehensive neck dissection provides the best framework for describing the four major categories of neck complications: wound, vascular, nerve, and chyle/chest.
- Components of these four categories can be applied selectively to other, less extensive neck surgical procedures.
- Awareness, early recognition, and prompt and effective management of complications can have a significant impact on outcomes.

Complications of neck surgery affect every surgeon regardless of experience and technical skill. Despite our best intentions, complications arise due to the intricate anatomy of the neck and complexities of the diseases and patients treated. Factors such as medical comorbidities (hypertension, hepatitis, etc.), substance abuse, prior radiation therapy, aerodigestive tract entry, prolonged anesthesia times, the volume of intraoperative fluid administered, and the need for microvascular free flap reconstruction have been associated with head and neck surgical complications in various studies.[1-4] Prevention and management of complications that occur both intraoperatively and postoperatively are essential to proper head and neck surgical care.

The history of neck dissection reveals a continuing quest to reduce complications and their sequelae.[5] The results of a systematic approach to cervical lymphadenectomy for the treatment of a series of patients with head and neck cancer was first reported by George Crile, MD, in 1906.[6] In that era, radical neck dissection (RND), with removal of the sternocleidomastoid muscle (SCM), the internal jugular vein (IJV), and the spinal accessory nerve (SAN), was considered the standard of care for patients with neck metastasis but resulted in significant functional and cosmetic morbidities.[7] Introduction of the modified radical neck dissection (MRND) and proof that it was oncologically sound led to improved functional outcomes without sacrifice of oncologic effectiveness.[8-11] Further technique refinements that established selective neck dissections (SND) were based on predictable patterns of spread from specific primary tumor locations.[12,13] This approach is highly effective for management of the clinically negative neck and may have applications in clinically positive necks as long as postoperative radiation therapy is administered.[14-17] In addition, SND may be the preferred approach for planned neck dissection after concurrent chemoradiation for advanced head and neck cancer because these patients have a low incidence of recurrence in the neck.[18] As head and neck surgical techniques have evolved, so have the type and frequency of complications. Shoulder disability from spinal accessory nerve injury was an expected sequela of RND but is now considered a potential complication of MRND. Internal jugular vein thrombosis and hemorrhage may occur more frequently in the modern era because this structure is more commonly preserved with MRND and SND.[19]

In this chapter, complications of neck dissection are considered primarily and are grouped into four major categories: wound, vascular, nerve, and chyle/chest. This framework provides structure for the informed consent process and individual components can be applied selectively to any neck surgery depending on the location and extent of a given procedure.

Wound Complications

Incision Planning

Carefully designed neck incisions must take into account the location and extent of the primary tumor; adequate exposure for the type of neck dissection planned; carotid artery coverage; excision of previously violated skin, when applicable; and cosmesis. Preferred incisions combine limbs that meet at right angles to create skin flaps that preserve the blood supply to neck skin, which includes branches of the facial and occipital arteries superiorly and branches of the transverse cervical and suprascapular arteries inferiorly.[20] Subplatysmal flap elevation should be used in all approaches to preserve the skin flap blood supply.

Numerous neck incisions for neck dissection have been described. Early designs such as the Crile single-Y and the Martin double-Y provided excellent exposure but placed a trifurcation over the carotid artery. Furthermore, they created tenuous posterior skin flaps and anterior skin flaps that relied partially on blood flow from branches of the contralateral external carotid artery. The Conley-modified Schobinger approach was an improvement, maintaining excellent exposure for comprehensive neck dissection with creation of a large, robust anterior flap and placement of the trifurcation posterior to the carotid artery.[20] MacFee introduced the use of two transverse incisions that appear to transect the dominant blood supply, but studies have shown that the central, bipedicled skin flap is resistant to ischemia and may be the preferred approach in the previously irradiated patient.[21,22] Certain incisions are well-suited to accompany the extirpation of specific primary tumors such as the apron flap for neck dissection with laryngectomy and the Attie incision for neck dissection with thyroidectomy.[23]

Figure 122-1. Seroma formation after modified radical neck dissection following prior radiation therapy. Fluid collection under the anterior skin flap has resulted in loss of the expected postoperative scaphoid appearance of the neck.

The principles of adequate exposure and protection of critical structures cannot be overemphasized and are equally important for comprehensive neck dissection as they are for less extensive procedures. For example, care should always be taken to place submandibular incisions, whether for supraomohyoid neck dissection, submandibular gland resection, or mandibular fracture repair, sufficiently below the lower border of the body of the mandible to avoid injury to the marginal mandibular branch of the facial nerve. Cosmesis must often be considered secondary to successful tumor extirpation and safety (e.g., when a small incision for lymph node biopsy of a posterior triangle node is desired but a slightly larger wound may improve surgical exposure and assist preservation of the spinal accessory nerve).

Wound Dehiscence and Flap Necrosis

Flap survival depends on incision design, surgical technique, and factors intrinsic to the patient. A study of 184 neck dissections using triradiate, modified MacFee, or apron incisions showed a wound dehiscence rate of 11%, 8%, and 0%, respectively, for each approach.[24] The same study showed a statistically significant increase in the overall rate of wound dehiscence in previously irradiated necks, particularly for the triradiate group, leading the authors to recommend the apron flap for neck dissection in patients who have received prior radiation therapy.[24] Whether or not preoperative radiation therapy increases the complication rate of neck dissection continues to be debated, but several reports indicate that higher total radiation doses are associated with a higher rate of wound complications.[25,26] Skin loss from involvement with tumor or excision of violated skin may lead to increased tension on the closure. Poor microvasculature, secondary to malnutrition, active tobacco use, or uncontrolled diabetes mellitus, contributes to the lack of tissue tolerance for surgical manipulation and a higher rate of wound dehiscence or flap necrosis.

Seroma

Division of lymphatic and adipose tissue during neck dissection allows for formation of seroma, the collection of serous fluid in the potential space between cervical skin flaps and underlying structures. Seromas present as enlarging masses under the skin, with or without overlying induration or erythema. Loss of the expected postoperative scaphoid appearance of the neck following neck dissection is cause for suspicion (Fig. 122-1). If left untreated, a seroma may lead to flap necrosis or infection. Many case series report seroma and hematoma formation together, with rates ranging from 3% to 10% with RND to as high as 20% with functional neck dissection.[27-29] These differences may be explained by the increased amount of native tissue preserved in MRND or SND compared with RND that can weep serous fluid into the wound bed. Causes of seroma include incorrect drain placement, drain failure, or early drain removal. Prevention consists primarily of proper management of closed suction drains that are left in place until the total output per drain falls below 25 mL in a 24-hour period. Some authors also advocate the routine use of fibrin glue, which has been shown in animal models to prevent seroma formation.[30] Some small seromas can be observed with anticipation of gradual resorption. In most cases, however, management of seroma includes needle aspiration and, in select patients, drain replacement. Pressure dressings do not appear to prevent fluid reaccumulation.

Wound Infection

Wound infection may manifest as a cellulitis with erythema, warmth, or induration of the cervical skin flaps, abscess formation from an infected seroma or hematoma, or fistula. Occasionally, purulent fluid will be seen in a closed suction drain. Early recognition and proper drainage or diversion of fluid away from the carotid artery and internal jugular vein are critical to prevention of spread of the infection and vascular rupture.

Aerodigestive tract entry is the single most important factor that contributes to the risk of wound infection. Neck dissection without exposure to oral flora is considered a clean procedure. In a study of 438 patients undergoing parotidectomy, thyroidectomy, or submandibular gland excision, three (0.7%) patients developed a wound infection, one of whom had received perioperative erythromycin.[31] Administration of prophylactic antibiotics for clean neck dissections is controversial. One study showed a 10% rate (9/92) of infection for those not receiving antibiotics compared with 3.3% (3/93) of patients receiving first-generation cephalosporins, clindamycin, or pencillin.[32] Although the difference did not reach statistical significance, the trend may justify its use.[32] Antibiotic prophylaxis in this setting has been shown to be cost-effective.[33] In terms of duration, no difference in the rate of infection was seen with 1-day versus 4- or 5-day antibiotic regimens for clean procedures.[34,35] Interestingly, significantly higher infection rates for RND compared with other clean surgical procedures have been documented, for reasons that remain unclear.[35]

The risk of wound infection increases significantly with entry into the oral cavity, pharynx, or larynx, ranging from 15% to 87%.[36,37] Factors associated with wound infection include the performance of bilateral neck dissections, total laryngectomy, advanced-stage tumors, and in some studies, a history of prior tracheotomy.[35] The benefit of antibiotic prophylaxis in surgery that required aerodigestive tract entry was demonstrated convincingly in a well-designed prospective clinical trial in which 20/23 (87%) patients who received a placebo developed an infection compared with 12/32 (38%) in a cefazolin-treated group.[36] In another prospective, randomized clinical trial of four antibiotic regimens, statistically significant reductions in the infection rate were seen with gentamicin-clindamycin (4% to 7%) compared with cefazolin (20% to 33%), demonstrating the importance of broad-spectrum coverage that includes gram-negative and anaerobic organisms.[37] A trend toward fewer infections with a 5-day course compared with 1 day of antibiotics was found.[37] Cefazolin-metronidazole prophylaxis is a suitable alternative regimen to gentamicin-clindamycin and avoids the potential ototoxicity associated with gentamicin.[38]

Once a wound infection is detected, action must be taken to minimize sequelae. Collections must be completely aspirated or incised and drained, wounds cultured, and antibiotics that target the potential or confirmed pathogens initiated. Ensuring that the infection does not spread to the major blood vessels is of utmost importance.

Salivary Fistula

Saliva may enter the wound from either aerodigestive tract communication or parotid leak (Fig. 122-2). With associated infection, an inflammatory response in adjacent tissue rapidly occurs. Erythema, edema, and induration of skin flaps, as well as a change in the character of drain output to that of saliva or purulent discharge, are common signs.

The risk of pharyngocutaneous fistula formation with aerodigestive tract entry during surgery varies from 10% to 30%.[39,40] Prevention consists of water-tight, inverted, and tension-free closure during the

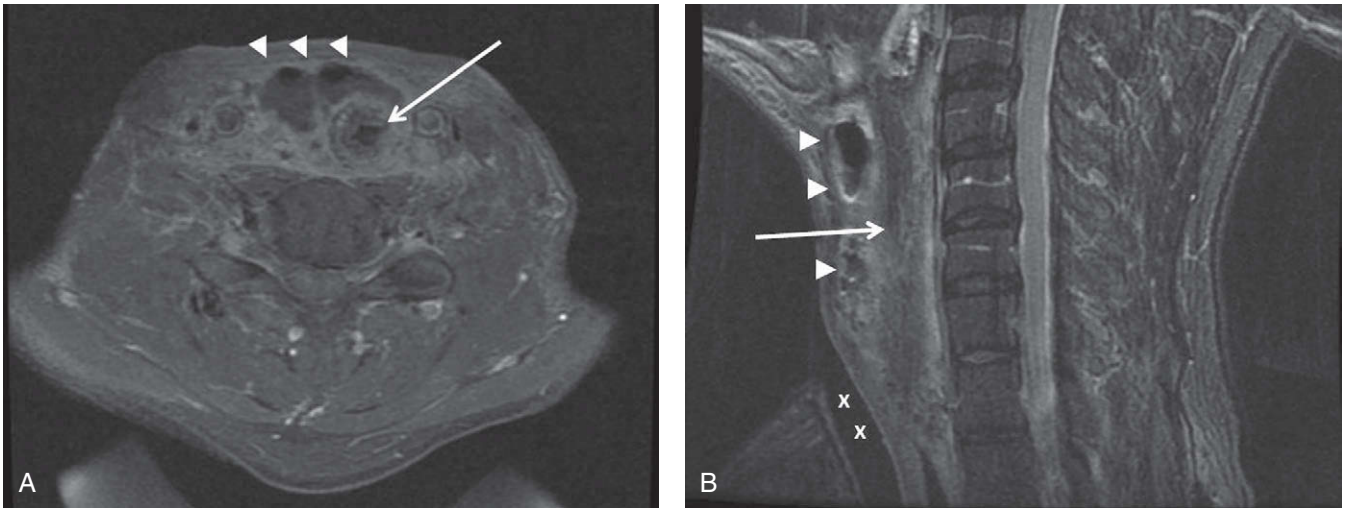

Figure 122-2. Magnetic resonance imaging of a pharyngocutaneous fistula after total laryngopharyngectomy, cervical esophagectomy, and tubed radial forearm free flap reconstruction for hypopharyngeal cancer. **A,** Axial T1-weighted gadolinium-enhanced image with fat saturation showing fluid and air *(arrowheads)* anterior to the proximal, pharyngeal anastomosis *(arrow)*. **B,** Midline sagittal T2-weighted image with fat saturation demonstrating the same fluid and air collection *(arrowheads)* anterior to the free flap *(arrow)* with no direct communication to the tracheostoma *(X)*.

primary surgical procedure and consideration of vascularized tissue coverage if the closure appears tenuous. Conservative management with broad-spectrum antibiotics and continued closed drainage is usually successful, although one should have a low threshold for opening a suture line to divert drainage away from the major blood vessels and gently packing the wound.[19] Nutritional status and glucose control should be optimized and thyroid-stimulating hormone levels checked, particularly in previously irradiated patients. Fistulae refractory to conservative measures require closure with vascularized tissue, either local-regional flaps or free flaps.

Postparotidectomy fistula does not carry a risk of major blood vessel rupture but can be annoying to patients. Most are small-volume leaks that exit the divided inferior cervical portion of the parotid gland. These normally respond well to conservative management.[41] Although numerous treatment modalities for persistent leaks have been proposed, injection of the parotid gland with botulinum toxin is usually effective.[42,43]

Scar Formation

Cosmetic principles that apply to neck surgery include placement of incisions in natural skin creases or relaxed skin tension lines, using gently curved vertical limbs to avoid linear scar contracture, and performance of a tension-free, everted skin closure.[44] Lapses in meticulous technique or postoperative wound infection may lead to the development of a hypertrophic scar (Fig. 122-3A). Formation of a keloid—scar tissue that exceeds the boundaries of the original incision—usually occurs in patients with a personal or family history of exuberant scar formation. Web formation along linear vertical limbs in the lateral neck may also occur (see Fig. 122-3B). Unilateral deep plane neck lift and midline platysmaplasty can be considered for rehabilitation of post–neck dissection asymmetry.[45]

Vascular Complications

Carotid Artery Hemorrhage

Complications involving the common carotid artery are the most feared sequelae of neck surgery. Intraoperative injuries to the common carotid artery generally require primary vascular repair. Vascular surgery consultation is highly recommended.

Acute postoperative carotid artery rupture, or "blowout," occurs in 3% to 4% of RNDs and is associated with a mortality rate of approximately 50%.[46-48] Factors associated with carotid artery hemorrhage include wound breakdown, necrosis, and infection; pharyngocutaneous fistula; prior radiation therapy; tumor involvement of the arterial wall; and rough handling of the adventitia during dissection.[47,48] Close surveillance of dehiscent or infected wounds for lack of improvement and signs of impending carotid rupture such as carotid exposure or a sentinel bleed is critical to postoperative management of the at-risk patient. This is because the mortality of elective carotid artery ligation is significantly lower than for emergency ligation,[49] rising from 14% to 64%, respectively, in one series.[50]

Emergent treatment consists of control of hemorrhage with application of direct pressure to the area of rupture and expeditious return of the patient to the operating room for definitive control. Fluid resuscitation with blood products and crystalloid is performed. Separate incisions are made inferior and superior to the region of infected or necrotic tissue, and proximal and distal vessel control is obtained.[51] Vessel ligation away from the contaminated wound is preferred in order to prevent rebleeding. The central wound is left packed or is covered with vascularized tissue. Endovascular techniques including angiography with selective embolization and temporary stent grafts for patients at high risk for stroke have been described.[52,53]

Internal Jugular Vein Complications

The theoretic benefits of preserving the internal jugular vein (IJV) during unilateral MRND or SND include decreased incidence of edema and less morbidity if a contralateral RND becomes necessary in the future,[54] although this practice has not been evaluated by any outcome studies. Preservation of at least one IJV during bilateral neck dissection is clearly beneficial to avoid facial or laryngeal edema, intracranial pressure elevations, stroke, and blindness (Fig. 122-4).[55] Techniques for reconstruction of the IJV from either the external jugular vein or a greater saphenous vein graft have been described[56] but are not used routinely. The widespread use of MRND and SND with IJV preservation has made possible other complications including IJV thrombosis and hemorrhage.

The IJV remains patent in approximately 86% of patients after MRND in studies using preoperative and postoperative imaging with CT or MRI.[54,57] Factors that predispose to immediate IJV thrombosis include damage to the adventitia, desiccation, and improper ligation of IJV branches intraoperatively, as well as the presence of central venous catheters.[19,58] One study of patients undergoing MRND examined with retrograde venography within 1 month postoperatively demonstrated IJV occlusion in 8/27 (29.6%) of operated necks.[59] Five of these patients had postoperative courses complicated by wound infection or salivary fistula, indicating that wound complications may lead to a high rate of IJV thrombosis.[59] Furthermore, postoperative radiation therapy may contribute to IJV thrombosis. An ultrasound study of patients

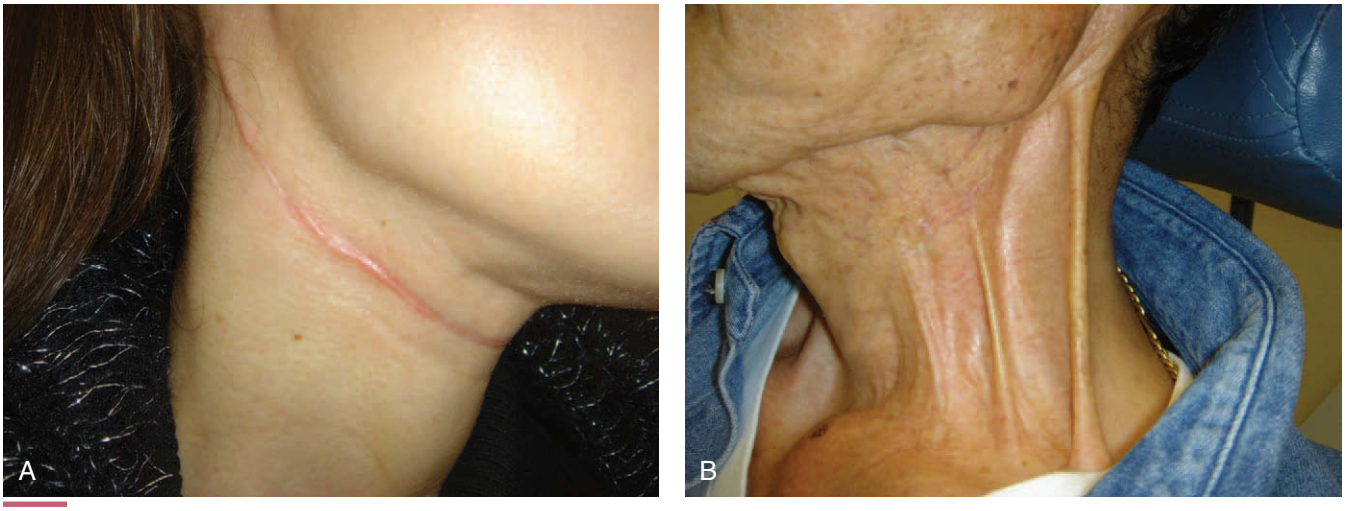

Figure 122-3. Scar complications. **A,** Hypertrophic scar after selective neck dissection. **B,** Web formation in the lateral neck after radical neck dissection.

Figure 122-4. Facial edema after left radical neck dissection. The patient had a right, peripherally inserted central venous catheter that impaired flow of the right internal jugular vein.

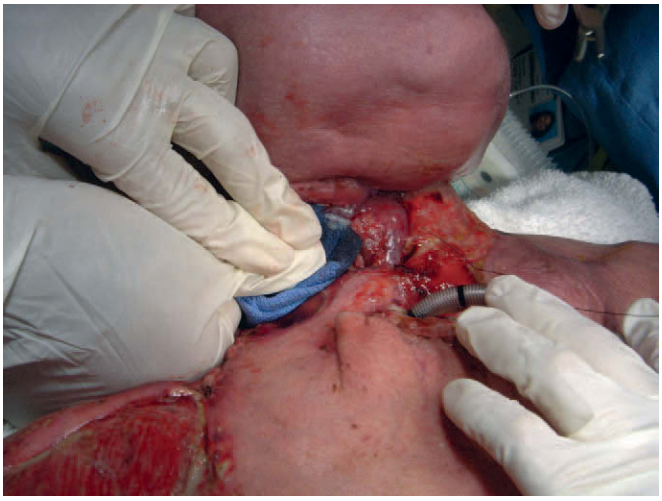

Figure 122-5. Internal jugular vein hemorrhage in the setting of pharyngocutaneous fistula. Direct pressure is being applied to the site of hemorrhage while the patient is transported emergently to the operating room for surgical control of the bleeding.

undergoing MRND alone, radiation therapy alone, or MRND plus postoperative radiation therapy showed a normal-appearing vein when compared with the contralateral, untreated IJV in 88%, 57%, and 18% of patients, respectively.[60] In the long term, the rate of IJV thrombosis may be significantly lower, only 5.8% in one ultrasound study, indicating that many thrombosed veins will recanalize with reestablishment of patency.[61]

Internal jugular vein hemorrhage is rare, occurring in less than 1.3% of MRND with concurrent laryngectomy or pharyngectomy.[62] Although often less severe than arterial bleeding, this event can be just as life-threatening (Fig. 122-5). Similar to carotid artery bleeding, the major risk factors for this complication include salivary fistula, significant tobacco use, and poor nutritional status.[63] Careful handling of the IJV and avoidance of circumferential dissection in cases involving aerodigestive tract entry may help in its prevention.[63]

Blindness, an exceedingly rare complication of neck dissection, may occur following unilateral or, more commonly, bilateral RND.[64,65] Prolonged intraoperative hypotension, increased cerebrospinal fluid pressure, and venous pressure on the optic nerve may be causative factors.[66]

Hematoma

Hematoma occurs in approximately 1% of neck dissections and 4% of major head and neck surgeries.[67,68] Hematoma can usually be differentiated from seroma by the presence of skin ecchymosis, firmness to palpation, or clotted drain output, although both complications can cause elevation of skin flaps and loss of the expected scaphoid contour of a dissected neck. Failure to recognize and properly treat a neck wound hematoma results in increased wound complications.[67] Even a small venous bleed or hematoma in an undesirable location, for example, in proximity of the vascular pedicle of a free flap reconstruction, can have serious consequences. Prevention consists of preoperative avoidance of anticoagulants and antiplatelet agents and meticulous intraoperative hemostasis. Treatment should include prompt evacuation of clotted blood, at the bedside if necessary, to prevent upper airway edema, and return of the patient to the operating room for wound exploration and control of any bleeding vessels.

Nerve Complications

Motor Nerves

Facial Nerve

The classic RND includes removal of a portion of the tail of the parotid gland. Surgical entry of the parenchyma of the parotid gland theoreti-

cally places the main trunk of the facial nerve at risk; however, during a standard neck dissection usually only the cervical and marginal mandibular branches of the facial nerve are encountered.

The cervical branch of the facial nerve innervates the platysma muscle, which lies in the superficial fascia of the neck and blends with depressors of the lower lip.[69] Sacrifice of the cervical branch does not usually produce clinically significant deficits, although loss of neck skin tone and some degree of decreased lip depressor function may occur due to either transection of the cervical branch of the facial nerve or division of the platysma muscle.

The marginal mandibular nerve is encountered during the approach to level I of the neck as it descends along the inferior border of the mandible and lateral to the submandibular gland before coursing superiorly to innervate the orbicularis oris, depressor anguli oris, mentalis, and depressor labii inferioris muscles.[69] The nerve is typically a single branch, but double branches can occur and its position with respect to the body of the mandible is highly variable. Injury to this nerve results in asymmetry of the lower lip at rest with inability to depress the lip during facial expression. A recently reported series of 258 submandibular gland excisions demonstrated a low rate of transient paresis of the marginal mandibular branch of the facial nerve (9%) and only one case of permanent paralysis (<1%).[70] Another study of 107 patients undergoing excision of submandibular gland neoplasms showed a transient paresis rate of 10% and a permanent paralysis rate of 1% for benign tumors, and rates of 8% and 6%, respectively, for malignant lesions; selective neck dissection was performed in 43% of cases overall.[71] In a large European series of patients with laryngeal or hypopharyngeal cancer and no prior radiation therapy, injury to the marginal mandibular branch of the facial nerve occurred in 9/714 (1.26%) of neck dissections.[72] The Hayes Martin maneuver for preventing marginal mandibular nerve injury involves ligation and superior retraction of the facial vein and submandibular fascia to carefully retract the nerve superiorly. With or without the aid of a nerve stimulator, identification of the marginal mandibular nerve is recommended before elevation of underlying tissue to avoid nerve injury.

Vagus Nerve

The main trunk of the vagus nerve exits the skull base at the jugular foramen and descends through the neck in the carotid sheath, initially medial to the internal jugular vein and carotid artery, then posterior to these structures lower in the neck.[69] Injury to the main trunk of the vagus nerve is rare but is known to occur during carotid endarterectomy, particularly during revision surgery in which the incidence of this complication approaches 2%.[73] During neck dissection, injury to the main trunk of the vagus nerve may occur during posterolateral to anteromedial clearance of level III and IV lymph nodes and ligation of the internal jugular vein in the inferior neck or at the skull base. An obscured operative field due to hemorrhage may contribute to this complication. High vagus nerve injuries result in significant dysphonia from vocal fold paralysis and dysphagia with pooling of secretions from loss of pharyngeal muscle function and sensory loss. The superior laryngeal nerve (SLN) arises from the nodose ganglion of the vagus nerve and divides into a larger internal branch, which carries sensation from the supraglottic larynx and an external branch that supplies the cricothyroid muscle. The recurrent laryngeal nerve (RLN) arises from the vagus nerve, looping under the subclavian artery on the right and the aorta on the left, and passes through the neck in the tracheoesophageal groove. SLN and RLN injuries are best discussed in the context of thyroid surgery (see Chapter 124).

Spinal Accessory Nerve

In the neck the spinal accessory nerve (SAN) consists entirely of motor fibers to the sternocleidomastoid muscle (SCM) and trapezius muscle.[69] As the SAN travels medial to lateral, it passes anterior to, posterior to, or through the internal jugular vein in 70%, 27%, and 3% of cases.[69] Branches to the undersurface of the SCM arise approximately 4 cm below the insertion of the muscle at the mastoid tip. The main portion of the SAN then either pierces the muscle (82% of cases) or passes posterior to it (18% of cases) before running obliquely through the posterior triangle to the trapezius muscle.[69] Usually at least one contribution from the cervical plexus (fibers from C2, C3, or both) occurs in the posterior triangle.[74] These contributions are thought to be primarily proprioceptive rather than motor nerve fibers.

Several landmarks for identifying the SAN during neck dissection exist. In SND, when dissecting the medial border of the SCM, the SAN lies in the same plane as the vessels that perforate the muscle. Secondly, the nerve commonly enters the posterior triangle 2 cm above Erb's point, where the greater auricular nerve emerges along the posterior border of the SCM.[74] Also, the nerve passes under and pierces the trapezius approximately 2 to 4 cm above the clavicle.[74]

The impetus for the development of the MRND was largely to avoid the morbidity of SAN sacrifice during RND. "Eleventh nerve syndrome" consists of shoulder drooping, aberrant scapular rotation, inability to fully abduct the shoulder, and a constant, dull ache secondary to atrophy of the trapezius muscle and adhesive capsulitis of the glenohumeral joint.[75] A temporary, reversible period of shoulder dysfunction can be seen with nerve dissection in MRND, whereas a profound and unrecoverable loss can occur in patients with sacrifice of the SAN,[76] although not universally.[77] Early studies comparing RND, MRND sparing only the SAN, and MRND with preservation of the SCM, IJV, and SAN showed SAN dysfunction in 60%, 50%, and 30% of patients, respectively.[78] Contemporary studies of SND have demonstrated a 5% rate of shoulder droop after dissection of levels II to IV compared with 30% when levels II to V were dissected.[79] In one large series of patients undergoing MRND, SAN transection occurred in 12 of 714 (1.68%) nerves at risk; less severe forms of dysfunction were not reported.[72] Shoulder function–specific quality of life (QOL) instruments have shown no significant change from pretreatment scores after SND.[80] MRND patients reported worse QOL at 6 months but improved to SND levels by 1 year, while those undergoing RND had persistent disability.[80] It is important to distinguish nerve damage from direct muscle injury; for example, stiffness and atrophy of the SCM may occur after division of perforating vessels or vigorous retraction and might be mistaken for spinal accessory nerve injury. In addition, adhesive capsulitis of the glenohumeral joint may occur due to lack of proper postoperative shoulder rehabilitation and cause ongoing shoulder disability despite recovery of SAN function.

Prevention of injury is achieved by proper identification of the SAN using the previously named landmarks and meticulous handling of the nerve once identified.[81] Intraoperative electrophysiologic monitoring of the SAN has been described,[82,83] although the benefit of this technique in reducing SAN injury is unclear and the use of handheld nerve stimulators with visualization of trapezius or SCM muscle contraction usually provides sufficient confirmation of the identity and integrity of the SAN. Local anesthesia should be avoided during posterior triangle lymph node biopsy to assist identification and protection of the SAN, and thin skin flaps should be raised because the nerve is most superficial in the midposterior triangle.

Unintentional spinal accessory nerve division is best treated with primary neurorrhaphy (Fig. 122-6). If a tension-free anastomosis cannot be achieved or if a long segment of the nerve must be sacrificed for oncologic purposes, cable grafting using the greater auricular nerve can be performed.[84] Cable grafting yields favorable results in terms of subjective shoulder function, strength testing, and electromyography findings compared with patients in whom the spinal accessory nerve was sacrificed, but it does not fully restore shoulder function to a level equivalent to patients with an anatomically intact nerve.

Hypoglossal Nerve

The hypoglossal nerve exits the skull base at the hypoglossal canal. As it passes lateral to the internal and external carotid arteries, it gives off the superior root of the ansa cervicalis (composed entirely of cervical nerve fibers) and then courses medial to the posterior belly of the digastric muscle and the stylohyoid muscle. Distally, under the sublingual gland, the hypoglossal nerve branches to innervate the ipsilateral intrinsic muscles of the tongue.[69] Hypoglossal nerve injury is a rare complication of neck dissection, occurring in 3 of 714 (0.42%) nerves at risk in one large study.[72] The nerve is susceptible to injury during dissection of levels I and II, near the greater cornu of the hyoid bone, and adjacent to the carotid artery. The rich venous plexus near the nerve

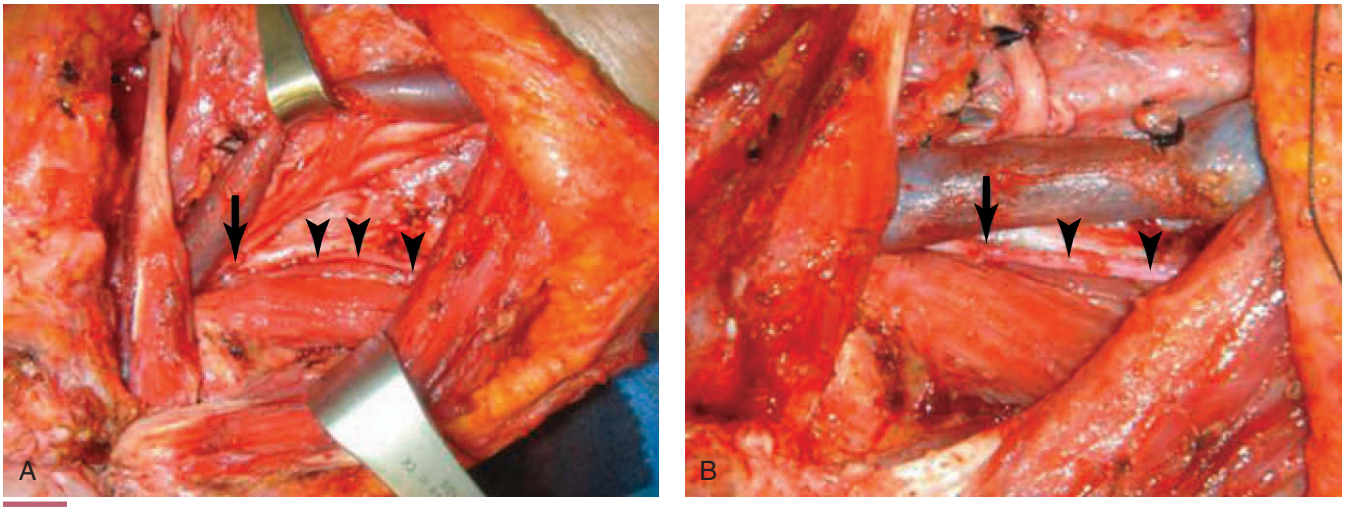

Figure 122-6. Spinal accessory nerve transection and repair. **A,** Right neck dissection with the internal jugular vein retracted medially and the sternocleidomastoid muscle retracted laterally, revealing a divided spinal accessory nerve (*arrow* at proximal stump, *arrowheads* along distal nerve). **B,** Appearance after primary neurorrhaphy *(arrow)* with a tension-free anastomosis (*arrowheads* along nerve). Normal shoulder function returned.

Figure 122-7. Phrenic nerve paresis. Postoperative chest radiograph showing right hemidiaphragm elevation after right radical neck dissection.

must be carefully controlled to prevent inadvertent injury. The deficits from hypoglossal injury include ipsilateral tongue weakness, deviation of the tongue to the affected side with protrusion, and difficulty with speech and swallowing. Management of nerve transection includes primary neurorrhaphy or cable grafting. Following nerve repair, residual tongue motion impairment occurs because of synkinesis but tongue atrophy is usually avoided.

Phrenic Nerve

The phrenic nerve arises from C3, C4, and C5 and is encountered in the base of the neck where it courses between the anterior scalene muscle and its overlying fascia.[69] The nerve then passes from the neck posterior to the subclavian vein to enter the thorax, innervate the ipsilateral diaphragm, and supply portions of the pericardium, mediastinum, pleura, and peritoneum.[19] Phrenic nerve paralysis is considered a rare complication of neck dissection, although phrenic nerve injury occurred in 14 of 176 (8%) consecutive neck dissections in one series.[85] Injury to the phrenic nerve leads to ipsilateral hemidiaphragm elevation with or without mediastinal shift on chest radiograph and symptoms such as cough, chest pain, or abdominal discomfort mediated by the somatic afferents (Fig. 122-7). The paresis is generally transient and without sequelae[86]; however, bilateral phrenic nerve injury with resultant respiratory failure has been reported.[87] Factors associated with phrenic nerve damage include a fibrosed or edematous anterior scalene muscle, tumor infiltration, or diffuse bleeding.[85] Preserving the fascial layer over the nerve and anterior scalene muscle is the primary method for prevention of injury.

Sensory Nerves

Lingual Nerve

The lingual nerve is primarily a branch of the mandibular division of the trigeminal nerve that carries general sensation from the anterior two thirds of the tongue. It also receives the chorda tympani nerve from the facial nerve, which carries taste from the same region of the tongue, as well as preganglionic parasympathetic fibers that enter the submandibular ganglion. The lingual nerve is encountered during level I lymph node dissection or other surgical procedures of the submandibular triangle. It is susceptible to injury because it is tethered inferiorly by its connections with the submandibular ganglion. Clinically, injury results in loss of taste from the ipsilateral anterior two thirds of the tongue. This complication occurs in up to 3% of patients undergoing submandibular gland excision[88] and may occur in neck dissections that include level I, although the exact rate of injury for the latter procedure has not been shown.

Greater Auricular Nerve

The greater auricular nerve (GAN) originates from the cervical plexus (C2, C3) and supplies sensation to most of the auricle and a small area of adjacent neck skin.[69] As mentioned previously, this nerve emerges from under the posterior border of the SCM in the top half of level V of the neck and travels across the lateral surface of the SCM toward the auricle. Sacrifice of this nerve during parotidectomy or neck dissection leads to a sensory deficit of the auricle that usually diminishes with time. Ear lobule numbness, however, tends to persist. Amputation neuroma of the divided GAN can occur. Recent reports with new modifications of technique indicate that preservation of at least the posterior branches of the GAN may be possible in approximately 70% of cases of parotidectomy with occasional transient sensory deficits.[89,90]

Cervical Sensory Nerves

Sensory branches of the cervical roots provide sensation to skin of the neck and shoulder. Sacrifice of these branches is often intentionally performed during RND or MRND and results in diffuse sensory loss across the entire neck. Some sensory deficit still occurs after SND with preservation of cervical rootlets, but the region of numbness is reduced significantly.[91]

Branches of the cervical plexus can also form amputation neuromas, which present as firm, painful masses in the lateral neck that are exquisitely

tender to palpation. Neuromas can be treated with excision, ligation, or implantation of the nerve stump into adjacent muscle or soft tissue.

Sympathetic Nerves

The cervical sympathetic chain consists of two to four ganglia with a connecting neural trunk running parallel and posteromedial to the carotid sheath.[69] Injury can occur during retraction of the carotid sheath to clear tumor or adjacent lymph nodes and may be temporary, related to traction, or permanent due to transection. Full loss of sympathetic innervation results in a classic Horner's syndrome (ptosis, miosis, and anhidrosis); the manifestations of partial losses vary depending on the location of the injury in relation to the ganglia (Fig. 122-8). Horner's syndrome occurred in 4 of 714 (0.56%) neck dissections in a recent case series.[72]

Figure 122-8. Right Horner's syndrome with ptosis and miosis after right neck dissection.

Sympathetic chain interruption is also thought to be the cause of first bite syndrome, the development of parotid region pain after the first bite of each meal associated with parapharyngeal space surgery.[92,93] The syndrome was first described in a series of patients undergoing vagal paraganglioma excision in which 9 of 46 (20%) patients experienced this complication.[92] Division of the sympathetic trunk does not always produce first bite syndrome—two patients in this series had known intraoperative transection of the sympathetic trunk but did not develop parotid pain.[92] Also, a recent study of surgical management of cervical sympathetic chain schwannomas showed that only 2 of 4 (50%) patients developed first bite syndrome.[94] The rate of this complication after neck dissection is unknown but low.

Chyle/Chest Complications

Chylous Fistula

A chyle leak is a complication of radical neck dissection in 1% to 2% of cases.[95,96] The majority of chyle leaks occur on the left side, where the thoracic duct enters the base of the neck and travels anterolaterally to empty into the left subclavian vein, usually at or within 1 cm of the junction with the internal jugular vein (Fig. 122-9A).[97] Up to 25% of

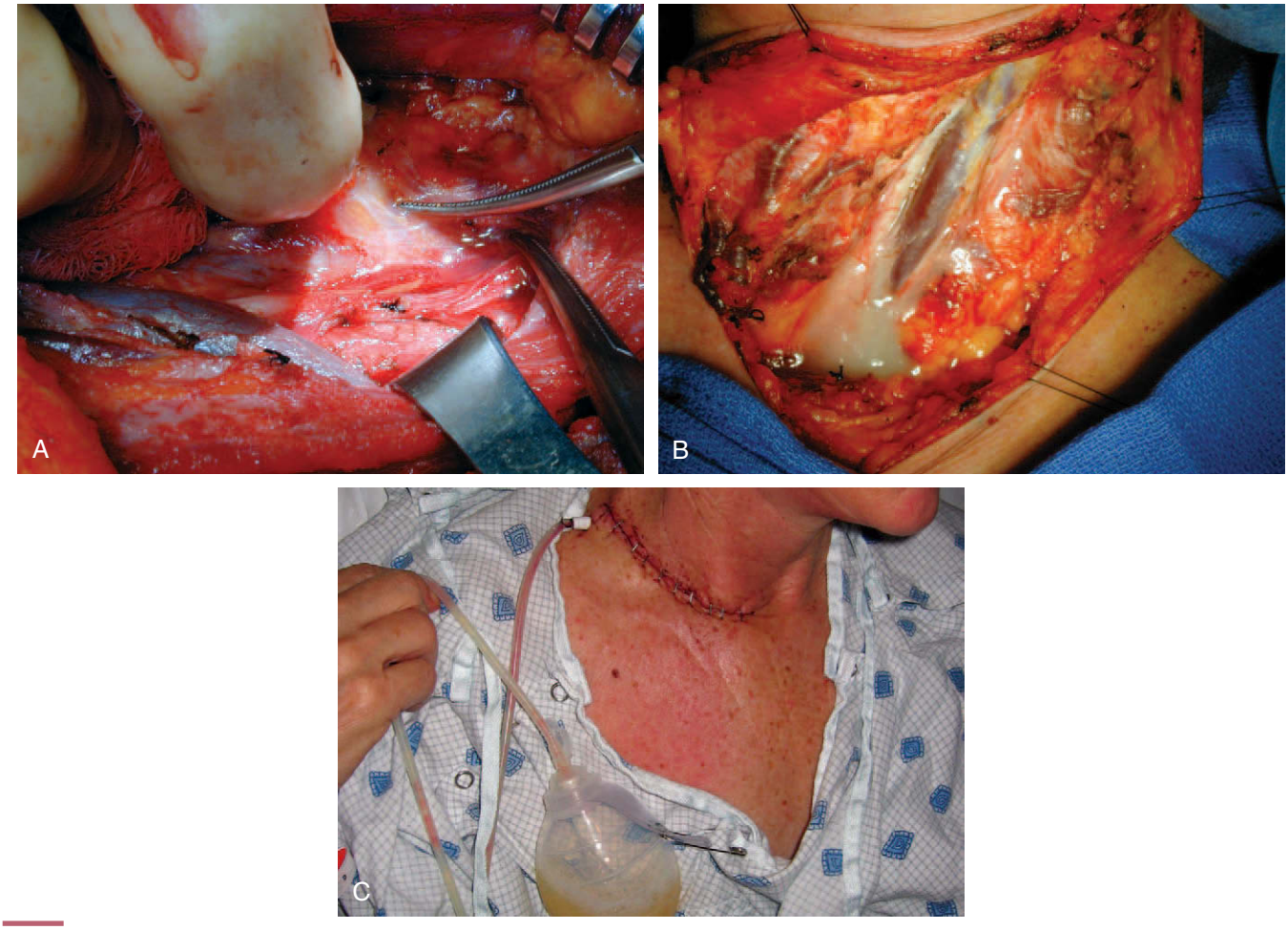

Figure 122-9. Thoracic duct and chylous fistula. **A,** An intact thoracic duct encountered during dissection of the inferior aspect of the neck. **B,** Intraoperative chyle leak noted during left neck dissection. **C,** Postoperative chyle leak presenting with typical milky drain output following resumption of oral diet.

chyle leaks, however, occur on the right side because of interruption of the right lymphatic duct on its path to the right subclavian vein.[98] The duct may be more accurately described as a plexus of tributaries and terminal ducts, each of which can create a chylous fistula if transected or incompletely ligated.[19]

Intraoperative suspicion of chyle leak during any lower neck dissection should be investigated by asking the anesthesiologist to administer positive ventilatory pressure. Pooling of milky fluid or visualization of discrete lymph vessels may occur (see Fig. 122-9B). Gentle exploration and meticulous ligation of the duct and identifiable branches with nonabsorbable sutures is recommended.[99] Adjunctive measures including use of the operating microscope, fat grafting, and application of Surgicel or a sclerosing agent to the region have been described.[100,101]

Postoperative leaks are usually discovered with the resumption of feedings. Most are easily diagnosed clinically by observing a change in the character of drain output from serosanguineous to milky (see Fig. 122-9C). Drain output fluid analysis may be helpful in diagnosis because the triglyceride (TG) level of normal neck dissection fluid is typically less than 100 mg/dL; a drain TG level greater than 100 mg/dL and greater than the serum TG level is diagnostic of chyle leak.[102] A chest radiograph is important to rule out concurrent chylothorax.

Several treatment algorithms for postoperative leaks have been proposed.[103] Conservative management with a medium chain triglyceride diet (which is absorbed directly into the portal circulation and circumvents the lymphatic system), closed drainage to promote adherence of skin flaps, and/or pressure dressings may be sufficient to promote spontaneous closure of most fistulae.[104] A potentially beneficial adjunctive measure is the use of a long-acting analog of the hormone somatostatin (octreotide 100 mcg subcutaneously three times a day), which reduces splanchnic blood flow and, therefore, decreases gastrointestinal chyle production.[105]

Conservative management is warranted for most chyle leaks, but high output leaks require operative intervention, regardless of the exact cutoff used (>500, >600, or >1000 mL per 24-hour period according to various studies).[96,98,103] Chylomas refractory to needle aspiration and pressure dressings may also require wound exploration for control.

Chylothorax

Chylothorax is a rare complication of neck dissection, but case reports continue to emerge.[106,107] Possible mechanisms include retrograde pressure formation from cervical thoracic duct ligation leading to extravasation or mediastinal propagation of a leak originating in the neck. Successful management includes dietary modifications and thoracentesis or thoracostomy tube drainage. Somatostatin analog injection may also be beneficial.[108] Rarely, operative intervention via thoracoscopic or open thoracotomy approaches are necessary to identify the leak and ligate the thoracic duct in the chest.

Pneumothorax

Extensive dissection at the base of either side of the neck can also threaten the cupula of the lung, with a risk of pleural transection leading to pneumothorax.[19] Early recognition of changes in ventilatory status, detection of decreased breath sounds on chest auscultation, and urgent treatment with needle decompression and/or thoracostomy tube placement are required. Air leak can also cause subcutaneous emphysema, which is rare during isolated neck dissection but may occur when concurrent tracheotomy is performed and the tracheotomy wound is closed too tightly.[19] The mechanism of postoperative pneumothorax may be extension of subcutaneous emphysema into the mediastinum and eventual rupture of the pleura.[109] Overall, pneumothorax is more common with tracheotomy, which carries a 1% to 2% risk of this complication.[109,110] The available evidence, however, does not support routine chest radiography after tracheotomy.[111,112] Chest radiographs after neck dissection are considered on a case-by-case basis.

Conclusion

Complications in neck surgery may occur despite the best efforts to prevent them. It is imperative that all head and neck surgeons be intimately aware of the risks associated with any given surgical neck procedure. Proper preoperative planning, early recognition of perioperative complications, and prompt, effective management can minimize the impact of complications that may occur.

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CHAPTER ONE HUNDRED AND TWENTY-THREE

Disorders of the Thyroid Gland

Phillip K. Pellitteri

Steven Ing

Brian Jameson

Key Points

- Thyroxine (T_4) and triiodothyronine (T_3), produced by the thyroid gland, are iodinated derivatives of tyrosine.
- Most circulating thyroid hormones are bound to one of several plasma proteins, the most important of which is thyroxine-binding globulin (TBG), which accounts for 70% of circulating hormone.
- Circulating T_3 accounts for most of the physiologic activity of thyroid hormone.
- The primary internal regulation of thyroid activity is through the anterior pituitary gland by way of thyrotropin-releasing hormone (TRH) released by the hypothalamus.
- The most effective biochemical study for assessing thyrometabolic status is through measurement of thyrotropin (thyroid-stimulating hormone [TSH]).
- The greatest clinical value of thyroglobulin measurement (TBG) is in the management of patients with differentiated thyroid cancer.
- Circulating thyroid antibodies, antimicrosomal and antithyroglobulin, are usually present in patients with autoimmune thyroid disease.
- The principal usefulness of the radioactive iodine uptake study is to differentiate hyperthyroidism into high-uptake and low-uptake states.
- A palpable, hypofunctional nodule in the presence of Graves' disease should be regarded as highly suspicious for harboring malignancy.
- A patient with Graves' disease, manifesting thyroid ophthalmopathy, should be treated with surgery and not radioactive iodine ablation to avoid complicating the ocular problems attributable to the disease.
- Acute or subacute thyroiditis may be treated with salicylates or nonsteroidal anti-inflammatory drugs. If the thyroiditis is resistant to these medications, a trial of prednisone may be considered.
- Acute suppurative thyroiditis is most commonly caused by staphylococcal and streptococcal species of bacteria.
- Toxic thyroid adenoma may be effectively treated by surgical resection, leaving a normally functioning thyroid remnant.
- Medical treatment for acute life-threatening thyrotoxicosis (thyroid storm) is antithyroid medication, propranolol to reduce peripheral effects of T_3, and glucocorticoid administration to combat cortisol degradation.
- Myxedema coma, a late manifestation of hypothyroidism, is managed with administration of large doses of intravenous T_4 and hydrocortisone.

Thyroid diseases are common. They occur in the form of abnormalities in the size and shape of the thyroid gland (goiter) and of abnormalities of thyroid secretion. Nonthyroidal illness can be accompanied by any alteration in thyroid physiology that can complicate the evaluation of thyroid status.

The scope of problems relating to thyroid disease can be so complex and encompassing as to create a major challenge to the diagnostic capabilities of the clinician. The patient may have such a variety of seemingly unrelated signs and symptoms as to lull the practitioner into a suspicion of hypochondriasis. This is especially true in our current "cost-effective" frame of mind, in which screening batteries of diagnostic tests are no longer in vogue, and time is of the essence. The patient's symptoms can be confusing and bizarre, leading the physician sometimes to nonspecific diagnoses, such as psychological problems with depression or anxiety, chronic fatigue syndrome, cardiac failure, fibromyalgia, and a host of other nonspecific entities. The dilemma is more than simply one of hyperfunction versus hypofunction or nodular versus diffuse or benign versus malignant. The examination should not merely comprise placing the thumb on the lower neck while the patient swallows a few sips of water and answers a couple of quick questions about heat intolerance, weight changes, and gastrointestinal function.

The thyroid gland controls body metabolism and has a profound effect on all bodily functions. In addition, the peculiarities of development and the strategic location of the thyroid gland may produce symptom complexes that divert the physician's attention away from the thyroid gland and toward the symptoms itself. To be proficient in the management of thyroid disease, the physician must be knowledgeable about all phases of the embryology, anatomy, endocrine function, genetic implications, and environmental issues that may affect the

thyroid, and he or she must be keenly suspicious of all the patient's signs and symptoms.

The patient's history and review of symptoms should be comprehensive. Generalized symptoms relating to hypothyroidism include weakness and fatigue with cold intolerance; weight gain; hair loss; edema of the hands and face; thick, dry skin and hair; and a decreased tendency to sweat. Otolaryngologic symptoms include hearing loss, dizziness, tinnitus, voice aberrations, middle ear effusion, and slurred speech with an enlarged tongue. Gastrointestinal symptoms include constipation, anorexia, intermittent nausea and vomiting, and dysphagia and bloating. Dysphagia is especially common if there is external compression on the esophagus by a circumferential or enlarged thyroid gland. Genitourinary symptoms include menstrual disorders and a tendency toward polyuria. Cardiovascular symptoms include bradycardia, some elevation of the blood pressure, intermittent angina, pericardial effusion sometimes, and peripheral edema. Central nervous system symptoms include daytime somnolence but insomnia at night, headaches and dizziness, mental and physical slowness, delayed reflexes, and psychological symptoms suggestive of depression or anxiety. Pulmonary symptoms include shortness of breath if there is tracheal compression or pleural effusion. Musculoskeletal symptoms include arthritis and stiffness of the joints with muscle cramps and weakness.

The general symptoms of hyperthyroidism commonly include a rapid heartbeat or perceptible palpitations, irritability, anxiety, easy fatigue, increased number of bowel movements with weight loss, and heat intolerance. Physical findings include tachycardia with or without arrhythmia; moist, warm skin; a fine tremor of the fingers; and often an enlarged thyroid. Eye signs may be present, including lid lag, eyelid retraction, and exophthalmos.

The thyroid gland is strategically located in the lower anterior neck in close relationship to the larynx, the trachea, the esophagus, the carotid sheath structures, the sympathetic chain, the recurrent laryngeal nerve, and the mediastinal structures. Diffuse or nodular enlargement, whether benign or malignant, may cause compression or invasion of these adjacent structures. Resulting symptoms include dysphagia, dyspnea, voice aberration, vocal cord paralysis, Horner's syndrome, superior vena cava syndrome, and sometimes pericardial or pleural effusions.

The medical history may disclose a history of thyroid agenesis; prior thyroidectomy; therapeutic irradiation with iodine-131 (^{131}I); external radiation therapy; Hashimoto's thyroiditis; history of laryngeal cancer or laryngectomy; history of cancer elsewhere with possible metastasis to the thyroid; and a history of other recent head and neck infections, which may have resulted in an inflammatory process within the thyroid gland.

Physical Examination

Facility with the examination of the thyroid and surrounding structures is essential for accurate diagnosis and appropriate management of malignant and benign thyroid disease. The patient is initially observed anteriorly. Some findings may be obvious, whereas others may be subtle. A clinical patient with hypothyroidism usually seems more lethargic, is perhaps overweight, and is slower in response. Skin and hair may appear dry and coarse. Conversely, a hyperthyroid patient may seem more anxious, is thinner, and is more apprehensive, with moist, warm skin and perhaps a visible tremor noted in the fingers. Eye signs, including exophthalmos, lid lag, or lid retraction, may or may not be present.

In either a hypothyroid or a hyperthyroid patient, a diffuse or nodular goiter commonly may be visible in the neck on simple inspection. The patient may have some aberration of the voice. The patient with hypothyroidism with myxedematous infiltration of the vocal cords has a husky, raspy tone of voice. A patient whose recurrent laryngeal nerve is compromised by pressure or tumor infiltration has the voice of a paralyzed vocal cord, which is breathy, barely audible, and inefficient as far as air use is concerned. In other circumstances, the voice may have a guttural quality signifying obstruction of the aerodigestive passage, usually at the level of the tongue base. This would suggest a lingual thyroid that has failed to descend along normal developmental pathways.

Horner's syndrome may be present with either benign or malignant thyroid disease. The patient may seem to have a hearing deficit in normal conversational situations. This may be the result of middle ear effusions, which can be drained and reversed. Inner ear myxedematous changes involving the cochlear or vestibular structures may contribute to a sensorineural type of hearing loss accompanied by tinnitus and vertigo. Facial swelling or plethora and the distention of the jugular veins may signify obstruction of the superior vena cava from benign or malignant substernal thyroid disease. Pemberton's sign should be elicited in patients with large goiters. Pemberton's sign is elicited by having the patient extend both arms above the head and observing for facial erythema, swelling, or distention of the jugular veins indicating cervicothoracic inlet obstruction.

After careful observation of the patient's general appearance, the neck is examined. The thyroid should be examined from behind the patient. The thyroid is palpated initially for gross pathology. The patient is then asked to swallow several sips of water. This moves the thyroid cephalad and makes the lower portion of the thyroid more easily approached. If the patient extends the neck less fully, the more inferior aspects of the thyroid (especially in patients with substernal goiter or kyphosis) may be easily and accurately examined. Moderate pressure in the tracheal groove on one side facilitates more accurate palpation of the contralateral lobe. The examiner notes the size relative to a normal thyroid gland. Similarly, the size and locations of nodules should be accurately recorded. A pyramidal lobe of the thyroid sometimes can be palpated in patients, especially patients with Graves' or Hashimoto's disease. A thyroid nodule with recent hemorrhage may be moderately tender, whereas an acute, suppurative, or subacute viral thyroiditis is usually exquisitely tender to palpation. Commonly, the pain from the thyroid radiates to the ipsilateral ear.

The texture of the thyroid may suggest the etiology of the disease. Autoimmune thyroid disease often is seen as a firm, bosselated (cobblestone-like) gland. This, in conjunction with a low or elevated serum thyroid-stimulating hormone (TSH) level, should strongly suggest Graves' disease (low TSH) or Hashimoto's thyroiditis (elevated TSH). Smooth nodularity of the thyroid usually represents colloid goiter. Although firm nodules may represent thyroid cancer, this clinical characteristic is not diagnostic.

Attention is next turned to the areas of lymphatic drainage of the thyroid. The superior pole and the lateral lobes drain superiorly and laterally toward the jugular lymph nodes, whereas the isthmus and lower poles of the thyroid drain inferiorly along the tracheoesophageal groove and into the mediastinum. Each side of the neck should be examined methodically from the mandible to the supraclavicular notch.

After observation of the external surfaces and examination of the external neck, attention is turned to the internal examination of the aerodigestive system. Intraorally, the tongue in a myxedematous patient may be enlarged and thickened. The base of the tongue should be examined carefully to rule out a lingual thyroid gland. If present, this would indicate a developmental anomaly. The lingual thyroid can enlarge during periods of increased hormonal demand, such as puberty and pregnancy. When this enlargement occurs, the guttural qualities of the voice may be even more profound. In addition, bleeding may occur from the lingual thyroid; finally, enlargement of the lingual thyroid may continue to the point of dysphagia and airway obstruction that may precipitate a semiemergent condition. Most commonly, hormonal treatment reduces the size of the mass on the back of the tongue. Occasionally, surgical intervention is required to ensure a safe airway. This area of the oropharynx and tongue base is usually readily examined with the aid of a tongue blade and a laryngeal mirror. In patients with an extremely active gag reflex, however, a better examination is usually obtained with a fiberoptic nasopharyngolaryngoscope.

The etiology of the patient's hoarseness is determined with a dynamic examination of the hypopharynx and larynx using the fiberoptic nasopharyngolaryngoscope. In the hypothyroid patient, the vocal cords are mobile. The vocal cords may exhibit myxedematous changes, however, causing them to be thickened and sometimes even polypoid along the edges of the vocal folds. The voice in these instances is quite harsh and raspy. The airway may become partially compromised by the

thickened myxedematous polypoid tissue, and sometimes it is necessary to trim this back surgically to ensure an adequate airway.

When one vocal cord is paralyzed, the airway initially becomes incompetent. The patient may cough or choke on liquids or secretions unless careful swallowing is followed. The larynx is inefficient and produces only two or three words per each breath of air. The voice is of an exaggerated, forced, whispered quality. As time passes, the larynx compensates by having the mobile vocal cord cross the midline to close the deficit in the airway partially. This compensation improves speech and swallowing almost to normal levels. It is important that preoperative laryngeal examination be done before thyroid surgery to establish the mobility of the vocal cords. Because it is possible to have a nearly normal sounding voice with one cord paralyzed, it is important for the operating surgeon to know that there is a paralyzed cord, as injury to the opposite cord would precipitate the more emergent situation of bilateral vocal cord paralysis, and the probable need for subsequent tracheostomy or thyroplasty or both. Paralysis of the vocal cords usually implies compromise of the recurrent laryngeal nerve on the ipsilateral side. This compromise may be secondary to pressure on the nerve, but more likely is caused by infiltration of the nerve by malignancy.

External compression on the trachea or esophagus or both by thyroid masses can lead to severe dyspnea or dysphagia or both. It is important to know whether the airway and esophageal involvement is secondary to external compression alone, or whether there is an element of tumor infiltration within these organs. Internal examination with a bronchoscope and an esophagoscope is necessary to determine the status of these organs. Radiographic studies sometimes are necessary to complement the examinations and to aid in surgical planning. Under such circumstances, barium swallow of the esophagus may outline the areas of obstruction. Elucidating the various etiologies of thyroid disease is often accomplished by considering the aggregate data obtained from the patient's history, clinical examination, chemical and imaging studies, and specific diagnostic examinations.

Physiology of the Thyroid Gland

The thyroid gland produces two hormones, 3,5,3′-triiodothyronine (T_3) and 3,5,3′,5′-tetraiodothyronine or thyroxine (T_4). Both are iodinated derivatives of tyrosine. Hormone production depends on an external iodine supply and on intrathyroidal mechanisms for concentrating ingested iodide and then incorporating it into the tissue-specific protein, thyroglobulin. The thyroid gland is unique within the endocrine system in having a large extracellular space, the follicular lumen, which is used for storage of the hormones and their precursors. As hormone is needed by the organism, thyroglobulin is retrieved by the cell, where the biologically active hormones are released from thyroglobulin before being passed into circulation (Fig. 123-1).

Iodide Transport

A daily dietary intake of at least 100 µg of iodine per day is required in humans to ensure adequate production of thyroid hormone. In North America, the average daily intake is higher than this, largely because of the use of iodine as a food additive.[1] In many parts of the world, however, consumption is significantly below the minimum level, and iodine deficiency is the leading cause of thyroid-related disorders.

The thyroid normally concentrates iodide 20-fold to 40-fold over the extracellular space and against an electrical gradient of approximately 40 mV. Key to this trapping action is a protein located in the basal membrane of the thyroid cell known as the sodium/iodide symporter (NIS).[2] NIS couples with the influx of Na^+ down its electrochemical gradient with the simultaneous influx of I^- up its electrochemical gradient. An Na^+,K^+-ATPase acts to maintain the Na^+ gradient. Iodide travels down its electrochemical gradient to the apical surface of the thyrocyte, where it is incorporated into thyroglobulin. More recent evidence suggests an apical membrane protein, pendrin, aids in releasing iodide into the follicular lumen.[3] Mutations in the gene and coding for this protein are responsible for the common hereditary disorder Pendred's syndrome, which is associated with mild hypothyroidism, goiter, and hearing loss.[3] Mutations in the gene coding for NIS have been identified in patients with iodide trapping defects, a rare cause of congenital hypothyroidism.[2]

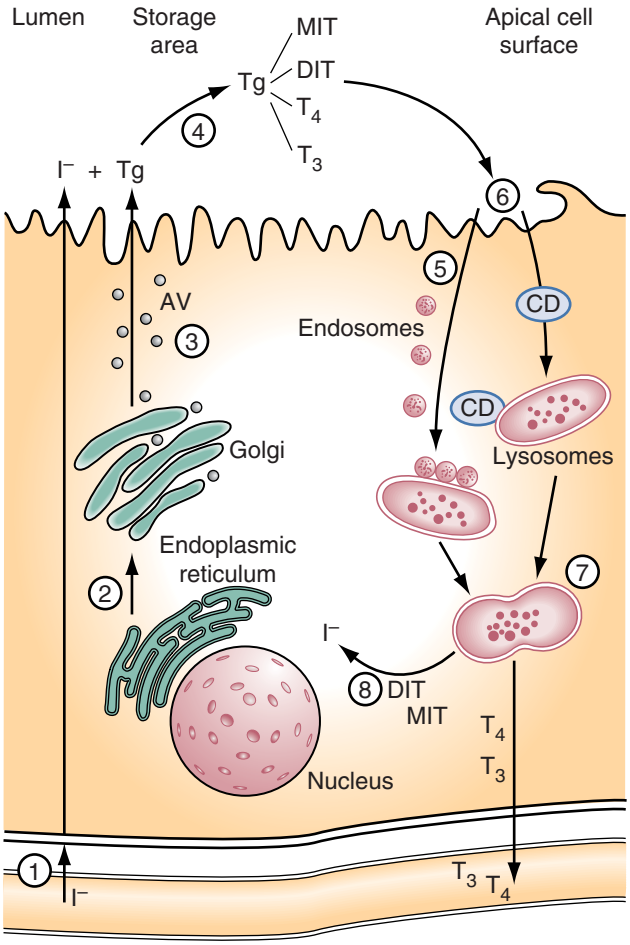

Figure 123-1. Synthesis and release of thyroid hormone. (1) Iodide transported into the thyrocyte at the basal cell membrane by the symporter (NIS) travels down its electrochemical gradient to the apical surface. (2) Polypeptide chain of thyroglobulin (Tg) is synthesized on the surface of the endoplasmic reticulum, then translocated into its lumen. Synthesis of carbohydrate units begins, and conformational changes transform the polypeptide chains into stable dimers. Tg enters the Golgi where carbohydrate units are completed. (3) Uniodinated Tg travels to the apical surface in small vesicles (AV). (4) Tg is iodinated, and iodotyrosyls are coupled to form T_4 and T_3 by thyroperoxidase in the presence of H_2O_2. (5) Tg, retrieved by micropinocytosis, enters the endosome-lysosomal pathway, where proteolysis and hormone release occurs. (6) Alternatively, Tg, retrieved by macropinocytosis, travels to lysosomes in colloid droplets (CD). (7) Thyroid hormones and precursors leave the lysosomes, and T_4 and T_3 enter the bloodstream. (8) MIT and DIT are deiodinated, and released iodide is recirculated. *(From Dunn AD. Thyroid physiology. In: Pellitteri PK, ed. Endocrine Surgery of the Head and Neck. New York: Delmar Publishing; 2003:50.)*

Thyroglobulin

Thyroglobulin is essential to thyroid physiology. It is a tissue-specific protein that serves as a matrix for the synthesis of hormone and as a vehicle for its storage.[4] The human thyroglobulin gene has been cloned and is located on the long arm of chromosome 8Q24. Thyroglobulin is a large dimeric glycoprotein of approximately 660 kD, consisting in humans of two identical polypeptide chains each of 2750 amino acids. About 10% of its weight is carbohydrate, and about 0.1% to 1% is iodine. Synthesis and maturation of thyroglobulin follow a pathway typical of proteins destined for secretion. The polypeptide chain is synthesized on the surface of the rough endoplasmic reticulum. As that passes through a series of intracellular compartments, it undergoes important post-translational modifications before reaching the

follicular lumen.[5] Carbohydrate units are added to the polypeptide chain as it is translocated into the lumen of the rough endoplasmic reticulum. Folding and dimerization of the polypeptide chain occurs within this compartment, aided by folding enzymes and a group of proteins known as molecular chaperones. Perturbations of this process result in block of protein transport beyond this point and cause congenital hypothyroidism.[5] Under normal circumstances, the properly folded thyroglobulin dimers migrate to the Golgi complex, where processing of the carbohydrate units are completed. Mature but as of yet uniodinated thyroglobulin is transferred from the Golgi complex to the apical cell surface in small vesicles.

Iodination and Thyroperoxidase

Newly formed thyroglobulin and iodide meet at the apical cell surface, where hormone synthesis occurs. This process includes (1) the oxidation of iodide; (2) its subsequent transfer to thyrosyl residues on thyroglobulin, producing monoiodotyrosine (MIT) and di-iodotyrosine (DIT); and (3) coupling of two iodotyrosine molecules, either one each of MIT and DIT to form T_3 or two of DIT to form T_4. Thyroperoxidase (TPO), an enzyme present in the apical cell membrane, is responsible for each of these steps.[6] Hydrogen peroxide (H_2O_2), required in the iodinating and coupling reactions, is generated at the apical membrane by a reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[7] Mutations in the TPO gene have been found in patients with congenital hypothyroidism caused by defective organification. Abnormalities in H_2O_2 generation seem to be more rare.

Under normal circumstances, iodide, when trapped, is rapidly incorporated into thyroglobulin so that little free iodide exists within the thyroid gland at any given time. The extent to which thyroglobulin is iodinated depends on the thyroid's iodide supply. At a level of 0.5% iodine, the thyroglobulin dimer in humans contains on average 5 residues of MIT, 5 of DIT, 2.5 of T_4, and 0.7 of T_3 of a total of 132 residues of tyrosine.[4]

Hormone formation involves the coupling of two residues of iodotyrosine within the thyroglobulin polypeptide chain. At the hormonogenic site, the "acceptor" DIT receives the iodinated phenol ring of the "donor" iodothyrosyl (either MIT or DIT) located at some distal site on the polypeptide chain. In the process, the alanine side chain of the donor remains behind, now presumably in the form of hydroalanine. Iodination in vitro of low iodine human thyroglobulin indicates that certain thyrocele sites are favored for early iodination, and that three or four major sites exist for hormone formation. The most important hormonogenic site is located five residues from the amino terminal thyroglobulin, whereas a second major site is located three residues from the carboxy terminal. The locations of donor thyrosyls are incomplete. To date, only one has been identified in human thyroglobulin, and this resides in the amino terminal region of the molecule.[4]

Storage and Release of Hormone

Most mature iodinated thyroglobulin is stored in the colloid as soluble dimers, although some (approximately 10%) highly iodinated molecules associate as tetramers. The colloidal nature of the follicular lumen is caused by its high concentration of protein. This intracellular space contains a large supply of iodine and hormone available to the organism, which protects it against times of iodine deprivation.

Hormone release is initiated by the retrieval of thyroglobulin from the follicular lumen. Under stimulatory conditions in some species, this process may occur by macropinocytosis. Pseudopods form at the thyrocytes' apical surface and engulf thyroglobulin as large colloid droplets. Under physiologic conditions in most species, however, including humans, thyroglobulin is retrieved by micropinocytosis into small vesicles. It is then passed through the endosome-lysosomal system, where the combined action of several acid proteases, including cathepsins B, D, and L, and lysosomal dipeptidase 1, releases the hormones and their iodotyrosine precursors from the polypeptide backbone.[4] Evidence suggests the iodo-amino acids may be preferentially cleaved first, but ultimately thyroglobulin is broken down into amino acids or small peptides within the lysosomes.

When released from thyroglobulin, the thyroid hormones and their precursors enter the cytosol; there MIT and DIT are deiodinated by an iodotyrosine-specific deiodinase, and the released iodide re-enters the iodine pool. Some T_4 is deiodinated to T_3 before it is released into the circulation by 5′-iodothyronine deiodinase similar to that found in peripheral tissue.[8] The mechanism by which T_4 and T_3 are released from the thyrocyte is unknown, but more recent evidence suggests a carrier protein may be involved.[9]

Circulating Thyroid Hormones

Less than 1% of circulating thyroid hormones exist as free iodo-amino acids. The remainder are bound in reversible, noncovalent linkage to one of several plasma proteins.[10] In humans, the most important of these is thyroxine-binding protein (TBG), accounting for approximately 70% of circulating hormone. The TBG molecule has one hormone-binding site with a very high affinity for T_4 and lower affinity for T_3. A second plasma protein transthyretin accounts for approximately 10% of circulating T_4 and T_3. Each transthyretin molecule has two hormone-binding sites, but the affinity of the first is lower than that of TBG, and that of the second site is very low for both hormones. Albumin also serves as a thyroid hormone transport protein. Although it has low affinity, its abundance allows it to account for 10% to 20% of bound circulating hormone.

The bound hormones are in equilibrium with the minute fraction of free circulating hormone that is available for use in peripheral tissue. Under euthyroid conditions, approximately 0.2% of T_4 and about 0.3% of T_3 in circulation is unbound. The larger free-to-bound ratio of T_3 to T_4 is caused by the lower affinity of TBG for T_3.[11] To date, no change in thyroid state has been attributed to abnormalities in these hormone-binding proteins, despite their apparent role in thyroid function homeostasis.

Metabolism of Thyroid Hormones

T_4 must first be deiodinated to T_3 to exert most of its biologic actions. Because little T_3 is directly synthesized on thyroglobulin, this transformation becomes an important step in hormonogenesis. Three iodothyronine deiodinases are present in mammals.[8] These are membrane-bound enzymes that are closely related structurally and are distinguished by the presence of selenocysteine at their active sites. Each has distinctive substrate preferences, activity characteristics, inhibitor sensitivities, and relative tissue specificity. Type I and II deiodinases, through their combined action, are responsible for generating approximately 80% of the total T_3 production.

Type I deiodinase is the primary source of circulating T_3 and is found in liver, kidney, and thyroid (where it is activated by TSH) tissues, and to a lesser extent in other tissues. Type I deiodinase is positively regulated by thyroid hormones and is greatly reduced under pathophysiologic states, such as starvation and nonthyroidal illnesses. It is inhibited by the antithyroid drug propylthiouracil. Type II deiodinase is present primarily in the central nervous system, the pituitary, the placenta, and the skin, and has more recently been found in the thyroid.[12] Its major role is thought to be in the local production of T_3, but it may also contribute to circulating T_3. In contrast to type I deiodinase, the type II enzyme is negatively regulated by thyroid hormone and is unaffected by propylthiouracil. Type III deiodinase inactivates T_4 and T_3 by inner ring deiodination in the five position, forming reversed T_3. The enzyme is present in the adult brain, skin, and placenta, and is present in high levels in fetal tissues, where it is thought to be important in protecting developing tissue from excess levels of thyroid hormone.[13]

Control of Thyroid Function

The anterior pituitary is the primary internal regulator of thyroid function, influencing virtually all phases of thyroid metabolism.[14] It secretes TSH, also known as thyrotropin, which is a 28- to 30-kD lipoprotein consisting of two subunits, α and luteinizing hormone. The α subunit is common to the pituitary hormones follicle-stimulating hormone and luteinizing hormone and to chorionic gonadotropin. The α subunit is unique to TSH, however, and is responsible for the binding of the hormone to its receptor in the basal membrane of the thyroid cell. On interaction with TSH, the receptor, a member of a family of G protein–coupled receptors, undergoes conformational changes that activate one

or two regulatory pathways. Most TSH effects are mediated by the activation of the cyclic adenosine monophosphate (cAMP) pathway; others involve the Ca^{2+}/phosphatidylinositol cascade. The pathway used to elicit a given effect may vary among species. TSH stimulates the efflux of iodide into the follicle and the resorption of colloid into the cell within minutes. Later effects include increased expression of the NIS, thyroglobulin, and TPO genes; stimulation of H_2O_2 production; promotion of glycosylation; and increased production of T_3 relative to T_4.

Circulating levels of TSH are controlled by the opposing influences of thyroid hormone and of thyrotropin-releasing hormone (TRH) from the hypothalamus.[15] The latter is a modified tripeptide secreted to the anterior pituitary by way of the hypothalamohypophyseal portal system. TRH binds to the plasma membrane of the thyrotrope and stimulates the release of TSH and the expression of its gene. Levels of circulating TSH are under strict control by the thyroid in a classic negative feedback system. As levels of thyroid hormone increase in response to TSH stimulation, T_4 and T_3 block the TRH-stimulated release of TSH in the thyrotrope. The thyroid hormones also act indirectly by inhibiting TRH gene expression in the hypothalamus.

Iodine supply is the major external factor influencing the thyroid state. Autoregulatory mechanisms present in the thyroid help to compensate for variations in iodide intake. In response to increasing doses of iodine, the thyroid initially increases hormone synthesis, but then reverses this process as intrathyroidal levels of iodide reach a critical level, and further organification is inhibited.

Withdrawal of iodide from the diet leads to a rapid decrease in serum T_4 and an increase in serum TSH. Serum T_3 levels initially are unaffected, but eventually decline with prolonged withdrawal. In response to TSH stimulation, the thyroid increases iodide uptake and organification, alters the distribution of iodo-amino acids within thyroglobulin by increasing the ratios of MIT to DIT and T_3 to T_4, and increases the intrathyroidal conversion of T_4 to T_3 by type I and II deiodinases.[8] With prolonged iodine deficiency, TSH-stimulated cell proliferation eventually leads to goiter.

Antithyroid Agents

Antithyroid drugs can inhibit thyroid hormone synthesis secretion or metabolism.[16] Common agents and their major actions are summarized in Table 123-1. Numerous agents used in the treatment of nonthyroidal illnesses may have profound effects on thyroid hormone production. Notable among these are the iodinated radiocontrast agents that are potent inhibitors of thyroid hormone deiodination, and can interfere with hepatic uptake of T_4 and binding of T_3 to nuclear receptors.[17] The antiarrhythmic agent amiodarone, which is also heavily iodinated, elicits similar alterations in thyroid hormone metabolism and action. Lithium, used in the treatment of bipolar illness, is a potent inhibitor of thyroid hormone release and acts by blocking thyroglobulin endocytosis.[18]

Table 123-1

Drugs Used in Hyperthyroidism

Drug	Usual Starting Dose
Propylthiouracil	200 mg PO tid
Methimazole	20 mg PO bid
Propranolol	10-40 mg PO qid
Saturated solution of potassium iodide (SSKI)	1-2 drops PO qd-tid
Compound solution of iodine (Lugol's solution)	2-5 drops PO qd-tid
Dexamethasone	2 mg PO qid
Prednisone	40-60 mg po qd
Ipodate	1 g PO qd
Lithium	300-450 mg PO tid
Perchlorate	1 g PO qd
Cholestyramine	2-4 g PO bid-qid
Colestipol	5 g PO one to five times a day
Octreotide	50-100 μg SC bid-tid
Diltiazem	120 mg PO tid

Thyroid Hormone Mechanism of Action

The thyroid has multiple effects on development, growth, and metabolism. The effects on development are widespread phylogenetically and can be dramatically observed during the course of amphibian metamorphosis. The appropriate levels of thyroid hormone during fetal and neonatal stages in humans are crucial for the normal maturation of the central nervous system, muscle, bone, and lung. In severe cases of thyroid hormone deficiency during this period, the syndrome of cretinism results with its associated mental retardation, deafness, mutism, and stunted growth.[19] Similarly, an excess of thyroid hormone during these critical developmental periods can result in neurologic abnormalities. The metabolic effects of thyroid hormone seem to be confined to birds and mammals, presumably evolving in response to the increased metabolic pressures of thermogenesis. Oxygen consumption and the metabolism of proteins, carbohydrates, and fats all are under thyroid hormone control.

Most effects of thyroid hormone are now believed to be exerted by interactions with specific nuclear thyroid hormone receptors, resulting in the altered expression of specific genes.[20] T_4 has little affinity for the nuclear receptors and first must be converted to T_3 to be effective. The receptors themselves belong to a large superfamily of nuclear receptors, which includes the steroid hormones, retinoic acid, and vitamin D. The thyroid hormone receptors are closely related isoforms, despite being encoded by two different genes (α and β).

The thyroid hormones may have some nongenomic actions, including plasma and mitochondrial membrane transport, familiarization of actin in astrocytes, and modulation of the activities of several enzymes including type II deiodinase. Such nongenomic effects tend to occur rapidly and, in contrast to nuclear events, T_4 may be as effective as, or more so than, T_3.

Thyroid Function Studies

Thyroid function may be assessed by measuring circulating thyroid hormone levels, serum TSH concentrations, and thyroidal ^{123}I uptake.

Circulating Thyroid Hormone Measurement

Radioimmunoassay remains the standard method for measuring serum total T_4, although isotopic methods may also be used. Previous methods, none of which are used today, include the protein-bound iodine test, the butanol extraction iodine test, and T_4 measurement by column or by competitive protein binding. Although the serum total T_4 measurement generally reflects the functional status of the thyroid gland, many factors may alter total T_4 levels without changing the individual's thyrometabolic status. The most common of these, in an ambulatory individual, is a change in concentration of TBG. High or low TBG states, with their respective increases and decreases in total T_4 concentrations, do not affect metabolic status.

Elevated total T_4 levels may also occur when there is production of endogenous antibodies to T_4, especially in patients with Hashimoto's thyroiditis or other autoimmune disorders, and occasionally in patients with Waldenström's macroglobulinemia associated with a benign monoclonal gammopathy.[21] Another condition of elevated total T_4 level is peripheral resistance to thyroid hormone. Individuals with this

condition may have goiter, and they may be hyperactive.[22] Patients with this disorder are euthyroid. Although rarely found, this disorder has led to inappropriate treatment for hyperthyroidism.

The most widely used measurement of thyrometabolic status is measurement of serum free T_4 by equilibrium dialysis.[23] When measured by the dialysis method, free T_4 is not affected by changes in binding protein concentrations or by nonthyroidal illness. This method is cumbersome and expensive, and it is not routinely performed. Commercial free T_4 levels are most commonly measured by immunoassay techniques, but their reliability is suboptimal because they may be affected by illness or significant changes in binding proteins.[24] The clinical usefulness of free T_4 measurements by any method may be limited.[25]

Although the thyrometabolic status is best reflected by the free T_4 level, from a clinical standpoint, an index or estimate of free T_4 is generally adequate. The free T_4 index is obtained by multiplying the serum total T_4 and an indirect assessment of thyroglobulin. Serum thyroglobulin is generally estimated by one of two methods—the thyroid uptake test and the T_3 uptake test.[25] The thyroid uptake test is directly proportional to thyroglobulin levels in serum, whereas the T_3 uptake test is inversely proportional to thyroglobulin levels.[26] The result, by use of either method, is that variances in serum thyroglobulin levels are largely eliminated, and the calculated free T_4 index accurately reflects actual free T_4 status. Extreme changes in thyroglobulin levels, or the presence of the severe nonthyroidal illness, may result in poor correlation between calculated and measured free T_4 levels.

T_3 is measured in serum by radioimmunoassay. Similar to T_4, T_3 is bound to thyroglobulin, although less avidly. Alterations in thyroglobulin levels result in changes in total T_3 (but not free T_3) concentrations. As with serum T_4, an estimate or index of free T_3 may be obtained by using the same formula employed in calculating the free T_4 index. Because most T_3 is derived from peripheral metabolism of T_4, clinical states or pharmacologic agents that impair normal T_4 metabolism result in lower T_3 levels.

The principles used for obtaining the serum T_3 are to determine the severity of hyperthyroidism and to confirm the diagnosis of suspected thyrotoxicosis in cases in which serum T_4 levels are normal or equivocal. In addition, the serum T_3 may be indicated in evaluating patients with autonomously functioning thyroid adenomas, in whom so-called T_3 toxicosis may be present. Such patients may have normal or borderline elevated serum T_4 levels along with suppressed serum TSH levels.[27]

Serum Thyrotropin Measurement

Until approximately 10 years ago, virtually all clinical TSH assays were performed by radioimmunoassay. By the mid-1980s, many commercial laboratories began using more sensitive immunometric TSH methods with either monoclonal or polyclonal antibodies. Functional sensitivity of these assays represented a 10-fold improvement in sensitivity over radioimmunoassay methods. More recently, nonisotopic immunometric TSH assays have been developed with a chemiluminescent label. These newer assays have a 10-fold greater sensitivity than the early immunometric TSH assays and are 100 times more sensitive than radioimmunoassay methods. These latest TSH assays, with a sensitivity of 0.01 mU/L, are currently termed third-generation TSH assays and represent the most sensitive method for detecting TSH level.[28]

The clinical application of TSH detection may be summarized as follows:

1. *The diagnosis of primary hypothyroidism*. The presence of an elevated TSH is confirmation of primary hypothyroidism. The degree of hypothyroidism may be determined by obtaining a serum T_4 level. TSH levels are also elevated in patients with subclinical hypothyroidism, in which total serum T_4 is normal or borderline low.

2. *Guidance of thyroid hormone replacement therapy*. The goal of treatment of primary hypothyroidism with levothyroxine is normalization of serum T_4 and TSH levels. Current TSH assays may detect over-replacement with levothyroxine because TSH concentrations would be low. Chronic over-replacement with levothyroxine may be associated with cardiac abnormalities, including ventricular arrhythmias and ventricular septal hypertrophy, and bone demineralization, especially in postmenopausal women.[29-31]

3. *Determination of TSH suppression in treating thyroid cancer*. Thyroid-suppressive therapy is part of the routine management of some patients with well-differentiated thyroid carcinoma because growth of these tumors may be TSH responsive. Treatment with levothyroxine is titrated to suppress TSH, while attempting to avoid clinical hyperthyroidism. With few exceptions, suppressed TSH levels, when measured in third-generation assays, correlate with absent TSH response.[32]

4. *Determination of suppressive therapy for nodular goiter*. TSH measurements are useful for following patients with either solitary or multinodular goiter, in whom suppressive thyroid hormone therapy may be used. Although the efficacy of levothyroxine suppression for benign goiter is not uniformly agreed on, it is still frequently used.

5. *Diagnosis of subclinical hyperthyroidism*. Patients with few or equivocal symptoms and signs of hyperthyroidism, with normal or borderline elevated total T_4 and total T_3 levels, and with suppressed serum TSH levels have subclinical hyperthyroidism.[33] Before the development of more sensitive TSH assays, these individuals usually went undiagnosed.

The fact that serum TSH is abnormal in hypothyroidism and hyperthyroidism would seem to make it ideally suited as a screen of thyroid status because, with rare exceptions, a normal TSH level would suggest normal thyroid hormone homeostasis. Experience in ambulatory individuals suggests that a normal TSH virtually excludes the possibility of thyroid dysfunction.[34] In addition, the serum TSH level is more sensitive than the serum T_4 level as a test for thyroid dysfunction because TSH can detect subclinical thyroid disorders in which serum total T_4 (and T_3) is usually normal. As a result of advances in TSH methodology, measurement of circulating thyroid hormones may become assigned to a second line of assessment of suspected thyroid dysfunction. Many investigators believe that the serum TSH is preferable as a screening method for thyrometabolic status.[11,29] Figure 123-2 is an algorithm for the use of TSH level in the evaluation of thyroid function.

Serum Thyroglobulin Measurement

Thyroglobulin is elevated in the serum of patients with nearly all types of thyroid disorders, limiting its usefulness as a diagnostic test. Its greatest clinical value is in managing patients with well-differentiated thyroid carcinoma. An elevated or increasing thyroglobulin level (after initial surgical and ablation therapy) suggests persistence or recurrence of tumor.[35] Thyroglobulin is measured by either radioimmunoassay or immunometric technique. Although antithyroid antibodies may cause interference with accurate thyroglobulin measurement in 10% of individuals, in these patients measurements of thyroglobulin and antithyroglobulin antibodies may be used concurrently to provide information regarding the tumor status.[35]

Thyroid Antibody Status

Circulating antithyroid antibodies, specifically antimicrosomal (AMA) and antithyroglobulin (ATA) antibodies, are usually present in patients with autoimmune thyroid disease.[36] Since the introduction of immunoassay techniques, the term antithyroperoxidase (anti-TPO) has become interchangeable with AMA. AMAs are detectable in more than 90% of patients with chronic autoimmune thyroid disease; nearly 100% of patients with Hashimoto's thyroiditis and more than 80% of patients with Graves' disease have positive titers.[37] Although ATAs are more specific than AMAs, they are less sensitive, and they are not as useful in the detection of autoimmune thyroid disease.[38] Elevated levels of AMA are also frequently positive in various other organ-specific autoimmune diseases, such as lupus, rheumatoid arthritis, autoimmune anemia, Sjögren's syndrome, type 1 diabetes mellitus, and Addison's disease.[39]

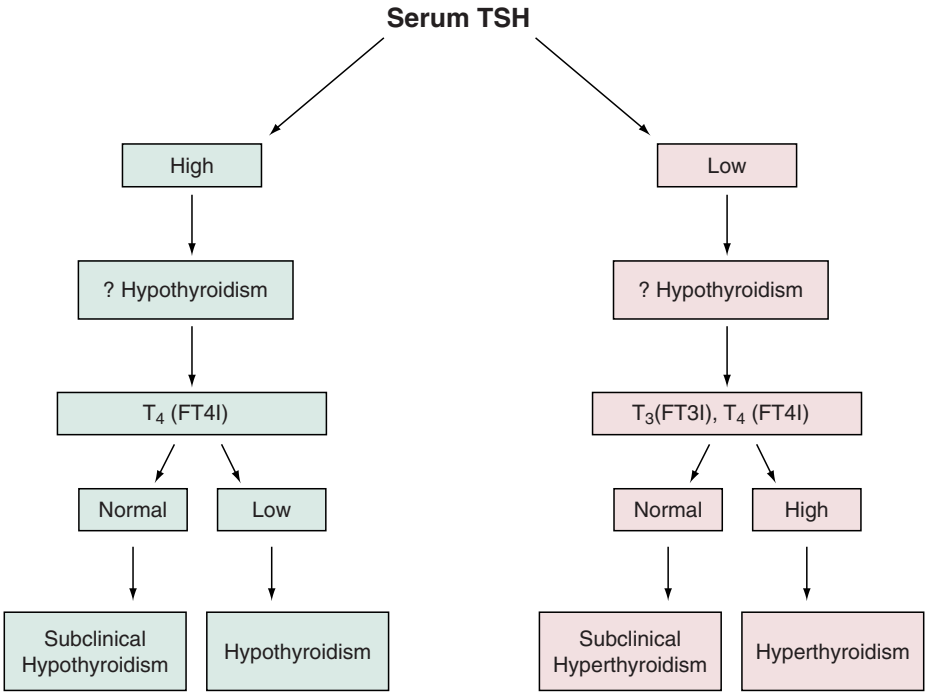

Figure 123-2. Algorithm for using the thyroid-stimulating hormone (TSH) level in the evaluation of thyroid function.

Approximately 15% of adults (especially women) in the United States have elevated AMA titers.[31] Prevalence of positive AMA titers increases with age, as does the incidence of primary hypothyroidism. The presence of a positive AMA titer should alert one to the possibility of hypothyroidism. Individuals with positive AMA and elevated TSH levels, even with normal serum total T_4 levels (subclinical hypothyroidism), had a 3% to 5% per year likelihood of clinical hypothyroidism developing.[40] In this manner, determination of AMA levels may be useful in the diagnosis of individuals with suspected autoimmune thyroid disease and in providing prognostic information when used in conjunction with TSH levels.

Thyroid-Stimulating Antibody Measurement

The immunopathogenesis of Graves' disease was first suspected in the mid-1950s, when it was observed that injecting sera of patients with Graves' disease into rats produced a prolonged uptake of radioactive iodine in the rat thyroid glands. The term long-acting thyroid stimulator (LATS) was coined.[41] Later, LATS was characterized as a 7S immunoglobulin, and in recent years several assays have been developed for the detection of LATS, or thyroid-stimulating antibodies. Two methods are commonly used; one depends on generation of cAMP, and the other is a radioreceptor method that relies on the TSH binding inhibitory properties of the immunoglobulin. The cAMP-generating assay is termed thyroid-stimulating immunoglobulin, and it is detectable in 90% to 95% of hyperthyroid patients with Graves' disease. The other assay detects stimulating and blocking antibodies termed TBII; it is detected in 85% of patients with hyperthyroid Graves' disease.[42] Thyroid-stimulating antibody measurements are not indicated for the routine diagnostic evaluation of suspected Graves' disease, but they may be useful when the diagnosis of Graves' disease is not evident.

Radioactive Iodine Uptake Test

The thyroidal radioactive iodine uptake test is performed by administering an isotope of iodine (usually ^{123}I) orally and measuring the percentage of the ^{123}I trapped by the thyroid gland. The test is usually performed 24 hours after administration of the isotope, although this may be done earlier. Before the development of sensitive and specific assays for thyroid hormones, the radioactive iodine uptake test was used as an adjunct to differentiate hyperthyroid from hypothyroid states, with elevated and low radioactive iodine uptake values implying hyperthyroidism and hypothyroidism. Today, the principal usefulness of this test is in differentiating hyperthyroidism into high-uptake or low-uptake states. Radioactive iodine uptake generally provides an accurate estimate of the thyroid gland's functional activity, provided that the iodide pool has not been expanded by iodine-containing drugs or radiocontrast materials.

Thyrotoxicosis

Thyrotoxicosis is a clinicopathologic and biochemical syndrome that results from exposure to excessive concentrations of thyroid hormones. The syndrome is usually categorized as overt or subclinical. Overt thyrotoxicosis is defined as high serum T_4 and T_3 concentrations and low serum TSH concentrations, whereby most patients have symptoms and signs of this entity. Subclinical thyrotoxicosis is defined as normal serum T_4 and T_3 concentrations and low serum TSH concentrations; most patients in this category have no symptoms or signs of this disorder. Thyrotoxicosis may develop suddenly or gradually, it may be transient or persistent, and it may be of little importance or life-threatening. The diagnosis may be obvious and may be confirmed easily by a few simple laboratory studies, or, conversely, it may be exceedingly difficult, requiring repeated serial investigations or prolonged clinical observation.

Thyrotoxicosis is a common disorder. The overall prevalence rates of overt and subclinical thyrotoxicosis gleaned from clinical surveys in the United States and Europe show an incidence of approximately 0.5 to 1 (United States) and 10 to 40 (Europe) per 1000 people.[43-46] Within these ranges, the rates are generally higher in older individuals, especially women, and seem to be lower in community-based screening programs.

Thyrotoxicosis is about 10 times more common in women than in men, especially with regard to overt thyrotoxicosis. The etiology is Graves' disease in 60% to 85% of patients, toxic nodular goiter in 10% to 30%, and toxic thyroid adenoma in 2% to 20%, with the remainder being represented by some type of thyroiditis.[47,48] The frequency of toxic multinodular goiter and toxic adenoma varies the most, being higher in areas of lower iodine intake.[48] Most individuals with Graves' disease are 30 to 60 years old, whereas individuals with toxic multinodular goiter or toxic thyroid adenoma are 40 to 70 years old.[49]

Pathophysiology

Thyrotoxicosis results from the unregulated release of T_4 and T_3 from the thyroid gland or the ingestion of excessive amounts of T_4, T_3, or both. It may be due to increased T_4 and T_3 synthesis and release because of intrinsic thyroid disease, excessive TSH, or, theoretically, excessive TRH secretion, or the production of other thyroid-stimulating hormones, such as TSH receptor stimulating autoantibody and chorionic gonadotropin. It also may be caused by the destruction of thyroid tissue with the subsequent release of stored T_3 and T_4.

Most patients with thyrotoxicosis have increased production of T_4 and T_3 and increased serum T_4 and T_3 concentrations. The increases in the production rate of T_3 and serum T_3 concentrations are characteristically greater than the increases found in T_4. Some patients with thyrotoxicosis have high serum T_3 concentrations, but normal serum T_4 concentrations. This is called T_3 thyrotoxicosis; in these patients, T_3 production is increased relative to that of T_4, even more than is the case in the usual patient with thyrotoxicosis. There are, however, no characteristic clinical manifestations of T_3. It is most common in patients whose thyrotoxicosis is due to a toxic thyroid adenoma or recurrent Graves' disease, but it may be due to hyperthyroidism of any cause. It is more common in regions where iodine intake is limited, and is rare in the United States. The abnormality responsible is probably relative intrathyroidal iodide deficiency.

Table 123-2 lists the causes of thyrotoxicosis. The cause of thyrotoxicosis can usually be identified with reasonable certainty by history and physical examination. The most important findings to elicit concern are the duration of symptoms, the degree and pattern of thyroid enlargement, and the presence or absence of thyroid pain and tenderness.

Graves' Disease

Graves' disease is the most common cause of thyrotoxicosis. It most commonly occurs in women 30 to 60 years old, but may occur in children and in men and women of any age. It is fundamentally an autoimmune disorder consisting of one or more of the following: hyperthyroidism (with thyrotoxicosis), diffuse thyroid enlargement, infiltrative ophthalmopathy (exophthalmos), localized myxedema (dermopathy), and thyroid acropachy. Toxic goiter may appear alone or may be seen before, during, or after ophthalmopathy develops. Ocular signs range from mild periorbital puffiness to severe extraocular muscle dysfunction with proptosis, corneal ulceration, and optic neuritis and blindness. The extrathyroidal manifestations of Graves' disease can occur in the absence of thyroid disease.

Table 123-2

Etiology of Thyrotoxicosis

- Graves' disease
- Thyroiditis
  - Subacute thyroiditis
  - Painless (silent) thyroiditis
  - Postpartum thyroiditis
  - Radiation-induced thyroiditis
- Exogenous thyrotoxicosis
  - Thyroid hormone–induced thyrotoxicosis
  - Iodine-induced thyrotoxicosis
  - Drug-induced and cytokine-induced thyrotoxicosis
- Toxic uninodular goiter (toxic thyroid adenoma)
- Toxic multinodular goiter
- Autosomal-dominant and sporadic thyrotoxicosis
  - McCune-Albright syndrome
- Ectopic thyrotoxicosis (struma ovarii)
- Thyroid carcinoma
- Thyrotropin-dependent thyrotoxicosis
- Pregnancy-related thyrotoxicosis
  - Gestational thyrotoxicosis
  - Trophoblastic tumors

The major gross anatomic abnormality in patients with Graves' thyrotoxicosis is diffuse thyroid enlargement. Microscopic examination reveals hypertrophy and hyperplasia of the thyroid follicular cells.

The natural history of Graves' thyrotoxicosis varies considerably among different patients. Some patients have a single episode of thyrotoxicosis (and Graves' disease) that subsides spontaneously in a few months or years. Other patients have lifelong thyrotoxicosis, and still others have repeated remissions and relapses. In patients who are treated with an antithyroid drug, the occurrence of a remission of Graves' disease means that prolonged therapy is not required. Although the disease potentially undergoes spontaneous remission, prolonged antithyroid medication, ^{131}I ablation, or surgery is usually necessary to control the thyrotoxicosis.

Well-differentiated thyroid cancer is approximately two times more prevalent in patients with Graves' disease than the general population.[50] Well-differentiated thyroid cancers may contain TSH receptors that can be stimulated by the thyroid-stimulating immunoglobulins. These tumors associated with Graves' disease tend to be larger and more aggressive and have more local invasion with more regional lymph node metastases than cancers occurring without Graves' disease.[51] When a palpable, hypofunctional thyroid nodule is found in a patient with Graves' disease, it has about 45% probability of being a thyroid malignancy.[51] A palpable hypofunctional nodule in a diffuse toxic goiter of Graves' disease should be regarded with great suspicion and, if proven to be malignant, should be managed aggressively.[50]

An antithyroid drug and ^{131}I are the two best treatments for patients with Graves' thyrotoxicosis. Both methods are effective, safe, and relatively inexpensive. They represent treatments for hyperthyroidism, rather than for the autoimmune process itself, although some antithyroid drugs may also have an immunosuppressive effect. The antithyroid drugs used in the United States are methimazole and propylthiouracil (PTU). These drugs inhibit thyroid hormone biosynthesis by inhibiting the oxidation and organification of iodine and the coupling of iodotyrosines, reactions that are catalyzed by thyroid peroxidase.[52] PTU also inhibits the thyroidal and extrathyroidal conversion of T_4 to T_3.[53] Both medications are concentrated in the thyroid, and intrathyroidal concentrations, especially of methimazole, remain high for considerably longer than do serum concentrations.[54]

Methimazole and PTU have immunosuppressive actions that may contribute to the occurrence of remissions of Graves' disease. Both drugs reduce the number of intrathyroidal T cells and inhibit lymphocyte function, including thyroid autoantibody production in vitro, although the latter actions require very high concentrations.[55]

The initial goal of antithyroid drug therapy is to inhibit thyroidal T_4 and T_3 synthesis almost completely. Neither drug has an effect on the release of thyroid hormones stored in the thyroid gland, and their onset of action is relatively slow, depending on the severity of disease, size of the goiter, drug dosage, and timing. Release of intrathyroidal hormone stores, which may be substantial, continues until they are depleted.

Adverse reactions to antithyroid drugs are uncommon and probably occur with equal frequency with either methimazole or PTU. Pruritus, urticaria or other rashes, arthralgia or myalgia, and fever occur in approximately 5% of patients taking either drug.[16] Both drugs may result in dysgeusia. The most dangerous adverse effect is agranulocytosis, which occurs in 0.2% or less of patients taking these medications.[46] Rare adverse effects include aplastic anemia, thrombocytopenia, hepatocellular hepatitis (with PTU), cholestatic hepatitis (with methimazole), and a lupus-like vasculitis (with PTU).[56,57]

Inorganic iodine inhibits thyroid hormone secretion, primarily by inhibiting thyroglobulin proteolysis, and inhibits thyroidal iodine transport, oxidation, and organification.[52] These actions require only a few milligrams of iodine daily, which may be administered in dosages of 5 to 10 drops of a saturated solution of potassium iodide (Lugol's solution) several times daily. This compound is often given in preparation for thyroidectomy, for its antithyroid action and because it reduces thyroid blood flow, theoretically reducing hemorrhage at the time of surgery. Lithium carbonate shows antithyroid action similar to that of inorganic iodine and has proved effective in doses of 300 mg three or four times daily.[58] Cholestyramine, when added to thionamides and

β-blockers, leads to a more rapid decrease in thyroid hormone levels, especially in the first few weeks.[53]

β-Blockers are valuable in the management of hyperthyroidism. Independent of alteration of thyroid function, these drugs minimize many of the sympathetic overdrive symptoms found in hyperthyroidism, such as tachycardia, excessive sweating, nervousness, tremors, and hyperdynamic cardiac activity. They are contraindicated in patients with severe thyrotoxic cardiomyopathy and heart failure, but may benefit patients with atrial fibrillation and heart failure.[59] β-Blockers are useful for reducing symptoms of thyrotoxicosis before and for several weeks after ^{131}I therapy, before subtotal thyroidectomy, in thyroiditis, and in thyroid storm.

In the United States, radioactive iodine is the preferred management for most adults, and for children in cases where thionamides fail or where the patient does not respond well to these medications. The goal of ^{131}I therapy is to reduce the amount of functioning thyroid tissue, and its efficacy is independent of whether a remission of Graves' disease occurs. A major advantage of ^{131}I therapy for patients with Graves' thyrotoxicosis are that usually only a single dose is necessary, it reduces thyroid size to normal in most patients, and it is safe.[60] Thionamides should be stopped for about 3 days before and after radioactive iodine therapy, which is usually effective in 2 to 4 months.

Radioactive iodine usually causes a transient exacerbation of thyrotoxicosis and rarely precipitates thyroid storm. This occurs within 1 to 2 weeks and is caused by radiation-induced thyroiditis; it is a major problem in seriously thyrotoxic or elderly patients. Thyrotoxicosis may also be exacerbated by stopping thionamides before radioactive iodine therapy. Hypothyroidism is not so much a complication of ^{131}I treatment as an almost inevitable consequence of it. Early hypothyroidism, defined as occurring within 1 year after treatment, is caused by the acute destructive effects of ^{131}I. Its frequency ranges from 40% to 80% in patients treated with higher doses of radioactive iodine.[61] Lower doses result in early hypothyroidism less often and persistent thyrotoxicosis more often.

Some physicians have been reluctant to treat young adults and especially adolescents and children with ^{131}I. The reasons are that it might cause thyroidal or other tumors or gonadal damage, or the patient may be pregnant, which is an absolute contraindication to the treatment. ^{131}I crosses the placenta and can destroy the fetal thyroid, and care must be taken to ensure that any woman about to be treated with ^{131}I is not pregnant.

Surgical therapy for thyrotoxic Graves' disease is effective and expeditious. The classic operation for surgical treatment of Graves' disease is subtotal thyroidectomy. Performing this operation either unilaterally or bilaterally, a narrow margin of thyroid tissue in the superolateral aspect of the thyroid where the recurrent laryngeal nerve enters the larynx is preserved by dividing across thyroid tissue at that location.[62] This operation provides the additional benefit of preserving the blood supply to the superior parathyroid gland on one or both sides. The intended goal of subtotal thyroidectomy is to leave 3 to 6 g of thyroid tissue, providing the benefit that patients become euthyroid without hormone replacement therapy.[32] The amount of thyroid tissue remnant preserved directly affects the recurrence rate of hyperthyroidism and the development of long-term hypothyroidism.[63] For patients who have larger remnants preserved, an increased incidence of recurrent hyperthyroidism is noted that can often be treated efficiently with radioactive iodine ablation because of the preserved small amount of residual thyroid tissue.[64] Patients in whom more complete thyroid removal is performed are generally guaranteed to have resolution of their hyperthyroidism; however, long-term hypothyroidism would be the outcome of therapy.[65]

Authors favoring more complete surgical resection of thyroid tissue in the form of near-total thyroidectomy for Graves' disease point out that long-term hypothyroidism may be easily remedied by appropriate hormone replacement therapy, whereas recurrent hyperthyroidism, as a result of leaving behind a larger than intended thyroid remnant, carries with it the need for further treatment.[66] Arguments have been raised in favor of subtotal thyroidectomy as a means by which complications such as permanent hypoparathyroidism and recurrent laryngeal nerve injury may be avoided.[66] The rate of permanent recurrent laryngeal nerve injury approaches zero, however, as does the rate of long-term hypocalcemia, in patients operated by experienced surgeons.[67] The general recommendation for the surgical approach in patients with indications for thyroidectomy is a near-total thyroidectomy, completely eliminating the potential for recurrent or persistent hyperthyroidism.[68,69]

The absolute indications for surgical treatment for Graves' disease are in patients who have significant adverse reactions to thionamide drugs and cannot be appropriately blocked before radioactive iodine administration.[70] Included in this category are patients with very severe skin reactions, hepatic damage, or agranulocytosis. Other indications for surgery in patients with Graves' disease include very large thyroid glands in excess of 75 g and neoplasia either suspected or proven within the setting of diffuse toxic nodular goiter.

Surgical therapy is relatively indicated in young women of childbearing age, who wish to attempt achieving pregnancy or who are in the process of lactating and want to continue to do so. An additional relative indication for surgery as opposed to radioactive iodine is moderate or severe ocular symptoms related to Graves' ophthalmopathy. Ophthalmopathy may be worsened with radioactive iodine administration secondary to the development of tissue edema and worsening of the ocular symptoms.[71]

Patients undergoing surgery for Graves' thyrotoxicosis require preoperative preparation so as not to induce thyrotoxicosis on induction of general anesthesia and subsequent manipulation of the thyroid intraoperatively. This is accomplished by administering antithyroid drug treatment 4 to 6 weeks and inorganic iodine treatment for 7 to 10 days preoperatively. Treatment with a β-adrenergic antagonist drug for several weeks, with or without concomitant inorganic iodide for 10 to 14 days, also has proved to be safe and effective preoperative therapy.[72]

Postoperative problems after thyroidectomy include wound hematoma, transient or permanent hypocalcemia, vocal paresis or paralysis, recurrent thyrotoxicosis, and transient or permanent hypothyroidism. The frequency of nonthyroid complications is low, especially in experienced surgical hands. Transient hypocalcemia may occur secondary to temporary hypoparathyroidism or the healing of thyrotoxic osteopenia. The incidence of wound hematoma is less than 1%, as is the incidence of permanent hypoparathyroidism. In addition, the risk of permanent injury to the recurrent laryngeal nerves in the setting of initial surgery is a fraction of 1%.[74]

Thyroiditis

The thyrotoxicosis that occurs in all forms of thyroiditis is caused by T_4 and T_3 release from thyroglobulin as a result of thyroid inflammation and disruption of thyroid follicles. Because the stores of thyroglobulin are limited, and the new T_4 and T_3 synthesis ceases, thyrotoxicosis is generally transient. Approximately half of patients with subacute or granulomatous thyroiditis have clinical manifestations of thyrotoxicosis, and a significant proportion of the remainder have high serum T_4 and T_3 concentrations.[75] This illness is dominated by nonspecific systemic manifestations of inflammation, including fever, malaise, and myalgias. In addition, local symptoms of thyroid pain and tenderness are also noted that may be severe. Approximately 50% of the patients have a history of a recent upper respiratory tract infection preceding the illness. Any manifestations of thyrotoxicosis together with thyroid pain and tenderness are usually short-lived, lasting approximately 4 to 6 weeks or less. This inflammatory and thyrotoxic phase may be followed by transient hypothyroidism, but permanent hypothyroidism is rare. The thyroid gland is usually firm in consistency and may be quite hard. Cervical lymphadenopathy is uncommon. If pursued, thyroid radionuclide uptake scanning is generally low, and ultrasonography reveals thyroid hypoechogenicity.[76]

Indirect evidence suggests that subacute thyroiditis may be a viral illness, but conclusive proof is lacking. The disorder has been associated with mumps, influenza, adenovirus, and other viral infections, and small epidemics of subacute thyroiditis have been reported.[77]

The inflammatory and the thyrotoxic components of subacute thyroiditis may be so mild and transient that no therapy is required. More often, thyroid pain and tenderness result in sufficient discomfort

to warrant anti-inflammatory therapy. Salicylates in dosages of 2.4 to 3.6 g daily or high doses of other nonsteroidal anti-inflammatory drugs usually provide effective relief. Patients with severe thyroid pain and tenderness and patients who do not improve readily and quickly with one of these medications should be treated with prednisone in a dosage of approximately 40 mg daily for 3 to 4 weeks, after which the dose should be gradually reduced and then discontinued to minimize the likelihood of recurrence. Anti-inflammatory therapy promptly relieves not only the symptoms of subacute thyroiditis, but also probably reduces thyroid hormone release, accelerating recovery from thyrotoxicosis. Thyrotoxicosis itself usually requires no therapy, but in patients in whom thyrotoxic symptoms may become a problem, a β-adrenergic drug may be administered for approximately 1 to 2 weeks.

Thyrotoxicosis, which is caused by thyroid inflammation in the absence of thyroid pain and tenderness, is known as painless or silent thyroiditis and has also been termed subacute lymphocytic thyroiditis. It is an uncommon cause of thyrotoxicosis. In contrast to Graves' disease, it occurs in almost equal proportions of men and women. The thyroid gland is not painful or tender and does not appear enlarged, or perhaps only slightly enlarged. In contrast to subacute thyroiditis, there is generally no history of antecedent upper respiratory tract infection. Generally, no extrathyroidal manifestations of Graves' disease are present in this disorder. When present, the thyrotoxicosis associated with painless thyroiditis lasts 2 to 6 weeks and is followed by either recovery or transient hypothyroidism that lasts an additional 2 to 8 weeks. Approximately half of the patients later had goitrous autoimmune thyroiditis, hypothyroidism, or both. Painless thyroiditis with thyrotoxicosis likely may represent a variant form of chronic autoimmune thyroiditis.

Radiation-induced thyroid follicular necrosis and inflammation occur regularly after ^{131}I therapy and occasionally are sufficiently intense to cause exacerbations of thyrotoxicosis, with or without thyroid pain and tenderness. These complications of ^{131}I therapy are most likely to occur 1 to 2 weeks after treatment, last 1 to 2 weeks, and then subside spontaneously.

Acute suppurative thyroiditis is most commonly caused by *Staphylococcus aureus,* hemolytic streptococcus, or *Streptococcus pneumoniae,* but occasionally is caused by other organisms, such as *Fusobacterium* and *Haemophilus*.[78] This bacterial infection of the thyroid gland may be the result of trauma, hematologic seeding from a distant infected site, or direct extension from a deep cervical infection. The infection is usually localized to a single lobe, and most commonly develops an abscess cavity that may rupture through the glans capsule, extending into the mediastinum or the deep neck spaces along fascial planes. This disorder is especially common in children, in whom a prodrome of malaise is followed by the acute onset of fever, neck pain and tenderness, severe systemic symptoms, and marked leukocytosis. Referred pain to the homolateral mandible and ear may be present, and typically the child fixes the head and neck in a single position similar to torticollis. Localized tenderness over the gland and pain on head movement is commonly noted. This disorder may be difficult to distinguish from subacute nonsuppurative thyroiditis, but the pain is generally more severe, the thyroid hormone levels are generally normal, the erythrocyte sedimentation rate is normal, and the leukocyte count is high. Although the diagnosis is generally made on clinical grounds, needle aspiration of the abscess cavity establishes the bacterial organism causing the infection.

The initial therapy is the administration of high-dose antibiotics, usually penicillinase-resistant penicillin together with a cephalosporin, although antibiotics that cover anaerobic organisms should be considered. Antibiotic therapy that is started before the cavitary phase of the infection may be successful in limiting the progression of infection. When an abscess has been shown on needle aspiration, however, surgical drainage is usually required. Drainage may involve a partial thyroidectomy to remove all evidence of abscess and necrotic tissue and to prevent recrudescence. The neck should be drained externally until purulence ceases, and antibiotics should be continued for at least 2 weeks after the surgical procedure. Thyrotoxicosis during the course of infection and post-treatment hypothyroidism rarely develop in this entity in contrast to other types of inflammatory thyroiditis.

Exogenous Thyrotoxicosis

Thyrotoxicosis may occur as a result of either intentional or accidental administration of inappropriately high doses of thyroid hormone initiated by caregivers or patients themselves. Important clues to the presence of exogenous thyrotoxicosis are the absence of thyroid enlargement or the failure of thyroid enlargement to regress much if the treatment was given for this purpose. This occurs together with normal or low serum T_4 concentrations if the patient is taking T_3 or preparations containing T_3. These patients also show low thyroid radioactive iodine uptake values and low serum thyroglobulin concentrations. Despite the ability of iodine supplementation to decrease the size of goiter and to improve thyroid function in patients living in regions of endemic goiter, it has the potential to induce thyrotoxicosis in these same patients. This usually occurs as a result of a preexisting thyroid abnormality that results in autonomous thyroid secretion—Graves' disease or, more commonly, a nodular goiter—but insufficient iodine intake to permit excessive production of T_4 and T_3. Iodine-induced thyrotoxicosis may also occur in nonendemic goiter regions.[79] Most of these patients have autonomously functioning thyroid tissue, such as a multinodular goiter or a thyroid adenoma, that transports iodide poorly.

Amiodarone, because it contains iodine, can cause iodine-induced thyrotoxicosis in patients with nodular goiter.[80] It may also cause painless thyroiditis that is sufficiently severe to cause thyrotoxicosis, apparently because of a direct toxic effect of the drug or one of its metabolites.

Approximately 2% of patients who are treated with interferon-α have thyrotoxicosis develop, caused mostly by painless thyroiditis, but sometimes by overt Graves' disease.[81] This thyrotoxicosis is generally more subclinical than overt.

Toxic Thyroid Adenoma

Toxic uninodular goiters or toxic thyroid adenoma are autonomously functioning thyroid neoplasms.[82] Among patients with these adenomas, about 20% have overt and 20% have subclinical thyrotoxicosis at the time of diagnosis.[83] Although these neoplasms occur in adults of all ages and occasionally in children, most patients having thyrotoxicosis are in older age groups. Hemorrhagic infarction of a nontoxic thyroid adenoma may result in a transient thyrotoxicosis.[84]

The characteristic finding in patients with toxic thyroid adenoma is a solitary thyroid nodule, which is usually 3 cm or more in diameter. Radionuclide uptake imaging of the thyroid shows intense nuclear uptake in the location of the palpable nodule and nearly complete absence of uptake in the remainder of the thyroid gland.

Management of the toxic adenoma is required unless spontaneous infarction occurs because the resultant thyrotoxicosis is usually permanent. Definitive treatment may be obtained by either surgical resection of the adenoma through thyroid lobectomy or ^{131}I ablative therapy. Definitive ^{131}I therapy carries a slight to moderate risk of either transient or permanent hypothyroidism after completion of therapy, although with appropriate dosing of ^{131}I, this risk may be minimized. Surgical resection may be carried out after 4 to 6 weeks of antithyroid drug administration and a 7- to 10-day course of inorganic iodine therapy in the form of Lugol's solution. Complications after lobectomy are generally exceedingly rare, and the surgical resection is usually definitive, resulting in no evidence of recrudescent thyrotoxicosis or evidence of hypothyroidism.[85]

An alternative approach that is performed more commonly in Europe than in the United States is the percutaneous administration of ethanol directly into the adenoma by use of ultrasound needle guidance. Although there may be some discomfort associated with the injections, long-term complications are rare, and it seems to be a safe procedure done in appropriately experienced hands. The shortcoming of this technique is that it may require multiple treatment sessions. This approach may be desirable in patients who are poor candidates for surgical resection and who wish to avoid exposure to radioactive iodine.

Toxic Multinodular Goiter

Thyrotoxicosis may occur late in the natural history of multinodular goiter, usually in women 50 years old or older. The characteristic

patient with this disorder has a long history of thyroid enlargement with insidious development of subclinical and then subsequently overt thyrotoxicosis. These patients generally do not have ophthalmopathy or localized myxedema and do not undergo spontaneous remissions; thyrotoxicosis generally persists until the autonomous thyroid tissue is destroyed.

^{131}I is generally the treatment of choice for patients with thyrotoxicosis caused by a multinodular goiter, primarily because spontaneous remission does not occur, and because surgical resection generally requires removal of most of the thyroid gland. Patients who are not candidates for radioactive iodine therapy or who refuse this modality may undergo surgery after preparation with an antithyroid medication and inorganic iodine therapy, similar to patients being treated for Graves' disease surgically. The usual operation is either bilateral subtotal thyroidectomy or near-total thyroidectomy with preservation of a 3- to 6-g remnant of thyroid tissue. Surgery is more effective in rapidly reducing the effects of thyrotoxicosis than is ^{131}I, and is attractive in terms of volume reduction of goiter size. Surgery may be more likely to result in long-term or permanent hypothyroidism.[86]

Ectopic Thyrotoxicosis

The only recognized etiologies of thyrotoxicosis secondary to excessive ectopic thyroid hormone secretion are dermoid tumors and teratomas of the ovary. Most of the uncommon patients with substantial amounts of thyroid tissue in their tumors (struma ovarii) who have thyrotoxicosis also have Graves' disease or a multinodular goiter.[87] They have one of the common causes of thyrotoxicosis, affecting the thyroid gland and the ectopic thyroid tissue within the ovarian tumor. In the absence of a functional thyroid gland because of surgical removal or radioactive iodine ablation, the ovarian tumor may be the only source of excessive thyroid hormone in these patients when it contains a toxic thyroid adenoma.[88]

Special Situations in Thyrotoxicosis

Subclinical Thyrotoxicosis

Subclinical thyrotoxicosis is characterized chemically by a normal serum T_4 and T_3 with low TSH concentrations. Most patients with subclinical thyrotoxicosis are asymptomatic, but a few may have nonspecific symptoms or physical signs compatible with overt thyrotoxicosis. The course of this disorder generally varies, with some patients showing resolution within weeks to years, others maintaining a state of subclinical thyrotoxicosis, and a smaller percentage (approximately 10%) showing the development of overt thyrotoxicosis.[89] There seems to be some increased risk of progression to overt thyrotoxicosis in patients who also have thyroid adenomas, multinodular goiters, or history of Graves' disease.[90,91]

If the disorder is due to overt administration of exogenous thyroid hormone, the treatment of choice is to reduce the dosage of thyroid hormone supplementation. If the disorder is secondary to native thyroid disease, treatment is rarely required, primarily because the disorder generally remains asymptomatic. If the disorder is associated with a solitary thyroid adenoma, surgical resection of the adenoma or ^{131}I therapy may be a treatment option. In the setting of multinodular goiter or Graves' disease, patients may be treated with ^{131}I or antithyroid medication or both.

Thyroid Storm

Severe, life-threatening thyrotoxicosis is referred to as thyroid storm. This disorder usually occurs abruptly in a thyrotoxic patient who has had an acute infection or other medical illness, an injury, or a major operation. It may also occur after ^{131}I therapy, discontinuation of an antithyroid medication, or spontaneously.

The index clinical findings in patients with thyroid storm are fever greater than 38.5°C, tachycardia, and generally some type of central nervous system dysfunction. Central nervous system abnormalities include anxiety; agitation and delirium; possibly acute psychosis or seizures; and, as a terminal event, coma. Severe cardiovascular effects, such as congestive heart failure or atrial fibrillation, may also be present.[92]

Determinative laboratory abnormalities in patients with thyroid storm are generally not found. Serum T_4 and T_3 concentrations may be high, but no more so than in ordinary thyrotoxicosis. Serum free T_4 and T_3 concentrations may be more elevated than in less ill patients with thyrotoxicosis.[93]

The treatment of thyroid storm should be directed toward decreasing production of T_4 and T_3, peripheral production of T_3, and the peripheral actions of thyroid hormone, and administering supportive treatment to maintain adequate cardiovascular and central nervous system function. Antithyroid medications should be given in large doses, if necessary by nasogastric tube or rectally. Propranolol given orally or intravenously is the most immediately effective treatment for tachycardia and neuromuscular dysfunction of thyroid storm. Glucocorticoids are usually given in large doses, such as 50 mg of hydrocortisone or 2 mg of dexamethasone intravenously every 8 hours. The rationale for glucocorticoid therapy is that adrenocorticotropic hormone and cortisol secretion may not increase sufficiently to meet cortisol requirements in patients who are quite ill and in whom cortisol degradation is increased. Inorganic iodine should be given orally or by nasogastric tube in a dose of 50 to 100 mg four times daily to inhibit the thyroidal release of T_4 and T_3 after administration of the antithyroid medication. Additional supportive systemic therapy should include treatment to reduce hyperpyrexia and appropriate parenteral fluid and electrolyte support.

Hypothyroidism

Prevalence

Hypothyroidism affects women fourfold to sixfold more often than men and increases with advancing age. The National Health and Nutrition Examination Survey (NHANES III), a sample of 17,353 individuals 12 years old and older representing the geographic and ethnic distribution of the U.S. population from 1988 to 1994, reported a prevalence of clinical hypothyroidism at 0.3% and subclinical hypothyroidism at 4.3%.[94] Thyroid peroxidase antibodies were elevated in 11.3%, and thyroglobulin antibodies were elevated in 10.4%. Thyroid peroxidase antibody positivity was associated with hypothyroidism (and hyperthyroidism), but thyroglobulin antibodies were not.

Etiology

Hypothyroidism can be classified (in order of decreasing frequency) as thyroid (primary), pituitary (secondary), or hypothalamic (tertiary) failure and thyroid hormone receptor resistance. Causes of primary hypothyroidism are listed in Box 123-1. Worldwide, the most common cause of hypothyroidism is iodine deficiency. In iodine-sufficient areas, such as the United States, the most common cause is chronic autoimmune (Hashimoto's) thyroiditis. With current administered doses of ^{131}I for patients with Graves' disease, approximately 90% become hypothyroid by the first year.[95] External neck irradiation in a cohort of 1677 patients with Hodgkin's disease followed for a mean of 9.9 years was associated with a cumulative incidence of hypothyroidism of 30.6%, highlighting the importance of continued clinical and biochemical evaluation.[96]

Clinical Features

The severity of clinical features depends on the severity of thyroid hormone deficiency, rather than etiology. Individuals with mild hypothyroidism with elevated TSH but normal free T_4 (subclinical hypothyroidism) may have few or no symptoms. At the opposite extreme, individuals with severe hypothyroidism may have myxedema coma. Even in individuals with overt biochemical hypothyroidism, severity of symptoms varies. Generally, patients are more symptomatic if hypothyroidism develops rapidly. Elderly patients have fewer symptoms than younger patients.[4] Common symptoms of hypothyroidism, such as fatigue, constipation, dry skin, and cold intolerance, may be mistakenly misinterpreted as part of the normal aging process.

Hypothyroidism should be suspected in individuals with goiter and risk factors (Box 123-2). With the widespread use of the serum TSH assay, hypothyroidism is frequently detected at an earlier stage.

Box 123-1

Causes of Primary (Thyroidal) Hypothyroidism

- Thyroid agenesis
- Destruction of thyroid tissue
  - Surgical removal
  - Therapeutic irradiation (^{131}I or external radiation)
  - Autoimmune (Hashimoto's) thyroiditis
  - Replacement by cancer and infiltrative diseases (amyloidosis, scleroderma)
  - Post-thyroiditis (acute or subacute)
  - Postlaryngectomy alone or with external irradiation
- Inhibition of thyroid hormone synthesis or release or both
  - Iodine deficiency
  - Iodine administration in individuals with underlying autoimmune thyroiditis (amiodarone, iodine-containing expectorants, kelp, SSKI, Lugol's solution, povidone-iodine, iodine-containing radiocontrast agents)
  - Other medications with antithyroid action (methimazole, propylthiouracil, lithium, interferon-α, interferon-β, interleukin-2)
  - Inherited enzyme defects
- Transient
  - After surgery or ^{131}I therapy
  - Postpartum
  - Recovery from thyroiditis
  - Autoimmune (Hashimoto's) thyroiditis
  - After withdrawal of thyroid hormone in euthyroid patients

Modified from Braverman LE, Utiger RD. Introduction to hypothyroidism. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the Thyroid: A Fundamental and Clinical Text*. 7th ed. Philadelphia: Lippincott-Raven; 1996:736.

Box 123-2

Risk Factors for Hypothyroidism

- Older age
- Female gender
- Graves' disease
- Hashimoto's disease
- Other autoimmune disease (e.g., type 1 diabetes, adrenal insufficiency, vitiligo)
- Post-thyroidectomy
- Goiter
- Prior neck irradiation
- Laryngectomy alone or with external irradiation
- Drugs: lithium, amiodarone, iodine-containing compounds

Box 123-3

Symptoms and Signs of Hypothyroidism

- General
  - Fatigue, weakness, lethargy
  - Weight gain
  - Cold intolerance
- Eye, ear, nose, throat
  - Macroglossia
  - Hearing loss, vertigo, tinnitus
  - Hoarseness of voice
  - Middle ear effusion
  - Blurred vision
- Central nervous system
  - Slowed speech, movement, and mentation
  - Delayed relaxation phase of deep tendon reflexes
- Gastrointestinal
  - Constipation
  - Anorexia, nausea, vomiting
  - Dysphagia
  - Ascites
- Cardiovascular
  - Bradycardia
  - Diastolic hypertension
  - Pericardial effusion
- Integumentary
  - Dry, rough, thick skin
  - Coarse hair
  - Nonpitting edema (myxedema)
  - Periorbital edema
  - Loss of lateral eyebrows
  - Decreased perspiration
  - Carotenemia
- Musculoskeletal
  - Arthralgia
  - Carpal tunnel syndrome
- Pulmonary
  - Pleural effusion
  - Dyspnea on exertion
- Genitourinary
- Menstrual irregularity (oligomenorrhea, menorrhagia)

Modified from Watanakunakorn, et al. *Arch Intern Med*. 1965;16:183.

The classic symptoms and signs of hypothyroidism are now less frequently found (Box 123-3).

Otolaryngologic Manifestations

Hearing Loss

Hearing loss may be conductive, mixed, or sensorineural in origin. It occurs more frequently and with greater severity in congenital than in adult hypothyroidism.[97] Progressive mixed hearing loss is reported in one half to nearly all children with endemic cretinism,[98] but only approximately 30% to 40% of adults with myxedema have bilateral sensorineural hearing loss. Substantial deafness persists after T_4 therapy in 10% of children with congenital hypothyroidism.[99] Although it mainly occurs in primary hypothyroidism, deafness has been reported with panhypopituitarism.[100]

Children with cretinism may have anomalous ossicles involving any bone in the middle ear, and may have atrophy of the organ of Corti.[101] The tectorial membrane is the first structure to change, followed by degeneration of hair cells at the basal turn of the cochlea, with prolongation of wave I; outer hair cells remain intact.[102] Patients with acquired hypothyroidism who have hearing loss may display similar abnormalities. Only a few adults and almost no children with a well-established hearing loss improve with thyroid hormone therapy.

Some adults with severe myxedema have bilaterally symmetric and progressive sensorineural hearing loss that worsens as the severity of hypothyroidism increases. Conductive losses also may occur as a result of edema of the eustachian tube mucosa.

Vertigo

Vertigo is experienced in two thirds of patients with hypothyroidism. Attacks are usually mild and brief, and are not associated with electronystagmography changes or concurrent hearing loss.[103]

Hoarseness

Gradual and progressive hoarseness occurs in hypothyroidism as a result of mucopolysaccharide infiltration of the vocal cords and possibly tissue edema in the ambiguous nucleus or the cricothyroid muscles.[104] Finding bilaterally edematous, mobile vocal cords should raise the suspicion of hypothyroidism. Hoarseness almost invariably dissipates with thyroid hormone replacement alone.

Goitrous Hypothyroidism

The most common cause of goitrous hypothyroidism in adults in the United States is autoimmune thyroiditis (Hashimoto's disease).[105] Other less common causes are drugs (lithium, amiodarone, sulfisoxazole, large doses of iodides, aminosalicylic acid, interferon, and antithyroid drugs), infiltration of the gland with tumor or inflammatory processes, and familial defects in thyroid hormonogenesis.

Transient Hypothyroidism

Hypothyroidism resulting from Hashimoto's thyroiditis is transient in approximately 10% of cases. Spontaneous remission is associated with the presence of a larger goiter, a high initial TSH level, and a family history of thyroid disease.[106] Autoimmune thyroid dysfunction may become apparent after surgery for Cushing's disease.[107] Smoking increases the metabolic effects of overt and subclinical hypothyroidism in a dose-dependent way.[108]

Excessive Iodine Intake

In iodine-sufficient areas of the world such as the United States, excess iodine intake can cause hypothyroidism in individuals with autoimmune thyroiditis, ^{131}I-treated or surgically treated Graves' disease patients, and patients treated with hemithyroidectomy for thyroid nodules.[46] Hypothyroidism may develop in individuals taking amiodarone, especially individuals with an underlying thyroid abnormality. Thyroid autoantibodies are risk factors for the development of hypothyroidism.[109]

Endemic Goiter

Endemic goiter is uncommon in the United States, but TSH levels are elevated in more than 50% of patients with this disorder, many of whom have no clinical features of thyroid failure.[110]

Familial Hypothyroidism

Kindreds with hypothyroidism usually have inherited defects in hormonogenesis, but rarely may have generalized thyroid hormone resistance.[111]

Nongoitrous Hypothyroidism

Nongoitrous hypothyroidism is most often caused by thyroid disease—most commonly autoimmune diffuse thyroid atrophy and management of Graves' disease with ^{131}I, thionamides, or thyroidectomy—but may be caused by pituitary and hypothalamic disorders.[112,113]

Hypothyroidism after Laryngectomy and Radiotherapy

Hypothyroidism may start within 4 months of surgery, but may not become clinically apparent for 1 year.[114] In a multivariate analysis of 221 patients, risk factors for hypothyroidism were high radiation dose, combination of radiotherapy and cervical surgery, time from therapy, and no shielding of the midline neck. Patients receiving irradiation to the neck—particularly patients undergoing neck dissections or total laryngectomy—should have routine thyroid function studies performed every 3 to 6 months the first year after management and annually thereafter.

Pituitary and Hypothalamic Hypothyroidism

Pituitary and hypothalamic hypothyroidism is uncommon and includes large pituitary tumors and pituitary apoplexy. Hypothalamic causes include lymphocytic hypophysitis, tumors, infarctions, trauma, and infiltrative diseases.

Subclinical Hypothyroidism

Diagnosis

The diagnosis of subclinical hypothyroidism is made by an elevated TSH with normal free T_4 or a free T_4 index. Clinically, there are no or a few mild symptoms of hypothyroidism. Some patients may have goiter, especially when antithyroid antibodies are positive.

Prevalence

In population-based studies, the prevalence of subclinical hypothyroidism is approximately 8% in women and 3% in men, higher in whites (versus blacks), and in individuals older than 75 years (versus 55 to 64 years).[115,116] NHANES III reported that in the 16,533 participants who reported no known thyroid disease, goiter, or thyroid hormone use, 4.3% had subclinical hypothyroidism.[94]

Natural History

Progression from subclinical to overt hypothyroidism is not inevitable in all individuals. In a large population study in Great Britain followed for more than 20 years, women with an elevated TSH and elevated antithyroid antibody titers progressed to overt hypothyroidism at a rate of 4.3% per year, greater than women with elevated TSH alone (2.6% per year) or antithyroid antibodies alone (2.1% per year).[46] In this study, there was no increase in all-cause or cardiac mortality in participants with subclinical hypothyroidism at baseline. In a natural history study of 26 elderly subjects with subclinical hypothyroidism, one third had overt biochemical hypothyroidism develop within 4 years of follow-up. Progression to overt hypothyroidism occurred in subjects with an initial TSH greater than 20 μIU/mL and in 80% with high-titer AMAs greater than 1:1600.[78] In a more recent prospective study of 82 women with subclinical hypothyroidism, the cumulative incidence of overt hypothyroidism was 43% of women with TSH 6 to 12 μIU/mL and 77% with TSH greater than 12 μIU/mL, and no women with TSH less than 6 μIU/mL followed for 10 years. TPO antibody positivity was associated with development to overt hypothyroidism.[117]

Effects on Lipids, Hypothyroid Symptoms, and Mood

Treatment of subclinical hypothyroidism prevents progression to overt hypothyroidism. Other potential benefits of therapy include improvement in hypothyroid symptoms and mood, improvement in lipid profile, and decrease in thyroid volume by 20%.

The relationship between subclinical hypothyroidism and effects of lipid profile are inconsistent. Some studies show that individuals with subclinical hypothyroidism have an atherogenic lipid profile (higher total cholesterol, low-density lipoprotein [LDL] cholesterol, lipoprotein (a), and apolipoprotein B, and lower high-density lipoprotein [HDL] cholesterol) than euthyroid individuals,[118-120] but other studies show no difference.[121-123] In the largest cross-sectional study of 25,862 subjects in the United States, subjects with subclinical hypothyroidism had a higher total cholesterol than the euthyroid group (223 mg/dL versus 216 mg/dL; $P < .003$), and had higher LDL cholesterol than the euthyroid group (144 mg/dL versus 140 mg/dL; $P < .003$).[43] In small studies, T_4 therapy of patients with subclinical hypothyroidism leads to an increase in HDL cholesterol[124] and decrease in total and LDL cholesterol.[119,121,125] Meta-analysis of T_4 therapy in subclinical hypothyroidism shows a 10 mg/dL decrease in LDL cholesterol and 7.9 mg/dL decrease in total cholesterol concentration.[126] Greater improvement was seen in subjects with baseline total cholesterol levels 240 mg/dL or greater versus subjects with total cholesterol less than 240 mg/dL.

T_4 therapy leads to significantly increased cardiac output, increased mean arterial pressure, and decreased systemic vascular resistance.[127] In a survey of postmenopausal women, subclinical hypothyroidism is associated with an increased risk of myocardial infarction (odds ratio 2.3) and aortic atherosclerosis (odds ratio 1.7), but no subsequent risk of myocardial infarction at 4.6 years of follow-up.[128] It is unclear whether

thyroid hormone therapy in subclinical hypothyroidism improves cardiac mortality.

Subclinical hypothyroidism is associated with depression in some,[129] but not in all, studies.[130] Similarly, some randomized placebo-controlled trials in subjects with subclinical hypothyroidism show improvement in symptoms of hypothyroidism,[131,132] but one reported no difference.[133] Depressed patients with subclinical hypothyroidism have a poorer response to antidepressant therapy than depressed patients who are euthyroid.[134] Individuals with subclinical hypothyroidism show impairment in neurobehavioral scores, such as memory, which improve with T_4 therapy. Treatment of subclinical hypothyroidism is reasonable in pregnant women to avoid impairment of intellectual potential of the fetus,[135] and in women who have ovulatory dysfunction with infertility.[131]

Treatment

Patients with subclinical hypothyroidism and positive TPO antibodies, with TSH greater than 10 μIU/mL, are prone to have overt hypothyroidism develop and should receive thyroid hormone replacement. Risk of overt disease may depend on the etiology of subclinical hypothyroidism. Individuals receiving radioactive iodine therapy or high-dose external radiation are likely to progress to overt hypothyroidism and should probably be treated with thyroid hormone. Others who may benefit include patients with goiter, individuals with elevated total or LDL cholesterol, pregnant women, and women with ovulatory dysfunction with infertility.[131] Small doses are usually needed (e.g., 50 to 75 μg daily), with monitoring of TSH and dose titration in 4 to 6 weeks until TSH is normalized. Patients with coronary artery disease should begin at a lower dose of 25 μg daily.

Nonthyroidal Illness

TSH elevation may occur in conditions other than hypothyroidism, including recovery from nonthyroidal illness, also known as sick euthyroid syndrome. Hospitalized and critically ill patients may have a decreased free T_4 index or free T_4 concentration by radioimmunoassay. When measured by equilibrium dialysis, however, free T_4 is normal or elevated. In one report, serum total T_4 levels less than 3 μg/dL were associated with mortality in 84% of critically ill patients.[136] In a randomized prospective study, T_4 treatment in an intensive care unit did not alter mortality.[137]

Laboratory Diagnosis

There is a set-point for optimal serum free T_4 concentration in a given individual. Because of the log-linear relationship between serum TSH and T_4 concentrations, small changes in free T_4 from this set-point lead to relatively large changes in TSH by negative feedback. The most sensitive test for hypothyroidism is an elevated serum TSH. In subclinical hypothyroidism, TSH is elevated, whereas free T_4 remains normal. If the disorder progresses to overt hypothyroidism, free T_4 is decreased (see Table 123-3 for thyroid function tests in hypothyroidism and other low T_4 syndromes). Radioactive iodine uptake is not indicated for the diagnosis of hypothyroidism because low, normal, or high values can occur, depending on the cause.

Central hypothyroidism caused by pituitary or hypothalamic disorder shows a low free T_4 and TSH that is low, inappropriately normal, or mildly elevated. TRH stimulation testing of TSH has traditionally been used to distinguish between these two entities, but is unreliable.[138,139]

Management

Oral synthetic levothyroxine (T_4) is the therapy of choice to correct hypothyroidism. Gastrointestinal absorption is 81%.[140] Because the plasma half-life of T_4 is long (6.7 days),[141] once-daily administration leads to stable T_4 and T_3 concentrations. Numerous brand name (Euthyrox, Levothroid, Levoxyl, Synthroid, Unithroid) and generic preparations of T_4 are available, each in varying doses with different color-coded tablets to allow dose titration at precise increments. In one study, comparison of two brand-name and two generic preparations in the United States showed bioequivalency.[142] Equivalent doses of different formulations of T_4 are generally interchangeable.

Table 123-3

Thyroid Function Tests in Hypothyroidism and Other Low Thyroxine Syndromes

	Free	T_4T_3	TSH
Hypothyroid hypothyroidism			
Primary hypothyroidism			
Overt	Low	NL/low	High
Subclinical	NL	NL	High
Pituitary (secondary)	Low	Low/NL	NL/low/slightly high
Hypothalamic (tertiary)	Low	Low/NL	NL/low/slightly high
Euthyroid hypothyroidism			
Low TBG	NL	Low	NL
Nonthyroidal illness			
Mild	NL	Low	NL
Severe	Low	Low	NL

NL, normal; T_4T_3, thyroxine and triiodothyronine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

One should repeat the TSH level 4 to 6 weeks after switching, however.[140,143]

In young, otherwise healthy adults, a full replacement dose can be prescribed at 1.6 μg/kg/day for nonmalignant conditions. In patients with known coronary disease, patients with multiple coronary risk factors, and elderly patients who may have previously silent coronary disease, conservative therapy with an initial dose of 25 μg/day is advisable. One should repeat TSH measurements with dose adjustment every 4 to 6 weeks (four to six half-lives of T_4) until serum TSH normalizes or cardiac symptoms arise that may limit therapy to less than a full replacement dose. In individuals without residual thyroid tissue, such as a patient with thyroid cancer who has undergone thyroidectomy, the mean T_4 dose required to achieve euthyroidism is generally higher (2.1 μg/kg/day).[144]

In patients with primary hypothyroidism, the goal of therapy is to normalize the serum TSH level. After initiation or change in dose of T_4, TSH should be repeated in 4 to 6 weeks. Ultimately, TSH measurements are needed annually, or sooner depending on clinical status. In individuals with central hypothyroidism, free T_4 alone should be normalized, also with repeat measurements free in 4 to 6 weeks. The use of the patient's symptoms to judge the adequacy of T_4 dosing is frequently inaccurate. When subjective symptoms were used to determine T_4 dosing, patients chose a dose that produced mild hyperthyroidism.[145]

Potential adverse effects of overtreatment with an excessive dose of T_4 include bone loss in postmenopausal, but not premenopausal, women,[146,147] and in elderly patients, cardiac complications, including cardiac arrhythmias, heart failure, angina, and myocardial infarction.[88] Occasionally, patients have manic behavior develop with T_4 replacement. Severe behavioral manifestations of T_4 therapy for juvenile hypothyroidism are uncommon, but mild behavioral symptoms and poorer school achievement may occur in approximately 25% of patients, who represent the most severe cases at the time of diagnosis.[148]

Poor patient compliance with taking thyroid hormone leads to therapeutic failure. Alternatives to a daily regimen include twice-weekly[149] or once-weekly regimens.[150] These probably should not be used in patients with coronary artery disease. Numerous medications may bind to and interfere with intestinal absorption of T_4, including aluminum hydroxide,[151] ferrous sulfate,[152] sucralfate,[153] cholestyramine,[94] and calcium carbonate.[139] Thyroid hormone administration should be separated in time from these medications by a few hours.

Thyroid hormone preparations that contain T_3 alone (e.g., Cytomel), combinations of T_4 and T_3 (e.g., Thyrolar), and desiccated thyroid extract (Armour Thyroid) should not be used for the treatment of hypothyroidism. Serum T_3 levels fluctuate widely because of the short half-life of T_3. Temporary T_3 therapy is indicated in patients with thyroid cancer who have undergone thyroidectomy and await thyroid remnant ablation to shorten the period of hypothyroidism. T_3 can be discontinued 2 weeks before ^{131}I.[154] In addition, temporary switching from T_4 to T_3 therapy in individuals undergoing thyroid hormone withdrawal whole-body scanning also reduces the period of hypothyroidism.

Thyroid hormone requirements are increased during pregnancy by an average of 45%[151] because of an estrogen-mediated increase in TBG, fetal T_4 transfer, and increased T_4 clearance. Serum TSH should be obtained at each trimester of pregnancy. If the T_4 dose requires adjustment, TSH should be remeasured in 4 weeks with further dose adjustment as necessary. After delivery, the prepregnancy T_4 dose should be resumed.[155] A hypothyroid woman starting oral estrogen therapy such as with hormone replacement therapy may also require a higher thyroid hormone dose,[156] and TSH should be obtained 3 months after initiation of estrogen to determine whether a dose increase is needed. Increases in dose may be necessary in patients who start medications that increase T_4 catabolism (e.g., phenytoin, carbamazepine, phenobarbital, rifampin), have gastrointestinal malabsorption, or have nephrotic syndrome develop.[157] A decreased thyroid hormone dose requirement may be seen in elderly patients[158] and in women with breast cancer treated with androgens.[159]

Myxedema Coma

Myxedema coma, a thyroid emergency, is a late manifestation of hypothyroidism, and is characterized by coma or precoma with severe clinical manifestations of myxedema. An underlying infection or other precipitating cause of the myxedema coma is usually present. Patients characteristically have extreme hypothermia, bradycardia, pleural and pericardial effusions, hyponatremia, hypoventilation, respiratory acidosis, and hypoxia. Focal or generalized seizures typically precede the coma.

Management is with large doses of intravenous T_4 and hydrocortisone. Although management is usually instituted without laboratory confirmation, the clinical diagnoses should be certain before large doses of intravenous T_4 are given. Supportive care includes intubation and assisted ventilation, cautious warming, support of blood pressure, and management of infection. Mortality rates are approximately 50% and depend on the severity of superimposed illnesses and underlying coronary heart disease.

Surgery

With mild to moderate hypothyroidism, postoperative complications are frequent, but are rarely serious or lasting, and necessary surgery should not be postponed simply to replete thyroid hormone.[160] This is not true for patients with severe myxedema, who should be given preoperative thyroid hormone except in the most urgent surgical emergencies or uncontrolled ischemic heart disease.

In euthyroid patients, total T_4 tends to decrease in the first postoperative day, then spontaneously normalizes in 7 days; the same occurs in hypothyroid patients, but T_4 levels do not normalize until thyroid supplementation is given.[161] It is usually unnecessary to increase the postoperative dose of T_4, however, and almost never necessary to use parenteral T_4, unless the patient cannot take medication by mouth for several weeks. If parenteral T_4 therapy is necessary, half of the patient's usual daily T_4 dose is ordinarily given, and attention is given to the patient's cardiac status because this therapy may precipitate cardiac arrhythmias, angina, and heart failure.

Cardiac and pulmonary problems are prevalent in elderly patients with hypothyroidism. The prevalence of coronary artery disease is high, but the diagnosis is easily overlooked because patients often have few symptoms because of their low metabolic activity or because they fail to communicate their symptoms clearly.[103] Pericardial effusions are often apparent and rarely cause tamponade. Patients with severe hypothyroidism also respond poorly to stress by having hypothermia and hypotension develop, and they do not have tachycardia develop in response to infection or hypotension. Shock responds poorly to vasoconstrictors.

Patients with severe hypothyroidism often display upper airway obstruction caused by oropharyngeal muscle dysfunction and tissue infiltration with mucopolysaccharide.[162] They may have central sleep apnea, insensitivity to hypoxia and hypercarbia,[163] and respiratory muscle weakness,[164] changes that often lead to severe postoperative hypoxia and difficulty in weaning from a ventilator. These defects are reversible with T_4 replacement therapy, but obstructive sleep apnea may be more closely related to obesity and male gender than hypothyroidism.[165]

A von Willebrand's disease–like defect is common in hypothyroidism, which may lead to bleeding.[166,167] It resolves promptly with infusion of desmopressin, suggesting that it acts through the β-adrenergic receptor.[89] This can be helpful in the acute management of bleeding. It resolves permanently with T_4 therapy.[168,169]

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CHAPTER ONE HUNDRED AND TWENTY-FOUR

Management of Thyroid Neoplasms

Stephen Y. Lai

Susan J. Mandel

Randal S. Weber

Key Points

- The incidence of thyroid cancer is increasing, although this increase may be mostly attributable to improved detection, rather than a true increase in incidence. Women are three times more likely than men to develop differentiated thyroid cancers, and two times more likely to have anaplastic thyroid cancer.
- Exposure to ionizing radiation remains the only well-established environmental risk factor for thyroid cancer.
- The molecular mechanism underlying thyroid carcinoma is incompletely understood, but seems to involve rearrangements of RET or activation of BRAF in papillary thyroid carcinoma, and is associated with RAS mutations in follicular thyroid carcinoma. RET mutations are frequently identified in medullary thyroid carcinoma, and specific point mutations are linked to the aggressiveness of the disease.
- A rational and systematic approach to the management of a thyroid nodule is necessary to classify benign versus malignant disease appropriately.
- Fine-needle aspiration cytology (FNAC) has become the procedure of choice in the evaluation of thyroid nodules. Increasingly, FNAC is being performed with ultrasound guidance to improve diagnostic accuracy and yield.
- The role of ultrasonography is evolving in the management of thyroid carcinoma. Ultrasonography may improve the detection of early, clinically occult cervical lymph node metastasis and alter surgical management. Additionally, ultrasonography is useful in the evaluation of the thyroid bed and neck in patients with a history of thyroid cancer who present with new neck masses or increasing thyroglobulin levels.
- Intraoperative ultrasound may be useful for the resection of radiographically identified, nonpalpable lesions within the thyroid bed or nodal basins.
- Central compartment (level VI) neck dissection should be considered in patients with papillary thyroid carcinoma and suspected Hürthle cell carcinoma. Elective neck dissection is not recommended.
- Bilateral central compartment neck dissection should be performed in patients with medullary thyroid carcinoma. Lateral neck dissection should be considered depending on the disease burden.
- In patients with well-differentiated thyroid carcinoma and cervical metastases, a comprehensive neck dissection should be performed, rather than selective cervical lymph node excision or "berry-picking."
- New surgical approaches provide improved cosmesis and decreased postoperative discomfort. These minimally invasive techniques use endoscopic instruments to provide surgeons with improved visualization of critical anatomic structures, such as the superior and recurrent laryngeal nerves.
- Patients with thyroid carcinomas require long-term follow-up and monitoring. The extent of this workup depends on the risk classification of each individual patient.

Thyroid neoplasms represent almost 95% of all endocrine tumors, although they are relatively uncommon, accounting for approximately 2.5% of all malignancies. In 2008, the estimated annual incidence of thyroid cancer in the United States was 37,340 cases, and approximately 1590 patients (4.3%) were expected to die from thyroid cancer.[1] The incidence of thyroid cancer has been steadily increasing over the past 2 decades, and thyroid cancer has the fastest increasing incidence of all major cancers in the United States (approximately 4% increase annually).[2] Mortality rates have remained stable, and evidence suggests that improved detection has primarily contributed to the increased incidence.

Although thyroid cancer is rare, the incidence of thyroid nodules is significantly greater, affecting approximately 4% to 7% of the U.S. population.[3] Although most of these nodules are benign, the challenge

is to identify the approximately 5% of patients with a malignant lesion. A subset of thyroid cancers is particularly aggressive with a potential for devastating morbidity. No reliable indicators are currently available to determine which patients will develop aggressive or recurrent disease, although risk categories based on clinical and pathologic criteria yield important prognostic information.

Most thyroid carcinomas are well-differentiated tumors of follicular cell origin.[4,5] These lesions are histologically defined as papillary carcinoma, follicular carcinoma, and Hürthle cell carcinoma. A survey of 53,856 patients described the overall incidence of thyroid cancer in the United States.[5] In this report, approximately 79% of cases were papillary carcinoma, 13% were follicular carcinoma, and approximately 3% were Hürthle cell carcinoma. A small proportion (6%) of patients with these lesions have a family history of thyroid cancer. Medullary thyroid carcinoma (MTC), which arises from parafollicular C cells, accounts for about 4% of thyroid carcinomas. Approximately 30% of patients with these lesions have a strong genetic contribution. Anaplastic carcinomas, lymphoma, and metastatic disease constitute a small portion of thyroid malignancies.

The most common presentation of a thyroid cancer is the development of a thyroid mass or nodule. Assessment of the lesion requires a careful history, physical examination, fine-needle aspiration cytology (FNAC), and perhaps imaging studies. With correct diagnosis and management, most patients with well-differentiated thyroid carcinomas have an excellent prognosis. The 10-year disease-specific mortality rate is less than 7% for papillary thyroid cancer and less than 15% for follicular thyroid cancer.[5-8] Controversy regarding the treatment of thyroid carcinomas and the extent of thyroidectomy to be performed arises because of the indolent course of most thyroid cancers. Interventions for thyroid cancer have been difficult to evaluate because of the long follow-up and the large number of patients needed to determine differences in survival. The morbidity that may accompany any aggressive intervention needs to be balanced with the generally good prognosis of patients with thyroid cancer.

In this chapter, we begin with a review of the surgical anatomy and embryology of the thyroid gland. After a brief overview of the present understanding of pathogenetic mechanisms leading to thyroid cancer, we review risk factors and staging of thyroid carcinomas. We describe an algorithm for the evaluation of a thyroid nodule, and assess available diagnostic tools, including the increasing role of ultrasound examination in the evaluation of the thyroid and neck. A review of the different forms of thyroid cancer, ranging from well-differentiated carcinomas to anaplastic and other, less common malignancies, is followed by a discussion of surgical management and postoperative adjuvant treatment.

Surgical Anatomy and Embryology

The thyroid medial anlage derives from the ventral diverticulum of the endoderm from the first and second pharyngeal pouches at the foramen cecum.[9,10] The diverticulum descends from the base of the tongue to its adult pretracheal position through a midline anterior path with the primitive heart and great vessels during weeks 4 to 7 of gestation. The proximal portion of this structure retracts and degenerates into a solid, fibrous stalk; persistence of this tract can lead to the development of a thyroglossal duct cyst with variable amounts of associated thyroid tissue. The lateral thyroid primordia arise from the fourth and fifth pharyngeal pouches and descend to join the central component. Parafollicular C cells arise from the neural crest of the fourth pharyngeal pouch as ultimobranchial bodies and infiltrate the upper portion of the thyroid lobes.[11] Because of the predictable fusion of the ultimobranchial bodies to the medial thyroid anlage, C cells are restricted to a zone deep within the middle to upper third of the lateral lobes.[12]

The thyroid gland is composed of two lateral lobes connected by a central isthmus, weighing 15 to 25 g in adults. A thyroid lobe usually measures about 4 cm in height, 1.5 cm in width, and 2 cm in depth. The superior pole lies posterior to the sternothyroid muscle and lateral to the inferior constrictor muscle and the posterior thyroid lamina. The inferior pole can extend to the level of the sixth tracheal ring. Approximately 40% of patients have a pyramidal lobe that arises from either lobe or the midline isthmus and extends superiorly (Fig. 124-1).

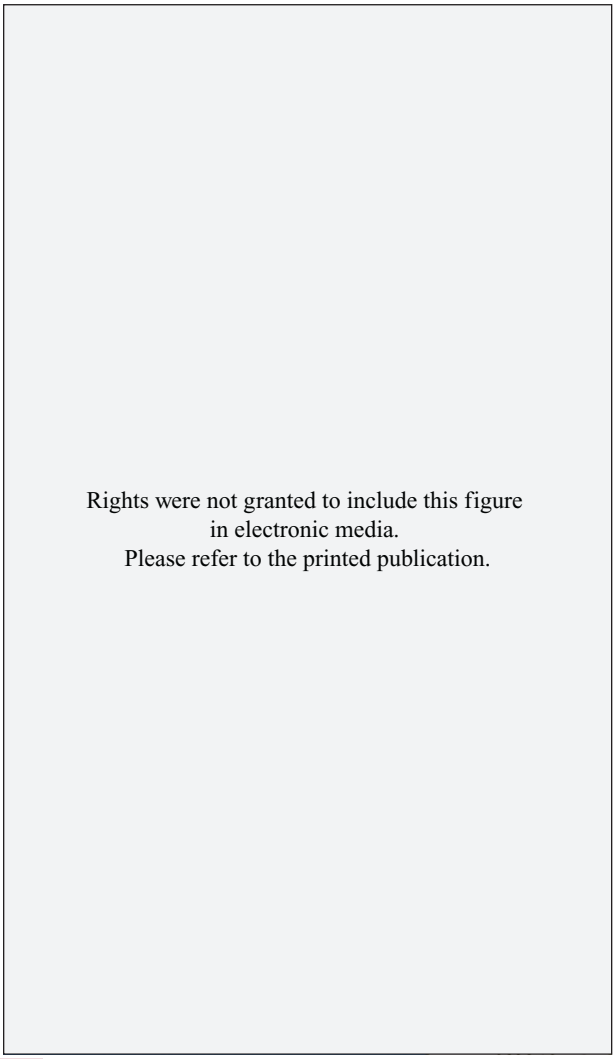

Figure 124-1. A and **B,** A pyramidal lobe of the thyroid gland may occasionally arise from the isthmus. This portion of the thyroid gland can be quite variable in size and should be carefully identified and removed with the surgical specimen. (***B,*** *From Lai SY, Weber RS. Thyroid cancer. In Ensley JF, Gutkind JS, Jacobs JR, et al, eds.* Head and Neck Cancer: Emerging Perspectives. *San Diego: Academic Press; 2002:419.*)

The thyroid is enclosed between layers of the deep cervical fascia in the anterior neck. The true thyroid capsule is tightly adherent to the thyroid gland, and continues into the parenchyma to form fibrous septa separating the parenchyma into lobules. The surgical capsule is a thin, filmlike layer of tissue lying on the true thyroid capsule. Posteriorly, the middle layer of the deep cervical fascia condenses to form the posterior suspensory ligament, or Berry's ligament, connecting the lobes of the thyroid to the cricoid cartilage and the first two tracheal rings.

Blood supply to and from the thyroid gland involves two pairs of arteries, three pairs of veins, and a dense system of connecting vessels within the thyroid capsule. The inferior thyroid artery arises as a branch of the thyrocervical trunk (Fig. 124-2). This vessel extends along the anterior scalene muscle, crossing beneath the long axis of the common carotid artery to enter the inferior portion of the thyroid lobe. Although variable in its relationship, the inferior thyroid artery lies anterior to the recurrent laryngeal nerve (RLN) in approximately 70% of patients.[13] The inferior thyroid artery is also the primary blood supply for the parathyroid glands.

The superior thyroid artery is a branch of the external carotid artery and courses along the inferior constrictor muscle with the superior thyroid vein to supply the superior pole of the thyroid. This vessel

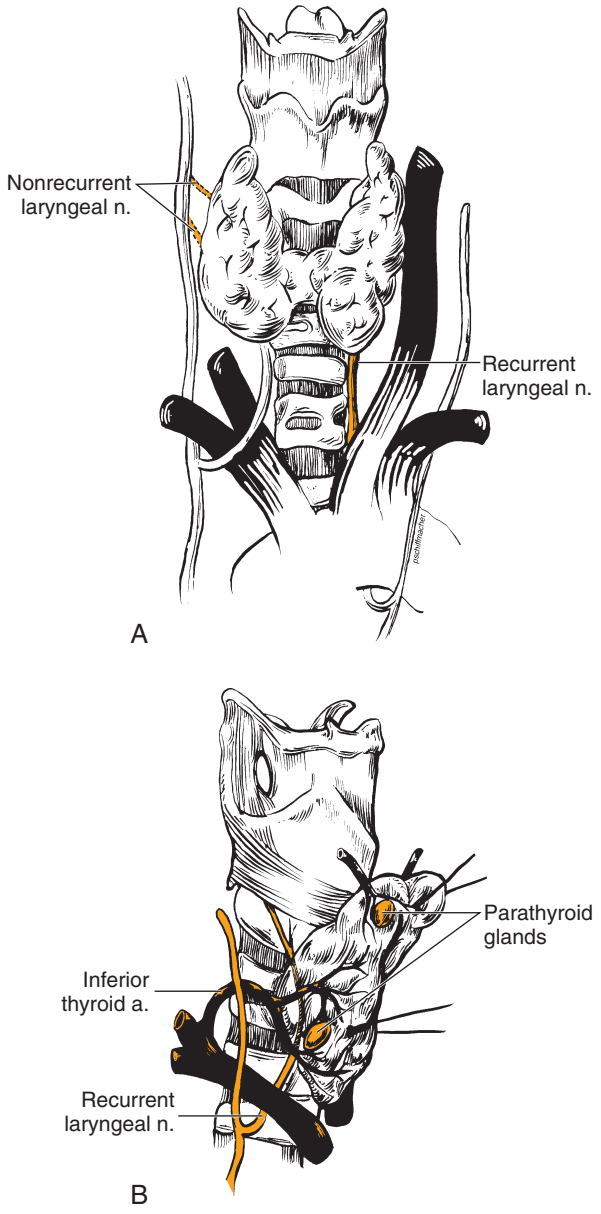

Figure 124-2. **A** and **B,** The thyroid gland is intimately associated with several important adjacent structures. In the lateral view, the gland has been mobilized medially to show the recurrent laryngeal nerve and its close relationship to the inferior thyroid artery. This relationship can vary between sides within a patient. See the text for details. The potential courses of the nonrecurrent laryngeal nerve have been indicated *(dashed lines)*. *(From Lai SY, Weber RS. Thyroid cancer. In Ensley JF, Gutkind JS, Jacobs JR, et al, eds.* Head and Neck Cancer: Emerging Perspectives. *San Diego: Academic Press; 2002:420.)*

lies posterolateral to the external branch of the superior laryngeal nerve (SLN) as the nerve courses through the fascia overlying the cricothyroid muscle. Care should be taken to ligate this vessel without damaging the SLN. Occasionally, arteria thyroidea ima may arise from the innominate artery, carotid artery, or aortic arch, and supply the thyroid gland near the midline.[13] Many veins within the thyroid capsule drain into the superior, middle, and inferior thyroid veins, leading to the internal jugular or innominate veins. The middle thyroid vein travels without an arterial complement, and division of this vessel permits adequate rotation of the thyroid lobe to identify the RLN and parathyroid glands.

The RLN provides motor supply to the larynx and some sensory function to the upper trachea and subglottic area. Careful management of thyroid carcinomas requires a thorough knowledge of the course of the RLN (see Fig. 124-2). During development, the RLN is dragged caudally by the lowest persisting aortic arches. On the right side, the nerve recurs around the fourth arch (subclavian artery), and on the left side, the nerve recurs around the sixth arch (ligamentum arteriosum).

The right RLN leaves the vagus nerve at the base of the neck, loops around the right subclavian artery, and returns deep to the innominate artery back into the thyroid bed approximately 2 cm lateral to the trachea. The nerve enters the larynx between the arch of the cricoid cartilage and the inferior cornu of the thyroid cartilage. The left RLN leaves the vagus at the level of the aortic arch, and loops around the arch lateral to the obliterated ductus arteriosus. The nerve returns to the neck posterior to the carotid sheath and travels near the tracheoesophageal groove along a more medial course than the right RLN. The nerve crosses deep to the inferior thyroid artery approximately 70% of the time and often branches above the level of the inferior thyroid artery before entry into the larynx.[14] The RLN travels underneath the inferior fibers of the inferior constrictor (i.e., the cricopharyngeus muscle) and behind the cricothyroid articulation to enter the larynx. A "nonrecurrent" laryngeal nerve may rarely occur on the right side and enters from a more lateral course (see Figs. 124-2 and 124-4C).[15] Typically, an aberrant retroesophageal subclavian artery (arteria lusoria) or other congenital malformation of the vascular rings is present.

The SLN arises beneath the nodose ganglion of the upper vagus and descends medial to the carotid sheath, dividing into an internal and external branch about 2 cm above the superior pole of the thyroid.[16] The internal branch travels medially and enters through the posterior thyrohyoid membrane to supply sensation to the supraglottis. The external branch extends medially along the inferior constrictor muscle to enter the cricothyroid muscle. Along its course, the nerve travels with the superior thyroid artery and vein. The nerve typically diverges from the superior thyroid vascular pedicle about 1 cm from the thyroid superior pole.

Proper management of the parathyroid glands during thyroid surgery is crucial to avoid hypoparathyroidism. The superior parathyroid glands are derived from the fourth pharyngeal pouch, whereas the inferior counterparts originate from the third pharyngeal pouch. The parathyroid glands are caramel-colored glands weighing 30 to 70 mg. The subtle distinction of tan and yellow coloration permits differentiation from adjacent fatty tissue, although with trauma, the glands can become mahogany in color. Four parathyroid glands exist in 80% of patients, and at least 10% of patients have more than four glands.[17] The glands are situated on the undersurface of the thyroid gland in predictable locations. The superior glands are located at the level of the cricoid cartilage, usually medial to the intersection of the RLN and the inferior thyroid artery.[17] The inferior glands are more variable in location than their superior counterparts. These glands may be on the lateral or posterior surface of the lower pole. In many patients, the position of the parathyroid glands on one side is similar to the other side and should be a useful guide.

Molecular Basis for Thyroid Neoplasms

Numerous genetic and molecular abnormalities have been described in thyroid neoplasms. Similar to other head and neck cancers, an accumulation of genetic alterations seems to be required for progression to a thyroid carcinoma. The specific molecular events and their order continue to be defined.

Alterations noted in the development of thyroid carcinomas include changes in total cellular DNA content. The loss of chromosomes, or aneuploidy, has been noted in 10% of all papillary carcinomas, but is present in 25% to 50% of all patients who die as a result of these lesions.[18] Similarly, the development of follicular adenomas is associated with a loss of the short arm of chromosome 11 (11p), and transition to a follicular carcinoma seems to involve deletions of 3p, 7q, and 22q.[19,20] Loss of heterozygosity involving multiple chromosomal regions is much more prevalent in follicular adenomas and carcinomas than in papillary carcinomas.[21]

Several oncogenes, altered genes that contribute to tumor development, have been identified in early thyroid tumor progression. Mutations in the thyroid-stimulating hormone (TSH) receptor and G-protein

mutations are found in hyperfunctioning thyroid adenomas.[22] These changes can lead to the constitutive activation of cell-signaling pathways, such as the adenylate cyclase–protein kinase A system. Point mutations of the G-protein Ras found in thyroid adenomas and multinodular goiters are believed to be an early mutation in tumor progression.[23] Somatic Ras mutations are associated with follicular adenomas, and to a lesser extent with follicular carcinomas. The resultant activation of the phosphatidylinositol 3′-kinase (PI3K) signal transduction pathway and AKT, a PI3K-related serine/threonine kinase, also seems to be specific to follicular thyroid carcinoma.[24]

Other genetic changes have also been associated with certain types of thyroid carcinoma. Mutations within the mitogen-activated protein kinase (MAPK) pathway are involved in malignant transformation to papillary thyroid cancer. Additionally, rearrangements or activation of RET or BRAF proto-oncogenes, which can also activate MAPK, are often found in papillary thyroid cancer.[25] Gene rearrangements involving tropomycin-receptor-kinase A, also known as neurotropic tyrosine receptor kinase type 1, a receptor for nerve growth factor, are associated with papillary carcinomas. Mutations in MET/hepatic growth factor have been linked to papillary and poorly differentiated thyroid carcinomas. Other growth factors, such as fibroblast growth factors, epidermal growth factor, and vascular endothelial growth factor, and their cognate receptors may have increased expression in thyroid tumors and contribute to tumor progression.

Different types of galectin, a carbohydrate-binding protein, seem to be differentially expressed in papillary and anaplastic carcinomas, and may be useful in distinguishing benign from malignant thyroid lesions.[26,27] In Cowden's disease (familial goiter and skin hamartomas), inactivating mutations of the phosphatase and tensin homolog (PTEN) gene have been identified.[28] PTEN may inhibit phosphorylation and kinase activity of AKT1, leading to the development of follicular adenomas and carcinomas.[24] The PAX8/PPARγγ1 (peroxisome proliferator-activated receptor) rearrangement seems to be unique to follicular thyroid carcinoma.[29] PAX8 is expressed at high levels during thyroid development, and the PAX/PPARγγ1 gene product seems to function as a dominant negative, blocking the activation of wild-type PPARγγ1. Mutations in the tumor-suppressor gene *p53,* a transcriptional regulator, seem to be involved in insular thyroid carcinomas and the progression from papillary to anaplastic carcinoma.[30,31]

The role of mutations of the RET oncogene in the development of papillary carcinoma and MTC has been extensively studied.[32] Located on chromosome 10, RET codes for a transmembrane tyrosine kinase receptor that binds glial cell line–derived neurotrophic factor. During embryogenesis, RET protein is normally expressed in the nervous and excretory systems. Abnormalities in RET expression result in developmental defects, including the disruption of the enteric nervous system (Hirschsprung's disease). Presumably, RET gene mutations result in the activation of the Ras/JNK/ERK1/2 signaling pathways, resulting in further genomic instability and prevention of entry into the apoptotic pathway.[33]

MTC and pheochromocytoma arise from neural crest cells containing RET point mutations. These point mutations have been well documented in patients with familial MTC, multiple endocrine neoplasia (MEN) type IIA, and MEN IIB.[34,35] The aggressiveness of the MTC that develops is linked to the specific RET mutation identified.[36] Somatic mutations of RET are also found in approximately 25% of sporadic MTCs. Many of these are identical to the codon 918 mutation found as a germline mutation in MEN IIB, although other codons are more infrequently involved.[37]

Rearrangements of the RET gene by fusion with other genes also create transforming oncogenes. Although more than 10 rearrangements have been described, three oncogene proteins—RET/PTC1, RET/PTC2, and RET/PTC3—account for most of the rearrangements found in papillary thyroid cancers, and are more frequently associated with childhood thyroid carcinomas.[38] Not all patients with papillary carcinomas express a RET/PTC gene however.[39] There are marked geographic differences, and the gene rearrangement is strongly associated with radiation exposure. After the Chernobyl nuclear disaster, 66% of the papillary thyroid cancers removed from affected patients had RET/PTC1 or RET/PTC3 rearrangements.[40] The RET/PTC3 rearrangement is most commonly associated with a "solid" follicular variant of papillary thyroid carcinoma, whereas RET/PTC1 is associated more often with the classic or diffuse sclerosing variants of papillary thyroid cancer.[41,42]

Risk Factors and Etiology

Although the specific molecular events related to the development of thyroid carcinomas remain incompletely defined, several patient and environmental factors have been closely examined. Women are three times more likely than men to develop differentiated thyroid cancer, and two times more likely to have anaplastic thyroid cancer. The median age at diagnosis is 47 years, with a peak in women at 45 to 49 years and in men at 65 to 69 years.[2] Epidemiologic studies have not shown a clear association between dietary iodine and thyroid carcinomas.[43] Also, there does not seem to be a simple relationship between benign goiter and well-differentiated thyroid carcinomas. Although papillary thyroid carcinomas are not associated with goiter, follicular and anaplastic thyroid carcinomas occur more commonly in areas of endemic goiter. Additionally, two particularly important risk factors, exposure to radiation and a family history of thyroid cancer, have been studied extensively.

Exposure to ionizing radiation increases patient risk for the development of thyroid carcinoma.[44,45] Ionizing radiation exposure is the only established environmental risk factor for thyroid cancer.[46] Low-dose ionizing radiation treatments (<2000 cGy) were used in the treatment of "enlarged thymus" to prevent "sudden crib death," enlarged tonsils and adenoids, acne vulgaris, hemangioma, ringworm, scrofula, and other conditions. The risk increases linearly from 6.5 to 2000 cGy, and typically has a latency period lasting 10 to 30 years. Although higher doses of ionizing radiation typically lead to the destruction of thyroid tissue, patients with Hodgkin's disease who receive 4000 cGy also have a higher incidence of thyroid cancer. Palpable thyroid nodularity may be present in 17% to 30% of patients exposed to ionizing radiation.[47] A patient with a history of radiation exposure who presents with a thyroid nodule has a 50% chance of having a malignancy.[48] Of these patients with thyroid cancer, 60% have cancer within the nodule, and the remaining 40% have cancer located in another area of the thyroid. The thyroid carcinoma tends to be papillary and frequently multifocal. There is also a higher risk of cervical metastases.

Similarly, patients exposed to radiation from nuclear weapons and accidents have a higher incidence of thyroid cancer. Children near the Chernobyl nuclear power facility had a 60-fold increase in thyroid carcinoma after the nuclear accident in 1986.[49] Most of these children were infants at the time of the accident, and many of these cases developed without the typical latency period. The thyroid gland seems to be particularly vulnerable to ionizing radiation in children and yet relatively insensitive in adults. In the life span study of atomic bomb survivors in Hiroshima and Nagasaki, the risk of thyroid cancer was associated with patient age at the time of the bombings.[50] The risk was greatest for individuals younger than 10 years, and no increased incidence of thyroid cancer was seen in individuals older than 20 years at the time of exposure.

Finally, familial and genetic contributions need to be fully evaluated. A patient with a family history of thyroid carcinoma may require specific diagnostic testing. Approximately 6% of patients with papillary thyroid cancer have familial disease. Papillary thyroid cancer occurs with increased frequency in certain families with breast, ovarian, renal, or central nervous system malignancies.[51] Gardner's syndrome (familial colonic polyposis) and Cowden's disease are associated with well-differentiated thyroid carcinomas. Patients with a family history of MTC, MEN IIA, or MEN IIB warrant evaluation for the RET point mutation.

Tumor Staging and Classification

Numerous staging and classification systems have been devised to stratify patients with thyroid carcinomas. These classifications have identified key patient-specific and tumor-specific characteristics that predict patient outcome. Risk-grouping has been used to focus aggressive treatment for high-risk patients and to avoid excessive treatment and its potential complications in patients with a lower risk for tumor recurrence or tumor-related death.

TNM Classification

The American Joint Commission on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) adopted a tumor-node-metastasis (TNM) classification system (Table 124-1). In this system, patient age at presentation influences the clinical staging of a thyroid carcinoma. Of patients with stage I disease, 82% had a 20-year survival of nearly 100%, whereas the 5% of patients with stage IV disease experienced a 5-year survival of only 25%.[52]

AMES

In the AMES system, patient *a*ge, the presence of *m*etastases, *e*xtent of tumor invasion, and tumor *s*ize were used to stratify patients into low-risk and high-risk groups (Table 124-2). Low-risk patients were young (men, <41 years old; women, <51 years old) without distant metastases and all older patients without extrathyroidal papillary carcinoma, without major invasion of the tumor capsule by follicular carcinoma or with a primary tumor less than 5 cm in diameter. In a review of 310 patients from 1961-1980, low-risk patients (89%) had a mortality of 1.8% compared with a mortality rate of 46% in high-risk patients (11%). Recurrence in low-risk patients was 5%, and in high-risk patients was 55%.[53] In DAMES, nuclear DNA content was added to the AMES system to improve risk-stratification for papillary thyroid carcinoma.[54]

AGES and MACIS

In the original AGES system, age at diagnosis, histologic tumor grade, extent of disease at presentation, and tumor size were used to calculate a prognostic score.[55] Because of the infrequent practice of tumor grading, a more recent modification of the system eliminated histologic tumor grade and incorporated metastasis and extent of resection. The MACIS system accounts for *m*etastasis, *a*ge at diagnosis, *c*ompleteness of surgical resection, extrathyroidal *i*nvasion, and tumor *s*ize.[56] The MACIS score is calculated as follows:

$$3.1\,(\text{patient age} < 40\text{ years}) \text{ or } 0.08 \times \text{age (patient age} \geq 40\text{ years)} + 0.3 \times \text{tumor size (in cm)} + 1\,(\text{if extrathyroidal extension}) + 1\,(\text{if incomplete resection}) + 3\,(\text{if distant metastases})$$

Patients were stratified by their prognostic scores into four groups with statistically significant differences in 20-year disease-specific mortality.

Other risk-classification systems with similar diagnostic criteria have been described.[57-59] Although numerous multivariable prognostic scoring systems have been developed, none is universally accepted. Additionally, none of these classifications has shown clear superiority, and application of these systems to a single population has shown incompatible findings compared with the original studies.[59,60] These systems do not apply to patients with poorly differentiated and more aggressive thyroid carcinomas.

Nevertheless, some general conclusions can be drawn from these studies regarding the prognosis of patients with well-differentiated thyroid carcinomas. Low risk for tumor recurrence and disease-specific mortality is noted in patients who are younger at diagnosis, have smaller primary tumors that lack extrathyroidal extension or regional/distant metastases, and have complete gross resection of disease at the initial surgery. Delay in treatment negatively affects prognosis. The most significant overall indicator of a poor prognosis is distant metastases, however, especially to bone.[6] Although a single risk-classification strategy is unavailable, these criteria should guide physicians to use therapeutic strategies that are directed toward the particular disease and risk for an individual patient, rather than applying a general treatment strategy for all patients with a particular form of thyroid carcinoma. More recent management guidelines from the American Thyroid Association (ATA) have recommended use of the AJCC/UICC staging system for all patients with differentiated thyroid cancer.

Evaluation of a Thyroid Nodule

The incidence of thyroid nodular disease is quite high, spontaneously occurring at a rate of 0.08% per year starting in early life and extending into the eighth decade.[47] Although thyroid nodules represent a wide spectrum of disease, most are colloid nodules, adenomas, cysts, and focal thyroiditis, with only a few (5%) being carcinoma. With a lifetime incidence of 4% to 7%, the annual incidence of thyroid nodules in the United States is about 0.1%, which is approximately 300,000 new nodules each year.[61,62] Most of these nodules are benign and do not require removal. With approximately 37,000 new thyroid cancers each year, about 1 in 20 new thyroid nodules contains carcinoma, however, and approximately 1 in 200 nodules is lethal. The challenge in treating patients with thyroid nodules is to identify the patients with malignant lesions and to balance the potential morbidity of treatment with the aggressiveness of their disease.

Clinical Assessment: History and Physical Examination

Numerous findings should raise suspicion of malignancy in a patient presenting with a thyroid nodule. Younger and older patients are more likely to have a malignant thyroid nodule. Patients younger than 20 years have an approximately 20% to 50% incidence of malignancy when presenting with a solitary thyroid nodule.[63] Nodular disease is more common in older patients, usually men older than 40 years and women older than 50 years. Although children may present with more advanced disease and even cervical metastases, malignancy in older patients has a considerably worse prognosis. Men often have more aggressive malignancies than women, but the overall incidence of thyroid nodules and malignancy is higher in women.

A family history of thyroid carcinoma should be carefully evaluated. Similarly, any history of medullary carcinoma, pheochromocytoma, or hyperparathyroidism should raise suspicion for the MEN syndromes. Gardner's syndrome (polyposis coli) and Cowden's disease also have been associated with well-differentiated thyroid carcinomas. As described previously, a history of previous head and neck radiation exposure significantly increases the risk of malignancy in patients with a thyroid nodule.

When evaluating the patient, rapid growth of a preexisting or new thyroid nodule is concerning, although the change may represent hemorrhage into a cyst. Throat or neck pain is rarely associated with carcinoma, but frequently occurs with hemorrhage into a benign nodule. Patients should be carefully questioned regarding any compressive or invasive symptoms, such as voice change, hoarseness, dysphagia, or dyspnea. The clinician should not rely on these findings alone, however, because unilateral vocal cord paralysis can be present without voice change or swallowing difficulties. Although most patients with thyroid cancer are euthyroid at presentation, symptoms of hyperthyroidism and hypothyroidism should be explored. Patients with large carcinomas that have replaced a significant portion of the normal thyroid gland may be hypothyroid, and patients with Hashimoto's thyroiditis may develop lymphoma. Although the history alone cannot determine the presence of thyroid cancer, important historic features are associated with thyroid carcinoma, and should not be discounted even if diagnostic tests indicated a benign lesion.

The physical examination of a patient with a thyroid nodule begins with careful palpation of the thyroid to assess the lesion. One should determine whether the lesion is solitary or the dominant nodule in a multinodular gland, although the risk of carcinoma in either setting is the same.[3,48] Having the patient swallow assists in the examination because nonthyroid pathology does not typically elevate with the thyroid during swallowing. Palpable nodules are typically 1 cm or larger. Smaller nodules can be found incidentally on radiographic studies for other reasons and may be monitored. Lesions greater than 1 cm in size warrant a complete workup. The firmness of the nodule may be associated with an increased risk of carcinoma by twofold to threefold.[64] Nodules greater than 2 cm in diameter and solid lesions have an increased incidence of harboring carcinoma. The evaluation of larger lesions also requires more caution because the rate of false-negative results during FNAC also increases.[65]

Potential substernal extension can be estimated by the relationship of the inferior aspect of the mass to the clavicle. Potential thoracic inlet obstruction owing to a substernal goiter can be assessed with Pemburton's maneuver. The patient raises his or her arms over the head, and positive findings of obstruction include subjective respiratory discomfort or venous engorgement, resulting in facial suffusion.

Table 124-1

TNM Staging for Thyroid Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor = 2 cm in greatest dimension, limited to thyroid
T2	Tumor >2 cm and = 4 cm in greatest dimension, limited to thyroid
T3	Tumor >4 cm in greatest dimension, limited to the thyroid *or* Any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All Anaplastic Carcinomas Are Considered T4 Tumors	
T4a	Intrathyroidal anaplastic carcinoma—surgically resectable
T4b	Extrathyroidal anaplastic carcinoma—surgically unresectable
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

	Age <45 Years	Age ≥45 Years
Papillary/Follicular		
Stage I	Any T any N M0	T1 N0 M0
Stage II	Any T any N M1	T2 N0 M0
Stage III		T3 N0 M0
		T1-T3 N1a M0
Stage IVA		T4a N0 M0
		T4a N1a M0
		T1-4a N1b M0
Stage IVB		T4b any N M0
Stage IVC		Any T any N M1
Medullary		
Stage I	T1 N0 M0	
Stage II	T2 N0 M0	
Stage III	T3 N0 M0	
	T1-3 N1a M0	
Stage IVA	T4a N0 M0	
	T4a N1a M0	
	T1-4a N1b M0	
Stage IVB	T4b any N M0	
Stage IVC	Any T any N M1	
Anaplastic		
Stage IVA	T4a any N M0	
Stage IVB	T4b any N M0	
Stage IVC	Any T any N M1	

From American Joint Committee on Cancer: *AJCC Cancer Staging Manual*. 6th ed. New York: Springer; 2002.

Table 124-2

Factors Used in Prognostic Classification Systems

	TNM	AMES	AGES	MACIS
Patient Factors				
Age	X	X	X	X
Gender	X	X		
Tumor Factors				
Size	X	X	X	X
Histologic grade		X		
Histologic type	X	X	*	*
Extrathyroidal spread	X	X	X	X
Lymph node metastasis	X			
Distant metastasis	X	X	X	X
Incomplete resection				X

*AGES/MACIS classifications for papillary carcinomas only.

Table 124-3

Risk Factors for Aggressive Behavior of Well-Differentiated Thyroid Carcinomas

History
Age
- Younger—<20 yr
- Older
  - Men—>40 yr
  - Women—>50 yr

Gender
- Male > female

History of radiation exposure/therapy
Family history of thyroid carcinoma

Physical Examination
Hard, fixed lesion
Rapid growth of mass
Pain
Lymphadenopathy
Vocal cord paralysis
Aerodigestive tract compromise
- Dysphagia
- Stridor

Histopathologic Factors*
Size (>4 cm)
Extrathyroidal spread
Vascular invasion
Lymph node metastasis
Distant metastasis
Histologic type
- Tall-cell variant of papillary carcinoma
- Follicular carcinoma
- Hürthle cell carcinoma

*At initial presentation.

Radiographic studies are more definitive in determining substernal involvement.

Further assessment of the patient may reveal the extent of involvement of a thyroid lesion. Palpable cervical nodes adjacent to the thyroid nodule increase the suspicion for malignancy, and may be the only presenting sign of a thyroid carcinoma. Adenopathy may be present, however, in a patient affected by Hashimoto's thyroiditis, Graves' disease, or infection.[66,67] Large lesions can potentially shift the larynx and trachea within the neck. The mobility of the nodule relative to the laryngotracheal complex and adjacent neck structures should be evaluated. Malignant lesions are more likely to be fixed to the trachea, esophagus, or strap muscles.

All patients with a thyroid lesion should have a complete vocal cord examination. Extension into the thyroid cartilage and larynx may result in a complete vocal cord paralysis that is clinically silent. Laryngoscopy should be performed to assess vocal cord motion.

Despite the importance of the initial clinical assessment, the history and physical examination are unreliable in predicting carcinoma. Many of the clinical signs of malignancy are manifest late in the course of disease. Additionally, many of these same findings may be caused by events associated with benign disease (e.g., hemorrhage into a benign nodule). The clinical assessment should provide a justification and a context for the interpretation of diagnostic studies, such as FNAC. Of particular note would be any patient and thyroid nodule features that might be concerning for aggressive carcinoma behavior (Table 124-3).

Diagnostic Studies

Laboratory Studies

Most patients who present with a thyroid nodule are euthyroid. The finding of hypothyroidism or hyperthyroidism tends to shift the workup away from thyroid carcinoma to a functional disorder of the thyroid gland, such as Hashimoto's thyroiditis or a toxic nodule.[68] Although many thyroid hormone tests are available, few are needed in the initial patient evaluation. TSH measurement serves as an excellent screening test. Full thyroid function tests can be performed if the TSH level is abnormal.

Measurement of thyroglobulin is generally not performed initially because thyroglobulin is secreted by normal and malignant thyroid tissue, and it is not recommended in the 2006 ATA guidelines.[69] Levels of thyroglobulin cannot differentiate between benign and malignant processes, unless levels are extremely high, as in metastatic thyroid cancer. Antithyroglobulin antibodies can also interfere with the assay. Thyroglobulin levels may be useful in studying patients who have undergone total thyroidectomy for well-differentiated thyroid cancer.

Serum calcitonin levels are not a typical initial test for patients with a thyroid nodule, unless the patient has a family history of MTC or MEN II. If FNAC shows or is suspicious for MTC, however, calcitonin levels should be obtained. In addition, if the patient has RET oncogene mutations, the possibility of a coexisting pheochromocytoma should be evaluated with abdominal magnetic resonance imaging (MRI) and a 24-hour urine collection to measure metanephrines and catecholamines (total and fractionated). The serum calcium level should be measured to exclude hyperparathyroidism.

Fine-Needle Aspiration Cytology

FNAC has become the procedure of choice in the evaluation of thyroid nodules.[69] The findings are highly sensitive and specific, although the accuracy of FNAC is related to the skill of the aspirator and the experience of the cytopathologist.[70] The procedure is minimally invasive and may be performed quickly with little patient discomfort. In contrast to large-bore needle biopsies such as the Tru-cut or Vim-Silverman needle, there are fewer complications. With the advent of this technique, the number of patients requiring surgery has decreased by 35% to 75%, and the cost in managing patients with thyroid nodules has been substantially reduced.[71-73] Also, the yield of malignancies has almost tripled in patients who have had thyroid surgery after FNAC.[73,74] The accuracy of FNAC diagnosis of papillary carcinoma is 99% with a false-positive rate of less than 1%.[75]

FNAC should be one of the initial steps in the surgical evaluation of a thyroid nodule. Approximately 15% of all aspirates are inadequate or nondiagnostic, largely because of the sampling from cystic, hemorrhagic, hypervascular, or hypocellular colloid nodules. Repeat aspiration of such a nodule is crucial because a nondiagnostic finding should never be interpreted as a negative finding for carcinoma. Surgical diagnoses after repeated nondiagnostic aspirations revealed malignant nodules in 4% of women and 29% of men.[76] Nodules that are difficult to localize and nodules that have yielded nondiagnostic aspirates on previous attempts may benefit from ultrasound-guided aspiration. FNAC is increasingly being performed with ultrasound guidance to improve diagnostic accuracy and yield. Cystic nodules with multiple nondiagnostic FNAC studies require close observation or surgical excision. Also, surgery should be more strongly considered for a solid nodule that is cytologically nondiagnostic.[69]

Successful FNAC categorizes a nodule into the following groups: benign, malignant, or suspicious. In 60% to 90% of nodules, FNAC reveals a benign or "negative" diagnosis. The likelihood of malignancy (false-negative rate) is 1% to 6%.[71,77] The diagnosis of malignancy, particularly papillary (including follicular variant), medullary, and anaplastic carcinomas and lymphomas, can be determined in about 5% of nodules. The likelihood of a false-positive finding is less than 5%.[71,77] Frequently, false-positive results occur because of difficulties in interpreting cytology in patients with Hashimoto's thyroiditis, Graves' disease, or toxic nodules. A benign cytology is a macrofollicular lesion or a colloid adenomatous nodule. The remaining "suspicious" samples are composed of lesions that contain abnormal follicular epithelium with varying degrees of atypia. This finding needs to be evaluated in the context of patient history and physical findings that may be suggestive of malignancy. A complete report of the FNAC detailing specimen adequacy and pathologic findings is crucial, and efforts have been made to standardize this information.[78,79]

Follicular neoplasms cannot be classified by FNAC alone. The presence of hypercellular, microfollicular arrays with minimal colloid increases the concern for carcinoma. The differentiation between follicular adenoma and follicular carcinoma depends on the histologic finding of capsular or vascular invasion, which requires evaluation of the entire thyroid nodule. Occasionally, patients with a diagnosis of follicular neoplasm on FNAC have an iodine-123 (^{123}I) thyroid scan. If the suspicious nodule is "cold," surgery is indicated. If the nodule is hyperfunctioning compared with the surrounding thyroid, surgery can be avoided. Overall, 20% of nodules diagnosed as follicular neoplasms by FNAC contain thyroid carcinomas.[80]

Similarly, Hürthle cell (oxyphilic) neoplasms can be difficult to evaluate. The presence of Hürthle cells in an aspirate may indicate an underlying Hürthle cell adenoma or carcinoma, but these cells can also be present in thyroid disorders, such as multinodular goiter and Hashimoto's thyroiditis. Carcinomas can be found in 20% of nodules identified as follicular and oxyphilic neoplasms.[81] Because of the risk of underlying carcinoma in these cases, surgery is recommended.

Imaging

Ultrasonography is tremendously useful and sensitive. These studies detect nonpalpable nodules and differentiate between cystic and solid nodules. Ultrasound detection of subcentimeter nodules is valuable because most are nonpalpable and not detected by other imaging modalities, even though they may harbor malignant disease. In patients with a neck that is difficult to examine (e.g., a patient with a history of head and neck irradiation), ultrasonography can also clarify findings. These studies provide key baseline information regarding nodule size and architecture. Ultrasonography is also a noninvasive and inexpensive method for following changes in the size of benign nodules. Ultrasonography can identify hemiagenesis and contralateral lobe hypertrophy, which may be misdiagnosed as a thyroid nodule. The utility of ultrasound studies has expanded from detection of thyroid nodules to examination of nodal basins for locoregional staging, intraoperative localization of nonpalpable lesions, and routine follow-up examination of the neck after thyroidectomy. Ultrasound examinations are being performed in the office by appropriately trained surgeons. Additionally, ultrasound guidance of FNAC has become integral to the initial workup, resulting in improved target selection and diagnostic yield.

A systematic ultrasound examination can be extremely valuable in the assessment of a patient with thyroid cancer, including color and power Doppler examination of the thyroid, specific nodules, and lymph nodes.[82,83] Examination of the nodal basins should be bilateral and include the jugular, submandibular, supraclavicular, paratracheal, and suprasternal regions. These studies may detect cervical nodes that may contain early clinically occult metastatic disease that would not otherwise have been included in a surgical dissection.[69,84] Characteristics of lymph nodes suspicious for metastatic deposits include loss of the fatty hilum, increased vascularity, rounded node configuration, hypoechogenicity of a solid nodule, and microcalcifications.[83,85,86] Ultrasonography is also useful in the evaluation of cervical lymph nodes in patients with a history of thyroid cancer who present with adenopathy or increasing thyroglobulin levels. These studies are not useful, however, in the evaluation of substernal extent of disease or the involvement of adjacent structures.

In a patient with multiple thyroid nodules, FNAC should be performed in conjunction with a diagnostic ultrasound study. Aspiration of the largest or "dominant" nodule alone may miss a thyroid malignancy. In the presence of two or more thyroid nodules larger than 1 to 1.5 cm, nodules with a suspicious ultrasound appearance should be aspirated preferentially. If none of the nodules has suspicious ultrasound characteristics, and multiple sonographically similar coalescent nodules are present, aspiration of the largest nodule only is reasonable.[69]

Currently, there is no role for ultrasonography in screening asymptomatic patients for thyroid nodules. Preoperative ultrasound evaluation of the lateral cervical lymph nodes is recommended for all patients with papillary and Hürthle cell thyroid cancer before initial thyroidectomy because operative management may be altered in 20% of patients.[87] In addition, intraoperative ultrasound examination may be useful in the localization of nonpalpable lesions in the thyroid bed or nodal metastases.

Computed tomography (CT) and MRI scans are usually unnecessary in the evaluation of thyroid tumors except for fixed or substernal lesions. Although these studies are not as effective as ultrasonography in the evaluation of thyroid nodules, they are more reliable in evaluating the relationship of the thyroid lesion to adjacent neck structures, such as the trachea and esophagus. These studies are useful in determining substernal extension, identifying cervical and mediastinal adenopathy, and evaluating possible tracheal invasion.[88] Anatomic imaging should be obtained when visceral compartment invasion is suspected and for localization in patients with nodal disease. Also, CT or MRI can supplement ultrasound imaging, which cannot visualize the regions behind the sternum, trachea, and esophagus. Caution must be exercised in the use of iodine-containing contrast material in patients with multinodular goiter if a hyperthyroid state is suspected, and in patients with well-differentiated thyroid cancer. In the latter group, iodinated contrast media preclude the use of postoperative radioactive iodine therapy for 2 to 3 months. Finally, MRI is more accurate than a CT scan in distinguishing recurrent or persistent thyroid tumor from postoperative fibrosis.

Thyroid Isotope Scanning

Radionuclide scanning with ^{123}I or technetium 99m (^{99m}Tc) sestamibi assesses the functional activity of a thyroid nodule and the thyroid gland. Nodules that retain less radioactivity than the surrounding thyroid tissue are termed "cold," nonfunctioning, or hypofunctional. These cold nodules are thought to have lost functions of fully differentiated thyroid tissue and to be at increased risk of containing carcinoma. In a meta-analysis of patients with scanned nodules that were surgically removed, 95% of all nodules were cold.[66,67] The incidence of malignancy in cold nodules was 10% to 15% compared with only 4% in hot nodules.

^{99m}Tc scanning tests iodine transport only, but can be performed in 1 day and involves less radiation exposure than ^{123}I. Cold nodules identified with this test are also cold with iodine scanning. Any "hot" nodules require ^{123}I scanning for confirmation, however. ^{123}I scanning tests transport and organification of iodine. This test is more expensive

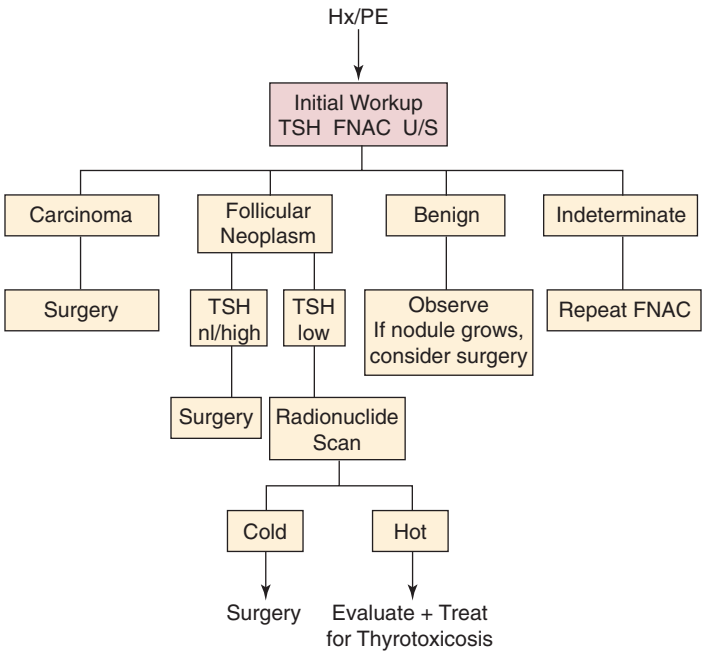

Figure 124-3. Algorithm for a rational approach to the evaluation and management of a thyroid nodule. Surgery is indicated for well-differentiated thyroid carcinoma. Anaplastic carcinoma and lymphoma require additional workup and assessment to determine treatment. Ultrasound guidance should be considered for repeat FNAC after an indeterminate result. FNAC, fine-needle aspiration cytology; Hx/PE, history/physical examination; TSH, thyroid-stimulating hormone; U/S ultrasonography.

and requires 2 days to complete. Cold lesions can be more difficult to visualize because of overlying thyroid tissue and glandular asymmetry, although oblique views during scanning can improve detection. In addition, ^{99m}Tc does not penetrate the sternum, and is not useful in confirming substernal extension.

With the evolution of FNAC, radionuclide scanning is not routinely performed in the evaluation of a thyroid nodule. More frequently, "cold" nodules are detected in patients during evaluation for hyperthyroid disorders. Patients who present initially with a thyroid nodule, however, and are found to be hyperthyroid on preliminary thyroid function testing should have radionuclide scanning to differentiate between a toxic nodule and Graves' disease and a nonfunctioning nodule. Also, after indeterminate FNAC, ^{123}I thyroid scan should be considered. Surgical treatment should be contemplated if a concordant autonomously functioning nodule is not seen.[69]

Rational Approach to Management of a Thyroid Nodule

Numerous diagnostic algorithms have been proposed for the evaluation of a thyroid nodule (Fig. 124-3).[70,89] Evaluation generally begins with a thorough history and physical examination to identify significant risk factors. Surgery may be deemed appropriate based solely on high-risk factors, such as age, sex, history of radiation exposure, rapid nodule growth, upper aerodigestive tract symptoms, and fixation.

Baseline TSH screening determines the diagnostic course. Patients with hyperthyroidism (suppressed serum TSH level) should receive radionuclide scanning to determine the presence of a toxic "hot" nodule, or Marine-Lenhart syndrome, or Graves' disease with a concomitant "cold" nodule.[90] A patient with hypothyroidism (elevated serum TSH level) should be appropriately treated by an endocrinologist, and then FNAC should be performed. Most patients are euthyroid (normal serum TSH level), and FNAC should be performed. Ultrasound examination can provide valuable diagnostic information, especially in the selection of a nodule for biopsy in a patient with multiple nodules, and may facilitate FNAC. In a patient with a thyroid malignancy, evaluation of the nodal basins may detect early clinically occult disease and alter surgical management. Patients with cytologic findings that are diagnostic or strongly suggestive of malignancy should be referred to a surgeon for removal of the lesion.

A diagnosis of follicular neoplasm by FNAC requires surgery to determine the presence of follicular adenoma or follicular carcinoma. FNAC suspicious for medullary carcinoma may be subject to immunohistochemical techniques to detect calcitonin. Before surgical intervention, a patient with FNAC suggestive of medullary carcinoma requires genetic studies and additional testing (discussed later in the section on MTC). Suspicious findings on FNAC must be assessed in the context of patient risk factors in determining the need for surgery. If a nonsurgical approach is taken, the nodule must be closely monitored, usually with ultrasonography. Benign lesions are usually observed and require surgical removal only in cases of cosmetic or symptomatic concerns. These nodules must be aspirated again to confirm the diagnosis if growth is detected.

Review of Thyroid Neoplasms

Thyroid Adenoma

Clinical Presentation

A thyroid adenoma is a true benign neoplasm derived from follicular cells. These follicular lesions are occasionally multiple and may arise in the setting of a normal thyroid, nodular goiter, toxic goiter, or thyroiditis. They occur most commonly in women older than 30 years. Patients usually present with a solitary, mobile thyroid nodule. The thyroid mass is often found incidentally on a routine physical examination and is frequently not associated with any other signs or symptoms. Sudden hemorrhage into the adenoma may cause a sudden increase in size and associated pain.

Pathology

The revised histologic classification of thyroid tumors divides epithelial tumors into the categories of follicular adenoma and other rare tumors (Table 124-4). Follicular adenomas are the most common benign thyroid lesions. Atypical follicular adenomas may show atypical microscopic features, including excess cellularity, increased mitotic figures, and necrotic foci. Although most of these lesions are benign, they may metastasize even in the absence of microinvasion.[91]

Table 124-4

World Health Organization Revised Histologic Classification of Thyroid Tumors

I. Epithelial tumors
  A. Benign
    1. Follicular adenoma
      a. Architectural patterns
        i. Normofollicular (simple)
        ii. Macrofollicular (colloid)
        iii. Microfollicular (fetal)
        iv. Trabecular and solid (embryonal)
        v. Atypical
      b. Cytologic patterns
        i. Oxyphilic cell type
        ii. Clear cell type
        iii. Mucin-producing cell type
        iv. Signet-ring cell type
        v. Atypical
    2. Others
      a. Salivary gland–type tumors
      b. Adenolipomas
      c. Hyalinizing trabecular tumors
  B. Malignant
    1. Follicular carcinoma
      a. Degree of invasiveness
        i. Minimally invasive (encapsulated)
        ii. Widely invasive
      b. Variants
        i. Oxyphilic (Hürthle) cell type
        ii. Clear cell type
    2. Papillary carcinoma
      a. Variants
        i. Papillary microcarcinoma
        ii. Encapsulated variant
        iii. Follicular variant
        iv. Diffuse sclerosing variant
        v. Oxyphilic (Hürthle) cell type
    3. Medullary thyroid cancer
      a. Variant
        i. Mixed medullary-follicular carcinoma
    4. Undifferentiated (anaplastic) carcinoma
    5. Other carcinomas
      a. Mucinous carcinoma
      b. Squamous cell carcinoma
      c. Mucoepidermoid carcinoma
II. Nonepithelial tumors
III. Malignant tumors
IV. Miscellaneous tumors
  A. Parathyroid tumors
  B. Paragangliomas
  C. Spindle cell tumors with mucous cysts
  D. Teratomas
V. Secondary tumors
VI. Unclassified tumors
VII. Tumor-like lesions
  A. Hyperplastic goiters
  B. Thyroid cysts
  C. Solid cell nests
  D. Ectopic thyroid tissue
  E. Chronic thyroiditis
  F. Riedel's thyroiditis
  G. Amyloid goiter

From Hedinger C, ed. *Histological Typing of Thyroid Tumours*. 2nd ed. Berlin: Springer-Verlag; 1988.

On gross examination, thyroid nodules and adenomas are well circumscribed and demarcated from adjacent normal thyroid tissue. The classic adenoma is fleshy and pale, although areas of necrosis, hemorrhage, and cystic change may be readily apparent. Microscopic findings include large and small follicles with abundant colloid. Cells may be flat, cuboidal, or columnar. The nuclei are small and round with an even chromatin pattern. Mixed populations of macrophages and lymphocytes, and fibrosis, hemosiderin, and calcification may be visible. Cystic areas may be present near areas of abundant papillae formation. Adenomas that exhibit pseudopapillary structures need to be distinguished from papillary carcinoma. Oxyphilic (Hürthle) cell adenoma contains mitochondria-rich eosinophilic cells. Thyroglobulin immunohistochemical staining can distinguish a clear cell adenoma from a parathyroid adenoma and metastasis from a renal carcinoma. This adenoma also needs to be differentiated from the clear cell variant of follicular carcinoma.

Nodules within a nodular goiter occasionally may be hyperfunctional or "hot." These lesions are termed *autonomously hyperfunctioning thyroid adenomas,* and may or may not cause thyrotoxicosis. These lesions often occur in women, and nodules associated with thyrotoxicosis are frequently in patients older than 40 years.

Management and Prognosis

Thyroid nodules that are determined to be benign require follow-up because of a low false-negative rate (approximately 5%) with FNAC.[92,93] Nodule growth alone is not an indication of malignancy, but growth is an indication for repeat biopsy. The 2006 ATA guidelines recommend serial clinical examination for easily palpable benign nodules at 6- to 18-month intervals.[69] All other benign nodules should be followed with serial ultrasound examinations 6 to 18 months after initial FNAC. Patients with nodules that remain stable in size may have subsequent examinations at longer time intervals. Patients with evidence of nodule growth should have repeat FNAC, preferably with ultrasound guidance.

The surgical evaluation of a thyroid nodule begins with FNAC that shows follicular neoplasm. Distinguishing follicular or Hürthle cell adenoma from carcinoma depends on histopathologic analysis after surgical excision. Concern for a potential malignancy increases with highly cellular findings or pseudopapillary structures on FNAC. The lack of tumor capsule and vascular invasion is characteristic of a follicular adenoma.

Surgical excision involves a thyroid lobectomy. A unilateral partial thyroid lobectomy is no longer an acceptable standard of care. Patients with a history of radiation to the head and neck, other head and neck cancers, potential high-risk factors, and comorbidities may benefit from a total thyroidectomy. Risk of surgical morbidity at the initial surgery must be balanced with the potential risks of reoperation. In most patients, thyroid hormone administration is unnecessary when the patient has undergone resection of a single thyroid lobe for a thyroid adenoma.

Autonomously hyperfunctioning thyroid adenomas are usually anatomically and functionally stable. Although most patients do not develop thyrotoxicosis, 20% of patients with lesions greater than 3 cm may develop thyrotoxicosis. Surgery and radioiodine therapy can be used to manage these lesions, although many physicians prefer surgery for patients younger than 40 years. These patients may require preoperative medications to control thyrotoxic symptoms. The lesions are typically removed with a unilateral thyroid lobectomy. The remaining thyroid tissue typically returns to normal function after several months. Ethanol injection has become increasingly common, especially in Europe, to manage these lesions.[94]

Thyroid Cyst

Clinical Presentation

Although a thyroid cyst is not a specific diagnosis, this entity is frequently encountered in clinical practice. Approximately 15% to 25% of all thyroid nodules are cystic or have a cystic component.[47] The presence of a cyst does not signify a benign lesion because papillary carcinomas and parathyroid tumors may manifest with cystic masses.

Papillary carcinoma may be present in 14% to 32% of all cystic nodules, although most of these lesions are benign adenomas or colloid nodules.[95,96]

Pathology

A thyroid cyst can result from congenital, developmental, or neoplastic causes.[95] Many cysts result from intranodular ischemia causing tissue necrosis and liquefaction. True epithelial-lined cysts are rare. Occasionally, parathyroid or thyroglossal duct cysts can be mistaken for thyroid nodules. A parathyroid cyst contains high parathyroid hormone levels within the clear fluid, and a thyroglossal duct cyst contains columnar epithelium. These lesions may also be differentiated by ultrasound imaging.

Management and Prognosis

When encountered during FNAC, a thyroid cyst should be drained completely. This procedure may prove curative in most simple cysts, although one or two additional drainage procedures may be required. If a cyst persists after three drainage attempts or reaccumulates quickly, the suspicion for carcinoma should increase. Brown fluid withdrawn from a cyst may represent old hemorrhage into an adenoma, but red fluid is more suspicious for carcinoma.[64] Clear, colorless fluid may be withdrawn from a parathyroid cyst and can be assessed for parathyroid hormone.[97] In suspicious cases, the surgeon and patient should consider ultrasound-guided FNAC to sample a solid component of the lesion or a unilateral thyroid lobectomy to obtain a definitive diagnosis. Because of the potential for thyroid carcinoma in cystic lesions, surgical excision for diagnosis is preferable to the injection of sclerosing agents.

Papillary Carcinoma

Clinical Presentation

Papillary carcinoma is the most common form of thyroid malignancy, accounting for 60% to 70% of all thyroid cancer.[58,98] This lesion typically occurs in patients 30 to 40 years old, and is more common in women, with a female-to-male ratio of 2:1. This ratio has decreased steadily over the past 40 years as the incidence in men has increased.[99] Papillary carcinomas are the predominant thyroid malignancy in children (75%). Although children more commonly present with advanced disease, including cervical and distant metastases, their prognosis remains quite favorable.

Most cases of papillary carcinoma occur spontaneously. Patients with a history of low-dose radiation exposure tend to develop papillary carcinomas (85% to 90%).[100] These lesions also are more common in patients with Cowden's syndrome (familial goiter and skin hamartomas), Gardner's syndrome (familial colonic polyposis), and familial polyposis. Only 6% of papillary carcinomas are associated with familial disease.

Papillary carcinoma can be classified into three categories based on size and extent of the primary lesion.[101,102] Minimal carcinoma or occult carcinoma/microcarcinoma tumors are 1.5 cm or smaller in size, and show no evidence of invasiveness through the thyroid capsule or to cervical lymph nodes. These lesions are typically nonpalpable and are usually incidental findings during operative or autopsy examination. Intrathyroid tumors are greater than 1.5 cm in diameter, but are confined to the thyroid gland with no evidence of extrathyroid invasion. Extrathyroid tumors extend through the thyroid capsule to involve the surrounding viscera. This latter form of papillary carcinoma is associated with substantial morbidity and decreased survival.[7,101]

Most patients present with a slow-growing, painless mass in the neck and are often euthyroid. Often, the primary lesion is confined to the thyroid gland, although 30% of patients may have clinically evident cervical nodal disease.[103,104] Histologic studies have shown the strong lymphotropic nature of papillary carcinoma, leading to multifocal disease within the thyroid and regional lymphatics. Microscopic disease has been identified in the cervical nodes of 50% to 80% of patients and in the contralateral lobe in 80% of patients with papillary carcinoma at the time of surgery.[105] The significance of this microscopic disease is unclear, however, because clinical recurrences in the neck and in the contralateral lobe occur in less than 10% of patients.[106] More likely, the prevalence of microscopic disease suggests that most papillary carcinomas have an indolent course that only occasionally becomes clinically evident. Definite predictors of the clinical course for papillary carcinoma are not well defined, however.

Advanced disease may be associated with symptoms of local invasion, including dysphagia, dyspnea, and hoarseness. Occasionally, cervical nodal involvement may be more apparent than the thyroid nodule. Distant metastases, especially to the lungs, are more commonly encountered in children, although 10% of all patients may ultimately develop distant disease.[81]

Thyroid cancer is often suspected in these patients after a thorough history and physical examination. The diagnosis is usually established by FNAC. Thyroid function tests are done routinely in the preoperative assessment. Radiographic imaging (CT or MRI) is selectively performed to define extensive local or substernal disease and to evaluate possible lymph node involvement.

Pathology

On gross examination, papillary carcinoma is firm, white, and not encapsulated. The lesion tends to remain flat on sectioning, rather than bulging the way normal thyroid tissue or benign nodular lesions do. Macroscopic calcifications, necrosis, or cystic changes may be readily apparent.[107]

Histologically, these lesions arise from thyroid follicular cells and contain papillary structures that consist of a neoplastic epithelium overlying a true fibrovascular stalk.[14] Cells are cuboidal with a pale, abundant cytoplasm. Large, crowded nuclei with folded and grooved nuclear margins may have intranuclear cytoplasmic inclusions. Prominent nucleoli account for the "Orphan Annie eye" appearance. Laminated calcium densities, psammoma bodies, are likely the remnants of necrotic calcified neoplastic cells and are present in 40% of cases.

Although a follicular component may predominate, lesions with any papillary features behave clinically as papillary carcinomas. The designation of "papillary carcinoma" includes mixed papillary follicular carcinoma and the follicular variant of papillary carcinoma. A more unfavorable prognosis is associated with certain histologic forms of papillary carcinoma, including diffuse sclerosing and tall-cell variants.[14,108] The tall-cell variant is characterized by well-formed papillae covered by cells that are twice as tall as they are wide. The rarer columnar cell variant is characterized by the presence of prominent nuclear stratification.[109]

Papillary carcinomas have a strong tendency for lymphatic spread within the thyroid and to local lymph nodes in the paratracheal and cervical regions. The tendency for intraglandular spread may lead to the multifocal disease often present in patients. Discrete lesions may be due to de novo formation, however, especially in patients previously exposed to ionizing radiation.[110]

Local invasion occurs in 10% to 20% of these tumors, leading to involvement of the overlying strap muscles, laryngeal and tracheal framework, RLNs, pharynx, and esophagus. This extension may evolve from the primary lesion or from extracapsular extension of metastatic nodes. Angioinvasion is a clear harbinger of increased risk for recurrence and worse prognosis.[58] A coexisting lymphocytic thyroiditis has been correlated with decreased recurrence and better overall prognosis.

Management and Prognosis

Most patients with papillary carcinoma do well regardless of treatment. Prolonged survival, even with recurrent disease, has led to controversy regarding the extent of thyroidectomy for patients with well-differentiated thyroid carcinomas (see section on extent of surgery under surgical management and technique). A balance must be achieved between an effective surgical treatment for these malignancies and the potential morbidity of this surgery. Numerous studies have attempted to categorize patients by their risk factors and to justify more aggressive surgical intervention for high-risk patients (see section on tumor staging and classification). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology provides specific recommendations for evaluation and management of well-differentiated thyroid carcinomas.[111]

Incidental micropapillary thyroid carcinoma is usually identified in a thyroid specimen removed for other reasons. Unilateral thyroid lobectomy and isthmectomy is usually sufficient surgical treatment, unless there is angioinvasion or tumor at the margins of resection. These patients can be treated with thyroid hormone to suppress TSH and closely followed up with ultrasonography. In patients with a small, encapsulated papillary thyroid carcinoma (<1 cm in diameter), a total lobectomy is sufficient.

When patients present with biopsy-proven disease or indications of disease in both lobes, total or near-total thyroidectomy is the procedure of choice. Additionally, patients stratified into high-risk categories in any of the classification schemes previously described (see section on tumor staging and classification) would probably benefit from a more extensive surgical procedure that includes paratracheal lymph node dissection. This procedure would permit possible thyroid hormone suppression therapy and radioiodine ablation of remaining disease.

Multifocal disease is present in 80% of patients in some reports.[104,108] This percentage may represent de novo multicentric tumor formation or intraglandular metastasis. The prevalence of multifocal disease lends credence to the argument for more complete surgical removal of the thyroid gland in patients with papillary thyroid cancer. Patients with partial thyroidectomy had higher local recurrence rates and increased pulmonary and cervical metastases.[33,112] Controversy remains, however, because this increased local recurrence did not compromise disease survival in some studies.[53,113]

Generally, invasive tumors are associated with a compromise in survival. Woolner and colleagues[107] reviewed 1181 thyroid cancer patients and found that no patient died of papillary cancer when the lesion was less than 1.5 cm in size. Only 3% of patients died when the lesion was larger but remained intrathyroid. Mortality increased to 16% of patients when extrathyroid disease was present.

After total thyroidectomy, patients may be monitored by following thyroglobulin levels, which should remain undetectable, and by neck ultrasonography to evaluate the central and lateral cervical compartments. Any increase in thyroglobulin levels is suspicious for disease recurrence and requires appropriate screening. Approximately 12% of patients with papillary carcinoma are not cured by initial treatment, leading to a prolonged clinical course.[114] Recurrent disease may occur after many years, involving the thyroid bed (5% to 6%), regional lymphatics (8% to 9%), or distant sites (4% to 11%).[115] Successful treatment of recurrence varies by site of involvement and the patient's initial risk classification.

Local recurrence is a serious complication and is associated with a disease-related mortality of 33% to 50%.[115] Typically, patients with nodal recurrence fare better than patients with tumor recurrence in the thyroid bed or distant sites. Studies have been inconsistent regarding the impact of cervical metastases on survival. Patients older than 40 years may have clinically evident nodal disease in 36% to 75% of cases and overall increased mortality.[6,99] Some studies suggest prognosis is better with more cervical node involvement.[56,116] Although the role of cervical metastasis in survival may be controversial, there is an association with an increased recurrence rate, especially in elderly patients.[114,116,117] Generally, lymph node metastases do not seem to have an impact on overall survival in most patients with low-risk and intermediate-risk disease.[101,118] Cervical recurrences occur in 20% of patients with low-risk disease, however, and 59% of patients with high-risk disease.[53,119] The continuing debate regarding extent of lymphadenectomy at the time of thyroidectomy reflects a shift in focus from overall survival to recurrence-free survival.

Because of these findings and the overall prevalence of microscopic cervical disease with uncertain prognostic implications, management of cervical metastasis tends to be conservative. There is no role for elective neck dissection in the clinically disease-free neck, especially considering the effectiveness of radioiodine therapy in ablating microscopic disease.[106] The central compartment from hyoid bone to mediastinum between the internal jugular veins (levels VI and VII) should be carefully inspected and palpated. The 2006 ATA management guidelines recommend considering routine central compartment (level VI) neck dissection for patients with papillary thyroid carcinoma and suspected Hürthle cell carcinoma, although postoperative radioiodine therapy may provide an alternative approach.[69]

Elective dissection of the pretracheal and ipsilateral paratracheal nodes may be reasonable, especially in patients with high-risk factors. Additionally, elective removal may potentially decrease nodal recurrence in this region and the need for reoperation. In patients with palpable or visible neck disease, a comprehensive neck dissection (levels II-V) should be performed, as opposed to selective cervical lymph node excision or "berry-picking." Although level I is seldom involved, metastatic disease is frequently noted on histologic examination of nodal levels II through V.[120] In addition, because the incidence of contralateral subclinical metastasis is less than 20%, elective treatment of the contralateral neck is not advocated.

The presence of distant metastasis is associated with a worse prognosis. Approximately 10% of patients with papillary thyroid carcinoma develop distant metastasis at some point during their disease course.[81] Most commonly, the lungs are involved, although bone sites and the central nervous system may also be affected.

In nearly every study, patient age at the time of diagnosis is an important prognostic variable.[6,116,121] Older patients (especially >40 years old) with papillary carcinoma have a worse prognosis. Extrathyroidal invasion seems to be more common in older patients. The prognosis for men younger than 40 years is comparable to women of the same age. Overall survival is worse for men, however, and the risk of death from papillary thyroid carcinoma may be twice as great.[53,116] In the last 40 years, the increase in incidence of papillary thyroid carcinoma in men has decreased the gender ratio of men to women with the disease from 1:4 to 1:2.[99]

Children fare better with this disease. Among patients younger than 15 years, 90% show cervical metastasis at some time during their disease course.[122] Twenty percent of children may present with pulmonary metastases.[123] Neither cervical nor pulmonary metastases seem to have any impact on survival, however. Perhaps these differences may be related to biologic differences in the disease process or between age groups.

Finally, the tall-cell variant of papillary thyroid carcinoma is different from other forms of this disease. A review of patients with tall-cell variant papillary carcinoma showed a more aggressive natural history in all age groups and a worse prognosis.[124]

Follicular Carcinoma

Clinical Presentation

Follicular carcinomas represent 10% of thyroid malignancies. The mean age of presentation is 50 years compared with 35 years mean age of patients with papillary carcinoma. Women more commonly have this lesion, with a female-to-male ratio of 3:1.[125] These lesions occur more frequently in iodine-deficient areas, especially areas of endemic goiter. Follicular carcinomas have been correlated with pregnancy and with certain HLA subtypes (DR1, DRw, and DR7). Also, a rare form of familial follicular carcinoma is reported in patients with dyshormonogenesis. The overall incidence of follicular carcinoma in decreasing in the United States.

Patients usually present with a solitary thyroid nodule, although some patients may have a history of long-standing goiter and recent rapid increase in size. These lesions are typically painless, although hemorrhage into the nodule may cause pain. Cervical lymphadenopathy is uncommon at initial presentation, although distant metastases are more frequently encountered than with papillary carcinomas. In rare cases (1%), the follicular carcinoma may be hyperfunctioning, and the patient presents with signs and symptoms of thyrotoxicosis.

Other than characterization of a follicular neoplasm, a definitive preoperative diagnosis is usually impossible by FNAC. Differentiation between follicular adenoma and follicular carcinoma requires an evaluation of the thyroid capsule for invasion or identification of vascular invasion. Typically, about 20% of thyroid nodules showing follicular neoplasm cytology contain carcinoma.

In contrast to papillary carcinoma, follicular thyroid carcinomas are less likely to metastasize via lymphatic pathways (found in <10% of patients).[88] More commonly, follicular carcinomas spread through

local extension and hematogenous spread. Often, the presence of cervical lymph node disease indicates significant local disease and visceral invasion.[99,126] Distant metastasis is also more common in follicular cancers than papillary cancers, especially at presentation.[127,128] A pathologic bone fracture may be the initial presentation of follicular carcinoma. Other common sites include liver, lung, and brain.

Pathology

Follicular thyroid carcinoma tends to manifest as solitary, encapsulated lesions. Cytologic analysis of follicular neoplasms reveals small follicular arrays or solid sheets of cells.[14] The follicular structures have lumens that do not contain colloid, and the overall architectural pattern depends on the degree of tumor differentiation. Increased cellularity may increase the suspicion for carcinoma, but cytology alone is insufficient to distinguish between a follicular adenoma and carcinoma.

Histologic findings are necessary to distinguish benign and malignant lesions. Malignant lesions are differentiated by the identification of capsular invasion and potential microvascular invasion of vessels along the tumor capsule.[91,129] Complete capsular evaluation must be performed. Frozen-section analysis is often inadequate, and definitive diagnosis requires complete assessment of permanent sections.

The degree of capsular invasion is important for patient prognosis. Follicular carcinomas can be divided into two broad categories. Minimally invasive tumors show evidence of invasion into, but not through, the tumor capsule at one or more sites. These lesions do not exhibit small-vessel invasion. Frankly invasive tumors show invasion through the tumor and often exhibit vascular invasion.[130] Tumor infiltration and invasion may be apparent at surgery, with tumor present in the middle thyroid or jugular veins.

Many other factors have been investigated as means to differentiate between adenomas and carcinomas. To date, no molecular markers have been clinically useful. DNA ploidy varies in adenomas and carcinomas with considerable overlap.[131] Aneuploid follicular carcinomas are noted to behave in a more aggressive manner.

Management and Prognosis

Patients diagnosed with a follicular lesion by FNAC should have a thyroid lobectomy with isthmectomy performed. The pyramidal lobe, if present, should be included in the resection. As described previously, cytologic findings alone cannot determine the presence of adenoma or carcinoma. Intraoperative frozen-section analysis is not helpful because of the incomplete assessment of the tumor capsule. Frozen sections should be analyzed, however, to confirm gross evidence of adjacent cervical lymphadenopathy. A total thyroidectomy is recommended if carcinoma is identified. In patients with a clinical suspicion for follicular carcinoma, the tendency is to perform a more complete resection. Total thyroidectomy is performed in older patients with a nodule greater than 4 cm in size diagnosed by FNAC as follicular neoplasm. In these patients, the risk of carcinoma is approximately 50%.[112] Additional factors that may favor a total thyroidectomy as the initial surgical procedure include a family history of thyroid carcinoma, history of radiation exposure, and patient preference.[69]

A diagnosis of follicular carcinoma after a thyroid lobectomy usually necessitates a completion thyroidectomy. Patients with minimally invasive follicular cancer have a very good prognosis, and the initial thyroid lobectomy may be sufficient treatment. Invasiveness of follicular carcinoma correlates directly with decreased survival, however. In patients with invasive follicular carcinomas, many surgeons tend toward completion and total thyroidectomy to permit radioiodine scanning for detection and ablation of metastatic disease. More aggressive surgical intervention does not improve survival because invasiveness already indicates the increased likelihood of distant metastasis. Neck dissection is performed if cervical lymphadenopathy is present. When cervical disease is present, consultation with the pathologist is warranted because the patient may have a follicular variant of papillary thyroid carcinoma. Elective neck dissections are unwarranted because nodal involvement is unlikely.[10]

The recurrence rate after initial management is approximately 30%.[132] Recurrence is related to the degree of invasiveness of the initial lesion, not the extent of initial thyroid surgery. Minimally invasive disease behaves similarly to follicular adenoma and is typically cured with conservative surgical procedures (thyroid lobectomy).[133] Recurrence of minimally invasive follicular carcinoma is approximately 1%. About 15% of patients with recurrent or metastatic disease can be cured. The prognosis of these patients relates to the site of recurrence and the patient's initial risk stratification. Survival outcomes are significantly poorer in patients with capsular invasion and angioinvasion.[134] Patients with cervical node recurrence have a 50% cure rate, whereas patients with distant metastases have a cure rate of about 9%.[115,132]

Overall, 5-year survival is 70% and decreases to 40% at 10 years for patients with follicular carcinoma. The presence of distant metastasis diminishes 5-year survival to 20%.[135] Factors that worsen prognosis include age older than 50 years at presentation, tumors greater than 4 cm in size, higher tumor grade, marked vascular invasion, extrathyroidal invasion, and distant metastasis at the time of diagnosis.[10] Extrathyroidal invasion beyond the capsule and into the thyroid parenchyma and local structures is the key factor decreasing patient survival. Risk stratification shows marked differences in patient survival. In one study, the low-risk group had a 5-year survival rate of 99% and a 20-year survival rate of 86%. In the high-risk group, the 5-year survival rate was only 47%, and this decreased to a 20-year survival rate of 8%.[125]

The prognosis for patients with follicular carcinoma has typically been reported to be worse than for patients with papillary carcinoma. Some reports that matched age, sex, and stage at time of diagnosis suggest that patients with papillary and follicular carcinomas have similar survival patterns.[6,8] The poor prognosis of patients with follicular carcinoma may be related to the increased number of patients who present at an older age and a more advanced disease stage. Also, in contrast to papillary carcinoma, mortality is directly related to recurrence in patients with follicular carcinoma.[99]

Hürthle Cell Tumor

Clinical Presentation

According to World Health Organization classification, Hürthle cell tumor is a subtype of follicular cell neoplasm. Hürthle cell tumor nodules can be found in patients with Hashimoto's thyroiditis or Graves' disease or within a nodular goiter. These tumors are derived from oxyphilic cells of the thyroid gland. Although the precise function of these cells is unknown, Hürthle cells express TSH receptors and produce thyroglobulin.

Hürthle cell neoplasms are typically diagnosed by FNAC. Approximately 20% of these lesions are malignant. Similar to follicular lesions, histologic criteria are required to diagnose carcinomas. Hürthle cell carcinomas represent approximately 3% of all thyroid malignancies. The mean age of presentation for patients with Hürthle cell carcinoma may be older than for follicular carcinoma.[80,136] Hürthle cell carcinomas are more aggressive than follicular carcinomas. They are often multifocal and bilateral at presentation. These malignancies also are more likely to metastasize to cervical nodes and distant sites.[137]

Pathology

FNAC of Hürthle cell tumor typically shows hypercellularity and the presence of eosinophilic cells. These neoplasms are characterized by sheets of eosinophilic cells packed with mitochondria. Cytologic differentiation between adenoma and malignant tumor by FNAC is extremely difficult. Histologic findings of capsular or vascular invasion confirm the presence of Hürthle cell carcinoma.

Management and Prognosis

The clinical approach to Hürthle cell tumors is similar to that for follicular neoplasms. With Hürthle cell adenoma, resection of the affected lobe and isthmus is sufficient. Invasive findings for Hürthle neoplasms on formal pathology warrant a total or completion thyroidectomy. Hürthle cell carcinomas tend to be more aggressive than other follicular carcinomas, and they are less amenable to radioiodine therapy because of their decreased tendency to uptake radiolabeled iodine. Because locoregional nodal metastases may occur, careful examination for local disease extension or adjacent cervical lymphadenopathy should

be performed. The paratracheal region should be carefully palpated and examined. The paratracheal nodes should be removed if disease is obvious during inspection. Also, a comprehensive neck dissection should be undertaken if lateral neck nodes are palpable.

Postoperative management should include TSH suppression and thyroglobulin monitoring, and periodic ultrasound evaluation of the central and lateral cervical compartments. A ^{99m}Tc scan may be useful for detecting persistent local or metastatic disease. A ^{123}I scan and ablation can be performed to remove any residual normal thyroid tissue to allow for better surveillance. This therapy is unlikely to be effective in tumor ablation, however, because few (approximately 10%) Hürthle cell carcinomas uptake radioiodine.[138]

Overall, survival rates for Hürthle cell carcinoma are significantly worse than for follicular thyroid cancer. The number of patients who die of Hürthle cell carcinoma is greater than the number who die of papillary or follicular carcinoma.[139] Additionally, Hürthle cell carcinoma is associated with the highest incidence of distant metastases among the well-differentiated thyroid carcinomas.[140]

Medullary Thyroid Carcinoma

Clinical Presentation

MTCs are a distinct category of disease and represent approximately 5% of all thyroid carcinomas. These malignancies arise from parafollicular C cells and may secrete calcitonin, carcinoembryonic antigen (CEA), histaminidases, prostaglandins, and serotonin. Measurement of secreted calcitonin is useful for the diagnosis of MTC and for postsurgical surveillance for residual and recurrent disease.

MTC shows an intermediate behavior between well-differentiated thyroid cancers and anaplastic carcinomas. Women and men are equally affected by MTCs.[141] Patients usually present with a neck mass associated with palpable cervical lymphadenopathy (≤20%).[142] Local pain is more common in these patients, indicating the presence of local invasion, and may be associated with dysphagia, dyspnea, or dysphonia. MTC may manifest along with papillary thyroid carcinoma because related mutations in RET are present in both diseases. Although MTC spreads initially to cervical nodes, distant metastases may be found in the mediastinum, liver, lung, and bone, and are present in 50% of patients at diagnosis.[143]

Most (70%) MTCs are spontaneous unifocal lesions in patients 50 to 60 years old without an associated endocrinopathy.[142] The remaining 30% of cases affecting younger patients are familial. These hereditary MTCs are inherited as autosomal dominant traits with nearly 100% penetrance. MTC in these patients is preceded by multifocal C-cell hyperplasia and leads to disease that is multicentric and bilateral in 90% of cases.[144,145] Familial MTC is not associated with any other endocrine pathology. Two forms of MEN syndrome are associated with MTC. Patients with MEN IIA exhibit MTC, pheochromocytoma, and hyperparathyroidism.[144,146] Patients with MEN IIB have a marfanoid body habitus and may have MTC, pheochromocytoma, or mucosal neuromas. Although penetrance for MTC approaches 100% in these patients, expression of other features varies.[145,147]

FNAC diagnosis of MTC is confirmed by elevated serum calcitonin. These patients also should have testing for mutation of the RET proto-oncogene. Genetic screening has replaced provocative pentagastrin-stimulation testing. Careful screening for hereditary diseases is also necessary when a patient is diagnosed with MTC. Hyperparathyroidism can be assessed by serum calcium levels and appropriate imaging studies. Patients should also be screened for the presence of a pheochromocytoma with 24-hour urinary levels for catecholamines and metanephrines, and should undergo abdominal MRI. An undiagnosed pheochromocytoma could lead to an intraoperative hypertensive crisis and death. Additionally, the detection of any hereditary form of MTC in a patient should lead to family screening. Affected family members can often be identified and treated at earlier stages of disease with improved survival.[148,149]

Pathology

MTC originates from parafollicular C cells of neuroectodermal origin.[150] The cells descend to join the thyroid gland proper and are concentrated mainly in the lateral portions of the superior poles. Most MTC lesions are located in the middle and upper thyroid poles. In patients with hereditary forms of MTC, the disease is often multifocal. Grossly, the tumor is solid and firm, and has a gray cut surface. The lesion is nonencapsulated, but well circumscribed.

These lesions are composed of sheets of infiltrating neoplastic cells that are heterogeneous in shape and size. The cells are separated by collagen, amyloid, and dense irregular calcification. The amyloid deposits are likely polymerized calcitonin and are virtually pathognomonic for MTC, although not all MTCs contain amyloid.[151] More aggressive tumors typically have increased mitotic figures, nuclear pleomorphism, and areas of necrosis. Immunohistochemistry for calcitonin and CEA are useful diagnostic studies.

Management and Prognosis

Specific guidelines were recently published by the American Thysoid Association regarding the management of MTC.[151a]

Preoperative workup includes measurement of calcitonin and serum CEA. Patients with germline RET mutations should be screened for pheochromocytoma (MEN IIA/IIB) and hyperparathyroidism (MEN IIA). CT scan of the chest and mediastinum and ultrasound examination of the neck are recommended.

Total thyroidectomy is the treatment of choice in patients with MTC because the lesions have a high incidence of multicentricity and an aggressive disease course. Patients with familial MTC or MEN II should have the entire gland removed, even in the absence of a palpable mass.

Because of the frequent involvement of cervical nodes, initial surgical management should include bilateral central compartment neck dissection. When central compartment nodes are involved, or when palpable lateral cervical nodes are present, treatment including an ipsilateral or bilateral comprehensive neck dissection (levels II-V) should be considered. When the primary lesion is greater than 1 cm (>0.5 cm for MEN IIB patients), or when central compartment lymph node metastases are present, elective ipsilateral comprehensive neck dissection should be considered because nodal metastases may be present in more than 60% of these patients.[111,152,153] The superior mediastinal lymph nodes (level VII) should be routinely removed as well.

Potentially associated conditions, such as hyperparathyroidism and pheochromocytoma, must be carefully evaluated and, if necessary, treated before thyroidectomy. A pheochromocytoma may need to be removed before treatment of the thyroid lesion. Alternatively, preoperative treatment with α-adrenergic blockade (phenoxybenzamine) or α-methyltyrosine is necessary to avoid a hypertensive crisis during surgery. In the presence of hypercalcemia, the parathyroid glands need to be identified during thyroidectomy. If the parathyroid glands are abnormal, they should be removed. Otherwise, they should be adequately marked to facilitate future identification, especially in patients with MEN IIA.

Children with any of the genetic disorders leading to MTC need to be treated aggressively. Typically, a total thyroidectomy should be performed by the time the patient is 2 to 3 years old, or before C-cell hyperplasia occurs. Removal of the thyroid gland should prevent development of MTC in these patients and improve survival. MTC has been diagnosed in MEN IIB patients 7 months old, however.[154]

After surgery, patients require close follow-up and monitoring of serum calcitonin and CEA levels. Calcitonin is more sensitive for detecting persistent or recurrent disease, but CEA levels seem to be predictive for survival.[153] Increasing or persistent calcitonin levels should increase suspicion for residual or recurrent disease. Localization studies should be performed to identify potential sites of disease involvement. Tumor debulking for metastatic disease or local recurrence can decrease symptoms of flushing and diarrhea, and may reduce the risk of death resulting from recurrent central neck disease.[143,155] MTCs do not respond to radioiodine therapy or TSH suppression therapy, however, because of their parafollicular C-cell origin.[149] External-beam radiation therapy (EBRT) has been controversial for patients with positive tumor margins or unresectable tumor, and there is no effective chemotherapy regimen.

Prognosis for patients with MTC is directly related to disease stage. The overall 10-year survival rate is 61% to 75%, but decreases to 45% if cervical nodes are involved.[149,156] The best outcome is for patients with familial MTC, then MEN IIA, sporadic disease, and MEN IIB.

Anaplastic Carcinoma

Clinical Presentation

Anaplastic thyroid carcinomas are one of the most aggressive malignancies, with few patients surviving 6 months beyond initial presentation.[62,157] These lesions represent less than 5% of all thyroid carcinomas.[158] These tumors affect patients 60 to 70 years old; presentation before age 50 years is extremely rare. Women are more commonly affected than men, with a ratio of 3:2. Of these malignancies, 80% may occur with a coexisting carcinoma and may represent transformation of a well-differentiated thyroid cancer.[157,159]

Typically, patients have a long-standing neck mass that enlarges rapidly. This sudden change is often accompanied by pain, dysphonia, dysphagia, and dyspnea. Often the mass is quite large and fixed to the tracheolaryngeal framework, resulting in vocal cord paralysis and tracheal compression. More than 80% have jugular lymph node involvement at the time of presentation, and greater than 50% have systemic metastases.[160] Most patients die of superior vena cava syndrome, asphyxiation, or exsanguination.

Pathology

In the case of anaplastic thyroid carcinoma, the gross specimen shows areas of necrosis and macroscopic invasion of surrounding tissues, often with lymph node involvement. Microscopically, sheets of cells with marked heterogeneity are present. Spindle, polygonal, and giant, multinucleated cells are present with occasional foci of differentiated cells. These cells do not produce thyroglobulin, do not transport iodine, and do not express thyroid hormone receptors.[157] These findings can often be established on FNAC, although a formal biopsy is occasionally necessary to exclude a diagnosis of lymphoma.

Management and Prognosis

Management of anaplastic carcinoma is extremely difficult, requiring a multidisciplinary approach and close consultation with the patient and family. Surgical debulking may be performed for palliation. Initial therapy should ensure airway protection with a tracheostomy and nutritional support. All treatment forms are disappointing, and median survival is 2 to 6 months.[158,161] One current treatment protocol involves doxorubicin, hyperfractionated radiation therapy, and potential surgical debulking.[162,163] Although survival beyond 2 years is only 12%, this is one of the only regimens currently available for these patients.

Retrospective evaluation of various treatment strategies identified a subset of patients who have had long-term survival.[5,86,164] Independent prognostic variables include resectability of local disease, absence of distant metastasis at diagnosis, and adjuvant treatment with radiation therapy. Additionally, many long-term survivors had small areas of anaplastic foci within well-differentiated carcinoma.

Other Forms of Thyroid Cancer

Insular Thyroid Carcinoma

Insular carcinoma was named for the clusters of cells that contain small follicles resembling pancreatic islet cells.[165] These tumors are very rare and manifest as an independent lesion or concomitantly with papillary or follicular thyroid carcinomas. These cells stain with thyroglobulin antibodies, but not for calcitonin. Typically, capsular and vascular invasion is present at the time of diagnosis.

These lesions are very aggressive when compared with follicular and papillary carcinoma, and seem to have an increased recurrence and mortality rate when present as an independent process.[166] Insular carcinoma located within follicular or papillary thyroid cancer does not seem to affect the clinical course adversely, however. Many insular thyroid carcinomas are able to concentrate radioiodine.

Lymphoma

Primary thyroid lymphoma is unusual and represents less than 5% of all thyroid malignancies.[167] Women are more commonly affected at a ratio of 3:1, and lymphoma typically manifests in patients older than 50 years. Patients may present with symptoms similar to anaplastic carcinoma, although the rapidly enlarging mass is often painless. Symptoms may also include regional adenopathy, dysphagia, and vocal cord paralysis caused by RLN invasion. Many affected patients are clinically hypothyroid or already receiving thyroid replacement therapy for conditions such as Hashimoto's disease.[168] Non-Hodgkin B-cell type lymphoma is most common, although Hodgkin's disease and plasmacytomas occur.[169] Thyroid lymphoma can arise as part of a generalized lymphomatous condition because many of these patients have Hashimoto's disease. A current hypothesis as to why this occurs is chronic antigenic lymphocyte stimulation that results in lymphocyte transformation.

A definite diagnosis needs to be made and frequently can be established by FNAC. Occasionally, a needle-core or open cervical lymph node biopsy may be necessary. Because of the rare incidence of primary thyroid lymphoma, a comprehensive survey must be done to exclude the presence of lymphoma at other sites.

Patients typically respond rapidly to chemotherapy, especially CHOP (cyclophosphamide, hydroxydaunomycin, vincristine [Oncovin], and prednisone).[170,171] Combined radiation and chemotherapy regimens have also been developed and have been promising. Thyroidectomy and nodal resection may be considered to alleviate symptoms of airway obstruction in patients who do not respond rapidly to treatment, but surgical options are not primary treatment modalities.

The prognosis depends on the histologic grade of the tumor and the presence of extrathyroidal disease. Overall, 5-year survival is about 50%. Intrathyroid disease survival is 85% and decreases to 40% for patients with extrathyroid disease.

Metastatic Carcinoma

The thyroid is a rare site for metastases from other cancers. Metastasis can occur, however, from primary lesions in the kidney, breast, lung, and skin (i.e., melanoma). The most common metastatic tumor to the thyroid is from a hypernephroma. Also, approximately 3% of bronchogenic carcinomas metastasize to the thyroid, but account for 20% of all metastases to the thyroid.[172]

Typically, the history and physical examination identify the source of the metastasis. FNAC is performed for definitive diagnosis. Thyroidectomy may be considered for palliation, especially when the primary lesion is very slow growing (e.g., renal cell carcinoma).[173]

Squamous Cell Carcinoma

Squamous cell carcinoma of the thyroid is very rare, representing less than 1% of thyroid cancers.[174] Older patients are most commonly affected, and the disease can progress rapidly with local invasion and metastasis. During the workup, metastasis from another site within the upper aerodigestive tract needs to be excluded. Early detection and aggressive surgical treatment seems to represent the best option for palliation and cure. As with other squamous cell carcinomas of the head and neck, radiation therapy is probably important, although not well characterized.[175]

Surgical Management and Technique

Approach to the Thyroid Gland

Before any thyroid surgery, any voice changes or previous neck surgery should prompt assessment of vocal cord mobility by indirect laryngoscopy. Although many patients with thyroid carcinomas are euthyroid, necessary medical therapy should be instituted for patients with thyrotoxicosis or hypothyroidism to avoid intraoperative metabolic derangements, such as hypertensive crisis. Details of this management are beyond the scope of this chapter, but management should include consultation with an endocrinologist.

The patient should be positioned supine on the operating table with an inflatable pillow or shoulder roll and adequate head support to permit full neck extension for optimal exposure. A symmetric, trans-

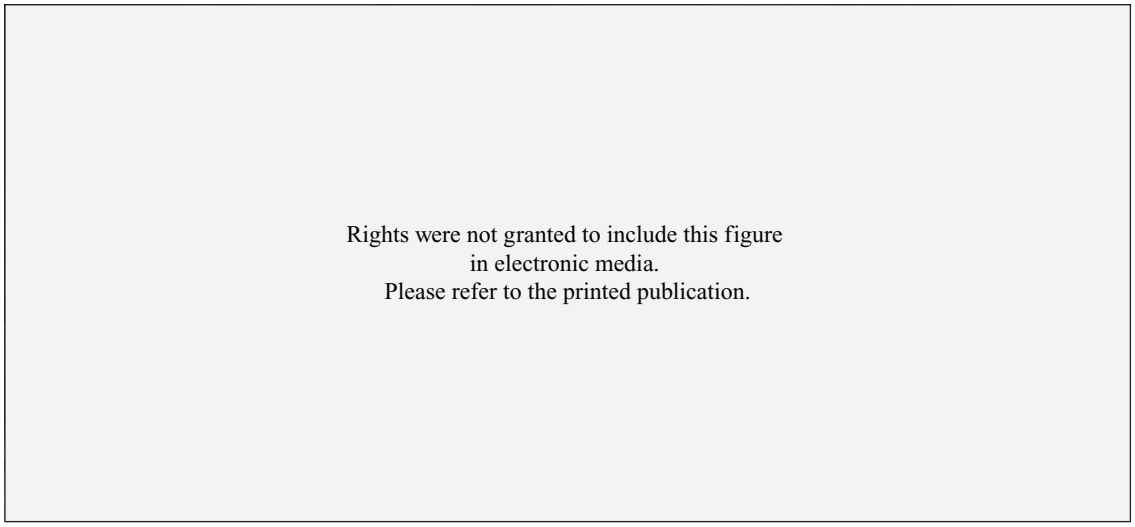

Figure 124-4. **A,** Careful dissection along the lateral portion of the thyroid lobe permits mobilization of the gland medially. The middle thyroid vein(s) should be carefully identified and ligated. **B,** The course of the recurrent laryngeal nerve along the tracheoesophageal groove is shown intraoperatively. **C,** The lateral course of a nonrecurrent laryngeal nerve has been revealed intraoperatively.

verse incision along a skin crease approximately 1 cm below the cricoid cartilage is made through the platysma. The length of the incision depends on the size of the thyroid gland. Larger incisions are necessary for patients with short, thick necks, difficulty with neck extension, or a low-lying thyroid gland. Subplatysmal skin flaps are raised superiorly to the level of the thyroid cartilage notch and inferiorly to the clavicle.

Exposure of the thyroid gland is obtained through a midline, vertical incision through the superficial layer of the deep cervical fascia between the sternohyoid and sternothyroid muscles. The strap muscles are bluntly separated, and dissection proceeds laterally along the thyroid capsule until the ansa cervicalis is noted at the lateral edge of the sternohyoid muscle/medial aspect of the internal jugular vein. Rarely, the strap muscles must be divided to gain access to a large thyroid lobe or tumor. This division should be done high on the muscle to preserve innervation from the ansa hypoglossal nerve. The strap muscles should be reapproximated before skin closure. Any evidence of frank invasion of thyroid carcinoma into the strap muscles should result in the en bloc resection of the section of the affected muscle with the thyroid lobe.

Through blunt dissection, the thyroid lobe is swept anteromedially to the tracheolaryngeal framework (Fig. 124-4A). The middle thyroid vein should be identified; division of this vessel improves lateral exposure. The cricoid and trachea should be identified in the midline, and continued mobilization is achieved by sweeping dorsally all tissue along the posterolateral border of the thyroid lobe. Meticulous hemostasis should be maintained to facilitate identification of the SLN, RLN, and parathyroid glands.

The pedicle along the superior thyroid pole is identified early by retracting the thyroid inferomedially. Dissection should be carried out close to the thyroid capsule to avoid possible injury to the external branch of the SLN. Occasionally, the external branch of the SLN that supplies the cricothyroid muscle can be visualized. The superior pole vessels should be individually identified and isolated for ligation close to the thyroid lobe. At this point, the tissues posterolateral to the superior pole can be swept away from the lobe in a posteromedial direction.

Identification of the RLN is best achieved through an inferior approach in a space defined by Lore and colleagues[176] as the RLN triangle. The triangle is bounded by the trachea medially, the carotid sheath laterally, and the undersurface of the retracted inferior thyroid pole superiorly. Careful dissection in this area parallel to the course of the RLN should safely identify the nerve (see Fig. 124-4B). A thyroid goiter or unusually large thyroid mass can potentially displace the nerve. The RLN, in these cases, can become fixed to and splay across the undersurface of the enlarged thyroid lobe. Great care needs to be taken in these situations, and identification of the nerve may require a superior approach, identifying the RLN at its entry into the larynx.

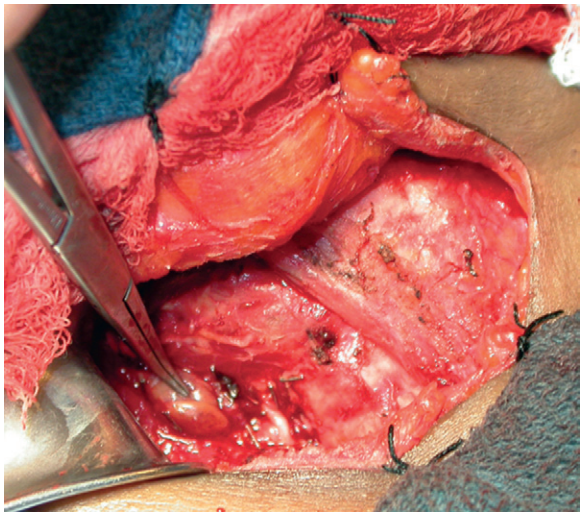

Figure 124-5. A parathyroid gland is shown in close proximity to the recurrent laryngeal nerve. Close dissection and ligation of vessels along the thyroid capsule ensure that the vascular supply to the parathyroid glands remains intact.

When identified, the RLN should be followed to its laryngeal entry at the level of the cricoid cartilage, passing under or through Berry's ligament and entering the larynx deep to the inferior constrictor muscle. The nerve may divide into multiple branches before entering the larynx.[177] The most difficult portion of the operation is typically in dealing with the dissection where the recurrent nerve passes through Berry's ligament. The RLN is in close proximity to the thyroid, tethered down by the ligament. Bleeding can occur at this site and should be controlled by gentle pressure before identification of the nerve to avoid injury. Use of electrocautery in this region should be strictly avoided. A small portion of thyroid tissue may be embedded with the ligament, accounting for a remnant of thyroid tissue left after total thyroidectomy. Although controversy exists regarding routine use of intraoperative RLN monitoring, it may be useful if nerve identification or handling or both are anticipated to be more difficult.[178-180] Examples of such situations include large tumors or goiters, paratracheal node disease or dissection, and reoperative cases in the thyroid bed or central compartment.

All vessels are ligated and divided on the capsule to reduce the risk of parathyroid devascularization (Fig. 124-5). Ischemic parathyroids and parathyroids situated anteriorly on the thyroid gland or removed with the thyroid lobe should be examined. Biopsy specimens should be obtained and confirmed by frozen-section examination. The parathyroid glands can be minced into pieces of 1 mm^3 and reimplanted in the ipsilateral sternohyoid muscle or sternocleidomastoid muscle with a silk suture or clip to mark the reimplantation site.

When the lobe is mobilized and key structures are identified, the isthmus can be transected close to the contralateral side. The edge of the isthmus is oversewn, and a careful search is made for a pyramidal lobe that should be removed in continuity with the thyroid lobe and isthmus, when present.

For a total thyroidectomy, the same procedure is repeated on the contralateral side. The decision to proceed to excision of the opposite thyroid lobe should depend on the course of the initial thyroid lobectomy. After removal of the thyroid specimen, hemostasis is verified, and a Jackson-Pratt suction drain is placed in the thyroid lobe bed. Divided strap muscles are reapproximated with absorbable sutures and closed along the midline to prevent tracheal adhesion to the skin. The platysma is reapproximated with absorbable sutures, and the skin is closed with a running subcuticular suture.

Special Surgical Situations

Management of Regional Lymphatics

Management of the neck in patients with well-differentiated thyroid carcinomas is typically conservative. Cervical node disease is rare in follicular carcinomas, but more common in papillary carcinomas. There is currently no role for elective neck dissection in cases of follicular carcinoma. Current ATA guidelines recommend consideration of central compartment (level VI) neck dissection for patients with papillary thyroid carcinoma and suspected Hürthle cell carcinoma.[69] If disease is present by palpation or visible inspection, patients with papillary or Hürthle cell thyroid carcinoma have a concurrent central compartment lymph node dissection with total thyroidectomy or the completion thyroid lobectomy.

Because of the higher frequency of microscopic tumor spread in MTCs and their lack of radioiodine uptake, elective central compartment lymph node dissection is commonly performed. When these patients present with palpable anterior lymph node disease, bilateral central compartment dissection is performed with the total thyroidectomy, and the lateral cervical nodes are carefully inspected. Central compartment dissection should include the Delphian, paratracheal lymphatic, and lymph nodes of the upper mediastinum. The RLN, inferior thyroid artery, and parathyroid glands should be clearly identified, and the lymphatics should be removed en bloc from the level of the cricoid to the innominate artery.

When performing bilateral central compartment dissection, preservation of the parathyroid glands can be difficult. Attempts should be made in the dissection, especially contralateral to the thyroid lesion, to identify and preserve the ascending branch of the inferior thyroid artery that supplies the superior parathyroid gland. If the vascular supply to the parathyroid gland is compromised, a biopsy specimen of the gland should be obtained to confirm the presence of parathyroid tissue and placed into a pocket in the sternocleidomastoid muscle. The gland should be minced into 1-mm pieces, and the implantation site should be marked with vascular clips.

When palpable lateral cervical nodes are present, and metastatic disease is confirmed by FNAC, a selective neck dissection, including levels II through V, should be performed. The submandibular and submental nodes (level I) are rarely involved and should be dissected only when there is clinically positive disease in this region.[105,181] Cervical involvement is frequently ipsilateral to the primary thyroid lesion.[182] Extension of the collar incision superior to the mastoid tip provides adequate exposure of the lateral neck if palpable disease is present. Careful inspection and dissection should be performed along the spinal accessory nerve because this is a frequent site of metastatic thyroid disease.[10] A more extensive modified radical neck dissection may be necessary to remove gross disease. Radioiodine ablation is an important adjunctive therapy for the management of cervical disease in these patients.

In patients with MTC, lymph node metastasis can occur in 81% of cases.[183] Retrospective analysis revealed a 10-year survival rate of 67% for patients with MTC treated with neck dissection versus 43% for patients who were not treated with neck dissection.[152] Palpable cervical disease necessitates central compartment and comprehensive neck dissection. In patients with clinically negative neck disease, surgical treatment should include total thyroidectomy, central compartment dissection, and elective, ipsilateral comprehensive neck dissection. Dissection of the contralateral neck in all patients should be considered, especially when the primary thyroid lesion is 2 cm or greater in size because bilateral neck dissection may be necessary to maximize regional control.[183]

Intrathoracic Goiter

Less than 1% of patients may have a thyroid gland that is partially or completely intrathoracic.[184,185] In most of these patients, the intrathoracic goiter can be removed via a collar incision in the neck without resorting to a sternotomy. The vascular supply, typically originating in the neck, is identified, ligated, and divided. Division of the isthmus may facilitate mobilization of the substernal goiter from beneath the sternum. Large sutures can be placed deeply into the goiter to facilitate traction and blunt dissection to permit delivery of the thyroid through the neck.

Patients with substernal goiters who have had previous thyroid operations, some patients with invasive malignant tumors, and patients with no thyroid tissue in the neck may require a median sternotomy. Occasionally, the substernal goiter may simply be too large to deliver through a cervical incision. In these cases, the thyroidectomy is usually performed in collaboration with a thoracic surgeon.

Recurrent Laryngeal Nerve Invasion

Surgical situations necessitating the sacrifice of the RLN are uncommon. If preoperative vocal cord paralysis is present, and carcinoma invasion is seen intraoperatively, the nerve may be sacrificed. More commonly, the RLN should be dissected free of gross disease. Among patients with well-differentiated thyroid carcinomas, there is no survival difference between patients with RLN sacrifice and patients treated postoperatively with radioiodine for gross disease left on the nerve.[171] Because of the lack of response by MTC to postoperative radioiodine treatment, RLN sacrifice must be considered to achieve complete removal of gross disease.

Sacrifice of the RLN requires the exclusion of nerve infiltration by benign disease processes. Graves' disease, Hashimoto's thyroiditis, and Reidel's thyroiditis can involve the RLN with or without vocal cord paralysis. Benign processes can cause stretch injuries to the RLN that resolve with surgical removal of the mass. Finally, lymphomas can involve the RLN, but treatment is rarely surgical and should not involve excision of the nerve.

Extended Surgical Resection

Surgical treatment of thyroid carcinomas should remove all gross disease, especially in patients with MTC. Fixation to the thyroid cartilage or trachea may require partial-thickness to full-thickness removal of those structures (Fig. 124-6). A thyroid cartilage lamina can be removed without major morbidity if the internal thyroid perichondrium is left intact. The trachea can be partially resected and repaired to permit en bloc tumor removal. Primary anastomosis can be performed for resections involving up to four tracheal rings.[186] Additionally, tracheal shaving can be performed, leaving the internal mucosa intact. Isolated full-thickness defects can be repaired with composite mucosal-cartilage grafts from the nasal septum. In patients with more extensive skeletal involvement, a partial laryngectomy may be required and has shown improvements in survival.[187,188] Total laryngectomy should be performed in only the most extreme cases of extensive intraluminal invasion, substantial cricoid involvement, or bilateral RLN dysfunction. Typically, this procedure would be done after the failure of radioiodine treatment, EBRT, or both. Pharyngeal and esophageal local invasion typically requires resection of the immediate area and primary closure (Fig. 124-7).

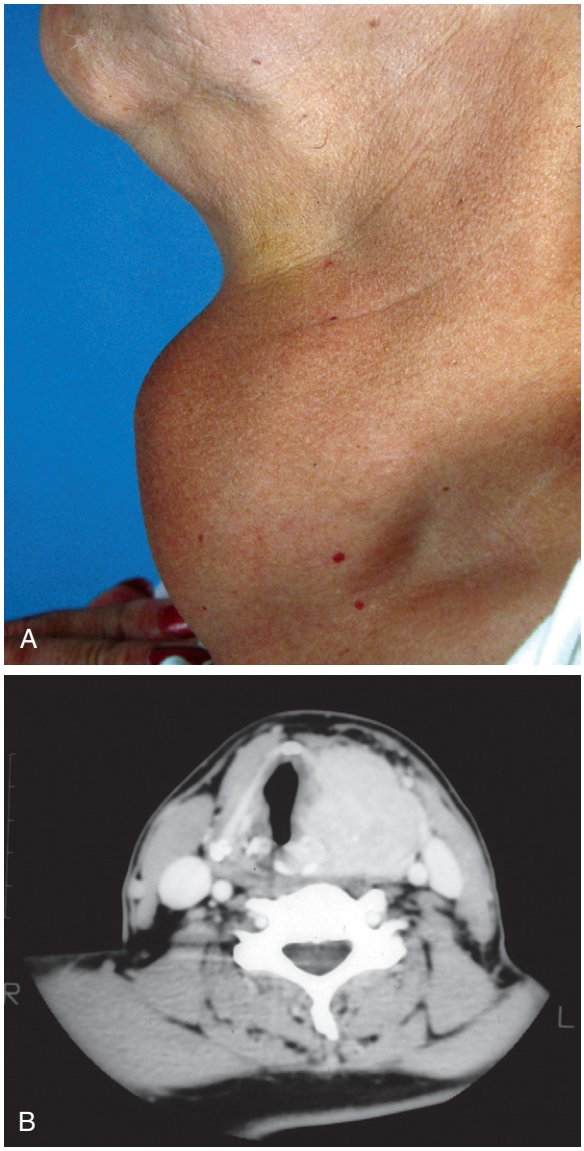

Figure 124-6. **A,** Lateral view of the neck shows a large, compressive thyroid mass. **B,** Axial CT scan reveals extensive local invasion by the thyroid lesion involving the thyroid cartilage, larynx, and esophagus.

Reoperative Thyroid Surgery

Reoperative thyroid surgery may be required in various clinical situations. A patient may have had a previous thyroid lobectomy and require a completion thyroidectomy. Recurrence of disease may require re-exploration of the thyroid bed or dissection of the cervical lymph nodes, including the central compartment (level VI). In addition, previous neck surgery, such as a parathyroidectomy, may have involved the thyroid bed.

Reoperative surgery has been associated with a higher incidence of complications than initial thyroid surgery. Scarring and fibrosis from prior surgery may cause difficulty in identifying tissue planes, resulting in an increased risk of injury to the RLN. Potential injury or devascularization of the parathyroid glands on one side of the neck creates increased concern for preservation of the glands on the contralateral side. Older series reported a high incidence of complications in reoperative surgery.[106,189] More recent reports indicate, however, that the risk of permanent hypoparathyroidism or RLN injury is less than 2%.[190-193]

Although reoperative thyroid surgery cannot be completely avoided, steps may be taken to minimize the need for reoperation. Before the initial surgery, preoperative preparation should include a thorough evaluation for thyroid mass fixation or RLN palsy or paralysis. In these patients, preoperative imaging and potential coordination with other surgeons help to prevent unexpected intraoperative findings.

The minimum adequate surgical treatment for a thyroid nodule is a thyroid lobectomy and isthmectomy. A unilateral subtotal thyroidectomy may encompass a suspected thyroid nodule, but leave residual disease behind. En bloc resection of the thyroid lobe can be performed safely, and often eliminates the need to return to the original surgical bed for re-exploration.

The effectiveness of FNAC has also directed surgeons to perform the appropriate surgery for a particular disease. The presence of a follicular or Hürthle cell adenoma should direct a surgeon to perform a unilateral thyroid lobectomy, avoiding exploration of the contralateral lobe. In cases of carcinoma, reoperation is safer because the contralateral lobe has been left undisturbed. When a patient has significant comorbidities that may preclude reoperation, the contralateral side can be addressed at the initial surgery by performing a total or near-total thyroidectomy. FNAC that shows papillary carcinoma prepares a surgeon for total thyroidectomy or more comprehensive surgery for MTC. Although intraoperative frozen-section analysis is controversial, frozen-section analysis in conjunction with cytologic examination can be valuable for cases diagnosed on preoperative FNAC as suspicious for papillary thyroid carcinoma.[194,195] Finally, ultrasound evaluation of the thyroid bed and lateral neck provides improved preoperative assessment of the extent of disease and facilitates surgical planning. Even in patients with palpable lymph node recurrences, ultrasound evaluation of the lateral and central compartments may change the extent of the surgical procedure in 40% of patients undergoing reoperative surgery.[87]

Typically, reoperation should be performed within 3 to 4 days of the initial operation, if definitive pathology is available, or after 3 months. Healing and inflammation during the early and late time points are typically manageable for reoperation. No control studies to date have addressed the issue of the degree of inflammation in the neck encountered during repeat surgery.

Before reoperation, the vocal cords should be visualized to identify any potential RLN injury. Imaging studies can be useful in cases of disease recurrence to identify local invasion or cervical disease and potential involvement of the RLN or parathyroid glands. During surgery, the RLN should be followed from a previously undissected area into the surgical bed. The surgeon should be familiar with numerous techniques to identify the RLN. A lateral approach from the medial border of the sternocleidomastoid, a low anterior neck approach, and a medial approach to the superior pole of the thyroid have been described.[192] Intraoperative monitoring of the RLN can be helpful, and an electrophysiologic nerve stimulator can facilitate and confirm nerve identification. Visualization of the RLN is crucial, and the use of loop magnification may be helpful to identify the RLN and parathyroid glands.

Because of the difficulties associated with permanent hypoparathyroidism, preservation of the parathyroid glands is crucial in reoperative surgery. As described for initial thyroid surgery, extracapsular thyroid dissection and close vessel ligation aid in preserving parathyroid gland vascular supply. Prior surgery may have disrupted the normal anatomic locations of the gland or created scarring that makes gland localization difficult. In these cases, all perithyroidal fat should be carefully mobilized and preserved. When reoperation includes central compartment dissection, the parathyroid glands may be removed en bloc with the disease.

The surgical specimen needs to be inspected carefully, and biopsy specimens of potential parathyroid tissue should be obtained. Identified parathyroid tissue should be reimplanted into the sternocleidomastoid muscle. All parathyroid tissue should be preserved when possible. The combination of parathyroid preservation in situ and autotransplantation of devascularized parathyroid tissue significantly reduces the risk of permanent hypoparathyroidism.[196] Parathyroid tissue that has been reimplanted functions even when other parathyroid glands have been left intact and in the absence of hypocalcemia.[197]

Intraoperative ultrasound may be useful for the resection of radiographically identified, nonpalpable lesions within the thyroid bed or nodal basins. The technique may be particularly helpful in patients who

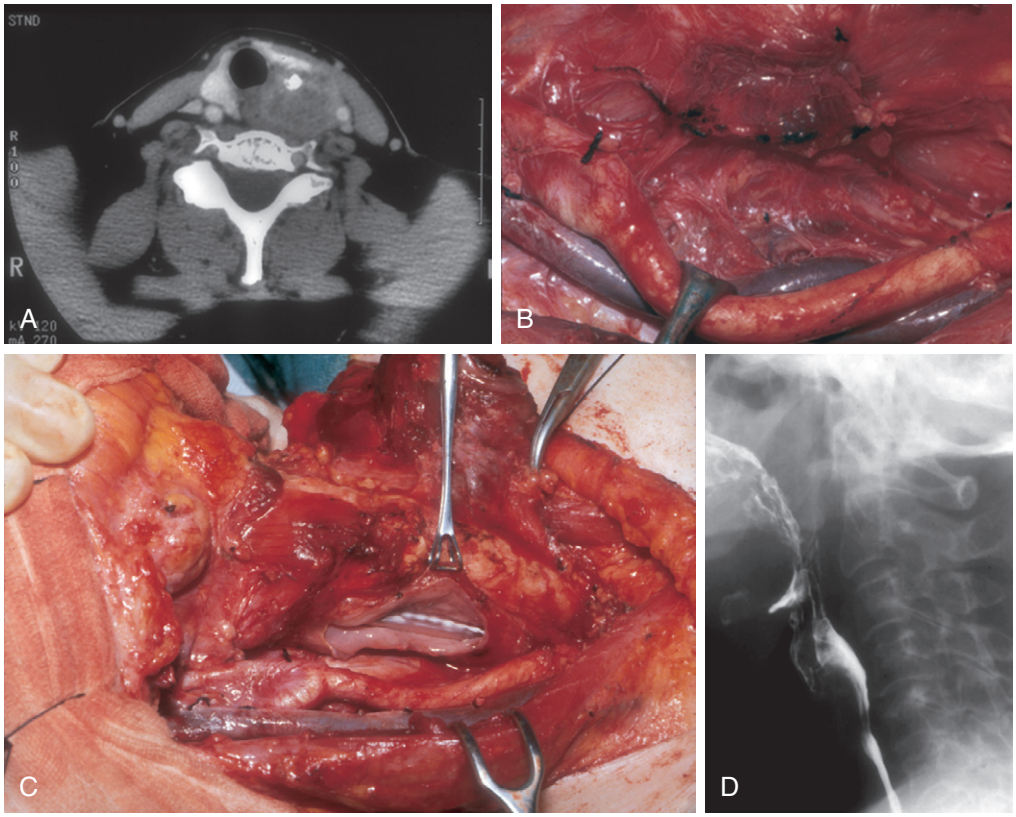

Figure 124-7. **A,** Axial CT scan shows a large, locally invasive thyroid mass. **B,** The large thyroid mass has been dissected free from adjacent structures, but involves the esophagus. **C,** Resection of the thyroid mass required excision of a portion of the esophagus. The esophagus was closed primarily. **D,** Postoperative barium swallow study showed that the esophagus was intact, and the patient was able to tolerate a regular diet. *(From Lai SY, Weber RS. Thyroid cancer. In Ensley JF, Gutkind JS, Jacobs JR, et al, eds.* Head and Neck Cancer: Emerging Perspectives. *San Diego: Academic Press; 2002:424.)*

have had EBRT or for lesions that are smaller than 2 cm, locally invasive, or adherent to the airway. Ultrasound can be performed through the strap muscles in an open wound, and a needle can be placed in the target lesion as a guide.

Extent of Surgery

Surgery is the primary modality for treatment of thyroid carcinomas. Although well-differentiated thyroid cancers can be extremely aggressive and lethal, most patients have prolonged survival even with residual or recurrent disease. Controversy exists regarding the extent of surgery to be performed in patients with well-differentiated carcinomas. The primary goals of surgical treatment should be to eradicate primary disease, to reduce the incidence of local or distant recurrence, and to facilitate the treatment of metastases. These oncologic goals should be achieved with minimal morbidity.

The large body of literature regarding thyroid carcinoma and its treatment has created a wide variety of terms for describing the extent of thyroid tissue removal. Most surgeons agree that a subtotal excision of a thyroid nodule is unacceptable, and that the minimum amount of thyroid removed should be a lobectomy and isthmectomy. Some surgeons have advocated in the past a near-total thyroidectomy that preserves the posterior portion of the gland on one side to avoid injury to the RLN and at least one parathyroid gland. A total thyroidectomy involves the complete removal of both thyroid lobes, although ^{123}I scans may reveal 2% to 5% residual tissue.[198]

Proponents of a more conservative surgical approach suggest that thyroid lobectomy and isthmectomy is sufficient treatment for most patients (>80%). These patients would be categorized as low-risk in the different classification schemes (see section on tumor staging and classification). Thyroid lobectomy and isthmectomy are simpler to perform and less time-consuming than a total thyroidectomy. The overall risk of morbidity from RLN, SLN, and parathyroid gland injury is less. Finally, compared with total thyroidectomy, this conservative approach does not adversely affect prognosis and survival.

Numerous studies support the conservative approach. In the AGES classification, low-risk patients with papillary carcinoma had the same 2% 25-year mortality rate regardless of whether they were treated with thyroid lobectomy or total thyroidectomy.[55] A study by Shah and associates[58] based risk classifications on the AJCC staging system. There was no difference in 20-year survival based on surgical treatment for patients with intrathyroidal tumors of less than 4 cm. Patients treated with total thyroidectomy had an increased risk of complications, however.

Although survival differences are not found, several studies report an increased incidence of local recurrence in patients treated with only a thyroid lobectomy.[199,200] Some controversy exists regarding the relationship of local recurrence to disease survival, especially with papillary carcinomas.[121,193] Finally, patients categorized as high-risk in these classification systems are treated with near-total or total thyroidectomy and radioiodine ablation therapy.

A more aggressive surgical approach favors total thyroidectomy in most cases and lobectomy for small, single lesions. Proponents of this approach favor total thyroidectomy as a better oncologic operation. Removal of the entire thyroid gland encompasses potential extracapsular extension and multicentric lesions. Morbidity of this procedure is low with good technique and an experienced surgeon.[191] Several studies showed improved survival and decreased local or distant recurrence.[101,114,201] Cautionary studies also show the risk of aggressive disease even in patients determined to be low-risk in the various classification schemes.[202,203]

Postoperative thyroglobulin levels are more valid with removal of all normal thyroid tissue. Total thyroidectomy also facilitates the use of postoperative diagnostic scans to evaluate for metastases and recurrence. Diagnostic radioiodine uptake should ideally be 3% or less after

total thyroidectomy. Subsequent radioiodine treatment does not need to be used to ablate excess normal tissue and can be concentrated on the removal of residual carcinoma and distant metastases. Finally, although rare, removal of the entire thyroid reduces the risk of transformation from a well-differentiated thyroid carcinoma to an anaplastic carcinoma.

Controversy surrounding the extent of surgery will continue to persist because no uniform set of characteristics can be used to classify the aggressiveness of well-differentiated thyroid carcinomas. Results of treatment will also continue to differ among institutions and surgeons. Nevertheless, initial surgery should address gross disease in the thyroid and neck nodes. The extent of the surgery should be guided by the patient's risk factors, operative findings, and intraoperative progress. Ultimately, the primary goal of thyroid surgery should remain the effective eradication of thyroid cancer with minimal morbidity.

Minimally Invasive Thyroidectomy

Over the past decade, surgical approaches have been developed to permit thyroid surgery through smaller incisions.[204,205] Some of these approaches advance to the thyroid bed from remote incisions in the axilla or chest.[206,207] In addition to improved cosmesis and decreased postoperative discomfort, these approaches have afforded surgeons superior visualization of critical structures such as the SLN through the use of endoscopic instruments (Fig. 124-8). In the transcervical approach, a surgical drain is often not required, and many patients are discharged after adequate same-day postoperative observation and instruction.[208] Implementation of these approaches has been careful with an emphasis on providing equal or improved operative outcomes relative to traditional open approaches.[209,210]

Special Treatment Situations

Children

In children, nodular thyroid disease is uncommon, with an incidence of 0.2% to 1.8%.[211] Most neck masses occurring in children are due to congenital or inflammatory causes. Malignant neck masses may be due to lymphoproliferative disorders, sarcomas, or thyroid carcinomas. Less than 6% of pediatric neck tumors are thyroid malignancies.[212] Approximately 10% of all thyroid carcinomas occur in patients younger than 21 years.[213]

Most children with thyroid neoplasms present with an asymptomatic mass within either the thyroid or the lateral neck. The lesions are often asymptomatic and frequently noted by a parent or pediatrician during a routine physical examination. A complete history should include special attention to family history and radiation exposure. The physical examination should carefully evaluate potential fixation of the thyroid gland to surrounding neck structures. Vocal cord mobility should be documented by indirect fiberoptic nasolaryngoscopy. The central compartment and lateral necks also should be carefully palpated. Lymph node metastases are present in more than 50% of children with differentiated thyroid cancer.[214] Local extension was reported in 18%. In addition, 15% of patients have distant metastasis, frequently identified with postoperative radioiodine.[215,216] A chest radiograph may be normal or may show a fine interstitial reticular pattern, potentially mistaken for miliary tuberculosis. Children with extensive pulmonary involvement may present with dyspnea on exertion.

The diagnostic workup in children should include FNAC and ultrasonography. An uncooperative child may require sedation and ultrasound guidance for FNAC. Because an advanced stage of disease is common in children at initial presentation, ultrasonography provides valuable information regarding the size and consistency of the thyroid mass. Ultrasound examination also can identify potential regional involvement of the paratracheal or cervical lymphatics.

Although the most common cause of a solitary thyroid nodule in children is a follicular adenoma (68.9%), malignancies are found in 16% to 25% of the nodules.[217,218] The most common malignant histologic type is papillary carcinoma, present in more than 80% of these cases. In contrast to thyroid carcinoma in adults, papillary carcinomas are usually follicular in pattern, and tall-cell and columnar-cell variants do not occur in children.[219,220] Hürthle cell carcinomas may manifest with multiple lesions and a papillary architecture as a familial syndrome.[221] MTCs constitute about 10% of pediatric thyroid carcinomas, and all family members need to be carefully evaluated for possible familial MTC or MEN syndromes.

Management of a child with thyroid carcinoma must balance the potential morbidity associated with treatment against the low probabil-

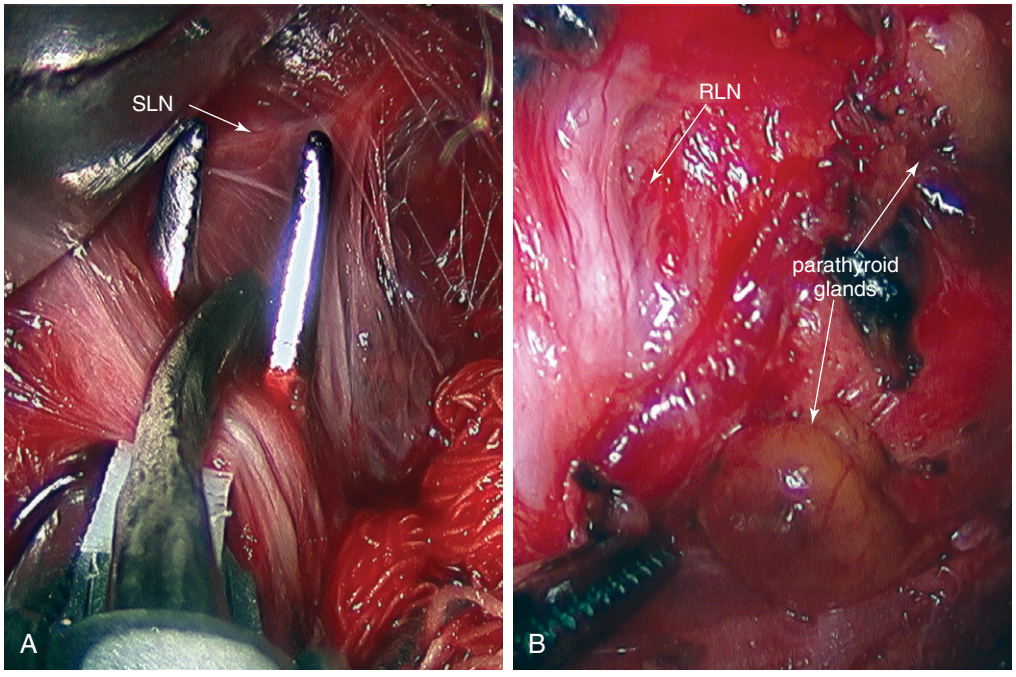

Figure 124-8. A and **B,** The magnification provided through a 5-mm 30-degree endoscope provides excellent intraoperative visualization of the superior laryngeal nerve (SLN) **(A)** and the recurrent laryngeal nerve and parathyroid glands (RLN) **(B)**. *(From Lai SY, Walvekar RR, Ferris RL. Minimally invasive video-assisted thyroidectomy: expanded indications and oncologic completeness.* Head Neck. *2008;30:1403-1407; used with permission from Wiley Periodicals, Inc.)*

ity that the patient will die of this disease. The primary goal of surgery is to remove gross disease completely at the primary and regional metastatic sites. A total or near-total thyroidectomy is recommended.[213,214,222,223] Multifocal disease is present in 10% to 30% of patients. In addition, a total or near-total thyroidectomy allows the use of serum thyroglobulin to monitor disease recurrence, and facilitates the use of radioiodine to identify and treat distant metastases. More recent studies have shown a low incidence of permanent hypoparathyroidism and RLN injury after total thyroidectomy. The recurrence rate is lower for patients undergoing total thyroidectomy than for patients undergoing lesser procedures.[224]

Children often present with cervical nodal metastases requiring therapeutic lymphadenectomy. In patients with nodal disease, the paratracheal and pretracheal lymph nodes are involved in 90% of cases.[32] The metastatic deposits are frequently compressive rather than infiltrative with respect to adjacent neck structures. Radical neck dissection is rarely necessary. Patients should have central compartment dissections when cervical disease is present, rather than simple node plucking. Care should be taken to identify and preserve the blood supply to the parathyroid glands. Also, lateral neck disease requires a comprehensive lateral neck dissection (levels II-V).

Although children and adolescents commonly present with more advanced disease than adults, their prognosis remains excellent. In several series, young patients have a 10-year survival near 100% and a 2- to 5-year survival rate near 90%.[225] Relapse is most common in the cervical lymphatics, and is more common in children than in adults. Recurrence seems to be more common in younger patients and patients with papillary histology.[226] Cervical disease can be surgically excised, and pulmonary recurrence is responsive to radioiodine therapy.[227]

Pregnancy

Because thyroid neoplasms occur more commonly in women and often during their childbearing years, physicians occasionally need to manage this disease in pregnant women. The incidence of thyroid nodules during pregnancy has been reported as 2% to 10%.[228,229] Management of these patients must protect the well-being of the mother and fetus, and minimize the risks of preterm labor or abortion. A crucial difference in thyroid nodule management during pregnancy and breastfeeding is the absolute contraindication for the use of radioactive iodine.[230]

During pregnancy, the thyroid gland physiology is markedly altered. The gland can increase significantly in size because of a relative iodine insufficiency and hormonal changes.[231,232] These physiologic and hormonal changes may increase the incidence of thyroid nodules or cause the enlargement of existing thyroid nodules.

The presence of any discrete thyroid nodule should be evaluated by FNAC.[233] Some authors argue that a pregnant patient beyond 20 weeks of gestation should have FNAC deferred until after the pregnancy to reduce patient anxiety.[229,234] These authors argue that treatment would likely occur after surgery, and they advocate FNAC only when the nodule shows continued growth or other suspicious features. Other authors advocate immediate FNAC at any stage of pregnancy.[230]

Ultrasonography may be used for initial assessment and continued monitoring. Ultrasound evaluation is effective for the evaluation of thyroid and cervical involvement. CT scans during pregnancy are not recommended, although MRI, if necessary, may be performed safely.

When FNAC is benign, the patient should be reassured, and ultrasonography can monitor the nodule for possible growth during pregnancy. A follicular neoplasm may be monitored closely or surgically explored. If FNAC is suspicious or shows thyroid carcinoma, surgery is recommended at the safest time possible.[228] Thyroid carcinomas identified late in pregnancy should be treated in the immediate postpartum period. Carcinomas diagnosed during the first and early second trimesters may be surgically treated during the 22nd through 26th gestational weeks, when the risk to fetal development and for preterm labor is lowest. The patient can be reassured that thyroidectomy and even cervical lymphadenectomy at midtrimester do not carry significant risks for the fetus. Maternal complications are similar to nonpregnant patients. A more recent study suggests, however, no difference in the natural history and prognosis of pregnant patients with a thyroid carcinoma diagnosed early in gestation who defer surgery until after labor.[235] Most patients would likely experience too much stress and anxiety to have an untreated cancer present throughout gestation.

Aggressive thyroid carcinomas that grow rapidly or invade adjacent cervical structures may demand immediate surgical attention. Additionally, a diagnosis of medullary or undifferentiated carcinoma in pregnant patients requires prompt treatment. These tumors are rare and often affect older women. Before starting treatment in these cases, the pregnancy should be terminated.

Complications

Among head and neck surgical procedures, thyroid surgery is very safe. Mortality rates are extremely low, and morbidity is relatively low. Generally, serious complications occur in less than 2% of all thyroid cases.[10] Complications can typically be divided into nonmetabolic and metabolic complications. Of particular concern are injuries to the RLN and the parathyroid glands.

Perioperative complications are unusual in thyroid surgery. Postoperative infections are very unusual because of the abundant blood supply in the thyroid bed. The prevention of scar widening or hypertrophy depends on proper placement of the incision. The incision can often be hidden within existing skin creases. The incision should not be placed too low in the neck to avoid the increased skin tension over the sternal notch. Pneumothorax is very rare and often associated with extended procedures that involve subclavicular dissection. Chylous fistulas may occur more often on the left side, but are usually self-limiting when wound drainage is adequate.

Bleeding Complications

Hemorrhage is uncommon when surgery is performed with meticulous hemostasis. Bleeding may occur, however, because of an undetected coagulopathy or a technical mishap. Significant hemorrhage in the immediate postoperative period can lead to life-threatening airway compression. A rapidly expanding hematoma requires immediate opening of the surgical incision and evacuation of blood. Airway control can be established, and the patient can be returned to the operating room for complete exploration to identify bleeding sites. A wound seroma may occur, especially after the removal of a large goiter. If a fluid collection is present, simple needle aspiration should manage the problem and prevent the risk of infection.

Superior Laryngeal Nerve Injury

Injury to the external branch of the SLN is believed to be rare, but the exact frequency is unknown. Often disturbance of SLN function is temporary and unrecognized by the patient and the surgeon.[236] Injury to the SLN alters function of the cricothyroid muscle. Patients may have difficulty shouting, and singers find difficulty with pitch variation, especially in the higher frequencies. The external branch of the SLN is not often visualized and lies near the superior pole vessels. Adequate exposure of the superior thyroid pole and close ligation of the individual vessels on the thyroid capsule may prevent SLN injury. Voice therapy may help patients to compensate in cases of SLN injury.

Recurrent Laryngeal Nerve Injury

Injury to the RLN has a much greater impact and is more noticeable than SLN injury. The incidence of permanent RLN paralysis is approximately 1% to 1.5% for total thyroidectomy and less for near-total procedures.[101,237,238] Temporary dysfunction because of nerve traction occurs in 2.5% to 5% of patients.[176] Incidence increases with second and third procedures. RLN injury is also more common in thyroidectomy with neck dissection, although this may reflect more advanced disease states.[239] Disease-specific risk factors for permanent nerve damage include recurrent thyroid carcinoma, substernal goiter, and various thyroiditis conditions. Vocal cord function should be evaluated and documented by indirect laryngoscopy, especially in patients who have had previous surgery.

Unilateral RLN injury leads to a vocal cord in the paramedian position, and the voice may be breathy and lack volume. Concurrent injury of the SLN results in a more laterally positioned vocal cord and worsens voice quality and glottic competence.[240] Occasionally, patients may have difficulty with aspiration and pneumonia.[239]

Bilateral RLN injury may manifest very dramatically. Immediate postoperative stridor and dyspnea may require immediate reintubation and a possible tracheostomy. Occasionally, bilateral RLN injury may not be immediately noticeable, and patients may adapt to the reduced airway. Over time, the vocal cords move to the midline compromising the airway.

Identification and careful dissection along the course of the RLN decreases the incidence of permanent injury. The surgeon should also be aware of the possibility of a nonrecurrent nerve, most commonly on the right side. If the nerve is transected during surgery, microsurgical repair of the nerve is recommended. Although the repair is unlikely to restore normal function, reanastomosis of the RLN may decrease the extent of vocal cord atrophy.[241] Some surgeons advocate anastomosis of the ansa hypoglossal nerve to the distal end of the severed RLN to prevent laryngeal synkinesis and possible vocal cord hyperadduction.[242,243]

Comprehensive management of vocal cord injury is beyond the scope of this chapter. In most cases, RLN injury is detected postoperatively. Management is supportive, although some surgeons favor reexploration when vocal cord paralysis is noted in the immediate postoperative period. Return of normal vocal cord function occurs 6 to 12 months after temporary RLN injury occurs. Speech therapy can be valuable. Serial examinations should document a potential return of function or compensation by the contralateral vocal cord. In patients with continued vocal incompetence or aspiration, treatment directed toward vocal cord medialization may consist of vocal cord injection, thyroplasty, or arytenoid medialization. In cases of bilateral RLN injury, management is directed at improving the airway, while not completely sacrificing airway quality, and may involve arytenoidectomy or transverse cordotomy.

Hypocalcemia

Transient symptomatic hypocalcemia after total thyroidectomy occurs in approximately 7% to 25% of cases, but permanent hypocalcemia is less common (0.4% to 13.8%).[244,245] The risk of hypoparathyroidism is related to the size and degree of invasion of the tumor, pathology, and extent of procedure and surgeon experience.[55,246] Changes in serum calcium levels are often transient and may not always be related to parathyroid gland trauma or vascular compromise.

Parathyroid autotransplantation may be considered when the risk of postoperative hypocalcemia is increased.[247,248] These situations may include thyroid carcinoma requiring total thyroidectomy with central neck dissection, en bloc resections that require removal of the parathyroid glands, and reoperation after previous thyroid or parathyroid surgery. Autotransplantation is commonly performed in the sternocleidomastoid muscle, although various locations, including the brachioradialis muscle of the nondominant forearm, have been used.[249]

Transient hypocalcemia is often related to variations in serum protein binding caused by perioperative alterations in acid-base status, hemodilution, and albumin concentration. These changes do not produce hypocalcemic symptoms. Sudden changes in levels of ionized serum calcium can result in perioral and distal extremity paresthesias, however. As calcium levels continue to decline, patients may experience tetany, bronchospasm, mental status changes, seizures, laryngospasm, and cardiac arrhythmias. Chvostek's sign and Trousseau's sign may develop with increased neuromuscular irritability as serum calcium levels decrease to less than 8 mg/dL.

Typically, serum calcium levels are measured in the immediate postoperative period and the next morning for patients with a total or completion thyroidectomy. Patients should have a stable or increasing serum calcium level. Patients undergoing a thyroid lobectomy do not usually require serum calcium monitoring. Findings that should be worrisome for hypoparathyroidism include hypocalcemia, hyperphosphatemia, and metabolic alkalosis. PTH levels may also be measured to predict potential hypocalcemia.[250]

Treatment for hypocalcemia is typically initiated if the patient is symptomatic or serum calcium levels decrease to less than 7 mg/dL. In these patients, cardiac monitoring is warranted. Patients should receive 10 mL of 10% calcium gluconate and 5% dextrose in water intravenously, titrated to symptom resolution and subsequent serum calcium level tests. Oral calcium supplementation should begin with 2 to 3 g of calcium carbonate per day. Calcitriol (1,25-dihydroxycholecalciferol) also should be initiated. Adjustments in supplemental calcium and vitamin D should be done in consultation with an endocrinologist.

Postoperative Management and Special Considerations

Thyroid Hormone Replacement

After total or completion thyroidectomy, exogenous supplementation of thyroid hormone is necessary to prevent symptomatic hypothyroidism.[6,77] To counteract potential trophic effects of TSH that could facilitate recurrence or progression of well-differentiated thyroid carcinomas, long-term supplementation with levothyroxine is monitored to suppress TSH to below-normal levels (<0.1 mU/L in high-risk patients and 0.1 to 0.5 mU/L in low-risk patients).[67] Patients receiving suppressive therapy have a lower recurrence rate and improved survival.[251,252]

In the immediate postoperative period, patients are frequently given liothyronine sodium (Cytomel). Liothyronine sodium has a shorter half-life than levothyroxine, decreasing the waiting period before radioiodine body scanning and possibly enabling ablative therapy to be performed.

Radioactive Iodine Treatment

Radiolabeled iodine has been used for more than 40 years to ablate normal thyroid tissue and to treat residual tumor and metastases.[253] The ^{131}I isotope emits β particles that penetrate and destroy tissue within a 2-mm zone. Patients classified as high risk with papillary thyroid carcinoma and most patients with follicular carcinoma are considered for treatment.[127] When administered as part of the initial therapy, postoperative ^{131}I treatment contributes to decreased recurrence and disease-specific mortality.[254-256] Despite poor radioiodine uptake in Hürthle cell and medullary carcinomas, these patients are often treated to provide any possible benefit.

Elevated TSH levels are necessary to enhance uptake of iodine by thyroid cancer cells. A TSH greater than 30 mU/L is associated with increased radioiodine uptake in tumors.[257] Patients are taken off thyroid hormone suppression therapy for 2 to 4 weeks before scanning and placed on a low-iodine diet.[69] Additionally, the administration of exogenous recombinant human TSH has proved safe and effective for stimulating radioiodine uptake and for detecting serum thyroglobulin in patients undergoing evaluation for thyroid cancer persistence and recurrence.[258,259]

Whole-body diagnotic scans stage the patient and determine the need and potential benefit of radioiodine therapy. The phenomenon termed *stunning* may occur, however, when scanning doses of ^{131}I induce follicular cell damage. Poor uptake by thyroid remnant and metastases of subsequent therapeutic ^{131}I doses reduces the potential benefits of this therapy.[260] Pretreatment scans are now performed with small doses of ^{131}I (2 to 3 mCi) or ^{123}I. The physical properties of ^{123}I permit better image quality and decrease possible stunning of functioning thyroid cells by the β particle emission of ^{131}I[261]; this permits the maximal benefit of ^{131}I in ablation after the diagnostic procedure.[262]

After the diagnostic scan, therapeutic ablative doses of ^{131}I can be given. Typically, 100 mCi of ^{131}I is given for uncomplicated cases with only thyroid bed uptake. Although a lower dose of 30 mCi has commonly been used, studies have shown this is not as effective. Current guidelines recommend employing the minimum activity necessary to achieve successful thyroid remnant ablation, particularly for low-risk patients.[69] Patients with uptake in cervical nodes, distant metastases, or more aggressive tumor histology (e.g., tall-cell, insular, columnar-cell carcinoma) receive 100 to 200 mCi.[263,264] Doses greater than 200 mCi have not been shown to be more effective in most cases.

No clear evidence exists regarding the superiority of ^{131}I delivery by empiric fixed amounts, quantitative tumor dosimetry, or blood/body dosimetry.[265] In addition, there are not enough outcome data currently to recommend recombinant human TSH–mediated ^{131}I therapy for patients with metastatic disease. Such use of recombinant

human TSH may be indicated, however, in patients with underlying comorbidities who would be at risk because of iatrogenic hypothyroidism. Post-treatment scans are typically performed approximately 1 week after radioactive iodine therapy to visualize potential metastases.

Diverse alternatives and protocols exist regarding the use of radioiodine therapy. Surgeons who favor total thyroidectomy for most thyroid carcinomas argue that removal of normal tissue enhances radioiodine ablation therapy. Proponents of more conservative treatment suggest that radioiodine therapy can be used to remove even a remaining thyroid lobe before whole-body scanning for residual tumor or metastases. The 2006 ATA guidelines recommend against the use of radioactive iodine ablation instead of completion thyroidectomy.[69] Continued work in this area is aimed at improving patient outcomes and decreasing disease recurrence.

External-Beam Radiotherapy and Chemotherapy

Because of the effectiveness of surgery and radioiodine treatment for most thyroid carcinomas, experience with EBRT and chemotherapy is more limited. EBRT seems to improve local control of well-differentiated carcinomas, especially when used in combination with doxorubicin.[182,216,266] The effect of EBRT on survival is uncertain, however.[266,267] Palliation of patients with distant metastasis of well-differentiated carcinomas, especially to the bone, seems to be improved with EBRT.[182] Current recommendations support consideration of EBRT for patients older than 45 years with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease.[69] EBRT also may be employed for patients with gross residual tumor unlikely to respond to further surgery or radioactive iodine.

Limited success with EBRT in combination with doxorubicin/cisplatin has been noted with anaplastic carcinoma.[86,268] This disease remains uniformly fatal, however, and palliation through local control and airway protection are the only realistic goals. Patients with metastatic medullary carcinoma may benefit from EBRT and chemotherapy to decrease local recurrence.[269,270] Typically, patients with regional nodal metastases recognized during surgery receive postoperative EBRT. Generally, the poorer outcomes for patients with medullary and anaplastic carcinomas have not been significantly altered by EBRT and chemotherapy. Overall, there is no role for the routine adjunctive use of chemotherapy with differentiated thyroid cancer.[69] Based on improved understanding of the biologic basis for thyroid cancer development and progression, numerous novel targeted-therapy agents, including kinase and angiogenesis inhibitors, are currently in clinical trials.[271] A more recent phase II clinical trial showed some promising results with the BRAF inhibitor sorafenib in patients with iodine-refractory metastatic disease.[272]

Follow-up Management

Patients treated for thyroid carcinomas require long-term follow-up and monitoring. Approximately 30% of patients with differentiated thyroid carcinomas have tumor recurrences within several decades, and 66% of these recurrences occur within the first decade after initial treatment.[6] Various staging systems for thyroid cancer, including the AJCC/IUCC system, were developed to predict risk for death, not recurrence.[69,273,274] After initial surgery and remnant ablation, low-risk patients have no local or distant metastases, complete resection of all macroscopic tumor, no locoregional tumor invasion, no aggressive histology, no vascular invasion, and no ^{131}I uptake outside the thyroid bed in the first post-treatment whole-body radioiodine scan. Intermediate-risk patients have microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery, aggressive histology, or vascular invasion. High-risk patients have macroscopic tumor invasion, incomplete tumor resection, distant metastases, or radioiodine uptake beyond the thyroid bed on the post-treatment scan done after thyroid remnant ablation.

In addition to regular physical examination, thyroid hormone and TSH levels are monitored to ensure adequate suppression. Thyroglobulin levels should be closely monitored, and diagnostic radioiodine scanning should be performed. These tests should be performed annually for the first 2 years and then every 5 years for 20 years.[275] Typically, thyroglobulin levels should be less than 2 ng/mL after total thyroidectomy and radioiodine ablation therapy (<3 ng/mL if the patient is off thyroid replacement therapy). Increasing serum thyroglobulin levels are highly sensitive (97%) and specific (100%) for thyroid cancer recurrence.[276] Elevation of thyroglobulin levels warrants repeat radioiodine scanning and therapy. More recent studies have shown the sensitivity of serum thyroglobulin measurements for predicting thyroid cancer recurrence after a patient has received two injections of recombinant human TSH.[277] Depending on risk classification, additional follow-up procedures vary. The 2006 ATA guidelines recommend measurement of serum thyroglobulin and a cervical ultrasound examination in low-risk patients approximately 12 months after initial treatment with surgery and radioiodine ablation, but not additional whole-body radioiodine scans.[69] In intermediate-risk and high-risk patients, cervical ultrasound examination and diagnostic whole-body radioiodine scans are recommended every 6 to 12 months.

Patients with MTCs require serial measurements of calcitonin and CEA. Suspected recurrences may also be detected with pentagastrin-stimulation test. See the section on medullary thyroid carcinoma for further details.

Summary

A great deal of literature addresses the treatment of thyroid carcinomas. Questions remain unresolved regarding the extent of thyroidectomy to perform in patients with well-differentiated carcinomas and the effect on patient survival. Because most patients with well-differentiated thyroid carcinomas do well, failures to resolve issues such as this are tolerated. Also, studies to address these issues require very large cohorts with long-term follow-up of 20 to 30 years.

Nevertheless, surgeons need to remain wary of the devastating progression of disease in MTCs and anaplastic thyroid carcinomas. Despite clinical classification schemes, even well-differentiated carcinomas can have unpredictably aggressive clinical manifestations. As understanding of the molecular and genetic mechanisms of thyroid carcinomas improves, better diagnostic tests should improve our ability to treat these cancers. Targeted therapies based on understanding of the biologic basis of thyroid cancer development and progression are currently in clinical trials, and may provide patients with additional treatment options.

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CHAPTER ONE HUNDRED AND TWENTY-FIVE

Management of Parathyroid Disorders

Phillip K. Pellitteri

Robert A. Sofferman

Gregory W. Randolph

Key Points

- Early reports of hyperparathyroidism involved symptomatic disease, including disorders of bone and kidney. In contrast, most current patients with hyperparathyroidism are minimally symptomatic at presentation.
- Genetic mutational events seem to trigger mechanisms of propagation, resulting in clonal expansion of cells as an etiology for parathyroid adenoma. These mutational events have been characterized as altering the *PRAD1* proto-oncogene together with loss of tumor suppressor gene function.
- Calcium homeostasis is modulated by the complex interrelationship of parathyroid hormone (PTH), vitamin D, and calcitonin.
- The intact (1-84) PTH molecule is the major circulating form of biologically active PTH, and possesses a very short half-life (approximately 3 to 5 minutes).
- PTH release is regulated predominantly by serum ionized calcium levels, the physiologically active component of total serum calcium.
- The major target end organs for PTH are the kidneys, skeletal system, and intestine.
- The parathyroid glands are derived from pharyngeal endodermal pouches—superior glands from the fourth pouch and inferior glands from the third pouch.
- The embryonic descent of the parathyroid glands into the neck account for their normal and potential ectopic locations.
- Superior glands are generally located within 1 to 2 cm of the cricothyroid muscle–recurrent laryngeal nerve junction.
- Inferior glands may be more difficult to locate because of the longer migratory descent during development.
- A cervical approach may be used to remove 95% of parathyroid adenomas.
- The major functional parenchymal cells of the parathyroid glands are chief cells.
- Oxyphil cells, the second most common parenchymal cell, concentrate sestamibi because of the high concentration of mitochondria.
- Solitary glandular enlargement (adenoma) accounts for 80% to 85% of primary hyperparathyroidism.
- Diffuse glandular enlargement (hyperplasia) is the etiology for most of the remaining patients with primary hyperparathyroidism and patients with renal failure–induced disease.
- The hallmark of parathyroid carcinoma is invasion of the soft tissue components of the central neck.
- The diagnosis of primary hyperparathyroidism is confirmed by the biochemical findings of hypercalcemia, elevated serum PTH, and elevated or normal levels of calcium in the urine.
- Hypocalciuria associated with hypercalcemia and elevated levels of PTH may indicate a nonsurgical genetic disorder known as familial hypocalciuric hypercalcemia.
- Vitamin D deficiency may cause falsely elevated levels of PTH, mimicking hyperparathyroidism, in a setting of high normal serum calcium levels.
- Localization of abnormal hyperfunctional parathyroid glands may be accomplished using nuclear uptake studies or anatomic imaging with ultrasound or computed tomography.
- Directed exploration for hyperparathyroidism exploits the ability to localize preoperatively abnormal parathyroid tissue together with the capability to confirm biochemically removal of all hyperfunctional parathyroid tissue using rapid measurement of PTH intraoperatively.
- Conventional bilateral neck exploration represents the gold standard by which all other, less extensive exploration procedures are measured.
- The ability to perform less extensive operations for hyperparathyroidism is not a substitute for a thorough knowledge of the embryoanatomic detail of the central neck, and the ability to conduct a comprehensive and meticulous four-gland exploration.

The recorded history of hyperparathyroidism in modern medicine is relatively recent. Owen, a renowned British anatomist and curator, is generally acknowledged as being the first to describe the existence of the parathyroid glands in 1852.[1] The discovery occurred subsequent to the death of the Zoological Society of London's Indian rhinoceros, the postmortem of which was conducted by Owen and subsequently reported to the Zoological Society. In 1877, the Swedish histologist Sandstrom reported the existence of distinct glandular tissue adjacent to the thyroid in a dog.[2] Over the subsequent 2 years, similar findings in other small mammals led to the search for, and ultimate discovery of, a similar organ in humans (glandulae parathyroideae), which Sandstrom reported on in 1880.

The earliest reports of clinical hyperparathyroidism involved bone disease, or *osteitis fibrosa cystica,* as termed by von Recklinghausen.[3] These reports did not associate the characteristic changes in bone from hyperparathyroidism with parathyroid gland abnormalities, however. In 1903, Askanazy[4] reported on an autopsy performed on a patient with osteomalacia and nonfusing long bone fractures in whom a large (>4 cm) tumor was seen adjacent to the thyroid gland, noting that it might represent a parathyroid tumor.

When Erdheim,[5] a Viennese pathologist, discovered parathyroid gland morphologic and histologic abnormalities in patients with bone disease, an association between osteomalacia and parathyroid gland function was suspected. Erdheim studied the parathyroid glands by autopsy on all patients who died with bone disease, and noted that many patients with osteomalacia and osteofibrosis cystica showed enlarged parathyroid glands. He postulated that these glandular enlargements were secondary to compensatory hyperplasia, and that the bone disease was the primary initiating factor. Following up on initial experiments performed in rats by Gley, a French physiologist, Erdheim showed that cautery destruction of the parathyroid glands in rats produced not only tetany, as shown by Gley, but also the typical dental changes consistent with calcium not being laid down.[5]

Numerous reports of large parathyroid glands and bone disease followed until Schlagenhaufer[6] suggested, at a meeting in Vienna in 1915, that if only a single parathyroid gland was thought to be enlarged, it should be excised. The event that followed this suggestion years later would usher in the future treatment of parathyroid disease. von Eiselberg,[7] a pupil of Billroth, is noted as having performed the first parathyroid transplant. After performing total thyroidectomy in cats, von Eiselberg autografted the thyroid gland and a parathyroid gland into the animal's abdominal wall. Postoperatively, the animals showed no sign of tetany, and, when subjected to histologic examination, these grafts showed evidence of neovascularization.[7]

Halsted's experience with chronic hypocalcemia in thyroidectomy prompted him to study parathyroid transplantation experimentally in dogs.[8] He showed that even very small portions of surviving parathyroid tissue autograft could be lifesaving in these animals, and tetany and death would result after removal. In addition, Halsted used intravenous calcium gluconate solution to treat animals after experimental thyroidectomy. These experiments and others sparked his ever-present mandate to perform thyroidectomy carefully and meticulously avoiding injury to the parathyroid glands and their blood supply. Halsted worked with Evans, a medical student at Johns Hopkins, to define the blood supply to the parathyroid glands using vascular casting technique, and emphasized that tetany after thyroidectomy was caused more by interruption of the vascular supply to the parathyroid glands than by their inadvertent removal.[8]

From a clinical standpoint, the treatment of parathyroid disease was to change significantly with the work of Mandle.[9] Albert Gahne, a tram conductor, lived in Vienna after a bout with tuberculosis, which he acquired while serving in the Army during the years 1914-1918. He subsequently developed bone pain and muscle fatigue in 1921 from which he became disabled. In 1924, after a fall that resulted in a fractured femur, he came under the treatment of Mandle, who recognized these events as being consistent with parathyroid abnormality. Believing that this case might represent compensatory parathyroid hyperplasia as postulated by Erdheim, Mandle administered fresh parathyroid extract to Gahne without improvement. Subsequently, Mandle transplanted fresh parathyroid glands obtained from the victim of a street accident into Gahne, which again did not result in any resolution of symptoms. Recalling Schlagenhaufer's suggestion of nearly 10 years earlier, Mandel explored the neck of the now severely crippled tram conductor and removed a parathyroid tumor.[9] Gahne experienced a remarkable and immediate improvement in bone pain, and nearly 4 years later was walking with a cane free of pain. The disease recurred, and the patient was subsequently re-explored, but died after the procedure.[10] This experience illustrated several important issues that would come to influence future work with surgical parathyroid disease, including clinical use of parathyroid transplantation in humans and the treatment of recurrent disease by re-exploration.

In 1924, Hanson developed a potent extract of the parathyroid glands, which when injected into animals led to increased serum calcium, decreased phosphate, and elevated output of calcium in the urine. When used chronically, this extract would produce osteoporosis in the animals.[11]

The association of elevated blood calcium levels and parathyroid dysfunction was well acknowledged when Charles Martell, a sea captain, was evaluated at the Massachusetts General Hospital in 1927, and found to have hypercalcemia and generalized demineralization of the skeleton believed to be caused by hyperparathyroidism. The first two of a total of six operations performed on Martell were done by Richardson, the Chief of Surgery at Massachusetts General Hospital. These first two neck explorations yielded only a single normal parathyroid gland on each side without identification of abnormal tissue.[12] A third neck exploration was performed in New York in 1929 by Patterson without success. As renal function began to deteriorate with increasing symptoms of parathyroidism, Martell returned to Massachusetts General Hospital under the care of Albright and Cope. Cope had experience in several parathyroid explorations under the supervision of Churchill, and began cadaver dissection in preparation for re-exploration of Martell, which he did on three occasions in 1932 without success. At the urging of Martell, who had read extensively about his own disease and the potential locations of ectopic parathyroid tissue, Churchill planned a mediastinal exploration, the seventh surgical procedure on Martell. With Cope assisting, Churchill identified and removed most of a 3-cm tumor from the mediastinum, leaving an attached remnant portion with its vascular pedicle intact to avoid profound hypocalcemia. Despite these measures, tetany developed postoperatively, which required treatment with calcium supplementation. Several weeks after surgery, Martell experienced renal colic from an impacted ureteral stone, which required surgery. Martell died from laryngospasm after an operation to relieve obstruction from the impacted stone.

Although the series of procedures performed on Martell predated it and received more notoriety, the first successful parathyroidectomy performed in the United States was performed by Olsch in 1928 at Barnes Hospital of Washington University. In this instance, a large adenoma was removed precipitating a profound decline in serum calcium, which required massive doses of parathyroid extract and intravenous calcium to save the patient.[12,13]

The Nobel work of Berson and Yalow in 1963 paved the way for accurate identification of parathyroid hormone (PTH) levels in serum, and heralded a new era in the presentation of patients with parathyroidism. In addition, multichannel autoanalyzing systems rapidly assessed blood chemical components including calcium in a routine fashion, changing the manner in which patients with hyperparathyroidism present for treatment. Instead of renal stones and bone abnormalities, patients now present in an asymptomatic fashion without significant subjective complaints and very few (if any) clinical signs. In most instances, the only abnormality facing the surgeon is an elevated serum calcium and PTH level. It is on these findings, and the assessment of risk of developing end organ damage that modern-day surgeons treating parathyroid disorders must base their management decisions.

Etiology and Pathogenesis of Hyperparathyroidism

Parathyroid adenomas apparently are monoclonal or oligoclonal neoplasms, whereby the mechanism of propagation is believed to be clonal

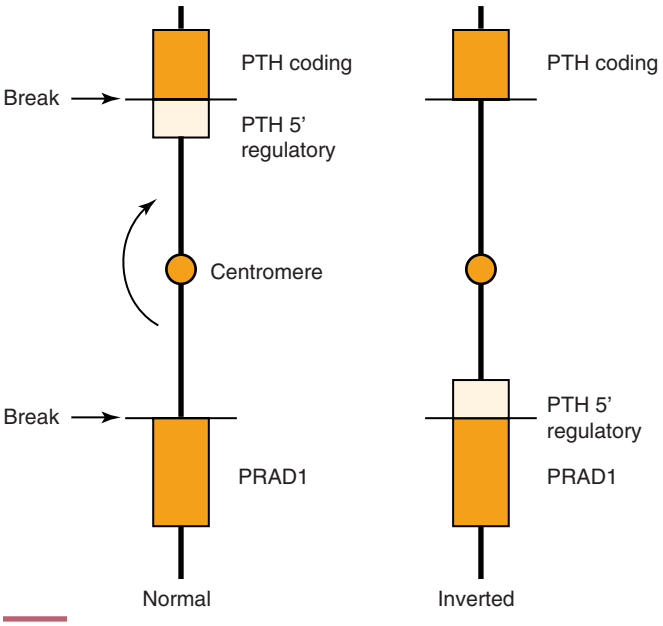

Figure 125-1. Genetic rearrangement of the parathyroid hormone (PTH) gene in primary hyperparathyroidism. Pericentromeric inversion of chromosome 11 illustrating *PRAD1* and PTH gene rearrangement. *(From Arnold A. Genetic basis of endocrine disease 5: molecular genetics of parathyroid gland neoplasia.* J Clin Endocrinol Metab. *1993;77:1108-1112. The Endocrine Society; reprinted with permission.)*

expansion of cells that have an altered sensitivity to calcium.[14] The work of Arnold and colleagues[14] indicates that the molecular events that seem to trigger clonal propagation are heterogeneous. The genetic mutational events that occur in hyperparathyroidism have been characterized in a few tumors. Among the events identified are genetic rearrangements of *PRAD1,* or parathyroid adenomatosis 1 oncogene, which is also known as cyclin D1. This proto-oncogene is located in the vicinity of the regulatory region of the gene for PTH production (Fig. 125-1).[15,16] Subsequent realignment of DNA in this event now combines a growth promoter (*PRAD1*) with a regulatory region that would ordinarily control only PTH synthesis. This genetic realignment has not been uniformly shown in most parathyroid adenomas, with only a few having been shown to manifest rearrangement.

A more common molecular event, postulated to occur in parathyroid neoplasia, is alteration in tumor suppressor gene expression (Fig. 125-2). For this gene to be inactivated and product deficient, both alleles on the gene must be affected by the mutational event. Tumorigenesis occurs as a sequential event by inactivation of both copies of the suppressor gene.[17] The most well known of these is the *MEN1* tumor suppressor gene, which shows somatic mutations in both gene copies in 20% of patients with primary hyperparathyroidism.[18] This gene was initially recognized in patients with multiple endocrine neoplasia type I (MEN-I) syndrome.[19] Evidence of loss of suppressor gene function on chromosome 1p has been postulated as being an even more common event in the development of sporadic parathyroid adenomas. It has been suggested that patients with this chromosomal abnormality may be subject to developing the same constellation of endocrine changes found in MEN-I syndrome and perhaps at an earlier age.[17] Suspected loss of tumor suppressor gene function has been identified in other chromosomal loci in patients with parathyroid adenomas including sites 15q, 9p, 6q, and 1q.[17]

Point mutations in the calcium-sensing receptor gene that reduced the activity of this gene have been elucidated as the basis for familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism.[20] This gene seems to represent a likely candidate for molecular rearrangement and altered calcium sensing function in patients with hyperparathyroidism. To date, however, a calcium-sensing receptor gene mutation or allelic inactivation has not been shown in these patients. It has been postulated that alterations in the calcium-sensing function in primary hyperparathyroidism may represent postgenomic events related to reduced RNA transcript or the actual protein receptor in the parathyroid cell clone.[21] Whether these events may represent the primary cause for, or secondary effect of, hypercalcemia remains to be determined. Abnormalities in the parathyroid cells vitamin D receptor similarly may represent changes occurring secondary to hypercalcemia and not a primary genetic event. An inactivating mutation in the gene coding for this receptor has been postulated in primary hyperparathyroidism, but results from these investigations are conflicting.[22]

Firm evidence supports the theory that ionizing radiation can represent the etiologic factor in several solid and humoral human cancers. Tisell and colleagues[23] observed that there seems to be an association between exposure to ionizing radiation to the head and neck at an early age and the late development of hyperparathyroidism. This finding is supported by other independent observations where hyperparathyroidism has developed, presumably as a late complication of radiation therapy to the head and neck, similar to the finding noted with differentiated thyroid cancer.

Calcium Homeostasis and Parathyroid Hormone Secretion and Regulation

Calcium homeostasis is maintained by the complex interrelationship of PTH, vitamin D and its derivatives, and calcitonin. The polypeptide PTH contains 84 amino acids. When secreted by the parathyroid glands, PTH undergoes immediate degradation into the amino- and carboxyl-terminal fragments. The amino-terminal fragment is biologically active, but is rapidly cleared from the circulation, whereas the carboxyl-terminal fragment is biologically inert, is predominately cleared from the circulation by the kidney, and persists for a longer time particularly in patients with renal failure.[24,25] The intact 1-84 molecule is the major circulating form of biologically active PTH; assays that measure the intact hormone more clearly reflect dynamic changes in PTH metabolism compared with the previous polyvalent assays, which measured a predominately inactive section of the PTH molecule.[26]

The release of PTH is regulated predominately by serum ionized calcium levels. PTH is secreted in response to a decrease in serum-ionized calcium, and is inhibited by an increase of serum-ionized calcium. Ionized calcium is considered to be the physiologically active component of total serum calcium.

The major target end organs for PTH action are the kidneys, skeletal system, and intestine.[27] PTH functions by binding to receptor sites in bone and kidney, which results in stimulation of the production of cyclic adenosine monophosphate (cAMP), which acts to carry out the cellular response of that specific target tissue to PTH.

The primary response to PTH by the kidney is to increase the tubular resorption of calcium and decrease the tubular resorption of phosphorus.[28,29] The action of PTH on bone to regulate serum calcium is through the remodeling effect of osteoclast and osteoblast activity. The osteoblasts and their precursor cells in bone have a PTH receptor site, and binding to this site results in the production of cAMP. The osteoclasts do not have a PTH receptor site, but are stimulated indirectly through the cAMP response in the osteoblasts.[30] The last important function of PTH occurs indirectly by increasing the rate of conversion in the kidney of 25-hydroxyvitamin D_3 (calcifediol) to 1,25-dihydroxyvitamin D_3 (calcitriol).[31] The coordinated actions of PTH on bone, kidney, and intestine increase the flow of calcium into the extracellular fluid and as a consequence increase the serum calcium levels.

PTH is the primary regulator of rapid changes of extracellular calcium levels. The action of vitamin D affects delayed changes in calcium balance as opposed to the more immediate direct action of PTH.[27] Calcitonin plays a much smaller role in calcium homeostasis. Calcitonin is secreted by the parafollicular cells of the thyroid gland and inhibits bone resorption. Calcitonin tends to be decreased in postmenopausal women, and may be increased by estrogen administration in these patients. Extremely high levels of calcitonin found in medullary carcinoma of the thyroid gland do not result in hypocalcemia.[32]

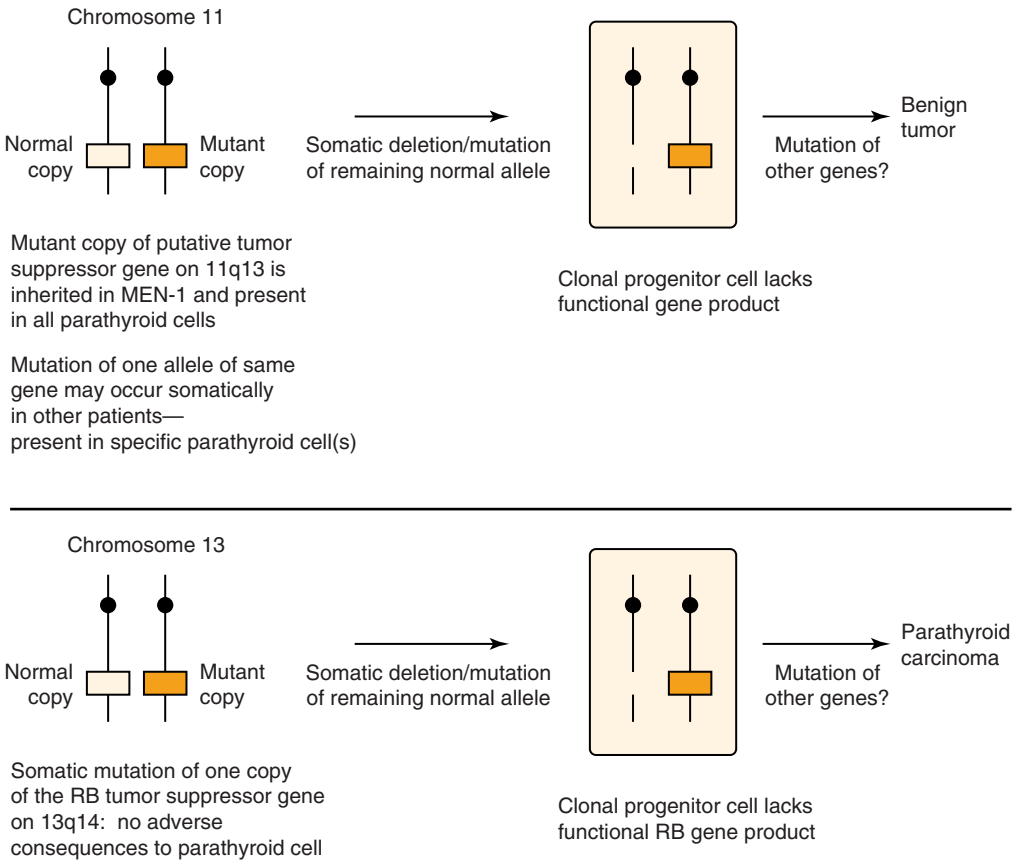

Figure 125-2. Hypothesized roles of inactivated tumor suppressor genes in the development of parathyroid neoplasia. *(From Arnold A. Genetic basis of endocrine disease 5: molecular genetics of parathyroid gland neoplasia.* J Clin Endocrinol Metab. *1993;77:1108-1112. The Endocrine Society; reprinted with permission.)*

Several endogenous substances, including peptides, steroid hormones, and amines, have been found to influence PTH release.[33,34] Calcium represents the most potent regulator of PTH secretion, however. Minor alterations within the physiologic calcium concentration range can induce considerable secretory responses—reduction of ionized plasma calcium by 0.04 mmol/L may elevate serum PTH by 100% or more. The rapid effect of extracellular calcium on PTH release suggests that calcium directly interferes with the release process, but the nature of this interference has been only partly clarified. It has been shown that external calcium mainly regulates secretion of newly synthesized hormone, which may bypass the few secretory granules in the parathyroid's chief cells.[35] Intracellular degradation with release of carboxy terminal PTH fragments occurs especially at high extracellular calcium concentrations; this attenuates the biologic activity of the secretory product because the calcium-regulating properties of PTH reside predominantly in its amino terminal portion.

Messenger RNA (mRNA) levels for PTH are increased within hours by low extracellular calcium, consistent with the effects of calcium on PTH secretion.[36,37] Calcitriol (1,25-dihydroxyvitamin D_3) reduces PTH mRNA levels and inhibits PTH secretion.[38]

Abnormalities in calcium-controlled PTH release represent a fundamental characteristic of the pathologic parathyroid tissue from hypercalcemic patients with parathyroid adenoma and hyperplasia of varying etiologies.[39,40] The representative disturbance is characterized by variable calcium insensitivity of PTH secretion. The calcium insensitivity of ionized calcium and PTH release correlate to each other and to the degree of hypercalcemia in the patient.[39]

Intact PTH 1-84 is rapidly cleared from the human circulation and has a half-life of only a few minutes.[41] Evidence does not exist to support dynamic regulation of peripheral PTH metabolism. PTH clearance mainly depends on high capacity uptake of Kupffer's cells in the liver and on glomerular filtration. A small amount of PTH appears in the urine, however, because of tubular resorption and proteolysis. Circulating PTH is heterogeneous and contains various carboxy-terminal peptide sequences arising by cleavage, mainly at residues 33 to 43. Although approximately 15% of intact PTH 1-84 is metabolized to such circulating fragments, they make up at least half, and sometimes substantially more, of the immunoactive PTH in the circulation.[42] The metabolism of such fragments depends virtually only on an intact renal function; consequently, they are accumulated to considerable degrees in renal insufficiency. In contrast, very few amino terminal PTH fragments exist in the circulation of euparathyroid individuals, although these fragments may become appreciable in primary and secondary hyperparathyroidism.

The diagnosis of primary hyperparathyroidism and evaluation of the extent or severity of secondary hyperparathyroidism have been facilitated by the development of immunometric "sandwich" assays. These assays use a pair of antibodies that recognize different regions of the PTH protein sequence.[43-45] Because of cooperative effort of the antibodies, such a sandwich assay is more sensitive than either of the antibodies alone in displacement radioimmunoassays. With careful selection of antibodies, the immunometric assays are specific and sensitive for intact PTH, which allows identification of insufficient PTH secretion of hypoparathyroidism and a wide range of PTH levels without sample dilution. The immunometric analyzing process is swifter than the radioimmunoassays. With a reduction in the incubation times, the analysis may be accomplished in 15 to 30 minutes and, consequently, may be applicable intraoperatively.[46,47]

Clinical analysis with immunometric PTH assays usually discriminates hypercalcemic patients with hyperparathyroidism from patients with other causes of hypercalcemia. This discrimination is particularly evident with regard to malignancies of nonparathyroid origin, although approximately 5% to 10% of these patients show intact serum PTH in the low-normal range. Nonparathyroid tumors

that produce intact PTH are exceptionally rare. These include ovarian and small cell carcinomas and thymoma.[48-50]

Parathyroid Anatomy and Histopathology

Normal Parathyroid Gland

The usual weight, size, and fat content of a normal parathyroid gland vary. The weight of a normal gland has been recorded to be as low as 40 mg, and a limit of 50 to 60 mg has been suggested.[51] One study showed that the weights of normal parathyroid glands have a skewed distribution.[51] The mean total weight in the study was 29.5 ± 17.8 mg, with an upper limit of 65 mg. The actual value for the 98th percentile was 75 mg, and this correlates with the operative findings typically noted in primary hyperparathyroidism.

Chronic illness, race, and other individual variations may affect the weights of normal parathyroid glands. In patients with chronic illness, total glandular weights are lower; in male and black patients, total glandular weights are higher. Glands that are removed from the patient may show wide variations in weight. One gland may be much smaller than another, and sometimes two glands may be small.

The dimensions of normal glands are rarely mentioned in the literature. Normal dimensions of 3 to 6 mm in length, 2 to 4 mm in width, and 0.5 to 2 mm in thickness, and an average of three dimensions of 5 mm × 3 mm × 1 mm have been proposed.[52] Normal glands measuring 12 mm and greater have been reported.[53]

Glandular weight, rather than glandular dimension, is accepted as a better measure of size. For the surgeon, knowing the normal dimensions of parathyroid glands is crucial. In most operative situations, enlargement of parathyroid glands is determined by the surgeon in the operating room through a judgment of size, rather than assessment of weight. The determination of weight or density requires the removal of the glands, which may not be indicated in all circumstances.

The stromal fat content of parathyroid glands is the hallmark in the evaluation of their functional status. Detailed studies of normal glands have shown wide variations in fat content.[54,55] The accepted percentage of normal fat content is approximately 50%. One study indicated that more than 75% of normal parathyroid glands had less than 30% stromal fat, 50% had less than 10%, and only a few had 40%.[54] The variability of fat content reported by different studies suggests that measurement of stromal fat within parathyroid glands has become nearly useless as an indicator of function.[54,55] In children and adolescents, parathyroid glands contain very sparse amounts of fat. After adolescence, stromal fat progressively increases until 25 to 30 years of age; subsequently fat content is largely determined by constitutional factors. Women seem to have a tendency to have higher glandular fat content, which may be related to total body fat concentrations.[56]

The characteristic cellular content of the normal gland is dominated by chief cells with rare water clear cells. Oxyphil cell concentrations tend to increase with age and are noted to be rare in young individuals. Oxyphil cell concentrations seem to be more common in adults older than 40 years.

Four parathyroid glands is the usual number found in humans. In dissection studies of 428 human subjects by Gilmour,[57] four parathyroid glands were found in 87% of all patients, and three glands were found in 6.3%. Akerstrom and coworkers[58] reported comparable rates in an autopsy study of 503 individuals. In this study, four parathyroid glands were found in 84% of patients, and three parathyroid glands were found in 3%. The presence of supernumerary parathyroid glands is rare, and may have important clinical consequences, especially with respect to patients with hyperparathyroidism resulting from multiple-gland disease.

In a series of 2015 patients who were operated on for primary hyperparathyroidism, a hyperfunctioning supernumerary fifth parathyroid gland was the source of hypercalcemia in 15 patients (0.7%).[59] Nine of these patients required reoperation to remove the supernumerary gland representing the parathyroid tumor. Most of these fifth gland tumors were located in the mediastinum, either in the thymus (seven tumors) or related to the aortic arch (three tumors). Edis and Levitt[60] reported a rate of persistent hyperparathyroidism of 10% resulting from an enlarged supernumerary parathyroid gland in patients with secondary hyperparathyroidism. In a series of 762 patients with primary hyperparathyroidism, Wang and colleagues[61] documented 6 patients with persistent hyperparathyroidism caused by hyperfunctional supernumerary glands (0.6%), all of which were located in or in close association with the thymus.

In the previously mentioned study by Gilmour,[57] supernumerary parathyroid glands were observed in 29 of 428 specimens (6.7%). Five parathyroid glands were observed in 25 specimens (5.8%), 6 parathyroids were observed in 2 specimens (0.05%), 8 parathyroids were observed in 1 specimen, and 12 parathyroids were observed in 1 other specimen. From the studies by Gilmour[57] and Akerstrom and coworkers,[58] it is evident that supernumerary parathyroids are most commonly found within the thymus or in relation to the thyrothymic tract.

Parathyroid Gland Location

The location of parathyroid glands may vary, as a consequence of the variation in degree of migratory descent during development. Additional influences on these variable locations involves displacement of enlarged parathyroid glands during the development of hyperparathyroidism. Enlarged parathyroid glands tend to migrate in a fibroareolar plane, which offers little resistance as a result of gravity and the action of swallowing and variations in intrathoracic pressure.[62]

Eighty percent of the superior parathyroid glands are found at the cricothyroid junction approximately 1 cm cranial to the juxtaposition of the recurrent laryngeal nerve and the inferior thyroid artery.[58] The superior parathyroids, which are intimately associated with the posterior capsule of the superior thyroid pole, are usually covered by an extension of the pretracheal fascia that envelopes the thyroid gland and connects it to the hypopharynx and esophagus and the carotid sheath. The relationship of these superior parathyroid glands with the pretracheal fascia is such that the glands themselves are allowed freedom of movement under this "pseudocapsule." This feature discriminates parathyroid glands from thyroid nodules, which cannot move freely because they are enveloped by the true capsule of the thyroid gland.

Normal superior parathyroid glands may be found in the retroesophageal or paraesophageal space in approximately 1% of all instances.[63] These spaces represent sites where enlarged superior parathyroid glands potentially descend to the superior and posterior mediastinum.

The inferior parathyroid glands tend to have a more variable location. Greater than 50% of the inferior parathyroid glands are situated neighboring the lower pole of the thyroid gland. Twenty-eight percent of the inferior parathyroids are found within the thyrothymic ligament or within the anterior superior mediastinal thymic gland. The migratory pattern of inferior parathyroid glands tends to follow a pathway into the anterior superior mediastinum, where one third of all missed parathyroid tumors may be found.

The incidence of intrathyroidal parathyroid glands is controversial. Akerstrom noted true superior intrathyroidal parathyroid glands in 3 instances (0.2%) among 503 autopsy specimens.[58] Wang[64] considered the superior parathyroid gland the most likely to be intrathyroidal primarily because of the close embryologic relationship of the primordium of the superior parathyroid gland with the lateral complex of the thyroid. In a series by Wheeler[64a] in which 8 intrathyroidal parathyroid tumors were noted in 7 of 200 patients (3.5%) undergoing neck exploration, 7 of these intrathyroidal glands were considered to originate from the inferior position. The overall incidence of intrathyroidal parathyroid glands ranges from approximately 0.5% to 3% as reported in the literature.[65-68]

Morphologic Characteristics of Parathyroid Glands

The visible discrimination between normal and abnormal hyperfunctioning parathyroid glands is essential to successful parathyroid surgery. The appearance of normal and abnormally functioning parathyroid glands varies and depends on the anatomic position and relationship to the thyroid capsule. Parathyroid glands that are located in loose connective tissue generally are more characteristically oval-shaped, bean-shaped, or teardrop-shaped. When parathyroid glands are closely

juxtaposed to the thyroid capsule compressed by the pretracheal fascia, their appearance tends to be more conforming resulting in a flat shape with well-defined edges. The color of normal parathyroid glands ranges from yellowish brown to reddish brown. Generally, the color may depend on the amount of stromal fat, oxyphil cell concentration, and degree of vascularity.[69] Normal glands tend to be more reddish brown or rust-colored in younger patients, whereas older individuals have parathyroid glands of a more yellow-brown or tobacco color. Enlarged hyperfunctional parathyroid glands have a color variation from dark brown to light yellow. Enlarged glands occurring in either secondary or tertiary hyperparathyroidism may have a lighter gray tone to the coloration. Parathyroid carcinoma can also show a mottled gray-to-white surface appearance.

Vascular Anatomy of the Parathyroid Glands

Normal parathyroid glands most commonly are supplied by a single dominant artery (80%).[70] The length of the dominant artery supplying the parathyroid gland may vary from 1 to 40 mm. In most instances, the superior and inferior parathyroid glands derive their dominant arterial blood supply from the inferior thyroid artery. Ligation of the inferior thyroid artery during thyroid surgery may not always compromise the blood supply to the superior parathyroid gland, however. Abundant arterial anastomoses exist between the parathyroid glands and include anastomoses with thyroid arteries and dominant arteries of the larynx, pharynx, esophagus, and trachea. Of the superior parathyroid glands, 20% or more may be vascularized solely by the superior thyroid artery. In an autopsy study by Delattre and associates,[70] 10% of the inferior parathyroid glands derived their dominant arterial supply from a branch of the superior thyroid artery. In most of these instances, the inferior thyroid artery was noted to be absent. Primary mediastinal parathyroid glands have shown an arterial supply that represents a thymic branch of the internal mammary artery.[71]

The venous drainage distribution of the parathyroid glands generally runs parallel to the arterial vessels and drains via the neighboring thyroid venous tributaries into the internal jugular system. Similarly, lymphatics from the parathyroid glands drain with the lymphatics of the thyroid gland into the paratracheal and deep cervical lymphatic basins.

Histopathology of the Parathyroid Glands

The parathyroid glands are enveloped in their own thin collagenous connective tissue capsule. This capsule extends septa into the gland, which separate the parenchyma into elongated chords or clusters of functional secretory cells. Blood vessels, lymphatics, and nerves travel along the septa to reach the interior of the gland.[72]

The major functional parenchymal cells of the parathyroid glands are the chief cells, which are slightly eosinophilic staining and measure 5 to 8 millimicrons in diameter. The chief cells contain many cytoplasmic granules (200 to 400 nm in diameter), which arise from the Golgi complex and represent the secretory granules.[72] These granules contain PTH, which is synthesized from a precursor of prepro-PTH. With increasing age, the secretory cells of the parathyroid glands may be replaced by adipose cells, which may make up 50% to 60% of the gland in older individuals.

The second cell type making up parathyroid glandular parenchyma is the oxyphil cell. Although their function is unknown, it is believed that oxyphil cells and a third cell type, sometimes described as intermediate cells, may represent inactive phases of a single cell type.[73] Oxyphil cells are less numerous, are larger (6 to 10 millimicrons in diameter), and stain more deeply with eosin than chief cells. Oxyphil cells tend to be more mitochondrial-rich, which may explain the increased ability of abnormal parathyroid glands with high oxyphil cell concentrations to concentrate technetium 99m (Tc 99m) sestamibi.[74]

By electron microscopy, chief cells show Golgi apparatus among dispersed granular endoplasmic reticulum and few secretory granules. The resting chief cells contain abundant lipid and glycogen, whereas during active phase the chief cells are smaller in size and contain decreased amounts of glycogen and lipid.[75] The oxyphil cells are characterized by their large size and numerous cytoplasmic mitochondria.[75]

Single Glandular Enlargement or Parathyroid Adenoma

Single glandular enlargement, or adenoma, is the most common cause of hyperparathyroidism. Because of the variation in pathologic interpretation and patient population, however, the reported incidence of parathyroid adenoma ranges from 30% to 90%.[76-80] In larger series of patients, where more uniformly accepted pathologic criteria were followed, approximately 80% to 85% of patients with primary hyperparathyroidism were found to have solitary parathyroid adenoma.[76-78] Parathyroid adenoma may occur in any of the four parathyroid glands, but tends to involve inferior glands more commonly than superior glands.[74]

The gross appearance of parathyroid adenomas varies, but adenomas generally are oval-shaped or bean-shaped, red-brown in color, and soft in consistency.[81,82] Adenomas may be bilobed or multilobulated in conformation. In 70% of adenomas, a rim of normal parathyroid tissue may be found around the hypercellular portion of the replaced normal gland. The absence of this characteristic does not exclude the presence of a parathyroid adenoma, however. The incised surface of an adenoma may appear smooth or nodular, or may show obvious areas of cystic change. Under light microscopy, adenomas appear similar to normal parathyroid glands, exhibiting a thin fibrous capsule with a cellular framework arranged in nests and cords invested by a rich capillary network. Other growth patterns include follicular, pseudopapillary, and acinar patterns.

Chief cells are the dominant cell types in most parathyroid adenomas. Oxyphil cells and transitional oxyphil cells are usually seen in varying proportions interspersed between the collections of chief cells.[80-82] The chief cells in adenomas may be larger than found in normal glands, and may exhibit a greater degree of nuclear pleomorphism and giant cell formation.[83,84] Nuclear atypia is of limited value, however, in distinguishing between parathyroid adenoma and carcinoma. Mitotic figures are uncommon in adenomas; however, they may be seen in a small percentage of cases.[85]

Variations in single glandular enlargement representative of parathyroid adenoma may occur and include the following subtypes: oncocytic adenoma, lipoadenoma, large clear cell adenoma, water clear cell adenoma, and atypical adenoma. Oncocytic adenoma is a rare subtype of parathyroid adenoma (4.4% to 8.4% of adenomas) that is composed predominantly (>80% to 90%) or exclusively of oxyphil cells.[86,87] Previously, adenomas of the oncocytic variety were believed to be nonfunctional; however, oxyphil adenomas associated with hyperparathyroidism have been reported.[88-90] Similar to typical adenomas, oncocytic tumors occur more frequently in women and are found most often in the sixth or seventh decade.[89,90] Grossly, the tumors tend to be large, reported to range in size from 0.2 to 61 g; they are soft, spherical, ellipsoid, lobulated, or nodular, and range in color from light tan to dark orange-brown or mahogany.[89,91] Microscopically, adenomas are composed predominantly of polygonal cells with abundant brightly eosinophilic granular cytoplasm and small round central hyperchromatic nuclei. Fat stain shows reduce cytoplasmic fat as per typical adenomas. Numerous mitochondria are densely packed throughout the cytoplasm on ultrastructural examination.

Lipoadenoma is another rare subtype of adenoma that was first described in 1958 as a parathyroid hamartoma.[92] The initial description was that of a nonfunctioning mass; subsequent reports documented that these lesions can be responsible for hyperparathyroidism.[93-95] The tumor comprises a lobulated yellow-tan mass composed of nests, acini, and cords of chief cells and occasional oxyphil and clear cells, intimately associated with large areas of adipose tissue or myxoid stroma or both. A rim of normal parathyroid tissue may be present at the periphery.

Water clear cell adenomas have been described, although their existence was initially doubted.[96] In contrast to the large clear cell adenomas that accumulate glycogen, true water clear cell adenomas show a glycogen-free cytoplasm that is filled with membrane bound vesicles.[97]

Atypical adenoma is the term used to describe parathyroid adenomas that exhibit atypical cytologic features without definite evidence of malignancy (i.e., vascular or soft tissue invasion or both or metastases).[98] It is important to distinguish these benign lesions from parathyroid carcinoma. The malignant potential of atypical adenomas in

terms of recurrent or metastatic behavior is uncertain. These lesions may exhibit conspicuous mitoses, adherence to surrounding tissues, trabecular cellular arrangements, capsular invasion, or broad fibrous bands.[99] One such lesion described consisted of a multifocal spindle cell proliferation that was mitotically active, averaging eight mitoses per 10 high-power fields within an otherwise typical parathyroid adenoma.[100]

Multiple Enlarged Glands or Parathyroid Gland Hyperplasia

Primary parathyroid hyperplasia is defined as proliferation of the parenchymal cells leading to increase in gland weight in multiple parathyroid glands in the absence of a known stimulus for PTH secretion. Two types of parathyroid hyperplasia are seen: the common chief cell hyperplasia and the rare water cell or clear cell hyperplasia.[76,77]

Chief Cell Hyperplasia

In 1958, Cope and associates[101] first showed chief cell hyperplasia as a cause of primary hyperparathyroidism. It accounts for approximately 15% of hyperparathyroidism in reported series; however, some reports have indicated that about half of primary hyperparathyroidism may be produced by hyperplasia. A variation in this reporting is generally attributable to discrepancies in pathologic interpretation of abnormal parathyroid glands. The stimulus for this disorder is unknown; some studies have indicated a role of a possible circulating factor that can induce proliferation of parathyroid cells in culture. Approximately 30% of patients with chief cell hyperplasia have some type of familial hyperparathyroidism or one of the MEN syndromes.[76,77,102,103] Molecular studies have shown that hyperplasias are monoclonal proliferations.[15,16]

Grossly, there is enlargement of all four glands. The glands may be of variable size, or they may be uniformly enlarged. By light microscopy, the dominant cell types are chief cells; however, one may also observe intermixed oxyphil cells and transitional oxyphil cells. The cellular proliferations may also give rise to nodular formation, and this can cause asymmetric gland enlargement.[76,77]

The amount of cytoplasmic fat in the chief cells is either reduced or absent.[76,77] The chief cell in the nodular areas may be totally devoid of any fat, whereas the cells between the nodules may contain fat. Abnormal nuclei or mitoses are distinctly rare.[77]

Water Clear Cell Hyperplasia

Water clear cell hyperplasia is rare and is characterized by a proliferation of vacuolated water clear cells in multiple parathyroid glands. It shows a female predilection and leads to pronounced hypercalcemia and severe clinical disease. This represents the only parathyroid disorder in which the superior glands are larger than the inferior parathyroid glands. The glands affected by water clear cell hyperplasia tend to be larger and more irregular in shape with lobular extensions to surrounding soft tissue. By light microscopy, the glands show diffuse proliferations of clear cells characterized by clear cytoplasm and small dense nuclei. On high-power magnification, the cytoplasm is shown to be filled with small vacuoles. Cytoplasmic lipid is generally not present; however, moderate amounts of glycogen may be identified. The histologic appearance of water clear cell hyperplasia bears a resemblance to that of renal cell carcinoma.[104]

Secondary parathyroid hyperplasia as a consequence of renal failure cannot be distinguished from primary hyperplasia with the exception that early in the disorder there seems to be a greater tendency for the glands to be more uniform in size.[105] As the disease progresses, asymmetry becomes more evident in renal failure–induced disease. The degree of glandular enlargement tends to reflect the severity of the underlying renal disorder.[106] The largest glands are noted in patients whose renal disease began in childhood.[107]

Parathyroid Carcinoma

Parathyroid carcinoma is a rare malignant neoplasm derived from the parenchymal cells of the parathyroid glands. It has been reported to be responsible for 0.1% to 5% of cases of primary hyperparathyroidism.[108-112] It is uncertain whether parathyroid carcinoma actually begins within preexisting benign parathyroid lesions.[112,113] Carcinoma has been postulated to arise in the setting of primary parathyroid hyperplasia, notably familial hyperplasia.[114-116] Only rare patients with parathyroid carcinoma have a history of prior neck irradiation.[110,112]

Morphologic features diagnostic of parathyroid malignancy are difficult in terms of definition and practical application during surgery. In one series of 40 patients with metastatic parathyroid cancer, 50% were thought to have benign disease by the operating surgeon and consulting pathologist during the time of initial exploration.[117] Metastases are the only certain sign of malignancy. Metastatic behavior at the time of presentation is distinctly rare, however.[108]

Parathyroid carcinomas are characteristically large tumors, with 30% to 50% being palpable at the time of presentation.[108,109] The tumors may measure 6 cm in diameter with a mean of approximately 3 cm.[108] Although the average weights of carcinomas are reported to be greater than those of adenomas, there seems to be great overlap, indicating that weight alone may not be a major distinguishing characteristic between benign and malignant lesions. Carcinomas generally arise in the usual parathyroid locations, although they have been described in ectopic supernumerary glands within the mediastinum.[118] Most parathyroid carcinomas are firm or hard in consistency and have a gray-to-white surface color as opposed to adenomas, which tend to be soft and tan in appearance. Adherence of the lesion to surrounding tissues is common, and these glands may be noted to extend to involve the soft tissues around the thyroid gland or the thyroid parenchyma itself. This may not prove to be a valuable differentiating feature because previous hemorrhage into a benign adenoma may be associated with fibrosis and adherence to adjacent structures in benign disease.[112]

Metastases at the time of presentation are unusual, but may rarely be found in regional lymph node basins.[117] As opposed to regional metastases, parathyroid carcinoma is more often associated with widespread local infiltration, with invasion into contiguous structures, such as thyroid gland, strap muscles, trachea, and recurrent laryngeal nerve. Advanced metastases may occur and may be found in the lungs, bone, cervical and mediastinal lymph nodes, liver, occasionally kidney, and adrenal glands.[117,119] Pulmonary metastases are the most common distant metastasis noted.[117]

Microscopic diagnosis of parathyroid carcinoma is a difficult task. The entire gland is traversed by broad fibrous bands that seem to originate from the capsule and extend into the substance of tumor leading to a lobulated appearance. The cells may be clear or rarely oxyphilic, and are arranged in nests and trabeculae.[120] The cell may be uniformly bland or may show metaplasia, but the cases with minimal atypical findings may be difficult to distinguish from an adenoma.[121-123]

Mitosis can be seen in most instances and has been suggested as a primary factor in diagnosing parathyroid carcinoma.[124] Mitotic figures may also be seen in parathyroid adenoma and hyperplasia, however, and their absence does not rule out a diagnosis of carcinoma.[125,126] It is generally acknowledged that mitoses in parathyroid lesions should be of concern, especially because the follow-up in reported benign cases of parathyroid tumor exhibiting mitoses has been limited. Increased mitotic activity in unequivocal parathyroid carcinoma is an indicator of poor prognosis.[127]

The only reliable indicators of malignancy in parathyroid carcinoma are invasion of the surrounding structures, metastases, or both.[127] Features such as desmoplastic reaction, mitotic activity, nuclear atypia, and necrosis may be more common in carcinoma than in benign lesions, but do not constitute criteria sufficient for a diagnosis of malignancy.[127] In the absence of an infiltrative growth pattern, the parathyroid lesion showing some other feature of malignancy including mitoses may be designated as *atypical adenoma*.[128] Nonfunctioning parathyroid carcinomas have been rarely described, tending to be large and consisting of clear or oxyphil cells.[129,130]

Parathyroid carcinoma usually grows slowly and can be an indolent tumor. Multiple recurrences after surgical resection are common and may occur over a 15- to 20-year period.[121,122] Patients with parathyroid carcinoma often die as a result of the effects of excessive PTH secretion and uncontrolled hypercalcemia, rather than growth of the tumor mass. Surgical excision of recurrence or metastases may provide excellent palliation by reducing tumor burden and consequently hormone production.[131,132]

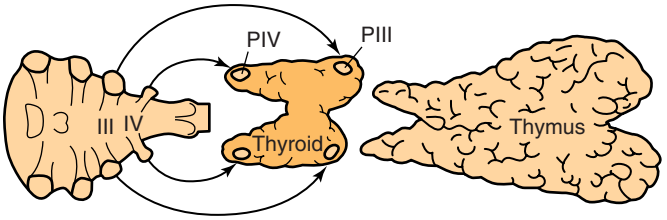

Figure 125-3. Embryologic derivation and subsequent descent of the parathyroid glands with associated structures.

Surgical Embryo-Anatomic Relationships in the Central Neck

Parathyroid tissue originates from primordial pharyngeal endoderm formed in the third and fourth pharyngeal pouches during the fifth week of embryologic development (Fig. 125-3). The epithelial lining of the dorsal wing of the third pharyngeal pouch differentiates into primordial parathyroid glandular tissue, whereas the ventral portion of the pouch differentiates into the thymus. As the thymus migrates medially and inferiorly, it pulls the inferior parathyroid gland (parathymus) with it into the thymic tail. Eventually, the main portion of the thymus migrates to its final position in the upper thoracic region, and its tail involutes, leaving the developing parathyroid gland to come to its position on the dorsal surface of the inferior pole of the thyroid gland. This glandular tissue eventually forms the inferior parathyroid gland. Simultaneously, the epithelium of the dorsal wing of the fourth pharyngeal pouch begins to differentiate into parathyroid glandular tissue. After separation from the regressing pouch, it becomes associated with the lateral portion of the caudally migrating thyroid, and is carried a short distance medially and inferiorly until it resides posterior to the superior pole of the thyroid gland. This tissue eventually develops into the superior parathyroid gland.

This embryologic pattern of development has significant implications for the identification of ectopic or normal glandular variance during the course of parathyroidectomy. The longer embryologic migration results in an extensive area of potential dispersal for the normal inferior parathyroid gland. In 61% of cases, the glands are situated at the level of the inferior poles of the thyroid lobes on the posterior, lateral, or anterior aspects. In 26% of cases, they are situated in the thyrothymic ligament or on the upper, cervical portion of the thymus. More rarely, in 7% of cases, they are situated higher up, at the level of the middle third of the posterior aspect of the thyroid lobes, and may then be confused with the superior parathyroid gland. Because the embryonic descent of the thymus extends from the angle of the mandible to the pericardium, anomalies of migration of the parathymus, whether excessive or insufficient, are responsible for high or low ectopic locations of the inferior parathyroid gland. The incidence of higher ectopia along the carotid sheath, from the angle of the mandible to the lower pole of the thyroid, does not seem to exceed 1% to 2%.[133-135] Alternatively, if the separation from the thymus is delayed, the inferior parathyroid gland may be pulled inferiorly into the anterior mediastinum to a varying degree. In this circumstance, they are usually within the thymus, at the posterior aspect of its capsule, or still in contact with the great vessels of the mediastinum. Lower ectopic regions such as these are noted in 3.9% to 5% of instances.[134,136]

The superior parathyroid glands follow the thyroid migration of the ultimobranchial bodies, which travel toward the lateral part of the main medial thyroid rudiment. In contradistinction to the inferior glands, the superior parathyroids have a limited descent within the neck. They remain in contact with the posterior part of the middle third of the thyroid lobes. This limited course of embryonic migration explains why they remain stable in their regional distribution when not pathologic. In most instances, they are grouped at the posterior aspect of the thyroid lobes, in an area 2 cm in diameter, whose center is situated about 1 cm above the crossing of the inferior thyroid artery and the recurrent laryngeal nerve.[134,137] Because of the more extensive descent of the inferior parathyroid gland, the descent of the parathymus result in the inferior and superior glands crossing during development. This embryonic crossing of the glands explains why their grouping at the level of the inferior thyroid artery, at the junction of the middle and inferior thirds of thyroid lobe, is in many respects quite close, depending on the degree of migration of the inferior parathyroid gland.

Because of the short migratory descent of the superior parathyroid gland, the area of dispersal of these glands is limited, and congenital ectopic positions of the superior gland are unusual. In 13% of instances, the glands are on the posterior aspect of the superior pole of the thyroid lobe in a laterocricoid, lateropharyngeal, or intercricothyroid position, and, exceptionally, in less than 1% of instances, they are above the upper pole of the lobe. In 1% to 4% of instances, they are clearly posteriorly based behind the pharynx or esophagus. Parathyroid glands that are found in the posterior superior mediastinum are usually neoplastic superior parathyroid glands that have migrated as a consequence of gravity and changes in intrathoracic pressure.[137]

Clinical Features of Primary Hyperparathyroidism

Incidence

The incidence of hyperparathyroidism has changed dramatically over the past 3 decades. In the early 1970s, before the widespread use of multichannel autoanalysis of blood chemistry, Heath and colleagues[138] reported an annual incidence of 7.8 cases/100,000 in Rochester, Minnesota. After the introduction of routine serum calcium assessment later in the 1970s, the incidence rate increased to 51 cases/100,000/year. After the most prevalent or clinically significant cases were managed, the incidence declined to 27 cases/100,000 annually, and more recent reports indicate that within the population associated with this area of Minnesota, a steady decline in the incidence of hyperparathyroidism has been noted since the late 1970s. This decline cannot be explained by the more limited routine use of multichannel autoanalyzing of blood, which has become part of cost-saving measures since the late 1990s; also, this declining incidence has not been similarly experienced in other populations nationally or internationally.

A higher rate of incidence was noted in the Stockholm study, which examined more than 15,000 subjects over a 2-year period (1971-1973) with a follow-up at 10 years. The early rate was assessed at 6 cases/1000, which at the 10-year follow-up was verified to be 4.4 cases/1000. This rate has not changed appreciably over a 20-year period, in contrast to the Rochester experience.[139] One may postulate that the Rochester experience is unique in that after obtaining a very high incidence rate promulgated by routine calcium screening, higher prevalence cases were eliminated to reveal a lower base incidence rate in a population that receives its treatment at a single major center, explaining the steady decline in this fixed population base.

There seems to be a distinct predilection for a higher incidence of hyperparathyroidism in women, especially women beyond menopause. The highest prevalence rate among women in the Stockholm experience confirmed at the 10-year follow-up was approximately 13/1000, which represented a female-to-male ratio of about 4:1. This experience is similar to that of other published reports.[138,140-143] Several of these studies based on serum calcium screening have shown that the prevalence of primary hyperparathyroidism in the general population is 0.1% to 0.3%, and in women older than 60 years, the prevalence is more than 1%.[138,139,144] The clear female preponderance points to the fact that every woman has a 1% risk of experiencing primary hyperparathyroidism during her lifetime. It has been estimated, however, that about 90% of individuals with primary hyperparathyroidism remain undiagnosed.[145] The screening of serum calcium has been a particularly important factor leading to the detection of patients with mild symptoms or no symptoms, especially among postmenopausal women.

Presentation

The concept of clinical features associated with primary hyperparathyroidism has changed during recent years. So-called classic, specific

symptoms (i.e., bone disease, renal stones, and hypercalcemic crisis) represent obvious manifestations of the disease. The relative proportion of patients with osteitis fibrosis cystica, nephrolithiasis, and hypercalcemic crisis has continuously decreased in clinical series because of the increase in the number of patients with nonspecific or nonapparent symptoms. Currently, osteitis fibrosis occurs in about 1% of patients, and only 10% to 20% of patients have renal stones.[146-148] Nonspecific symptoms include malaise, fatigue, depression and other psychiatric symptoms, sleep disturbance, weight loss, abdominal pains, constipation, vague musculoskeletal pains in the extremities, and muscular weakness.

The term *asymptomatic hyperparathyroidism* has been commonly applied when the disorder is detected during health screenings and population studies, or coincidentally during medical examinations. The usual presenting abnormality in these patients is an abnormally elevated serum calcium detected on routine blood chemistry screening. Despite the lack of obvious abnormalities noted at the time of diagnosis, caution should be exercised before declaring that a patient is asymptomatic. Many seemingly asymptomatic patients may manifest subtle or even "silent" sequelae of hyperparathyroidism at the time of presentation, and these patients may be more appropriately described as minimally symptomatic because nonspecific symptoms and unidentified complications of hyperparathyroidism would be eliminated by parathyroidectomy.[149] Some of these nonspecific sequelae include emotional complaints, muscular fatigue, constipation, bone and joint pain, and silent objective findings such as asymptomatic renal calculi and decreased bone mineral density. In most patients with asymptomatic or minimally symptomatic hyperparathyroidism, these symptoms are subtle and may be so common in the general population that they preclude establishment of a causal relationship to primary hyperparathyroidism.

Among patients in whom symptoms are present or evolving at the time of diagnosis, two populations may be identified. In the first group, the disease progresses insidiously over several years and eventually manifests as renal colic. The second group manifest symptoms over a considerably shorter time with marked elevations in serum calcium leading to weight loss, acute gastrointestinal symptoms, anorexia, bone pain, and occasionally pathologic fracture. Traditionally, clinical manifestations are described according to the organ system affected.

Kidney and Urinary Tract

Historically, greater than 50% of patients with hyperparathyroidism develop renal symptoms manifested by nephrolithiasis and nephrocalcinosis. This percentage decreased significantly to approximately 4% after the widespread use of screening tests for serum calcium levels.[150] Most stones are composed of calcium oxalate; however, calcium phosphate stones may also occur. The symptoms associated with urolithiasis include renal colic, hematuria, and pyuria. Metabolic acidosis may also be a part of the clinical syndrome.

Skeletal System

Abnormalities of the skeletal system in the form of osteitis fibrosis cystica, previously a common malady in patients with primary hyperparathyroidism, are now rarely encountered (<10%). These changes include subperiosteal erosion of the distal phalanges, bone wasting and softening, and chondrocalcinosis as a result of bone demineralization. Bone disease may manifest as bone pain, pathologic fracture, cystic bone changes, or focal areas of bone swelling (epulis of the jaw or "brown tumors") representing accumulations of osteoclasts, osteoblasts, and fibrous matrix. Symptoms attributable to joint pathology include gout and pseudogout.

Bone loss in hyperparathyroidism occurs at cortical bone sites generally sparing trabecular bone.[151] Because of this finding, the role of hyperparathyroidism in osteoporosis is unclear, especially for patients in whom symptoms are minimal or absent, and in whom the disease is mild. Postmenopausal women with primary hyperparathyroidism exhibiting early signs of osteoporosis seem to be at significant risk for developing more severe bone disease and resultant sequelae (i.e., vertebral and hip fractures). The benefit of parathyroidectomy is most apparent in these patients.[152]

Neuromuscular System

Muscle weakness, particularly in the proximal extremity muscle groups, together with progressive fatigue and malaise, may occur in symptomatic primary hyperparathyroidism. Electromyography changes may be seen in these patients together with atrophy of the skeletal muscle on biopsy specimens.[153-155] Although the severe symptoms are rarely encountered, some signs of muscle fatigue and weakness may be present in 40% of patients with mild primary hyperparathyroidism.[156] Usually these subtle symptoms are manifested as muscle aches and fatigue on rising from a chair or climbing stairs. Progression of the disease may ultimately result in weakness that limits activity and ambulation over weeks to months. This neuromuscular syndrome is noted to improve after parathyroidectomy in 80% to 90% of the patients affected.[157,158]

Neurologic System

Neurologic manifestations of primary hyperparathyroidism are represented by a spectrum of symptoms ranging from anxiety and mild emotional disturbance to frank psychosis. Depression, nervousness, and cognitive dysfunction may commonly occur to varying degrees in primary hyperparathyroidism. Cerebral dysfunction characterized by organic brain syndrome is more common in elderly patients with an underlying mild cognitive abnormality exposed to hypercalcemia. Other neurologic changes occasionally seen in patients with hyperparathyroidism include deafness, dysphagia, dysosmia, and dysesthesia.[159] Many of the psychiatric symptoms in patients with primary hyperparathyroidism are improved after parathyroidectomy.[158,160] Fifty percent of patients with depression or anxiety, or both, improve after surgery. A favorable effect has also been shown in about 50% of patients with organic brain syndrome and dementia. Some older patients experience dramatic improvement; however, it is impossible to predict whether any specific patient will improve after surgery.[160]

Gastrointestinal System

Gastrointestinal disorders that may occur in hyperparathyroidism include acid peptic disease, pancreatitis, and cholelithiasis. Peptic ulceration occurs with increased frequency in these patients secondary to increased serum gastrin and gastric acid secretion stimulated by hypercalcemia. Hyperparathyroidism may be the heralding manifestation of endocrine disease in patients with MEN-I syndrome. Patients with Zollinger-Ellison syndrome show the highest incidence of peptic ulceration. The lower gut also may be affected by hyperparathyroidism. Frequently, patients with "asymptomatic disease" complain of sluggish bowels or constipation, which improves after surgery and achievement of normocalcemia.

Cardiovascular System

Hypertension may occur in 50% of patients with hyperparathyroidism.[161] Convincing evidence of a pathogenic mechanism does not exist, however, and parathyroidectomy results in a reduction in blood pressure in a few of these patients.[162] Swedish investigators reported an association with myocardial ischemia and left ventricular dysfunction in patients with hyperparathyroidism and various symptoms, which exhibited reversibility after parathyroidectomy.[163]

Hypercalcemic Abnormalities

Hypercalcemic syndrome occurring as a result of hyperparathyroidism includes polydipsia and polyuria, anorexia, vomiting, constipation, muscle weakness and fatigue, mental status changes, and skin abnormalities. Patients developing markedly elevated serum calcium levels approaching 15 mg/dL may present with severe mental status changes or coma, a so-called hypercalcemic crisis. If untreated, this condition may progress to acute renal failure and the onset of dysrhythmias, which may precipitate sudden death.[164] Other abnormalities include metastatic calcifications at the corneal-scleral junction (so-called band keratopathy), shortened Q-T interval on electrocardiogram, ectopic calcium deposits in various organs, and pruritus. Some patients also may present with a nonspecific debility manifested by anorexia, fatigue, anemia, weight loss, and advancing osteitis, all of which are reversible after parathyroidectomy.

Clinical Course of Untreated Hyperparathyroidism

Several 8- to 10-year prospective studies have shown a benign course of untreated mild hyperparathyroidism in most patients, with no significant progression of symptoms, hypercalcemia, bone marrow density loss, or renal function impairment. No pathologic fractures or kidney stones developed during these observation periods.[165,166] There was evidence, however, of disease progression in 27% of patients, including marked hypercalcemia, hypercalciuria, or loss of bone mineral density in 10%.[167]

The clinical manifestations of hyperparathyroidism tend to relate to the level of hypercalcemia, even if this is not always evident because of slowed disease progression, individual susceptibility, and sex-dependent and age-dependent symptoms. Younger men are particularly prone to have renal stones, sometimes even with only mild hypercalcemia. For renal stones, the individual susceptibility is more than the level of hypercalcemia, and the risk of this particular symptom is probably more efficiently revealed by the patient history. In postmenopausal women, renal stones occur infrequently (generally <5%) and are often clinically silent.

Osteitis fibrosis cystica is currently uncommon in patients with primary hyperparathyroidism, and is most often seen in patients with severe hypercalcemia. Bone density measurements have shown an average reduction in cortical bone of 17% among current patients with primary hyperparathyroidism, however, and the bone loss tends to be the most pronounced in postmenopausal women.[167-169] Total and trabecular bone mass is often significantly but less markedly reduced.[170] No bone loss has been detected in postmenopausal women with borderline hypercalcemia, but losses were significant when the serum calcium level was greater than 2.74 mmol/L.[168]

Clinically evident renal failure is currently an unusual complication of primary hyperparathyroidism. Reduction of creatinine clearance and urinary concentrating capacity occur in more than one third of patients with mild hypercalcemia, however, indicating that impairment of glomerular and tubular function may occur silently.[168] Serum creatinine measurements are crude estimates, and increase only after creatinine clearance is substantially reduced. Serum creatinine levels also decrease with declining muscle mass of aging.[168]

Rare patients with initially mild hypercalcemia but rapidly advancing disease may have parathyroid carcinoma.[171] In addition, stepwise "clinical progression" may occur during observation in patients with primary hyperparathyroidism, possibly representing development of secondary mutations that cause accelerated growth of the tumor. Bleeding in parathyroid tumor may also cause an abrupt increase in serum calcium levels. A history of mild primary hyperparathyroidism has been reported in one third of patients with hypercalcemic crisis. Because it is impossible to predict whether progressive disease will occur in any patient, extended follow-up is crucial if surgery is deferred in primary hyperparathyroidism.[172-174] Younger patients seem to be at greater risk for progressive disease. Medical surveillance is inappropriate in younger patients and in patients with more marked hypercalcemia. The indications for surgical intervention and the alternative of medical surveillance are discussed later.

Diagnosis of Hyperparathyroidism

Evaluation of Hypercalcemia

Hypercalcemia has been reported to occur in 1% to 3.9% of the general adult population and 0.2% to 2.9% of hospitalized patients.[175] These patients present with widely variable clinical symptoms, depending on the severity of the elevated serum calcium. In most situations, mild hypercalcemia is asymptomatic, but severe hypercalcemia may become life-threatening, especially when the serum calcium is greater than 14 mg/dL.

The definition of hypercalcemia depends on the range of normal serum calcium—this is generally reported as 8.5 to 10.5 mg/dL. Variations in this normal range as reported by various laboratories depend largely on differences in assay procedures. Of circulating serum calcium, 47% binds to proteins, and approximately 10% binds primarily to albumin or complexes to circulating anions such as bicarbonate, phosphate, citrate, or sulfate. The remaining 43% is found as the free ionized form. Only the free ionized form of serum calcium exerts physiologic effects. Serum ionized calcium is the major regulator of PTH secretion.

Table 125-1

Causes of Parathyroid Hormone–Mediated Hypercalcemia

Primary hyperparathyroidism
Parathyroid adenoma
Parathyroid lipoadenoma
Parathyroid hyperplasia
Parathyroid carcinoma
Neck or mediastinal parathyroid cyst
Secondary hyperparathyroidism
Tertiary hyperparathyroidism

Several factors may influence measured serum total or ionized calcium. Alterations in serum albumin level increase or decrease serum total calcium without affecting the ionized calcium level. Of the circulating calcium that is bound to protein, 70% is albumin bound, having 12 calcium binding regions per molecule. Under normal circumstances, only about 20% of these specific calcium binding sites are actually occupied by serum calcium. Decreases in serum albumin less than 4 g/dL decrease total calcium by 0.8 mg/dL for each 1-g/dL decrease in serum albumin. Increases in serum albumin greater than 4 g/dL increase serum total calcium by 0.8 mg/dL for each 1-g/dL increase in serum albumin. Dehydration may increase total serum total calcium because of the resulting hemoconcentration. Acidosis increases serum ionized calcium by decreasing binding of calcium to albumin, and alkalosis decreases ionized calcium by increasing binding of calcium to albumin, without affecting serum total calcium. Under most clinical circumstances, it is adequate and appropriate to measure serum total calcium, but serum ionized calcium should be measured in clinical situations that may be associated with changes in albumin concentration or serum pH.[176,177]

Serum calcium reflects the balance between calcium influx into and calcium efflux out of extracellular fluid. Calcium influx into extracellular fluid is derived from intestinal absorption, skeletal resorption, and renal reabsorption, and calcium efflux out of extracellular fluid is determined by intestinal secretion, skeletal uptake, and renal excretion. Hypercalcemia usually results when the rate of calcium influx into the extracellular fluid exceeds the rate of calcium efflux out of the extracellular fluid.

The differential diagnosis of hypercalcemia is varied and extensive. The most common etiology of hypercalcemia in nonhospitalized patients is primary hyperparathyroidism, and the most common cause of hypercalcemia in hospitalized patients is malignancy. In most circumstances, the differential diagnosis of hypercalcemia may be categorically divided into causes that are mediated by PTH and causes that are not (Tables 125-1, 125-2 and 125-3). Hypercalcemia that is mediated by PTH is most frequently caused by primary hyperparathyroidism (see Table 125-1). Additionally, physiologic secondary hyperparathyroidism, which is defined as hyperparathyroidism caused by a physiologic source without associated renal insufficiency, or pathologic secondary hyperparathyroidism with associated renal failure may result in PTH-mediated hypercalcemia.

Secondary hyperparathyroidism from a nonrenal physiologic source may occur in patients with insufficient calcium intake, decreased intestinal calcium absorption, insufficient vitamin D intake or malabsorption, or renal hypercalciuria, and represents the homeostatic attempt to maintain a normal serum calcium level by any means necessary. It is important to distinguish physiologic secondary hyperparathyroidism from primary hyperparathyroidism before embarking on surgical correction of presumed primary hyperparathyroid disease.

Table 125-2

Causes of Hypercalcemia of Malignancy

Parathyroid hormone–related protein secretion by lung, esophagus, head and neck, renal cell, ovary, bladder, and pancreatic cancers; thymic carcinoma; islet cell carcinoma; carcinoid; sclerosing hepatic carcinoma
Ectopic parathyroid hormone secretion by small cell lung cancer, small cell ovarian carcinoma, squamous cell lung carcinoma, ovarian adenocarcinoma, thymoma, papillary thyroid carcinoma, hepatocellular carcinoma, undifferentiated neuroendocrine tumor
Ectopic 1,25-dihydroxyvitamin D production by B-cell lymphoma, Hodgkin's disease, lymphomatoid granulomatosis
Lytic bone metastases caused by multiple myeloma, lymphomas, breast cancer, invasive sarcoma
Tumor production of other cytokines by T-cell lymphomas/leukemias, non-Hodgkin's lymphoma, other hematologic malignancies

Pathologic secondary hyperparathyroidism and tertiary hyperparathyroidism occur as a result of renal insufficiency or renal failure. Hyperparathyroidism associated with these conditions results from subtle ionized hypocalcemia persisting over months to years, resulting in chronic stimulation of the parathyroid glands. Parathyroid glands may become autonomous after long-standing renal disease, and consequently no longer respond to regulation by serum ionized calcium in the course of developing tertiary hyperparathyroidism.

An important entity that must be considered in the differential diagnosis of hypercalcemia is familial hypocalciuric hypercalcemia.[178,179] This disorder has the ability to mimic the serum biochemical appearance of primary hyperparathyroidism, but is not treated surgically. Familial hypocalciuric hypercalcemia is an autosomal dominant disorder that is linked to chromosomes 3q, 19p, and 19q, and is largely caused by inactivating mutations in the parathyroid cell calcium-sensing receptor.[180] Patients with familial hypocalciuric hypercalcemia have low 24-hour urinary calcium excretion relative to their hypercalcemia. Presently, the most useful study to distinguish familial hypocalciuric hypercalcemia from primary hyperparathyroidism is the 24-hour urinary calcium-to-creatinine clearance ratio.[178] Patients with familial hypocalciuric hypercalcemia typically have ratios of less than 0.01, whereas patients with primary hyperparathyroidism have ratios greater than 0.01.

The second most common etiology of hypercalcemia is malignancy (see Table 125-2). Humoral hypercalcemia of malignancy, which is caused by excessive PTH-related protein secretion by tumors of various types, represents the most common source of malignancy-associated hypercalcemia.[181] Numerous solid tumors have been reported to secrete excessive PTH-related protein, including cancers of the lung, esophagus, head and neck, kidney, ovary, bladder, breast, and pancreas. Other tumors that have been variably noted to secrete PTH-related protein include thymic carcinoma, islet cell carcinoma, malignant carcinoid, and hepatic carcinomas. Patients with adult T-cell leukemia or lymphoma or B-cell lymphoma have also been variably shown to produce excess PTH-related protein.[182,183]

Ectopic PTH secretion has been shown in small cell lung cancer, small cell ovarian carcinoma, squamous cell lung carcinoma, ovarian adenocarcinoma, thymoma, papillary thyroid carcinoma, hepatocellular carcinoma, and undifferentiated neuroendocrine tumor.[184,185] Ectopic 1,25-dihydroxyvitamin D has been found to be secreted by B-cell lymphomas, Hodgkin's disease, and lymphomatoid granulomatosis.[186-190] Excessive cytokine production that may result in hypercalcemia has been associated with T-cell lymphomas and leukemias, non-Hodgkin's lymphomas, and other hematologic malignancies.

Table 125-3

Causes of Non–Parathyroid Hormone–Mediated, Nonmalignant Hypercalcemia

Benign Tumors
Parathyroid hormone–resecreting ovarian dermoid cyst or uterine fibroid
Endocrine Disease
Thyrotoxicosis
Pheochromocytoma
Addison's disease
Islet cell pancreatic tumors
VIPoma
Granulomatous Disorders
Sarcoidosis
Wegener's granulomatosis
Berylliosis
Silicone-induced and paraffin-induced granulomatosis
Eosinophilic granuloma
Tuberculosis (focal, disseminated, *Mycobacterium avium* complex in AIDS)
Histoplasmosis
Coccidioidomycosis
Candidiasis
Leprosy
Cat-scratch disease
Drugs
Vitamin D excess (oral or topical)
Vitamin A excess
Thiazide diuretics
Lithium
Estrogens and antiestrogens
Androgens
Aminophylline, theophylline
Ganciclovir
Recombinant growth hormone treatment of AIDS patients
Foscarnet
8-Chloro-cyclic adenosine monophosphate
Miscellaneous
Familial hypocalciuric hypercalcemia
Immobilization with or without Paget's disease of bone
End-stage liver failure
Total parenteral nutrition
Milk-alkali syndrome
Hypophosphatasia
Systemic lupus erythematosus
Juvenile rheumatoid arthritis
Recent hepatitis B vaccination
Gaucher's disease with acute pneumonia
Aluminum intoxication (long-term hemodialysis)
Manganese intoxication
Primary oxalosis

AIDS, acquired immunodeficiency syndrome; VIPoma, vasoactive intestinal polypeptide–secreting tumor.

Another source of hypercalcemia resulting from malignancy is that of calcium released by extensive lytic bone metastasis as a consequence of multiple myeloma, lymphomas, breast cancer, or invasive sarcomas.[191]

Table 125-3 is an extensive list of causes of non–PTH-mediated hypercalcemia. Nine tumors, including ovarian dermoid cysts or

uterine fibroids, may occasionally secrete PTH-related protein or other bone-resorbing cytokines.[192] Endocrine disorders, including thyrotoxicosis (resulting from increased bone resorption), pheochromocytoma (caused by coexisting primary hyperparathyroidism in MEN syndrome), adrenal insufficiency or crisis (caused by volume depletion or hemoconcentration), and VIPomas (resulting from excess secretion of vasoactive intestinal peptide causing dehydration and metabolic acidosis), may also cause non–PTH-mediated hypercalcemia.[193-197] Granulomatous disease in the absence of malignancy or endocrine disorder may be a source of hypercalcemia, especially in younger and middle-aged patients, and may manifest with elevated serum calcium levels. The source of this hypercalcemia is generally increased production of 1,25-dihydroxyvitamin D, and has been shown in patients with sarcoidosis, Wegener's granulomatosis, berylliosis, silicone-induced or paraffin-induced granulomatosis, eosinophilic granuloma, focal or disseminated tuberculosis, histoplasmosis, coccidioidomycosis, candidiasis, leprosy, and cat-scratch disease.[198-210]

Medications may cause hypercalcemia via various mechanisms. Excessive vitamin D intake, or hypervitaminosis D, may stimulate intestinal calcium absorption, and thiazide diuretics may directly inhibit renal calcium excretion.[211,212] Lithium compounds may interfere with the ability of calcium to interact with parathyroid and renal calcium-sensing receptors, increasing PTH secretion by the parathyroid glands.[213] Numerous other agents, including estrogens, antiestrogens, androgens, aminophylline, theophylline, ganciclovir, and recombinant growth hormone in acquired immunodeficiency syndrome (AIDS) patients, and hypervitaminosis A may affect other physiologic mechanisms resulting in hypercalcemia.[214-220] Miscellaneous disorders that can also be associated with hypercalcemia are listed in Table 125-3.

Diagnosis of Primary Hyperparathyroidism

The diagnosis of primary hyperparathyroidism is usually straightforward, and is based on minimal criteria involving the serum total calcium and measurement of intact PTH levels. Generally, patients present with increased serum total calcium with overtly increased or inappropriately high-normal PTH levels. Some patient with surgically proven primary hyperparathyroidism present with high-normal serum total calcium, and inappropriately high-normal or increased PTH levels. Patients with primary hyperparathyroidism almost always have documented increased serum total or ionized calcium sometime during the course of their disease, recognizing that serum calcium exhibits some variation over time.

It may be difficult to establish a diagnosis of primary hyperparathyroidism in patients in whom serum calcium documentations are noted to be in the middle to lower normal range over time, even if they are found to have increased intact PTH levels. This difficulty is due to the possibility that these patients may have physiologic secondary hyperparathyroidism (see earlier). Patients with serum calcium levels in the middle to lower normal range associated with increased intact PTH levels should be evaluated further to ensure that they do not have low calcium or vitamin D intake, calcium or vitamin D malabsorption, inability to convert 25-hydroxyvitamin D to biologically active 1,25-dihydroxyvitamin D, or significant hypercalciuria. These entities could explain why PTH levels are increased in the setting of serum calcium determinations in the middle to lower normal range.

Patients with primary hyperparathyroidism usually have serum phosphate levels in the low-normal to mildly decreased range. Patients with simultaneously high-normal or increased serum calcium and high-normal or increased serum phosphate should be investigated further for intestinal hyperabsorptive states or hypervitaminosis D.

Intact PTH, determined by current immunoradiometric or immunochemiluminometric assays, is mildly increased or inappropriately high normal for the level of simultaneously measured serum calcium in patients with primarily hyperparathyroidism. The use of current assays prevents any cross-reactivity between PTH and PTH-related protein, making the distinction between primary hyperparathyroidism and PTH-related protein–mediated hypercalcemia of malignancy certain. Patients with primary hyperparathyroidism almost always have suppressed PTH-related protein levels when checked, and patients with PTH-related protein–mediated hypercalcemia of malignancy almost always have suppressed intact PTH levels. Patients who are receiving thiazide diuretics or lithium compounds may have mild hypercalcemia and increased intact PTH levels without coexisting primary hyperparathyroidism, and so it is important to remove these medications for at least 1 month before assessing levels of serum total calcium and intact PTH to make the correct diagnosis. Hypercalcemic patients who are being treated with thiazides or lithium therapy and who have coexisting primary hyperparathyroidism have persistent hypercalcemia and increased intact PTH levels after discontinuation of the medication.

Accurate diagnosis of primary hyperparathyroidism is essential before surgical exploration and attempted parathyroidectomy. Careful attention to the biochemical parameters as described with special notice of the serum total calcium, phosphate, and intact PTH levels is essential in making the correct diagnosis. A 24-hour total urinary calcium level is also important in eliminating the possibility of familial hypocalciuric hypercalcemia from the differential diagnosis.

Localization Studies and Their Application

Although a comprehensive bilateral exploration of all appropriate cardinal parathyroid locations in the surgical management of hyperparathyroidism remains the gold standard, and must be fundamental to the armamentarium of all parathyroid surgeons, the development of more effective imaging methods or parathyroid localization has permitted surgeons to employ more limited procedures in neck exploration, while achieving the same, or improved, surgical outcomes as achieved by four-gland exploration.[74,221] Aside from the application of these imaging techniques for parathyroid localization in more limited, focused explorations of the neck for primary hyperparathyroidism, the use of localization studies before re-exploration for persistent or recurrent hyperparathyroidism has been universally accepted.[222-224] Localization methods may be operationally classified as preoperative (invasive or noninvasive) and intraoperative (Table 125-4).

Noninvasive Preoperative Localization

Pertechnetate (Technetium 99m) Thallous Chloride (Thallium 201) Imaging

Thallium uptake by parathyroid adenomas was initially reported by Fukunaga and others.[225-232] Subsequently, Ferlin and Young and their colleagues[226,227] performed the clinical application using Tc 99m together with thallium 201 (Tl 201). Subtraction of the resulting two

Table 125-4

Localization Studies in Hyperparathyroidism

Noninvasive Preoperative Methods
Ultrasonography
Radioiodine or technetium thyroid scan
Thallium-technetium scintigraphy
Technetium 99m sestamibi scintigraphy
Computed tomography scan
Magnetic resonance imaging
Invasive Preoperative Methods
Fine-needle aspiration
Selective arteriography or digital subtraction angiography
Selective venous sampling for parathyroid hormone assay
Arterial injection of selenium-ethionine
Intraoperative Methods
Intraoperative ultrasonography
Toluidine blue or methylene blue
Urinary adenosine monophosphate
Quick parathyroid hormone intraoperative

images helped to locate the abnormal parathyroid gland or glands. This technique required prolonged patient immobilization for obtaining images as the patient remained in the same position for both radionuclide administrations. Results of this localization technology have been variable, with sensitivity rates ranging from 27% to 82% reported.[228,229] Sensitivity has been reported to be improved by the application of single-photon emission computed tomography (SPECT) techniques with three-dimensional images.[230] The previously noted advantages of this imaging technique are widespread availability, minimal irradiation, and low risk. False-positive results, attributable to patient motion during the examination or as a result of concurrent thyroid abnormalities, have resulted in poor acceptance of this technique as a reliable preoperative localization method for limited parathyroid exploration.

Technetium 99m Sestamibi Scintigraphy

In 1989, Coakley and colleagues[231] reported using Tc 99m sestamibi for cardiac function studies. Chiu and coworkers[232] showed the incorporation of Tc 99m into the cytoplasm and mitochondria of mouse fibroblasts in response to certain stimuli. Parathyroid cells have large numbers of mitochondria that enable sestamibi to enter parathyroid tissue more intensely than into the neighboring thyroid parenchyma.[233] O'Doherty and associates[234] compared radionuclide uptake in parathyroid tissue, and noted a greater uptake per gram for sestamibi than for Tl 201.

In 1992, Taillefor and colleagues[235] proposed a dual-phase scan using Tc 99m sestamibi and cervicothoracic planar parathyroid scintigraphy. In this method, the patient is intravenously injected with 20 to 25 mCi of Tc 99m sestamibi. Subsequent images are obtained at 10 to 15 minutes and then at 2 to 3 hours after the injection. Late phase is usually preferable for detecting parathyroid adenomas because the thyroid and thyroid nodules clear of uptake faster than do parathyroid neoplasms. Jofre and associates[236] showed that 70% of delayed images are best seen at 2 hours, and only 15% are best seen at 4 hours. In certain circumstances, oblique or lateral images can be obtained to attempt to add a third dimension to the study. The advantages of the technique include the ability to use this imaging method without patient immobilization between images.

The sensitivity reported for solitary adenomas is 100%, with a specificity of approximately 90%.[237-239] Few false-positive results have been reported using this imaging technique, and are predominantly due to solid thyroid nodules, predominantly adenomas.[240] Hürthle cell carcinoma and malignant thyroid lymph node metastases have also been noted to result in false-positive sestamibi imaging results; however, cystic lesions of the thyroid gland have not.[74,241]

False-negative results may be attributable to smaller parathyroid adenoma size or suboptimal dosing of Tc 99m sestamibi.[74] Intrathyroid, mediastinal, and deep cervical parathyroid glands have been located with Tc 99m sestamibi; location seems to be independent of its efficiency (representing an advantage over technetium/thallium subtraction scanning). This technique has shown the presence of multiple-gland disease in the form of double parathyroid adenomas (Fig. 125-4).[74] Sestamibi, similar to Tl 201, is inaccurate in patients with diffuse four-gland parathyroid hyperplasia.

Tc 99m sestamibi has been combined with iodine 123 and recorded simultaneously in nonoverlapping windows and subtraction. In a series by Hindie and colleagues,[242] 25 of 27 solitary adenomas were identified with a sensitivity of 94%. In the same population, examination with Tc 99m sestamibi as the sole radionuclide identified 22 of these 27 patients correctly for a sensitivity of 79%. Neumann and associates[243] used Tc 99m sestamibi/iodine 123 subtraction and SPECT in patients with secondary hyperparathyroidism with a sensitivity of 77%. In this series of 13 patients with recurrent secondary hyperparathyroidism, all hyperplastic parathyroids were predicted and subsequently correctly identified at surgery.

Technetium 99m Sestamibi with Single-Photon Emission Computed Tomography

The application of SPECT uses a camera collimator that rotates 360 degrees around the patient in the axial plane, and in essence portrays a three-dimensional image as the sequence progresses from mandible through the thorax. Some investigators have shown a superior sensitivity and localization in the early phase compared with cervicothoracic planar images, whereas the delayed images are approximately equivalent.[244] The images appear to have a higher resolution and have two definite recognized advantages over planar sestamibi images: (1) anatomic localization in ectopic adenomas within the carotid sheath, and (2) localization of mediastinal lesions to the anterior or posterior compartment, allowing planning of surgery by lateral thoracotomy versus median sternotomy.[245]

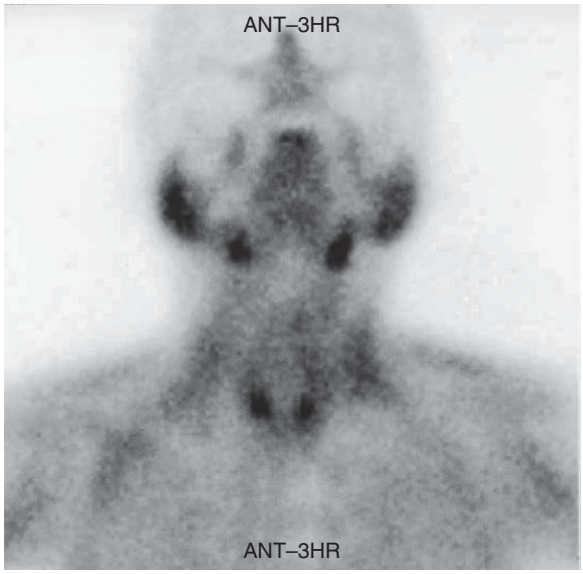

Figure 125-4. Two-hour delayed Tc 99m sestamibi nuclear scan in a patient with hyperparathyroidism secondary to double parathyroid adenomas. Nuclear uptake is shown bilaterally on the image, indicating the location of both adenomas confirmed at surgery.

Computed Tomography–Sestamibi Fusion

Although the regional anatomic localization provided by MIBI-SPECT imaging has been shown to be superior over that of planar imaging, the anatomic relationship of imaged parathyroid tissue with other cervical structures (bony, vascular, visceral) is not clearly defined by these physiologic imaging techniques. Computed tomography (CT)–sestamibi fusion is a combined imaging modality whereby anatomic and physiologic images are combined (fused) to create a single image providing concise anatomic localization of physiologically hyperactive parathyroid tissue (Fig. 125-5). Images are created after the acquisition of contrast-enhanced CT scans of the neck and mediastinum and a standard Tc 99m sestamibi scan with planar and SPECT imaging. The delayed (3-hour) SPECT image is "fused" with the CT scan using specialized software, which provides an automated alignment using a matrix of coordinates. The radiopharmaceutical uptake resolution within the fused image is fine-tuned manually by the radiologist to produce the final localized region. Images are depicted in three dimensions (axial, coronal, and sagittal) in 3-mm slices to provide precise anatomic localization and correlation with other central neck structures in each plane of orientation.

One of the authors (P.K.P.) has accrued experience with this technique in more than 300 patients; the analysis of this experience has yielded specific clinical settings for which this modality has shown clear superiority over planar and SPECT imaging. These settings include refining the directed "minimally" invasive approach (Fig. 125-6); the accurate localization of ectopic glands (i.e., thymic, retroesophageal, mediastinal, intrathyroid) (Figs. 125-7, 125-8, and 125-9); and for patients in whom re-exploration is being carried out in a previously operated region with significant fibrovascular change (Figs. 125-10 and 125-11), to focus the approach and limit dissection in hopes of minimizing the risk of complications. In contrast, early experience suggests that CT-MIBI fusion has limited advantage in distinctly localizing

solitary parathyroid glands that are tightly juxtaposed to the thyroid capsule, especially inferior glands. Although CT-MIBI fusion has shown superiority over conventional sestamibi imaging, selection criteria for routine implementation have not been defined and require further investigation.

Ultrasonography

High-resolution ultrasonography (10 or 12 MHz) was introduced by Edis and Evans in 1979.[246] High-resolution ultrasonography provides for sonographic exploration of the thyroid, carotid, and jugular areas and the cervical area between the thyroid cartilage and the sternal margin. The advantages of this technique are that it is easy to perform, it is well tolerated by the patient, it does not require the injection of a radiotracer, and it can be performed rapidly and at low cost. Disadvantages include localization of enlarged parathyroid glands in the retroesophageal, retrotracheal, retrosternal, and deep cervicothoracic inlet regions. Intrathyroid parathyroid adenomas have reportedly been localized more efficiently with ultrasonography than with other techniques, although they may be confused with cystic thyroid lesions.[247] The sensitivity of ultrasonography in identifying abnormal parathyroid glands varies according to the ultrasonographer's experience, the frequency of the transducer, the resolution of the image, and parathyroid gland size.[248]

Gray-scale ultrasound with high-resolution linear array transducers is the ideal modality for parathyroid study. Transverse and longitudinal scans are required. Transverse scans are useful in identifying adenomas, whereas longitudinal scans better show the relationship of the adenoma to the thyroid and its internal architecture and vascularity. A parathyroid adenoma typically appears as a hypoechoic mass posterior or inferior to the thyroid gland in its usual extracapsular location. Retrothyroid lesions tend to be oval or flat, whereas infrathyroid lesions are usually spherical. Some parathyroid adenomas may show cystic portions within, but calcification is rare. Given that the most common false-positive image with a Tc 99m sestamibi image is that caused by a thyroid adenoma (Fig. 125-12), this particular entity may be reconciled with adjunctive ultrasonography. A discrete blood supply to the mass within the thyroid parenchyma identified by color Doppler suggests a diagnosis of intrathyroidal parathyroid adenoma, rather than a lesion of the thyroid itself (Fig. 125-13).

False-positive ultrasound studies have resulted from thyroid nodules, adenopathy, and esophageal lesions.[248] The presence of surgical clips can also make interpretation more difficult. The overall false-positive rare has been reported to be approximately 15% to 20%.[247,249,250]

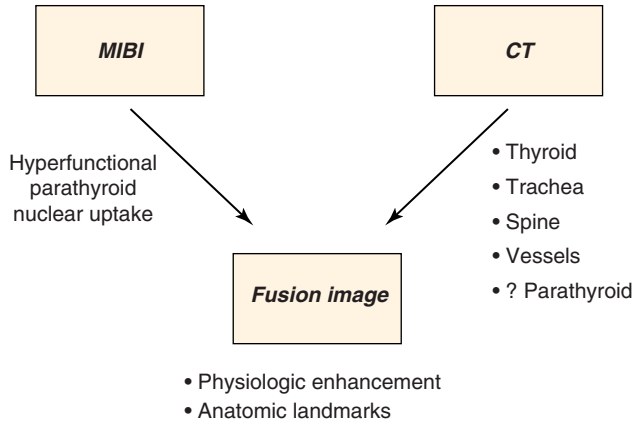

Figure 125-5. Schematic depicting combination imaging for parathyroid localization exploiting the characteristics of nuclear uptake with Tc 99m sestamibi and CT.

Computed Tomography

CT is a less sensitive method than magnetic resonance imaging (MRI). It is relatively expensive, exposes the patient to radiation, and

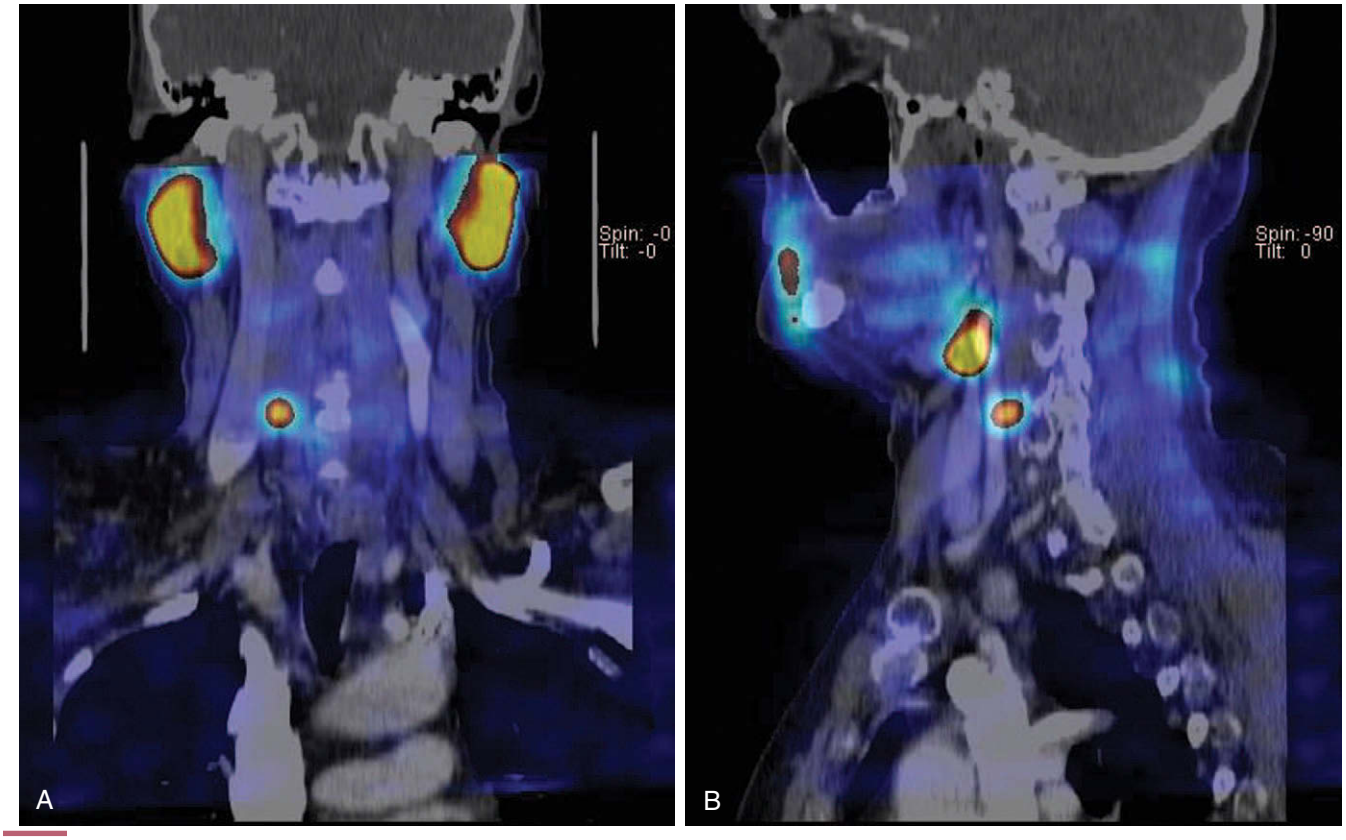

Figure 125-6. **A** and **B,** CT-MIBI fusion image in coronal and sagittal planes showing ectopic superior parathyroid adenoma located superior to the thyroid lobe.

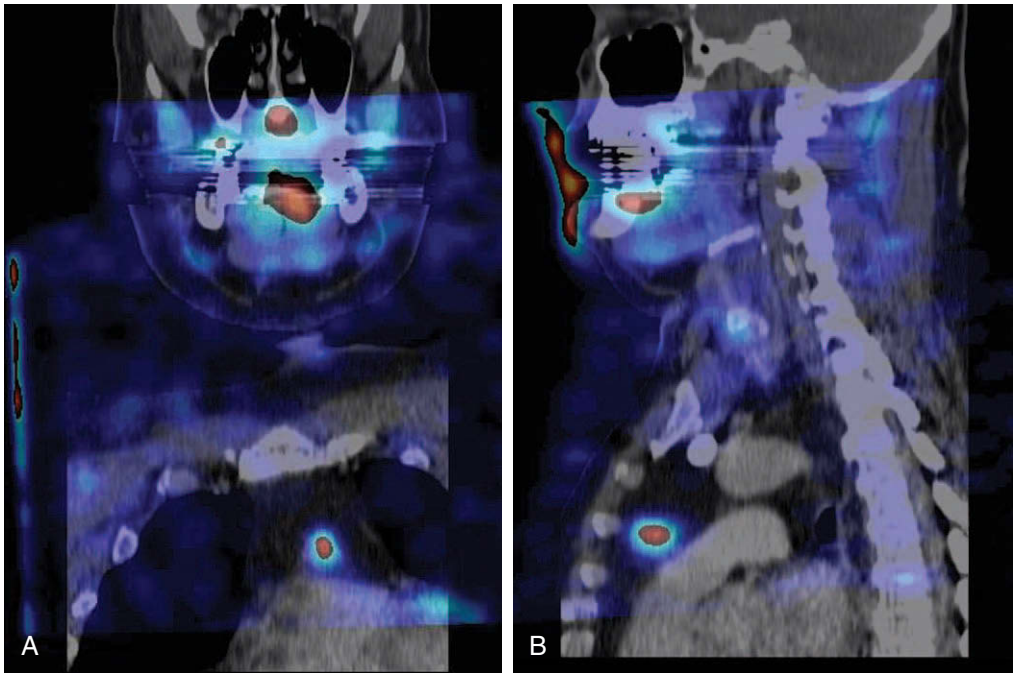

Figure 125-7. **A** and **B,** CT-MIBI fusion image showing ectopic parathyroid adenoma within anterior mediastinal compartment in coronal and sagittal planes.

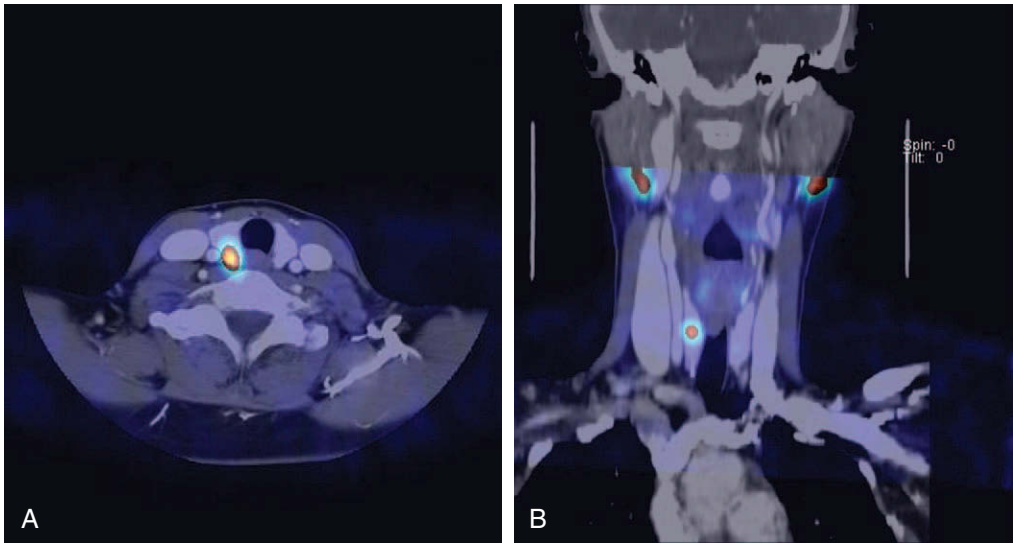

Figure 125-8. **A** and **B,** CT-MIBI fusion image (axial and coronal planes) showing ectopic hyperplastic supernumerary parathyroid gland within the thyroid lobe in a patient with multiple endocrine neoplasia syndrome type I.

requires the administration of contrast material to obtain optimal imaging. It may be useful for ectopic parathyroid glands (retrotracheal, retroesophageal, and mediastinal), but is less effective for parathyroid adenomas that reside in a normal anatomic location. Metal clips distort the image of CT. Perithyroidal lymph nodes and ectopic vasculature may make identification of adenoma difficult.[251] This technique does not selectively image endocrine tissue, and is not physiologically based, supplying only anatomic information. False-positive results are usually more frequent than with other techniques and may be 50%, making this technique impractical for most clinical situations.[252,253]

Magnetic Resonance Imaging

MRI is generally believed to be superior to CT because it does not require the administration of radioiodinated contrast material, and there is no interference from surgical clips left in the neck after initial exploration. A parathyroid neoplasm usually has a low signal intensity in T1-weighted imaging (similar to muscle or thyroid) and a high signal intensity (more than or the same as fat) in T2-weighted imaging (Fig. 125-14).[254]

MRI may be more useful for identifying ectopic parathyroid tissue. In an investigation evaluating patients undergoing reoperation for recalcitrant hyperparathyroidism, Jeelos and colleagues[255] noted that MRI localized 79% of ectopic glands and only 59% of enlarged glands situated in a normal position. Parathyroid adenomas located in a superior position have been noted to be difficult to locate posterior to the thyroid at the level of the cricoid cartilage.[256]

The sensitivity for MRI has been reported to be superior than that for CT, ranging from 50% to 80%.[252,255] MRI, similar to Tl 201 scanning, shows false-positive findings as a consequence of enlarged lymph

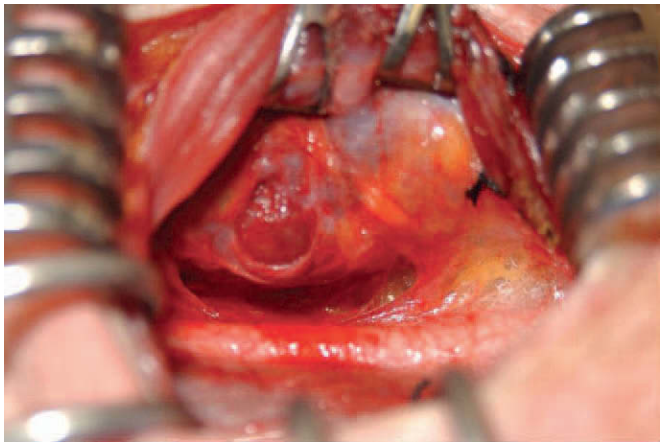

Figure 125-9. Intraoperative photograph showing thyroid lobotomy to expose intrathyroid parathyroid gland in the patient from Figure 125-8.

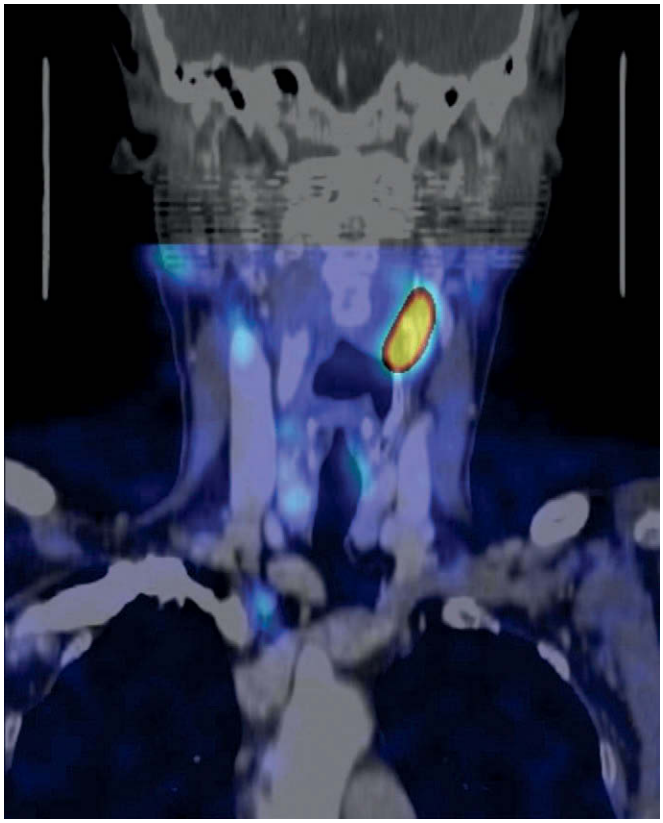

Figure 125-10. Sagittal CT-MIBI fusion image showing intense focus of nuclear activity in left superior position in a patient with hyperparathyroidism who previously underwent total thyroidectomy and neck dissection for thyroid cancer.

nodes.[257] Thyroid adenomas may also lead to false-positive results with MRI.

MRI and CT offer limited application in preoperative localization; however, the relative cost of these procedures and their inconsistent results generally preclude their universal use before initial exploration. MRI and CT are important modalities to be used in patients who have recalcitrant hyperparathyroidism and require re-exploration.

Invasive Preoperative Localization

Invasive localization studies are indicated when the combined results of noninvasive tests are negative, equivocal, or conflicting. These studies

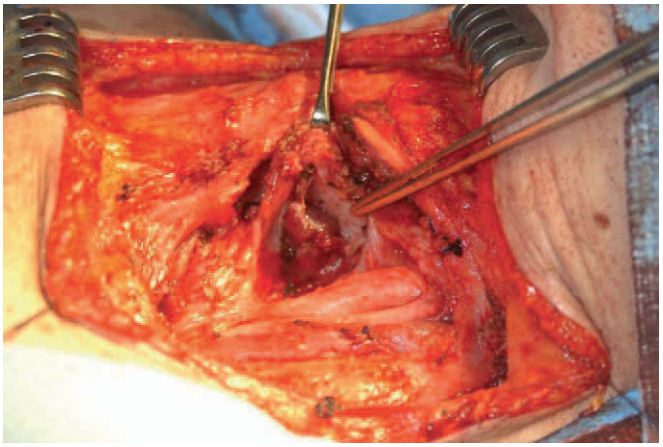

Figure 125-11. Intraoperative photograph showing large parathyroid adenoma in previously operated central neck compartment in the patient from Figure 125-10.

Figure 125-12. Tc 99m sestamibi nuclear scan in a patient with hyperparathyroidism and nodular thyroid disease. Nuclear uptake in right lower cervical region on delayed image represents uptake by a thyroid adenoma.

are generally indicated in the setting of recalcitrant hyperparathyroidism before re-exploration.

Parathyroid Arteriography

Appropriate parathyroid arteriography includes examination of both thyrocervical trunks (search for glands in the superior mediastinum, tracheoesophageal sulcus, or intrathyroid or juxtathyroid glands), the internal mammary arteries (glands in the thymus and the anterior mediastinum) and carotids (juxtathyroid or undescended glands), and sometimes the selected catheterization of the superior thyroid artery. Parathyroid adenomas appear highly vascularized and oval or round in shape. Conventional arteriography has a reported sensitivity of about 60%, although the results obtained with digital subtraction arteriography are slightly better.[258-260]

Selective Venous Sampling for Parathyroid Hormone

Angiography is performed primarily to outline the venous drainage, facilitating sampling for PTH assay. This investigation is expensive and technically difficult. Sampling must be obtained as selectively as possible from the smallest venous branch to document the exact location of the parathyroid tumor.[261] Published reports suggest, however, that

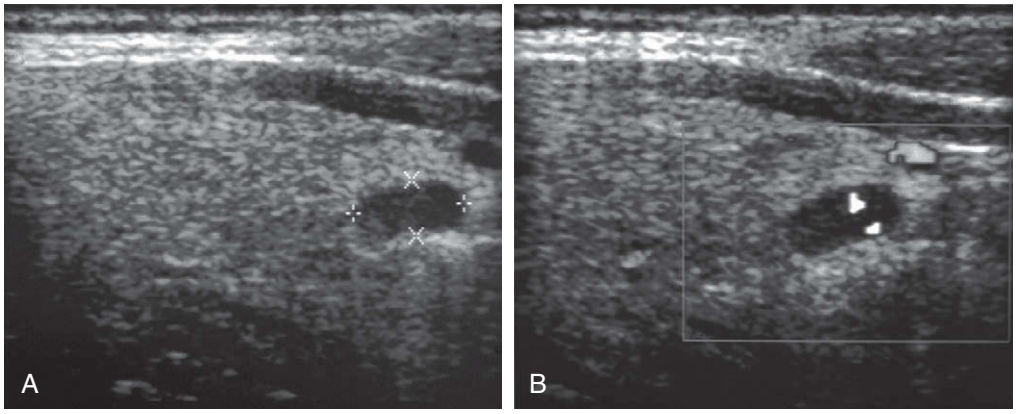

Figure 125-13. **A,** A small but hyperfunctioning parathyroid adenoma is shown on sagittal ultrasonography to be completely within the thyroid gland. **B,** Doppler ultrasonography shows a discrete blood supply that differs from the more diffuse perinodular vascular support for a thyroid adenoma from its surrounding parent gland.

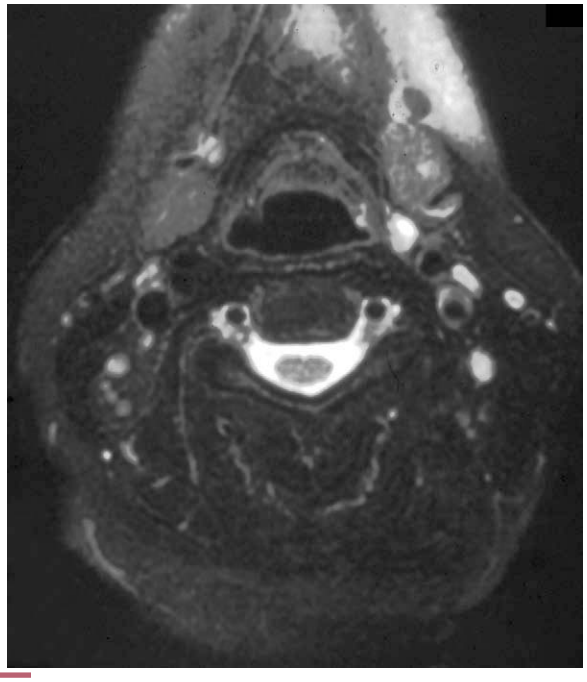

Figure 125-14. MR image showing a mass in the left submandibular triangle consistent with an undescended superior parathyroid adenoma.

sampling from large veins such as the internal jugular vein, innominate vein, and superior vena cava may yield optimal results.[262] A twofold gradient between the PTH concentration in peripheral blood and that in the selectively sampled venous tributary establishes the site of the venous drainage from the tumor.

This technique is generally believed to be the most sensitive, lateralizing about 80% of the parathyroid tumors.[255,259,263,264] It seems to be just as effective in localizing mediastinal glands as it is for cervical glands, and depends on physiologic properties of the parathyroid gland rather than size. It may be helpful in multiple-gland disease, and has the ability to reconcile an equivocal noninvasive study so that localization may be achieved.

Ultrasound-Guided Fine-Needle Aspiration

Fine-needle aspiration of a parathyroid tumor performed under ultrasound guidance may offer an improvement over the results obtained with ultrasound. Fine-needle aspiration may provide for direct cytologic examination, or it may facilitate the use of a bioassay of the aspirate to determine PTH level. When the aspirate is positive for PTH, it confirms the presence of parathyroid tissue within the enlarged gland.[265] PTH determination is generally more helpful than cytology examination for diagnosing parathyroid lesions because of the difficulty in differentiating between parathyroid and thyroid tissue in such a limited sample.[266] In one study reported by Tikkakosky and associates,[267] 100% of abnormal parathyroid glands were diagnosed by bioassay, but only 60% were diagnosed by cytologic examination.

Intraoperative Localization Methods

High-resolution intraoperative ultrasonography may be useful in many operative settings, including primarily re-exploration for hyperparathyroidism in a neck that shows significant surgical fibrosis. The injection of methylene blue or toluidine blue is of little value because the pathologic gland has to be identified.[268] Methylene blue has been used in the setting of reoperation within 1 to 2 days after initial parathyroidectomy for persistent hyperparathyroidism. Because postoperative edema and seroma fluid makes re-exploration difficult in this circumstance, the blue color may be helpful in identifying parathyroid tissue.

Norman and colleagues[269,270] have advocated radiation-guided parathyroid gland identification and removal. Hand-held gamma probes developed for operating room use are used to detect the gland concentrating Tc 99m sestamibi, which is injected on the day of operation usually within approximately 2 hours of the operation. The initial scan provides information regarding localization of putative adenomas and the presence of delayed uptake of nuclear material within the thyroid gland. If excessive delayed activity is present in the thyroid, the patient is subjected to thyroid suppression for 6 to 8 weeks before operation to reduce background radiation in the thyroid bed, and to increase the accuracy of the probe. This is the usual circumstance in reoperative settings. After identification and removal of the abnormal gland or glands, the final abnormal gland removed is checked for the degree of radioactivity ex vivo against background tissues in the surgical bed. Based on previous reported data, excised glandular tissue emitting radiation greater than 20% of that found in tissues in the surgical bed was confirmed as the hyperfunctional parathyroid tissue implicated in disease.[269]

Surgical Management

Indications for Exploration

The decision to perform surgical exploration in a medically stable patient with primary hyperparathyroidism is predicated on the potential for development of complications from prolonged exposure to hypercalcemia and the long-term benefit of surgery. Generally, patients should be assessed for the risk of developing complications on the basis of disease severity at the time of diagnosis; patients who have received a previous diagnosis in whom complications have arisen over a short interval since the diagnosis are at significant risk of developing further problems.

Patient age should not represent an exclusive determinate of candidacy for surgery; general medical condition and the potential for pursuing an active lifestyle should play a more prominent role in determining the recommendation for treatment. Generally, younger patients, who potentially will have longer exposure to hypercalcemia, are at a substantially greater risk for developing complications.

The severity of hypercalcemia represents a consideration in the decision to perform surgery. Although no absolute level of serum calcium provides stringent criteria for surgery, most endocrine surgeons consider a serum calcium level of 11.5 mg/dL or greater as an absolute indication for surgery. Surgery in postmenopausal women should be given special consideration independent of the severity of hypercalcemia or absence of symptoms. Women in this population are at greater risk for development of long term skeletal complications from generalized demineralization and osteopenia (i.e., hip and vertebral fractures).[271]

A major factor to be considered in determining the need for surgery is the potential for long-term benefits and prospects for cure. In 85% to 90% of patients, hyperparathyroidism occurs as a result of a single adenoma. Exploration and removal of the adenoma is curative in greater than 95% of patients, and the long-term benefit and potential for cure is high. Primary hyperplasia occurs in approximately 10% to 12% of patients with hyperparathyroidism. Surgery in these patients involves subtotal parathyroidectomy, with the amount of tissue left ultimately determining the long-term benefit of the surgery. Because of the variable amount of parathyroid tissue left in the neck, and potential for variable activity, the prospect for cure is less reliable than for patients with adenoma. These patients have cure rates significantly reduced compared with patients in whom an adenoma is removed.[272]

Because of the considerations mentioned previously, the decision to perform surgery on patients who seem asymptomatic and who have no obvious metabolic complications is problematic. Although early surgical intervention seems to be favored, stringent criteria as to whether or not these patients should undergo surgery have not been clearly defined. About 50% of asymptomatic patients go on to develop metabolic complications from hyperparathyroidism within 5 to 7 years of the onset of hypercalcemia.[273]

Because of the uncertainties about the indications for surgery in asymptomatic patients, a consensus conference held by the National Institutes of Health in 1990 addressed the question of management in this clinical situation.[274] Recommendations for surgical management or surveillance or both for patients with primary hyperparathyroidism derived from that conference predated much of what has evolved over the course of the last decade with respect to clinical experience with asymptomatic primary hyperparathyroidism, the evolution of contemporary surgical technique, and the development of newer technologies in preoperative localization. This conference was reconvened in early 2002 in an effort to re-evaluate the original recommendations from the 1990 symposium and contemporize recommendations on the management of asymptomatic primary hyperparathyroidism.[275] The indications for surgery as suggested by the conference are as follows:

1. Serum calcium is greater than 1 mg/dL above the upper limit of normal.
2. Creatinine clearance is reduced more than 30% for age in the absence of another cause.
3. Measurement of 24-hour urinary calcium is greater than 400 mg/dL.
4. Patients are younger than 50 years of age.
5. Bone mineral density measurement at the lumbar spine, hip, or distal radius is reduced more than 2½ standard deviations (by T-score).
6. Patients request surgery, or patients are unsuitable for long-term surveillance.

These recommended indications are conservative; they provide a framework for surgical decision making, but are not absolute or universal. The decision to perform surgery on a patient with primary hyperparathyroidism and metabolic complications is straightforward. The decision is less clear in asymptomatic patients and must be guided by the potential benefits of surgery, the patient's risk of developing complications from disease, the wishes of the patient, and, importantly, the experience of the surgeon. The success rate of surgery and the incidence of complications after parathyroidectomy have been documented to vary greatly depending on the surgeon's experience. In one study, experienced Swedish surgeons achieved normal calcium in greater than 90% of patients with recurrent laryngeal nerve complications in less than 1%. Surgeons who perform fewer than 10 parathyroidectomies per year had a success rate of 70%, but with 15% of patients remaining hypercalcemic and 14% becoming permanently hypocalcemic.[276] In weighing potential benefits of surgery against risks for patients with asymptomatic hyperparathyroidism, the experience of the surgeon should be a primary consideration.

Although patients with mild to moderate hypercalcemia seldom experience rapid elevation in serum calcium level, hypercalcemia and the risk of developing occult symptoms and risks for potential end organ damage increase with time. As a result, patients with untreated primary hyperparathyroidism are at risk for major morbidity and mortality from cardiovascular disease.[277,278] The benefits derived from parathyroidectomy in patients with occult or minimally symptomatic disease were discussed earlier in the section on clinical manifestations of hyperparathyroidism. In addition, parathyroidectomy seems to offer a distinct and measurable advantage in patients with mild asymptomatic primary hyperparathyroidism, as indicated by the results of a randomized trial in which patients were subjectively surveyed using a standardized health survey instrument.[279] In this investigation, patients with mild symptomatic hyperparathyroidism were randomly assigned to surgery or observation, and assessed every 6 months after randomization for 2 years using the SF-36 Health Survey, an instrument that measures wellness.[280] Significantly improved function was noted in patients after parathyroidectomy compared with patients who were observed.

Technique of Parathyroidectomy

(see Key Indicator Video on website)

Anesthesia and Preparation

Exploration of the neck in patients with hyperparathyroidism is generally performed under general anesthesia with endotracheal intubation. In patients who are medically unfit for general anesthesia, parathyroid exploration for removal of a solitary adenoma localized preoperatively may be performed under local anesthesia supplemented by intravenous sedation.[281,282]

Positioning of the patient on the operating table is very important. The patient's neck should be hyperextended dorsally to provide optimal access to the neck, particularly in patients with a short wide neck, and access to the cervicothoracic junction. The arms of the patient should lie along aside the body to allow the surgeon and the assistant to stand on both sides of the neck comfortably. Long ventilation tubes are helpful in facilitating placement of the ventilator at some distance from the operating table, which allows for rotation of the operating table away from the anesthesia personnel. Patients in whom exploration is being performed in a directed or minimally invasive fashion should have an accessible intravascular site, intravenous or intra-arterial, from which a peripheral sample of blood may be drawn to assess PTH levels intraoperatively. After complete positioning and preparation of the patient on the operating table, the table may be adjusted in the reverse Trendelenburg position to decrease venous congestion around the thyroid bed and central neck.

Exploration of the Neck

A low transverse cervical incision (Kocher) is designed two fingerbreadths above the suprasternal notch, usually over a natural skin crease, and is carried down through the platysma. The incision may be tailored according to the surgeon's preference with respect to the type of exploration being carried out. More directed, focused procedures

Figure 125-15. Exposure achieved through anteromedial rotation of the thyroid gland with demonstration of superior and inferior parathyroid gland positions.

require a shorter incision than a traditional bilateral four-gland exploration. In any event, the incision should not extend beyond the sternocleidomastoid muscles. After incising the platysma, the cranial skin-platysma flap is dissected upward to the notch of the thyroid cartilage, and the caudal-platysma flap is dissected inferiorly to the suprasternal notch. A self-retaining retractor is useful in spreading the cranial and caudal flaps to expose the midline strap muscles in the region of the thyroid bed and central neck structures. The midline raphe of the strap muscles is identified and separated from the thyroid notch to the suprasternal notch, allowing the sternohyoid muscles to be retracted laterally. It is usually unnecessary to divide the sternohyoid muscles. The sternothyroid muscle is separated over the thyroid lobe on the side of the neck to be explored first, carefully elevating the muscle away from the thyroid capsule.

In contrast to the plane between the strap muscles, which is predominantly avascular, the plane separating the sternothyroid muscle from the true thyroid capsule may be quite vascular, and particular attention to hemostasis is important in carrying out this maneuver. Hemostasis during parathyroid exploration cannot be overemphasized because blood-stained tissues hinder the ability of the surgeon to identify abnormal and normal parathyroid glands within the fatty tissue of the central neck.

The thyroid lobe on the side being explored is retracted anteromedially to access the potential space posterior to the thyroid lobe. This is facilitated by exposing the dominant middle thyroid venous tributaries, dividing and ligating them to access this region. Ligation of the superior or inferior thyroid artery is unnecessary for adequate rotation of the thyroid anteromedially during this maneuver.

After this region has been accessed, blunt dissection of fibroareolar tissue facilitates evaluation of the area where normal and abnormal parathyroid glands generally reside. This dissection permits visualization or palpation, or both, of enlarged parathyroid tissue with minimal dissection to prevent staining of tissues with blood. It is essential to maintain anteromedial retraction of the thyroid gland to expose the angle of visualization and subsequent exploration (Fig. 125-15); this is facilitated further by opening the fascial sheath (pretracheal fascia) connecting the carotid sheath and the thyroid gland. This maneuver provides access to the paraesophageal and retroesophageal spaces. Although identification of the recurrent laryngeal nerve is not generally mandatory, dissection in either the retroesophageal or paraesophageal space requires visualization of the nerve to prevent injury.

A systematic approach to the surgical identification of the parathyroid glands is essential to ensure a high success rate, and to avoid missing abnormal glands. It is important to develop a methodical and disciplined sequence of exploration to minimize the potential for missing either normal or abnormal glands. The ability to palpate abnormal glands cannot be overemphasized. Often glands within the paraesophageal space just dorsal to the juxtaposition of the recurrent laryngeal nerve and the inferior thyroid artery may be palpated before they are seen. Palpation in this area generally directs the surgeon to this region so that focal areas of meticulous dissection may be carried out, minimizing the potential for significant tissue staining by blood and inadvertent devascularization of normal parathyroid glands. Initial palpation along the posterior aspect of the thyroid capsule, especially adjacent to the superior pole above the inferior thyroid artery entrance to the gland, sometimes reveals the presence of an enlarged superior parathyroid gland closely situated against the true thyroid capsule underneath a covering of pretracheal fascia.

Depending on surgical preference, the usual trend is to identify the inferior glands initially. They tend to be larger and more anterior; however, their location may also be less predictable and constant. Typically, they are found adjacent to the inferior pole of the thyroid gland or within a tongue of thymic tissue inferior to the thyroid, the so-called thyrothymic ligament. Commonly, the inferior glands may be located anterior and slightly medial to the juxtaposition of the inferior thyroid artery and recurrent laryngeal nerve. The superior parathyroid glands are most commonly found along the posterior capsule of the thyroid gland at a point slightly lateral and posterior to the juxtaposition between recurrent nerve and inferior thyroid artery. Blunt dissection along the posterior capsule often reveals the superior gland to be suspended in a teardrop fashion within 1 cm of the entrance of the recurrent laryngeal nerve under the cricothyroid muscle. A helpful maneuver in exposing this superior location is to divide the sternothyroid muscle close to the superior thyroid pole to provide maximal medial mobilization without devascularizing the superior pole of the thyroid gland.

Parathyroid glands are often (partially) surrounded by fat. Any lobule of fat that is noted at sites that may harbor parathyroid glands should be carefully inspected. This inspection is facilitated by opening the thin fascia that covers the fat lobule and applying pressure allowing the parathyroid gland to extrude or "blossom" out of the fat. Most normal parathyroid glands have a light brown or tobacco color. This color is important in differentiating parathyroid glands from fat, which is generally more yellow, versus thyroid nodules, which are more rust-red in color.

Parathyroid glands also have a degree of freedom of mobility along the true thyroid capsule in relationship to the thyroid gland. It is helpful to dissect bluntly along the thyroid capsule with a Kitner (peanut) dissector to visualize moving structures within fat and adjacent to the true thyroid capsule. The close relationship of the pretracheal fascia overlying these pseudosubcapsular parathyroid glands allows this freedom of movement on blunt dissection. In contradistinction, a thyroid nodule mimicking a parathyroid gland does not enjoy this freedom of movement, and is more firmly attached to the central thyroid lobe without a plane of cleavage between it and the thyroid gland, and without a vascular pedicle.

Perithyroidal lymph nodes, particularly those within the thyrothymic ligament, may be confused with parathyroid glands. The consistency of lymph nodes is more firm, however, than that of parathyroid glands, and lymph nodes are noted to be more of a translucent white-gray than are parathyroid glands.

During the exploration for normal and abnormal parathyroid glands, the vascular anatomy of these glands should be observed. Dissection of the superior parathyroid glands should be initiated at the outermost tip of this gland to prevent injury to the parathyroid vessels, which usually ascend from arterial anastomoses originating from the inferior thyroid artery. The dissection of the inferior parathyroid gland should begin at the caudal end of the parathyroid because the vascular pedicle generally enters on the upper or cranial side of the inferior parathyroid gland. Suspected devitalization of a normal parathyroid gland during dissection generally requires that it be autotransplanted within cervical muscle. This procedure involves sharply fragmenting the gland into cubic millimeter pieces and implanting them in a hemostatic fashion within the sternocleidomastoid muscle of the same side.

After it is identified, the abnormal gland is removed and sent for pathologic analysis. A thorough search is conducted to locate the second gland on the same side; if found, it too is removed and sent for pathologic determination. If the enlarged gland is reported as hypercellular, and the second gland is normal or suppressed, the operation proceeds by accessing the viscerovertebral angle of the opposite side. Surgical

preference and the type of procedure advocated (directed unilateral versus traditional bilateral) determine the extent of exploration at this point. If the biopsy specimen of the second gland on the side explored first is found to be abnormal, or if it appears enlarged, all four glands should be identified and histologically examined. In this instance, the presumptive diagnosis is hyperplasia, which requires subtotal (3½ gland) parathyroidectomy. The distinction between adenoma and hyperplastic parathyroid tissue is difficult or impossible on frozen section analysis; the surgeon cannot rely on histologic analysis of a single gland for definitive therapy.

The appearance of normal and diseased parathyroid tissue is generally readily recognizable, provided that the fibroareolar tissues remain free of excessive blood staining. In contrast to normal parathyroid tissue, parathyroid adenomas appear rust-red or beefy red in situ. They may be mottled or variegated in their coloring, and usually lighten on resection. In contrast, hyperplastic glands generally appear darker than adenoma, usually a dark rust, brown, or chocolate color resembling more the color of thyroid tissue.

Failure to identify a missing gland suspected to be an adenoma or, in the case of hyperplasia, failure to locate all glands mandates a thorough dissection in an effort to locate abnormally located or ectopic parathyroid tissue. A systematic approach is undertaken to examine all areas potentially harboring an ectopic gland. It is imperative that the surgeon know which gland is missing with the understanding that a search is predicated on the likely variable or ectopic sites. Surgical dissection should address all areas accessible through a cervical approach, including the removal of thymic tissue within the superior mediastinum, examination of the retroesophageal space and carotid sheath to the hyoid, and thyroid lobectomy (lobotomy), if necessary. Approximately 90% of all parathyroid adenomas are resectable through a transcervical approach, and a missing gland is usually harbored in an ectopic location accessible to the surgeon at initial operation.

Closure of the Incision

After completion of the surgical exploration, the operative field is irrigated with warm saline solution and inspected for adequate hemostasis. Particular attention to any normal parathyroid glands that were isolated and dissected is important to document apparent viability. Parathyroid glands judged to be poorly vascularized or of compromised viability should be autotransplanted as discussed previously. Depending on the extent of exploration, the body habitus of the patient with respect to depth of dissection within the cervicothoracic junction, and degree of bleeding encountered, a drain may or may not be used. In most cases, drainage of the wound is not required because most dissections are limited and hemostatic. Depending on surgical preference, the skin may be closed in either a cuticular or a subcuticular fashion after reapproximation of the strap muscles in the midline and closure of the platysma. An occlusive dressing is placed to prevent fluid collection under the incision.

Postoperative Care

Successful parathyroid exploration with removal of a solitary adenoma results in a decrease in total serum calcium level, which usually reaches a nadir at approximately 48 hours after the operation. Postoperative hypocalcemia may be seen in patients with severe skeletal depletion of calcium, resulting in "bone hunger." In some patients, symptoms of hypocalcemia or tetany may develop while the serum calcium level is normal. This phenomenon may be due to a rapid decrease in serum calcium after removal of the parathyroid tumor, causing an increased neural excitability, but may also persist after calcium replacement because of accompanying hypomagnesemia.[283]

Depending on surgeon preference, postoperative total serum calcium levels should be measured at least once within the first 24 hours after operation either in the hospital or in an outpatient facility. Normocalcemia at 6 months postoperatively is the usual standard assessment for surgical success, and total serum calcium level and intact PTH level should be assessed at 1 month and 6 months postoperatively.

Surgical Strategy and Approach to Exploration

The optimal surgical approach in managing primary hyperparathyroidism is one in which normocalcemia is achieved, while minimizing potential surgical morbidity, including recurrent laryngeal nerve injury, postexploration hypocalcemia, and persistent or recurrent hyperparathyroidism requiring reoperation. Additionally, the approach selected should be individualized to the patient and disease entity (suspected single-gland versus multiple-gland disease), and should be time and cost efficient. The development of a surgical strategy in managing patients with primary hyperparathyroidism has evolved in recent years from the routine performance of bilateral cervical exploration to a more directed unilateral approach. In theory, because most patients with primary hyperparathyroidism have a single hyperfunctioning adenoma as the offending lesion, it follows that the ideal surgical approach would involve directed removal of the solitary abnormal gland in the least invasive and potentially traumatic manner. Incorporating this theoretical ideal into a practical and reliable surgical approach had previously been limited by two constraints. The first of these was accurate preoperative localization of the abnormal gland, and the second was an inability to confirm intraoperatively removal of all hyperfunctioning parathyroid tissue without performing a bilateral cervical exploration and examining all four parathyroid glands.

Traditionally, the argument for a bilateral cervical exploration in patients with suspected adenoma has been the high success rate in achieving normocalcemia with a conventional bilateral approach in experienced hands (>95% cure), the inability to predict accurately which side to explore selectively, and the potential risk of missing unsuspected multiple-gland disease such as double adenoma or unsuspected hyperplasia.[284-289] More recent technologic advances have helped address these areas of concern, and there is now growing consensus for a less extensive, directed exploration in the approach to primary hyperparathyroidism. The first impetus to this shift in surgical philosophy was provided by improvements in preoperative imaging for the accurate localization of hyperfunctioning solitary adenomas through the use of Tc 99m sestamibi imaging (see section on noninvasive preoperative localization). The second major advance involved the quest for a more precise and timely means of judging surgical success, which led to the development of assays to measure the intact PTH molecule. With the ability to confirm biochemically removal of all hyperfunctioning parathyroid tissue intraoperatively, the theoretical advantages of a directed unilateral cervical approach have increasingly become reality.[290-292]

Single-Gland Disease

Directed Unilateral Cervical Exploration

Directed unilateral cervical exploration employs preoperative localization with Tc 99m sestamibi and the implementation of intraoperative assay for PTH determination for the surgical management of primary hyperparathyroidism secondary to anticipated parathyroid adenoma. In the initial preoperative evaluation, all patients with disease entities exhibiting multiple-gland hyperplasia, such as patients with familial hyperparathyroidism and MEN-I or MEN-IIA, are determined to be candidates for standard bilateral cervical exploration and do not have localizing studies performed before initial operation. A preoperative Tc 99m sestamibi scan is obtained on all other patients with primary hyperparathyroidism and, depending on surgical preference, may be combined with high-resolution ultrasound evaluation of the thyroid bed and central neck.

If the scan is inconclusive or equivocal, as judged by the surgeon and nuclear medicine specialist, a standard bilateral cervical exploration is planned and carried out, whether or not an enlarged gland is found on the side explored first. Failure to localize with an optimally performed Tc 99m sestamibi scan, in the absence of significant thyroid disease, is strongly suggestive of sporadic diffuse hyperplasia.[293,294] If the nuclear scan identifies a discrete nuclear focus on delayed imaging, suggestive of adenoma, a directed exploration to the side localized is performed, and biochemical confirmation of removal of all hyperfunctioning parathyroid tissue is obtained through the use of intraoperative assay for PTH determination.

It has been previously shown that the most precipitous decrease in PTH levels occurs 5 minutes after removal of all hyperfunctioning parathyroid tissue.[295] The short half-life of PTH (roughly 2 to 5 minutes) allows peripheral blood samples to be obtained intraopera-

tively for rapid PTH testing 7 to 10 minutes after excision of all suspected hyperfunctioning parathyroid tissue.[293] A peripheral blood sample for rapid PTH assays is drawn at the time of abnormal gland identification (baseline) and subsequently at 10 minutes after removal of all suspected hyperfunctioning parathyroid tissue. A degradation in the serum PTH level exceeding 50%, noted in the postexcision PTH level compared with the pre-excision level, provides biochemical confirmation of removal of all hyperfunctioning parathyroid tissue, allowing the procedure to be concluded without identification or biopsy of any other parathyroid glands. If the postexcision PTH level is greater than 50% of the baseline pre-excision level, suggesting the presence of residual hyperfunctioning parathyroid tissue, a standard bilateral cervical exploration is performed.

Intraoperative PTH determination may be carried out by many methodologies. One method uses a radioimmunoassay developed through a simple, previously described modification of an intact PTH overnight assay method.[294] The intact PTH assay is a two-antibody sandwich system. One antibody (the capture antibody) is fixed to a plastic bead; the second is conjugated with a measurable marker. The amount of intact PTH present in a plasma sample can be determined by measuring the amount of the marker material remaining after all unbound solutions have been removed. Results of this rapid PTH assay are generally available within 8 to 10 minutes after submission to the radioimmunoassay laboratory.

To overcome problems associated with sensitivity of the rapid immunoradiometric assay, researchers began conjugating the labeling antibody with chemiluminescent tracers to avoid the handling issues of their radioactive predecessors.[291,292,295] Since the introduction of the immunochemiluminometric assay in 1993, researchers have experimented with several different variations on this theme, and some manufacturers now offer so-called quick kits. Experience with this assay is consistent among the investigators in that a decrease of 50% or greater between the postexcision and baseline pre-excision PTH values is indicative of removal of all hyperfunctioning parathyroid tissue.[293-301] The major drawback of these kits is their high cost. Because the assay negates the need for frozen section analysis in most cases, however, the overall cost is only slightly more expensive than the traditional unilateral approach.[291] These modifications can provide a cost-effective alternative to preformed kits, especially when weighed against the potential costs of a missed ectopic adenoma.[74]

The kinetics of postadenoma resection are important to understand if logical management strategies are based on these objective data. Libuttis[302] showed that the half-life of PTH varies within a brief window—0.42 to 3.81 minutes. Randolph[303] showed that the lowest values occur within 1 to 3 days. In 38% of patients with successful resection of a single parathyroid adenoma and return to normocalcemia, intact PTH levels may remain elevated at 1 month. Suggested mechanisms are cortical bone remineralization, increase in calcium receptor set-point, and a relative secondary hyperparathyroidism.

In situations where localization studies are inconclusive or equivocal (lacking mutual agreement by the surgeon and radiologist), or where clinical circumstances suggest multiple-gland disease (e.g., MEN, familial hyperparathyroidism), a traditional bilateral cervical exploration is recommended. Specifically, both sides of the neck are explored in an attempt to identify at least four parathyroid glands, independent of whether or not the first side explored yields an enlarged gland. Routine biopsy of all normal-appearing glands is not recommended. Instead, incisional biopsy of glands is performed selectively. Intraoperative PTH determination remains an important adjunct in the bilateral approach because this modality serves to confirm biochemically removal of all hyperfunctioning parathyroid tissue, and reduce the chance of missing ectopic multiglandular disease, whether as a result of "double adenoma" or ectopic supernumerary glands.

Minimally Invasive Techniques

Surgical techniques that derive from the basic cervical exploration described previously have been termed *minimally invasive* techniques primarily because of modifications resulting from advances in technology. Scanned directed surgery under local or regional anesthesia has been advocated by many investigators reporting excellent surgical results.[302,303] These techniques capitalize on the ability to administer effective regional anesthesia to an awake, sedated patient to perform directed unilateral focused exploration with removal of a localized solitary parathyroid adenoma. The technique employs preoperative scanning with Tc 99m sestamibi using planar and SPECT imaging and intraoperative PTH assay for biochemical confirmation of removal of all hyperfunctioning parathyroid tissue.

Advantages of this technique have been reported as improved patient comfort postoperatively, the performance of ambulatory procedures, and reduced cost.[302] Disadvantages of the technique include the potential for conversion to a comprehensive bilateral dissection if the adenoma is not found in the area indicated by the scan (necessitating general anesthesia), and the potential for patient anxiety or discomfort or both requiring conversion to general anesthesia.

The ability to localize solitary parathyroid adenomas accurately using Tc 99m sestamibi has allowed numerous investigators to pursue intraoperative nuclear mapping to isolate and recover the enlarged parathyroid gland representing the adenoma. This procedure has been termed *radioguided parathyroidectomy,* using preoperative administration of Tc 99m sestamibi immediately before operation combined with intraoperative use of the hand-held gamma detection device (gamma probe).[269,304,305] In this technique, the patient is administered approximately 18 to 20 mCi of Tc 99m sestamibi approximately 2 hours before surgery. The timing of the preoperative injection may be modified by the visualized washout sequence shown by the solitary parathyroid gland on review of delayed images.

After appropriate positioning of the patient on the operating table, intravenous sedation is administered. The gamma probe is applied to the anterior surface of the neck to measure the radioactivity of the thyroid isthmus, which is used to determine the background radioactive count. The threshold of the gamma probe is set to filter out background radioactivity. Radioactive counts are measured in each quadrant of the neck, and a marking pen is used to mark the area of maximal radioactivity, the location of which should correspond to the location of the adenoma on the sestamibi scan. The size of the incision may be considerably smaller than that used for conventional four-gland bilateral parathyroid exploration. The area to be incised is anesthetized with a local anesthetic, and a small 2- to 3-cm incision is made directly over the area of maximal radioactivity. A gamma probe is used to guide the surgical dissection by repeatedly placing it into the operative field allowing a precise surgical dissection.

When the adenoma is found, it is carefully dissected close to its capsule; its pedicle is identified, clipped, and divided insuring first that the recurrent laryngeal nerve is not within the dissected field. Radioactivity of the removed parathyroid adenoma (ex vivo) and the operative basin is measured, the sum of which should roughly equal the radioactivity in the corresponding quadrant of the neck before making the incision. In most cases, frozen section analysis is unnecessary, but a permanent histopathologic assessment on the specimen is performed. As experience with this procedure has increased, the technique has been applied more selectively to exclude the following clinical situations: deep retroesophageal lesions, ectopic glands, superior adenomas in men, and persistent or recurrent hyperparathyroidism.[305]

Endoscopic Parathyroid Exploration

Parathyroid exploration performed in humans was first described by Gagner in 1996.[306] With the advent of improved technology and video-assisted endoscopic technology, several pioneering investigators have evaluated this technique in the management of hyperparathyroidism.[307-310] This procedure is generally done under general anesthesia on patients who have shown focal areas of nuclear uptake on delayed imaging using Tc 99m sestamibi scanning for parathyroid localization. The instrumentation allows for minimal access surgery through several very small incisions placed in the cervical region, the upper chest wall, or the axilla.[308-310] Miccoli and colleagues[310] reported a larger series of video-assisted parathyroidectomy with limited use of insufflation in 137 patients.

Potential advantages of the endoscopic approach to parathyroid removal include excellent cosmesis, negligible discomfort, and minimal problems with cervical motion. Investigators advocating this technique

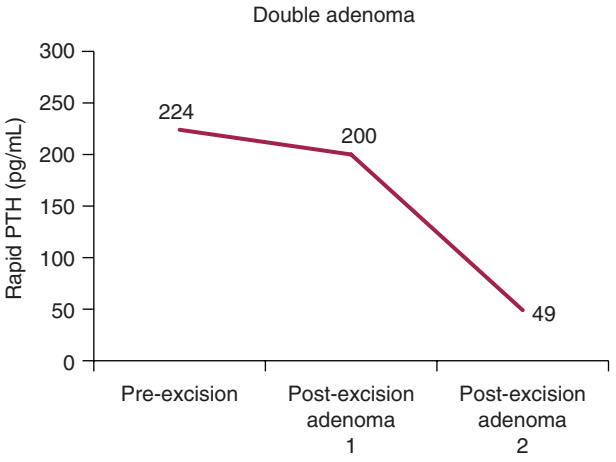

Figure 125-16. Sequential serum parathyroid hormone (PTH) levels assessed by intraoperative rapid PTH immunoassay after removal of the first and then second parathyroid adenoma in a patient with hyperparathyroidism and double adenomas.

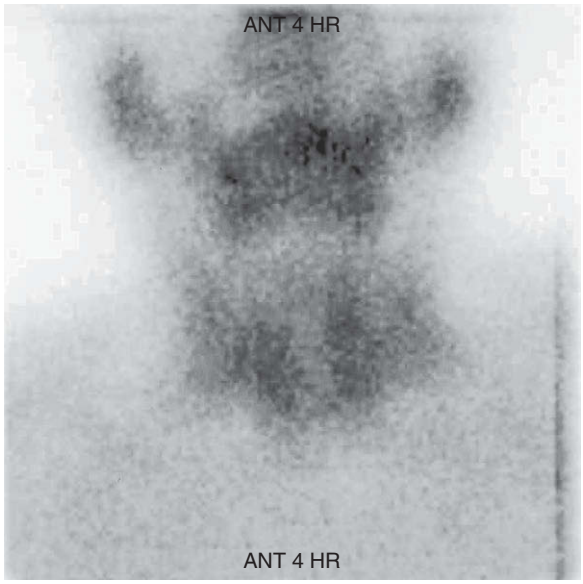

Figure 125-17. Delayed Tc 99m sestamibi nuclear scan performed on a patient with hyperparathyroidism secondary to diffuse four-gland hyperplasia. Note the absence of any focus of nuclear uptake on the image.

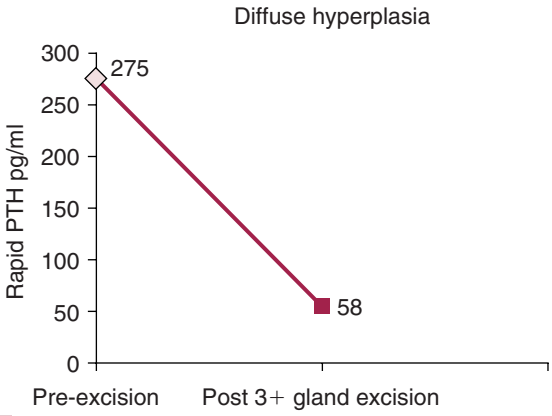

Figure 125-18. Sequential serum parathyroid hormone (PTH) levels as assessed by intraoperative rapid PTH immunoassay comparing hormone level obtained before and 10 minutes after a 3½-gland subtotal parathyroidectomy in a patient with diffuse 4-gland hyperplasia.

have indicated that the selection process in determining which patients are candidates for the procedure is a crucial aspect with regard to surgical success. Generally, the criteria for consideration of the procedure include initial explorations, single-gland disease, and the absence of significant thyroid enlargement or multinodularity. All patients must have a preoperative localization study performed with unequivocal focus of nuclear uptake on delayed imaging. In addition, all patients should have PTH levels assessed intraoperatively using the intraoperative PTH assay to confirm biochemically removal of the suspected hyperfunctional parathyroid gland. Although endoscopic cervical exploration for parathyroid disease represents the least invasive and most focused of the minimally invasive surgical techniques, the time required to perform this procedure may be extensive, and in some ways counterproductive to limiting anesthesia time and cost.[311] At this point, although this procedure shows promise, the role of endoscopic parathyroid exploration remains undefined.

Multiple-Gland Disease

True Double Adenoma

The incidence of double parathyroid adenomas seems to increase with age. Synchronous double adenomas have been variably reported at rates ranging from 1% to 2% to 10% in patients older than 60 years of age.[312,313] Approximately 50% of true double adenomas image accurately to each of the two locations (see Fig. 125-4). Bilateral exploration is required despite high suspicion on localization because of the possibility of asymmetric hyperplasia. Intraoperative PTH assay provides biochemical confirmation that all hyperfunctional parathyroid tissue has been removed: a sequential decrease in PTH levels is noted after successive excision of the first and then second enlarged gland (Fig. 125-16). At least one other normal gland should be identified, but surgical biopsy and histologic analysis of additional glands is unnecessary, provided that the final postexcision PTH level ultimately decreases beyond 50% of the pre-excision level intraoperatively to within a normal range.

Sporadic Hyperplasia

Multiglandular disease secondary to diffuse hyperplasia of the parathyroid glands may occur in 10% to 15% of patients with sporadic primary hyperparathyroidism. The approach to these patients includes performance of a nuclear imaging study using Tc 99m sestamibi preoperatively unless the patient is known to have a MEN syndrome.

A scan that does not indicate an unequivocal area of nuclear uptake on delayed images raises the surgeon's suspicion of diffuse hyperplasia. In a series performed by one of the authors (P.K.P.), 40% of equivocal scans were associated with the ultimate finding of multiglandular hyperplasia at exploration (Fig. 125-17). An equivocal scan showing the absence of a distinct focus of delayed uptake of nuclear material mandates the performance of a bilateral exploration with histologic identification of at least one abnormal and one normal gland, and the assurance that no additional grossly enlarged glands exist on either side. After removal of all enlarged glands (either single or multiple), and the demonstration of a histologically normal gland (in the event of less than four gland disease), rapid PTH assessment (Fig. 125-18) is performed to confirm the removal of all hyperfunctional parathyroid tissue, per the same protocol used in the directed exploration strategy. Failure to achieve this degree of PTH degradation mandates further exploration, for either an ectopically located gland or, uncommonly, a supernumerary gland.

When all hyperplastic glands have been located in situ, the three largest glands are removed and histologically confirmed. Subtotal excision of the remaining gland follows, leaving at least one third to one half of the gland as a viable vascularized remnant. Titration of PTH levels is helpful using rapid PTH assay. If the postexcision level

declines to less than 10 pg/mL, consideration should be given to cryopreservation of parathyroid tissue excised from the fourth gland. Although this is rarely necessary, this approach is favored over routine forearm autotransplantation of parathyroid tissue because additional surgery is avoided, and because a measurable PTH level detected intraoperatively is generally predictive of euparathyroid function and normocalcemia.[74,314]

Familial Hyperparathyroidism

Familial hyperparathyroidism accounts for less than 5% of all cases of hyperparathyroidism.[315] Familial hyperparathyroidism comprises a spectrum of autosomal dominant inherited diseases that include MEN-I, MEN-IIA, non-MEN, and familial neonatal hyperparathyroidism. In contrast to sporadic hyperparathyroidism, patients with familial hyperparathyroidism are younger and more likely to have multiglandular disease, and persistent or recurrent hyperparathyroidism after parathyroidectomy. Subtotal or total parathyroidectomy in combination with bilateral transcervical thymectomy is more frequently necessary for definitive treatment, rather than simple excision of an adenoma, which is all that is required for approximately 80% of patients with sporadic primary hyperparathyroidism. It is imperative that long-term follow-up of patients with familial hyperparathyroidism be performed for early detection and treatment of other endocrine neoplasms associated with these disorders, and for the diagnosis of recurrent hyperparathyroidism. In addition, screening of family members represents an important aspect of the overall management of familial hyperparathyroidism. As a result of the identification of causative genetic components in these disorders, genetic screening of family members to allow for a global treatment plan for members identified as gene carriers is now possible.

Multiple Endocrine Neoplasia Type I

MEN-I is an autosomal dominant inherited syndrome characterized by the presence of neoplastic lesions involving the parathyroid glands, the anterior pituitary, the pancreas, and the duodenum. Patients may also have carcinoid tumors of the bronchus or thymus; tumors of the ovaries, thyroid gland, or adrenal glands; or multiple lipomas. MEN-I is an uncommon disorder, with an incidence of 2 to 20/100,000.[316] Not all patients with MEN-I present with the complete syndrome indicating a variable degree of penetrance. Primary hyperparathyroidism is the most common manifestation of MEN-I, occurring in greater than 95% of patients, usually before age 30 and as the initial manifestation of the syndrome.[317-319] Pancreatic endocrine tumors are most often multiple and are distributed throughout the pancreas. Nonfunctioning tumors, gastroma, and insulinoma are the islet cell tumors that are most often associated with MEN-I. A pituitary tumor is diagnosed in 30% to 40% of patients and is most commonly a prolactinoma.

The syndrome of hyperparathyroidism may occur 10 years before the onset of other endocrine disorders, and MEN-I should be considered in any patient diagnosed with primary hyperparathyroidism at an early age or with multiglandular disease.[318] The hyperparathyroidism in MEN-I is due to diffuse four-gland parathyroid hyperplasia.[318-323]

Generally, the clinical manifestations of primary hyperparathyroidism in patients with MEN-I are similar to manifestations found in patients with sporadic primary hyperparathyroidism. Some of the symptoms in primary hyperparathyroidism associated with MEN-I may be masked by Zollinger-Ellison syndrome or insulinoma.[318] Alternatively, the symptoms associated with hyperparathyroidism may also aggravate the clinical manifestations of Zollinger-Ellison syndrome as a result of calcium stimulation of gastrin secretion.[318]

Biochemical findings (serum calcium and PTH levels) in MEN-I patients are similar to findings in patients with sporadic primary hyperparathyroidism, and the diagnosis is made by documenting hypercalcemia associated with an inappropriately elevated PTH level.[324] If a patient with hyperparathyroidism has a family history of the same disorder or other endocrinopathies, further screening for tumors of the pituitary gland and pancreas is warranted.[319] This screening should consist of serum prolactin levels, glucose, basal serum gastrin, and pancreatic polypeptide levels.

Werner[325] noted that 50% of the offspring of individuals with MEN-I inherited the disorder (without gender differentiation), and that this inheritance did not skip generations. This pattern of inheritance is characteristic of an autosomal dominant trait with a high degree of penetrance.[319,326]

The *MEN1* locus has been mapped to a section of chromosome 11[327]; this was further shown to involve a mutation at the 11q13 locus.[327] Subsequently, the *MEN1* gene has been identified as a tumor suppressor gene that encodes the protein menin.[328] Greater than 90% of MEN-I patients have germline menin gene mutations, and most MEN-I families have their own unique mutation.[329] The predisposition to MEN-I is a heterozygotic mutation.[324]

The finding of multiple abnormal parathyroid glands and, commonly, supernumerary glands in patients with MEN-I represents a formidable management dilemma in these patients. The inability to recognize a supernumerary gland at the time of initial exploration for this disorder is a well-documented cause of persistent disease.[318,330-332]

The surgical approach should consist of a routine bilateral neck exploration with identification of all four parathyroid glands. The extensiveness of surgical resection of the parathyroid glands, after they have been identified, is controversial with advocates of subtotal and total parathyroidectomy. Numerous authors have reported their experience with subtotal parathyroidectomy in patients with MEN-I and hyperparathyroidism with differing degrees of surgical success.[318,320,321,330] Edis and colleagues[331] reported that 82% of patients with chief cell hyperplasia had normal parathyroid function at least 1 year after subtotal parathyroidectomy. Of these, only 6 of 55 had hyperparathyroidism secondary to MEN-I syndrome, however. In 12 patients undergoing subtotal parathyroidectomy for hyperparathyroidism of MEN-I as reported by Prinz and colleagues,[330] only 5 ultimately achieved normocalcemia.

It has been postulated that the difference in success rates between hyperparathyroidism attributable to sporadic four-gland hyperplasia and hyperparathyroidism associated with MEN-I may be due to persistent exposure of a trophic factor. A potential parathyroid mitogenic humoral factor was identified by Brandi and coworkers[333] in 1986 from the serum of patients with familial MEN-I syndrome. The mitogenic activity of this humoral factor persisted in the patient's plasma for 4 years after total parathyroidectomy.[333] As a consequence, any parathyroid remnant remaining after subtotal parathyroidectomy would be exposed to this humeral factor, potentially increasing the chance of recurrence. This theory was supported by a finding by Prinz and colleagues,[330] who reported a patient with persistent hypoparathyroidism requiring calcium supplementation for 10 years after subtotal parathyroidectomy before development of recurrent disease. The re-exploration of this patient showed that remnant parathyroid hyperplasia was the etiology of recurrence.

Total parathyroidectomy with autotransplantation of fragmented parathyroid tissue has been advocated by other investigators as the procedure of choice for the initial operation for patients with primary parathyroid hyperplasia caused by MEN-I syndrome.[334,335] In this procedure, four glands are identified and removed with sectioning of the most morphologically normal-appearing gland into cubic centimeter fragments. These fragments are implanted into the brachioradialis muscle of the nondominant forearm. Sections from this gland may also be cryopreserved and successfully autotransplanted if the primary autograft does not function. Wells and associates[335] pioneered this approach, and reported that 30% of their patients developed recurrent, graft-dependent hyperparathyroidism. Autotransplantation of cryopreserved parathyroid autografts has been successful in only 50% of patients resulting in permanent hypoparathyroidism.[336]

The concept that a humoral factor may be initiating growth in the remnant parathyroid tissue is supported further by the finding of Mallete and colleagues,[322] who reported a higher incidence of graft-dependent recurrence in MEN-I patients treated with total parathyroidectomy with autotransplantation than in patients with sporadic hyperplasia undergoing the same operation. Independent of a humoral stimulating factor for parathyroid cell proliferation is the finding that MEN-I–associated hyperparathyroidism is associated with the finding of supernumerary parathyroid glands. This factor contributes to the

potential for missed glands at the time of initial operation, increasing the risk of recurrence. The implementation of intraoperative assay for PTH determination has been helpful in reconciling this problem in patients with hyperparathyroidism associated with MEN-I.[74]

Primary surgical explorations in patients with MEN-I and hyperparathyroidism may result in cure rates greater than 90%. The requisite for identifying all four parathyroid glands in these patients is emphasized in a report by O'Riordan and colleagues.[320] In this series, immediate cure was noted in 94% of patients; however, hypercalcemia was noted to be persistent in 19% of patients in whom fewer than four glands were visualized at initial operation compared with 3% of patients in whom four glands or more were noted at initial surgery. Generally, persistent and recurrent disease rates are higher in patients who have less than total parathyroidectomy performed and in whom fewer than four glands are found at the time of initial operation.[319,320]

Multiple Endocrine Neoplasia Type IIA

MEN-IIA is a syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, lichen planus amyloidosis, and Hirschsprung's disease. In 1932, Eisenberg and Wallerstein[337] first reported a pheochromocytoma and concurrent thyroid carcinoma in a patient at autopsy. In 1961, Sipple[338] estimated that the incidence of thyroid cancer in patients with pheochromocytoma was 14 times higher than that of the normal population; Cushman[339] subsequently reported a family with hereditary thyroid carcinoma and pheochromocytoma in which one affected member had a parathyroid tumor. These reports resulted in the description and characterization of the syndrome, formerly known as Sipple's syndrome, now known as MEN-IIA.[340]

The penetrance of the independent entities for patients with MEN-IIA syndrome is variable, with the exception of medullary thyroid carcinoma, which is seen in essentially all affected individuals. Pheochromocytoma and hyperparathyroidism show variable penetrance with pheochromocytoma occurring in 70% of individuals affected, and hyperparathyroidism reported least commonly in approximately 20% to 35% of affected patients.[341-345]

Hyperparathyroidism is usually diagnosed as a result of screening patients or family members with MEN-IIA, or incidentally during thyroidectomy for C cell hyperplasia or medullary thyroid carcinoma.[346] In a review of 67 patients with hyperparathyroidism associated with MEN-IIA syndrome, Raue and coworkers[345] noted that 75% were diagnosed at the time of thyroidectomy for either C cell hyperplasia or medullary thyroid carcinoma. These patients had normal serum calcium and PTH levels preoperatively, and the diagnosis was based on intraoperative morphology or histology. Uncommonly, a diagnosis of hyperparathyroidism is made because of the development of clinical symptoms that are similar to those encountered in sporadic primary hyperparathyroidism.[344]

MEN-IIA–associated hyperparathyroidism usually develops after the third decade of life in the form of mild hypercalcemia with rare hypercalcemic crises.[343,345] It is generally acknowledged that the hyperparathyroidism associated with MEN-IIA is less aggressive than its counterpart noted for MEN-I or non-MEN syndromes.[320,344] Patients with MEN-IIA generally have lower serum calcium levels, fewer symptoms or complications of hypercalcemia, less frequent multiple-gland involvement, and a lower incidence of persistent or recurrent disease after surgical treatment than patients with MEN-I or non-MEN hyperparathyroidism. A circulating humeral factor that stimulates parathyroid cell proliferation has not been postulated to exist in association with the hyperparathyroidism associated with MEN-IIA.

Similar to MEN-I, MEN-IIA is a genetic disease that is transmitted in an autosomal dominant fashion with a high degree of penetrance but with variable expression. In the late 1980s, the inherited defect of the MEN-II syndrome was mapped to the pericentromeric region of chromosome 10.[347,348] Subsequent work identified the ret proto-oncogene as a segment on chromosome 10 that encodes for a specific cell surface receptor complex, the exact function of which is poorly characterized. Mutations in the segment of the ret proto-oncogene coding for the extracellular domain of the tyrosine kinase receptor protein are responsible for producing the MEN-IIA phenotype.[349] Although the mutation has been well characterized for its association with medullary thyroid carcinoma, the exact relationship to parathyroid disease is unknown.

If parathyroid exploration for hyperparathyroidism associated with MEN-IIA syndrome is required, the presence of a pheochromocytoma must be excluded in patients before surgery. Surgery on a patient with an unrecognized pheochromocytoma may result in a hypertensive crisis intraoperatively with potential catastrophic sequelae. These patients should be screened for the presence of a catecholamine-producing neoplasm of the adrenal, and a plasma collection for catecholamines, metanephrine, and nonmetanephrine levels should be performed before parathyroid exploration. When this is ensured, the surgical approach in these patients is generally more conservative than in patients with MEN-I–associated hyperparathyroidism.

A bilateral neck exploration is performed with identification of all four parathyroid glands. Although the hyperparathyroidism associated with MEN-IIA–affected patients shows a higher incidence of multiglandular disease than in patients with sporadic primary hyperparathyroidism, it is not as high as found in patients with MEN-I syndrome. Subtotal parathyroidectomy with removal of only the obviously morphologically enlarged parathyroid glands is the approach of choice in patients with MEN-II–associated hyperparathyroidism. Transcervical thymectomy is generally unnecessary because supernumerary gland involvement is uncommon in these patients. If all four glands are involved, transcervical thymectomy may be performed concurrent with subtotal parathyroidectomy. In surgery for medullary thyroid carcinoma, normal parathyroid glands in the superior position are generally preserved with resection of the inferior parathyroid and subsequent autotransplantation so that lymph nodes in the central neck compartment and the anterior mediastinum are not missed.

Surgical exploration for patients with MEN-IIA–associated hyperparathyroidism is generally quite effective. Cance and Wells[341] reported a 100% surgical success rate and 3% recurrence rate treating patients with primary hyperparathyroidism associated with MEN-IIA. In contrast to MEN-I, in which the extensiveness of parathyroid gland resection is important in defining operative success, the degree of parathyroid gland resection does not seem to influence the success rate significantly in patients operated for hyperparathyroidism associated with MEN-IIA. O'Riordan and colleagues[320] reported a 100% cure rate with no recurrences whether total parathyroidectomy, subtotal parathyroidectomy, or excision of enlarged glands independently was performed.

Non–Multiple Endocrine Neoplasia Familial Hyperparathyroidism

Non-MEN familial hyperparathyroidism, also known as familial isolated hyperparathyroidism, refers to hyperparathyroidism occurring in the absence of other endocrinopathies in patients with at least one first-degree relative with surgically proven hyperparathyroidism and no personal or family history of MEN. Familial hyperparathyroidism occurs in young patients with a mean age at diagnosis of approximately 36 years. Some of these patients experience this disorder as children, although it is rare before age 10 years.[350] In contradistinction, patients with sporadic primary hyperparathyroidism typically present during the fifth or sixth decades of life.[315] Familial hyperparathyroidism seems to be more aggressive than sporadic or MEN-related hyperparathyroidism; frequently, patients with this disorder manifest profound hypercalcemia and more frequently present with hypercalcemic crisis.[350,351] Renal lithiasis occurs in one third to one half of patients reported with familial hyperparathyroidism; patients commonly also present with other nonspecific signs and symptoms, such as fatigue, weakness, hypertension, and peptic ulcer disease.[350] It has been postulated that familial hyperparathyroidism may be associated with an increased risk for the development of parathyroid cancer.[350,352,353]

A high incidence of persistent or recurrent disease after treatment seems to be a characteristic feature of the clinical profile of non-MEN–related familial hyperparathyroidism. Of the 97 patients reported in the literature, persistent or recurrent disease has been noted to occur at a rate of 33%. This degree of recalcitrant disease contrasts markedly with the very low rate of recurrent disease after treatment in patients with sporadic hyperparathyroidism undergoing parathyroidectomy.

This characteristic bears strong consideration in planning the appropriate operative strategy in patients with non-MEN–related familial hyperparathyroidism.

Before initiating treatment for this disorder, it is important to exclude all other familial sources for hyperparathyroidism, and the entity known as benign familial hypercalciuric hypercalcemia. When these other entities have been excluded, patients with non-MEN–related familial hyperparathyroidism should be considered for parathyroid exploration because of the aggressive biologic behavior of this disorder. There is a high incidence of multiglandular and supernumerary gland disease accounting for the high rate of recalcitrance after initial surgery. Similar to the other familial hyperparathyroidism disorders, a bilateral neck exploration with identification of all four parathyroid glands is performed.

Either subtotal or total parathyroidectomy together with bilateral cervical thymectomy is generally performed with autotransplantation of parathyroid tissue as necessary depending on the extent of parathyroid gland resection. If only one or two parathyroid glands are morphologically abnormal and enlarged, the goal of therapy is to resect all abnormal parathyroid tissue from one side of the neck, and leave existing remnant parathyroid tissue in only one side.[350] Intraoperative PTH determination is helpful in determining the degree of hyperfunctional parathyroid tissue remaining after subtotal parathyroidectomy in these patients, and may serve as an indicator of remnant parathyroid function after abnormally enlarged glands have been removed. The visualization and subsequent removal of abnormally enlarged glands and the intraoperative PTH findings guide the extensiveness of surgery in patients who manifest this disorder and have fewer than four glands appearing abnormal. It is important that these patients be followed long-term to recognize if and when recalcitrant disease occurs.

Familial Neonatal Hyperparathyroidism

Neonatal hyperparathyroidism is a rare condition characterized by severe hypercalcemia occurring in association with severe hypotonia, poor feeding, constipation, failure to thrive, and respiratory distress. The clinical manifestations of this disorder become evident during the first week of life; however, the disorder may not become manifest until age 3 months or older.[350] Most patients with familial neonatal hyperparathyroidism have been part of families with a known history of benign familial hypercalciuric hypercalcemia. The disease locus for familial hypercalciuric hypercalcemia has been identified on the long arm of chromosome 3, and patients with familial hypercalciuric hypercalcemia are heterozygous for the mutation, with one affected allele.[354,355] The occurrence of two defective alleles is believed to cause severe neonatal hyperparathyroidism.[356] Most patients with this disorder require urgent parathyroid exploration and resection of all four glands. Total parathyroidectomy is advocated together with parathyroid autotransplantation, bilateral transcervical thymectomy, and cryopreservation of parathyroid tissue because of the high recalcitrance rate for this disorder.

Renal Failure–Induced Hyperparathyroidism

The indications for parathyroid exploration in patients with renal failure–induced hyperparathyroidism may be characterized as those manifested before and after renal transplantation. Surgery is generally indicated when medical therapy fails to control progressive secondary hyperparathyroidism.[357-359] The clinical manifestations occurring in this disorder include persistent or worsening skeletal symptoms, intractable pruritus, and soft tissue calcifications.[360] Additional indications for a parathyroidectomy include the presence of biopsy-proven, high-turnover bone disease, calciphylaxis, or both in a patient with chronic renal failure and secondary hyperparathyroidism.[361-363] Parathyroidectomy may be indicated in some patients after successful renal transplantation because of the development of clinical manifestations similar to the manifestations of primary hyperparathyroidism, including hypercalcemia with nephrolithiasis, pancreatitis, central nervous system manifestations, and overt bone demineralization.[364] The presence of mild hypercalcemia in and of itself does not seem to be a serious threat to a patient after renal transplantation, but impaired kidney function in the presence of high PTH levels and hypercalcemia represents an indication for parathyroidectomy, as is the association of kidney stones and long-standing hypercalcemia.[365-368]

Generally, preoperative localization studies are not recommended before initial exploration for renal failure–induced hyperparathyroidism. This is principally due to the need to perform bilateral exploration with visualization of all four parathyroid glands, and the finding that nuclear imaging with Tc 99m sestamibi is not as effective for localization as it is for single-gland disease. In contrast to the directed exploration protocols for minimally invasive operations performed for solitary adenoma, the operation of choice for patients with renal failure–induced hyperparathyroidism at initial surgery is traditional four-gland bilateral exploration. The surgical principal of "not removing anything before seeing everything" is aptly applied to this situation.

The two most widely used initial surgical procedures for the management of renal failure–induced hyperparathyroidism are subtotal parathyroidectomy and total parathyroidectomy with parathyroid autotransplantation with or without cryopreservation of parathyroid tissue. If subtotal parathyroidectomy is the procedure of choice, the smallest, most normal-appearing parathyroid gland is selected to represent the remnant gland left in situ. The pole opposite the vascular pedicle is excised leaving approximately one third to one half of the entire gland as a vascularized remnant. All parathyroid glands need to be in situ when this excision is accomplished so that if the remnant proves to be nonviable after its sectioning, the next most normal-appearing gland is selected for the remnant, and the initial remnant is completely removed. It is generally easier to leave a superior remnant with a viable pedicle than an inferior remnant because of the proximity of the vascular pedicle to the normal position of the gland. The remnant is marked with a nonresorbable suture or metal surgical clip.

If only three parathyroid glands are found after a comprehensive exploration, all three are removed. This circumstance has been noted to result in approximately 30% of patients with persistent hyperparathyroidism.[369] If total parathyroidectomy and autotransplantation with or without cryopreservation is planned, all four glands are removed after discovery with the most normal-appearing gland selected as the autograft.[370] Because hemorrhage into the implant beds may result in poor "take" of the grafts, 10 to 15 cubic millimeter fragments of the selected autotransplant gland are placed into intramuscular pockets in the brachioradialis muscle of the nondominant forearm in a hemostatic fashion.[335] Cryopreservation of the remaining portion of this autotransplant gland should be performed if sufficient parathyroid function does not develop after revascularization of the implants.

Numerous reports supporting one procedure versus the other are noted in the literature, but objective controlled trials dealing specifically with renal failure–induced hyperparathyroidism are rare. Of the few trials conducted, the only prospective randomized series was reported by Rothmund and colleagues,[371] who found that parathyroidectomy with autotransplantation was superior to subtotal thyroidectomy in controlling symptoms in a group of 40 patients with renal failure–induced hyperparathyroidism. In this series where follow-up was noted over a mean of 4 years, four patients who were randomly assigned to the subtotal parathyroidectomy cohort experienced recurrent disease. The elimination of bone pain was significantly improved proportionally in patients who underwent total parathyroidectomy with autotransplantation. Three independent reports compared both techniques in a retrospective analysis and found that both procedures resulted in similar outcomes.[372-374] In assessing the merit of each technique, one should keep in mind that most surgeons find the procedure they routinely use and have more experience with to be the most applicable and appropriate in dealing with patients with this disorder.

The success of subtotal parathyroidectomy depends mainly on the size and viability of the remnant parathyroid gland left in situ. Remnants that are nodular are more likely to grow and result in recurrent hyperparathyroidism. This procedure has a theoretical advantage of producing less postoperative hypocalcemia because the remnant continues to function. The main disadvantage is that if these remnants become hyperfunctional, the reoperations often are tedious, are difficult technically, and carry increased risk of complications such as injury to the recurrent laryngeal nerve. Generally, successful subtotal parathyroidectomy alleviates bone pain to a lesser degree than total parathy-

roidectomies with autotransplantation, but carries less risk of postoperative low-turnover bone disease.[375]

The success of total parathyroidectomy with autotransplantation depends mainly on the nodularity of the gland from which the graft is obtained, and number and weight of the fragments that are implanted. As in recurrent disease within a nodular remnant after subtotal parathyroidectomy, graft-dependent recurrence is three times higher when implanting a nodular gland instead of a diffusely hyperplastic one.[376] The advantage of autotransplantation is that if hyperparathyroidism recurs in the graft remnant, this may be partially resected under local anesthesia with minimal potential complications. Several studies show a 5% to 38% rate of postoperative hypercalcemia attributable to a hyperfunctional graft with a 2% to 6% chance of recurrence requiring graft resection, and a 5% to 30% chance of hypocalcemia lasting more than 12 months secondary to poor graft viability and function.[377-385]

Re-exploration for Recalcitrant Hyperparathyroidism

The distinction between *persistent* (hypercalcemia persisting or recurring within 6 months after initial operation) and *recurrent* (hypercalcemia recurring after 6 months of normocalcemia following the initial surgery) hyperparathyroidism after a prior cervical or mediastinal exploration for hypercalcemia has been applied loosely, but poses an equitable management dilemma and technical challenge to the surgeon. It has been estimated that 2% to 10% of surgical failures may be attributed to an incorrect diagnosis.[386,387] The first requirement for success in reoperative parathyroid surgery is proper diagnosis. By definition, hyperparathyroidism (primary or secondary) must be proven by elevation of serum calcium levels associated with high or inappropriately elevated PTH levels. Elevated serum chloride and decreased serum phosphate levels are frequently noted. In addition, urinary calcium should be appropriately elevated to exclude a diagnosis of familial hypocalciuric hypercalcemia. If all these parameters are not present, other causes of hypercalcemia must be considered because a repeat surgical procedure is almost guaranteed to be unsuccessful.[388] The diagnosis of hyperparathyroidism is currently more straightforward with immunoradiometric and immunochemiluminescent assays of PTH levels. Diagnostic errors in hyperparathyroidism can result from medications (calcium, vitamin D, furosemide, thiazide diuretics, calcitonin, lithium), familial hypocalciuric hypercalcemia, malignancy (bone metastasis or humoral hypercalcemia), granulomatous disease, acute renal failure, bone disease (Paget's disease, immobilization), hyperthyroidism, or adrenal insufficiency.

The indications for surgical intervention in secondary cases must be solid because the morbidity and technical difficulty are increased. Generally, the guidelines for surgery in primary hyperparathyroidism, as outlined in the National Institutes of Health 2002 Consensus Conference, serve as a framework for surgical decision making in patients requiring further treatment after initial failed exploration.

Causes of Failed Exploration

The most common finding on parathyroid re-exploration by an experienced parathyroid surgeon is a missed single adenoma. Akerstrom and colleagues[389] reported on 84 parathyroid re-explorations in 69 patients with primary hyperparathyroidism. Of these patients, 37 had missed adenomas; 4 of these patients had double "adenomas" with only one adenoma being resected on the initial exploration. Most of the remaining patients had persistent hyperparathyroidism secondary to inadequate resection of parathyroid hyperplasia, with only four patients showing recurrent "single" adenomas. Rotstein and colleagues[390] analyzed their series of 28 reoperations for primary hyperparathyroidism. They identified solitary adenomas in 24 patients, with 2 patients each having hyperplasia and carcinoma. Norman and Denham[391] have used the technique of minimally invasive radiation-guided parathyroidectomy for reoperative disease and resected 23 solitary adenomas from 24 patients. Jaskowiak and associates[392] reviewed their experience at the National Institutes of Health with 288 patients with persistent or recurrent hyperparathyroidism. Of these patients, 222 (77%) were ultimately shown to have solitary adenomas.

In patients with secondary hyperparathyroidism, hyperplasia is the expected histopathology. Cattan and colleagues[393] explored 89 patients for persistent or recurrent secondary hyperparathyroidism; 53 of these patients had undergone subtotal parathyroidectomy, whereas 36 had prior total parathyroidectomy with autotransplantation. They identified hypertrophy of the remnant as the principal cause of recurrence in the subtotal group. In the group receiving total parathyroidectomy, recurrence was located in the autotransplant in half; hyperplastic disease was identified in the neck or mediastinum in the other half.

Equally as important is the finding that the cause of recalcitrant hyperparathyroidism is a solitary adenoma in most patients, through the observation that in most of these cases the adenoma is in a "standard" location. In the report by Akerstrom and colleagues,[389] only eight patients required sternotomy for ectopic adenomas identified in the mediastinum, despite 17 sternotomies being performed. In 5 of the 17 patients who had sternotomy, the offending lesion was ultimately identified in a normal location in the neck. Of the more unusual ectopic locations, one was ventral to the left atrium, one was ventral to the aortic root, and one was in the aortopulmonary window. Only one gland was truly intrathyroid, despite 19 thyroid lobectomies performed as part of the re-exploration.

In the series by Norman and Denham,[391] only one gland was in the mediastinum (just anterior to the right atrium), whereas two were intrathyroid. Jaskowiak and associates[392] identified adenomas in the posterior superior mediastinum, specifically in the tracheoesophageal groove in 27% of their patients (59 of 215). This was the most common location of the adenoma in the failed first exploration. This site is easily explored transcervically, and should be considered as an inferior extension of the normal superior gland position. The authors point out that these adenomas were almost always in direct apposition to the recurrent laryngeal nerve, perhaps suggesting that inadequate dissection around the nerve initially contributed to the failure. Another 24.3% of patients had their adenomas in the normal positions adjacent to the thyroid gland.[394]

In the National Institutes of Health series, the most common ectopic site was within the thymus or mediastinum, accounting for 16.7%.[394] This value is lower than other reports of 22% intrathymic tumors at the initial operation and 38% for reoperation.[393] An intrathyroidal lesion was noted in 10% (22 patients) of their study population. A similar percentage of patients had undescended parathyroid glands. These so-called parathymus lesions are located at the bifurcation of the carotid artery, high in the neck, and represent an inferior gland that is arrested in the descent from the third branchial pouch. Other "typical" ectopic locations included lesions within the carotid sheath and the retroesophageal space. Unusual ectopic locations include the aortopulmonary window in two patients, the hypopharynx at the base of the tongue in one patient, the wall of the nasopharynx near the nasal septum in one patient, and within the vagus nerve high in the neck at the level of C1-C2 vertebrae. Three patients had lesions "seeded" within the strap muscles, most likely because of the first exploration.[394]

Preoperative Assessment

Because a missed single adenoma located in a "standard" position accounts for most patients who fail initial procedures, accessing the records from the original exploration, including the operative note and the pathology report, is essential. Notes from the original operation may describe in detail the thoroughness of the exploration—which parathyroid glands remain in situ, whether the recurrent laryngeal nerve was identified and thoroughly skeletonized, and whether any "atypical" but regional areas were explored. Pathology reports should document what histologic items were identified (i.e., whether all normal parathyroid glands were biopsy proven). Ideally, all four glands should be identified before calling an initial exploration negative.

No matter what the original surgical and pathologic reports state, endocrine surgeons universally agree that preoperative imaging studies are an essential component of reoperative parathyroid surgery. Various invasive and noninvasive techniques are available to image or localize abnormal parathyroid glands, and these have been discussed previously.

Operative Risk in Re-exploration

When a decision has been made to pursue re-exploration for persistent or recurrent hyperparathyroidism, the patient and surgeon must review

and mutually understand the inherent risks of such surgery. The risk of injury to the recurrent laryngeal nerve, a potentially very problematic complication, is greater in re-explored necks than the risk for initial exploration. In two large studies, the incidence of vocal paralysis exceeded 6% after parathyroid re-exploration, in sharp contrast to the exceedingly low rate (<1%) after initial bilateral exploration.[395] Although more limited approaches to parathyroid re-exploration (e.g., targeted exploration, minimally invasive radiation-guided surgery) are likely to result in a reduced incidence of nerve injury after reoperation, surgical treatment of the operated neck will always be associated with increased risk. In addition to an incidence of recurrent nerve injury, re-exploration carries with it a greater likelihood for postoperative temporary and permanent hypocalcemia.[396] Finally, although the success rate for reoperative parathyroid surgery may exceed 90% in experienced hands, this remains substantially less than the near-perfect success rate for initial surgery. In addition to reconfirmation of the diagnosis and careful patient preparation, it is important that the risks associated with reoperation be discussed candidly with the patient.

Operative Strategy

After the decision to proceed with re-exploration has been made, and a review of the initial operative procedure and localization studies have been performed, the surgeon considers the operative approach. Ideally, the objective is to remove a single gland without extensive dissection, which may result in injury to the surrounding structures (i.e., recurrent laryngeal nerve or devascularization of remaining parathyroid tissue). The likelihood of accomplishing this objective depends on two factors: the experience of the initial operating surgeon and the demonstration of an enlarged parathyroid gland on correlative localization studies. In most cases, reoperation after initial surgery by an experienced surgeon is difficult and tedious because the initial dissection will have been comprehensive, and the surgical bed will have significant fibrosis. In contradistinction, the extensiveness of initial exploration and resulting degree of fibrosis may be significantly less in patients having had the original surgery performed by a relatively inexperienced surgeon. In both of these circumstances, the localizing studies are of prime importance in targeting the putative hyperfunctional gland and limiting the reoperative dissection.

The best of all scenarios, and the most common, is unequivocal localization to a cervical site, which may also include the anterior superior mediastinum. The previous neck incision is generally used for access, in some cases by excising the old scar completely. The usual superior and inferior flaps are raised, and access is gained to the side of the neck indicated by the localization studies. A lateral to medial approach to dissection is undertaken to avoid the dense scarification and fibrosis in the region of the tracheoesophageal groove where the recurrent laryngeal nerve resides. In this manner, dissection proceeds medially from the sternomastoid muscle superficial to the great vessels and then directly to the region overlying the cervical spine.

This approach exploits the concept of the visceroverterbral angle as described by Tenta and Keyes.[397] This potential anatomic space is defined as the area bordered laterally by the carotid sheath structures, medially by the trachea and esophagus, anteriorly by the thyroid, and posteriorly by the cervical spine (Fig. 125-19). In accessing this region, the surgeon may take advantage of a tissue plane with relatively little vascularity and fibrosis. This area allows the surgeon to examine the superior mediastinum inferiorly, the retroesophageal compartment medially, and as far superiorly as the hyoid bone, all within planes of dissection that separate with relative freedom. Although unnecessary in most cases, the recurrent laryngeal nerve may be identified and isolated for protection by following this approach because dense fibrosis is infrequently encountered over the prevertebral space, even after a thorough initial exploration.

If a gland is suspected in the superior retrothyroidal area, the nerve should be identified because it may be lateral to a medially displaced superior gland. Most missed adenomas, which are accessible through a cervical incision, may be approached using this technique, which also allows for thyroid lobectomy if an intrathyroidal gland is suspected. A situation whereby localization studies indicate a mediastinal location usually mandates a thoracic approach, either by median sternotomy or by lateral thoracotomy, depending on the involved area within the mediastinum. An enlarged gland identified within the anterior mediastinum is usually associated with the thymus and may be accessed by median sternotomy. These glands are usually found at the level of the innominate vein within thymic tissue, but may also be found adjacent to the aortic arch or between the thymus and pleura.

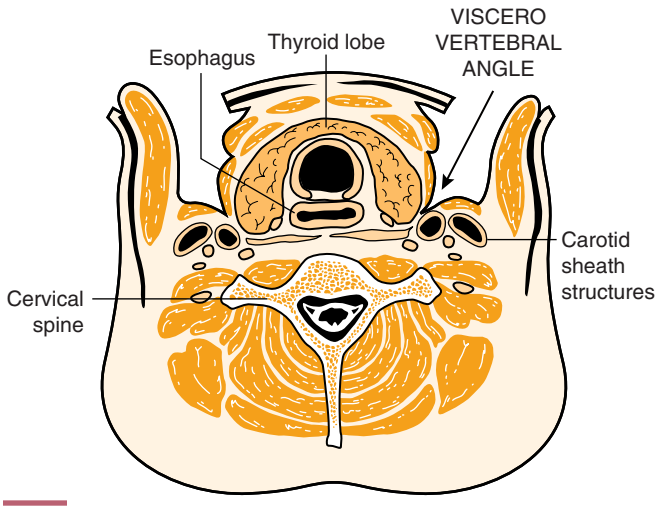

Figure 125-19. Viscerovertebral angle approach relative to parathyroid exploration.

If the localizing studies show a posterior-based mediastinal gland, a lateral or posterolateral thoracotomy should be strongly considered to avoid attempts at dissection through critical structures in the anterior mediastinum. These posterior glands may reside in the aortopulmonary window or the retroesophageal region. The recurrent laryngeal nerve may be injured when approaching the posterior mediastinum through a left lateral thoracotomy. Despite what may be interpreted as compelling localization results, the surgeon should be prepared to perform concurrent cervical exploration if initial intraoperative PTH levels do not confirm removal of all hyperfunctional parathyroid tissue.

The most problematic preoperative scenario to confront is that in which localization fails to identify any suspicious site. In this situation, reoperative surgery for hyperparathyroidism is potentially the least successful and the most morbid. Failure to localize usually mandates a bilateral cervical exploration that comprehensively and methodically addresses all potential sites that may harbor a missing gland or glands. A properly constructed initial operative note that accurately documents remaining histologically identified parathyroid glands and regions explored is crucial and of potential value for the reoperating surgeon. An orderly systematic approach to re-exploration is required in these circumstances to locate the missing gland or glands and limit morbidity.

The order in which regions are approached may vary according to the surgeon; however, it is important that all potential areas be accessed to increase the chance of success and avoid a failed re-exploration. The preferred approach is to explore each side through the visceroverterbral angle via a lateral-to-medial orientation. Regions of dissection are addressed in the following manner: The anterior superior mediastinum is dissected first, with careful attention to the thyrothymic ligament and tracheoesophageal groove region adjacent to the recurrent nerve (Fig. 125-20). Cervical thymectomy, if not performed during initial surgery, is completed at this time (Fig. 125-21). Dissection then turns to the retropharyngeal, retroesophageal region where blunt dissection within the prevertebral space allows for digital exploration superiorly above the cricoid larynx and inferiorly into the posterior mediastinum. Enlarged glands in this anatomic plane may often be felt before they are seen using these techniques. Next, the thyroid lobe is mobilized, possibly truncating the superior vascular pedicle to rotate the gland anteromedially so that the posterior thyroid capsule may be closely examined for a folded, lobulated parathyroid gland under the capsular fascia (Fig. 125-22). Using this maneuver, the thyroid lobe is

Figure 125-20. A gloved finger inserted beneath the pretracheal fascia overlying the cervical spine shows the "pseudo" ectopic location of a descended superior parathyroid adenoma in the tracheoesophageal groove.

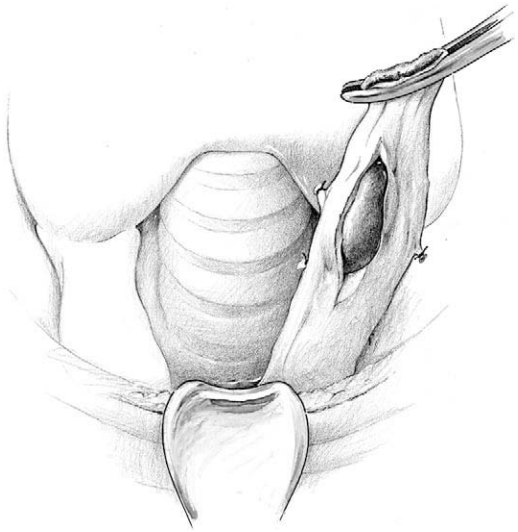

Figure 125-21. Cervical thymectomy showing an intrathymic inferior parathyroid adenoma.

palpated for any nodular densities that may be suspicious for an intrathyroidal parathyroid gland. The carotid sheath is opened from the superior mediastinum to the hyoid bone, inspecting and palpating for nodular structures within the sheath (Fig. 125-23).

Failing identification on the side explored first, the dissection proceeds contralaterally in the same manner with orderly inspection of all of the above-noted regions. If a bilateral exploration fails to identify the offending gland, thyroid lobectomy or lobotomy is usually performed on the side suspected to harbor the missing gland. During these maneuvers, it is important to document carefully all normal parathyroid tissue found, or if glands are not identified, the putative missing parathyroid gland by position.

If all maneuvers previously described are unsuccessful in identifying the missing gland, the procedure is terminated, and further measures are undertaken to identify the gland's position by imaging and possibly angioinvasive studies. Mediastinal exploration should not be performed in this setting, predominantly because of the lack of localization and element of time involved with the unsuccessful bilateral cervical exploration just completed.

Special Circumstances

Parathyroid Hormone Level Considerations

The utility of intraoperative PTH is only as valuable as the appropriateness of its application. As patients with primary hyperparathyroidism

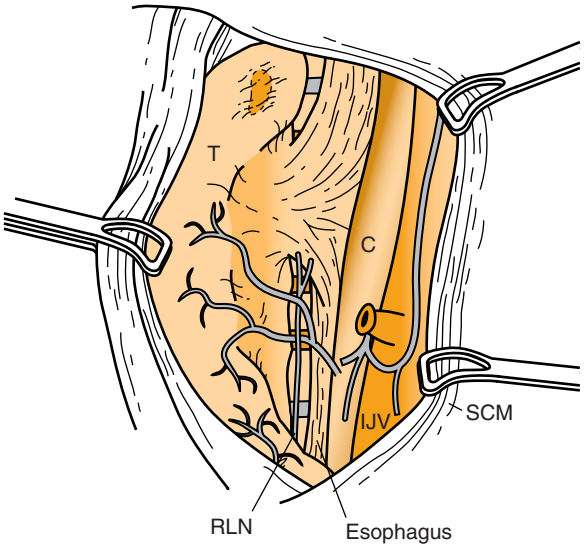

Figure 125-22. Superior parathyroid adenoma located under the pretracheal fascia over the posterior aspect of the thyroid gland, a "pseudo" subcapsular parathyroid gland. C, carotid sheath; IJV, internal jugular vein; RLN, recurrent laryngeal nerve; SCM, sternomastoid muscle; T, thyroid gland.

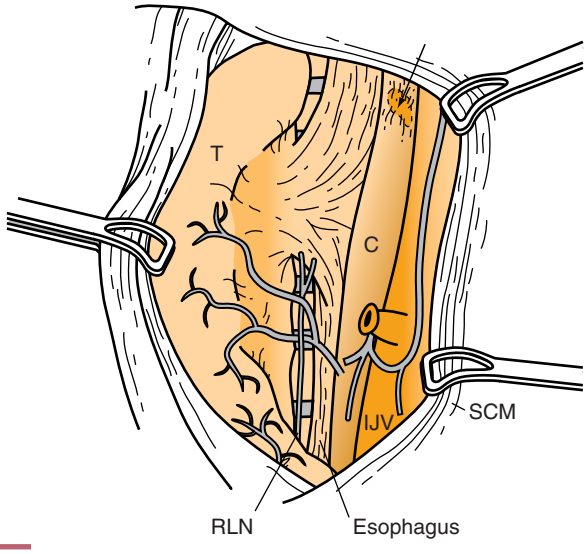

Figure 125-23. Ectopic parathyroid adenoma *(arrow)* illustrated within the carotid sheath. C, carotid sheath; IJV, internal jugular vein; RLN, recurrent laryngeal nerve; SCM, sternomastoid muscle; T, thyroid gland.

are diagnosed and evaluated for surgery earlier in the course of their disease, the potential exists for variations in the baseline levels of PTH to influence PTH degradation profiles and the accuracy of the test.

The interpretation of intraoperative PTH levels may be confounded by unrecognized PTH "spikes," whereby pre-excision values may variably exceed baseline or preincision levels. These acute differences in PTH levels have been postulated to occur from various etiologies, including technical problems with the assay performance, acute changes in renal status, pharmacologic influences, and pre-excision gland manipulation. In most instances, when technical assay problems are excluded, manipulation of the hyperfunctional gland before resection would seem to present the most plausible explanation for these "spikes." Riss and colleagues[398] noted that a substantial delay in PTH degradation beyond 10 minutes post resection in patients shows PTH

"spikes" thought to be due to gland manipulation before excision. This study and the authors' own experience acknowledge the importance of recognizing PTH "spikes" and reacting to them by delaying postexcision PTH measurements 20 to 25 minutes. A subthreshold decline (<50%) beyond this interval should prompt further exploration. PTH "spikes" may best be recognized by comparing the pre-excision value with the baseline obtained before surgery, provided that the same laboratory was used for both determinations.

A finding that may result in considerable frustration and anxiety is an elevated PTH level in a normocalcemic patient after curative parathyroid surgery. Approximately 20% (and perhaps more) of patients achieving normocalcemia after parathyroid surgery, during which intraoperative PTH determination predicted curative resection, have persistently elevated PTH levels postoperatively. This phenomenon has been postulated to occur as a result of the development of secondary hyperparathyroidism in response to a rapidly changing serum calcium level, variably explained by vitamin D deficiency, changes in renal function, or peripheral resistance to PTH.[399,400] In a setting of normocalcemia after curative parathyroid surgery, PTH levels obtained postoperatively do not seem to improve on the predictive value of intraoperative PTH levels. Further elevations in PTH levels in these patients postoperatively do not indicate operative failure in most patients in whom intraoperative PTH levels predicted curative resection.[399]

A growing body of evidence suggests that a disparity exists in the predictive value of intraoperative PTH between patients with low and high baseline levels of PTH determined before treatment. This evidence indicates that patients with lower baseline levels of PTH may not experience a predictable decline in hormone levels after what is thought to be curative surgery, suggesting that this cohort of patients may be at risk for unrecognized multiple-gland disease.

The concept that time-indexed PTH decay curve kinetics held potential for discriminating between single-gland and multiple-gland disease, and that this may be influenced by baseline PTH levels, was investigated by Miller and associates.[401] Two groups of patients were investigated: patients noted to have indexed PTH levels greater than (high baseline) and less than (low baseline) 100 pg/mL. Using PTH decay curve slope analysis and two time points for each group individually and combined, data were generated and correlated with pathologic findings (i.e., single-gland versus multiple-gland disease), and then compared with the standard (50% rule) arithmetic results. This study yielded two important findings with reference to the patients with low baseline (<100 pg/mL) hormone levels: (1) 50% degradation was less valid in confirming single-gland disease, and (2) multiple-gland disease was more prevalent in low baseline patients.

One of the authors (P.K.P.) has examined a series of 304 patients surgically treated for primary hyperparathyroidism and categorized them into a high baseline (>100 pg/mL) and low baseline (<100 pg/mL) PTH group based on levels obtained before initiating treatment. Twenty percent of the low baseline group ($n = 146$) was noted to have multiple-gland disease compared with 8% of the high baseline ($n = 158$) group. A significant (>50%) decline in PTH was not realized in 15% of the low baseline group, whereas only 6% of the high baseline group experienced a suboptimal decline. More importantly, optimal decline in the intraoperative PTH level did not consistently signal solitary gland disease in the low baseline group, in which 21 patients were noted to have multiple-gland disease despite intraoperative PTH degradation greater than 50%. It would seem from these investigations that the variability in baseline levels of PTH can influence the predictive value of intraoperative hormone determination. Patients with low baseline levels of PTH seem to be at greater risk for harboring multiple-gland disease, and do not consistently show intraoperative PTH degradation kinetics that are predictive of surgical care.

Unsuccessful Localization

In most situations, failure to localize to a discrete area of the neck after sestamibi imaging occurs as a result of unrecognized multinodular thyroid disease (Fig. 125-24). In the absence of a nodular thyroid gland, one must suspect diffuse hyperplasia or, less likely, an ectopically located cervical or mediastinal gland. One must be careful that an appropriately dosed (minimum 23 to 26 mCi) and correctly conducted nuclear scan has been carried out in all studies. SPECT Tc 99m sestamibi imaging may be helpful in reconciling equivocal planar images.[402,403] A failure to localize on delayed nuclear imaging mandates the performance of a standard bilateral exploration.

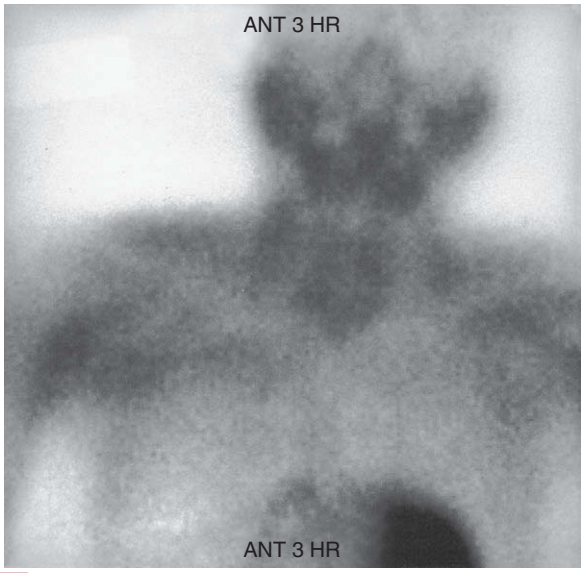

Figure 125-24. Tc 99m sestamibi nuclear scan in a patient with hyperparathyroidism and nodular thyroid disease.

A false-positive sestamibi scan (i.e., discrete areas of delayed nuclear uptake representing false-positive localizations shown at surgery) may occur. Almost without exception, this false-positive scan occurs as a result of unsuspected nodular thyroid disease. In a series examined by one of the authors (P.K.P.), nodular thyroid abnormalities accounting for false-positive scans were exclusively solid in consistency. In contrast, none of the cystic lesions concurrently noted during exploration for hyperparathyroidism were associated with a false-positive localization study.

This finding suggests the importance of performing high-resolution ultrasound evaluation in patients with nodular thyroid disease because the finding of a cystic nodule would decrease suspicion that the localization result is a false-positive result. Even in the presence of solid nodular thyroid disease, subcapsular and intrathyroidal abnormal parathyroid glands have been encountered that have imaged correctly. This finding emphasizes the importance of evaluating all nodularity within or associated with the thyroid gland in the event that these abnormal parathyroid glands be located in a "hidden" region either between thyroid nodules or tightly held under the pretracheal fascia representing the "pseudocapsule" over the thyroid gland (Fig. 125-25). More likely, however, is that solid thyroid nodularity with a false-positive sestamibi image is consistent with an adenomatous thyroid nodule, mandating bilateral cervical exploration.

Mediastinal Exploration

Initial exploration or re-exploration for parathyroid disease may require exploration of the mediastinum. Ectopic parathyroid glands located within the mediastinum and below the level of the thymus account for a small percentage (0.2%) of all abnormally located glands.[404] In contrast, Wang[405] and Norton[406] have shown that a more substantial proportion, 18% (Wang[405]) and 20% (Norton[406]), of ectopically located adenomas reside in the mediastinum accessible only through a mediastinal approach. These inferior parathyroid glands are associated in almost all circumstances with the thymus with which they descend during embryonic development, having arisen with the thymus as a third pharyngeal pouch derivative.

Several approaches to the mediastinum are available for exploration. The choice of approach depends on the location of the putative adenoma. Localization studies that, in combination, corroborate

and specify the mediastinal location are required before undertaking exploration. In the experience of most investigators Tc 99m sestamibi imaging together with MRI represents the optimal combination of physiologic and anatomic imaging for localization (Fig. 125-26).

The techniques available for approaching the mediastinum include transcervical substernal with thymectomy using anterior retraction of the sternum for superior mediastinal glands; median sternotomy with direct approach to the anterior middle and caudal mediastinal compartments; posterolateral thoracotomy for selective, posteriorly based glands in the lower mediastinal compartment; and endoscopic, minimally invasive mediastinal dissection for selectively focused exploration.[407] Most glands are approached via a median sternotomy, owing to this technique's capability to address safely numerous areas within the mediastinum and the lower cervical region immediately posterior to the clavicular heads and manubrium. This technique also allows uninterrupted visualization of both recurrent laryngeal nerves, preventing inadvertent injury to these structures within the mediastinum. Surgical adjuncts that may aid in the intraoperative localization of adenomas, and that may be employed after median sternotomy include intraoperative ultrasound and gamma probe after preoperative sestamibi injection.

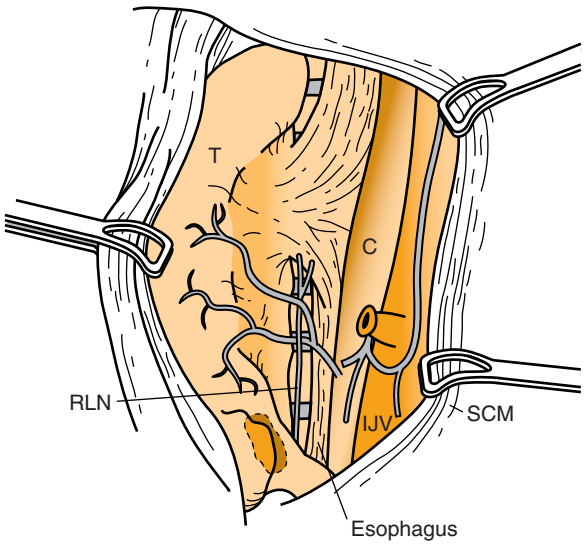

Figure 125-25. Inferior parathyroid adenoma shown deep to the true thyroid capsule between nodular thyroid projections. C, carotid sheath; IJV, internal jugular vein; RLN, recurrent laryngeal nerve; SCM, sternomastoid muscle; T, thyroid gland.

Gamma Radiation Detection Device

Minimally invasive surgical exploration using a gamma radiation detection device has been developed and advocated by Norman and Chheda[269] to assist actively and expedite initial surgery for parathyroid adenoma (see the section on intraoperative localization).[404] This methodology exploits the nuclear uptake characteristics of parathyroid adenoma with respect to Tc 99m sestamibi, and the ability of the gamma probe to localize these glands in the neck intraoperatively after preoperative sestamibi injection.

This technique has been applied by one of the authors (P.K.P.) in mediastinal exploration after sternotomy with satisfactory results (Fig. 125-27). Despite uptake of sestamibi by myocardial tissue, background radioactivity within the mediastinum seems to be less than that of thyroid tissue, facilitating a focused dissection with minimal disturbance of surrounding mediastinal structures. Reoperation for multiple-gland disease in secondary and tertiary hyperparathyroidism has been aided with the use of the gamma probe when supernumerary glands are present. In one notable instance in this series, three additional parathyroid glands (two cervical and one mediastinal) were recovered in a patient with tertiary hyperparathyroidism who previously underwent documented four-gland parathyroidectomy during preparation for cadaveric renal transplantation. The gamma probe was instrumental in identifying one of the cervical glands and one mediastinal gland, which was the only parathyroid gland that was localized accurately on initial sestamibi imaging. The gamma probe may also be applied for removal of hyperfunctional parathyroid tissue autotransplanted to the forearm in the setting of secondary or tertiary hyperparathyroidism.

Parathyroid Carcinoma

Parathyroid carcinoma is reported to be the cause of primary hyperparathyroidism in only 0.1% to 4% of individuals affected.[404-407] Parathyroid carcinoma occurs with equal frequency in male and female patients; in contrast, parathyroid adenomas occur more frequently in female patients.[408] The epidemiology of parathyroid carcinoma offers few clues about its etiology and pathogenesis. The development of cancer of the parathyroid glands has been linked to chronic renal failure and dialysis,[409-411] and familial hyperparathyroidism syndromes including MEN-I and MEN-IIA and the hereditary hyperparathyroidism–jaw tumor syndrome.[412] The hyperparathyroidism–jaw tumor syndrome is

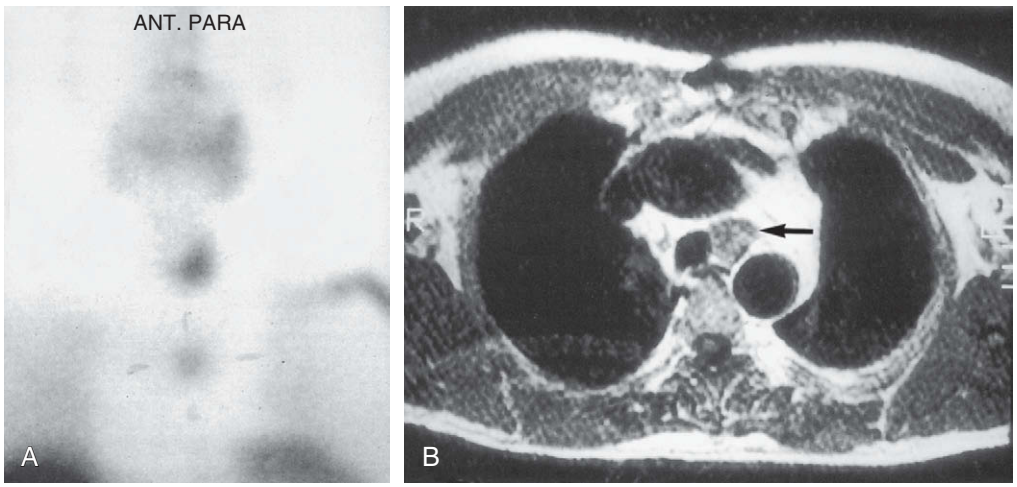

Figure 125-26. Tc 99m sestamibi scan **(A)** and MRI scan **(B)** in a patient with a mediastinal parathyroid adenoma. The area of nuclear uptake noted on the sestamibi scan correlates anatomically with the nodule shown in the aortopulmonary window on MRI. Adenoma was removed via left lateral thoracotomy.

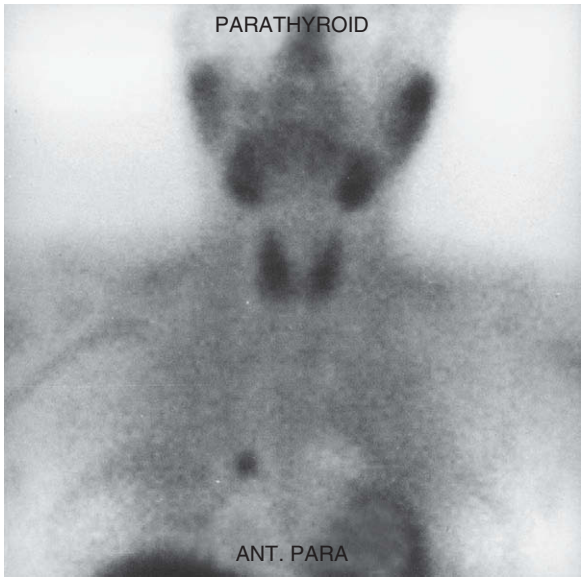

Figure 125-27. Tc 99m sestamibi imaging showing mediastinal parathyroid that represented a fifth hyperplastic gland missed at initial surgery, at which time four hyperplastic glands were removed.

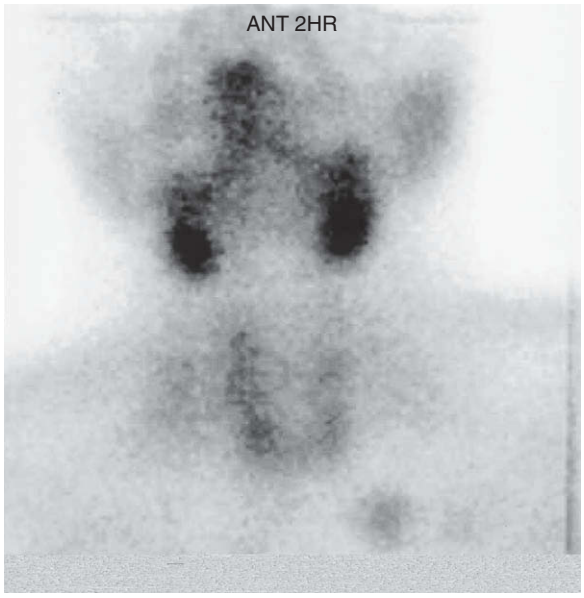

Figure 125-28. Tc 99m sestamibi image showing delayed uptake in the left superior mediastinum in a patient with recurrent parathyroid carcinoma.

characterized by recurrent parathyroid adenomas, fibroosseous tumors of the mandible, and Wilms' tumors.[412]

Generally, patients with parathyroid cancer have higher serum calcium levels, higher levels of intact PTH, and more profound metabolic abnormalities than patients with parathyroid adenoma or hyperplasia. Approximately 70% of patients with parathyroid carcinoma have serum calcium levels greater than 14 mg/dL and intact PTH levels at least five times the upper limit of normal.[413-417] Approximately 80% of patients with parathyroid cancer are either symptomatic or have some metabolic abnormality associated with their disease, and 40% were found to have a palpable neck mass.[413,415] This finding contrasts with the presentation in patients with benign causes of hyperparathyroidism; 50% of that cohort are asymptomatic in diagnosis, and the presence of a neck mass is rare.

A definitive preoperative diagnosis of parathyroid carcinoma is impossible to make; metabolic manifestations of parathyroid cancer overlap with the manifestations of parathyroid adenoma. A high index of suspicion of parathyroid carcinoma should be maintained especially in patients with serum calcium levels greater than 14 mg/dL and a palpable neck mass.[413,415,417] Recurrent laryngeal nerve palsy manifesting in a patient with hyperparathyroidism is also highly suggestive of parathyroid cancer.[418]

The definitive treatment of parathyroid cancer is en bloc resection of the tumor and areas of potential local invasion or regional metastasis or both. Parathyroid cancer frequently recurs in the central neck compartment, and typically exhibits a natural history marked by recurrent hypercalcemia. Performance of the appropriate surgical procedure during the initial operation is crucial, and is one of the most important prognostic factors in parathyroid cancer.[419] The integrity of the parathyroid capsule should be maintained during dissection using an en bloc resection of the ipsilateral central neck contents, including the thyroid lobe and tracheoesophageal soft tissues and lymphatics.[420] Structures such as the recurrent laryngeal nerve, esophageal wall, or strap muscles may require sacrifice if the tumor adheres to them; this reduces the risk of tumor spillage and local recurrence. The increased local control achieved with resection of the recurrent laryngeal nerve outweighs the complication of vocal cord paralysis, which may be managed by phonosurgical rehabilitative procedures.

A central compartment (level 6 and possibly level 7) neck dissection together with resection of soft tissues within the superior anterior mediastinum is important to stage appropriately any lymph node involvement that is not directly palpable during the initial surgery. Lymph node metastasis lateral to the jugular vein is rare in parathyroid cancer during the initial presentation.[413] Prophylactic modified radical or selective dissection of levels 1 through 5 is not generally recommended. Neck dissection is reserved for patients with lymph node metastasis detected radiographically or by clinical examination in the jugular distribution, or for patients with massive soft tissue invasion of lateral neck structures.

Although cure after resection of recurrent parathyroid carcinoma is rare, aggressive resection of local recurrence is recommended to control severe hypercalcemia. Selected patients achieve prolonged disease-free intervals after one or more surgical procedures for recurrence in the neck or anterior superior mediastinum.[421]

In addition to the approach for initial surgery of parathyroid carcinoma and local recurrence, an aggressive surgical approach to metastatic parathyroid cancer has been advocated to control marked hypercalcemia. Obara and colleagues[420] reported on lung resection for metastasis from parathyroid cancer in which 32% of patients resected achieved a significant reduction in total serum calcium levels, and 14% achieved long-term survival ranging from 9 to 30 years. Surgery for locally recurrent parathyroid cancer may be guided by preoperative localization studies to define better the extent and location of recurrent parathyroid cancer (Fig. 125-28). Localization studies should be interpreted with caution, however, because not all tumor foci may be detected, and in patients with very high intact PTH levels, benign lesions of bone (brown tumors) may mimic metastases.[422-426]

The low incidence of parathyroid cancer has made it difficult to study the roles of radiation and chemotherapy. A report issued by the National Cancer Database described the use of radiation therapy in combination with surgery in less than 7% of the 286 cases included.[408] Some reports have advocated the importance of complete en bloc resection followed by radiation therapy to increase local control.[427,428] The results of these reports must be tempered, however, by the finding that patients in these series may not have had advanced poorly resectable disease, a finding that characterized investigations in which radiation therapy was believed to be a factor that worsened prognosis for parathyroid cancer.

Chemotherapy has a very limited role in the management of parathyroid cancer. Some response to therapy has been noted with a combination of fluorouracil, cyclophosphamide, and dacarbazine, and the combination of methotrexate, doxorubicin, cyclophosphamide, and

lomustine. These agents were not administered in a controlled study environment, and patient numbers were exceedingly few.[429,430]

Hyperparathyroidism during Pregnancy

Hyperparathyroidism during pregnancy is rare, and pregnant women usually represent a very small fraction of the total number of patients treated for this disease.[431] As in nonpregnant patients, a single parathyroid adenoma is the most likely to be the cause of hyperparathyroidism, although hyperplasia and carcinoma have been reported.[432-434]

During pregnancy, there is a degree of protection in the mother against hypercalcemia provided by calcium transport across the placenta.[432] Large amounts of calcium depress the fetal parathyroid function and result in fetal hypoparathyroidism. After delivery, when maternal calcium is no longer available, neonatal tetany develops as a consequence of hypercalcemia; this is the most common presenting sign for maternal hyperparathyroidism in pregnancy.[434] Additional fetal complications described in mothers with hyperparathyroidism include spontaneous abortion, prematurity, intrauterine growth restriction, and stillbirth.[431] Although many pregnant women are asymptomatic, presenting symptoms of hyperparathyroidism during pregnancy may include muscle weakness, abdominal symptoms, disorientation, coma, and death.[433]

The risk of obstetric complications has been shown to be significantly greater in women who do not undergo surgery for hyperparathyroidism while pregnant.[433] Some investigators believe that neonatal hypocalcemia is transient and treatable, and maternal disease can be successfully controlled medically when the diagnosis is already known.[434,435] The opposing opinion is that regardless of symptom complex severity, all pregnant patients with hyperparathyroidism should undergo neck exploration to prevent the array of potential maternal and fetal complications.[436]

There seems to be uniform agreement that in severely symptomatic patients, surgery should not be postponed until after delivery. The ideal safe period for parathyroidectomy is the second trimester, when chances of pregnancy loss or premature labor as a consequence of surgical intervention are minimal.[436] If the diagnosis is made during the third trimester, parathyroid exploration usually can be postponed until after labor and delivery. Preoperative hypercalcemia may be successfully controlled with fluids, diuretics, and orally administered phosphate. Plicamycin, an antineoplastic agent, should be avoided during pregnancy, however, because it is highly toxic to the fetal bone marrow, liver, and kidney. The most severe cases of hypercalcemia may require hemodialysis for appropriate control and stabilization.[432]

Medical Management of Hyperparathyroidism

It may be necessary in selected patients with hyperparathyroidism to consider medical therapy, including patients in whom significant comorbidity may render them at risk for significant complications as a consequence of surgical exploration or patients with unresectable parathyroid carcinoma and uncontrolled hypercalcemia. Consideration for medical therapy should be weighed in relation to the patient's symptom complex, age, and overall medical condition and health status.

A few general management schemes may be used to treat hypercalcemia. Expansion of intravascular volume by hydration together with the administration of loop diuretics should enhance urinary calcium excretion. Pharmaceuticals that reduce osteoclastic bone resorption, such as bisphosphonates, calcitonin, and plicamycin, may be used for various clinical settings.

The type of treatment employed generally depends on the severity of the hypercalcemia and resultant clinical setting. In patients not fulfilling any criteria for surgery and in the absence of any circumstances that would make the patient unsuitable for medical monitoring as currently accepted, no treatment is recommended except adequate hydration and avoidance of thiazide diuretics and immobilization. Estrogens have a theoretical advantage of potentially reducing serum calcium, while providing known beneficial effects on bone in the prevention of osteoporosis in postmenopausal women. The potential for the development of malignancies of the uterus and breast with estrogen use limits the practicality of this approach to reduce calcium levels. In addition, estrogen may increase levels of PTH. Considering these variables, estrogen should be used cautiously in these patients, and if estrogen is needed to control calcium levels, surgical exploration should be more strongly considered.

For patients in whom calcium levels are 12 mg/dL or less, enhancement of urinary calcium excretion should be the initial approach. Most patients in this category are volume depleted because of the loss of water resulting from hypercalciuria. Volume correction with appropriate oral intake of salt and fluids most often corrects the serum calcium level. Diuresis should be implemented carefully in these patients because the use of diuretics may worsen volume depletion and exacerbate hypercalcemia. If diuresis is warranted to enhance calciuria, loop diuretics such as furosemide may be used. Thiazide compounds, which may worsen hypercalcemia, should be avoided.

The use of oral phosphate salts has been advocated in the treatment of mild hypercalcemia in controlled situations.[437] This approach may reduce the serum calcium by 1 mg/dL through a series of complex mechanisms involving decreased calcium absorption from the gut, decrease in circulating 1,25-dihydroxyvitamin D, and reciprocal reduction of serum calcium by increasing serum levels of phosphorus. Bisphosphonates are among the most effective inhibitors of bone resorption, and are conceptually offered as an alternative in treatment for mild hypercalcemia caused by primary hyperparathyroidism, but so far they have not provided for a substantial reduction in serum calcium levels.[438] More recent clinical evidence has suggested, however, that the postmenopausal osteoporosis dose of alendronate (10 mg/day) effectively reversed bone loss in hyperparathyroidism.[439] Alendronate increased bone density within 1 year by more than 5% in the spine, similar to its effect in postmenopausal osteoporosis. It may be inferred that bone loss associated with hyperparathyroidism may be controlled by treatment with bisphosphonates, and this treatment could protect the bone in cases where surgery is contraindicated.

Long-term medical management of hypercalcemia in patients with mild hyperparathyroidism or patients in whom surgery may carry unacceptable risks remains problematic. Direct reduction of PTH levels by manipulating the calcium-sensing receptors on parathyroid cells has ushered in a new class of pharmaceuticals called calcimimetic agents.[440,441] These agents act at the level of the parathyroid cell calcium receptor as a G-protein, such that when coupled with the receptor, the receptor G-protein complex recognizes calcium as its ligand.[442] In the presence of increased extracellular calcium, the receptor complex is activated, which results in a signal to the cell via a G-protein–transducing pathway to increase intracellular calcium, inhibiting PTH secretion. One such calcimimetic agent under investigation is R-568, which was found to increase cytoplasmic calcium and reduce PTH secretion in vitro.[441] Further investigational experience was noted in postmenopausal women with primary hyperparathyroidism in whom administration of R-568 resulted in decreased PTH secretion and reduced serum calcium concentrations.[440] Larger clinical trials are expected to clarify further the therapeutic potential of these calcimimetic compounds, but it seems that they may offer a therapeutic alternative to parathyroidectomy in the long-term management of hypercalcemia, especially in patients with mild hyperparathyroidism, or patients in whom surgery is contraindicated or impossible (i.e., parathyroid carcinoma).

Summary

The management of hyperparathyroidism mandates a thorough, methodologic approach to diagnosis, patient evaluation and preparation, and development of a comprehensive therapeutic strategy. Advances in nuclear imaging and the ability to assess the serum level of PTH rapidly have allowed the fundamental surgical approach to become accurately directed, more refined, and less extensive, leading to improvements in outcome and reductions in treatment time, morbidity, and cost.

Although these changes have revolutionized the manner in which surgeons approach disorders of the parathyroid glands, they may not be universally applicable, and should not serve as a substitute for a well-founded and traditional knowledge base in surgical embryology, anatomy, and technique. Most patients with hyperparathyroidism who undergo surgical therapy benefit symptomatically and metabolically.

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CHAPTER ONE HUNDRED AND TWENTY-SIX

Management of Thyroid Eye Disease (Graves' Ophthalmopathy)

Douglas A. Girod

Richard D. Wemer

Key Points

- Graves' disease is an autoimmune disorder that is associated with hypermetabolism, enlargement of the thyroid gland, and exophthalmos.
- In Graves' ophthalmopathy, retrobulbar fibroblasts secrete glycosaminoglycans, causing engorgement of extraocular muscles and orbital fat, resulting in increased volume of the orbital contents.
- Advanced Graves' ophthalmopathy can result in significant proptosis and optic neuropathy, with potential loss of vision.
- Conservative measures for Graves' ophthalmopathy include medical therapy, administration of steroids, and radiation therapy. Failure of conservative measures requires surgical decompression of the orbit.
- Orbital decompression can be performed via external, transantral, transconjunctival, endoscopic, or combined approaches. Two-wall and three-wall decompressions have been described with varying degrees of reduction in proptosis and improvement in vision.
- Ancillary procedures for Graves' ophthalmopathy include optic nerve decompression, extraocular muscle surgery, and eyelid surgery.

In 1835, Graves described a clinical syndrome that included symptoms such as hypermetabolism, diffuse enlargement of the thyroid gland, and exophthalmos. Although others also had recognized this entity, Graves defined the thyroid as playing a central role in the disease. Graves' disease is now recognized as a multisystem disorder characterized by one or more of the following: (1) hyperthyroidism associated with diffuse hyperplasia of the thyroid gland, (2) infiltrative ophthalmopathy (leading to exophthalmos), and (3) infiltrative dermopathy (localized pretibial myxedema). More recent work has helped to establish Graves' disease as an autoimmune process targeted at the thyroid-stimulating hormone (TSH) receptor in the thyroid.[1-3] In addition, retro-ocular fibroblasts have been found to play a key role in the development and progression of the ophthalmopathy seen in some patients with Graves' disease.[4,5]

Despite these advances in understanding of Graves' disease pathogenesis, only limited progress has been made in the management of the disease. Therapy is still primarily directed at the manifestations of the disease in a palliative fashion, rather than at preventing the underlying destructive autoimmune process. This chapter focuses on the evaluation and management of the ophthalmic manifestations of Graves' disease.

Pathophysiology

Extensive research in recent years has led to important insights into the pathologic mechanisms involved in Graves' disease and Graves' ophthalmopathy. As understanding progresses, so should the ability to deal with this challenging disorder.

Graves' Disease

Current theory describing the development of Graves' disease involves autoreactive T cells, which arise through an escape from clonal deletion, through failure of suppressor T-cell activity, or through molecular mimicry to become reactive to TSH receptors.[6,7] Most of the T cells responsible for the reaction are located in the thyroid gland itself. Subsequent thyroid damage from any etiology (e.g., chronic thyroiditis, radiotherapy, smoking, drugs) results in the release of the thyroid autoantigen (TSH receptors). As the autoimmune process amplifies, T lymphocytes are activated, and humoral immunity produces antibodies to the TSH receptor that are stimulatory, resulting in hyperthyroidism. In some patients, underlying chronic thyroiditis may dramatically reduce thyroid reserve, or TSH receptor–blocking antibodies may be present, resulting in "euthyroid" patients with Graves' disease.

Graves' Ophthalmopathy

The extraocular muscles are the site of the most clinically evident changes in patients with Graves' ophthalmopathy. Although the muscles are enlarged on computed tomography (CT) scan, the myocytes themselves appear fairly normal histopathologically.[8] There is an associated intense proliferation of perimysial fibroblasts and dense lymphocytic infiltration. Early reports of circulating autoantibodies against eye muscle antigen in sera from patients with Graves' ophthalmopathy led to the theory that the disease was a result of an autoimmune response directed against the extraocular eye muscle fibers.[9] This theory

began to lose favor as study of these autoantibodies proved them to be neither tissue-specific nor disease-specific. The lack of histologic evidence of cytotoxicity against eye muscle in vivo also argues against this theory.

Attention has now focused on the retrobulbar fibroblast as playing a key role in the pathogenesis of Graves' ophthalmopathy. These fibroblasts have several capabilities that place them at the center of the changes seen in the eye. They secrete a range of glycosaminoglycans (predominantly hyaluronate), the deposition of which is a hallmark of Graves' ophthalmopathy and causes interstitial edema as a result of their intensely hydrophilic nature. These cells can also produce major histocompatibility complex (MHC) class II molecules, heat shock proteins, and lymphocyte adhesion molecules, which allow them to act as target and effector cells in the ongoing immune process in patients with Graves' ophthalmopathy.[10] In addition, autoantibodies against fibroblast antigens have been found in most patients with Graves' ophthalmopathy. These antibodies share some characteristics with TSH receptor antibodies (TRAbs).[5] More recently, probes to TSH receptor messenger RNA (mRNA) have labeled mRNA within the retrobulbar fibroblasts of patients with Graves' ophthalmopathy.[6] The "fibroblast antigen" may be similar to all or part of the TSH receptor, and it represents a shared thyroid-eye antigen. Such an antigenic similarity would explain the immune cross-reactivity between these two seemingly unrelated tissue sites.

Lymphocytes also are active in the ongoing immune process of Graves' ophthalmopathy. Orbital lymphocyte infiltrates have been found to be primarily T cells, including $CD4^+$ (T helper cells) and $CD8^+$ (T suppressor and cytotoxic cells). Cytokines released by T cells have been shown to induce fibroblast proliferation and collagen and glycosaminoglycan deposition. Grubeck-Loebenstein and colleagues[11] cultured retrobulbar suppressor and cytotoxic T cells out of tissues removed at the time of orbital decompression, and found them capable of targeting the retrobulbar fibroblasts. Interactions with fibroblasts resulted in pronounced T-cell cytokine production and fibroblast proliferation without evidence of fibroblast cytotoxicity. The T cell–retrobulbar fibroblast interaction may be responsible for the clinical manifestations of Graves' ophthalmopathy.

Epidemiology and Etiology

An accurate estimate of the prevalence of Graves' ophthalmopathy is difficult to determine and depends in part on the diagnostic criteria used to define the presence of ophthalmopathy. "Lid lag" and "stare" are nonspecific signs and can be seen with thyrotoxicosis stemming from etiologies other than Graves' disease. In an exhaustive review of the literature, Burch and Wartofsky[6] found an incidence of ophthalmopathy in patients with Graves' disease of 10% to 25% if these nonspecific signs were excluded, and 30% to 45% if lid findings were included as diagnostic criteria. When intraocular pressure on upgaze or CT findings also were included, the incidence increased to nearly 70%. The most severe form of Graves' ophthalmopathy with optic nerve involvement and visual impairment occurs in only 2% to 5% of patients with Graves' disease.[12,13]

Effects of Genetics and Sex

The role of genetic predisposition and MHC antigen patterns in patients with Graves' ophthalmopathy has been extensively studied, but remains poorly characterized.[6] Ethnicity seems to play some role; Tellez and coworkers[14] found that European patients with Graves' disease were six times more likely to develop ophthalmopathy than Asian patients with Graves' disease. More important are the influences of sex on the development of Graves' disease and the associated ophthalmopathy. A strong 3:1 female-to-male preponderance exists for Graves' disease,[15,16] which decreases to about 2:1 for patients with Graves' ophthalmopathy. Overall, male patients with Graves' disease have a higher incidence of ophthalmopathy that is more severe and tends to develop later in life.[6]

Effects of Tobacco

Several studies have reported an increased incidence of goiter in tobacco smokers compared with nonsmokers, attributing this to thiocyanate, a known goitrogen that is present in inhaled tobacco smoke.[17,18] Studies have also reported an association between smoking and the incidence and severity of Graves' ophthalmopathy.[14,19] This relationship was not found in patients with other forms of thyroid disease, and suggests the tobacco effects are specific to Graves' disease. It is possible that the decrease in female preponderance in Graves' ophthalmopathy, especially in the more severe forms, may be a reflection of the higher incidence of smoking among male patients, rather than a true sex difference.[6]

Effects of Thyroid Status

The role of thyroid hormonal status in the development and severity of Graves' ophthalmopathy has been particularly difficult to ascertain because of the overlap of thyrotoxicosis with antithyroid therapy in these patients. Thyrotoxicosis alone is thought to have little direct effect on the autoimmune process. It serves as a poor marker for disease severity because the prevalence and course of hyperthyroidism correlate poorly with that of Graves' ophthalmopathy.[6] An improvement in eye status with maintenance of euthyroidism during antithyroid therapy may be more a reflection of improving immune function than a decreased circulating thyroid hormone.

Elevated circulating TSH levels seem to promote eye disease in patients with Graves' disease. Hamilton and colleagues[20] have reported an increased incidence of progressive ophthalmopathy with hypothyroidism, which followed antithyroid therapy. Tamaki and associates[21] described a marked improvement in eye status and a reduction of circulating TRAb in two patients receiving thyroid hormone replacement during antithyroid therapy. The mechanism by which elevated TSH achieves its influence is unclear, but it may serve to up-regulate TSH receptors (apparent autoantigens; discussed later) in thyrocytes[22] and possibly lymphocytes.[23]

Natural History

On summarizing the available literature on the natural history of Graves' ophthalmopathy, Burch and Wartofsky[6] noted the disease tended to progress through a phase of rapid progression (6 to 24 months), followed by a prolonged plateau phase with subsequent slow but incomplete regression of eye changes. Lid retraction and soft tissue changes, such as chemosis and eyelid edema, tended to be short-lived with improvement or resolution over 1 to 5 years (60% to 90%). Ophthalmoplegia resolved incompletely and less rapidly, although 30% to 40% of patients showed some improvement in ocular motility without specific therapy. Proptosis is the eye finding least likely to improve or resolve spontaneously (10%). Trobe[24] reviewed 32 patients with untreated Graves' optic neuropathy and found that vision improved spontaneously in most, but 21% had a final visual acuity of 20/100 or worse, with 5 patients progressing to near blindness. Facing potential loss of sight, it is not surprising that attempts at medical and surgical intervention, some of them heroic, have occurred for the past 80 years.

Clinical Features

Thyroid Disease

A patient with Graves' ophthalmopathy most commonly visits an endocrinologist for management of thyroid disease or an ophthalmologist for evaluation of eye complaints. A thorough history, examination, and high level of suspicion are required to make the diagnosis. Classically, the patient is experiencing hyperthyroidism, and the expected hypermetabolic findings are present at the time of presentation with eye disease. In a review of more than 800 cases from the literature, Burch and Wartofsky[6] found, however, that 20% of patients presented with eye disease before any manifestation of hyperthyroidism, 39% presented concurrently with thyroid disease and eye disease, and 41% presented with eye disease after clinical hyperthyroidism already was evident. In 80% of the patients in whom both diseases eventually manifested, both became clinically evident within 18 months of each other, although some patients may never present with thyroid disease and eye disease, or many years may separate the two presentations.

Pretibial Myxedema

Pretibial myxedema, or thyroid dermopathy, is the localized thickening of the skin, usually in the pretibial area. It occurs in 4.3% of patients with Graves' disease, but at a higher rate (12% to 15%) in patients with Graves' ophthalmopathy,[25,26] and usually is a late manifestation. Conversely, almost all patients with pretibial myxedema have Graves' ophthalmopathy, although the dermopathy may precede the ophthalmopathy. Symptomatic lesions consist of shiny, erythematous-to-brown plaques, nodules, or areas of nonpitting edema, which most commonly occur in the anterior or lateral aspects of the leg or at sites of old or recent trauma. Involvement of other body sites is rare. Almost all patients have high circulating levels of TRAbs, although the true pathogenesis of the dermopathy is not understood. Pretibial myxedema usually is of cosmetic importance only, but if the feet or hands become massively swollen, it can cause functional difficulties.

Graves' Ophthalmopathy

As described previously, Graves' disease occurs more commonly in women and over a broad age range (16 to 81 years), with a mean age in the fifth and sixth decades.[27-29] Eye involvement is bilateral in most patients with Graves' disease, although 5% to 14% of patients have unilateral disease depending on the method of detection.[6] With careful testing (i.e., CT scan), 50% to 90% of these patients show changes in both eyes. In contrast, major asymmetry in the extent of eye involvement is common. Graves' ophthalmopathy remains the most common etiology of "unilateral" proptosis in adults.[30]

Ophthalmopathy Classification

The spectrum of eye changes ranges from eyelid retraction (resulting in the appearance of a "stare"), to proptosis, corneal exposure and ulceration, diplopia, and loss of vision. A clinical classification system for eye involvement by Graves' disease was proposed by Werner in 1969,[31] approved by the American Thyroid Association (ATA), and subsequently modified in 1977.[32] The ATA's detailed classification is shown in Table 126-1. This classification is strictly clinical and has been helpful for reporting purposes. The disease does not progress systematically through the classes, and may skip one or more classes entirely. In addition, the classification system has been criticized for not considering disease activity (stable or rapidly progressing), which is crucial for making patient treatment decisions.[33]

In response to these deficiencies and several other proposed classification schemes, an international ad hoc committee representing the American, European, Asia-Oceanic, and Latin America Thyroid Associations recommended in 1992 a new characterization of Graves' ophthalmopathy (Table 126-2). This system is recommended for use in attempting objective clinical assessment and documenting disease activity, as in clinical studies. The older ATA classification system is still used for educational purposes and clinical evaluation.

Eye Findings

Lid lag and the appearance of a stare are seen in the mildest form (ATA class I disease) of eye involvement by Graves' disease. This involvement is thought to occur initially as the result of an increased sympathetic sensitivity to catecholamines as seen with patients with hyperthyroidism.[34] As the disease progresses, and the lymphocytic inflammatory reaction infiltrates the extraocular muscles and orbital fat, the fibroblasts proliferate and deposit glycosaminoglycans, predominantly hyaluronic acid.[35,36] The resulting muscle and fat enlargement combines with interstitial edema to cause an increase in intraocular pressure.

Intraocular pressure is increased in primary gaze (straight ahead) and even more so in upward gaze (supraduction). This increase in intraocular pressure can lead to a misdiagnosis of glaucoma, with a subsequent delay in appropriate therapy.[28] Over time, increases in intraocular pressure also produce conjunctival chemosis, excessive lacrimation, periorbital edema, and photophobia (ATA class II disease).

As enlargement of orbital muscle and fat progresses, the volume of the orbital contents increases. The orbital cavity has four fixed bony walls with an average volume of 26 mL.[37] In healthy individuals, the globe takes up 30% of this volume, with retrobulbar and peribulbar structures taking up the remaining 70% of the volume. With nowhere else to expand, an increase of only 4 mL in the volume of the orbital contents results in 6 mm of proptosis (ATA class III disease).

As the extraocular muscles become increasingly enlarged by edema and infiltration, they also become dysfunctional, resulting in reduced ocular mobility and diplopia (ATA class IV disease). Over time, the inflammatory response provokes the deposition of collagen by the fibroblasts, replacing the normally elastic muscles of the eye and ultimately causing a permanent fibrotic, restrictive ophthalmoplegia.

Progressive proptosis also dramatically interferes with the protective mechanisms of the cornea, causing exposure, desiccation, irritation, and, ultimately, ulceration (ATA class V disease). Corneal ulceration becomes a vision-threatening problem, with a risk of permanent corneal scarring, and requires immediate attention.

In its most severe form, Graves' ophthalmopathy involves the optic nerve to impair vision (ATA class VI disease). Optic nerve

Table 126-1

Detailed Classification of Eye Changes of Graves' Disease

Classes	Grades	Ocular Symptoms and Signs
0		No signs or symptoms
I		Only signs, no symptoms (signs limited to upper lid retraction and stare, with or without lid lag and proptosis)
II		Soft tissue involvement with symptoms and signs
	o	Absent
	a	Minimal
	b	Moderate
	c	Marked
III		Proptosis ≥3 mm in excess of upper normal limit, with or without symptoms
	o	Absent
	a	3- to 4-mm increase over upper normal
	b	5- to 7-mm increase
	c	≥8 mm increase
IV		Extraocular muscle involvement (usually with diplopia, other symptoms or signs)
	o	Absent
	a	Limitation of motion at extremes of gaze
	b	Evident restriction of motion
	c	Fixation of a globe or globes
V		Corneal involvement (primarily a result of lagophthalmos)
	o	Absent
	a	Stippling of cornea
	b	Ulceration
	c	Clouding, necrosis, perforation
VI		Sight loss (caused by optic nerve involvement)
	o	Absent
	a	Disk pallor or choking, or visual field defect: vision 20/20 to 20/60
	b	Same, but vision 20/70 to 20/200
	c	Blindness (i.e., failure to perceive light, vision <20/200)

Table 126-2

Characterization of Graves' Ophthalmopathy: Recommendations of an International Ad Hoc Committee*

Category of Disease	Objective Criteria Monitored
Eyelid	Maximal lid fissure width Upper lid to limbus distance Lower lid to limbus distance
Cornea	Exposure keratitis assessed by rose bengal or fluorescein staining (indicate presence or absence)
Extraocular muscles	Single binocular vision in central 30 degrees of vision (indicate presence or absence, with or without prisms) One or more of the following measurement techniques Maddox rod test Alternate cover test Hess chart measurements Lancaster red-green test Optional Intraocular pressure in downward gaze CT or MRI
Proptosis	Exophthalmometer reading (CT or MRI measurement may also be used for measurement)
Optic nerve	Visual acuity Visual fields Color vision
Activity score	Sum of 1 point each for any of the following Spontaneous retrobulbar pain Pain with eye movement Eyelid erythema Eyelid edema or swelling Conjunctival injection Chemosis Caruncle swelling
Patient self-assessment	Satisfaction with the following (indicate change with therapy in each using a scale such as *greatly improved, improved, unchanged, worse, much worse*) Appearance Visual acuity Eye discomfort Diplopia

*Consensus of an 18-member ad hoc committee comprising representatives from the American, European, Asia-Oceanic, and Latin America Thyroid Associations.
From Classification of eye changes of Graves' disease. *Thyroid*. 1992;2:235.

involvement typically manifests as a painless gradual loss of visual acuity or visual field,[12] although it can occur precipitously over days to weeks. Although originally thought to be caused by ischemia or venous congestion of the nerve as a result of increased intraocular pressure, there now is convincing evidence to support crowding and compression of the optic nerve at the orbital apex by the enlarged extraocular muscles as the etiology of nerve dysfunction.[38]

Optic nerve function is measured in several ways, one or all of which may be impaired. In one study of 31 patients with optic nerve involvement,[28] visual acuity was 20/25 or worse in 100% of eyes; color vision was decreased in 64%; and visual fields were decreased in 70%, with inferior scotomata and cecocentral scotomata defects most common. Impaired visual fields or color vision also may be found in patients with normal visual acuity.[27]

Clinical Evaluation

Differential Diagnosis

Graves' ophthalmopathy presents a spectrum of clinical manifestations that are reminiscent of other clinical entities. Eye changes range from minimal—requiring a detailed eye examination or CT scan for identification—to dramatic, disfiguring, and vision-threatening changes that eclipse the manifestations of the underlying thyroid disease. The high prevalence of asymmetric eye involvement may also lead the clinician to suspect a unilateral disease process, rather than a systemic one. Although the differential diagnosis for proptosis is extensive (Table 126-3), most other disease entities have only superficial similarities to Graves' ophthalmopathy and can be quickly ruled out. Most importantly, the clinician should maintain a high degree of suspicion if the diagnosis of Graves' ophthalmopathy is to be made in a timely fashion.

Thyroid Function

A full endocrinology workup is essential in the diagnosis and management of Graves' disease. Laboratory testing should include thyroid function tests and a TSH level. In some apparently euthyroid patients, more detailed dynamic testing of thyroid function may be required to uncover thyroid dysfunction. These studies include the suppression of radioactive iodine uptake with triiodothyronine (T_3) to assess for non–TSH-mediated thyroid stimulation, the thyrotropin-releasing hormone stimulation test to determine the presence of low-grade suppression of the hypothalamic-pituitary axis, and TSH stimulation tests of thyroid reserve. Serologic evaluation for evidence of thyroid autoimmunity also can be performed, including microsomal antibody, thyroglobulin antibody, and TRAb assays. Overall, with sufficient scrutiny, most, if not all, patients with euthyroid ophthalmopathy can be shown to have some degree of thyroid dysfunction.[6]

Eye Evaluation

A thorough examination by a skilled ophthalmologist is crucial for the diagnosis and management of Graves' ophthalmopathy. Serial eye examinations are required to monitor disease activity, progression, and response to therapy. The eye examination should include attention to soft tissue changes, including lid edema and retraction, chemosis, scleral injection, limitation of ocular motility, documentation of proptosis (Hertel's exophthalmometer) and intraocular pressure in primary and upward gaze (Schiotz's tonometer), strabismus and visual function in the form of acuity (Snellen's wall chart), color vision (Ishihara's color plates), and visual fields (Goldmann's perimetry).

Imaging Studies

CT scans of the orbit can be helpful in the diagnosis of Graves' ophthalmopathy in euthyroid patients, and are essential if surgical intervention is being considered. Typical findings include a twofold to eightfold enlargement of the extraocular muscle bodies, sparing the tendinous portions (Fig. 126-1). The changes are bilateral in 90% of patients, although asymmetry in the extent of involvement is the rule. The medial and inferior rectus muscles are involved most commonly, although any or all of the muscles may be enlarged.[39] The orbital and extraocular muscle volume can be estimated using CT images.[40-42] Although estimates of extraocular muscle volume have correlated with the presence of optic neuropathy, subsequent studies have not found a correlation between muscle volume estimates and the severity of optic neuropathy or the effectiveness of decompression,[28,43] limiting the usefulness of these estimates.

Table 126-3

Differential Diagnosis of Proptosis

Endocrine
Graves' ophthalmopathy
Cushing's syndrome
Orbital neoplasms
Primary neoplasms
Hemangioma
Lymphoma (may be systemic)
Optic nerve glioma
Choroidal melanoma
Lacrimal gland tumors
Meningioma
Rhabdomyosarcoma
Extension of paranasal sinus tumors
Metastatic disease
Malignant melanoma
Breast carcinoma
Lung carcinoma
Kidney
Prostate
Inflammatory
Orbital pseudotumor
Orbital myositis
Granulomatous
Sarcoidosis
Wegener's granulomatosis
Infectious
Orbital cellulitis
Syphilis
Mucormycosis
Parasitic (trypanosomiasis, schistosomiasis, cysticercosis, echinococcal disease)
Vascular
Miscellaneous
Carotid-cavernous fistula
Lithium therapy
Cirrhosis
Obesity
Amyloidosis
Dermoid and epidermoid cysts
Foreign body

Ultrasound (orbital echography) has been reported to be reliable and effective in evaluating extraocular muscle size.[44] Although not as beneficial in the initial diagnosis and surgical planning as CT scan in patients with Graves' disease, it is proposed as an inexpensive, noninvasive method for monitoring response to therapy (steroids or radiation).

Magnetic resonance imaging (MRI) of the orbits has proved excellent for the evaluation of the soft tissues of the orbit. Extraocular muscle volume can be readily estimated from a single coronal MRI section.[45] Studies have suggested that T2-weighted MR images may provide a sensitive measure of active inflammation in the orbit, giving much needed information on disease activity.[46,47] MRI provides little detail of the bony anatomy of the orbit, which is required if surgical intervention is being considered.

Nuclear medicine studies, such as single photon emission computed tomography (SPECT) imaging using technetium 99m diethylenetriaminepentaacetic acid and gallium 67, have also been used to image the orbit. These studies give reliable information about the level of disease activity within the extraocular muscles.[48,49]

Management of Graves' Ophthalmopathy

A multispecialty team approach for the treatment of patients with Graves' disease and Graves' ophthalmopathy is recommended because of the multiple organ systems involved and the various diagnostic and therapeutic modalities needed to provide optimal care of this complex entity. Team members from endocrinology, radiology, nuclear medicine, radiotherapy, ophthalmology, otolaryngology, head and neck surgery, and neurosurgery are involved to varying degrees. A coordinating member of the team (usually the endocrinologist for Graves' disease and the ophthalmologist for Graves' ophthalmopathy) is crucial for maintaining records, tracking disease progression, and providing continuity of care for long periods.[50]

Medical Therapy

Thyroid Therapy

The management of the thyroid in patients with Graves' disease is controversial, and a complete discussion is beyond the scope of this chapter. The impact of thyroid management on Graves' ophthalmopathy is only now becoming clear. As previously discussed, the correlation between the severity of hyperthyroidism and the prevalence or course of Graves' ophthalmopathy is poor at best. For patients with thyrotoxicosis, the thyroid may be managed with antithyroid drugs (i.e., propylthiouracil and methimazole), radioactive iodine ablation (iodine 131), or thyroidectomy (usually subtotal). Reports on the effect of each of these modalities on the development or progression of ophthalmopathy are conflicting in the literature, although in a more recent prospective study, Tallstedt and colleagues[51] randomly assigned 168 patients into groups receiving antithyroid drugs, radioactive iodine ablation, or surgery. There was no difference in the rate of new-onset or progression of existing ophthalmopathy between the antithyroid drug and surgery groups (10% to 16%), but the radioactive iodine ablation group showed a higher incidence (33%) of these problems.

One possible mechanism for the increase in patients with ophthalmopathy receiving radioactive iodine ablation includes transient hypothyroidism and the release of thyroid antigens, promoting an acceleration of the autoimmune process. In support of this hypothesis, investigators have found that TRAb levels briefly decrease and then show a sustained increase after iodine 131 ablation for Graves' disease.[52] After thyroidectomy, however, TRAb levels showed a transient increase followed by a gradual decrease.[53] Potentially least concerning were TRAb levels, which gradually declined after antithyroid therapy alone. It would seem that radioactive iodine ablation of the thyroid may not be the best option for the management of thyrotoxicosis in patients with Graves' disease. As mentioned previously, thyroid hormone replacement and suppression during antithyroid drug therapy or after radioactive iodine or surgical ablation (before the onset of measurable hypothyroidism) seem to result in a decrease in the prevalence or progression of ophthalmopathy in patients with Graves' disease and should be considered.[21]

Local Therapy

Most patients with Graves' ophthalmopathy experience a self-limited disease course requiring only local measures for symptomatic relief. Corneal exposure and drying respond well to eye drops and nocturnal taping of the eyelid. Some clinicians have found the use of diuretics helpful in decreasing swelling. Sunglasses help with photophobia, and prisms may help with mild strabismus. Topical guanethidine eye drops have been found to reduce lid retraction and lid lag, reportedly by sympathetic blockade of Müller's muscle in the upper lid, but they are poorly tolerated and rarely used.

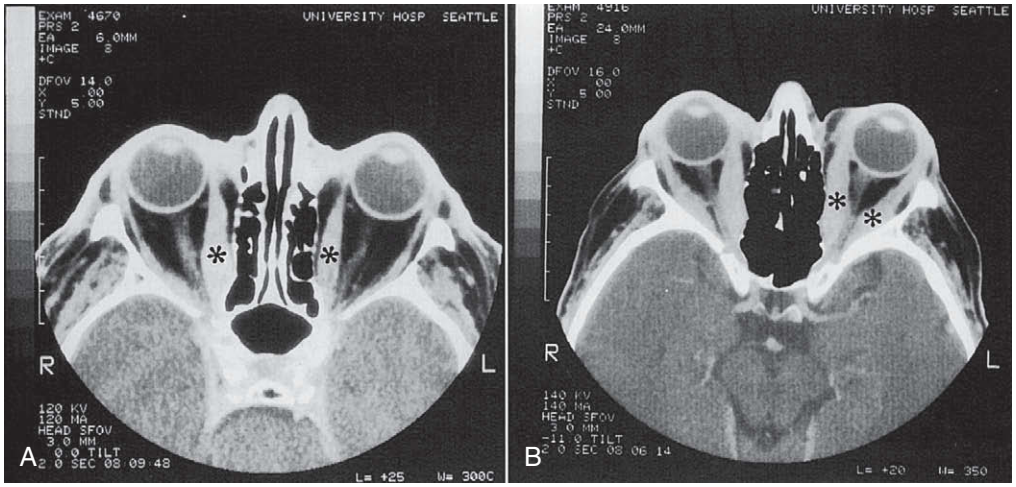

Figure 126-1. **A** and **B,** CT scans through the orbits in two patients with Graves' ophthalmopathy, showing medial rectus muscle enlargement (*asterisks*) with normal lateral rectus muscle size (**A**) and medial and lateral rectus muscle enlargement (*asterisks*) with orbital apex crowding, causing optic neuropathy (**B**).

Steroid Therapy

High-dose corticosteroids (prednisone, 80 to 100 mg/day) are commonly used as the first-line management of more severe Graves' ophthalmopathy. The administration of high doses is maintained for 2 to 4 weeks, followed by a slow taper over several months. Patients experience rapid relief of pain, erythema, and conjunctival edema, and improved vision. Trobe and associates[13] reported a 48% success rate after 2 months of therapy. Steroids may be only temporizing, however, with recurrence of visual loss on taper. Improvement in proptosis and ophthalmoplegia may also be seen with corticosteroid therapy, but generally less so, and these conditions are more likely to recur on steroid withdrawal. The multiple adverse effects of steroid therapy are well known and include glucose intolerance, weight gain, psychosis, peptic ulcer disease, and osteoporosis with vertebral fracture. Corticosteroid therapy should be considered temporizing, while either regression and stabilization of disease or definitive therapy is awaited.

Immunosuppression with cyclosporine also has been evaluated for patients with Graves' ophthalmopathy and has been found to be less effective than prednisone in single-agent therapy.[6] The beneficial effects of both drugs seem to be additive, and maintenance cyclosporine therapy may be corticosteroid-sparing. Careful drug-level monitoring is necessary to avoid nephrotoxicity. Other common adverse effects include hypertension, liver enzyme elevation, gum hypertrophy, and paresthesias. Plasmapheresis to remove circulating antibodies and other immunomodulatory drugs have also been used, but the results suggest further evaluation before widespread use.

Radiotherapy

Radiotherapy to the orbit has been used for more than 85 years for patients with Graves' ophthalmopathy. Traditionally, radiotherapy is accomplished by delivering 20 Gy in 10 fractions of 2 Gy over 2 weeks. The fractions are delivered to a field just behind the lateral canthus to spare the cornea and lens. In a 1989 review of the literature, Sautter-Bihl and Heinze[54] found an overall good to excellent response in 35% to 92% of patients, and improvement of impaired visual acuity in 33% to 85% of patients treated with orbital radiation. The mechanism of action of radiation to the orbit is thought to be in large part an effect on the lymphocytes infiltrating the orbital muscles and fat during the inciting stages of the disease. Patients treated early in the course of the disease with pronounced soft tissue involvement are most likely to benefit. Proptosis, ophthalmoplegia, and optic neuropathy are less responsive, and patients with long-standing stable disease are unlikely to benefit. The portion of the radiation dose delivered to the lens is less than 5% and has not been reported to be harmful.

More recent studies have cast considerable doubt on the efficacy of radiotherapy for Graves' ophthalmopathy. In 2003, Gerling and colleagues[55] found no difference in the documented improvement when patients were treated with very low dose radiotherapy (2.4 Gy) and more standard doses (16 Gy). In another study, improvement in symptoms and clinical findings was not different between patients treated with steroids alone compared with patients treated with steroids plus 24 Gy of radiotherapy.[56] In a prospective randomized trial treating one orbit of each patient with 20 Gy of radiotherapy, Gorman and coworkers[57] were unable to show any significant benefit over the nontreated orbit at 1 year. Long-term follow-up in an uncontrolled fashion also found no benefit from the radiotherapy.[58] Because radiotherapy has potential long-term adverse effects, its usefulness in Graves' ophthalmopathy should be questioned.

Surgical Therapy

Indications for surgical decompression of the orbit have evolved over the years and have included cosmetic management of proptosis, lid lag, and stare, and the management of optic neuropathy.[27,34,59,60] New-onset strabismus after orbital decompression has been reported in 30% to 64% of patients, suggesting that patient selection should be done with caution.[2,60] As a result, many centers perform orbital decompression primarily in the setting of optic nerve involvement combined with failure to respond or inability to tolerate steroid therapy, or for the relapse of symptoms with the taper of steroid therapy.[12,28] Radiotherapy is generally reserved for patients who refuse, cannot tolerate, or fail surgical decompression, although some authors still advocate primary radiotherapy.[61,62]

The goal of surgical decompression of the orbit is simply to expand the bony orbital confines to make room for the increased volume of the orbital contents. Surgical decompression was first described by Dollinger,[63] who advocated removal of the lateral orbital wall for decompression into the temporal fossa (Krönlein's procedure). Twenty years later, Naffziger[64] reported removal of the orbital roof with decompression into the anterior cranial fossa via a transcranial approach. Decompression into the paranasal sinuses was first advocated by Sewell,[65] who described decompression into the ethmoid air cells, and Hirsch,[66] who later reported inferior decompression into the maxillary sinus by removal of the orbital floor. Walsh and Ogura[67] combined the inferior and medial approaches into a single transantral decompression of two orbital walls using the Caldwell-Luc approach (Fig. 126-2). This approach is extracranial, decompresses two walls of the orbit into the largest empty space, and allows gravity to aid in the expansion of orbital contents into the paranasal sinuses. For these reasons, it has become the most widely used technique.

Predicting the results of transantral decompression in patients with severe Graves' ophthalmopathy remains a challenge. In a retrospective analysis of 428 patients, Fatourechi and colleagues[68] reported

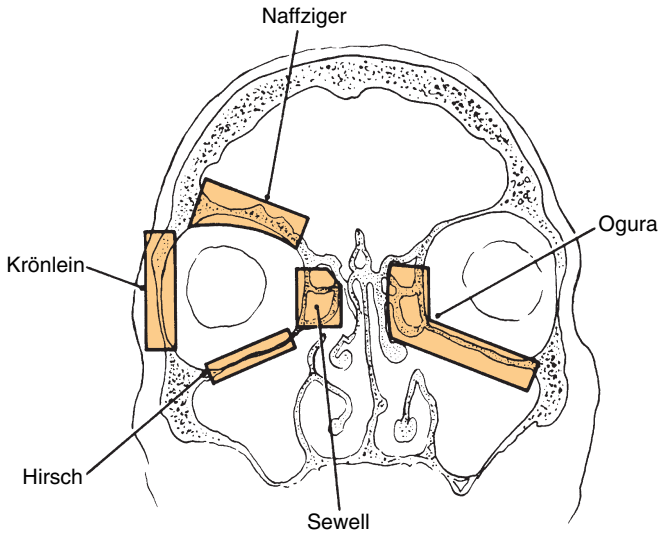

Figure 126-2. Diagram of a coronal section through the skull and paranasal sinuses showing portions of the orbit removed for various methods of orbital decompression.

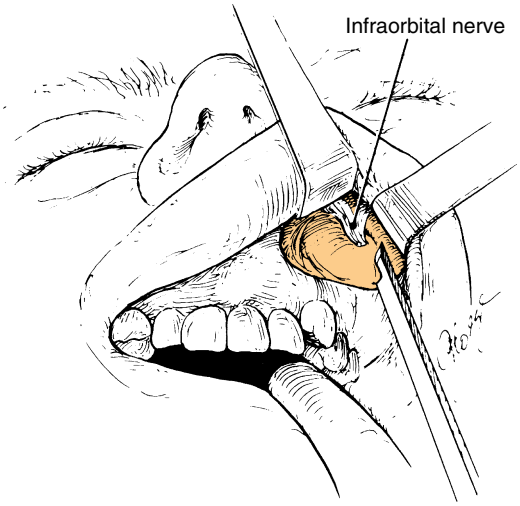

Figure 126-3. Sublabial buccogingival incision that exposes the anterior wall of the maxillary sinus. An osteotome is used to create the antrostomy.

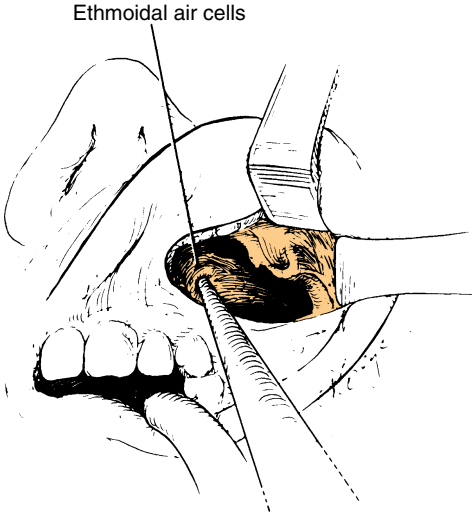

Figure 126-4. Ethmoidal cells are entered with a curette and subsequently removed by curettage and bone-biting forceps.

that young men with long-standing eye symptoms were likely to have more severe initial proptosis. Only the severity of the initial proptosis and the longer postoperative follow-up period correlated with greater recession of proptosis after decompression. Failure of corticosteroid or orbital radiotherapy did not affect the degree of recession of proptosis or improvement in visual acuity. A greater degree of recession of proptosis postoperatively was associated with better visual acuity, but also with a greater likelihood of persistent strabismus. Patient satisfaction with postoperative eye appearance was associated only with procedures performed for cosmetic indications.

Transantral Orbital Decompression

SURGICAL TECHNIQUE. The transantral decompression (Walsh-Ogura method) of the orbital floor and medial wall is performed during general anesthesia with an oral Ray endotracheal tube secured in place. The eyes are protected with topical ointment and are not taped to allow examination of the pupil during the procedure. Intravenous broad-spectrum antibiotics and high-dose corticosteroids (dexamethasone, 8 to 10 mg) are administered before the surgery. A curved sublabial incision with a standard Caldwell-Luc antrostomy and ethmoidectomy is performed (Fig. 126-3). Care is taken to identify and preserve the inferior orbital nerve in its bony canal. An extensive ethmoidectomy should be performed, while preserving the lamina papyracea, middle turbinate insertion, and fovea ethmoidalis (Fig. 126-4). The remaining mucosa is carefully stripped from the maxillary sinus roof, keeping in mind that the inferior orbital nerve is partially or completely dehiscent in 29% of patients.[69]

The bone of the maxillary sinus roof (orbital floor) medial to the infraorbital nerve is carefully removed (Fig. 126-5). This maneuver can be performed using a drill with cutting or diamond burrs or with small osteotomes, as long as the underlying periorbita is not violated. Some surgeons find the operating microscope useful at this stage of the procedure. The lamina papyracea (medial orbital wall) is gently fractured medially and removed up to the posterior ethmoid neurovascular bundle, preserving the periorbita. A No. 12 scalpel blade is used to make incisions in the posterior-to-anterior direction through the periorbital fascia, which allows the immediate herniation of orbital fat through the incision and into the sinuses (Fig. 126-6). This process is begun medial and superior to avoid the loss of visualization as the fat herniates from the orbit. The number of incisions required is determined intraoperatively by assessing the degree of residual proptosis after each incision.

Calcaterra and Thompson[34] recommended operating on the more severe eye first with planned incomplete recession because an additional 1 to 2 mm of recession develops during the first 3 months after surgery. The less severe eye then is decompressed to match the position of the first eye. Four to six incisions in the periorbita usually are adequate.[70] Finally, a large nasoantral window is created, and the sinus is packed with a large Penrose drain coated in antibiotic ointment, which is brought out through the nose for removal the next day. The sublabial incision is closed with absorbable suture. The patient is given antibiotics and corticosteroids intravenously overnight and then orally after discharge from the hospital.

Immediately after surgery, all patients (unless it is medically contraindicated) are given high-dose corticosteroids with a slow taper. The rate of steroid taper is determined by the clinical response to the surgery. In one study, steroid use was discontinued in 80% of patients within 2 months of surgery.[28]

SURGICAL OUTCOME. The results of transantral orbital decompression surgery depend on the indications for the operation. For patients with optic neuropathy, Walsh-Ogura decompression was effective in improving vision in 92% of patients (Fig. 126-7). Equally important, these patients had stabilization of disease with successful taper of steroid therapy. Major improvement in proptosis of 1 to 12 mm can be achieved (Fig. 126-8A), with an average improve-

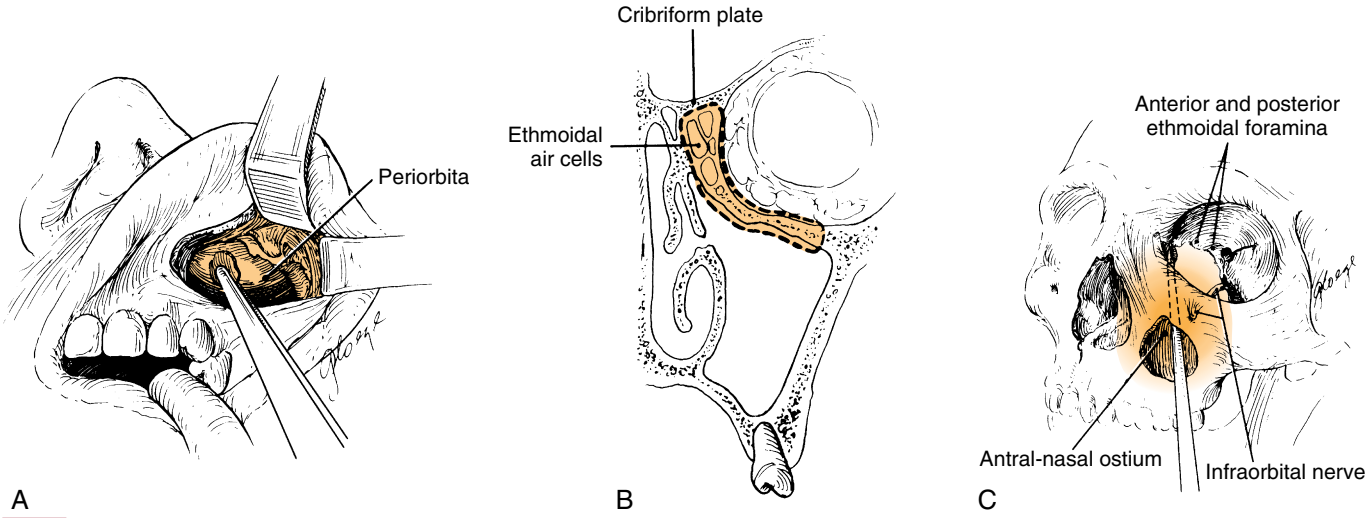

Figure 126-5. **A,** Removal of the floor of orbit after eggshell fracturing of bone. **B,** Coronal section of paranasal sinuses showing the extent of bone removal. **C,** View of the skull showing completion of ethmoidectomy and removal of the lamina papyracea.

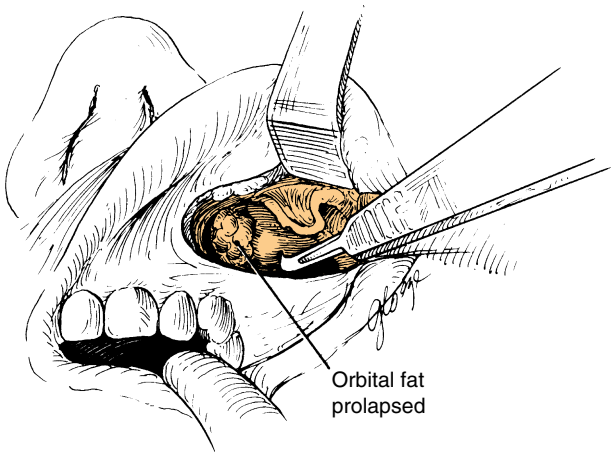

Figure 126-6. Radial incisions in the intact periorbita with a scalpel, permitting prolapse of orbital fat into the sinuses.

ment of 3.4 to 5.3 mm.[28,45,51,60] This decrease in proptosis is of functional and cosmetic benefit and is not seen with either medical therapy or radiotherapy. Major reduction in intraocular pressure (100% of patients) (Fig. 126-8B), improvement of extraocular motility (36%), and improvement of strabismus (47%) are other benefits of decompression.

Transantral decompression failed to stabilize the disease in 3% to 8% of patients who underwent surgery for severe ophthalmopathy.[28,60] In this setting, repeat CT scanning with coronal cuts can be helpful to assess the adequacy of the decompression, and to decide between further surgery using the same approach or via a lateral or superior approach,[71] or proceeding with radiotherapy.

The earlier the diagnosis of Graves' optic neuropathy is made and intervention initiated, the better the outcome will be. When preoperative visual acuity was limited to detecting hand motion or worse, decompression provided little improvement in vision (see Fig. 126-7).[28] When visual acuity allowed counting fingers or better, all patients experienced a favorable outcome.

Ocular dysmotility and strabismus remain a major problem in surgical patients despite decompression. Extraocular motility was impaired (primarily in supraduction) in 92% of patients undergoing decompression; only one third showed improvement, and 9% experienced a worsening of motility postoperatively.[28] Strabismus (diplopia) was present preoperatively in 67% to 85% of patients and in 71% to

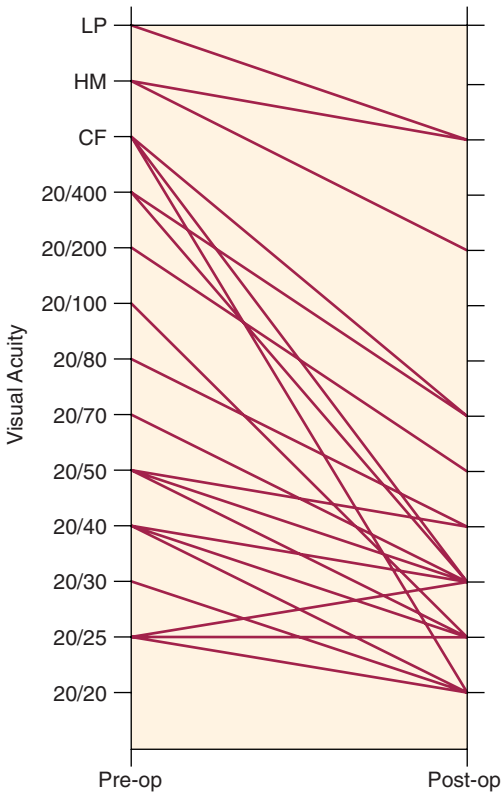

Figure 126-7. Preoperative (*left*) and postoperative (*right*) best corrected visual acuity for 36 eyes in 20 patients undergoing transantral orbital decompression for Graves' optic neuropathy. CF, counts fingers; HM, hand motion; LP, light perception. *(From Girod DA, Orcutt JC, Cummings CW. Orbital decompression for the preservation of vision in Graves' ophthalmopathy.* Arch Otolaryngol Head Neck Surg. *1993;119:229.)*

80% of patients postoperatively.[28,60] When the eye disease was stable, 70% of patients underwent extraocular muscle surgery to correct diplopia, and some were able to be corrected with prisms alone. One long-term follow-up evaluation (average 8.8 years) of 355 patients with decompression reported only 17% having double vision most or all of the time.[60]

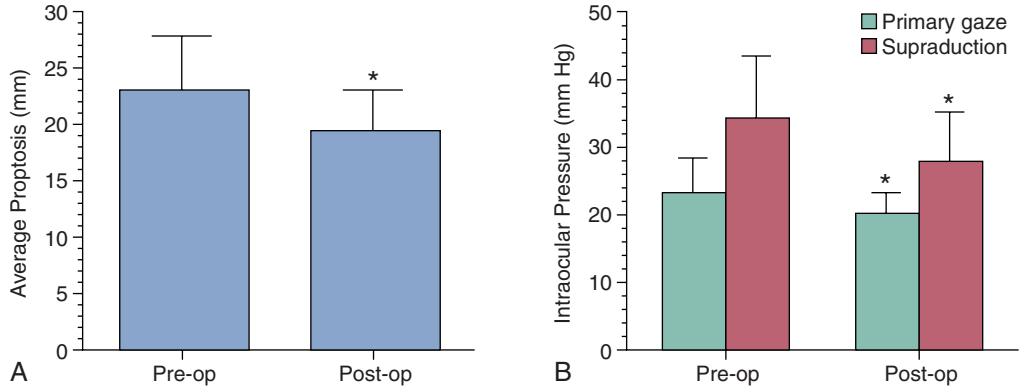

Figure 126-8. A, Preoperative (*left*) and postoperative (*right*) average proptosis for 36 eyes undergoing decompression (see Fig. 126-7). **B,** Intraocular pressure in the same eyes in primary gaze and upward gaze before and after decompression surgery. *$P < .05$.

Transantral decompression for cosmetic indications should be evaluated carefully because it carries the risk of lower patient acceptance of adverse effects than when vision is threatened. Fatourechi and colleagues[59] reviewed the outcomes of 34 patients who underwent transantral decompression for cosmesis and noted a dramatic improvement in proptosis (average 5.2 mm), but no major change in asymmetry between the eyes. Postoperative diplopia developed in 73% of patients who did not have diplopia preoperatively. Half of the patients underwent subsequent extraocular muscle surgery and eyelid surgery. On long-term follow-up evaluation (average 12 years after surgery) of 29 patients, 82% reported they were satisfied with their current eye status. Decompression surgery for cosmetic indications may be appropriate in a select group of patients who are willing to undergo subsequent eye muscle surgery for diplopia.

SURGICAL COMPLICATIONS. Patients uniformly complain of hypoesthesia in the distribution of the inferior orbital nerve immediately after decompression as a result of intraoperative stretching of the nerve with retraction. This hypoesthesia resolves spontaneously over several months in greater than 95% of patients. In one large series, Garrity and associates[60] reported other infrequent complications, including sinusitis (4%), lower eyelid entropion (9%), cerebrospinal fluid leaks (3%), and frontal lobe hematoma (0.2%). Blindness from nerve injury or orbital hemorrhage is rare, but does occur.[48,72] Although theoretically possible, orbital infection has not been reported.

Modifications of Transantral Orbital Decompression

Transantral orbital decompression has held up well to the test of time since its description in 1957. Only in the past several years have advances in surgical technique and instrumentation led to the description of major modifications to the Walsh-Ogura operation. A transorbital approach using a modified blepharoplasty (subciliary) incision provides excellent exposure to the anterior orbital floor and decreases the risk to the infraorbital nerve.[12] This approach also provides access for a lateral orbital wall decompression without disrupting the orbital rim or canthal tendon, providing a three-wall decompression.[73] This method is reported to have a lower incidence of postoperative strabismus, although the reason for this is unclear. Other authors have reported using the transconjunctival approach for the antral-ethmoidal decompression.[72,74] The major criticism of these anterior approaches is limited exposure to the medial orbit, which can restrict the degree of decompression around the orbital apex as is required in patients with optic neuropathy.

Endoscopic Orbital Decompression

With the rapid development and dissemination of endoscopic instrumentation and techniques for transnasal paranasal sinus surgery, it is not surprising that this technology has been applied to include antral-ethmoidal decompression of the orbit. Despite concerns about adequate anterior orbital floor access, Kennedy and coworkers[75] reported equivalent results with transantral decompression and endoscopic decompression. Reports of an average of 3.2- to 5.1-mm reduction of proptosis with an endoscopic decompression of the medial and inferior orbital walls compare well with the traditional approach.[76-78] Metson and Samaha[77] reported a modification to the standard endoscopic decompression that preserves a horizontal sling of periorbita to support the globe position without limiting the degree of decompression. This modification has resulted in a significant decrease in the incidence of new-onset or worsening diplopia after surgery.

Advances in image-guided surgery have resulted in improved intraoperative localization during endoscopic sinus surgery. This technology has found a role in endoscopic orbital decompression surgery as well. The use of the CT-guided technology allows a safer and more aggressive decompression of the orbital apex, orbital nerve (if indicated), and superior medial orbital wall. The inferior orbital nerve also can be easily identified and preserved. Equally helpful is the ability to assess and measure the degree of orbital content decompression into the sinuses intraoperatively using measurements on the CT scans (Fig. 126-9).

Combined Endoscopic and Open Approach to Orbital Decompression

For a more thorough optic nerve decompression, Khan and associates[79] have described a combined transconjunctival-endoscopic decompression of the orbit. The addition of a small medial external skin incision also aided the retraction of the orbital contents to allow the dissection of the medial wall beyond the posterior ethmoidal neurovascular bundle up to the optic canal. Experience with 72 orbital decompressions in 41 patients resulted in an average reduction of proptosis of 3.65 mm, an 89% improvement in vision, and minimal complications.[80] Other authors have combined the endoscopic orbital decompression with a percutaneous lateral orbital wall decompression via the upper lid crease resulting in additional decompression (≤6.9 mm).[76,81] In addition, Metson and colleagues[82] have successfully performed combined endoscopic and lateral wall decompressions during local anesthesia, which has the advantage of avoiding general anesthesia and permitting intraoperative monitoring of visual function, crucial for surgery on an only-seeing eye. In this setting, if both eyes are to be decompressed, they are done so in stages.

Balanced Orbital Decompression

In an attempt to reduce the incidence of new-onset diplopia after orbital decompression surgery, several authors have advocated removing the medial and lateral walls of the orbit without decompressing the orbital floor. This "balanced" approach decompresses equally medially and laterally and is less likely to affect the position of the globe.[81,83,84] Postoperative new-onset diplopia is reported in 0% to 15% of patients with this technique. The degree of decompression with this two-wall approach can be comparable to the three-wall medial-inferior-lateral decompression if orbital fat is resected at the time of the decompression.[81]

Combined Endoscopic Orbital and Optic Nerve Decompression

A more recent adjunct to standard endoscopic orbital decompression for dysthyroid ophthalmopathy is endoscopic optic nerve decompression. In certain cases of thyroid ophthalmopathy with progressive optic neuropathy, it has been hypothesized that direct compression of the optic nerve is the cause of visual deterioration. In a study on patients with optic neuropathy, analysis of CT scans showed that patients have increased apical crowding with flattening of the optic nerve at or near the orbital apex from compression by enlarged extraocular muscles compared with controls.[38] The compressive forces are thought to result in conduction block and focal demyelination, as the optic nerve remains in its fixed bony canal. Release of the nerve from its bony confines may alleviate the detrimental effects of the compressive forces.[85]

Previously, surgical approaches for optic nerve decompression were developed for traumatic optic neuropathy and have included transorbital, extranasal transethmoid, transantral, intranasal microscopic, and craniotomy approaches. Advances in endoscopic equipment, in addition to curved diamond burrs and image guidance systems, have allowed for safe endoscopic optic nerve decompression all the way back to the orbital apex. After a standard sphenoethmoidectomy is performed, the sphenoid face is widely opened, and the carotid artery and optic canal bulge are identified on the lateral sphenoid wall. The medial orbital wall is decompressed, and the thick bone overlying the optic canal is thinned with a diamond burr with careful avoidance of the prominence overlying the carotid artery. A microcurette is used to fracture the bone medially and allow for decompression of the optic nerve from its bony canal. Preliminary studies have not shown whether the additional incisure of the optic nerve sheath is necessary for adequate decompression considering the possible damage to optic nerve fibers and the ophthalmic artery, and cerebrospinal fluid leak.[85,86]

Reports of this technique are very preliminary in the literature. Luxenberger and colleagues[86] described four patients in whom a combined endoscopic orbital and optic nerve decompression was performed. In that study, two patients had improved vision, one patient's vision improved and then deteriorated, and the final patient did not have sufficient ophthalmologic data. In a more recent review of this new technique combining endoscopic optic nerve decompression with standard endoscopic orbital decompression, Pletcher and associates[85] noted an improvement in visual acuity in 8 of 10 patients with nontraumatic optic neuropathy, including Graves' ophthalmopathy.

Other Approaches for Orbital Decompression

A modification of the Walsh-Ogura method called the three-wall orbital decompression refers to the addition of the lateral wall decompression to the standard antral-ethmoidal decompression. This addition can be achieved by any combination of approaches, including a modified blepharoplasty incision, a sublabial or transconjunctival incision plus an anterior orbitotomy, or a bicoronal forehead flap. The advantage of the three-wall decompression is that it allows the further enlargement of the orbital volume by expansion into the temporal fossa and the paranasal sinuses. Metson and colleagues[76] were able to increase the recession of proptosis from an average of 3.2 to 5.6 mm with the addition of the lateral decompression to the endoscopic antral-ethmoid

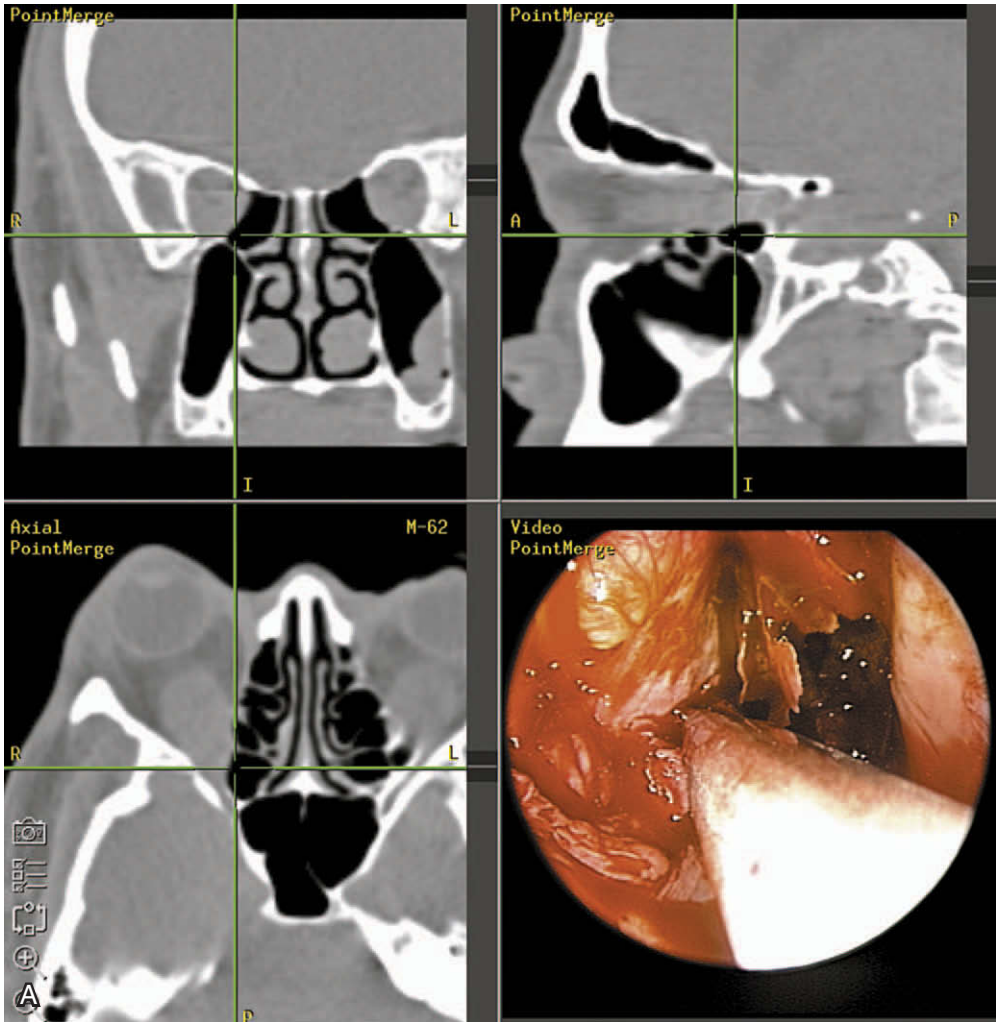

Figure 126-9. View from a CT image–guided system during orbital decompression surgery. **A,** Images showing initial periorbita incision at the orbital apex with herniation of orbital fat seen on the video image.

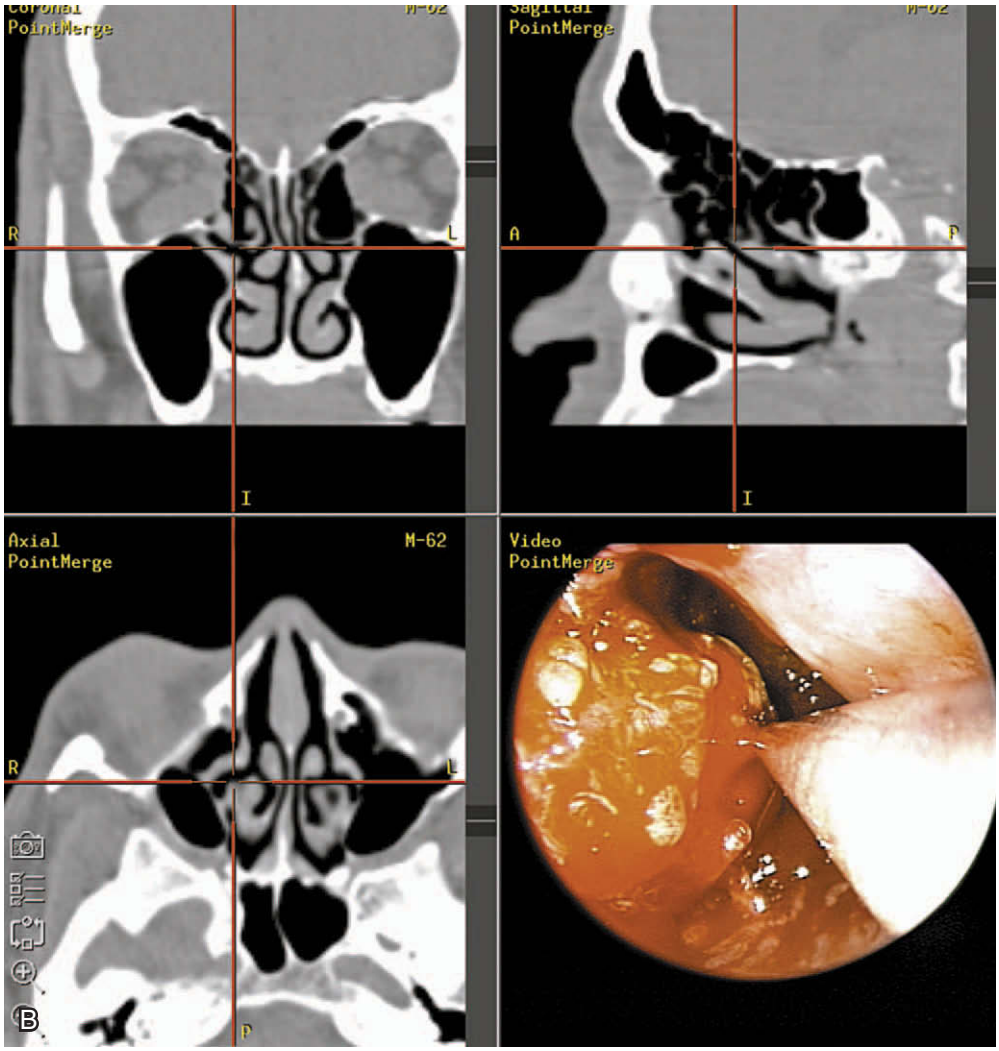

Figure 126-9, cont'd **B,** Images showing inferomedial periorbita incision with extensive orbital fat decompression into the sinus cavity. The degree of decompression can be readily assessed on the CT images.

decompression. Other authors[87,88] prefer the bicoronal approach to the three-wall decompression, even for unilateral decompressions. Although dramatic decompression is reported (average 7.5 mm), a high complication rate can be expected, including infraorbital hypoesthesia (70%), supraorbital hypoesthesia (60%), and frontalis palsy (30%).[87]

A two-wall decompression of the superior-lateral orbit can be achieved through a bicoronal incision with subsequent frontal craniotomy[64,89] or a lateral rim approach.[90] This approach allows decompression of the orbital contents into the anterior cranial fossa and temporal fossa. Expansion of orbital contents into the empty paranasal sinuses with the help of gravity would be predicted to provide a more adequate decompression, although in a cadaveric study, Stanley and coworkers[91] found the superior-lateral decompression to be as effective as the antral-ethmoidal decompression in withstanding intraocular pressure increases and in allowing orbital recession. The craniotomy approach has the advantages of direct access to the optic canal for superior decompression and of potential additional medial orbital wall decompression via the ethmoid sinuses. The orbital rim approach has the advantage of less dural exposure and the ability to advance the superior orbital rim with plates, screws, and bone grafts to increase orbital volume further.[90] Because the superior-lateral decompression is a more involved procedure with the violation of the cranial cavity, regardless of the approach, most centers reserve it for patients in whom antral-ethmoidal decompression has failed.

Classic descriptions of orbital decompression have always referred to the removal of one or more orbital bony walls. Trokel and associates[62] have reported successful decompression of the orbit strictly by the removal of orbital fat via superior and inferior orbitotomies without any bone removal. This procedure was reserved primarily for cosmetic indications in patients with inactive disease. An average reduction in proptosis of 1.8 mm was achieved, although patients with large amounts of fat seen by CT scan and with greater preoperative proptosis had more dramatic reductions. There were no new long-term motility problems commonly reported with bony orbital decompression for cosmesis, which may be an important decompression option for cosmetic indications in an attempt to reduce postoperative strabismus and the need for subsequent eye muscle surgery.

Ancillary Procedures

Extraocular Muscle Surgery

Extraocular motility problems resulting from Graves' ophthalmopathy are not likely to resolve spontaneously with disease regression and are mostly refractory to medical management. Extraocular motility problems are also the manifestation of eye involvement most likely to develop or worsen after orbital decompression.[92] Although disturbing, this is not surprising because irreversible extraocular muscle fibrosis is seen late in the disease. In one study, 70% of patients with decompression ultimately underwent eye muscle surgery for strabismus after the eye disease was stable.[60]

The indications for eye muscle surgery are diplopia in the primary and reading positions, with the goal being to restore single vision in

these positions. It is unlikely that eye muscle surgery would achieve single vision in all positions because of the baseline restrictive ophthalmoplegia induced by the disease. Dyer[93] reviewed 290 patients with Graves' ophthalmopathy requiring eye muscle surgery, and found 59% required a single procedure, 30% required two procedures, and 12% required three or more procedures to achieve single vision in the primary and reading positions.

The timing of eye muscle surgery is crucial for predictable results. Patients not requiring orbital decompression for Graves' ophthalmopathy should manifest stable disease with corticosteroid administration for 6 months to avoid subtle changes in the muscles over time. If these patients have serious proptosis, orbital decompression should be considered before eye muscle surgery, which may exacerbate the proptosis and corneal problems.[93] In addition, a decompression is likely to alter the position of the globes and disturb the gaze, and it should be completed before eye muscle surgery. Because recession of the globe is progressive for several months after an orbital decompression, it is advisable to delay eye muscle surgery for 2 to 3 months.

Eyelid Surgery

Surgery on the eyelids may be required early or late in the management of Graves' ophthalmopathy. Early in the disease, a lateral tarsorrhaphy may be needed urgently to provide corneal coverage and protection as a temporizing measure while medical therapy is instituted. Late in the course of the disease, eyelid surgery may be indicated for cosmesis and corneal protection in patients with permanent lid retraction. Multiple upper eyelid procedures have been described, including excision or recession of Müller's muscle, levator aponeurosis transection or recession with or without scleral grafts, and levator myotomy.[6] Similar procedures have been described for the lower lid. In the overall rehabilitation of the eye, eyelid surgery should be delayed for 1 year after control of hyperthyroidism and at least 6 months after eye disease stabilizes.

Summary

Although more recent studies on the etiology of Graves' disease suggest a common thyroid-eye antigen (TSH receptor), this difficult and debilitating disease is still not preventable. Further advances in the identification of the specific autoantigenic site in the eye and the thyroid, and in antigen-specific immunotherapy are necessary before a major shift in management can occur. Until that time, therapy for Graves' disease and the associated Graves' ophthalmopathy remains palliative. A team approach to these patients is warranted because of multiple organ system involvement and the complexity of manifestations encountered. Optimal therapy can be provided only through close collaboration between team members.

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CHAPTER ONE HUNDRED AND TWENTY-SEVEN

Anatomy of the Temporal Bone, External Ear, and Middle Ear

Howard W. Francis

Key Points

- The temporal bone consists of four embryologically distinct components: the squamous, mastoid, petrous, and tympanic parts.
- The temporal line is located about 5 mm inferior to the lowest level of the middle fossa floor.
- The mastoid antrum is located deep to the depressed cribriform area located posterior to the spine of Henle, known as Macewen's triangle.
- The stylomastoid foramen is located at the anterior limit of the digastric groove.
- The arcuate eminence is the prominence of the superior semicircular canal on the middle fossa floor.
- Potential paths of tumor spread from the external auditory canal (EAC) and include the bony-cartilaginous junction, the foramen of Huschke, and the fissures of Santorini.
- The outer and middle ears are derived from the first and second branchial grooves and pouches. The middle ear structures arise from the corresponding arches.
- The epitympanum and mesotympanum are separated by the ossicular chain and associated mucosal folds leaving only narrow apertures for air supply to the attic and antrum.
- Middle ear landmarks of the facial nerve include the cochleariform process, the oval window, and the pyramidal eminence.
- The most vulnerable portion of the ossicular chain is the long process of the incus, which possesses a single nutrient vessel and lacks collateral circulation.
- The supratubal recess, located at the anterior extreme of the attic and superior to the opening of the eustachian tube, is a site in which cholesteatoma or blind surgical dissection can injure the facial nerve. The geniculate ganglion is located just deep to its medial wall and may be dehiscent.
- The labyrinthine segment of the facial nerve is particularly vulnerable to injury because of watershed vertebrobasilar/external carotid circulation, narrow bony canal, and proximity to the genicular ganglion where herpetic infections and traumatic distortion of thin surrounding bone may produce nerve swelling and entrapment in the labyrinthine segment.

Multiple intracranial and extracranial regions interface with the temporal bone, the anatomy of which reflects its unique role in the embryology of the head and neck, and in the transit of vessels, nerves, and pathogens between these regions. Understanding of this anatomy is required for a full appreciation of the etiology and safe and effective treatment of diseases of the ear. This chapter presents anatomic features of the ear that inform the clinician's understanding of disease and surgical management. More detailed descriptions of structure can be found in cited references.

Osteology of the Temporal Bone

The temporal bone articulates with the sphenoid, parietal, occipital, and zygomatic bones, contributing to the cranial, skull base, and facial structure. The temporal bone has a pyramidal shape, the sides of which form the middle fossa floor (superior face), the anterior limit of the posterior fossa (posterior face), muscle attachments of neck and infratemporal fossa (anteroinferior face), and the muscular-cutaneous–covered side of the head (lateral), which forms the base of the pyramid. The temporal bone consists of four embryologically distinct components: the squamous, mastoid, petrous, and tympanic parts.[1]

The squamous part forms the lateral wall of the middle fossa (Fig. 127-1). It consists of a plate of bone with an anterior extension known as the zygomatic process, which forms the bony roof of the glenoid fossa. The temporalis muscle inserts on the outer cortex, whereas the masseter muscle inserts on the zygomatic process. A horizontal ridge known as the temporal line is formed along the most inferior insertion by the temporalis muscle, is aligned with the zygomatic process, and is used as a surface landmark that estimates the location of the middle fossa floor,[2] with an average offset of about 4.7 mm.

The mastoid part is a bulbous bony structure shaped by the expansion of air-filled spaces within (see Fig. 127-1). The constant pull by the sternocleidomastoid muscle and posterior belly of the digastric muscle elongates the mastoid inferiorly to form the mastoid tip or process. The mastoid cortex is perforated by multiple small emissary vessels that drain from the central air cell or antrum, forming a depressed cribriform area at the anterior junction of the mastoid process with the tympanic bone. The foramen of a single emissary vein is evident near the posterior limit of the outer mastoid cortex, and communicates with the sulcus of the sigmoid sinus, which is evident on the posterior medial aspect of the temporal bone. The site of the sternocleidomastoid muscle

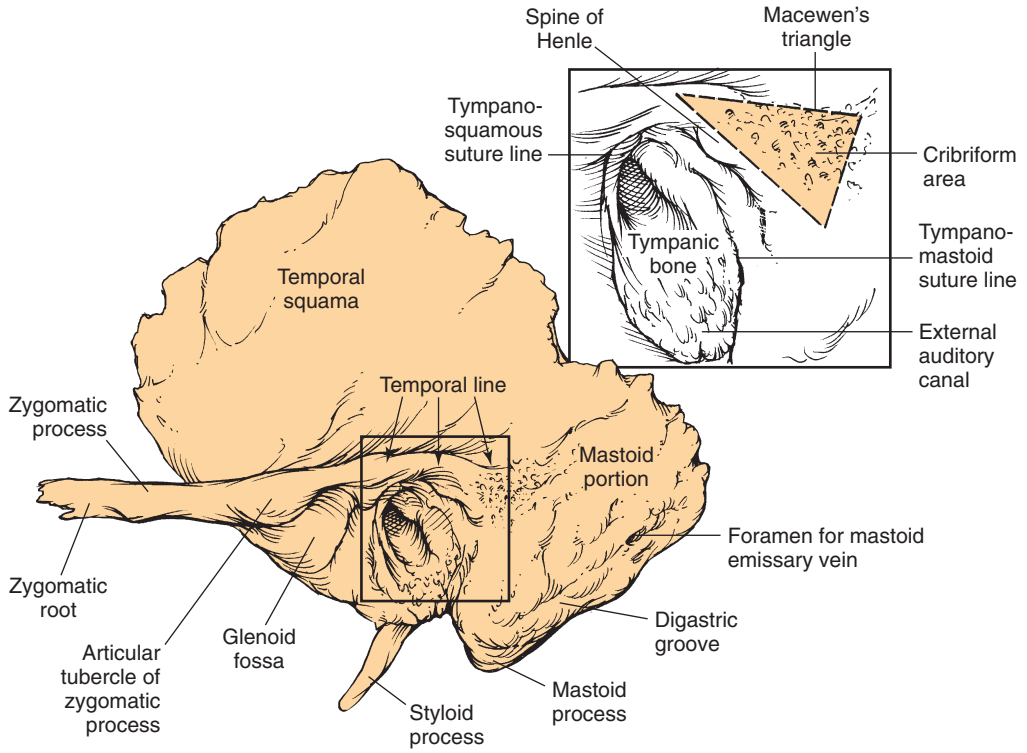

Figure 127-1. Lateral view of left temporal bone surface, showing squamous, tympanic, and mastoid portions. *(Redrawn from art by Sarah Williamson, provided courtesy of H. W. Francis and J. K. Niparko.)*

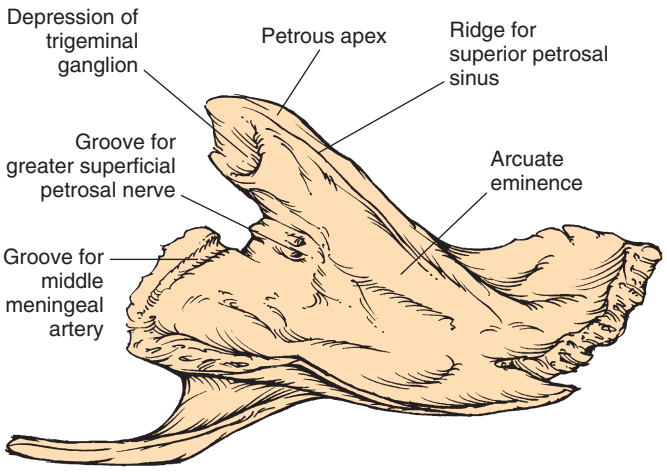

Figure 127-2. Superior view of left temporal bone showing petrous and squamous portions forming the floor of the middle fossa and anterior limit of the posterior fossa. *(Redrawn from art by Sarah Williamson, provided courtesy of H. W. Francis and J. K. Niparko.)*

insertion is indicated by a rough, irregular surface at the mastoid tip. Medial to the mastoid tip, the posterior belly of the digastric muscle is inserted in a sulcus that terminates anteriorly at the stylomastoid foramen. Medial and almost parallel to the digastric sulcus is the sulcus for the occipital artery.

The petrous part has the shape of a pyramid whose base is united with the mastoid laterally; the apex is oriented anteromedially between occipital and sphenoid bones. The *anterior surface* forms the posteromedial margin of the middle fossa floor (Fig. 127-2). Significant surface features include (1) medially, the arcuate eminence formed by the prominence of the superior semicircular canal, and the sulcus of the superior petrosal sinus; (2) anteriorly, at the junction with the greater sphenoid wing, the musculotubal canal containing the more superficial semicanal of the tensor tympani and a deeper semicanal of the eustachian tube; and (3) at the apex, a smooth depression occupied by the trigeminal ganglion, just posterior to which is located foramina and sulci of the greater and lesser superficial petrosal nerves, running parallel to the sphenoid suture line. The roof of the middle ear and mastoid is located lateral to the arcuate eminence.

The *posterior surface* of the petrous part of the temporal bone is oriented in the vertical plane forming the anterior bony limit of the posterior fossa (Fig. 127-3). This surface is framed by sulci for the sigmoid sinus, and the superior petrosal and inferior petrosal sinuses. At the center of the posterior face is the porus acusticus at the fundus of which can be seen the falciform (horizontal) crest, Bill's bar (vertical crest), and foramina of cranial nerves VII and VIII. The subarcuate artery emerges from a depression superior and lateral to the acoustic meatus, whereas the endolymphatic sac and duct occupy the depression and opening located inferolaterally, known as the operculum. The jugular foramen is formed at the junction between the petrous and occipital bones (Fig. 127-4), and is partitioned into the pars nervosa (posterior) and pars venosa (anterior) by the jugular spine or process.[3]

The *inferior surface* of the temporal bone is irregular because of the presence of multiple muscle attachments (Fig. 127-5). The external aperture to the cochlear aqueduct is located just medial and anterior to the jugular spine within the pars nervosa, and marks the superiormost limit of the jugular foramen. The glossopharyngeal nerve enters the jugular foramen adjacent to the opening of the cochlear aqueduct. In the translabyrinthine approach to the internal auditory canal, the cochlear aqueduct is an important inferior limit of dissection used to protect the lower cranial nerves. The cochlear aqueduct eventually opens into the scala tympani at the cochlear base.[4-6] The jugular bulb occupies a dome-shaped compartment located lateral to the pars venosa of the jugular foramen directly under the middle ear space. The inferior foramen of the carotid canal is located directly anterior to the jugular bulb depression, from which it is separated by a wedge-shaped bone called the keel. The tympanic canaliculus penetrates the keel to transmit sensory and preganglionic parasympathetic fibers from the inferior

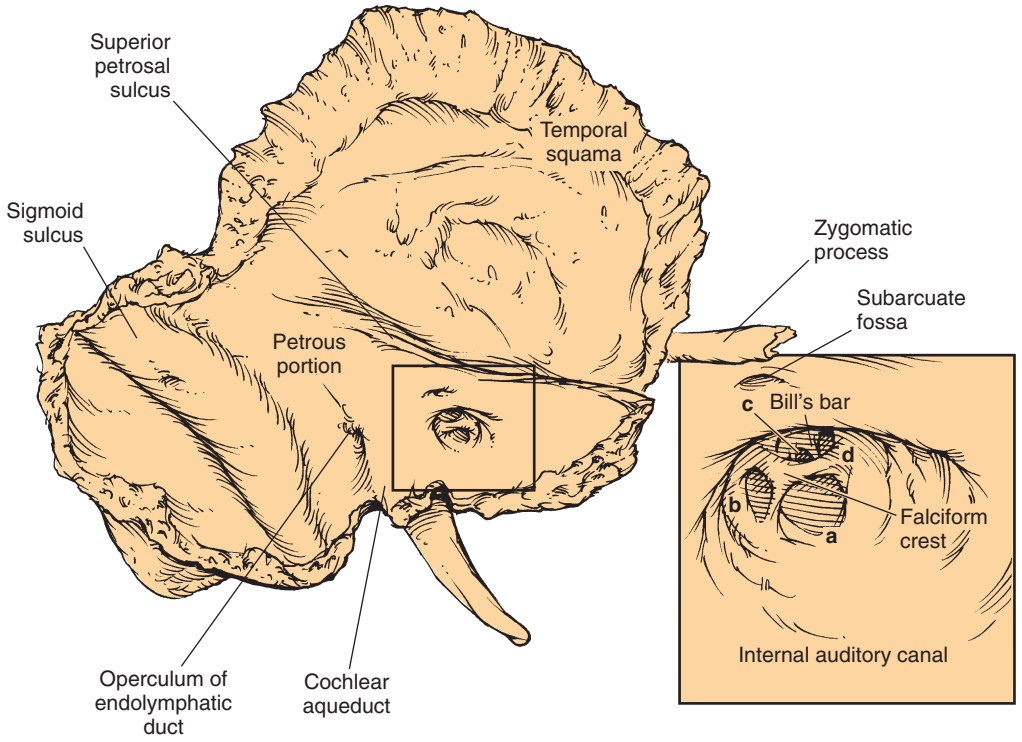

Figure 127-3. The posterior surface features of the left temporal bone, including the fundus of the internal auditory canal. Foramina for cranial nerves VIII (*a,* cochlear division; *b,* inferior vestibular division; *c,* superior vestibular division) and VII (*d*) are shown. *(Redrawn from art by Sarah Williamson, provided courtesy of H. W. Francis and J. K. Niparko.)*

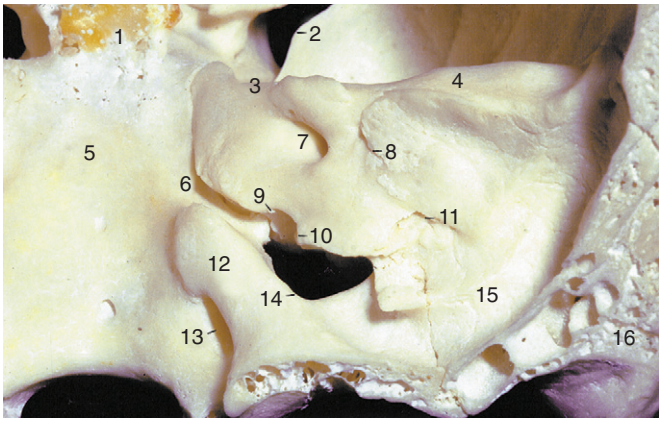

Figure 127-4. Medial view of petrous bone (right side). *1,* sella; *2,* superior orbital fissure; *3,* trigeminal impression; *4,* superior petrosal sinus impression; *5,* clivus; *6,* petro-occipital sulcus; *7,* internal auditory canal; *8,* subarcuate fossa; *9,* cochlear aqueduct; *10,* jugular process; *11,* vestibular aqueduct; *12,* jugular tuberculum; *13,* hypoglossal nerve canal; *14,* jugular foramen; *15,* sigmoid sinus impression; *16,* mastoid bone.

ganglion of the glossopharyngeal nerve into the middle ear as Jacobson's nerve.[1,5] The styloid process is located anterior to the stylomastoid foramen, and both are located at the anterior limit of the digastric groove.

The tympanic part of the temporal bone forms the anterior wall, floor, and part of the posterior wall and roof of the bony external auditory canal (EAC), and the anterior wall and floor of the middle ear (see Fig. 127-1). The anterior edge of this open ring forms the tympanosquamous suture line within the EAC, and the petrotympanic suture line within the middle ear, through which the chorda tympani exits the ear. The posterior edge of the tympanic ring forms the tympanomastoid suture line, which curves from the posterior EAC inferiorly to within millimeters of the stylomastoid foramen, serving as a landmark for the main trunk of the facial nerve as it exits the temporal bone (see Fig. 127-5).

External Ear

The auricle is a funnel-shaped cartilaginous structure that is continuous with the meatus and EAC (Fig. 127-6). Intricate ridges and depressions formed by the auricular cartilage and cutaneous envelope are shown and labeled in Figure 127-5. The blood supply of the external ear originates from the external division of the carotid artery via the posterior auricular and superficial temporal vessels. The EAC (Fig. 127-7) is about 2.5 cm long and is composed of a lateral cartilaginous (membranous) portion and a medial bony portion.[1,7] The membranous portion accounts for the lateral third of the EAC, whereas the bony portion forms the medial two thirds. The skin lining the membranous canal is thicker, more mobile, and endowed with sebaceous and apocrine (ceruminous) glands and hair follicles. Sebaceous and apocrine ducts empty into a follicular canal surrounding each hair follicle.[5,7]

The bony portion of the canal is lined by thin, immobile skin that lacks hair and glands, and is continuous with the epithelium of the tympanic membrane. The bony-cartilaginous junction is the narrowest point or isthmus of the EAC, where a fibrous interface serves as a potential pathway for spread of malignant disease beyond the ear. For this reason, en bloc resection of the lateral temporal bone is necessary to eradicate primary malignancies of the EAC. The bony-cartilaginous junction is also the site at which underlying osteomyelitis manifests as mounds of granulation tissue in the EAC, a finding that is pathognomonic for malignant otitis externa. The incomplete ossification of the anterior bony canal produces an opening into the infratemporal region, known as the foramen of Huschke, which may also serve as a means for extension of malignant tumors from the EAC to the deep lobe of the parotid gland. Naturally occurring defects in the cartilaginous portion of the EAC, known as the fissures of Santorini, also provide avenues of spread to the superficial lobe of the gland.

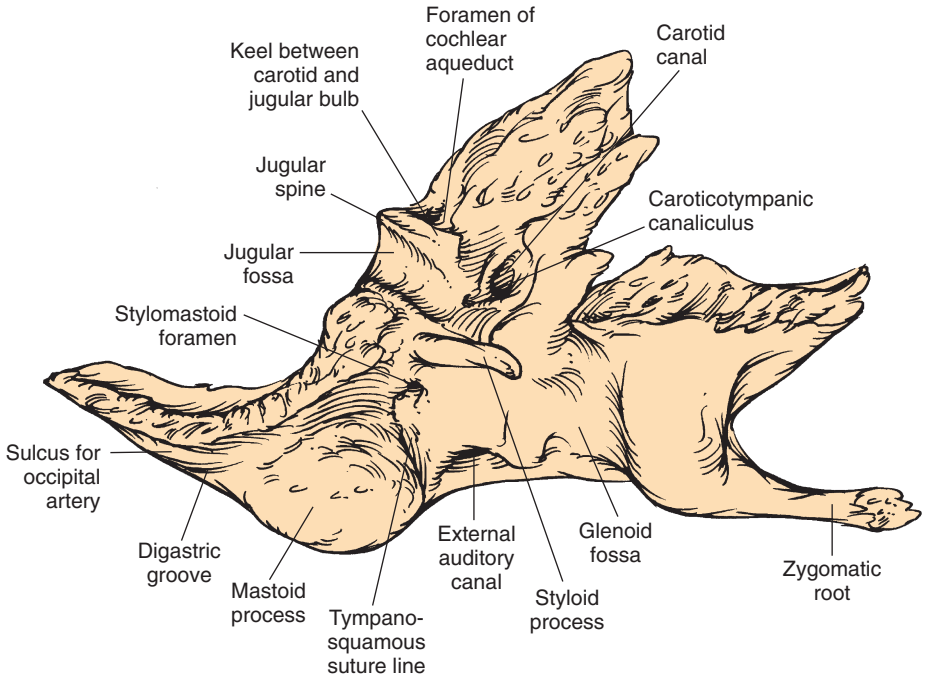

Figure 127-5. Inferior view of the left temporal bone. Note the linear relationship between the stylomastoid foramen, digastric groove, and styloid process. *(Redrawn from art by Sarah Williamson, provided courtesy of H. W. Francis and J. K. Niparko.)*

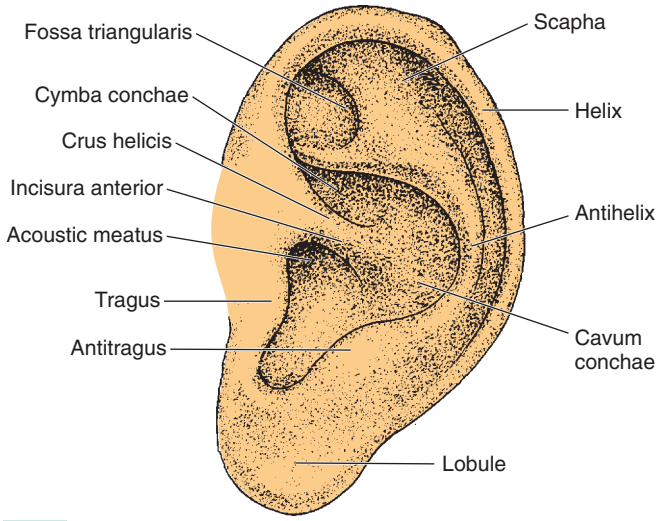

Figure 127-6. Surface anatomy of the auricle. *(Adapted from Adamson PA, Tropper GJ, McGraw BL. Otoplasty. In: Krause CJ, Mangat DS, Pastorek N, eds.* Aesthetic Facial Surgery. *Philadelphia: Lippincott; 1991:709.)*

The external ear is developed from ectodermal and mesodermal components of the first and second branchial arches and the intervening first branchial groove.[8,9] Distinct condensations of tissue, known as the hillocks of His, give rise to the tragus and most of the helix from the first branchial arch, and to the antihelix, antitragus, lobule, and inferior helix from the second branchial arch. Sensory innervation is provided by the corresponding first branchial nerve: the auriculotemporal branch of the trigeminal nerve and a cutaneous branch of the facial nerve. The EAC develops from the dorsal portion of the first branchial cleft, which extends toward and eventually makes contact with endoderm of the expanding tubotympanic recess. There is a transient obstruction of the medial canal by proliferating epithelial cells to form a meatal plug that eventually dissolves, leaving a patent canal.

Errors of embryogenesis may result in impaired hearing or render the ear vulnerable to other conditions. The failed or incomplete involution of the meatal plug results in canal atresia or severe stenosis with conductive hearing loss and the risk of canal cholesteatoma. Auricular anomalies may also result from imperfect development of the hillocks of His with consequences ranging from anotia to the development of preauricular cysts and sinuses by duplication of the first branchial groove and arch.[10]

Tympanic Membrane

The tympanic membrane forms the medial wall of the EAC and much of the lateral wall of the middle ear space. It is a four-layered, concave-shaped membrane connected centrally to the manubrium of the malleus and peripherally to the tympanic sulcus.[1,4,5] The tip of the malleus is attached to the depression known as the umbo, superior to which the manubrium forms the mallear stria, which extends to the mallear prominence formed by the lateral process (Fig. 127-8).

Two dense fibrous layers provide the structural support for thin EAC skin laterally and middle ear mucosa medially. The outer radiate fibrous layer inserts on the manubrium of the malleus, and the deeper circular fibrous layer is arranged circumferentially near the circumference of the tympanic membrane. Both layers become integrated peripherally into a fibrocartilaginous ring, the annular ligament that anchors the tympanic membrane to a bony sulcus within the tympanic ring. This tympanic sulcus terminates superiorly at anterior and posterior spines, to which the most superior edge of the fibrous layer is attached to form posterior and anterior mallear folds that insert on the lateral process of the malleus. The small area of tympanic membrane located superior to the anterior and posterior mallear folds lacks a fibrous layer and is attached superiorly to the bony rim of the notch of Rivinus. The thinner superior segment of tympanic membrane is known as pars flaccida or Shrapnell's membrane, and the thicker inferior area is known as pars tensa.

The otoscopic examination consists of the careful evaluation of the EAC skin, the surface anatomy of the tympanic membrane, and direct or indirect examination of middle ear anatomy as seen through the translucent membrane or perforations. The round window, long process of the incus, incudostapedial joint, and chorda tympani are identifiable through the intact tympanic membrane to varying

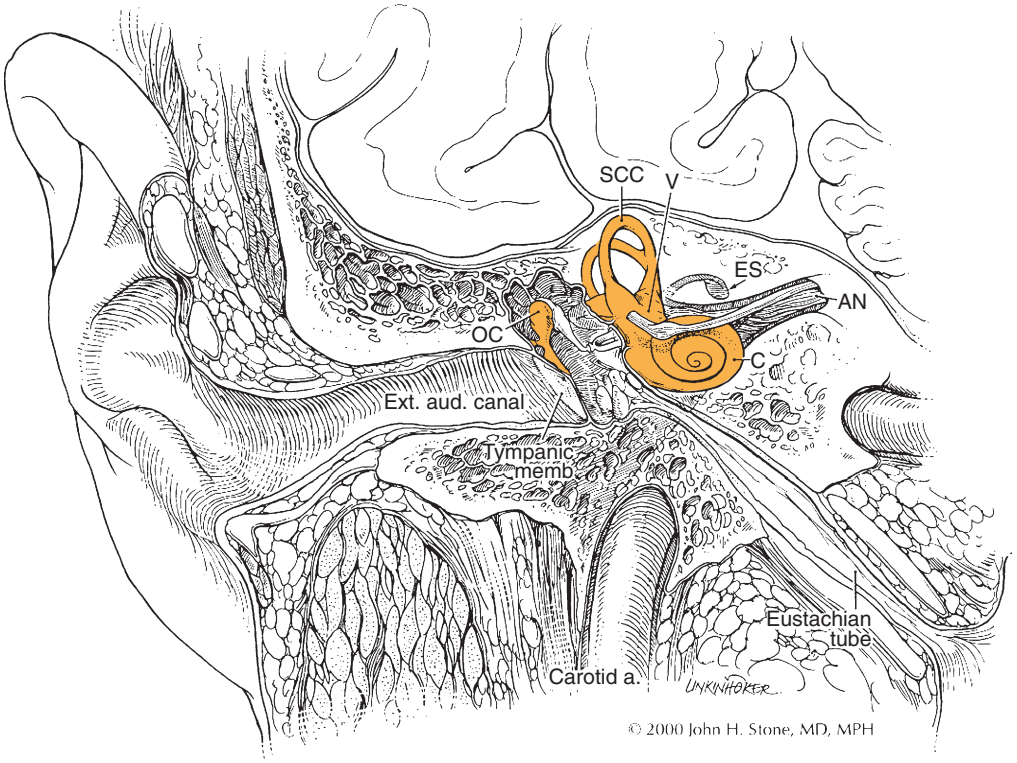

Figure 127-7. Anatomy of the external, middle, and inner portions of the ear. AN, auditory nerve; C, cochlea; ES, endolymphatic sac; OC, ossicular chain; SCC, semicircular canals; V, vestibule. *(From Stone J, Francis H. Immune-mediated inner ear disease.* Curr Opin Rheumatol. *2000;12:32-40.)*

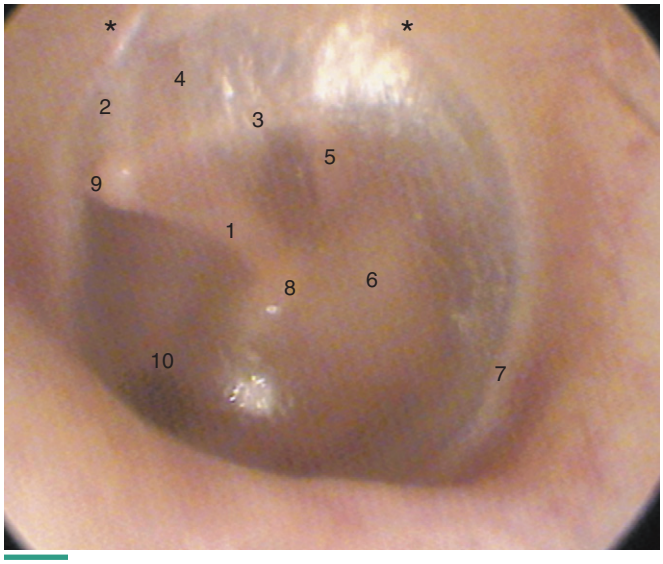

Figure 127-8. Surface features of the left tympanic membrane. *1,* manubrium of the malleus (mallear stria); *2,* anterior malleal fold; *3,* posterior malleal fold; *4,* pars flaccida (Shrapnell's membrane); *5,* long process incus; *6,* pars tensa through which the promontory and round window are visible; *7,* tympanic anulus; *8,* umbo; *9,* lateral process; *10,* eustachian tube opening; *asterisk,* anterior and posterior tympanic spines.

degrees as seen in Figure 127-6, depending on its translucency, extent of retraction, and the mucosal health within the middle ear.

Middle Ear

The middle ear is an air-filled space formed by extension of the foregut into the anlage of the temporal bone. The expanding first pharyngeal pouch forms multiple cul-de-sacs that coalesce to form a common airspace partitioned by the ossicular chain and associated ligaments and mucosal folds. The resorption of mesenchymal tissue further expands the size of the middle ear and mastoid into niches, compartments, and bony tracts of air cells.[1,9,11] These additional areas vary considerably among individuals and between ears, influenced by heredity, airflow via the eustachian tube, and disease in the early years of life.

The eustachian tube is the conduit through which air is exchanged between the middle ear space and upper aerodigestive tract. It is angled by about 45 degrees from the middle ear to the nasopharyngeal opening at the torus tubarius.[12-14] The proximal third of the tube is formed in petrous bone. The distal two thirds segment is fibrocartilaginous and is collapsed at rest. The fibrocartilaginous portion is composed of an open tube that is shaped like an inverted "J" in cross section. A fibrous membrane closes this tube laterally. The tensor veli palatini muscle is inserted on this membrane retracting it on muscular contraction to enlarge the tubal lumen during swallowing and yawning. The bony-cartilaginous junction is the narrowest point along the eustachian tube. The internal carotid artery is closely associated with the medial wall of the eustachian tube at its tympanic opening, where the overlying bone may be quite thin or even dehiscent.

The middle ear cavity can be spatially divided into hypotympanum, mesotympanum, and epitympanum, the limits of which are defined by their location relative to the tympanic anulus (see Figs. 127-8 and 127-9). The mesotympanum is the space just medial to the tympanic membrane, which extends from the eustachian tube opening anteriorly to the facial nerve posteriorly. The carotid artery is located medial to the eustachian tube opening, and the tensor tympani muscle occupies the semicanal superior and parallel to the eustachian tube. The cochlear promontory forms the medial wall of the mesotympanum marked posteriorly by the oval window superiorly, which is occupied by the stapes, and the round window inferiorly. The mesotympanum extends into a recess of varying depth that lies posterior to the oval and round windows, and medial to the vertical facial nerve. Known as the sinus tympani, this space may harbor occult cholesteatoma despite careful and thorough removal of bone around the facial nerve, which

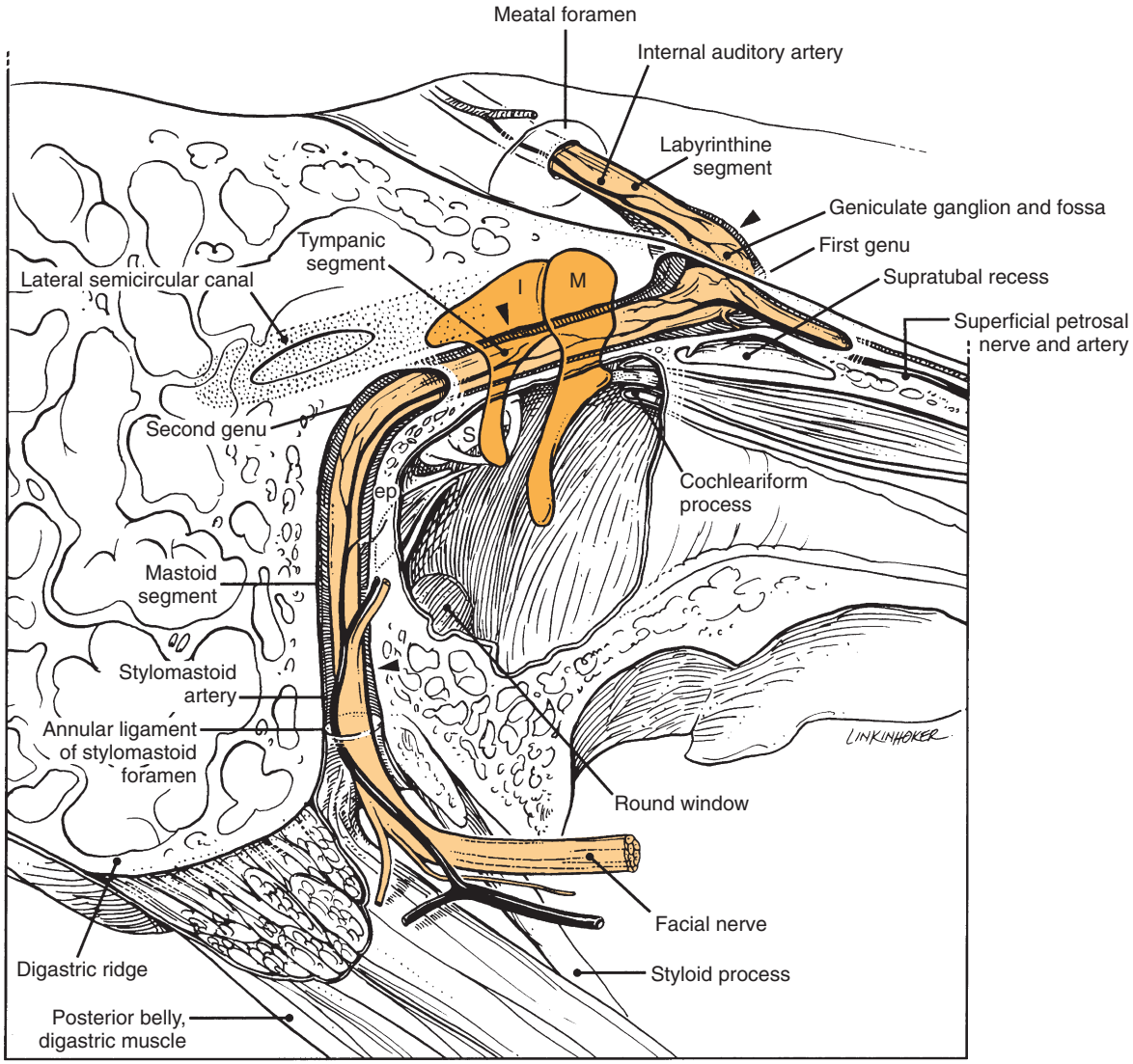

Figure 127-9. Anatomy of the infratemporal portion of the facial nerve and associated middle ear structures. Sites of vulnerability to injury (*arrowheads*): *Perigeniculate region*—increased susceptibility of geniculate fossa to fracture, nerve compression and ischemia occur in the narrow meatal foramen and labyrinthine segment in response to nerve injury, first genu is tethered by the greater superficial petrosal nerve increasing susceptibility to shearing injuries, vascular watershed area of branches of the external carotid artery and posterior circulation, geniculate ganglion is susceptible to injury during surgical dissection in the supratubal recess of the anterior epitympanum. *Tympanic segment*—the nerve is most frequently dehiscent above oval window, distal tympanic segment and second genu susceptible to injury in cholesteatoma surgery owing to pathologic dehiscence or distorted anatomy and failure to identify important surgical landmarks. *Mastoid segment*—in the lower portion of its vertical course and just distal to the stylomastoid foramen the nerve is positioned lateral to the tympanic anulus and is susceptible to injury during surgery of the external auditory canal. *(From Francis HW. Facial nerve emergencies. In: Eisele D, McQuone S, eds.* Emergencies of the Head and Neck. *St. Louis: Mosby, 2000:337-366.)*

forms its lateral wall. The pyramidal eminence transmits the stapedial tendon to the stapes superstructure, and is located just anterior to the second genu of the facial nerve as it transitions from the tympanic (horizontal) to mastoid (vertical) segment. The inferior anulus of the tympanic membrane marks the inferior limit of the mesotympanum and superior limit of the hypotympanum. The hypotympanum is limited inferiorly by the jugular bulb posteriorly and may extend inferomedial to the cochlea.

The ossicular chain, associated ligaments, and mucosal folds almost completely partition the epitympanic space from the mesotympanum except for small openings anterior and posterior to the stapes superstructure (Fig. 127-10).[12] The body of the incus articulates with the head of the malleus to form an ossicular mass that occupies most of the epitympanum. These ossicles are suspended within this space without touching its bony walls, by the anterior and superior malleal and posterior incudal ligaments. They are further supported by investments of the lateral and long processes of the malleus into the tympanic membrane, and by the incudostapedial articulation. The presence of a single nutrient vessel within the long process of incus and the absence of collateral circulation render this segment of bone susceptible to aseptic necrosis secondary to middle ear infections (Fig. 127-11).

The lateral process of the malleus and spines of the notch of Rivinus are otoscopic landmarks for the inferior limit of the epitympanum. The superior medial wall of the bony canal or scutum forms the lateral wall of the epitympanum, and is subject to erosion by cholesteatomas arising secondary to retraction of the pars flaccida. The epitympanum is divided further into (1) Prussak's space, just medial to pars flaccida and lateral to the head and neck of the malleus; (2) the compartment anterior to the malleus; and (3) the posterior compartment, which communicates with the antrum. The folds and ossicles

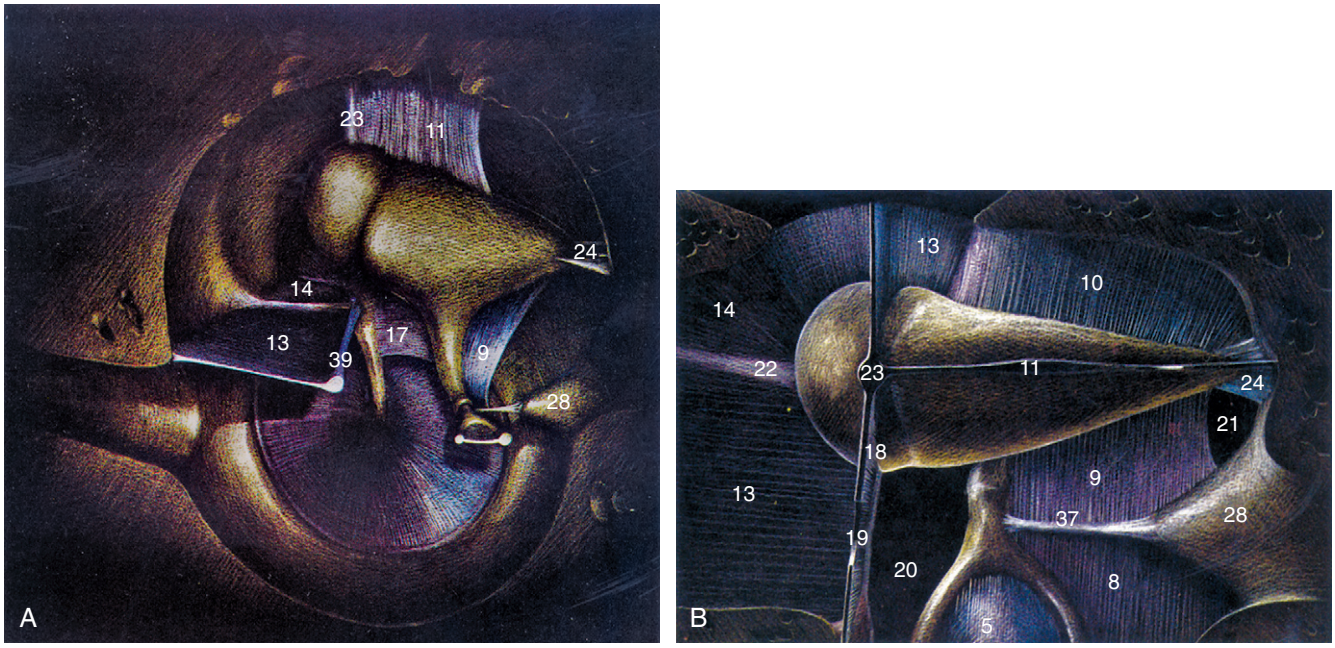

Figure 127-10. **A** and **B,** Partitioning of the middle ear by ossicular chain and associated mucosal folds. Lateral (**A**) and inferior (**B**) views of the middle ear show separation of mesotympanic and epitympanic regions by the tensor fold (no. 13), the interosseous fold (no. 17), and the medial incudal fold (no. 9), leaving the isthmus tympani anticus (no. 20) and isthmus tympani oticus (no. 21) as the only remaining openings. *5,* obturatoria stapedis; *8,* plica stapedis; *11,* superior incudal fold; *14,* anterior malleal fold; *18,* superior malleal fold; *19,* incisura tensoris; *22,* anterior malleal ligament; *23,* superior malleal ligament; *24,* posterior incudal ligament; *28,* pyramidal eminence; *39,* tensor tympani tendon. *(From Proctor B. The development of the middle ear spaces and their surgical significance. JLO. 1964;78:631-648.)*

that partition this space provide distinct pathways along which cholesteatoma can spread within and beyond the attic.[6,12] Attic retraction cholesteatomas are directed posteriorly from Prussak's space through an opening into the posterior epitympanum. From here, there is extension into the antrum through the aditus ad antrum or inferiorly into the posterior mesotympanum, or both. In advanced cases, disease may extend medial to the ossicles and to the anterior attic. In cholesteatoma surgery, removal of the incus and the head of the malleus is required to identify and address the anterior extension of disease.

The close association between the tympanic segment of the facial nerve and pathology in the attic requires a detailed understanding of neuroanatomy of this region (see Fig. 127-9). The geniculate ganglion and first genu of the facial nerve are located just medial to a bony cul-de-sac at the anterior limit of the attic, known as the supratubal recess. The posterior opening of this recess is marked by the cochleariform process inferiorly and the "cog" superiorly, an incomplete bony septum oriented in the coronal plane.[15] The facial nerve is vulnerable at the first genu to disease or surgical dissection within the supratubal recess, from which it may be separated by minimal or no bone.[16] The cog should be removed to visualize the entire supratubal recess for safe removal of disease.[15] The tympanic segment of the facial nerve projects in a posterior direction at a slight inferior incline. It skims just superior to the cochleariform process, which serves as a durable landmark for the midportion of the tympanic segment of the facial nerve.

The fallopian canal serves as the bony superior limit of the oval window niche. In 55% of cases, however, the facial nerve is partially exposed because of bony dehiscence. In some cases, the nerve herniates from the canal into the oval window niche, becoming vulnerable during stapes surgery. The pyramidal eminence, from which the stapedius tendon emerges to insert on the stapes capitulum, is a reliable landmark for the second genu of the facial nerve distal to which the nerve is directed vertically toward the stylomastoid foramen. The facial nerve is most vulnerable to iatrogenic injury just proximal to the second genu and in its vertical path.[17] An understanding of facial anatomy and the use of sound surgical technique are required to identify and preserve the nerve and its function during ear surgery.[18]

The tegmen tympani forms the superior limit of the epitympanum, which also corresponds to the cortical floor of the middle fossa. This bone may be very thin and even dehiscent in some cases. Ectopic arachnoid granulations positioned on the bony floor of the middle fossa may erode over time into the mastoid owing to pulsations of cerebrospinal fluid. When accompanied by the thinning of dura, meningoencephaloceles develop that may spontaneously leak cerebrospinal fluid to generate middle ear effusions, rhinorrhea, or otorrhea.[6,19,20]

The lateral and superior semicircular canals form the medial walls of the posterior epitympanum at its opening into the antrum, known as the aditus ad antrum. The lateral semicircular canal forms a prominence at the inferior aspect of the aditus ad antrum. Impacted cholesteatoma erodes the otic capsule that forms this prominence leading to the formation of a perilymphatic fistula over time. The second genu of the facial nerve hugs the anteroinferior aspect of the lateral semicircular canal (see Fig. 127-9).

Facial Nerve

The facial nerve provides afferent and efferent innervation to structures derived from the second branchial arch. Most fibers are *special visceral efferents* that supply nerve input to striated muscles of facial expression, the stapedius muscle, the stylohoid muscle, and the posterior belly of the digastric muscle.[5,18,21] *General visceral efferent fibers* form the nervus intermedius, which innervates (1) the lacrimal gland and seromucinous glands of the nasal cavity via the greater superficial petrosal nerve and pterygopalatine ganglion, and (2) the submandibular and sublingual glands via the chorda tympani and the submandibular ganglion. *Special sensory fibers* for taste innervate the anterior two thirds of the tongue via the chorda tympani, and the tonsillar fossae and palate via the greater superficial petrosal nerve. The geniculate ganglion contains the cell bodies of these sensory neurons. *Somatic sensory fibers* provide sensation to touch of the EAC and conchal skin of the auricle, and proprioceptive information from the facial muscles. *Visceral afferent fibers* supply the mucosa of the nose, pharynx, and palate. Motor, preganglionic, and sensory modalities have the

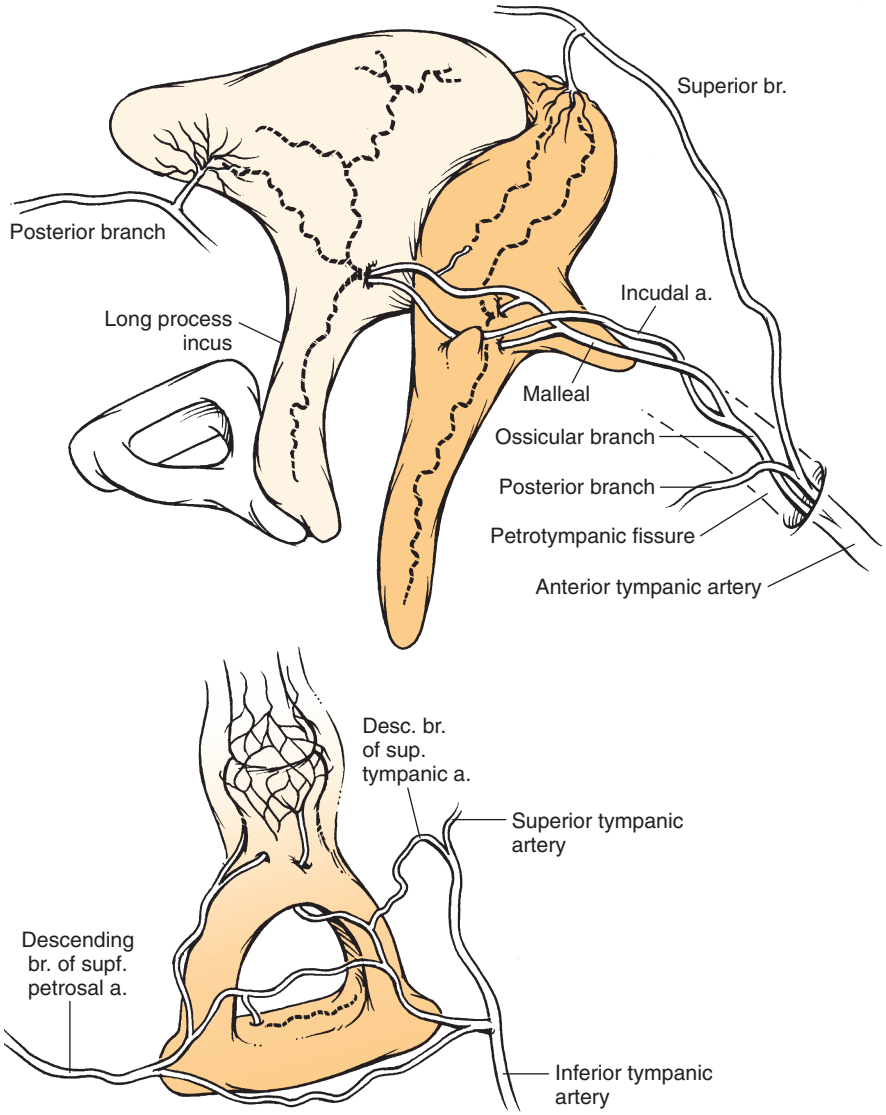

Figure 127-11. Blood supply of the middle ear ossicles. The long process of the incus has a single nutrient vessel. Other portions of the ossicular chain are supplied by two or more sources. *(Redrawn from Nager G.* Pathology of the Ear and Temporal Bone. *Baltimore: Williams & Wilkins; 1993.)*

following brainstem origins: the motor nucleus (motor), the superior salivatory nucleus (preganglionic), and the nucleus of the solitary tract (sensory).

The facial nerve traverses the temporal bone within a bony canal known as the fallopian canal, which begins at the fundus of the internal auditory canal and terminates at the stylomastoid foramen (see Fig. 127-9).[1,4-6] Within the internal auditory canal, the nerve lacks a fibrous sheath or endoneurium and is surrounded by a thin layer of arachnoid. The labyrinthine segment is the first, shortest, and narrowest segment of the fallopian canal.[22,23] It travels superior to the cochlea and opens into the geniculate fossa located just deep to the supratubal recess. The geniculate ganglion is separated from the middle fossa by only a very thin layer of bone, which is dehiscent in about 25% of ears. The facial nerve acquires a fibrous sheath at and distal to the geniculate ganglion. This is also the location of the facial hiatus, where the greater superficial petrosal nerve projects anteriorly along the middle fossa floor, and of the first genu, at which the main trunk makes an acute posterior and slightly inferior turn to enter the tympanic or horizontal segment of the fallopian canal. The horizontal segment of the facial nerve occupies the medial wall of the anterior attic, skims over the superior aspect of the cochleariform process, and forms the superior wall of the oval window niche posteriorly.

At the pyramidal eminence, from which the stapedial tendon emerges, the facial nerve makes a second genu into the mastoid or vertical segment. This turn is positioned just anteroinferior to the lateral semicircular canal, and anterior to a line drawn through the short process of the incus. A superior extrapolation of the vertical segment would approximately bisect the prominence of the lateral semicircular canal. Although the anatomic position of the horizontal segment is quite consistent, particularly relative to the cochleariform process, oval window, and pyramidal eminence, there is greater variability in the path taken by the vertical segment before exiting the stylomastoid foramen. Chorda tympani and stapedial branches occur at varying points along this segment. The space between the mastoid segment of the facial nerve and the chorda tympani is a space through which a posterior tympanotomy (or facial recess) can be surgically created to access the middle ear. The distal aspect of the vertical segment of the fallopian canal and the stylomastoid foramen itself are lined by the aponeurosis of the posterior belly of the digastric muscle. As the facial nerve exits the fallopian canal, it receives blood supply from this closely applied aponeurosis. The preservation of this relationship on rerouting the nerve during skull base surgery may result in better facial nerve function.[24,25] Identification of this aponeurosis anterior to the cephalic edge of the digastric muscle serves as a valuable landmark for the stylomas-

toid foramen and the vertical segment of the nerve as it exits. A more in-depth discussion of facial nerve anatomy is also helpful in understanding the mechanisms of injury.

Each segment of the facial nerve has unique anatomic features that render it susceptible to injury.[26] The fallopian canal not only provides a protective path for the facial nerve in the temporal bone, but also plays an important role in the pathophysiology of injury. The narrow meatal foramen[23] and labyrinthine segment[22] are sites where facial nerve edema secondary to inflammatory or traumatic causes leads to progressive compression, vascular compromise, and axonal injury. This narrow segment is made further vulnerable by being a watershed area between terminal arterioles of the vertebrobasilar and external carotid artery systems. Vertebrobasilar supply is via labyrinthine branches of the anterior inferior cerebellar artery, and supply by the external carotid artery is via the petrosal branch of the middle meningeal artery and the stylomastoid artery that branches from the posterior auricular artery.[27] The labyrinthine segment is made further vulnerable by the lack of epineurium and associated vascular plexus that provides a barrier to injury and a rich collateral blood supply.

The facial nerve is susceptible to injury in the region of the geniculate ganglion for three main reasons. First, the thin and sometimes dehiscent bone surrounding the geniculate ganglion makes it a common path through which temporal bone fractures travel. Second, as previously discussed, the ganglion is susceptible to injury from pathology or surgical dissection within the supratubal recess. Third, the greater superficial petrosal nerve, which projects anteriorly, tethers the facial nerve at the hiatus and may exert intraneural traction and shearing forces during temporal bone trauma. Any of these traumatic mechanisms, in addition to inflammation due to herpetic infection, may compromise facial nerve integrity through direct axonal injury, or may produce edema and secondary compressive injury in the adjacent labyrinthine segment.

The tympanic segment is the most common site of congenital dehiscence of the bony canal, especially above the oval window.[23] Bony dehiscence by cholesteatoma is also common proximal to the second genu, where the adjacent aditus ad antrum acts as a bottleneck through which disease must pass en route to the antrum, eroding structures in the posterior attic along the way. The dehiscent horizontal fallopian canal places the facial nerve at risk for injury by the unwary surgeon, especially when disease or previous surgery alters anatomy. The vertical segment has the most variable path, especially in association with congenital malformations, such as canal atresia. The nerve also courses lateral to the tympanic anulus as it approaches the stylomastoid foramen and can be injured in transcanal procedures.[17] In the newborn, the mastoid tip is underdeveloped, placing the styloid process and the adjacent facial nerve more superficial in the neck. The nerve is susceptible to surgical injury in routine postauricular approaches and to compression injuries during forceps delivery.

Mastoid and Other Pneumatized Regions of the Temporal Bone

Similar to the mastoid, all pneumatized regions of the temporal bone consist of a collection of mucosa-lined bony compartments that are ventilated through the aditus ad antrum or via other cell tracts that open into the middle ear space. This network of bony air cells primarily arises from the diploë of squamous and petrous portions of the temporal bone. The mastoid is the largest pneumatized region, located lateral to the labyrinth and communicating directly with the attic via its medial compartment, the antrum. The mastoid also extends posteriorly into the occipital bone and communicates with medial cell tracts. The vestibular portion of the inner ear forms the medial wall of the antrum, and Körner's septum, the embryologic junction between petrosal and squamosal portions of the temporal bone, forms the lateral limit.

There is considerable variation in the extent of temporal bone pneumatization and the architecture of cell tracts in and around the mastoid. The extent of pneumatization depends on early otologic history, including factors that influence middle ear ventilation,[28] history of otitis media,[29] and presumably heredity. The interaction between osteoclastic activity and the resorption of mesenchymal cells determines the speed of pneumatization, and is influenced by genetic and local middle ear factors.[11]

The extent and anatomic distribution of pneumatization has relevance to the surgical management of ear disease. Surgical access is aided by the presence of large pneumatized regions that permit navigation to deeper structures without compromise of intracranial contents, the labyrinth, the facial nerve, and the sigmoid sinus. The decision to maintain or remove the bony separation between the mastoid and EAC is also influenced by the extent of pneumatization. Poor pneumatization is associated with a greater likelihood of chronic ear disease[28] because it is a marker of reduced capacity to ventilate the middle ear and mastoid. Exteriorization of the poorly aerated mastoid may avoid chronic consequences of hypoventilation, including otomastoiditis and cholesteatoma.

Pneumatization may be organized into regions and tracts. The primary regions of pneumatization are as follows[5,30]:

- The mastoid (the antrum, central mastoid tract, tegmental, sinodural, sinal, facial, and tip cells)
- Perilabyrinthine (supralabyrinthine and infralabyrinthine areas)
- Petrous apex (peritubal area and apical area)
- Accessory region (zygomatic, squamous, occipital, styloid)

Air cell tracts are paths along which diploic bone and mesenchyme are resorbed during maturation, and through which air subsequently flows to deeper spaces. These tracts circumnavigate the labyrinth, and cortical plates of bone that line the middle and posterior fossa dura, sigmoid sinus, carotid artery, and facial nerve. They have relevance to the surgical access of temporal bone and intracranial areas, and the pathogenesis and spread of ear disease. These tracts are also pathways for drainage of spinal fluid to the ear canal or nasopharynx associated with surgery, trauma, or spontaneous meningoencephaloceles. These tracts can be categorized as follows:

- Posterosuperior (sinodural)
- Posteromedial (retrofacial and retrolabyrinthine)
- Subarcuate
- Perilabyrinthine (supralabyrinthine and infralabyrinthine)
- Peritubal (associated with the eustachian tube)

When obstructed by edema, postinflammatory scarring, or organized clots, unventilated deeper spaces may accumulate sterile fluid, including transudates or by-products of inflammation and hemoglobin to form the so-called cholesterol granuloma,[31] an expanding collection of thick dark fluid often compared with crankcase oil. Superinfection of these obstructed tracts creates a chronic source of sepsis that is not always cleared with antibiotics alone. Because of its deep location and narrow air cell tracts, the petrous apex is vulnerable to these postobstructive processes, making it a well-recognized location for cholesterol granulomas and apicitis. Gradenigo's syndrome consists of symptoms that result from the inflammatory effect of petrous apicitis on adjacent intradural structures, including cranial nerves VI and V_1, accompanied by otorrhea.[32]

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CHAPTER ONE HUNDRED AND TWENTY-EIGHT

Anatomy of the Auditory System

Christina L. Runge-Samuelson

David R. Friedland

Key Points

- The neuroanatomy of the central and peripheral auditory systems is organized to extract specific information from the complex waveforms of speech and music.
- The cochlea is organized tonotopically with low frequencies at the apex and high frequencies at the base. This tonotopic organization is reiterated throughout the central auditory system.
- The organ of Corti is the principal sensory structure in the cochlea and contains the inner and outer hair cells.
- Afferent auditory neurons are bipolar, have their cell bodies in the spiral ganglion, and connect the hair cells to the central auditory system.
- The cochlea generates auditory nerve impulses that are fed to the cochlear nucleus where parallel ascending pathways independently extract temporal, spectral, and intensity cues from environmental stimuli.
- The cochlear nucleus is the only entry point for all peripheral auditory information to the central nervous system.
- The superior olivary complex and inferior colliculus are important in sound localization.
- The inferior colliculus is the gateway for almost all ascending and descending pathways between the telencephalon and the lower centers.
- The medial geniculate body and auditory cortex integrate auditory information with multiple other sensory modalities.
- Efferent auditory neurons arise from the superior olivary complex and innervate outer hair cells of the ipsilateral and contralateral cochlea.

This chapter provides a basic overview of the anatomy of the auditory system from the cochlea to the cortex. Auditory processing involves the encoding of sound energy into electrical signals. This process begins in the periphery at the cochlea and progresses through the cochlear nerve, the brainstem, and the midbrain, and undergoes final integration within the cortex. Knowledge of the neuroanatomy of these regions is important for understanding most forms of congenital and hereditary deafness; auditory processing disorders; and the indications for, and functions of, cochlear and auditory brainstem implants. These neuroanatomic regions also may play crucial roles in age-related difficulties with word recognition, hearing in noise, and the generation and perception of tinnitus.

Cochlear Anatomy

Osteology

The inner ear is contained in the petrous apex of the temporal bone, and is encased in a bony structure called the osseous or bony labyrinth. The bone forming the cochlea and vestibular labyrinth is the hardest bone in the human body and is akin to ivory in its density. The labyrinth consists of three continuous sections: the vestibule, the cochlea, and the semicircular canals. The initial point of communication between the middle and inner ears occurs at the oval window of the vestibule, where the stapes footplate abuts the oval window membrane. At the basal end of the cochlea is the round window membrane, which communicates with the middle ear space. The cochlea is a snail-shaped structure that has a wide diameter at the base, which narrows for 2¾ turns until it reaches its apex. Figure 128-1 shows a cross section of the cochlea, illustrating the cuts through each turn.The core of the cochlea is the modiolus, which is highly porous bone that allows passage of auditory nerve fibers as they travel from the internal auditory meatus to the hair cell synapse. Extending from the modiolus into the osseous labyrinthine space is a bony shelf, or the osseous spiral lamina. The osseous spiral lamina coils around the center of the cochlea and provides partial division of the upper and lower cochlear chambers into the scala vestibuli and scala tympani. At the apex of the cochlea, they communicate at the helicotrema. The spiral lamina is also the point of attachment for the basilar membrane, which is the lower border of the membranous labyrinth encasing the scala media.

Along the length of the cochlea, the widths of the spiral lamina and basilar membrane are inversely related, with the spiral lamina wider at the base and narrowing toward the apex, and the basilar membrane narrower at the base and wider at the apex. This is one of several contributing factors to the frequency specificity of basilar membrane motion. At the basal turn of the cochlea is the cochlear aqueduct, a bony channel that allows communication between the perilymphatic fluid and cerebrospinal fluid of the subarachnoid space in the posterior fossa.

Membranous Labyrinth and Inner Ear Fluids

The membranous labyrinth of the cochlea follows the shape of the osseous cochlea and forms a third cochlear chamber—the scala media. The sensory organ of hearing resides within the membranous labyrinth. Figure 128-2 shows a cross section of the membranous labyrinth and its structures. The membranous labyrinth is bordered superiorly by

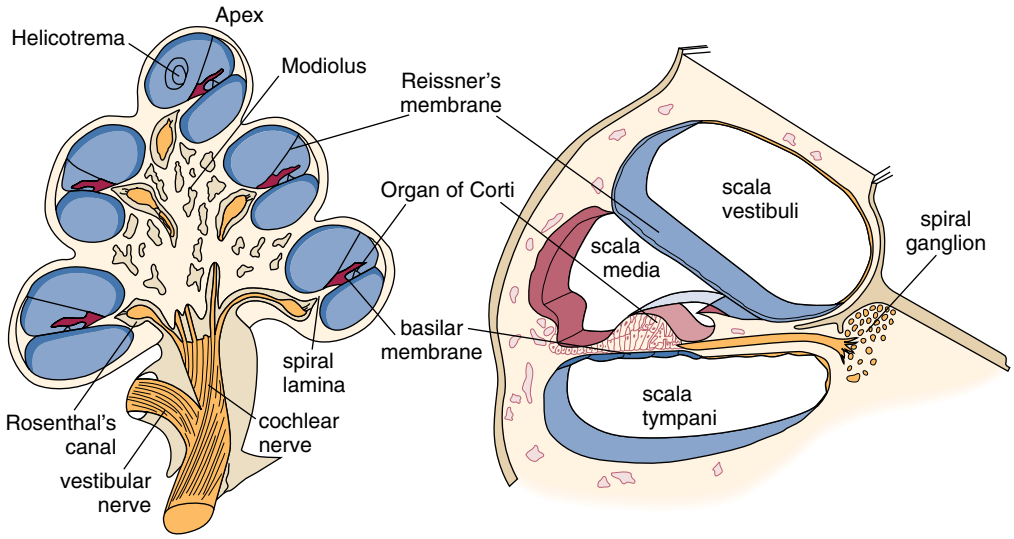

Figure 128-1. Cross section of the cochlea showing the passage of the cochlear nerve through the modiolus to the organ of Corti (*left*). Higher power view shows the osseous cochlear duct and membranous compartments within the cochlea (*right*).

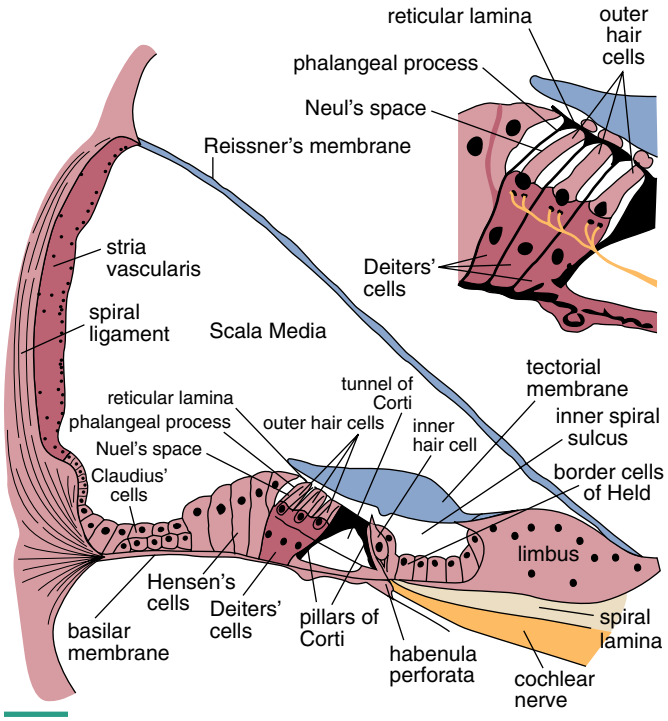

Figure 128-2. Cross section of the organ of Corti showing the major cellular structures.

Reissner's membrane, inferiorly by the basilar membrane, and laterally by a portion of the outer cochlear wall to which it is anchored by the spiral ligament. Within the membranous labyrinth, along the lateral wall, is the stria vascularis, highly vascular tissue that is responsible for the metabolic environment of the scala media. The intricate structures that comprise the organ of Corti are situated on the basilar membrane.

The organ of Corti runs longitudinally along the length of the basilar membrane and consists of many types of epithelial cells and structures. Medially, seated atop the osseous spiral lamina is the spiral limbus, a thickened band of periosteum that serves as the point of medial attachment for Reissner's membrane and gives rise to the tectorial membrane. The tectorial membrane lies over the inner and outer hair cells. It is a compliant gelatinous structure composed primarily of collagen II fibers, and serves as a mass load that moves similar to a rubber band.[1-3] Lateral to the spiral limbus is the inner spiral sulcus, which is lined with the border cells of Held. One row of inner hair cells is present, and the cell bodies are surrounded by supporting cells called phalangeal cells.

Between the inner and outer hair cells lie the pillars of Corti, which originate on the spiral lamina and basilar membrane and converge at the top to form the tunnel of Corti. Lateral to this are three rows of outer hair cells, which are securely cupped inferiorly by the supporting Deiters' cells. Each Deiters' cell has a phalangeal process that projects apically, and the space between the outer hair cell and phalangeal process is referred to as Nuel's space. The phalangeal cells, phalangeal processes of the Deiters' cells, and the superior surfaces of the hair cells form the reticular lamina, a tightly interwoven matrix that supports the apices of the hair cells. The reticular lamina forms a barrier from endolymph, the fluid in the scala media, which owing to its ionic composition is toxic to hair cells. Lateral to the outer hair cells are Hensen's cells and Claudius' cells.

The two fluid systems within the cochlea create an environment crucial to the mechanical displacement of the basilar membrane traveling wave and to the cellular depolarization and subsequent synaptic activity. Between the osseous and membranous labyrinths is perilymphatic fluid, or perilymph, which has a high concentration of sodium and low concentration of potassium, similar to what is found in cerebrospinal fluid and blood serum. The presence of perilymph in the intercellular spaces within the organ of Corti has been identified in humans and guinea pigs.[4,5]

Within the membranous labyrinth is endolymphatic fluid, or endolymph, with a high concentration of potassium and low concentration of sodium, such as is typically found intracellularly. The ionic concentrations of endolymph are maintained by the cells within the stria vascularis. The endolymphatic sac communicates with the membranous labyrinth via the endolymphatic duct and vestibular aqueduct. Disorders of the endolymphatic system resulting from disease, congenital deformities, or other insults can lead to potentially severe auditory and vestibular symptoms. An enlarged vestibular aqueduct, defined as a diameter larger than 1.5 mm at the vestibular aqueduct midpoint or greater than 2 mm at the operculum, may lead to sudden and progressive sensorineural hearing loss in children, particularly after even minor head trauma.[6]

Hair Cells

The inner and outer hair cells function as receptor cells that transduce mechanical movement into an electrochemical signal to stimulate the

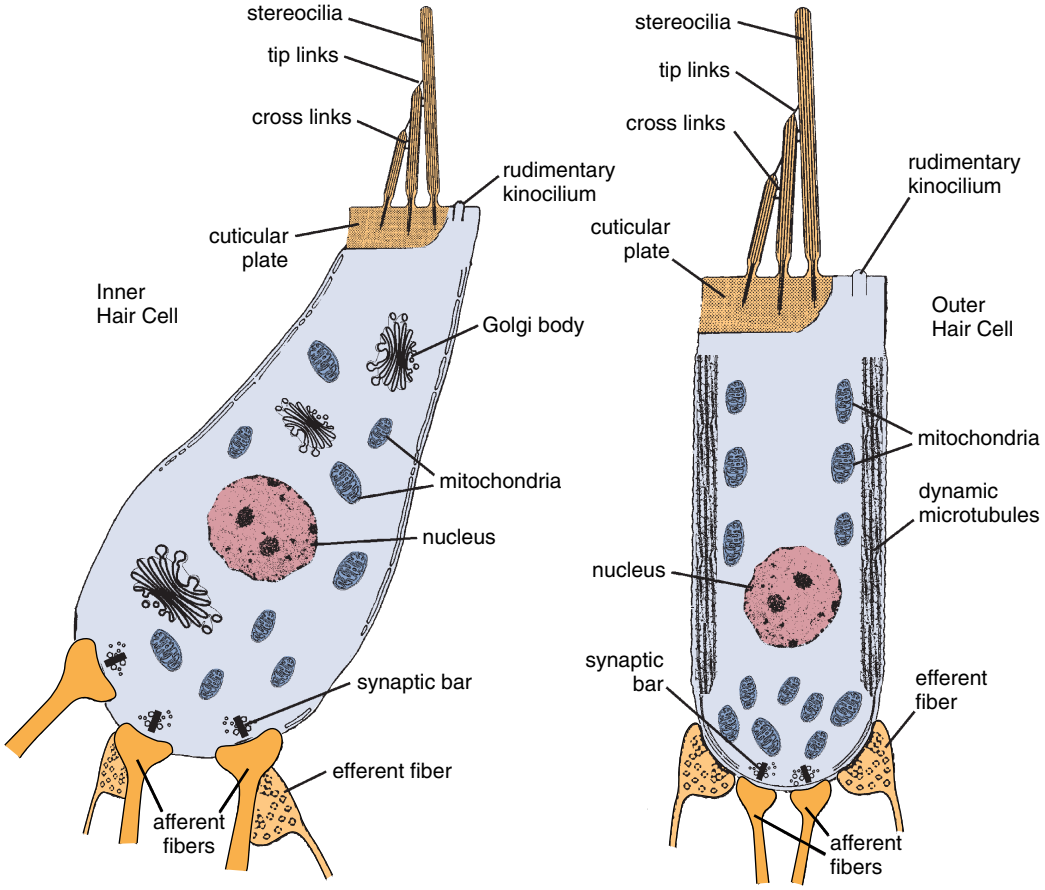

Figure 128-3. Schematic depictions of inner (*left*) and outer (*right*) hair cells. Inner hair cells are flask-shaped, receive extensive afferent innervation, and receive indirect efferent innervation. Outer hair cells are cylindrical and receive direct afferent and efferent innervation.

auditory nerve. Figure 128-3 presents schematic examples of inner and outer hair cells. The apical portion of all hair cells includes a thickened region called the cuticular plate, which in conjunction with the supporting cells forms the reticular lamina. Rooted in the cuticular plate of each hair cell and projecting through the reticular lamina are bundles of actin filaments called stereocilia, stiff hairlike structures that deflect with mechanical disturbances. Adjacent to this is a noncuticular region that contains a rudimentary kinocilium.

There are approximately 3500 inner hair cells arranged in one row on the modiolar side of the tunnel of Corti and 12,000 outer hair cells in three rows on the strial side. Figure 128-4 is a scanning electron micrograph of the reticular lamina of the organ of Corti showing the stereocilia arrangement for the three rows of outer hair cells and single row of inner hair cells. The stereocilia on outer hair cells form a "V" or "W" shape with the bottom facing away from the modiolus. The inner hair cell stereocilia form a shallow "U" that opens toward the modiolus. On each hair cell, there are rows of stereocilia, two or more on inner hair cells, and three or more on outer hair cells. For both types of hair cells, the stereocilia lengths are graduated from longest on the strial side to shortest on the modiolar side. The longest stereocilia on the outer hair cells contact the tectorial membrane, which results in deflection of the stereocilia with basilar membrane movement. The stereocilia are connected to each other by filamentous links laterally by cross-links and from the tips of shorter stereocilia to the sides of the taller ones by tip-links. These ensure that the connected stereocilia move as a unit when the longer stereocilia are deflected.

The structural aspects of the inner and outer hair cell bodies themselves differ significantly and are reflective of their functional differences. The inner hair cells are flask-shaped, wide at the bottom and narrower at the top, and contain high concentrations of organelles that

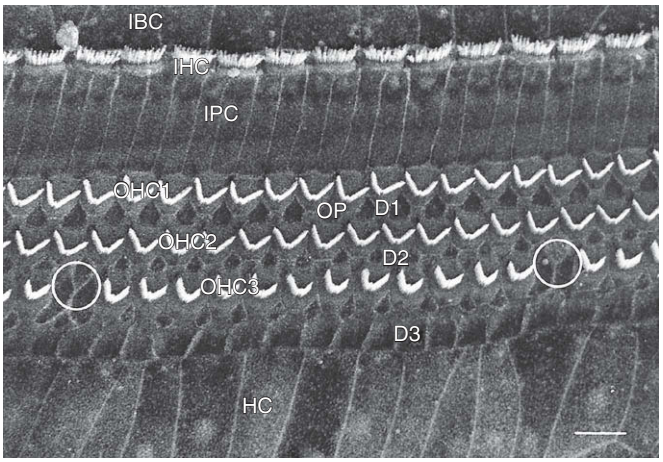

Figure 128-4. Scanning electron micrograph showing reticular lamina of organ of Corti. Note inner border cells (IBC), inner hair cells (IHC), inner pillar head plate (IPC), three rows of outer hair cells (OHC), three rows of Deiters' cell phalangeal processes (D), outer pillar cell phalangeal process (OP), and Hensen's cells (HC). Two phalangeal scars (*circled*) are present in row 3, which indicates loss of two outer hair cells. Bar = 10 µm.

are involved in metabolic activity, particularly Golgi bodies and mitochondria. Although highly metabolic, inner hair cells are considered to be passive transducers in the auditory system. Outer hair cells are cylindrical in shape and contain microfilaments and microtubules along the length of the cell that give rise to motile activity.[7] The motile properties have been shown empirically to result in highly tuned, frequency-specific contractile activity even when stimulated in isolation from the basilar membrane.[8] All hair cells have synaptic bars at afferent synapses, which serve as sites for presynaptic vesicle docking and release for subsequent stimulation of auditory nerve fibers.

Innervation

Afferent innervation of the cochlear hair cells consists of approximately 30,000 auditory nerve fibers in humans, and is responsible for providing ascending information from the cochlea to the central auditory system. The cell bodies of afferent fibers make up the spiral ganglion that resides in Rosenthal's canal within the modiolus. Nerve fibers reach the hair cells by traveling through the modiolus, and into the osseous spiral lamina, where they pass through holes in the lamina referred to as the habenulae perforatae. The nerve fibers are classified as type I and type II. Type I fibers are bipolar, of large diameter, and myelinated, and they constitute nearly 95% of the total number of fibers. Each type I fiber has a direct and independent synapse on the body of a single inner hair cell, and each inner hair cell is innervated by approximately 20 such fibers.[9,10] Type II fibers constitute the remaining 5%, and are smaller and may be myelinated or unmyelinated. Type II fibers synapse directly on the outer hair cells, with a single fiber diverging to form branches that synapse with multiple other outer hair cells.

The efferent auditory pathway originates from the olivocochlear bundle and provides central inhibitory modulation of hair cell activity via descending information. The olivocochlear bundle has about 1600 fibers, and these constitute the uncrossed olivocochlear bundle and crossed olivocochlear bundle.[11-15] These pathways originate from the medial superior olive (MSO) and lateral superior olive (LSO) regions on both sides. For the uncrossed olivocochlear bundle, the LSO projects many small-diameter, unmyelinated efferent fibers toward the ipsilateral inner hair cells, where they synapse with the afferent fibers. The MSO projects fewer myelinated fibers ipsilaterally that synapse directly on the outer hair cells. For the crossed olivocochlear bundle, the MSO projects large-diameter myelinated fibers to the contralateral outer hair cells, and the LSO projects a few unmyelinated fibers to the contralateral inner hair cell afferents. The fibers from the crossed olivocochlear bundle cross midline at the level of the fourth ventricle. To illustrate the pathways, Figure 128-5 shows a schematic example of the uncrossed olivocochlear bundle and crossed olivocochlear bundle innervation for the left organ of Corti.

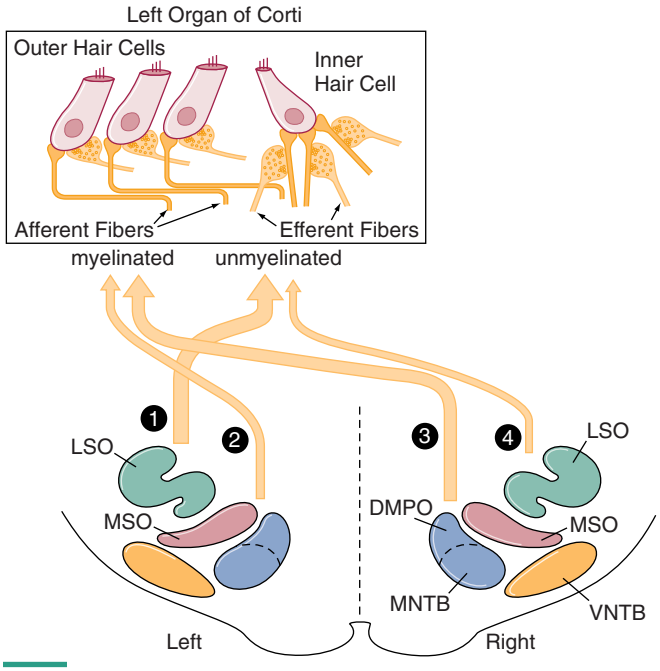

Figure 128-5. Illustration of the efferent uncrossed and crossed olivocochlear bundle pathways to the hair cells in the left organ of Corti. *Yellow* entities represent the efferent fibers and synapses. The arrow widths represent the relative amount of innervation. Uncrossed pathway: *1,* small-diameter fibers from left lateral superior olive (LSO; *green*) synapsing on left inner hair cell afferents; *2,* myelinated fibers from left medial superior olive (MSO; *pink*) to left outer hair cells. Crossed pathway: *3,* large-diameter myelinated fibers from right MSO to left outer hair cells; *4,* unmyelinated fibers from right LSO to left inner hair cell afferents. DMPO, dorsomedial periolivary nucleus; MNTB, medial nucleus of the trapezoid body; VNTB, ventral nucleus of the trapezoid body.

Central Auditory Pathways

Central auditory pathways involve all ascending and descending neuronal projections interconnecting the auditory nerve, brainstem, midbrain, thalamus, and cerebral cortex (Fig. 128-6). Most of the understanding of the anatomy, physiology, and function of these regions is inferred from animal studies. This section provides a broad overview of central auditory anatomy and may not entirely reflect the uniquely human condition. Many of the functions of these regions are inferred from animal behavioral or electrophysiologic studies, and the precise localization of human sound processing activities is not completely mapped. The reader should take away from this section a general understanding of central auditory anatomy and the complex interactions of sound processing pathways.

Cochlear Nerve

The cochlear nerve, a trunk of the cochleovestibular or eighth cranial nerve, contains afferent fibers transmitting auditory information from inner and outer hair cells to the brainstem. The cell bodies of these afferent neurons are located within the spiral ganglion of the cochlea. Spiral ganglion neurons are bipolar, with one process extending toward inner and outer hair cells and the other projecting to the brainstem. Approximately 90% to 95% of the traversing axons are large myelinated fibers, and the remaining 5% to 10% are thinner, unmyelinated axons.[16,17] The larger neurons are type I ganglion cells, which project from the inner hair cells. The smaller neurons are type II ganglion cells, which contact the outer hair cells. Both these cell types project to the cochlear nucleus, and their fibers form the cochlear nerve within the internal auditory canal and cerebellopontine angle.

The cochlear nerve is located anterior and inferior within the lateral internal auditory canal, and is separated laterally from the anterior-superior facial nerve by the transverse crest. Auditory nerve fibers entering the cochlea in this region are delicate, and care must be taken during acoustic neuroma surgery for hearing preservation to avoid lateral-to-medial traction on the nerve.[18] At the fundus, or lateralmost extent, of the internal auditory canal, the cochlear nerve is anterior to the vestibular nerves. As the trunk traverses the internal auditory canal, there is a 90-degree rotation of the complex so that the cochlear nerve lies inferior to the vestibular nerve trunk within the cerebellopontine angle. Although they join to form the cochleovestibular nerve proper, a plane of dissection generally remains apparent between the two trunks. The cochlear nerve may also appear to be a brighter white than the duller vestibular division. These features are important for identifying the proper nerve trunk during vestibular nerve section for intractable Meniere's disease.

The myelin of the cochlear and vestibular nerves transitions from peripheral Schwann to central myelin within the cerebellopontine angle. This transition zone has traditionally been thought to be the site of origin for most acoustic neuromas (i.e., vestibular schwannomas), but such an origin has been contested more recently.[19] The cochleovestibular nerve continues medially and enters the central nervous system at the pontomedullary junction. The root entry zone can be identified surgically within the foramen of Luschka after retraction of the flocculus and identification of the choroid plexus. This is the site of place-

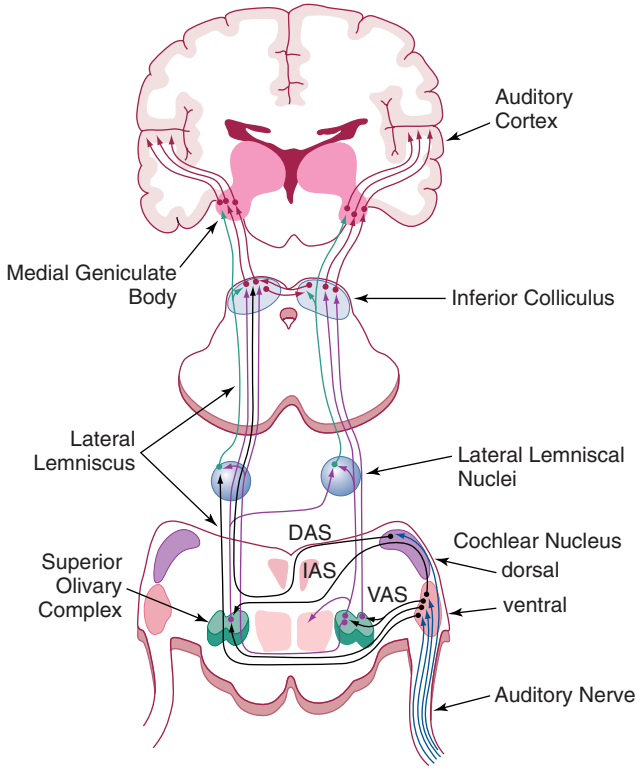

Figure 128-6. Illustration of the major central ascending auditory pathways for sound entering via the right cochlea. Commissural pathways and descending feedback projections from higher centers are not depicted. DAS, dorsal acoustic stria; IAS, intermediate acoustic stria; VAS, ventral acoustic stria.

ment of an auditory brainstem prosthesis along the lateral aspect of the cochlear nucleus.[20] The vestibular division enters the pontomedullary junction more medial than the cochlear division.

The olivocochlear bundle providing efferent innervation to the cochlea does not send fibers to the periphery through the cochlear division. Rather, the efferent innervation to the cochlea travels with the inferior division of the vestibular nerve. These fibers pass through the saccular ganglion and enter the spiral ganglion via the vestibulocochlear anastomosis of Oort.[21] Efferent fibers provide direct innervation of outer hair cells and indirect modulation of inner hair cells.

Cochlear Nucleus

All peripheral auditory information enters the central auditory system through the cochlear nucleus. Within the cochlear nucleus, initial auditory processing occurs, and fibers are distributed to higher brainstem centers. In most mammals, the cochlear nucleus forms a prominent bulge on the lateral surface of the brainstem. In humans, the cochlear nucleus is less conspicuous and is typically identified by its location along the floor of the lateral recess of the fourth ventricle.

The cochlear nucleus is traditionally segregated into ventral and dorsal subdivisions. These divisions are demarcated by the small granular cell domain, which may play a role in integrating nonauditory sensory information with auditory processes.[22] Such integration may explain the modulation of tinnitus in many individuals by jaw position or head turning.[23] The dorsal cochlear nucleus is typically laminar in organization and is more akin to the structure of the cerebellum than to other brainstem nuclei. It is less robust in humans than in other mammals, which typically have mobile pinnae and the dorsal cochlear nucleus may play a role in orienting to a sound source.[24] The dorsal cochlear nucleus has been implicated in several studies as a potential site for the generation of tinnitus.[25,26] The dorsal cochlear nucleus is tonotopically organized with low frequencies represented ventrolaterally and higher frequencies dorsomedially.[27]

The ventral cochlear nucleus is divided into anterior ventral and posterior ventral subnuclei, each with an individual tonotopic map.[16] These subnuclei have unique and shared neuronal subclasses that serve as the initial processors of auditory nerve information. Prominent spherical bushy cells, characteristic of the anterior ventral nucleus, send large-caliber axons to the olivary complex and function in sound localization.[28] The multipolar or stellate neurons, associated most with the posterior ventral cochlear nucleus, send multiple fine axons to several other brainstem centers, including the contralateral cochlear nucleus, the ipsilateral dorsal cochlear nucleus, and the contralateral inferior colliculus.[29] These cells likely play a role in encoding frequency and spectral shape, and sound intensity.[30] The octopus cells in the caudal regions of the posterior ventral cochlear nucleus may have similar functions.[31,32]

The axons of cochlear nucleus neurons project to other brainstem regions via the ventral, intermediate, and dorsal acoustic stria (see Fig. 128-6). The ventral acoustic stria, or trapezoid body, contains axons of spherical and globular bushy cells and traverses the medulla and pons to innervate the LSO, the MSO, the medial nucleus of the trapezoid body, and the inferior colliculus.[33,34] The intermediate acoustic stria contains octopus cell axons and projects to the ventral nucleus of the trapezoid body, LSO, and periolivary region. The dorsal acoustic stria transmits axons from dorsal cochlear nucleus fusiform and giant neurons to the central nucleus of the contralateral inferior colliculus.[35,36]

Superior Olivary Complex

The superior olivary complex (SOC), in the caudal aspect of the pons, is traditionally divided into three major subnuclei. These appear less distinct in human brainstems than in the brainstems of lower mammals. These subdivisions include the MSO, the LSO, and the medial nucleus of the trapezoid body. Small groups of neurons constituting the periolivary nuclei surround these and form the dorsomedial, dorsal, and dorsolateral periolivary nuclei. The periolivary group in humans is not as distinctly subdivided as in other mammals and appears disorganized with loosely arranged neurons.[37]

The SOC is the first central auditory center to receive binaural innervation, and it maintains the tonotopic organization seen in the cochlea and cochlear nucleus. Binaural innervation is indicative of the major role this nucleus plays in localizing sounds in space. Localization of sound is a combined comparison of interaural time delays by the MSO and interaural intensity differences by the LSO.[38,39] Additional roles of the SOC include sound detection and complex sound processing. The SOC also has an efferent limb providing feedback to the cochlear nucleus and cochlea.

Projections from the SOC entail ascending and descending pathways (see Fig. 128-6). The ascending fibers project via the lateral lemniscus to the nucleus of the lateral lemniscus and the inferior colliculus. This ascending pathway functions in sound localization. The descending pathway represents the olivocochlear bundle and provides efferent innervation to the cochlea hair cells (see Fig. 128-5). This descending pathway influences cochlea sensitivity or tuning through modulation of outer hair cell activity.[14,40] The integration of afferent and efferent activities makes the SOC potentially important in influencing signal-to-noise ratios and aspects of hearing in noise.

Lateral Lemniscus

The lateral lemniscus is the principal pathway by which medullary and pontine auditory nerve fibers reach the inferior colliculus. There are two subnuclei associated with this tract (i.e., ventral and dorsal) that receive differential innervation from the ipsilateral and contralateral cochlear nuclei and SOC subdivisions.[41] In some nonhuman mammals, a third subnucleus, the intermediate nucleus of the lateral lemniscus, has been identified. Most fibers from these nuclei innervate the central nucleus of the inferior colliculus, but minor tracts ascend to the superior colliculus and descend back to the SOC and trapezoid body. The dorsal lemniscal nuclei also send commissural fibers to each other from the contralateral lateral lemniscus. The lateral lemnisci are closely associated with the SOC and play a role in many of the same sound

localization and processing functions. The lateral lemniscus is also an important component of the acoustic startle reflex pathway, which includes the ventral cochlear nucleus.[42] These pathways through the lateral lemniscus correlate with aspects of the wave III to V interval of the auditory brainstem response.[43]

Inferior Colliculus

The inferior colliculus is a midbrain structure that receives extensive innervation from higher and lower brain regions. Almost all ascending and descending auditory pathways between the brainstem and forebrain synapse within the inferior colliculus.[44] Principal functions of the inferior colliculus involve sound localization, frequency determination, and integration of auditory with nonauditory systems.

The inferior colliculus is generally divided into three main neuronal groups: the central nucleus of the inferior colliculus, the cortex of the inferior colliculus, and the paracentral nuclei.[45] Each of these subdivisions is divided further into regions based on neuronal morphology and cellular organization. The central nucleus is the dominant region, and its structure is well conserved among species. There is a laminar organization, likely related to the tonotopic map, which subdivides the central nucleus into a pars lateralis, pars centralis, and pars medialis. Projections to the central nucleus of the inferior colliculus can be direct and monaural (from the contralateral cochlear nucleus), indirect and binaural (from the cochlear nuclei by way of the SOC), or polysynaptic (via the cochlear nuclei, SOC, and lateral lemniscus).

The cortex of the inferior colliculus is a laminar structure typically seen histologically to comprise four layers. This region forms a cap around the dorsal and caudal aspects of the inferior colliculus. Innervation to the cortex of the inferior colliculus is primarily from the forebrain and includes primary and secondary auditory cortex. These projections show tonotopic arrangement. There are few fibers to the inferior colliculus cortex from the lower brainstem, and typically only from cochlear nuclei. Surrounding nonauditory midbrain structures provide additional innervation to the cortex of the inferior colliculus. The paracentral nucleus of the inferior colliculus also receives nonauditory innervation, primarily from the somatosensory system.

The inferior colliculus also interacts with the proximate superior colliculus, which is associated with saccadic eye movements.[46] Ascending fibers from the subnuclei of the inferior colliculus all synapse in the medial geniculate body, where fibers are distributed to multiple auditory and nonauditory cortical structures. These tracts are likely the initial pathways for integrating auditory, somatosensory, and special sensory systems. These patterns of innervation argue for the multiintegrative function of the inferior colliculus.

Medial Geniculate Body

The medial geniculate body of the thalamus is the portal for all ascending auditory innervation to the telencephalon. Similar to other auditory centers, it is subdivided into several subnuclei—ventral, medial, and dorsal divisions.[47] Each of these divisions receives innervation from the nuclei of the inferior colliculus and descending fibers from the auditory cortex.

The ventral division of the medial geniculate body is secondarily organized into three distinct regions: the pars lateralis, pars ovoidea, and marginal zone. The pars lateralis is the dominant region and has a laminar appearance because of the orientation of its large bushy cells and intrinsic interneurons. These layers reflect an underlying tonotopic organization. The bushy cells project to layers III and IV of the auditory cortex, where the tonotopic map is recapitulated. Similar neuronal populations are found in the pars ovoidea and marginal zone, but with a less distinct laminar appearance.

The dorsal division of the medial geniculate body is a heterogeneous-appearing region comprising 10 subnuclei. The most basic description contains the dorsal, superficial dorsal, and deep dorsal nuclei, and the suprageniculate and posterior limitans nuclei. Inputs to the dorsal division include inferior colliculus and other thalamic nuclei. These auditory and nonauditory connections may play a role in attending to acoustic stimuli.

The medial division of the medial geniculate body contains some of the largest neurons in the geniculate body. Axons from these neurons project to all auditory cortical regions and many nonauditory centers. Innervation to the medial division has some auditory origin, but also nonauditory contributions from the vestibular nuclei and spinal cord. These varied interconnections may play a role in arousal to auditory stimuli.

Auditory Cortex

The principal human auditory cortex is located deep within the sylvian fissure on the superior surface of the temporal lobe. The auditory cortex consists of multiple defined tonotopically organized regions.[48] These include AI (primary), AII (secondary), the anterior auditory fields (AAF or A), the ventral auditory field (V), the ventral posterior auditory fields (VP), and the posterior auditory field (P). The primary auditory cortex is often referred to as AI (or Brodmann area 41), and the secondary cortex is referred to as AII (or Brodmann area 42). These regions lie within the transverse gyri of Heschl in continuity with the posterior aspect of the superior temporal gyrus (Fig. 128-7). These regions are structurally organized, similar to much of the cortex, into layers I through VI, each containing dominant populations of neurons and unique patterns of innervation and projection.

Numerous cortical association areas surround the primary auditory cortex. The posterior aspect of the superior temporal gyrus and the deeper planum temporale are known as Wernicke's area (left side), or area 22. Classically, this region has been viewed as a neural substrate for receptive language and is dominant on the left side in most humans. The enlarged left planum temporale has been thought to be a uniquely

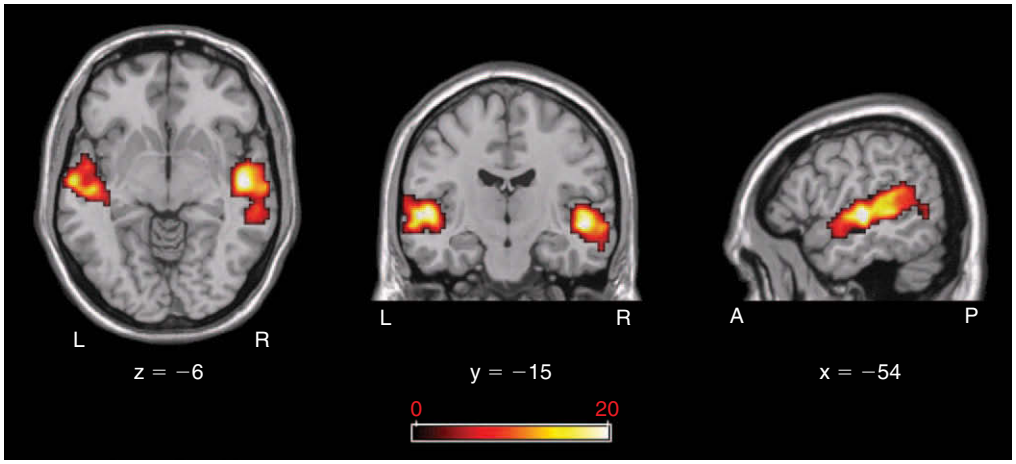

Figure 128-7. Functional MRI of the brain in a musician listening to music. The primary and secondary auditory cortex in both hemispheres shows strong activation. The brighter colors indicate more intense cortical activation. *(Copyright © 2008 C. Limb, MD. Published with permission.)*

human condition, but more recent evidence shows that the structural basis for this human trait is present in other apes.[49,50]

Just posterior to area 22, in the inferior parietal lobe, are the angular gyrus and supramarginal gyrus (areas 39 and 40). These cortical regions integrate auditory, somatosensory, and visual information. Higher orders of language integration, such as in reading and writing, may occur in these areas. Functional imaging studies also suggest that the angular gyrus may play a role in tinnitus perception.[51]

The arcuate fasciculus connects these association areas with the anteriorly located pars triangularis, which is part of the frontal operculum. This region of the inferior frontal gyrus is also known as Broca's area, or area 44 and 45. Similar to Wernicke's area, this region apparently is left hemisphere dominant and is important for expressive language, and the perception of musical syntax.[52]

Advances in functional imaging using functional magnetic resonance imaging (MRI), positron emission tomography, and magnetoencephalography have expanded the understanding of cortical processing of complex auditory information, such as music. Additional regions, such as the prefrontal cortex, cerebellum, and limbic system, may be important in music interpretation and production, including the processing of different musical features, such as dissonance.[53,54] There also seem to be segregated cortical pathways for the perception of musical elements such as melody and timber analogous to speech and the interpretation of verbal content versus the recognition of the speaker's voice.[55]

Reciprocal projections exist between the auditory cortex and lower auditory nuclei. Although not definitively identified in humans, three principal descending pathways to the thalamus, midbrain, and brainstem have been reported. The primary auditory cortex projects to other cortical regions and to the medial geniculate body.[56] Projections from cortex to SOC and inferior colliculus seem to contact neurons that feedback to higher centers.[57] Direct cortical projections to cochlear nucleus also have been reported in mammalian models.[58] These pathways may enable the cortex to modulate ascending auditory input.

Acknowledgments

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CHAPTER ONE HUNDRED AND TWENTY-NINE

Physiology of the Auditory System

Wade Chien

Daniel J. Lee

Key Points

- The external ear funnels acoustic signals into the ear and plays an important role in sound localization, while the middle ear (including the tympanic membrane and the ossicular chain) matches the impedance between the air-filled external environment and the fluid-filled inner ear, or cochlea.
- A traveling wave is initiated on the basilar membrane as sound energy enters the cochlea.
- The basilar membrane maps frequency-specific information (tonotopic organization) and its displacement causes deflection of the stereocilia on hair cells, resulting in depolarization/hyperpolarization of the hair cells.
- Hair cells transduce mechanical energy (acoustic energy) to an electrochemical signal that is propagated as an action potential along the auditory nerve.
- Inner hair cells are innervated by type I auditory afferents and conduct sound information to the cochlear nucleus.
- Outer hair cells contract with depolarization and elongate with hyperpolarization to alter the mechanical properties of the basilar membrane.
- The auditory nerve carries information about which fibers are responding to sound, as well as the rate and timing pattern from each fiber.
- The cochlear nucleus is the first relay station for all ascending auditory information originating in the ear and receives inputs from the spiral ganglion cells through the auditory nerve.
- The auditory brainstem processes interaural timing and amplitude differences between ears to determine the location of the sound source.
- Binaural hearing improves auditory perception using three mechanisms: the head shadow effect, binaural squelch, and summation.
- The primary auditory cortex is located on Heschl's gyrus and is tonotopically organized. This region processes complex auditory signals to enable language comprehension.
- Descending pathways to the ear (auditory efferents) modulate the responses of the middle ear (acoustic reflex) and inner ear (medial olivocochlear reflex) to certain types of sounds.

A fundamental understanding of normal auditory physiology is the basis by which otolaryngologists can correlate structural changes with pathologic disturbances in the auditory system. Passive and active mechanisms in the auditory system work synergistically to provide sensitive hearing in humans. This chapter summarizes current knowledge of the exquisite mechanisms of sound and speech perception and processing by the peripheral and central auditory pathways.

Sound and Its Measurement

Sound is produced by a disturbance in particle density (whereby a particle is made up of many molecules of the sound-propagating medium) triggered by a sound-producing body, or sound source. If this disturbance in particle density travels through an elastic medium, such as air or fluid, sound propagation occurs. As a tuning fork (a sound source) is struck, it causes the air particles adjacent to it to vibrate. The vibration of these air particles causes other nearby air particles to vibrate, enabling sound propagation. The velocity of sound propagation in dry air is about 340 m/sec at room temperature, whereas in water, sound travels at around 1500 m/sec.

Simple harmonic motion provides the framework for understanding acoustic energy (Fig. 129-1). Simple harmonic motion is a periodic motion that undulates around a null point with equal amplitudes, similar to a sine function. The *frequency* of a simple harmonic motion is the number of cycles per second and is measured in *Hertz* (Hz). The *period* of a cycle is the inverse of its frequency ($1/f$), and represents the duration of a single cycle. The *amplitude* is the maximum amount of displacement from the null point in one direction. The sound produced by simple harmonic motion is called a *pure tone*. In the everyday environment, most sound sources do not produce sounds that follow simple harmonic motion. Any vibration that does not follow simple harmonic

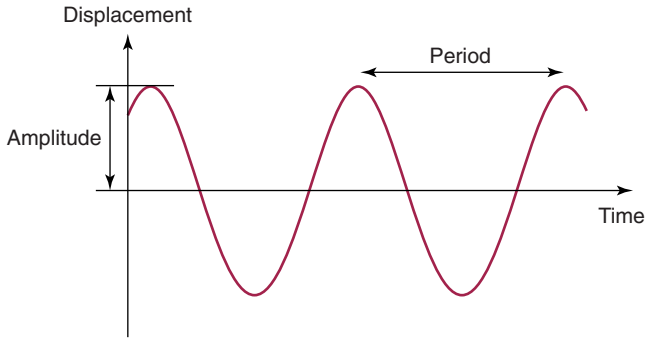

Figure 129-1. Simple harmonic motion. Simple harmonic motion is a periodic motion that undulates around a null point with equal amplitudes. The amplitude is the maximum amount of displacement from the null point in one direction. The frequency of a simple harmonic motion is the number of cycles per second, and is measured in Hertz (Hz). The period of a cycle is the inverse of its frequency ($1/f$), and represents the duration of a single cycle.

motion is said to be complex. If there is a repetitive periodic pattern to the complex vibration, it produces *tones*. If the complex vibration has no repetitive pattern, it results in *noise*.

One way to quantify sound is by its intensity, which is cumbersome to measure directly. Sound *pressure,* which is related to the square root of intensity, is relatively easy to measure, however, and is the most common way of quantifying sound. Sound pressure, which has units of *pascal* (Pa) (which is Newton per meter squared [N/m^2]), represents the amount of force that vibrating sound particles exert on a surface area.

Because the human ear is capable of perceiving a huge dynamic range of sound intensity (about 10^{12}-fold), a convenient way of expressing sound intensity is by taking the logarithmic ratio of two sound intensities (the numerator being the sound intensity of interest, and the denominator being a reference sound intensity) and multiplying by 10. This is called the *decibel scale*. The formula for determining decibels for sound intensity is: $dB = 10 \log_{10} J/Jr$, where J is the intensity of the sound of interest, and Jr is the intensity of reference.

Because pressure varies as the square root of intensity, it is necessary to square the pressures in the decibel formula when sound pressure is being used. The formula for determining decibels for sound pressure is $dB = 10 \log_{10} P^2/Pr^2 = 10 \log_{10} (P/Pr)^2 = 20 \log_{10} P/Pr$, where P is the sound pressure of interest, and Pr is the reference sound pressure. If the sound of interest has 10 times more pressure than the reference sound pressure, the sound of interest is 20 dB louder than the reference. If the sound of interest has 100 times more pressure, it is 40 dB louder than the reference. The most commonly used reference sound pressure is 20 µPa, which is referred to as *sound pressure level* (SPL). Another reference sound pressure that is occasionally used is *hearing level* (HL), which is the threshold sound pressure at a specific frequency (as measured in normal subjects); this threshold sound pressure varies across the frequency range.

Impedance

Impedance generally can be thought of as the impediment to movement. In the study of acoustics, impedance is defined as the ratio of the acoustic pressure over the volume velocity generated by the acoustic pressure. Imagine an acoustic stimulus striking an elastic membrane (e.g., the tympanic membrane); the greater the sound pressure of the acoustic stimulus, the larger the motion of the membrane, and the higher the velocities achieved by that motion. The exact relationship between the pressure of the acoustic stimulus and the membrane volume velocity is governed by acoustic impedance.

There are three components to acoustic impedance: stiffness, resistance (damping), and mass. If the membrane were stiffer than normal, the volume velocity generated by the acoustic stimulus would be decreased. Similarly, if the mass of the membrane were increased, one would also expect the volume velocity generated by the acoustic stimulus to decrease. In addition, a small amount of sound energy is lost because of the damping effect of the system. In a simple acoustic resonator, stiffness varies inversely with frequency and dominates the acoustic impedance at low frequencies, whereas the impedance of a mass increases with frequency and dominates at high frequencies. When the acoustic impedance is at its lowest point (i.e., at the frequency where the stiffness and mass components of the acoustic impedance cancel each other out), it is said that the system is in resonance.

External Ear

The external ear is composed of the pinna and the external auditory canal. The external ear funnels sound from the external environment into the ear. The peculiar shape of the pinna and the external auditory canal gives rise to specific resonant frequencies as these structures are struck by sound: the concha has a resonant frequency of around 5300 Hz, and the external auditory canal has a resonant frequency of around 3000 Hz. The external ear plays an important role in sound localization.

Sound localization is achieved by two major mechanisms: interaural time difference and interaural amplitude difference. Because the left and the right ears are located on opposite sides of the head, the amount of time it takes for a sound stimulus to arrive at each individual ear is governed by the distance of the sound source to that particular ear: the farther the distance, the longer it takes for the sound stimulus to arrive. The differences in the time arrival of the sound stimulus between the two ears can be used as a cue for sound localization. The differences in amplitude perceived by the two ears can also be used as a cue for sound localization.[1,2] This difference in amplitude is increased further by the "head shadow" effect: sound coming from one side is attenuated by the head as it travels to the contralateral ear. The head shadow effect in binaural hearing helps to improve the signal-to-noise ratio in adverse listening environments; one ear can be closer to the source of sound or speech, whereas the contralateral ear is exposed to the background noise. It has been shown that the interaural time difference is important for low-frequency sound localization, whereas the interaural amplitude difference is important for higher frequency sound localization.[3]

Middle Ear Mechanics

The middle ear is composed of the tympanic membrane, the ossicles (malleus, incus, and stapes), and the stapedius and tensor tympani muscles. As a sound stimulus enters the external auditory canal, it causes the tympanic membrane to vibrate. The malleus, which is coupled to the tympanic membrane, vibrates in response to the motion of the tympanic membrane. This causes the entire ossicular chain to vibrate, resulting in sound transmission to the inner ear via the stapes footplate. This pathway of sound transmission is referred to as *ossicular coupling*.[4] The ossicular chain has two synovial joints that are mobile: the incudomalleal and the incudostapedial joints.[5] The ossicular chain vibrates along an axis that projects through the head of the malleus and the body of the incus in an anterior-to-posterior direction (Fig. 129-2). The stapes, the smallest bone in the body, transmits the output of the middle ear into the inner ear through the oval window.

Because the inner ear is fluid-filled, if the sound stimulus strikes the inner ear fluid directly, most of the acoustic energy is deflected, as the impedance of fluid is much greater than the impedance of air. The pathway of sound transmission to the inner ear in the absence of the ossicular system is referred to as *acoustic coupling*.[4] It has been shown that the difference between ossicular coupling and acoustic coupling is about 60 dB, which is the maximal amount of hearing loss expected in patients with ossicular discontinuity.[6] The middle ear plays an important role in the process of "impedance matching" between the air-filled middle ear and the fluid-filled inner ear, allowing for efficient sound transmission. The most important factor in the middle ear's impedance matching capability comes from the "area ratio" between the tympanic membrane and the stapes footplate (see Fig. 129-2). The human tympanic membrane has a surface area approximately 20 times larger than

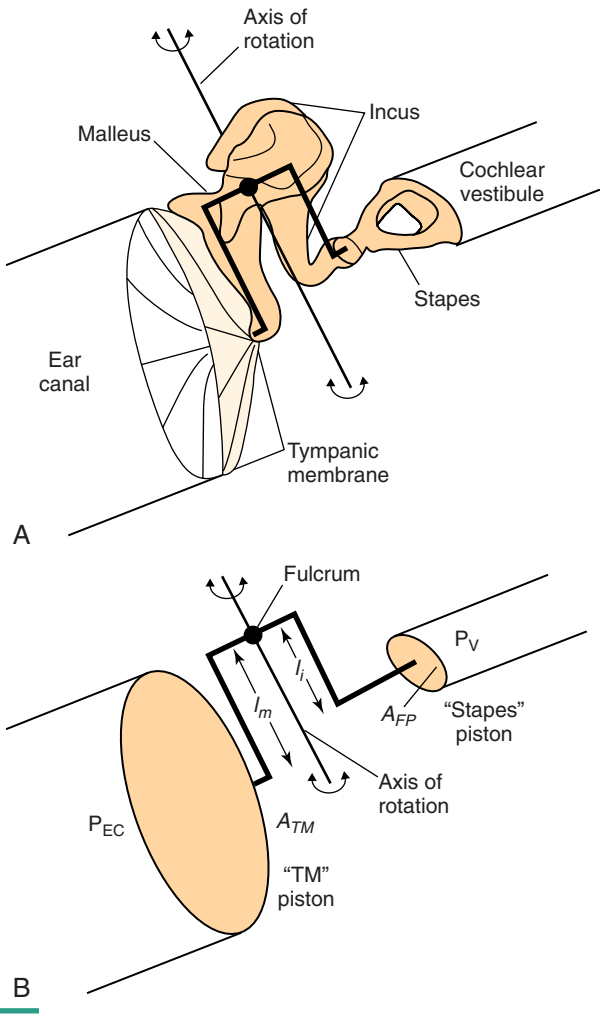

Figure 129-2. Schematic of the middle ear system. **A,** Motion of the ossicular chain along its axis of rotation. **B,** Concept of area ratio (ATM/AFP) and lever ratio (*lm*/*li*). AFP, area of the footplate; ATM, area of the tympanic membrane; *li,* length of the incus long process; *lm,* length of the manubrium; PEC, external canal sound pressure; Pv, sound pressure of the vestibule. *(From Merchant SN, Rosowski JJ. Auditory physiology. In: Glasscock ME, Gulya AJ, eds.* Glasscock-Shambaugh Surgery of the Ear. *5th ed. Ontario: Decker; 2003:64.)*

the stapes footplate (69 vs. 3.4 mm^2).[7] If all the force applied to the tympanic membrane were to be transferred to the stapes footplate, the force per unit area would be 20 times larger (26 dB) on the footplate than on the tympanic membrane.

A second mechanism for impedance matching is called the *lever ratio,* which refers to the difference in length of the manubrium of the malleus and the long process of the incus. Because the manubrium is slightly longer than the long process of the incus, a small force applied to the long arm of the lever (manubrium) results in a larger force on the short arm of the lever (incus long process). In humans, the lever ratio is about 1.31 : 1 (2.3 dB).[8] The combined effects of the area ratio and the lever ratio give the middle ear output a 28-dB gain theoretically. In reality, the middle ear sound pressure gain is only about 20 dB[9]; this is mostly due to the fact that the tympanic membrane does not move as a rigid diaphragm. At higher frequencies, it vibrates in a complex manner, with multiple areas that vibrate differently.[10] The effective area of the tympanic membrane involved with impedance matching is smaller than its total area. Nevertheless, the 20-dB middle ear sound pressure gain assists sound transmission from the air-filled middle ear into the fluid-filled inner ear.

Inner Ear Physiology

The inner ear is enclosed in a bony cavity called the *otic capsule*. It has two mobile windows: the oval and the round windows. The two important functions of the inner ear are hearing and balance. The portion of the inner ear that deals with hearing is the cochlea, and the portion of the inner ear that deals with balance is collectively known as the vestibular organs (semicircular canals, utricle, and saccule). The cochlea is shaped like a snail, and has a spiral configuration with two and a half turns (Fig. 129-3A). The center portion of the spiral is called the *modiolus*. The portion of the cochlea that is closest to the oval window is referred to as the base, whereas the portion of the cochlea that is farthest away from the oval window is referred to as the apex. The cochlea is a fluid-filled space with three compartments: scala tympani, scala media, and scala vestibuli (Fig. 129-3B). The scala tympani and the scala media are separated by the basilar membrane, and the scala media and the scala vestibuli are separated by Reissner's membrane. The scala tympani and the scala vestibuli join together at the apex of the cochlea to form the helicotrema.

The scala media contains the organ of Corti, which rests on the basilar membrane. Taken together, organ of Corti and the basilar membrane are also referred to as the cochlear partition. The organ of Corti has an arch at its center, called the arch of Corti, which is formed by the inner and the outer pillar cells. The inner hair cells are flask-shaped cells that rest on the side of the inner pillar cells, whereas the outer hair cells are cylindrical-shaped cells that rest on the side of the outer pillar cells. The human cochlea contains about 3000 inner hair cells that extend in a single row from the base to the apex; there are about 12,000 outer hair cells arranged in three or four rows. The hair cells derive their names from having hairlike projections on their apical surface. These hairlike projections are stereocilia, which play an important role in the signal transduction properties of the hair cells.

The scala vestibuli and the scala tympani are filled with perilymph, which has a similar composition to the extracellular fluid (high in sodium, low in potassium) (Fig. 129-4A). The scala media is filled with endolymph, which has a similar composition to the intracellular fluid (low in sodium, high in potassium).[11] The unique electrolyte composition of the scala media sets up a large electrochemical gradient, called the *endocochlear potential,* which is +60 to +100 mV relative to the perilymph (Fig. 129-5).[12] The maintenance of such a large electrochemical gradient is performed by the *stria vascularis,* which resides on the outer wall (away from the modiolus) of the scala media. The stria vascularis contains multiple active ion channels, and maintains the chemical composition of the endolymph and its positive electrical potential.[13]

As sound energy travels through the external and middle ears, it causes the stapes footplate to vibrate. The vibration of the stapes footplate results in a compressional wave in the inner ear fluid, which travels across the scala vestibuli, around the helicotrema, and out across the scala tympani toward the round window. An inward motion of the stapes causes an outward motion of the round window. As this compression wave travels across the scala vestibuli, however, the pressure in the scala vestibuli is higher than the pressure in the scala tympani. This sets up a pressure gradient, which causes the cochlear partition to vibrate.

von Bekesy[12] first described the vibration of the cochlear partition in cadaveric human cochleas. He showed that as the cochlear partition is deflected by the compressional wave created by the stapes footplate vibration, it sets up a traveling wave on the basilar membrane, which travels from the base of the cochlea to its apex (Fig. 129-6). von Bekesy[12] also found that the basilar membrane varied in its stiffness along its length, with higher stiffness near the base and lower stiffness near the apex. This property of the basilar membrane allows it to respond to various frequencies differently (i.e., the amplitude of the traveling wave peaks [resonates] at a specific place along the basilar membrane), with the higher frequencies at the base and the lower frequencies toward the apex. The basilar membrane is able to act as a series of filters, responding to specific sound frequencies at specific locations along its length. In other words, the basilar membrane is *tonotopically tuned* to different frequencies along its length. von Bekesy's

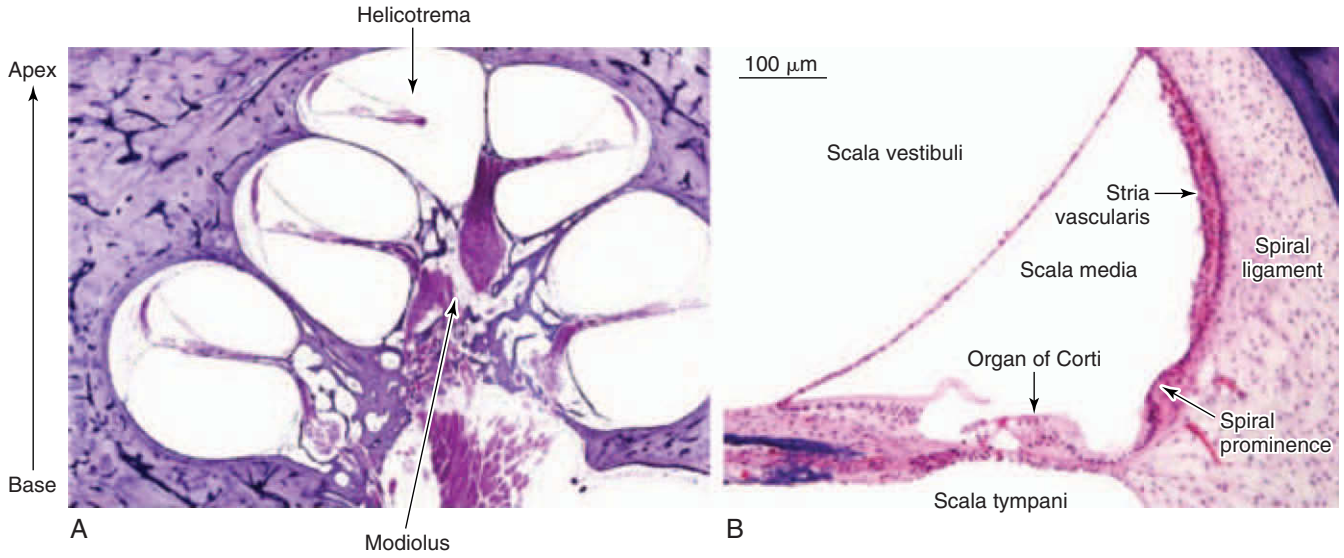

Figure 129-3. **A,** Histologic section showing normal human cochlea. The cochlea is shaped like a snail, and has a spiral configuration with two and a half turns. The center portion of the spiral is called the modiolus. The portion of the cochlea that is closest to the oval window is referred to as the base, and the portion of the cochlea that is farthest away from the oval window is referred to as the apex. (H&E stain.) **B,** Higher magnification of the histologic section in **A** showing the organ of Corti. The cochlea is a fluid-filled space with three compartments: scala tympani, scala media, and scala vestibuli. The scala tympani and the scala media are separated by the basilar membrane, whereas the scala media and the scala vestibuli are separated by Reissner's membrane. The scala tympani and the scala vestibuli join together at the apex of the cochlea to form the helicotrema. The scala media contains the organ of Corti, which rests on the basilar membrane. The organ of Corti and the basilar membrane together are sometimes referred to as the cochlear partition. The stria vascularis plays an important role in maintaining the electrochemical environment of the cochlea. (H&E stain.) *(Modified from www.temporalboneconsortium.org.)*

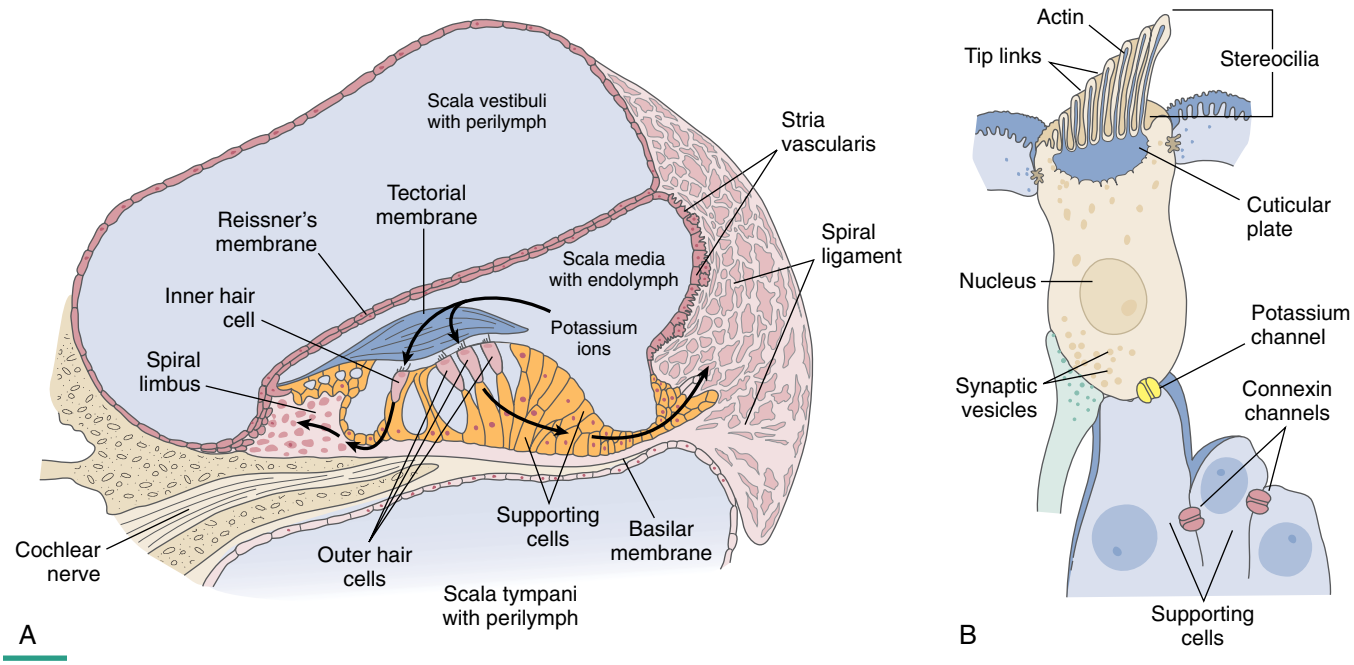

Figure 129-4. Mechanoelectrical transduction of the auditory signal depends on the recycling of potassium ions in the organ of Corti. **A,** Schematic cross-sectional view of the human cochlea. The scala media (cochlear duct) is filled with endolymph, and the scala vestibuli and tympani are filled with perilymph. The endolymph of the scala media bathes the organ of Corti, located between the basilar and tectorial membranes and containing the inner and outer hair cells. A high concentration of potassium in the endolymph of the scala media relative to the hair cell creates a cation gradient that is maintained by the activity of the epithelial supporting cells, spiral ligament, and stria vascularis. **B,** Hair cells contain stereocilia along the apical surface and are connected by tip links. The potassium gradient shown in **A** is essential to enable depolarization of the hair cell in **B** after influx of potassium ions in response to mechanical vibration of the basilar membrane, deflection of stereocilia, displacement of tip links, and opening of gated potassium channels. Depolarization results in calcium influx through channels along the basolateral membrane of the hair cell, causing degranulation of neurotransmitter vesicles into the synaptic terminal and propagation of an action potential along the auditory nerve, shown in *blue*. Gap junction proteins between the hair cells (potassium channel, *yellow*) and epithelial supporting cells (connexin channels, *red*) allow for the flow of potassium ions back to the stria vascularis where they are pumped back into the endolymph. *(From Willems PJ. Genetic causes of hearing loss.* N Engl J Med. *2000;342:1101-1109. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)*

seminal work on cochlear mechanics earned him the Nobel Prize in Physiology or Medicine in 1961.

Although the cochlea is usually thought of as having two mobile windows (the oval and round windows), the possibility of a third mobile window has been proposed.[14] More recently, a select group of patients with an air-bone gap on audiologic testing (which is typically associated with middle ear pathology) who do not have any middle ear pathology on intraoperative exploration has been described.[15-17] It has been shown that the air-bone gap in this group of patients can be explained by a pathologic "third window" in the inner ear.[18] Perhaps the most well-studied example of this phenomenon is seen in superior semicircular canal dehiscence (Fig. 129-7; video clip available on website).

Patients with superior semicircular canal dehiscence often complain of autophony, aural fullness, sound-induced or pressure-induced vertigo, and hearing loss.[19-22] It is thought that the dehiscence in the superior semicircular canal acts as a third mobile window of the inner ear (in addition to the oval and round windows), shunting acoustic energy away from the cochlea, resulting in a decreased sensitivity to air-conducted sound and an air-bone gap seen on audiologic testing.[20,23-25] This third window is also theorized to decrease cochlear input impedance at the oval window, increasing the pressure gradient across the cochlear partition, and resulting in hypersensitivity to bone-conducted sound.[23] Repair, or plugging, of superior semicircular canal dehiscence in some cases results in improvement of the preoperative air-bone gap (see Fig. 129-7). The third window hypothesis has also been used to explain the air-bone gap associated with other temporal bone anomalies, such as large vestibular aqueduct syndrome and other inner ear malformations.[26-28]

As the cochlear partition is deflected in response to the compressional wave initiated by the stapes, it causes a shearing force between the stereocilia of the hair cells and the tectorial membrane. This shearing force causes a deflection of the hair cell stereocilia. The hair cell stereocilia are arranged in rows, and the rows are arranged in an orderly fashion by height (see Fig. 129-4B). The tip of each stereocilia is connected from one row to another by an elastic filament called the *tip link*.[29] It is thought that as the stereocilia is deflected toward the direction of the tallest row, it causes the tip links to stretch. The stretch of the tip links causes the opening of stretch-sensitive cationic channels located on the stereocilia (Fig. 129-8).

Because there is a large electrochemical gradient across the apical surface of the hair cells (with a large positive endocochlear potential on one side, and a large negative intracellular potential on the other side), the opening of these stretch-sensitive cationic channels on the stereocilia causes a large influx of cationic current, which leads to hair cell depolarization. As the stereocilia is deflected away from the tallest row, the tip links relax, decreasing the probability of ion channel opening; this leads to hyperpolarization of the hair cell.[30-32] The relationship between the degree of stereocilia deflection and hair cell depolarization or hyperpolarization is not symmetric or linear. Stereocilia deflection in the depolarization direction produces a greater response than deflection in the hyperpolarization direction (Fig. 129-9).[30] The deflection of the hair cell stereocilia and the resulting hair cell depolarization or hyperpolarization represents an important step in the signal transduction process of the hair cell (i.e., by converting a mechanical signal [inner ear fluid wave] into an electrochemical signal).

Because potassium is the major cation in the endolymph, it is believed that potassium current plays an important role in triggering the signal transduction process in hair cells. When inner hair cells are depolarized, voltage-gated calcium channels open.[33] These voltage-gated calcium channels are clustered in several "hot spots" along the basolateral surface of the inner hair cells, where synaptic contacts with primary afferent auditory nerve fibers are located.[34] The calcium current mediated by these voltage-gated ion channels are important for triggering neurotransmitter release across the synapse, which leads to activation of the auditory nerve fibers. The neurotransmitter involved in this process has not been definitively identified, but is believed to be a molecule closely related to glutamate.[35]

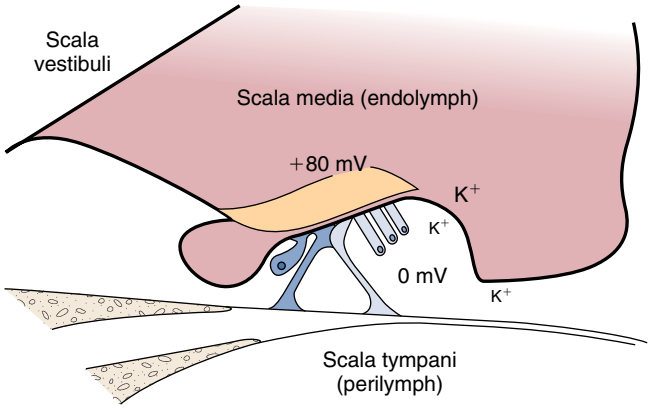

Figure 129-5. Schematic showing the electrochemical environment of the cochlea. The scala vestibuli and the scala tympani are filled with perilymph, which has a low potassium concentration. The scala media is filled with endolymph, which has a high potassium concentration. The unique electrolyte composition of the scala media sets up a large electrochemical gradient, called the endocochlear potential, which is about +80 mV relative to perilymph. The maintenance of such a large electrochemical gradient is performed by the stria vascularis. *(From Geisler CD.* From Sound to Synapse: Physiology of the Mammalian Ear. *New York: Oxford University Press; 1998:85.)*

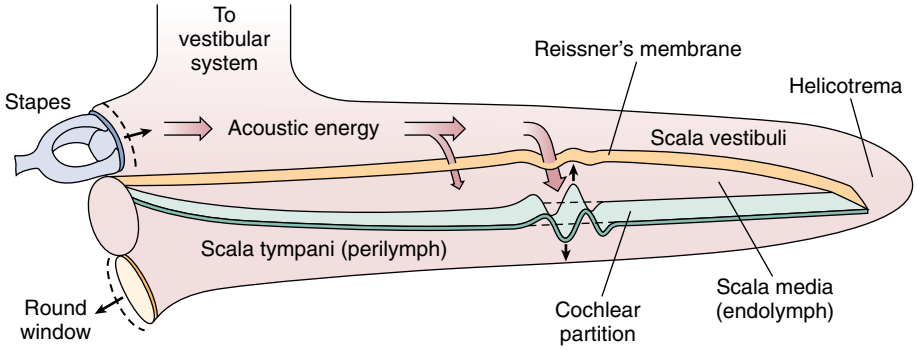

Figure 129-6. Schematic showing sound propagation in the cochlea. As sound energy travels through the external and middle ears, it causes the stapes footplate to vibrate. The vibration of the stapes footplate results in a compressional wave on the inner ear fluid. Because the pressure in the scala vestibuli is higher than the pressure in the scala tympani, this sets up a pressure gradient that causes the cochlear partition to vibrate as a traveling wave. Because the basilar membrane varies in its stiffness and mass along its length, it is able to act as a series of filters, responding to specific sound frequencies at specific locations along its length. *(From Geisler CD.* From Sound to Synapse: Physiology of the Mammalian Ear. *New York: Oxford University Press; 1998:51.)*

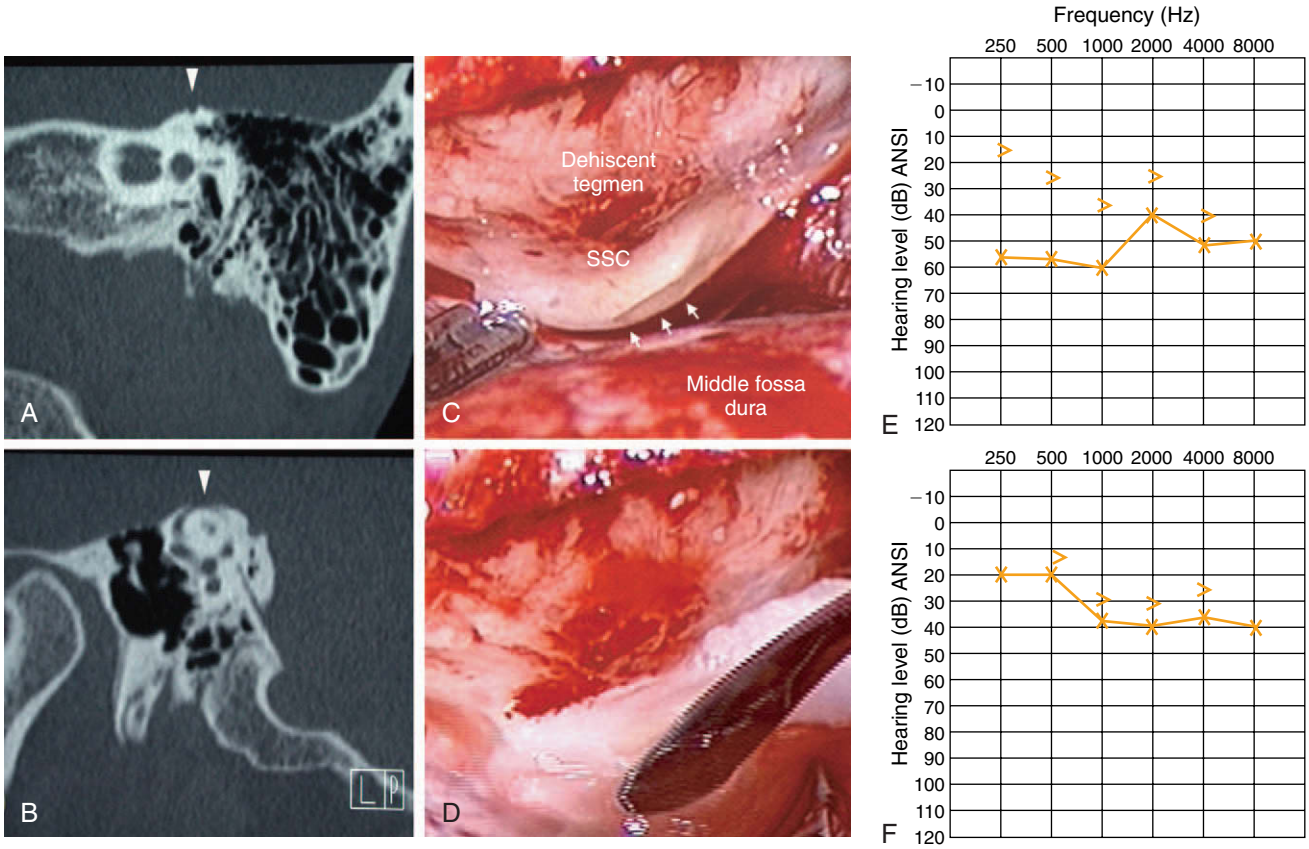

Figure 129-7. Inner ear impedance changes resulting from superior semicircular canal dehiscence (SSCD) are associated with an air-bone gap on audiometric testing. **A-F,** Clinical images from a 28-year-old woman with autophony, hearing loss, and sound-induced and pressure-induced oscillopsia and dizziness. Left-sided SSCD syndrome was diagnosed. **A** and **B,** Temporal bone CT scans reformatted to Stenver (**A,** perpendicular to the superior canal) and Pöschl (**B,** parallel to the superior canal) of the left ear showing a 4-mm SSCD *(arrowheads)*. **C** and **D,** Intraoperative photos of left SSCD during middle fossa craniotomy and dural retraction. Note the exposed membranous labyrinth of the superior canal and surrounding dehiscent tegmen in **C** that correlates with radiologic images in **A** and **B**. **D** shows plugging of left SSCD with bone wax. Temporalis fascia and a split-calvarial bone graft were also used to reconstruct the dehiscent middle fossa floor. **E** (preoperative audiogram) and **F** (post-SSCD plugging audiogram) show closure of air-bone gap associated with SSCD. SSC, superior semicircular canal. *(Modified from Watters KF, Rosowski JJ, Sauter T, Lee DJ. Superior semicircular canal dehiscence presenting as postpartum vertigo.* Otol Neurotol. *2006;27:756-768.)*

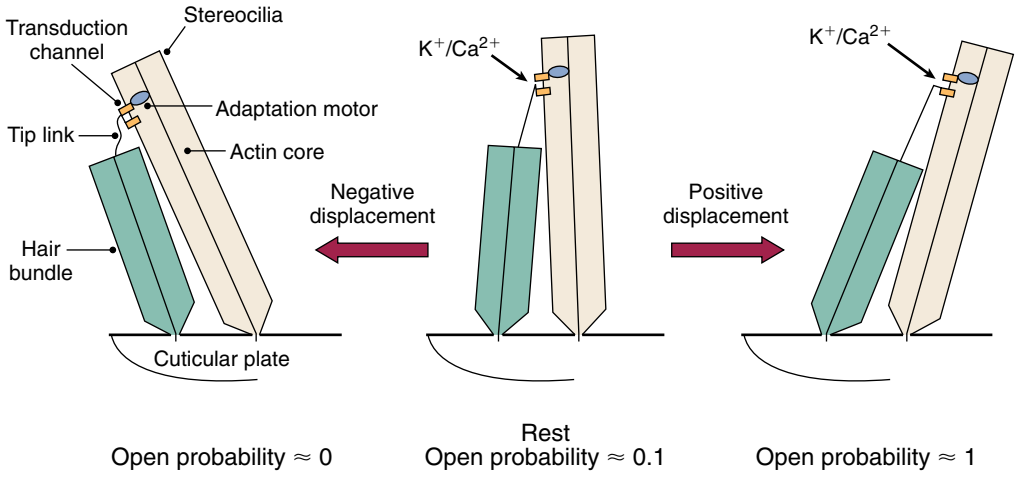

Figure 129-8. Schematic showing the role of tip links in hair cell signal transduction. It is thought that as the stereocilia is deflected toward the direction of the tallest row, it causes the tip links to stretch. The stretch of the tip links causes the opening of stretch-sensitive cationic channels located on the stereocilia. The opening of these stretch-sensitive cationic channels on the stereocilia causes a large influx of cationic current, which leads to hair cell depolarization. As the stereocilia is deflected away from the tallest row, it causes a relaxation of the tip links, which decreases the probability of ion channel opening. This leads to hyperpolarization of the hair cell. *(From Gillespie PG. Molecular machinery of auditory and vestibular transduction.* Curr Opin Neurobiol. *1995;5:449-455.)*

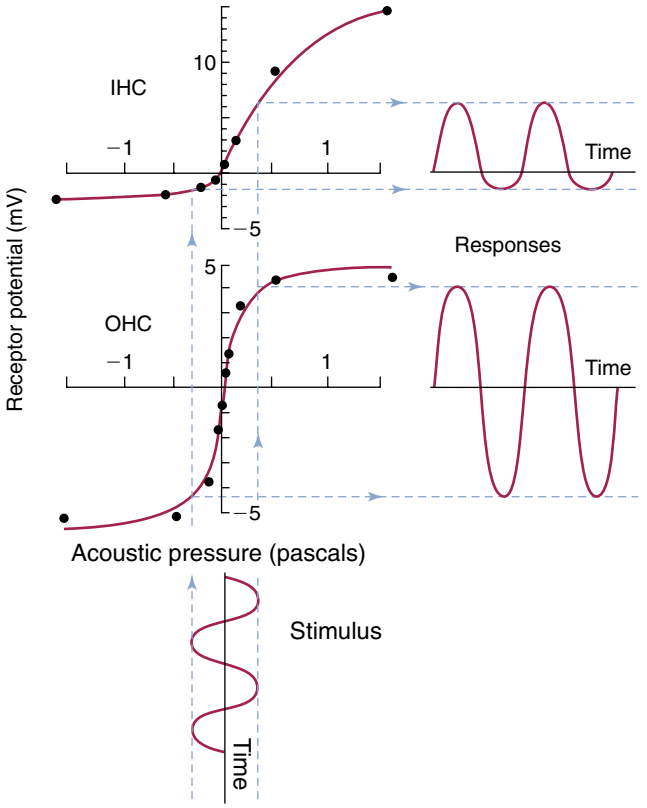

Figure 129-9. Generation of receptor potentials in inner hair cells (IHC, *upper panel*) and outer hair cells (OHC, *lower panel*) in response to a sound stimulus of 84 dB sound pressure level (SPL). The sound stimulus changes the receptor potential according to each hair cell's input-output curve *(left)*. The input-output curves for both types of hair cells are nonlinear. *(From Russell IJ, Cody AR, Richardson GP. The responses of inner and outer hair cells in the basal turn of the guinea-pig cochlea and in the mouse cochlea grown in vitro.* Hear Res. *1986;22:199-216.)*

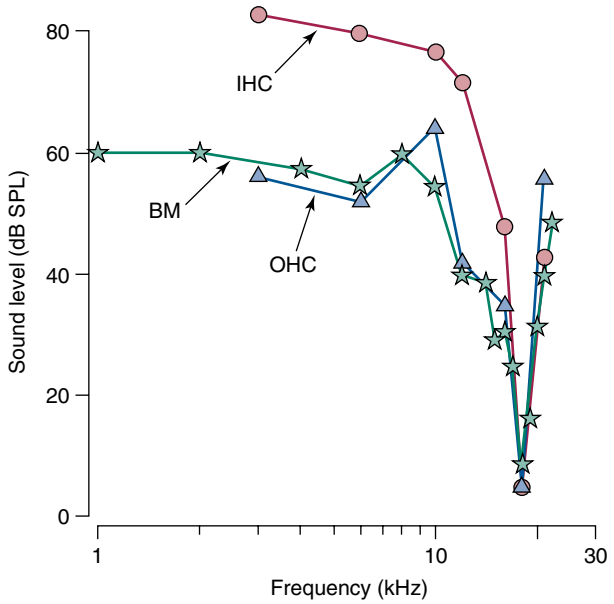

Figure 129-10. Tuning curves of the basilar membrane (BM) and the inner and outer hair cells (IHC and OHC) at a basal location in the guinea pig cochlea. The tuning curve plots the sound level required to produce a fixed level of response at a given location along the cochlear partition. The required sound level is lowest when the sound stimulus is at its characteristic frequency. The tuning curves for the basilar membrane and the inner and outer hair cells at the same location of the cochlear partition are very similar, indicating that the tonotopic arrangement of the basilar membrane is preserved in inner and outer hair cells. SPL, sound pressure level. *(From Russell IJ, Kossl M, Murugasu E. A comparison between tone-evoked voltage responses of hair cells and basilar membrane displacements recorded in the basal turn of the guinea pig cochlea. In: Manley GA, Klump GM, Koppl C, et al, eds.* Advances in Hearing Research. *Singapore: World Scientific; 1995:136-144.)*

In contrast to the inner hair cell, an outer hair cell can also change its length in response to voltage changes; it contracts with depolarization and elongates with hyperpolarization.[36] The molecular motor that is associated with rapid changes in outer hair cell length is a voltage-dependent, integral membrane protein called prestin.[37] The change in outer hair cell length in response to voltage changes is believed to add energy into the basilar membrane motion through a mechanical feedback scheme. In other words, the outer hair cell acts as a cochlear amplifier, augmenting the signals transmitted into the inner ear by the stapes vibration.[38] The importance of prestin in hearing is supported further by the finding that in animal studies in which prestin has been knocked out or altered, the hearing sensitivity and frequency selectivity are impaired.[39,40]

Because different regions of the basilar membrane are tonotopically tuned to specific frequencies, and because the hair cells reside on top of the basilar membrane, it is logical to assume that the hair cells from different regions are also tonotopically tuned to specific frequencies. The frequency tuning curves for outer and inner hair cells have been recorded in guinea pigs in response to various frequencies, and the hair cells in different regions along the basilar membrane are tonotopically tuned to specific frequencies that correspond to the tonotopic arrangement of the basilar membrane (Fig. 129-10).[41] The frequency to which a hair cell is most sensitive is called the *characteristic frequency*. As discussed subsequently, this tonotopic arrangement is essential for the processing of auditory information, and is preserved throughout the entire auditory pathway.

Auditory Nerve

When the mechanical vibration of the cochlear partition is transduced into electrochemical signals by the hair cells, the information carried by these signals is propagated by the afferent auditory nerve fibers into the brain for processing across neuronal stations and pathways. The afferent auditory neurons are bipolar in nature, sending peripheral processes to make contact with hair cells, while sending central projections to the auditory brainstem. Their cell bodies, also known as the spiral ganglion cells, are located in Rosenthal's canal. Humans have approximately 30,000 spiral ganglion cells.[42]

There are two types of spiral ganglion cells. Type I spiral ganglion cells are myelinated, and account for approximately 90% of all spiral ganglion cells. Each one of these type I cells sends a single peripheral process to form a single synapse with a single inner hair cell.[43,44] Type II spiral ganglion cells are unmyelinated, and account for approximately 10% of all spiral ganglion cells. Each one of these type II cells sends a peripheral process to form synapses with multiple outer hair cells. Each inner hair cell forms synapses with multiple type I spiral ganglion cells; each type II spiral ganglion cell forms synapses with multiple outer hair cells.

Through electrophysiologic recordings made in the guinea pig and in the cat, it has been shown that type I spiral ganglion cells can discharge spontaneously.[45,46] The spontaneous activity of these type I cells is believed to be mediated by neurotransmitter release from inner hair cells, and stops if there is a reduction in perilymphatic calcium levels (crucial for neurotransmitter release).[47] When the spontaneous discharge rates of different type I spiral ganglion cells were examined, it was discovered that type I cells have different spontaneous discharge rates (Fig. 129-11). The spontaneous discharge rate can be used to group the type I spiral ganglion cells into three categories: cells with high spontaneous activity (>18 spikes/sec), cells with medium spontaneous activity (0.5 to 18 spikes/sec), and cells with low spontaneous activity (<0.5 spikes/sec).[48]

The difference in spontaneous discharge rate of type I spiral ganglion cells is probably correlated with the diameter of the terminal axon,

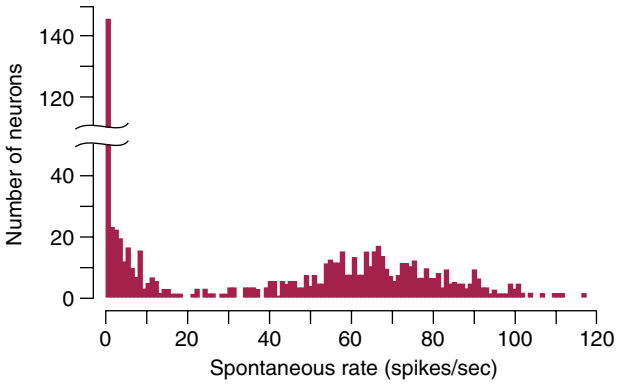

Figure 129-11. Histogram showing the distribution of spontaneous firing rates recorded from many type I afferent neurons in cats. The spontaneous discharge rate can be used to group the type I spiral ganglion cells into three categories: high spontaneous (>18 spikes/sec), medium spontaneous (0.5 to 18 spikes/sec), and low spontaneous (<0.5 spikes/sec). *(From Liberman MC. Auditory-nerve response from cats raised in a low-noise chamber.* J Acoust Soc Am. *1978;63:442-455.)*

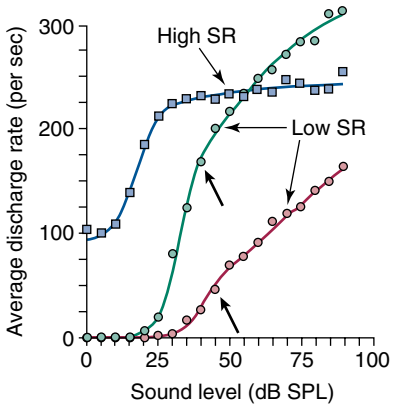

Figure 129-12. Response of three primary auditory neurons to tones of characteristic frequency with varying sound levels in the guinea pig. The single neuron with high spontaneous rate (SR) shows a low threshold and small dynamic range. In contrast, the two low-spontaneous neurons exhibit higher thresholds and larger dynamic ranges. SPL, sound pressure level. *(From Muller M, Robertson D. Shapes of rate-versus-level functions of primary auditory nerve fibres: test of the basilar membrane mechanical hypothesis.* Hear Res. *1991;57:71-78.)*

with high spontaneous neurons having a larger diameter, and low spontaneous neurons having a smaller diameter.[49] As the sound pressure increases over a certain level, the afferent neurons begin to discharge at a higher rate than the spontaneous rate. This sound pressure level is called the threshold. There is generally a monotonic relationship between the discharge rate of the afferent neurons and sound pressure, with neurons discharging at a higher rate as the sound pressure increases.[50] This relationship is a nonlinear one, however, because as the sound pressure increases over a certain level, the discharge rate of the afferent neurons begins to saturate. The difference between the sound pressures at threshold and at saturation is called the dynamic range of the afferent neuron.

It has been shown that the threshold and saturation, and the dynamic range of afferent neurons of various spontaneous rates are different, with the high-spontaneous neurons having lower threshold and saturation sound pressure levels than lower spontaneous neurons (Fig. 129-12). The low-spontaneous neurons also have a larger dynamic range.[51,52] These findings lead to the conclusion that the high-spontaneous neurons are important for detecting low-level sounds (because of their low threshold), whereas low-spontaneous neurons are important for signaling amplitudes at high level sounds (because of their large dynamic range).

The afferent auditory neurons are also tonotopically tuned, similar to the basilar membrane and the hair cells. The tuning curves of the basilar membrane, hair cell, and afferent neuron share many similar attributes. At a given location along the cochlear partition, the basilar membrane, the hair cells, and the afferent neurons all have the same characteristic frequency. As a sound stimulus enters the cochlea, its frequency components are analyzed by the basilar membrane as a series of filters. This frequency information is preserved through the hair cells and the auditory afferent neurons, and is transmitted to the central nervous system.

The threshold sound pressure for auditory neurons can be −10 dB SPL, which is equivalent to 7 μPa.[53] This sound pressure is so low that it produces ossicular chain vibration on the order of $^{1}/_{1000}$ the diameter of a hydrogen atom (approximately 10^{-13} m). The fact that such low sound pressure can be readily detected speaks to the incredible efficiency of the mammalian auditory system.

Auditory Brainstem and Midbrain

Cochlear Nucleus

The auditory nerve travels along the course of the internal auditory canal to terminate on the second-order neurons of the auditory system located in the cochlear nucleus. The cochlear nucleus is the critical first relay station for all ascending auditory information originating in the ear, and is located in the pontomedullary junction of the dorsolateral brainstem in humans (Fig. 129-13). The cochlear nucleus contains many cell types, each having unique somatic and dendritic characteristics.[54,55] These cell types display varying response properties to auditory stimulation[56-60] and project to different targets.[61-63]

The distribution of cell types subdivides the cochlear nucleus into its major subdivisions: the dorsal cochlear nucleus, the anterior ventral cochlear nucleus, and the posterior ventral cochlear nucleus. Each subdivision has a restricted population of cell types. The second-order neurons of the cochlear nucleus are tonotopically organized. The spatial representation of frequency-specific information in the cochlea is preserved in the cochlear nucleus.[64] Isofrequency lamina (sheets of neurons that have the same characteristic frequency) are distributed from dorsal to ventral across each major cochlear nucleus subdivision, and are seen in higher auditory nuclei.[65]

Inputs from auditory nerve drive multiple cell types in different subdivisions of the cochlear nucleus, with each cell type projecting centrally to different targets in the superior olivary complex, lateral lemniscus nuclei, and inferior colliculus. Because individuals with normal hearing use both ears, sound localization is accomplished by neural processing of intensity and timing cues from each ear in the auditory brainstem. The temporal and spectral features of sound originating in the ear are processed in the cochlear nucleus, and the cochlear nucleus is the origin of parallel pathways. These pathways that project to the auditory brainstem, midbrain, and cortex integrate information from the ear to determine (1) the identity of the sound source, (2) the intensity of the sound source, and (3) the location of the sound source.

The ventral cochlear nucleus contains many different cell types: (1) spherical bushy cells found primarily in the anteroventral cochlear nucleus (rostral), (2) globular bushy and multipolar cells found centrally, and (3) octopus cells found posteriorly (caudal). Spherical and globular bushy cells receive large auditory terminals with multiple synaptic specializations (end-bulbs of Held). This extensive contact allows the second-order neurons (bushy cells) to have primary-like responses to action potentials from the auditory nerve, preserving temporal and spectral information that is sent to higher auditory brainstem nuclei, the thalamus and, ultimately, the auditory cortex. End-bulbs of Held are vulnerable to sensory deprivation. Congenital deafness is associated with unambiguous changes to these large synaptic terminals. Specifically, the postsynaptic density is larger and dysmorphic in deaf animals compared with normal-hearing controls,[66,67] and these changes may be reversible with electrical stimulation using a cochlear implant.[68]

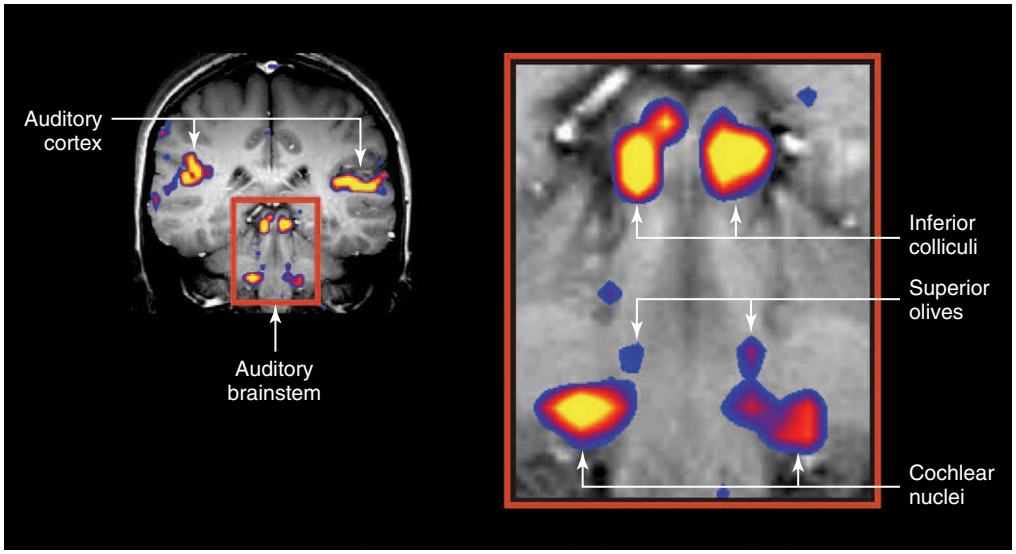

Figure 129-13. Functional magnetic resonance imaging showing the ascending pathways of auditory processing from the auditory brainstem to the auditory cortex. This figure shows activation of the cochlear nuclei (seen as areas of activation in the pontomedullary junction of the dorsolateral brainstem bilaterally), superior olives, inferior colliculi, and auditory cortex during bilateral acoustic stimulation in a normal-hearing adult patient. *(Image courtesy of Jennifer Melcher, PhD, and adapted from Hawley ML, Melcher JR, Fullerton BC. Effects of sound bandwidth on fMRI activation in human auditory brainstem nuclei.* Hear Res. *2005;204:101-110.)*

From the cochlear nucleus, three fiber tracts project auditory information to the contralateral inferior colliculus: the dorsal stria (also called the stria of Monaco), the intermediate stria (also called the stria of Held), and the ventral stria (also known as the trapezoid body). These fiber tracts collectively form the lateral lemniscus. Some fibers from the cochlear nuclei do not cross the midline and project to the ipsilateral inferior colliculus. There are also connections between the cochlear nuclei on both sides, which represent the most peripheral connections between the auditory pathways bilaterally.[69] The function of these connections is not well understood, however.

Superior Olivary Complex

The superior olivary complex is located medial to the cochlear nucleus in the caudal portion of the pons. It contains three main nuclei: the medial superior olive, the lateral superior olive, and the nucleus of the trapezoid body. The superior olivary complex serves as a relay station for auditory information from both ears, and some of the fiber tracts from the cochlear nucleus give off collaterals to the superior olive before forming the lateral lemniscus. Auditory information from both cochlear nuclei is integrated in the superior olivary complex; this region plays an important role in sound localization by analyzing interaural time and amplitude differences. Specifically, the medial superior olive receives inputs from the bushy cells of both cochlear nuclei, and is exquisitely sensitive to interaural time differences. In contrast, the lateral superior olive responds to interaural amplitude differences and receives excitatory inputs from the bushy cells of the ipsilateral cochlear nucleus and inhibitory inputs from the contralateral cochlear nucleus.[70]

The processing of auditory information from both ears by the brainstem nuclei not only allows for sound localization, but it also helps to enhance auditory perception by two additional mechanisms: binaural squelch and summation. *Binaural squelch* refers to the ability of the brainstem auditory nuclei to increase the signal-to-noise ratio of the incoming sound stimulus through information processing.[71] *Summation* refers to the fact that a sound signal received by both ears is greater in amplitude (by 3 dB) than the same signal received by a single ear.[72] This increase in perceptual loudness is thought to improve speech intelligibility in a noisy environment. Binaural squelch, summation, and the head shadow effect (see earlier section on external ear) are three mechanisms in binaural hearing that enhance auditory perception.[73] The superior olivary complex also plays an important role in the efferent pathways of the auditory system, which is discussed later in this chapter.

Lateral Lemniscus

The lateral lemniscus is formed by the three fiber tracts from the cochlear nucleus. It is one of the most prominent fiber tracts in the auditory pathway. On its way to the contralateral inferior colliculus, the lateral lemniscus sends multiple branches to terminate in the superior olivary complex, and to the dorsal and ventral nuclei of the lateral lemniscus.

Inferior Colliculus

The inferior colliculus is located in the midbrain just caudal to the superior colliculus. The inferior colliculus, similar to the cochlear nucleus, processes frequency-specific information along isofrequency lamina in the caudorostral dimension of the central nucleus.[74] The inferior colliculus receives projections directly from the cochlear nucleus and information about interaural time and amplitude differences from the medial superior olive and lateral superior olive. The inferior colliculus also integrates information from auditory and nonauditory sources. Anatomic and physiologic studies show that the inferior colliculus receives auditory inputs from the lateral lemniscus, the cochlear nucleus, and the superior olivary complex,[74,75] and projections from the somatosensory system,[76] and the visual and vestibular systems.[77] The inferior colliculus processes the information it receives and sends fibers to the medial geniculate body of the thalamus. The number of fibers from the inferior colliculus to the medial geniculate body is about 250,000, which is almost 10 times as many as the number of auditory nerves.[78] This increase in the number of nerve fibers at the level of the inferior colliculus indicates the substantial amount of signal processing that occurs in the central auditory system.

Thalamus and Auditory Cortex

Medial Geniculate Body

The medial geniculate body is the thalamic auditory relay center that receives auditory information from the inferior colliculus. It has three divisions: ventral, dorsal, and medial.[79] The ventral division of the medial geniculate body projects to the primary auditory cortex, and the dorsal division of the medial geniculate body projects to the auditory association cortex. The auditory processing performed by the medial geniculate body is greatly influenced, however, by an abundance of inputs from the auditory cortex that are believed to outnumber the projections it receives from the midbrain and lower auditory brainstem.[70] The medial geniculate body is thought to play an important

role in sound localization and processing of complex vocal communications, such as human speech.

Auditory Cortex

The main auditory portion of the cerebral cortex resides in the temporal lobe, close to the sylvian fissure. In this region, the two major centers for auditory processing are the primary auditory cortex and the association auditory cortex. The primary auditory cortex is located on the superior surface of the temporal lobe (Heschl's gyrus). This is also known as area A1, and corresponds to Brodmann's area 41. The auditory association cortex is also known as area A2, and corresponds to Brodmann's areas 22 and 42. It has been shown that the primary auditory cortex is tonotopically tuned, with high frequencies being represented more medially, and low frequencies being represented more laterally.[80] The primary auditory cortex is involved with integrating and processing complex auditory signals, including language comprehension. The auditory association cortex is located lateral to the primary auditory cortex, and it is part of a language reception area known as Wernicke's area. Functional imaging studies have shown that the auditory association cortex plays an important role in speech perception.[81,82] In addition, consonant perception deficits have been found in otherwise normal subjects when direct electrical interference is applied to the auditory association cortex,[83] further supporting the integral role that auditory association cortex plays in speech perception.

In addition to the primary auditory cortex and the auditory association cortex, auditory information from the subcortical structures also projects to other parts of the brain, such as the amygdala, which is a part of the limbic system.[84] This projection can help to explain why sounds such as music can evoke strong emotional responses.

Efferent Auditory System

The auditory brainstem not only projects to higher centers of auditory processing, but also provides efferent input to the ear via two major descending systems: (1) the middle ear muscle reflex pathways, and (2) the olivocochlear reflex pathways.

Middle Ear Muscle Reflex Pathways

The middle ear muscle reflex is another major feedback system to the auditory periphery. The pathways for the stapedius reflex to one side (ipsilateral side) are shown in Figure 129-14. The stapedius and tensor tympani muscles are the target organs of the middle ear muscle reflex, and are innervated by the efferent fibers originating in the motoneurons around and near the facial and trigeminal nerve nuclei. Activation of this neural pathway results in contraction of the middle ear muscles in response to specific sound stimuli. Contraction of the stapedius and tensor tympani muscles exerts forces perpendicular to the stapes and malleus to increase the impedance of the ossicular chain.[85]

The detailed pathway of the stapedial reflex arc is shown in Figure 129-14. Acoustic stimuli presented to either ear activate stapedius muscle contraction in both ears, similar to the consensual pupillary response to light. The reflex begins as afferent auditory input from the cochlea. The signal is transmitted along the auditory nerve to the cochlear nuclei. Interneurons that have not yet been identified (but may be located in the ventral cochlear nucleus)[86] project either directly or indirectly from the cochlear nuclei to the stapedius motoneurons (see Fig. 129-14). These central pathways are not completely understood at this point. Stapedius motoneurons project to the middle ear by way of the facial nerve to innervate the stapedius muscle (stapedial nerve). The stapedius muscle is attached to the posterior neck of the stapes capitulum; contraction stiffens the stapes suprastructure and increases middle ear impedance.

Acoustic impedance measurements have proven that the stapedius is the primary sound-evoked middle ear muscle.[87-89] In contrast to some animal models, in which the stapedius and tensor tympani contract in response to sound, the stapedius reflex is the dominant sound-evoked pathway in humans.[89,90] Two major functions of the stapedius reflexes have been proposed: (1) modulation of the middle ear impedance and attenuation of acoustic energy reaching the cochlea,[91-93] and (2) high-pass filtering of low-frequency sound (background noise) to prevent masking of speech frequencies. The function of the middle ear muscle reflex pathway seems to be protective; contraction of the middle ear muscles results in frequency-dependent sound attenuation in the presence of intense acoustic stimuli. This effect is more pronounced for low sound frequencies.[94,95] This frequency-specific attenuation of the middle ear muscle reflex supports the hypothesis that this reflex pathway preserves speech frequency information from masking by intense background noise, which is typically lower in frequency.[96-100] The stapedius muscle also contracts in response to internally or self-generated vocalization,[98] and may serve to prevent self-stimulation.

Electromyography of tensor tympani muscles has shown minimal electrical activity in response to sound presentation.[101-103] Patients who have a paralyzed stapedius muscle from facial palsy or a severed stapedius tendon from stapes surgery (and intact tensor tympani function) have absent middle ear muscle reflexes,[104] supporting previous observations that the tensor tympani plays a minor role in the middle ear muscle reflex pathway to loud sounds in humans. Measurable activity of the tensor tympani muscle seems to be associated with stimuli that cause a startle reaction.[94,100,105,106] Cortical input in addition to the auditory reflex pathway may help to modulate responses of both middle ear muscles.

The tensor tympani is a slender, feather-shaped muscle that is approximately 25 mm in length, lying in a bony canal above the eustachian tube.[88] It consists of short striated muscle cells that are arranged in parallel fibers. This arrangement permits considerable tension with minimal displacement.[88] The muscle arises from the cartilaginous portion of the eustachian tube and travels perpendicularly to insert at the neck of the manubrium of the malleus. Muscular contractions pull the malleus in an inward direction, stiffening the tympanic membrane and ossicles, and increasing the acoustic impedance.[88]

The tensor tympani is separated from the eustachian tube by a bony partition. The precise reason for this partition is unclear. von Bekesy[12] suggested that the partition prevented muscular vibrations from interfering with sound perception and acting as a mode of insulation. More than a third of the tensor tympani tendon contains elastic tissue, which dampens the ossicles during excessive stimulation and renders the muscular tractions more controlled.[88] Abundant amounts of fat are also found in the tensor tympani of humans, but the physiologic significance of this is uncertain.[88]

There is a dense concentration of motor and proprioceptive nerve fibers in the muscle that is innervated by the mandibular branch of the fifth cranial nerve. This nerve travels to the tensor tympani via the otic ganglion.[107,108] Motor fibers form an extensive and rich network on the muscle. These are thinner than other skeletal muscle nerves, but with shorter axons, still ensuring rapid conduction velocities.[107] Sensory input from the tensor tympani and the surrounding connective tissue is minimal. This is in contrast to extraocular or masticatory muscles,[109] which have rich afferent supplies. The postsynaptic regions are smaller compared with stapedial fibers, and have less mitochondrial activity in the motor end plates.[109]

The tensor tympani seems to respond to loud sound stimuli[104] and nonauditory inputs.[110] The middle ear muscles are anatomic antagonists but work synergistically to stiffen the ossicular chain, whereas the stapedius stiffens the stapes at the oval window of the cochlea, the tensor tympani exerts forces on the manubrium of the malleus, resulting in an inward deflection and stiffening of the tympanic membrane. The tensor tympani may play a protective role against loud acoustic stimuli and prevent overstimulation from self-generated vocalization or swallowing.[104,110] The multiple circuits that mediate these auditory and nonauditory functions are not fully understood, although we do know that activation of the tensor tympani reflex requires tensor tympani motoneurons, the common efferent limb of this circuit diagram.[111-113] The interneurons in the brainstem that project to tensor tympani motoneurons have not been identified, however, and the nonauditory sources that provide input to tensor tympani motoneurons are unknown.

The function of the tensor tympani muscle in humans is far from being understood. Several theories have been proposed to explain the auditory and nonauditory roles of the tensor tympani. Continued research of tensor tympani physiology is needed to help us understand this elusive muscle in greater detail.

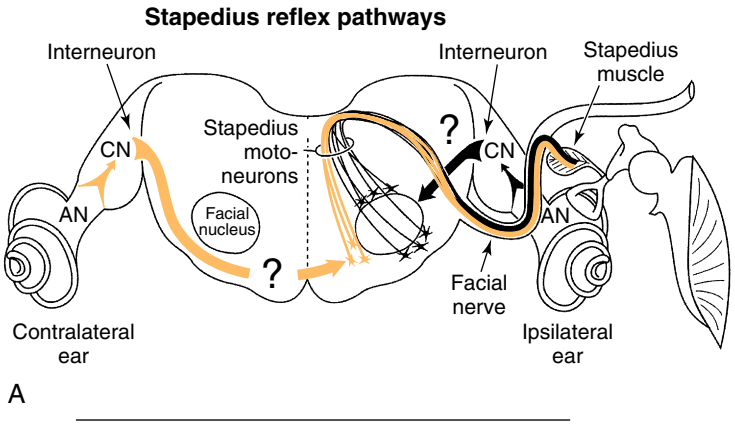

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Figure 129-14. Auditory efferent pathways. **A,** Stapedial reflex pathways. Only the pathways that activate contraction of the stapedius muscle in the ipsilateral ear are shown. Intense, low-frequency sound (or broadband noise) presented to the ipsilateral *(black pathways)* or contralateral *(gold pathways)* or both ears can trigger contraction of the ipsilateral stapedius muscle. After transduction of the auditory signal by the hair cells of the cochlea, the action potential is propagated along the auditory nerve (AN), and activates unidentified interneurons located in the ventral cochlear nucleus (CN).[86] Interneurons, either directly or indirectly, project from the cochlear nuclei to the stapedius motoneurons (*black* and *gold arrows*). Interneurons from the ipsilateral or contralateral CN synapse on stapedius motoneurons (*black* and *gold* terminals shown above). Efferent motor projections originating in stapedius motoneurons terminate on the stapedius muscle. The afferent inputs from the cochlea and efferent projections from the motoneurons to the middle ear muscles have been well characterized. The circuitry of the middle ear muscle reflex interneurons is not completely understood. **B,** Medial olivocochlear (MOC) reflex pathways that begin as sound in the ear and terminate on outer hair cells of the cochlea. Only the MOC pathways to one ear, the ipsilateral cochlea, are shown. Sound activates the outer and inner hair cells of the organ of Corti, giving rise to projections to the CN. These projections synapse on interneurons of the MOC pathways. These interneurons are believed to be multipolar cells found in the posteroventral cochlear nucleus.[130] These MOC reflex interneurons in the CN project across the midline to terminate on contralateral MOC neurons *(thick black arrow)*. These MOC neurons project axons back to the outer hair cells of the ipsilateral ear *(thin black lines)*. The MOC reflex pathway is also activated by contralateral sound to the ear *(gold pathways)*, giving rise to projections that cross the midline to innervate Contra MOC neurons *(gold stars)*. These MOC neurons project to the outer hair cells of the ipsilateral ear. *(**A** modified from Lee DJ, de Venecia RK, Guinan JJ Jr, Brown MC. Central auditory pathways mediating the rat middle ear muscle reflexes.* Anat Rec A Discov Mol Cell Evol Biol. *2006;288:358-369. **B** modified from Brown MC, de Venecia RK, Guinan JJ Jr. Responses of medial olivocochlear neurons: specifying the central pathways of the medial olivocochlear reflex.* Exp Brain Res. *2003;153:491-498.)*

Olivocochlear Reflex Pathways

There are two olivocochlear efferent pathways: medial and lateral olivocochlear pathways. The medial olivocochlear (MOC) fibers originate from the medial portion of the superior olivary complex, and travel along the vestibular nerve to the cochlea to innervate the outer hair cells. The lateral olivocochlear (LOC) fibers originate from the lateral portion of the superior olivary complex, and travel along the vestibular nerve to the cochlea to innervate the auditory nerves under the inner hair cells.[114] The MOC fibers are large and myelinated, whereas the LOC fibers are thin and unmyelinated.[115] The MOC pathway is much better understood than the LOC pathway because it is much easier to make electrophysiologic recordings on myelinated fibers.

The MOC and LOC neurons receive auditory inputs from the cochlear nucleus. MOC neurons are more sensitive to low-frequency sound information; LOC neurons are more responsive to higher frequency information. The ipsilateral MOC reflex is shown in Figure 129-14 and involves the following pathways: (1) sound activates the afferent auditory fibers, which innervate the interneurons in the ipsilateral posteroventral cochlear nucleus; (2) the interneurons of the cochlear nucleus innervate the contralateral MOC neurons; and (3) the contralateral MOC neurons send fibers to the ipsilateral cochlea, completing the pathway.[116] Electrophysiologic recordings from MOC neurons reveal that these neurons are sharply tuned and are tonotopically arranged, similar to the basilar membrane and the auditory nerves.[117,118] The tonotopic tuning of the MOC neurons continues back to the cochlea, with the MOC neurons innervating the region of the cochlea with similar characteristic frequency.[117-119]

The main function of the MOC pathway is to reduce cochlear responses by decreasing the gain of the cochlear amplifier. The MOC neurons achieve this by triggering hyperpolarization of the outer hair cells through an acetylcholine-mediated pathway.[120,121] The decreased cochlear amplifier gain in the presence of MOC stimulation is evi-

denced by the elevated threshold required for auditory nerve activation (level shift), and the blunting of the tuning curve at the characteristic frequency.[122,123] In the presence of background noise, the MOC pathway can increase auditory responses to transient sounds.[124-126] It is thought that the MOC pathway decreases the auditory responses to background noise, and more neurotransmitters are preserved for use in response to transient sounds. This effect is called MOC "unmasking."

The functions of the olivocochlear efferent pathways, especially the MOC pathway, are (1) to protect the ears from acoustic trauma, and (2) to discriminate transient sounds from background noise. Numerous studies support the notion that MOC pathway provides protection from acoustic trauma. In a study by Maison and Liberman,[127] the MOC systems in different animals were studied using otoacoustic emissions to classify them as weak, average, and strong. The animals were subjected to acoustic trauma. Animals with weak MOC systems were found to sustain the most damage in their hearing, whereas animals with strong MOC systems sustained the least damage. There have also been animal studies that support the important role the MOC pathway plays in discriminating transient sounds from background noise. It has been found that cats with cut olivocochlear fibers perform poorly on tasks involving formant discrimination or intensity discrimination of high-frequency tones in noise.[128,129] The role of the LOC pathway remains unclear at this time.

Conclusion

The normal auditory system provides humans with exquisitely sensitive binaural hearing for sound perception and speech understanding; it is able to decipher complicated acoustic signals with enormous dynamic and frequency ranges and process them in a way that is understandable to us. As the acoustic signal enters the ear, it is first transformed into a mechanical signal by the middle ear, which plays a crucial role in impedance matching. This mechanical signal is transmitted to the inner ear, where its frequency components are analyzed by the basilar membrane. The signal, which is embedded in the traveling wave of the basilar membrane, is transformed again into electrochemical form by the hair cells. This signal is propagated by the afferent auditory neurons as action potentials to auditory brainstem, midbrain, thalamus, and auditory cortex for further processing. In addition to the afferent pathway, the auditory system has two major efferent pathways that prevent acoustic overstimulation and enhance speech discrimination in background noise.

Although a clearer picture of the mechanics of the human auditory system is starting to emerge, many unanswered questions still remain. Continued research on the anatomy and physiology of the peripheral and central auditory systems using animal models and clinical research will help to clarify the exquisite mechanisms of hearing in humans.

Acknowledgment

We thank John J. Rosowski, PhD, Professor, Department of Otology and Laryngology, Harvard Medical School, for his comments on previous versions of this chapter.

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CHAPTER ONE HUNDRED AND THIRTY

Anatomy of the Vestibular System

Anna Lysakowski

Key Points

- The labyrinth develops from the otic placode, which invaginates to become the otic pit, and then pinches off to form the otic cyst or otic vesicle.
- The vertical canals are oriented at 45 degrees with regard to the sagittal plane, and the horizontal canal is tilted upward anteriorly about 30 degrees from the horizontal plane.
- Scarpa's ganglion has two parts, the superior ganglion and the inferior ganglion. The former gives rise to nerves supplying the superior (anterior) and horizontal crista and the utricular macula; the latter supplies the posterior crista and the saccular macula.
- The blood supply to the vestibular labyrinth is the labyrinthine artery, which has two branches: anterior vestibular artery, supplying the superior and horizontal ampullae and the utriculus, and common cochlear artery, which divides into the proper cochlear artery and the vestibulocochlear artery. The latter splits into a cochlear branch and the posterior vestibular artery, which supplies the posterior ampulla and the sacculus.
- Hair cells are embedded in a matrix of supporting cells, and form tight junctions with the supporting cells, dividing the labyrinth into endolymphatic and perilymphatic compartments.
- Hair cells have a staircase arrangement of actin-filled stereocilia, anchored in a cuticular plate, on their apical surface with a single kinocilium that defines the morphologic polarization for the hair cell.
- Hair cells make synaptic contacts with their afferents by means of ribbon synapses. Vestibular afferents are of three types: calyx afferents, which enclose one or more type I hair cells; bouton afferents, which contact type II hair cells; and dimorphic afferents, which receive synaptic contacts from both types of hair cells. Efferents contact afferents and type II hair cells.
- Calyx afferents are found in the central (striolar) region of the crista (macula). Bouton afferents are found in the peripheral (extrastriolar) region of the crista (macula). Dimorphic afferents are found throughout the sensory epithelium.
- Vestibular afferents give rise to two branches in the vestibular nuclei: rostral branch projecting to the superior and medial vestibular nuclei, and the cerebellum, and caudal branch projecting to the inferior and medial vestibular nuclei, and to the ventrolateral part of the lateral vestibular nucleus.
- The vestibular nuclei are divided into four main subdivisions—superior, medial, lateral, and inferior vestibular nuclei—and several minor cell groups.
- The superior and medial vestibular nuclei project to the oculomotor complex and are involved in the vestibuloocular reflex. The medial vestibular nucleus also gives rise to the medial vestibulospinal tract, which projects to oculomotor and neck muscles, for the vestibulocollic or cervicovestibuloocular reflexes.
- The lateral vestibular nucleus contains giant Deiters' cells that give rise to axons in the somatotopically organized lateral vestibulospinal tract, which projects to ventral horn cells in the cervical and lumbar spinal cord.

The vestibular system is the system of balance and equilibrium. It consists of five distinct sensory organs: three semicircular canals, which are sensitive to angular accelerations (head rotations), and two otoliths, which are sensitive to linear accelerations (e.g., motion in a vehicle or an elevator). This chapter describes the anatomic basis for these functions.

The *semicircular canals* are arranged as a set of three orthogonal sensors (Fig. 130-1)—that is, each canal is at approximately right angles to the other two. Each canal is maximally sensitive to rotations that lie in the plane of that canal. The result of this arrangement is that the three canals can uniquely specify the direction and amplitude of any arbitrary head rotation. Each of the canals acts as an integrating accelerometer; the necessary stimulus for the canal is an angular acceleration, but the information that is encoded by the firing of the afferent nerve fiber is more closely related to angular velocity. Finally, the canals are organized into functional pairs wherein both members of the pair lie in the same plane. Any rotation in that plane is excitatory to one of the members of the pair and inhibitory to the other. Although in the horizontal system the two horizontal canals form a functional pair, the situation is more complex in the vertical system. Here, the anterior canal on one side is parallel and coplanar with the posterior canal on the opposite side; for example,

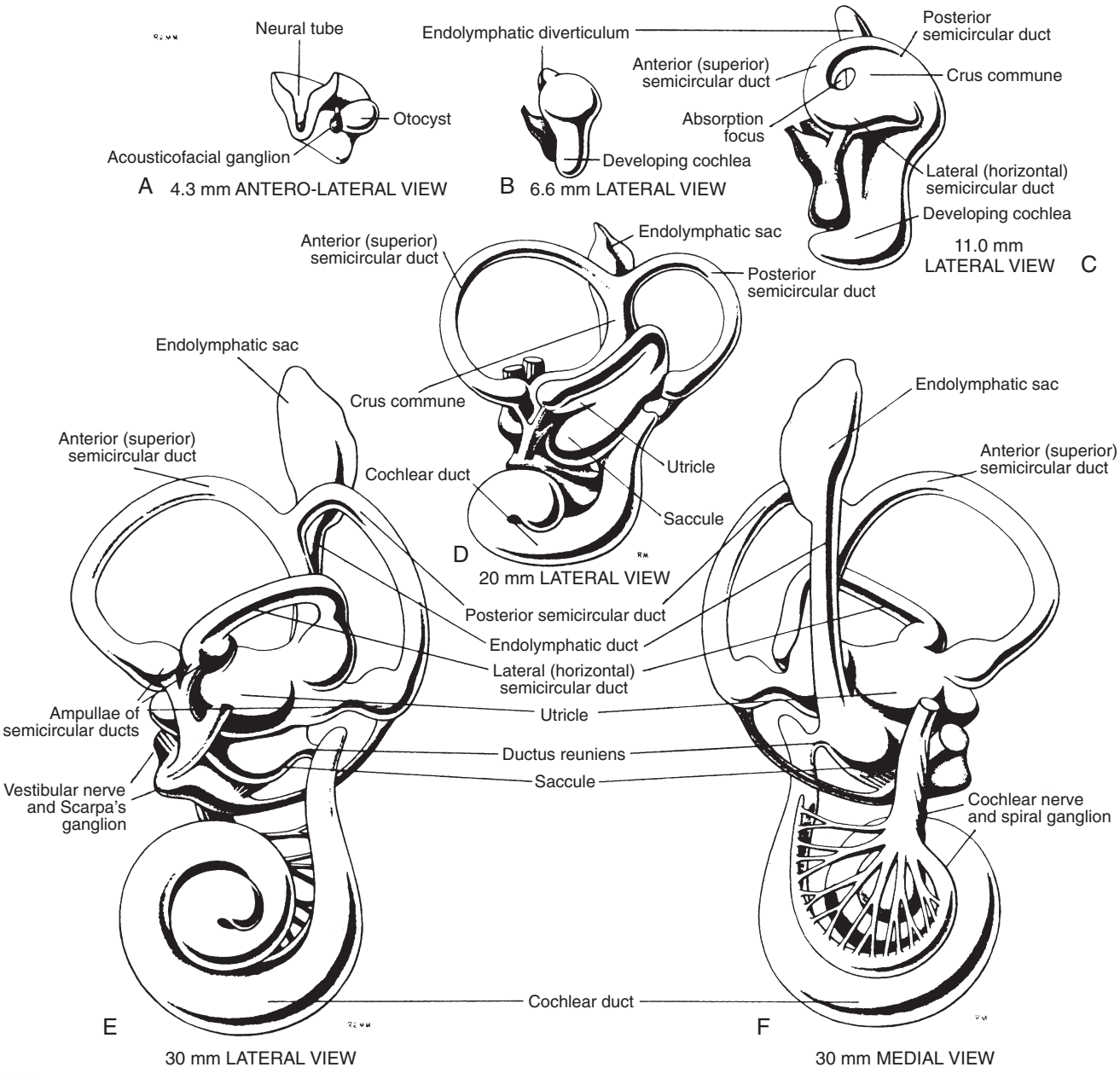

Figure 130-1. Development of vestibular apparatus in humans. **A,** Embryo of 4.3 mm (approximately 23 days old). **B,** Embryo of 6.6 mm (approximately 30 days old). **C,** Embryo of 11 mm (approximately 41 days old). **D,** Embryo of 20 mm (approximately 50 days old). **E** and **F,** Embryo of 30 mm (approximately 56 days old). See text for details. *(Modified from Williams PL, Warwick R.* Gray's Anatomy. *36th ed. Philadelphia: Saunders; 1980.)*

the right anterior canal and the left posterior canal form a functional pair.

Because the primary vestibular afferent fibers exhibit a substantial resting firing rate (60 to 80 spikes per second in mammals), each canal is able to report rotations in either its excitatory direction (by increasing its firing rate) or its inhibitory direction (by decreasing its firing rate). This observation explains why it is possible to function reasonably well after the loss of one labyrinth.

The vestibular system forms the basis for many fundamental reflexes: the vestibulocollic reflex (head stabilization), vestibulospinal reflex (control of upright posture) and vestibuloocular reflex (retinal image stabilization). The last of these, the vestibuloocular reflex, has been studied far more extensively than the others and is the best understood; this reflex forms the basis for most clinical testing (e.g., calorics, rotation tests). See also Chapters 163 and 164 for clinical applications.

This chapter describes the anatomy of the vestibuloocular reflex in some detail, but without exploring every possible aspect. Many of the details that are described have been obtained from experiments in animal species, principally the cat and monkey. Nevertheless, the information is applicable to humans because the vestibular system has changed little during the evolution of vertebrates.

Embryology of the Vestibular Apparatus

The development of the inner ear is a complex process that starts at the beginning of the 4th week and is completed at about 25 weeks of gestational age. By that time, the vestibular apparatus has achieved adult form and size. A brief description of this process of development in human embryos follows. Further details can be found by consulting more detailed references.[1-3] An excellent description of the molecular aspects of development can be found in Post,[4] and a review by Kelley[5] discusses these molecules in relation to potential hair cell regeneration (see also Chapters 1 and 2).

When the human embryo reaches the seven-somite stage (about 22 days), surface ectoderm overlying the future site of the inner ear (at

about the level of the first occipital somite) thickens to form the *otic placode*. The otic placode invaginates into the mesenchyme, forming an otic pit. At about 30 days, the otic pit becomes pinched off, forming the *otic vesicle* or *otocyst* (see Fig. 130-1). Concurrently at about 4 weeks, a portion of the neural crest migrates to the vicinity of the otic vesicle and becomes the acousticofacial ganglion. The geniculate ganglion soon migrates away from this cluster of neurons, leaving the vestibulocochlear ganglion in close proximity to the otic vesicle.

Within 1 or 2 days after formation of the otic vesicle, its more medial portion, the *endolymphatic diverticulum,* becomes distinguishable from the lateral *utriculosaccular chamber*. This chamber differentiates by a constriction of its middle into (1) a utricular chamber that gives rise to the *utriculus* and the *semicircular ducts,* and (2) a saccular chamber that gives rise to the *sacculus* and the *cochlea*. The utricular chamber differentiates first by a rapid expansion into three diverticula. At about 35 days, the centers of these diverticula fuse together and break down, leaving spaces around the perimeter that become the three semicircular ducts. The superior semicircular duct forms first, at about 6 weeks, with the posterior and lateral ducts forming soon afterward in that order. Dilations of one end of each of the semicircular ducts become the ampullae. The ampullar ends and the opposite ends of the ducts remain connected to the utriculus.

The saccular chamber differentiates by expansion and coiling of the cochlear duct. This duct becomes separated from the sacculus by a narrowing of the duct at its dorsal end to form the *ductus reuniens*. While morphogenesis proceeds within the otocyst, histogenesis of the sensory epithelium is also occurring. The arrival of afferent endings in the epithelium precedes hair cell differentiation.[6,7] In the 3rd week, a common macula, or specialized neuroepithelium, appears. Its upper part becomes the utricular macula and crista ampullaris of the superior and lateral semicircular ducts, and its lower part becomes the saccular macula and crista ampullaris of the posterior semicircular duct. At 9 weeks, the hair cells in the vestibular end organs are well differentiated, and they exhibit typical synapses with nerve endings. The maculae reach adult form at about 14 to 16 weeks; the cristae, at about 23 weeks; and the organ of Corti, at about 25 weeks. The mesoderm surrounding the membranous labyrinth becomes the bony otic capsule, or *bony labyrinth*. The *membranous labyrinth* is suspended in fluid (perilymph) within the bony labyrinth by a loose connective tissue termed *periotic tissue*.

Overall Organization of Labyrinth: Relationship to Skull and Cochlea

The vestibular apparatus is enclosed within a bony labyrinth, the vestibule, in the petrous portion of the temporal bone. The vestibular end organs include three semicircular canals, each oriented in a different plane, and two maculae, one roughly in the horizontal plane (the utriculus) and one in the vertical plane (the sacculus). There are two vertical semicircular canals, the anterior (also known as the superior) and posterior canals, and one horizontal (also known as the lateral) canal. The vertical canals are oriented roughly at 45 degrees in relation to the sagittal plane, and the horizontal canal is tilted upward about 30 degrees anteriorly from the horizontal plane (Fig. 130-2). The five vestibular end organs, along with the cochlea, are contained within an endolymph-filled membranous labyrinth (the endolymphatic space), which is itself contained in the perilymph-filled bony labyrinth (the perilymphatic space) (Fig. 130-3).

The vestibule is situated between the internal auditory meatus anteromedially and the middle ear cavity laterally (Fig. 130-4). The entrance to the mastoid antrum (the *aditus ad antrum*) is just lateral to the horizontal semicircular canal. The cochlea sits anterior to the vestibule and is connected to the vestibule by the narrow ductus reuniens (Fig. 130-5; see Fig. 130-3). Posterior and lateral to the vestibule are the mastoid air cells. Directly medial is the posterior cranial fossa, into which the endolymphatic duct and sac extend beneath the dura.

The seventh (facial and intermediate) and eighth (vestibulocochlear) cranial nerves emerge from the brainstem laterally at the cerebellopontine angle. They enter the vestibule and cochlea from the internal auditory meatus (see Fig. 130-4), located medial to a point midway between the cochlea and vestibule. The facial nerve lies anterior and dorsal to the vestibulocochlear nerve. The two nerves separate just inside the meatus, and the facial and intermediate nerves continue laterally in their own canal, past the vestibule. When past the vestibule, the facial nerve makes a 90-degree turn inferiorly to exit the temporal bone through the *stylomastoid foramen*. The vestibulocochlear nerve splits into a vestibular division, which turns posteriorly to supply the vestibule, and a cochlear division, which turns anteriorly to supply the cochlea.

The vestibular (Scarpa's) ganglion sits at the bottom of the internal auditory meatus. It has two parts, the superior vestibular ganglion and the inferior vestibular ganglion (see Fig. 130-5). Large ganglion cells in the superior and inferior ganglia provide afferent innervation to the central regions of the cristae and maculae, and small ganglion cells innervate the peripheral regions of these end organs (the regional specialization within the end organs is discussed in more detail subsequently). A nerve branch is associated with each ganglion. The superior (or anterior) vestibular nerve supplies the anterior and horizontal cristae and the utricular macula. The inferior (or posterior) vestibular nerve supplies the posterior canal and saccular macula. There are also a few small branches that anastomose between the larger divisions of CN VIII. One such small branch is Voit's anastomosis, which runs from

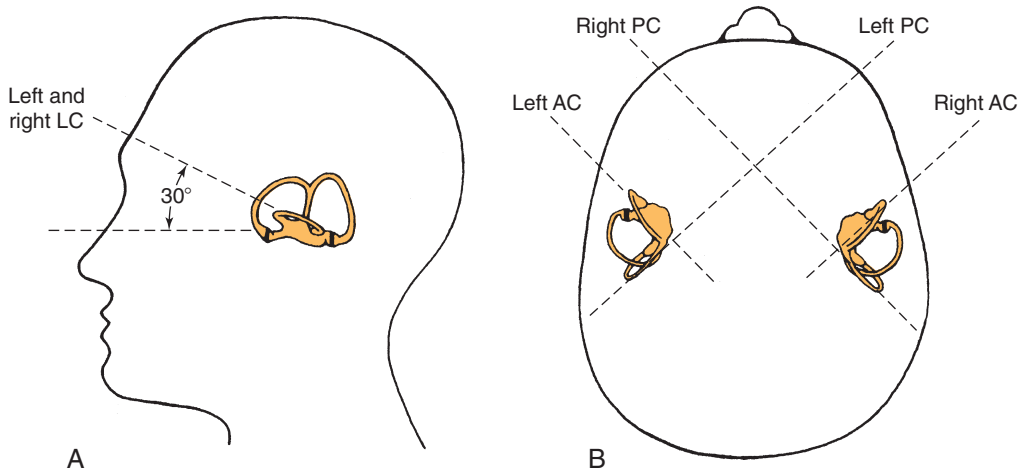

Figure 130-2. Orientation of semicircular canals in head. **A,** Horizontal canal is tilted 30 degrees upward from horizontal plane at its anterior end. LC, lateral canal. **B,** Vertical canals are oriented at roughly 45 degrees from midsagittal plane. AC, anterior canal; PC, posterior canal. *(From Barber HO, Stockwell CW.* Manual of Electronystagmography. *St. Louis: Mosby-Year Book; 1976.)*

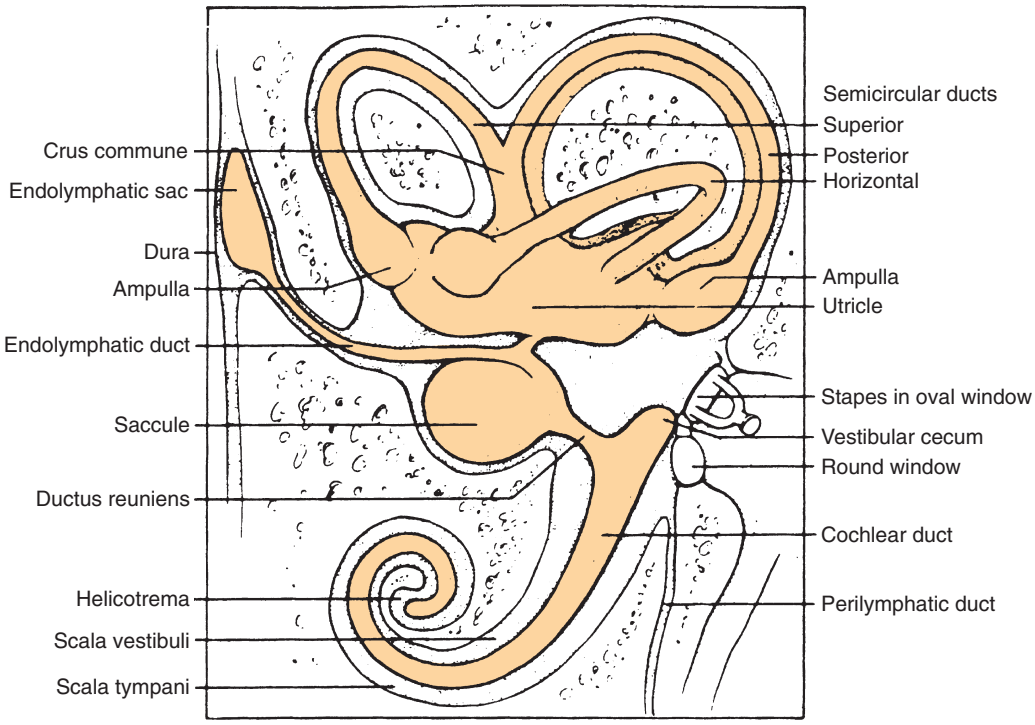

Figure 130-3. Membranous labyrinth situated within bony labyrinth. Note crus commune, a duct shared by superior (anterior) and posterior ducts. Note also endolymphatic duct originating as fusion of utricular duct and saccular duct, and ductus reuniens connecting vestibular apparatus with cochlear duct (uncoiled in this diagram). *(Modified from Kandel ER, Schwartz JW.* Principles of Neural Science. *2nd ed. New York: Elsevier Science; 1985.)*

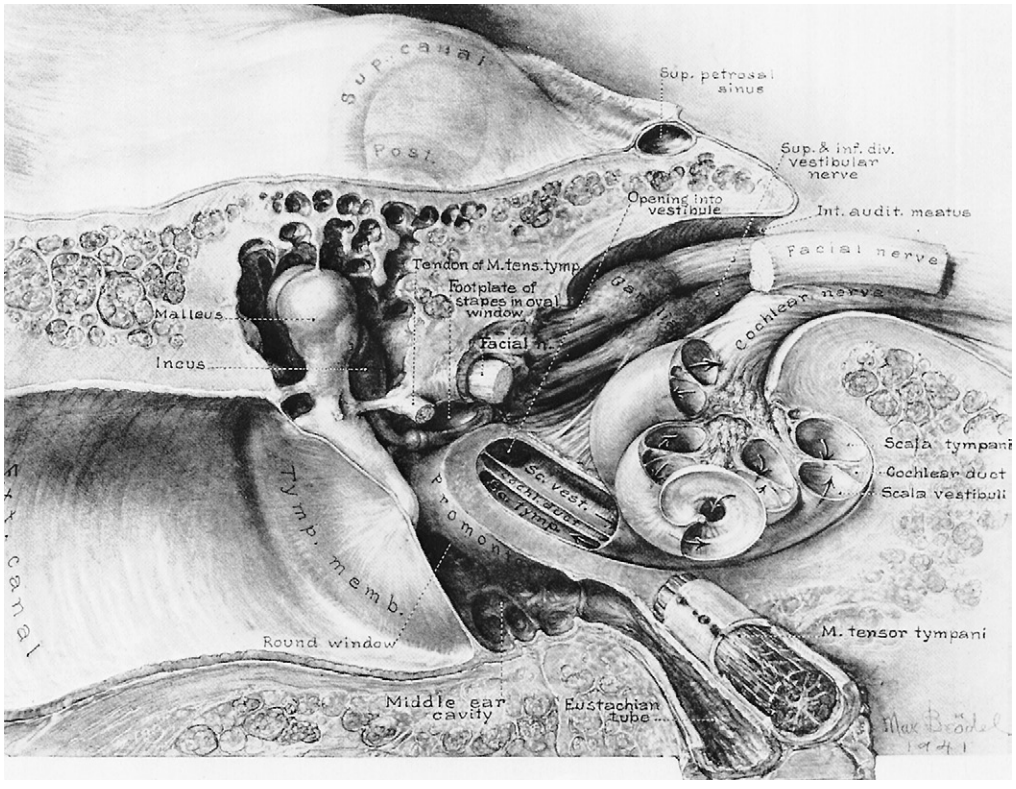

Figure 130-4. Course of vestibulocochlear nerve within the auditory meatus. *(From Brodel M.* Three Unpublished Drawings of the Anatomy of the Human Ear. *Philadelphia: Saunders; 1946.)*

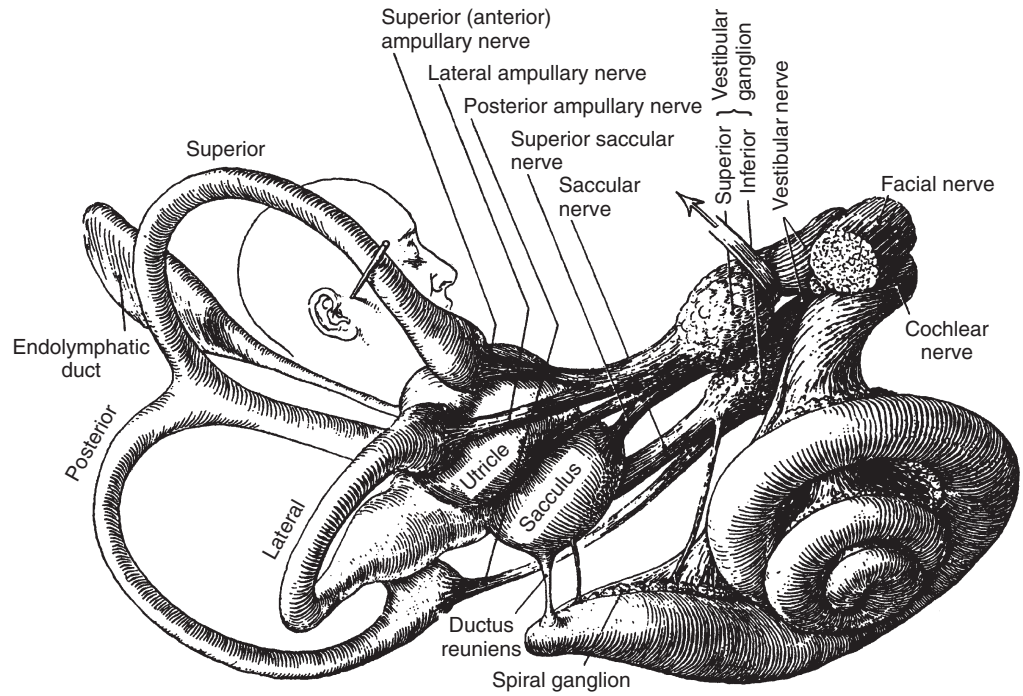

Figure 130-5. Distribution of vestibular nerve to end organs. *(From Brodel M.* Three Unpublished Drawings of the Anatomy of the Human Ear. *Philadelphia: Saunders; 1946.)*

the superior vestibular nerve to the anterosuperior part of the sacculus. Another is the vestibulocochlear (Oort's) anastomosis, which runs from the inferior vestibular nerve to the cochlear nerve and carries cochlear efferents (see later). In addition, some intermediate nerve fibers cross to the vestibular nerve proximal to the superior vestibular ganglion, and others cross back to the intermediate nerve distal to Scarpa's ganglion. It has been suggested that this facial-vestibular anastomosis carries parasympathetic innervation to the vestibular labyrinth; for details on these and other small fiber connections, see Lindemann.[8]

Efferent Innervation of Peripheral Vestibular Apparatus

The efferent supply to the vestibular end organs arises from a small group of about 200 neurons lateral to the abducens nucleus and the genu of the facial nerve, the so-called *group e* (see later).[9] These neurons project ipsilaterally and contralaterally (Fig. 130-6). The contralateral pathway crosses the midline at the level of the facial genu and joins the ipsilateral pathway; both pass ventral to the vestibular nucleus. At this point, they are joined by cochlear efferents originating from the superior olivary complex (olivocochlear bundle). All of the efferents enter the vestibular nerve, coursing through the middle of the nerve in a small distinct bundle. At the end organs, these few fibers branch profusely to innervate the entire sensory epithelium. More recent work suggests that the ipsilaterally projecting efferents supply the central regions of the crista, whereas the contralaterally projecting efferents supply the peripheral zone.[10] The efferent fibers terminate as highly vesiculated boutons, making synaptic contacts with hair cells and afferent fibers.[11,12] For an excellent review of the neurochemistry of the vestibular efferent system, see Goldberg and colleagues.[13]

Autonomic Supply of Peripheral Vestibular Apparatus

Postganglionic sympathetic fibers from neurons in the superior cervical ganglion also innervate the vestibular end organs. They are of two types: perivascular and nonvascular. The nonvascular sympathetic fibers run among the myelinated afferent fibers. The terminals of these nonvascular sympathetic fibers are found as free endings near the cells of Scarpa's ganglion, distal to the ganglion and underneath the sensory epithelium. They do not seem to penetrate the basement membrane into the sensory epithelium and do not seem to have a direct effect on the hair cells or afferent fibers.[14] Their functional role remains unexplored, along with the functional role of any parasympathetic innervation of the vestibular sensory epithelium.

Blood Supply to Vestibular End Organs

The main blood supply to the vestibular end organs is through the internal auditory (labyrinthine) artery, which arises most often (45%) from the anterior cerebellar artery, superior cerebellar artery, or basilar artery, according to a radiographic study by Wende and coworkers.[15] Shortly after entering the inner ear, the labyrinthine artery divides into two branches: the anterior vestibular artery and the common cochlear artery (Fig. 130-7). The anterior vestibular artery provides the blood supply to most of the utriculus and the superior and horizontal ampullae, and some blood to a small portion of the sacculus. The common cochlear artery forms two divisions, the proper cochlear (or spiral modiolar) artery and the vestibulocochlear artery. The latter divides into a cochlear ramus and a vestibular ramus, also known as the posterior vestibular artery. The posterior vestibular artery is the source of the blood supply to the posterior ampulla, the major part of the sacculus, and parts of the body of the utriculus and horizontal and superior ampullae.

Anatomy of End Organs

At the dilated end of each semicircular duct is the ampulla. It contains the neuroepithelium (crista ampullaris), the cupula, supporting cells, connective tissue, blood vessels, and nerve fibers. The crista is a saddle-shaped, raised section of the wall that extends across the floor of the ampulla at right angles to its long axis. The crista has been found to be divided into central (near the apex) and peripheral (on the slope) zones based on the morphology and physiology of vestibular afferents supplying the different regions (see later).[16,17] The shape of the crista facilitates maximal packing of the specialized mechanoreceptor hair cells.

The hair cells and the supporting cells are modified columnar epithelial cells that have microvilli on their apical surfaces. In the hair cells, many of these microvilli are elongated to form stereocilia, which

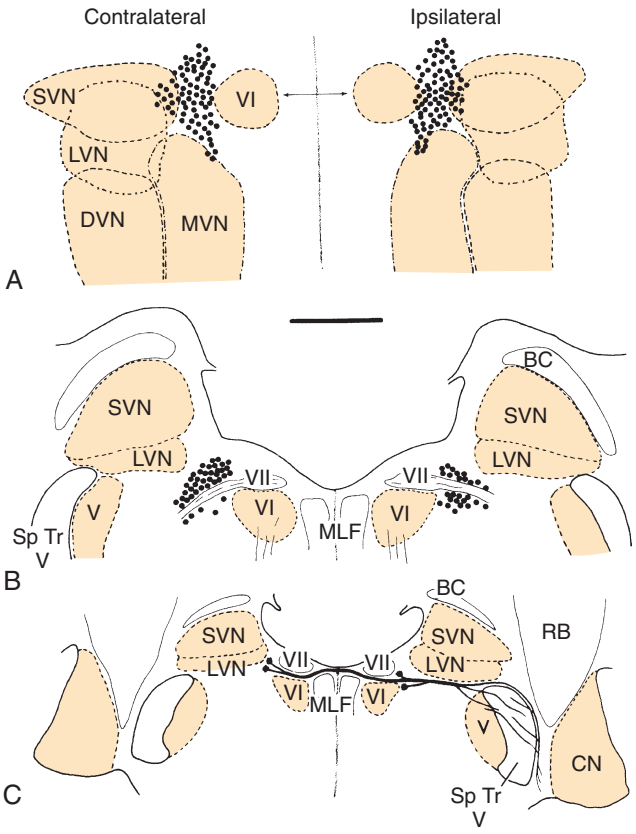

Figure 130-6. Origin and course of efferent vestibular system in a cat. **A,** Distribution of efferent retrogradely labeled neurons after unilateral horseradish peroxidase injection into labyrinth of newborn animal. This group of cells has been termed *group e*. Horizontal section. *Top of diagram,* rostral direction. *Each dot,* Approximately five neurons; *bar,* 1 mm. DVN, LVN, MVN, SVN, descending, lateral, medial, superior, vestibular nuclei; VI, abducens nucleus. **B,** Frontal section (see *arrow* in **A**) from same specimen. *Each dot,* One labeled neuron. BC, brachium conjunctivum; MLF, medial longitudinal fasciculus; SpTrV, trigeminal spinal tract; V, spinal trigeminal nucleus; VII, facial nerve. **C,** Intramedullary course of efferent pathways based on acetylcholinesterase histochemistry. CN, cochlear nuclei; RB, restiform body. *(From Goldberg JM, Fernández C. The vestibular system. In: Darian-Smith I, ed.* Handbook of Physiology. The Nervous System. *Sect I. Vol III. Pt 2. Bethesda, MD: American Physiological Society; 1984: 977-1031.)*

are grouped in an organ pipe–like arrangement (Fig. 130-8). In addition, each hair cell has a single long kinocilium, a true cilium showing the 9 + 2 arrangement of microtubules. This kinocilium is longer than the stereocilia and eccentrically located, imparting a certain polarization to the hair cell that has important functional implications (see Chapter 163). In the cristae, the kinocilium on each hair cell is located on one end of the cell (Fig. 130-9). In the horizontal cristae, the kinocilia are located on the side of the hair cell that is closest to the utriculus. In the vertical cristae, the kinocilia are located on the side of the hair cell furthest from the utriculus, the canalicular side. The entire hair bundle extends upward into the cupula (Fig. 130-10).

The cupula is a gelatinous mass, consisting of mucopolysaccharides within a keratin meshwork,[18] which extends from the surface of the cristae to the roof and lateral walls of the membranous labyrinth, forming a fluid-tight partition. There is a distinct subcupular space in the region of the cupula overlying the apex of the center of the crista (see Fig. 130-10). This subcupular space is believed to provide space for freedom of movement and more sensitive responses to endolymph flow for the stereocilia on the hair cells in the central zone. The space may be artifactual and due to fixation methods commonly used to prepare tissue for histology. The specific gravity of the cupula is approximately 1, which is about the same as that of the endolymph.[19] This matching of the specific gravity of the cupula and the endolymph is necessary to prevent the cupula from floating upward in certain head positions and causing an enduring nystagmus. Disruption of this match in specific gravity is likely the cause of postalcoholic nystagmus.

A torsion pendulum model is used to describe the mechanics of cupular and endolymph displacement.[20] For a description of the mathematic details of the response of canal afferents, see Goldberg and Fernández.[21] More details are also given in Chapter 163.

Similar to the cristae ampullares, the maculae of the utriculus and sacculus consist of neuroepithelium, supporting cells, blood vessels, and nerve fibers. The utricular macula is oriented in the horizontal plane, and the saccular macula is oriented in the vertical plane (Fig. 130-11). Cilia from the hair cells in both maculae extend upward into their respective otolithic membranes (Fig. 130-12)—gelatinous membranes analogous to the cupula. In the upper surface of the otolithic membranes, the otoliths (or otoconia) are embedded. Otoliths are inorganic crystalline deposits composed of calcium carbonate or calcite.[22] They vary in size from 0.5 to 30 µm, with most being about 5 to 7 µm.[8] The specific gravity of the otolithic membrane is much higher than that of the endolymph, about 2.71 to 2.94.[19] Within the otolithic membrane is the striola,[23] a specialized central region that has a snowdrift-like appearance. The striola is identifiable as a thin stripe running down the center of the otolith membranes of both maculae. In the striola, the otoliths are very small (about 1 µm), and the thickness of the otolithic membranes is either reduced, as in the utricular macula, or increased, as in the saccular macula. These regional differences in the otolithic membranes are paralleled by morphologic and physiologic differences in the afferent fibers supplying the hair cells in the underlying sensory epithelium.[24-26]

The kinocilia on the hair cells in the maculae are also dynamically polarized, but the pattern of polarization is much more complex than in the cristae (see Figs. 130-9 and 130-11). In the utricular macula, the kinocilia are oriented so that they point toward the striola, whereas in the saccular macula, the kinocilia point away from the striola. Because both maculae are curved areas, and the striolae are curved lines, the arrangement is so complex (see Fig. 130-11) that static head tilts in any direction cause some hair cells to be excited and others to be inhibited in one or both of the otolithic organs. The stimulus is encoded by means of stimulation of hair cells in the appropriate sector of the macula.

The otolith organs are sensitive not only to gravity, but also to other linear acceleration forces, such as forward motion and bobbing movements of the head during walking. Static head tilts are represented by a vector and the afferent response predicted by a trigonometric function based on the tilt angle. One would expect a linear model based on this simple relationship; however, there is a response asymmetry in that the excitatory response is larger than the inhibitory response. Consequently, the equation describing this force-response relationship is by necessity nonlinear (for more mathematical details, see Fernández and Goldberg[27,28]).

Cellular Morphology of Vestibular Sensory Epithelium

The sensory epithelium is composed of several different elements: hair cells, supporting cells, afferent nerve fibers and their synaptic terminals, and efferent nerve fibers and their synaptic boutons. Two basic cell types are present within the sensory epithelium: supporting cells and hair cells (Fig. 130-13). Supporting cells extend from the basement membrane to the apical surface. Their nuclei are usually found just above the basement membrane and below the hair cells. In sections taken tangential to the apical surface, several supporting cells can be seen to form a ring around an individual hair cell. The supporting cells themselves contain well-developed Golgi complexes, many mitochondria, and occasional lipid droplets. The upper part of the supporting cells contains large numbers of round or ovoid granules. These secretory granules are likely responsible for the formation of the cupula and otolithic membrane.[29,30]

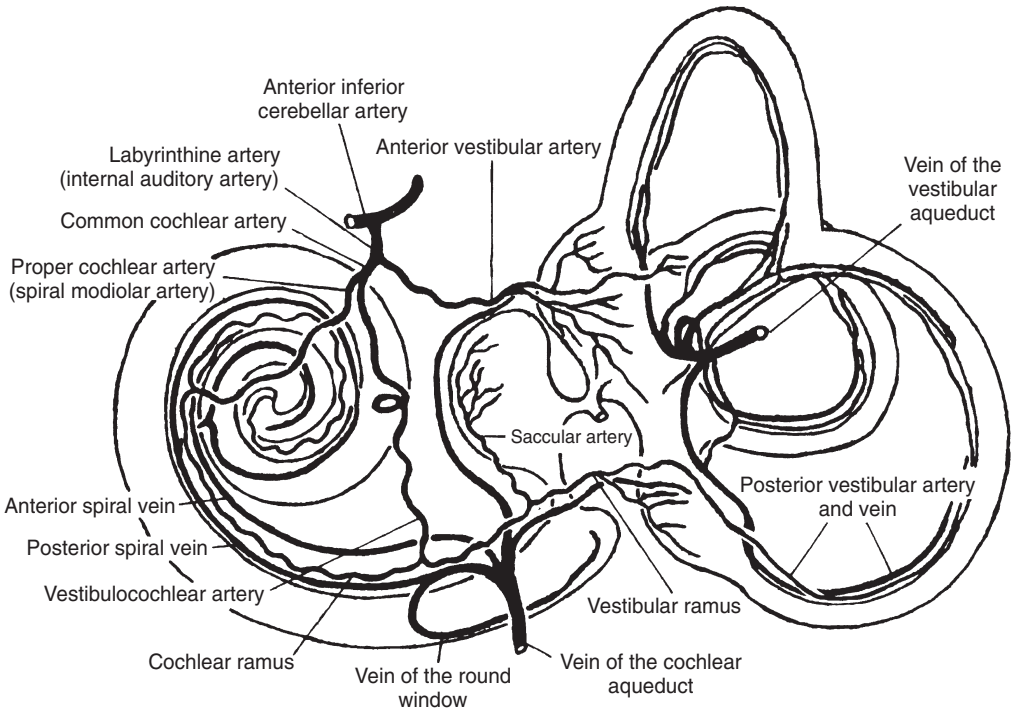

Figure 130-7. Blood supply to inner ear labyrinth. See text for details. *(Modified from Nabeya D. A study of the comparative anatomy of the blood-vascular system of the internal ear in Mammalia and in Homo [Japanese].* Acta Schol Med Imp Kioto. *1923;6:1.)*

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Figure 130-8. Cross section from hair bundle close to cell surface illustrating regularity in arrangement of stereocilia (Stc) and peripheral position of kinocilium (KC) with arrangement of nine peripheral double tubules and two centrally located single tubules in kinocilium. *(From Wersäll J, Bagger-Sjöback D. Morphology of the vestibular sense organ. In: Kornhuber HH, ed.* Handbook of Sensory Physiology. *New York: Springer-Verlag; 1974:124-170.)*

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Figure 130-9. Morphologic polarization of sensory cells and polarization pattern of vestibular sensory epithelia. Morphologic polarization *(arrow)* of sensory cell is determined by position of kinocilium in relation to stereocilia. **A,** Section perpendicular to epithelium. **B,** Section parallel to epithelial surface. **C,** Sensory cells on crista are polarized in same direction. **D** and **E,** Macula sacculi **(D)** and macula utriculi **(E)** are divided by arbitrary curved line into two areas, the pars interna and the pars externa, with opposite polarization. On macula sacculus, sensory cells are polarized away from the dividing line; on macula utriculus, sensory cells are polarized toward the line. Constant irregularities are found in areas corresponding to continuation of striola peripherally (*rectangles* in **D** and **E**). *(From Lindemann HH. Studies on the morphology of the sensory regions of the vestibular apparatus.* Ergeb Anat Entwicklungsgesch. *1969;42:1-113.)*

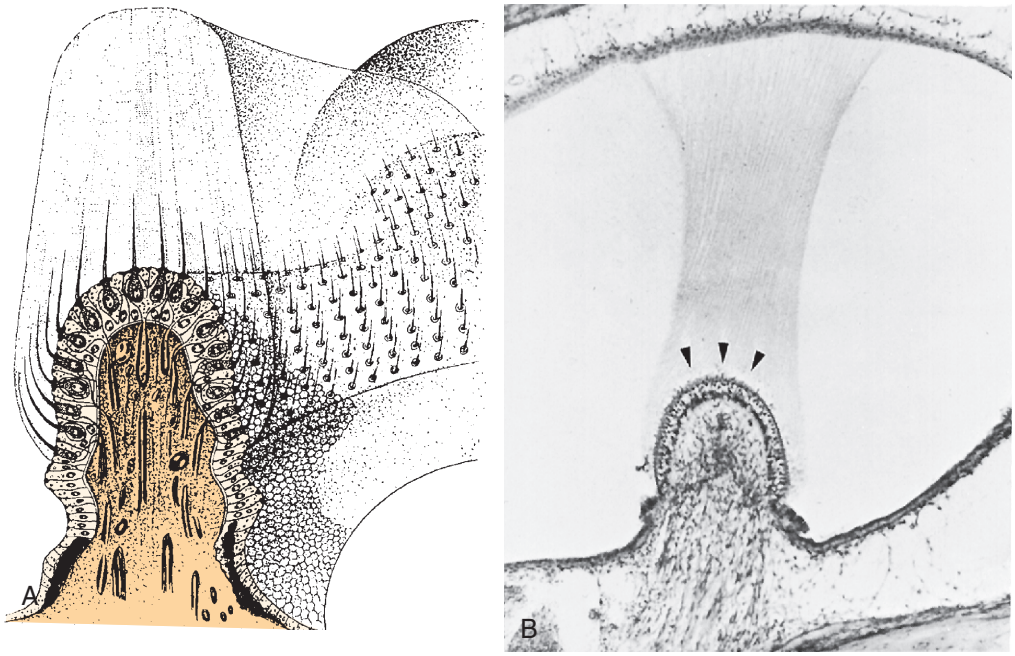

Figure 130-10. **A,** Three-dimensional diagram of surface of guinea pig crista from midtransverse plane to planum semilunatum. **B,** Histologic transverse section of monkey crista with cupula very well preserved, stretching from apex of crista to opposite wall of membranous ampulla. *Arrowheads* indicate subcupular space. *(**A** from Wersall J, Lundquist PG. Morphological polarization of the mechanoreceptors of the vestibular and acoustic systems. In: Graybiel A, ed.* Second Symposium on the Role of Vestibular Organs in Space Exploration, NASA SP-115. *Washington, DC: U.S. Government Printing Office; 1966:57-72. **B** from Igarashi M. Dimensional study of the vestibular end organ apparatus. In: Graybiel A, ed.* Second Symposium on the Role of Vestibular Organs in Space Exploration, NASA SP-115. *Washington, DC: U.S. Government Printing Office; 1966:33-46.)*

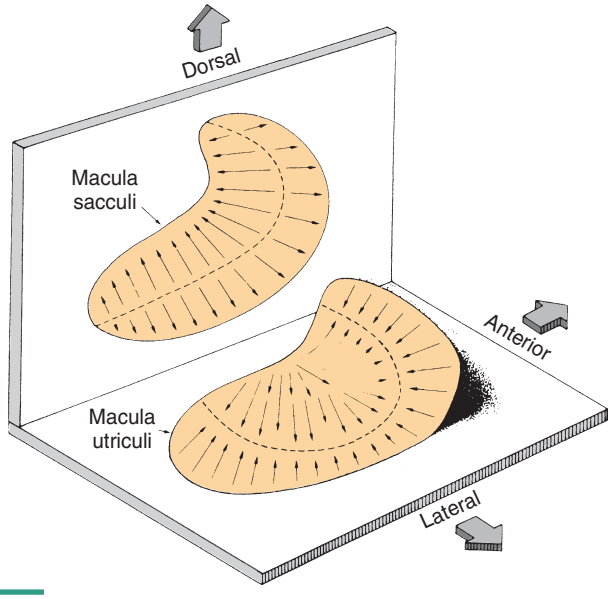

Figure 130-11. Orientation of two maculae. Utricular macula is in horizontal plane, and saccular macula is in vertical plane. *(From Barber HO, Stockwell CW.* Manual of Electronystagmography. *St. Louis: Mosby-Year Book; 1976.)*

Hair cells generally contain a bundle of stereocilia attached to their apical surface and grouped in a staircase arrangement. These stereocilia are densely packed with longitudinally oriented actin filaments that extend into the hair cell and are anchored in a thickened region near the apical surface, termed the *cuticular plate*. The cuticular plate is a dense filamentous meshwork of randomly oriented actin filaments that fills up the area just under the apical surface of the cell except for the region of the kinocilium. A basal body and many large vesicles are usually in the region of the kinocilium. Hair cells are surrounded by supporting cells, as mentioned earlier, and form tight junctions and desmosomes with the supporting cells, separating the endolymphatic space, in which endolymph bathes the stereocilia above the cells, from the perilymphatic space below the apical surface. Another general feature that applies to hair cells is that they are presynaptic to the afferent nerve fibers that they contact. Hair cells make synaptic contacts by means of synaptic specializations termed *synaptic ribbons* or *bars,* electron-dense structures with synaptic vesicles clustered around them.

Synaptic Morphology of Vestibular Afferents

Hair cells are of two types, type I and type II, defined by the presence or absence of a calyx, or chalice, a specialized type of large afferent ending that completely surrounds the cell except for the near-apical and apical surfaces (see Fig. 130-13). Type I hair cells are flask-shaped cells surrounded by a calyx ending. Usually, a calyx surrounds a single type I hair cell. In this case, the calyx ending is termed a *simple calyx ending*. Sometimes one calyx surrounds two to four type I hair cells (Fig. 130-14); this is termed a *complex calyx ending*. Complex calyx endings are much more common in the central zone (or striola) than in the periphery (or extrastriola). Histologically, the existence of complex endings is a criterion that can be used to define the central zone.

The ratio of type I to type II hair cells is approximately 1:1, and this ratio changes very little from the central to the peripheral zone, based on studies in which rodents have been used to quantify cell distributions.[31,32] More recent work in the crista of the squirrel monkey has shown, however, that although the total number of hair cells is similar to rodents, the ratio of type I and type II hair cells in the central zone is increased from 1:1 to about 5:1 in primates compared with rodents.[33] This ratio may reflect the relative importance of type I hair cells for primates. The same is not the case, however, for the monkey otolith organs, in which type II hair cells outnumber type I hair cells by 2:1.[34]

Type II hair cells are cylinder-shaped cells that are contacted at their basal surfaces by numerous afferent and efferent synaptic boutons.

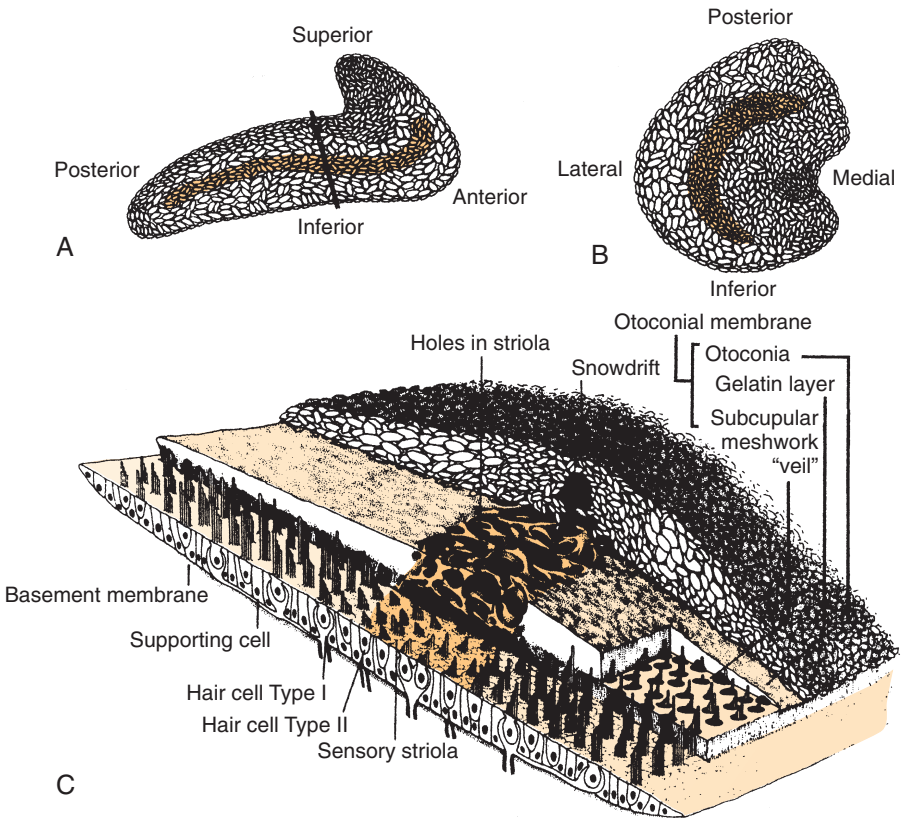

Figure 130-12. Arrangement of otoliths in two maculae. **A,** Sacculus. **B,** Utriculus. **C,** Diagram of composition of saccular otoconial membrane in section taken at level shown in **A**. *(From Paparella MM, Shumrick DA.* Textbook of Otolaryngology. *Vol 1. Philadelphia: Saunders; 1980.)*

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Figure 130-13. Schematic drawing of two types of sensory cells in mammalian labyrinth showing fine structural organization of type I and type II sensory cells and their innervation. *(From Wersäll J, Bagger-Sjöback D. Morphology of the vestibular sense organ. In: Kornhuber HH, ed.* Handbook of Sensory Physiology. *New York: Springer-Verlag; 1974:124-170.)*

Afferent boutons contain mitochondria and few vesicles and receive synaptic contacts from the hair cell. They transmit the impulse centrally to the vestibular nuclei and are postsynaptic to the hair cell. Efferent boutons contain many vesicles and smaller mitochondria and vesicles than those found in afferent boutons. They form synapses with hair cells and afferents, and transmit impulses from the efferent group of neurons located in the brainstem. It has long been assumed that hair cells from different regions had approximately the same number of afferent boutons contacting them, and that each bouton formed about the same number of synapses with a given hair cell. More recent ultrastructural work[12,34] has shown that there are regional variations in the synaptic innervation of type II hair cells (see Fig. 130-14). Type II hair cells in the periphery (or extrastriola) make synaptic contact with many afferent boutons, each of which receives one synapse from the adjacent hair cell. Type II hair cells in the central zone (or striola) make synaptic contact with relatively few afferent boutons, but make multiple contacts with each of these. In addition, type II hair cells in the central zone make synaptic contacts with the outer surface of the calyx endings surrounding type I hair cells, a type of synapse rarely found in the peripheral zone.

Synaptic Morphology and Function of Vestibular Afferents

More recent morphologic and physiologic work on vestibular afferents[16,17,24-26,33,35] has defined, structurally and functionally, specialized subregions within the sensory epithelium (loosely analogous to the fovea and periphery of the retina): the central and peripheral zones of the vestibular sensory epithelium. These studies have involved experiments in which vestibular afferent nerve axons were impaled with microelectrodes; characterized electrophysiologically using responses to galvanic, rotational, and linear acceleration stimuli; and injected with horseradish peroxidase used as an intracellular dye. The horseradish peroxidase–filled afferent nerve fibers were recovered histologically, their position within the sensory epithelium was reconstructed, and their nerve terminals and axons were drawn. In this manner, these investigators were able to define morphologically three types of afferent endings—pure calyx (or chalice) endings, bouton endings, and dimorphic endings (which contained calyx and bouton terminals) (Figs.

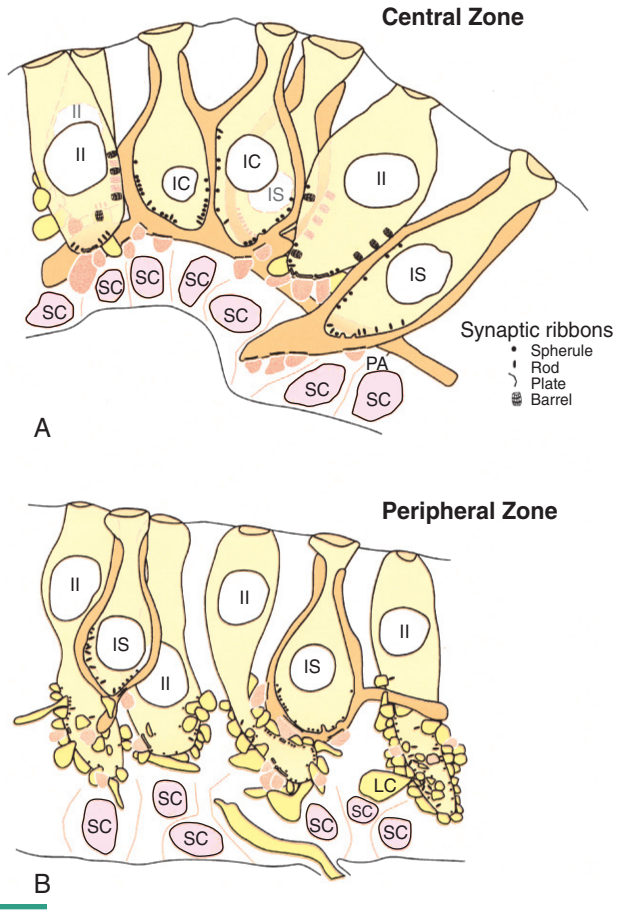

Figure 130-14. Regional variations in synaptic innervation of type I and type II vestibular hair cells. Schematic based on electron micrographs taken from a chinchilla superior crista. **A,** This portion of the central zone contains three type II hair cells (II) and four type I hair cells, including two in a complex calyx (IC) and two others, each in a simple calyx (IS). Supporting cell (SC) nuclei are seen at the bottom. Efferent boutons are shaded *black,* and afferent boutons are *unshaded*. Calyx endings are shaded *orange,* as is the parent axon (PA) running from right to left and giving rise to the complex calyx. Hair cells are wider and calyces are thicker than in the peripheral zone. There are fewer afferent boutons per type II hair cell in the central zone, but each central bouton makes multiple ribbon synapses. Type II hair cells in the central zone also synapse with the outer faces of neighboring calyx endings. Synaptic ribbons occur in different shapes (see key on figure). Efferent synapses are made with type II hair cells, with calyx endings, and with other afferent processes. **B,** Four type II hair cells (II) and two type I hair cells (IS) are shown from the peripheral zone. Hair cells and calyces are thinner, and there are many more afferent boutons per type II hair cell. Most afferent boutons contact one ribbon synapse. Complex calyx endings and outer face ribbons are rare in the periphery. Efferent innervation appears similar in the two regions. *(From Lysakowski A, Goldberg JM. A regional ultrastructural analysis of the cellular and synaptic architecture in the chinchilla cristae ampullares.* J Comp Neurol. *1997;389:419-443.)*

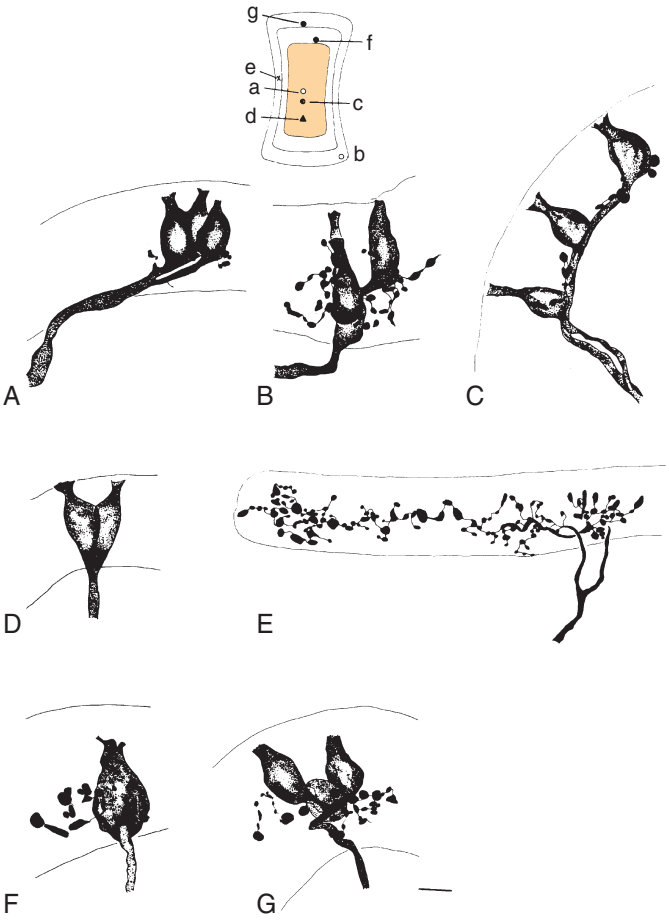

Figure 130-15. A-G, Reconstruction of seven afferents labeled by intra-axonal injections of horseradish peroxidase. Dimorphic units innervating horizontal **(A-C)** or superior **(F, G)** cristae, including regular **(A, B)**, intermediate **(C)**, and irregular **(F, G)** afferents. Regular bouton **(E)** and irregular calyx **(D)** units are also shown; bouton and calyx units supply superior (bouton) and horizontal (calyx) cristae. Location of labeled fibers is indicated in map at *upper left*; calyx and bouton units. For dimorphic units, regular, intermediate, and irregular units are indicated. *Thin lines* in each drawing indicate top of epithelium *(top)* and basement membrane *(bottom)*. *Bar,* 10 µm. *(From Baird RA, Desmadryl G, Fernández C, et al. The vestibular nerve of the chinchilla. II. Relation between afferent response properties and peripheral innervation patterns in the semicircular canals.* J Neurophysiol. *1988;60:182-203.)*

130-15 and 130-16)—and to determine that the distribution of these three types was segregated within the sensory epithelium.

These three morphologic types of afferents fell into two physiologic types that were also segregated within the sensory epithelium. Pure calyx endings had a very irregular discharge pattern and were insensitive (low gain) in response to sinusoidal head rotation. Calyx endings were found only in the central region. Bouton and dimorphic endings were distributed along a continuum in which discharge regularity and response dynamics were linearly correlated; that is, bouton endings were very regularly discharging and had low sensitivity to sinusoidal head rotation, whereas dimorphic endings could vary from very regular to very irregular in discharge rate, and from very low gain to very high gain response dynamics. Bouton endings were always found near the periphery. Dimorphic endings were found throughout the sensory epithelium, but irregular dimorphic endings were found in the central zone, and regular dimorphic endings were in the peripheral zone. The functional classification of vestibular afferents into regularly and irregularly discharging afferents, which correlates with numerous other physiologic and morphologic features,[13,36] has proved useful in understanding peripheral and central terminations, as discussed subsequently.

Central Pathways of Vestibular System

Terminations of Vestibular Nerve in Brainstem

The vestibular nerve enters the brainstem at the ventrolateral aspect of the pontomedullary junction in close proximity to the cochlear and facial nerves, which accompany it to the internal auditory meatus. After

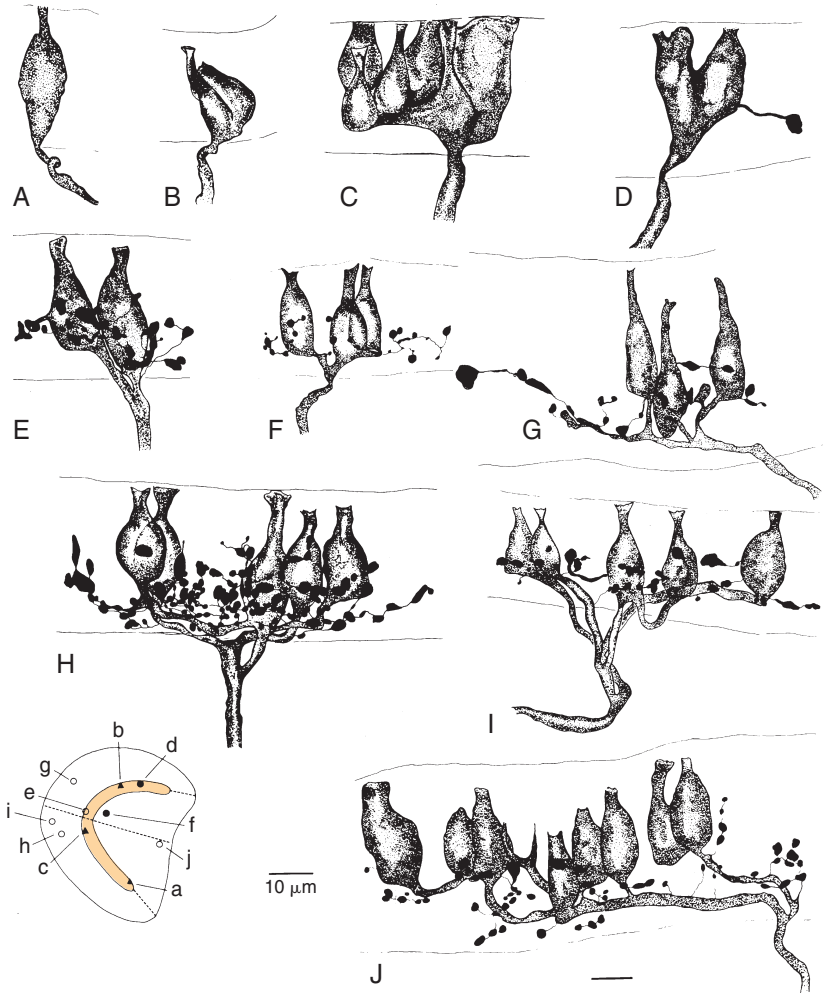

Figure 130-16. A-J, Reconstruction of 10 utricular afferents labeled by intra-axonal injections of horseradish peroxidase and their locations on a standard map of the macula *(lower left)*. *Bar,* 10 μm. See Figure 130-15 for further explanation. *(From Goldberg JM, Desmadryl G, Baird RA, et al. The vestibular nerve of the chinchilla. V. Relation between afferent response properties and peripheral innervation patterns in the utricular macula.* J Neurophysiol. *1990;63:791-804.)*

entering the brainstem, the fibers of the vestibular nerve course dorsally and medially, passing between the inferior cerebellar peduncle and the descending tract of the trigeminal nerve, and enter the vestibular nuclei. On entering the nuclei, most vestibular fibers give rise to two branches in the vestibular nuclei, one rostral and one caudal (Fig. 130-17).[37] The rostral branch projects to the superior and medial vestibular nuclei, and sends a collateral branch to the cerebellum. The caudal branch projects to the inferior and medial vestibular nuclei and to the ventrolateral part of the lateral vestibular nucleus. Regularly discharging vestibular afferents, described in the previous paragraph, terminate on small to medium-sized vestibular nuclear neurons, whereas irregularly discharging afferents terminate on medium-sized to large vestibular nuclear neurons (see Fig. 130-17).[38] There are two major projection sites in the brain—the vestibular nuclei and the cerebellum.[39] No primary vestibular afferents cross the midline.

Projections of Vestibular Nerve to Cerebellum

It has been estimated that about 70% of primary vestibular afferents[40] terminate by means of mossy fibers in the granular layer of the most caudal lobules of the cerebellar vermis, specifically in the uvula and nodulus. This region of the cerebellum is thought to be involved in coordinating movements of the head and eyes. Purkinje cells in the posterior vermis project either to the fastigial nucleus or to the vestibular nuclei. The fastigial nucleus is the deep cerebellar nucleus that receives collateral projections from primary afferents in addition to inputs from the vermis.[41,42] Another region of the cerebellar cortex that projects directly to the vestibular nuclei, the cerebellar flocculus, does not seem to receive significant direct inputs from the vestibular nerve, although it does receive secondary inputs.[43]

Anatomic Subdivisions of Vestibular Nuclei

The vestibular nuclei have been classically divided into four main regional subdivisions[44-46]—superior, medial, lateral, and inferior vestibular nuclei—and several minor cell groups (Fig. 130-18). The superior vestibular nucleus (of Bechterew) is located dorsally and rostrally in the vestibular complex. It can be subdivided into a central region that contains many medium-sized neurons and a peripheral region that contains mostly smaller cells. The superior vestibular nucleus is involved in vestibuloocular reflex pathways. Neurons in this nucleus fire in relation to eye movements and head movements (see Chapter 163), and a prominent efferent projection of this nucleus is to the oculomotor nucleus via the medial longitudinal fasciculus. This tract is particularly important in the control of the vestibuloocular reflex.

The lateral vestibular nucleus (of Deiters) can be subdivided on anatomic and functional grounds into two subnuclei: the dorsal lateral vestibular nucleus (or Deiters' nucleus) and the ventral lateral vestibular nucleus. The dorsal lateral vestibular nucleus contains the many giant cells of Deiters that give rise to the lateral vestibulospinal tract, and the ventral lateral vestibular nucleus contains medium-sized neurons that give rise to vestibuloocular pathways, the medial vestibulospinal tract, and vestibulothalamic pathways. The two subdivisions of the lateral vestibular nucleus also differ in regard to their afferent

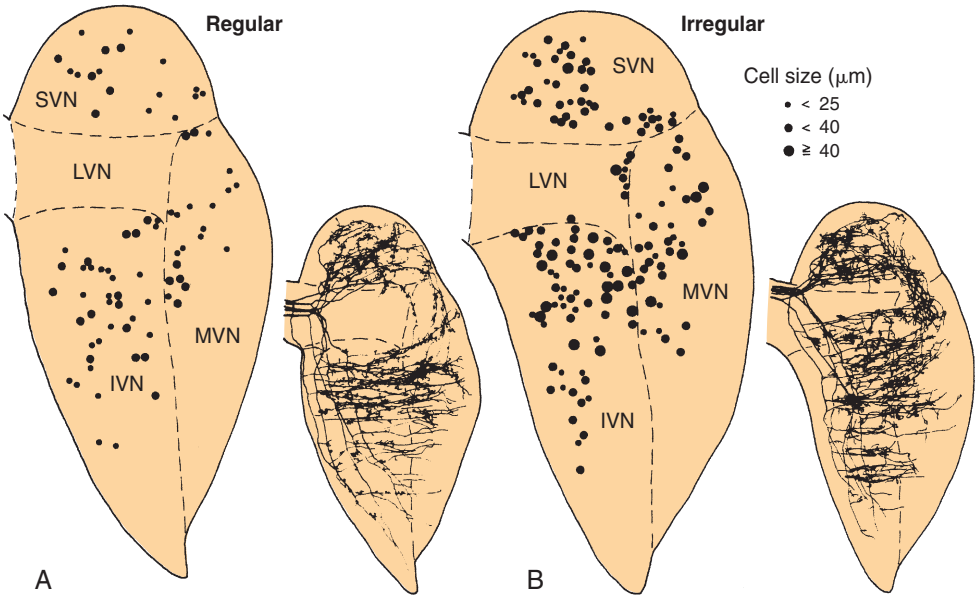

Figure 130-17. Central terminations of regularly **(A)** and irregularly **(B)** discharging canal fibers in vestibular nuclei. Irregular fibers, which are thicker and originate from larger ganglion cells than regular fibers, have a tendency to terminate on larger sized secondary vestibular neurons. IV, LV, MV, SV, inferior, lateral, medial, superior vestibular nuclei. *(From Sato F, Sasaki H. Morphological correlations between spontaneously discharging primary vestibular afferents and vestibular nucleus neurons in the cat.* J Comp Neurol. *1993;333:554-566.)*

inputs (see later). There is a somatotopic representation within the lateral vestibular nucleus,[47] such that the anterior and superior part of the nucleus supplies the cervical cord, whereas the posterior and inferior part supplies the lumbosacral cord. The lateral vestibulospinal tract terminates directly on the ventral horn cells either directly or indirectly by means of interneurons. This tract is particularly important for vestibulospinal and vestibulocollic reflexes.

The medial vestibular nucleus (of Schwalbe) extends rostrocaudally in the brainstem from the level of the abducens nucleus to the hypoglossal nucleus. It is bounded medially by a functionally related nucleus, the nucleus prepositus hypoglossi, and laterally by the inferior vestibular nucleus. More recent studies indicate that the medial vestibular nucleus can be subdivided into a rostral magnocellular region and a parvocellular region and a caudal region with small to medium-sized neurons.[39,48] The rostral medial vestibular nucleus, similar to the superior nucleus, contains many neurons that project to the oculomotor nuclei and whose firing behavior is related to eye movements.[49-51] Little is known about the functions of the caudal region of the medial vestibular nucleus, although many of the cells in this region seem to project to the cerebellum.[52] The medial vestibular nucleus also gives rise to the medial vestibulospinal tract, which descends in the medial longitudinal fasciculus to terminate on interneurons in the cervical spinal cord, and ascends to terminate in the eye motor nuclei. This tract is particularly important for cervicovestibuloocular reflexes.

The inferior (or descending) vestibular nucleus merges rostrally with the ventral lateral vestibular nucleus and extends most caudally in the vestibular complex. This region of the vestibular nuclei is one of the primary recipients of vestibular afferents that innervate the otolithic organs.[53] Some of the cells in this nucleus contribute to the vestibulospinal pathways, but the major projections from this area seem to be to the cerebellum and reticular formation.

The minor cell groups associated with the vestibular nuclei have been named alphabetically in lower case letters: cell groups f, l, x, y, z, and e. Cell group f is a caudal subdivision of the descending vestibular nucleus, consisting of medium-sized cells. Cell group l is a small group of medium-sized cells at the caudal and lateral border of the lateral vestibular nucleus, adjacent to the restiform body. It can be distinguished from the many giant cells of Deiters in the nucleus. In addition, most of its projections are to the spinal cord below T1.[47] Cell group z is not properly included in the vestibular nuclei. It is located in the caudal part of the vestibular complex, and it receives its primary input from fibers that travel in the spinal dorsal columns; its cells contribute to ascending somatosensory pathways to the thalamus.

Cell groups x and y are important functional subdivisions of the vestibular nuclei. Cell group x is also located in the caudal part of the vestibular complex. This area receives a prominent input from the spinal cord, and it projects to the cerebellum. The y group is located caudal and lateral to the superior vestibular nucleus and has a dorsal boundary with the lateral vestibular nucleus and a ventral boundary with the inferior cerebellar peduncle. The dorsal and ventral parts of the y group of cells seem to be functionally different. The ventral part of the y group consists of small fusiform neurons that receive inputs from vestibular afferents that innervate the sacculus.[53] The dorsal part of the y group contains larger neurons and is traversed by a fiber tract, termed the *floccular peduncle,* which passes from the cerebellar flocculus to the vestibular nuclei. Many of the cells in the dorsal part of the y group seem to be functionally related to the flocculus and to eye movement control, particularly eye movements in the vertical plane.[54]

Cell group e (also see Fig. 130-6) is associated with the vestibular nuclei, but contains neurons projecting out to the labyrinth instead of receiving primary afferents. There is some suggestion, however, that it may receive collaterals of primary afferents, which would constitute a type of feedback circuit. It is located at the ventromedial aspect of the rostral medial vestibular nucleus, and it contains the cells that give rise to the efferent pathway from the brain to the vestibular end organs.[9]

Organization of Vestibular Nerve Inputs to Vestibular Nuclei

The vestibular nerve terminates in virtually all parts of the vestibular nuclei.[53] The details of the terminations of the afferents that innervate individual vestibular end organs are not yet completely known, but cells whose activity is related primarily to otolith function have been found mainly in the dorsal lateral and inferior vestibular nuclei. In contrast, cells whose activity is primarily related to semicircular canal function have been found mainly in the superior, medial, and ventral lateral vestibular nuclei. Although the results of physiologic studies suggest that afferents that innervate different vestibular end organs do not synapse directly on the same cells in the vestibular nuclei,[55] the activity of individual cells in the vestibular nuclei is not always clearly related to a single end organ.[56] This finding suggests that there is some func-

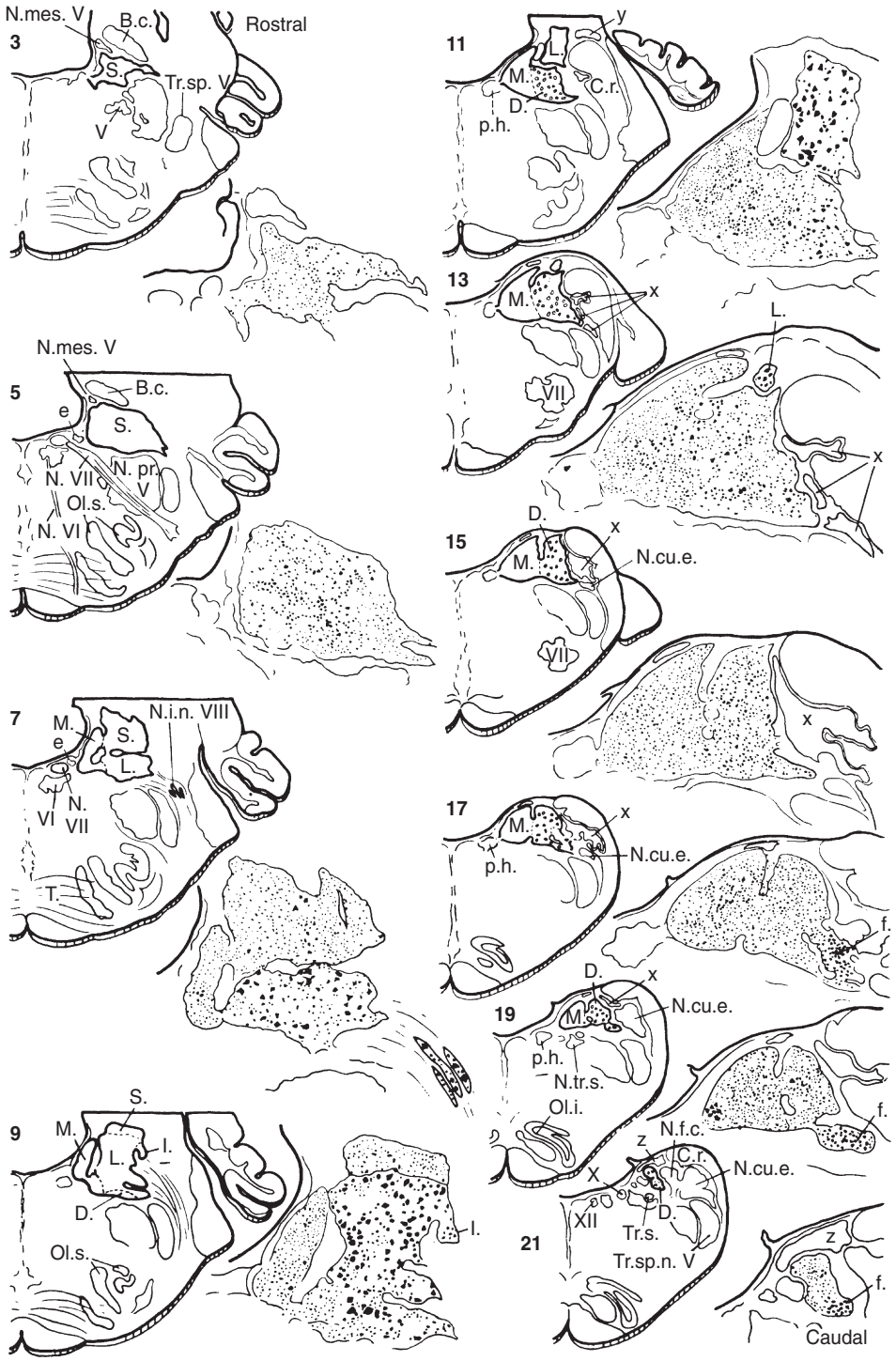

Figure 130-18. Different subdivisions of vestibular nuclei in the cat showing their relationship to other brainstem structures. The cells in each section are also pictured at higher magnification to illustrate the varying size of neurons in different subdivisions. The cell group e from the work of Goldberg and Fernández[9] has been added to this figure. B.c., brachium conjunctivum; C.r., restiform body; D., descending (inferior) vestibular nucleus; e, small cell group containing vestibular efferent neurons; f., ventrolateral caudal subdivision of the descending vestibular nucleus; l., subdivision of the descending vestibular nucleus containing medium-sized cells; L., lateral vestibular nucleus; M., medial vestibular nucleus; N.cu.e., external cuneate nucleus; N.f.c., nucleus fasciculus cuneatus; N.i.n.VIII, interstitial nucleus of the vestibular nerve; N.mes.V, mesencephalic nucleus of trigeminal nerve; N.pr.V, principal nucleus of trigeminal nerve; N.tr.s., nucleus of tractus solitarius; N.VI and N.VII, abducens nerve and facial nerve; Ol.s., superior olive; Ol.i., inferior olive; p.h., nucleus prepositus hypoglossi; S., superior vestibular nucleus; T., trapezoid body; Tr.s., tractus solitarius; Tr.sp.V, spinal tract of trigeminal nerve; Tr.sp.n.V, tract of spinal trigeminal nucleus; V, trigeminal motor nucleus; VI, abducens nucleus; X, dorsal motor nucleus of the vagus nerve; XII, hypoglossal nucleus; x, y and z, cell groups x, y, and z. *(Slightly modified from Brodal A, Pompeiano O, Walberg H.* The Vestibular Nuclei and Their Connections, Anatomy and Functional Correlations. *Edinburgh, Scotland: Oliver & Boyd; 1962.)*

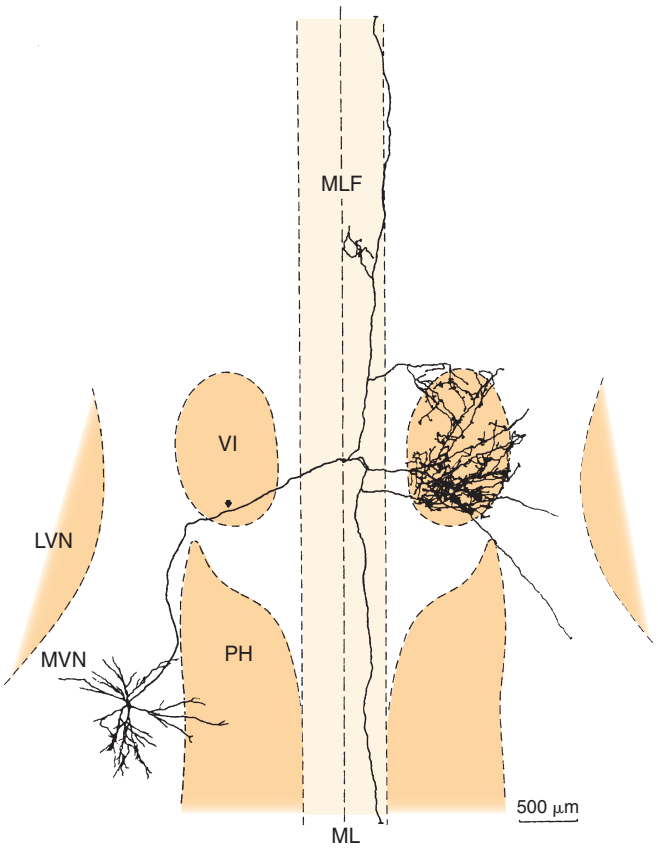

Figure 130-19. Portion of the entire dendritic and axonal arborization of a single type I vestibular nuclear neuron that projects extensively to the contralateral abducens nucleus and other targets. LVN, lateral vestibular nucleus; ML, midline; MLF, medial longitudinal fasciculus; MVN, medial vestibular nucleus; PH, perihypoglossal complex; VI, abducens nucleus. *(From Ohgaki T, Curthoys IS, Markham CH, et al. HRP morphology of functionally identified vestibular type I neurons in the cat.* Adv Otorhinolaryngol. *1988;41:14-19. With permission from S. Karger AG, Basel.)*

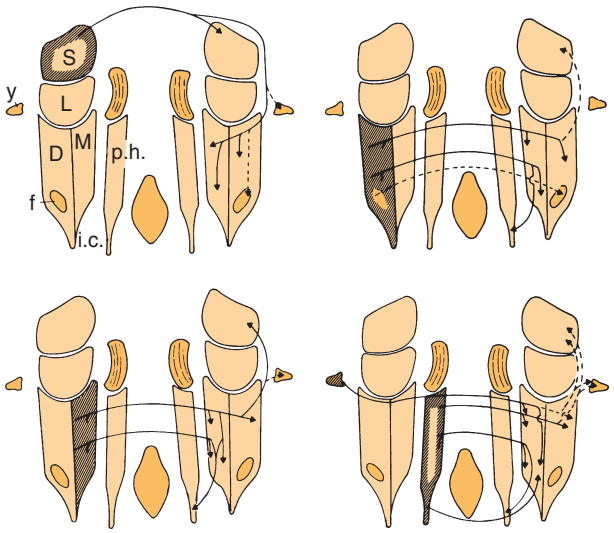

Figure 130-20. Major projections of the vestibular commissural system. Although each nucleus tends to project to its opposite member, considerable divergence is also seen. Commissural connections of the perihypoglossal complex and y group are also illustrated. D, L, M, S, descending (inferior), lateral, medial, superior vestibular nuclei; f, f group; i.c., nucleus intercalatus (Staderini); p.h., perihypoglossal complex; y, y group. *(From Pompeiano O, Mergner T, Corvaja N. Commissural, perihypoglossal and reticular afferent projections to the vestibular nuclei in the cat: an experimental anatomical study with the method of retrograde transport of horseradish peroxidase.* Arch Ital Biol. *1978;116:130-172.)*

tional convergence of inputs from different end organs in some vestibular nuclear cells.

Some neurons in the vestibular nuclei do not receive direct inputs from the vestibular nerve. One example is a group of cells that respond preferentially to stimulation of the contralateral vestibular nerve (see later).[57,58] The head movement sensitivity of most of the cells in the vestibular nuclei depends on bilateral activation of the vestibular end organs. Removal of one vestibular nerve typically reduces the head movement sensitivity of vestibular nuclear neurons approximately in half,[59] which suggests that commissural pathways between the vestibular nuclei contribute significantly to the physiologic sensitivity of vestibular nuclear neurons.

Four physiologic types of neurons are found in the vestibular nuclei.[57,58] These are described briefly here. Type I neurons are excited, whereas type II neurons are inhibited, by ipsilateral rotations of the head. The former receive ipsilateral input from primary afferents, whereas the latter receive either contralateral or commissural input. Type III neurons are excited by both directions of rotation, whereas type IV neurons are inhibited by either type of rotational acceleration. Type I neurons are the most common; there are also numerous type II neurons. Type III and type IV neurons are rare. Figure 130-19 shows a vestibular type I neuron in the medial vestibular nucleus that has been characterized morphologically and physiologically and projects to the abducens nucleus and other targets.[60]

Vestibular commissural pathways arise from every part of the vestibular nuclei except the dorsal lateral vestibular nucleus.[48,61] Although there is a tendency for a particular region of the vestibular nuclei to project heavily to its contralateral counterpart, there is also considerable divergence in the commissural pathways to other parts of the vestibular nuclei (Fig. 130-20). Functionally, the commissural pathways between the vestibular nuclei seem to play an essential role in the ability to compensate for unilateral vestibular lesions.[62] Because most vestibular nuclear neurons fire spontaneously even when the head is not moving,[49] and because most vestibular functions are organized bilaterally, an imbalance between the spontaneous firing rate of one vestibular nucleus compared with the other results in the central perception of head movement and dysfunctional operation of reflex pathways (e.g., ocular nystagmus is usually produced when the vestibular nuclei are unilaterally damaged). The vestibular commissural pathways seem to play an important role in maintaining the balance in the output of the two sides.

Other Inputs to Vestibular Nuclei

The vestibular nerve is not the only source of input to the vestibular nuclei. Many regions of the brainstem and the cerebellum also project to the vestibular nuclei. Most of the nonvestibular inputs arise from the flocculonodular lobe of the cerebellum,[63] from the fastigial nucleus,[64] and from regions of the brainstem in the vicinity of the vestibular nuclei, although the vestibular nuclei also receive inputs from the spinal cord and from nuclei located in the midbrain and caudal diencephalon.

Although the function of each source of nonvestibular afferents to the vestibular nuclei is not completely known, the physiologic responses of vestibular nuclear neurons have been clearly shown to be affected by behaviors and stimuli not related to vestibular nerve activity. Perhaps the most common nonvestibular input to the vestibular nuclei is an input from the visual system. Most vestibular nuclear neurons that are sensitive to head movements are also sensitive to movements of the visual world; that is, they are sensitive to optokinetic stimuli.[65] The semicircular canals are insensitive to low-frequency (<0.05 Hz) movements of the head. The visual system is capable of detecting extremely low-frequency movements of the visual scene, however. The brain uses visual information to supplement the information obtained from the labyrinth. The anatomic pathways by which the visual optokinetic signals reach the vestibular nuclei have not been completely worked out, but several midbrain pretectal nuclei (in particular, the nucleus of

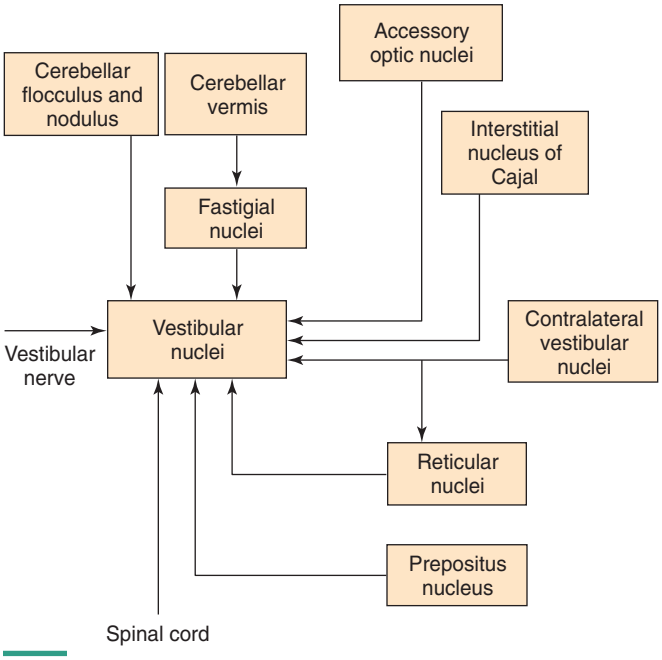

Figure 130-21. Afferent pathways to vestibular nuclei. See text for details. *(Schematic courtesy of Robert McCrea.)*

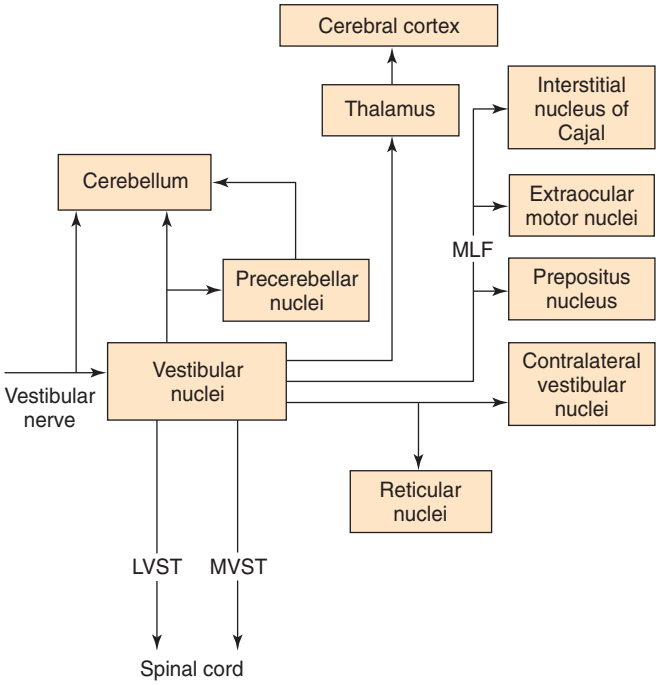

Figure 130-22. Efferent connections of vestibular nuclei. See text for details. LVST, lateral vestibulospinal tract; MLF, medial longitudinal fasciculus; MVST, medial vestibulospinal tract. *(Schematic courtesy of Robert McCrea.)*

the optic tract and the accessory optic nuclei) seem to play an essential role. These midbrain nuclei do not project directly to the vestibular nuclei themselves; rather, they project to other brainstem nuclei. These other nuclei project to the vestibular nuclei (e.g., the prepositus nucleus[66]) or to regions of the cerebellum that project to the vestibular nuclei (e.g., visual signals reach the cerebellum via the inferior olive[67] and the pontine nuclei[68]).

Pathways from the cerebellum to the vestibular nuclei not only contribute to the visual responsiveness of vestibular nuclear neurons, but also are essential for adaptive modification of the head movement sensitivity of vestibuloocular pathways and compensation for unilateral vestibular lesions. The cerebellar flocculus is particularly important for adaptive modification of vestibuloocular reflex pathways.[49,69] The Purkinje cells in this region of the cerebellar cortex are sensitive to optokinetic visual stimuli and to movements of small visual targets on the fovea.[70,71] When eye movements produced by vestibuloocular pathways fail to stabilize images on the retina, the Purkinje cells of the flocculus change their firing rate and modify the head movement sensitivity of some of the vestibular nuclear neurons that project to the extraocular motor nuclei.

As noted earlier, many of the neurons in the superior, medial, and ventral lateral vestibular nuclei change their firing rate during eye movements even when the head is not moving and the vestibular nerve activity is unchanging. In a study by Chen-Huang and McCrea,[72] the size of the utricular signal traveling to the oculomotor nucleus in the ascending tract of Deiters depended on the fixation distance. This finding implies the existence of an important neural multiplier system in the vestibular nuclei, and not a simple disynaptic relay between the utricle and the oculomotor nucleus. Vestibular nuclear neurons that project to the extraocular motor nuclei fire during steady fixation, saccadic eye movements, and ocular smooth pursuit.[73,74] The vestibular nuclei apparently contribute to the generation of each of these oculomotor behaviors. The regions of the brain that provide these oculomotor-related inputs include the prepositus nucleus,[75] the interstitial nucleus of Cajal,[76] and the pontine and medullary reticular formation.[77]

The spinal cord, particularly the cervical spinal cord, is another important source of nonvestibular afferents to the vestibular nuclei. The neurons in the dorsal lateral vestibular nucleus that project to the spinal cord also receive inputs from the spinal segments to which they project.[78] Neurons in the medial and ventral lateral vestibular nuclei that project to the extraocular motor nuclei receive inputs from the cervical spinal cord.[79] These inputs are probably important for mediating the cervical ocular reflex, which is a reflex that can help the vestibuloocular reflex to stabilize gaze during head movements, particularly when the labyrinth is damaged. These pathways provide a possible explanation for the nystagmus often seen after neck injury.

There are other nonvestibular inputs that are functionally important but whose anatomy is poorly defined. It is likely that some vestibular nuclear neurons receive inputs related to central autonomic functions and behavioral state (e.g., alertness). Several observers have noted that the spontaneous firing rate and sensitivity to eye and head movements of many vestibular nuclear neurons are profoundly reduced during slow wave sleep or reduced alertness despite the fact that vestibular nerve activity is apparently unaffected. The central anatomic pathways that mediate these effects are unknown. The major afferent connections to the vestibular nuclei are summarized in Figure 130-21.

Efferent Projection Pathways from the Vestibular Nuclei

The vestibular nuclei project to numerous regions of the brainstem, cerebellum, and spinal cord. In addition, the vestibular nuclei are highly interconnected. The intrinsic connections of the vestibular nuclei are not limited to the commissural pathways described earlier, but also include connections between the various vestibular nuclei on the same side of the brain.[48,61]

Figure 130-22 provides an overview of the major vestibular efferent projections. All of the vestibular nuclei except the dorsal lateral vestibular nucleus contain neurons that project to the cerebellum. The cerebellar vermis, the flocculonodular lobe, and the fastigial nucleus are the regions of the cerebellum to which these vestibulocerebellar pathways project.[80] These are the regions of the cerebellum that are thought to be involved in coordinating movements of the axial musculature, the head, and the eyes. The output of the cerebellar cortex is organized in parasagittal efferent strips.[81] There is an efferent parasagittal cortical strip in the vermis that projects to the neurons in the dorsal lateral vestibular nucleus that gives rise to the lateral vestibulospinal tract. Another efferent strip in the vermis projects to the fastigial nucleus. Strips in the cerebellar cortex of the flocculonodular lobe project to the neurons in the superior, medial, and lateral vestibular nuclei that give rise to the vestibuloocular reflex pathways.[69] There are reciprocal con-

nections between the vestibular nuclei and regions in the cerebellum that receive vestibular inputs.

The medial, superior, and ventral lateral vestibular nuclei give rise to major bilateral efferent projections to the regions of the brainstem involved in controlling eye movements.[82-84] The vestibular nuclei give rise to an important set of reflex pathways involved in the vestibuloocular reflex. The axons that make up these pathways usually join the medial longitudinal fasciculus near the abducens nucleus.

The function of the vestibuloocular reflex is to stabilize vision during head movements. This stabilization is accomplished by moving the eyes at the same speed as the head, but in the opposite direction. The vestibuloocular reflex pathways are organized reciprocally such that the motor neurons that innervate each extraocular muscle receive excitatory and inhibitory inputs from the vestibular nuclei. For more details on vestibuloocular reflex function, see Chapter 163.

A second major efferent vestibular pathway that aids in gaze stabilization is the medial vestibulospinal tract. This pathway originates from cells in the medial and ventral lateral vestibular nuclei and projects bilaterally in the medial longitudinal fasciculus to the ventral horn of the cervical spinal cord. Approximately half of these cells also contribute to the vestibuloocular reflex pathways via axon collaterals.[85] The medial vestibulospinal tract functions to stabilize the head on the shoulders by generating neck muscle contractions that resist passive movements of the head.[86]

The lateral vestibulospinal tract plays an important role in maintaining postural balance. This pathway arises from cells in the dorsal lateral vestibular nucleus and projects ipsilaterally to the ventral horn of the spinal cord, as far as the lumbar enlargement. The cells in the dorsal lateral vestibular nucleus are particularly sensitive to tilting of the head. The lateral vestibulospinal tract is tonically active and provides a powerful tonic excitatory synaptic input to postural extensor motor neurons. With unilateral labyrinthine lesions, the tonic excitatory input to ipsilateral postural extensors is reduced, particularly when visual cues are absent, and there is a tendency to fall toward the side of the lesion.

Vestibulothalamic pathways arise from cells in the ventral lateral vestibular nucleus and project to thalamic regions that border and include the ventral posterolateral, ventral posteromedial, and ventral lateral nuclei of the thalamus.[87-89] The vestibular nuclei also project to another thalamic nucleus, the ventral lateral geniculate nucleus.[90] This nucleus is adjacent to the dorsal lateral geniculate nucleus, and has anatomic connections that suggest it is involved in visual processing. Presumably, vestibulothalamocortical pathways play a role in the conscious perception of vertigo, or of self-motion, in the absence of visual stimulation.

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CHAPTER ONE HUNDRED AND THIRTY-ONE

Anatomy and Physiology of the Eustachian Tube

Robert C. O'Reilly

Isamu Sando

Key Points

- The eustachian tube is involved in pressure equalization, mucociliary clearance, and middle ear protection.
- The principal dilator of the eustachian tube is the tensor veli palatini muscle.
- Anatomic changes in the tube with growth and development include increased length and diameter, increasing tubal angle, change in cellular composition of tubal cartilage, and increased efficiency of tubal opening.
- Tubal function can be adversely affected by viral and bacterial infections, adenoid disease, craniofacial anomalies, neoplasm, genetic predisposition, sinonasal disease, and gastroesophageal reflux.
- Current tubal function tests have limited prognostic value.

Since Eustachius first described the anatomy of his eponymous tube in 1563, understanding of its function in healthy and diseased ears has continued to evolve.[1] An anatomic connection between the middle ear space and the nasopharynx was recognized, but the role played by the eustachian tube was unclear. Although this connection was initially thought to be an organ of respiration, later observers realized that it was vital to the health of the tympanic membrane and middle ear as a whole. Pioneering otologists including Toynbee, Politzer, and Bezold developed a paradigm that held that the eustachian tube regulates and modulates the pneumatic status of the middle ear and mastoid to maintain the appropriate milieu for optimal sound transmission by the tympanic membrane and ossicular chain.

Initial concepts regarding the physiology of tubal function were found to be too simplistic. New information has led to a model of the eustachian tube as an "organ" because of its complex anatomy, function, and interdependent relationship with surrounding structures.[2] A comparison of early otology texts with contemporary work reveals an evolution of the study of tubal function from limited therapeutics applied directly to the tube to an attempt to understand and modify intrinsic and extrinsic pathologic influences on its function.

Embryology and Postnatal Development

The eustachian tube is derived from the first pharyngeal pouch.[3] The endoderm lining the tubotympanic sulcus invaginates between the first and second arch mesoderm to form the tubotympanic recess. The recess expands to form the tympanic cavity and the mastoid antrum. The osseous portion of the tube forms from the petrous and squamous parts of the temporal bone and the greater wing of the sphenoid bone. The cartilaginous tube has at least two discrete centers of chondrification.[4] In patients with cleft palate, there is often a deficiency in the development of the lateral lamina.[5]

The muscles associated with the tube are the tensor veli palatini (TVP), dilator tubae (DT) (which is the medial bundle of TVP muscle),[6] tensor tympani (TT), levator veli palatini (LVP), and salpingopharyngeus. These muscles appear early in development and form from the mesenchyme of the first (mandibular) arch together with the muscles of mastication.[7] The TVP, DT, and TT are innervated by the mandibular branch of the trigeminal nerve, whereas the LVP is innervated by the vagus nerve.[8] The TVP and DT change position during intrauterine development to form a more acute angle with the tube, particularly at the upper portion of the lateral lamina.[7,9,10]

The eustachian tube is patent during embryologic development, allowing for free flow of amniotic fluid into the middle ear space.[11] Early patency explains the occasional finding of keratin and lanugo hairs in the middle ear cleft in infants, and may limit the ability to detect otoacoustic emissions during newborn hearing screening. It is conceivable that this route of entry of squamous epithelium may produce a congenital cholesteatoma, although the more likely mechanism seems to be epidermoid formation from the ectoderm of the first pharyngeal cleft.[12]

The most rapid development of the petrous and squamous portions of the temporal bone occurs in the first 2 years of life, and eustachian tubal development parallels this.[13] Tubal length progresses from 17.5 mm in infants to reach an adult length of 37.5 mm. The length and area of the entire lumen increase more than twofold when comparing adults with young children, although the ratio of the cross-sectional diameter of the lumen to tubal length remains constant.[7,14,15]

The length of the osseous portion of the tube triples during development, whereas the cartilaginous tube increases 1.6-fold.[16] The cartilaginous (nasopharyngeal) portion of the tube is three times as large in adults as in children, and the cross-sectional area, and presumably the efficiency of the dilatory muscles, increases with age.[17,18]

More significantly, with an increase in cartilage size, there are important changes in cellular composition and shape with aging that result in a less "floppy" tube in adults compared with children. The cartilage cell density decreases in the midcartilaginous portion, and intercellular elastin, present in the hinge region between the medial and lateral laminae, is far more abundant in adults than in children. The

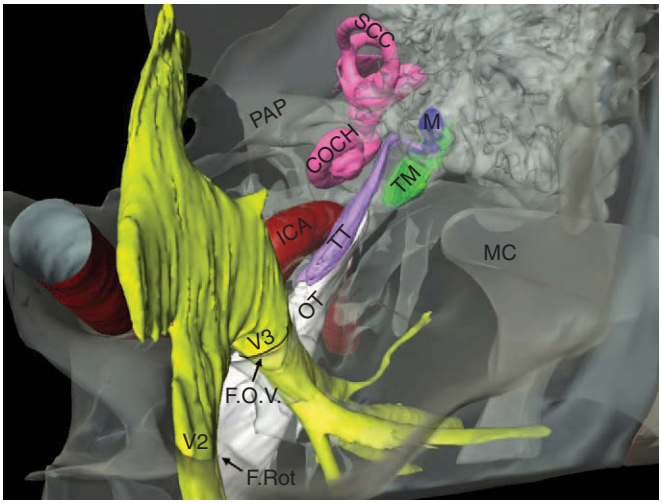

Figure 131-1. Superior view of the left eustachian tube showing its course through the skull base. Note the relationship to the plane of the tympanic membrane. COCH, cochlea; FOV, foramen ovale; F.Rot, foramen rotundum; ICA, internal carotid artery; M, head of malleus; MC, mandibular condyle; OT, osseous eustachian tube; PAP, petrous apex; SCC, superior semicircular canal; TM, tympanic membrane; TT, tensor tympani muscle; V2, maxillary division trigeminal nerve; V3, mandibular division trigeminal nerve. *(Courtesy of Michael Teixido, MD, Mads Sorensen, and Haobing Wang.)*

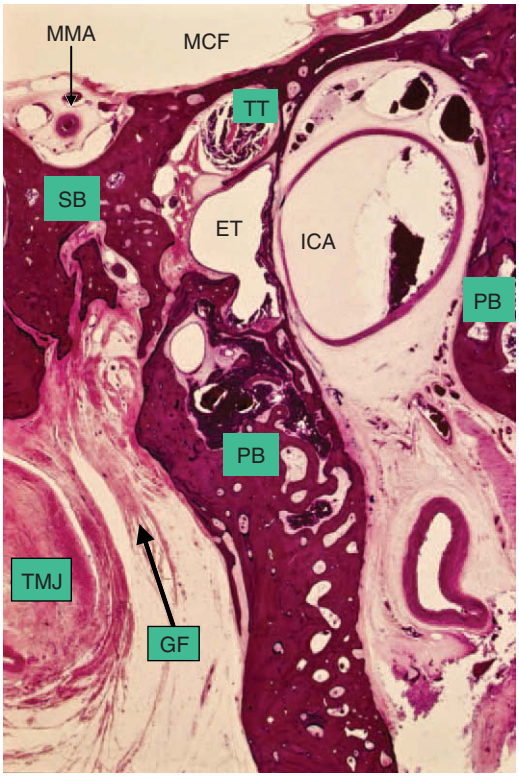

Figure 131-2. Photomicrograph of cross section of osseous portion of eustachian tube. The tubal lumen (ET) is bounded by the petrous (PB) and sphenoid bones (SB). The tensor tympani muscle (TT) courses above the lumen below the middle cranial fossa (MCF). Very thin bone separates the lumen from the internal carotid artery (ICA). The tubal lumen is adjacent to the temporomandibular joint (TMJ) in the glenoid fossa (GF). MMA, middle meningeal artery. *Top,* Superior. *Right,* Medial. *(From Sando I, Ikui A, Sudo M. Microscopic sectional anatomy with 3-D reconstruction of the temporal bone. In: Janecks IP, Tiedemann K, eds.* Skull Base Surgery, Anatomy, Biology, and Technology. *Philadelphia: Lippincott-Raven; 1997:151-159.)*

medial lamina develops more than the lateral lamina, and when viewed in cross section, the lateral lamina and lateral wall of the tube develop a greater "S" shape. These changes allow for more efficient tubal recoil.[14,19-22]

Other anatomic changes lead to an improvement in the efficiency of tubal function. During growth, there is a shift in the orientation of the cartilaginous portion to the osseous portion of the tube. When viewed from above, the long axis of the tube describes a greater curve with the increasing inferior and lateral movement of the cartilaginous tube. This augments middle ear protection.[16] Additionally, the angle of insertion of the dilatory muscles (DT) becomes more perpendicular to the cartilaginous tube, and the tube becomes more dependent relative to the middle ear cleft.[23] All these elements may play a part in the decreased incidence of otitis media with age.[15]

Anatomy

The function of the eustachian tube in pressure equalization, middle ear protection, and clearance can be understood only when its anatomic subtleties are appreciated. The tube is located in the skull base and connects the anterior portion of the middle ear cleft with the nasopharynx. Its anatomic course brings it close to many critical structures. The general shape of the eustachian tube can be described as two cones joined at their apices. It comprises an osseous, intratemporal portion and a cartilaginous, nasopharyngeal portion. These describe a gentle outward curve when viewed from above as it extends from the middle ear to the nasopharynx (Fig. 131-1).[7]

In adults, the osseous portion accounts for less than one third of the length of the tube, and the cartilaginous portion constitutes more than two thirds of the length, even if the central (junctional) region is considered part of the osseous tube.[15,16] The orifice of the tube in the middle ear originates in the anterior mesotympanum (protympanum), with the mouth of the tube above the level of the floor of the middle ear. The orifice is not dependent, unless the head is tilted forward. It is triangular to oval in shape with a diameter of 5 mm × 3 mm and marks the entrance to the osseous tube.[24] This portion of the tube progresses anteromedially to its isthmus portion along its longitudinal section of the petrous portion of the temporal bone.[25] The petrous bone surrounds most of the osseous portion of the tube except for a part of the lateral wall that is surrounded by the sphenoid bone (Fig. 131-2).[7] Because of the rigid walls in this anatomic segment, the lumen is always patent, unless obstructed by mucosal thickening or debris.

The osseous portion of the eustachian tube lies close to several structures (Fig. 131-3). The glenoid fossa of the temporomandibular joint is lateral and inferior to the osseous tube, the middle fossa dura lies superior, and the internal carotid lies medial. The medial wall of the tube is composed of two parts: a posterior labyrinthine portion and an anterior carotid portion.[26] The horizontal segment of the petrous carotid artery is capped by thin bone (see Fig. 131-2). This bone has been found to be dehiscent in 2% of normal adult specimens and exceptionally thin in 22.2%.[27,28] Distance between the bony wall and anterior tympanic anulus was found to be an average 4.9 mm. The TT runs just lateral to the midthird of the cochlea. Its semicanal can be found above the osseous tube on the nasopharyngeal side, but runs more medially as it approaches the middle ear. The average distance from the lumen of the tube to the dura of the middle fossa is 3.6 mm.[24] All these structures are in jeopardy when the tube is surgically manipulated, and caution must be exercised when removing disease from the lumen.

Approximately 33% of patients have pneumatization of the petrous apex, and the osseous tube can be variably surrounded by peritubal air cells. Computed tomography (CT) has revealed that in 92% of patients, these cells can open directly into the osseous tube anterior to its tympanic orifice. This opening may play a role in persistent cerebrospinal fluid rhinorrhea after cerebellopontine angle surgery despite packing of the tympanic orifice of the tube.[29]

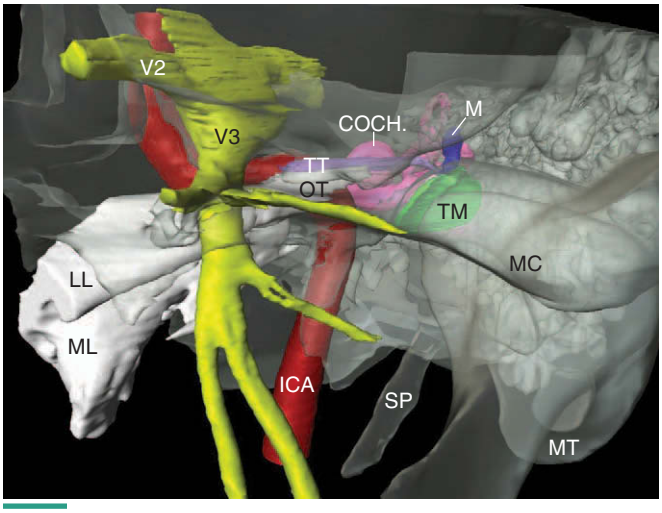

Figure 131-3. Lateral view of the left eustachian tube showing the relationship to adjacent structures. COCH, cochlea; ICA, internal carotid artery; LL, lateral cartilaginous lamina; M, head of malleus; MC, mandibular condyle; ML, medial cartilaginous lamina; MT, mastoid tip; OT, osseous eustachian tube; SP, styloid process; TM, tympanic membrane; TT, tensor tympani muscle; V2, maxillary division trigeminal nerve; V3, mandibular division trigeminal nerve. *(Courtesy of Michael Teixido, MD, Mads Sorensen, and Haobing Wang.)*

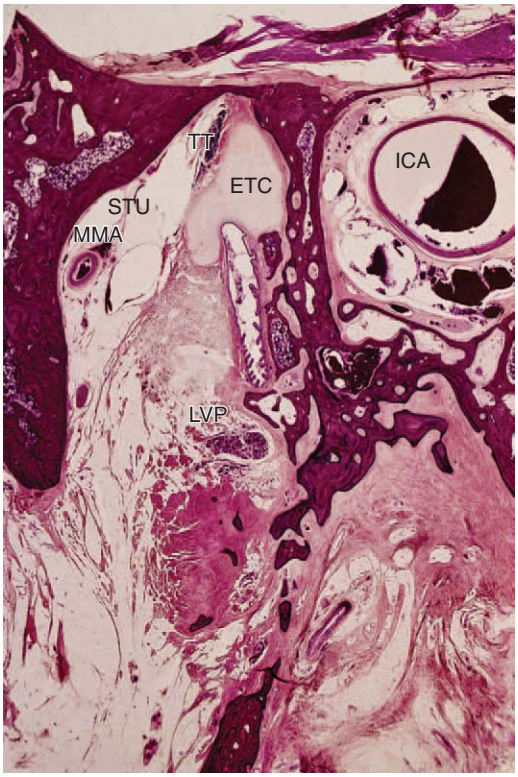

Figure 131-4. Photomicrograph of cross section of junctional portion of the eustachian tube. The eustachian tube cartilage (ETC) is suspended by the superior tubal ligament in the sulcus tubarius (STU). In this portion of the tube, the cartilage covers only the superior aspect of the lumen. The levator veli palatini muscle (LVP) originates from the inferior surface of the petrous apex. ICA, internal carotid artery; MMA, middle meningeal artery; TT, tensor tympani muscle. *Top,* Superior. *Right,* Medial. *(From Sando I, Ikui A, Sudo M. Microscopic sectional anatomy with 3-D reconstruction of the temporal bone. In: Janecks IP, Tiedemann K, eds.* Skull Base Surgery, Anatomy, Biology, and Technology. *Philadelphia: Lippincott-Raven; 1997:151-159.)*

The osseous portion of the tube progressively narrows as it approaches the cartilaginous portion. Small endoscopes 0.8 mm in diameter are able to pass through this region.[30] At its most anterior tip, the fibrocartilage of the cartilaginous tube extends slightly into the lumen of the bony canal. This area has been called the isthmus; however, it is not the narrowest part of the tube. Histopathologic studies measuring the circumference of the internal lining and the cross-sectional area of the tube have revealed that the narrowest portion of the tube in the closed and in the fully open positions lies in the proximal cartilaginous tube. Sando and coworkers[15] proposed that the divisions of the eustachian tube be reclassified as osseous (lumen surrounded by bone), cartilaginous (lumen surrounded by cartilage), and "junctional" (lumen surrounded by bone and cartilage) (Fig. 131-4).

The cartilaginous portion of the tube has a complex shape reflecting the nuances of its function (Fig. 131-5). It is composed of two distinct rhomboidal plates when viewed from the side, with a large medial lamina and a much smaller lateral lamina. These are joined at the apical hinge region. In three dimensions, the cartilage is bell-shaped with a largest transverse diameter of 9 mm. When viewed from the nasopharynx, the fibrocartilage is in a distinct "crook" shape with the longer arm located medially. Its projection into the nasopharynx is covered by a layer of respiratory mucosa and is distinctly seen on nasopharyngoscopy as the torus tubarius. Although the laminae are principally composed of fibrocartilage, the hinge region contains an abundance of elastic cartilage allowing for efficient tubal opening (Fig. 131-6). The nasopharyngeal opening of the eustachian tube lies opposite the lateral aspect of the choana behind the posterior end of the inferior turbinate. It is partially protected from nasal airflow. This location makes blind cannulation of the tube challenging.

At the skull base, the cartilaginous tube is fixed superiorly to a shallow depression in the bone of the greater wing of the sphenoid (sulcus tubarius). Laterally, it is held in place by the medial pterygoid plate. This base of support prevents vertical and rotational movement of the pliable cartilage during opening. The angle the tube forms with the Frankfort horizontal plane has previously been estimated in infants and children, using gross anatomic measurements, to be approximately 10 degrees. As the skull and midface expand vertically, and the hard and soft palates descend, this angle increases to 45 degrees in adults.[3] Imaging studies have revealed these angles in a Japanese population to

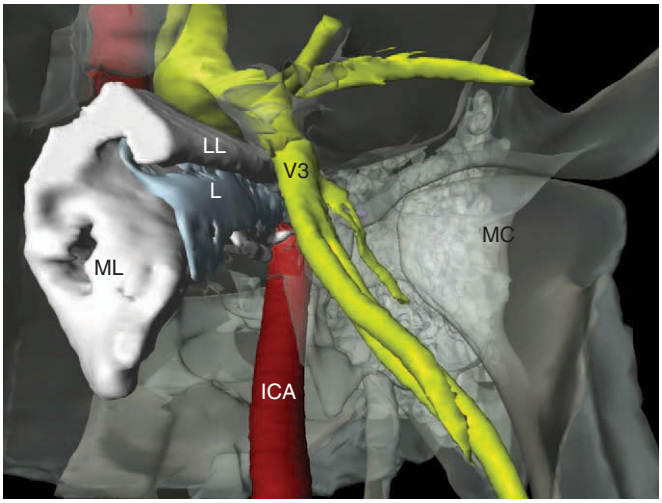

Figure 131-5. Anterior view of the left eustachian tube showing the shape of the cartilaginous laminae. ICA, internal carotid artery; L, air in tubal lumen; LL, lateral cartilaginous lamina; MC, mandibular condyle; ML, medial cartilaginous lamina; V3, mandibular division trigeminal nerve. *(Courtesy of Michael Teixido, MD, Mads Sorensen, and Haobing Wang.)*

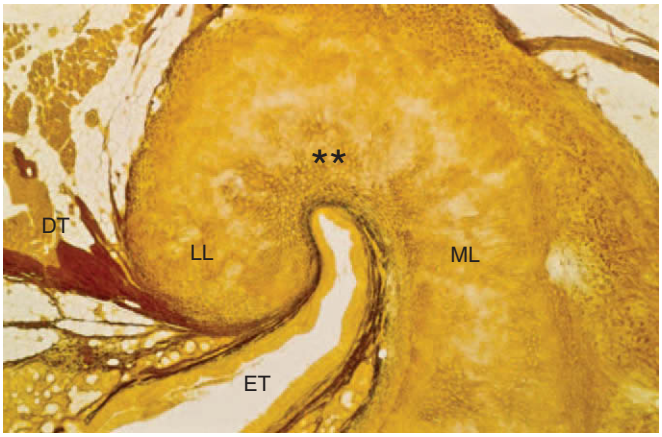

Figure 131-6. Weigert's elastin stain of cross section through the midcartilaginous portion of the eustachian tube. Note the rich, mesh-like distribution of elastin in the hinge region (**) and the attachment of the dilator tubae muscle (DT) (which is the medial bundle of the tensor veli palatini muscle) to the free edge of the lateral lamina (LL). ET, eustachian tube lumen; ML, medial lamina. *Top,* Superior. *Right,* Medial. *(From Matsune S, Sando I, Takahashi H. Elastin at the hinge portion of the Eustachian tube cartilage in specimens from normal subjects and those with cleft palate.* Ann Otol Rhinol Otolaryngol. *1992;101:163-167.)*

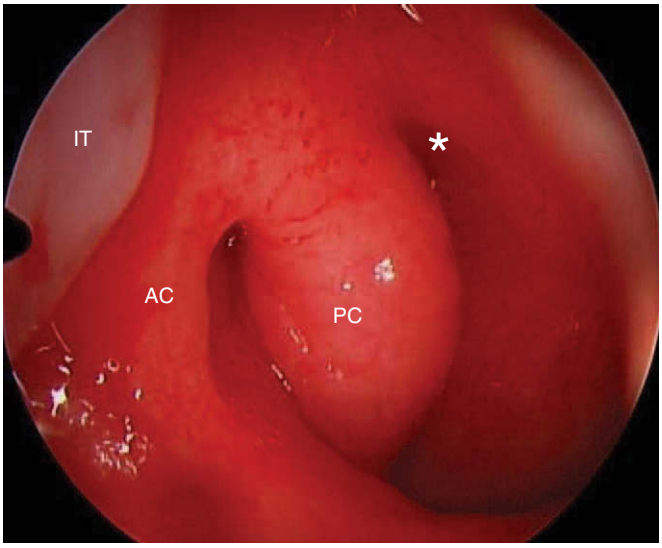

Figure 131-7. Endoscopic view of right torus tubarius. The anterior cushion (AC) lies posterior to the inferior turbinate (IT). PC, posterior cushion. *, fossa of Rosenmüller. *(Courtesy of James S. Reilly, MD, and Douglas Leventhal, MD.)*

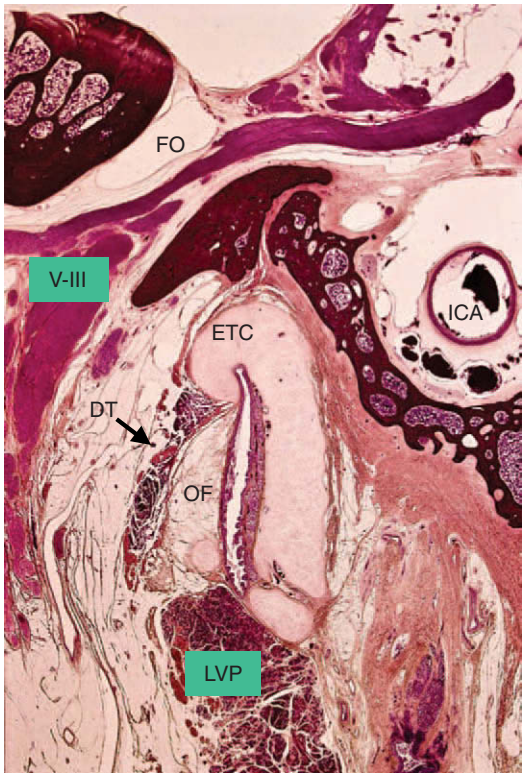

Figure 131-8. Photomicrograph of the cartilaginous portion of the eustachian tube showing the relationship of the dilatory muscles. Ostmann's fatty tissue (OF) is located principally between the dilator tubae portion of the tensor veli palatini muscle (DT) and the lumen of the eustachian tube. The mandibular division of the trigeminal nerve (V-III) can be seen coursing through the foramen ovale (FO). ETC, eustachian tube cartilage; ICA, internal carotid artery; LVP, levator veli palatini muscle. *Top,* Superior. *Right,* Medial. *(From Sando I, Ikui A, Sudo M. Microscopic sectional anatomy with 3-D reconstruction of the temporal bone. In: Janecks IP, Tiedemann K, eds.* Skull Base Surgery, Anatomy, Biology, and Technology. *Philadelphia: Lippincott-Raven; 1997:151-159.)*

be approximately 20 degrees in infants and children and 27 degrees in adults, with adult angles reached at approximately 7 years of age.[31]

The adenoid pad occupies the area between the nasopharyngeal openings of the tubes. A depressed space medial to each torus forms the fossa of Rosenmüller, an area of particular interest in the diagnosis of nasopharyngeal carcinoma (Fig. 131-7). This fossa extends posterolaterally and superiorly to the area behind the midportion of the tube. The distance between the deepest part of the fossa and petrous apex was found to be only 4 mm.[32] Above this lies the foramen lacerum, a hiatus between the sphenoid and petrous bones, through which nasopharyngeal tumors may spread intracranially.

The muscles that allow for opening of the cartilaginous tube are arranged in a complex fashion. The principal and perhaps only dilator of the tube is the tensor TVP. It is composed predominantly of fast-twitch muscle fibers, but also contains slow-twitch fibers to maintain tone.[18] This muscle has several distinct segments. The main body of the muscle originates in the base of the skull at the angular spine of the sphenoid and the scaphoid fossa at the root of the medial pterygoid plate. It progresses in a lateral and anteroinferior direction to curve around the hook of the hamulus.[15] As it becomes tendinous, it fans out to insert into the aponeurosis of the soft palate and posterior edge of the hard palate. Secondary attachments in the maxillary tuber and the palatoglossal arch may be important in preserving muscle function after infraction of the hamulus during cleft palate repair surgery.[33]

The TVP is said to have three anchoring points on which it isometrically contracts: the pterygoid hamulus, Ostmann's fat pad, and the medial pterygoid muscle (Fig. 131-8).[34] The fibers roughly parallel the plane of the lateral lamina of the cartilaginous tube. An additional segment of the TVP originates from the area of the hamulus and projects more perpendicularly to this plane. It attaches to the short lateral lamina of the cartilaginous tube and to a condensation of connective tissue lateral to the tubal wall and a portion of Ostmann's fat pad.[35,36] This segment has been termed the DT and may be a separate muscle.

The TVP also is prolonged superomedially to form the muscle belly of the tensor tympani. The TVP continues in a posteromedial direction through the semicanal to emerge into the middle ear cleft through the cochleariform process; in middle ear surgery, this serves as a convenient marker for the first genu of the facial nerve in its tympanic segment. The tendon of the TT attaches to the medial aspect of the

handle of the malleus. Occasionally, this tendon must be divided to release the malleus during ossiculoplasty. Spasm of the TT can create a fluttering of the tympanic membrane and a "popping" tinnitus; this produces characteristic oscillations on open bridge tympanometric measurements. Although division of the TT tendon can relieve this condition, the otologist must be aware that the stapedius muscle may also be responsible.

Less important dilators of the cartilaginous tube include the levator veli palatini (LVP) and the salpingopharyngeus muscles. The LVP originates from the petrous apex. Here it lies medial to the tube, but its anterior segment is immediately inferior to the floor of the tube, separated by connective and fatty tissue.[15,16] It inserts in a radiating fashion into the nasal surface of the soft palate. The LVP has been observed to facilitate tubal opening by elevating the floor of the tube and moving the medial lamina toward the midline during contraction. The salpingopharyngeus attaches to the edge of the cartilaginous tube medially and is directed inferolaterally. Its role in tubal function remains speculative. Swallowing, yawning, and clenching teeth may activate all these muscles.[37]

The histology of the tubal lumen is vital to its action. The bony canal is lined by a prolongation of the low cuboidal, ciliated mucosa of the middle ear. After the junctional region is passed, the mucosa transitions to pseudostratified, ciliated, columnar epithelium identical to the epithelium lining the upper respiratory tract.[38] The density of ciliated and goblet cells gradually increases in a distal and inferior direction.[39,40] Within the cartilaginous tube, the floor of the triangular-shaped lumen is different than the walls. The floor contains an abundance of mucus-producing goblet cells and is heavily rugated; in the upper half of the tube, the walls contain far fewer goblet cells and are generally smooth. It has been suggested that the lower half of the tube is principally involved with clearance of the mucociliary blanket, whereas the upper half is important to pressure equalization and gas exchange.[15]

Mucosa-associated lymphoid tissue is found submucosally throughout the eustachian tube and is particularly prominent around the inferior half of the cartilaginous tube.[41] This tissue may be a factor in luminal obstruction when inflamed. The lateral mucosal wall is bounded laterally by a collection of adipose tissue termed Ostmann's fat pad.[42,43] This tissue represents one segment of a collection of adipose tissue around the tube and is in the shape of a cone with the base anterior. During conditions of metabolic stress, loss of this fat results in an abnormally patulous eustachian tube.

The arterial supply to the osseous tube consists of a branch of the accessory meningeal artery called the tubal artery and the caroticotympanic arteries arising from the internal carotid artery. The superior tympanic artery, which originates from the middle meningeal artery, supplies the TT. The deep auricular and pharyngeal arteries from the internal maxillary artery, the ascending palatine artery, and the ascending pharyngeal artery supply the cartilaginous tube. The venous drainage generally parallels the arterial supply with the pterygoid venous plexus of particular importance.[44,45] Manipulation and air insufflations of the eustachian tube can result in intracranial complications owing to intracranial venous anastomoses, proximity of the internal carotid artery, and potential osseous dehiscence of the skull base.[46-50]

Physiology

The proper and efficient functioning of the eustachian tube is vital to the health of the ear. The tube is said to have several functions related to the middle ear, including pressure equalization, mucociliary clearance and "drainage," and protection from the influences of the nasopharyngeal environment and loud sounds. Understanding of tubal function and the ability to measure its function accurately continues to evolve.

Pressure Equalization

In its resting state, the cartilaginous tube is closed at its nasopharyngeal orifice. As pressure external to the middle ear cleft changes with fluctuations in atmospheric pressure and during nonphysiologic pressure alterations (e.g., airplane flight, diving in water), it must open to equalize middle ear pressure to ambient pressure. This opening allows for a state conducive to efficient sound conduction through the tympanic membrane and ossicular chain. This pressure equilibration is also accomplished by bidirectional gas exchange and transudation of fluid.[51]

During swallowing, the muscles that dilate the eustachian tube are activated; this occurs during a pause in respiration in the expiratory phase.[51] As the soft palate is elevated and seals the nasopharynx, the TVP isometrically contracts providing a base of support for the DT. This muscle pulls on the lateral lamina and the connective tissue lateral to the tube. The superior half of the tube is typically C-shaped at rest. With lateral movement of the lateral lamina, owing to the hinge action between the laminae where the elastin fibers are in abundance, it becomes more circular in cross section.[3,14,52] The medial lamella remains relatively rigid, and the sequence of muscular contraction allows for concerted tubal opening and flow of gas. Because the cartilaginous tube extends slightly into the osseous tube between the semicanal of the TT and the tubal lumen, there is no crimping of the tube during dilation. Other mechanisms that can initiate tubal opening include yawning, sneezing, and, in some patients, forced pressurization by swallowing with a closed glottis (Toynbee maneuver) or with insufflations of air (politzerization).

Slow-motion videoendoscopy has revealed four steps in tubal opening: (1) palatal elevation with medial movement of the lateral pharyngeal wall and medial rotation of the medial lamina (initiation of opening of the distal cartilaginous tube presumably by the LVP), (2) lateral movement of the lateral wall with dilation of the orifice laterally and vertically, (3) propagation of dilation of the tubal lumen from distal to proximal by the TVP/DT, and (4) opening of the proximal cartilaginous tube adjacent to the junctional region with formation of a round to crescent-shaped lumen.[53] During this event, the tube remains open for 0.3 to 0.5 second, but is open much longer during yawning.[51] In normal individuals, the eustachian tube fully opens once or twice hourly.[54]

To be fully opened, the dilatory muscles must overcome the intraluminal surface tension generated by the apposition of the mucosal surfaces. Surfactant protein B, similar to that obtained in bronchoalveolar lavage, has been identified in the secretory granules of surface cells lining the eustachian tube. The ability of surfactant to reduce the opening pressure in the eustachian tube has been shown experimentally.[55-58] The surface tension in the normal eustachian tube is typically 58 mN/m, but is elevated in serous and mucoid otitis media.[56,59] Tubal surface tension is also influenced by the amount and composition of tubal secretion. This is under control of the autonomic nervous system, and increased parasympathetic transmission has been shown to impair tubal opening.[60]

Tubal closure depends on adhesion of the intraluminal mucous blanket, elastic forces of the supporting tissues, and hydrostatic pressure of venous blood.[51] The position of Ostmann's fatty tissue in the posterolateral half of the tube enables it to assist in restoring the tube to its closed position.[61]

According to the classic theory of eustachian tube dysfunction suggested by Politzer in the 19th century, the gas contained in the middle ear/mastoid system tends to be absorbed into the bloodstream by the capillaries of the middle ear/mastoid mucosa when the tube is hermetically sealed.[62] This was termed the "hydrops ex-vacuo" model. Although under normal conditions the middle ear maintains a very slight negative pressure a few millimeters of H_2O lower than the nasopharynx, unless the tube periodically opens, the absorption of gas would result in a large negative pressure differential.[63] Mechanical obstruction of the tube or impaired opening of the tube predisposes to middle ear pathology. In histologic specimens of patients with otitis media, the cross-sectional area of the tubal lumen tends to be smaller than in patients without otitis media, particularly in the osseous portion.[64] This is due to a combination of submucosal inflammatory infiltrates and an increased density and hyperplasia of goblet cells.[65]

The continuity of the middle ear cleft to the volume of gas in the mastoid air cell system is likely to be important in pressure equalization. Bluestone and colleagues[66] described a "flask" model in which the volume supplied by the mastoid air cell system acts as a buffer protecting against abrupt pressure changes and reflux of nasopharyngeal secretions into the middle ear. A well-developed mastoid air cell system facilitates maintenance of normal middle ear pressure, although the

mastoid mucosa is unlikely to be important in gas exchange because of its paucity of submucosal blood vessels. More likely, the mastoid mucosa acts as a simple pressure reservoir according to Boyle's law.[67] The mastoid air cell system is often found to be hypoplastic in patients with chronic ear disease, although it has not been determined whether this is a result of or a contributor to this disease.[68,69]

Bidirectional gas exchange in the middle ear also facilitates maintenance of ambient pressure. The gas composition of the middle ear is similar to venous blood. This similar composition reflects a bidirectional exchange in middle ear homeostasis; otherwise, the gas composition would more closely resemble air. Under conditions of mucosal inflammation, this process is disturbed. Dilation of the mucosal vessels leads to increased perfusion. Nitrogen clearance into the blood may exceed the rate that may be balanced by eustachian tube ventilation. A vacuum is created, and, at negative pressures less than 100 mm H_2O, it is possible to develop a transudation of serum in the middle ear.[67]

Proponents of the "classic" theory of eustachian tube function have focused on the opening capability of the tube; however, other investigators have suggested that a failure of closure of the eustachian tube under normal physiologic conditions is to blame for middle ear pathology.[51] Experimental observations show that middle ear tympanometric pressures are positive after sleep or time spent in the supine position, and cannulation of the eustachian tube in an animal model leads to an egress of gas from the middle ear. Specifically, carbon dioxide preferentially diffuses from the bloodstream into the middle ear, and nitrogen contained in air is sequestered in the middle ear because of its slow diffusion into the bloodstream. Hypoventilation with increasing serum carbon dioxide levels (during sleep) can lead to a positive middle ear pressure that moves to a slight negative gradient when the person is erect and breathing normally. Based on this observation and others that in most cases of otitis media the eustachian tube is not found to be physically obstructed, otitic conditions may reflect an abnormally compliant eustachian tube. With sniffing, the tube would be susceptible to opening, and evacuation of the middle ear gas would produce negative pressure.[51,70]

Mucociliary Clearance and Drainage

Clearance of the middle ear cleft depends on programmed movement of the mucous blanket out of the eustachian tube. The middle ear mucosa and respiratory epithelium of the tube are covered with cilia that transport the mucous blanket from the tympanic orifice of the tube toward the nasopharynx. The morphology of the cartilaginous tube reflects this function. The dependent floor of the tube involved in clearance is rich in goblet cells and is corrugated; the superior portion of the tube involved with ventilation/pressure equalization is smooth and lacks mucus-producing cells.

Mucus of the tube is composed of a thick, more superficial, gel phase and a thin sol phase. The cilia move in the sol phase with their tips contacting the overlying gel phase, propelling the mucous blanket. Surfactant potentiates the movement of the gel over the sol phase.[56,71,72] Mucins are high-molecular-weight glycoproteins and constitute the major component of the mucous secretions.[73] Nine human mucin genes have been identified, and their expression is epithelium specific. They lubricate the epithelial surface, and trap bacteria and viruses. Mucin genes, particularly *MUC5AC,* have been found to be upregulated in otitis media.[74] The periciliary fluid is provided by serous epithelial cells and a group of integral membrane proteins called aquaporins that facilitate the passage of water through cell membranes.[75]

The tympanic opening of the tube lies above the level of the floor of the hypotympanum. Tube transport is an active process that is not gravity dependent. Material instilled through tympanic membrane perforations in humans and experimentally placed in the middle ear cleft of animals is actively cleared into the nasopharynx.[76-78]

Disturbance of this mechanism leads to a propensity to develop otitis media. This propensity is particularly apparent in conditions such as primary ciliary dyskinesia, in which otitis media is almost universal.[79-81] The viscosity of the mucus, as determined by the ratio of its component materials, is important to ciliary beat frequency. Conditions of hyperviscosity, such as those found in sinusitis, middle ear effusions, and cystic fibrosis, lead to reduction in beat frequency and efficiency of mucociliary clearance.[56,82,83]

Impairment of ciliary action by upper respiratory viruses is intrinsic to the development of otitis media. After viral damage, ciliated cells may take 1 month to regenerate.[84] Bacterial infection also leads to compromise of mucociliary clearance through the release of endotoxins and the stimulation of injurious inflammatory pathways.[85-88] This process disrupts middle ear protection and has been shown experimentally. Nasopharyngeal radiographic tracers enter the middle ear cleft of children with otitis media, but not children who are otologically normal.[76,89] Physiologically, this "reflux" up the eustachian tube is less difficult when the tympanic membrane is perforated because the middle ear and mastoid gas "cushion" is removed.[2]

Middle Ear Protection

In the resting state, the middle ear is protected from the bacterial environment of the nasopharynx by the closed orifice of the cartilaginous tube and innate protective mechanisms present within the tube. This protection is particularly important because the bony portion of the tube remains permanently open.

The middle ear space typically is sterile and has very few immunocompetent cells.[90] It develops an immune response only after inflammation has occurred. When bacterial organisms reach the middle ear space, the cascade of inflammatory events leads to migration of immunocompetent cells (lymphocytes) and antigen-presenting cells (macrophages). Local immunologic mechanisms and normal bacterial flora in the nasopharynx assist in protection from bacterial pathogens. Secretory IgA from the nasopharyngeal immune system and possibly antigen-specific IgA in breast milk reduce nasopharyngeal colonization with pathogens that are typically present, but in small numbers (*Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis*).[91] The ratio of commensal organisms (viridans streptococci) to potential pathogens in a healthy subject is greater than 5 : 1 and helps to down-regulate the spread of the pathogens.[92]

Respiratory viruses can disrupt tube bacteriology. Viruses have been shown to predispose to otitis media by (1) releasing cytokines and inflammatory mediators in the nasopharynx causing tubal dysfunction, (2) increasing nasopharyngeal colonization with bacterial pathogens, and (3) altering the host immune response through immunosuppression of cell-mediated immune response.[93]

Sterility of the middle ear space is also guarded by molecules of innate immunity secreted by the tubal mucosa.[73] Antimicrobial molecules that function through various mechanisms are all actively secreted into the tubal lumen.[73] These include lysozyme (muramidase that creates cell wall disruption), lactoferrin (iron-binding glycoprotein that acts synergistically with immunoglobulins), beta defensins (antimicrobial peptides that increase permeability of cell walls), and colectins (oligomeric polypeptide chains that bind microbial carbohydrates assisting phagocytosis). Additionally, cellular proliferation in the lymphatic tissue associated with the tube (mucosa-associated lymphoid tissue) plays an important role in the local immune response. Lymphocyte trafficking into the middle ear during inflammation has been shown.[90,94]

Surfactant proteins found in the eustachian tube lining may play a more important role in host defense than eustachian tube opening. They are apparently prophagocytic and anti-inflammatory.[56] Surfactant is a mixture of mostly phospholipids and one of four surfactant proteins (surfactant protein A through D) that are tissue-specific.[95] The most abundant surfactant protein in the eustachian tube is SP-A, produced in the tubal floor.[96] The primary role of surfactant protein A seems to be mucosal defense through facilitation of phagocytosis. The principal role of surfactants in antimicrobial defense may be as releasing agents and antiadhesives.[56,97]

Sound protection is also an important function of the eustachian tube. Sound pressure generated by the glottis can reach a high level in the pharynx and oral cavity, and would be transmitted directly through the tube into the middle ear unless the tube remained sealed. The tube also is involved in sound protection from loud noises in the external auditory canal that impinge on the tympanic membrane. It has been

shown experimentally that these sounds lead to a coordinated contraction of the stapedius, TT, TVP, and DT muscles. This muscle contraction causes the middle ear cleft, mastoid, and nasopharynx to form one continuous cavity assisting in dissipation of sound pressure. This muscle contraction also seems to be a generalized response to noxious stimuli.[37,98]

The eustachian tube is involved in sealing the middle ear from nasopharyngeal airflow. The nasopharyngeal orifice of the eustachian tube is directly in the intranasal respiratory stream, but autophony and an audible movement of the tympanic membrane with breathing occur only when the tube is abnormally patulous. In this condition, otoscopy reveals synchronous movement of the tympanic membrane with respiration and swallowing. There is no widely accepted or definitive treatment for a patulous eustachian tube. Therapeutic initiatives have included application of caustics to the torus tubarius to promote tubal closure, section of the TT muscle, occlusion of the osseous tube, and myringotomy tube placement.[99-102] Endoscopic examination of the patulous eustachian tube has revealed a scaphoid defect in the superolateral surface of the orifice of the cartilaginous tube. This area has been termed the "tubal valve," and relief of autophony has been achieved by submucosal graft implantation to restore convexity.[103]

Eustachian Tube Dysfunction

Under nonphysiologic pressure changes, such as ascent or descent in an airplane, hyperbaric oxygen treatment, or diving in water, the function of the eustachian tube is stressed. When the condition change involves a decrease in ambient pressure relative to the middle ear (ascent in an airplane or from a dive), the eustachian tube opens readily, and "overpressurized" middle ear gas passively opens the tube, assisting in active dilation during swallowing. During descent, if the tube is not frequently opened, it may "lock" from increasing negative pressure in the middle ear. This can induce barotrauma with resulting middle ear effusion, with the possibility of hemorrhage (hemotympanum), tympanic membrane rupture, and perilymph fistula. Delayed barotrauma may occur in a diver who descends using pure oxygen because this would be principally concentrated in the middle ear. On ascent, the oxygen diffuses into the circulation more rapidly than it can be replaced by inhaled nitrogen, setting up a middle ear gas deficit and negative pressure.[67]

Tubal opening is adversely affected by the supine position because it results in engorgement of the pterygoid venous plexus and protrusion of the lateral wall of the eustachian tube toward the lumen.[104] This can be a diagnostic clue in a patient with an abnormally patulous tube because typically symptoms are relieved or improved by lying flat. The importance of the peritubal venous system can be dramatically shown in patients receiving hemodialysis. Although they can develop dysfunction of the eustachian tube through ossification of the medial lamina and Ostmann's fat pad, a patulous condition has been noted to develop after hemodialysis, presumably from a decrease in extraluminal hydrostatic pressure.[105,106]

In adults with eustachian tube dysfunction, abnormalities in lateral wall movement have been documented. The most common pathologic finding is mucosal edema of the lateral wall resulting in inadequate lateral excursion. Other observed pathologies include inadequate or abnormal muscular movements and disorganization or absence of the typical dilatory wave.[107] Attempts have been made to correlate the degree of dynamic dysfunction with manometric studies and severity of middle ear disease.[108]

The pathophysiology of otitis media most certainly relates to dysfunction of the eustachian tube and failure of middle ear pressure regulation, despite controversies regarding the exact mechanisms. Middle ear effusions have been produced by viral inoculation of the nasopharynx and paralysis of the tubal muscles.[109-110] Generally, tubal dysfunction can be mechanical from intraluminal (middle ear pathology, inflamed mucosa, polyps) or extraluminal (hypertrophic adenoids, nasopharyngeal neoplasm) blockage, or can be functional (inability to dilate the tube actively).[111] Both mechanisms may coexist and may lead to a relative middle ear negative pressure. Depending on its severity, this negative pressure may result in atelectasis and vasodilation of the tympanic membrane.

Although only a minimal decrease in middle ear pressure has been experimentally measured under these conditions, it is sufficient to produce an effusion. In serous otitis media, this effusion has the characteristics of an inflammatory exudate.[63,112] Over time, nasopharyngeal bacterial contamination of the effusion can result in recurrent acute otitis media. It has been postulated that the mucous produced in this inflammatory state obstructs the lumen of the eustachian tube and is held in place by the negative middle ear pressure. A myringotomy relieves the negative pressure and allows the plug to be propelled into the nasopharynx.[67] Although inflammation progresses from the eustachian tube to the middle ear cleft, and resolution of inflammation follows an opposite course, the degree of mucosal inflammation in the middle ear does not always parallel the degree of inflammation in the lumen of the eustachian tube, and studies have shown that rarely is the eustachian tube completely, intraluminally blocked in otitis media.[111,113-115] Shambaugh and Glasscock[116] have described the clinical appearance of the phases of otitis media: the negative pressure "hyperemic phase" followed by the exudative and suppurative phase. If the tubal function improves, a phase of resolution ensues in which the remaining serous effusion slowly resolves. Persistence of eustachian tube dysfunction can lead to persistent serous effusion (serous otitis media) or proteinaceous concentration in the effusion (mucoid otitis media) with the possibility of irreversible atelectasis, contraction, and adhesion of the tympanum.

Anatomic changes relevant to pressure equalization and middle ear protection occur with aging and likely account for a difference in susceptibility to otitis media. The ability to equilibrate negative middle ear pressure is less efficient in children than adults, and the protective function of the tube seems to be compromised in children.[117,118] The shorter length of the tube, its more horizontal orientation, and relative compliance of the cartilaginous portion allow it to be forced open by nasopharyngeal pressure. The shallower alignment of the tube counteracts gravitational forces and theoretically makes mucociliary clearance less efficient. An infant feeding in the supine position is susceptible to nasopharyngeal pooling and retrograde flow. These anatomic points do not seem to account completely for the susceptibility to otitis media, however. Although the angle and length of the eustachian tube have been found on CT studies to be more horizontal, shorter, and straighter in children than in adults, no differences were found in these parameters between children with and without otitis media.[31]

Other important influences on tubal function and susceptibility to otitis media have been identified, including adenoidal hypertrophy, allergy, sinonasal disease, craniofacial anomalies such as cleft palate and Down syndrome, neoplasm, extraesophageal reflux, and genetic predisposition.[119] Hypertrophic adenoids may extrinsically compress the nasopharyngeal orifice of the tube, and may act as a bacterial reservoir in cases of chronic infection (Fig. 131-9). Hyperplasia of the lateral portion of the adenoid pad adjacent to the torus tubarius seems to be particularly important in this phenomenon.[120] Patients with a large adenoid pad and shallow nasopharynx are predisposed to middle ear effusion and negative middle ear pressure.[121] Adenoidectomy has been shown to improve manometric measures of eustachian tube function and diminish needed myringotomies in children.[122,123] The removal of a source of chronic infection may be more important than direct effects on tubal function.[124] With advancing age, the volume of the adenoid tends to regress, modifying its effect on the patency of the eustachian tube.

Nasal allergy may affect tubal function through mucosal inflammation. Four mechanisms of action have been proposed with varying levels of proof: (1) targeting of middle ear mucosa in the allergic reaction, (2) eustachian tube obstruction by mucosal edema, (3) inflammatory obstruction of the nose and nasopharynx, and (4) insufflation or reflux of allergic nasopharyngeal secretions into the middle ear.[125]

In a patient with cleft palate, persistence of eustachian tube dysfunction and susceptibility to otitis media seem to be related to anomalies in the course and insertion of the TVP and the shape and development of the cartilaginous tube. Anomalies include a poorly developed lateral lamina that does not describe the typical "S" shape with the lateral tubal wall and an abnormal attachment of the TVP to this lamina (Fig. 131-10).[5,20,126] In some patients with cleft palate, the abnormal position of the LVP causes the muscle to occlude rather

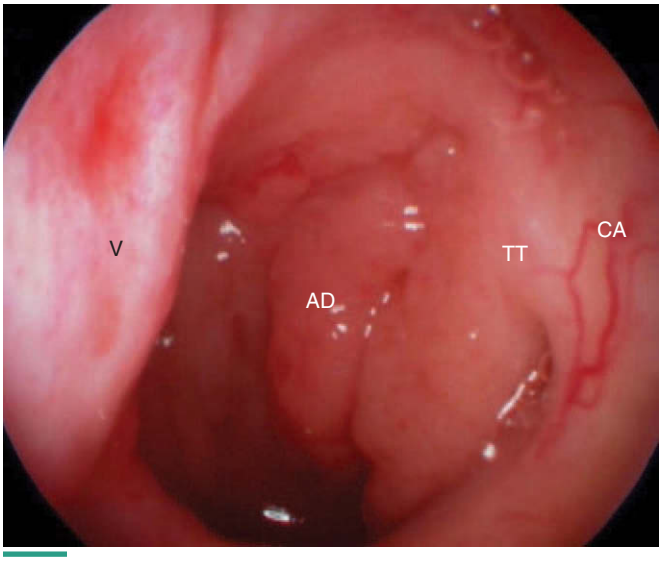

Figure 131-9. Endoscopic view of the left torus tubarius (TT) showing the lateral portion of the adenoid pad (AD). The choanal arcade (CA) is a constant vascular landmark. V, septal vomer. *(Courtesy of Richard Schmidt, MD, and Douglas Leventhal, MD.)*

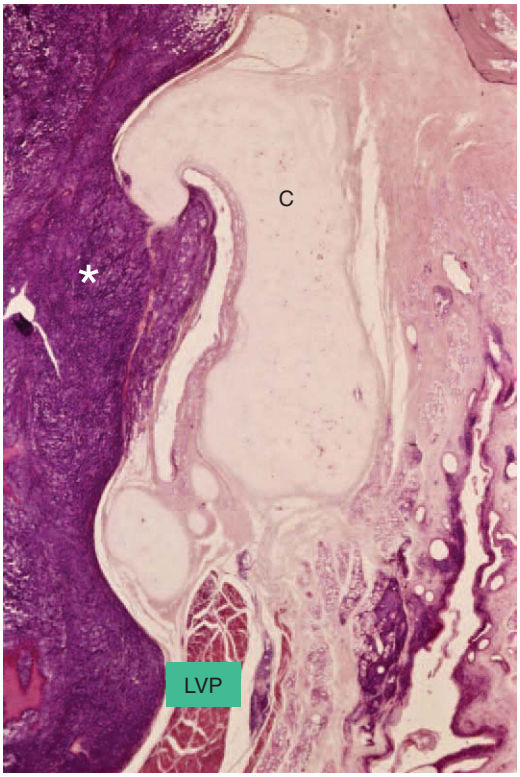

Figure 131-11. Photomicrograph of cross section through the eustachian tube showing invasion and destruction of the tensor veli palatini muscle and dilator tubae muscle by neoplastic cells (*) in a patient with lymphoma involving the temporal bone. C, eustachian tube cartilage; LVP, levator veli palatini muscle. *Top,* Superior. *Right,* Medial. *(From Takahara T, Bluestone CD, Sando I, Myers E. Lymphoma invading the anterior eustachian tube: temporal bone histopathology of functional tubal obstruction.* Ann Otol Rhinol Laryngol. *1986;95:101-105.)*

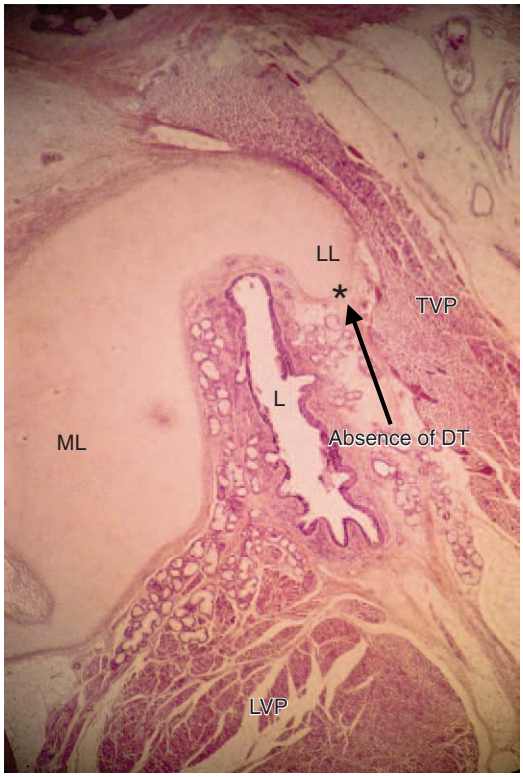

Figure 131-10. Photomicrograph of cross section through the midcartilaginous eustachian tube of a 7-week-old infant with cleft palate. The cross-sectional area of the lateral lamina (LL) is small, and the eustachian tube lumen (L) is slitlike, rather than C-shaped as found in normal specimens. Note the absence of attachment of the dilator tubae muscle (DT) (*). LVP, levator veli palatini muscle; ML, medial lamina; TVP, tensor veli palatini muscle. *Top,* Superior. *Right,* Lateral. *(From Matsune S, Sando I, Takahashi H. Abnormalities of lateral cartilaginous lamina and lumen of eustachian tube in cases of cleft palate.* Ann Otol Rhinol Laryngol. *1991;100:909-913.)*

than open the tube during contraction.[127] Of patients with cleft palate, 96% have middle ear disease, and nearly 50% require more than one set of myringotomy tubes.[128] Tubal dysfunction does not improve with repair of the cleft despite the fact that there is a trend toward improvement with age. Improvements in tubal function after cleft repair seem to be contingent on the integrity of the pterygoid hamulus and the TVP.[34]

In patients with neoplasms of the nasopharynx, eustachian tube function can be disturbed by occlusion of the nasopharyngeal orifice of the tube and, more commonly, by direct invasion of malignant cells into the paratubal muscles causing functional obstruction (Fig. 131-11).[129-131] In either case, unilateral serous otitis media should raise suspicion of a mass lesion in the nasopharynx. Eustachian tube dysfunction and serous otitis media commonly persist after surgical resection and radiation therapy of the nasopharynx.[132,133]

Extraesophageal reflux seems to play a role in the pathophysiology of otitis media through disruption of eustachian tube function. Animal experiments of simulated extraesophageal reflux have produced clinically apparent eustachian tube dysfunction. Additionally, pepsin, a gastric, proteolytic enzyme, has been identified in the middle ear space of patients with otitis media.[134-136]

There apparently is a hereditary component to eustachian tube dysfunction. Racial differences in the prevalence of otitis media have been documented notably in Native American and Inuit populations.[45] In a prospective study of monozygotic and dizygotic same-sex twins and triplets, the correlation of the proportion of time with middle ear effusion between sibs was consistently higher in the monozygotic twins and triplets.[137] It is unclear if the hereditary factors are purely anatomic, such as mastoid pneumatization or eustachian

tube anatomy, or also include intrinsic immunologic protective mechanisms.[138-140]

Assessing Function of the Eustachian Tube

The clinical utility of eustachian tube function tests is currently limited. None are uniformly able to determine the adequacy of tubal function in candidates for surgical closure of a tympanic membrane perforation or to assess the risk of otitis media in candidates for myringotomy tube placement.[141] Perhaps the shortcoming is that these tests involve nonphysiologic conditions.[51] The results of single tubal function tests have been found to have low prognostic value because of pronounced intraindividual variability.[142] Often, "normal" subjects cannot equilibrate middle ear pressure during eustachian tube function, but they do not have signs or symptoms of otologic disease.[143,144]

Generally, tubal function tests are of two types: tests that measure passage of air through the tube, and tests that measure active muscular opening of the tube.[46] Tympanometry is an adjunct measure that determines the flow of acoustic energy through the middle ear system (immitance testing) and indirectly measures eustachian tube function by determining the relative middle ear pressure. Tympanometry can be used during tests of tubal function to determine objectively middle ear pressure changes.

Tests that measure airflow through the tube include inflation and deflation tests. The Politzer test involves placement of a rubber reservoir with a nasal tip into the nostril while occluding the contralateral nostril. When the patient swallows or phonates, with elevation of the palate, air is forced into the nasal cavity. In the Valsalva test, the patient pinches the nose and attempts to exhale with a closed mouth forcing air into the tube.

The Toynbee test is performed similarly, but involves a swallow while the nose is occluded. The Toynbee test is considered positive if an alteration in middle ear pressure is measured by tympanometry before and after the test (in an intact tympanic membrane) or during the test (in a perforated tympanic membrane). An expansion of the Toynbee test that may be performed in an ear with an intact tympanic membrane is the nine-step inflation-deflation tympanometric test developed by Bluestone.[145] This test involves measurements of the patient's ability to equilibrate applied positive and negative pressures with swallowing. It gives useful information about tubal function when positive, although even normal children can have trouble performing the test.[145]

The forced opening test may be performed in a patient with a perforated tympanic membrane and involves placement of positive pressure in the external canal. The pressure is recorded continuously, and the pressure is increased until a sudden decrease occurs when the tube opens ("opening pressure"). In healthy ears, a slight positive pressure remains ("closing pressure"). This test may also be performed with the patient swallowing (forced response test) with the resistance to airflow through the tube measured during the resting condition (passive resistance) and at the moment of swallowing (active resistance).[51]

The active opening of the tube can also be measured by sonotubometry. A constant sound is applied to the nostril, while a microphone in the external auditory canal measures the transmitted sound pressure. The sound levels are measured with the patient swallowing. An increase in sound pressure in the ear canal of 5 dB or more is considered indicative of tubal opening.[146] Advantages of this measure include assessment of tubal function under physiologic conditions without externally applied pressure and the ability to perform it with an intact tympanic membrane. Continuous middle ear pressure measurements can also be performed for long periods, but these require a perforated tympanic membrane and the use of a wearable measuring unit with a stable measuring system.[147]

Treatment of Eustachian Tube Dysfunction

Since Armstrong reintroduced Politzer's concept of myringotomy with insertion of pressure-equalizing tubes, this procedure has become commonplace in the treatment of eustachian tube dysfunction.[148,149] In a systematic review, oral and topical intranasal steroids alone or combined with antibiotics were found to hasten the resolution of otitis media with effusion in the short-term, but there was no evidence of long-term benefit.[150] More recently, surgery targeting mucosal edema impairing function of the cartilaginous tube has been successful. Laser and microdébrider removal of tissue from the "posterior cushion" overlying the medial lamina has been shown to improve tubal function.[151-153] Extreme care must be taken to stay superficial to this lamina, however, to prevent injury to the underlying carotid artery.

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CHAPTER ONE HUNDRED AND THIRTY-TWO

Neural Plasticity in Otology

Robert V. Harrison

Key Points

- Neural plasticity underlies many clinical events in otolaryngology. Adaptation to a vestibular insult, rehabilitation after hearing loss, and auditory learning after a cochlear implant all are mediated by "neural rewiring."
- In the studies described, changes to the pattern of peripheral input in the auditory system always have an effect on central neural organization. Cochlear hearing loss does not imply simply cochlear dysfunction, but a change in the whole ascending auditory pathway up to and including cerebral cortex. After a period of deafness, many functional and structural changes occur in the auditory brain. In part, these can be reversed by stimulation with a hearing aid or cochlear implant.
- Neural plasticity is age-related. Maximum change or compensation can be expected in early development. For interventions such as a cochlear implant or hearing aid for a congenitally deaf child, the earlier the intervention is applied, the better. This imperative requires the early detection and diagnosis of hearing loss, such as afforded by universal neonatal hearing screening.

For centuries, much has been known about neural plasticity, but that precise term has not always been used to describe the phenomenon. Otologists have observed recovery of vestibular and auditory function after inner ear insult, calling these processes "adaptation" or "rehabilitation." Clinicians have observed the significant progress achieved in speech understanding and language development in hearing-impaired children fitted with an auditory prosthesis. This process has simply been called learning to hear.

It has been recognized for a long time that whatever the lesion or disease, a recovery of function is better achieved in infants than in adults. Otologists now use terms such as "age-related plasticity" and "critical period" to express the notion that, during early development, neural plasticity is greater and has more potential than in a more mature brain. Many examples also exist of how the adult brain maintains a high degree of neural plasticity; this is manifest in the learning and memory mechanisms that humans have throughout life. What is most different between the developing brain and the mature brain is, however, the ability of the former to recover function after serious lesions or sensory deficits.

Increased awareness about neural plasticity has been fueled by many basic science experiments, which have illustrated clearly how the neural networks in the brain reorganize after various manipulations of sensory input. This body of work has been paralleled by even more basic level studies on the neuronal and synaptic mechanisms that can mediate the plastic changes. Scientific reductionism has not stopped there, for we now enter the era of genomics, which promises to explain, among other things, how genes control neurotransmitter synthesis and secretion from presynaptic sites, and the synthesis and distribution of ion channels of the postsynaptic cell membrane. In this chapter, we do not consider mechanisms at this molecular level of organization; the focus is on cellular and systems level physiology.

In this chapter, we review some examples of neural plasticity as they pertain to the auditory system. These examples are laboratory experiments and clinical studies that illustrate neural plasticity at work. For the most part, we concentrate on the auditory system. This system, following perhaps in the wake of pioneering studies in visual and somatosensory systems, has provided much direct knowledge about the neurophysiology of plasticity. This chapter does not specifically consider the plasticity in the vestibular system. Plastic change in this system, as manifest in the recovery of balance function after peripheral lesions, is well known to clinicians, and there is extensive literature on the plasticity of the vestibular ocular reflex in human and animal experiments. Although we do not consider these in detail, behind the specialized complexity of all sensory organs there lies a brain, whose neural elements tend to follow similar rules, independent of their source of excitatory input. In this sense, the examples of auditory system plasticity given in the following sections and the discussion of basic mechanisms are as relevant to the vestibular system as they are to any other sensory system.

In the following sections, we carefully define what we mean by plastic change in otology. We discuss different types of plasticity and introduce the important distinction between developmental plasticity and adult plasticity. We then consider in detail experimental studies that serve to illustrate key aspects of plasticity in the auditory system. This is followed by a review of some important underlying mechanisms of plasticity. We consider these mechanisms at a systems physiology level, and at more basic cellular and subcellular levels. The review is far from exhaustive, and can be supplemented by other key studies[1-8] and the more comprehensive textbooks listed under Suggested Readings. In the final section, we discuss what this new knowledge about sensory system plasticity means to the otologist or hearing health care professional.

Definition of Plasticity

A broad definition of *plasticity,* as it pertains to otology, is the inherent ability of the auditory (or vestibular) system to modify or reorganize. The term "plasticity" is used to cover a wide spectrum of phenomena, and it can mean different things to different people. Consider the variety of experimental methods that have been used to reveal plastic change in the auditory system. Various anatomic studies have established that plasticity relates to physical change in the brain. Some of the earliest observations made, including the pioneering work of Levi-Montalcini,[9] were of the anatomic changes to auditory pathways after experimental lesions to the inner ear. In such studies, cell counts, axonal pathway changes, and alterations to neural structure were observed to

follow partial or total auditory deafferentation. Further examples of anatomic studies of plasticity in the auditory system are given in a subsequent section.

The research literature also contains many physiologic studies in which short-term or long-term change in central auditory system function has been observed after experimental manipulations to auditory input. In this chapter, many of these studies are presented in detail. The methods for the evaluation of plasticity of auditory function include various electrophysiologic studies in animal models (see later sections) and in humans,[10,11] and functional neuroimaging methodologies. The latter include positron emission tomography, functional magnetic resonance imaging, and magnetoencephalographic studies.[12,13]

Finally, myriad behavioral studies have monitored hearing performance change after some manipulation of auditory input. These studies range from systematic, well-controlled psychophysical experiments, to clinical outcome studies, to simple post-treatment observations of patients. In regard to this last category, any clinician who has noted an improved sensory function, over time, in a patient with a hearing (or vestibular) loss, or a performance change after some intervention, has observed neural plasticity in action.

Time Course of Plastic Change

The term "plasticity" is currently used in auditory neuroscience to describe phenomena that differ considerably in their time courses. Plasticity is used to describe changes to the auditory system occurring very rapidly, over a span measured in minutes, and much longer term changes over weeks, months, and years. As an example of acute plasticity, auditory neuron receptive fields (excitatory and inhibitory frequency tuning curves) have been observed to change within 10 minutes after induction of cochlear lesions or partial deafferentation.[14,15] It is reasonable to suppose that short-term plastic change reflects small-scale neural alterations, with subtle synaptic modifications to existing neural networks. With such acute observations, initial stages of plastic change may have occurred, but it is unclear whether these changes would be consolidated in the longer term (see the section on basic mechanisms of plastic change).

More extensive auditory system reorganization seems to occur over a longer time course. Numerous studies show a modification of central tonotopic mapping as a result of cochlear lesions or partial deafferentation.[16-21] In these studies, the time course of plastic change apparently is completed over many weeks. In such cases, underlying synaptic strengthening seems to be consolidated. Sometimes very extensive reorganization is observed, which suggests that long-term processes, such as new axonal growth and synaptogenesis, have occurred. To use a computer analogy, short-term plasticity might be considered to be software changes, whereas long-term changes might also include hardwiring modifications.

Age-Related Plasticity

Perhaps the most important factor to consider when reviewing studies relating to plasticity is the age, or rather the developmental state, of the subject. As shown in subsequent examples, reorganization of tonotopic maps after cochlear lesions is significantly different when experimental manipulation is done in the neonate compared with the adult animal. There are numerous other examples of age-related plasticity in the auditory system. Perhaps the most familiar to the otologist is the performance of a congenitally deaf child provided with a cochlear implant at an early age compared with a deaf child implanted at a much later age.[22] Studies such as this and other clinically related aspects of auditory system plasticity are explored in the final section of this chapter, where we consider what all this new knowledge about plasticity means to the practitioner.

Experiments Showing Plastic Change in Otology

Over the past few decades, a large body of experimental evidence has accumulated showing that the central auditory brain develops and is maintained under the influence of the patterns of neural excitation that originate at the ears. It is definitely not the case that we have a central auditory nervous system and independent inner ear sensory organs. Not only does the cochlea send acoustically related signals to the central system, but also these activity patterns seem to promote initially the development and then the maintenance of the central system. The functions of the periphery and central components are intimately linked, and this is most evident during an early developmental period, when alterations of central neural wiring patterns can result from abnormal sensory input.

Historical Background

Two pioneering studies drew attention to the notion that early sensory input has a crucial role in central brain development. These two experiments paved the way for many modern studies of sensory brain plasticity. The seminal study was in the developing chick auditory system by Levi-Montalcini,[9] who documented the anatomic changes to central auditory pathways after the otocyst of the chick embryo was removed or damaged. In later, seemingly unrelated studies, Wiesel and Hubel[23,24] showed that visual cortical wiring responsible for ocular dominance columns is disrupted in cats if, during an early postnatal period, the animals have had visual input from one eye only (i.e., after neonatal monocular deprivation).

These seminal experiments were followed by many others in visual, somatosensory, vestibular, and auditory systems. In otologic research, numerous studies revealed the considerable anatomic changes that result from neonatal ablation of one cochlea. These changes include loss, or pathologic change, to neurons in brainstem and midbrain,[25-27] and, importantly, the formation of novel innervation patterns, particularly from the cochlear nucleus on the normal side to more central nuclei.[28,29]

From a clinical perspective, such unilateral ablation studies highlight the importance of bilateral input during early development, and, by extrapolation, a balanced input from both ears. This is an important "normal condition" for auditory development. One could speculate that central auditory development could be more normal with a symmetric, mild to moderate sensorineural hearing impairment than with a very asymmetric loss.

Other relevant studies were made in other sensory systems. The visual experiments by Wiesel and Hubel[23,24] have already been mentioned. In addition, work in the somatosensory system pointed the way to analogous experiments in the auditory system. The reorganization of somatosensory maps in cortex after damage or partial deafferentation of the sensory inputs was initially shown after whisker removal in young rodents,[30] and after peripheral nerve damage or digit removal in developing and adult animals.[31-33] These experiments were significant because they noted reorganization of the cortical somatotopic maps, which can be considered, as Merzenich and associates[32] would say, the "mainline functional organization" of this sensory system. These studies also showed that deafferented cortical areas (i.e., no longer receiving input from the periphery) become connected to areas corresponding to the border of the peripheral lesion. In terms of cortical space, these border areas become overrepresented. As discussed in the following sections, there are considerable similarities between the somatosensory data and data from analogous experiments in the auditory system.

Reorganization of Central Tonotopic Maps after Cochlear Lesions

The main experimental studies I have chosen to illustrate "plastic change in otology" are those in which central tonotopic map reorganization occurs after lesions are made to the cochlea. These experiments show how peripheral activity patterns can influence the establishment and maintenance of central frequency maps. Analogous to the central somatotopic projections mentioned previously, tonotopic maps can be considered the mainline organizational feature of the auditory system. In the auditory system, the topographic order of afferent neurons is well maintained from the sensory epithelium of the cochlea up to the cortex.[34,35] Strictly speaking, we should refer to this projection system as "cochleotopic," analogous to the similarly organized retinotopic visual system and the somatotopic pathways of the somatosensory system. The interchangeability of "cochleotopic" and "tonotopic" is possible because of the place coding of sound frequency along the

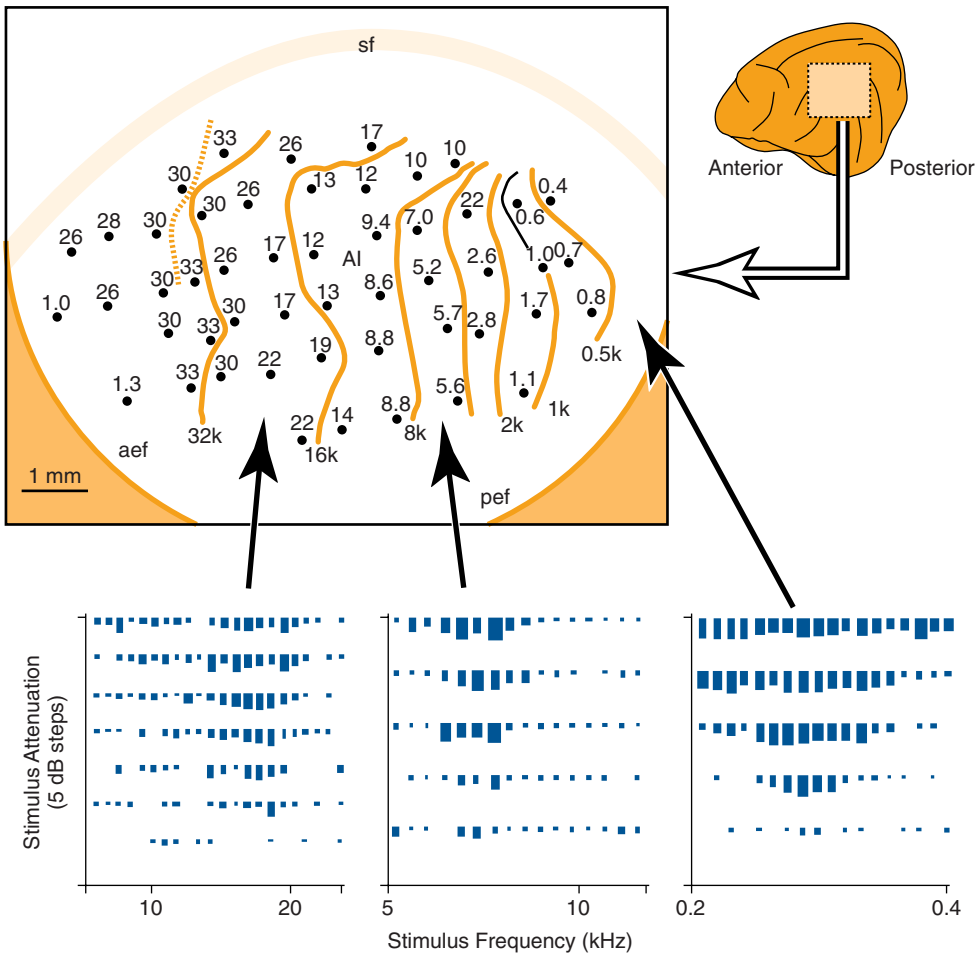

Figure 132-1. Tonotopic map in normal cat auditory cortex (AI) as determined by multiple microelectrode recordings. At each indicated electrode position, the frequency tuning of neural units is determined from receptive field raster plots as indicated (*lower panels,* three example neurons). The best frequency of response, or characteristic frequency, is indicated on the tonotopic map in kHz. Isofrequency contours shown are at octave intervals. aef, anterior ectosylvian fissure; pef, posterior ectosylvian fissure; sf, sylvian fissure. *(Adapted from Harrison RV, Nagasawa A, Smith DW, et al. Reorganization of auditory cortex after neonatal high frequency cochlear hearing loss.* Hear Res. *1991;54:11-19.)*

cochlear length. Some caution is advised, however, on the interchangeability of these terms when considering systems having pathologic cochleas; under such conditions, considerable distortion of the normal place coding of sound frequency is possible.

To set the scene for the experimental studies that follow, let us consider the normal cochleotopic (tonotopic) mapping at the level of the auditory midbrain and cortex. Figure 132-1 shows a tonotopic map in the primary auditory cortex of a cat, as determined by recording from cortical neurons at several sites.[18] Each data point indicates the microelectrode recording site, and the sound frequency to which neurons respond best is indicated in kilohertz. The lower panels of Figure 132-1 indicate how the response of (three) individual neurons is analyzed. Each raster shows the response (spike count) to stimuli of different frequency and intensity combinations. The isofrequency contours that are drawn through the cortical map are plotted at octave intervals. Similar microelectrode recording techniques were used to determine tonotopic maps in the inferior colliculus of the midbrain. Such a map from a normal chinchilla is shown in Figure 132-2A.[16]

Tonotopic Map Reorganization in a Developmental Model

Figure 132-3 shows two examples of cortical tonotopic maps in cats treated shortly after birth with the ototoxic aminoglycoside amikacin.[18] This treatment resulted in basal cochlear hair cell lesions. Amikacin was given systemically, and cochlear lesions were bilaterally symmetric. Histologic evaluation in subject A showed that the basal region of the cochlea was totally damaged (inner and outer hair cell loss), but in more apical areas, above the 6- to 8-kHz region, a normal sensory epithelium was present. This is consistent with the auditory brainstem response (ABR)–derived audiogram showing normal tone pip evoked ABR thresholds up to the high-frequency cutoff slope. The cortical tonotopic map for this subject is characterized by a normal representation of low frequencies, but the cortical region that has been deprived of normal input by the partial cochlear deafferentation now contains neurons that are all tuned to 6 to 8 kHz (shown as the shaded area). The boundary region of the cochlear lesion is abnormally overrepresented in terms of cortical space.

In subject B (see Fig. 132-3B), the results are more revealing. In this kitten, the cochlear lesion was more extensive, with a severe basal lesion, but also with scattered hair cell loss up to apical regions. This is reflected in the ABR audiogram that gradually slopes down across all frequencies measured. This kitten also developed a cortical frequency map in which there was a very large isofrequency area (shown as a shaded area) where all neurons have common 6.6-kHz frequency tuning. In addition, the low-frequency region of the tonotopic map is severely distorted compared with normal (compare with Fig. 132-1). It seems that a reduced or abnormal stimulus-driven activity pattern from cochlear areas more apical to the main lesion has had an influence on normal map development.

Cortical Frequency Map Reorganization in Adult Subjects

The experimental results shown in Figure 132-3 were from studies in which the cochlear lesions were induced in neonates.[18] Qualitatively,

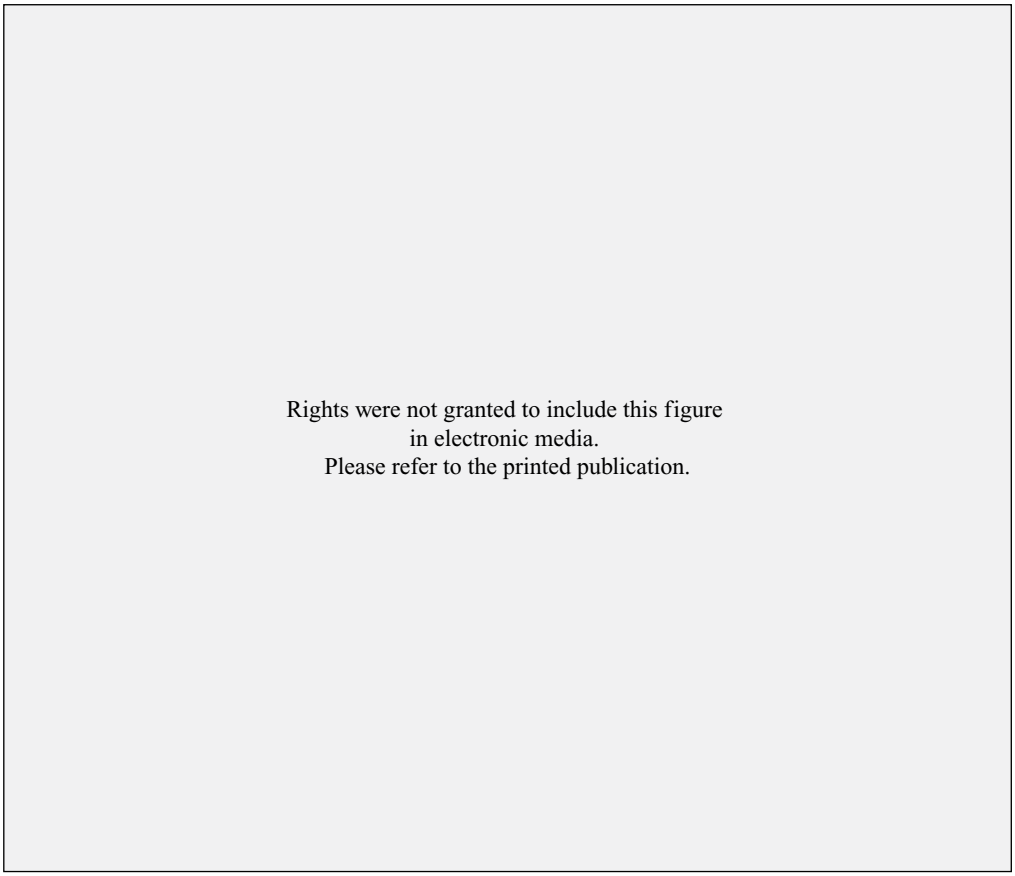

Figure 132-2. Tonotopic maps in the inferior colliculus (central nucleus) of a chinchilla. All maps were derived from single neuron recordings in electrode tracks along the dorsoventral axis of the inferior colliculus as shown. Neuron characteristic frequency was derived from receptive field plots similar to those shown in the cat experiments of Figure 132-1. The *upper graphs* plot neuron characteristic frequency as a function of electrode excursion. The *lower diagrams* represent the tonotopic maps; isofrequency contours are indicated at octave intervals. **A,** Results from a normal adult subject. **B,** In this subject, a basal cochlear lesion was made within days of birth, and the inferior colliculus tonotopic map was derived 4 months later. In the map, the *shaded area* shows the ventral region of the inferior colliculus in which all neurons had a common characteristic frequency. **C,** In this subject, the cochlear lesion was made in the adult animal and was mapped 3 weeks later. *(Adapted from Harrison RV, Ibrahim D, Mount RJ. Plasticity of tonotopic maps in auditory midbrain following partial cochlear damage in the developing chinchilla.* Exp Brain Res. *1998;123:449-460.)*

similar results are also found at the cortical level if the lesions are made in an adult animal. This was initially reported by Robertson and Irvine,[21] who were the first authors to report observations of altered central tonotopic maps resulting from peripheral lesions. Other studies subsequently confirmed these findings in adult animals.[19,20,36]

Figure 132-4 shows results from a chinchilla. Here a normal tonotopic map (Fig. 132-4A) is compared with a map recorded from an adult animal (Fig. 132-4B) with cochlear lesions induced.[19] The anatomic extent of the lesion is shown on the cochleogram, and the corresponding ABR audiogram shows the functional consequences. A typical finding is an overrepresentation of neurons with characteristic frequency of approximately 2.5 to 3.5 kHz (shaded area). In the adult animal, as with the developing subject, neurons in deafferented cortical regions seem to become connected to adjacent noninterrupted ascending input. Similar principles of adult cortical map reorganization are found in somatosensory and visual systems.[2,37,38]

These modifications to cortical frequency maps seem to be the result of neural rewiring, not an experimental artifact. The excitatory receptive fields of neurons tuned to the common frequency are qualitatively similar in shape. They have similar minimum thresholds and bandwidths, independent of where they are located across cortical space. This is an important observation because it argues against the possibility that the common characteristic frequency is an artifact caused by simply truncating all neuronal tuning curves above a certain frequency (corresponding to the lesion boundary along the cochlear sensory epithelium). This possible "pseudoplasticity" (i.e., the appearance of reorganization when there is really none) has been discussed by Kaltenbach and colleagues.[39]

Adult versus Developmental Plasticity of Sensory Systems

The importance of early sensory stimulation in driving the development of the mature brain has been emphasized by many investigators starting with Wiesel and Hubel[23,24] and reinforced by other experiments in various sensory systems.[3,31,40,41] At the level of auditory cortex, there seems to be a pattern of reorganization of tonotopic maps after cochlear lesions induced in the developing neonate similar to that of the adult animal. Intuitively, one might expect considerable differences in the extent of the cortical tonotopic map reorganization in subjects with lesions made in early development compared with lesions made in adulthood. Qualitatively, this seems to be the case,[19] but there have been no careful within-species studies to answer this question specifically. If we explore tonotopic map reorganization in subcortical auditory nuclei, however, there are significant differences in map reorganization after lesion experiments in a developmental model compared with the mature subject. At subcortical levels, we see evidence of age-related plasticity.

Tonotopic Map Reorganization at Subcortical Levels

In cats with cortical map reorganizations similar to those shown in Figure 132-3, Stanton and Harrison[42] injected neural tracers (e.g.,

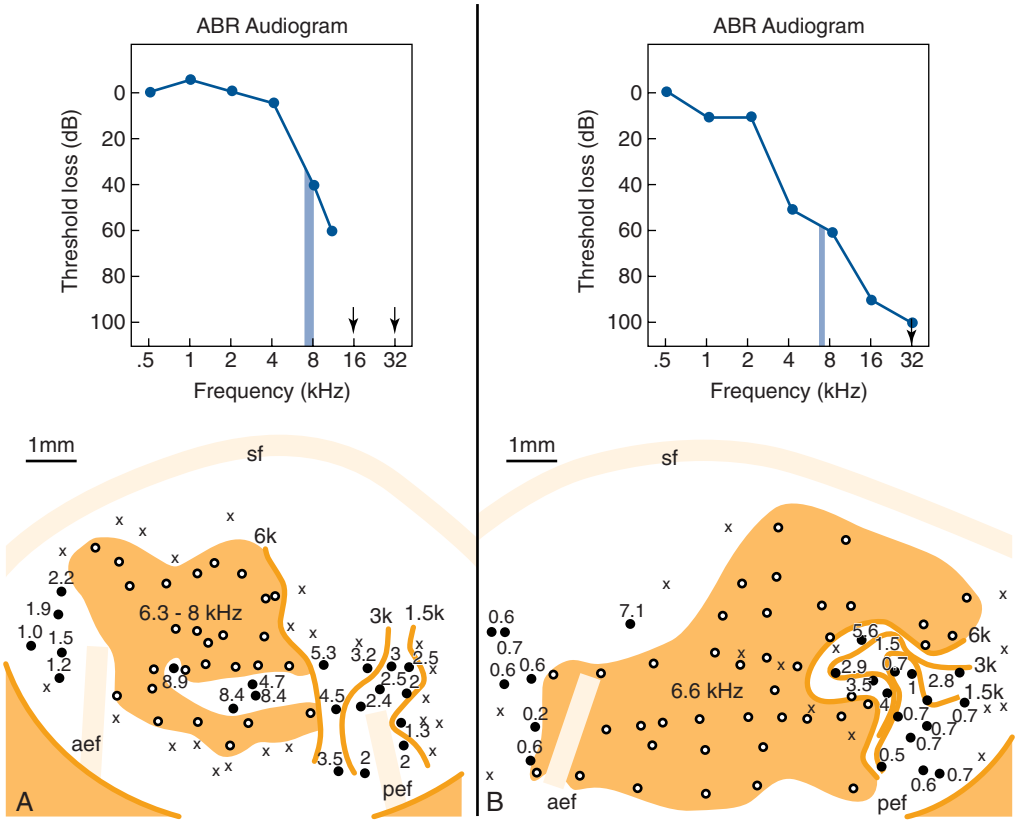

Figure 132-3. Cortical tonotopic maps that developed in two cats with neonatal basal cochlear lesions. The kittens were treated with the ototoxic aminoglycoside amikacin to produce basal lesions to the cochlea. The effects of such lesions are reflected in the auditory brainstem response (ABR)–derived audiograms (*upper panels*). **A,** In this subject, the cochlear lesion was confined to the basal region. **B,** In this subject, hair cell damage was maximal at the cochlear base, but scattered hair cell loss extended up to apical regions. Tonotopic maps are plotted as for Figure 132-1. Isofrequency contours are at octave intervals. *Shading* indicates regions in which all neurons have similar tuning properties. *(Adapted from Harrison RV, Nagasawa A, Smith DW, et al. Reorganization of auditory cortex after neonatal high frequency cochlear hearing loss.* Hear Res. *1991;54:11-19.)*

horseradish peroxidase and fluorogold) into the reorganized, frequency-overrepresented cortical areas, and followed the connections back to the medial geniculate body of the thalamus. They found that the projections were as ordered, (i.e., had the same point-to-point trajectories) as in normal animals. The observed cortical map reorganizations must also be present at the thalamic level. In a developmental plasticity model, cortical frequency map reorganization in large part reflects reorganization occurring at a subcortical level.

More direct evidence for this conclusion comes from studies made at the level of the inferior colliculus. Figure 132-2A shows the normal tonotopic map of the chinchilla inferior colliculus (central nucleus). The orderly progression of the neuron characteristic frequency as the recording electrode is moved through the inferior colliculus is shown in the upper plot. Figure 132-2B shows the result of an experiment in which the inferior colliculus tonotopic organization was determined after a cochlear lesion was made in a neonate.[16,17] The lower plot presents an overview of the results. It shows normal, octave-spaced frequency contours within the inferior colliculus up to the 10-kHz region, then in further, more ventral areas, there is a large region containing identically tuned neurons. The upper plot of the neuron characteristic frequency versus recording electrode position (along the dorsal ventral inferior colliculus axis) clearly shows the grouping of neurons tuned to 10 kHz (arrow in Fig. 132-2B). These results are qualitatively similar to earlier work by Willott[43,44] in inferior colliculus recordings from presbycusic mice.

These studies establish that tonotopic map reorganization occurs at low levels in the auditory pathway after basal cochlear lesions induced in an early postnatal period. Such subcortical reorganization apparently does not occur for similar lesions made in the adult, however. In adults, partial cochlear deafferentation produces no true reorganization at the level of the cochlear nucleus[39,45] or at the midbrain level.[46] Figure 132-2C illustrates the effects of a basal cochlear lesion made in an adult chinchilla, on the tonotopic map in the inferior colliculus. In the adult, there is little evidence of an isofrequency region, which is typical of map reorganization in the developmental model.

The schematic diagram depicted in Figure 132-5 is helpful in summarizing the differences in tonotopic map connectivity in developmental versus adult models. Unless there is future evidence to the contrary, it would seem that the plasticity of subcortical regions (in terms of remodeling tonotopic projections) is possible only during an early developmental period. In adults, such plastic change seems to be confined to the cortex (or perhaps the thalamocortical complex). In this sense, these experimental data exhibit an age-related plasticity in the auditory system. We return to consider in more detail the wiring patterns of Figure 132-5 in the later discussion of basic mechanisms of plasticity.

Tonotopic Map Changes after Long-term Local Excitation of the Cochlea

In the studies outlined so far, in which cochlear lesions (deafferentation) have been induced, the general conclusion is that changes in the pattern of peripheral neural excitation can modify the development or maintenance of central tonotopic projections. What happens if, instead of reducing activity, we locally augment cochlear afferent activity? One such experiment[47] has been reported in which kittens were reared (for many weeks postnatally) in an environment where an 8-kHz acoustic signal was constantly present. To be more accurate, the 8-kHz (± 1 kHz) signal was at a level of 55 to 60 dB. Being suprathreshold, it actually stimulated cochlear neurons across a 7- to 12-kHz range. The 8-kHz tone was frequency modulated (± 1 kHz; at 1 Hz) to

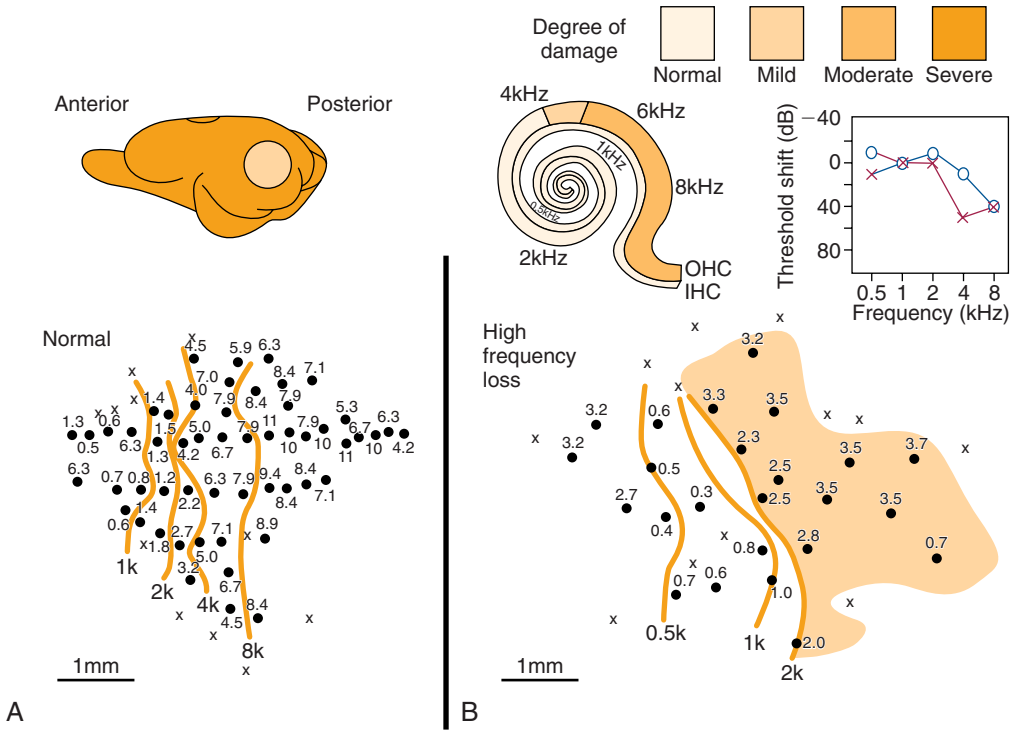

Figure 132-4. Cortical tonotopic maps in a normal adult chinchilla (**A**) and in a subject 4 weeks after making cochlear lesions by amikacin treatment (**B**). Methods for cortical maps were derived with methods similar to those described for Figures 132-1 and 132-3. Isofrequency contours are octave spaced. The peripheral deficit in the treated chinchilla (**B**) is reflected in the cochleogram and in the auditory brainstem response audiogram. The *shaded* area in the abnormal cortical map indicates the regions in which most neurons had very similar tuning properties. IHC, inner hair cell; OHC, outer hair cell. *(Adapted from Kakigi A, Hirakawa H, Mount RJ, et al. Tonotopic mapping in auditory cortex of the adult chinchilla with amikacin-induced cochlear lesions.* Audiology. *2000;39:153-160.)*

circumvent auditory adaptation effects and to avoid cochlear hair cell trauma. Six months after this initial rearing period, cortical tonotopic maps were assessed.

Figure 132-6 summarizes the main result. Compared with normal age-matched control subjects (Fig. 132-6A), the "augmented" kitten (Fig. 132-6B) showed a significant increase in the cortical space devoted to the frequency region extending from 8 to 12 kHz (shaded area in Fig. 132-6B). The ambient sound signal had no obvious behavioral significance to the young kittens and perhaps can be considered as simply causing an increased firing rate of a group of midcochlear neurons compared with the surrounding basal and apical cochlear regions. The lower schematics are hypothetical wiring patterns to help represent the experimental results.

Conditions for Plasticity in the Adult Cortex

In adult animals, there have been numerous studies that have explored the plasticity of sensory cortex after repeated chronic exposure to well-specified stimuli. Many of these studies report that plastic changes are evident only if the sensory stimulus has some behavioral significance to the animal. Long-term changes in the auditory neuron receptive field were induced in tonal stimulation associated with various behavioral conditioning tasks.[48-50] Based on evidence that such plastic changes are potentiated by the presence of acetylcholine, a useful model was proposed by Weinberger and Bakin[51] suggesting that the nucleus basalis, the source of cholinergic projections to the sensory cortex, has an important role in plastic modifications to cortical networks. Many experimental studies in which sensory neuron receptive field changes were facilitated by electrical stimulation of nucleus basalis or by local application of acetylcholine support such a model.[52-54]

Apparently, stimulus-initiated plastic change (e.g., to auditory neuron receptive fields) is often achieved in an adult subject only with a behaviorally relevant paradigm. The developing system may be significantly different. As the 8-kHz rearing experiment outlined previously shows, a "passive" overstimulation paradigm can result in the development of a modified tonotopic map. It could be suggested, however, that the kittens develop some behavior to avoid the polluting acoustic signal, so perhaps it is not entirely passive.

Animal Models of Deafness and Effects of Cochlear Implant Electrical Stimulation

In animal models, a wide range of structural and functional changes have been observed in the auditory system in association with experimental and naturally occurring deafness.[55-62] One view of the observed changes is that they result from a reduction or lack of stimulus-driven activity. A term sometimes applied here is "negative plasticity," which describes a system that is not undergoing the usual plastic changes that accompany physiological activity. It is also difficult to separate negative plasticity effects with some more basic underlying neural pathology associated with the hearing loss. In any case, a clinically important question relates to whether stimulation with a cochlear implant can serve to restore critical features of auditory function, such as synaptic integrity.

Such questions have been addressed directly by the study of cochlear electrical stimulation in animal models of deafness. Auditory nerve endings in deaf white cats exhibit morphologic abnormalities that are (partly) reversible with restored activity with cochlear implantation.[63,64] Investigators have also observed positive effects of electrical stimulation on auditory brainstem nuclei,[58,65] the midbrain,[66-68] and auditory cortex.[57,69,70] There may be considerable residual limitations to auditory neuron performance after functional restoration induced by electrical stimulation.[71] At the cortical level, restorative effects seem to promote normalized, layer-specific activity within the primary auditory cortex in young kittens, but not in older cats.[57] Such findings implicate a critical period or at least an age-related plasticity for the developing auditory cortex.

Basic Mechanisms of Plastic Change

It is impossible in the context of this chapter to provide a comprehensive review of basic mechanisms of plastic change, but the otologist or

Figure 132-5. A schematic to summarize salient aspects of developmental and adult plasticity experiments, with suggestions for possible neural wiring patterns. Each panel represents the ascending auditory pathway from cochlea to cortex. **A,** Early developmental stage when neural projections between levels have considerable divergence. **B,** Normally developed projection system. It is characterized by good point-to-point connections between auditory nuclei. **C** and **D,** Data from subjects after basal cochlear lesions induced neonatally (**C**) and in an adult (**D**).

hearing health care professional might benefit from this overview of some commonly proposed mechanisms for neural plasticity and synaptic strengthening. Neuronal reorganization is the result of numerous mechanisms, some of which we know about in detail, some of which we know about only vaguely, and many of which are still unknown. The behavior of interconnected neurons depends on the establishment of synaptic connections in the first place, perhaps the "pruning" of underused synapses, then the adjustment of the strength or efficacy of individual connections. Finally, there might be some consolidation process to maintain the new organization. In addition, as mentioned in the preceding section, there are additional external neural and hormonal factors that can play a role in facilitating plastic change. In the case discussed previously, it was the modulating influence of an acetylcholine system that facilitated, or perhaps consolidated, plastic change.

Some mechanisms present during an early developmental period may not play such an important role in the mature brain. The initial period of formation of auditory connections from the cochlea to the thalamus and then axonal growth into primary auditory cortex involve chemotropic guidance of axons to target cells and myelination processes that may not exist in the mature brain. In addition, the drastic pruning of interneuronal connections that occurs during early development is impossible in the more mature brain. It is important to keep in mind the distinction between adult and developmental plasticity when thinking about mechanisms of plasticity. In the following sections, we discuss such mechanisms of plastic change, first at the "systems physiology" level, focusing on the examples of tonotopic map reorganization already presented. After that, we review some of the cellular and subcellular mechanisms that might underlie the experimental observations.

Mechanisms of Plasticity at a Systems Physiology Level

Let us first consider the reorganization of tonotopic maps resulting from neonatal cochlear lesions. Figure 132-5 provides a simple schematic to help conceptualize the tonotopic organization in normal and reorganized conditions. Figure 132-5B depicts the normal, point-to-point, cochleotopic projection system from cochlea to cortex in an adult subject. Figure 132-5A depicts an early developmental phase characterized by "divergent" neural projections throughout the system. With a normal pattern of activity from the cochlea, the divergent innervation pattern (see Fig. 132-5A) develops into the normal point-to-point projection system (see Fig. 132-5B).

Many mechanisms are likely involved in this normal developmental process. When growing neurons are attempting to make connections with target cells, there may be a physical space competition such that the neurons that are most proximal win out. Synaptic strengthening, through various mechanisms of long-term potentiation (LTP), may strengthen the most direct connections and promote their survival over connections that are less direct. Sound-driven neural activity likely is more influential in the formation of the adult-like point-to-point connectivity than non–stimulus-driven spontaneous activity. This would definitely be the case if the synaptic strengthening follows hebbian rules.[72] Further details about hebbian processes are given in the next section. In short, a robust strengthening of connection between neurons

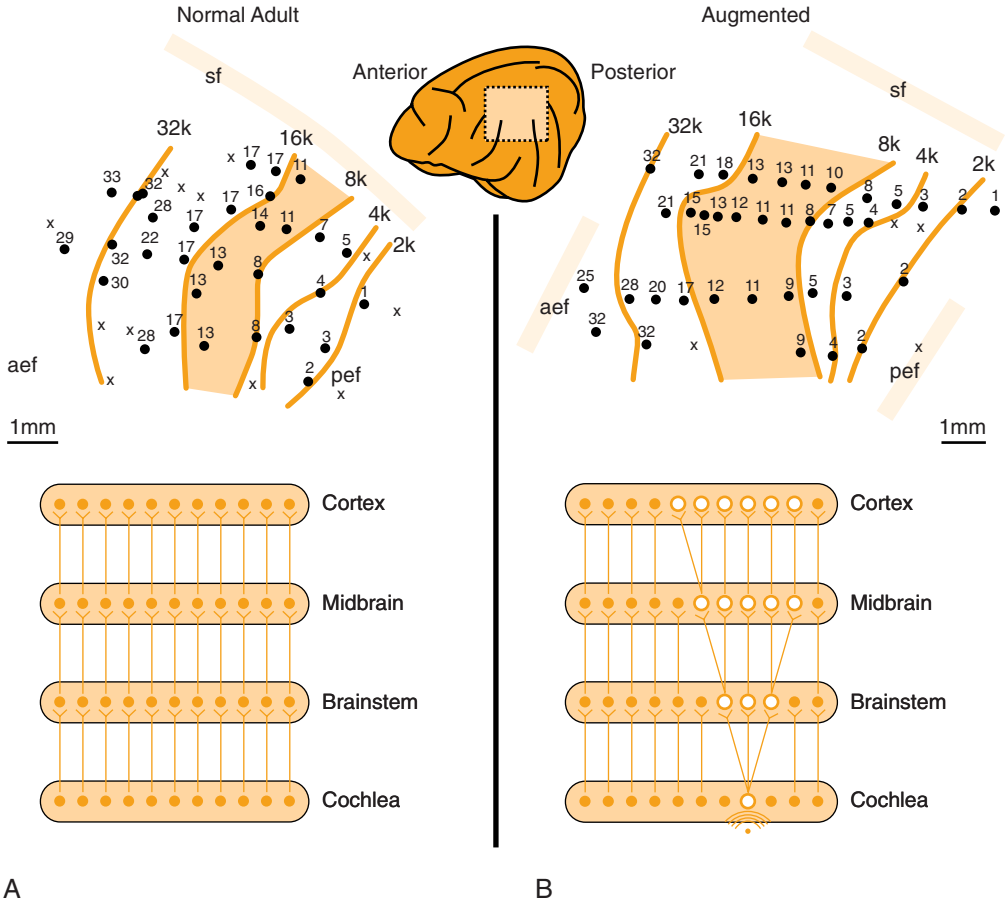

Figure 132-6. Tonotopic maps in the auditory cortex of a cat. Methods for constructing the maps are the same as those noted for Figure 132-1. Isofrequency contours are at octave intervals. **A,** Frequency map is from a normal control subject. **B,** Map is from a cat that spent about 1 month postnatally in an acoustic environment with a constant 8-kHz signal. In both examples, the 8- to 16-kHz octave interval is shaded to emphasize the main difference between the subjects. Hypothetical wiring patterns, representing the results, are shown below the maps. aef, anterior ectosylvian fissure; pef, posterior ectosylvian fissure; sf, sylvian fissure. *(Adapted from Stanton SG, Harrison RV. Neonatal auditory augmentation modifies cochleotopic mapping in primary auditory cortex of the cat.* Aud Neurosci. *1996;2:97-107.)*

is achieved under conditions where patterns of presynaptic and postsynaptic activity (depolarization) are highly correlated. This would particularly be the case when acoustic stimuli drive identical patterns of activity in neighboring cell groups. Conditions for hebbian synaptic strengthening are unlikely to occur when local groups of neurons do not have a common (stimulus-driven) activity, or simply have independent and random patterns of spontaneous firing.

Tonotopic Map Reorganization in the Developing Subject

Figure 132-5C depicts the auditory projections that result from making a basal cochlear lesion during an early developmental period (e.g., in neonatal kittens or chinchilla pups). At the level of the auditory cortex and at the midbrain, experimental data show that deafferented areas contain neurons that seem (based on characteristic frequency tuning) to be connected to a common point along the cochlea, typically the border of the cochlear lesion. It is possible to invoke numerous possible mechanisms that could produce such a wiring diagram. The most economical scheme is to suppose that the divergent neural projections that exist in very early development (as depicted in Fig. 132-5A) are simply not eliminated because in the adjacent, deafferented region, there are no longer neurons competing for target cells.

Perhaps we do not need to consider the supposed divergent innervation pattern in early development, but rather assume that there is always a small degree of divergence associated with tonotopic projections. Then it is possible that a modest "edge-effect" spread, resulting from the lack of neural competition on the deafferented side at each synaptic level in the auditory pathway, would accumulate to become a substantial area of overrepresentation at the cortical level.

The other developmental plasticity experiment that we considered involved rearing kittens such that the 8-kHz region of the cochlea is chronically excited.[47] The resulting reorganization of the cortical tonotopic map is shown in Figure 132-6, together with a hypothetical tonotopic wiring diagram. Here it is easy to suppose that within the driven region of the neural array, LTP, especially if operating under hebbian rules, would significantly strengthen and consolidate active connections compared with connections in less excited adjacent areas. The physical spread of enhanced connectivity, to produce overrepresentation at the cortex, could be explained by having edge-effect spread on both sides of the activated region of the neural array, and incrementing at each auditory nucleus up to the auditory cortex.

Cortical Map Plasticity in Adult Subjects

The schematic in Figure 132-5D represents data from studies of tonotopic map changes after cochlear lesions in a mature animal. Very little evidence of frequency map reorganization has been found at subcortical levels, at least in terms of an overrepresentation of a specific sound frequency (or, more correctly, the overrepresentation of activity from a specific cochlear location). The "incremental with level" model of Figure 132-5C does not apply here. Rewiring to produce overrepresentation would seem to be largely confined to the thalamocortex. We need to consider other possible mechanisms, which one can divide into two categories: (1) alterations to preexisting neural connections made

by increasing or reducing their relative strengths, and (2) new growth processes, such as neurogenesis, axon sprouting, and synaptogenesis.

Within the auditory cortex and thalamus, and in all auditory nuclei, there is some degree of divergent input, there are laterally connecting local interneurons, and often there are longer range interneuronal connections. It has been suggested that much of the activity of these preexisting lateral connections is normally inhibited, but that local deafferentation serves to release that inhibition. In other words, there is an "unmasking" of existing lateral connections. There is evidence that lateral inhibition is reduced in cortical neurons of subjects with cochlear lesions[73] and in the brainstem and midbrain auditory areas after trauma to the cochlea.[14,15,74,75]

Such findings seem to be correlated with observations of reduced γ-aminobutyric acid levels in central auditory areas of deafened animals.[76,77] Perhaps because of their release from inhibition, or unmasking, local lateral connections become more active and are strengthened. Now that our discussion is at the level of individual neuronal connections, it is appropriate to consider some cellular and subcellular mechanisms that are known to contribute to synaptic strengthening. In the following section, we briefly review LTP, hebbian synaptic strengthening, and the *N*-methyl-D-aspartate (NMDA) receptor.

Cellular Level Mechanisms of Plasticity

Any discussion of mechanisms of synaptic plasticity should perhaps start with "post-tetanic potentiation." This was one of the first described neurophysiologic mechanisms related to synaptic strengthening. In an experimental situation in which a presynaptic neuron excites a second neuron, repeated presynaptic stimulation can result in an increased effectiveness of the synapse that is maintained for some time (minutes to hours). The classic theory behind this relatively short-term plasticity is that it is caused by presynaptic calcium ion accumulation that temporarily enhances neurotransmitter release; more recent studies have embellished this story, but the mechanism is primarily presynaptic.

Long-Term Potentiation

The next major step forward occurred a few decades ago with reports that long-term modifications of mammalian synapses (lasting for weeks and months) could be experimentally induced.[1,78] This LTP can result from a repeated activation of the synapse. It was originally observed in experiments in the hippocampus, but LTP is now known to exist almost ubiquitously in the brain. In seeking mechanisms for LTP, attention was drawn first to the postsynaptic receptors, in particular the NMDA receptor. The NMDA receptor is a fast, ionotropic ion channel that is activated by glutamate, the major excitatory transmitter in the brain. Synapses with NMDA receptors can develop LTP, but not when the receptor is blocked. The key aspect of the NMDA receptor is that its ion channel has a voltage-dependent Mg^{2+} block that can alter the cell excitability, partly by controlling Ca^{2+} permeability. Although the NMDA receptor was the first to be implicated in the synaptic strengthening underlying LTP, it is only one of many. The metabotropic glutamate receptor can be involved in LTP processes. Other receptor types are likely involved with synapses that exhibit the corollary of LTP—long-term depression.

Hebb's Postulate

One significant feature of synaptic systems involving NMDA receptors is that they often (but not always) follow hebbian rules. In 1949, Hebb[72] put forward many ideas concerning the conditions that might cause synaptic strengthening. His main postulate is as follows: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficiency, as one of the cells firing *B*, is increased." This notion has commonly been expressed as: "Cells that fire together, wire together."

In modern studies of LTP, many systems have been shown to follow such hebbian rules. As discussed previously, the conditions commensurate to hebbian-type strengthening of connections in the auditory pathway are optimally produced when there is sound-driven activity. Acoustic stimulation results in groups of auditory neurons in ascending arrays with highly correlated activity. Such conditions could be important for establishing and maintaining tonotopicity in the auditory system. In addition, hebbian-type synaptic strengthening resulting from the correlated, driven activity of bilateral auditory input undoubtedly plays a major role in establishing sound localization mechanisms.

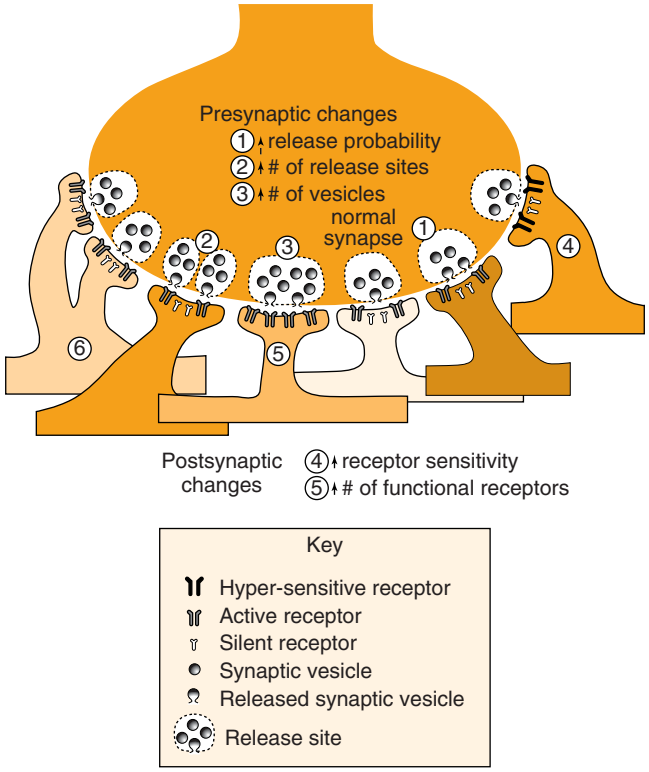

Figure 132-7. Overview of six possible presynaptic or postsynaptic mechanisms for enhancing synaptic efficacy. *1,* More presynaptic vesicles undergo exocytosis at a release site compared with the normal synapse. *2,* An increase in the number of release sites. *3,* Potentiation of a release site because of an increase in number of vesicles available for release. *4,* Increase in the sensitivity of existing postsynaptic receptors. *5,* Increase in the number of receptors. *6,* Synaptogenesis (i.e., new growth of synaptic contacts). *(Adapted from Wang JH, Ko GY, Kelly PT. Cellular and molecular bases of memory: synaptic and neuronal plasticity.* J Clin Neurol Physiol. *1997;14:264-293.)*

Other work exploring mechanisms of synaptic strengthening has implicated changes in presynaptic and postsynaptic areas. The potential complexity of various mechanisms that might contribute to changing the efficacy of a single synapse is emphasized by Figure 132-7.[79] Any combination of up to six presynaptic or postsynaptic mechanisms can modify the performance of a synapse. A typical auditory neuron can have many hundreds of synapses; the possibilities for modification seem almost limitless.

Finally, we come to the processes whereby synapses, modified in various ways, have their plastic changes consolidated. What mechanisms can make LTP permanent? The short answer is that structural components of synapses, including the number and type of presynaptic release sites and the postsynaptic receptors, have to be maintained in cells with substrates that are constantly turning over. Mechanisms of protein synthesis and gene expression play an important role.

Practical Issues Relating to Neural Plasticity in Otology

What does all this new knowledge about neural plasticity mean to the otologist or hearing health care professional? What practical benefits can arise from an understanding of mechanisms of plastic change? In the following sections, we discuss some common practical issues in

otology, now illuminated by our appreciation of neural plasticity; some of the discussion is speculative.

In many areas, this new knowledge has no immediate impact on the practice of health care, other than offering some further explanations of cause (e.g., understanding the genesis of some types of tinnitus). In other areas, a further understanding of the mechanisms of plastic change could potentially change otologic case management. This has been the case in relation to the early detection and intervention in sensorineural hearing loss. The concepts and concerns raised by developmental neural plasticity experiments have heightened our appreciation of age-related plasticity, and this has significantly improved practice.

Hearing Loss in Infants

The take-home message from numerous clinical observations and experimental studies, some described here, is that central auditory system development largely depends on the pattern of neural activity from the periphery. Hearing loss, especially during early development, may negatively affect central development. Perhaps there is a critical period during which cochlear function needs to be particularly intact.

Many of the experimental animal studies of plasticity that clearly show central structural and functional alterations involve drastic manipulations, such as total cochlear ablation or partial deafferentation. We have to extrapolate beyond such radical examples, however, to consider that more subtle types of hearing loss also change normal peripheral stimulation patterns. Mild sensorineural hearing loss, chronic conductive hearing loss (especially in repeated episodes of otitis media), and bilaterally asymmetric hearing loss, which might not be considered to impair "significantly" ongoing hearing function, may nevertheless alter normal central pathway development.

One of the difficulties with testing such notions is that the manifestation of abnormal auditory development might be delayed. Neonatal hearing disorders that might lead to problems in language development become evident only 4 or 5 years later, when such development can be assessed. Perhaps the best practical strategy is to assume the worst and make every possible effort to normalize hearing during early postnatal years. This strategy involves having an early detection of hearing problems through neonatal or infant hearing screening programs and subsequent early intervention with hearing aids, cochlear implants, and auditory habilitation training. We are presently in the midst of implementing these strategies.

Our concerns about early detection of hearing loss and early intervention have been fueled by experimental evidence from animal and human studies. With regard to the latter, some of the best "experiments" have been in deaf children with cochlear implants. Figure 132-8 shows data from our own pediatric cochlear implant program.[22] Each panel shows average postimplantation performance on a standard speech understanding test. All children were prelingually (mainly congenitally) deaf, and the population was homogeneous in terms of degree of residual hearing, school setting, and access to habilitation therapy. The data set has been divided into children implanted at an early age compared with children implanted later. On average, children implanted at a young age eventually outperform others. Similar conclusions are reached from a wide range of other intervention outcome studies in vision, sensorimotor training, and education. Compensation for any neural deficit is best achieved by early intervention.

Central auditory system development is significantly guided by cochlear activity patterns. It follows that a cochlear implant or other hearing prosthesis provided to a young infant would have a dual purpose. Not only does the device aid "hearing," but also the augmented stimulation of the system would have an influence on central development. Many questions arise from this notion. Is a stimulation paradigm designed to provide good auditory input the most optimal for stimulating developmental change? It may be more beneficial to have implant devices that are constantly active, even when not being used for hearing, so that they constantly provide stimulation to the developing auditory brain. Does the pattern of stimulation from a cochlear implant result in the development of an unusual central auditory system? To the latter I would say, almost certainly, yes. If so, what does this mean for changing devices, or even speech coding paradigms, later in life? In the future, as we intervene in even younger infants, we will need to give more attention to the developmental aspects of cochlear implants (and infant hearing aids).

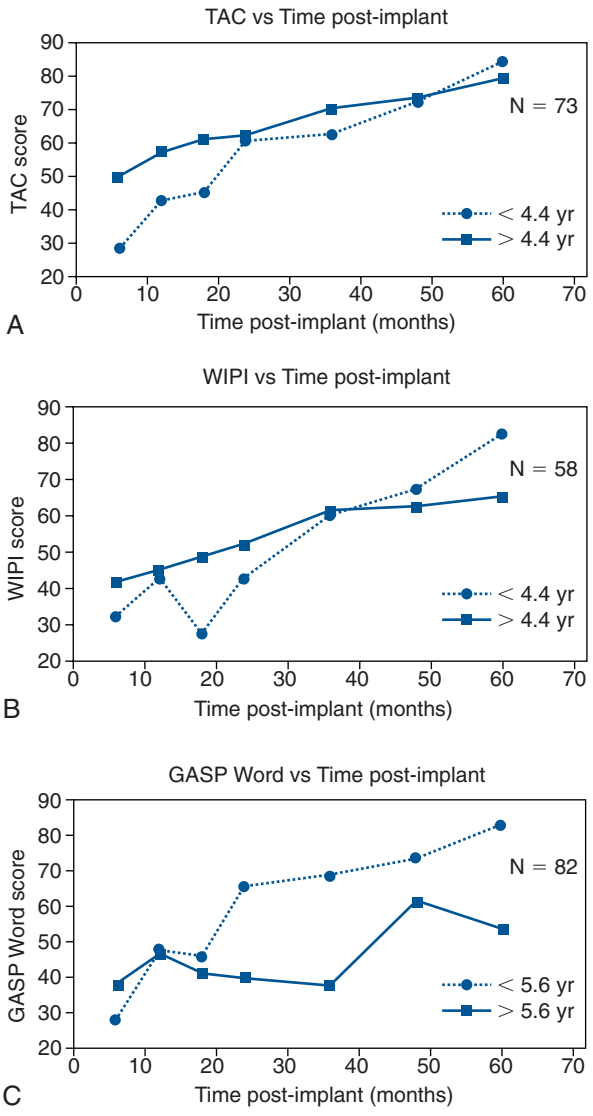

Figure 132-8. The influence of age at implantation on various speech/hearing tests in congenitally or prelingually deaf children using cochlear implants. **A,** Average performance over time after implantation for Test of Auditory Comprehension (TAC) scores. Data are from 73 children divided into groups implanted before and after age 4.4 years (*dotted lines,* <4.4 years; *solid lines,* >4.4 years). **B,** Average performance of children implanted before or after age 4.4 years (*dotted lines,* <4.4 years; *solid lines,* >4.4 years) on the Word Intelligibility by Picture Identification (WIPI) test. Data are based on 58 subjects. **C,** Results using Glendonald Auditory Screening Procedure (GASP). Data from 82 children are divided into groups implanted before or after age 5.6 years (*dotted lines,* <5.6 years; *solid lines,* >5.6 years). *(Adapted from Harrison RV, Panesar J, El-Hakim H, et al. The effects of age of cochlear implantation on speech perception outcomes in prelingually deaf children.* Scand Audiol. *53(30 Suppl):73-78, 2001.)*

Other Hearing Disorders

There is much evidence of radical plastic change in the brains of congenitally deaf or blind subjects, where cortical areas that no longer serve one modality seem to take on some function for the remaining, dominant sense.[80-82] In a signing deaf subject, some processing of visual information is carried out in the auditory cortex.[83] These are examples

of brains that have developed with very unusual alterations to sensory input. From a practical perspective, such knowledge might be useful when considering whether a cochlear implant would be beneficial to a signing, congenitally deaf adult.

In extrapolating to humans from the animal plasticity studies outlined in this text, any type of sensorineural hearing loss, whether from ototoxic poisoning, acoustic trauma, or presbycusis, might result in some organizational change at the cortical level. Does such change have any functional significance? Does it improve auditory processing, or does it contribute further to hearing dysfunction? Presently, we do not have good answers to such questions. There is no evidence that the cortical overrepresentation of certain sound frequencies has any correlate in an improved psychophysical performance. On the negative side, however, it is easy to speculate that such isofrequency areas would contribute to loudness recruitment and perhaps the generation of some types of tinnitus. In an experimental animal (as in Figs. 132-3 and 132-4) with a large region of auditory cortex apparently connected to a narrow region of the cochlea, certain frequencies of acoustic stimulus would "light up" vast areas of the auditory cortex. It is difficult to imagine that this degree of cortical activation would not be reflected in a perceived increase in loudness.

With regard to tinnitus, a few speculative comments are in order. First, certain types of tinnitus could arise from auditory neurons that somehow develop self-perpetuating activity. The brain is full of networks that might allow this, such as local and reciprocal intracortical connections or thalamocortical feedback loops. With our understanding that synaptic efficacy can be considerably increased by LTP and hebbian mechanisms, it is easy to conceive of local circuits being reinforced to the point of reverberation (i.e., having a positive feedback mode). For this and other reasons, the need for extensive and continuous inhibitory control within the brain is obvious. When there are extensive isofrequency areas in the auditory cortex with the potential for massive synchronous activity, it is possible that such inhibitory mechanisms cannot sufficiently suppress positive feedback processes.

An even simpler mechanism for tinnitus production is plausible. Suppose that the synchronous firing of these extensive isofrequency neural populations results in them all being connected together. This is quite feasible; remember Hebb's rule: "Cells that fire together, wire together." Assuming that conscious perception has some basis in cortical neuronal activity, perhaps even low levels of "resting" activity in a vast, linked network of cells could give rise to a chronic sound sensation.

In light of the experimental data on plasticity, one further comment about tinnitus is relevant. There is much discussion about the different types and origins of tinnitus. One distinction often made is between "central" and "peripheral" tinnitus. The studies on central auditory plasticity draw attention to the fact that a cochlear lesion can cause central reorganization. It is plausible that some traumatic event at the cochlear level, causing either less afferent input (after hair cell loss) or more afferent input (injury discharge from dying neurons), could set up connection patterns that result in cortical overrepresentation. Although the central neurons are presumably the immediate cause of the tinnitus sensation, the intimate link to a causal peripheral lesion blurs any notion about the real origin of the tinnitus.

Summary

Many aspects of plastic change in otology have not been adequately covered in this chapter. In particular, the plasticity of the vestibular system, and that of sound localization, have not been addressed. Nevertheless, we have covered considerable ground in relation to auditory system plasticity, and we have reviewed some important basic mechanisms relevant to all sensory systems. We have also initiated some discussion on the clinical relevance of this new knowledge

We tend to think about the brain as a complex, wired system that, under certain circumstances, is capable of being rewired. These reorganizations, as noted in some of the studies described here, are often initiated by alterations to sensory input. As we learn more about the plasticity of synaptic connections and the variety of potential mechanisms that can alter how neurons connect and communicate, it has become clear (at least to this author) that the brain is a constantly reorganizing system. Plasticity is the rule, not the exception. Sometimes it seems that we should be seeking not the evidence and mechanisms of plastic change, but rather the mechanisms that stabilize the brain and prevent plasticity. In a final note on age-related plasticity in the auditory system, perhaps this is what maturity is all about. It is not so much a decline in plasticity, but the gradual application of a stabilizing brake.

SUGGESTED READINGS

Berlin CI, Weyland T, eds. *The Brain and Sensory Plasticity: Language Acquisition and Hearing*. New York: Thomson Delmar Learning; 2003. (The focus in this text is on hearing habilitation including language development.)

Lomber S, Eggermont JJ, eds. *Reprogramming the Cerebral Cortex: Plasticity following Central and Peripheral Lesions*. Oxford, England: Oxford University Press; 2006. (This is a more recent textbook containing useful up-to-date reviews of neural plasticity in auditory, visual, and somatosensory systems.)

Moller A, ed. *Neural Plasticity and Disorders of the Nervous System*. Cambridge, England: Cambridge University Press; 2006. (This text provides up-to-date coverage of plasticity in the auditory system with an emphasis on pathology including hearing loss and tinnitus.)

Parks TN, Rubel EW, Fay RR, Popper AN, eds. *Plasticity of the Auditory System*. New York: Springer; 2004. (This text covers plasticity and development in auditory pathways from brainstem through to cortex and includes studies on auditory plasticity in nonmammalian species [e.g., birds and insects].)

Ruben RJ, Van de Water TR, Rubel EW, eds. *The Biology of Change in Otolaryngology*. Amsterdam: Elsevier Science; 1986. (This text contains some good basic studies on auditory system development, plasticity, and injury repair. Although a little out of date now, this text is still relevant.)

Syka J, Merzenich MM, eds. *Plasticity and Signal Representation in the Auditory System*. New York: Springer; 2005. (This text covers widely the many research fields related to the development and plasticity of hearing, including speech, music, and neuroimaging studies.)

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CHAPTER ONE HUNDRED AND THIRTY-THREE

Diagnostic Audiology

Paul R. Kileny

Teresa A. Zwolan

Key Points

- The audiologic test battery encompasses a range of behavioral/psychophysical and objective/physiologic tests that provide key insights into otologic disorders.
- Some components of the auditory test battery are nonspecific (e.g., tonal and speech audiometry); others (e.g., electrocochleography) are specific for the diagnosis of specific auditory system pathologies.
- It is necessary to apply certain basic tests, such as pure-tone audiometry, speech audiometry, immittance testing, and otoacoustic emissions, to characterize the basic properties of the auditory system for every new patient with auditory complaints.
- More specific and physiologic tests need to be tailored based on patient complaints, the results of the basic test battery, and clinical suspicion.
- If administered and interpreted correctly, physiologic tests, such as electrocochleography, auditory brainstem response testing, and otoacoustic emission testing, offer substantial specificity and sensitivity. Critics citing low specificity and sensitivity of audiologic tests (i.e., auditory brainstem response in the diagnosis of small acoustic neuroma) do not take into consideration poor technical quality.

Audiologic Test Battery

In his book, *Practical Observations on Aural Surgery and the Nature and Treatment of Diseases of the Ear,*[1] Wilde stated:

> The degree of deafness may be learned, and the hearing distance measured by holding an ordinary watch near the external meatus, and the distance at which the tickings can be accurately counted, and at which the patient is conscious of an interval between these sounds, should be recorded. To effect this properly, the watch should be approached gradually to the ear until it gets to within the hearing point, and again applied directly to the auricle, and gradually removed to some distance.

Wilde[1] continued, "It is absolutely necessary, if we wish to watch the progress of a case not only to conduct these observations with great care, but also to take a written note of the hearing distance the first and each subsequent time we see the patient." Wilde also recommended placing the watch "gently between the teeth of the patient, and the amount of hearing thus obtained likewise noted"—an early attempt at bone conduction testing.

Founded on such clear, practical thinking, the clinical science of audiology has advanced through the availability of instrumentation that accurately quantifies the sensitivity and acuity of human hearing. In his book, *Disease of the Ear,*[2] Dench stated that "it is scarcely necessary to mention the more complicated instruments which from time to time have been devised for determining quantitative audition. Their use has never become universal on account of the complex construction." Dench[2] described and illustrated the electric audiometer developed by Urbantschitsh in 1890—a device that extended technology made available by the invention of the telephone. He further discussed the phenomena of crossover and interaural attenuation, cautioning against errors that may occur when a loud sound is presented to a profoundly deaf ear in the presence of a normal-hearing contralateral ear.

Similar to otologists today, these early otologists used the results of auditory testing in two ways: to quantify hearing loss and to assist in the differential diagnosis of ear disease on the basis of auditory phenomena. Today, our clinical armamentarium consists of highly sophisticated and specific clinical test modalities that provide accurate quantitative information regarding a patient's hearing sensitivity. Other tests capitalize on specific auditory phenomena to provide differential diagnostic site-of-lesion information. The clinical audiology test battery can be classified into two groups on the basis of how the results are obtained: (1) behavioral or psychophysical tests, requiring a specific behavioral response to an auditory stimulus, and (2) objective tests, which are based on a physical or a physiologic measurement associated with an auditory stimulus. An example of a physical measurement is the acoustic immittance typically used to determine middle ear status. An example of a physiologic measurement is the auditory brainstem response (ABR) and other electrophysiologic phenomena.

Typically, diagnosis is based on a combination of information obtained from the patient's history, physical examination, and audiologic test battery results. As a rule, there is a hierarchy of auditory diagnostic tests specifically based on patient symptoms and complaints, and results obtained in one manner can often be verified by the results obtained using a different modality. An air-bone gap shown by pure-tone audiometry can be confirmed by an abnormal tympanogram, the typical otoscopic appearance of a retracted eardrum, and its poor mobility on pneumatic otoscopy to determine the presence of a conductive hearing loss caused by middle ear pathology.

Tests for Hearing Sensitivity or Acuity

Pure-tone audiometry is the most commonly used test for evaluating auditory sensitivity. Auditory pure-tone signals are delivered primarily through air conduction and bone conduction. The American National Standards Institute (ANSI)[2a] defines the threshold of audibility as "the minimum effective sound pressure level of an acoustic signal producing an auditory sensation 'in a specified fraction of the trials.'" Most often, threshold is defined as the lowest signal intensity at which multiple presentations are detected 50% of the time.[3]

When used clinically, audiometric threshold data are most often displayed on a graphic plot called an audiogram (see Figs. 133-2 through 133-4). Various symbols are used to represent data obtained for the right and left ears by use of air-conducted and bone-conducted signals. The current audiogram representation was recommended by the American Speech, Language, and Hearing Association in 1974, and was adopted by ANSI S3.21-1978. Data are presented in hearing level (HL), which is calibrated to referent sound pressures (ANSI S3.6-1969, 1970) that represent the hearing sensitivity of normal young adults when tested under reasonably quiet test conditions. An audiogram represents a patient's ability to hear sounds compared with the hearing sensitivity of a group of normal young adults.

Pure-Tone Air-Conduction Testing

Pure-tone air-conduction thresholds measure the function of the total hearing system, including the external, middle, and inner ear. In typical audiometric testing, pure tones that range in octave spacings from 250 to 8000 Hz are presented to the listener by headphones or insert earphones. Threshold is usually determined by the use of a version of the Hughson-Westlake "ascending method,"[4] in which sounds are initially presented well above threshold, and are then presented in decreasing steps of 10 to 15 dB until the sound is inaudible. The tone is increased in "up 5-dB, down 10-dB steps" until the single HL at which a response is obtained three times is reached.[5]

Because air-conduction thresholds measure the acuity of the entire hearing system, when evaluated alone they provide little information regarding the etiology of hearing loss and specific auditory pathology. When examined in conjunction with thresholds obtained by bone-conduction testing, however, they help determine the type and the severity of the hearing loss. When plotted on an audiogram, pure-tone thresholds also provide information regarding the severity of the hearing loss. Thresholds that fall into the 0- to 25-dB range are considered normal, whereas thresholds greater than 25 dB represent various levels of hearing loss (see Fig. 133-1).

Pure-Tone Bone-Conduction Testing

Pure-tone bone-conduction thresholds provide auditory threshold information when the cochlea is stimulated more or less directly, with stimuli bypassing external and middle ear structures. Differences between thresholds obtained through air and bone conduction are used to determine the type of hearing loss (normal hearing versus conductive loss versus sensorineural hearing loss [SNHL]) and the magnitude of conductive hearing loss if it exists.

The location of the bone-conduction thresholds on the audiogram helps determine the severity of the hearing loss (Figs. 133-1). In bone-conduction testing, a bone oscillator is typically placed on the mastoid process. Although this placement does not guarantee that the responses obtained are from the ear located on the side on which the oscillator was placed, such placement provides an enhanced dynamic range compared with other placements, such as at the frontal bone.[6] Most audiometers currently in use are calibrated for placement of the vibrator on the mastoid.

The relationship between air-conduction and bone-conduction thresholds is used to determine the type of hearing loss. When air-conduction thresholds are elevated relative to normal bone-conduction thresholds—a phenomenon referred to as an *air-bone gap*—the loss is classified as conductive (Fig. 133-2). When air-conduction and bone-conduction thresholds indicate the same amount of hearing loss, the loss is classified as sensorineural (Fig. 133-3). Finally, when air-conduction thresholds are elevated relative to abnormal bone-conduction thresholds, the loss is classified as mixed (Fig. 133-4).

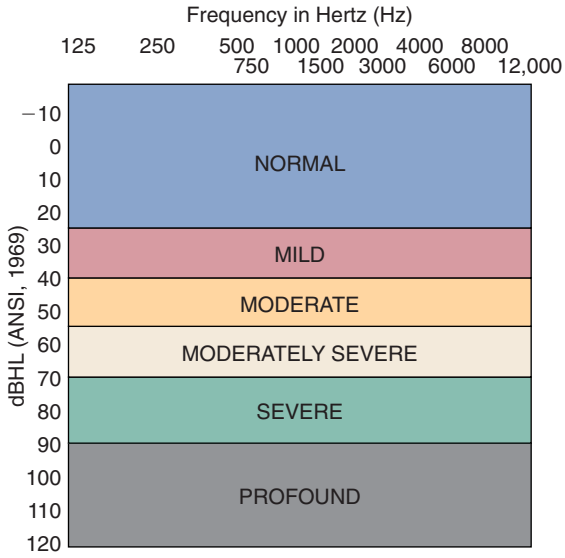


Figure 133-1. Graphic representation of categories of hearing loss.

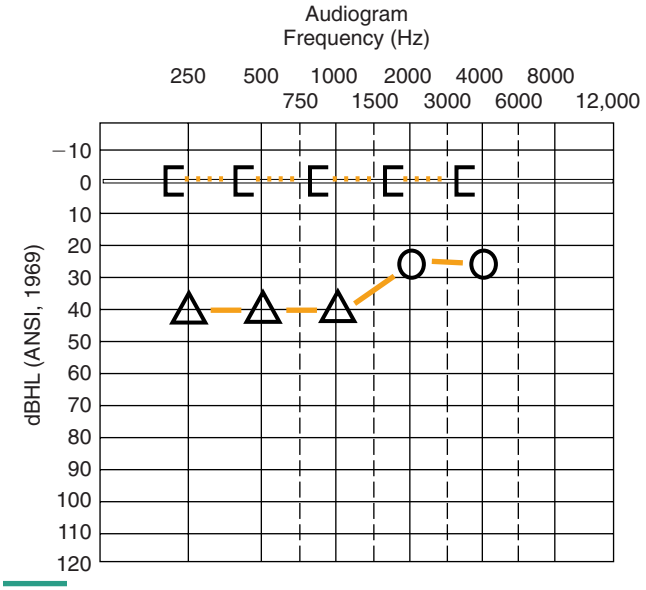


Figure 133-2. Example of an audiogram characterized by an air-bone gap indicating a conductive hearing loss.

Speech Testing

Another essential component of the audiologic test battery is the evaluation of the listener's ability to detect and recognize speech. Three speech tests are commonly included in the audiologic test battery: determination of the speech detection threshold (SDT), determination of the speech reception threshold (SRT), and speech discrimination or recognition. The SDT indicates the intensity level at which a listener can barely discern the presence of a speech signal 50% of the time.[7] With such a task, the listener is not required to recognize the stimulus, but is merely asked to acknowledge its presence. Conversely, the SRT represents the intensity level at which a listener can repeat 50% of the speech material.[7] In contrast to the SDT, the SRT requires the listener to repeat the word that was presented. The SRT is usually 8 to 9 dB higher than the SDT,[8] whereas the SDT usually coincides with the pure-tone average (PTA), an average of the pure-tone thresholds obtained at 500 Hz, 1000 Hz, and 2000 Hz. The

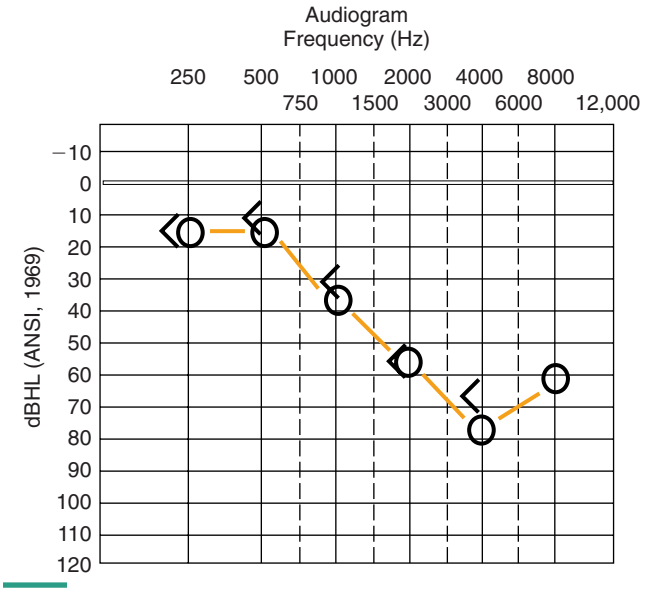


Figure 133-3. Audiogram showing a sloping, high-frequency sensorineural hearing loss (air-conduction and bone-conduction thresholds are identical).

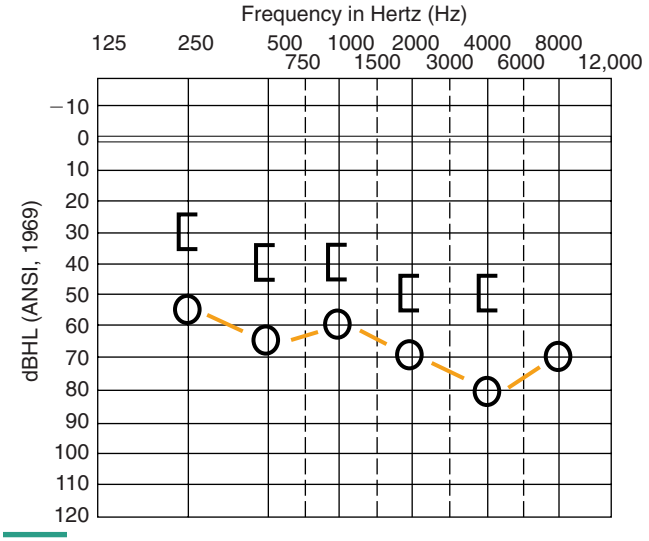


Figure 133-4. Audiogram showing a mixed hearing loss. Air-conduction and bone-conduction thresholds are elevated; however, there is also an air-bone gap.

SDT and SRT can be obtained using either air conduction or bone conduction.

Determination of speech discrimination is a more complex task than determination of either SDT or SRT. Speech discrimination is an important part of the audiologic test battery because it provides information regarding the listener's ability to recognize speech under well-controlled conditions. Speech discrimination test results are used in conjunction with the findings of other tests to help determine the differential diagnosis of hearing loss; provide information about the listener's ability to communicate effectively; aid in decision making regarding candidacy for various surgical procedures; provide useful information about rehabilitative needs, including the effectiveness of hearing aids or cochlear implants; and provide information regarding central auditory function.[7]

Various materials and formats have been used to evaluate speech discrimination. The most commonly used as part of an adult audiometric test battery include monosyllabic words presented in an open-set format, such as the CID W-22 word lists[9] and the Northwestern University Auditory Test No. 6 (NU-6).[10] Although taped materials are optimal when evaluating speech discrimination, materials are often presented through live voice for rapidity and ease of administration. Speech discrimination materials are usually presented 50 dB above the patient's SRT—a level that should be well within their audible range.

Patients with a conductive hearing loss frequently have excellent speech discrimination scores when test stimuli are presented at a sufficiently loud level. Patients with a cochlear sensory hearing loss often have reduced scores on speech discrimination tests, even when the stimuli presented are well within their audible range. Patients with lesions of the eighth cranial nerve or beyond tend to have lower speech discrimination scores than patients with a cochlear lesion site, and may have reduced speech discrimination in the presence of normal auditory pure-tone thresholds. The extreme of this phenomenon may be found in patients with cortical lesions who are unable to understand speech or any type of complex auditory signal.[11]

Masking

If a sufficiently loud signal is presented to the test ear, it may cross the skull where it will be perceived by the nontest ear, a phenomenon referred to as *crossover*. It may be necessary to deliver a masking signal to the ear that is not being tested. When crossover occurs, responses to air-conducted pure tones that have crossed over from the poorer ear shadow the thresholds of the better ear. Such "shadow" responses reflect the threshold levels of the better ear elevated by the amount of interaural attenuation at each test frequency.

Interaural attenuation refers to the reduction in sound when it crosses from one ear to the other. The lower limit for interaural attenuation for bone-conduction testing is essentially 0 dB across frequencies.[12,13] Because of this, masking should be used routinely with bone-conduction testing when threshold levels between ears are asymmetric. Additionally, because the signal primarily travels to the nontest ear through bone conduction, the need for masking arises when air-conduction thresholds for the test ear are poorer than the bone-conduction thresholds for the nontest ear. Masking is useful in such situations because it shifts the sensitivity of the cochlea of the nontest ear to prevent it from hearing the signal that is delivered to the test ear.

The need for masking with air-conducted signals depends on how the signal is delivered. Interaural attenuation ranges from 35 to 50 dB for stimuli delivered via headphones and 60 to 65 dB for earphones,[14] depending on the frequency of the test signal, with a tendency for greater interaural attenuation at the higher frequencies.[12] Insert earphones have less contact with the lateral temporal bone than standard headphones, so less sound energy is delivered contralaterally. Greater levels of effective masking to the nontest ear are possible, with less crossover occurring to the test ear, when insert earphones are used.

Masking should be used with air-conduction testing when the air-conduction threshold of the test ear and the air-conduction or bone-conduction threshold of the nontest ear differ by the interaural attenuation factor for the frequency being tested. When determining the SRT, masking should be used whenever the SRT of the test ear and the SRT, air-conduction PTA, or bone-conduction PTA of the nontest ear differ by 45 dB or more. With speech discrimination testing, masking should be used whenever the presentation level used to deliver stimuli to the test ear is 45 dB or more above the SRT, air-conduction PTA, or bone-conduction PTA of the nontest ear.[12]

The critical bandwidth concept dictates that the extent of threshold shift produced by a masking signal is affected by its frequency and intensity.[12] The term *effective masking* refers to the intensity level of the test signal that is barely masked by presentation of a masking noise to the ipsilateral ear. When selecting a masking signal, the goal is to select a signal that provides the largest shift in threshold with the least intense noise. Because the effective masking level depends on the structure of the test signal, various types of noises are used for clinical masking. Narrow band noises centered around a specific frequency identical to that of the pure-tone test signal are most often used with pure-tone testing, whereas speech noise of a more complex nature is most often used when masking for speech tests.

Occasionally, test situations arise in which masking is necessary, but is impossible, such as with cases of bilateral conductive or mixed hearing loss. This phenomenon—referred to as a *masking dilemma*—may occur when bone-conduction thresholds for both ears are normal, and the air-conduction thresholds equal or exceed interaural attenuation. In such cases, unmasked air-conduction thresholds likely reflect the responses of the nontest ear, whereas masked air-conduction and speech thresholds may seem worse than they actually are because of overmasking. Overmasking occurs when the masking noise presented to the nontest ear "crosses over" and affects the responses obtained for the test ear.

Tests to Evaluate Middle Ear Function

The term *acoustic immittance* is used to refer to either acoustic admittance (the ease with which energy flows through a system) or acoustic impedance (total opposition to the flow of sound energy). Acoustic immittance measures are used clinically as screening and diagnostic tools for the identification and classification of peripheral (particularly middle ear) and central auditory disorders, and may be used as a tool to estimate auditory sensitivity objectively.[15] The acoustic immittance measures used most often clinically include tympanometry and stapedial reflex measures.

Tympanometry measures the acoustic immittance in the ear canal as a function of variations in air pressure in the ear canal. Testing includes placement of a probe into the ear canal to form an airtight seal. Air pressure within the canal is varied in positive and negative directions (relative to ambient pressure) while a probe tone is delivered to the ear. The amount of acoustic energy that is reflected from the eardrum is measured, providing information about the transmission characteristics of the middle ear. The magnitude of the reflected acoustic energy changes as a function of middle ear and eardrum status: the less compliant the system, the greater the intensity of the reflected tone. In a normal ear, acoustic admittance is maximal near ambient pressure and decreases as the pressure in the ear canal is either decreased or increased relative to the ambient pressure.

Specifically, tympanometry provides an estimation of intratympanic pressure, eustachian tube function, tympanic membrane integrity and mobility, and continuity of the ossicular chain. Acoustic admittance is optimal when the same air pressure is present on both sides of the tympanic membrane. The peak of the tympanogram reflects the resting pressure in the middle ear. Because the eustachian tube serves to ventilate the middle ear space, the tympanogram peak also provides information regarding eustachian tube function; a negative tympanogram pressure peak almost invariably indicates that the eustachian tube is not adequately ventilating the middle ear space because of eustachian tube obstruction caused by inflammation, infection, a mass lesion, or neuromuscular dysfunction.

A commonly used procedure is employed in classification schemes for tympanogram shapes. It was first described by Liden[16] and later modified by Jerger,[17] Jerger and colleagues,[18] and Liden and colleagues.[19] This classification of tympanogram shapes is described in Figure 133-5.

Type A tympanograms indicate normal middle ear pressure as indicated by a tympanogram peak at decaPascal. There are two subcategories of type A tympanograms: type A_D and type A_S. Type A_D shapes indicate an unusually high pressure peak and may indicate tympanic membrane or ossicular chain hypermobility caused by an atrophic tympanic membrane scar or an ossicular chain discontinuity. Type A_S shapes indicate a pressure peak at 0, although the peak is reduced in amplitude. This reduction may be caused by the presence of ossicular chain fixation, which may be caused by otosclerotic stapes footplate fixation. A type B tympanogram is flat, indicating no point of maximum compliance. Type B tympanograms may be seen in cases of otitis media with effusion, space-occupying lesions of the tympanic cavity, and tympanic membrane perforations. A type C tympanogram indicates negative middle ear pressure as reflected by a negative pressure peak and may indicate eustachian tube dysfunction. A type C tympanogram also may be present in the early stages of otitis media without effusion. A type D pattern, which has a notch in the pressure peak, is often seen with scarred eardrums or with normal, hypermobile eardrums.

Acoustic immittance tools also provide information regarding the volume of air medial to the probe. This information, when used in conjunction with that derived from the evaluation of a tympanogram's shape, can provide useful diagnostic data. Generally, ear canal volumes normally range from 0.5 to 1 mL in children and 0.6 to 2 mL in

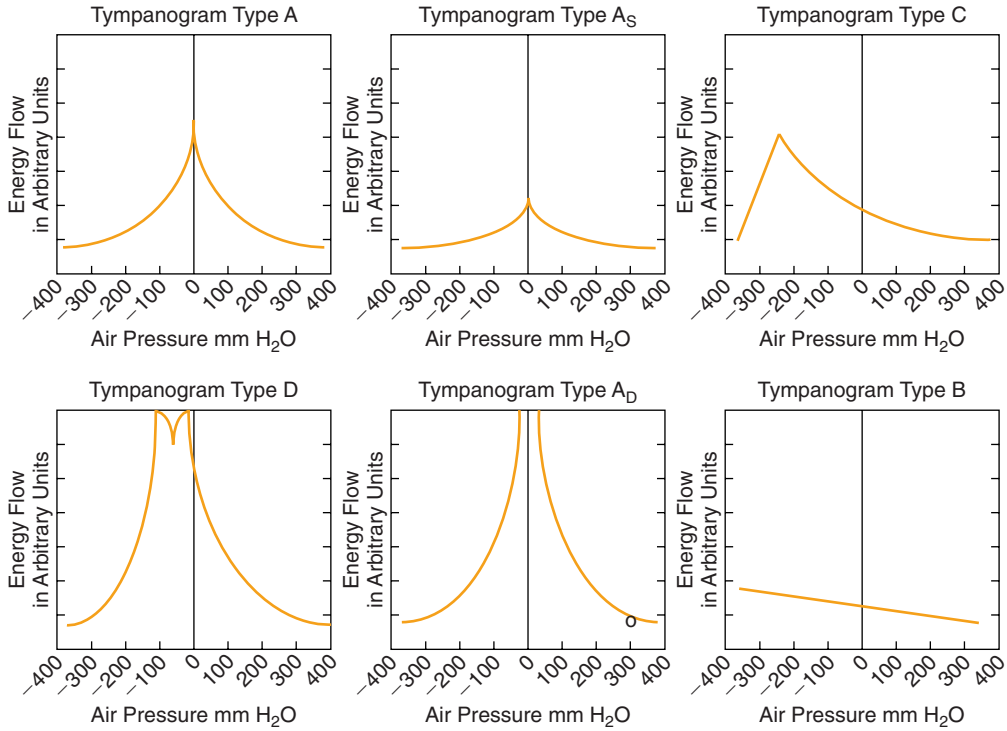


Figure 133-5. Classification of tympanograms: type A, type A_S, type C, type D, type A_D, and type B.

adults.[20] Volume measurements greater than 2 mL in children and greater than 2.5 mL in adults usually indicate a tympanic membrane perforation or a patent pressure equalization tube[21,22] because the volume measurement includes the ear canal and the tympanic cavity.

Stapedial reflex measures are also part of the middle ear test battery, and provide important and useful diagnostic information. The two most commonly used stapedial reflex measures include the acoustic reflex threshold and acoustic reflex decay. Both of these tests measure changes in tympanic membrane compliance caused by contraction of the stapedius muscle and are particularly useful for differentiation of cochlear and retrocochlear lesion sites. The acoustic reflex threshold test determines the softest level of sound that elicits stapedial muscle contraction. This normally occurs bilaterally after either ipsilateral or contralateral stimulation when a pure tone or noise is presented to a normal-hearing ear at levels of 70 to 100 dB HL.[23] The neural network of the acoustic reflex is located in the lower brainstem. The contralateral acoustic reflex arc includes the acoustic nerve and ventral cochlear nucleus, the medial superior olive, the contralateral motor nucleus of cranial nerve VII, and the contralateral stapedius muscle.[23]

Any type of middle ear disorder prevents the tympanic membrane from showing a change in compliance when the stapedius muscle is contracted. Ipsilateral and bilateral reflexes are absent bilaterally when the patient has a conductive hearing loss in the test ear. In cochlear pathologic conditions, the acoustic reflex often occurs when the impaired ear is stimulated at a level of 60 dB or less, indicating the presence of loudness recruitment. As the cochlear loss increases to greater than 60 dB HL, however, the chance of observing an acoustic reflex threshold decreases.[23] In most cases of retrocochlear pathology, the acoustic reflexes are absent when the involved ear is stimulated. If acoustic reflexes are present, an ear with a retrocochlear disease frequently is unable to sustain contraction of the stapedius muscle as measured with the acoustic reflex decay test. Finally, the absence of contralateral reflexes, with ipsilateral reflexes intact, may be seen in patients with brainstem disease as a result of the presence of a lesion in the area of the crossed brainstem pathways.[23]

The stapedius reflex also provides valuable clinical information regarding the level of a facial nerve lesion in patients with facial nerve paralysis. If the lesion is proximal, an absent stapedius reflex may be expected. If the lesion is distal to the stapedius branch, an intact reflex may be expected. Stapedius reflex measurement should be included routinely in the evaluation of patients with facial paralysis.

Acoustic reflex decay measures the ability of the stapedius muscle to maintain sustained contraction. During this test, a signal is presented 10 dB above the acoustic reflex threshold for 10 seconds. A response is considered abnormal if the response amplitude decreases to one half or less of its original amplitude within 5 seconds. Because reflex decay is common in many normal ears at higher test frequencies, frequencies of 500 Hz and 1000 Hz are most often used in acoustic reflex decay tests. Abnormal reflex decay may indicate retrocochlear disease. Patients with a cochlear or conductive hearing loss show negative acoustic reflex decay when an acoustic reflex threshold is present in the test ear.

Objective Tests for Differential Diagnostic Applications

Otoacoustic Emissions

Until more recently the term *objective test,* when referring to the auditory system, denoted exclusively the measurement of neuroelectric events associated with auditory stimulation, beginning with Davis' discovery of the cortical auditory evoked potential in 1939.[24] The discovery of the ABR by Jewett and Williston[25] marked the beginning of a revolution in the clinical application of auditory electrodiagnostic tests. The ABR changed the way hearing was tested in newborns and infants, and provides physicians and audiologists with a reliable and informative neurodiagnostic tool and a reliable technique to monitor auditory function during surgery. With the discovery of the evoked otoacoustic emissions,[26] it became possible to analyze and investigate auditory function from hair cells to the auditory cortex. Otoacoustic emissions are not electric events, however. Rather, they are audiofrequency signals that can be recorded with a sensitive microphone by use of sophisticated signal processing, and they are thought to reflect the motility of the cochlea's outer hair cells.

The active motility of outer hair cells is thought to serve as an amplifier of the displacement of the cochlear partition, resulting in various forms of otoacoustic emissions as by-products that are detectable at low intensities.[27] These acoustic by-products of outer hair cell motility are often referred to as *cochlear echoes*. Acoustic emissions may be divided into spontaneous emissions, which occur without acoustic stimulation of the ear, and evoked otoacoustic emissions, which represent a response to an acoustic stimulus delivered to the ear.[28] The evoked otoacoustic emissions may be subdivided further into transient evoked otoacoustic emissions, elicited by a transient, brief stimulus such as a click or a brief tone burst; stimulus-frequency otoacoustic emissions, elicited by a pure tone; and distortion-product otoacoustic emissions, generated by pure tones separated by a specific frequency difference. With some exceptions, evoked otoacoustic emissions may be obtained from essentially all ears with normal hearing, and may be reduced or absent in ears with a hearing loss greater than 35 to 40 dB.

Compared with evoked potential measurements, an advantage of evoked otoacoustic emission measurements is the simple and brief patient preparation and examination. The test requires a probe containing a miniature loudspeaker and a microphone to be sealed into the ear canal. The stimulus eliciting the evoked otoacoustic emission is delivered by the loudspeaker, and the microphone samples the output or the emission for approximately 20 ms after stimulus stimulation. The output from the microphone is filtered, amplified, and averaged to enhance the signal-to-noise ratio. The transient evoked otoacoustic emissions consist of a delayed echo of the stimulus.[26] Transient evoked emissions span a frequency range from 0.4 to 6 kHz. The latency is typically 5 to 20 ms in humans, and the amplitude of transient evoked otoacoustic emissions tends to decrease as frequency increases.[28-30]

Distortion-product otoacoustic emissions are elicited by two stimulus tones delivered at a 55- to 85-dB sound pressure level, separated in frequency. The most prominent distortion-product otoacoustic emission occurs at the cubic difference frequency described by the expression $2f_1$-f_2, in which f_1 represents the lower frequency stimulus, and f_2 represents the higher frequency primary tone. The resultant emission typically has an amplitude that is 60 dB lower than the levels of the primary tones. It is advantageous for the two primary tones to be 10 to 15 dB apart.[28] It has been shown that there is little intrasubject variability in otoacoustic emission measurements, and that such measurements are stable over several years for any one ear.[26,28,31,32] Otoacoustic emissions also provide functional information about well-defined, frequency-specific regions of the cochlea, assisting the tracking of change in inner ear pathology characterized by outer hair cell dysfunction, such as noise-induced hearing loss or ototoxicity. Figure 133-6 illustrates transient-evoked and distortion-product otoacoustic emissions obtained from the same normal-hearing individual.

Otoacoustic emissions may be useful differential diagnostic tools for acoustic neuroma, including treatment planning. The presence of robust otoacoustic emissions indicates full cochlear outer hair cell and efferent fiber integrity, and this may serve as supplemental information supporting a planned hearing preservation surgical approach. Additionally, as shown later in this chapter, otoacoustic emissions represent an integral diagnostic measure for the diagnosis of auditory neuropathy or dyssynchrony.

The following case illustrates the differential diagnostic use of transient evoked otoacoustic emissions and ABRs. A 53-year-old man in good health noticed high-pitched tinnitus in his left ear. Pure-tone audiometry revealed normal hearing bilaterally through 2000 Hz, with bilateral notches at 4000 Hz at 20 dB in the right ear and 25 dB in the left ear. Speech recognition scores were excellent (100% for the right ear and 92% for the left ear). Because of the presence of unilateral tinnitus, however, ABR testing was carried out (Fig. 133-7). All of the component peaks of the ABR were present with left ear and right ear stimulation. Although the I to III interpeak latency was 2.28 ms for

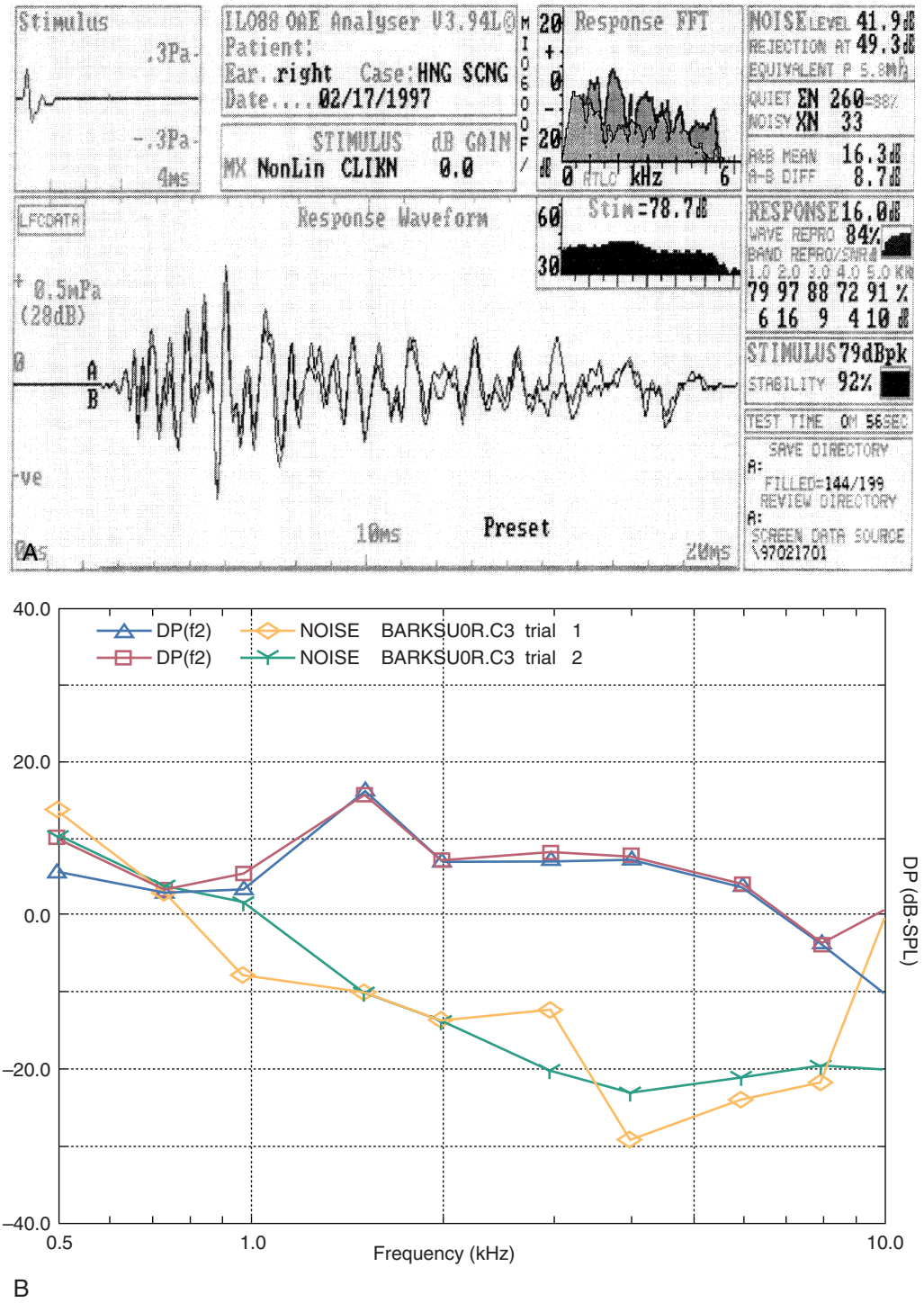


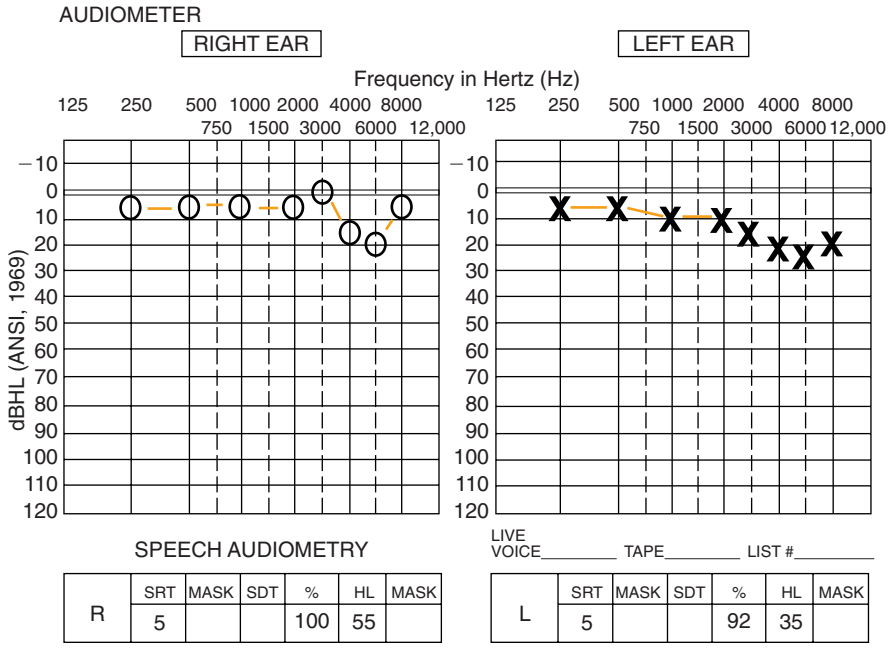
Figure 133-6. Transient evoked otoacoustic emissions **(A)** and distortion-product otoacoustic emissions **(B)** from the same normal-hearing ear.

the right ear (within normal limits), it was outside the normal limits in the left ear (2.58 ms). Magnetic resonance imaging (MRI) identified a 7-mm enhancing mass in the porus acusticus region of the left internal auditory canal.

Otoacoustic emission testing was also done to determine if there was any significant cochlear involvement (see Fig. 133-7B). This consisted of reproducible emissions at 1000 Hz and 2000 Hz (72% and 92% reproducibility), with no discernible emissions at the higher frequencies. Despite the minimal high-frequency hearing loss, this result indicated some early, subclinical cochlear involvement. Although still speculative, our observation is that impaired otoacoustic emissions in patients diagnosed with an acoustic neuroma indicate a poor prognosis for postoperative hearing preservation.

Electrocochleography

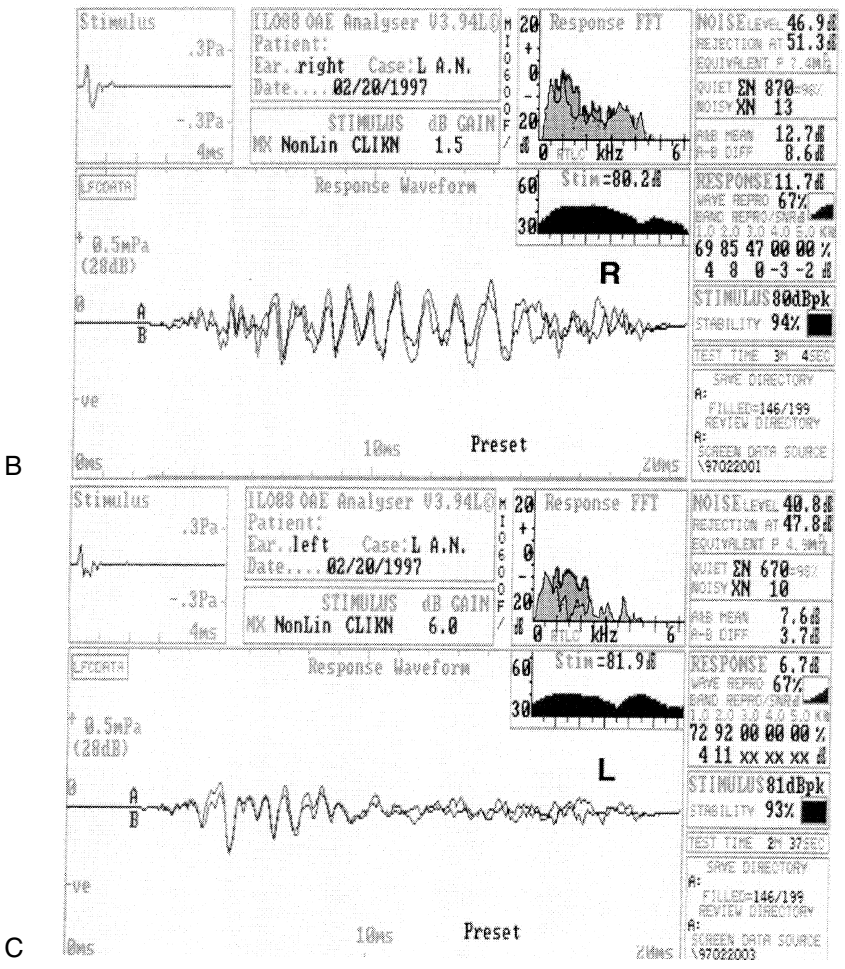
The term *electrocochleography* refers to the measurement of neuroelectric events generated by cochlear structures and the auditory nerve in response to acoustic stimulation. Depending on the mode of stimulus delivery, the electrocochleographic response may consist of the cochlear microphonic, the summating potential (SP), and the whole-nerve action potential (AP) generated by the auditory nerve. A primary clinical application of electrocochleography is in the differential diagnosis



	SRT	MASK	SDT	%	HL	MASK
R	5			100	55	

	SRT	MASK	SDT	%	HL	MASK
L	5			92	35	

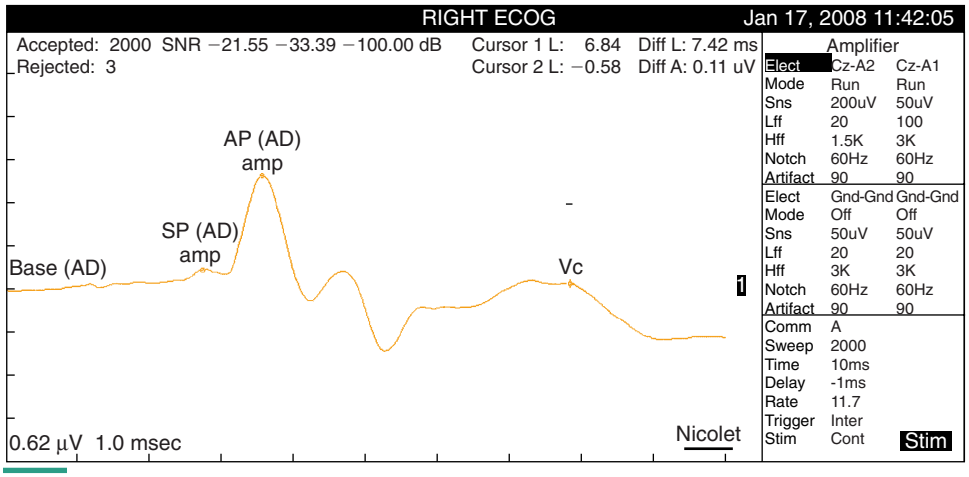
A



B

C

Figure 133-7. Audiogram **(A)**, transient evoked otoacoustic emissions **(B)**, and auditory brainstem responses **(C)** from a patient with a 7-mm intracanalicular left-sided acoustic neuroma.



RIGHT ECOG

Base (AD)	−0.58ms		
SP (AD)	1.74ms		
amp	0.30uV	SP/AP (AD)	0.18 A
AP (AD)	2.56ms		
amp	1.67uV		
Vc	6.84ms		

Figure 133-8. Electrocochleography waveform (or electrocochleogram) obtained with a tympanic membrane, hydrogel surface electrode from a normal ear. The summating potential-to-action potential (SP/AP) ratio is normal with a value of 0.18.

of hydropic conditions of the cochlea that may be associated with Meniere's disease or other diseases. It is believed that the presence of hydrops affects the elasticity of the basilar membrane and contributes to the increased amplitude of the SP relative to that of the AP. A relatively large SP/AP ratio is considered diagnostic of endolymphatic hydrops.[33] The SP/AP amplitude ratio is used instead of the absolute amplitude of the SP to avoid contamination of this measurement by interpatient variability. Patients with endolymphatic hydrops are thought to exhibit relatively larger SP/AP ratios. In one study, SP/AP ratios measured for subjects with normal hearing for their age were found to range from 0.04 to 0.59.[34] Gibson and associates[35] reported transtympanic SP/AP percentage ratios ranging from 10% to 63%. Coats and colleagues[36] found that 44% of ears considered to have Meniere's disease were below the 95% upper limit values for normal ears.

Measurement of these events requires an electrode placed as close as possible to their source. The components of the electrocochleographic response are most prominent when recorded directly with an electrode placed on the round window. Because this requires surgical exposure of the middle ear, however, it is not widely accepted for routine outpatient clinical applications. An alternative method is the use of a transtympanically placed needle electrode referenced to an electrode external to the ear (forehead or tragus).

Other, less invasive recording techniques are available as well, including the use of electrodes (e.g., the Coats leaf electrode, a gold foil–wrapped foam plug, or a tympanic membrane surface electrode) placed extratympanically in the external ear canal. The tympanic membrane surface electrode is gaining in popularity because of ease of placement and the clarity and amplitude of the responses it provides.

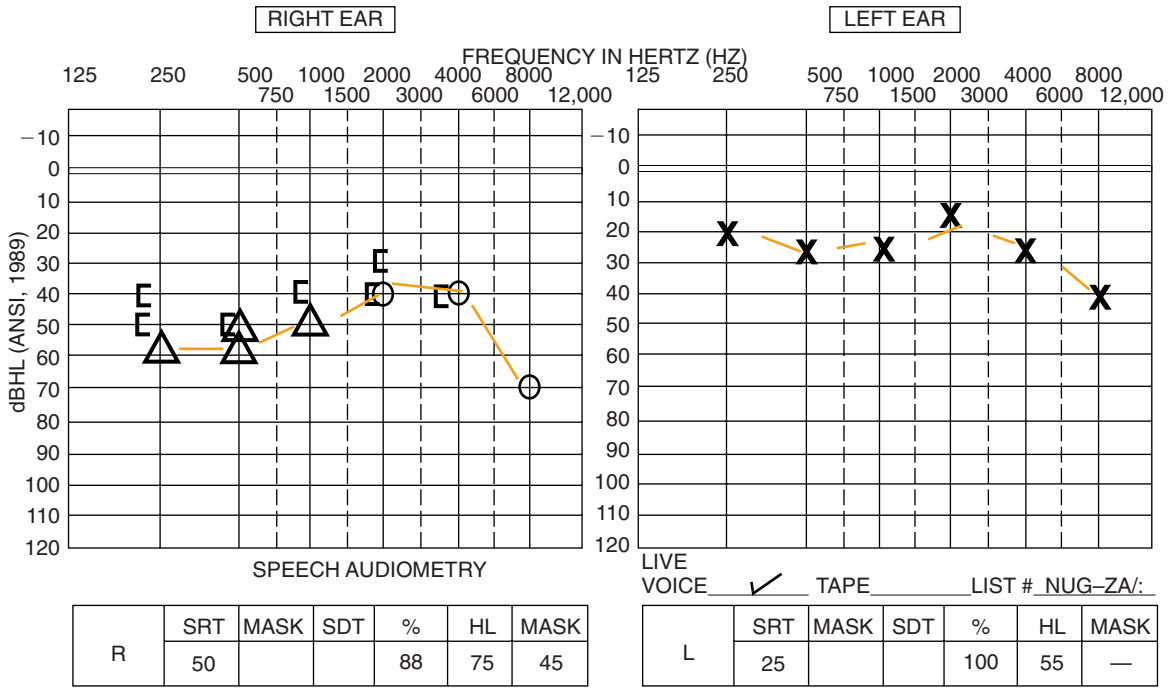
One type of tympanic membrane surface electrode consists of a hydrogel tip encasing a silver wire threaded through a soft polyethylene tube. This electrode is positioned gently over the lateral surface of the eardrum under microscopic visualization with a small nasal or Lempert speculum to avoid dislodging the electrode, as would be the case if a standard ear speculum were used. Although the amplitude of the response obtained with the tympanic membrane surface electrode is attenuated compared with a transtympanic needle recording, its ease of placement and noninvasive nature make up for this disadvantage. Figure 133-8 illustrates an electrocochleographic response recorded with a hydrogel tympanic membrane surface electrode. This response was elicited by an alternating click presented at an 85-dB normal hearing level (nHL) and clearly consists of a well-defined SP and AP.

Gibson[37] evaluated the use of electrocochleography in the diagnosis of Meniere's disease, and suggested that measurement of the absolute amplitude of the SP from responses to 1-kHz tone-burst stimuli was optimal. He considered an SP with an amplitude exceeding 3 mV abnormal. Margolis and coworkers[38] used tympanic membrane surface electrodes and provided detailed statistical information on the click-evoked SP/AP ratio, the latency difference of the AP when elicited by condensation versus rarefaction clicks, and the absolute amplitude of the SP from responses to 1- and 2-kHz tone-burst stimuli. This was a normative study involving 53 subjects. The authors found mean SP/AP ratios to depend on stimulus level, ranging from 0.22 at 78-dB nHL to 0.29 at 68-dB nHL. Ratios in the 95th percentile ranged from 0.40 to 0.49. The authors also determined normative ranges for absolute SP amplitude from responses to tone bursts. By use of a criterion of 0.35 or less for a normal SP/AP ratio and 0.5 or larger for a definitely abnormal test, Pou and associates[39] found that 57% of patients with clinically diagnosed endolymphatic hydrops were correctly identified.

The following case illustrates the utility of electrocochleography in the management of a patient with Meniere's disease. A 51-year-old woman has been followed in our department for the past 7 years. She initially presented in our clinic with a complaint of episodic vertigo, fluctuating hearing loss, aural fullness, tinnitus, and subjective hearing distortion in her right ear. Her right-sided fluctuating hearing loss has been well documented with low-frequency thresholds varying from 20 to 60 dB and values in between. She also presents with a stable high-frequency hearing loss in her right ear. The audiogram in her left ear has shown stable hearing with slightly elevated low-frequency thresholds, normal hearing in the middle frequencies, and a mild high-frequency hearing loss (Fig. 133-9).

The patient was treated conservatively with a low-salt diet and diuretics with which she was compliant; however, her hearing thresholds continued to fluctuate, and she continued to present with episodic vertigo and the frequent sensation of impending attacks. After 7 years of these symptoms, it was decided to treat her with right-sided labyrinthectomy because her hearing loss remained consistently in the moderate range with poor speech discrimination (52%). Before undertaking the operative procedure, however, it was important to confirm right-sided hydrops by electrocochleography and to rule out hydrops in her left ear to avoid ablative surgery in a case of potentially bilateral Meniere's disease.

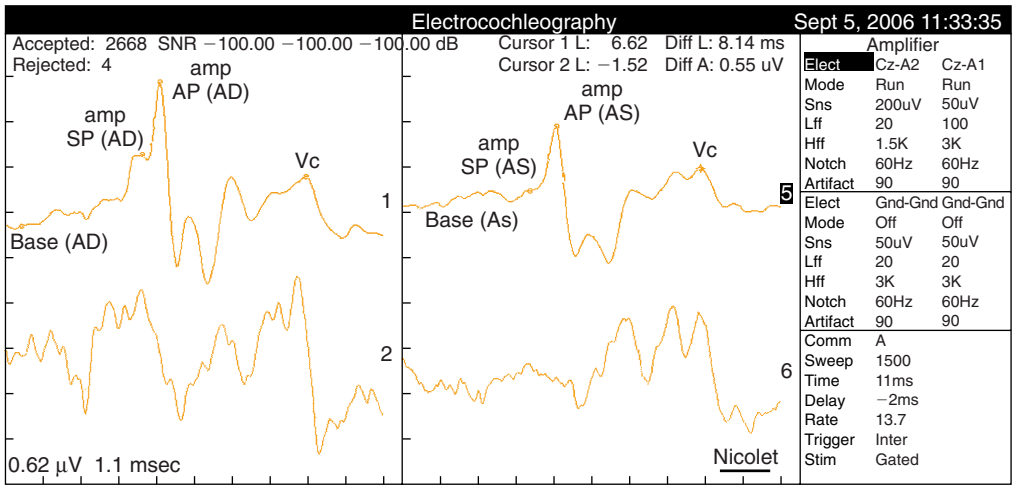
Electrocochleography was done using a combination of surface electrode and a tympanic membrane surface electrode introduced under microscopic observation. The tympanic membrane surface electrode consists of a Silastic tube–enclosed silver wire with its uninsulated tip surrounded by hydrogel. For optimal recording, the hydrogel was briefly dipped into conductive electrode cream and inserted into the external ear canal using a small nasal speculum and the otomicroscope. It is important for the hydrogel end of the electrode to make contact with the tympanic membrane. The electrode is secured in the canal using the compressible foam tip of the insert transducer used to deliver the auditory stimuli to elicit the response.



	SRT	MASK	SDT	%	HL	MASK
R	50			88	75	45

	SRT	MASK	SDT	%	HL	MASK
L	25			100	55	—

Figure 133-9. Audiogram of a patient with right-sided Meniere's disease.



Electrocochleography

Base (AD)	−1.52ms		Base (AS)	−1.52ms	
SP (AD)	1.96ms		SP (AS)	1.70ms	
amp	1.01uV	SP/AP (AD) 0.50 A	amp	0.24uV	SP/AP (As) 0.22 A
AP (AD)	2.49ms	Vc-AP-AD 4.22ms	AP (AS)	2.44ms	Vc-AP (As) 4.18ms
amp	2.00uV		amp	1.12uV	
Vc	6.71ms		Vc	6.62ms	

Figure 133-10. Electrocochleography results from a patient with right-sided Meniere's disease. The summating potential-to-action potential (SP/AP) ratio was elevated to 0.50 on the right, involved side and was normal with a value of 0.22 on the left, uninvolved side.

Figure 133-10 shows the results of the electrocochleography evaluation. A two-channel recording protocol is illustrated: the upper trace is the electrocochleography recording using the tympanic membrane electrode, the lower trace is a contralaterally recorded auditory brainstem response (ABR). In this fashion, it is possible to record and evaluate the ABR simultaneously. With right (symptomatic) ear stimulation, a prominent SP was noted, and when calculating the amplitude ratio of the SP to AP (reference to a prestimulus baseline), the ratio for the right ear was elevated with a value of 0.5 and the ratio for the left, asymptomatic ear was normal with a value of 0.22. These results confirmed the presence of hydrops in the patient's right symptomatic ear and ruled out hydrops in her left ear. She subsequently underwent a right-sided labyrinthectomy with no complications. At the same time, she received a bone-anchored hearing aid on the right side to compen-

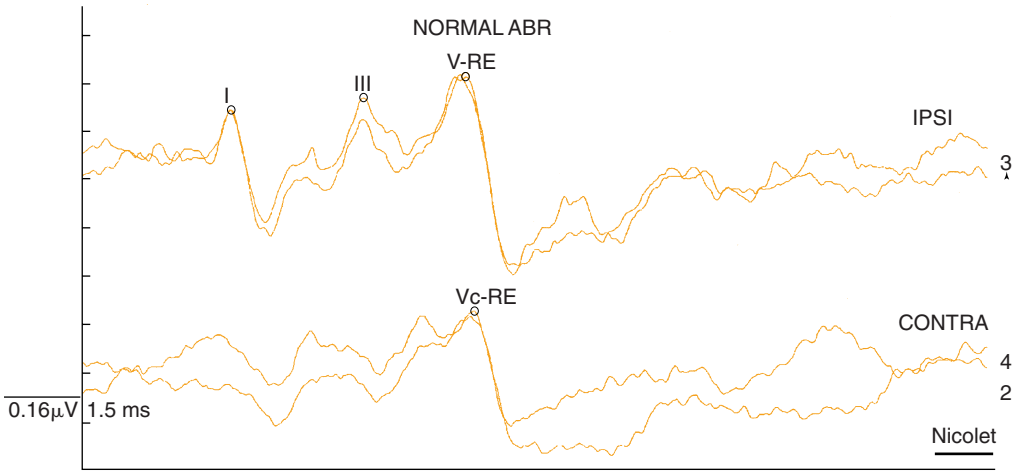


Figure 133-11. Typical two-channel auditory brainstem response recording obtained from a normal-hearing patient using 75-dB nHL clicks.

sate for the complete loss of hearing on the right resulting from labyrinthectomy. This patient has been followed in our otology clinic for several months since her surgery, and she is completely free of her previous vestibular symptoms.

Auditory Brainstem Response

The ABR is a surface-recorded averaged response representing the activity of the distal portion of the auditory pathway. It is used to determine auditory sensitivity objectively, to diagnose neuropathology along the auditory pathway, and to serve as a reliable intraoperative monitoring tool during surgical procedures that place auditory structures at risk. A normal ABR contains five to seven peaks occurring within a time frame of less than 10 ms. For neurodiagnostic purposes, the first five positive polarity peaks (waves I through V) are typically considered. Audiometric evaluation must always precede the ABR test to ascertain that the level of stimuli used to elicit the ABR is within the patient's auditory dynamic range. Clicks and brief frequency-specific tonal stimuli may be used to elicit the ABR. Clicks are brief rectangular pulses (typically 100 ms in duration) delivered to an acoustic transducer at constant or alternating polarity. Tone-pips are brief sinusoidal stimuli (one to two cycles) with short rise and fall times. Both types of stimuli have the ability to generate the synchronized activation of auditory nerve fibers necessary to elicit an evoked potential. Typically, 1000 to 3000 sweeps triggered to coincide with the onset of the stimulus should be averaged to obtain a robust, well-defined ABR. Replication of each condition is advisable to confirm the presence and configuration of the response.

The ABR may be recorded with standard or disposable surface electrodes placed high on the forehead below the hairline or at the vertex (noninverting electrode); on the medial surface of the ipsilateral earlobe; or on the medial surface of the contralateral earlobe (ipsilateral and contralateral inverting electrodes) and on the center of the forehead (ground electrode). These electrodes may be used for a typical two-channel montage with the ipsilaterally referenced channel emphasizing wave I (synonymous to the N1 of the electrocochleogram), and the contralaterally referenced channel emphasizing the separation between waves IV and V.

In addition to signal averaging, the configuration of the response is improved and shaped further through the use of bandpass filtering. Typically, a high-pass filter setting of 100 Hz and a low-pass filter setting between 1000 Hz and 3000 Hz are used. The use of a high-pass filter setting significantly greater than 100 Hz is not advised to avoid the reduction of the amplitude of wave V. A robust wave V is desirable for hearing sensitivity testing applications and neuro-otologic applications.

Investigations by Moller and Jannetta[40] suggest that the neural generators of peaks I through V originate from the cochlear nerve through the nucleus of the lateral lemniscus in the midbrain. Waves I and II of the ABR reflect the activation of the distal and proximal segments of the cochlear nerve. The two APs generated by the cochlear nerve may be attributed to the change from Schwann's cell endoneurium peripherally to the neuroglial cover of the proximal segment of the nerve. This shift occurs near the porus acusticus, and contributes to a change in neural conduction properties. Waves III and IV reflect the activation of the cochlear nucleus complex and the superior olivary complex.

Moller and Jannetta's study[40] also indicates that wave V is associated primarily with the activation of the lateral lemniscus and not the inferior colliculus as was previously considered. Ponton and colleagues[41] have shed further light on the generator sources and maturation of the ABR. They concur with Moller and Jannetta[40] regarding the generator sources for waves I and II. Their studies indicate that wave III originates from axons coursing from the cochlear nuclei in the ventral acoustic stria. The studies further indicate that waves IV and V also are associated with the activation of parallel subpopulations of ascending axons originating from the cochlear nuclei continuing on to higher brainstem levels. The III to IV interpeak interval indicates axonal conduction within the pathway from the cochlear nuclei to the contralateral lateral lemniscus and inferior colliculus.

Figure 133-11 illustrates a typical two-channel ABR elicited from a normal-hearing patient by 75-dB nHL clicks. The ipsilaterally referenced channel strongly emphasizes wave I, whereas the contralaterally referenced channel emphasizes the separation between waves IV and V.

The ABR reflects the activation of the auditory pathway from the cochlear nerve through the first two or three synapses of the afferent auditory pathway. ABR thresholds correlate well with behavioral auditory thresholds (see Chapters 134 and 190), and changes in the configuration or latency structure may provide information regarding the presence of neuropathology in the cerebellopontine angle or brainstem. Because the brainstem is relatively impervious to sedatives, anesthetics, and central nervous system depressants, it is an ideal tool to determine auditory sensitivity objectively, to diagnose neuropathology along the auditory pathway, and to serve as a reliable intraoperative monitoring tool during surgical procedures that place auditory structures at risk.

Neurodiagnosis with the Auditory Brainstem Response

The typical effect of mass lesions in the vicinity of the auditory pathway or, more specifically, in the cerebellopontine angle is associated with abnormal ABR configuration as a result of pressure-related displacement or attenuation of neural components of the auditory pathway. ABR abnormalities associated with such pathologies may range from a complete absence of ABR coexisting with reasonable hearing thresholds to absent ABR components or simply to delayed peak latencies. The presence of hearing loss, which is common in patients who undergo

workup for retrocochlear disease, should be carefully considered when interpreting the ABR. If audiologic information is ignored, an absent ABR may be interpreted as an extreme abnormality associated with a mass lesion of the auditory pathway, when it actually may result from the use of inadequate auditory stimulus levels given the magnitude of the patient's hearing loss. The authors propose a hierarchy of ABR interpretation meant to take into consideration auditory sensitivity and neuropathologic aspects.[42,43] This diagnostic analysis consists of the following three steps:

1. The first step is determination of the presence or absence of an ABR when an appropriate stimulus is used. A complete absence of ABR elicited by 85-dB nHL clicks in a patient with severe to profound hearing loss may not indicate retrocochlear pathology. Every effort needs to be made to elicit a response at levels that would be expected based on the patient's auditory thresholds.

2. Given the presence of a replicated response, the presence or absence of all major component peaks needs to be established. This is done considering that wave V is the most robust of the ABR components and persists with significant degrees of hearing loss; waves I and III are less robust. Wave I is difficult to resolve with hearing loss exceeding 40 to 45 dB at higher frequencies, with wave III persisting beyond that. Failure to identify wave I does not correlate with neuropathology along the auditory pathway. An absent wave V in the presence of a replicated wave I or III is a definitive diagnostic indicator of retrocochlear involvement, however.

3. Given that the presence of a response has been established, and ABR component peaks I, III, and V are clearly present and replicable, diagnostic decisions are based on the measurement of interpeak latencies I to III, interpeak latencies III to V, or the absolute latency of wave V and its interaural latency difference. This is especially helpful when interpeak latencies cannot be measured because of the absence of wave I. Interpeak latencies such as I to III or I to V are considered the most sensitive measures of retrocochlear involvement. Audiometric configuration needs to be taken into consideration, however, because it may affect the I to V interpeak latency.[44] Notched high-frequency hearing loss may be associated with increased I to V interpeak latencies in the absence of mass lesions of the cerebellopontine angle. This is most likely a reflection of the greater role assumed by high-frequency generators in producing wave I relative to those responsible for generating wave V. The I to III interpeak latency is affected to a lesser degree by cochlear hearing impairment. The most sensitive interpeak latency measure seems to be the increase in the I to III interpeak latency of the affected side.[45,46] Measurement of waves I and III is the gold standard for neurologic diagnostic applications. At our facility, we have used the following interpeak latency and interaural absolute latency diagnostic criteria for click stimuli since 1985: I to III, 2.3 ms or higher; III to V, 2.1 ms or higher; I to V, 4.4 ms or higher; and interaural latency difference to V, 0.4 ms or higher.

We also routinely use 1000-Hz tone-pips to elicit ABRs in an attempt to disregard the effects of elevated auditory thresholds in the 2000- to 4000-Hz frequency range on absolute and interpeak latencies of the click-evoked ABR.[47] By use of a Blackman Gating function[11] with a rise or fall time of 2 ms and no plateau, we established that it is possible to elicit ABRs from patients with normal hearing across the frequency range and from patients with high-frequency hearing loss. We compared wave V latency for 1000-Hz tone-pips between two groups of patients with cochlear SNHL; one group consisted of subjects with normal hearing, and one group consisted of subjects with hearing loss at 2000 to 4000 Hz or greater. These two groups had identical, normal thresholds at 1000 Hz. There were no significant differences in wave V latencies for 1000-Hz tone-pips between the two groups. Conversely, there was a statistically significant difference in absolute latency of wave V to click stimuli, with patients with high-frequency hearing loss greater than 1000 Hz presenting with prolonged absolute wave V latencies despite the absence of retrocochlear involvement.

Next, wave V latency values for 1000-Hz tone-pips were compared for two audiometrically identical groups. The first group consisted of subjects with cochlear hearing loss, and the second group consisted of subjects with confirmed acoustic neuromas, but pure-tone audiograms identical to those of subjects with cochlear losses. The results of the study indicated that patients with confirmed acoustic neuromas had significantly delayed wave V latency values compared with the control group with identical pure-tone profiles. Subjects with cochlear hearing losses had a mean wave V latency for 1000-Hz tone-pips of 6.7 ms, whereas subjects with confirmed acoustic neuromas had a mean wave V latency of 7.6 ms for the same stimuli, representing a statistically significant difference.[47] We also found small differences in wave V latency for ABRs elicited by 1000-Hz tone-pips, especially when stimulus levels were 85- or 95-dB nHL. At the same time, the wave V latencies obtained for four patients with confirmed acoustic neuromas significantly exceeded the latencies of patients with identical hearing losses.[48] Because latency differences with increased hearing thresholds diminished when higher level stimuli were used (≥85-dB nHL), we now recommend that 1000-Hz tone-pips be delivered at 85- to 95-dB nHL (see Fig. 133-7) regardless of pure-tone hearing sensitivity.

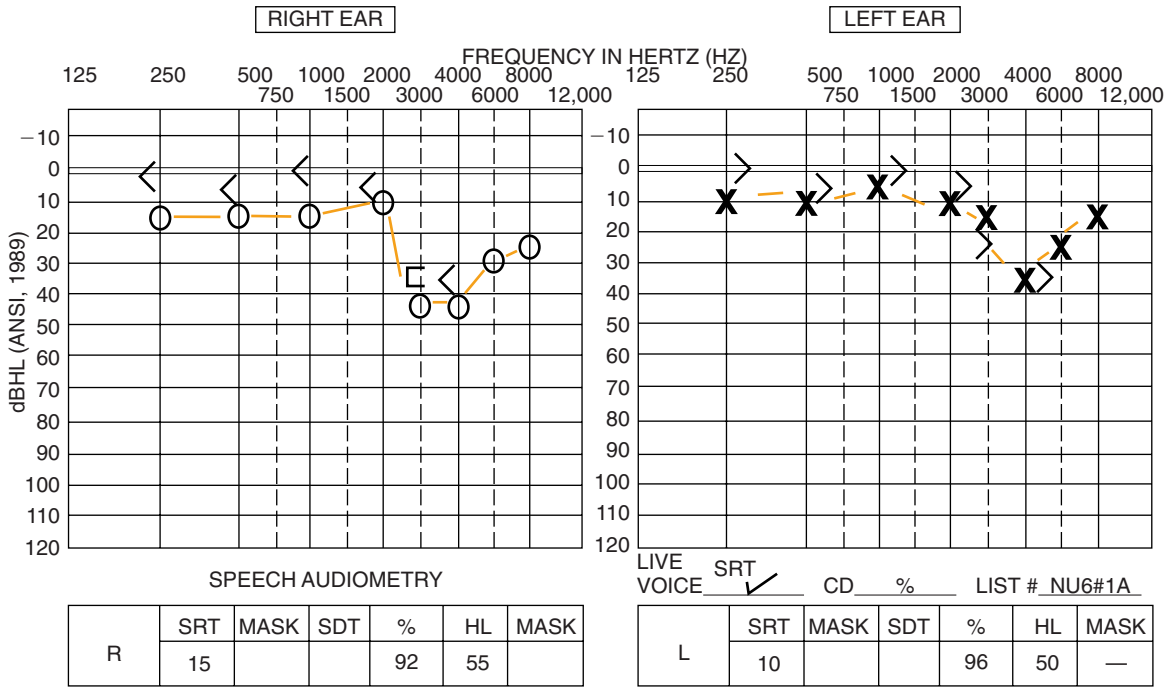
The following case illustrates the diagnostic application of ABR testing and the supplemental information derived from otoacoustic emission testing in patients in whom an acoustic neuroma was eventually diagnosed. The intraoperative monitoring use of the ABR is also illustrated by this case study.

A 56-year-old man presented with a complaint of a slight right-sided subjective hearing loss. He had a positive history of noise exposure, but was otherwise healthy, and had no other previous otologic problems. The pure-tone audiogram obtained (Fig. 133-12) shows normal hearing in low and middle frequencies in the left ear with a 35-dB notch at 4000 Hz with a slight improvement of threshold in higher frequencies. In the right ear, he had normal hearing in the low and middle frequencies (although 10 to 15 dB elevated compared with the left ear) and a 4000-Hz notch with a threshold of 50 dB (compared with 35 dB in the left ear). Speech discrimination was excellent in the left ear (100%) and still very good in the right ear (96%). Tympanograms were normal (type A) bilaterally, and ipsilateral and contralateral acoustic reflex thresholds were between 85 dB and 90 dB bilaterally with negative reflex decay in the left ear and the right ear.

Distortion product otoacoustic emission testing was also carried out with left ear and right ear stimulation. In the left ear, robust emissions (>6 dB above noise floor) were obtained at six test frequencies ranging from 700 to 4000 Hz. With right ear stimulation, robust emissions were obtained at the same frequencies as in the left. Otoacoustic emission testing ruled out outer hair cell involvement bilaterally within low and middle frequencies. Emissions were absent bilaterally in the high frequencies compatible with the noise-induced hearing loss–associated notch.

ABR studies were also done because of the patient's complaint and slightly asymmetric hearing loss (Fig. 133-13). Robust responses were obtained bilaterally with peaks I through V easily identified and well replicated. Steps 1 and 2 in our diagnostic protocol were negative. Next, peak and interpeak latencies were evaluated. With left ear stimulation using clicks, the I to III (2.16 ms) and I to V (4.02 ms) interpeak latencies were normal. The absolute latency of wave V with 1000-Hz tone-burst stimulation was also normal with a value of 7.8 ms. With right ear stimulation, the I to III (2.70 ms) and the I to V interpeak latency (4.50 ms) were outside normal limits, suggesting the presence of retrocochlear involvement. The absolute latency of wave V with 1000-Hz tone-burst stimulation was also abnormally prolonged to 7.80 ms (as opposed to 7.08 ms with left ear stimulation).

These results indicate a high likelihood for the presence of retrocochlear involvement, and subsequent MRI studies identified an 8-mm right-sided acoustic neuroma. Because of the good hearing, the presence of robust otoacoustic emissions, the excellent speech discrimination score (96%), and the small size of the tumor, a middle cranial fossa approach with planned hearing preservation procedure

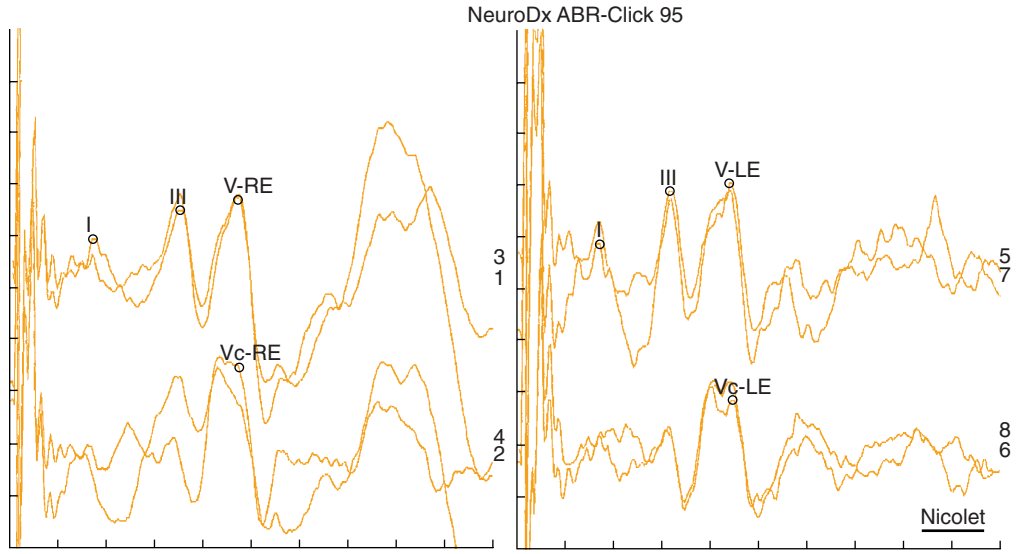


SPEECH AUDIOMETRY

	SRT	MASK	SDT	%	HL	MASK
R	15			92	55	

	SRT	MASK	SDT	%	HL	MASK
L	10			96	50	—

Figure 133-12. Audiogram of a patient with right-sided acoustic neuroma.



Sensitivity and Sweep Time per Division

1	0.16 µV	1.5 msec	2	0.16 µV	1.5 msec	3	0.16 µV	1.5 msec	4	0.16 µV	1.5 msec
5	0.16 µV	1.5 msec	6	0.16 µV	1.5 msec	7	0.16 µV	1.5 msec	8	0.16 µV	1.5 msec

NeuroDx ABR - Click

I	2.52ms	RE I-III	2.70ms	I	2.52ms	LE I-III	2.16ms
		RE III-V	1.80ms			LE III-V	1.86ms
III	5.22ms	RE I-V	4.50ms	III	4.68ms	LE I-V	4.02ms
		I/V Ratio				I/V Ratio	
V-RE	7.02ms			V-LE	6.54ms		
Vc-RE	7.08ms			Vc-LE	6.66ms		

Figure 133-13. Auditory brainstem responses from a patient with right-sided acoustic neuroma.

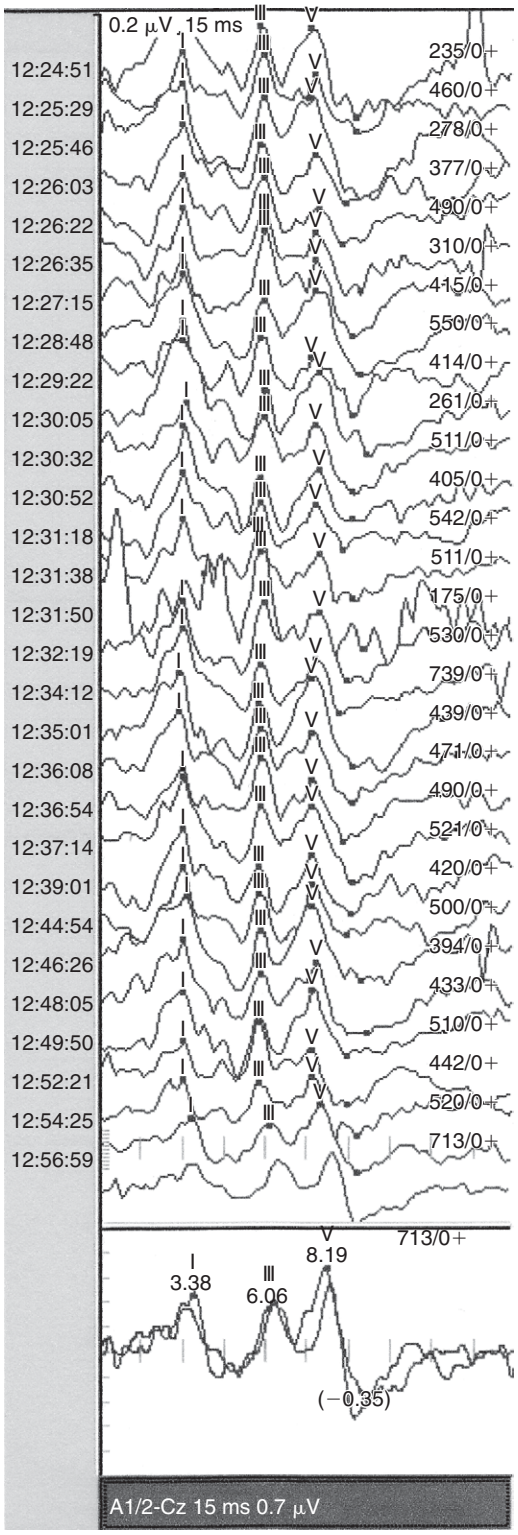


Figure 133-14. Sequence of auditory brainstem responses obtained during intraoperative monitoring during a middle cranial fossa resection of a right-sided acoustic neuroma.

was undertaken. During the surgical procedure, continuous facial muscle electromyography and ABR monitoring were carried out. Figure 133-14 shows a sequence of ABRs obtained during the middle cranial fossa surgical resection of this mass. As can be seen in this figure, the ABR remained robust with minor changes in overall latency. The bottom two superimposed traces represent the baseline ABR obtained before tumor resection but after the opening of the dura. The second superimposed wave form is the final measurement obtained after the successful resection of this mass. These two responses are almost completely identical, attesting to an excellent prognosis for postoperative hearing preservation. Serial audiograms obtained postoperatively over 1 year indicate minimal changes in right-sided audiometric thresholds. At the most recent evaluation, speech discrimination scores in the right ear were measured to be 100%.

Neurodiagnostic Studies in Patients with Auditory Neuropathy or Dyssynchrony

Auditory neuropathy or dyssynchrony is a condition that may be referred to in simpler terms as *neural hearing loss*. This condition is diagnosed predominantly in infancy and early childhood, and has received particular attention in recent years. Although there are many variants of this condition, and different degrees of severity, the condition is typically characterized by significant hearing loss that is evident behaviorally and, if some form of audiometry can be obtained, audiometrically.

Although most cases of newly diagnosed nonconductive hearing loss are due to a cochlear etiology (i.e., either a diminished or absent outer hair cell population or a complete absence of hair cells), this condition is by all indications not specifically related to cochlear function. Experimental studies[49] have shown, however, that this condition can be modeled by temporarily disabling inner hair cell function. Similar diagnostic test results may be obtained in patients with substantial hyperbilirubinemia and respiratory distress syndrome. In this population, this condition may be reversible in some cases during the first year of life.

The ideal management of these patients is subject to disagreement among audiologists and otolaryngologists. Some clinicians strongly oppose even the attempt of acoustic amplification; others consider this a condition similar to other types of sensorineural hearing loss, and believe that at least an initial trial with amplification is warranted. There is, however, reasonable agreement in the field that if all else fails many of these patients may be considered cochlear implant candidates, and there is now evidence that many of these patients do well with a cochlear implant.

The diagnostic battery in these patients includes ABR testing with constant polarity stimuli (rarefaction *and* condensation) to attempt to identify the presence of a cochlear microphonic in the absence of an ABR, and otoacoustic emissions. The "typical" picture is of a child or infant with all behavioral indications of significant hearing loss; a completely absent ABR—a completely absent wave V at even high intensities the presence of appropriate phase cochlear microphonics (i.e., the polarity should mirror the polarity of the stimulus); and relatively intact otoacoustic emissions.

The presence of a cochlear microphonic and of the otoacoustic emissions serves as an indication for the presence of relatively intact outer hair cell function. The absent wave V at even high stimulus intensities coincides with the behavioral and audiometrically demonstrated hearing loss. If an electrically evoked ABR is carried out in these patients preoperatively using transtympanic stimulation,[50] wave V appears. Some workers have used this information to conclude that because electrical stimulation is more effective to recruit neural synchrony, and a wave V is identifiable with electrical stimulation, the underlying problem is one of poor neural synchrony, which results in an absent acoustic ABR and the aforementioned behavioral manifestations.

First, let us dispel a myth: "Only patients with auditory neuropathy have a cochlear microphonic." Figure 133-15 illustrates ABRs from a normal-hearing subject using rarefaction and condensation clicks. As can be seen in this figure, following the click is electromagnetic stimulus artifact; opposite-polarity cochlear microphonics can be seen in the early portion of these tracings preceding robust wave Vs obtained with rarefaction and condensation click stimulation. The bottom traces illustrate an attempt to obtain ABRs using rarefaction and condensation clicks from a patient with auditory neuropathy.

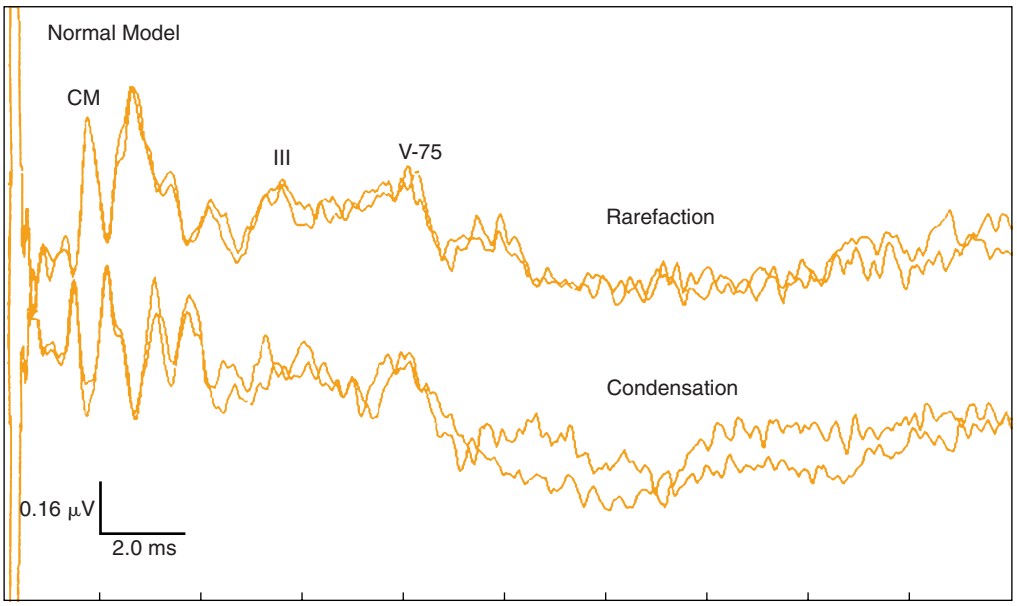


Figure 133-15. Auditory brainstem responses including robust cochlear microphonics obtained from a normal-hearing infant using condensation and rarefaction clicks.

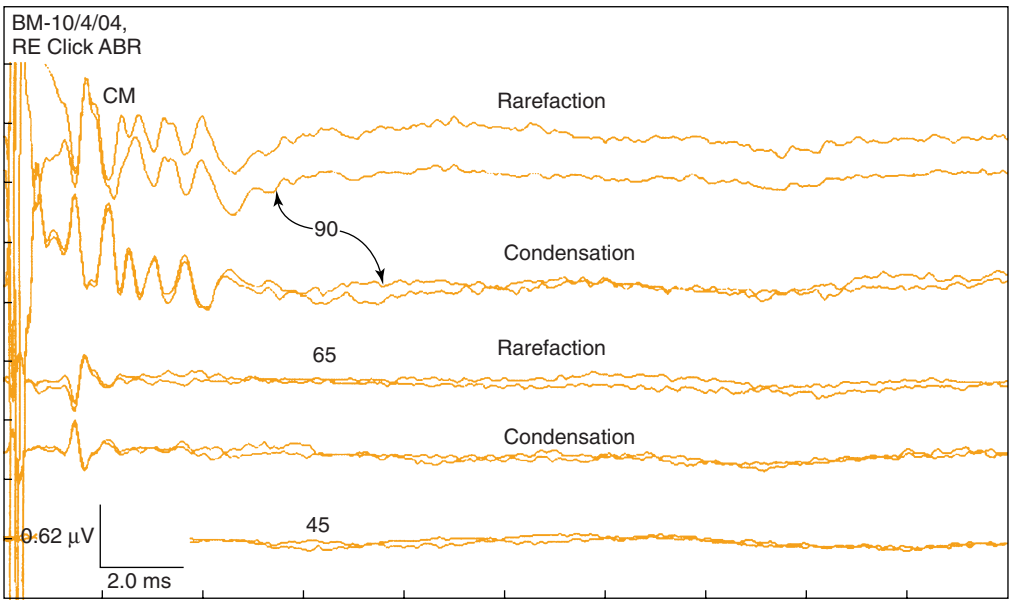


Figure 133-16. Cochlear microphonics without auditory brainstem response components obtained using condensation and rarefaction clicks from a patient diagnosed with auditory neuropathy or dyssynchrony.

Opposite-polarity microphonics can be identified particularly in the upper set of traces obtained at 90 dB; however, no synchronous electrophysiologic activity, such as wave V, can be seen in the continuation of this time window.

If one so desires, one can look at cochlear microphonics in patients with normal hearing, but in those cases the cochlear microphonic is followed by waves I, II, III and V of the ABR, which are not present in patients with auditory neuropathy. Most of the time, however, we do not attempt to obtain cochlear microphonics, in particular if wave V is noted at any intensity. Most clinicians do not comment on the presence or absence of cochlear microphonics in patients with normal hearing as indicated by the ABR or in patients with a hearing loss characterized by a threshold elevation where wave V is present at threshold and separate threshold levels.

The following case illustrates the use of otoacoustic emissions and ABRs and cochlear microphonics in the diagnosis of auditory neuropathy. This patient was diagnosed with severe to profound sensorineural hearing loss at 10 months of age. A neurodiagnostic evaluation indicated completely absent ABRs—no wave V was identified at the limits of the equipment (95 dB); however, as illustrated in Figure 133-16, cochlear microphonics were present when using rarefaction and condensation clicks. Otoacoustic emissions were present at most frequencies tested. When combining the presence of behavioral hearing loss, lack of adequate speech and language development,

absence of wave V at even high intensities, presence of cochlear microphonics, and otoacoustic emission, the conclusion was that this patient presented with a hearing loss secondary to some type of auditory neuropathy.

The patient was considered to be a cochlear implant candidate. Transtympanic promontory, electrically evoked ABR testing was carried out to determine if the auditory neural pathway could be synchronously activated with electrical stimulation. This testing resulted in the presence of a wave V with electrical stimulation, and indicated the strong likelihood that this patient would respond positively to a cochlear implant. Cochlear implant candidacy and issues related to auditory neuropathy and cochlear implants are discussed in Chapters 134 and 158 through 160.

Evaluation of Functional Hearing Loss

Functional hearing loss, or pseudohypoacusis, is more common in adults than in children. Motivating factors in children seen with pseudohypoacusis often involve attention-seeking behavior or the avoidance of some unwanted activity, whereas direct or indirect financial gain is often a motivating factor in adults. The diagnosis of patients suspected to have pseudohypoacusis involves two components: the diagnosis of the pseudohypoacusis and the determination of the patient's true hearing sensitivity. Many patients ultimately diagnosed with pseudohypoacusis also may have an underlying true hearing loss. When taking the patient's history, it is important to note the presence of inconsistencies, complaints, and exaggerated listening effort. The patient's voice and speech quality provide important information. A patient claiming bilateral significant hearing loss with normal voice level and articulation should be suspected of functional behavior.

A simple and straightforward audiometric indicator of pseudohypoacusis is disagreement between the 500-, 1000-, and 2000-Hz PTA threshold and SRT. Typically, these two measures should agree within 5 dB. Elevated PTA thresholds with a lower SRT should be a reason to suspect pseudohypoacusis.

All patients with a unilateral hearing loss should undergo a pure-tone Stenger test.[51] This test is based on the principle that when two acoustic stimuli identical in every regard but intensity are introduced simultaneously into the left and right ears, the patient would perceive only the louder of the two stimuli. When used for the determination of pseudohypoacusis, it is common to present a tone to the better ear at about 10 dB above its threshold simultaneously with an identical tone into the poorer ear at approximately 10 dB below its voluntary threshold. If the patient's threshold in the poorer ear is correct, the patient would naturally respond to the tone presented at 10 dB above threshold in the admitted better ear. If the patient exaggerates hearing loss in the poorer ear, however, he or she would perceive the louder tone presented to the poorer ear, would be unaware of the suprathreshold tone presented to the better ear, and would not respond to these stimuli. Essentially, the patient's lack of response in this situation is an admission of having perceived the tone in the so-called poorer ear (positive Stenger).

One can bracket thresholds in the poorer ear by maintaining the suprathreshold stimulus in the better ear at a fixed intensity, while increasing the intensity of the stimulus in the allegedly poorer ear in 5-dB steps. The patient's actual threshold in the poorer ear would coincide with the level at which he or she ceases to respond despite the fact that the suprathreshold stimulus is consistently present in the better ear. This technique is referred to as minimum contralateral interference levels.

The Stenger test also can be administered using spondee words as stimuli presented simultaneously to the left and right ears. As in the case of the pure-tone Stenger, this test is appropriate if the interaural SRT difference the patient is admitting to is at least 20 dB. It is important that a sloping or rising audiometric configuration be ruled out before extended effort is invested in resolving functional hearing loss in a patient. Some patients may have a true SRT of 10-dB HL along with a steeply sloping high-frequency SNHL with normal thresholds in the low-frequency range.

Sources of Error in Audiologic Testing

Audiologic errors may originate from two main sources: faulty clinical judgment or decision and technical errors.

Errors in Clinical Judgment

Inappropriate diagnostic test selection and failing to refer a patient for further audiologic or other diagnostic tests are the most common errors related to clinical judgment. Failure to follow up on a discrepancy between the three-frequency PTA threshold (500 Hz, 1000 Hz, and 2000 Hz) and SRT may lead to failure to diagnose functional hearing loss. Failure to continue the audiologic testing with a Stenger test in a case of apparent unilateral hearing loss, especially when the patient's history is contributory, also may result in missing the diagnosis of functional hearing loss. Stenger testing is strongly recommended for every patient with a unilateral or asymmetric hearing loss. Another error related to clinical judgment is the failure to recommend and carry out appropriate follow-up in a patient with preexisting bilateral SNHL who has an asymmetric unilateral progression of hearing loss. This failure may lead to a misdiagnosis or delayed diagnosis of retrocochlear involvement, among other problems. The following case is illustrative of this type of error.

A 61-year-old man with a 7-year history of bilateral, high-frequency SNHL came to our clinic for a second opinion. The patient had reported a further progression of his hearing loss, predominantly in the left ear, approximately 6 months before coming to the clinic. He was seen elsewhere and was reassured that he was experiencing an expected change in hearing related to his preexisting hearing loss. Figure 133-17 illustrates this patient's two most recent audiograms (not taken at our clinic), which were obtained approximately 1 year apart. Over the course of 1 year, there was a progression of hearing loss in the right ear at 4000 Hz and 8000 Hz of 20-dB HL and 25-dB HL. In the left ear, hearing thresholds were elevated across the frequency range, more so for the high frequencies, where up to a 55-dB threshold shift was observed at 8000 Hz. Speech discrimination scores remained very good at 96% and 92%, for the right and the left ears.

ABR testing carried out during his first visit to the clinic (Fig. 133-18) consisted of normal configuration and normal peak and interpeak latencies for the right ear and a poorly resolved response in the left ear with reduced amplitude and abnormal increased interpeak latencies. MRI showed a small cerebellopontine angle mass on the left side, with most of the mass within the porus acusticus. This was subsequently diagnosed as a vestibular schwannoma and resected through a translabyrinthine approach. In this case, inattention to the more pronounced progression of hearing loss in the patient's left ear, coupled with the maintenance of normal speech discrimination scores in the affected ear, may have contributed to the lack of concern and the failure to consider further clinical tests. It is clear, however, that hearing loss in the patient's left ear progressed more substantially than that in the right ear, and warranted further clinical investigation.

Technical Errors

Lack of attention to interaural attenuation and insufficient or excessive masking are the most common sources of technical error. This is most pronounced in patients with mixed, bilateral hearing loss who give rise to the so-called masking dilemma. The main problem in these patients is that when attempting to mask the nontest ear, overcoming the conductive component may involve masker levels exceeding interaural attenuation. This causes the masker to cross over to the test ear, resulting in artificial elevation of its threshold. Conversely, inadequate masking in unilateral moderate to severe SNHL may create a false air-bone gap, and the impression of a surgically correctable conductive hearing loss. This would occur because in the presence of inadequate masking, bone-conduction thresholds in the test ear with a true, severe SNHL would continue reflecting the shadow curve of the contralateral ear, exhibiting a false air-bone gap between the true air-conduction thresholds and the false bone-conduction thresholds. Because of the more substantial interaural attenuation associated with air-conducted signals, it is easier to obtain accurate, masked

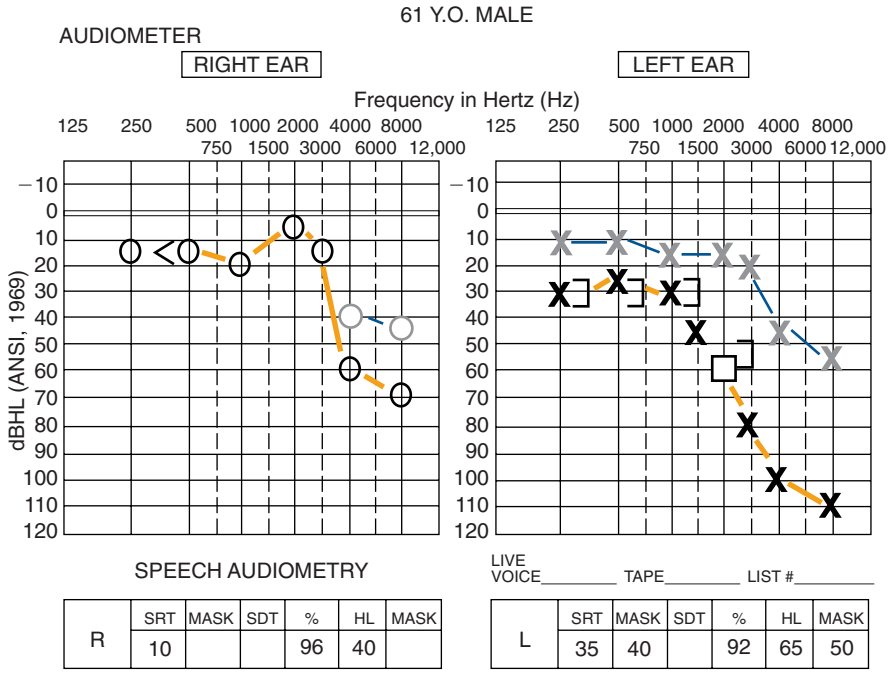


Figure 133-17. Audiograms showing asymmetric threshold shift (left more than right) occurring over a 1-year period in a patient subsequently diagnosed with a left-sided acoustic neuroma.

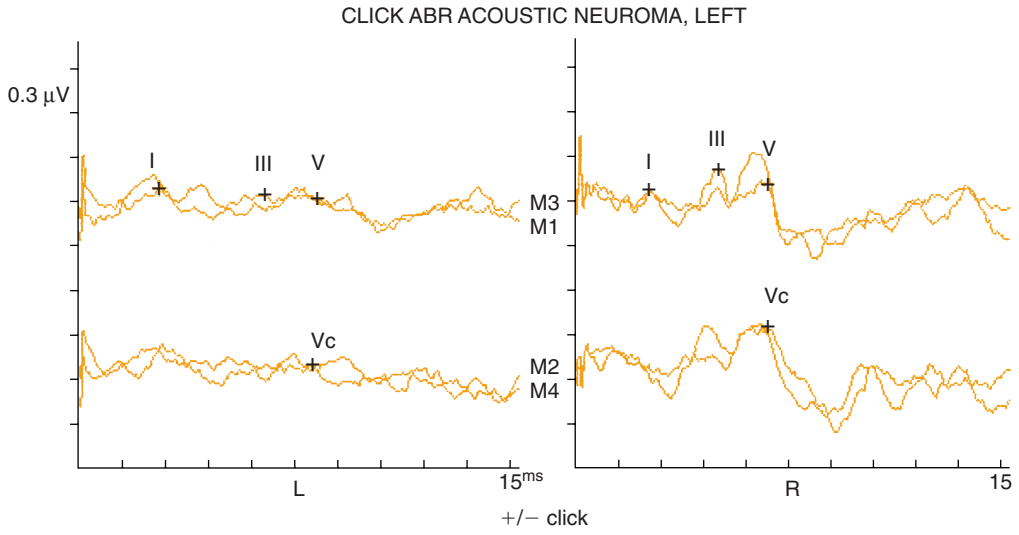


Figure 133-18. Auditory brainstem responses (ABRs) from a patient with left-sided acoustic neuroma. The left ABR is characterized by reduced amplitude and abnormal inner peak intervals.

air-conduction thresholds. Sufficient masking of the nontest ear can resolve such a problem.

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CHAPTER ONE HUNDRED AND THIRTY-FOUR

Electrophysiologic Assessment of Hearing

Carolyn J. Brown

Tiffany A. Johnson

Key Points

- Otoacoustic emissions are sounds generated in the cochlea and recorded in the ear canal that reflect activity of the outer hair cells.
- Otoacoustic emissions can be recorded in quiet, but more commonly are evoked in response to acoustic stimulation. Clicks or tone bursts can be used to elicit transient evoked otoacoustic emissions (TEOAEs). Continuous sinusoidal stimuli are used to evoke distortion product otoacoustic emissions (DPOAEs).
- Otoacoustic emissions can be used to assess the status of cochlear outer hair cells. Specifically, the presence of otoacoustic emissions (either TEOAEs or DPOAEs) is consistent with normal outer hair cell function, and indicates that the individual being tested is likely to have no worse than a mild to moderate sensorineural hearing loss.
- Otoacoustic emissions have also proven to be useful in diagnosing dyssynchrony within the auditory periphery.
- Electrocochleography is a measure of the synchronous response of the auditory nerve to the presence of an acoustic stimulus. It is optimally recorded using an electrode placed on the tympanic membrane or the promontory of the middle ear. Clinical applications include assisting in the differential diagnosis of Meniere's disease and as a method of assessing the response of the auditory nerve during otoneurologic surgery.
- Auditory brainstem responses (ABRs) are far-field recordings of the synchronized response of neurons within the synaptic relay stations of the auditory brainstem, and can be used to detect impaired neural conduction from various potential neurotologic pathologies.
- The primary application for the ABR in medical settings today is as a tool that can be used to estimate auditory sensitivity in very young or otherwise difficult-to-test populations.
- The auditory steady-state response (ASSR) is an evoked potential that reflects a far-field recording of electroencephalographic activity evoked using continuous sinusoidal stimuli that are either amplitude or frequency modulated.
- The ASSR has emerged as an alternative to tone burst evoked ABR for estimating auditory sensitivity.
- Although less frequently recorded in routine clinical practice, numerous cortical or precortical auditory evoked potentials can be used to assess higher level auditory function. These responses generally require less neural synchrony than the ABR, and as a result have the advantage of being able to be recorded using longer duration, more frequency-specific tonal stimuli or speech.
- Each of the acoustically evoked auditory potentials described in this chapter can also be elicited in response to electrical stimulation provided by a cochlear implant.
- Electrically evoked auditory potentials can be used to assist with the process of fitting the speech processor of the cochlear implant, to help differentiate between cochlear implant failures and lack of neural response in patients who are showing limited or no benefit, and to monitor changes over time in the neural response to electrical stimulation.
- When applied in a strategic manner, the techniques of electrophysiologic recording from the auditory pathology described here provide complementary and highly specific guidance in the clinical assessment of auditory, vestibular, and skull base disorders.

This chapter describes the range of electrophysiologic techniques that can be used to assess hearing sensitivity, and to assist in the differential diagnosis of the site of a lesion within the auditory system for individuals with impaired hearing. These measures include otoacoustic emissions (OAEs), electrocochleography (ECoG), auditory brainstem response (ABR), auditory steady-state responses (ASSRs), middle and long latency evoked potentials, and a similar range of electrically evoked auditory potentials. This chapter provides the reader with an overview of these measures: how they are recorded, their strengths, their weaknesses, and potential clinical applications. Chapter 133 expands this focus to provide case studies and a series of examples of how these evoked potentials can be used to inform clinical decision making.

Otoacoustic Emissions

In 1978, Kemp[1] showed that the healthy inner ear emitted very low intensity sounds that could be measured using a sensitive microphone

sealed into the ear canal. These responses not only occurred spontaneously, but also could be evoked. Kemp theorized that these low-level acoustic signals originated from the outer hair cells (OHCs) of the cochlea and were a by-product of the nonlinear processing of the healthy inner ear. In the years that followed, support for Kemp's theories grew. In the early 1980s, Brownell[2] showed that OHCs were capable of changing shape (contracting and elongating) when stimulated, and in the 1990s, Mammo and Ashmore[3] showed that electrical stimulation of isolated OHCs could move or modify the motion of the basilar membrane.

The general thinking today is that the normal cochlea functions much like a highly tuned, exquisitely sensitive amplifier, and it is the inherently nonlinear nature of such a system that results in the generation of OAEs. Consistent with this theory are observations that ears with damaged OHCs generally exhibit reduced sensitivity, broader tuning, and absent OAEs.[4-7] This link between the presence or absence of OAEs and the function of the OHCs has made OAEs a powerful tool for researchers and for clinicians.

There are two general classes of OAEs: spontaneous and evoked. Spontaneous OAEs are low-level acoustic signals that can be recorded in the ear canal without any external stimulation. Spontaneous OAEs are recorded only in 50% to 70% of ears with normal hearing sensitivity.[8,9] They are recorded more frequently in women than men,[10,11] and in some cases are intense enough to be detected without amplification or sophisticated recording equipment.[12,13] The presence of spontaneous OAEs is not strongly correlated with the presence of tinnitus, and the amplitude and the frequency of the spontaneous OAE can vary significantly across time.[14,15] All these factors limit the clinical applicability of spontaneous OAEs. Although their presence may indicate that at least a portion of the OHC system is intact, their absence is not clinically significant.

There are several different types of evoked OAEs, but the two that are most widely used in clinical settings are transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs). TEOAEs are low-level acoustic signals that are recorded after presentation of a brief acoustic stimulus, typically a fairly high-level click (e.g., 80 dB peSPL). The click itself has a broad frequency spectrum, and elicits oscillatory responses from OHCs located across a wide section of the cochlear partition. These local vibrations are transmitted back through the middle ear and create low-level, typically inaudible, sound pressure waves in the ear canal. TEOAEs are recordings of sound pressure waves recorded using a microphone in the ear canal. TEOAEs are typically recorded within approximately 20 ms after onset of the stimulus. High-frequency components in the response, which originate from locations near the base of the cochlea, require a shorter travel time, and consequently are recorded earlier than the low-frequency components, which reflect response from OHCs located closer to the apex of the cochlea.

TEOAEs are usually analyzed in the frequency domain. Despite the fact that the stimulus used to elicit the TEOAE is broadband, the response itself provides frequency-specific information about the status of the cochlea between approximately 1000 Hz and 4000 Hz. Typical criteria used to establish the presence or absence of a response within a specific frequency band are signal-to-noise ratios of greater than 6 dB coupled with reproducibility measures of more than 90%. The presence of TEOAEs in ears with normal middle ear function suggests normal OHC function and is considered to be indicative of normal audiometric sensitivity. Conversely, the absence of TEOAEs within a specific frequency band is typically interpreted as evidence of audiometric thresholds worse than 25 to 30 dB HL.[7]

Figure 134-1 shows audiograms and TEOAEs recorded from three different listeners. Figure 134-1A shows results obtained from an individual with normal hearing; B and C show results from individuals with sensorineural hearing loss (SNHL). The TEOAEs recorded from the listener with normal hearing are robust for frequencies ranging from 1000 to 4000 Hz. The subject whose data are shown in Figure 134-1B has a relatively flat, moderate SNHL and no measurable TEOAE. Figure 134-1C shows results obtained from an individual with normal hearing for frequencies less than 2000 Hz and a moderate SNHL for audiometric frequencies between 3000 Hz and 8000 Hz. This subject has measurable TEOAEs only for frequencies less than 2500 Hz. No response was obtained for frequencies between 3000 Hz and 8000 Hz. The presence of TEOAEs suggests normal OHC function, and typically indicates that the listener has good audiometric sensitivity, at least for frequencies ranging from 1000 to 4000 Hz.

It is also possible to evoke OAEs using frequency-specific stimuli. DPOAEs are recorded in response to the presentation of two continuous sinusoidal signals (F1 and F2) that are introduced simultaneously into the ear canal. Because the normal cochlea is highly nonlinear, the response that is recorded in the ear canal shows evidence of distortion. The recording made using a sensitive microphone sealed into the ear canal not only includes energy at the two primary frequencies, F1 and F2, but also includes energy at numerous other frequencies that are mathematically related to the primaries. These are called *distortion products*. The distortion product most frequently used to assess auditory function is 2F1-F2. The presence of significant amounts of energy at the 2F1-F2 frequency is considered a sign that the OHCs in the region of the primaries are functioning normally, and is a finding typically observed in individuals with normal audiometric sensitivity. SNHL is often associated with loss or damage to OHCs. When the OHCs are no longer functional, the movement of the basilar membrane becomes more linear, and the energy at the distortion product frequency decreases.

Studies have shown that the most robust DPOAEs are recorded when the frequency ratio of F2 to F1 is approximately 1.2.[16,17] Additionally, for clinical applications, the levels of the two tones typically are set at 65 dB SPL and 55 dB SPL (L1 and L2) because these levels most accurately identify the ear as either normal hearing or hearing impaired.[18] By systematically varying the frequency of the two primary tones, DPOAEs can be recorded across a wide frequency range from 1000 Hz through approximately 8000 Hz. The amount of energy at the 2F1-F2 frequency that is recorded in the ear canal is compared with estimates of the noise floor of the recording system. DPOAE amplitude-to-noise ratios of approximately 6 dB typically are required before a response is considered present. To interpret the response, the amplitude of the DPOAE is compared with normative values.[6]

Figure 134-2 shows the relationship between DPOAEs and audiometric thresholds for two subjects. Figure 134-2A shows DPOAE results for a listener with normal hearing. DPOAE amplitudes ranging from −5 to 15 dB SPL were obtained for each of the test frequencies. These amplitudes were compared with the normative ranges, which are indicated by the shading on the figure. Responses above the top boundary of the shaded area are consistent with normal DPOAEs and indicate normal hearing. Responses below the lower boundary are consistent with abnormal DPOAEs and indicate hearing loss. Responses falling within the shaded region are equivocal because amplitudes in this range can be produced by ears with normal and impaired hearing. The DPOAE results shown in Figure 134-2A are above the upper boundary of the shaded region, indicating normal DPOAEs and normal hearing. The DPOAE results shown in Figure 134-2B are for a listener with normal hearing through 3000 Hz and a high-frequency hearing loss from 4000 to 8000 Hz. Consistent with these audiometric findings, DPOAEs recorded for frequencies less than 4000 Hz are normal; however, DPOAEs from 4000 to 8000 Hz fall below the lower boundary of the shaded region, indicating abnormal DPOAEs and hearing loss. Consistent with the results shown in Figure 134-2, the absence of DPOAEs in a patient with normal middle ear function suggests audiometric thresholds greater than 30 to 35 dB HL.[6]

Clinical Applications

DPOAEs and TEOAEs have become a routine part of the audiologic assessment battery in many clinics nationwide. Both of these OAEs assess the same underlying cochlear phenomenon. A finding that a patient has robust evoked OAEs, regardless of the type, is a strong indicator that the patient has normal or near-normal OHC function. This finding is typically correlated with normal hearing sensitivity. Neither DPOAEs nor TEOAEs are reliably recorded in ears with conductive pathology, nor are they recorded from individuals with more than a mild to moderate degree of SNHL. There is some indication that TEOAEs may be more sensitive to very mild amounts of hearing loss than DPOAEs, particularly at 1000 Hz. Conversely, DPOAEs may

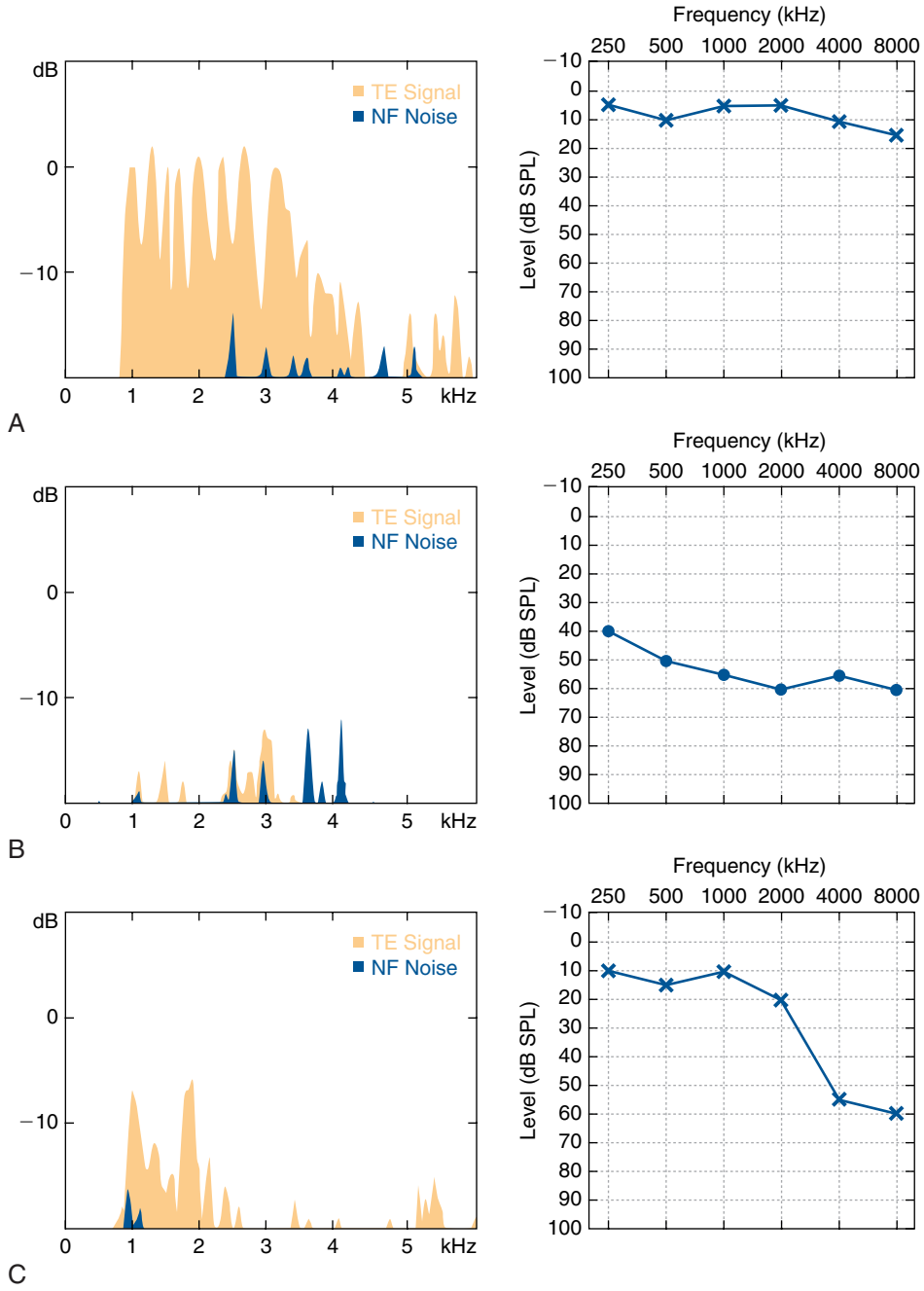

Figure 134-1. **A-C,** Transient evoked otoacoustic emissions (TEOAEs) and pure-tone audiograms are shown for three subjects. The results shown in **A** were obtained from an individual with normal hearing. Results shown in **B** and **C** were obtained from individuals with sensorineural hearing loss. The spectral components of the TEOAE are shown in *yellow* (TE Signal). The noise floor of the measurement system is shown in *blue* (NF Noise).

be slightly more sensitive to mild degrees of hearing loss for frequencies between 4000 Hz and 6000 Hz.[7,19]

The strength of evoked OAEs as a clinical tool is for screening (see Chapter 133). These responses can be recorded from neonates. They are not affected by sleep or sedation, and do not require application of recording electrodes or active participation by the child. Absence of evoked OAEs does not indicate that a child is deaf, however, and the presence of an evoked OAE does not tell anything about the integrity of the auditory nerve or central auditory system. Evoked OAEs have been recorded in profoundly hearing-impaired individuals whose hearing loss is the result of neural involvement.

The presence or absence of evoked OAEs (either TEOAEs or DPOAEs) also frequently plays a role in differential diagnosis of the cause of hearing loss—particularly for pediatric patients. Evoked OAEs can be used to assess cochlear function in patients who present with sudden-onset idiopathic hearing loss. A finding of significant evoked OAEs in an ear with audiometric thresholds worse than approximately 40 dB HL suggests that the hearing loss may have a primarily neural origin, that it may be the result of damage to structures in the cochlea other than the OHCs (e.g., the inner hair cells), or that it may serve as a red flag that should cause the clinician to question the validity of the behavioral thresholds.

The amplitude of an evoked OAE is not strongly correlated with audiometric sensitivity.[6] Evoked OAEs cannot be used to determine the degree of hearing loss an individual patient has at a given frequency. Evoked OAE amplitudes are known to be stable and repeatable across

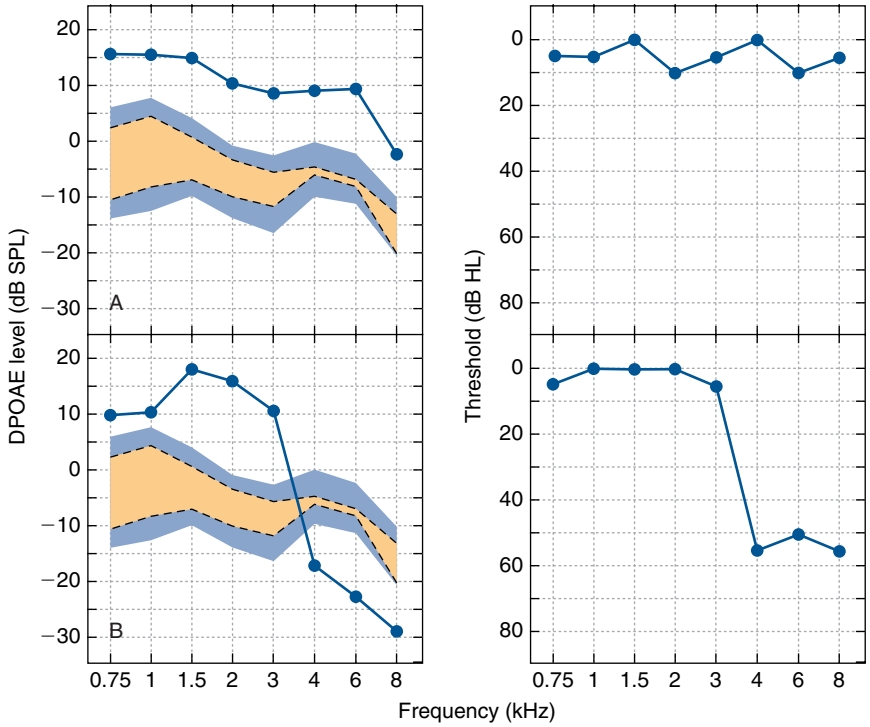

Figure 134-2. **A** and **B,** Distortion product otoacoustic emission (DPOAE) responses and audiometric thresholds obtained from an individual with normal hearing **(A)** and an individual with high-frequency hearing loss **(B)**. *(Shaded area on the graph represents normative data from Gorga MP, Neely ST, Ohlrich B, et al. From laboratory to clinic: a large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss.* Ear Hear. *1997;18:440-455.)*

time, however, with estimates of test-retest variability ranging from ±3 to 5 dB.[20] Clinically, a change in evoked OAE amplitude of more than 4 to 5 dB may signal a change in hearing sensitivity relative to a previously established baseline. Consequently, many clinicians use evoked OAEs to help monitor hearing during or immediately after ototoxic drug exposure. For patients who are very sick at the time of testing, the objective nature of the evoked OAE test itself may prove to be more reliable than behavioral thresholds, and changes in the evoked OAEs may precede changes in cochlear sensitivity.

Finally, *auditory neuropathy* and *auditory dyssynchrony* are terms that are used to describe a condition in which a patient presents with measurable evoked OAEs or cochlear microphonics or both, but with a grossly abnormal or absent ABR. The implication is that for these individuals, the hearing loss is not cochlear in origin, but is the result of some type of nonspecific damage or dysfunction of the auditory nerve. Individuals diagnosed with auditory neuropathy may or may not have other peripheral neuropathies. Audiometric thresholds can vary widely from normal to profound, but many individuals with this disorder have poor speech discrimination and receive limited benefit from amplification.[21-23]

Although many children diagnosed with auditory neuropathy have been shown to benefit from cochlear implantation, others have not shown any benefit.[24,25] Imaging studies have shown that some of these children do not have a viable cochlear nerve despite having residual OHCs, a measurable cochlear microphonic, and robust OAEs.[26] The observation of measurable evoked OAEs in a child who is being considered for cochlear implantation should suggest the medical team working with that child proceed with caution. Care must be taken to rule out the possibility that technical problems were the cause for the absent ABR, and every effort should be made to obtain behavioral thresholds before surgery. Such caution is warranted because there are numerous reports in the literature of individuals with absent ABRs and measurable evoked OAEs who are able to attain reasonable levels of word recognition without the use of a cochlear implant.

Electrocochleography

When a brief acoustic stimulus is introduced to the ear canal of an individual with normal hearing, a large section of the cochlear partition is displaced. Movement of the basilar membrane results in shearing of the stereocilia at the apical surface of the auditory hair cells, a change in the intracellular potential, and release of neurotransmitter into the synaptic cleft. This chain of events can lead to generation of an action potential by the primary afferent neurons that synapse with that hair cell.

It is possible to use electrophysiologic recording techniques to measure this chain of events. This recording is often referred to as ECoG. ECoG is a combination of three distinct evoked potentials: the cochlear microphonic (CM), the summating potential (SP), and the whole nerve or compound action potential (AP). All three potentials are recorded within a 3- to 4-ms time window after presentation of the stimulus and have been described in detail in the literature.

The CM is an intracellular evoked potential that consists of a series of deflections that follow the stimulus and reflect the instantaneous displacement of the basilar membrane.[27] The SP is characterized by a DC shift in the baseline that occurs during stimulation. It is thought to be a measure of the net depolarization of the hair cells within the organ of Corti.[28,29] Neither the CM nor the SP has a measurable response latency—a fact that often makes separation of these neural potentials from the stimulus artifact problematic. Presence of a CM or SP or both can be interpreted as being consistent with the presence of viable cochlear hair cells.

The AP is a recording of the synchronous response of numerous auditory nerve fibers. Although the CM and the SP are measured most easily using long-duration stimuli, the AP is an onset response that is typically recorded using brief stimuli such as clicks or short-duration tone bursts. In humans, the first negative peak of the AP (N1) is the most prominent feature and typically occurs with a latency of 1 to 2 ms. The N1 peak of ECoG reflects postsynaptic neural activity generated by the primary afferent auditory nerve fibers.

ECoG can be recorded noninvasively from numerous different recording electrode positions. The largest amplitude responses are obtained when a transtympanic electrode positioned on or near the promontory of the middle ear is used for recording. As the recording electrode is moved away from the cochlea, the amplitude of the response decreases.[30,31] It is still possible, however, to record ECoG from an ear canal or mastoid electrode if use of a transtympanic or tympanic membrane electrode is not feasible.

For most clinical applications, the CM is minimized through the use of alternating polarity stimulation. The magnitude of ECoG is computed by calculating the amplitude of SP and comparing that with the amplitude of the primary negative peak (N1) of the AP. Because the position of the recording electrode within the ear can have a strong effect on all three components of ECoG, investigators and clinicians often quantify the magnitude of the response that is elicited by computing the SP : AP amplitude ratio.

Clinical Applications

It is possible to use ECoG to assess auditory sensitivity. If a transtympanic or tympanic membrane recording electrode is used, ECoG thresholds can be recorded at stimulation levels that are near or only slightly above behavioral detection thresholds, and several authors have reported finding good correlations between ECoG and behavioral hearing thresholds.[32-34] Many patients do not tolerate placement of a tympanic or transtympanic recording electrode, however, and no study has shown that threshold estimates obtained using ECoG are superior to estimates obtained using the more easily recorded ABR. As a result, in recent years interest in this application for ECoG has waned. Today, the two primary clinical applications of ECoG are as a means of evaluating patients suspected to have Meniere's disease and as a method of assessing the response of the auditory nerve during otoneurologic surgery.

Meniere's disease is a progressive, debilitating disorder characterized by episodic and recurrent vertigo, fluctuating SNHL, a sensation of aural fullness, and tinnitus. The underlying cause of this disorder is thought to be increased endolymphatic pressure within the scala media. There is no way to confirm the presence of endolymphatic hydrops in vivo, and although the disorder was originally described in the medical literature more than a century ago,[35] diagnosing Meniere's disease remains a challenge.

Several studies have shown that ECoG recordings from individuals diagnosed with classic Meniere's disease exhibit enlarged SPs compared with recordings from individuals with normal hearing or SNHL resulting from an etiology other than Meniere's disease.[33] This observation led to the use of the SP : AP ratio in the diagnostic process at many otolaryngology clinics across the United States. In a meta-analysis of the literature published before 2000, Ferraro[36] showed that mean SP/AP ratios in normal ears range from approximately 0.16 to 0.31. SP : AP ratios larger than approximately 0.4 or 0.5 were considered abnormally large consistent with a possible diagnosis of Meniere's disease. The sensitivity and specificity of this electrophysiologic procedure is relatively low, causing many clinicians to question its role in the diagnostic process.[37] What does seem clear is that although the observation of an enlarged SP : AP ratio may support a diagnosis of Meniere's disease, the finding of a normal SP : AP ratio is of limited diagnostic significance.

It is also possible to record ECoG and ABR simultaneously. This is done by using an electrode montage that includes a reference electrode placed on the tympanic membrane or on the promontory of the middle ear. The use of a recording electrode located in such close proximity to the cochlea results in an ABR with a significantly enhanced wave I. This approach allows the response of the peripheral neural response to be measured more quickly and accurately than when the standard ABR recording montage is used; it is a recording technique that is often employed for intraoperative monitoring purposes.

Auditory Brainstem Response

The ABR is a far-field recording of the synchronized response of numerous neurons in the auditory pathways within the brainstem. The ABR was first described by Sohmer and Feinmesser in 1967.[38] Shortly thereafter, Jewett and others[39,40] published a series of studies that contained more detailed descriptions of the ABR. Since that time, research has focused on how best to record and interpret this evoked potential, and today the ABR has become a routine part of standard clinical practice.

The ABR is recorded using differential amplification with an active electrode positioned at the vertex or high forehead, and reference electrodes positioned at the mastoids or on the earlobes. The stimulus used most frequently to evoke the ABR is a 100-μs rectangular pulse or "click." Clicks are ideal because they have a broad frequency response and result in the synchronous or near synchronous firing of numerous auditory nerve fibers. For applications where frequency specificity is important, it is also possible to record an ABR in response to short bursts of a sinusoidal acoustic stimulus (i.e., a tone burst).

In normal-hearing adults, the ABR consists of a series of vertex positive peaks or waves that are traditionally labeled with roman numerals I to V. Wave I of the click-evoked ABR occurs with a latency of approximately 1.5 ms in normal-hearing adults. Each of the subsequent peaks follows at approximately 1-ms intervals such that wave V is recorded 5 to 6 ms after onset of the stimulus. The individual peaks of the ABR reflect the response from neurons located at progressively more central locations within the auditory pathways. Wave I is a measure of the collective response of numerous auditory nerve fibers. Wave V reflects neural activity generated primarily from neurons located within the lateral lemniscal tracks that run between the superior olivary complex and the inferior colliculi.[41]

The effect of intensity on the ABR is illustrated in Figure 134-3. As intensity is decreases, the amplitude of the individual peaks of the ABR decreases, and the latency increases. Near behavioral detection thresholds, the only component of the ABR that can still be resolved is wave V. Figure 134-3 also illustrates the effect of stimulus type on the ABR. The left panel of the figure shows responses recorded using clicks. The right panel shows responses recorded using 500-Hz tone bursts. When low frequencies are used, the response morphology changes. The early peaks of the ABR often become more difficult to identify, peak latencies increase, and response thresholds are slightly elevated relative to behavioral detection thresholds. These trends reflect the fact that, compared with responses recorded using click stimuli, low-frequency tone bursts result in a recording that is dominated by neural activity originating near the apex of the cochlear partition where cross-fiber synchrony is reduced.

A major advantage that the ABR has over other auditory evoked potentials is that it is not strongly affected by attention, sleep, or sedation. This is because the ABR reflects neural activity generated at the level of the brainstem. As a result, the ABR can also be recorded reliably in neonates, making it an ideal tool for pediatric applications.

At birth, the ABR consists primarily of three peaks corresponding to waves I, III, and V of the adult ABR. In very young infants, the amplitude of wave I may be equal to or sometimes even larger than the amplitude of wave V, and the absolute latency of all three waves (I, III, and V) and the I-III and I-V interpeak intervals are prolonged relative to adult norms.[42-44] As a child matures, absolute and interpeak latencies shorten, waves II and IV become more pronounced, and the relative amplitude of wave V increases until the ABR attains its normal adult form by approximately 2 years of age.[42,45,46] These maturational changes in the ABR are significant enough to require the use of age-matched normative data for children younger than 2 years. Although it is possible to record the ABR in premature infants 27 to 30 weeks of gestation, there is evidence of threshold elevation in these very young infants.[44,47] This elevation is most likely a product of an immature auditory system and the suboptimal test environment that is typical of most neonatal intensive care units.

Clinical Applications

There are two primary applications for the ABR. The first is as a tool for estimating audiometric thresholds. The second is as a method of assessing the integrity of the neurologic pathways associated with audition at the level of the brainstem.

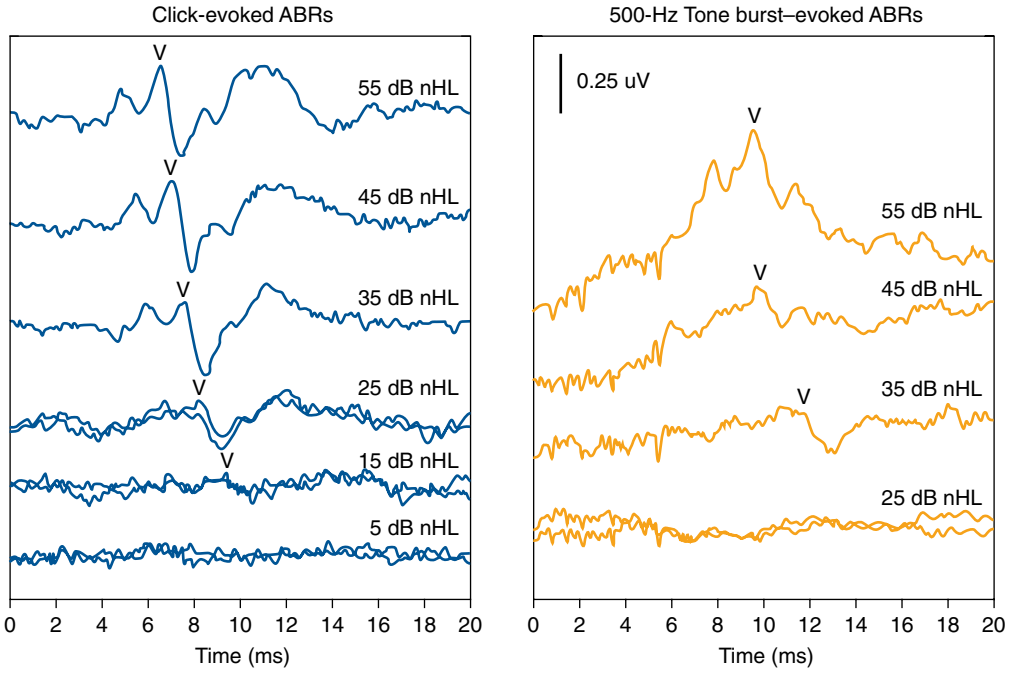

Figure 134-3. A series of auditory brainstem responses (ABRs) recorded from an individual with normal hearing are shown. The *panel on the left* shows responses recorded using click stimuli. The *panel on the right* shows responses recorded using 500-Hz tone burst stimuli.

Assessing Hearing Sensitivity

The stimulus used most frequently to evoke an ABR is a click. Clicks are advantageous because they result in maximum cross-fiber neural synchrony and optimal response morphology. Click-evoked ABRs can be recorded near behavioral detection threshold, and considerable effort has gone into assessing the extent to which the click-evoked ABR can be used to predict audiometric thresholds and type of hearing loss (conductive vs. sensorineural). The major limitation of the click-evoked ABR as a tool for estimating hearing sensitivity is that it is not frequency-specific. To obtain more frequency-specific threshold estimates, most clinicians use tone bursts in place of or in addition to clicks for purposes of threshold estimation.

Estimating Audiometric Thresholds Based on Click-Evoked Auditory Brainstem Response Thresholds

Although it is possible to record an ABR in response to a click stimulus at levels that are very close to the behavioral detection threshold (0 dB nHL), the question of interest is how well ABR thresholds predict audiometric thresholds. This relationship has received a great deal of attention in the scientific literature over the past 2 decades. Some studies have shown click-evoked ABR thresholds to compare best with the average of the 2000-Hz and 4000-Hz audiometric thresholds.[48-50] Other investigators report finding optimal correlations between ABR thresholds and the mean of the 1000- to 4000-Hz audiometric thresholds.[40,51,52] Additionally, the slope of the ABR latency versus intensity function has been shown to help predict the shape of the audiogram. Subjects with steeply sloping high-frequency hearing losses tend to have steeper ABR latency-intensity functions compared with subjects with flat audiometric contours.[49] What is clear from the literature is that there is no correlation between click-evoked ABR thresholds and audiometric thresholds for frequencies less than 1000 Hz, and it is impossible to use the ABR to distinguish between severe and profound SNHL.[53,54]

The click-evoked ABR can be helpful in determining the site of a lesion within the auditory system. A well-formed click-evoked ABR can rule out auditory neuropathy as a cause of hearing loss. Additionally, the click-evoked ABR can be used to distinguish ears in which the hearing loss has a conductive component from ears in which the hearing loss is purely sensorineural. Click-evoked ABRs recorded from patients with conductive hearing loss typically show normal interpeak latencies, but prolonged absolute latencies compared with age-based norms.[55,56] Differences between ABR thresholds obtained using bone-conduction stimuli and similar measures obtained using air-conduction stimuli are also frequently observed in ears with conductive pathology. Although there are challenges associated with recording ABRs in response to a stimulus presented via bone conduction (e.g., excess stimulus artifact and low maximum output levels), it is possible to use the ABR to distinguish between a loss that is purely sensorineural and one that is conductive or possibly mixed. It is also possible to use the ABR to obtain a rough estimate of the magnitude of the conductive component in the test ear, and such information can be extremely important in clinical practice.

Estimating Audiometric Thresholds Based on Auditory Brainstem Responses Evoked Using More Frequency-Specific Stimuli

Much research published during the past 2 decades has focused on identifying ways in which the ABR might be used to obtain more frequency-specific estimates of audiometric threshold. Two general approaches have been described. The first approach is to record the ABR using brief tone bursts rather than clicks. This is the approach used most widely today. Depending on their duration and the way in which they are gated on and off, tone bursts can be considerably more frequency-specific than clicks, and most commercially available evoked potential units have the capability of producing a range of different types of tone burst stimuli. A second approach is to use ipsilateral masking presented simultaneously with a click or tone burst to record the ABR. Ipsilateral masking is used to minimize the contribution to the ABR from neurons located outside a restricted frequency range. Numerous studies have shown that the use of either method results in improved audiometric threshold predictions compared with threshold estimates obtained using clicks.[49,57-60]

Few commercial evoked potential units have been capable of providing a click or tone burst and an ipsilateral acoustic masker. More recent evidence from a within-subject study of individuals with steeply sloping SNHL failed to reveal significant differences in the accuracy of these two approaches to audiometric threshold prediction (i.e., tone bursts presented in quiet vs. clicks presented in an ipsilateral notch noise masker).[61]

Today, tone burst–evoked ABRs have become a routine part of the clinical evoked potential assessment battery. In 2000, Stapells[62]

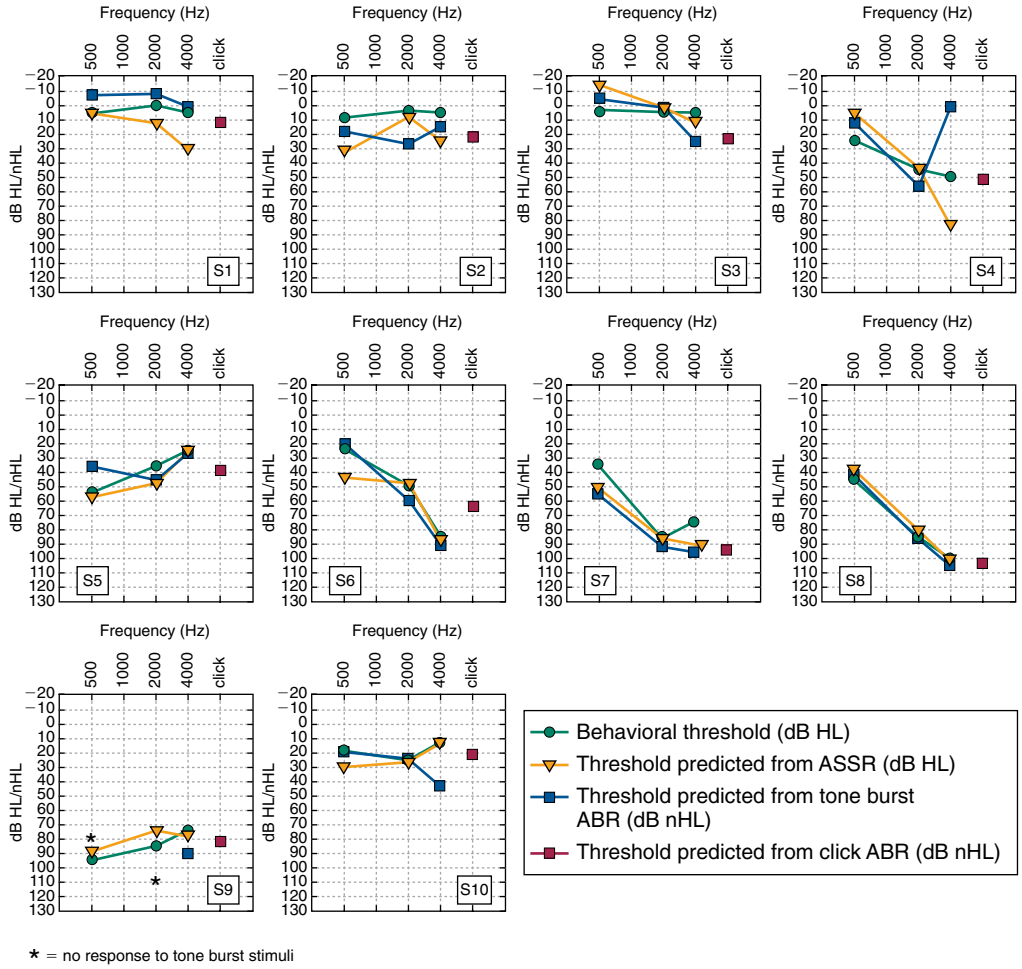

Figure 134-4. Within-subject comparison of behavioral audiometric thresholds and thresholds predicted based on auditory steady-state response (ASSR) and auditory brainstem response (ABR) recordings.

published a meta-analysis of the published ABR literature. This analysis showed that when appropriate filter settings (30 to 3000 Hz) are used, tone burst–evoked ABR thresholds can be recorded within 10 to 15 dB of behavioral audiometric threshold. The size of the correction factor was frequency-dependent—largest for a 500-Hz tone burst and smallest for 2000- to 4000-Hz stimuli. The accuracy of these threshold predictions varied according to the tone burst frequency and the age of the subject, but were approximately 5 dB for 2000- to 4000-Hz tone bursts and 10 dB for 500-Hz stimuli.

From a practical standpoint, several challenges are associated with recording frequency-specific ABRs. The morphology of the ABR elicited using tone burst stimuli is often not as good as it is when a click stimulus is used (see Fig. 134-3). Additionally, when frequency-specific stimuli are used, the latency of wave V of the ABR depends on the stimulus frequency,[49] making identification of the response in the time domain more challenging. Finally, in contrast to the click, calibration standards for tone burst stimuli have not been widely agreed on.

Despite these challenges, tone burst–evoked ABRs are used routinely to estimate residual hearing capacity for individuals who are either too young or are otherwise unable to be tested using behaviorally based audiometric procedures. Figure 134-4 provides an illustration of how ABR thresholds, evoked using tone bursts and clicks, compare with audiometric thresholds. Data are shown for a group of 10 subjects from our clinic with a range of hearing losses and audiometric configurations. Although the agreement between the audiometric thresholds and the ABR thresholds is not perfect, it is typical of what can be expected in clinical practice and is accurate enough to inform decision making relative to amplification and habilitation options for pediatric patients.

Otoneurologic Applications

Historically, the ABR has also been used to assist with the detection of lesions affecting the auditory pathways within the brainstem.[63] Such lesions include space-occupying growths such as vestibular schwannomas and dysfunction resulting from other neurologic conditions, such as multiple sclerosis, stroke, or trauma. In the 1980s, radiographic imaging techniques were not as accurate or widely available as they are today, and the ABR was an important tool in the diagnostic process. Today, reliance on ABR as a diagnostic tool has declined largely owing to the availability and widespread use of computed tomography and magnetic resonance imaging (MRI). Improved imaging has led to a decrease in the typical size of the tumor at the time of diagnosis. A systematic review of the literature has shown a decline in sensitivity of the ABR as a diagnostic tool in recent years. There are still patients and circumstances where radiographic imaging is contraindicated, however. In such cases, the ABR can still prove useful. Additionally, many surgeons have come to rely on intraoperative measures of auditory function during skull base surgery. For both of these applications, the stimulus used to evoke the ABR is a high-level click.

Differential Diagnosis

The ABR is altered in several ways by the presence of pathology affecting the neural pathways within the auditory centers of the brainstem. The ABR may be absent in an individual with good hearing sensitivity, or the ABR that is recorded may consist only of early waves. Such gross

morphologic changes have been interpreted as evidence of potential abnormality and are thought to reflect partial conduction block or significant loss of cross-fiber synchrony along the neural pathways between the cochlea and the inferior colliculus. Space-occupying lesions that impinge on the auditory nerve can also slow neural conduction and result in abnormally long wave V latencies and prolonged interpeak intervals. For normal-hearing individuals, high-level clicks generate an ABR with a wave V latency of approximately 5.5 ms and a I-V interpeak latency of approximately 4 ms. When the absolute latency of wave V is longer than approximately 6.4 ms, or when the interval between wave I and wave V is longer than 4.4 ms, the presence of retrocochlear pathology cannot be ruled out. Finally, vestibular schwannomas typically manifest as unilateral lesions. Interaural differences of greater than 0.3 ms in either the absolute latency of wave V or the length of the I-V interval are also indicative of potential retrocochlear pathology. For a comprehensive review of the criteria used to diagnose an acoustic neuroma, the interested reader is referred to Hall.[64]

Several investigators have attempted to quantify the sensitivity and relative specificity of the ABR as a tool for identifying ears with vestibular schwannomas.[65-69] The results of these studies vary, but depending on the specific criteria used, sensitivity rates of 85% to 100% are common, and there is evidence of reduced sensitivity in ears with smaller tumors. Such sensitivity comes at a cost, however, and false-positive rates for the ABR as a test of the presence of retrocochlear pathology have been reported to be as high as 30%.

In 1997, Don and colleagues[70] described a technique for recording the ABR that they referred to as "stacked ABR." This technique requires recording the ABR in response to a click that is presented simultaneously with a series of six different maskers. One masking condition uses a wide band noise. In the other five masking conditions, the noise is high-pass filtered at cutoff frequencies ranging from 500 to 8000 Hz. Derived band techniques are used to estimate the contribution to the ABR from five different frequency regions along the basilar membrane. The derived band ABR waveforms are temporally aligned (or "stacked") before being summed. The result is a waveform that more accurately represents contributions from neurons across the length of the whole basilar membrane.

In 2005, Don and colleagues[71] reported sensitivity and specificity rates for the stacked ABR relative to the standard ABR in a group of 54 patients with small acoustic tumors and 78 normal-hearing adult controls. Results indicated that the stacked ABR procedures outperformed traditional ABR procedures in this patient population. This approach to neurologic assessment may represent an improvement over traditional electrophysiologic assessment procedures, and may have merit in populations where MRI is not feasible or otherwise contraindicated.

Intraoperative Monitoring

Another application where ABR is used in clinical practice is as a tool to monitor the status of the auditory nerve during skull base surgery. The goal of intraoperative monitoring is to provide the surgeon with feedback about the status of the auditory nerve; this is done by continuously monitoring the latency of wave V or the I-V interpeak interval during the surgical procedure. Prolongation of either index can result from surgical trauma. In some cases, these changes can be reversible. The major drawback to using the ABR for this purpose is that it is a small-amplitude potential that cannot be clearly identified in the ongoing electroencephalography activity. Averaging is required to define peak latencies clearly.

Even in ideal situations, where the ABR is robust and noise levels are manageable, it is impossible to provide the surgeon with instantaneous feedback relative to auditory nerve function. Larger amplitude responses can be recorded if a recording electrode montage is used that includes an electrode placed directly on the exposed auditory nerve during surgery. Although this modification to the recording paradigm can allow for near-instantaneous feedback during the surgical procedure, positioning the recording electrode so that it does not interfere with the surgical field can be challenging.

Although there have been studies that suggest the presence of a viable ABR at the conclusion of a surgical procedure targeting the skull base is correlated with outcome on postoperative hearing tests,[72,73] surgeons do not agree on the importance or efficacy of intraoperative monitoring, and definitive studies addressing the relative efficacy of this procedure are lacking. One thing that seems to be true, however, is that adequate intraoperative monitoring requires that the individual doing the monitoring be technically competent, familiar with surgical procedures, and, perhaps most importantly, able to communicate effectively with the surgical and anesthesia teams. Even with effective monitoring, successful preservation of hearing is sometimes impossible. In our experience, the greatest contribution of intraoperative monitoring is to alert the surgeon when there is a need to slow down or, if possible, to change his or her approach to the tumor.

Additional Applications

In recent years, two new and potentially important applications for ABRs have emerged. One is a procedure called CHAMP, which was initially described by Don and colleagues[74,75] and grew out of their work on the stacked ABR paradigm. In the process of validating the stacked ABR software, these authors tested a numerous patients with Meniere's disease and found that the stacked ABR measures obtained from individuals with this specific disorder differed from those recorded from other individuals with normal hearing or other forms of SNHL. Don and colleagues[74] described results obtained from 23 individuals with confirmed and active Meniere's disease and compared their results with data obtained from a set of 38 normal-hearing controls. Masking levels intense enough to mask wave V of the ABR in normal-hearing listeners were insufficient to mask wave V in the ABR evoked from patients with Meniere's disease. Also, very little change in wave V latency was observed in these patients between the response obtained using a click alone versus one obtained using high-pass, ipsilateral masking.

The hypothesis that is used to explain the lack of change in latency of wave V of the ABR that was observed in the masked condition is that endolymphatic hydrops results in a significant and measurable change in cochlear mechanics. The report describes sensitivity and specificity rates that approach 100%, and although more data are needed, these preliminary results suggest that this test may represent an important addition to the diagnostic protocol used for patients with suspected Meniere's disease.

Finally, Banai and Wible and their colleagues[76,77] described measures of the ABR evoked in response to the presentation of a brief, synthetic speech stimulus (/da/). The response that is recorded has been shown to contain an onset response (the ABR) and a series of steady-state components that are elicited in response to the vowel. This speech-evoked ABR has been shown to be abnormal for a subset of school-age children who have been identified as having learning difficulties. These investigators have theorized that for this subset of children, rapid temporal variations in the speech signal have not been well coded at the level of the brainstem and lead to processing problems. The authors suggest that such recordings might be used to help identify children with learning problems affecting the auditory modalities that may be responsive to treatment. Additional studies are needed to assess the potential impact such a response might have on clinical practice.

Auditory Steady-State Response

The ASSR is an evoked potential that was first described in the mid-1980s.[78,79] It is a far-field recording of electroencephalography activity evoked using continuous sinusoidal stimuli that are either amplitude or frequency modulated. The brain wave activity recorded from surface electrodes on the scalp contains periodic amplitude or frequency variations that follow the slow modulations in the stimulus waveform. The recordings are analyzed in the frequency rather than the time domain. Statistically based software has been developed that allows the presence or absence of a response to be determined automatically.

As a clinical tool, the ASSR has several potential advantages over the ABR. Specifically, the stimuli used to elicit ASSRs are more frequency-specific, the maximum output of the ASSR system is higher than that typically achieved when transient stimuli are used, and no "peak picking" is required. The primary disadvantage of the ASSR is that this is a very small-amplitude response—considerably smaller than the ABR. As a result, obtaining quality ASSR recordings requires par-

ticularly quiet subjects and good control of physiologic and nonphysiologic noise sources.

Clinical Applications

The primary application for the ASSR is as a tool for estimating audiometric thresholds. When originally described, modulation frequencies of approximately 40 Hz were common, and reasonable correlations between ASSR thresholds and audiometric thresholds were reported.[78-80] Initial optimism about this response as a tool for predicting audiometric thresholds in difficult-to-test populations waned when it was noted that these responses were adversely affected by sleep and sedation.[81,82] Subsequent research has shown, however, that if modulation rates between 75 Hz and 100 Hz are used, the ASSR can be successfully recorded even from sleeping children.[82,83] Numerous studies comparing ASSR thresholds with audiometric thresholds followed. These studies typically reported finding good correlations between ASSR thresholds and audiometric thresholds.[84] Commercial instrumentation for recording the response was soon available, and in many otolaryngology clinics, ASSR measures assumed a prominent role—either in place of or in addition to ABR—as a means of estimating audiometric thresholds in pediatric populations. Additionally, it was soon apparent that the ASSR could be recorded from individuals with no measurable ABR.[54,85] As a result, this response has gained popularity as a tool for evaluation of children being considered for cochlear implantation.

Today, clinicians struggle with finding the best way to incorporate the ASSR into their routine evoked potential battery. Although it seems possible to estimate audiometric thresholds using the ASSR with a fair degree of accuracy, less is known about the effects of factors such as auditory neuropathy, age, the impact of recording electrode position, and stimulation. Concerns have been raised about the possibility that the ASSR can be adversely affected by stimulus artifact, particularly when stimuli are presented either at a high level or via a bone-conduction transducer, and within-subject comparisons between the ASSR and tone burst–evoked ABR are limited. Such comparisons are shown in Figure 134-3; results from 10 subjects with a range of audiometric thresholds and configurations are shown. This figure illustrates the generally good correspondence between ASSR-based and ABR-based threshold estimates and audiometric thresholds. These preliminary data revealed a generally good correspondence between ASSR-based and ABR-based threshold estimates, and this conclusion was later substantiated by Johnson and Brown,[61] who tested individuals with steeply sloping audiometric configurations, and found the two evoked potentials to predict audiometric thresholds with approximately similar degrees of accuracy. Future research is likely to define more fully how ASSR can best be incorporated into clinical practice.

Middle and Long Latency Evoked Potentials

Two auditory evoked potentials that are recorded less frequently in clinical practice are the middle latency response and the long latency P1-N1-P2 response complex. These two evoked potentials are named based on the time window in which they are recorded, and can be used to assess neural processing of acoustic stimuli at the level of the auditory midbrain or cortex or both. The middle latency response is characterized by a series of peaks, typically labeled Na, Pa, Nb, and Pb, which are consistently recorded within a time window that extends from about 10 to about 70 ms. Cortically generated evoked potentials such as the P1-N1-P2 response complex (Fig. 134-5) are recorded between about 80 ms and 300 ms after presentation of the stimulus. Generally, both responses are larger in amplitude than the ABR and have been used to estimate auditory sensitivity.

One advantage that the middle latency response and more cortically generated auditory evoked potentials have over their more peripherally generated counterparts is that they are not as dependent on neural synchrony, and consequently can be measured using a wider range of stimuli than are typically used to record the ABR. Clinical applications for these longer latency potentials include (but are not limited to) assessing low-frequency sensitivity and evaluation of higher level auditory processing. There are, however, numerous practical limitations that have limited enthusiasm for these responses in clinical settings. Most problematic is the fact that both responses are adversely affected by sleep, sedation, and anesthesia, and both have a long developmental trajectory.[86,87] Today, acoustically evoked middle and long latency auditory evoked potentials are recorded infrequently in all but a few otolaryngology clinics in the United States, and typically only in cases where the integrity of the higher order auditory pathways is in question.

Electrically Evoked Auditory Potentials

Cochlear implantation has become the treatment of choice for profound, bilateral SNHL. Since cochlear implants were introduced in the early 1980s, researchers and clinicians alike have been interested in finding ways to record electrically auditory evoked potentials. Initially, the goal was to find an electrically evoked auditory potential that might correlate with the status of the surviving auditory nerve. It was thought that if such a potential could be identified, this would help predict postimplant performance. As the age of implantation decreased, and as more individuals with multiple physical and developmental delays began receiving cochlear implants, the focus shifted toward finding ways in which electrically evoked auditory potentials could be used to facilitate the process of fitting or programming the speech processor of the cochlear implant to the individual.

Early studies focused on the electrically evoked auditory middle latency response (EMLR), primarily because this evoked potential had peak latencies long enough that they could be recorded without significant contamination by electrical artifact. It quickly became clear, however, that the populations for whom such measures were potentially most important were very young children and infants. As a result, the focus quickly shifted to the electrically evoked auditory brainstem response (EABR). In 1990, the first studies were published describing a method for recording electrically evoked compound action potentials (ECAPs).[88] The ECAP is a gross potential that reflects the synchronous firing of numerous electrically stimulated auditory nerve fibers. The ECAP provided a relatively direct measure of the response of the auditory nerve to electrical stimulation and was not adversely affected by muscle artifact—making it an ideal evoked potential for pediatric applications. Although initially it was possible to record this neural response only from a small group of cochlear implant users with percutaneous connections to the intracochlear electrodes, the major manufacturers of cochlear implants soon developed hardware and software that has made recording the ECAP routine.

Today, the ECAP has largely replaced the EABR and EMLR as a tool for assessing neural response to electrical stimulation in cochlear implant recipients. The ECAP has limitations, however. Specifically, it is a very peripheral measure of the response of the auditory nervous system to a simple electrical stimulus. It cannot easily be recorded using speech stimuli, and it cannot be used to assess the impact of higher level processing within the auditory system. As a result, more recently there has been a resurgence of interest in cortically generated evoked potentials such as the P1-N1-P2 complex. The following sections provide a description of each of these responses and discuss current clinical applications for electrically evoked auditory potentials.

Electrically Evoked Compound Action Potential

The ECAP is a recording of the synchronized firing of numerous electrically stimulated auditory nerve fibers. To record this response, a cochlear implant system is required that has two-way telemetry capabilities and software that allows the electrical stimulus artifact to be minimized. Cochlear Corporation first introduced such technology in 1995. Cochlear Corporation refers to the evoked potential measurement system used to record the ECAP as "neural response telemetry." Shortly thereafter, Advanced Bionics and Med El corporations followed suit introducing new cochlear implants that were similarly equipped.

The primary component of the ECAP is a single negative peak typically labeled N1. This electrically evoked response is in many ways analogous to acoustically evoked ECoG, however, because there is no traveling wave and no time required for transmission between the auditory hair cells and the primary afferent auditory nerve fibers; the N1 of the ECAP has a shorter latency than N1 of the ECoG (see Fig. 134-5). Typical response latencies for the ECAP range from 0.3 to 0.5 ms. The

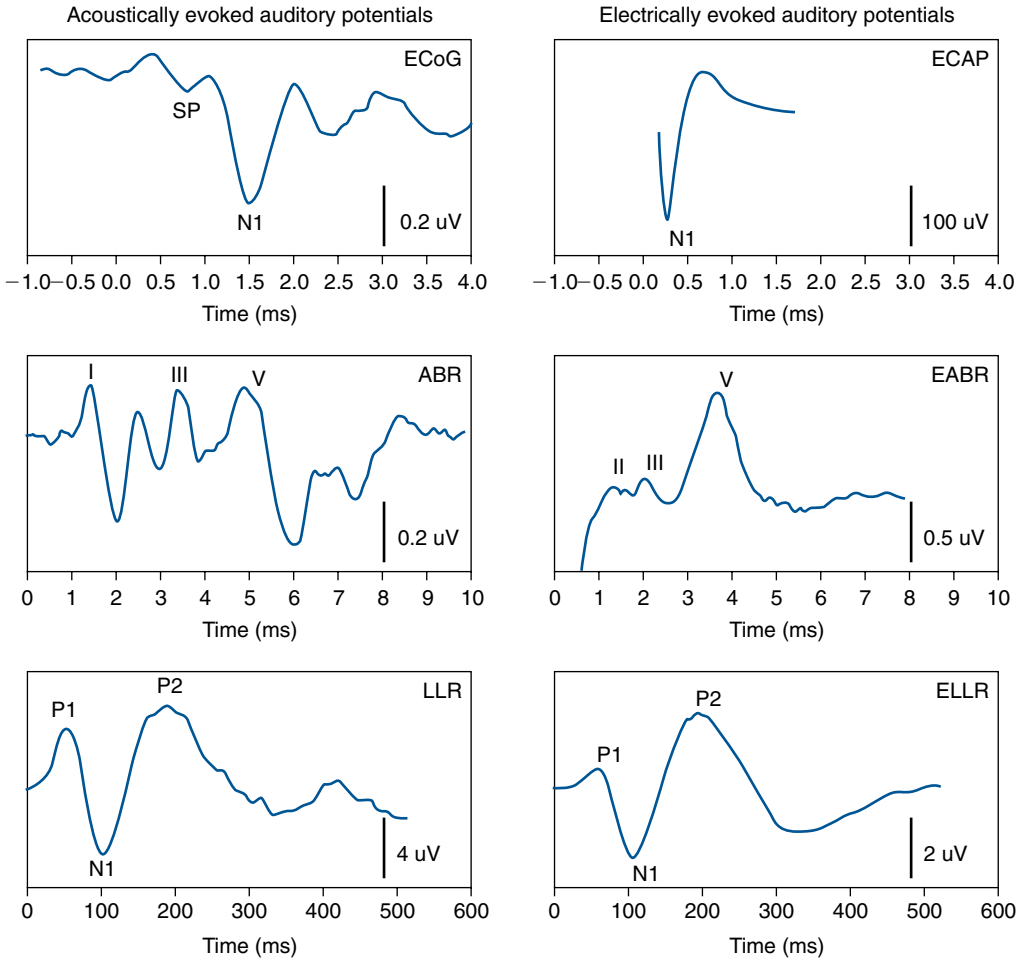

Figure 134-5. Auditory evoked potentials recorded in response to acoustic stimulation from individuals with normal hearing and in response to electrical stimulation from individuals who use a cochlear implant. ABR, auditory brainstem response; EABR, electrically evoked auditory brainstem response; ECAP, electrically evoked compound action potential; ECoG, electrocochleography; ELLR, electrically evoked long latency response; LLR, long latency response.

amplitude of the ECAP is also larger than the amplitude of the N1 peak of the ECoG. This is a direct reflection of the fact that the recording electrode is located within the cochlea, and the fact that auditory neurons respond more synchronously when electrical as opposed to acoustic stimulation is used. Typical ECAP amplitudes range from 100 to 500 μV, and responses measuring 2 to 3 mV have been reported.

The ECAP has several important advantages over other electrically evoked auditory potentials. Specifically, it can be recorded more easily and faster than the EABR. Surface recording electrodes are unnecessary. Perhaps most importantly, because it is recorded from an intracochlear electrode, the ECAP is large in amplitude, and does not require the subject to sleep or even stay still during recording sessions. These factors meant that in contrast to other evoked potentials, the ECAP could be recorded not only at the time of surgery, but also during any of the postoperative visits. During the past decade, the scientific literature has included many studies in which the ECAP was used either to help expand our understanding about the way electrical stimuli are coded at the level of the auditory nerve or to define ways in which this evoked potential could be used to facilitate the process of programming the speech processor of the cochlear implant.

Electrically Evoked Auditory Brainstem Response

The first descriptions of the EABR were published in the mid-1980s.[89-91] The EABR shares many features with its acoustic counterpart the ABR, and similar to the ECAP, the EABR has significantly shorter peak latencies than the ABR. Wave I of the EABR is difficult to record from surface electrodes, however, because it is often contaminated by electrical artifact (see Fig. 134-5). Additionally, the latency of wave V of the EABR changes very little with stimulation level, presumably reflecting the fact that there is no time delay introduced by the traveling wave in the cochlea when electrical as opposed to acoustic stimulation is used. As a result, clinicians must rely on amplitude-intensity as opposed to latency-intensity functions to characterize how an individual ear responds to electrical stimulation.[92,93]

The EABR can be recorded, even from congenitally deaf children, using standard electrode montage and recording parameters intraoperatively and postoperatively.[93-95] Although typically the cochlear implant itself is used to provide the stimulus, an isolated current source coupled to the ear via a transtympanic, extracochlear stimulating electrode that is placed on or near the round window niche can also be used to evoke this response.[96,97] Some cochlear implant teams have argued preoperative or perioperative EABRs can be used to help select the best ear to implant, or to determine whether or not the ear to be implanted is "stimulable."[96,97] Efficacy data are limited, however, and today many of the major cochlear implant programs have chosen to abandon preoperative or perioperative measurement of the EABR in routine cases.[98]

Electrically Evoked Middle and Long Latency Responses

It is also possible to use electrical stimulation to elicit middle and long latency auditory evoked potentials. Evoked middle latency responses (EMLRs) and evoked long latency responses (ELLRs) share most of the latency and morphologic characteristics of their acoustic counterparts. The EMLR is characterized by a series of slow vertex positive peaks occurring within a time window of 10 to 50 ms after stimulation. Electrically ELLRs consist of a series of potentials occurring within a

time window of approximately 50 to 300 ms (see Fig. 134-5). The EMLR reflects electrically evoked neural activity at the level of the auditory midbrain. ELLRs reflect neural activity generated at cortical or precortical regions of the auditory system.

Although less widely studied than the EABR or the ECAP, these more centrally generated, electrically evoked potentials have some distinct advantages over either the EABR or the ECAP. Specifically, EMLRs and ELLRs are less susceptible to contamination by electrical stimulus artifact, and in contrast to their peripherally generated counterparts (the ECAP and EABR), both can be evoked using speech or more speechlike stimuli.

Clinical Applications

Today, children 12 months old and children with multiple physical or developmental challenges are considered candidates for cochlear implantation. Programming the speech processor of the cochlear implant for patients in either of these categories can be challenging. Consequently, one of the more important clinical applications for electrically evoked auditory evoked potentials has been (and continues to be) as a tool that can inform the programming process. Several studies have reported correlations between ECAP thresholds and the levels used to program the speech processor of the cochlear implant.[94,99-103] Depending on the stimulation rates used to program the speech processor of the cochlear implant, ECAP thresholds indicate stimulation levels where the programming stimulus is audible but not uncomfortable for most users. For many subjects, the contour of the ECAP threshold versus stimulating electrode curve roughly parallels the contour in the MAP. There is considerable cross-subject variability evident in each of these studies, however, and a range of different methods have been proposed for improving the accuracy of the ECAP-based MAP predictions.[99,101,102]

ECAP-based MAPs are not perfect, but the evidence suggests that it is possible for most users to attain acceptable levels of speech perception with these programs. They also can serve as a first-order approximation of the MAP that will be fit when the child is able to participate more easily in the fitting process.[102,104]

Perhaps equally important applications for electrically evoked auditory potentials in clinical practice are as tools to help diagnose potential device failures. There are instances where it is helpful to know if there is a neural response to electrical stimulation. Such measures can provide helpful information about how the auditory system is responding over time, and can be used to determine if changes in stimulus characteristics, such as pulse width, level, and rate, are appropriately coded at the auditory periphery. Although they represent the minority of patients who receive cochlear implants, there are times when children (or adults) fail to respond to electrical stimulation, fail to progress as expected with the implant, or show some evidence of a decline in performance over time. If the patient is unable to report accurately changes in perception that may accompany these changes in device function, objective measures such as the ECAP can be particularly helpful.

Today, the EABR is recorded routinely in only a few cochlear implant centers. It has largely been replaced by the ECAP. In many ways, the information provided by these two potentials is redundant. There are situations, however, where the EABR can be particularly useful. Excess stimulus artifact can make it particularly difficult to record an ECAP from patients with congenital cochlear malformations or patients who have very high stimulation thresholds. In such circumstances, the EABR, owing to its longer response latency and the fact that there is more spatial separation between the stimulating and recording electrodes, can often be successfully recorded. Good correspondence between the ECAP and EABR thresholds has been reported.[99,105]

Many studies in the literature have described protocols for measuring the EMLR in clinical populations; however, this response, similar to its acoustic counterpart, is difficult to record reliably in very young children, can be adversely affected by sleep and sedation, has a long developmental trajectory, and has variable response morphology. All of these factors have served to limit the potential clinical applications of this specific evoked potential.

More recently, interest in electrically evoked cortical potentials has resurged. This renewed interest in cortically generated, electrically evoked auditory potentials is due primarily to work by Sharma and coworkers,[106,107] Ponton and colleagues,[86,87] and others who have shown that it is not only possible to record electrically ELLRs in pediatric cochlear implant users, but also that the latency of these responses is affected by factors known to correlate with performance, such as the length of profound deafness before implantation. Specifically, cogenitally deaf children who were implanted after about 7 years of age were shown to have cortical P1 response latencies that were significantly prolonged relative to similar measures made in children who were born deaf but implanted before approximately 2 years of age. Additionally, evidence has shown that the latency of the electrically evoked P1 response can change during the first few weeks or months after hookup, presumably reflecting the plasticity of the auditory system in very young children,[107] and some clinical researchers have advocated the use of electrically evoked cortical potentials to help assess adequacy of the fit of the cochlear implant or hearing aid or to document sensitivity to changes in an ongoing electrical stimulus.[108,109]

Obtaining electrically evoked cortical potentials from pediatric cochlear implant users is not easy. Although the children are not required to participate in the testing procedure, recording these responses requires application of multiple surface recording electrodes and a child who can sit quietly without sleeping for extended periods. The studies described here are generally based on data collected in laboratory, rather than clinical settings. The results are important, however, because they suggest that electrically evoked cortical responses could potentially play an important role in clinical practice. Future research is needed to determine whether or not the information about auditory processing that these electrically evoked auditory potentials can provide outweighs the challenges inherent in recording these responses in clinical settings.

Conclusion

In this chapter, we have reviewed many of the objective measures that are used in clinical practice today to evaluate auditory function in individuals who are either too young or otherwise unable to be tested using behavioral means. Recording these potentials takes training, specialized equipment, and attention to detail. None of these procedures is foolproof, and, perhaps more importantly, none replaces good behavioral assessment techniques. The careful application of these techniques can have a positive impact on the clinical practice of otology, however, and can teach us a great deal about the normal and the impaired auditory system.

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CHAPTER ONE HUNDRED AND THIRTY-FIVE

Neuroradiology of the Temporal Bone and Skull Base

Frank M. Warren, III

Clough Shelton

Richard H. Wiggins, III

Key Points

- CT evaluation of the temporal bone with and without contrast enhancement shows bony erosion and adjacent soft tissue inflammation or abscess or both in cases of malignant external otitis.
- Cholesteatoma has distinct imaging characteristics on MRI. The lesion is isointense to hypointense on T1-weighted imaging, is intermediate on T2-weighted imaging, and does not enhance with the addition of contrast medium. Most importantly, the lesion does not restrict on diffusion-weighted imaging.
- MRI and CT are used in the evaluation of glomus tumors. CT is best to determine the degree of involvement of the jugular bulb, and discriminates between a glomus tympanicum or glomus jugulare. MRI defines the extent of disease that is in the neck, the extent of disease that is intracranial, and the amount of carotid involvement.
- High-resolution T2-weighted MRI is the study of choice for screening for acoustic neuromas.
- The diagnosis of superior semicircular canal dehiscence is made using high-resolution CT (HRCT). The dehiscent segment must be greater than 2 mm, with the area of absent bone visualized in three consecutive coronal images. Alternatively, the scan can be reformatted in the plane of the superior canal, and the dehiscent area can be measured directly.
- HRCT imaging is the best modality for evaluation of pediatric patients with sensorineural hearing loss. HRCT detects cochleovestibular abnormalities, internal auditory canal abnormalities, and enlarged vestibular aqueduct.
- The diagnosis of petrous apex lesions is based on their CT and MRI characteristics.
- Lesions of the cerebellopontine angle are discriminated based on their MRI characteristics.
- High-resolution T2-weighted MRI is the study of choice for preoperative evaluation for cochlear implantation. This allows for clear definition of cochlear morphology and evaluation of the seventh and eighth cranial nerve complexes.

Diagnostic imaging is indispensable in the evaluation of otologic patients. Magnetic resonance imaging (MRI), computed tomography (CT), angiography, and nuclear medicine studies aid otolaryngologists in the diagnosis of various conditions and are often crucial in surgical planning. This chapter reviews the utility of MRI and CT for visualizing the structures and identifying pathology in the temporal bone and skull base. The chapter focuses on different anatomic subdivisions of the region: the temporal bone, the cerebellopontine angle (CPA) and internal auditory canal (IAC), and the skull base.

Over the decade leading up to the year 2008, diagnostic imaging of the skull base, temporal bone, CPA, and associated vascular and neurologic structures has improved significantly. As magnet strength has increased to 3 Tesla, the limitations of MRI have diminished, improving the signal-to-noise ratio and leading to resolution of smaller structures. Research continues with scanners of higher strength, up to 7 Tesla, which have not been used clinically. In addition, the use of radiofrequency coils has led to further improvement in resolution by increasing the effective magnetic field strength. These improvements have led to much more detailed images in the temporal bone, as is reflected in the use of high-resolution T2-weighted imaging for the evaluation of cochlear nerve aplasia. MRI is most helpful for visualizing soft tissue structures and the vasculature of the skull base using MR arteriography and MR venography.

CT continues to improve as well; the resolution has increased, while the amount of radiation exposure the patient receives has decreased with the advent of multidetector scanners. The maximum resolution of current CT technology is 0.3 mm, providing unprecedented detail of the temporal bone. CT is best used for visualization of the bony anatomy, especially the cochlea, semicircular canals, vestibule, and vestibular aqueduct. CT is also useful for defining middle ear and mastoid pathology.

Temporal Bone

Temporal bone imaging requires identification and distinction of bony and soft tissue structures, necessitating the use of CT and MRI. Dividing this area into anatomic subsites of the external auditory canal (EAC), the middle ear, the inner ear, the petrous apex, and the intratemporal facial nerve facilitates the discussion of structures in the area.

External Auditory Canal

Congenital lesions rarely affect the EAC. The most common lesions are atresia of the EAC and first branchial cleft fistulas and cysts. Atresia and stenosis of the EAC is best evaluated with high-resolution CT (HRCT) of the temporal bones. The contribution of soft tissue and bony components of the stenosis or atresia is easily defined (Fig. 135-1). The presence of an EAC cholesteatoma behind the atresia plate can be determined. The middle ear may be hypoplastic, and typically the malleus and incus are fused into one ossicular mass that is connected to the stapes. The stapes may be malformed as well, and there may be an associated oval window atresia (Fig. 135-2).[1-3] The position of the facial canal can be quite anomalous; the nerve tends to be dehiscent in the tympanic segment and can be overlying the oval window. The mastoid segment tends to run in a more anterior and lateral position, and the nerve can exit into the glenoid fossa or lateral to the styloid process. All of these anomalies are important in the assessment of the surgeon's ability to perform an atresia repair.[4]

Imaging of severe infections affecting the EAC is generally used to assess for malignant or necrotizing otitis externa. This process typically involves the soft tissues and bone of the EAC, and extends into adjacent soft tissues. Findings on CT typically show soft tissue swelling in the EAC and auricle, with associated bony erosion and an osteomyelitic appearance of the inferior EAC. Contrast-enhanced CT shows enhancement of the soft tissues of the EAC and surrounding cellulitis and abscess (Fig. 135-3). The infection can spread in any direction, and can extend inferiorly to the parotid, masticator, and parapharyngeal spaces; posteriorly into the mastoid air cells; medially into the middle ear and petrous apex; and anteriorly into the temporomandibular joint. Rim-enhancing fluid collections can also be seen in these areas because associated abscesses can develop.

MRI of these lesions shows similar soft tissue thickening. Contrast-enhanced T1-weighted imaging shows diffuse enhancement of the auricle and EAC, with adjacent enhancement in cases with cellulitis, and rim-enhancing fluid collections in cases with abscess. T2-weighted imaging reveals diffuse high signal in areas of cellulitis.[5,6]

Inflammatory lesions of the EAC include cholesteatoma, keratosis obturans, and medial canal fibrosis. The hallmark imaging finding of cholesteatoma, regardless of location, is bony erosion. The typical imaging finding associated with EAC cholesteatoma is a homogeneous, erosive soft tissue mass in the EAC. These masses tend to occur predominantly in the inferior and posterior EAC. CT shows a soft tissue mass, with scalloped bone in the EAC with flecks of bone within the lesion itself (Fig. 135-4).[7] Contrast enhancement is typically not helpful in these cases, but may show rim enhancement in cases with associated inflammation. CT is the study of choice for these lesions.

Keratosis obturans is an abnormal accumulation of keratinous debris within the EAC *without* erosive bony changes.[8] This clinical entity can be confused with cholesteatoma, leading practitioners to perform imaging of the ear. HRCT reveals soft tissue filling the EAC, most typically with an intact tympanic membrane. The bony EAC may be enlarged, without scalloping or erosion of the osseous EAC itself (Fig. 135-5).[9] Enhanced HRCT is not helpful in these cases.

Postinflammatory medial canal fibrosis can be difficult to evaluate in the clinic because the ear canal becomes foreshortened and scarred. This entity is the sequela of chronic inflammation in the EAC, typically resulting from chronic otitis externa, but also can be of autoimmune origin.[10,11] Nonenhanced HRCT with axial and coronal images is most helpful. One typically finds soft tissue in the medial one third to one half of the canal that is indistinguishable from the tympanic membrane without erosion or expansion of the bony ear canal (Fig. 135-6); this often has the appearance of a crescent. In the very early stages, there

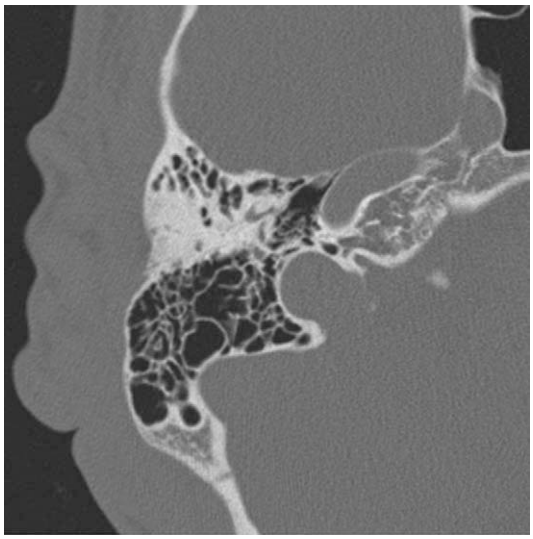

Figure 135-1. Axial noncontrast CT image through the right temporal bone shows a case of external auditory canal (EAC) atresia with membranous and osseous atresia of the EAC, with an abnormal pinna.

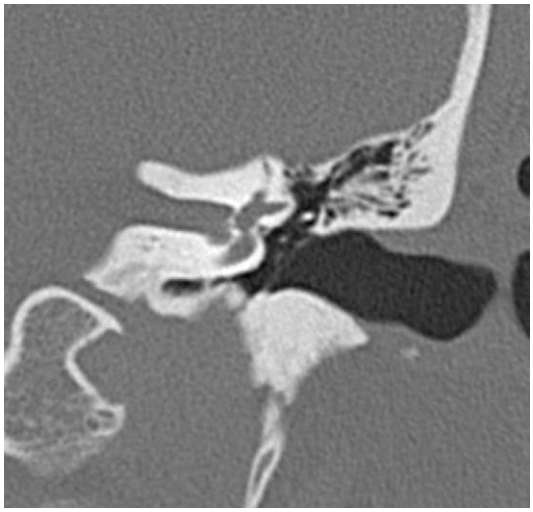

Figure 135-2. Coronal bone algorithm CT image through the left temporal bone in a case of oval window atresia, with a facial nerve tympanic segment overlying the atretic window.

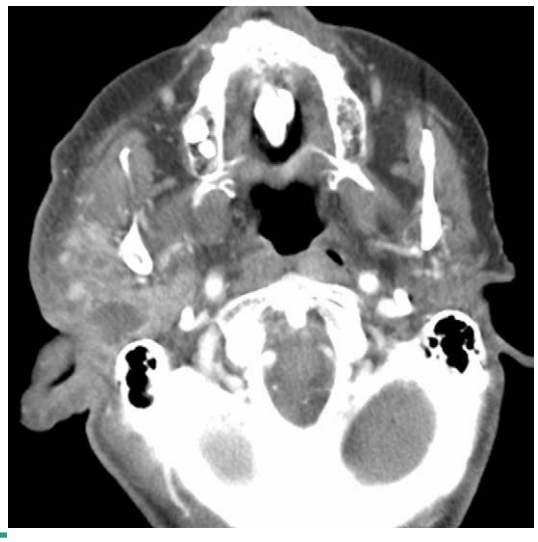

Figure 135-3. Axial postcontrast CT image through the suprahyoid neck shows abnormal patchy enhancement within the right parotid space, below the right external auditory canal secondary to inferior spread of infection.

Figure 135-4. Coronal magnified bone algorithm CT image through the right temporal bone shows osseous destruction of the inferior right external auditory canal (EAC) with bony flecks, consistent with an EAC cholesteatoma.

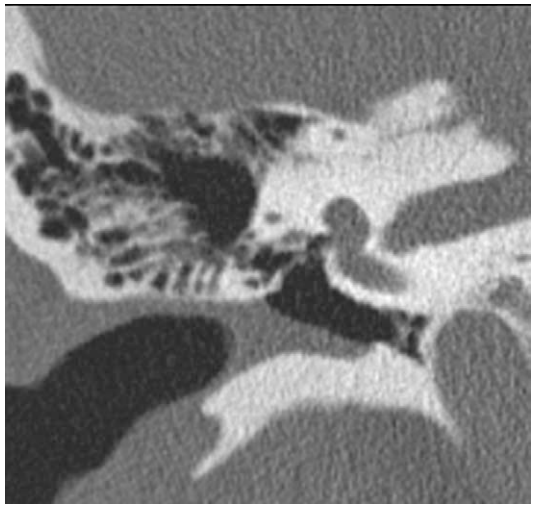

Figure 135-6. Coronal CT image through the right temporal bone shows findings consistent with medial canal fibrosis, with a classic "crescent" of soft tissue adjacent to the intact tympanic membrane.

Figure 135-5. Coronal CT image through the right temporal bone shows classic keratosis obturans findings with benign-appearing soft tissue filling the external auditory canal, without osseous changes.

Figure 135-7. Axial bone algorithm CT image of the right temporal bone shows classic circumferential osseous overgrowth of the osseous external auditory canal, consistent with exostoses or "surfer's ear."

may be thickening of the tympanic membrane only, especially anteriorly. The middle ear and mastoid are not involved.

Benign neoplasms of the EAC include EAC exostoses and osteomas. Exostoses, also known as "surfer's ear," can be diagnosed without imaging, but are frequently seen on temporal bone imaging in some regions where cold water swimming is common. On HRCT, these lesions are typically circumferential bony overgrowths with normal overlying soft tissue that begin past the isthmus of the EAC (Fig. 135-7). These are almost always bilateral, and typically occur at the suture lines. EAC osteomas can be differentiated from these lesions by several distinct features. Similar to exostoses, they have normal overlying soft tissue, but they are typically ovoid in shape and less than 1 cm in size (Fig. 135-8). Usually discovered as an incidental finding, these lesions tend to be isolated, asymptomatic, and unilateral.

Malignant lesions of the EAC are uncommon, and are typically limited to local squamous cell carcinomas and the occasional metastatic carcinoma to the region. The imaging characteristics associated with squamous cell carcinoma are most commonly a soft tissue mass within the EAC with aggressive underlying bony changes. HRCT without contrast enhancement to delineate the bony extent of tumor and MRI with and without contrast enhancement to delineate the extent of soft tissue involvement are recommended for the radiologic evaluation of these lesions because the bony and soft tissue extent of tumor can impact surgical planning.[12,13] HRCT shows the tumor and adjacent bony erosion, which are typically isolated to the EAC (Fig. 135-9). Contrast-enhanced HRCT may show a heterogeneously enhancing mass and spread to adjacent areas. These lesions tend to spread locally to the lining of the EAC and the auricle, sparing the middle ear. Regional metastases to the parotid and neck can be shown as enhancing nodes often greater than 1 cm in size (Fig. 135-10). MRI appearance of these lesions is generally low signal on T1-weighted imaging, which enhances peripherally with contrast medium. T2-weighted imaging commonly shows a heterogeneous high signal invasive lesion.[13]

Middle Ear and Mastoid

Common lesions affecting the middle ear and mastoid include cholesteatoma, glomus tympanicum, and an aberrant internal carotid artery.

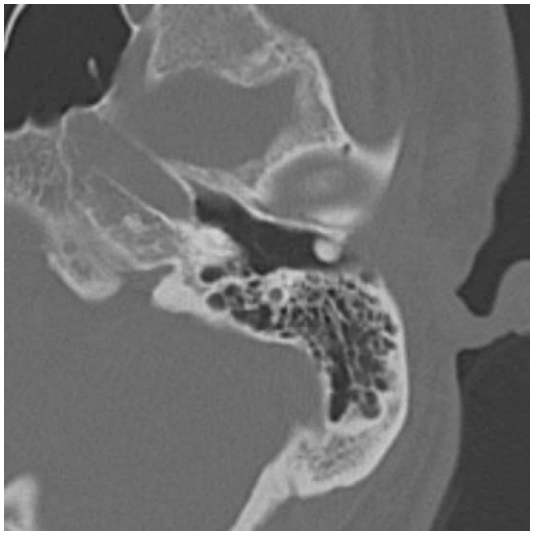

Figure 135-8. Axial CT image through the left temporal bone shows a small osseous lesion near the junction of the membranous and osseous external auditory canal (EAC), consistent with an EAC osteoma.

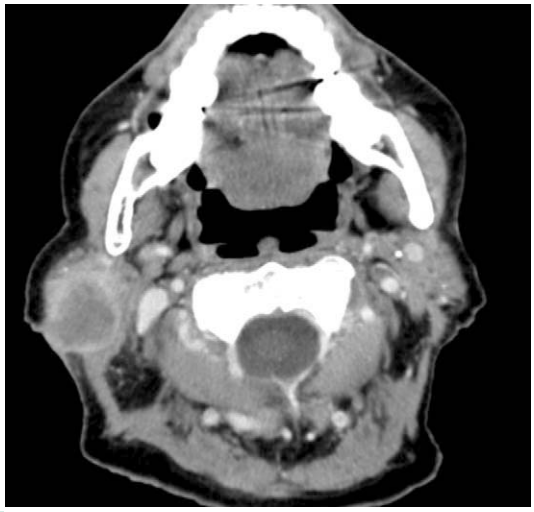

Figure 135-10. Axial postcontrast CT image through the suprahyoid neck shows a large necrotic node within the right parotid gland from an external auditory canal squamous cell carcinoma primary.

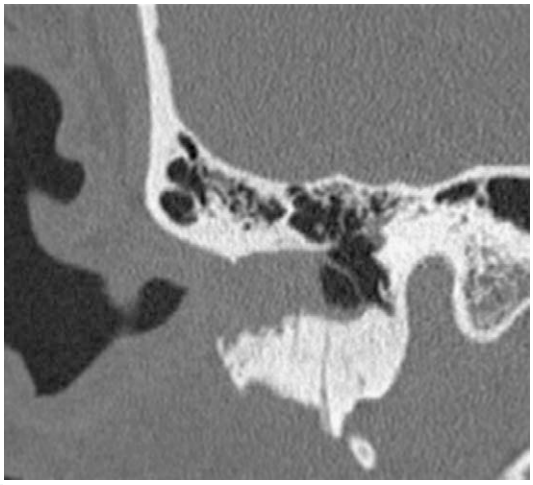

Figure 135-9. Coronal CT image of the right external auditory canal (EAC) shows a destructive lesion of the floor of the EAC, found to be a squamous cell carcinoma.

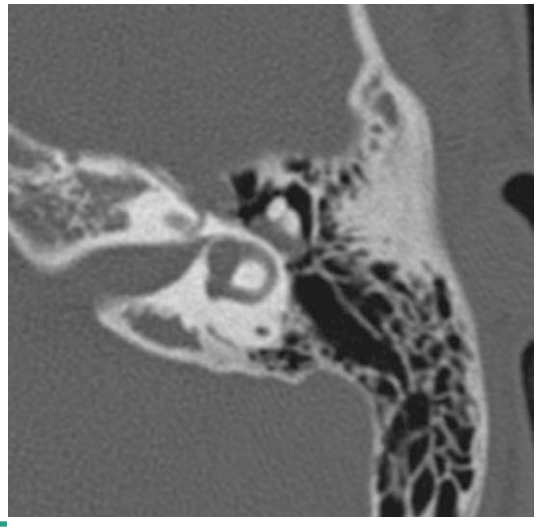

Figure 135-11. Axial CT image through the left middle ear cavity shows a soft tissue mass adjacent to the ossicles with some destruction of the short process of the incus, consistent with a cholesteatoma.

Cholesteatoma, although not strictly a radiologic diagnosis, does have specific radiologic characteristics. Congenital cholesteatomas are by definition found behind an intact tympanic membrane and can be very small, limited to the anterior tympanum, or, more rarely, can fill the entire tympanum and extend into the mastoid.[14] CT without contrast enhancement shows a homogeneous soft tissue lesion, usually in the anterior tympanum adjacent to the eustachian tube with or without adjacent bony erosion (Fig. 135-11). As these lesions enlarge, they may fill the entire middle ear and erode the ossicles (Fig. 135-12), the fallopian canal, the tegmen, or the otic capsule. As the lesion extends posteriorly, it may widen the antrum and obstruct the mastoid air cells, which may be opacified by trapped secretions (Fig. 135-13).[15]

An acquired cholesteatoma has a different CT appearance because it develops in the epitympanum, eroding the scutum and ossicles (Fig. 135-14), and can extend posteriorly to involve the mastoid. MRI of any cholesteatoma is diagnostic because it has a characteristic appearance regardless of location on temporal bone. T1-weighted imaging shows an isointense to hypointense lesion (Fig. 135-15) that does not enhance, but may show a rim of enhancement (Fig. 135-16). T2-weighted imaging shows an intermediate or increased signal intensity lesion, occasionally with high signal secretions in the mastoid cavity (Fig. 135-17). Fluid-attenuated inversion recovery (FLAIR) imaging shows incomplete attenuation, whereas diffusion-weighted imaging shows restricted diffusion (Fig. 135-18).[15] These imaging characteristics are typical of all cholesteatomas within the temporal bone, regardless of location.

An aberrant internal carotid artery is a rare finding, but can be easily confused with a glomus tympanicum if careful attention is not paid to the imaging findings. Nonenhanced HRCT is diagnostic because it shows the characteristic enlargement of the inferior tympanic canaliculus, anterolateral to the jugular bulb, through which the carotid enters the middle ear (Fig. 135-19). From here, the carotid can traverse the middle ear, crossing the promontory and joining the petrous carotid through a dehiscence in the carotid canal. The carotid foramen and the vertical segment of the carotid are absent, with the aberrant carotid taking a more lateral position in the temporal bone.[16] This lesion can be discriminated from a glomus tympanicum by the shape of the

Figure 135-12. Axial CT image of the right middle ear shows a large cholesteatoma with complete ossicular destruction.

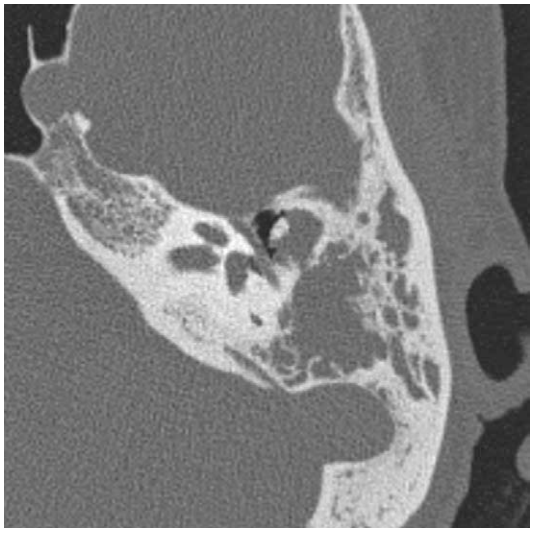

Figure 135-13. Axial CT image of the left middle ear shows destruction of the short process of the incus, and secondary opacification of the mastoid air cells.

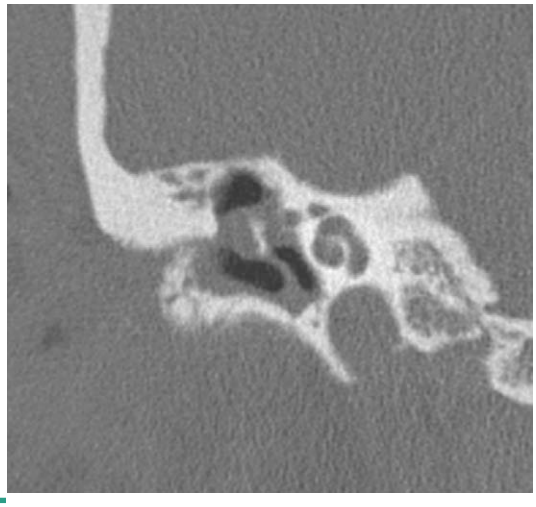

Figure 135-14. Coronal CT image of the right temporal bone shows scutum and ossicle destruction from a cholesteatoma.

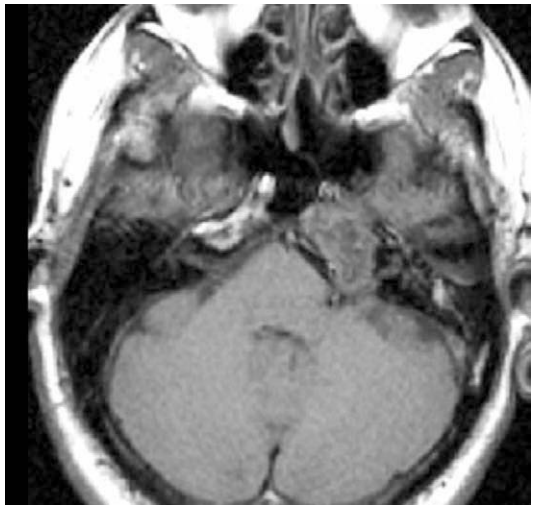

Figure 135-15. Axial T1-weighted noncontrast MR image through the temporal bone shows an isointense mass of the left petrous apex.

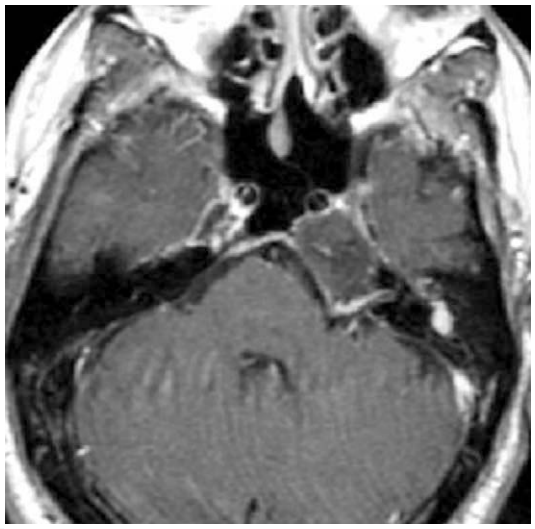

Figure 135-16. Axial postcontrast MR image through the left petrous apex in the same case as in Figure 135-15 shows a nonenhancing lesion with some peripheral enhancement.

middle ear mass (tubular versus ovoid). A glomus tympanicum is limited to the middle ear space (Fig. 135-20). It is imperative to review the images in these cases carefully because the aberrant artery may appear to be an isolated ovoid middle ear mass if visualized only on one cut of the scan. MR angiography is also helpful in the diagnosis of the aberrant artery, showing a more lateral course of a narrowed internal carotid artery (Fig. 135-21).

Inner Ear

Imaging of the temporal bone can produce excellent visualization of the structures of the inner ear. The cochlea, vestibule, and semicircular canals all can be well visualized on HRCT (Fig. 135-22) and high-resolution T2-weighted MRI (Fig. 135-23). The diagnosis of superior semicircular canal dehiscence on imaging has improved significantly as higher resolution scans are acquired with submillimeter cuts and reconstructions in the plane of the superior semicircular canal that show the absence of bone over the canal (Fig. 135-24). In lieu of these reconstructions, the diagnosis is made by visualizing the lack of bone over the canal on three consecutive coronal cuts (Fig. 135-25).[17,18]

Figure 135-17. Axial T2-weighted MR image of the same case shows increased T2 signal intensity within the lesion.

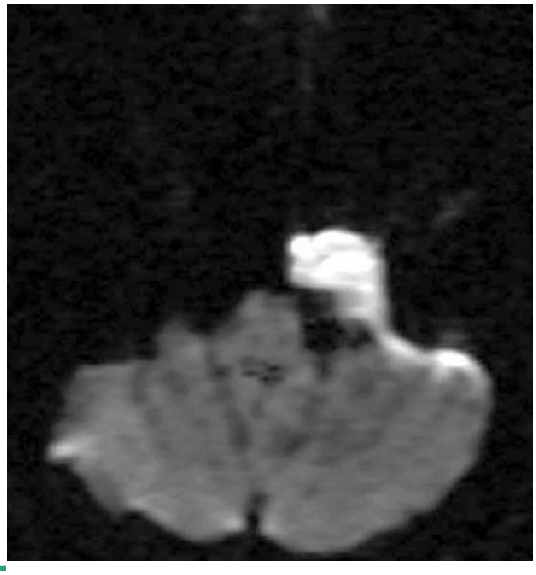

Figure 135-18. Axial diffusion-weighted MR image through the same lesion shows restricted diffusion (bright signal) consistent with a cholesteatoma.

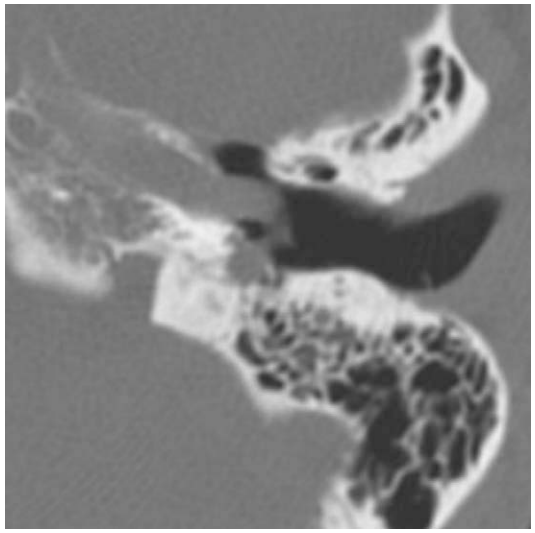

Figure 135-19. Axial CT image through the left temporal bone shows extension of the horizontal segment of the carotid canal into the middle ear, consistent with an aberrant carotid artery.

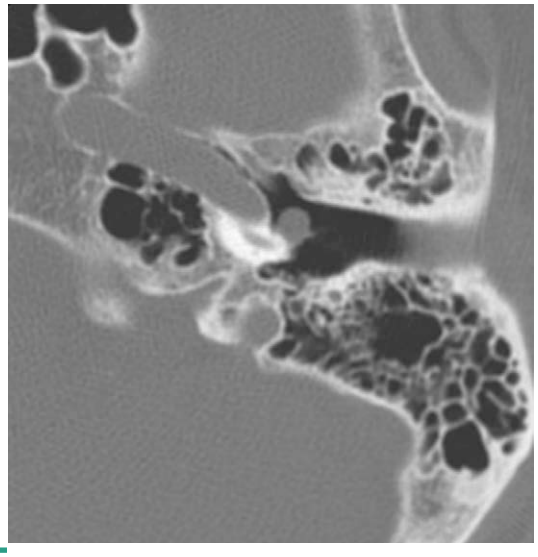

Figure 135-20. Axial CT image through the left temporal bone shows a small mass on the cochlear promontory, separate from the carotid, found to be a small glomus tumor.

Congenital abnormalities of the inner ear can also be well defined using HRCT. Cochlear anomalies such as common cavity and cochlear hypoplasia are readily apparent (Fig. 135-26).

Enlarged vestibular aqueduct can be diagnosed on either MRI or CT, with the characteristic enlargement of the duct leading up to the posterior canal clearly identified on this axial CT image (Fig. 135-27).[19] It is generally accepted that the duct should not measure wider than 1.5 mm in diameter at the midpoint of the bony endolymphatic duct. High-resolution T2-weighted images are necessary to make this diagnosis on MRI (Fig. 135-28).[20,21] Semicircular canal dysplasia is characterized by an abnormal development of the vestibular system during the 6th to 8th week of embryogenesis. This can vary from an enlarged diameter of the semicircular canal to a featureless cavity, and can be diagnosed on HRCT or thin T2-weighted MRI (Fig. 135-29).

In the evaluation of patients with sensorineural hearing loss, the inner ear may be affected by inflammation or neoplasm. These pathologic entities can be difficult to discriminate on imaging, and careful examination must be undertaken. Inflammation in the inner ear associated with labyrinthitis may lead to enhancement of the vestibule or cochlea or both on T1-weighted gadolinium-enhanced images. An intralabyrinthine or intracochlear schwannoma has a similar appearance, but the differentiation can be made on thin T2-weighted images that show evidence of a space-occupying lesion in the area of enhancement with loss of the normal fluid signal (Figs. 135-30 and Fig. 135-31).[22,23] The exception to this is that the late sequela of inflammation in the inner ear, labyrinthitis ossificans, would lead to bone formation within the cochlea or vestibule and lead to a similar appearance. This can be differentiated on CT, which is abnormal in the setting of late labyrinthitis ossificans with increased density within the inner ear (Fig. 135-32).[24]

Fenestral and cochlear otosclerosis (otospongiosis) appears as demineralization of the bone of the otic capsule. HRCT shows osteolytic foci of the otic capsule, surrounding the cochlea or involving the fissula ante fenestram, or both (Fig. 135-33).[25,26] As the resolution of CT

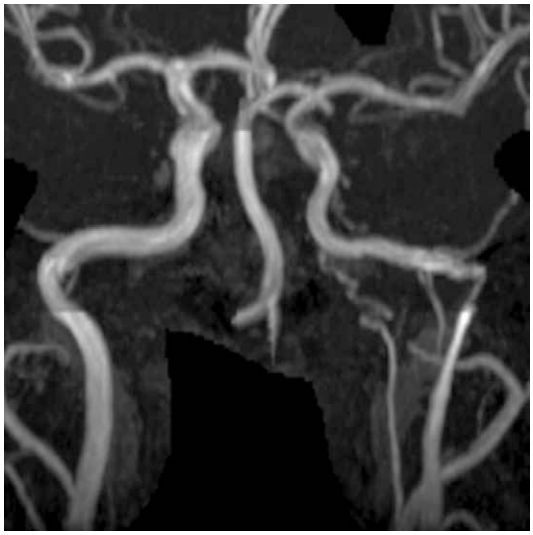

Figure 135-21. Anterior collapsed MR arteriography view shows lateral displacement of the left horizontal segment of the carotid artery, consistent with an aberrant carotid artery.

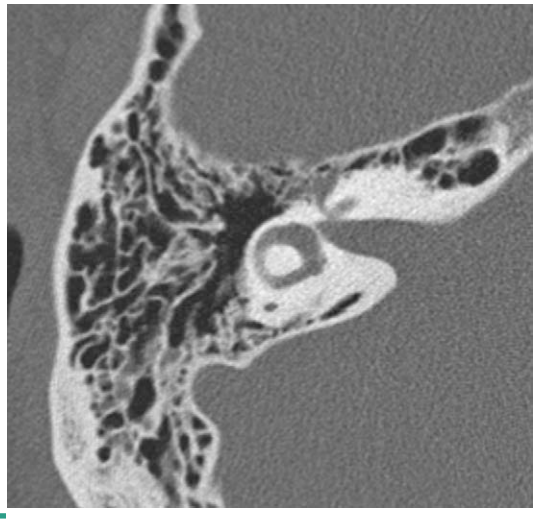

Figure 135-22. Axial CT image through the right temporal bone internal auditory canal shows the normal configuration of the vestibule and lateral semicircular canal.

imaging has increased with multidetector scanners, the ability to diagnose fenestral otosclerosis has improved significantly. The diagnosis of cochlear otosclerosis is possible on MRI, but the sensitivity of this technique is less than that of HRCT. On T1-weighted imaging, the otosclerotic plaque may be visualized as a ring of intermediate signal in the pericochlear and perilabyrinthine regions. On T2-weighted imaging, one may see focal areas of high signal around the cochlea in very large otosclerotic foci. T1-weighted imaging with contrast enhancement shows enhancing foci surrounding the cochlea.[27] HRCT is the most sensitive test to make the diagnosis of otosclerosis.

Petrous Apex Lesions

When clinically faced with a petrous apex lesion, clinicians rely on CT and MRI. Most lesions affecting this area have characteristic imaging features that facilitate the diagnosis (Table 135-1). The most common presentation is the incidental finding on a brain MR image or head CT scan that elicits a consultation with an otolaryngologist. Frequently, the "abnormality" is simply asymmetric marrow in the petrous apex, with

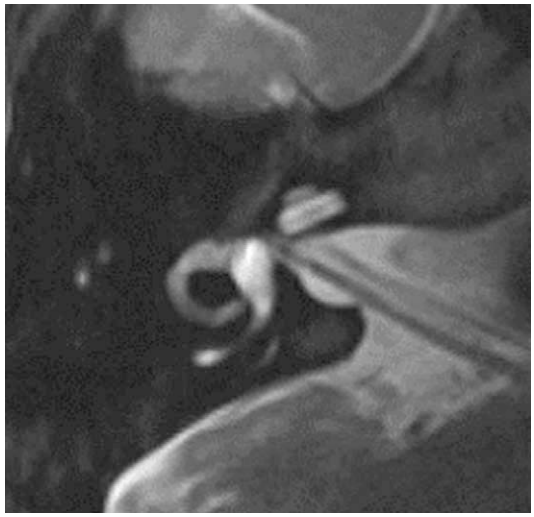

Figure 135-23. Axial thin-section T2-weighted MR image through the internal auditory canal shows the normal bright signal of the cochlea, vestibule, and lateral semicircular canal.

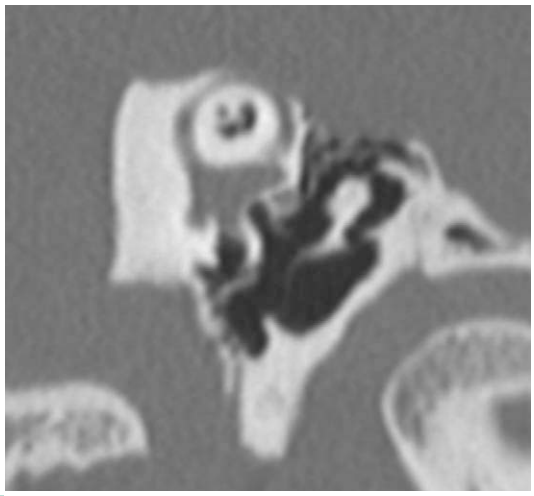

Figure 135-24. Oblique transverse sagittal CT reconstructed image through the left temporal bone shows focal dehiscence of the posterior roof of the superior semicircular canal.

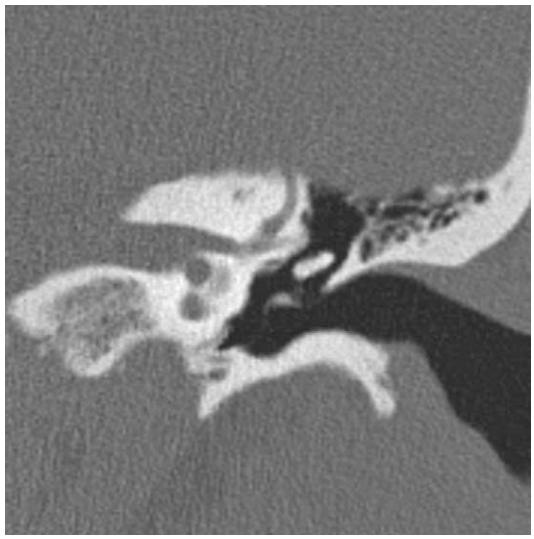

Figure 135-25. Coronal CT image of the left temporal bone shows focal dehiscence of the roof of the superior semicircular canal.

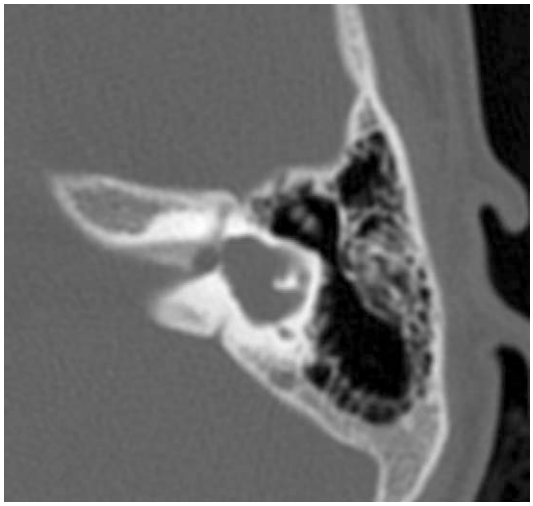

Figure 135-26. Axial CT image of the left temporal bone shows abnormal cystic changes of the left vestibule.

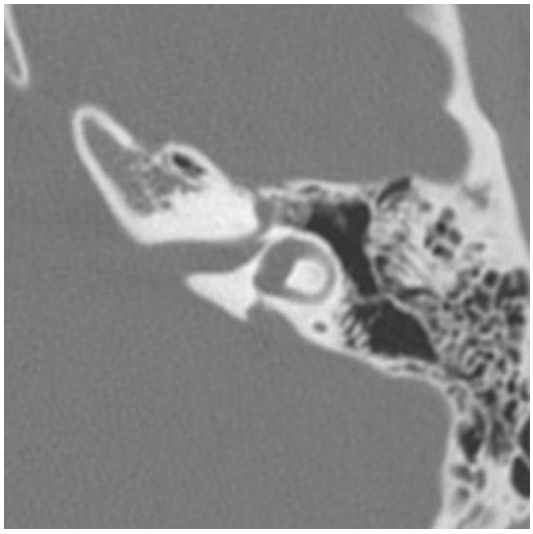

Figure 135-27. Axial CT image of the left temporal bone shows abnormal enlargement of the left endolymphatic duct, posterior to the vestibule.

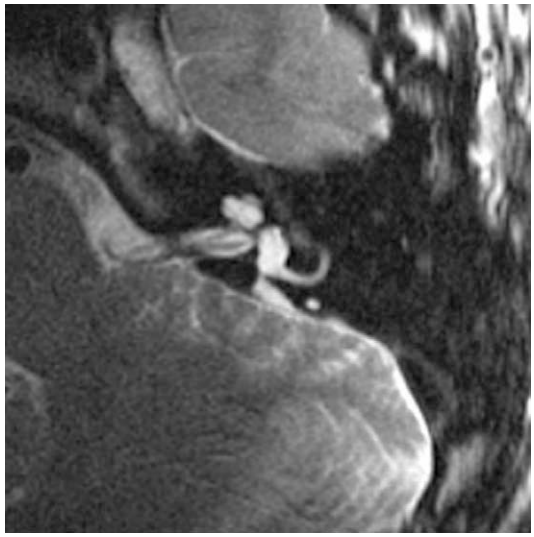

Figure 135-28. Axial thin-section T2-weighted MR image of the left temporal bone in the same case as in Figure 135-27 shows abnormal enlargement of the bright signal intensity of the left endolymphatic duct, posterior to the vestibule.

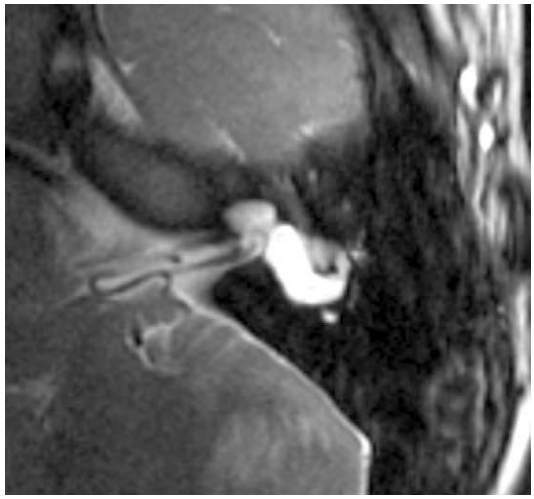

Figure 135-29. Axial thin-section T2-weighted MR image of the left temporal bone shows abnormal increased signal intensity, enlargement of the vestibule, and abnormal configuration of the cochlea.

normal pneumatization on one side and fatty marrow on the other. The bone marrow shows high signal on T1-weighted imaging (Fig. 135-34), which disappears with fat suppression. These lesions may also appear of intermediate signal if the bone marrow has not been infiltrated with fat. T2-weighted imaging shows increased signal in cases with fatty marrow, following the signal of subcutaneous fat. There is no enhancement with the addition of contrast material.

CT of these patients reveals normally aerated petrous apex across from a normal marrow space on the contralateral side (Fig. 135-35). Another commonly found incidental finding is trapped fluid in the petrous apex cells. This trapped fluid appears as a high signal lesion on T2-weighted imaging that has low signal on T1-weighted imaging, but with the preserved bony trabeculae and cortical integrity (Fig. 135-36). Mucoceles of this region show an expansile lesion with trabecular breakdown on CT with low signal on T1-weighted imaging and high signal on T2-weighted imaging. These have rim enhancement on contrast administration.[28]

Cholesterol granuloma is another lesion that is often found incidentally. These granulomas are expansile masses that form within petrous apex air cells that become isolated. As they expand, they can become symptomatic as they come in contact with surrounding structures, such as the IAC, Dorello's canal, and the CPA. On MRI, these lesions typically have smooth, well-circumscribed edges with high signal on T1-weighted imaging (Fig. 135-37) and T2-weighted imaging (Fig. 135-38). The findings on CT are typically an expansile lesion that is well circumscribed and has smooth edges (Fig. 135-39). If the lesion is large, there is associated breakdown of trabeculae and cortical thinning over the lesion. It may extend into the IAC and clivus, and expose the petrous carotid artery.[29]

In contrast, cholesteatoma of the petrous apex has identical signal characteristics as seen in cholesteatoma of the middle ear and mastoid as previously described. MRI shows a smooth, expansile mass with low signal on T1-weighted imaging and high signal on T2-weighted imaging. These lesions also show restricted diffusion on diffusion-weighted imaging (see Figs. 135-15 through 135-18).[30]

Malignant lesions of the petrous apex are uncommon. The most common primary lesion of this region is chondrosarcoma of the skull

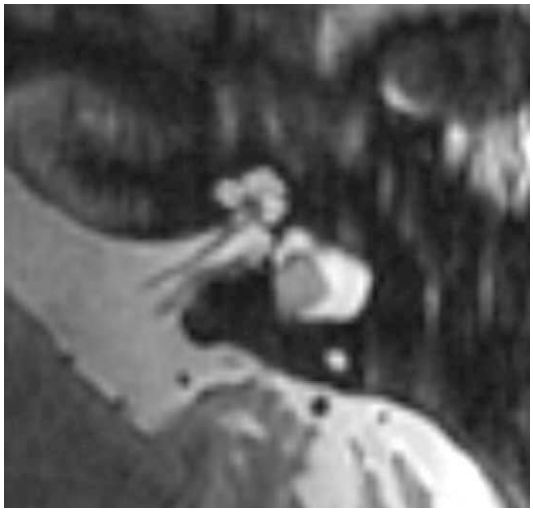

Figure 135-30. Axial thin-section T2-weighted MR image through the left vestibule shows a small focal filling defect within the posterior vestibule, surrounded by normal bright signal intensity of the fluid within the inner ear.

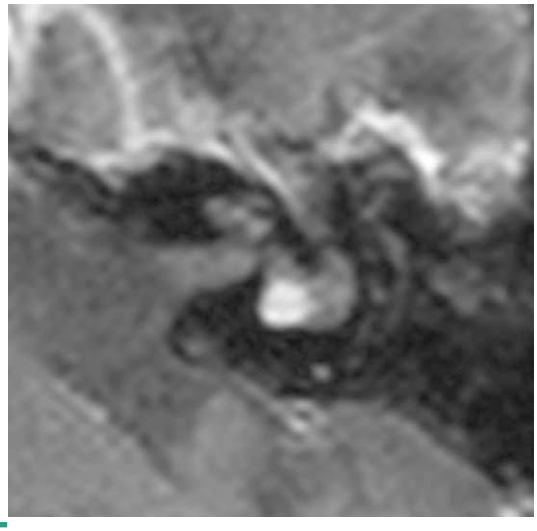

Figure 135-31. Axial postcontrast thin-section MR image through the left vestibule in the same case shows enhancement of this intravestibular schwannoma.

Table 135-1

Imaging Characteristics of Petrous Apex Lesions

Lesion	CT	T1	T2	T1 + Contrast	Notes
Asymmetric pneumatization	Bone marrow filled, no air cells	Hyperintense to intermediate intensity	Hypointense	No enhancement	T1 signal disappears with fat suppression
Retained secretions	Air cell trabecular preservation, nonexpansile	Hypointense	Hyperintense	No enhancement	
Cholesterol granuloma	Air cell trabecular breakdown, expansile	Hyperintense	Hyperintense	No enhancement	
Mucocele	Air cell trabecular breakdown, expansile	Hypointense	Hyperintense	Rim enhancement	
Cholesteatoma	Air cell trabecular breakdown, expansile	Hypointense	Hyperintense	May have rim enhancement if granulation tissue present	DWI does not restrict (bright signal)

DWI, diffusion-weighted imaging.

base. This lesion develops most commonly in the petro-occipital fissure or the basisphenoid. This lesion grows in the medial petrous apex, involving surrounding structures such as cranial nerves III, IV, V, VI, VII, and VIII, and the petrous carotid. A characteristic imaging finding of this lesion is intratumoral chondroid calcification on bone CT (Fig. 135-40). There is bony destruction in greater than 50% of these lesions. There is variable enhancement with the administration of contrast material. The MRI appearance of these lesions shows low to intermediate intensity signal to white matter on T1-weighted imaging. T2-weighted imaging reveals high signal. T1-weighted imaging with contrast enhancement reveals heterogeneous enhancement, with whorls of enhancement within the mass (Fig. 135-41).[31,32]

Facial Nerve

Imaging for facial nerve paralysis becomes necessary when the clinical picture suggests a tumor involving the facial nerve. Although herpetic (Bell's) palsy is the most common cause of acute facial paralysis, it is generally agreed that not all patients with herpetic palsy require imaging. It is important to differentiate cases of viral etiology from cases with a neoplastic origin, however, because enhancement and thickening of the nerves can be seen in cases of herpetic palsy and herpes zoster oticus.[33] In cases of simple herpetic palsy, T1-weighted imaging with contrast enhancement shows linear enhancement of portions of the facial nerve, from the distal IAC through the labyrinthine segment, the geniculate ganglion, and the anterior portion of the tympanic segment (Fig. 135-42). The enhancement pattern varies, and it most commonly involves the facial nerve in the distal IAC and the labyrinthine segment.[34] CT is normal in these cases. Patients with an atypical presentation should be imaged, including patients who (1) present with recurrent ipsilateral paralysis, (2) have no return of function over 6 months, and (3) present with weakness associated with twitching.

Radiologic evaluation for facial nerve tumors employs MRI and CT for complete detail about the facial nerve canal and enhancement in the nerve itself. MRI evaluation for facial nerve tumors requires

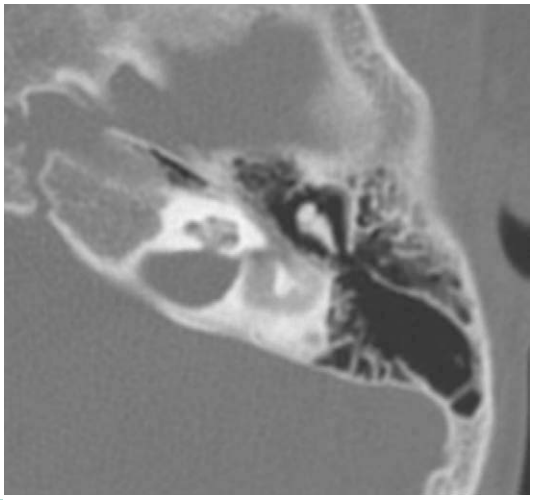

Figure 135-32. Axial CT image through the left temporal bone shows abnormal increased density within the left lateral semicircular canal, consistent with labyrinthitis ossificans.

Figure 135-34. Axial T1-weighted noncontrast MR image through the petrous apexes shows increased signal intensity of the right petrous apex, consistent with normal asymmetric marrow.

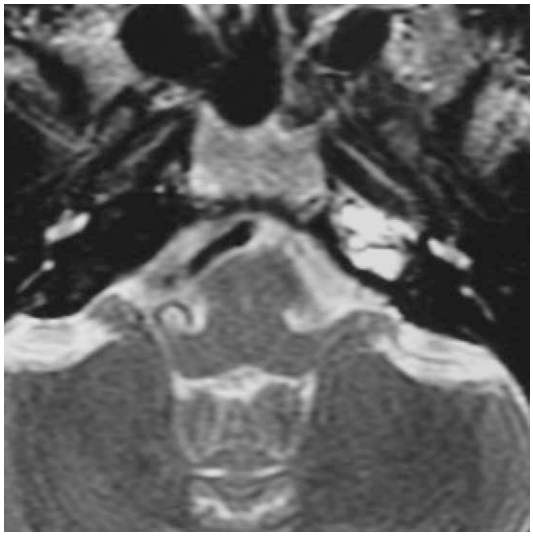

Figure 135-36. Axial T2-weighted MR image shows increased signal intensity within the left petrous apex, consistent with benign petrous apex trapped fluid.

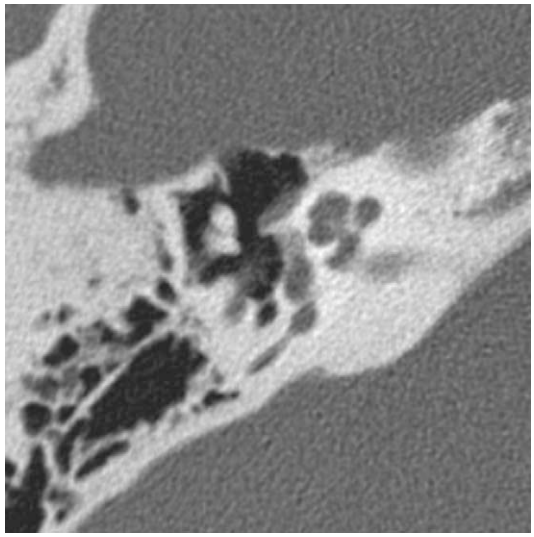

Figure 135-33. Axial magnified CT image of the right temporal bone shows subtle loss of normal bright osseous density of the fissula ante fenestram, just anterior to the lateral basal turn of the cochlea.

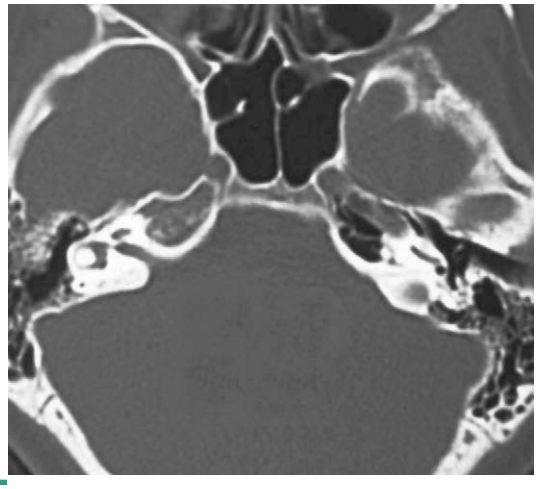

Figure 135-35. Axial bone algorithm CT image through the same level as the prior image shows normal osseous marrow of the right petrous apex, without surrounding aggressive features.

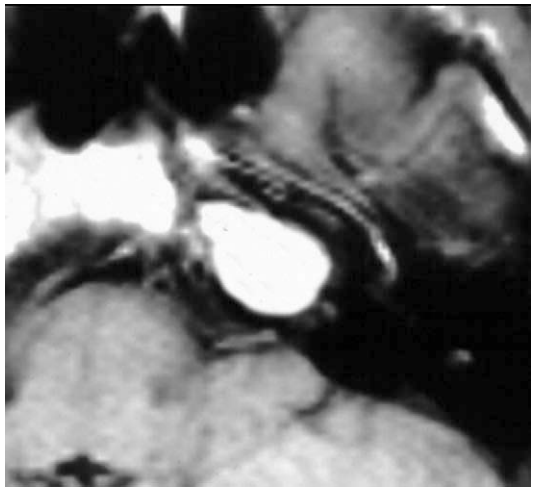

Figure 135-37. Axial magnified T1-weighted MR image of the left temporal bone shows increased signal intensity of the left petrous apex, with slight expansion.

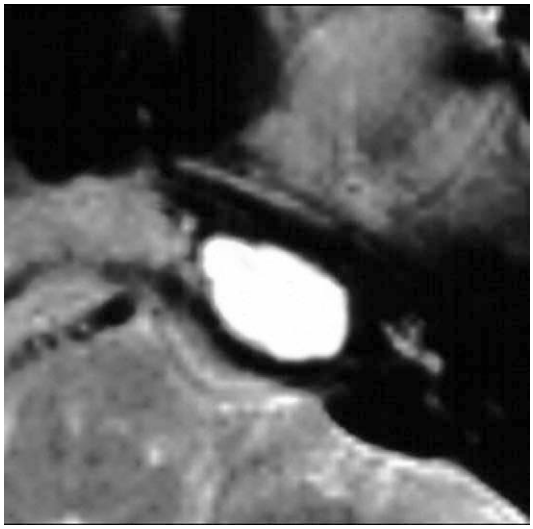

Figure 135-38. Axial magnified T2-weighted image through the same level as the prior image shows correlating bright T2 signal intensity, consistent with a cholesterol granuloma.

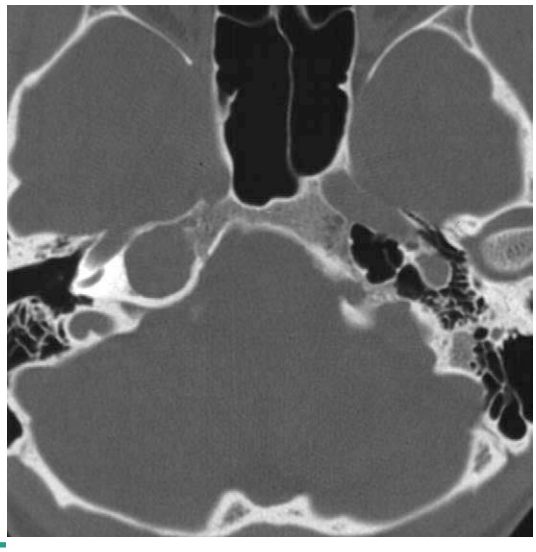

Figure 135-39. Axial bone algorithm CT image through the base of the skull shows benign expansion of a lesion within the right petrous apex, consistent with a cholesterol granuloma.

Figure 135-40. Axial bone algorithm CT image through the base of the skull shows the subtle chondroid calcification matrix at the right petro-occipital suture, consistent with a chondrosarcoma.

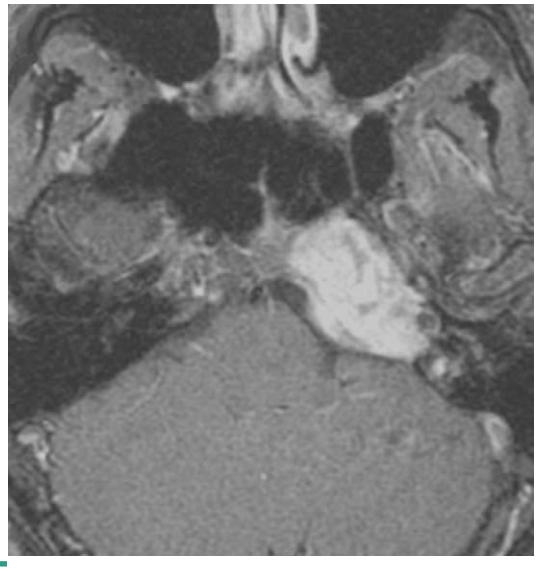

Figure 135-41. Axial T1-weighted postcontrast image through the left petro-occipital suture shows whorls of enhancement, consistent with a chondrosarcoma.

imaging of the facial nerve from the brainstem out to the parotid gland. Malignant parotid tumors may track up the facial nerve and manifest with intratemporal involvement. Intrinsic facial nerve tumors include facial nerve schwannomas and hemangiomas. Facial nerve schwannomas commonly manifest with hearing loss and gradual onset of facial paresis. Imaging in these cases reveals an expansile mass with smooth margins that enhances with contrast medium. T1-weighted MRI shows an isointense lesion in the course of the facial nerve. T2-weighted imaging shows a high signal lesion. T1-weighted imaging with contrast enhancement shows a homogeneously enhancing mass along the course of cranial nerve VII (Fig. 135-43).

The tumor can occur in the IAC, the labyrinthine segment, the geniculate, the tympanic segment, the mastoid segment, and the greater superficial petrosal nerve. Bone windows on HRCT show enlargement of the facial nerve canal in the regions involved, with associated soft tissue mass (Fig. 135-44).[35] Facial nerve hemangiomas frequently manifest with facial nerve paralysis out of proportion to the size of the lesion. These lesions frequently occur at the geniculate ganglion and arise from capillaries around the facial nerve. Typical imaging findings on HRCT are a poorly marginated lesion at the geniculate fossa with "honeycomb" bone within the substance of the tumor (Fig. 135-45). The MRI appearance of a hemangioma shows a mixed signal lesion on T1-weighted imaging with intratumoral low signal corresponding with areas of ossification. T2-weighted imaging shows high signal with areas of low signal, whereas T1-weighted imaging with contrast enhancement shows bright enhancement (Fig. 135-46), and may mimic an acoustic neuroma if the lesion is limited to the fundus of the IAC.[36,37]

Cerebellopontine Angle and Internal Auditory Canal

A common indication for imaging in otology is to rule out retrocochlear pathology. These patients commonly present with unilateral otologic complaints, such as progressive sensorineural hearing loss, sudden sensorineural hearing loss, tinnitus, and occasionally vertigo. The

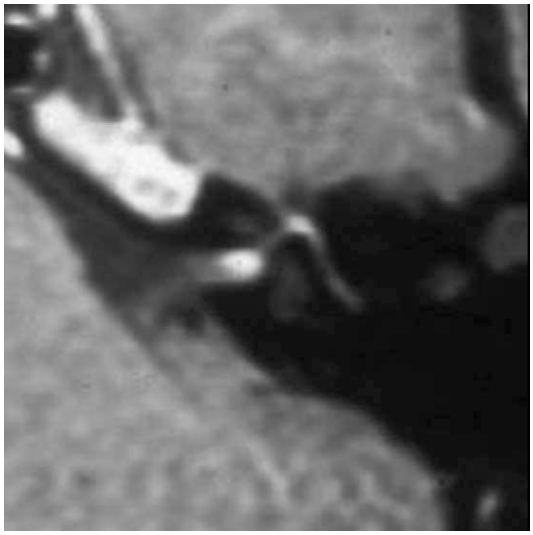

Figure 135-42. Axial T1-weighted postcontrast MR image through the left temporal bone shows abnormal enhancement along the intratemporal course of the facial nerve labyrinthine, geniculate ganglion, and tympanic segments, with a "tuft" of enhancement within the lateral internal auditory canal, consistent with a herpetic, or Bell's, palsy.

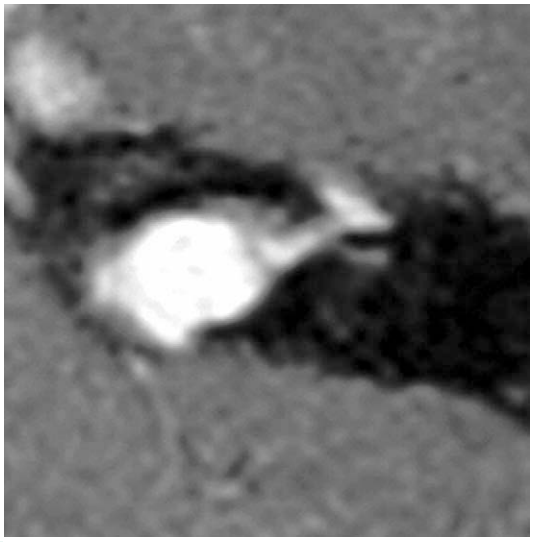

Figure 135-43. Axial magnified postcontrast T1-weighted MR image through the left temporal bone shows avid enhancement within the lateral internal auditory canal, and the labyrinthine segment of the facial nerve, extending into the geniculate ganglion, found to be a facial nerve schwannoma.

evaluation of these patients primarily involves the use of contrast-enhanced MRI. Auditory brainstem response can be a useful clinical adjunct, but it has been shown in the literature that it can miss small intracanalicular lesions.[38] CT scanning is insensitive to the detection of vestibular schwannomas, even when performed with contrast medium.

Contrast-enhanced MRI is the study of choice to detect these lesions, whereas air contrast CT cisternography is reserved for patients who are unable to undergo MRI. Advances in MRI allow the use of screening MRI studies using fast spin-echo (FSE) sequences to acquire submillimeter resolution in the IAC and CPA without the use of contrast material. FSE allows for detection of very small lesions along the seventh and eighth cranial nerve complexes, but misses intra-axial and intratemporal pathology. The cost of these scans approaches that for auditory brainstem response.[39,40]

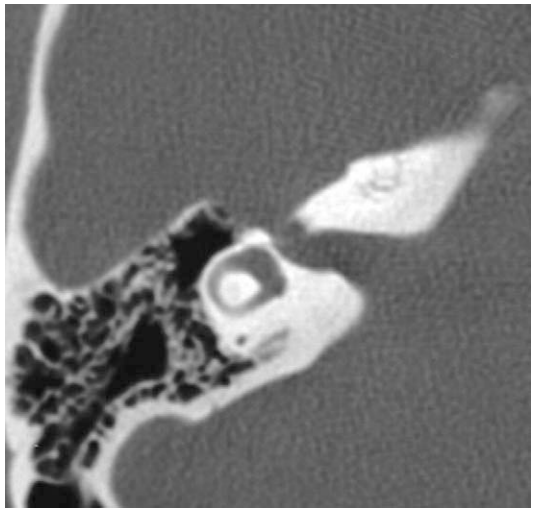

Figure 135-44. Axial CT image of the right temporal bone shows benign enlargement of the labyrinthine segment of the facial nerve from a facial nerve schwannoma.

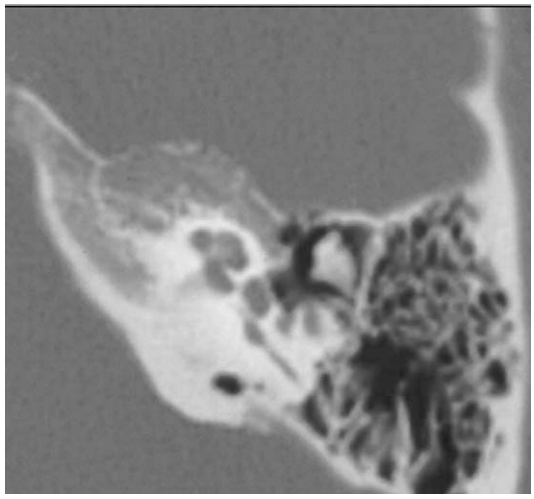

Figure 135-45. Axial magnified CT image through the left temporal bone shows abnormal "honeycombing" osseous changes at the geniculate ganglion, classic for a facial nerve hemangioma.

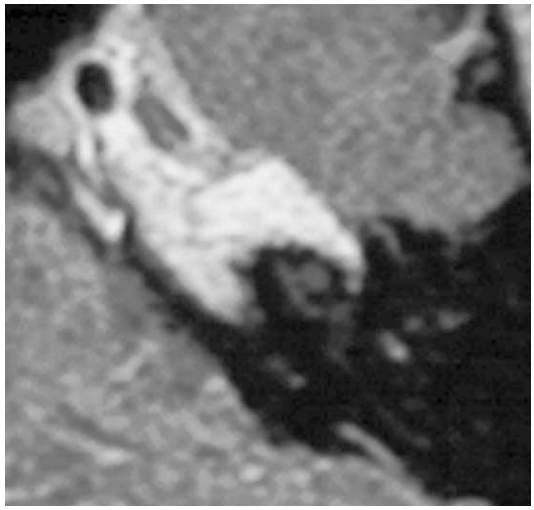

Figure 135-46. Axial magnified postcontrast T1-weighted image through the same level as the prior image shows avid enhancement, classic for a facial nerve hemangioma.

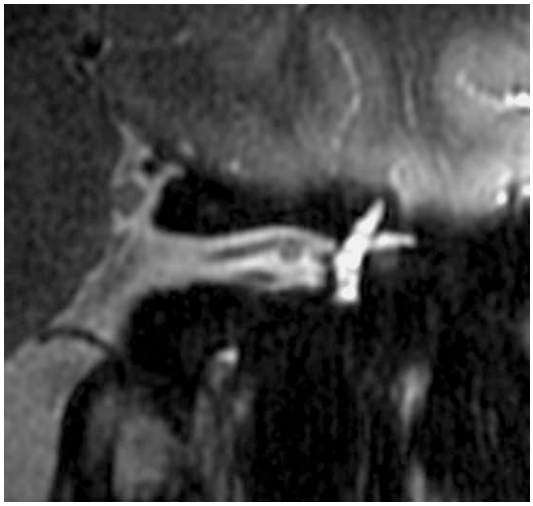

Figure 135-47. Coronal thin-section T2-weighted image through the left internal auditory canal shows a small filling defect within the normally bright cerebrospinal fluid, adjacent to the superior vestibular nerve, consistent with a small vestibular schwannoma.

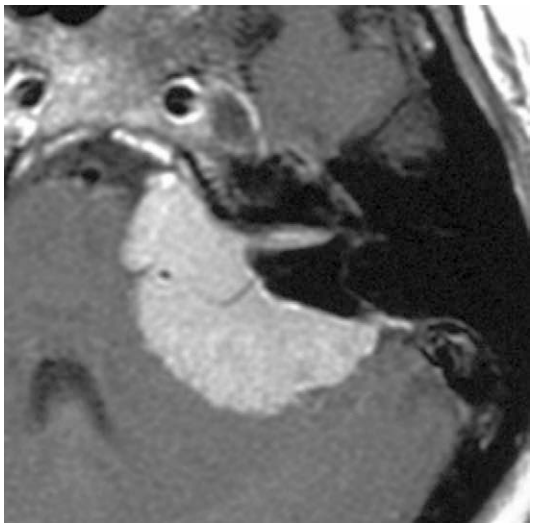

Figure 135-48. Axial postcontrast T1-weighted MR image through the left cerebellopontine angle shows an avidly enhancing lesion with dural tails, consistent with a meningioma.

Vestibular schwannomas are one of the most common extra-axial lesions of the posterior fossa. These lesions enhance avidly with the administration of contrast material on T1-weighted imaging, and are isointense without contrast enhancement. T2-weighted imaging is mildly hyperintense. Vestibular schwannomas may be isolated to the IAC, and high-resolution T2-weighted imaging can show if the tumor originates from the inferior or superior vestibular nerve in small lesions (Fig. 135-47). Larger vestibular schwannomas with extension into the CPA are centered on the IAC, and typically have an IAC component. They typically intersect the dura of the posterior fossa at an acute angle, which can help to differentiate them from meningiomas. Approximately 15% of these tumors have a cystic component.[37]

Meningiomas have a similar appearance to vestibular schwannomas on MRI. These lesions are isointense on T1-weighted imaging, with a variable appearance on T2-weighted imaging. Meningiomas also enhance with administration of contrast material, and have a more "obtuse" relationship to the posterior fossa dura than vestibular schwannomas, with an associated dural tail (Fig. 135-48). The location also helps to differentiate these lesions from vestibular schwannomas because

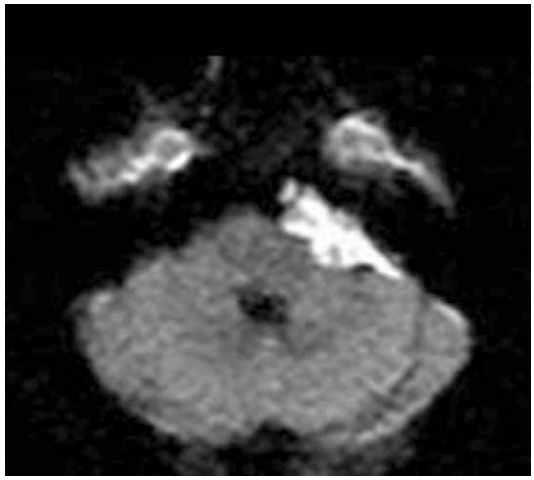

Figure 135-49. Axial diffusion-weighted MR image through the left cerebellopontine angle shows restricted diffusion (bright signal) consistent with an epidermoid tumor.

they tend to arise off center from the IAC, and rarely have an IAC component. These tumors may also have calcification within the lesion, which help to differentiate them from a vestibular schwannoma.[41] Very rarely, meningiomas can arise from the dura of the IAC and can present as an intracanalicular mass.[42]

Facial nerve neuromas may arise in the posterior fossa, and have a very similar appearance to vestibular schwannomas.[43] Occasionally, these can be differentiated from a vestibular schwannoma by identifying tumor extension along the labyrinthine segment of the facial nerve, which is the most sensitive sign of a facial nerve schwannoma. Another imaging characteristic of facial nerve tumors is that the CPA component may be eccentric to the IAC.[44] The involvement of the facial nerve may not be apparent until the time of surgery, however.

Other lesions of the CPA are significantly less common. The MRI characteristics of these lesions aids in their diagnosis (Table 135-2). Epidermoid tumors, which are pathologically identical to cholesteatoma, appear as irregular tumors that are hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI. These lesions do not enhance with the administration of contrast material. Arachnoid cysts have a similar appearance, with hypointense signal on T1-weighted imaging and hyperintense signal on T2-weighted imaging, which follows the signal intensity of cerebrospinal fluid. These lesions do not enhance with contrast material. Arachnoid cysts and epidermoid tumors can be easily differentiated using diffusion-weighted imaging, which shows restricted diffusion when imaging an epidermoid tumor (Fig. 135-49).[45]

Lipomas of the posterior fossa can mimic a schwannoma, and care must be taken to look carefully at the T1-weighted images, which show a hyperintense lesion. Lipomas have an isointense appearance on T2-weighted images. The administration of contrast medium on T1-weighted images does not alter the high signal, and lipomas appear to be "enhancing" if the precontrast images are not taken into consideration. T1-weighted images with fat suppression result in the signal in these lesions being suppressed.[46]

Cochlear Nerve

In the evaluation of children and adults for sensorineural hearing loss, high-resolution MRI is an extremely valuable tool. This imaging modality using FSE sequences can obtain submillimeter resolution of cranial nerves VII and VIII as they traverse the posterior fossa and the IAC. In addition, these images provide excellent detail of the fluid-containing compartments of the cochlea and vestibule. As mentioned previously, this study is an excellent screening modality for vestibular schwannomas.[39]

HRCT has been advocated for evaluation of children with sensorineural hearing loss.[47] HRCT can provide valuable diagnostic

Table 135-2

Imaging Characteristics of Cerebellopontine Angle Lesions

Lesion	T1	T2	T1 + Contrast	Notes
Vestibular schwannoma	Isointense to brain	Slightly hyperintense	Enhances	
Meningioma	Isointense to brain	Hypointense/hyperintense	Enhances	T2 signal depends on calcium content
Arachnoid cyst	Hypointense	Hyperintense	No enhancement	Signal characteristics mirror CSF
Epidermoid	Hypointense	Hyperintense	No enhancement	T2 signal slightly more dense than CSF, DWI does not restrict
Lipoma	Hyperintense	Hypointense	No enhancement	T1 signal disappears with fat suppression

CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging.

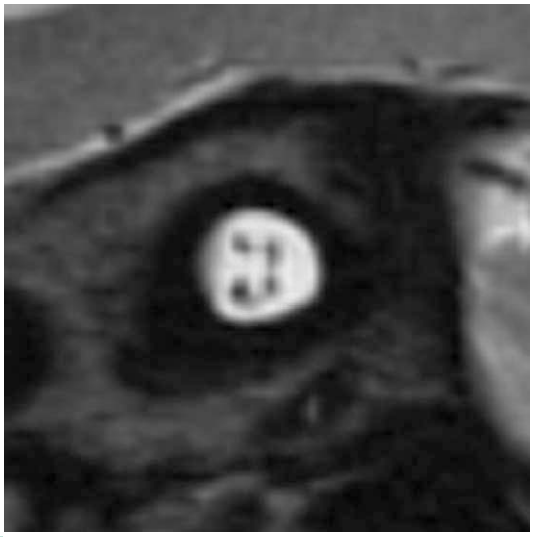

Figure 135-50. Oblique sagittal thin-section T2-weighted MR image through the right internal auditory canal (IAC) shows the normal configuration of the IAC nerves, with the facial nerve superior to the left (anterior), the superior vestibular nerve superior to the left (posterior), the cochlear nerve inferior to the left (anterior), and the inferior vestibular nerve inferior to the right (posterior).

Figure 135-51. Thin-section T2-weighted MR image of the right inner ear shows the normal anatomy of the membranous capsule.

and prognostic information for parents, although it infrequently leads to changes in therapeutic recommendations. The detection of enlarged vestibular aqueduct allows for counseling, however, regarding prognosis and activity modification to avoid head trauma. T2-weighted FSE images may also detect abnormalities in the membranous labyrinth.[48] Older children with suspicion of neurofibromatosis type 2 are best imaged with gadolinium-enhanced MRI.

T2-weighted FSE MRI can also be used for preoperative evaluation of patients for cochlear implantation; oblique sagittal images through the IAC provide excellent detail of the contents of the IAC, allowing visualization of the cochlear, facial, and superior and inferior vestibular nerves (Fig. 135-50), and detection of possible cochlear nerve aplasia. High-resolution T2-weighted imaging has been advocated over HRCT for this reason.[49,50] The detail of the inner ear also allows assessment of the patency of the cochlear duct for implantation (Fig. 135-51).[51] MRI does not provide adequate information, however, about the position of the facial nerve in cases of inner ear malformations, necessitating the addition of HRCT. HRCT can also be valuable in the evaluation of cochlear nerve aplasia if MRI shows two nerves within the canal, but CT shows that there is not a patent cochlear nerve canal entering the cochlea.

Skull Base

Evaluation of patients who present with deficits of lower cranial nerves raises the suspicion of a lateral skull base lesion that involves the jugular foramen, such as a glomus jugulare, meningioma, or schwannoma. Evaluation of these lesions with CT and MRI is diagnostic. Paragangliomas have a characteristic "salt-and-pepper" appearance on T1-weighted MRI, and enhance avidly with contrast medium. T2-weighted imaging shows a hyperintense mass with intervening flow voids ("pepper") (Fig. 135-52). These tumors may extend into the jugular vein and sigmoid sinus, and have a variable involvement of the middle ear and mastoid. Angiography shows a hypervascular tumor that is primarily fed by the external carotid system. HRCT shows erosion of the jugular foramen, with permeative and destructive bony changes, often eroding the jugular spine and involving the vertical segment of the carotid artery (Fig. 135-53).[52]

Jugular foramen meningiomas have unique imaging characteristics that allow them to be differentiated from glomus tumors. The CT

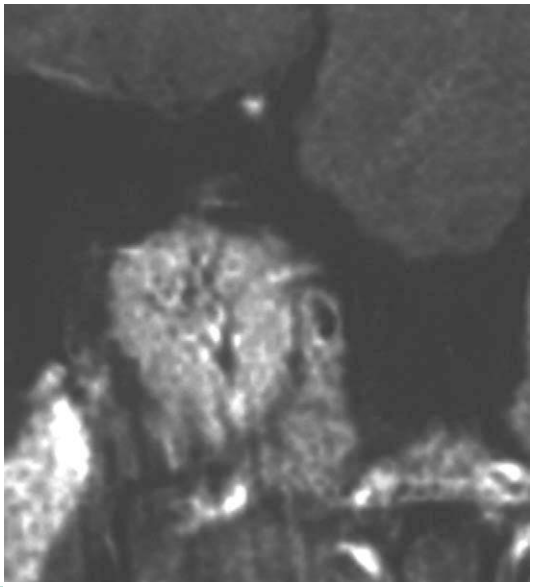

Figure 135-52. Coronal postcontrast T1-weighted MR image through the right jugular foramen shows an avidly enhancing lesion with internal flow voids ("pepper") consistent with a jugular foramen paraganglioma.

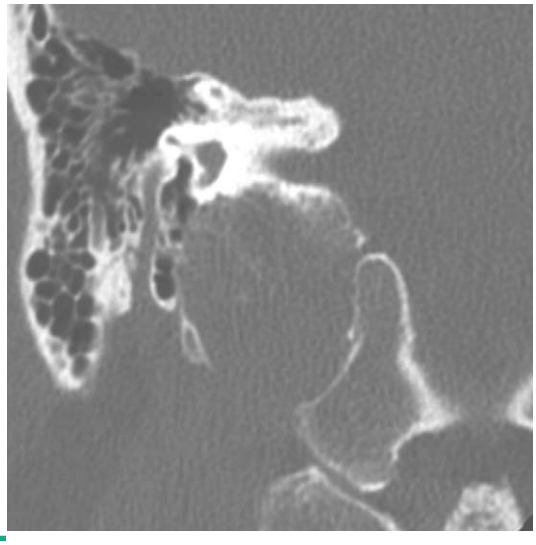

Figure 135-53. Coronal bone algorithm CT image through the same level as the prior image shows correlating permeative changes to the right jugular foramen, consistent with a paraganglioma.

appearance, in particular, shows a more hyperdense mass with intratumoral calcification and a surrounding sclerotic reaction (Fig. 135-54). The T1-weighted MRI appearance shows a hypointense to isointense mass that does not have flow voids. The tumor enhances with contrast medium, with characteristic dural tails. A relative hypointense T2 appearance is very suggestive of meningioma. FLAIR imaging can show adjacent brain hyperintensity reflecting recruitment of pial vasculature.[41] Schwannomas of the jugular foramen show smooth enlargement of the jugular foramen with a thin sclerotic border on CT (Fig. 135-55). Schwannomas are isointense on T1-weighted imaging, are hyperintense on T2-weighted imaging (in contrast to meningiomas), and enhance avidly with the administration of contrast material. There are no flow voids in these lesions, differentiating them from glomus tumors.[53]

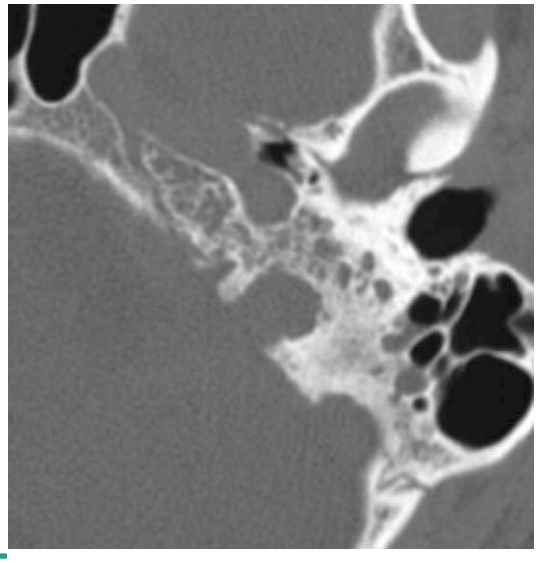

Figure 135-54. Axial bone algorithm CT image through the left jugular foramen shows the subtle osseous sclerotic changes of a left jugular foramen meningioma.

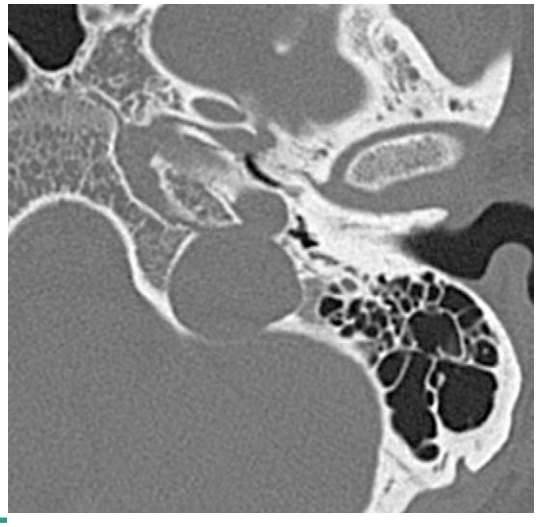

Figure 135-55. Axial bone algorithm CT image of the left temporal bone shows benign scalloped, almost surgical margins of the left jugular foramen from a jugular foramen schwannoma.

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CHAPTER ONE HUNDRED AND THIRTY-SIX

Interventional Neuroradiology of the Skull Base, Head, and Neck

Richard E. Latchaw

Sheri L. Albers

Key Points

- Superb equipment to visualize and perform image-guided neurologic interventional procedures is of paramount importance.
- The balloon occlusion test should be accompanied by an imaging procedure to evaluate the effects on cerebral blood flow during carotid occlusion.
- The goal of the interventional procedure must be defined at the outset—presurgical or definitive therapy.
- Preoperative embolization of vascular tumors of the head and neck can be extremely helpful by decreasing the blood loss during surgery.
- Endovascular and image-guided percutaneous techniques can be definitive for epistaxis, arteriovenous malformations, arteriovenous fistulas, pseudoaneurysms, and venous malformations.

Interventional neuroradiologic techniques are essential in the management of certain disorders involving the skull base, face, and neck. These image-guided techniques are used for a variety of purposes, such as to test the potential effects of closing major arteries during surgery for lesions of the skull base, to occlude significant arterial feeders to neoplastic lesions preoperatively, to infuse a chemotherapeutic agent into a metastatic tumor, and to treat a variety of vascular disorders.

Rather than presenting an exhaustive discussion of the management of individual diseases, this chapter introduces the referring clinician to the use of the tools and the basic principles of endovascular and image-guided percutaneous management for lesions of the skull base and the face and neck. This knowledge should not only lead to an appreciation of the sophistication of the interventional techniques, including the capabilities, limitations, outcomes, and possible complications of these procedures, but it also should support the role of an interventionalist when dealing with difficult vascular and neoplastic lesions.

Materials and Techniques

Before performing angiographic or percutaneous therapy, cross-sectional studies such as computed tomography (CT) or magnetic resonance imaging (MRI) are thoroughly analyzed to delineate the precise topography and extension of the lesion and its relationship to nearby structures, including displacements and alterations of blood vessels. It is essential that the goals of an interventional procedure are well defined by the entire therapeutic team to tailor the procedure to the overall treatment of a patient.

Angiographic Equipment

It is essential during endovascular interventional procedures to define the blood supply of a lesion with the highest possible resolution in all projections. Arteries or their collateral channels act as conduits for embolic material to the lesion. Of equal importance is the visualization of the many dangerous collateral vessels leading to the intracranial circulation or to the blood supply of the cranial nerves. Superb visualization and an excellent knowledge of the vascular anatomy are of paramount importance, as is an understanding of the potential clinical symptoms from embolization into an unwanted vascular territory and occlusion of the blood supply to normal tissues.[1]

The anatomic complexity of the neck, skull base, and face makes it essential that sophisticated C-arm positioners be used to allow variable projections of the area of interest. Biplane visualization is helpful for superselective catheterization of the small tortuous channels feeding the lesion. High-resolution techniques, including electronic "road-mapping," are essential. Injection of embolic agents suspended or diluted in contrast material during real-time high-resolution subtracted fluoroscopy (road-mapping) permits visualization of the progressive occlusion of the vessels feeding the lesion. Monitoring the procedure with high-resolution fluoroscopy helps to avoid the complications of reflux of embolic material or flow to collateral branches, thus preserving the blood supply to normal tissues.

Angiographic Catheters

The catheters most commonly used for diagnostic angiography are 4F and 5F polyethylene catheters. Superselective catheterization of tiny arteries feeding tumors, fistulas, and other lesions facilitates the most effective embolization, frequently beyond sites of anastomoses to dangerous collaterals, and is achieved by the use of microcatheters. Wire-directed microcatheters approximately 2F to 3F in size have extremely flexible distal portions that are variable in length. They are used with microguidewires 0.008 to 0.018 inch in diameter. Flow-directed catheters also are used for tortuous vessels feeding high-flow lesions.

If it is impossible to catheterize feeders to a tumor selectively, percutaneous puncture of the hypervascular neoplasm can be per-

formed under image guidance, gaining access to the intratumoral blood supply. Injections of contrast material during digital subtraction angiography are performed to ensure there is no filling of the arterial supply to normal tissues. Injections of the embolic agent are made under low pressure during fluoroscopy with road-mapping or digital subtraction angiography.

Embolic Agents

Several embolic agents are available for the various lesions found at the skull base and in the face and neck. The choice of the embolic material in a given patient depends on the goal of the procedure; the selectivity of the accomplished catheterization; the angioarchitecture and flow dynamics of the lesion; and the proximity of the catheter tip to the blood supply to vital structures such as the brain, cranial nerves, eyes, and skin, or to potential collateral channels to these organs. These embolic agents include particulate materials, metallic coils, liquid agents, and detachable balloons. Each has its own place in the interventionalist's armamentarium.

Two commonly used particulate materials are Gelfoam (Upjohn Pharmaceuticals, Kalamazoo, MI) and polyvinyl alcohol (PVA) (PVA Foam, Cook, Inc., Bloomington, IN; Trufill, Cordis Endovascular Systems, Miami Lakes, FL; Ivalon, Inc., San Diego, CA; Contour Emboli, Boston Scientific/Target Therapeutics, Inc., Fremont, CA).[2,3] Gelfoam breaks down 72 hours after embolization, and this lack of permanence detracts from its efficacy if surgery is not performed within a few days after the procedure. Gelfoam has been used as a preoperative embolization material for neoplasms that are to be operated on within 48 hours, and for patients with epistaxis in whom the goal is to slow the bleeding sufficiently so that the body's normal hemostatic mechanisms stop the hemorrhage. Gelfoam powder always should be used with care because its particles (approximately 50 μm) in solution act as a liquid, easily passing through tiny arteries, which may result in skin necrosis or damage to cranial nerves, or through collateral channels communicating with the intracranial circulation.

PVA is more permanent than Gelfoam, but much of the efficacy of the vascular occlusion is a result of a combination of PVA plus intravascular thrombus. The stellate-shaped particles slow the intravascular flow, and thrombus forms.[2-4] This thrombus may be metabolized before fibrosis occurs, however, resulting in partial or complete recanalization over weeks to months. PVA is easy to use, being supplied as uniform particles within a narrow range of size (150 to 1250 μm). In most patients with neoplasms, the smallest size (150 μm) is used because the particles can be easily injected through a small microcatheter placed selectively into tiny feeding arteries and penetrate into the tumoral vascular bed.

Because of the stellate shape of PVA particles, they do not form a tightly packed embolic mass, allowing recanalization as the interspersed thrombus undergoes lysis. Various types of beads and spheres have been produced to overcome that limitation, such as Embosphere Clear (Biosphere Medical, Inc., Rockland, MA). Their more uniform size and spherical geometry theoretically produce more complete and more permanent vascular occlusion. Similar spheres might also be filled with a chemotherapeutic or other agent for more prolonged treatment of a nonsurgical neoplasm. Microfibrillary collagen (Avitene; Avicon, Inc., Fort Worth, TX) is a hemostatic agent that may be mixed with contrast material for embolization[5] or mixed with other embolic agents such as PVA and ethanol.[6]

There are two broad categories of metallic coils: coils that are pushed from a catheter with a metal coil pusher or guidewire, and coils that are released by breaking a bond between the coil and the pushing wire. The latter is the type used for treating intracranial aneurysms. In head and neck lesions, metallic coils are used for occluding vessels that measure a few millimeters to 1 cm or more in diameter. Their size prohibits their moving more distally into the embolized lesion. They are best used for occluding the feeding artery after particulate embolization; the particles are embolized deeply into the lesion, with the coil producing the final occlusion of the feeding artery. Coils have been used to occlude bleeding vessels, such as in epistaxis or after trauma.

Detachable balloons with a valve mechanism to keep the balloon inflated are currently unavailable in the United States, but should be available again in late 2009. They are used primarily for fistulas with a single artery-to-vein connection. Most experience was with intracranial post-traumatic carotid-cavernous sinus fistulas, but this technique was also used for vertebral artery–vertebral venous fistulas (usually post-traumatic) or for any other type of fistula in the face or neck.[7-9] They were also used for occlusion of a parent artery leading to an unclippable aneurysm, a dissected carotid or vertebral artery producing embolization into intracranial vessels, or a carotid artery to be sacrificed at tumor surgery. Electrolytically detachable coils are used now instead of the currently unavailable detachable balloons. Many coils are usually necessary, however, to do what one balloon could accomplish, increasing the complexity and expense of the procedure.

There are numerous liquid embolic agents, the most commonly used being absolute alcohol (100% ethanol) and various tissue adhesives, including the cyanoacrylates and Onyx (MicroTherapeutics, Inc., Irvine, CA). Absolute ethanol is extremely toxic to the endothelium,[10] and is highly effective at producing sclerosis of vascular lesions, such as venous and lymphatic malformations.[11-13] Although it has also been used to treat arteriovenous malformations and dural arteriovenous fistulas, the problem with these fast-flowing lesions is the need to increase the "dwell time" of the ethanol to interact with the intima, often requiring temporary balloon occlusion more proximally. It has also been used for tumors, via endovascular and percutaneous access, particularly recurrent tumors that are surgically inaccessible.

The injection of ethanol is extremely painful, requiring deep sedation or, more commonly, general anesthesia. It is necessary to see where the embolic agent is going, and so opacification is necessary. Opacification of the ethanol with a liquid contrast agent produces dilution of the ethanol, however, decreasing its effectiveness, which is maximum if used undiluted. Metrizamide powder (Nycomed, Oslo, Norway) was used previously for opacification because a powder does not dilute the ethanol, but provides acceptable opacification. Metrizamide powder is no longer available in the United States, however.

Sodium tetradecyl sulfate (Sotradecol) 3% also is an excellent sclerosing agent, is less painful on injection than ethanol, and may be opacified, although it seems to be less effective than ethanol for venous malformations, and is not considered to be an acceptable alternative. Doxycycline, a tetracycline-like antibiotic, is an effective agent at producing sclerosis of venous, lymphatic, and other slow-flow vascular malformations in which there is an adequate "dwell time." Tetracycline has been associated with darkening of the tooth enamel in young children, so this drug is usually reserved for patients older than 11 years, after the formation of the permanent teeth. Povidone-iodine (Betadine) can also be injected into lymphatic malformations, with less pain than with alcohol and with good success.

Cyanoacrylates such as isobutyl-2-cyanoacrylate (IBCA) or *N*-butyl-2-cyanoacrylate (NBCA) produce polymerization of rapidly flowing blood within seconds. They not only produce immediate thrombosis and have tissue adhesive properties, but they also initiate a giant cell inflammatory reaction of the vessel wall.[14] These embolic liquids are excellent for lesions with rapidly flowing blood, such as an arteriovenous malformation or an arteriovenous fistula. Neoplasms have slow flow, so there is no need to use these agents, which are associated with more risk than particulate materials injected intra-arterially or other agents injected percutaneously.

The newest "liquid" agent is Onyx, which is an ethylene vinyl alcohol copolymer containing dimethyl sulfoxide as the agent facilitating absorption through endothelial barriers.[15] This tissue adhesive is a needed new addition to the armamentarium of the neurointerventionalist because it slowly permeates into tiny vessels feeding a vascular lesion, "creeping" into these feeders during fluoroscopic visualization and control, without the rapid setup time of the cyanoacrylates.[15,16]

Any embolization procedure with a liquid agent should be approached with trepidation because occlusion of the end-arteries to the face, tongue, and cranial nerves may lead to necrosis, and intracranial embolization may occur as the liquid passes through tiny collateral channels to vessels feeding normal structures. Liquid embolization should be performed only when superselective catheterization can be done directly into the direct feeders to the lesion, or with percutaneous puncture of the lesion and direct visualization of the flow of

the agent,[17] to prevent unwanted extension to the blood supply of vital structures.

Provocative Testing to Ensure the Safety of Embolization

Two important techniques help to ensure the safety of vascular occlusion at the skull base. The first involves the injection of lidocaine (Xylocaine) 1% without preservatives into an arterial feeder that is considered a candidate for embolization, to predict the potential of permanent cranial nerve palsy from the embolization procedure.[18] This provocative test anesthetizes the cranial nerve if there is blood supply leading to it from the vessel catheterized. Critics of this test suggest that a false-positive test may occur because a liquid anesthetic can be injected into the capillary bed, whereas particles used for embolization stop short of terminal arterioles so that devascularization is rare. It is likely that a negative test result is truly negative and reassuring.

The second provocative test is the temporary balloon occlusion test (BOT) of the internal carotid or vertebral artery, with the addition of blood flow measurement for precise quantification of the potential effects on cerebral blood flow during temporary or permanent occlusion of the artery during surgery or endovascular therapy. Carotid or vertebral artery occlusion might be necessary during the surgical removal of a skull base tumor, during the temporary occlusion of a major intracranial artery during surgical clipping of an aneurysm, for the thrombosis of an unclippable aneurysm via occlusion of the parent artery, or if carotid occlusion has to be performed to close a carotid-cavernous sinus fistula or any other type of traumatic vascular lesion.

First, a complete angiographic evaluation of all cerebral vessels is performed to evaluate their contribution to the particular lesion and the adequacy of collateral flow via the anterior and posterior communicating arteries. If communicating arteries are present, the traditional BOT is performed, consisting of occlusion of the internal carotid artery (ICA) with a nondetachable balloon catheter placed at the level of the future permanent occlusion. After systemic heparinization, the balloon is inflated, and the patient is evaluated for 30 minutes. Careful neurologic examinations are performed throughout the occlusion period, with special emphasis on the neurologic functions subserved by the vessel that is being tested. If the patient develops a neurologic deficit, the balloon is immediately deflated. If the patient has no neurologic deficit from the carotid occlusion, it is assumed that blood flow is adequate for permanent occlusion to occur. Such a qualitative test does not provide precise quantification of the blood flow to the hemisphere at risk, however. Blood flow values greater than 20 to 25 mL/100 g of tissue per minute allow normal neuronal function, with values less than that precipitating neuronal dysfunction. It is conceivable that blood flow values slightly greater than 20 to 25 mL/100 g/min would leave the patient without symptoms while on the angiography table, but superimposed intraoperative or postoperative hypotension, decreased cardiac output, or decreased oxygenation might precipitate cerebral infarction.

Different methods have been used during temporary occlusion to evaluate the physiologic effects of the BOT on cerebral blood flow to predict the risk of cerebral infarction after definitive occlusion. These methods include electric studies such as evoked potentials or electroencephalography,[19] measurements of arterial stump pressures distal to the site of temporary occlusion,[20] induced hypotensive challenges, and transcranial Doppler studies. Also, several cerebral blood flow imaging methods, including xenon-enhanced CT (Fig. 136-1),[21] single photon emission computed tomography (SPECT), positron emission tomography, and MRI and CT perfusion studies, have been used to evaluate cerebral blood flow during BOT to determine the potential risk of ischemia after permanent occlusion.[22,23] We prefer to use SPECT because it adds little to the basic BOT and easily provides the needed information. After the balloon has been inflated for a short time, the radionuclide is injected intravenously, and the patient is scanned a few hours after the completion of the angiographic study (the radiopharmaceutical "sticks" to the brain tissue during its initial circulation in proportion to the blood flow to that tissue).

Nevertheless, these techniques have turned out to be imperfect predictors of the ischemic risk associated with permanent carotid occlusion. Clinical deficits have been reported after permanent occlusion, even when there has been a negative BOT with accompanying normal physiologic or cerebral blood flow studies. Many, if not most, of these postocclusion deficits probably are a result of marginal cerebral perfusion accompanied by hypotension or decreased cardiac output, clot propagation from the residual stump, or de novo emboli at the time of vascular occlusion.

Endovascular Treatment of Neoplasms

Paragangliomas

Paragangliomas, also known as *chemodectomas* or *glomus tumors,* are neoplasms related to chemoreceptor tissue. They usually are benign, but locally invasive and highly vascularized. Most glomus tumors originate within the temporal bone (48%), including lesions along the promontory of the middle ear (glomus tympanicum tumors) and lesions related to chemoreceptor tissue in the jugular bulb (glomus jugulare tumors). Tumors related to the vagus body (11%) in the high cervical region are called *glomus vagale tumors,* and tumors related to

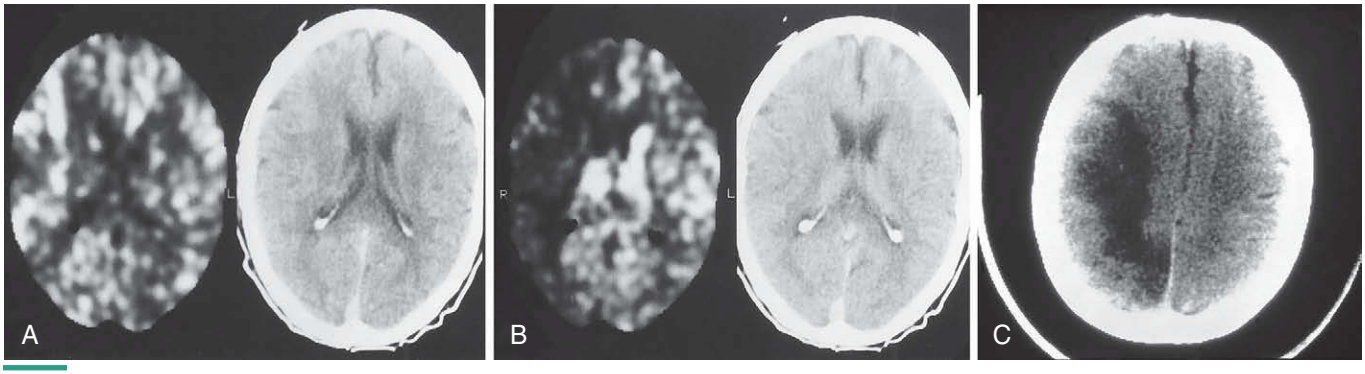

Figure 136-1. Xenon-enhanced CT during balloon test occlusion. This 60-year-old patient with squamous cell carcinoma invading the skull base was to undergo skull base resection and probable permanent carotid occlusion. A Swan-Ganz catheter was placed in the right internal carotid artery. Temporary blockage of the internal carotid flow for 15 minutes did not produce neurologic deficit. **A,** Xenon-enhanced CT scan for the production of a blood flow map *(left)* at the midventricular level *(right)* during balloon deflation reveals symmetric flows to the middle cerebral artery distributions bilaterally. **B,** With the balloon inflated, there is a marked reduction in the blood flow to the right middle cerebral distribution *(left)* relative to the left middle cerebral distribution. Flows to the right middle cerebral distribution are approximately 22 mL/100 g/min. This case was early in the authors' experience, and a bypass procedure was not performed after permanent carotid occlusion during the skull base tumor resection. **C,** Postoperatively, the patient became mildly hypotensive, resulting in infarction in the distribution predicted by the temporary carotid occlusion blood flow test.

the carotid body (35%) at the common carotid artery bifurcation in the neck are called *carotid body tumors*. Multiple tumors are found in approximately 10% of patients (Fig. 136-2), and a familial form exists.[24]

Glomus Tympanicum Tumor

The glomus tympanicum is a tiny tumor that usually manifests with pulsatile tinnitus and otoscopically is seen as a reddish blue mass behind the tympanic membrane. CT scanning allows the differentiation of this small tumor from an extension into the middle ear cavity of a larger glomus jugulare tumor. It also is necessary to exclude an aberrant ICA. In the former, the bony plate between the jugular foramen and the middle ear is destroyed, whereas in the latter, the posterior bony margin of the carotid canal is missing.[25] This tumor is usually small enough for surgery to be performed without embolization.

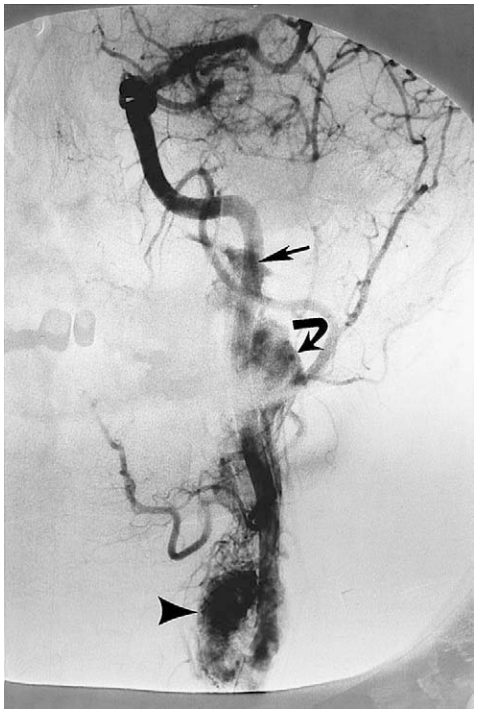

Figure 136-2. Multiple chemodectomas. This 38-year-old woman was one of many members of a family with chemodectomas. There is a small glomus jugulare tumor *(straight arrow)*, a glomus vagale tumor *(curved arrow)*, and extension of tumor along the carotid sheath to end in a carotid body tumor *(arrowhead)*.

Glomus Jugulare Tumor

A patient with a glomus jugulare tumor usually presents with dysfunction of cranial nerves IX, X, or XI, and XII if the tumor is large. Pulsatile tinnitus also is common. Contrast-enhanced CT or MRI usually is the first diagnostic test performed, with the diagnosis generally made and the extension of the tumor shown. The tumor begins in the region of the jugular foramen and may extend inferiorly into the upper neck, superolaterally into the middle ear by destroying bone, posteromedially and posterolaterally into the posterior fossa, and anteriorly to envelop the petrous ICA. Bone destruction can be extensive, simulating a malignant tumor, as the chemodectoma spreads through the skull base. Destruction around the foramen magnum may occur, with compression of the brainstem.[26]

The tumor is fed by multiple external carotid artery (ECA) branches, with each of these arteries feeding a specific compartment of tumor. The ascending pharyngeal (bilaterally at times) and middle meningeal (posterior division) arteries are the most commonly involved, with the stylomastoid branch of the occipital and the posterior auricular arteries providing supply less frequently (Fig. 136-3). If the tumor extends posteriorly around the foramen magnum, supply may be from the anterior and posterior meningeal branches of the vertebral artery. Intradural tumor within the posterior fossa may be fed from the anterior and posterior inferior cerebellar arteries. Tumor surrounding the high cervical or petrous portions of an ICA may parasitize tiny branches of these segments (see Fig. 136-3).[27-29]

The glomus jugulare tumor is highly vascular, which makes surgery difficult in this confined bony area. Embolization may be of great help.[30] Because the diagnosis generally has been made on the basis of CT or MRI before angiography, the patient is prepared with consent forms for angiography and embolization in the same sitting. The arterial feeders are mapped with high-resolution digital subtraction angiography in multiple planes, as previously described (Fig. 136-4). Selective catheterization of the multiple feeders is

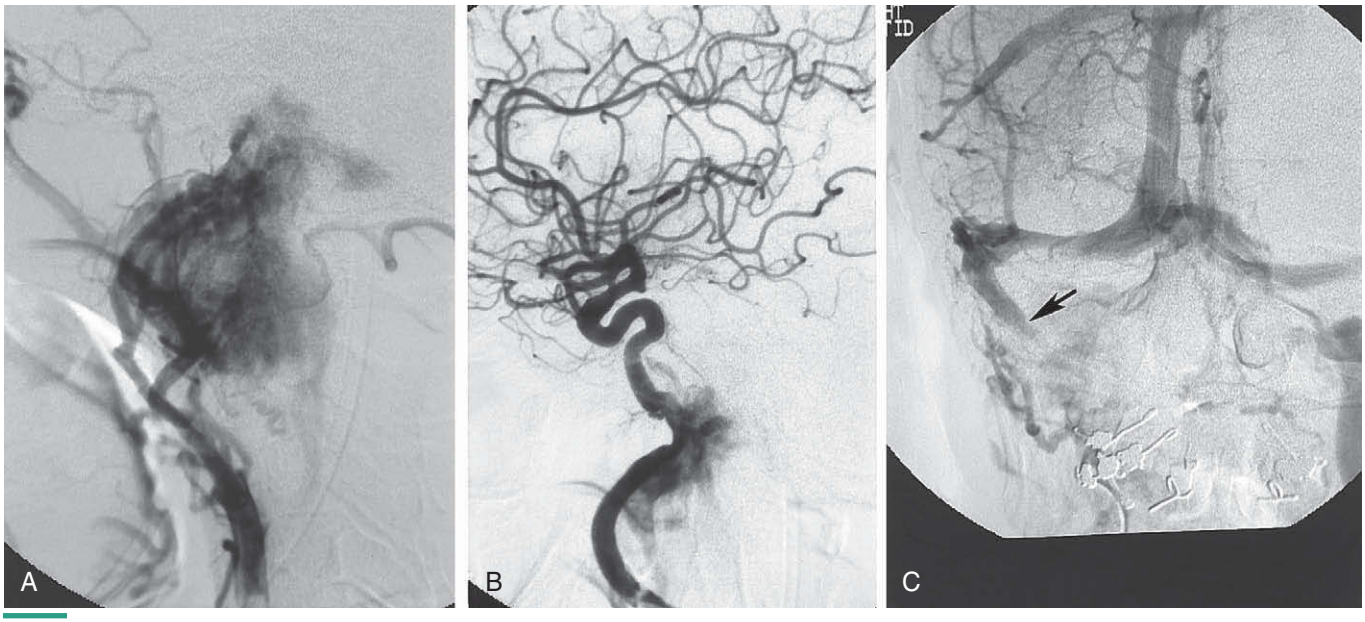

Figure 136-3. Glomus jugulare/vagale tumor. **A** and **B,** Cerebral angiography shows multiple enlarged external carotid branches providing most of the blood supply to this tumor **(A)**, although there is parasitization of the vasa vasora of the high cervical internal carotid artery **(B)** by the circumferential tumor. **C,** There is complete occlusion of the distal sigmoid sinus *(arrow)* and nonopacification of the jugular bulb and vein.

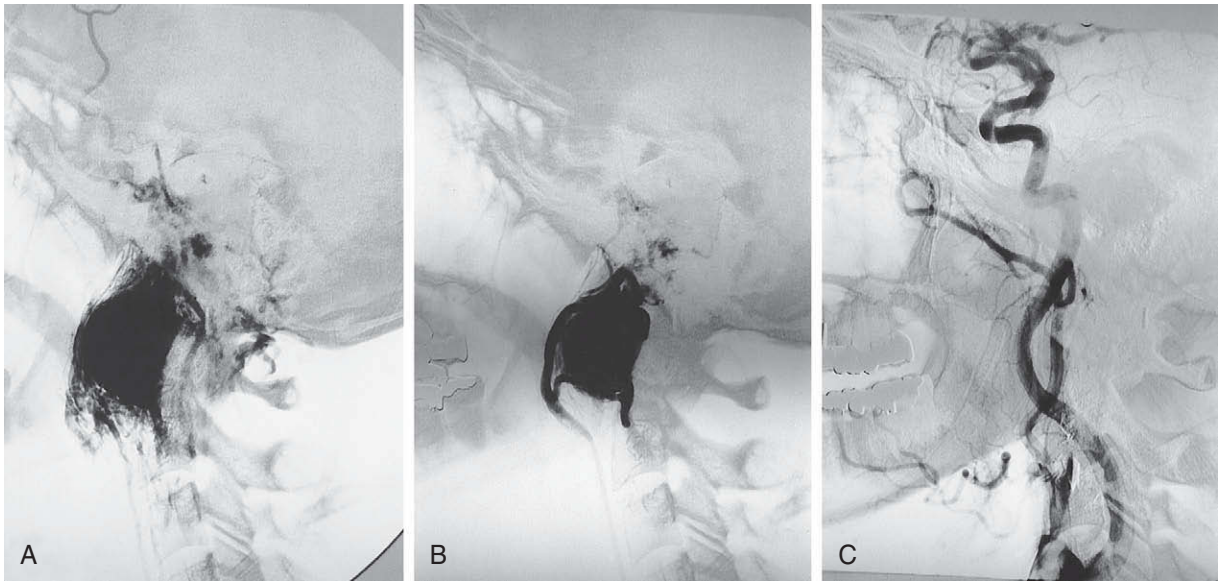

Figure 136-4. Embolization of a glomus jugulare/vagale tumor. **A,** Global external carotid artery injection shows a large homogeneously hypervascular mass lesion within the confines of the petrous bone, extending anteriorly in the region of the carotid canal, and extracranially in the high neck, a position typical for a glomus vagale tumor. **B,** Selective injection of the ascending pharyngeal artery shows filling of most of the tumor from this source. Embolization of this and other branches was performed with polyvinyl alcohol particles measuring 150 to 300 mm. **C,** Common carotid artery injection after embolization shows lack of visualization of the hypervascular lesion, but anterior displacement of the high cervical internal carotid artery typical for the vagale portion of the tumor.

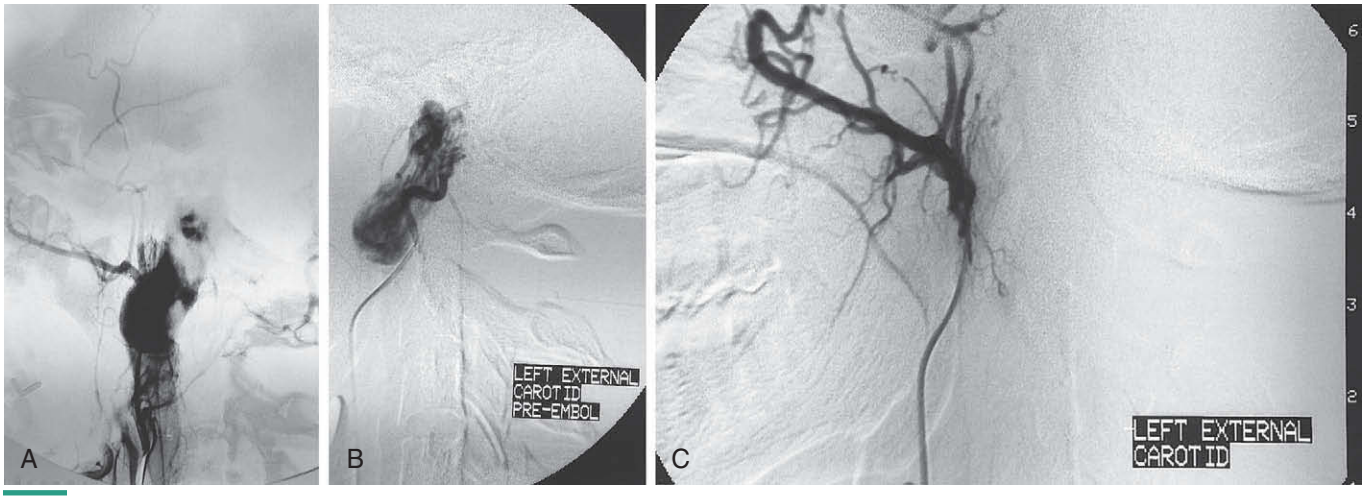

Figure 136-5. Embolization of glomus vagale tumor. Most of this tumor was below the skull base, typical of a glomus vagale tumor, although a small component extended superiorly in the region of the jugular bulb. **A,** Global external carotid artery injection showed the homogeneous hypervascular mass. **B,** Selective injection was made into one branch of an enlarged ascending pharyngeal artery, showing that most of the tumor below the skull base was filled from this vessel. Other branches of the ascending pharyngeal artery were primarily responsible for the intracranial component. All these tributaries were embolized with polyvinyl alcohol particles measuring 150 to 300 mm. **C,** Postembolization global left external carotid injection failed to show the hypervascular mass.

performed, followed by embolization of particulate material, most commonly PVA of small size (e.g., 150 μm) (see Fig. 136-4). Before injecting external carotid branches that may supply cranial nerve VII, particularly the stylomastoid artery, 1% lidocaine is injected as a provocative test to ensure that the cranial nerve is not devascularized during the embolization procedure, as previously discussed.[18]

Glomus Vagale Tumor

The glomus vagale tumor originates from the vagus body high in the neck at the C1-2 level. The tumor may extend superiorly so that differentiation from a glomus jugulare tumor is difficult and may be moot. The typical appearance is that of anterior displacement of the high cervical ICA. Blood supply is from multiple branches of the ECA, particularly the ascending pharyngeal artery. The arterial supply is mapped as for the glomus jugulare tumor, although there generally are fewer sources of supply (Fig. 136-5). Potential supply from ascending and deep cervical branches of the thyrocervical and costocervical trunks and of neuromuscular branches from the ipsilateral vertebral artery also should be evaluated. The feeding vessels are catheterized and embolized to the point of fluoroscopic devascularization, particularly with tiny PVA particles (see Fig. 136-5). The lidocaine provocative test is used

if there is any question regarding potential cranial nerve insult during the procedure.

Carotid Body Tumor

A carotid body tumor is a highly vascular mass occurring in the crotch between the origins of the internal and external carotid arteries, splaying them apart. There are commonly many tiny feeders from the distal common carotid and proximal internal carotid arteries that are too small to be catheterized selectively to the degree necessary to avoid reflux of particles into the ICA, although there usually are major feeders from the ECA, particularly the ascending pharyngeal, superior thyroidal, lingual, facial, and carotid body arteries (Fig. 136-6). These can be selectively catheterized, and much of the tumor may be appropriately embolized with tiny PVA particles to make surgery easier with less blood loss (see Fig. 136-6). Some surgeons do not want preoperative embolization, believing that a potential secondary inflammatory reaction from embolization makes it more difficult to define tumor planes for removal.[31]

Juvenile Angiofibroma

The usual history of angiofibroma is that of recurrent epistaxis and nasal obstruction in an adolescent boy. The tumor has a typical location adjacent to the nasal choana and within the nasopharynx and pterygopalatine fossa. The tumor may extend anteriorly through the nasal cavity or superiorly into the sphenoid sinus. Occasionally, it extends into the subtemporal fossa. Bone destruction of the lateral wall of the sphenoid sinus or of the anterior temporal fossa allows it to enter the intracranial cavity.

Typically, blood supply is from the ascending pharyngeal artery (which may be bilateral and may require common carotid rather than

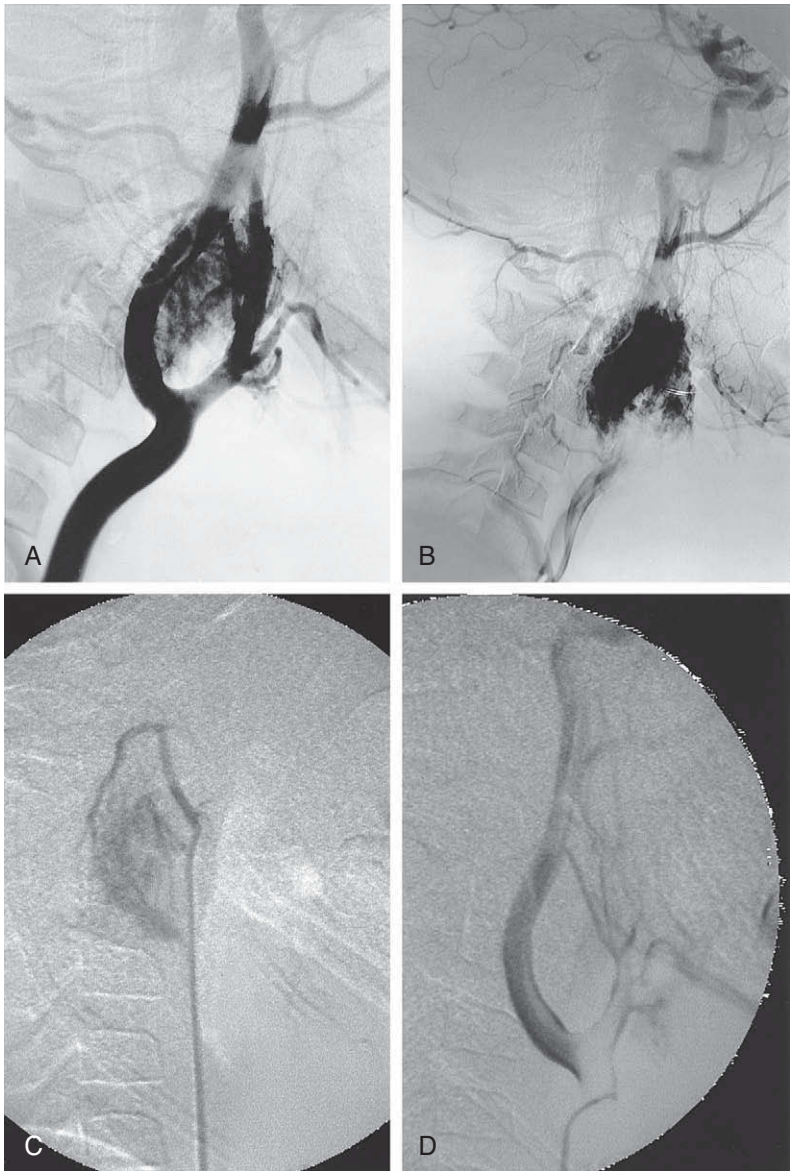

Figure 136-6. Embolization of carotid body tumor. This 8-year-old child had MRI evidence of a carotid body tumor. No other family members were known to have a chemodectoma. **A,** Common carotid artery injection showed the classic separation of the internal and external carotid trunks because of the hypervascular mass between them. There were multiple twigs from the internal and external carotid arteries supplying this tumor. **B,** No other chemodectomas at or above the skull base were shown. **C,** Selective catheterization of the artery to the carotid body during online digital fluoroscopy showed a large blood supply to the tumor from this vessel, which was subsequently embolized with polyvinyl alcohol particles measuring 150 to 300 mm. Two other smaller branches of the external carotid artery were also embolized. **D,** After embolization, a common carotid artery injection during digital subtraction fluoroscopy failed to show the hypervascular mass.

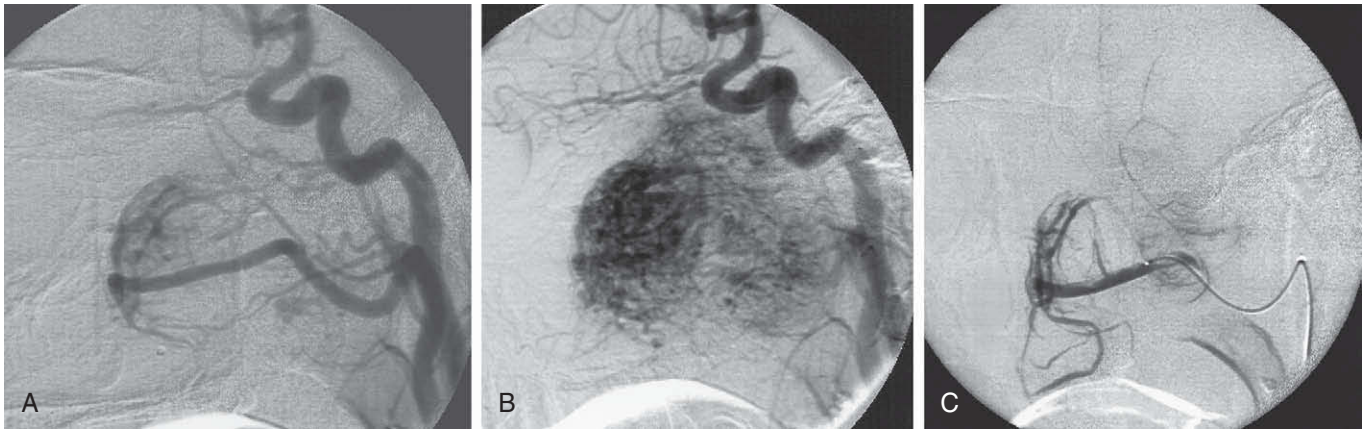

Figure 136-7. Embolization of angiofibroma of the nasopharynx. This 15-year-old boy was seen with nasal bleeding. **A** and **B,** Common carotid artery injection **(A)** showed the classic appearance of an angiofibroma of the nasopharynx, fed primarily by the internal maxillary artery, with a dramatic degree of vascularity of the tumor **(B)**. Catheterization of the internal maxillary artery was performed beyond the middle meningeal and accessory meningeal arteries, for embolization with polyvinyl alcohol particles, initially by use of 150 μm for the tiniest peripheral tumor branches, followed by 300 to 500 μm for the larger feeders. **C,** Embolization resulted in a dramatic decrease in vascularity of the tumor on follow-up angiography.

ECA injections to visualize because of the possible origin of this vessel near the common carotid bifurcation), and the internal maxillary artery and its branches, particularly the ascending and descending palatine arteries (Fig. 136-7). Tumor may remain extracranial and receive supply from collaterals of the petrous and cavernous segments of the ICA.[32-34] Intracranial extension may be supplied from the middle meningeal and accessory meningeal branches of the internal maxillary artery, and from branches of the petrous and cavernous internal carotid arteries. Because the middle meningeal, accessory meningeal, and foramen rotundum arteries supply cranial nerves within the cavernous sinuses,[33] it is preferable to catheterize the internal maxillary artery beyond the origin of the accessory meningeal artery for particulate material embolization (150 μm) of tumors that are purely extracranial (see Fig. 136-7). Supply from the middle meningeal and accessory meningeal arteries should be embolized with care, usually preceded by a lidocaine test. Other arteries are catheterized and embolized as necessary. Such embolization usually dramatically decreases the blood loss at the time of surgery.[32-35]

Meningiomas

Meningiomas are the most common intracranial nonglial tumors, accounting for approximately 20% of all primary intracranial tumors. They originate from the arachnoid, occur most often in patients 30 to 69 years old, and predominate in women. Their most common locations are over the cerebral convexities and in the parasagittal and parafalcine regions (50%), but meningiomas originating from various sites along the skull base and tentorium account for at least 40% of the cases.

Meningiomas derive their primary blood supply from arteries supplying the meninges. External carotid branches, such as the middle meningeal and ascending pharyngeal arteries, play a significant role in this supply, but dural branches of the intracranial carotid, ophthalmic, and vertebral arteries also are significant. As meningiomas grow, they may parasitize pial branches of the cerebral circulation.

Whether to embolize a meningioma in a given location depends on the risk-to-benefit ratio of the intervention and the ability to catheterize the appropriate blood supply selectively.[36,37] Frontobasal meningiomas involve the orbital roof, the olfactory groove, and the planum sphenoidale. Their blood supply is primarily from ethmoidal branches of the ophthalmic arteries. Because of the potential risk to vision, selective catheterization of an ophthalmic artery and subsequent embolization usually is not performed. Sphenoid wing and middle cranial fossa tumors may derive significant blood supply from the middle meningeal artery. If so, selective embolization of the middle meningeal artery, taking care to place the microcatheter above the origins of the branches supplying the cranial nerves, may be a valuable preoperative intervention, especially because the location of this tumor may make control of the blood supply difficult at surgery.

Cavernous sinus meningiomas have various potential sources of blood supply from branches supplying the dura in this region. The inferolateral trunk from the C4 portion of the ICA frequently represents a major supply to meningiomas in this region, and, if enlarged, may be selectively catheterized with a microcatheter. If catheterization is impossible, a nondetachable balloon may be placed in the ICA above the origins of the dural branches, and embolization with tiny particles performed.[38,39] Other sources of blood supply include the accessory meningeal and the middle meningeal arteries. Both of these latter vessels provide blood supply to the cranial nerves, so there is the potential of cranial nerve injury if these vessels are embolized. Provocative testing with the use of 1% lidocaine can be performed, and catheterization beyond the origins of the cranial nerve blood supply.

If a microcatheter with an inner diameter of 0.014 inch is used, 150-μm particles can be used to penetrate the meningioma; these particles usually are too large to penetrate the vessels supplying the cranial nerves. Gelfoam powder with particles of 40 to 60 μm behaves more like a liquid, and has a greater potential of producing cranial nerve palsies and passing through dangerous anastomoses. True liquids, such as cyanoacrylates and ethanol, carry too high a risk for cranial nerve injury or passage into anastomotic channels to be used as a preoperative agent. Occasionally, for patients with recurrent, nonoperative tumors requiring shrinkage for palliation of mass effect, absolute ethanol can be used, acknowledging the higher risk of cranial nerve injury (Fig. 136-8). Meningiomas in this region may infiltrate the ICA or middle cerebral artery. If en bloc resection of the tumor, including the ICA, is contemplated, preoperative occlusion of the ICA with a detachable balloon may be performed.[39]

Posterior fossa meningiomas include lesions in the clival, petroclival, and paraclival regions, and lesions involving the petrous bone, cerebellopontine angle, jugular foramen, and foramen magnum. The dural blood supply depends on their location, and these tumors may be embolized in the same manner as described for supratentorial tumors.

Other Neoplasms

Hypervascular solid masses involving the face and neck, other than those previously discussed, are uncommon. Occasionally, a hypervascular thyroid tumor receiving its blood supply from the superior and inferior thyroidal arteries is amenable to embolization. The inferior thyroidal artery is a branch of the thyrocervical trunk, and the superior thyroidal artery usually is the first branch of the external

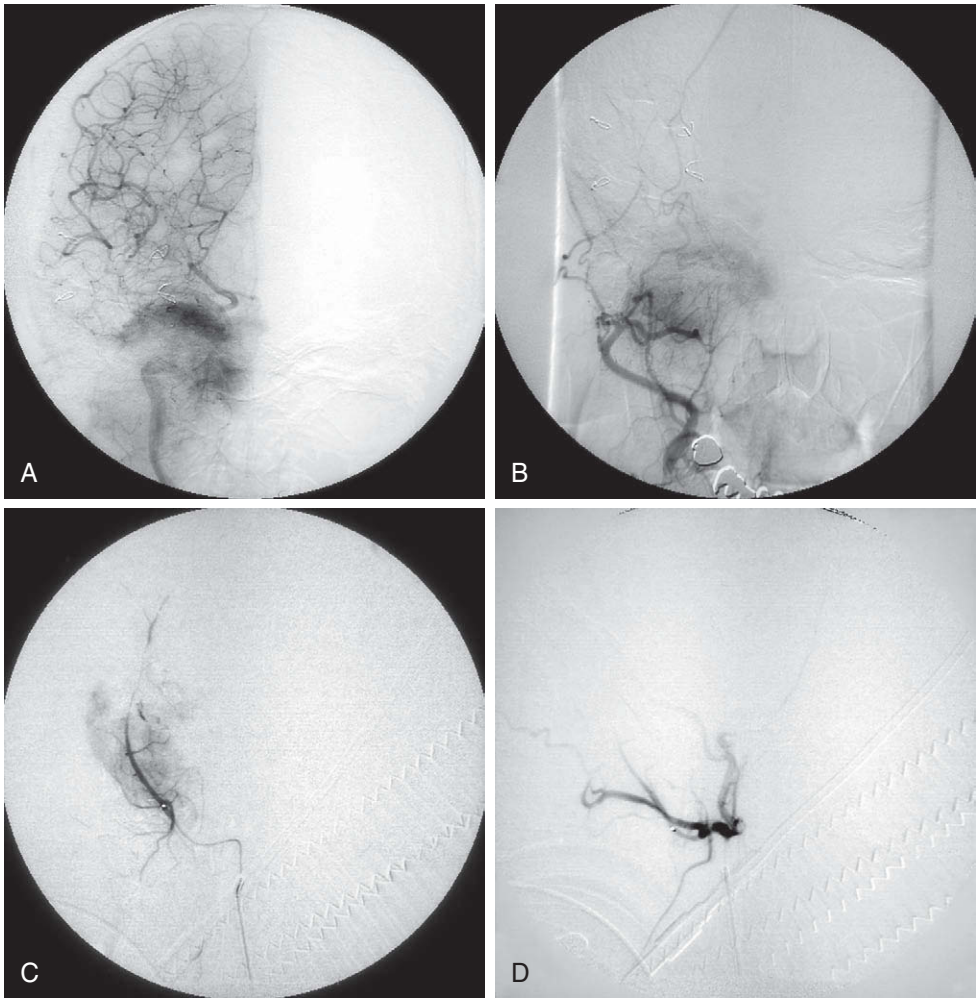

Figure 136-8. Embolization of a recurrent intracranial meningioma with alcohol. A 65-year-old woman had recurrence of a meningioma around the right middle cerebral artery. **A,** Right internal carotid artery angiography showed the "stain" of the meningioma wrapping around the middle cerebral artery and deriving blood supply from tiny feeders from that vessel. **B,** Right external carotid artery study showed a significant supply from the right middle meningeal artery. **C,** Selective catheterization of the right middle meningeal artery was performed, and angiography revealed its selective supply. **D,** To stop the tumor from occluding the middle cerebral artery, it was elected to perform embolization of the tumor. Small amounts of absolute alcohol were slowly infused into the tumor, which produced occlusion of the tiny feeding branches over a 15-minute period. An alternative therapy might have been gamma knife irradiation to stop the tumor growth.

carotid; both generally are easy to catheterize. Selective lingual or facial angiography and injections into the thyrocervical and costocervical trunks should be done to evaluate tumor extension or other sources of blood supply. Embolization usually is performed with particulate materials.

Intra-arterial Chemotherapy

Endovascular techniques permit the selective perfusion of high concentrations of chemotherapeutic agents directly into a tumor, while minimizing systemic side effects. This technique has been used for advanced primary head and neck tumors, and metastatic tumor to cervical lymph nodes.[40] A new delivery technique involves intra-arterial injection of ethylcellulose microspheres containing chemotherapeutic agents. These biodegradable microspheres can remain in the tissue for weeks while they slowly release their anticancer drugs.[41]

Lesions of Vascular Etiology

Epistaxis

Epistaxis may result from trauma, tumor, coagulopathy, or a congenital vascular malformation, such as in hereditary hemorrhagic telangiectasia (or Osler-Weber-Rendu disease). The most common cause is spontaneous bleeding, with or without hypertension, from small vessels along the nasal septum and superior margins of the nasal cavity. Spontaneous bleeding from the anterior aspect of the nasal cavity usually is self-limited and does not require endovascular therapy, but posterior nasal hemorrhage (20%) is more inaccessible and more difficult to manage clinically. Cautery, ligations of the internal maxillary arteries, and nasal packing may be ineffective. Nasal packing may be associated with pulmonary or cardiac problems in elderly patients; embolization may be an effective and rapid therapy.

In all patients, bilateral selective internal and external carotid angiography should be performed to visualize the feeders to the bleeding site (Fig. 136-9).[42,43] Superselective catheterization of internal maxillary artery, facial, and ascending pharyngeal vessels is performed with a microcatheter for angiography. If a bleeding site is found, all feeders and potential collaterals to the site are embolized by moving the microcatheter distal to branches potentially feeding cranial nerves such as the middle meningeal and accessory meningeal arteries. If no bleeding site is found, distal internal maxillary artery and facial artery embolization is performed bilaterally to ensure hemostasis (see Fig. 136-9).[32,44-47] Particles 150 μm provide excellent hemostasis, and there is no risk of devascularizing normal facial tissues. Distal rather than proximal vascular occlusion decreases the chance of recurrent bleeding from col-

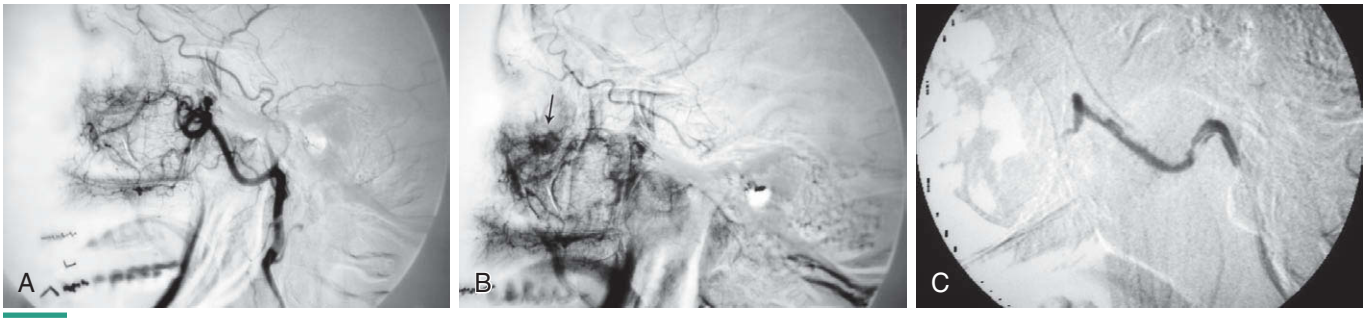

Figure 136-9. Embolization for epistaxis. A 69-year-old woman had recurrent epistaxis requiring nasal packing. **A** and **B,** Selective left external carotid artery injection **(A)** showed a hypervascular area in the region of the superior aspect of the left side of the nose (*arrow* in **B**). Embolization of polyvinyl alcohol particles, 150 µm, was performed under the control of digital subtraction angiography road-mapping. **C,** Postembolization study showed occlusion of the distal internal maxillary artery and no site of bleeding. Clinically, there was no recurrent epistaxis.

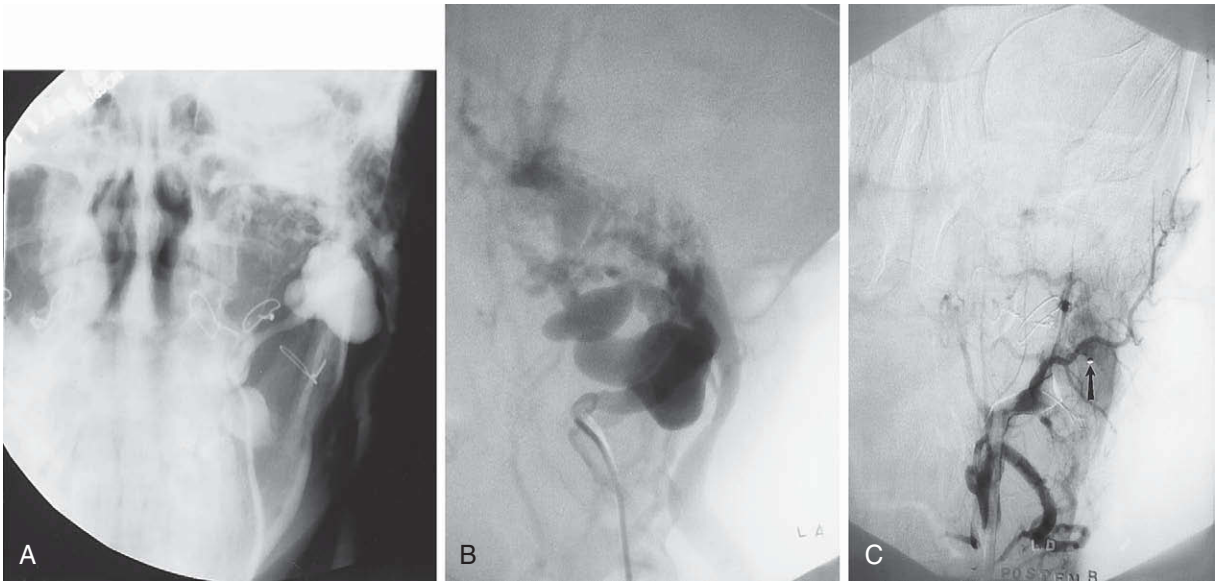

Figure 136-10. Iatrogenic facial arteriovenous fistula with embolization. Surgery had been performed on the left maxillary antrum for chronic sinus disease. One month postoperatively, a large pulsatile mass was noted below the left temporomandibular joint. **A** and **B,** Selective left internal maxillary artery injection showed an arteriovenous fistula with a large venous varix. **C,** A detachable balloon was placed at the site of the fistula (*arrow* denotes metallic marker on balloon) to produce complete occlusion of the fistula.

lateral circulation. With the development of coaxial microcatheter systems and the heightened awareness of functional facial vascular anatomy, success rates of 91% to 97% with complication rates of 0% to 3% have been reported.[46]

Facial Arteriovenous Fistulas

Arteriovenous fistulas may occur after direct facial trauma or from iatrogenic trauma such as facial surgery or image-guided biopsy.[48] Temporomandibular joint or maxillary sinus surgery may result in an arteriovenous fistula (Fig. 136-10). Arteriovenous fistulas also may be congenital in origin. Whatever the cause, selective angiography defines the site of the fistula, which generally is easy to occlude with an appropriately sized detachable balloon (see Fig. 136-10),[7] or with detachable coils. Metallic coils also may be used to pack the venous and arterial sides of a fistula via superselective arterial or venous approaches. To do so, a catheter with a nondetachable balloon is introduced from one femoral artery and placed proximal to the fistula, to be inflated to provide flow control so that the coils do not get swept downstream. A second catheter is introduced via the other femoral artery and placed proximal to the fistula. This second catheter is a guiding catheter with a lumen that accommodates a microcatheter that is manipulated across the fistula into the venous side. Coil occlusion is performed during proximal balloon inflation, progressively pulling the microcatheter back to occlude the arterial side.

Dural Arteriovenous Fistulas

Dural arteriovenous fistulas represent direct communications between small arterial channels within the dura and the underlying dural sinus or veins draining into that sinus. Two types of dural arteriovenous fistulas are considered: fistulas that involve the transverse and sigmoid sinuses and fistulas involving a cavernous sinus.

Transverse and sigmoid sinus dural arteriovenous fistulas are acquired lesions, probably resulting after sinus thrombosis and increased venous pressure, which opens tiny arteriovenous shunts in the dura, with or without subsequent sinus recanalization.[49] Increased flow in the transverse and sigmoid sinuses produces a subjective bruit. The prolonged high flow may lead to intimal hyperplasia of the sinus wall, stenosis, and recurrent occlusion. Persistent or recurrent occlusion of the transverse and sigmoid sinuses produces increased outflow in the contralateral sinuses. Compromise of this venous drainage produces retrograde flow into cortical venous channels, venous hypertension, and tissue congestion, resulting in neurologic deficits.[50] Further venous hypertension may lead to intraparenchymal or subarachnoid hemorrhage.[51] The arterial supply to a transverse and sigmoid sinus dural

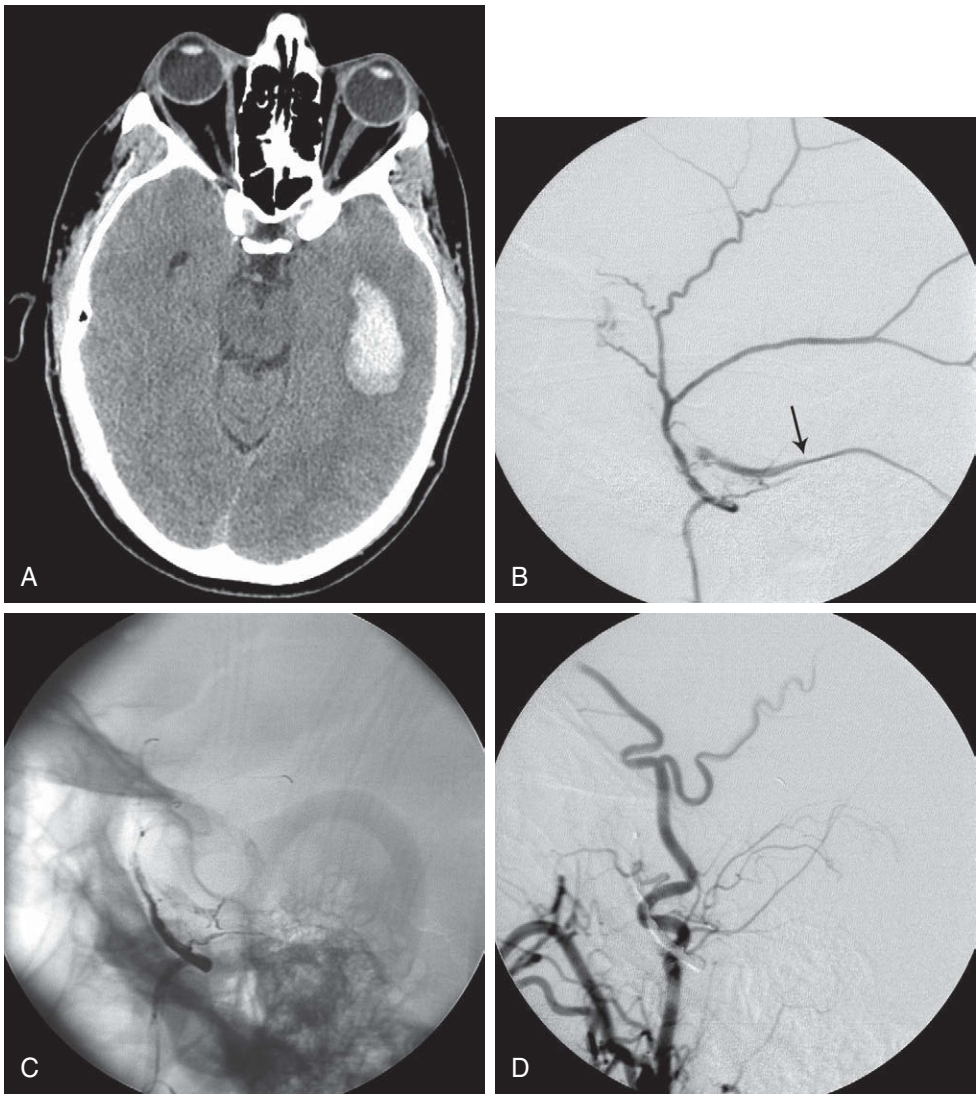

Figure 136-11. Anterior temporal fossa dural arteriovenous fistula treated with intra-arterial Onyx infusion. **A,** A 52-year-old man presented with a spontaneous hemorrhage in the left temporal lobe. The differential diagnosis was a "cryptic" arteriovenous malformation or a dural arteriovenous fistula, such as from the superior petrosal sinus. **B,** Selective middle meningeal artery injection showed early filling of the vein of Labbé *(arrow)* from multiple middle meningeal artery feeders. As a soccer goalie, this patient might have had a skull base fracture and a traumatic arteriovenous fistula. **C,** Onyx was infused into the middle meningeal artery, leaving a "cast" of the tantalum-containing compound. **D,** Subsequent external carotid angiogram did not show the fistula; it was not shown on follow-up angiography 1 year later.

arteriovenous fistula is from multiple ECA branches bilaterally, particularly the occipital arteries and the tentorial branches of the internal carotid arteries. Meningeal branches of the vertebral arteries also may be involved.[52]

If the patient complains of only a mild bruit but is otherwise asymptomatic, the risk-to-benefit ratio does not warrant treatment. In patients in whom the bruit has become so severe that the patient is incapacitated, treatment may be undertaken. The presence of cortical venous outflow, with or without neurologic deficit, indicates a high-risk lesion that should be managed with endovascular techniques. Lesions producing neurologic deficit, dementia, and previous hemorrhage require management.

Arterial embolization alone may be only palliative, with multiple other dural sources increasing in size as the primary feeders are occluded. Embolization with particles is particularly discouraging; if only the arterial side is embolized, a tissue adhesive such as Onyx (Fig. 136-11), or alcohol, may be very effective. Another solution is a combination of arterial and venous approaches. After decreasing the arterial flow rate with particle embolization, coils are deposited in the transverse and sigmoid sinuses via a transvenous approach (usually transfemoral venous catheterization of the jugular bulb with a large guiding catheter, through which a smaller catheter is manipulated into the transverse sinus for coil deposition along the length of the transverse and sigmoid sinuses).[53] If transfemoral venous access is impossible, intraoperative exposure of the sinus for coil packing may be necessary. Some transverse and sigmoid sinus dural arteriovenous fistulas are complex; recurrences are frequent, and therapy may require the combined expertise of the interventionalist and the surgeon over multiple sessions.

The etiology of cavernous sinus dural arteriovenous fistulas is unclear. They are most common in elderly women and manifest with symptoms of proptosis, chemosis, conjunctival injection, decreased vision, and occasionally cranial nerve palsies. The blood supply is from the external carotid and ICA branches to the dura of the cavernous sinus. These lesions behave differently than transverse and sigmoid sinus dural arteriovenous fistulas because they may close spontaneously or after angiography, or subsequent to air travel with its barometric changes. Intermittent compression of the ipsilateral carotid artery may produce closure of the fistula. Progressive loss of vision or cortical venous drainage requires therapeutic intervention. ECA embolization with particles may lead to closure, in contrast to transverse and sigmoid

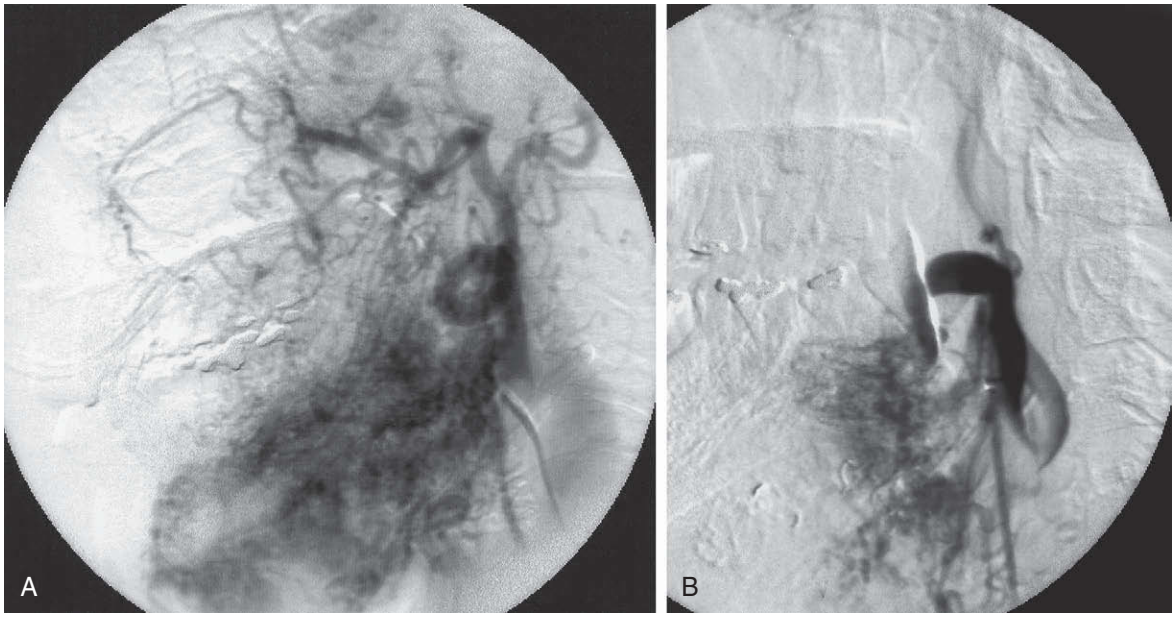

Figure 136-12. Facial arteriovenous malformation (AVM) embolized with intra-arterial alcohol. This 38-year-old woman had a long history of a bilateral facial AVM, and had undergone multiple embolization procedures in the past. **A,** Left external carotid artery study showed an enormous AVM involving the soft tissues of the mandibular region. Two balloons were placed for flow control, one in the external carotid artery and one in the left facial artery. The latter was a balloon surrounding a catheter with a lumen, through which 100% alcohol was injected. The balloon in the facial artery kept the alcohol in contact with the AVM endothelium, whereas the proximal balloon prevented reflux into other external carotid artery branches and into the internal carotid artery. **B,** Postembolization study showed a marked reduction in visible AVM. Three more procedures on the left and three on the right were performed over the subsequent 9 months, markedly reducing the facial deformity.

sinus dural arteriovenous fistulas. Inferior petrosal vein catheterization via a transvenous femoral approach permits the deposition of coils or rarely a tissue adhesive into the cavernous sinus, which is highly effective management with a low complication rate.

Facial Vascular Malformations

Venous malformations of the face manifest as bluish lesions that may distend with the Valsalva maneuver. Although they are congenital, they usually are dormant until some type of factor, such as local trauma, causes them to enlarge.[54,55] MRI studies show lesional hyperintensity on T2-weighted sequences, and the size and the extent of the lesion. Management is for cosmetic purposes. Percutaneous puncture allows the deposition of sclerosing agents. Absolute ethanol is more effective than sodium tetradecyl sulfate, but produces more swelling and is much more painful on injection, requiring deep sedation or anesthesia.[10-13]

Arteriovenous malformations of the face are rare. If surgery or irradiation of a facial arteriovenous malformation is impossible for cosmetic reasons, embolization may be undertaken as a palliative treatment. In such a case, ethanol can be injected intra-arterially, particularly with flow control to keep the agent in proximity to the endothelium for as long as possible (Fig. 136-12). The major complication is flow of the ethanol into the tiny arteries feeding the skin and cranial nerves, producing necrosis. Even with flow control, the rapid flow in the arteries feeding the malformation usually sweeps the ethanol into the venous system for dilution, preventing such complications.

Hemangiomas of the Face and Neck

Hemangiomas have a proliferative phase followed by involution, so that 90% of hemangiomas that are present at birth regress by early childhood.[55] Therapy for infantile or early childhood hemangioma is necessary only if there is airway obstruction, such as from hemangioma of the tongue or subglottic tissues. Even if the hemangioma is in the periorbital region and interferes with normal eye function, time should be allowed for regression, followed by eye muscle and cosmetic surgery. In adolescents or adults, problems may be simply cosmetic, although the hemangioma may infiltrate surrounding tissues such as the alveolar ridge, resulting in hemorrhage when eating, or narrow the airway or esophagus. If there is a slow arterial component, embolization with PVA particles can be performed. If there is primarily a capillary or venous component, direct puncture of the lesion with the instillation of a sclerosing agent, such as absolute ethanol or sodium tetradecyl sulfate, may be effective. In most patients, embolization is followed by surgical removal.

Pseudoaneurysms

Cranial trauma resulting in cavernous carotid artery laceration usually produces a carotid-cavernous sinus fistula, although a pseudoaneurysm may be formed instead, with enlargement over time, erosion into the sphenoid sinus, and rupture, producing massive life-threatening epistaxis. Emergency balloon occlusion of the ICA may be necessary because the lack of a true arterial lining of the pseudoaneurysm predisposes to recanalization after intra-aneurysmal coil or balloon placement.

Rapid hyperextension of the neck with contralateral head rotation forces the high cervical ICA against the lateral mass of C2, or stretches a vertebral artery at C1-2 between its contained segments within the C2 foramen transversarium and the dura at the foramen magnum,[56] resulting in arterial dissection and subsequent pseudoaneurysm formation. Surgical repair may be difficult, necessitating the use of endovascular techniques. Because the pseudoaneurysm lacks a true arterial wall, frequently has a wide neck, and may contain semisoft clot of variable age, successful occlusion with intra-aneurysmal balloons or coils usually is impossible. The endovascular placement of a stent across the neck of a pseudoaneurysm is the preferred method of management; the combination of stenting and intra-aneurysmal coil placement may be even more successful. If necessary, occlusion of the parent artery with balloons[57] or coils placed above and below the aneurysm is definitive, but should be preceded with the BOT and assessment of cerebral blood flow after carotid occlusion via collateral channels.

Inadvertent biopsy of an aberrant carotid artery in the middle ear cavity has been reported, leading to severe otorrhagia and massive epistaxis. These lesions generally are best handled by trapping with balloons or coils proximal and distal to the aneurysm (Fig. 136-13).[58]

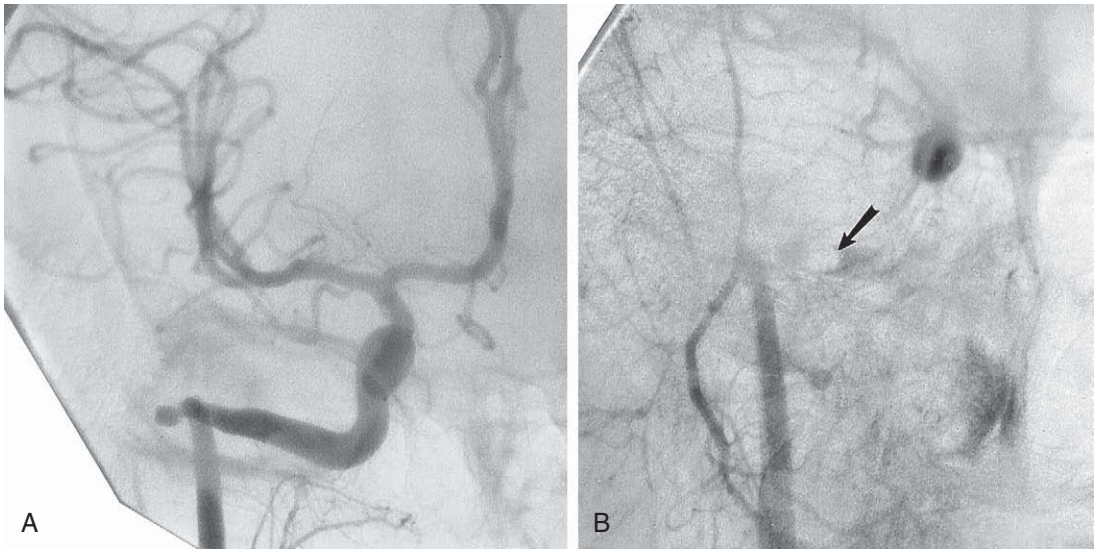

Figure 136-13. Pseudoaneurysm of an aberrant right internal carotid artery after biopsy with balloon occlusion. This 6-year-old child had a reddish mass behind the tympanic membrane. A biopsy of the mass was performed by an otolaryngologist, producing rapid blood loss through the myringotomy. The ear was packed, and the patient was sent for evaluation. **A,** Right common carotid angiography showed the arcuate appearance of the petrous portion of the right internal carotid artery characteristic of an aberrant internal carotid artery extending into the middle ear cavity, with a pseudoaneurysm extending laterally representing the site of biopsy. **B,** A releasable balloon was placed above the aneurysm in the horizontal portion of the petrous segment (*arrow* marks distal margin of balloon). A second balloon was placed in the high cervical carotid artery for trapping of the aneurysm. Excellent cross-flow from left to right through the anterior communicating artery prevented neurologic sequelae after carotid occlusion.

Tinnitus-Producing Fibromuscular Dysplasia of the Carotid Artery

Fibromuscular dysplasia of the ICA, which usually occurs at the level of C2, is one of the many causes of pulsatile tinnitus. Vascular webs that characterize this entity may be stretched by angioplasty,[59] and stent placement may be necessary to prevent recurrence.

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External Ear

CHAPTER ONE HUNDRED AND THIRTY-SEVEN

Infections of the External Ear

Joel Guss

Michael J. Ruckenstein

Key Points

- The external ear and ear canal are affected by various bacterial, fungal, and viral infections, and noninfectious inflammatory conditions.
- Meticulous débridement of the ear canal is a crucial first step in managing all infections.
- Most cases of external otitis should be managed with topical medications.
- Infections that have spread beyond the confines of the ear canal skin require culture-directed systemic antibiotics.
- Malignant or necrotizing otitis externa is a life-threatening infection that requires a high index of suspicion and proper selection of radiographic and nuclear studies for prompt diagnosis.
- Infection of the auricular cartilage can lead to significant cosmetic deformity and requires aggressive treatment with systemic antipseudomonal antibiotics and, in many cases, surgical débridement.
- Viral infections of the ear canal include zoster oticus and, most likely, bullous myringitis; both may be associated with sensorineural hearing loss.
- Keratosis obturans and external auditory canal cholesteatoma are two poorly understood disorders marked by accumulation of squamous debris and bony remodeling of the ear canal; both are treated by débridement, but occasionally require aggressive surgical management.

Applied Anatomy

The external ear consists of the auricle and the external ear canal. The auricle, with the exception of its lobule, is formed by a framework of elastic cartilage. The perichondrium is tightly bound to the cartilage on its lateral surface and more loosely bound to its medial surface. Sebaceous glands and hair follicles are found in the subcutaneous layer of the auricle. Adipose tissue is generally restricted to the lobule. Keratinizing squamous epithelium covers the auricle. The ear canal measures approximately 2.5 cm in length, with the anterior portion being approximately 6 mm longer than the posterior wall. The lateral one third of the canal possesses a cartilaginous skeleton, a subcutaneous layer containing hair follicles, sebaceous and apocrine glands, and a squamous epithelial surface layer. The hydrophobic, slightly acidic (pH 6.0 to 6.5) cerumen is formed by glandular secretions and sloughed epithelium in this portion of the canal.

Transverse slits on the floor of the cartilaginous canal (the fissures of Santorini) allow for spread of infection or neoplasms from the external canal to the soft tissues surrounding the ear canal. The osseous portion of the canal begins at the narrow isthmus and is formed mostly by the tympanic portion of the temporal bone and a thin layer of squamous epithelium continuous with the lateral surface of the tympanic membrane. It lacks a subcutaneous layer.

The skin of the ear canal possesses a unique, self-cleansing mechanism. The sloughed keratinous layer of tympanic membrane migrates in a centrifugal fashion to the ear canal. This migratory process continues from the medial to lateral portions of the osseous canal, where the sloughed epithelium is deposited into the cartilaginous portion of the canal and is extruded as a component of cerumen.

Otitis Externa

Definition

Otitis externa is an inflammatory (typically infectious) disorder of the external ear canal.

Incidence and Epidemiology

Acute otitis externa affects approximately 4 of every 1000 children and adults per year.[1] Approximately 80% of cases occur in the summer, particularly in warm, humid environments.[2] Other predisposing factors include anatomic obstructions of the ear canal (e.g., stenosis, exostoses, impacted cerumen), hearing aid or ear plug use, self-induced trauma (e.g., by cotton swabs), and swimming.

Pathogenesis

Bacterial

The initiating event is believed to be an abrogation of the hydrophobic ceruminous coating of the external canal.[3] This event exposes the underlying epithelium to water and other contaminants, leading to edema and excoriation of the epithelial layer. These violations of the epithelium allow for bacterial infection. The resulting infection and inflammatory response lead to progressive erythema and edema of the epithelial and subcutaneous layers. These pathologic changes are associated with the symptoms of itching, pain, and otorrhea.

Fungal

Fungal infections of the external canal are generally considered to be opportunistic, occurring after treatment of bacterial infection.

Figure 137-1. Otomycosis. This florid infection with *Aspergillus flavus* has infected the deep canal, with tufts of fungus crowned by white conidiophores.

Superficial infection of the ear canal by yeast (*Candida* sp) can be seen in patients who use hearing aids. *Aspergillus* sp may induce a more aggressive infection, involving the epithelial and subcutaneous tissues (Fig. 137-1).

Chronic

Chronic otitis externa represents different disease states with distinct etiologies, as follows:

- Allergic otitis externa may result from an allergic reaction to topical agents, most commonly neomycin. It manifests as a maculopapular eruption on the skin of the conchal bowl and ear canal.
- A contact dermatitis can result from contact with various agents, including hairsprays, shampoos, and hearing aid molds.
- Psoriasis or systemic dermatitides such as seborrhea can involve the ear canal. The chronic inflammatory reaction typically results in hyperkeratosis and lichenification of the ear canal skin.
- Granular otitis externa is thought to result from chronic infection of the ear canal by bacteria or fungi or both. The ear canal skin and tympanic membrane manifest granulation and excoriation.

Microbiology

Roland and Stroman[2] evaluated the microbiology of otitis externa. The results of their study are summarized in Table 137-1. *Pseudomonas aeruginosa* was the most common bacteria responsible for infections. *Staphylococcus* sp were the next most common pathogens. Fungi were responsible for only 2% of cases, but may be more prominent in cases of persistent or chronic infection.

Clinical Manifestations

Pain is a common symptom associated with bacterial infection. The pain may be severe and is exacerbated by manipulation of the auricle or the tragus. Itching may be experienced in early bacterial infections, and in fungal infections and in all forms of chronic otitis externa. Aural fullness and decreased hearing may be experienced in any case of otitis externa resulting in accumulation of debris in the ear canal. Otorrhea is more common in bacterial infections.

Examination of the canal may reveal the following findings:

1. An erythematous canal with scant discharge in cases of early bacterial otitis externa
2. An edematous canal filled with purulent-squamous debris in cases of well-established bacterial otitis externa
3. An accumulation of white debris sprouting hyphae best seen with the otologic microscope, typical of candidal otitis externa
4. An accumulation of a moist white plug dotted with black debris ("wet newspaper") typical of *Aspergillus niger*
5. A maculopapular eruption on the conchal bowl and in the ear canal consistent with an allergic reaction to a topical agent (e.g., neomycin)
6. A thickened, erythematous canal associated with an allergic or contact dermatitis
7. Granulation tissue in the canal and on the tympanic membrane caused by chronic infection

Table 137-1

Microbiology of Otitis Externa

Organism	%
Pseudomonas aeruginosa	40
Staphylococcus epidermidis	9
Staphylococcus aureus	8
Other *Staphylococcus* sp	8
Coryneform (diphtheroids)	9
Other gram-negative rods	9
Streptococcus, Enterococcus	4
Aspergillus, Candida	2

From Roland PS, Stroman DW. Microbiology of acute otitis externa. *Laryngoscope*. 2002;112:1166-1177.

Investigations

Investigations are rarely required for cases of otitis externa. Cultures for bacteria and fungus are indicated in cases of persistent or refractory infection, particularly to identify fungal infection. Special reference must be made to the value of sensitivities of the infectious organism to various antibiotics provided by laboratory culture tests. These sensitivities are based on expected tissue levels of systemically administered antibiotics. Sampling of otorrhea after administration of topical preparations has shown a concentration of antibiotic several orders of magnitude greater than can be obtained by systemic administration, however, even 8 hours after dosing.[4] Organisms listed as "resistant" to a particular antibiotic are likely to be susceptible to the antibiotic when it is given topically. This is true for so-called resistant cases of *Pseudomonas* sp or methicillin-resistant *Staphylococcus aureus*. As long as the topical drop can reach the infected site, systemic antibiotics are unnecessary even in cases of infection by "resistant" bacteria.

Biopsy of the external auditory canal should be undertaken in cases of presumed otitis externa that do not respond to appropriate antimicrobial therapy. Biopsy is done to exclude malignancy, most commonly squamous cell carcinoma of the ear canal skin, which may manifest with otalgia and otorrhea and may be misdiagnosed as infection.

Treatment

Careful débridement of the ear canal in any case of otitis externa is crucial to facilitate clearance of the infectious organism and to allow topical medications to reach the target tissue. If the ear canal is so edematous that topical medication would not reach its medial extent, an ear wick may be inserted. Classically, the physician made these from

strands of cotton. Currently available Merocel wicks (Medtronic, Inc., Jacksonville, FL) offer better absorption of the drug, however, and expand when wet to decrease canal edema substantially. Although unpopular in North America, good results can also be obtained by packing the ear canal with antibiotic-impregnated ribbon gauze.[5]

Acidification of the ear canal is toxic to many bacteria (including *Pseudomonas*) and fungi, and effectively treats many early infections. A homemade mixture of equal amounts of white vinegar and rubbing alcohol acidifies and dries the ear canal. Commercial solutions of acetic acid (VoSol) or acetic acid with aluminum acetate (Domeboro) also are available. Acidifying solutions may also be used prophylactically by at-risk patients, such as after swimming. A hair dryer on a low heat setting may be used to dry the ear canal gently.

Antibiotic drops remain the mainstay of treatment for otitis externa. The ideal drops possess the following properties:

1. Broad-spectrum coverage for pathogenic bacteria (see Table 137-1)
2. An acidic vehicle
3. No potential for ototoxicity, which is an important property in the case of a perforated tympanic membrane
4. No potential for allergic reactions
5. No deposition of precipitate from the drop
6. Low cost
7. A steroid to decrease edema more rapidly and, perhaps, alleviate pain more rapidly

No current drop possesses all these properties. For many years, the mainstay of treatment was a combination solution of polymyxin, neomycin, and hydrocortisone (PNH) (Cortisporin). This combination is available in solution and suspension, and is produced by various manufacturers. Polymyxin provides coverage against *Pseudomonas*; polymyxin and neomycin are effective against *S. aureus* and other gram-negative organisms.

Quinolone antibiotics are available in otic and ophthalmic solutions. They offer single-agent coverage for pathogenic bacteria, with virtually no risk of contact dermatitis or ototoxicity. Ofloxacin (Floxin) is available for treatment of external and middle ear disease and is equal to PNH in efficacy.[6,7] Its main disadvantages are a neutral pH (6.2 to 6.8), the absence of a steroid, and expense. Ciprofloxacin is available as an otic preparation combined with hydrocortisone and as a newer formulation combined with the more potent dexamethasone (Cipro HC and Ciprodex). These solutions are acidic and contain a steroid. The hydrocortisone in Cipro HC may leave a precipitate in the canal, and both solutions are expensive.

When choosing a topical treatment of otitis externa, there is currently minimal clinical evidence to support the use of one solution over another. Existing literature is difficult to interpret because studies differ in their outcome measures and in the degree of aural toilet used. A systematic review of topical treatments by Rosenfeld and colleagues[8] reached the following conclusions: (1) topical antimicrobial and topical antiseptic drops were superior to placebo; (2) a topical antiseptic (with a steroid in most cases) was as effective as a topical antibiotic; (3) topical quinolone and nonquinolone antibiotics were equally effective except in achieving a bacteriologic cure, where the quinolones were more effective; and (4) a topical antibiotic is as effective as a topical antibiotic and steroid preparation. Chapter 138 contains further information on costs and emerging resistance with quinolone ototopicals.

Fungal otitis externa can be treated with meticulous débridement and acidification of the ear. As with bacterial infection, topical treatment cures most cases, although recurrence rates are high. Clotrimazole 1% solution (Lotrimin) is available over the counter and provides broad-spectrum antifungal activity. Cresylate otic and ketoconazole ointment are effective as well.[9] An alternative popular treatment is painting the canal and tympanic membrane with dyes that possess antifungal properties (e.g., gentian violet). Tolnaftate (Tinactin) solution can be used safely in the presence of a tympanic membrane perforation.[10,11] Finally, persistent *Aspergillus* infections associated with considerable canal edema or infections failing to respond to topical treatment may require the administration of oral itraconazole. The senior author has found that virtually all cases of fungal otitis externa can be quickly resolved by débridement of the canal and then filling the canal with a combination cream—Lotrisone (clotrimazole and betamethasone). The cream is loaded into a 3 cc syringe and passed through an angiocath into the ear canal.

Contact or allergic dermatitis should be treated by elimination of the offending agent, débridement, and the administration of a topical corticosteroid solution/lotion.[12] Chronic granular otitis externa can be difficult to treat. This is most frequently seen in individuals who are dependent on their hearing aids. Minimizing or alternating hearing aid use is crucial to the success of the treatment regimen. Culture of the ear for bacteria and fungus may provide evidence of the causative organisms. Repeated débridement, cauterization of the granulations, and filling the canal with topical antibiotic or antifungal creams can be effective. Topical gentian violet may also be effective at drying the ear canal and eliminating the chronic infection. Surgical therapy may be required.

In patients with long-standing inflammation of the ear canal that does not respond to traditional ototopical treatments, we have found that filling the ear canal with a mixture of equal parts of bacitracin and polymyxin ointment, clotrimazole cream 1%, and betamethasone 0.05% cures most patients.[13] This mixture of an antibiotic, antifungal, and steroid is inexpensive and is easily instilled using a syringe and an 18-gauge angiocatheter tip. The ointment can be débrided after 1 week and reapplied as needed.

Complications

Cellulitis, perichondritis, and chondritis may result from otitis externa. In adults, the presence of these complications should prompt the administration of a systemic quinolone antibiotic. In children, in the case of a cellulitis, an oral antistaphylococcal drug may be initiated; however, if *Pseudomonas* is detected on ear culture, parenteral administration of antipseudomonal antibiotics is required. Specific treatment of perichondritis and chondritis is addressed in a subsequent section.

Medial canal fibrosis represents a thick fibrous scar at the medial end of the ear canal, just lateral to the tympanic membrane, and is the end stage of chronic otitis externa.[14] Physical examination reveals what appears to be a lateralized tympanic membrane and an absence of typical landmarks (Fig. 137-2). Surgical treatment of this disorder can be challenging. The affected portion of the canal lining is resected, bony canalplasty is performed, and the canal is relined with split-thickness skin grafts. In more favorable cases, a space remains between the fibrous scar and the tympanic membrane, avoiding the need for tympanoplasty.

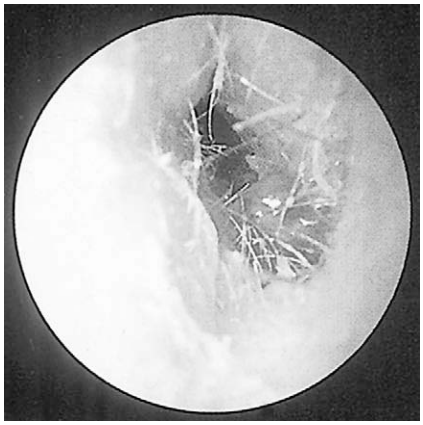

Figure 137-2. Chronic external otitis. The hallmarks are atrophy of the skin of the canal and stenosis caused by chronic irritation. This patient used cotton swabs in the ear, and debris from the canal with cotton fibers has been pushed medially against the tympanic membrane.

When the tympanic membrane is involved, however, a total-drum tympanoplasty is required. Meticulous technique is required to avoid blunting the anterior tympanic sulcus. Recurrence after surgical treatment is common.

Tympanic membrane perforation is particularly common with fungal otitis externa caused by *Aspergillus* sp. Elimination of the offending fungus allows for a high rate of spontaneous healing of these perforations.[15]

Malignant Otitis Externa

Definition

Malignant otitis externa is an aggressive and potentially fatal infection originating in the external canal, with progressive spread along the soft tissues and bone of the skull base, ultimately involving intracranial structures.[16] It is also (more accurately) known as necrotizing otitis externa.

Incidence and Epidemiology

Malignant otitis externa is a rare disorder occurring predominantly in immunocompromised patients. Elderly individuals with diabetes mellitus are the most commonly affected patients,[16,17] although malignant otitis externa has been reported in various other immunocompromised states, including myeloid malignancies, pharmacologic immunosuppression, and HIV/AIDS.[18-20] It has also been reported to occur in immunocompetent patients.[21-23]

Microbiology

Most cases are caused by *P. aeruginosa* followed by *S. aureus*.[16,24,25] Case reports have implicated other organisms. *Aspergillus* sp are the most common fungal pathogens to cause this disorder,[24] but infections by more exotic molds have also been reported. Fluoroquinolone-resistant *Pseudomonas* is an increasing problem,[24,25] and is particularly frustrating because the fluoroquinolones are the only enterally administered antibiotics with antipseudomonal activity.

Clinical Manifestations

Patients are initially seen with long-standing otalgia, which can be severe, and otorrhea. The hallmark finding is granulation tissue protruding through the floor of the ear canal at the bony-cartilaginous junction (Fig. 137-3).[16] In its initial stages, the infection is confined to the skin and soft tissues of the ear canal.[26] As it progresses, the infection involves the bony structures of the temporal bone. At its most advanced stages, it extends beyond the temporal bone along the skull base or intracranially or both.[26] The facial nerve is the most common cranial nerve involved, with paralysis resulting from involvement at the stylomastoid foramen. Further progression leads to involvement of the lower cranial nerves at the jugular foramen and hypoglossal canal. Intracranial spread results in headaches, fever, neck stiffness, and altered levels of consciousness.

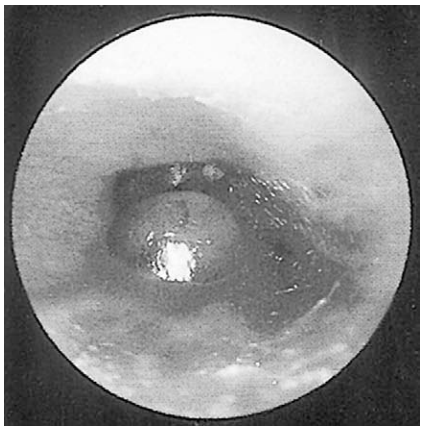

Figure 137-3. Malignant otitis externa. A nubbin of granulation tissue sits on the floor of the ear canal at the junction of the bony and cartilaginous portions.

Investigations

When malignant otitis externa is suspected, bacterial and fungal cultures of otorrhea should be obtained at the time of initiation of treatment. Early diagnosis of malignant otitis externa requires a high index of suspicion and use of appropriate imaging modalities, as follows.

- High-resolution computed tomography (CT) scans are readily obtainable and relatively inexpensive. The CT scan shows even small cortical erosion of the tympanic bone and is a useful first-line test.[27-30] Disadvantages of CT include an underappreciation of the soft tissue and intracranial extent of disease, and the inability to distinguish infection from malignancy.[27] Because normalization of bony changes may never occur despite resolution of the infection, CT is also limited in following the response to treatment.

- Although magnetic resonance imaging (MRI) misses subtle bony erosion, it is superior in detecting soft tissue changes and may show dural enhancement.[27,29] These are more likely to resolve with treatment, making MRI more useful in following the course of disease.[27]

- Technetium-99m bone scanning shows areas of osteoblastic activity and is highly sensitive for bony infection. Traditional planar imaging or single photon emission computed tomography (SPECT) can be used. SPECT provides good anatomic localization and may highlight areas of bony involvement before the CT scan shows structural changes, making it particularly useful when the clinical suspicion for malignant otitis externa is high, but the CT scan is negative.[28] Because bony repair persists long after the infection has resolved, the technetium bone scan is not used to follow response to treatment.

- Gallium-67 citrate and indium-111–labeled leukocyte scans show areas of inflammatory cell activity. These tests are sensitive, and uptake values return to normal quickly with resolution of infection, making them useful in following response to treatment.[28] These are expensive and time-consuming tests to perform, and false-positive results may occur secondary to inflamed soft tissues surrounding bone. A greater degree of diagnostic accuracy (and expense) may be afforded by the simultaneous acquisition of a SPECT technetium-99m bone scan and indium-111–labeled leukocyte scan.[31]

Treatment

Cure of this infection is predicated on early diagnosis and aggressive medical therapy. Administration of antipseudomonal antibiotics is the cornerstone of treatment. Early infections may be treated solely with an oral fluoroquinolone (most commonly ciprofloxacin) except in cases of resistant organisms.[25,32] In more advanced stages, parenteral antibiotics may be indicated initially, with discharge of the patient home on oral fluoroquinolones. Total duration of treatment is typically 6 weeks, or as indicated by the results of radiologic studies and clinical response. Although hyperbaric oxygen therapy has been used as an adjuvant resulting in cure of some advanced cases,[33-35] it has never been tested in a randomized controlled study.[36]

The role of surgical treatment for this disorder has never been critically evaluated. Surgical débridement of nonviable sequestra of bone has been mentioned; however, it remains unclear when surgical resection is mandated. Involvement of bone occurs along the skull base, so traditional mastoidectomy should theoretically not be effective in débriding the infection. Similarly, because the facial nerve is involved in the region of the stylomastoid foramen, facial nerve decompression of the proximal segments would seem to be inappropriate. Medical therapy for this disorder seems paramount. Surgical resection should be reserved for cases in which bone involvement is resistant to therapy. In addition, surgical resection should be incorporated in more heroic efforts to abort a rampant or progressive infection. In these cases, surgical intervention would include a wide resection of the bony skull base, including the stylomastoid foramen and jugular bulb, together with the

Figure 137-4. Herpes zoster. Note the infectious vesicles with erythematous margins involving the concha, and a crusted older lesion over the mastoid.

introduction of viable, vascularized tissue (e.g., temporalis muscle flap or microvascular free tissue transfer) into the bed.

Herpes Zoster Oticus

Herpes (or varicella) zoster virus can cause a recrudescent infection involving the external ear. It is an uncommon infection that more frequently affects immunosuppressed patients or elderly individuals in whom immunity to the virus has waned.[37] Other stimuli for viral reactivation involve various physical and psychological stressors. Often, no precipitating event is identified. After primary infection (chickenpox), varicella-zoster virus is harbored in a latent state in sensory ganglia, and reactivates with infection spreading along dermatomes. When the ear is involved, virus is most commonly believed to be harbored in the geniculate ganglion and spreads along the sensory fibers of the facial nerve.[38] Other sensory ganglia have also been implicated, including the fifth and eighth cranial nerves.[39]

Clinical manifestations include a prodrome of otalgia, which may be severe. A vesicular eruption is seen in the canal and concha (Fig. 137-4). Ultimately, these vesicles rupture and form crusts. A subgroup of patients manifest Ramsay Hunt syndrome, defined by facial paralysis in the presence of herpes zoster oticus. If cranial nerve VIII is involved, sensorineural hearing loss or vertigo or both may be present. Treatment is empiric and not based on many scientific studies. It includes local ear care, the administration of topical antibiotic/steroid drops, and the administration of an antiherpetic agent at the onset of the syndrome (e.g., valacyclovir, 1000 mg three times daily for 7 days).[40] High-dose steroids (e.g., prednisone, 1 mg/kg/day) should be added in the presence of facial paralysis or sensorineural hearing loss or both.[41] Particular attention should be directed to eye care, and ophthalmologic consultation should be obtained with any evidence of a herpetic keratitis. Postherpetic neuralgia can be a significant problem. Universal vaccination of infants against varicella-zoster virus and the U.S. Food and Drug Administration approval of a zoster vaccine for older adults may result in a decreased incidence of zoster infections. These vaccines are not indicated for treatment of zoster or postherpetic neuralgia.[37]

Bullous Myringitis

Bullous myringitis is an inflammatory/infectious condition involving the lateral surface of the tympanic membrane and the medial portion of the canal wall. It typically occurs in association with upper respiratory infections and is more common in winter. The etiology is believed to be primarily viral; however, *Mycoplasma* has been identified in some cases.[42-44] Clinical manifestations include acute, severe otalgia; serosanguineous otorrhea; and hearing loss. Physical examination reveals bullae on the tympanic membrane that are filled with serous or serosanguineous fluid (Fig. 137-5). Spontaneous rupture of the bullae leads to the observed discharge. Primary care practitioners frequently mistake this disorder for acute otitis media. A serous otitis media is a frequently associated finding in 30% to 40% of cases.[43-46] More significant is the association of this disorder with a sensorineural hearing loss. Sixty-five percent of patients manifest a sensorineural or mixed hearing loss, with the sensorineural component recovering completely in approximately 60%.[45,46]

Figure 137-5. Bullous myringitis. The deep ear canal and tympanic membrane are acutely inflamed. A large bulla is seen over the posterior tympanic membrane.

Treatment includes analgesics, topical antibiotic/steroid drops to prevent bacterial superinfection, and lancing the bullae, which may result in some pain relief. Because *Mycoplasma* sometimes can be associated with this infection, the administration of a macrolide or quinolone antibiotic may be prudent. The role of systemic steroids has not been established.

Cellulitis

Cellulitis of the ear typically results from a spreading otitis externa or a penetrating injury. It is distinguished from perichondritis by the lack of induration. It manifests as an erythematous ear. Treatment is with systemic, antistaphylococcal antibiotics.

Erysipelas

Erysipelas is a dermal infection that may involve the skin of the head and face, including the ear, caused by β-hemolytic streptococcus. The involved tissue is erythematous, indurated, and tender. The hallmark of the infection is that it spreads along a well-demarcated border (Fig. 137-6). Treatment is with oral systemic antibiotics (e.g., penicillin).

Perichondritis and Chondritis

Perichondritis and chondritis represent infections of the auricular perichondrium or cartilage. They result from blunt or penetrating trauma to the ear or by direct extension from an otitis externa. In the case of a blunt trauma, a hematoma on the lateral surface of the pinna that becomes infected is the initiating event. Penetrating trauma may result from various injuries, including ear piercing, assaults, bites, and iatrogenic injuries. Increasingly popular piercing of the ear cartilage as opposed to the lobule may predispose to infection, and outbreaks have been reported.[47] *Pseudomonas* is the most frequent causative organism.

Physical examination reveals a tender, erythematous, indurated pinna. Fluctuance indicates the presence of an abscess and possible chondritis. Treatment of perichondritis consists of elimination of any foreign bodies and the administration of an oral quinolone antibiotic. An abscess must be drained, and any necrotic cartilage must be resected. The wound can be packed with antibiotic-impregnated ribbon gauze, or, when cartilage is resected, a through-and-through Penrose drain may be placed. A permanent deformity of the cartilage ("cauliflower ear") may result. Recurrent or bilateral auricular swelling should prompt a rheumatologic workup for relapsing polychondritis.

Figure 137-6. Erysipelas. Note the diffuse erythema and swelling of the auricle and the advancing margin of cellulitis involving the face. The line of demarcation between involved and uninvolved areas is clearly defined.

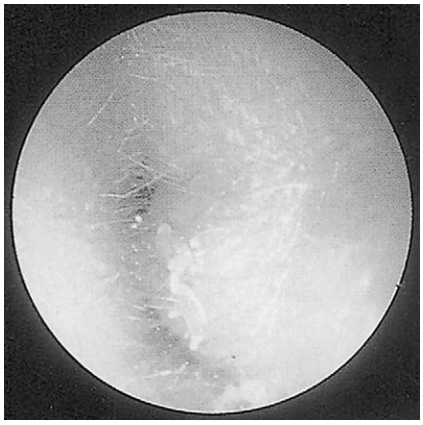

Figure 137-7. Furuncle of the ear canal. The small abscess forms a localized swelling at the entrance of the ear canal. The furuncle is pointing and has begun to rupture.

Furunculosis

A furuncle (abscess or boil) is a walled-off collection of pus that is seen as a painful, firm, or fluctuant mass (Fig. 137-7). It arises from the hair follicles of the lateral ear canal. The causative organism is typically *S. aureus*. Clinical manifestations include localized pain, particularly to touch. Early manifestations include a nodular swelling that proceeds to fluctuance. Treatment includes the application of warm compresses and topical antibiotic ointment. Antistaphylococcal oral antibiotics should be administered. A fluctuant lesion should be incised and drained under local anesthetic.

Keratosis Obturans and External Auditory Canal Cholesteatoma

Keratosis obturans and external auditory canal cholesteatoma are two conditions marked by the abnormal accumulation of keratin in the medial portion of the ear canal. Although the two terms were long used interchangeably, they are now generally held to represent separate disease entities.[48]

Keratosis obturans represents a diffuse disorder of the entire circumference of the medial external auditory canal skin. Affected patients accumulate a dense plug of keratin that can completely occlude the auditory canal and cause a conductive hearing loss. Frequently, such patients have severe pain from an aggressive secondary external otitis. Both ears are frequently involved, although not always to the same extent. If the condition is neglected, the pressure exerted by the keratin plug can cause widening of the bony ear canal or formation of an "automastoidectomy" cavity. Thickening and mucosalization of the tympanic membrane may occur, as can blunting of the periannular canal skin from chronic inflammatory scarring. Rare cases of tegmen dehiscence, facial palsy, and lateral semicircular canal erosion have been reported.[49]

The condition primarily affects adults, usually 30 to 60 years old. Corbridge and colleagues[50] documented faulty epithelial migration patterns of the epithelial layer of the tympanic membrane and external auditory canal skin in affected patients, whereas others have proposed that excessive production of epithelial cells underlies the disease.[51] The factors responsible for these alterations are unknown.

The treatment is atraumatic removal of the epithelial debris. Occasionally, preliminary softening with otic drops or even general anesthesia is necessary. After cleaning, follow-up visits are scheduled to clean the canals and remove debris prophylactically before inflammation and infection can occur. Over time, the interval between cleanings can increase. The condition frequently ameliorates, although lifelong débridements may be necessary.

External auditory canal cholesteatoma is rare and seems to represent a distinct clinical entity. Ulceration of the canal skin and necrosis of the underlying bone develop at the inferior-posterior portion of the bony ear canal just lateral to the anulus. It is unclear whether invasion of the bone by squamous epithelium with subsequent necrosis begins the process, or whether a focus of injured bone (secondary to trauma or infection) with invasion of epithelium from the margins of the overlying ulcer is the initiating event.[51] The focal nature of the disease distinguishes it from keratosis obturans, which circumferentially affects the ear canal. Patients typically present with signs and symptoms of an external otitis including otorrhea. On examination, granulation tissue may be seen at the edge of a bony crater filled with infected keratin debris.

Treatment is to resolve the granulation tissue and external otitis with cleaning, removal of debris, and medications. Follow-up visits are scheduled to try to prevent flare-ups by periodic cleaning and topical agents. Surgery may be necessary in refractory cases, and entails removal of the cholesteatoma matrix and necrotic bone followed by placement of a fascial graft in the cavity to promote healthy re-epithelialization.[51]

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CHAPTER ONE HUNDRED AND THIRTY-EIGHT

Topical Therapies of External Ear Disorders

Joyce Colton House

Daniel J. Lee

Key Points

- An understanding of the efficacy and side-effect profile of prescription and nonprescription topical therapies of external ear disorders is important for successful management of a patient who presents with otitis externa.
- Débridement under binocular microscopy in the otolaryngologist's office is diagnostic and therapeutic for common conditions involving the external ear.
- Most ototopical therapies are safe for the management of uncomplicated infections of the outer ear, provided that the tympanic membrane is intact.
- Aminoglycosides and acidifying agents should be avoided when a tympanic membrane perforation is present because of the possible risk of ototoxicity.
- An emphasis on meticulous ear hygiene and avoidance of self-manipulation is crucial to avoid recurrent or chronic infections.
- Systemic therapy should be considered in severe or chronic infections or in patients who are immunocompromised.
- Persistent infections should be cultured, and biopsy specimens of suspicious or diseased tissue should be obtained to exclude the possibility of a malignancy.
- Dermatologic and rheumatologic evaluations should be considered in refractory or bilateral cases of eczematoid otitis externa.

Topical therapies for external ear disorders are among the most commonly prescribed medications for pediatric and adult patients who present to an otolaryngology office. The local delivery of antibiotic and anti-inflammatory medications to the external ear has several advantages over systemic therapies, including (1) ease of patient use, (2) increased concentration of drug levels in the affected region, (3) decreased systemic side effects, and (4) lower cost. Ototopical antibiotics in particular avoid the selection of resistant organisms in the gastrointestinal and respiratory tracts that can be seen with systemic therapy. Disadvantages include the difficulty of using topical medications in an edematous or occluded external auditory canal, hypersensitivity or allergic reactions, and a theoretical risk of injury to the inner ear when the tympanic membrane is perforated or tympanostomy tubes are present. This chapter provides an evidence-based discussion of topical therapies for external ear disorders based on disease categories. These categories include bacterial otitis externa (OE), fungal OE, myringitis, eczematoid OE, viral infections of the external ear, cerumen impaction, and chronic draining ear.

History

Topical therapies have been used to manage external ear disorders for thousands of years. According to Myer,[1,2] mixtures including red lead, tree resin, olive oil, frankincense, goose grease, cream from cow's milk, crushed soda, vermilion, cumin, ass ear, and hatet oil were used to treat chronic draining ears 3500 years ago. A process known as "ear candling" dates back more than 1000 years and was originally adopted as a method of removing cerumen from the canal. In this process, a hollow candle is lit on one end creating a vacuum at the other end that, when inserted into the ear, draws out debris from the canal. Contemporary studies have shown that ear candling is largely ineffective, and this technique can deposit hot candle wax into the canal, resulting in burns.[3] In the 1800s, "rattlesnake oil" (turpentine, camphor, menthol, and sassafras) was marketed as a cure for otorrhea.

By the early 1900s, astringents and alcohols were introduced, and the acidity and high alcohol concentration made these preparations effective if given early in the course of an infection. They had no targeted antimicrobial activity, however. Topical antibiotics and antifungals against the most common pathogens associated with OE and otitis media were not developed until the mid-20th century.[1,2] In particular, ototopical aminoglycosides have been available for more than 20 years and are still frequently prescribed; newer fluoroquinolone agents are gaining in popularity because studies have shown potentially less ototoxicity associated with their use.[3,4]

Mechanism of Action

The external auditory canal is lined with squamous epithelium, providing a natural barrier against the environment. The successful delivery of topical medications requires penetration across this barrier, and the stratum corneum (the most superficial layer of the epidermis) provides the greatest resistance to the permeation of drugs.[5] Passive diffusion allows for most of the transport across the stratum corneum, and the degree of absorption is related to the properties of the agent being used.[5] Two routes of passive diffusion across the stratum corneum have been proposed: transappendageal and epidermal.[6] Because only 0.1% of skin

area is composed of appendages such as hair follicles and sebaceous glands, the epidermal route is thought to be the more important route of drug permeation.[5,6] Topical medications can diffuse through the epidermis transcellularly or intercellularly.[6] Transcellular transport is used by hydrophilic drugs, whereas intercellular diffusion occurs with lipophilic compounds.[5,6] The agent or vehicle used in a particular ototopical agent will affect its absorption and diffusion across the epidermis.

Topical Antibiotics

Extremely high local concentrations (3000 µg/mL for a 0.3% otic solution) of ototopical antibiotics can be achieved in the external canal. The minimum inhibitory concentrations (MICs) for antibiotics against common pathogens associated with external ear infections are typically less than 100, but can be in the mid-200's for resistant *Pseudomonas*.[7,8] The local concentrations associated with ototopicals are significantly higher than MICs for all pathogens that have been isolated from external ear infections, including resistant organisms.[7,8] In contrast, the local concentration of antibiotics in the *middle* ear after *oral* administration of amoxicillin, erythromycin, azithromycin, or cefixime (given in standard adult doses) may not be more than the MICs for the offending organisms, ranging from 1 to 15 µg/mL, although the concentration can be 35 µg/mL for intravenous ceftriaxone.[7,9-11] These levels were observed 4 hours after oral administration in human subjects and were measured in middle ear fluid samples obtained using tympanocentesis. No studies have examined the concentrations of antibiotics given systemically in the *external* ear; however, it is unlikely that they would be vastly different from the concentrations observed in the middle ear.

Topical Anti-inflammatories

The most commonly used prescription anti-inflammatories for external ear conditions also include an antibiotic or antifungal, although occasionally an otolaryngologist may prescribe a topical steroid alone for chronic pruritus or eczema. Most of the current understanding of how the steroid component of these preparations is absorbed regionally through topical application can be found in the dermatologic literature. The efficacy of a particular steroid preparation is associated with the inherent potency of the compound and its ability to penetrate the epidermis.[12] Lipophilic (nonpolar) preparations are transported across the stratum corneum more effectively than hydrophilic (polar) molecules.[12] The stratum corneum can also act as a reservoir for topical steroids, allowing for a prolonged regional effect after therapy is stopped.[5,12] Vehicles such as ethanol or propylene glycol increase the solubility of a topical agent to enhance permeability.[12] The hydration of the stratum corneum can also be enhanced by using occlusive vehicles such as ointments that improve drug penetration.[12]

Acute Bacterial Otitis Externa

See Chapter 137 for a definition and description of acute bacterial OE.

Topical Therapy Options for Acute Bacterial Otitis Externa

The most common bacterial pathogen is *Pseudomonas aeruginosa,* followed by *Staphylococcus aureus,* gram-negative bacteria, and anaerobes.[13-15] Treatment of acute OE often involves topical antibiotic preparations, with or without steroids. In mild acute or chronic OE, or as a preventive measure, acidifying agents may be used. Systemic antibiotics are indicated in severe or refractory cases, or in patients who are immunocompromised. Regardless of the therapy chosen to treat acute OE, removal of debris from the external canal and evaluation of the status of the tympanic membrane is crucial before using any ototopicals,[14,16-18] and oral analgesics are often needed in moderate or severe cases. Repeat débridement of the canal under binocular microscopy is essential to improve an infection that remains refractory to ototopical therapies.

In cases where the canal is extremely edematous, it may be impossible to visualize the tympanic membrane—care should be taken in this instance to avoid the use of ototopicals with potential ototoxic side effects.[16] Significant swelling and edema also requires wick placement to ensure proper delivery of ototopical antibiotics medially in the canal (Fig. 138-1). The wick should be changed or removed within 3 to 5 days of its insertion. If the canal is patent, tragal massage helps deliver the medication to the medial external auditory canal, and holding the head in a dependent position for several minutes allows for sufficient filling of the infected cavity.

Ototopical Antibiotics

Ototopical antibiotic preparations, with or without steroids, are the most common agents used to treat acute OE in the otolaryngology office. These preparations achieve local tissue concentrations approximately 1000 times that of systemic antibiotics, have a favorable side-effect profile, and show a lower incidence of bacterial resistance compared with systemic antibiotics.[7,14] The American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF) developed a Clinical Practice Guideline in 2006 for the treatment of OE. The group made firm recommendations to use "topical preparations for initial therapy of diffuse, uncomplicated [acute OE]; [systemic] antimicrobial therapy should not be used unless there is extension outside of the ear canal or the presence of specific host factors that would indicate a need for systemic therapy" (e.g., diabetes, prior radiotherapy, or immunocompromise).[16]

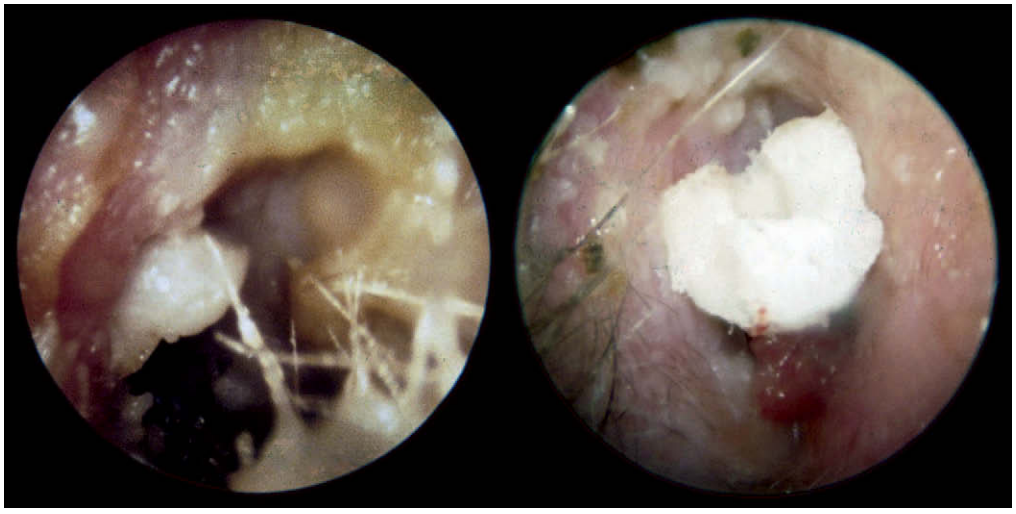

Figure 138-1. Acute otitis externa. Erythema, edema, and copious purulent debris are seen in the *left image*. In some cases, an edematous canal with granulation tissue (*right image*) necessitates the placement of an ear wick to assist topical drug delivery in the acute setting. *(Courtesy of John House, MD.)*

The following are commonly used preparations for the topical management of acute OE:

1. Cortisporin otic suspension and solution (neomycin + polymyxin + hydrocortisone 1%) have antibacterial and anti-inflammatory properties. The suspension is a milky white agent and has been a popular choice for uncomplicated bacterial acute OE for many years because of its efficacy, patient tolerance, and low cost. The suspension and solution each contain a 3.5-mg neomycin base, 10,000 polymyxin B units, and 10 mg of hydrocortisone 1% per mL. The suspension vehicle ingredients include cetyl alcohol, propylene glycol, polysorbate, and water; ingredients of the solution include cupric sulfate, glycerin, hydrochloric acid, propylene glycol, and water (Package insert, Cortisporin Otic Solution, 2003; Package insert, Cortisporin Otic Suspension, 2003, both from DSM Pharmaceuticals, Inc., Greenville, NC). The suspension has a less acidic pH (3.0 compared with 2.0 for the solution), and is better tolerated. Neomycin has been in use more than 40 years and is one of the oldest aminoglycosides. *Pseudomonas* has developed resistance to neomycin,[8,19] with less than 20% of *Pseudomonas* retaining sensitivity.[8] Polymyxins are cationic detergent antibiotics that disrupt the bacterial cell membrane. They work well against gram-negative rods, especially *Pseudomonas.* Although neomycin and polymyxin have ototoxic potential in animal studies, human data are equivocal.[14,20-23] The manufacturer recommends that Cortisporin otic should not be used in patients with tympanic membrane perforations (package insert, Cortisporin Otic Solution, 2003; package insert, Cortisporin Otic Suspension, 2003).

2. Ofloxacin (Floxin otic solution—ofloxacin 0.3%; benzalkonium chloride 0.0025%; sodium chloride 0.9%; water, pH 6.5) is a topical fluoroquinolone commonly used in acute OE. It can be used with tympanic membrane perforations and ventilation tubes because it has no known risk of ototoxicity,[4,24,25] making ofloxacin a reasonable choice for ear surgery prophylaxis. Ofloxacin otic is approved by the U.S. Food and Drug Administration (FDA) for use in patients with suppurative otitis media and perforated tympanic membranes (package insert, Floxin Otic, 1995, Daiichi Sankyo, Inc., Edison, NJ). Similar to all fluoroquinolones, ofloxacin acts by inhibiting DNA synthesis and bacterial growth by binding to DNA gyrase and topoisomerases. Commonly reported side effects include pruritus and bitter taste if used with a perforated tympanic membrane. Clinical cure rates for acute OE after treatment with ofloxacin have been shown to be greater than 80% in adults and greater than 95% in children.[24]

3. Ciprofloxacin + hydrocortisone (Cipro HC Otic—ciprofloxacin 0.2%; hydrocortisone 1%; benzyl alcohol as preservative) is a topical fluoroquinolone that also contains a steroid agent. It has broad-spectrum coverage, including *Pseudomonas,* although it has no activity against anaerobes. Ototoxicity has not been shown to be a concern with topical ciprofloxacin, and it is believed to be safe for use with tympanic membrane perforations.[26,27] Although many physicians use Cipro HC otic in the presence of tympanic membrane perforations, the manufacturer recommends against this because the bottle is nonsterile (package insert, Cipro HC Otic, 2002, Alcon Cusí, S.A. El Masnou, Barcelona, Spain, Alcon Laboratories, Fort Worth, TX).

4. Ciprofloxacin + dexamethasone (Ciprodex—ciprofloxacin 0.3%; dexamethasone 0.1%) also combines ciprofloxacin with a steroid for anti-inflammatory properties. It is safe for use with tympanic membrane perforations, and is FDA approved for use in patients with patent tympanostomy tubes (package insert, Ciprodex Otic Suspension, 2002, Alcon Laboratories, Fort Worth, TX). Ciprodex has been shown in randomized clinical trials to be more effective at resolving acute OE than neomycin/polymyxin/hydrocortisone,[28] and has been shown in a large randomized blinded study to be superior to ofloxacin in treating acute otitis media with otorrhea through tympanostomy tubes.[29] There is no study directly comparing Ciprodex with Cipro HC otic suspension in humans, although Sobol and colleagues[30] showed in an animal model that Ciprodex was superior to Cipro HC at treating granulation tissue in the external and middle ear.

5. Tobramycin + dexamethasone (Tobradex—tobramycin 0.3%; dexamethasone 0.1%; benzalkonium chloride 0.01% as a preservative) is an ophthalmic preparation with antibacterial and anti-inflammatory activity. Tobramycin is an aminoglycoside that binds to the 30S and 50S ribosomal subunits leading to a defective bacterial cell membrane. It should be avoided in patients with tympanic membrane perforations or tympanostomy tubes because of possible ototoxicity.[31-33]

6. Gentamicin (Garamicin Ophthalmic—gentamicin 0.3%, pH 7) is another ophthalmic solution that can be used in acute OE, especially when additional gram-negative coverage is needed. Gentamicin should be avoided with tympanic membrane perforations because of concerns of ototoxicity.[31-33]

Evidence-based Data on Ototopical Antibiotics in Acute Otitis Externa

Roland and colleagues[28] performed one of the few randomized multicenter studies comparing ototopical antibiotics. The clinical efficacy of 1 week of ciprofloxacin/dexamethasone (Ciprodex) or neomycin/polymyxin B/hydrocortisone (Cortisporin) was studied in 468 adults and children with acute OE and intact tympanic membranes. Ciprofloxacin/dexamethasone showed higher bacterial eradication rates and more rapid symptom improvement compared with neomycin/polymyxin B/hydrocortisone. Rahman and coworkers[34] also compared the efficacy of Ciprodex and Cortisporin drops in 1072 adults and children with acute bacterial OE in a multicenter, randomized, prospective, blinded trial. Cortisporin dosed three times daily and Ciprodex dosed twice daily for 7 days resulted in a 98% cure rate at 18 days for Ciprodex and a 97% cure rate for Cortisporin. The time to cure was 0.6 days shorter for Ciprodex.[34]

van Balen and associates[35] performed a randomized clinical trial of ototopical therapies that compared acetic acid alone, acetic acid and corticosteroid, and antibiotic and corticosteroid for acute OE. In 213 adults with acute OE, patients who received preparations that included steroids (either acetic acid or antibiotics) had significantly higher cure rates compared with acetic acid alone.[35] The acetic acid–alone group also had higher recurrence rates of OE.[35] Schwartz[36] performed a randomized multicenter blinded study in which patients with acute OE received either ototopical ofloxacin administered *once* daily or neomycin/polymyxin/hydrocortisone administered *four* times daily. In 278 pediatric patients with pseudomonal OE, both agents were *equally* effective at eradicating disease and had similar safety profiles.[36] Given the decreased ototoxic potential of ofloxacin and the easier dosing schedule, the authors concluded that ofloxacin might be a better first-line agent,[36] although neomycin/polymyxin/hydrocortisone is significantly less expensive than ofloxacin. The same conclusion was reached by Simpson and Markham[24] in a meta-analysis of the literature concerning ofloxacin use for acute OE.

Rosenfeld and colleagues[37] found 18 studies concerning ototopical therapy for acute OE that compared any of the following groups: antimicrobial versus placebo, antiseptic versus antimicrobial, fluoroquinolone antibiotic versus antibiotic, steroid/antimicrobial versus antimicrobial, or antimicrobial/steroid versus steroid. Clinical cure rates were 65% to 80% within 10 days of therapy with all of the above-mentioned ototopical antibiotics, and there was no statistical difference in *clinical* cure rates among any of the treatment groups.[37] Fluoroquinolones did have an 8% higher *bacteriologic* cure rate compared with nonquinolone ototopicals; however, the clinical cure rate and rates of adverse side effects were the same as those of the other preparations.[37] The addition of a steroid to fluoroquinolone agents decreases the symptomatic period by approximately 0.8 days[1,3] As discussed subsequently, however, steroids do have a small risk of causing a hypersensitivity reaction.

Resistance Associated with Ototopical Antibiotic Therapy

Weber and colleagues[38] found that there is overall grade B evidence (at least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks) that no significant antibiotic resistance develops from the use of ototopical antibiotic therapy. Cantrell and colleagues[19] examined the susceptibility of isolates from acute OE to neomycin/polymyxin and ofloxacin. The MICs of each antimicrobial drug for the major pathogens (*Pseudomonas* and *Staphylococcus aureus*), bacterial eradication, and clinical efficacy were studied from 1995-1996 and from 1999-2000.[19] The MICs for all pathogens increased above the breakpoint for polymyxin B in the data from 1999-2000, but the MICs of all isolates for ofloxacin remained similar between the two time periods, indicating that resistance developed to neomycin/polymyxin, but not to ofloxacin.[19] In 2003, Wai and Tong[25] noted that minimal resistance had been documented against ofloxacin since its initial use in the 1980s, and mentioned that only two strains of *Pseudomonas* have been shown to have slight resistance to ofloxacin. Contrary to these findings, Jang and Park[39] examined 88 patients with chronic suppurative otitis media that was refractory to treatment with topical ciprofloxacin and found that *Pseudomonas* isolates in all cases were resistant to topical ciprofloxacin. There is still ongoing concern and debate over the possibility of bacterial resistance to Cortisporin *and* ofloxacin drops, and this is an area that needs to be studied further in years to come. At this time, owing to extremely high local concentrations achieved with topical therapies that far exceed even the highest MICs for resistant *Pseudomonas,* it is unlikely that resistance would be a large factor in the choice of ototopical antibiotics.

Acidifying Agents in Acute Bacterial Otitis Externa

Acidifying agents may be used in mild acute or chronic cases of OE where there is minimal otalgia, but their main usefulness is in the preventive care of patients prone to developing recurrent acute or chronic OE (e.g., swimmers, hearing aid users). Alkaline pH has been shown to be a risk factor for the development of acute and chronic OE[40,41]; restoring the natural acidity of the external canal can inhibit the growth of bacteria responsible for OE. The acidic pH of these preparations may also limit patient compliance because of pain and local irritation.[18] These agents are contraindicated if a tympanic membrane perforation or tympanostomy tube is present because of possible ototoxicity.[3,42]

The following are commonly used acidifying solutions for treatment of mild OE, treatment of chronic OE or preventive care of the external canal:

1. Alcohol-vinegar solution contains ½ alcohol, ¼ white vinegar, and ¼ distilled water. Typically, several drops (4 to 5) are used in the affected ear two to four times daily until symptoms resolve and can be easily delivered with a syringe. This solution is contraindicated in patients with tympanic membrane perforations or ventilation tubes, or if the patient has a hypersensitivity to any of the components.

2. Acetic acid in aluminum acetate drops (Domeboro) may be used in mild cases of OE to help acidify and dry the canal. Five drops are applied to the affected ear two to four times daily. This solution should not be used if a tympanic membrane perforation or ventilation tube is present (package insert, Bayer Corp, West Haven, CT, 1995).[42]

3. Propylene glycol and acetic acid otic solution (VoSol) and hydrocortisone 1% propylene glycol acetic acid otic solution (VoSol HC) also work well in superficial infections. The acetic acid has antibacterial properties, whereas the hydrocortisone helps reduce inflammation and pruritus. Both of these preparations are quite viscous and have a pH of approximately 3. Two to four drops are applied two to four times daily. This solution should not be used in the setting of a tympanic membrane perforation or ventilation tube because of concern for ototoxicity (package insert, Wallace Labs, Cranbury, NJ, 1999).[43]

Table 138-1

Considerations if Acute Otitis Externa Fails to Respond to Initial Ototopical Therapy

Self-instrumentation trauma
Malignant external otitis
Contact dermatitis
Failure to adhere to preventive measures such as avoiding water in the ear
Improper administration of ototopical
Immunosuppression resulting from diabetes, or prior radiotherapy
Inadequate penetration of ototopical owing to debris or thickened canal skin
Misdiagnosis such as psoriasis, cancer, or tuberculosis
Organism resistant to ototopical choice

Systemic Therapy for Acute Bacterial Otitis Externa

The AAO-HNSF recommends adding a systemic antibiotic in patients with OE and a history of prior radiation therapy, diabetes, or immunocompromised state.[16] Patients with concomitant parotitis or cellulitis extending to the auricle, face, or neck, and patients with concurrent otitis media without tympanic membrane perforation or tympanostomy tube also should receive oral antibiotics. Finally, patients who fail to respond to a full course of ototopicals may benefit from oral antibiotics.[7,15,16,18] It may be prudent to obtain a culture in patients with refractory OE before starting oral antibiotics, or before starting topical therapy in patients with underlying immunocompromise.

Special Considerations in Chronic Bacterial Otitis Externa

When initial therapy fails to treat acute OE, the physician should consider not only the possibilities of improper administration or ineffectiveness of the ototopical, but also other possible diagnoses, such as malignant OE, underlying canal cholesteatoma, keratosis obturans, contact dermatitis, and malignancy (Table 138-1).[14] Symptoms lasting longer than 3 months may indicate chronic OE. This condition can be the result of inadequately treated infectious OE, but noninfectious causes should also be considered and are discussed subsequently in the section on eczematoid OE.[14,44] In chronic OE, topical antibiotic therapies may not be as effective in resolving long-standing inflammation. Daily irrigation with an acidifying or dehydrating agent and use of a hair dryer on a low, cool setting after water exposure help to optimize daily ear hygiene. Dry powder preparations (discussed subsequently) are a reasonable alternative to topical drops because continued moisture from long-term ototopical use can contribute to maceration of the external canal skin and chronic infection. Topical steroid creams have been used with topical antibiotics to improve the efficacy of treatment in chronic OE.

Ototoxicity Associated with Topical Antibiotics

The possible risk of ototoxicity with the use of topical antibiotics, particularly aminoglycosides (gentamicin, neomycin, streptomycin), continues to be a concern. Free radicals are generated by aminoglycosides in the inner ear that can injure vestibular and cochlear hair cells. Two mutations in the mitochondrial 12S ribosomal RNA gene have been reported to predispose carriers to aminoglycoside-induced ototoxicity.[31] The vestibulotoxic and cochleotoxic side effects were initially recognized after systemic use of aminoglycosides, and subsequent research has examined their toxicity when used in topical form. Animal studies performed since the 1950s have consistently confirmed the ototoxic potential of topical aminoglycosides. Wright and Meyerhoff[20] showed near-total destruction of all the hair cells in the inner ear of the chinchilla with only a single application of neomycin, polymyxin, or chloramphenicol.

No large randomized controlled trials examine the issue of ototoxicity from topical antibiotic therapy in humans. The data that do exist from human studies are equivocal, and the incidence of topical aminoglycoside–associated ototoxicity may be only approximately 1 in 10,000 patients.[4,45] Possible explanations for this difference in ototoxicity between humans and animals are that humans have thicker round window membranes, a deeper round window niche (providing greater protection), and often a pseudomembrane (mucous membrane) overlying the round window that may minimize topical absorption.[7] Polymyxin, a component of Cortisporin otic drops, has ototoxic properties in animal studies (even more so than neomycin), and may have ototoxic potential in humans in the presence of tympanic membrane perforations.[20,46] In contrast to aminoglycosides and polymyxin, no ototoxicity from fluoroquinolones has been reported in animals or humans.[25]

In 2007, the Clinical Audit and Practice Advisory Group of the British Association of Otolaryngologists–Head and Neck Surgeons (ENT-UK) reviewed the literature with the goal of establishing a clinical guideline for the use of aminoglycosides in acute OE in humans. They found no convincing data regarding the ototoxicity of topical aminoglycosides, but recommended that these agents should be used only in the presence of obvious infection and for no longer than 2 weeks.[47]

Linder and associates[48] examined 134 patients who were evaluated for possible ototopical antibiotic–related ototoxicity, and found only two patients with significant sensorineural hearing loss attributable to excessive administration of framycetin-containing and polymyxin-containing ear drops in the presence of tympanic membrane perforations. Matz and colleagues[49] performed a review of the literature and found 14 articles that dealt directly with the evaluation of either hearing loss or changes in vestibular function after the use of ototopical antibiotic drops. Although most articles were in the level 3 to 3b evidence category (*opinions* of respected authorities based on clinical experience, descriptive studies, or reports of expert committees), two were in the 1b category (evidence obtained from at least one properly designed randomized controlled trial). Fifty-four cases of gentamicin-induced vestibular toxicity were documented, and cochlear toxicity was noted in 24 of these patients. Eleven cases of cochlear toxicity and 2 cases of vestibular toxicity associated with neomycin-based ototopicals were also observed.[49]

Berenholz and coworkers[50] performed a retrospective review of 500 patients who received Cortisporin drops after ventilation tube placement. They found no cases of new-onset sensorineural hearing loss, and noted that Cortisporin drops were less than half as expensive as topical fluoroquinolones. A Cochrane Database article in 2006 addressed the safety concerns of ototopicals and found no adequate evidence to suggest ototoxicity for either Cortisporin or fluoroquinolone drops.[51]

A consensus panel of the AAO-HNSF made recommendations in 2004 on the use of topical aminoglycosides in the middle ear or in the presence of tympanic membrane perforation.[4] The panel determined that, whenever possible, "topical antibiotic preparations free of potential ototoxicity should be used in preference to ototopical preparations that have the potential for otologic injury if the middle ear or mastoid are open." They pointed out that aminoglycoside topical agents are not FDA approved for use in the middle ear, and warning labels from the manufacturer state that they should not be used if the tympanic membrane is perforated. The panel did agree that the potential ototoxic side effects of aminoglycosides are quite infrequent, and that the data from human trials are equivocal, but determined that because antibiotics without any known ototoxic potential are available and are efficacious, they should be considered as a first-line treatment.[4] Finally, evidence exists that combining aminoglycoside ototopicals with steroids (i.e., TobraDex) results in significantly less ototoxicity than using the aminoglycoside alone,[52] indicating that the combination drops may be a better option if an aminoglycoside is indicated.

Hypersensitivity Associated with Ototopical Antibiotics

In addition to the potential for ototoxicity, the possibility of drug hypersensitivity reaction may help to guide the selection of antibiotic preparations for treatment of OE. Patients who present with a hypersensitivity reaction complain of pruritus and tenderness of the ear associated with clear otorrhea. Examination often reveals an erythematous, maculopapular rash associated with edema and thickening of the external auditory meatus and conchal bowl where pooling of the topical preparation has occurred. Neomycin is the most common sensitizer, followed by gentamicin.[53] Smith and coworkers[54] showed an incidence of 32% neomycin hypersensitivity in patients with chronic OE. Other studies report a lower incidence ranging from 5% to 18%.[14,55]

Millard and Orton[22] found that in 45 patients with documented drug-induced hypersensitivity reactions, 76% of those were due to neomycin, followed by framycetin and gentamicin. Holmes and colleagues[56] performed patch testing on 40 patients with chronic OE and found that 35% had a medication-induced allergic contact dermatitis. Neomycin, framycetin, clioquinol, and gentamicin were the major sensitizers in this study.[56] Finally, aminoglycosides are capable of cross-sensitization, so careful selection of alternative therapies should be made when a patient develops a reaction to one member of this class.

Hypersensitivity to steroid preparations has also been documented, but is significantly less common (<0.1% for hydrocortisone). Lauerma[57] performed patch testing using three different corticosteroids on 727 patients, and found that 3.9% reacted to tixocortol pivalate, 1.4% to hydrocortisone butyrate, and 0.4% to hydrocortisone. Preservatives such as benzalkonium chloride, thimerosal, and propylene glycol (which also increases the solubility of the drug in the epidermis) can also incite local sensitization and should be considered as possible culprits if topical therapy does not resolve otorrhea.[14,18,55]

Fungal Otitis Externa

For a definition and description of fungal OE, see Chapter 137.

Topical Therapy Options for Fungal Otitis Externa

The treatment of choice for fungal OE includes thorough débridement followed by topical application of antifungal agents.[58-60] As with bacterial OE, acidification of the external canal with ototopical preparations is effective at clearing mild cases of otomycosis. The acidification helps inhibit bacterial and fungal growth. Re-establishing a dry external auditory canal with routine hygiene, water precautions, and maintenance irrigations with acetic acid or mild alcohol solutions (in the setting of an intact tympanic membrane) is important to prevent recurrent fungal OE. Refractory fungal OE may require more specific antifungal preparations.

Acidifying Agents for Fungal Otitis Externa

Aluminum acetate otic drops (Burow's solution), acetic acid/propylene glycol/hydrocortisone 1% (VoSol HC), acetic acid (Domeboro Otic), and boric acid solution all are acidifying agents that are commonly used to treat uncomplicated otomycosis. Acidifying agents have been shown to treat most mild cases of fungal OE successfully, especially when combined with thorough débridement of the external canal. Ho and colleagues[58] found that aluminum acetate drops were greater than 80% effective in mild cases of fungal OE. del Palacio and associates[61] also confirmed that boric acid solution was as effective as antifungal 11% ciclopirox olamine cream (or 1% solution) in treating patients with otomycosis, but that the boric acid group had significantly more discomfort. Kiakojuri and colleagues[62] showed in a prospective study that acidification of the canal in combination with topical antifungals (miconazole) did not improve efficacy compared with miconazole alone.

Topical Antifungals for Fungal Otitis Externa

The following are commonly used antifungal preparations for the topical management of fungal OE:

1. Clotrimazole (Lotrimin, Mycelex) cream: Ologe and Nwabuisi[59] showed a 96% symptom-free rate after a single application of clotrimazole cream following débridement of the canal. Complications were rare, and included a recurrence rate of less than 3%. The one-time application required is tolerated well by most patients and

is cost-effective. Stern and colleagues[60] showed that clotrimazole 1% cream was effective against all common fungal pathogens in vitro when measuring zones of inhibition of various antifungals. Similar to Stern and colleagues,[60] Maher and coworkers[63] showed that clotrimazole was effective against the large variety of fungi isolated from clinical otomycosis specimens. Greater than 94% of the 59 fungus species had MICs less than 0.1 μg/mL, and for the remaining 6% MICs were between 0.4 μg/mL and 1 μg/mL.[63]

2. Miconazole 2%: Kiakojuri and colleagues[62] showed in a prospective trial that miconazole was effective at treating otomycosis, and that the addition of acidifying drops (acetic acid 3% + alcohol 97%) did not significantly improve outcome.

3. Ketoconazole: Ho and colleagues[58] showed that ketoconazole had a better efficacy and lower recurrence of otomycosis compared with Cresylate otic and aluminum acetate.

4. Tolnaftate (Tinactin): Maher and coworkers[63] showed in an in vitro study the efficacy of tolnaftate and clotrimazole. The MIC for each of the drugs was <1 μg/mL for all 59 species of fungi tested from patients with otomycosis.

5. Nystatin is a polyene antifungal agent that damages fungal membranes by altering permeability. It can be used as a topical suspension, cream, or powder. Stern and colleagues[60] found that nystatin had the widest range of activity against a variety of pathogens when measuring the zones of inhibition of various antifungals.

6. Ciclopirox olamine 0.77% antifungal cream or solution: del Palacio and associates[61] in a randomized prospective trial showed ciclopirox olamine 0.77% to have equal efficacy compared with boric acid, but was better tolerated by patients.

Topical Antiseptics for Fungal Otitis Externa

The following are commonly used topical antiseptics for the management of fungal OE:

1. Cresylate otic drops 25%: Ho and colleagues[58] determined Cresylate otic drops to be greater than 80% effective.

2. Gentian violet: Gentian violet is useful in refractory cases, but should be avoided with perforated tympanic membranes.

3. Merbromin (Mercurochrome): Chander and associates[64] found merbromin to be more effective than clotrimazole or miconazole.

4. Silver nitrate gel 1%: van Hasselt and Gudde[65] found in a prospective randomized trial that a single application of 1% silver nitrate gel cured 92% of ears with refractory otomycosis within 1 week.

Ototoxicity Associated with Topical Antifungal Therapy

Ototoxicity of topical antifungal therapies has not been well studied. Tom[23] showed that clotrimazole, miconazole, and tolnaftate had no ototoxic effects when applied to the middle ear of guinea pigs compared with normal controls and animals that received topical neomycin (an agent known to cause ototoxicity) applied to the middle ear. Nystatin likewise had no ototoxicity, but did leave a persistent residue at the round window niche. Gentian violet was found to be extremely ototoxic.[23] Marsh and Tom[66] observed that preparations containing acetic acid or propylene glycol caused elevation of brainstem response thresholds when applied to the middle ear of guinea pigs, whereas clotrimazole and tolnaftate had no ototoxic effects.

Myringitis

Definition

Myringitis is an inflammatory condition of the tympanic membrane and can be acute or chronic. Acute bullous or hemorrhagic myringitis can be the consequence of a bacterial infection, such as *Streptococcus pneumoniae* or *Staphylococcus* species, or a viral infection, such as influenza or herpes zoster. Fungal myringitis, eczematoid myringitis, and granular myringitis may also occur.

Topical Therapy Options

Treatment of myringitis depends on the etiology. For acute primary bacterial myringitis, or myringitis associated with acute otitis media, oral antibiotics are the primary therapy. Systemic antibiotics should be directed against the most common pathogens associated with otitis media, *S. pneumoniae* and *Haemophilus influenzae.* For individuals with acute OE, standard therapy includes topical antibiotic and steroid ear drops. The topical preparations mentioned earlier are effective in treating external canal disorders with associated myringitis. Kaga and Ichimura[67] performed a small pilot study examining the efficacy of ofloxacin on infantile myringitis and chronic otitis media. Treatment with twice-daily ofloxacin eradicated the causative pathogen in most of the 21 patients examined in their cohort.[67] For fungal infections involving the tympanic membrane, the topical antifungals mentioned earlier are the mainstay of treatment. Treatment for chronic myringitis may include antibiotic ear drops, but may also respond to acetic acid ear canal irrigations followed by application of steroid cream.

Granular myringitis is a chronic inflammatory condition of the epidermal layer of the tympanic membrane and may be treated with surgical removal, chemical cauterization, or vinegar irrigations—although no large randomized controlled studies address this question.[68] Jung and colleagues found a 96% reduction in granular myringitis recurrence with daily dilute vinegar irrigations in a sample size of 15 patients.[68a]

Eczematoid Otitis Externa

See Chapter 137 for a definition and description of eczematoid OE.

Management Options in Eczematoid Otitis Externa

When identified, offending agents (i.e., lotions, jewelry, foods, ototopicals) related to eczematoid OE should be avoided, but there are often significant delays in diagnosis because of the similarities in presentation between infectious and noninfectious causes of OE. Careful débridement of the affected ear under microscopy and management of any associated infection are crucial; it is also crucial to use appropriate ototopical antibiotics when a superimposed bacterial infection is present (and when the possibility of sensitivity to a previously used ototopical has been eliminated).

If the elimination of possible sensitizing agents and ear hygiene are unsuccessful in managing eczematoid OE, anti-inflammatory medical therapy is warranted. Topical glucocorticoids are the gold standard for management of eczematous OE. Many steroid preparations are available and are frequently prescribed to help reduce inflammation and skin flaking and to decrease pruritus. Refractory cases may warrant systemic steroids and a referral to a dermatologist and a rheumatologist.

Steroids for Eczematoid Otitis Externa

Jacobsson and colleagues[69] performed a double-blinded study of 60 patients with eczematoid OE who were randomly assigned to a placebo group or a treatment group in which they received therapy with budesonide (a glucocorticoid). The treatment group had significant improvement of erythema, edema, and drainage compared with the placebo group.

No clinical trials have explored the efficacy of the different steroid preparations in the treatment of eczematoid OE; however, it may be possible to extrapolate findings from the dermatology literature. Juhlin[70] performed a randomized, double-blind, parallel-group study of 120 patients to examine the efficacy of fluticasone propionate cream 0.05% and hydrocortisone butyrate cream 0.1% in the treatment of eczema. Both preparations had minimal side effects, and there was no statistically significant difference in efficacy at reducing the severity of eczema. James[71] performed a randomized, double-blind trial of 125 patients to compare the same two preparations (fluticasone propionate cream 0.05% and hydrocortisone butyrate cream 0.1%) in the treatment of psoriasis. In this study, fluticasone propionate cream was superior to

hydrocortisone butyrate cream. Ashton and coworkers[72] compared 0.25% and 0.05% desoxymethasone, 0.1% betamethasone valerate, and 1% hydrocortisone creams in the treatment of eczema in a randomized controlled trial of 96 patients. The 0.25% desoxymethasone cream was the most effective treatment, hydrocortisone was the least effective, and 0.05% desoxymethasone and 0.1% betamethasone were of intermediate effectiveness.

Fluocinolone acetonide oil 0.01% (DermOtic Oil) is currently the only FDA-approved treatment for chronic pruritus of the external ear. The manufacturer states that the peanut oil vehicle moistens the ear canal and loosens cerumen, and the corticosteroid reduces irritation and inflammation. It is approved for patients older than 2 years, and twice-daily usage for 2 weeks is recommended. In clinical studies sponsored by the manufacturer, 90% of patients had near-resolution of their symptoms within 2 weeks.[73]

Generally, it is reasonable to start with a readily available, over-the-counter mild topical glucocorticoid such as hydrocortisone 1% for a patient with eczematous OE. If the initial treatment regimen fails, changing to a more potent glucocorticoid is a reasonable option.

Classes of Topical Steroids

The strength of a steroid is determined by a standardized test that measures the extent to which it can cause blood vessels to constrict in the upper dermis. Table 138-2 lists some popular steroids in each class in order of decreasing potency.

Ototoxicity Associated with Ototopical Steroid Use

Ototoxicity has not been documented from the topical use of glucocorticoids. Multiple studies have shown that they may have a protective effect on inner ear function. Ye and coworkers[74] and Kiefer and colleagues[75] showed that round window application of triamcinolone has no ototoxic effect in a gerbil model, and that intracochlear application via a cochleostomy resulted in an increased recovery of cochlear function after surgical trauma. Intratympanic injections of high-dose steroids such as dexamethasone or methylprednisolone are used to treat idiopathic sudden sensorineural hearing loss.[76-78] Kiliç and associates[79] showed in a prospective randomized controlled trial of 37 patients that intratympanic injection of methylprednisolone improved hearing results in patients who failed a trial of oral steroids for sudden sensorineural hearing loss. Xenellis and colleagues[80] confirmed these results in their randomized controlled prospective trial of 37 patients with sudden sensorineural hearing loss who also failed oral steroid treatment. These studies are small, but many in vitro and in vivo studies have supported an otoprotectant role of topical steroids.

Anti-inflammatory and Immunosuppressive Agents

Tacrolimus (FK-506, Fujimycin, Protopic) is a macrolide immunosuppressant drug that inhibits calcineurin, inhibiting T-lymphocyte signal transduction and interleukin-2 transcription. It has been shown to be as effective as some moderate-strength steroids, and can be used for long periods because it does not have the same side-effect profile of topical steroids that includes skin atrophy. It can also be used in regions of fragile or sensitive skin. Side effects include burning, pruritus, flulike symptoms, and headache.[81,82] Randomized controlled prospective trials have shown that topical 0.03% and 0.1% tacrolimus ointments were more effective than 1% hydrocortisone acetate and similarly effective as 0.1% hydrocortisone butyrate and 0.1% methylprednisolone aceponate ointments in adults and children with moderate to severe atopic dermatitis.[83,84]

Caffier and associates[81] and Harth and coworkers[82] studied the efficacy of tacrolimus ointment for chronic noninfectious OE in a prospective trial of 53 patients whose disease was refractory to standard management. Otowicks infused with tacrolimus ointment were placed every 2 to 3 days for a total of three treatments. In the short-term, 85% of the patients had significant improvement in otalgia, edema, otorrhea, erythema, pruritus, and desquamation. In the 10- to 22-month follow-up, 46% of patients had no relapsing symptoms, and the 54% of patients who did have relapses had longer symptom-free periods.[81,82]

Pimecrolimus cream 1% is also a calcineurin inhibitor and is used in milder cases of dermatitis. Pimecrolimus is more highly skin-selective than tacrolimus (which is also used as a general immunosuppressant for transplant patients). It has fewer side effects than topical steroids, has a better side-effect profile than tacrolimus, is safe in infants, and is safe for intermittent long-term therapy of dermatitis.[85,86] The direct drug cost of pimecrolimus compares favorably with tacrolimus, but it is significantly more expensive than generic topical steroid creams.[86] Djalilian and Memar[87] performed a retrospective chart review of 36 patients with pruritic external ears who were treated with 3 months of topical pimecrolimus ointment. Thirty-four of 36 patients experienced significant improvement in pruritus compared with a group of 19 control patients who received only aural hygiene.[87]

For the treatment of eczematous OE and pruritic ears, some clinicians still depend on an old remedy, coal tar, although no randomized controlled trials exist to prove its efficacy in treating this disorder. Coal tar has been used for more than 100 years, and was the mainstay for treating inflammatory skin conditions before the development of topical steroids.[88] Coal tar has anti-inflammatory, antibacterial, antipruritic, and antimitotic effects; common short-term side effects are folliculitis, irritation, and contact allergy. Hoare and colleagues[89]

Table 138-2

Potencies of Topical Steroids

Group I (*Most Potent*)
Clobetasol propionate 0.05% (Temovate)
Betamethasone dipropionate 0.25% (Diprolene)
Halobetasol propionate 0.05% (Ultravate)
Diflorasone diacetate 0.05% (Psorcon)

Group II
Fluocinonide 0.05% (Lidex)
Halcinonide 0.05% (Halog)
Amcinonide 0.05% (Cyclocort)
Desoximetasone 0.25% (Topicort)

Group III
Triamcinolone acetonide 0.5% (Kenalog, Aristocort cream)
Mometasone furoate 0.1% (Elocon ointment)
Fluticasone propionate 0.005% (Cutivate)
Betamethasone dipropionate 0.05% (Diprosone)

Group IV
Fluocinolone acetonide 0.01-0.2% (Synalar, Synemol, Fluonid)
Hydrocortisone valerate 0.2% (Westcort)
Hydrocortisone butyrate 0.1% (Locoid)
Flurandrenolide 0.05% (Cordran)
Triamcinolone acetonide 0.1% (Kenalog, Aristocort A ointment)
Mometasone furoate 0.1% (Elocon cream, lotion)

Group V
Triamcinolone acetonide 0.1% (Kenalog, Aristocort cream, lotion)
Fluticasone propionate 0.05% (Cutivate cream)
Desonide 0.05% (Tridesilon, DesOwen ointment)
Fluocinolone acetonide 0.025% (Synalar, Synemol cream)
Hydrocortisone valerate 0.2% (Westcort cream)

Group VI
Alclometasone dipropionate 0.05% (Aclovate cream, ointment)
Triamcinolone acetonide 0.025% (Aristocort A cream, Kenalog lotion)
Fluocinolone acetonide 0.01% (Capex shampoo, Derma-Smoothe/FS)
Desonide 0.05% (DesOwen cream, lotion)

Group VII (*Least Potent*)
Hydrocortisone 2.5% (Hytone cream, lotion, ointment)
Hydrocortisone 1% (many over-the-counter brands)

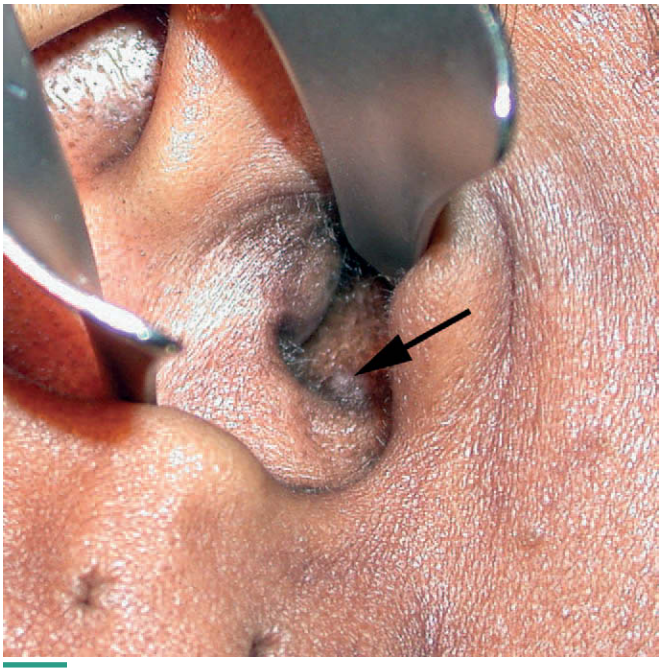

Figure 138-2. Human papillomavirus infection of the right external auditory canal. The previous biopsy site is seen in the posterior-superior quadrant. This otherwise healthy woman presented with chronic pruritus bilaterally and muffled hearing, and no previous history of human papillomavirus infection. Examination revealed numerous, circumferential papillomas of the lateral external auditory canal bilaterally. She was referred to a dermatologist for treatment with topical immune-response modifiers. The *arrow* points to a papilloma.

performed a meta-analysis on the treatments for atopic eczema and determined there is insufficient evidence to make recommendations on the use of coal tar in the treatment of the disease. Potential carcinogenicity of coal tar is still a concern, although there is no clear evidence of an increased risk of skin tumors or internal tumors in randomized clinical trials using coal tar for eczema.[90]

Viral Infections

Viral lesions of the external ear are extremely rare. In aural papillomatosis, papillomas fill the external auditory canal (Fig. 138-2). Human papillomavirus type 6 (HPV-6) has been shown to be the cause of aural papillomatosis.[91] Middle ear inverting papillomas are rarely described in the literature, and may extend through a tympanic membrane perforation into the external canal.

Management Options

Only a few cases of aural papillomatosis have been reported, and successful treatment has involved primary resection.[92] Blair and colleagues[93] managed a patient with aural papillomatosis with CO_2 laser removal. Yadav and associates[94] treated a 3-year-old patient with surgical excision of the external canal aural papillomatosis. No trials exist to document the use of topical therapies for aural papillomatosis; however, the immune-response modulator imiquimod 5% (Aldara) has been used topically with good success in treating HPV-6-associated papillomatosis of the external genitalia.[95] Topical treatment with imiquimod 5% three times weekly for 16 weeks resulted in 50% complete resolution of disease and 74% partial resolution of disease in randomized, controlled trials.[95] Mild localized side effects of imiquimod include erythema, itching, and burning, and are the most commonly reported adverse events, occurring in 67% or less of patients applying imiquimod 5% cream three times a week in a meta-analysis of the literature.[96] Based on these data, topical imiquimod therapy may be a reasonable nonsurgical option for aural papillomatosis. Imiquimod is currently being used by some practitioners to minimize keloid recurrence after excision from the auricle.[97,98] These studies are small and uncontrolled so far, but have shown that there are no significant side effects other than mild localized skin irritation with the use of topical imiquimod 5% on the external ear.[97,98]

Cerumen Impaction

Cerumen impaction is an extremely common problem for which patients seek otolaryngologic advice and treatment because it can cause discomfort, hearing loss, tinnitus, dizziness, and chronic cough.[99] Cerumen impaction is present in approximately 10% of children, 5% of healthy adults, 57% of elderly patients in nursing homes, and 36% of patients with mental retardation.[100] Chronic manipulation with cotton-tip applicators, narrow external canals, hair in the lateral canal, hearing aids, and earplug use have been associated with an increased incidence of cerumen impaction. Cerumen removal is the most common otolaryngologic procedure performed in the primary care setting.[99,101]

Therapy Options

Many approaches for removing cerumen, including manual débridement, irrigation, and ceruminolytics, have been described in the literature. There are, however, no data from large randomized prospective trials comparing the efficacy of the different methods of cerumen removal. Manual removal and irrigation are effective, but may risk trauma to the canal skin, infection, or tympanic membrane perforation. Irrigation should not be done if a tympanic membrane perforation or myringotomy tube is present.

Initial treatment of cerumen impaction with ceruminolytics is reasonable in most cases. There are three types of cerumen-softening preparations: water-based, oil-based, and non–water-based/non–oil-based (Table 138-3). Water-based and non–water-based/non–oil-based agents increase cerumen miscibility, whereas oil-based preparations lubricate the wax. All agents should be avoided in patients with tympanostomy tubes or tympanic membrane perforation; manual removal of cerumen, ideally using a binocular microscope, may be the best option for this population.

Comparing ceruminolytics, Hand and Harvey[102] concluded in their review of the literature that triethanolamine was better than saline, and that longer treatment duration with softening agents was better than a shorter duration in overall efficacy of treating cerumen impaction. These authors also noted that docusate sodium was not statistically better than triethanolamine or saline.[102] Roland and associates[103] found no statistical difference in resolution of cerumen impaction in 74 patients randomly assigned to saline, Cerumenex, or Murine ear wax removal products, and Whatley and coworkers[104] found no difference among saline, Colace, and triethanolamine.

The use of ceruminolytics before irrigation may increase the success of irrigation by 97%.[102] Use of a ceruminolytic agent 15 to 30 minutes before irrigation was found to be as effective as several days of treatment,[105] and a water-based agent (water, saline, or triethanolamine) was found to be superior to carbamide peroxide (a non–water-based/non–oil-based preparation) before irrigation.[102] Overall, no ceruminolytics when used immediately before irrigation seemed to be superior to saline, making saline an inexpensive first-line agent. McCarter and colleagues[99] stated that "based on current evidence, if treatment with a ceruminolytic agent followed by irrigation is chosen, an initial attempt at irrigation with water should be made. If irrigation is unsuccessful, the water should be instilled and left in the external auditory canal for 15 to 30 minutes, after which another attempt at irrigation should be made. If this second attempt is also unsuccessful, it would be reasonable to use a ceruminolytic for two to three days, followed by another trial of irrigation."[106]

Ear Hygiene and Chronic Draining Ear

In patients with chronic otorrhea or moist ears, a thorough history and physical examination is required to rule out hypersensitivity to previous ototopical therapy, autoimmune condition, cholesteatoma, granuloma, or malignancy. Chronic inflammation or low-grade chronic infection with the same bacteria responsible for chronic OE may result in persistent otorrhea. Ear hygiene and dry ear precautions (use of ear plugs or

Table 138-3

Cerumen-Softening Agents for Cerumen Removal

Agent	Use	Dosing
Water-Based		
10% Trolamine polypeptide oleate-condensate (Cerumenex)	Soften cerumen before irrigation	Fill affected ear canal 15-30 min before irrigation
Docusate sodium (Colace)	Soften cerumen before irrigation	Fill affected ear canal with 1 mL 15-30 min before irrigation
3% Hydrogen peroxide	Soften cerumen before irrigation	Fill affected ear canal 15-30 min before irrigation
2.5% Acetic acid	Home treatment of impacted cerumen	Fill affected ear with 2-3 mL twice daily for up to 14 days
10% Sodium bicarbonate	Soften cerumen before irrigation or as an alternative to irrigation	Fill affected ear with 2-3 mL 15-30 min before irrigation, or alternatively for 3-14 days at home with or without irrigation
Water or saline	Soften cerumen before irrigation	If irrigation is attempted without softening and is ineffective with the first irrigation attempt, instill water and wait 15 min before repeating irrigation
Non–Water-Based/Non–Oil-Based		
Carbamide peroxide (Debrox, Murine removal kit)	Soften cerumen before irrigation or as an alternative to irrigation	Put 5-10 drops into affected ear twice daily for up to 7 days
50% Choline salicylate and glycerol (e.g., Earex Plus, Audax); ethylene oxide polyoxypropylene glycol (Addax); propylene glycol; 0.5% chlorbutol	Soften cerumen before irrigation or as an alternative to irrigation	Put 3 drops into affected ear twice daily for 4 days
Oil-Based		
57.3% Arachis oil, 5% chlorbutol, 2% paradichlorobenzene, 10% oil of turpentine (e.g., Cerumol)	Soften cerumen before irrigation or as an alternative to irrigation	Fill affected ear with 5 mL twice daily for 2-3 days
Arachis oil, almond oil, rectified camphor oil (e.g., Otocerol, Earex)	Soften cerumen before irrigation or as an alternative to irrigation	Put 4 drops into affected ear twice daily for up to 4 days
Olive oil, almond oil, or mineral oil	Soften cerumen before irrigation	Put 3 drops into affected ear at bedtime for 3-4 days

From McCarter D, Courtney A, Pollart S. Cerumen impaction. *Am Fam Physician*. 2007;75:1523-1528.

cotton balls with petrolatum jelly) are crucial. The safest way to dry ears is with a hair dryer on the cool setting, or with a specifically designed ear dryer.[107,108]

Acidifying or alcohol drops can be used as a preventive measure during the at-risk period (e.g., swim season, scuba diving trip), and can be used as treatments in patients with chronic draining ears. Acetic acid solutions (i.e., Domeboro, trichloroacetic acid solutions) and alcohol solution[14,17,109] evaporate moisture and help prevent bacterial overgrowth. A review of the literature indicates that acetic acid and alcohol-based drops may be ototoxic, and should be avoided in patients with tympanic membrane perforations or tubes.[42,110,111] Iodine and Burow's solution do not seem to have ototoxic or vestibulotoxic potential.[111,112]

Various powders designed for use in the external ear canal have been developed as treatments for chronically moist canals and mastoid bowls. Most preparations are a mixture of antibacterial antibiotics, antifungal agents, and steroids. Two preparations are used at the University of Texas Southwestern Medical Center. *Gold dust* comprises chloramphenicol, sulfanilamide, and hydrocortisone. The chloramphenicol in gold dust powder has ototoxic potential and should not be used with perforated tympanic membranes.[113-115] *Mastoid powder* comprises ciprofloxacin powder, clotrimazole powder, dexamethasone powder, and boric acid. Compared with gold dust, the mastoid powder seems more effective, is easier to apply, and has no ototoxic potential.[4,7,23-25,76-78] The House Ear Institute developed a mastoid powder that consists of chloromycetin, 50 mg; sulfanilamide, 50 mg; and Fungizone, 5 mg (CSF powder). Hydrocortisone powder may also be added to make CSF-HC. At Johns Hopkins, a preparation consisting of hydrocortisone powder 4% and boric acid 96% is used. These powders are not always readily available because a pharmacy capable of compounding is needed.

A bulb insufflator was developed in 1983 by House and Sheehy at the House Ear Clinic for the topical application of these powders to the external auditory canal or mastoid bowl. This bulb is commonly used today and accepts No. 3 medication capsules (Fig. 138-3).

Finally, in many cases, the underlying cause of chronic otorrhea may be the presence of granulation tissue. Silver nitrite can be applied topically to the granulation tissue.[116,117] In patients who have had a canal wall down mastoidectomy, it is essential to note whether the facial nerve is dehiscent before using silver nitrite to avoid accidentally chemically cauterizing the nerve. Because the silver nitrite sticks are frequently too large and imprecise to place directly on granulation tissue in the external ear, small slivers can be obtained and used with alligator forceps to apply the chemical cautery precisely using a binocular microscope. Care should be taken to use as little as possible because the depth of burn cannot be easily controlled.

Conclusion

Many topical therapies in suspension, solution, lotion, ointment, or powder forms are available to the otolaryngologist to treat external ear disorders (Table 138-4). Although most ototopicals can be used safely for the management of common bacterial and fungal infections of the external ear, the possibility of ototoxicity and hypersensitivity must be kept in mind, especially in refractory cases or in patients with a perforated tympanic membrane. Systemic therapy should be used in

Table 138-4

Summary of Available Ototopical Agents

Generic Names	Brand Names	Indication	Dose Range	Frequency	Duration of Treatment	Contraindications	Pregnancy*	Lactation	Children	Notes	Cost
Acidifying Agents											
Alcohol-vinegar mix: ½ alcohol, ¼ white vinegar, and ¼ distilled water		Prevention of OE, treatment of mild cases of acute bacterial OE	4-5 drops	2-4 times per day		TM perforation, tubes, hypersensitivity reaction	Safe	Safe	Safe	May be used more copiously for irrigation if copious debris present	
Acetic acid in aluminum acetate	Domeboro/ modified Burow's solution	Treatment of mild fungal/ bacterial OE	5 drops	2-4 times daily	10 days	TM perforation, tubes, hypersensitivity reaction	Unknown	Unknown	Safe	May be used more copiously for irrigation if copious debris present	~$70 for 100 packets
Propylene glycol and acetic acid otic solution	VoSol	Treatment of mild fungal/ bacterial OE	2-4 drops	2-4 times daily	10 days	TM perforation, tubes, hypersensitivity reaction	Unknown	Unknown	Safe >3 yr old		~$7 for 10 mL
Hydrocortisone 1%, propylene glycol and acetic acid otic solution	VoSol HC	Treatment of mild fungal/ bacterial OE	2-4 drops	2-4 times daily	10 days	TM perforation, tubes, hypersensitivity reaction	Category C	Unknown	Safe >3 yr old		
Antibiotics											
Ofloxacin	Floxin (0.3% solution)	Treatment of bacterial OE, prevention of otorrhea post ear surgery; treatment of OM with tubes	Adults: 10 drops Children (<13 yr): 5 drops	qd or bid qd or bid	7-10 days 7-10 days	Hypersensitivity	Category C	Unknown	Safe	Safe in middle ear	10 mL: $136.03
Ciprofloxacin + hydrocortisone	Cipro HC (0.2%/1% suspension)	Treatment of bacterial OE	3 drops	bid	7 days	Hypersensitivity, viral external ear infection, TM perforation	Category C	Probably safe	Safe		10 mL: $91.39
Ciprofloxacin + dexamethasone	Ciprodex (0.3%/0.1% suspension)	Treatment of bacterial OE, treatment of OM with tubes	4 drops	bid	7 days	Hypersensitivity, viral external ear infection	Category C	Probably safe	Safe	Safe in middle ear	7 mL: $94.68
Neomycin, polymyxin B, hydrocortisone	Cortisporin (solution, suspension)	Treatment of bacterial OE	Adults: 4-5 drops; children: 3 drops	3-4 times daily	Maximum 10 days	Hypersensitivity, TM perforation, tubes, viral ear infection	Category C	Unknown	Safe	Solution burns—recommend suspension	10 mL: $72.99 (suspension or solution)

Continued

Table 138-4

Summary of Available Ototopical Agents—cont'd

Generic Names	Brand Names	Indication	Dose Range	Frequency	Duration of Treatment	Contraindications	Pregnancy*	Lactation	Children	Notes	Cost
Tobramycin + dexamethasone	TobraDex ophthalmic (0.1%/0.3% suspension)	Treatment of bacterial OE	3-4 drops	tid	7 days	Hypersensitivity, TM perforation, tubes	Category C	Unknown	Safe		10 mL: $126.97
Gentamicin	Gentamicin ophthalmic (0.3% drops)	Treatment of bacterial OE	3-4 drops	tid	7 days	Hypersensitivity, TM perforation, tubes	Category C	Unknown	Unknown		5 mL: $9.99
Antifungals											
Clotrimazole (1% cream, solution)	Lotrimin AF, Mycelex	Treatment of fungal OE	Cream: 1 application Solution: 3-4 drops	bid	7 days	Hypersensitivity	Category B	Probably safe	Safe		12-g tube: $8.99
Miconazole (2% cream)	Micatin, Monistat	Treatment of fungal OE	1 time application to external canal			Hypersensitivity	Category C	Probably safe	Safe		
Ketoconazole (2% cream)	Nizoral, Xolegel	Treatment of fungal OE	1 time application to external canal			Hypersensitivity	Category C	Safety unknown	Safe		15-g tube: $14.99
Tolnaftate (1% cream)	Tinactin	Treatment of fungal OE	1 time application to external canal			Hypersensitivity	Category C	Unknown	Safe		
Nystatin (100,000 U/g cream, ointment)	Mycostatin	Treatment of fungal OE	1 time application to external canal			Hypersensitivity, TM perforation	Category C	Safe	Safe		2 tubes, 15 g: $7.99
Ciclopirox olamine 0.77% cream, suspension	Loprox	Treatment of fungal OE	1 time application to external canal			Hypersensitivity	Category B	Safe	>10 yr		1 tube, 15 g: $24.99
Antiseptics											
Gentian violet 1% or 2%		Treatment of mild fungal OE	Adult: 1 application Children: 1 application	bid-tid qd-bid	3 days 3 days	Hypersensitivity, TM perforation	Category C	Safe	Safe	Causes staining	
Cresylate acetate otic 25%	Cresylate	Treatment of mild fungal OE				Hypersensitivity	Unknown	Unknown			

**Pregnancy Category B*: Animal reproduction studies have failed to show a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women *or* animal studies that have shown an adverse effect, and adequate and well-controlled studies in pregnant women have failed to show a risk to the fetus in any trimester. *Pregnancy Category C*: Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
OE, otitis externa; OM, otitis media; TM, tympanic membrane.

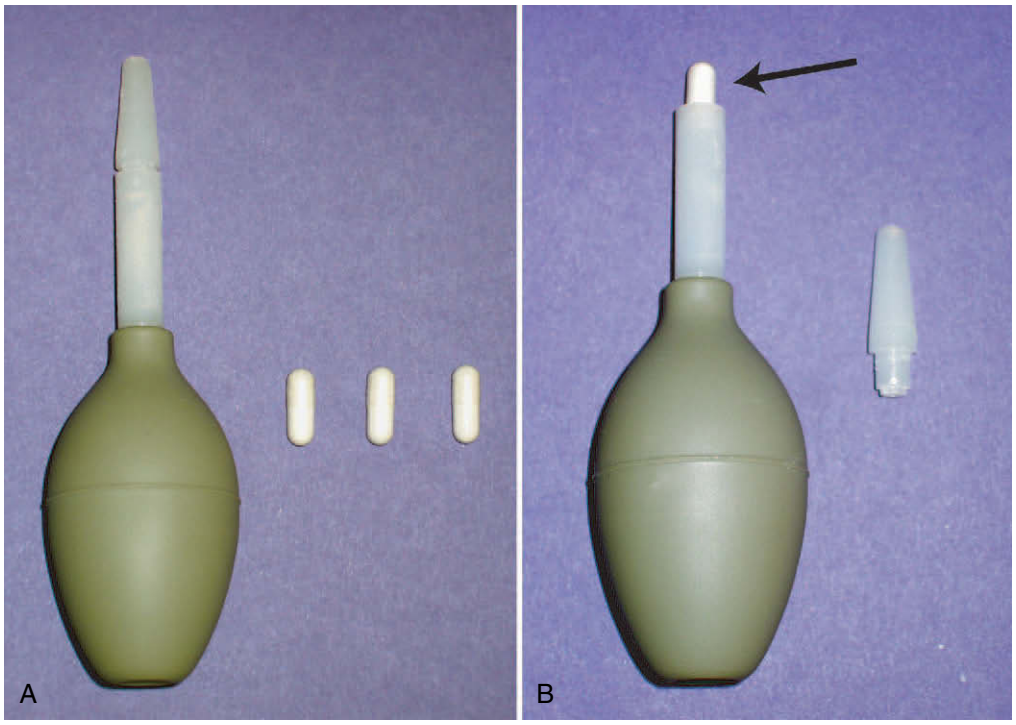

Figure 138-3. Powder insufflator. **A,** Assembled insufflator and No. 3 capsules filled with compounded antibacterial and steroidal components. **B,** An individual capsule is opened, and the open end containing the medicated powder is inserted *(arrow)* and left in the insufflator before reassembly. Care should be taken to avoid overapplication.

immunocompromised patients. Severe or chronic infections that do not respond to aggressive ototopical therapy, systemic therapy, and manual débridement must be carefully re-evaluated to exclude the possibility of a malignancy, cholesteatoma, keratosis obturans, an autoimmune disorder, hypersensitivity, or malignant OE. In most cases, meticulous ear hygiene and avoidance of self-manipulation contribute to better outcomes for patients with infectious and inflammatory conditions of the external ear.

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CHAPTER ONE HUNDRED AND THIRTY-NINE

Chronic Otitis Media, Mastoiditis, and Petrositis

Richard A. Chole

Holger H. Sudhoff

Key Points

- Otitis media is one of the most common diseases of childhood, and may result in complications including acute and chronic mastoiditis, petrositis, skull base osteomyelitis, intracranial infection, and the sequelae of early childhood auditory deprivation.
- Acute otitis media may result in persistent otitis media with effusion, which is now recognized as the leading cause of childhood hearing loss.
- Aural cholesteatomas are epidermal inclusion cysts of the middle ear or mastoid, and are classified as congenital and acquired.
- Cholesteatomas can be eradicated from the temporal bone only by surgical resection.
- Osteoclastic bone resorption in chronic otitis media with or without cholesteatoma is stimulated by various factors, including inflammation, local pressure, keratin, specific cytokines, and bacterial toxins.
- The mechanism of bone resorption in chronic otitis media with and without cholesteatoma is an increased number and activity of osteoclasts.
- Tympanosclerosis is tympanic membrane or middle ear hyalinization. It results from chronic inflammation or trauma, but it often leads to conductive hearing loss caused by ossicular fixation.
- Petrous apicitis is an extension of infection from the mastoid air cell tract into a pneumatized anterior or posterior petrous apex.
- The management of petrous apicitis is directed toward control of the infection, such as topical and systemic antibiotic management and surgical approach through many surgical routes.

Otitis media is the most common disease of childhood after viral upper respiratory infections. The acute bacterial infection occurs in 80% of children 1 to 6 years old, and it is the disease most frequently managed with antibiotics in the United States. The infectious and noninfectious complications of otitis media in childhood may result in serious morbidity. Later in life, the infectious complications, including acute and chronic mastoiditis, petrositis, and intracranial infection, still occur despite the widespread use of antibiotics for this disease. The noninfectious sequelae, including chronic perforation of the tympanic membrane, ossicular erosion, labyrinthine erosion, and tympanosclerosis, are major causes of hearing loss throughout the world.

Some cases of acute otitis media (AOM) result in persistent otitis media with effusion (OME), which is recognized as the leading cause of childhood hearing loss. The exact cause of OME is unclear; however, more recent data suggest that reflux of gastric contents may be associated with OME in children.[1-4] Although eustachian tube dysfunction alone may lead to effusion of the middle ear, there is mounting evidence that most cases of OME occur as a sequelae of AOM, or at least share the same etiologic factors. Specific causes can be identified in many cases of adult-onset otitis media, such as paranasal sinus disease, nasopharyngeal carcinomas and tumors, and postradiation sequelae.

In most children, AOM and OME subside spontaneously or after medical intervention. It is unknown how many children with OME eventually have complications. The sequelae of otitis media can be considered in two broad categories: (1) direct destructive effects of the localized process, and (2) the effects of auditory deprivation during early childhood. Otitis media may be complicated by acute or chronic perforation of the tympanic membrane, acute mastoiditis, middle ear atelectasis, adhesive otitis media, tympanosclerosis, ossicular erosion or fixation, petrous apicitis, cholesteatoma, chronic otomastoiditis, labyrinthitis, facial paralysis, and intracranial infection. There is evidence that sensorineural hearing loss may result from chronic otitis media with or without cholesteatoma. There is also evidence that the auditory deprivation associated with childhood otitis media may lead to indirect sequelae, such as language and speech delays.

Effects on Mastoid Pneumatization

It has been observed that patients with a history of chronic OME have more sclerotic mastoids with decreased pneumatization compared with healthy subjects. There are two theories to explain this observation: (1) the hereditary theory, which states that children with hypoaeration of the mastoid are prone to OME, and (2) the environmental theory, which states that chronic OME results in hypopneumatization of the mastoid.[5] Although measurable correlations between mastoid hypocellularity and OME,[6,7] and between the length of the mastoid process or the degree of pneumatization and an abnormal eardrum[8] have been proven, a cause-and-effect relationship is unclear. Available evidence generally supports the concept that chronic inflammation in early

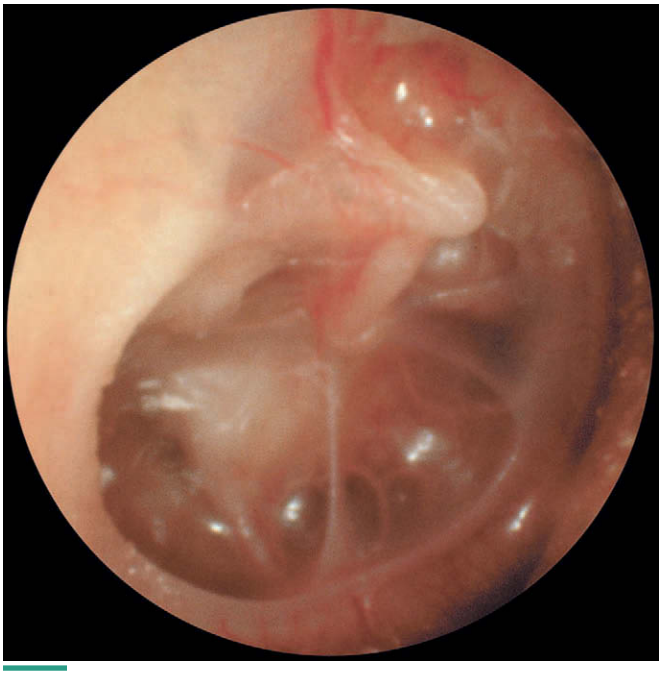

Figure 139-1. Middle ear atelectasis.

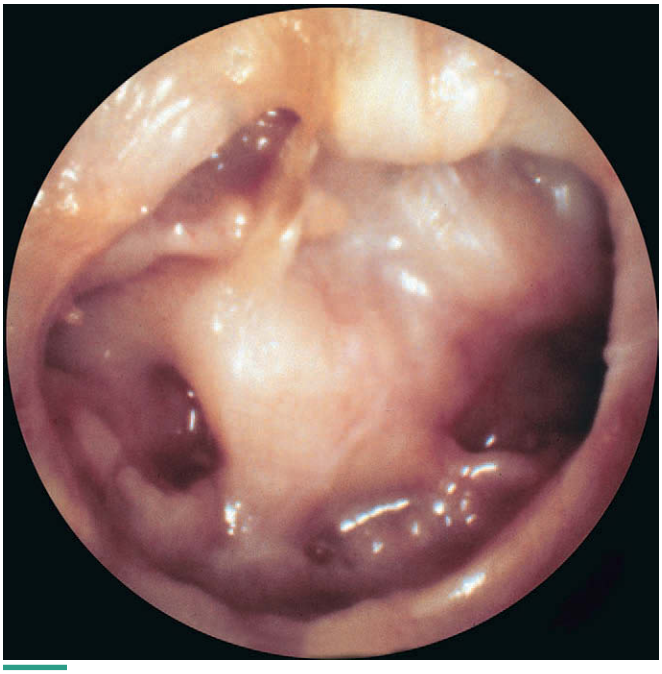

Figure 139-2. Middle ear atelectasis with ossicular erosion.

childhood may lead to new bone formation within the middle ear and mastoid and, subsequently, decreased size of mastoid air cells. Shatz and Sadé[9] measured the distance from the lateral sinus to the external auditory canal and found it to be significantly smaller in patients with sclerotic mastoids; they believed that this finding supported the hereditary theory because it was unlikely that otitis would change the position of the lateral sinus. A chronically inflamed mastoid in a young child may not develop normally, however.

Hasebe and colleagues[10] carried out a study to establish which type of cholesteatoma is controllable by conservative treatment from the viewpoint of mastoid ventilation. Their clinical observations suggest that progressiveness of cholesteatoma is related to the ventilatory conditions in the mastoid, rather than eustachian tube function, and that conservative treatment may be effective if ears with cholesteatoma have aeration in the mastoid.

Middle Ear Atelectasis and Adhesive Otitis Media

Middle ear atelectasis (Fig. 139-1) is thought to result mainly from long-standing eustachian tube dysfunction. One of the main functions of the eustachian tube is ventilation of the middle ear and mastoid. Opening of the eustachian tube allows exchanging of gases and equalization between the environment and middle ear. The middle ear gases also are exchanged with the middle ear mucosa. Bilateral diffusion between the middle ear cavity and the blood may be an important factor in middle ear atelectasis because the gas composition of the middle ear basically resembles that of venous blood.[11]

If the atelectasis develops, the tympanic membrane becomes retracted onto the promontory and the ossicles of the middle ear. In atelectatic ears, the middle ear space is partially or completely obliterated, but the tympanic membrane is not adherent to the medial wall of the middle ear, and the mucosal lining of the middle ear is intact. In contrast, adhesive otitis media exists when the middle ear space is totally obliterated, and the tympanic membrane is adherent to the ossicles and promontory; mucosal surfaces are not present. Retraction of the tympanic membrane may lead to erosion of the long process of the incus and the stapes suprastructure (Fig. 139-2).

Not all patients with chronic OME develop atelectasis; in most patients with OME, retraction of the tympanic membrane is limited. In patients with bilateral OME, 1.5% of untreated ears and 2% of ears treated with tubes developed severe atelectasis.[12] It may be that repeated bouts of AOM lead to weakening and thinning of the membrane, which allows atelectasis. Sadé and Berco[13] showed destruction of the collagen-containing fibrous layer of the tympanic membrane in some ears with recurrent infection. Collagen destruction within the tympanic membrane may lead to another complication of OME—tympanosclerosis. Sadé and Berco[13] and Tos and Poulsen[14] described four stages of tympanic membrane retraction: stage I, retracted tympanic membrane; stage II, retraction with contact onto the incus; stage III, middle ear atelectasis; and stage IV, adhesive otitis media (Fig. 139-3).

Middle ear atelectasis may be reversible with ventilating tubes. Sadé[15] showed that ventilating tubes improved the state of atelectatic ears. Graham and Knight[16] reported three cases in which atelectatic tympanic membranes were restored to their normal position by administration of nitrous oxide during anesthesia and insertion of a ventilating tube.

Atelectasis and adhesive otitis media usually coexist with OME, although OME may resolve in these ears, allowing aeration of the attic and mastoid, but leaving a collapsed middle ear. In extreme cases, when hearing loss or ossicular erosion occurs, a myringoplasty for the reinforcement of atelectatic tympanic membrane may be indicated.[6,17] Cholesteatomas may originate from deep retraction pockets in which desquamated keratin debris would not be cleared into the ear canal.[18,19] These retraction pockets may occur in the pars tensa or pars flaccida of atelectatic ears, and should be considered precursors to cholesteatomas (see discussion of cholesteatoma). Nonpneumatized mastoids may have a limited ability to buffer pressure changes and can manifest as an atelectasis, a retraction pocket, or a cholesteatoma.[20]

Chronic Otitis Media with Cholesteatoma

Aural cholesteatomas are epidermal inclusion cysts of the middle ear or mastoid (in the case of a retraction pocket cholesteatoma, the "cyst" opens into the external auditory canal). They contain the desquamated debris (principally keratin) from their keratinizing, squamous epithelial lining. Cruveilhier[21] first described aural cholesteatoma as a "pearly tumor" of the temporal bone. The term *cholesteatoma,* coined by the German physiologist Müller[22] in 1838, is a misnomer because this entity does not contain cholesterol; the white-yellow keratin flakes found within cholesteatomas grossly resemble cholesterol crystals. Cholesteatomas of the temporal bone may be congenital or acquired.

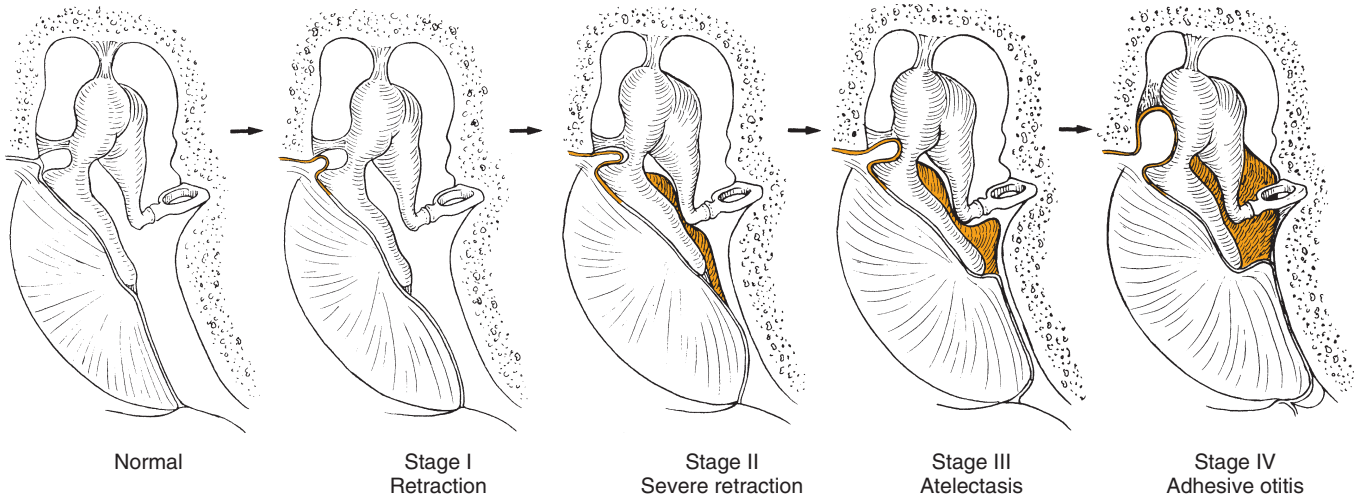

Figure 139-3. Four stages of middle ear atelectasis. *(Adapted from Sadé J, Berco E. Atelectasis and secretory otitis media.* Ann Otol Rhinol Laryngol. *1976;85(Suppl 25):66.)*

Acquired cholesteatomas are the consequence of OME, AOM, or both. An understanding of the pathogenesis and pathophysiology of aural cholesteatoma is particularly important because the destructive nature of this entity is responsible for much of the morbidity associated with chronic otitis media. The propensity of cholesteatomas to erode bone and the lack of effective, nonsurgical management add importance to the understanding of this disease.

Diagnosis

The diagnosis of aural cholesteatoma is made on otoscopic examination, including endoscopic and microscopic evaluation or surgical exploration. Special imaging procedures, such as high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), may suggest the presence of cholesteatomas within the temporal bone, and may be used to complement the clinical examination. High-resolution CT is useful for operative planning and is recommended for all revision mastoid operations. The symptoms of cholesteatoma vary; some cholesteatomas are asymptomatic, whereas others become infected and rapidly cause bone destruction. Some patients seen by the physician show slowly progressive conductive hearing loss, and frequently patients with cholesteatomas consult a physician because of chronic otitis with purulent otorrhea. The otorrhea from an infected cholesteatoma often is malodorous because of the frequent infection with anaerobic bacteria.[23]

Patients with infected cholesteatoma occasionally are misdiagnosed as having external otitis. Careful follow-up evaluation and thorough canal débridement of a patient with otorrhea are mandatory because the cholesteatoma may not be evident during an acute flare-up. Some patients have signs and symptoms of the complications of a cholesteatoma: vertigo and hearing loss caused by a labyrinthine fistula, facial nerve paralysis, or intracranial infection.

The otoscopic appearance of an aural cholesteatoma also varies. A typical attic retraction cholesteatoma (Fig. 139-4) appears as a defect of variable size adjacent to the posterosuperior portion of the tympanic membrane. The center of the defect contains keratin debris (primary acquired cholesteatoma). In other patients, keratinizing epithelium has migrated through a perforation into the middle ear (secondary acquired cholesteatoma) (Fig. 139-5). Cholesteatomas sometimes appear behind or within an intact tympanic membrane—so-called congenital cholesteatoma (Fig. 139-6). These cholesteatomas have been considered to be congenital, but more recent experimental evidence raises the possibility that they may originate during an inflammatory process.[24] An infected cholesteatoma sometimes manifests as an "aural polyp." These "polyps" actually are granulation tissue at the junction between an eroding cholesteatoma and bone. The presence of an aural polyp in a chronically infected ear should be considered to be a cholesteatoma until proved otherwise. Occasionally, a cholesteatoma cannot be seen otoscopically, but is discovered during tympanomastoid surgery.

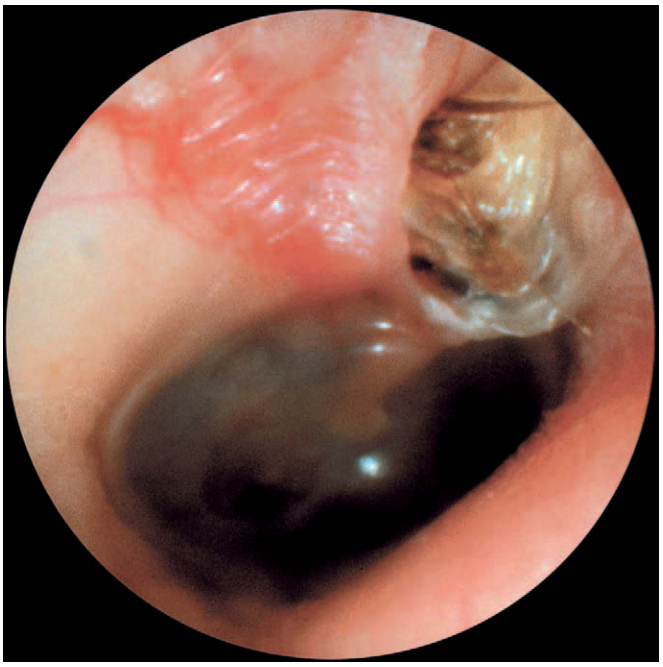

Figure 139-4. Primary acquired cholesteatoma in the region of the pars flaccida with scutum erosion.

The exact prevalence of cholesteatoma is unknown. In 1978, there were 4.2 hospital discharges per 100,000 population with cholesteatoma.[25] In addition, there were 13.8 hospital discharges per 100,000 population with chronic otitis media without cholesteatoma. Studies by Harker[23] documented an annual incidence of 6 cholesteatomas per 100,000 population. Tos[26] found an annual incidence of 3 cholesteatomas in children and 12.6 cholesteatomas in adults per 100,000 population. In the human temporal bones with chronic otitis media, cholesteatoma was observed in 36% of ears with perforations and in 4% of ears without the perforated tympanic membranes.[27]

Pathogenesis

Congenital cholesteatomas, by definition, originate from areas of keratinizing epithelium within the middle ear cleft. Michaels[28] showed that

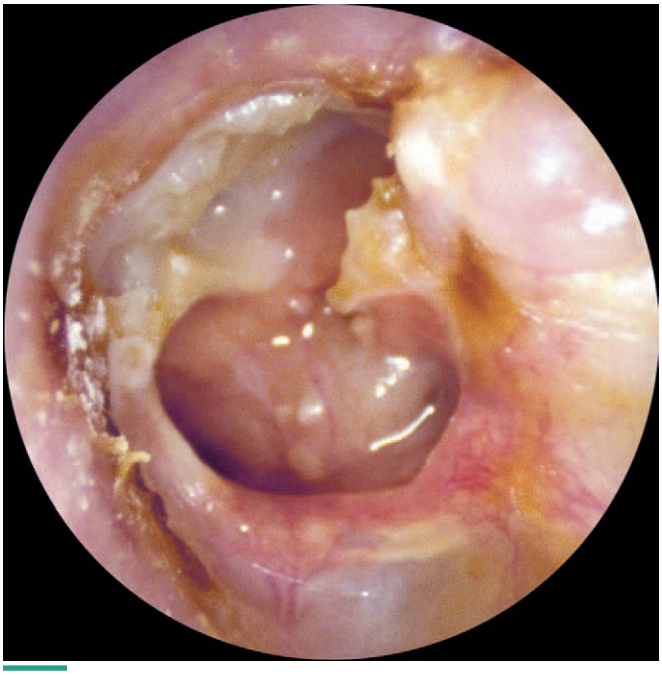

Figure 139-5. Cholesteatoma developing at the margin of perforation (secondary acquired cholesteatoma) with secondary infection.

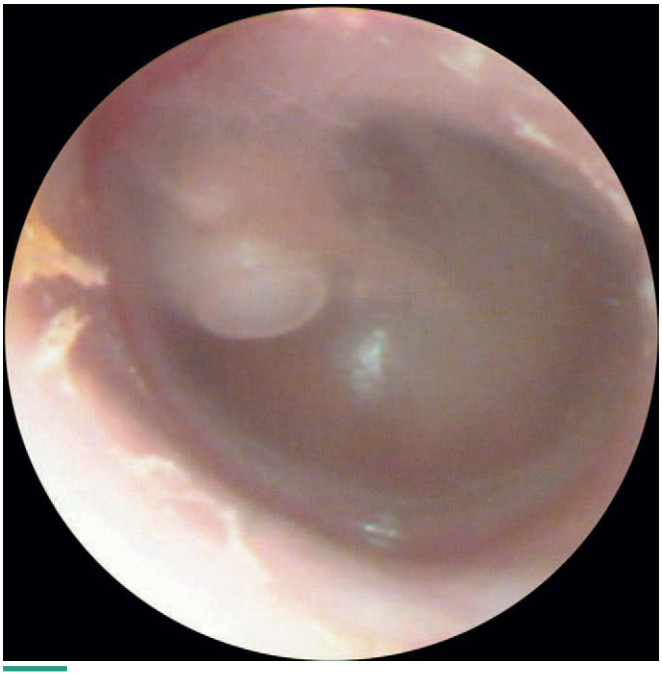

Figure 139-6. Cholesteatoma behind intact tympanic membrane.

a small area in the anterior tympanum in the developing fetus often contains a small area of keratinizing epithelium. He found epidermoid formation in 37 of 68 temporal bones of fetuses at 10 to 33 weeks' gestation. Congenital cholesteatomas may originate in this region. Although congenital cholesteatomas generally are seen as pearl-like masses behind an intact membrane, Koltai and coworkers[29] presented a convincing case that some congenital cholesteatomas advance to perforate and become chronically infected, taking on the appearance of an acquired cholesteatoma. Potsic and colleagues,[30] in a review of 172 series of congenital cholesteatomas, developed a useful staging system: stage I, limited to one quadrant; stage II, involving multiple quadrants without ossicular involvement; stage III, ossicular involvement without mastoid extension; and stage IV, mastoid involvement. They showed a correlation between stage and risk of residual disease; stage IV carries a 67% risk of residual cholesteatoma.

The pathogenesis of *acquired* cholesteatoma has been debated for more than a century. There are four basic theories of the pathogenesis of acquired aural cholesteatoma: (1) invagination of the tympanic membrane (retraction pocket cholesteatoma), (2) basal cell hyperplasia, (3) epithelial ingrowth through a perforation (the migration theory), and (4) squamous metaplasia of middle ear epithelium (Fig. 139-7). Additionally, Sudhoff and Tos[19] proposed a combination of the invagination and basal cell theories as an explanation for retraction pocket cholesteatoma formation.

Invagination Theory

The invagination theory[5] of the genesis of cholesteatoma generally is regarded as one of the primary mechanisms of the formation of attic cholesteatomas. Retraction pockets of the pars flaccida deepen because of negative middle ear pressure and possibly repeated inflammation (see Fig. 139-2). As the retraction pocket deepens, desquamated keratin cannot be cleared from the recess, and a cholesteatoma results. The origin of such retraction pocket cholesteatomas is thought to be eustachian tube dysfunction (or OME) with resultant negative middle ear pressure (*ex vacuo* theory). Usually, the pars flaccida, being less fibrous and less resistant to displacement, is the source of the cholesteatoma.

The result of this type of cholesteatoma (so-called primary acquired cholesteatoma) is an apparent defect in the posterosuperior quadrant of the tympanic membrane and erosion of the adjacent canal wall.[31] Although these defects have the appearance of a marginal perforation, it is not a perforation, but rather an invagination. Sadé[20] showed that epithelial migration patterns within attic retraction pockets are altered. This failure of epithelial migration may allow the accumulation of keratin within a retraction pocket, with subsequent enlargement merely from the accumulation of keratin within a relatively closed space. This theory has been supported by the experimental creation of retraction pockets by use of the eustachian tube obstruction,[32] and external auditory canal ligation.[33]

Ruah and colleagues[31] suggested that inflammation of middle ear and persistent mesenchyme lead to a greater inflammatory reaction in pars flaccida and posterosuperior quadrant of the tympanic membrane of the human temporal bones with serous and purulent otitis media in children. These findings support this theory of primary acquired cholesteatoma in children. Retraction pockets are considered as precursors to cholesteatoma. Bacteria can infect the keratin matrix, forming biofilms leading to chronic persistent infection. The presence of bacterial biofilms in the cholesteatoma matrix may lead to epithelial proliferation and invasion of the cholesteatoma.[34,35]

Basal Cell Hyperplasia Theory

Another possible mechanism for the histogenesis of cholesteatoma was suggested by Lange in the 1920s.[49] In this theory, he proposed that epithelial cells (prickle cells) of the pars flaccida could invade the subepithelial tissue by means of proliferating columns of epithelial cells. Nearly 40 years later, Ruedi[50] supported this hypothesis with clinical and experimental evidence. For epithelium to invade into the lamina propria, the basal lamina (basement membrane) should be altered. Basal lamina disruptions now have been documented in human[51,52] and animal[53] cholesteatomas.

Huang and colleagues[54] and Masaki and coworkers[55] provided experimental support of this theory by showing that epithelial ingrowth from the tympanic membrane can be induced by instillation of propylene glycol into the middle ear of chinchillas. These basal lamina breaks allow the invasion of epithelial cones into the subepithelial connective tissue and the formation of microcholesteatomas. This mechanism may explain some types of human cholesteatomas, even those occurring behind an intact tympanic membrane.[56] According to this theory, microcholesteatomas may enlarge and then perforate secondarily through the tympanic membrane, leaving the typical appearance of an attic cholesteatoma. This sequence of events has not been documented, although the alternations in the differentiation of keratinocytes and basal cell layer of cholesteatoma matrix have been observed in several studies.

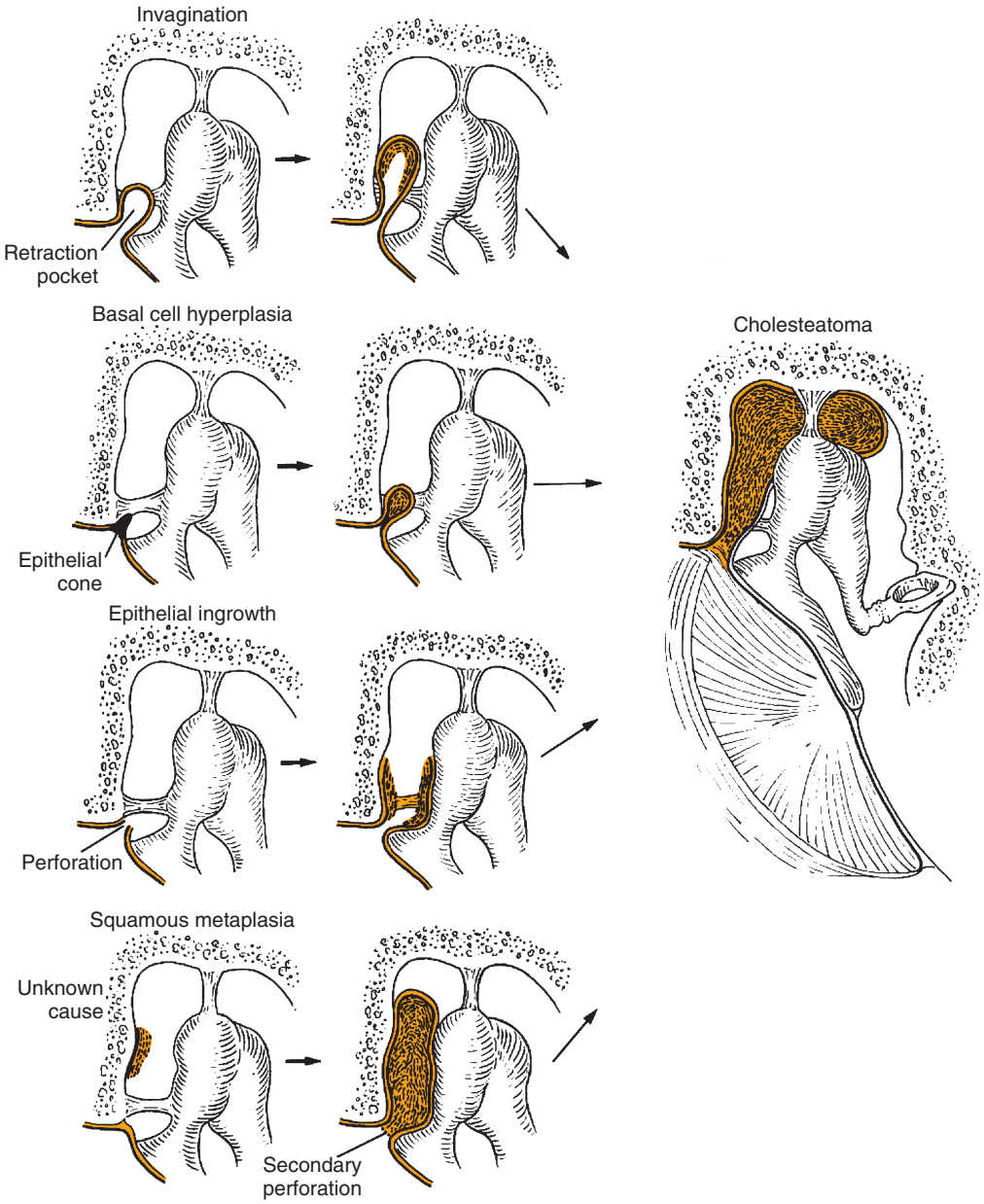

Figure 139-7. Theories of pathogenesis of aural cholesteatoma.

Abnormal distribution of epidermal differentiation markers, such as filaggrin and involucrin,[57] c-jun and p53 proteins,[58] and increased epidermal growth factor receptor,[59,60] has been shown in middle ear cholesteatoma matrix. Increased levels of proteins cytokeratin 13 and cytokeratin 16, which are markers for differentiation and hyperproliferation, were also found.[61] Kim and Chole[39] showed the increased expression of cytokeratin 13 and cytokeratin 16 in the area of the peripheral area of the pars tensa of induced cholesteatoma by ear canal ligation and in the peripheral and central area of pars tensa of induced cholesteatoma by eustachian tube obstruction. Sakamoto and associates[62] found ErbB-2 protein to be overexpressed, and cell proliferation and apoptosis of keratinocytes accelerated. Caspases play a key role in apoptosis; Miyao and coworkers[63] suggested that caspase-8, which is activated by the induction of tumor necrosis factor-α, leads to activation of caspase-3, which activates apoptotic nucleases in cholesteatoma tissue.

Human toll-like receptors are crucial in the induction and activation of innate immunity in the course of an infection. Expression of toll-like receptor–3 on the epithelium and some cells within the perimatrix and the presence of T cells may suggest that apart from innate immune responses, mechanisms of adaptive immunity also operate in cholesteatoma.[64] Data from Parisier and colleagues[65] suggested that fibroblasts in the subepithelium of cholesteatomas showed an invasive phenotype, whereas fibroblasts from postauricular and ear canal skin appeared either weakly invasive or not invasive. In a similar study, Chole and colleagues[66] found that normal fibroblasts and fibroblasts from induced cholesteatomas did not exhibit the invasive phenotype characteristics of true neoplastic cells.

Other lines of evidence support the basal cell hyperplasia/migration theory. Increased expression of human intercellular adhesion molecule-1 and intercellular adhesion molecule-2 has been shown, suggesting a role in cell migration into tissue.[40] The presence of heat shock proteins 60 and 70 suggested proliferation and active differentiation of basal keratinocytes in cholesteatomas.[58] There are some reports that immune response is involved in the hyperproliferative state of cholesteatoma epithelium.[52,67,68] Langerhans cells may initiate immune reaction and promote proliferation of keratinizing epithelium via an interleukin (IL)-1α and transforming growth factor (TGF)-β mechanism.[42,67,69]

Epithelial Invasion Theory

The epithelial invasion theory[36] states that keratinizing squamous epithelium from the surface of the tympanic membrane invades or migrates into the middle ear from a perforation in the tympanic membrane. This theory is supported by clinical observation and experimental evidence. Weiss[37] showed that epithelial cells could migrate along a surface by a process that he called *contact guidance,* and that, when they encounter another epithelial surface, they stop migrating, for which he used the term *contact inhibition*. van Blitterswijk and Grote[38] reported that cytokeratin 10, which was seen in the meatal epidermis and migrating epithelium, was preferentially expressed in the cholesteatoma matrix, rather than in the middle ear mucosa. This finding suggests an epidermal origin of cholesteatoma. Kim and Chole[39] showed increased cytokeratin 10 expression in the peripheral area of the pars tensa of induced cholesteatoma by ear canal ligation and in the peripheral and the central area of the pars tensa of induced cholesteatoma by eustachian tube obstruction. The findings of this study also support the basal cell hyperplasia hypotheses for the pathogenesis of aural cholesteatoma, with regard to hyperproliferation, migration, and an altered differentiation of keratinocytes.[39] High levels of fibronectin and tenascin and focal disruptions of the basement membrane, were reported in the middle ear cholesteatoma, supporting the concept of the invasion theory.[40-43]

This theory also is supported by investigations in animal cholesteatoma models and human temporal bones. Jackson and Lim[44] gave histologic and ultrastructural evidence that keratinizing epithelium can migrate into the cat bulla by contact guidance. It is likely that in some tympanic membrane perforations, inflammation damages the inner mucosal lining of the tympanic membrane, allowing the outer keratinizing epithelium to migrate inward and generate a cholesteatoma. Hueb and associates[45] showed similar evidence in chinchillas. Palva and colleagues[46] showed histologic evidence for this theory in human temporal bones. Cholesteatomas originating after temporal bone fractures may result from this mechanism; fractures within the ear canal may allow ingrowth of keratinizing epithelium by contact guidance.[47] 7,12-Dimethylbenz[a]anthracene, a chemical carcinogen, could induce the advancing of the keratinizing squamous epithelium into or under the mucosal layer, and ingrowth and spreading over the middle ear cavity and eustachian tube in the rat ear.[48]

Squamous Metaplasia Theory

Wendt[70] theorized that the simple squamous or cuboidal epithelium of the middle ear cleft could undergo a metaplastic transformation into keratinizing epithelium. Sadé[15,71] supported this theory, noting that epithelial cells are pluripotent and can be stimulated by inflammation to become keratinizing. According to this theory, an area of keratinizing epithelium within the middle ear would enlarge because of accumulated debris and contact with the tympanic membrane. With intercurrent infection and inflammation, the cholesteatoma would lead to lysis of the tympanic membrane and perforation, resulting in the typical appearance of an attic cholesteatoma. This theory is supported by the demonstration that biopsy specimens from the middle ear of children with OME sometimes contain islands of keratinizing epithelium.[15]

Some experimental evidence supports the contention that middle ear mucosa can become metaplastic and keratinize. Chole and Frush[72] showed that extreme vitamin A deficiency leads to the formation of keratinizing epithelium within the middle ear and eustachian tube of rats. None of their experimental animals had developed cholesteatomas. Consequently, there is no direct evidence that cholesteatomas arise by squamous metaplasia of the middle ear mucosa.

From a clinical perspective, it seems that each of these pathogenic mechanisms accounts for a proportion of acquired cholesteatomas. Regardless of the pathogenesis of aural cholesteatomas, they all share certain properties. Cholesteatomas are prone to recurrent infection, and they characteristically erode the bone of the ossicles and the otic capsule. Aural cholesteatomas originating from the vicinity of the tympanic membrane exhibit typical growth patterns into the temporal bone. Because most acquired cholesteatomas originate by invagination of the pars flaccida, their growth is limited by the mucosal folds and suspensory ligaments of the ossicles. The pars flaccida may invaginate into the lateralmost portion of the epitympanum (Prussak's space) and then into the recesses of the epitympanum posteriorly, lateral to the body of the incus, inferiorly into the middle ear by way of the pouch of von Tröltsch (Fig. 139-8), or anteriorly into the protympanum (Fig. 139-9).[73-75]

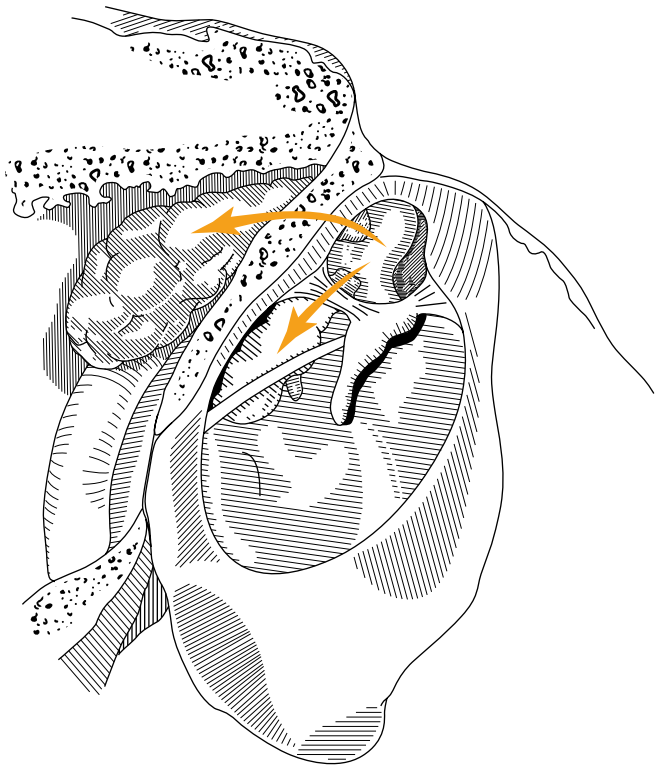

Figure 139-8. Posterior mesotympanic cholesteatoma. This sac forms because of retraction of the posterior portion of the pars tensa, and frequently invades the sinus tympani and facial recess. Extension to the mastoid occurs medial to ossicle heads *(arrows)*. *(From Jackler RK. The surgical anatomy of cholesteatoma.* Otolaryngol Clin North Am. *1989;22:883.)*

Complications

The expansion of cholesteatoma may result in bone erosion of the ossicles, otic capsule, fallopian canal, tegmen tympani, and tegmen mastoideum. These complications may cause intracranial complications (Box 139-1). The erosion of ossicles, most commonly in the incus, may result in conductive hearing loss. The severity of hearing loss is related to the status of the ossicles and the position of the cholesteatoma sac. Erosion of the otic capsule occurs most commonly in the lateral semicircular canal and rarely in the cochlea. A labyrinthine fistula has been reported in 10% of cholesteatomas in adults and children,[76] which may result in sensorineural hearing loss and vertigo. Sensorineural hearing loss may result from the secondary suppurative labyrinthitis or from the cochlear hair cell loss adjacent to cholesteatoma.[66] Facial nerve paralysis may occur acutely as a result of infection or slowly as a result of expansion of the cholesteatoma. Erosion of the tegmen tympani or the tegmen mastoideum may lead to development of a brain hernia or cerebrospinal fluid leakage.[77]

Because cholesteatomas contain keratin debris enclosed in a tissue space, they are subject to recurrent infection. The bacteria found in infected cholesteatomas differ from bacteria found in AOM or OME. Significant anaerobic bacteria are present. The most common aerobic bacterium is *Pseudomonas aeruginosa,* and the most common anaerobic microorganism is *Bacteroides* sp (Table 139-1).[78]

Management

Congenital and acquired cholesteatomas can be eradicated from the temporal bone only by surgical resection. The goals of surgery are to

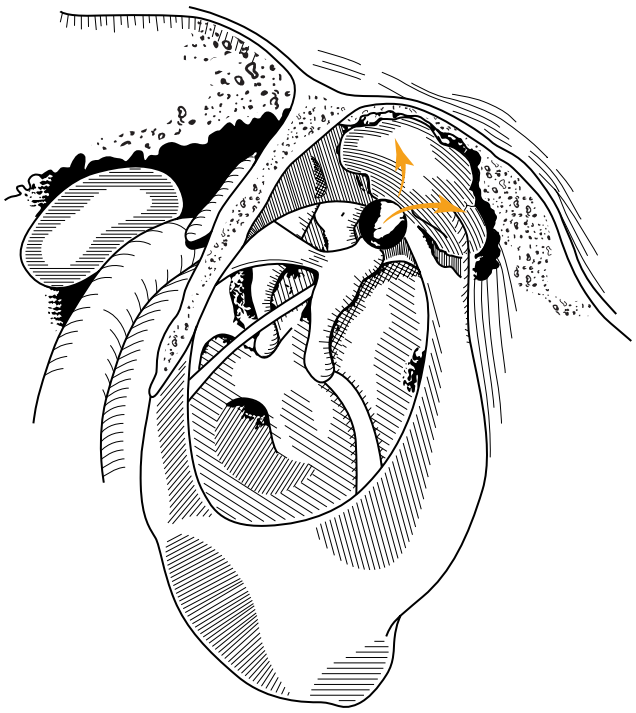

Figure 139-9. Anterior epitympanic cholesteatoma. Invagination of the epitympanum anterior to the malleus head and neck creates a cholesteatoma sac that threatens the horizontal facial nerve and geniculate ganglion. Forward extension into the supratubal recess is common (*arrows*). *(From Jackler RK. The surgical anatomy of cholesteatoma.* Otolaryngol Clin North Am. *1989;22:883.)*

Table 139-1

Bacteriology of Infected Cholesteatomas in 30 Children and Adults

Bacteria	No. of Cases
Aerobes	
Pseudomonas aeruginosa	11
Pseudomonas fluorescens	2
Streptococcus sp	8
Proteus sp	4
Escherichia coli	4
Klebsiella, Enterobacter, Serratia	4
Alcaligenes, Achromobacter	3
Staphylococcus epidermidis	2
Staphylococcus aureus	1
CBC group F	
Anaerobes	
Bacteroides sp	13
Peptococcus, Peptostreptococcus	11
Propionibacterium acnes	8
Fusobacterium sp	4
Bifidobacterium sp	3
Clostridium sp	3
Eubacterium sp	2

Modified from Harker LA, Koontz FP. The bacteriology of cholesteatomas. In: McCabe BF, Sadé J, Abramson M, eds. *Cholesteatoma: First International Conference*. New York: Aesculapius Publishers; 1977.

Box 139-1

Complications and Emergency States of Chronic Otitis Media with Cholesteatoma

Hearing loss—conductive, sensorineural, mixed type
Labyrinthine fistula—mainly horizontal semicircular canal, rarely cochlea
Facial nerve paralysis—acute or chronic
Intracranial infections
Brain hernia or cerebrospinal fluid leakage

eradicate disease and manage complications and, secondarily, to reconstruct the middle ear. The decision whether to perform surgery depends on the nature and extent of disease, the existence of complications, mastoid pneumatization, eustachian tube function, hearing status of both ears, the reliability of the patient, and the experience and skill of the surgeon.[77,79] Surgical approaches include atticotomy, simple mastoidectomy, canal wall-up or canal wall-down procedures, radical mastoidectomy, modified radical mastoidectomy, and Bondy procedure.

The open (canal wall-down) and the closed (intact canal with facial recess) procedures have advantages and disadvantages (Table 139-2). The reported results of both procedures vary. Residual disease and recurrent disease occur in 11% to 27% and 5% to 13% of patients undergoing the closed procedure, whereas residual or recurrent disease occurs in 2% to 10% of patients undergoing the open procedure.[80] In the cases of labyrinthine fistula, facial nerve paralysis, and intracranial complications, surgery should be performed as soon as possible.

In some patients, a cholesteatoma can be débrided of entrapped keratin by direct removal or by irrigation. In some cases, surgical intervention is impossible or not advisable; the patient may not be medically able to withstand surgery, or the risks of surgery may not outweigh the benefits in some patients with only-hearing ears. Irrigation with 1:1:1 distilled white vinegar, distilled water, and 70% isopropyl alcohol may keep some cholesteatomas stable if their opening into the ear canal is sufficiently large (Box 139-2). If surgery is required for a cholesteatoma in an only-hearing ear, careful preoperative evaluation and operative planning, perioperative use of antibiotics and steroids, ossicular reconstruction, and postoperative care should be considered.[81]

Chronic Otitis Media without Cholesteatoma

Acute or recurrent infection of the middle ear may result in a permanent perforation of the tympanic membrane. Ears with chronic perforations without cholesteatoma may be chronically or intermittently infected. Three times as many operations were performed in the United States for this disease as were performed for cholesteatomas.[25] Paparella and Kim[81a] reported that of 375 primary tympanomastoid operations for chronic mastoiditis, two thirds were performed in ears with granulation tissue and without cholesteatoma.

Diagnosis

Tympanic membrane perforation (Fig. 139-10) may result from AOM, chronic otitis media, or trauma (injury or surgery). In some instances, a dry, simple perforation results from a single episode of AOM (i.e., necrotizing otitis media). Perforation of the tympanic membrane, especially involving the tympanic anulus, may allow ingrowth of the keratinizing epithelium of the ear canal or tympanic membrane, leading to cholesteatoma. An ear with a simple perforation may become infected because of contamination from the ear canal or because of a smoldering infection in the mastoid. A simple perforation commonly is seen as a low-frequency conductive hearing loss clinically. This finding is supported by experimental perforation in rats.[82] The tympanic membrane velocity was found to be decreased in the low frequency in a small perforation and in the high and low frequencies in a large perforation.[83]

Table 139-2

Advantages and Disadvantages of Canal Wall-Up and Canal Wall-Down Procedures in Chronic Otitis Media with Cholesteatoma

Advantages	Disadvantages
Canal Wall-Up	
Physiologic position of tympanic membrane	Residual and recurrent cholesteatoma may occur
Enough middle ear space	Incomplete exteriorization of facial recess
No mastoid cavity problem	Second-stage operation often required
Canal Wall-Down	
Residual cholesteatoma easily found on follow-up evaluation	Mastoid cavity problem often
Recurrent cholesteatoma rare	Middle ear shallow and difficult to reconstruct
Total exteriorization of facial recess	Position of pinna may be altered; second-stage operation sometimes required

Modified from Harker LA, Koontz FP. The bacteriology of cholesteatomas. In: McCabe BF, Sadé J, Abramson M, eds. *Cholesteatoma: First International Conference*. New York: Aesculapius Publishers; 1977.

Box 139-2

Management of Chronic Otitis Media with Cholesteatoma

Factors for Determination of Treatment

Extent of disease
Presence of complications
Hearing states of both ears
Eustachian tube function
Mastoid pneumatization
Patient factors: general medical condition, age, occupation, reliability
Surgeon's skill

Conservative Treatment

Removal of entrapped keratin: direct
Irrigation with 1:1:1 distilled white vinegar, distilled water, and 70% isopropyl alcohol for stabilization

Surgical Approach

Atticotomy: transcanal
Simple mastoidectomy
Canal wall-up procedure (intact wall) with or without facial recess approach
Canal wall-down procedure (canal down): radical or modified radical mastoidectomy, Bondy procedure

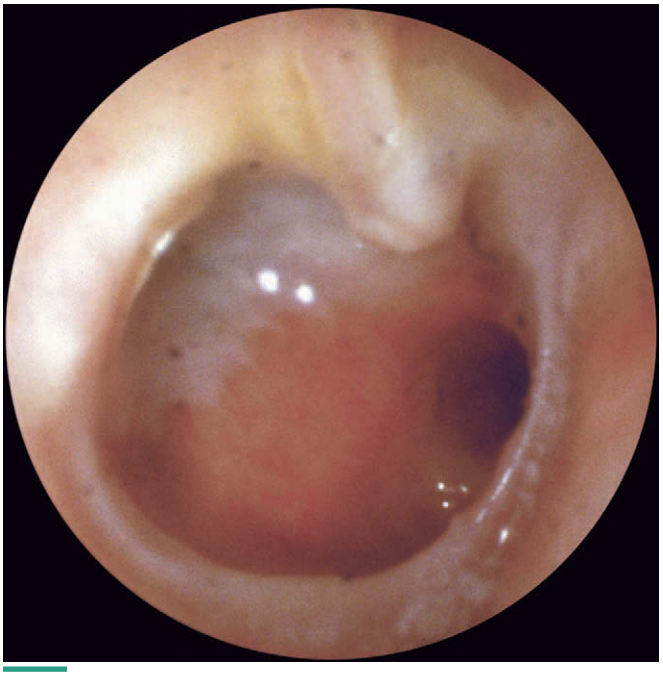

Figure 139-10. Tympanic membrane perforation.

Pathogenesis

Chronic otomastoiditis without cholesteatoma is marked by the presence of irreversible inflammatory changes within the middle ear and mastoid. The factors that allow acute infections within the middle ear and mastoid to develop into chronic infections are unclear. da Costa and colleagues[27] found granulation tissue in 96%, ossicular changes in 96%, tympanosclerosis in 43%, cholesteatoma in 36%, and cholesterol granuloma in 21% of the human temporal bones of patients with chronic otitis media with a perforated tympanic membrane (Table 139-3). Aeration of the middle ear, antrum, and mastoid depends on the free movement of gases from the eustachian tube into the mastoid air cells. In the human temporal bone, gases must travel around the ossicles in the epitympanic space to get into the antrum (Fig. 139-11).

Proctor[74] showed that the middle ear is separated from the antrum not only by the ossicles, but also by mucosal folds. He found that there were only two constant openings: (1) between the tendon of the tensor tympani muscle and the stapes, and (2) between the short process of the incus and the stapedial tendon. Edema and inflammation with granulation tissue may block these communicating openings, preventing drainage of the antrum and mastoid. Chronic obstruction of the attic and antrum with infection leads to "irreversible" changes in the mucosa and bone of the antrum and mastoid. Granulation tissue within the temporal bone can lead to bone erosion; 4 of 123 temporal bones in this series had active bone erosion. Thomsen and colleagues[84] found that bone erosion in patients with chronic otitis media was more prevalent when cholesteatoma was present, but it still occurred in the absence of cholesteatoma. Moriyama and associates[85] found osteoclastic bone resorption in rats with chronic otitis media.

Chronic otitis media may occur in patients who have indwelling tympanostomy tubes. Otorrhea may be a complication of tympanostomy tube insertion; it has been reported to occur in 9% to 34% of children undergoing this procedure.[86] Chronic otorrhea that is resistant to therapy has been reported to occur in 5.5% of children with tubes.[87]

Table 139-3

Pathologic Findings in the Temporal Bones with Chronic Otitis Media

Pathologic Finding	Perforated Tympanic Membrane (n = 116) (%)	Nonperforated Tympanic Membrane (n = 28) (%)
Granulation tissue	113 (97.4)	27 (96.4)
Ossicular changes	105 (90.5)	27 (96.4)
Tympanosclerosis	23 (19.8)	12 (42.9)
Cholesterol granuloma	14 (12.1)	6 (21.4)
Cholesteatoma	5 (4.3)	10 (35.7)

Modified from da Costa SS, Paparella MM, Schachern PA, et al. Temporal bone histopathology in chronically infected ears with intact and perforated tympanic membranes. *Laryngoscope*. 1992;102:1229.

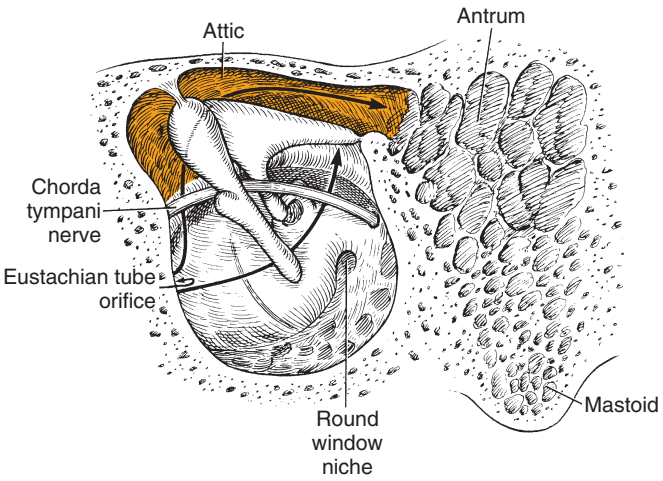

Figure 139-11. Aeration of the antrum and mastoid depends on communication around the ossicle within the attic. Obstruction of these narrow openings may result in chronic infection.

It is unclear whether such chronic infection is a result of the indwelling tube or of the drainage of an already smoldering infection. Giebink and coworkers[88] found the risk of otorrhea on the second postoperative day was significantly increased by the presence of a bacterial pathogen in the ear canal or in the middle ear effusion, and by the presence of inflamed middle ear mucosa at tympanostomy tube insertion. The bacteria that are found in such cases are bacteria found in chronic otitis media generally: *P. aeruginosa* and *Staphylococcus aureus*. Erkan and colleagues[89] reported the culture results of aspiration of exudate in 183 patients with chronic otitis media. Aerobes were found in 39% of the samples, anaerobes were found in 11%, and aerobes and anaerobes were found in 50%. *P. aeruginosa, S. aureus,* and *Klebsiella pneumoniae* were commonly found in aerobes, and *Bacteroides* sp were most commonly isolated in anaerobes. The colonization of tympanostomy tubes in the form of microbial biofilms may lead to persistence and recurrence of infection.[90]

Management

Most infected perforations can be managed conservatively with topical antibiotics. Antibiotic otic suspensions with or without steroids usually are effective. The antibiotics should be chosen to eradicate the most common pathogens, *P. aeruginosa* and *S. aureus*. In cases with recurrent or chronic infections, cultures should be used to adjust antibiotics. Many topical otic antibiotic preparations contain potentially ototoxic substances, including aminoglycoside antibiotics and propylene glycol. Studies of these substances applied to the middle ear have shown ototoxicity in rodents[91] and primates.[92] Although there are reports suggesting that sensorineural hearing loss may occur after topical use of these preparations,[93,94] no conclusive evidence is available proving ototoxicity of commercially available otic preparations in the human middle ear.

Potentially ototoxic topical preparations should be applied to the middle ear only when potential benefits outweigh the potential risks. Topical antibiotics also can be applied in powder form by insufflation. Various agents have been used individually or in combination, including boric acid, sulfamethoxazole, chloramphenicol, and hydrocortisone. This technique is particularly useful in the presence of epithelialitis and in a moist mastoid cavity, although patients may become sensitized to sulfamethoxazole or amphotericin. Systemic antibiotics should be used in refractory cases when specific pathogens are found on culture. Several quinolones such as ciprofloxacin, ofloxacin, and norfloxacin may be useful in these patients. In ears that become repeatedly infected but clear between episodes, tympanoplasty should be considered. Ideally, an ear with a tympanic membrane perforation should be free from infection for 3 months before tympanoplasty.

In some patients, chronic infection with otorrhea, but without cholesteatoma, persists despite aggressive medical therapy. In these cases, two options should be considered: long-term (6 to 8 weeks) intravenous antibiotics or tympanomastoid surgery. Antibiotic therapy can be administered at home or in the hospital. Aggressive local débridement is required. The goals of tympanomastoidectomy include aeration of the middle ear and mastoid, removal of irreversibly diseased tissue, closure of the middle ear, and reconstruction of the sound-conducting mechanism. These goals are not always achieved in a single stage.

Otorrhea occurs after insertion of tympanostomy tubes in approximately 10% of ears. The incidence of immediate postoperative otorrhea usually can be decreased by the use of topical antibiotics at the time of tube insertion.[95,96] The use of Silastic tympanostomy tubes impregnated with silver oxide was shown to decrease the incidence of otorrhea significantly in a randomized clinical trial.[86] If infection persists, intravenous antibiotic therapy directed at specifically identified organisms should be considered. Because chronically infected tympanostomy tubes may have persistent bacterial biofilms, removal of the tympanostomy tube may be necessary in some refractory cases.[90,97]

Bone Erosion in Cholesteatoma and Chronic Otitis Media

In Virchow's description of the pathology of aural cholesteatoma in 1854, he noted that "the cholesteatoma extended through the bone to the external auditory canal, sometimes, also, in the cranial cavity."[98] Since that time, clinicians and investigators have studied the pathophysiology of bone resorption from this disease. Although much progress has been made in the understanding of the resorptive process, the actual sequence of events and their relative importance are not completely understood.

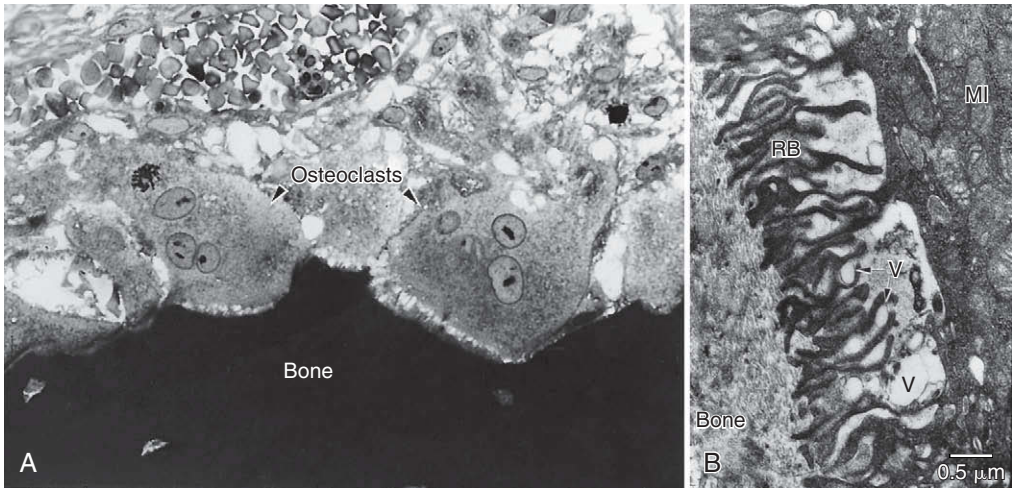

Figure 139-12. **A,** Multinucleated osteoclasts actively absorbing bone beneath human cholesteatoma in a surgical biopsy specimen. **B,** Transmission electron micrograph of the ruffled border (RB) of an osteoclast showing mitochondria (MI) in the cytoplasm and vacuoles (V) containing acid proteases in the eroding zone.

In the first half of the 20th century, it was believed that the bone resorption seen adjacent to cholesteatomas was a result of pressure necrosis,[99] although clinical observations led to the abandonment of the pressure necrosis theory. It was thought to be highly unlikely that cholesteatomas could exert pressure exceeding capillary perfusion pressure (approximately 25 mm Hg), and this was later confirmed by Orisek and Chole[100] using direct measurements of the pressure exerted by experimental cholesteatomas (1.3 to 11.9 mm Hg). Lautenschlager[101] first suggested that cholesteatomas may elaborate enzymes that directly erode bone, and some investigators showed that cultured human cholesteatoma could degrade guinea pig collagen.[63,102] Direct extracellular dissolution of bone was never shown, however.

It is now clear that inflammatory processes in the temporal bone induce the development and activation of osteoclasts, the only cell capable of resorbing bone. Several early human temporal bone studies revealed osteoclastic bone resorption adjacent to cholesteatoma matrix.[103,104] Because of the relative scarcity of osteoclasts seen in surgical specimens, however, numerous investigators hypothesized that mononuclear histiocytes were the predominant cell associated with erosive cholesteatomas.[105-107] Bernstein and colleagues[108,109] noted that early studies were based on biopsy material taken during tympanomastoid surgery, and surgery often is preceded by attempts to control active inflammation; biopsy material may represent the reparative phase instead of the resorptive phase. Chole[110] showed ultrastructural evidence in human and experimental cholesteatomas that bone resorption is primarily a result of the action of multinucleated osteoclasts on bone (Figs. 139-12 and 139-13). Although many mononuclear cells (histiocytes and fibroblasts) were present in the vicinity of active bone resorption, only multinucleated osteoclasts were seen to disrupt the lamina limitans of bone and cause resorption lacunae. It is established that multinucleated osteoclasts caused bone resorption in patients with cholesteatoma and chronic otitis media.[110-114]

For bone resorption to occur, enzymatic removal of the organic and inorganic components must occur. These enzymes likely are elaborated or activated by the resorbing cells (osteoclasts) in their immediate microenvironment. These enzymes include acid phosphatase,[54,110,115,116] collagenase,[54,116] and acid proteases.[117] In studies by Blair and colleagues,[117] a cathepsin-like proteolytic enzyme with maximal activity at pH 4.0 was shown to be active in the microenvironment of the ruffled border of the osteoclast.

Numerous factors may lead to localized osteoclast recruitment and activation in regions of inflammatory osteolysis. It has been shown that bone remodeling and bone loss are controlled by a balance between the receptor activator of NF-κB (RANK) and its ligand, RANKL.[113] The RANKL receptor, or RANK, has been identified on dendritic cells, chondrocytes, osteoclast precursors, and mature osteoclasts.[113] Hamzei and coworkers[118] indicated an increased number of osteoclast precursor cells in the perimatrix of cholesteatoma tissue concomitant with an enhanced expression of RANKL, osteoprotegerin, and macrophage colony-stimulating factor. The cholesteatoma-induced inflammatory process is associated with the release of RANKL from stromal cells and activated T cells, which triggers osteoclastogenesis.[113,118]

The localized control of osteoclastogenesis is complex, and signaling pathways may vary during the natural course of an inflammatory process. The type of bone undergoing resorption may also modify the process. The endochondral bone of the otic capsule seems to be more resistant to erosion than the intramembranous bone of the middle ear and mastoid.[119]

Some investigators have noted that the keratin debris within a cholesteatoma sometimes extrudes into the subepithelium adjacent to bone eliciting an inflammatory and osteoclastic response. Yuasa and colleagues[120] showed that the pH of keratin debris within cholesteatomas was acidic, which they believed led to demineralization of the hydroxyapatite of bone. Some investigators have shown that the keratin itself may induce an inflammatory reaction (foreign body granuloma), which leads to cellular bone resorption.[85,121,122]

The extracellular matrix exhibits alterations in cholesteatoma, and many studies have evaluated the role of enzymes in cholesteatoma-induced bone resorption. By immunocytochemistry and zymography, the expression of matrix metalloproteinases (MMP-1, MMP-2, MMP-3, and MMP-9) was found to be strictly confined to the basal and suprabasal cell layers of the cholesteatoma epithelium.[123-126] The neutrophil collagenase showed a more disseminated expression in the epithelium and the granulation tissue. The tissue inhibitor of metalloproteinases, TIMP-1, could be detected only in very limited areas of the granulation tissue in a quite randomized manner.[126] Because of their destructive capacity, matrix metalloproteinases are normally tightly controlled. A derailment of these regulatory mechanisms in favor of proteolysis was postulated to play a role in the invasion of cholesteatomas into the temporal bone.[125,126]

Collagenase plays an important role in the mechanism of local invasion by aural cholesteatoma.[116,127] Neutral collagenase may stimulate osteoclastic resorption by degrading the osteoid surface of bone, allowing osteoclastic activity.[128] Neutral collagenase has not been found within osteoclasts,[129] but has been localized in the vicinity of resorbing bone.[116] In the collagenase cascade, procollagenase is activated to collagenase by plasmin. Plasminogen is activated to plasmin by plasminogen activator. Plasminogen activator is thought to play a role in keratinocyte proliferation, migration, and differentiation.[130] Plasminogen activator can be divided into two types: tissue-type plasminogen activator and urokinase-type plasminogen activator. Tissue-type plasminogen activator is known to activate osteoclasts in vitro.[131] Naka-

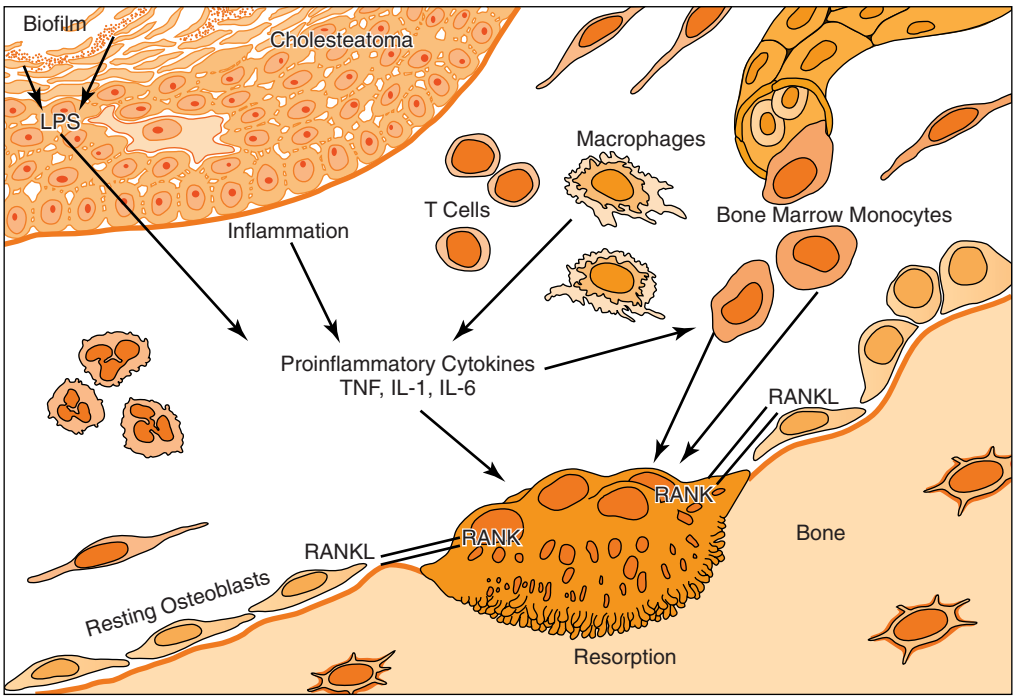

Figure 139-13. The bone resorption associated with cholesteatomas occurs as a result of the recruitment of osteoclasts. Osteoclasts are derived from bone marrow mononuclear cells. The receptor activator of NF-κB ligand (RANKL) on osteoblasts or T cells binds to receptor activator of NF-κB (RANK) on monocytes forming osteoblasts. Osteoclast activation is potentiated further by numerous proinflammatory cytokines (tumor necrosis factor [TNF], IL [interleukin]-1, IL-6) that are produced in response to factors produced by the cholesteatoma or bacterial products such as lipopolysaccharide (LPS).

mura and associates[132] showed both types of plasminogen activator in two of six tissue extracts of human cholesteatoma.

Ohsaki and colleagues[133] showed that bone adjacent to cholesteatomas is demineralized. Although their study suggested that demineralization by acidic cholesteatomas may explain bony destruction, intimate contact of the cholesteatoma matrix with bone does not seem to be necessary for bone resorption. Bone resorption has been shown to occur in patients with chronic otitis media with or without cholesteatoma.[84] Macri and Chole[134] showed that an implanted silicone barrier between a cholesteatoma and underlying bone did not prevent osteoclastic bone resorption in experimental cholesteatoma. It is likely that indirect effects (e.g., pressure or inflammation) may activate the cellular events of bone resorption.[135] More recent studies have shown that pressure with[85,136] or without[32,137] inflammation is sufficient to induce bone resorption in experimental animals. The histologic appearance of pressure-induced bone resorption is similar to that seen in cholesteatoma, showing osteoclasts and granulation tissue.[111] It has been postulated that the physical effects (pressure) of cholesteatomas may lead to transient electrical potentials[138] and the recruitment of monocytes into the subepithelial space. These monocytes may activate the downstream cellular events leading to bone resorption.

Activated monocytes can produce arachidonic acid metabolites such as prostaglandins and leukotrienes, which are potent inflammatory mediators. Prostaglandin E_2 (PGE_2)[139] has been shown to stimulate bone remodeling similar to the kallikrein-kinin system.[51] Prostaglandins, produced from the cyclooxygenase pathway of arachidonic acid metabolism, can be inhibited by aspirin, indomethacin, and ibuprofen. Indomethacin has been shown to impede bone resorption by inhibiting the production of PGE_2 in vitro.[140] This study also showed that in vivo indomethacin can inhibit pressure-induced bone resorption in an animal model. Ibuprofen, another prostaglandin inhibitor, has also been shown to inhibit bone resorption in a dose-dependent manner.[141] Leukotrienes are 5-lipoxygenase metabolites of arachidonic acid. Although the role of leukotrienes in cholesteatoma is unclear, the peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) stimulate isolated osteoclasts to accumulate tartrate-resistant acid phosphatase and resorb bone.[142]

Although the mechanism is unknown, osteoclast activity can be inhibited by bisphosphonates, also known as antiosteolytic agents such as 1-hydroxyethylidene-1,1-bisphosphonate (HEBP), risedronate, and zoledronate. These drugs inhibit the localized recruitment and activation of osteoclasts in vivo and in vitro.[143,144]

Proinflammatory cytokines play an important role in middle ear infections and cholesteatoma. They are released by macrophages, T lymphocytes, monocytes, and many other cells at the site of infection. IL-1 was identified in cholesteatoma matrix,[8] and was shown to stimulate fibroblasts and macrophages to produce PGE_2 and collagenase.[105] Cultured cholesteatoma specimens produced IL-1α and IL-1β, and both isoforms have been detected within cholesteatoma tissue.[41,145,146] IL-1α and IL-1β are potent inducers of bone resorption and may act by increasing PGE_2. Human recombinant IL-1 receptor antagonist blocked bone resorption in mouse calvaria as a result of IL-1β, but not IL-1α.[147]

Concomitantly, a parallel process of osteoblastic bone deposition invariably accompanies osteoclastic bone resorption. Factors known to induce new bone formation such as transforming growth factor (TGF)-β and bone morphogenetic protein-2 have been identified in cholesteatomas.[105,148,149] Cytokines such as TGF-β1 and TGF-β2 may potentially slow the proliferation and tissue destruction associated with human cholesteatoma.[150] TGF-β is involved in matrix formation and stimulates numerous matrix proteins, such as collagen, laminin, and fibronectin. TGF-β may also initiate bone formation by recruitment and proliferation of osteoblast precursor, whereas bone morphogenetic protein-2 seems to be important in inducing differentiation of pluripotent progenitor cells.

Fujioka and Huang[151] identified platelet-derived growth factor in human cholesteatoma tissue, which stimulates monocytes to form multinucleated osteoclast-like cells. Additionally, Bujia and coworkers[60] and Sudhoff and colleagues[59] showed abnormal expression of epidermal growth factor in human cholesteatoma, which is a potent stimulator of cell proliferation and differentiation. Production of parathyroid hormone–related protein was detected in cholesteatoma cell cultures and may increase incidence of bone resorption.[152]

Vascularization within the perimatrix of cholesteatoma showed a fivefold increase compared with middle ear mucosa and a twofold increase compared with skin.[152] Sudhoff and colleagues[153] found a close relationship between the density of capillaries, degree of inflammation, and expression of different angiogenic factors. Because proliferating tissues such as middle ear cholesteatoma require an enhanced blood supply, angiogenesis seems to be necessary for the expansion of cholesteatoma matrix within the middle ear cavity.

The role of other cells in the pathophysiology of bone erosion in patients with chronic otitis media is unclear. Gantz[154] suggested that Langerhans cells within the matrix of cholesteatomas might initiate an immunologic response to the presence of antigens (keratin and bacterial debris); these cells may induce the cellular events outlined previously. These cells may also promote proliferation of keratinized epithelial cells by means of IL-1α in vitro.[92] Aberg and associates[155] found no increase in Langerhans cells compared with ear canal epithelium, however, suggesting that these cells may not have a primary role in the development of cholesteatoma. Mast cells are seen in cholesteatoma matrix, but their role is unknown.[156]

The important role of infection in the pathogenesis of cholesteatoma is highlighted by the more recent identification of bacterial biofilms in otitis media[157] and cholesteatoma.[35,158] Biofilms are bacterial communities enclosed in a self-produced matrix adherent to a surface.[147] Many bacterial species relevant to otologic infections are known to form biofilms, including *P. aeruginosa, H. influenzae, Streptococcus pneumoniae,* and *S. aureus*.[34] Bacteria within biofilms are more resistant to antibiotics and are likely responsible for the chronicity and recurrence of these infections. The presence of antibiotic-resistant bacterial biofilms in cholesteatomas may also explain their aggressiveness.[35] Bacterial biofilms within cholesteatomas may elaborate lipopolysaccharide and other bacterial products that stimulate osteoclastogenesis. Zhuang and colleagues[159] showed that lipopolysaccharide derived from *P. aeruginosa* can induce osteoclast development in vitro and potently stimulates in vivo bone resorption through a toll-like receptor–4–dependent mechanism.[159]

Sensorineural Hearing Loss

The destructive effects of an expanding cholesteatoma within the middle ear or mastoid and concomitant chronic infection are not limited to the bony structures of the temporal bone. Paparella and coworkers[160] observed sensorineural hearing loss in patients with chronic otitis media, and Chole and Chiu[161] observed loss of cochlear hair cell stereocilia in animals with experimental cholesteatomas with or without infection. In a study of age-matched, staged cholesteatomas, McGinn and Chole[162] showed loss of cochlear hair cells in areas subjacent to areas of bone erosion, suggesting that ototoxic substances may traverse the bony wall of the cochlea directly. Meyerhoff and associates[163] found that 17.9% of temporal bones with chronic otitis media had histologic evidence of labyrinthitis.

Vartiainen and Karjalainen[164] compared 874 chronically infected ears with and without cholesteatoma with 609 control ears, and found significantly worse bone conduction in the infected group; ears with cholesteatomas were generally worse than ears without cholesteatomas. Fria and coworkers[165] found that there was a tendency for bone conduction thresholds to be elevated at 2 kHz and 4 kHz in the ears with chronic OME compared with bone conduction thresholds in children with or without OME. In animal experiments, the inner ear is particularly sensitive to injury by middle ear infection. Morizono and associates[166] found that otitis media in chinchillas resulted in significant increase in tone-burst elicited compound action potentials after the otitis had cleared, indicating a sensory hearing loss.

In contrast, after correcting for the artificial elevation of bone conduction thresholds from conductive hearing loss, also known as the Carhart effect, Browning and Gatehouse[167] found no difference in the bone conduction thresholds between 395 ears with chronic otitis media and 920 control ears. These results were supported by MacAndie and O'Reilly,[168] who pointed out that the presence of cholesteatoma or ossicular erosion, or both, was not associated with a significantly increased risk of sensorineural hearing loss. Rahko and colleagues[169] studied bone conduction thresholds in 359 children with a history of recurrent AOM and found no correlation between the number of bouts of infection and permanent sensorineural hearing loss.

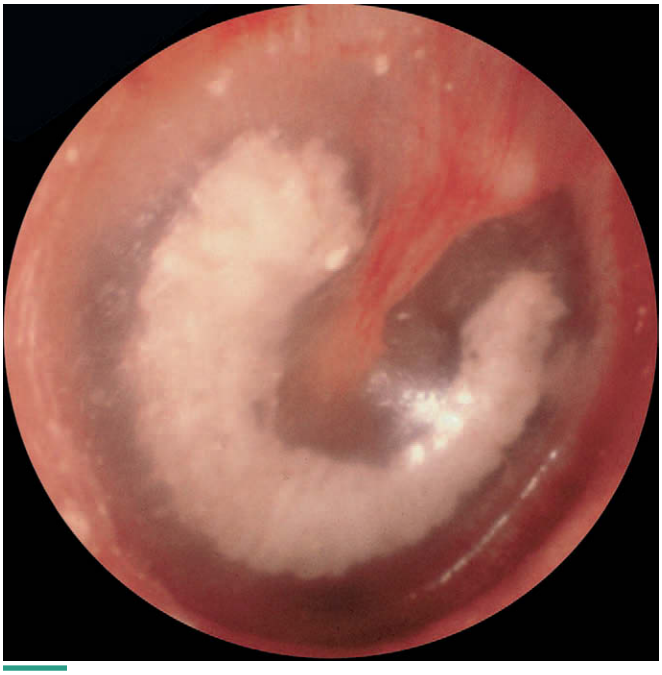

Figure 139-14. Tympanic membrane tympanosclerosis (myringosclerosis).

Tympanosclerosis

Diagnosis

Tympanosclerosis is thought to be a complication of otitis media in which acellular hyalin and calcified deposits accumulate within the tympanic membrane and the submucosa of the middle ear. In most patients, these plaques are clinically insignificant and cause little or no hearing impairment. Tympanosclerotic plaques within the tympanic membrane appear as a semicircular crescent or horseshoe-shaped white plaque within the tympanic membrane (Fig. 139-14).

Pathogenesis

Tympanosclerosis is a consequence of resolved otitis media or trauma. Hussl and Mueller[170] found tympanosclerosis to be a frequent sequela of chronic OME; they found tympanosclerosis in 19.7% of drumheads 6 to 8 years after the insertion of ventilating tubes for OME. They also noted that middle ear tympanosclerosis often was seen after recurrent bouts of AOM. Tos and Stangerup[171] found a significant increase in tympanosclerosis in ears in which grommets were placed (59%) compared with the contralateral ears, in which only myringotomy was performed (13%). Daly[172] reported the weighted average incidence of tympanosclerosis is 10% in children 4 to 15 years old, with an average follow-up period of 4 years. The incidence of tympanosclerosis in chronic otitis media has been reported to range from 9% to 38%. Kinney[173] found that 20% of 1495 patients undergoing surgery for chronic otitis media or its sequelae had tympanosclerosis. Mangat and coworkers[174] found that 23.6% of 1274 patients treated with tympanostomy tubes had tympanosclerosis.

Tympanosclerosis appears histologically as an acellular hyalinization of the subepithelial connective tissue of the tympanic membrane and middle ear. In most instances, calcification is present. Osteoneogenesis also can occur within these lesions. The bone deposition and ossicular fixation occur most frequently in the attic associated with the heads of the malleus and incus. When plaques occur within the tympanic membrane, they are limited to the lamina propria. Hussl and Lim[175] found these plaques to be a degenerative process resulting in calcification in connective tissue of the middle ear. They hypothesized

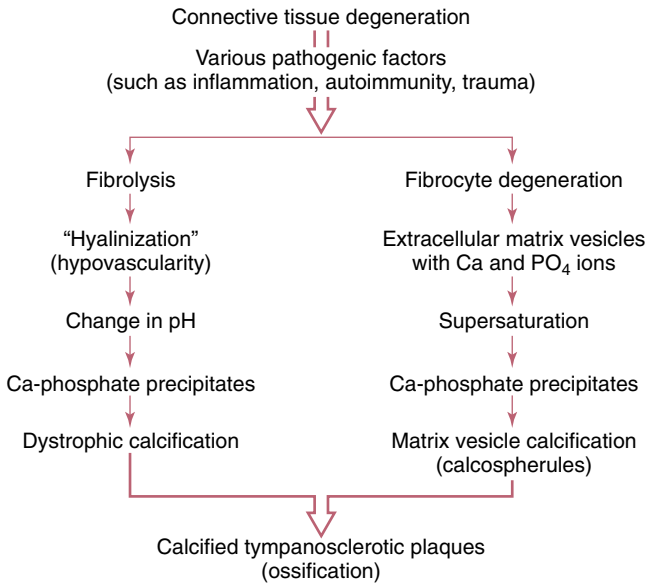

Figure 139-15. Two possible mechanisms for formation of tympanosclerotic plaques. *(Adapted from Hussl B, Lim DJ. In: Lim DJ, Bluestone CD, Klein JO, eds.* Recent Advances in Otitis Media with Effusion. *St. Louis: Mosby; 1984.)*

that OME or AOM led to a destructive process within connective tissue, which led to degeneration of collagen and subsequently dystrophic calcification and tympanosclerosis.

The degeneration of collagen may be a direct result of inflammation or infection within the middle ear (e.g., by bacterial proteinases and collagenases). Wielinga and colleagues[176] showed that eustachian tube obstruction alone, without infection, caused tympanosclerosis in rats; they hypothesized that deformation alone was sufficient to cause the plaques to form. Another possible cause of tympanosclerosis is an autoimmune process occurring within the tympanic membrane. Schiff and associates[61] prepared antisera to guinea pig lamina propria and passively immunized guinea pigs. When the tympanic membranes of these animals were traumatized, tympanosclerotic plaques developed. Chole and Henry[177] found that LP/J inbred mice spontaneously developed middle ear lesions that resembled tympanosclerosis and may be immunologically mediated.[178] Hussl and Lim[175] proposed two possible mechanisms for the formation of tympanosclerotic plaques, beginning with collagen degeneration (Fig. 139-15). Russell and Giles[179] found that the process of tympanosclerosis started in the submucosal connective tissue layer and progressed to involve all connective tissue sublayers in an animal model. The extent of calcium deposition and fibrosis across the membrane was related to the duration of OME.

Management

Tympanosclerosis within the middle ear (Fig. 139-16) is histologically similar to tympanosclerosis occurring within the tympanic membrane, but it often leads to conductive hearing loss caused by ossicular fixation. Although some authors have stated that tympanosclerosis tends to recur after surgical removal, others have reported stable hearing results in these patients. Smyth and colleagues[180] reported excellent hearing results in 79% of tympanosclerotic ears in which ossicular reconstruction (stapedectomy and total ossicular reconstruction) was performed in two stages, although Gormley[181] found that only 7% of his cases had an air-bone gap of less than 21 dB on long-term follow-up evaluation, questioning the advisability of stapedectomy in ears with tympanosclerosis. In the earlier series[182] in which one-stage procedures were performed, 21% of 57 cases resulted in cochlear losses. Tympanoplasty and ossicular reconstruction can be performed in ears with tympanosclerosis, but the risks of cochlear damage seem to be greater than in other middle ear diseases because of the extensive dissection that is required in tympanosclerotic ears and the coexistence of labyrinthine erosion.

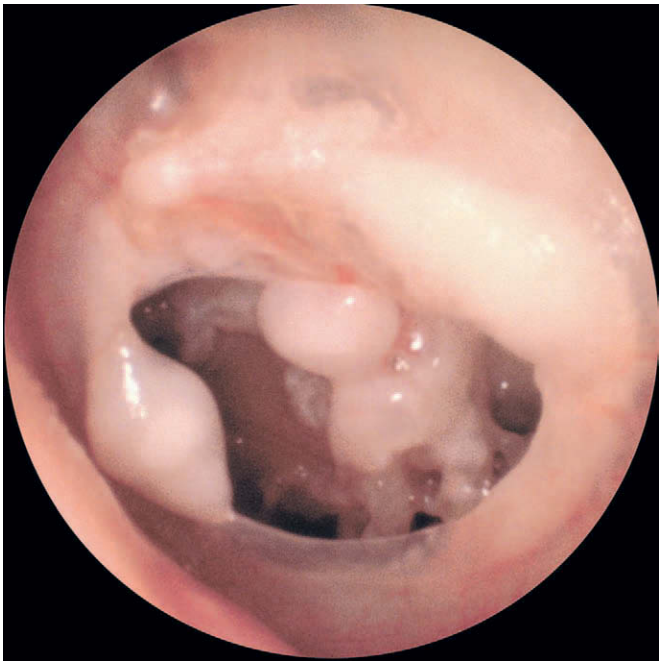

Figure 139-16. Advanced tympanosclerosis of the tympanic membrane and the middle ear.

Petrositis

Infection of the mastoid and middle ear may be complicated by the spread of infection within the temporal bone into the petrous apex. Petrous apicitis is an extension of infection from the mastoid air cell tract into a pneumatized anterior or posterior petrous apex. In the preantibiotic era, otitis media often was complicated by a spread into the petrous apex and further intracranial complications. The classic symptoms of petrous apicitis include deep facial pain, otitis media, and ipsilateral abducens nerve paralysis. This triad, called Gradenigo's syndrome,[183] is rare, although suppurative processes in the petrous apex occur in patients with AOM and chronic otitis media, but most often manifest as chronic infection with otorrhea and sometimes deep pain after adequate surgery. More recently, otologic diseases have been observed as complications in patients with acquired immunodeficiency syndrome (AIDS). Chandrasekhar and colleagues[184] reported six of seven specimens had petromastoiditis in the temporal bones of AIDS patients.

Historical Note

The history of petrous apicitis and its management has been reviewed more recently.[185] A patient with petrous apicitis and Gradenigo's triad was first described by Goris.[186] In Gradenigo's review of previously published cases of 57 patients with petrositis, 24 actually had the pure triad; others had multiple complications. In the early part of the 20th century, there was a controversy as to whether petrous apicitis can develop in diploic (marrow-filled) or pneumatic (air-filled) petrous apices.[187] It is generally believed that petrous apicitis occurs in patients who have pneumatized petrous apices. In the 1930s, Almour[188] and Kopetzky and Almour[189] described surgical approaches for petrous apicitis in which fistulous tracts were followed into the petrous apex. Ramandier in 1933,[190] and soon thereafter Lempert[191] described the now classic operation for exenteration of the anterior petrous apex. The histopathology of petrous apicitis was described by Lindsay.[192] An additional surgical approach for suppuration of the petrous apex was described in a case report by Hendershot and Wood,[193] in which they drained an osteomyelitis of the petrous apex through the middle cranial fossa.

Anatomy

The petrous apex is a truncated pyramid, which is the portion of the temporal bone medial to the inner ear labyrinth (Fig. 139-17). The

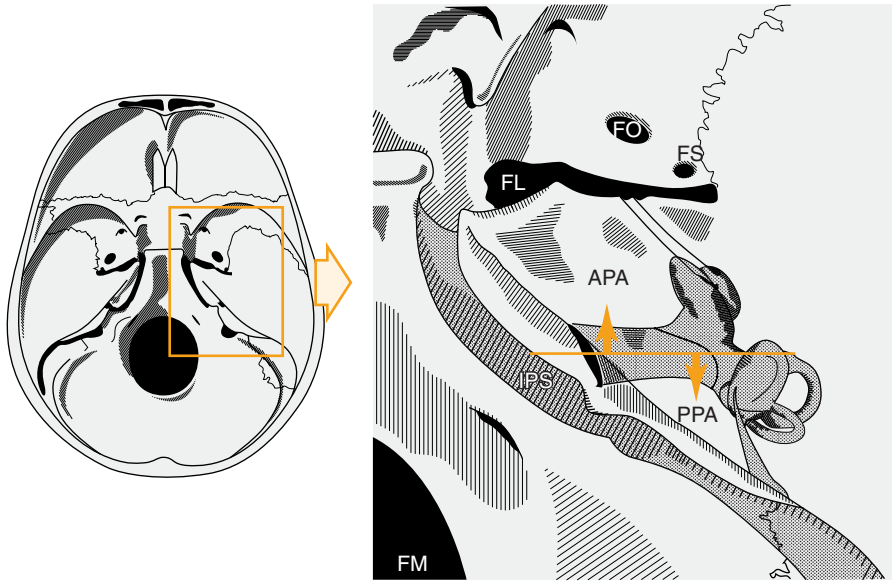

Figure 139-17. Base of skull viewed from above, revealing the relationship of the petrous apex to the foramen magnum (FM) and the rest of the temporal bone (*box*,enlarged on right). The anterior petrous apex (APA) is a truncated pyramid based on labyrinth *(shaded)* and bound by foramen lacerum (FL) anteriorly and inferiorly and inferior petrosal sinus (IPS) posteriorly. If the petrous apex is viewed from above, it can be divided into anterior and posterior sections by a line drawn through the internal auditory canal. APA is located medial to the cochlea and internal auditory canal, and posterior petrous apex (PPA) is medial to the semicircular canals. FO, foramen ovale; FS, foramen spinosum. *(Modified from Chole RA. Petrous apicitis: surgical anatomy.* Ann Otol Rhinol Laryngol. *1985;94:251.)*

petrous apex is the most surgically inaccessible portion of the temporal bone.[194] The apex may be arbitrarily bisected by a coronal plane through the internal auditory canal (see Fig. 139-17). This plane divides the apex into an anterior portion, the peritubal area, and a posterior portion, the perilabyrinthine area. The posterior petrous apex, which is pneumatized in 33% of patients, is just medial to the semicircular canals. The anterior apex, which is pneumatized in 10% of patients, is anterior and medial to the cochlea. The carotid artery traverses the anterior petrous apex.

The petrous apex may be pneumatic (air cell filled), diploic (marrow filled), or sclerotic (solid bone). Direct extension of infection from the mastoid and middle ear through pneumatized air cell tracts into the petrous apex is thought to be the etiology of petrous apicitis. It has been estimated that 30% of posterior petrous apices are pneumatized, and in a study of 84 normal human temporal bones, 9% of anterior petrous apices were found to be pneumatized (Fig. 139-18).[195]

The anatomic relationship at the petrous tip may explain some of the symptoms of petrous apicitis. An undetected and poorly drained infected air cell of the petrous apex must trail through small air cell tracts into the middle ear and mastoid. These cell tracts consist of the infralabyrinthine air cell tract, the retrofacial tract, and the peritubal air cells superior to the eustachian tube. If the bony cortex of the anterior petrous apex is involved by the extension of infection, the infection may cause an epidural abscess in the region or damage nearby cranial nerves. On the superior aspect of the petrous tip lies the trigeminal or gasserian ganglion. Damage or irritation to the ganglion may explain the deep facial pain that some patients with apicitis experience. Extending from the tip of the petrous apex to the clinoid is the petroclinoid ligament. The abducens nerve travels below the petroclinoid ligament in a small canal called Dorello's canal.[196] Entrapment or inflammation in the ear of Dorello's canal is thought to account for the presence of abducens paralysis in some patients with petrous apicitis.

Diagnosis

Symptoms of petrositis usually are subtle. Typically, a patient who has had previous mastoid surgery complains of persistent infection and deep facial pain. In a series of 22 patients during 20 years, 16 patients (72.7%) had otalgia, and 13 patients (59.1%) had deep facial pain and headache; trigeminal nerve paralysis (68.2%) most frequently involved the cranial nerve; 6 (27.3%) had facial nerve paralysis, 4 (18.2%) had abducens nerve paralysis, and 2 had coma (Table 139-4).[197] Patients with suppuration may manifest various symptoms, none of which are pathognomonic for the syndrome. In patients with long-standing chronic otomastoiditis, deep pain, and persistent infection, the diagnosis of petrositis should be considered. In a more recent series of patients with petrous apicitis, the predominant organism was *P. aeruginosa*. The physical findings of petrositis usually include those of chronic otitis media with chronic otorrhea. In some patients, the infection can be

Table 139-4

Symptoms Found in 22 Patients with Petrous Apicitis from 1976-1995

Symptom	No. Patients (%)
Deep pain and headache	13 (59)
Otalgia	16 (72)
Otorrhea	13 (59)
Fever	5 (22)
Coma	2 (9)
Cranial nerve paralysis	
V	15 (68.2)
VI	4 (18.2)
VII	6 (27.3)
VIII	9 (40.9)
IX	1 (4.5)
X	1 (4.5)

From Chole RA, Gadre AK. Petrous apicitis—symptomatology, pathology, and management [Abstract]. *Skull Base Surgery Symposium,* Sacramento, CA, 1995.

limited to the anterior petrous apex, and the middle ear is normal.[197] Many patients have involvement of cranial nerves V, VI, and VII.

Diagnostic Tests

When the diagnosis of petrous apicitis is suspected on clinical grounds, the most appropriate diagnostic procedure is CT. High-resolution CT usually shows details of the petrous apex and provides important details about potential surgical routes. A pneumatized petrous apex on the uninvolved side can sometimes be contrasted with a fluid-filled or sclerotic petrous apex on the involved side, although Roland and colleagues[198] have shown that asymmetry of the petrous apex is not diagnostic for apicitis because asymmetric pneumatization of the apex can occur in healthy subjects. If CT scan indicates a potential apicitis, MRI may add information about the nature of the fluid or tissue within the apex (Fig. 139-19). A gallium bone scan may provide additional information, showing increased uptake on the side of the apicitis. A combination of MRI and CT is necessary to evaluate normal anatomic variations and to be capable of differentiating diagnosis.[199]

Management

The management of petrous apicitis is directed toward control of the infection. If topical and systemic antibiotic management is inadequate to control the suppuration, various surgical approaches are available. Surgical therapy aims to achieve drainage of the petrous apex through the mastoid and middle ear into the petrous apex. These air cells have been well defined anatomically[194]; they include the subarcuate and sinodural angle cells toward the posterior petrous apex and the peritubal, retrofacial, infralabyrinthine, and infracochlear tracts toward the anterior petrous apex. The anterior apex may be widely exposed through the glenoid fossa with the approach of Ramandier[190] and Lempert.[191] If adequate air cells cannot be identified through the middle ear and mastoid, the middle cranial fossa approach can be used to enter the roof of the anterior petrous apex.[193] Brackmann and Toh[138] found the translabyrinthine approach useful in nonhearing ears. In hearing individuals, anatomy permitting, the transcanal infracochlear approach with stenting was the preferred approach for drainage of the petrous apex.

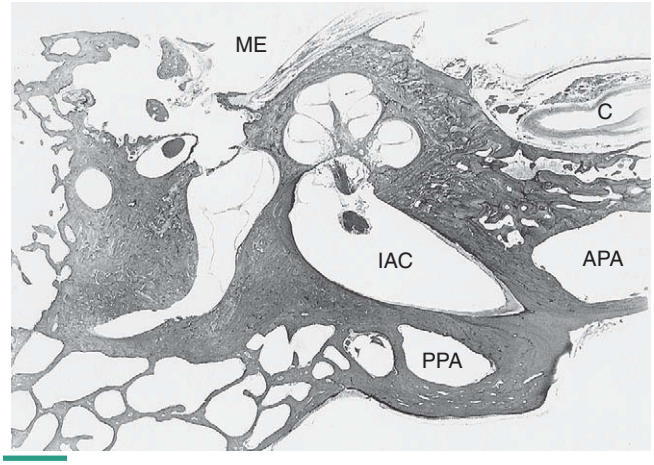

Figure 139-18. Pneumatic anterior petrous apex (APA) and posterior petrous apex (PPA) in horizontal temporal bone histopathologic section. There is a large air cell in APA and air cells in PPA. C, carotid artery; IAC, internal auditory canal; ME, middle ear. *(From Chole RA. Petrous apicitis: surgical anatomy.* Ann Otol Rhinol Laryngol. *1985;94:251.)*

Summary

Otitis media is one of the most common diseases of childhood, and the most frequent disease managed with antibiotics in children. The infectious and noninfectious complications of otitis media may result in significant morbidity and complications, including acute and chronic mastoiditis, petrositis, and intracranial infection. The noninfectious sequelae, including chronic perforation of the tympanic membrane, ossicular erosion, labyrinthine erosion, and tympanosclerosis, are major causes of hearing loss.

Acute or recurrent infection of the middle ear may result in a permanent perforation of the tympanic membrane and irreversible inflammatory changes within the middle ear and mastoid known as chronic otomastoiditis. Chronic otitis media may occur in patients who have indwelling tympanostomy tubes. Most cases of chronic otitis media can be managed with topical antibiotics.

Aural cholesteatomas are epidermal inclusion cysts of the middle ear or mastoid, and are classified as congenital and acquired. Acquired cholesteatomas possibly result from OME or AOM or both. There are four basic theories of the pathogenesis of acquired aural cholesteatomas, which are supported by clinical and experimental evidence. The diagnosis of aural cholesteatoma is made on otoscopic examination and special imaging procedures, such as high-resolution CT and MRI. The expansion of cholesteatomas may result in erosion of surrounding structures, which may result in local and intracranial complications. Cholesteatomas can be eradicated from the temporal bone only by surgical resection; various surgical approaches are available.

The main mechanism of bone resorption in chronic otitis media with and without cholesteatoma is thought to be the increased number and activity of osteoclasts. Many metabolites and cytokines are known to activate osteoclasts locally. PGE_2, osteoprotegerin, and macrophage

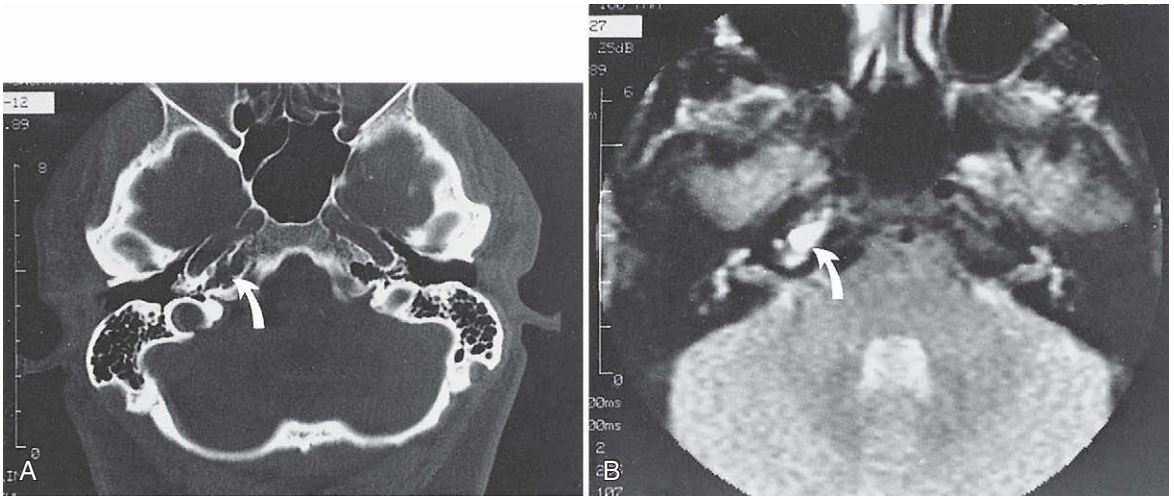

Figure 139-19. CT **(A)** and MRI **(B)** are helpful adjuncts in the diagnosis of petrous apicitis. **A,** In the CT scan, the fluid-filled petrous apex *(arrow)* can be compared with the opposite air-filled apex. **B,** In the MRI scan, the area of increased signal is present in involved apex *(arrow)*. An amber-colored, fluid-filled cyst was found at surgery.

colony-stimulating factor are some of the most potent osteoclast-activating metabolites. Cytokines and growth factors such as IL-1, IL-6, tumor necrosis factor-α, epidermal growth factor, parathyroid hormone–related protein, and TGF-β seem to play an important role in middle ear infections and cholesteatoma. Tissue-type plasminogen activator and collagenase also may play a role in local invasion of cholesteatoma. More recent evidence suggests that bacterial biofilms within chronically infected cholesteatomas may contribute to their aggressiveness by local elaboration of lipopolysaccharide.

Sensorineural hearing loss and tympanosclerosis are thought to be complications of otitis media. Tympanosclerosis in the middle ear often leads to conductive hearing loss caused by ossicular fixation. Petrous apicitis may be complicated by the spread of infection within the temporal bone into the petrous apex. The appropriate diagnostic procedure is high-resolution CT scanning. MRI and gallium bone scan may provide additional information. The management of petrous apicitis is directed toward control of the infection and includes topical and systemic antibiotic management and surgical approach through many surgical routes.

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CHAPTER ONE HUNDRED AND FORTY

Complications of Temporal Bone Infections

Hussam K. El-Kashlan

Lee A. Harker

Clough Shelton

Nafi Aygun

John K. Niparko

Key Points

- Although declining in incidence, the complications of temporal bone infections continue to carry the potential for extensive morbidity and mortality.
- Because of the complexity of their pathogenesis, complications related to otitis require a thoughtful diagnostic approach. Although the management of such complications is invariably urgent, a stepwise approach should be taken, and time efficiency is gained by fully considering the patient history and physical examination.
- The management of intratemporal complications of infection that are suppurative in nature, or related to cholesteatoma, can be facilitated by recognizing patterns of extension within the temporal bone and neurovascular involvement.
- The management of intracranial complications of temporal bone infection should be guided by a similarly thoughtful diagnostic approach. The evaluation should be supported by history, findings, awareness of cerebrospinal fluid and cerebrovascular dynamics, and neurosurgical collaboration when an intradural process is identified.
- Microbiologic testing and imaging modalities are essential tools in the contemporary management of complications of temporal bone infections.
- Imaging with CT and MRI offers precise assessment of disease extension and characteristics of the offending lesion itself.

General Considerations

Although the incidence and prevalence of complications related to otitis are now diminished, their clinical impact requires a thorough understanding of related pathophysiology and management. This chapter reviews the complications of acute otitis media (AOM) and chronic otitis media (COM), including their etiology, pathophysiology, diagnosis, and treatment.

Epidemiology

Table 140-1 presents the age distribution of extracranial, intracranial, and combined complications in a large series of patients. Nearly 80% of extracranial complications and 70% of intracranial complications occurred in children in the first 2 decades of life. Extracranial complications, led by postauricular abscess, most commonly occurred in children younger than 6 years.[1] In a series of 93 intracranial and extracranial complications of otitis media, 58% were present in patients younger than 20 years.[2] Low socioeconomic status and overcrowding confer either greater risk of or diminished resistance to an infection with an extended course and complications. Associations with inadequate health education and limited access to medical care likely contribute to heightened risk of complication. For this reason, most of the current reports of otogenic brain abscesses come from underdeveloped countries. Although the number of cases with immunodeficiency has increased, large series of patients with complications of otitis media have not been reported in patients with human immunodeficiency virus infection or acquired immunodeficiency syndrome, or in patients receiving immunosuppressive therapy after organ transplantation, even though such individuals do have heightened risks of suppurative ear disease.

Table 140-2 shows the classification of extracranial and intracranial complications, and Table 140-3 summarizes the relative frequencies of those complications. The dominant extracranial complication is postauricular abscess, and the dominant intracranial complication is meningitis. Complications tend to occur multiply, especially intracranial complications, as shown in Tables 140-4 and 140-5. Although all of the complications originate from infection in the pneumatized spaces of the middle ear and mastoid, the mechanisms by which complications occur in AOM differ from the mechanisms associated with COM. We discuss these two entities separately.

Acute Otitis Media

An estimated 85% of all children experience at least one episode of AOM, making it the most common bacterial infection of

Table 140-1

Age Distribution of 268 Patients with Complications of Otitis Media between January 1985 and December 1990

Age in Years	Extracranial (*n*)	Intracranial (*n*)	Combined (*n*)
	87	50	31
0-5	33.3	8	6.5
6-10	23	21.3	19.4
11-20	21.8	39.3	38.7
21-30	9.2	8.6	12.9
31-40	3.4	12.6	9.7
41-50	5.7	6	6.5
51-60	3.4	0.6	3.2
>60	0	3.3	3.2

From Singh B, Maharaj TJ. Radical mastoidectomy: its place in otitic intracranial complications. *J Laryngol Otol*. 1993;107:1113-1118.

Table 140-2

Classification of Complications of Acute and Chronic Otitis Media

Extracranial	Intracranial
Acute mastoiditis	Meningitis
Coalescent mastoiditis	Brain abscess
Chronic mastoiditis	Subdural empyema
Masked mastoiditis	Epidural abscess
Postauricular abscess	Lateral sinus thrombosis
Bezold abscess	Otitic hydrocephalus
Temporal abscess	
Petrous apicitis	
Labyrinthine fistula	
Facial nerve paralysis	
Acute suppurative labyrinthitis	
Encephalocele and cerebrospinal fluid leakage	

From Harker LA. Cranial and intracranial complications of acute and chronic otitis media. In: Snow JB, Ballenger JJ, eds: *Ballenger's Otorhinolaryngology Head and Neck Surgery*. 16th ed. Hamilton, Ontario: Decker; 2003.

Table 140-3

Distribution of Intracranial and Extracranial Complications

	Osma*		Singh†	
	n	%	*n*	%
Intracranial Complication				
Meningitis	41	71.9	22	12
Brain abscess	10	17.5	93	51
Epidural abscess	4	7	19	10
Lateral sinus thrombosis	1	1.8	36	20
Cerebritis	1	1.8		
Subdural empyema			36	20
Extracranial Complication				
Mastoid abscess	25	64.1	65	75
Labyrinthitis	5	12.8	—	—
Facial nerve paralysis	5	12.8	15	14.9
Bezold abscess	4	10.3	5	5.7
Petrous apicitis	—	—	2	2.2

*Osma U, Cureoglu S, Hosgoglu S. The complications of chronic otitis media: report of 93 cases. *J Laryngol Otol*. 2000;114:97-100.
†Singh B, Maharaj TJ. Radical mastoidectomy: its place in otitic intracranial complications. *J Laryngol Otol*. 1993;107:1113-1118.

Table 140-4

Intracranial Complications in 181 Patients with Otitis

Complication	*n*	No. with Associated Complications	AC%
Meningitis	22	4	18.2
Brain abscess	93	15	16.1
Subdural empyema	36	12	33.3
Epidural abscess	19	14	73.7
Lateral sinus thrombosis	36	10	27.8

AC%, percentage of patients with each complication who also had additional complication(s).
Adapted from Singh B, Maharaj TJ. Radical mastoidectomy: its place in otitic intracranial complications. *J Laryngol Otol*. 1993;107:1113-1118.

childhood.[3] Predisposing factors include young age; male sex; receiving bottle feedings; and being exposed to a daycare environment, crowded living conditions, or smoking within the home. Medical conditions such as cleft palate; Down syndrome; and mucous membrane abnormalities such as cystic fibrosis, ciliary dyskinesia, and immunodeficiency states also predispose individuals to otitis media.

AOM is a bacterial infection of the middle ear space characterized by vascular dilation and proliferation (manifested externally by tympanic membrane edema and erythema), mucosal edema, exudation, bacterial proliferation, white blood cell infiltration, and pus formation. AOM here refers only to an acute infection that arises de novo, in a previously normal middle ear, rather than an acute clinical infection arising in long-standing otitis media with effusion. This distinction underscores that patterns of complications are different in AOM versus COM.

After the first few weeks of life, acute suppurative otitis media is caused primarily by three organisms: *Streptococcus pneumoniae,*

Table 140-5

Interrelationship of Intracranial Complications

Complication	*n*	Meningitis	Brain Abscess	Epidural Abscess	Subdural Empyema	Lateral Sinus Thrombosis
Meningitis	22	—	—	2	—	1
Brain abscess	93	—	—	3	9	3
Subdural empyema	36	—	9	2	—	1
Epidural abscess	19	2	3	—	2	5
Lateral sinus thrombosis	36	1	3	5	1	—

From Singh B, Maharaj TJ. Radical mastoidectomy: its place in otitic intracranial complications. *J Laryngol Otol*. 1993;107:1113-1118.

Haemophilus influenzae, and *Branhamella catarrhalis,* composing roughly 30%, 20%, and 10% of isolates.[3] Optimal treatment for acute suppurative otitis media with complications includes appropriate antibiotics in addition to myringotomy and placement of a ventilating tube. Tympanocentesis is used primarily to obtain material for culture and sensitivity to identify the offending organism, but it can also reduce the bacterial population. Myringotomy and tube placement also provide material to identify the involved organism. After treatment, the physician should document that the AOM has completely resolved by tympanometry and otoscopy if the tympanic membrane is intact, and by otoscopy if a ventilating tube is in place. If the complication was intracranial, a computed tomography (CT) scan or magnetic resonance imaging (MRI) study should be obtained.

Chronic Otitis Media

AOM is primarily a middle ear infection that extends into the contiguous mastoid, whereas COM reflects persistent mastoid infection with concurrent otitis media. COM is present when an infectious process persists for longer than the 1 to 3 weeks usually necessary for resolving AOM in a previously healthy ear. COM can occur with or without cholesteatoma. Without cholesteatoma, there is typically a tympanic membrane perforation. A third type of COM is evident in young children with persistent otorrhea with a patent middle ear ventilating tube.

If infection in the middle ear and mastoid does not resolve, mucosal edema and exudation increase, and mucous glands and secretory elements proliferate. Mucosal edema in the spaces between the middle ear and the epitympanum and in the aditus between the epitympanum and mastoid antrum block the normal pathways for aeration and decrease oxygenation and vascularity. At the same time, the blockage prevents pharmacologic agents from reaching the attic and mastoid. Radiographically, the mastoid air cell system is partly or completely opaque, reflecting the loss of aeration.

COM changes are accompanied by a characteristic bacteriology compared with acute conditions. Harker and Koontz[4] cultured 30 cholesteatomas at surgery and isolated at least one anaerobic organism in 67% of the cases, at least one aerobic organism in 70%, and both organisms in 50%. In 57% of the cholesteatomas, multiple organisms were cultured; in 30%, five or more bacteria were identified. Even without clinical infection, anaerobes, such as *Propionibacterium acnes,* were frequently isolated. An ear with COM is highly likely to harbor multiple bacteria of anaerobic and aerobic types.

COM that develops in patients with indwelling middle ear ventilating tubes has a different bacterial flora. In most instances, these cases begin with an upper respiratory infection or with water contamination. A series of events, including treatment with antibiotic drops, treatment with oral antibiotics, repeated contamination, repeated culture and sensitivity tests, increasing patient and physician frustration, decreasing patient compliance, and fungal overgrowth, frequently results in resistant organisms developing. The resistant bacteria most often found are *Pseudomonas aeruginosa, Achromobacter xylosoxidans,* and methicillin-resistant *Staphylococcus aureus,* although the etiologic importance of individual organisms identified on swab culture is unclear. A fungal component of the external auditory canal and the middle ear and mastoid should be considered.

Pathophysiology

Complications associated with AOM may occur during the first few days of the infection as a result of associated bacteremia. Alternatively, bacteria can extend infection to a new location. A patient may develop partial or complete facial paralysis because of dehiscence of the bony fallopian canal in the tympanic segment. If there are preformed pathways leading to the meninges or the labyrinth, patients with AOM are at risk to develop meningitis, subdural effusion, or suppurative labyrinthitis. Developmental anomalies, such as an enlarged vestibular aqueduct or Mondini's deformity, present such a risk. Bacteria can propagate along preformed pathways left from previous surgery or temporal bone fractures. With AOM, there is no granulation tissue formation or bone destruction; complications develop by hematogenous dissemination or by direct extension along preformed pathways. The usual medical treatment of the AOM resolves the otitis, and mastoidectomy is unnecessary. It is crucial to know whether the middle ear was normal before the current AOM began.

In COM and mastoiditis, complications occur with bone destruction, granulation tissue formation, or the presence of cholesteatoma. Bacteria gain access to the involved structures most commonly by direct extension from mastoid infection, and by infecting and propagating along veins leading from the mastoid to adjacent structures. Direct extension can come about as a result of bone resorption from cholesteatoma or osteitis, or it can occur without bone erosion if the patient has preformed pathways from previous mastoid surgery, temporal bone fracture, congenital dehiscences, or other conditions that removed the intervening bone. The mechanisms by which bone is actively resorbed, although incompletely understood, probably include enzymatic degradation, suppuration, and decreased blood supply.

Diagnosis

History

The clinician must establish when the patient's ear was last free of disease and perfectly normal to differentiate AOM from COM because the bacteriology, medical treatment, and most probable complications are different for each. Key questions relate to the following: (1) prior evaluation of the involved ear, (2) past history and treatment of the otitis media, (3) the order of appearance and magnitude of symptoms, and (4) objective evidence that the ear was normal recently (e.g., tympanogram, radiographic study that included the ears).

Intracranial complications, most notably meningitis, intraparenchymal brain abscess, and subdural empyema, can alter the patient's level of consciousness. Of patients in the study by Singh and Maharaj,[1] 15% were drowsy on admission, 18% were stuporous, and 2% presented in a comatose state. Establishing the chronology of this alteration

of sensorium helps the physician differentiate among diagnoses of brain abscess, meningitis, and subdural empyema. A brain abscess takes weeks to develop, whereas it takes only a few hours to several days for meningitis and subdural empyema to become fulminant and progress to coma.

Physical Examination

The vital signs, especially the temperature, provide a pretreatment baseline and one parameter for following the course of the disease and the treatment; however, if the patient has previously received oral or parenteral antibiotics, he or she may present without a fever. Although some patients with extracranial or intracranial complications remain afebrile during the entire course of their illnesses, the temperature curve can provide useful information in other patients.

Patients with intracranial or multiple complications often appear more systemically ill than patients with otitis alone. They can present with toxicity or with obtundation, manifesting depressed levels of consciousness that can vary from lethargy to total unresponsiveness. Focal neurologic signs may be absent, subtle, or florid. The physical examination of the ear itself usually does little to pinpoint a specific complication, unless there is an obvious postauricular, cervical, or temporal abscess.

A complete neurologic examination is essential. The clinician should evaluate the mental status and evaluate the station and gait along with the Romberg and sharpened Romberg tests. The motor and sensory function of the extremities should be evaluated, and a complete cranial nerve evaluation should be performed, including an assessment of vision, extraocular muscle function, facial nerve function, and facial sensation. The presence of nystagmus should be assessed. The clinician should evaluate cerebellar function by checking the alternate motion rate of the extremities, determining whether past pointing is present or absent, and performing the finger-to-nose test. Ocular saccades and smooth pursuit should be assessed.

It is crucial to determine whether nuchal rigidity is present, and if so, Kernig's and Brudzinski's signs must be sought. The optic discs should be observed with an ophthalmoscope to determine whether papilledema is present.

The otologic examination should begin with an assessment of the color, size, shape, and position of the pinna compared with the opposite side. The clinician should make note of any erythema, tenderness, or drainage, and any evidence of trauma, excoriation, or protrusion outward or downward. Next, the clinician should observe the regions adjacent to the auricle and note any swelling, erythema, tenderness, purulent drainage, or fluctuation.

The external auditory canal and tympanic membrane should be examined using a microscope and fine suction. If purulent secretions are present, a culture test should be performed. The clinician should document the presence of any edema, and whether it primarily affects the posterosuperior bony canal wall or the entire canal circumference. A drawing of the tympanic membrane should be made, illustrating any perforation, granulation tissue, or epithelial debris, and any erosion of the scutum. Pneumatic otoscopy should determine if there is conjugate deviation of the eyes suggesting a labyrinthine fistula.

The tympanic membrane can appear normal or near-normal even when an otologic complication is suspected because it reflects only the status of the middle ear. Although mastoid infection always begins with a middle ear infection, suppuration in these two locations can proceed differently, in that the middle ear may revert to normal or near-normal under treatment, whereas the mastoid may not.

We make special notation of the problem of an aditus block. The middle ear can appear normal after several courses of antibiotics while symptoms from the mastoid persist (see section on masked mastoiditis). When evaluating a patient with any infectious condition that could be caused by AOM or COM, a CT scan can evaluate the possibility of an aditus block as the cause, even if the tympanic membrane appears normal.

Imaging Techniques

CT scanning is essential for all patients suspected to have complications of otitis media. CT is a fast and reliable method for assessing the status of the middle ear and the mastoid air cell system and diagnosing intracranial complications of otitis media.[5,6] CT reveals bony details of the middle ear, epitympanic, and mastoid structures, and documents pneumatization versus opacification by inflammatory process. CT can show progressive demineralization and loss of the bony septa of air cells in coalescent mastoiditis, and reveal erosion of the bony plates covering the sigmoid sinus, cerebellum, or tegmen of the middle ear, mastoid, and bony labyrinth itself.

CT scans can help to establish the specific primary otologic diagnosis (e.g., AOM, COM, cholesteatoma), and several of the specific cranial and intracranial complications of otitis media. In addition to their diagnostic value, CT scans are useful in assessing the results of therapy, and provide a baseline post-treatment study of the mastoid for comparison in case of further complications.

When the patient is somnolent or unstable, and when intracranial complications are suspected, CT may be the study of choice because it is fast and gives the health care team better access to the patient during the study than MRI does. Even without enhancement, CT scanning can be an adequate diagnostic tool for a febrile, stuporous patient with meningeal irritation when ruling out the presence of an intraparenchymal brain abscess or communicating hydrocephalus before performing lumbar puncture to establish the diagnosis of meningitis. Intravenous injection of an iodinated contrast agent is essential, however, when using CT to diagnose cerebritis, cerebral abscess, subdural empyema, and ventriculitis.

MRI provides sensitive imaging for diagnosing intracranial complications because paramagnetic contrast agents such as gadolinium-DTPA (pentetic acid) cross the blood-brain barrier in areas of cerebritis or abscess. Meningeal enhancement is easily seen with MRI (and not on CT scanning, in which the adjacent bony skull often obscures the meninges). T2-weighted MR images can show intraparenchymal edema from subtle brain infection much earlier than a CT scan can. When otitic complications are suspected, CT scans and MRI provide valuable complementary information.

Fibrous tissue in the mastoid that is a result of previous (nonactive) COM or prior surgery enhances on MRI and may be misinterpreted by the radiologist as "mastoiditis." In such cases, the enhancement reflects the increased vascularity of this fibrous tissue and is analogous to the routine observation of enhancement of the highly vascular nasal turbinates with gadolinium.

Lumbar Puncture

To detect meningitis, the physician must perform a lumbar puncture, measuring the cerebrospinal fluid (CSF) pressure when starting and ending the procedure. The CSF is examined for bacteria on direct smear and measured for glucose, chloride, and protein to compare with their concentrations in serum. Lumbar puncture should be undertaken only after clinical assessment, ophthalmoscopic examination (noting that papilledema sometimes requires hours to develop), and CT scan have ruled out significantly increased intracranial pressure that can result in herniation of the cerebellar tonsils during or after the procedure. Lumbar puncture is contraindicated in the presence of elevated intracranial pressure with brain abscess and subdural empyema.

Treatment

Although each complication has its own separate treatment, there are certain general management principles for treating the underlying otitis. For each patient, the treatment of the underlying acute or chronic otitis and the treatment of any complications can be medical or surgical, and can be administered sequentially or concurrently. In nearly all instances of complications resulting from AOM, appropriate antibiotic therapy is sufficient to resolve the otitis without any need for surgery. This usually includes aspiration by tympanocentesis or myringotomy, as previously discussed.

When complications have resulted from COM and mastoiditis, initial antibiotic therapy should involve broad-spectrum antibiotics effective against anaerobic and aerobic organisms. In all of these cases, some form of mastoidectomy is required. When surgery is necessary for intracranial complications, the neurosurgeon operates first. Temporal bone management is considered separately. A mastoidectomy may be

performed at the same sitting if the patient's condition permits. In most instances (except for brain abscess and subdural empyema), the COM and its complications are treated entirely through the mastoid. When intracranial and otologic surgical procedures are necessary, the surgeons must plan the order of procedures, preparation, draping, and incisions to limit duration of anesthesia and optimize surgery.

A mastoidectomy under these circumstances is hampered by inflammation, and landmarks can be obscured. When no cholesteatoma is associated with the mastoiditis, the external auditory canal wall can be left intact unless visibility is inadequate. An open cavity, canal wall down procedure is preferred in the presence of cholesteatoma.[1]

Alternatively, these cases can be operated as canal wall up procedures, wherein the cholesteatoma is debulked and infection is cleared. Several months later, after the inflammation has resolved, the residual cholesteatoma is removed at definitive surgery. Allowing the inflammation to resolve may improve the effectiveness of cholesteatoma removal. With this approach, a second-stage operation (third procedure) is often required.

Postoperative follow-up is an essential part of the general treatment of patients who experienced life-threatening complications of AOM or COM. Even when the patient responded perfectly, the surgeon should consider follow-up CT scan to confirm objectively the status of the mastoid at the termination of treatment because there is a risk of recurrence or emergence of new intracranial complications. In patients who have experienced lateral sinus thrombosis, epidural abscess, subdural empyema, or brain abscess, follow-up evaluation with enhanced MRI 2 to 4 weeks after treatment is recommended.

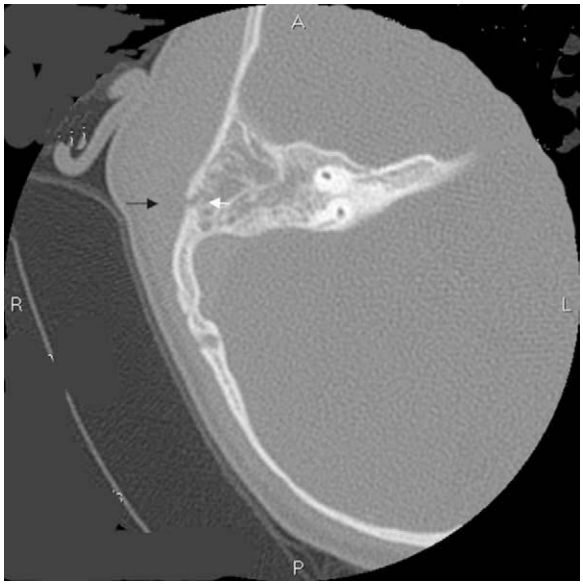

Figure 140-1. Axial temporal bone CT scan showing opacification of mastoid with preservation of bony septa. Note defect in cortical bone *(white arrow)* and postauricular swelling and fluid collection *(black arrow)*.

Extracranial (Intratemporal) Complications

Acute Mastoiditis

Acute mastoiditis can develop when AOM fails to resolve. According to Luntz and colleagues,[7] acute mastoiditis exists when there are signs of AOM on otoscopy and local inflammatory findings over the mastoid process (e.g., pain, erythema, tenderness, auricular protrusion), or when the mastoid inflammatory changes coexist with radiographic or surgical findings of mastoiditis with or without evidence of AOM. Other authors insist on the concomitant presence of AOM, mastoid physical findings, and radiologic findings.[8]

Luntz and colleagues[7] reported results of a multicenter retrospective study of 223 such patients that provided valuable insight into the process. Of patients, 28% were younger than 1 year at diagnosis, 38% were 1 to 4 years old, and 21% were 4 to 8 years old. Although one third of patients experienced signs and symptoms of AOM immediately preceding the mastoiditis, two thirds did not. Thirty percent of the patients had a history of recurrent AOM, and 5% (all of whom had recurrent AOM) had a prior episode of acute mastoiditis.

One third of the patients exhibited symptoms for 48 hours or less before diagnosis, and another third had symptoms for 2 to 6 days before presenting with acute mastoiditis. Spontaneous tympanic membrane perforation occurred in less than one fourth of patients; the tympanic membrane was bulging or erythematous in two thirds. Twenty-two percent of the patients presented with complications on admission, the most common of which was subperiosteal abscess (Fig. 140-1), followed by meningoencephalitis and occasional cases of other complications.

Despite parenteral antibiotics, 8% of the patients who had been free of complications on admission developed complications of acute mastoiditis during hospitalization. The most common was subperiosteal abscess, but three patients developed intracranial complications, and two developed facial paralysis while receiving parenteral antibiotics. One third of patients required surgery because they had extracranial or intracranial complications on admission, failed to exhibit satisfactory clinical improvement, or developed complications despite adequate antibiotic treatment during hospitalization.

Bak-Pedersen and Ostri[9] reviewed the records of 79 patients who underwent acute cortical mastoidectomy for acute mastoiditis. All patients had erythema and swelling and pain over the mastoid associated with a current or recent episode of AOM that did not improve after 24 to 48 hours of intravenous antibiotics. The average age in the series was 16 months, and the average duration from the onset of disease (AOM) until admission for acute mastoiditis was 9 days. Only one third of the patients exhibited an asymptomatic interval between AOM symptoms and the mastoiditis.

Both of the aforementioned studies established that acute mastoiditis is a disease of the very young. Also, they dispelled the classic notion that acute mastoiditis develops only after an asymptomatic period of 3 to 4 weeks.

Van Zuijlen and colleagues[10] pointed out that in countries such as the Netherlands, where it is unusual to prescribe antibiotics as first-line treatment for AOM, the incidence of acute mastoiditis is considerably higher than in countries where antibiotics are routinely prescribed for AOM. Lower overall costs and reduced incidence of allergic reactions resulting from withholding antibiotics in routine AOM must be weighed against heightened risks of mastoiditis and other complications.

Coalescent Mastoiditis

Etiology

Sometimes when a patient has AOM and mastoiditis that persist unabated for 2 to 4 weeks, coalescent mastoiditis develops. This mastoiditis is an acute progressive clinical infection with corresponding changes in the bone and mucoperiosteum of the mastoid air cell system. Coalescent mastoiditis is a disease affecting especially boys. Most patients are 4 years old or younger when they contract this disease. Bacterial virulence and decreased host resistance are important in its etiology, but mastoid development also plays a role. The condition rarely develops in children who have had chronic ear disease or in children with poorly pneumatized mastoids containing few air cells. Rather, coalescent mastoiditis tends to occur in children with well-developed air cell systems that contain numerous small pneumatic spaces, and in children who have had little or no previous otologic disease.

Pathology

Initially, hyperemia and edema of the mucoperiosteal lining of the mastoid air cells block the narrow aditus and disrupt aeration. The mucous membrane thickens, and impaired ciliary function prevents normal middle ear drainage through the eustachian tube. The serous

exudate becomes purulent as inflammatory cells accumulate. Continued inflammation, hyperemia, and accumulation of purulent debris result in venous stasis, localized acidosis, and decalcification of the bony septa. The osteoclastic activity in the inflamed periosteum softens and decalcifies the bony partitions, causing the small air cells to coalesce into a larger cavity.[11]

Pathophysiology

As the infection grows, elevated pressure within the mastoid may extend the infection beyond the confines of the mastoid. In the presence of intense inflammation and infection, phlebitis and periphlebitis are common and spread the infection to the adjacent meninges, sigmoid sinus, cerebellum, and temporal lobe.[12] Infection may extend to the meninges, sigmoid sinus, labyrinth, or facial nerve. The most common pathway for infection to extend beyond the mastoid is through the lateral cortex behind the ear. Less commonly, it can extend to the soft tissues in the upper portion of the neck (see section on Bezold's abscess) and, rarely, to the soft tissue anterior and superior to the auricle either by direct extension through eroded bone or by phlebitis and periphlebitis. Go and coworkers[13] found only 8 of 118 patients in whom the mastoiditis had caused an intracranial complication.

Diagnosis

Symptoms of coalescent mastoiditis (purulent otorrhea, fever, toxicity, and ear pain) are the same as symptoms seen in patients with uncomplicated AOM. The strongest historic suggestion of coalescent mastoiditis is the chronology of the infection in which purulent drainage or significant otalgia persists for 2 or more weeks, recurs after 10 to 14 days, or significantly worsens after that time interval. As a group, children with coalescent mastoiditis look sicker and have more toxicity with higher temperature and more persistent fevers than children with AOM. Older children may be able to localize the pain to the postauricular area rather than the ear canal. Physical findings that are most helpful include mastoid tenderness to percussion, mastoid erythema, and sagging of the posterosuperior external auditory canal wall.

The clinician should order a complete blood count and hematologic studies followed by CT scanning, which can establish the diagnosis by documenting the breakdown of the bony cell walls and opacification of the pneumatized spaces (Figs. 140-2 and 140-3). If any suggestion of an intracranial complication exists, the clinician should obtain an enhanced MRI scan.

Treatment

Treatment for coalescent mastoiditis can be either medical or surgical. Without question, complete mastoidectomy with ventilating tube placement in conjunction with appropriate antibiotic therapy provides prompt, precise eradication of all infected tissue in an expeditious and cost-effective manner. This approach is the most conservative management of this potentially serious complication. Because the increased vascularity and granulation tissue greatly increase the difficulty of the operation, however, it should not be undertaken lightly. Another consideration is that pneumatization has not progressed to incorporate the mastoid tip in children younger than 2 years, so there is risk of surgical injury to the facial nerve. The primary author's experience with cochlear implant surgery in children 12 to 24 months old suggests, however, that the facial nerve does not exit through the lateral surface of the mastoid in this age group as is commonly taught, and the risk of facial nerve injury in this age group is not substantial.

Appropriate intravenous antibiotics for a minimum of 3 to 6 weeks also eradicate the disease process in most infected infants who have no additional complications. The therapeutic choice for a specific patient depends on the clinical factors present and regional preferences. At the end of medical therapy, it is essential to document that the disease process has been completely eradicated. The patient should continue receiving antibiotic therapy until a CT scan documents that the mastoid air cell system is no longer opacified, and the middle ear is normally aerated.

Chronic Mastoiditis

Etiology

Chronic mastoiditis can occur in association with a long-standing tympanic membrane perforation, with cholesteatoma, or as a complication from an infection after placement of a middle ear ventilating tube. As noted previously, ventilating tube mastoiditis tends to occur in young children who have experienced water contamination and have undergone cultures and treatment with multiple antibiotic drops and oral antibiotics. Mastoiditis with tympanic membrane perforation occurs when an episode of AOM with perforation pursues a course of chronic infection, rather than resolving or developing into coalescent mastoidi-

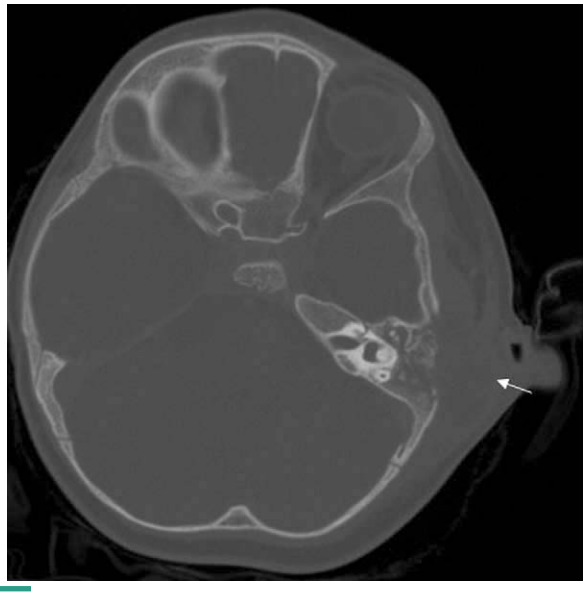

Figure 140-2. Axial temporal bone CT scan showing opacification of mastoid with loss of bony septa. Note defect in cortical bone and postauricular fluid collection *(arrow)*.

Figure 140-3. Coronal temporal bone CT scan of patient in Figure 140-2. Note defect in cortical bone *(arrow)*.

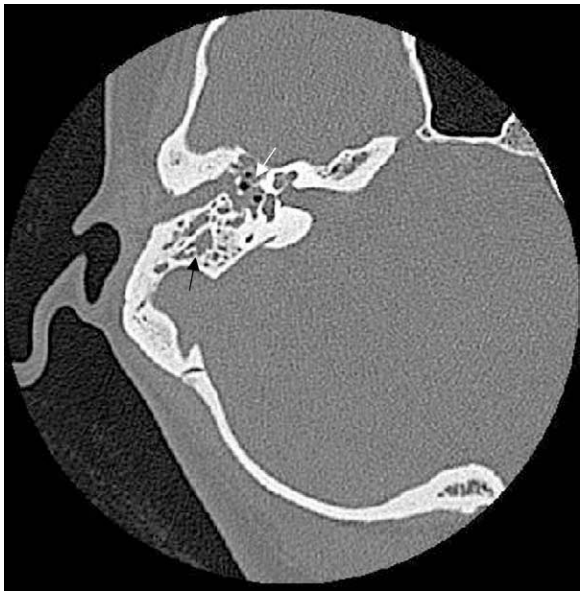

Figure 140-4. Axial temporal bone CT scan showing opacification of middle ear *(white arrow)* and mastoid *(black arrow)*.

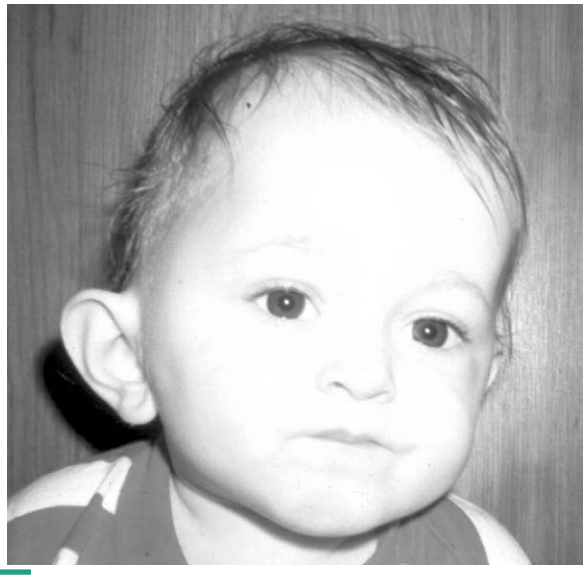

Figure 140-5. Postauricular abscess associated with coalescent mastoiditis. Auricle is displaced laterally and inferiorly. *(From Harker LA. Cranial and intracranial complications of acute and chronic otitis media. In: Snow JB, Ballenger JJ, eds.* Ballenger's Otorhinolaryngology Head and Neck Surgery. *16th ed. Hamilton, Ontario: Decker; 2003.)*

tis. Chronic mastoiditis of this type can also begin when a long-established uninfected central perforation becomes infected and extends to the mastoid (Fig. 140-4).

Although cholesteatoma frequently remains uninfected for long periods, it tends to suppurate, form granulation tissue, and erode bone. When any type of mastoiditis causes continuous purulent drainage, there is little likelihood of complete resolution with antibiotics. Chronic mastoiditis requires surgical intervention to heal, and an infected cholesteatoma requires surgical ablation, regardless of duration. Complications in patients with chronic mastoiditis with tympanic membrane perforation can develop at any time, but often occur only after weeks or months of otorrhea. In contrast, cholesteatoma typically requires months or years to produce complications.

Masked Mastoiditis

Chronic otitis with granulation tissue formation and bone erosion can occur without otorrhea. It can persist despite a normal or near-normal tympanic membrane. This condition has been referred to as *masked mastoiditis* and usually occurs in patients who have received numerous courses of antibiotics. In this complication, the middle ear and much of the mastoid respond to the antibiotics, but a focal area of persistent infection somewhere in the mastoid does not. Patients experience chronic but not severe auricular and postauricular pain, slight but definite tenderness to percussion of the mastoid cortex, and CT scan evidence of a localized area of opacification in an otherwise normal mastoid. Surgical excision eliminates the symptoms.

Samuel and Fernandez[14] described 21 cases of mastoiditis with retroauricular swelling and an intact tympanic membrane in a South African population (19 patients were <13 years old) in whom the duration of symptoms was shorter than that usually seen with coalescent mastoiditis. The predominant finding at mastoidectomy was granulation tissue filling the mastoid cavity and the antrum. The tympanic membrane was described as hyperemic, dull, bluish, bulging, or retracted. In addition to their mastoiditis, 10 patients had postauricular abscesses, 3 had Bezold's abscesses, and 2 had facial nerve palsy. Four patients had cellulitis or abscess in the posterior fossa. Although these cases do not represent masked mastoiditis, they show the important fact that medically significant mastoiditis can exist without purulent otorrhea. There are two keys to the successful diagnosis and management of masked mastoiditis: (1) mastoid disease is not always reflected by the appearance of the tympanic membrane, and (2) chronic mastoiditis is a surgical condition, regardless of the appearance of the tympanic membrane. In this regard, the diagnosis and management of masked mastoiditis are no different from the diagnosis and management of mastoiditis with otorrhea emanating from other causes.

Postauricular Abscess

Postauricular abscess is the most common complication of mastoiditis. It is most often seen accompanying acute or coalescent mastoiditis in young children. The infection extends from the mastoid to the subperiosteal space; this usually occurs by direct extension subsequent to bone destruction or by phlebitis and periphlebitis of mastoid veins. The tiny pits in adult temporal bones that make up the cribriform area of the mastoid near the spine of Henle exist in newborns as a series of open channels between the interior of the mastoid and the cortex. Until these channels have closed, infection can pass directly from the mastoid to the subperiosteal space in these very young children. Regardless of how it starts, soft tissue infection leads to tissue necrosis and abscess formation. The surrounding soft tissue exhibits thickening, inflammation, erythema, tenderness, and fluctuation.

The diagnosis is usually obvious. Because only the upper part of the mastoid is pneumatized, the process develops in that upper portion, and the tissue edema and the abscess drive the auricle downward and laterally (Fig. 140-5). In the early stages, if fluctuation is not obvious, the clinician should use imaging studies or ultrasonography to document the presence of air within the soft tissue or an abscess cavity with its capsule (Figs. 140-6 and 140-7). When mastoiditis has produced an abscess, excision and drainage in conjunction with mastoidectomy is indicated. Only in the most unusual of circumstances would treatment by prolonged antibiotics and drainage of the abscess without mastoidectomy be appropriate.

Bezold's Abscess

In his 1913 text, *Diseases of the Ear,* Kerrison[15] described a Bezold abscess as a condition:

> ... caused by a perforation in the bony plate forming the inner surface of the tip of the mastoid. It occurs presumably in cases in which the tip cells are especially large and in which the bony plate forming the inner or medial wall of the tip is very thin, and the outer cortex thick. Pus escaping through such a perforation burrows down-

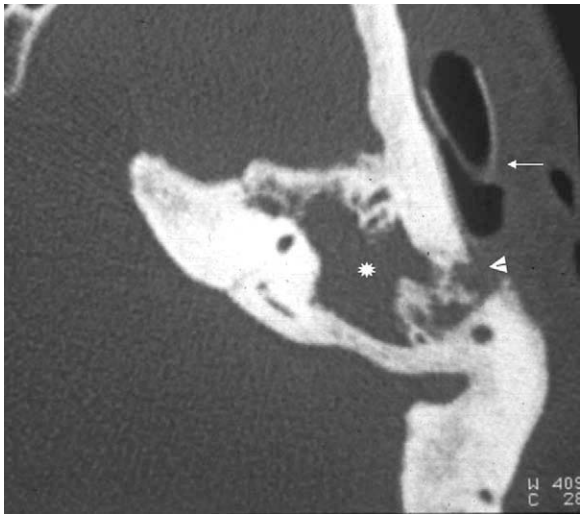

Figure 140-6. Axial temporal bone CT scan (soft tissue) showing abscess cavity with gas *(arrow)*. Note cortical defect *(arrowhead)* and mastoid opacification and loss of bony septa *(star)*.

Figure 140-7. Axial temporal bone CT scan (soft tissue) with contrast enhancement. Note postauricular abscess with enhancing capsule *(arrow)*.

ward in the neck beneath the sternomastoid, or may be confined between layers of the deep cervical fascia.

The cervical infection develops into an abscess in the upper neck deep to the sternocleidomastoid muscle. Bezold's abscess can also develop without any erosion or penetration of the inner and outer cortex of the mastoid if phlebitis and periphlebitis propagate the infection to the same area. Because infants have limited mastoid pneumatization, Bezold's abscess occurs more commonly in older children in whom pneumatization has extended into the mastoid tip and in adults who have either chronic mastoiditis or cholesteatoma.

Often, the diagnosis of Bezold's abscess is not considered initially in young patients with deep, tender, upper cervical masses because inflamed lymph nodes from many causes are so common. If the history and physical examination do not reveal a specific etiology, the clinician should obtain a CT scan to identify or rule out a mastoid source (Figs. 140-8 through 140-11).

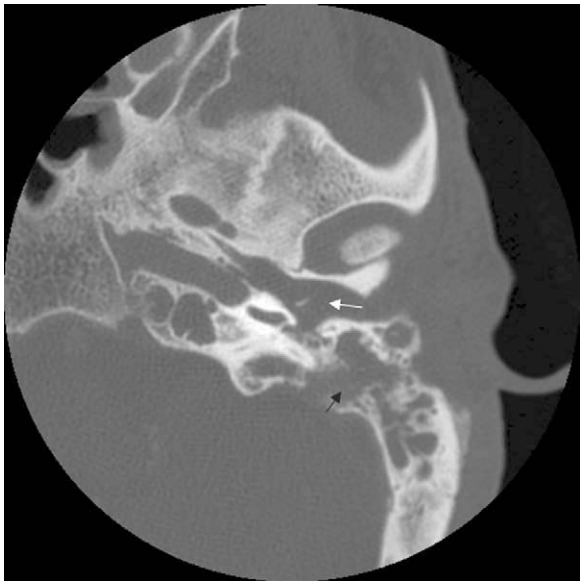

Figure 140-8. Axial temporal bone CT scan showing opacification of external auditory canal and middle ear *(white arrow)*. Also note the destruction of bony septa in the inferior part of the mastoid process *(black arrow)*.

The recommended treatment is complete surgical excision of the mastoid pathology, drainage of the abscess, and removal of any associated granulation tissue. The surgeon should use bipolar electrocautery, copious suction irrigation, and coarse diamond burs to allow him or her to visualize the pathology adequately and exenterate all of the diseased cells thoroughly. The surgeon should drain the mastoid and the abscess cavity.

Temporal Root Abscess

The soft tissues above and even anterior to the auricle can become infected and form an abscess from suppuration that involves the cells of the zygomatic root of the mastoid (temporal root of the zygoma). Similar to Bezold's abscesses, temporal root abscesses can form by direct extension via bone erosion through epitympanic temporal root cells or via phlebitis. The clinical picture may be confusing because abscesses in this location are rare. CT scanning is always recommended to rule out mastoiditis as the source. Surgical drainage is recommended.

Petrous Apicitis

Each petrous apex is undeveloped (sclerotic), contains marrow, or exhibits a variable degree of pneumatization. Pneumatization develops in only approximately 30% of temporal bones.[12] Much has been written about the different cell tracts that extend into and pneumatize the petrous apex. Basically, the cells extend into the apex above (supralabyrinthine) (Fig. 140-12), behind (retrolabyrinthine) (Fig. 140-13), beneath (infralabyrinthine) (Fig. 140-14), or in front of the labyrinth (anterior labyrinthine). Petrous apicitis is essentially mastoiditis that occurs in the petrous apex. It is rare because infection in sclerotic apices or petrous apices containing marrow is uncommon, and because the prevalence of pneumatization is low. Petrositis develops by direct extension of a mastoid infection, but the mastoid may respond to medical or surgical treatment without apical resolution. Just as there can be disjunction between the state of infection in the middle ear and the mastoid, the same holds true between the mastoid and the petrous apex.

The pathology of the infection can mirror that seen in coalescent mastoiditis, with dissolution of thin cellular septa and coalescence, or it can resemble the formation of granulation tissue with chronic bone erosion seen with chronic mastoiditis. Rarely, there is extension of

Figure 140-9. Axial temporal bone CT scan of the patient in Figure 140-8 at level of the root of styloid process *(white arrow)* showing destruction of bone at the anterior aspect of mastoid tip *(black arrow)*.

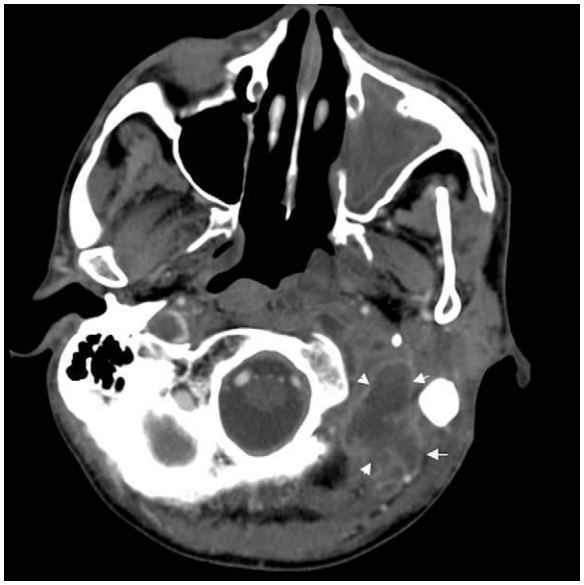

Figure 140-10. CT scan of patient in Figure 140-8 showing Bezold's abscess with enhancing capsule *(arrows)* at level of the mastoid tip.

Figure 140-11. CT scan of patient in Figure 140-8 showing the abscess cavity *(arrows)* extending lower in the neck to level of hyoid bone *(arrowhead)*.

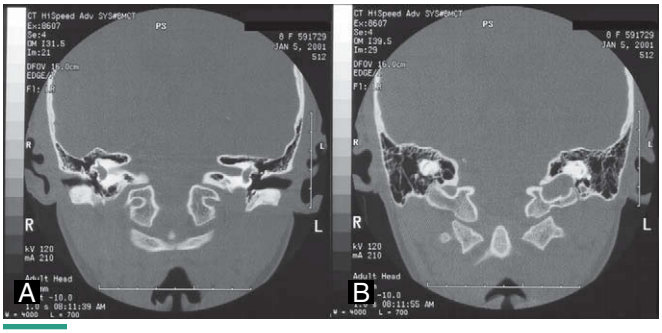

Figure 140-12. **A** and **B,** Petrous apex pneumatization via supralabyrinthine cell tract at level of vestibule **(A)** and posterior semicircular canal **(B)**. *(From Harker LA. Cranial and intracranial complications of acute and chronic otitis media. In: Snow JB, Ballenger JJ, eds.* Ballenger's Otorhinolaryngology Head and Neck Surgery. *16th ed. Hamilton, Ontario: Decker; 2003.)*

cholesteatoma to the apex. Imaging studies usually include CT and MRI. CT scan shows the bony details of the septa of the air cells and the size and contour of the entire apex (Figs. 140-15 through 140-20). MRI differentiates marrow from mucus or CSF. CT and MRI studies are essential to establish when there is opacification of the air cells in the petrous apex under suspicion, as opposed to asymmetric pneumatization. When one petrous apex is well pneumatized, a small sclerotic or marrow-containing apex on the opposite side can be misinterpreted as a pneumatized apex opacified by fluid or infection.

The symptoms of infection in the petrous apex reflect the innervation of the air cells and the structures adjacent to the apex itself. Although increased pressure within the mastoid air cell system causes pain in the region of the mastoid and the ear itself, pressure within the petrous apex usually results in pain referred to the retro-orbital area or deep within the skull. Patients with petrous apicitis can have symptoms that reflect infection in the middle ear and mastoid, and symptoms emanating from the apex. The most common symptoms are deep or retro-orbital pain (from irritation of the contiguous trigeminal ganglion in Meckel's cave), paralysis of cranial nerve VI as it passes through Dorello's canal abutting the petrous apex, dysfunction of cranial nerves VII and VIII, or labyrinthitis. In 1904, Gradenigo described the triad of retro-orbital pain, sixth cranial nerve paralysis, and otorrhea, since known as Gradenigo's syndrome.[12] Only a few patients with petrous apicitis exhibit the full triad today.

The treatment of the apicitis depends on the duration, severity, and presence or absence of associated complications. Because of the anatomic complexities and the necessity to work around the labyrinth and the carotid artery, petrous apex air cell disease cannot be excised. Established drainage and prolonged antibiotics are an integral part of treatment, with or without surgery. When there is obvious necrotic

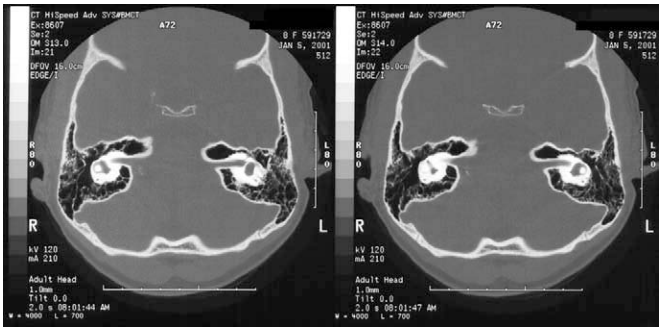

Figure 140-13. Petrous apex pneumatization via retrolabyrinthine cell tract at two levels of internal auditory canal and vestibule. *(From Harker LA. Cranial and intracranial complications of acute and chronic otitis media. In: Snow JB, Ballenger JJ, eds.* Ballenger's Otorhinolaryngology Head and Neck Surgery. *16th ed. Hamilton, Ontario: Decker; 2003.)*

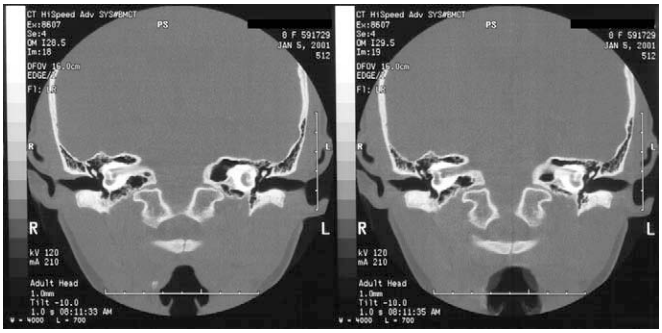

Figure 140-14. Petrous apex pneumatization via infralabyrinthine cell tract in right temporal bone at level of internal auditory canal. *(From Harker LA. Cranial and intracranial complications of acute and chronic otitis media. In: Snow JB, Ballenger JJ, eds.* Ballenger's Otorhinolaryngology Head and Neck Surgery. *16th ed. Hamilton, Ontario: Decker; 2003.)*

Figure 140-15. Axial temporal bone CT scan showing left petrous apicitis. Note opacification of the petrous apex with destruction on bony septa *(star)*. A dehiscence of the carotid canal and narrowing of the petrous carotid artery (*arrow)* also are seen on this contrast study.

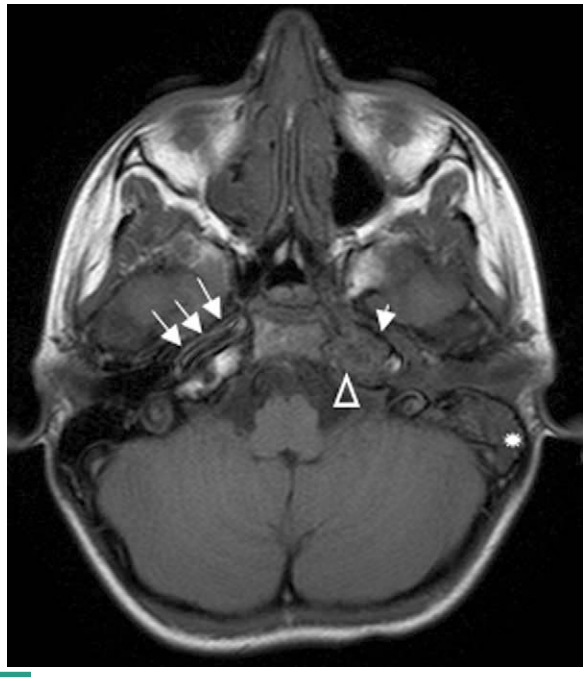

Figure 140-16. Axial non–contrast-enhanced T1-weighted MRI of the patient in Figure 140-15 showing mastoid opacification *(star)*. The left petrous apex is also opacified *(triangle)* in contrast to the bright fat signal seen on the right side. Note narrow caliber of left internal carotid artery *(short arrow)* compared with internal carotid artery on the right *(arrows)*.

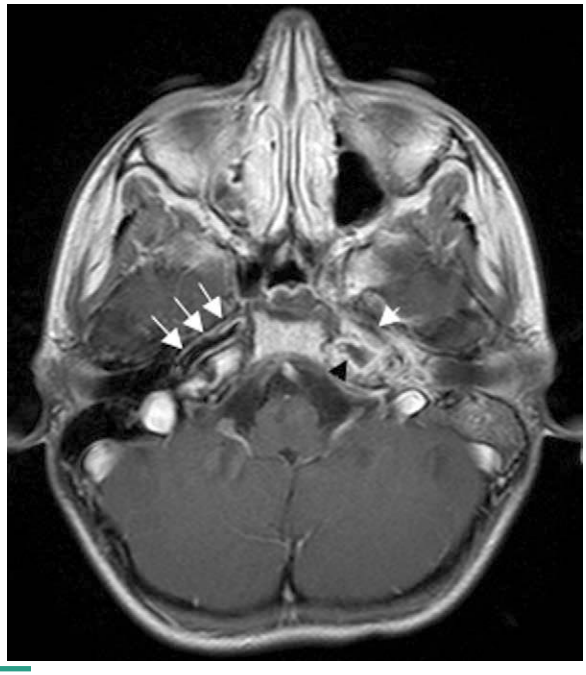

Figure 140-17. Axial contrast-enhanced T1-weighted MRI of the patient in Figure 140-15 showing low signal in left petrous apex with peripheral contrast enhancement *(black arrowhead)* consistent with inflammation. Note narrow caliber of left internal carotid artery *(short arrow)* compared with internal carotid artery on the right *(arrows)*.

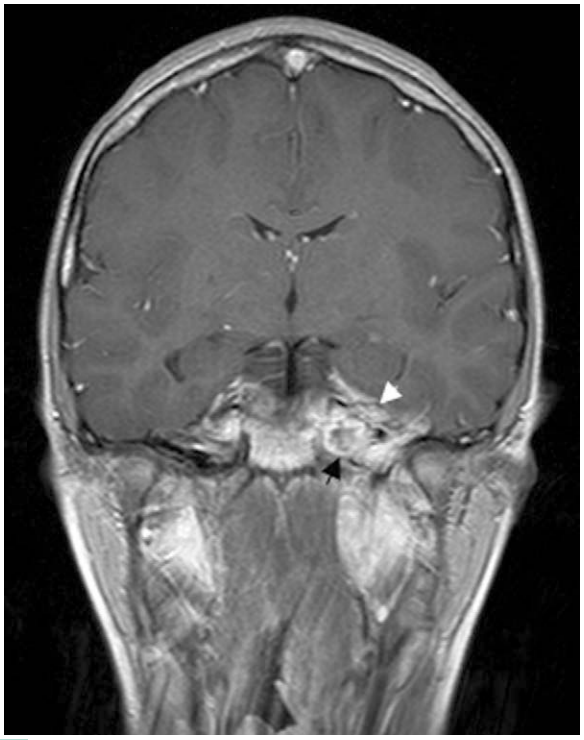

Figure 140-18. Coronal contrast-enhanced T1-weighted MRI of the patient in Figure 140-15 showing low signal in left petrous apex with peripheral contrast enhancement *(black arrow)*. Note enhancement of dura and temporal lobe adjacent to petrous apex *(white arrowhead)*.

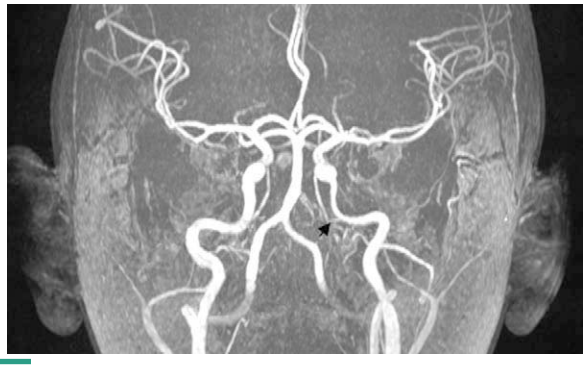

Figure 140-19. MR angiography of the patient in Figure 140-15 showing narrowing of left petrous internal carotid artery *(arrow)*.

bone, surgical drainage is a necessary adjunct to intravenous antibiotic therapy. When there is adequate access and widespread disease, even partial apicectomy can reduce the bacterial load so that antibiotics and host defenses can control the disease.

The surgical approach to the apex depends on available air cell pathways and the portion of the apex involved. In some temporal bones, access can be gained by a route posterior to the posterior semicircular canal; in others, the best route is subcochlear, infralabyrinthine. In a small percentage of temporal bones, there is an opportunity to provide drainage via cells extending over the superior semicircular canal and through the "hole in the doughnut," working through the center of the superior semicircular canal. Air cell tracts containing granulation tissue can usually be followed into the apex. The original anterior petrous apex drainage procedure described by Lempert necessitated a radical mastoidectomy and is rarely used today. Occasionally, with evidence of osteitis or abscess formation in the apex, and limited or inadequate access via the existing air cells pathways, the middle cranial fossa approach can provide access for exposure, culture, and irrigation.

Figure 140-20. MR angiography of the patient in Figure 140-15 showing normal caliber of internal carotid artery after resolution of narrowing *(arrow)*.

Labyrinthine Fistula

Labyrinthine fistula represents an erosive loss of the endochondral bone overlying the semicircular canals without loss of perilymph (distinguished from perilymphatic fistula, discussed elsewhere in this text). This loss of the overlying protective bone allows pressure or mass-induced motion of the underlying endosteum, perilymph, and, by contiguity, endolymphatic compartment, evoking vestibular and sometimes auditory symptoms. Most labyrinthine fistulas involve only the lateral semicircular canal. In a few instances, these erosions expose the superior or posterior semicircular canal, the vestibule, or the cochlea.

This bone resorption is almost exclusively secondary to cholesteatoma, and it occurred in 7% of the cholesteatomas in the large series by Gersdorff and Nouwen.[16] Higher percentages have been reported, but the actual incidence is hard to determine. Most reports of labyrinthine fistulas caused by cholesteatoma are from tertiary care referral centers that include many large or previously operated cases, perhaps biasing the prevalence. Studies reviewing suppurative complications of otitis media usually do not include all cases of labyrinthine fistulas because many are not infected, or do not cause significant symptoms and are detected only at surgery. The mechanisms by which cholesteatoma causes this bony erosion are not fully understood, and are the subject of other chapters. Suffice it to say, first there is demineralization of the dense endochondral bone, and then loss of bone substance, so that the perilymph and its surrounding endosteal membrane have less and less bone between them and the overlying cholesteatoma matrix. As the bone becomes thin, it can be observed at surgery as a "blue line" parallel to the underlying semicircular canal lumen because the illuminating light along the blue line is no longer reflected off the dense bone, but absorbed into the underlying fluid.

Manolidis[17] reviewed the records of 111 inner-city patients in Texas with labyrinthine fistulas, and assessed their coexisting complications. Two associations were prominent. The facial nerve was involved with cholesteatoma or functionally damaged by a cholesteatoma in 60% of the patients, and dehiscences of the tegmen occurred in 39%. Most of these cases were reoperations, with an average of 2.6 operations per patient. Although the data are biased by the number of revision operations, surgeons should always assume that the bony fallopian canal is eroded and the facial nerve is in direct contact with cholesteatoma whenever a lateral semicircular canal fistula is suspected, and they should consider the possibility of defects in the tegmen in such patients, especially patients with previous mastoid surgery.

Most patients present with signs and symptoms of the underlying cholesteatoma. Symptoms attributable to labyrinthine fistulas are primarily vestibular. Patients recount brief periods of imbalance, dysequilibrium, or vertigo, but have normal equilibrium most of the time. Some may be able to recall causing momentary imbalance by pushing on their external ear canal, such as with a washcloth, or have noticed that loud sounds provoke brief imbalance (Tullio's phenomenon).

Figure 140-21. Axial temporal bone CT scan showing soft tissue density in a mastoid cavity eroding into horizontal semicircular canal *(arrow)*.

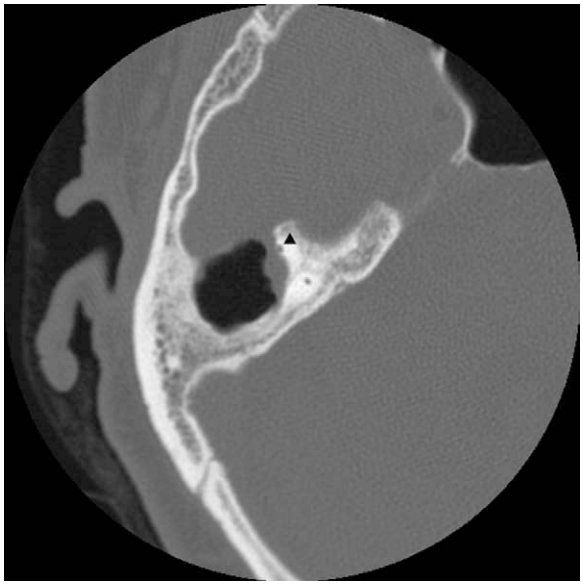

Figure 140-22. Axial temporal bone CT scan of the patient in Figure 140-21 showing erosion of anterior limb of superior semicircular canal *(arrowhead)*.

After a suspicious history, the principal diagnostic maneuver is the fistula test. The clinician occludes the external auditory canal of the ear with the pneumatic otoscope, and then gently increases and decreases the external auditory canal pressure so that the changes are transmitted from the external auditory canal to the middle layer and mastoid air cells system via an intact or perforated tympanic membrane. During the procedures, the patient is asked to fix the eyes in the cardinal position, and the physician observes the patient's eyes for any deviation from that cardinal position. In the case of a normal ear, no eye motion or symptoms are provoked. With a lateral canal fistula, positive external auditory canal pressure causes compression of the lateral semicircular canal endosteum, and utriculopetal endolymph flow resulting in conjugate deviation of the eyes away from the side of compression, a positive fistula sign. Negative external auditory canal pressure results in conjugate deviation toward the ear under the test. The patient may subjectively note motion of the environment or slight nausea during the pressure alterations.

The fistula test results are reported as positive in only 55% to 70% of patients with lateral canal erosion, but if positive, they are highly reliable and facilitate surgical planning and execution.[18] CT scanning (Figs. 140-21, 140-22, and 140-23) also provides preoperative evidence suggesting a labyrinthine fistula, and images in the bone algorithm usually document the bone erosion of the lateral semicircular canal and show other signs suggestive of cholesteatoma.

The treatment of labyrinthine fistulas addresses the underlying cholesteatoma. When there are other, more grave complications, their management supersedes that of the fistula. The decision whether to remove the external auditory canal and perform an open cavity mastoidectomy or to retain the canal wall in a canal wall up technique is made on the basis of the surgeon's ability to eradicate the cholesteatoma completely, the degree of pneumatization of the temporal bone (adequate access), and the surgeon's confidence that he or she can completely remove the cholesteatoma matrix from the fistula site. Whether the canal wall up or canal wall down technique is used, the operation is completed, leaving the fistula site for last.

The surgeon identifies the blue line of the actual fistula and the adjacent thinned layer of bone on either side of it. The plane separating the matrix and the endosteum is developed, and under high magnification with good hemostasis a flat dissector wider than the semicircular canal itself is used to peel the matrix gently from the underlying endosteum. A fine microsuction elevates the cholesteatoma and facilitates visualization and removal. If the endosteum is torn, it is best to replace

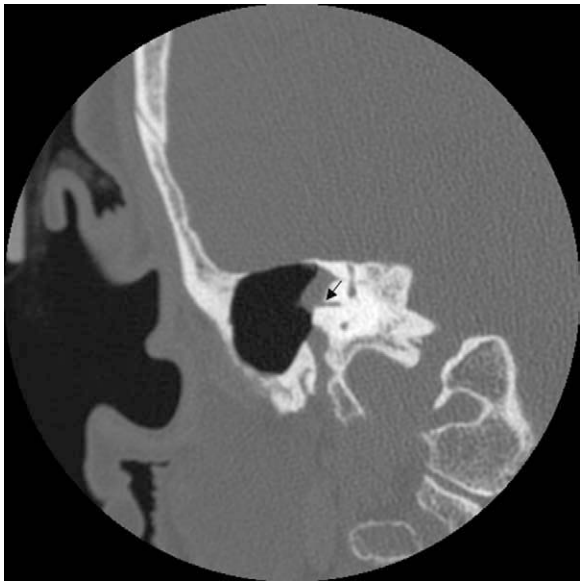

Figure 140-23. Coronal temporal bone CT scan of the patient in Figure 140-21 showing erosion of horizontal semicircular canal *(arrow)*.

the adjacent matrix and terminate the procedure. If it is successfully removed, a small piece of tissue or a shaped cap of bone is placed over the site and secured in place with fibrin glue or packing. In some cases, especially with large fistulas, it may be best to perform a canal wall down procedure and leave the fistula covered by matrix, which later forms the mastoid cavity lining.

Removal of the fistula generally improves the vestibular symptoms, although symptoms related to pressure transmitted from the external auditory canal can persist for some time. Because there is no protective bone to prevent compression of the endolymphatic compartment by pressure changes in the external auditory canal, a positive fistula sign persists until there is a regrowth of bone. Loss of hearing in the involved ear and worsening of existing hearing are the risks that always accompany the procedure, but these have been reported to occur in less than 20% of carefully managed fistula cases.[9]

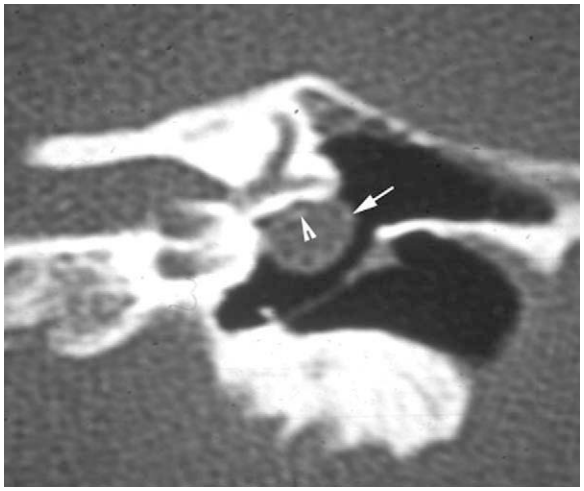

Figure 140-24. Coronal temporal bone CT scan showing cholesteatoma *(arrow)* eroding the facial nerve canal *(arrowhead)*.

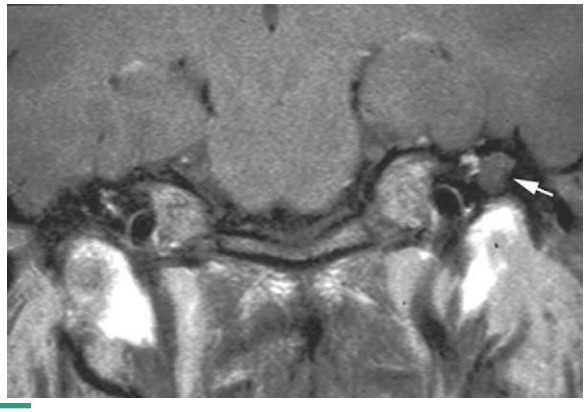

Figure 140-25. Coronal T1-weighted MRI of the patient in Figure 140-24 showing cholesteatoma *(arrow)*.

Figure 140-26. Axial temporal bone CT scan showing chronic mastoiditis with opacification of mastoid, external auditory canal, and middle ear. Note erosion and involvement of vestibule *(arrowhead)*.

Facial Nerve Paralysis

Facial nerve paralysis can result from AOM, COM without cholesteatoma, or cholesteatoma. Bacteria reach the nerve because of congenital dehiscences of the bony fallopian canal or via erosion with granulation tissue or cholesteatoma. Facial nerve function is lost with inflammatory pressure or suppurative neurapraxia. If the edema persists, axonotmesis can ensue.

In young children, facial paralysis that is caused by AOM is frequently incomplete and probably occurs only in infants with congenital dehiscence of the fallopian canal in the middle ear adjacent to the stapes. Facial weakness in these cases rarely lasts longer than 3 weeks even when complete paralysis is present.

Facial nerve paralysis caused by COM without cholesteatoma also usually affects the horizontal portion of the facial nerve near the stapes.[19] In these cases, the clinical course of the paralysis is more likely to be prolonged, with a gradual progression from slight weakness to full paralysis; sometimes the progression to complete paralysis is rapid (Figs. 140-24 and 140-25). Facial nerve paralysis caused by cholesteatoma can produce extensive erosion of the horizontal segment of the fallopian canal—especially common in large, uninfected, primary acquired cholesteatomas. An erosive cholesteatoma can expose the facial nerve anywhere in the temporal bone and cause paralysis. In these cases, the onset of the paralysis is usually gradual, and sometimes the progression is so slow that patients do not seek medical attention for months. When the onset of facial paralysis is this slow, the paralysis is more likely to persist after surgical treatment.

When facial paralysis is caused by AOM, appropriate antibiotic therapy for AOM may be adequate treatment, although myringotomy with evacuation of the purulent material and reduction of the numbers of bacteria is recommended. When facial nerve paralysis follows chronic suppurative otitis media (with or without cholesteatoma), the surgeon should remove the infection surrounding the nerve as part of the mastoidectomy. The surgeon gradually approaches the granulation tissue or cholesteatoma overlying the nerve from the proximal and distal portions of the nerve, which are uninvolved by the chronic infection. Diamond burs should be used to remove carefully the bone of the fallopian canal on both sides of the diseased portion. The surgeon uses a flat blunt instrument to dissect the chronic inflammatory tissue from the nerve while elevating the diseased tissue with a small suction tip. It may be necessary to use sharp dissection to separate the inflammatory tissue from the epineurium. The outcome for surgical decompression of the facial nerve caused by chronic suppurative otitis media primarily depends on whether the nerve has undergone complete degeneration before surgery.

Acute Suppurative Labyrinthitis

Bacterial invasion of the labyrinth is always promptly followed by total loss of auditory and vestibular function (Figs. 140-26 through 140-29). Usually, AOM extends into the labyrinth through a weakened or dehiscent oval window membrane, as occurs in congenital labyrinthine deformities such as Mondini's deformity and enlarged vestibular aqueducts, and in individuals who have undergone stapes surgery. Although it is not proven, suppurative labyrinthitis may be a common mechanism for unilateral anacusis in children with Mondini's deformity. These children are at additional risk. The foramina of the internal auditory canal opening into the medial aspects of the labyrinth may also be weak or dehiscent, and those foramina and the cochlear aqueduct can permit bacterial infection to progress from the labyrinth to the meninges or vice versa. It is unknown how frequently suppurative labyrinthitis causes meningitis, or how often meningitis subsequently causes bacterial labyrinthitis, but both probably occur, especially in the special population of children with congenital labyrinthine abnormalities.

Direct bacterial invasion of the labyrinth through a cholesteatomatous lateral semicircular canal fistula is another cause for acute suppurative labyrinthitis. In this situation, infected granulation tissue beneath the cholesteatoma matrix lies directly on the endosteal membrane and its underlying perilymph. The bacteria causing the labyrinthitis are those of the underlying AOM or the cholesteatoma.

The diagnosis of acute suppurative labyrinthitis is clinical. Tinnitus and dizziness rapidly progress to whirling vertigo, pallor, dia-

Figure 140-27. Coronal temporal bone CT scan of the patient in Figure 140-26. Note the erosion and involvement of the fundus of the internal auditory canal *(arrowhead)*.

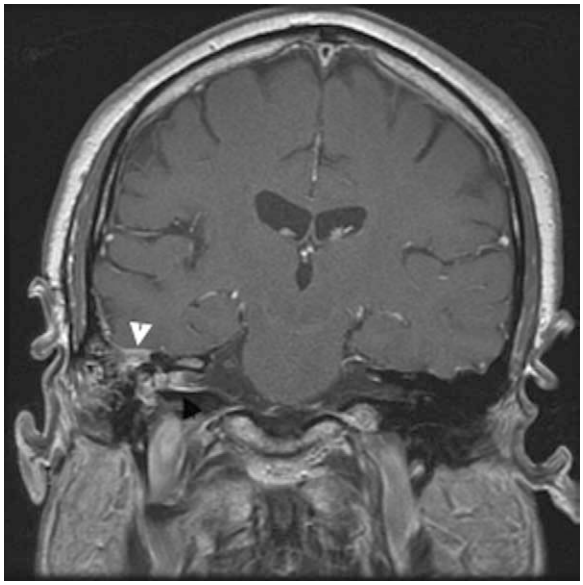

Figure 140-29. Coronal contrast-enhanced T1-weighted MRI of the patient in Figure 140-26 showing enhancement of temporal lobe dura *(white arrowhead)* and internal auditory canal *(black arrowhead)*.

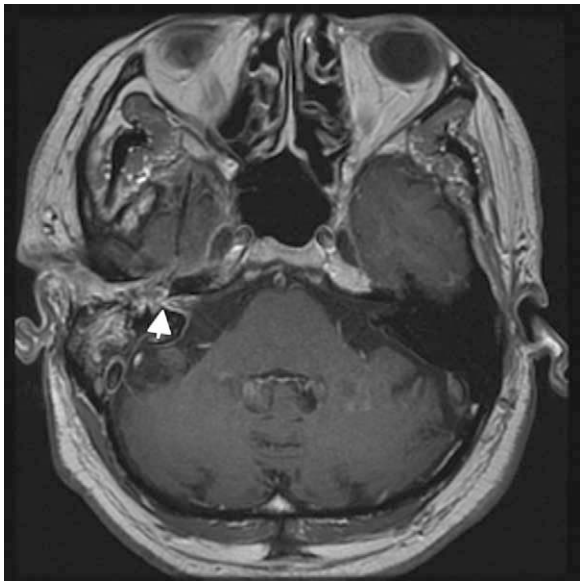

Figure 140-28. Axial contrast-enhanced T1-weighted MRI of the patient in Figure 140-26 showing enhancement of middle ear, vestibule, and internal auditory canal *(arrowhead)*.

phoresis, nausea, and vomiting. Brisk labyrinthine nystagmus directed toward the opposite ear accompanies the vertigo. After the first several hours, the spontaneous vertigo and nystagmus gradually begin to abate. Symptomatic improvement continues during the next few days. Over the next 2 to 3 weeks, central nervous system compensation occurs, and normal or near-normal balance is restored. Tinnitus often abates, but all hearing is lost.

No specific diagnostic studies are necessary when the typical clinical picture develops in a patient with AOM or COM and a predisposing condition. Although there is no possibility of reversing the clinical course, appropriate antibiotic treatment for 10 days is recommended to eradicate the labyrinthine infection and to prevent propagation to the meninges. Other therapeutic measures are dictated by the underlying otitis, but labyrinthectomy is unnecessary in labyrinthitis secondary to AOM.

Encephalocele and Cerebrospinal Fluid Leakage

Encephalocele (brain hernia, brain fungus, meningoencephalocele) and CSF leakage are associated with cranial or intracranial complications when they coexist with AOM or COM. Three different clinical patterns can occur.

Spontaneous CSF leakage sometimes develops in conjunction with defects in the tegmen tympani or, less commonly, the tegmen mastoideum. May and colleagues,[20] Lundy and associates,[21] and others have reported this in more than 50 patients who have not undergone previous otologic surgery. Of such patients, 70% to 80% are older than 45 years. The defects range in diameter from 2 mm to 2 cm, and sometimes are multiple. Usually, an encephalocele protrudes through the defect (Figs. 140-30 and 140-31). There is no agreement as to why the dura breaks down and allows protrusion of cerebral contents and escape of CSF in these older patients, although Jackson and colleagues[22] have suggested that aging, increased intracranial pressure, low-grade inflammation, arachnoid granulation, and irradiation can play a part. Patients frequently visit their physicians because of hearing loss secondary to reduced ossicular motion from the middle ear fluid or the encephalocele. Myringotomy and placement of a ventilating tube manifest profuse watery otorrhea that tests positive for CSF. Other patients present with signs and symptoms of meningitis, and many of these patients have experienced one or more previous bouts of that disease.

Encephalocele and CSF leakage secondary to COM occur when a cholesteatoma and granulation tissue erode through the bony plates separating the mastoid from the temporal lobe, the cerebellum, and the dura adjacent to the bone. The mastoid and epitympanic tegmen are involved more frequently than the cerebellar plate. A cholesteatoma needs to be present for many months to years to cause this degree of bone erosion, cerebral prolapse, and dural erosion.

Traumatic encephalocele and CSF leakage is the most common pattern. Although a few of these cases occur because of temporal bone fracture, most are a consequence of surgical trauma, such as when portions of the tegmen or cerebellar plates have been surgically removed, and the dura is exposed and sometimes traumatized. In these situations, the disease process and the surgery can contribute to the bony and dural trauma that facilitates the development of an encephalocele, CSF leakage, and intracranial complications. Manolidis[23] reported a series of 29 such patients from an inner-city population. More than 80% of the patients had cholesteatoma, and half had undergone one or two previous operations. All had dural herniations and encephaloceles, but

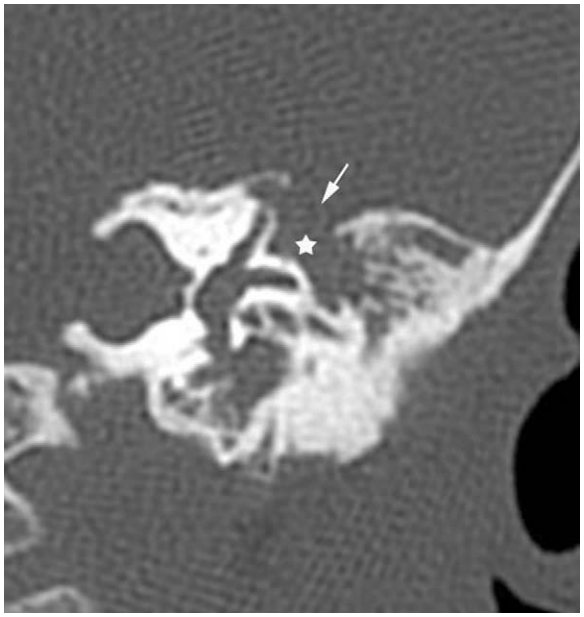

Figure 140-30. Coronal temporal bone CT scan showing encephalocele *(star)* going through a tegmen defect *(arrow)*.

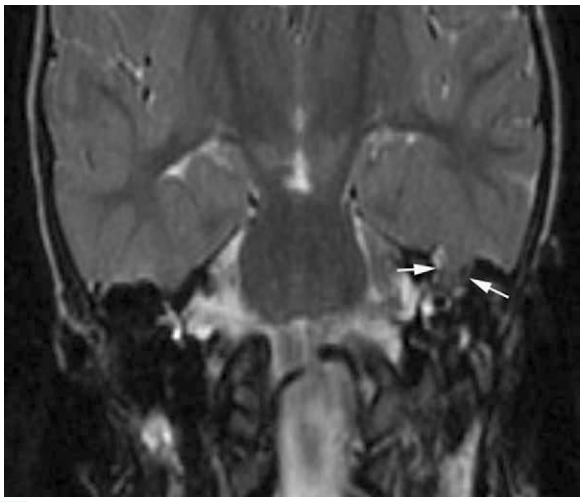

Figure 140-31. Coronal T2-weighted MRI of the patient in Figure 140-30 showing encephalocele *(arrows)*.

only one had CSF leakage. Labyrinthine fistulas, suppurative intracranial complications, and associated facial paralysis were noted.

Jackson and colleagues[22] have written an excellent review of this subject. The size of the bony defect and the volume of herniated brain are two of the important factors in choosing a surgical approach. Small defects are managed adequately through the mastoid; multiple and larger defects are repaired by the middle cranial fossa approach in combination with mastoid exposure.

The middle fossa approach provides excellent exposure of the tegmen defect and access to repair the dural defect. A temporalis fascia graft is used to repair the dura, which is often quite attenuated. The bony defect can be repaired with a split calvarial bone graft taken from the inner table of the craniotomy flap. It is fashioned larger than the bony defect, and is placed on the intracranial surface so that it can support the brain. Another technique to repair the tegmen defect is the use of hydroxyapatite cement. The floor of the middle fossa can be reconstituted, and a watertight seal can be obtained. Care must be taken to avoid cement contact with the ossicles, or a conductive hearing loss results.

Intracranial Complications

Meningitis

A dramatic reduction in the incidence of meningitis caused by AOM and COM has occurred because of immunizations against the common causative organisms. Two decades ago, *H. influenzae* and *S. pneumoniae* caused nearly all cases of otogenic meningitis. After *H. influenzae* type B vaccination became part of routine pediatric immunizations in the United States in the early 1980s, *H. influenzae* meningitis dramatically decreased and has now almost disappeared. Today, pneumococcal conjugate vaccine PCU-7 (Prevnar), the multivalent pneumococcal vaccine effective in young children, is also a routine pediatric immunization in the United States, and similar reductions in otogenic streptococcal meningitis are occurring in the most susceptible age group—younger than 2 years old. In any given country, the incidence of meningitis as a complication of suppurative otitis is inversely proportional to the prevalence of immunizations against these two bacteria.

In the past, meningitis was the most common complication of AOM and COM. In the series by Gower and McGuirt[24] of 100 consecutive patients with intracranial complications of AOM and COM, 76 had meningitis, and 53 of those patients were younger than 2 years. In that age group, most cases occurred by hematogenous dissemination of infection during AOM. Sometimes, these patients are not tabulated in reports documenting the complications of otitis,[1,25] and in those reports the frequency of otitis-induced meningitis is low.

Conditions that allow CSF to gain access to the middle ear cavity predispose to the development or recurrence of bacterial meningitis. CSF otorrhea is common after lacerations of the dura by longitudinal temporal bone fractures. Congenital defects of the tegmen, with or without encephalocele, can also be accompanied by CSF leakage into the epitympanum and middle ear, as can unrecognized injury to the dura of the posterior or middle cranial fossae during mastoid surgery. Patients with syndromic or nonsyndromic congenital stapes fixation, Mondini's dysplasia, and enlarged vestibular aqueducts also are at risk for a bacterial middle ear infection to spread to the CSF. The pathway can be obvious, such as when a "perilymph gusher" is discovered during stapes surgery, or it can be more subtle, when there are microscopic disruptions of the continuity of the oval or round windows, the internal auditory canal, and the cochlear aqueduct. Meningitis can occur even in individuals with normal middle ear and labyrinthine anatomy if AOM complicates conditions such as traumatic stapes dislocation or perilymphatic fistula and then progresses on to acute suppurative labyrinthitis.

The predominant symptoms of meningitis are a generalized severe headache, nausea, and social withdrawal. The patient tends to lie quietly, with photophobia and general hyperesthesia. The patient's level of consciousness may vary from normal to unresponsive. Fever is universal, high, and sustained. Nuchal rigidity and pain with attempted flexion of the neck are ominous cardinal signs, and abnormal abdominal reflexes strengthen the clinical impression. In Brudzinski's sign, passive flexion of the head on the chest is followed by involuntary flexion of both thighs and both legs. In Kernig's sign, the patient is in the supine position, and the thigh is flexed to a right angle, and attempts at passive extension at the knee produce pain and resistance owing to spasm of the hamstring muscles. Funduscopic examination may reveal papilledema.

Whenever meningitis is suspected, a CT scan can rule out the presence of brain abscess, cerebritis, or subdural empyema, and determine that it is safe to perform lumbar puncture (i.e., intracranial pressure is not inordinately increased). CSF from the lumbar puncture is examined for intrathecal pressure, cells, bacteria, glucose, protein, chloride, and other factors. CSF pressure is increased early in the course of the disease, and protein and glucose concentrations increase compared with serum values as it progresses, but bacteria are not present until late in the disease.

When meningitis is caused by AOM or suppurative labyrinthitis, myringotomy and appropriate antibiotics are adequate, and no surgery is indicated. When meningitis develops from COM and mastoiditis, however, the mastoid must be exenterated. When otogenic meningitis is associated with a profound ipsilateral sensorineural hearing loss, a

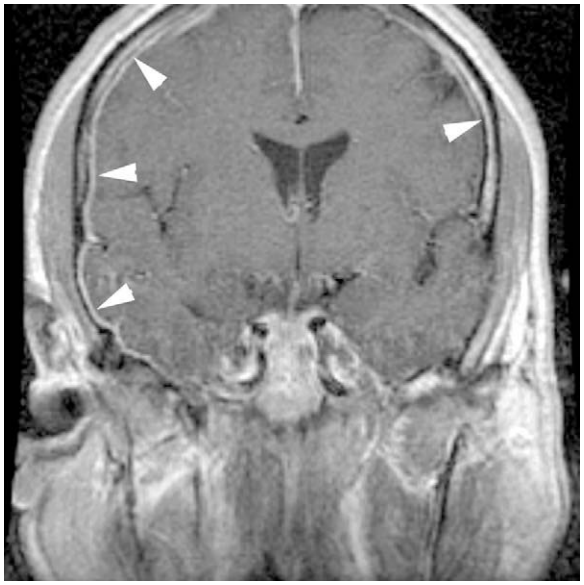

Figure 140-32. Contrast-enhanced coronal MRI showing dural enhancement *(arrowheads)* caused by otogenic meningitis. *(From Head and Neck Archive, Advanced Medical Imaging Reference Systems [AMIRSYS], Salt Lake City, UT. Accessed January 2003.)*

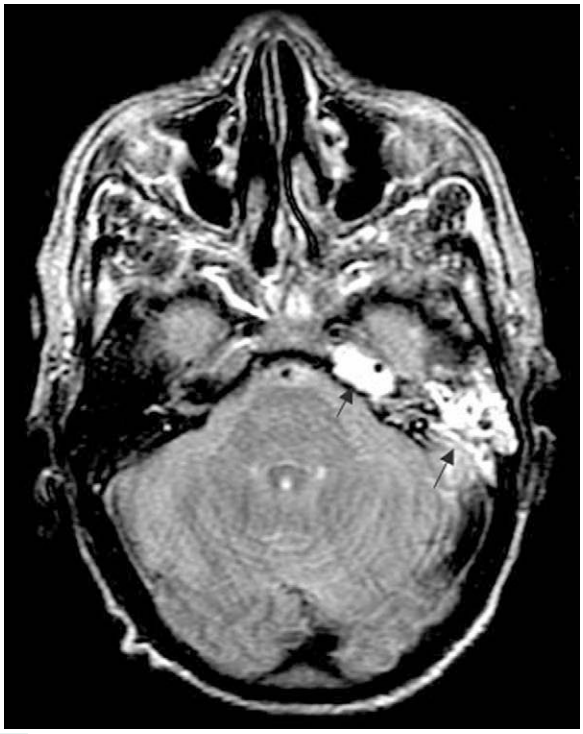

Figure 140-33. Axial T2-weighted MRI showing left mastoiditis and petrous apicitis *(arrows)* as high signal in mastoid and petrous apex.

route of infection to the meninges through the labyrinth is apparent. If the sensorineural function in the affected ear remains at the patient's premeningitis baseline, the route was extralabyrinthine. Some patients with severe AOM experience a partial sensorineural hearing loss because of associated serous labyrinthitis. This partial loss may be reversible. Although the patient has already had a CT scan before the lumbar puncture, an enhanced MRI study should be obtained to rule out the presence of any additional intracranial complications (Fig. 140-32). The neurologic condition of the patient determines the timing of the surgery, and the mastoidectomy should be performed as soon as the patient is stable. Meningitis is one of the gravest complications of acute or chronic otitis, and it seems that it is more lethal when caused by COM and mastoiditis than when it is a hematogenous complication of AOM in the first 2 years of life.

Brain Abscess

The incidence and mortality of intraparenchymal brain abscesses have decreased considerably, and almost all reports in the past 2 decades are from centers outside North America and Western Europe. Excellent reports from Africa and Asia using new imaging techniques have documented improvements in diagnosis and therapy, however, and have clarified some aspects of surgical treatment. The series by Yen and colleagues[26] of 122 consecutive patients seen in a Taiwan hospital between 1981 to 1994 revealed that otogenic causes were the third most common cause of intraparenchymal brain abscess, exceeded only by causes associated with cyanotic congenital heart disease and abscesses resulting from head injury or neurosurgery. Seventy-five percent of abscesses occurred in male patients—principally individuals in the lower socioeconomic classes. In the 1990s, four reports from India, Turkey, and South Africa discussed 149 patients with otogenic brain abscesses.[1,2,27,28] Abscesses from AOM and COM were almost always found on the same side as the otitis and occurred nearly equally in the temporal lobe and cerebellum. Almost three fourths were secondary to cholesteatoma, 50% occurred in the second decade of life, and two thirds affected male patients.

A brain abscess begins when bacteria propagate in and around venous channels leading from the mastoid into the adjacent brain parenchyma. The first event after the arrival of bacteria into the cortex or white matter is the migration of polymorphs into local capillaries with endothelial swelling and focal cerebritis. At this stage, the disease can be successfully managed by intravenous antibiotics alone. With more time, the tissue becomes edematous, hemorrhagic, and necrotic, and the abscess is formed. Brain abscesses may vary greatly in size, often have an irregular shape, and frequently are multilocular. At first, the capsule is poorly defined, but over time it becomes firmer and can easily be stripped from the underlying edematous brain.[29]

In addition to symptoms and signs reflecting general intracranial sepsis, cerebellar abscess is often accompanied by coarse horizontal nystagmus, dysmetria, dysdiadochokinesia, or action tremor. Temporal lobe abscess (Figs. 140-33 through 140-36) can cause homonymous visual field defects, contralateral hemiparesis, and other focal signs listed later for subdural empyema. The physician should examine the patient and the imaging studies looking for other intracranial complications because two thirds of patients with intraparenchymal abscesses have more than one intracranial complication.[27]

The physician should immediately begin the administration of broad-spectrum intravenous antibiotics directed at aerobic and anaerobic organisms. If imaging studies suggest no other complications, and the patient's condition is stable, neurosurgical drainage or abscess excision is performed within the first 24 hours of admission and is followed immediately by mastoidectomy, performed through a separate surgical field. If this course is followed, mortality has decreased to approximately 10%.

Subdural Empyema

Subdural empyema is a fulminating purulent infection that develops between the dura and the pia arachnoid membranes, and represents one of the most immediate of neurosurgical emergencies. It constitutes only about 20% of all cases of localized intracranial bacterial infection, and an otologic etiology is uncommon compared with bacterial contamination (from trauma or a neurosurgical operation), suppurative sinus disease, and meningitis. At least two thirds of the cases occur in men, and most occur in the second decade of life. The abscess usually begins by direct spread from adjacent infected bone or by retrograde venous propagation. When infection enters the subdural space, pus forms rapidly and spreads widely, and thrombophlebitis of cortical veins is virtually guaranteed. Swelling, necrosis, and infarction of the cortex accounts for many of the clinical features and explains how a barely detectable thin layer of subdural pus can cause such devastating

Figure 140-34. Axial contrast-enhanced T1-weighted MRI of the patient in Figure 140-33 showing left temporal lobe abscess with enhancing capsule *(arrow)*.

Figure 140-35. Axial T2-weighted MRI of the patient in Figure 140-30 showing abscess cavity and surrounding edema *(arrow)*.

consequences as increased intracranial pressure, focal signs, and seizures.[30]

Clinically, a patient with subdural empyema exhibits a cascade of symptoms including a severe headache, the earliest and the most persistent symptom. The patient's temperature increases dramatically as the disease progresses. General malaise, chills, and nuchal rigidity indicate that the patient is becoming seriously ill. After an unpredictable period, the patient's level of consciousness may abruptly decline, and focal signs

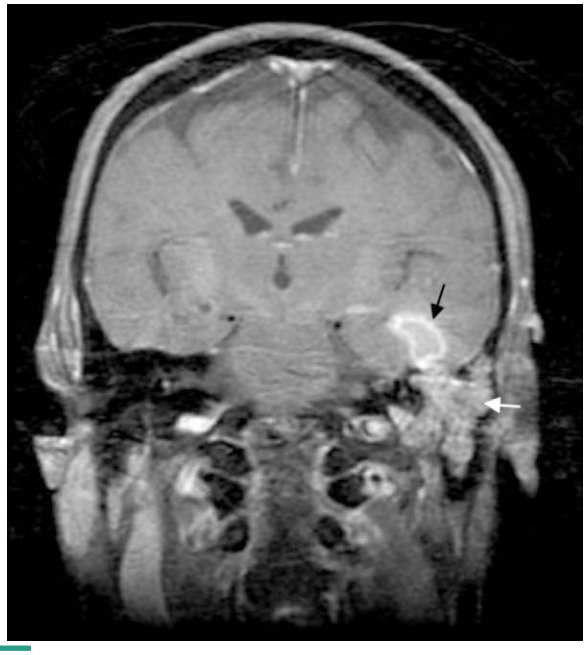

Figure 140-36. Coronal enhanced T1-weighted MRI of the patient in Figure 140-33 showing enhancing tissue in left mastoid *(white arrow)* and temporal lobe abscess with enhancing capsule *(black arrow)*.

and symptoms may develop. Most patients with left-sided collections develop aphasia and a progressive contralateral hemiparesis. Paralysis of conjugate gaze to the contralateral side and deviation of the eyes toward the side of the lesion are also common. Jacksonian seizures are common at this stage, and papilledema may be evident. In patients with posterior fossa collections, localizing signs are often absent, but marked neck stiffness and papilledema are always present. The entire clinical picture of subdural empyema can evolve in a few hours or can take 10 days to develop.

In a well-developed subdural empyema, a contrast-enhanced CT scan shows a crescent-shaped, low-density collection of pus displacing the brain away from the inner table of the skull, with enhancement of the adjacent edge of the cortex. The scan may appear normal early in the course of the disease. When this happens, the clinician should obtain a contrast-enhanced MRI study or repeat the CT scan after a suitable interval. Lumbar puncture is dangerous and is contraindicated because it can precipitate transtentorial coning with elevated intracranial pressure. If the CT scan fails to detect the lesion, and focal signs are absent, lumbar puncture may be unavoidable to rule out meningitis.

Emergency neurosurgical drainage and appropriate antibiotic therapy are necessary. Survival is related to the level of consciousness at the time of surgery. The presence of localizing signs in any patient with COM whose level of consciousness is declining requires immediate and decisive action.

Subdural empyema can also develop in neonates as a complication of meningitis. In 30% of cases of *H. influenzae* meningitis, a collection of fluid develops in the subdural space (usually bilaterally) that varies from 5 to 100 mL.[31] This problem is less common after meningitis from other organisms and is decreasing in frequency because universal immunization against *H. influenzae* has dramatically reduced the incidence of meningitis. Uninfected subdural collections after meningitis are called *subdural effusions*. If bacteria are evident on direct examination of the fluid, the collections are called *infected subdural effusions,* and if the fluid is grossly purulent, they are classified as *subdural empyemas*. Subdural collections from meningitis secondary to COM that require otologic attention are rare in the neonatal age group.

Epidural Abscess

Epidural abscess results from bone erosion caused by cholesteatoma, granulation tissue, or coalescence. In addition to the bone erosion,

an intense inflammatory response to the infection results in granulation tissue formation and forms an abscess between the temporal bone and the underlying dura mater. The involved dura thickens in response to its contact with granulation tissue on its surface (pachymeningitis). Although it can occur as the only complication of chronic mastoiditis, epidural abscess is frequently associated with lateral sinus thrombophlebitis, meningitis, and cerebritis or brain abscess. Rarely, epidural abscess can result from acute otitis and mastoiditis in the same way as was described for lateral sinus thrombosis.

Most patients experience deep mastoid pain, but there are no signs or symptoms specifically attributable to epidural abscess, and many of the cases without associated complications are discovered only at surgery. If it is large enough, the abscess can be detected on contrast-enhanced CT or MRI scans as a fluid-filled cavity between the temporal bone and the enhanced dura. Surgery is the only recommended treatment. The surgeon performs the type of mastoidectomy that is appropriate for the underlying otitis and mastoiditis.

After removal of the cortex, the surgeon should progressively exenterate the air cells, proceeding from lateral to medial, and from regions with less disease to regions with more disease. When the locus of pathology is the cerebellar plate, the surgeon should smooth the tegmen mastoideum and the tegmen tympani first, and then the thin posterior aspect of the bony external auditory canal; the tip cells should be removed. This removal maximizes exposure and hemostasis. Then the surgeon approaches the diseased area along the cerebellar plate from the superior, the inferior, the lateral, and finally the medial direction, removing the overlying bone down to a thin plate. Because the dura is thickened by the infection, blunt flat instruments such as a Freer elevator or large curets can safely scrape the granulation tissue from the abscess cavity and identify the most centripetal extent of the abscess. The surgeon should remove all of the bone overlying the abscess using diamond burs, rongeurs, or curets until healthy dura without granulation tissue is evident on all margins of the abscess. When the abscess involves the tegmen, the order is changed, and the surgeon should complete the surgery in the other areas first, addressing the tegmental abscess last.

Lateral Sinus Thrombosis

Thrombosis of the lateral sinus usually forms as an extension of a perisinus abscess that develops after mastoid bone erosion from cholesteatoma, granulation tissue, or coalescence (Figs. 140-37 and 140-38).[32] The perisinus abscess exerts pressure on the dural outer wall of the sinus leading to necrosis. The necrosis extends to the intima and attracts fibrin, blood cells, and platelets. A mural thrombus forms, then becomes infected, enlarges, and occludes blood flow through the sinus. Fresh thrombus can propagate and extend in a retrograde direction to the transverse sinus (Fig. 140-39), to the torcular Herophili, and even to the superior sagittal sinus. In the opposite direction, the clot can extend via the jugular bulb into the internal jugular vein in the neck, and can extend to the cavernous sinus via the inferior or superior petrosal sinus. The infected clot frequently showers the bloodstream with bacteria, giving rise to the signs and symptoms of septicemia and the possibility of metastatic abscesses (most commonly to the lungs).

Because of the relative frequencies of the various types of mastoiditis and the ages of the patients affected, presently lateral sinus thrombosis is most common in adults or older children with cholesteatoma, and less common from the other types of chronic mastoiditis. In addition to cases arising by direct extension from bone erosion, lateral sinus thrombosis can also be caused by osteothrombophlebitis during AOM and mastoiditis. In this situation (and in occasional cases of chronic mastoiditis), the bony sinus plate is intact at the time of surgical exploration.

Because the sinus is a continuation of the cerebellar dura mater, extension of an infection by only a few millimeters can result in meningitis, epidural abscess, subdural empyema, cerebritis, or cerebellar abscess, all equally grave complications. In two series,[32,33] 14 of 19 patients with lateral sinus thrombosis had one or more of these additional complications.

Figure 140-37. Axial enhanced temporal bone CT scan showing absent enhancement of left sigmoid *(white arrow)* next to an opacified mastoid. Note the normal enhancement of the right sigmoid *(black*

Figure 140-38. Coronal contrast-enhanced CT scan of the patient in Figure 140-37 showing absent flow in left internal jugular vein at the skull base *(white arrow)* and normal flow in right internal jugular vein *(black arrow)*.

Although the frequent association with other complications tends to obscure the clinical picture, the diagnosis of lateral sinus thrombosis can be strongly suspected when there are signs and symptoms of septicemia or blockage of blood flow through the sinus. The picket-fence fever pattern with diurnal temperature spikes exceeding 103° F has been described with this condition for decades. Although some more recent articles have pointed out that this pattern is not seen as frequently, in part because many patients present with previous or current antibiotic therapy, most of the 36 patients reported by Singh[25] were receiving intravenous antibiotics and still exhibited that fever pattern. Unless the patient has been transferred from another hospital, on admission there is only one temperature measurement to observe. Nonetheless, a single high fever reading should alert the clinician to the possibility of sigmoid

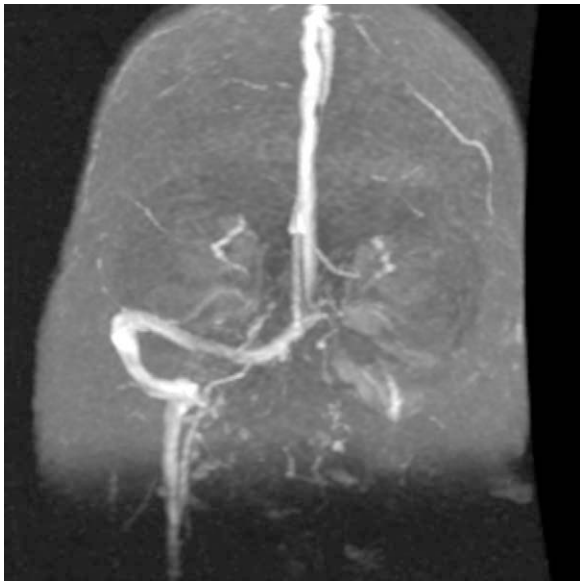

Figure 140-39. MR venogram showing occlusion of left transverse–sigmoid sinus system. *(From Head and Neck Archive, Advanced Medical Imaging Reference Systems [AMIRSYS], Salt Lake City, UT. Accessed January 2003.)*

sinus thrombophlebitis. Singh[25] also pointed out that the neck pain in lateral sinus thrombosis may be mistakenly attributed to the neck stiffness of meningitis, when it actually represents pain and tenderness along the anterior border of the sternocleidomastoid muscle, and he suggested that percussion tenderness of the mastoid tip is another important sign.

More ominous are the signs of sudden intracranial hypertension resulting from decreased venous drainage from the skull (see section on otitic hydrocephalus). Most prominent is the occurrence or sudden worsening of a severe headache. This headache is more likely to occur with the obstruction of the dominant venous drainage system (the right side in 60% of patients). More grave is progressive obtundation; this may herald the development of cerebral edema from the increased intracranial pressure caused by involvement of the superior sagittal sinus or the cavernous sinus, and it carries a very high mortality.

Imaging studies and lumbar puncture are essential to sort out the possible types of complications in obtunded patients. If the patient's condition permits, contrast-enhanced CT scan and contrast-enhanced MRI should be performed (see Fig. 140-32). The delta sign seen on the CT scan, enhancement of the wall of the sigmoid sinus, allows preoperative diagnosis. Wall enhancement is more sensitively evaluated by MRI, which can also document abscess formation within the sinus and exclude adjacent subdural empyema, cerebritis, or cerebellar abscess.

All patients with sigmoid sinus thrombosis require mastoidectomy to treat the underlying mastoid disease adequately. When a brain abscess is also present, surgical drainage of that abscess takes precedence over a mastoid procedure (see section on brain abscess), but if the patient's condition permits, neurosurgical drainage of the brain abscess should be followed in the same anesthetic by expeditious mastoidectomy.

Management of the clot can involve anticoagulation, ligation of the jugular vein in the neck, and opening the sinus and evacuating the infected clot. Use of anticoagulants is rarely indicated, but anticoagulation should be strongly considered when extension of the clot to the transverse sinus or cavernous sinus is suspected or documented. Other considerations in these deteriorating patients include neurosurgical decompression and steroids. Intravenous thrombolytics are not routinely used in the presence of the infected vessel wall. Similarly, routine ligation of the jugular vein in the neck seems unnecessary, but it should be considered whenever there is evidence of extension of the clot into the neck, and should be strongly considered when septic emboli are present.

The sinus is usually addressed only after mastoidectomy. The sinus and adjacent dura are addressed by removing the overlying bone. The surgeon passes an 18- or 20-gauge needle through the sinus wall, and if there is no free blood on aspiration, a linear incision is made through the sinus wall, and the abscess and any infected clots are evacuated. Further sinus incision can enable clot evacuation proximally and distally until free bleeding occurs. The mastoid and cerebellar walls of the sinus are usually thick and indurated as a result of the chronic infection. The surgeon can safely scrape them gently with a broad flat instrument such as a Freer elevator to remove the infected tissue. Syms and colleagues[33] reported treating six patients with lateral sinus thrombosis and concomitant intracranial complications with mastoidectomy, but without opening and evacuating the lateral sinus clot. All patients survived, but the average hospital stay was more than 49 days; it was 38 days when the patient with the longest stay was not included. In contrast, patients reported by Kaplan and Kraus[32] underwent surgery that included incision of the sinus and evacuation of the clot or abscess, and their mean hospital stay was only 17 days.

Otitic Hydrocephalus

Otitic hydrocephalus is an entity wherein an otologic condition has resulted in signs and symptoms of acute hydrocephalus. The condition seems to result from diminished venous drainage of the cranium. With reduced venous outflow, intracranial pressure increases, brain edema ensues, and signs and symptoms of acute intracranial hypertension manifest. In most cases, otitic hydrocephalus results from initial occlusion of the sigmoid or lateral sinus, with or without extension to the transverse sinus, inferior petrosal sinus, or cavernous sinus. The likelihood that symptoms will develop after occlusion of the lateral sinus adjacent to the mastoid reflects the following: (1) the size of the involved lateral sinus compared with the opposite lateral sinus; (2) the adequacy of the collateral venous network, including the cavernous sinus and opposite inferior petrosal sinus; and (3) the likelihood that propagation of the process will involve additional venous outflow.

Some authors view otitic hydrocephalus as a distinct clinical entity consisting of intracranial hypertension and resolved or resolving (usually acute) otitis media, having no relationship to lateral sinus thrombophlebitis.[24] Others view it more as a pathophysiologic consequence of lateral sinus thrombosis that occurs more commonly as a result of AOM than COM and depends on the three factors mentioned in the previous paragraph. The distinction is less important than recognizing the relationship between the symptom complex, ear disease, lateral sinus, and emergent nature of the treatment.

In the early stages, a diffuse severe headache dominates the clinical picture. In uncomplicated cases with (or occasionally without) medical management, the continuous headache gradually ameliorates and dissipates over 3 to 7 days. If collateral venous drainage is inadequate, and intracranial pressure remains sufficiently elevated long enough, signs of dulling of the sensorium or decreased visual acuity from retinal vein occlusion appear. Progression to coma and death is possible. CT scanning and immediate neurologic and neurosurgical consultation are appropriate.

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CHAPTER ONE HUNDRED AND FORTY-ONE

Tympanoplasty and Ossiculoplasty

Meredith E. Adams

Hussam K. El-Kashlan

Key Points

- The ultimate goals of tympanoplasty are to restore middle ear function by eradicating infection and middle ear pathology, to re-establish a tympanic membrane that resists infection and epithelial ingrowth, and to secure a durable connection between the tympanic membrane and the inner ear.
- Medial and lateral techniques refer to the placement of the graft either medial or lateral to the tympanic membrane remnant. The graft is placed medial to the malleus handle in either technique.
- The success of any given technique depends on how well it is performed by the surgeon, rather than on the technique itself. There are no absolute indications for a particular technique.
- The lateral technique tympanoplasty is an extremely useful technique for challenging and revision cases of chronic suppurative otitis media with drum pathology. Its utility lies in considerable potential for inviting vascular ingrowth to promote graft healing and epithelialization. Success with lateral tympanoplasty requires that the surgeon summon refined techniques in preparing the external canal and the middle ear. To prevent blunting after lateral technique tympanoplasty, the acute angle between the anterior canal wall and the tympanic membrane should be developed with effective canalplasty. The lateral technique is more technically demanding and should be considered carefully by the novice or inexperienced ear surgeon.
- Good graft support in the anterosuperior quadrant is important to avoid failure in anterosuperior and total perforations.
- Temporalis fascia and perichondrium are the most commonly used materials for tympanic membrane reconstruction. Cartilage may be considered for reinforcement of retraction pockets, atelectatic membranes, and other conditions associated with increased failure rates with traditional techniques.
- The goal of ossiculoplasty is to re-establish the transfer of induced vibratory energy from the tympanic membrane to the undersurface of the stapes footplate, maximizing the postoperative gain in hearing.
- Allograft prostheses are gaining popularity. In particular, good hearing results, low extrusion rates, and ease of use have led to widespread application of titanium implants.
- Decisions regarding the appropriate reconstructive technique should be based on a careful assessment of the mobility, position, orientation, and integrity of the remaining ossicles.
- Postoperative conductive hearing loss may persist even with a perfectly placed prosthesis owing to ongoing middle ear disease.

Tympanoplasty

Tympanoplasty is a surgical procedure performed to eradicate infection and restore the function of the middle ear.[1] Wullstein[2,3] introduced a classification for tympanoplasty that is based on two things: (1) the remaining structures of the middle ear after all pathology has been eradicated, and (2) how sound is transferred to the oval window while the round window is being protected. The basic principles behind this classification still hold true today, but the practice of tympanoplasty has been modified by advances in the fields of optics, microsurgical instruments, middle ear prostheses, and surgical techniques. The presence of different tympanoplasty techniques is an indication that the otologic surgeon should be flexible when tailoring the procedure to fit the disease, rather than having a "one-size-fits-all" approach to surgery for chronic ear disease. This chapter reviews various tympanoplasty techniques and techniques for reconstructing the ossicular chain. Tympanoplasty is often performed in conjunction with mastoidectomy in cases of active chronic suppurative otitis media. Mastoidectomy techniques are reviewed in Chapters 127 and 142.

Functional Considerations

Restoration of the middle ear transformer mechanism requires a secure connection between an intact tympanic membrane and inner ear fluids. The tympanic membrane should close an air-filled, mucosa-lined middle ear cavity. Traditional teaching attributes most of the middle ear gain to the hydraulic effect, which is the ratio of the effective vibrating area of the tympanic membrane to the area of the mobile stapes footplate.[4] Round window protection to avoid phase cancellation (i.e., when sound impacts the oval and round windows at the same time) was also thought to be an important contributor to effective sound transmission to the inner ear. More recent investigations of human

middle ear mechanisms modified these classic teachings in the following ways[5]:

1. Sound can be transmitted from the ear canal to the cochlea by two mechanisms: ossicular and acoustic coupling. Ossicular coupling is the sound pressure gain that occurs through the tympanic membrane and the ossicular chain. Acoustic coupling is the difference in the sound pressure that is acting directly on the oval and round windows. In normal ears, acoustic coupling is negligible, but it may play a significant role in diseased and reconstructed ears.

2. When sound input to the cochlea depends solely on acoustic coupling (e.g., ossicular interruption behind an intact tympanic membrane, complete absence of the tympanic membrane and ossicles), the stimulus to the cochlea depends on the relative magnitude and the phase (timing difference) of the oval and round window pressures. The magnitude difference is more important than the phase difference.

3. The pressure gain that results from ossicular coupling in normal ears is frequency-dependent, and its magnitude is less than traditionally believed. The mean middle ear gain is about 20 dB between 250 and 500 Hz, reaches a maximum of about 25 dB around 1 kHz, and then decreases at about 6 dB per octave at frequencies greater than 1 kHz.

4. There is also a contribution of the stapes-cochlear impedance and the round window membrane to middle ear function. Normally, motion of the stapes footplate is "opposed" by the annular ligament, the cochlear fluids and partition, and the round window membrane. Pathologic changes in the impedance of the annular ligament, the cochlea, or the round window can cause hearing loss, such as that caused by otosclerotic stapes fixation. Also, in a nonaerated middle ear, the presence of fluid or fibrous tissue within the round window niche can increase the round window impedance and cause conductive loss.

5. Aeration of the middle ear plays an important role in sound transmission. In addition to contributing to normal stapes-cochlear impedance (see previously), aeration is crucial for normal ossicular coupling. The compressible air within the middle ear allows the tympanic membrane and the ossicles to move.[6,7] Impaired middle ear aeration can adversely affect ossicular coupling by altering a pressure difference that is important to middle ear function. In the normal human middle ear, sound pressure in the ear canal is higher than sound pressure within the middle ear; tympanic membrane motion is driven by this pressure difference. Reductions in middle ear air volume that result from disease or surgery lead to elevated middle ear airspace impedance and an increase in middle ear sound pressure. This leads to a reduction in the pressure difference across the tympanic membrane, with a subsequent reduction in tympanic membrane and ossicular motion.[5] The minimum amount of air required to maintain ossicular coupling within 10 dB of normal has been estimated to be 0.5 mL.[8]

A perforation of the tympanic membrane causes hearing loss by reducing the difference in sound pressure across the two sides of the tympanic membrane, causing decreased ossicular coupling.[9] Hearing loss is proportional to the size of perforation and is frequency dependent, with the largest losses occurring at the lowest sound frequencies.[10] It also varies inversely with volume of the middle ear airspace (including the mastoid); this may explain why seemingly identical perforations in size and location produce different degrees of hearing loss, and why hearing loss may fluctuate in a given perforation with the presence or absence of otorrhea, which would decrease middle ear and mastoid airspace, causing increased hearing loss. More recent investigations also suggest that hearing loss does not vary appreciably with the location of perforation, in contrast to the long-held belief that posteroinferior perforations result in greater hearing loss than perforations at other locations owing to increased phase cancellation at the round window.[10,11]

Preoperative Evaluation

A detailed history and careful physical examination are essential to the planning of the surgical approach and the counseling of patients regarding the expected outcome. The extent of tympanic membrane perforation and the condition of the ossicular chain are evaluated. The health of the remaining membrane is assessed, paying particular attention to atrophic areas and the degree of myringosclerosis. The size of the external canal is evaluated, and canalplasty is planned if a prominent anterior canal wall prevents complete visualization of the perforation. Comprehensive audiometric evaluation is performed, and tuning fork tests are used to confirm the audiogram. Radiographic evaluation is usually not needed if clinical examination reveals a dry central perforation.

As mentioned previously, postoperative aeration of the middle ear is key to the success of tympanic membrane repair and the restoration of hearing. The otologic surgeon has no direct control over this factor, however, which depends mostly on eustachian tube function. There is currently no test that accurately predicts postoperative eustachian tube function. Some indicators—the aeration of the opposite ear, increased age in children, fewer episodes of otorrhea, and normal middle ear mucosa—may suggest reasonable eustachian tube function. In many cases, however, surgery is the ultimate test, and may result in improved eustachian tube function by preventing recurrent infections through contamination from the external auditory canal.

This chapter deals mainly with techniques for repair of dry tympanic membrane perforations. Techniques for handling active chronic otitis media with or without cholesteatoma are described in other chapters. In brief, it is recommended that the ear be dry for 3 to 4 weeks before proceeding with tympanoplasty. There are situations, however, in which the ear cannot be successfully treated medically, and tympanoplasty with or without mastoidectomy may be the best therapeutic option.

Graft Materials

Temporalis fascia is the most commonly used material for the repair of tympanic membrane perforations; it was introduced for this use in the early 1960s.[12] Temporalis fascia can be harvested at the time of tympanoplasty through a small incision posterosuperior to the helix in the hair-bearing scalp when using a transcanal approach, or via superior dissection from a postauricular or endaural incision. Other grafting materials have also been used.[13-15] In 1960, Shea[15] described the use of vein grafts in tympanoplasty. Perichondrium is frequently used in tympanoplasty, particularly if there is no temporalis fascia available (e.g., in cases of multiple revisions) or if a composite cartilage/perichondrium graft is needed to prevent retraction of the reconstructed membrane when there is suspected persistent eustachian tube dysfunction. The periosteum on the medial surface of the temporalis muscle can also be used as a graft material when temporalis fascia is unavailable if the surgeon wishes to avoid the additional incision needed to harvest tragal perichondrium.

Ringenberg[14] used free autologous fat grafts in the early 1960s. A more recent study reported success rates with fat grafts to be comparable to success rates with temporalis fascia.[16] AlloDerm (LifeCell Corporation, Branchburg, NJ) has also been studied and used as a graft material.[17-20] To support the use of AlloDerm as a possible alternative to autologous fascia, advocates cite the avoidance of external incisions, potential reduction of surgical time, and comparable success rates.[20]

Minimalist Techniques

There are some clinical situations in which a minimalist approach to tympanoplasty is possible or desirable. Small, uninfected, established perforations of 1- to 2-mm diameter can often be managed in an office setting in this way. The epithelium at the margins of the perforation is cauterized or removed, and a fat plug that is slightly larger than the diameter of the perforation is removed from the lobule to use as a graft. It is placed through the opening in a dumbbell fashion and covered with a dressing such as Gelfoam or Gelfilm (Pharmacia & Upjohn Company, Kalamazoo, MI, a division of Pfizer Inc., New York, NY). Other surgeons prefer simply to cauterize the perforation edges with trichloroacetic acid or phenol and apply a patch of Gelfoam, Gelfilm,

cigarette paper, or a hyaluronic acid film (Epidisc; Medtronic Xomed Inc., Jacksonville, FL). Traumatic perforations also are often managed by patching only after the perforation edges are realigned. In addition, a more recent study described the use of a simple device in the shape of a sealed tympanostomy tube (Medtronic Xomed Inc., Jacksonville, FL) that is designed to be inserted into tympanic membrane perforations in patients when surgery is contraindicated or refused by the patient.[21]

Formal Tympanoplasty (see Key Indicator Video on website)

Anesthesia

Tympanoplasty can be performed under local or general anesthesia. In children and anxious adults, general anesthesia is preferred. In either case, the ear canal skin is injected with lidocaine (usually 1%) with epinephrine (1:100,000) for vasoconstriction. Care should be taken to avoid the formation of fluid blebs in the skin, which can occur if excessive force is used to inject, especially if a larger syringe is used. Injection should be done using a microscope, preferably before preparing the ear so that there is time allowed for vasoconstriction to occur. If liquid povidone-iodine (Betadine) is used to prepare the ear, its entry into the middle ear should be avoided.

Approaches and Incisions

Three main approaches are used in tympanoplasty: transcanal, endaural, and postauricular. The approach used depends on the perforation size, the anatomy of the external auditory canal, and the surgeon's preference. Most importantly, the approach used should provide complete visualization of the perforation. The transcanal approach is usually employed for small posterior perforations or for medium-sized perforations when the ear canal anatomy is favorable, and the entire perforation and an anterior tympanic membrane rim can be seen; it should be avoided in cases in which the anterior margin of the perforation is not well visualized, particularly in the hands of surgeons with less experience. The endaural approach can be used with all perforations and is more commonly used in Europe; it is most useful if a limited atticotomy is anticipated in conjunction with tympanoplasty. A self-retaining retractor can be used with this approach. The postauricular approach is the most commonly used approach for tympanoplasty in the United States. It can be used with all perforation sizes, and offers a better angle of visualization of the anterior tympanic membrane, even without canalplasty. The use of self-retaining retractors allows for easier use of both hands for instrumentation and suctioning.

Transcanal incisions outline a medially based tympanomeatal flap. Superior and inferior incisions start at 12 o'clock and 6 o'clock. Either the incisions converge to meet on the posterior canal wall, forming a triangular skin flap (Fig. 141-1A), or each incision may be extended laterally for 6 to 7 mm, at which point the lateral ends of the incisions are connected by a horizontal incision that forms a rectangular flap (Fig. 141-1B). Before the elevation of the flap, the edge of the perforation is excised. A sharp straight pick is used to create small holes around the periphery of the perforation, similar to those of a postage stamp (see Fig. 141-1A); this outlined edge can be removed with a cupped forceps.

The excision of the perforation edge to disrupt the epithelial union is an integral part of any tympanoplasty procedure, whatever the approach, incision, or technique used. Any large areas of tympanosclerosis should be removed. The outlined skin flap is elevated medially usually using a round knife. Care is taken to minimize suctioning on the flap. Suctioning should be done between the instrument used to elevate the flap and the bony canal. Elevation should be performed along the entire breadth of the flap rather than by the creation of a tunnel in the middle. After the anulus is reached, it is elevated from the tympanic sulcus, exposing the middle ear mucosa, which is divided to enter the middle ear. Elevation of the anulus from the sulcus is continued superiorly and inferiorly under direct vision; this minimizes the risk of injury to a dehiscent, high-riding jugular bulb. Care should be taken to avoid injury of the chorda tympani with superior elevation of the flap. When elevation has reached the limits of the incision, it is usually possible to tuck the tympanomeatal flap anteriorly, where it is not interfering with the surgical field.

The endaural incision has a vertical limb that usually starts at 12 o'clock at the bony cartilaginous junction and extends laterally and superiorly into the cartilage-free incisura terminalis between the superior aspect of the tragus and the root of the helix (Fig. 141-2A). The incision is deepened to expose the inferior edge of the temporalis muscle, where a fascial graft can be taken. The vertical limb can be combined with one of the medially based tympanomeatal flaps described previously, an inferiorly based skin flap (Fig. 141-2B), or a laterally

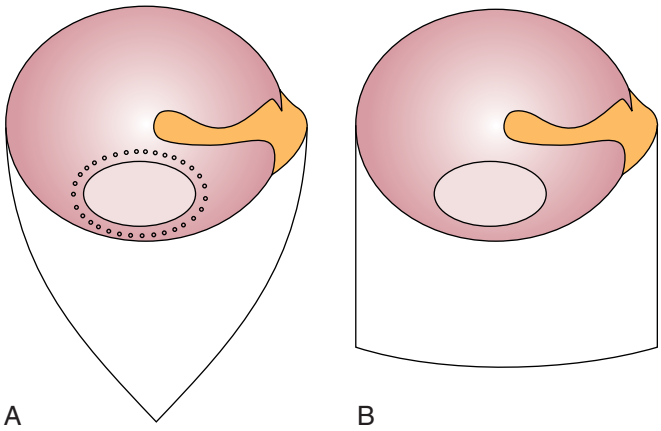

Figure 141-1. A, Triangular tympanomeatal flap; perforation edge is prepared for excision by creating small holes along the perimeter. **B,** Rectangular tympanomeatal flap.

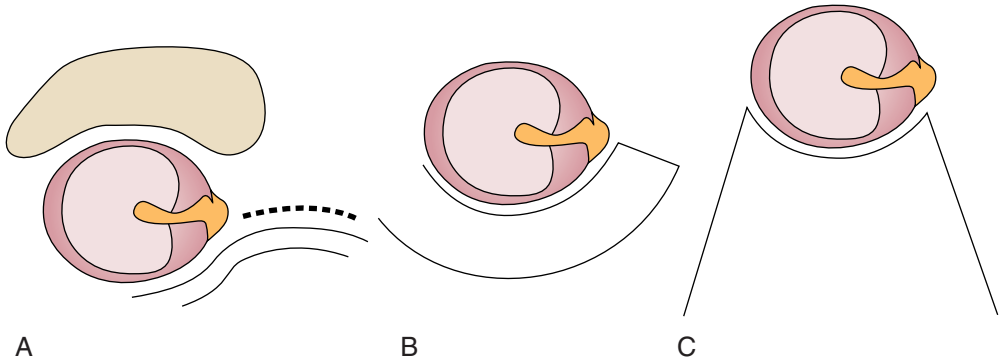

Figure 141-2. A, *Hatched line* shows the vertical limb of the endaural incision starting at the bony cartilaginous junction and extending laterally and superiorly into the cartilage-free incisura terminalis, between the superior aspect of the tragus and the root of the helix. **B** and **C,** The vertical limb can be combined with an inferiorly based skin flap **(B)**, or a laterally based Koerner flap extending onto the concha **(C)**.

based Koerner flap extending onto the concha (Fig. 141-2C) (allowing cartilage excision and meatoplasty), depending on the planned surgery.

The postauricular incision usually extends from the mastoid tip to just above the attachment of the helix, about 5 to 6 mm from the postauricular crease. The incision is deepened in layers, with care taken not to injure the periosteum. Care is also taken not to elevate the auricle as a separate layer from the periosteum because this can lead to a lop-ear deformity postoperatively. The temporalis muscle and fascia are exposed. The periosteum is incised in a "7" or "T" fashion. The presence of this acute angle allows for the precise repositioning of the periosteum during closure, avoiding any misalignment of the auricle or any change of its vertical position postoperatively. The periosteum is elevated forward, exposing the spine of Henle and the ear canal.

There are several options for handling the posterior canal wall skin. The canal skin can be elevated from behind with care taken not to tear the skin, particularly at its attachment at the tympanomastoid and tympanosquamous suture lines. If there is a very prominent tympanosquamous suture line, it is often helpful to incise the fibrous tissue within the suture line using a sickle knife or a 59-10 Beaver blade. The skin is elevated down to the anulus, which should be left intact at this time; vascular strip incisions can be made from behind to access the ear canal. Vertical incisions placed at the 6 o'clock and 12 o'clock positions are connected by a horizontal incision just lateral to the anulus to create a long vascular strip. The other option is to perform the vascular strip incisions through the ear canal before starting the postauricular incision.[22] In cases in which there is no perforation, and surgery is performed for a second look or for ossiculoplasty (especially if an incus interposition is contemplated), it is possible not to do any canal incisions, and instead to elevate the canal skin and anulus in continuity, entering the middle ear for inspection and ossicular reconstruction.

Graft Placement

Medial and lateral techniques refer to the placement of the graft either medial or lateral to the tympanic membrane remnant. Although some surgeons advocate a certain technique for graft placement in a particular situation, the success of any technique depends on how well this technique is performed by the surgeon, rather than on the technique itself. Consequently, there should not be an absolute indication for a particular technique in a certain perforation. Medial technique can be used to repair total perforations or in revision cases if done properly by an experienced surgeon.

Lateral Graft Technique

In lateral technique tympanoplasty, which is also known as the overlay technique, the graft is placed lateral to the fibrous layer of the tympanic membrane remnant, but medial to the malleus handle. This technique requires complete removal of the squamous epithelium from the lateral surface of the tympanic membrane remnant to avoid iatrogenic cholesteatoma formation. During elevation of the tympanomeatal flap, the anulus is left in the tympanic sulcus, and the dissection is transitioned from the bony external canal onto the lateral surface of the tympanic membrane, separating the superficial squamous layer from the middle fibrous layer. If the perforation is of medium size, the dissected epithelium can be left attached anteriorly and can be replaced on top of the graft. In total perforations, it is usually necessary to remove the skin of the external canal completely to ensure complete removal of squamous epithelium.

Canalplasty can be performed to remove the prominent anterior canal wall to visualize the entire perforation without having to move the microscope.[23] This is accomplished by connecting the lateral ends of the vascular strip incisions along the anterior canal wall just medial to the bony-cartilaginous junction (Fig. 141-3A). The skin is dissected

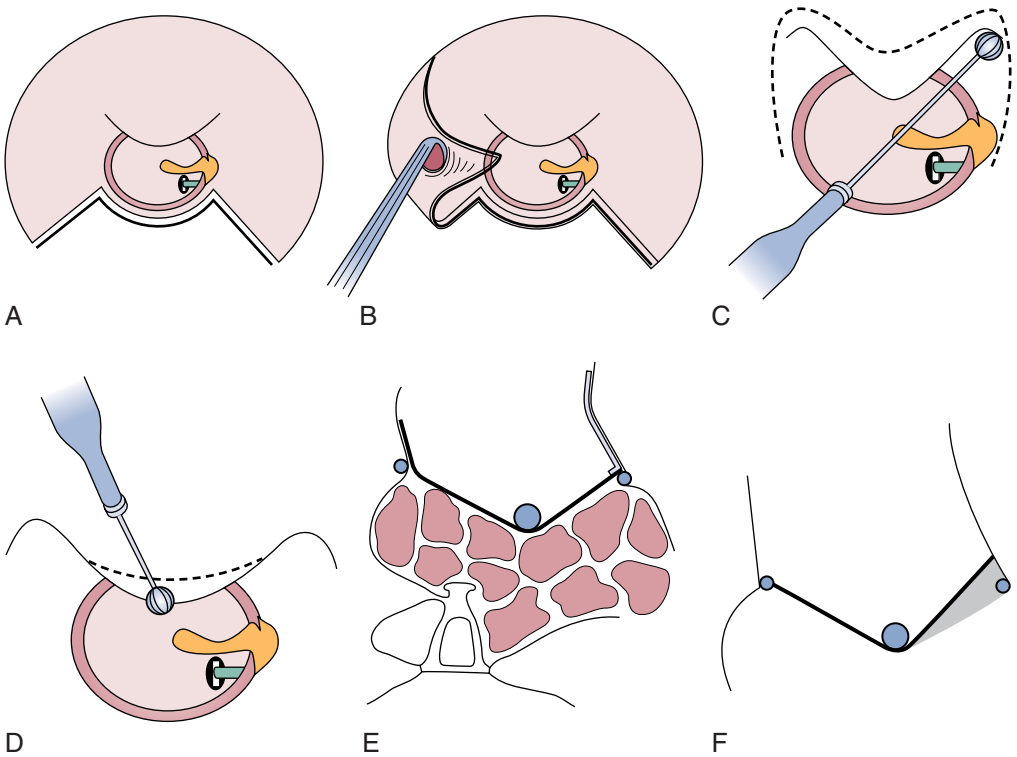

Figure 141-3. **A,** Vascular strip incisions on posterior canal wall; the lateral ends of the vertical incisions are connected along the anterior canal wall just medial to the bony-cartilaginous junction. **B,** The canal skin is dissected medially toward the anulus. **C,** Visualization of the anterior sulcus may require removal of a significant amount of the anterior canal bone; bone is first removed in the superior and inferior corners of the anterior bony canal. **D,** The bony bulge is gradually taken down between the two corners. **E,** Placement of the graft *(thick black line)*, with its anterior edge at the anulus supported by Gelfoam in the middle ear; the medial end of the replaced anterior canal skin *(gray)* should cover only 1 to 2 mm of the anterior end of the graft. **F,** Anterior blunting *(gray)*; this is the result if the graft is placed on the anterior canal wall, or if the anterior canal skin covers a large area of the graft without maintaining the acute anterior tympanomeatal angle.

medially toward the anulus (Fig. 141-3B). When the elevation reaches the area medial to the anterior canal bulge, the dissection is usually done by feel until the anulus is reached. The elevation of the epithelium from the tympanic membrane remnant is performed by developing a plane superiorly or inferiorly at the level of one of the original canal incisions, near the anulus. The squamous epithelium of the tympanic membrane remnant is usually left in continuity with the previously elevated canal skin. The anterior canal skin is trimmed of irregular tags and stored in a moist sponge.

To ensure optimal graft placement, the anterior sulcus should be well visualized. This may require removal of a significant amount of the anterior canal bone (Fig. 141-3C). This removal is accomplished by using an otologic drill first to remove bone in the superior and inferior corners of the anterior bony canal. The bony bulge is gradually taken down between the two corners, keeping in mind that the prominent middle portion represents the posterior wall of the temporomandibular joint (Fig. 141-3D). It is of paramount importance to avoid violating the temporomandibular joint because this can lead to erosion of the condyle into the ear canal, which is extremely difficult to correct. In cases in which there is no anterior tympanic membrane remnant, placement of the graft may be facilitated by drilling a small trough just lateral to the anulus to create additional support for the graft anteriorly. Another alternative is to elevate the anulus from the sulcus anteriorly in continuity with the mucosa of the lateral wall of the eustachian tube, which provides a pocket to support the anterior portion of the graft.

If there is enough tympanic membrane remnant to support the graft, Gelfoam may be unnecessary in the middle ear. In large perforations, Gelfoam is placed in the middle ear to support the graft. The graft is trimmed to the proper size. The graft should be wide enough to cover the entire tympanic membrane region and long enough to drape onto the posterior canal wall. In placing the graft, care should be taken not to overlap any portion of the anterior canal wall, or blunting may occur (see later). Although the graft is placed lateral to the anulus, it should be placed medial to the malleus handle to prevent lateralization. This is usually accomplished by cutting a vertical slit in the anterosuperior corner of the graft to accommodate the malleus handle. If a significant tympanic membrane remnant is still attached to the malleus, incisions should be made sharply on either side of the malleus handle to allow for medial placement of the graft.

The trimmed anterior canal skin is repositioned with its thin medial part overlying approximately 1 mm of the graft (Fig. 141-3E). The anterior tympanomeatal angle should be maintained at an acute angle (≤90 degrees) by placing pressed, rolled, dry Gelfoam in the sulcus during healing. If the graft is placed on the anterior canal wall, or the acute anterior tympanomeatal angle is not preserved, a dead space is created that gets filled with fibrous tissue, resulting in blunting (Fig. 141-3F). This reduces the area of the vibratory portion of the tympanic membrane and causes persistent conductive hearing loss. Additional Gelfoam is placed over the graft except for the portion of the fascia that extends onto the posterior canal wall. The vascular strip skin is placed back, with care taken to unfurl the skin edges to avoid burying epithelium. Ideally, the vascular strip should be long enough to overlie a portion of the graft that is resting on the posterior canal wall. The periosteum is closed, with care taken not to lift the ear forward to avoid displacement of the vascular strip. After several sutures are placed in the periosteum, the vascular strip position is reinspected through a speculum, and the ear canal is filled with Gelfoam or antibiotic ointment. The postauricular wound is closed.

Advantages of the lateral technique include wide exposure and the ability to use it for all perforation sizes. The disadvantages include a longer healing time because of extensive dissection; a more technically demanding and difficult-to-master procedure for the surgeon who performs ear procedures only occasionally; epithelial pearls, and possibly iatrogenic cholesteatoma as a result of incomplete squamous epithelium removal; blunting; and lateralization that occurs as a result of the separation of the graft from the middle fibrous layer (this generally occurs only if the graft was placed lateral to the malleus). The gap becomes filled with fibrous tissue, and this results in a significant conductive hearing loss. The tympanic membrane loses all landmarks, and the ear canal becomes significantly reduced in depth.

Medial Graft Technique

The medial technique can be used with any of the aforementioned approaches. The tympanomeatal flap is elevated as described earlier in the transcanal approach. If a prominent canal wall prevents complete visualization of the anterior edge of the perforation, canalplasty can be performed. A segment of the anterior canal skin overlying the canal bulge can be removed, and the bulge can be drilled down. The skin can be replaced as a free graft at the end of the procedure. Another option is to create a medially based anterior canal skin flap down to the level of the anulus, which is left intact. The skin flap is laid over the tympanic membrane and covered by a template of suture packet aluminum foil to protect it from accidental injury during drilling. Canalplasty can be performed to remove the anterior canal bulge; the anterior canal skin is then reflected back in place, where it usually stays owing to surface tension. This technique can routinely expose the anterior anulus, allowing the use of this technique even for total perforations.

For anterior perforations, the attachment of the tympanomeatal flap to the malleus can prevent adequate visualization of the anterior part of the mesotympanum (Fig. 141-4A). Several techniques can be used to overcome this difficulty. The tympanomeatal flap can be divided from the lateral edge to the perforation; the resulting flaps can be reflected like an open book, allowing for easier access to place the graft. Another technique allows for complete exposure of the middle ear and better placement of the graft medial to the anterior anulus for total perforations. The attachment of the tympanic membrane remnant to the malleus is divided by using a sickle knife to incise the periosteum on the posterior aspect of the malleus, and the tympanic membrane is dissected forward and can be reflected upward on the anterior canal wall (Fig. 141-4B and C). The middle ear and anterior anulus are completely exposed. The middle ear is prepared for grafting, and the area of the eustachian tube is packed well with Gelfoam to provide adequate support to the graft in this area (Fig. 141-4D).

The most common area of tympanoplasty failure when repairing total perforations is the anterosuperior area owing to a lack of support. A platform of Gelfilm is prepared and placed lateral to the Gelfoam, but medial to the malleus and anterior anulus (Fig. 141-4E and J). The anterior edge of this platform extends into the protympanum area, which is packed with Gelfoam to support the platform and get it in contact with the anulus. It acts as a smooth surface over which the graft can slide and be tucked anteriorly medial to the anulus (see Fig. 141-4J).

The fascial graft is fashioned with a small hole in the anterosuperior part (Fig. 141-4F); this hole accommodates the manubrium of the malleus. The umbo is introduced through the hole, and then the graft is pulled superiorly where the hole surrounds the malleus neck (Fig. 141-4G and H). This provides good stability of the graft and prevents its movement if it is accidentally caught in the suction tip; it also provides a fulcrum around which the graft can be rotated for optimal positioning. The tympanomeatal flap is returned back to its native position (Fig. 141-4I). Advantages of the medial graft include the avoidance of the disadvantages of the lateral technique, an easier to master technique for the general otolaryngologist, and, if the graft is performed properly, the achievement of high success rates compared with lateral technique. Experienced surgeons should be successful in closing tympanic membrane perforations in approximately 90% of cases, regardless of the technique of graft placement.[24,25]

Special Considerations

Tympanosclerosis

The tympanic membrane remnant often contains areas of myringosclerosis, which, if extensive, can make repair of the perforation more difficult. Smaller areas of myringosclerosis have no effect on hearing and can be left alone. Tympanosclerosis that affects a large area of the tympanic membrane remnant should be removed and replaced with the fascial graft.

Atrophic and Atelectatic Tympanic Membrane

When eustachian tube function is normal, small areas of atrophic tympanic membrane away from the perforation can also be left alone.

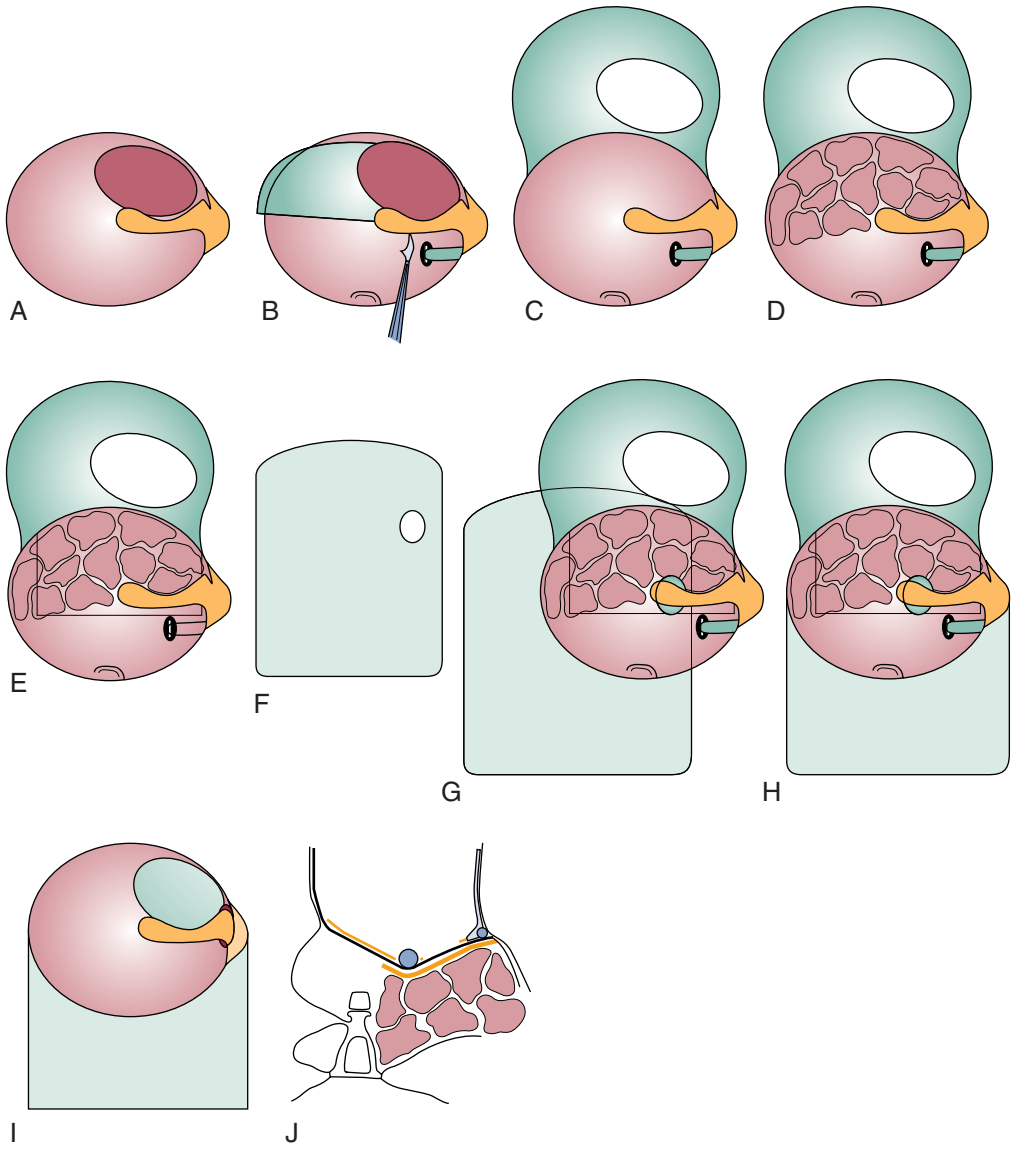

Figure 141-4. **A,** Anterior tympanic membrane perforation. **B,** Reflected tympanomeatal flap still attached to the malleus; the periosteum is incised along the posterior aspect of the malleus. **C,** Tympanomeatal flap freed from the malleus, dissected forward, and reflected upward onto the anterior canal wall, which shows through the perforation. **D,** Gelfoam is placed anteriorly to support the graft. **E,** A platform of Gelfilm is placed lateral to the Gelfoam and medial to the malleus and the anterior anulus. **F,** Fascial graft with a small hole created in the anterior superior aspect. **G,** The umbo is passed through the hole in the graft. **H,** The graft is pulled superiorly so that the hole surrounds the malleus neck; the anterior edge of the graft is tucked medial to the anterior anulus and lateral to the Gelfilm platform. **I,** The tympanomeatal flap is returned to its position; the graft is showing through the perforation. **J,** Schematic diagram that shows the placement of the Gelfilm platform and graft medial to the anterior anulus supported by Gelfoam in the anterior tympanum.

In many instances, however, much of the dystrophic tympanic membrane is removed in an attempt to obtain a healthy mobile tympanic membrane from the graft. The atrophic posterosuperior quadrant, whether retracted or not, presents a special situation. Tympanoplasty that involves a composite cartilage/perichondrial graft to provide structural support for this area while preserving tympanic membrane mobility is gaining wide acceptance. The cartilaginous graft can be made quite thin and of a small enough diameter to bolster only the weakened portion of the involved tympanic membrane.[24]

The atelectatic ear also poses a special problem. Many such ears are dry and produce no symptoms other than hearing loss. Many otologists think of the atelectatic ear as an end-stage ear with very poor eustachian tube function, and they recommend only regular follow-up to ensure the absence of cholesteatoma. Other otologists believe that hearing loss should be corrected and recommend cartilage tympanoplasty for such ears.[26] (*Note*: The risk here is that a dry, asymptomatic ear may be converted into one requiring ongoing care and revision surgeries. The risk-to-benefit ratio of proceeding with surgical management of the atelectatic ear should be carefully considered.)

Cartilage Tympanoplasty

Although high tympanic membrane closure rates and good hearing results have been reported for temporalis fascia and perichondrial grafts, certain situations are associated with graft atrophy and failure, regardless of placement technique.[27] The tissue rigidity of cartilage and its resistance to resorption and retraction, even in the setting of ongoing eustachian tube dysfunction, has led to the growing acceptance of its use in middle ear reconstruction.[28] Cartilage grafts placed between the tympanic membrane and an ossicular prosthesis decrease extrusion risk and can augment the prosthesis-tissue interface, allowing for better long-term hearing results.[29] If a second-stage ossiculoplasty with an allograft is anticipated, a cartilage graft may be placed beneath the

central portion of the membrane at the time of tympanoplasty. In addition to the more common use of cartilage to provide structural support to posterosuperior retraction pockets,[24] more recent literature supports the use of cartilage for the atelectatic ear and other conditions associated with increased failure rates with traditional techniques (e.g., revision surgery, perforation >50%, drainage at time of surgery, bilateral perforations) and, although more controversial, for reconstruction after cholesteatoma.[30-32]

Several different techniques and types of cartilage grafting have been described, including placement of composite cartilage/perichondrial grafts of varying sizes and shapes, and creation of cartilage palisade arrays. Cartilage may be harvested with its attached perichondrium from the tragus or the concha. Tragal cartilage is thicker and flatter than conchal cartilage, and may be more suitable for larger perforations.[30] A composite cartilage/perichondrium graft may be constructed by carving an eccentrically located disk of cartilage that remains attached to its perichondrial flap. The cartilaginous graft can be made quite thin and of a small enough diameter to bolster only the weakened portion of the involved tympanic membrane, or may be shaped to fill a pantympanic perforation. It also may be modified to allow space for the malleus handle, the incus, or a prosthesis. The graft is placed in an underlay fashion, and the remaining perichondrium is used to augment the tympanic membrane repair or to drape over the posterior canal wall.[30] Other modifications of this concept can be seen in the tragal cartilage shield graft[28,33] and the butterfly cartilage graft inlay technique.[34,35]

After noting that larger plates of cartilage may become distorted with time, Heermann and colleagues[36] proposed the used of palisades, or strips, of cartilage for membrane reconstruction. The traditional palisade technique involves the placement of thin rectangular cartilage slices medial to the bony anulus and parallel to the malleus handle. Modifications have been described, including the placement of custom-carved slices of cartilage to reconstruct the round shape of the tympanic membrane.[30,32] The reconstruction may be covered with perichondrium or fascia.

Many studies have established the efficacy of cartilage grafts in tympanoplasty and shown no detrimental effect on hearing.[28,32,35,37-43] Here, the acoustic transfer properties of cartilage seem to depend on cartilage thickness. Reducing cartilage thickness optimizes acoustic transfer properties, with thickness 500 µm or less resulting in a highly favorable vibratory transfer.[43] In his analysis of 636 cartilage tympanoplasties, Dornhoffer[30] reported a successful graft take and membrane closure in greater than 95% of cases performed for high-risk perforations and atelectatic ear drums. Hearing results were not significantly different from fascial or perichondrial repairs. Because of the increased thickness and opacity of cartilage grafts, postoperative monitoring for effusion and cholesteatoma is challenging, and tympanometry may be unreliable.

Pediatric Tympanoplasty

Traditionally, tympanoplasty was not recommended in children younger than 7 years because it may affect the normal growth of the bony external canal, and because it was thought to have a high rate of recurrence owing to immature eustachian tube function. Several studies have shown that tympanoplasty, even in children as young as 2½ years old, has a good success rate and long-term stability.[44-49] It was suggested that evidence of ongoing eustachian tube dysfunction (as shown by otitis media with effusion and negative middle ear pressure in the contralateral ear) may predict poor outcome in pediatric tympanoplasty.[50]

Ossiculoplasty

Pathophysiology

Ossicular Fixation

Tympanosclerosis can hinder motion of the eardrum and the ossicles, and, in severe cases, can totally immobilize the stapes, malleus, and incus. It appears as a chalky white mass that involves the tympanic membrane and the middle ear (or attic), and is the end product of chronic infection or inflammation. Microscopically, there is increasing collagen and fibrous tissue with hyaline degeneration within the lamina propria of the pars tensa and the middle ear mucosa. The deposition of hyaline occurs in layers similar to the rings of an onion and may reach a thickness of a few millimeters.

Tympanosclerosis most commonly involves the tympanic membrane—myringosclerosis—but this condition usually does not have much of an adverse effect on hearing. Significant conductive hearing loss is usually a result of the fixation of the ossicles in the middle ear or epitympanum. With roughly equal frequency, the disease fixes the stapes in the oval window region, and the incus and malleus in the attic, or involves the ossicles in the oval window and the attic simultaneously. Ossicular fixation from tympanosclerosis should be suspected as the cause of conductive hearing loss when there is a history of chronic infections, or when tympanosclerosis is seen on the tympanic membrane.

Bony fixation of the ossicles can occur as a result of infection, surgical trauma, or temporal bone fracture, or as a congenital anomaly. Infection is the most common of these, and it is usually associated with a current or past history of either cholesteatoma or chronic otitis media with granulation tissue. Isolated fixation of the malleus is the most common manifestation, and usually occurs at some location on the anterior surface of the malleus head. Fixation of the incus is the next most common manifestation, and it can bind any of the free surfaces of the incus body to an adjacent wall of the attic. Combined fixation of the malleus and incus occurs as commonly as isolated incus fixation. Nonotosclerotic bony fixation of the stapes is uncommon and is usually manifested by a small bridge of new bone between the fallopian canal and one of the crura.

It may be possible to diagnose malleus fixation preoperatively by microscopic observation during pneumatic otoscopy. In these cases, the umbo and the anterior (short) process of the malleus can be seen to move less than in normal ears or not at all.

Ossicular Discontinuity

Chronic otitis media in almost any form can result in the disruption of the integrity of the ossicular chain. Chronic eustachian tube insufficiency and tympanic membrane retraction that results in prolonged contact of the tympanic membrane with the tip of the incus can cause this type of erosion, even without active infection. Cholesteatoma is the most common cause, however; chronic otomastoiditis without cholesteatoma can also cause erosion of the ossicles. The pathology can be restricted to the incudostapedial joint with loss of the lenticular process, sometimes with preservation of a soft tissue connection; usually, however, there is a complete loss of some portion of the distal incus. The entire long process of the incus can be eroded, particularly in cases of cholesteatoma, along with the stapes superstructure. In some cases, the incudostapedial erosions are associated with partial or total malleus fixation.

Surgical removal of the ossicles during cholesteatoma removal is another obvious and common cause of ossicular discontinuity. In most instances, this involves the entire (remaining) incus and the head of the malleus.

Trauma can also result in ossicular discontinuity, especially longitudinal temporal bone fractures. The force of the fracture tears the incus from its articulations with the malleus and stapes, and the incus does not completely return to its normal position. The stapes superstructure may also be fractured.

Audiometric Correlates

With complete ossicular discontinuity, the most common audiometric pattern is that of a near-maximum (55 to 60 dB) conductive hearing loss across all frequencies.[51] This is because, as mentioned previously, sound input to the cochlea depends solely on acoustic coupling. The intact tympanic membrane presents a barrier to the sound trying to reach the oval and round window membranes. The limited sound reaching those membranes strikes them at the same time (no phase protection) with a similar low sound pressure (absent ossicular coupling). When a significant tympanic membrane perforation is present, along with ossicular discontinuity, that barrier is removed, and hearing is improved by 10 to 15 dB. An interesting variation is the uncommon situation of a partial incudostapedial separation (fibrous union of the incus and stapes). Audiometrically, the air-bone gap is greater in the

high frequencies than in the low frequencies. Tympanometry also helps to identify cases of complete ossicular disruption because the discontinuous ossicular chain allows a wide excursion of the tympanic membrane in response to changing ear canal pressure, and a deep tympanometric pattern results.

Audiometrically, ossicular fixation presents contrasts to ossicular discontinuity. Because the fixation of the ossicles restricts the motion of the malleus and the tympanic membrane, the tympanogram is flatter than normal; a Carhart notch is usually seen. This is a 5-, 10-, 15-, and 5-dB depression in bone-conduction thresholds at 500, 1000, 2000, and 4000 Hz. This is not a true depression in bone conduction, but rather an artifact caused by a lack of the normal contribution of the mobile ossicular chain to bone conduction. This depression improves after the mobility of the ossicular chain is restored. The Carhart values are averages from numerous subjects, and in some cases, changes are much greater. The air-conduction thresholds in ossicular fixation are poorest in the low frequencies. When the air-conduction and the bone-conduction thresholds are plotted, the pattern looks like an hourglass on its side; the air-conduction thresholds are best in the midfrequencies and poorer at high and low frequencies. Air-conduction and bone-conduction thresholds in cases of ossicular discontinuity look like parallel lines 50 to 60 dB apart across the frequencies, without better hearing at the midfrequencies and without the bone-conduction depression seen in ossicular fixation.

Materials

The materials used in the reconstruction of the ossicular chain are autografts, homografts, and allografts. Autografts are either bone or cartilage. Autograft ossicles are removed from the patient and sculpted to serve as an interposition graft; the incus is used most commonly. The advantages include immediate availability, obvious biocompatibility, low cost, and a low extrusion rate. Disadvantages include concerns about possible disease recurrence when used in patients with cholesteatoma, the potential for fixation to adjacent bone of the promontory or the canal wall, and ossicle unsuitability owing to demineralization or erosion. In addition, autografts and homografts require time and skill to shape appropriately in the operating room. Autograft cartilage is usually taken from the tragus or occasionally from the auricular cartilage. Homograft ossicles and en bloc tympanic membranes with attached ossicles are available through regional tissue banks, and graft rejection is extremely rare. Their usage has decreased considerably, however, largely as a result of the fear of potential transmission of human immunodeficiency virus, hepatitis, and Creutzfeldt-Jakob disease.

During the past 20 years, there has been increasing interest in and use of allografts. The major advantages are sterility, availability, and, for some, the ability to bond to tissues. During their developmental history, the disadvantages of allografts have been difficulties with biocompatibility (extrusion) and cost. There have been three principal groups of allografts: polymers, ceramics, and metals. The polymers include polyethylene, polytetrafluoroethylene (Teflon; DuPont, Wilmington, DE), and silicone rubber (Silastic; Dow Corning, Midland, MI). Polycel and Plasti-Pore are high-density polyethylene sponge products. The ceramics include the glass ceramics Ceravital (Ernst Leitz, Wetzlar, Germany) and Bioglass and the calcium phosphate ceramic hydroxyapatite. Hydroxyapatite can achieve real integration with bone without encapsulation, and it can be made in a porous and a dense form; it is brittle and difficult to sculpt or modify.[52]

Allografts have been manufactured in two basic configurations: total ossicular replacement prosthesis (TORP) and partial ossicular replacement prosthesis (PORP). There are many variations in the shape of the platform of the tympanic membrane portion of the prosthesis. Some contact the undersurface of the tympanic membrane, whereas others are designed to conform to the undersurface of the malleus. In addition, prostheses are designed to be used for ossicular discontinuity that is restricted to separation of the incudostapedial joint.

Attempts have also been made to combine various allografts. A hydroxyapatite platform is frequently combined with a Plasti-Pore shaft. The hydroxyapatite has less extrusion potential and can bond to tissue, whereas the Plasti-Pore can be cut to the appropriate length more easily. Other materials have been used in such composite prostheses. These include Polycel (thermal-fused Plasti-Pore), polytetrafluoroethylene, a mixture of hydroxyapatite and Silastic, and hydroxyapatite-reinforced polyethylene composites.[53,54]

The choices and preferences of ossicular prostheses by U.S. otologists have changed over time. In a 1989 survey, autograft and homograft bone prostheses were used by 93% of respondents, cartilage prostheses were used by 78%, and Plasti-Pore prostheses were used by 81%. Hydroxyapatite had just been introduced as a biomaterial.[55] Ten years later, a similar survey revealed that hydroxyapatite prostheses were used by 82% of respondents, autograft and homograft bone prostheses were used by 72%, and autograft or homograft cartilage prostheses were used by 62% (only 4% listed cartilage as their first preference). Plasti-Pore prosthesis use had declined to 59% of respondents.[56] The trend toward increasing use of allografts over autografts was confirmed in a 2005 survey of British otolaryngologists.[57]

More recently, titanium prostheses have been gaining popularity.[58-62] The titanium prosthesis combines low weight (<4 mg) and high rigidity. The prosthesis is the closest in mass to the ossicles it tries to replace. These characteristics lead to reduction in acoustic impedance and sound damping, particularly for higher frequencies.[63] All of the current designs of titanium prostheses have an open head plate (toward the tympanic membrane) that allows the surgeon better visualization of the medial end of the prosthesis during placement. The medial end of the titanium PORP fits better over the stapes head because of its clawlike design, which achieves a secure connection. In addition, titanium prostheses are not top heavy similar to hydroxyapatite prostheses, and tend to stay upright. Titanium was also found to be more user-friendly by most surgeons compared with hydroxyapatite and other allograft materials.[64,65] These properties may ease the learning curve for titanium ossiculoplasty, allowing less experienced ear surgeons to achieve good results. Cartilage is used to interpose between the prosthesis and the tympanic membrane to prevent extrusion. A cartilage interface that is equal to the diameter of the prosthesis head has been shown to have little effect on acoustic transmission in cadaver studies.[66]

The numerous types of prostheses available attest to the fact that no one implant is perfect. A review of alloplastic materials in ossiculoplasty showed that results are still comparable for the alloplastic materials that are currently in use, with different series reporting different success and extrusion rates using the same prosthesis.[67] In 2001, House and Teufert[68] reported on the use of Plasti-Pore in 1040 cases. The air-bone gap was less than 20 dB in 69% of PORP cases and in 61% of TORP cases. In 1990, Grote[69] reported on the long-term results achieved with hydroxyapatite prostheses with an air-bone gap less than 20 dB in 84% of PORP cases and in 64% of TORP cases. Dalchow and colleagues,[70] in 2001, reported on more than 1300 cases that involved the use of titanium prostheses, with 76% achieving an air-bone gap of less than 20 dB; PORPs and TORPs were combined. Since then, other groups have reported on titanium ossiculoplasties, with achievement of an air-bone gap less than 20 dB in 50% to 85% of PORP cases and 40% to 50% of TORP cases.[60,71-75] In a more recent comparative study of titanium versus hydroxyapatite PORP and TORP results, no statistically significant differences were found between the two groups at 2 months.[75] Based on an analysis of studies reporting long-term follow-up of ossiculoplasties, Yung[76] estimated that the 5-year success rate for PORPs and TORPs is two thirds for PORPs and one third for TORPs.[76]

Factors That Affect Surgical Decisions

The goal of ossiculoplasty is to re-establish efficiently the transfer of induced vibratory energy from the tympanic membrane to the undersurface of the stapes footplate, maximizing the postoperative gain in hearing. Many factors have a bearing on the potential success of such operations. The technical skills of the surgeon have a major effect. Independent of surgical judgment and experience, the psychomotor skills necessary to perform this type of surgery and obtain optimal results are substantial. In addition, sufficient general otologic experience is necessary so that the surgeon may obtain adequate exposure for the operation in the face of difficulties such as a small external auditory canal, the limited ability of the patient to turn the head, or a large body habitus, especially in the neck and shoulder areas. Inadequate or mar-

ginal exposure greatly increases the degree of difficulty of the procedure. The presence of concomitant tympanic membrane perforation also elevates the degree of difficulty because a separate graft is required for the perforation.

A major decision to be made during surgery for chronic otitis media (especially for cholesteatoma) is whether to perform ossiculoplasty at the time of the cholesteatoma excision or to perform ossiculoplasty as a planned procedure some months later.[71] Important factors relevant to this decision include the following: (1) status of the middle ear mucosa, (2) amount of bleeding, (3) advisability of reoperation for possible cholesteatoma recurrence, and (4) eustachian tube function in the involved ear and the contralateral ear. Middle ear mucosa that is thickened, infected, traumatized, or partially missing is likely to heal with fibrous tissue formation that may displace a perfectly placed prosthesis. Middle ear bleeding not only obscures visualization and makes the surgery more difficult, but it also increases the risk of unfavorable fibrosis.

Some surgeons perform ossiculoplasty in the same setting with every cholesteatoma operation, even when a second-look procedure for recurrent or residual disease is planned. When economic considerations prevent the second look, this approach seems appropriate, although hearing restoration is always a goal that is secondary to complete cholesteatoma excision. Other surgeons prefer to defer ossiculoplasty and, at the first operation, to try to decrease postoperative middle ear fibrous tissue formation by placing a sheet of Silastic, Gelfilm, or Epidisc between the promontory and the tympanic membrane (graft). After healing is complete, these surgeons assert that the level of the tympanic membrane vis-à-vis the promontory is established and will be stable after the second-stage ossiculoplasty; this makes it easier to judge the appropriate length for a prosthesis that connects the tympanic membrane or malleus to the stapes capitulum or footplate.

The major factor that affects the choice of the prosthesis is the status of the ossicles. When the undersurface of the manubrium of the malleus anchors the prosthesis laterally, consideration must be given to the anteroposterior distance from the manubrium to the footplate compared with the mediolateral distance between them, which is really the depth of the middle ear. A favorable relationship should allow the interposed prosthesis to lie in a more vertical position (Fig. 141-5A). With a wide anteroposterior distance and a narrow middle ear, an unfavorable vector for energy transfer would exist, and the hearing result would be poor (Fig. 141-5B). In that situation, it is preferable to anchor the lateral portion of the prosthesis to the posterosuperior quadrant of the tympanic membrane, which is more directly lateral to the stapes capitulum or footplate (Fig. 141-5C).

Goldenberg and Driver[77] reported a higher incidence of closure of the air-bone gap (<20 dB) when a hydroxyapatite prosthesis interfaces with the malleus versus the tympanic membrane (67% versus 42%), a finding consistent with the idea that prosthetic reconstruction to the malleus may preserve the benefits of the caternary lever.[78] Another malleus consideration exists when the umbo is chronically retracted and lies near the promontory; this restricts malleus motion and tympanic membrane motion. In these cases, the platform of a TORP or PORP lies at an unfavorable angle to the tympanic membrane surface and cannot be at the desired right angle to the shaft of the prosthesis. Severing the tensor tympani tendon allows the tympanic membrane to lateralize to a more favorable angle and level, and increases the prosthesis efficiency.

Surgical Techniques (see Key Indicator Video on website)

Ossicular Fixation

Tos[79] has written extensively about the surgical treatment of ossicular fixation that results from tympanosclerosis. Whenever possible, an intact ossicular chain is preserved. When the disease is restricted to the attic, a wide atticotomy is performed, with preservation of a bony bridge lateral to the ossicles. Tympanosclerosis is progressively removed from the lateral, anterior, superior, and medial surfaces of the malleus and incus. When the tympanosclerosis is restricted to the stapes, radical removal of the plaques without opening into the vestibule or removing the footplate is preferred. The dissection is performed without separating the incudostapedial joint, and from a posterior to an anterior direction, using slow motions and using the stapedius tendon for stability. When attic and stapedial tympanosclerosis are present, the attic is addressed first to see if a mobile intact malleus and incus can be achieved. If stapedectomy is unavoidable (or desirable), it is delayed until the end of the procedure.

If the entire stapes is to be removed, it is extracted very slowly, only after a control opening has been made on the most accessible part of the footplate. Stapedotomy also has been reported in cases of tympanosclerotic fixation of the stapes. An air-bone gap of less than 20 dB was obtained in 70% of cases in one series.[80] Stapedectomy should not be performed in conjunction with tympanic membrane repair in a potentially infected ear because of the risk of labyrinthitis and profound hearing loss.

Acquired bony fixation of the malleus can be surgically managed in two ways: (1) by the direct removal of the bony fixation, with the restitution of an intact ossicular chain, or (2) by the removal of the incus and the malleus head, with the interposition of an allograft between the manubrium and the stapes. Tos[79] strongly advocates the former approach and performs an atticotomy that is large enough to provide adequate exposure. After the atticotomy, a small diamond bur is used to reduce the fixation point to a thin shell, which is vaporized with a laser to avoid transmitting mechanical energy to a mobile stapes, causing sensorineural hearing loss. The attic bone adjacent to the fixation point is removed further with a drill, and a Silastic sheet is interposed between the malleus head and the adjacent attic wall.[81]

The alternative procedure also requires an atticotomy to remove the incus and the malleus head because the malleus fixation does not allow the incus to be rotated out of its position in the usual manner. The long process of the incus often needs to be removed (after careful separation of the incudostapedial joint) before the incus can be rotated and extracted; the malleus head is then removed. The malleus to stapes

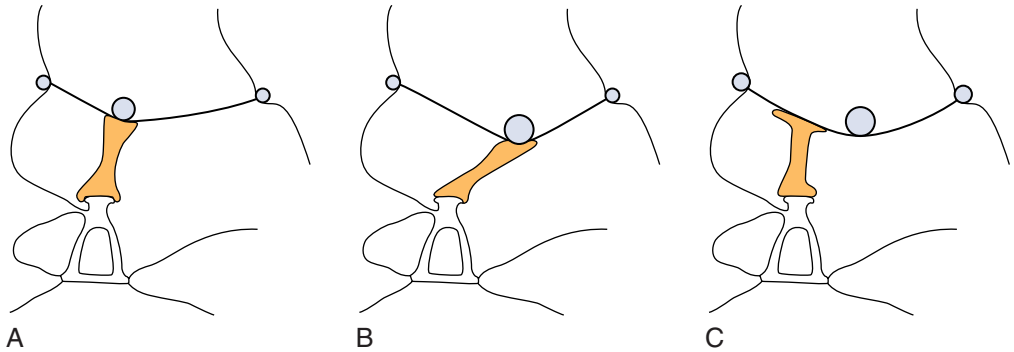

Figure 141-5. A, Favorable relationship between the malleus and the stapes, allowing a more vertical position of the interposed prosthesis. **B,** Unfavorable relationship, which results in a more horizontal position of the prosthesis. **C,** Prosthesis connecting the stapes head to the posterior superior quadrant of the tympanic membrane in an ear with an unfavorable malleus-stapes relationship.

interposition prosthesis is less stable because the malleus is hypermobile after removal of its head. Both techniques are technically difficult.

Ossicular Discontinuity

When only the tip of the incus is missing, a specially designed allograft prosthesis that fits on top of the capitulum of the stapes and has a concave arm that rests beneath and supports the distal incus works well.[82] A similar autograft cartilage prosthesis can be sculpted at surgery. Insertion requires simultaneous lifting of the incus and placement of the prosthesis on the stapes. A prosthesis that attaches to the incus, and that has a cup that fits on the stapes capitulum is also available and is reported to give good results.[83] If only the lenticular process is eroded, and the incus long process is intact, a simple cartilage block interposition can be used. Bone cement may also be used to reconstruct the missing part of the incus and the incudostapedial joint with good hearing results.[83-86]

When the long process of the incus is absent, the two factors of greatest importance are the condition of the stapes superstructure and the condition of the malleus. When the stapes superstructure is present and connected to the footplate, most surgeons prefer to attach the prosthesis to the head of the stapes as a PORP because the medial anchor of the prosthesis is stable and cannot slip. If the superstructure is absent, the stapes footplate is the medial point of fixation, and a TORP is used. Securing this medial anchor point has been more difficult, and, generally, results of TORPs are poorer than those of PORPs.

Using the medial surface of the malleus handle as the lateral anchoring point for the prosthesis is more stable than the tympanic membrane alone, and extrusion is less likely. To use the malleus successfully, however, the surgeon should be able to answer affirmatively the following questions:

1. Does the malleus have normal mobility?

2. Is there adequate space between the umbo and the promontory?

3. Is the vector between the malleus and stapes capitulum or footplate favorable?

If the answer to all three questions is yes, the malleus can be used. If not, the posterosuperior portion of the tympanic membrane is a better choice.

Causes of Failure

An occasional cause of ossiculoplasty failure is incomplete or erroneous diagnosis. Routine palpation of all three ossicles in middle ear surgery trains the surgeon to recognize the normal range of motion for each ossicle. When assessing stapes mobility, it is important to observe the footplate under high magnification and to identify one bright spot of reflected light, which is called the light reflex. The slightest motion of the footplate would cause that light reflex to move. Motion of the light reflex in response to palpation is the most accurate means of intraoperatively identifying that the footplate is mobile. Conversely, a lack of motion of the light reflex to palpation indicates that the footplate is fixed, the superstructure is fractured, or there is ossicular discontinuity between the point of palpation and the footplate. Possible misdiagnoses include (1) missing a fixed malleus in the presence of otosclerosis; (2) failing to identify a fractured stapes superstructure; and (3) failing to identify a bony incudostapedial disarticulation when the soft tissue connection is preserved.

A much more common cause of ossiculoplasty failure is extrusion of the prosthesis; this is most common with allograft prostheses that directly contact the tympanic membrane (as opposed to the undersurface of the manubrium). Although the incidence is much lower if a thin piece of cartilage is placed between the tympanic membrane and the platform of the prosthesis, extrusion still occurs.

Finally, ossiculoplasty failure occurs most commonly in ears that continue to exhibit eustachian tube malfunction or that develop the problem after surgery. As mentioned earlier, aeration of the middle ear is an important factor in sound transmission. If the middle ear is not aerated, even a perfectly placed prosthesis would still result in a significant conductive hearing loss. Although it is impossible to predict this outcome, the status of the function of the eustachian tube in the opposite ear is a reasonable guide, at least in children.

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CHAPTER ONE HUNDRED AND FORTY-TWO

Mastoidectomy

Paul R. Lambert

Key Points

- Although all major components of the temporal bone are present in infants, the mastoid tip is yet to develop. The stylomastoid foramen is located more superficially, making the facial nerve vulnerable to surgical trauma.
- The temporal line approximates the level of the middle cranial fossa dural plate. The position of the tegmen and the degree of mastoid pneumatization can vary, however.
- An important landmark when performing mastoid surgery is the antrum. Key principles that assist in locating the antrum include saucerization, identification of the tegmen plate, and thinning of the posterior canal wall.
- Failure to identify the superior limit of the mastoid dissection (tegmen plate) could result in looking for the antrum too inferiorly, injuring the horizontal semicircular canal or the genu of the facial nerve, or both.
- A mastoid cavity may appear small because air cells have not been adequately removed from the back of the bony external auditory canal.
- The most important landmarks for identifying the mastoid segment of the facial nerve are the horizontal semicircular canal, the short process of the incus, and the posterior bony external auditory canal.
- An intact canal wall mastoidectomy obviates long-term postoperative concerns of a mastoid cavity, such as infection and the requirement for periodic cleaning.
- Identification of the facial nerve is key to a canal wall down procedure (i.e., appropriate lowering of the posterior canal wall) and the intact canal wall approach (i.e., opening the facial recess).
- The incidence of residual or recurrent cholesteatoma is higher in intact canal wall versus canal wall down mastoid procedures. The incidence is approximately 20% in adults and almost twice that in children.
- Dehiscence of the facial nerve in cholesteatoma cases is approximately 20%, with the most common area being in the region of the oval window.

This chapter focuses on mastoid surgery as it relates to chronic ear disease. Although a mastoidectomy is required in various other surgical procedures (e.g., cochlear implantation; access to the cerebellopontine angle, skull base, and petrous apex; labyrinthectomy; endolymphatic sac decompression; repair of facial nerve disorders; cerebrospinal fluid leaks), the principles to be reviewed in the context of chronic otitis media and cholesteatoma have broad application.

History

The first scholarly treatise on mastoid surgery for suppurative disease was by Schwartze in 1873.[1,2] The procedure he described was a cortical mastoidectomy with limited exenteration of mastoid air cells. For acute and coalescent mastoiditis, which were prevalent in the preantibiotic era, this procedure proved remarkably efficacious. As one might expect, however, the simple mastoidectomy rarely cured chronic otitis media or cholesteatoma. During the next 20 years, it became evident that creating an open cavity was necessary for these diseases, and in 1890, Zaufal described removing the superior and posterior canal wall, tympanic membrane, and lateral ossicular chain, a procedure now known as the radical mastoidectomy.[3] This procedure was modified by Bondy, who recognized that disease limited to the pars flaccida could simply be exteriorized, leaving the uninvolved middle ear alone. His description of the "modified radical mastoidectomy" or "Bondy procedure" in 1910 represented one of the first reports addressing hearing function.[1]

Interest in hearing preservation and restoration gained further attention after Lempert introduced the fenestration operation in 1938, and Zollner and Wullstein described tympanoplasty techniques in the early 1950s.[4-6] During the next decade, Jansen, Sheehy, and others extended these principles of restoring function and maintaining normal anatomy with the introduction of the intact canal wall mastoidectomy with facial recess approach.[7,8]

Anatomy

The temporal bone consists of four parts: squamous, tympanic, mastoid, and petrous (Figs. 142-1 and 142-2). The smallest part is the tympanic portion, which forms the external auditory canal. This chapter focuses primarily on the mastoid portion, which articulates with the parietal and occipital bones and houses the mastoid air cell system, which is in continuity with the air cells of the petrous pyramid. Transmastoid procedures provide access to the facial nerve, internal carotid artery, jugular bulb, labyrinth, internal auditory canal, and petrous apex.

Important surface landmarks on the mastoid include the temporal line, which extends posteriorly from the zygomatic root and is the insertion site for the temporalis muscle. There is considerable variability in the prominence of this structure among individuals. The suprameatal spine or spine of Henle is a small bony protuberance extending superficially from the posterior and superior bony external auditory canal. It is located just inferior to the temporal line, and shows

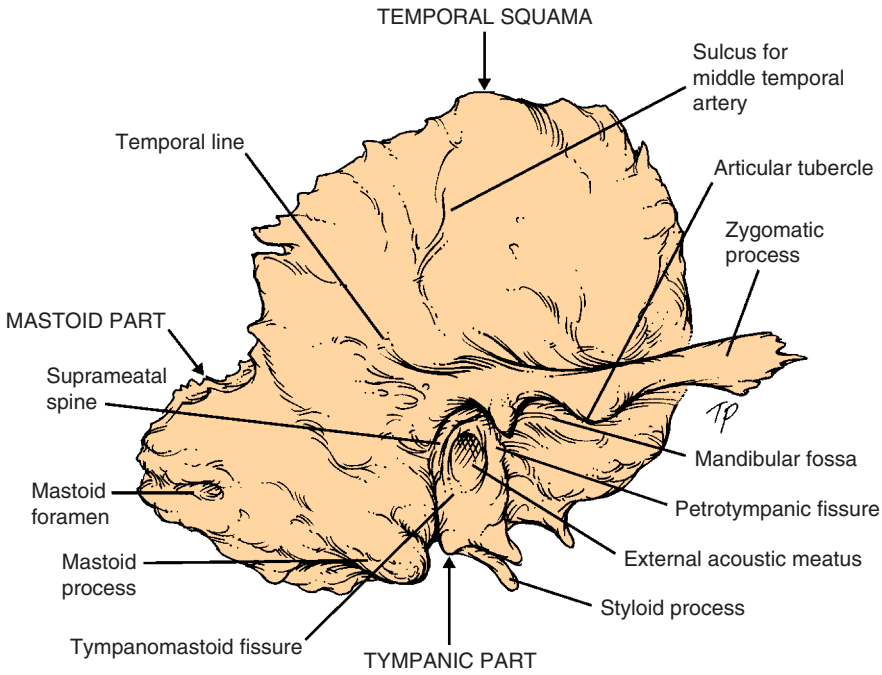

Figure 142-1. Right temporal bone. Lateral view. *(From Donaldson JA, Duckert LG, Lambert PR, Rubel EW, eds.* Surgical Anatomy of the Temporal Bone. *4th ed. New York: Raven Press; 1992.)*

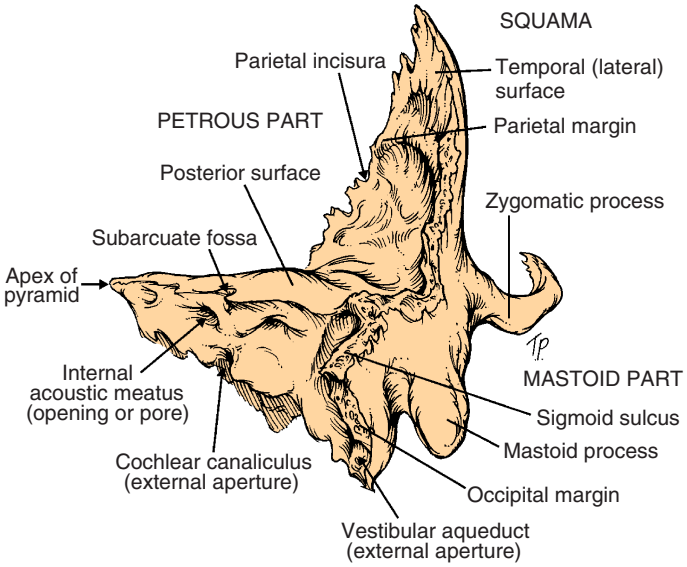

Figure 142-2. Left temporal bone. Posterolateral view. *(From Donaldson JA, Duckert LG, Lambert PR, Rubel EW, eds.* Surgical Anatomy of the Temporal Bone. *4th ed. New York: Raven Press; 1992.)*

variability in size among individuals. Just posterior to this spine is a cribriform area, which approximates the location of the underlying mastoid antrum.

All major components of the temporal bone are present in infants, but there is one notable difference that has surgical implications. In infants, the mastoid tip has yet to develop, and the stylomastoid foramen is located more superficially, making the facial nerve vulnerable to surgical trauma.

Nomenclature

The otologic surgeon has various mastoid procedures from which to choose, depending on extent of disease. In addition, variations on these standard approaches are often discussed in the literature. The nomenclature for mastoid surgery can seem confusing at first. Concomitant surgery involving the middle ear requires additional terminology, such as *tympanoplasty* or *ossiculoplasty*. Box 142-1 lists the standard mastoid procedures for addressing chronic ear disease.

Box 142-1

Mastoid Procedures

Simple mastoidectomy
Canal wall up mastoidectomy
Canal wall down mastoidectomy
Radical mastoidectomy
Modified radical mastoidectomy
Mastoid obliteration

Simple Mastoidectomy

Simple mastoidectomy involves removing the mastoid cortex and varying amounts of the air cell system, depending on the disease process. Only a limited air cell exenteration may be needed to drain a coalescent mastoiditis with subperiosteal abscess, whereas a more extensive dissection to expose the antrum would be necessary to inspect for cholesteatoma.

Canal Wall Up Mastoidectomy

Canal wall up mastoidectomy involves a more complete removal of the air cell system than simple mastoidectomy. Because this procedure and simple mastoidectomy maintain the superior and posterior canal walls intact, however, there is some potential overlap. Usually, canal wall up mastoidectomy includes a facial recess approach, and this addition uniquely qualifies the procedure. More recent variations on canal wall up mastoidectomy include removing a portion of the canal wall, then reconstructing the defect with bone, cartilage, or an alloplastic material, to maintain the normal anatomic barrier between the external ear canal and mastoid cavity.

Canal Wall Down Mastoidectomy

The canal wall down mastoidectomy involves a thorough removal of the mastoid air cells, aggressive saucerization of the cortical edges of the

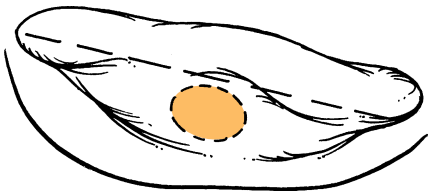

Figure 142-3. Postauricular incision is placed about 1 cm behind the postauricular crease, facilitating skin closure. *(From Sheehy JL. Surgery of chronic otitis media. In: English GE, ed.* Otolaryngology. *Philadelphia: Lippincott; 1986:1.)*

mastoid, a complete removal of the superior and posterior canal walls, and a meatoplasty.

Radical Mastoidectomy

Radical mastoidectomy is a canal wall down procedure with exteriorization of the middle ear. No attempt at restoring middle ear function is made. The eustachian tube is occluded, and the malleus and incus (and possibly the stapes superstructure) are removed. The tympanic membrane remnant is excised, and no graft is placed, leaving the middle ear open. The expectation is for squamous epithelium to grow over the middle ear and mastoid cavity. This procedure is rarely performed today, but may be indicated in situations in which cholesteatoma cannot be completely excised (e.g., cochlear fistula, disease tracking into the petrous apex).

Modified Radical Mastoidectomy

Most of the confusion over terminology centers on modified radical mastoidectomy. Frequently, the term *modified radical mastoidectomy* is used interchangeably with canal wall down mastoidectomy. Classically, modified radical mastoidectomy refers to the Bondy procedure, in which disease limited to the epitympanum is simply exteriorized by removing portions of the adjacent superior or posterior canal wall. The uninvolved middle ear is not entered, and the cholesteatoma matrix on the lateral surface of the ossicular heads is maintained in place as a lining for the created cavity. Small cholesteatomas are frequently amenable to the Bondy approach; I prefer to use the term *modified radical mastoidectomy* in that context.

Mastoid Obliteration

The indications for and extent of obliterating mastoid air cells varies considerably from surgeon to surgeon. Various materials are used, including autogenous bone and cartilage, free or vascularized soft tissue, and bioactive or biocompatible alloplastic materials. Mastoid obliteration is typically used when the canal wall has been removed to decrease the size of the mastoid cavity and make it as care-free as possible. In rare cases, the eustachian tube and external ear canal are closed, completely isolating the mastoid from the exterior.

Operative Procedure (see Key Indicator Video on website)

The surgical site is prepared by shaving 1 to 2 cm of hair around the ear and injecting 5 to 10 mL of local anesthetic with a vasoconstrictor (e.g., 1% lidocaine with 1:100,000 epinephrine) postauricularly and within the external ear canal. To facilitate closure, the C-shaped incision is placed about 1 cm behind the postauricular crease, rather than within it (Fig. 142-3). If extensive saucerization of the mastoid cavity is planned (e.g., translabyrinthine or retrolabyrinthine approach to the cerebellopontine angle, skull base tumor resection), the incision is placed more posteriorly.

Superiorly, the incision is carried down to the temporalis fascia. Inserting a small Weitlaner retractor and lifting it laterally facilitates this dissection. The subcutaneous tissues are elevated off the fascia and easily incised. Inferiorly, the incision is extended to the anterior lateral surface of the mastoid tip. An incision placed more posteriorly on the mastoid involves the insertion of the sternocleidomastoid muscle and results in more bleeding and postoperative discomfort. Making two periosteal incisions—one along the temporal line and the second perpendicular to this and extending to the mastoid tip—exposes the mastoid bone itself. The periosteum is elevated and retracted forward with the auricle.

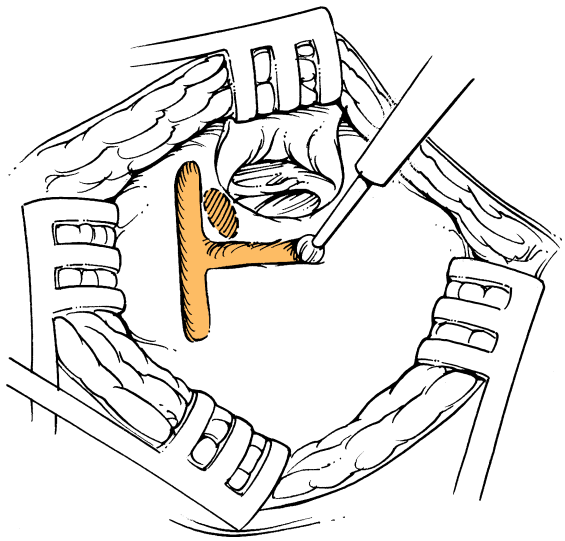

Figure 142-4. Initial bur cuts are along the temporal line and tangential to the bony canal. *(From Sheehy JL. Mastoidectomy: the intact canal wall procedure. In: Brackmann DE, Shelton C, Arriaga MA, eds.* Otologic Surgery. *Philadelphia: Saunders; 1994.)*

With the mastoid cortex fully exposed, the first bur cut is made along the temporal line, which approximates the level of the middle cranial fossa dural plate. It is important to recognize, however, the variability of the position of the tegmen, depending on the degree of mastoid pneumatization. The second bur cut is made perpendicular to this and tangential to the external bony canal; it should be carried inferiorly to the mastoid tip (Fig. 142-4).

Although various drill systems are available, several common principles relate to bur selection and fluid irrigation. When possible, larger rather than smaller burs are preferable for bone dissection. This facilitates saucerization and exposure, and it avoids creating small openings in the bone that can more easily damage underlying structures. It is important, however, to choose a bur that is not so large that it obstructs the field of dissection. It is also critical to note the backside of the bur while drilling, to prevent injuring structures opposite the point of dissection.

A variety of burs exist, ranging from burs that aggressively remove bone to those that are used more for bone polishing. A bur with a cutting or fluted surface is selected for removing cortical bone, whereas a fine diamond grain surface is required when removing the last layer of bone over the facial nerve or sigmoid sinus. When drilling over an irregular surface, a fluted bur has a tendency to "skip" in the direction of the bur rotation.

Appropriate irrigation is necessary to clear bone dust from the field of dissection, to prevent excessive heat transfer to underlying structures (especially the facial nerve), and to maintain a clean cutting surface on the bur. Whether a self-irrigating drill or a suction irrigation system is being used, appropriate adjustment of the level of irrigation facilitates accurate and safe bony dissection.

A key landmark in performing mastoid surgery is the antrum with the dome of the horizontal semicircular canal (HSCC) along its floor. The ease of locating the antrum depends largely on the degree of mastoid pneumatization. Three key principles assist this part of the dissection: saucerization, identification of the tegmen plate, and thinning the posterior canal wall. The deepest dissection is at the point where the initial cortical bone cuts intersect, but widely saucerizing toward the tegmen and especially posteriorly (from the sinodural angle to the mastoid tip) as the antrum is approached is essential. Posteriorly, one must consider the sigmoid sinus, which could be far forward in a poorly pneumatized mastoid. Appropriate saucerization helps identify

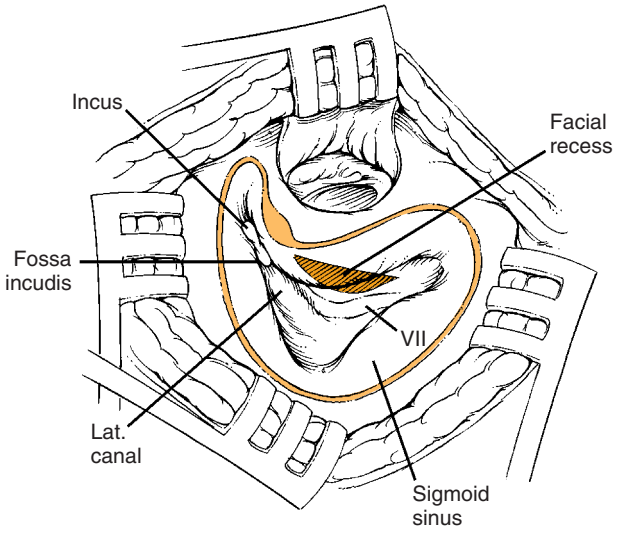

Figure 142-5. The facial recess is shown as the triangle. *(From Sheehy JL. Mastoidectomy: the intact canal wall procedure. In: Brackmann DE, Shelton C, Arriaga MA, eds.* Otologic Surgery. *Philadelphia: Saunders; 1994.)*

its lateral surface and prevent injury. The importance of identifying the tegmen plate cannot be overemphasized. All mastoid air cells should be removed superiorly, effectively skeletonizing this structure. The tegmen is followed medially, anticipating that the plane of the tegmen will vary, usually bulging slightly into the cavity midway between the cortex and the floor of the antrum. Failure to identify the superior limit of the mastoid dissection could result in opening the antrum too inferiorly, injuring the HSCC or the genu of the facial nerve, or both.

All air cells should be removed from the back of the bony external auditory canal. A mastoid cavity may appear small simply because insufficient attention was directed toward this area of dissection. In addition, a thin posterior canal wall assists localization of the facial nerve, as described later.

As the dissection is carried medially and the antrum is approached, a bony septum (Körner's septum) may be encountered. This plate is a remnant of the petrous squamous septum, and simply separates more superficial air cells from deeper ones. Dissection should be carried into the zygomatic root, thinning bone over the tegmen plate and bony external auditory canal to gain appropriate access. This dissection requires progressively smaller burs. Care must be exercised to avoid touching the heads of the ossicles with the bur, which could injure the inner ear by a transfer of excessive vibration. As noted later, however, identifying the short process of the incus provides an important landmark for facial nerve dissection.

Facial Nerve

Identifying the facial nerve is fundamental to performing good mastoid surgery. Except for simple mastoidectomy, it is always safer to define the location of this structure than simply to avoid it. In intact canal wall mastoidectomy (or when a cochlear implant is placed), the space between the facial nerve and the chorda tympani nerve—the facial recess—provides access into the middle ear (Fig. 142-5). In canal wall down approaches, identifying the facial nerve allows the surgeon to lower the facial ridge appropriately, creating a more care-free cavity.

The most important landmarks for the facial nerve are the HSCC, the short process of the incus, and the posterior bony external auditory canal; the digastric ridge is also a landmark, although I use this landmark less commonly unless full exposure of the facial nerve to the stylomastoid foramen is required (e.g., skull base procedures). The genu and proximal portion of the mastoid segment of the facial nerve lie anterior and just medial to the dome of the HSCC. The mastoid segment of the facial nerve also lies medial to the plane of the short process of the incus at the base of the posterior canal wall.

Removing air cells from the posterior bony canal wall until it is only a few millimeters thick is essential. Separating the soft tissue of the membranous canal from the bone at the lateral edge of the bony canal wall helps gauge the thickness of the wall as the bony dissection proceeds. If the canal wall is not thinned appropriately, a wall of air cells continues to cover the facial nerve, and the dissection is carried too far posteriorly, potentially exposing the posterior side of the facial nerve to injury. Ideally, the lateral surface of the facial nerve is first identified in the middle two thirds of its course, avoiding the areas just adjacent to the HSCC and the mastoid tip.

After locating the antrum, a diamond bur is used to open the aditus ad antrum, which leads into the epitympanic space. The short process of the incus is exposed. With this landmark visible, a larger cutting bur or coarse diamond bur removes bone over the area of the facial nerve, with continued thinning of the posterior bony canal wall as the dissection is carried medially. A broad plane of dissection is maintained from the canal wall back into the mastoid because the exact anteroposterior location of the nerve can vary slightly. This broad plane of dissection avoids creating a trough and helps ensure that the lateral surface of the nerve, rather than its side, is exposed. When the plane of the short process of the incus is reached, it is anticipated that the facial nerve will be 1 to 2 mm deeper, and the bur type is changed to a fine diamond.

This last level of dissection should be carried out with copious irrigation (essentially drilling beneath a layer of water) to facilitate discerning the fine capillary network on the epineurium that shows through a thin shell of bone. Bur strokes are made in a longitudinal direction, paralleling the course of the facial nerve. The facial nerve takes a slightly lateral course as it descends from the second genu to the stylomastoid foramen. Dehiscences of the mastoid portion of the fallopian canal, even in the presence of mastoid disease, are infrequent. This is in contradistinction to the tympanic segment of the facial nerve, where congenital and disease-mediated dehiscences are common.

Additional landmarks that may appear during the dissection include the chorda tympani nerve and the air cell systems of the facial recess and retrofacial area. Appropriately thinning the canal wall often exposes the chorda tympani nerve, which can be distinguished from the facial nerve by size and course of direction. If necessary, the chorda can be followed back to its takeoff from the facial nerve trunk for positive identification. In well-pneumatized mastoids, a large air cell system tracking behind and deep to the facial nerve is present. The facial nerve courses just anterior to these retrofacial air cells. Likewise, the identification of the facial recess cells indicates that the facial nerve is coursing just medial to them.

Opening the Facial Recess

The facial recess is the space bounded laterally by the chorda tympani nerve, medially by the facial nerve, and superiorly by the fossa incudis (see Fig. 142-5). This recess varies in size, depending on where the chorda tympani nerve branches from the facial nerve, and in pneumatization. Opening the facial recess provides access to the middle ear from the mastoid (Fig. 142-6). The promontory, round window niche, stapes, long process of the incus, cochleariform process, medial side of the tympanic membrane and malleus handle, and eustachian tube all are well seen.

The facial recess can be extended superiorly and inferiorly, providing a large "posterior tympanotomy." Sacrificing the chorda tympani nerve permits additional dissection inferiorly with good exposure of the hypotympanum. In such cases, the lateral limit of the dissection is the tympanic membrane anulus. Frequently, in chronic ear surgery, the long process of the incus has been eroded, and that ossicle is removed. In such cases, the fossa incudis is taken down, connecting the facial recess with the aditus ad antrum, providing wide exposure over the HSCC and the genu of the facial nerve into the epitympanum (Fig. 142-7).

Opening the Epitympanum

In intact canal wall mastoid surgery, it is frequently necessary to expose the epitympanum. Cholesteatoma can track medially to the heads of the ossicles and extend into the anterior epitympanic space, also termed the *supratubal recess*. Opening the epitympanum is much

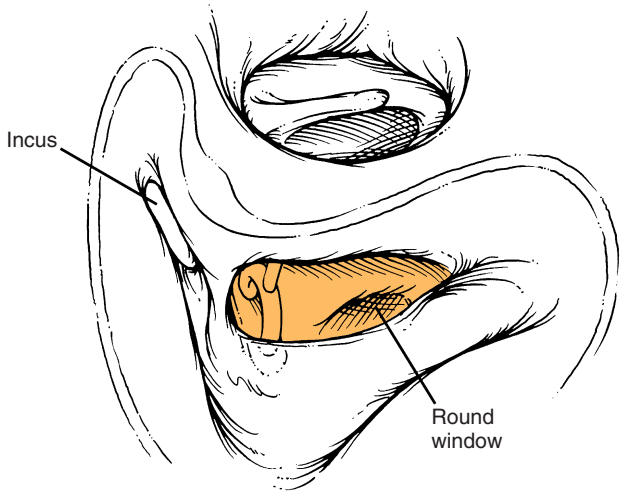

Figure 142-6. The facial recess is opened. *(From Sheehy JL. Mastoidectomy: the intact canal wall procedure. In: Brackmann DE, Shelton C, Arriaga MA, eds.* Otologic Surgery. *Philadelphia: Saunders; 1994.)*

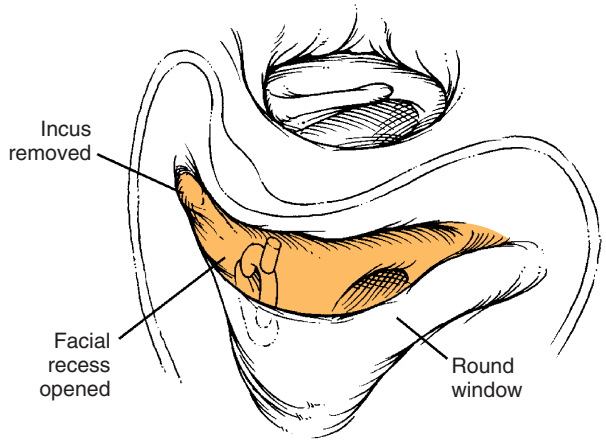

Figure 142-7. The facial recess is enlarged by removing the incus and fossa incudis. *(From Sheehy JL. Mastoidectomy: the intact canal wall procedure. In: Brackmann DE, Shelton C, Arriaga MA, eds.* Otologic Surgery. *Philadelphia: Saunders; 1994.)*

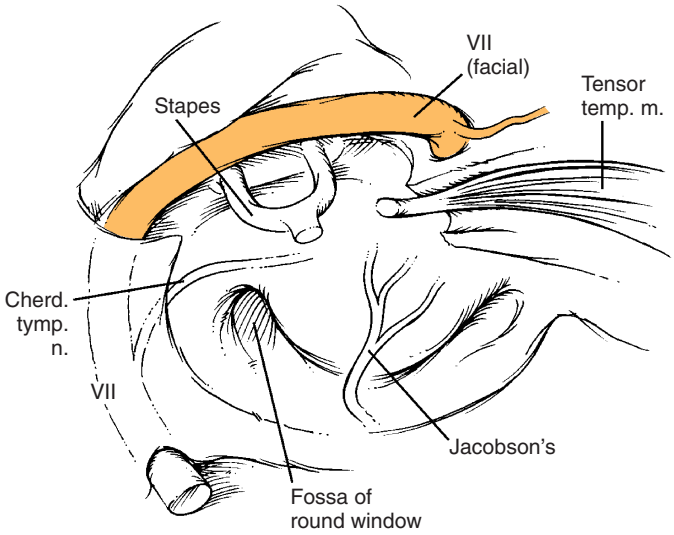

Figure 142-8. Course of the tympanic segment of the facial nerve. *(From Donaldson JA, Duckert LG, Lambert PR, Rubel EW, eds:* Surgical Anatomy of the Temporal Bone. *4th ed. New York: Raven Press; 1992.)*

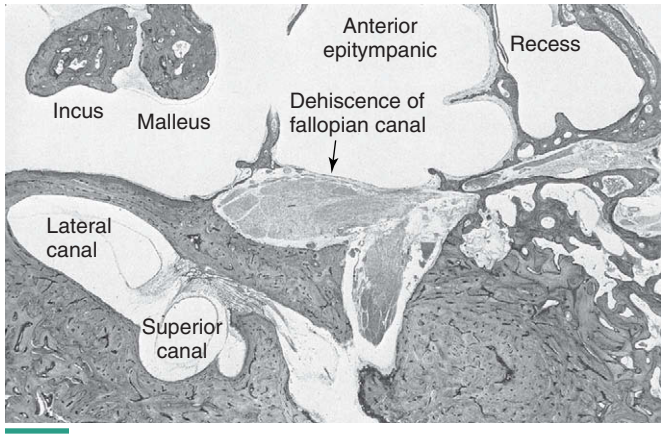

Figure 142-9. Anterior epitympanic space with dehiscent facial nerve. *(From Schuknecht HF.* Pathology of the Ear. *2nd ed. Philadelphia: Lea & Febiger; 1993.)*

easier if there is discontinuity of the ossicular chain (e.g., eroded long process of the incus). In such cases, the incus remnant and the head of the malleus are removed, providing good access into the anterior aspect of the epitympanum. The position of the tegmen varies, and, depending on the degree of pneumatization, the space between the dural plate and superior canal wall may be constricted. Progressively smaller burs, usually with a diamond surface, are required as the epitympanic dissection proceeds anteriorly. A thin plate of bone is maintained over the dura, and the superior canal wall is thinned in a manner similar to the thinning of the posterior canal wall.

It is important to appreciate the anatomic relationships of the facial nerve within the epitympanic space. As the nerve is traced anteriorly from the mastoid genu to the geniculate ganglion, it takes a slightly medial course. It passes superior to the oval window and cochleariform process (Fig. 142-8). The facial nerve in the floor of the anterior epitympanic space can be dehiscent, especially if extensive cholesteatoma involves this region (Fig. 142-9).

Canal Wall Down Mastoidectomy

Many of the disadvantages of a canal wall down procedure can be minimized with proper creation of the mastoid cavity. Crucial components of the procedure include the following:

- Aggressively saucerizing the cavity
- Eliminating irregularities within the cavity (e.g., deep recess and bony overhangs)
- Removing the posterior bony canal wall to the level of the facial nerve
- Creating a large meatus

Saucerization decreases the depth and the size of the mastoid cavity. The cortical edges of the cavity are taken down to the approximate level of the tegmen superiorly, sigmoid sinus posteriorly, and digastric ridge inferiorly (Fig. 142-10). The facial nerve is positively identified by removing the posterior bony canal until only a thin shell of bone remains over the nerve. This dissection is continued toward the stylomastoid foramen until there is no bony spur (inferior or posterior buttress) between the floor of the external bony canal and the mastoid cavity. In a similar manner, the anterior extent of the superior canal wall (anterior buttress) is completely removed, creating a smooth, gently curving transition from the anterior epitympanum to the anterior canal wall.

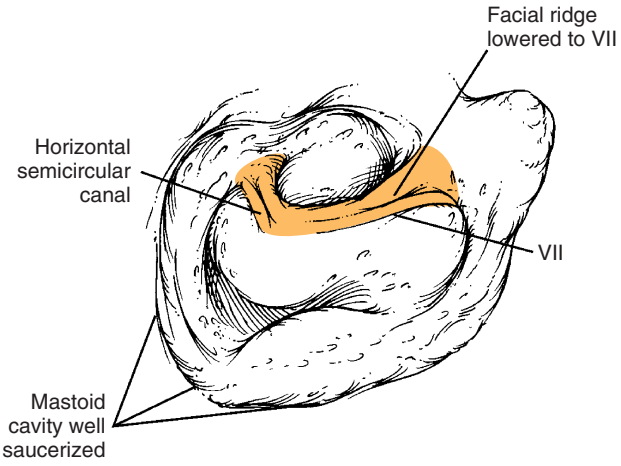

Figure 142-10. Canal wall down mastoidectomy. *(From Brackmann DE, Shelton C, Arriaga MA, eds.* Otologic Surgery. *Philadelphia: Saunders; 1994.)*

Ideally, the contours of the cavity itself should be smooth, without bony recesses or overhangs. Small amounts of bone plate collected during saucerization of the cortical edges can be used to fill irregularities within the cavity. Obliterating these areas, however, should not be performed if one is not confident that all cholesteatoma remnants have been thoroughly removed. Last, a large meatus ensures adequate ventilation of the mastoid cavity and appropriate access for postoperative cleaning. Conchal cartilage must be removed to create a properly sized meatal opening.

Intact Canal Wall versus Canal Wall Down Procedures

The intact canal wall and canal wall down mastoidectomy procedures each have inherent advantages and limitations that involve ease of disease removal, incidence of recurrent or residual disease, and extent of postoperative care.[9] For cholesteatomas involving the middle ear, epitympanum, and mastoid, the superior and posterior canal walls partially obscure the disease. An intact canal wall approach necessitates more surgical manipulations (e.g., facial recess approach and alternately working on the canal and epitympanic sides of the canal wall) and usually more operative time. As described later, cholesteatoma that has extended into the sinus tympani and adjacent recesses may be difficult to remove, regardless of whether the canal wall is left intact or removed.

Because disease exposure is more difficult when the canal wall is left intact, inadvertently leaving a small focus of squamous epithelium behind is possible. Maintenance of the canal wall also provides potential spaces into which retraction pockets can form. The resulting increased incidence of residual or recurrent cholesteatoma is not trivial, especially in children. Studies have shown the incidence to be 20% in adults and 35% to 45% in children.[3,10-13] As a result, the decision to maintain the canal wall necessitates more surgical procedures to ensure disease eradication than would a canal wall down approach.

Several possible reasons can be considered for the higher incidence of residual and recurrent disease in children compared with adults. First, children frequently have well-pneumatized temporal bones with deep cell tracks, which can complicate complete disease removal. In contrast, the mastoids of adults are typically sclerotic. Second, the poor eustachian tube function in children predisposes to retraction pockets and recurrent disease. It also predisposes children to otitis media and secondary infection of the cholesteatoma, causing it to behave in a more aggressive fashion. Also to be considered is the fact that the growth potential of tissue is greater in children than in adults because of the normal elaboration of various growth factors. Studies have shown a greater tendency of squamous cell proliferation in pediatric cholesteatomas compared with adult cholesteatomas. There may be a true biologic difference in the disease process.[14]

The principal advantages of the intact canal wall technique are more rapid healing postoperatively and, more importantly, the obviation of many long-term postoperative concerns. Epithelialization of the mastoid cavity in canal wall down cases may be a slow process (months), and certain areas may require various topical therapies to promote healing. There is also the potential need for long-term care of the cavity because the self-cleaning character of the normal external auditory canal has been altered. The irregular contours of the new canal/mastoid disrupt the normal migration of keratin debris, which can accumulate and foster bacterial or fungal growth. Proper creation of the mastoid cavity, as previously described, can significantly ameliorate this potential problem.

Patients requiring mastoid surgery for cholesteatoma may need amplification in the future because of a residual conductive hearing loss. If so, patients with a canal wall down cavity are at slightly more risk for infection because decreased ventilation of the canal and mastoid from the hearing aid compounds the keratin accumulation problem. In contrast, healing of the intact canal wall down mastoidectomy is usually rapid, periodic ear cleanings are unnecessary, and the incidence of external ear infections is not increased. There are no limitations of water activities, which is a particular issue for pediatric patients. If needed, an in the ear canal–type hearing aid is well tolerated.

The advantages of the canal wall down procedure usually relate to the improved access into the mesotympanum and epitympanum at the time of surgery. Cholesteatoma removal is made easier, resulting in a significantly decreased incidence of residual disease.[6] In addition, it is much easier to detect any residual disease postoperatively in these cases because the only area inaccessible to direct visualization is the mesotympanum covered by an intact tympanic membrane. Although the epitympanum and mastoid cavity are lined by squamous epithelium, the close approximation of this tissue layer to the underlying bone enables early detection of any cholesteatoma growth in these areas. An exception is cases in which tissue flaps, bone plate, or other obliterating materials have been used in the mastoid cavity. The ear is not unequivocally safe from complications of chronic otitis media simply because a canal wall down procedure has been performed. I have encountered abscesses in the petrous apex and in the epidural and intradural spaces in patients with a canal wall down mastoidectomy.

Intact Canal Wall versus Canal Wall Down Indications

Intact canal wall and canal wall down mastoid surgery for cholesteatoma, when properly performed, can manage this disease process effectively. Despite the fact that the literature is replete with reports advocating one approach as superior to the other, a definitive prospective, randomized clinical trial to address this controversy has not been performed, and may never be. Most surgeons with a large chronic ear practice perform both procedures. Typically, surgeons have a bias for one approach and specific indications for choosing the other.

I prefer the intact canal wall approach primarily because normal anatomy is preserved, and the potential for long-term care issues is diminished. The canal wall down technique may be preferable, however, in certain preoperative settings, or if specific intraoperative findings are encountered. Preoperative concerns that would favor a canal wall down procedure include a patient with an only-hearing ear, a patient who is a poor anesthetic risk, or a patient in whom follow-up is problematic. In these circumstances, eradicating the disease and preserving or restoring auditory function in a single operation is desirable. Because the canal wall down approach has a lower incidence of recurrent and residual disease, it is preferred.

In most cases, the decision to remove the canal wall is made intraoperatively on the basis of mastoid anatomy and specific disease findings. A low-lying middle cranial fossa dura and an anteriorly positioned sigmoid sinus create a small mastoid cavity and limit access into the epitympanum. Removing the canal wall under such circumstances facilitates disease removal, and if proper attention is given to creating the mastoid cavity, minimal long-term care is needed.

A fistula of the HSCC may also necessitate a canal wall down approach. Depending on the extent of bone erosion over the semicir-

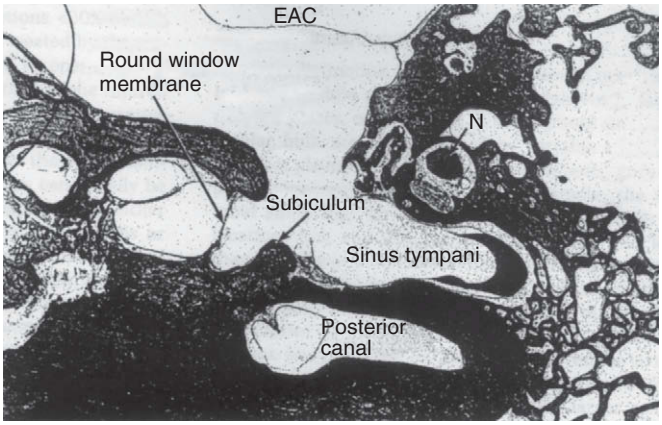

Figure 142-11. Histologic section showing a deep sinus tympani. EAC, external auditory canal; N, nerve. *(From Schuknecht HF. Pathology of the Ear. 2nd ed. Philadelphia: Lea & Febiger; 1993.)*

cular canal, it may be prudent to maintain the cholesteatoma matrix over the fistula. In this circumstance, the canal wall must be removed, and the cholesteatoma over the labyrinth simply becomes part of the epithelial coverage of the mastoid cavity.

In many cases, the most difficult aspect of cholesteatoma surgery, whether the canal wall is left intact or taken down, is removal of disease from the posterior mesotympanum.[8] Squamous epithelium that deeply infiltrates the posterior recesses, especially the sinus tympani, presents a special challenge (Fig. 142-11). The size and depth of extension of the sinus tympani varies. In some cases, the sinus is just a shallow indentation medial to the bone overlying the fallopian canal. Conversely, the sinus tympani may be large, extending deep and posterior to the canal wall and mastoid segment of the facial nerve. In such cases, performing a canal wall down mastoidectomy affords only modest benefit because the overlying facial canal continues to limit access. Extensive posterior mesotympanic disease is not an indication for a canal wall down approach. Techniques to improve exposure include drilling away the posterior anulus and skeletonizing the anterior aspect of the mastoid segment of the facial nerve. With deep posterior recesses, blunt instrumentation is still required to remove cholesteatoma matrix. Complete removal is ensured only if the retraction pocket remains intact without any tears visible. Rigid telescopes are advised for inspecting the posterior recesses after removal of cholesteatoma is considered complete. A second-look procedure 6 to 12 months later is also recommended.

Complications

Potential complications in mastoid surgery include damage to the dura, facial nerve, labyrinth, and sigmoid sinus and jugular bulb.

Dura

Exposure of a small area of dura without significant surface abrasion is common in mastoid surgery and is rarely of consequence. A dural tear or significant abrasion with herniation of arachnoid tissue with or without a cerebrospinal fluid leak requires repair. Instituting a broad-spectrum antibiotic with cerebrospinal fluid penetration should also be considered. Dural defects are best repaired with a layered closure using soft tissue such as fascia or perichondrium combined with a more rigid support material such as bone or cartilage. If an actual dural tear has occurred, part of this packing is placed intradurally into the subarachnoid space. Firmly packing the mastoid (or epitympanum) with absorbable gelatin sponge (Gelfoam) (with or without fibrin glue) can be used to support the repair as needed.

Horizontal Semicircular Fistula

A fistula of the HSCC should always be considered when performing chronic ear surgery, regardless of the patient's preoperative history or computed tomography scan findings. In a study of 416 consecutive surgeries for cholesteatoma, HSCC fistula was noted in 6.5%.[15] The incidence of a fistula was more than twice as high in patients who had a facial nerve dehiscence. At surgery, a flattened HSCC dome suggests labyrinthine erosion. In such cases, the cholesteatoma sac is opened, the desquamated epithelium is removed, and the matrix is left intact over the canal. This area is palpated for any underlying bony defect as the matrix is slowly dissected away. In cases in which the canal has been "blue lined" (i.e., exposure of the endosteum, without penetration into the perilymphatic space), the overlying disease tissue can be safely removed.

If an actual erosion into the fluid space of the HSCC is encountered or suspected during palpation, the cholesteatoma matrix should be left in place. When all other disease is removed, several options are possible: remove all matrix, and cover the defect with soft tissue or bone wax; perform a canal wall down procedure, and allow the matrix to remain in place as part of the mastoid cavity; or perform an intact canal wall procedure and leave the matrix in place to be removed at a second stage when the ear is sterile. Experience and extent of erosion dictate the approach used. A broad-spectrum antibiotic and steroids should be considered if the canal has been entered.

An iatrogenic injury to the HSCC requires immediate closure, usually with bone wax. Although soft tissue can provide an adequate seal, its use is problematic if continued drilling and use of irrigation fluid are necessary. A short course of a broad-spectrum antibiotic and steroids can be considered. The risk is bacterial labyrinthitis with resulting vertigo and severe sensorineural hearing loss. If the iatrogenic injury is recognized and treated immediately, however, the sequelae can be minimized. Some degree of dizziness is expected, but this may be transient without loss of sensorineural function.[16]

Facial Nerve

Most otologic surgeons agree that the key to mastoid surgery is the facial nerve. Identification, rather than avoidance, of this structure is fundamental for the canal wall down procedure (i.e., appropriate lowering of the posterior canal wall) and the intact canal wall approach (i.e., opening the facial recess). Although the use of the facial monitor has merit in chronic ear surgery, it is not a substitute for a thorough knowledge of facial nerve anatomy. Rarely is a facial nerve injury secondary to an anomalous course of the nerve; rather, it is usually caused by excessive manipulation of a disease-exposed or congenitally dehiscent tympanic segment, or misadventure with the drill at the second genu or mastoid portion of the nerve.

A study of 416 consecutive surgeries for cholesteatoma revealed a facial nerve dehiscence rate of almost 20%.[15] The most common area of dehiscence (80%) was just superior or adjacent to the oval window. Even in cases of extensive disease, only 1% of the patients had a dehiscence involving the mastoid segment of the nerve. As noted previously, the facial nerve can be dehiscent in the anterior epitympanic space. In this study, 7% of the dehiscences were located in this area. A statistically significant correlation existed between patient age and rate of dehiscence, with patients 19 years old and older having a 3.6 times greater likelihood of a facial nerve dehiscence than patients 18 years old and younger.

Opening the fallopian canal with exposure of the epineurium is of no consequence, and even minor abrasion of the nerve sheath usually causes no immediate or delayed dysfunction. A more penetrating injury causing frayed nerve bundles does require attention. In such a situation, it is important to gauge the depth of injury. Generally, nerve transections less than 30% to 40% of the diameter of the nerve can be treated by decompression. The fallopian canal should be opened for at least 3 to 4 mm proximally and distally to the injured segment, and the epineurium should be incised. Intraoperative and postoperative steroids are administered. If the transection is more than 40% to 50% of the nerve diameter, superior long-term facial function usually can be achieved by resecting the injured segment, and mobilizing the two ends for primary anastomosis or placing an interposition graft. The zone of injury extends beyond the apparent physical disruption of the nerve. Consulting a colleague intraoperatively for an objective assessment of the extent of neural damage is always appropriate.

A postoperative facial paralysis that is delayed (days) in onset can usually be treated expectantly. Steroids are administered, and if there is a paresis only, no further intervention is required; a good recovery is anticipated. In cases of a delayed complete paralysis, the patient needs periodic electrical testing (Hilger or electroneurography) to determine the degree of injury. Loss of electrical excitability greater than a 90% degeneration by electroneurography within 2 weeks of mastoid surgery is an indication for nerve exploration.

Care for a patient with an immediate postoperative facial paralysis is dictated by intraoperative circumstances. If the surgeon recognized the injury and decompressed the nerve, no immediate intervention is required. Periodic electrical testing provides prognostic information. If the surgeon did not recognize nerve damage intraoperatively, more immediate attention is necessary. The often quoted dictum, "the sun should not set on a postoperative facial paralysis without first exploring the nerve," is ill advised, however. Logistically, returning to the operating room immediately may be difficult. Allowing 1 to 2 days for the emotional impact of this outcome on the surgeon and family to defuse is advantageous. A short delay also allows time for consultation with a colleague who can provide objective advice and, as needed, become involved in the re-exploration surgery. Most importantly, the delay would have no adverse impact on outcome.

At the time of re-exploration, the facial nerve first should be identified, if possible, in an area not involved in the initial surgery (i.e., the distal mastoid or proximal tympanic segments). The normal nerve is followed to the area of injury. Exposure of the sides of the fallopian canal, not just its lateral surface, aids in determining the depth of injury. As described previously, depth of injury dictates whether decompression versus resection with primary repair or interposition graft is necessary.

Sigmoid Sinus and Jugular Bulb Injury

In contradistinction to the fixed location of most mastoid and middle ear structures (i.e., labyrinth, facial nerve, ossicles, carotid artery), the sigmoid sinus and jugular bulb are characterized by variable anatomy. This fact places these structures at risk for inadvertent injury. In poorly pneumatized mastoids, the sigmoid sinus may be very superficial and anterior in location, just beneath the mastoid cortex and less than 1 cm from the posterior canal wall. Similarly, the jugular bulb may be small with minimal presentation in the mastoid cavity, or it may be high in the mastoid just inferior to the posterior semicircular canal. Injury to these low-pressure, but high-volume, venous structures is initially treated with digital pressure. For small tears, bone wax may suffice; for larger rents, cellulose-type surgical packing is required. Packing beneath remaining bony ledges helps maintain appropriate pressure. If additional drilling is required, covering the packing with bone wax protects it from being dislodged by the bur.

Although infrequent, a significant injury to the sigmoid sinus can result in thrombosis of that vessel. Depending on collateral and contralateral venous drainage, otitic hydrocephalus can develop secondary to increased venous pressure and decreased cerebrospinal fluid absorption from the arachnoid villi. Postoperative occurrence of persistent headache or visual change should prompt magnetic resonance imaging/magnetic resonance venography studies and funduscopic examination by an ophthalmologist.

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CHAPTER ONE HUNDRED AND FORTY-THREE

Clinical Assessment and Surgical Treatment of Conductive Hearing Loss

Alejandro I. Torres

Douglas D. Backous

Key Points

- The external ear and middle ear serve to aid sound localization, augment sound pressures through resonances, and perform the vital function of impedance matching wherein sound waves are effectively transferred to the fluid medium of the cochlear scalae. Impedance matching of sound pressure delivered to the inner ear through the conductive pathway results from the interaction of the catenary, ossicular, and hydraulic lever systems.
- Sound amplification from the middle ear impedance matching system is 35 dB. Amplification from the pinna and external auditory canal can be up to 15 dB, depending on the azimuth of sound delivery.
- Radiologic imaging is rarely necessary in cases of conductive hearing loss and should be ordered based on findings from the history and physical examination.
- Conductive hearing loss in the presence of normal acoustic reflexes and elevated bone thresholds should prompt radiologic investigation for superior semicircular canal dehiscence syndrome before middle ear exploration.
- Surgical repair for conductive hearing loss occurring as a result of superior semicircular canal dehiscence syndrome remains controversial.
- The type of reconstruction is heavily influenced by comfort and preferences of the operative surgeon.
- The Baha system is effective in treating conductive hearing loss by bypassing the damaged middle ear system, transmitting vibromechanical energy to the cochlea via direct bone conduction. Baha is also very effective as an alternative to surgical reconstruction in patients with auricular atresia.
- Tuning fork testing is an effective method to screen for hearing loss, determine conductive versus sensorineural loss, and validate audiometric findings.

An applied understanding of the mechanics of the conductive portion of the auditory periphery and a physiologically directed assessment of the external and middle ear are the cornerstones to optimizing hearing results and minimizing the incidence of complications after surgical reconstruction for conductive hearing loss. This chapter summarizes fundamental physical properties of the conductive portion of the auditory system, outlines an appropriate diagnostic evaluation, and proposes a framework for planning surgical treatment of external auditory canal (EAC) and middle ear defects (Box 143-1).

Mechanical Properties of the Conductive Hearing Pathway

Sound Transfer in the Middle Ear

Sound, defined in the physical dimension, is vibratory energy produced by an object that possesses inertia and elasticity. Within the frequency range for human sound perception, 10 Hz to 24 kHz, there are no limitations to the type of vibration required to generate audible sensations of sound, provided that the source moves from one position to the other and back again. Alternating condensation and rarefaction of sound pressure passes through the external ear structures to the tympanic membrane. The speed of the sound wave is proportional to the density of the medium through which it passes.[1,2]

The acoustic resistance to the passage of sound through a medium is termed *impedance*. The transduction of vibratory energy from the air in the EAC (low impedance) to the cochlear fluids (high impedance) is possible as a result of the impedance matching function of the middle ear. This complex system consists of frequency-dependent stiffness and inertia reactances, along with a frequency-independent frictional component. Conditions that alter ossicular stiffness, such as otosclerosis, produce prominently low-frequency hearing loss. Changes in the mass of the middle ear structures, classically described as producing high-frequency deficits, actually result in hearing losses that vary according to where the mass change occurs on the tympanic membrane or ossicular chain.[3] Tympanosclerosis, which affects the mass and the stiffness

Box 143-1

Pathologic Conditions Leading to Conductive Hearing Loss

Congenital/Hereditary
Anotia/microtia
Atresia
Cup ear deformity
Treacher Collins syndrome
Mohr syndrome
Orofacial cervical syndrome
Otopalatal-digital syndrome
Pierre Robin syndrome
Pyle's disease
Crouzon's disease
Apert's disease
Goldenhar's disease
Turner's syndrome
Otosclerosis (autosomal dominant or idiopathic)
Osteogenesis imperfecta
Osteopetrosis
Paget's disease
Achondroplasia
Marfan syndrome
Mucopolysaccharidoses
Ossicular fixation to tegmen

Inflammatory/Infectious
Otitis externa
Acute otitis media
Serous otitis media
Chronic otitis media
Cholesteatoma
Furunculosis
Otomycosis
Malignant otitis
Myringosclerosis
Tympanosclerosis
Herpes zoster oticus
Chondritis/perichondritis
Cellulitis
Erysipelas
Bullous myringitis
Tympanosclerosis
Tuberculous otitis
Syphilis

Iatrogenic
Surgical complication or failure
Traumatic canal cleaning
Trauma
Burns
Foreign body
Barotrauma
Cauliflower ear
Auricular hematoma
Canal laceration (with and without clot)
Avulsion
Temporal bone fracture
Penetrating injury
Hemotympanum

Neoplasia
Squamous cell carcinoma
Basal cell carcinoma
Melanoma
Hidradenomas
Adenoma
Pleomorphic adenoma
Adenoid cystic carcinoma
Sebaceous cell carcinoma
Paraganglioma
Neurofibroma
Rhabdomyosarcoma
Hemangioma
Hemangiopericytoma
Lymphangioma
Leukemia
Multiple myeloma

Metabolic/Systemic
Cerumen
Keloid/hypertrophic scarring
Wegener's granulomatosis
Relapsing polychondritis
Fibrous dysplasia
Eosinophilic granuloma
Polyarteritis nodosa
Sarcoidosis
Keratosis obturans

Other
Canal osteoma
Canal exostosis
Spontaneous hemotympanum

of the ossicular chain, results in a flat hearing loss recorded at high and low frequencies.

In 1868, Helmholtz[4] defined the principles of impedance matching by the middle ear. He proposed three levers to accomplish the required pressure transformation. The tympanic membrane, which is rigidly fixed at the periphery and mobile centrally, acts as a catenary lever, exerting its force on the malleus handle in response to pressure changes transmitted through the EAC.[5] A twofold gain in sound pressure level is generated at the malleus. Although the pars flaccida seems to allow free movement of the malleus head in the epitympanum and may decrease middle ear/external ear atmospheric pressure differences, it has only a minor acoustic role in humans.[6]

The ossicular lever is produced when the incus and the malleus rotate as a unit around an axis extending from the anterior mallear ligament through the incudal ligament.[7] The ossicular lever taken alone produces a small mechanical advantage for sound transmission. Further studies by Tonndorf and Khanna[5] showed the catenary lever was tightly coupled to the ossicular lever because the tympanic membrane is extensively adherent to the malleus handle. Corrected calculations revealed a combined catenary and ossicular lever ratio of 1:2.3. According to studies done on fresh cadaver human temporal bones, the mean sound pressure gain produced by the human middle ear is 26.6 dB, and is centered around its resonant frequency (0.9 to 1 kHz). Beyond 1 kHz, the pressure gain measured at the stapes footplate decreases at a rate of −8.6 dB/octave.[8]

The hydraulic lever assists the transmission of the sound pressure, which is collected over the larger tympanic membrane and passed on to the much smaller stapedial footplate. For the hydraulic lever to be

functional, the stapes should move in a "piston-like" fashion, which has been elegantly described by Guinan and Peake.[9] The increased force is proportional to the ratio of the areas of the tympanic membrane to the footplate. The area of the tympanic membrane is approximately 85 mm^2, and that of the stapes footplate is 3.2 mm^2.[10] After studying 43 human temporal bones, Saunders[11] concluded that the "areal ratio" was the most important component of the middle ear impedance matching system. Ratios varied from ear to ear, but averaged 20.8 : 1.

In a nondiseased ear, sound is transmitted to the oval window with increased energy and at an earlier phase than to the round window. Intensity differences and phase protection cause differential displacement of cochlear fluids, which sets a fluid wave in motion along the tectorial membrane, producing mechanical stimulation of sensory hair cells.

The pinnae gather sound from an arc of 135 degrees relative to the direction of the head and increase sound pressure by 6 dB. They reject sounds arriving from the rear, which assists in the determination of sound origin.[2] The EAC is a closed cylinder approximately 2.5 to 3.5 cm in length. Because ear canal resonance occurs at a frequency whose wavelength is four times the canal length, the corresponding resonant frequency is roughly 3500 Hz. The addition of the conchal component of the pinna increases the EAC length, resulting in a lower resonant frequency, which has been measured at 2700 Hz. The overall increase in sound pressure transduction caused by external ear structures and measured at the tympanic membrane is estimated at 15 to 22 dB.[10,12]

The increased gain in sound pressure level from the impedance matching system of the middle ear and tympanic membrane measures roughly 34 dB. The EAC and auricle, primarily the conchal component of the pinna, provide an additional increase of up to 15 dB, depending on the azimuth of sound delivery and functional length of the canal.

Specific Defects in the Conductive Auditory Periphery and Resultant Hearing Loss

In his 1978 review, Austin[1] identified five categories of anatomic defects in the middle ear sound-conducting system and described each within the context of the associated prototypic hearing loss (Table 143-1). In the first category, tympanic membrane perforation with undisturbed ossicular continuity produced a hearing loss that was linearly proportional to the size of the perforation (loss of areal ratio plus loss of catenary lever). The degree of hearing loss, flat across speech frequencies, was not altered by the location of the perforation on the drumhead.

In the second category, tympanic membrane perforation combined with ossicular disruption occurred in approximately 60% of Austin's patients, and was the most common form of conductive hearing loss requiring surgical therapy. Incudostapedial joint erosion was the most frequent ossicular anomaly. Caution was taken when interpreting audiograms in these patients because underestimation of the magnitude of the conductive loss frequently occurred. Falsely depressed bone-conducted hearing levels (≤10 dB in speech frequencies) resulted from impedance variation occurring at the oval window caused by the ossicular discontinuity. Correction of the ossicular problem typically increased bone levels, reflecting the re-establishment of impedance matching at the oval window. The predicted 38.3-dB hearing loss, when adjusted for falsely depressed bone levels, was primarily a result of decreased function of the hydraulic lever added to dysfunction in the catenary/ossicular lever. Perforation size and the condition of the stapes footplate accounted for variations in this patient group.

In the third category, total loss of the tympanic membrane and ossicles created a condition wherein sound pressure contacted the oval and round windows simultaneously, resulting in partial phase cancellation of the sound wave in the cochlear fluids. Conductive hearing loss was flat across speech frequencies and averaged 50 dB when corrected for the previously described misleading bone levels. More complete phase cancellation caused increased hearing loss compared with patients with partial perforations.

The fourth category included patients with ossicular disruption behind an intact tympanic membrane. This defect resulted in a maximal conductive hearing loss of 55 to 60 dB. The intact eardrum reflected sound energy back into the EAC, causing an additional 17-dB conductive loss beyond what was expected from removal of the hydraulic and catenary/ossicular lever action. The decreased sound pressure also reached the round and oval windows nearly simultaneously, inducing phase cancellation in the labyrinthine fluids.

The fifth category described various congenital malformations with ossicular disruption and closure of the oval window; also included were cases of obliterative otosclerosis with closure of the oval and round windows behind an intact drum. The expected flat loss from such a defect is 60 dB.[2]

Diagnostic Evaluation

The use of advanced audiometric testing, laboratory studies, or diagnostic imaging is rarely indicated in patients with isolated conductive

Table 143-1

Specific Lesions of the Conductive Apparatus and Associated Hearing Loss

Classification	Component Disrupted	Expected Loss (dB)
Perforation of tympanic membrane	Loss of areal ratio, catenary lever	Proportional to size of perforation
Perforation of tympanic membrane with ossicular interruption	Hydraulic lever, areal ratio, catenary lever	38.3
Total loss of tympanic membrane and ossicular chain	Hydraulic lever, areal ratio, catenary lever, phase cancellation	50
Ossicular interruption with intact tympanic membrane	Hydraulic lever, areal ratio, catenary lever, phase cancellation, reflection of sound energy away from middle ear at tympanic membrane	55-60
Ossicular interruption with intact tympanic membrane and closure of oval window (distinct congenital malformation)	Hydraulic lever, areal ratio, catenary lever, phase cancellation, reflection of sound energy away from middle ear at tympanic membrane	55-60

From Austin DF. Sound conduction of the diseased ear. *J Laryngol Otol.* 1978;92:367; and Austin DF. Acoustic mechanisms in middle ear sound transfer. *Otolaryngol Clin North Am.* 1994;27:641.

hearing loss. Complete assessment of a patient with hearing loss begins with a careful history. A thorough head and neck examination with cranial nerve testing and otoscopy is mandatory. Otomicroscopy is useful to remove foreign bodies and to examine the tympanic membrane and middle ear structures more precisely, and is a prudent step in preoperative evaluation. The use of 256-Hz, 512-Hz, and 1024-Hz tuning forks assists in the localization of the side of greatest auditory deficit and verifies audiometric findings.

The Weber test is effective in lateralizing hearing loss. The fork is gently struck by the examiner and placed on the forehead or on the vertex of the skull, and the patient states on which side he or she hears the tone more clearly. Placement of the tuning fork over the nasal bones or on the teeth may present a stronger stimulus for Weber testing in difficult-to-test patients.[13] Lateralization of the tone represents either a conductive loss ipsilateral to the side of localization or a sensorineural loss greater in the contralateral ear. The 256-Hz tuning fork is the most sensitive of the available frequencies,[14] but it can yield an unacceptable number of false-positive results. The most clinically useful single fork is the 512-Hz fork.[15]

Rinne testing using all three fork frequencies can accurately estimate the conductive component of a hearing deficit (Table 143-2).[16] The test is performed by activating the tuning fork and by placing it firmly on the skin over the cribriform area of the mastoid bone. When the tone can no longer be heard, the fork is placed, tines oriented parallel to the head/frontal plane, in front of the meatus of the EAC. The patient indicates whether the tone is present or absent. A negative or abnormal Rinne result is found when bone conduction is perceived longer than air conduction. A positive, or normal, result occurs when the air conduction is greater than bone. Tuning fork testing should be carried out in any patient before surgery for a conductive anomaly to verify audiometric results and to establish a baseline for comparison for postoperative assessment.

Table 143-2

Degree of Hearing Loss Estimated by Rinne Testing

Rinne Test Result*	Estimated Conductive Loss (dB)
Negative, 256 Hz	Mild conductive loss of 20-30
Positive, 512 Hz and 1024 Hz	
Negative, 256 Hz and 512 Hz	Moderate conductive loss of 30-45
Positive, 1024 Hz	
Negative, 256 Hz, 512 Hz, 1024 Hz	Severe conductive loss of 45-60

*Negative Rinne test = bone conduction greater than air conduction (abnormal). Positive Rinne test = air conduction greater than bone conduction (normal).
From Miltenburg DM. The validity of tuning fork tests in diagnosing hearing loss. *J Otolaryngol.* 1994;23:254.

Pure-tone audiometry and speech testing follow in the workup. The diagnosis of a conductive loss is made in the presence of an air-bone gap on the pure-tone audiogram with speech testing commensurate to the results measured audiometrically (Fig. 143-1). Concurrent sensorineural deficits should be noted. Falsely depressed bone-conducted hearing levels can present in patients with ossicular abnormalities secondary to earlier discussed impedance mismatching.[1]

Acoustic immittance testing may be useful in distinguishing between conductive and sensorineural hearing loss. Voluntary responses are not required for successful measures of static compliance, tympanometry, and acoustic reflexes, making them an important component of the auditory test battery. A probe is placed in the EAC to form an airtight seal. The middle ear static compliance is determined by subtracting the compliance at 200 mm H_2O from the total compliance when pressure is equal on both sides of the tympanic membrane. Normal values range from 0.3 to 1.6 mL, mainly reflecting the condition of the tympanic membrane. Tympanometry, a graphic representation of the compliance of the middle ear during dynamic pressure conditions, tests tympanic membrane integrity and ossicular mobility. The type A tympanogram indicates normal middle ear compliance; the type A_s tympanogram indicates ossicular fixation, and the type A_d tympanogram indicates ossicular discontinuity. The type B tympanogram suggests otitis media with effusion, cerumen impaction, or a perforated tympanic membrane. Conditions with negative middle ear pressure result in a type C tympanogram.[17]

Acoustic reflex testing assesses a reflex arc bridging the cochlea, auditory nerve, cochlear nucleus, trapezoid body, medial superior olivary complex, motor nucleus of CN VII, and facial nerve. Conductive hearing loss produces an abnormal result by interfering with the afferent limb of the reflex arc. The absence of acoustic reflexes in the presence of a conductive hearing loss indicates an ossicular anomaly. Normal acoustic reflexes in the presence of a conductive hearing loss suggests either a partial ossicular fixation or the possibility of a "third window" effect, such as seen in superior semicircular canal syndrome.

A subset of patients with superior semicircular canal syndrome experience conductive or mixed hearing loss. In a series of 20 superior semicircular canal syndrome patients with conductive hearing loss and

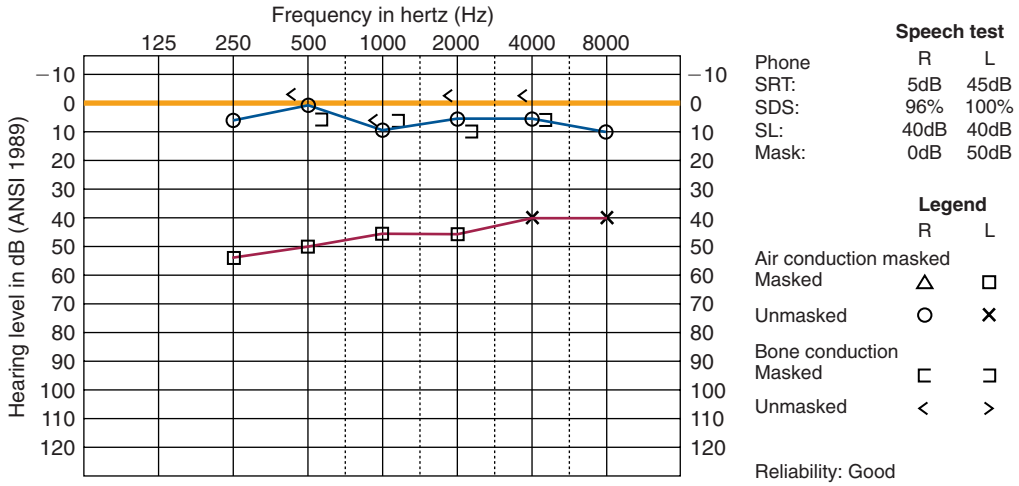

Figure 143-1. Audiogram showing a clinically significant left-sided conductive hearing loss. Note the air-bone gap, normal speech discrimination, and normal masked bone conduction in the left ear.

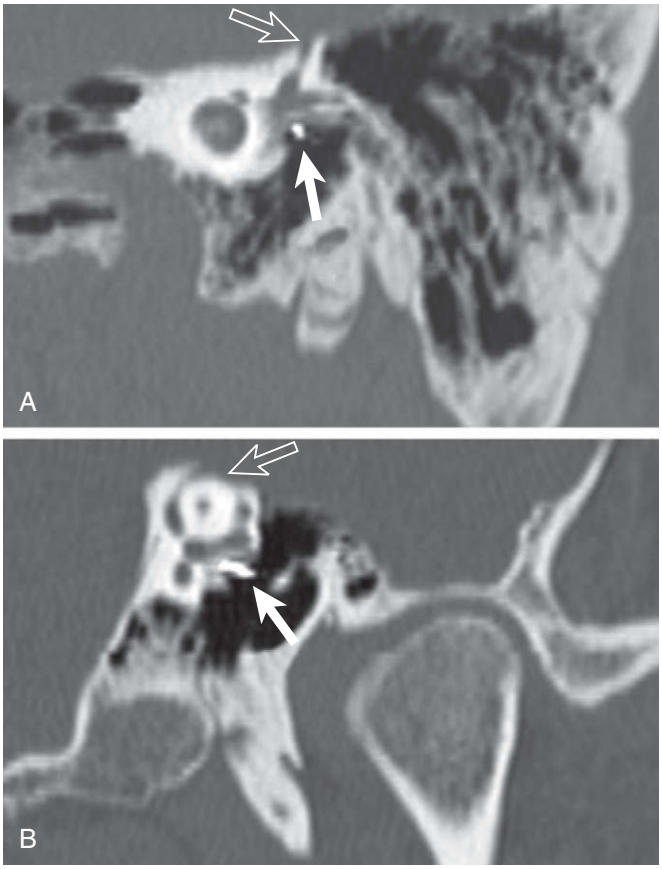

Figure 143-2. Thin-cut CT scan of the left temporal bone after a stapedectomy with no improvement of conductive hearing loss. **A,** Coronal view with the superior canal dehiscence (*open arrow*) and stapes piston prosthesis in good position (*closed arrow*). **B,** Reformatted sagittal or "bagel" view of the same structures.

no vestibular symptoms, Merchant and colleagues[18] identified six common findings. First, 10- to 60-dB air-bone gaps primarily occurred in frequencies less than 2000 Hz. Second, in some cases, bone-conduction thresholds less than 2000 Hz were negative. Third, the acoustic (stapedial) reflex was present. Fourth, measurement of umbo velocity by laser Doppler vibrometry showed slight hypermobility of umbo motion. Fifth, the vestibular-evoked myogenic potential response was present, with thresholds that were abnormally low. Sixth, the middle ear was normal at exploratory tympanotomy, including normal mobility of the ossicles and a patent round window niche.

The dehiscent superior semicircular canal is theorized to form a "third window" in addition to the oval and round windows found in the normal labyrinth. This third window is capable of dispersing incoming vibromechanical energy resulting in an improvement in bone conduction, a decrement in air conduction, and possibly a Carhart notch noted with routine audiometry.[19] Conductive hearing loss in a patient with normal acoustic reflexes and elevated bone thresholds less than 2000 Hz should prompt a high-resolution temporal bone computed tomography (CT) scan to rule out superior semicircular canal syndrome before surgical exploration (Fig. 143-2). Because of the risk of iatrogenic sensorineural hearing loss, surgical repair of a superior semicircular canal dehiscence to correct a conductive hearing loss in patients without disabling vertigo is not recommended (Box 143-2).[18]

Treatment

Treatment of conductive hearing loss requires appropriate patient selection and intraoperative localization of the site of the abnormality. Planning a reconstruction hinges on understanding the impact of the specific defect and repair on normal conduction mechanics. The choice of prosthesis and the particular reconstructive technique also depend heavily on the skills and preferences of the operating surgeon.

Conditions of the External Auditory Canal Contributing to Conductive Hearing Loss

Narrowing of the EAC to less than 3-mm diameter results in loss of high-frequency sound perception. As the diameter of the EAC lumen narrows further, low-frequency stimuli are blocked from making contact with the tympanic membrane.[20] Removal of offending foreign bodies, eradication of infection when present, and correction of anatomic aberrations to maintain long-term patency are essential for normal conduction of sound pressure to the oval window.

Foreign bodies in the EAC require complete removal in a controlled environment. Children may require restraint, sedation, and occasionally general anesthesia. Otomicroscopy is necessary when the object is medial to the bony canal isthmus, when the tympanic membrane is perforated or not clearly visualized, or in any situation with heightened risk for iatrogenic damage to the EAC or tympanic membrane.

External otitis is managed with aggressive aural toilet and acidifying otic solutions to bring the pH of the EAC skin to a normal acidic level (pH 4 to 5). Antibiotic (with or without steroids) solutions or suspensions should be reserved for resistant infections. In cases with significant soft tissue edema and narrowing, otowicks can be inserted into the inflamed canal to optimize delivery of topical medicines to more medially located tissues. Oral or intravenous antibiotics are necessary in patients with extensive cellulitis extending beyond the EAC meatus and in patients presenting with major risk for malignant external otitis. Severe pain with ipsilateral cranial nerve deficits in immunocompromised hosts should prompt aggressive evaluation of skull base osteomyelitis (Fig. 143-3).

Furuncles should be drained and managed with topical antibiotics and otowicks as necessary. Otomycosis usually resolves with aural toilet followed by instillation of compounds that mildly acidify the external canal skin. Occasionally, the application of antifungal or steroid creams, or both, onto the external canal skin may be necessary.

Most cerumen impactions are easily removed otoscopically. More tenacious cerumen most often is seen in older patients or in patients with previous radiation exposure to the temporal region. Ototopical antibiotic preparations or docusate sodium 1% solution for 1 to 2 weeks often softens cerumen to facilitate subsequent manual removal. External canal irrigations should be avoided in patients suspected to have tympanic membrane perforations. When used, body temperature irrigant is optimal to avoid caloric stimulation and discomfort to patients with external canal blockage. Management of keratosis obturans requires patience by the clinician to avoid excessive pain to the patient during removal of debris. Careful otomicroscopic inspection should follow cleaning to exclude the presence of bony canal erosion, tympanic membrane perforation, or external canal cholesteatoma.

Soft tissue stenosis of the EAC can occur as a result of local inflammation or as a manifestation of systemic disease. If possible, the cause of the soft tissue proliferation should be identified and treated. Hypertrophied soft tissue that persists after adequate medical management can be initially treated with local infiltration of steroid. If persistent, fibrosed skin can be resected to enlarge the external canal diameter. Circumferential endaural incisions, down to periosteum, are placed laterally to the stenotic segment. Next, elevation of the thickened skin, as for tympanoplasty, is carried out with removal of all scar tissue and involved canal epithelium. The tympanic anulus is left undisturbed, and a plane is developed between the fibrous and the squamous layers of the drumhead. The squamous layer of the drum typically is involved with the stenotic process.

After removing any bony obstruction in the external canal with the otologic drill, the lateral tympanic membrane and exposed bony canal are grafted with split-thickness skin. The technique described by Jahrsdoerfer[21] for skin grafting the external canal after congenital atresia surgery or the use of small "pinch grafts" of postauricular skin to denuded areas provides resurfacing. The external canal is packed as for tympanoplasty (Fig. 143-4). Although rarely necessary, the surgeon should be prepared to perform a formal tympanoplasty to repair defects on the residual drum. Restenosis is more common in patients with

Box 143-2

History and Physical Examination for Hearing Loss

Onset
Age at onset
Abrupt versus gradual
Progressive, intermittent, or continuous
Antecedent illness
Duration of symptoms

Associated Symptoms
Tinnitus
Dizziness or vertigo
Aural fullness
Pain
Allergy symptoms
Actions that change intensity of symptoms
Distorted auditory perception
Worsening with pregnancy or oral contraceptive use

Further History
Family history of hearing loss
Occupational noise exposure
Recreational noise exposure
Trauma
Surgical history
Previous or current draining from ear
Quality of drainage
Systemic infections and treatments
Meningitis
Syphilis
Previous use of a hearing aid
Ototoxic medications
Cancer chemotherapy
Antibiotics
Recent air travel
Recent underwater diving

Examination
Complete head and neck examination
Cranial nerve examination
Otoscopy with microscope as needed
Otoneurologic examination as indicated
Tuning fork testing (256 Hz, 512 Hz, 1024 Hz)
Weber test
Rinne test

Radiographic and Laboratory Evaluation
CT as indicated
MRI as indicated
Erythrocyte sedimentation rate; fluorescent treponemal antibody, absorbed; Lyme titers; complete blood count; thyroid function tests; electrolytes; urinalysis
Additional studies are indicated to work up suspected systemic diseases

Audiometric Evaluation
Pure-tone audiometry
Air conduction
Bone conduction
Speech testing
Speech reception threshold
Speech discrimination testing
Immittance testing
Static compliance
Tympanometry
Acoustic reflexes

Additional Audiometric Testing
Auditory brainstem response
Electrocochleography
Otoacoustic emissions

systemic (i.e., connective tissue) diseases or when underlying chronic infection is not controlled preoperatively. Hearing results typically are excellent, particularly when the tympanic membrane and ossicles are not disrupted.[22]

Bony and soft tissue overgrowth can cause stenosis of the EAC. Exostoses and osteomas are thought to originate along the tympanomastoid and tympanosquamous suture lines during phases of bony growth and after prolonged or repetitive exposure of the ears to cold water. Most of these lesions require no specific treatment. In patients with continued debris buildup between the narrowed portion of the canal and the tympanic membrane, or in whom conductive hearing loss develops, the osseous growths should be removed. Skin incisions can be placed postauricularly or endaurally with careful dissection of canal skin off the lateralmost portion of the aberrant bone. Careful drilling into the bony overgrowth while maintaining a thin shelf of bone between the neocanal and the tympanomeatal flap protects the canal skin. Curettage of the residual bony shelf removes the remaining abnormality with minimal damage to residual canal skin.[23] Skin flaps are replaced, and the external canal is packed (Fig. 143-5). Tympanoplasty may be necessary if the bony lesions traverse the tympanic anulus. Recurrence is rare, and hearing results should be excellent.

Conditions of the Tympanic Membrane Contributing to Conductive Hearing Loss

Perforation of the tympanic membrane affects the areal ratio and catenary lever system in sound conduction. The condition of the ossicles and middle ear ligaments, the health of the middle ear mucosa, the degree of chronic inflammation, and the presence or absence of cholesteatoma should be assessed before surgical intervention. Successful ossiculoplasty depends on a mobile and properly oriented tympanic membrane, normalized middle ear pressure and mucous clearance, and an efficient sound-conducting mechanism.[24] An array of techniques can be used to repair the tympanic membrane and to reconstruct the ossicular chain. The technique chosen for repairing the perforation should provide adequate vascular and structural support to the healing drum.

The overlay or lateral graft can be used to reconstruct any type or size of perforation. The drawbacks of this method include graft lateralization, blunting of the anterior sulcus, and excessive tympanic membrane thickness. The canal skin is completely removed, and the drum remnant is de-epithelialized to prevent cholesteatoma formation or delayed healing. When the ear canal is drilled to expose the tympanic anulus fully, the tympanic membrane graft is positioned, and the ear canal skin is replaced.

Underlay or medial grafting is more commonly used by many surgeons and is particularly reliable when performed through a postauricular incision. The main limitation with this method is the added difficulty in obtaining sufficient vascular and structural support of the anterior aspect of the graft. Recurrent perforation in a medial grafted tympanic membrane most commonly occurs at the anterior sulcus region, where perforators from the tympanic anulus weakly perfuse the drumhead.[25]

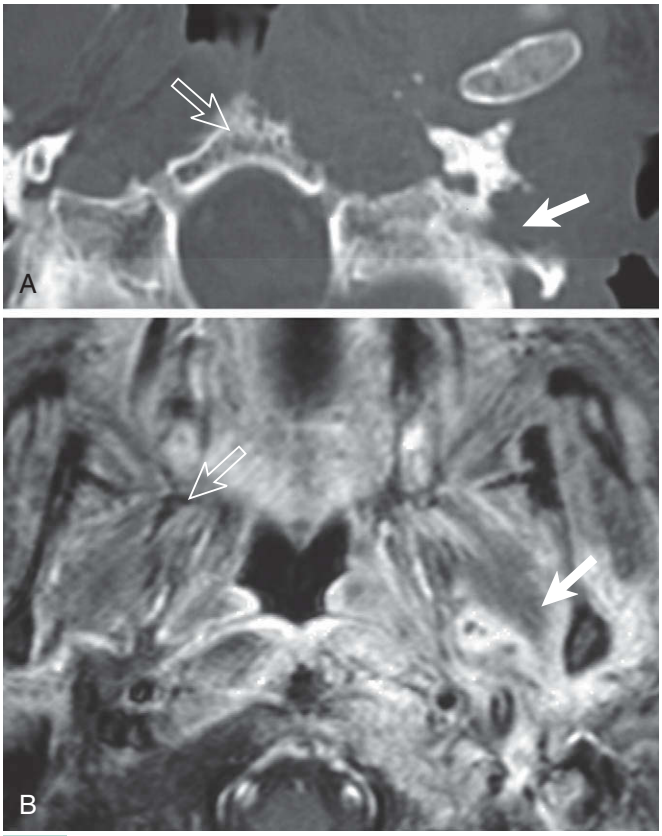

Figure 143-3. Malignant external otitis. **A,** Temporal bone CT scan without contrast material at the level of the foramen magnum showing bony demineralization crossing the midline (*open arrow*) and significant demineralization of the mastoid and hypotympanic structures (*closed arrow*). **B,** Axial MRI with gadolinium of the skull base. Ipsilateral parapharyngeal soft tissue involvement (*closed arrow*); contralateral uptake reflecting crossover beyond the midline (*open arrow*).

Although both techniques can be used on any type of perforation by a surgeon, lateral grafting is recommended for perforations located anterior to the malleus and involving the anterior sulcus of the tympanic ring. Medial grafting is most useful in perforations posterior to the long process of the malleus where the mallear artery provides a hearty blood supply. The use of alloplastic materials for tympanic membrane reconstruction is rarely necessary.

Conditions of the Middle Ear Contributing to Conductive Hearing Loss

When middle ear disease is eradicated, and the middle ear mucosa appears healthy and well aerated, ossicular reconstruction can be done with the highest chance of success. Dornhoffer and Gardner[26] studied 200 ears operated in 185 patients who had either total ossicular replacement prostheses (TORPs) or partial ossicular replacement prostheses (PORPs) placed. They found that the absence of the malleus, mucosal fibrosis, revision ear surgery, and the removal of the ear canal wall had a significant detrimental impact on hearing outcome.[26] Adequate stabilization of the reconstructed ossicles at the time of surgery assists healing and optimization of hearing. Avoiding direct contact of prosthetic materials with the tympanic membrane prevents drum erosion and extrusion. Placement of thinly sculpted conchal or tragal cartilage between the graft and the tympanic membrane avoids this complication. The prosthesis, positioned perpendicular to the tympanic membrane and in the vertical plane from the center of the stapes footplate, is stabilized with the mild tension from the drum.[27] Stapes footplate fracture, subluxation, and perilymph leak are avoided by properly sizing the prosthesis before placement.

Patient selection for ossicular reconstruction is largely based on findings on the preoperative audiogram and on the potential to regain serviceable hearing. Ossiculoplasty in patients with preoperative speech reception threshold of 30 dB or less or within 15 dB of the opposite ear is controversial. Alternatively, patients with speech reception threshold values greater than 30 dB often require amplification to gain access to conversational speech levels. Even small gains in hearing after surgery are appreciated by these patients and may decrease the power needs of a hearing aid or free the patients of continued amplification. Bringing the operative ear to within 15 dB of the contralateral ear enhances binaural input to auditory centers.[24] Salient points in preoperative assessment of patients being considered for hearing reconstruction are presented in Box 143-3.

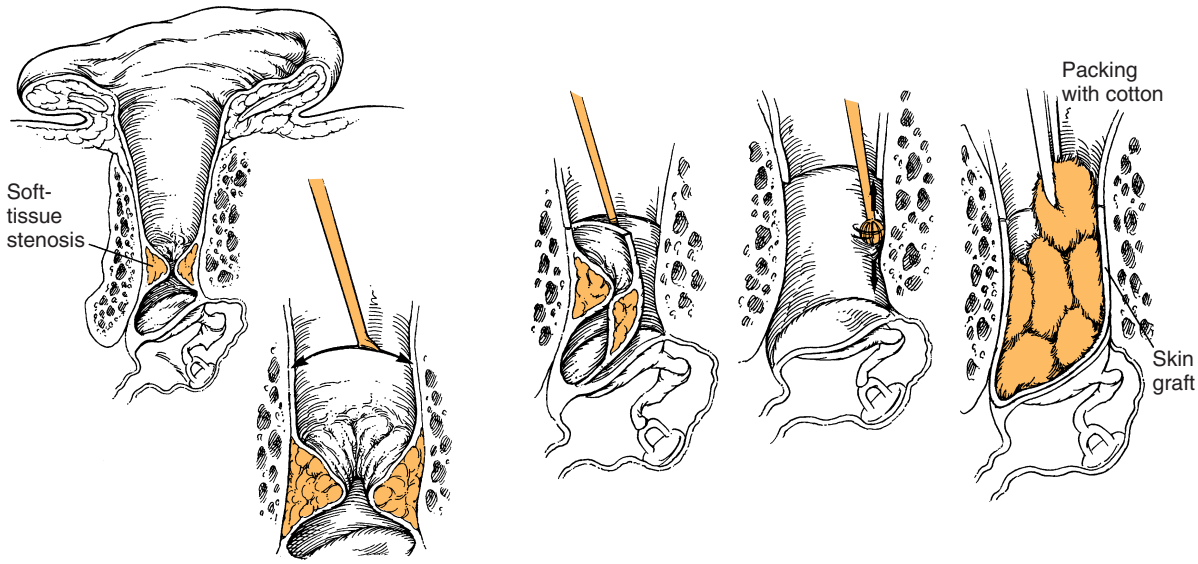

Figure 143-4. Repair of soft tissue stenosis of the external auditory canal. Circumferential skin incisions are made in the canal after opening with a postauricular incision. The stenotic tissue is dissected off the canal bone and from the fibrous layer of the tympanic membrane. The squamous layer of the drum is taken with the specimen. Sculpting of the bony canal is performed with a diamond bur before applying skin grafts and canal packing.

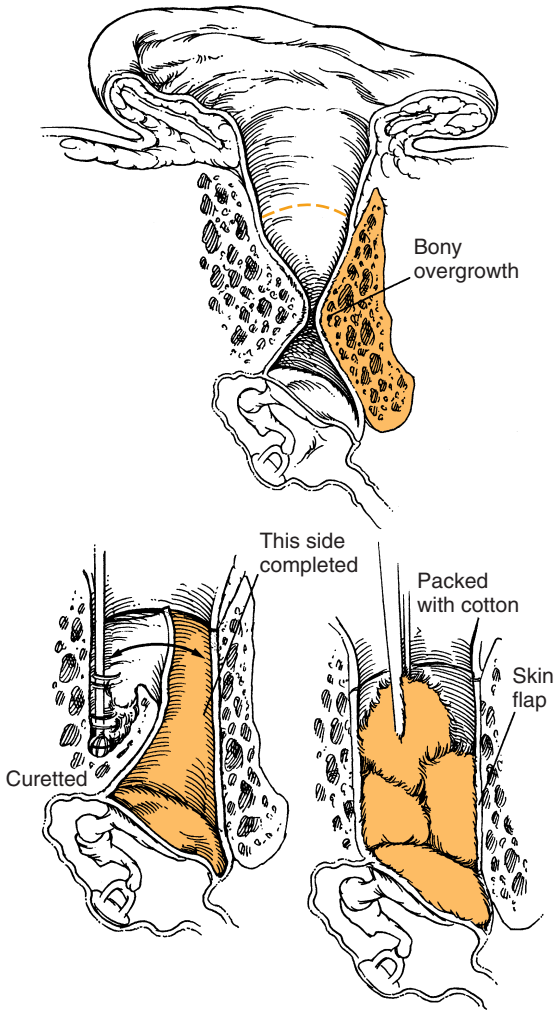

Figure 143-5. Repair of external auditory canal exostosis. Care is taken to elevate the canal skin from the osseous deposition, to drill away the pathology while maintaining a thin eggshell of bone to protect the skin flap, and to curet away the bony remnant before packing the external canal.

Box 143-3

Key Points in Preoperative Assessment of Patients Considering Ossicular Reconstruction

- A preoperative air-bone gap >20-25 dB is consistent with ossicular discontinuity or fixation.
- Elective ossicular reconstruction in the presence of an open mastoid cavity often is unsatisfactory.
- Patients with a preoperative air-bone gap <30 dB should be approached with caution because even slight decreases in hearing levels may require amplification.
- Reconstructive results in patients with bone (sensorineural) levels >30 dB often are unsatisfactory if avoidance of amplification is a priority.
- In patients with severe mixed hearing loss, ossicular reconstruction can be considered because it may enhance the use of amplification.[46]
- Improving the threshold of a poorer hearing ear to within 15 dB of the contralateral ear may facilitate binaural inputs to central auditory pathways.[24]

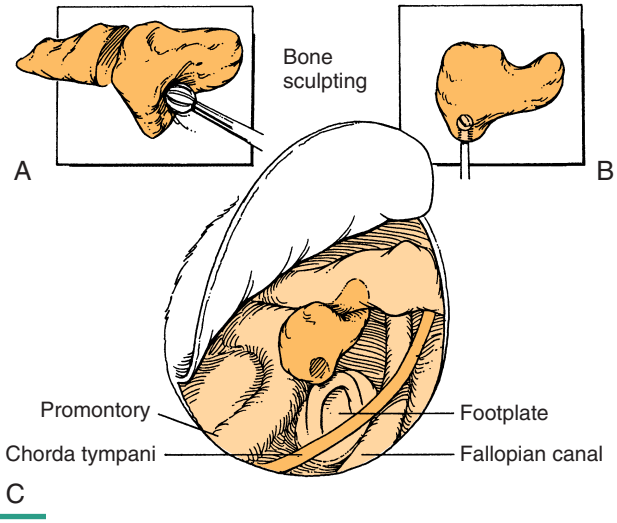

Figure 143-6. Incus interposition. **A** and **B,** Incus is sculpted to fit between the capitulum of the stapes and the malleus handle. **C,** The modified incus is positioned to restore continuity in the ossicular chain.

Assessment of the ossicular chain intraoperatively provides the most accurate information needed for reconstructive planning. An absent lenticular process of the incus is the most commonly encountered ossicular abnormality. Provided that the stapes superstructure is intact, and the malleus long process is present and in a favorable position without head fixation, the preferred method of reconstruction is with a sculpted incus interposed as a strut from the capitulum to the malleus handle or a PORP. For incus interposition, after the incus is removed from the middle ear, the residual long process is shortened with the malleus nipper, and a shallow cavity is drilled into the short process to facilitate placement on the stapes capitulum.[28] The posterior scutum is curetted to prevent contact between the graft and the canal wall. The fashioned ossicle is positioned between the malleus handle and the capitulum in such a way as to tent the tympanic membrane slightly. The graft should hold its position without stabilization by absorbable gelatin sponge (Gelfoam) (Fig. 143-6). Silastic sheeting or hyaluronic acid gel can fill the middle ear to prevent fixation of the graft to the promontory or to the facial ridge. If the interposed incus does not bridge the vertical distance between the capitulum and the malleus, the incus can be resculpted according to the technique by Wehrs.[29] Alternatively, PORPs can be used (Fig. 143-7). Reconstruction prostheses should be fitted with a cartilage cap placed directly against the posterior and superior drum to reduce extrusion.[30]

In patients with an absent stapes superstructure, a TORP reconstruction is necessary. The particular prosthesis chosen is less important than the ability of the surgeon to gauge accurately the optimal size and orientation of an implant. Extrusion rates and the incidence of secondary retraction pockets are reduced with the interposition of cartilage between the tympanic membrane and the prosthetic material. The perichondrium should be stripped from the cartilage graft on the surface in contact with the prosthesis and left intact on the surface contacting the tympanic membrane. The orientation of the implant and the tension of the tympanic membrane on the prosthesis are critical to maximizing sound transmission (Figs. 143-8 and 143-9).[24]

Ossicular fixation should be ruled out before reconstruction. Disarticulating the incudostapedial joint and removing the incus are key to managing malleus head fixation. The epitympanum is opened either by curettage of the scutum or by atticotomy, and the bony union is released.[31] The head is removed with the malleus nipper. Incus interposition or another ossiculoplasty techniques can proceed with the expectation for good results. The fixed incus is managed with removal and interposition or prosthetic graft placement. Stapes footplate fixation should be ruled out and, if present, can be managed with stapedotomy or stapedectomy. Staging the stapedotomy may be necessary to avoid opening the inner ear fluids to an infected middle ear. Tym-

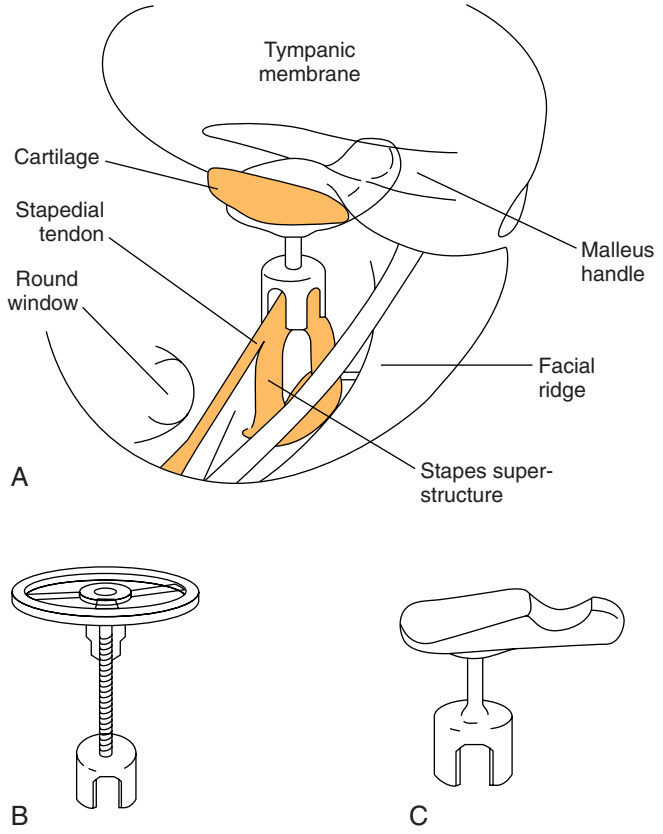

Figure 143-7. **A,** Ossicular defect repaired with a partial ossicular replacement prosthesis (PORP) bridging the stapes capitulum to the malleus handle. A cartilage cap prevents later implant extrusion. The decision to preserve or sacrifice the tensor tympani tendon is made intraoperatively. **B,** Adjustable PORP. **C,** Fixed length PORP.

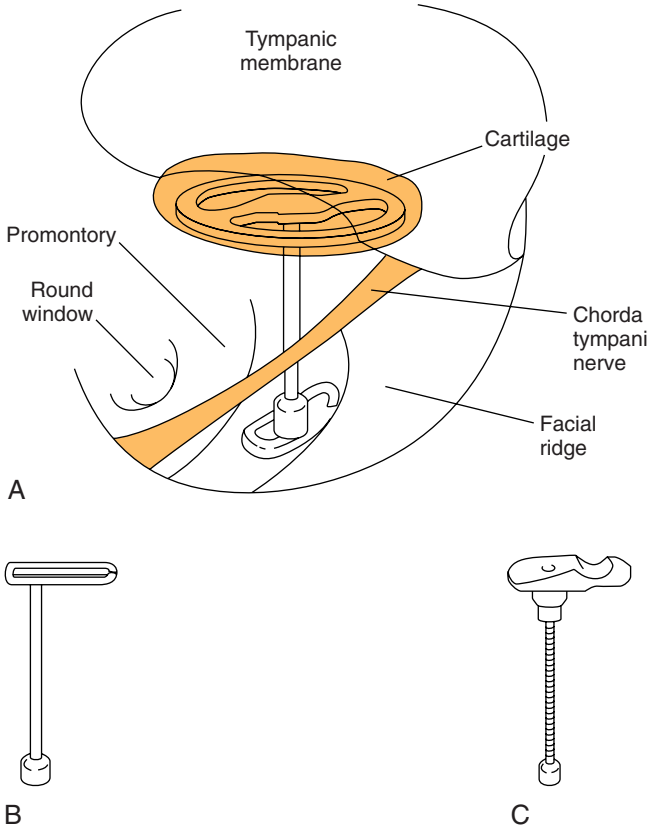

Figure 143-8. **A,** Total ossicular replacement prosthesis (TORP) is positioned between the stapes footplate and the tympanic membrane. **B,** Fixed length titanium/hydroxyapatite prosthesis. **C,** Adjustable TORP. Note cartilage is placed between the head of the prosthesis and the tympanic membrane to prevent extrusion.

panosclerosis is the clinical presentation of dystrophic calcification and hyaline deposits in the submucosal tissues of the middle ear caused by recurrent acute or chronic infection. Any of the bony or ligamentous structures in the middle ear can be involved.[32] Conservatism is in order when managing tympanosclerosis because of the high rate of recurrence of the underlying disease process, regardless of middle ear reconstruction.

Traditionally, autographs and homographs fashioned from the body of the incus or the head of the malleus were considered the gold standard for ossicular reconstruction. Concerns of infectivity of transplanted tissue, the need for often time-consuming intraoperative sculpting of autograph and homograph tissue, and a desire to avoid tissue banking have led to the development of alloplastic materials for ossiculoplasty. In the early 1960s, Austin and Shea[33] pioneered the use of polyethylene and polytetrafluoroethylene (Teflon) implants, but found an unacceptably high extrusion rate. Shea and Emmett[34] later introduced Proplast and Plastipore implants with the concept of increased biocompatibility as a result of the porous properties of these materials. Extrusion rates and hearing results with these implants did not match those of homographs. Calcium phosphate–containing materials, such as hydroxyapatite, glass, and glass and ceramic (Cervital), and titanium offered advantages of biocompatibility and decreased resorption.[35] The propensity for implants to coalesce with adjacent bone offers the theoretical advantage of direct coupling to the stapes superstructure or footplate.

Tension between the malleus or tympanic membrane and the stapes head or footplate is affected by the length of the prosthesis, which can alter the sound transmission across the middle ear. A short prosthesis causes a reduction of sound transmission at higher frequencies and increases the risk of dislodgment as the ear recovers from tympanoplasty. Long prostheses can produce excessive tension, and may be

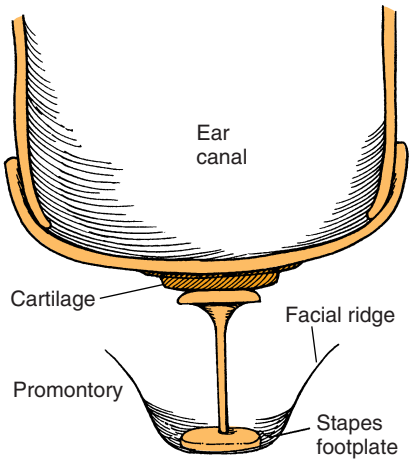

Figure 143-9. Schematic of a total ossicular replacement prosthesis positioned between the stapes footplate and the tympanic membrane. An adequate amount of tension is present on the reconstructed drum, and the prosthesis is as close to perpendicular to the footplate as possible to ensure optimum sound transmission. Also, note the cartilage between the drum and the prosthesis.

acoustically inefficient at low frequencies because of increased dampening of ossicular vibration secondary to stretching of the annular ligaments of the stapes and the suspensory ligaments of the malleus and possibly the tympanic membrane.

In recent years, more surgeons are choosing titanium prostheses because of the advantages of improved visualization during insertion,

Table 143-3

Closure of PTA Pure Tone Average to Less than 20 dB with Partial/Total Ossicular Reconstruction: Extrusion Rate

Reference	Homograft	Plastipore	Hydroxyapatite Cap	Cervital	Titanium
Glasscock[47]	80%/86% (combined)				
Wehrs[48]*	85%/83%: 2%				
Smyth[49]		64%/59%: 12%			
Schuring and Lippy[50]	87%/71%: 2%				
Jackson et al[51]		49%/43%: 10%†			
Sheehy[52]		70%/43%: 4.7%†			
Brackmann et al[53]		73%/55%: 7%†			
Portman et al[54]		57%/24% (combined)		64%: 8%† (combined)	
Babighian[55]				68%/63%: 8%†	
Austin[56]		48%: 29%†‡			
Reck and Helms[35]				69%/61%	
Gersdorff et al[57]		62%/41%		63%/62%: 4%†	
Niparko et al[58]				75%/41%: 3%†	
Goldenberg[59]			58%/38%: 4%		
Dalchow et al[38]					76%: 0.9% (combined)§
Hillman and Shelton[36]		69.8%/48.8%: 0%			60%/26.1%: 1.9%
Truy et al[37]			72%/51.4%: 0.9%§		66.7%/54.8: 3.2%§

*Homograft ossicle and Teflon shaft.
†Tissue interposition.
‡Proplast.
§Results limited to 2 months' follow-up.

low extrusion rate, and easy handling. Studies comparing titanium prostheses with other biomaterials are limited; however, Hillman and Shelton[36] compared Plastipore with titanium prostheses and found that there was no significant difference in the hearing results, or extrusion rates. The Plastipore prosthesis performed better when a TORP was needed. These results are consistent with studies comparing hydroxyapatite with titanium prostheses.[37]

Dalchow and colleagues[38] suggested that titanium middle ear implants offer an ideal implant material. They performed 1304 titanium implants, including PORPs and TORPs, from which 790 were reviewed. Of the patients with titanium prostheses, 76% had a postoperative air-bone gap of 20 dB or less. The results were limited to short-term follow-up and did not separate partial from total prostheses.[38] Table 143-3 lists the reported extrusion rates and hearing results observed with the various implant materials. It is expected that 5-year and 10-year follow-up will determine the efficacy and true extrusion rates of titanium in ossiculoplasty. Follow-up to 15 years after ossiculoplasty in patients with chronic otitis media revealed a slowly progressive deterioration in hearing levels regardless of the implant material chosen.[24]

Management of Conductive Hearing Loss in Children

The most common cause of childhood conductive hearing loss is otitis media followed by congenital anomalies, trauma, and otosclerosis. Theringer and coworkers[39] studied Swedish children 5 years and younger, and found an incidence of hearing loss severe enough to require amplification of 0.6 in 1000. Of these subjects, 64% had genetic etiologies.

Age-specific audiometric testing is mandatory for children as soon as hearing loss is suspected. Amplification optimizes speech and language development and should be implemented as early as possible. Elective surgical correction of ossicular fixation lateral to the stapes can be done at any age. Treatment of stapes fixation in children should be delayed until the child is old enough to contribute to the decision for surgery or can be managed with a traditional head band–type bone-conducting hearing aid or Baha system (Cochlear Corp., Lane Cove, Australia). Bilateral conductive losses require surgical attention before the child enters school, particularly if hearing aids are not providing necessary sound perception to assist speech development.[39a]

Raz and Lustig provide a complete review of the treatment of conductive hearing loss in children.[39a] General anesthesia is essential because children rarely can remain still during a local or sedation anesthetic. The middle ear is most commonly approached through a postauricular incision, which allows for maximal exposure of the middle ear structures and easily assists mastoidectomy when necessary. Thorough middle ear inspection identifies concurrent congenital or infection-related processes. Ossiculoplasty techniques are identical to the techniques used in adults, and long-term follow-up is necessary. Patients with an only-hearing ear should be advised against elective tympanoplasty.[40]

Expanding Role of Implantable Devices

In children and adults, the Baha system offers amplification up to the level of cochlear reserve without risking potential complications with manipulating the middle ear. Baha provided significant improved benefit compared with traditional hearing aids in cases of chronic serous otitis media. McNamara and associates[41] reported 84% of patients with decreased frequency of episodes and no cases of increased incidence of otorrhea in a large cohort of patients with average follow-up of 24 months. Baha was a useful alternative in cases of Treacher Collins syndrome where atresia repair routinely produces poor hearing outcomes.[42]

When used as a primary treatment or as a bridge to later atresia repair, Baha provides near-complete closure of the air-bone gap with minimal risk to the facial nerve or to sensorineural hearing levels. In cases where later microtia repair is planned, the fixture should be placed 1.5 to 2 cm more posterior than the 5.5 cm from the external meatus site normally recommended.[43] Baha is also suggested as the "third option" for surgical treatment of patients with otosclerosis.[44] Maximal conductive hearing losses incurred after lateral skull base surgery can be overcome safely and effectively with Baha placement either at the time of resection or at a second stage. Bilateral Baha has shown enhanced auditory performance compared with unilateral bone conduction alone.[39]

Siegert and colleagues[45] described the use of the Otologics (Boulder, CO) fully implantable middle ear system in five patients with congenital auricular atresia. The middle ear transducer was attached via a modified Kurz PORP to the stapes capitulum. Follow-up was limited to 3 months. The mean functional gain measured at four frequencies (1 kHz, 2 kHz, 3 kHz, 4 kHz) was 36 dB with an average improvement of 70% in speech discrimination at a sound level of 65 dB hearing loss. This technique is under further investigation, and long-term results are needed to determine true efficacy. Although the Otologics device has the promise for better sound localization, the Baha implantation requires much less complicated surgery with minimal risk to the facial nerve or loss of cochlear reserve.[45]

Conclusion

Practical knowledge of the basic physics of the middle ear sound-conducting mechanism is paramount to planning optimal surgical intervention for conductive hearing loss. Adherence to general guidelines facilitates consistency in obtaining the best possible reconstructive outcomes with minimal complications. Surgical management should be individualized to fit the needs of the patient and the comfort level of the operating physician.

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CHAPTER ONE HUNDRED AND FORTY-FOUR

Otosclerosis

John W. House

Calhoun D. Cunningham, III

Key Points

- Otosclerosis is the most common cause of progressive conductive hearing loss in adults.
- The prevalence of otosclerosis is greater in women, with a 2:1 female-to-male distribution.
- The typical age of onset of noticeable hearing loss is in the third decade of life, and hearing loss is bilateral in 70% of cases.
- Otosclerosis is transmitted in an autosomal-dominant fashion, with variable penetrance.
- The pathologic changes of otosclerosis begin as spongification of the bone of the otic capsule.
- Assessment of hearing with tuning forks provides important information on which to base clinical decisions.
- Management options include stapes surgery or hearing aids; rarely, cochlear implantation may be indicated.
- Stapes surgery options include total stapedectomy, partial stapedectomy, or small fenestra stapedotomy. Footplate fenestration may be accomplished with a laser or microdrill.
- Prosthesis options include pistons, wires, or clips (MRI compatible); prosthesis measurement is taken from the incus to the footplate.
- Complications of stapes surgery include sensorineural hearing loss, vertigo, fistula, infection, and tympanic membrane perforation.
- The surgeon performing stapes procedures should be aware of the possibility of a fixed malleus accounting for a conductive hearing loss.
- Cochlear otosclerosis manifests with sensorineural hearing loss and may be amenable to stabilization with fluoride therapy.

Otosclerosis is a disease of bone that is unique to the otic capsule. It may cause a conductive hearing loss, a mixed conductive-sensorineural hearing loss, or occasionally a purely sensorineural hearing loss. In 1860, Toynbee[1] first described the condition causing a hearing loss by fixation of the stapes. In 1893, Politzer[2] referred to the fixation of the stapes as *otosclerosis*. Siebenmann[3] revealed on microscopic examination that the lesion seemed to begin as spongification of the bone and termed the process *otospongiosis*.

Clinically, otosclerosis patients present with progressive hearing loss. If the otospongiotic process primarily involves the stapes, the hearing loss is conductive. The most common area for stapedial fixation is the anterior crura. The process may progress to involve the entire footplate or may continue anteriorly toward the cochlea, causing a sensorineural hearing loss.

Otosclerosis is an autosomal-dominant hereditary disease with variable penetrance and expression. Two thirds of patients are women. The hearing loss usually begins in the late teens or early 20s, but may not occur until the 30s or early 40s. At the House Ear Clinic, the youngest patient with surgically confirmed otosclerosis was 6 years old.[4] It may be accelerated by pregnancy. Many female patients first report hearing loss during or shortly after their first pregnancy.

The prevalence of otosclerosis varies with race and its expression (Table 144-1). In whites, the disease is found in 7.3% and 10.3% of temporal bones for men and women. The stapes appears fixed in only 12.3% of patients with histopathologic evidence of otosclerosis. Clinical otosclerosis is rare in blacks, Asians, and Native Americans.[5-11]

Histopathology

Early lesions appear adjacent to the fissula ante fenestram as sheets of connective tissue replacing bone. Bone is absorbed by osteoclastic activity, and new bone is deposited by osteocytes. The osteocytes are found at the advancing edge of the lesion, which extends into the otic capsule in finger-like projections. These lesions contain vascular spaces in the center. The result is disorganized bone rich in osteocytes with enlarged marrow spaces rich with blood vessels and connective tissue. These lesions have an affinity for hematoxylin, which makes the bone appear darker. Healthy surrounding bone has few viable osteocytes and chondrocytes, and is relatively avascular. The osteoclasts are multinucleated and appear in the center of the lesion, absorbing the already disorganized bone.

The extent and location of these lesions vary. Some are small and do not involve the stapes. Lesions that have ceased all activity appear sclerotic. As the disease advances, the lesions spread across the stapedial annular ligament, causing stapedial fixation. If the lesion progresses medially to involve the endosteum of the cochlea, sensorineural hearing loss results (Fig. 144-1). It may spread in both directions, resulting in a mixed sensorineural conductive hearing loss (Fig. 144-2).

The type of stapedial fixation varies depending on the site of the lesion. If the lesion begins in the posterior oval window and spreads to the stapes through the anterior and posterior annular ligament, it causes bipolar stapes fixation. When the lesion flows across the ligament onto the footplate, it totally obliterates any remnant of the original annular ligament. If the center of the footplate remains uninvolved, it retains its characteristic cartilaginous vestibular and bony tympanic surface.

Table 144-1

Occurrence of Clinical Otosclerosis

Reference	Prevalence
Fowler and Fay, 1961, U.S.[44]	5% of patients with hearing loss*
Morrison and Bundey, 1970, England[45]	0.3% of East London's population
Surján et al, 1973, Hungary (two sites)[46]	5.1% of patients with hearing loss; 2.4% of patients with hearing loss
Hall, 1974, Norway[47]	0.3% of Norway's population
Pearson et al, 1974, U.S.[48]	239:100,000 in Rochester, MN, in 1970
Moscicki et al, 1985, U.S.[49]	0.52% of a cohort study begun 29 years earlier
Huang and Lee, 1988, Taiwan[50]	1.13% of patients with hearing loss
Reference	**Incidence**
Hall, 1974, Norway[47]	56:100,000 for Norway's population (1960-1969)
Pearson et al, 1974, U.S.[48]	13:700,000 in Rochester, MN, from 1950-1969; 8.9:100,000, from 1950-1959
Stahle et al, 1978, Sweden[51]	12:100,000 yearly
Levin et al, 1988, Sweden[8]	6.1:100,000 for 1981

*Discounted patients with cerumen impaction.
From Cummings CW, Fredrickson JM, Harker LA, Krause CT, Schuller DE, eds. *Otolaryngology–Head and Neck Surgery*. 2nd ed. St. Louis: Mosby; 1993.

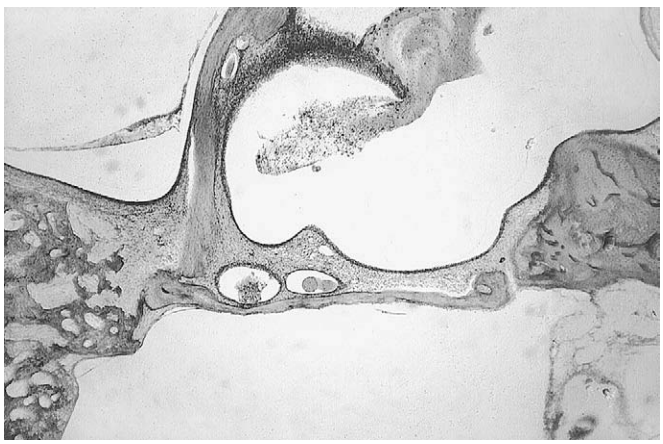

Figure 144-1. Stapes footplate and anterior crus adjacent to an anterior oval window otosclerotic process seen on the left. There is a small extension of otosclerosis in the annular ligament extending to the stapedial footplate and causing minimal fixation.

Figure 144-2. Three otosclerotic lesions involving the cochlear capsule. The largest one in the anterior oval window area also is fixing the stapedial footplate. This patient had sensorineural hearing loss and conductive loss caused by stapedial fixation.

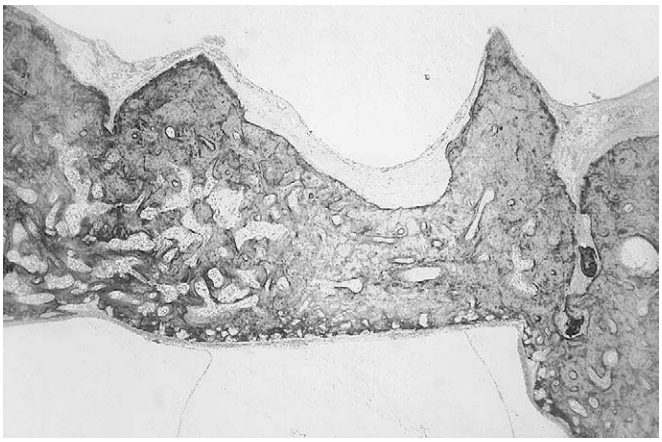

Figure 144-3. A solid stapedial footplate wherein the annular ligament has been totally replaced with otosclerosis.

The lesion may replace the entire footplate, causing a solid footplate (Fig. 144-3).

Occasionally, the lesion may involve only the cochlea, causing an isolated sensorineural hearing loss (Fig. 144-4). Sometimes the entire cochlea is surrounded by otosclerosis, causing total deafness. In the United States, 20 of the first 57 patients to have a cochlear implant were made deaf by otosclerosis.[12]

Evaluation

History

History is one of the most important aspects of the evaluation. Typically, with otosclerosis, hearing loss is of gradual onset and progresses slowly over several years. Approximately 70% of otosclerosis cases are bilateral and become apparent in individuals in their late teens or 20s. Hearing loss may not become apparent to the patient until age 30 or 40 years. Because most patients with otosclerosis have a conductive hearing loss, the patients report difficulty hearing conversation while chewing and may hear better in noisy rooms because of a phenomenon known as paracusis of Willis. This phenomenon is characteristic of conductive hearing loss and occurs because people speak louder in noisy surroundings. Unilateral hearing loss is less noticeable to the patient. With unilateral hearing loss, patients tend to have difficulty with direction of sound and in noisy rooms.

There is usually a positive family history of hearing loss and often of surgical correction of hearing loss. The patient usually has a negative

Figure 144-4. Large otosclerotic lesions surround the cochlea, but spare the oval window area and the stapes. This patient had sensorineural hearing loss.

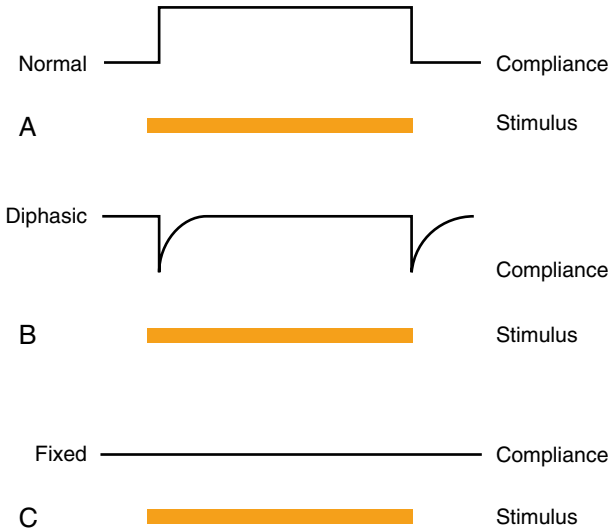

Figure 144-5. Progressive changes in the configuration of the acoustic reflex with stapedial fixation. **A,** Healthy reflex with a sustained change in compliance as long as the stimulus is on. **B,** Diphasic reflex with an on-off pattern. This is seen in cases of early otosclerotic stapedial fixation. **C,** As the stapes becomes fixed, the diphasic reflex is replaced by an absent acoustic reflex.

history for infections or trauma as a possible cause of the conductive hearing loss.

Physical Examination

Physical examination includes careful otoscopy, often with the operating microscope. Pneumo-otoscopy is important to rule out middle ear serous fluid or a small perforation that could be the cause of a conductive hearing loss. There may be a red blush over the promontory or the area anterior to the oval window, known as the Schwartze sign. Tuning forks are essential for evaluation of any patient with a hearing loss[13] because they may confirm or dispute the finding of a conductive hearing loss on audiometry.

The Weber test is performed by placing a 512-Hz fork on the center of the forehead, bridge of the nose, or anterior incisors. The Weber test lateralizes to the ear with the conductive or greater conductive hearing loss (in the case of bilateral disease). It lateralizes with 5 dB of conductive hearing loss. The Rinne test compares the patient's perception of the relative loudness of air conduction versus bone conduction. It is performed by placing the base of a 512-Hz or 1024-Hz fork over the antrum behind the ear. The sound is compared with the loudness when the tines are placed about 2 to 3 cm from the external ear canal. The tines of the fork should be parallel with the plane of the canal. The Rinne test is sensitive and can be used to predict the degree of the conductive component of the hearing loss. When the 512-Hz fork reveals bone conduction greater than air conduction, the patient has at least a 15-dB to 20-dB conductive hearing loss. If the patient reverses the 512-Hz and 1024-Hz forks, the loss is at least 30 dB. Surgery should not be performed on a patient with a conductive hearing loss if the 512-Hz fork does not reverse.

Audiometry

The audiometric evaluation includes air conduction, bone conduction, and speech audiometry, and is usually performed by a trained audiologist. Because otosclerosis may cause unilateral conductive hearing loss, masking is important and may present problems for the tester.

The immittance audiometry battery consists of tympanometry, static compliance, and acoustic reflex testing. Immittance audiometry can be helpful in some cases of otosclerosis, confirming lack of mobility of the stapes with absent acoustic reflexes. The middle ear pressure is not affected by otosclerosis, and the tympanogram is normal with a distinct peak that occurs within the normal range. Many conditions affect the tympanogram, such as scarring of the tympanic membrane or tympanosclerosis. These conditions may coexist with otosclerosis. The peak may be lower than normal in the presence of a healthy-appearing tympanic membrane, alerting the examiner to the possible diagnosis.

Acoustic reflexes are a sensitive measure of the movement of the stapes. In the presence of otosclerosis, the reflex is absent. With early stapes fixation, the reflex may be abnormal in that there is a negative on-off effect or diphasic reflex (Fig. 144-5). With more advanced disease, the reflex is absent when the probe is in the involved ear. As the disease and hearing loss worsen, the contralateral reflex is affected as a result of the degree of conductive hearing loss in the otosclerotic ear. Hannley[14] wrote an excellent article about audiologic evaluation of a patient with otosclerosis.

Surgery

Small Fenestra Stapedotomy

Before surgery is considered, the risks, complications, and alternatives are thoroughly discussed with the patient. Although the risk of sensorineural hearing loss is low, the patient needs to be informed of this possibility. Total sensorineural hearing loss occurs in about 0.2% of cases, but the patient is told that there is a less than 2% chance of further hearing loss, and a less than 1% chance of losing all hearing in the operated ear. Because of the slight chance of further or total hearing loss. the poorer hearing ear is selected for surgery. We never operate on the only-hearing ear or better hearing ear.

There is a slight chance of dizziness postoperatively. This possible complication must also be discussed with the patient before surgery. Dizziness is usually transient and brief, but may persist, and in extremely rare cases could be permanent. The possibility of facial palsy is mentioned in written material, but is not discussed because of the extremely rare incidence of this complication. In a review of more than 700 stapedectomies at the House Ear Clinic, only 2 patients had transient facial weakness of delayed onset. Since the senior author has been performing small fenestra stapedectomy, he has not seen postoperative temporary facial palsy.

Surgery is usually performed as an outpatient procedure with the patient under local anesthesia. We prefer local anesthesia because (1) an awake patient can inform the surgeon if vertigo occurs, and (2) the surgery is usually of short duration with minimal discomfort and does not warrant the risks or costs of general anesthesia.

An intravenous line is placed, and the patient is given sedation with midazolam (0.5 to 2 mg) as needed; this is occasionally supplemented with intravenous morphine (2 to 4 mg). The ear is anesthetized with 1% or 2% lidocaine with epinephrine 1:100,000. To lessen the pain associated with the injection, 18 mL of lidocaine can be buffered with 2 mL of 7.5% bicarbonate.

Figure 144-6. The operating room during stapes surgery. The nurse is on the opposite side of the patient, and the microscope is at the head of the table.

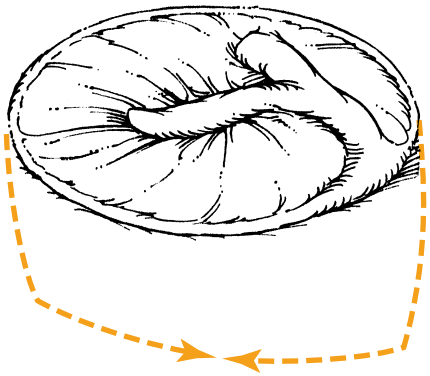

Figure 144-7. The tympanomeatal flap is elevated after the initial incisions are performed.

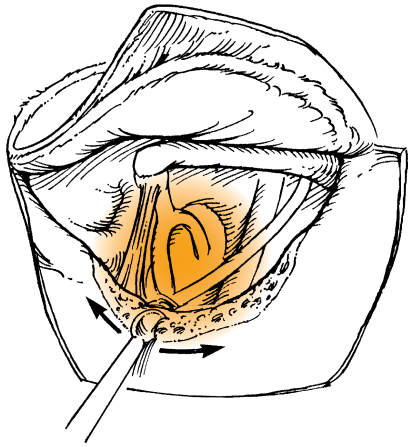

Figure 144-8. The curet is used to remove the posterior superior bony canal wall to obtain better visualization of the stapes.

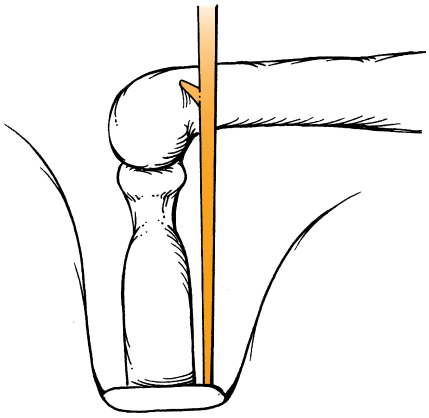

Figure 144-9. The distance from the incus to the footplate is measured from the lateral or medial surface of the incus. The usual distance from the lateral surface to the footplate is 4.5 mm.

The patient is placed supine on the operating table with the head turned away from the surgeon. The microscope is placed at the head of the table with the nurse standing across the table from the surgeon (Fig. 144-6). If general anesthesia is used, the anesthesiologist is seated at the foot of the table.

There are many variations in the basic stapedectomy technique. Any technique that produces comparably good results should be continued.

The four quadrants of the ear canal are injected at the level of the hair-bearing area. This injection works best if placed just under the skin. A fifth injection is placed in the vascular strip down to the bone. If a tissue graft is to be used, the superior postauricular area is prepared and injected. Some surgeons use a vein graft; in this case, the graft is harvested from the hand before beginning the stapes surgery.

Incisions are performed with a sickle knife (No. 1) at the lateral process of the malleus and inferiorly at about the lower one fourth of the canal extended laterally approximately 8 mm. These two incisions are connected laterally with a House canal knife (No. 2). This flap is elevated evenly from lateral to medial with a canal elevator or a round knife (Fig. 144-7). It is important to elevate all of the flap at the same time so as not to tear it. When the anulus is reached, it is carefully exposed and elevated out of its bony canal with an anulus elevator "gimmick". Care is taken during elevation to identify the chorda tympani nerve so that it is not stretched or injured. The superior elevation is carried forward to the malleus. Care is taken not to dislocate the incus. Usually the stapes is not entirely visualized because of the bony posterior superior external auditory canal overhang. This overhang is removed with a curet; alternatively, some surgeons prefer a microdrill (Fig. 144-8). The exposure is adequate when the facial nerve can be visualized superiorly, and the pyramidal process can be visualized posteriorly.

When adequate exposure is established, the malleus, incus, and stapes are palpated to ascertain mobility. The distance from the incus to the stapes footplate is measured (Fig. 144-9). The usual distance from the lateral surface of the incus to the footplate is 4.5 mm. Because the piston prosthesis is usually measured from the medial surface of the incus, 0.25 mm is subtracted to allow for this distance (incus = 0.5 mm + extension into vestibule of 0.25) (Fig. 144-10). The most common piston size is 4.25 mm.

A 0.7-mm diamond microdrill is used to create the fenestra. Usually there is adequate room between the facial nerve and the crus of the stapes to use the drill on the footplate. Despite this, part of the posterior crura is drilled to warn the patient of the drill noise, weaken the crura for easy fracture, and, at times, allow better access to the footplate (Fig. 144-11). The laser can be employed to begin the fenestra. If the footplate is thin, the drill may not be needed to complete the opening.

The fenestra is created with a light touch of the drill (Fig. 144-12). The diamond is allowed to create the fenestra without applying pressure. Excess pressure may fracture the footplate. When the drill is felt to drop into the vestibule, a perfect 0.7-mm fenestra is completed. The 4.25-mm length, 0.6-mm diameter platinum Teflon (polytetrafluoroethylene) prosthesis is placed from the incus to the fenestra (Fig. 144-13). It is crimped firmly on the incus (Fig. 144-14). The incudostapedial joint is separated, and the stapedial tendon is sectioned. The

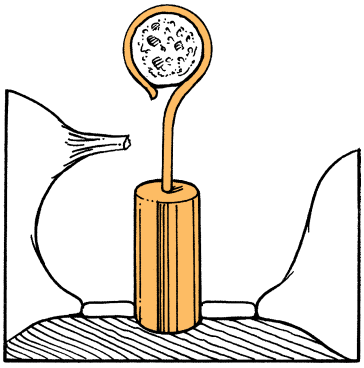

Figure 144-10. Cross section of the stapes footplate with the prosthesis extending about 0.25 mm through the footplate into the vestibule.

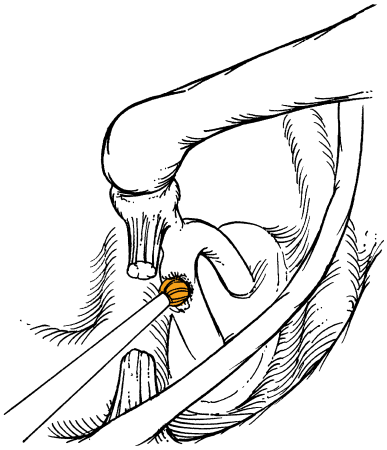

Figure 144-11. The diamond bur sometimes may be used to remove the posterior crus or weaken it.

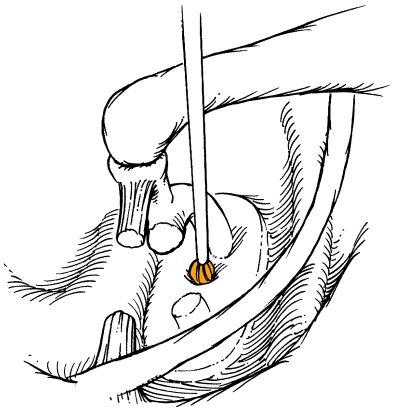

Figure 144-12. The microdrill and 0.7-mm diamond bur create a fenestra in the center of the stapes footplate. The fenestra is created before removal of the stapes superstructure.

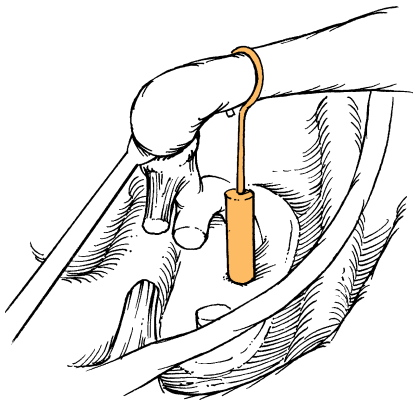

Figure 144-13. The piston is placed from the incus to the fenestra before removal of the superstructure.

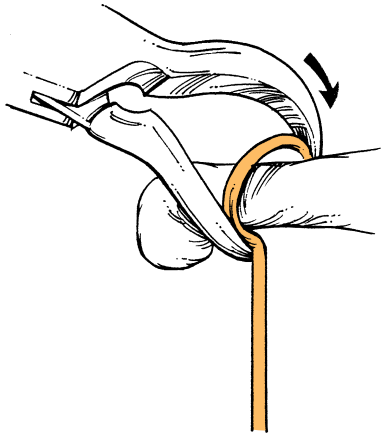

Figure 144-14. The piston is crimped around the incus before removal of the superstructure of the stapes.

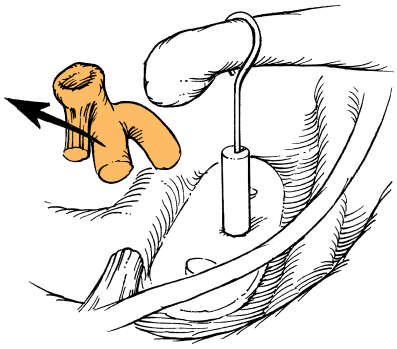

Figure 144-15. After removal of the stapes superstructure, blood is placed into the oval window as a seal.

superstructure of the stapes is fractured inferiorly with a quick, decisive movement and removed (Fig. 144-15). A test of the prosthesis is performed to check the position. The medial lateral excursion is checked with light manipulation. The patient is asked if this causes vertigo. If it does, the prosthesis may be too long. If it does not, the anterior posterior movement is checked. If the prosthesis is properly in the fenestra, there is no anterior posterior displacement.

Blood is placed around the prosthesis as a seal in the oval window, and the tympanomeatal flap is returned to its normal position. Minimal packing is required on the flap, a cotton ball is placed in the meatus, and a bandage is applied to the ear.

Postoperative Care

Immediately after surgery, the patient's head is elevated about 30 degrees to reduce the perilymph pressure in the vestibule. The patient is kept at bed rest for about 1 hour and then allowed to get up. If no vertigo or dizziness is present, the patient may go home about 2 hours after surgery. Most patients stay in the hospital for 2 to 4 hours. The

patient is instructed to remove the bandage and cotton the next day and return to the office in 3 weeks. Patients are also instructed to call if they experience any unusual problems, such as pain, drainage, or vertigo. The first audiogram is obtained at the 3-week postoperative visit. Patients can fly after postoperative day 5, if necessary.

After stapes surgery, some patients inquire about resuming sports such as scuba diving or skydiving, which presumably increase the risk of inner ear barotrauma and associated perilymphatic fistula. A uniform consensus on barorestrictions after stapes surgery has yet to be reached; however, review of patients who continue to participate in these activities after stapedectomy reveals no increased risk of inner ear barotrauma.[15] In our practice, postoperative guidelines typically call for dry-ear precautions for the first 3 weeks, with swimming and diving permitted 3 weeks after surgery.

Variations of Surgical Technique

Stapedectomy versus Stapedotomy

The past 50 years have seen many innovations in the surgical management of otosclerosis. The original stapedectomy as described by Shea[16] was a total stapedectomy that used picks and hooks to remove the entire footplate and replace it with a vein graft and polyethylene strut. This technique evolved to the use of a wire or piston prosthesis. House[17] used a total stapedectomy with wire over an absorbable gelatin sponge (Gelfoam) or fat graft. Glasscock and colleagues[18] reported 25 years' experience with total stapedectomy by use of a tissue seal over the oval window. Others have performed a partial stapedectomy, removing only the posterior half of the footplate. With these large fenestra techniques, the footplate is opened with either picks or a microdrill.

More recently, there has been a greater trend away from total stapedectomy and large fenestra techniques to small fenestra stapedotomy.[19-21] Proponents of small fenestra techniques argue that limited opening of the vestibule carries a lower risk of damage to the inner ear and resultant sensorineural hearing loss (particularly for the 2-kHz and 4-kHz frequencies)[19,20] or vertigo or both. Comparisons[22-24] of short-term and long-term results of stapedectomy with results of stapedotomy show slightly better early and late postoperative air-conduction thresholds at 4 kHz in patients undergoing small fenestra stapedotomy. Likewise, a lower rate of postoperative high-frequency sensorineural hearing loss is noted in the stapedotomy group. No significant difference in early or late postoperative pure-tone average, pure-tone average air-bone gap, or speech discrimination scores is noted, and outcomes in both groups remain stable over long-term follow-up. Generally, either technique can be used in the hands of an experienced surgeon to obtain satisfactory and stable long-term hearing results.

Laser versus Microdrill

Current methods of performing small fenestra stapedotomy involve various techniques, including the use of lasers, microdrills, or fine picks. Two types of lasers are being used by surgeons to create the fenestra in the footplate of the stapes: the visible argon or potassium-titanyl-phosphate (KTP-532) and the infrared carbon dioxide (CO_2). The visible argon laser beam can be carried through fiberoptic cable, whereas the CO_2 requires a series (usually ≥12) of carefully aligned mirrors and lenses to deliver the beam to the microscope. Recently, OmniGuide has developed a flexible fiber that has eliminated the need for the fixed mirrors. Perkins[25] was the first to describe the use of the argon laser to create a small fenestra. Horn and coworkers[26] modified his technique by developing a fiberoptic laser delivery system. The argon laser is similar in frequency to the KTP-532. The beam from both lasers is preferentially absorbed by red pigment, such as hemoglobin. Horn and coworkers[26] believe that the handheld probe has the advantage in that the laser beam has a greater divergence than the microscope-mounted micromanipulator, and it has less potential to damage the contents of the vestibule. The argon laser and the KTP laser have been shown to be safe and effective in creating the footplate fenestra.[24]

Lesinski and Newrock[27] prefer the CO_2 laser for primary and revision stapes surgery. These authors believe that the CO_2 laser energy is more efficiently absorbed by collagen and bone than is visible argon laser energy. In their opinion, a pulsed CO_2 laser is more effective in performing primary stapes and revision stapes procedures. Lesinski and Newrock[27] point out that because visible lasers are poorly absorbed by collagen and pass readily through perilymph, they should not be used for stapedectomy revision surgery.

Successful small fenestra stapedotomies have been performed with lasers and microdrills. Proponents of the laser argue that it may reduce the mechanical trauma to the stapes, causing decreased labyrinthine irritation and possibly better results.[24] In our experience, the microdrill is just as safe and efficacious as the laser and, in some ways, is the better choice because of its increased usefulness when one is faced with a thick footplate. One may use the laser to thin the footplate and finish the fenestra with the 0.7-mm diamond bur. Comparison of the microdrill with visible wavelength lasers (argon and KTP) in performing small fenestra stapedotomy reveals no significant differences in the postoperative pure-tone average or individual frequencies.[24] Evaluation of postoperative sensorineural hearing loss shows no significant difference between the two methods used to create the fenestra.

Laser Stapedotomy Minus Prosthesis

In addition to standard techniques of surgically treating otosclerosis, newer, alternative methods of attempting hearing restoration continue to evolve. In cases of minimal otosclerosis confined to the fissula antefenestrum, Silverstein[28] advocates a linear, laser stapedotomy at the anterior one third of the footplate followed by vaporization of the anterior stapes crus to allow the stapes to become mobile. The stapedotomy is sealed with adipose tissue. In this way, the patient's stapes and stapedius tendon can be preserved, avoiding the need for a prosthesis. At some point in the future, should the stapes become refixed, a revision procedure with the use of a prosthesis can be performed. Early hearing results in patients undergoing laser stapedotomy minus prosthesis (STAMP) are comparable to results obtained after conventional stapedotomy with prosthesis; however, long-term follow-up is required to determine whether these hearing results are maintained.

Surgical Problems

Exposed, Overhanging Facial Nerve

Exposed facial nerve occurs in about 9% of stapes procedures. Usually, it does not present a problem. Occasionally, the exposed nerve blocks access to the footplate, making the completion of the procedure impossible. It is possible to retract the nerve gently superiorly with a small suction while the drill or laser is used to create the fenestra (see Fig. 144-11). Prosthesis touching the facial nerve does not create a problem for postoperative hearing or facial function.

Fixed Malleus

Fixed malleus is a rare problem, but should be checked in every procedure. It is usually associated with stapes fixation, but it may be an isolated finding. When this occurs, the sound-conducting mechanism can be re-established with an incus replacement prosthesis or a total ossicular replacement prosthesis and tragal cartilage.

Solid or Obliterated Footplate

A solid or obliterated footplate can be managed with a microdrill to create a fenestra. It was a greater problem in the past when a total stapedectomy was performed. It was difficult to drill through the footplate, and the bony closure would commonly regrow and cause increasing conductive hearing loss. In the past, these drill-outs were associated with a higher incidence of sensorineural hearing loss.[29]

Floating Footplate

A floating footplate is rare with the use of the laser or microdrill, especially when the crura are left in place until after the prosthesis is placed. This complication can be managed by carefully drilling a small hole in the promontory at the inferior edge of the footplate. A small hook can be used to elevate the footplate gently out of the oval window. Another alternative is to place a slightly short wire or piston from the incus to the floating footplate. If the conductive hearing loss recurs, the procedure can be revised with a laser to create the fenestra.

Perilymph Gusher

A rare occurrence, a perilymph "gusher" is the profuse flow of cerebrospinal fluid immediately on opening the vestibule. It has a reported incidence of 0.03%, and is most often associated with congenital footplate fixation in pediatric patients.[30] It is advisable to obtain a high-resolution, thin-section computed tomography (CT) scan in children with congenital conductive or mixed hearing loss to rule out inner ear deformity. In this way, the gusher can be avoided. This cerebrospinal fluid leak is thought to be due to either a widened cochlear aqueduct or a defect in the fundus of the internal auditory canal. Management of a perilymph gusher typically involves placement of a tissue graft over the oval window and completion of the procedure, if possible, rather than packing the ear and terminating the surgery. A lumbar drain can also be used to reduce cerebrospinal fluid pressure.

Tympanic Membrane Perforation

A perforation of the tympanic membrane may occur during elevation of the tympanomeatal flap. This complication usually occurs during elevation of the tympanic membrane from the sulcus in the posterior inferior area and can be avoided with careful identification of the annular ligament. Perforation does not preclude completion of the operation, and small perforations usually heal with placement of a small piece of Gelfoam or paper patch over the hole. Larger tears may require an underlay myringoplasty using tissue.

Chorda Tympani Nerve Damage

Damage to the chorda tympani nerve may occur in 30% of cases because of stretching and mobilization of the nerve during removal of the posterior superior bony canal wall.[30] Patients may complain of temporary dry mouth, tongue soreness, or a metallic taste that usually subsides in 3 to 4 months. Less severe symptoms are reported with complete sectioning of the nerve, rather than stretching or partial tearing.

Intraoperative Vertigo

A prosthesis that is too long may induce vertigo at the time of placement, or when its mobility is checked. In this situation, a shorter prosthesis generally corrects this problem. After placement of the prosthesis, the ossicular chain should be palpated, and the patient should be questioned about the occurrence of dizziness. Rarely, postoperative patients complain of brief vertigo when they burp or push on the ear canal. They have a positive "fistula test." This vertigo is usually due to a slightly long prosthesis. If this does not resolve, and the patient is bothered by the symptom, the prosthesis can be removed and replaced with a 0.25-mm shorter piston.

Postoperative Complications

Sensorineural Hearing Loss

The most devastating complication, sensorineural hearing loss, occurs in less than 1% of cases, and the cause is often unclear. In our review of more than 1000 stapedectomies, total sensorineural hearing loss occurred in 2 cases.[31] In one, the patient had a postoperative infection, and in the second, the patient probably had concurrent Meniere's disease. In both cases, there was no associated vertigo. Sensorineural hearing loss may be mild or isolated to high frequencies. When sensorineural hearing loss is suspected, prednisone is started immediately and tapered over 10 days. The course begins with 60 mg/day for 5 days. On the sixth day, the dose is reduced to 40 mg for 1 day, followed by a 10-mg/day reduction until the 10th day.

Serous labyrinthitis is common after stapedectomy because of a certain amount of inflammation within the inner ear. Clinically, patients may exhibit mild unsteadiness, positional vertigo, or a slight decrease in high-frequency hearing. These symptoms typically resolve within several days to weeks.

Rarely seen today, postoperative reparative granuloma has previously been recognized as a cause of sensorineural hearing loss after stapedectomy.[30] Patients typically have initial improvement in hearing followed by a gradual or sudden deterioration 1 to 6 weeks postoperatively. Vertigo may also be associated with hearing loss, and clinical examination often reveals a reddish discoloration in the posterior superior quadrant of the tympanic membrane. Granuloma formation is believed to be associated with the previous use of Gelfoam or fat as a covering over the oval window. Treatment consists of prompt recognition and removal of the granuloma from around the oval window.

Vertigo

Mild vertigo or dizziness is common and occurs in about 1 of 20 cases. The vertigo usually lasts for a few hours and subsides rapidly. It is rarely prolonged or severe. Management is usually unnecessary or may be supportive only.

Facial Paralysis

Rarely, delayed onset of facial palsy occurs about 5 days postoperatively and lasts for a few weeks. It is usually incomplete and responds quickly to prednisone.

Tinnitus

After stapedectomy, most patients note an improvement in preexisting tinnitus. A few patients complain of new-onset tinnitus, however. This symptom is possibly related to serous labyrinthitis and may improve as the ear continues to heal. Patients with persistent tinnitus are treated with reassurance and routine tinnitus measures.

Taste Disturbance

Taste disturbance occurs in about 9% of patients. This is more common in patients whose chorda tympani nerve was stretched rather than sectioned. If the nerve has been stretched or otherwise injured, it is preferable to section it. Most taste disturbance resolves in 3 to 4 months.

Tympanic Membrane Perforation

If the patient returns to the office with a small marginal perforation, the edges are freshened, and a paper patch is applied. The patient should be seen about once per month so that the paper patch can be removed, and if the perforation has not healed, the edges are freshened and the patch reapplied. Most of these perforations heal quickly. If they do not heal, a myringoplasty can be performed.

Perilymph Fistula

Perilymph fistula is a rare complication after stapes surgery. The incidence varies from 3%[32] to 9% or 10%.[33-35] The most common cause of fistula in fistula exploration surgery was poststapedectomy.[36] These cases date back many years and were performed by use of total stapedectomy with a Gelfoam and wire technique. With the use of a small fenestra technique, fistula is rarely seen as a cause of failure in stapes surgery. The presenting problem with fistula is usually a mixed conductive sensorineural hearing loss. It may be associated with some vague unsteadiness and, rarely, vertigo. At revision surgery, the prosthesis is carefully removed, a tissue seal is placed over the open oval window, and the prosthesis is replaced. A laser is helpful to remove granulation and scar tissue.

Alternative Treatment

Hearing Aids

All patients with conductive hearing loss caused by otosclerosis may use hearing aids as an alternative to surgery; this should be discussed with the patient as an option. If the patient has a significant sensorineural component to the hearing loss, a hearing aid may be required even after successful stapedectomy. A patient with far-advanced otosclerosis requires a hearing aid at all times, but with a successful surgery, the patient can use a less powerful hearing aid. Many patients with far-advanced otosclerosis require time to adjust to the new hearing level and are sensitive to the sound of their hearing aid. It may take 4 months before these patients can tolerate and benefit from the hearing aid.

Fluoride Therapy

Sensorineural hearing loss often develops in patients with otosclerosis because of spongiotic foci involving the otic capsule. Injury to the inner ear is believed to occur as a result of the spread of proteolytic enzymes

to the inner ear fluids from an active otospongiotic focus, with resultant injury to the organ of Corti and spiral ligament.[37] In patients with evidence of progressive sensorineural hearing loss, fluoride therapy has been shown to reduce the progression of hearing loss.[37] The mechanism of action is believed to be the conversion of the active otospongiotic lesion to a more stable otosclerotic lesion. Patients are typically treated with Florical, 8 mg three times per day, until hearing loss stabilizes. Gastric distress is a side effect of fluoride medications; however, most patients tolerate this effect without difficulty.

Special Considerations

Far-Advanced Otosclerosis

Patients with far-advanced otosclerosis seemingly have a blank audiogram, or what seems to be a profound sensorineural hearing loss, yet they may benefit from a stapedectomy. The hearing loss seems profound only because the limit of the audiometer for bone conduction is 70 dB; if the bone conduction threshold were greater, the patient would seem to have no response. This condition is suspected if the patient can benefit from a hearing aid and has relatively normal speech and good speech comprehension. These patients typically have a positive family history for otosclerosis and a history of a progressive hearing loss since the second or third decade. At surgery, a fixed stapes is found with postoperative improvement of hearing. Such patients subsequently obtain better use of a hearing aid. Because of long-standing, severe hearing loss, these patients require time to improve their tolerance to amplification.

Patients with far-advanced otosclerosis who progress to profound hearing loss with significant deterioration in speech discrimination despite hearing aids may be candidates for cochlear implantation. Careful evaluation of these patients is undertaken to ensure that they would not benefit first from a stapedectomy and hearing aid. The patient undergoes routine evaluation through the cochlear implant program. Results at our own institution (unpublished observation) and results of other authors[38] show that these patients derive significant benefit from cochlear implantation and are capable of achieving excellent speech comprehension.

Meniere's Disease

Endolymphatic hydrops may occur with otosclerosis as two separate disease entities or as a result of otosclerosis itself. Stapedectomy in the presence of uncontrolled Meniere's disease can potentially result in a dead ear and should be avoided. Fluoride therapy and hearing aids are an acceptable treatment in such patients. Shea and coworkers[39] note that if Meniere's symptoms can be controlled for at least 1 year, as evidenced by electrocochleography, stapedectomy can be performed with a decreased risk of hearing loss. Review of patients with otosclerosis and Meniere's disease at the House Ear Clinic revealed that stapedectomy does not increase the risk of sensorineural hearing loss for patients with bone conduction thresholds of 35 dB or better at 500 Hz and no high-tone hearing loss. Stapedectomy is contraindicated for patients with levels of 45 dB or greater at 500 Hz and with high-tone loss. In this latter group of patients, postmortem histopathologic analysis revealed contact of the saccular membrane or Reissner's membrane with the stapes footplate, which increased the risk of significant postoperative sensorineural hearing loss.[40]

Stapedectomy in Children

Stapedectomy in children is performed for correction of conductive hearing loss caused by congenital footplate fixation or juvenile otosclerosis. Before considering surgery, a CT scan should be performed to evaluate abnormalities of the otic capsule, such as defects in the fundus of the internal auditory canal as seen in patients with X-linked mixed deafness. Stapedectomy in these patients may lead to a perilymph gusher and additional hearing loss.

Generally, the results of stapedectomy in children seem to be as satisfactory as results in adults. When recommending surgery to children, a good outcome can be anticipated in approximately 80% of cases.[4,41] Children younger than age 5 with a conduction hearing loss greater than 30 dB should be fitted with a hearing aid after otitis media and cholesteatoma have been ruled out. In unilateral cases with a normal contralateral ear, surgery may be postponed until the child is old enough to participate in the decision process. Children who are older than age 5 with bilateral congenital stapes fixation, an air-bone gap greater than 30 dB, and speech reception threshold greater than 35 dB may be considered surgical candidates if the child or parents do not accept hearing aids. Parents are warned of the potential risks and complications associated with surgery.

Revision Stapedectomy

Revision stapedectomy is considered to be more challenging than primary surgery, and hearing results are typically not as good. A more recent review of revision stapedectomy procedures at the House Ear Clinic revealed an overall rate of air-bone gap closure to within 10 dB and 20 dB of 60% and 78%.[42] The most common cause for failure of primary stapedectomy is displaced prosthesis (53%), incus erosion (26%), and bony regrowth (14%). The rate of postoperative sensorineural hearing loss is 7.7%, and profound loss is 1.4%. Revision stapedectomy is technically more difficult; however, acceptable hearing results can be obtained in appropriately selected patients.

We believe that revision surgery is best performed under local anesthesia so that the patient can be monitored for vertigo. If the piston has been displaced into the vestibule, it may be extracted carefully while asking the patient if he or she is experiencing vertigo. In these cases, the incus is eroded and can no longer support the prosthesis. The incus can be reinforced using Mimix bone cement, an offset prosthesis such as the Kurz angular prosthesis (www.kurzmed.de/int/angular-piston.html), or a total ossicular replacement prosthesis from the tympanic membrane to the oval window.

A wide variety of stapes prostheses are available for primary and revision stapes surgery. The magnetic resonance imaging (MRI) compatibility of the myriad types of stapes prostheses has been confirmed, with the rare exception of a line of prostheses manufactured in 1987.[43]

Summary

Hearing loss caused by otosclerosis is typically a progressive conductive loss that begins in individuals in their 20s and may progress to a mild, moderate, or, in rare cases, severe hearing loss. It is not unusual to have some degree of sensorineural component to the hearing loss. Surgery for otosclerosis has evolved over the past 70 years to a safe and effective method for restoring hearing. Complications are rare, and the surgery is performed as an outpatient procedure with local anesthesia in most cases. Hearing aids also have improved over the past 70 years, and are an option for patients who choose not to have surgery.

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CHAPTER ONE HUNDRED AND FORTY-FIVE

Management of Temporal Bone Trauma

Hilary A. Brodie

Key Points

- Otic capsule disrupting fractures have a fourfold to fivefold higher risk of facial paralysis and a twofold to fourfold increased risk of a cerebrospinal fluid (CSF) fistula when compared with otic capsule sparing fractures.
- Temporal bone fractures in the pediatric population are associated with a higher incidence of intracranial complications (58%) and a lower incidence of facial paralysis (3%) than in adults.
- Seven percent of temporal bone fractures are complicated by facial paralysis.
- The most important prognostic factor in facial paralysis following temporal bone fractures is whether there is an immediate onset complete paralysis upon admission to the emergency department. Delayed-onset facial paralysis generally has an excellent recovery of function.
- In the absence of immediate onset of complete facial paralysis following temporal bone trauma, rarely is surgical exploration and decompression warranted.
- Facial nerve exploration, decompression, and repair can often be achieved via a supralabyrinthine approach without a middle fossa exposure.
- The incidence of meningitis following a temporal bone fracture without a CSF fistula is 1%.
- The incidence of CSF fistulas with temporal bone fractures is 17%.
- Meningitis occurs in 5% to 11% of CSF fistulas that persist for less than 1 week; the percentage increases to 88% if left to leak indefinitely.
- Hearing results following ossicular reconstruction in patients with temporal bone fractures is superior to the results in patients with chronic otitis media.

Epidemiology

Motor vehicle accidents commonly result in head trauma of varying degrees of severity. In the past, 75% of motor vehicle accidents resulted in a head trauma; however, the increased use of seatbelts and the advent of airbags may alter these statistics in the future. When the head trauma is of sufficient magnitude to fracture the skull, 14% to 22% of injured patients sustain a temporal bone fracture.[1,2] In the largest series of temporal bone fractures reported to date, 31% of the fractures resulted from motor vehicle accidents (Fig. 145-1).[3]

Temporal bone fractures are reported to occur across all age groups, with more than 70% of fractures occurring during the second, third, and fourth decades of life.[3] These fractures occur predominantly in men in a ratio of 3:1,[3] which is attributed to involvement in riskier activities rather than to structural weaknesses in the male skull.

Pathophysiology

The temporal bones are pyramidal structures in the thick bone of the skull base and consequently require a great force to fracture. The force of lateral impact required to fracture the temporal bones of fresh cadavers is estimated at 1875 pounds.[4] The fractures take the path of least resistance, which is along the structurally weakened points, such as the various foramina that perforate the skull base.

The temporal bone houses or encapsulates many important structures, including the facial nerve, cranial nerves IX through XI, the cochlea, the labyrinth, the ossicles, the tympanic membrane, the carotid artery, and the jugular vein. Any of these structures can be injured with a fracture of the bone. Fracture of the temporal bone can violate dura, resulting in cerebrospinal fluid (CSF) fistula, meningitis, and brain herniation. In addition to neurotologic manifestations of involved structures within the temporal bone, associated intracranial injuries, such as epidural or subdural hematomas, cerebral edema, post-traumatic encephalopathy, and elevated intracranial pressure, may occur. Neurotologic symptoms can also result from shearing strain within the brain tissue with disruption of vessels, axons, synapses, and dendrites.[5]

Sixty percent of temporal bone fractures are categorized as open fractures, presenting with bloody otorrhea, brain herniation, or CSF draining from the ear canal, eustachian tube, or penetrating wound site.[3] Eight percent to 29% of temporal bone fractures occur bilaterally.[3,6,7]

Classification

Temporal bone fractures have traditionally been divided into transverse and longitudinal categories on the basis of the relationship of the fracture line to the axis of the petrous ridge.[8] This classification has given

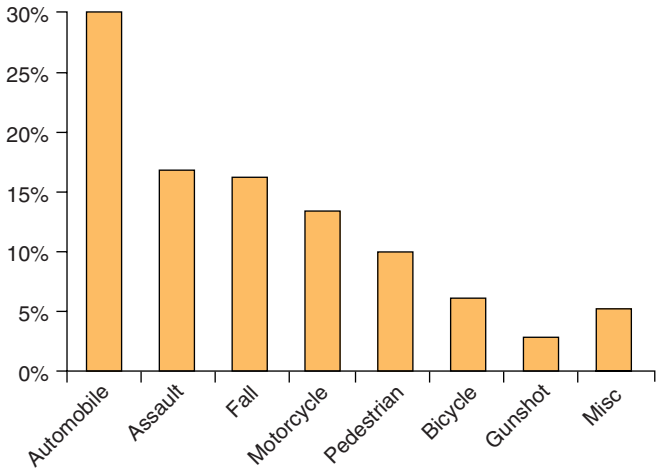

Figure 145-1. Type of injury. *(Data from Brodie HA, Thompson TC, Management of complications from 820 temporal bone fractures*. Am J Otol. *1997;18:188.)*

Figure 145-2. Axial-cut high-resolution computed tomography scan that demonstrates a longitudinally oriented fracture that is sparing the otic capsule. *Black arrows* point along the fracture line.

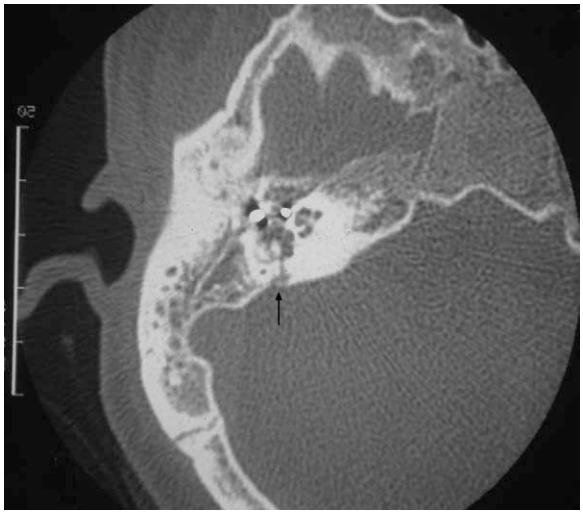

Figure 145-3. Axial-cut high-resolution computed tomography scan that demonstrates a transverse-oriented fracture resulting from a gunshot injury and disrupting the otic capsule. The *black arrow* points to the fracture line.

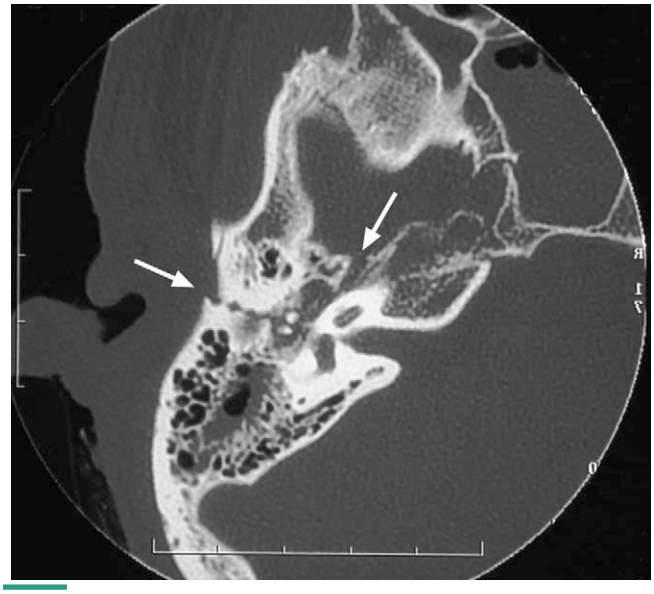

Figure 145-4. Axial-cut high-resolution computed tomography scan that demonstrates a mixed-oriented fracture that spares the otic capsule. The *white arrows* point to the fracture lines.

way to a new scheme that classifies fractures by whether they disrupt or spare the otic capsule (the bone that houses the cochlea and the semicircular canals) (Figs. 145-2 through 145-4).[3,9]

Fractures that spare the otic capsule typically involve the squamosal portion of the temporal bone and the posterosuperior wall of the external auditory canal. The fracture passes through the mastoid air cells and the middle ear and then fractures the tegmen mastoideum and tegmen tympani. The fracture proceeds anterolateral to the otic capsule, typically fracturing the tegmen in the region of the facial hiatus. Otic capsule–sparing fractures typically result from a blow to the temporoparietal region.

Otic capsule–disrupting fractures pass through the otic capsule, generally proceeding from the foramen magnum across the petrous pyramid and the otic capsule. The fracture often passes through the jugular foramen, the internal auditory canal, and the foramen lacerum; these fractures do not typically affect the ossicular chain or the external auditory canal.[10] Otic capsule–disrupting fractures generally result from blows to the occipital region.

Longitudinal fractures reportedly make up 70% to 90% of temporal bone fractures, with the remaining 10% to 30% categorized as transverse.[8-14] In two large series using the newer classification scheme, only 2.5% to 5.8% of fractures disrupted the otic capsule,[3,15] suggesting that many fractures that are oriented perpendicular to the petrous ridge do not actually cross the otic capsule. Many of the otic capsule–disrupting fractures are actually oriented in the longitudinal plane.[15]

The rationale for changing the classification scheme is to focus on the functional sequelae and complications of temporal bone fractures as opposed to merely describing the anatomic orientation of the fracture. Fractures that disrupt the otic capsule almost always result in a sensorineural hearing loss, although there are reported exceptions.[16] Otic capsule–sparing fractures tend to have conductive or mixed hearing loss,[3] whereas otic capsule–disrupting fractures have a much higher incidence of facial nerve paralysis (30% to 50% vs. 6% to 14%).[3,15] In addition, Fisch[17] reported a much higher incidence of nerve disruption in fractures involving the otic capsule. There is a twofold to fourfold increase in CSF fistula in otic capsule–disrupting fractures as

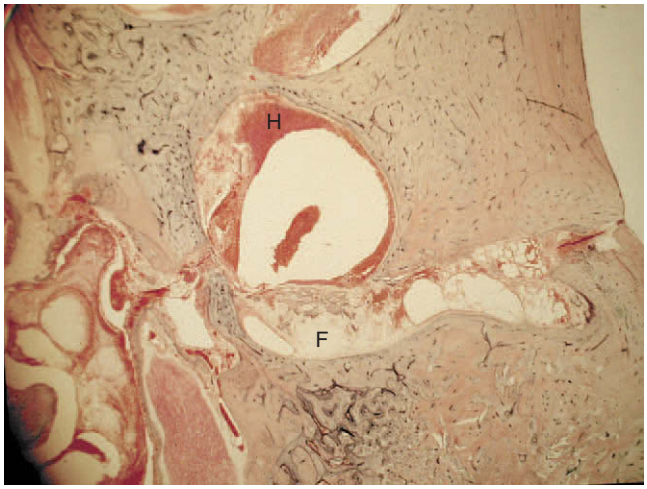

Figure 145-5. Histopathology of a patient who died of meningitis several decades after an otic capsule–disrupting temporal bone fracture. F, Fibrosis with a small amount of ossification within the fracture line in the otic capsule; H, hemorrhage and purulence.

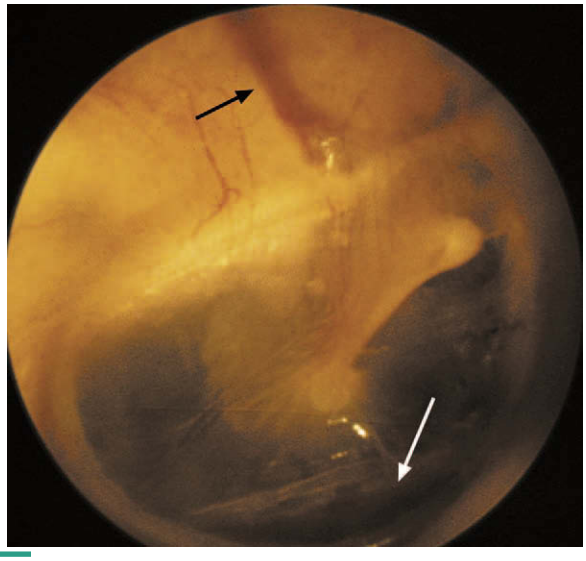

Figure 145-6. Otoscopic image that demonstrates a nondisplaced fracture along the scutum *(black arrow).* Blood is layering out inferiorly *(white arrow).*

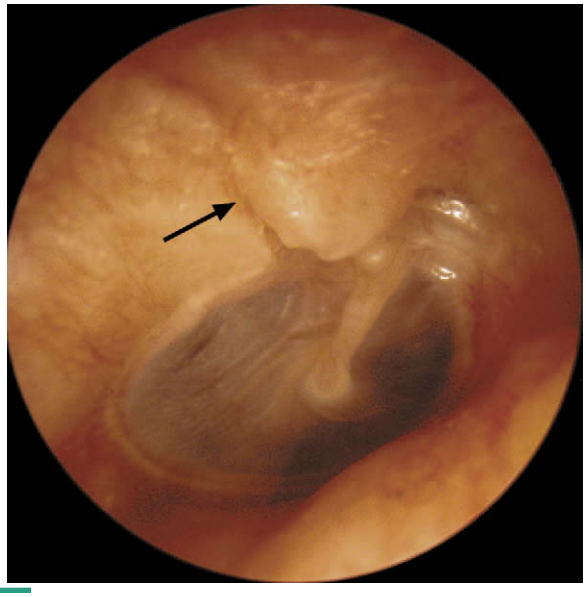

Figure 145-7. Otoscopic image that demonstrates a displaced fracture along the scutum *(black arrow).*

well as a much greater risk of intracranial injuries.[3,15] These fractures may also carry a higher risk of delayed meningitis due to an inability of the otic capsule enchondral bone to remodel and heal.[18,19] Pollak and colleagues[19] reported the case of a 51-year-old man who died of meningitis after having suffered an otic capsule–disrupting fracture during childhood. The histopathology of his temporal bone revealed pus in the middle ear extending through an unhealed fracture line across the otic capsule, and the fracture line contained a loose fibrous tissue. The membranous bone along the tegmen has the capability to heal, whereas the enchondral bone of the otic capsule does not. Fractures through the otic capsule generally partially fill with fibrous tissue and potentially seal with periosteal bone reaction on the surface of the otic capsule (Fig. 145-5).[19]

In addition to the predictive value for various complications and comorbidity, categorizing the fractures according to whether they are otic capsule sparing or disrupting guides the indications for surgical interventions for CSF fistula and facial paralysis as well as the surgical approach to be used in their repair.

Temporal bone fractures in the pediatric population differ somewhat from those in adults. There is a higher incidence of intracranial complications (58%) and a lower incidence of facial nerve paralysis (3%) in children.[20]

Evaluation

It is uncommon for temporal bone fractures to occur in isolation; consequently, the initial evaluation and management is focused on the emergent life-threatening issues of securing an airway, controlling hemorrhage, evaluating the neurologic status, and stabilizing and evaluating the cervical spine. The neurotologic examination assesses facial nerve function in the emergency department as early as possible, particularly before the administration of muscle relaxants, as discussed below. The ear examination focuses on the condition of the auricle, the ear canal, the tympanic membrane, and the middle ear.

The auricles are inspected for lacerations and hematomas. Lacerations are closed after thorough cleaning and débridement of exposed cartilage. Hematomas are drained, and pressure bolsters are sutured in place to close the dead space and prevent a recollection of blood. Untreated, the auricular hematomas result in an auricular chondropathy, which is also called "cauliflower ear."

The ear canal is inspected for fractures along the roof, CSF otorrhea, the degree of hemorrhage, and the presence of brain herniation. The ear is examined as aseptically as possible. Blood and cerumen in the ear canal should never be débrided with irrigation. After stabilization and transfer, the ear can be carefully examined with the aid of an operating microscope. Typical findings include fractures along the scutum and roof of the external auditory canal and tympanic membrane perforations. Hemotympanum or bloody otorrhea is almost invariably present (Figs. 145-6 to 145-8).

The ear canal is not packed initially unless packing is required to control significant hemorrhaging. If profuse hemorrhaging cannot be controlled with packing, the patient is taken to either the operating room for carotid ligation or the angiography suite for balloon occlusion.

When severely traumatized ear canals are identified, particularly in the presence of a penetrating injury, the patient is at high risk of stenosis or cholesteatoma formation. Although the ear canal is not stented acutely, it is imperative that the problem be identified and the patient followed closely. Early intervention with stenting at the onset of the stenosis can effectively prevent a problem that is much more difficult to address once the stenosis is mature.

The integrity of the tympanic membrane is assessed. Traumatic tympanic membrane perforations generally heal spontaneously; consequently no acute intervention is entertained.

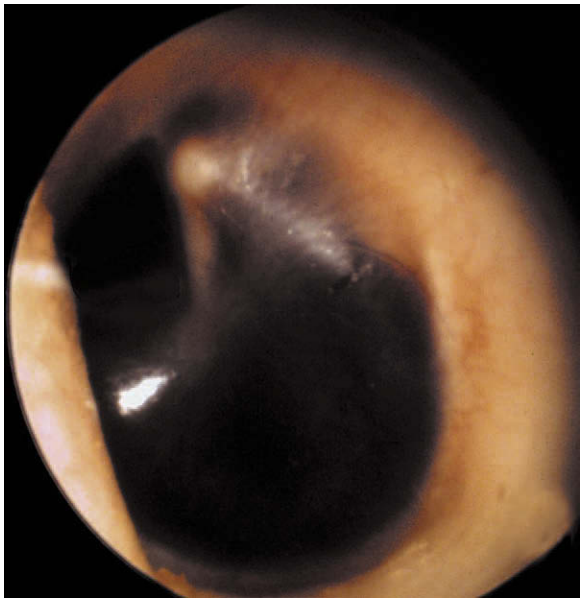

Figure 145-8. Otoscopic image that demonstrates a hemotympanum.

Figure 145-9. Otoscopic photograph that demonstrates a distracted fracture along the roof of the external auditory canal and scutum, thus allowing for the potential ingrowth of canal skin.

The neurotologic examination should also note the presence or absence of nystagmus and the type of nystagmus. Peripheral vertigo generally manifests with horizontal or rotatory nystagmus and is suppressible with visual fixation. Central vertigo may present with vertical or direction-changing nystagmus that fails to suppress and may even enhance with fixation. The most common type of vertigo after head trauma is benign paroxysmal position vertigo, which manifests with transient rotatory nystagmus with the Halpike maneuver.[21] The nystagmus occurs with the affected ear down. There is a 2- to 10-second latency followed by 10 to 20 seconds of rotatory nystagmus; the nystagmus is fixed in direction and is fatigable. Central vertigo induces direction-changing nystagmus, which has no latency and is not fatigable. Interestingly, the incidence of vertigo does not closely correlate with the severity of the trauma.[22]

The vast majority of posttraumatic vertigo cases resolve spontaneously. If the symptoms persist after discharge, an electronystagmogram can be obtained on an outpatient basis. A fistula test, which consists of applying positive and negative pressure in the ear canal with a pneumatic otoscope, is also not performed in the acute setting. The risk of additional iatrogenic injury and the potential for introducing infection or air into the inner ear outweighs the potential diagnostic benefits. If the patient continues to experience vertigo for 1 week after injury or is experiencing fluctuating or progressive hearing loss, a perilymph fistula is suspected, and a fistula test is performed. Nystagmus and vertigo suggest the presence of a perilymph fistula. The fistula test is not performed if there is evidence of a CSF fistula or of infection in the middle ear.

Hearing is assessed clinically at the bedside with a progressively louder whispered voice and with the use of tuning forks, but audiograms are not typically obtained until the patient's condition is stabilized. However, in the presence of the complications of facial paralysis or a CSF fistula, an audiogram is required before the surgical intervention, because the outcome of the audiogram significantly influences the treatment algorithm, as discussed later.

Patients with severe head trauma of the magnitude required for a temporal bone fracture generally already have had a computed tomography (CT) scan of the head to assess for intracranial hemorrhage. Additional imaging of the temporal bone with axial and coronal high-resolution CT scanning (HRCT) is indicated in the presence of facial paralysis, CSF fistula, disruption of the superior wall of the external auditory canal or scutum with potential trapping of epithelium (Fig. 145-9), or suspected vascular injury. HRCT of the temporal bone is also indicated if surgical intervention is required for the management of an otologic complication. Hearing loss (conductive or sensorineural) in the absence of other complications does not warrant additional temporal bone imaging. Demonstrating a transverse fracture through the otic capsule in a profound sensorineural hearing loss does not alter the treatment plan. Preoperative assessment with CT scanning in patients with a conductive hearing loss of sufficient magnitude to warrant exploration and ossicular reconstruction may provide useful information that may influence the surgical approach.

The role of HRCT in the evaluation of potential carotid artery injuries is unclear. Resnick and colleagues[23] reported a 5% incidence of carotid injury in basilar skull fractures if the fracture spares the carotid canal and an 18% incidence of carotid injury in patients with fractures through the carotid canal seen on HRCT. However, Kahn and colleagues[24] argues that, in an asymptomatic patient, HRCT demonstration of a fracture through the carotid canal yields no valuable additional information. Subsequent angiography performed in cases of asymptomatic carotid canal fractures yielded no evidence of carotid artery injury and provided no clinical utility.[24] Consequently, in completely asymptomatic patients who have sustained temporal bone fractures and who are neurologically intact, HRCT and angiography are not required. On the other hand, if there are any transient or persistent neurologic deficits in patients with basilar skull fractures, HRCT of the temporal bone and CT angiography are indicated (Fig. 145-10).

Conventional radiographs including Schüller, Towne, Chamberlain, Stenvers, and basal views as well as tomograms have been supplanted by HRCT scanning and no longer play a role in the evaluation of patients who are suspected of having a temporal bone fracture.

Management of Complications

The morbidity and mortality associated with temporal bone fractures result from injuries to the structures that pass through the temporal bone or that abut the temporal bone as described previously. The common complications include the facial nerve paralysis, sensorineural hearing loss, conductive hearing loss, CSF fistula, stenosis of the ear canal, cholesteatoma formation, and vascular injuries. The evaluation and management of these complications are discussed.

Facial Nerve Injury

Facial paralysis is a severely disfiguring complication of temporal bone fractures. Seven percent of temporal bone fractures result in facial paralysis; 25% of such cases involve complete paralysis.[3] The reported incidence in the literature of up to 30% is exaggerated by sampling error due to omitting simple uncomplicated temporal bone fractures that are not referred for otolaryngologic consult. The incidence of facial paralysis is also overestimated by including patients in retrospective

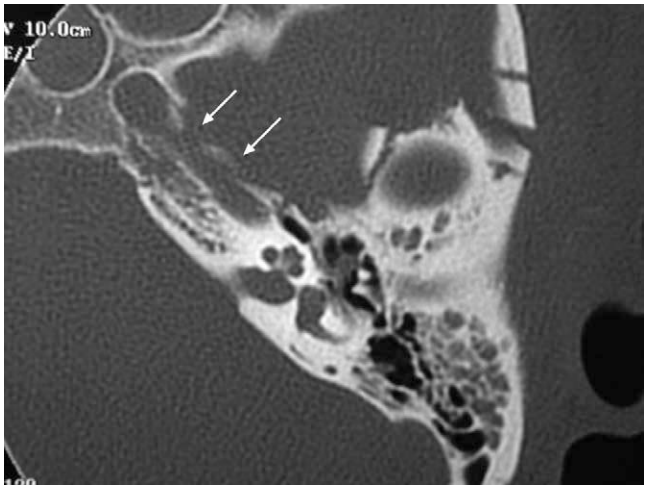

Figure 145-10. Axial-cut high-resolution computed tomography scan that demonstrates a fracture along the carotid canal. *White arrows* point to the fractured carotid canal.

reviews who have been referred to the tertiary care center for the management of complications of temporal bone fractures (e.g., facial paresis). Because the entire pool of temporal bone fracture patients is not included in the statistics, the incidence of complications becomes quite biased.

If head trauma patients are carefully evaluated in the emergency department upon admission (before the administration of muscle relaxants), 27% of the facial nerve injuries will present with immediate-onset facial paralysis. Seventy-three percent will have facial motion in the initial examination and subsequently deteriorate.[3] The latency of delay in onset of facial palsy ranges from 1 to 16 days. It is crucial to differentiate "delayed onset" from "delayed diagnosis." Delayed onset of facial paralysis is defined as documented facial function in the emergency department that subsequently deteriorates; delayed diagnosis of facial paralysis occurs when the patient is given a paralytic agent and is intubated before the examination of facial function. In this situation, an assessment of facial function is delayed until extubation. These patients should be categorized as *unestablished onset* and treated in a manner that is similar to the immediate onset patients. In one large series, 10% of patients fell into this unestablished onset category.[25]

Many aspects of the management of facial nerve injuries remain controversial. One of the main issues to be resolved is that of which patients should undergo surgical exploration. Because the vast majority of traumatic facial palsies resolve spontaneously, the choice of which patients should undergo exploration is based on prognostic factors for poor outcome. The factors that are assessed to predict the recovery of facial function include the timing of onset (delayed vs. immediate onset), the severity of the injury (penetrating vs. nonpenetrating), and the presence of associated infection.

The delay of onset of paralysis after temporal bone fracture is the most important of the predictive factors. In one series of 37 delayed-onset facial palsies, five were lost to follow-up, and the remainder recovered to a House-Brackmann grade I or II.[3] McKennan and Chole[26] described their experience with 17 patients with immediate-onset facial paralysis and 19 patients with delayed-onset paralysis. Complete spontaneous recovery of facial function occurred in 94% of the patients with delayed-onset paralysis; the one remaining patient had a House-Brackmann grade II recovery. By contrast, 8 of the 17 immediate-onset paralysis patients had facial nerve transsections.

Turner[7] reviewed a large series of traumatic facial paralysis patients who were treated conservatively. His paper included 36 immediate-onset and 34 delayed-onset facial palsies. Complete recovery occurred in 94% of the delayed-onset cases and 75% of immediate-onset cases. The one patient with delayed-onset paralysis who had no recovery of function developed the facial palsy coincident with acute otitis media. By contrast, Maiman and colleagues[27] found no correlation between immediate- or delayed-onset facial paralysis (treated nonsurgically) and outcome. However, 44 of 45 of their patients (including both immediate- and delayed-onset patients) had satisfactory recovery. Review of the literature argues strongly against surgical exploration and decompression of delayed post-traumatic and facial paralysis. The natural course of delayed facial paralysis is almost always the recovery of facial function to a House-Brackmann grade I or II. There are no convincing data in the literature that demonstrate that surgical intervention in delayed-onset paralysis will increase the probability of complete recovery of function.

May[28] describes the difficulty in differentiating immediate-onset from delayed-onset facial paralysis. He explored reported delayed-onset palsies and found, on occasion, a severed nerve; this observation highlights the necessity of careful examination in the emergency department. Even in comatose patients, painful stimuli generally induce a grimace. Admittedly information about the immediate facial nerve function is not always available. Sometimes the examination is omitted because attention is given to other life-threatening complications or because the patient has already received muscle relaxants with intubation. Some patients are not responsive to pain, and a grimace cannot be induced; the critical issue is whether or not any facial function has been identified. If facial function is present in the emergency department and subsequently deteriorates, our experience is that the patient will recover without surgical treatment. When reliable information from the emergency department is unavailable, the patient is never documented to have facial function, and the diagnosis of facial palsy is delayed by a few days, these cases must be categorized as "unknown onset" and considered as part of the immediate-onset group.

The degree of facial nerve injury is also a critical factor for guiding the management algorithm. Incomplete paresis rarely fails to resolve spontaneously unless an additional insult to the nerve, such as infection, occurs.[3] Consequently, only patients with complete paralysis of immediate or unknown onset are considered for surgical exploration.

The degree of the injury can be assessed not only clinically with facial motion but also with electrodiagnostic testing using the Hilger facial nerve stimulator, evoked electromyography (EEMG), and standard electromyography (EMG). The role of electrodiagnostic testing is to assist the clinician in differentiating a neuropraxic injury from a neural degenerative injury and to assess the proportion of degenerated axons. Nerves that have sustained a neuropraxic injury proximal to the stimulated portion of the nerve maintain electrical stimulability. Partial or complete disruption of the nerve results in wallerian degeneration and consequent decrease or loss of stimulability. However, the distal segment of the nerves maintains electrical stimulability for 3 to 5 days[29]; consequently, electrodiagnostic testing cannot reliably differentiate a neuropraxic injury from a laceration of the nerve for up to 3 to 5 days.

Sunderland[30] classified nerve fiber injuries into five categories. The first-degree injury is anatomically intact, with a conduction blockade (neuropraxia); these lesions tend to recover completely. The second-degree injury transects the axons but maintains an intact endoneurium (axonotmesis); these lesions also tend to resolve without subsequent deficits. The third-degree injury transacts the axon and endoneurium but maintains an intact perineurium (neurotmesis); aberrant regeneration can occur with third-degree injuries and leave patients with some weakness and synkinesis. Fourth-degree injuries transect the entire nerve trunk but maintain an intact epineural sheath (neurotmesis). Loss of the conduit of the epineural sheath allows regenerating axons to cross into adjacent fascicles, thereby resulting in a loss of topographic organization. A proportion of the regenerating fibers are also lost as a result of the healing process and scarring. These lesions result in a high incidence of residual weakness, synkinesis, and hyperkinesis. Complete transection of the entire nerve trunk and epineurium is classified as a fifth-degree injury (neurotmesis) and is associated with poor (if any) likelihood of spontaneous recovery, depending on the degree of diastasis of the nerve ends.

The Hilger facial nerve stimulator is used to perform both the minimal nerve excitability test (NET) and the maximal stimulation test (MST). The facial nerve is stimulated percutaneously adjacent to the stylomastoid foramen and the various distal branches. In NET, the current is increased until the threshold is reached, which is manifested

with facial twitching. A threshold difference of 3.5 mA or greater between the affected and nonaffected sides of the face suggests significant neural degeneration. The test is most useful between days 3 and 14 after injury in patients with dense facial paralysis to differentiate between neuropraxic and degenerative injuries. The testing is unnecessary in incomplete paralysis, in which there is almost always 100% recovery.

May and colleagues[31] argue that the MST provides a more reliable estimation of the degree of degeneration. In the MST, stimulation is performed similar to the way it is for NET, but the intensity of the stimulus is increased until the amount of facial contraction plateaus or is limited by patient intolerance. The degree of contraction is subjectively assessed by the physician and compared with electrical stimulation of the unaffected side of the face. The difference in contraction is expressed as equal, mildly decreased, markedly decreased, or no response; the latter two categories are associated with poorer prognosis. Much like NET, MST is most useful between days 3 and 14 after injury in patients with dense facial paralysis.

EEMG has been popularized by Fisch[32] in a version called electroneuronography (ENoG). ENoG differs from EEMG only in the use of bipolar stimulating and recording electrodes. Both techniques measure the evoked compound muscle action potential (CAP) and provide similar information to the MST, but in an objective fashion. The stimulating electrode is placed adjacent to be stylomastoid foramen, and the recording electrode is placed in the nasolabial crease. The diminution in the amplitude of the CAP is indicative of the percentage of degenerated nerve fibers. EEMG has been demonstrated to be the most accurate electrodiagnostic test for prognostic information.[33] Fisch[34] reported that patients in whom the degeneration on EEMG reaches 90% within 6 days of onset of traumatic facial paralysis have a poorer outcome and consequently should undergo facial nerve decompression. Sillman and colleagues[35] demonstrated a significant association between a CAP decline of more than 90% and poor recovery of function for idiopathic paralysis, but they demonstrated no significant association between a CAP decline of more than 90% and clinical outcome in traumatic paralysis.

The value of EMG for the acute management of traumatic facial paralysis remains controversial. Standard monopolar EMG is performed with the insertion of an EMG electrode into the muscle, and the spontaneous electrical activity is then recorded. Two types of information are obtainable: voluntary activity and fibrillation potentials. If voluntary activity is present during the acute postinjury period, the patient has a very high probability of good recovery.[35] However, May and colleagues[36] reported only 75% accuracy for predicting a poor recovery and 62% accuracy for predicting a favorable result. Fibrillation potentials result from denervation of the muscle but are delayed for 2 to 3 weeks after the injury and consequently offer little additional information in the acute setting.

After defining the at-risk population for poor recovery of function, the next question to address is whether surgical intervention alters the outcome. In 1944, Turner[7] reported about 69 patients with varying degrees of facial paralysis after temporal bone trauma. Thirty of these patients had complete facial paralysis, and all were treated nonoperatively. This group of patients was unbiased in that none of this series underwent surgical decompression. Good recovery occurred in 63% of the patients, incomplete recovery with synkinesis in 23%, and poor recovery in 13%. Maiman and others[27] reported on the outcome of 21 patients with posttraumatic complete facial paralysis. Full recovery occurred in 52% of the patients and incomplete recovery in 43%; one patient had a poor outcome. Brodie and Thompson[3] studied eight patients with complete paralysis who met the criteria for facial nerve decompression and who, for a variety of reasons, did not undergo surgical exploration. Seven of the eight patients had good recovery of function, and one patient had a poor outcome. The combined rate of good recovery of function in the aforementioned three studies is 63%. The outcomes for patients who underwent facial nerve decompression in various series, as well as for those who received conservative management, are summarized in Table 145-1.[3,7,25,27,37-39]

The combined rate of good recovery of facial function after decompression was 39%; this figure excludes severed facial nerves. It is difficult to compare the results of recovery of facial nerve function of patients who have undergone surgical versus nonsurgical management. The criteria to be included in the surgical groups were that the nerves were no longer stimulable or that they demonstrated more than 90% degeneration within 6 days or 95% degeneration within 14 days. The patients included in the observation studies did not necessarily meet these same criteria. In an extensive review and analysis of the literature by Chang and Cass,[40] the authors concluded that there are no studies that prove or disprove the efficacy of facial nerve decompression.

Because wallerian degeneration is not documented on electrodiagnostic testing for 3 to 5 days after the neurotmesis, surgical intervention is delayed until several days after the nerve has degenerated. Although decompression of the facial nerve prophylactically in acoustic neuroma surgery has been proved to be efficacious, the decompression is performed before wallerian degeneration has occurred.[41] Demonstrating that decompression of a posttraumatic, nonsevered nerve is efficacious remains to be proven in a randomized, prospective study.

The key factor in the decision to surgically explore a facial nerve is whether the nerve is suspected of being severed, crushed, or impaled with bone fragments. The incidence of transected nerves in the large series ranges from 6% to 45%.[17,25,37,38,39] The high frequency of severed nerves in some of these reports is biased by patient selection. Patients are referred to the tertiary centers that perform nerve explorations when they fail to spontaneously recover. However, the vast majority of patients do recover spontaneously and are not referred to tertiary centers.

The probability of severing the facial nerve is quite low, but the outcome after observation alone of a transected nerve is poor. Because one cannot differentiate a Sunderland fifth-degree injury (severed nerve) from a third- or fourth-degree injury on the basis of electrodiagnostic testing, exploration is warranted only in patients with complete immediate-onset paralysis in whom electrical stimulability is lost; these are the patients at risk for crushed, partially severed, and transected nerves.

The site of injury of the facial nerve in temporal bone fractures is in the perigeniculate region in 80% to 93% of patients.[17,37,39] Lambert and Brackmann[39] found a second lesion in the mastoid segment of 4 of 21 patients; thus the approach used for the nerve exploration must expose these regions. Fisch[34] advocates a translabyrinthine approach for transverse fractures and a combined transmastoid/middle cranial fossa approach for longitudinal fractures. May[42] described a transmastoid/supralabyrinthine approach to the region of the geniculate ganglion for facial nerve decompression. Goin[43] studied this approach in cadaveric temporal bones and found that he could consistently expose the distal labyrinthine segment and the geniculate ganglion; however, the fundus of the internal auditory canal (IAC) could be exposed in only 60% of the temporal bones. Yanagihara[44] applied the transmastoid/supralabyrinthine approach in 36 patients; only five temporal bone fractures in his series of 41 patients required a middle cranial fossa approach to expose the geniculate region.

The translabyrinthine approach is advocated for facial nerve exploration in patients with profound hearing loss. The approach provides excellent exposure for decompression, nerve rerouting with direct reanastomosis, and cable grafting. In otic capsule–sparing fractures with ossicular discontinuity, the nerve is explored via a transmastoid/supralabyrinthine approach. This approach generally requires the dislocation of the incus and ossicular reconstruction at the completion of the operation. If the patient has any contralateral hearing loss or the anatomy is not conducive for supralabyrinthine exposure, a middle cranial fossa approach is used.

Timing of facial nerve repair has, in the past, been controversial. McCabe[45] advocated repairing the nerve within the first 3 days or else delaying facial nerve reanastomosis for 20 days after injury; this recommendation was made on the basis of the observation that regeneration and axoplasmic flow were greatest at 3 weeks after injury. Barrs[46] studied the timing of facial nerve repair in micropigs and found no advantage in waiting the 3 weeks until the neuronal cell body metabolic activity was maximal.

Fisch[47] advocates exploration when the ENoG indicates that 90% degeneration has occurred within 6 days, and he argues that decompres-

Table 145-1

Facial Nerve Outcome Following Complete Facial Paralysis

Treatment	*n*	Good (HB I or II)	Incomplete (HB III or IV)	Poor (HB V or VI)	Transected Nerve
Nonoperative					
Turner[7]	30	19	7	4	
Maiman[27]	21	11	9	1	
Brodie[3]	8	7	0	1	
Operative					
Kamerer[38]	62	18	15	9	20
Lambert[39]	17	11	0	0	6
Coker[37]	12	5	4	1	2
Brodie[3]	6	4	0	2	0
Darrouzet[25]	65	25	35	5	9

HB, House-Brackmann grade.

sion should be performed early to minimize further degeneration. May also advocates early exploration[28]; his series demonstrated a correlation of best results with a shorter interval between injury and repair.

Late exploration for potentially severed nerves is still indicated, but the role of late decompression remains controversial. Quaranta and others[48] reported on nine patients who underwent facial nerve decompression 2 to 3 months after their temporal bone fractures. Seventy-eight percent recovered to a House-Brackmann grade I or II at 1 year after decompression; the question regarding whether these patients would have recovered spontaneously to the same degree remains unanswered. Clearly, if the nerve was severed and not approximated, spontaneous recovery to a House-Brackmann grade I or II would not occur. In that scenario, a House-Brackmann grade VI would be anticipated.

The range in latency to recovery of facial function varies from 1 day to 1 year. Fifty-nine percent of facial palsies that recover spontaneously do so within 1 month after injury, and 88% recover by 3 months after injury.[3]

Summary of Facial Nerve Treatment Algorithm

Patients with delayed-onset facial paralysis are placed on a 2-week course of systemic corticosteroids (unless medically contraindicated) and observed. Although there are inadequate data in the literature to support or contradict this recommendation, the rationale for corticosteroid use is based on its antiinflammatory activity and the assumption that neural edema is a primary factor in the progression of neural injury (Fig. 145-11).[40] Patients with complete paralysis of immediate onset are tested with the Hilger nerve stimulator between days 3 and 7 after injury. If no loss of stimulability occurs, the patients are observed. If the nerve loses stimulability within 1 week of the injury, facial nerve exploration is performed.

Facial nerve injuries that occur in an otic capsule–disrupting fracture are explored via a translabyrinthine approach; for otic capsule–sparing fractures, two surgical approaches are used. In patients with well-aerated mastoid air cell systems or with ossicular discontinuity, a transmastoid/supralabyrinthine approach is chosen. If the patient has a poorly aerated mastoid air cell system or total facial nerve decompression cannot be achieved via the transmastoid/supralabyrinthine approach, a combined transmastoid/middle cranial fossa approach is used. If a severed facial nerve is encountered using the transmastoid/supralabyrinthine approach and inadequate exposure for cable grafting occurs, a middle cranial fossa approach is performed.

The transmastoid facial nerve decompression begins with a complete mastoidectomy and the skeletonizing of the tegmen mastoideum superiorly, the sigmoid sinus posteriorly, and the posterior external auditory canal (EAC) wall anteriorly. The antrum is opened, thus exposing the short process of the incus and the lateral semicircular canal. The semicircular canals are then skeletonized. The facial recess is opened, and the facial nerve is skeletonized from the second genu to the stylomastoid foramen. If there is any evidence of bony trauma in this region, a complete decompression is performed; however, the nerve sheath is not incised. The buttress to the incus is subsequently removed, and the tympanic portion of the nerve is decompressed. If there is adequate room to proceed, a supralabyrinthine decompression of the intralabyrinthine portion of the facial nerve is performed (Fig. 145-12). A laceration of the facial nerve in this region is cable grafted with a section of the greater auricular nerve. The cable graft is placed in the bony channel of the fallopian canal, abutting the sharply incised edges of the facial nerve. To improve exposure, the eggshelled tegmen can be retracted superiorly.

If the exposure remains inadequate, a middle fossa craniotomy is performed. If the fracture involves the proximal portion of the intralabyrinthine segment of the facial nerve, a middle fossa craniotomy is performed.

The squamosal portion of the temporal bone is exposed by extending the postauricular skin incision in a "lazy S" shape up toward the vertex, first extending anteriorly, then posteriorly. The temporalis fascia is reflected inferiorly, and the temporalis muscle is split vertically and elevated off of the squamosal portion of the temporal bone. The dissection should extend underneath the zygomatic arch to allow for adequate exposure for the craniotomy. The self-retaining retractors are adjusted to hold both muscle and skin. A bone window is created with a 5- or 6-mm cutting burr and suction irrigation. This bone window is 4 by 4 cm in size and is set at the level of the zygomatic root. Two thirds of the window is anterior to the vertical plane of the EAC, and the other third of the window is posterior to the canal. A rongeur is used to remove the bone at the inferior edge of the craniotomy down to the level of the floor of the middle cranial fossa; this allows for the optimal surgical line of site, with minimal temporal lobe retraction. The House-Urban middle fossa retractor is engaged, with the prongs in the edge of the craniotomy. The blade is gradually advanced as the dura is elevated off of the floor of the middle fossa. It is common to encounter dural venous bleeding at the anterior extent of the dissection; this can usually be controlled with a hemostatic agent (e.g., Surgicel, Johnson & Johnson).

The landmarks in the middle fossa are the middle meningeal artery at the foramen spinosum, the greater superficial petrosal nerve at the facial hiatus, and the arcuate eminence. The geniculate ganglion may be exposed without a bony covering on the floor of the middle cranial fossa, so care should be exercised during dural elevation. The fracture line and hematoma are generally encountered in the region of the facial hiatus. The landmark for the superior semicircular canal is the arcuate eminence, but the precise location of the canal does not uniformly correspond with the arcuate eminence. A coronal CT scan may be helpful for ascertaining the relationship between the two; it will show the contours of the middle fossa floor as they relate to the superior semicircular canal and the distance between the superior semicir-

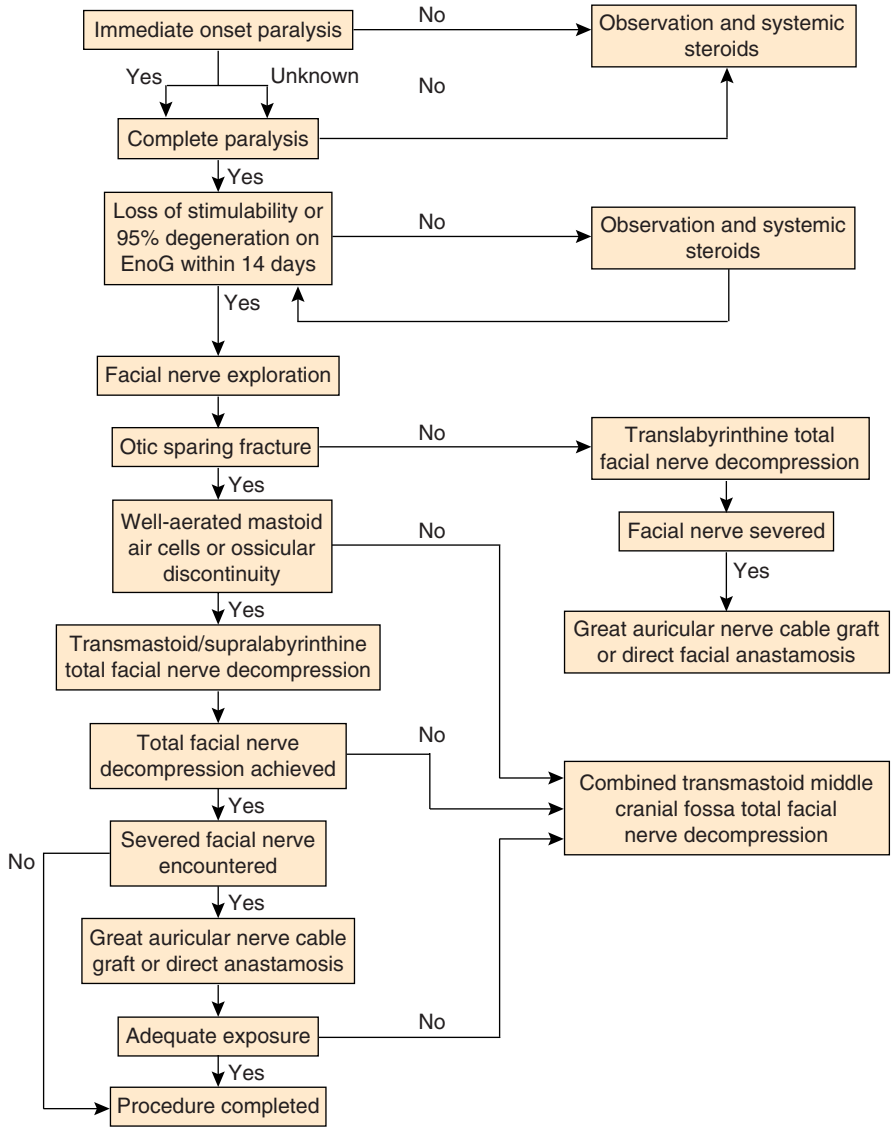

Figure 145-11. Management of traumatic facial paralysis.

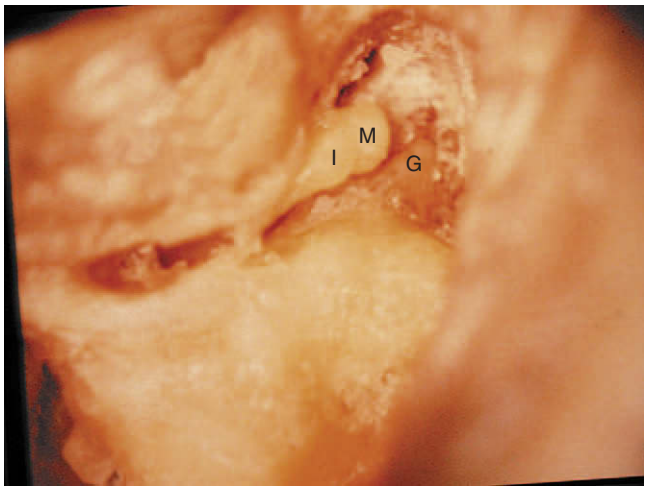

Figure 145-12. Supralabyrinthine exposure of the geniculate ganglion and the intralabyrinthine portion of the facial nerve. I, Incus; M, malleus; G, geniculate ganglion.

cular canal and the floor of the middle cranial fossa. The canal may have very little bone coverage, it may be seen as a blue line after simple dural elevation, or there may be a large number of air cells between the canal and the surface of the tegmen.

If the superior semicircular canal cannot be located by drilling over the arcuate eminence, two other methods may be considered. First, the tegmen tympani may be opened, thus exposing the ossicles. The location of the superior semicircular canal can be established by the spatial relationships. Second, the greater superficial petrosal nerve can be followed retrograde back through the facial hiatus to the geniculate ganglion. The intralabyrinthine portion of the facial nerve passes between the cochlea and the ampulla of the superior semicircular canal. The bone over the superior semicircular canal is removed using suction irrigation and diamond burrs.

A light medial to lateral stroke is used until the blue line of the superior canal is identified. After the superior canal has been identified, dissection proceeds along the meatal plane, which is the bone within a 60-degree angle from the blue line of the superior canal. Drilling within the confines of this plane will reduce the risk of inadvertent injury to the cochlea. Note that much wider drilling may be performed medially, whereas, at the lateral extent of the IAC, there is very little space between the cochlea and the ampulla of the superior semicircular canal.

The burr should hug the line of the superior canal as bone removal progresses. The dissection will appear to be quite deep before the IAC is encountered. Bone should be removed 180 degrees around the IAC, from the lateral aspect of the meatus to the porus acusticus. An eggshell thickness of bone should be left over the IAC. The last steps in the exposure of the canal are careful removal of this bone and copious irrigation to remove bone dust.

At the most lateral extent of the IAC, the vertical crest (also known as Bill's bar) is identified, with the facial nerve anteriorly and the superior vestibular nerve posteriorly. The dura of the IAC is incised in a longitudinal fashion, along the posterior edge, away from the facial nerve. If the facial nerve is lacerated, the proximal edge is freshened with microscissors. The nerve graft is secured proximally with a single 9-0 nylon suture and distally placed into the bony channel of the tympanic portion of the fallopian canal. A piece of temporalis muscle is placed in the bony defect, and the pedicled temporalis fascia flap is reflected over the floor of the middle cranial fossa. The bone flap is returned to its original position and the temporalis muscle is closed superiorly.

Cerebrospinal Fluid Fistulas

CSF fistulas and the potential for meningitis are among the most serious complications of temporal bone fractures, occurring in 17% of such fractures.[3] CSF fistulas in otic capsule–sparing fractures typically occur through the floor of the middle cranial fossa (tegmen tympani and tegmen mastoideum) and into the epitympanum, antrum, and mastoid air cell tract. The CSF flows out of the ear canal if the tympanic membrane is disrupted or into the eustachian tube, which results in CSF rhinorrhea. In otic capsule disrupting fractures, CSF flows from the posterior cranial fossa through the disrupted otic capsule into the middle ear.

The onset of CSF leakage following trauma was delayed for more than 1 week in 28% of the 192 cases surveyed by Lewin.[49] It has been theorized that the delays in CSF leakage result from either of the following: (1) herniation of dura or a brain fungus into the bony defect created by the trauma or surgery, or (2) a hematoma obstructing the outlet of the CSF flow. Eventually the CSF leaks as a result of separation of the fibers in the dural herniation, atrophy of the brain fungus, increased intracranial pressure subsiding with retraction of the herniation, or resolution of the occluding hematoma. The CSF fistula will continue to leak until fibroblastic proliferation creates a fibrous barrier that closes the subarachnoid space or the sinus or air cell mucosa covers the bony defect.[50] However, during the early stages of repair, the fibrous barrier is weak and the mucosal barrier remains fragile. If the CSF pressure gradient is greater than the healing tensile strength of these vulnerable barriers, the leak will continue. The newly formed barrier may be ruptured by nose blowing or straining.[51] A unique characteristic of a fracture through the otic capsule is the absence of healing. The otic capsule is adult size at birth and undergoes minimal remodeling throughout life.[52] After a fracture, fibrous tissue will partially fill the crevice, and the adjacent periosteal bone may seal off the fracture, but the enchondral bone itself will not heal. The potential tract places the patient at continued risk of delayed meningitis.

A CSF fistula is suspected when clear watery drainage is noted in the ear canal or from the nose. Otorhinorrhea often drains down the back of the throat, and the rate of flow of the discharge usually increases with exertion or leaning forward. Consequently, when evaluating a patient for a suspected CSF fistula, the patient is asked to lean forward with the neck flexed, and nasal discharge is collected into a sterile container. Patients often complain of headaches that are dull, continuous, and bilateral. The origin of aural and nasal drainage is often obscured by concurrent bleeding or by the lysis of an old blood clot. If a nasal discharge is suspected of being CSF, it can be differentiated from watery rhinitis, lacrimal secretions, or serosanguineous discharge on the basis of its composition. CSF has elevated glucose, less protein, and less potassium than nasal secretions. Qualitative tests, such as those that involve the use of glucose oxidase test strips, have been shown to lack specificity and result in a substantial proportion of false-positive results.[53] Quantitative glucose, protein, and potassium determinations are more accurate for the diagnosis of a CSF fistula.

A noninvasive technique for identifying and localizing a CSF fistula using protein electrophoresis for β_2 transferrin was first described by Meurman and colleagues.[54] β_2 transferrin is specific for CSF. In addition to being noninvasive, a major advantage of this technique is the small amount of CSF required for the test (50 μL).

HRCT generally demonstrates the potential sites of a CSF fistula. When a fracture is seen but the exact site of the fistula has not been identified, CT cisternography with intrathecal contrast (Omnipaque, Amersham Health Inc., Princeton, NJ) can be useful. HRCT shows bony defects in 70% of patients with a CSF fistula.[55] When a defect cannot be demonstrated by HRCT, CT cisternography or radionuclide cisternography may (rarely) detect a site of leakage.[55] Radionuclide scans tend to lack sensitivity and specificity.

Intrathecal fluorescein is a sensitive and specific test for investigating the presence of a CSF fistula. After a lumbar puncture, 0.5 mL of a 5% solution of fluorescein is mixed with 10 mL of the patient's CSF and reinjected. The otorrhea or rhinorrhea can be collected on micropledgets and examined under a Wood's lamp for green fluorescence. Although occasional reports of neurotoxicity (e.g., paraparesis, grand mal seizures) after the intrathecal injection of fluorescein appear in the literature, these complications were infrequent, occurred at higher doses of fluorescein than are currently recommended, and have not resulted in permanent damage.[51,56,57] No persistent side effects or complications have been reported with the current recommended dosing. Fluorescein is frequently successful for localizing fistulas when all other methods have failed.[57-59] Therefore, the continued use of fluorescein may be justified, and the risks of increased morbidity following failure to locate a CSF fistula preoperatively may outweigh the risks involved with its use. None of the localizing techniques are useful if the CSF leak is quiescent at the time of the test.

The incidence of meningitis in patients with CSF leaks ranges from 2% to 88%.[3,51,60-63] The wide range in incidence is a result of multiple factors, the most significant of which is the duration of leakage.[51,60,61,64] Mincy[61] and Leech and Patterson[60] compared the incidence of meningitis in patients with CSF leaks that lasted 7 days or less with those persisting for more than 7 days. Leech and Patterson found only a 5% incidence of meningitis in patients with CSF fistulas of less than 7 days' duration, and Mincy reported a similarly low incidence of 11% in his group. The incidence of meningitis in patients with leakage for more than 7 days in Leech and Patterson's series was 55%, and it was 88% in Mincy's series. Spetzler and Wilson[64] demonstrated a 33% incidence of meningitis in persistent fistulas, and Grahne[51] found that meningitis developed in 54% of his patients with chronic CSF leakage.

Many studies over the past 25 years have demonstrated no benefit of prophylactic antibiotics for temporal bone fractures in the absence of CSF fistulas.[60,62,65-71] The incidence of meningitis in this group is quite low. Rathore[72] pooled the data from many of these studies and found a 4% incidence of meningitis in patients with basilar skull fractures receiving prophylactic antibiotics and a 3% incidence in patients not receiving prophylactic antibiotics. Brodie and Thompson[3] demonstrated a 1% incidence of meningitis in 578 patients with temporal bone fractures and no CSF fistulas. Hoff and colleagues[65] conducted a prospective randomized trial that assigned patients with temporal bone fractures into a prophylactic antibiotic treatment group or to a no antibiotic group; meningitis did not develop in any patient in either group. All of these studies conclude that prophylactic antibiotics are not indicated given the low incidence of meningitis in temporal bone fractures without a CSF fistula and the lack of evidence demonstrating any benefit of prophylactic antibiotics in this situation. However, the risk of meningitis is significantly higher in patients with temporal bone fractures when CSF fistulas are present; consequently, the role of prophylactic antibiotics must be examined in relation to this subset of trauma patients. Multiple studies over the past 3 decades have concluded that prophylactic antibiotics did not have a statistically significant effect on the incidence of meningitis in patients with CSF fistulas.[62,64,66,68,71,73] However, the number of patients included in the various studies was inadequate for valid statistical analysis. Re-evaluation of the literature from the past 25 years in two independent meta-analyses revealed conflicting results. In the first study, a statistically significant reduction in meningitis using prophylactic

antibiotics in patients with CSF fistula was demonstrated. Three hundred and twenty patients were included in the analysis.[74] The incidence of meningitis in patients with posttraumatic CSF fistulas treated with prophylactic antibiotics was 2.1%. In patients who did not receive prophylactic antibiotics, the incidence of meningitis was significantly higher, at 8.7% ($P < .02$). Individually, however, none of the studies included in the metaanalysis demonstrated a statistically significant effect of prophylactic antibiotics, which points out the pitfall of statistical analysis with inadequate numbers of patients. In a second study, no statistically significant effect of antibiotic prophylaxis was demonstrated.[75] The problem with this second analysis is the inclusion of one study that reported on patients whose fistulas persisted for weeks to months.[76] In the meta-analysis,[75] 20 of 29 patients in whom meningitis developed while on prophylactic antibiotics were in this one study,[76] which permitted this very long duration of leakage.

In addition to the inadequate numbers of patients in these prior studies, there are significant problems inherent in this type of retrospective study. How do we define adequate prophylaxis? Do 3 days of perioperative antibiotics for the repair of a concomitant open femur fracture constitute adequate prophylaxis for a CSF fistula that persists for 5 days? Do therapeutic antibiotics for a concurrent infection constitute adequate prophylaxis for a CSF fistula? One very important risk factor that increases the risk of meningitis in patients with CSF fistulas is the presence of a concurrent infection. Brodie and Thompson[3] found a 20% incidence of meningitis in patients with concurrent infection and a 3% incidence of meningitis in the absence of concurrent infection. In that study, in the absence of concurrent infection, meningitis did not develop in any patient receiving prophylactic antibiotics the first month after injury. Clearly these confounding variables must be controlled in a prospective, multi-institutional study to adequately address the question of the efficacy of prophylactic antibiotics.

The most common infecting organisms in meningitis that occur in the presence of a CSF fistula are *Streptococcus pneumoniae* and *Haemophilus influenzae*.[62,77,78] Fifty-seven percent to 85% of post-traumatic fistulas that are treated conservatively cease leaking within 1 week.[49,61] Because acute posttraumatic CSF fistulas are associated with a high probability of early spontaneous closure and a low incidence of meningitis, they can be treated conservatively for 7 to 10 days; this treatment includes total bed rest with elevation of the head of the bed; stool softeners; instructions to avoid nose blowing, sneezing, and straining; and repeat lumbar punctures or lumbar drain if the leak persists. These measures are directed at maintaining the CSF pressure gradient below the healing tensile strength of the healing barrier. Because of the increased risk of meningitis after persistent CSF fistulas, the closure of fistulas that persist for more than 7 to 10 days is recommended.

Closure of CSF Fistulas

The treatment algorithm for CSF fistulas is presented in Fig. 145-13. In a patient with a fracture of the otic capsule that results in profound sensorineural hearing loss, obliteration of the mastoid and middle ear is recommended.[79,80] The ear canal, the tympanic membrane, the incus and malleus, and the middle ear mucosa are all excised. The external auditory meatus is closed in a two-layer closure, and a complete mastoidectomy is performed. The mucosa of the eustachian tube is inverted, and a muscle plug is inserted. The incus is then inserted as well, wedging the muscle into place. The eustachian tube and the fracture

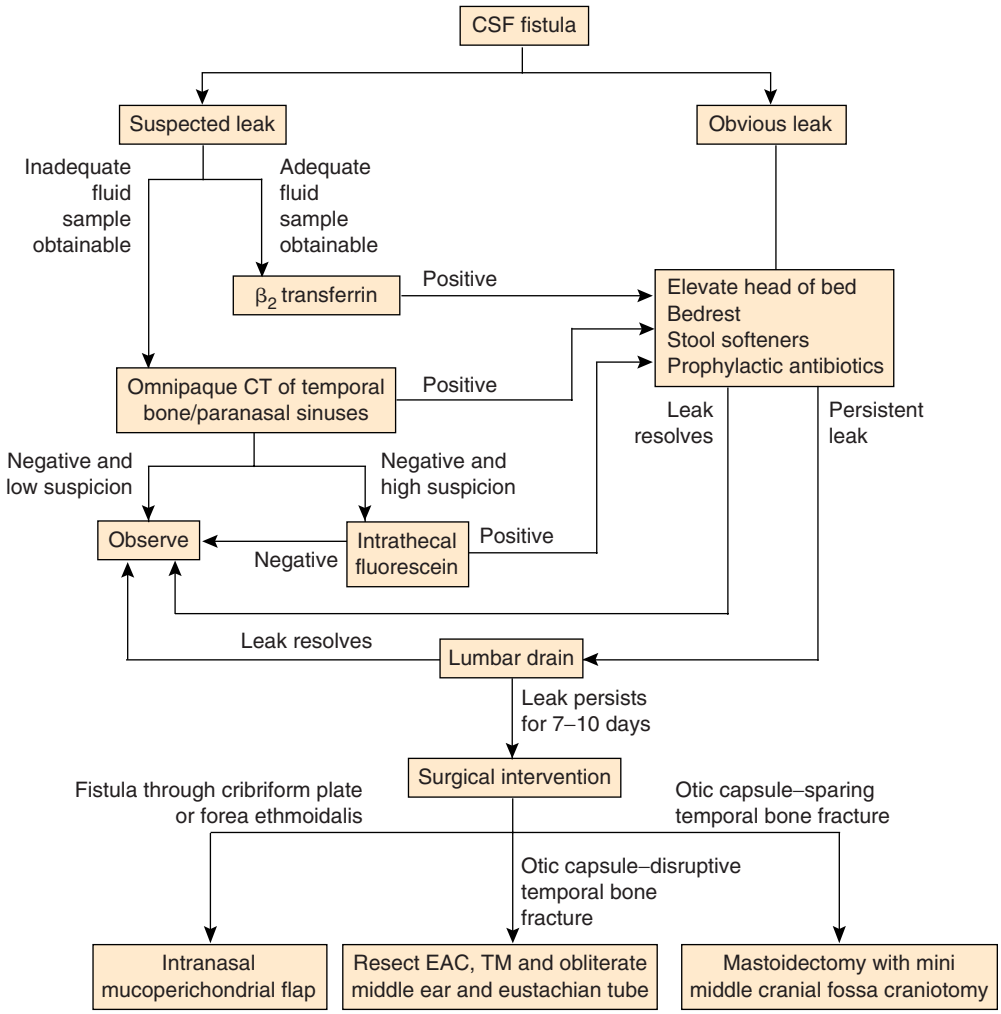

Figure 145-13. Management of traumatic cerebrospinal fluid (CSF) fistula. EAC, external auditory canal; TM, tympanic membrane.

line are covered by temporalis fascia, and the mastoid cavity and middle ear are obliterated with an abdominal fat graft.

The approach for the closure of a fistula that results from an otic capsule–sparing fracture is dictated by the location of the fracture along the floor of the middle cranial fossa, the presence of brain herniation, and the status of the ossicular chain. Fistulas that occur laterally in the middle cranial fossa are accessible through a complete mastoidectomy and can be repaired by sealing the mastoid cavity off from the epitympanum and middle ear by placing a temporalis fascia graft over the antrum, the facial recess, and the retrofacial air cell tracts. A second fascia graft is placed over the fistula, and the mastoid cavity is obliterated with a fat graft. Fistulas that occur more medially along the tegmen tympani or that are associated with brain herniation are addressed with a combined approach. When the temporal lobe herniates through the tegmen, the damaged brain is débrided via the transmastoid approach, and the remaining brain and dura are elevated back up into the middle fossa via the middle fossa craniotomy. Temporalis fascia is placed over the floor of the middle cranial fossa. If a bony defect is present in the tegmen, the craniotomy bone window is split or thinned with a burr and placed along the floor of the middle cranial fossa superior to the fascia to prevent subsequent prolapse. A piece of Gelfilm is inserted through the mastoid cavity and antrum and placed over the top of the ossicles in the epitympanum to avoid adhesions and postoperative conductive hearing loss.

In the case of a fistula through the tegmen tympani in a patient with an ossicular discontinuity and the absence of brain herniation, the fistula can often be closed via a transmastoid approach alone. A tragal cartilage graft is inserted superior to the superior EAC wall and extending to the tympanic portion of the facial nerve. The cartilage graft seals off the epitympanum and prevents the herniation of tissue into the middle ear. The epitympanum is filled with a temporalis fascia graft.

Additional techniques have been advocated by other authors. Glasscock and colleagues[81] have advocated an intradural as opposed to an extradural approach for large defects, arguing that a better closure can be achieved intradurally. Kveton and Goravalingappa[82] reported on the successful closure of 13 cases of CSF leakage using hydroxyapatite cement through a transmastoid approach. This approach is highly successful for closing CSF leaks that follow the translabyrinthine removal of acoustic neuromas, but care must be taken in traumatic CSF leaks, where the field is much more contaminated. Placement of a foreign body in a potentially contaminated wound increases the chance of infection. One of the other potential complications of the closure of tegmen CSF fistula with hydroxyapatite cement is conductive hearing loss, which may occur if any of the cement migrates to the ossicular chain.

There is a high risk of EAC stenosis and cholesteatoma formation when the ear canal is severely traumatized as is seen with gunshot wounds to the temporal bone.[83,84] In this situation, the CSF fistulas are generally closed, with resection of the EAC and tympanic membrane and obliteration of the mastoid and middle ear as described previously. Extreme care is taken to avoid leaving any fragments of epithelium that may subsequently lead to cholesteatoma formation. All mucosa is removed, and the eustachian tube and external meatus are closed as described previously.

Hearing Loss

Temporal bone trauma can cause conductive hearing loss, sensorineural hearing loss, or mixed loss. Otic capsule–sparing fractures extend along the roof of the EAC, often tearing the tympanic membrane in the region of the notch of Rivinus. The fracture proceeds along the tegmen tympani, and, in 20% of patients, disrupts the ossicular chain.[8] The most common injuries to the ossicular chain are separation of the incudostapedial joint (82%), dislocation of the incus (57%), and fracture of the stapes crura (30%) (Fig. 145-14).[85] The majority of stapedial fractures do not occur in isolation but rather are associated with incus dislocations.[8] Fixation of the ossicles in the epitympanum (25%) and fracture of the malleus (11%) occur less frequently.[85] One third of patients have multiple middle ear problems.

Almost universally, patients with temporal bone fractures experience a hemotympanum with associated conductive hearing loss. Over

Figure 145-14. Dislocated incus protruding through the tympanic membrane.

a few days to a few weeks after injury, the middle ear will re-aerate, with resolution of the hearing loss attributable to the middle ear fluid. Factors that increase the duration of the middle ear fluid include endotracheal intubation, associated craniofacial fractures, and the presence of a CSF leak. Eighty percent of cases of conductive hearing loss resolves spontaneously without the need for surgical intervention.[86] Residual conductive hearing loss following resolution of the hemotympanum and healing of the tympanic membrane suggests the possibilities of ossicular fracture or discontinuity. The indication for exploratory tympanotomy and ossicular reconstruction is conductive hearing loss of more than 30 dB that persists for more than 2 months after injury. However, if the conductive hearing loss is in the only hearing ear, then surgery is contraindicated. The audiogram of a mixed hearing loss must be critically assessed to establish the true potential benefit of ossicular reconstruction. If the bone conduction thresholds are more than 30 dB worse than in the contralateral ear, reconstruction—even with an excellent closure of the conductive component of the hearing loss—will provide minimal subjective improvement. In this scenario, the patient would still require a hearing aid to attain usable hearing in the surgical ear. Consequently, unless the mixed loss is profound and the patient cannot benefit preoperatively from a hearing aid, ossicular reconstruction is not recommended.

The most conducive injury for ossicular reconstruction is a dislocation of the incudostapedial joint. In this situation, an Applebaum hydroxyapatite prosthesis is inserted between the long process of the incus and the capitulum of the stapes and generally results in near closure of the air-bone gap. Dislocation of the entire incus requires bridging the gap between the stapes suprastructure and the manubrium of the malleus. A sculpted incus interposition graft is preferred. Partial ossicular replacement prostheses are also available. Incus interposition is accomplished by drilling a cup in the end of the short process of the incus that will fit over the capitulum of the stapes. The long process of the incus is removed and the body sculptured with an articular surface that will fit medial to the manubrium. If, in addition to the incus dislocation, the stapes suprastructure is fractured, then the long process of the incus is left intact, and the body and short process are sculptured. The superior surface of the body of the incus is fashioned to rest under the manubrium, and the long process sits on the footplate. A variety of total ossicular replacement prostheses are also available for this purpose. A more unique problem occurs when the stapes suprastructure is fractured but the incus remains connected to the malleus; these patients are good candidates for a laser stapedotomy.

Ossicular reconstruction for traumatic ossicular disruptions are superior to those performed for chronic otitis media. Hough and

Stuart[85] report closure of the air-bone gap to within 10 dB in 78% of patients and complete closure in 45%.

Otic capsule–disrupting fractures typically result in severe to profound sensorineural hearing loss. Multiple pathogenic mechanisms can contribute to the deafness, including disruption of the membranous labyrinth, avulsion or trauma to the cochlear nerve, interruption of the cochlear blood supply, hemorrhage into the cochlea, and perilymphatic fistulas. Another proposed mechanism is endolymphatic hydrops, which results from the obstruction of the endolymphatic duct by the temporal bone fracture.[87] Acoustic trauma associated with temporal bone fractures and incus dislocations frequently contributes to a sensorineural component to a mixed hearing loss; 50% of patients with traumatic incus dislocations have at least 10 dB of sensorineural hearing loss, and 18% have more than 30 dB of loss.[88] The loss occurs primarily in the 2000- to 4000-Hz range. The prognosis for recovery of function in patients with anacusis or profound deafness is extremely poor; however, patients with moderate to severe loss may have some recovery.[86,89] Patients who are experiencing progressive or fluctuating sensorineural hearing loss, which is suggestive of a possible underlying perilymphatic fistula, may benefit from exploration and patching of the fistula.[90]

Cholesteatoma and External Auditory Canal Stenosis

Cholesteatoma formation may occur many years after a temporal bone fracture.[84,91] There are four pathogenic mechanisms responsible for posttraumatic cholesteatoma formation: (1) epithelial entrapment in the fracture line; (2) ingrowth of epithelium through the unhealed fracture line or a rent in the tympanic membrane; (3) traumatic implantation of tympanic membrane skin into the middle ear; (4) trapping of epithelium medial to a stenosis of the EAC. The typical location for cholesteatoma resulting from epithelium trapped within the fracture line is in the epitympanum and the antrum. The fracture line along the posterior superior canal wall and scutum expands and then closes, thus trapping the canal skin. As the trapped skin grows, it expands into the epitympanum and antrum, thus forming a cholesteatoma; the ingrowth of epithelium through a displaced fracture line may also extend into the same region. Traumatic implantation of tympanic membrane skin results in cholesteatoma formation within the mesotympanum. Blast injuries can result in the displacement of keratinizing stratified squamous epithelium into the mastoid air cells, the mesotympanum, the epitympanum, and even intracranially.[92] The fourth mechanism of cholesteatoma formation in a canal cholesteatoma. Posttraumatic canal cholesteatomas are the most preventable by careful follow-up, débridement, and stenting when narrowing progresses. The ear canal can be dilated with the insertion of increasing numbers of Oto-Wicks (Meditronic Xomed, Jacksonville, FL) that have been saturated with a nonototoxic antibiotic drop and that are replaced every few days. After the canal is adequately dilated, Merocel (Meditronic Xomed) sponge is inserted to maintain the lumen. A large vented custom ear mold is occasionally required to maintain the lumen after severe canal injuries; the mold is used throughout the day for 3 to 6 months. When the stenosis is complete and dilation is not possible, a canaloplasty and, possibly, a tympanoplasty are required. A lateral stenosis of the EAC should not be allowed to persist, even if it is completely benign in appearance, because of the very high probability of cholesteatoma formation.

Post-traumatic cholesteatoma involving the attic, antrum, or mastoid air cells often grows for many years before detection. Until the cholesteatoma involves the ossicular chain (with resultant conductive hearing loss), erodes into the labyrinth (causing vertigo or sensorineural hearing loss), compresses the facial nerve (resulting in facial paresis), or grows into the middle ear and can be visualized on physical examination, the growth goes undetected.

Carotid Artery Injury

Carotid artery injury can occur in up to 1% of severe blunt head trauma. York and colleagues reported a review of 43 patients who underwent cerebral angiograms for suspected carotid injuries following blunt head trauma. Eleven carotid injuries were identified in 10 patients.[93] They used a fracture of the carotid canal identified on CT as a predictive indicator of carotid artery injury and found that it had a 60% sensitivity and 67% specificity. Thirty-five percent of patients with carotid canal fractures suffered a carotid artery injury. The incidence is high in this study when compared with the literature and probably represents the selection criteria of entry into the study (i.e., patients in whom angiograms were obtained because of a high suspicion for a vascular injury). Recommended criteria for obtaining carotid angiography include a neurologic examination not consistent with the brain CT scan; lateralizing neurologic deficits (hemiparesis, transient ischemic attacks, cerebrovascular accident, amaurosis fugax); Horner's syndrome; cervical bruit; or displaced fracture through the carotid canal.[94]

Another potential delayed complication of temporal bone fractures is a carotid cavernous fistula. These arteriovenous fistulas may manifest with pulsatile or nonpulsatile exophthalmos, chemosis, and a bruit detected with auscultation over the affected orbit.[95]

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CHAPTER ONE HUNDRED AND FORTY-SIX

Cochlear Transduction and the Molecular Basis of Auditory Pathology

JoAnn McGee

Edward J. Walsh

Key Points

- Animal models have played a key role in the effort to elucidate the role of gene products in peripheral auditory physiology and the molecular basis of deafness.
- Congenital hearing loss generally is inherited, and the phenotypic spectrum produced by mutations in a particular gene can be attributed to the severity of the mutation, allelic heterogeneity, alternative splicing, and the contribution of modifier genes. In addition, some genes interact with the environment (e.g., noise, aminoglycoside antibiotics) to increase susceptibility to hearing loss.
- The physical characteristics of the cochlear partition (i.e., its mass and stiffness) vary from one end of the cochlea to the other, creating a basoapical gradient that results in a mechanical system with resonant properties that are continuously distributed and span the audiometric range of hearing from high to low frequency.
- The tectorial membrane, a gelatinous extracellular matrix overlying the organ of Corti, provides the necessary structure to convert basilar membrane displacement to radial shearing forces, which in turn influence hair bundle deflection and subsequent mechanoelectrical transduction. Defects in genes encoding extracellular matrix proteins that are components of the tectorial membrane (e.g., TECTA, COL11A2, COL9A1) result in hearing deficits.
- Cochlear amplification refers to a physiologically vulnerable mechanism that increases sensitivity to sound, enhances frequency selectivity, and broadens the dynamic operating range. Cochlear amplification is the result of unique voltage-dependent contractile properties of outer hair cells, which rely on the *SLC26A5* gene that encodes the essential motor protein prestin.
- Numerous proteins that are localized to sensory hair cells are critical for the normal development and/or maintenance of the intricate structure and/or function of the hair bundle and when defective are responsible for various forms of deafness. These include motor proteins (e.g., myosin IIIa, VI, VIIa, XVa), cytoskeletal proteins (e.g., espin, γ-actin, TRIOBP, radixin, diaphanous 1), adhesion proteins (e.g., cadherin 23, protocadherin 15, usherin, Vlgr1), scaffolding proteins (e.g., harmonin, SANS, whirlin), and other necessary proteins of unknown function (e.g., TMC1, TMHS, TMIE).
- Hearing impairments categorized as "auditory neuropathy" include those associated with defective inner hair cell ribbon synapse function (e.g., those caused by mutations in the genes *OTOF* and *VGLUT3*), as well as neuropathies involving faulty conduction along auditory nerve fibers, which often occur when components of the Schwann cell myelin sheath are defective (e.g., MPZ, GJB1, PMP22).
- Development of the epithelial barrier forming the endolymphatic compartment within the cochlear duct requires the vital tight junction components claudin-14 and tricellulin. In addition, the gap junction proteins connexin 26, connexin 30, and connexin 31 (encoded by *GJB2*, *GJB6*, and *GJB3*, respectively) are essential for ion homeostasis, as are numerous ion channel subunits (e.g., KCNQ4, BSND, KCNE1, KCNQ1) and ion pumps and transporters (e.g., ATP6B1, SLC26A4 [PDS, pendrin]).
- Many other proteins, including transcription factors and regulators, enzymes, ligands and receptors, and proteins produced by mitochondrial genes, have been associated with human deafness. Moreover, many genes underlying deafness in mouse models have been identified for which human deafness has not yet been established, and vice versa.
- A thorough, comprehensive understanding of the role that distinctive proteins play in normal cochlear development and peripheral auditory function will require a continuing aggressive effort on the part of the scientific community, and the knowledge gained from the use of animal models will help guide clinical diagnoses and provide direction for appropriate treatment strategies.

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Deafness, in all of its forms, affects an estimated 186 of every 100,000 newborns in the United States[372] and increases in prevalence with advancing age. For example, by the age of 60 years, one of every three people in the United States experiences communication difficulties as a consequence of lost hearing, and by the age of 85 years, one half of the population has some degree of hearing disability. In most cases, peripheral auditory disease involves some form of cochlear abnormality that disrupts sensory transduction, and various etiologic factors have been recognized, including genetic abnormalities, trauma (acoustic and mechanical), ototoxic agents, bacterial and viral infections, and disturbances in other organ systems that influence cochlear physiology indirectly. This chapter describes the physiologic mechanisms underlying cochlear transduction at both the systemic and molecular levels. In addition, basic mechanisms of cochlear transduction are correlated with a subset of inner ear disorders that are representative of various classes of disease.

Significant breakthroughs in the identification of genes and gene products that serve as integral elements of cochlear transduction have been made beginning in the mid to late 1990s. Clearly, pathogenic mutations of many of these genes are implicated in various forms of deafness (Table 146-1). Although numerous cases of inherited deafness had been identified historically on the basis of phenotype, the etiopathogenic mechanisms responsible for deafness remained unknown before technologic advances allowed for the identification and cloning of genes associated with normal hearing. By comparing human genes with orthologous genes that are known to cause deafness in animals, the cell biology and disease associated with particular gene mutations can be studied, leading to an understanding of the role of gene products in sensory transduction. Although a variety of nonhuman species have played indispensable roles in the study of cochlear transduction and sensory pathology, in recent years the mouse model has emerged as particularly useful (Table 146-2; see also Table 146-1). This movement is fueled, in large part, by the highly successful, comprehensive investigation of the murine genome and the ever-expanding availability of tools that allow the targeting and manipulation of specific genes, technologic changes that greatly extend the capability of researchers to examine the role of gene products in the transduction process. However, although much has been learned about the molecular and genetic basis of cochlear function, or malfunction as the case may be, much work remains to be done in the ongoing effort to unravel the intricacies associated with cochlear transduction and deafness.

Approximately 68% of all cases of congenital hearing loss are inherited, and of these, at least 70% are nonsyndromic—that is, auditory disability is the only manifestation of the disorder.[372] Nonsyndromic hearing losses are grouped according to their inheritance mode: DFNA refers to autosomal dominant cases, DFNB to autosomal recessive, and DFN to X-linked or mitochondrial cases; a unique numeral following each acronym has been used to identify each chromosomal locus discovered in chronologic order. As a consequence of a major effort to identify and classify inherited hearing disabilities, it is clear that the nonsyndromic basis of inherited deafness is highly heterogeneous. Many loci known to produce autosomal dominant forms of deafness when mutated have been genetically mapped, although only a subset of the genes responsible for autosomal dominant forms have been identified and cloned. Autosomal recessive forms of inherited hearing loss account for most nonsyndromic abnormalities (approximately 80%). It has become increasingly clear, however, that different mutations in a given gene may be responsible for differences in the severity of hearing loss, different patterns of inheritance, and susceptibility to environmental factors such as noise or aminoglycoside antibiotics, as well as the involvement of other organ systems. For example, mutations in a number of genes (e.g., *COL11A2*, *ESPN*, *GJB2*, *GJB3*, *GJB6*, *MYO6*, *MYO7A*, *PJVK*, *TECTA*, *TMC1*) are responsible for both autosomal dominant and autosomal recessive forms of nonsyndromic deafness. Moreover, mutations in several genes (e.g., *CDH23*, *COL11A2*, *GJB2*, *GJB3*, GJB6, *MYH9*, *MYO7A*, *MYO15A*, *PCDH15*, *SLC26A4*, *USH1C*, *WFS1*, *WHRN*) are responsible for both nonsyndromic and syndromic forms of deafness (see Table 146-1). The phenotypic spectrum produced by mutations in a gene has been attributed to the severity of the mutation, allelic heterogeneity, alternative splicing, and the contribution of modifier genes.[60,136,171,254,336,362,486]

This chapter reviews basic mechanisms underlying sensory transduction associated with hearing and integrates contemporary models of transduction with the latest acquired information regarding the molecular structure and organization of key inner ear systems. Because of the sheer number of factors now known to be necessary for normal inner ear development, maintenance, and function, a comprehensive accounting is not possible here—not all such factors are addressed. Of note, the stated biologic role of most of the proteins discussed here remains speculative, and substantial work is needed to determine their precise role in the inner ear, as well as the nature of their interactions with other proteins. Excellent reviews that are relevant to the subject of this chapter are listed in the Bibliographic References.[29,61,170,187,215,236,310,320,443,453,585,588,631]

Passive Cochlear Mechanics

The cochlea, and the organ of Corti in particular, constitute an evolutionary marvel of biologic engineering as intricate, microscaled mechanical systems. Although the hallmark of peripheral auditory function in mammals may be the evolutionary adaptation of a relatively simple, passive resonant system into an active one that consumes energy and efficiently detects and amplifies vibratory energy, it is useful to note that the fundamental nature of cochlear mechanics is evident even in cadavers, as so elegantly demonstrated by Nobel prize winner Georg von Békésy.[586] Because cochlear mechanics at this level of function are independent of other factors—neither requiring nor consuming adenosine triphosphate (ATP), for example—the sound-driven motion of the organ of Corti observed by von Békésy and others is commonly referred to as passive.

The primary elements of passive cochlear transduction are hydromechanical in character, and the integrated contributions of many structural elements are known to determine the resonant character of cadaveric and therefore mechanically passive cochleae (Fig. 146-1). The cochlear partition is composed of an epithelial sheet known as the tympanic cover layer that supports the fibroelastic basilar membrane, itself the central structure of the end organ both functionally and anatomically. This partition supports, in turn, both the sensory and nonsensory supporting epithelium. The fluid-filled major chambers of the cochlea—specifically, the scala vestibuli and scala tympani, which are filled with perilymph, and the scala media, which is filled with endolymph—also play an important role in transduction. These structural elements, together with the tectorial membrane (an extracellular gelatinous structure secreted by nonsensory inner ear epithelial cells) that extends from the spiral limbus radially over the apical surface of the organ of Corti, comprise the principal elements that give rise to passive mechanical transduction. Although Reissner's membrane separates scala media from scala vestibuli and therefore plays an important homeostatic role in the maintenance of cochlear electrochemistry, it does not seem to play a significant role as an element of passive cochlear mechanics.

Because the focus of this chapter is on cochlear transduction, we will only remind the reader that sound waves collected in the external ear canal produce vibrations of the tympanic membrane, which in turn vibrate middle ear ossicles (Fig. 146-2A). It is, of course, the vibratory motion of the stapedial footplate that transmits the mechanical energy of the ossicular chain directly through the oval window of the cochlea, effectively delivering sound pressure waves to the scala vestibuli and translating mechanical motion into pressure waves that propagate through the virtually incompressible cochlear fluids at a velocity approximating 1.5 km/sec. At this rate of propagation, the spread of the pressure wave throughout the volume of the cochlea is nearly instantaneous. Because the bony walls of the cochlea are rigid and its fluid contents incompressible, the higher pressure (or lower, depending on the direction of motion of the stapedial footplate) in scala vestibuli relative to scala tympani produces a pressure differential across the cochlear partition that creates intracochlear forces that set the partition into motion (see Fig. 146-2D). As described in more detail in a later section, the physical makeup of the organ of Corti, and of the basilar

Text continues on p. 2060

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
ACTG1	Actin γ1	DFNA20, DFNA26[572,639]	Targeted null[406]	Intracellular protein, cytoskeletal nonmuscle actin isoform	Hair cell stereocilia, cuticular plate, and adherens junctions
ATP2B2 (*PMCA2*)	Ca^{2+}-ATPase 2, Ca^{2+}-transporting, plasma membrane 2	Increased severity of autosomal recessive hearing loss associated with a missense mutation in *CDH23*[486]	Deafwaddler (*dfw*), targeted null—increased susceptibility to noise-induced hearing loss[297,298,532]	Calcium pump	Hair cells
ATP6B1	β-Subunit of renal apical H^+-ATPase pump	Renal tubular acidosis with deafness[265]	Targeted null—normal hearing[131]	Ion pump, ATPase	Interdental cells, endolymphatic sac, kidney
BSND	Barttin (NKCC2)	Bartter syndrome type IV (with sensorineural deafness)[53,145]	Bsnd conditional knockout[447]	Cl^- channel β-subunit	Strial marginal cells
CCDC50	Coiled-coil domain–containing protein 50/Ymer	DFNA44[369]		Cytoplasmic protein (associated with microtubule-based cytoskeleton and mitotic apparatus); effector of EGF-mediated cell signaling	Pillar cells, stria vascularis; during development also expressed in cells lining cochlear duct, spiral ganglion, spiral limbus, OHCs, spiral ligament, Deiters cells
CDH23	Cadherin 23, otocadherin	DFNB12, Usher syndrome type 1D[58,60]	Waltzer (v), age-related hearing loss (*ahl*), modifier of deafwaddler (*mdfw*)[120,384]	Cell adhesion protein	Hair cells, retina
CLDN14	Claudin-14	DFNB29[606]	Targeted null[45]	Tight junction component	Hair cells, Deiters cells, inner and outer phalangeal cells, epithelial cells lining inner spiral sulcus
COCH	Coagulation factor C homology/cochlin	DFNA9[452]	Targeted null—not deaf; targeted missense—late-onset hearing loss[348,451]	Extracellular matrix component	Spiral ligament, spiral limbus, and osseous spiral lamina
COL1A1	Type I collagen α1 chain	Osteogenesis imperfecta[37]	Mov13, transgene[19,59]	Extracellular matrix component	Mineralized and nonmineralized connective tissue
COL2A1	Type II collagen α1 chain	Stickler syndrome type I[7]	Disproportionate micromelia (*Dmm*); spondyloepiphyseal dysplasia congenita (*sedc*); mutant transgenes[48,126,347]	Extracellular matrix component	Spiral ligament and limbus, tectorial membrane, basilar membrane, cartilage

Continued

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
COL4A3	Type IV collagen α3 chain	Alport syndrome[368]	Targeted null[89]	Extracellular matrix component	Basal lamina of cochlear duct and strial blood vessels, kidney
COL4A4	Type IV collagen α4 chain	Alport syndrome[368]		Extracellular matrix component	Basal lamina of cochlear duct and strial blood vessels, kidney
COL4A5	Type IV collagen α5 chain	Alport syndrome, X-linked[36]		Extracellular matrix component	Basal lamina of cochlear duct and strial blood vessels, kidney
COL9A1	Type IX collagen α1 chain	Stickler syndrome[566]	Targeted null[537]	Extracellular matrix component	Tectorial membrane, fibrocytes of spiral ligament
COL11A1	Type XI collagen α1 chain	Stickler, syndrome type II, Marshall, syndrome[198,442]	Chondrodysplasia (*cho*)[74,326]	Extracellular matrix component	Greater epithelial ridge and lateral wall of the cochlea early in development; inner sulcus, Claudius cells, and Boettcher cells during development
COL11A2	Type XI collagen α2 chain	DFNB53, DFNA13, Stickler syndrome type III (nonocular), otospondylomega-epiphyseal dysplasia (OSMED) syndrome[71,361,581]	Targeted null[361]	Extracellular matrix component	Tectorial membrane
CRYM	μ-Crystallin (NADP-regulated thyroid hormone–binding protein)	DFNAi[2]	Targeted null—normal hearing[538]	Involved in K^+ recycling?	Lateral region of spiral ligament and fibrocytes of spiral limbus
DFNA5	Deafness, autosomal dominant 5, ICERE-1	DFNA5[569]	Targeted null—normal hearing[570]		Organ of Corti, limbus, stria (RT-PCR only)
DIAPH1 (*HDIA1*)	Diaphanous homolog 1	DFNA1[346]	Targeted null—hearing not assessed[404]	Cytoplasmic protein regulating actin polymerization	Inner ear (RT-PCR only)
DSPP	Dentin sialophosphoprotein	DFNA39 associated with dentinogenesis imperfecta type 1[620]			
EDN3	Endothelin 3	Waardenburg syndrome type IV, Waardenburg-Hirschsprung disease[138]	Lethal spotting (*ls*)[39]	Ligand	Strial intermediate cells, pigmentation, gut
EDNRB	Endothelin receptor type B	Waardenburg syndrome type IV, Waardenburg-Hirschsprung disease[34]	Piebald (s)[232]	Receptor	Widespread in pigmentation, gut

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
ESPN	Espin	DFNB36, DFNAi[129,381]	Jerker (*je*)[634]	Actin-bundling protein	Hair cell stereocilia
ESRRB (*NR3B2*)	Estrogen-related receptor β	DFNB35[80]	Targeted conditional null[69]	Orphan nuclear receptor; alters cell fate of strial epithelial cells	Strial marginal cells
EYA1	Eyes-absent 1 homolog (*Drosophila*)	Branchio-oto-renal syndrome type 1[1]	Targeted null, spontaneous mutant[250,621]	Transcriptional coactivator	Neuroepithelia, ganglia, otic capsule and middle ear mesenchyme, kidney, jaw
EYA4	Eyes-absent 4 homolog (*Drosophila*)	DFNA10[599]	Targeted null[116]	Transcriptional coactivator	Eustachian tube and middle ear?
FGFR3	Fibroblast growth factor receptor 3	Craniosynostosis with deafness, Muenke syndrome[125,224]	Targeted null[81]	Growth factor receptor; affects support cell fate	Pillar cells, Deiters cells, hair cells during development, skull
FOXI1 (*FKH10*)	Forkhead box I1	Pendred syndrome[625]	Targeted null[242,243]	Transcriptional activator of SLC26A4	Endolymphatic duct/sac
GATA3	GATA-binding protein 3	Hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome[567]	Targeted null[266,571]	Enhancer-binding protein (for T-cell antigen receptor gene activation); zinc finger transcription factor	Otocyst and periotic mesenchyme; developing sensory epithelia, OHCs, spiral ganglion neurons, olivocochlear efferent neurons
GJB1 (*CMT*) (*CX32*)	Gap junction membrane channel protein β1, connexin 32	Charcot-Marie-Tooth type 1X syndrome (X-linked)[49]		Gap junction component	Schwann cells of auditory nerve and other peripheral nerves
GJB2 (*CX26*)	Gap junction membrane channel protein β2, connexin 26	DFNB1, DFNA3, keratitis-ichthyosis-deafness syndrome, palmoplantar hyperkeratosis, palmoplantar keratoderma[269,439,441]	Targeted, conditional null; dominantnegative transgene[79,305]	Gap junction component	Fibrocytes of the spiral ligament and spiral limbus; nonsensory epithelial cells in the region of the organ of Corti
GJB3 (*CX31*)	Gap junction membrane channel protein β3, connexin 31	DFNA2, DFNBi; erythrokeratodermia variabilis, peripheral neuropathy[340,342,440,618]	Targeted null—no hearing loss[421]	Gap junction component	Fibrocytes of the spiral ligament and spiral limbus; Schwann cells of auditory nerve and other peripheral nerves
GJB6 (*CX30*)	Gap junction membrane channel protein β6, connexin 30	DFNB1, DFNA3, Clouston syndrome[108,197]	Targeted null[544]	Gap junction component	Cells of the spiral limbus, the spiral ligament, the stria vascularis, and in supporting cells of the organ of Corti
KCNE1 (*IsK*, *MinK*)	Potassium voltage-gated channel, IsK-related subfamily, member 1	Jervell and Lange-Nielsen syndrome locus 2[487,561]	Targeted null; spontaneous mutant (*pkr*)[323,580]	K^+ channel β-subunit	Strial marginal cells, heart

Continued

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
KCNQ1 (*KvLQT1*, *KCNA9*)	Potassium voltage-gated channel, subfamily Q, member 1	Jervell and Lange-Nielsen syndrome locus 1[382]	Targeted null[66,315]	K^+ channel subunit	Strial marginal cells, heart
KCNQ4	Potassium voltage-gated channel, subfamily Q, member 4	DFNA2[304]	Targeted null, targeted knock-in[275]	K^+ channel subunit	Hair cells, spiral ganglion neurons
Kit	Kit proto-oncogene	Piebald syndrome[183]	Dominant spotting (*W*)[180,528]	Transmembrane protein, receptor for tyrosine kinase	Developing melanocytes (including strial intermediate cells)
LRTOMT	Leucine-rich transmembrane *O*-methyltransferase	DFNB63[9]		Fusion gene that gives rise to *LRTOMT1* and *LRTOMT2*	Hair cells and supporting cells
MITF	Microphthalmia transcription factor	Waardenburg syndrome type IIA, Tietz syndrome[20,541]	Microphthalmia (*mi*)[222]	Transcription factor	Strial intermediate cells during development, pigmentation
MPZ (P_0)	Myelin protein zero (P_0)	Charcot-Marie-Tooth syndrome type 1B with sensorineural deafness (auditory neuropathy), Déjérine-Sottas syndrome, congenital hypomyelinating neuropathy[212,213]	Transgenic mouse line[638]	Cell adhesion molecule and main component of compact myelin in peripheral nervous system	Schwann cells of auditory nerve and other peripheral nerves
MYH9	Myosin heavy chain IX, nonmuscle heavy chain IIA (NMHC IIA)	DFNA17, May-Hegglin anomaly, Sebastian, Fechtner, and Epstein syndromes[309,497]	Gene-trapping, homozygotes—embryonic lethal, heterozygotes—normal hearing[400]	Motor protein	Hair cells, spiral ligament, spiral limbus, spiral ganglion
MYH14	Myosin heavy chain XIV, nonmuscle heavy chain IIC (NMHC IIC)	DFNA4[128]		Motor protein	Organ of Corti, stria vascularis, Hensen cells, Claudius cells, external sulcus cells, epithelium of the spiral prominence
MYO1A	Myosin IA	DFNA48[127]	Targeted null—normal startle response[560]	Motor protein	
MYO3A	Myosin IIIA	DFNB30[591]		Motor protein	Hair cells
MYO6	Myosin VI	DFNB37, DFNA22[10,363]	Snell's waltzer (*sv*), tailchaser (*tlc*) (ENU)[35,219]	Motor protein	Hair cells
MYO7A	Myosin VIIA	DFNB2, DFNA11, Usher syndrome type 1B[338,339,600]	Shaker 1 (*sh1*)[182]	Motor protein	Hair cells, retina
MYO15A	Myosin XVa	DFNB3; Smith-Magenis syndrome[330,592]	Shaker 2 (*sh2*)[422]	Motor protein	Hair cells

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
ND	Norrie disease protein, norrin	Norrie disease[46,72]	Targeted null[47,429]	Extracellular matrix component	Stria, spiral ganglion, eye, brain
OTOA	Otoancorin	DFNB22[640]		Glycosylphosphatidylinositol-linked membrane protein	Apical surface of interdental cells; apical surface of border epithelial cells lying adjacent and medial to IHCs during development
OTOF	Otoferlin	DFNB9[626]	Targeted null[455]	Synaptic vesicle–trafficking protein	IHCs
PAX2	Paired box gene 2	Renal-coloboma syndrome[137]	Targeted null[552]	Transcription factor	
PAX3	Paired box gene 3	Waardenburg syndrome types I, III[234,542]	Splotch (*Sp*)[141,530]	Transcription factor	Developing dorsal neural tube, pigmentation
PCDH15	Protocadherin-15	DFNB23, Usher syndrome types 1F[11,12,15]	Ames waltzer (*av*)[14]	Cell adhesion protein	Hair cells
PJVK	Pejvakin	DFNB59, DFNAi[109,488]	DFNB59 knock-in, sirtaki (ENU)[109,488]		Hair cells, spiral ganglion, brainstem auditory neurons
PMP22	Peripheral myelin protein 22	Charcot-Marie-Tooth syndrome type 1A with sensorineural deafness (auditory neuropathy)[296]	Trembler (*Tr*)[536,638]	Hydrophobic intrinsic membrane protein of myelin sheaths in peripheral nervous system	Schwann cells of auditory nerve and other peripheral nerves
POU3F4 (*BRN4*.0)	POU domain, class 3, transcription factor 4	DFN3 (X-linked)[107]	Targeted null, sex-linked fidget (*slf*)[366,412,414]	Transcription factor	Mesoderm around otic vesicle and lateral wall; spiral ligament, Reissner's membrane
POU4F3 (*BRN3c*)	POU domain, class 4, transcription factor 3	DFNA15[564]	Targeted null, dreidel (*ddl*)[143,619]	Transcription factor	Hair cells
RDX	Radixin	DFNB24[273]	Targeted null[289]	Cross-link actin filaments to plasma membrane	Hair cells
SALL1 (*HSAL1*)	Sal-like 1	Townes-Brocks syndrome[292]	Targeted mutation producing truncated protein[280]	Transcription factor (repressor)	
SANS	Scaffolding protein containing ankyrin repeats and SAM (sterile alpha motif) domain	Usher syndrome type 1G[377,601]	Jackson shaker (*js*)[283]	Scaffold protein	Hair cells
SIX1	Homolog of *Drosophila* sine oculis homeobox 1 gene	Branchio-oto-renal or branchio-otic syndrome type 3[458]	Targeted null[637]	Transcriptional regulator	Embryonic development of ear, kidney, muscle; branchial arch

Continued

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
SIX5	Homolog of *Drosophila* sine oculis homeobox 5 gene	Branchio-oto-renal syndrome type 2[231]	Targeted null[291,479]	Transcriptional regulator	Embryonic development of ear, kidney; branchial arch
SLC17A8 (*VGLUT3*)	Solute carrier family 17 (sodium phosphate cotransporter), member 8; vesicular glutamate transporter-3	DFNA25[457]	Targeted null[457,490]	Vesicular glutamate transporter	IHCs (synaptic vesicles)
SLC19A2	Solute carrier family 19 (thiamine transporter), member 2; high-affinity thiamine transporter 1 (Thtr1)	Thiamine-responsive megaloblastic anemia syndrome (diabetes mellitus, megaloblastic anemia, sensorineural deafness)[121,158,308]	Targeted null[390]	Thiamine transporter	Hair cells, greater expression in IHCs than in OHCs
SLC26A4 (*PDS*)	Solute carrier family 26, member 4 (pendrin)	DFNB4, Pendred syndrome, enlarged vestibular aqueduct, Mondini dysplasia[151,325]	Targeted null[150]	Anion transporter (pumps bicarbonate into endolymph and maintains pH homeostasis)	Spiral prominence epithelial cells, root cells, endolymphatic duct and sac, thyroid gland
SLC26A5 (*PRES*)	Solute carrier family 26, member 5 (prestin)	DFNB61[337]	Targeted null, targeted knock-in[103,328]	Cl^- translocator/motor protein	OHCs
SLUG, *SNAI2*	Snail homolog 2	Waardenburg syndrome type II[474]	Targeted null[474]	Transcription factor	Embryonic neural crest
SOX2	Sex-determining region of the Y chromosome–related (SRY-related) high-mobility group (HMG) box gene 2	Syndromic: anophthalmia or microphthalmia, sensorineural hearing loss, anterior pituitary hypoplasia, hypogonadism[268]	Light coat and circling (*lcc*); yellow submarine (*ysb*)[130,281]	Transcription factor	Developing CNS and placodes—involved in hypothalamopituitary and reproductive axes; prosensory domain of cochlear epithelium
SOX10	SRY-box containing gene 10	Waardenburg syndrome type IV[419]	Dominant megacolon (*dom*)[217,521]	Transcription factor	Otocyst, pigmentation, gut
STRC	Stereocilin	DFNB16[576]	Targeted null[577]	Transmembrane or extracellular protein?	Hair cells (component of horizontal top connectors between adjacent stereocilia and the tops of the tallest OHC stereocilia that attach to the tectorial membrane)
TBX1	T-box 1	DiGeorge syndrome[73]	Transgene overexpression, targeted null[172,582]	Transcription factor	Otocyst
TCOF1	Treacle	Treacher Collins syndrome[123]	Targeted null heterozygotes[122]	Nucleolar trafficking protein	Neural crest cells

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
TECTA	α-Tectorin	DFNB21, DFNA8/DFNA12[378,574]	Targeted null, targeted missense[317,318]	Extracellular matrix component	Tectorial membrane; also in inner sulcus and Hensen cells during development
TFCP2L3 (*GRHL2*)	Transcription factor cellular promotor 2-like 3 (grainyhead-like 2)	DFNA28, age-related hearing loss[408,568]		Transcription factor	Organ of Corti, stria vascularis, Reissner's membrane, interdental cells, cells lining the scala media
THRB	Thyroid hormone receptor β	Thyroid hormone resistance[473]	Targeted null[167]	Transcription factor	Cochlear sensory epithelium, Kolliker's organ, spiral ganglion, Hensen cells, stria vascularis
TIMM8A (*DDP1*)	Translocase of mitochondrial inner membrane 8A; DDP1 (deafness dystonia peptide 1)	Mohr-Tranebjaerg syndrome/Jensen syndrome (X-linked)[248,553,554]		Mitochondrial protein	Widespread including muscle
TMC1	Transmembrane channel-like gene 1	DFNB7/DFNB11, DFNA36[306]	Deafness (*dn*); Beethoven (*Bth*)[306,587]	Transmembrane protein	Hair cells
TMHS (*LHFPL5*)	Tetraspan membrane protein of hair cell stereocilia; lipoma HMGIC fusion partner-like 5	DFNB66/DFNB67[263,498]	Hurry-scurry (hscy)[341]	Transmembrane protein	Transient expression in hair cells (especially stereocilia) during development
TMIE	Transmembrane inner ear expressed gene	DFNB6[380]	Spinner (*sr*), circling (*cir*)[75,367]	Transmembrane protein	Hair cells
TMPRSS3 (*ECHOS1*)	Type II transmembrane protease, serine 3	DFNB8/DFNB10[489]		Transmembrane serine protease	Stria vascularis, inner and outer pillar cells, Deiters cells, Hensen cells, epithelial cells lining the inner spiral sulcus, spiral ganglion
TRIC (*MARVELD2*)	Tricellulin (Marvel domain–containing protein 2)	DFNB49[435]		Tight junction membrane protein at tricellular contacts	Tricellular tight junctions in sensory epithelium, including among hair cells and supporting cells, and among strial marginal cells
TRIOBP (*TARA*)	TRIO (triple functioning domain) and filamentous actin [F-actin]–binding protein (TRIO-associated repeat on actin)	DFNB28[436,499]		F-actin–binding protein	Hair cells

Continued

Table 146-1

Selected Genes Underlying Various Forms of Deafness in Humans—cont'd

Gene	Name/Protein	Human Disorder	Murine Disorder	Type of Molecule	Localization
USH1C	Usher 1C, harmonin	DFNB18, Usher syndrome type 1C[13,575]	Deaf circler, (*dfcr*), targeted null, targeted knock-in[252,316,321]	Scaffold protein	Hair cells, photoreceptors
USH2A	Usherin	Usher syndrome type 2A[147]	Targeted null[335]	Transmembrane protein (component of ankle links of hair cell stereocilia)	Hair cells, photoreceptors
USH3A (*CLRN1*)	Clarin-1	Usher syndrome type 3[6,249]	Targeted null (unpublished)	Transmembrane protein	Hair cells, photoreceptors
VLGR1 (*MASS1*; *GPR98*)	Very large G–protein–coupled receptor 1	Usher syndrome type 2C[603]	Targeted mutation producing truncated protein, targeted null, frings, rueda (ENU)[255,359,623]	Transmembrane protein (component of ankle links of hair cell stereocilia)	Hair cells, photoreceptors
WFS1	Wolfram syndrome gene 1, wolframin	DFNA6/DFNA14/ DFNA38, Wolfram syndrome[51,534,629]		Transcellular ion movement (component of endoplasmic reticulum, especially canalicular reticulum)	Hair cells, Deiters cells, Hensen cells, Claudius cells; epithelial cells lining the external spiral sulcus, spiral prominence, spiral ligament; interdental cells; Reissner's membrane
WHRN	Whirlin	DFNB31; Usher syndrome type 2D[136,358]	Whirler (*wi*)[358]	Scaffold protein involved in elongation and maintenance of hair cell stereocilia	Hair cells, photoreceptors

ATPase, adenosine triphosphatase; CNS, central nervous system; EGF, epithelial growth factor; HMGIC, high mobility group I-C proteins; IHC, inner hair cell; NADP, nicotinamide-adenine dinucleotide phosphate; OHC, outer hair cell; RT-PCR, reverse transcriptase–polymerase chain reaction.

Table 146-2

Selected Genes Underlying Murine Deafness for Which Human Deafness Has Not Been Determined

Gene	Name/Protein	Murine Disorder	Type of Molecule	Localization
Bsn	Bassoon	Targeted disruption—Bassoon (*Bsn*) mice exhibit characteristics of auditory neuropathy; anchoring of ribbons in inner hair cells is impaired[277]	Presynaptic scaffolding protein	Hair cells
Cacna1D ($Ca_V1.3$)	Calcium channel, voltage-dependent, L type, α1D subunit	Targeted null mice are deaf[420]	Voltage-sensitive calcium channel	Hair cells
Cdkn2d (*Ink4D*)	Cyclin-dependent kinase inhibitor 2D	Targeted null mice—the postmitotic state of sensory hair cells is disrupted: they reenter the cell cycle and subsequently undergo apoptosis, resulting in progressive hearing loss[70]	Cell cycle regulation	Hair cells
Cldn11	Claudin-11	Targeted null mice are hearing-impaired; endocochlear potential is reduced[195,290]	Tight junction protein	Strial basal cells

Table 146-2

Selected Genes Underlying Murine Deafness for Which Human Deafness Has Not Been Determined—cont'd

Gene	Name/Protein	Murine Disorder	Type of Molecule	Localization
Clic5	Chloride intracellular channel 5	Jitterbug (*jbg*) mice are hearing-impaired; hearing loss is progressive[175]	May associate with radixin and stabilize connection between actin core of stereocilia and plasma membrane	Hair cells
Gfi1	Growth factor–independent 1	Targeted null mice lack an acoustic startle reflex; outer hair cells degenerate[218,590] Humans with a missense mutation show no evidence of hearing loss[407]	Transcriptional repressor oncoprotein; regulated by POU4F3	Hair cells, spiral ganglion cells
Itga8	Integrin $\alpha 8\beta 1$	Targeted null mice die soon after birth; utricular hair cells lack stereocilia or have malformed stereocilia[334]	Cell surface glycoprotein that mediates cell-cell and cell–extracellular matrix interactions (signaling molecule)	Apical hair cell surface where stereocilia form
Kcnj10 (*Kir4.1*)	Potassium channel, inwardly rectifying, subfamily J, member 10	Targeted null mice are deaf (absent endocochlear potential; reduced endolymph volume and K^+ concentration)[353]	K^+ channel	Strial intermediate cells
Math1 (*Atoh1*)	Mouse homolog of atonal 1	Targeted null mice are deaf (hair cells do not develop)[50]	Basic helix-loop-helix transcription factor	Hair cells
Otog	Otogelin	Twister (*twt*), targeted null mice are hearing-impaired[508,509]	Extracellular matrix component	Tectorial membrane
Otos	Otospiralin	Targeted null mice are moderately hearing-impaired; type II and IV fibrocytes degenerate[112]		Fibrocytes of the spiral limbus and spiral ligament
Ptprq	Protein tyrosine phosphatase receptor Q	Transgenic mice are hearing-impaired and have progressive hair cell loss in the base of the cochlea[190]	Receptor-like protein tyrosine phosphatase	Hair cells
Slc4a7 (*Nbc3*)	Solute carrier family 4 (sodium bicarbonate cotransporter), member 7; Nbc3	Targeted null mice develop hearing impairment[57]	Sodium bicarbonate cotransporter (Nbc); pH regulation	Type I and II fibrocytes
Slc12a2 (*Nkcc1*)	Solute carrier family 12 (sodium-potassium-chloride transporter), member 2	Shaker-without-syndactylism (*sy-ns*)[124]; Targeted null mice are deaf[110,157]	Na^+-K^+-$2Cl^-$ cotransporter	Strial marginal cells, distal nephron
Slc12a6 (*Kcc3*)	Solute carrier family 12 (potassium-chloride cotransporter), member 6; Kcc3	Targeted null mice develop a slowly progressive hearing loss[56]	K^+-Cl^- cotransporter	Supporting cells of hair cells, epithelial cells of organ of Corti, type I and III fibrocytes, neurons, renal proximal tubule
Slc12a7 (*Kcc4*)	Solute carrier family 12 (potassium-chloride cotransporter), member 7; Kcc4	Targeted null mice are deaf, develop renal tubular acidosis[55]	K^+-Cl^- cotransporter	Deiters cells, supporting cells of inner hair cells

Continued

Table 146-2

Selected Genes Underlying Murine Deafness for Which Human Deafness Has Not Been Determined—cont'd

Gene	Name/Protein	Murine Disorder	Type of Molecule	Localization
Spnb4	β-Spectrin 4	Quivering (*qv*) mice have moderate to severe abnormalities in ABR wave I; later peaks generally are absent[401]	Ion channel localization in myelinated nerves	Spiral ganglion neurons (axons)
Tbx18	T-box transcription factor 18	Transgenic mice are deaf; endocochlear potential is absent; stria vascularis is disrupted[555]	Transcription factor	Otic mesenchyme that differentiates into fibrocytes
Tectb	β-Tectorin	Targeted null mice have significantly elevated thresholds below 20 kHz and sharper tuning at high frequencies[462]	Extracellular matrix component	Tectorial membrane
Tmprss1 (*Hpn*)	Transmembrane protease serine 1 (hepsin)	Targeted null mice exhibit profound hearing loss[201]	Transmembrane serine protease	Inner ear
Trpml3 (*Mcoln3*)	Transient receptor potential cation channel, mucolipin subfamily member 3	Varitint-waddler (*Va*) mice are deaf, have reduced endocochlear potential and pigmentation defects[65,119]	Transmembrane protein; ion channel protein of intracellular endosomes and lysosomes	Hair cells (cytoplasmic vesicles, stereocilia, plasma membrane), strial intermediate cells

ABR, auditory brainstem response.

membrane in particular, establishes a space-frequency map that determines the limits of hearing and the capacity of the subject to resolve frequency differences among vibrations that contain energy in the audible range.

Physical Dimensions

At the basal end of the cochlea near the round window, the width of the basilar membrane, as measured between the tympanic lip of the spiral limbus and the basilar crest of the spiral ligament, is narrow relative to dimensions representing more apical locations (Fig. 146-3). In fact, the width of the basilar membrane progressively increases along a base-to-apex gradient in mammals, such that in humans, for example (see Fig. 146-3 E), the width at the base is approximately 100 µm and approaches 500 µm near the apex.[604] In association with graded basilar membrane width, the number of mesothelial cells, or tympanic border cells, lining the basilar membrane increases along the basoapical length of the end organ, as does the length of outer hair cells (OHCs) and associated stereocilia. Conversely, the thickness of the basilar membrane and the density of radial filaments embedded in the homogenous ground matrix of the partition decrease progressively from base to apex (see Fig. 146-3C). It is notable that radial filaments are composed primarily of collagen type II,[132,545,558] whereas the ground matrix of the partition itself is composed primarily of fibronectin, tenascin, proteoglycans containing keratin sulfate and chondroitin sulfate, and emilin-2 (*e*lastin *m*icrofibril *i*nterface-*l*ocated prote*in*-2).[21,375,475,539,611] Consequently, the basilar membrane and organ of Corti complex is stiffer and less massive at the base than at the apex (see Fig. 146-3F). The result is an end organ with resonant properties that are continuously distributed from base to apex that supports a mechanical system that separates, or filters, complex fluid waves into sinusoidal constituents. As a result, high-frequency acoustic events are preferentially transduced in the base (see Fig. 146-3G), because it is stiff and less massive. The inverse is true in the case of low-frequency acoustic events.

Another physical characteristic of the cochlea that exerts influence over the mechanics of transduction is the relative volume of perilymphatic fluid compartments that are larger at the base than at the apex (see Fig. 146-1). Consequently, there is a clear difference in fluid-mass loading of basilar membrane motion along the length of the end organ. The magnitude of the intracochlear fluid load is thought to dominate longitudinal coupling along the length of the cochlea. Of note, very little coupling occurs otherwise between adjacent regions of the basilar membrane—beyond, that is, simple stretching and compression forces.[204,394,395,583] At rest, therefore, the basilar membrane seems to be under very little tension, and without direct mechanical coupling, the traveling wave cannot propagate further apically after reaching its resonant peak, or place. Moreover, the viscous friction between the basilar membrane and cochlear fluids produces a damping effect that limits its displacement.

The Traveling Wave

The hydromechanical consequences of introducing a pressure pulse, or wave, into perilymphatic fluids is a traveling wave that propagates along the organ of Corti from the base to the apex (see Fig. 146-2). The traveling wave propagates basoapically, because the stiffness of the cochlear partition decreases longitudinally from the base to the apex (see Fig. 146-3F) as its mass increases. The motion and direction of the wave that travels along the basilar membrane are independent of the location of the vibratory source. von Békésy[586] observed this feature of cochlear mechanics by introducing a pressure pulse through an artificial window carved into the bony labyrinth near the cochlear apex. Traveling waves created under these conditions are essentially indistinguishable from traveling waves triggered by ossicular vibration. The basoapical propagation of the traveling wave is an outcome of the end organ's physical makeup, with the stiffer and less massive elements forming the base of the organ of Corti being set into motion by an instantaneous pressure difference between the major scalae before the more compliant and massive sections of the apical cochlea. The resultant traveling wave reflects the more or less independent, yet orderly, sequential movement of loosely coupled basilar membrane segments that form a frequency decomposition system generally thought of as the *space-frequency* or *tonotopic map* (see Fig. 146-3G).

As the traveling wave propagates toward the apex, traveling initially at a high rate of speed, the velocity of the wave decreases, with production of progressively shorter wavelengths for any given input frequency as a consequence (see Fig. 146-2E). As the amplitude of the propagating wave steadily increases as it passes toward the apex,

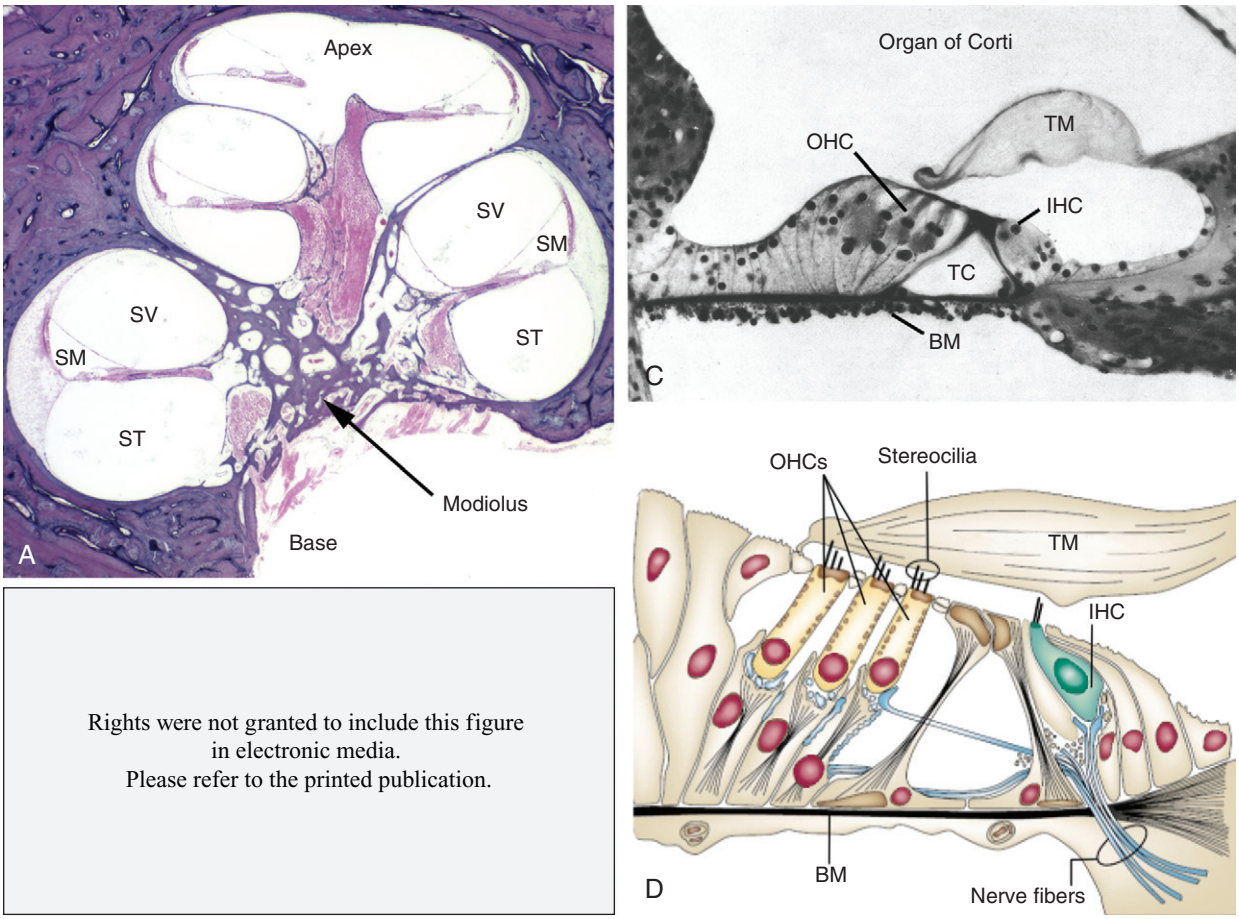

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Figure 146-1. **A,** Midmodiolar section through a human cochlea showing the basal *(lower)*, middle, and apical *(upper)* turns. The modiolus is the central core of the cochlea and houses spiral ganglion neurons. The cochlear duct, otherwise known as the scala media (SM), contains endolymph and is separated from the perilymphatic fluid chambers, scala tympani (ST), and scala vestibuli (SV) by the cochlear partition and Reissner's membrane, respectively. At the cochlear apex, the fluids of the ST and SV mix through an opening called the helicotrema. **B,** Higher-magnification image of a modiolar section through the basal turn of the cochlea of a Rhesus monkey. The organ of Corti rests on the cochlear partition, a structure that includes the basilar membrane (BM) and a layer of mesothelial cells lining the BM and facing the ST. The stria vascularis (StV) and spiral ligament (SLig) form the lateral boundary of SM. **C,** Cross section of the organ of Corti from the middle turn of a cat cochlea. The triangular-shaped tunnel of Corti (TC), formed by the inner and outer pillar cells, separates the inner hair cell (IHC) from the outer hair cells (OHCs). The tectorial membrane (TM) can be seen pulled away from the sensory cells. **D,** Representation of the organ of Corti, showing the one row of IHCs and three rows of OHCs. Note the fluid spaces surrounding the OHCs, and that the tallest stereocilia of OHCs are embedded in the tectorial membrane, whereas the stereocilia of IHCs do not reach the tectorial membrane. *(**A,** Courtesy of Dr. William B. Warr; **B,** from Engstrom H, Angelborg C. Morphology of the walls of the cochlear duct. In: Zwicker E, Terhardt E, eds.* Facts and Models in Hearing. *New York: Springer-Verlag; 1974:3; **C,** from Engstrom H, Ades HW, Andersson A.* Structural Pattern of the Organ of Corti. *Baltimore: Williams & Wilkins; 1966; **D,** from Dallos P, Fakler B. Prestin, a new type of motor protein.* Nat Rev Mol Cell Biol. *2002;3:104.)*

partition displacement reaches a maximum value at its characteristic place—where intrinsic resonance meets, and nearly matches, the vibratory frequency of the triggering acoustic event (see Fig. 146-2F). As pointed out previously, the stiffness of the basilar membrane decreases exponentially with distance from the stapes,[205,394,395,586] so it is not surprising that the resonant frequency also decreases exponentially as a function of distance from the stapes, because the characteristic place is determined by the stiffness of the cochlear partition. Thus, the aforementioned space-frequency, or tonotopic, map is created, whereby the peak in vibration amplitude is located at the base of the cochlea for high frequencies and at progressively apical regions for lower frequencies.

Just as stiffness dominates the physics of the traveling wave as it travels toward its characteristic place, basilar membrane motion at and just above the characteristic place is dominated by the mass of the system. It is important to point out that the actual peak of the traveling wave occurs at a location just basal to the true resonant place, characterized by a match between intrinsic resonance and the triggering vibratory energy. At the place of peak displacement, the traveling wave slows to an essential standstill (i.e., it stalls) before remaining energy is completely dissipated, and the partition is completely and rapidly restored to its resting position slightly apical to the resonant place. Near the characteristic place for a given stimulus frequency, the pressure wave returns to the basal end of the cochlea through the fluids of the scala tympani, where the flexible round window membrane is displaced in an equal but opposite direction to that of the volume displacement of the stapes footplate.

At the apical end of the cochlea, the endolymphatic space terminates just short of the bony labyrinthine wall and maintains a firm physical boundary between endolymph and perilymph, allowing the fluids in the scala vestibuli and scala tympani to communicate directly by way of a small duct called the helicotrema (see Fig. 146-3B). The helicotrema acts as an acoustic shunt across the cochlear partition that reduces the pressure difference between the scalae produced by very-low-frequency stimulation.[96] The size of the helicotrema is thought to determine the low frequency cutoff of the system; that is, large

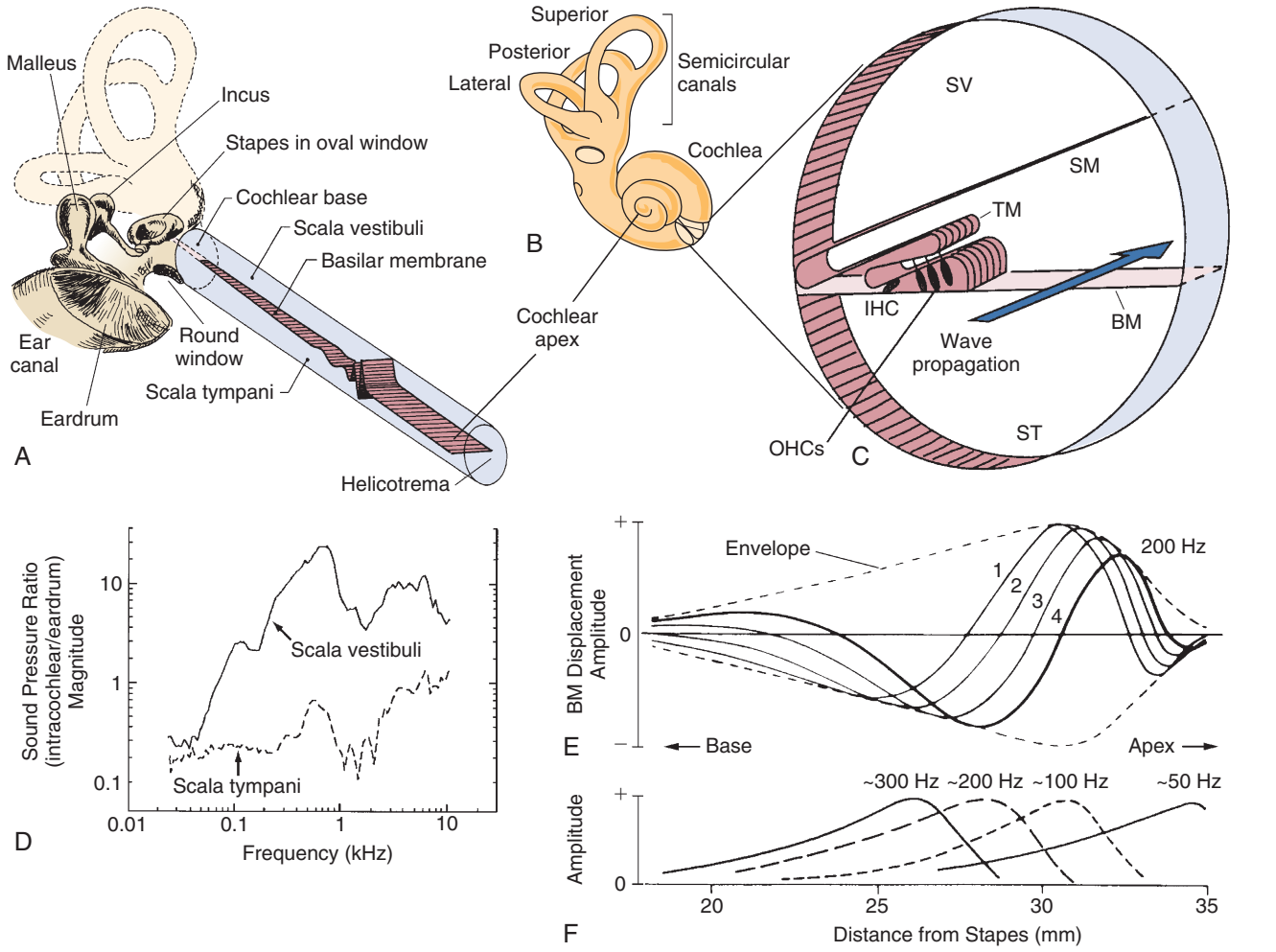

Figure 146-2. **A,** Schematic illustration of the inner ear with the cochlea uncoiled revealing the basilar membrane (BM) and a traveling wave at one instant in time in response to a pure tone. The eardrum (tympanic membrane) and middle ear ossicles also are shown in relation to the semicircular canals. The oval window opens into scala vestibuli (SV) and the round window to scala tympani (ST). **B,** Drawing of the inner ear with a segment of a cochlear turn extracted to expose the scalae. **C,** Diagram of a section through the cochlea showing the location of inner and outer hair cells (IHC and OHCs, respectively) in relation to the BM and TM and the direction of wave propagation. SM, scala media. **D,** The ratio of pressures measured within the SV and ST to the pressure at the eardrum produced in response to tone bursts are plotted as a function of stimulus frequency; responses were recorded from a cat. The difference between SV and ST pressures is responsible for displacement of the basilar membrane. **E,** BM displacements produced in a cadaveric human cochlea in response to 200 Hz at four separate points in time. The envelope of the traveling wave also is indicated. **F,** Envelopes of traveling waves measured along the BM in a cadaveric human cochlea in response to four stimulus frequencies, showing the relationship between the location of peak displacement and frequency (higher frequencies produce peaks at locations progressively closer to the base). *(**A,** From Dallos P, Fakler B.* Nat Rev Md Cell Biol. *2002;3:104; **B,** from Holme RH, Steel KP. Genes involved in deafness.* Curr Opin Genet Dev. *1999;9:309; **C,** adapted from Ashmore JF, Kolston PJ. Hair cell based amplification in the cochlea.* Curr Opin Neurobiol. *1994;4:503; **D,** from Nedzelnitsky V. Sound pressures in the basal turn of the cat cochlea.* J Acoust Soc Am. *1980;68:1676; **E** and **F,** from von Bekesy G.* Experiments in Hearing. *New York: McGraw-Hill; 1960.)*

openings shunt pressure waves extending to higher frequencies than those associated with small helicotrema. The shunting effect of helicotrema reduces the pressure differential across the cochlear partition, and it is this aspect of cochlear design that is thought to decrease damage to the cochlea produced by intense low-frequency pressure fluctuations.[403]

Active Cochlear Mechanics

Von Békésy recognized more than half a century ago that the envelope of the traveling wave measured in cochleae from human cadavers is broadly tuned—so broadly tuned as to be inconsistent with a living person's ability to discriminate closely spaced frequencies. Numerous groups of investigators have since confirmed the findings of von Békésy and have shown with clarity that sharp tuning and high sensitivity are lost in physiologically compromised cochleae or cochleae from cadavers.[432,494] Only after mechanical measurements were made in vivo with nonhuman species did it become clear that the peak of the traveling wave in living animals is, in fact, very sharply tuned at low levels of stimulation and exhibits nonlinear growth as sound levels increase.[274,314,433,454,494] The seminal study of Rhode,[433] which showed the amplitude of basilar membrane vibration relative to stapes displacement to be as much as two to three orders of magnitude greater under low-stimulus-level conditions than at higher levels in normal animals, led most directly to the contemporary understanding of cochlear mechanics as a nonlinear phenomenon (i.e., high sensitivity to changes in stimulus pressure at low levels, marked compression in the midlevel range, and linear growth at high levels) (Fig. 146-4).

Active mechanics associated with basilar membrane amplification is a metabolically labile, energy-consuming process that is, consequently, physiologically vulnerable. It is of particular importance to

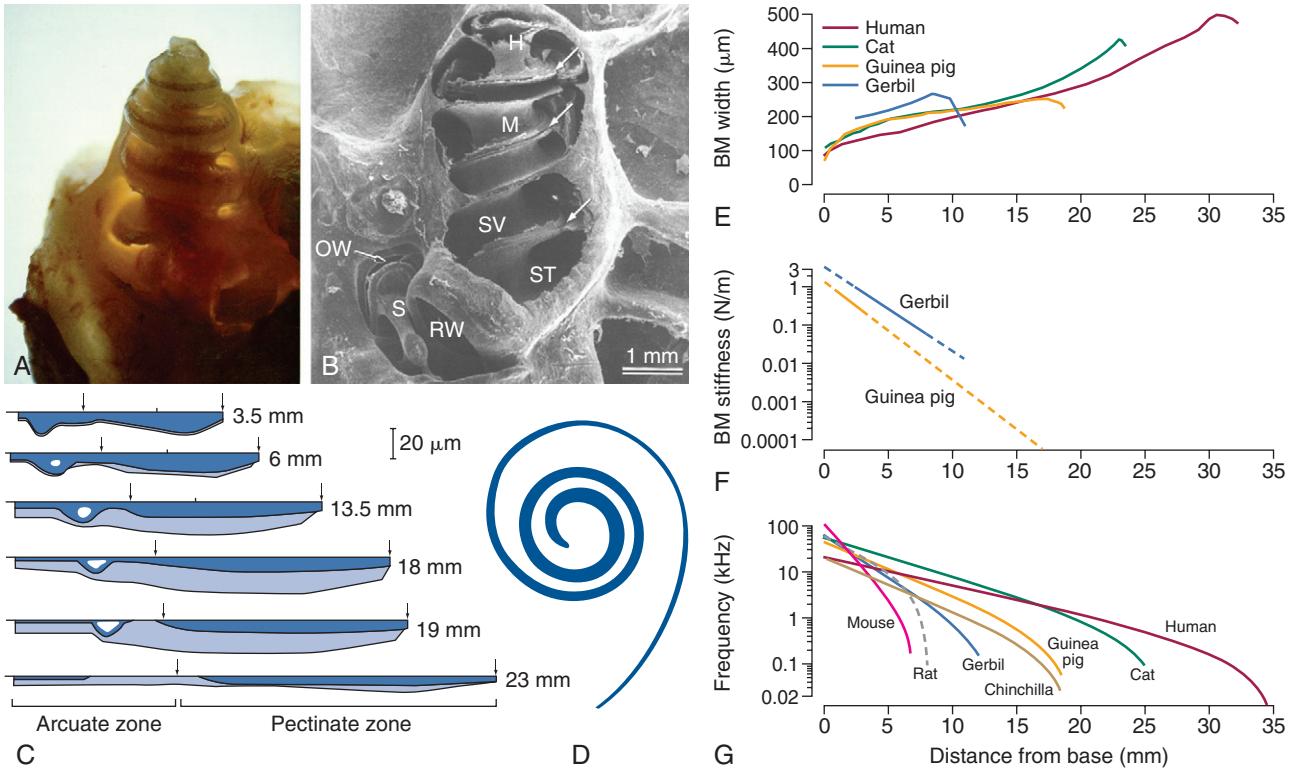

Figure 146-3. **A,** Photograph of the cochlea of a guinea pig after the outer bony shell has been thinned. **B,** Scanning electron micrograph (SEM) of a chinchilla cochlea after the bone on one side has been removed. The bony modiolus (M) is shown in the center, and the fluid-filled scala tympani (ST) and scala vestibuli (SV) are indicated in the basal turn. The helicotrema (H) is shown at the apex, and the *arrows* indicate the osseous spiral lamina to which the cochlear partition is attached at its medial extent. The round window (RW) and the stapes (S) are indicated, and the footplate of the stapes has been pulled away slightly, exposing the oval window (OW). **C,** Schematic illustration of the variation in thickness of the basilar membrane *(dark blue area)* and the associated mesothelial layer *(light blue area)* and the width of the basilar membrane *(horizontal axis)* at six locations along the cochlear spiral of the cat; specified locations are relative to the base. The demarcation between the arcuate and pectinate zones is indicated by the *left arrow* at each location; the arcuate zone (pars tecta) extends from the lip of the osseous spiral lamina to the foot of the outer pillar cell (OPC) and the pectinate zone from the OPC to the basilar crest of the spiral ligament *(right arrows)*. **D,** Scaled representation of the ribbon-like nature of the human basilar membrane indicating its width relative to its length. **E,** Quantitative relationship between the width of the basilar membrane (BM) and the distance from the base for the human,[604] cat,[64] guinea pig,[154] and gerbil.[445] **F,** Estimates of the stiffness of the basilar membrane in the guinea pig[205] and gerbil[139] as a function of location. **G,** Maps of the characteristic frequency (CF) of a cochlear location (i.e., peak of the envelope of the traveling wave) as a function of position along the basilar membrane for several species. Note that the lengths of the basilar membrane for each species can be estimated by the distance that each curve occupies along the x-axis. Frequency-position maps were based on a formulation developed by Greenwood[196] using empirical fits to data for the species shown here, except for rat, which was developed by Muller.[374] *(**A,** From Wasterstrom SA. Accumulation of drugs on inner ear melanin. Therapeutic and ototoxic mechanisms.* Scand Audiol Suppl. *1984;23:1; **B,** from Harrison RV, Hunter-Duvar IM. An anatomical tour of the cochlea. In: Jahn AF, Santos-Sacchi J, eds.* Physiology of the Ear. *New York: Raven Press; 1988:160; **C,** from Cabezudo LM. The ultrastructure of the basilar membrane in the cat.* Acta Otolaryngol. *1978;86:160; **D,** from Wever EG.* Theory of Hearing. *New York: Dover Publications; 1949.)*

recognize that the active mechanical event underlying amplification is highly localized. That is, the principle of active mechanics applies to a circumscribed portion of the cochlear partition that is limited to the immediate vicinity of the characteristic place for a given stimulus frequency (see Fig. 146-4A and B). At frequencies removed from the characteristic place, the properties of cochlear partition vibration in a living animal follow linear rules of growth, as in cadaverous tissue (Fig. 146-5).[179] Another important point is that the traveling wave peaks at increasingly apical regions of the cochlear partition with increasing stimulus level, shifting the cochlear place-frequency map toward lower frequencies at any given place.

Role of Outer Hair Cells in Active Mechanics

Many early studies indicated that OHCs play a fundamental role in active cochlear mechanics, as indicated by estimates of diminished cochlear sensitivity and frequency selectivity and loss of nonlinear operating properties when OHCs are missing from the end organ (see Fig. 146-4). The identification of specializations that distinguish inner hair cells (IHCs) from OHCs of the mammalian cochlea offered early clues that the contribution of OHCs to the transduction process is unique (Fig. 146-6). For example, only approximately 5% of all auditory nerve fibers innervate OHCs,[371,525,524] yet there are at least three times as many OHCs as IHCs (Fig. 146-7). These findings suggested that the transmission of sensory information to the central nervous system (CNS) probably is not the primary function of OHCs. In studies of acute preparations, investigators noted that the cochlea, and OHCs in particular, are highly vulnerable to hypoxia or other forms of insult.[76,148,293,432,433,448,449,494] In animal models of chronic damage, OHCs were found to be more susceptible to noise-induced or aminoglycoside-induced damage than IHCs, and when OHCs were lost, with IHCs appearing unaffected, cochlear sensitivity was significantly reduced, as was frequency selectivity, and input-output curves acquired a more linear character in the region of OHC damage.[77,97,101,149,208,278,279,329,450,465] In addition, other cochlear nonlinearities, such as two-tone suppression (i.e., the reduction in the response to one tone elicited by the presence of another) and distortion tones (i.e., the appearance of additional tones not present in the stimulus produced by the interaction of two or more primary tones, such as $2f_1$-f_2 or f_2-f_1, where f_1 and f_2 represent the

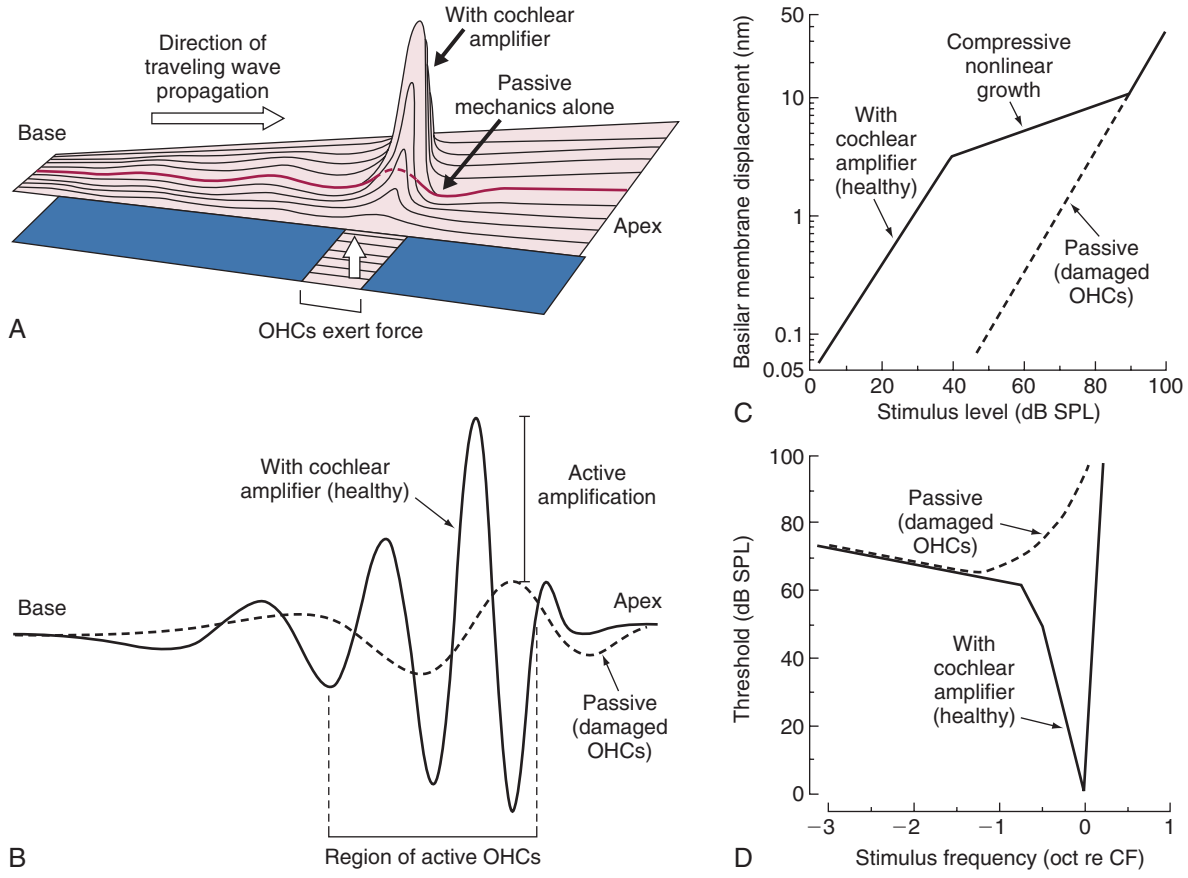

Figure 146-4. **A,** Schematic representation of traveling waves propagating along the basilar membrane (BM) in response to a pure tone. When the cochlear amplifier is functioning, outer hair cells (OHCs) within a restricted region of the traveling wave peak exert a force that enhances BM motion relative to that observed during passive mechanics alone for low-level stimuli. **B,** Similar to **A,** except note that the peak of the traveling wave produced with cochlear amplification is much narrower than the peak produced during passive mechanics alone, which is important for frequency discrimination. Also note that during active amplification, the peak of the traveling wave occurs slightly more basal than that produced during passive mechanics. **C,** Schematic relationship between stimulus level and BM displacement. When OHCs are normal, stimulus level increments of less than 40 dB sound pressure level (SPL) produce a linear increase in BM displacement. Between approximately 40 and 80 dB SPL, OHC responses saturate, producing a compressed response and nonlinear growth. Above 80 dB SPL, growth becomes linear again. When OHCs are damaged, displacements occur only to higher level stimuli and exhibit linear growth. **D,** The relationship between stimulus frequency (measured in octaves relative to the characteristic frequency [oct re CF] at that location) and the level required to elicit a criterion or "threshold" response at a given point along the BM (e.g., tuning curves). When the cochlear amplifier is operational, thresholds may be 40 to 60 dB lower and frequency selectivity greatly enhanced compared with a passive cochlea. *(**A,** From Ashmore JF, Kolston PJ. Hair cell based amplification in the cochlea.* Curr Opin Neurobiol. *1994;4:503.* ***B,** from Gummer AW, Preyer S. Cochlear amplification and its pathology: emphasis on the role of the tectorial membrane.* Ear Nose Throat J. *1997;76:151.)*

primary tones, with f_1 less than f_2), are either lost or diminished when OHCs are traumatized.[102,480] The discovery of sound-evoked otoacoustic emissions, sounds that are generated by the end organ during transduction and are measured in the external ear canal,[270] along with spontaneous otoacoustic emissions,[608] and their dependence on OHCs provided additional evidence that an active, OHC-driven mechanism operates within the cochlea, which is capable of producing energy and propagating it in the reverse direction. The influence of OHCs on cochlear mechanics was further suggested on the basis of observations made after stimulating the crossed olivocochlear bundle (OCB), a brainstem pathway populated by large, myelinated fibers that arise among neurons located in the medial region of the superior olivary complex that cross the brainstem at the floor of the fourth ventricle and terminate in calyx-like presynaptic terminals on OHCs.[200,287,427,428,518,597,598] Specifically, OCB activation altered cochlear output,[118,155,156,176,605] as well as otoacoustic emissions[373,505] and basilar membrane displacement,[376] supporting the notion that OHCs directly influence cochlear mechanics. Further support for the view that OHCs play an essential role in active mechanics comes from the work of Mammano and Ashmore,[349] who demonstrated that outer hair cell motility induced by electrical stimulation of the excised cochlea displaced both the reticular lamina and the basilar membrane.

Prestin (SLC26A5) Is Essential for Outer Hair Cell Motility and Active Transduction

The finding that OHCs contract or elongate at very high rates (up to at least 70 kHz) along the length of their longitudinal axes when depolarized or hyperpolarized, respectively,[30,62,63,98,99,168,177,261,478,630] led to the suggestion that OHCs may amplify the displacement of the basilar membrane if forces generated by their motility are produced on a cycle-by-cycle basis and precisely timed relative to passive mechanical events (see Fig. 146-6E). Somatic length changes of up to 5% of the total length of OHCs are determined directly by the magnitude of the transmembrane voltage and not by ionic currents. In addition, the voltage-motility relationship observed among OHCs is highly nonlinear (Fig. 146-8B). Unlike in IHCs, the lateral wall of OHCs is densely packed with particles that are integral components of the plasma membrane,[165,202,264,470] and these particles are thought to be oligomers of the protein recently identified as the molecular motor underlying fast somatic motility (see Fig. 146-6C and E).

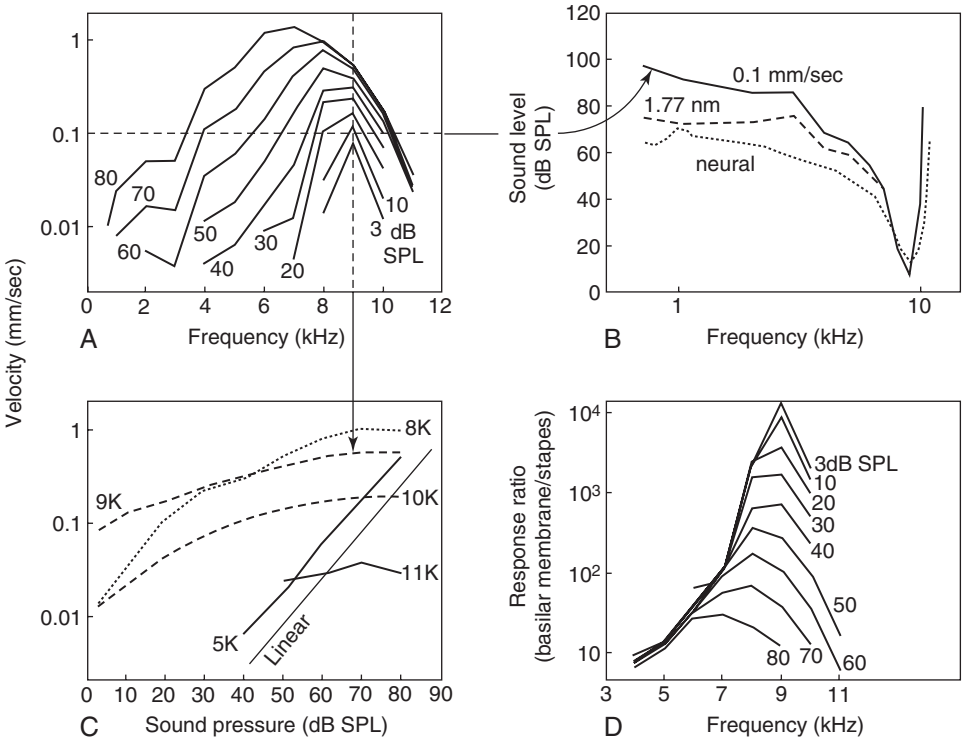

Figure 146-5. Measurements of basilar membrane (BM) motion in a healthy chinchilla cochlea at one location near the base in response to tone bursts. **A,** Measurement of BM velocity in response to tone bursts of different frequencies *(abscissa)* at various levels (parameter). The characteristic frequency (CF) at this location is 9 kHz. SPL, sound pressure level. **B,** Tuning curves (i.e., stimulus levels required to generate a criterion response as a function of stimulus frequency) are shown for a criterion BM velocity of 0.1 mm/sec and for a criterion displacement amplitude of 1.77 nm. Data were taken from **A.** A tuning curve from an auditory nerve fiber that innervates this BM location is also shown. **C,** BM velocities as a function of stimulus level for various frequencies. A line showing a linear relationship between velocity and level also is shown. **D,** The ratio between BM velocity and stapes velocity (i.e., gain) as a function of stimulus frequency. Note the high gain (i.e., amplification) at low stimulus levels near the CF location that is reduced as a stimulus level increases. *(**A** and **B,** From Ruggero MA, Rich MC. Application of a commercially-manufactured Doppler-shift laser velocimeter to the measurement of basilar-membrane vibration.* Hear Res. *1991;51:215; **C,** from Ruggero MA. Responses to sound of the basilar membrane of the mammalian cochlea.* Curr Opin Neurobiol. *1992;2:449; **D,** from Ruggero MA, Robles L, Rich NC, Recio A. Basilar membrane responses to two-tone and broadband stimuli.* Philos Trans R Soc Lond B Biol Sci. *1992;336. The figure was prepared by Geisler CD.* From Sound to Synapse: Physiology of the Mammalian Ear. *New York: Oxford University Press; 1998.)*

The discovery that OHC motility is accompanied by gating currents that reflect a nonlinear capacitance led to the suggestion that it was the movement of charged particles within the domain of the plasma membrane that operates as the motive force of contractility.[31,476] The voltage-sensitive motor protein underlying the process was identified in 2000 and given the name prestin (SLC26A5). Prestin (Fig. 146-8A) is a modified anion-transporter protein belonging to the solute carrier 26 (SLC) family of proteins.[633] Antibodies to prestin have been localized in OHC membranes, and developmental changes in the expression of prestin immunoreactivity follow a temporal profile that overlaps the development of electromotility, providing further support for the view that prestin is the motor protein.[42] Although the precise location of the voltage sensor remains unknown, and although it may be an integral component of the prestin molecule itself, findings from recent studies suggest that intracellular Cl^- ions act as extrinsic charged voltage sensors (see Fig. 146-8B, inset). In this model, Cl^- ions occupy a position in the intracellular domain of the membrane-bound prestin protein and move along an inward electrical gradient away from the extracellular domain during depolarization. This charge movement produces, in turn, a conformational change in the protein that reduces its surface area and shortens the cell; the opposite action occurs during hyperpolarization, when Cl^- ions move toward the extracellular space within the domain of the protein (although the anion is never translocated to the extracellular space), causing an increase in surface area and lengthening of the cell.[100,391] Salicylates, which are known to cause temporary hearing loss when administered at high doses,[535] are permeable to the plasma membrane and act as competitive antagonists of Cl^-, thereby reducing electromotility and, presumably, diminishing sensitivity.[391] The role of prestin in transduction was studied directly in a mouse strain in which prestin was deleted. The knockout mouse exhibited a loss of OHC electromotility in homozygous mutant animals (see Fig. 146-8D), a 40- to 60-dB loss in sensitivity, and loss of OHCs in the base of the cochlea (see Fig. 146-8C).[328] In addition, the frequency selectivity of individual auditory nerve fibers is diminished in knockout mice.[68] Although the length and stiffness of OHCs are reduced in the knockout mouse, these findings collectively suggest that active transduction is a direct product of OHC somatic motility. Confirmation of prestin's role in cochlear amplification was recently established in a study of a "knock-in" mouse model, in which the protein's function was diminished but OHCs exhibited normal length and stiffness.[103] Natural mutations of the prestin gene have been identified in humans, and the resulting condition is transmitted as a recessive, nonsyndromic form of congenital deafness. In this case, however, hearing loss is in the severe to profound category (i.e., on the order of 90 dB or greater) and exists as a bilateral form of deafness among persons who are homozygous for the trait. The degree of hearing loss is more variable among heterozygotes, ranging from normal in one case to mild (40 dB) and even moderate to profound (60 dB) in others, suggesting the semidominance of the abnormal allele through haploinsufficiency.[337]

Conversion of Basilar Membrane Displacement to Radial Shearing Forces

All existing models of transduction center on the idea that displacement of the basilar membrane results in a radial shearing motion between

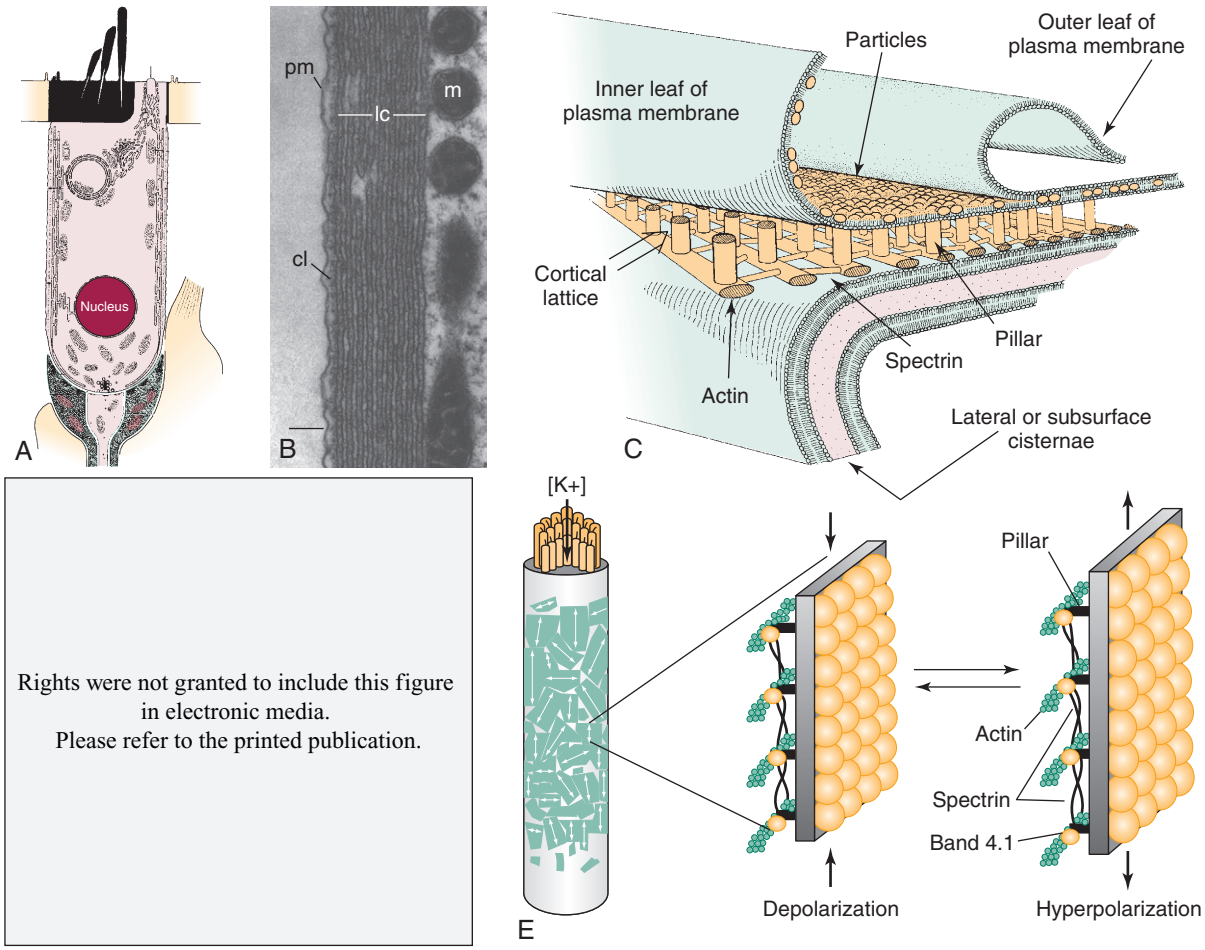

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Figure 146-6. **A,** Drawing of an outer hair cell (OHC) showing the cylindrical soma; the nucleus located near the basal end of the cell; the cuticular plate at the apex of the cell where the rootlets of the stereocilia insert; the subsurface cisternae, which are stacks of smooth endoplasmic reticulum that line the lateral sides of the cell; and Hensen's body, which is a continuation of the endoplasmic reticulum, located beneath the cuticular plate. This structure probably functions as a Golgi apparatus. **B,** Transmission electron microscopy of the lateral membrane of a guinea pig OHC, showing the plasma membrane (pm), the cortical lattice (cl) just beneath the membrane, the lateral cisterns (lc), and mitochondria (m) just inside the cisterns. Scale bar is 200 nm. **C,** Diagram of the OHC lateral membrane, where the inner and outer leaflets of the plasma membrane have been separated revealing a high density of membrane particles not present in IHCs, which presumably are oligomers of the motor protein prestin. The cortical lattice is composed of many subdomains of parallel actin filaments oriented circumferentially around the cell that are cross-linked by spectrin. The actin filaments are bound to the plasma membrane by pillar molecules (composition unknown), and the subsurface cisternae lie just inside the cortical lattice. **D,** Illustration of the expanded apical surfaces of the inner and outer pillar cells (IP and OP, respectively) in relation to the apical surfaces of OHCs and the phalangeal processes of Deiters cells (D1, D2, D3) forming the reticular lamina. **E,** Diagram of the orientation of several subdomains of membrane particles *(left)* and an array of particles that undergo conformational changes that alter particle packing density associated with a change in transmembrane voltage. During depolarization, tighter packing results in shortening of the subdomain, as well as the hair cell itself, and during hyperpolarization, elongation occurs. *(**A,** from Lim DJ. Functional structure of the organ of Corti: a review.* Hear Res. *1986;22:117; **B,** from Holley MC. Outer hair cell motility. In: Dallos P, Popper AN, Fay RR, eds.* The Cochlea. *New York: Springer-Verlag; 1996:386; **C,** adapted from Oghalai, et al.* J Neurosci. *1998;18:48; **D,** from Slepecky NB. Structure of the mammalian cochlea. In: Dallos P, Popper AN, Fay RR, eds.* The Cochlea. *New York: Springer-Verlag; 1996:44; **E,** from Frolenkov GI, Atzori M, Kalinec F, Mammano F, Kachar B. The membrane-based mechanism of cell motility in cochlear outer hair cells.* Mol Biol Cell. *1998;9:1961.)*

the reticular lamina and the tectorial membrane, a motion that serves as the mechanical trigger of transduction currents. The reticular lamina consists of the interdigitating heads of the inner and outer pillar cells, the apical surfaces of the phalangeal processes of Deiters cells, and the apical surfaces of the hair cells through which the stereocilia project (see Fig. 146-6D). The apical surfaces of the supporting cells are flattened and are composed of microtubules and actin microfilaments, lending support to the idea that the reticular lamina is a relatively rigid structure that moves in concert with basilar membrane motion. The tectorial membrane is firmly attached to the spiral limbus and overlies the reticular lamina, with its tip or marginal zone connected to Hensen cells. The tallest row of stereocilia protrude from the apical surface of each outer hair cell and embed within the inferior surface of the tectorial membrane along the entire length of the cochlear spiral.[288,333] Bundles of radially oriented filaments, consisting of type II, V, IX, and XI collagens, are embedded within the gelatinous matrix of the mammalian tectorial membrane (see Fig. 146-10A and B).[209,361,444,514,515,545,546] The presence of collagen enhances the rigidity of the structure, making it less compressible and less elastic, particularly in the radial dimension.[3,199,446] These features support a system in which the shearing motion between the reticular lamina and the tectorial membrane causes stereocilia to bend in the direction of the modiolus or the spiral limbus, depending on whether the basilar membrane is displaced toward the scala tympani or scala vestibuli, respectively.

In contrast with OHCs, the stereocilia of IHCs do not appear to firmly contact the tectorial membrane (see Fig. 146-1D). Therefore,

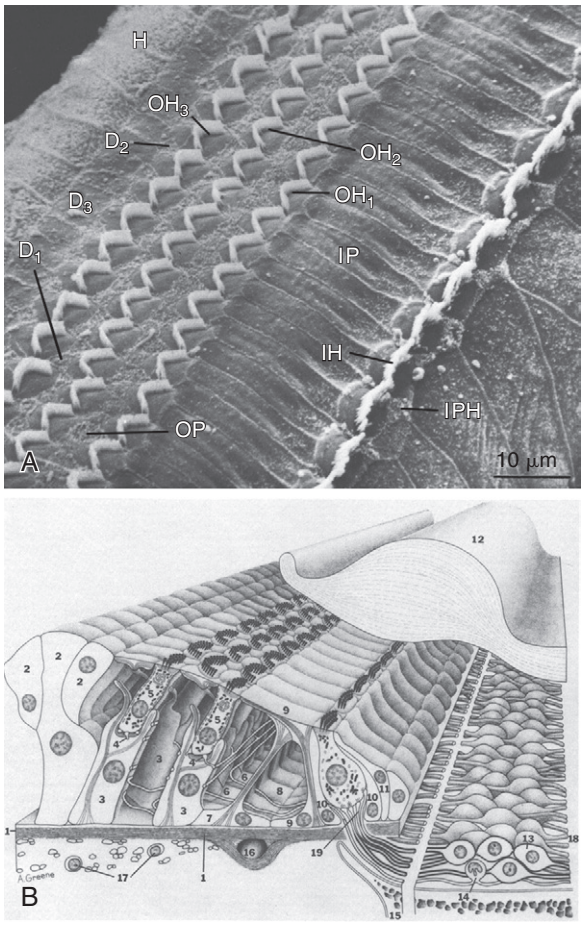

Figure 146-7. A, Scanning electron micrograph of the surface of the organ of Corti of a chinchilla showing the three rows of outer hair cells (OH_1, OH_2, OH_3), one row of inner hair cells (IH), inner and outer pillar cells (IP and OP, respectively), inner phalangeal cell (IPH), Deiters cells (D_1, D_2, D_3), and Hensen cells (H). **B,** Schematic illustration of the structure of the organ of Corti: 1, basilar membrane; 2, Hensen cells; 3, outer phalangeal cells; 4, nerve endings; 5, outer hair cells; 6, outer spiral fibers; 7, outer pillar cells; 8, tunnel of Corti; 9, inner pillar cells; 10, inner phalangeal cells; 11, border cells; 12, tectorial membrane; 13, type I spiral ganglion cell (SGC); 14, type II SGC; 15, bony spiral lamina; 16, spiral blood vessel; 17, spindle cells; 18, auditory nerve fibers; 19, radial fiber. *(**A,** From Lim DJ. Functional structure of the organ of Corti: a review.* Hear Res. *1986;22:117; **B,** from Kiang NY: Peripheral neural processing of auditory information. In: Darian-Smith I, ed.* Handbook of Physiology. *New York: Oxford; 1984:639.)*

during basilar membrane vibration, the relevant mechanical stimulus to IHC stereocilia is thought to be the flow of endolymph within the subtectorial space, the narrow channel between the reticular lamina and tectorial membrane into which the stereocilia protrude.[387] Fluid coupling is then thought to lead directly to the displacement of IHC stereocilia in proportion to basilar membrane velocity at low frequencies (less than 500 Hz) and to basilar membrane displacement at higher frequencies; sustained displacements of the basilar membrane, or very-low-frequency displacements, do not effectively bend IHC stereocilia.[403]

Radial Displacement Patterns of the Basilar Membrane

The dynamics of basilar membrane displacement at the characteristic frequency place are more complex when examined radially. Inner and outer pillar cells that form the fluid-filled tunnel of Corti are packed with bundles of microtubules and actin microfilaments arranged in parallel that are cross-linked and are thought to produce structural rigidity within the cochlear partition.[25,140,244] The foot of the inner pillar cell lies near the bony spiral lamina, whereas the foot of the outer pillar cell lies over the basilar membrane and is not supported by bone (Fig. 146-9). Therefore, when the basilar membrane is displaced in a passive cochlea, movement occurs maximally near the foot of the outer pillar cell, with the basilar membrane pivoting at the foot of the inner pillar cell.[104] When OHCs contract, the reticular lamina pivots at the apex of the tunnel of Corti, and the basilar membrane and reticular lamina are pulled together, enhancing overall basilar membrane displacement.[168,349,350,383] Furthermore, unlike in passive mechanical events, in which the full width of the basilar membrane moves uniformly (synchronously), during active mechanics, the magnitude and phase of displacement vary in the radial dimension.[83,383,388,395,396,431,495,563,609,622] Although differences among studies from different laboratories are significant regarding the precise pattern of basilar membrane movement in the radial direction after displacement, many workers suggest that the position of greatest motion is in the domain of the OHC, and that motion in the OHC region is out of phase relative to the foot of the outer pillar cell. This finding has significant implications in the ongoing effort to understand the relationship between inner and outer hair cell responses during the transduction process.

Tectorial Membrane Pathophysiology

The tectorial membrane is composed of two primary matrix elements: a group of radially oriented collagen fibrils and a striated sheet matrix that is made up of tightly packed, small-diameter filaments that are interlinked by cross-bridges to give it a striated appearance.[209,288,300,333,559] In addition to the variety of collagens making up the core structure, a collection of glycoproteins—α-tectorin, β-tectorin, and otogelin—also are constituent elements of the tectorial membrane.[78,193,285,319,444] Otogelin, a glycoprotein that is found in essentially all of the acellular membranes of the inner ear, is associated with the large collagen fibrils, whereas α-tectorin and β-tectorin are components of the striated sheet matrix.

The mass and stiffness of the tectorial membrane are important variables that together determine the resonant properties of the structure that, in turn, affects its displacement pattern during acoustic stimulation. Much like dimensional changes that have been measured along the length of the basilar membrane, the cross-sectional area of the tectorial membrane has been shown to increase from the base to the apex as indicated by morphometric measurements of fully hydrated tissue specimens (Fig. 146-10C).[445] Moreover, base-to-apex stiffness gradients in both the transverse and radial axes of the tectorial membrane have been observed,[199,446] and they are similar to those reported for basilar membrane stiffness gradients (see Fig. 146-10C).[139,205] Taken together, basoapical gradients in the physical properties of the tectorial membrane suggest the possibility that the structure may support longitudinally propagating traveling waves,[181] giving rise to a second cochlear frequency-place map. Some investigators have suggested that the resonant frequency of the tectorial membrane lies approximately one-half octave below that of the basilar membrane's characteristic or resonant frequency at any given position along the cochlear spiral.[17,18,203,641] However, until the opportunity to study mutant mice in which the tectorial membrane is completely detached from the spiral limbus and the surface of the organ of Corti[317] presented itself, direct evidence regarding the precise role of the tectorial membrane as an element of transduction was largely unavailable.

Targeted disruption of the gene that encodes α-tectorin (*Tecta*) in mice ($Tecta^{\Delta ENT/\Delta ENT}$) leads to loss of not only α-tectorin but also β-tectorin and otogelin.[317] In addition, the striated sheet matrix is absent, and collagen fibrils are disorganized in the tectorial membranes of mice that are homozygous for the deletion, not to mention that the structure is detached from the spiral limbus and floats freely in scala media. Like the IHC stereocilia of normal animals, the stereocilia of OHCs in α-tectorin–mutant mice are fluid-coupled to end organ motion, and mice exhibit elevated thresholds that reflect that condition (i.e., generally elevated neural thresholds decrease at a rate of approximately 6 dB/octave with increasing frequency). Mechanical input-output curves constructed from responses to tone bursts presented at characteristic frequency also are more linear (although approximately 35 dB less sensitive), and frequency selectivity is normal, or at least

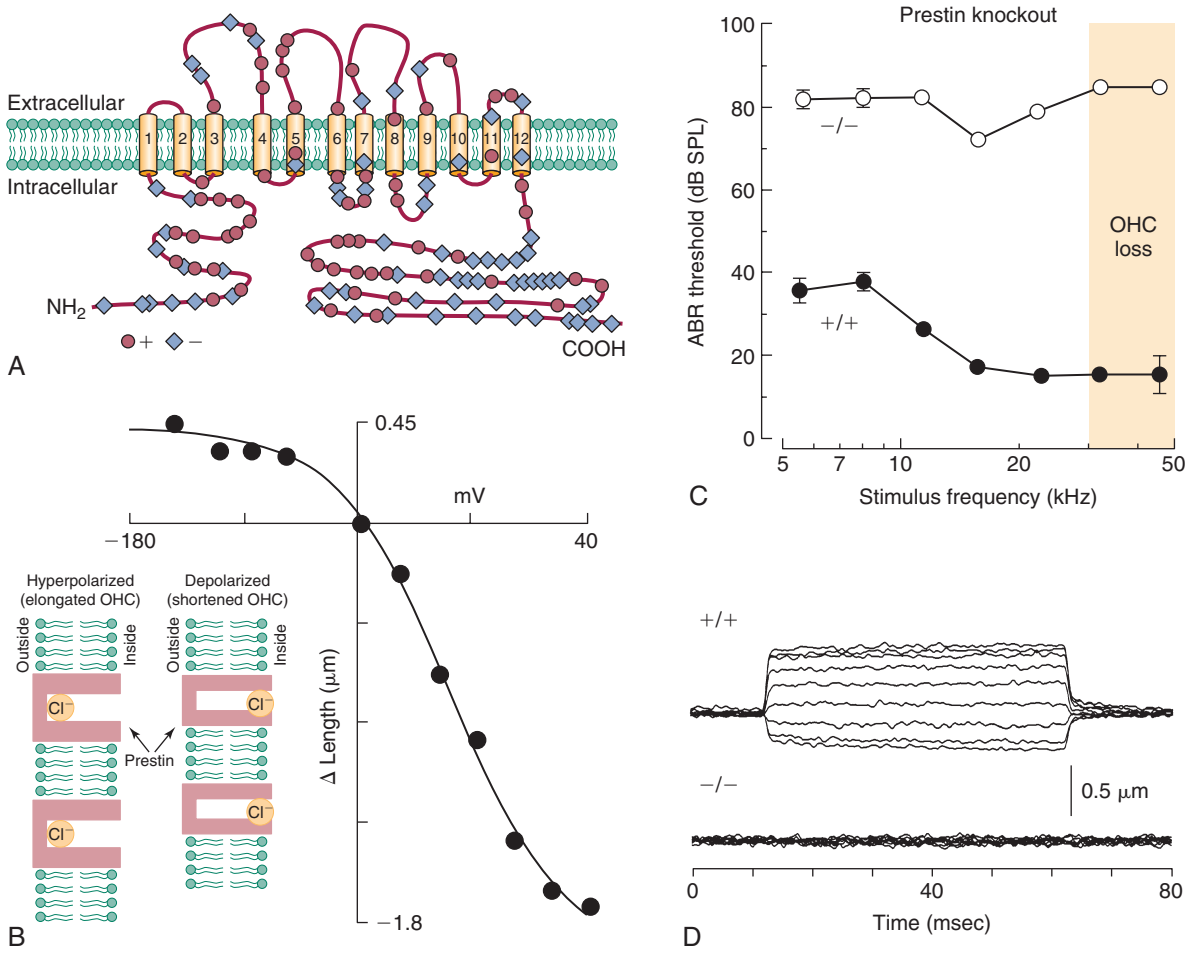

Figure 146-8. **A,** Schematic representation of the membrane topology of prestin (SLC26A5). Prestin consists of 744 amino acids and is predicted to have 12 transmembrane domains and intracellular amino-terminal (NH_2) and carboxyl-terminal (COOH) ends. *Circles* and *diamonds* represent positively and negatively charged amino acids, respectively. **B,** Change in the length of an isolated outer hair cell (OHC) as a function of voltage stepped from a holding potential of –68.4 mV. The *inset* is an illustration of single prestin molecules located in the plasma membrane that can toggle between two conformational states, depending on transmembrane voltage. The larger the depolarization, the greater likelihood that the shorter state will be adopted, and vice versa. The nonlinear capacitance associated with length changes may be due to the translocation of anions, such as Cl^- *(yellow circles)*, that move closer to the extracellular side during hyperpolarization and toward the intracellular side during depolarization. **C,** Targeted disruption of prestin results in severely elevated auditory brainstem response (ABR) thresholds in homozygous mice, and somatic motility is absent in isolated OHCs (**D**). *(**A,** From Dallos P, Fakler B. Prestin, a new type of motor protein.* Nat Rev Mol Cell Biol. *2002;3:104; Reprinted by permission from Macmillan Publishers Ltd. **B,** from Santos-Sacchi J. On the frequency limit and phase of outer hair cell motility: effects of the membrane filter.* J Neurosci. *1992;12:1906;* inset, *prepared by M. Walsh; **C,** and **D,** adapted from Liberman MC, Gao J, He DZ, et al. Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier.* Nature. *2002;419:300.)*

nearly so. Of interest, a second region of sensitivity in basilar membrane tuning curves that is approximately 0.5 octave below the best frequency in normal mice is not observed in α-tectorin mutant mice, suggesting that the tectorial membrane may be responsible for that second resonance.

These findings suggest that the tectorial membrane is required for OHCs to amplify displacement of the basilar membrane at low stimulus levels. In humans, mutations in the *TECTA* gene are responsible for both recessive and dominant forms of deafness—DFNB21, DFNA8, and DFNA12.[378,574] In patients with DFNA8 or DFNA12, hearing loss is congenital and nonprogressive[574] and can be more severe in the midfrequency than other frequency ranges, whereas patients with DFNB21 experience severe-to-profound deafness, and the onset can be either prelingual or postlingual.[378]

Further insight into the tectorial membrane's role in transduction can be found by studying a strain of mice in which the *Tecta* gene is disrupted at the same location (Y1870C)[318] as a mutation found in patients with autosomal dominant hearing loss associated with a missense mutation in the *TECTA* gene.[574] The tectorial membrane is detached and individuals exhibit a phenotype similar to that observed in $Tecta^{\Delta ENT/\Delta ENT}$ mice in the case of homozygotes, whereas the tectorial membrane remains attached in heterozygous mice, although the striated sheet matrix is disrupted, Hensen's stripe is lost, and the subtectorial space in the region of IHCs is enlarged. Although basilar membrane thresholds are minimally elevated (approximately 10 dB) in heterozygotes, neural thresholds are elevated by approximately 55 dB, suggesting that the precise spatial relationship between the tectorial membrane and reticular lamina in the region of the IHCs is a critical factor associated with fluid coupling between IHCs and OHCs.

As with mice expressing an abnormal *Tecta* gene, loss of β-tectorin in the tectorial membrane is associated with the loss of the striated sheet matrix and Hensen's stripe, although the tectorial membrane itself remains attached to the spiral limbus.[462] Both α-tectorin and otogelin have been detected in the tectorial membrane of mutant animals, and imprints of the tallest row of outer hair cell stereocilia have been observed on the underside of the membrane. Although basilar membrane sensitivity is just slightly diminished at the base of the cochlea in affected animals (i.e., tuning curve tips are elevated approximately 10 dB), tuning curve sharpness is enhanced, and the second resonance normally observed below the best frequency is lost. In contrast with

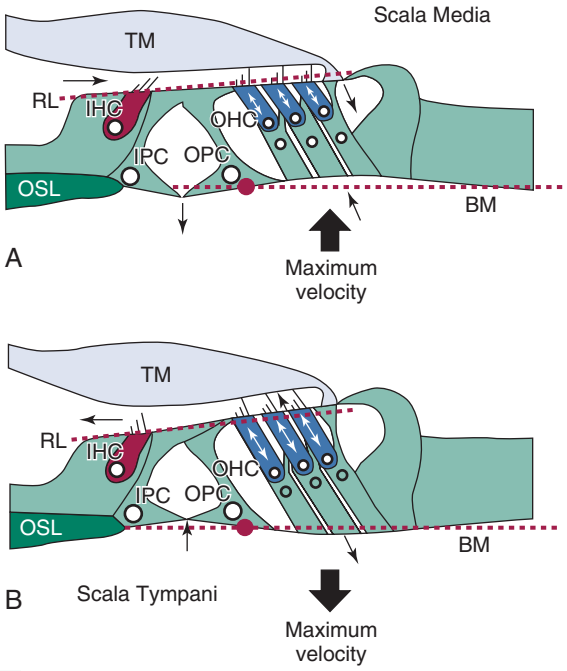

Figure 146-9. Model of basilar membrane (BM) vibration across the radial extent of the membrane. **A,** As the BM moves toward scala vestibuli, at the point of maximum BM velocity, the shearing motion between the BM and tectorial membrane (TM) causes the stereocilia to bend in the excitatory direction, producing depolarization and contraction or shortening of the outer hair cells (OHCs), pulling the reticular lamina (RL) toward the BM. IHC, inner hair cell; IPL, inner pillar cell; OPC, outer pillar cell; OSL, osseus spiral lamina. **B,** As the BM moves toward the scala tympani, and at the point of maximum BM velocity, hair bundles are deflected in the inhibitory direction, causing hyperpolarization and elongation of the OHCs. *Dotted lines* indicate the positions of the BM and RL at rest. Note that the *large red dot* along the BM located at the foot of the OPC represents a pivot point, which allows the displacement of the BM beneath the tunnel of Corti to be out of phase with the displacement that occurs under the OHCs. *(Redrawn from Nilsen KE, Russell IJ. The spatial and temporal representation of a tone on the guinea pig basilar membrane.* Proc Natl Acad Sci U S A. *2000;97:11751.)*

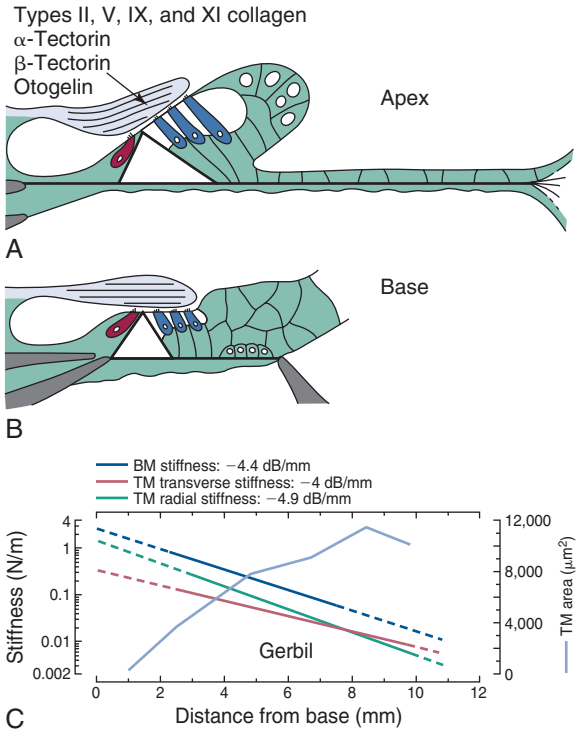

Figure 146-10. **A** and **B,** Schematic representation of the organ of Corti from the apical (**A**) and basal turns (**B**) of the cochlea showing the location of the tectorial membrane (TM) in relation to the surface of the organ of Corti. Major proteins of the TM include types II, V, IX, and XI collagen, α- and β-tectorin, and otogelin. Note the differences in basilar membrane (BM) width and thickness and outer hair cell lengths at the two locations. **C,** The cross-sectional area of the TM[445] and its stiffness,[446] measured in both the transverse and radial directions, are shown as a function of distance from the base of the cochlea for the gerbil. Stiffness of the gerbil's basilar membrane[139] is plotted for comparison. *(**A** and **B,** Adapted from Spoendlin H. Innervation densities of the cochlea.* Acta Otolaryngol. *1972;73:235.)*

findings observed in the base, neural sensitivities were elevated by 40 to 50 dB at frequencies below 20 kHz. The enhanced frequency selectivity observed in the base of the cochlea in β-tectorin–deficient mice may be a consequence of the loss of the striated sheet matrix in that region and the concomitant reduction of longitudinal elastic coupling that reduces, in turn, the spread of excitation, although this explanation remains speculative.

Mice with a targeted disruption of the gene that encodes otogelin (Otog) exhibit abnormalities in the tectorial membrane, primarily in the region near the spiral limbus. The tectorial membrane of these animals lacked normal fibrils, and anomalous rodlike structures within the limbal zone of the tectorial membrane were observed in the apex of the cochlea in some cases and along its entire length in others.[508] The degree of hearing loss in otogelin-null mutants is highly variable, even within individual mice. Some animals seemed to experience mild, frequency-independent deficits, whereas others seemed to be profoundly deaf and have a progressive loss of hearing. Heterozygous mice, on the other hand, had normal phenotypes. Although mutations in the human otogelin gene have not been reported, results from mouse studies suggest that abnormalities in otogelin mutants may increase susceptibility of the tectorial membrane to mechanical stress.

Absence of the α2 chain of collagen type XI (Col11a2) also produces defects in the tectorial membrane, as well as moderate to severe hearing loss.[361] In mutant mice, the tectorial membrane is slightly thicker than normal, and collagen fibrils seem to be less densely and evenly packed and more disorganized than in control animals. Col11a2 is thought to play an important role in the maintenance of the tectorial membrane by influencing the spacing of interfibrillar distances among type II fibrils, which are present in large numbers. It is interesting that phenotypic differences are observed between heterozygous mice and wild-type mice. In patients expressing *COL11A2* mutations, a continuum of defects is observed, the mildest form being an autosomal dominant, nonsyndromic form of deafness (DFNA13),[361] whereas autosomal recessive, nonsyndromic deafness (DFNB53),[71] Stickler's syndrome locus 3 (without eye involvement), and autosomal dominant or autosomal recessive otospondylomegaepiphyseal dysplasia (OSMED) syndrome[418,510,581] represent the most severe forms. Hearing loss in patients with DFNA13 occurs prelingually, is nonprogressive, and primarily affects the midfrequency range of hearing[361]; hearing loss in patients with DFNB53 is prelingual, nonprogressive, and profound.[71]

It is noteworthy that type IX collagen forms heterotypic fibrils with type II collagen in the tectorial membrane.[514] In this regard, a mutation in the *COL9A1* gene has been identified that causes Stickler's syndrome.[566] The condition is inherited as an autosomal recessive trait and is characterized by moderate to severe hearing loss, with greater insensitivity in the high-frequency domain. Although type IX collagen has been detected in fibrocytes of the spiral ligament, abnormalities, including disorganized collagen fibril patterns, are limited to the tectorial membrane of *Col9a1*-targeted null mice. However, auditory brainstem response (ABR) thresholds are elevated on P30, and sensitivity is progressively diminished with age in this mouse strain.[537]

Hair Cell Transduction

Although hydromechanical events produce organ of Corti vibration patterns that serve as the effective sensory stimulus for hearing and form the basis of the relationship between cochlear place and characteristic frequency (i.e., tonotopy), the hair cell is the central element of sensory transduction because it is the receptor cell, a mechanoreceptor that converts mechanical to electrical energy. In the human cochlea there are approximately 3500 IHCs and 12,000 OHCs, with densities corresponding to approximately 86 IHCs/mm and 343 OHCs/mm, although considerable variability exists within the population generally.[562,614] The lengths of OHCs increase continuously from the base of the cochlea to the apex, whereas the lengths of IHCs remain fairly consistent (Fig. 146-11C). Unlike some sensory systems (e.g., olfactory and somatosensory systems), in which primary afferent fibers display specialized peripheral endings designed to sense external stimuli and transmit that information directly to the CNS, the statoacoustic system, as well as the visual and gustatory systems, senses its environment by means of specialized epithelial cells, the receptor cells, that are housed in specialized peripheral organs (e.g., the cochlea, the semicircular canals, the otolith organs). Furthermore, receptor cells serving the statoacoustic system are innervated by primary afferents and do not enter the CNS directly.

Hair Cell Stereocilia

To understand the dynamics of transduction, it is necessary to look carefully at the apical surface of statoacoustic receptor cells (see Fig. 146-11A and B). In doing so, it is immediately apparent that they are highly differentiated. Numerous shaft-like protrusions, referred to individually as "hairs" and collectively as "hair bundles" by early anatomists, project from each receptor cell. These apical extensions came to be known as stereocilia, even though they clearly are not true cilia (i.e., they do not conform to the well-defined organizational plan of true cilia, in which two central tubules are surrounded by nine doublet microtubules) and are more appropriately thought of as specialized

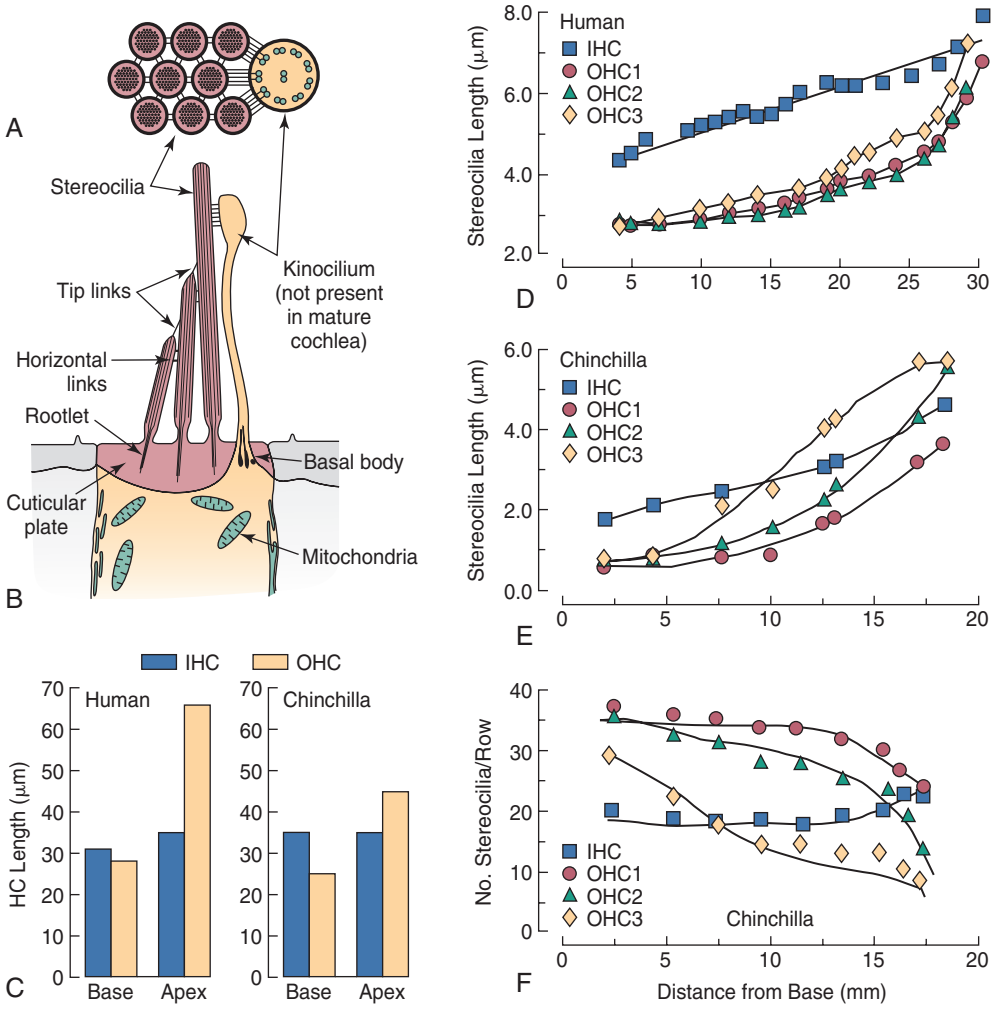

Figure 146-11. **A,** Drawing of a cross section through hair cell stereocilia and the kinocilium, which is present on auditory hair cells only during early development, showing the dense, regular packing of actin filaments that constitute the central core of each stereocilium and the single doublet surrounded by nine pairs of microtubules that make up kinocilia. **B,** Representation of the apical region of hair cells, illustrating tip links that connect the tips of shorter stereocilia with the adjacent taller stereocilia and horizontal links that cross-link all adjacent stereocilia, as well as the kinocilium (also shown in **A**). **C,** The lengths of inner hair cells (IHCs) populating the base and apex are similar, as are IHCs from humans and chinchilla, whereas outer hair cell (OHC) lengths increase from base to apex—quite dramatically in the case of human OHCs. Data for human hair cells are from Nadol[379] and those for chinchillas are from Lim.[331] **D** and **E,** The length of the stereocilia in the tallest row of a hair bundle increases progressively from base to apex in humans (**D**) and chinchillas (**E**). Data for humans were obtained by Wright,[612] and those for chinchillas by Lim.[332] **F,** The number of stereocilia per row as a function of distance along the cochlear partition. Data from Lim.[332] (***A,*** *From Thurm U, et al. Studies of mechanoelectric transduction in concentric hair bundles of invertebrates. In: Lewis ER, et al, eds.* Diversity in Auditory Mechanics. *Singapore: World Scientific; 1997:119;* ***B,*** *from Pickles JO.* An Introduction to the Physiology of Hearing. *2nd ed. London: Academic Press; 1988.)*

microvilli. All vestibular hair cells and all auditory hair cells of lower vertebrates are equipped with a single kinocilium, a true cilium that protrudes from the apical surface of each receptor cell. The functional role of kinocilia is uncertain, in no small measure owing to the observation that hair cell transduction remains unchanged after its microsurgical ablation.[241] It also is interesting that kinocilia project from the surface of immature auditory hair cells of mammals but are lost during the final stages of differentiation.

Approximately 50 to 70 stereocilia protrude from each IHC and approximately 150 from each OHC, although toward the apex of the cochlea, the number of stereocilia on OHCs decreases to less than half of the number found on OHCs populating the basal turn of the cochlea in humans,[613] as in other mammals (see Fig. 146-11F). Stereociliary lengths for both IHCs and OHCs progressively increase from the base to the apex of the cochlea (see Fig. 146-11D and E). The orientation and pattern of stereocilia within a bundle are highly stereotypical, and the overall configuration for auditory hair cells is conserved among mammals. Individual hair bundles are organized into approximately three rows of stereocilia that are arranged according to a nearly linear motif in the case of IHCs and in the form of a W in the case of OHCs, with the base of the W facing the lateral wall of the cochlea (Fig. 146-12). Stereocilia within each row are approximately the same height, and the longest row is located on the side of the cell that is proximal to the spiral ligament and adjacent to the kinocilium, or the basal body in the case of mature auditory hair cells. The length of stereocilia decreases in an orderly manner in rows that are located progressively proximal to the modiolus, producing what is commonly described as a stairstep configuration. As a result of this arrangement, the hair bundle has a plane of bilateral symmetry, providing the foundation for directional sensitivity (see the following).

The stereocilium tapers near its point of insertion into the surface of the receptor cell (see Figs. 146-11B and 146-12C), and only a small fraction of the total number of actin filaments penetrate the cuticular plate, itself a dense network of randomly oriented, interconnected actin filaments packed into the apical fraction of the receptor cell body.[117,160,220,549] The rootlets of actin filaments projecting from the base of stereocilia are anchored firmly within the cuticular plate and are linked to the actin filaments within the plate, enhancing the rigidity of the structure. The protein spectrin is a major actin linkage element within the overall assembly,[133] and along with fimbrin, α-actinin (which attaches to the ends of the actin filaments), tropomyosin, profilin (a protein that regulates actin polymerization and sequesters actin monomers), myosin, calmodulin, and calbindin, these compounds are the major proteinaceous components of the cuticular plate.[513,516,517,627] The stereociliary neck produced by the constriction of the stereocilium at its insertion point allows the structure to pivot, as opposed to flexing, near the surface of the receptor cell, acting like a stiff lever when mechanically distorted.

Much of what is known about the receptor cell trigger mechanism, an event characterized by the deformation or bending of stereocilia, comes from studies in which stereocilia are physically displaced throughout their dynamic range. In that context, it is remarkable to note that the deflection of a hair bundle by 30 to 60 nm generates a receptor potential equal to approximately 90% of a receptor cell's dynamic range,[463] reflecting a very steep and very sensitive deflection-response relationship. This deflection is less than the typical diameter of a single stereocilium (i.e., approximately 200 nm). It is in this dimension that we can begin to appreciate the intrinsic value of the elaborate design of the cochlea. The ability to detect acoustic events as faint as 0 dB sound pressure level (SPL) clearly requires the sensory cell to perform optimally, and optimization is achieved by placing the cell in a highly stable environment (a fluid-filled bony labyrinth) and supporting it within a rigid but flexible infrastructure (the organ of Corti). The need for such architectural sophistication becomes apparent with the recognition that the sensitivity of hearing is ultimately limited by the Brownian motion of hair bundles, estimated to be on the order of 1 nm[52] but reduced to approximately 0.1 nm as a consequence of inherent mechanical filtering.[95] It is relatively easy to gain perspective on this matter by considering the observation that the absolute threshold of hearing requires a displacement of the basilar membrane of a mere 0.1 nm,[494] a motion that would be reduced to approximately 0.001 nm were it not for the basilar membrane amplification provided by actively motile OHCs. The amplified motion of the basilar membrane at threshold translates into displacement of hair cell stereocilia of approximately 1 nm and sensitivities on the order of 30 mV per degree of rotation, corresponding to approximately 0.4 mV per nm of displacement at the tip of a 3- to 4-μm-long bundle.[463]

Hair Bundle Deflections and Receptor Potentials

Statoacoustic receptor cell potentials, like receptor cells in sensory systems in general, are graded in response to stimulation, and the displacement-voltage curve associated with the movement of a stereociliary bundle throughout its dynamic range generally is sigmoidal.[91,240,460,463] The nature of this relationship is consistent with the observation that the magnitude of the receptor potential is proportional to the degree of stereociliary deflection in the most sensitive region of its operating range but saturates with larger deflections in either direction (see Fig. 146-12G). When the bundle is deflected toward the tallest stereocilia, the hair cell depolarizes, and deflections of the bundle in the direction opposite the tallest stereocilia hyperpolarize the cell (see Fig. 146-12G, inset). These findings support the view that hair bundle polarity is an essential element of normal hair cell function.[343] In addition, the displacement-voltage curve is highly asymmetrical relative to its resting state, such that responses saturate with smaller deflections directed away from the taller stereocilia than in the excitatory or depolarizing direction, and that deflection of the hair bundle in a direction perpendicular to this axis produces no response. Furthermore, displacement along an intermediate or oblique axis elicits a response that is proportional to its vectorial projection along the axis of symmetry.[159,503]

Hair Cell Transduction Channels

Conductance changes in hair cells associated with mechanically evoked responses indicate that when stereocilia are deflected in the excitatory direction, transduction channels in the membrane open, producing current flow leading to membrane depolarization, whereas movement of the stereocilia in the inhibitory direction causes the closure of transduction channels.[240] The latency of hair cell responses to bundle displacement is remarkably fast, on the order of 40 μsec at 22° C,[86] and kinetic analyses of the receptor current have shown that it takes approximately 100 μsec to reach steady-state currents at 4° C in response to large bundle displacements.[85] Activation time is inversely related to the magnitude of bundle displacement and is temperature-dependent, and fast offset times associated with receptor current follow positive voltage steps.[85] Because enzymatic systems or second messengers would be too slow to underlie the transducer response, these data suggest that transducer channel activation is directly coupled to displacement of the stereocilia.[85] Additional studies support a two-state model, whereby transduction channels operate in either an open or a closed state, with the probability of being in one or the other state depending on the degree of hair bundle deflection.[90,230,389] Moreover, the concept of an elastic mechanical linkage, or gating spring, associated with the transduction channel was established on the basis of the observation that the offset dynamic of transducer currents after a positive prepulse is independent of bundle position for negative stereociliary bundle displacements beyond a certain critical limit. According to this model, these linkages relax at negative displacements and therefore do not influence the state of the channel.[85]

On the basis of this model, the asymmetrical displacement-voltage curve described previously is explained by the fact that a small population of transduction channels, roughly 10% to 15%, is in the open state at rest. When stereocilia are bent toward the tallest stereocilia, the probability that channels will open increases, driving membrane resistance to lower values. Conversely, during maximal deflection of stereocilia in the inhibitory direction, transduction channels that were open at rest close and hyperpolarize the cell. The proportion of time spent in the open or the closed state is a function of the degree of mechanical displacement of stereocilia. Moreover, it is known that the stiffness of the hair bundle is at its minimum at the point of maximum sensitivity of the displacement-receptor potential curve

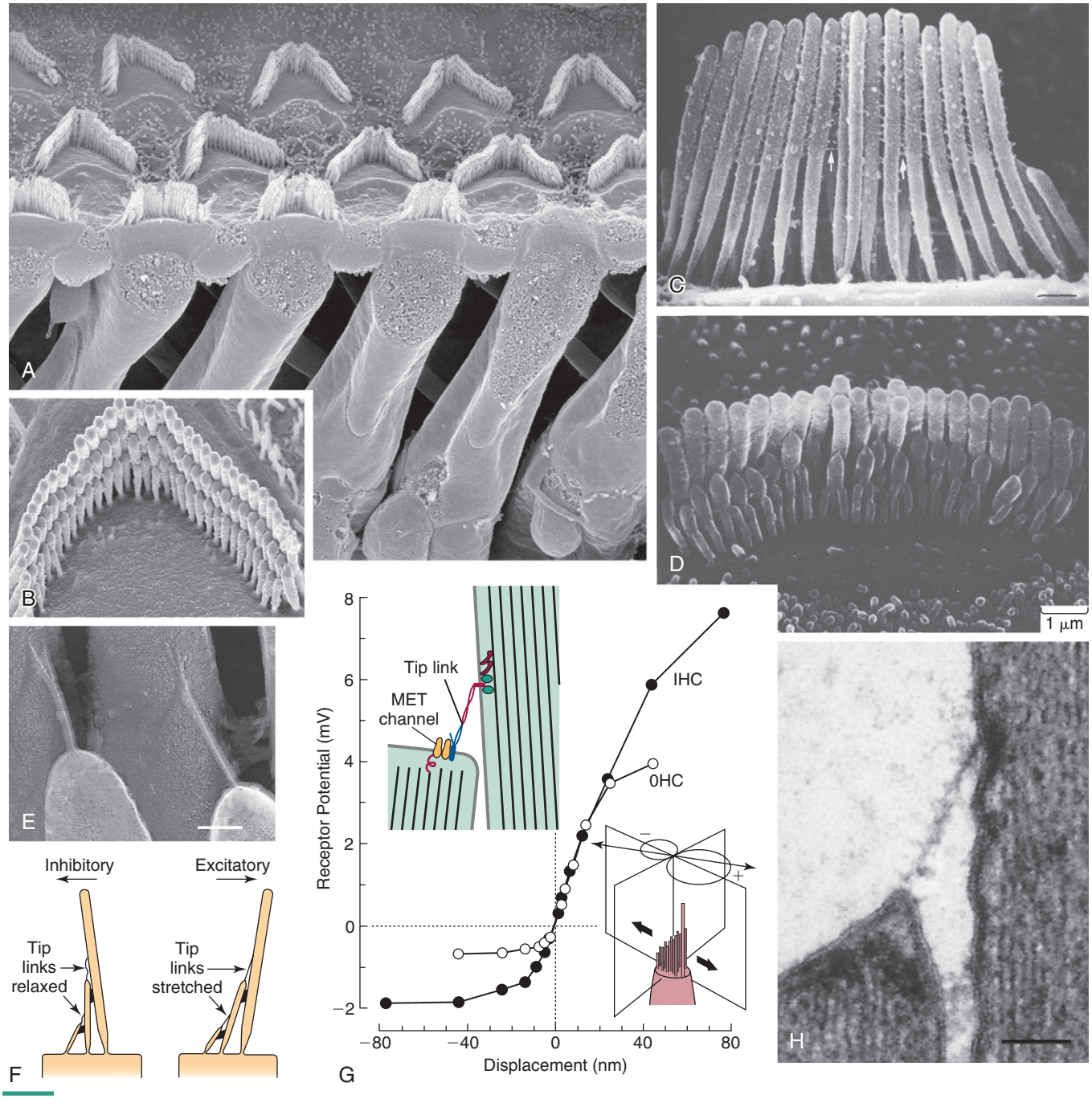

Figure 146-12. **A,** Scanning electron micrograph (SEM) of the outer hair cell (OHC) region of a mouse cochlea after the tectorial membrane and pillar cells have been removed, showing the large intercellular chamber that OHCs occupy in situ. **B,** Higher magnification of an SEM showing the highly ordered hair bundle of a single OHC. **C,** SEM of the tallest row of stereocilia of an inner hair cell (IHC) from a guinea pig cochlea. The view is looking toward the modiolus. Note the horizontal links adjoining adjacent stereocilia *(arrows)* and the narrowing of each stereocilium as each approaches the apical surface of the hair cell. Scale bar is 500 nm. **D,** SEM of an IHC from a guinea pig cochlea showing the nearly straight alignment of stereocilia compared with the V-shape or W-shape arrangement characteristic of OHCs. **E,** High-resolution images of tip links in a hair cell from a guinea pig cochlea showing splaying of the link at the upper insertion point on the taller stereocilium. Scale bar is 100 nm. **F,** Schematic illustration showing deflection of the hair bundle toward the taller stereocilia causes stretching of tip links *(right)* and opening of transduction channels, and hair bundle deflection toward the shorter stereocilia, produces tip link compression *(left)*, closing any transduction channels that were open. **G,** Receptor potential for an IHC and an OHC from the apical turn of a mouse cochlea maintained in vitro in response to hair bundle displacement. *Upper inset*, Illustration of a tip link and associated mechanoelectrical transduction (MET) channel at each end of the link. *Lower inset*, Directional sensitivity of a hair bundle showing that movements of the hair bundle perpendicular to the axis of symmetry produce no responses, and displacements at angled directions produce reduced responses. **H,** Transmission electron micrograph showing a tip link under tension. Note the electron densities at each end of the tip link and the pulling of the stereocilium's membrane to a point at which tension is high (see **B, C,** and **E**). *(**A** and **B,** From Friedman TB, Hinnant JT, Fridell RA, et al. DFNB3 families and Shaker-2 mice: mutations in an unconventional myosin, myo 15.* Adv Otorhinolaryngol. *2000;56:131; **C, D,** and **F,** from Pickles JO.* An Introduction to the Physiology of Hearing. *2nd ed. London: Academic Press; 1988; **E** and **H,** from Kachar B, Parakkal M, Kurc M, et al. High-resolution structure of hair-cell tip links.* Proc Natl Acad Sci U S A. *2000;97:13336; **G,** data from Russell IJ, Richardson GP, Cody AR. Mechanosensitivity of mammalian auditory hair cells in vitro.* Nature. *1986;321:517;* upper inset, *adapted from Holt JR, Corey DP. Two mechanisms for transducer adaptation in vertebrate hair cells.* Proc Natl Acad Sci U S A. *2000;97:11730;* lower inset, *from Flock A. Transducing mechanisms in the lateral line canal organ receptors.* Cold Spring Harb Symp Quant Biol. *1965;30:133.)*

when approximately 50% of the channels are open, a finding that supports the gating spring model.[238,461]

Focal measurements of extracellular potentials at various locations in the vicinity of hair bundles during the activation phase of transduction,[239] along with studies designed to block transduction by the local application of an aminoglycoside antibiotic[299] at different sites around the hair bundle,[246] revealed that the transduction channels are situated near the tips of the stereocilia. Additional support for this view has been advanced through imaging studies in which calcium was identified in the tips of stereocilia initially after bundle deflection and later in the base of the structure,[113] a finding that supports the view that Ca^{2+} enters the stereocilia through a transduction channel located at the tip.

Estimates indicate that the number of transduction channels per cell corresponds roughly to the number of stereocilia in a hair bundle (see Fig. 146-11F),[230,238,460] and transduction channels seem to be present in stereocilia of all heights within a bundle.[113]

Because of the small number of transduction channels present on hair cells, the effort to identify their molecular composition has been difficult at best.[84,94] However, results from invertebrate studies in *Drosophila melanogaster* and from studies of nonmammalian vertebrates (zebrafish) suggest that the best candidates for the transduction channel gene in mammalian hair cells belong to the transient receptor potential (TRP) gene family.[286,504] Nonetheless, it remains clear that additional studies are necessary to answer the question.

Transduction Channel Ion Selectivity

Hair cell transduction channels are permeable to a large number of monovalent and divalent cations, including small organic cations, such as choline and tetramethylammonium, suggesting that the internal diameter of the channel is relatively large, on the order of 0.7 nm, and the channel is relatively nonselective.[87,389] It is known that K^+ carries the major portion of the receptor current in vivo, as indicated by three observations: (1) the high concentration of K^+ in endolymph[27,259,519]; (2) the reversal potential of the transducer current is the same as the endocochlear potential[459]; and (3) that the concentration of K^+ found in perilymph increases after stimulation.[257] As a result of the combined positive endocochlear potential (+80 mV) and the negative intracellular potential of hair cells (−40 to −60 mV), a large potential gradient (greater than 120 mV) is established across the apical hair cell membrane (Figure 146-13). When hair bundles are deflected and transduction channels open, K^+ ions in the endolymph are flushed down a large electrochemical gradient through stereociliary transduction channels. This inward transducer current flows across the basolateral membrane, producing the receptor potential, and voltage-gated Ca^{2+} channels are activated, resulting in an influx of Ca^{2+} and release of neurotransmitter from the base of the hair cell.

Gating of Transduction Channels

Anatomic support for the presence of mechanical linkages that gate the opening and closing of transduction channels was acquired with the

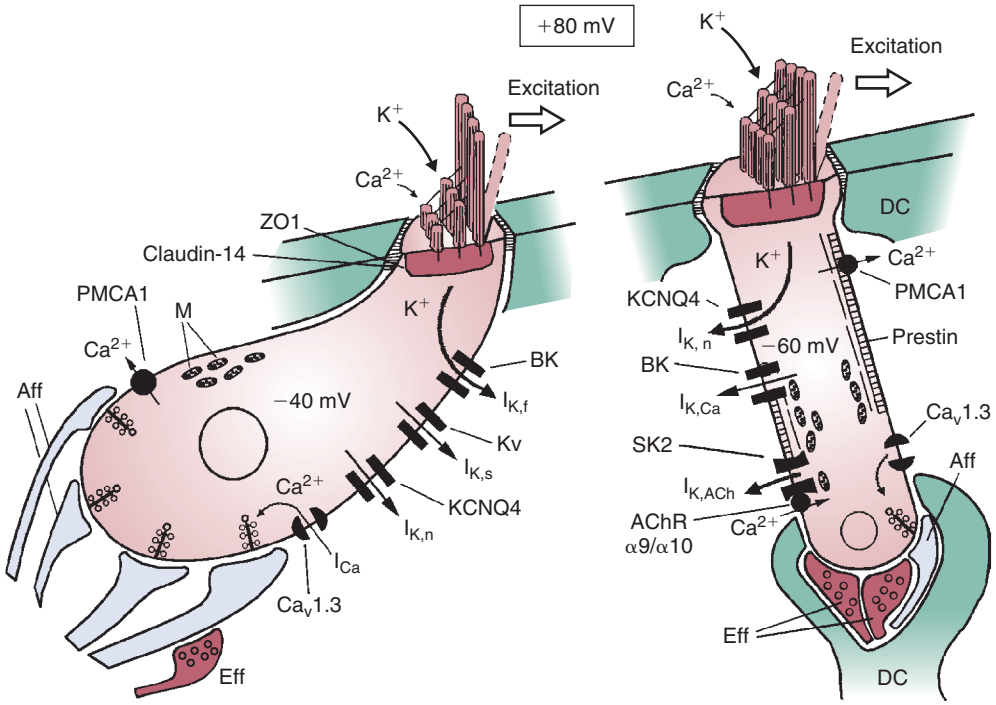

Figure 146-13. Drawing of an inner hair cell (IHC) *(left)* and an outer hair cell (OHC) *(right),* illustrating some of the basolateral membrane ion channels, pumps, and contacts by nerve endings. Three potassium currents in the IHC are shown: The K^+ current with fast kinetics, $I_{K,f}$, is carried by the large-conductance Ca^{2+}-dependent and voltage-dependent K^+ channel, BK; the $I_{K,s}$ current with slow kinetics is carried by a voltage-gated potassium channel (Kv). Both of these are outwardly rectifying. A slow delayed rectifier activated at negative potentials, $I_{K,n}$, carried by KCNQ4 channels also is shown. In OHCs, the major basolateral membrane K^+ current is $I_{K,n}$, which is active at negative potentials and carried by voltage-dependent KCNQ4 channels. A smaller voltage-dependent and Ca^{2+}-dependent current, $I_{K,Ca}$, carried by BK channels also is present. In addition, acetylcholine (ACh) released by efferent nerve terminals binds to acetylcholine receptors (AChR α9/α10) on OHCs that activate Ca^{2+}-permeable excitatory channels, which evoke a hyperpolarizing potassium current ($I_{K,ACh}$) mediated by a small-conductance Ca^{2+}-activated potassium channel (SK2). Both IHCs and OHCs have voltage-gated Ca^{2+} currents (I_{Ca}) mediated by L-type Ca^{2+} channels ($Ca_V1.3$) that open during depolarization, causing Ca^{2+} to enter the cell and trigger neurotransmitter release. Ca^{2+} is extruded from both hair cell types through plasma membrane Ca^{2+}-ATPase isoform 1 (PMCA1) pumps, and PMCA3 is localized to the cuticular plate region of IHCs (PMCA2a is concentrated in the stereocilia). Note that most channels are actually located in the basal portion of the membrane. In addition, claudin-14 is localized to the tight junctions near the apical membrane, and zona occludens-1 (ZO-1) is located near the tight junctions and cuticular plate of both hair cell types, as well as supporting cells. Prestin is present along the lateral cytoplasmic membrane of OHCs. Aff, afferent nerve ending; Eff, efferent nerve ending; DC, Deiters cell; M, mitochondria. *(Modified from Geisler CD.* From Sound to Synapse: Physiology of the Mammalian Ear. *New York: Oxford University Press; 1998.)*

discovery of tip links that stretch between shorter stereocilia and adjacent taller stereocilia (see Fig. 146-11B), connecting the distal tip of each stereocilium with the side of the longer adjacent stereocilium (Fig.e 146-12).[415] Tip links are aligned parallel to the axis of polarization of the hair bundle[82] and therefore play a role in the mechanism that determines the sensitivity of hair bundles to direction of displacement. When the bundle is deflected toward the taller stereocilia, tip links are stretched, which physically opens transduction channels, causing excitation (see Fig. 146-12G). When the bundle is deflected away from the taller stereocilia, tip links relax, causing the channel to close. Movement of the bundle perpendicular to the axis of symmetry produces little or no response, because the tension on tip links does not change. Orthogonal displacement of stereociliary bundles, on the other hand, produces reduced responses that are proportional to the exerted force.

The presence of tip links also may account for the rapid response of the transduction channel, and elastic linkages, like those considered previously, also may explain why transduction channels can be pulled open but not pushed shut. Moreover, the arrangement of tip links may explain why the number of transduction channels per hair cell is so small. Finally, although still an outstanding question, some studies suggest that transduction channels may be located at each end of the tip link,[113] as depicted schematically in Figure 146-12G.

The chemical composition of tip links is glycoproteinaceous, and glycoproteins seem to organize as two intertwined helical filaments that bifurcate and attach at two points on the side of the taller stereocilium (see Fig. 146-12E) by way of an electron-dense insertional plaque (see Fig. 146-12H) and at the level of an electron-dense region at the tip of the shorter stereocilium by way of three anchor filaments.[262] The molecular integrity of the tip link depends on the presence of calcium, as demonstrated by treating preparations with the Ca^{2+} chelator BAPTA (1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid), which breaks tip links and eliminates mechanoelectrical transduction.[33] Acoustic overstimulation can also cause tip link breakage.[416,540] Zhao and colleagues[632] made the important observation that tip links broken as a result of exposure to BAPTA regenerate within 24 hours, restoring mechanoelectrical transduction in the process. Perhaps a similar dynamic is operative in the case of recovery from temporary threshold shifts associated with acoustic overstimulation.

Recent studies have shown that tip links are composed of the extracellular domains of two proteins belonging to the cadherin superfamily of proteins, which generally mediate adhesion between cells—cadherin 23 (CDH23) and protocadherin 15 (PCDH15).[8,507,520] Tip links appear to form as an asymmetrical complex, consisting of homodimers of CDH23 localized to the upper segment of the tip link and homodimers of PCDH15 localized to the lower segment, with the two proteins interacting in the trans configuration at their NH_2 termini (see Fig. 146-15C).[267]

The gene that encodes cadherin 23 is defective in both patients with DFNB12[60] and persons with Usher syndrome type 1D,[58,60] as well as the waltzer (*v*) mouse[120,589,610] and the mutant zebrafish sputnik.[520] Usher syndrome type 1D is characterized by a constellation of signs and symptoms, including congenital sensorineural hearing loss, retinitis pigmentosa, and vestibular dysfunction.[58] Persons in the DFNB12 category exhibit profound, prelingual sensorineural hearing impairment.[67] Stereociliary abnormalities observed in waltzer mice during the late embryonic and early postnatal period include misplacement of the kinocilium and the presence of multiple stereociliary bundle islets on individual hair cells.[120,589,610] Although stereocilia are properly oriented early in development among waltzer mice, the characteristic polarization found in normal stereociliary bundles is lost, and orientation becomes chaotic as they degenerate. ABRs to intense acoustic stimuli cannot be detected in homozygous $Cdh23^{v\text{-}2J}$- or $Cdh23^{v\text{-}6J}$-mutant animals at the age of 3 to 4 weeks[120] and have not been detected at any age in yet another allelic variant of a waltzer mutant, $Cdh23^{v\text{-}Bus}$.[628]

Genetic complementation tests have shown that the locus for age-related hearing loss (AHL), a common characteristic of inbred mouse strains,[144,251,253,607,636] is allelic with Cdh23.[384] In addition, a predisposition to noise-induced hearing loss has been linked to this locus.[105,226,635] Thus, although certain mutations of Cdh23 are directly associated with deafness, others may enhance susceptibility to hearing loss associated with aging, environmental factors such as acoustic trauma, or other genetic factors, possibly as a consequence of altered binding capacity or decreased stability of Cdh23.

Defects in the gene that encodes protocadherin 15 cause deafness in patients with Usher syndrome type 1F,[12,15] in DFNB23,[11] and in the Ames waltzer (*av*) mouse.[14] In addition to congenital deafness, persons affected by Usher syndrome type 1F exhibit signs of vestibular dysfunction and suffer the consequences of retinitis pigmentosa.[12,15] The stereociliary bundles of hair cells in various mutant strains of Ames waltzer mice consistently display abnormal morphology followed by hair cell death and degeneration of the organ of Corti.[12,15,16,207,398,426] Stereocilia of both IHCs and OHCs become disorganized early in postnatal life, with loss of the stereotypical staircase profile of normal hair bundles as the clearest expression of stereociliary abnormality. Similar pathology has been observed in vestibular hair cells.[426] Acoustic stimuli fail to elicit responses in mice that are homozygous for several of the alleles that have been studied,[16,398,426] although mice that are homozygous for the $Pcdh15^{av\text{-}Jfb}$ allele appear to respond to high-level acoustic stimulation.[207] Of note, some of the hair cell abnormalities observed in Cdh23- and Pcdh15-mutant mice may be the result of other roles played by these proteins (see later on).

Composition of Stereocilia

As mentioned previously, stereocilia are not true cilia—they are microvillous extensions of the apical plasma membrane of hair cells. These extensions are tightly packed with microfilaments that run the length of each specialized villus.[163] Like microvilli of other epithelial cells (e.g., the brush border of intestinal epithelial cells), the longitudinally arrayed microfilaments of stereocilia are composed of hexagonally organized, tightly compacted actin filament bundles. Filamentous actin monomers are polar molecules, and individual filaments within a bundle are arranged in parallel and exhibit common polarity (Fig. 146-14A).[161,548] This organizational scheme provides a framework for the renewal of stereocilia, because actin monomers are incorporated into actin filaments at the tips of stereocilia as older components of actin filaments cycle toward the cell body at a rate of approximately 2.5 μm/day.[467,482] These data suggest that the actin core of the tallest stereocilia turns over completely every 2 days, approximately, in the base and every 3 days in the apex of the human cochlea. These rates are considerably slower than the overall turnover rates for shorter, conventional microvilli, like those found on Hensen cells and outer phalangeal cells.[194] The continuous renewal of actin filaments within stereocilia appears to play an important role in repair and recovery from acoustic overstimulation, and the failure of this system to operate properly may have significant otopathologic consequences.

The hexagonal pattern of actin bundles comprising the stereociliary core is maintained by actin-bundling proteins, including plastin/fimbrin and espin that form cross-linkages and fasten together individual actin filaments (see Fig. 146-14B). These bridging proteins occur at frequent and uniform intervals along the shafts of actin filaments[133,160,501,548,551] and, in keeping with the stereotypical association with crossover points of the α-helical subunits, are highly organized and coaligned.[548] The extensive cross-linking among adjacent actin filaments imparts a high degree of stiffness to each stereocilium (see Fig. 146-14C)[533] and consequently minimizes independent movement of actin elements during deflection such that an individual stereocilium moves as a rigid rod, one that will fracture much like glass if excessively deflected.[162] Moreover, actin filaments are neither stretched nor compressed during bundle deflection but appear to slide past one another as a result of the flexibility of the bond between the actin cross-linking proteins and the actin filaments.[549,584] It is noteworthy that cross-bridges between stereociliary actin filaments are reduced in number after acoustic overstimulation resulting in temporary threshold elevation, a condition that reduces stereocilia stiffness as a consequence.[550]

Defects in Cytoskeletal Proteins Lead to Deafness

Cytoskeletal actin exists in one of two highly conserved forms, either the β- or the γ-form, and the proteins differ from one another by a mere four amino acids located at the NH_2-terminal ends of the

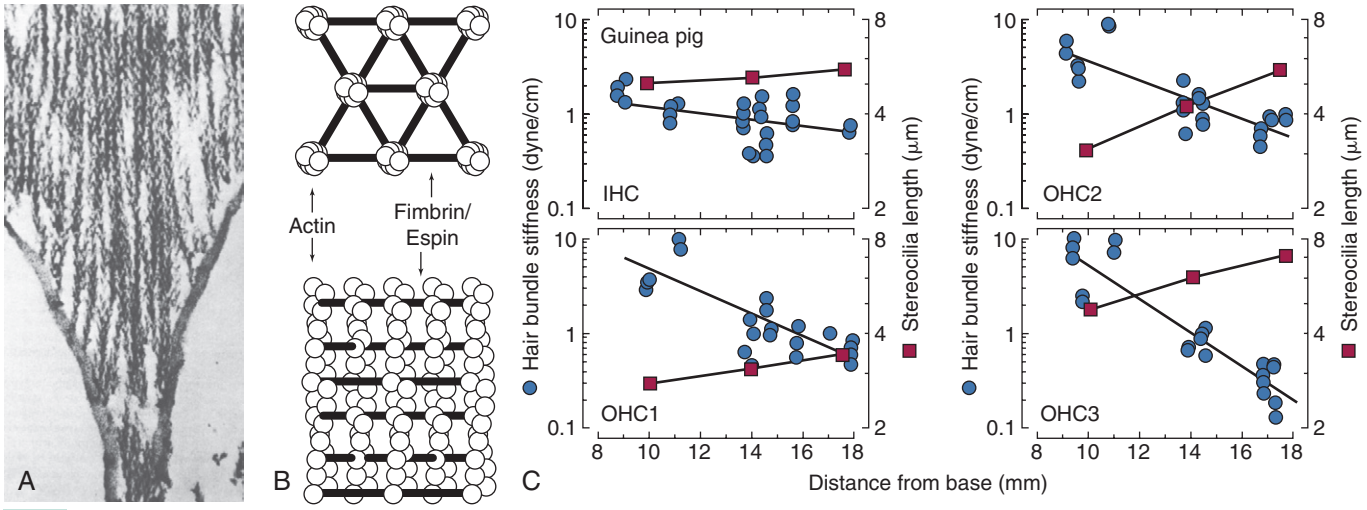

Figure 146-14. **A,** The uniform polarity of actin filaments within the stereocilium is demonstrated in a lizard cochlea by incubating preparations with the S1 fragment of myosin, thereby marking the polarity of the filament. The arrowhead-like appearance of actin filaments indicates that their pointed ends are located proximal to the hair cell body and that the barbed ends of actin filaments are located at the stereocilia tips. **B,** Paracrystalline array of actin filaments depicted in the longitudinal orientation *(bottom)* and in cross section *(top)*, showing the cross-linkages composed of fimbrin and espin. **C,** Stiffness of hair bundles of guinea pig hair cells as a function of distance along the cochlear partition *(circles)*. Also shown are lengths of the tallest row of stereocilia for each hair cell row at three basilar membrane locations *(squares)*. IHC, inner hair cell; OHC, outer hair cell. *(**A,** From Tilney LG, DeRosier DJ, Mulroy MJ. The organization of actin filaments in the stereocilia of cochlear hair cells.* J Cell Biol. *1980;86:244; **B,** from Tilney LG, Egelman EH, DeRosier DJ, Saunder JC. Actin filaments, stereocilia, and hair cells of the bird cochlea. II. Packing of actin filaments in the stereocilia and in the cuticular plate and what happens to the organization when the stereocilia are bent.* J Cell Biol. *1983;96:822; **C,** data from Strelioff D, Flock A. Stiffness of sensory-cell hair bundles in the isolated guinea pig cochlea.* Hear Res. *1984;15:19.)*

molecule.[142] Both forms generally are coexpressed in mammalian nonmuscle cells[272]; however, unlike in most nonmuscle cells, in which β-actin is expressed as the principal form, in auditory hair cells γ-actin is the principal variant of the protein, and it is distributed ubiquitously within the cell.[223] β-Actin expression, on the other hand, is restricted to stereocilia.[482] Mutations in the γ-actin gene (*ACTG1*) lead to autosomal dominant progressive hearing loss (DFNA20/26)[572,639] that presumably is the consequence of a diminished ability to repair the actin cytoskeleton (Fig. 146-15) among affected persons. A mouse model expressing a functional null mutation in the gene encoding γ-actin is available, and animals from this strain acquire normal hearing during the early postnatal period.[41] However, this relatively brief period of normalcy gives way to progressive hearing loss, as indicated by ABR and distortion product otoacoustic emission (DPOAE) recordings.[406] The first morphologic sign of pathology appears in the form of hair bundle disruption and is followed shortly thereafter by the loss of hair and supporting cells. These data suggest that whereas β-actin is sufficient for the normal development of stereociliary bundles, γ-actin is required for their normal maintenance. Insight into the role that γ-actin may play in maintenance can be gleaned from noise exposure studies. It turns out that occasional gaps appear in phalloidin-stained F-actin filaments forming the core of stereocilia after noise exposure, and that these gaps are labeled by an antibody to γ-actin. These findings suggest, naturally enough, that γ-actin may be required to repair traumatized hair bundles. Similar gaps have been observed in mature actin filaments associated with *Actg1*$^{-/-}$ mice, again suggesting that γ-actin is a necessary player in the maintenance of stereociliary structural integrity.[41]

An essential role for the actin-bundling protein espin in the maintenance of stereociliary infrastructure also has been identified in deaf mice that are homozygous for the jerker (*je*) mutation,[634] a finding that led to the identification of mutations in the *ESPN* gene in autosomal recessive, prelingual and profound hearing loss (DFNB36) in humans.[381] The jerker trait arose spontaneously, and homozygous mutant animals exhibit stereociliary abnormalities, hair cell degeneration, deafness, and vestibular system dysfunction.[26,115,511,512,529] Although stereocilia seem to develop normally, they are shorter than normal as a rule, and degenerative changes occur during the early postnatal period. Homozygous mutant animals are unresponsive to acoustic stimuli throughout life. Of interest, overexpression of espin in hair cells results in abnormally long stereocilia, suggesting that the level of espin expression is critical for normal stereocilia development.[466] Espin is expressed primarily in hair bundles and is distributed along the entire stereociliary length (see Fig. 146-15),[634] although light espin staining has been observed in the cuticular plate and soma in chicks.[324] Although fimbrin also plays a role cross-linking actin filaments, in contrast with espin, its activity is inhibited by Ca^{2+}.[38] Thus, in the absence of espin, Ca^{2+} entry into stereocilia may destabilize the actin core and serve to trigger pathologic changes as a consequence.[634] Also of note is that espin binds to actin with higher affinity than does fimbrin and may play a role as an important stabilizing factor after formation,[38] although data from studies in the chick suggest that espin is expressed early on when stereocilia first begin to elongate.[324] Autosomal dominant forms of hearing loss resulting from mutations in ESPN in humans also have been identified.[129]

In the context of linkage proteins that have a clear role in peripheral auditory function, a gene family of integral membrane proteins that appear to link the actin cytoskeleton to the plasma membrane and are essential elements of audition have been identified, and include proteins in the ezrin-radixin-moesin family. The highest concentration of the protein radixin is found at the base of hair cell stereocilia in a variety of species, including frog, chicken, zebrafish, and mouse (see Fig. 146-15A). Radixin appears to anchor the pointed ends of actin filaments to the plasma membrane in the region of the stereocilium taper.[402] In the absence of radixin, mice are profoundly deaf, and both IHC and OHC stereocilia become progressively disarrayed and hair cells subsequently degenerate, even though the system appears to develop normally.[289] Of interest, whereas radixin alone is detectable in cochlear hair cells from normal adult mice, both radixin and, to a lesser extent, ezrin are found in adult vestibular hair cells. In radixin-null mice, ezrin appears to compensate for radixin, promoting development of both cochlear and vestibular hair cell stereociliary bundles. However, unlike vestibular hair cells, cochlear hair cells require radixin for continued maintenance beyond early postnatal life. As in the mouse, radixin is required for normal hearing in humans as well, with pathogenic mutations producing prelingual, bilateral, and profound hearing loss that is inherited as an autosomal recessive trait (DFNB24).[273] Moreover, immunoreactiv-

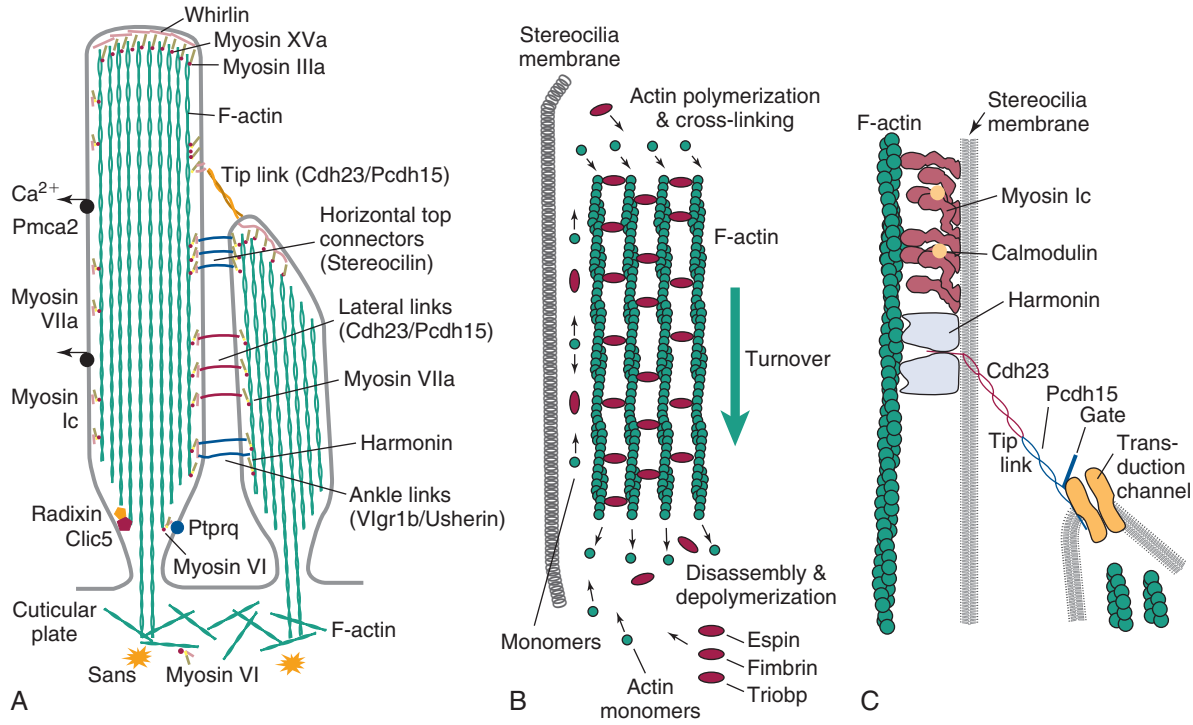

Figure 146-15. A, Schematic illustration of a longitudinal section through two stereocilia located in adjacent rows, connected by a tip link, and other linkages. Note that lateral links and ankle links are found only in developing cochlear hair cells. Unconventional myosins found in the mature hair cell include myosin XVa and myosin IIIa, which concentrate at stereocilia tips; myosin VIIa and myosin 1c, which are are found along the shafts of stereocilia; and myosin VI, the only known member of the myosin superfamily that moves toward the pointed end of actin filaments, found at the base of stereocilia and in the cuticular plate. Whirlin also concentrates at tips of stereocilia, whereas radixin, Clic5, and Ptprq concentrate near the base of stereocilia. Transmembrane proteins with long extracellular domains include cadherin 23, protocadherin 15, Vlgr1b, and usherin, which appear to be components of specific interstereociliary linkages, along with stereocilin, which may be an extracellular protein. The intracellular scaffolding protein, harmonin, may serve to anchor the transmembrane proteins with long extracellular domains to the F-actin core. **B,** The treadmill model of actin turnover within a stereocilium depicting actin polymerization and cross-linking occurring at the barbed ends of actin filaments located at the tips of stereocilia, and disassembly and depolymerization of actin filaments occurring at the base of stereocilia. **C,** Schematic illustration of the transduction channel, including the tip link complex, myosin motors for adaptation, and harmonin. *(**A** and **B,** Adapted from Rzadzinska AK, Schneider ME, Davies C, et al. An actin molecular treadmill and myosins maintain stereocilia functional architecture and self-renewal.* J Cell Biol. *2004;164:887; **C,** adapted from Gillespie PG, Cyr JL. Myosin-1c, the hair cell's adaptation motor.* Annu Rev Physiol. *2004;66:521.)*

ity to radixin is reduced in mice carrying the spontaneous mutation Jitterbug, responsible for a mutation in Clic5, an intracellular chloride channel that is expressed in normal hair cell stereocilia, particularly at the stereociliary base.[175] Stereocilia of mice deficient in Clic5 develop normally but show progressive degeneration after the onset of hearing. Studies suggest that Clic5 may associate with a radixin-actin cytoskeletal complex that appears to be necessary for stereocilia maintenance.

Other proteins associated with actin and that are critical for hearing include TRIOBP and diaphanous 1. Mutations in a long isoform of TRIOBP have been shown to cause autosomal recessive deafness (DFNB28),[436,499] whereas mutations in DIAPH1 are associated with autosomal dominant hearing loss.[346] TRIOBP is associated with filamentous actin, is relatively resistant to the F-actin destabilizer latrunculin B, and is thought to regulate the organization of the actin cytoskeleton.[492] Numerous isoforms of TRIOBP are present in the cochlea, in both IHCs and OHCs, and the protein colocalizes with F-actin along the length of stereocilia (see Fig. 146-15B).[436,499] Diaphanous belongs to the formin family of proteins, which are known to interact with the growing, or barbed, end of actin and recently have been shown to act as effectors for Rho GTPases, key regulators of actin dynamics. Although its role remains unproved, diaphanous is thought to participate in the regulation of cytoskeletal actin turnover, but the protein also may be involved in endosome motility.[397] Diaphanous has been identified within the cochlea by use of a reverse transcription–polymerase chain reaction (RT-PCR) approach,[346] but its precise localization remains unknown. As with many other proteins, the role of both TRIOBP and diaphanous 1 in transduction requires additional investigation.

Dynamic Regulation of Stereocilia Length

In addition to *Espn*, other genes that are required for the development of normal stereocilia height include *Myo15a* and *Whrn* (see Fig. 146-15A). *Myo15a* encodes myosin XVa, an unconventional myosin that is localized near the site of actin polymerization at the tip of each stereocilium in both auditory and vestibular hair cells.[43] *MYO15A* is indispensable for hearing, and pathogenic mutations result in a form of nonsyndromic deafness, DFNB3, in humans,[592] and persons who are homozygous for the mutation are congenitally deaf. The shaker 2 (*sh2*) mutant mouse strain also carries a defect in *Myo15*.[422] The condition is inherited as an autosomal recessive trait, and 1-month-old homozygous mutant mice are unresponsive to acoustic stimulation.[327] Although hair cells are present at this age and stereociliary bundles are present, stereocilia of both IHCs and OHCs are notably shorter than normal, and the normal gradation in stereociliary height is less prominent among adjacent hair cell rows.[422] The stereocilia of vestibular hair cells in both otolith organs and semicircular canals also are abnormally short in mutant mice.[22] It is noteworthy that myosin XVa immunoreactivity is first detected in mice at about the time that stereocilia begin to grow differentially and establish the row-dependent stereociliary bundle height gradation that is characteristic of normal mammals.[43] Labeling also is more intense in the tallest stereocilia, suggesting that formation of the graded stereociliary row pattern requires the presence of myosin XVa.[43,467] Thus, although normal development of the hair bundle is arrested in the absence of functional myosin XVa, the precise mechanism of its action will be the subject of continued investigation.

Whrn encodes a putative scaffolding protein known as whirlin, and genetic abnormalities of the gene, *WHRN*, are the source of deafness in persons with DFNB31; likewise, *Whrn* abnormalities are responsible for deafness in mice designated whirler mutants.[358] DFNB31 is characterized by profound, prelingual sensorineural hearing loss, and mutant whirler (*wi*) mice also exhibit profound deafness, as well as vestibular abnormalities. Hair bundles associated with both IHCs and OHCs in homozygous mutant whirler mice are abnormal.[225] Specifically, IHC stereocilia are significantly shorter than normal as early as embryonic day 18.5. However, stereociliary shaft lengths do continue to increase until approximately 1 day after birth, when the process actually reverses and individual stereociliary lengths begin to decrease. During this period, the organization of stereocilia within hair bundles remains normal, and although relative height gradations are normal, height differences between rows are clearly less prominent than in normal mice. Likewise, overall stereociliary height along the length of the cochlear spiral, a morphologic feature that normally is characterized as a gradient in which height increases continuously from base to apex, is notably reduced in mutant mice.

As with IHCs, OHC stereociliary lengths generally are smaller than normal in whirler mutants, although OHC defects appear slightly later than in IHCs in affected animals. However, an interesting variation in the pattern of stereociliary anomaly has been described in whirler-mutant mice: Specifically, abnormally short stereocilia are located on the edges of each row, although the number of rows appears normal, and stereociliary rows are graded in height. Also of note is that hair bundles do not conform to the classic V- or W-shape observed in normal hair cells. Instead, bundle patterns exhibit a more curvilinear profile. Hair cell degeneration, starting with OHCs, is first observed at approximately the 60th postnatal day and is followed by IHC degeneration,[225] and extensive degeneration generally occurs by the 90th postnatal day, particularly in the basal and middle turns of the cochlea.[358]

In addition to the independent roles played by whirlin and myosin XVa, normal hair bundle development appears to depend on their interaction. Indirect evidence supporting this view suggests that myosin XVa may guide whirlin to stereociliary tips, thereby promoting length enhancement. The rationale for this scenario, speculative as it is, is driven by the observation that the amount of whirlin measured at stereociliary tips is directly proportional to the amount of myosin XVa measured at the same location.[44,111,282] Of interest in this regard is that whirlin expression is down-regulated after stereociliary maturation, whereas myosin XVa expression continues throughout life.[282] In addition to whirlin and myosin XVa, differences in hair bundle morphology between *sh2* and *wi* mice, reviewed earlier,[370] suggest that other interacting proteins are likely to be involved in the development and maintenance of stereocilia.[357] One such protein may be myosin VIIa (see later). Specifically, Prosser and colleagues made the observation that stereocilia grow abnormally long in the absence of myosin VIIa and that whirlin expression persists at the tips of mature stereocilia, rather than undergoing naturally programmed down-regulation. In addition, when either whirlin or myosin XVa is absent from hair cells, myosin VIIa is expressed at the tips of the abnormally short stereocilia, suggesting that myosin VIIa is critically important in regulating the dynamics of stereocilia elongation during maturation.[423]

Another unconventional myosin that is expressed in stereociliary tips is myosin IIIa. This myosin variant appears to concentrate around the tips of stereocilia in a "thimble-like" pattern, in contrast with the "caplike" pattern of myosin XVa expression.[483] Although myosin IIIa does not appear to play a role in development, it has been shown to cause bilateral, autosomal recessive nonsyndromic hearing impairment that begins in the second decade of life. The pattern of hearing loss associated with this condition is such that high-frequency sensitivity is affected initially, with losses occurring progressively in the case of middle- and low-frequency sensitivity.[591]

Interstereociliary Linkages

Like actin-binding proteins, which cross-link actin filaments and help form the core of individual stereocilia, stereocilia are themselves interconnected by way of a complex array of extracellular fibrous cross-linkages (see Fig. 146-15A). At the most fundamental level of organization, filamentous links bind stereocilia within a bundle into a mechanical unit by connecting a stereocilium with neighboring stereocilia on all sides.[173,399,415,434] In adult animals, these proteinaceous links run parallel to the apical surface of the cell connecting different rows of stereocilia, as well as stereocilia of the same row (see Fig. 146-11A), and are thought to contribute to the overall cohesiveness and stiffness of the hair bundle.

Numerous morphologically and biochemically distinct* interstereociliary linkages are recognized; however, some are permanent features of the system, whereas others appear transiently during development.[173,189,191,192,193,415,417,434,547,556,557] For example, although horizontal top connectors are present in both IHCs and OHCs of adults, shaft connectors, located beneath the top connectors in roughly the middle section of the shaft, are found in inner hair cells throughout life but are expressed in outer hair cells only during development. Lateral links, which are located along stereocilia sides, and ankle links, which are located at the stereociliary base, are expressed transiently in both IHCs and OHCs during hair bundle development. Linkages between the kinocilium and two to three adjacent stereocilia from the tallest row are present during the developmental period when kinocilia are a feature of IHCs and OHCs.

Like tip links, kinocilial links are sensitive to BAPTA and resistant to the protease subtilisin. These linkage proteins appear to be composed of both Cdh23 and Pcdh15.[8,192,365] Of interest, transient lateral links also appear to be composed of Cdh23; however, in sharp contrast with tip links, these lateral linkages are insensitive to BAPTA and sensitive to subtilisin.[365] Links resistant to both BAPTA and subtilisin treatment include horizontal top connectors. Stereocilin (STRC) appears to be a primary constituent of top connectors, as well as being present in the attachments between the tallest row of OHC stereocilia and the tectorial membrane.[576,577] Mutations in STRC are associated with nonsyndromic autosomal recessive deafness (DFNB16),[576] and stereocilin-null mice show progressive hearing loss, suggesting that horizontal top connectors are an essential hair bundle feature.[577] The formation of shaft connectors, which are resistant to BAPTA but sensitive to subtilisin, requires protein tyrosine phosphatase receptor Q (Ptprq), and when the *Ptprq* gene is disrupted in mice, stereocilia of hair cells located in the base of the cochlea become disorganized during the early postnatal period and are sporadically lost—an event that leads to hair cell death.[190] Finally, ankle links, which are sensitive to both BAPTA and subtilisin, appear to be composed of both Vlgr1 (*v*ery *l*arge *G*-protein–coupled *r*eceptor 1) and usherin.[4,359] Gene mutations affecting these proteins in humans result in Usher syndrome type 2C and type 2A, respectively.[147,603] Mice carrying functional null alleles for Vlgr1 are profoundly hearing impaired by the age of 3 weeks and lack ankle links at the base of hair cell stereocilia, with progressive disorganization of hair bundles, eventually leading to hair cell loss.[359] By contrast, auditory deficits in usherin-null mice are mild and limited to high frequencies and are not progressive.[335]

Usher syndrome is a genetically heterogeneous disease and the leading cause of combined deafness and blindness around the world. No fewer than 10 forms of the syndrome are recognized, many of which are associated with well-characterized gene defects that produce a group of abnormal gene products collectively referred to as the Usher proteins. Included in that collection is the unconventional myosin VIIa (Usher syndrome type IB [USHIB]),[600] the scaffold protein harmonin (USH1C),[13] the novel cytoplasmic protein sans (USH1G),[377,601] and the transmembrane protein clarin-1 (USH3).[6,249] Spontaneous mutations in orthologous murine genes also have been identified and include shaker-1 (*sh1*),[182] deaf circler (*dfcr*),[252] and Jackson shaker (*js*),[283] representing mutations in *Myo7a, Ush1c,* and *Sans,* respectively. Persons affected by Usher syndrome type I exhibit severe to profound congenital hearing loss, vestibular system dysfunction, and early-onset, progressive retinitis pigmentosa, whereas those affected by Usher syndrome type II have moderate to severe high-frequency hearing impairment, normal vestibular function, and progressive retinitis pigmentosa.

*Differing sensitivities to the Ca^{2+}-chelating agent BAPTA and the protease subtilisin are commonly used to distinguish biochemical differences among interstereociliary linkages being considered in this chapter.

The clinical phenotypes of patients suffering with Usher syndrome type III are highly variable, often leading to misdiagnosis of the disorder as either type I or type II.[405]

Like mice exhibiting abnormalities Cdh23, Pcdh15, or Vlgr1, mice with defective genes encoding myosin VIIa, harmonin, or Sans also are deaf, and hair bundle abnormalities that appear during development constitute a common feature in all three animal models.[182,252,283] The common morphologic phenotype shared by affected animals suggests that these proteins interact with one another, each satisfying a unique role with respect to hair bundle development. Furthermore, the proteins in question do not appear to compensate for one another; pathology ensues when any one of the group is lost or is defective.

Predictably, in keeping with the close functional association of the Usher proteins, numerous interprotein interactions have been identified in recent years. For example, harmonin has been shown to bind with both Cdh23 and Pcdh15, as well as actin filaments, and on the basis of the molecular characteristics of Cdh23 and Pcdh15, some investigators have suggested that harmonin anchors Cdh23 and Pcdh15 to the actin core of stereocilia.[5,54,506] Harmonin also binds to myosin VIIa, and it is especially informative that harmonin cannot be found in the hair bundles of *sh1*-mutant mice, animals exhibiting an abnormal version of Myo7a. This finding suggests that myosin VIIa transports harmonin from the cytoplasmic compartment of the cell body to the stereocilia.[54] Likewise, protocadherin 15 binds to myosin VIIa, and neither protein is "correctly" localized when one of the partners is lost or disrupted, a finding that supports a model in which the two proteins interact critically to ensure the proper spatial maintenance of the protein complex as the hair bundle matures.[496]

Harmonin also binds with both Vlgr1 and usherin,[4,430] as does whirlin,[4,573] and myosin VIIa binds with Vlgr1, usherin, and whirlin.[111,364] Vezatin, a transmembrane protein that also is localized to the basal region of stereocilia,[307] binds to usherin and may be a constituent of the ankle link complex,[364] an idea that is supported by the finding that vezatin, in addition to usherin and whirlin, cannot be detected in the stereocilium of *Vlgr1*-null animals.[364] In an especially revealing study, Vlgr1, usherin, and whirlin, as well as vezatin, cannot be detected in hair cell stereocilia in animals without functional myosin VIIa. This observation suggests that proteins associated with the ankle links are transported to the stereocilia by myosin VIIa,[364] an actin-based motor that is capable of transporting cargo toward the plus, or barbed, ends of actin filaments (i.e., toward stereocilia tips).[565] These findings—that is, the absence of usherin, vezatin, and Vlgr1 in stereocilia of whirler-mutant animals—implicate whirlin as a scaffold protein supporting the ankle link complex.[364] The protein Sans is unusual among the Usher proteins in that it is localized not in stereocilia but in the region beneath the cuticular plate.[5] Sans interacts with harmonin,[5,601] as well as myosin VIIa, and it may regulate the trafficking of at least some of the Usher proteins to the stereocilium, as supported by its location at the interface of the cell body and the hair bundle.[5] Finally, it has been shown that harmonin, Vlgr1b, and usherin are found together in the synapse between hair cells and afferent or efferent fibers in adult cochleae. This observation suggests that Usher proteins may play yet another functional role in mammals, one that influences neural processing within the auditory pathway.[430]

Myosin VI

Numerous unconventional myosins are essential for normal hair cell function, including myosin VI. Mutations in the *MYO6* gene are responsible for autosomal dominant hearing loss, DFNA22[363]; autosomal recessive deafness, DFNB37[10]; and the phenotype observed in Snell's waltzer (*sv*) and tailchaser (*tlc*) mice,[35,219] as well as mutant satellite zebrafish.[491] People affected with DFNB37 have profound congenital sensorineural hearing loss with complementary vestibular dysfunction, whereas hearing deficits in persons affected with DFNA22 are sensorineural in nature, but the onset of the condition is postlingual, and the anomaly develops progressively, unlike in the case of DFNB37-mediated deafness. The degree of hearing loss in these patients ranges from moderate to profound, and affected persons show no signs of vestibular dysfunction.

Like other myosin proteins, myosin VI is a molecular motor that binds to actin filaments or microtubules; however, it is unique as the only myosin thus far identified that moves backward toward the pointed end of actin filaments.[210,602] Of interest, the phenotype of the myosin VI mutant is limited to hair cell dysfunction.

Myosin VI is localized at the base of the stereocilia,[35,211] where the pointed ends of core stereociliary actin filaments project into the cuticular plate and rootlets of stereociliary actin filaments terminate (see Fig. 146-15A). More specifically, myosin VI is located in the circumferential region surrounding the lateral margins of the cuticular plate, an area that is rich in cytoplasmic vesicles, a finding that is particularly evident in amphibian hair cells. More recent localization studies suggest that myosin VI may be found along the length of stereocilia.[219] Unlike with the mutations in mice causing an Usher-like phenotype, the basal aspect of adjacent stereociliary membranes in *Myo6*-mutant animal models appears to fuse, reducing the numbers of individual stereocilia and leading to the formation of "giant" stereocilia that are both longer and wider than normal and often display swollen or bulbous tips, and branching of stereocilia also is observed occasionally. Sequentially, giant stereocilia collapse onto the apical surface of the organ of Corti and appear to fuse with the apical membranes of hair cells and supporting cells, and the organ of Corti undergoes degeneration. During the period of stereocilia fusion, stereocilia branching also is observed, and the apical surfaces of hair cells appear to bulge outward. Ultrastructural examination indicates the presence of extraneous material within the fused stereocilia, possibly components normally found in the apical cytoplasm of hair cells.[219,472,491,493]

Although numerous hypotheses have been advanced to explain hair cell abnormalities observed in *Myo6*-mutant animals, recent studies suggest that the protein may serve to tether Ptprq to the actin cytoskeleton at the base of the stereocilia, maintaining the stereocilia taper and preventing fusion between adjacent stereocilia.[472] In that regard, unlike with the focal localization of Ptprq in the stereociliary base of normal animals, the protein is distributed throughout the stereocilium in Snell's waltzer mice, suggesting that the proteins normally interact with one another directly.[472] Moreover, as an inositol lipid phosphatase, Ptprq would be in a key position to regulate the phosphoinositide phospholipid content of the hair cell membrane.[190] The reciprocal distribution of phosphatidylinositol 4,5-bisphosphate (PIP_2) and Ptprq in stereocilia[221] suggests that Ptprq may play a role in the regulation of actin and membrane turnover, a process that is disrupted in the absence of functional myosin VI.[472]

Adaptation of Mechanoelectrical Transduction Currents

It is well known that receptor currents adapt after sustained deflection of hair bundles (Fig. 146-16A). Adaptation is associated with a horizontal shift in input-output curves after bundle displacement (see Fig. 146-16B), without a change in the slope of the steepest portion of the curve. Shifts in the horizontal position of input-output curves, like those described here, reflect the actions of a dynamic system in which the central operating point is restored after sustained depolarization, re-establishing the sensitivity of the system. The prevailing model used most often to explain adaptation entails a reduction in tip link tension when the bundle is deflected in the excitatory direction and an increase in tension for deflections in the inhibitory direction.[85,88,135,227,502]

Two mechanisms of adaptation have been described: one that underlies rapid adaptation, a phenomenon characterized by a time constant of less than a few milliseconds, and another with a time constant greater than 10 msec, which can achieve values as high as several hundred milliseconds under some circumstances. In the case of *rapid* adaptation, Ca^{2+} ions entering the cell through transduction channels bind directly to an intracellular site that is part of the transduction channel itself (see Fig. 146-16D), which in turn modifies the relationship between tension and the probability that the channel is in the open state.[90,438] In the case of *slow* adaptation, an active motor is thought to slide the transduction channel associated with the taller stereocilium down the actin filament core of the stereocilium (see Fig. 146-16C), thereby reducing tension on the tip link and decreasing the probability that the channel will be in the open state.[32,184,237] Conversely, moving

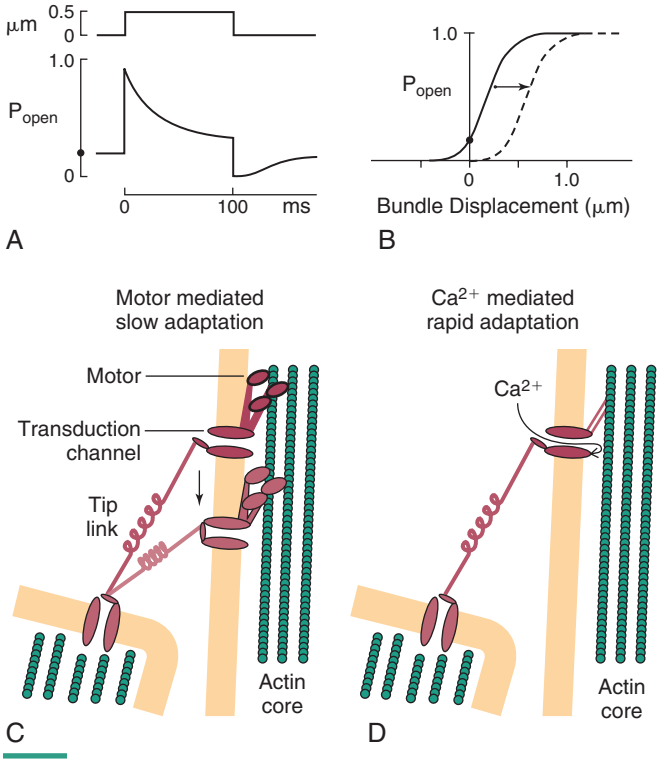

Figure 146-16. **A,** Diagram depicting positive (depolarizing) deflection of a hair bundle and the resulting adaptation observed as a decrease in the probability (*P*) of transduction channel opening over time during sustained bundle deflection. **B,** During the adapted state, the bundle displacement–versus–open probability curve is shifted horizontally along the x-axis, such that still larger bundle displacements are required to evoke a response comparable to that observed at the onset of stimulation. Two models have been proposed to account for adaptation: a motor-mediated slower process that requires resetting tip link tension by slippage of the entire transduction channel along the actin filaments (**C**) and a direct Ca^{2+}-mediated adaptation (**D**) that results from Ca^{2+} entry through the transduction channel and binding to an intracellular site of the channel, altering it to prefer the closed state. *(**A** and **B,** From Pickles JO, Corey DP. Mechanoelectrical transduction by hair cells.* Trends Neurosci. *1992;15:254; **C** and **D,** adapted from Holt JR, Corey DP. Two mechanisms for transducer adaptation in vertebrate hair cells.* Proc Natl Acad Sci U S A. *2000;97:11730.)*

the hair bundle in the inhibitory direction is thought to cause tip links to relax and close channels that were open at rest. During the adaptation phase, transduction channels are thought to climb along the actin core, resetting the operating point and increasing the probability of channel opening. In addition to Ca^{2+}, the latter mechanism requires an active motor, presumably an unconventional myosin that interacts directly with the actin core. Although both forms of adaptation exist in individual hair cells, rapid adaptation is much faster in mammalian IHCs and OHCs than in nonmammalian hair cells.[214,247,271,303,526]

Myosin 1c (myosin 1β) may be the best candidate for the adaptation motor associated with slow adaptation (see Fig. 146-15C).[184,185,228] This view is supported by the observation that slow adaptation profiles are altered when myosin 1c mutations occur.[228] Recent studies suggest that myosin 1c also may influence fast adaptation profiles.[527] In addition, binding between the tip link–associated protein cadherin 23 and myosin 1c has been reported,[507] and the binding character is modulated by calmodulin and is sensitive to calcium chelators, which are known to break tip links.[411] Furthermore, although myosin 1c is detected in stereocilia from mice with abnormal copies of cadherin 23 or myosin VIIa, only in *Cdh23*-mutant mice is its stereociliary binding profile disrupted, suggesting that myosin 1c regulates the gating characteristics of the transduction channel by interacting with cadherin 23.[411] Finally, myosin 1c associates with PIP_2, which normally concentrated in the upper two thirds of the stereocilia, and agents that deplete or sequester PIP_2 significantly reduce the rates of fast and slow adaptation, suggesting that the complex has a role in the regulation of the adaptation process.[221]

Although in early studies it was determined that myosin 1c was localized in the tips of stereocilia, or near each end of the tip link in vestibular hair cells,[178,185,211,531] more recent studies of mammalian auditory hair cells suggest that myosin 1c is distributed throughout the entire stereocilium, and not at the very tip.[483] Accordingly, the protein may play different or additional roles in hair cells of the mammalian auditory system. In that regard, abnormal adaptation profiles have been observed in auditory hair cells of *Myo7a*-mutant mice, indicating that myosin VIIa may anchor or play a role in anchoring transduction channels to the actin core.[302] Moreover, as indicated by the observation that myosin IIIa is localized in the lower insertion site of the tip link, this protein may influence adaptation indirectly by exerting tension at the tip of the stereociliary membrane.[483] Further experimentation is clearly needed to identify the motor of adaptation and to determine the precise role(s) of myosin 1c in auditory hair cells.

Effects of Deficiencies of Other Hair Cell Channels on Hearing

Numerous K^+ channels have been identified in the basolateral membrane of vertebrate hair cells (Fig. 146-13), including BK (large-conductance, Ca^{2+}-activated K^+ channels), SK2 (small conductance Ca^{2+}-activated K^+ channels), and KCNQ4. It is notable that mutations in the gene that encodes KCNQ4 result in the autosomal dominant (DFNA2) form of deafness,[304] a finding that implicates the channel as a particularly important factor in inner ear potassium homeostasis. Persons carrying the mutant allele gradually acquire hearing loss, first in the high-frequency portion of the audible spectrum and slowly progressing to include lower frequencies, suggesting that the mutation leads to slow degeneration of hair cells. KCNQ4 is strongly expressed in OHCs but also has been detected in IHCs.[40,276,392] It appears that the protein is an essential component of the channel that carries the major K^+ current in OHCs, the outwardly rectifying $I_{K,n}$ current,[229,235,275,351] because targeted mutations of *Kcnq4* result in loss of $I_{K,n}$ in OHCs, both in vivo[275] and in organotypic cultures of transfected hair cells.[229] Although response thresholds of mutant mice improve during the first 3 postnatal weeks of life, normal sensitivity is never achieved, and thresholds progressively deteriorate thereafter, reaching a plateau loss of approximately 60 dB, the rate of loss being dependent on which specific mutation is expressed.[275] Hair cell degeneration is the expected histologic correlate of the hearing loss in mutant animals, and the process starts in the base of the cochlear spiral and progresses apically. IHCs are preserved throughout the cochlea and OHCs are preserved in the apical turn. Whereas IHCs from mutant animals are slightly more depolarized at rest when compared with control subjects, OHCs from mutant animals are more significantly depolarized at rest, suggesting that the hearing loss of DFNA2 is the consequence of chronic OHC depolarization resulting from loss of the ability to extrude K^+, which leads in turn to OHC degeneration.[275]

The principal K^+ current in IHCs, on the other hand, is the fast, voltage- and Ca^{2+}-activated current, $I_{K,f}$, which is carried by BK channels[301] composed of α-, β1-, and β4-subunit.[311] Of interest, cochlear thresholds in mice lacking the BKβ1- or the BKβ4-subunit, or both, are normal, strongly suggesting that neither subunit is critical for hearing.[424,464] Nevertheless, an early report suggested that OHCs do indeed degenerate in *BKα*-deficient mice, a condition leading to high-frequency hearing loss[464]; other studies suggest that cochlear thresholds and frequency selectivity are normal in mutant animals.[393,424] However, although IHCs from *BKα*-deficient mice are slightly depolarized at rest, maximum driven discharge rates are reduced, and timing, measured as both increased jitter in first-spike latency and reduced phase-locking, is impaired in many auditory nerve fiber responses. These findings clearly indicate that BK channels play a key role in the temporal processing of acoustic signals.[393]

Although the impact of SK2 channel abnormalities per se on hearing has not been studied, affected animals exhibit Preyer's reflex,

and voltage-gated ionic currents (other than those produced by SK2) in hair cells generally are unaffected.[256,294] However, SK2 channels are known to play an essential role in the maintenance of repetitive spiking activity of immature IHCs,[256] which may have a long-term influence on the normal maturation of the end organ. Of interest, efferent-mediated synaptic currents are absent in OHCs of SK2 mutants, as well as in immature IHCs, which are known to receive a transient cholinergic innervation during maturation.[294] In addition, the absence of SK2 leads to a significant reduction in the efferent innervation of OHCs, and OHC responses to cholinergic agents are absent, suggesting that the SK2 channel regulates or maintains the functional status of acetylcholine receptors.[294] Olivocochlear innervation also is disrupted in mice with deficiencies in the α9- or α10-subunit of nicotinic acetylcholine receptors, although these subunits are not necessary for the development of normal cochlear thresholds.[578,579]

Because the transduction channel is highly permeable to Ca^{2+},[87,113,345,389,437] a mechanism must exist for its extrusion after depolarization. This generally is accomplished by means of the action of plasma membrane Ca^{2+}-ATPases.[344] Pmca2 (also known as Atp2b2) is the primary Ca^{2+}-ATPase isoform expressed in hair bundles,[93,134] where it is found in high concentrations, with estimates reaching approximately 2000 molecules/μm^2 of stereocilia membrane.[28,93,532,624] Mutations in the *Pmca2* gene produce the phenotype observed in deafwaddler (*dfw*) mice, and the consequences of targeted deletion of the gene are deafness and vestibular abnormality.[298,532] In addition, heterozygous $Pmca2^{+/-}$ mice are more susceptible to noise-induced hearing loss,[297] and the severity of age-related hearing loss in mice carrying the mutant *ahl* allele of *Cdh23* (i.e., modifier of deafwaddler [*mdfw*]) is increased by heterozygosity for dysfunctional Pmca2.[384,385] A similar exacerbation in the severity of autosomal recessive hearing loss associated with a missense mutation in *CDH23* by a hypofunctional variant of PMCA2 is observed in humans and underlines the importance of Ca^{2+} homeostasis in the inner ear.[486]

Finally, mice that are deficient in voltage-gated L-type Ca^{2+} channels ($Ca_V1.3$, Cacna1D, or D-LTCC), which are responsible for most of the voltage-gated Ca^{2+} entry into IHCs by way of the basolateral membrane, are congenitally deaf.[420] It generally is thought that the current carried by these L-type Ca^{2+} channels control neurotransmitter release. Degenerative changes in both IHCs and OHCs, as well as spiral ganglion cells, have been observed early in postnatal life,[188] suggesting that this channel is indispensable for normal hearing.

Defects in Hair Cell–Afferent Dendrite Synapses Lead to Deafness

In addition to the requirement for calcium entry into IHCs for normal synaptic transmission, an event that is dependent on the Ca^{2+} channels composed of $Ca_V1.3$ subunits reviewed earlier, the hair cell–afferent dendrite synapse is distinct from other synapses in several ways. First, and perhaps foremost, the synapse in question is characterized by a large presynaptic dense body commonly referred to as a "ribbon." Each afferent dendrite receives input from a single "ribbon synapse" (Fig. 146-17A). The physical arrangement of vesicles attached to the ribbon is thought to provide a readily and continuously available pool of synaptic vesicles that can support a highly efficient and coordinated process of vesicular exocytosis that leads in turn to the synchronous release of neurotransmitter when hair cell depolarization occurs. Such a system is optimally designed to support fine temporal coding of acoustic stimuli.[386] IHC–afferent ribbon synapses also exhibit molecular specializations that differ in some ways from conventional synapses, as well as ribbon synapses found in association with other pathways. For example, IHC ribbon synapses lack synaptophysin, synapsin, and synaptotagmins I and II,[322] and they contain the proteins Ribeye and Piccolo, as well as the presynaptic scaffolding protein Bassoon (see Fig. 146-17B). It is thought that Bassoon is required to anchor the ribbon to the presynaptic membrane.[277] Mice deficient in Bassoon exhibit abnormal ABRs, elevated thresholds, a reduced rate of "fast" exocytosis, and normal DPOAEs—a constellation of characteristics that satisfy the definition of auditory neuropathy.[277]

When depolarized, $Ca_V1.3$ channels open and allow calcium to rapidly enter the cell, and intracellular Ca^{2+} activates the protein otoferlin, which in turn triggers the fusion of synaptic vesicles with the presynaptic membrane and subsequent vesicular exocytosis at the hair

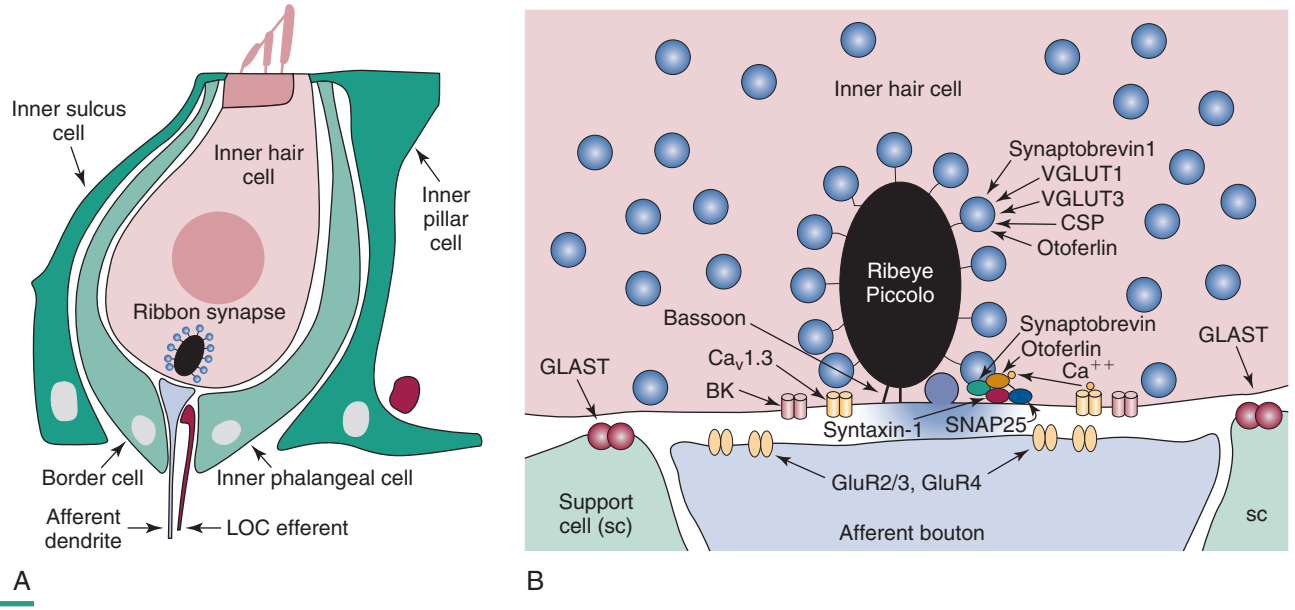

Figure 146-17. **A,** Schematic illustration of an inner hair cell (IHC) and a ribbon synapse with a type I radial afferent dendrite. Supporting cells shown include a border cell located adjacent to the modiolar side of the IHC and an inner phalangeal cell located on the opposite side; an inner sulcus cell and inner pillar cell also are illustrated. A lateral olivocochlear efferent fiber (LOC) is depicted making an axodendritic contact with the radial afferent fiber. **B,** Drawing of a single IHC ribbon synapse and proteins associated with the synapse. The synaptic ribbon is an electron dense body, holding numerous synaptic vesicles *(blue spheres)*, anchored to the presynaptic membrane. BK, large-conductance Ca^{2+}-activated K^+ channel; CSP, cystein-string protein; GluR, glutamate receptor; GLAST, glutamate-aspartate transporter; SNAP-25, synaptosomal-associated protein 25kDa; VGLUT, vesicular glutamate transporter. *(**A,** Adapted from Ruel J, Wang J, Rebillard G, et al. Physiology, pharmacology and plasticity at the inner hair cell synaptic complex.* Hear Res. *2007;227:19; **B,** adapted from Fuchs PA, Glowatzki E, Moser T. The afferent synapse of cochlear hair cells.* Curr Opin Neurobiol. *2003;13:452 and Nouvian R, Beutner D, Parsons TD, Moser T. Structure and function of the hair cell ribbon synapse.* J Membr Biol. *2006;209:153.)*

cell–afferent bouton synapse. Like synaptotagmin in conventional synapses, otoferlin acts as a Ca^{2+} sensor and interacts, in a calcium-dependent manner, with the t-SNARE proteins syntaxin-1 and SNAP-25, which are integrated into the presynaptic plasma membrane. The v-SNARE protein synaptobrevin (the vesicle-associated membrane protein [VAMP]) is located within the synaptic vesicle[468] and when activated initiates fusion of the exocytic vesicle with the presynaptic plasma membrane and subsequent release of neurotransmitter into the synaptic cleft. Mutations in otoferlin result in autosomal recessive, prelingual deafness (DFNB9) in humans,[626] and otoferlin-deficient mice also are congenitally deaf.[455] Although ABRs cannot be elicited from targeted null mice, presumably a consequence of failed vesicular exocytosis, ribbon synapses appear intact from a histologic perspective, and DPOAEs are normal; a clear case of auditory neuropathy. Interestingly, however, ABRs can be elicited electrically in null mice, suggesting that DFNB9 patients may be prime candidates for cochlear implants.

Other vesicular proteins of interest include the cysteine-string protein (CSP) is also found in hair cell vesicles[153] and is thought to act as a co-chaperone and protect tonically active synapses from neurodegeneration.[481] The vesicular glutamate transporters VGLUT1[174] and VLGUT3, the latter an unconventional but essential transporter, are located in the synaptic vesicle membrane and are responsible for loading L-glutamate into synaptic vesicles. Mutations in VGLUT3 (SLC17A8) lead to progressive deafness (DFNA25) in humans,[457] as well as in targeted null mice.[457,490] The glutamate-aspartate transporter (GLAST), or excitatory amino acid transporter 1 (EAAT1), is located on adjacent support cells (border and inner phalangeal cells) and is responsible for uptake and recycling of glutamate.[174,186] GLAST-deficient mice accumulate excess glutamate in the perilymph and are more susceptible than normal to acoustic overstimulation. This finding is consistent with the view that GLAST has a significant role to play in the clearance of glutamate from the extracellular milieu and, in doing so, protecting dendrites from glutamate neurotoxity.[206] Neurotransmitter-induced activation of the ionotropic AMPA-type receptors GluR2/3 and GluR4, located in postsynaptic afferent boutons,[355] leads to depolarization of the primary afferent dendrite and transmission of encoded acoustic information to the central nervous system.

Auditory Neuropathy

Auditory neuropathy–type pathologic conditions have been associated with a number of mutated genes that encode proteins located in the presynaptic compartment of the IHC–afferent dendrite synapse, as shown in the previous section. Perhaps those pathologic conditions should be thought of as auditory "synaptopathy"–type pathologic processes because of their locus of origin. These proteins prominently include the $Ca_V1.3$ subunit, Bassoon, otoferlin, and VGLUT3 (SLC71A8). In the following discussion, pathologic conditions associated with synaptic protein abnormalities are differentiated from those that fit more neatly into the "true" auditory neuropathy category—those that are associated with the nerve fiber itself. A good representative of a true auditory neuropathy model is the spontaneous mutant mouse *quivering*, in which defects in the protein β-spectrin 4 (Spnb4) lead to the abnormal distribution of ion channels in spiral ganglion axons, as well as axons of other peripheral and central neurons.[401] In mutant mice, the voltage-gated potassium channel Kcna1 is abnormally distributed along the length of auditory nerve axons, rather than being localized in a juxtaparanodal cluster as in normal animals. β-Spectrin 4 normally is detected in axonal initial segments and the nodes of Ranvier of nerve fibers, and it is generally suspected that the protein may serve to anchor ion channels to the juxtaparanodal region in myelinated nerve fibers and thereby influence saltatory nerve fiber conduction. Response amplitudes and latencies of ABR wave I are distinctly abnormal in β-spectrin 4–mutant mice, and later occurring peaks generally are absent from the response waveform. Likewise, disruption of the myelin sheath of the auditory nerve due to defects in peripheral myelin protein 22 (PMP22) or myelin protein zero (MPZ), also denoted P_0, as observed in Charcot-Marie-Tooth syndrome types 1A[296] and 1B,[212] respectively, leads to true auditory neuropathy in both humans and mice.[638] As in the case of β-spectrin 4–mutant mice, ion channel distributions in auditory nerve fiber axons are disrupted in these animal models as well.[233,593]

Perilymphatic-Endolymphatic Barrier

Normal mechanoelectrical transduction requires the separation of the endolymphatic and perilymphatic inner ear compartments, and the barrier that divides the major perilymph filled scalae from scala media is fashioned by tight junctions that form at the boundaries between cells that limit the endolymphatic space (Fig. 146-18A). These barriers, naturally, prevent the passage of water, ions, and molecules through intercellular spaces (see Fig. 146-18B), thereby maintaining a unique endocochlear milieu and separating the environment of the hair cells' apical surface from the basolateral plasma membrane of the cell by virtue of tight junctions formed between cells that make up the reticular lamina. To maintain this separate endolymphatic compartment, tight junctions are found in all epithelial cells lining the boundaries of the scala media, including the sensory epithelium, supporting cells within the sensory epithelium, cells lining the inner and outer sulci and the spiral limbus, marginal cells of the stria vascularis, and cells of Reissner's membrane. In addition, tight junctions are found in basal cells of the stria vascularis, forming an intrastrial compartment that is separate from both endolymph and perilymph.

Proteins of the claudin family (see Fig. 146-18C) are essential tight junction elements that form connections with the actin cytoskeleton by way of the protein zona occludens 1 (ZO-1), which has been identified as a component of the reticular lamina,[425] the scaffold protein shroom2, and myosin VIIa (see Fig. 146-18D).[146] Mutations in the gene (*CLDN14*) that encodes claudin 14, which is localized in the sensory epithelium, are responsible for an autosomal recessive form of deafness known as DFNB29.[606] Targeted deletion of *Cldn14* in the mouse leads to deafness associated with OHC degeneration that is followed by IHC degeneration. It generally is presumed that cellular death observed under these conditions is due to the increased permeability of cations through cells composing the paracellular pathway of the reticular lamina.[45] Although the endocochlear potential is normal in affected animals, claudin 14 is nonetheless required for the maintenance of the endolymphatic-perilymphatic ionic barrier, which breaks down in its absence. By contrast, tight junctions between strial basal cells are composed of claudin 11, and animals with null mutations in the encoding gene have reduced endocochlear potentials and elevated thresholds, although potassium recycling appears to be normal.[195,290] Moreover, specialized tight junctions connecting tricellular contact points composed of the protein tricellulin (see Fig. 146-18E) are essential for hearing and are responsible for autosomal recessive deafness (DFNB49) when dysfunctional.[435] Mutations associated with other components of tight junction–adherens junction complexes will almost certainly prove to be responsible for as yet unknown statoacoustic abnormalities in both human and nonhuman animals.

Endolymph Homeostasis

Homeostatic mechanisms involving the maintenance of separate endolymphatic and perilymphatic compartments, as well as preservation of the normal ionic environments within each scala, are essential for normal auditory function. Numerous genes, including several genes encoding gap junction proteins (Fig. 146-19), that alter homeostasis and are responsible for hereditary hearing impairments when mutated have been identified. The functions of a subset of these proteins are described in the following paragraphs.

It generally is understood that extrusion and recycling of K^+ after the depolarization of sensory cells are necessary components of mechanoelectrical transduction (Fig. 146-20). As described earlier, after entering hair cells through transduction channels, K^+ ions are extruded through channels located in the basolateral membrane, and enter the extracellular perilymphatic space. Once extruded, the K^+-Cl^- cotransporters Kcc3 and Kcc4, proteins that are encoded by *Slc12a6* and *Slc12a7*, respectively, take K^+ up by way of Deiters cells, which are situated underneath OHCs, and phalangeal cells that surround IHCs.[55,56] Kcc3 also is found in other epithelial cells of the organ of Corti, as well as type I and type III fibrocytes of the spiral ligament.[56] Absence of either protein produces a progressive form of deafness

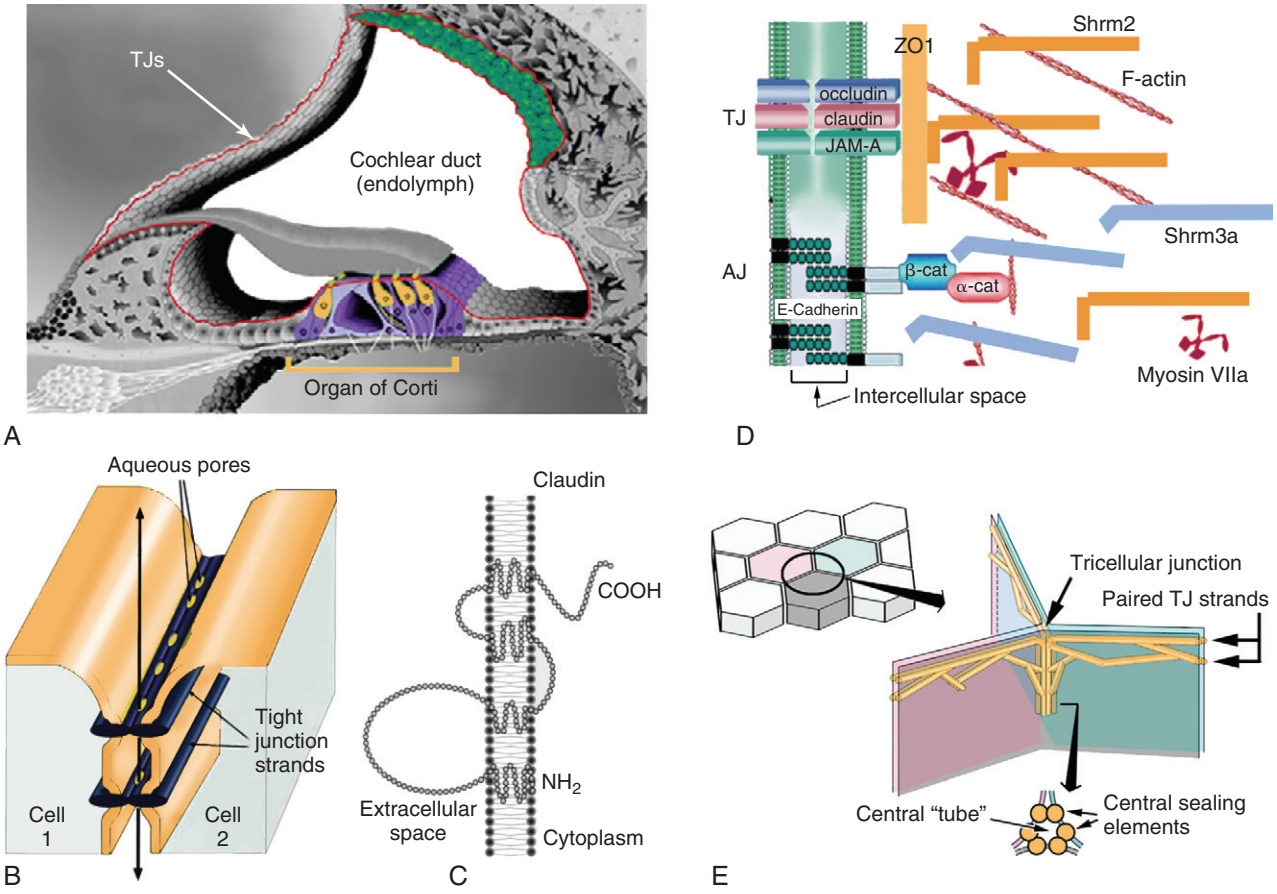

Figure 146-18. **A,** Schematic representation of the location of tight junctions (TJs), composed of claudin-14 within the epithelial barrier forming the cochlear duct, and those composed of claudin-11 between strial intermediate cells forming the barrier between intrastrial fluid and perilymph. **B,** Representation of bicellular TJ strands connecting the most apical region of the lateral membrane of two adjacent cells. TJs function as barriers to establish distinct fluid compartments separating the apical surface of the epithelial cells from the basolateral compartment by preventing admixture of molecules located above the apical surface of the cells from those surrounding the lateral membranes. TJ strands associate laterally with those in apposing membranes, forming paired strands. The aqueous pores regulate the passive paracellular passage *(arrow)* of ions, water, and various molecules, and these vary among epithelial cells in terms of size and charge selectivity. **C,** Proteins in the claudin family are integrally responsible for the formation of TJ strands and have four transmembrane domains and two extracellular loops, and both the amino and carboxyl termini are located on the intracellular side of the membrane. **D,** Claudins located on adjacent cells can form homotypic as well as heterotypic associations, resulting in intercellular adhesion, and they connect to the actin cytoskeleton by means of the scaffolding protein zona occludens 1 (ZO-1), as well as other members of the ZO family. Occludin and the junctional adhesion molecule (JAM-A) also are transmembrane components of TJs, sealing the paracellular space. Shroom 2 and 3a (Shrm2, Shrm3a) are proteins associated with TJs and adherens junctions (AJs), respectively, that may form a network between the actin cytoskeleton and unconventional myosins, such as myosin VIIa, which also is located at the site of TJs. **E,** Schematic illustration of the organization of tricellular TJs, composed of the essential protein tricellulin, as well as occludin. TJs between two adjacent cells become discontinuous at tricellular contact zones and extend basolaterally, forming a central tube; the tricellular TJs become vertically oriented and are composed of three pairs of TJ strands called "central sealing elements," forming a paracellular barrier at tricellular contacts. *(**A** and **D,** Adapted with permission from Etournay R, Zwaenepoel I, Perfettini I, et al. Shroom2, a myosin-VIIa- and actin-binding protein, directly interacts with ZO-1 at tight junctions.* J Cell Sci. *2007;120:2838; **B** and **C,** adapted from Tsukita S, Furuse ML. The structure and function of claudins, cell adhesion molecules at tight junctions.* Ann NY Acad Sci. *2000;915:129; **E,** from Ikenouchi J, Furuse M, Furuse K, et al. Tricellulin constitutes a novel barrier at tricellular contacts of epithelial cells.* J Cell Biol. *2005;171:939.)*

in mice beginning near the onset of hearing. Pathology progresses faster in the case of Kcc4 null mice. Hair cell loss is observed in affected animals, and loss of Kcc4 also is associated with renal tubular acidosis.

K^+ taken up by support cells then diffuses through gap junctions to other epithelial cells of the outer sulcus that include Hensen and Claudius cells and into root cells of the spiral ligament,[245,284,477] where the ion is extruded into the extracellular space within the connective tissue of the spiral ligament. Type II fibrocytes, which express Na^+,K^+-ATPase (ATPA1 and ATPB1) and the Na^+-K^+-$2Cl^-$ (Slc12a2, Nkcc1) transporter,[92,484,485,522] take up K^+, which then passes through gap junctions to type I fibrocytes and into basal cells and intermediate cells of the stria vascularis. Intermediate cells that contain KCNJ10 channels extrude K^+ into the intrastrial space,[23,353] where it is taken up by the basolateral membranes of marginal cells, through Na^+-K^+-$2Cl^-$ (Slc12a2, Nkcc1) transporters[295,354,594] and Na^+-K^+-ATPase, including the ATP1A1, ATP1B1, and ATP1B2 subunits.[360,409,484,485,543] In addition, the marginal cell basolateral membrane contains Cl^- channels that associate with a protein called Barttin, encoded by *BSND* (*B*artter syndrome with *s*ensori*n*eural *d*eafness, or Bartter syndrome type IV), which forms the β-subunit required to transport ClC-Ka and ClC-Kb channels to the plasma membrane.[24,53,145,216,469] These channels are responsible for passive diffusion of Cl^- into the intrastrial space. Marginal cells secrete K^+ from their apical membrane by way of heteromeric K^+ channels composed of KCNQ1 (KvLQT1) and KCNE1 (IsK) subunits into scala media.[352,471,500,594,596]

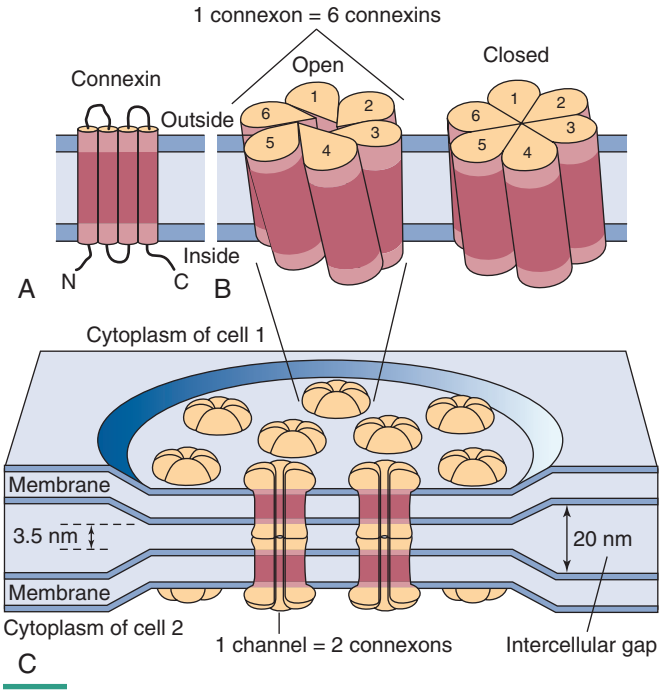

Figure 146-19. A, Gap junctions, which allow the direct passage of low-molecular-weight ions, second messengers, and metabolites (less than 1 kDa in size) between the cytoplasm of adjacent cells, are formed by the connexin family of proteins. Each connexin molecule has four transmembrane α-helical domains, and the amino and carboxyl termini are located intracellularly. Six connexins assemble to form a connexon or hemichannel (**B**). Connexons of adjacent cells form apposing partners to form a gap junction (**C**). Different types of channels can be formed, depending upon the combination of connexin proteins assembling to form the connexon, and depending upon the combination of connexons forming the channel. The channel pore can be regulated by protein kinase C, Ca^{2+}, calmodulin, cyclic adenosine monophosphate (cAMP), and pH, as well as other factors. Aggregates of gap junctions form large semicrystalline arrays where the apposing plasma membranes are in close proximity (3.5 nm) compared with the typical extracellular distance between cells (20 nm). (***A*** *to* ***C,*** *Modified from Kandel ER, Siegelbaum SA, Schwartz JH. Synaptic transmission. In: Kandel ER, Schwartz JH, Jessel TM, eds.* Principles in Neural Science. *New York: Elsevier; 1991:123.)*

Numerous proteins that are components of gap junctions have been identified in the cochlea, including the connexins CX26 (GJB2), CX30 (GJB6), and CX31 (GJB3). These proteins are particularly evident in supporting cells, interdental cells of the spiral limbus, root cells, and fibrocytes, as well as in basal and intermediate cells of the stria vascularis.[164,166,169,258,284,312,313,615-617] Mutations of the *GJB2* gene cause autosomal recessive and autosomal dominant forms of deafness (DFNB1, DFNA3), in addition to syndromic conditions that include deafness.[114,269,439,441] Mutations of *GJB6* also are responsible for autosomal recessive (DFNB1)[108] and autosomal dominant (DFNA3)[197] forms of deafness, and mutations in *GJB3* are associated with autosomal dominant (DFNA2)[618] and autosomal recessive forms of hearing loss.[340]

Similarly, genetically targeted ablation or mutation of CX26[79,305] or CX30[544] in mice results in hearing impairment, with associated degeneration of supporting cells in the organ of Corti, initially in the region of IHCs, followed by hair cell loss. These findings suggest that both CX26 and CX30 play a particularly important role in organ of Corti homeostasis. Similar degeneration of the sensorineural epithelium was observed in a human temporal bone associated with CX26-related hearing loss.[260]

Mutations in KCNQ1 (KVLQT1) or KCNE1 cause deafness associated with Jervell and Lange-Nielsen syndrome, as well as cardiac manifestations including a prolonged QT interval.[382,487,561] In addition, the endolymphatic compartment of transgenic mice lacking Kcnq1[66,315] or KCNE1,[580] or mice carrying spontaneous mutations of *Kcne1*,[323] is collapsed, and affected animals are deaf. Mutations in *BSND* cause Bartter syndrome, which is associated with sensorineural deafness and kidney failure,[53] suggesting that Cl^- extrusion from marginal cells into the intrastrial fluid space is essential for hearing. Similarly, mice with targeted disruption of *Bsnd* in the inner ear exhibit congenitally elevated thresholds as a result of a reduction in endocochlear potential, although the K^+ concentration in endolymph remains normal.[447] Of interest, mice lacking the ClC-Ka subunit are not deaf,[356] suggesting that the channel formed by the ClC-Kb subunit is sufficient for hearing. Targeted deletion of the *Nkcc1* (Slc12a2) gene that encodes the Na^+-K^+-$2Cl^-$ transporter protein in mice leads to deafness,[110,157] and a spontaneously occurring mutation in the gene is responsible for deafness in the mouse mutant called no syndactylism (*sy-ns*), which is transmitted as an autosomal recessive trait.[124] These findings suggest that abnormalities of this protein may cause human deafness as a consequence of defective endolymph secretion. In transgenic mice lacking the KCNJ10 (Kir4.1) channel, the endocochlear potential is eliminated, endolymphatic K^+ concentration is reduced, and Reissner's membrane is partially collapsed, producing deafness as assessed by absent Preyer's reflexes,[353] and sensory cells degenerate early in the postnatal period,[456] suggesting that KCNJ10 is necessary for providing the force for endocochlear potential generation.

Ablation of the *Pou3f4* gene, located on the X chromosome and known to encode a POU transcription factor expressed in fibrocytes of the spiral ligament, results in a reduced endocochlear potential and profound deafness in mice,[366,414] as does a spontaneous mutation named sex-linked fidget (*slf*).[412] Not surprisingly, developmental defects in the formation of the cochlea also are known to occur in affected animals, including an enlarged internal auditory meatus, stapes malformation, a reduction in the number of cochlear turns, thinning of the bony capsule and spiral limbus, and reduced scala tympani volume. Pou3f4 is expressed extensively in cochlear tissues of mesenchymal origin during development.[413] In humans, mutations of *POU3F4* are associated with X-linked (DFN3) deafness, resulting from both a conductive hearing loss caused by stapes fixation and progressive sensorineural pathology.[106] Reports also indicate that persons carrying this mutation seem to produce large volumes of perilymphatic flow (perilymphatic "gusher") during stapes surgery and exhibit abnormally large internal auditory meatuses.

Other ion transporters involved with homeostasis include pendrin (SLC26A4, PDS), an anion exchanger associated with Pendred's syndrome and prelingual profound deafness, and DFNB4,[325] which involves enlargement of the vestibular aqueduct.[410] Pendrin is expressed in cells of the spiral prominence and in the endolymphatic duct and sac,[152] where it may function to secrete bicarbonate into endolymph[595] and maintain pH homeostasis. Targeted disruption of the *Pds* gene in mice results in deafness and hair cell degeneration.[150,595] Although essential components of the proposed pathway described here remain to be identified, it is clear that homeostasis within the endolymphatic compartment is essential for hearing.

Summary

In the 21st century, the prospect of rescuing the victims of deafness from a life of relative isolation is bright, but the challenge to make sense of the complex interplay between genes and environment that shape the peripheral auditory system is more than significant. As has been emphasized throughout this chapter, the molecular and genetic basis of transduction is complex, and the molecular and cellular mechanisms for both transduction and deafness require further elucidation. Despite the steep learning curve for scientists around the world, reflecting an enormous and an emerging database centered on the role of integral proteins in the development and maintenance of inner ear anatomy and physiology, the precise mechanism of action is understood for only a small number of the known gene products that work harmoniously to support effective mechanoelectrical transduction, we are

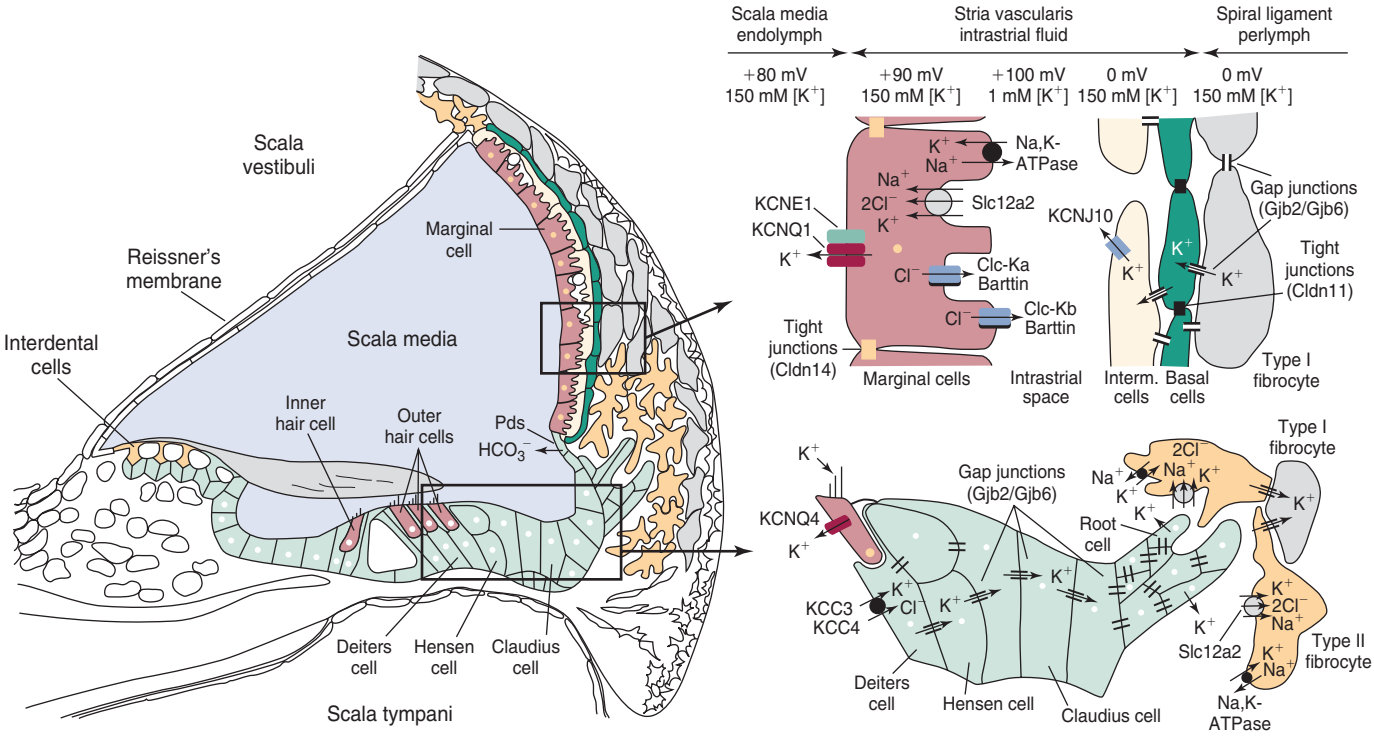

Figure 146-20. A proposed scheme for ion transport within the cochlea focused on K^+ circulation from cells within the stria vascularis *(upper right)* to the endolymphatic compartment *(left)*, through the sensory cells, and transportation back to the stria vascularis through the epithelial cell gap junction network into the outer spiral sulcus, and then through the connective tissue gap junction network of the spiral ligament *(lower right)*. Although the illustrated scheme is focused on a laterally oriented pathway from the organ of Corti toward the spiral ligament, a medial pathway has been proposed as well.[523] Several key proteins within this pathway have been identified as essential for normal hearing. See text for details. *(Modified from Heller S. Application of physiological genomics to the study of hearing disorders.* J Physiol. *2002;543:3.)*

nonetheless on the brink of what promises to be a breathtaking period of achievement.

Acknowledgments

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CHAPTER ONE HUNDRED AND FORTY-SEVEN

Genetic Sensorineural Hearing Loss

Michael S. Hildebrand

Murad Husein

Richard J. H. Smith

Key Points

- It is estimated that at least 50% of congenital hearing impairment has a genetic origin.
- A hearing loss can be defined by numerous clinical criteria, including causality, time of onset, age of onset, clinical presentation, anatomic defect, severity, and frequency loss.
- The worldwide rate of profound hearing loss is 4 in every 10,000 infants born.
- The term *homozygosity* means that a person carries two identical alleles of a gene; *heterozygosity* represents the state in which a person carries two different variants of a given gene.
- The basic forms of inheritance can be mendelian (single-gene inheritance—autosomal or X-linked), mitochondrial, or complex (chromosomal, new mutations, germline mosaicism, genomic imprinting, polygenic, and multifactorial inheritance).
- Nonsyndromic hearing impairment in the absence of other phenotypic manifestations accounts for 70% of hereditary hearing loss.
- Mutations in *GJB2* have been shown to cause 50% of autosomal recessive nonsyndromic deafness in many world populations.
- Syndromic hearing impairment refers to deafness that cosegregates with other features, forming a recognizable constellation of findings known as a syndrome. Sensorineural deafness has been associated with more than 400 syndromes.
- The most common syndromic form of hereditary sensorineural hearing loss, Pendred syndrome, is inherited in an autosomal recessive fashion; affected individuals also have goiter.
- A well-performed patient history, physical examination, and audiologic evaluation are keys to assessing the cause of hearing loss, and may aid in ascertaining etiology.
- Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells.
- Cochlear implantation is becoming an increasingly important option for individuals with severe to profound deafness.

It was famously put by Terry Savage that "… a child will hear his mother's voice for the rest of his life…." Many children never hear their mother's voice, however, and others do not hear it very well throughout their lives. Hearing loss is a common human sensory defect. The incidence of congenital hearing impairment is at least 1 child in every 1000 born.[1] A hearing impairment commonly involves damage to or loss of cochlear hair cells; this is referred to as a sensorineural hearing loss (SNHL). Individuals with SNHL are often referred to as deaf (lower case "d") by the community. The term *Deafness* (capital "D") is used to describe an individual with SNHL who is part of a cultural group based on their use of sign language for communication. Members of this group tend to be the offspring of Deaf parents and generally have congenital SNHL. In contrast, individuals who acquire SNHL later in childhood or adulthood generally do not use sign language and persist with oral communication. These individuals are usually not part of the Deaf community.

It is estimated that at least 50% of congenital hearing impairment has a genetic origin.[1] Late-onset hearing loss can also be caused by genetic defects. As understanding of the genetics of deafness increases, the role of the otolaryngologist in diagnosing, interpreting, and managing this form of hearing loss has mandated a basic understanding of genetics. This chapter provides an introduction to the genetics of hearing loss. An overview of hearing loss is followed by discussion of the fundamentals of genetics and a synopsis of syndromic and nonsyndromic deafness. The final section focuses on the clinical approach to a child with suspected genetic deafness and potential therapies for genetic hearing loss.

Background

Classification of Hearing Impairment

A hearing loss can be defined by numerous clinical criteria, including causality, time of onset, age of onset, clinical presentation, anatomic

Table 147-1

Hearing Loss Classification

Criteria	Classification	Comment
Causality	Genetic Environmental Multifactorial	Hereditary Nonhereditary
Time of onset	Congenital Acquired	At birth Late-onset
Age of onset	Prelingual Postlingual	Before speech development After speech development
Clinical presentation	Nonsyndromic Syndromic	Hearing loss only symptom Hearing loss and other symptoms
Anatomic defect	Conductive Sensorineural Mixed	Dysfunction of outer or middle ear Dysfunction of inner ear
Severity	Mild Moderate Moderately severe Severe Profound	Range 20-40 dB Range 41-55 dB Range 56-70 dB Range 71-90 dB Range >90 dB
Frequency loss	Low-frequency Midfrequency High-frequency	Range <500 Hz Range 501-2000 Hz Range >2000 Hz
Ears affected	Unilateral Bilateral	One ear affected Both ears affected
Prognosis	Stable Progressive	Severity remains unchanged Severity increases over time

Table 147-2

Quantification of Hearing Impairment

Impairment (%)	Pure Tone Average (dB)*	Residual Hearing (%)
100	91	0
80	78	20
60	65	40
30	45	70

*Pure tone average of 500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz.

defect, severity, and frequency loss (Table 147-1). Etiologically based classifications can be broadly divided into genetic versus nongenetic factors. This distinction is important because hereditary deafness does not imply congenital deafness; the latter describes a condition present from birth regardless of causality. Hereditary deafness may be present at birth or develop any time thereafter.

It is well known that heritable and environmental factors can make strong contributions to hearing loss. There are three types of anatomic defects—conductive, sensorineural, or a combination of both (mixed)—and these defects may arise from syndromic or nonsyndromic conditions. Generally, when discussing hereditary deafness, a clinically based classification reflecting the presence or absence of coinherited anomalies—that is, syndromic or nonsyndromic deafness—is most useful. Syndromic and nonsyndromic conditions can be subclassified by inheritance pattern as autosomal dominant, autosomal recessive, X-linked, mitochondrial, or complex. Hearing loss can also be distinguished by differences in severity and frequency loss. Additional features of a hearing loss that are assessed include whether one or both ears are affected, and the prognosis for the condition (see Table 147-1).

Although these classifications assist clinicians in their assessment of patients and lead to better clinical outcomes, they do not adequately represent the complex interactions that underlie most forms of hearing loss. This limitation is exemplified in hearing loss that is attributable to exposure to the ototoxic antibiotics, aminoglycosides. Although at high concentration these antibiotics interfere with the normal function of the cochlea, individuals with an A1555G mutation in their mitochondrial 12S rRNA gene are more susceptible to the ototoxic effect of these drugs.[2] In some cases, hearing loss is attributable to genetic and environmental factors, and this dual causality can make classifying hearing loss less informative.

Diagnosis of Hearing Impairment

The primary diagnosis of hearing loss is by auditory testing to detect loss in hearing acuity. Hearing function is measured in decibels and is considered normal if the lowest level (threshold) a sound can be perceived is between 0 and 20 dB. The value of 0 dB is defined as the point at which a tone burst of a given frequency is perceived 50% of the time by a young adult. The severity and frequency loss sustained during a hearing impairment are given in Tables 147-1 and 147-2. Hearing acuity can be readily measured quantitatively and objectively by numerous physiologic tests, including auditory brainstem response (ABR) measurements, auditory steady-state responses, impedance testing (tympanometry), and otoacoustic emissions. For all these auditory tests except tympanometry, normal middle ear function is required for a normal response to be generated.

ABR testing records the electrophysiologic response of the auditory nerve (eighth cranial nerve) and brainstem to tone bursts (sound wave trains consisting of several cycles of the same frequency) or clicks (unidirectional rectangular voltage pushes) applied to the outer ear.[3,4] The waveform patterns are detected by electrodes connected to the skin, with maximal obtainable values at 94 to 100 dB sound pressure level. Sound pressure level refers to the ratio of the pressure of a sound wave to the standard air pressure level. Otoacoustic emissions are distinct from ABRs in that they are sounds generated only from the cochlea, and represent the activity of outer hair cells in response to transient or continuous stimulation. The emissions are measured in the external auditory canal, and are usually absent in individuals with hearing loss greater than 40 to 50 dB.[4]

The audiometry steady-state response has some similarity to the ABR, but the stimulus is continuous. A continuous tonal stimulus generates a higher sound pressure level than is possible with click stimuli, and allows a better estimation of hearing acuity in profoundly deaf individuals.[4] Impedance audiometry is used in conjunction with ABR, otoacoustic emissions, or auditory steady-state response testing because it does not measure hearing. This technique is used routinely to determine middle ear pressure, movement of the tympanic membrane and middle ear ossicles, and eustachian tube activity.[4]

Epidemiology of Hearing Impairment

Hearing loss is a prevalent human sensory defect. The worldwide rate of profound hearing loss is 4 in every 10,000 infants born.[5,6] The rate of SNHL determined in universal newborn screening programs in developed countries of 2 to 4 children per 1000 born compares favorably with this figure.[7,8] The incidence of congenital SNHL in developing countries is likely to be much higher,[9,10] although more data are required. The implications for the personal and social development of these children are significant.

Historical Background of Genetics

Mendel is considered the father of modern genetics. His work formulating the fundamentals of heredity by experimenting on the garden pea is well known to all school students. From this work, he postulated the principles of segregation and independent assortment, publishing these concepts in 1865. In the early 1900s, the impact of these ideas was recognized. Johannsen described the basic unit of heredity as the gene in 1909, and Avery showed that genes are composed of deoxyribonucleic acid (DNA) in 1944. In 1953, Watson and Crick described the physical structure of DNA, and 3 years later, the correct number of human chromosomes was confirmed to be 46. Sequencing these chromosomes was the goal of the Human Genome Project, initiated in 1991 and completed with first-pass data in 2001. The impact of this project on medicine has been tremendous, with the field of genetic deafness being just one of many areas of medical science to have flourished. A list of the current known deafness genes can be found on the Hereditary Hearing Loss Homepage.[11]

Fundamentals of Genetics

Each person has 46 chromosomes—22 pairs of autosomes and one pair of sex chromosomes (XY in males or XX in females). According to Mendel's principle of segregation, in sexually reproducing organisms, each partner contributes only one member of each chromosome pair to an offspring. This fact means that each individual has inherited one copy of each chromosome from each parent. Carried on these chromosomes are genes, estimated to number approximately 30,000. Variations in these genes impart uniqueness to each individual. These variations, termed *alleles,* can sometimes be deleterious.

If a mutation occurs in the normal or wild-type sequence of a gene expressed in the inner ear, and if the protein translated from this new allele variant does not function as well as the normal protein, deafness may result. If the remaining normal protein (recall that each gene is represented in duplicate) is able to cover for the abnormal protein, however, deafness manifests only in the individuals who carry two copies of the abnormal gene. This scenario is an example of autosomal recessive inheritance. If the abnormal protein interferes with the normal protein function, deafness manifests in an individual carrying a single abnormal gene. This scenario is an example of autosomal dominant inheritance.

In describing these inheritance patterns, we are describing a person's genotype or genetic makeup. The term *homozygosity* means that a person carries two identical alleles of a gene; *heterozygosity* represents the state in which a person carries two different variants of a given gene. The observable consequence that derives from an individual's genotype is his or her *phenotype*. Often individuals carrying identical genetic mutations exhibit a spectrum of different phenotypic features. Not every person with Waardenburg's syndrome type 1 has synophrys, premature graying of the hair, or heterochromia irides, a phenomenon called *variable expressivity*. In some cases, the phenotype can be so subtle as to be entirely absent, and the causative genetic mutation is said to be incomplete or nonpenetrant. This occurrence can give the impression that a disease "skips" generations.

Patterns of Inheritance

The basic forms of inheritance can be mendelian (single-gene inheritance—autosomal or X-linked), mitochondrial, or complex (chromosomal, new mutations, germline mosaicism, genomic imprinting, polygenic, and multifactorial inheritance). Pedigrees for these inheritance patterns are shown in Figure 147-1. Mendelian and mitochondrial forms of inheritance are discussed in this chapter; for the reader who is interested in complex forms of inheritance, we recommend more appropriate texts.[12,13] Punnett squares are used to show inheritance patterns by displaying the outcomes of crosses with both parents and allowing probability estimates for the offspring (Fig. 147-2).

Autosomal Dominant

In autosomal dominant diseases, heterozygotes express the disease phenotype. The affected parent can pass either a disease allele or a normal allele to offspring, with the likelihood of each event being 0.5, or 50%. This fact means that 50% of offspring inherit the normal allele, and 50% inherit the disease allele. In the case of dominant diseases, 50% of offspring express the disease.

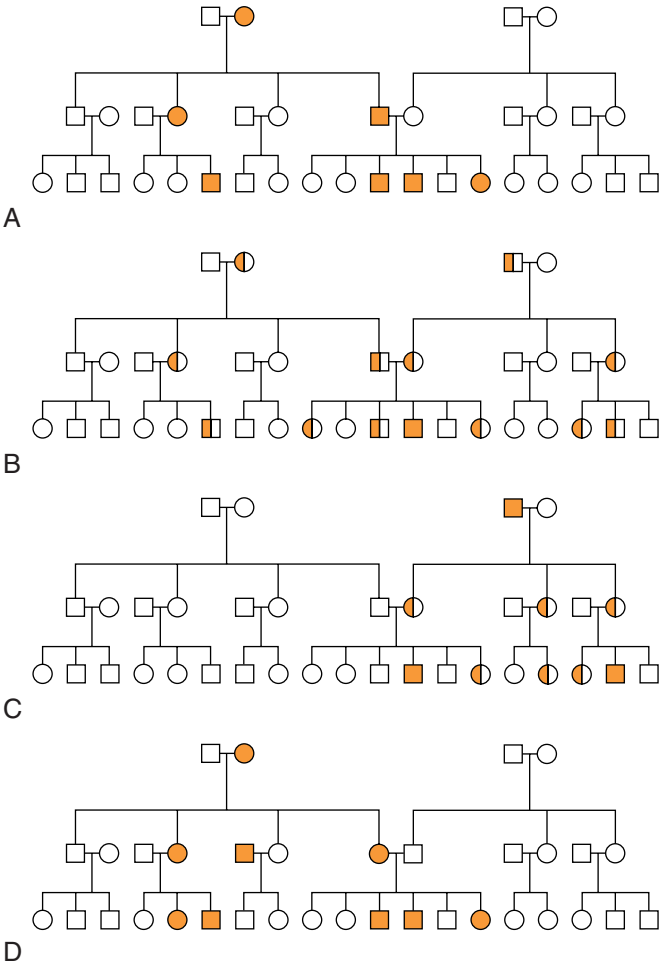

Figure 147-1. Inheritance patterns. **A,** Pedigree illustrating autosomal dominant inheritance. The inheritance pattern shows vertical transmission of the affected phenotype including father-to-son transmission. There are no skipped generations. **B,** Pedigree of autosomal recessive inheritance. Note the disease phenotype is not usually seen in the parents or other ancestors. Likelihood of affected males to females is equal. Refer to Punnett square in Figure 147-2 for estimating risks for recessive inheritance in heterozygous parents. **C,** Pedigree of X-linked recessive inheritance. The disease phenotype is present with one disease allele in the male, but requires a homozygous genotype to be expressed in the female. **D,** Pedigree illustrating mitochondrial inheritance. Note the maternal transmission of the affected phenotype. There is no paternal transmission.

There are several implications of autosomal dominant transmission. First, there is no sexual predilection for the disease phenotype; males and females are equally likely to be affected, and to transmit the disease allele to their offspring. Second, unless the disease gene is nonpenetrant, the disease does not skip generations. This type of transmission is called *vertical transmission*. Third, male-to-male (father-son) transmission is seen. This observation in a pedigree rules out mitochondrial or X-linked inheritance.

Autosomal Recessive

In contrast to autosomal dominant inheritance, in autosomal recessive inheritance, a homozygous genotype is necessary for expression of the disease phenotype. A homozygous parent transmits the disease allele to all offspring, but offspring do not show the disease phenotype unless the other parent carries at least one mutant copy of the same gene. More frequently, however, neither parent is affected, but both carry a single

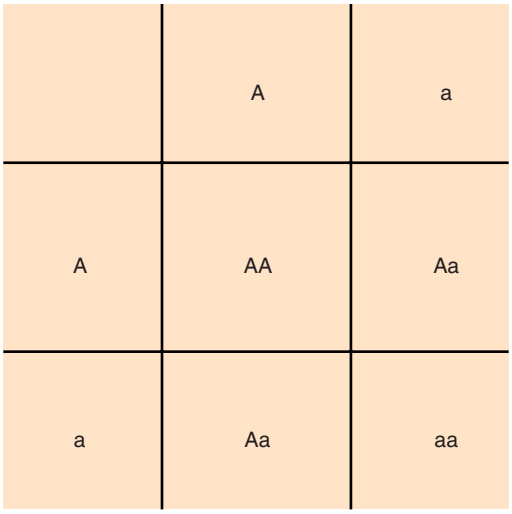

Figure 147-2. Punnett squares may be used to estimate inheritance probabilities for mendelian inheritance patterns. This Punnett square illustrates the mating of two individuals who are heterozygous carriers of an autosomal recessive gene, showing that there is a 25% chance of having a child with the recessive phenotype (aa), a 50% chance of having a child who carries the recessive allele but is not affected (Aa), and a 25% chance of having a child who does not carry the recessive allele (AA).

mutant gene, and by chance each passes this mutant copy on to the offspring. In this scenario, 25% of offspring carry two mutant copies of the gene and express the disease phenotype, 50% of offspring are carriers of a mutant copy (similar to the parents), and 25% of offspring have two wild-type copies of the gene. As with autosomal dominant diseases, there is no sexual predilection—males and females are equally likely to be affected—but vertical transmission is rarely seen. Recessive diseases tend to be generation specific. If the disease is exceptionally rare, the likelihood of parental consanguinity, albeit distant, is high.

X-Linked Inheritance

X-linked inheritance may be either recessive or dominant. In recessive X-linked inheritance, females are unlikely to be affected because a homozygous disease genotype is needed for the disease phenotype to manifest. Heterozygous females do occasionally exhibit subtle aspects of the disease phenotype, however, because of the phenomenon of X chromosome inactivation (the Lyon hypothesis). In each cell, only one of the two X chromosomes in females is active, and if X chromosome inactivation is entirely random, 50% of cells in a heterozygous female express the disease-carrying X chromosome. Through mechanisms that are not clearly understood, this process is not random, and inactivation of the mutated X chromosome is much higher than is inactivation of the normal X chromosome. Males have only a single X chromosome, and always express the disease phenotype.

In a pedigree showing X-linked recessive inheritance, the trait is seen more frequently in males; there is no father-son transmission; affected fathers transmit the disease allele to all female offspring, who may have affected males ("skipped generation"); and heterozygous females transmit the disease allele to half of all sons, who manifest the disease, and half of all daughters, who are heterozygous and phenotypically normal. In X-linked dominant inheritance, affected fathers transmit the disease allele to all daughters who exhibit the disease phenotype (with complete penetrance); there is no father-son transmission. Heterozygous females are affected and transmit the trait to half of all sons and to half of all daughters.

Mitochondrial Inheritance

Mitochondria are the "powerhouses" of the human cell and the site of oxidative phosphorylation, the process that leads to the production of adenosine triphosphate (ATP). Mitochondria possess their own intrinsic DNA, with several copies of the mitochondrial genome in each mitochondrion. The mitochondrial genome is a 16,569 base pair circular molecule that encodes two ribosomal RNAs, 22 transfer RNAs, and 13 polypeptides.[14] The remaining mitochondrial proteins required for oxidative phosphorylation are encoded by the nuclear genome.

Mitochondrial DNA (mtDNA) is inherited solely through the maternal lineage, reflecting the presence of large amounts of mtDNA in the cytoplasm of the egg. If all of the mtDNA molecules are abnormal, a condition known as *homoplasmy,* all progeny cells contain abnormal mitochondria. If normal and abnormal mtDNA molecules coexist, a condition known as *heteroplasmy,* there is a wide range of expression of the mutant phenotype, reflecting the random distribution of mitochondria to progeny cells. Because mitochondria lack a DNA repair mechanism, mtDNA accumulates mutations at a higher rate than nuclear DNA.

Table 147-3

Prevalence of Different Forms of Congenital Hearing Loss

Form	Prevalence (%)
Environmental	50
Genetic	50
Syndromic	15
Nonsyndromic	35
Autosomal recessive	28
Autosomal dominant	7
X-linked and mitochondrial	<1

Genetic Hearing Impairment

Nonsyndromic Hearing Impairment

Genetic hearing loss is common in humans. Nonsyndromic hearing impairment in the absence of other phenotypic manifestations accounts for 70% of hereditary hearing loss.[15] More than half of SNHL that occurs in neonates is attributable to simple mendelian inherited traits (Table 147-3). In most cases, the inheritance pattern is recessive (75% to 80% of cases), and consequently the parents of affected children generally do not exhibit the phenotype. Congenital nonsyndromic hearing loss is inherited in an autosomal dominant (approximately 20%), X-linked (2% to 5%), or mitochondrial (approximately 1%) mode. Nomenclature is based on the prefix "DFN" to designate *nonsyndromic deafness*. DFN followed by an "A" implies dominant inheritance, a "B" implies recessive inheritance, and no letter means X-linked inheritance. The integer suffix denotes the order of locus discovery. DFNA1 and DFNB1 were the first autosomal dominant and recessive nonsyndromic deafness loci to be identified. Table 147-4 lists the genes included in clinical screens for nonsyndromic SNHL.

Autosomal Recessive Nonsyndromic Hearing Impairment

Autosomal recessive nonsyndromic hearing impairment is usually prelingual and severe to profound across all frequencies.[16] To date, 67 loci have been mapped, and 23 causative genes have been cloned (Table 147-5).[11] Although autosomal recessive SNHL is heterogeneous, mutations in the connexin 26 (*GJB2*) gene at the DFNB1 locus contribute about half of all hereditary cases in Australia, the United States, Israel, and many European countries.

DFNB1

In 1994, Guilford and coworkers[17] mapped the first autosomal recessive nonsyndromic deafness locus to 13q12-13 and called it DFNB1. Three

Table 147-4

Hearing Loss Genes Currently Screened for Clinical Diagnostics

Syndromic Hearing Loss	Gene
Branchio-oto-renal (BOR) syndrome	*EYA1*
Mohr-Tranebjaerg syndrome (deafness–dystonia–optic atrophy syndrome)	*TIMM8A*
Pendred syndrome	*SLC26A4*
Usher syndrome type 1B	*USH1B*
Usher syndrome type 2A	*USH2A*
Usher syndrome type 3	*USH3A* (one mutation)
Wolfram syndrome	*WFS1*
Nonsyndromic Hearing Loss	
DFNA3 and DFNB1	*GJB2* and *GJB6*
DFN3	*POU3F4*
DFNB4	*SLC26A4*
DFNA 6/14	*WFS1*
DFNA8/12	*TECTA*
DFNA9	*COCH*
DFNB9	*OTOF*
DFNB21	*TECTA*
Mitochondrial Hearing Loss	
	MTRNR1, MTTS1, MTTL1

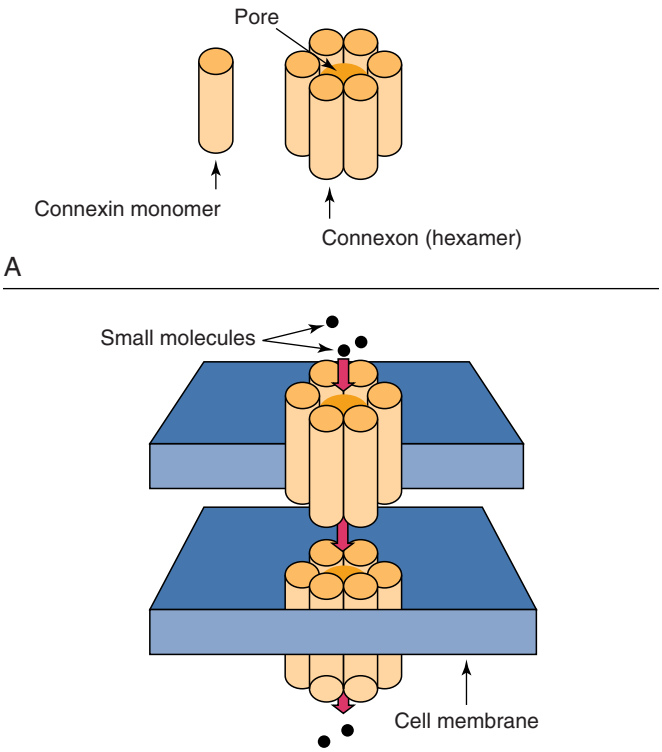

Figure 147-3. Diagram of a gap junction and its constituents. **A,** Three-dimensional view of a connexon hexamer composed of six connexin monomers. **B,** Three-dimensional view of a gap junction composed of two connexons in adjacent cells. Small molecules can pass through the gap junction from one cytoplasm to another without having to cross two cell membranes.

years later, Kelsell and colleagues[18] identified the DFNB1 gene as a gap junction gene called *GJB2*. The encoded protein, connexin 26 (Cx26), oligomerizes with five other connexin proteins to form a connexon; the docking of two connexons in neighboring cells results in a gap junction (Fig. 147-3). These gap junctions are thought to be conduits through which potassium ions are recycled from the outer hair cells back through the supporting cells and spiral ligament to the stria vascularis.[19] The ions are pumped into the endolymph to perpetuate the mechanosensory transduction of hair cells. Mutations in *GJB2* may disrupt this recycling process and prevent normal mechanosensory transduction.[18] This role is consistent with the expression of *GJB2* in the stria vascularis, nonsensory epithelial cells, spiral ligament, and spiral limbus of the inner ear.[18]

Mutations in *GJB2* have been shown to cause 50% of autosomal recessive nonsyndromic deafness in many world populations.[20] More than 90 deafness-causing mutations are described, with several being very common in specific ethnic groups.[21] The 35delG mutation predominates in populations of European descent[22]; this mutation has a carrier frequency in the Midwestern United States of 2.5%.[23] In the Ashkenazi Jewish population, the most common mutation is the 167delT; its carrier frequency is approximately 4%.[24] In Japanese populations, the 235delC mutation is the most common deafness-causing allele variant of *GJB2*.[25]

The DFNB1 auditory phenotype is varied, although homozygosity for protein-truncating mutations is generally associated with impaired gap junction activity and moderate to profound deafness.[21,26] With missense mutations, the degree of residual hearing can be substantially greater.[21] Most frequently, the loss is symmetric between ears, and does not progress over the long-term. Temporal bone anomalies are not part of the DFNB1 phenotype, obviating the need for routine temporal bone imaging.

Genetic testing is available to diagnose *GJB2*-related deafness and is warranted because the relative contribution of this gene to the total genetic deafness mutation load is high. Mutation screening facilitates genetic counseling and prediction of the chance of recurrence. It also provides prognostic information because several studies have shown that cochlear implant recipients with *GJB2*-related deafness do very well.[27]

Autosomal Dominant Nonsyndromic Hearing Impairment

To date, 54 loci for autosomal dominant nonsyndromic deafness have been mapped, and 21 causative genes have been cloned (Table 147-6).[11] Generally, the onset of deafness is postlingual, progressive, and milder than recessive forms, with several loci having characteristic audioprofiles.[28,29] Several common forms of dominant hearing impairment have unique or characteristic audioprofiles. One of the most common types of autosomal dominant nonsyndromic deafness is high-frequency hearing loss resulting from *KCNQ4* mutations at the DFNA2 locus.[30]

DFNA2 (High-Frequency Hearing Loss)

Autosomal dominant high-frequency hearing loss can be the consequence of mutations in numerous different genes (i.e., *KCNQ4* [DFNA2], *DFNA5* [DFNA5], *COCH* [DFNA9], *POU4F3* [DFNA15]). Mutations in some of these genes cause autosomal dominant deafness through a dominant-negative mechanism of action.[30-32] One example is deafness at the DFNA2 locus, which is caused by dominant-negative mutations in *KCNQ4*.[30,32] *KCNQ4* is organized into 14 exons that encode a protein with six transmembrane domains and a P-loop to confer K^+ ion selectivity to the channel pore.[32] A voltage sensor in the fourth transmembrane domain drives a conformational

Table 147-5

Autosomal Recessive Nonsyndromic Hearing Loss

Locus Name	Chromosomal Locus	Gene Symbol	Phenotype*
DFNB1	13q11q12 13q12	*GJB2* *GJB6*	Prelingual† hearing loss that remains stable[17,18]
DFNB2	11q13.5	*MYO7A*	Prelingual or postlingual hearing loss of unspecified type[164,165]
DFNB3	17p11.2	*MYO15*	Prelingual hearing loss that remains stable[166,167]
DFNB4	7q31	*SLC26A4*	Prelingual or postlingual hearing loss that may be stable or progressive. May also be associated with dilation of vestibular aqueduct[102,103]
DFNB5	14q12		Prelingual hearing loss that remains stable[168]
DFNB6	3p21	*TMIE*	Prelingual hearing loss that remains stable[169,170]
DFNB7/11	9q13-q21	*TMC1*	Prelingual hearing loss that remains stable[171,172]
DFNB8/10	21q22.3	*TMPRSS3*	Postlingual (DFNB8)‡ or prelingual (DFNB10) hearing loss that may be progressive or stable[173,174]
DFNB9	2p22-p23	*OTOF*	Prelingual hearing loss that remains stable[175,176]
DFNB12	10q21-q22	*CDH23*	Prelingual hearing loss that remains stable[177,178]
DFNB16	15q15	*STRC*	Prelingual hearing loss that remains stable and is more pronounced in higher frequencies[179]
DFNB18	11p15.1	*USH1C*	Prelingual hearing loss that remains stable[180,181]
DFNB21	11q22-q24	*TECTA*	Prelingual severe to profound isolated SNHL[41]
DFNB22	16p12.2	*OTOA*	Prelingual moderate to severe SNHL[182]
DFNB23	10q21.1	*PCDH15*	Prelingual severe to profound SNHL[183]
DFNB28	22q13.1	*TRIOBP*	Prelingual severe to profound SNHL[184,185]
DFNB29	21q22.3	*CLDN14*	Prelingual profound SNHL[186]
DFNB30	10p11.1	*MYO3A*	Progressive hearing loss that first affects high frequencies and begins in the 2nd decade; is severe in high and middle frequencies and moderate at low frequencies by age 50[187]
DFNB31	9q32-q34	*DFN31*	Prelingual profound SNHL[188,189]
DFNB36	1p36.31	*ESPN*	Prelingual hearing loss of unspecified or unknown type[190]
DFNB37	6q13	*MYO6*	Prelingual hearing loss of unspecified or unknown type[191]
DFNB67	6p21.1-p22.3	*TMHS*	Prelingual profound SNHL[192-194]

*Most important references are cited.
†Prelingual deafness also includes congenital deafness.
‡The onset of DFNB8 hearing loss is postlingual (10-12 years old), whereas the onset of DFNB10 hearing loss is prelingual (congenital). This phenotypic difference reflects a genotypic difference—the DFNB8-causing mutation is a splice site mutation, suggesting that inefficient splicing is associated with a reduced amount of normal protein, which is sufficient to prevent prelingual deafness, but insufficient to prevent eventual hearing loss.
SNHL, sensorineural hearing loss.
Adapted from Van Camp G, Smith RJ. Hereditary Hearing Loss Homepage. Available at http://webh01.ua.ac.be/hhh/. 2009.

change that leads to channel opening. *KCNQ4* subunits are typically organized into homotetramers to form functional channels.[32]

The G285S allele was the first DFNA2 mutation identified, and a knockout mouse model of this variant has been generated.[33] The substitution of a serine for a glycine affects the first highly conserved glycine in a GYG signature sequence of the P-loop of the channel pore, and abolishes channel function by preventing correct subunit assembly. Impaired *KCNQ4* function in the inner ear affects K^+ ion recycling. Normally, mechanosensory transduction leads to an increase in cytosolic K^+ in the outer hair cells of the cochlea, the major site of *KCNQ4* expression. *KCNQ4* channels expressed in the base of these cells transport K^+ extracellularly, where the ion is taken up by supporting cells and cycled back into the scala media.[30] The consequence of abnormal *KCNQ4* function is apoptosis of the outer hair cells. The clinical

Table 147-6

Autosomal Dominant Nonsyndromic Hearing Loss

Locus Name	Chromosomal Locus	Gene Symbol	Phenotype*
DFNA1	5q31	*DIAPH1*	Postlingual low-frequency hearing loss (1st decade)[195,196]
DFNA2	1p35.1 1p34	*GJB3* *KCNQ4*	Postlingual high-frequency hearing loss (2nd decade)[30,32,197]
DFNA3†	13q11-q12 13q12	*GJB2* *GJB6*	Prelingual high-frequency hearing loss[31,198,199]
DFNA4	19q13	*MYH14*	Postlingual hearing loss with flat/gently downsloping audioprofile[200]
DFNA5	7p15	*DFNA5*	Postlingual high-frequency hearing loss (1st decade)[201,202]
DFNA6/14/38‡	4p16.1	*WFS1*	Prelingual low-frequency hearing loss[45,203,204]
DFNA8/12†	11q22-q24	*TECTA*	Prelingual midfrequency hearing loss[36]
DFNA9	14q12-q13	*COCH*	Postlingual high-frequency hearing loss (2nd decade)[205,206]
DFNA10	6q23	*EYA4*	Postlingual hearing loss with flat/gently downsloping audioprofile (3rd/4th decade)[207,208]
DFNA11	11q13.5	*MYO7A*	Postlingual hearing loss (1st decade)[165,209]
DFNA13	6p21.3	*COL11A2*	Postlingual midfrequency hearing loss (2nd decade)[42,43]
DFNA15 DFNA17 DFNA20/26 DFNA22	5q31 22q11.2 17q25 6q13	*POU4F3* *MYH9* *ACTG1* *MYO6*	Postlingual high-frequency hearing loss[210-214]
DFNA28 DFNA36	8q22 9q13-q21	*TFCP2L3* *TMC1*	Postlingual hearing loss with flat/gently downsloping audioprofile[171,215]
DFNA39	4q21.3	*DSPP*	Postlingual high-frequency hearing loss[216]
DFNA48	12q13-q14	*MYO1A*	Postlingual hearing loss[217,218]

*Most important references are cited.
†Most autosomal dominant loci cause postlingual hearing impairment. Some exceptions are DFNA3, DFNA8, and DFNA12.
‡DFNA6/14 is noteworthy because the hearing loss primarily affects the low frequencies.
Adapted from Van Camp G, Smith RJ. Hereditary Hearing Loss Homepage. Available at http://webh01.ua.ac.be/hhh/. 2008.

manifestation of this damage is hearing loss that is progressive and biased to the high frequencies.[30]

DFNA8/12 and DFNA13 (Midfrequency Hearing Loss)

Identification of phenotype-genotype correlations is crucial in determining the etiology of autosomal dominant sensorineural hearing loss (ADSNHL),[34] and has implications for prognostic and therapeutic outcomes. Some correlations are very robust, such as the low-frequency audioprofile associated with *WFS1*-related hearing loss (DFNA6/14/38)[35] and the "cookie-bite" (midfrequency) audioprofile associated with *TECTA*-related hearing loss (DFNA8/12),[36] whereas other correlations, such as high-frequency hearing loss, are more difficult to define. Hearing loss at the DFNA8/12 locus is unusual among dominant forms because midfrequencies are predominantly affected, it is congenital, and it is nonprogressive.[37] The causative gene at this locus, α-tectorin (*TECTA*), was identified in Austrian DFNA8[37] and Belgian DFNA12[36,38] families. In both families, missense mutations were identified that are thought to have a dominant-negative effect leading to disruption of the structure of the tectorial membrane.[36]

α-Tectorin is the major noncollagenous component of the tectorial membrane of the inner ear. A mouse mutant generated with a *TECTA* missense mutation showed elevated neural thresholds, broadened neural tuning, and decreased sensitivity of the tip of the neural tuning curve, indicating that the tectorial membrane enables the motion of the basilar membrane optimally to drive the inner hair cells at their best frequency.[39] *TECTA* has also been implicated in recessive deafness at the DFNB21 locus.[40,41] Hearing loss in these families was also congenital, but severe to profound across all frequencies rather than restricted to the midfrequencies.

DFNA13 is a related form of dominant hearing impairment that is also characterized by initial midfrequency loss and disruption of the tectorial membrane. In this case, missense mutations were identified in the *COL11A2* gene of American and Dutch DFNA13 families, and were predicted to affect the triple helical domain of the collagen protein.[42,43] A Col11a2$^{-/-}$ mouse model displayed moderate to severe hearing loss and an enlarged tectorial membrane attributable to disorganized and widely spaced collagen fibrils.[43] Defects in genes encoding components of the collagenous and noncollagenous regions of the tectorial membrane can induce autosomal dominant midfrequency hearing impairment.

DFNA6/14/38 (Low-Frequency Hearing Loss)

Mutations in the Wolfram syndrome 1 gene (*WFS1*) at the DFNA6/14/38 locus are a common cause of low-frequency sensorineural hearing loss. *WFS1* was originally identified in human disease as a cause of Wolfram syndrome, an autosomal recessive neu-

Table 147-7

X-Linked Nonsyndromic Hearing Loss

Locus Name	Chromosomal Locus	Gene Symbol	Phenotype*
DFN2	Xq22	—	Prelingual profound SNHL in all frequencies[219]
DFN3	Xq21.1	*POU3F4*	Mixed variable prelingual hearing loss that progresses to profound in all frequencies[50]
DFN4	Xp21	—	Stable prelingual profound SNHL in all frequencies[54]
DFN5	Withdrawn	—	—
DFN6	Xp22	—	Progressive severe to profound postlingual (1st decade) SNHL that begins with high-frequency hearing loss that evolves to include all frequencies by adulthood[53]
DFN7	Withdrawn	—	—
DFN8	Reserved	—	—

*Most important references are cited.
SNHL, sensorineural hearing loss.
Adapted from Van Camp G, Smith RJ. Hereditary Hearing Loss Homepage. Available at http://webh01.ua.ac.be/hhh/. 2009.

rodegenerative disorder comprising diabetes mellitus, optic atrophy, and often deafness.[44] Later, *WFS1* was implicated in autosomal dominant, nonsyndromic hearing loss at the DFNA6/14 locus in six families segregating delayed-onset, slowly progressive, low-frequency SNHL.[45] These families all carried missense mutations located in a region of exon 8 that encodes the C-terminal domain.[45] Although the protein is known to contain nine putative transmembrane domains, its function and role in causing low-frequency SNHL remain unclear. One of the original *WFS1* mutations, V779M, was identified in 1 of 336 control individuals.[45] This frequency is comparable to that of heterozygous carriers of Wolfram syndrome, which has been estimated to be 0.3% to 1%.[46] Because an increased risk of SNHL had been reported for these carriers,[46] it was predicted that *WFS1* was a common cause of low-frequency SNHL. This assumption has been supported by the subsequent discovery of *WFS1* mutations at high frequency in families with low-frequency SNHL from different populations.[47,48]

X-Linked Nonsyndromic Hearing Impairment

X-linked nonsyndromic hearing impairment accounts for less than 2% of nonsyndromic hearing loss.[1] Five loci and one causative gene have been identified (Table 147-7). Re-examination of the original family used to map DFN1 has revealed other cosegregating features, including mental retardation. This type of deafness is now recognized as a form of X-linked syndromic hearing loss.[49] Of the remaining DFN loci, DFN3 is most common. It is due to mutations in a transcription factor called POU3F4,[50] and manifests as congenital stapes fixation with radiologic findings that include widening of the lateral internal auditory canal and dilation of the vestibule.[51] Hearing loss is usually mixed, and stapedectomy is typically attended by a perilymph gusher.[52] The hearing impairment associated with the other loci is variable.[53,54]

Mitochondrial Nonsyndromic Hearing Impairment

Mitochondrial nonsyndromic deafness can be caused by various mtDNA mutations, although the 1555 A-to-G mtDNA has been characterized best (Table 147-8). As mentioned earlier, this mutation is also associated with aminoglycoside ototoxicity. As a cause of nonsyndromic deafness, the phenotype is similar to aminoglycoside ototoxicity with a mild, high-frequency loss that shows progression.[55] The loss is generally of later onset in individuals who have not been exposed to aminoglycosides.[2]

Presbycusis, or age-related hearing loss, also may have a mitochondrial basis.[56-59] Because mtDNA mutations accumulate at several times the rate of nuclear DNA mutations, mitochondrial function ultimately may be impaired, resulting in age-related cochlear dysfunction.[57] In support of this hypothesis, an increase in the mtDNA mutation load has been shown in aged cochlea.[59]

Table 147-8

Mitochondrial Nonsyndromic Hearing Loss

Gene Symbol	Mutation	Phenotype*
MTRNR1	961 different mutations c.1494 C>T c.1555 A>G	Commonly secondary to aminoglycoside use with variable severity and highly variable penetrance[138,220]
MTTS1	c.7445 A>G c.7472 ins C c.7510 T>C c.7511 T	Variably severe hearing loss with highly variable penetrance[221-224]

*Most important references are cited.

Syndromic Hearing Impairment

Syndromic forms of hereditary SNHL are less common than nonsyndromic forms (Table 147-9). Syndromic hearing impairment refers to deafness that cosegregates with other features, forming a recognizable constellation of findings known as a syndrome. Sensorineural deafness has been associated with more than 400 syndromes. A discussion of a few of the more common syndromes follows.

Autosomal Dominant Syndromic Hearing Impairment

Branchio-oto-renal Syndrome

Melnick coined the term *branchio-oto-renal (BOR) syndrome* in 1975 to describe the cosegregation of branchial, otic, and renal anomalies in

Table 147-9

Syndromic Forms of Hearing Loss

Syndrome	Chromosomal Locus	Gene*
Autosomal Dominant		
Branchio-oto-renal		
BOR1	8q13.3	*EYA1*[65]
BOR2	1q31	Unknown[225]
BOR3	14q	*SIX1*[66]
	19q13.3	*SIX5*[67]
Waardenburg's		
WS1	2q35	*PAX3*[85]
WS2†	3p14.1-p12.3	*MITF*[86]
		SNAI2[87]
WS3 (Klein-Waardenburg)	2q35	*PAX3*[88]
WS4†	13q22	*EDNRB*[89]
Shah-Waardenburg or Waardenburg-Hirschsprung	20q13.2-q13.3	*EDN3*[90]
	22q13	*SOX10*[91]
Stickler		
STL1	12q13.11-13.2	*COL2A1*[76]
STL2	6p1.3	*COL11A1*[77]
STL3	1p21	*COL11A2*[79]
STL4	6q13	*COL9A1*[78]
Neurofibromatosis		
NF2	22q12	*NF2*[226]
Treacher Collins		
TCOF1	5q32-q33.1	*TCOF1*[227]
Autosomal Recessive		
Pendred		
PDS	7q21-34	*SLC26A4/PDS*[96]
Foxi1	5q34	*Foxi1*[104]
Usher		
USH1A	14q32	Unknown[228,229]
USHIB	11q13.5	Unknown[115]
USH1C	11p15.1	*MYO7A*[230]
		USH1C[231-233]
USH1D	10q22.1	*CDH23*[177]
USH1E	21q21	Unknown[234,235]
USH1F	10Q21-22	*PCDH15*[183]
USH1G	17Q24-25	*SANS*[236-239]
USH2A	1q41	*USH2A*[116]
USH2B	3p23-24.2	Unknown[240,241]
USH2C	5q14.3-q21.3	*VLGR1*[242]
USH3	3q21-q25	*USH3A*[243,244]
Jervell and Lange-Nielsen		
JLNS1	11p15.5	*KCNQ1*[106,107]
JLNS2	21q22.1-q22.2	*KCNE1*[108]
Biotinidase deficiency	3p25	*BTD*[245]
Refsum disease	10pter-p11.2	*PAHX*[246]
	6q22-q24	*PEX7*[119]
Alport syndrome	2q36-2q37	*COL4A3*[247]
	2q36-2q37	*COL4A4*[247]
X-Linked		
Alport syndrome	Xq22	*COL4A5*[123]
Mohr-Tranebjaerg syndrome	Xq22	*TIMM8A*[248]
Norrie's disease	Xp11.3	*NDP*[249]
Mitochondrial		
MELAS	mtDNA	tRNA(Leu)(UUR)[133]
NIDDM	mtDNA	tRNA(Leu)(UUR)/deletions[250]
MERRF	mtDNA	Large deletions[251]

*Most important references are cited.
†Although Waardenburg's syndrome (WS) is usually inherited in an autosomal dominant manner, sometimes WS2 can be inherited in an autosomal recessive manner. WS4 is always inherited in an autosomal recessive manner.

deaf individuals.[60] Inheritance is autosomal dominant, penetrance is nearly 100%, and prevalence is estimated at 1 in 40,000 newborns.[61] BOR affects 2% of profoundly deaf children.[61] Otologic findings can involve the external, middle, or inner ear. External ear anomalies include preauricular pits (82%), preauricular tags, auricular malformations (32%), microtia, and external auditory canal narrowing[62,63]; middle ear anomalies include ossicular malformation (fusion, displacement, underdevelopment), facial nerve dehiscence, absence of the oval window, and reduction in size of the middle ear cleft[62]; and inner ear anomalies include cochlear hypoplasia and dysplasia.[64] Enlargement of the cochlear or vestibular aqueducts may be seen,[63] or merely hypoplasia of the lateral semicircular canal.[64]

Hearing impairment is the most common feature of BOR syndrome and is reported in almost 90% of affected individuals.[61] The loss can be conductive (30%) or sensorineural (20%), but is most often mixed (50%). It is severe in one third of individuals and is progressive in one quarter.[61] Branchial anomalies occur in the form of laterocervical fistulas, sinuses, and cysts, and renal anomalies ranging from agenesis to dysplasia are found in 25% of individuals.[61] Less common phenotypic findings include lacrimal duct aplasia, short palate, and retrognathia.[61]

One causative gene is *EYA1,* the human homologue of the *Drosophila* eyes absent gene.[65] The gene contains 16 exons encoding for 559 amino acids.[65] *EYA1* mutations are found in approximately 25% of patients with a BOR phenotype, and this phenotype is hypothesized to reflect a reduction in the amount of the EYA1 protein. Mutations in two additional genes, *SIX1* and *SIX5,* also have been shown more recently to cause BOR syndrome.[66,67] Both genes act within the genetic network of the *EYA* and *PAX* genes to regulate organogenesis.

Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2) is characterized by the development of bilateral vestibular schwannomas and other intracranial and spinal tumors (schwannomas, meningiomas, gliomas, and ependymomas). In addition, patients may have posterior subcapsular lenticular opacities. Diagnostic criteria include (1) bilateral vestibular schwannomas that usually develop by the second decade of life, or (2) a family history of NF2 in a first-degree relative, plus one of the following: unilateral vestibular schwannomas at less than 30 years of age, or any two of meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract. The causative gene is a 17 exon gene that codes for a 595-amino acid protein named merlin on chromosome 22q12.[68] Merlin is a tumor suppressor that regulates the actin cytoskeleton.[69,70] Although its mechanism of action is not completely understood, microarray analysis has identified numerous other genes that become deregulated during tumorigenesis.[71]

The incidence of NF2 is 1:40,000 to 1:90,000.[70] Hearing loss is usually high frequency and sensorineural; vertigo, tinnitus, and facial nerve paralysis may be associated findings. The diagnosis rests on the clinical and family history, physical examination, and imaging studies (magnetic resonance imaging [MRI]). Treatment of the vestibular schwannomas usually consists of surgery, although Gamma knife surgery is considered in selected cases.[72] Auditory brainstem implants have been used with success in patients with vestibular schwannomas, although their use is limited if there is a history of Gamma knife treatment.[72,73]

Stickler Syndrome

In 1965, Stickler described a family followed at the Mayo Clinic for five generations that segregated syndromic features, including myopia, clefting, and hearing loss.[74] The disease, now known eponymously as Stickler syndrome (SS), has a prevalence of 1:10,000,[75] and is caused by mutations in *COL2A1, COL11A2,* or *CO11A1* genes that encode for the constituent proteins of type II and type XI collagen.[76-79] On the basis of criteria set forth by Snead and Yates,[80] the diagnosis of SS requires (1) congenital vitreous anomaly, and (2) any three of myopia with onset before age 6 years, rhegmatogenous retinal detachment or paravascular pigmented lattice degeneration, joint hypermobility with abnormal Beighton score, SNHL (audiometric confirmation), or midline clefting. Other manifestations include craniofacial anomalies such as midfacial flattening, mandibular hypoplasia, short upturned nose, or a long philtrum. Micrognathia is common, and if severe leads to the Robin sequence with cleft palate (28% to 65%).[81] Clefting may be complete, with a U-shaped cleft palate secondary to Robin sequence, but is more commonly limited to a submucous cleft.[82]

SS type 1 is caused by mutations in *COL2A1*.[76] The phenotype includes the classic ocular findings with a "membranous" vitreous. SS type 2 is due to missense or in-frame deletion mutations in *COL11A2,*[79] and is unique in that there are no ocular abnormalities because *COL11A2* is not expressed in the vitreous. SS type 3 is caused by mutations in *COL11A1*.[77] The vitreous in these patients shows irregularly thickened fiber bundles that may be visualized on slit-lamp examination.[77,80]

The hearing loss associated with SS can be conductive, sensorineural, or mixed. If it is conductive, the loss typically reflects the eustachian tube dysfunction that commonly occurs with palatal clefts. SNHL is more common in the older age groups. Its pathogenesis is incompletely understood, but possible mechanisms include primary neurosensory deficits because of alterations in the pigmented epithelium of the inner ear or abnormalities of inner ear collagen.[81] Computed tomography (CT) has not shown gross structural abnormalities. Patients with SS type 3 tend to have moderate to severe hearing loss, patients with SS type 1 have either normal hearing or only a mild impairment, and patients with SS type 2 fall in between.[75]

The ocular findings in SS are the most prevalent feature and warrant special discussion.[82] Most affected individuals are myopic,[80] but also may have vitreoretinal degeneration, retinal detachment, cataract, and blindness.[74] Retinal detachment leading to blindness is the most severe ocular complication and affects approximately 50% of individuals with SS.[81] Detachment typically occurs in adolescence or early adulthood.

Waardenburg Syndrome

Waardenburg published an article defining a auditory-pigmentary disease in 1951.[83] The association, now known as Waardenburg syndrome (WS), is classified under four types and has an aggregate prevalence of 1:10,000 to 1:20,000.[84] WS type 1 is recognized by SNHL, white forelock, pigmentary disturbances of the iris, and dystopia canthorum, a specific displacement of the inner canthi and lacrimal puncti.[83] Other features include synophrys, broad nasal root, hypoplasia of the alae nasi, patent metopic suture, and a square jaw. WS type 1 is caused by mutations in *PAX3,* a DNA-binding transcription factor homologous to mouse Pax-3, the gene implicated in the Splotch mouse mutant.[85] *PAX3* is expressed in neural crest cells in early development, and strial melanocytes are absent in affected individuals.[85]

WS type 2 is distinguished from WS type 1 by the absence of dystopia canthorum. Approximately 15% of WS type 2 cases are caused by mutations in *MITF,* a transcription factor also involved in melanocyte development.[86] Mutations in *SNAI2,* a zinc-finger transcription factor expressed in migratory neural crest cells, have also been shown to cause WS type 2.[87] WS type 3 is called Klein-Waardenburg syndrome, and is characterized by WS type 1 features with the addition of hypoplasia or contracture of the upper limbs. *PAX3* is the causative gene.[88] WS type 4 is also known as Waardenburg-Shah syndrome, and involves the association of WS with Hirschsprung disease. Three genes have been implicated: endothelin 3 (*EDN3*), endothelin receptor B gene (*EDNRB*), and *SOX10*.[89-91] Although WS types 1 to 3 are inherited as dominant diseases, WS type 4 is autosomal recessive (see Table 147-9).

The hearing loss in WS shows considerable variability between and within families. Congenital hearing impairment is present in 36% to 66.7% of cases of WS type 1 versus 57% to 85% of cases of WS type 2.[84] Most commonly, the loss affects individuals with more than one pigmentation abnormality and is profound, bilateral, and stable over time. Audiogram configuration varies, with low-frequency loss being more common. Nadol and Merchant[92] examined the inner ear of a 76-year-old woman with WS type 1 and found intact neurosensory structures only in the basal turn of the cochlea. Temporal bone imaging is typically normal, although malformation of the semicircular canals and cochlear hypoplasia can be found.[93] Risk chance prediction of the

findings associated with WS is difficult because of variability in disease expression.

Treacher-Collins Syndrome

Treacher-Collins syndrome is an autosomal dominant syndrome characterized by abnormalities of craniofacial development. The phenotype includes maldevelopment of the maxilla and mandible, with abnormal canthi placement, ocular colobomas, choanal atresia, and conductive hearing loss secondary to ossicular fixation.[94] The causative gene is *TCOF,* which encodes for the protein treacle.[94]

Autosomal Recessive Syndromic Hearing Impairment

Pendred Syndrome

The most common syndromic form of hereditary SNHL, Pendred syndrome (PS) was described by Pendred in 1896.[95] The condition is autosomal recessive, and affected individuals also have goiter.[96] The prevalence of PS is estimated at 7.5 to 10 per 100,000 individuals, suggesting that the syndrome may account for 10% of hereditary deafness.[96] The hearing loss is usually congenital and severe to profound, although progressive mild to moderate SNHL is sometimes seen.[96] Bilateral dilation of the vestibular aqueduct is common, and may be accompanied by cochlear hypoplasia. Most cases of PS result from mutations in the *SLC26A4* gene that encodes an anion transporter known as pendrin that is expressed in the inner ear, thyroid, and kidney.[97] Expression of *SLC26A4* has been shown throughout the endolymphatic duct and sac, in distinct areas of the utricle and saccule, and in the external sulcus region within the developing cochlea.[98] Pendrin is thought to be involved in chloride and iodide transport and not sulfate transport.[99]

Affected individuals have thyroid goiter develop in their second decade, although they usually remain euthyroid.[97] Thyroid dysfunction can be shown with a perchlorate discharge test, in which radioactive iodide and perchlorate are administered. Mutations in *SLC26A4* prevent rapid movement of iodide from the thyrocyte to the colloid, and perchlorate blocks the Na/I symporter that moves iodide from the bloodstream into the thyrocyte. The net effect is that iodide in the thyrocyte washes back into the bloodstream in affected individuals, with a release of greater than 10% radioactivity considered diagnostic for PS.[95,100] The sensitivity of this test is low, making genetic testing the preferred diagnostic method.[95] The hearing impairment is usually prelingual, bilateral, and profound, although it can be progressive.[95] Radiologic studies always show a temporal bone anomaly, either dilated vestibular aqueducts or Mondini dysplasia.[95,101]

Mutations in *SLC26A4* also cause a type of nonsyndromic autosomal recessive deafness called DFNB4.[102,103] Whether the phenotype is syndromic or nonsyndromic may reflect the degree of residual function in the abnormal protein. PS and DFNB4 can be diagnosed by screening this gene for mutations. More recently, mutations in the transcription factor *FOXI1* have also been shown to cause PS in patients heterozygous for a mutation in *SLC26A4*.[104]

Jervell and Lange-Nielsen Syndrome

In 1957, Jervell and Lange-Nielsen described a syndrome characterized by congenital deafness, prolonged Q-T interval, and syncopal attacks.[105] Long Q-T syndrome itself can be dominantly or recessively inherited. The dominant disease is called Romano-Ward syndrome. It is more common and does not include the deafness phenotype.[105] The recessive disease is known as Jervell and Lange-Nielsen syndrome (JLNS).

JLNS is genetically heterogeneous with mutations in *KVLQT1* and *KCNE1* causing this phenotype.[106-108] These genes encode for subunits of a potassium channel expressed in the heart and inner ear. Hearing impairment is due to changes in endolymph homeostasis caused by malfunction of this channel and is congenital, bilateral, and severe to profound.[106-108] Although the prevalence of JLNS among children with congenital deafness is only 0.21%,[109] it is an important diagnosis to consider because of its cardiac manifestations. The prolonged Q-T interval can lead to ventricular arrhythmias, syncopal episodes, and death in childhood.[109] Effective treatment with β-adrenergic blockers reduces mortality from 71% to 6%.[109]

Usher Syndromes

The Usher syndromes (US) are a genetically and clinically heterogeneous group of diseases characterized by SNHL, retinitis pigmentosa, and often vestibular dysfunction.[110] Prevalence is estimated at 4.4 : 100,000 in the United States with 3% to 6% of congenitally deaf individuals carrying this diagnosis.[111] It is the cause of 50% of deaf-blindness in the United States.[111]

Three clinical variants of US are recognized. Type 1 is phenotypically distinguished by the presence of severe to profound congenital hearing loss, vestibular dysfunction, and retinitis pigmentosa that develops in childhood[112]; type 2 is distinguished by moderate to severe congenital hearing loss, with uncertainty related to progression, no vestibular dysfunction, and retinal degeneration that begins in the third to fourth decade[112,113]; and type 3 is characterized by progressive hearing loss, variable vestibular dysfunction, and variable onset of retinitis pigmentosa.[112] Within each subtype, there is genetic heterogeneity, and numerous subtypes are recognized, although the two most common forms are US type 1B (USH1B) and US type 2A (USH2A), which account for 75% to 80% of the Usher syndromes.[114] USH1B accounts for 75% of US type 1 and is caused by mutations in an unconventional myosin called *MYO7A*.[115] USH2A is the most common form, and the causative gene encodes a 1551-amino acid protein named usherin that is a putative extracellular matrix molecule.[116] Numerous other genes have been implicated in US subtypes, and these are listed in Table 147-9.

Biotinidase Deficiency

Biotinidase deficiency is secondary to an absence in the water-soluble B-complex vitamin biotin. Biotin covalently binds to four carboxylases that are essential for gluconeogenesis, fatty acid synthesis, and catabolism of several branched-chain amino acids. If biotinidase deficiency is not recognized and corrected by daily addition of biotin to the diet, affected individuals develop neurologic features such as seizures, hypertonia, developmental delay, ataxia, and visual problems. In at least 75% of children who become symptomatic, SNHL develops, and can be profound and persistent even after treatment is initiated.[117] Cutaneous features are also present and include a skin rash, alopecia, and conjunctivitis. With treatment that consists of biotin replacement, the neurologic and cutaneous manifestations resolve; however, the hearing loss and optic atrophy are usually irreversible. If a child presents with episodic or progressive ataxia and progressive sensorineural deafness, with or without neurologic or cutaneous symptoms, biotinidase deficiency should be considered. To prevent metabolic coma, diet and treatment should be initiated as soon as possible.[117,118] If untreated, 75% of affected infants develop hearing loss, which can be profound, and persists despite the subsequent initiation of treatment.[117]

Refsum Disease

Refsum disease is a postlingual severe progressive SNHL associated with retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid without an increase in the number of cells.[119] It is caused by defective phytanic acid metabolism, and the diagnosis is established by determining serum concentration of phytanic acid. Two genes, *PHYH* and *PEX7,* have been implicated in most cases of Refsum disease, although a few patients exist in whom mutations have not been found.[119] Although extremely rare, it is important that Refsum disease be considered in the evaluation of a deaf person because it can be easily treated with dietary modification and plasmapheresis.

X-Linked Syndromes

Alport Syndrome

Alport syndrome (AS) is a disease of type IV collagen that is manifested by hematuric nephritis, hearing impairment, and ocular changes. The inheritance pattern, although predominantly X-linked (approximately 80%), can be autosomal recessive or dominant.[120] Prevalence is estimated at 1 : 5000 in the United States; a significant proportion of renal transplant patients have AS.[121] Diagnostic criteria include at least three of the following four characteristics[122]: (1) positive family history of

hematuria with or without chronic renal failure, (2) progressive high-tone sensorineural deafness, (3) typical eye lesion (anterior lenticonus or macular flecks or both), and (4) histologic changes of the glomerular basement membrane of the kidney.

Mutations in *COL4A5* are the cause of X-linked AS.[123] Type IV collagen is the major component of basement membranes and is formed by the trimerization of various combinations of six type IV collagen genes. Deficiency of this protein results in complete or partial deficiency of the trimerized 3-4-5 complex in the basement membranes of the kidney, cochlea, and eye.[123] More than 300 disease-causing mutations of 5 have been identified with 9.5% to 18% arising de novo.[121,124]

The disease phenotype is more pronounced in males, as expected for X-linked diseases. Gross or microscopic hematuria is the hallmark of disease, and all males ultimately have end-stage renal disease, although the rate of progression depends on the underlying mutation.[125] Ocular manifestations are present in one third of patients and are characterized by anterior lenticonus, an anomaly in which the central portion of the lens protrudes into the anterior chamber of the eye, causing myopia.[125] End-stage renal disease develops before age 30 in patients with anterior lenticonus.[121] Maculopathy and corneal lesions may also be found in patients with AS. Diffuse esophageal leiomyomatosis has been associated with deletion mutations of *COL4A5* and *COL4A6*.[122,125]

Hearing impairment is common in AS and is usually a symmetric, high-frequency sensorineural loss that can be detected by late childhood and progresses to involve all frequencies.[125] Pathogenesis is thought to be related to the loss of the 3-4-5 network, which is important for radial tension on the basilar membrane. Diagnosis currently relies on clinical and histopathologic confirmation, although genetic confirmation can allow the stratification and prediction of severity of the disease phenotype.

Mohr-Tranebjaerg Syndrome

Mohr-Tranebjaerg syndrome was first described in a large Norwegian family with apparent progressive postlingual nonsyndromic hearing impairment and classified as DFN1.[126] Re-evaluation of this family revealed additional findings, however, including visual disability, dystonia, fractures, and mental retardation, indicating that this form of hearing impairment is syndromic, rather than nonsyndromic.[49] The gene for this syndrome, *TIMM8A,* is involved in the translocation of proteins from the cytosol across the inner mitochondrial membrane (TIM) system and into the mitochondrial matrix.[127,128]

Mitochondrial Syndromes

Mitochondrial diseases typically cause a phenotype in tissues with high energy demands, such as muscle, retina, brainstem, pancreas, and cochlea.[55,57] The process by which mitochondrial diseases lead to SNHL is debated and is confounded by the demonstration that nuclear modifier genes have an impact on the outcome.[129] Syndromic mitochondrial diseases are usually multisystemic, with hearing loss present in 70% of affected individuals.[57] Examples include MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes) syndrome, MERRF (myoclonic epilepsy and red ragged fibers) syndrome, and Kearns-Sayre syndrome (KS) (see Table 147-9).

In MELAS syndrome, hearing loss is sensorineural, progressive, and bilateral, and more severely affects the higher frequencies[130-132]; temporal bone histopathologic findings show severe atrophy of the stria vascularis.[92] MERRF syndrome is characterized by hearing loss, ataxia, dementia, optic nerve atrophy, and short stature. In contrast to MELAS and MERRF, which are caused by point mutations in mtDNA, KS is caused by large duplications and deletions.[133] First described in 1958, KS involves progressive external ophthalmoplegia, atypical retinal pigmentation, and heart block typically starting before age 20.[134,135] SNHL is present in 50% of patients with KS,[57,131] and temporal bone histopathologic findings show cochleosaccular degeneration.[132]

Maternally inherited diabetes and deafness is another syndromic mitochondrial disease. It affects an estimated 0.5% to 2.8% of diabetic patients.[136] The hearing loss occurs late, and is progressive, bilateral, and high frequency; its presence is correlated with the level of heteroplasmy for the 3243 A-to-G mtDNA mutation.[57,130]

Susceptibility to aminoglycoside ototoxicity is also maternally inherited. It is caused by the 1555 A-to-G mtDNA mutation, a nucleotide change found in 17% to 33% of individuals with aminoglycoside-induced hearing loss.[137,138] This mutation changes the 12S rRNA gene, altering its structure to make it more similar to bacterial rRNA, the natural target of aminoglycosides.[137,138] Hearing loss develops even when aminoglycosides are administered at normal doses, with residual thresholds varying widely among individuals. Hearing losses can be seen months after aminoglycoside exposure. Outer hair cells in the basal turn of the cochlea are affected first, but damage eventually extends to include apical outer hair cells and inner hair cells.[139] The same mutation causes nonsyndromic mitochondrial hearing loss.[2]

PATIENT MANAGEMENT

Diagnosis

The evaluation of a deaf patient should involve a team of health care professionals that includes an audiologist, clinical geneticist, ophthalmologist, and otolaryngologist, with the otolaryngologist most frequently coordinating overall care. A well-performed history, physical examination, and audiologic evaluation are keys to assessing the cause of hearing loss.[140]

The American College of Medical Genetics more recently released genetic evaluation guidelines for the diagnosis of congenital hearing loss.[141] Specific details of the family history that should be covered include a pedigree with attention to consanguinity and hearing status of first-degree relatives. Ethnicity, inheritance patterns, audiometric characteristics, and an inquiry of syndromic versus nonsyndromic features are necessary.[141] To assess for the presence of a syndrome related to hearing loss, questions and physical examination regarding endocrine abnormalities (diabetes, thyroid nodules), pigmentary anomalies (white forelock, heterochromic irides), visual anomalies (retinitis pigmentosa, retinal detachment), craniofacial anomalies (dystopia canthorum, aural atresia, cleft palate, branchial anomalies), cardiac manifestations (syncope, arrhythmias, sudden death), and renal anomalies should be performed.[141,142] The patient history and physical examination also should include a search for acquired causes of hearing loss, such as intrauterine infections, meningitis, hypoxia, and ototoxic drugs.

The audiologic evaluation is a crucial part of the initial diagnostic workup. In infants, behavioral testing is often impossible. Electrophysiologic tests such as ABR and otoacoustic emissions provide a means of objectively documenting hearing impairment, and can be used to provide information regarding auditory thresholds. Behavioral tests can be used when infants reach 6 months of age. A trained pediatric audiologist can measure hearing losses of 20 dB in the better hearing ear. The frequency of testing is usually decided on a case-by-case basis, although Tomaski and Grundfast[143] recommend a more rigid schedule in cases of confirmed SNHL in children. They recommend testing every 3 months in the first year of life, followed by every 6 months during the preschool years, and once a year while in school.

No cause of hearing loss may be apparent in 30% of cases even after a thorough history and physical examination.[141] To increase the yield further, additional investigations are necessary. In the past, a battery of tests including thyroid function studies, urinalysis, electrocardiogram, and temporal bone imaging was routinely ordered. Today, genetic screening should supplant these tests. Screening for *GJB2* mutations should be completed; if the diagnosis of DFNB1 is made, further testing is not required.[144] If CT shows dilated vestibular aqueducts or Mondini dysplasia, mutation screening of *SLC26A4* is warranted. Additional known deafness genes may be screened depending on the clinical presentation and the gene testing available at some institutions (see Table 147-4).

Acquired congenital deafness must also be considered. The most frequent cause is in utero cytomegalovirus infection, a diagnosis that can be made definitively only in the neonatal period before the possibility of postnatally acquired cytomegalovirus, which can confound the diagnosis of a congenital infection.[145] MRI has a place in the evaluation of hereditary hearing impairment if a patient is suspected to have NF2, if the hearing loss is progressive, and if the audiologic battery suggests retrocochlear pathology.[143] Other potential investigations include

thyroid function studies, electrocardiogram, urinalysis, renal ultrasonography, and electroretinography.

Genetic Testing

In the United States, congenital SNHL occurs about three times more frequently than Down syndrome, six times more frequently than spina bifida, and more than 50 times more frequently than phenylketonuria, making it the most frequently occurring birth defect.[146] An estimated 4000 infants are born each year with severe to profound bilateral hearing loss,[147,148] and another 8000 are born with unilateral or mild to moderate bilateral SNHL.[5] At least 50% of congenital hearing loss has an underlying genetic cause; this is a compelling reason to provide genetic testing services to all children diagnosed with congenital hearing loss. The implementation of the Early Hearing Detection and Intervention (EHDI) program in the United States and similar universal hearing screening programs around the world has facilitated increased detection, genetic diagnosis, and intervention for these children.[149] In addition, advances in genetic technologies have led to an increase in the availability of genetic diagnostic services for infants with hearing loss.[149]

Despite the fact that genetic SNHL is heterogeneous, mutations in the *GJB2* gene (DFNB1) have been shown to account for at least half of all severe to profound congenital nonsyndromic SNHL in the United States, many European countries, Israel, and Australia.[150-153] *GJB2*-related SNHL also has been repeatedly described in several Asian, Latin American, and African countries, but it is less common in these regions. Based on this frequency, first-pass screening of all individuals with congenital hearing loss for *GJB2* mutations is warranted.

For individuals not diagnosed with DFNB1, US should be the next consideration because it accounts for approximately 3% to 6% of all children who have severe to profound hearing loss and is second to *GJB2* mutations as a cause of deafness in the congenitally deaf cochlear implant population.[154] The three different types of US are caused by mutations in at least nine different genes.[155] Determining which genes to screen can be based on the onset and severity of the hearing loss and the presence or absence of vestibular dysfunction.

The third most common genetic cause of early childhood hearing loss is the PS-DFNB4 deafness spectrum. PS accounts for approximately 10% of all syndromic forms of hearing loss and is present in approximately 3% of individuals with hereditary hearing loss.[156] A diagnostic feature of PS is enlarged vestibular aqueducts with or without cochlear dysplasia (Mondini's dysplasia) that is detectable by CT scanning or MRI; the presence of thyroid goiter differentiates PS from DFNB4. Most cases of PS-DFNB4 are due to mutations in the *SLC26A4* gene, and individuals with diagnosed enlarged vestibular aqueducts should be screened for mutations in this gene. More recently, mutations in another gene, *Foxi1,* have also been found to cause PS-DFNB4, and this gene should also be considered in genetic analyses of these families.[104]

ADNSHL is a genetically heterogeneous disorder that is typically postlingual in onset and progressive. It accounts for approximately 15% of inherited hearing loss. To date, 21 genes for nonsyndromic ADNSHL have been identified, and a further 30 dominant loci have been mapped to chromosomal regions.[157] Individuals with apparent ADNSHL should be considered for genetic screening, with criteria for gene selection based on their audioprofile. Identification of phenotype-genotype correlations is crucial in determining the etiology of ADNSHL,[34] and has implications for prognostic and therapeutic outcomes. Some phenotype-genotype correlations are very robust, such as the low-frequency audioprofile associated with *WFS1*-related hearing loss (DFNA6/14/38)[35] and the "cookie-bite" audioprofile associated with *TECTA*-related hearing loss (DFNA8/12)[36]; other correlations are more difficult to define. Autosomal dominant high-frequency hearing loss can be the consequence of mutations in numerous different genes (e.g., *KCNQ4* [DFNA2], *DFNA5* [DFNA5], *COCH* [DFNA9], *POU4F3* [DFNA15]).

Current recommendations for genetic testing are to screen individuals with low-frequency ADNSHL for mutations in *WFS1* and individuals with midfrequency ADNSHL for mutations in *TECTA*. *WFS1* mutations account for approximately 75% of all cases of low-frequency ADNSHL.[45] For individuals with high-frequency hearing loss, because of the number of potential candidate genes, mutation screening is offered only on a research basis. Computer algorithms are being developed, however, to analyze audiograms and to construct audioprofiles as a method of selecting genes for mutation screening for all types of ADNSHL.

Prenatal Testing

Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells. Fetal material can be obtained by amniocentesis at 15 to 18 weeks' gestation or chorionic villus sampling at 10 to 12 weeks' gestation. Gestational age is expressed as menstrual weeks calculated from the first day of the last normal menstrual period or by ultrasound measurements. The deafness-causing allele of a deaf family member must be identified before prenatal testing can be performed.

Requests for prenatal testing for conditions such as hearing loss are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination, rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate. Preimplantation genetic diagnosis may be available for families in which the deafness-causing mutation has been identified in a deaf family member.

Treatment

When a diagnosis is made, directed treatment is possible. Appropriate consultation and management of the associated conditions should be considered. A diagnosis of JLNS may necessitate therapy with β-blockers to reduce the chance of life-threatening arrhythmias. If US is considered, close ophthalmologic follow-up is mandatory. In contrast, a genetic diagnosis of *GJB2*-related deafness requires no other consultation because there is no associated comorbidity.

Genetic counseling should be offered to patients and their families by a professional trained in clinical genetics. Most otolaryngologists do not have an adequate understanding of recurrence chances to provide accurate data.[158] Green and coworkers[23] have estimated the recurrence chance for a normal-hearing couple with a deaf child to have a second deaf child at 17.5%, much higher than earlier estimates of 9.8%. Factors that explain this increase include an improved ability to identify syndromic forms of deafness and a decrease in congenital acquired deafness.[23] A well-trained genetic counselor can also help to interpret medical data and potential treatment options. Counseling sessions should occur before and after genetic testing has been done.

Management of hearing loss should be directed at providing appropriate amplification as soon as possible. Hearing aids provide significant benefits to individuals with mild to moderate hearing loss. Cochlear implantation is becoming an increasingly important option for individuals with severe to profound deafness.[27] The Joint Committee on Infant Hearing recommends that diagnosis and rehabilitation be instituted by 6 months of age to minimize delays in communicative language development. Coupled with this recommendation, universal screening is becoming a reality throughout the United States. For the detection of congenital hearing loss, the U.S. government has facilitated the creation of EHDI programs for early newborn hearing screening (http://www.infanthearing.org). EHDI programs aim to screen neonates for hearing loss immediately after birth or before hospital discharge. The programs include a follow-up arm to confirm hearing loss in neonates who do not pass the initial screening test so that intervention can be initiated to prevent delayed language acquisition.[159]

EHDI program guidelines include three phases: screening, audiologic evaluation, and intervention. In the first phase, newborns are screened with otoacoustic emissions and ABR to detect permanent bilateral or unilateral sensory or conductive hearing loss averaging 30 to 40 dB SPL (sound pressure level) or more in the frequency region important for speech recognition. In the second phase, all infants who do not pass the initial screen are evaluated with a series of diagnostic audiologic tests, preferably before age 3 months. In the third phase,

early intervention services are implemented before age 6 months for all infants with confirmed hearing loss.[159]

Prevention of Hearing Impairment

Although experimental methodologies to restore auditory function are currently being developed and tested,[160,161] no effective therapy is clinically available. Existing measures must focus on the prevention of hearing loss to decrease the frequency of acquired and genetic hearing loss.[4] Improved implementation of vaccination programs in developing nations, avoidance of exacerbating factors such as noise, and focused genetic counseling and health education in populations with a high prevalence of consanguinity are several methods that if implemented would reduce the incidence of acquired and hereditary hearing loss.

Cultural Considerations

Having discussed the management of a patient with hearing loss, a mention of the Deaf (written with a capital "D") culture is necessary. Individuals who identify with the Deaf culture consider themselves as culturally Deaf and understandably wish to preserve their culture. Generally, members of the Deaf community look on genetics negatively.[162,163] A study by Middleton and colleagues[163] found that 55% of deaf respondents at a conference on the "Deaf Nation" thought genetics would do more harm than good. Of respondents, 46% thought that the use of genetics may devalue deaf people. This response may represent sample bias, however, because a study by Stern and associates[162] found that most deaf individuals have a positive view of the field of genetics. These studies highlight an important point—that attitudes about hearing loss, or more specifically deafness, are culturally dependent. The medical community must understand and appreciate this perspective, and try to offer advances in diagnosis, counseling, and treatment in a nonjudgmental manner.

Acknowledgment

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CHAPTER ONE HUNDRED AND FORTY-EIGHT

Otologic Manifestations of Systemic Disease

Saumil N. Merchant

Joseph B. Nadol, Jr.

Key Points

- A wide variety of systemic diseases can affect the temporal bone, including granulomatous and infectious diseases, neoplasms, disorders of bone, storage and metabolic diseases, and autoimmune and immunodeficiency disorders.
- Otologic manifestations of a particular systemic disease are determined by location and extent of involvement within the temporal bone, and the nature of the disease. Any part of the temporal bone may be affected, and the clinical features may include conductive or sensorineural hearing loss, vestibular manifestations, otalgia, and facial nerve paralysis.
- Systemic disease may mimic more common otologic disorders, such as acute or chronic otitis media, sudden idiopathic deafness, and Bell's palsy.
- Otologic manifestations may constitute a small part of a wider constellation of symptoms and signs, or may be the sole and initial presenting feature of a systemic disease.
- Diagnosis may be challenging, requiring a high level of suspicion, with use of ancillary tests such as laboratory studies, radiographic evaluation, and biopsy.
- Management of otologic symptoms must be individualized and often requires coordinated care across multiple disciplines.

Systemic diseases that may involve the ear include granulomatous and infectious processes, tumors, bone disorders, storage diseases, collagen vascular and autoimmune diseases, and immunodeficiency disorders (Table 148-1). In some of these diseases, the initial clinical symptoms may occur in the temporal bone and be confused with other diseases that are limited to the ear.

Granulomatous and Infectious Diseases

Chronic otitis media with otorrhea, inflammation, and granulation of the middle ear and mastoid is one of the most common entities treated by otolaryngologists. Several more generalized disease entities, such as the Langerhans cell histiocytosis (LCH), tuberculosis, Wegener's granulomatosis (WG), and mycotic diseases, may closely mimic the symptoms of chronic suppurative otitis media, whereas others, such as Lyme disease and sarcoidosis, may mimic idiopathic cranial neuropathy.

Langerhans Cell Histiocytosis

LCH (formerly called histiocytosis X) refers to a group of disorders that are characterized by a proliferation of cytologically benign histiocytes. The term *histiocytosis X* was proposed by Lichtenstein,[1] who considered eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease to be related disorders because of the similarity of their pathologic lesions. The severity of these diseases and prognosis and treatment differ greatly, however. Histopathologically, the primary lesion of LCH is formed by collections of pathologic Langerhans cells with variable numbers of eosinophils, macrophages, and lymphocytes. Diagnostic characteristics of the pathologic Langerhans cells include nuclei that are deeply indented and elongated on light microscopy, cytoplasm that is pale and abundant, Birbeck granules on electron microscopy, expression of CD1 on the cell surface, and positive immunostaining for S100 protein and for the so-called Langerin protein.[2,3] The etiology and pathogenesis of LCH remain unknown, although more recent research has begun to shed some light on these.[2,4,5] Current thinking favors the notion that LCH results from immunologic dysfunction, resulting in unchecked proliferation of pathologic Langerhans cells.[5]

Unifocal eosinophilic granuloma, which occurs in children and young adults, shows a male predominance. It appears as a solitary osteolytic lesion in the femora, pelvis, scapulae, vertebrae, ribs, mandible, maxilla, or skull (including the temporal bone). The lesion may be asymptomatic, or it may cause pain, local swelling, or pathologic fracture. There are no systemic manifestations. The clinical course is typically benign, the prognosis is excellent, and spontaneous regression may occur. Local curettage with or without low-dose irradiation (approximately 60 Gy)[6] is usually curative. Temporary splinting or casting may be necessary for weight-bearing bones. Follow-up examination with a radiographic skeletal survey should be performed to detect lesions at other sites; such lesions are almost always found within 1 year.

Hand-Schüller-Christian disease may be best understood as a multifocal form of LCH. It usually occurs in children younger than 5 years old, and it is characterized by multifocal osteolytic lesions with limited extraskeletal involvement of skin, lymph nodes, and viscera. Multiple lesions are evident at diagnosis or develop within 6 months after a unifocal lesion appears. Systemic manifestations include fever, anorexia, recurrent upper respiratory infections, anterior cervical lymphadenopathy, otitis media, and hepatosplenomegaly. The classic triad

Table 148-1

Systemic Diseases That Affect the Ear

Granulomatous and infectious diseases
Langerhans cell histiocytosis
Tuberculosis
Wegener's granulomatosis
Sarcoidosis
Syphilis
Lyme disease
Mycotic diseases
Neoplastic diseases
Multiple myeloma
Leukemia
Metastatic neoplasms
Diseases of bone
Paget's disease (osteitis deformans)
Osteogenesis imperfecta
Fibrous dysplasia
Osteopetroses
Osteitis fibrosa cystica
Storage and metabolic diseases
Mucopolysaccharidoses
Gout
Ochronosis
Collagen vascular and autoimmune diseases
Immunodeficiency disorders
Primary or congenital
Humoral immunodeficiency disorders
Cellular immunodeficiency disorders
Disorders of phagocyte function
Complement system defects
Acquired
Acquired immunodeficiency syndrome
Genetically determined defects

of osteolytic skull lesions, exophthalmos as a result of orbital bone involvement, and diabetes insipidus secondary to pituitary disease may be seen in 25% of patients.[7] Chest radiograph may show diffuse pulmonary infiltration, particularly in central and perihilar areas. Hilar lymphadenopathy is rare. Diagnosis requires biopsy of an accessible lesion. Spontaneous regression may occur, but the disease is typically chronic, and low-dose chemotherapy may be required to control systemic manifestations.

Letterer-Siwe disease is a disseminated form of LCH that occurs in children younger than 3 years old and manifests with the diffuse involvement of multiple organs. Manifestations include fever, seborrheic or eczema-like rash, oral lesions, lymphadenopathy, hepatosplenomegaly, multiple bony lesions, diffuse replacement of marrow with resulting blood dyscrasias, and pulmonary infiltration with respiratory failure. The disease is virulent, with a poor prognosis and a high mortality rate. Treatment consists of varying combinations of corticosteroids and cytotoxic drugs such as methotrexate, mercaptopurine, vincristine, vinblastine, chlorambucil, cyclophosphamide, and etoposide. High-dose chemotherapy and radiation followed by bone marrow transplantation or hematopoietic stem cell transplantation has been reported to be successful in a few advanced refractory cases of LCH.[8]

Otologic Manifestations

The mastoid is a common site of involvement in LCH. When small, the lesion is asymptomatic. As it expands, the lesion may manifest in several ways: by erosion of the posterior bony canal wall; by erosion through the cortex of the mastoid, zygomatic, or squamosal portions; or by secondary infection.[9] The otic capsule and facial nerve are relatively resistant. Although sensorineural hearing loss (SNHL), vertigo, and facial nerve paralysis can occur, they are infrequent. Similarly, extension beyond the temporal bone involving the jugular fossa and skull base is rare.

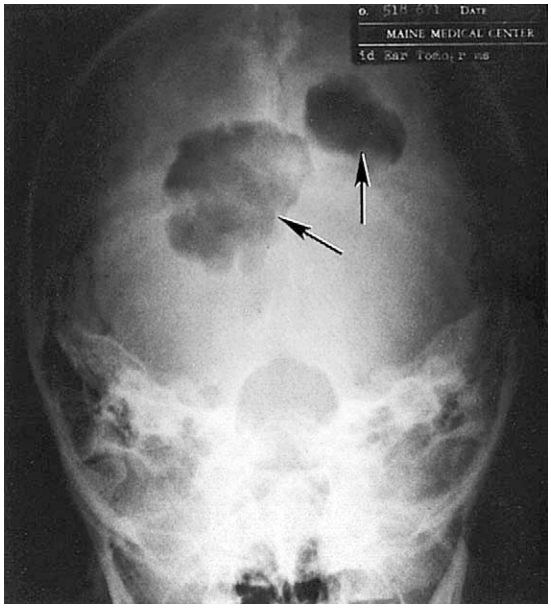

Figure 148-1. Multiple eosinophilic granulomas in a 32-year-old woman. There are two lytic lesions of the skull showing beveled edges *(arrows)* and nonsclerotic margins, which are typical of this disease.

The reported incidence of otologic manifestations in patients with LCH is 15% to 61%,[7] and they may be the initial presentation of the disease. The most common symptom is otorrhea, followed by postauricular swelling, hearing loss, and vertigo.[10,11] The most common sign is granulation tissue or aural polyps in the external auditory canal. The disease may manifest with perforation of the tympanic membrane, otitis media, otitis externa, fistula between the mastoid and the external canal, or nontender postauricular swelling. Occasionally, inner ear symptoms and a positive fistula test are found in the presence of an intact tympanic membrane. The disease often mimics chronic otitis media, and mastoid surgery is frequently performed before the diagnosis is made.[9]

Diagnosis of LCH is suggested by an inflammatory disorder of the middle ear and mastoid that does not respond to routine antibiotic therapy, bilateral destructive ear disease, an elevated erythrocyte sedimentation rate in the absence of acute infection, exuberant granulation tissue after mastoid surgery with a persistently draining cavity, and associated skin and systemic lesions. Radiographs show destructive lesions in the mastoid and temporal bones (Figs. 148-1 and 148-2).[9,10,12] The diagnosis is established by biopsy; because the surface of the granulation tissue often shows infection, necrosis, and fibrosis, tissue should be acquired from deeper parts of the lesion.[13] Microscopic findings include sheets of histiocytes with a variable number of eosinophils, plasma cells, polymorphonuclear leukocytes, and multinucleated cells (Figs. 148-3, 148-4, and 148-5). Areas of hemorrhage and necrosis are common. A definitive diagnosis of LCH is usually made on the basis of immunostaining and electron microscopic studies.[2,4]

Tuberculosis

The incidence of tuberculous otitis media has decreased dramatically. During the early part of the 20th century, 1.3% to 18.6% of all cases of chronic otitis media were reportedly caused by tuberculosis, whereas more recent studies report tuberculous otitis media rates of 0.05% to 0.9%.[14] The last 20 years have witnessed an increase in incidence of tuberculosis, however, which is caused in part by the aggressive nature of tuberculosis in individuals infected with human immunodeficiency virus (HIV), and by an emerging resistance to antituberculosis drugs.[15]

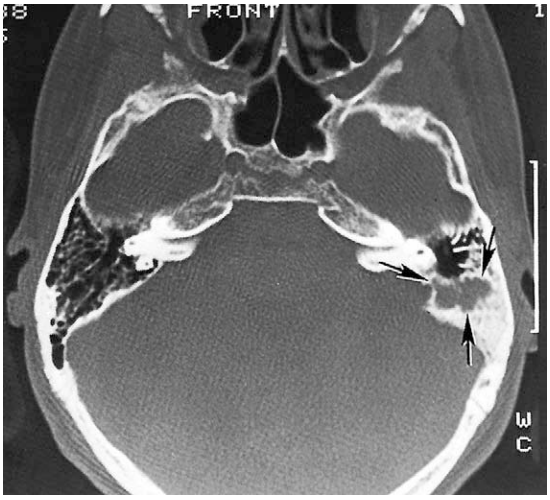

Figure 148-2. Irregular lytic lesion in the mastoid bone *(arrows)* of a 13-year-old boy with unifocal eosinophilic granuloma.

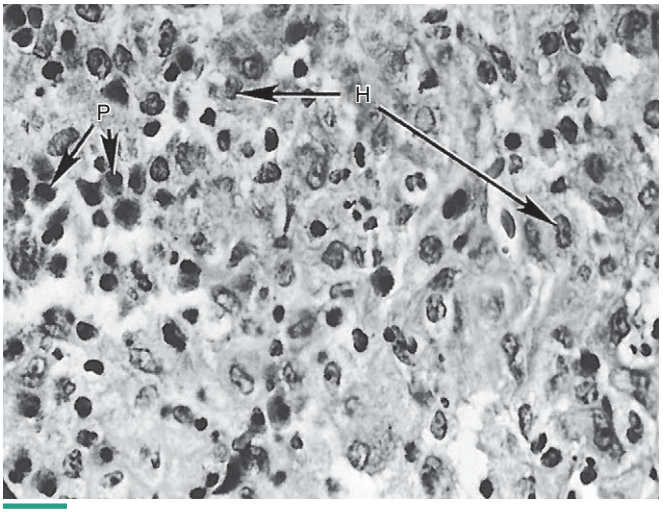

Figure 148-5. Eosinophilic granuloma of the external ear canal with plasma cells (P), eosinophils, and histiocytes (H), which show "folded" nuclei, a morphology that is peculiar to the histiocytoses (×640).

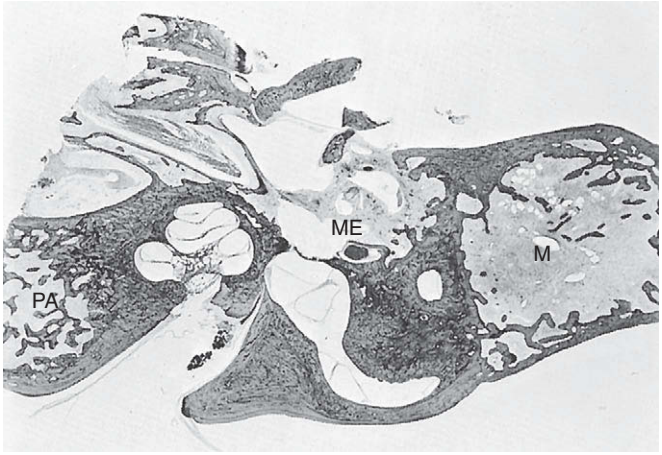

Figure 148-3. Letterer-Siwe disease affecting the temporal bone of a 4-year-old boy. Granulation tissue typical of histiocytosis can be seen in lytic lesions within the mastoid (M), middle ear (ME), and petrous apex (PA) (×4).

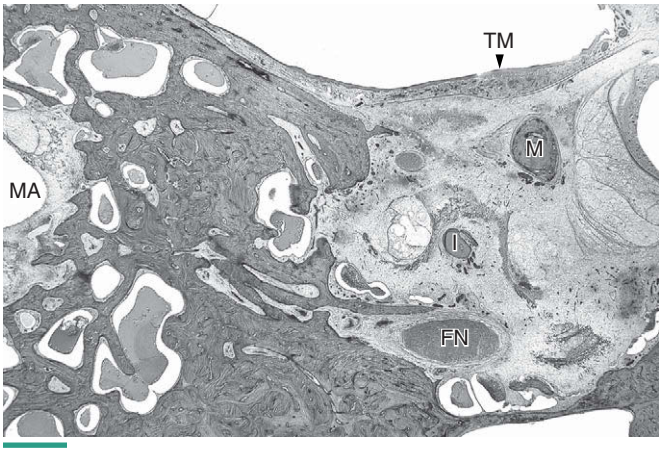

Figure 148-6. Tuberculous granulation tissue filling the middle ear of a 57-year-old man who died of miliary tuberculosis (×12.35). FN, facial nerve; I, incus; M, malleus; MA, mastoid; TM, tympanic membrane.

Figure 148-4. A higher power view of part of the middle ear area seen in Figure 148-3. The infiltrate consists of histiocytes, eosinophils, and multinucleated cells. The incus (I) has been partially resorbed (×45).

Mycobacterium tuberculosis is the infective organism in most cases; occasionally, atypical mycobacteria (e.g., *Mycobacterium avium* and *Mycobacterium fortuitum*) are responsible.[16]

Tuberculosis of the middle ear and mastoid may occur as a result of hematogenous or lymphatic spread, or by extension to the middle ear cleft through the eustachian tube. Direct inoculation through a perforation of the tympanic membrane is also possible. Middle ear involvement in the absence of active pulmonary disease is rare, but may occur.

During the early stages of tuberculous otitis media, the tympanic membrane becomes thickened, and the otoscopic landmarks become obliterated. There is a conductive hearing loss as a result of middle ear effusion, a thickening of the tympanic membrane and middle ear mucosa, and a destruction of the ossicles (Figs. 148-6 and 148-7). There is no characteristic pain or tenderness, but lymphadenopathy in the high jugular chain occurs early. Multiple small perforations of the tympanic membrane may occur, with seropurulent drainage. The perforations quickly coalesce to cause loss of the tympanic membrane. Likewise, a myringotomy site in an intact tympanic membrane may enlarge quickly. The middle ear mucosa appears to be hyperemic with polypoid granulation. Osseous involvement results in the sequestration of bone and the destruction of the inner ear, the facial nerve, or both.

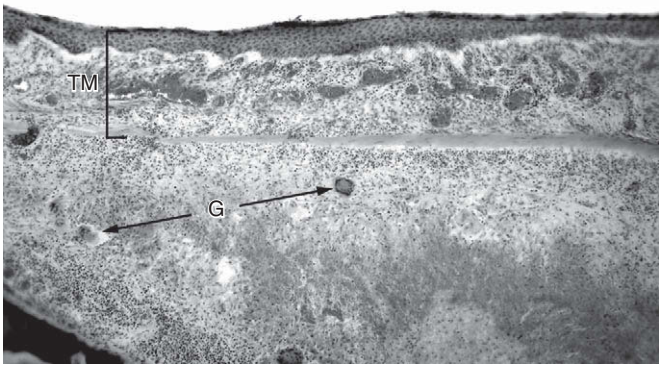

Figure 148-7. A higher power view of the tympanic membrane (TM) seen in Figure 148-6. The TM is intact, but greatly thickened by tuberculous granulation tissue containing the typical epithelioid cells, round cells, and multinucleated giant cells (G) (×100).

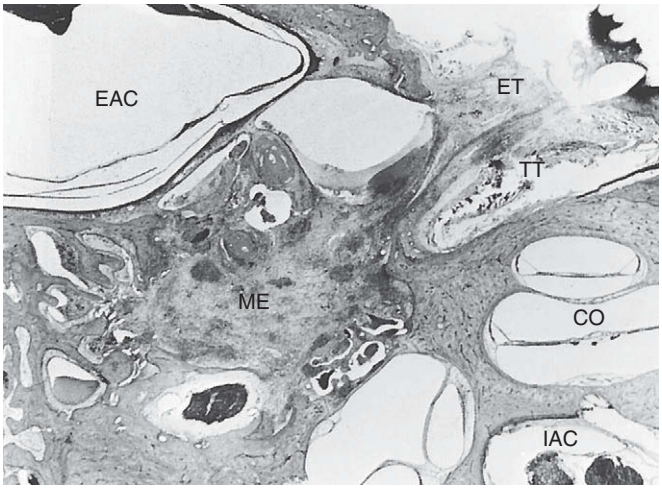

Figure 148-8. Wegener's granulomatosis causing blockage of the eustachian tube (ET) and infiltration of the middle ear (ME) in a 41-year-old man (×10). CO, cochlea; EAC, external auditory canal; IAC, internal auditory canal; TT, tensor tympani. *(Courtesy of Leslie Michaels, MD, Institute of Laryngology and Otology, London.)*

Destruction of the mastoid tip may result in an asymptomatic, nontender Bezold's abscess (i.e., a "cold" abscess). Rarely, tuberculosis can also manifest as primary tuberculous petrositis,[17] or as SNHL caused by chronic labyrinthitis and tuberculous meningitis.[18]

The diagnosis of tuberculous involvement of the middle ear is usually delayed. The characteristic signs and symptoms include multiple perforations of the tympanic membrane that quickly coalesce to form total tympanic membrane loss, nontender cervical lymphadenopathy, intractable otitis media with polypoid granulation, and bony sequestration; these should alert the physician to this possible diagnosis. Otic capsule involvement with resultant loss of auditory and vestibular function may be the first symptom, which indicates a process that differs from the more typical chronic otitis media. Definitive diagnosis is made by histopathologic examination of tissue from the middle ear or mastoid showing a granulomatous process with multinucleated giant cells (Langhans cells) (see Figs. 148-6 and 148-7) and histologic demonstration of acid-fast organisms of tuberculosis. The accurate identification of the mycobacterial species and drug-resistant isolates by culture is still the gold standard. Culture takes several weeks, however, and is time-consuming. The process is facilitated by the use of several different types of nucleic acid amplification tests that have been approved by the U.S. Food and Drug Administration for rapid identification of *M. tuberculosis*.[15,19]

Multiple perforations of the tympanic membrane, exuberant polypoid granulation within the middle ear, and early loss of inner ear function also are seen in WG. These two diseases are distinguished on the basis of skin tests for tuberculosis and the histologic demonstration of acid-fast organisms of tuberculosis in granulation tissue, cultures of the middle ear, the presence of antineutrophil cytoplasmic antibodies (ANCAs) in WG, and the systemic manifestations of each process.

The mainstay of management of tuberculosis of the middle ear and mastoid is the systemic use of standard antituberculous chemotherapy.[14] Mastoid surgery may be required to remove sequestrated bone. Reconstructive surgery of the ossicles and tympanic membrane is feasible after the infection has been controlled.

Wegener's Granulomatosis

WG is a granulomatous inflammatory process with necrotizing vasculitis. It primarily affects the upper and lower respiratory tracts and kidneys, but WG can involve essentially any organ in the body. The disease occurs equally in men and women, and the mean age of onset is 40 years. Common presenting symptoms include headache, sinusitis, rhinorrhea, otitis media, fever, and arthralgia.[20,21] Upper airway and sinus involvement occurs in 75% to 90% of cases. Pulmonary manifestations include cough, pleuritic chest pain, hemoptysis, and nodular or cavitary infiltrates on chest radiography. Pulmonary manifestations occur in 65% to 85% of cases. Other manifestations include glomerulonephritis (60% to 75% of cases); eye involvement in the form of conjunctivitis, iritis, scleritis, or proptosis (15% to 50% of cases); and dermatologic findings of necrotic ulcerations, vesicles, or petechiae.

Laboratory findings in WG may include normochromic, normocytic anemia; thrombocytosis; positive rheumatoid factor; and hyperglobulinemia, particularly of IgA. The erythrocyte sedimentation rate is almost always elevated. The discovery in 1985 of autoantibodies directed against the cytoplasmic constituents of neutrophils (ANCA, c-ANCA) in patients with WG was a major advance in the diagnosis and understanding of WG.[22] A positive ANCA test, especially proteinase 3–specific c-ANCA, is very helpful in establishing or supporting a diagnosis of WG. The specificity of positive c-ANCA testing in WG is greater than 95%; the sensitivity is variable and depends on the phase and type of WG. c-ANCA is positive in more than 90% of patients with systemic and active WG, whereas in limited WG (e.g., ear or head and neck only or inactive disease), the sensitivity of c-ANCA is only 65% to 70%. In addition, the antibody titer parallels the activity of the disease, although there have been conflicting data about the value in using the titer as a guide for immunosuppressive therapy.

The diagnosis of WG is made histologically by the presence of necrosis, granulomatous inflammation with multinucleated giant cells, vasculitis, and microabscess formation (Figs. 148-8 and 148-9). Small biopsy specimens (e.g., from the ear or upper airways) may lack all of the various diagnostic features, however. In such cases, a diagnosis of WG can be made on the basis of the clinical presentation, ANCA testing, and repeat biopsy specimens taken from the same or related sites.

The etiology and pathogenesis of WG are unknown. Infectious, genetic, and environmental risk factors and combinations thereof have been proposed. The evidence to date suggests that WG is a complex, immune-mediated disorder in which tissue injury results from the interplay of an initiating inflammatory event and a highly specific immune response.[23] Part of this response consists of the production of ANCA, directed against antigens present within the primary granules of neutrophils and monocytes; these antibodies produce tissue damage by interacting with primed neutrophils and endothelial cells.

The prognosis of WG has dramatically improved from a mortality rate of 82% before the era of immunosuppressive therapy to the current remission rate of more than 75% with appropriate medical therapy.[24] Induction of remission is usually achieved with high doses of corticosteroids, cyclophosphamide, or methotrexate given for 3 to 6 months. Maintenance of remission is achieved with lower doses of corticosteroids and less toxic alternatives to cyclophosphamide, such as azathioprine, methotrexate, trimethoprim-sulfamethoxazole, or other drug

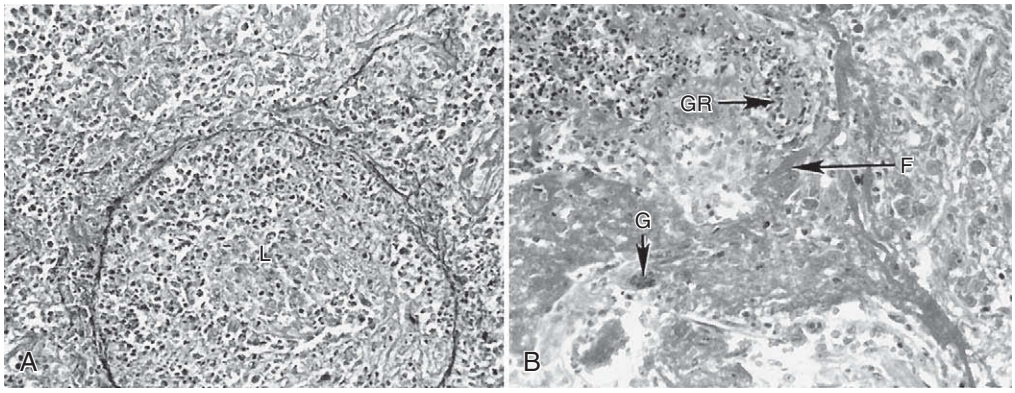

Figure 148-9. Wegener's granulomatosis in lung biopsy specimen. **A,** Arteriole showing necrotizing vasculitis with obliteration of the lumen (L) and infiltration of the vessel wall with polymorphonuclear leukocytes (elastic stain; ×256). **B,** Vessel wall showing fibrin deposit (F), giant cells (G), and granuloma (GR) (hematoxylin-eosin stain; ×256).

combinations. Other therapies that have been used include leflunomide, mycophenolate mofetil, and the tumor necrosis factor inhibitors etanercept and infliximab.

Otologic Manifestations

The middle ear and mastoid are the most common sites within the temporal bone that are involved in patients with WG.[20,25] WG may cause obstruction of the eustachian tube with resultant serous otitis media and conductive hearing loss (see Fig. 148-8). Some patients also have purulent otitis media, and others may have frank granulomatous involvement of the middle ear and mastoid. The process can extend to involve the facial nerve and the inner ear, which is usually manifested as rapidly progressive SNHL and loss of vestibular function. Otologic disease may be the sole and initial presenting feature in some patients with WG.

Sarcoidosis

Sarcoidosis is a chronic multisystem disorder of unknown etiology that is characterized by the presence of noncaseating granulomas. It most frequently affects the lungs, although almost all body parts can be affected. The disease shows a female predominance, and is 10 times more common in blacks than in whites. The onset of disease is usually during the third to fourth decade of life. Common presenting manifestations include bilateral hilar adenopathy on chest radiography, cough, and granulomatous skin rash. Other manifestations include iridocyclitis, keratoconjunctivitis, peripheral lymphadenopathy, hepatosplenomegaly, cardiac failure, myalgia, and arthralgia. Neurologic involvement includes central and peripheral manifestations. The facial and optic nerves are the most commonly affected cranial nerves. Either peripheral mononeuritis or polyneuritis may be seen. Laboratory findings may include hilar adenopathy on chest radiography (Fig. 148-10), hypercalcemia, and elevated serum angiotensin-converting enzyme. The histopathologic feature of the sarcoid lesion is noncaseating epithelioid granulomas (Fig. 148-11).

The etiology and pathogenesis of sarcoidosis are unknown. The initial pulmonary lesion is an alveolitis characterized by the accumulation of $CD4^+$ T cells, followed by development of noncaseating granulomas. The antigenic stimulus that initiates the disease process remains elusive. Several possible associations have been investigated, including mycobacteria, certain HLA complexes, abnormalities of T cells and the T-cell antigen receptor, and involvement of several different cytokines.[26]

Spontaneous resolution occurs in many patients. Corticosteroids are beneficial for patients with progressive symptoms or with ocular, cardiac, or central nervous system involvement. For patients who cannot tolerate or do not respond to corticosteroids, alternative drugs include methotrexate, cyclophosphamide, azathioprine, chlorambucil, cyclosporine, chloroquine, pentoxifylline, and antagonists of human tumor necrosis factor-α such as etanercept (Enbrel) and infliximab (Remicade).[27]

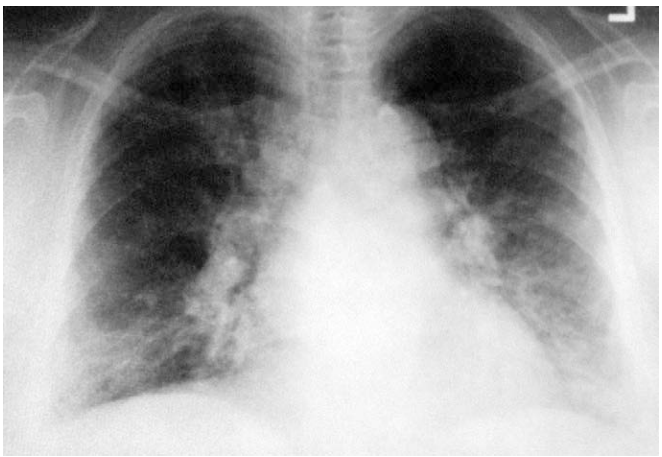

Figure 148-10. Bilateral hilar adenopathy and linear parenchymal densities in a 56-year-old woman with pulmonary sarcoidosis.

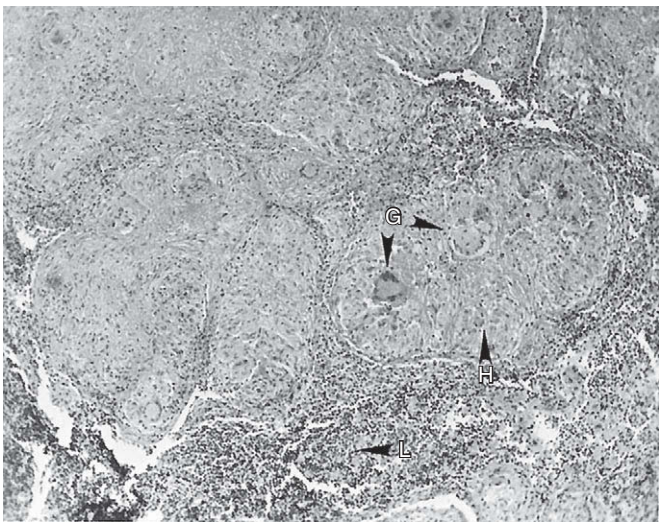

Figure 148-11. Sarcoidosis in a lymph node specimen. There are noncaseating granulomas with giant cells (G), histiocytes (H), and lymphocytes (L) (×79).

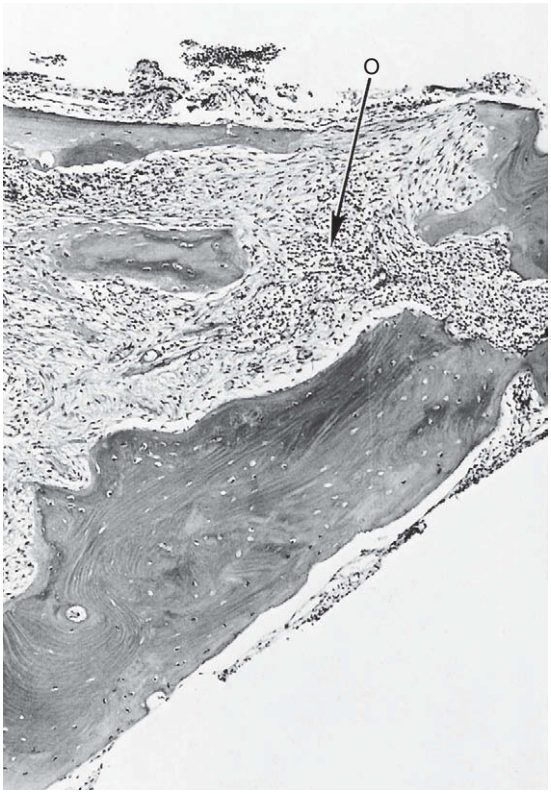

Figure 148-12. Section of the incus in a patient with acquired syphilis. There is an active round cell osteitis (O), with involvement of the periosteum (×120).

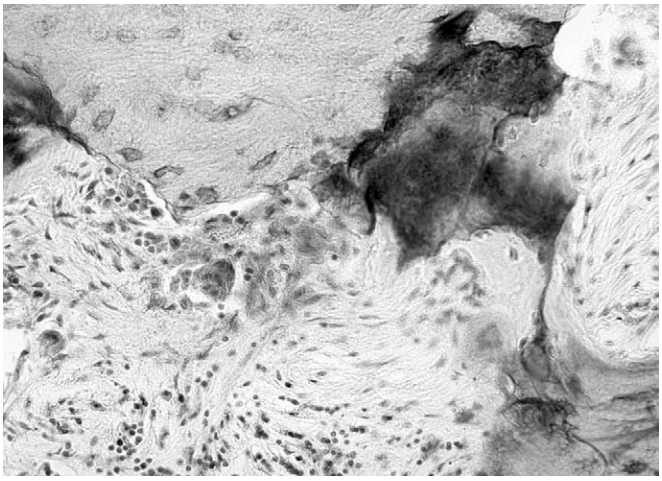

Figure 148-13. Area of active bone resorption in a 43-year-old patient with congenital syphilis. The inflammatory infiltrate includes lymphocytes, plasma cells, and multinucleated giant cells (×396).

Otologic Manifestations

Otologic manifestations of sarcoidosis include SNHL, vestibular dysfunction, and facial nerve paralysis, and occasionally granulomatous disease of the external or middle ear and mastoid.[28-31] The facial nerve is the most commonly affected cranial nerve and is usually involved as part of the triad of uveoparotid fever (Heerfordt's syndrome) that is characterized by parotitis, uveitis, facial nerve paralysis, and mild pyrexia. The facial paralysis may be sudden in onset, it is often bilateral, and it may resolve spontaneously. Histopathology of the temporal bone in sarcoidosis has been reported in only one case; the main findings were perivascular lymphocytic infiltration and granulomatous inflammation involving the cochlear, vestibular, and facial nerves within the internal auditory canal.[32]

Syphilis

Congenital and acquired syphilis may affect the middle ear in the late latent and tertiary forms. In the late latent form, the middle ear and mastoid may be affected by a rarefying osteitis with leukocytic infiltration of the ossicles and mastoid bone (Figs. 148-12 and 148-13). A similar but larger lesion of tertiary syphilis, the gumma, shows obliterative arteritis and central necrosis. A gumma of the ear canal or middle ear may result in perforation of the tympanic membrane and a granulomatous appearance of the middle ear mucosa. Definitive diagnosis of syphilis of the middle ear requires a positive serologic test and a histologic demonstration of *Treponema pallidum*. Syphilitic involvement of the tympanic membrane and middle ear may mimic tuberculosis, and superinfection may result in chronic otitis media.

Inner ear involvement may occur in the absence of macroscopic changes in the tympanic membrane or middle ear. Hennebert's sign, which is the induction of ocular deviation with positive or negative pressure in the external auditory canal, was believed to indicate a true fistula between the middle and inner ear because of rarefying osteitis of the otic capsule. The more probable cause is fibrous adhesions, however, between the stapes footplate and the membranous labyrinth as a result of endolymphatic hydrops.[33] Combined antibiotic and corticosteroid therapy is beneficial for the management of SNHL.[34]

Lyme Disease

Lyme disease is a multisystem inflammatory disorder that primarily affects the skin, nervous system, heart, and joints. It is caused by a spirochete, *Borrelia burgdorferi,* that is transmitted to humans by certain *Ixodes* ticks that are part of the *Ixodes ricinus* complex. The known primary reservoirs of the disease are white-footed mice and white-tailed deer. The disease was initially recognized in 1975 because of a clustering of patients with arthritis in Lyme, Connecticut, but it is now known that Lyme disease has been present for several decades in Europe, where it is called Bannwarth's syndrome.

Infection is usually acquired in the summer, and individuals of all ages and both sexes can be affected. Three clinical stages that are similar to the stages seen with cases of syphilis are recognized.[35] The first stage (early, localized infection) begins 3 to 33 days after a tick bite with a characteristic skin lesion (erythema migrans). This lesion occurs in 60% to 80% of patients and may be accompanied by minor constitutional symptoms. The second stage (early, disseminated infection) occurs within days or weeks after inoculation and begins with hematogenous dissemination of the organism from the site of inoculation. The symptoms, which mimic a systemic viral illness, include fever, migratory arthralgia, myalgia, headache, meningismus, generalized lymphadenopathy, malaise, fatigue, and secondary annular skin lesions.

After hematogenous spread, *B. burgdorferi* seems to be able to sequester itself in certain niches and cause localized inflammation in the nervous system, heart, or joints. Neurologic involvement is manifested by meningitis, encephalitis, cerebrospinal fluid lymphocytosis, peripheral neuropathy, myelitis, or cranial neuropathy (including facial nerve paralysis). Cardiac manifestations include atrioventricular block or other arrhythmias, myocarditis, and pericarditis. Joint disease manifests as brief attacks of asymmetrical oligoarticular arthritis, primarily in large joints (especially the knee). The third stage (late or persistent infection) occurs more than 1 year after onset, and can result in chronic, prolonged arthritis; chronic encephalomyelitis; chronic axonal peripheral polyradiculopathy; keratitis (similar to syphilis); acrodermatitis chronica atrophicans; and localized scleroderma-like lesions. A patient may experience one or all of the stages and the infection may not become symptomatic until the second or third stage. Affected tissues show infiltration by lymphocytes and plasma cells. Mild vasculitis and hypercellular vascular occlusion can occur. There is generally no tissue necrosis. In contrast to the findings in patients with syphilis, granulo-

mas, gummas, multinucleated giant cells, and fibrinoid necrosis have not been observed as yet.[36]

In recent years, the complete genome of the spirochete has been sequenced, and animal models have been developed for studying the pathogenesis of Lyme disease using mice and primates. The animal models have shown that inflammatory innate immune responses are critical in the pathogenesis of the disease, and that genetic factors may be important in determining the severity of some of the manifestations.

The diagnosis of Lyme disease is usually based on the recognition of the characteristic clinical features, a history of exposure in an area where the disease is endemic, and detection of a specific antibody to *B. burgdorferi* by enzyme-linked immunosorbent assay and Western blotting.[35] The antibody test must be interpreted properly using the criteria of the Centers for Disease Control and Prevention because false-negative and false-positive results can occur. In addition, *B. burgdorferi* may cause asymptomatic infection, in which case the symptoms caused by another disease may be wrongly attributed to Lyme borreliosis.

The spirochete is highly sensitive to doxycycline, but only moderately so to penicillin. Other effective antibiotics include amoxicillin, erythromycin, cefuroxime, ceftriaxone, and imipenem. Steroids have been used for severe carditis and arthritis. Among patients managed early in the course of the disease, the specific antibody response usually disappears within months, and patients may become reinfected in the future. Among patients with late manifestations such as arthritis, titers decline after successful management, but patients remain seropositive. Although two vaccines were developed and found to be effective in clinical trials, they are not currently being marketed.[37]

Otologic Manifestations

Facial nerve paralysis is the most common otologic manifestation, with a reported incidence of 3% to 11%[38,39]; it may be bilateral in 25% of cases. This type of paralysis is seen in the second stage of the disease, and it affects patients of all ages and both sexes. The onset is acute, the duration is weeks to a few months, and the return of function is spontaneous and is usually complete. There may be a history of preceding otalgia, ipsilateral facial pain, or paresthesias.[40] Although other neurologic features of the second stage may be seen, facial nerve paralysis can occur as the sole neurologic abnormality (including normal cerebrospinal fluid).

Antibiotics or steroids do not seem to influence the duration or outcome of facial paralysis,[38] but they are recommended to treat concurrent symptoms and to prevent the more serious late complications. There is no role for surgery. The precise cause and histopathology of facial nerve palsy have not been elucidated. Histology from other involved peripheral nerves shows perineural and perivascular infiltration by lymphocytes and plasma cells. In chronic and severe neuropathies, demyelination and loss of nerve fibers similar to wallerian degeneration occur.[36] It is unclear whether neural lesions result from an inflammatory response to the spirochete or an immune-mediated epiphenomenon.

A well-documented otologic manifestation is an unusual skin lesion called a lymphocytoma, in which intensely red and violet nodules occur on the earlobe during the second stage of disease.[35] The lesion consists of benign but hyperplastic lymphocytic follicles in the dermis.[36]

Auditory and vestibular manifestations, such as SNHL, sudden hearing loss, positional vertigo, and Meniere's-like symptoms have been described.[41-44] More clinical data and temporal bone studies are needed to substantiate these preliminary observations.

Mycotic Diseases

Fungi are ubiquitous in the environment and are of low intrinsic virulence. Systemic invasive clinical disease reflects some defect in host defenses, such as diabetic ketoacidosis, chemotherapy for malignancy, corticosteroid therapy, or acquired immunodeficiency syndrome (AIDS). Aspergillosis, mucormycosis, candidiasis, cryptococcosis, coccidioidomycosis, and histoplasmosis are systemic mycoses that can cause disseminated disease, including involvement of the temporal bone. Diagnosis is made by biopsy and culture. Treatment consists of control of the underlying predisposing condition, surgical débridement of necrotic tissues, and systemic chemotherapy, usually with amphotericin B.

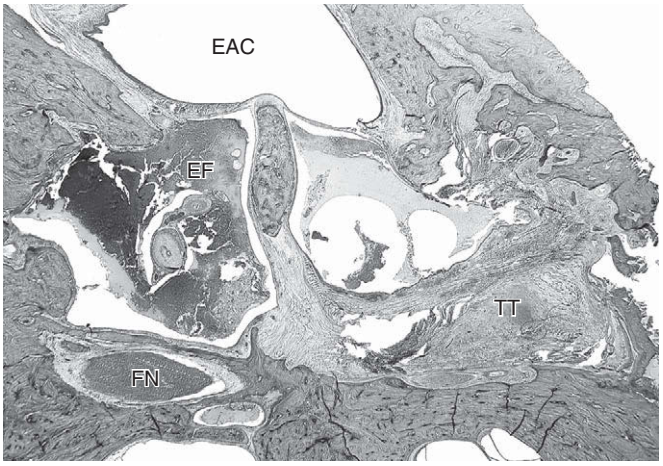

Figure 148-14. Mucormycosis in a 37-year-old man with diabetes. Inflammatory cells have invaded and destroyed the tensor tympani muscle (TT), and there is a hemorrhagic effusion (EF) in the mesotympanum (×12.35). EAC, external auditory canal; FN, facial nerve.

Otologic Manifestations

The middle ear and mastoid can be involved as a result of ascending infection along the eustachian tube and tensor tympani (often seen in mucormycosis) (Fig. 148-14) or through superinfection of existing chronic otitis media.[45] Destruction of the middle ear cleft ensues, often with extension to the surrounding structures, including thrombosis or rupture of the internal carotid artery.[46] Other routes of infection include hematogenous embolic dissemination, which can result in multiple granulomas throughout the temporal bone, and through cryptococcal involvement of the central nervous system, which can cause invasion and degeneration of the nerve trunks in the internal auditory canal.[47]

Neoplastic Diseases

Although neoplasms of the temporal bone are discussed elsewhere (see Chapters 176 and 177), three neoplasms—multiple myeloma, leukemia, and metastatic tumors—warrant mention here because temporal bone manifestations can occur with these diseases.

Multiple Myeloma

Multiple myeloma is a malignancy of plasma cells derived from B lymphocytes, and its major feature is the demonstration of an abnormal monoclonal protein (M component) in blood, urine, or both. There is a slight male predominance, and the median age of onset is 60 years. Clinical manifestations are the result of multiple plasma cell tumors, and consist of severe bone pain, pathologic fractures, failure of the bone marrow, renal failure, hypercalcemia, and recurrent infections.

Laboratory findings include the demonstration of the M component on serum or urine electrophoresis; normochromic, normocytic anemia; hypercalcemia; and elevated blood urea nitrogen levels. Typical radiographic findings include punched-out osteolytic lesions, which are particularly well seen on lateral skull radiography. Bone marrow aspirates show infiltration by plasma cells. For decades, the mainstay of therapy has been the use of alkylating agents, such as melphalan and corticosteroids; with this regimen, the median survival is approximately 3 years. Important advances have been made more recently that have substantially altered therapy for patients with myeloma. These advances include the use of hematopoietic cell transplantation; improved supportive care measures such as the use of bisphosphonates and erythropoietin; and novel agents such as thalidomide, lenalidomide, and bortezomib.[48,49]

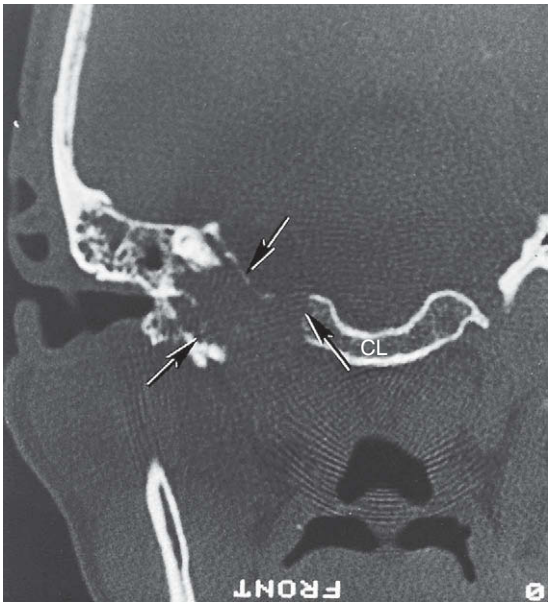

Figure 148-15. Coronal CT scan showing a large lytic destructive lesion *(arrows)* of the clivus (CL), petrous temporal bone, middle ear, and jugular foramen area caused by multiple myeloma in a 72-year-old man. The presenting symptoms were facial nerve paralysis and otorrhea.

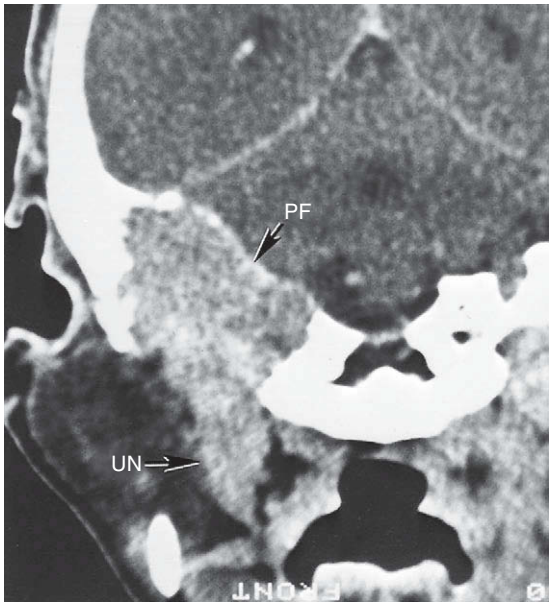

Figure 148-16. Coronal CT scan with contrast enhancement and a soft tissue technique in the same patient from Figure 148-15 shows a slightly enhancing mass that has destroyed the mastoid bone and extends to the posterior fossa (PF) and upper neck (UN).

Occasionally, only one plasma cell tumor (without marrow plasmacytosis) can be found. These lesions can occur in bone (solitary bone plasmacytoma) or soft tissue (extramedullary plasmacytoma), including the temporal bone. Both lesions can affect younger individuals, are associated with an M component in less than 30% of the cases, and have an indolent course with survival rates of 10 years or more. Local radiotherapy (40 Gy) is usually sufficient management. Periodic evaluation of serum and urine globulins and a skeletal radiographic survey should be performed to detect conversion to multiple myeloma.

Otologic Manifestations

The temporal bone is frequently involved in cases of multiple myeloma. Radiography may show rounded lytic lesions of the calvaria and temporal bone (Figs. 148-15 and 148-16). At a microscopic level, the marrow spaces of the petrous bone are commonly replaced by myeloma cells, and discrete lytic bone lesions may be seen in the otic capsule (Fig. 148-17).[50] Symptoms referable to temporal bone involvement are usually overshadowed by manifestations of diffuse disease. Occasionally, these may be the presenting feature of myeloma,[51] or they may be the only evidence of disease (plasmacytoma of the temporal bone).[52] Symptoms are nonspecific and include hearing loss, tinnitus, vertigo, otalgia, and facial paralysis.[53]

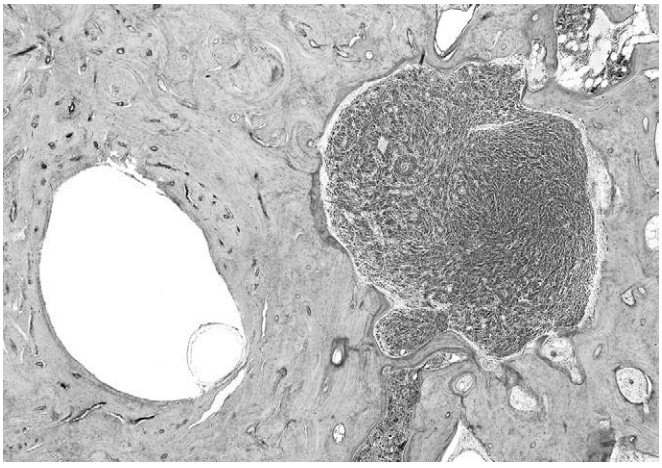

Figure 148-17. One of several osteolytic lesions of the temporal bone of a 69-year-old woman with multiple myeloma. The lesion shows sharp bony margins and consists of immature plasma cells (×39.6).

Leukemia

Leukemic infiltrates may occur in the temporal bone. They are common in the submucosa of the pneumatized areas of the middle ear and mastoid, including the tympanic membrane (Fig. 148-18), and in the bone marrow of the petrous apex (Fig. 148-19).[54,55] Secondary bacterial infection of the middle ear and mastoid often results from an immunocompromised state that is a result of either the disease itself or chemotherapy. Hemorrhage commonly occurs in association with infiltrates and can occur in the middle ear, mastoid, or inner ear. Clinical manifestations include middle ear effusion, acute and chronic suppuration in the middle ear and mastoid, thickening of the tympanic membrane, conductive hearing loss, SNHL (including sudden SNHL), vertigo, facial paralysis, and skin lesions in the auricle or external auditory canal.[56,57]

Granulocytic sarcoma or chloroma is a localized extramedullary tumor that is composed of immature myeloid cells. It is related to acute or chronic myelogenous leukemia, and its appearance may precede, coincide with, or follow the diagnosis of leukemia. Such a lesion can occur in the temporal bone,[58-60] and otologic manifestations can constitute the initial presentation. Management is by local irradiation and systemic chemotherapy.

Metastatic Neoplasms

Secondary malignant tumors usually involve the temporal bone through hematogenous dissemination. The most common sites of origin, in order of decreasing frequency, are the breast, the lung, the prostate, and the skin.[61] The lesions are usually destructive and osteolytic (Fig. 148-20); however, some lesions, such as from the prostate or breast, may be osteoblastic. The petrous apex and internal auditory canal seem to be sites of predilection for metastases, although any part of the temporal bone may be involved (Fig. 148-21). The otic capsule seems to be resistant to neoplastic invasion.[62]

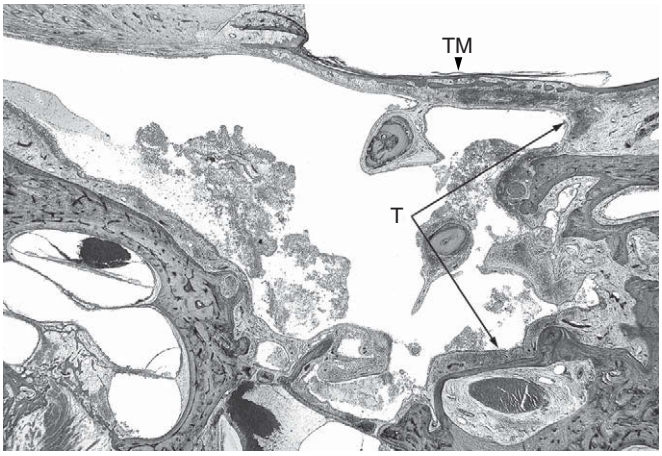

Figure 148-18. Acute lymphocytic leukemia in a 9-year-old boy. Ten days before his death, the patient complained of ear pain. Otoscopic examination revealed a hyperemic tympanic membrane (TM). The TM and mucosa of the middle ear are infiltrated by tumor cells (T), and the middle ear space contains a purulent exudate (×12.35).

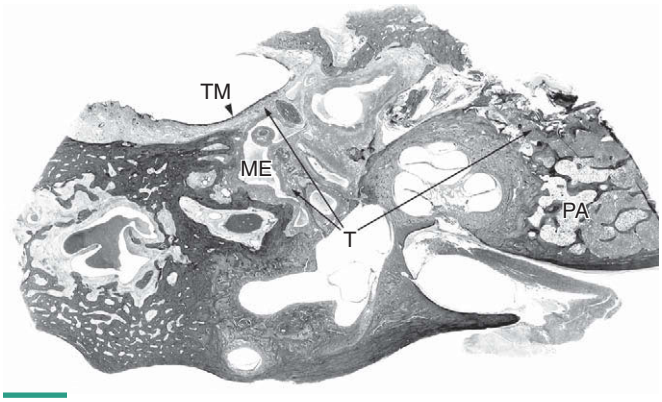

Figure 148-19. Acute myelogenous leukemia in a 38-year-old man. Leukemic infiltrates (T) are seen in the tympanic membrane (TM), middle ear (ME), and marrow spaces of the petrous apex (PA) (×6.7).

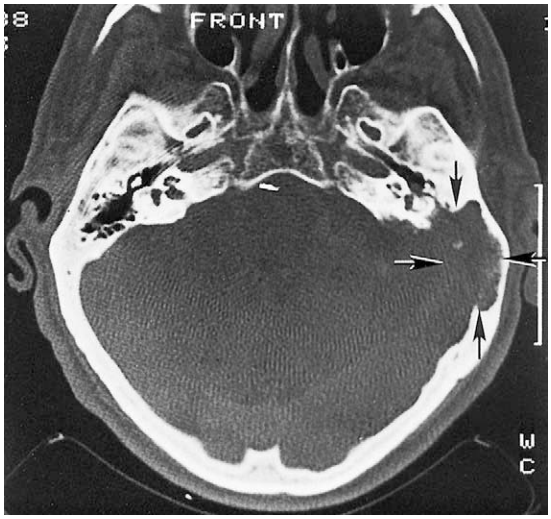

Figure 148-20. Axial CT scan of an 82-year-old woman with metastatic breast adenocarcinoma showing a large lytic lesion *(arrows)* destroying the mastoid, squamosa, otic capsule, and labyrinth.

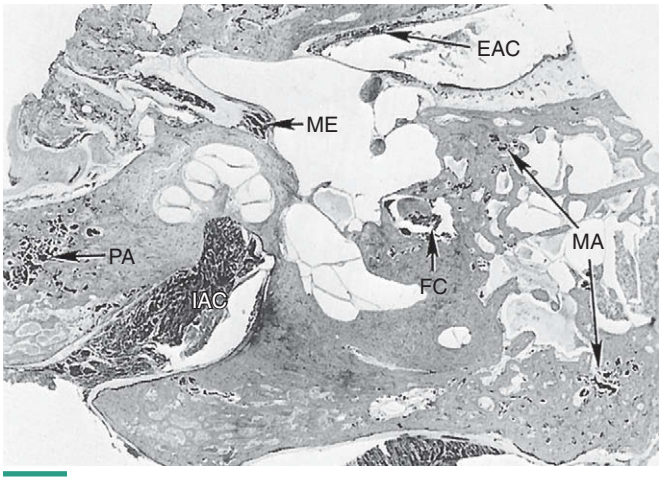

Figure 148-21. Metastatic breast adenocarcinoma in a 75-year-old woman involving the nerve trunks in the internal auditory canal (IAC), petrous apex (PA), subcutaneous tissues of the external auditory canal (EAC), facial canal (FC), middle ear (ME), and mastoid (MA) (×4.5).

Although otologic manifestations infrequently are the first evidence of malignant disease, more often they are preceded by other systemic symptoms. Involvement of the external canal, the middle ear cleft, or the eustachian tube may cause conductive hearing loss and pain; involvement of the otic capsule may produce SNHL, vertigo, and facial nerve paralysis. In meningeal carcinomatosis, rapidly progressive unilateral or bilateral SNHL is a common presenting symptom.[63] Unilateral SNHL may mimic a cerebellopontine angle tumor, and bilateral SNHL may mimic immune-mediated inner ear disease. Diagnosis is made by cytology of the cerebrospinal fluid.

Diseases of the Bone

Several generalized bone diseases affect the middle ear and temporal bone, and occasionally the initial symptoms of the disease occur in the temporal bone. Paget's disease, osteogenesis imperfecta (OI), and osteopetrosis can sometimes mimic the clinical features of otosclerosis.

Paget's Disease

Paget's disease of bone (osteitis deformans) is a chronic and sometimes progressive disease of unknown etiology. It is characterized by osteolytic and osteoblastic changes that mainly affect the axial skeleton. Genetic factors play a role in the pathogenesis of Paget's disease, which may be inherited in an autosomal dominant manner with high penetrance. Four susceptibility loci have been identified, one on chromosome 18, one on chromosome 6, and two on chromosome 5.[64] Mutations in the *SQSTM1* gene encoding the sequestosome 1 protein have been found in some individuals. Viral infection also seems to play a role in the etiology of Paget's disease, based on electron microscopy and immunohistochemical studies.[65,66] It is possible that the disease develops from a slow virus infection in susceptible individuals who have an underlying genetic predisposition.

Paget's disease affects 3% of the population that is 40 years old and older and 11% of the population that is 80 years old and older.[67] Men are affected more commonly than women. The onset of clinical manifestations is usually in the sixth decade of life, and includes enlarging skull; progressive kyphosis; and deformities of the pelvis, femur, and tibia. Radiographic findings (Figs. 148-22 and 148-23) include a thickened skull table; patchy, ill-defined densities of the skull; and poor definition of the cortical margins of the inner ear and internal auditory canal, particularly in the lytic phase of the disease. The bisphosphonates, which inhibit the resorption of bone, constitute the mainstay of medical therapy for symptomatic Paget's disease.[68] Other antipagetic drugs include calcitonin, mithramycin, ipriflavone, and gallium nitrate.

Figure 148-22. Lateral skull radiograph in a patient with Paget's disease. Findings include thickening of the skull table, multiple patchy densities, and platybasia.

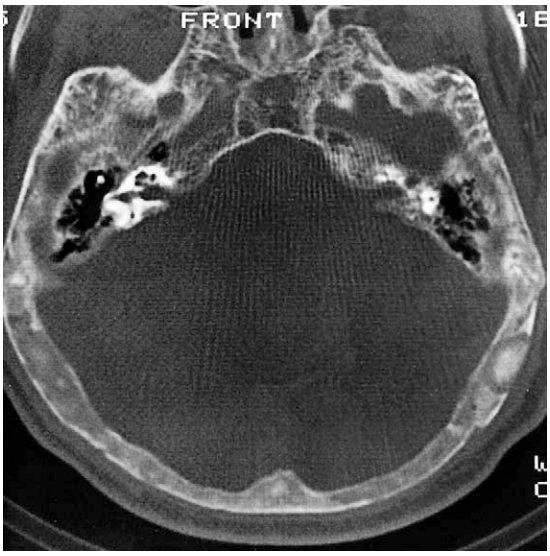

Figure 148-23. Axial CT scan of a 75-year-old man with Paget's disease. There is diffuse expansion of the skull table and involvement of both temporal bones, with patchy demineralization.

Otologic Manifestations

Clinical manifestations include hearing loss, tinnitus, and mild vestibular dysfunction. The facial nerve is spared. Hearing loss occurs in 5% to 44% of patients,[67] and may be sensorineural, mixed, or, rarely, conductive only. Most often, there is a mixed loss, with a descending pattern for bone conduction and relatively flat air conduction thresholds. Hearing losses are progressive and greater than hearing losses of age-matched healthy subjects. Distinguishing features of Paget's disease (compared with otosclerosis, which is the most common differential diagnosis) include a later age of onset (sixth decade), greater SNHL (with a descending pattern), enlarged calvaria, enlargement and tortuosity of the superficial temporal artery and its anterior branches,[67] elevated serum alkaline phosphatase level, and radiographic evidence of pagetic changes in the temporal bones.

None of the many published clinical and histologic reports has clearly identified a consistent pathologic basis for these hearing losses[69]; specifically, the apparent conductive hearing loss is not caused by ossicular fixation, and SNHL is not caused by the compression of cochlear nerve fibers. Attempts at the surgical correction of conductive loss are generally not considered worthwhile. Monsell and colleagues[70,71] reported a statistically significant correlation between the bone mineral density of the cochlear capsule (measured in vivo by quantitative computed tomography [CT]) and the high-frequency pure-tone air-conduction thresholds and the air-bone gap in patients with Paget's disease of the skull. It is unclear whether this finding is only a marker of disease effect, or a phenomenon that is closely related to the mechanism of hearing loss.

Figure 148-24. Pagetic involvement of the temporal bone in a 70-year-old man. The pagetic bone encroaches on the posterior margin *(arrow)* of the internal auditory canal (IAC). The mastoid is largely replaced by pagetic bone (×6.7).

The histopathologic appearance of pagetic bone is variable, and depends on the relative osteoclastic and osteoblastic activity. Typical findings include osteoclastic resorption of marrow-containing bone, with an increase in vascularity and formation of fibrous tissue. New bone formation occurs in an irregular manner and produces its typical mosaic pattern as a result of irregular and curved cement lines (Fig. 148-24). Pagetic bone changes occur in three phases: an initial osteolytic phase, a mixed or combined phase, and an osteoblastic or "burnt-out" phase. In the temporal bone, a fourth phase can be identified, which is the remodeling of inactive pagetic bone into normal-appearing lamellar bone.[69] The disease usually begins in periosteal bone and extends to involve enchondral and endosteal bone.

Osteogenesis Imperfecta

OI (also known as van der Hoeve–de Kleyn syndrome) is a genetically determined disorder of the connective tissue that is characterized clinically by fragile bones that break with minor trauma. Approximately 80% to 90% of patients with OI have mutations of one of the two type I collagen genes (*COL1A1* and *COL1A2*). Many hundreds of unique mutations of *COL1A1* and *COL1A2* have been identified in individuals with OI. The older terms OI congenita and tarda have been replaced by a classification system (OI types I through IV) that is based on clinical features, radiologic criteria, and mode of inheritance.

OI type I has an autosomal dominant mode of inheritance. It is the mildest form and is associated with blue sclerae, nondeforming fractures, and normal stature. Hearing loss is common, occurring in 30% to 50% of cases. OI type II is the most severe form, with multiple fractures occurring in utero and often resulting in stillbirth. This type either is acquired as a sporadic new mutation or is inherited in an autosomal recessive manner. OI type III is characterized by multiple fractures, progressive bone deformity during childhood and adolescence, and sclerae that are bluish at birth but white later in life. Hearing loss occurs in about 50% of individuals. The long bones may be slender and bowed, with abrupt widening near the epiphyses. Kyphoscoliosis, pectus excavatum, weak joints, dental abnormalities, and wormian bone in the skull table are common (Figs. 148-25 and 148-26). The mode of inheritance varies; it may be autosomal dominant, autosomal recessive, or due to a new mutation. OI type IV is a dominantly inher-

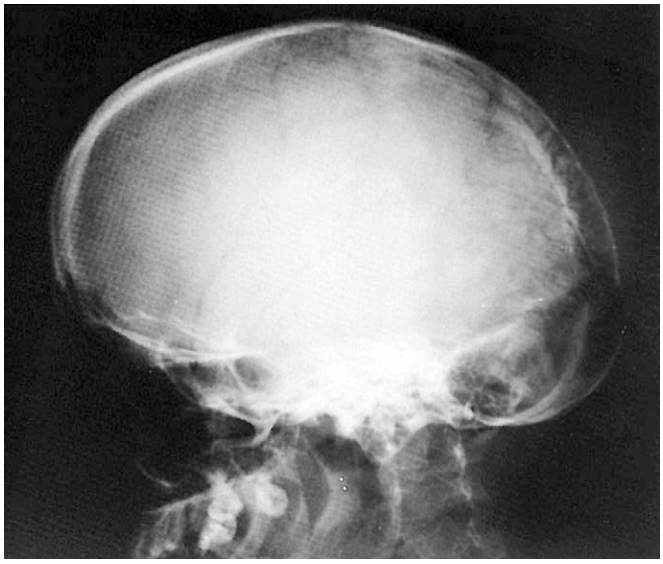

Figure 148-25. Lateral radiograph of the skull in a patient with osteogenesis imperfecta. Wormian bone is seen, particularly in the posterior table.

Figure 148-26. Radiograph of the arm of a patient with osteogenesis imperfecta. There is a pathologic fracture, demineralization of the humerus, and gross abnormalities of the elbow joint.

Figure 148-27. Osteogenesis imperfecta (OI) in a 15-year-old girl. The osteogenesis has replaced the enchondral and periosteal layers of the otic capsule. The neck of the malleus (M) is also involved (×8.5).

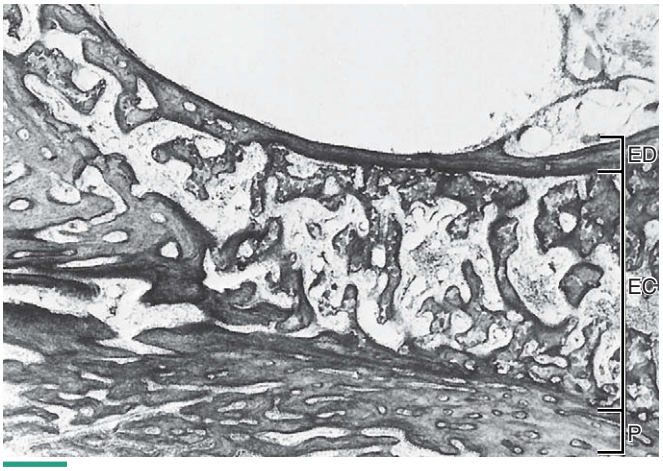

Figure 148-28. Osteogenesis imperfecta involving the otic capsule of a newborn boy. The enchondral (EC) and periosteal (P) layers have been replaced by finely trabeculated bone with an increase in fibrous tissue and vascular spaces. The endosteal layer (ED) is normal (×60).

ited form; it is similar to OI type I except that the sclerae are white (normal). Hearing loss is less common than it is with type I, occurring in 10% to 30% of cases.[72,73]

Management consists of treatment of fractures, orthopedic surgery to correct deformities, use of orthotic devices, and physical and occupational therapy. Bisphosphonate therapy is being increasingly used because these drugs are potent inhibitors of bone resorption and bone turnover.[74] Other therapies under investigation include use of growth hormone and allogeneic bone marrow transplantation.

Otologic Manifestations

Conductive hearing loss and SNHL occur in patients with OI. Severe SNHL has been estimated to occur in approximately 40% of patients, and has a high correlation with gray or white sclerae. Conductive hearing loss usually accompanies blue sclerae, which first becomes apparent by 20 to 25 years of age, and then becomes severe enough to cause the patient to seek medical attention 15 to 20 years later.[75] There is no relationship between hearing loss and frequency or severity of fractures.[73] Some patients with mild OI present with conductive hearing loss similar to that seen with otosclerosis. Early age of onset of hearing loss, high compliance values on tympanometry, a history of fractures after minor trauma in childhood that ceased after puberty, a family history of OI, and blue sclerae are helpful diagnostic clues.

The conductive loss reflects structural changes in the ossicles. Microfractures of the manubrium,[76] fragility of the long process of the incus, and fracture or resorption of the crura of the stapes have been reported.[75,77,78] The stapedial footplate is typically described as thick, soft, and chalklike or granular, and is usually fixed.[79] Rehabilitation can be accomplished by amplification or surgery.[80-82] A stapedectomy can give results similar to those seen with otosclerosis, but the procedure is extremely delicate. Crimping the prosthesis around the incus may cause a pathologic fracture, and a platinum ribbon is preferred to stainless steel wire.[75]

Histopathology of the temporal bone (Figs. 148-27 and 148-28) in cases of OI type II has shown deficient ossification of the endochondral layer of the otic capsule, which shows increased amounts of fibrous tissue with numerous blood vessels. The periosteal layer is often thin and deficient (see Fig. 148-28). The stapes crura are often thin and incomplete. The otopathology in cases of OI type I is very similar if not identical to that seen in cases of otosclerosis.[83,84] The abnormal bone involves the periosteal and endochondral layers of the otic capsule (see Fig. 148-27), and may result in the fixation of the stapes footplate.

Fibrous Dysplasia

Fibrous dysplasia is a benign, chronic, slowly progressive bone disorder of unknown etiology that is characterized by the replacement of normal

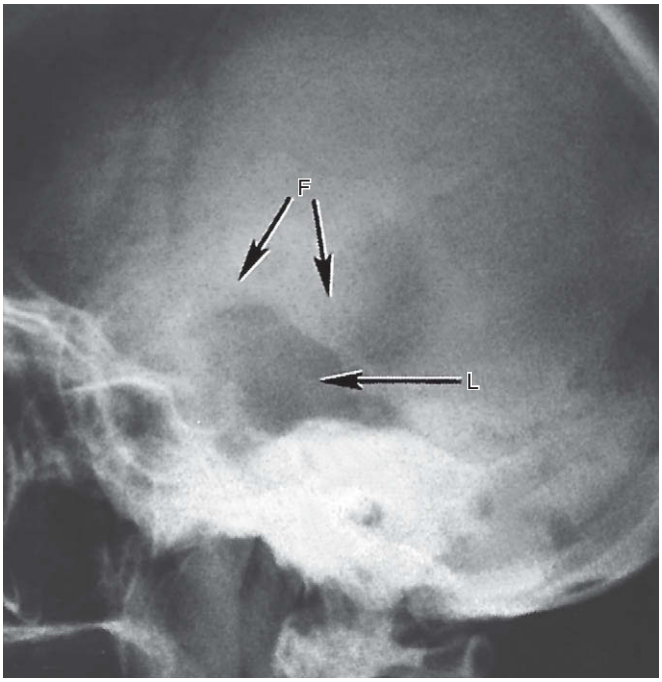

Figure 148-29. Lateral radiograph of the skull of a patient with fibrous dysplasia showing lytic (L) and fibrous (F) phases of disease. Spicules of new bone are responsible for the ground-glass appearance of the fibrous phase.

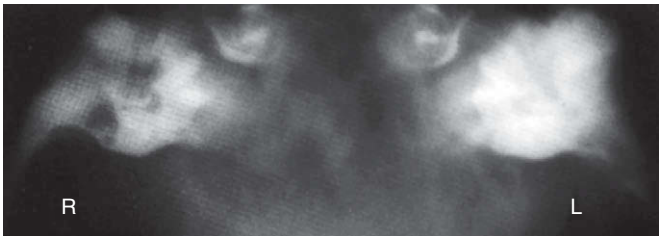

Figure 148-30. Coronal tomographic radiograph of a patient with fibrous dysplasia. New bone formation causes a dense appearance of the involved left temporal bone.

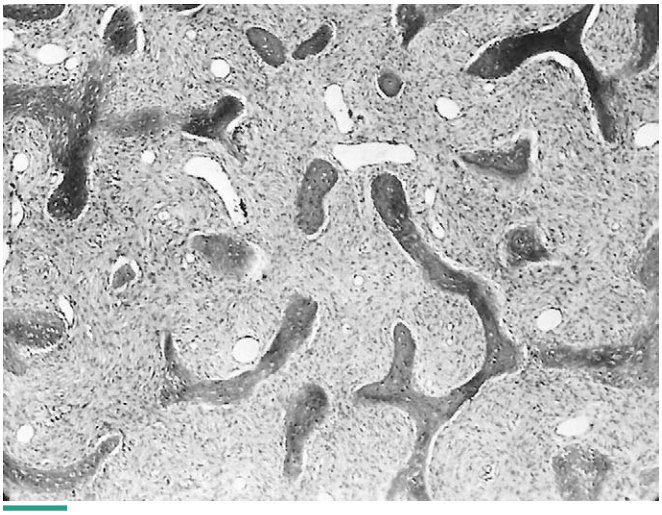

Figure 148-31. Fibrous dysplasia. The irregularly arranged spicules of woven bone in a fibrovascular stroma show a whorled pattern (×64).

bone with a variable amount of fibrous tissue and woven bone. It may occur as part of Albright's syndrome (characterized by multiple bony lesions, abnormal pigmentation, endocrine dysfunction, and precocious puberty in girls), or it may exist alone as the monostotic or polyostotic form. The monostotic form is more common and usually occurs in the skull, ribs, proximal femur, or tibia. In the polyostotic form, skull lesions are seen in more than 50% of patients.

Clinical manifestations of fibrous dysplasia include bony deformity, pathologic fracture, and cranial nerve palsies. The disease starts early in life, usually in childhood; the monostotic form may become quiescent at puberty, whereas the polyostotic form can continue to progress. Sarcomatous transformation can occur, with an estimated incidence of 0.4%.[85] Laboratory findings include elevated serum alkaline phosphatase level in 30% of patients with polyostotic fibrous dysplasia, with usually normal serum calcium and phosphorus levels. The typical radiographic findings include a radiolucent area with a well-defined smooth or scalloped edge and a ground-glass appearance. Areas of increased radiodensity may also be seen (Figs. 148-29 and 148-30). The histopathology of fibrous dysplasia consists of the replacement of normal cancellous bone by a fibrous stroma arranged in a whorled pattern. A variable amount of irregularly arranged spicules of woven bone cause the ground-glass radiographic changes (Fig. 148-31).

Advances have been made toward understanding the cellular and molecular basis of fibrous dysplasia. The lesion is composed of immature mesenchymal osteoblastic precursor cells. There is an activating mutation in the gene that encodes the α subunit of stimulatory G protein.[86] Elevated levels of cyclic adenosine monophosphate result that affect the transcription and expression of multiple downstream genes, which ultimately result in the pathologic lesion.[87] Treatment consists of bisphosphonate therapy and orthopedic surgery for correction of deformities and treatment of pathologic fractures.[88]

Otologic Manifestations

The temporal bone occasionally may be involved in cases of fibrous dysplasia, with about 100 cases reported to date.[89-91] Of these, the monostotic form occurred in 70%, the polyostotic form occurred in 23%, and Albright's syndrome occurred in 7%. All parts of the temporal bone can be involved, but the process generally begins as a painless, slowly progressive swelling that involves the mastoid or squama. Progressive narrowing of the external auditory canal with conductive hearing loss is the most common manifestation and occurs in about 80% of cases. This narrowing may be mistaken for exostoses, but fibrous dysplasia is encountered during the second or third decade of life; at surgery, it is vascular with a characteristic soft, spongy, and gritty consistency. Entrapment of keratin debris medial to a stenotic canal can cause an external canal cholesteatoma. Involvement of the middle ear and ossicles or obstruction of the eustachian tube also can cause conductive hearing loss. Erosion of the fallopian canal with facial nerve paralysis or erosion of the otic capsule with SNHL and vertigo is seen occasionally. An isolated lesion of the mesotympanic bone can simulate a glomus tympanicum tumor and manifest as a reddish mass behind an intact tympanic membrane with pulsatile tinnitus and hearing loss.

Management of fibrous dysplasia is symptomatic. Operative procedures should be limited to biopsy and relief of functional deficits. Stenosis of the external canal often requires surgical removal with canalplasty and meatoplasty. Restenosis as a result of regrowth of fibrous dysplasia occurs, and multiple procedures are sometimes needed. Compared with simple canalplasty, a postauricular canal wall down mastoidectomy with wide canalplasty and skin grafting gives better results, with long-term canal patency. Radiotherapy is contraindicated because of an increased rate of malignant degeneration.[85] Long-term follow-up is indicated because of the potential for facial nerve involvement and for the progression of conductive hearing loss to profound SNHL.[90]

Osteopetroses

Osteopetroses are rare genetic disorders that are characterized by greatly increased bone density.[92-94] Osteopetroses result from the

defective function of osteoclasts, which results in a failure of normal bone resorption while normal bone formation by osteoblasts continues, with deposition of excessive mineralized osteoid and cartilage. Four types of osteopetrosis have been defined, although patients with atypical symptoms are frequent, which suggests that there are additional types.

Malignant osteopetrosis is an autosomal recessive form that manifests in infancy and is rapidly progressive, with a high mortality rate. Many cases have been shown to be due to mutations in the gene encoding for the TCIRG1 subunit of the vacuolar proton pump within osteoclasts. The disease is characterized by the encroachment of bone marrow that leads to anemia, thrombocytopenia, hepatosplenomegaly, increased susceptibility to infection, and encroachment of the neural foramina, which causes neural degeneration. Optic atrophy, facial paralysis, SNHL, hydrocephalus, and mental retardation are common, and death usually occurs during the first or second decade of life. The only effective treatment is bone marrow transplantation. Another type of autosomal recessive osteopetrosis is due to a mutation in the gene for cytoplasmic carbonic anhydrase II. This type is very rare (approximately 50 cases have been reported), and it is associated with distal renal tubular acidosis.

Autosomal dominant type II osteopetrosis (also known as Albers-Schönberg disease and marble bone disease) is the most frequent type. It is associated with normal life expectancy and may be asymptomatic. Many cases have been shown to result from mutations in the *CLCN7* chloride-channel gene.[92] Clinical manifestations include an increased incidence of fractures (osteopetrotic bone is fragile despite its solid appearance); osteomyelitis of the mandible from dental infection; progressive enlargement of the head and mandible; clubbing of the long bones; and cranial neuropathies such as progressive optic atrophy, trigeminal hypesthesia, recurrent facial paralysis, and SNHL. Patients may have syndactyly of the fingers or toes and abnormal fingernails; these abnormalities can aid the physician in making the clinical diagnosis. Radiographic evaluation reveals a great increase in the density of all bones.

Autosomal dominant osteopetrosis type I is an extremely rare type (it has been reported in only three families), and it seems to be linked to a locus on chromosome 11q12-13.[94] Patients with this type of osteopetrosis are often asymptomatic, but some have pain and hearing loss. This is the only type of osteopetrosis that is not associated with an increased rate of fractures.

Otologic Manifestations

The endochondral layer of the otic capsule and ossicles in the temporal bones of infants and children with the malignant recessive form of osteopetrosis consist mainly of dense calcified cartilage.[95] The mastoid is not pneumatized, and the stapes persists in fetal form (Figs. 148-32 and 148-33). The inner ears appear normal. Dehiscence of the tympanic segment of the facial nerve (often with herniation of the nerve into the oval window niche) has been a consistent finding.[95-97] There seems to be no observable nerve compression, however. These children often have recurrent episodes of acute otitis media, serous otitis media, stenosis of the external auditory canal, conductive hearing loss or SNHL, and unilateral or bilateral facial nerve paralysis.[98,99]

In the more benign adult (autosomal dominant type II) form, the temporal bone is markedly sclerotic, with obliteration of the mastoid air cells and a narrowing of the eustachian tube and the external and internal auditory canals. Exostotic overgrowth of the periosteal bone surrounding the tympanic cavity can occur (Fig. 148-34), with ankylosis of the ossicles and obliteration of the oval and round window niches (Fig. 148-35). These changes explain the common finding of conductive hearing loss. SNHL also occurs, but the inner ears appear normal. Narrowing of the eustachian tube predisposes a patient to serous otitis media.[100] Recurrent acute facial nerve paralysis that is similar to Bell's palsy (involving one or both sides) is a frequent manifestation. There is a tendency toward progressive residual weakness with each episode. Radiographic studies should be performed in any child or young adult with recurrent facial nerve paralysis to determine the possibility of osteopetrosis. Total decompression of the facial nerve has been advocated to ameliorate recurrent palsies.[101,102]

Figure 148-32. Recessive osteopetrosis of the temporal bone of a 15-month-old boy. The endochondral layer of the otic capsule and stapes is composed of calcified cartilage (×12.3).

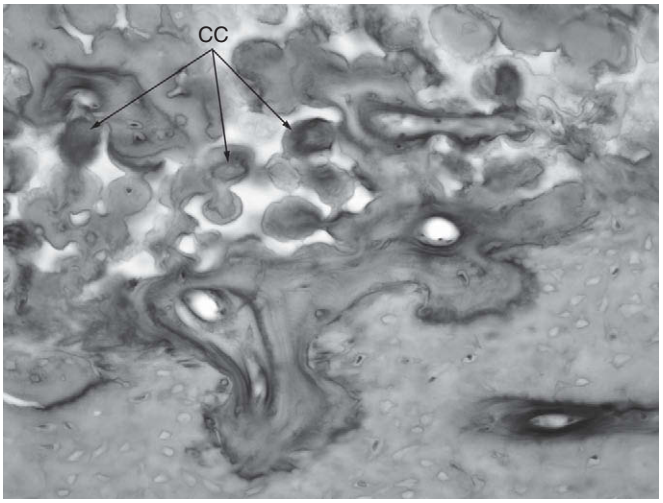

Figure 148-33. Higher magnification of the temporal bone seen in Figure 148-32. The calcified cartilage (CC) of endochondral bone appears as densely staining, round-to-ovoid profiles (×396).

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica (von Recklinghausen's disease) is a bone lesion caused by excess parathyroid hormone, and it is characterized in classic cases by osteoclastic bone resorption, marrow fibrosis, bone cysts, bone pain, and fractures. In most cases, it is caused by primary hyperparathyroidism, which is usually due to an adenoma. Other manifestations relate to hypercalcemia and hypercalciuria. Although the temporal bone can be affected in this disorder,[103,104] it is very rare in clinical practice. The otic capsule is replaced by abnormal bone composed of loosely arranged trabeculae of varying size and shape that are interspersed with marrow spaces that contain fibrous tissue. SNHL has been attributed to osteitis fibrosa involving the temporal bone.

Storage and Metabolic Diseases

Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are a group of diseases that are caused by an inherited deficiency of one of several lysosomal enzymes that degrade mucopolysaccharides. As a result, undergraded mucopolysaccharides accumulate intracellularly, which gives rise to large cells

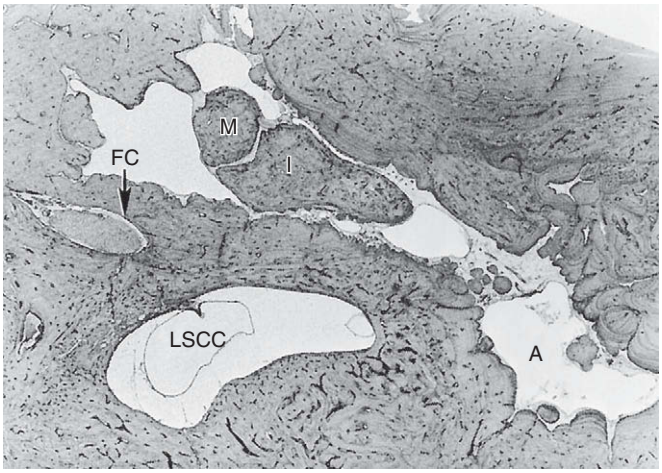

Figure 148-34. Osteopetrosis in a 30-year-old man showing overgrowth of dense lamellar bone around the epitympanum, with jamming of the malleus (M) and incus (I). The facial nerve canal (FC) is narrowed (×9). A, antrum; LSCC, lateral semicircular canal.

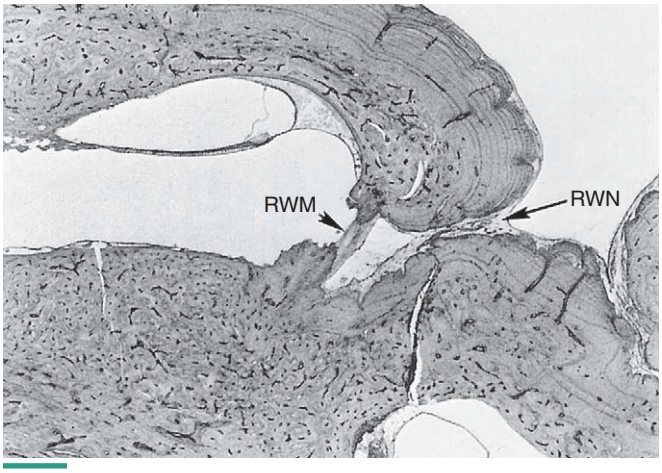

Figure 148-35. Osseous obliteration of the round window niche (RWN) of the same patient as seen in Figure 148-34. There is fluid in the niche adjacent to the round window membrane (RWM) (×18).

with vacuolated cytoplasm. Ten enzyme deficiencies have been identified to date and are classified into seven types or syndromes. All are transmitted as autosomal recessive traits except for Hunter's syndrome (MPS II), which is X-linked recessive. Diagnosis is made either by an assay of the specific enzyme in plasma or serum or by tissue culture using fibroblasts or leukocytes. Management is mainly supportive and symptomatic. MPS are potentially amenable, however, to enzyme replacement therapy and to procedures such as bone marrow transplantation or gene transfer.[105]

Hurler's syndrome (MPS I) is caused by a deficiency of L-iduronidase that leads to the accumulation of heparan sulfate and dermatan sulfate. Clinical manifestations include corneal clouding, abnormal facies, hepatosplenomegaly, mental retardation, dysostosis multiplex, joint stiffness, and hernias. Radiographic features include a broadening and shortening of long bones; hypoplasia and fractures of the lumbar vertebrae, causing kyphosis; and enlargement of the sella turcica. Death usually occurs during the first decade of life.

Hunter's syndrome (MPS II) results from a deficiency of iduronate-2-sulfatase, which leads to an accumulation of heparan sulfate and dermatan sulfate. The syndrome is similar to Hurler's syndrome, but corneal clouding is not seen. Survival to adulthood may occur.

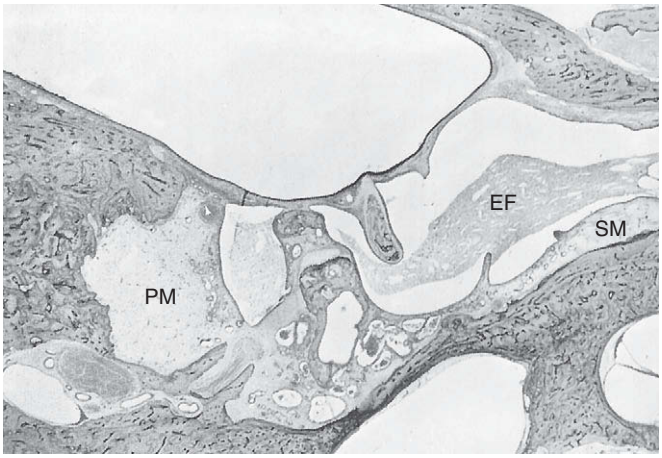

Figure 148-36. Hunter's syndrome in a 24-year-old man. The middle ear contains an effusion (EF) as a result of eustachian tube dysfunction. The submucosa (SM) is thickened, and the posterior mesotympanum (PM) contains unresorbed mesenchymal tissue (×11).

Morquio's syndrome (MPS IV) is attributable to a deficiency of *N*-acetylgalactosamine-6-sulfatase or of β-galactosidase, resulting in excessive urinary excretion of keratan sulfate. Clinical manifestations include spondyloepiphyseal dysplasia. Spinal cord compression caused by hypoplasia of the odontoid process and cervical dislocation are common and may be the cause of death.

Otologic Manifestations

Hearing loss in MPS is usually conductive and sensorineural. The conductive component is attributable to serous otitis media as a result of dysfunction of the eustachian tube and chronic thickening of the mucosa of the middle ear (Fig. 148-36). Unresorbed mesenchyme has been described in the middle ear and mastoid in Hurler's syndrome.[106] Large cells with vacuolated cytoplasm have been described in the middle ear mucosa in both Hunter's syndrome[107] and Hurler's syndrome.[108] The cause of SNHL is unknown, but it has been attributed to abnormal metabolism within neural elements.[107-110]

Gout

Gout is a metabolic disease that results from the deposition of crystals of monosodium urate within joint spaces and cutaneous structures.[111,112] The crystals stimulate production of interleukin-1 and other cytokines by monocytes and macrophages, leading to inflammation and tissue damage. Patients with gout invariably have hyperuricemia (serum urate level >7 mg/dL). Genetic factors influence the renal clearance of uric acid and may be involved in the familial incidence of hyperuricemia and gout. More recent studies have implicated loci on the X chromosome and on chromosome 16 in the pathogenesis of hyperuricemia.[113] Other risk factors for gout include alcohol use, exposure to lead, diuretics, hypertension, and renal insufficiency.

The clinical manifestations of gout include acute gouty arthritis, aggregates of crystal in connective tissue (tophi), urate urolithiasis, and, rarely, gouty nephropathy. Laboratory abnormalities include hyperuricemia, leukocytosis, and an elevated erythrocyte sedimentation rate. The diagnosis of gout depends on the identification of urate crystals within joint fluid or within tophi under polarized light. The treatment of acute gouty arthritis includes bed rest, nonsteroidal anti-inflammatory agents, and colchicine. Uricosuric drugs such as probenecid are useful for patients with hyperuricemia as a result of the decreased renal clearance of uric acid. Xanthine oxidase inhibitors such as allopurinol are useful if excess production of uric acid is the basis of the hyperuricemia.

Otologic Manifestations

Tophaceous deposits can occur in multiple areas in the head and neck.[111] The helical rim of the pinna is the classic site of

involvement. Such tophi are usually asymptomatic and do not require any treatment.

Ochronosis

Ochronosis is a rare disease that is caused by an inherited lack of the enzyme homogentisic acid oxidase. The presence of homogentisic acid in urine is called *alkaptonuria*. The result of this inborn error of metabolism is the deposition of a dark pigment in tissues that are rich in collagen. Patients often present with symptoms and signs during the third decade of life. Manifestations include ochronotic arthropathy, ocular and cutaneous pigmentation, obstruction of the genitourinary tract by ochronotic calculi, and cardiovascular manifestations as a result of ochronosis affecting the aortic valve. There is no effective management or cure for the condition. Treatment is based on symptomatic therapy.[114]

Otologic Manifestations

Ochronosis has manifestations in the external ear; cartilage is a site of predilection for the deposition of the pigment of ochronosis. Blue or mottled-brown macules can appear on the pinna and in other areas of the head and neck, including the nose, buccal mucosa, tonsils, pharynx, larynx, and esophagus.

Collagen Vascular and Autoimmune Diseases

The ear may be a target organ in several systemic (non–organ-specific) diseases that are thought to be autoimmune in nature (e.g., polyarteritis nodosa, relapsing polychondritis, Cogan's syndrome), or it may be the sole target of an immune-mediated (organ-specific) inner ear process that causes progressive SNHL with or without vestibular dysfunction. The latter was described by McCabe,[115] although the theoretical concept was proposed by Lehnhardt in 1958.[116] Histopathologic findings in the temporal bone in both groups of disorders are similar and include destruction and degeneration of the inner ear tissues; scattered infiltrates of lymphocytes, plasma cells, and macrophages; focal or diffuse proliferation of fibrous tissue and bone; and a variable degree of endolymphatic hydrops.[117] The otologic manifestations of these diseases are discussed in Chapter 153 and in published reviews.[118-120]

Immunodeficiency Disorders

Infections of the middle ear and mastoid can occur as part of the clinical spectrum of congenital and acquired immunodeficiency disorders. Occasionally, otologic manifestations may constitute the presenting feature of the disease.

Primary or Congenital Immunodeficiency Disorders

Primary or congenital immunodeficiency disorders constitute a diverse group of conditions that can be subdivided into four broad categories. Humoral immunodeficiency disorders are characterized by the inability to produce antigen-specific antibodies. Patients commonly have recurrent and chronic respiratory tract infections owing to high-grade extracellular bacteria, such as *Haemophilus influenzae, Streptococcus pneumoniae,* and *Streptococcus pyogenes*. Diagnosis is based on the analysis of immunoglobulin subtypes and the assessment of specific antibody production. Management is symptomatic with appropriate antibiotics and replacement therapy with immune human serum globulin. Individual syndromes within the group are classified according to the type of immunoglobulin deficiency, the mode of genetic transmission, and the specific clinical features, including X-linked infantile agammaglobulinemia (Bruton's), autosomal recessive agammaglobulinemia, acquired agammaglobulinemia (common variable immunodeficiency), X-linked immunodeficiency with hyper-IgM, and selective IgA deficiency.

Cellular immunodeficiency disorders exhibit partial or severe deficiencies in the function of T lymphocytes. Patients with these disorders typically have recurrent infections owing to intracellular, low-grade, opportunistic pathogens including viruses, fungi, protozoa, and some bacteria. Diagnosis is based on quantitative and qualitative tests of T-cell function, and there is often an associated deficiency of antibody production. Syndromes include thymic hypoplasia (DiGeorge's syndrome), Wiskott-Aldrich syndrome, ataxia-telangiectasia, chronic mucocutaneous candidiasis, hyperimmunoglobulinemia E (Job's syndrome), and severe combined immunodeficiency.

Disorders of phagocyte function are primarily disorders of neutrophils that leave patients vulnerable to pyogenic bacterial or fungal infections of varying severity and chronicity. This group includes neutropenia, which may be inherited or acquired; if severe, it can cause fulminant sepsis, chemotactic defects that result in pyogenic respiratory infections, and microbicidal disorders such as chronic granulomatous disease and Chédiak-Higashi syndrome. Therapy includes antibiotics, neutrophil transfusions, and bone marrow transplantation.

Complement system defects include deficiencies of the individual components or of the regulatory proteins. Clinical features vary with the type of defect and include recurrent *Neisseria* infections (C5, C6, C7, and C9 deficiency), recurrent staphylococcal infections (C3b inactivator deficiency), lupus-like syndromes (C1, C4, and C2 deficiency), and angioedema (C1 esterase-inhibitor deficiency). All complement defects are inherited (generally autosomal recessive); management is symptomatic and supportive.

Major advances in the understanding of the genetic basis and molecular mechanisms of immunodeficiency disorders have occurred.[121,122] As a result, most of the more than 100 primary immunodeficiency diseases can be diagnosed by molecular techniques. These molecular approaches have also resulted in significant insight into the pathophysiology of the various conditions, which has permitted early diagnosis of many of these conditions by neonatal screening of umbilical cord blood. The immunodeficiency syndromes have also played a major role in the development of human gene therapy, which is being actively pursued in many centers.

Otologic Manifestations

Otologic disease has been described in all four categories of immunodeficiency disorders. Humoral immune defects result in recurrent and persistent acute and serous otitis media. Chronic suppurative otitis media (with all its attendant complications) may develop and is often refractory to medical and surgical therapy.[123,124] A subgroup consists of children with selective IgG subclass 2 deficiency who have been shown to be susceptible to recurrent episodes of otitis media.[125] DiGeorge's syndrome (T-cell deficiency as a result of thymic hypoplasia) can manifest varying degrees of anomalies of the external, middle, and inner ears with conductive, sensorineural, or mixed hearing losses[126]; there is also a high incidence of Mondini's dysplasia in these ears. Recurrent episodes of acute and chronic otitis media have also been described with neutrophil chemotactic defects,[127] microbicidal disorders (chronic granulomatous disease),[128] and complement system defects.[129]

Acquired Immunodeficiency Syndrome

AIDS, which was first recognized in 1981, is caused by HIV. HIV is lymphotropic and attacks primarily T-helper lymphocytes, rendering the patient susceptible to numerous opportunistic infections (see Chapter 15).

Otologic Manifestations

Otologic manifestations are infrequent in patients with AIDS except in children, in whom serous otitis media is common.[130] When otologic disease does occur, the microbiology is similar to that of non-AIDS patients, with the addition of unusual opportunistic organisms (protozoa, fungi, viruses, and mycobacteria).

Middle ear and mastoid manifestations include acute otitis media, acute mastoiditis, serous otitis media, and bullous myringitis; the severity of these infections varies and depends on the immune status of the patient. External ear disease such as otitis externa and Kaposi's sarcoma can also occur. Tissue diagnosis by biopsy or tympanocentesis is indicated to identify the causative agent before initiating therapy.

Pneumocystis jiroveci is an unusual opportunistic protozoan that is a common cause of middle ear and external ear disease in patients with AIDS. Subcutaneous masses in the external canal or aural polyps arising from the canal, the tympanic membrane, or the mesotympanum can result in conductive hearing loss, otorrhea, or otalgia. Presumed routes of infection include hematogenous spread from another source (e.g., pulmonary), ascending infection through the eustachian tube from

pharyngeal colonization, or airborne transmission of the aerosolized organism directly to the external canal.[131,132] A biopsy specimen shows the characteristic organism, and the infection responds to treatment with oral trimethoprim-sulfamethoxazole. Otologic disease resulting from *P. jiroveci* may be the only and the initial presenting symptom of AIDS.[131-133] Inner ear symptoms such as SNHL (including fluctuating and sudden hearing loss), vertigo, and tinnitus can occur.[134,135] SNHL is ascribed to various causes, including otosyphilis, cryptococcal meningitis, tuberculous meningitis, central nervous system toxoplasmosis, and ototoxic medication.[133,136] HIV is neurotropic and may itself be the primary cause of SNHL. The facial nerve can be involved by herpes zoster (Ramsay Hunt syndrome).

In a study of 49 temporal bones from 25 patients with AIDS, Michaels and colleagues[137] found low-grade otitis media in 60% of cases, severe otitis media in 20%, cytomegalovirus inclusion-bearing cells in the inner and middle ears in 24%, labyrinthine cryptococcosis in 8%, and Kaposi's sarcoma deposit in the eighth cranial nerve in 4%. They concluded that the ear is no less susceptible to AIDS-associated diseases than any other organ, and that it is particularly prone to cytomegalovirus infection. The spectrum of otologic manifestations and their pathophysiologic mechanisms in AIDS is most likely to expand as more clinical and histopathologic data accrue.

Genetically Determined Defects

Numerous syndromic disorders secondary to genetic defects may have otologic manifestations consisting of hearing loss or vestibular dysfunction or both. Examples include syndromes caused by mutations in single genes (autosomal or sex-linked), mutations in mitochondrial genes, or chromosomal abnormalities. Such disorders are beyond the scope of this chapter, and the reader is referred to Chapter 147 or other sources.[138]

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CHAPTER ONE HUNDRED AND FORTY-NINE

Sensorineural Hearing Loss in Adults

H. Alexander Arts

Key Points

- Sensorineural hearing loss (SNHL) is one of the most common clinical disorders, and is associated with a multitude of etiologies.
- Because of the wide range of genetic, infectious, vascular, neoplastic, traumatic, toxic, iatrogenic, degenerative, and immunologic and inflammatory pathologies that can affect the cochlea, a systematic approach to assessment is crucial to identifying the responsible etiology. Audiologic, serologic, blood chemistry, and radiologic testing can be used strategically for a cost-effective approach to diagnosis of SNHL.
- SNHL results from cochlear hair cell or auditory nerve dysfunction. Psychophysical abnormalities that result from impaired auditory physiology combine to challenge effective listening.
- Sudden SNHL is a clinical syndrome with a lengthy differential diagnosis. Prompt assessment and management of sudden SNHL may offer the opportunity to reverse or ameliorate the hearing loss using more recently developed therapeutic protocols.

Sensorineural hearing loss (SNHL) is an extremely common disorder, with a spectrum of effect ranging from an almost undetectable degree of disability to a profound alteration in the ability to function in society. Because its onset is frequently insidious, and because it is frequently accompanied by subtle compensatory strategies, hearing loss is frequently overlooked by physicians and patients. The auditory system is complex, depending on the performance of many different systems for its continued function. Normal hearing function depends on the mechanical integrity of the middle ear mechanism and cochlear duct, micromechanical and cellular integrity of the organ of Corti, homeostasis of the inner ear biochemical and bioelectric environment, and adequate function of the central nervous system (CNS) pathways and nuclei. These depend on normal vascular, hematologic, metabolic, and endocrine function. As a result, disease of almost any human physiologic system has the potential to affect auditory function.

This chapter addresses the clinical evaluation, differential diagnosis, natural history, and pathogenesis of SNHL in adults, and provides a systematic review of the broad array of etiologies of SNHL. There is inevitably some overlap with other chapters in this text, and in these cases the reader is referred elsewhere for a more detailed discussion.

Clinical Evaluation of the Patient with Hearing Loss

History

Evaluation of patients with sudden SNHL begins with a careful history. The degree of loss from the patient's perspective and its laterality (unilateral or bilateral) and chronicity (sudden onset, rapidly progressive, slowly progressive, fluctuating, or stable) should be assessed. Patients should be questioned for associated symptoms, such as tinnitus, vertigo, dysequilibrium, otalgia, otorrhea, or headache, and ophthalmologic or neurologic complaints should be sought. A sensation of aural fullness or pressure may be present, and may be the patient's only complaint.

A thorough medical history should be obtained with particular attention to cardiovascular, rheumatologic, endocrine, neurologic, and renal disorders, and to any exposure to potentially ototoxic drugs. Surgical history should be evaluated, and a history of skull trauma, penetrating trauma to the ear canal, and compressive force applied to the ear canal (e.g., slap injury) should be queried. The patient's history of exposure to noise, occupational and otherwise, should be specifically addressed. The type of noise, its estimated level, duration of exposure, and use of hearing protection should be documented. Patients and physicians frequently underestimate the importance of a patient's occupational noise exposure, and avocational exposures, such as hunting and power tool use. Finally, family history with regard to hearing loss is particularly important and frequently overlooked.

Physical Examination

Physical examination of the ears in patients with SNHL is frequently unrevealing. The whisper test and tuning fork testing can be used to estimate the degree of hearing loss and to determine whether the loss is predominantly conductive or sensorineural. With the exception of these findings, no abnormality generally is seen in patients with SNHL. Otoscopic examination of the ears should exclude the possibility of acute or chronic otitis media. Neoplasm within the middle ear may rarely be noted. Pulsatile tinnitus may be heard by the examiner with a standard or Toynbee stethoscope. Other cranial nerve abnormalities and stigmata of associated systemic disease or hereditary abnormalities should be specifically sought. The nonotologic portion of the physical examination is more likely to reveal positive findings.

Audiometric Testing

Only a brief discussion of audiometric testing is presented here. Conventional audiometric testing is discussed more thoroughly in Chapter 133, and electrophysiologic testing is addressed in Chapter 134.

Audiometric testing serves to verify and to quantify the degree of hearing loss. Air-conduction, bone-conduction, and speech audiometry and tympanometry constitute the minimum test battery in patients with suspected SNHL. Bone-conduction and air-conduction pure-tone audiometry helps to determine the type of hearing loss (conductive, sensorineural, or mixed). Speech audiometry verifies the pure-tone audiometric results. Speech discrimination testing with assessment of the performance-intensity function helps to define further the nature of the SNHL (cochlear vs. retrocochlear) and provides essential prognostic information regarding the potential benefits of amplification. Tympanometry with acoustic reflex testing verifies the conductive or sensorineural nature of the hearing loss and provides additional clues regarding etiology. Tympanometry can be especially helpful in excluding the possibility of a conductive component in patients with profound losses or bilateral losses in the presence of a masking dilemma.

Basic audiologic tests also can provide essential diagnostic clues as to whether SNHL is cochlear or "retrocochlear" in origin. By "retrocochlear," we mean a lesion proximal to the cochlea, the most common retrocochlear lesion being vestibular schwannoma. The examiner should have a high degree of suspicion for retrocochlear etiologies when there is asymmetry of loss, abnormally reduced or asymmetric speech discrimination, abnormal performance-intensity relationships ("rollover") on speech discrimination testing, or acoustic reflex abnormalities. Other cranial nerve findings, asymmetric tinnitus, or vestibular complaints (even if mild) should increase the level of suspicion.

Auditory brainstem response (ABR) testing is useful in evaluating the possibility of a retrocochlear etiology, and for establishing thresholds in difficult-to-test patients (young children or malingerers). In the past, the ABR was believed to be a highly sensitive test for the presence of a retrocochlear lesion. It is less commonly used in this role today because of reduced sensitivity in patients with small vestibular schwannomas—tumors that are readily detected with the high accuracy offered by magnetic resonance imaging (MRI).[1-3] New modifications of the ABR may increase this study's sensitivity.[4]

Electrocochleography differs from ABR testing in that the reference electrode is placed closer to the cochlea (on or close to the tympanic membrane or promontory). This allows measurement of the cochlear microphonic potential, the summating potential, and the auditory nerve action potential. Wave I of the ABR corresponds to the action potential of electrocochleography. Approximately two thirds of patients with classic Meniere's disease have an elevated summating potential-to-action potential ratio. It is believed that such a finding suggests the presence of endolymphatic hydrops.[5,6] Electrocochleography can also be useful in patients in whom wave I of the ABR is weak or not present because the location of the reference electrode inherently enlarges wave I.

Otoacoustic emissions consist of acoustic energy generated by the cochlea and recorded with a microphone in the external auditory canal. These emissions can be spontaneous in onset or, more commonly, evoked by an acoustic stimulus delivered to the ear canal. If the acoustic stimulus consists of a transient sound (a click or tone pip), the resulting emission is termed a transient-evoked otoacoustic emission. If the stimulus consists of continuous pure tones of two separate frequencies (F1, F2), the resulting emission is a continuous tone of frequency 2F1-F2, and is termed a distortion product otoacoustic emission. Otoacoustic emissions are clearly generated within the cochlea and are believed to be a by-product of the "cochlear amplifier," which is dependent on outer hair cell function. They depend highly on the physiologic state of the cochlea and, if present, suggest normal cochlear function. Otoacoustic emissions are rarely present with hearing thresholds greater than 30 dB HL, regardless of etiology. In addition, for an otoacoustic emission to be present, the middle ear mechanism must be functioning normally because the stimulus and the response must traverse the middle ear. The presence of an otoacoustic emission in an ear with SNHL suggests a retrocochlear etiology or possible pseudohypacusis. Because these etiologies are extremely rare in neonates, otoacoustic emissions also have been useful in neonatal hearing screening programs.

Vestibular Testing

Vestibular testing can be a useful adjunct in the evaluation of SNHL in selected patients. Evidence of ipsilateral peripheral vestibular hypofunction in a patient with unilateral progressive SNHL suggests the presence of a retrocochlear lesion.

Laboratory Testing

Laboratory testing rarely proves to be helpful in determining the etiology of SNHL. In most patients, either the fluorescent treponemal antibody absorption test or the microhemagglutination test for *Treponema pallidum* should be obtained because the prevalence of syphilis is relatively high, it is frequently asymptomatic, it is important to manage, and it is a potentially treatable cause of SNHL. The Venereal Disease Research Laboratory (VDRL) test is not helpful in this regard because it frequently becomes negative with inadequate management, in the latent phase of the disease, or in neurosyphilis. Routinely obtaining hematologic, metabolic, and endocrine studies does not seem to be necessary or cost-effective. Similarly, routine screening for autoimmune disorders does not seem warranted. If these disorders are clinically significant, they typically are apparent from the history and physical examination. In addition, there seems to be no clear relationship between the results of any of these tests and the presence of autoimmune hearing loss.

Radiographic Testing

Radiographic imaging is warranted in selected patients with SNHL. MRI with gadolinium enhancement is currently the gold standard in evaluating potential retrocochlear hearing losses. The role of MRI versus ABR testing in this regard is controversial. It is clear, however, that MRI with gadolinium is much more sensitive than ABR for diagnosis of small lesions.[1-3] Selective T2-weighted fast spin-echo MRI may be almost as sensitive as gadolinium-enhanced standard MRI and is less expensive.[7] Computed tomography (CT) is useful in patients with suspected labyrinthine anomalies, such as large vestibular aqueduct syndrome or Mondini dysplasia. CT may also be useful in patients with suspected labyrinthine fistula or temporal bone fractures. High-resolution CT with reformatted images in the plane of, and perpendicular to, the semicircular canals is the study of choice for showing semicircular canal dehiscence syndrome.[8]

Etiology of Sensorineural Hearing Loss

Developmental and Hereditary Disorders

Hereditary Disorders of Adult Onset

The discussion of hereditary causes of hearing loss in this chapter is limited to the more common etiologies primarily presenting in adulthood. Hereditary factors frequently play a role in SNHL, and research in this area is expanding rapidly. For a complete categorization and review of these disorders, the reader is referred to an excellent and encyclopedic work by Toriello and colleagues.[9]

Nonsyndromic Hereditary Hearing Loss

Most hereditary SNHL is not associated with other hereditary abnormalities. Hereditary hearing loss without associated abnormalities is much more common than generally appreciated and frequently is overlooked. It is likely that genetic factors play a role in presbycusis and in susceptibility to noise-induced hearing loss (NIHL).[10-13] Distinct patterns of hereditary hearing loss transmitted in autosomal-dominant, autosomal-recessive, and X-linked fashion have been well described. Recessive or dominant isolated SNHL can be progressive or static, and may be congenital, present first at birth, manifest in childhood, or manifest in adulthood. Approximately 90% of inherited SNHL is recessive.

Waardenburg's Syndrome

Waardenburg's syndrome is transmitted in an autosomal-dominant fashion and consists of a constellation of findings, including (1) dysto-

Figure 149-1. Ocular findings in Waardenberg's syndrome. Note the dystopia canthorum, the broad nasal root, the confluence of the eyebrows, and the heterochromia iridis.

pia canthorum (lateral displacement of the medial canthi), (2) broad nasal root, (3) confluence of the medial portions of the eyebrows, (4) partial or total heterochromia iridis, (5) a white forelock, and (6) SNHL (Fig. 149-1). There is extreme variability in the expression of this disorder, and the hearing loss can vary from profound to none at all. The hearing loss can be unilateral or bilateral, and can be associated with vestibular abnormalities.

Alport's Syndrome

Alport's syndrome is characterized by interstitial nephritis, SNHL, and, much less commonly, ocular manifestations.[14] This disease is unique because it is more common in women, but typically is much more severe in men. In the past, it has been thought to be transmitted in an autosomal-dominant fashion. It is now clear that there is significant genetic heterogeneity. Hearing loss is progressive and variable, usually beginning in the second decade of life. By age 20 to 40 years, 50% to 75% of men develop end-stage renal failure.

Usher's Syndrome

Usher's syndrome consists of the combination of retinitis pigmentosa and SNHL, with or without vestibular deficits. Three distinct groups have been defined. Usher's syndrome type I accounts for 85% of all cases, and is characterized by profound congenital hearing loss, absent vestibular response, and the development of retinitis pigmentosa by age 10 years. Type II accounts for 10% of cases, and is characterized by congenital moderate to severe stable hearing loss, normal vestibular responses, and onset of retinitis pigmentosa in patients 17 to 23 years old. Type III is typified by progressive hearing loss with onset in childhood or late adolescence and variable onset of retinitis pigmentosa. Approximately 5% of patients have type III. The disease is transmitted in an autosomal-recessive fashion, and it is estimated that 1 of 100 people is a carrier of the trait.

Inner Ear Anomalies

Many patterns of dysplasia of the inner ear have been described, and most have been associated with SNHL. These dysplastic patterns of development may be inherited, sporadic, or the result of chromosomal abnormalities. Commonly used descriptive terms for these dysplasias include Scheibe dysplasia (cochleosaccular dysplasia, involving membranous labyrinth only), Mondini dysplasia (dysplasia of bony and membranous labyrinth), and common cavity deformity (otocyst-like labyrinth with no cochlea or clear vestibular organs). Patterns of labyrinthine dysplasias form a spectrum with all manner of anomalies and patterns of hearing loss.[15]

Large Vestibular Aqueduct Syndrome

One form of inner ear dysplasia is unique because it has been associated with delayed onset of SNHL. An enlarged vestibular aqueduct is commonly seen in combination with other inner ear dysplasias, but more recently, it has been noted as an isolated finding in many ears. These patients may have any level of hearing from normal to a profound loss. Frequently, both ears are affected, and the losses are asymmetric. Fluctuation of hearing is common and usually affects one ear at a time; this may manifest as anacusis in one ear with fluctuation in the other. There is often evidence of a conductive component to the low-frequency portion of hearing loss. In patients who have been followed over time, a progressive stepwise loss has been noted in many.[15] This syndrome

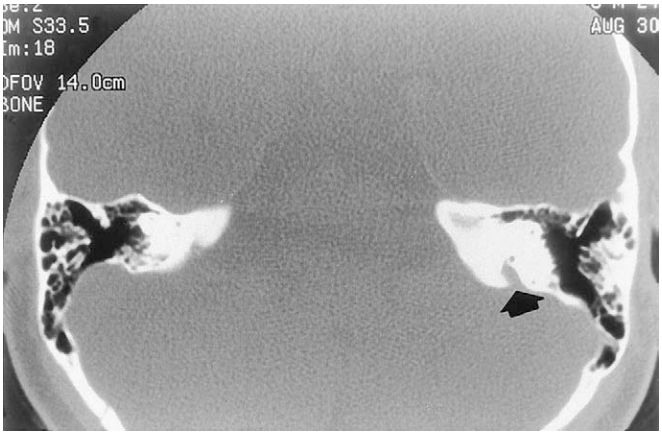

Figure 149-2. CT scan of the temporal bone showing the large vestibular aqueduct syndrome. *Arrow* indicates the enlarged vestibular aqueduct.

has been found to be familial in some cases, and probably occurs much more commonly than generally appreciated.[16] It is seen in isolation, as part of the Mondini malformation, and in patients with branchio-oto-renal syndrome[17] and Pendred syndrome.[18] It is well shown on high-resolution CT imaging of the temporal bone (Fig. 149-2).

Infectious Disorders

Infectious disease is a leading cause of SNHL in children and less so in adults. Infectious etiologies causing SNHL primarily in adults are discussed.

Labyrinthitis

An infectious or inflammatory process within the labyrinth can take two forms pathologically: serous (sometimes referred to as "toxic") or suppurative. Serous labyrinthitis is defined as an abnormal process within the labyrinth, caused by the degradation of the tissue-fluid environment within the inner ear.[19] It may be caused by bacterial toxins or contamination of perilymph with blood, products of tissue injury, or air at surgery. Bacterial toxins may enter the inner ear during the course of acute or chronic otitis media, presumably through either the oval or the round window membranes. Because both acute and chronic suppurative otitis media are common, and because SNHL associated with either condition is rare, these membranes seem to provide an excellent barrier preventing transmission of bacteria or their toxins to the inner ear. The principal abnormal finding in patients with serous labyrinthitis is endolymphatic hydrops, and the hearing loss and vestibular dysfunction associated with this state can be permanent or transient.

Commonly, a clinical diagnosis of labyrinthitis is made when patients present with sudden onset of SNHL and acute vertigo. The exact etiology in cases such as this is uncertain, but it is probably identical or similar to the etiology of sudden SNHL. The evidence tends to support the theory that this is most commonly caused by a viral labyrinthitis.[20,21]

Suppurative labyrinthitis is caused by bacterial invasion of the inner ear, and it is manifested by profound hearing loss and acute vertigo. The route of invasion can be otogenic, from acute or chronic otitis media, most commonly caused by a fistula between the middle ear and the labyrinth. Alternatively, the route of invasion can be meningogenic, through the cochlear aqueduct or internal auditory canal. This is the most common etiology of deafness associated with meningitis.

Otitis Media

SNHL is rarely associated with acute otitis media. No study has shown a relationship between SNHL and frequency of acute otitis media.[22] Patients with long-standing chronic otitis media commonly have a mixed hearing loss. Whether the sensorineural component of this loss is a result of the infectious process itself, or a result of other factors such

as surgery or chronic use of ototoxic topical antibiotics, has been a long-standing controversy. When controlled for sensorineural losses associated with surgery, there seems to be no increase in SNHL in patients with chronic otitis media.[23]

Viral Infections

Herpes zoster oticus is a varicella-zoster infection most commonly associated with facial paralysis and a herpetic skin eruption over the auricle or within the external auditory canal. Although facial paralysis is the most frequent finding, hearing loss and vertigo can occur singly or in combination.

Measles is now rare in the developed world because of widespread vaccination. In the past, measles was a common cause of deafness in children. The hearing loss usually is bilateral and moderate to profound in degree. Vestibular function can be similarly affected.

Similar to measles, mumps is uncommon in the developed world because of widespread vaccination. Mumps is a paramyxovirus infection causing parotitis. Complications of mumps include orchitis, pancreatitis, SNHL, prostatitis, nephritis, myocarditis, and meningoencephalitis. SNHL resulting from mumps is unique because it is almost always unilateral. Bilateral involvement is rare. Unilateral deafness in otherwise healthy children or sudden deafness in adults may be caused by subclinical mumps infection in individuals without previous immunity.

Cytomegalovirus infection is thought by some authors to be a common cause of congenital and progressive hearing loss in children.[24-27] It has been proposed to be a cause of sudden SNHL in adults.[28] Hearing loss associated with acquired immunodeficiency syndrome (AIDS) may represent reactivation of latent cytomegalovirus infections.[29]

Syphilis

Congenital or acquired syphilis has been well established as a cause of SNHL. Although hearing loss is not associated with primary acquired syphilis, its incidence has been estimated to be 80% in patients with symptomatic neurosyphilis, 29% in patients with asymptomatic neurosyphilis, 25% in patients with late latent syphilis, and 17% in patients with congenital syphilis.[19] The mechanism of hearing loss in syphilis is either a meningolabyrinthitis as seen in neurosyphilis, or an osteitis of the temporal bone with secondary involvement of the labyrinth as seen in late congenital, late latent, or tertiary syphilis.[30] Pathologically, a resorptive osteitis is seen in the temporal bone, with progressive endolymphatic hydrops noted within the labyrinth. Clinically, the presentation of syphilitic hearing loss often is indistinguishable from Meniere's disease, with fluctuating hearing loss, tinnitus, aural fullness, and episodic vertigo. Hennebert's sign (a positive fistula test without middle ear disease) and Tullio's phenomenon (vertigo or nystagmus on exposure to high-intensity sound) have been strongly associated with otosyphilis.[19] The generally recommended treatment consists of an antibiotic protocol adequate for neurosyphilis with the addition of systemic corticosteroids.[31]

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is a tickborne infection caused by *Rickettsia rickettsii*. Headache, fever, myalgias, and an expanding petechial rash follow the tick bite by approximately 1 week. The disease results in systemic vasculitis, resulting in encephalitis, nephritis, and hepatitis. Rapidly progressive SNHL has been associated with Rocky Mountain spotted fever and may be transient.[32,33] Vasculitis involving the auditory system has been postulated to be the etiology of the hearing loss. Diagnosis is made primarily by clinical presentation and is confirmed by serologic titers. Treatment is with broad-spectrum antibiotics.

Lyme Disease

Lyme disease is a tickborne spirochetal illness caused by *Borrelia burgdorferi*. Although the most well-known otolaryngologic manifestation of the disease is facial paralysis, there is some evidence that the disease can be a cause of SNHL.[34-37] Although its true significance remains unclear, Lyme disease should be considered a possible etiology of SNHL in endemic areas.

Pharmacologic Toxicity

Aminoglycosides

At least 96 different pharmacologic agents have potential ototoxic side effects.[38,39] Among these, aminoglycoside antibiotics are perhaps the most common offending agents. This group of antibiotics includes streptomycin, dihydrostreptomycin, kanamycin, neomycin, amikacin, gentamicin, tobramycin, and netilmicin. Drugs that are ototoxic frequently are also nephrotoxic and vice versa (aminoglycosides, loop diuretics, potassium bromates, and nonsteroidal anti-inflammatory drugs [NSAIDs]). Alport's syndrome, described earlier, is a hereditary disorder affecting the kidneys and the inner ear, and there are developmental disorders resulting in renal and inner ear abnormalities. The strong association between pathology of the renal and auditory systems has not been well explained.

Aminoglycosides target the hair cells and enter the hair cell in an energy-dependent process. The end result is death of the hair cell. The reader is referred to excellent reviews of the current understanding of the mechanism of aminoglycoside ototoxicity (see Chapter 154).[40-42] The final common pathway of hair cell damage consists of the generation of reactive oxygen species. Different aminoglycosides have affinities for differing groups of hair cells, which result in different patterns of ototoxicity with different aminoglycosides. Kanamycin, tobramycin, amikacin, neomycin, and dihydrostreptomycin are more cochleotoxic than vestibulotoxic. Others, such as streptomycin and gentamicin, are more vestibulotoxic than cochleotoxic. The time course of the toxicity can vary.[39] Neomycin toxicity is typically rapid and profound, whereas a significant delayed effect has been noted for systemically administered streptomycin, dihydrostreptomycin, tobramycin, amikacin, and netilmicin, and for gentamicin administered through the middle ear.[43]

The hearing loss may be unilateral or asymmetric and can progress during or after cessation of therapy. Some degree of reversibility of the hearing loss sometimes is noted weeks to months after treatment.[39] Protective agents, including antioxidants, show promise for preventing or reducing aminoglycoside toxicity. More recently, the use of salicylates has been proposed.[44] A placebo-controlled clinical trial in China has shown a beneficial effect from the use of aspirin during aminoglycoside administration.[45]

Well-defined risk factors for aminoglycoside-induced ototoxicity have been established and include (1) presence of renal disease; (2) longer duration of therapy; (3) increased serum levels (either peak or trough levels); (4) advanced age; and (5) concomitant administration of other ototoxic drugs, particularly the loop diuretics. Peak and trough serum levels should be routinely monitored when these drugs are being used, and particular attention should be paid to avoidance of dosing intervals that are too short. With the more recent increased use of prolonged home-based intravenous antibiotic therapy, an increase in ototoxic complications has been noted, possibly a result of reduced attentiveness to serum levels and dosing intervals.

Ototopical Preparations

Topical preparations containing neomycin, gentamicin, and tobramycin have long been used directly in the ear for treatment of otitis externa and chronic otitis media. Placement of aminoglycosides within a healthy middle ear space frequently results in cochlear or vestibular ototoxicity as shown in experimental animals and in patients. This effect is now used to perform a titrated chemical labyrinthectomy for patients with Meniere's disease.[46,47] These same drugs have been used extensively over the years in countless ears with chronic otitis media with little to no apparent clinically significant effect on hearing or vestibular function.[48,49] Reduced permeability of the inflamed round and oval window membranes and dilution of the toxic drugs by purulent fluids and increased absorption into the vascular system by the hyperemic mucosa probably account for this decreased toxicity in the presence of otitis media.

It is clear, however, that use of aminoglycosides in the middle ear of animals does cause significant and predictable cochlear and vestibular toxicity in animals.[50] Based on this toxicity, and on the now widespread effective use of aminoglycosides to create a chemical labyrinthectomy, it is now generally regarded as unwise to use topical

aminoglycoside antibiotics for treatment of otitis media. The American Academy of Otolaryngology–Head and Neck Surgery convened a consensus panel in 2004 that, after careful review of the literature, recommended against the use of aminoglycosides in topical form in the middle ear unless no alternative was available.[51] Other ingredients of older ototopical preparations also have ototoxic potential (e.g., polymyxin B, propylene glycol, acetic acid, and antifungal agents).[52,53] It seems prudent to use only agents specifically designed and approved for use in the middle ear for treatment of chronic otitis.

Loop Diuretics

The loop diuretics ethacrynic acid, bumetanide, and furosemide exert their diuretic effect by blocking sodium and water reabsorption in the proximal portion of the loop of Henle. The use of these drugs has been associated with a reversible SNHL and with the potentiation of aminoglycoside-induced hearing loss. The loss typically is bilateral and symmetric, and may be sudden in onset.[54,55] These drugs seem to alter metabolism in the stria vascularis, resulting in alteration of endolymphatic ion concentration and endocochlear potential.[56] Risk factors for loop diuretic–induced ototoxicity include (1) renal failure, (2) rapid infusion, and (3) concomitant aminoglycoside administration.[125]

Antimalarials

Quinine has long been known to be associated with the development of tinnitus, SNHL, and visual disturbances.[57] The drug, derived from the bark of the cinchona tree, has a colorful history as an antipyretic. It was dispensed by quacks and in secret remedies in the 17th and 18th centuries. The syndrome of tinnitus, headache, nausea, and disturbed vision is termed *cinchonism*. Larger doses may cause a more severe form of the syndrome, which also includes gastrointestinal, CNS, cardiovascular, and dermatologic manifestations. Quinine is used as an adjunct in the treatment of malaria and nocturnal leg cramps.[58] The ototoxic effect of quinine seems to be primarily on hearing and usually is transient. Permanent hearing loss may occur with large doses or in sensitive patients. Chloroquine and hydroxychloroquine (Plaquenil) are currently used antimalarial drugs structurally related to quinine. They have also been associated with ototoxicity and retinopathy. Ototoxicity with these drugs seems to be rare and possibly reversible.[59,60]

Salicylates

Aspirin and other salicylates are strongly associated with tinnitus and reversible SNHL. The hearing loss is dose-dependent and can be in the moderate-to-severe range. On discontinuation of the drug, hearing returns to normal within 72 hours.[57] Tinnitus consistently occurs at a dose of 6 to 8 g/day of aspirin and at lower doses in some patients.[61,62] Caloric responses also can be reduced by salicylates.[63] The site of the ototoxic effect seems to be at the level of basic cochlear mechanics, as evidenced by SNHL, loss of otoacoustic emissions, reduced cochlear action potentials, and alteration of the "tips" of auditory nerve fiber tuning curves.[64] These effects may be a result of alteration in turgidity and motility of outer hair cells.[65]

Nonsteroidal Anti-inflammatory Drugs

NSAIDs share many of the therapeutic actions and side effects of salicylates. Although there are isolated reports of hearing loss caused by naproxen,[66] ketorolac,[67] and piroxicam,[68] ototoxicity resulting from use of NSAIDs generally is rare compared with salicylates.[57,69] Similar to salicylates, animal models of NSAID ototoxicity show only reversible physiologic changes, without major morphologic changes.

Vancomycin

Vancomycin generally is believed to be ototoxic, but the available data are difficult to evaluate.[70] In clinical reports of vancomycin ototoxicity, patients almost always also received loop diuretics or aminoglycosides. Vancomycin has been associated with ototoxicity when administered intravenously, but not when given orally. Auditory impairment has been reported to be permanent or transient and is extremely unusual if serum concentrations are less than 30 mg/mL. In animals, vancomycin ototoxicity does not occur, unless toxic levels are administered.[71] Vancomycin is nephrotoxic and excreted by the kidneys. Renal failure can prolong vancomycin half-life and increase the likelihood of ototoxicity. Ototoxicity and nephrotoxicity are reputed to be less common with newer, more purified formulations of vancomycin.[72] When given orally, or in appropriate intravenous doses, vancomycin ototoxicity seems to be very rare, but vancomycin may potentiate other ototoxic drugs.[73,74] There is one reported case of severe, irreversible hearing loss associated with intrathecal administration of vancomycin.[75]

Erythromycin

Numerous case reports document SNHL associated with erythromycin administration.[76] In almost all reports, the drug was given intravenously rather than orally. The hearing loss seems to be uncommon and, in most cases, recovers within 1 to 3 weeks after the drug is stopped. The risk of erythromycin ototoxicity seems to be greater in patients with renal or hepatic insufficiency. There have also been reports of ototoxicity associated with the newer macrolide antibiotic azithromycin.[77] Limited histologic data suggest that the site of lesion in erythromycin toxicity is the stria vascularis.[78]

Cisplatin and Carboplatin

cis-Diamminedichloroplatinum (cisplatin) is a cell cycle–nonspecific cancer chemotherapeutic agent that produces dose-limiting SNHL and peripheral neuropathy, and a dose-related cumulative renal toxicity, hematologic toxicity, and gastrointestinal toxicity.[79] The incidence of hearing loss varies in adults (25% to 86%) and children (84% to 100%). Children seem to be significantly more susceptible to ototoxicity.[80] The hearing loss initially is worse at high frequencies, bilateral, and irreversible. It occasionally is accompanied by tinnitus or vertigo. The degree of hearing loss is dose-related, but there is considerable variability. Occasionally, severe hearing loss can occur after a single dose.[81] If ultra-high-frequency hearing is tested, 100% of patients show a loss. Many factors influence this variability, including mode of drug administration, tumor site, age, renal function, diet, cranial irradiation, interaction with aminoglycosides and loop diuretics, preexisting hearing loss, cumulative dose, and total dose per treatment.[79,82,83]

Carboplatin is a cisplatin analogue with a similar spectrum of antineoplastic activity. Carboplatin is less nephrotoxic than cisplatin. Myelosuppression is the dose-limiting toxicity with carboplatin. It was initially thought that carboplatin was less ototoxic than cisplatin. More recent studies have shown higher rates of ototoxicity than initially appreciated, however. In a series of children, high-dose carboplatin therapy was associated with a very high rate of ototoxicity.[84]

Cisplatin and carboplatin ototoxicity seems to be due to the creation of reactive oxygen species within the inner ear that target the hair cells. Cisplatin results in greater outer than inner hair cell damage, whereas carboplatin seems to affect the inner hair cells preferentially.[85]

Nitrogen Mustards

Nitrogen mustards are antineoplastic agents that include mechlorethamine (Mustargen), chlorambucil (Leukeran), cyclophosphamide (Cytoxan), melphalan (Alkeran), and ifosfamide (Ifex). Of these drugs, only mechlorethamine has ototoxicity as a serious adverse effect, and it has limited usefulness today because of its severe toxic profile. Animal and human studies with mechlorethamine ototoxicity have revealed severe loss of outer hair cells.[69] Other studies have shown shrinkage of the organ of Corti and loss of inner and outer hair cells.[86]

Vincristine and Vinblastine

The vinca alkaloids vincristine and, to a lesser extent, vinblastine are notable for their potent neurotoxicity. Peripheral neuropathy is common. Cranial neuropathies, ataxia, and hearing loss have been reported. Vincristine has been shown in animals to cause loss of hair cells and primary auditory neurons, whereas vinblastine has been shown to result in only hair cell loss.[79]

Eflornithine

Eflornithine (difluoromethylornithine) is a potent inhibitor of ornithine decarboxylase and is very effective in the treatment of trypanosomiasis. It also has proven useful in some patients with *Pneumocystis carinii* pneumonia, cryptosporidiosis, leishmaniasis, and malaria. It has

shown potential as an antineoplastic agent. This drug has been reported to cause major and dose-related SNHL.[87]

Deferoxamine

Deferoxamine is an iron-chelating agent used in some patients with chronic iron overload or acute, severe iron intoxication. Auditory and visual neurotoxicity have been reported, particularly with larger doses in younger patients. SNHL is reversible in some patients when the dosage is reduced.[88]

Lipid-Lowering Drugs

Although optic and vestibulocochlear nerve degeneration (wallerian-like degeneration) have been seen in dogs given high doses of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, no clinically significant effect on vision or hearing has been found.

Renal Disorders

Numerous genetic causes of SNHL are associated with renal abnormalities; Alport's syndrome is the most well recognized.[9] Acquired renal disorders have an unclear association with SNHL. Chronic renal failure, especially when managed with hemodialysis or renal transplantation, has been associated with progressive, fluctuating, or sudden SNHL. Oda and coworkers[89] found that 15% of 290 hemodialysis and renal transplantation patients developed SNHL. The etiology of the SNHL is difficult to determine precisely and probably is multifactorial. In addition to the electrolyte and metabolic abnormalities caused by the renal failure and subsequent hemodialysis, these patients typically receive frequent doses of loop diuretics, aminoglycoside antibiotics, and vancomycin. Because of the altered pharmacodynamics of these drugs caused by renal failure, their ototoxic potential is increased.

Trauma

Head Injury

Blows to the head can cause labyrinthine injury and resultant SNHL, either directly through fracture of the labyrinth resulting from temporal bone fracture or indirectly through labyrinthine concussion. The most common type of temporal bone fracture, longitudinal fracture, uncommonly extends through the labyrinth. The hearing loss associated with longitudinal fractures typically is similar to that of acoustic trauma (i.e., limited to the high frequencies and worse at 4 kHz). Similarly, blunt head injury alone, without temporal bone fracture, can result in concussive injury of the labyrinth, resulting in SNHL. Transverse fractures almost always traverse the labyrinth, resulting in complete loss of auditory and vestibular function. Penetrating injuries to the inner ear are rare, but they most commonly involve subluxation of the stapes into the vestibule, with resultant profound SNHL.

Noise-Induced Hearing Loss and Acoustic Trauma

The fact that excessive noise exposure could cause hearing loss was first recognized in the 18th century. In the early 20th century, NIHL was termed "boilermaker's deafness." Careful descriptions of the hearing loss sustained in industry would await development of the audiometer and were first published in the 1930s.[90] NIHL is now recognized as one of the most common occupationally induced disabilities, and noise exposure is now regulated by the Occupational Health and Safety Administration.[91]

Noise can be defined loosely as "unwanted sound," and subdivided by intensity, time course (continuous, fluctuating, intermittent, impact, impulse), and spectral content (pure-tone, narrow-band, broad-band). Impact noise is noise caused by collision of two objects and is common in industry. Impulse noise is noise resulting from sudden release of energy, such as an explosion or weapon fire.

Hearing loss caused by noise is sensorineural in nature. Rarely, extremely intense impulse exposures can result in tympanic membrane perforations, causing a conductive component. Most hazardous noise exposure produces a temporary SNHL that recovers over the next 24 to 48 hours. This reversible loss is termed a *temporary threshold shift* (TTS). If the noise is of high enough intensity or is repeated often enough, a permanent loss of hearing results, and is referred to as a *permanent threshold shift* (PTS). Two distinct types of hearing loss are caused by excessive noise exposure: NIHL versus acoustic trauma. NIHL is caused by repeated exposures to sound that is too intense or too long in duration. Each exposure is followed by a TTS, which recovers, but eventually a PTS develops. Acoustic trauma consists of a single exposure to a hazardous level of noise, resulting in a PTS without an intercurrent TTS.

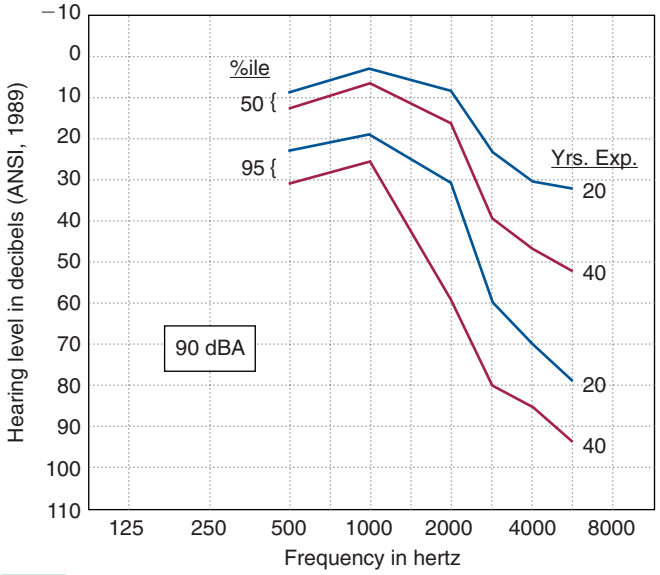

Figure 149-3. Predicted hearing thresholds (median and extreme values) after 20 years and 40 years of occupational noise exposure at 90 dBA. *(ISO-1999, from Dobie RA.* Medical-Legal Evaluation of Hearing Loss. *New York: Van Nostrand Reinhold; 1993.)*

NIHL almost always results in a symmetric, bilateral hearing loss. It almost never results in a profound loss. Early in the course of NIHL, the loss usually is limited to 3 kHz, 4 kHz, and 6 kHz. The greatest loss usually occurs at 4 kHz. As the loss progresses, lower frequencies become involved, but the loss at 3 to 6 kHz is always far worse. The loss progresses most rapidly during the first 10 to 15 years of exposure and thereafter grows at a much-reduced rate. Figure 149-3 shows the 50% and 95% confidence limits for 20-year and 40-year exposures to 90 dBA (decibel, with "A"-weighting that fully weights 700-9000 Hz) sound. Figure 149-4 shows an example of the rate of growth of NIHL over time. The International Organization for Standardization has established standards for determining and quantifying occupational hearing loss and noise-induced hearing impairment.[92]

The hearing loss from acoustic trauma is similar to that from NIHL (i.e., worse at high frequencies with a 4-kHz "notch"), although other patterns also are seen. The other, most common patterns include flat losses and downsloping losses. Acoustic trauma frequently is unilateral or asymmetric. There is considerable variability in hearing loss among subjects with identical exposure. Age, gender, race, and coexisting vascular disease have been carefully studied, and when adequately controlled for other factors, they have not been shown to correlate with susceptibility to NIHL. An attractive theory suggests that patients who are more susceptible to TTS would be more susceptible to PTS and NIHL; this has not been shown to be the case. At present, there is no known way to predict susceptibility to NIHL.

There are three exceptions. Conductive hearing losses are clearly protective for NIHL in the same way that earplugs or earmuffs would be. The lack of an acoustic reflex has been shown to predispose patients to NIHL (the protective effect of the acoustic reflex is primarily ≤2 kHz).[19] Finally, patients with an unusually large PTS already should be considered to be more susceptible. TTS and PTS are commonly accompanied by tinnitus, and tinnitus after a noise exposure should be considered a warning sign.

There is little a clinician can do in the management of NIHL or acoustic trauma. The primary role of otolaryngologists and audiologists is in prevention and early identification. Many hazardous noise expo-

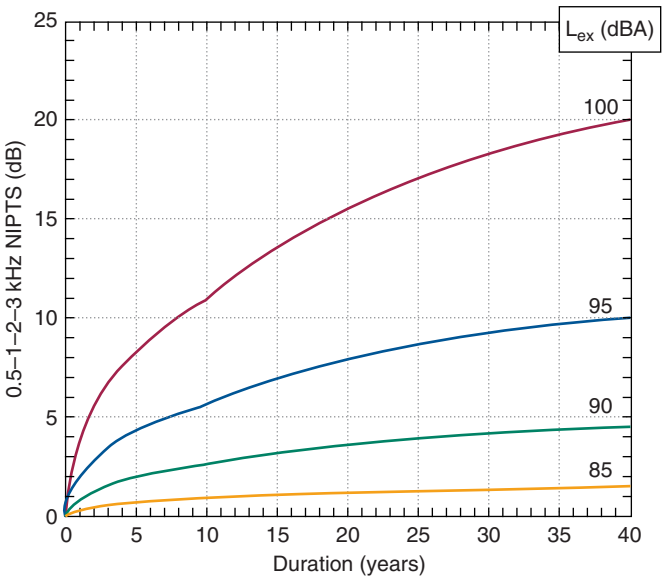

Figure 149-4. Speech frequency average noise-induced permanent threshold shift (NIPTS) as a function of level of exposure (in dBA-TWA) and duration. *(ISO-1999, from Dobie RA.* Medical-Legal Evaluation of Hearing Loss. *New York: Van Nostrand Reinhold; 1993.)*

sures are not occupational in origin. Many companies either are unable or unwilling to provide hearing conservation programs.

Barotrauma and Perilymphatic Fistula

Otitic barotrauma consists of traumatic injury of the tympanic membrane and middle ear caused by unequalized pressure differentials between the middle and external ears. The injury typically occurs during flying or underwater diving, and consists of pain, hyperemia, and possible perforation of the tympanic membrane, and edema and ecchymosis of the middle ear mucosa. These symptoms can be followed by the development of a hemotympanum or a transudative middle ear effusion. Conductive hearing loss may result. Any abnormality resulting in compromised eustachian tube function may predispose to barotrauma.

A perilymphatic fistula consists of a pathologic communication between the perilymphatic space of the inner ear and the middle ear. Perilymphatic fistulas can be congenital or acquired in origin. The fistulas can occur at either the round or the oval windows.[93]

Congenital defects can occur in the stapes footplate in patients with labyrinthine anomalies such as Mondini dysplasia.[94,95] These fistulas can communicate with the subarachnoid space and result in cerebrospinal fluid leak and possible meningitis. Typically, these ears have a profound hearing loss. This phenomenon should be a consideration in the differential diagnosis of patients with recurrent meningitis.[96-98]

Acquired perilymphatic fistulas can result from barotrauma, direct or indirect trauma to the temporal bone, or a complication of stapedectomy surgery. A typical history attributed to perilymphatic fistula consists of the sudden development of SNHL and vertigo after a head injury, barotrauma, or heavy lifting or straining. The event is sometimes associated with an audible "pop." Patients may have a positive Hennebert sign and positional nystagmus when the involved ear is placed in a dependent position.[99] Some authors believe that perilymphatic fistulas develop spontaneously.[100,101]

Diagnosis is made by middle ear exploration. Visualization of fluid in the region of the oval or round windows is not definitive evidence of a fistula because serous fluid can ooze from the middle ear mucosa, or lidocaine from the local anesthetic can collect in the vicinity.[102,103] Treatment consists of packing the area in question with tissue. Because of the lack of a definitive diagnostic test for the presence of a fistula, and because even surgical exploration does not reliably diagnose or exclude the possibility of a fistula, there is considerable controversy with regard to the management of this entity.[93,100,104,105] In the 1980s and early 1990s, it was commonly believed that spontaneous perilymphatic fistulas were a common cause of otherwise unexplained hearing loss and vertigo. Many surgical fistula repairs were performed as a result of this belief. It has since become clear that spontaneous perilymphatic fistula is rare.[106] No clear consensus exists regarding diagnosis or management.

Finally, labyrinthine fistula can result from erosion by cholesteatoma, or may develop spontaneously as in the superior semicircular canal dehiscence syndrome. The reader is referred to Chapters 140, 163, and 165 of this book for detailed descriptions of these entities.

Irradiation

The cochlea seems to be resistant to radiation injury at doses less than 45 Gy. At doses greater than 45 Gy, there is a clear, dose-dependent toxicity that manifests as hearing loss.[107-109] Radiation also seems to cause a dose-dependent toxicity to the auditory nerve and brainstem.[110] The latency period from radiation exposure to clinical hearing loss can be 12 months or more. One report notes that early-onset SNHL after radiation can recover to some degree.[111] Fractionated irradiation has been used to a limited extent in the past to treat vestibular schwannoma. Whether it has had an effect on hearing in these patients is difficult to determine because of the limited data available.[112] More recently, there has been much more extensive experience with stereotactic irradiation (radiosurgery) for vestibular schwannoma. This modality seems to be associated with substantial risk of SNHL, at least as high as with microsurgical removal.[113]

There is a relative paucity of published literature on the experimental effects of radiation on hearing. In a histologic study in chinchillas, sacrificed 2 years after fractionated irradiation of the cochlea, Bohne and coworkers[114] showed a dose-dependent loss of inner and outer hair cells. Early studies of the effects of radiotherapy involving the cochlea on human hearing were flawed because lack of controls, inadequate follow-up, and the retrospective nature of the studies. Many well-designed studies now have shown that radiotherapy involving the cochlea causes SNHL in 50% of patients.[107-109,115-117] The hearing loss occurs in a dose-dependent fashion, and seems to increase significantly at doses greater than 45 Gy. Advanced age, preexisting hearing loss, and adjuvant ototoxic chemotherapeutic agents are likely to amplify the effects of radiation. The hearing loss occurs with a latency of 0.5 to 2 years post-treatment and is probably progressive.[111] This delayed onset, and the fact that many patients do not survive for sufficient follow-up, results in underestimation of the frequency and severity of this complication. Dose-dependent injury to the auditory nerve and brainstem also occurs; however, the frequency in the absence of other neurologic complications is difficult to determine.[110]

An understanding of the effects of radiation on hearing has become much more clinically relevant more recently because of the popularity of stereotactic radiotherapy for the treatment of vestibular schwannoma and other similar lesions. Although many reports suggest that the risk of hearing loss is minimal, these studies are limited by (1) their retrospective design, (2) lack of long-term follow-up, and (3) incomplete audiologic characterization. In addition, it is difficult to compare the studies that are available because of differences in tumor size, radiation dose, radiation field, technique of radiation administration, and follow-up. There is a wealth of literature on the treatment outcomes after stereotactic radiotherapy; however, almost all of them are limited by one of the above-mentioned shortcomings. More recent studies report hearing preservation rates (defined in different ways and with different follow-up periods) between 36% and 61%.[118-121] The time course of hearing loss after stereotactic radiotherapy is poorly characterized; available data would suggest that the loss is progressive, and that early results may not predict later outcomes.

Neurologic Disorders

Multiple Sclerosis

Multiple sclerosis is a chronic disease characterized pathologically by multiple areas of CNS demyelination, inflammation, and glial scarring. The clinical course is variable, ranging from a benign, almost symptom-free disease to a rapidly progressive, disabling disorder. Early in the patient's course, the disease is characterized by remissions and relapses.

The disease is said to result in dissemination of neurologic lesions in time (remissions and relapses) and in space (variability of multiple deficits). The age at onset is typically between 20 and 30 years, rarely occurring before age 10 years or after age 60 years. Multiple sclerosis is more common in women than in men. There are striking racial and geographic differences in prevalence, with the disease being most common in whites and in individuals living at higher latitudes. The cause is unknown, but seems to be related to genetic factors, autoimmune mechanisms, and viral infection.

SNHL develops in 4% to 10% of patients with multiple sclerosis.[122,123] The hearing loss can be progressive or sudden in onset, and can be bilateral, unilateral, symmetric, or asymmetric.[124-128] Frequently, the loss is sudden and unilateral, and can recover after days or weeks.[125,129] Audiometrically, speech discrimination can be normal or reduced out of proportion to the increase of pure-tone thresholds. Abnormal patterns of acoustic reflexes can be seen in some patients.[126,130,131] Abnormalities of the ABR frequently are seen and are a diagnostic criterion for multiple sclerosis. Patterns of abnormality vary and include latency prolongation of wave I or the later waves, absence or poor morphology of waveforms, and waveform abnormalities with increased stimulus presentation rate.[124,128,130,132-134] MRI frequently is abnormal in multiple sclerosis and typically reveals periventricular white matter plaques on T2-weighted images. Plaques can be seen in the cochlear nucleus or inferior colliculus in patients with SNHL.[135-138]

Benign Intracranial Hypertension

Benign intracranial hypertension, also known as pseudotumor cerebri, probably is better termed *idiopathic intracranial hypertension* because it is not always benign in nature. The disorder consists of increased intracranial pressure without evidence of mass lesion, obstructive hydrocephalus, intracranial infection, or hypertensive encephalopathy. It is associated with a long list of medical disorders, but frequently manifests as an isolated phenomenon. The underlying pathophysiology is poorly understood. The most common presenting symptoms are headache and visual blurring. Pulsatile tinnitus, SNHL, and vertigo also may be present. It is more commonly seen in obese women.[139,140]

The pulsatile tinnitus is usually objective and is eliminated by jugular venous compression.[141,142] SNHL typically is a fluctuating, low-frequency loss that is unilateral or bilateral. Vertigo and aural fullness also may be present. The most serious manifestation of the disorder is progressive visual loss caused by optic atrophy. The disease is characterized by remissions and relapses. The diagnosis is confirmed by documentation of papilledema on funduscopy or cerebrospinal fluid pressure greater than 200 mm H_2O. ABR and electrocochleography abnormalities can be seen. Management consists of weight loss, acetazolamide, furosemide, and occasionally, lumbar-peritoneal shunting.[142,143]

Vascular and Hematologic Disorders

Migraine

Migraine is a common disorder, usually restricted to headache and sometimes the neurologic symptoms of an aura. Numerous subtypes of migraine are associated with different neurologic deficits. Basilar migraine has been associated with numerous auditory and vestibular symptoms and signs, including episodic vertigo, SNHL, tinnitus, aural fullness, distortion, and recruitment. Fairly complex and specific diagnostic criteria have been established for basilar migraine.[144] In a series of 50 patients meeting the criteria for basilar migraine, 46% had bilateral, low-frequency SNHL, and an additional 34% had unilateral low-frequency SNHL.[145] The hearing loss frequently fluctuated and occasionally was severe. Basilar migraine has been implicated as an occasional cause of SNHL. Because of their similarity, there has been considerable speculation in the literature of an etiologic association between basilar migraine and Meniere's disease.

Migraine headache can be managed with β-blockers, calcium channel blockers, acetazolamide, NSAIDs, and antiserotonin agents. No systematic study evaluating the use of these drugs in patients with basilar migraine is currently available. The reader is referred to the excellent reviews of Olsson[145] and Harker,[146] and to Chapter 165 for a more detailed discussion.

Vertebrobasilar Arterial Occlusion

Several eponyms have been applied to brainstem syndromes, but all apply to neoplasms with the exception of Wallenberg's syndrome (lateral medullary syndrome). Classic brainstem infarction patterns are seen less often than incomplete or mixed clinical pictures. To result in SNHL, the occlusion generally has to involve the anterior inferior cerebellar artery (AICA). Occlusion of the AICA results in ischemic infarction of the regions of the brainstem supplied by this artery. The occlusion typically results from thrombosis or embolism, and rarely from other vascular disorders or surgical occlusion of the vessel. The area infarcted includes the inferior pons, and many of the findings are similar to Wallenberg's syndrome. In addition, the AICA usually gives rise to the internal auditory artery, which is the principal blood supply to the labyrinth. The findings in patients with acute AICA infarction include acute vertigo with associated nausea and vomiting, facial paralysis, SNHL, tinnitus, ipsilateral gaze paralysis, ipsilateral loss of pain and temperature sensation on the face, contralateral partial loss of pain and temperature sensation on the trunk and extremities, and ipsilateral Horner's syndrome. The vertigo and hearing loss are caused by ischemic injury of the cochlear and vestibular nuclei in the brainstem and in the labyrinth itself.[19] Isolated cerebellar infarction can result in hearing loss, vertigo, facial pain or numbness, headache, or ataxia.[147]

Rheologic Disorders and Blood Dyscrasias

Waldenström's macroglobulinemia is a plasma cell disorder in which abnormally large amounts of IgM are synthesized and circulate in the plasma. The result is increased blood viscosity and subsequent ischemic lesions. Progressive and sudden hearing losses caused by this disorder have been reported, and some patients with SNHL have responded to treatment with alkylating agents or plasmapheresis.[148]

Cryoglobulinemia results from immune-complex disease, in which the resulting immune complexes are soluble at body temperature and precipitate at lower temperatures. The deposition of these complexes results in glomerulonephritis, vasculitis, and arthritis. The disorder can be associated with progressive or sudden SNHL.[149]

Sickle cell disease is associated with an increased incidence of SNHL.[150-152] It has been estimated that SNHL is present in 22% of patients with sickle cell disease.[153] The hearing loss may be progressive or sudden, and associated with sickle cell crises.[154-156] Leukemias and lymphomas also have been associated with SNHL caused by either leukemic infiltrates or hemorrhage within the inner ear or by vascular occlusion and resulting labyrinthine ischemia.[19]

Cardiopulmonary bypass has been associated with a slightly increased risk of SNHL.[157-159] The loss most often is sudden, but one study suggests an increased incidence of bilateral high-frequency loss postoperatively.[160] The etiology would seem to be either embolic phenomenon or reduced perfusion of the inner ear.

Vascular loops within the cerebellopontine angle or internal auditory canal have been proposed to be a cause not only of SNHL, but also of tinnitus, vertigo, and Meniere's disease.[161-164] Although the concept of vascular compression of cranial nerves causing intermittent neurologic dysfunction has been reasonably well accepted in trigeminal neuralgia and hemifacial spasm, it has achieved far less support in auditory and vestibular dysfunction. Vessel loops are found in contact with these nerves routinely during cerebellopontine angle surgery for other reasons, and these patients seem to be suffering no ill effects as a result. The entire CNS is subjected to such pulsation continuously. To date, nothing other than anecdotal evidence has been published supporting this theory.

Immune Disorders

Systemic Autoimmune Disorders

Various systemic (non–organ-specific) autoimmune disorders have been associated with SNHL.

Cogan's Syndrome

Cogan's syndrome is perhaps the prototypical autoimmune disorder affecting the inner ear. It consists of attacks of acute nonsyphilitic

interstitial keratitis together with auditory and vestibular dysfunction. SNHL may be unilateral or bilateral, and associated with severe vertigo, nausea, vomiting, and tinnitus. If untreated, the hearing loss frequently progresses to a profound loss over months. Other ophthalmologic findings may be present. If treated early enough, SNHL typically is responsive to aggressive treatment with steroids. Immunosuppressive agents sometimes are required.[165]

Polyarteritis Nodosa

Polyarteritis nodosa consists of a necrotizing vasculitis of small-sized and medium-sized arteries. It can manifest with myriad findings, including weight loss, fatigue, fever, anorexia, arthritis, neuropathy, hypertension, renal failure, abdominal pain, and SNHL. Diagnosis is made by demonstration of the necrotizing vasculitis on biopsy specimen of involved tissue. SNHL may precede the development of systemic symptoms or occur late in the disease. It may be unilateral or bilateral, and either rapidly or slowly progressive. Facial paralysis also may be seen. Aggressive doses of steroids and immunosuppressive drugs are given for management.[166,167]

Relapsing Polychondritis

Relapsing polychondritis consists of an inflammatory reaction in multiple cartilages. The auricles usually are the first cartilages to be affected. Arthritis and eye findings are commonly present. The disorder frequently is present in conjunction with other autoimmune diseases. The associated hearing loss may be conductive, sensorineural, or mixed. SNHL can be sudden or progressive in onset, and may be associated with vestibular disturbances. Therapy includes steroids, immunosuppressive drugs, or dapsone.[168,169]

Wegener's Granulomatosis

Wegener's granulomatosis is a syndrome of necrotizing granulomatous vasculitis involving principally the lungs, airway, and kidneys. Hearing loss usually is conductive because of involvement of the eustachian tube or middle ear. SNHL may be present if the granulomatous disease or secondary infection extends into the inner ear.[170-172]

Other Autoimmune Disorders

Other systemic autoimmune disorders less commonly associated with SNHL include scleroderma,[173] temporal arteritis,[174] systemic lupus erythematosus,[175,176] sarcoidosis,[177,178] and Vogt-Koyanagi-Harada syndrome.

Primary Autoimmune Inner Ear Disease

McCabe[179] first described patients with bilateral SNHL responsive to immunosuppressive drugs. The loss can be sudden or progressive in onset. The loss usually involves both ears, either simultaneously or alternately. The hearing loss frequently is associated with vestibular symptoms and can strongly mimic Meniere's disease. Myriad nonspecific tests of humoral autoimmunity may be abnormal. The hallmark of the disease is the responsiveness of the hearing loss to steroids or cytotoxic drugs. In some patients, a course of drug treatment can produce a long-lasting improvement in hearing, and in others, the hearing improvement depends on continued use of the medications.[180] In these patients, methotrexate is sometimes used to reduce the need for continued high-dose steroids and their resultant side effects.[181] In still others, SNHL progresses despite aggressive treatment.

Sera of many of these patients have been shown to contain an antibody to a 68-kD protein of bovine or guinea pig inner ear extracts. The responsiveness of SNHL to steroid treatment correlates with the presence of this antibody.[182-185] This 68-kD protein has been shown to be a member of the heat shock protein 70 family (HSP70).[186,187] A significant percentage of patients with Meniere's disease show similar reactivity, suggesting that autoimmunity may play a role in at least a subset of patients with Meniere's disease.[188,189] Chapter 153 contains a full discussion of autoimmune inner ear disease.

Acquired Immunodeficiency Syndrome

SNHL is among the numerous neurologic manifestations of AIDS. The hearing loss may be a result of an infectious complication of AIDS, particularly cryptococcal meningitis or syphilis, or as a primary neurologic manifestation of the disease. Human immunodeficiency virus (HIV) should be a consideration in patients with otherwise unexplained SNHL when risk factors are present.[190-197]

Paraneoplastic Syndromes

Neurologic paraneoplastic syndromes consist of neurologic abnormalities associated with malignant neoplasms not metastatic to the nervous system. Rarely, the abnormality may involve the auditory or vestibular system.[198]

Bone Disorders

Otosclerosis

Otosclerosis primarily causes a conductive hearing loss, but it is commonly associated with a progressive SNHL, especially later in the course of the disease. The precise mechanism remains unclear. CT images of the cochlea in these patients frequently reveal a radiolucent area immediately surrounding the cochlea. Histologically, otosclerotic bone frequently involves the endosteum, but the degree of endosteal involvement does not clearly correlate with the degree of SNHL.[199] It is doubtful that isolated cochlear otosclerosis without stapedial involvement (and conductive hearing loss) occurs with any clinically significant frequency.[200] Treatment with sodium fluoride has been reported to retard the progression of hearing loss in these patients.[200-203] The efficacy of this treatment remains controversial.[204-207] Patients with very advanced otosclerosis can have a bilateral profound mixed hearing loss, which can be audiometrically indistinguishable from a profound SNHL. In these patients, stapedectomy can result in useful hearing improvement.[30,208,209]

Paget's Disease

Paget's disease (osteitis deformans) is a common but poorly understood disorder of bone. It is most common in older individuals, with an estimated incidence ranging from 1% in individuals 40 to 49 years old to 19% in individuals 80 to 89 years old. Approximately 50% of patients with Paget's disease manifest hearing loss. The loss can be conductive, sensorineural, or mixed. The stapes footplate is rarely fixed, and surgical ossicular chain reconstruction is rarely beneficial.[210] The treatment of Paget's disease consists of calcitonin or etidronate disodium. Some evidence indicates that medical treatment may stabilize or reverse SNHL.[211,212]

Neoplasms

When patients are initially seen with unilateral or asymmetric SNHL, particularly when the presentation is not typical for Meniere's disease, neoplasm should be a principal diagnostic consideration. All patients with asymmetric or progressive SNHL should be evaluated for a neoplastic etiology. Lesions resulting in SNHL usually are located within the internal auditory canal or cerebellopontine angle, but tumors located anywhere in the skull base or temporal bone can result in SNHL if the labyrinth is invaded.

Vestibular schwannoma is the most common neoplasm resulting in SNHL (Fig. 149-5). Best known as acoustic neuroma, vestibular schwannomas originate from the vestibular nerves, within the cerebellopontine angle or the internal auditory canal. Acoustic neuroma is common, constituting 6% of all intracranial neoplasms.[213] It has been estimated that 2500 new acoustic neuromas are diagnosed in the United States annually.[214] Acoustic neuromas account for approximately 80% of all cerebellopontine angle neoplasms.[213] The most common presenting feature of acoustic neuroma is progressive unilateral SNHL. Any pattern of hearing loss can occur, but most frequently the loss initially involves principally the high frequencies. Commonly, speech discrimination is reduced out of proportion to the pure-tone thresholds. Acoustic neuroma can manifest as a sudden loss in 10% of patients, although most sudden losses are not a result of acoustic neuroma.[215] Unilateral or asymmetric tinnitus, with or without hearing loss, also is a common manifestation of acoustic neuroma. Patients may have mild or severe vestibular symptoms or may have none. Bilateral acoustic neuromas are pathognomonic for neurofibromatosis type 2 (Fig. 149-6). The reader is referred to Chapter 177 in this text for a

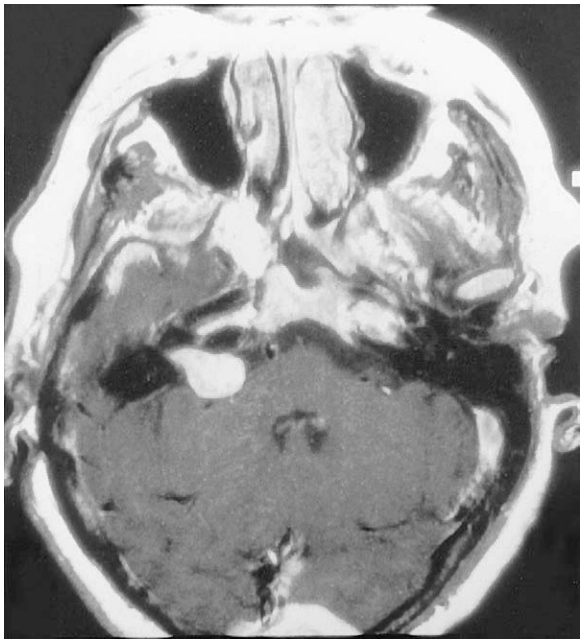

Figure 149-5. Gadolinium-enhanced MR image showing a medium-sized vestibular schwannoma.

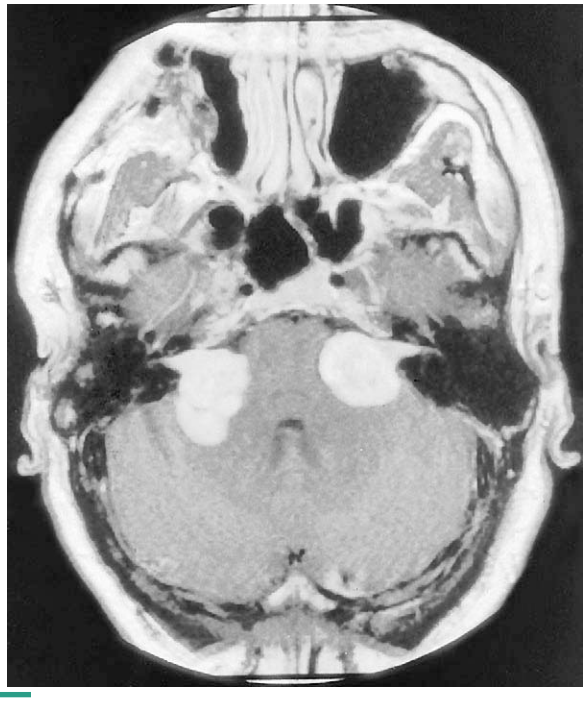

Figure 149-6. Gadolinium-enhanced MR image showing bilateral vestibular schwannomas pathognomonic for neurofibromatosis type 2.

more complete discussion of the pathogenesis, evaluation, and management of these common lesions.

Meningiomas account for approximately 15% of cerebellopontine angle neoplasms. The manifestation of cerebellopontine angle meningiomas is very similar to that of acoustic neuromas. For reasons that are unclear, meningiomas generally have less effect on hearing for a given size than do acoustic neuromas (Fig. 149-7). The remaining 5% of cerebellopontine angle lesions include dermoid cysts (congenital cholesteatoma), lipomas, arachnoid cysts, cholesterol granulomas, and hemangiomas. Metastatic lesions, particularly adenocarcinoma, also

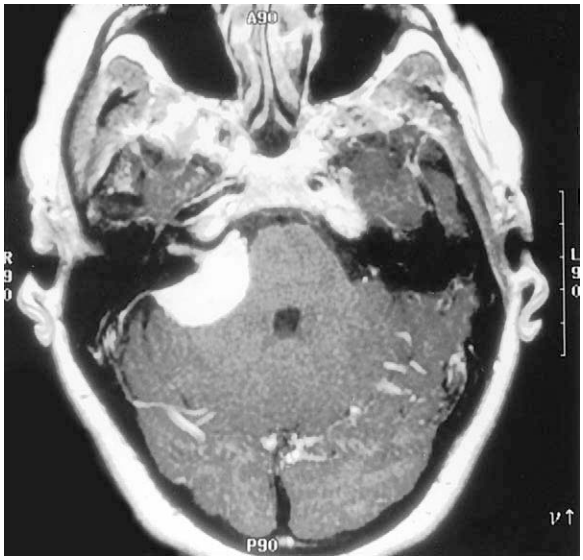

Figure 149-7. Gadolinium-enhanced MR image showing a large cerebellopontine angle meningioma. This patient had tinnitus and normal hearing, and had normal hearing after surgical removal of the lesion.

can occur in the internal auditory canal. Tumors occurring elsewhere in the skull base that can cause SNHL by involvement of the labyrinth include paragangliomas, chondrosarcoma, hemangioma, middle ear adenoma, rhabdomyosarcoma, lymphoma, and leukemia.[19]

Endocrine and Metabolic Disorders

It would seem logical that the diffuse large and small vessel atherosclerotic disease resulting from diabetes would be associated with an increased incidence of SNHL; however, this has not proven to be the case. There seems to be no significant association between the presence of diabetes and SNHL, when adjusted for expected hearing loss as a result of age.[216]

Although there is a definite association between SNHL and congenital hypothyroidism, there is little to no evidence that adult-onset acquired hypothyroidism can result in SNHL.[217-220] Similarly, reports have suggested that there is an association between hypoparathyroidism and hyperlipidemia. No convincing studies have shown either association.[221-223]

Pseudohypacusis

Pseudohypacusis is simply a factitious or exaggerated hearing loss and is common, especially in situations in which there is secondary gain to patients. Pseudohypacusis should be considered whenever the pattern of loss does not fit the clinical picture. Discordance between the speech reception threshold and the pure-tone average is a strong indicator of a factitious loss. Other audiometric studies, such as the Stenger test, ABR, and otoacoustic emissions, are helpful in clarifying such situations.

Disorders of Unknown Etiology

Presbycusis

SNHL associated with the aging process is termed *presbycusis*. In the strictest sense, only SNHL specifically caused by the aging process, and not by genetic factors, accumulated noise injury, vascular and metabolic factors, and so on, should be attributed to presbycusis. Because of the limitations of controlled studies in such a situation, it is difficult, if not impossible, to establish absolutely the existence of presbycusis. A better term for such a loss is age-related hearing loss, and this applies to any loss associated with age without other apparent etiology. Age-related hearing loss is a major public health issue. Actual prevalence of age-related hearing loss depends on its definition and is difficult to determine. It has been difficult in large epidemiologic studies to exclude

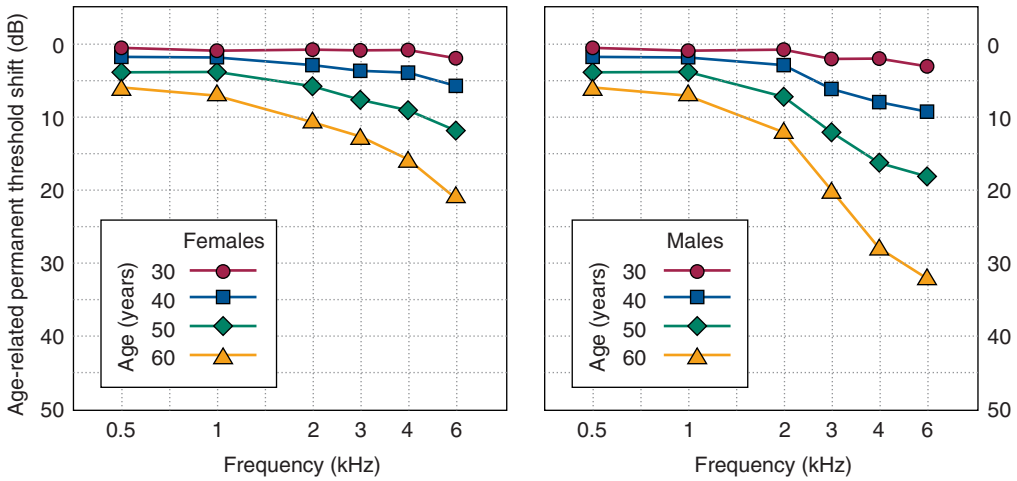

Figure 149-8. Median audiograms for patients with little to no noise exposure as a function of gender, frequency, and age. *(From Dobie RA. Medical-Legal Evaluation of Hearing Loss. New York: Van Nostrand Reinhold; 1993.)*

NIHL from study groups. Approximately 30% of individuals older than 65 years admit to a hearing loss.[91] Because at least 12% of the population is older than 65 years, there probably are more than 9 million people in the United States with age-related hearing loss.

Age-related hearing loss typically is worse for high frequencies and is more severe in men.[224] The rate of loss accelerates with time, so that the older patient is, the greater the threshold shift that can be expected in the future. Many large studies document the degree and prevalence of age-related hearing loss. Figure 149-8 shows the median pure-tone thresholds of a group "highly screened" to exclude noise exposure.

Schuknecht[19] has defined four separate types of presbycusis on the basis of pathologic findings in human temporal bones. In sensory presbycusis, hair cells are progressively lost beginning at the base of the cochlea. Patients with this abnormal pattern tend to have steeply sloping high-frequency hearing losses. Neural presbycusis implies a loss of auditory nerve fibers. These patients tend to have reduced speech discrimination out of proportion to their pure-tone thresholds. Atrophy of the stria vascularis was seen in strial presbycusis, and these patients have relatively flat audiograms. Finally, Schuknecht[19] described a fourth type of presbycusis termed *cochlear conductive* or *mechanical presbycusis*. No light microscopic abnormalities are seen in these specimens, and Schuknecht theorized that an age-related change in the stiffness of the basilar membrane resulted in the hearing loss. These patients have gradually descending (approximately 25 dB/octave) pure-tone thresholds.[19] These patterns are not useful clinically because there is variability of audiometric shape and severity in individuals with age-related hearing loss, and clinically the losses do not fall naturally into these patterns.[225]

Meniere's Disease and Endolymphatic Hydrops

Meniere's disease is a common disorder consisting of fluctuant SNHL, tinnitus, episodic vertigo, and aural fullness. The hearing loss typically begins as a fluctuating low-frequency loss, but progresses, gradually or quickly, to a permanent loss involving any or all frequencies. The tinnitus is most commonly described as "buzzing" or "roaring," and can fluctuate in loudness and character. The aural fullness perhaps is the most consistent and stable complaint, but it also typically fluctuates. The vertigo of Meniere's disease is the most disabling aspect of the disorder.

The typical presentation consists of episodic, spontaneous attacks of severe, spinning vertigo that lasts for several hours. The attacks frequently are associated with nausea, vomiting, and diaphoresis. After the attacks, patients usually are fatigued for 24 hours or more. The attacks of vertigo may be associated with a concomitant or preceding change in their hearing loss, tinnitus, or aural fullness. Many patients also have various combinations of dysequilibrium or motion-provoked vertigo between the classic attacks. Subtypes of Meniere's disease are described that have only vestibular symptoms (vestibular Meniere's) or auditory symptoms (cochlear Meniere's).

The hallmark of Meniere's disease is variability and unpredictability, and this holds true for the hearing loss associated with the disease. The hearing loss may fluctuate wildly or be quite stable over many years. It also may manifest as a sudden, permanent loss. Although most patients progress over the years to a moderate to severe loss, many do not, and progression to a profound loss is rare. The low frequencies are more commonly involved than middle or high frequencies, especially in the early stages of the disease, but there is considerable variability. The disease is bilateral in perhaps 30% of cases.[226-229] Patients who have bilateral disease usually develop bilaterality early in the course of the disease. Patients who maintain hearing loss in only one ear for the first few years rarely develop it in the contralateral ear. This finding supports the idea that the syndrome we have labeled as Meniere's disease is actually the manifestation of several different pathologies.

Although vestibular destructive therapy (chemical or surgical labyrinthectomy, vestibular nerve section) is effective in controlling the episodic vertigo associated with Meniere's disease, no therapy to date has been proven to be effective in the treatment of the hearing loss. The most widely accepted medical therapy for Meniere's disease, a sodium-restricted diet and diuretic administration, is based on the hypothesis that the hydropic distention of the membranous labyrinth can be reduced by altering body water distribution, as in the management of hypertension. This regimen of sodium restriction and diuretics was first proposed by Furstenberg and has gained wide acceptance.[230,231] Despite this wide acceptance, few studies have been able to show definitively that there is a beneficial therapeutic effect with regard to improvement or preservation of hearing.[232-234]

The creation of an intralabyrinthine shunt (cochleosacculotomy) has been proposed as a mechanism to control the hydrops and prevent the recurrent membrane ruptures thought to traumatize the organ of Corti. This procedure has been shown to be beneficial in controlling vertigo, but has been associated with an unacceptably high incidence of severe hearing loss.[235,236] Surgical decompression of the endolymphatic sac, with or without shunting of the sac into the mastoid or the subarachnoid space, has been proposed as a way to correct the presumed defective sac physiology. Although excellent results have been reported, double-blind, randomized studies comparing endolymphatic sac with mastoid shunt procedures with mastoidectomy alone have failed to show any significant difference in maintenance of hearing or control of vertigo.[237-241] The unpredictable, fluctuating nature of Meniere's disease, the lack of an objective diagnostic test, and the high incidence of spontaneous resolution of symptoms make it extremely difficult to come to valid statistical conclusions with regard to therapeutic efficacy in Meniere's disease.

Meniere's disease may be considered to be idiopathic endolymphatic hydrops. Although it is the most common cause of endolymphatic hydrops, many other entities result in similar clinical presentations and pathologic findings. The syndrome of delayed endolymphatic hydrops consists of the initial development of a profound SNHL in one ear, followed by development of symptoms of endolymphatic hydrops years later in either the ipsilateral ear (ipsilateral delayed endolymphatic hydrops) or the contralateral ear (contralateral delayed endolymphatic hydrops).[242] Other pathologic processes have been associated with development of endolymphatic hydrops, including syphilis, temporal bone trauma, serous labyrinthitis, stapedectomy, and autoimmune disease.[19] The reader is referred to Chapter 165 for a more extensive discussion of Meniere's disease.

Sudden Sensorineural Hearing Loss

A subset of patients with SNHL develop hearing loss rapidly, frequently awakening with it in the morning or developing a progressive loss over 12 hours or less. This commonly is a frightening experience for the patient, who might assume that this is a life-threatening disorder or will lead to profound, bilateral deafness. Neither scenario typically is the case. The etiology and appropriate evaluation and management of this common syndrome have been the subject of much debate over the years, illustrated by the fact that there have been more than 100 proposed etiologies for this disorder.[243]

Prevalence, Natural History, and Prognosis

Sudden SNHL is a syndrome and not a diagnosis. Most commonly, the syndrome has been referred to as sudden deafness or sudden SNHL and has many possible etiologies. In most patients, the cause is idiopathic. Among patients with no identifiable etiology, there seem to be several different pathogenetic mechanisms. In reviewing the natural history of the disorder, one should keep in mind that the described natural history is most likely the sum of the histories of patients with differing abnormalities. Because of this, and because of the difficulty of studying such an entity, either in clinical trials or in animal models, much remains to be learned about sudden SNHL.

A universal definition of sudden SNHL does not exist, and the rate of progression of SNHL can vary from seconds to days. For purposes of this discussion, sudden SNHL develops over 12 hours or less. This rate of progression can sometimes be unclear in the history because some patients notice their loss only on using a telephone. In other patients, sensation of fullness or tinnitus is the patient's primary initial complaint. The incidence of sudden SNHL has been estimated to range from 5 to 20 per 100,000 persons per year.[244] In a typical otologic practice, this may account for 2% to 3% of unselected outpatient visits. Any age group can be affected, but the peak incidence seems to be in the sixth decade. The male/female distribution is essentially equal.[245] Bilateral involvement is rare, and simultaneous bilateral involvement is very rare.[246]

The most common presentation is a patient noticing a unilateral hearing loss on awakening. Others notice a sudden, stable hearing loss or a rapidly progressive loss. Occasionally, patients note a fluctuating hearing loss, but most patients have a stable loss. A sensation of aural fullness in the affected ear is common and frequently is the only complaint. Tinnitus is present in the ear to a variable degree, and the hearing loss sometimes is preceded by the onset of tinnitus. Vertigo or dysequilibrium is present to a variable degree in approximately 40% of patients.[247]

Four variables seem to affect the prognosis of untreated idiopathic sudden SNHL: severity of loss, audiogram shape, presence of vertigo, and age. The more severe the loss, the lower the prognosis for recovery, and profound losses have an exceptionally poor prognosis. Upsloping and midfrequency losses recover more frequently than downsloping and flat losses. The presence of vertigo, particularly with a downsloping loss, is a poor prognostic indicator, although not all studies concur on this point. Reduced speech discrimination carries a poor prognosis. Finally, most studies show that children and adults older than 40 years have a poorer prognosis than others.[244,245,247,248] Most recovery occurs within the first 2 weeks after onset; as a corollary, the prognosis for recovery decreases the longer the loss persists. Without treatment of any kind, a significant proportion (30% to 65%) of patients experience complete or partial recovery.[247,248]

Etiology of Sudden Sensorineural Hearing Loss

The management of sudden SNHL should be focused on excluding known causes of the syndrome, especially conditions that require treatment. Similar to causes of SNHL in general, these disorders can be conveniently broken down into infectious, neoplastic, traumatic, ototoxic, immunologic, vascular, developmental, psychogenic, and idiopathic etiologies. Despite a thorough search for an etiology, most cases remain idiopathic. There has been, and continues to be, considerable debate regarding the pathogenesis of the disease in these patients. Principal theories include viral infection, vascular occlusion, intracochlear membrane breaks, and autoimmunity.

Infectious Disorders

Viral Infection

Viral neuritis or cochleitis has long been thought to be the most common cause of sudden SNHL, although much of the evidence for this is circumstantial. SNHL can complicate clinically evident infections with mumps, measles, herpes zoster, and infectious mononucleosis and with congenital rubella and cytomegalovirus. Of patients presenting with sudden SNHL, 28% report a viral-like upper respiratory infection within 1 month before the onset of their hearing loss.[245,249] With the possible exception of mumps parotitis and herpes zoster infections, however, the clinical diagnosis of viral infections is unreliable. Azimi and colleagues[250] reported that 53% of mumps meningoencephalitis occurs without parotitis. Other evidence for a viral etiology for sudden SNHL includes studies documenting increased viral titers in such patients,[249] pathology consistent with viral infection,[251-254] and viral seroconversion studies.[255-258] These seroconversion studies showed a mixture of viruses, including herpes simplex, herpes zoster, cytomegalovirus, influenza, parainfluenza, mumps, measles, and adenovirus. The studies failed to show a relationship between titer results and severity of hearing loss or frequency of recovery.

For some viruses, the evidence of a causative relationship is more convincing. The mumps virus has been isolated from the perilymph of patients with sudden SNHL,[259] and experimental mumps labyrinthitis has been reproduced in hamsters by inoculation of the subarachnoid space with mumps virus.[259,260] Lassa fever, an arenavirus infection endemic in West Africa, has been shown to be associated with sudden SNHL in approximately two thirds of the patients.[261] The time course, the results of audiometric testing, and the patterns of recovery in Lassa fever are very similar to that in idiopathic sudden SNHL.[262] Measles and rubella also are well-documented causes of labyrinthitis,[253] but these cases rarely manifest in a manner typical of sudden SNHL. Herpes zoster oticus also can cause sudden SNHL, although it is a clinical entity distinct from idiopathic sudden SNHL. The evidence that herpes zoster may be associated with idiopathic sudden SNHL is limited to viral seroconversion studies. Sudden hearing loss associated with infectious mononucleosis is rare but has been reported.[263] For a few viruses, there seems to be strong evidence that they may be an occasional cause of idiopathic sudden SNHL. For most other viruses, there is an association with idiopathic sudden SNHL, although convincing evidence of a causal relationship is lacking.

Meningitis

Meningitis is a well-recognized and common etiology of acquired severe to profound SNHL. It is possible that rare cases of idiopathic sudden SNHL may be caused by subclinical meningoencephalitis.

Syphilis

It has been estimated that the incidence of syphilis in patients with sudden SNHL is 2% or less. Syphilitic hearing loss may manifest at any stage of the disease, and may be associated with other manifestations of syphilis, with vestibular symptoms, or alone. It may manifest with unilateral or bilateral sudden SNHL. More typical presentations of syphilitic hearing loss are discussed in other sections of this chapter.

It is important to consider the possibility of reactivation of syphilis in patients with HIV infection.[194,196]

Lyme Disease

Lyme disease is a well-established etiology of acute facial paralysis, and it would not be unreasonable to assume that it could also cause SNHL. Hearing loss has not been strongly associated with Lyme disease, however. The literature contains several descriptions of associations between positive Lyme titers and acute or chronic SNHL, but a causal relationship seems doubtful. In one large study, Lyme titers were found in 21% of patients with sudden SNHL, and there was no difference in outcome between patients with or without positive titers, despite antibiotic treatment of all seropositive patients.[264] Reports of hearing loss in patients with Lyme disease with improved hearing after antibiotic treatment are limited to a few case reports.[35,265]

Acquired Immunodeficiency Syndrome

At autopsy, 88% of HIV-positive patients have evidence of CNS involvement,[266] and approximately 10% of patients with AIDS present because of neurologic symptoms.[190] It is not surprising that sudden SNHL may be associated with HIV infection. Sudden SNHL is not a common manifestation of AIDS, but it has been well documented in the literature.[191-194,197,267] In the presence of HIV infection, sudden SNHL may occur with or without the presence of opportunistic infection, and may occur without clinical evidence of AIDS. Sudden SNHL caused by reactivation of latent syphilis may complicate any stage of HIV infection.[193,194,196] As previously mentioned, some cases of sudden SNHL associated with AIDS may be the result of reactivation of latent cytomegalovirus infection.

Neoplasms

Acoustic Neuroma

It is common for a sudden SNHL to be the initial manifestation of a vestibular schwannoma (acoustic neuroma). According to Moffat and associates,[215] 10.2% of acoustic neuromas initially manifest with sudden SNHL. The prevalence of acoustic neuroma among patients with sudden SNHL is less clear. Estimates range from 0.8%[246] to 3%.[268,269] There are no clear criteria that suggest that sudden SNHL may be a result of an acoustic neuroma. The presence of tinnitus in the ipsilateral ear before sudden SNHL is suggestive, but not present in most cases.[269] In addition, midfrequency and high-frequency hearing loss are more commonly associated with acoustic neuroma than are low-frequency losses, and electronystagmography abnormalities are more common with acoustic neuroma.[269]

Responsiveness of the hearing loss to treatment with steroids is an unreliable indicator that a retrocochlear lesion is not present. There have been many reported cases of steroid-responsive SNHL and SNHL with spontaneous recovery, which have been found to be caused by acoustic neuroma.[269,270] One should have a high level of suspicion for acoustic neuroma in any patient with SNHL. Most investigators recommend that ABR or gadolinium-enhanced MRI be obtained in patients with sudden SNHL.[271] There is no relationship between tumor size and SNHL.[269] Because of this and the numerous more recent reports of false-negative ABR tests in patients with small acoustic neuromas,[3,272-274] it seems warranted to evaluate all patients with sudden SNHL with gadolinium-enhanced MRI.

Other Neoplasms

Neoplasms of the cerebellopontine angle or internal auditory canal other than acoustic neuromas have been associated with SNHL. These include meningioma,[275] cholesteatoma, hemangioma,[276] arachnoid cyst, and metastatic neoplasms. In addition, skull base neoplasms eroding into the inner ear can rarely manifest with SNHL.

Trauma and Membrane Ruptures

Head Injury

Sensorineural hearing loss of any degree can occur after closed or open head injury. The mechanism of injury in such patients has been shown pathologically to vary from mild loss of outer or inner hair cells or cochlear membrane breaks to fracture across the labyrinth or intralabyrinthine hemorrhage.[19] Many of these injuries are pathologically indistinguishable from injuries of acoustic trauma.[277] Some patients experience a variable degree of recovery from head injury–induced hearing loss, a process probably equivalent to the temporary threshold shift seen with acoustic trauma.

Perilymphatic Fistula

Round or oval window fistulas can occur congenitally, after stapedectomy, or after barotrauma. SNHL is well described after events causing barotrauma.[278,279] Some investigators theorize that these fistulas can occur after heavy lifting or straining or even spontaneously. Patients with such fistulas can have sudden or fluctuating SNHL and varying degrees of vestibular symptoms. There is no reliable test for the presence of such a fistula, and even surgical exploration is subject to error.[280] Except in poststapedectomy patients, it is doubtful that perilymph fistula is a significant cause of SNHL.

Intracochlear Membrane Breaks

Intracochlear membrane ruptures and fistulas have been documented pathologically in patients with endolymphatic hydrops.[19] Such breaks have been proposed to be an etiology of SNHL.[281] Schuknecht and Donovan[253] found no evidence of such breaks in a series of temporal bones from patients with sudden SNHL. Gussen[282-284] found evidence to support the membrane break theory in a few temporal bones, however.

Pharmacologic Toxicity

Toxicity from any of the drugs discussed in the previous section on ototoxic causes of SNHL may result in the relatively sudden onset of hearing loss. In addition to these drugs, others have been associated with sudden SNHL. Interferon has been associated with SNHL, which has been reversible in most patients.[285,286] The insecticides malathion and methoxychlor have been associated with bilateral SNHL.[287]

Immunologic Disorders

The finding that many patients with SNHL seem to benefit from glucocorticoid therapy, and the finding of cross-reacting circulating antibodies in many patients with sudden and rapidly progressive SNHL suggest that at least a subset of SNHL cases are caused by inner ear autoimmunity.[185] In addition, many well-known autoimmune diseases have been associated with SNHL, including Cogan's syndrome,[288,289] systemic lupus erythematosus,[175] temporal arteritis, and polyarteritis nodosa.

Vascular Disorders

Sudden hearing loss can occur with occlusion of the cochlear blood supply. Because of the abruptness of onset of SNHL, and the fact that the cochlea depends on a single terminal branch of the posterior cerebral circulation, vascular occlusion has been thought by some authors to be an attractive hypothetical etiology for idiopathic sudden hearing losses. Other aspects arguing against a circulatory etiology include high incidence of spontaneous recovery, significant incidence in young patients, lack of an apparent increased incidence in diabetics, the fact that the loss frequently is limited to just a few frequencies, and the fact that most patients do not have vertigo. Similar to viral etiologies, a few cases of SNHL are clearly a result of vascular occlusion, but most cases remain idiopathic. Temporal bone studies have not found evidence of vascular occlusion in cases of idiopathic SNHL.[19] Series of patients with idiopathic SNHL have been evaluated for hemostatic abnormalities, and no significant association has been found.[290] The role of vascular occlusion versus viral infection in these idiopathic cases has been the subject of extensive debate over the years. At this point, it seems doubtful that a significant proportion of cases of idiopathic sudden SNHL have a vascular etiology.

Migraine,[145,291,292] hemoglobin SC disease,[151,153-156] and macroglobulinemia[148,149] have been documented to be associated with sudden SNHL. Rare cases of thromboangiitis obliterans (Buerger's disease) have been associated with sudden SNHL.[293] Small cerebellar

infarctions may mimic labyrinthine lesions, including sudden onset of hearing loss.[294] Cardiopulmonary bypass[158,159] and noncardiac surgery[157] have been associated with an increased risk of sudden SNHL. Sudden SNHL has been reported after spinal manipulation with probable injury to the vertebrobasilar arterial system.[295]

It has long been believed that patients with diabetes have a higher incidence of idiopathic sudden SNHL than nondiabetics. This belief has been based on the higher incidence of other acute cranial neuropathies and on the diffuse vascular abnormality found in patients with diabetes. Histologic studies of human temporal bones from patients with diabetes mellitus have not consistently found any abnormal alterations.[19,296] In a careful study of the relationship of idiopathic sudden SNHL to diabetes, Wilson[28] found that diabetic patients with idiopathic sudden SNHL were less likely to recover hearing at higher frequencies. There was no significant difference in audiologic pattern between diabetic and nondiabetic patients with idiopathic sudden SNHL. An attempt to compare the incidence of diabetes in patients with idiopathic sudden SNHL with a control population was inconclusive.

Developmental Abnormalities

Large vestibular aqueduct syndrome is associated with SNHL, which frequently occurs in a stepwise fashion associated with minor head trauma. It seems plausible that other, as yet undefined, developmental abnormalities may predispose individuals to sudden SNHL, either spontaneously or after minor head trauma.

Idiopathic Disorders

Meniere's Disease

Some patients seen with typical sudden SNHL ultimately may develop a history more suggestive of endolymphatic hydrops or even frank Meniere's syndrome; this probably constitutes only 5% of all patients with sudden SNHL. In a review of 1270 patients with Meniere's disease, Hallberg[297] found that only 4.4% had initially been seen with sudden SNHL. A subset of these patients very likely have an autoimmune etiology of their hearing loss.

Multiple Sclerosis

Multiple sclerosis is a demyelinating disorder of the CNS manifested by differing neurologic lesions separated by space and time. Sudden SNHL is a rare initial manifestation of multiple sclerosis.[124,137,298] Among patients with multiple sclerosis, auditory abnormalities are common.[127,130]

Sarcoidosis

CNS manifestations are rare (incidence of 1% to 5%), although among patients with neurosarcoidosis, 20% have eighth cranial nerve findings. This eighth cranial nerve involvement may manifest as sudden SNHL, although it only rarely is an isolated finding.[178]

Psychogenic Disorders

Pseudohypacusis frequently manifests as a sudden loss. In most patients, malingering is readily apparent after initial audiologic studies.

Treatment

Treatment of sudden SNHL should be based on its etiology. If an etiology is apparent, the appropriate treatment should follow: appropriate antibiotics for infectious causes, withdrawal of the offending drug for ototoxicity, and so on. Most cases are idiopathic, and treatment decisions should be made on the basis of empirical guidelines. Because of the poor understanding of idiopathic sudden SNHL, controversy surrounds its treatment. Because of the dictum, "first, do no harm," new or unconventional treatment protocols should be well reasoned and carefully applied. It seems prudent to avoid the use of potentially harmful treatment protocols outside of controlled clinical trials because serious complications and deaths have been reported after treatment of idiopathic sudden SNHL.[299]

Steroids in moderate doses have become the most widely accepted treatment option for idiopathic sudden SNHL. Wilson and associates[248] performed a double-blind randomized trial of steroids versus placebo for idiopathic sudden SNHL. Their active drug group was treated with either a 10-day or 12-day course of orally administered dexamethasone or methylprednisolone at tapering doses. They found that all patients ($n = 14$) with midfrequency losses (loss at 4 kHz better than 8 kHz) had a complete recovery regardless of treatment. They noted that among patients with losses greater than 90 dB HL at all frequencies, there was no difference in recovery between the steroid-treated versus placebo-treated groups. Among the remaining patients (nonprofound losses with hearing at 4 kHz better than 8 kHz), there was a significant increase in recovery in the steroid-treated group. Of patients, 78% in the steroid-treated group experienced complete or partial recovery compared with 38% in the placebo-treated group.

In a similar study, Moskowitz and colleagues[300] confirmed a significantly improved recovery rate in a steroid-treated group compared with a nontreated control group. Direct steroid treatment to the inner ear, via middle ear instillation or round window microcatheter, has seen increasing use on an empiric basis. This treatment has the potential advantage of very high steroid concentrations within the inner ear without the associated systemic side effects. Anecdotal reports indicate that this treatment may be more effective than orally administered steroids, and that local complications are infrequent.[301] Refer to Chapter 153 for a more complete discussion.

An alternative management regimen proposed by some investigators involves attempts to improve blood flow or oxygenation to the inner ear. Vasodilators have been used extensively in the treatment of sudden SNHL. Any proposed vasodilator would have to cross the blood-brain barrier and have an effect on intracranial circulation. Intravenous histamine infusion, oral papaverine, and oral nicotinic acid have been used most frequently. Fisch and others[302,303] have shown that breathing a gas mixture with increased partial pressures of oxygen and carbon dioxide (carbogen) results in increased perilymph oxygen tension in cats and humans.

Other agents proposed to improve cochlear blood flow include low-molecular-weight dextran, mannitol, pentoxifylline, and heparin. In addition, the iodinated radiographic contrast agent diatrizoate (Hypaque) was serendipitously noted during a vertebral angiogram to improve the hearing in patients with sudden SNHL. Morimitsu and coworkers[304] showed in the same report that, in a small series, 54% of patients treated with diatrizoate had a complete recovery compared with 19% of a control group treated with vasodilators. It was later shown that triiodinated benzoic acid derivatives such as diatrizoate had a specific effect on the stria vascularis, protecting the endocochlear potential from furosemide-induced depression.[305]

Clinical studies that used the previously mentioned agents have shown poor to mixed results. The varying definition of recovery used by different authors complicates the interpretation of these results. No controlled study has shown a beneficial effect from papaverine, nicotinic acid, or pentoxifylline. Donaldson[306] found no improvement with aggressive heparin therapy in a series of patients. In a prospective, randomized double-blind study, Probst and colleagues[307] found no difference in outcome between placebo and treatment with low-molecular-weight dextran, pentoxifylline, or both. In a randomized prospective trial comparing papaverine/dextran infusion treatment with inhaled carbogen, the average hearing improvement in the carbogen group was better, although no significant difference in hearing recovery was seen between the two groups after 5 days of treatment.[302] After 1 year of treatment, there was a statistically significant improvement in hearing in the carbogen-treated group.[308]

Redleaf and coworkers[309] reviewed their 10-year experience with diatrizoate and dextran, and noted that 74% of their 36 patients showed audiometric improvement with treatment. Only 36% improved to 50% of their premorbid hearing levels, however, very close to the 32% recovery noted in the placebo group of the Wilson study.[248] Another, even more empirical, treatment protocol is the so-called shotgun regimen, which uses most of the proposed agents in hopes that one or more will be beneficial. Wilkins and associates[310] reviewed their results with a protocol of dextran, histamine, diatrizoate, diuretics, steroids, oral vasodilators, and carbogen inhalation. Although it was a

retrospective study and limited by methodologic problems, these authors were unable to show any difference in recovery between patients who had the "full" protocol versus patients who had only portions of the total regimen. Their overall results were no better than the results expected for spontaneous recovery.

Still other treatment ideas are directed at other presumed etiologies. Because endolymphatic hydrops is a common final pathology for many inner ear injuries and may be associated with some cases of sudden SNHL, some authors have advocated treatment with a sodium-restricted diet and a diuretic.[311] Because of the evidence for a viral etiology and specifically evidence of herpesvirus, treatment with oral antiviral medications has been proposed. Because these drugs rarely have adverse side effects, many practitioners routinely treat patients with sudden hearing loss with antivirals in addition to steroids. In a double-blind, randomized, placebo-controlled multicenter trial, Tucci and colleagues[312] found no difference in hearing recovery outcome between patients treated with steroids and valaciclovir versus steroids and placebo. Some authors have advocated aggressive management with very large (mega) doses of steroids or even cytotoxic medications. Clinical studies supporting the efficacy of any of these treatments have yet to be published.

The author believes that a reasonable treatment approach to sudden SNHL is as follows: Sudden SNHL is regarded as an otologic emergency, and patients are evaluated audiometrically and by an otolaryngologist on an urgent basis. Known etiologies are excluded by a thorough history; physical examination; and appropriate laboratory, special audiologic, and radiologic studies. Gadolinium-enhanced MRI of the internal auditory canal and cerebellopontine angle is obtained in all patients. A 10-day course of prednisone, approximately 1 mg/kg/day, is prescribed, followed by a slow taper. If a partial recovery is noted at the end of the 10 days, the full dose is extended another 10 days, and the cycle is repeated until no further improvement is noted. Valaciclovir, 1000 mg three times daily for 10 days, also is considered because it may be beneficial, and because the risks and side effects are minimal. A 2-g sodium diet is recommended with a hydrochlorothiazide-triamterene diuretic combination. Despite the possible efficacy of carbogen treatment, it is not routinely offered to patients with sudden SNHL. The treatment requires inpatient hospitalization, which renders it expensive and inconvenient. Insurers typically regard carbogen as investigational, which results in significant expense to patients. Because of these issues and its controversial nature, most patients do not accept carbogen if it is offered. It would be more strongly considered in exceptional situations, such as a patient with sudden SNHL in an only-hearing ear or in a particularly motivated patient.

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CHAPTER ONE HUNDRED AND FIFTY

Tinnitus and Hyperacusis

Carol A. Bauer

Key Points

- Tinnitus is common, affecting 30% of people older than age 55, with an annual incidence of 5%.
- Disturbing tinnitus that impairs daily life activity affects 3% to 5% of individuals with tinnitus.
- Auditory deprivation from hearing loss induces central neural changes that result in tinnitus. Mechanisms responsible for tinnitus involve peripheral triggers and central plasticity.
- Sound therapy is an effective form of tinnitus treatment, and benefits most patients when combined with education and adjunct treatments directed toward factors that exacerbate tinnitus.
- Tinnitus that can be modulated with somatic manipulation may respond to therapy targeting temporomandibular joint and cervical spine disorders.
- Medications are helpful for specific forms of tinnitus.
- Functional imaging studies suggest that temporoparietal cortex and cortical association areas may be important targets for electric and magnetic modulation of tinnitus.
- Clinicians knowledgeable in auditory function and head and neck physiology are well equipped to provide most tinnitus patients with effective treatment, including education, rehabilitation of hearing loss, and identification and treatment of exacerbating factors.

Tinnitus

Tinnitus is the perception of sound without an external source. Although 30 million Americans are estimated to have chronic tinnitus, for most it is not a problem sufficient for them to seek treatment. Tinnitus is a chronic sensation virtually all would prefer not to experience, but for most it is not disabling. Disturbing tinnitus occurs in 3% to 5% of individuals with tinnitus.[1] Until more recently, treatments available for disturbing tinnitus were limited. Significant advances in auditory neuroscience have advanced the treatment of tinnitus beyond the traditional recommendation instructing the patient to "learn to live with it." This chapter reviews current theories and mechanisms of idiopathic subjective tinnitus. It also outlines a clinical strategy for evaluating tinnitus and determining tinnitus subtypes, and reviews current management strategies for tinnitus.

Tinnitus can be classified as objective or subjective. Objective tinnitus can be detected by an observer using a stethoscope or ear canal microphone. Objective tinnitus arises from vascular or muscular sources. Objective tinnitus usually has a pulsatile quality. Table 150-1 lists the causes of pulsatile tinnitus. Many of these causes are uncommon and are not responsible for most instances of tinnitus. Because there are excellent reviews of treatments for objective tinnitus, this uncommon form is not addressed further.[2]

In contrast to objective tinnitus, subjective tinnitus is not audible to an observer. This form is more common, with a 5-year incidence of 5.7%.[3] Estimates of subjective tinnitus prevalence range from 8% to 30%, depending on the definition of tinnitus, tinnitus severity, the population sampled, and assessment methodology.[3-5] In a large population-based study of participants 55 to 99 years old, combining detailed tinnitus questionnaires with audiologic assessment, 30% reported experiencing tinnitus, with prevalence related to audiometric threshold, but not age or gender.[5] Mildly annoying tinnitus was reported in 50% of respondents, and extremely annoying tinnitus was reported in 16%. Tinnitus prevalence in individuals with normal hearing was 26.6% compared with 35.1% in individuals with hearing loss. An estimated 20% of individuals with profound hearing loss do not experience tinnitus.[6] These data illustrate that chronic tinnitus is associated with, and may be triggered by, hearing loss, but they also indicate that hearing loss is not an invariable cause of tinnitus. The pathology necessary to initiate tinnitus may be quite subtle. The survey data also confirm that as a clinical problem tinnitus is more than the presentation of its sensory features.

Idiopathic Subjective Tinnitus

Idiopathic subjective tinnitus is the most common form affecting adults, and is the focus of this chapter. By definition, this form of tinnitus excludes known objective causes, such as conductive hearing loss, endolymphatic hydrops, and cerebellopontine angle neoplasms. Historically, the pathology underlying idiopathic tinnitus was unknown, and the symptom was generally viewed as refractory to intervention. Advances in tinnitus research have revealed mechanisms likely responsible for some forms of idiopathic tinnitus. Two examples are tinnitus-associated pathology of the cochlea or head and neck, and tinnitus susceptible to somatic modulation. Both mechanisms are discussed subsequently.

Subjective tinnitus can be subtyped based on etiology, the pattern of associated hearing loss, psychoacoustic features (simple versus complex), exacerbating factors, psychological comorbidities, and the presence of somatic modulators. Tinnitus subtype classification schemes can be useful in identifying forms of tinnitus that are responsive to specific targeted treatment programs. Table 150-2 lists some useful features for subtyping tinnitus.

Hearing Loss Subtypes

The two most common types of hearing loss associated with tinnitus are noise-induced hearing loss (NIHL) and presbycusis. NIHL is a

Table 150-1

Objective Tinnitus

Pulsatile

- Synchronous with pulse
  - Arterial etiologies
    - Arteriovenous fistula or malformation
    - Paraganglioma (glomus tympanicum or jugulare)
    - Carotid artery stenosis
    - Other atherosclerotic disease (subclavian, external carotid)
    - Arterial dissection (carotid, vertebral)
    - Persistent stapedial artery
    - Intratympanic carotid artery
    - Vascular compression of cranial nerve VIII
    - Increased cardiac output (pregnancy, thyrotoxicosis)
    - Intraosseous (Paget's disease, otosclerosis)
  - Venous etiologies
    - Pseudotumor cerebri
    - Venous hum
    - Jugular bulb anomalies
- Asynchronous with pulse
  - Palatal myoclonus
  - Tensor tympani or stapedius muscle myoclonus

Nonpulsatile

- Spontaneous otoacoustic emission
- Patulous eustachian tube

Table 150-2

Subjective Tinnitus Subtypes

- Pattern of hearing loss
  - Noise-induced hearing loss
  - Presbycusis
  - Unilateral
  - High-frequency hearing loss
  - Outer hair cell dysfunction
- Somatic tinnitus
  - Temporomandibular joint dysfunction
  - Cervical dysfunction
  - Gaze-evoked
  - Cutaneous-evoked
  - General somatosensory modulated
- Typewriter tinnitus
- Exacerbated by sleep or rest
- Musical/complex
- Associated affective disorder
- Intrusive (versus habituated)

significant and growing health problem. Although reduction of exposure to occupational noise has been effective in the last several decades, there has been a notable increase in the incidence of NIHL from recreational and leisure activity in children and adolescents, and military combat–related noise exposure in young adults.[7-9] A Web-based survey of 9693 adolescents determined that 61% of respondents experienced hearing loss and temporary tinnitus after attending concerts.[10] Acute transient tinnitus is nearly universal immediately after unprotected exposure to loud acoustic stimuli such as gunfire and amplified music. Tinnitus prevalence among Army personnel evaluated for hearing complaints after deployment was 30% compared with 1.5% in personnel not deployed.[8]

The prevalence of chronic tinnitus associated with NIHL is 50% to 70%.[11] Subjectively, the sensory aspects of acute and chronic tinnitus can be very similar. Chronic tinnitus occurs in a delayed time course for a significant portion of individuals with a history of exposure to damaging sounds. It is unknown if the pathology of transient acoustic trauma–induced tinnitus is the same as the pathology responsible for chronic tinnitus associated with permanent noise-induced threshold shifts. Chronic tinnitus induced by acoustic trauma occurs at a younger age than tinnitus associated with other types of hearing loss. Consequently, acoustic trauma–induced tinnitus is experienced for a longer portion of the life span than other forms of tinnitus.

NIHL and associated tinnitus are preventable. In addition to obvious proactive methods, such as wearing ear protective hardware, intervention in the periexposure period may prove useful in preventing the onset or progression of NIHL, and possibly the incidence of tinnitus. Intense sound exposure triggers a reduction of blood flow and a cascade of metabolic events in the cochlea, with formation of reactive oxygen and nitrogen species that damage cellular lipids, proteins, and DNA, culminating in increased cell death.[12] Interventions targeting these molecular mechanisms of NIHL include antioxidant therapy such as vitamin E, salicylate, and *N*-acetylcysteine.[13] *Ginkgo biloba* extract contains multiple compounds with vasotropic, potential neuroprotective, and antioxidant effects. Although uncontrolled trials and anecdotal reports have suggested the efficacy of ginkgo, a more recent review failed to show efficacy in treating tinnitus.[14]

Serum magnesium levels have been correlated with NIHL in animals.[15] Controlled studies in humans have shown the prophylactic efficacy of oral magnesium in preventing temporary and permanent NIHL.[16,17] It is unknown, however, if these interventions are also effective in decreasing the risk of immediate or delayed onset of tinnitus after traumatic injury.

Presbycusis is sensorineural hearing loss related to aging. Most cases of presbycusis cannot be strictly and solely attributed to aging, but rather involve some combination of cochlear injury from additional sources, such as cumulative noise injury, metabolic or vascular dysfunction, and genetic predisposition. Elderly patients with diabetes have significantly higher pure-tone thresholds, lower otoacoustic emission amplitude, and lower speech recognition in noise[18] than age-matched individuals without diabetes.[19] Interactions between age and other factors affecting the cochlea and auditory pathway make identification of a single mechanism for presbycusis-associated tinnitus and an effectively targeted intervention a challenge.

Somatic Tinnitus Subtype

Somatic tinnitus is a unique form of tinnitus in which the loudness, laterality, or tonality of the tinnitus can by modulated by somatic stimuli. This form of tinnitus was originally observed in a small group of patients after surgical removal of large vestibular schwannomas.[20,21] Postoperatively, these patients had the ability to modulate their chronic tinnitus by exaggerated eye movements, leg motion, or gentle cutaneous stimulation of the hands or face.[22,23] The presumed mechanism of action for this unusual form of tinnitus is neural sprouting or aberrant reinnervation after auditory deafferentation. Subsequent to these observations, however, a more general form of somatosensory modulation has been found in patients with idiopathic tinnitus. In these cases, tinnitus is modulated by maneuvers or stimulation of the head and neck region. It has been reported that forceful isometric contraction of the head and neck muscles can modify the loudness and pitch of tinnitus in 65% to 80% of patients with mild, idiopathic tinnitus.[24-26] Tinnitus can be induced by strong contractions of muscles in the jaw, head, or neck in 58% of subjects without a history of tinnitus.[25]

The association between tinnitus and somatic pathology of the head and neck is underscored by the reported higher incidence of tinnitus in individuals with temporomandibular joint dysfunction and normal audiometric thresholds compared with controls.[27] One third of patients with symptoms of temporomandibular joint dysfunction reported modulation of tinnitus with jaw movement or pressure applied

to the temporomandibular joint.[28] When tinnitus occurs in association with disorders of the head and neck, such as temporomandibular joint dysfunction, unilateral facial pain, otalgia, and occipital or temporal headache, successful tinnitus alleviation may be possible using interventions targeting the somatic dysfunction.

Animal research has established that multimodal and in particular somatic inputs to the auditory pathway are evident from auditory brainstem to cortex.[29-33] These inputs allow integration of information from vision, head position, and internal sound (e.g., vocalization) to be used in important functions, such as sound localization and auditory selective attention. It has been hypothesized that aberrations in these multimodal connections can either trigger tinnitus or modulate existing tinnitus. Reduction of normal afferent input to the auditory brainstem (e.g., cochlear nuclei) may trigger inappropriate compensatory up-regulation of somatosensory inputs to these regions. Stimulus-driven or spontaneous activity within the nonauditory somatic pathways may be perceived as an audible "sound."[33]

Recognition of somatic tinnitus is important because it may be amenable to targeted intervention. Levine and colleagues[34] systematically reviewed the efficacy of treatments targeting somatosensory systems. They defined somatic tinnitus syndrome as tinnitus that is (1) perceived in the ear and (2) ipsilateral to the somatic trigger and (3) not associated with any new hearing complaints. Tinnitus that is strongly lateralized to one ear in the presence of symmetric hearing (including symmetric hearing loss) would theoretically have a somatic etiologic component by the definition of Levine and colleagues.[34] The review by these authors presents evidence that somatic tinnitus is often responsive to acupuncture, electric stimulation of the scalp and auricle, trigger point treatment, and treatment of temporomandibular joint dysfunction.[34]

Typewriter Tinnitus Subtype

Typewriter tinnitus is defined, as its name implies, by a characteristic sensation. The tinnitus has a staccato quality, similar to a typewriter tapping, popcorn popping, or Morse code signal. Its presence is intermittent and chronic. It may be confused with tinnitus arising from a muscular source, such as spasm of the tensor tympani or stapedius muscle, or palatal myoclonus. That typewriter tinnitus is a condition distinct from these somatic sources is supported by a case history of a patient with typewriter tinnitus that failed to respond to multiple treatments, including tensor tympani and stapedius resection. The patient was successfully treated, however, with carbamazepine (Tegretol). This case illustrates the importance of accurate recognition and diagnosis of typewriter tinnitus.[35] A small case series reporting successful treatment with carbamazepine suggested that typewriter tinnitus may be caused by vascular compression of the auditory nerve ipsilateral to the tinnitus.[36]

Tinnitus Treatment Strategies

Auditory Deprivation and Neural Plasticity

Acoustic-based tinnitus treatments encompass a range of delivery systems and types of sound. The rationale for using external sound to treat tinnitus derives from the hypothesis that hearing loss leads to deafferentation-induced reorganization of the auditory pathway. Hearing loss decreases the afferent stream of neural activity from the cochlea to the auditory cortex. Chronic deafferentation alters activity in the auditory brainstem and midbrain, and may change the tonotopic organization of the auditory cortex. Brainstem spontaneous activity may increase, and midbrain patterns may change (e.g., with aberrant synchronization or bursting) because of compensatory down-regulation of inhibition. Altered activity in the auditory pathway may be responsible for the tinnitus percept. Stimulus interventions that restore afferent input to more normal levels may act through improved inhibition. They may also restore cortical tonotopic organization to normative levels and reduce tinnitus.

A related phenomenon that illustrates the concept and treatment of deafferentation-induced cortical plasticity is phantom limb pain.[37] The phantom limb syndrome is the continued sensation of the presence of an absent limb, in a distorted or painful manner, after amputation. Amputation of a limb is an extreme form of deafferentation. The parallels between tinnitus and phantom limb pain, in terms of onset rate, persistence, and affected ages, are striking. Greater than 90% of amputees experience a vivid limb phantom immediately after amputation.[37] Phantoms are more likely to occur in adults than in children.[38] In many cases, the phantom sensation fades after days or weeks, but it persists chronically for decades in 30% of patients.[37]

It is well known that the adult and the immature brain can undergo plastic change. Neural plasticity is the ability of a neuron or neural network to change its function, organization, and connectivity through long-term alterations in synaptic efficiency.[39] Neurons can significantly alter their response to inputs, and receptive field sizes change, as a consequence of either decreased or increased input and training procedures.[40] The changes can be extensive. Magnetoencephalographic studies have shown that stimulation of intact body areas distant from the amputation site is perceived, with corresponding central neural activity, at the cortical site of the amputated limb.[41] Similar changes of auditory cortical representation may underlie tinnitus.[42] Primary auditory cortex steady-state evoked magnetic fields were enhanced in tinnitus patients compared with controls, and the degree of enhancement correlated with the perceived intensity and intrusiveness of the tinnitus.[43] Functional imaging studies in humans have suggested that expanded representation of frequency regions in the auditory cortex may underpin tinnitus.[44-47]

Animal models have been important in studying the deafferentation-loss-of-inhibition hypothesis of tinnitus, and have been used to evaluate sound therapy for reversal of pathologic neural plasticity. A key study by Norena and Eggermont[48] illustrates the effect of noise trauma and therapeutic sound stimulation on receptive fields of primary and secondary auditory cortex. Cats exposed to a traumatizing noise were evaluated for changes in the location and responsiveness of auditory cortex neurons to acoustic stimuli. The frequency tuning of cortical neurons was altered after the trauma, distorting the overall representation of sound and over-representing frequencies surrounding the exposure sound. A second cohort of cats, exposed to the same traumatizing sound, was subsequently reared in an enriched acoustic environment for several weeks before mapping the auditory cortex. The enriched environment was spectrally composed to compensate for the anticipated frequency distortions induced by hearing loss.

Two important outcomes were obtained in the cats raised in the enriched environment: (1) Their hearing loss was significantly reduced compared with the cats with similar sound exposure raised in a quiet environment, and (2) there was no evidence of plastic reorganization of the auditory cortex. The tonotopic organization of the exposed and treated cats was similar to that of unexposed control cats. These results suggest that tinnitus may be partly the result of abnormal reorganization of the auditory cortex. These results show that therapeutic acoustic intervention may be effective in reducing or eliminating the abnormal cortical organization associated with, and potentially responsible for, tinnitus. The implications for tinnitus treatment using sound therapy are obvious.

Using Sound to Decrease Loudness and Annoyance of Tinnitus

Acoustic stimulation is an important component of successful management of tinnitus in many patients. A wide range of acoustic delivery strategies are currently available. Most patients with tinnitus, including patients with minimal threshold shift on standard audiometric testing, can benefit from acoustic stimulation. Patients with severe to profound hearing loss that is not amenable to conventional amplification can achieve tinnitus relief from other modes of auditory pathway stimulation, such as cochlear implantation or cortical stimulation (discussed later).

Ambient Stimulation

The simplest method of increasing afferent input to reverse putative central reorganization and tinnitus is environmental sound enrichment. Use of supplemental environmental sound to treat tinnitus has been recommended for more than 50 years.[49] Enrichment can be achieved using background music, relaxation tapes or CDs, tabletop nature sound machines, or waterfalls or fountains. Patients are typically instructed to use a source of constant background sound to decrease attention to their tinnitus. Sound enrichment is not intended to mask

the tinnitus in the conventional sense of completely eliminating the tinnitus percept (discussed subsequently). Rather, by elevating the level of ambient sound using a constant, spectrally rich stimulus, the tinnitus sensation becomes less noticeable.

Hearing loss is present in more than 90% of patients with tinnitus. Conversely, epidemiologic studies have reported tinnitus prevalence of 50% in hearing-impaired patients.[50] Effective use of sound stimulation for managing tinnitus in hearing-impaired patients can be achieved only with appropriate amplification. Typically, amplification is achieved with hearing aids. Even without supplemental sound, the therapeutic effect of hearing aids for tinnitus patients is well documented.[51,52] Hearing aids reduce the awareness of tinnitus through amplification of ambient sound and reduce the perception that tinnitus masks hearing and impedes communication.

Surr and coworkers[53] reviewed the initial effect of hearing aid use on tinnitus in 124 patients. Approximately one half of patients reported that the hearing aid reduced (26%) or eliminated (29%) the tinnitus. Folmer and Carroll[54] reviewed their clinical experience with 50 patients with mild to moderate sensorineural hearing loss fitted with hearing aids for tinnitus management. Patients were re-evaluated 6 to 48 months after initial fitting (mean 18 months), and 70% reported significant improvement in their tinnitus. Similar results were obtained in a larger study of 1440 patients fitted with hearing aids for unilateral or bilateral hearing loss.[55] In this study, digital hearing aids provided significantly greater tinnitus relief than analog hearing aids. Of patients fitted with digital hearing aids for unilateral hearing loss, 65% reported greater than 50% improvement in tinnitus compared with 39% reporting a similar degree of improvement after fitting with an analog aid. An even greater therapeutic effect was obtained with bilateral digital hearing aids: 85% of patients reported greater than 50% improvement in tinnitus compared with 30% fitted with bilateral analog aids.

Programmable digital hearing aids can selectively amplify within the high-frequency range, a region where most tinnitus patients typically have some measurable threshold loss. Current-generation digital aids have significant output gain up to 10 kHz, which significantly benefits tinnitus patients with hearing loss in the high-frequency range. An open-fit, nonoccluding ear mold is crucial to minimize the occlusion effect, which can amplify the tinnitus percept.[56]

Personal Listening Devices

Tinnitus management can be implemented through the use of personal listening devices, such as flash-memory music players. Miniaturization, data storage, and digital software have greatly expanded the available tools that clinicians and patients can use to produce a customized sound library. Inexpensive online sources are also available for downloading digital sound specifically developed for tinnitus therapy (e.g., http://www.vectormediasoftware.com). Patients can build and use a small library of sounds, which may include music to their liking, nature sounds, and noise bands of different spectral composition. Important key features of any regimen of amplified sound therapy are (1) use of open-fit, nonoccluding ear level drivers, (2) long-term exposure to the sounds, (3) sound spectral composition that is reasonably broad, and (4) sound levels below that of the perceived tinnitus.

Appropriate patient education is crucial to successful treatment. Many treatment failures occur because patients erroneously expect complete elimination of tinnitus after a few days to weeks of treatment. Patients must be counseled about the typical slow time course of improvement, and must be encouraged to have realistic expectations about the benefits of sound therapy. Sound therapy can decrease the subjective loudness and significantly decrease the annoyance of tinnitus, but this may require weeks to months of daily application.[57,58]

Total Masking Therapy

Total masking therapy is the use of sound with spectral characteristics and sufficient volume to render the tinnitus inaudible. This form of sound therapy has likely been used for centuries, and derives from empirical experience that certain environmental sounds are efficient tinnitus maskers. The clinical use of total masking therapy has a long history.[59] A formal masking therapy program was first proposed by Vernon and Schleuning.[60] Patients are fitted with ear-level devices that generate sound. The devices can be adjusted to have outputs with different frequency spectra and levels. There is no codified scheme for selecting effective masker characteristics. The general fitting principle is to determine the minimum level of broadband noise that masks the tinnitus without interfering with communication. The fitting is empirical because there is a wide range of patient preference in the type and level of sound that masks the tinnitus and is not perceived as annoying.[61,62] Two significant benefits likely attend the successful application of total masking therapy: (1) Patients have control over their tinnitus, and (2) patients experience immediate relief with complete elimination of tinnitus.[63]

Benefits from masking therapy have been shown in a large prospective controlled study of chronic significant tinnitus in U.S. veterans.[64] Validated standardized tinnitus severity questionnaires were used to screen and enroll 123 subjects with clinically significant tinnitus. Subjects were quasirandomly assigned to either the total masking group or a tinnitus retraining therapy (TRT) group. Subjects in the total masking group received hearing aids, maskers, or combination instruments, and all received information counseling over an 18-month follow-up period. Subjects in the TRT group received standardized TRT treatment (see later). All subjects were evaluated for response to treatment at 6, 12, and 18 months. Subjects in both treatment groups showed improvement on multiple measures of tinnitus over the course of the study. Subjects in the total masking group who rated their tinnitus as a "moderate" problem had effect sizes between 0.27 and 0.48 compared with effect sizes for the TRT group of 0.77 and 1.26 at 18 months. Mean effect sizes in subjects with tinnitus rated as a "very big problem" were 0.64 in the total masking group and 1.08 in the TRT group. Although both therapies resulted in clinically significant improvement in tinnitus with medium (>0.5) to large (>0.8) effect sizes, optimal outcomes were obtained with long-term TRT treatment.

Acoustic Stimulation Combined with Education and Counseling

TRT combines sound therapy with a formalized program of directive counseling to achieve habituation to tinnitus.[65] TRT is based on the assumption that tinnitus distress derives from activation of an emotional and an autonomic response to tinnitus.[66] Within this theoretical framework, tinnitus emerges as a result of damage or dysfunction within the auditory pathway, and is detected at subcortical levels of the brain. The critical event that leads to clinically significant tinnitus is not its sensory features, but rather the perception and evaluation of the tinnitus-related neural activity that occurs in the auditory cortex, and subsequent cortical interaction with the limbic system, prefrontal cortex, and cortical association areas.[65] According to Jastreboff and Hazell,[65] tinnitus becomes clinically significant when a negative affective response to the tinnitus has been established.

The goals of TRT are to remove, decrease, or change the perception of tinnitus by promoting habituation of the reactions to the tinnitus sensation. Habituation of the reaction to tinnitus would reduce the derived annoyance, anxiety, and stress. A key feature of TRT involves behavioral retraining of the associations induced by the tinnitus sensation. TRT uses five distinct levels of therapy, aimed at stratified patient groups. Stratification is based on tinnitus distress, associated hearing impairment, presence of sound-induced exacerbation of tinnitus, and comorbid hyperacusis (see later). The five strata are (1) patients with tinnitus that causes minimal distress (category 0); (2) patients with tinnitus causing distress (category 1); (3) patients with distressing tinnitus and hearing loss (category 2); (4) patients with distressing tinnitus, normal hearing, and hyperacusis (category 3); and (5) patients with distressing tinnitus, normal hearing, hyperacusis, and prolonged sound-induced exacerbation of tinnitus (category 4). Treatment is specific for each patient category, and uses directive counseling, auditory enrichment, hearing aids, and sound generators.

Jastreboff and Hazell[65] described directive counseling as a teaching session in which patients are instructed on the mechanisms of tinnitus generation. Directive counseling demystifies tinnitus for the patient, and attempts to eliminate anxiety and fear of tinnitus through education. Auditory enrichment is typically achieved through the use of broadband noise generators. Ear-level devices physically similar in design to maskers are used, but sound output is distinctly lower than

that used in masking therapy where sound levels render the tinnitus inaudible. In TRT, the volume of noise is set at a partial masking level, which allows continued perception of the tinnitus. The concept is that habituation would normally occur to the noise, much as one habituates to the background sound of a running air conditioner. Because the external noise and the internal tinnitus are equivalent in loudness, or "mixed," habituation generalizes to the tinnitus and its attendant emotional reactions.

Retrospective clinical trials evaluating the efficacy of TRT have generally been positive with a consensus that TRT reduces the annoyance and impact of tinnitus within a time frame of 12 to 18 months. Sheldrake and associates[67] reported a retrospective review of clinical outcomes on 224 patients completing a course of TRT. Outcome measures were percentage of time of tinnitus awareness, tinnitus distress, and the number of life factors affected by tinnitus. A successful outcome was defined as either a 40% improvement in tinnitus annoyance and awareness or 40% improvement in annoyance or awareness plus an improvement or facilitation of one life factor. At 6 months, 70% of patients had a successful outcome, and this percentage increased to 84% by 18 months. The mean awareness of and distress related to tinnitus before therapy were 63% and 45%, whereas after 18 months of therapy these percentages were 15% and 5%.

Bartnik and colleagues[68] retrospectively reviewed the 12-month outcomes of 108 clinic patients treated with TRT for chronic tinnitus. Significant improvement was defined as a minimum decrease of 20% in at least three of these parameters (impact on daily life, time aware of tinnitus, degree of annoyance, and tinnitus intensity). Significant improvement was reported for patients treated with counseling alone (79%), counseling combined with noise generators (73%), and counseling combined with hearing aids (88%).

Berry and coworkers[69] reported the 6-month results of a nonrandomized, prospective analysis of 32 patients treated with TRT. Treatment outcomes included psychophysical measures of loudness discomfort levels; minimal masking levels; and a standardized, validated measure of tinnitus severity and disability (Tinnitus Handicap Inventory [THI]; see later). Average THI score (pretreatment total score 52) significantly improved after 6 months of therapy (post-treatment total score 24; $P < .001$). Nine patients with sound sensitivity (hyperacusis) before treatment had a significant ($P < .05$) increase in sound tolerance after therapy, indicated by a 14 dB HL improvement in loudness discomfort level.

TRT is derived from a reasonable set of assumptions about the mechanism of disruptive chronic tinnitus, and may provide an effective therapeutic option for some patients. Evaluation of TRT effectiveness using the gold standard of a randomized controlled trial with multiple outcome measures is yet to be reported, however.

Acoustic Desensitization Protocol

The acoustic desensitization protocol is a proprietary tinnitus treatment program (Neuromonics, Bethlehem, PA) that combines features of sound therapy; systematic desensitization; directive counseling; and supportive intervention for stress management, sleep disruption, and coping strategies. Systematic desensitization is a psychological technique originally developed for the treatment of phobias. Progressive gradual controlled exposure to the phobic stimulus within the context of a deeply relaxed state of mind results in a gradual desensitization of the phobic response to the stimulus.[70] This technique has been adapted to the treatment of tinnitus, by targeting the individual's tinnitus as the stimulus that provokes the phobic, or at least negative emotional, response.

Patients listen to their tinnitus in gradual, progressive increments within a background context of pleasant, relaxing therapeutic sound. The therapeutic sound has three key features that are fundamental to the protocol. The sound used is music spectrally modified in accord with the patient's hearing loss, with enhancement of loudness levels of frequencies where hearing loss is pronounced, re-establishing stimulation of the auditory pathway over a wide frequency range. Music that is nonintrusive and has a slow rhythm is used to maximize relaxation during treatment. The music has a dynamic component that permits intermittent tinnitus perception alternating with tinnitus masking. The gradual exposure to one's tinnitus in the context of therapeutic music is achieved using a staged treatment program. In the initial stage, the spectrally modified music is embedded within a background sound of high-frequency noise that masks the tinnitus. In the second stage, the masking noise is removed, and the tinnitus percept becomes gradually and progressively more audible.

A Neuromonics-sponsored outcome study of the acoustic desensitization protocol has shown positive effects.[71] In the study, 35 patients with moderate to severe tinnitus received Neuromonics tinnitus treatment and were tested for subjective (distress, awareness) and objective (minimum masking levels, loudness discomfort levels) changes at four time points, including 1 year, after therapy. Within the first 6 months of treatment, 91% of participants reported an improvement in tinnitus distress, reflecting a mean improvement of 65% in the Tinnitus Reaction Questionnaire. The reported "percent of time aware of tinnitus" before therapy was 90%, which was significantly reduced to 30% after 12 months of therapy.

Cognitive-Behavioral Therapy for Tinnitus

Cognitive-behavioral therapy (CBT) is a well-established psychotherapy based on identification of maladaptive behaviors and their modification using therapist-mediated cognitive restructuring. The technique has been successfully applied to tinnitus for many years, and forms the basis of another type of habituation therapy for tinnitus.[66] CBT for tinnitus is based on the concept that the normal response to meaningless stimuli is habituation, and tinnitus distress results from a failure to habituate. Jakes and associates[72] summarized the causes of habituation failure to include emotional responses, orientation to stimuli, arousal, and unfavorable signal-to-noise ratio. When a normal subject is presented repeatedly with a meaningless stimulus, responses to the stimulus, such as orientation, attention, and cognitive processing, soon habituate (i.e., the responses drop out). When the same subject is presented repeatedly with a noxious stimulus (e.g., the cry of a baby), sensitization occurs (i.e., the response to the stimulus becomes more pronounced and may have an emotional component). CBT uses techniques of reassurance, relaxation training, and selective attention distraction to induce habituation to tinnitus. It may be, as suggested by some, that defusing the emotional component of tinnitus, with or without concomitant changes in tinnitus loudness, is sufficient for improving patient outlook and perception.[72]

A review of CBT as a tinnitus treatment by the Cochrane Collaboration evaluated six trials comprising 285 participants.[73] The primary outcome measure was subjective tinnitus loudness, and the secondary outcome measures were improvement in symptoms of mood disturbance and quality-of-life evaluation. The pooled results for the five trials reporting subjective loudness before and after treatment showed no significant difference between treatment with CBT and either a waiting list control or an alternative treatment. There was also no significant treatment effect for the secondary outcome measures of depression and mood disturbance. There was a significant improvement, however, in the quality of life of CBT participants, as measured by a global decrease in tinnitus severity, with a standardized mean difference of 0.70 (95% CI 0.33 to 1.08). The reviewers conclude that CBT has a significant impact on the qualitative aspects of tinnitus and contributes positively to the management of tinnitus.

Nevertheless, controversy continues regarding the relative benefits of CBT and sound stimulation in promoting psychological and physiologic habituation in patients who have chronic tinnitus. Hiller and Haerkotter[74] followed 124 outpatients with chronic tinnitus, randomly assigned to either CBT alone or CBT combined with sound stimulation using noise generators. Tinnitus-related distress and psychosocial functioning were significantly improved in both groups, with no additive benefit observed in the sound-stimulation group.

Transcranial Magnetic Stimulation

The more recently developed diagnostic and treatment technique of transcranial magnetic stimulation (TMS) has opened a novel avenue for investigating the causal and associational aspects of tinnitus-related cortical activity, and may provide an effective tinnitus therapy for some patients. TMS uses a brief intense current in a surface coil applied to the scalp to induce a magnetic field in the underlying brain. The mag-

netic pulse induces a temporary focal disruption of neural activity in a discrete area of cortex. This "virtual lesion" briefly, and reversibly, disrupts cortical activity and allows the investigator to determine if the cortical region of interest contributes to a specific behavior or perception.[75] The effect of a single pulse-induced magnetic field is short-lived, on the order of milliseconds. Repetitive TMS over seconds to minutes causes neuronal depolarization within the superficial cortex. Low-frequency (<1 Hz) repetitive TMS decreases cortical excitability,[76] whereas high-frequency (5 to 20 Hz) repetitive TMS increases cortical excitability.[77] All repetitive TMS frequency parameters can induce long-term plastic changes in cortical function that reportedly outlast the stimulation period by hours to days.[78]

TMS can be combined with functional imaging techniques to locate regions of interest for TMS application, and to examine the effect of cortical stimulation on distant structures. The combined techniques of TMS and functional brain imaging may be useful for investigating cortical mechanisms of tinnitus, and may be of clinical value as a treatment for some forms of tinnitus. Enhanced cerebral blood flow in temporoparietal cortex was shown using positron emission tomography (PET) imaging in patients who could modulate their tinnitus with orofacial movement[46] or eye position.[45] The association between tinnitus loudness and temporoparietal cortical blood flow was also observed in studies using lidocaine as a tinnitus modulator.[47,79,80] To date, there have been no studies correlating changes in regional cerebral blood flow and altered tinnitus sensation modulated by repetitive TMS, although combining these methods might be revealing.

The functional relevance of temporoparietal cortex activity to tinnitus was first suggested by studies examining the effect of repetitive TMS on auditory hallucinations. Three patients with schizophrenia and persistent auditory hallucinations were studied in a double-blind crossover design using low-frequency (1 Hz) repetitive TMS to the left temporoparietal cortex versus sham stimulation. All three subjects reported significant improvement in severity of hallucinations after active treatment compared with sham stimulation. Two subjects had near-complete cessation of hallucinations for 2 weeks after treatment.[81] Meta-analysis of the effect of repetitive TMS on auditory hallucinations in schizophrenic patients has supported these early results, and shows a significant positive effect.[82]

Plewnia and coworkers[83] showed short-term suppression of idiopathic subjective tinnitus after high-frequency (10 Hz) TMS stimulation of temporoparietal cortex. Fourteen adults with chronic tinnitus were stimulated at 12 cortical locations with 10 Hz repetitive TMS for 3 seconds, repeated five times, and at two control locations for sham stimulation. Eight of the 14 subjects reproducibly reported on more than one trial an immediate decrease in tinnitus loudness after repetitive TMS, ranging from slight decrease to complete suppression. Five subjects did not perceive a reproducible attenuation of tinnitus, and one subject reported transient increase in tinnitus loudness that persisted for 2 weeks. Post-hoc analysis showed that the strongest tinnitus attenuation was obtained with stimulation of left temporal and left temporoparietal cortex.

Long-term inhibition of cortical hyperactivity can be induced using low-frequency repetitive TMS.[76,84] In a double-blind, crossover, placebo-controlled (sham stimulation) trial of low-frequency repetitive TMS, PET-guided neuronavigation was used to target hyperactive areas within the superior temporal gyrus of 14 patients with chronic tinnitus (tinnitus durations of 1 to 30 years). The left temporal lobe was targeted in 12 patients, and the right lobe was targeted in 2 patients. After 5 days of treatment (2000 stimuli/day) there was a 7-day nontreatment interval, followed by 5 days of sham treatment. A significant reduction in standardized tinnitus questionnaire score was observed after active treatment ($P < .005$), but not after sham stimulation ($P = .336$).[85] At 6-month follow-up, five patients reported worse tinnitus, with a mean increase in tinnitus questionnaire score of 5, and eight patients had an average 12. 4 decrease in tinnitus questionnaire score. Three of the eight patients had a clinically significant reduction in score of 16 to 34 points. There was no correlation between initial tinnitus severity or tinnitus duration and the response to active treatment.

Plewnia and coworkers[86] subsequently examined the immediate effect of neuronavigated low-frequency repetitive TMS and sham stimulation on tinnitus loudness in another eight subjects in a single-blind crossover trial. Tinnitus loudness was assessed using an 11-point visual analog scale, with −5 indicating suppression of tinnitus, 0 no change, and +5 indicating increased loudness. Areas shown to be correlated with the tinnitus percept on PET imaging were primarily in sensory association cortex, but not primary auditory cortex. These included the left middle and inferior temporal cortex, the right gyrus angularis, and the posterior cingulum. Two of the eight subjects showed a decrease in tinnitus loudness (−3 and −5) after active low-frequency repetitiveTMS, and no change after sham stimulation. Three subjects were nonresponders during active and sham stimulation, and the three remaining subjects reported moderate (−2) to significant (−5) reduction in tinnitus loudness after active stimulation and sham stimulation. The outcomes of these evaluations of TMS were very mixed.

If TMS is effective in reversing neurogenic pathology, its mechanism of action remains unclear. High-frequency repetitive TMS can result in long-lasting clinical improvement in cases of chronic neurogenic pain, suggesting that the therapeutic effect may not be related to a reduction in cortical excitability, but rather be through reversal of chronic maladaptive plastic changes.[87] The long-term effect of different repetitive TMS stimulation rates delivered to the left temporoparietal cortex was assessed in 39 subjects with chronic tinnitus (duration 6 months to 25 years).[88] Subjects were randomly assigned to one of four stimulation groups (1 Hz, 10 Hz, 25 Hz, or sham stimulation) and treated with five sessions over a 2-week period. All subjects in the active repetitive TMS groups reported significant improvement ($P < .05$) in tinnitus severity on the standardized THI questionnaire at 4 months after completing treatment compared with the sham treatment group. Tinnitus improvement occurred regardless of stimulation rate for active repetitive TMS. A greater proportion of subjects experienced an 80% or greater improvement in THI score after treatment with 10 Hz (29%) and 25 Hz (35%), however, than after 1 Hz (6%). As reported in other studies, there was a negative correlation between tinnitus duration and percent improvement 4 months after treatment.

Further work is needed in this area to understand the mechanisms of TMS and its efficacy in treating tinnitus. It is unknown if the tinnitus-associated hyperactivity in secondary auditory cortex normalizes after subjectively successful treatment with repetitive TMS. There currently is no consensus on the relationship of hemispheric dominance and metabolic hyperactivity to tinnitus. Some studies have shown left temporoparietal activity is associated with tinnitus,[45,46] and others have shown right-sided dominance.[47,80] Finally, there are conflicting results on the effect of tinnitus duration on responsiveness to TMS.

Electric Stimulation

Electric stimulation has been used to treat tinnitus since the advent of Volta's battery in the early 19th century.[89] Although anodal direct current has been used by multiple investigators to suppress tinnitus, practical use is limited by tissue damage induced by chronic stimulation with direct current.[90] Nondestructive methods of delivering electric current required the development of improved noninvasive techniques, such as transcutaneous electric stimulation, and surgically implanted devices using alternating current, such as cochlear implants and cortical stimulators.

Transcutaneous Electric Stimulation

Initial systematic attempts to decrease tinnitus using transcutaneous electric stimulation used the Audimax Theraband, a device that delivers inaudible, transdermal electric current to the mastoid eminence. Lyttkens and colleagues[91] showed complete tinnitus suppression in one of five patients treated with transcutaneous stimulation. In a larger double-blind crossover study, 20 patients were treated first using the active device followed by a placebo device in which the internal circuitry was deactivated. Four patients (20%) reported reduction with the placebo, whereas two patients (10%) reported tinnitus reduction with the active device. One of the responders was examined further with random trials of either active or placebo stimulation, and reported a median 70% tinnitus decrease during active stimulation and 16% decrease during placebo stimulation.[92] A subsequent single-blind cross-

over study of 30 patients showed a similar proportion of patients responded to stimulation.[93] Levine and coworkers[34] reviewed the characteristics of tinnitus patients who respond to transcutaneous electric stimulation and concluded that the common finding present in all cases is tinnitus with features of somatic modulation.

Herraiz and associates[94] prospectively studied the effect of transcutaneous electric nerve stimulation in 26 patients with tinnitus categorized as somatically modulated. Although the trial lacked a placebo control, a striking effect was obtained in this sample from a selected population, with tinnitus elimination in 23% and tinnitus improvement in 23%. Further analysis by tinnitus type showed that the group most responsive to transcutaneous electric nerve stimulation treatment had typewriter tinnitus, with 88% experiencing improved or eliminated tinnitus.

Cochlear Implants

Suppression of tinnitus as a secondary benefit of cochlear implantation was noted in the early days of cochlear implant development.[95] Although there is a large variability in the methods of assessing and reporting tinnitus, most studies report a consistent and clinically significant beneficial effect of cochlear implantation on tinnitus suppression.[96] A significant proportion of patients (38% to 85%) report either a decrease or complete suppression of tinnitus after intracochlear electrode insertion before initial stimulation.[97] Although there have not been extensive studies, there does not seem to be a significant difference in effective tinnitus suppression with different device manufacturers. Cochlear stimulation has been reported to reduce tinnitus intensity perceived in the ear contralateral and ipsilateral to the implant.[97] This is not paradoxical because the brainstem cochlear nuclei have contralateral connections, and bilateral elevation of spontaneous activity in the dorsal cochlear nucleus has been shown in animals with tinnitus induced by unilateral acoustic trauma.[98]

The effectiveness of cochlear stimulation on decreasing tinnitus loudness increases over time. Tinnitus was suppressed in 65% of patients on initial stimulation, but after a 2-month period, stimulation suppressed tinnitus in 93% of patients. These observations suggest that the mechanism responsible for tinnitus suppression by cochlear implants may relate to reversal of maladaptive central plastic changes associated with auditory deprivation.

Multiple factors may contribute to the efficacy of tinnitus suppression after cochlear implantation, including etiology, duration, and extent of hearing loss, and stimulation strategy. Potentially, there is much to be learned about tinnitus mechanisms from patients with cochlear implants. Studies that systematically investigate the impact of these factors are few, however.

Pharmacologic Tinnitus Treatments

Written accounts indicate medical treatment of tinnitus dates back to the Egyptians (2660-2160 B.C.E.).[99] An ear that was bewitched or humming would be infused with oil, frankincense, tree sap, herbs, and soil. Mesopotamian writings considered the psychological aspects of tinnitus, possibly the earliest recognition that stress and emotional factors are significant components of tinnitus dysfunction. These early attempts at treatment contained elements that presage modern views of tinnitus pathology.

Until more recently, most pharmacologic interventions for tinnitus were empirically determined. Anecdotal experience and fortuitous observations of tinnitus relief were the primary sources of innovation. Over the past 50 years, pharmacologic treatment of tinnitus has become more rational. Anesthetics (lidocaine, tocainide, mexiletine), anticonvulsants (carbamazepine, gabapentin), and tranquilizers (diazepam, clonazepam, oxazepam) have been investigated as tinnitus treatments. They have in common the general property of facilitating neural inhibition. Antidepressants such as trimipramine, nortriptyline, amitriptyline, and selective serotonin reuptake inhibitors have been tested for their ability to ameliorate the comorbid mood disturbance associated with tinnitus. Considering only well-controlled trials, mixed results have been obtained for all drugs tested to date.

The hypothesis that tinnitus emerges from increased central neural activity after loss of inhibition can be used to guide pharmacologic intervention. Animal models of tinnitus support the loss of inhibition and enhanced neural activity hypothesis.[98,100,101] The loss-of-inhibition hypothesis provides a rational basis for numerous pharmacologic interventions, including lidocaine, carbamazepine, alprazolam, and gabapentin.

Despite the increase in targeted tinnitus drug trials, using a single agent to treat a heterogeneous large sample of subjects has been for the most part unsuccessful. Several reasons, not mutually exclusive, may account for this lack of success. Most tinnitus clinical trials randomly select and assign participants to treatment groups. There is emerging evidence, however, that tinnitus is a heterogeneous disorder with variable pathologic features.[34,102,103] Testing drugs with a single mechanism of action is unlikely to succeed when using randomly determined heterogeneous sample groups. For the same reason, trials using small dose ranges may fail.

Studies that enroll subjects with a single tinnitus etiology may be more likely to identify successful treatments. A study that examined the effect of gabapentin on tinnitus in two specific patient subpopulations obtained positive results.[104] The study was designed to test the hypothesis that acoustic trauma leads to a loss of inhibition in the auditory pathway mediated by the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The hypothesis was advanced after an animal experiment that showed gabapentin, a GABA analogue, to be effective in reducing the loudness of tinnitus in rats.[100] This study used a very wide dose range, and tested one group of patients with objective and historical evidence of traumatic sound exposure, and a second group without such evidence. Gabapentin was found to reduce tinnitus annoyance significantly in the trauma group at a daily dose level of 1800 to 2400 mg. In contrast, a subsequent clinical trial studying the effect of only a single dose in a randomly selected group of patients did not obtain a significant effect.[105] The therapeutic effect was likely missed because only a single dose level was used, and the treatment group included various tinnitus etiologies. Drugs with a specific mechanism of action are unlikely to be effective in all subjects characterized by such heterogeneity. Stratified study designs with segregation of tinnitus types, etiology, and hearing characteristics should be more successful in identifying effective drug therapies.

The most extensively used drugs for tinnitus treatment are antidepressants. Attempting to treat tinnitus with antidepressants is sensible for two reasons. There is a well-recognized association between severe tinnitus and mood disorders. The pharmacologic mechanism of action of many antidepressants involves receptors and neurotransmitters that are located in the auditory pathway.[106] Although GABA deficiency seems to contribute to tinnitus pathology,[104,107-109] the role of other neurotransmitter systems in triggering or maintaining tinnitus is currently unknown. Serotonin is known to function as a modulator of sensory systems, learning, and memory. Along with acetylcholine, serotonin can affect behavioral conditioning and associated plastic changes in auditory cortex. Both neurotransmitters may be important in the distress associated with tinnitus.

Treatment with sertraline, a selective serotonin reuptake inhibitor, improved tinnitus loudness ($P = .014$) and severity ($P = .024$) in a group of tinnitus patients with an associated depressive or anxiety disorder.[110] Despite this positive evidence, it is unclear whether selective serotonin reuptake inhibitor treatment improved tinnitus directly or indirectly through alleviation of mood disorder. A placebo-controlled trial of the selective serotonin reuptake inhibitor paroxetine in a group of subjects without coexisting mood or anxiety disorder did not produce improvement in any tinnitus measure over placebo.[111]

Clinical Evaluation of Tinnitus

Clinical treatment of a patient with tinnitus should begin with a general medical evaluation followed by a complete head and neck examination. Objectives of the evaluation include a descriptive characterization of the tinnitus (psychoacoustic properties, impact on daily life, reactive components); determination of etiology; and identifying factors that exacerbate, ameliorate, or trigger the tinnitus. At a minimum, the results of the examination educate the patient about the tinnitus. Patient education is a powerful therapeutic component of the clinical process, which should not be undervalued or underestimated. A thor-

ough examination also facilitates development of a directed individual treatment plan.

Tinnitus can be described in terms of its psychoacoustic properties and in terms of the affective or reactive responses to the tinnitus. The psychoacoustic properties of tinnitus can be determined from psychophysical assessment of its features. Important features include tonality; noise aspects such as hissing, buzzing, humming, sizzling, and roaring; unilateral-bilateral localization in the head; temporal features (e.g., pulsatile vs. steady); and interaction with external sounds, including masking, inhibition, and exacerbation. The affective or reactive components include the comorbid problems of depression, sleep disruption, difficulty with concentration, sadness, anxiety, and fear. The reactive components of tinnitus are highly individual and are significant factors in tinnitus disability. Careful evaluation of both components is important for the clinician to appreciate fully the impact of the tinnitus on the individual, and to formulate a directed treatment plan.

The auditory qualities of tinnitus can be assessed using standardized questionnaires and psychophysical measurements. Basic information about the auditory characteristics of tinnitus includes localization (left, right, in the head, outside of the head), constancy (episodic, fluctuating, constant, pulsatile), pitch, loudness, and sound quality (tonal, hissing, buzzing, clicking, ringing). This information can be useful in determining etiology. Pulsatile tinnitus can imply a vascular source. Fluctuating tinnitus may be linked to specific triggers, such as foods, illnesses, stress, or acoustic trauma. Episodic tinnitus may relate to unstable hearing thresholds deriving from cochlear dysfunctions, such as hydrops or perilymph fistulas. Clicking or tapping tinnitus may occur with mechanical disorders affecting either the middle ear muscles (stapedial or tensor tympani spasm) or the auditory nerve (vascular loop or demyelination). Identification of tinnitus with specific characteristics such as these is very useful, and can lead to a directed course of therapy.

Standardized Outcome Measures

Numerous standardized questionnaires are available for measuring tinnitus severity and perceived disability. Standardized assessment is useful for documenting clinical outcomes and reporting the results of clinical trials. Standardized measures are also crucial for determining the subjective impact of tinnitus. Finally, standardized questionnaires are useful for stratifying patients according to the severity and impact of their tinnitus, which facilitates identification of specific problems, and serves to triage patient care from minimal counseling to intensive rehabilitation.

The THI is a widely used self-assessment tool.[112] It is a 25-item questionnaire that has good construct validity, strong internal consistency, and good test-retest reliability. The THI yields a total score and three subscale scores. The subscales encompass functional limitations in mental (e.g., difficulty concentrating), social, occupational and physical domains (e.g., difficulty sleeping); emotional responses to tinnitus (e.g., anger, depression, anxiety); and catastrophic reactions to tinnitus (e.g., desperation, loss of control, failure to cope). In addition to its good internal consistency and test-retest reliability, the THI has high convergent validity with the 27-item Tinnitus Handicap Questionnaire and the 52-item Tinnitus Questionnaire.[113] The 95% confidence interval for the THI is 20 points, suggesting that a difference in scores of 20 points or greater represents a statistically and clinically significant change.[112]

Tinnitus Comorbidities

As previously mentioned, severe debilitating tinnitus is frequently associated with depression, anxiety, and other mood disorders.[114-116] Comorbid emotional disturbance is not unique to tinnitus, and has been shown to accompany many chronic illnesses.[117,118] It is well recognized that coexisting mood disorders hamper improvement and interfere with treatment of conditions such as chronic pain and tinnitus. Identifying and treating comorbid conditions in tinnitus patients is an important aspect of the clinical evaluation. Tools are available to screen for mood disorders in an outpatient setting (e.g., Beck Depression Inventory, Hamilton Anxiety Scale). An important therapeutic adjunct is teaching coping skills through behavior modification and cognitive therapy.[119]

Tinnitus and Insomnia

Patients commonly report that tinnitus interferes with their ability to fall asleep, and sleep disruption is a significant comorbid condition in adults and children.[120,121] A robust correlation has been shown between the reported loudness and severity of tinnitus and degree of sleep disruption.[122,123] A positive feedback loop may exist in which tinnitus leads to sleep deprivation, and the sleep deprivation exacerbates somatic complaints, tinnitus among them. Depression and anxiety exacerbated by sleep loss may significantly interact with and compound the cycle of tinnitus and poor quality sleep. Coping ability may also deteriorate as a result of sleep deprivation or lack of restorative sleep. Interventions that break this cycle by improving sleep have been shown to improve tinnitus.

Pharmacologic sleep aids such as melatonin can reduce tinnitus severity, particularly in patients with pronounced sleep difficulties.[14,125] Bedside sound generators have also been shown to improve sleep quality significantly and lessen tinnitus distress. The bedside sounds most frequently chosen are often selected for their perceived positive emotional effect.[126]

Sleep difficulties include insufficient sleep, poor quality sleep, and nonrestorative sleep. Psychological and behavioral management of sleep disturbance is an effective treatment modality.[127] McKenna and Daniel[128] have outlined a treatment strategy that addresses tinnitus and insomnia as components adversely affected by anxiety.

Hyperacusis

There is no single, universally accepted definition of hyperacusis, and there is no consensus on the physiologic mechanisms that cause the condition. Hyperacusis has been defined as noise intolerance, annoyance caused by ordinary sounds, and abnormal discomfort for suprathreshold sound.[129] These definitions distinguish hyperacusis, considered by many to be a central phenomenon, from recruitment. Recruitment is the rapid growth of perceived loudness with increasing stimulus level, and is observed in association with cochlear hearing loss and outer cell dysfunction. Hyperacusis frequently occurs in association with tinnitus, but can be present without tinnitus or any associated hearing loss. Hyperacusis can occur after the loss of the stapedial reflex in association with acute facial paralysis,[130] in association with general conditions such as migraine attacks,[131] in association with Lyme disease,[132] as a result of benzodiazepine withdrawal,[133] or as part of a syndrome.[134] Patients with tinnitus and hyperacusis frequently have loudness discomfort levels that are lower than loudness discomfort levels of individuals with similar levels of sensorineural hearing loss, indicating that these phenomena are distinctly different from recruitment.[135]

Andersson and associates[136] assessed the prevalence of hyperacusis in the general population in two surveys of the adult Swedish population. The point prevalence of hyperacusis was 5.9% (postal survey) and 7.7% (Internet survey). Participants reporting hearing impairment were excluded from the prevalence calculations, minimizing the inclusion of patients with cochlear damage and reduced dynamic range in the sample. Other reports of hyperacusis prevalence in the general population are 22%.[137] The prevalence of hyperacusis within the tinnitus population is unknown. Estimates range from 40% to 80%, but no systematic survey has been conducted for accurate estimation.[138,139] In the general population and the tinnitus population, the adopted operational definition of hyperacusis would determine its estimated prevalence.

Objective tests of loudness discomfort or sound intolerance in patients with hyperacusis have been adapted from procedures developed for assessing recruitment.[140,141] There are several variations on the technique for measuring loudness discomfort levels, but no consensus or standardization has been established. In addition, issues of intersubject and intrasubject variability,[142] test-retest reliability,[143] operator dependency, and poor face validity for test stimuli all limit the utility of adapting measures of loudness intolerance to patients with hyperacusis.

There are very few validated, well-established self-report questionnaires that specifically target hyperacusis. Two questionnaires developed in France are available, but have not yet been validated in English translation. Dauman and Bouscau-Faure[139] have developed a scale for

assessing hyperacusis in patients with tinnitus: The Multiple-Activity Scale for Hyperacusis (MASH). MASH employs a structured interview for rating the annoyance induced by sound exposure from different physical and social activities. Dauman and Bouscau-Faure[139] reported hyperacusis was present in 197 of 249 (79%) clinical patients screened with the instrument, with substantial to severe annoyance from hyperacusis present in 42%. There was no correlation between the severity of hyperacusis, as indicated by MASH, and audiometric threshold shift, indicating that hyperacusis is a phenomenon distinct from loudness recruitment. The Hyperacusis Questionnaire is a 14-item instrument, also developed in French, in which hyperacusis is assessed using a four-alternative Likert scale.[144]

The impact of hypersensitivity to sound can range from general avoidance of social situations such as concerts and restaurants to specific sound aversions (e.g., vacuum cleaners, traffic, clinking dishes, children playing). In extreme cases, patients with severe hypersensitivity become housebound in an effort to control acoustic exposure, wearing ear plugs and ear muffs for extended periods. In all cases of sound hypersensitivity, it is important to address the physiologic component of loudness discomfort and reduced dynamic range, and the psychological component of fear, anxiety, social withdrawal, and maladaptation that accompanies the condition. The cognitive influence on sound sensitivity has been shown by the high correlation of loudness tolerance with anxiety.[99]

The efficacy of sound therapy for treating hyperacusis has had mixed results. Dauman and Bouscau-Faure[139] reported that TRT was more effective in improving hyperacusis (63%) than tinnitus (47%) in 32 patients evaluated at three time points after therapy. They reported that hyperacusis remains a problem for a significant proportion of patients treated with TRT. Gold and associates[145] reported a retrospective study on the effect of TRT on selected patients with reduced sound tolerance. Hyperacusis was defined as average loudness discomfort levels for 1 kHz, 2 kHz, 4 kHz, and 8 kHz below 100 dB HL and patient reports of physical discomfort with exposure to sounds. Hearing thresholds were unchanged between initial measures and follow-up after 9 months of therapy; however, mean loudness discomfort levels were improved 12.48 dB, and the dynamic range was significantly increased by a mean 11.32 dB. A corresponding improvement in the number of activities avoided because of sound tolerance problems was noted as well.

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CHAPTER ONE HUNDRED AND FIFTY-ONE

Noise-Induced Hearing Loss

Brenda L. Lonsbury-Martin

Glen K. Martin

Key Points

- Noise-induced hearing loss (NIHL) is second only to age-related hearing loss as the most prevalent form of hearing loss.
- NIHL resulting from relatively brief noise exposures can be reversible, as happens with exposure occurring at an evening spent in a loud entertainment venue.
- Permanent NIHL is caused by either an acoustic trauma (i.e., a brief exposure to a very intense blastlike sound) or a chronic long-term exposure to the loud sounds associated with a noisy occupation.
- An accelerating incidence of high-frequency hearing loss in younger individuals points to early, chronic noise exposure, possibly from personal entertainment devices.
- NIHL is a complex condition that is influenced by environmental and genetic factors.
- Genetic association studies have identified genetic factors primarily related to oxidative stress that influence an individual's susceptibility to NIHL.
- Current research on the administration of certain antioxidants before or after noise exposure shows promise for developing a pharmacologic treatment for NIHL in the near future.
- NIHL is a preventable condition and the otolaryngologist plays a critical role in educating patients about protecting their ears from the adverse effects of noise overexposure.

One of the most common causes of permanent hearing impairment is exposure to excessive sounds. Millions of individuals worldwide have noise-induced hearing loss (NIHL), resulting in a reduced quality of life because of social isolation, and possible inexorable tinnitus and impaired communication with family members, coworkers, and friends.[1] The costs in terms of compensation and early retirement payments for work-related NIHL are immense. The U.S. Department of Veterans Affairs spends approximately $700 million a year on disability compensation and treatments for NIHL. NIHL is the single largest disability expenditure of the Veterans Benefits Administration.[2]

This chapter presents and discusses more recent perspectives on the effects of excessive noise on hearing that address the scientific and practical aspects of NIHL. Although NIHL has been studied experimentally for more than a century, only in the last few decades have some major breakthroughs occurred in our basic understanding of the ear's reaction to damaging sounds, along with a better understanding of the environmental and genetic factors that contribute to NIHL. This steady progression in the knowledge base about NIHL promises to improve significantly the detection and treatment of this disorder over the coming years.

Measurement of Noise

The term *noise* is commonly used to designate an undesirable sound. In the scientific and clinical fields that deal with hearing, this term has come to mean any excessively loud sound that has the potential to harm hearing. The temporal patterns of environmental noise are typically described as continuous, fluctuating, intermittent, or impulsive.[3] Continuous or steady-state noise remains relatively constant, whereas fluctuating noise increases and decreases in level over time, and intermittent sounds are interrupted for varying time periods. Impulsive or impact noises caused by explosive or metal-on-metal mechanical events have rapidly changing pressure characteristics consisting of intense, short-lasting (i.e., milliseconds) wave fronts, followed by much smaller reverberations and echoes that occur over many seconds. The amount of noise, usually referred to as the sound pressure level (SPL), is conventionally measured by a sound-level meter in decibel (dB) units using a frequency-weighting formula called the A-scale. The dBA-scale metric of sound level essentially mimics the threshold-sensitivity curve for the human ear, so the low-frequency and high-frequency components are given less emphasis as auditory hazards. Standard sound-level meters have electronic networks designed to measure noise magnitude automatically in dBA, whereas to measure impulse or impact noise, a more intricate peak-reading sound-level meter is needed that is capable of accurately measuring sounds with essentially instantaneous onset times.

The personal noise dosimeter is typically used to measure noise exposure in the workplace. This instrument provides readout of the noise dose or the percent exposure experienced by a single worker, typically over a specific shift. The logging dosimeter integrates a function of sound pressure over time and calculates the daily (8-hour) dose with respect to the current permissible noise level for a continuous noise of less than or equal to 85 dBA lasting 8 hours. More recently, personal noise dosimeters have been offered to the consumer as a portable, compact, and affordable device that can be used as hearing protectors. The instrument measures and displays noise dose continuously for 16 hours. The dosimeter provides an early warning that the user is approaching overexposure and should use hearing protection. A particular noise (e.g., from power tools, music concerts, sporting events) can also be measured for 2 minutes, and then the estimated dose per

hour is calculated and displayed to determine if permissible exposure levels would be exceeded. By putting valuable health information into the hands of consumers, such easy-to-use, inexpensive (<$100) dosimeters empower them to take appropriate steps to prevent NIHL.

Nature of the Hearing Loss

Depending on the level of the sound exposure, either reversible or permanent damage can occur to the peripheral auditory end organ. The reversible loss, typically referred to as a *temporary threshold shift* (TTS), results from exposures to moderately intense sounds, such as might be encountered at a philharmonic orchestra concert. Hearing problems associated with TTS include elevated thresholds, particularly for the higher midfrequency region that includes the 3- to 6-kHz frequencies. The TTS condition is often accompanied by many other common symptoms of hearing impairment, including tinnitus, loudness recruitment, muffled sounds, and diplacusis. Depending on the duration of the exposure, recovery from TTS can occur over periods ranging from minutes to hours and days. After exposure, if TTS does not recover before the ear is re-exposed to excessive sound, a permanent change in hearing can occur, which is referred to as a *permanent threshold shift* (PTS).

In PTS, the elevation in hearing thresholds is irreversible because lasting structural damage occurs to the critical elements of the cochlea. The precise relationship between the TTS and PTS stages of hearing loss caused by noise exposure is unknown. Although it seems logical to assume that repeated episodes of TTS would eventually lead to PTS, experimental findings imply that the fundamental processes underlying the development of reversible versus permanent NIHL are unrelated. Nordmann and colleagues[4] using a survival fixation approach showed that the histopathologic manifestations of TTS and PTS noise damage to the chinchilla cochlea are distinct. Specifically, TTS was correlated with a buckling of the supporting pillar cell bodies in the frequency region of the maximal exposure effect. The morphologic abnormality that was consistently correlated with PTS was a focal loss of hair cells, and a complete degeneration of the corresponding population of nerve fiber endings. Because PTS eventually develops from repeated exposures to stimuli that initially produce only TTS, it is likely that the latter condition is also associated with subtle changes to the sensitive outer hair cell (OHC) system that go undetected by conventional light microscopy.

Traditionally, PTS caused by acoustic overstimulation has been separated in two distinct classes. One type, called *acoustic trauma,* is caused by a single, short-lasting exposure to a very intense sound (e.g., an explosive blast), and results in a sudden, usually painful, loss of hearing. The other type of hearing loss is commonly referred to as NIHL, and results from chronic exposure to less intense levels of sound. A great deal more is known about the anatomic processes underlying the symptoms of and recovery from acoustic trauma than is known about NIHL. Consequently, it is well established that a single exposure to a severe sound causing violent changes in air pressure can produce direct mechanical damage to the delicate tissues of the peripheral auditory apparatus, including components of the middle ear (tympanic membrane, ossicles) and inner ear (organ of Corti). In contrast, regular exposure to less intense but still noisy sounds involves the insidious destruction of cochlear components that eventually and unavoidably leads to an elevation in hearing levels, along with other common symptoms of hearing impairment.

Acoustic trauma was previously a relatively rare event that was typically associated with accidental explosions in industrial settings. Military servicemen and servicewomen caught in roadside bomb explosions in the current armed conflicts in Iraq and Afghanistan are returning home in epidemic numbers, however, with profound permanent hearing losses and tinnitus.[5] Consequently, acoustic trauma is a hearing problem that is increasing, at least in combat troops. Because many of these postdeployment cases are being treated in the private sector, all otolaryngologists may see acoustic trauma in increasing numbers.

Irreversible NIHL is a specific pathologic state exhibiting a recognized set of symptoms and objective findings.[6] NIHL includes (1) a permanent sensorineural hearing loss with damage principally to cochlear hair cells, and primarily to OHCs; (2) a history of a long-term exposure to dangerous noise levels (i.e., >90 dBA for 8 hours/day) sufficient to cause the degree and pattern of hearing loss described by audiologic findings; (3) a gradual loss of hearing over the first 5 to 10 years of exposure; (4) a hearing loss involving initially the higher frequencies from 3 to 8 kHz before including frequencies less than or equal to 2 kHz; (5) speech-recognition scores that are consistent with the audiometric loss; and (6) a hearing loss that stabilizes after the noise exposure is terminated.

A patient with NIHL commonly consults a physician because of difficulties in hearing and understanding ordinary speech, especially in the presence of background noise. Many variations can be found in the detailed configuration of the audiogram of a noise-damaged ear, depending on the temporal and spectral distribution of the noise stimulus, and on the stage of hearing loss. The pattern of hearing loss most commonly associated with the earlier stages of NIHL is illustrated in Figure 151-1A. The beginning region of impairment involves the sensitive midfrequency range, primarily 3 to 6 kHz, and the corresponding hearing loss is classically described as the "4-kHz notch." This pattern of maximal hearing loss, with little or no loss at less than 2 kHz, typically occurs regardless of the noise-exposure environment. The audiogram results in Figure 151-1A also show the sensorineural aspect of NIHL in that thresholds for bone-conducted stimuli are essentially identical to the thresholds for air conduction. The profile of noise-induced threshold hearing is usually symmetric for both ears, particularly for individuals who have been working in noisy industrial settings in which there are "surround" sounds.

Commonly, other forms of noxious sound, such as the gunfire associated with sport shooting, cause an asymmetric pattern of hearing loss similar to the one illustrated in Figure 151-1B. In this case, the ear pointed toward the source of noise (gun barrel), which is the right ear of the left-handed shooter depicted in Figure 151-1B, would have worse hearing than the ear directed away from the source (in this example, the left or protected ear) by 15 to 30 dB or more, and particularly at higher frequencies because of the absence of the protective head-shadow effect.

The development of a hearing loss caused by habitual exposure to moderately intense levels of noise typically consists of two stages. Initially, the middle to high frequencies exhibit the resulting hearing loss. As the length of time of exposure to loud noise increases, hearing loss becomes greater and begins to affect adjacent higher and lower frequencies. In a classic cross-sectional study of occupational NIHL, Taylor and colleagues[7] showed the gradual loss of hearing sensitivity in workers caused by habitual exposure to the intense sounds of dropforging tools that are commonly used in foundries. Figure 151-2 illustrates the progressive effects of exposure to the wideband noise (Fig. 151-2A) of two types of forging tools, presses and hammers, on the magnitude of hearing loss as the length of exposure increased. For the operators of the press and hammer equipment (Fig. 151-2B and C), the approximate 10- to 20-dB threshold shifts, typically observed at the higher frequencies during the first 1 to 2 years of exposure, grew to be a 20-dB or greater loss, from 3 to 6 kHz, after a 3-year exposure. There was a 40-dB or greater threshold shift after an 8-year exposure.

Detailed comparisons of the NIHL growth curves of Figure 151-2B and C reveal that with continuing exposure, hearing loss worsened at the higher frequencies and spread to the lower frequencies. In addition, for average exposure times of less than 10 years, hearing levels for the press and hammer operators who were exposed to mean levels of 108 and 99 dB SPL deteriorated similarly. For long-term exposures of 10 years or more, the results of Taylor and colleagues[7] indicated that hearing losses resulting from the hammer-induced impact noise were greater than the losses resulting from the more continuous noise of the press equipment. Finally, a characteristic feature of NIHL, which is clearly documented in Figure 151-2B and C, is that hearing levels are increased rarely beyond about 70 to 90 dB of hearing loss, on average, even after more than 31 years of continuous noise exposure.

Cochlear Damage

The primary site of anatomic damage is at the level of the mechanosensory receptors of the auditory system's end organ. Loud sound damages the inner hair cells and OHCs of the organ of Corti, with the

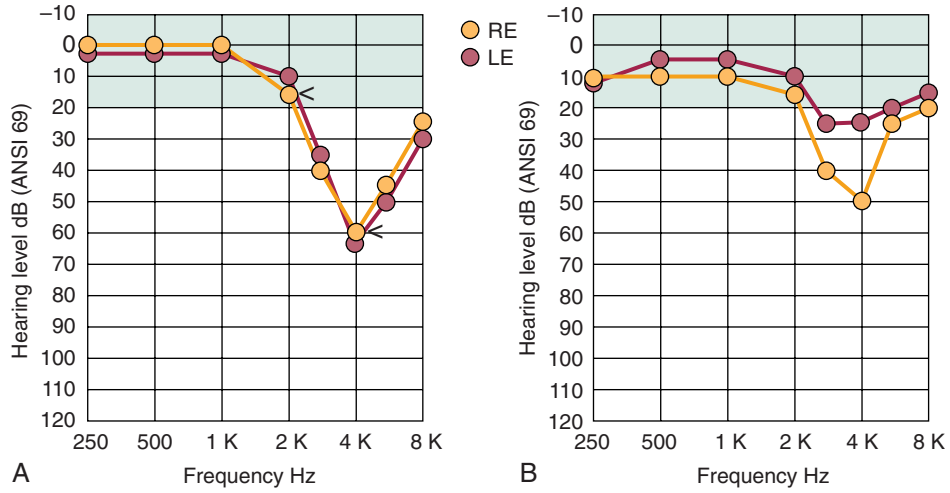

Figure 151-1. Audiometric patterns of hearing levels from patients in beginning stages of noise-induced hearing loss. **A,** A "4-kHz notch" symmetric pattern for a 44-year-old male factory worker. Thresholds for bone-conducted stimuli *(arrows)* were similar to thresholds determined with routine air-conduction methods. **B,** Asymmetric pattern for a 45-year-old man who was a recreational rifle shooter. For this left-handed patient, note greater impairment in the right (*yellow circles*) rather than the left (*red circles*) ear because of protective head-shadow effect. <, unmasked right ear.

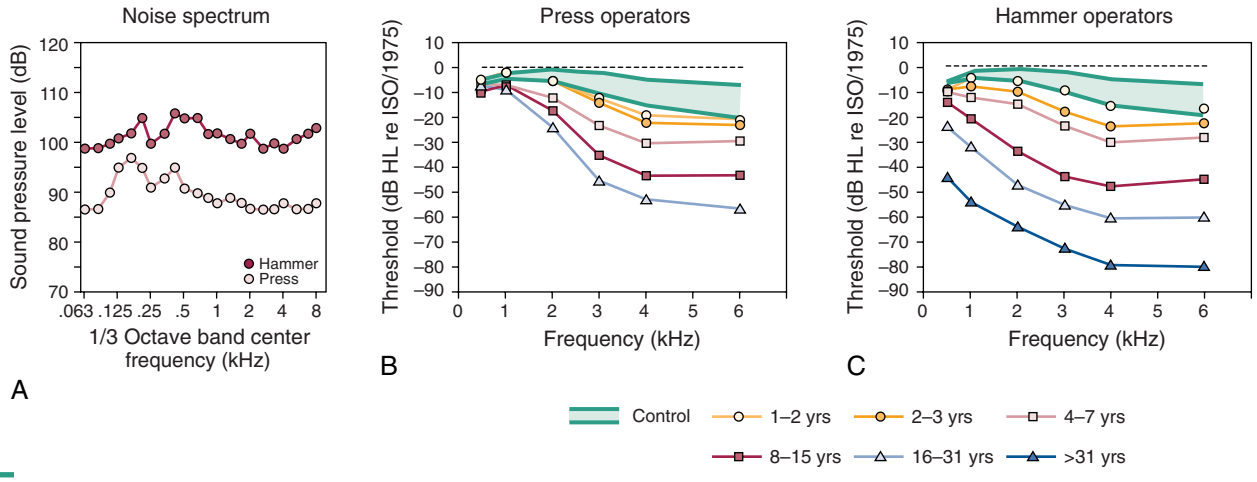

Figure 151-2. Development of the audiometric pattern of noise-induced hearing loss as a function of years of exposure to constant occupational noises. **A,** Spectra of noise produced by hammer *(red circles)* and press *(yellow circles)* equipment, with maximal energy centered in 0.2- to 1-kHz and 0.125- to 0.5-kHz regions. **B** and **C,** Resulting hearing losses for press **(B)** and hammer **(C)** operators. Noise-induced hearing losses occurred at frequencies above peak energy in the exposure. *Geometric symbols* represent experimental subjects according to years of noise exposure. *Shaded areas* indicate effects of aging on hearing levels in control subjects of similar age (i.e., 23 to 54 years old), who worked in non-noisy parts of the same drop-forging plants. *(Adapted from Taylor W, Lempert B, Pelmear P, Hemstock I, Kershaw J. Noise levels and hearing thresholds in the drop forging industry.* J Acoust Soc Am. *1984;76:807-819.)*

OHCs in particular being most affected in the initial stages. In instances involving very intense acoustic stimulation, supporting-cell elements also can be directly affected. Depending on the physical attributes of the exposure stimulus (e.g., time-varying characteristics or the intensity, frequency, or spectral content, duration, or schedule), noise can cause damage to hair cells ranging from total destruction to effects evident only in the ultrastructure of specialized subcellular regions (e.g., the fusing or bending of the individual cilia that make up the stereociliary bundle). Whenever degenerative processes or structural modifications to the cochlea reach a significant level, an associated reduction in hearing capability can be detected.

Johnsson and Hawkins[8] were among the first investigators to describe the typical patterns of cochlear injury for humans with chronic exposure to different types of loud sound. The photomicrograph of the cochlear tissue in Figure 151-3A depicts some common histopathologic consequences of NIHL for a patient with a lengthy history of noise exposure. The authors reported that the 50-year-old patient had worked intermittently over a 5- to 6-year period in an automotive body–stamping plant, and that he had a long history of using recreational firearms. The sharp transition in the basal end (following the uncoiling to the right) from the normal-looking organ of Corti (a darkish stripe corresponding to the region of inner hair cells and OHCs), with its dense network of nerve fibers, to the complete absence of hair cells and their corresponding nerve fibers (the much lighter adjacent area) can be noted. Figure 151-3B graphically reconstructs the histopathologic features of this cochlea as a cytocochleogram by depicting the number of remaining hair cells, in the form of percentages, averaged over 1-mm sections. A typical finding in individuals exposed to the occupational noise exemplified in this case is the almost symmetric pattern of degeneration observed for the two ears. The *inset* at the top right of the cytocochleogram shows the patient's audiogram obtained about 1 year before his death, which shows the severity of the anatomic damage in functional terms by revealing an abrupt hearing loss for test frequencies greater than 2 kHz.

Examination of human temporal bone specimens by numerous laboratories[8-10] has yielded documentation of the progressive stages of

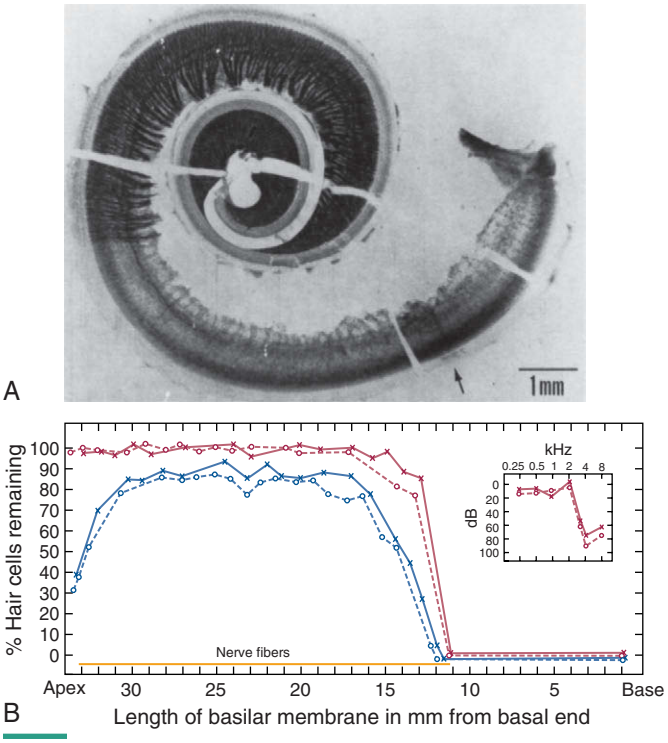

Figure 151-3. **A,** Low-power photomicrograph of a soft surface preparation of organ of Corti from the left cochlea of a 50-year-old man exposed extensively to occupational noise, showing a pattern of abrupt degeneration of basal region. *Arrow* indicates a small patch of remaining organ of Corti near basal end. **B,** Modified cytocochleograms for two ears along with an audiogram that was measured 1 year earlier, showing sharp pattern of hair cell degeneration (expressed as percentage remaining per millimeter of length of basilar membrane measured from basal end) and nerve fiber degeneration. Note relative symmetry of corresponding abrupt high-frequency loss of cochlear elements. Separate curves represent inner *(solid lines)* and outer *(dashed lines)* hair cells (averaged over three rows of outer hair cells) for left *(X)* and right *(O)* ears. *Yellow horizontal line* along abscissa indicates presence of nerve fibers in osseous spiral lamina. *(Adapted from Johnsson LG, Hawkins JE. Degeneration patterns in human ears exposed to noise.* Ann Otol Rhinol Laryngol. *1976;85:725-739.)*

noise damage as depicted by epidemiologic data such as those of Figure 151-2. First, in the predictable sequence of events, a small region of hair cell and nerve fiber degeneration appears bilaterally at a cochlear region corresponding to the 4-kHz notch. Typically, these discrete lesions gradually grow in the basal-ward direction (i.e., toward the high-frequency extent of the cochlea) to involve a greater portion of the organ of Corti. Finally, as exposure to noise continues over years, the remaining sensory and neural elements in the basal end of the cochlea are destroyed, resulting in an abrupt loss of midfrequency to high-frequency hearing, such as that depicted by the clinical audiogram of Figure 151-3.

Research on Noise-Induced Hearing Loss

Scientific interest in the damaging effects of excessive sound on hearing has a long history for many reasons. First, the experimental strategy of exposing animals to noise and examining their ears for the sites of the resulting acoustic injury was used in the past as the independent variable in establishing some of our basic knowledge about hearing. Particularly, with the use of intense tones as the damaging agents, frequency information relating physical distance along the basilar membrane to the "best" frequency of the injured region provided an initial basis for understanding the tonotopicity of the cochlea and the central projection of such frequency-related information.[11] Additionally, noise-damage strategies have been used to contribute to our understanding of the function of inner hair cells and OHCs by permitting differences in their central terminations in the ventral and dorsal cochlear nuclei to be distinguished.[12]

Although useful as an analytic strategy, the major impetus behind the more contemporary interest in the effects of noise on hearing originates from a desire to understand the fundamental processes by which exposure to loud sound leads to acoustic injury. The reward of achieving an appreciation of the basic processes underlying NIHL lies in the ability to prevent, or at least predict, an individual's susceptibility to PTS, or perhaps even to initiate regeneration of damaged or lost critical cellular components, which would eventually lead to the recovery of hearing.

The research literature on the effects of noise on hearing and the anatomic elements of the ear is voluminous. Early experiments performed more than 65 years ago were straightforward anatomic studies based on the strategy of exposing various animal models to intense noises, followed by a general description of the resulting histopathology at the cellular level. More modern noise studies in animal models have attempted to establish a structure/function relationship between noise-induced morphologic damage and the inability to detect auditory signals.

In this extensive literature, a great disparity in the experimental findings relating the effects of missing hair cells to the corresponding hearing sensitivity is frequently apparent. Such contrasting findings and the confusion they have caused are related to numerous confounding variables, including poor analysis of the problem, experimental error, and a failure to understand the limitations of the functional and anatomic techniques used. Also, such disparate studies typically exposed animal subjects to a single noise at levels much greater than 100 dB SPL in an attempt to mimic, within a relatively brief study interval, damage patterns that develop in humans from intermittent exposure to much less intense noises over many years. Consequently, although early noise studies showed that the longer an animal was exposed to extreme levels of sound, the greater was the resulting cochlear injury, they contributed little to our knowledge concerning how NIHL develops in humans working for long periods in noisy work settings.

In contrast, research conducted over the past few decades has made use of more realistic experimental protocols that incorporate intermittent exposure stimuli of intensities and durations designed to approximate the effects of a working lifetime of exposure to occupational noise. Additionally, most more recent studies have been developed sequentially within a program of research, so that a thorough understanding of a particular effect is achieved.

Anatomic Mechanisms Underlying Noise Damage

Experimental studies have led to an increased understanding of some major features of NIHL. It is well-accepted that the origin of the 4-kHz notch in the NIHL audiogram is related to the resonator function of the external auditory ear canal,[13] rather than to indeterminable innate properties of the cochlea, such as a reduced vascular supply to this region of the organ of Corti.[14] The primary research interest has always been, however, in the fundamental mechanism by which the sensory cell degenerates or is damaged after exposure. Numerous mechanisms[15] have been proposed, including mechanical injury caused by severe motion of the basilar membrane, metabolic exhaustion of activated cells, activity-induced vascular narrowing that causes ischemia, and ionic poisoning from interruption of the normal chemical gradients of the cochlea owing to minuscule disruptions in the organization of sensory and supporting cells.

Although the many years of experimental research have not yet produced a major breakthrough in understanding of damage mechanisms, the current most convincing morphologic evidence supports a combination of the mechanochemical theories. First, at the ultrastructural level, it is likely that alterations in the stereocilia in the form of shortened or broken rootlets are involved in the initial pathologic processes that lead to TTS and, if such injuries are not repaired, then PTS.[16-18] More recent findings showed that hair bundles are capable of rebuilding their ultrastructure from top to bottom over a 48-hour

period.[19,20] If damage is so severe that it overwhelms this self-repair mechanism as exposure continues, a discrete but direct mechanical disruption likely results in a toxic mixing of endolymph and perilymph through microbreaks in the structural framework of the cochlear duct,[21] which leads to secondary effects, including loss of hair cells and their corresponding nerve fibers.

New Knowledge about Cellular and Molecular Mechanisms of Noise-Induced Hearing Loss

The research frontiers that promise to provide fresh insights into the fundamental basis of NIHL and eventually into the development of a cure for this disorder consist of hair cell regeneration or repair or both, "training" protocols that target the cochlear-efferent system to make hair cells more resistant, the use of protective agents before and after noise exposure, and understanding the genetic basis of susceptibility and resistance to the adverse effects of sound overexposure.

Hair Cell Regeneration and Repair

In the late 1980s, several seminal reports on hair cell regeneration in avian species established that hair cells in neonatal and adult birds regenerate after exposure to either damaging levels of sound[22-24] or ototoxic antibiotics.[25] Additionally, follow-up studies showed that recovery of cochlear function accompanied the cellular-recovery process.[26-28] In the best-studied model for hair cell regeneration, the neonatal chick, it was shown that new hair cells arose as progeny from an otherwise nondividing supporting-cell population that was induced to proliferate by the damaging insult.[29]

Generally, noise-induced hair cell loss in the mammalian cochlea is irreversible. Experimental findings using in vitro cultures of neonatal mouse cochleas showed, however, that overexpression of mammalian atonal homolog 1 (Atoh1), also known as Math 1, a basic helix-loop-helix transcription factor known to be necessary for hair cell differentiation during development, leads to an increase in the production of extranumerary hair cells.[30] Consequently, it seems that certain cells in the mammalian organ of Corti, at least in young animals, can be redirected toward a hair cell fate by the overexpression of Math 1.[31] In addition, a most exciting finding was the discovery that new hair cells can be grown in a mature mammalian ear using the Math 1 gene. Kawamoto and colleagues[32] injected an adenovirus carrying the Math 1 gene into the endolymph of mature guinea pigs. Using scanning electron microscopy, 1 to 2 months after the inoculation of the Math 1 gene insert, immature hair cells within the nonsensory supporting cells of the organ of Corti were detected. Most importantly, follow-up studies in the deafened guinea pig showed that not only did Math 1 induce regeneration of hair cells in the adult, deafened guinea pig, but also substantially improved hearing thresholds were measured.[33] These findings that Math 1 (Atoh1) can direct hair cell differentiation and induce hearing function in mature nonsensory cells support the notion that adenoviral gene therapy based on expressing crucial developmental genes for cellular and functional restoration in damaged auditory epithelium may lead some day to a new treatment for NIHL.

Protection from Conditioning the Cochlear Efferent System

The outcomes of other experiments indicate that the mammalian cochlea may be capable of actively adapting to certain high-level sounds by receiving "exposure experience." The notion that the cochlea can become resistant over time to the consequences of excessive sound was reported initially by noting "conditioning" effects in several animal models.[34-37] The typical conditioning paradigm consists of providing a pre-exposure training experience using a moderate-level stimulus that, at a more intense level, becomes the subsequent overexposure stimulus. Together, these findings in animal models suggested that the mammalian cochlea might be capable under certain conditions of dynamically adapting to excessive sound.

For humans, the practical implications of the capacity to develop a "resistance" to loud sounds are obvious. A follow-up study in teenagers used a TTS-type paradigm to show the relevance of resistance training to humans. In this experiment,[38] the investigators provided a pre-exposure training period in which the young subjects were exposed to 6 hours of pop/rock music at around 70 dBA. Threshold shifts in response to a 10-minute exposure to a 105-dB SPL, one-third octave-band noise centered at 1 kHz were compared for pretraining versus post-training intervals. The major result was that the "trained" ears exhibited significant decreases in TTS compared with their baseline values, showing that the "conditioning" effect, or the development of "resistance," can be shown in human subjects, at least under brief TTS-exposure conditions.

Such human studies of the relationship between noise exposure and permanent hearing loss are more difficult to perform for many reasons including the ethical issues involved in the deliberate exposure of study subjects to noises, even though they are thought to be reversibly damaging. More recent research into the protective role of cochlear efferents in NIHL has depended more on the benefits of diagnostic testing with evoked otoacoustic emissions (OAEs) to predict potential susceptibility to the aftereffects of noise exposure.[39] This simple, noninvasive, and objective procedure is based on the systematic measurement of a class of cochlear responses (i.e., the OAEs) that are primarily generated by the OHCs.[40] Not only are OHCs exquisitely sensitive to the initial effects of acoustic overstimulation, which makes them excellent indicators of sound-induced ultrastructural damage, but also the final common pathway of the descending auditory-efferent system preferentially innervates the OHCs.

To take advantage of the ability of OAEs to measure efferent activity, several experimental paradigms were developed including a common one[41] that uses contralateral acoustic stimulation to elicit medial olivocochlear-induced reductions of OAEs from the ipsilateral test ear. The other procedure[42] is based on measurements of a subtype of evoked emissions represented by distortion product OAEs (DPOAEs) at $2f_1$-f_2. In this strategy, long-lasting f_1 and f_2 primary tones of approximately 1 second are applied binaurally to elicit an efferent-based fast adaptation response that tests the ability of the combined medial and lateral cochlear-efferent systems to suppress DPOAEs in the test ear.

Experiments in guinea pigs documented the ability of the fast-adaptive DPOAE response to predict vulnerability to acoustic injury based on the vigor of efferent activity.[43] The robustness of the olivocochlear efferents was inversely correlated with the degree of cochlear dysfunction after subsequent noise exposure, in that animals exhibiting large adaptive effects showed smaller postexposure losses than animals displaying small amounts of efferent-induced adaptation. It is clear from these findings that a modification of this assay could easily be applied to human populations to screen for individuals most at risk in noisy environments.

Some studies[44] simply relating the presence or absence of the contralateral acoustic stimulation–induced reduction of emissions in human ears have reported such suppression is absent in most industrial workers who otherwise have normal OAEs. One implication of such observations is that a lack of efferent-related activity may be an early indication of cochlear damage from exposure to noise. Experimental studies such as these will eventually determine whether inherent efferent processes can account for and predict the remarkable individual variation in susceptibility to NIHL. The use of efferent-induced suppression of evoked OAEs in predicting susceptibility to NIHL, or in monitoring of noise effects in hearing-conservation programs, represents a promising line of future investigation.

Pharmacologic Protection from Noise-Induced Hearing Loss

It has long been recognized that hypoxia is a major pathogenic factor in NIHL. Based on the assumption that oxidative stress plays a substantial role in the genesis of noise-induced cochlear injuries that lead to permanent hearing loss, numerous pharmacologic strategies have been developed primarily in animal models to enhance the intrinsic defense mechanisms of the cochlea against this condition.[45] Kopke and colleagues[46] postulated several causes of noise-induced oxidative stress, all of which are amenable to pharmacologic treatments. Specifically, these investigators proposed that noise-induced oxidative stress leading to cochlear injury was related to (1) impaired mitochondrial function with respect to bioenergetics and biogenesis; (2) glutamate-induced excitotoxicity, which is the main excitatory neurotransmitter in the

peripheral and central auditory systems; and (3) depletion of glutathione (GSH), an antioxidant that protects cells from toxins such as free radicals.

Related experimental work showed a reduction in NIHL and hair cell loss in the chinchilla model after application of pharmacologic agents specific to these oxidative stress–related states. Acetyl-L-carnitine, an endogenous mitochondrial membrane compound that helps maintain mitochondrial bioenergetics and biogenesis in the face of oxidative stress; carbamathione, which acts as a glutamate antagonist for cochlear *N*-methyl-D-aspartate (NMDA) receptors; and the GSH-repletion drug, D-methionine (MET), all improved hearing in noise-exposed animals as indexed by auditory brainstem responses, along with reductions in inner hair cell and OHC loss compared with counterpart measures in saline-treated control subjects.[46]

Based on the assumption that a potential mechanism of NIHL is the generation of damaging free radicals through the activation of reactive oxygen species such as hydrogen peroxide, hydroxyl radicals, and superoxide, many other studies have tested the influence of antioxidants and related compounds on noise-induced cochlear dysfunction and organ of Corti morphology. Such candidate substances include GSH,[47] the xanthine oxidase blocker allopurinol,[48] *N*-L-acetylcysteine (L-NAC),[49] and GSH peroxidase and superoxide dismutase.[50] Together, all these findings support the notion that combating cellular oxidative stress, principally with prophylactic administration of antioxidant compounds, eliminates noise-induced cochlear injury in animal models. More recently, Kopke and colleagues[51] reported on some promising results using L-NAC in military recruits to reduce the NIHL sometimes associated with the basic training related to military operations. The success of such a pharmacologic approach essentially ensures the development in the near future of a therapeutic intervention that reduces NIHL clinically.

Susceptibility

A long-standing observation in NIHL has been that some ears are more easily damaged by noise than others. Individually varying susceptibilities to noise-induced hearing impairment have been found in humans and research animals. Because of the widespread interest in NIHL and its prevention, it is important to develop valid and reliable indices to predict human susceptibility to various noise levels. It is commonly assumed that such variability in susceptibility is a manifestation of biologic factors unique to each subject. A genetically based imperfection in the physical characteristics of the cochlea (e.g., stiffness of the cochlear partition) and variability in cochlear ultrastructure (e.g., density of hair cells) have been proposed as contributing to susceptibility.[52]

Identifying individual differences among various factors has long been a focus of interest. Numerous potentially important variables that have been investigated in the past and continue to be examined include age[53]; gender[54]; race[55]; previous damage to the cochlea[56]; efficiency of the acoustic reflex[57]; smoking habits[58]; and the influence of certain disease states such as hypercholesterolemia[59] or hypertriglyceridemia,[60] diabetes,[61] and cardiovascular disease represented by hypertension.[62] Although many pertinent factors have been uncovered, most data are inconclusive. In addition, although a few factors, such as pigmentation,[63] seem to have some relationship to potentiating noise damage, others, such as age, simply produce additive effects,[64] although this latter relationship remains controversial.[65] Possibly, as McFadden and Wightman[66] suggested in their review of the contribution of the psychoacoustic method toward understanding the symptoms of clinical hearing disorders, the orthogonally based research approach, which assumes a causal relationship between factors, will not reveal meaningful relationships. Perhaps the uncovering of interrelationships among myriad individual differences by application of a multivariate test battery would be more successful in identifying the basic factors that predict susceptibility to NIHL.

One of the most exciting areas in current experimental research is aimed at examining the genetic origin of differences in susceptibility to noise damage using the mouse model. A clear benefit of the mouse as an experimental animal is the great amount of knowledge that exists about the mouse genome. Additionally, mice from the same inbred strain are considered to be genetically identical. Consequently, assessing individual variability to noise damage in subjects that are homozygous at all chromosomal loci offers a unique opportunity to isolate genetic factors responsible for susceptibility to NIHL. To date, several studies[67,68] have shown that the inbred, mutant C57BL/6J (C57) strain, often used as a model of early age-related hearing loss, is more susceptible to noise damage than the CBA/CaJ (CBA) strain, which is frequently used as a model of normal hearing. Other observations supporting the potentiation of noise damage by the age-related hearing loss gene, *Ahl,* relate to the finding that when C57 (B6) mice are backcrossed with a mouse strain (e.g., CAST/Ei) exhibiting normal aging, the B6/CAST progeny display neither age-related hearing loss nor susceptibility to noise exposure aftereffects.[69]

Just as susceptible mutant mouse strains are readily available, there are also strains with normal cochlear function that are exceptionally resistant to acoustic overstimulation, such as wild-type inbred MOLF/Ei (MOLF) mice. Figure 151-4 compares the effects of an intense noise exposure (105-dB SPL, octave-band noise centered at 10 kHz, for 8 hours) on control CBA and MOLF mice at 2 months of age.[70] Although CBA mice showed only an expected minor recovery of DPOAEs to baseline levels at 2 days and 1 and 2 weeks postexposure, MOLF DPOAEs had essentially returned to their pre-exposure levels by 1 to 2 weeks postexposure. In combination, findings in inbred mouse models of NIHL provide the basis for applying suitable molecular techniques that permit the mapping of an NIHL gene to specific chromosomal loci (e.g., identifying differentially expressed genes using DNA microarrays and suppressive subtractive hybridization). Successful identification of this gene and perhaps its related modifier genes would have great implications for developing a diagnostic indicator of the susceptibility of a particular human ear to the adverse effects of sound overexposure.

Genetic association studies on oxidative stress genes have identified the first heritable factors that likely influence an individual's susceptibility to NIHL. Konings and coworkers[71] investigated whether variations in the form of single nucleotide polymorphisms of the catalase gene, which is one of the genes involved in oxidative stress, influenced noise susceptibility. By comparing audiometric data and DNA samples from the 10% most susceptible and 10% most resistant Swedish and Polish noise-exposed workers, significant interactions were observed between noise-exposure levels and several single nucleotide polymorphisms in both populations. These findings indicate that catalase is potentially a noise susceptibility gene.

Although the findings of more recent studies in particular have resulted in advancing our scientific knowledge of the sound-damage process, many major empirical issues remain to be satisfied. These issues include development of low-cost technical methods for controlling noise at the source, physical protection of individuals from excessive exposure, identification of individuals who are in the early stages of NIHL, prediction of the degree of risk from potentially hazardous noises, and determination of whether particular individuals or ears already damaged by noise are more susceptible to injury.

Ethical issues prevent the deliberate exposure of human subjects to extreme noises as a means of studying NIHL experimentally. The complexity of measurements demanded by the alternate cross-sectional study design that describes the hearing of humans exposed occupationally is considerable, however. These difficulties include differences inherent in the population (e.g., race, gender, presence of ear disease); problems involved in controlling concomitant exposure to no occupational noise or past exposure history; and technical problems with the descriptive techniques themselves, ranging from variability in audiometric measures to difficulties in performing valid measurements of the noise environment itself. Because of the complicated experimental designs demanded by all of these controls, there have been few faultless clinical, epidemiologic, or experimental studies of the effects of excessive noise on hearing in humans.

The importance of performing longitudinal field studies of communities or particular population segments, such as elderly individuals, children, and chronically ill individuals, who are habitually exposed to loud environmental noises produced by road traffic or aircraft, is obvious to determine effective health criteria for controlling such

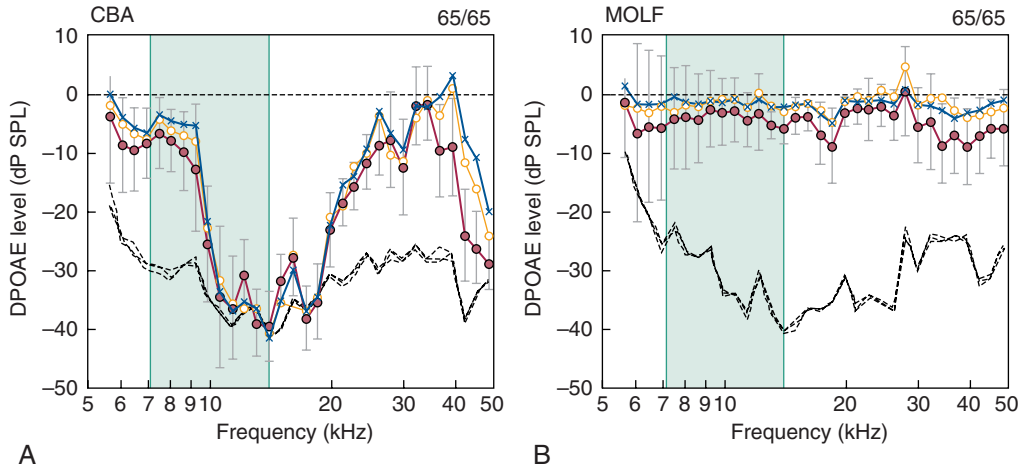

Figure 151-4. **A** and **B,** Mean difference DP-grams (i.e., pre-exposure distortion product otoacoustic emission [DPOAE] levels – postexposure DPOAE levels) for 65-dB SPL primary tones comparing effects of an extreme 8-hour exposure to a 10-kHz octave band of noise (*shaded region* from approximately 7 to 14 kHz) at 105 dB SPL for 2-month-old CBA **(A)** compared with 7-month-old MOLF **(B)** mice. *Bold horizontal dotted line* at 0 indicates no change between pre-exposure baseline DPOAE levels and postexposure counterparts measured at 2 days *(filled circles)*, 1 week *(open circles)*, and 2 weeks *(x)* after overexposure session. Note only minor recovery of DPOAEs for CBA mice between 2 days and 2 weeks postexposure, especially for frequencies greater than 30 kHz. In contrast, DPOAEs for MOLF mice essentially returned to baseline values. Although not shown here, immediately after exposure, both strains exhibited essentially no DPOAEs greater than approximately 10 kHz. Noise-floor differences *(dashed lines without symbols in lower portion of plots)* represent pre-exposure DPOAEs subtracted from postexposure noise floors to indicate maximum possible DPOAE loss. *Vertical bars* represent ±1 SD for 2 days postexposure. CBA, n = 10, 19 ears; MOLF, n = 8, 15 ears.

noises. Most notably, a great disadvantage in gaining a more complete understanding of NIHL in humans is that there have been no more recent studies of the hearing status of contemporary workers, at least in the countries of North America and Europe. Reliance on data collected 30 or more years ago, such as those illustrated in Figure 151-2,[7] has likely resulted in underestimates of the amount of hearing loss that is due to occupational noise, especially for individuals with intermittent or impulsive noise exposures.

Early Detection of Noise-Induced Hearing Loss

One aspect of NIHL that has not received a great deal of research attention is the development of more sensitive measures that are capable of detecting small acoustically induced injuries to the organ of Corti (i.e., the beginning stages of NIHL) so that individuals vulnerable to the long-term damage caused by continuous exposure can be identified. In recent years, evidence has been accumulating that the routine audiometric testing of behavioral thresholds to pure tones at octave intervals does not meet this need because by the time such a loss is identified using methods that test behavioral hearing sensitivity, permanent cochlear damage has occurred. Many threshold and suprathreshold psychoacoustic tests to detect subtle deteriorations in hearing acuity, including psychophysical tuning curves and frequency discrimination tasks, either have not proved to be of general usefulness or have proved to be too cumbersome methodologically to implement in a clinical or workplace setting because of the limitations associated with the necessarily brief evaluation periods.

The diagnostic technique incorporating OAEs is ideal for assessing the normality of cochlear processing in ears suspected of being overstimulated by loud sound because of its well-recognized sensitivity to the OHC class of receptor cell, which is primarily involved in the initial stages of NIHL. The functional status of OHCs in established instances of NIHL has been well described in many more recent studies on the practical applicability of evoked OAE testing in the audiology clinic.[72] Numerous reports in the literature have shown that in groups of noise-exposed humans who have been followed serially, reductions in OAE levels are more sensitive than pure-tone audiometric thresholds in detecting the early states of permanent noise-induced cochlear damage.[73-77] In these studies, decreases in emission magnitudes were measured in the absence of any change in the corresponding audiometric threshold frequencies.

In Figure 151-5, the ability of the two major types of evoked OAEs, the DPOAE, in its DP-gram form depicting emission level as a function of the f_2 test frequency (*lower left* in Fig. 151-5), and the transient-evoked OAE (TEOAE), elicited by clicks, in its spectral form (*right plots* in Fig. 151-5), to describe the configuration of a developing NIHL is illustrated. The 43-year-old woman in this example had participated in recreational rifle shooting for 3 years before OAE testing, and she claimed to have worn protective headphone devices continuously during this period. This right-shouldered shooter presented in the otology clinic with complaints of hearing loss, tinnitus, muffled hearing, and difficulty in understanding speech in background noise. It is clear from the test results that the magnitude and frequency extents of the TEOAEs reflected the pattern of normal hearing illustrated by the clinical audiogram at top left of Figure 151-5. The DP-gram clearly shows abnormal activity, however, with the right ear showing below-average response levels and the left ear exhibiting a significant reduction in emitted responses for frequencies greater than 3 kHz. True to classic principles, the left ear, which was exposed more to the muzzle end of the gun, went unprotected by the head-shadow effect. This example of the ability of evoked OAEs to detect cochlear pathology caused by noise exposure attests to the potential usefulness of emission procedures in identifying the primary site of pathology associated with hearing complaints secondary to a sensorineural loss, and in monitoring the development of potential hearing impairments in hearing-conservation programs.

Other evidence supporting the usefulness of evoked OAEs in examining patients with noise damage is illustrated in Figures 151-6 and 151-7. In Figure 151-6, the results of OAE testing in a 21-year-old man, who had just completed 3 years of military service in the infantry, show the precision of DPOAEs in particular in tracking the asymmetric pattern of hearing loss for this left-handed shooter. Additionally, the OAE findings presented in Figure 151-7 show the ability of evoked emissions to reflect accurately the magnitude and frequency extent of the more severe, but essentially symmetric hearing loss experienced by a 49-year-old man who had been working for more than 20 years in a fish cannery.

Both examples attest to several other benefits of OAE testing in NIHL patients. A significant advantage of the digital hearing aid over

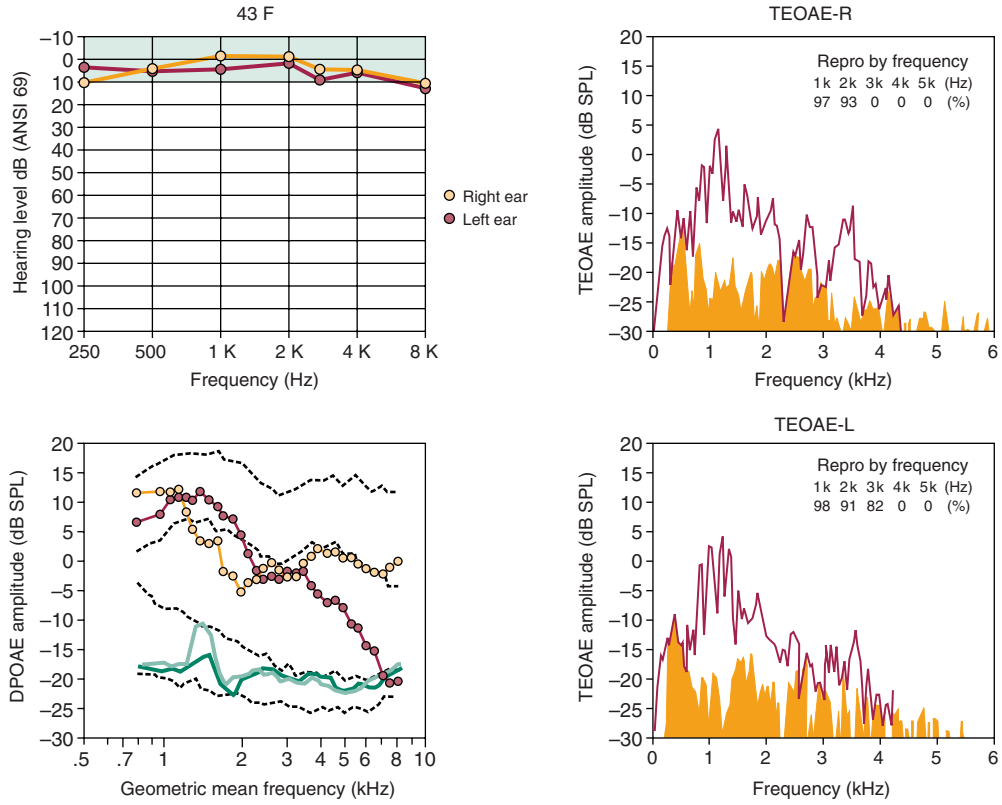

Figure 151-5. Early detection of noise-induced hearing loss in a 43-year-old female rifle shooter who complained of muffled hearing, tinnitus, and difficulty hearing speech in background noise. Note normal pure-tone audiogram bilaterally *(top left)*. In corresponding DP-grams at *lower left,* greater functional loss in the left *(red circles)* compared with the right *(yellow circles)* ear, particularly for frequencies greater than 3 kHz, was due to protective head-shadow effect for this right-handed individual. Emission levels for $2f_1$-f_2 distortion product otoacoustic emission (DPOAE) are plotted in response to 75-dB SPL primary tones as a function of geometric mean of two eliciting stimuli (f_1, f_2). Spectral plots of click-evoked otoacoustic emissions are shown on the *right* (transient-evoked otoacoustic emission [TEOAE]). Emitted response *(open area)* for the better-functioning right (R) ear was more prominently distributed above related noise floor *(shaded area)* than were emissions for the left (L) ear for frequencies greater than 3 kHz. In addition, higher "Repro" values for the right ear *(top right of each plot)* reflected its more robust activity levels. In DP-gram plot, variability of emission level (±1 SD) in normal-hearing ears is represented by *bold dashed lines in top portion of plot*. Similar variability of related noise floor is indicated by pair of *shorter dashed lines along bottom of plot*.

the older analog models is its ability to provide frequency-specific amplification based on the configuration of a particular patient's hearing loss. Knowledge of the pattern of surviving OHCs in an impaired ear based on tests of OAEs and particularly the DP-gram can assist the clinician in achieving an optimal match between the patterns of hearing-aid amplification and hearing loss.

Also, especially important to hearing conservation is the correct identification of individuals exhibiting pseudohypacusis, who seek monetary compensation for a purported work-related hearing impairment. An example of this application is illustrated in Figure 151-8 for a 42-year-old man who was referred to the audiology clinic for assessment by a local worker's compensation committee. In this case, the patient claimed to have poor hearing caused by on-the-job exposure to intense noise to the extent that he could not hear frequencies greater than about 4 kHz. According to the OAE findings, it is likely that the patient, a wood-lathe operator, had an asymmetric noise-related hearing loss that was worse in the ear (right) that was more exposed to the tool. Based on the type of hearing-loss data presented in Figure 151-1A for an industrial worker, however, it is unlikely that lathe-related noises could cause such a profound deafness for frequencies greater than 4 kHz. Additionally, the normal levels of DPOAEs and TEOAEs for frequencies less than 2 kHz do not support the patient's claim that the elevated audiometric hearing levels over the low-frequency to midfrequency regions were due to noise overexposure. Findings such as these support the use of objective tests of evoked OAEs in determining the authenticity of compensation claims for work-related hearing problems.

Interactive Effects

It is well established that noise in combination with certain chemical agents produces stronger reactions than each stimulus applied singly. The four major categories of ototoxic drugs are aminoglycoside antibiotics, platinum derivative antitumor agents, "loop" diuretics, and salicylates. The latter two classes of drug cause reversible effects, whereas aminoglycosides and platinum derivatives cause permanent damage to the inner ear and to hearing. Many laboratories have established in animal models that kanamycin, neomycin, or amikacin applied in combination with different types of noise produces a marked potentiating interaction.[78,79] Other studies of the temporal aspects of interactive effects indicate that the degree of potentiating interaction is the same whether the drug is given concurrently with the noise exposure or several months later.[80] Other evidence from humans[81] and controlled laboratory research in a rat model[82] indicates that additional loss may occur when subjects are treated with aspirin and exposed to noise concomitantly, although other findings infer that the combination of salicylate plus noise does not produce greater effects than noise alone.[83] Finally, experimental evidence in several animal models showed that the heavy-metal, antineoplastic agent *cis*-diamminedichloroplatinum, commonly known as cisplatin, significantly increased the amount of hearing and sensory cell losses from exposure to noise.[84,85]

In recent years, the interactive effects of noise with chemical agents common to industry and the environment have been reported. In a series of experimental studies in the rat model, Fechter and colleagues[86] discovered that the simultaneous exposure to noise and the environ-

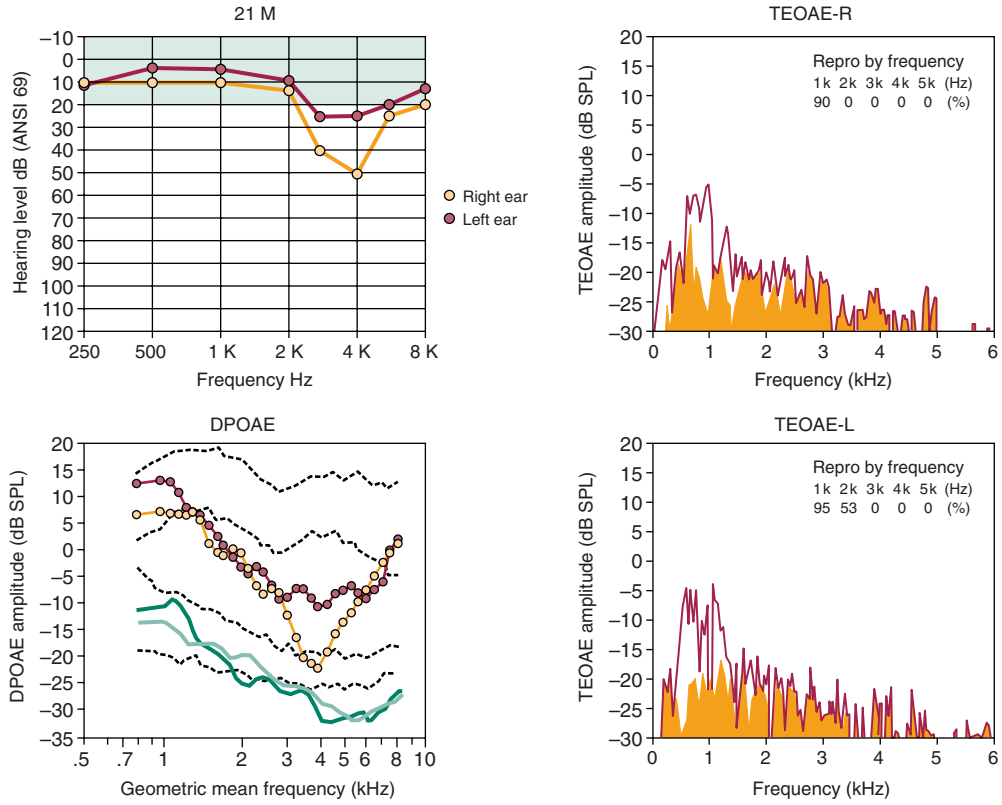

Figure 151-6. Early stages of noise-induced hearing loss in a 21-year-old military veteran, who had just completed a 3-year tour of duty. For this left-handed infantryman, note greater hearing loss from approximately 3 to 4 kHz for the right ear *(yellow circles)* depicted in the audiogram *(top left)*. In corresponding DP-gram, note abnormally low levels of distortion product otoacoustic emission (DPOAE) activity for frequencies greater than 1.5 kHz, which were poorer for the right ear. Click-evoked otoacoustic emission spectra on the *right* (transient-evoked otoacoustic emission [TEOAE]) also show poorer emitted responses from 1 to 2 kHz and lower "Repro" values for the right (R) ear. There is no emitted response for either ear greater than 2 kHz. See legend for Figure 151-5 for an explanation of click-evoked spectra and two sets of *dashed lines* in DP-gram.

mental pollutants carbon monoxide or hydrogen cyanide produced more permanent hearing loss at the high frequencies than the sum of the losses produced by each agent administered alone. Various other chemicals present in the environment as commercial products or chemical intermediaries and contaminants, such as the organic solvents toluene and hexane, the pollutants methyl mercury and lead acetate, and the organic compounds trimethyltin chloride and styrene used in the manufacture of plastics and polyurethane foam and rubber, have been identified as potent ototoxic agents that potentially interact synergistically with excessive noises. The ototoxicity of environmental agents such as metals, solvents, and asphyxiants and their interaction with noise are issues that have received a great deal of attention in the literature.[87] Although many of these environmental toxicants have been associated with direct injury to inner ear structures, possible additional anatomic damage to more central auditory pathways is also very likely.

Other Adverse Effects Caused by Noise

Damage to the vestibular system is a potential problem with noise because balance receptors are coupled physically with the auditory receptors; that is, they share the membranous labyrinth. In addition to the anatomic proximity of the vestibular labyrinth to the acoustic-energy delivery system, the great similarity in cochlear and vestibular hair cell ultrastructure, and the common arterial blood supply of the cochlea and vestibular end organs via the same end artery support the possibility of vestibular damage associated with NIHL. Theoretically, the limiting membrane, the membranous partition that separates the utricle and semicircular canals from the rest of the vestibule, protects most vestibular sensory cells from the adverse effects of intensive stapes vibration.

Nevertheless, some studies of industrial workers and military personnel have reported a high occurrence of vestibular symptoms and signs, and complaints of dysequilibrium.[88] Such simple correlations between noise exposure and vestibular disturbances are highly controversial because of the typical low incidence of clinical vestibular symptoms associated with gradually developing NIHL.[89] A study of military personnel with mild to severe NIHL using sophisticated vestibular testing in the form of a computerized rotatory-chair system along with routine electronystagmographic measures of caloric responses showed more direct correlations between hearing loss and vestibular upset.[90] In combination, the results showed a symmetrically centrally compensated decrease in the response of the vestibular end organ that was associated with a symmetric hearing loss. A more recent study[91] combining caloric testing with vestibular-evoked myogenic potentials in patients with chronic NIHL showed absent or delayed electrophysiologic potentials, indicating that the vestibular system, especially the sacculocollic reflex pathway, was damaged in addition to the cochlear portion of the inner ear.

Together, these findings imply that a subclinical, well-compensated malfunction of the vestibular system is associated with NIHL. Beyond the medicolegal implications is the daunting possibility that a currently asymptomatic vestibulopathy produced by noise exposure might progress to a disturbing vertigo under certain environmental conditions.[92]

There has been considerable interest more recently in the interaction of vibration and noise, which are common cofactors in the workplace. Although most research shows that vibration alone does not affect hearing, the results of epidemiologic studies in humans and controlled laboratory studies in animal models indicate a synergistic

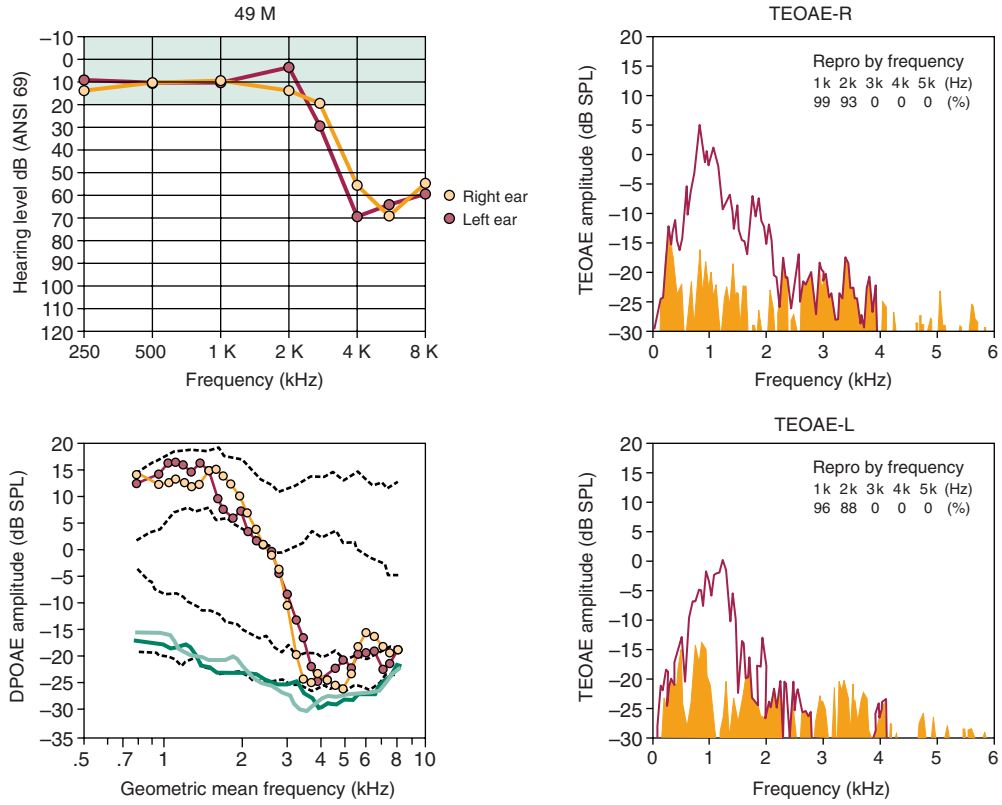

Figure 151-7. More advanced stage of noise-induced hearing loss for a 49-year-old man, who had worked for more than 20 years in a fish cannery. Audiograms at *top left* exhibit symmetric hearing loss for frequencies greater than 2 kHz. DP-grams indicate symmetric pattern of dysfunction in a similar manner. Click-evoked otoacoustic emission spectra on the *right* (transient-evoked otoacoustic emission [TEOAE]) also show a lack of emitted responses for frequencies greater than 2 kHz. See legend for Figure 151-5 for an explanation of click-evoked spectra and two sets of *dashed lines* in DP-grams. DPOAE, distortion product otoacoustic emission.

interaction of concomitant vibration (either whole-body or hand-arm) and noise that results in an increase in the degree of NIHL.[93]

Exposure to infra-frequency and ultra-frequency sounds outside of the human hearing range has also been studied. Infrasonic or vibratory stimuli are defined as sounds in the range of 0.1 to 20 Hz. There are no known instances in which infrasound alone clearly caused permanent damage to the human cochlea. Studies in the chinchilla model showed, however, that the presence of intense sounds in the audible frequency range along with simultaneous infrasound increases cochlear damage.[94]

In contrast, some reports have shown detrimental effects of microwaves on hearing.[95] The thermal properties of ultra-high-frequency sound waves in the gigahertz range, rather than mechanical energy, seem to have produced these adverse experimental effects. Overall, it is probably safe to conclude that the auditory system's built-in, middle ear filter limits the extreme frequencies of sound that are hazardous to the inner ear.[96]

Magnetic resonance imaging (MRI) systems have acoustic noise associated with their clinical scanning actions. For specific protocols that are incorporating faster and noisier sequences, peaks of 120 to 130 dBA have been measured, particularly during high-speed echoplanar imaging.[97] Early on, Brummett and associates[98] showed that sounds generated by MRI are sufficiently intense to cause some TTS in a significant number of patients. Their results also showed, however, that earplugs help attenuate the noise sufficiently to prevent TTS in most patients undergoing MRI evaluation. The use of the higher gradient fields that are applied at faster slew rates, which are used in current functional MRI, demands increased hearing protection systems to minimize the risk of noise trauma.[99]

Other nonauditory problems concern the general bothersome or fatiguing effects of noise, which may lead to nonspecific health disorders because of interference with the restorative processes associated with rest and sleep. In conditions of chronic exposure, noise is considered to act as a biologic stressor that can lead to prolonged activation of the autonomic nervous system and the pituitary-adrenal complex, resulting in general health impairment.[100] Noise has also been related to disorders involving gastrointestinal motility, such as peptic ulcers,[101] and, as noted earlier, to circulatory problems such as hypertension.[102] Certain types of noise can be annoying and lead to emotional unrest.[103] Finally, noise can have a deleterious effect on task performance, especially if speech understanding is involved.[104] Generally, data relevant to the nonauditory effects of noise tend to be inconclusive because the variables are difficult to identify and isolate for objective study.

Legal Issues

One practical issue that the lawmakers of industrialized societies have had to consider concerns the balancing of two conflicting goals: How can laborers be protected against the hazards of the workplace without placing an enormous financial burden on society, either by satisfying compensatory obligations or by preventing such work-related effects through costly engineering modifications of the industrial process? Over the years, concerns about protecting the public and work force from environmental insults such as noise have been written into a combination of law and governmental regulations. Federal, state, and community legislative and regulatory actions are continually being reviewed and altered. Although the purpose of this review is not to detail such legal controls, regarding either their historical development or their current status, a brief discussion is appropriate. For a lucid analysis of governmental statutes and regulations pertaining to noise control, see the review by Dobie.[6]

The major difficulty encountered in composing regulatory control has been in defining in practical terms what constitutes a hazardous noise. The equal-energy principle[105] embodies one popular approach toward expressing the danger of a particular noise by a simple number.

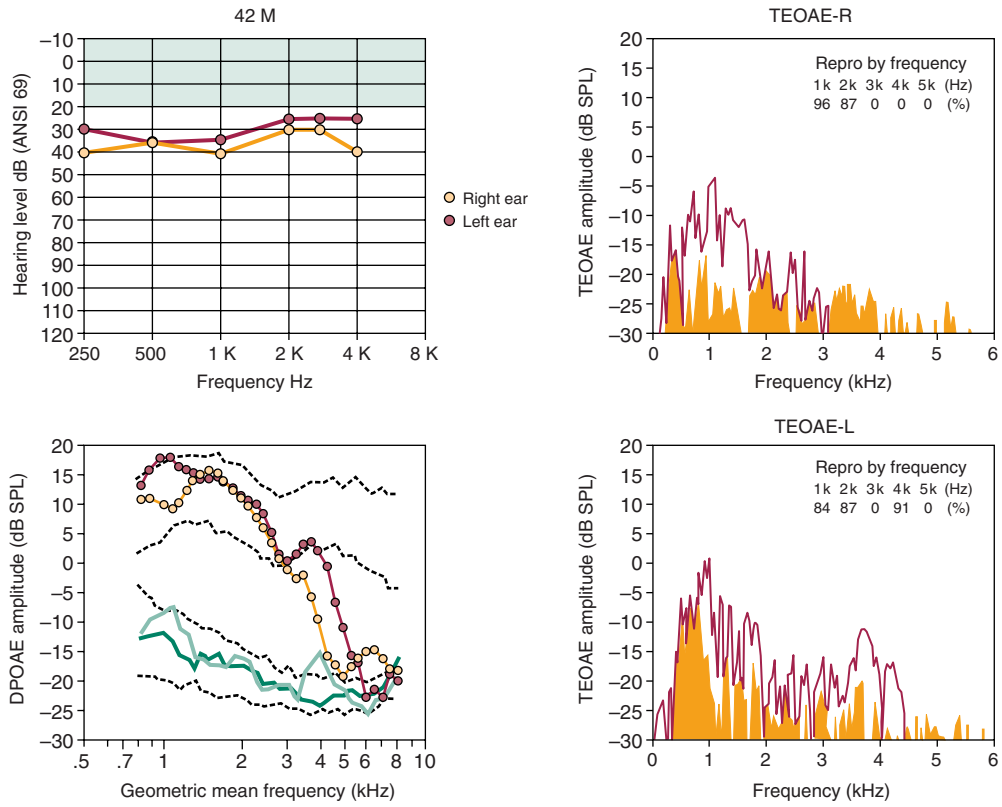

Figure 151-8. A possible case of pseudohypacusis in a 42-year-old male factory worker, who operated a wood lathe. Audiograms at *top left* show a relatively flat hearing loss up to approximately 4 kHz. For frequencies greater than 4 kHz, the patient claimed that test tones were inaudible. DP-grams show normal-like function up to approximately 3 to 4 kHz, when reductions in distortion product otoacoustic emission (DPOAE) levels are evident, occurring initially for the right ear *(yellow circles)*, which was more exposed to the lathe. Spectral plots on the *right* (transient-evoked otoacoustic emission [TEOAE]) also show poorer click-evoked otoacoustic emissions for the right ear. Together, normal levels of evoked emissions for frequencies less than 3 kHz and asymmetric pattern of reduction in otoacoustic emissions suggest that exposure to noise and aging contributed to decreased levels of activity for frequencies greater than 3 kHz. See legend for Figure 151-5 for an explanation of click-evoked spectra and two sets of *dashed lines* in DP-grams.

The equal-energy principle assumes that permanent damage to hearing is related to total sound energy, which is a product of the noise level in dBA and the duration of exposure. One tenet of this postulate is that an equal amount of noise energy causes an equal amount of hearing loss.

Burns and Robinson,[106] who investigated the hearing loss of thousands of industrial workers, concluded that the equal-energy principle could be applied to determine daily exposure doses because hearing loss caused by work-related noise exposure seemed to be a simple function of noise energy. Atherley and Martin[107] extended the concept to impulse noise by application of the equivalent continuous sound level (L_{eq}) principle. The L_{eq} is defined as the A-weighted level of a continuous, steady sound that produces, in a specified interval, an exposure that has the same total acoustic energy as that of an actual time-varying sound over the identical interval.[108] In other words, if one sound contains twice as much energy as a second sound but lasts half as long, both sounds would be characterized by the same equivalent sound level. The L_{eq} concept holds that these two exposures produce the same damage to the ear.

Although notions such as the equal-energy principle have proved useful in the practical definition of noise-control variables, their validity has been more difficult to establish. Over the years, experimental evidence has been conflicting in that it has tended to be either for or against the equal-energy rule. Generally, it seems that the principle cannot be generalized indiscriminantly to stimuli throughout the range of noise parameters because exposure to impulse or intermittent noises may lead to more or less degeneration in the organ of Corti than would be expected according to the equal-energy principle. Some aspect of the equal-energy concept has been adopted by most industrialized nations, however, including the United States, as a means of measuring the potential hazard of a particular noise exposure. Present regulations use a 5-dB exchange rate, along with a 90-dBA time-weighted average to define the permissible exposure limit over an 8-hour work day.[109] Consequently, exposure to 90 dBA for 8 hours is equivalent in sound-energy terms to an exposure of 85 dBA for half that time (i.e., 4 hours).

Currently, industries that employ laborers who work where noise is greater than 85 dB SPL implement a hearing-conservation program consisting of several components as dictated by the U.S. Occupational Safety and Health Administration (OSHA).[109] First, pre-employment audiometric assessment and annual audiometric monitoring are required so that noise-induced cochlear impairment can be detected before becoming too severe. When a hearing loss is identified, the worker must be notified of the disorder and counseled about the use of personal hearing protectors. The second portion of the conservation program requires workers in areas of high-noise levels (≥85 dBA) to wear ear protectors and to participate in a noise education program that informs the employee of the hazardous effects and the correct fitting of personal protectors. An important part of hearing conservation is the otologic referral (see next), which is essential when in-plant audiometry has detected a substantial hearing loss.

Role of the Otolaryngologist

Patients with NIHL constitute a notable portion of an otolaryngologist's patient population, particularly for otolaryngologists who are in private practice. With the increase in the population older than 65 years, the psychological, economic, and social impact of NIHL is still growing. Modern stereo systems in the form of personal music players such as the MP3 and iPod systems have sufficient noise levels and

listening durations to put consumers at risk for developing NIHL.[110,111] The widespread use of these devices, particularly among children and adolescents, is a growing worry,[112] particularly as reported by the mainstream media. Such concern is supported by the finding uncovered in the audiometric database of a large-scale national cross-sectional survey of an accelerating prevalence of sensorineural hearing loss in young adults 20 to 29 years old.[113] This growing prevalence of a high-frequency hearing loss in young adults may relate to an increase in personal stereo player use. The outcome of at least one relevant experimental study using similarly aged subjects, who were systematically exposed to music from an MP3 player at their preferred listening levels, does not agree with this explanation, however.[114] In any case, otolaryngologists are expected to continue to be conspicuously involved with the problem of NIHL.

Although a known prevention exists, it is unlikely for fiscal and technical reasons that the general loud sound levels of our environment will be reduced. Although the inhalation of hyperoxygenated air as a prophylaxis[115] has been proposed, and, as noted previously, clinical trials on the safety and efficacy of certain antioxidant compounds to prevent or reverse NIHL are currently in progress, to date, no proven treatment or cure for noise damage exists. Consequently, detecting the early stages of NIHL is important to prevent further injury to the crucial sensory-cell receptors of the organ of Corti.

The role of the otolaryngologist is first to identify the cause and extent of a reported hearing loss through systematic medical and audiometric evaluation. As part of the course of otologic management, the patient should be educated about the hazards of noise, and about preventive measures to preserve remaining hearing. The physician should make basic decisions about the appropriate aural rehabilitative course of action. Finally, the otolaryngologist should be sensitive to any emotional problems the patient may have in accepting a hearing impairment, which may be dealt with by counseling or special provisions.

Although NIHL is not medically or surgically treatable, it is almost entirely preventable. Its prevention requires education, engineering, and administrative controls, and the proper use of hearing protection. One of the otolaryngologist's most important contributions is in teaching the patient to guard against further losses.[116] When recommending the use of personal hearing protectors or reinforcing compliance with ongoing hearing-protection measures, the physician should be aware that the commonly used personal protectors in the form of inserted earplugs or earmuffs vary considerably in effectiveness, and produce an attenuation that is highly frequency dependent.[117,118] When sealed correctly into the ear canal, earplugs reduce the noise reaching the middle ear by 15 to 30 dB, and work best for the midfrequency to higher frequency range (i.e., 2 to 5 kHz). Earmuffs are more effective protectors, especially for frequencies between 500 Hz and 1 kHz, where noise is attenuated by 30 to 40 dB.[119] In areas with extremely high noise levels, earplugs do not afford sufficient protection, and individuals should be advised to wear both earplugs and earmuffs. Also, sound energy associated with high noise levels may reach the inner ear by passing through vibrating bone and tissues adjacent to the ear. Bone-conduction and tissue-conduction thresholds set a practical limit to the possible attenuation provided by hearing-protection devices.

A final point concerning the use of hearing protectors should be impressed on the patient. When data relating the maximal protection in dBA to the percentage of time that the devices are worn are considered, it is clear that hearing protectors should be worn all the time because if they are removed for even a few minutes, their effective cumulative attenuation capability is severely reduced. Removing hearing protection for only 15 minutes of an 8-hour work shift can cut protection efficacy in half. Similarly, a poorly fitting hearing protector does not prevent hearing loss.[1]

In many states, compensation is available for occupational NIHL. Physicians are required sometimes to serve as expert witnesses as to the probable cause of a claimant's hearing loss. Such medicolegal testimony requires that the patient undergo careful otologic and audiometric evaluation so that hearing losses caused by unrelated ear disorders, such as cerumen impaction, middle ear effusion, aging, genetic deficits, otosclerosis, and an array of other ear diseases (e.g., Meniere's disease, acoustic neuroma), can be excluded. To permit the reversible (i.e., TTS) effects to recover, most states require a recovery time (ranging from 14 "quiet" hours to 24 weeks) away from the occupational noise source before audiometric assessment. By ruling out organic disease, giving careful attention to the history of job-related and recreation-related noise exposure, and documenting the extent and degree of involvement of both ears, an informed decision concerning any causal relationship between the noted disability and the work environment can be made.

Hearing impairment is the medical term used to refer to the hearing level at which individuals begin to experience difficulties in everyday life. Hearing impairment manifests in practical terms, such as a difficulty in understanding speech. By the time an individual becomes aware of decreased speech intelligibility, considerable damage to the organ of Corti likely has occurred because speech reception is not altered greatly until a hearing loss is more than 40 dB. The amount of loss at frequencies most important to speech (i.e., at 2 kHz, 3 kHz, and 4 kHz) is used by OSHA[108] as a basis for calculating amounts of compensation because NIHL occurs initially at greater than or equal to 2 kHz. The measure of hearing impairment is called the hearing handicap, which is always based on the functional state of both ears. An official guide devised by the American Academy of Otolaryngology–Head and Neck Surgery[120] provides a detailed explanation of how to evaluate and compute an NIHL handicap. Generally, the disability benefits of the U.S. Social Security Administration[121,122] are less generous than are the benefits for either military veterans or typical worker's compensation programs.

Because of an increasingly noisy environment and the probability that many individuals will unwittingly sustain hearing losses because of exposure to loud sounds at home, on the job, and during recreational activity, otolaryngologists, along with other health care professionals dealing with hearing problems, should educate the public about hearing conservation. Such education is needed especially for children and adolescents, who, as noted previously, are regularly exposed to the amplified music associated with personal music players, stereos, dance clubs, and live concerts. A common image that can be used to motivate the public and workers in industry to be aware of the insidious damage of noise exposure is the grass metaphor representing the sensory cells of the inner ear. Typically, blades of grass straighten up after they have been bent by being walked on. If one continues to tread on the same patch day after day, however, the grass eventually dies, leaving a bare spot; this is similar to what happens to the ear's hair cells when assaulted continually by high-intensity sounds.

The physician can be particularly effective in teaching individuals how to recognize the danger signals of potential NIHL including the need to shout to be heard and the development of the sensation of pain, muffled sound, and tinnitus.[123,124] The influence of otolaryngologists as hearing experts in the areas of education and motivation can be a major force in preventing NIHL.

Summary

We know more now than ever about the workings of the human ear, including how it responds initially to excessive sound, and how it eventually fails to reverse the progressive damage. We also know how much more we need to learn about basic ear processes before such damage can be corrected. As understanding of the fundamental mechanisms involved in the process of NIHL progresses, developing a medical intervention to minimize permanent injury seems achievable. In the meantime, we know what needs to be done to prevent or check the damage process. In light of the economic impracticability of noise control at the engineering or administrative level, especially in industry, it seems that education of the public about the potential hazards of excessive sound and the beneficial use of protective devices will be the major weapons against NIHL. Consequently, the educational role of otolaryngologists is paramount for the conservation of hearing that is threatened by habitual noise exposure.

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CHAPTER ONE HUNDRED AND FIFTY-TWO

Infections of the Labyrinth

Larry E. Davis

Key Points

- RNA and DNA viruses, bacteria, and fungi cause infections of the human labyrinth in fetuses, children, and adults.
- Selective vulnerability of inner ear structures varies by the virus, and results in different inner ear pathologies.
- Some viruses and bacteria primarily destroy sensorineural epithelium causing permanent hearing loss, whereas other viruses, such as cytomegalovirus, cause little direct damage to cochlear sensorineural structures, and apparently cause deafness by another mechanism.
- The precise role viral infections play in sudden sensorineural hearing loss, vestibular neuritis, and Meniere's disease is unclear.
- There is increasing evidence that hearing loss from otosclerosis is associated with a persistent rubeola virus infection of the stapes footplate.
- There currently are no good antiviral agents for most viruses that infect the inner ear.
- Administration of mumps, rubella, rubeola, and varicella-zoster vaccines is the best method to prevent viral inner ear infections.
- Placement of cochlear implants is successful treatment for children born with congenital deafness from cytomegalovirus or rubella.

Infectious agents, particularly viruses and bacteria, are thought to play a direct or indirect role in causing several inner ear disorders.[1] Each year, several thousand infants are born deaf or with impaired hearing. At least 18% of these cases are proven to be caused by congenital viral infection, and a greater percentage are suspected to have an infectious cause.[2] Each year, about 10 out of every 100,000 individuals are stricken by so-called sudden deafness, which occurs as unilateral or bilateral sensorineural hearing loss (SNHL) of varying degrees.[3] Infectious agents are often suspected as the cause. Bacterial labyrinthitis with profound hearing loss occurs in 10% of patients with bacterial meningitis.[4] Thousands of individuals each year have vestibular neuritis, which many authors think has an infectious origin.[5]

Although many infectious agents are thought to play important etiologic roles in labyrinthine disorders, there are many difficulties in proving that a given infectious agent infects the human labyrinth.[1]

1. Otologic examination shows the degree of functional deficit of the inner ear, but seldom establishes the cause.

2. Cranial computed tomography (CT) shows the shape of the bony labyrinth, but does not show the membranous labyrinth or facial nerve.

3. Resolution of cranial magnetic resonance imaging (MRI) is presently insufficient to show clearly details of the membranous labyrinth.

4. The inner ear is encased within a dense temporal bone, making viral culture of inner ear fluids or tissue from the spiral or vestibular ganglia difficult and seldom done.

5. Acute hearing loss or vertigo is rarely fatal; acute inner ear tissue is rarely available from autopsies.

6. The temporal bone is seldom removed at routine autopsies, so inner ear tissue seldom becomes available for histologic examination even when the illness was remote.

7. Decalcification of temporal bones is slow (months), and often involves agents such as nitric acid that damage the inner ear tissue morphology, often making the tissue inadequate for immunohistochemical studies.

8. Serologic studies can determine that an individual was infected by a given virus, but do not prove the virus caused the labyrinthine damage.

9. Serologic studies of herpes simplex virus (HSV) are difficult to interpret because studies of healthy individuals show that fourfold increases and decreases in HSV antibody titers commonly occur without disease.[6]

10. Isolation of virus from the mouth or nasopharynx does not imply that the virus caused the inner ear damage. HSV and adenoviruses are commonly latent in humans and are intermittently shed in the oropharynx.[7] Other viruses, such as enteroviruses, can be isolated from the throats or stool of asymptomatic individuals, especially when the virus is prevalent in the community.[7]

11. HSV and varicella-zoster virus (VZV) (and likely other herpesviruses) can establish viral latency in neuronal populations and never reactivate during the life of the individual. Detection of viral nucleic acid by polymerase chain reaction (PCR) within neurons does not in itself prove that the latent virus was the cause of the tissue damage.

Establishing whether a given virus is the cause of the patient's deafness or vertigo is difficult. The criteria in Box 152-1 are proposed for determining causality.

Box 152-1

Optimal Proof for Infectious Cause of Inner Ear Infection

1. Clinical association of infectious agent with a specific cochlear or vestibular syndrome
   Epidemiologic studies of infectious agent and syndrome
   Clinical studies of syndrome and isolation of infectious agent at other sites or serologic antibody titer rise
2. Clear evidence of infectious agent presence within inner ear tissue
   Isolation of infectious agent RNA (vRNA) or messenger RNA (mRNA) (excluding mRNA latency-associated transcripts) in inner ear tissue
   Histologic demonstration in inner ear tissue by electron microscopy of infectious agent or by light microscopy finding of inclusion bodies or characteristic cell morphology plus isolation of infectious agent at other body sites
3. In experimental animals, demonstration that suspect infectious agent can cause similar auditory or vestibular signs and inner ear pathology

Modified from Davis LE. Neurovirology of deafness, labyrinthitis and Bell's palsy. In: Johnson RT, ed. *Neurovirology*. Minneapolis: American Academy of Neurology; 2002.

PCR has become a powerful tool in the detection of nucleic acid from infectious agents in human tissues. PCR is difficult to use, however, when tissues, such as temporal bones, have been fixed in formalin and decalcified for weeks with nitric acid. Formalin fixation cross-links DNA and RNA, and nitric acid harms nucleic acids. PCR has been helpful in analyzing small amounts of fresh perilymph removed during surgery and detecting cytomegalovirus (CMV).[8-10]

At present, an unresolved controversy exists regarding the significance of detection of latent herpesvirus DNA in human tissue. Several PCR studies have detected HSV DNA in neurons at autopsy from previously healthy patients from several sites, including the brainstem and cerebral cortex[11] and spiral and vestibular ganglia.[12-14] To date, culture of neuronal explants from these sites has not yielded isolation of HSV similar to culture of trigeminal or sacral ganglia.[15] Clear evidence for the breaking of viral latency and subsequent viral replication currently is lacking. It is unclear whether vestibular and cochlear neurons are dead-end cells, capable of developing latency, but incapable or poorly capable of breaking latency. The latter possibility might allow for occasional patients developing a solitary episode of vestibular neuritis or sudden hearing loss, whereas many patients develop repeated episodes of lip or genital HSV blisters from repeated breakage of latency in the trigeminal and sacral ganglia.

To date, only a few infectious agents have been recovered from or identified within human labyrinthine tissues. CMV[8,9,16] and mumps virus[17] have been isolated from perilymph. CMV antigen has been detected by immunohistochemistry within inner ear tissues.[16,18] Morphologic identification of infectious agents within the labyrinth has been accomplished for several bacteria,[19,20] fungi,[20,21] and *Treponema pallidum*.[22] A multinucleated giant cell, typical of rubeola (measles) virus infection, has been seen within the scala vestibuli.[22] HSV DNA[10,12,23] has been identified within vestibular and cochlear ganglia neurons by PCR assay. One study reported detection of HSV DNA by PCR in vestibular labyrinth tissue.[24] To date, intranuclear inclusion bodies or viral antigens have not been identified within inner ear tissues.

Although rubella has been closely associated epidemiologically with congenital deafness, and has been isolated from many sites in congenitally deaf infants, the virus has never been isolated from or viral antigens have never been identified within inner ear tissues. Histopathologic changes of the temporal bone are not specific for rubella. Nevertheless, available evidence strongly argues that rubella can cause congenital deafness.

Box 152-2

Infectious Agents Associated with Acquired Sudden Sensorineural Hearing Loss or Vertigo*

Viruses
Mumps
Herpes simplex
Epstein-Barr
Varicella zoster
Hepatitis viruses
Adenovirus
Enterovirus
Lassa fever
Rubella
Yellow fever
Variola (smallpox)
Measles (rubeola)
Influenza B virus
Influenza A virus
Parainfluenza
Western equine encephalitis
St. Louis encephalitis
Encephalomyocarditis
Russian-spring-summer encephalitis
Tick-borne encephalitis
Lymphocytic choriomeningitis
Hantavirus

Bacteria
Borrelia burgdorferi
Treponema pallidum
Mycoplasma pneumoniae
Brucella sp
Mycobacterium tuberculosis

Fungi
Cryptococcus neoformans

Rickettsia
Rickettsia prowazekii

*__Bold__ indicates the most common causes.

It is assumed that infectious agents are not normally present in the membranous labyrinth or adjacent ganglia; isolation of an infectious agent from the inner ear carries considerable etiologic significance. This assumption is not based on comprehensive bacteriologic or virologic studies, however. Healthy guinea pigs may harbor herpeslike viruses in the spiral ganglia neurons.[25,26]

Many infectious agents have been reported to be associated with deafness or vertigo. For some infectious agents, the association has been based on case reports that describe acute deafness or vertigo that developed during a systemic infection. For other infectious agents (e.g., rubella), the epidemiologic association has been strong between systemic infection of the individual or mother, and subsequent deafness or vertigo. Box 152-2 lists infectious agents that have been associated with deafness or vertigo, but have yet to fulfill the criteria for optimal proof of causality.

Congenital Hearing Loss

Cytomegalovirus

Clinical Features

CMV is the most common infectious cause of congenital hearing loss in the United States, accounting for 2600 to 4000 cases of SNHL each

year.[27,28] The incidence of congenital CMV infection is about 0.3 to 1 case/100 live births.[29-31] Less than 5% of all congenital CMV infections result in the severe infection termed *cytomegalic inclusion disease*. In this multiorgan infection, the incidence of SNHL is 50% in infants who survive the neonatal period.[32] Hearing loss when measured years later is bilateral, symmetric, and often severe.[33] High-frequency hearing loss is usually greater than lower frequency hearing loss.

Most (>95%) congenital CMV infections are silent, and the newborn appears normal at birth. When 12,371 newborns were screened for the presence of CMV in urine that would indicate a congenital infection, the incidence of SNHL was found to be 1.1/1000 live births.[30] Another study of 307 infants with asymptomatic congenital CMV infection reported 7.2% had SNHL that ranged from mild to profound.[28] Fifty percent had bilateral hearing loss, and 20% had late-onset hearing loss. Other studies have reported that 5% to 15% of children born with silent congenital CMV infection and normal hearing in the neonatal period subsequently developed mild to moderate bilateral SNHL that may be progressive.[31,34-36] Occasionally, these children progress to profound hearing loss in one or both ears. Studies estimate the prevalence of moderate or worse SNHL caused by congenital CMV to be 0.2 to 0.6 case/1000 live births.[29]

Diagnosis

Congenital CMV is diagnosed in symptomatic and asymptomatic infants by isolation of CMV from fresh urine during the first 1 to 2 weeks of life. CMV DNA can also be detected by PCR from urine, blood, cerebrospinal fluid (CSF), and infected tissues.[37] Of congenitally infected infants, 60% to 75% have detectable IgM antibodies to CMV in the umbilical cord or infant serum. Antibodies of the IgM class imply fetal synthesis because maternal IgM antibody normally does not cross the placenta. This serologic test is difficult to perform and should be done only in qualified laboratories. CMV has been isolated from the amniotic fluid of mothers with a congenitally infected fetus.[38,39] After 1 year of age, diagnosis of congenital CMV infection is very difficult. Healthy infants may acquire the virus infection asymptomatically, shedding the virus in their urine and developing antibody titers. Because most maternal infections are asymptomatic, no reliable history can be obtained retrospectively from the mother.

Temporal Bone Pathology

Limited histologic studies of infants dying with cytomegalic inclusion disease show labyrinthitis of the endolymphatic system.[18,40-43] Inclusion-bearing cells have been identified in the auditory and vestibular portions of the inner ear (Fig. 152-1). Within the cochlea, damage is most severe along the basal turn. Evaluating the condition of the organ of Corti has been difficult because of postmortem autolysis, but it seems that the major hair cell degeneration seldom occurs, and that the tectorial membrane remains normal. There is little histologic damage to the auditory and vestibular nerves along with the spiral and vestibular ganglia. Hydrops of the cochlea and saccule and collapse of Reissner's membrane have been observed. In one patient with cytomegalic inclusion disease, a thick layer of these inclusion-bearing cells was found inside the membranous walls of the utricle in the regions where dark cells are located.[41]

The temporal bones of an infant with severe cytomegalic inclusion disease and bilateral deafness who survived 14 years were studied.[44] Chronic pathologic changes were seen in the cochlear and vestibular and nonsensory tissues. Reissner's membrane was collapsed in the more apical turns. Strial atrophy and a loss of cochlear hair cells were observed along the entire length of the basilar membrane. Vestibular neuroepithelial regions were degenerated, and fibrosis was seen within the vestibular perilymphatic tissue spaces. In cochlear and vestibular spaces, isolated regions of calcifications were present. The fibrosis and calcifications suggest that late pathologic changes developed months to years after the acute viral damage had subsided.

In infants dying of cytomegalic inclusion disease, CMV antigen has been identified within cells lining the membranous labyrinth by immunofluorescent antibody staining.[41] Virus particles belonging to the herpesvirus family have been seen within cells of the membranous labyrinth by electron microscopy.[40,41]

CMV has been isolated from perilymph obtained at autopsy from an infant with cytomegalic inclusion disease.[41] CMV also has been isolated from the perilymph of a 5-month-old infant who died with asymptomatic congenital CMV infection whose inner ear morphology was normal by light microscopy.[42] CMV has been detected by PCR in perilymph removed during placement of cochlear implants in children 4½ years old with congenital CMV,[8] but CMV was not isolated from perilymph, or cytomegalic inclusion body–containing cells were not

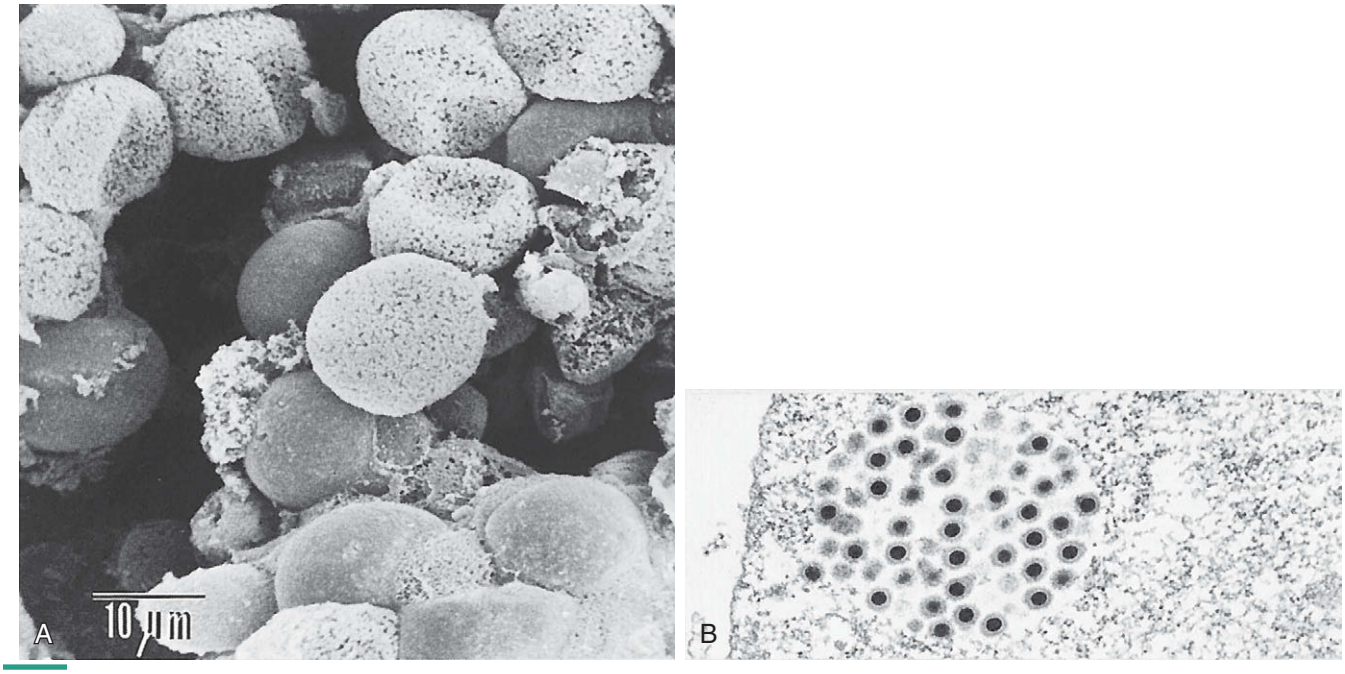

Figure 152-1. Congenital cytomegalovirus infection in a 1-month-old infant. **A,** Scanning electron micrograph shows large osmiophilic cytomegalovirus inclusion-bearing cells lining the membranous wall of utricle. **B,** Transmission electron micrograph shows cytomegalovirus particles with dense cores forming aggregates in the cytoplasm of utricular epithelium (×34,500). *(From Davis LE, Johnsson L-G, Kornfeld M. Cytomegalovirus labyrinthitis in an infant: morphological, virological, and immunofluorescent studies.* J Neuropathol Exp Neurol. *1981;40:9.)*

seen in a child with cytomegalic inclusion disease and bilateral deafness who survived 14 years.[44] It seems that CMV can persist for years in children with congenital viral infections. What role CMV persistence plays in the delayed hearing loss of asymptomatically infected children is unclear.

Management and Prevention

Four approaches have had limited success in preventing or treating SNHL in congenital CMV. Toward prevention of primary CMV infection in a CMV-seronegative woman of childbearing age, several experimental CMV vaccines have been developed and are in clinical testing. These include protein subunit vaccines, DNA vaccines, vectored vaccines using viral vectors, peptide vaccines, and live attenuated vaccines.[45,46]

Treatment of pregnant women with primary CMV infection has been tried by passive immunization using hyperimmune CMV gamma globulin. A nonrandomized study of pregnant women with primary CMV infections showed a significant reduction in symptomatic infected newborn infants at 2 years of age.[47] Valacyclovir at 8 g/day given to pregnant women with primary CMV infection has been shown to achieve therapeutic levels in maternal and fetal blood with a reduction in fetal viral load.[39] Mixed clinical outcomes occurred in the 21 fetuses treated at 28 weeks of gestation, however.

The antiviral drugs, ganciclovir and valganciclovir, have had some success in treating infants with cytomegalic inclusion disease.[48-52] Ganciclovir requires phosphorylation to ganciclovir triphosphate in part by enzymes from CMV. The triphosphate molecule inhibits viral DNA polymerase with inhibition of CMV replication.[48] In a randomized controlled trial, intravenous ganciclovir begun in the neonatal period of symptomatically infected infants was effective in preventing hearing deterioration at 6 months, and may prevent hearing deterioration past 1 year.[49]

Ganciclovir can be delivered only by the intravenous route, and so creates a major problem for extended delivery of the agent. Valganciclovir, a monovalyl ester of ganciclovir, is an oral prodrug of ganciclovir, and in small studies seems to have similar efficacy in treating congenital CMV infections.[50,51] Both drugs reduce CMV viral load in blood and urine, but rarely eliminate the virus from the host. Both drugs also frequently cause neutropenia, so dosages must be carefully monitored.

There is increasing evidence that deafness from congenital CMV is not a contraindication for cochlear implantation. Studies of these children have shown hearing improvement results similar to other congenitally deaf children, and no unusual complications have developed.[53,54]

Experimental Cytomegalovirus Inner Ear Infections

The human strain of CMV has not been shown to infect the labyrinth of small animals. The mouse and guinea pig strains of CMV have been shown to infect primarily perilymphatic structures of the cochlea and vestibule with variable secondary degeneration of the organ of Corti.[55] In guinea pigs, guinea pig CMV has been inoculated directly into the basal turn of the cochlea, resulting in inflammation and cytomegalic cells within the perilymphatic duct along with variable secondary degeneration of the organ of Corti.[56,57] These strains are also capable of infecting neurons in the spiral and vestibular ganglia. Guinea pig CMV has been shown to reach the cochlea by the intravenous route, and to cross the placenta to infect the fetal cochlea.[58] Electrophysiologic recordings of cochlea microphonic and eighth cranial nerve have shown objective hearing loss in N1 compound action potential thresholds of infected guinea pigs.[59-61] To date, all experimental models differ from human inner ear infection in that the animal viruses have primarily infected cells of the perilymphatic system, whereas human CMV primarily infects cells of the endolymphatic system.

Congenital Rubella Deafness

Clinical Features

Rubella infection of the pregnant mother as a cause of neonatal deafness was first recognized during the 1939 Australian rubella epidemic.[62] From 1964 to 1965 during the U.S. rubella epidemic, more than 12,000 infants were found with hearing loss and congenital rubella.[63] Since the introduction of rubella vaccine, the number of cases in developed countries has dramatically decreased, but not disappeared. The World Health Organization estimates that more than 100,000 infants are born each year with congenital rubella syndrome with 50% having hearing impairment.[64] In many developed countries, it is estimated that 15% to 20% of women in childbearing years are susceptible to rubella infection, a number that is similar to that in industrialized countries in the prevaccination era.[65] Since 2001 in the United States, there have been less than 25 cases of rubella each year, and no reported cases of congenital rubella syndrome.[66]

Maternal rubella infection during the first trimester of pregnancy places the fetus at the highest risk of congenital infection and subsequent hearing loss. In addition to the hearing loss, infants are often born with cardiac malformations, vision loss, and mental retardation.[67] Approximately 50% of infants born with symptomatic congenital rubella have hearing loss. Infants infected with rubella during the second and third trimesters often are born with silent rubella infection and appear healthy at birth. Ten percent to 20% of these children are subsequently identified as hearing impaired.[68]

Hearing Loss

Congenital rubella infection involving the inner ear usually results in bilateral, often asymmetric, hearing loss. In a series of 8168 children with hearing loss from congenital rubella, 55% had profound hearing loss (≥91 dB ISO [International Standards Organization]), 30% had severe hearing loss (71 to 90 dB), and 15% had mild to moderate hearing loss (<70 dB).[63] The audiograms of most children were usually flat, with hearing deficits occurring in all frequencies, but some had the greatest hearing loss in the midfrequency range of 500 to 2000 Hz, which is the range of voice.[69] Children with rubella deafness may have poor speech discrimination, and a few may experience progressive hearing loss. Some children have had delayed or impaired speech development, but still have healthy pure tone hearing, which suggests a central auditory imperception.[70] Adults who experience rubella infection rarely develop hearing loss.[71]

The vestibular system seems to be involved to a lesser extent than the auditory system.[72] Caloric stimulation with 1 mL of ice water has suggested that some children have reduced caloric responses in one or both ears.[73]

Diagnosis

Congenital rubella may be diagnosed by (1) isolation of rubella or detection of rubella-specific RNA from urine or throat cultures during the first weeks of life, (2) identification of IgM antibodies against rubella in serum from the neonate, or (3) increased antibody titer to rubella in an infant during the first few months of life who did not receive the rubella vaccine. Identification of IgM antibodies against rubella is difficult and should be performed only in qualified laboratories. In children older than 1 year, congenital rubella is difficult to diagnose because many children have received the rubella vaccine. A maternal history of rash during pregnancy is unreliable for establishing or ruling out the diagnosis. Congenital rubella has been diagnosed in utero by isolation of rubella from amniotic fluid. No specific management for children exists because no antirubella virus drugs are available. Management should be directed toward minimizing the consequences of the hearing loss and possible use of a cochlear implant.

Temporal Bone Pathology

Histopathologic changes seen in the temporal bones of congenital rubella deafness show characteristic changes, but the histopathologic findings are not specific for a rubella infection. The predominant abnormality is cochleosaccular degeneration and strial atrophy of varying degrees.[74,75] Reissner's membrane and the wall of the saccule may sag and even collapse (Fig. 152-2). The tectorial membrane is frequently abnormal, often displaced from the organ of Corti toward the limbus. The stria vascularis shows varying degrees of atrophy. Inflammatory cells in the cochlea are seldom seen. Cells with inclusion bodies do not occur. The vestibular neuroepithelia and their nerves

Figure 152-2. Congenital rubella infection in a premature infant. Cochlea shows partial collapse of Reissner's membrane onto the organ of Corti in all turns (hematoxylin-eosin stain, ×40.) *(Courtesy of G. Nagar, Baltimore, MD.)*

usually appear healthy. There are no animal models for congenital rubella or rubella deafness.

Acquired Sensorineural Hearing Loss

Sudden Sensorineural Hearing Loss

Clinical Features

Many causes of SNHL have been described in children[76,77] and adults.[78] Although several definitions exist, most require a loss of greater than 30 dB in three contiguous frequencies that occurs in less than 3 days in the absence of a skull fracture.[79] The incidence of severe SNHL is about 10/100,000 persons per year.[3,80] The incidence of mild cases is unknown because many individuals do not seek medical attention. Most patients awaken with the hearing loss, or the loss develops within minutes to several hours. The hearing loss is unilateral in more than 90% of cases. Approximately half of the patients note accompanying vertigo or imbalance. Recovery of hearing ranges from 45% to 60%.[3,81] The usual recovery period is days to weeks. After 1 month, little recovery occurs.[3] The extent of recovery is related to age and severity of initial hearing loss. Untreated patients younger than 40 years of age have a better recovery rate. For individuals older than 40 years, the recovery rate may be only 30%.[79]

Temporal Bone Pathology

The mechanisms involved in the sudden hearing loss have not been fully clarified because there are few available temporal bone studies from patients during the acute period. A viral infection of the cochlear endolymphatic structures or spiral ganglia is one of several theories that has been postulated as the cause. Schuknecht[82,83] examined the temporal bones of 12 patients with idiopathic sudden SNHL in his series and reviewed 9 additional published cases. Vertigo was noted in 47% of cases. Histologic abnormalities were identified in the organ of Corti (76%), tectorial membrane (53%), stria vascularis (62%), cochlear neurons (48%), saccule (43%), fibrosis with ectopic bone formation (10%), and tears in Reissner's membrane or oval or round windows (10%). Schuknecht[82,83] concluded that a viral infection of the endolymphatic labyrinth was the most tenable pathogenesis. Another study of 15 temporal bones from patients with SNHL reported the most prominent histologic findings to be loss of hair cells and supporting cells of the organ of Corti (with or without atrophy of the tectorial membrane), stria vascularis, spiral limbus, and cochlear neurons.[84] This study reported examination of one temporal bone from a patient who died 9 days after unilateral sudden hearing loss and failed to find evidence of cochlear inflammation.

Several studies have attempted to define the infectious causes of idiopathic SNHL. Two viruses, mumps and measles (rubeola), have been recognized for centuries as a cause of acquired hearing loss in children. For other viruses, associations generally have been made on the basis of fourfold elevations in viral antibody titers in convalescence or case reports with isolation of the candidate virus from the nasopharynx or mouth. In addition to viruses, syphilis is recognized to cause acute hearing loss[85]; Lyme disease may also be a cause.[86] Box 152-2 lists these candidate infectious agents. To date, associations of infectious agents have represented only a small fraction of the total SNHL cases.

Management

Administration of high-dose corticosteroids shortly after the onset of SNHL has been shown to have a significant benefit in recovery of hearing.[87-89] More recently, nonrandomized studies of repeat treatment with intratympanic dexamethasone in patients who failed systemic corticosteroids reported that occasionally additional hearing recovery ensued.[90-92] Because of the possibility that SNHL might be due to reactivation of HSV, a prospective, randomized, double-blind clinical trial of systemic prednisolone versus corticosteroids and acyclovir was performed on 91 patients.[93] The investigators reported no additional benefit of the acyclovir over prednisolone only. If the sudden severe hearing loss permanently involved both ears, these patients may be candidates for cochlear implants.

Major Causes of Acquired Deafness from Viruses

Mumps Deafness

Clinical Features

Mumps was first recognized to cause deafness in 1860. Since then, it is estimated that 5 of every 10,000 patients with mumps have hearing loss develop.[94] The widespread use of the mumps vaccine in developed countries has dramatically reduced the incidence. Mumps deafness continues to occur, however, in developing countries that do not have major vaccination programs. A study of 115 children with profound bilateral deafness reported that mumps was responsible for 7% of the cases.[95] There has been a more recent increase in mumps in college-aged individuals in the United States (>2600 cases) and United Kingdom.[96] Many of these individuals had previously received two doses of the mumps vaccine. It is unclear how often the mumps caused hearing loss in these patients.

Deafness associated with mumps usually develops in children toward the end of the parotitis, but can occur from a subclinical infection in the absence of parotitis.[97-100] The onset of the deafness is usually rapid and unilateral in 80%. Hearing loss is maximal at high frequencies. Tinnitus and fullness in the involved ear are common. In two patients with acute mumps deafness, MRI showed enhancement of the labyrinth and CN VIII[101] and the cochlea and vestibule.[102]

The hearing loss is often profound and usually permanent. A prospective study by Vuori and colleagues[103] found the hearing loss to be transient in some patients, however. Some patients have vertigo develop that usually resolves over several weeks, but the patient may be left with permanent diminished or absent caloric responses in that ear. Absent caloric responses have also been found in patients with deafness associated with mumps, but without a history of vertigo.

Diagnosis

Mumps is diagnosed by (1) isolation of mumps virus from the saliva or CSF, or detection of mumps virus RNA, or (2) a fourfold or greater serologic increase in mumps antibodies between acute and convalescent serum samples. Sensitive real-time reverse transcriptase PCR assays are available for rapid detection of mumps virus from saliva.[104] Mumps virus has been isolated from the perilymphatic fluid in one patient with acute unilateral deafness associated with parotitis.[17] Currently, no specific antiviral drugs for mumps deafness exists, and it is unclear whether administration of corticosteroids improves hearing recovery. Administration of mumps vaccine in infancy effectively prevents subsequent mumps infections in childhood and adulthood.

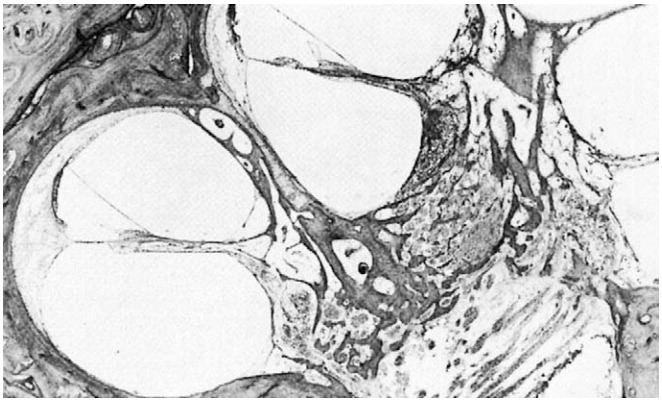

Figure 152-3. Acquired mumps virus deafness 13 years previously. Cochlea shows absent organ of Corti in the basal turn with secondary degeneration of some ganglion cells and severe degeneration of their distal processes in osseous lamina (hematoxylin-eosin stain, ×22.) *(From Smith GA, Gussen R. Inner ear pathologic features following mumps infection: report of a case in an adult.* Arch Otolaryngol. *1976;102:108. Copyright © 1976, American Medical Association.)*

Temporal Bone Pathology

Temporal bones from two patients with mumps-associated deafness have been examined.[105,106] The cochlea showed severe atrophy of the organ of Corti and the stria vascularis, with partial collapse of Reissner's membrane in the basal turn (Fig. 152-3). The tectorial membrane in one case was folded, thickened, and displaced from the organ of Corti. The upper turns of the cochlea showed less damage with occasional loss of hair cells. Cochlear ganglion neurons may be decreased in the area of the basal turn. Minimal vestibular abnormalities were seen.

Experimental Mumps Viral Labyrinthitis

Mumps virus inoculated into the inner ear of hamsters, guinea pigs, and monkeys principally infected non-neuroepithelial cells of the membranous labyrinth, which included cells of Reissner's membrane, stria vascularis, and supporting cells of the organ of Corti.[73,107,108] In the cochlear basal turn, degeneration of the organ of Corti and damage to the stria vascularis developed. Cells of the inner ear could be infected if the virus was inoculated directly into the inner ear, or if the virus entered the perilymphatic fluid of the scala tympani by way of the cochlear aqueduct after intracerebral inoculation.

Because the virus could reach the perilymph from the CSF in the model, the question arises as to whether this route of infection could occur in humans. Support for this hypothesis is severalfold. Mumps viral meningitis occurs in one third of infected children.[109] The cochlear aqueduct is more often patent in children than adults, and dilated cochlear aqueducts have been recognized by CT in 6% of children with SNHL.[76,110] Finally, deafness often develops toward the end of the first week of parotitis, a time consistent with spread of mumps virus from the infected CSF because of the meningitis from the cochlear aqueduct to the scala tympani. Spread of virus from CSF to the inner ear could also occur by way of the CN VIII pathway through the internal auditory canal to the spiral ganglion. Against both hypotheses is one study that did not find a correlation between mumps meningitis and deafness.[103]

Measles Deafness

Clinical Features

Rubeola virus is the cause of measles and continues to be an important cause of acquired hearing loss in developing countries. The incidence of deafness after measles is slightly less than 1 out of every 1000 cases of measles. Before the introduction of rubeola virus vaccine in developed countries, rubeola virus caused 3% to 10% of all acquired deafness in children. Now rubeola deafness occurs primarily in developing countries without measles vaccination programs.

Measles virus involvement of the labyrinth usually is seen with the abrupt onset of bilateral hearing loss at the time of the rash, but occasional children have only unilateral hearing loss develop. In one large study, 45% of the children were left with severe bilateral hearing loss, and 55% had mild to moderate hearing loss.[111] The typical audiogram shows bilateral loss that is often asymmetric and maximal at higher frequencies. The hearing loss is usually permanent and acutely may be accompanied by vertigo and tinnitus. Seventy percent of patients are left with absent or diminished caloric responses in one or both ears even though the vertigo has subsided.[111]

Conductive hearing loss from otosclerosis is becoming highly associated with persistent rubeola virus infection of the stapes footplate. Rubeola virus RNA has been detected by PCR in the stapes footplate removed at stapedectomy from patients with otosclerosis, but not stapes footplates of other diseases.[104,112,113] Tissue culture explants of the stapes footplates also showed rubeola virus RNA.[114] In addition, filamentous structures in osteoblast-like cells resembling nucleocapsids of rubeola virus were seen by electron microscopy.[115] One laboratory was unable, however, to detect by PCR or immunofluorescence rubeola RNA or antigen in stapes footplates or their explants.[116] Epidemiology studies in Denmark and Germany have shown a significant reduction in stapedectomies, particularly in younger patients, since the rubeola vaccination campaign began.[117] The pathogenesis of how measles virus can persistently infect the stapes footplate in healthy individuals and cause otosclerosis is still unclear.

Diagnosis

Measles can be diagnosed by (1) isolation of rubeola virus from throat cultures; (2) detection of rubeola viral RNA from clinical specimens; (3) identification of rubeola viral antigen by immunofluorescent staining of exfoliated epithelial cells obtained by swabbing of the pharynx, conjunctiva, or buccal cavity; or (4) demonstration of a fourfold or greater serologic increase in measles antibody titer between acute and convalescent serum samples. At present, no antiviral medication has shown benefit in the treatment of deafness from measles. It is unclear whether administration of steroids is beneficial.

Temporal Bone Pathology

Only a few temporal bones have been examined from patients with deafness associated with measles.[22,82,118] The major histopathology was a sensorineural degeneration seen in the cochlear and vestibular system. The cochlear degeneration was most severe in the basal turn. The tectorial membrane was often thickened and distorted. Atrophy of the stria vascularis was seen and was maximal at the basal turn. The saccule had collapsed, and the membranous wall adhered to the degenerated macular epithelium. The macula utriculi and the crista ampullaris frequently showed minimal changes. In one case, a subacute inflammatory process with granulomas and a giant cell was seen in the endolymphatic fluid attached to the stria vascularis.[22] Multinucleated giant cells are characteristic of rubeola virus infections.

Experimental Rubeola Virus Labyrinthitis

Experimental rubeola virus infections of hamsters have been shown to cause an inner ear infection with viral antigen principally seen within sensory structures of the cochlea, utricle, saccule, and semicircular canals.[119,120] Cochlear and vestibular ganglion cells were infected, and viral antigen could be identified in their distal nerve processes. Giant cells typical for rubeola virus were seen within the organ of Corti and spiral ganglion neurons. No experimental studies of rubeola infection of stapes have been reported.

Lassa Fever Hearing Loss

Lassa fever is an arenavirus that is endemic throughout West Africa, where 100,000 cases occur each year.[121] The virus is spread to humans from infected urine of rodents. The disease is characterized by an insidious onset of fever, weakness, and malaise followed by cough, back pain, and pharyngitis.[121-123] The mortality rate is estimated at 15% of hospitalized patients. Survivors have hearing loss develop with an incidence of approximately 30%, the highest incidence of hearing loss of any acquired viral illness.[7,124] The hearing loss usually develops during

the convalescent phase of the illness; hearing loss is unrelated to severity of the acute disease. The mean auditory threshold of affected patients is 55 dB. Approximately half the patients show improvement in hearing over 3 to 4 months, but the other half are left with a moderate to severe SNHL. Of 24 patients with imported Lassa fever, only one has developed sudden SNHL, and that was during convalescence.[125] Because temporal bones from these patients have not been examined, the pathology is unclear. The pathogenesis of cochlear damage could be from direct arenavirus infection, from vascular thrombosis or hemorrhage, or most likely secondary from an immune response to the arenavirus in the inner ear.[121,126]

Varicella-Zoster Virus Deafness and Vertigo

Clinical Features

Hearing loss occasionally occurs after chickenpox, but this is usually caused by secondary viral or bacterial otitis media producing a conductive hearing loss. Herpes zoster oticus, or Ramsay Hunt syndrome, is caused by a VZV infection that became latent in the geniculate ganglia during the period of acute chickenpox. Decades later, the VZV breaks latency and replicates first in the geniculate ganglion and then travels down the peripheral facial nerve, causing a peripheral facial palsy that resembles Bell's palsy. Approximately 25% of patients experience vestibular or cochlear symptoms (or both) apparently caused by spread of inflammatory cells from the geniculate ganglion to the inner ear, spiral, and vestibular ganglia.[127-130] Occasionally, patients develop prominent vertigo or hearing loss before or along with the facial palsy that may be mild.[131,132]

Vesicles, which may be painful, usually develop on the skin of the pinna of the ear, behind the pinna, and along the external auditory canal (Fig. 152-4). This development is followed 1 to 2 days later by unilateral facial paralysis and deep ear pain.[133] The facial weakness usually improves over weeks, but is occasionally permanent. In one fourth of patients, symptoms also include vertigo, nystagmus, tinnitus, and hearing loss. Although patients may complain of auditory symptoms, SNHL occurs in only approximately 6% of patients. Audiograms vary, and may suggest primary cochlear involvement or cochlear nerve damage.[35] Caloric tests often show decreased to absent responses in the involved ear.

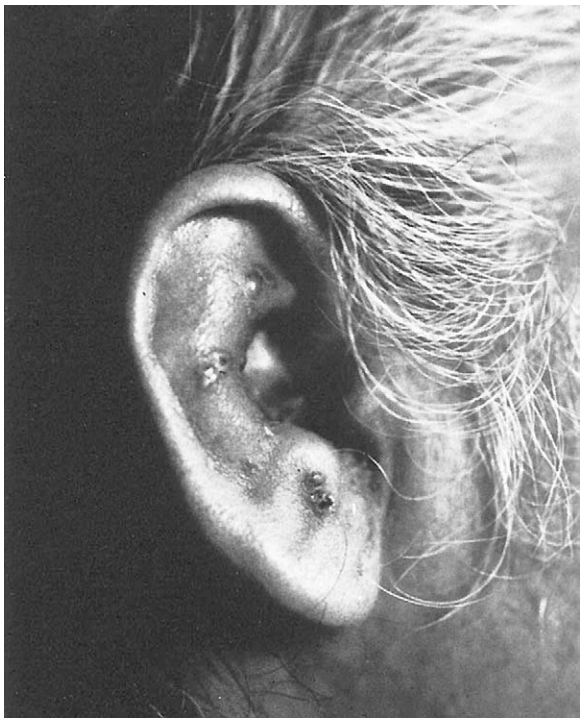

Figure 152-4. Right ear pinna of a 50-year-old woman with herpes zoster oticus. Intense vertigo followed 1 day later with right facial weakness. Multiple vesicles are seen over the pinna, from which varicella-zoster virus was isolated.

Diagnosis

The diagnosis of herpes zoster oticus can be suspected in a patient with acute facial weakness and vesicles on the auricle or in the external canal.[134] Gadolinium-enhanced MRI of the temporal bone of patients with only herpes zoster oticus show enhancement of the involved geniculate ganglion and facial nerve.[135] One MRI report from a patient with herpes zoster oticus and inner ear symptoms found enhancement in the distal internal auditory canal and labyrinthine segments of patients.[136] The diagnosis can be confirmed by isolation of VZV from vesicle fluid; detection of VZV DNA by PCR assay in vesicle fluid, facial nerve sheath, or CSF[134,137-139]; or histologic presence of multinucleated giant cells in vesicle scrapings.

Management

Acute treatment with high-dose acyclovir (800 mg PO five times daily for 7 days), famciclovir (500 mg PO three times daily for 7 days), or valaciclovir (1 g PO three times daily for 7 days) plus a tapering 6-day course of prednisone (beginning usually at 1 mg/kg PO) is widely administered for herpes zoster oticus.[140] One retrospective study compared patients given treatment within the first 3 days of onset with others starting 4 to 7 days after onset or later than 7 days.[141] Patients beginning steroids and acyclovir early did significantly better than patients starting later. Other studies support their use.[142-144] No prospective randomized study has been done, however.

The hearing loss, vertigo, and facial weakness slowly improve over weeks to several months.[145] Serial audiograms showed complete hearing recovery in 66% of children and 38% of adults. Some patients have permanently reduced caloric responses.

A new adult varicella vaccine (Zostavax) has been approved by the U.S. Food and Drug Administration for the prevention of shingles. A randomized, double-blind, placebo-controlled study of more than 38,000 adults older than 60 years showed a 51% reduction in the incidence of shingles.[146] Widespread administration of this vaccine in elderly individuals should reduce the incidence of herpes zoster oticus.

Temporal Bone Pathology

In patients with auditory and vestibular symptoms, the inflammation seems to spread to involve CN VIII and the labyrinth.[78,147] Temporal bones of patients with herpes zoster oticus show facial nerves with active neuritis, including inflammatory cells, edema, hemorrhages, and axon degeneration throughout the facial nerve sheath, but maximally near the geniculate ganglion. The geniculate ganglion usually shows inflammation, edema, and neuronal degeneration. The facial nerve nucleus in the brainstem is not involved.

Pathologic changes in the auditory nerve and labyrinth also have been reported. In all cases, patients had vertigo and hearing loss associated with facial nerve paralysis. Several months after acute paralysis, inflammatory cells have been seen along CN VIII, particularly the vestibular branches. Inflammatory cells have also been seen in the macula of the utricle and saccule. In one case, the branch of the vestibular nerve going to the lateral and superior semicircular canals was atrophic.[78,148,149] Corresponding atrophy and loss of hair cells of the cristae of the corresponding semicircular canal were also seen.

Herpes Simplex Virus Deafness

Infants surviving HSV encephalitis may have permanent hearing loss.[150] Even infants surviving the milder HSV infection of skin occasionally have subsequent hearing loss. An adult with HSV encephalitis has also been reported to have severe bilateral SNHL develop.[151] To date, there have been no histopathologic studies of temporal bone from patients dying after HSV encephalitis. One elderly woman was reported who first developed vertigo and jerk nystagmus with normal MRI followed 3 days later with proven ipsilateral HSV encephalitis.[152] The authors speculate that HSV vestibular neuritis first developed followed by the encephalitis.

For more than 30 years, there has been clinical suspicion that HSV can cause SNHL. To date, the evidence remains inconclusive. In favor

of HSV as a cause of SNHL, HSV DNA has been detected by PCR assay in spiral ganglia in 50% of specimens obtained at routine autopsies.[13,23] HSV seems capable of becoming latent in the spiral ganglia. HSV has been isolated from the oropharynx of patients with sudden hearing loss. Acute and convalescent antibody studies of patients with sudden hearing loss have shown some patients have an increase in antibody titer to HSV. Other studies have shown a higher prevalence of HSV antibodies in children and adults with SNHL than control children.[153,154] In experimental animals, HSV can infect cells of the inner ear of hamsters, guinea pigs, mice, and monkeys.[119,155-157] The resulting infections usually involve cells of the endolymphatic labyrinth and corresponding vestibular and spiral ganglia.

There is also evidence against HSV as a cause of sudden hearing loss. HSV has not been isolated from perilymphatic fluid or inner ear tissues, and Cowdry type A inclusion bodies (typical for HSV infection) have not been identified in inner ear tissue. Several studies have not found the percentage of patients with HSV antibodies or HSV titer elevations different from controls.[158-160] No study has found differences in the clinical features of patients with presumed HSV SNHL compared with other patients with SNHL. HSV can be isolated from the mouth in 10% of normal children[7] and 7.4% of healthy adults without herpes vesicles.[161] The occasional HSV isolation from the mouth of patients with SNHL easily could be coincidental. Likewise, interpretation of increases in HSV antibody titers cited by some authors is problematic because increases and decreases in HSV antibody titer are common in healthy individuals.[6]

The known biology of HSV makes the virus a poor candidate for SNHL. Labial and genital herpes frequently recur, but SNHL rarely does, and the age distribution of SNHL does not match that of HSV recurrences from the trigeminal ganglia or the sacral ganglia. Finally, one randomized, double-blind study assessed the value of acyclovir treatment in patients with SNHL and found no beneficial effect on hearing recovery from combining acyclovir and prednisone compared with administering prednisone alone.[162]

Bacterial and Fungal Labyrinthitis

Bacteria and fungi can damage the peripheral auditory and vestibular systems through (1) suppurative labyrinthitis, (2) toxic labyrinthine damage from bacterial or fungal toxins or inflammatory cell cytokines that reach the perilymph through the round window or modiolus, (3) purulent exudate enveloping CN VIII with nerve infarction or entrapment, (4) purulent exudate or infectious agent reaching the cochlear perilymphatic space by way of the cochlear aqueduct from an infected CSF subarachnoid space, and (5) ototoxic antibiotics to manage infection with elevated concentrations in blood. In most cases, suppurative labyrinthitis seems to be the most important mechanism, with bacteria or fungi reaching the cochlea from blood, the subarachnoid space (meningitis), temporal bone (osteomyelitis), or middle ear (otitis media). In meningitis, bacteria or fungi reach the scala tympani from the subarachnoid space by way of a patent cochlear aqueduct or up the internal auditory canal passing through perineural and perivascular spaces.[19]

Temporal Bone Pathology

When bacteria infect the labyrinth, suppurative labyrinthitis ensues.[163] The acute bacterial infection elicits an acute inflammatory response of neutrophils that results in severe destruction of the membranous labyrinth.[164] Usually, severe hearing loss and acute vertigo occur. The hearing loss is usually permanent, whereas the vertigo slowly resolves over weeks to months. There is often permanent loss of caloric responses.

After appropriate antibiotic management, the acute inflammation slowly resolves. Macrophages may invade from the bloodstream, giving rise to granulomas. Over months to years, fibroblasts may invade the membranous labyrinth to cause permanent scarring of endolymphatic structures.[20] Primitive multipotential mesenchymal cells invade and proliferate from the adjacent modiolus, the bony endosteum lining, and other sites to become osteoblasts. The osteoblasts may form ectopic ossification sites with bony spicules in the perilymphatic space. Eventually, the spicules and trabeculae become vascularized to become new ectopic bone that may partially obliterate the old membranous labyrinthine space.[20] When fungal infections such as mucormycosis[21] and coccidioidomycosis[19] infect the labyrinth, the pathologic changes are similar except that ectopic bone formation seems to be less common.

Bacterial Meningitis Hearing Loss

Approximately one third of all hearing deficits acquired after birth are caused by complications of bacterial meningitis.[165] In a careful prospective study of acute bacterial meningitis in children, Dodge and colleagues[4] found persistent SNHL in 10% of patients. The incidence of deafness in a meta-analysis found the average to be 10%, with a range from 2.4% to 20%.[166] In the study by Dodge and colleagues,[4] SNHL was bilateral in 5% and unilateral in 5%. A transient conductive hearing loss was found in 16%. In adults, pneumococcal meningitis is also associated with a 20% incidence of hearing loss.[167] The incidence of hearing loss varies by strain of bacteria isolated from the CSF: *Streptococcus pneumoniae,* 20%; *Haemophilus influenzae,* 12%; and *Neisseria meningitidis,* greater than 5%.[166] The incidence of hearing loss does not seem to increase when the pneumococcus is penicillin-nonsusceptible.[168]

The hearing loss usually results from purulent exudate damage to the cochlea and spiral ganglia. A histologic study of 41 temporal bones from patients dying of bacterial meningitis reported suppurative labyrinthitis in the cochlea in 49% and in vestibular organs in 25%.[169] The scala tympani of the basal turn had the most inflammation. The sensory and neural structures often appeared intact, but in 12% the spiral ganglia showed extensive degeneration. A study of seven adults with bacterial meningitis that used high-resolution MRI with gadolinium also found abnormal contrast enhancement, mainly in the first cochlear turn, distal CN VIII, and vestibular structures.[170] Over time, damage to the organ of Corti and the membranous labyrinth may progress, with labyrinthitis ossificans developing.

On the basis of the preceding observations, the pathogenesis of hearing loss from bacterial meningitis seems to develop from inflammatory cells and bacteria traversing a patent cochlear aqueduct from the subarachnoid space to enter perilymph in the basal turn of the scala tympani,[171] or by extension of inflammation into the internal auditory canal reaching the cochlear modiolus.[169] The cochlear aqueduct is often patent in small children and progressively closes as the head grows.[172]

Clinical Features

Deafness generally occurs early in the course of the meningitis, but may develop at any time in the clinical course. Early diagnosis and management of the meningitis may not prevent deafness.[154] Children of all ages seem equally susceptible to deafness developing, which may be unilateral or bilateral. The hearing loss usually involves all frequencies and is often profound. Although most patients with SNHL after meningitis have a permanent loss of hearing, clinical hearing improvement occurs in occasional patients, especially if the initial hearing loss was partial.[19] One study of 124 children with bacterial meningitis that conducted repeated audiologic assessments found 10.5% of the children had a transient hearing loss that began within 6 hours and resolved within 24 hours.[173] More recent studies have reported that the incidence of postmeningitis hearing loss is similar for all the commonly involved bacteria.[174]

Evoked-response audiometry is sensitive in detecting SNHL and helpful in diagnosing hearing loss in young uncooperative children.[4] Vestibular symptoms (vertigo, nausea, vomiting, and ataxia) often develop in children regardless of whether hearing loss is present.

Management

Treatment of bacterial meningitis with appropriate antibiotics is essential. Broad-spectrum antibiotics should be given early and modified when bacteria are isolated and antibiotic sensitivities are determined. Evidence that administration of corticosteroids reduces the incidence of hearing loss in children and adults is accumulating.[72,166,175-177] A more recent MEDLINE survey concluded, however, that the benefit of corticosteroids remains unclear.[178] Maximal benefit occurs when the corticosteroids are given early in the course of meningitis in individuals from developed countries.[179]

When hearing loss has developed, no management modifies its severity or permanency. Because hearing deficits are common in patients with bacterial meningitis, a hearing evaluation of all patients during recovery is recommended. If the child is young or uncooperative, evoked-response audiometry should be used.[154]

Vaccines to Prevent Hearing Loss

Bacterial and viral vaccines are playing an increasing role in prevention of hearing loss in adults and children through prevention of meningitis and acute otitis media. The pneumococcal vaccines have significantly reduced the incidence of invasive pneumococcal disease, including pneumococcal meningitis in elderly individuals[180] and children.[180,181] *H. influenzae* type B used to be the most common cause of bacterial meningitis in children.[182] Since the introduction of *H. influenzae* type B vaccine for children, the incidence of *H. influenzae* meningitis has dramatically decreased.[182] Several studies have recommended the administration of these vaccines to children receiving cochlear implants to reduce to risk of bacterial meningitis.[183,184]

Acute otitis media is responsible for conductive hearing loss and SNHL in children. Bacteria are responsible for about 70% of cases of acute otitis media, with *S. pneumoniae,* nontypable *H. influenzae,* and *Moraxella catarrhalis* as the most common causes.[185] Viruses including influenza, respiratory syncytial, rhinovirus, and parainfluenza account for the remaining 30%. Immunization of young children with vaccines that contain *S. pneumoniae*[181,186] or killed influenza virus[187,188] have been shown in some studies to reduce the incidence of acute otitis media. Other studies report less benefit, however.[189,190] The creation of specific childhood vaccines to prevent otitis media are being considered.[185]

Cochlear Implant Infections

Placement of cochlear implants is associated with several types of infections involving the inner ear or meninges. Since 2003, an average of 4% of cochlear implants develop a delayed major infectious complication requiring hospitalization, intravenous antibiotics, and often removal of the device.[191] The risk of infectious complications does not vary whether the cause was congenital or postmeningitis, and cochlear implants seem to improve patient communication equally.[192] Studies have varied regarding whether children or adults are more prone to device infections. The most common bacteria encountered are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Repeated episodes of otitis media and poor chronic health conditions increase the risk of infection. Some cochlear implant infections are associated with *S. aureus* biofilms on the implanted device that are difficult to cure with antibiotics.[193]

Bacterial meningitis from *S. pneumoniae* and *H. influenzae* occurs about 30 times more often in children with cochlear implants than in normal children.[194,195] About half the infections have been associated with a device positioner that has been discontinued. The risk of meningitis continues for many years, however, and argues that these children should receive the pneumococcal and *H. influenzae* B vaccines repeatedly.[196]

Congenital and Acquired Syphilitic Deafness

Clinical Features

SNHL can be a complication of congenital and acquired syphilis.[197] Hearing loss from congenital syphilis can occur early (birth to 3 years old) or late (8 to 20 years old). In 2002, 450 cases of congenital syphilis were reported to the Centers for Disease Control and Prevention, an incidence of 11 cases per 100,000 live births.[198] Extensive multisystem damage from syphilitic infections of other organs usually accompanies early congenital syphilitic hearing loss, which is a bilateral profound symmetric SNHL. Relatively few vestibular symptoms and signs are noted.

Patients with late congenital syphilitic hearing loss are usually 8 to 20 years old when symptoms first appear, but occasionally the hearing loss takes longer to occur. These patients usually have a progressive but fluctuating hearing loss that is asymmetric. Audiograms show a flat sensorineural type of hearing loss. Frequently, there are low speech discrimination scores that are disproportionate to the loss in pure tone thresholds. Tinnitus may occur intermittently. These patients also may experience episodes of acute vertigo similar to episodes of Meniere's disease. Hennebert's sign (a positive fistula test with intact tympanic membranes) may be present. Frequently, decreased caloric responses are found.

Acquired syphilitic deafness usually occurs during secondary syphilis.[85] The hearing loss usually has an abrupt onset, tends to be bilateral, and is progressive. Usually minimal vestibular symptoms exist. Patients may have headaches, stiff necks, cranial nerve palsies, optic neuritis, secondary syphilitic rashes, and lymphadenopathy. The CSF shows lymphocytic pleocytosis, elevated protein, and normal glucose.

Acquired syphilitic hearing loss can also develop during the tertiary stage of syphilis.[199] Similar to the late congenital form, the hearing loss is progressive, fluctuating, asymmetric, and sensorineural. Tinnitus may occur. Episodes of vertigo similar to those in Meniere's disease may be experienced. Loss of speech discrimination may be disproportionate to the pure tone hearing loss. Decreased caloric responses and a positive fistula test with an intact tympanic membrane may exist. The CSF may show minimal pleocytosis and elevated or normal protein. Electrocochleographic features of endolymphatic syphilitic lesions generally resemble the features found in Meniere's disease.[200]

Diagnosis

The diagnosis of all types of syphilitic hearing loss requires recent SNHL in the presence of a positive serum rapid plasma reagin test and a positive fluorescent treponemal antibody absorption test or a positive CSF Venereal Disease Research Laboratory test. Spirochetes have been shown by dark-field examination of perilymph obtained from a diagnostic stapes footplate labyrinthotomy.

Management

The Centers for Disease Control and Prevention recommends aqueous crystalline penicillin G, 3 to 4 million U by intravenous injection every 4 hours for 10 days, to treat neurosyphilis.[201] In addition, administration of prednisone, 30 to 60 mg by mouth every day or every other day, is usually given for the first week unless contraindicated.[202] If hearing loss recurs after tapering, long-term maintenance of prednisone (10 to 20 mg every other day) may be necessary. This complication occurs most commonly in the late congenital and late acquired forms of the disease.

The prognosis is poor in the early congenital form; bilateral profound permanent hearing loss usually results. In the late congenital or acquired forms of syphilitic hearing loss, the prognosis is better. Overall, 50% of patients show minor to considerable improvement after management.

Temporal Bone Pathology

The pathology in cases of early congenital syphilitic hearing loss is primarily that of a labyrinthitis with lymphocytic infiltration and destruction of the labyrinth and CN VIII. Spirochetes have been shown in temporal bones obtained at autopsy and stained with a silver stain.[203] In late congenital syphilis, an osteitis of the otic capsule exists with secondary involvement of the membranous labyrinth[204]; this may give rise to endolymphatic hydrops. In early acquired syphilis, the predominant finding is a basilar meningitis affecting CN VIII, particularly its auditory branch. In late acquired syphilitic deafness, temporal bone osteitis is seen, resulting in secondary degeneration of the cochlear end organ.[199] Damage to the membranous labyrinth may occur, giving rise to endolymphatic hydrops.

Hearing Loss in Immunocompromised Patients

Immunocompromised patients are particularly susceptible to middle ear or inner ear infections. Most commonly, chronic fungal or bacterial middle ear infections spread to the inner ear by way of the oval or round window or from osteomyelitis of the petrous bone. Approximately 30% of patients with acquired immunodeficiency syndrome (AIDS) have otologic complaints that include dizziness, hearing loss, tinnitus, and

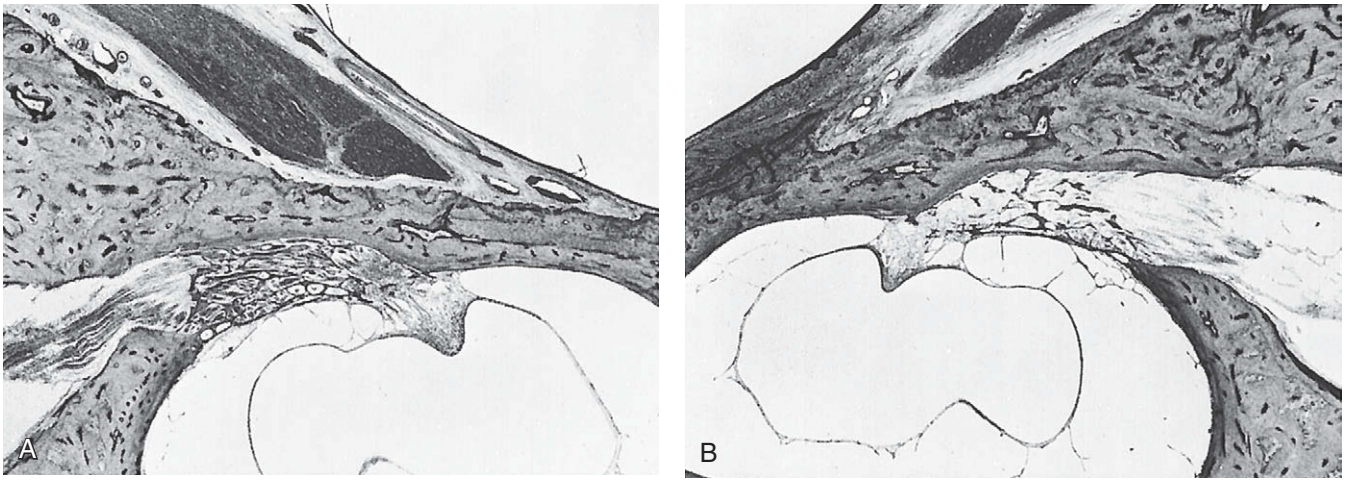

Figure 152-5. Vestibular neuritis developed in this man at ages 55 and 60 years, reducing caloric responses in the left ear. **A,** Right semicircular canal; nerve and crista are normal. **B,** Left semicircular canal; atrophy of nerve and partial atrophy of crista. *(From Schuknecht HF, Kitamura K. Vestibular neuritis.* Ann Otol Rhinol Laryngol. *1981;90[Suppl]:1.)*

otalgia.[205,206] CMV, adenovirus, and HSV have been recovered from perilymphatic fluid of patients with AIDS at death.[207] Histologic damage to the cochlea in viral infections was minimal, suggesting viral entry occurred immediately before death, or the inability of the patient to mount an immune inflammatory response resulted in little inner ear damage.[140,208] Other organisms implicated in SNHL include *Pneumocystis carinii, Candida albicans, S. aureus, Mycobacterium tuberculosis, Toxoplasma gondii, T. pallidum,* and *Cryptococcus neoformans.*[209] Some antiretrovirus medications, including azidothymidine, dideoxyinosine, and dideoxycytidine, have also been associated with SNHL.[209]

Vestibular Neuritis

Clinical Features

Vestibular neuritis has also been called epidemic vertigo, acute labyrinthitis, vestibular paralysis, vestibular neuropathy, and vestibular ganglionitis. The name *vestibular neuritis* is currently used because available pathology suggests that the vestibular nerve is the most common site of damage.[5,210]

The incidence of vestibular neuritis is unknown, but a Japanese questionnaire survey reported 35 cases per 100,000 population.[211] The peak onset of vestibular neuritis is between 30 and 60 years of age. Most patients experience an abrupt onset with a single, severe attack of prolonged vertigo.[212-215] Patients occasionally experience a flurry of attacks over several weeks.[213] Vestibular neuritis should not be accompanied by acute hearing loss or severe tinnitus, although some patients complain of "stuffiness" in the ear. Other neurologic signs or symptoms should not be present. Patients usually have a vigorous spontaneous nystagmus toward the uninvolved side, usually of a horizontal or horizontal-rotary type. Usually only one ear is involved. Caloric responses are diminished or absent in the involved ear in about 50% of patients, and the canal paresis may be permanent.[211,216] CSF examination and electroencephalograms are normal. The diagnosis is made on the basis of characteristic clinical signs. Unilateral diminished or absent caloric tests support the diagnosis.

Management

Early treatment of the patient with methylprednisolone has been shown in a randomized double-blind, placebo-controlled study to improve outcome.[217] Patients were given a 21-day tapering course of methylprednisolone beginning at 100 mg/day. The addition of acyclovir or valaciclovir in two studies did not improve outcome, however.[162,217] During the acute phase, nausea and vomiting may be severe enough to cause clinical dehydration and require hospitalization of the patient and the administration of intravenous fluids. The acute vertigo usually lasts many hours to 1 to 2 weeks.[218]

Spontaneous recovery occurs over weeks to months. There has been concern on the basis of animal studies that prolonged administration of antivertiginous medications may prolong the time to recovery.[219] Many physicians ask patients to stop medication as soon as they can tolerate it. By 6 months, most patients have fully recovered, but may still experience transient positional vertigo triggered by sudden head movements. With recovery, the caloric responses may return to normal or remain diminished or absent.

Temporal Bone Pathology

Studies of temporal bones have been reported from only a few patients with vestibular neuritis.[5,199,214] No patient who died during the acute illness has had his or her temporal bones studied. Most studies from patients dying in the subacute stage have shown primary damage to a branch of the vestibular nerve.[5] Partial to total loss of the superior division of the vestibular nerve supplying the horizontal and superior ampullae has been reported (Fig. 152-5). Associated degeneration of the hair cells occurs in the corresponding sensory organ.

Infectious Causes

Infectious illness, especially colds, sinusitis, and other respiratory tract infections, precede or occur with vestibular neuritis approximately 50% of the time.[211,212] Several viruses have been suggested to be a cause.[220] Patients with mumps may experience vertigo. In a study of proven mumps meningoencephalitis, 37% had impairment of balance, 13% experienced vertigo, and only 2% had an associated hearing loss.[147] In herpes zoster oticus caused by VZV, approximately 25% of patients have vertigo, and may have diminished or absent caloric responses on the ipsilateral side. Some patients have vertigo without an accompanying hearing loss. Patients with influenza often have transient dizziness and vertigo.[221,222] Enterovirus infections have been associated with vestibular neuritis, and the virus has been detected by PCR in CSF in one patient.[223,224] Patients with infectious mononucleosis from an infection with Epstein-Barr virus may have transient vertigo with vertical or horizontal nystagmus.[225] Human herpesvirus type 7 has been associated with one case of vestibular neuritis.[149]

HSV is also associated with vestibular neuritis. Evidence in favor of this association is severalfold. HSV-1 DNA has been identified in vestibular ganglia from tissue obtained at routine autopsies. In some vestibular ganglia, latency-associated transcripts to HSV-1 have been found by reverse transcriptase PCR.[14] Latency-associated transcripts are thought to be responsible for maintaining latency in neurons. Another study could not identify HSV latency-associated transcripts in vestibular ganglia, however.[12]

Studies using a nested PCR assay of 21 randomly selected temporal bones at autopsy reported finding HSV DNA in 62% of vestibular

ganglia and 48% of tissue taken from semicircular canals and macular organs.[226,227] The finding of HSV DNA within vestibular tissue suggests that a focal labyrinthine HSV recurrence could occur. Bacteria (*Borrelia burgdorferi* [Lyme disease] and *T. pallidum* [syphilis]) have also been associated with vertigo attacks similar to vestibular neuritis.[228,229]

Experimental Viral Infections of the Vestibular System

Several other viruses, including rubeola, HSV, mumps, and reoviruses, have been shown to infect the endolymphatic cells in the vestibular system and the vestibular ganglia after intracerebral, intravenous, or direct inoculation through the round window.[119] Generally, these viruses also infected the cochlea. When HSV-1 virus was inoculated into the auricle of 99 mice, 5% developed ataxia 6 to 8 days later.[230] Degeneration of Scarpa's ganglia was found in four of the five mice, and HSV viral antigen was identified in two ganglia. To date, there has been no experimental model that selectively damages branches of the vestibular nerve.

Meniere's Disease

Clinical, diagnostic, and management aspects of Meniere's disease are discussed in Chapters 149 and 164. The cause of Meniere's disease or endolymphatic hydrops remains elusive. Available temporal bone pathologic studies suggest an abnormality of endolymphatic overproduction or underabsorption.[231] Various pathophysiologic mechanisms have been proposed, with several suggesting an abnormal immune mechanism or persistence of a viral infection.[232,233]

In previous years, otitic syphilis was identified as a cause,[234] but more recently syphilis has rarely been found. Viruses have received considerable attention as a possible cause of Meniere's disease.[83,233,235] To date, viral associations have been mainly based on serologic studies.[236] No virus has been isolated from endolymphatic fluid or inner ear structures, and histologic studies have not identified characteristic viral inclusion bodies or viral antigens.

The herpesviruses have gained considerable interest because these viruses establish latency and could recur, causing repeated attacks of vertigo. CMV has been considered because approximately 1 in 100 to 200 infants are born with asymptomatic congenital CMV infection.[30] Some congenitally infected children subsequently have hearing loss that can occur more than 10 years after birth.[18] Evidence for persistence of CMV in the inner ear into adulthood is negligible, however. To date, CMV or its latent state has rarely been found in histologic material of inner ear tissue obtained at autopsy or endolymphatic shunt surgery from patients with Meniere's disease. Experimental inoculation of guinea pig CMV into adult seronegative or seropositive guinea pig endolymphatic sacs has produced the histologic picture of endolymphatic hydrops.[237]

HSV infections have also been considered to cause Meniere's disease.[236,238] Patients with Meniere's disease have been reported to have higher HSV serum antibody titers than controls.[233,236,239] HSV IgG antibody has been reported in perilymph of patients with Meniere's disease and in patients with otosclerosis.[238] One study reported HSV DNA in 100% of 25 vestibular ganglia from patients with Meniere's disease versus 81% of 37 vestibular ganglia from control patients.[240] Another study performed PCR assays for HSV, CMV, and VZV on 22 endolymphatic sacs obtained from patients with Meniere's disease.[241] On finding only two endolymphatic sacs positive for HSV DNA, the authors concluded that ongoing herpesvirus infection in the endolymphatic sac was an infrequent factor in the development of Meniere's disease. Another study using in situ hybridization on 10 endolymphatic sac specimens obtained at surgery for Meniere's disease reported VZV in 7, Epstein-Barr virus in 3, CMV in 1, and HSV in 0.[242]

The two aforementioned studies are difficult to interpret because, except for Epstein-Barr virus, DNA of the other herpesviruses is known to be latent only in neuronal cell bodies, which would not be expected to be present in endolymphatic sacs. Additional evidence against HSV as the etiology comes from several studies. HSV DNA has not been found in the vestibular ganglia of 11 individuals with Meniere's disease.[243] Palva and coworkers[244] were unable to culture HSV from Scarpa's ganglia of patients with Meniere's disease. Cowdry type A intranuclear inclusion bodies or HSV-like viral particles have not been identified in inner ear tissue of patients with Meniere's disease. Finally, Meniere's disease occurs usually in older adults, whereas recurrent herpetic infections occur typically in children and young adults. The current weight of evidence does not support a role for HSV, CMV, or VZV as an important cause of Meniere's disease.

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CHAPTER ONE HUNDRED AND FIFTY-THREE

Autoimmune Inner Ear Disease

Steven D. Rauch

Marc A. Cohen

Michael J. Ruckenstein

Key Points

- Autoimmune inner ear disease (AIED) is a rare entity characterized by bilateral sensorineural hearing loss that progresses over weeks to months, and is responsive to steroids.
- Primary AIED refers to pathology restricted to the ear, and secondary AIED refers to inner ear involvement of multisystemic autoimmune diseases.
- Autoimmune diseases associated with the inner ear include Cogan's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjögren's syndrome, and celiac disease.
- Approximately 50% of patients with AIED have vestibulopathy.
- Studies have shown that the inner ear does not represent an immune-privileged site, but can generate a local immune response after either local or systemic immunization of antigen.
- Studies suggest that there is likely B-cell and T-cell involvement in AIED, but the pathogenesis has not been elucidated.
- Diagnosis of AIED relies on clinical evaluation and a comprehensive assessment of immunologic markers; Western blot for an antibody to a 68-kD protein that binds heat shock protein 70 is not the standard of care in the evaluation of AIED.
- Treatment of AIED is not urgent because there is a 6- to 12-month period in which a significant recovery of hearing is possible with administration of high-dose corticosteroids.
- Initial therapy for AIED is 60 mg of prednisone per day for 4 weeks.
- Response to steroids varies, and treatment is tailored to the initial response.
- Neither etanercept nor methotrexate has been shown to be efficacious in improving hearing loss in patients with AIED.
- Research regarding AIED is important because this is a reversible cause of sensorineural hearing loss; protocols must be informed by expanding knowledge of the pathophysiology of the disorder, and multicenter studies are necessary to evaluate the best use of immunosuppressive drugs.

Otologists and otologic researchers have long believed that the immune system might be capable of damaging the inner ear or eighth cranial nerve, leading to symptoms of hearing loss or dizziness. Some well-documented examples in which systemic autoimmune disease can do this include systemic lupus erythematosus, ulcerative colitis, Cogan's syndrome, and multiple sclerosis. There are some inner ear diseases, such as Meniere's disease and idiopathic sudden sensorineural hearing loss (SNHL), in which an immune-mediated mechanism has been hypothesized but not shown.

One condition—characterized by the clinical presentation of idiopathic, rapidly progressive, bilateral SNHL—has come to be known as autoimmune inner ear disease (AIED), immune-mediated inner ear disease, or immune-mediated cochleovestibular disease. Whether all patients with this presentation have the same underlying pathophysiology, and whether the pathophysiology is autoimmune are unknown. Research regarding AIED is important because the disease represents one of the few medically reversible causes of SNHL.

Definition

Defense against microorganisms is the prevalent concept explaining the evolution and need for the immune system. The immune system must possess the capacity to respond to potential environmental pathogens, and must maintain mechanisms that allow it to distinguish between foreign constituents and the host's own tissue. An autoimmune reaction ensues when the immune system's ability to distinguish between self and nonself is disturbed.

The classic definition of AIED, as provided by McCabe,[1] is that of rapidly progressive (over weeks to months) bilateral SNHL that responds to the administration of immunosuppressive agents. Although McCabe is often credited as the first to describe AIED, the concept of autoimmune hearing loss was first described in the German literature by Lehnhardt in 1958,[2] who described an "antigen-antibody reaction" in the "hearing organs," which improved with steroids. Although this entity is likely an immune-mediated disorder, there is no direct evidence that it is autoimmune in etiology. Nonetheless, the nomenclature coined by McCabe has become established and accepted in the literature.

The disorder defined earlier as AIED refers to a pathology restricted to the ear (primary AIED). Multisystemic, organ-nonspecific autoimmune diseases may involve the inner ear (secondary AIED), however. Such disorders include Cogan's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, and the various systemic vasculitides.

Epidemiology

Primary AIED is a rare disorder. Because of the lack of a definitive diagnostic test for AIED, the precise incidence cannot be determined. It is less common, however, than sudden SNHL, which occurs with an incidence of 1 case per 5000 to 10,000 population per year.[3]

With several exceptions, inner ear involvement is rare in multisystemic autoimmune disorders. Cogan's syndrome, the archetypal AIED, is defined by the presence of labyrinthine and ocular pathology (described in more detail later). Wegener's granulomatosis manifests a significant incidence of ear disease (30% to 50%), with most patients having middle ear pathology, such as chronic otitis media and conductive hearing loss.[4] The presence of concomitant SNHL in patients with middle ear involvement is approximately 30%.[4,5] AIED has been associated with other systemic diseases of the immune system, including rheumatoid arthritis, scleroderma, Sjögren's syndrome, and celiac disease.

Pathology and Pathogenesis

Animal Studies

Various experimental approaches have been used to gain insight into the pathogenesis of AIED. None of these studies has yielded an animal model that is definitively analogous to the human condition, however.

Harris and colleagues[6-8] have contributed significant information to the literature pertaining to the processes mediating inflammation in the inner ear. Using a sterile labyrinthitis, Harris and colleagues[6-8] showed in these studies that the inner ear does not represent an immune-privileged site, but can generate a local immune response after either local or systemic immunization of antigen. These immune responses depend on the presence of an intact endolymphatic sac.[9] Cells that mediate the labyrinthitis enter the scala tympani via the spiral modiolar vein.[10] The ensuing labyrinthitis results in physiologic dysfunction, loss of sensory cells, and, ultimately, fibrosis and osteoneogenesis within the cochlea.[11]

Although these studies shed light on the mechanisms by which an immune-mediated response can be elicited within the cochlea, they do not specifically address the issues of an autoimmune response. To that end, a model of AIED was proposed in which heterologous (bovine) temporal bone antigen and immune adjuvant were used to immunize guinea pigs systemically.[12] This model showed modest changes in physiologic measures of hearing and cochlear morphology. The model has proven to be difficult to replicate, however. The main contribution of this work pertains to the detection of a specific antibody that binds to a 68-kD bovine inner ear antigen on Western blot analysis. This antibody has been found in the guinea pig model, and in humans with AIED.[13] The same antibody also binds to the inducible form of bovine (but not human) heat shock protein 70 (HSP-70), although it does not seem that this antibody is primarily directed against HSP-70 in the in vivo setting. The primary antigenic epitope against which this antibody is directed is unknown, and its role in mediating AIED is unclear.

Another approach to understanding the etiology of this disorder was taken by Nair and coworkers.[14-18] They immunized mice with chick and guinea pig inner ear extracts and created monoclonal antibodies against inner ear cells. One particular antibody, KHRI-3, binds to supporting cells of the organ of Corti, creating a characteristic wine-glass staining pattern when observed through immunofluorescence.[15-18] Infusion of KHRI-3 into live guinea pigs produces hearing loss.[15,16] The KHRI-3 antibody also binds to a 68- to 72-kD antigen on a Western blot of inner ear extract.[18] Sera from some humans with AIED strongly stained a 68- to 72-kD inner ear antigen immunoprecipitated from guinea pig inner ear extract with KHRI-3, and these same patient sera stained organ of Corti–supporting cells in a wine-glass pattern.[19] This is strong evidence that KHRI-3 and human antibodies recognize the same inner ear–supporting cell antigen.

More recent data suggest that KHRI-3 targets multiple peptides similar to those present in the highly conserved protein CTL2, which is abundantly expressed in the guinea pig and human inner ear.[14] CTL2 coprecipitates with the protein cochlin, which is one of the most expressed proteins in the inner ear. Cochlin is critical to the structure and function of the inner ear, and mutations are known to cause cochleovestibular pathology. More recent work reveals that cochlin-specific serum antibody titers are significantly elevated in individuals with AIED compared with age-matched controls.[20] The same study also implicates T-cell response to this specific protein, supporting cochlin as a possible target antigen susceptible to B-cell and T-cell influence.

A third approach has incorporated the study of animal models of multisystemic, organ-nonspecific autoimmune disease. These mouse models of systemic lupus erythematosus spontaneously develop autoimmune disease; they do not require any experimental manipulation. Various strains have been examined, with the most detailed studies focusing on the MRL-Fas^{lpr} and C3H-Fas^{lpr} mice. These strains develop elevations in auditory thresholds, degeneration of the stria vascularis, and antibody deposition within the strial capillaries.[5,21-25] These changes occur in the absence of inflammatory response. The etiology of the observed strial degeneration is unknown. The administration of corticosteroids improves cochlear function in these animals without impeding the development of the morphologic changes.[24,25] Studies have shown that there is similar efficacy in resolution of hearing loss with glucocorticoid and mineralocorticoid administration. These results suggest that the mechanism of reversal of hearing loss occurs as a result of alterations in local ion transport in the cochlea.[25-27]

These studies illustrate that immune-mediated and autoimmune pathology can affect the inner ear. The various pathologies observed in these models do not correlate well, however, with the clinical entity known as AIED.

Human Temporal Bone Studies

A few studies have been performed on human temporal bones derived from patients with autoimmune disease, specifically Wegener's granulomatosis, polyarteritis nodosa, Cogan's syndrome, and systemic lupus erythematosus.[5,21-23] Morphologic changes show findings consistent with two different pathogenic mechanisms. Some bones show fibrosis and osteoneogenesis within the scalae, findings consistent with the end stages of inflammation, as described earlier. Other bones show changes more consistent with ischemia, including cellular atrophy in the absence of inflammation. In cases of ischemia, the vascular compromise is likely secondary to a nonspecific vasculopathy in which the labyrinthine artery becomes occluded in the absence of vascular inflammation and necrosis associated with vasculitis.

Clinical Presentation

The hallmark of AIED, as originally described by McCabe,[1] is the presence of bilateral SNHL that progresses over weeks to months. The hearing loss may initially be unilateral, and it may take months for the bilaterality to emerge. Fluctuations in hearing may occur, but the overall course is one of a relentless deterioration in auditory function. Approximately 50% of patients have symptoms of vestibular dysfunction, with 20% of patients experiencing episodes of vertigo consistent with those seen in Meniere's disease.[5]

Cogan's syndrome represents the classic autoimmune disorder leading to inner ear dysfunction.[21,22] The original definition included the presence of nonsyphilitic interstitial keratitis, SNHL, vertigo, and tinnitus. Labyrinthine pathology may be coincident with the ocular manifestations, or may occur 6 months before or after the onset of eye disease. Other forms of ocular inflammation, including uveitis, iritis, episcleritis, or conjunctivitis, may occur instead of the keratitis, in which case the disorder may be defined as atypical Cogan's syndrome.[21,22] Many patients with Cogan's syndrome note a prodrome with symptoms of an upper respiratory tract infection, symptoms often seen with autoimmune disorders.[28]

Vogt-Koyanagi-Harada syndrome manifests with symptoms similar to those seen in Cogan's syndrome. It also includes depigmentation of the hair and skin around the eyelashes, loss of eyelashes, and onset of aseptic meningitis. This syndrome may represent an autoimmune reaction to melanin-containing cells.[4]

Wegener's granulomatosis is another multisystemic autoimmune disease associated with inner ear dysfunction. The disease is characterized by the granuloma formation and vasculitis typically initially affect-

ing the upper and lower respiratory tracts. Ultimately, it may progress to a more diffuse granulomatous vasculitis with renal involvement. As noted earlier, the disorder is more commonly associated with middle ear disease resulting in a conductive hearing loss. Approximately 10% of patients may manifest an SNHL.[5]

Antiphospholipid antibody syndrome is a disorder of the immune system that causes coagulopathy and is defined by recurrent thrombosis, spontaneous abortions in women, and the presence of antiphospholipid antibodies (anticardiolipin or antilupus anticoagulant antibody). Investigators have noted the association of this autoimmune disorder with SNHL, likely related to microthrombus formation; 25% of all patients who fit the diagnostic criteria for Meniere's disease and idiopathic SNHL have at least one positive antiphospholipid antibody marker.[29]

Systemic vasculitides, such as polyarteritis nodosa, may rarely result in a rapidly progressive hearing loss.[30] In one prospective controlled study, the incidence of SNHL in patients with systemic lupus erythematosus was noted to be 58%.[31] Confounding variables in this study included the administration of potentially ototoxic medications and the presence of renal failure. One temporal bone derived from a patient with lupus did manifest evidence of intracochlear inflammation, including fibrosis and osteoneogenesis.[32]

Differential Diagnosis

AIED may initially manifest in a fashion similar to that seen in sudden SNHL. AIED and idiopathic sudden SNHL are two distinct disorders, however. AIED is considerably rarer than sudden SNHL. AIED is by definition bilateral, although at initial presentation AIED may not have affected both ears, whereas sudden hearing loss is virtually always unilateral. Sudden hearing loss develops in 72 hours or less. In contrast, AIED progresses over days to months; serial audiograms on a monthly basis show continued decline. Sudden hearing loss is an otologic emergency with a treatment window of perhaps 2 to 4 weeks, during which a short burst and taper of corticosteroids must be administered to achieve optimal recovery.

AIED is not urgent. Patients with hearing loss progression over 6 to 12 months can still achieve significant recovery with administration of a long course of high-dose corticosteroids or other immunosuppressive drugs. Throughout the otolaryngology community, there is general awareness that some cases of SNHL are potentially reversible with corticosteroids. There is little awareness, however, that these two entities are quite different in etiology, presentation, workup, and management. Hasty administration of a short tapering course of steroids can delay diagnosis of AIED, and can confuse interpretation of serologic testing.

The clinical presentation of AIED may closely mimic the presentation of Meniere's disease. During the first months of evaluation, the two entities may be difficult to differentiate. Both can manifest fluctuations in hearing and episodic vertigo. If corticosteroids are administered, a spontaneous recovery in hearing, as seen in Meniere's disease, may be mistaken for a positive response to immunosuppressive therapy. Ultimately, the more aggressive course of AIED allows for the differentiation of these two disorders. It has been suggested that a subgroup of patients with symptoms of Meniere's disease may share a common pathophysiology with patients who have AIED. This association is based on studies that have noted that approximately one third of patients with Meniere's disease may have a positive Western blot assay for anti-HSP-70 antibodies.[33,34] This finding was not supported by a later study, however, in which the commercially available assay was used.[35]

Otosyphilis is a disorder that can closely mimic AIED, and must be ruled out as part of the workup. An acoustic neuroma may manifest with sudden or progressive unilateral SNHL. Rarely, meningitis, multiple sclerosis, or malignancy (e.g., metastatic disease, lymphoma) involving the dura may manifest as rapidly progressive bilateral hearing loss.

Diagnosis

In patients suspected to have AIED, an appropriate review of systems would include questions pertaining to recurrent or chronic ocular disease, nephritis, arthritis, pneumonitis, sinusitis, and inflammatory bowel disease. Routine serologic tests in patients who may have AIED include a complete blood count with differential white blood cell count, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody test, anti–double-stranded DNA antibodies, anti-SSA/B antibodies, antiphospholipid antibodies, C3 and C4 complement levels, antigliadin antibodies, and Raji cell assay for circulating immune complexes. A fluorescent treponemal antibody absorption test (or a *Treponema pallidum* hemagglutination test) must be obtained to rule out otosyphilis. A human immunodeficiency virus test may be considered to rule out hearing loss associated with acquired immunodeficiency syndrome. This workup is aimed at detecting evidence of systemic immunologic dysfunction. None of these tests has been shown to correlate with the diagnosis of primary AIED. Magnetic resonance imaging with paramagnetic enhancement must be obtained to rule out the retrocochlear lesions discussed earlier in this chapter.

Diagnosis of primary AIED can be difficult. No serologic or immunologic test has yet shown sufficient diagnostic accuracy to allow for the establishment of a definitive diagnosis. Tests of cellular immunity have been advocated by McCabe[23] (lymphocyte migration-inhibition assay), and Hughes and coworkers[36] (lymphocyte transformation test). These tests have never been adequately validated, and their diagnostic accuracy has not been determined. During the 1990s, most attention was focused on the role of Western blotting for detection of an antibody that binds to a 68-kD antigen derived from bovine temporal bone extract and to the inducible form of HSP-70.[5,13,37,38] As noted earlier, these antibodies were first determined to be significant when they were detected in guinea pigs immunized with bovine inner ear extract and in humans manifesting AIED.[13]

In a prospective controlled study, with well-defined entry criteria, Moscicki and colleagues[39] showed that 89% of patients with active, rapidly progressive hearing loss did have detectable levels of this antibody, whereas none of the control patients had positive Western blots. Subsequently, 66 additional cases of possible immune-mediated inner ear disease were studied using the same diagnostic criteria of Moscicki and colleagues.[39] Five patients were excluded from analysis because they had Cogan's syndrome, an autoimmune vasculitis characterized by SNHL, vertigo, and interstitial keratitis of the eyes, leaving 61 patients with AIED. Results are shown in Table 153-1. Demographic features and trends in the correlation of Western blot assay with steroid response in this group of patients are essentially the same as Moscicki's original cohort. The proportion of patients with positive Western blot assay and the proportion of Western blot–positive patients who responded to steroids are lower than in the retrospective study by Moscicki and colleagues.[39]

More recent studies have evaluated the use of positron emission tomography (PET) scan as a tool for the diagnosis of AIED. Although initial observations suggested an association between AIED and positive PET scans, the more recent work fails to show any diagnostic benefit to PET scan.[40,41] At this time, there is no role for PET in diagnosis of AIED.

The diagnosis of primary AIED is based on clinical evaluation, the demonstration of progressive SNHL on audiometric assessment done at monthly intervals, and, most importantly, a positive response to the administration of corticosteroids. The presence of a positive Western blot may support the diagnosis of AIED, but can neither confirm nor rule out the diagnosis.

Treatment

Corticosteroid therapy for AIED evolved during the mid-1980s through the 1990s as a result of clinical experience. Niparko and associates[42] reported a prospective, randomized trial that showed most patients with suspected AIED responded to corticosteroids, although the response was highly variable. These data seem to substantiate the current practice of most otologists. Initial therapy for adults consists of a therapeutic trial of prednisone (60 mg daily for 4 weeks). Pediatric patients receive 1 mg/kg/day of prednisone for 4 weeks. Although patients may occasionally respond early in the 4-week period, many do not begin to improve until late in the month; shorter courses of treatment usually result in relapse.

Table 153-1

Relationship of Western Blot Assay for Anti–Heat Shock Protein 70 Antibodies and Response to Corticosteroid Therapy in 61 Patients with Autoimmune Inner Ear Disease

		Steroid Response	
Western Blot	Positive	Negative	No Prescription
Positive	14	11	7
Negative	5	12	8
Undetermined	2	2	—

From Moscicki RA, San Martin JE, Quintero CH, et al. Serum antibody to increase ear proteins in patients with progressive hearing loss, correlation with disease activity and response to corticosteroid treatment. *JAMA*. 1994;272:611.

Patients' hearing is tested at the initiation of therapy and again at 4 weeks. If the threshold has improved by 15 dB or more at one frequency or 10 dB at two or more consecutive frequencies, or if the discrimination is significantly improved, patients are considered steroid responders. Nonresponders are tapered off their medication in 12 days. Responders continue full-dose therapy until monthly audiograms confirm that they have reached a plateau of recovery. Their medication is slowly tapered over 8 weeks to a maintenance dose of 10 to 20 mg every other day. This maintenance dose is continued for a variable time. Clinical observation suggests that patients with a treatment duration of less than 6 months are at increased risk of relapse compared with patients treated for 6 months or longer.

Patterns of response to corticosteroid therapy vary. Some patients have improvement in threshold, some have improvement in discrimination only, and some experience improvement in both areas. Some patients with hearing loss fluctuation and progression before therapy show stabilization in hearing without actual improvement. Historically, these cases have been considered nonresponders, but this issue is currently being reassessed. Most responders slowly taper off the steroid dose, wean from steroids, and do well. A subset of AIED patients relapses while tapering or after discontinuing the medication. In some instances, additional corticosteroid therapy is effective. Occasionally, the hearing loss becomes refractory to corticosteroids. In such cases, alternative immunosuppressive drugs are considered. Some patients, especially children, may occasionally show steroid-dependent hearing loss. In other words, they cannot be weaned below a certain level of steroid dosage without decline in hearing. Such patients often develop unacceptable side effects of long-term steroid administration. Methotrexate has been used as part of a prednisone-sparing regimen; however, a more recent randomized, prospective controlled, multicenter trial has shown methotrexate to be no better than placebo at maintaining a remission in these patients.[43]

Corticosteroid therapy has limitations. The risks of long-term administration include gastritis and ulcers, fluid retention and weight gain, blood pressure lability, altered blood glucose metabolism and diabetes, avascular necrosis of the hip, mood changes or psychiatric problems, sleep disturbance, accelerated cataract formation, osteoporosis, and cushingoid habitus. Overall steroid response rate is approximately 60% in AIED patients. Some initial responders become refractory at the time of relapse. Despite these limitations, corticosteroid therapy remains the mainstay of AIED treatment on the basis of the extensive clinical experience with its use.

Alternatives to systemic corticosteroids include methotrexate, etanercept, and cyclophosphamide. Low-dose methotrexate seemed to be useful as an adjunct in management of steroid-dependent hearing loss.[44] As noted earlier, a more recent large trial indicates that methotrexate may not serve an effective role as a prednisone-sparing drug.

Etanercept, an inhibitor of tumor necrosis factor-α, has been used to treat AIED. Anecdotally, it seems to work well in combination with methotrexate because of its steroid-sparing effect. As seen in rheumatoid arthritis, etanercept alone does not seem to be nearly as effective. In an open-label and blinded, prospective study, etanercept was shown not to be efficacious in improving hearing loss in patients with AIED.[40,45] A more recent study of nine patients showed, however, that the administration of transtympanic tumor necrosis factor-α inhibitor may aid in the tapering of high-dose steroids in AIED.[46] Although this is a pilot study, the results are promising and warrant further investigation.

Cyclophosphamide is a potent cytotoxic agent generally used for cancer chemotherapy and treatment of Wegener's granulomatosis. Although some authors advocate its use as a first-line drug,[23] the high risk of toxicity makes it a better choice as a salvage drug or treatment of last resort. An initial dose of 1 mg/kg/day orally for 4 to 6 weeks may be instituted. When no response is apparent, the dose is doubled to 2 mg/kg/day. Responders are treated for 6 to 12 months. Toxicity includes severe myelosuppression, opportunistic infection, hair loss, cystitis, infertility, and increased risk of malignancies. Weekly monitoring of hematologic status is mandatory. Many patients, when confronted with the risk of this medication, would rather consider cochlear implantation.

Intratympanic steroid therapy, intratympanic tumor necrosis factor-α inhibitor, systemic IgG injections, and plasmapheresis are possible treatments with sound theoretic justification. Intratympanic steroid therapy is particularly appealing because it is minimally invasive and enables direct application of the drug to the affected site with low risk of systemic effects. There are, however, no published series in which these treatments have been systematically applied. The best role for any of these treatment modalities remains to be determined.

The only drugs of proven utility in the management of AIED are the corticosteroids. All other immunosuppressants currently employed have not been systematically evaluated and carry with them serious toxicity risks. In a patient who cannot be maintained on corticosteroids because of complications, the possibility of withdrawing treatment, with the intention of inserting a cochlear implant when hearing becomes significantly impaired, must be considered.

Summary and Future Directions

The story of AIED from the initial description by McCabe to current therapy practices has been presented here as a simple and direct path. That has not been the actual case. It has been a broad and meandering path with significant contributions by many investigators and numerous important digressions. It is a story that still has far to go. The clinical description of this disorder is confined to its auditory manifestations. As noted earlier, 50% of AIED patients have vestibular symptoms. This aspect of the illness has not been well characterized clinically. Just as there are many AIED patients with auditory symptoms exclusively, there may be an equal number with vestibular symptoms exclusively. Such a presentation has not yet been reported.

Little is understood about the underlying pathophysiology of AIED. That SNHL can be reversible flies in the face of accepted dogma that, after SNHL, hearing cannot be restored. It is interesting to consider what pathophysiologic mechanism could disable neural signal transduction or transmission in the auditory system, yet be reversed months later by anti-inflammatory or immunosuppressive drugs. A solution to this puzzle is expected to come from systematic research into the nature of the humoral and cell-mediated immune response of affected patients. Although the Carey model using KHRI-3 is promising, as yet there is no widely accepted animal model of the AIED phenomenon in which to carry out such research, and human studies progress slowly because of the lack of the clinical material. This scarcity does not diminish the significance of the topic, however.

Understanding the mechanism of AIED would provide a new level of insight into the role of systemic and organ-specific immune reactions in disease of the inner ear. The fact that 20% of AIED patients

have a clinical presentation overlapping with Meniere's disease, and 33% of Meniere's disease patients have evidence of antibodies to the 68- to 72-kD antigen by Western blot assay is strong evidence of a shared pathophysiologic mechanism. Although AIED is rare, Meniere's disease is not. In the United States alone, there are an estimated 125,000 cases yearly. New ways of understanding Meniere's disease could have great public health benefit.

Diagnosis of AIED currently relies on clinical factors alone. As stated earlier, the observation that many AIED patients carry serum antibodies reactive with HSP-70 does not seem to implicate HSP-70 in the pathophysiology of AIED. HSP-70 may carry an epitope shared with the true target antigen, or may otherwise colocalize with it biochemically. Despite poor understanding of AIED pathophysiology, detection of this, CTL2, cochlin, or other marker antibodies may become clinically useful. The utility of an assay would be greatly enhanced by development of a quantitative measure that enables clinicians to follow antibody titers by serial testing. In addition, estimation of sensitivity and specificity of the assay must be made by its broad application to a wide variety of ear diseases and immunologic disorders.

Current AIED therapy is based on empiric experience gathered during the late 1980s and through the 1990s, and validated by more recent clinical studies; this is despite a clear understanding of the underlying pathophysiology. Future therapeutic protocols must be informed by expanding knowledge of the pathophysiology of the disorder. Large multicenter studies are necessary to evaluate carefully the best use of corticosteroids and other immunosuppressive drugs. Consensus must be achieved on the clinical diagnostic criteria and treatment regimens to enable comparison between studies. Even with strict adherence to rigorous methodology, it may take many years to address these questions. For the foreseeable future, AIED will remain one of the most interesting, important, and challenging problems confronting otologists and otologic researchers.

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CHAPTER ONE HUNDRED AND FIFTY-FOUR

Vestibular and Auditory Ototoxicity

Leonard P. Rybak

Key Points

- Measurement of peak and trough serum levels of aminoglycosides provides rough guidelines for therapeutic efficacy, but is not an absolute guarantee for prevention of ototoxicity, particularly vestibular ototoxicity.
- Bacteremia, fever, hepatic dysfunction, the presence of another ototoxic, and renal dysfunction have been associated with increased incidence or severity of ototoxicity of aminoglycosides.
- Aminoglycosides seem to form an ototoxic complex with iron.
- Ototoxicity from aminoglycosides may be reduced by pretreatment with salicylates.
- Although some clinical improvement can be seen beginning 2 months after onset of symptoms, recovery from oscillopsia resulting from aminoglycoside ototoxicity is rarely complete.
- Cisplatin and aminoglycoside antibiotics damage outer hair cells in the base of the cochlea, resulting in high-frequency sensorineural hearing loss that may later involve lower frequencies.
- There is a genetic predisposition to aminoglycoside-induced hearing loss that involves a mutation of mitochondrial DNA.
- Ototoxicity caused by aminoglycosides and cisplatin seems to be related to the production of reactive oxygen species that damage the hair cells, resulting in cell death and hearing loss.
- Hearing loss caused by cisplatin seems to be highly variable, and seems to be related to dose; age of the patient; and other factors such as noise exposure, exposure to other ototoxic drugs, depleted nutritional state including low serum albumin and anemia, and cranial irradiation.
- Ototoxicity with difluoromethylornithine, salicylates, and erythromycin is nearly always reversible.
- Hearing loss caused by abuse of hydrocodone does not respond to corticosteroids.

Ototoxicity refers to the tendency of a drug or chemical agent to cause inner ear dysfunction, producing symptoms of hearing loss, dizziness, or both. Inner ear tissues may be damaged either temporarily or permanently. Many agents can cause ototoxicity. This chapter discusses some common drugs that can cause hearing loss or injury to the cochleovestibular apparatus.

Aminoglycoside Antibiotics

The aminoglycoside antibiotics are an important class of anti-infectious agents. They were developed to combat tuberculosis and other life-threatening infections. The first members of this class of drugs were streptomycin and dihydrostreptomycin. Initial clinical trials showed that these compounds could damage the kidneys and the inner ear. Since then, many new aminoglycosides have been developed. Dihydrostreptomycin proved to be too toxic and was taken off the market. Neomycin was found to be too toxic for systemic use and has been relegated to local application. Other members of this group of drugs include kanamycin, gentamicin, tobramycin, amikacin, netilmicin, and sisomicin. Some of these agents are more toxic to either the cochlea or the vestibular apparatus, although their ototoxicity is not completely selective. Toxicity generally occurs only after days or weeks of exposure. The overall incidence of aminoglycoside auditory toxicity is estimated to be approximately 20%, whereas vestibulotoxicity may occur in about 15%.[1]

Pharmacokinetics

Aminoglycosides are highly charged molecules and are poorly absorbed orally. Only approximately 3% of an orally administered dose is absorbed from the gastrointestinal tract. Aminoglycosides are normally used parenterally for severe systemic infections. The concentrations of aminoglycosides in tissues are usually approximately one third of the corresponding serum concentration. Penetration of the blood-brain barrier is generally poor, so aminoglycosides are injected intrathecally to treat meningitis. Previous studies have suggested that aminoglycosides are not metabolized. A toxic metabolite may be formed in the inner ear, however.[1] Aminoglycosides are excreted primarily by the kidney by glomerular filtration, and high concentrations of drug in the urine may be achieved. Impaired renal function reduces the rate of excretion. Renal failure is a risk factor for ototoxicity, and dosing of aminoglycosides must be modified to compensate for delayed renal excretion.

Measurement of peak and trough serum levels of aminoglycosides provides rough guidelines for therapeutic efficacy, but is not an absolute guarantee for prevention of ototoxicity, particularly vestibular ototoxic-

ity. An association between trough levels of aminoglycosides and ototoxicity has been pointed out.[2] Ototoxicity is likely related to the area under the curve of blood levels over time, rather than individual peak and trough measurements.[3] An animal study showed no relationship between ototoxicity and plasma level of aminoglycoside. The total dose or area under the curve was a much better predictor of amikacin ototoxicity in this animal model.[4]

Suggested guidelines for monitoring serum levels of aminoglycosides are as follows:

1. In patients with normal kidney function, the peak level is measured within the first 1 or 2 days of treatment, the trough level is measured within 1 week, and peak and trough levels are measured about every week after that.

2. In patients with impaired but stable renal function, the peak level is determined within the first 2 days of treatment, the trough and another peak level are determined within 1 week, and peak and trough levels are measured about twice weekly thereafter.

3. In the presence of impaired and unstable kidney function, peak and trough levels are obtained within the first 2 days of therapy. Serum levels may need to be measured every day as long as renal function is unstable.

4. After any changes in dosage, peak and trough levels are determined within the next 2 days.[5]

Aminoglycoside ototoxicity may be detected, but because of a life-threatening infection and a lack of suitable alternative antibiotic therapy, it may be necessary to continue treatment. Antibiotic ototoxicity may continue even after cessation of aminoglycoside therapy.[5]

More recent studies in animals and in humans have shown the presence of a metabolite of streptomycin in the serum of patients with tuberculosis treated with streptomycin. Five male patients treated with streptomycin for 35 to 90 days with 1 g/day presenting with mild to severe inner ear malfunction were found to have streptidine present. Streptidine may represent an ototoxic metabolite of streptomycin.[6]

Histopathology

Animal and human temporal bone histopathologic studies show that the cochlear and vestibular hair cells serve as primary targets for injury. In the organ of Corti, the outer hair cells of the basal turn are damaged first. As drug treatment is continued, the damage may spread to more apical regions. Inner hair cells seem to be more resistant to injury than outer hair cells. This difference could be a result of the higher concentration of the natural antioxidant, glutathione, in the inner hair cells and in the apical turn outer hair cells compared with in the outer hair cells of the basal turn.[7] Progressive destruction of spiral ganglion cells has been shown in animal studies and in human temporal bone reports.[8,9] In some patients, spiral ganglion cells may be damaged directly by aminoglycosides without injury to outer hair cells.[10] The stria vascularis may become thinner as a result of marginal cell death.[11] In the vestibular system, the hair cell damage may begin in the apex of the cristae and in the striola regions of the maculi.[12] Hair cell destruction may extend to the periphery of the vestibular sensory epithelium, where type I hair cells are primarily affected.[13]

A quantitative study of 17 temporal bones was carried out in patients with well-documented clinical evidence of aminoglycoside ototoxicity, and the results were compared with age-matched controls. Streptomycin caused a significant loss of type I and type II hair cells in all vestibular organs, with a greater loss of type I hair cells in the cristae, but not in the maculae. The vestibular toxic effects of kanamycin seemed to be similar to streptomycin, but neomycin did not cause the loss of any vestibular hair cells. There was no significant loss of Scarpa's ganglion cells for any of the aminoglycosides.[14]

Clinical Manifestations

High-frequency hearing loss tends to occur first and may be detectable before it becomes clinically noticeable.[15] Continued exposure to aminoglycosides may result in hearing loss that progresses to lower frequencies, including the important speech range, interfering with communication skills. A hearing loss of 20 dB or more at two or more adjacent frequencies should be documented to confirm the diagnosis of drug-related hearing loss after exclusion of other causes of hearing loss.

Delayed ototoxicity may occur after cessation of treatment with aminoglycoside antibiotics. Delayed onset of hearing loss usually manifests within 1 to 3 weeks after the end of therapy.[16]

Onset of vestibular ototoxicity is unpredictable, and may not correlate with cumulative dose of ototoxic medication.[17] Ambulatory patients are asymptomatic until they notice the presence of imbalance and ataxia, dramatically worsened by motion, with relative freedom from symptoms during periods of complete immobility. Patients change from being normal to being symptomatic during an easily identifiable 1- or 2-day period, after which symptoms are always present during motion or ambulation. The severity of symptoms varies, ranging from imbalance and staggering to complete inability to walk without assistance. Severely affected individuals also usually experience oscillopsia. Although some clinical improvement can be seen beginning 2 months after onset of symptoms, it is rarely complete.[18]

Rotational vestibular testing in a few patients indicated that results were normal in patients receiving aminoglycoside therapy who were asymptomatic. When abnormalities were observed, as they always were in symptomatic patients, the low-frequency rotational responses were affected first and most severely. When responses to all frequencies were absent, oscillopsia and severe imbalance were usually present. Improvement in function sometimes could be shown by rotational testing. This improvement was always greatest in the high frequencies, and clinical recovery was often not as great as the improvements in test results would have suggested.[18]

Various risk factors have been studied to determine whether they play a role in increasing the likelihood of ototoxicity in various patient populations. Bacteremia, fever, hepatic dysfunction, and renal dysfunction have been associated with ototoxicity in prospective, double-blind clinical trials of gentamicin, tobramycin, and amikacin.[19] Combinations of another ototoxic drug and an aminoglycoside may increase the risk and severity of ototoxicity. Ethacrynic acid was reported to exacerbate the ototoxicity of aminoglycosides in patients with uremia.[3] Furosemide was reported to result in severe sensorineural hearing loss (SNHL) in a patient who had received only five doses of gentamicin for pneumonia.[20] An extremely important risk factor is a mitochondrial RNA mutation, which dramatically increases the risk of ototoxicity. This mutation may sensitize a patient to even a single dose of aminoglycoside. This mutation follows a maternal inheritance pattern, and has been described in Chinese, Arab-Israeli, Japanese, and North American families.[21] Seventeen percent of patients with aminoglycoside-induced hearing loss may have this mutation.[1]

Mutations in mitochondrial 12S ribosomal RNA render patients highly susceptible to aminoglycoside ototoxicity. The first described mutation was an A1555G mutation in the 12S rRNA gene. Mutations in the mitochondrial 12S rRNA make this mammalian RNA more similar to the bacterial rRNA, the primary target of the bactericidal activity of aminoglycosides.[22] This mutation has been associated with spontaneous and aminoglycoside-induced hearing loss. In China, where this mutation seems to occur in 5% to 6% of sporadic patients, approximately one third of patients with aminoglycoside ototoxicity seem to have the A1555G mutation.[22] For an unknown reason, only the auditory system, but not the vestibular part of the inner ear, is sensitized to the toxic effects of aminoglycosides in patients with this mutation.[1]

The risks of intratympanic therapy for Meniere's disease and the use of potential otoprotective agents to prevent or reduce aminoglycoside ototoxicity are discussed in greater detail in Chapters 149, 155, and 165.

Mechanisms of Ototoxicity

Aminoglycosides, such as dihydrostreptomycin, enter the mouse outer hair cell through the mechanoelectrical transduction channel and act as a permeant blocker.[23,24] This channel can act as a one-way valve for aminoglycoside entry, promoting the accumulation of aminoglycoside

within the cell. There seems to be a competition between the aminoglycoside and calcium for entry into the outer hair cell. The normal low endolymph concentration of calcium promotes intracellular accumulation of aminoglycosides.[24]

The aminoglycoside reacts with inner ear tissues to form an active, ototoxic metabolite. The drug in its inactive form combines with iron to form an ototoxic complex. This complex reacts with oxygen to produce reactive oxygen species (ROS). These ROS can react with various cell components, primarily in the outer hair cell.

ROS formation by aminoglycosides in vitro requires iron and the presence of polyunsaturated lipids as electron donors. Electron spray ionization mass spectrometry showed that gentamicin strongly binds to L-R-phosphatidylinositol 4,5-bisphosphate (PIP_2), a membrane lipid rich in arachidonic acid. Studies using lipid-coated membranes confirmed that iron ions and gentamicin can form ternary complexes among gentamicin, iron, and phospholipids. Peroxidation of PIP_2 by ferrous ions significantly increased in the presence of gentamicin, and oxidative damage to PIP_2 was accompanied by the release of arachidonic acid. Arachidonic acid also forms a ternary complex with Fe^{2+}/Fe^{3+}-gentamicin. This complex reacts with lipid peroxides and molecular oxygen, leading to arachidonic acid peroxidation.[25] These ROS can react with various cell components, including the phospholipids in the cell membrane, proteins, and DNA to disrupt the function, primarily in the outer hair cell. This process can trigger programmed cell death, resulting in apoptosis.[1]

Data from experimental studies strongly suggest that aminoglycosides trigger apoptosis at clinically relevant doses,[26] whereas higher doses may trigger necrotic cell death.[27] The ototoxic effects of neomycin[28,29] seem to be mediated by c-Jun N-terminal kinase (JNK). JNK[30] and extracellular regulated kinase (ERK) 1/2 mitogen-activated protein kinases seem to be associated with gentamicin-induced apoptosis in the inner ear.[31] Gentamicin seems to trigger apoptosis by ROS and to be mediated by Ras/Rho GTPases.[30]

Inhibitors of apoptosis proteins play an important role in regulating apoptosis by preventing activation of effector caspases. The effects of specific inhibitors of the X-linked inhibitor of apoptosis (XIAP) on hair cell death caused by gentamicin were examined in basal turn organ of Corti explants from postnatal day 3 or 4 rats in tissue culture exposed to gentamicin. XIAP inhibitors increased gentamicin-induced hair cell loss, but an inactive analog had no effect. A caspase-3 inhibitor decreased caspase-3 activation and hair cell loss from gentamicin plus an XIAP, but caspase-8 and caspase-9 inhibitors did not. These findings indicate that XIAP acts normally to decrease caspase-3 activation and hair cell loss during gentamicin ototoxicity.[32]

Apoptosis may be related to the enzyme protein kinase C zeta. Amikacin treatment in animals induced the cleavage of this enzyme and nuclear translocation, leading to chromatin condensation and decreased nuclear factor kappa B (NFκB) levels in the nucleus. These deleterious effects were prevented by pretreatment with aspirin, resulting in protection of hair cells and spiral ganglion neurons.[33]

Concentration-dependent protection against the ototoxicity of kanamycin combined with ethacrynic acid was found in guinea pigs receiving dexamethasone by intracochlear administration with an osmotic minipump before and after the ototoxic treatment. A statistically significant preservation of outer hair cell counts and lower auditory brainstem evoked potential threshold shifts were found in the dexamethasone-infused ears. No significant rescue was observed.[34]

Antineoplastic Agents

Cisplatin

Cisplatin is a potent antineoplastic agent that is used to treat various malignant tumors, including ovarian, testicular, bladder, lung, and head and neck carcinomas. Side effects include nausea and vomiting, neurotoxicity, ototoxicity, and nephrotoxicity.

Pharmacokinetics

The pharmacokinetics of cisplatin follow a biphasic clearance pattern. After a 1-hour intravenous infusion of 70 mg/m^2, the plasma half-lives in patients were 23 minutes and 67 hours; 17% ± 2.7% of the dose administered was excreted in the urine within the first 24 hours, primarily by glomerular filtration. Cisplatin is extensively bound to serum proteins. This bound form is inactive against tumor cells. The half-lives of free cisplatin in serum are much shorter than the total platinum, with half-lives of 8 minutes (free cisplatin) and 40 to 45 hours (total platinum).[35] The liver rapidly converts cisplatin into nontoxic metabolites within 1 hour after administration. The cytosol of the liver cells seems to form adducts of cisplatin with glutathione and cysteine. Cisplatin is taken up into the cells of the cortex and outer medulla of the kidney during the time when nephrotoxicity begins.[36]

Clinical Ototoxicity

Hearing loss caused by cisplatin seems to be highly variable, and seems to be related to dose; age of the patient; and other factors such as noise exposure,[37] exposure to other ototoxic drugs, depleted nutritional state including low serum albumin and anemia,[38] and cranial irradiation.[39] Children seem to be more susceptible than adults.[40] Hearing loss tends to be permanent and bilaterally symmetric. Symptoms of ototoxicity include subjective hearing loss, ear pain, and tinnitus.[41] Tinnitus has been reported in 2% to 36% of patients treated with cisplatin, and may be transient or permanent.[41] Although higher frequencies are affected first, hearing impairment may extend into the middle frequency range when doses greater than 100 mg/m^2 are used. When ultra-high-frequency audiometric testing is used, 100% of patients receiving high-dose cisplatin (150 to 225 mg/m^2) may show some degree of hearing loss.[38] Dose-related ototoxicity is illustrated by a report that 20% of patients treated with cisplatin for testicular cancer experienced permanent ototoxicity, but more than 50% of patients who received cisplatin in doses of greater than 400 mg/m^2 cumulative dose had permanent hearing loss.[37]

Pediatric patients were studied for cisplatin ototoxicity by use of otoacoustic emissions. A good correlation between transient otoacoustic emissions and pure-tone audiometric threshold was shown in children with normal middle ear function. In this series, 90.5% of patients had a significant SNHL at 8 kHz. The magnitude of the hearing loss was associated with young age at first dose of cisplatin administration, large number of cycles of chemotherapy, and high cumulative dose of cisplatin.[42]

The incidence and severity of hearing loss are reportedly enhanced by cranial irradiation.[39] Patients with nasopharyngeal carcinoma seem to be particularly susceptible to the interaction of cochlear irradiation and cisplatin chemotherapy. The required dose of radiation that acts on the cochlea is greater than 48 Gy in such patients.[43] A more recent study reported that radiation therapy for brain tumors, such as medulloblastoma, can be modified to reduce the doses of radiation to the cochlea, while still delivering full doses to the desired target volume of tissue. Using the technique of intensity-modulated radiation therapy for these tumors, far fewer patients had hearing loss. Only 13% of patients receiving the intensity-modulated radiation therapy protocol with cisplatin had grade 3 or 4 hearing loss compared with 64% of the conventional radiation therapy group.[39]

Whether hearing loss progresses after cessation of cisplatin chemotherapy has been a matter of controversy. It has been reported that 8 years after cisplatin therapy for testicular cancer, elevated urinary and serum platinum levels can be measured; nevertheless, no long-term toxicity was detected in these patients.[44] Long-term audiometric studies of 26 women treated with moderate-dose cisplatin (50 mg/m^2 body surface area every 4 weeks) for gynecologic cancer showed progressive hearing loss equal to or greater than 15 dB at long-term (59 to 115 months after treatment) follow-up in 14 patients (54%). These changes were considered to be small and restricted to three frequencies or fewer in one ear. Only two patients (8%) showed more severe threshold changes. The authors concluded that adult patients who receive treatment with moderate-dose cisplatin have a negligible long-term risk of drug-induced social disability from hearing.[45]

Delayed ototoxicity from cisplatin seems to be much more significant in children. Pediatric patients treated with cisplatin at cumulative doses approaching 400 mg/m^2 showed worsening of hearing with time after treatment. Audiograms showed hearing loss in 5% of patients before the end of therapy. After more than 2 years of follow-up, 44%

had significant hearing loss.[46] A more recent study found that the median time for first significant decrease in hearing was 135 days in children. Additional follow-up for 6 to 44 months showed mild further progression of hearing loss of 10 to 15 dB after completion of therapy.[47]

Studies of vestibular function in patients receiving cisplatin chemotherapy have suggested vestibulotoxic effects, especially in patients with preexisting vestibular problems.[48] With the vestibular autorotation test to study the vestibulo-ocular reflex, patients receiving cisplatin were screened for vestibulotoxicity. Vestibulo-ocular reflex gains at 3.1 Hz, 3.9 Hz, and 5.1 Hz were decreased, and phase lags at 3.1 Hz and 3.9 Hz were increased.[49]

Because chemoradiation protocols with intra-arterial cisplatin include thiosulfate protection, one may think that there would be less ototoxicity with this regimen than with intravenous cisplatin. This does not seem to be the case, however. A prospective study[50] evaluated 146 patients receiving high-dose intra-arterial cisplatin chemotherapy (150 mg/m^2 for four courses) with sodium thiosulfate rescue and concurrent radiation therapy (70 Gy) for locally advanced head and neck cancer. After treatment, 23% of the ears were recommended to need hearing aids. With multivariate analysis, cumulative dose of cisplatin and radiation, and young age were found to have a causal relationship with increased SNHL during and after therapy. In the multivariate prediction analysis, the pretreatment hearing level of the involved ear was found to be an independent predictive factor for hearing capability after therapy.

Maximum threshold shifts occurred after the second cisplatin infusion, and occurred at 8 kHz. Hearing loss seemed to reach a plateau at higher levels (75 to 80 dB hearing loss) for frequencies greater than compared with frequencies less than 8 kHz (45 to 60 dB hearing loss). Recovery was detected after therapy in 27 ears that had extensive losses at 1 kHz, 2 kHz, and 4 kHz.[51]

Risk Factors

There seems to be considerable individual variation in susceptibility to cisplatin ototoxicity. The severity of hearing loss seems to be related to the cumulative dose.[43] Age seems to be an important risk factor for ototoxicity. Children younger than 5 years and elderly adults are more susceptible to cisplatin-induced hearing loss than younger adults.[52,53] Additional factors, such as renal insufficiency and preexisting hearing loss and noise exposure, may increase the probability of cisplatin ototoxicity.[37]

Genetic Predisposition

Genetic predisposition to cisplatin-induced hearing loss may be related to mitochondrial mutations. Five of 20 cancer survivors with cisplatin ototoxicity were clustered in a rare European J mitochondrial haplogroup that is also associated with Leber's hereditary optic atrophy.[54] Other genetic factors may render patients susceptible to cisplatin ototoxicity. Testicular cancer survivors who received cisplatin chemotherapy showed differences in functional polymorphisms for glutathione-S-transferase. Having both alleles of 105Val-GSTP1 seemed to offer protection against hearing loss from cisplatin. The risk of having a poor hearing result was more than fourfold greater in patients with 105Ile/105Ile-GSTP1 or 105Val/105Ile-GSTP1. Genotypes associated with poorer hearing after cisplatin could indicate patients with a limited amount of glutathione for detoxification of cisplatin.[55]

Another potential genetic variant that could influence cisplatin susceptibility is megalin. Megalin is a member of the low-density lipoprotein family that is highly expressed in kidney proximal tubular cells and in marginal cells of the inner ear. Marginal cells have been shown in experimental animal studies to accumulate high levels of platinum-DNA adducts.[56] Twenty-five patients who developed hearing loss after cisplatin therapy were compared with 25 patients who received cisplatin chemotherapy without hearing loss, and were tested for nonsynonymous single nucleotide polymorphisms of megalin. A higher frequency of the A-allele of rs2075252 was observed in patients with hearing impairment compared with patients with normal hearing after cisplatin treatment. These findings suggest that single nucleotide polymorphisms at the megalin gene may affect individual susceptibility to cisplatin ototoxicity.[57]

Histopathology

Human temporal bone histopathology studies have shown the effects of cisplatin on the inner ear. The cochlea of a 9-year-old child with a brain tumor who sustained hearing loss after cisplatin showed degeneration of outer hair cells in the lower turns of the cochlea, spiral ganglia, and cochlear nerve. The vestibular ganglion cells and vestibular nerve were reportedly normal.[58] Scanning electron microscopic studies of the inner ear tissues of five patients with cisplatin ototoxicity revealed fusion of stereocilia of the outer hair cells, with damage to the cuticular plate.[59] Another study of patients receiving cisplatin with or without irradiation revealed a decreased number of inner and outer hair cells and spiral ganglion cells. The stria vascularis was also found to be atrophic.[60]

Experimental Studies

Histopathologic studies of the inner ear in animals mirror the findings reported in humans. The outer hair cells of the basal turn of the cochlea are damaged first, which extends to the more apical cells when dosing is continued.[41,61] The first row of outer hair cells seems to be most vulnerable.[41] Damage progresses to the outer hair cells, with dilation of the parietal membrane, softening of the cuticular plate, vacuole formation, and increased number of lysosome-like bodies in the apical portion of the hair cells. Stereocilia abnormalities, including fusion, on inner and outer hair cells are visible.[62] Damage to the stria vascularis can also occur, especially after exposure to high-dose cisplatin.[63] Electrophysiologic studies have shown that cisplatin ototoxicity can be manifested by a decrease in the endocochlear potential,[64] by elevation in auditory brainstem response thresholds,[64-67] and by elevations of the distortion product otoacoustic emissions (DPOAE).[65,68,69] The DPOAE input/output protocol is most sensitive for early detection of hair cell damage.[65] Elevations of DPOAE thresholds 4 days after cisplatin infusion in dogs could not be attributed to differences in peak plasma platinum levels. The variability in susceptibility in individual animals could not be explained by variations in plasma concentration of filterable platinum between animals.[69]

Mechanisms of Ototoxicity

The ototoxicity of cisplatin seems to be mediated by the production of ROS. Reactive oxygen molecules such as superoxide anion, hydrogen peroxide, and reactive nitrogen species such as nitric oxide can cause cell damage by reacting with cellular lipids, proteins, and DNA. The inner ear has an antioxidant defense system, consisting of the tripeptide glutathione and its related antioxidant enzymes, such as glutathione peroxidase, glutathione reductase, and the other antioxidant enzymes catalase and superoxide dismutase. Glutathione and the antioxidant enzymes have been shown to be decreased in association with cisplatin-induced ototoxicity in the rat.[66,67] Cisplatin has been shown to increase the formation of ROS in the cochlea by use of electron paramagnetic resonance spectrometry[70] and fluorescent dyes.[71] The production of superoxide anions inside the cochlear hair cells has been shown in vitro by use of the nitroblue tetrazolium reduction assay.[72] Superoxide dismutates to hydrogen peroxide either spontaneously or by means of superoxide dismutase. Increased hydrogen peroxide formation has been detected in the inner ear after cisplatin exposure.[70]

One of the enzymes that can produce superoxide radicals is an isoform of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, NOX-3, which is unique to the cochlea. Cisplatin has been shown to activate this enzyme, leading to a dramatic increase in superoxide production[73] not only in cochlear cell lines, but also in the cochlea of rats exposed to cisplatin.[74] Superoxide can lead to the formation of hydrogen peroxide, as just shown. The latter can be catalyzed by iron to form the very reactive hydroxyl free radical, which can react with polyunsaturated fatty acids in membranes to form the extremely toxic aldehyde, 4-hydroxynonenal. Superoxide can also react with nitric oxide to form peroxynitrite, which reacts with proteins to form nitrotyrosine. Cochlear hair cells of cisplatin-treated guinea pigs show immunoreactivity for 4-hydroxynonenal, but auditory neurons were found to be immunopositive for 4-hydroxynonenal and nitrotyrosine.[75]

Because iron chelators have been shown to provide partial protection to hair cells exposed to cisplatin in vitro, it has been proposed that

part of the ototoxic mechanism of cisplatin includes an iron-dependent pathway.[72] The reaction of ROS with the plasma membrane leads to the formation of membrane lipid peroxidation products such as 4-hydroxynonenal, which are highly reactive and can lead to cellular damage and cell death.[76] The primary target of cisplatin ototoxicity seems to be the outer hair cells, with the hair cells in the basal turn being most susceptible. This increased susceptibility may result from the relatively low stores of glutathione in the outer hair cells of the basal turn compared with the inner hair cells and the outer hair cells in the more apical turns.[7] The ROS and reactive nitrogen species can attack cellular components as discussed previously, and superoxide anion can react with nitric oxide to form the highly toxic peroxynitrite, which can also attack cellular components.

A partial scheme for the mechanism for cisplatin ototoxicity has been shown in vitro. The reactive molecules, such as superoxide anion, nitric oxide, and others, can activate a cellular protein, p53. This activation can activate enzymes in the cell death pathway, the caspases. Caspase-8 has been shown to be activated, which converts a cellular protein BID from an inactive to an active form, truncated BID. Activated BID acts on a cytosolic protein, BAX, which translocates to the mitochondria. Activated BAX makes the mitochondrial membrane leaky, and the mitochondrial enzyme cytochrome-*c* leaks out into the cytoplasm. Cytosolic cytochrome-*c* interacts with another cell death enzyme, caspase-9, which activates caspase-3 and caspase-7, resulting in apoptosis or death of hair cells.[77] The application of caspase inhibitors to organ of Corti explants before and during exposure to cisplatin in vitro prevented apoptosis of hair cells.[78] This finding provides further evidence that cisplatin ototoxicity may be mediated by the cell death pathways, resulting in hair cell death and permanent hearing loss. These results need to be confirmed by the use of in vivo models of cisplatin ototoxicity. Additional research may provide clinically useful drugs that can block parts of these pathways and protect against ototoxicity of cisplatin.

A more recent study in rats treated with cisplatin confirmed that cisplatin induces an intrinsic apoptotic pathway in the cochlea. Cisplatin significantly increased the levels of caspase-3 and caspase-7 activity, active caspase-3 protein expression, and caspase-9 activity, and increased BAX protein expression accompanied by a decrease in the anti-apoptotic protein Bcl-2 expression in the cochlea. These changes were accompanied by elevation of auditory brainstem response threshold measurements.[79]

Cisplatin-induced cell death may be independent of p53 and caspases. A more recent study using the OC-k3 cell line exposed to cisplatin suggested that the mitogen-activated protein kinase cascade may be involved in induction of cell death by cisplatin. Cells exposed to cisplatin were found to express an increased phosphorylation of ERK 1/2 that was inhibited by PD98059 and suramin. Both of these inhibitors protected these cells from cisplatin-induced cytotoxicity. Activated ERK 1/2 may be a main effector of cell death, causing nuclear fragmentation, actin cytoskeleton rearrangement, and cell death. Cell death from cisplatin apparently occurred in a p53-independent and caspase-independent manner because these cell lines are functionally depleted of p53.[80]

Inflammatory cytokines may also play a role in cisplatin ototoxicity. These cytokines (tumor necrosis factor [TNF], interleukin-1β, and interleukin-6) may be up-regulated by activation of ERK and NFκB; this was shown in HEIOC1 cells in vitro. Neutralization of these cytokines by antibodies and pharmacologic inhibition of ERK significantly reduced the death of these cells exposed to cisplatin. These in vitro studies were confirmed in vivo using rats treated with cisplatin. TNF was immunolocalized to the spiral ligament, spiral limbus, and organ of Corti. NFκB protein expression was very strong in cells where TUNEL-positive staining was observed—the organ of Corti, spiral ligament, and stria vascularis. These findings suggest that proinflammatory cytokines, especially TNF-α, play a significant role in cochlear damage caused by cisplatin.[81]

A more recent review of potential protective agents tested against cisplatin ototoxicity pointed out that no successful clinical trials of protective agents against cisplatin had yet been published. Although numerous successful experiments showed protection in animal models, it is important to try to translate these results to the patients. One concern about the use of systemic protective agents, such as antioxidants, is the possible interference with the therapeutic effect of cisplatin. This problem could be circumvented with intratympanic administration of the protective agent, provided that it diffuses through the round window membrane and penetrates into the inner ear. Positive results with otoprotective regimens in clinical practice may increase the efficacy of cisplatin, and improve the quality of life in survivors of chemotherapy with cisplatin.[82]

Intratympanic dexamethasone has been reported to protect against cisplatin ototoxicity in guinea pigs and mice. In the study of guinea pigs, intratympanic saline also seemed to be protective.[83] In the mouse study, dexamethasone provided significant protection against auditory brainstem response threshold shifts with clicks, 8 kHz and 16 kHz compared with the contralateral, saline-injected ear.[84] A clinical study reported that, contrary to previous studies in the literature, amifostine (600 mg/m^2), given as an intravenous bolus immediately before and 3 hours after cisplatin and craniospinal irradiation in children with medulloblastoma, provided significant protection against hearing loss. One year after treatment initiation, 13 (37.1%) controls compared with 9 (14.5%) amifostine-treated patients had hearing loss sufficient to require a hearing aid in at least one ear ($P = .005$ chi-square one-sided test). There was no evidence that the amifostine interfered with the efficacy of the cisplatin, and the side effects of amifostine therapy were mild and well tolerated.[85]

Carboplatin

Carboplatin is a newer platinum compound that has been found to be less nephrotoxic than cisplatin. Preliminary data suggested that carboplatin was less ototoxic than cisplatin. The primary dose-limiting toxic side effect of carboplatin is bone marrow suppression. The latter effect can be overcome by autologous stem cell rescue and the use of hematopoietic growth factors; this has allowed the administration of higher doses of carboplatin to improve its antitumor efficacy and its therapeutic index. Carboplatin may be more ototoxic than initial studies indicated. High-dose carboplatin (2 g/m^2 total dose) was associated with hearing loss in 9 of 11 children (82%), with hearing losses in the speech frequencies that were sufficiently severe that hearing aids were recommended.[86] These children had each received prior treatment with cisplatin, and several of them had been treated with aminoglycoside antibiotics.

Carboplatin is highly effective in treating malignant brain tumors when given in conjunction with mannitol to open the blood-brain barrier. Fifteen of 19 patients (79%) had high-frequency hearing loss develop when this treatment regimen was used.[87] Patients with ovarian cancer were treated with combination therapy of carboplatin and cisplatin for six courses. A retrospective study of the first course area under the curve (AUC) concentration-time data for carboplatin was carried out. No patients with a low AUC had ototoxicity, but 12% of patients in the high AUC group were found to have hearing loss, and 45% had thrombocytopenia.[88]

Nearly half of a group of children undergoing hematopoietic stem cell transplantation were found to have deterioration in hearing. Children with neuroblastoma receiving carboplatin "conditioning" and children with renal dysfunction were found to be at higher risk for ototoxicity associated with hematopoietic stem cell transplantation[89]; all nine patients receiving high-dose carboplatin for cisplatin-resistant germ cell tumors were reported to develop a clinically manifested hearing loss.[90] A study of 30 children with unresectable neuroblastoma reported only one mild case of hearing loss at 6 years of follow-up.[91] The ototoxicity of carboplatin seems to vary according to the dose administered.

Carboplatin seems to be unique in that it has been shown to damage inner hair cells preferentially in the chinchilla.[92] The mechanisms of ototoxicity of carboplatin may be related to the production of ROS and reactive nitrogen species.[93] This idea is supported by the finding that pretreatment with butathione sulfoximine (BSO) enhances the ototoxicity of carboplatin in the chinchilla. BSO inhibits the synthesis of glutathione. Animals treated with BSO by continuous intracochlear infusion had significantly greater losses of inner and outer hair

cells than animals treated with carboplatin alone. DPOAE and evoked potentials recorded from the inferior colliculus were found to be significantly reduced in amplitude in animals receiving BSO in combination with carboplatin compared with animals receiving carboplatin alone.[94]

Difluoromethylornithine

Clinical Studies

D,L-α-difluoromethylornithine (DFMO) was developed as an irreversible inhibitor of the enzyme ornithine decarboxylase. It was hoped to be effective in chemotherapy for hyperproliferative diseases, including cancer and certain infectious processes. DFMO was found to cause treatment-limiting, but reversible ototoxicity at high doses.[95] DFMO is an antitumor agent and a chemoprotective compound that reduces the incidence and frequency of tumors, and is useful clinically in treating infections with *Trypanosoma brucei gambiense* (West African sleeping sickness).

In phase I studies, doses of 12 g/m^2/day for 28 days resulted in thrombocytopenia and gastrointestinal disturbances. Larger doses (64 g/m^2/day intravenously for 25 to 43 days by continuous infusion) caused diarrhea and metabolic acidosis. In phase II studies, hearing loss was observed. A clinical trial of DFMO administered orally daily for 6 months was carried out in 27 patients after surgery for cancer or who were at high risk for development of cancer. The dose-limiting toxicity was defined as high-tone hearing loss on audiogram. Hearing loss was determined in seven patients. It was not stated whether the hearing loss was reversible or irreversible. The total drug dose that resulted in ototoxicity was highly variable among patients studied.[96]

A clinical trial was carried out in 66 volunteer subjects with previously treated bladder, prostate, or colon cancer without evidence of recurrent or residual disease or healthy individuals at increased risk for developing colon cancer who were tested for potential ototoxicity of DFMO. Predictable shifts in auditory thresholds occurred that were related to the dose of DFMO. As the dose of drug increased, the magnitude and incidence of hearing threshold shift increased, and the time of its onset decreased. Threshold changes were greater in the lower frequencies than in the higher frequencies. No association could be made between the gender, age, or renal function of the subjects and hearing loss. Threshold shifts were reversible with discontinuation of DFMO.[97]

A prospective, placebo-controlled phase II clinical trial of DFMO in patients with a prior history of adenomatous colon polyp was carried out with long-term, low-dose administration of DFMO to assess the effects on hearing. Volunteers ($N = 123$) with normal hearing for frequencies between 250 Hz and 2000 Hz were tested for audiometric thresholds at baseline and 1, 3, 6, 9, and 12 months after starting treatment with either DFMO or placebo, and follow-up testing was done 3 months after cessation of treatment if there was a suggestion of audiometric changes at the 12-month measurement. Subjects receiving doses of 0.075 to 0.4 g/m^2/day for 12 months had little evidence for shifts in auditory pure-tone thresholds, and there were no statistically significant shifts in DPOAEs. There was only a subtle, approximately 2- to 3-dB hearing threshold elevation at the two lowest frequencies of 250 Hz and 500 Hz. The authors concluded that the administration of low-dose DFMO for 12 months did not produce hearing loss, in contrast to other studies that examined the ototoxicity of higher doses.[98]

Irreversible hearing loss has been reported in a patient treated with DFMO as a chemopreventive for Barrett's esophagus. After taking 0.5 g/m^2/day of DFMO for approximately 13 weeks, hearing loss of 15 dB was noted at 250 Hz, 2000 Hz, and 3000 Hz in the right ear, and hearing loss of greater than 20 dB was noted at 4000 to 6000 Hz in the left ear. These threshold shifts persisted for 7 months after DFMO was discontinued. This was the first reported case of irreversible ototoxicity related to DFMO administration.[99]

Animal Studies

Studies of DFMO ototoxicity in guinea pigs revealed that DFMO administered for 12 weeks resulted in loss of hair cells in the hook and first turn. Inner hair cell loss was greater than loss of outer hair cells. Hearing loss was confirmed by brainstem audiometry.[100]

Daily intragastric administration of D,L-DFMO did not produce any auditory dysfunction in rats given doses of 200 mg/kg/day to 1.2 g/kg/day for 8 weeks. In contrast, substantial ototoxicity was found in guinea pigs given intraperitoneal doses of D,L-DFMO of 500 mg/kg/day to 1 g/kg/day. Damage to inner and outer hair cells in the cochlea, with greater loss of inner hair cells, especially in the basal turn, occurred. These histologic findings corresponded to loss of compound action potential sensitivity. The ototoxicity of the enantiomers was also studied in the guinea pig. It was found that 1 g/day of the D-enantiomer of DFMO did not produce any evidence of hearing impairment; 1 g/kg/day of the L-enantiomer of DFMO produced a threshold shift greater than the same dose of the racemic mixture.[101]

Studies in neonatal gerbils at 21 days of age were designed to test DFMO ototoxicity. Click-evoked auditory brainstem response testing was carried out before and 3 weeks after completion of an 18-day regimen of daily subcutaneous injections of DFMO at 1 g/kg/day. DFMO administration resulted in click threshold elevations of 20 to 60 dB, which recovered by 3 weeks after cessation of the drug.[102] This study was repeated using tone pips at 2 kHz, 4 kHz, 8 kHz, 16 kHz, and 32 kHz in neonatal gerbils to see whether specific frequencies were affected, and to examine cochlear tissues after DFMO administration. Dosing regimens of 750 mg/kg/day or 1 g/kg/day subcutaneously administered were employed in two groups of gerbils. Hearing threshold shifts of 21 to 29 dB were found in the higher dose group, whereas threshold elevations of 11 to 17 dB were observed in gerbils receiving the lower dose. Higher thresholds were shown at the higher frequencies, although a broad frequency range was affected. No significant cochlear abnormalities were observed at the light microscopic level, consistent with the fact that the hearing threshold changes were reversible after 3 weeks of recovery.[102] The ototoxicity of DFMO may be mediated by alteration of the inward rectification of Kir4.1 channels, leading to a marked reduction in endocochlear potential and elevation of auditory brainstem response thresholds in mice.[103]

Conclusions

From the animal studies reported to date, it seems that DFMO has species-specific ototoxicity that apparently is dose related, but variable, depending on the rodent model used. The rat is resistant to DFMO ototoxicity, perhaps because DFMO may not inhibit polyamine synthesis in the rat cochlea to a critical level. The rat may not be used as a reliable animal model for the study of DFMO ototoxicity.[101] The guinea pig seems to be quite sensitive to DFMO ototoxicity. DFMO, particularly the L-enantiomer, caused hearing threshold changes and hair cell loss in the high-frequency region. Inner hair cells seem to be more sensitive to damage from DFMO than do outer hair cells. The neonatal gerbil apparently has an intermediate sensitivity to DFMO. Long-term administration of DFMO resulted in temporary threshold elevations, which recovered within 3 weeks after cessation of treatment, and no evidence of cochlear tissue damage was ascertained with light microscopy.[102] In mice, DFMO seemed to affect primarily the stria vascularis by altering the inward-rectification of potassium channels (Kir4.1). This alteration resulted in a concomitant elevation of auditory brainstem response thresholds. It was not specified whether this effect was temporary or permanent, and no histology was reported.[103]

Clinical studies have shown that DFMO administration is associated with reversible hearing loss. One article reported permanent hearing loss in one patient that persisted for 7 months.[99] It seems appropriate to warn patients about potential ototoxicity of this chemopreventive agent before its use. Future human temporal bone studies may shed additional light on the effects of DFMO on human cochlear tissues.

Loop Diuretics

The loop diuretics are potent synthetic drugs that exert therapeutic effects through their action on the loop of Henle of the kidney. They inhibit the reabsorption of sodium, potassium, and chloride ions by blocking an Na/K/2Cl carrier.[104] Through this action on the kidney, loop diuretics produce a rapid and dramatic increase in the volume of urine output. The most commonly used loop diuretics are furosemide and bumetanide. Ethacrynic acid is used less frequently. These drugs are used to treat congestive heart failure in infants and adults, to reduce

high blood pressure, to remove excess fluid from the lungs in newborns with immature lungs, and to assist in the control of edema from liver or kidney failure.

Ethacrynic acid can be administered either orally or by intravenous injection. It was soon discovered to cause hearing loss after it was introduced into clinical medicine in the 1960s. Numerous cases of transient and permanent deafness have been reported.[105] Permanent, profound midfrequency and high-frequency SNHL has been reported in a kidney transplant patient who was treated with ethacrynic acid. This patient was successfully rehabilitated with binaural hearing aids.[106]

Furosemide can be administered orally or by intravenous injection. Approximately 65% of an oral dose is absorbed after oral ingestion.[107] This diuretic follows a three-compartment pharmacokinetic model with an average half-life of 29.5 minutes for renal elimination. The half-life of furosemide increases dramatically in patients with severe renal failure, in whom the half-life may be 10 to 20 hours.[105] Furosemide has also been found to cause temporary and some permanent cases of hearing loss. Permanent hearing loss has been reported in certain adults[105] and in high-risk premature infants treated with furosemide.[108] Plasma levels of furosemide greater than 50 mg/L have been associated with hearing loss.[109,110] SNHL may be accompanied by tinnitus and vertigo. The incidence of ototoxicity with furosemide was reported to be approximately 6% in a small series of patients.[111]

Bumetanide, a more potent sulfonamide loop diuretic, has been reported to cause a much smaller incidence of hearing loss than furosemide.[111,112] A related loop diuretic, piretanide, was found to be equally effective as furosemide in treating patients with congestive heart failure in a study of a small group of patients, and no patients were found to have hearing loss.[113]

Studies of experimental animal and human temporal bones[114] show that the primary target of loop diuretics is the stria vascularis, where extensive edema develops in conjunction with loss of auditory function.[105] The primary target in the stria vascularis seems to be the Na/2Cl/K transporter (SLC12A2),[115] which may be similar to or identical to the transporter that furosemide and bumetanide inhibit in the kidney.[116] Mice lacking this transporter are deaf,[117] but it is unknown whether mutations of SLC12A2 contribute to human deafness.[118] The action of loop diuretics on the stria vascularis results in a reduction of the endocochlear potential, with an elevation of the threshold for the compound action potential.[119] Immature rats[120] and rats with low albumin[121] are more susceptible to the ototoxic effects of furosemide. This finding suggests that the ototoxic action of loop diuretics depends on the unbound fraction of drug in the serum.[121]

Clinical studies suggested that the ototoxicity of furosemide may be reduced by infusing the drug at rates of less than 15 mg/min.[110] Studies in the chinchilla have suggested that the ototoxicity of ethacrynic acid may be caused by impaired blood flow in the lateral wall of the cochlea. In these experiments, the blood vessels to the modiolus, spiral lamina, and vestibular end organs seemed normal. The vessels supplying the spiral ligament and stria vascularis had poor flow at 2 minutes after ethacrynic acid injection, however, and the vessels seemed to lack red blood cells 30 minutes after injection. The compound action potential, cochlear microphonics, and summating potential all declined without recovery after the microcirculatory changes in the lateral wall vessels, and reperfusion was delayed in the stria vascularis arterioles to other blood vessels in the lateral wall. Ischemia followed by reperfusion generates large quantities of oxygen free radicals that could cause structural and functional damage to the stria vascularis and organ of Corti.[122] Outer hair cell loss in the basal turn of the cochlea has been observed in temporal bone studies of patients experiencing ethacrynic acid ototoxicity.[114]

Torsemide, a new loop diuretic, was found to cause reversible hearing loss in cats at a dose that was similar to that of furosemide.[123] No evidence of ototoxicity has been shown in humans to date.[124]

Analgesics

Hydrocodone

Hydrocodone is a narcotic analgesic. It is often combined with acetaminophen, and is frequently prescribed for the relief of acute and chronic pain.[125] Common adverse reactions to this combination analgesic drug include dizziness, nausea, vomiting, drowsiness, and euphoria. More severe side effects include respiratory depression and mood disturbances. Because hydrocodone is a narcotic, abuse can lead to psychological and physical dependence. It is the most widely prescribed opioid narcotic analgesic in the United States, and is one of the most widely abused prescription drugs.[125]

Hearing loss from hydrocodone abuse has been reported in a few cases, but the incidence may be much greater than previously suspected. Two cases of rapidly progressive sensorineural deafness with relative sparing of the vestibular system and normal magnetic resonance imaging scans were reported in two patients taking huge doses of this combination. One patient took 15 tablets four times a day, and the second patient took up to 35 tablets per day. Neither patient responded to high-dose oral prednisone therapy. The first patient received a cochlear implant, with restoration of functional hearing, but no information was provided about auditory rehabilitation in the second patient, who progressed to profound bilateral SNHL.[126]

Hydrocodone abuse was associated with rapidly progressive SNHL in 12 patients reported from the House Ear Clinic. In four patients, the initial presentation was unilateral, and two patients also experienced vestibular symptoms. High-dose prednisone therapy was unsuccessful in improving hearing in any of the patients. Seven of eight patients who underwent cochlear implantation had early success with these devices. An additional series of five patients with a history of chronic ingestion of hydrocodone in doses ranging from 10 to 300 mg/day was reported. The duration of use varied from months to years. The initial audiogram showed typically a moderate SNHL. Subsequent audiograms showed rapid progression of hearing loss. Communication was severely affected. There was no spontaneous recovery of hearing in any patient reporting cessation of drug use. Hearing loss was asymmetric in three patients. Tinnitus was reported by three patients. The only significant comorbidity in this series was hepatitis C. All five patients underwent cochlear implantation and became successful users.[125]

The mechanisms of ototoxicity of hydrocodone/acetaminophen are unknown. Opioid receptors of the mu type have been shown in spiral and Scarpa's ganglia,[127,128] whereas delta and kappa receptors have been shown in hair cells.[127] Genetic abnormalities of drug-metabolizing enzymes and comorbidities such as hepatitis C infection may be factors in development of ototoxicity from this drug combination. More research is required to confirm or refute this theory, however.[125]

The following guidelines have been recommended:

1. The clinician should document rapidly progressive SNHL that is bilateral.
2. There should be no vestibular symptoms (although this is contradicted in a previous series).[129]
3. There should be no response to steroid therapy.
4. There should be no symptoms or laboratory evidence of intracranial infection or concurrent autoimmune disease with the exception of possible hepatitis C–induced autoimmune hepatitis.
5. The clinician should document prolonged daily use of hydrocodone or oxycodone, or high doses over a short interval preceding the onset of hearing loss.[125]

Salicylates

Salicylates are derivatives of benzoic acid that have been used to treat mild to moderate pain, such as headache, dental pain, and arthritis. These drugs have an anti-inflammatory and an analgesic effect. Salicylates are tightly bound to serum proteins after oral absorption, and only a small percentage of the concentration of salicylate in blood is unbound or free.

In animal experiments, it has been reported that after systemic administration, salicylates rapidly enter the perilymph. The percentage

of the corresponding blood level achieved in the perilymph can be 25% to 33%[130,131] in chinchillas,[130] and in rats,[132] the relationship between serum and perilymph concentrations is nearly linear. Serum levels of 25 to 50 mg/dL were reported in chinchillas receiving 450 mg/kg of salicylate intraperitoneally. The chinchillas were found to have threshold elevations for auditory brainstem response of 30 dB, on the average, primarily at the higher frequencies.[130] Guinea pigs receiving the same dose were found to have increased spontaneous activity of inferior colliculus neurons, which may be a neural correlate of tinnitus.[132] The effects of salicylates on the cochlea may be caused by changes in blood flow, and by changes in the stiffness of the lateral membrane of the outer hair cells.[133]

Hearing loss in humans may be related to the concentration of salicylates in blood. Patients with blood levels of 20 to 50 mg/dL can have hearing losses of 30 dB.[134] Lower concentrations of salicylate may correlate with hearing loss. At concentrations of 11 mg/dL, hearing loss was 12 dB. There seems to be a linear relationship between hearing loss and free salicylate concentrations.[135] Site of lesion testing in patients with salicylate-induced hearing loss shows a cochlear site of lesion.[136] Tinnitus seems to increase continuously with increasing plasma concentrations of salicylate over 40 to 320 mg/dL. Histopathologic studies of animal and human temporal bones from patients with documented hearing loss after receiving salicylates do not show significant hair cell damage or injury to the stria vascularis.[137] No damage to the spiral ganglion cells or myelin sheath of the eighth cranial nerve has been shown.[138]

Experiments in rats suggest that salicylate induces tinnitus throughout activation of *N*-methyl-D-aspartate (NMDA) receptors in the cochlea. The application of NMDA antagonists into the perilymph blocked the increase in pole-jumping behavior induced by salicylate, a behavioral procedure to measure tinnitus.[139] Salicylates probably cause a reversible SNHL by altering the function of the motor protein, prestin, in outer hair cells.[140]

Quinine and Related Drugs

Quinine is an alkaloid drug that is used to treat malaria and leg cramps. It is also present in tonic drinks. Quinine toxicity can manifest as a syndrome termed *cinchonism*. The symptoms include deafness, vertigo, tinnitus, headache, visual loss, and nausea. Twenty percent of patients may complain of high-frequency hearing loss with prolonged courses of treatment. There may be a 4-kHz notch, and speech discrimination score may be less than 30%, but the hearing loss may be reversible.[141] If hearing loss occurs within the speech frequencies, the loss may be permanent.[142] Guinea pigs were found to have increasing hearing loss with increasing blood concentrations of quinine.[143] Chinchillas receiving a single intramuscular injection of quinine, 150 mg/kg, were found to have a reversible 20-dB threshold elevation of auditory brainstem response, and similar shifts were observed after application of quinine to the round window.[144] Perceptual tinnitus may occur after quinine administration. A conditioned-suppression study of rats revealed a dose-dependent induction of behavioral tinnitus after quinine treatment. These effects were blocked by nimodipine, a calcium channel blocker.[145] Nimodipine did alter the threshold elevation of compound action potential observed after quinine, however.[146]

Chloroquine is an aminoquinoline drug initially used to treat malaria. In the 1950s, it began to be used to treat rheumatoid arthritis, then later other connective tissue diseases. It is chemically related to quinine. It seems to be ototoxic, but only a few cases have been reported. The ototoxicity may be reversible if detected early by auditory brainstem evoked response audiometry followed by cessation of therapy with chloroquine and administration of steroids and plasma expanders.[147,148]

Hydroxychloroquine is also a quinoline compound used to treat rheumatoid arthritis and lupus. It rarely causes ototoxicity. It has been reported to cause reversible SNHL in an adult with rheumatoid arthritis after 5 months of treatment.[149] Permanent SNHL was reported in two adults with lupus erythematosus[150] and in a 7-year-old girl after 2 years of treatment for idiopathic pulmonary hemosiderosis.[151]

Erythromycin and Related Macrolide Antibiotics

Erythromycin was introduced into clinical medicine in the 1950s. This antibiotic has been found to be useful in the treatment of various infections, including pneumonia caused by *Legionella pneumophila,* which has resulted in increased use of erythromycin by the intravenous route. It was screened for possible ototoxicity early on, but only vestibular testing was carried out. Nevertheless, it was concluded that erythromycin was not ototoxic. In 1973, the first case of ototoxicity in patients was reported.[152] Many cases of bilateral SNHL have been reported after intravenous or oral administration. Most of these patients were elderly and had liver or kidney disease, or had been treated with high-dose erythromycin for legionnaires' disease.

Ototoxic symptoms include "blowing" tinnitus, loss of hearing, and vertigo in some cases. Some patients complained of confusion, fear, psychiatric disturbances,[153] visual changes, slurred speech, a sensation of having been drugged, or lack of control.[154] Most cases of hearing loss and tinnitus have been transient. Recovery of normal hearing usually occurs within 1 to 2 weeks after stopping erythromycin.[155] Two cases of permanent ototoxicity have been reported, however: one with permanent tinnitus[156] and one with permanent hearing loss.[157] Hearing loss from erythromycin has been reported in liver or kidney transplant patients. The incidence of hearing loss in these patients seems to be dose related. Hearing loss was observed in 16% of patients receiving 2 g daily, but increased to 53% in patients treated with 4 g daily. Complete reversal of hearing loss occurred after modification of therapy.[158] In a separate series of three liver transplant recipients, it was believed that an interaction occurred between erythromycin and cyclosporine that may have caused the hearing loss.[159]

The audiometric pattern in patients with erythromycin ototoxicity can be a flat type of SNHL, although some patients manifest a high-frequency loss. Auditory brainstem response testing in two patients with erythromycin ototoxicity showed absence of waves I to III during erythromycin therapy, when pure-tone audiograms documented SNHL. The auditory brainstem response pattern and the audiograms normalized after cessation of erythromycin.[160]

Several guidelines have been recommended for the prevention of erythromycin ototoxicity: (1) Pretreatment audiograms should be obtained in elderly patients and in patients who have impaired liver or kidney function. (2) Caution should be used in combining erythromycin with other potentially ototoxic drugs. (3) If the serum creatinine is greater than 180 mol/L, the daily dose of erythromycin should not be greater than 1.5 g.[161]

Azithromycin is a newer antibiotic related to erythromycin. Similar to erythromycin, it is also ototoxic. This side effect was first reported in patients with acquired immunodeficiency syndrome undergoing long-term treatment for disseminated *Mycobacterium avium* infections. Three patients complained of hearing loss, and audiograms confirmed mild to moderate SNHL, which resolved within 2 to 4 weeks after cessation of treatment.[162] Another series of patients had reversible ototoxicity associated with high-dose oral azithromycin therapy (2400 mg/day). It took an average of 5 weeks for hearing to recover after cessation of treatment.[163] Two additional cases of reversible SNHL with azithromycin have been reported.[164] Two cases of apparently permanent hearing loss have been reported. A 47-year-old woman became completely deaf after 8 days of treatment with azithromycin.[165] A 39-year-old woman had tinnitus develop bilaterally within 24 hours of taking the drug and subjective hearing loss after the second day when she stopped taking the medication. An audiogram revealed moderate to severe high-frequency SNHL in the right ear and mild to moderate high-frequency loss on the left side. The tinnitus and hearing loss were still present 12 months later, although the tinnitus was less severe.[166] Guinea pigs treated with azithromycin or a related drug, clarithromycin, were found to have a reversible alteration of transiently evoked otoacoustic emissions.[167] The mechanisms of ototoxicity of these macrolide antibiotics are unknown.

Deferoxamine

Among a group of 153 children with β-thalassemia and treated with regular blood transfusions and iron overload chelation with deferoxam-

ine, 38% were found to have a significant SNHL at high frequencies with recruitment. Younger patients had a greater hearing loss. The hearing loss was apparently correlated with mean and peak doses of deferoxamine, and was more severe in patients with lower iron load.[168]

In a population of 75 adult transfusion-dependent patients with thalassemia major and other hematologic diseases treated with regular transfusions, 93% (70 of 75) had a history of long-term subcutaneous or intravenous deferoxamine therapy. Audiometric testing revealed hearing loss that was attributed to deferoxamine therapy in 22 of 75 patients (29%). Of patients with thalassemia, 35% (21 of 59) had hearing loss attributable to deferoxamine ototoxicity. These patients with deferoxamine ototoxicity had high-frequency SNHL. Seven of the 21 patients had a notch at 6 kHz, and 1 had a notch at 3 kHz. Few of the hearing losses were considered as disabling, however. Audiologic monitoring was recommended for patients undergoing deferoxamine therapy.[169]

Hearing loss was attributed to deferoxamine therapy in 6 of 30 patients 7 to 25 years old. Most of the patients with hearing loss had Cooley's anemia requiring regular blood transfusions and deferoxamine therapy in a dose of 40 to 50 mg/kg subcutaneously overnight for 8 to 10 hours by pump, 4 to 7 days per week. The hearing loss was sensorineural, mild to moderate, and involved the high frequencies (3 to 12.5 kHz). Only one patient had hearing loss at less than 6 kHz. Only one patient reported tinnitus. Transient evoked otoacoustic emissions and DPOAEs were abnormal in 27% and 33% of patients.[170]

Wide variations in the incidence of ototoxicity in transfusion-dependent patients receiving deferoxamine have been reported, ranging from 3.8% to 57%.[170] Although it has been reported that patients with deferoxamine ototoxicity were younger and had received higher doses of deferoxamine than patients who were not affected,[171] the doses of deferoxamine used in the 1980s were higher than the doses used in more recent years.[170] The latter study found no association between age and ototoxicity. Twenty-two patients had abnormal audiograms in the 4- to 8-kHz region, with thresholds of 30 to 100 dB. Of the 22 patients, 18 received deferoxamine doses greater than the recommended dose of 50 mg/kg subcutaneously. When deferoxamine was discontinued, audiograms in seven cases reverted to normal or near-normal in 2 to 3 weeks, and 9 of 13 patients who had symptomatic hearing losses became asymptomatic. When therapy was restarted with lower doses, no further ototoxicity was shown except in two cases. It was recommended that in patients with symptomatic hearing loss, the drug should be stopped for 4 weeks, and when the repeat audiograms were stable or improved, therapy could be restarted at 10 to 25 mg/kg per dose. The authors recommended serial audiograms every 6 months in asymptomatic patients receiving deferoxamine, and more frequent audiograms in young patients with normal serum ferritin values and in patients with hearing loss shown on audiograms.[172]

A therapeutic index has been recommended to avoid deferoxamine ototoxicity. This index is obtained by dividing the daily deferoxamine dose (mg/kg) by the serum ferritin level (ng/mL). A therapeutic index of 0.025 was considered safe.[173] For a patient with a ferritin level greater than 2000 ng/mL, deferoxamine doses of less than 50 mg/kg are considered as safe.[170] Audiometric screening for ototoxicity should include measurements of pure-tone thresholds at 6 kHz, which is the frequency most affected in patients with deferoxamine ototoxicity.[170] A more recent study showed that DPOAE testing was extremely sensitive and superior to pure-tone audiometry.[174]

Vancomycin

Vancomycin is a glycopeptide antibiotic that is used to treat methicillin-resistant infections caused by *Staphylococcus aureus* and *Staphylococcus epidermidis,* and other difficult-to-treat infections, such as enterococcal endocarditis in patients with penicillin allergies. It has been reported to be ototoxic. Vancomycin is used orally to treat pseudomembranous colitis caused by *Clostridium difficile*. Because of poor oral absorption, vancomycin is usually given intravenously. Multicompartment pharmacokinetic models have been described.[175,176] It is usually given every 12 hours in patients with normal renal function, but a once-daily regimen has been described more recently that has equivalent efficacy and a similar safety profile.[182]

As mentioned previously, vancomycin is given orally to treat pseudomembranous colitis. Usually, no significant absorption occurs after oral dosing.[9] It is sometimes administered intrathecally to treat bacterial meningitis, and severe SNHL has been reported in a patient receiving vancomycin by this route.[177] Elderly patients, even if they have normal renal function, have reduced renal clearance of vancomycin.[176] The half-life is significantly longer in premature infants; careful monitoring of blood levels in premature infants has been recommended.[178] Vancomycin administered to pregnant women did not cause hearing loss in their infants who were tested after birth.[179] In a large-scale newborn hearing screening, vancomycin was not associated with failure on automated auditory brainstem response.[180]

Vancomycin given in near-lethal doses in guinea pigs was found to be not ototoxic, but potentiation of gentamicin ototoxicity in guinea pigs was found.[181] A critical review of previously reported cases of permanent ototoxicity attributed to vancomycin suggested that most cases could be explained by concomitant aminoglycoside exposure.[181] Vancomycin seems to have a low probability of causing permanent ototoxicity if it is not given in combination with another ototoxic agent. Although the incidence of audiometrically proven hearing loss was 1 in 31 (3.2%) and 5 in 32 (15.6%) in patients receiving once-daily or twice-daily vancomycin therapy, these findings were based on a single post-treatment audiogram compared with the pretreatment baseline. It is unknown whether these hearing losses were temporary or permanent.[182]

Ototoxicity Monitoring for Hearing Loss

Audiometric monitoring for ototoxicity depends on the risk of the treatment regimen. For a low-dosage or short-duration treatment protocol for aminoglycosides with no clinical risk factors, the use of a pretreatment and post-treatment audiogram with a weekly self-assessment checklist monitoring may be adequate, but would not provide an early warning of potential hearing loss. For a high-risk, long-duration course of therapy with a high-risk agent such as amikacin, pretreatment and post-treatment testing with intervening weekly or biweekly monitoring of conventional audiometry and high-frequency audiometry may be advisable. For aminoglycosides, the final audiogram after treatment should not be performed until a few weeks after conclusion of therapy because additional delayed effects on hearing may occur.[183] For cisplatin treatment protocols, monitoring at baseline, just before beginning each cycle, when the patient is less ill and is able to cooperate better, and after the conclusion of therapy may be sufficient to document hearing loss and provide guidelines for rehabilitation because lifesaving therapy may impossible to modify.

As protective agents progress into clinical use, high-frequency audiometry may help to monitor the efficacy of the protective protocols.[183] DPOAEs seem to be more sensitive and superior to pure-tone audiometry in detecting early hearing loss caused by cisplatin[65,184] and deferoxamine.[174]

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CHAPTER ONE HUNDRED AND FIFTY-FIVE

Pharmacologic and Molecular Therapies of the Cochlear and Vestibular Labyrinth

Anil K. Lalwani

John F. McGuire

Key Points

- The round window membrane (RWM) is a three-layered dynamic biologic structure capable of active and passive transport. Key features of RWM permeability have been described.
- The kinetics of RWM drug delivery are primarily affected by the method of delivery, the permeability of the substance applied, and the rate of clearance from the perilymph.
- Adhesions over the RWM may significantly alter delivery of therapeutics. Some clinicians advocate microscopic removal of adhesions before the administration of therapeutics.
- The concentration of steroids in perilymph is much higher after intratympanic application than after oral administration.
- The two principal indications of intratympanic steroids are Meniere's disease and sudden sensorineural hearing loss. Data are mixed on the use of intratympanic steroids for Meniere's disease. There are strong data for the use of intratympanic steroids as a salvage therapy after failure to respond to oral steroids. Results of salvage intratympanic steroid administration for sudden sensorineural hearing loss are best when steroids are applied as early as possible after the onset of symptoms.
- The use of intratympanic gentamicin has been studied extensively for its ability to relieve vertigo symptoms in Meniere's disease, but the incidence of hearing loss with this therapy is also high. There is currently no consensus on the intratympanic gentamicin protocol that best relieves vertigo, while preserving hearing.
- The pharmacodynamics of intratympanic gentamicin injections are much more variable than the pharmacodynamics of sustained-release intratympanic administration. Variability in pharmacodynamics may be responsible for the unpredictable incidence of hearing loss.
- Otoprotective therapies of the cochlea and labyrinth are in the experimental phase. Many of the new otoprotective strategies employ the use of neurotrophins.
- Gene therapy for the cochlea and labyrinth is also in the experimental phase. The primary mechanical issues with gene therapy for the cochlea and labyrinth are the choice of vector for gene transfer and the method of delivery of this vector to the cochlea. Optimizing safety of gene transfer continues to be a research priority.
- Most attempts at gene therapy to date involve up-regulating the production of neurotrophins. There have also been attempts to up-regulate apoptosis inhibitors, and to stimulate hair cell regeneration through gene therapy.

Protected by one of the hardest bones in body, the cochlea is nearly an impenetrable structure, frustrating bacteria and humans trying to gain access to it. Were it not for its windows, delivery of therapeutic agents to the inner ear would always necessitate traumatic disruption of the bony walls and fearful consequences to hearing. In the past 20 years, there has been a resurgence of interest in directed therapy to address inner ear disorders because indirect, systemic therapy has shown limited success and significant morbidity. Experimentally, as reviewed later, investigators have shown that intratympanic and intracochlear therapy is feasible and efficacious. The direct intracochlear application of therapeutic agents, previously feared, may become the standard therapy of the future. Inner ear "surgery" is expected to be developed to the fullest to prevent hearing loss and to restore hearing. This chapter reviews the knowledge regarding delivery of material into the inner ear and its therapeutic consequences. The dawning of a new era in ototherapy is here.

Round Window Membrane

Anatomy

The round and oval windows sit on the medial wall of the middle ear. The conduction apparatus of the middle ear converges on the oval window, an arrangement designed to transfer the mechanical energy of

sound waves into fluid waves that pass through the cochlea. Although situated at the tail end of this apparatus, the round window membrane (RWM) plays an essential role in acoustic dynamics because the compliance of the membrane allows for this mechanical energy to be released from the cochlea; without this outlet, no waves could travel through the perilymph. The actual RWM sits in the round window niche (fossula fenestrae cochleae) just posteroinferior to the promontory. When viewed from the intact tympanic membrane, the round window niche can be found an average of 3.44 mm (±0.68 mm) from the umbo, at an average angle of 113.2 degrees (±9.8 degrees) from the long process of the malleus.[1]

The RWM is a three-layered structure designed to protect the inner ear from middle ear pathology and to facilitate active transport. There is an outer epithelial layer that faces the middle ear, a central connective tissue layer, and an inner epithelial layer interfacing with the scala tympani. The outer epithelial layer is continuous with the promontory. Mucoperiosteal folds from the neighboring epithelium sometimes can obstruct the round window niche, forming a "false" RWM. The most prominent feature of the outer epithelial layer is the extensive interdigitations and tight junctions of its cells; in addition, there is a continuous basement membrane layer. This architecture, with tight junctions and a continuous basement membrane, functions as a defensive shield designed to protect the inner ear from middle ear infections. The cells also feature a well-developed rough endoplasmic reticulum and Golgi complex with occasional microvilli, suggesting that active transport of elements across the middle and inner ear compartments may occur.

The connective tissue core contains fibroblasts, collagen, and elastic fibers, and houses blood and lymph vessels. The connective tissue layer is divided roughly into thirds, differing by fiber type and cellular material. Closest to the middle ear epithelium are coarse, loosely arranged collagen fibers, devoid of elastic fibers. In the middle of this layer, these fibers are joined by fibroblasts and ground substance, with occasional blood vessels and elastic fibers. Bordering the inner ear epithelium, there is a gradual increase in fibroblasts, collagen, and elastic fibers. As a whole, the connective tissue layer is responsible for providing compliance to the RWM. A discontinuous inner epithelial layer bathes in the perilymph of the scala tympani. Cells in this layer house pinocytotic vesicles and amorphous intracellular components, and feature long lateral extensions that bathe in the perilymph, suggesting that the RWM participates in some form of active transport.[2] Figure 155-1 depicts the histologic complexity of the RWM.

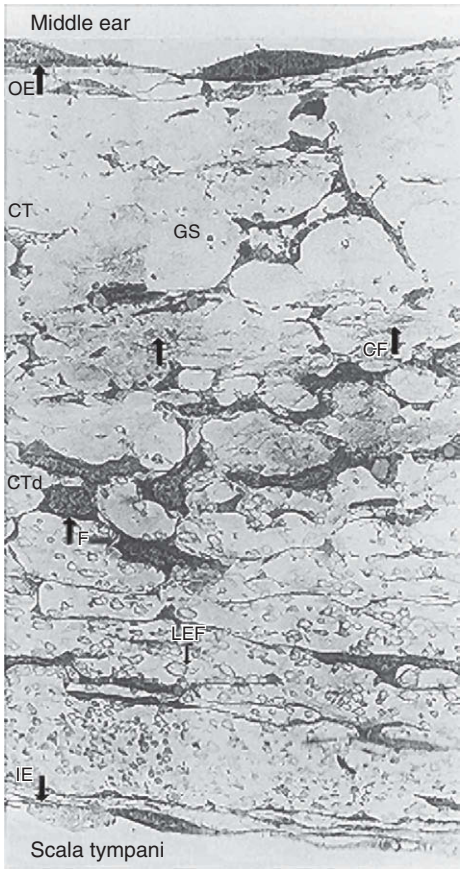

Figure 155-1. Normal human round window membrane in a 70-year-old individual. CF, collagen fibers; CT, area of loose connective tissue; CTd, area of dense connective tissue; F, fibroblasts; LEF, large elastic fibers; GS, ground substance (uranyl acetate–lead citrate); IE, inner epithelium; OE, outer epithelium. ×3000. *(From Goycoolea MV. Clinical aspects of round window membrane permeability under normal and pathological conditions.* Acta Otolaryngol. *2001;121:437.)*

Physiology

The RWM is a dynamic biologic membrane. All three layers of the RWM participate in a defensive response to pathogen insult. In the context of otitis media, the outer epithelial cells become hyperplastic, whereas blood vessels within the connective tissue layer become edematous and dilated, permitting extravasation of neutrophils and macrophages. Fibroblasts also become hyperplastic, displaying an increased volume of basophilic cytoplasm.[2] Yoon and Hellstrom[3] found that although all layers of the RWM are involved in the defense response, the most dramatic changes are seen in the subepithelial space close to the basement membrane (Fig. 155-2). Certain toxins can also initiate these metaplastic changes, resulting in a thicker RWM. The thickness of the RWM doubles after exposure to *Pseudomonas* exotoxin.[4] Streptolysin O has been shown to cause breakdown of the RWM, increasing its permeability to substances in the middle ear space.[5]

Another dynamic aspect of the RWM is its ability to transport macromolecules. This process seems to be receptor mediated.[6] Transport starts at the outer layer, where molecules are taken up by pinocytosis and are brought into the connective tissue layer. From there, substances either are absorbed by blood or lymphatic vessels or are mobilized further to the inner epithelial layer, where they are released by pinocytosis into the perilymph. The RWM may also participate in the absorption of perilymph because experimental evidence has shown the passage of tracer substances from the perilymph compartment into the RWM.[2]

The RWM displays dynamic changes as it ages. Although there is no change in the thickness of the RWM with aging, changes in cellular density and elastic fiber patterns can be seen. These changes may decrease the compliance of the membrane and compromise the overall function of the auditory system.[7]

Permeability

A large range of materials are able to cross the RWM, including various antimicrobials, steroids, anesthetics, tracers, albumin, horseradish peroxidase, latex spheres, germicidal solutions, water, ions, and macromolecules (including bacterial toxins).[8] Several factors contribute to the permeability of the RWM, including size, charge, the morphology of the compound, and the thickness of the RWM. Size has proved to be a factor in permeability because 1-μm microspheres cross the RWM, but 3-μm microspheres do not.[9] Substances with a molecular weight of less than 1000 kD diffuse across the RWM rapidly, whereas substances greater than 1000 kD are transported by pinocytosis.[10] Charge of the molecule can also affect its ability to traverse the RWM: cationic ferritin crosses the RWM, but anionic ferritin does not.[9] The implication is that liposolubility is a factor in RWM permeability, a feature that is important in the design of liposome vectors for gene therapy.[8] The morphologic features of the compound can stimulate pinocytosis, presumably by a receptor-mediated mechanism.[8,10] Increased thickness of the RWM decreases permeability of substances.[8] Although the average thickness of the human RWM is 10 to 30 μm, this thickness can double in inflammatory conditions.[11,12]

RWM permeability can be altered with the use of exogenous adjuvants. Chandrasekhar and colleagues[6] compared the ability of three exogenous adjuvants to increase the perfusion of dexamethasone applied to the round window niche. These compounds included hista-

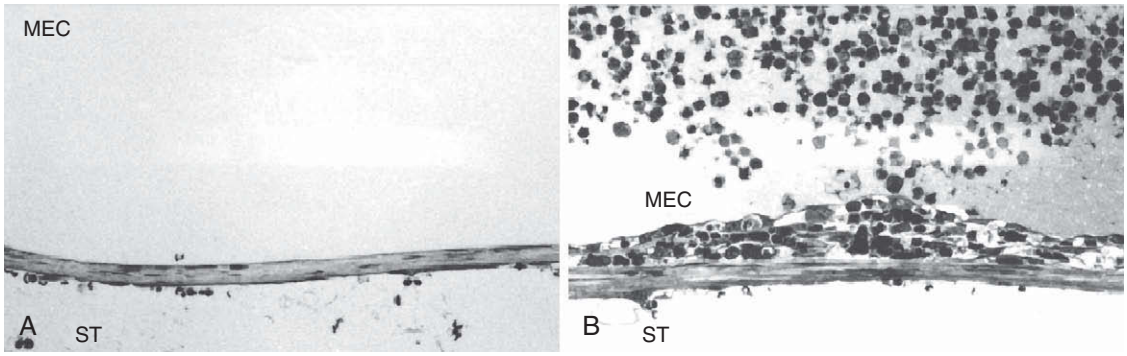

Figure 155-2. **A** and **B,** Light microscopic changes in the thickness of the round window membrane stained for toluidine blue on normal control **(A)** and day 1 in pneumococcus-induced otitis media **(B)**. The change was most prominent on day 1, which was most evident in the outer epithelium and subepithelial space of the round window membrane. MEC, middle ear cavity; ST, scala tympani. ×200. *(From Yoon YJ, Hellstrom S. Ultrastructural characteristics of the round window membrane during pneumococcal otitis media in rat.* J Korean Med Sci. *2002;17:230.)*

mine (for its vasodilatory effects), hyaluronic acid (for its proposed osmotic effect), and dimethyl sulfoxide (for its ability to increase medication solubility in perilymph). Histamine adjuvant with dexamethasone resulted in significantly higher perilymph steroid levels than all other combinations, whereas hyaluronic acid and dimethyl sulfoxide had no significant effect. Although this study failed to show an increase in steroid perfusion with the use of hyaluronic acid, several practitioners advocate use of hyaluronic acid in their intratympanic steroid protocols.[1,13]

Kinetics

Delivery of therapeutic agents across the RWM displays a nonuniform distribution in the perilymph. Concentrations of the delivered agent are usually high in the basal turns in close proximity to the RWM, and are low at the apical turns. The permeability characteristics of the substance across the RWM and the rate of its clearance from the perilymph are the two major factors that determine the dispersal characteristics of substances in perilymph; this can include a combination of clearance to blood, clearance to any other scala, uptake or binding by cells, or metabolism by any of the cochlear tissues.[14] Knowing the RWM permeability and clearance rates of a given agent permits the simulation of its perilymphatic distribution with reasonable accuracy.

With these observations, Salt and Ma[14] described the development of a computer-simulated model of drug distribution in the perilymphatic space (Fig. 155-3). Their model, the Washington University Cochlear Fluids Simulator, is a public-domain program that is available on the Internet at http://otowustl.edu/cochlea/. An example of the power of this program is provided in the study by Plontke and coworkers,[15] in which a model of gentamicin kinetics in the perilymph was closely approximated to published in vivo kinetics data by adjusting input parameters defining RWM permeability, clearance, and interscala drug exchange. These investigators were able to establish that intratympanically administered gentamicin spreads from the RWM to the vestibule by communication through the scala, rather than by diffusion through the helicotrema. The study also suggested that drug concentrations and distribution in the perilymph were substantially influenced by the delivery method and the duration of exposure of the drug to the RWM. These computer-generated simulations are useful because they permit the optimization of different treatment protocols in humans, without resorting to simple trial and error or costly animal trials.

Another important finding from this simulated research is that the distribution of substances in perilymph is dramatically altered after perforation of the otic capsule. This finding is important because many previous pharmacokinetic studies have perforated the otic capsule to access perilymph for drug concentration sampling; their findings may be distorted by this phenomenon.[14]

Adhesions

As noted previously, the epithelium that neighbors the round window niche sometimes can create a veil that separates the RWM from the middle ear. Other reactive changes, such as scarring from repeated middle ear infections or from prior middle ear surgery, may also lead to adhesions that obstruct the RWM.[16] In a cadaveric study of 202 ears to determine the rate and nature of RWM obstruction, Alzamil and Linthicum[17] identified RWM obstruction in one third of ears. In their series, 21% had false RWMs, 10% had fibrous plugs, and 1.5% had fatty plugs. In cases in which temporal bones came from the same cadaver, 57% had no obstruction, 22% had bilateral obstruction, and 21% had unilateral obstruction. These investigators noted that the plugs filling the round window niche are 1 mm (in contrast to the RWM, which is approximately 20 µm thick).

Silverstein and coworkers[16] provided further evidence of RWM obstruction. In a series of 41 patients, they found that 17% of ears had partial obstruction and 12% had total obstruction of the round window niche. Because these adhesions may cause significant variability in the

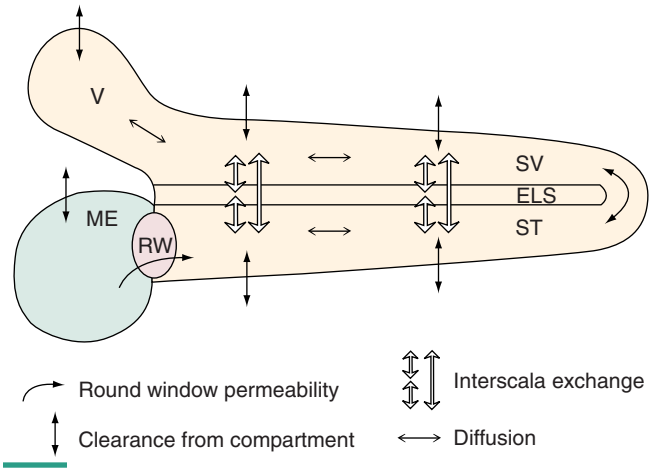

Figure 155-3. Schematic of the physical processes incorporated into the simulation program (the Washington University Cochlear Fluids Simulator, version 1.6, a public-domain computer program available at http://oto.wustl.edu/cochlea/). The compartments shown include the middle ear (ME), scala tympani (ST), cochlear endolymphatic space (ELS), scala vestibuli (SV), and vestibule (V). Drug enters through the round window (RW) in an amount depending on the permeability, and spreads longitudinally by diffusion. Local interscala exchange allows drug to spread to the endolymphatic space and the scala vestibuli, and from there to the vestibule. Drug clearance (losses to other compartments such as to blood) occurs from each compartment. Diffusion, clearance, and interscala exchange are calculated for each 0.1-mm segment of the fluid space. *(From Plontke SKR, Wood AW, Salt AN. Analysis of gentamicin kinetics in fluids of the inner ear with round window administration.* Otol Neurotol. *2002;23:967.)*

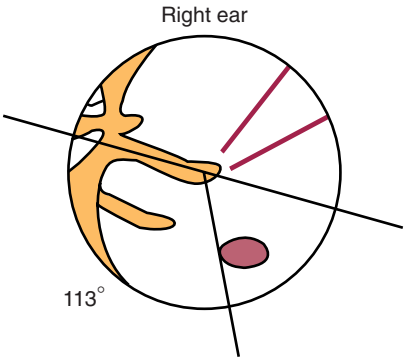

Figure 155-4. Illustration shows how the angle between the handle of the malleus and the round window (shown in the supine operative position) was calculated. *(From Silverstein H, Durand B, Jackson LE, et al. Use of the malleus handle as a landmark for localizing the round window membrane.* Ear Nose Throat J. *2001;80:444.)*

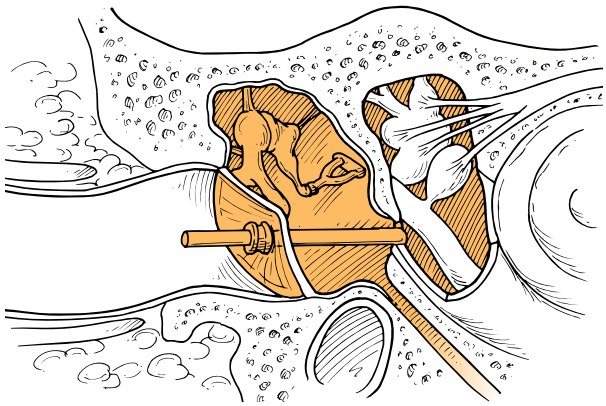

Figure 155-5. Silverstein MicroWick. *(Reprinted with permission of Micromedics, Inc.)*

pharmacokinetics of intratympanically applied medications, these authors recommended that endoscopic removal of these adhesions should be performed before any intratympanic drug treatments. In their practice, they use a 1.7-mm endoscope with 0-degree and 30-degree viewing angles. Adhesions, if identified, are removed with a small right-angle pick. The clinical and therapeutic advantages of lysing adhesions before intratympanic drug therapy have yet to be shown in controlled clinical trials.

Delivery Method

Following is a description of how typical intratympanic injections are performed. The patient lies flat with the affected ear facing the ceiling. The external ear canal is cleaned of debris, and the tympanic membrane is visualized with an operating microscope. The round window niche can be found an average of 3.44 mm (±0.68 mm) from the umbo, at an average angle of 113.2 degrees (±9.8 degrees) from the long process of the malleus (Fig. 155-4).[18] Local anesthetic is applied to the tympanic membrane. Anesthetic preparations include topical tetracaine with alcohol, topical 15% phenol preparation, or ear canal injection of 1% lidocaine with 1:100,000 epinephrine.[19] If endoscopy is to be performed, a generous myringotomy incision is made from the umbo posteriorly to the anulus, large enough to pass the endoscope (with scope diameters of approximately 1.7 to 2.4 mm). If simple injection is performed, myringotomy may still be necessary because there needs to be a vent for air to escape the middle ear space as it is filled with fluid.

If endoscopic examination is performed, the round window niche is identified, and any mucosal adhesions are removed by use of an angled pick. The injection follows with a 1-mL tuberculin syringe and a spinal needle. Cutting 2 inches off of the tip shortens the needle and dulls the tip, decreasing the risk of a traumatic puncture of surrounding tissue. The injection should be administered slowly and directed so that the solution pools around the round window niche. Because the solution often drains into deeper air cells after the first injection, a second injection can be applied. The patient should remain with the injected ear toward the ceiling for approximately 15 to 30 minutes. It is important to instruct the patient to refrain from swallowing, talking, or yawning during this time.

Some protocols call for multiple injections over a short time. In these cases, it is useful to place a tympanostomy tube after the initial myringotomy. Montandon and colleagues[20] found that placement of tympanostomy tubes resulted in resolution of vertigo in 71% of patients with Meniere's disease in their study; if tubes are going to be used in a study, they should be acknowledged as a confounding variable.

Advances in microendoscopes may significantly increase the ease and accuracy of intratympanic drug delivery. Plontke and associates[21] described the development of a 1.2-mm endoscope that incorporates a thin fiberoptic, a working/laser channel (0.3 mm), and a suction/irrigation channel (0.27 mm). This new device would allow for several manipulations to occur at once, including direct observation of the RWM, lysis of adhesions (if present), and application of medications directly to the RWM.

Intratympanic injection is inherently inaccurate because the injected medication can leak down the eustachian tube, escape out of the external canal, or be sequestered in the middle ear. The amount of medication delivered potentially changes with each patient and each dose.[22] In an attempt to address this problem, several static sustained-release vehicles have been developed. A dry 2 mm × 3 mm Gelfoam (Upjohn, Kalamazoo, MI) pledget can be placed directly in the round window niche against the RWM. The treatment compound can be injected directly onto the Gelfoam pad. Because of the slow dissipation of Gelfoam, this injection can be repeated several times (as in titration protocols for gentamicin treatment of Meniere's disease).[19] Gelfoam slurry can also be used to suspend the medicine. This slurry can be directly injected into the middle ear space. This method has the advantage of the Gelfoam being easily removed from the middle ear in the case of an adverse reaction to the applied medicine.[23]

A two-component fibrin glue system also can be used (developed by Red Cross–Holland Lab, College Park, MD). The first component of the glue is deposited in the round window niche. The other component is mixed with the medicine and is added to the first (which is already in the round window niche). The two are mixed in situ and subsequently solidified, allowing the medicine to be slowly released from the glue onto the RWM.[23]

The ultimate degree of pharmacokinetic control is achieved with the use of mechanical sustained-release devices. These devices allow researchers to manipulate inner ear kinetic curves reliably by changing the rate and amount of dose delivered to the RWM.[22] Two devices are currently approved for use in humans and have been studied in clinical trials: the Silverstein MicroWick (Micromedics, Eaton, MN) and the IntraEar Microcatheter (Durect, Cupertino, CA). The Silverstein MicroWick (Fig. 155-5) is made from polyvinyl acetate and measures 1 mm × 9 mm long, small enough to fit through a tympanostomy tube. The wick absorbs medication (which can be administered by the patient at home) that has been applied to the external ear canal and delivers it to the RWM. The advantage of this system is that fitting the device is a simple, minimally invasive procedure (only nominally more invasive than tympanostomy tube placement), and the device can be removed without anesthesia. Long-term use is not advised because the wick material may become adherent to the mucosa of the round window niche. This device has been used to deliver steroids and gentamicin treatments in human clinical trials.[19]

The IntraEar Microcatheter (Fig. 155-6) consists of an electronic pump (Disetronics, Minneapolis, MN) connected to a catheter tip that is placed directly on the RWM. Implantation of the microcatheter is more invasive and requires the elevation of a tympanomeatal flap. Several sizes are available to secure a good fit of the catheter tip into the round window niche. The rate and dose of drug delivery are set by the practitioner at the time of implantation, but can be adjusted in the

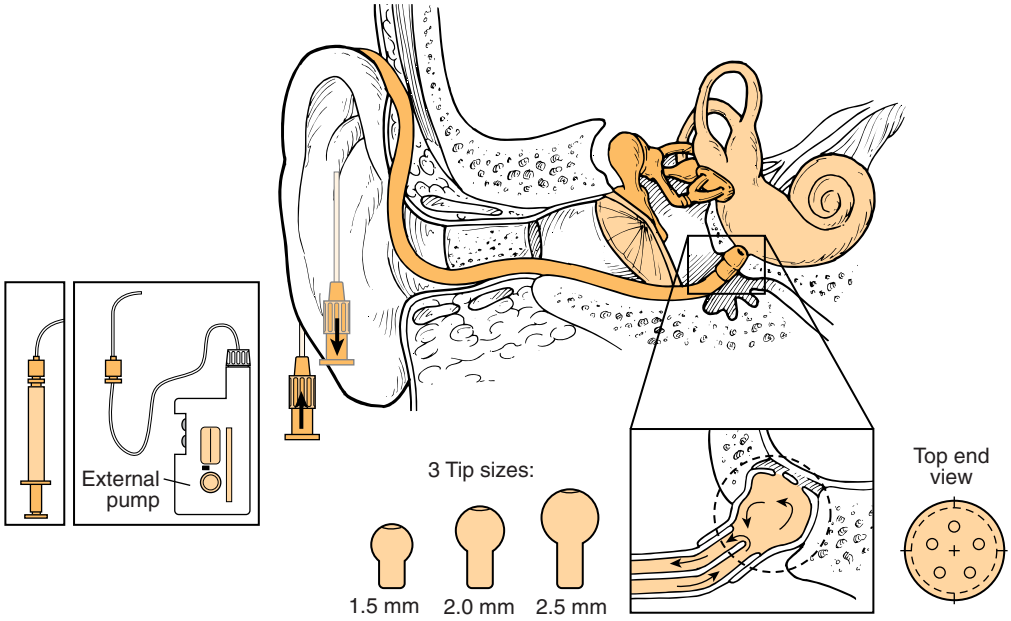

Figure 155-6. IntraEar Microcatheter. *(Reprinted with permission of the DURECT corporation.)*

middle of the treatment period. This device has also been extensively tested in human subjects for steroid and gentamicin therapy to the inner ear.[24]

Several new therapeutic agents (e.g., neurotrophins) require long-term or continuous application, which presents a serious challenge from a delivery point of view. In an attempt to address the need for a long-term delivery device, Praetorius and colleagues[25] developed a fully implantable micropump system. The device is made from pure titanium, polyethylene, and silicone, and is designed for lifelong implantation in humans. To place the device, a cavity is drilled out of the mastoid bone to house the pump and reservoir system, a procedure that is similar to the one used to place cochlear implants or implantable hearing devices. The catheter tip is placed into the round window niche. The design allows for variation in kinetics, enabling bolus and continuous infusions. The device is designed so that it can be refilled by a simple procedure without the need for reimplantation.

Steroids

The two principal indications for intratympanic steroids are sudden sensorineural hearing loss (SNHL) and Meniere's disease. The pathogenesis, pathophysiology, and diagnostic criteria for these indications are subject to controversy, making a comprehensive evaluation of the use of intratympanic steroids as a treatment for these conditions exceedingly difficult. The mechanism of action of steroids in the inner ear is incompletely understood. We review what is known about how steroids affect the inner ear, their systemic use for treatment of inner ear diseases, and the reported clinical outcomes of intratympanic steroid therapy.

Mechanism of Action

Steroids mitigate the destructive processes caused by the immune response by decreasing the number of circulating blood leukocytes and inhibiting the formation and liberation of inflammatory mediators.[26] They also inhibit the release of chemoattractive and vasoactive factors, decrease the secretion of lipolytic and proteolytic enzymes, and inhibit the release of proinflammatory cytokines, such as interferon-γ, granulocyte/monocyte colony-stimulating factor, interleukins, and tumor necrosis factor-α.[27] These actions decrease the damage from an inflammatory response, whether the insult is secondary to mechanic, hypoxic, ischemic, infectious, or autoimmunologic causes.[28]

Several studies have established how steroids attenuate pathogen-induced immune responses in the ear. On exposure to lipopolysaccharide, cultured endothelial modiolar cells and tissue exhibit a generic response and release proinflammatory cytokines.[29] These proinflammatory cytokines cause vasculitis, vascular leakage syndrome, entry of immunocompetent cells, and perivasculitis, ultimately leading to cochlear ischemia, intracochlear tissue damage, and hearing loss. Administration of dexamethasone can inhibit this cytokine immune response, and can potentially interrupt the beginnings of the inflammatory cascade at the level of cytokine expression.

Several other studies support the role of steroids in ion homeostasis in the inner ear. Serum glucocorticoid levels are directly correlated with activity and concentration of Na^+,K^+-ATPase in the inner ear.[30] Lee and Marcus[31] found that potassium secretion by marginal cells is immediately increased after the administration of steroids. Because the kinetics are too rapid for transcriptional activation to cause this change (it takes at least 30 minutes for RNA polymerase to be activated), a nongenomic mechanism is implicated. Modern theories of steroid pharmacology include not only nongenomic and genomic pathways of steroid hormone action, but also a nongenomic modulation of the genomic effects.[32] These relationships in the inner ear are just beginning to be understood.

Pharmacokinetics

Intratympanic administration yields much higher concentrations of steroids in the inner ear than either intravenous or oral administration.[6,33] Parnes and colleagues[33] compared intravenous and intratympanic administration of hydrocortisone, methylprednisolone, and dexamethasone (short-acting, intermediate-acting, and long-acting steroids). Although all three steroids successfully penetrated the blood-labyrinthine barrier, there was a much higher concentration of steroids in inner ear tissues with intratympanic administration. Other investigators have shown that the metabolism of steroids, including uptake and elimination, is different in cochlear tissues compared with other organs.[34] Methylprednisolone had the highest concentration and longest duration in perilymph and endolymph of the three compounds.[33] Similar concentrations of steroids were found in the scala tympani and scala vestibuli. The authors argue that the concentration of steroids in the endolymph implies some form of active transport through the membranous labyrinth.

The findings regarding the superior concentrations of methylprednisolone are controversial. First, other forms of steroids have been tolerated much better by middle ear tissues. Dexamethasone seems to be better tolerated and less irritative to middle ear tissues. Second, higher concentrations have not led to superior clinical results. It may be that higher perilymph and endolymph concentrations do not

translate into greater efficacy. In addition, although high methylprednisolone concentrations and high anti-inflammatory activity associated with attainable levels are observed with methylprednisolone, therapeutic efficacy may rely on other mechanisms of action. One possibility relates to Na^+-K^+ channel activity. The mineralocorticoid and glucocorticoid classes of steroids induce markedly different responses in Na^+-K^+ channel activity.[31] At this point, it is reasonable to use the less morbid middle ear therapeutic agents (i.e., dexamethasone) until more definitive studies can determine whether the higher concentrations in the study by Parnes and colleagues[33] translate into better clinical results, despite decreased tolerability.

Systemic Steroids

Currently, systemic steroids are the treatment of choice for sudden SNHL[35,36] and acute vestibular vertigo.[37] The most frequently used protocol of oral steroids for inner ear disease is 60 mg of prednisone (or 1 mg/kg/day for adults) taken for 10 to 14 days in idiopathic sudden SNHL or for 1 month in suspected autoimmune inner ear disease.[38] Both indications call for a gradual taper after the initial treatment period is finished. If hearing loss returns during the taper, a higher dose of prednisone is restarted. Relapse of hearing loss is often preceded by tinnitus.[39] Shea[40] recommended that in addition to oral steroids, 16 mg of intravenous dexamethasone should be perfused over 3 hours. The value of adjunctive intravenous delivery of steroids in addition to oral therapy remains to be established.

Meniere's Disease

Meniere's disease may be due in some cases to immune dysfunction. Steroids are often used in Meniere's disease treatment protocols.[1] Itoh and Sakata[41] reported the first intratympanic steroid protocol in 1987, in which four to five weekly injections of 2 mg of dexamethasone were administered to 61 patients with unilateral Meniere's disease. This protocol resulted in relief of vertigo in 80% of patients and reduction in tinnitus in 74% of patients. Subsequently, additional studies have used intratympanic steroids to treat Meniere's disease, some with more promising results than others.

Sennaroglu and colleagues[42] placed tympanostomy tubes in 24 patients with Meniere's disease with intractable vertigo and applied 5 drops of 1 mg/mL dexamethasone solution into the middle ear space every other day for 3 months (administered at home by the patient). This protocol resulted in a vertigo control rate of 72%, improved hearing in 17%, decreased tinnitus in 75%, and reduced aural fullness in 75%. This protocol is attractive because the drug is self-administered, the entire procedure can be accomplished under local anesthesia, and the delivery method provides flexibility to titrate the dose. The authors acknowledge that their results may be confounded by a placebo effect secondary to the tympanostomy tubes. They cite a study by Montandon and associates[20] that reported that tympanostomy tube placement prevented vertigo attacks in 71% of patients.

Barrs and coworkers[43] also used tympanostomy tubes to administer intratympanic dexamethasone. They used a dose of 0.3 to 0.5 mL of 4 mg/mL dexamethasone. Injections were given daily for the first 2 days and weekly thereafter for a total of 1 month and five treatments. The vertigo control responses were reported in time intervals, with an 86% response at less than 3 months, a 52% response at 3 months, and a 43% response at 6 months. There was an average of 2.7-dB hearing loss, but one patient had a 35-dB hearing loss. The authors propose that intratympanic steroid treatment is effective for short-term management of vertigo, but is less successful for long-term vertigo control.

Shea[40] reported on a protocol that uses a combination of intravenous, intratympanic, and oral dexamethasone to treat patients with Meniere's disease. A mixture of 0.5 mL hyaluronan containing 16 mg/mL of dexamethasone is injected into the middle ear after argon laser myringotomy and removal of RWM adhesions. The patient sits with the injected ear up for 3 hours while receiving 16 mg of intravenous dexamethasone. This treatment is performed for 3 consecutive days. Then 0.25 mg of oral dexamethasone is taken for 30 to 90 days, depending on the response to treatment. This protocol resulted in a vertigo control rate of 77%, hearing improvement in 35.4%, and hearing loss in 6.3%. With the 6-point functional level score recommended by the American Academy of Otolaryngology–Head and Neck Surgeons (AAO-HNS) guidelines,[44] 61.3% of patients were improved, 32.3% were unchanged, and 6.4% were worse after treatment.

In a rare controlled trial, Silverstein and colleagues[1] conducted a prospective, randomized, double-blind, crossover trial of intratympanic dexamethasone and placebo in 17 patients with Meniere's disease. All patients had stage IV Meniere's disease by the Shea classification (they no longer had vertigo, had poor hearing, and had significant fullness and tinnitus). Patients received intratympanic injection of either placebo (0.2 to 0.3 mL of 1:1 normal saline and sodium hyaluronate) or 0.2 to 0.3 mL of a 1:1 mixture of 16 mg/mL dexamethasone and sodium hyaluronate. This treatment was performed for 3 consecutive days. Three weeks after the initial treatment, the groups received the crossover treatment (the placebo group received intratympanic steroids and vice versa). The parameters recorded were audiometric data, electronystagmography recordings, and tinnitus evaluations; several questionnaires and telephone interviews were included. Intratympanic steroids provided no significant benefit over placebo in any of the parameters recorded, and patients could not guess which arm of the study they were in. This study would seem to confirm the lack of benefit of intratympanic steroid use for Meniere's disease. The severely diseased patient population (all stage IV) may be a selection bias not present in other studies, however, leaving open the possibility that intratympanic steroids may be useful in less severe cases. Also, most successful intratympanic steroid protocols involve steroid treatments that last longer than 3 days.

In another well-designed study, Garduño-Anaya and associates[45] conducted a prospective, placebo-controlled, double-blind, randomized study with 2-year follow-up, and found dramatically different results than Silverstein and colleagues.[1] A regimen of 5 consecutive days of intratympanic dexamethasone (4 mg/mL) versus saline for placebo control was administered to 11 study patients and 11 controls, all having unilateral disease as outlined by the 1995 AAO-HNS Committee on Hearing and Equilibrium. In the dexamethasone group at 2-year follow-up, complete control of vertigo (class A) was achieved in 9 of 11 patients (82%), and substantial control of vertigo (class B) was achieved in the remaining 2 patients. In the control group, only 7 of 11 patients finished the trial, and of these, 4 patients (57%) achieved class A vertigo control, 2 patients (29%) achieved class C, and 1 patient (14%) achieved class F. These results were statistically significant. There were several other outcome measures with variable results, with significant improvement in AAO-HNS 6-point functional level; Dizziness Handicap Inventory; and subjective vertigo, tinnitus, and aural fullness scores in the treatment group, but no significant changes in the Tinnitus Handicap Score, pure-tone average, speech discrimination score, electronystagmography, or electrocochleography tests between the two groups. The final verdict on intratympanic steroid use for Meniere's disease is still pending, and more data on optimal dosing and protocols are needed.

Sudden Sensorineural Hearing Loss

Systemic and intratympanic steroid therapy has also been used for treatment of sudden SNHL. The major prognostic factors predicting response to treatment for sudden SNHL are initial severity of hearing loss and time between onset and treatment.[6,46] There is a high spontaneous recovery rate of 30% to 60%; treatment efficacy of any intervention has to be greater than the spontaneous recovery rate. Oral steroid therapy within the first 2 weeks has shown recovery rates approaching 80% and decreasing thereafter.[46,47] Because of the high initial response to oral steroids, few practitioners have attempted to use intratympanic steroids, and most intratympanic steroid trials enroll patients who had oral treatment fail. That being said, numerous studies, mostly retrospective, have shown that intratympanic steroids do provide an excellent method for salvage of hearing in the case of systemic steroid treatment failure.

Gianoli and Li[35] reported results of a trial of intratympanic steroids for patients with sudden SNHL who had failed to improve after high-dose systemic steroids (1 mg/kg/day of prednisone for a minimum of 1 week). The protocol consisted of tympanostomy tube placement followed by instillation of 0.5 mL of steroid solution consisting of either

25 mg/mL of dexamethasone or 62.5 mg/mL of methylprednisolone. Four treatments were administered over 10 to 14 days, and audiometric data were recorded 1 to 2 weeks after treatment. The results showed a pure-tone average improvement of 10 dB or greater in 44% of patients. The authors argued that although this improvement seems modest, this is in a cohort of patients who would otherwise be considered refractory to steroid treatment. Although there was a trend toward better outcomes for methylprednisolone, there was no significant difference between the two steroid solutions.

Kopke and colleagues[46] reported results of the use of methylprednisolone perfusion by means of an RWM microcatheter in patients with sudden SNHL who failed oral prednisone therapy. The catheter delivered 62.5 mg/mL of methylprednisolone at a continuous rate of 10 µL/hour for 14 days with an electronic pump. Audiometric changes were the main outcome measures recorded. Of the six patients who had catheter placement 6 weeks or less after the onset of hearing loss, five had improvements of 10 dB or more in pure-tone averages, and four of these had a return to baseline pure-tone averages. Results were less promising for patients receiving treatment more than 6 weeks after onset of symptoms; in one patient, there was additional hearing loss associated with vertigo.

Several other, smaller reports have been published. Chandrasekhar[47] reported results from a series of 10 patients treated with intratympanic dexamethasone. The dexamethasone concentration and number of intratympanic injections varied among patients, and several patients were taking oral medications in addition to intratympanically administered steroids, making outcomes difficult to assess. Of the 10 patients treated, 6 experienced hearing improvements greater than 10 dB, however. Parnes and colleagues[33] reported results from a similar series of 13 patients with sudden SNHL treated with intratympanic steroids. Because there was considerable variation in the number of treatments applied and the drug administered (dexamethasone vs. methylprednisolone), the results are difficult to assess. Of the 13 patients treated, 6 showed hearing improvements of 10 dB or more.

One point of consensus about these studies is that they show that the longer between the insult and the administration of intratympanic steroid treatment after oral steroid failure, the lower are the chances of salvaging hearing. If intratympanic steroids are to be used, they should be used as soon as possible after it becomes clear that oral steroids are not improving hearing, preferably within the first 2 weeks of the original insult.[48]

Dosing

The most widely used steroid for intratympanic protocols is dexamethasone, followed by methylprednisolone. Intratympanic dexamethasone preparations vary from 1 to 25 mg/mL.[49,50] Some studies use a hyaluronic acid preparation consisting of a 1:1 mixture of 16 mg/mL of dexamethasone and 0.5 mg/mL of hyaluronate sodium.[1,40] Most intratympanic methylprednisolone studies use a solution of 62.5 mg/mL.[22,46] The amount of solution injected in each protocol is designed to fill the middle ear space (which is 0.3 to 0.5 mL). The interval of dosing depends mostly on the instillation method. Protocols that include self-administration through tympanostomy tubes have every-other-day dosing.[49] Intratympanic injection protocols are much less frequent, and often include "shotgun" dosing with multiple injections over the first 2 weeks of treatment.[1,51]

Side Effects

The side effects of long-term systemic steroid use are well known and include compromise of the immune system leading to infections, osteoporosis, peptic ulcers, hypertension, myopathy, ocular effects, impaired healing, psychologic effects, and avascular necrosis.[52] In contrast, intratympanic steroids are characterized by minor local morbidities. Several preclinical studies have documented that intratympanic steroids cause no morphologic or functional compromise in animal models.[27,53] Human clinical trials have reported benign side-effect profiles, even after multiple and long-term treatments.[33] There are several reports of decreased hearing in human clinical trials of patients with Meniere's disease,[40,43] but it is unclear whether this is a side effect of treatment or part of the natural course of the disease.[51,54] There are some reports of tympanic membrane perforations and otitis media secondary to the perfusion process.[35] Some patients experience a mild burning sensation in the ear after injection of methylprednisolone. This side effect has been avoided by combining 0.1 mL of 1% lidocaine with 0.9 mL of standard intravenous methylprednisolone solution (40 mg/mL).[33]

Summary

There is currently no consensus on the mechanism of action of steroids in the inner ear. Experience with intratympanic steroids is insufficient to recommend their routine use in autoimmune hearing loss, sudden SNHL, or Meniere's disease. Intratympanic steroid use is proving to have a role as a salvage therapy, however, for sudden SNHL unresponsive to oral steroids.

Gentamicin

Fowler[55] first described the use of aminoglycosides for chemical ablation of the labyrinth in 1948, using systemic streptomycin to treat patients with Meniere's disease with intractable vertigo. Bilateral cochlear damage led to the abandonment of this effort, but in 1957, Schuknecht[56] revived interest in chemical ablation with the introduction of intratympanic administration of aminoglycosides. Although loss of hearing was almost as common as the resolution of vertigo, his work set the stage for the development of modern intratympanic chemical ablation protocols. In the mid-1970s, Beck and Schmidt[57] described a low-dose strategy that departed from the goal of total vestibular ablation. They compared a high-dose ablative protocol with a low-dose, low-injection-frequency protocol, and found that although vertigo control was essentially the same, the hearing loss rate decreased from 58% to 15%. This improvement rekindled interest in intratympanic gentamicin therapy, and led to the development of strategies that maximize vertigo control, while minimizing hearing loss.

Mechanism of Action

Despite the widespread belief that gentamicin is selectively toxic to vestibular hair cells, this assertion is not fully supported by the literature. Several researchers have shown that gentamicin and streptomycin cause parallel and dose-dependent damage to vestibular and cochlear hair cells.[58,59] Wanamaker and colleagues[59] stated, "When the vestibular system was severely damaged, the cochlea was severely damaged; when loss in the vestibular system was mild, loss in the cochlea was mild. We did not observe any dose-related selectivity for the vestibular system over the cochlea." The clinical finding of significant correlation between loss of caloric response and hearing loss after gentamicin exposure further betrays the notion of selective vestibular toxicity.[60,61]

If there is no selective vestibular toxicity, how is it that clinicians have achieved good vertigo control with minimal hearing loss? In part, the answer may lie in pharmacokinetics.[22,62,63] Hoffer and colleagues[22] compared the kinetic profiles of intratympanic injection versus microcatheter delivery of gentamicin, and correlated these data with the functional and morphologic changes observed in the inner ear. Despite the fact that the total dose in both methods was roughly equal, the resulting morphologic changes were quite different. Intratympanic injection led to erratic changes, sometimes causing obliteration of auditory functioning within 4 hours, and in other cases showing significantly delayed ototoxic effects. In contrast, controlled perfusion by microcatheter caused predictable and uniform damage.

Hoffer and colleagues[22] explained that these different morphologic changes may be due to two different patterns of hair cell loss, patterns that correlate with the timing and concentration of aminoglycoside delivery. These patterns include a necrotic pattern that is associated with rapid and high-dose perfusion, and an apoptotic pattern that is associated with slower or chronic perfusion.[53,64] This complicated relationship may be secondary to saturation of anionic binding sites on the cell membrane or to modifiable active uptake patterns that depend on gentamicin kinetics.[65] In addition to the amount of gentamicin that accumulates in the perilymph over time, the nature of the distribution curve, timing of the peak, and total dose determine morphologic and functional consequences of aminoglycoside exposure.

There is overwhelming clinical evidence that vestibular ablation is not required for vertigo control. These observations have caused a shift

in strategy from vestibular ablation to *chemical alteration* or *subablation*. These terms describe the clinical goal of balancing vertigo control and hearing loss. This quest has spawned numerous clinical trials with various dosing protocols and delivery methods, all designed to achieve this goal.

What is the histologic and physiologic correlate of partial ablation? It is known that gentamicin damages type I hair cells more rapidly and severely than type II hair cells.[66] In the chinchilla, investigators showed that type II hair cells regenerated to approximately 55% of the baseline population, whereas type I hair cells showed no regeneration at all. It may be that these patterns of hair cell destruction and regeneration describe the partial vestibular ablation seen in intratympanic gentamicin clinical trials. Carey and associates[67] examined the changes in the angular vestibulo-ocular reflex after a single dose of intratympanic gentamicin, and found that in all cases there was a decreased, but not abolished, angular vestibulo-ocular reflex gain. These authors concluded that this finding provides evidence of incomplete hair cell destruction, which may account for the phenomenon of "partial ablation." Minor[68] speculated that there may be a critical level of vestibular activity required to initiate an episode of vertigo, and that the regions of vestibular epithelium or groups of afferent nerve fibers responsible for vertigo may be more susceptible to gentamicin toxicity than others. Minor[68] also speculated that hair cell regeneration may explain the phenomenon of recurrent vertigo after initial control with intratympanic gentamicin.

Although selective hair cell destruction and regeneration have yet to be established in humans, this may explain some of the more puzzling findings documented in clinical trials. Numerous trials have reported that there is an increase in hearing after gentamicin treatment.[61,69,70] In addition, in the microdose infusion trials by Hoffer and colleagues,[71] vestibular function improved in 78% of patients. These findings are hard to reconcile with traditional models of aminoglycoside toxicity.

The alternative explanation for how gentamicin achieves a selective vestibular effect is the proposal that gentamicin primarily affects secretory, rather than sensory, cells; this is known as the dark cell theory. Although cited in almost every article related to intratympanic gentamicin treatment, there is no firm documented scientific evidence showing how the effect actually occurs. Vestibular dark cells are important (but not essential) in creating and maintaining ion homeostasis in the inner ear.[72-74] Several studies have documented that aminoglycosides induce structural and functional alteration of these dark cells.[19,75] This damage is thought to alter the ionic homeostasis of the inner ear in such a way that it brings the ionic dysregulation in endolymphatic hydrops back into balance.[76,77] This theory helps explain how the hearing restoration and vestibular improvement referenced earlier might occur; re-establishment of ionic homeostasis would restore baseline function in the cochlea and labyrinth. There is uncertainty, however, whether this dark cell damage occurs before damage to sensory cells. Chen and colleagues[58] looked at secretory and sensory cells in response to aminoglycoside challenge, and found no significant changes in dark cells, despite extensive damage in cochlear and vestibular hair cells in the same animal. If dark cells are responsible for the selective effect of gentamicin, this has yet to be established in any preclinical models. Explanation of this mechanism, if it exists, would be a great advance in otology.

Pharmacokinetics

Intratympanic gentamicin kinetics in the perilymph follow a one-compartment model.[22,78] Gentamicin rapidly diffuses across the RWM; the kinetics of gentamicin in perilymph are largely determined by the method of delivery.[22,78,79] Intratympanic injection has a faster absorption phase, shows higher peak concentrations, and exhibits significantly more variability in all measurements than sustained-release delivery methods.[22,80] In pharmacokinetic studies, large value ranges and standard deviations are characteristic of intratympanic injection delivery (Fig. 155-7).[22]

Elimination of gentamicin from the perilymph compartment is rapid and dose-dependent.[78] Because of this rapid elimination, a sustained-release vehicle for drug delivery, such as a fibrin-based glue[80] or delivery by microcatheter, is the only way to maintain high concentrations of gentamicin in perilymph.[22] Although elimination in perilymph is rapid, there seems to be significant uptake of gentamicin in inner ear tissues, essentially constituting a second, "deeper" compartment. Access of aminoglycosides to the organ of Corti is probably directly from the perilymph, rather than from the endolymph.[81] That gentamicin appears in the endolymph at all seems to be a function of it being slowly released from inner ear tissues. This delayed release may explain why aminoglycosides are not immediately toxic when applied into the perilymph, whereas toxicity in vitro (without compartments) is seen immediately.[82] Hiel and coworkers[83] showed that gentamicin is rapidly and specifically captured by hair cells, such that there is significant uptake of gentamicin before morphologic ototoxic changes occur. Hair cells store aminoglycosides in lysosomes, essentially constituting the "deep" intracellular compartment referred to previously. This compartment provides prolonged exposure of these cells to aminoglycosides, and may be the basis for the delayed morphologic and functional effects seen clinically.

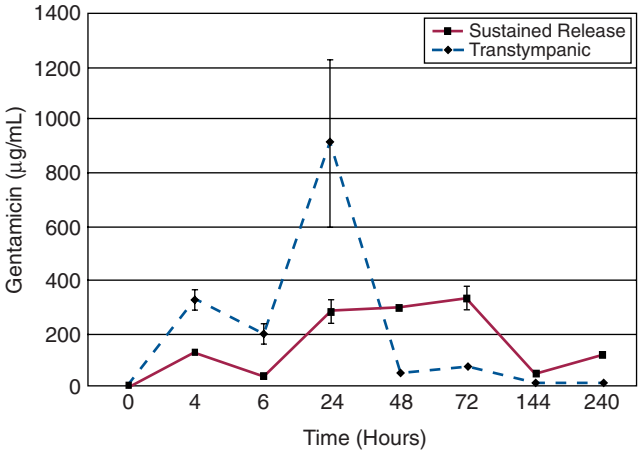

Figure 155-7. Perilymph gentamicin kinetics after sustained-release and transtympanic local delivery. Kinetic curves of perilymphatic gentamicin concentrations after sustained-release and transtympanic delivery are depicted. *Solid line* shows the sustained-release curve. The transient 4-hour peak followed by sustained delivery from 24 to 72 hours with the presence of gentamicin at 6 and 10 days is also depicted. *Dashed line* is the transtympanic curve with rapid uptake and almost total elimination within 48 hours. The SEM bars are much larger for transtympanic delivery than for sustained-release delivery. *Note*: The *x*-axis (time) is not to scale. *(From Hoffer ME, Allen K, Kopke RD, et al. Transtympanic versus sustained-release administration of gentamicin: kinetics, morphology, and function.* Laryngoscope. *2001;111:1343.)*

The pharmacokinetic data generated in animal models seem to fit what occurs in humans. Becvarovski and colleagues[79] devised an in vivo human pharmacokinetic study by recruiting patients who were undergoing either translabyrinthine surgery or labyrinthectomy and exposing them to gentamicin intraoperatively through the facial recess. In these patients, there was rapid diffusion of gentamicin into the perilymph that peaked after 30 minutes. After this peak, concentrations were in a stable range until the limit of the experiment at 110 minutes. Although there was no evidence of gentamicin in the cerebrospinal fluid, gentamicin was detected in serum shortly after administration (1 to 2 hours). This study confirms that rapid diffusion of gentamicin across the RWM occurs in humans. This study indicates that the elimination of gentamicin involves crossing the blood-labyrinthine barrier because gentamicin was detected in the serum shortly after administration.

As mentioned previously, progress in understanding gentamicin pharmacokinetics has been made with computer simulations. Plontke and colleagues[15] approximated published in vivo kinetics data by adjusting input parameters defining RWM permeability, clearance, and interscala drug exchange. The results are shown in Figure 155-8. They were able to establish that intratympanically administered gentamicin spreads from the RWM to the vestibule by communication through the scala,

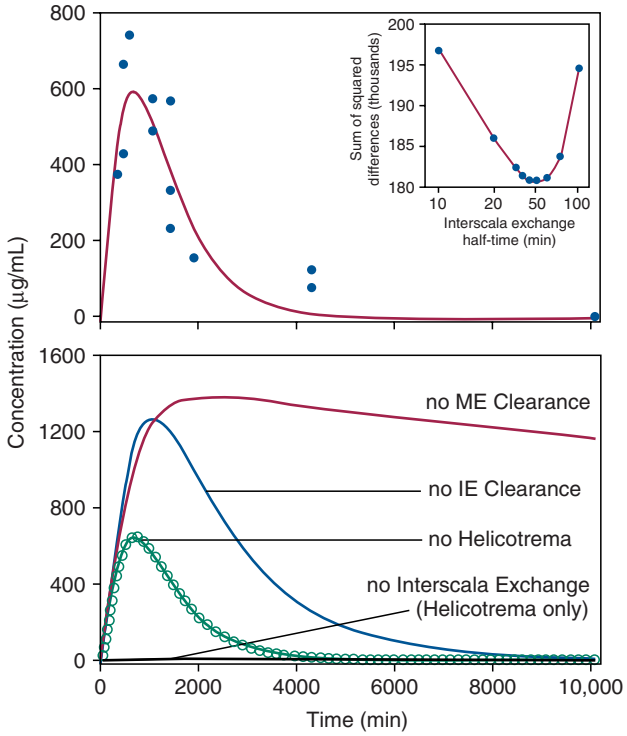

Figure 155-8. *Top,* Experimental measurements of gentamicin levels in perilymph samples taken from the vestibule after application to the round window *(solid circles)*. Data are replotted from Hoffer and colleagues and Balough.[23,80,169] *Solid line* shows best fit of the concentration time course established by the simulator (the Washington University Cochlear Fluids Simulator, version 1.6) based on physical processes of solute movement. The curve represents the calculated concentration of a simulated 15-µL sample taken from the vestibule (as described in the text). *Inset graph,* A unique best fit (using methods described in the text) was found to occur with an interscala exchange half-time of 45 minutes. *Bottom,* Calculated gentamicin time course in the vestibule with best-fit parameters *(open circles)* and with specific processes in the simulator disabled *(solid lines)*. *(From Plontke SKR, Wood AW, Salt AN. Analysis of gentamicin kinetics in fluids of the inner ear with round window administration.* Otol Neurotol. *2002;23:967.)*

rather than by diffusion through the helicotrema. The study also suggested that drug concentrations and distribution in the perilymph were substantially influenced by the delivery method and the duration of exposure of the drug to the RWM.

Clinical Protocols

Although many studies that used intratympanic gentamicin have been published, because of extreme differences in the quality of data, comparison of the different intratympanic gentamicin protocols is exceedingly difficult. Instead, several studies representing various strategies are discussed, and their results are summarized. There are three basic strategies used in intratympanic gentamicin therapy: fixed protocols, titrated protocols, and sustained-release protocols. Fixed protocols use a specific dose and number of injections in all patients. Titration protocols adjust the total dose delivered to a predetermined end point, such as paralytic nystagmus, decreased tandem gait, subjective dysequilibrium, or, more simply (and more commonly), relief from vertigo.[76] Sustained-release protocols work on various principles, depending on the delivery mechanism.

There is little difference between fixed and titration protocols because most fixed protocols can be repeated if no clinical response is seen, and most titration protocols deliver a fixed number of injections in the beginning of the protocol, and then repeat them as necessary. The supposed advantage of fixed protocols is that each patient receives the same treatment, making outcomes easier to interpret across individuals. Fixed protocols can be more cost-effective because excessive testing and clinical visits are avoided.[61] The flexible structure of titrated protocols supposedly allows for more control of the ototoxic effects of gentamicin, decreasing the risk of hearing loss.[84] Close monitoring for ototoxic symptoms does not confer the ability to reverse these symptoms, however.[85]

Much of the controversy in intratympanic gentamicin therapy in the 1990s concerned a form of fixed protocol known as a "shotgun" protocol. The classic "shotgun" protocol was popularized by Nedzelski and colleagues in 1992.[86] There have been periodic reports on this original "shotgun" protocol, and it is now one of the largest series in the literature, spanning a decade and including more than 90 patients. The protocol calls for three daily injections for 4 consecutive days of 26.7 mg/mL of gentamicin, and results in a vertigo control rate of 94% and hearing loss rate of 26%.[60,61,86] The main argument against "shotgun" protocols is that they lead to higher rates of hearing loss,[87] and that the hearing loss realized is profound.[69] Toth and Parnes[87] followed the classic "shotgun" protocol outlined previously, but encountered an unacceptable rate of hearing loss (57%) following 18 patients. After they changed to a titration protocol that involved weekly injections, the hearing loss rate decreased to 19%. Altlas and Parnes[69] pointed out that in "shotgun" protocols, the proportion of patients who experience hearing loss greater than 30 dB (10% to 24%) is much higher than the proportion seen in titration protocols (0% to 4%).

More recently, "hybrid" protocols have been introduced. Quaranta and associates[88] used a fixed schedule of two 0.5-mL intratympanic injections of 20 mg/mL of gentamicin solution spaced 1 week apart. Patients who did not achieve vertigo control after the first two doses were offered additional doses to a total of four doses. This was a prospective study that included a control group of patients with Meniere's disease who refused treatment. At the 2-year follow-up point, the vertigo control rate was 93% versus 47% for the untreated group. Hearing loss was 7% for the treated group versus 47% for the untreated group. Tinnitus rate and aural pressure relief were 20% and 40% for the treated group versus 27% and 27% for the untreated group. In the protocol, 47% of patients had residual vertigo after two doses and went on to receive a third dose, and 27% went on to receive a fourth dose. This study illustrates the paradoxic effect that intratympanic gentamicin actually improves hearing outcomes of patients with Meniere's disease. Improvement in hearing from the baseline decline encountered in untreated Meniere's disease is not a logical outcome if the mechanism of action of intratympanic gentamicin is merely the selective ablation of vestibular hair cells.

The microcatheter delivery method has been recommended to provide sustained gentamicin levels in the perilymph. Schoendorf and associates[89] used a high-precision insulin pump and a microcatheter to deliver 40 mg/day of gentamicin to the RWM. The treatment was continued at this fixed rate until vestibular symptoms appeared (in essence, a titration protocol). Although vertigo control was achieved in most patients, 8 of 11 patients treated became deaf. The authors claim that the occurrence of deafness was not correlated with dose because one deafened patient received 720 mg and another received only 60 mg, and hearing was unchanged in a patient who received 240 mg. The authors noted that continuous perfusion protocols should not use titration strategies because the adequate dose for vertigo control may be quickly exceeded. This study highlights the notion that kinetics can have a larger impact on morphologic and functional outcomes than dose-related effects.

In contrast to the preceding study, most continuous-delivery protocols use microdose, slow-infusion strategies. Seidman and colleagues[90] reported retrospective data from a multi-institutional trial that compared results of different microcatheter infusion rates. The vertigo control rate was 90% in the group receiving infusions of 1 µL/hr versus 79% in the group receiving infusions of greater than 10 µL/hr, a nonsignificant difference. The hearing loss rate was 23% in the group receiving 1 µL/hr versus 50% in the group receiving greater than 10 µL/hr, however, and this difference was statistically significant. The authors recommended the slow infusion rate and suggested that infusion rates less than 1 µL/hr might have even lower hearing loss rates, while maintaining equal clinical efficacy.

In a study that epitomizes the microdose, slow perfusion rate strategy, Hoffer and colleagues[91] reported the 2-year results of 27 patients who underwent microcatheter gentamicin therapy. The study used a pediatric solution of 10 mg/mL, with the pump set at 1 µL/hr for 10 days, resulting in total dose of 2.4 mg. This strategy achieved vertigo control in 93% of patients, hearing loss in only 4%, tinnitus relief in 63%, and elimination of aural pressure in 74%. The protocol included a wide variety of vestibular tests, including vestibulo-ocular gain, phase, and symmetry; posturography score; and step velocity testing. Ninety-six percent of patients had no decrease in vestibular function; however, caloric testing was not performed. The investigators found that vestibular function was improved in 79% of patients.[71] These results represent some of the most impressive results of intratympanic gentamicin therapy.

Chia and coworkers[92] conducted a meta-analysis of intratympanic gentamicin trials. The study included seven studies ($N = 218$) that used multiple daily dosing technique (delivery three times per day for ≥4 days), two studies ($N = 84$) that used weekly dosing technique (weekly injections for four total doses), eight studies ($N = 253$) that used the low-dose technique (one to two injections with re-treatment for recurrent vertigo), four studies ($N = 156$) that used continuous microcatheter delivery, and six studies ($N = 269$) that used the titration technique (daily or weekly doses until onset of vestibular symptoms, change in vertigo, or hearing loss). The titration method of gentamicin delivery showed significantly better complete (81.7%; $P = .001$) and effective (96.3%; $P < .05$) vertigo control compared with other methods. The low-dose method of delivery showed significantly worse complete vertigo control (66.7%; $P < .001$) and trended toward worse effective vertigo control (86.8%; $P = .05$) compared with other methods. The weekly method of delivery trended toward less overall hearing loss (13.1%; $P = .08$), and the multiple daily method showed significantly more overall hearing loss (34.7%; $P < .01$) compared with other groups. No significant difference in profound hearing loss was found between groups, and the degree of vestibular ablation after gentamicin therapy was not significantly correlated with the resulting vertigo control or hearing loss status.

As with all meta-analyses, caution needs to be used when interpreting these results. Differences in patient profiles, dose and concentration of gentamicin delivered, quality of follow-up analysis, and multiple other factors are necessarily bracketed for the sake of getting a reasonable idea of what treatments are best for patients. Perhaps the best outcome of this effort is that it can guide a rational design for a well-run, controlled trial that would provide a new level of evidence regarding superior treatment for patients with vertigo.

Practical Considerations

The argument for the use of intratympanic injection is that it is the simplest, most cost-effective, and least invasive method of delivery, and from published studies, it provides comparative vertigo control and hearing preservation rates to sustained-release protocols. Blakely[93,94] argued that even though there are no head-to-head comparisons of these methods, the published results suggest that there is no reason to use anything but the simplest administration protocols. The argument for using sustained-release mechanisms, particularly continuous infusion devices, is that they seem to produce lower rates of hearing loss, allow for standardization across individuals, lead to more predictable and uniform results, and improve vestibular and auditory functioning.[71]

Dose

Eklund and coworkers[95] found that frequency of deafness was dose-dependent in their intratympanic injection study. There is no minimum safe dose, however, because the lowest documented intratympanic gentamicin dose to produce hearing loss is 0.24 mg.[96] The method of delivery is as important as dose in terms of ototoxicity; this was illustrated earlier in the trial by Schoendorf and colleagues,[89] in which a microcatheter delivered a severely ototoxic dose of gentamicin, a dose that would be considered to be a "low dose" in intratympanic injection protocols. Per the pharmacokinetic studies of Hoffer and colleagues[22] mentioned previously, functional and morphologic end organ damage depends less on the total dose delivered to the inner ear than on the kinetics of how the drug reaches inner ear tissues.

Concentration

The concentration of gentamicin used varies among different studies. Low-dose protocols use the pediatric formulation of gentamicin, which comes in a preparation of 10 mg/mL.[96] The adult preparation of 40 mg/mL is often diluted to 30 mg/mL. Abou-Halawa and Poe[76] compared outcomes between intratympanic gentamicin preparations of 30 mg/mL and 40 mg/mL, and found that although both cohorts had similar vertigo control and hearing loss rates, the cohort receiving 40 mg/mL required fewer injections to achieve these results. Several other studies have confirmed that with low-dose protocols, more periodic treatments are needed, and there is an increase in the recurrence rate.[71]

Interval

The injection interval depends on the end point chosen for the study. There is increasing support for spacing the injections over at least a week, primarily because of the delayed onset of gentamicin toxicity. The typical deafferentation syndrome occurs only 3 to 5 days after injection.[88,97] Other advocates say that if a patient has Meniere's disease with episodes that are only every other week, it is unreasonable to check for results on a weekly basis.[98] In Blakely's review of intratympanic gentamicin protocols,[93,94] he argued that differences in injection intervals have little impact, if any, on outcomes.

Number of Injections

The general belief in the literature is that the fewer intratympanic gentamicin injections, the better. Youssef and Poe[70] found that the chances of gentamicin being effective after three injections are significantly reduced. Other reasons to limit the number of injections include an increased risk of permanent perforation of the tympanic membrane with each injection (unless tympanostomy tubes are placed), the increased cost and inconvenience to the patient and the physician, and an increase in the risk of hearing loss (although this is not supported by all studies).[87]

Complications

The most notorious complication of intratympanic gentamicin treatment is hearing loss. Risk factors for hearing loss have been inconsistently identified across studies; this is partially due to the substantial differences in protocols between studies. Kaplan and associates[60] found that the only factor related to hearing loss was poor hearing before treatment. Although some series have reported that the rate of hearing loss increases after multiple daily injections,[87] others have found no correlation between the number of injections and hearing loss.[70,72,95] There may be a genetic disposition to hearing loss after aminoglycoside treatment because of a maternally inherited 1555 A-to-G nucleotide substitution in the 12s mitochondrial ribosomal RNA.[99] Several patients who experienced hearing loss secondary to intratympanic gentamicin have been tested for this substitution, and, to date, not one has been positive for this substitution.[60,93,94,100]

One issue that has been raised in assessing hearing loss across studies is the extent of the hearing loss. Most studies document hearing loss as being greater than 10-dB pure-tone average loss or greater than 15% decrease in speech discrimination scores (1995 AAO-HNS guidelines[44]). This may be a poor reporting format, however, because it does not indicate whether hearing loss is serviceable or profound. As noted previously, Altlas and Parnes[69] argued that "shotgun" protocols result in substantial rates of hearing loss greater than 30 dB (range 10% to 24%[84,86,97,101]), whereas titration methods report low rates of substantial hearing loss (range 0% to 3.5%[69,96,98,102]). Although scientifically valid comparisons of these studies are impossible because of substantial difference in protocols, this trend is a troubling feature of "shotgun" protocols.

Reporting of hearing loss n gentamicin trials does not distinguish whether the deficit is due to drug-induced toxicity or the natural consequence of Meniere's disease. The long-term hearing outcome for untreated Meniere's disease has been reported to be approximately 30% with medical therapy.[68] This figure is close to the hearing loss rates

reported by most intratympanic gentamicin trials. The implication is that any intratympanic gentamicin trial that reports rates significantly better than 30% hearing loss rate of untreated patients may represent an actual prevention of hearing loss.

Determination of when hearing loss occurs in the course of therapy may be just as important as if hearing loss occurs. Several studies reported that if severe hearing loss occurs, it is noticed within 24 hours of gentamicin administration.[96] Kaplan and associates[60] reported updated data from patients who underwent the classic "shotgun" protocol, including statistics on the hearing loss rates at 1 month and 2 years. Of the 22 patients with worse hearing at 2 years, 80% realized this loss in the first month after treatment. Similarly, 91% of patients whose hearing was unchanged at the 1-month checkup had unchanged hearing at the 2-year checkup. Of the patients who experienced early hearing loss, 14 of 17 had profound hearing loss (defined as >50 dB or <50% word discrimination score), whereas of the patients who experienced late hearing loss, 4 of 5 had nonprofound hearing loss. These findings imply that the 1995 AAO-HNS guidelines[44] might be improved if they asked clinicians to report hearing results immediately after treatment and at the 2-year interval. This information also supports efforts to use otoprotective agents to salvage hearing after toxic gentamicin treatment. Finally, although no formal data have been published to date, Jackson and Silverstein[19] described initial efforts to use steroids as a salvage treatment for hearing loss secondary to ototoxic side effects of gentamicin treatment in patients with Meniere's disease.

Acute vestibular deafferentation syndrome should be an anticipated outcome of treatment, and in this sense it is not strictly a complication. Acute vestibular deafferentation syndrome, also known as acute chemical labyrinthine upset, is the consequence of unilaterally insulting the vestibular apparatus.[103] This phenomenon usually occurs 3 to 5 days after the injection. Symptoms include vertigo, nausea, oscillopsia, and dysequilibrium. Patients can readily distinguish these symptoms from symptoms typically related to Meniere's disease. These symptoms become progressively worse until they peak 1 week after onset. During this peak, patients usually require 2 to 3 days of bed rest. Gradual resolution is achieved in 2 to 4 weeks in most patients.[88,97] Because acute vestibular deafferentation syndrome is an expected outcome of therapy, some authors recommend that a vestibular rehabilitation team be available to work with severely affected patients.[104]

Other vestibular-related side effects include constant unsteadiness and dizziness, insecure gait in dark rooms, instability of the field of vision when turning the head, and very short episodes of losing control over balance or gait (or so-called Tumarkin attacks, which characterize the symptoms of some patients with Meniere's disease). Tumarkin attacks may not depend on the vestibular function because these attacks have been reported in patients with no caloric response after treatment.[89] Visual vestibular mismatch is currently being investigated as a possible side effect of gentamicin therapy. Visual vestibular mismatch is a syndrome in which visual and vestibular information is poorly coordinated in the brain, resulting in complaints of malaise and "dizziness." Classic complaints include feeling uneasy, nauseous, or unsteady in supermarket aisles or in shopping malls, new-onset motion sickness, a dislike of fluorescent lights, or an aversion to elevator and escalator rides. This syndrome is believed to result from an overreliance on visual signals. Longridge and colleagues[105] found that 17 of 28 patients with Meniere's disease who had previous gentamicin therapy had visual vestibular mismatch. Currently, visual vestibular mismatch is a clinical diagnosis, does not correlate with posturography or caloric tests, and is a relatively new diagnostic category; conclusions about visual vestibular mismatch and gentamicin therapy should be interpreted with caution.

Indications and Contraindications

Intratympanic gentamicin treatment is indicated in patients with Meniere's disease who have had conservative therapy fail and have recurrent vertigo. Conservative therapy consists of a diuretic and diet restrictions (salt, caffeine), and is effective in 70% of cases. Some patients try additional medical treatments, including vasodilators, vestibular suppressants, tranquilizers, calcium antagonists, betahistine, antidepressants, histamine, and steroids.[72] Most practitioners consider intratympanic gentamicin therapy only after conservative therapy has failed after being tried for at least 1 year. At this junction, intratympanic steroids, endolymphatic sac surgery, and intratympanic gentamicin therapy are considered.

Sennaroglu and coworkers[42] argued that it is reasonable to try to use intratympanic steroids before using intratympanic gentamicin. In a prospective study that compared intratympanic dexamethasone (n = 24) and gentamicin (n = 16), they found that vertigo control rates were 72% and 75%. Intratympanic gentamicin was considerably more cochleotoxic than intratympanic steroids, however. Vestibular nerve section and labyrinthectomy are reserved for only the most severe and refractory cases with and without residual hearing.

Some practitioners recommend that elderly patients should be treated with caution because central compensation for peripheral vestibular loss is less effective in elderly patients.[104] Bilateral Meniere's disease (incidence of 15% to 30%) is considered by some practitioners to be a contraindication for unilateral intratympanic gentamicin treatment because if hearing loss results from treatment the remaining ear may be vulnerable to hearing loss as a natural course of the disease.[106] If bilateral disease is treated, some authors advocate that an intramuscular streptomycin protocol, rather than an intratympanic protocol, be used.[107] Patients with no serviceable hearing in the problematic ear are generally considered candidates for labyrinthectomy, but some authors recommend that the low-morbidity, low-cost intratympanic gentamicin protocol should be attempted in these patients before surgery is considered.[108]

There is some debate as to whether otologic surgery is a contraindication to intratympanic gentamicin treatment. Minor[68] reported that of patients with prior otologic surgery, only one of six achieved vertigo control. Eklund and colleagues[95] also noted that patients with prior endolymphatic sac surgery had poorer hearing outcomes. Other authors have found that prior otologic surgery does not affect either vertigo or hearing outcomes.[24] The importance of this debate is that several practitioners advocate endolymphatic shunt procedures before resorting to intratympanic gentamicin when treating intractable vertigo in patients with Meniere's disease.[68]

Summary

Gentamicin has complex pharmacokinetics, depending on the dose and route of delivery. Its toxicity is related to peak dosage, dosage interval, and route of delivery. For some practitioners, intratympanic gentamicin therapy, using low doses with long intertherapy intervals, has become the treatment of choice for medically recalcitrant Meniere's disease. The primary complication of intratympanic gentamicin is permanent hearing loss.

Otoprotective Agents

Several otologic conditions may benefit from protective or preventive treatment, including noise-induced hearing loss, exposure to ototoxic medications, and salvage of spiral ganglion neurons (SGNs) for the purposes of maximizing the effectiveness of cochlear prostheses. Otoprotective agents can be categorized as either primary or secondary interventions to the overall pathophysiologic process. Primary interventions act directly at the site of insult, whereas secondary interventions act on the intracellular sequelae of primary insults (i.e., apoptosis). Examples of primary interventions include MK801, an *N*-methyl-D-aspartate receptor antagonist, which has shown protection against acoustic trauma and aminoglycoside toxicity,[109,110] and methionine for gentamicin and cisplatin toxicity.[111,112] Secondary interventions include steroids,[28] apoptosis inhibitors,[95] and neurotrophins.[113]

There is a sort of "intermediate intervention" that is possible with noise-induced hearing loss and the use of antioxidants. The contribution of free radical damage in noise-induced hearing loss results from metabolic and oxidative stress, ionic flux and dysregulation of calcium homeostasis, and mitochondrial injury. A more recent example of antioxidant treatment for noise-induced hearing loss is the use of *N*-acetyl cysteine.[114] We focus here mainly on neurotrophins as otoprotective agents because these are most cogent to the emerging pharmacology of the cochlea and labyrinth.

Apoptosis has been shown to be the major pathway of cell death in various conditions, including aminoglycoside toxicity,[53] cisplatin

toxicity,[115] hypoxia,[116] acoustic trauma,[77] neurotrophin withdrawal,[113,115] and presbycusis.[117] Neurotrophic support may be crucial in preventing apoptosis. Malgrange and associates[113] prevented apoptosis in explanted outer hair cells by administering various neurotrophins. In the same experiment, these investigators prevented apoptosis by administering protein synthesis inhibitors. These observations imply that neurotrophic support (among other things) provides tonic suppression of proteins in the apoptotic cascade. Rong and colleagues[118] provided proof of this notion by showing that nerve growth factor (NGF) promotes cell survival by regulating proteins that are essential to the apoptotic cascade.

Free radicals also play an important role in hearing loss. They are primary inducers of apoptosis (as in free radical–generating aminoglycoside-iron compounds) and secondary consequences of cochlear insult (as in the oxidative stress of excitotoxicity). The generation of free radicals may be a required step in apoptosis. There is a strong connection between free radicals and neurotrophins. Dugan and coworkers[119] showed that removal of NGF from cultured auditory neurons caused a rapid increase in intracellular free radical generation and subsequent apoptosis. Reapplying NGF rapidly diminished the concentration of these free radicals and decreased apoptotic cell death. Shulz and coworkers[4] showed that inhibition of caspases (proteases associated with apoptosis) not only blocked apoptosis, but also blocked the formation of free radicals, implying that the formation of free radicals is downstream from caspases in the apoptotic cascade. Likewise, exogenous brain-derived neurotrophic factor (BDNF) not only protects cisplatin-exposed neuronal cultures from apoptosis, but also reduces the free radical species in the culture.[120] These results have led researchers to believe that free radicals are effector molecules in the apoptotic cascade, and that they can be regulated not only by antioxidants, but also by neurotrophins.

Neurotrophins modulate calcium homeostasis,[94] regulate apoptotic proteins,[118] and alter expression of endogenous free radical scavengers,[4,119,120] and any of these functions may account for their otoprotective effects. Several specific neurotrophins have been used for in vivo models of noise-induced hearing loss with variable success. Glial cell line–derived neurotrophic factor (GDNF) greatly enhances the survival of guinea pig cochlear neurons (but not hair cells) if administered 4 days after noise-induced trauma.[121] Keithley and associates[122] showed that hair cells are preserved if GDNF is administered before or immediately after toxic noise exposure. Damage was attenuated if GDNF was applied after 2 hours, but not after 4 hours. The method of delivery in this experiment was topically to the RWM.

Shoji and coworkers[123] found that GDNF provides bilateral protection even when administered in only one ear. Because their experiment used long-term application of GDNF, it may have diffused through the cerebrospinal fluid. Another possibility is that GDNF influences higher cortical centers in the auditory pathway, which has a rich efferent projection and is highly bilateral. Yamasoba and colleagues[124] combined GDNF with antioxidants to determine whether synergistic protection could be achieved. They found that additional functional, but not morphologic, protection was achieved, implying that the interventions in antioxidant and neurotrophin therapy are additive, not synergistic. Neurotrophin-3 (NT-3) showed equal or greater physiologic and histologic protection from acoustic trauma relative to GDNF (with the same animal model).[125] BDNF and fibroblastic growth factor show no protective effect against toxic noise.[125]

Many experimental otoprotective treatments have been shown to be effective only if administered prophylactically or immediately after injury. Many of these injuries clinically manifest long after the initial insult, precluding any hope of salvaging hair cells. There is a much larger window of opportunity to salvage the auditory neurons after injury, however. Although there is rapid degeneration of the peripheral processes of the auditory nerve after inner hair cell loss (within hours or days), the degeneration of SGN soma and central auditory projections takes much longer (weeks to years).[126] There is intense interest in the use of neurotrophic agents to enhance SGN survival, mostly in anticipation of future cochlear implantation. This is because the hearing benefits of cochlear implants are directly related to the number of surviving auditory neurons[127] and their proximity to stimulating electrodes.[126,128]

Neurotrophins are essential not only for the normal development of the central and peripheral nervous systems, but also for their maintenance and normal function.[126] The destruction of cochlear hair cells and supporting cells because of exogenous insults (e.g., ototoxicity, acoustic trauma) results in the de facto withdrawal of trophic support. The ensuing degeneration of SGNs after cochlear insult is most likely a result of the loss of cochlear trophic support, rather than from direct toxic insult.[126] Withdrawal of neurotrophins in vitro causes apoptosis in SGNs.[116] The application of antisense oligonucleotides to inhibit expression of BDNF and NT-3 induces programmed cell death in explanted auditory neurons.[115] Apoptosis inhibitors have been shown to block neurotrophin withdrawal–induced cell death.[116]

Numerous neurotrophins have been shown to be effective in preventing SGN demise after experimental destruction by various insults. Exogenously applied NT-3,[129,130] BDNF,[130-132] BDNF in combination with a ciliary neurotrophic factor analogue,[133] NGF,[134] and 4-methylcatechol (an inducer of NGF synthesis)[135] enhance SGN survival after aminoglycoside insult. BDNF and GDNF enhance SGN survival after acoustic trauma[121]; BDNF[136] and GDNF[137] enhance SGN survival after cisplatin exposure. The enhancement of SGN survival with electric stimulation may also involve neurotrophins because depolarization induces an autocrine neurotrophin loop.[138] A strategy to use neurotrophins to enhance SGN survival before implantation and electric stimulation to promote autocrine neurotrophin release after implantation may be effective in enhancing hearing outcomes in patients receiving cochlear implants.

Aside from neuronal salvage, numerous studies have documented the ability of neurotrophins to stimulate innate regenerative and repair capabilities in auditory cells. Enfors and colleagues[129] showed that NT-3 induced neurofilament growth after aminoglycoside ototoxicity, as evidenced by the appearance of Gap 43, a growth cone marker. Lefebvre and colleagues[139] showed that NGF is a potent stimulator of repair and reinnervation in auditory neurons. Ylikoski and coworkers[121] showed that GDNF has potent trophic effects on the cochlear-neuron perikarya. Fibroblastic growth factor alone[140] or in combination with BDNF[141] produces a dose-dependent increase in the number and length of SGNs. These and other similar findings are significant because closer contact between stimulating electrodes on cochlear implants and auditory neurons leads to reduced stimulation thresholds, increased dynamic range of responsiveness, and potentially enhanced specificity of excitation.[126,128] It is possible that these growth-stimulating properties of neurotrophins could be exploited to engineer intimate contact with implanted electrodes, such that increasingly focused tonotopic stimulation could be matched to advanced signal-processing strategies.[126]

Preliminary studies on the interactions between auditory neurons and alloplastic cochlear implant materials have been performed, paving the way for the development of implant-tissue interfaces for the next generation of cochlear prostheses.[142] Neurotrophins are expected to play a role in this effort to unite biologic and synthetic materials, an effort that may lead to the development of a fully functional artificial cochlea. Neurotrophins have also been tested as a secondary intervention after aminoglycoside toxicity. Ruan and colleagues[143] used long-term infusion of NT-3 and BDNF in the setting of aminoglycoside challenge, and found that NT-3, and to a much lesser extent BDNF, protected hair cells from aminoglycoside toxicity. Although the mechanism of action is unclear, the authors speculate that just as SGNs rely on trophic support from hair cells, these hair cells may have trophic dependence on SGNs. This notion is supported by an increasing body of evidence showing that there is anterograde transport, transcytosis, and recycling of neurotrophic factors in neural networks.[144] Hair cell survival is partly determined by neurotrophin support. Malgrange and colleagues[113] tested a panel of 13 different growth factors and found that acidic fibroblastic growth factor, insulin-like growth factor-1, epidermal growth factor, transforming growth factor-β1, and GDNF were able to sustain adult explanted outer hair cells (which otherwise experience rapid demise in in vitro culture media).

Table 155-1

Features of Various Gene Therapy Vectors

Vector	Genome	Insert Size	Site	Efficiency	Cell Division	Expression	Advantages	Disadvantages
AAV	ssDNA	4.5 kB	Genome	Variable	Not required	Permanent	No human disease	Difficult to produce
Retrovirus	RNA	6-7 kB	Genome	Low	Required	Permanent	Suited for neoplastic cells	Insertional mutagenesis
Adenovirus	dsDNA	7.5 kB	Episome	Moderate	Not required	Transient	Ease of production	Inflammatory response
Herpesvirus	dsDNA	10-100 kB	Episome	Moderate	Not required	Transient	Neural tropism	Human disease
Plasmid	RNA/DNA	Unlimited	Episome	Very low	Not required	Transient	Safe, easy production	Low transfection
Liposome	RNA/DNA	Unlimited	Episome	Very low	Not required	Transient	Safe, easy production	Low transfection

Summary

One of the goals of rational drug discovery is to dissect the specific molecular mechanisms in a given pathophysiologic process, and determine where they are redundant and where they are independent. If nonredundant mechanisms can be identified, synergistic strategies to treat the pathologic process can be devised. In the context of hearing loss, multiple interventions can be constructed that are nonredundant and synergistic, as in the combination of an antioxidant, a neurotrophin, and an apoptosis inhibitor. The new understanding of the molecular mechanisms of hearing loss is creating quantum advances in otopharmacology by supplying researchers with a multitude of potential targets for therapeutic intervention and prosthetic augmentation.

Gene Therapy

Although gene therapy of the inner ear is a technology still in its infancy, advances in pharmacologic and gene therapy offer prospects to manage degenerative disorders of the labyrinth. Much of the experimental data so far concern the development of suitable vectors for gene transfer and methods of delivering these vectors to their target. Some teams have reported successful gene transfer of therapeutic genes, however. These advances may be able to stimulate hair cell regeneration and, ultimately, restoration of the transduction potential within the organ of Corti.

Otologic science was revolutionized by the observation that avian hair cells regenerate after insult.[145,146] Since then, barriers to inducing regeneration within the mammalian cochlea have been elucidated, including strategies that can address mature and damaged inner ear.[147] Beyond hair cell regeneration, there is the related problem of inducing synaptogenesis and nerve regrowth to these newly created hair cells.[148] These and a host of other concerns are currently being investigated. The ultimate vision is to orchestrate through pharmacology and gene therapy a recapitulation of the embryonic events that lead to a functioning auditory system. Although this section deals mainly with gene therapy, there are exciting new stem cell therapies that address similar topics on the horizon as well.[149]

Vectors

There is no single ideal vector for gene transfer because each vector has characteristics that make it more or less suitable to each application (Table 155-1). The length of the gene to be transferred, the specific inner ear tissue that is targeted, the desired method of delivery, and the duration of transgene expression are all factors that determine the most suitable vectors. Various viral and nonviral vectors are available to the gene therapist. The variability in the transgene expression pattern with different gene transfer vectors is likely a consequence of numerous factors, including the size of the viral particle, presence or absence of viral receptors, and mode of delivery. Inspection of Table 155-1 allows for some generalization about the ability of various viral vectors in transfecting cochlear tissues. The spiral ganglion cells, spiral ligament, and Reissner's membrane were transfected by every virus tested. Only adenovirus showed transgene expression within the stria vascularis. Immune response was present in the cochlea after transfection with adenovirus, herpes simplex virus, and vaccinia virus.

Delivery

Local gene therapy to the inner ear is feasible because of its relatively closed anatomy. Developing a delivery method for genetic vectors to the inner ear without causing local destruction is a significant obstacle. Several delivery methods have been used, including mini–osmotic pump infusion (either through cochleostomy or through the RWM), microinjection into the RWM, injection into the endolymphatic sac, and diffusion across the RWM after local Gelfoam placement. Cochleostomy has been shown to cause histopathologic alterations (including localized surgical trauma and inflammation), and may lead to hearing loss.[150]

Introduction of viral vector by means of infusion with a mini–osmotic pump was characterized by evidence of trauma at the basal turn adjacent to the cochleostomy associated with an inflammatory response and connective tissue deposition. Carvalho and Lalwani[150] showed preservation of preoperative auditory brainstem response thresholds in the lower frequencies (1 to 2 kHz), mild postoperative elevation of thresholds (<10 dB) in the midfrequencies (4 to 8 kHz), and marked increase (>30 dB) in auditory brainstem response thresholds at higher frequencies (>16 kHz) after mini–osmotic pump infusion by way of a cochleostomy.

Several studies have documented that direct microinjection through the RWM can be accomplished without causing permanent hearing loss or tissue destruction seen with cochleostomy.[56,124] Histologically, cochleae microinjected through the RWM showed intact cochlear cytoarchitecture and an absence of inflammatory response 2 weeks after microinjection through the RWM. Microinjection through the RWM did not cause permanent hearing dysfunction.[151]

The potential for surgical trauma, inflammation, and hearing loss associated with these infusion or microinjection techniques led to the investigation of a less invasive delivery method. Diffusion across the RWM has been shown to be an effective, atraumatic, but vector-dependent method of delivery for gene transfer vectors. Jero and coworkers[152] investigated the potential to deliver various vectors across an intact RWM by loading vectors onto a Gelfoam patch that was placed in the round window niche. Adenovirus and liposome vectors, but not the AAV vector, effectively infected inner ear tissues, as evidenced by detection of reporter genes. Lipocomplexed plasmid vectors have also been shown to cross the RWM effectively.[153]

Preclinical Applications

Most of the preclinical applications for gene therapy in the inner ear have concerned neurotrophin therapy. This is because for some applications of exogenous neurotrophins (e.g., to maintain SGN survival or to induce neurite outgrowth), the neurotrophins must be applied long-term. In this sense, gene therapy is being used as a long-term drug delivery strategy, rather than to replace defective or missing genes.

Staecker and colleagues[130] used a herpes simplex virus-1 vector to deliver BDNF to the inner ear. After neomycin injection, the gene therapy group showed a 94.7% salvage rate for SGNs, in contrast to a 64.3% loss of SGNs in control animals. Although BDNF staining was ubiquitous in inner ear tissues, this was not the case for the reporter gene, β-galactosidase. Although only 50% of cells were transfected (as determined by the number of β-galactosidase cells), this was enough to cause cochlea-wide BDNF distribution and to ensure 95% SGN survival. The authors speculate that SGNs must require only a few BDNF-producing cells to ensure the survival of the entire ganglion.

Lalwani and colleagues[154] used in vitro and in vivo models to test effectiveness of an AAV vector for BDNF transfer. They found a significant survival effect from controls after aminoglycoside challenge in cochlear explants. Although direct measurements of BDNF could not be recorded, the vector's ability to salvage SGNs was tested against a gradient of known BDNF concentrations. They found that the vector system was able to achieve the same protective effects as 0.1 ng/mL of BDNF. This dose is subtherapeutic because the most efficient dose was determined to be 50 ng/mL, a concentration of BDNF that results in almost total SGN protection. In the in vivo experiment, animals infused with AAV-BDNF with a mini-osmotic pump displayed enhanced SGN survival. The protection from AAV-BDNF therapy was region specific; there was protection at the basal turn of the cochlea, but not the middle or apical turn. The authors propose that this regional selectivity is a pharmacokinetic phenomenon.

NT-3 gene transfer for protection against cisplatin-induced ototoxicity has been achieved by the use of a herpes simplex virus-1 amplicon–mediated delivery system.[155,156] Chen and associates[156] established efficacy of the vector in an in vitro study, in which amplicon-mediated transfer of NT-3 (shown by production of NT-3 mRNA proteins and by reporter gene expression) conferred increased survival to cochlear explants after cisplatin exposure. Bowers and colleagues[155] confirmed these effects in an in vivo model, in which amplicon-mediated transfer of NT-3 to SGNs suppressed cisplatin-induced apoptosis and necrosis. The authors suggest that these findings not only may be useful to prevent cisplatin-related injury, but also may provide preventive treatment for hearing degeneration because of normal aging.

Several studies have established the efficacy of an Ad vector carrying the GDNF gene (Ad.GDNF) to protect against various ototoxic insults. When administered before aminoglycoside challenge, Ad.GDNF significantly protects cochlear[157] and vestibular[158] hair cells from cell death. Pretreatment with Ad.GDNF also provides significant protection against noise-induced trauma.[50] Finally, Ad.GDNF enhances SGN survival when administered 4 to 7 days after ototoxic deafening with aminoglycosides.[159]

Some studies have used gene therapy to induce the expression of target proteins other than neurotrophins. Several studies have transduced genes that express proteins that inhibit the apoptosis cascade, and protect against ototoxic insult. Liu and associates[160] used an AAV vector to induce Bcl-x(L), an apoptosis inhibitor to mitigate aminoglycoside toxicity. Chan and colleagues[161] successfully induced the expression of the X-linked apoptosis inhibitor using an AAV virus, and this proved to be protective against cisplatin toxicity. In another line of research, attempts are being made to overexpress *Math1* through gene transfer. The significance of *Math1* gene is that it is intimately associated with cochlear and vestibular stem cells, and the overexpression of the *Math1* protein stimulates hair cell regeneration. Izumikawa and colleagues[162] used an adenovirus vector to induce overexpression of *Math1* after aminoglycoside deafening, and showed cellular and functional repair in the organ of Corti. Similarly, Staecker and coworkers[163] used an adenovirus vector to induce expression of *Math1* after vestibulotoxic aminoglycoside exposure, and successfully induced the regeneration of vestibular hair cells. These and other studies are adding to the list of potential targets for gene therapy for the inner ear.

Safety Concerns

Early investigations in the development of gene transfer in the cochlea identified potential safety concerns. Through use of AAV as the gene therapy vector, Lalwani and associates[164] observed transgene expression within the contralateral cochlea of the AAV-perfused animal, albeit much weaker than within the directly perfused cochlea. Subsequently, Stover and colleagues[165] showed transgene expression in the contralateral cochlea using adenovirus. This finding of transgene expression in the contralateral cochlea raises concern about dissemination of the virus from the target tissue. The appearance of the virus, distant from the site of infection, may be due to its hematogenous dissemination to near and distant tissues; however, this is unlikely.[165,166] Other possible explanations include migration of AAV by way of the bone marrow space of the temporal bone[166] or the cerebrospinal fluid space to the contralateral ear.[165,166] The perilymphatic space into which the virus is perfused is directly connected to the cerebrospinal fluid by way of the cochlear aqueduct; transgene expression within the contralateral cochlear aqueduct has been shown after introduction of the viral vector in the ipsilateral cochlea. Collectively, these results suggest potential routes for AAV dissemination from the infused cochlea through the cochlear aqueduct, or by extension through the temporal bone marrow spaces. Subsequent investigations have shown that dissemination outside the target cochlea can largely be eliminated by the use of microinjection or RWM application of vector, and avoidance of the infusion technique.[152,167,168]

Summary

A crucial step forward toward the eventual application of gene therapy for hearing disorders has been accomplished: viral and nonviral vectors have been shown to introduce and express exogenous genes capably into the peripheral auditory system. Future refinements will include the development of newer hybrid vectors that assimilate the infectivity and stability of the viral vectors and the safety of liposomes. The hybrid vectors will largely replace the current generation of vectors. The preferred mode of introduction of gene therapy vectors will be one that minimizes tissue damage and hearing loss, such as microinjection or application of the vector at the RWM. Safety concerns, especially regional and distant dissemination of the therapeutic agent, will need to be monitored and minimized.

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CHAPTER ONE HUNDRED AND FIFTY-SIX

Otologic Symptoms and Syndromes

Carol A. Bauer

Herman A. Jenkins

Key Points

- Otalgia in the absence of detectable ear pathology can arise from a wide range of sources and requires a complete head and neck examination for accurate diagnosis.
- Chronic painful bloody otorrhea should prompt an evaluation for malignant otitis externa or neoplasia of the external auditory canal.
- The most informative features in evaluating hearing loss are the time course of the loss, associated symptoms, and age of the patient.
- The most common bacterial pathogens causing otitis externa are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
- Radiographic imaging of the temporal bone with high-resolution CT is essential in the evaluation of clear watery otorrhea.
- A complete history with a careful description of the symptoms is needed to discriminate between central and peripheral causes of vertigo.

Various symptoms can be either suggestive or diagnostic of ear disease. Accurate clinical assessment is facilitated by understanding the significance of symptom combinations and the relative frequency of specific otologic diseases in different patient populations. This chapter reviews the common symptoms associated with otologic diseases and the diagnoses to be considered when evaluating these symptoms. Common symptoms that indicate an otologic problem are otorrhea, otalgia, aural fullness, hearing loss, vertigo, and tinnitus. The symptoms of hearing loss, vertigo, and tinnitus are discussed in other chapters, and are addressed only briefly here.

Otorrhea

In adults and children, otorrhea can arise from numerous sources (external ear canal, middle ear, mastoid) and may have a variety of etiologies (Box 156-1). Diagnostic considerations and subsequent treatment plans are directed by the source of the otorrhea; the age of the patient; the type of otorrhea (clear, mucoid, purulent, or bloody); the nature of the drainage (acute, chronic, or pulsatile); and the presence of other symptoms, such as otalgia, neurologic deficits, or associated systemic disease or symptoms. Evaluation requires meticulous suctioning of secretions under a microscope to identify the source of the drainage, and to differentiate between a primary infection or purulent drainage occurring secondary to an underlying inflammatory process.

Common causes of otorrhea differ between adults and children. In children, otorrhea is caused most commonly by either acute otitis media with tympanic membrane rupture or chronic otitis media in the presence of a tympanic membrane perforation. In adults, otorrhea results most commonly from either external otitis or chronic otitis media with a perforation. The initial history and physical examination should be directed toward establishing the time course of the symptom and the source of the otorrhea (ear canal, middle ear, mastoid).

The diagnosis of external otitis as the source of purulent otorrhea is suggested by a history of ear trauma or swimming-related water contamination of the canal. Trauma resulting in external otitis may occur from the use of cotton-tip swabs, irrigators for cerumen removal, in-the-canal hearing aids, or digital ear thermometers. A history of otalgia and drainage after swimming easily leads to a diagnosis of external otitis. Although typically painful, there are usually no additional systemic symptoms associated with this localized infection. The typical findings on physical examination include an exquisitely tender ear canal that is partially to completely obstructed by edematous skin, and associated with preauricular tenderness.

Purulent otorrhea may develop secondarily in patients with chronic dermatitis or eczema of the ear canal, without any prior history of trauma or water contamination. Bacterial or fungal infections may complicate this chronic skin condition. Symptoms of chronic dermatitis of the ear canal include complaints of dry, itchy ears. Secondary infection of chronic dermatitis of the ear canal is usually painless. Important points include a history of recent use of topical antibiotic ointments or solutions that may cause an localized allergic skin reaction with canal pruritus, edema, and purulent drainage. Physical examination should document the presence of fungal hyphae in the canal, keratin debris from chronic dermatitis, or, uncommonly, a canal cholesteatoma or keratoma. After suctioning all purulent material from the canal, the tympanic membrane must be examined for evidence of a retained foreign body, such as a pressure equalizing tube with localized granulation tissue, as the source of the otorrhea.

The most common bacterial pathogens causing external otitis are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Less commonly, other aerobic, facultative, and anaerobic organisms have been cultured from infected ears. Rarely, external otitis results from a local or regional infection that involves the ear secondarily. *Actinomyces israelii* is an

Box 156-1

Sources of Otorrhea

External Canal
Otitis externa (fungal, bacterial, viral)
Necrotizing otitis externa
Acute dermatitis
Keratosis obturans
Canal cholesteatoma
Neoplasm
Regional infection (parotid)

Tympanic Membrane
Granulation tissue
Granular myringitis
Bullous myringitis
Retraction pocket with cholesteatoma

Middle Ear
Acute otitis media with perforation
Chronic otitis media with perforation
Neoplasm

Mastoid
Mastoiditis, acute or chronic, with perforation
Granulomatous disease
Cholesteatoma
Neoplasm

Cerebrospinal Fluid
Temporal bone fracture
Tegmen defect
Cochlea deformity
Hyrtl's fissure

anaerobic gram-positive bacterium that can cause external otitis from a primary dental or parotid infection. This infection may manifest as refractory otitis externa with granulation tissue in the ear canal and thick yellow otorrhea. Recognition of this entity is important because treatment involves surgical débridement and prolonged antibiotic therapy.[1]

Malignant or necrotizing external otitis is a locally aggressive, potentially progressive form of otitis externa. Inflammation and necrosis can extend beyond the ear canal skin to involve underlying cartilage and bone. Extensive disease involves local and regional osteomyelitis of the temporal bone, resulting in severe, deep ear pain. Malignant otitis externa occurs most commonly in adults. The diagnosis should be considered, however, in children with poor general health or concurrent systemic disease with acute onset of painful otorrhea. Fifteen cases of malignant external otitis occurring in infants and children 2 months to 15 years old have been reported in the literature.[2,3] Risk factors in these patients included poor general health, immunosuppression, and diabetes mellitus. Common presenting findings on physical examination include granulation tissue within the external auditory canal, preauricular and auricular edema and erythema, tympanic membrane necrosis, and facial nerve paralysis. *P. aeruginosa* is the most common causative organism in children and adults with malignant external otitis.

Fungal infections of the ear (otomycoses) are typically limited to the external ear canal as a superficial infection. Rarely, these infections are invasive and involve the temporal bone. Common fungal species infecting the external ear canal are *Aspergillus niger* and *Candida albicans*. The former is easily recognized as pigmented fungal tufts atop a tangle of hyphal threads resembling a ball of cotton. *Candida* spp. also may colonize the ear canal, especially in patients previously treated with prolonged courses of antibiotic eardrops. A canal infected with *Candida* appears wet and macerated, filled with soft, curdlike debris. If the fungal infection has an associated bacterial component, the fungal elements may not be immediately evident. Rarely, the external ear canal and mastoid are primarily involved with coccidioidomycosis, which may resemble eczema or an allergic dermatitis.[4]

Secondary mycosis of the temporal bone is quite rare and may arise from a primary focus of infection involving the meninges or the paranasal sinuses. Causative agents include *Cryptococcus, Candida, Blastomyces,* and *Mucor*. Primary otogenic invasive fungal infections can occur in immunocompromised hosts who are human immunodeficiency virus positive, elderly individuals, and patients with diabetes mellitus. These cases may develop invasive fungal disease within the mastoid and temporal bones, resulting in rapidly progressive hearing loss and facial paralysis. *Aspergillus fumigatus* and *Aspergillus flavus* are sources of invasive fungal mastoiditis with serious morbidity and mortality.

An uncommon cause of purulent otorrhea arising from the external canal in children is infection of a first branchial cleft cyst. In some forms of this congenital anomaly, there is a sinus tract adjacent to the external canal causing localized edema, whereas in others a fistula may be present with an external opening into the external ear canal. The anomaly may not be recognized until drainage and swelling of the ear canal occur. An even rarer source of secondary external canal otorrhea in children and adults is a primary infection of the parotid gland that extends into the external ear canal through the fissures of Santorini. These fibrous channels within the cartilaginous ear canal can serve as a direct route of disease extension.

Severe otalgia associated with bloody or serous otorrhea should prompt examination of the canal and tympanic membrane for evidence of vesicles. Bullous external otitis and myringitis result in hemorrhagic vesicles on the bony external canal and tympanic membrane. This uncommon infection causes exquisite ear pain out of proportion to the physical examination. The infection may be viral, but *Mycoplasma pneumoniae* and *Haemophilus influenzae* have also been cultured from the vesicles. Conductive hearing loss secondary to an associated middle ear effusion often accompanies the localized infection. A mixed loss with a significant sensorineural component has been shown in 30% to 65% of cases of bullous myringitis in which audiometric assessment was performed. The hearing loss completely resolved in 60% of cases.[5,6]

Herpes zoster oticus (Ramsay Hunt syndrome) should be considered if vesicles with an erythematous base are evident on the external canal, pinna, or soft palate. Significant otalgia described as a burning sensation is present with this infection, along with hearing loss, vertigo, and facial paralysis.

Tympanic Membrane, Middle Ear, and Mastoid Sources of Otorrhea

If the physical examination shows a normal-appearing external ear canal, the source of the otorrhea is the tympanic membrane, the middle ear, or the mastoid. Acute otitis media, chronic otitis media, and cholesteatoma are the most common sources of purulent or mucoid drainage from the middle ear and mastoid. Less common causes of chronic otorrhea from the middle ear and mastoid are neoplasms that become secondarily infected and systemic diseases with otologic manifestations.

If a patient with chronic otorrhea has undergone prior mastoid surgery, the physical examination should be directed toward establishing whether the drainage is from a superficial infection of the mastoid cavity or is caused by recurrent or residual mastoid disease. When the mastoid cavity is inspected, any anatomic factors should be noted that predispose toward poor aeration and bowl hygiene, such as a small meatus, high facial ridge, or large dependent mastoid tip. In these cases, the tympanic membrane may appear normal, and the middle ear may be aerated, but because of poor hygiene the mastoid bowl collects debris, and a superficial infection develops. The infection may be fungal or bacterial in nature; examination with meticulous cleaning under a microscope establishes the diagnosis.

In most cases, débridement and treatment with topical antifungal or antimicrobial eardrops or acidifying and drying agents, such as boric acid and alcohol solution, or dilute vinegar solution, suffice as manage-

ment. In chronic infection, granulation tissue and mucosalized epithelium in the bowl can develop, however, requiring more aggressive treatment with chemical cauterization. Meticulous inspection of the mastoid bowl also reveals evidence of retained mastoid air cells or recurrent cholesteatoma debris as the cause of recurrent otorrhea. Revision mastoid surgery is usually required to eliminate these sources of infection.

In the case of otorrhea from acute otitis media, the drainage may be bloody, mixed with mucus, or mucopurulent, and is typically short-lived. Bloody or purulent otorrhea associated with pain also may occur either immediately or in a delayed fashion after placement of pressure equalization tubes. This otorrhea may occur because of granulation tissue obstructing the tube lumen, middle ear contamination after bathing or swimming, acute otitis media, or reflux of nasopharyngeal secretions through the eustachian tube into the middle ear.

Neglected or inadequately treated acute or chronic otitis media may progress to acute coalescent mastoiditis or chronic bacterial otomastoiditis. Typically, acute otomastoiditis manifests with otalgia, mastoid tenderness, and purulent drainage from the middle ear. Uncommonly, mastoiditis may result from obstruction of the aditus ad antrum; the tympanic membrane and middle ear appear normal in this situation. In acute mastoiditis, the ear canal typically is edematous and tender, resembling external otitis with retroauricular extension. In addition to external canal edema, patients with acute mastoiditis may have auricle protrusion, mastoid tenderness, and swelling, and possibly systemic symptoms of fever. Additional symptoms may be present if there are aural or intracranial complications of the acute or chronic infection. Aural complications include subperiosteal abscess, petrositis, facial paralysis, and labyrinthitis. Intracranial complications include extradural abscess; thrombosis or thrombophlebitis of the sigmoid sinus, transverse sinus, or sagittal sinus; subdural abscess; brain abscess; meningitis; and otitic hydrocephalus. A high index of suspicion and a thorough neurologic examination are required to detect possible aural and intracranial complications of a mastoid infection.

Acquired cholesteatoma is a common cause of painless, recurrent purulent otorrhea in adults and children. The otorrhea may be scant or profuse depending on the extent of the disease, and whether the keratin debris is infected. There is usually an associated long-standing hearing loss. Vestibular symptoms are typically not present, unless there is extensive bone destruction by the cholesteatoma. Erosion of the lateral semicircular canal with formation of a labyrinthine fistula may occur, and the patient may note dysequilibrium that is either spontaneous or induced by loud sounds (Tullio's phenomenon) or positive pressure applied to the external ear canal. Diagnosis of cholesteatoma as the source of otorrhea is evident after meticulous cleaning of the ear canal and examination with binocular microscopy. Typically, a retraction pocket is seen in the posterosuperior quadrant of the tympanic membrane or in the pars flaccida region. The otorrhea and keratin debris emanating from the abnormal retraction are indicative of the acquired cholesteatoma.

Granular myringitis is an uncommon, idiopathic, inflammatory process involving the tympanic membrane. Granulation tissue and mucosalized epithelium extend over patchy areas of the tympanic membrane. In extensive cases, the entire tympanic membrane is thickened, and the granulation tissue exudes a thin transudate that may become secondarily infected.[7]

Systemic Disease Associated with Otorrhea

Noninfectious Causes

Granulomatous diseases of the temporal bone are uncommon. Presenting symptoms can mimic acute or chronic mastoiditis. Children with histiocytosis of the temporal bone can present with symptoms of painful purulent or bloody otorrhea. The three forms of histiocytosis (eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease) all may involve the temporal bone.[8] In addition to complaints of localized ear pain, there is evidence of suppurative drainage from the middle ear and mastoid, granulation tissue within the external auditory canal, local swelling of the postauricular or preauricular region, and bone destruction on radiographic imaging. Auditory and vestibular deficits, facial palsy, and lower cranial nerve deficits also may be present.[9]

Wegener's granulomatosis is a granulomatous disorder consisting of inflammatory vasculitis of the upper and lower respiratory tracts and kidney. Almost one fourth of patients have otologic disease at some point during their illness. Otologic involvement may manifest as a serous otitis media or a suppurative otitis media with either thickening or perforation of the tympanic membrane. Granulation tissue may be present within the middle ear and mastoid, causing a painless chronic otorrhea that is associated with conductive, sensorineural, or mixed hearing loss.[10] A high index of suspicion and confirmation with an elevated cytoplasmic antineutrophil cytoplasmic autoantibody titer facilitate the diagnosis.

Churg-Strauss syndrome is an autoimmune disease that may have otologic manifestations in the late stages of the disease. Asthma, recurrent sinusitis, peripheral neuropathy, eosinophilic infiltrates, systemic vasculitis, and peripheral eosinophilia are hallmarks of the disease. In advanced disease, otologic involvement may include a dense aural discharge, granulomatous eosinophilic infiltrates of the middle ear and mastoid, and severe to profound mixed hearing loss. Recognition of this entity is important because the disease is highly responsive to systemic steroids.[11]

Infectious Causes

Aural tuberculosis and nontuberculous mycobacterial mastoiditis are granulomatous infections with presentations that may mimic either otitis externa or chronic otomastoiditis in adults or children. The typical history is that of an indolent infection of the external canal or middle ear with chronic painless otorrhea that is thin, watery, or serous in nature. In documented cases of aural tuberculosis, patients have had acute otalgia with purulent drainage when a bacterial superinfection is present. Typically, patients with aural tuberculosis do not have a history of pulmonary infection or exposure to a known source of tuberculosis. The diagnosis of tuberculous or atypical mycobacterial otomastoiditis is suspected when the infection fails to clear after multiple treatments with antibiotics. The ear canal and middle ear have granulation tissue, polyps, and inflammatory tissue, all of which may be diffusely destructive. In addition, there may be associated cervical, postauricular, or occasionally preauricular adenopathy and systemic symptoms of fever and malaise. The physical examination findings of a postauricular fistula associated with preauricular adenopathy, a denuded malleus, and multiple tympanic membrane perforations are reported to be pathognomonic of aural tuberculosis. Facial palsy associated with aural tuberculosis has been reported in 45% of patients.[12-14]

Neoplastic Disease Causing Otorrhea

The presenting signs and symptoms of neoplastic involvement of the temporal bone include conductive and sensorineural hearing loss, otalgia, mastoiditis, facial nerve paralysis, and purulent or bloody otorrhea. The chronic purulent or bloody otorrhea can arise from neoplasms in the ear canal, middle ear, or mastoid. In adults, the most common neoplasms of the external canal causing otorrhea are squamous cell carcinoma, basal cell carcinoma, and ceruminous gland tumors. In the early stages of disease, these neoplasms may remain asymptomatic and unnoticed until a secondary bacterial infection develops. Advanced disease with temporal bone destruction is associated with chronic deep otalgia. Examination of the ear canal with binocular microscopy after removal of purulent debris may reveal the tumor as an erosive or fungating lesion. These lesions also may manifest as persistent granulation tissue that is refractory to routine management. Biopsy of the granulation tissue is indicated to rule out an underlying neoplastic process. Glomus tumors may be isolated to the middle ear or jugular foramen region and usually do not result in otorrhea. Large tumors may fill the mesotympanum and extend into the ear canal, however, resulting in bloody or purulent otorrhea. Performing a biopsy of glomus tumors extending into the ear canal can result in profuse bleeding and should be avoided.

Metastatic lesions to the temporal bone rarely manifest with otorrhea as an initial symptom. Primary tumors from the breast, lung,

kidney, prostate, and stomach are the common sources of temporal bone metastatic lesions.[15] These tumors metastasize predominantly to the petrous apex marrow through hematogenous dissemination. Metastatic involvement of the mastoid air cells and the tympanic cavity may occur. Lymphoma and leukemia also may infiltrate the petrous apex and subsequently involve mastoid air cells. Infiltration into the middle ear cleft along mucosal folds and into the fallopian canal and internal auditory canal is common.[16]

Acute myelogenous leukemia may involve the temporal bone by chloroma formations, which are masses of leukemic cells seen as discrete green collections within the mastoid or internal auditory canal. In children, uncommon neoplasms that result in otorrhea include histiocytosis, rhabdomyosarcoma, leukemia, and lymphoma. Because the presenting symptoms can resemble chronic otitis media with purulent or bloody otorrhea, granulation tissue, and aural polyps, diagnosis of the underlying neoplasm is often delayed.

Intracranial Sources of Otorrhea

The unique presentation of continuous or intermittent clear otorrhea may represent cerebrospinal fluid (CSF). Clear otorrhea may manifest spontaneously through a perforated tympanic membrane or through a pressure equalizing tube. It may be caused by an underlying congenital anomaly or an idiopathic dural dehiscence within the temporal bone. CSF otorrhea may occur as a direct result of trauma or as a complication of neoplasia, infection, or previous surgery. Regardless of the etiology, all cases of clear otorrhea must be investigated because of the risk of meningitis associated with a persistent CSF leak. If possible, the clear fluid should be collected and the sample analyzed for the presence of β_2-transferrin. This is a protein found in CSF and perilymph, but not in blood, nasal secretions, or inflammatory effusions.[17] If the fluid is identified as CSF, immunization for *Streptococcus pneumoniae* should be considered to prevent meningitis, in addition to pursuing appropriate measures directed to stop the CSF leakage. Occasionally, serous discharge from chronic mastoiditis (or through a ventilating tube) can be profuse and mimic CSF leakage.

Radiographic imaging using high-resolution computed tomography (CT) is essential in the diagnostic evaluation of patients with clear otorrhea. Axial and coronal views should be obtained and evaluated for evidence of congenital labyrinthine abnormalities, erosive changes within the mastoid air cells, dehiscence of the middle or posterior cranial fossa dural plates, or temporal bone fractures.

Congenital labyrinthine abnormalities are an uncommon cause of CSF otorrhea. The most common labyrinthine anomaly associated with spontaneous CSF leak is a Mondini malformation. The leak may manifest as recurrent meningitis in childhood or as intermittent leakage of clear fluid from a tympanic membrane perforation or myringotomy tube. CSF leakage occurs through a defect in the lamina cribrosa of the internal auditory canal in association with a defect in the stapes footplate. A high index of suspicion should be maintained when evaluating a child with a history of recurrent clear otorrhea and sensorineural hearing loss. A much rarer source of CSF in the middle ear is through a persistently patent perilabyrinthine pathway, such as a persistent Hyrtl's fissure. This bony cleft extends medially from below the round window niche to the posterior fossa and normally ossifies during development.[18] In the absence of normal ossification, this tympanomeningeal fissure may persist as an abnormal connection between the middle ear and the subarachnoid space, resulting in a CSF fistula.

Spontaneous CSF leaks also may occur from the middle or posterior cranial fossae secondary to progressive erosion and weakening of the dura by aberrant arachnoid granulations. These leaks typically occur after the fifth decade, and manifest as a persistent unilateral effusion or profuse clear otorrhea after myringotomy.[19,20] The leakage site often is evident on CT scan as a dehiscent area of either the superior or the posterior surface of the temporal bone.

Temporal bone CSF leaks can also occur after mastoidectomy, skull base surgery, or any surgical approach to the internal auditory canal or cerebellopontine angle (e.g., translabyrinthine, middle cranial fossa, posterior cranial fossa). Inadequate dural closure at the time of surgery results in CSF leakage. Occasionally, the CSF leak occurs weeks, months, or years after temporal bone surgery in which dura was exposed but not damaged. In open mastoid cavities with exposed dura, subsequent infections may incite the formation of granulation tissue with subsequent weakening of the underlying dura. The weakened dura allows prolapse of either the temporal lobe or the cerebellum into the mastoid cavity. Over time, intracranial pressure results in erosion and exposure of the subarachnoid space with leakage of CSF. When this occurs, surgical exploration and direct dural repair with tissue grafts and supporting packing is necessary.

In an ear previously known to be normal, watery otorrhea after severe head trauma almost certainly represents meningeal laceration and CSF leakage. Egress of fluid from the ear canal occurs most commonly in cases of longitudinal temporal bone fractures because the tympanic membrane often is disrupted in these situations. Leakage of CSF from the external auditory canal occurs in 21% to 44% of temporal bone fractures.[21,22] Because the drainage typically is mixed with blood, the presence of CSF should always be suspected. If profuse clear otorrhea follows trauma that is confined to the external auditory canal and tympanic membrane, stapes dislocation and a congenital abnormality of the labyrinth are suggested. Prompt surgical exploration and, if appropriate, oval window sealing are necessary.

A rare source of clear, painless otorrhea that is not CSF in origin is gustatory otorrhea or Frey's syndrome of the external ear canal.[23] Excisional biopsy of the canal skin showing thickened skin with sudomotor gland hyperplasia is diagnostic. A parotid fistula to the external canal is another diagnostic consideration for symptoms of gustatory otorrhea.

Otalgia

Otalgia most commonly reflects either localized otologic pathology or a problem within a contiguous, periauricular structure. The physical examination usually reveals the source of the pain. It is common, however, for a patient to complain of ear pain and have no identifiable pathology within the ear. Evaluation of patients with otalgia is facilitated by a thorough understanding of the innervation of the ear. Appreciation of the anatomy underlying shared neural pathways and the potential causes of referred otalgia arising from a distant site enables an astute physician to reach a diagnosis when evaluating a patient with the complaint of ear pain.

The auricle, periauricular region, external canal, and middle ear are supplied with sensory afferents from the trigeminal, facial, glossopharyngeal, and vagal nerves, and the cervical plexus. The auriculotemporal branch of the mandibular division of the trigeminal nerve provides sensation to the tragus, anterior pinna, anterior lateral surface of the tympanic membrane, and anterosuperior external auditory canal wall. The vagus nerve provides sensation to the larynx, hypopharynx, trachea, esophagus, and thyroid gland. The auricular branch of the vagus nerve (Arnold's nerve) provides sensation to the concha, inferoposterior external auditory canal, tympanic membrane, and postauricular skin. The glossopharyngeal nerve provides sensory innervation to the oropharynx, tonsils, and tongue base. Jacobson's nerve is the tympanic branch of the glossopharyngeal nerve that provides sensation to the medial surface of the tympanic membrane, mucosa of the middle ear, eustachian tube, and mastoid air cells. The cervical roots C2 and C3 provide sensation to the postauricular region. The facial nerve innervates the skin of the lateral concha and antihelix, lobule, mastoid, posterior external auditory canal, and posterior portion of the tympanic membrane.

Primary Otalgia

Primary otalgia arises from local or regional pathology. Sources of primary otalgia include acute otitis media, otitis externa, mastoiditis, eustachian tube dysfunction, cerumen impaction, inflammation or infection of the auricle, or ear trauma. Regional causes include temporomandibular joint dysfunction and periauricular lymphadenopathy from scalp or neck infections.

Referred Otalgia

Pain may be referred to the ear from distant sources, such as periodontal or dental disease, parotitis, sinusitis, thyroiditis, tonsillitis, laryngitis, or hiatal hernia with gastroesophageal reflux. Referred pain to the ear

can arise from any structure within the head and neck that shares a common neural pathway with the temporal bone and periauricular region. In the initial assessment, examination of the ear indicates whether the otalgia is local or regional in origin. If the ear examination is normal, it is helpful to ask the patient to point with one finger to the area of maximal pain.

The trigeminal nerve has a wide sensory distribution throughout the head and neck. Infection and neoplasms within the nasal cavity or paranasal sinuses, particularly the sphenoid or maxillary sinuses, can cause irritation of the vidian nerve, resulting in referred otalgia. Contact points between the turbinates and septal spurs can cause a similar type of pain. Nasopharyngeal surgery and neoplasms and infections in this region are common sources of referred otalgia. In children, erupting dentition is the most common cause of referred ear pain, which is recognized as ear pulling in preverbal children. Similarly, an impacted molar in an adult may cause symptoms of ear pain. Dental malocclusion resulting from temporomandibular joint dysfunction (Costen's syndrome) can cause referred ear pain from masticator muscle spasms. A history of excessive gum chewing, malocclusion, and bruxism may suggest this diagnosis. Sluder's neuralgia consists of lancinating pain in the lower face that radiates to the orbit, temple, forehead, and upper neck. The sphenopalatine branch of the trigeminal nerve is the source of this pain.

The facial nerve can be involved in referred ear pain in cases of geniculate neuralgia, Bell's palsy, and herpes zoster oticus. The ear pain of herpes zoster oticus can occur even in the absence of a significant vesicular eruption. The otalgia associated with Bell's palsy frequently occurs before the onset of facial paralysis.

The glossopharyngeal and vagus nerves can transmit referred ear pain as a result of pathology originating from anywhere within the upper aerodigestive tract. The ninth cranial nerve can be stimulated from pathology in the pharynx, such as tonsillitis, postoperative tonsillectomy, peritonsillar abscess, and neoplasms. Lingual tonsillitis and impacted foreign bodies within the tongue can also cause otalgia. Eagle's syndrome consists of ear pain secondary to stretching and irritation of the glossopharyngeal nerve from elongation of the styloid process. Glossopharyngeal neuralgia is similar to tic douloureux or trigeminal neuralgia. The pain is sharp and lancinating in quality, and originates in the tongue base, soft palate, or tonsillar fossa and radiates to the ear. Rosenmüller's fossa may be the trigger zone with this form of neuralgia.

Neoplasms within the larynx and esophagus have long been recognized as causes of referred otalgia. Ulcerations, foreign bodies, and reflux also can be seen in this manner. Chronic or subacute inflammation of the thyroid gland may cause referred ear pain through stimulation of the vagus nerve.

Aural Fullness

Patients often describe aural fullness as a stuffy feeling in the ear, ear pressure, or a clogged sensation. This subjective symptom may be associated with various ear disorders.

Aural fullness may occur because of obstruction of the external ear canal by cerumen, debris, or a foreign body. A sensation of fullness also may result from a soft tissue mass either in the middle ear or arising from the tympanic membrane. Cholesteatoma and neoplastic disease can manifest in this manner. If the patient's history reveals associated ear pain, drainage, or hearing loss, the physical examination easily establishes the diagnosis.

An abnormally patent or an obstructed eustachian tube also may elicit the sensation of aural fullness. Patients complain of autophony and of hearing breath sounds in the ear. A history of weight loss, steroid use, or hormonal therapy may precede the onset of symptoms. Evidence for an abnormally patent eustachian tube includes relief of symptoms (1) when the patient is supine or bending over, (2) during periods of nasal congestion, and (3) with sniffing. Evidence for a chronically obstructed eustachian tube orifice includes the inability to insufflate the ear with Valsalva's maneuver, chronic retraction of the tympanic membrane, and a history of nasal congestion and allergic disorder.

Aural fullness is part of the symptom complex of Meniere's disease. When the fullness is associated with fluctuating hearing and discrete spells of vertigo, its significance is apparent. Aural fullness also may occur as the result of a perilymphatic fistula. Seltzer and McCabe[24] noted that 25% of patients with fistulas confirmed at exploratory tympanotomy had aural fullness.

Box 156-2

Hearing Loss in Adults

Acute
Sudden idiopathic sensorineural hearing loss
Infection (acute otitis media, external otitis, syphilis, Lyme disease, viral)
Perilymphatic fistula
Ischemia of retrocochlear structures
Multiple sclerosis
Autoimmune disease
Traumatic
Metabolic (chronic renal failure)
Hematologic (sickle cell anemia)

Gradual
Presbycusis
Noise-induced
Familial
Retrocochlear neoplasm
Chronic otitis media, cholesteatoma
Otosclerosis
Endocrine (hypothyroidism, diabetes mellitus)
Paget's disease
Metabolic (chronic renal failure, hyperlipoproteinemia)
Mucopolysaccharidosis

Fluctuating
Perilymphatic fistula
Meniere's disease
Multiple sclerosis
Migraine-associated hearing loss
Infection (syphilis)
Autoimmune (Cogan's syndrome, systemic lupus, polyarteritis nodosa, Wegener's syndrome, temporal arteritis, scleroderma)
Sarcoidosis

Rapidly Progressive
Autoimmune inner ear disease
Meningeal carcinomatosis
Vasculitis secondary to infection (Rocky Mountain spotted fever)
Lyme disease
Ototoxic exposure (aminoglycosides, diuretics, chemotherapy)

Hearing Loss

A complaint of hearing loss can reflect a wide variety of abnormalities (Box 156-2), and diagnostic considerations are different in pediatric and adult patients. Evaluation should determine whether the loss is unilateral or bilateral or fluctuating in nature. The time course of the hearing loss should be established, and associated symptoms should be documented. The medical history should investigate current and past treatments with oral and intravenous medications, and nonprescription drug use. The patient should be screened for systemic diseases, including cardiovascular, metabolic, endocrine, neurologic, hematologic, infectious, and autoimmune diseases. Prior ear surgery, cardiac bypass surgery, and lumbar puncture also may be relevant to the current complaint of hearing loss.[25] A family history of hearing loss, neoplasms, renal disease, and balance disorders should be obtained. Finally, previ-

ous sharp or blunt head trauma, noise trauma, or barotrauma should be noted.

The most informative features that facilitate determining the etiology of hearing loss are the time course of the loss, associated symptoms, and age of the patient. It should be determined whether the loss is acute or gradual in onset, long-standing, fluctuating, rapidly progressive, or of unknown duration. Associated symptoms of aural fullness, pain, otorrhea, vertigo, tinnitus, or cranial neuropathies can assist diagnosis. The clinical feature of unilateral or bilateral hearing loss is less revealing in determining the etiology of hearing loss.

Acute Hearing Loss

Acute unilateral hearing loss may result from a range of disease states. Sudden or acute sensorineural hearing loss may be idiopathic; iatrogenic; a complication of a viral or bacterial infection, labyrinthine fluid abnormality, vascular event, trauma, neoplasm, autoimmune abnormality, or neurologic disease; or a side effect of medication.

Viral infections such as mumps, rubella, rubeola, and Epstein-Barr virus may involve the ear directly by causing varying degrees of transient or permanent hearing loss with or without associated vertigo. These infections may also cause a serous labyrinthitis, causing sensorineural hearing loss from toxins affecting the inner ear. Ramsay Hunt syndrome is an example of a viral polyneuropathy that typically involves facial and cochleovestibular dysfunction. Bacterial and fungal meningitis may also extend to the labyrinth, causing sudden hearing loss. Other infectious causes of sudden hearing loss are acute otitis media, suppurative labyrinthitis from acute or chronic otitis media, and syphilis. In most of these cases, the history, physical examination, and appropriate serology establish the etiology of the hearing loss.

Abnormalities of labyrinthine fluid include hydrops and perilymphatic fistula. Both of these conditions typically cause fluctuating hearing loss, but sudden, permanent loss also is possible. A history of recent heavy lifting or straining, head trauma, or barotrauma suggests a possible perilymphatic fistula. Hydrops typically causes low-frequency hearing loss. The presence of diplacusis and recruitment on examination and associated spells of recurrent vertigo support the diagnosis.

Sudden hearing loss may occur as the result of a vascular event involving the cochlea. Thrombosis or embolic occlusion of the labyrinthine and cochlear arteries is an uncommon but well-recognized cause of hearing loss. Hyperviscosity states such as polycythemia vera may result in cochlear ischemia. Obstruction of small vessels as a result of diabetes mellitus, atherosclerosis, and sickle cell anemia should also be considered when no other causes of hearing loss can be identified.

Head trauma, barotrauma, and noise trauma all can result in acute hearing loss that may be transient or permanent. Direct head trauma resulting in temporal bone fracture may cause either a conductive or a sensorineural hearing loss. Hearing loss also may occur because of a concussive injury to labyrinthine membranes without an associated temporal bone fracture. The history is usually sufficient in these cases to establish the cause of the hearing loss.

Sudden transient or permanent hearing loss is an atypical presentation of a retrocochlear neoplasm in the cerebellopontine angle. This diagnosis can be difficult to make because associated symptoms from a tumor manifesting in this manner are uncommon, particularly in the case of small tumors. Radiographic imaging should always be performed in cases of sudden hearing loss without any identifiable etiology.

When evaluating a patient with sudden or rapidly progressive hearing loss, the presence or absence of other neurologic symptoms should be investigated. Hearing loss that is unilateral, bilateral, sudden, subacute, or insidious may be the presenting symptom for multiple sclerosis.[26,27] Presentation of hearing loss associated with ophthalmologic disease should prompt investigation of Susac's syndrome. First described in 1979, Susac's syndrome is characterized by the triad of retinal arterial occlusions, encephalopathy, and cochlear microangiopathy. The neurotologic features are frequently misdiagnosed as multiple sclerosis, delaying the effective treatment and control of symptoms with systemic immunosuppression.[28]

In adults, a gradual or long-standing hearing loss may reflect various disorders (see Box 156-2). Bilateral gradual hearing loss may reflect presbycusis, noise-induced hearing loss, or familial sensorineural hearing loss. A history of exposure to ototoxic medication should also be investigated. If the sensorineural hearing loss is unilateral, a retrocochlear lesion should be investigated as the cause of the loss. If the loss has a conductive component, diagnoses such as otosclerosis, chronic otitis media with effusion, malleus head fixation, tympanosclerosis, myringosclerosis, tympanic membrane perforation, cholesteatoma, or ossicular chain disruption should be considered.

Table 156-1

Lower Cranial Nerve Deficits Associated with Jugular Foramen Syndromes

	Cranial Nerve			
Syndrome	**IX**	**X**	**XI**	**XII**
Avellis		X		
Tapia		X		X
Vernet	X	X	X	
Jackson		X	X	X
Collet-Sicard	X	X	X	X

Patients with tumors of the jugular foramen commonly present with unilateral hearing loss. This loss may be conductive because of a mass effect of the tumor impinging on the tympanic membrane and ossicles, or sensorineural secondary to erosion of the cochlea or compression of the eighth cranial nerve within the internal auditory canal and cerebellopontine angle. Although symptoms related to these tumors may be subtle, diagnostic suspicion should be high when evaluating a patient with a middle ear or external auditory canal mass associated with pulsatile tinnitus. Dysfunction of the lower cranial nerves may occur in many combinations (Table 156-1), depending on the size and location of the tumor.

Fluctuating Hearing Loss

Fluctuating hearing loss can reflect various diseases. The most common causes are Meniere's disease, perilymphatic fistula, and luetic labyrinthitis. Less commonly, systemic diseases such as multiple sclerosis, tuberculosis, and sarcoidosis cause fluctuating hearing loss. Meniere's disease is usually easily recognized because of the associated vestibular symptoms. Diagnosis of a perilymphatic fistula can be challenging because the symptoms can be quite variable. A history of prior ear surgery, head trauma, barotrauma, or straining may increase suspicion for perilymphatic fistula. Syphilitic inner ear disease also can be an elusive diagnosis because of the various possible presenting symptoms. When hearing loss is associated with either autoimmune disorders or sarcoid, the patient typically has other systemic symptoms relating to the primary disorder that facilitate recognition of the nature of the hearing loss.[29] Autoimmune diseases with cochlear involvement can mimic Meniere's disease early in the course of the disease, before permanent nonfluctuating sensorineural hearing loss occurs.

An uncommon cause of fluctuating hearing loss is an endolymphatic sac tumor. These tumors originate from the epithelium of the vestibular aqueduct and endolymphatic sac. A high index of suspicion is needed to diagnose these tumors, which manifest with symptoms similar to Meniere's disease.[30]

Rapidly Progressive Hearing Loss

Rapidly progressive hearing loss may occur as a result of isolated autoimmune inner ear disease or systemic autoimmune disease with otologic involvement. The hearing loss may be unilateral initially, but progresses to bilateral involvement. Less commonly, the loss may fluctuate or manifest as a sudden sensorineural hearing loss. Autoimmune diseases associated with hearing loss are Cogan's syndrome (nonsyphi-

litic interstitial keratitis with audiovestibular involvement),[31,32] polyarteritis nodosa, relapsing polychondritis, sarcoid, ulcerative colitis, systemic lupus erythematosus, Wegener's disease, Churg-Strauss syndrome, and Behçet's disease.

An unusual cause of rapidly progressive or sudden hearing loss is neoplastic disease metastatic to the brain or temporal bone from a distant primary site. Hearing loss is usually associated with additional symptoms, such as tinnitus, vertigo, dysequilibrium, and facial nerve paralysis. Metastatic disease may involve the brain and skull base by several mechanisms. Metastatic disease may involve the temporal bone directly through hematogenous spread to petrous bone marrow. Metastases may be single or multiple intraparenchymal or epidural lesions. Diffuse multifocal seeding of the leptomeninges (meningeal carcinomatosis) also may occur. The most common sources of metastatic disease directly affecting the temporal bone are breast, lung, kidney, stomach, bronchus, and prostate neoplasms. The most common tumor type that causes intraparenchymal lesions is carcinoma of the lung. Generally, 20% of intraparenchymal brain metastases occur in the cerebellum and brainstem. Prostate carcinoma and breast cancer have a propensity to metastasize to the dura. Non-Hodgkin's lymphoma, breast carcinoma, and melanoma are the most common tumor types associated with leptomeningeal metastasis. A high index of suspicion for metastatic disease should always be maintained when evaluating a patient with a known history of cancer who presents with new cranial nerve deficits.[15,33,34]

Pediatric Sensorineural Hearing Loss

Pediatric hearing loss can be categorized as congenital (present at birth) or acquired (auditory function was present initially with subsequent loss of hearing). Congenital and acquired hearing loss may result from an abnormality in the genetic code (syndromic or nonsyndromic, single gene or chromosomal abnormality), or may result from perinatal insults that are infectious, toxic, or systemic in nature. The Joint Committee on Infant Hearing[35] has outlined the identifiable risk factors associated with neonatal hearing loss. These risk factors include a family history of hereditary childhood sensorineural hearing loss; perinatal infection with cytomegalovirus, rubella, syphilis, herpes, or toxoplasmosis; evidence of craniofacial abnormalities; birth weight less than 1500 g; significant hyperbilirubinemia requiring exchange transfusion; treatment with ototoxic medications; history of bacterial meningitis; history of Apgar scores between 0 and 4 at 1 minute, or 0 and 6 at 5 minutes; history of prolonged mechanical ventilation in the postnatal period; or any other findings on physical examination suggestive of a syndrome associated with hearing loss.

Diagnostic considerations for nongenetic causes of hearing loss include kernicterus, prematurity with low birth weight, birth trauma, postnatal anoxia requiring mechanical ventilation, use of extracorporeal membrane oxygenation therapy, and treatment with ototoxic medications in the postnatal period. Perinatal infections can result in congenital and delayed hearing loss. Young children are particularly vulnerable to bacterial meningitis, and the incidence of hearing loss after such an infection is 3.5% to 37%.[36] Prenatal exposure to toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and syphilis can result in mild to profound sensorineural hearing loss. Box 156-3 lists the 10 most common syndromes associated with hearing loss and some rare disorders in which hearing loss is a major feature.[37]

Approximately 20% of patients with congenital sensorineural hearing loss have radiographic evidence of an inner ear malformation.[38] Malformations of the inner ear may occur in isolation or associated with other physical abnormalities as part of a syndrome. The malformation may result from exposure to teratogens (chemical or viral) during embryogenesis, or may be idiopathic in nature. Congenital inner ear abnormalities constitute a spectrum of recognized malformations that are associated with various hearing loss patterns. Complete aplasia of the labyrinthine capsule (Michel's aplasia) is associated with profound deafness. The most common malformation is cochleosaccular dysgenesis (Scheibe's aplasia), which is a malformation limited to the membranous portion of the pars inferior. The Mondini deformity derives from arrested development of the labyrinthine capsule during the 7th week of gestation, resulting in a small cochlea with an incomplete partition and an abnormally dilated vestibular aqueduct and vestibule.

Box 156-3

Hearing Loss in Congenital and Genetic Conditions

Syndromes Most Commonly Associated with Hearing Loss

1. Oculoauriculovertebral spectrum (hemifacial microsomia, Goldenhar's syndrome)
2. Stickler's syndrome (hereditary arthro-ophthalmopathy)
3. Congenital cytomegalovirus
4. Usher's syndrome
5. Branchio-oto-renal syndrome
6. Pendred's syndrome
7. CHARGE association (coloboma [of eyes], *h*earing deficit, choanal *a*tresia, *r*etardation of growth, genital defects [males only], endocardial cushion defect)
8. Neurofibromatosis type 2
9. Mitochondrial disorders
10. Waardenburg's syndrome

Rare Disorders with Hearing Loss as a Major Feature

1. Otopalatal-digital syndromes
2. Skeletal dysplasias (osteogenesis imperfecta)
3. Metabolic storage diseases (mucopolysaccharidoses, Refsum's disease)
4. Townes-Brock syndrome
5. Wildervanck's syndrome
6. Biotinidase deficiency

Variable degrees of hearing loss and vestibular dysfunction are associated within the spectrum of labyrinthine developmental abnormalities. Generally, the more severe the malformation, the greater the associated hearing loss.

More than half of all cases of prelingual sensorineural hearing loss are the result of a genetic abnormality. Autosomal recessive patterns of inheritance are responsible for almost three quarters of these cases, and most are nonsyndromic. Most of these inherited forms of hearing loss are permanent and irreversible. An exception is the sensorineural hearing loss associated with biotinidase deficiency. This is an autosomal recessive disorder of failure to recycle the vitamin biotin, resulting in mental retardation, hypotonia, seizure disorder, alopecia, and skin rash. Sensorineural hearing loss is now recognized to occur in 75% of children with a symptomatic biotinidase deficiency. Early recognition in the neonatal period is crucial for initiating appropriate therapy.[39]

One third of the inherited forms of congenital hearing loss occur as part of a syndrome.[40] Recognition of these forms of hereditary hearing loss is assisted by the identification of associated physical and metabolic abnormalities. The presence of renal abnormalities suggests the possibility of Alport's syndrome, which can be inherited in an autosomal dominant, autosomal recessive, and X-linked pattern. Branchio-oto-renal syndrome should be considered if there are structural abnormalities, such as auricular pits, malformed pinnae, or branchial cleft fistulas or cysts, in association with conductive, mixed, or sensorineural hearing loss. A complete eye examination, including electroretinography, is crucial to early identification of retinitis pigmentosa associated with Usher's syndrome.[41] Associated metabolic dysfunction may be obvious, as in inherited mucopolysaccharidoses, or more subtle, as in Pendred's syndrome. A family history of fatal cardiac arrhythmias should suggest the possibility of Jervell-Lange-Nielsen syndrome. Pigmentary abnormalities such as a bicolored iris, white eyelashes, or piebald skin are associated with Waardenburg's syndrome.

Pediatric Conductive Hearing Loss

Most pediatric conductive hearing loss is the result of acute or chronic otitis media and the sequelae of these diseases. Noninfectious causes of congenital conductive hearing loss include congenital cholesteatoma,

external auditory canal atresia,[42] and labyrinthine structural abnormalities such as ossicular chain fixation and congenital absence of the oval window.[43-45] A rare developmental abnormality that results in a prominent conductive hearing loss in children is a salivary gland choristoma of the middle ear. Twenty-six cases of heterotopic salivary gland tissue in the middle ear have been documented in the literature. Patients are seen at a young age with a persistent conductive hearing loss and a middle ear mass. Often the mass is adherent to the tympanic or descending portions of the facial nerve. Associated malformations of the ossicular chain and external ear also have been found.[46-48]

Vertigo

The sensations of vertigo and dysequilibrium in children and adults may reflect disease within the labyrinth, a retrocochlear abnormality involving either the eighth cranial nerve or more central structures, or the effects of a systemic abnormality. A thorough and well-directed history discriminates otologic from nonotologic causes of vertigo in most cases. Identification of associated symptoms, the time course of the vertigo or dysequilibrium, precipitating and alleviating factors, and the general medical history should be assessed in patients with vertigo.

The patient's description of symptoms helps in discriminating between central and peripheral causes of vertigo. A sensation of spinning or motion commonly results from acute vestibular dysfunction, such as viral neuronitis, labyrinthitis, and Meniere's disease. Nonvestibular causes of imbalance, such as cardiogenic, metabolic, neurogenic, or psychogenic dysfunction, are often described as a more nonspecific sensation of light-headedness. Encouraging the patient to describe the symptoms or spells in detail without using the word *dizzy* can be helpful.

The time course of the patient's symptoms is crucial to distinguish between otologic and nonotologic causes of vertigo (Box 156-4). Vertigo that is continuously present for weeks without fluctuation is generally not the result of a peripheral vestibular abnormality. Acute injury to the inner ear or eighth cranial nerve initially results in severe and prolonged vertigo. As central compensation progresses, the vertigo subsides over days to weeks. Persistent vertigo indicates an uncompensated labyrinthine or eighth cranial nerve lesion, or a central abnormality.

Vertigo in discrete isolated spells should be characterized by the frequency and duration of symptoms. Vertigo that lasts for less than 1 minute can represent benign paroxysmal positional vertigo. Spells lasting several minutes may represent migraine-associated vertigo or transient ischemia of the vertebrobasilar circulation. Vertigo that is prolonged for hours is typical of Meniere's disease or endolymphatic hydrops. Vertigo that persists for days but gradually subsides is seen with vestibular neuritis.

Box 156-4

Time Course of Vertigo

Seconds to Minutes to Hours
Perilymphatic fistula
Benign paroxysmal positional vertigo
Otosclerosis
Vascular
Migraine
- Vertebrobasilar insufficiency (anterior inferior cerebellar artery)
- Wallenberg's syndrome
- Hyperviscosity syndromes

Hours
Meniere's disease
Migraine
Metabolic
Iatrogenic
Syphilis

Days
Labyrinthitis
Temporal bone trauma
Iatrogenic
Viral neuronitis
Vertebrobasilar infarction
Cerebellar/brainstem hemorrhage
Autoimmune neurolabyrinthitis
Multiple sclerosis

Labyrinthine Vertigo

Diseases affecting the labyrinth that result in vertigo may be categorized as infectious, post-traumatic, metabolic, autoimmune, ischemic, drug-induced, hydropic, or multifactorial in character. The most common infectious cause of acute vertigo is viral labyrinthitis. Most patients with viral labyrinthitis have isolated vestibular dysfunction of sudden onset, without associated hearing loss. In some cases, identification of the inciting agent is evident because of systemic manifestation of the disease, such as with measles, mumps, infectious mononucleosis, herpes zoster, and cytomegalovirus. Bacterial infection from acute or chronic otitis media also may result in a toxic or serous labyrinthitis with vestibular symptoms. A more severe infection can result in suppurative labyrinthitis either from direct bacterial invasion into the inner ear from chronic otomastoiditis (through a labyrinthine fistula from a cholesteatoma) or from bacterial meningitis contaminating the perilymphatic space of the labyrinth through the cochlear aqueduct or internal auditory canal. Chronic infections such as syphilis and Lyme disease may cause persistent or recurring symptoms of vertigo and dysequilibrium through direct invasion of the otic capsule or by leptomeningeal involvement.

Traumatic causes of vertigo include temporal bone fractures, labyrinthine concussion, and perilymphatic fistula. Transverse fractures of the temporal bone extend from the posterior fossa across the petrous portion of the temporal bone into the vestibule. Rupture of the membranous labyrinth and laceration of the cochleovestibular nerve in these cases result in profound deafness and severe vertigo. Longitudinal temporal bone fracture without violation of the labyrinth and blunt head trauma without associated temporal bone fracture also may cause hearing loss and vertigo because of a concussive injury to the membranous labyrinth.

Metabolic causes of vertigo should always be considered when a labyrinthine or central etiology is absent. Systemic metabolic abnormalities that can affect vestibular function include hyperviscosity syndromes (hyperlipidemia, polycythemia, macroglobulinemia, and sickle cell anemia), diabetes mellitus, hyperlipoproteinemia, and hypothyroidism. Hormonal fluctuations occurring in the premenstrual and perimenopausal periods and oral contraceptives and estrogen replacement therapy also may cause neurotologic symptoms, including vertigo. Metabolic dysfunction isolated to the labyrinth may occur because of cochlear otosclerosis. In addition to sensorineural hearing loss, cochlear otosclerosis may cause vestibular symptoms of dysequilibrium or vertigo. Altered cochlear microvascularization, direct otosclerotic degeneration of vestibular nerve fibers, and humoral toxicity secondary to proteolytic enzymes within the perilymph all have been proposed as mechanisms for vertigo associated with otosclerosis.

Numerous collagen vascular disorders have been associated with vestibular dysfunction as a form of autoimmune inner ear disease. Common disorders of this type include rheumatoid arthritis, polyarteritis nodosa, temporal arteritis, nonsyphilitic interstitial keratitis, lupus, sarcoid, relapsing polychondritis, dermatomyositis, and scleroderma.

Ischemia of small labyrinthine vessels causes isolated infarction of the vestibular labyrinth and vertigo. Occlusion of larger vessels, such as the anterior inferior cerebellar artery or its branches, causes sudden and profound loss of auditory and vestibular function and regional infarction of the brainstem.[49]

Aminoglycoside ototoxicity is a well-recognized cause of drug-induced vertigo. The degree of cochlear and vestibular toxicity of these drugs varies with each drug, the duration of treatment, concomitant exposure to noise, and genetic susceptibility of the individual.[50]

Endolymphatic hydrops or Meniere's disease is defined by the well-recognized symptoms of vertigo, hearing loss, tinnitus, and aural fullness. The underlying mechanism that causes abnormal homeostasis of endolymph resulting in distention and rupture of the membranous labyrinth is unknown. Histopathologic findings suggest that fibrosis of the endolymphatic sac, altered glycoprotein metabolism, and viral infections may be pathogenic mechanisms, but further study in this area is needed.[51]

Retrocochlear Vertigo

Retrocochlear causes of vertigo can be categorized as neoplastic, paraneoplastic, vascular (infarction or ischemia), and demyelinating in origin. Diagnosis relies on a thorough history and physical examination documenting other associated cranial nerve or neurologic deficits, evidence of malignancy, and identification of risk factors for vascular disturbances.

Cerebellopontine angle tumors such as acoustic neuroma and meningioma more commonly cause a sense of dysequilibrium or unsteadiness rather than true vertigo. Because these tumors are slow-growing, central compensation occurs over time for the unilateral loss of vestibular function. In addition, these space-occupying lesions of the posterior fossa may cause dysequilibrium and positional vertigo because of cerebellar compression. Brainstem tumors such as gliomas and medulloblastomas commonly manifest with vestibular and cochlear symptoms in addition to long tract signs, cranial nerve deficits, ataxia, and headache.

Although paraneoplastic syndromes associated with carcinoma are uncommon causes of vertigo, they are worthy of mention because the vestibular symptoms may precede the diagnosis of underlying malignancy.[52] Paraneoplastic encephalomyelitis is an autoimmune process most commonly associated with small cell carcinoma of the lung. Inflammatory changes may occur throughout the neuraxis, with subsequent neuronal destruction and glial activation. When the brainstem is involved, degeneration of the vestibular nuclei and the lower cranial nerves is common. Paraneoplastic cerebellar degeneration has been associated with lymphoma and with carcinoma of the ovary, breast, and lung. Paraneoplastic cerebellar degeneration may manifest as sudden-onset vertigo or progressive truncal and extremity ataxia with nystagmus, dysarthria, and diplopia.

Cerebellar atrophy and diffuse small vessel ischemia associated with aging may cause mild unsteadiness, but rarely true vertigo. The coexistence of multisensory deficits with decreased peripheral sensitivity and proprioception and poor visual acuity exacerbates any central or vestibular hypofunction resulting in dysequilibrium.

Acute vascular events affecting the cerebellum and brainstem usually produce more pronounced and severe symptoms. Transient ischemia of the vertebrobasilar system may cause acute onset of vertigo that lasts only minutes and resolves without sequelae. Occlusion of the vertebral artery or the posterior inferior cerebellar artery results in infarction of the dorsolateral medulla (Wallenberg's syndrome). Cerebellar ataxia, vertigo with nausea and vomiting, Horner's syndrome, conjugate gaze paresis, and contralateral loss of pain and temperature sensation are the associated signs and symptoms.

Episodic vertigo may be a component of a migraine aura. The vertigo may occur in conjunction with or precede the migraine headache. Vertigo also may occur without headache; this is known as migraine equivalent.

Demyelinating disorders of the central nervous system are uncommon causes of vertigo and dysequilibrium. Unusual causes of demyelination include exposure to toxins (carbon monoxide, lead, and methotrexate), nutritional disorders (vitamin B_{12} deficiency), postviral syndromes (measles and papovavirus), and hereditary degeneration. Multiple sclerosis is the most common demyelinating disorder encountered by otolaryngologists assessing cochleovestibular dysfunction. Although vertigo is the presenting symptom in only 5% of patients with multiple sclerosis, dysequilibrium and unsteadiness are common in most of these patients at some point in their disease.

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Auditory Prosthetic Stimulation, Devices, and Rehabilitative Audiology

CHAPTER ONE HUNDRED AND FIFTY-SEVEN

Implantable Hearing Aids

Lawrence R. Lustig

Charles C. Della Santina

Key Points

- Limitations of conventional hearing aids compared with newer implantable hearing aids include insufficient amplification, acoustic feedback, distortion of spectral shape and phase shifts, nonlinear sound distortion, occlusion effects, poor auditory transduction, and cosmetic appearance. Abnormalities in the ear canal also prevent the use of a conventional hearing aid.
- All middle ear implantable hearing aids include a transducer (either piezoelectric or electromagnetic) and couple to one of the three middle ear bones in one of many ways to drive the ossicular chain directly. Some newer designs also couple directly to the round window.
- Economic factors have limited the availability of middle ear implantable hearing aids in the United States; there is more widespread application in Europe.
- Bone-anchored hearing aids are useful for patients with conductive hearing loss who cannot use a conventional hearing aid for a variety of reasons, including patients with chronically draining ears despite multiple corrective attempts, patients with discomfort from the sound levels required from a traditional hearing aid, and patients with a large mastoid bowl or meatoplasty.
- Bone-anchored hearing aids are beneficial in patients with otosclerosis, tympanosclerosis, or canal atresia, and in patients who have undergone external auditory canal closure after extensive skull base surgery.
- Patients with unilateral deafness benefit from a bone-anchored hearing aid through improved hearing in noise, although objective evidence of improved sound localization is unavailable.

Hearing aids are the principal means of auditory rehabilitation for patients with sensorineural hearing loss (SNHL). Hearing aids may also play a role in the management of patients with conductive hearing losses (CHL), particularly losses that result from pathologies that are not amenable to medical and surgical treatment. Improvements in signal processing capabilities and increasing miniaturization of hearing aids have increased their acceptance among patients. Hearing aids remain a "tough sell" to many patients who could potentially benefit from them, however, owing to lack of sufficient perceived benefit, expense, complications of external auditory canal occlusion, and cosmetic concerns. In a restaurant, multiple competing sound sources, such as conversations, the ventilation system, and music, can undermine the ability to detect and resolve speech cues. Many other patients simply cannot wear a hearing aid because of problems with the external auditory canal, chronic infections, or extreme discomfort. Although newer hearing aid technologies have tried to address many of these difficulties, many patients still find that hearing aids fall short in meeting expectations in a variety of situations (Box 157-1). Partly for these reasons, less than one in eight eligible adults actually use a hearing aid.[1]

These inherent limitations in hearing aids, combined with the social stigma of their use, have led to the development of implantable hearing aids (Figs. 157-1 and 157-2). Implantable hearing aids offer patients with hearing loss several potential advantages over conventional hearing aids, including increased gain and dynamic range, reduced feedback, reduced maintenance, improved appearance, and freedom from ear canal occlusion. These potential benefits must be weighed against the possible downsides of their use, including the risk of surgical implantation, difficulty of maintenance, and increased initial device cost (Table 157-1). Complicating this risk-benefit calculation is the uncertain future of corporations marketing and supporting various implantable hearing aids. Before discussing each of the implantable hearing aids currently available or in development, it is important to review in more detail *why* there is a desire for their implementation in the first place.

Limitations of Auditory Rehabilitation Using Traditional Hearing Aids

Physical Factors

Traditional hearing aids are limited in their ability to amplify sound without imparting distortion or generating feedback, in part because these three aspects of performance are physically interrelated.

Insufficient Gain

For patients with severe to profound hearing loss, sound amplification (or *gain*) is a primary concern. For a patient with air-conduction thresholds of 80 dB hearing level (HL) to perceive quiet sounds at a normal threshold of 0 dB HL, a hearing aid must amplify sound intensity by 80 dB, generating a 10,000-fold increase in sound pressure wave amplitude and a 100,000,000-fold increase in sound power intensity.[2] This represents the limit of existing traditional hearing aids. The maximum amplification at 1 kHz for a behind-the-ear (BTE) Phonak SuperFront PPCL4 power digital hearing aid is about 75 to 82 dB.[3] Gain generally scales with hearing aid size, so that cosmetically less

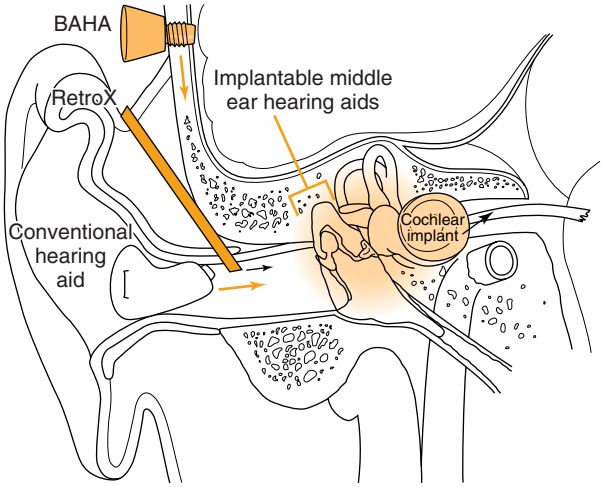


Figure 157-1. Overview of how various implantable hearing aids interface with the auditory system. Conventional hearing aids amplify from within the canal, whereas bone-anchored conductive devices are applied to the retroauricular skull to provide hearing via bone conduction. The RetroX sits behind the ear, but delivers sound through a channel that emerges in the external auditory canal. Implantable middle ear hearing aids interface at the level of the ossicles, bypassing the eardrum. In contrast, cochlear implants directly stimulate the remaining neural elements within the cochlea. BAHA, bone-anchored hearing device. *(Adapted from Nikolas Blevins, MD.)*

Box 157-1

Nonideal Features of Conventional Aids

Insufficient amplification
Acoustic feedback
Spectral distortion
Nonlinear/harmonic distortion
Occlusion of external auditory canal
Appearance/visibility
Lack of directionality

obtrusive hearing aids offer less gain. The maximum gains for digital in-the-ear (ITE), in-the-canal (ITC), and completely-in-canal (CIC) hearing aids currently are about 55 to 65 dB, 45 to 55 dB, and 35 to 50 dB.[3]

Acoustic Feedback

In practice, feedback often limits the useful gain of traditional hearing aids to less than the above-listed maximum gains. Acoustic waves from the hearing aid speaker leak through the air space between the hearing aid body and the external auditory canal wall back to the microphone, where (for a subset of frequencies) they add to existing microphone input and are amplified further. The resulting positive feedback loop causes the familiar squealing and hum that signify a poorly fitting or overamplified aid. Potential for feedback is worst for CIC aids, in which the microphone is closest to the speaker, and for ears with mastoid bowls, in which an air seal is difficult to obtain. At very high amplification, it is a problem even for BTE aids. Fitting aids tightly into the external auditory canal can decrease feedback, but at the cost of increased discomfort, and the risk of otitis externa, autophony, and blockage of natural sound input.

Distortion of Spectral Shape and Phase Shifts

Traditional hearing aids are limited in the frequency range over which they amplify sound. Most are optimized for performance in the speech band (500 to 2000 Hz) and cannot provide much amplification at less than 100 to 200 Hz or greater than 5000 to 6000 Hz. Although the most important spectral components for speech recognition are amplified, the loss of "bass" and "treble" can give the resultant sound percept an artificial character. Isolated severe hearing loss at low frequencies (e.g., in Meniere's disease) or high frequencies (e.g., in presbycusis or ototoxic exposure) can be difficult to remediate with traditional hearing aids without overamplifying the midrange frequencies at which a patient may have normal hearing. Even in the 500- to 2000-Hz band, steep changes in audiometric threshold at neighboring frequencies (e.g., noise-induced hearing loss) cannot be perfectly fit because of inherent limitations in the rate of change of gain across frequencies. Too steep a change in amplifier gain across frequencies typically imparts phase shifts that distort sound percepts such as pitch and timbre. Digital signal processing technology has greatly improved spectral shaping options compared with analog aids, but these fundamental limitations persist.

Nonlinear Distortion

Similar to most other amplifiers, hearing aids are designed under assumption of linearity—that is, if a given sound input at the microphone leads to some output at the speaker (amplified and spectrally shaped by the aid), doubling the sound input's magnitude should exactly double the output, without changes in spectral content or phase shifts. For high-intensity speaker output, this assumption breaks down as the speaker is driven into the range of movements for which it begins to saturate or clip. An input sinusoid can appear at the output as a waveform with blunted peaks. This nonlinear distortion imparts aberrant spectral components into the sound percept, giving it an artificial or robotic character. Although digital signal processing can mitigate distortion effects within an aid's amplification circuitry, distortion produced by a speaker generating loud sounds in air remains a fundamental limitation of traditional hearing aids.

Occlusion Effects

To minimize feedback, most traditional hearing aids are fit to create an airtight seal with the external auditory canal wall, with the hearing aid's speaker being isolated in the occluded ear canal. Canal occlusion has several undesirable effects. First, it can be uncomfortable because of pressure on canal skin. Second, it increases the likelihood of otitis externa because of disturbance of wax egress and air circulation. Some patients with chronic suppurative otitis media cannot tolerate hearing aids because of exacerbation of otorrhea. Third, it causes autophony and a sense of aural fullness that can worsen with changes in ambient barometric pressure. Fourth, it blocks the normal pathway for sound entry to the ear. Finally, canal occlusion disrupts the spectral shaping that normally occurs as a result of external auditory canal resonances.

Poor Appearance

Many patients reject hearing aids because of the social stigma of being seen as old or infirm. Eight percent of hearing aid candidates wearing the less noticeable ITC hearing aids listed poor cosmetic appearance as a major contributing factor in their decision not to use a hearing aid.[4] Hearing aids are difficult to conceal in patients who are balding or who wear their hair short. Miniaturization of electronics continues to improve hearing aids in this regard, and CIC hearing aids are essentially invisible to the casual observer. Miniaturization comes at the cost of lower gain, more feedback, and higher cost, however. Ultimately, battery size becomes the limiting factor, with smaller batteries costing more and requiring more frequent replacement.

Poor Transduction Efficiency

Loss of energy because of impedance mismatching and transduction losses is another inherent drawback of conventional hearing aids. The mechanical impedance (change in pressure for a given displacement flow) of the air-filled external auditory canal differs from that of the fluid-filled cochlea. Without a middle ear mechanism, most of the acoustic energy striking the stapes footplate reflects back into the air. When the tympanic membrane and ossicular chain are functioning normally, they act as an impedance-matching transformer by virtue of

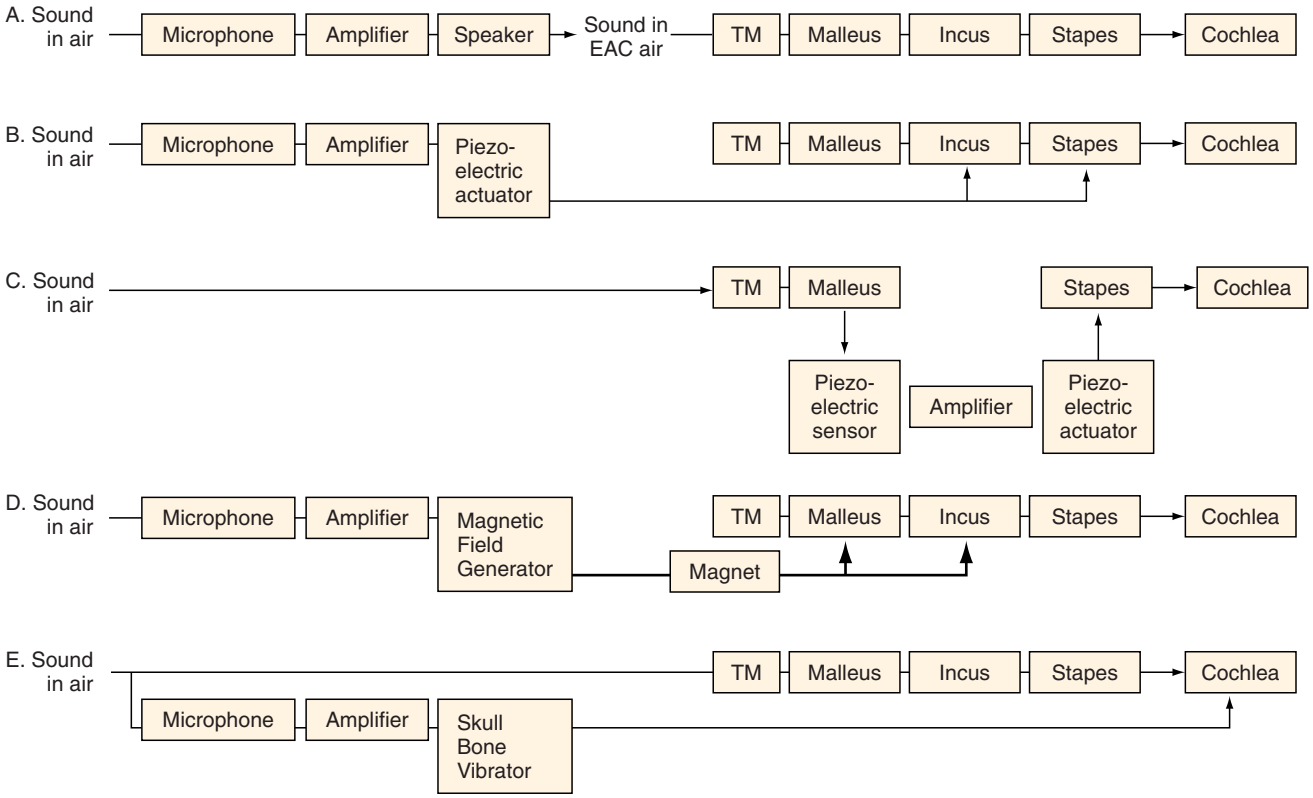


Figure 157-2. Sound transduction and coupling to the auditory system for different classes of hearing aids. **A,** Conventional air-conducting hearing aid. **B,** Implantable aids with piezoelectric actuator (e.g., Rion-E, Otologics MET, and Implex TICA). **C,** Implantable aids with piezoelectric sensor and actuator (e.g., St. Croix Envoy). **D,** Implantable aids with magnetic actuator (e.g., Vibrant Med-El Soundbridge, Soundtec DDHS). **E,** Bone-anchored hearing aid (e.g., Cochlear/Entific BAHA). EAC, external auditory canal; TM, tympanic membrane.

the relative areas of the tympanic membrane and stapes footplate, and by the lever action of the ossicular chain.[5] The relatively large-displacement, low-pressure movements of air against the tympanic membrane are transduced to the relatively small-displacement, high-pressure movements of the footplate. Except for bone-conducting hearing aids, all traditional hearing aids use a speaker to output an (amplified) acoustic wave into the air of the external auditory canal. When this middle ear apparatus is malfunctioning, as occurs in otosclerosis, tympanic membrane perforation, or a canal wall down mastoidectomy, traditional hearing aids must overcome the impedance mismatch. The result is reduced effective gain, increased distortion, or both.

Even when the ossicular chain is functioning normally, the transduction of acoustic energy from air at the input of a traditional hearing aid to stapes footplate motion is imperfect. Whenever a signal flows from one physical realm (e.g., electric current in a speaker) to another (e.g., acoustic waves in air), some energy is lost (e.g., to heat) and noise or distortion can add to the desired signal. There are several transduction steps for a traditional hearing aid—from acoustic waves in ambient air, to electric current in a microphone, to a larger electrical current in a speaker wire or piezoelectric driver, to acoustic waves in air within the external auditory canal, to movement of the tympanic membrane and ossicular chain, to acoustic waves in perilymph, to hair cell stereociliary deflection and depolarization. Most steps are unavoidable (although cochlear implants bypass these steps through direct cochlear nerve stimulation). Directly coupling a hearing aid actuator movement of the ossicular chain can delete some of these transduction steps, however, boosting gain and reducing distortion. Nearly all implantable hearing aids make use of this approach.

Human Factors

Although not specific to traditional hearing aids, SNHL imposes additional constraints on the degree to which sound amplification can overcome hearing deficits. These factors must be considered when evaluating whether technical improvements such as increased amplification gain are worth pursuing for a given patient.

Recruitment and Compression of Dynamic Range

A primary source of frustration of patients with SNHL is reduced speech intelligibility. The common complaint, "I can hear, but I cannot understand," underscores this point. This problem relates to abnormal frequency resolution and aberrant patterns of growth in loudness, each of which reduces speech intelligibility in challenging listening conditions such as noisy surroundings.[6,7]

SNHL also imposes severe constraints on the dynamic range of perceived sound. For normal listeners, the dynamic range from sensing soft sounds to the loudest tolerable noise is more than 100 dB. Within this wide dynamic range of hearing lies an approximately 35-dB dynamic range of conversational speech. In contrast, the dynamic range of patients with SNHL is often narrowed by an increase in the threshold of audibility and a lowering of the ceiling of tolerance to high-intensity sounds. This compaction of dynamic range leads to "recruitment," an abnormal growth in loudness as sound intensity increases.[8,9] What sounds normal for someone with normal hearing may be too soft for someone with recruitment, whereas what is too loud for someone with normal hearing is *also* too loud for a patient with recruitment. In effect, there is a much narrower range of sound intensity that a patient with recruitment can tolerate. Further adding to the difficulty, recruitment is observed in frequencies that are most impaired, in the high frequencies, which also carry crucial information for speech understanding.

Recruitment remains one of the principal challenges of hearing aid rehabilitation, and is responsible for a common phenomenon most clinicians dealing with hearing loss have witnessed or experienced: At average speaking levels, an individual with recruitment may ask a speaker to talk more loudly, yet with even a slight increase in intensity the speech becomes intolerably loud, and the speaker is told not to

Table 157-1

Comparison of Implantable and Nonimplantable Hearing Aids

Device (Manufacturer)	Sensor	Actuator	Regulatory Approval	Totally/Partially Implanted	Surgical Placement	Audiologic Indications	MRI	Special Advantages/ Disadvantages	EAC Occlusion
Envoy (St. Croix Medical, Intl., St. Paul, MN)	Piezoelectric, coupled to malleus/ TM	Piezoelectric, to stapes	In clinical trials	Total	Transmastoid, mandatory incus removal	Figure 157-9		Very high power; requires incus removal	No
MET Middle Ear Transducer (Otologics, LLC, Boulder, CO)	Piezoelectric, coupled to malleus	Piezoelectric, to incus	FDA clinical trials Phase 2	Partial	Transmastoid	Moderate to severe		High-powered output; fully implantable; ossicles remain intact; adjustable for ossicular abnormalities	No
Vibrant Soundbridge (Vibrant-Med-El, Innsbruck, Austria*)	External BTE microphone	Magnetic, clipped to incus	Approved, U.S. FDA and CE Mark	Partial	Transmastoid and endaural	Figure 157-4		First FDA approved, largest install base	No
Bone-anchored device (BAHA) (Cochlear Corp., Lane Cove, Australia)	External microphone	Electromagnetic vibrator, coupled to titanium screw in skull	Approved, U.S. FDA and CE Mark	Partial	Cortical skull bone screw	CHL unable to tolerate conventional HA	+	Simple placement, nothing in ear or mastoid	No
RetroX (Auric Hearing Systems, Rheine, Germany)	External BTE microphone	Acoustic, to TM	Approved U.S. FDA and CE Mark	Partial	Transconcha	Mild to severe CHL or SNHL	+	Noninvasive placement; acoustic coupling	Yes
Conventional Digital BTE (many manufacturers)	External BTE microphone	Acoustic, to TM	Yes	NA	NA	Mild to severe CHL or SNHL	NA	No surgery required; visible, EAC occlusion	Yes
Conventional Digital CIC (many manufacturers)	External microphone at lateral end of CIC device	Acoustic, to TM	Yes	NA	NA	Mild to moderate CHL or SNHL	NA		

*Symphonix Devices, Inc., San Jose, CA, until 2003.
BTE, behind-the-ear; CHL, conductive hearing loss; CIC, completely-in-canal; EAC, external auditory canal; HA, hearing aid; MRI, magnetic resonance imaging; NA, not applicable; SNHL, sensorineural hearing loss; TM, tympanic membrane.

shout. Although many hearing aids can be programmed to prevent sound from amplifying into a range that is uncomfortable, even the most advanced aids cannot fully replicate the complex, nonlinear response patterns of a healthy cochlea.[9]

Disordered Perception of Pitch and Sound Localization

Another challenge faced by conventional hearing aids relates to impaired pitch resolution and sound localization. Although simple amplification strategies can compensate for this loss of sensitivity, they do little to restore the exquisite selectivity of the cochlea in organizing pitch information. Much of the benefit provided by the normal auditory system is based on the presence of two ears that independently sample the acoustic environment and send this information to the brain for comparison and analysis. Sound detection is an important first step in hearing, and can be performed reasonably well by one sensitive ear. There is significant additional auditory benefit, however, when sound input occurs through both ears. When only one ear functions, or when there is a drastic difference in hearing levels between ears, the ability to locate the source of sound decreases, as does suppression of background echoes and the ability to "block out" background noise.

All of the aforementioned factors play a role to various degrees in patients, and combine to increase the noncompliance rate in hearing aid users. For most patients, these are the principal reasons why hearing aids are unacceptable.[10] With all these challenges concerning conventional hearing aids, it is not surprising that many hearing aid users feel frustrated when hearing aids fail to perform to expectations.

Promise of Implantable Hearing Aids

The limitations of traditional air-conduction hearing aids have constituted the driving force behind the new generation of implantable hearing aids. Can implantable hearing aids solve these difficult challenges? Implantable hearing aids face most of these same challenges, but also have the added obstacle of requiring surgery for their placement, and being potentially much more costly. Their appeal includes the possibility of improved signal-to-noise ratios, greater amplification/gain potential, invisibility, loss of distortion and feedback, getting the aid out of the canal with the associated occlusion effect, greater dynamic range, and improved cosmetics. For some patients who simply cannot wear a hearing aid because of underlying medical problems or extreme discomfort, implantable hearing aids may be the only option.

It is widely accepted that implantable hearing aids should provide distinct advantages over conventional hearing aids, including better cosmetics, improved fidelity, broader frequency response, less distortion, reduction or elimination of feedback, and better speech understanding, without reducing residual hearing, limiting patient activities, or predisposing patients to infection.[11,12] In other words, implantable hearing aids should be at least as good as, and preferably better than, the best available noninvasive method of hearing rehabilitation: binaural amplification with the best available aid.[13]

Although significant strides have been made in many of these areas, implantable hearing aids have yet to deliver on all these features. There also remain questions regarding candidacy for implantation and willingness of patients to accept the costs and surgical risks. As noted by Junker and colleagues,[14] the number of patients in a fairly typical population of hearing-impaired individuals who would be considered realistic candidates is limited, on the order of 0.09%. The market for implantable hearing aids may not be sufficiently large to support the current array of device manufacturers. The 2002 financial failing of Symphonix Corp., the first company to gain U.S. Food and Drug Administration (FDA) approval and market their implantable middle ear hearing aid in the United States, strongly underscores this point, as do the subsequent withdrawal of the Soundtec and TICA devices described subsequently in the review of technologies.

The focus of the remainder of this chapter is on critical reviews of the advantages and disadvantages of each of the implantable hearing aids that are either in development or already in clinical use. A different type of implantable hearing aid, the bone-anchored hearing aid (BAHA), is widely used in hearing rehabilitation for some very specific indications, and this also is discussed.

Middle Ear Implants

Basic Design Features

Transducer Design

Conventional hearing aids function by receiving acoustic energy through a microphone, processing and amplifying the signal (in either an analog or a digital fashion), and transmitting the signal through a speaker adjacent to the eardrum. This amplified sound travels through the normal auditory pathway of the tympanic membrane and ossicles to the inner ear. Implantable middle ear hearing aids also employ a microphone that senses sounds and a signal processor that amplifies and alters the sound signal, just as in a conventional hearing aid. From here, they differ from conventional hearing aids. In one of several mechanisms unique to each device, the implantable middle ear hearing aids convert the electric signal into a mechanical energy that is coupled directly to the ossicular chain (see Fig. 157-1).The critical components of these systems are the transducer, which enables the device to output a signal that can be received by the ossicles, and the mechanism by which the transducer is coupled to the ossicles, which can either be a direct or indirect contact.[15] Variations in these critical components distinguish the various implant designs (see Fig. 157-2). Goode and colleagues[11] previously outlined the history of the development of implantable middle ear hearing aids.

Two basic types of transducers have been incorporated into middle ear implantable hearing aids: *piezoelectric* and *electromagnetic*. Piezoelectric implantable hearing aids function by connecting the ossicles to an amplifier using a piezoelectric crystal vibrator. Piezoelectric materials are dielectric materials with coupled electrical and mechanical properties. Applying a voltage across an appropriately designed piezoelectric rod causes it to bend or lengthen, with a predictable change in deflection based on the voltage applied. Within the implant, sounds picked up by a microphone are converted by the signal processor to an electrical signal, and sent to the piezoelectric rod. As this rod vibrates in response to the converted auditory signal, it lies in direct contact with the ossicles. In this manner, sound waves are transferred directly to the ossicles, which travel along the normal auditory pathway. A critical feature of implants that use a piezoelectric transducer is direct contact between the piezoelectric unit and the ossicles.

Implantable middle ear hearing aids may also incorporate an electromagnetic transducer. These transducers generate a magnetic field using a coil carrying a current that encodes the microphone output. This magnetic field from the coil can cause motion in a ferromagnetic substance that is nearby, causing it to vibrate.[15] As applied to middle ear implants, sound received from a microphone is converted by the signal processor, amplified, and sent to the electromagnetic transducer. The electromagnetic field that is set up vibrates a ferromagnetic unit coupled directly to the ossicles. In contrast to the piezoelectric unit that must be in direct contact with the ossicles, electromagnetic transducers need only to be near the ossicles, which have attached to them the ferromagnetic device that transmits the auditory signal to the ossicles.

These two types of amplification have different advantages for use in an implantable hearing aid. Electromagnetic transducers do not directly contact the ossicular chain, but rely on electromagnetic transmission to a ferromagnetic unit that is attached to the ossicles. Electromagnetic transducers can be packaged in a smaller housing, an important factor in the ear. In contrast, piezoelectric devices are larger and couple directly to the ossicular chain. The advantage of this type of transducer is its ability to deliver more distortion-free amplification directly to the ossicular chain.[15] In either event, to accommodate patients with moderate to severe SNHL in the 55- to 90-dB hearing level range, any implant, whether electromechanical or piezoelectric, should be able to deliver a maximum mechanical stimulation output equivalent to 120 to 130 dB sound pressure level (SPL).[16,17] How each implant achieves this output level is described subsequently.

Ossicular Coupling

As noted by Huttenbrink,[18] to obtain optimal efficiency in implantable hearing aids, they must adapt to the mechanics of the middle ear and ossicular chain. As the third ossicle in the chain, and the one in conti-

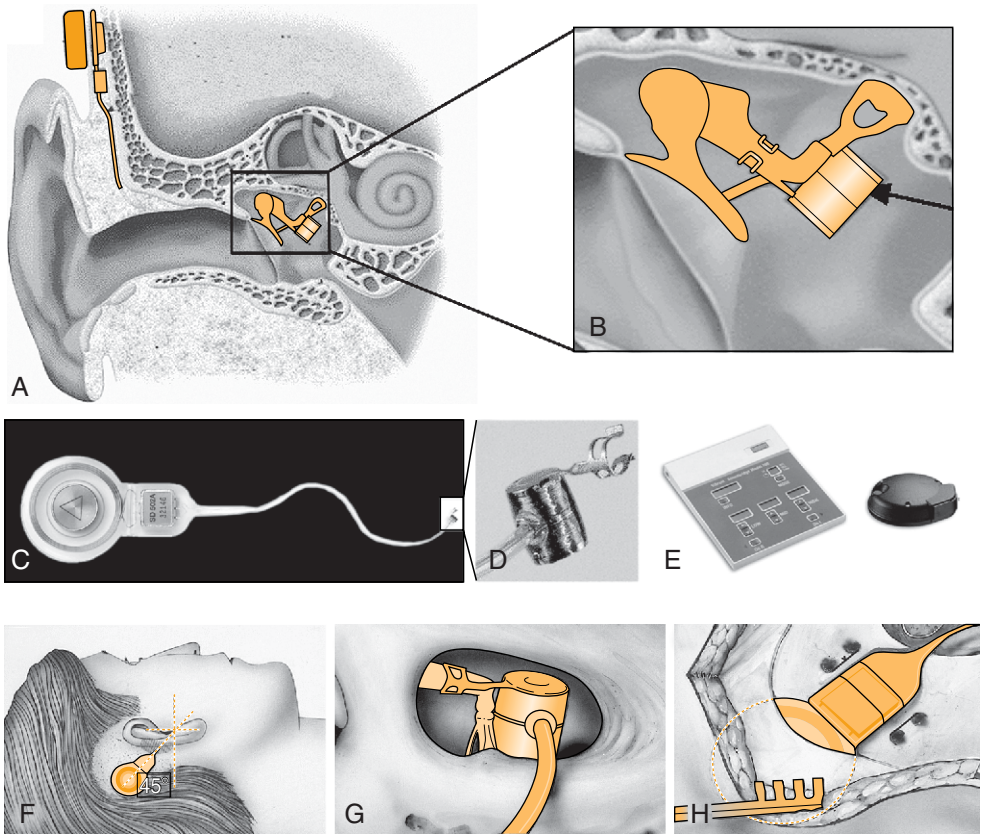


Figure 157-3. **A-H,** Med-El Vibrant Soundbridge semi-implantable hearing aid. **A** and **B,** External microphone couples via an inductive transcutaneous link to the actuator, a vibrating ossicular prosthesis (VORP) that couples to the incus long process **(B)**. **C,** Implanted component of device. **D,** VORP actuator. **E,** Programming unit and external circuitry. **F-G,** Inductive link is implanted against retromastoid cortical bone, similar to a cochlear implant **(F** and **H)**. VORP is clipped to the incus via a facial recess approach **(G)**.

nuity with the inner ear, the motion of the stapes is crucial in sound transmission. The stapes moves in a piston-like fashion.[19] The ideal motion of the stapes by a prosthesis would be in this piston-like fashion. Any implant that directly attached to the stapes would function best by mimicking this motion.[20,21]

Various implants employ numerous ways to couple vibration stimuli to the inner ear. Some employ a piezoelectric transducer to contact either the stapes head directly (e.g., St. Croix Envoy/Esteem-Hearing Implant) or the incus body (e.g., Implex TICA). Others use an electromagnetic transducer typically attached to the incus (e.g., Med-El Vibrant Soundbridge, Otologics Carina/MET), but sometimes adapted to contact the stapes capitulum, stapes footplate, or round window membrane. Others clip to the incudostapedial joint (e.g., Soundtec Direct Drive System). Each of these systems is described in greater detail individually.

Total versus Partially Implantable Hearing Aids

Implantable middle ear hearing devices may be either totally or partially implantable. Partially implantable devices consist of an external microphone and speech processor that are connected to a transmitter with an external coil that transmits electrical energy transcutaneously to the internal device, in much the same way cochlear implants are now powered. The battery-powered system is contained within the external device, decreasing the size of the implanted component. The internal device consists of an internal receiving coil, which provides electric energy to the mechanical driver connected to the ossicular chain.

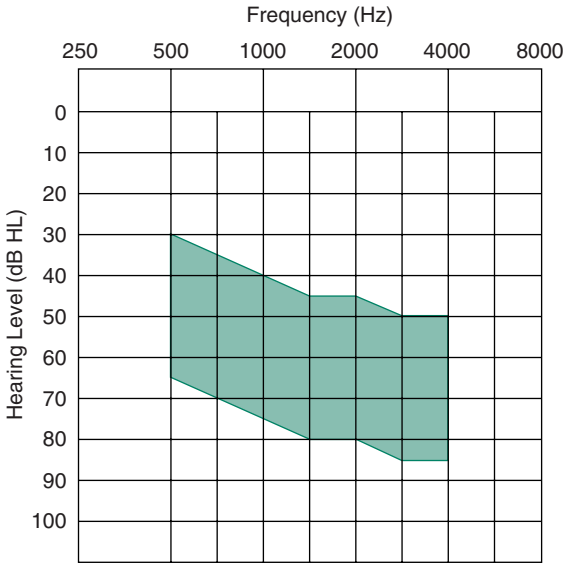
In contrast, the fully implantable systems house all of the above-mentioned components within the implanted portion of the device, including the battery pack. Although the size and complexity of the implanted components are increased, the visibility of the device is reduced, a feature that is desirable among hearing aid users. Because of the finite life of the rechargeable batteries, the totally implantable designs employed in clinical settings so far require reoperation at approximately 5-year intervals to exchange the spent device with one containing a new battery.

Electromagnetic Middle Ear Implantable Hearing Aids

Vibrant Soundbridge

To date, the implantable middle ear hearing aid with the most clinical data is the Vibrant Soundbridge, manufactured by Symphonix Corporation until 2002, when Symphonix was dissolved and the Vibrant technology was bought and later re-released by a subsidiary of the Med-El Corporation (Innsbruck, Austria), which resumed Vibrant Soundbridge sales in 2004. Because it was the first commercially available, FDA-approved middle ear hearing aid, a thorough review of this device is instructive.

The Vibrant Soundbridge is a semi-implantable hearing aid that was first introduced in 1997 (Fig. 157-3). Since its introduction in 1997, more than 2300 patients have been implanted worldwide.[14] The device was approved for commercial availability in Europe in 1998, and in the United States in 2000. The electromagnetic transducer uses a proprietary vibrating ossicular prosthesis (VORP), which typically is attached to the long process of the incus. The VORP contains a rare earth magnet surrounded by a receiving coil, a demodulator package, a conductor link, and a proprietary floating mass transducer (FMT).[22,23] The transducer was developed by Ball, and incorporated prior conceptual work performed by Goode and colleagues.[11,22,24] The VORP is electrically connected to the internal receiver.[25] These internal components are coupled to the audio processor via a telemetry link, similar to a cochlear implant. The processor, which is worn behind the ear, contains the microphone, audio processing electronics, magnet, telemetry transmission equipment, and room for a standard 675 zinc battery to power the implant.



Soundbridge Clinical Indications:
Pure-tone air-conduction thresholds within selection criteria
Normal middle ear anatomy
Word recognition score of ≥50% using recorded material
Absence of retrocochlear or central involvement
≥18 years old

Figure 157-4. Audiologic selection criteria for the Soundbridge. The Soundbridge is indicated in patients with moderate to severe sensorineural hearing loss of 70 dB pure-tone average hearing thresholds. The shaded area of the figure corresponds to the pure-tone audiometric implant criteria.

The function of the externally worn processor is similar to a conventional hearing aid. Sound is picked up by the microphone and processed by the external receiver by the electronics. The signal is sent via telemetry to the internal receiver. From here it is sent to the demodulator, which provides a safety feature to limit maximum power output and prevent overstimulation. The demodulator generates a current encoding the sound, and this current travels to the FMT, causing the FMT to vibrate through inductive interaction with the magnet. Because the FMT is firmly attached to the incus using a titanium clip, amplified sound is transmitted directly to the ossicular chain. Because the FMT includes a magnetic component, implantation of this device prevents a patient from undergoing magnetic resonance imaging (MRI) without device removal.

The Vibrant Soundbridge is indicated in patients with moderate to severe SNHL and desire for an alternative to an acoustic hearing aid (Fig. 157-4).[23] Studies have indicated that it may be suitable for patients with hearing loss of 70 dB pure-tone average (PTA) hearing thresholds.[26] When first introduced, the externally worn audio processor was an analog device that incorporated a wide dynamic range compression. Because of inadequate gain of the device, particularly at lower frequencies and with low sound levels,[27] a newer, more powerful digital audio processor was introduced in 1999. Studies done shortly after its introduction failed to show superior hearing results compared with conventional aids, although patients preferred the device, in part because of ability to wear it for a much longer time without discomfort.[26]

The device typically is implanted using a standard transmastoid, facial recess approach to the middle ear. The VORP is crimped into the long process of the incus. The internal receiver is placed in a bony trough in the retrosigmoid bone several centimeters behind the ear, in a location similar to the receiver placed during cochlear implantation. One potential drawback of this design concerns the size of the VORP. Because of the confined space between the eardrum and the incus, the dimensions and mass of the FMT are limited, restricting its output.[28] A second potential drawback is erosion of the incus long process, owing to ischemia at the clip attachment site. Modifications of the typical surgical approach allow treatment of mixed hearing losses resulting from otosclerosis or ossicular erosion or agenesis through direct placement of the VORP on the stapes superstructure, round window, or oval window.[29-32]

Owing to its primacy in regulatory approval processes and patient availability, to date more clinical data are available for the Vibrant Soundbridge than for all other middle ear implants. Results from the phase III clinical trial of 53 patients were sufficiently favorable to merit FDA approval of the device (phase I trials typically test feasibility and safety in a small group of subjects, phase II trials typically test effectiveness in a slightly larger group, and phase III trials assess safety and effectiveness in a large group).[23] Patients in the study were analyzed with conventional analog hearing aids, digital hearing aids, and the Vibrant Soundbridge. Standard audiologic tests included pure-tone air-conduction and bone-conduction thresholds (250 to 8000 Hz), functional gain, speech recognition tests, the Profile of Hearing Aid Performance, and the Hearing Device Satisfaction Scale.

Although one patient had a shift of 18 dB after device placement, the effect of implantation on residual, native hearing was believed not to be significant (<10 dB PTA at 500 to 2000 Hz). This finding corroborated earlier studies that showed little to no effect of the presence of the FMT on hearing sensitivity.[33] When compared with presurgical conventional hearing aid test scores, the implant showed a statistically significant improvement in functional gain at all frequencies and greater than 10 dB improvement at 2 kHz, 4 kHz, and 6 kHz. No significant difference was noted in speech recognition (NU-6 word list) between the preoperative hearing aid and the implant. On the revised speech reception in noise score, 7 patients (13%) showed significantly better scores, 70% showed no change, and 17% had worsening of their scores. As an entire group, there were no significant differences between the conventional hearing aid and implant group test scores on speech reception scores. Significant improvements were noted in the implanted group on the two self-assessment questionnaires (Profile of Hearing Aid Performance and Hearing Device Satisfaction Scale).

It seemed from the results of this phase III study that there were some objective gains in auditory scores with the implants compared with conventional hearing aids, and patient perceptions of the implant were better than conventional aids. Most of the subjective benefits of the implant centered around the ability to wear the device all day without the discomfort afforded by conventional aids.

The European experience with the Vibrant Soundbridge seems similar to the experience in the United States.[24,25,34] A multicenter study from Europe, which included 63 patients, focused on the gain provided by the implant and attempted to assess the quality of the amplified speech.[25] In contrast to the U.S. FDA phase III study, the European study did not compare results with a conventional hearing aid, but used the unaided condition as a comparison. The study noted a large variability in gain for each patient. For most patients, the greatest gain was in the 1- to 2-kHz region, where the transducer has its resonance.[22] The authors reasoned that an inefficient coupling in some patients (e.g., the FMT may be loose) may be responsible for the wide variability seen, and highlighted the importance of effective placement of the VORP on the incus.

When the authors compared gain at threshold and gain at normal speech, there was only a small difference noted (6 dB), indicating that the gain is effective at normal speech levels. The authors also concluded that the amplified sound from the Vibrant Soundbridge had adequate quality for speech intelligibility. Overall, the authors believed that there was clear benefit from the Vibrant Soundbridge, but there was a subgroup of patients with low gain, secondary to the limited bandwidth of the amplified signal. Other work from this same multicenter European group has shown a significant improvement in communication in various listening conditions with the Vibrant Soundbridge compared with conventional aids.[24,34]

A more recent report relates the Belgian experience with the Vibrant Soundbridge.[35] In a study of 13 patients, the average functional gain between 500 Hz and 4000 Hz was 30 dB, similar to prior European and American studies published. The authors noted, however, that not all of their patients studied were able to afford the best possible digital hearing aid preoperatively, and they could not adequately compare

satisfaction levels. The cost of the implant is severalfold higher than for the top-of-the-line digital aids, and it is likely that these patients could not afford the implant on their own. The authors reported high satisfaction of all the users of the device, and the "impressive" functional gains, particularly at higher frequencies.

One study that has specifically addressed the functional gain of the Vibrant Soundbridge with conventional hearing aids is from Todt and associates.[36] Examining five patients first fit with an analog and then digital conventional processor, the authors compared results with a digital processor of the Vibrant Soundbridge. As with previous studies, no significant differences were noted in underlying, residual hearing as a result of implant placement. Their data showed a significant improvement of hearing compared with conventional aids in quiet (approximately 10 dB PTA), and a better functional gain in noise for the Soundbridge compared with conventional aids. Subjective outcomes of a hearing aid questionnaire (Abbreviated Profile of Hearing Aid Benefit) also showed significant improvement of the Symphonix implant compared with conventional aids. As with other studies, the greatest gains were noted in the higher frequencies.

Placement of the Vibrant Soundbridge on the round window for treatment of conductive and mixed hearing loss has become commonplace in Europe. FDA approval in the United States for this approach and indication is still under investigation in a clinical trial that started in 2008.

The Vibrant Soundbridge story provides a cautionary insight into potentially the future of all implantable hearing aids. In late 2002, before the ultimate purchase of Symphonix by Med-El Corp., the Symphonix corporate website abruptly announced dissolution of the company. The Symphonix announcement raised poignant medical and ethical questions not just for the more than 600 patients already implanted with Symphonix devices, but also for the middle ear implantable hearing aid field as a whole. When novel implantable technologies are championed by small companies dependent on venture capital for continued support of operations, the longevity of corporate support of a device must be in question. Should there arise a serious liability issue with the device in the future, would implanted patients have any recourse? In this instance, an established company (Med-El Corporation, a manufacturer of cochlear implants) bought the technology and offered to provide patient support. Would a similar bailout occur if another of the middle ear implantable hearing aid companies fails? Surgeons and patients must consider these issues before implanting a middle ear hearing aid from a company without a proven track record of product reliability and financial stability.

MET (Middle Ear Transducer) and Carina

The Otologics MET (Middle Ear Transducer) is an electromechanical middle ear hearing aid using a mechanism initially developed by a group headed by Fredrickson in collaboration with Storz Instrument Co. It is now manufactured by Otologics LLC.[16] Although the original MET (on which most data reviewed here are based) was semi-implantable, that design has been replaced by a fully implantable version marketed as the Carina (Fig. 157-5).

The MET implantable unit consists of the transducer coupled to an electronic receiver.[16,37] The transducer vibrates a probe that is in direct contact with the incus. For the semi-implantable version, two external devices were developed. The device initially used in clinical trials was a modified version of Oticon's JUMP-1 hearing aid (Oticon Inc., Copenhagen, Denmark), and comprised a BTE signal processor, microphone, amplifier, and battery. This device was attached to a transmitter coil via a short cable. A newer unit housed the transmitter coil together with the BTE components. These semi-implantable designs enabled the MET to deliver the equivalent of greater than 135 dB SPL over a frequency range of 250 to 6250 Hz.[16] This output should theoretically provide adequate gain for patients with moderate to severe SNHL.

Placement of the MET Ossicular Stimulator requires a general anesthetic and approximately a 2-hour operation (Fig. 157-6). Using a standard, postauricular approach to the mastoid cortex, the root of the zygoma, posterior canal, and linea temporalis are clearly delineated (see Fig. 157-6).[16] A limited mastoidectomy (antrostomy) is performed

Figure 157-5. Otologics Carina fully implantable system. *(Courtesy of Otologics, LLC, Boulder, CO.)*

directly superior to the external canal and inferior to the tegmen tympani using a 6-mm bur, and extended until the incus body (approximately a 10-mm width) and head of malleus are exposed. When complete, a mounting system is attached over the opening using bone screws. The MET Ossicular Stimulator is maneuvered into the mounting system with the transducer probe tip fully retracted. A laser is used to make a small hole in the incus body to accept the probe tip. The tip is advanced into position using a micrometer screw, and ultimately becomes firmly attached to the incus from fibrous tissue. The receiver capsule and transducer electronics are placed in a recess drilled in the mastoid, similar to cochlear implant electronics.

Ultimately, 282 patients were implanted with the semi-implantable MET in Europe and the United States during phase I and II trials.[16] Pure-tone audiometry, speech recognition, and subjective assessment of benefit were tested before the surgery and 12 months after. Group mean postoperative bone-conduction and air-conduction thresholds were not significantly changed from preoperative levels compared with a well-fit digital hearing aid used preoperatively. A slight (approximately 5 dB) increase in CHL was attributed to mass loading by the transducer on the ossicles. Sufficient gain was available to make the device useful for subjects with moderate to severe SNHL. Speech and subjective assessment of patient preference indicated that patients did as well or better with the MET compared to their "walk-in" aid or the standardized digital hearing aid (Fig. 157-7).[37]

The Otologics Carina fully implantable hearing system is similar to the original MET except that it requires no external components apart from a charger and remote.[38] It uses a subcutaneous microphone rather than an external microphone, and it is designed to work for waking hours of 1 day between charging sessions that require 1 hour. Phase I trial results in the United States showed 10 to 20 dB of functional gain across audiometric frequencies at 3 months postoperatively.[39,40] Pure-tone bone averages were minimally changed from preoperative values. Pure-tone air averages and monaural word recognition scores were initially slightly worse with the device than measured preoperatively with the walk-in aid, but patients reported greater subjective benefit with the implanted device.

Within 12 months postoperatively, a high rate of device failure was observed, leading to explantation in 5 of the 20 adult study subjects as of early 2008. Failure modes included partial device extrusion, inability to communicate to external components, and failure of the recharging mechanism. Even among devices that did not require explantation, degradation in hearing performance commonly occurred at approximately 6 months after implantation and was attributed to movement of the subcutaneous microphone. These observations led to a redesign

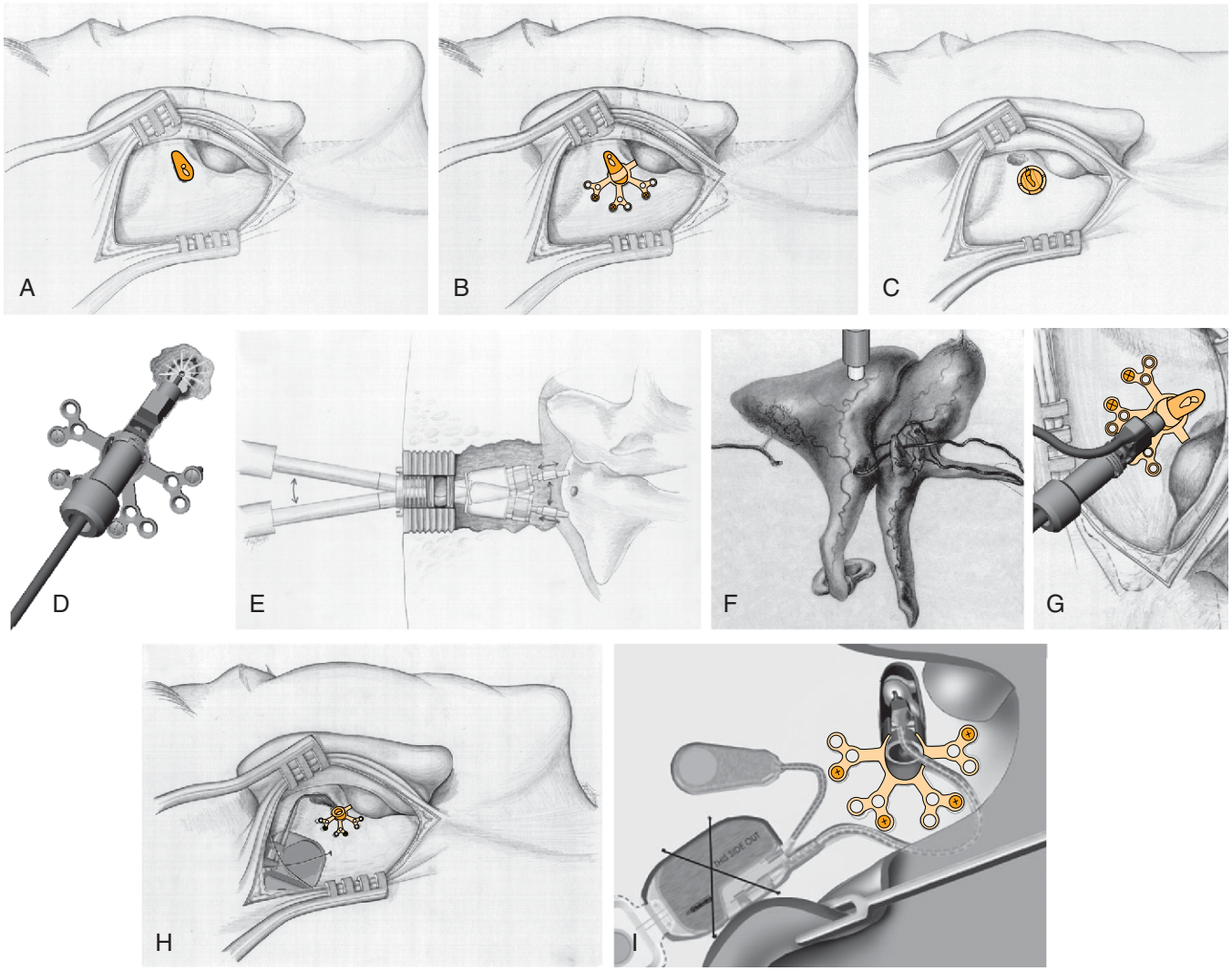


Figure 157-6. **A-I,** Surgical implantation of the Otologics MET or Carina begins with a limited antrostomy **(A)** sparing cortical bone ledges for attachment of a metallic stage **(B, C)**, which is used to steady a laser **(D)** for creation of a small hole in the posterosuperior incus **(E)**. The laser is removed and replaced with the MET actuator, the tip of which inserts into the incudotomy **(F)**. The actuator is secured to the stage **(G)**, and the remainder of the implanted device is secured to retromastoid cortical bone **(H)**. In the Carina totally implantable version of this device **(I)**, a subcutaneous microphone beneath the skin covering the mastoid replaces the external microphone and inductive link used in the MET, but the implantation procedure is otherwise similar.

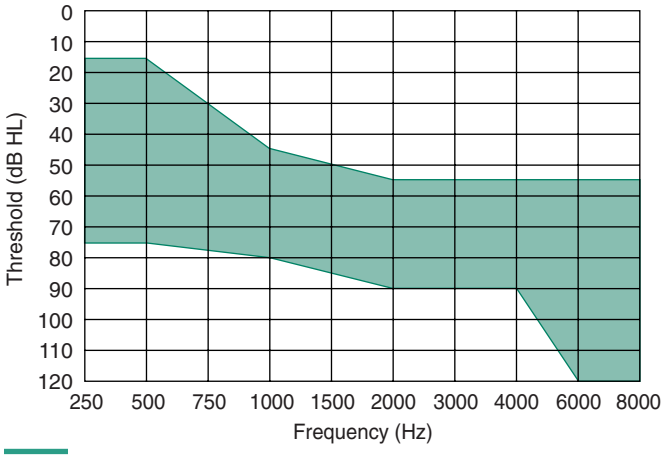


Figure 157-7. Audiologic selection criteria for Otologics MET. The shaded area of the figure corresponds to the pure-tone audiometric implant criteria.

and revision in surgical technique emphasizing creation of a well adequately deep to prevent device extrusion and a tie-down mechanism to prevent microphone migration. Intraoperative measurement and optimization of ossicular coupling compression resulted in more consistent and better coupling efficiency of the transducer to the ossicles.[41,42]

The Carina has received the CE Mark for clinical use in Europe, and phase II trials are under way in the United States. As of early 2008, more than 50 patients had been implanted with the redesigned device, and the failure modes identified during the phase I trial had not recurred.[39] Variations on the size and length of the ossicular coupling have expanded the application of the Carina to patients with aural atresia and ossicular discontinuity, via direct attachment of the device on the stapes capitulum, stapes footplate, and round window.[41,43]

Piezoelectric Middle Ear Implantable Hearing Aids

Esteem-Hearing Implant

A piezoelectric bimorph placed on the malleus head can effectively use the tympanic membrane as a microphone, offering a viable alternative to a subcutaneously implanted microphone. Studies in cadaveric temporal bones have shown that such a device had a dynamic range of

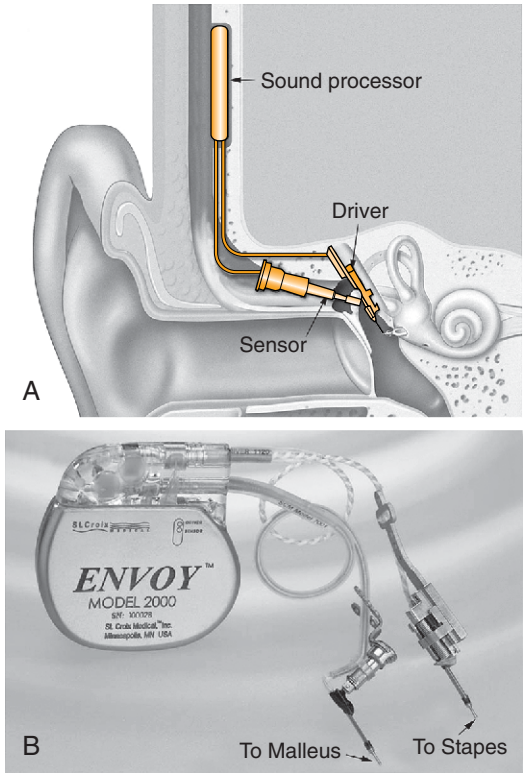


Figure 157-8. The Envoy/Esteem piezoelectric totally implantable hearing aid. **A,** Implantation schematic. Instead of a microphone, sound enters the device via a piezoelectric transducer coupled to the malleus and tympanic membrane. A piezoelectric actuator produces amplified stapes motion. The incus has been removed to prevent feedback. **B,** Complete device.

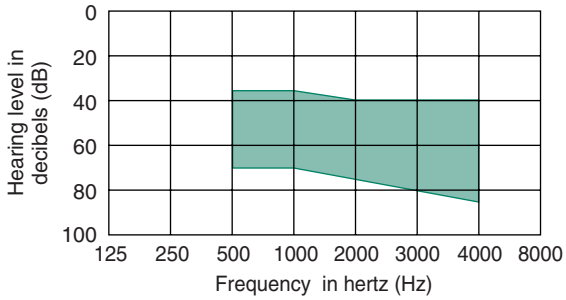


Figure 157-9. Audiologic selection criteria for the Envoy. The Envoy is designed for patients with moderate to severe hearing loss (35 to 85 dB) between 500 Hz and 4000 Hz in the implanted ear that is equal to or worse than the hearing loss in the nonimplanted ear, normal tympanometry, and speech discrimination 60% or greater. The shaded area of the figure corresponds to the pure-tone audiometric implant criteria.

80 dB at 1000 Hz, with precise ossicular tracking out to 4000 Hz.[44] The Esteem-Hearing Implant developed by Envoy Medical (formerly called the Envoy device and developed by St. Croix Medical, Inc., Minneapolis, MN) is a fully implantable piezoelectric device that uses this approach (Fig. 157-8). It received the CE Mark in Europe in 2006 and as of 2008 was in a phase II clinical trial in the United States.

Similar to all passive transducers, piezoelectric devices are bidirectional. The Esteem/Envoy uses a piezoelectric crystal to convert malleus vibrations (owing to sound waves impinging on the tympanic membrane) into a voltage encoding sound. After amplification, this electric signal is applied to a piezoelectric output transducer, which converts from the applied voltage to mechanical vibration coupled to the stapes. Power is provided by a nonrechargeable lithium-iodine battery designed to last 5 years between replacements, according to the manufacturer.[45] Programming and control of the device are accomplished through a radiofrequency transcutaneous link to a hand-held device or laptop computer.

By using acoustic input measured at the malleus, the Esteem/Envoy should maintain the spectral shaping and sound-localizing characteristics of the pinna, external auditory canal, and tympanic membrane. Implantation of the Esteem/Envoy requires partial removal of the incus, however, to prevent feedback from actuator to sensor; this ensures a maximal CHL in the event of device failure or removal, unless an ossiculoplasty is performed. This drawback has presented a significant hurdle to acceptance of the Envoy, which has not yet obtained FDA approval for routine clinical use in the United States despite earning a CE Mark in 2006. The internal battery must be replaced approximately every 5 years, and this requires repeated surgeries.

The Esteem/Envoy is designed for patients with moderate to severe hearing loss. Indications include age 18 years or old, mild to severe (35 to 85 dB) SNHL between 500 Hz and 4000 Hz in the implanted ear that is equal to or worse than the hearing loss in the nonimplanted ear, a healthy ear with normal pneumatization and adequate space for device implantation on computed tomography (CT), normal tympanometry, and speech discrimination 60% or greater (Fig. 157-9). A phase I trial in the United States and Germany was completed in 2003. By 1 year after implantation, three of seven subjects continued to use the implant, three had been revised and then explanted, and one was awaiting revision surgery. For the three subjects with functioning implants, there was no significant change in bone thresholds, and the 4-frequency (500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz) average functional gain was 17 dB ± 6 dB, which was comparable to conventional hearing aids except at 3000 Hz, where the Envoy performed less well than conventional hearing aids. The decline in performance was attributed to a gradual ingress of moisture in the transducers.[46]

Implantable Bone-Conduction Hearing Aids

Conductive and mixed hearing losses are highly prevalent disorders that often may be effectively treated using standard surgical techniques or rehabilitated with traditional hearing aids. For a variety of reasons, a large subset of these patients are not suitable surgical candidates for correction of their deficit, however, or are unable to tolerate a conventional hearing aid. This group includes patients with chronically draining ears despite multiple corrective attempts, patients with discomfort from the sound levels required from a traditional hearing aid, and patients unable to tolerate a hearing aid because of a large mastoid bowl or meatoplasty after chronic ear surgery. Additionally, patients with otosclerosis, tympanosclerosis, or canal atresia, and who have a contraindication to surgical repair may also fall into this category of patients who defy traditional attempts at hearing restoration. Patients who have undergone external auditory canal closure after extensive skull base surgery also are not amenable to traditional hearing aid rehabilitation. The osseointegrated BAHA device was originally intended for this group of patients.[47-49] The BAHA device now has also been used extensively for patients with unilateral deafness with good results.[49]

Conventional bone-conducting hearing aids have been advocated as an alternative for patients with conductive or mixed hearing loss who cannot benefit from a traditional hearing aid. The utility of these devices is constrained, however, by several physical factors. Because the bone conductor must be applied with steady pressure to the mastoid cortex (usually via a headband or eyeglasses), patients often experience pain, headache, and skin irritation at the contact site. Sound fidelity is limited by soft tissue attenuation, variable placement of the vibrator, and flaccidity of the securing device (usually eyeglass frames).[50,51] Coupling the bone vibrator to an osseointegrated implant, as originally performed by Tjellstrom and colleagues[51] at the Institute of Applied Biotechnology in Sweden in 1977, circumvents many of these drawbacks. This new generation of osseointegrated conductive hearing aids

now offers an effective alternative to hearing rehabilitation for this difficult subset of hearing-impaired patients.

Osseointegration

Background

In the 1960s, Branemark and associates[52] from Gothenburg, Sweden, discovered that titanium had a unique ability to become firmly anchored in bone without interposed soft tissue, while at the same time achieving a reaction-free epithelial penetration of the implant. In these permanent fixtures, Branemark presciently foresaw the ability of implanted titanium to support functional prostheses, and termed this state *osseointegration*. Osseointegration is considered to be successful if the implant became rigidly anchored into adjacent bone with no reaction at the implant-bone interface.[53] This concept was initially applied to dental implants, but in 1975, Branemark's group began studying the possibility of creating a *skin*-penetrating implant. By the 1980s, Branemark and colleagues, including Albrektsson, Jacobsson, and Tjellstrom,[54] had developed a clinical program with percutaneous titanium implants to provide an anchor for facial prosthetics (pinna, eye, or nose), and an attachment for a BAHA device.

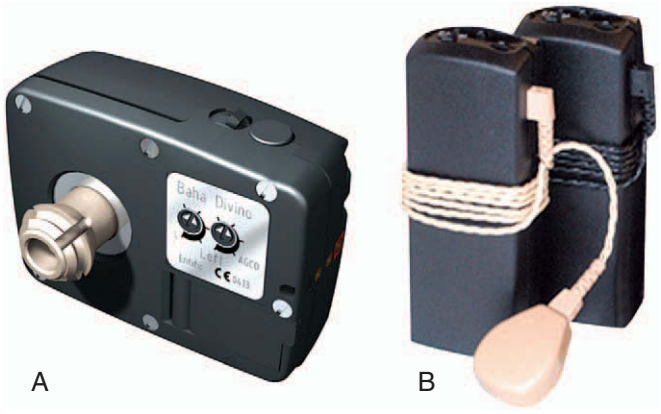


Figure 157-10. Osseointegrated bone-anchored hearing aid (BAHA). **A,** BAHA Divino is shown with its schematic attachment to the abutment and titanium implant. **B,** For patients with a more severe sensorineural component, the Cordelle offers increased amplification. *(Courtesy of Cochlear Corp, Lane Cove, Australia.)*

Biophysical Principles

Implant Material

One initial determinant of successful osseointegration is the chemical composition of the implant. Titanium has survived osseointegration's "test of time," and now represents the standard by which all other biomaterials are measured. Titanium is available commercially as "pure" titanium, which is 99.75% pure titanium, and titanium alloy, containing 90% titanium, 6% aluminum, and 4% vanadium. Titanium, similar to all other metals, forms several types of oxides on exposure to oxygen. In contrast to many of its metallic counterparts, however, titanium has the ability to create a tightly bonded and corrosion-resistant oxide layer on the surface of the implant. This oxide coating of the implant is in contact with the host tissue, which seems most important in determining the biocompatibility of titanium.[55,56] Because the implant may be worn for several decades or longer, the toxicity and carcinogenicity of the oxide coating take on particular importance.[53] Reports have shown that titanium is superior to stainless steel, lacking steel's high potential for corrosion or the toxicity of its components.[56] To date, pure titanium has shown none of these adverse sequelae, and continues to represent an ideal implant material.[55]

Implant Design

Implant microstructure and macrostructure also impact the likelihood of osseointegration. Although a rough-surfaced implant would theoretically better distribute a weight-bearing load, a rough, porous surface less than 100 µm would greatly increase the surface area and increase the risk of implant corrosion, even with a relatively corrosion-free material such as titanium. According to Eriksson and Branemark,[53] it is important that the microarchitecture of the implant surface features a topography with micropits that fit the dimensions of the cell membrane and large biomolecules; this facilitates direct bonding of the implant's oxide surface with the bone matrix. Parametric studies also show that *threaded,* screw-shaped implants have a greater likelihood of osseointegrating, and seem to distribute stress more efficiently than T-shaped or cylindric types of implants.[53,57] The threaded design success is probably most critical in conferring stability in the initial healing phase. If an implant is not absolutely stable after placement, connective tissue may form between the implant and the bone, preventing sufficient osseointegration.

Biology and Histology

Various studies have addressed the biologic correlates of osseointegration. First, there must be *direct* contact between the bone matrix and the implant, without interposed fibrous or soft tissue.[52] Pure (99.75%) titanium has shown this capability histologically, whereas titanium alloys, despite some clinical success, have not. Additionally, for successful osseointegration to occur, there should be no evidence of inflammation at the implantation site, including an infiltrate surrounding the implant or evidence of osteolysis with bone loss.[58] Pure titanium, as opposed to alloyed titanium, has also been shown to be superior in this regard.[51,55] Lastly, there should ideally be no evidence of a connective tissue capsule on the implant surface, although studies have shown that an implant with a capsule less than 30 µm in thickness may achieve osseointegration.[59] By all the above-mentioned criteria, pure titanium seems superior in every category for successful osseointegration compared with alloyed titanium. This superiority is borne out by several clinical studies as well.[50,60,61] Most authors continue to recommend pure titanium for implant material.

Radiologic Implications

A chief disadvantage of any metallic implant is interference with subsequent radiologic studies. Many osseointegration implant candidates are considered for implantation because of surgical defects caused by tumor extirpation, or other medical problems that require long-term surveillance with repeated postoperative CT or MRI scans. The presence of an implant that diminishes the quality of these scans, by introducing echo artifact, takes on increased importance. Pure titanium produces little degradation of images on either CT or MRI. Because of backscatter emissions, a radiation dose delivers 11% of the radiation dose in front of the implant, and 89% behind it.[62] This scatter effect produces little effect on the quality of CT images produced. Similarly, MRI is not contraindicated with the presence of a titanium implant. Any attached components must be removed before the MRI scan, however.

Operative Technique

Complete insertion of osseointegrated implants for the BAHA generally is done in a single stage (Figs. 157-10 and 157-11).[63] Although most surgeons perform the BAHA application in the operating room, there are reports of performing the procedure in an outpatient clinic setting.[64] Because of the importance of the implant's surface-bone interface, the surgeon must use a meticulous and precise method of implant insertion. This method sets the stage for osseointegration with minimal surrounding tissue damage. Only a single implant is needed for a BAHA. According to Branemark's original studies, insertion of the implant *must* be performed meticulously and as gently as possible to minimize thermal damage to surrounding bone.[65] This insertion is optimally performed with a high-torque drill at slow speeds (1500 to 3000 rpm) with sharp drill bits. The use of disposable drill bits avoids the possibility of worn cutting surfaces that damage the implant bed. Maximal irrigation is employed to prevent temperature elevations greater than 33° C. Previous studies have shown that heating tissue to 47° C for 1 minute obviates osseointegration because osteocytes are lost.

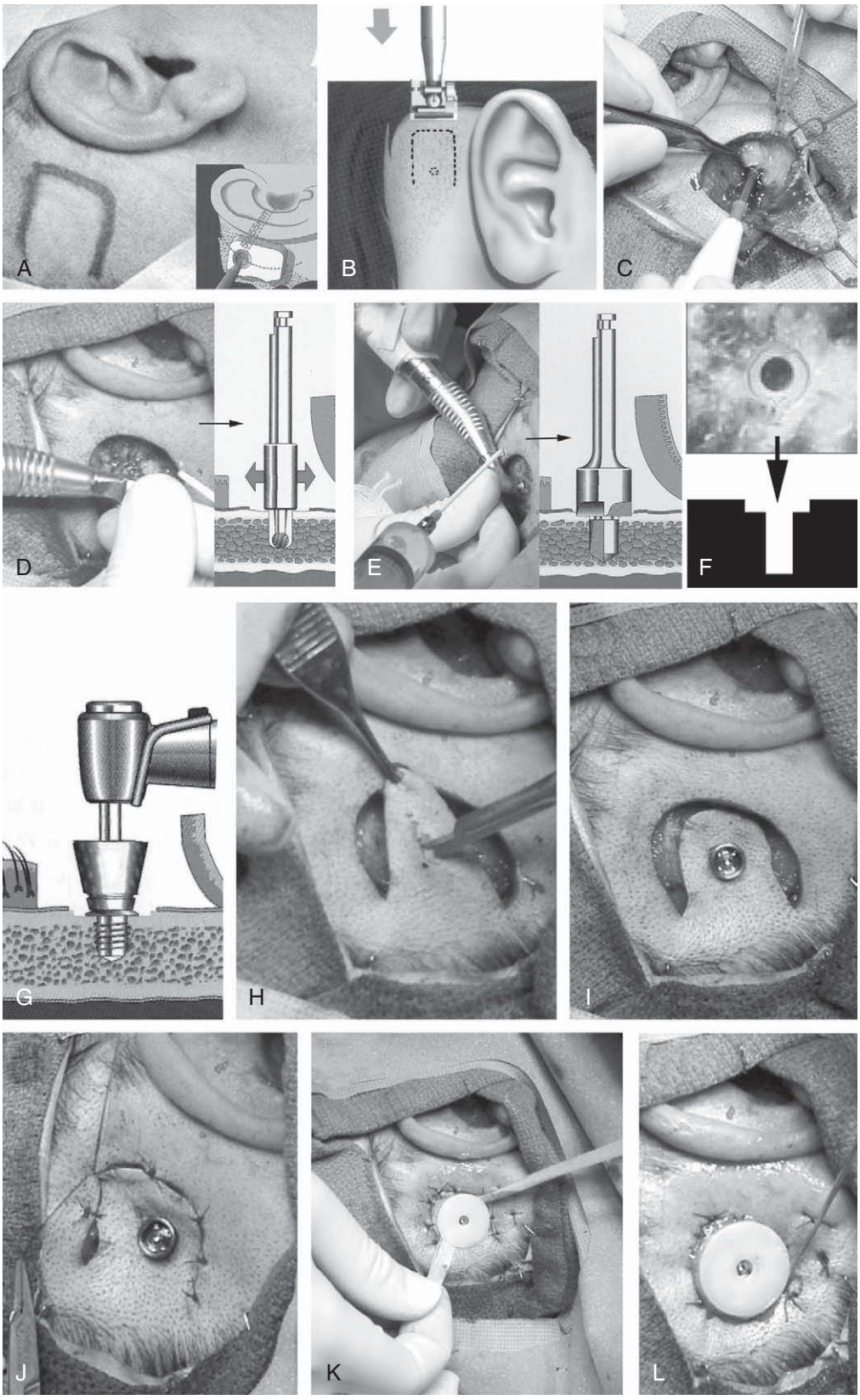


Figure 157-11. **A-L,** Operative technique for placement of Entific BAHA. **A,** Posterior-based skin flap is outlined. **B,** BAHA dermatome is used to elevate a thin flap (in this schematic the flap is inferiorly based). **C,** Soft tissues beneath and adjacent to flap are excised to create a smooth transition from surrounding tissue to thin central skin flap. **D,** A 3- to 4-mm hole is drilled in mastoid or retromastoid cortex. **E** and **F,** Countersink creates a recessed surface for implant placement. **G,** In the single-stage procedure used most commonly, the titanium implant with attached abutment is drilled into the skull at low torque. For a staged procedure, the abutment is removed, and the implant is closed laterally with a sealing screw (not shown). **H** and **I,** Skin flap is replaced, and a hole punch is used to create an opening to transmit the abutment. **J,** Flap is sutured closed. **K** and **L,** Healing cap is placed with gauze wrapped medially to apply pressure to the skin flap. *(Courtesy of Cochlear Corp, Lane Cove, Australia.)*

High-speed drilling typically used in surgery causes temperature elevations to 89° C.[66]

During the surgery, the postauricular skin surrounding the implant must be prepared for percutaneous attachment. The cutaneous-implant interface, as originally conceived by Branemark, is based on biologic principles found elsewhere in the body and throughout nature. Teeth and nails in humans, and talons, tusks, or claws as found in other species, all interface with a thin, firmly attached cutaneous or mucosal border, with little to no hair. This arrangement limits tissue mobility and increases stability of the area, while inhibiting the penetration of microbes with subsequent inflammation or infection.[67,68]

To recreate surgically a reaction-free implant-cutaneous junction, two preconditions *must* be met: The skin penetrated by the implant must be hairless, to facilitate keeping the implant site clean, and subcutaneous tissue should be aggressively thinned to minimize skin mobility in relation to the implant. The dermal layer is allowed to heal directly on the mastoid periosteum, creating a solid, immobile foundation for the implant.[63] To achieve these prerequisites in the temporal bone, hair-bearing skin overlying the implant is aggressively thinned, and hair follicles are removed from the level of the dermis. Some authors originally advocated removal of skin and replacement with a full-thickness skin graft, but this was associated with an increased incidence of skin breakdown surrounding the implant.[69] More recently, a dermatome has been developed specifically for use with the BAHA that has decreased the incidence of skin necrosis.[70] The final skin flap or graft should be less than 1 mm thick at the implant site and adjacent area. The edges of the surrounding skin flaps are sutured down to the periosteum to minimize tension on the flap.

After cutaneous work, disposable 3- and 4-mm drill bits are used to drill a hole in the skull corresponding to the central region of the flap, located at a distance approximately 5.5 cm posterior to the external auditory canal. This hole may be moved for specific anatomic irregularities or the presence of a plate from a prior skull base operation, ensuring that the placement of the abutment would not allow the hearing aid to contact the auricle. After the pilot drill hole, the countersink of the appropriate depth is used, again using maximal irrigation. Subsequently, the titanium implant with attached abutment is drilled into the skull under low torque until secured.

A hole is punched in the skin directly over each implant, and the abutment is screwed into the implant. A healing cap is placed over the abutment with antibiotic ointment–soaked gauze wrapped underneath, which helps prevent hematoma formation during the healing phase by anchoring the flap or graft to the mastoid cortex. After allowing for 12 weeks (adults) or 16 weeks (children) for osseointegration, the BAHA is simply snapped onto the abutment.

Bone-Anchored Hearing Aid in Young Children

The manufacturer of the BAHA recommends the osseointegration procedure in children older than 5 years. For children younger than 5 years in need of bone-conduction hearing rehabilitation, the BAHA-Softband is available.[71] Similar to a conventional bone-conduction hearing aid, the Softband allows bone-conduction hearing by coupling a standard BAHA device to a soft headband, providing hearing that is nearly equivalent to the osseointegrated hearing aid.

Some groups have advocated a traditional osseointegrated implant in this younger age group.[72,73] One complication that must be overcome, however, is the higher incidence of nonintegration in this younger age group, reported to be 15%.[74] Several recommendations have been proposed to avoid this complication. One is to use a two-stage procedure, whereby the implant is placed into the bone without the abutment, and the skin closed directly over this.[72,73] At a later second stage (6 months later if the skull is particularly thin), the skin flap is re-elevated, the abutment is placed, and the remainder of the procedure is finished as with the single stage. One can also leave the abutment in place during the first stage.[72] During the second stage when elevating the skin flap, a scalpel is used rather than the dermatome when the skin is tented by the healing screw, or the flap is infiltrated with local anesthetic to balloon it before using the dermatome. A final recommendation is to create an extremely thin flap to prevent cellulitis during the healing period.[72] Studies have shown that equal hearing results can be obtained when applying this staged approach in children younger than 5 years.[73]

Complications Associated with Osseointegration

The most frequently encountered complication associated with osseointegration is a soft tissue reaction at the percutaneous implant site. Soft tissue and skin reactions associated with percutaneous attachments were studied during the initial development phases of osseointegration technology. In one of the first large studies to address this issue specifically, Holgers and coworkers[75] monitored the soft tissue reactions of 67 patients who underwent osseointegrated implantation. With an average follow-up of 3 to 96 months, 14 of the 67 patients eventually developed adverse tissue reactions. One patient required removal of the abutment because of an infection, 5 patients developed redness and moisture at the abutment site requiring surgical revision (usually subcutaneous tissue thinning), 2 patients had redness with moisture requiring only local treatment, and 13 patients had developed minor erythema requiring temporary local treatment.

Jacobsson and colleagues[76] also published a case report of a patient who developed a soft tissue infection at an abutment site, eventually necessitating implant removal. Despite the presence of an ongoing infection, the implant showed histologic evidence of osseointegration. Niparko and associates[61] reported the first U.S. results with extraoral osseointegrated implants in 14 patients, noting a 3.5% incidence of symptomatic soft tissue reactions, with no implant extrusion. In the largest series to date, Tjellstrom and Hakansson[63] reported implant results on 456 patients, noting a 3.4% incidence of adverse tissue reactions; 3 patients required implant removal for infection, 3 required revision surgery for continued erythema and moisture, and 23 had tissue reactions requiring local treatment only. In the first large U.S. survey of BAHA devices, soft tissue complications were minimal and consisted of local inflammation at the percutaneous-implant junction (three patients).[47] A study of 149 consecutive cases showed that skin overgrowing the abutment was the most common complication (7%), which occurred on average 1 year after the initial surgery.[77]

Observations from these studies indicate that soft tissue reactions with percutaneous implants are largely prevented by soft tissue reduction and attachment of dermis to subjacent bone, to achieve immobility, and patient compliance with routine cleaning of the abutment site and close monitoring of skin attachment of the implant to the abutment. Complications other than adverse skin reactions are rare. Osseointegration failure is the second most common complication of the technique. In the study by Tjellstrom and Hakansson,[63] of 149 patients, 5 were considered failures; 4 failed to osseointegrate, whereas the fifth implant was lost through direct trauma. The first large U.S. series had only one patient with osseointegration failure,[47] whereas a more recent study by House and Kutz[77] had a 3.4% rate of implant extrusion. A rarely described complication is an intracerebral abscess.[78] Overall, studies consistently show that when Branemark's original surgical guidelines are followed, osseointegrated implantation is associated with high surgical success, and a low rate of morbidity and subsequent complications.

Results

In the largest series to date, Hakansson and colleagues[79] reported on their 10-year experience in 147 patients who received the BAHA. Patients were divided into three groups based on their PTA bone thresholds: 0 to 45 dB, 46 to 60 dB, and greater than 60 dB. The authors noted a strong relationship between PTA thresholds and successful rehabilitation. In the group with the best cochlear reserve (PTA <45 dB), 89% of patients' hearing was subjectively improved by the implant, whereas 8% believed their hearing was worse. Conversely, in the groups with progressively less cochlear function, 46 to 60 dB and greater than 60 dB, 61% and 22% of patients reported subjective hearing improvement. On average, speech discrimination scores improved from 14% unaided and 67% with a traditional hearing aid to 81% with the BAHA. This number increased to 85% if subjects with SNHL less than 60 dB HL were excluded, and to 89% if subjects with PTA less than 45 dB were excluded. Based on these results, the authors recommended that to be in consideration for a "high success

Table 157-2

Indications and Contraindications for Bone-Anchored Hearing Aid

Indications	Contraindications
Any patient using a conventional BC hearing aid	PTA BC thresholds (0.5-3.0 kHz) worse than 45 dB HL, SDS >60%
Any AC hearing aid user with chronic otorrhea	Emotional instability, development delay, or drug abuse
Any AC hearing aid user experiencing too much discomfort because of chronic otitis media or otitis externa	Age <5 yr
Any AC hearing aid user experiencing uncontrollable feedback because of a radical mastoidectomy or large meatoplasty	
Otosclerosis, tympanosclerosis, canal atresia with a contraindication to repair, such as in an only-hearing ear. Also, otosclerosis in combination with second, third, and fourth indications	

AC, air conduction; BC, bone conduction; HL, hearing loss; PTA, pure-tone average; SDS, speech discrimination score.

rate" with the BAHA, patients should have a PTA less than 45 dB, although improvements in hearing should still be expected for a PTA of 60 dB (Table 157-2).

In describing the Birmingham experience, Stevenson and colleagues[80] reported on the BAHA in seven children. Four children obtained improvements in PTA by 5 dB or more compared with their previous hearing aid, whereas four had changes in their thresholds of less than 5 dB. Only one of the six children tested for speech discrimination postoperatively had a significant improvement over his prior hearing aid, although the average speech discrimination score in this group was about 90% compared with 0% unaided. Liepert and DiToppa,[81] citing the Edmonton experience in 15 patients, reported an average gain of 30 dB SRT with the NAS compared with unaided speech. In the 10 patients queried, all reported that the BAHA was "better" to "much better" than their previous hearing, with or without their prior hearing aid, in all situations. Overall, the BAHA seems to offer patients with a PTA less than 45 dB a high degree of hearing rehabilitation, and excellent patient satisfaction with the device.

In the initial review of the U.S. experience with the BAHA,[47] the most common indications for implantation included chronic otitis media or draining ears and external auditory canal stenosis or aural atresia. Patients who had undergone skull base surgery and had complete closure of the external auditory canal were also included. Overall, each patient had an average improvement of 32 dB ± 19 dB with the use of the BAHA. Closure of the air-bone gap to within 10 dB of the preoperative bone-conduction thresholds occurred in 80% of patients, and closure to within 5 dB occurred in 60%. Nearly one third of patients showed "overclosure" of the preoperative bone-conduction threshold of the better hearing ear.

The BAHA Compact and the older BAHA Classic 300, on which these earlier studies are based, use an analog technology. A newer device, termed the Divino, featuring more contemporary signal processing has been developed. A more recent review comparing the Compact and Divino showed roughly equivalent results, with an average improvement over all frequencies of 27 to 28 dB for each device.[82] For speech understanding in noise, an advantage of 2.3 dB for the BAHA Divino versus the BAHA Compact was found, if noise was emitted from a loudspeaker to the rear of the listener, and the directional microphone noise reduction system was activated. Subjectively, the Divino was rated better in terms of overall sound quality by the patients.[82]

The BAHA Cordelle is the device with the most powerful gain. Although the recommended levels of hearing loss for the traditional BAHA (Classic, Compact, and Divino) encompass a PTA bone-conduction loss at 500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz at less than 40 dB HL, the body-worn BAHA Cordelle is recommended for patients with a more compromised cochlear reserve. Studies have shown that bone-conduction PTAs of less than 65 dB are acceptable for fitting.[83] There is also the BAHA Intenso, and similar to the Divino, but with additional power for an intermediate sensorineural component.

Bone-Anchored Hearing Aid for Unilateral Sensorineural Hearing Loss

BAHA is gaining increasing popularity for the rehabilitation of unilateral SNHL.[49,84,85] It is hypothesized that using the BAHA device on the deafened ear can expand the sound field for the patient and improve the patient's speech understanding in noise, similar to a contralateral routing of signal (CROS) hearing aid or transcranial CROS system. A prospective trial of subjects with unilateral deafness using benefit surveys, source identification testing, and hearing in noise testing was undertaken by Niparko and colleagues.[84] This study consisted of 10 adults with unilateral deafness (PTA >90 dB, SD <20%) for a variety of etiologies, including acoustic neuroma, meningitis, sudden SNHL, and sudden SNHL with chronic suppurative otitis media. Patients were fitted with contralateral routing of offside signal amplification devices (CROS) for 1 month and tested with contralateral routing of offside signal before mastoid implantation of the deaf ear, fitting, and testing for BAHA.

The results of this study showed that there was consistent satisfaction with BAHA implantation and amplification, and poor acceptance of CROS amplification. Sound localization was poor at baseline and with BAHA and contralateral routing of offside signal. Relative to baseline, CROS and the BAHA produced significantly better speech recognition in noise under most conditions. The BAHA enabled significantly better speech recognition than CROS in quiet and in a composite of noise conditions, a result that may have been related to averting the interference of speech signals delivered to the better ear, as occurs with conventional CROS amplification. The study showed that the BAHA, when placed on the side of a deaf ear, yielded greater benefit in subjects with normal monaural hearing than did CROS amplification.

Another study by Wazen and colleagues[85] has also evaluated the BAHA for unilateral SNHL. This prospective study of nine patients included hearing loss from congenital aural atresia or mastoidectomies secondary to chronic ear infections with or without cholesteatoma, or temporal bone tumor excision. Comparing BAHA-aided with the unaided condition, the authors showed that all patients had tonal and spondee threshold improvement with BAHA compared with thresholds before treatment. Speech recognition performance in BAHA-aided conditions was comparable to the patient's best score in unaided condition, and patients reported a significant improvement in their hearing handicap scores with the BAHA.

A more recent study by Lin and coworkers[86] for patients with unilateral SNHL showed consistent satisfaction with BAHA amplification and poor acceptance of CROS amplification. Sound localization was worse when using the CROS aid, but showed no benefit with the BAHA. In keeping with prior studies, the BAHA produced significantly better speech recognition in noise. Similar findings have been borne out by other studies.[87] These studies show that the BAHA is an excellent tool for rehabilitation of unilateral SNHL, and seems to outperform the only other rehabilitative option available for this difficult problem, the CROS hearing aid. The primary benefit seems to be improved hearing in noise, whereas the BAHA provides no objective benefit of sound localization.

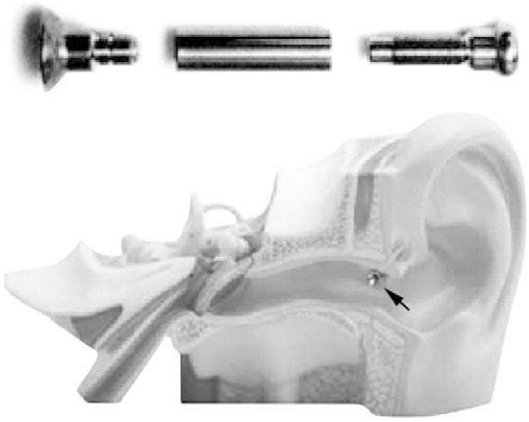


Figure 157-12. Auric metallic tube and transcutaneous placement from retroauricular sulcus to external auditory canal.

Implantable Adjuncts to Conventional Hearing Aids

RetroX

The RetroX (Auric Hearing Systems, Rheine, Germany) consists of an inert titanium metal tube that passes from the postauricular sulcus to the posterior aspect of the external auditory canal, passing just lateral to the mastoid cortical bone and external auditory canal bone (Fig. 157-12). Its major purported advantages are that it does not block the external auditory canal, and it does decrease feedback by separating the device microphone (which lies in a BTE unit) and the output of the speaker in the external auditory canal. Secondarily, there is a cosmetic advantage over traditional BTE aids in that the device is largely hidden behind the pinna, with no speaker tube visibly entering the external auditory canal. According to the manufacturer, the device is appropriate for patients with SNHL or CHL to 30 dB HL at 1 kHz and less and 30 to 80 dB HL loss at 3 to 8 kHz, and is especially suitable for cases of high-frequency SNHL with a steep slope (ski-slope audiogram).

To date, few peer-reviewed reports of device results have appeared in the literature. In one study of 10 patients, all were satisfied with the hearing improvement provided by the RetroX.[88] There was an improvement of pure-tone thresholds at 1 kHz, 2 kHz, and 4 kHz, whereas in quiet, the speech reception threshold improved by 9 dB. Speech audiometry in noise showed that intelligibility improved by 26% for a signal-to-noise ratio of −5 dB, by 18% for a signal-to-noise ratio of 0 dB, and by 13% for a signal-to-noise ratio of +5 dB. Complications included one patient with acoustic feedback and one patient with a granulomatous reaction to the foreign body that necessitated removing the implant. Refinements to the surgical process of placing the titanium tube seem to have diminished the rate of this complication.[89]

A subsequent study of 25 patients by this same group was reported after 2.5 to 15 months of use.[90] Of 25 patients, 23 were satisfied with the device, whereas 4 patients developed a persistent granulomatous reaction that disappeared after explantation, and 2 patients complained of acoustic feedback and needed supplementary fitting. The authors of this study observed a statistically significant improvement of the pure-tone thresholds, with similar speech in quiet and noise scores as their initial study. A study in 2005 by Barbara and colleagues[91] showed that the RetroX provided better hearing in noise with higher rates of satisfaction compared with a CIC hearing aid.[91]

Conclusion

Technology has brought about new and revolutionary means of rehabilitating patients with SNHL and CHL. Totally implanted and semi-implanted hearing aids have the potential to deliver improved sound quality, greater amplification, less distortion, better directional hearing, and better cosmetic appearance than conventional hearing aids. Whether this potential will be fully realized depends on further refinements of their design, acceptance by patients and third-party payers, and the financial viability of the corporations promoting them. Although current economic and financial obstacles may make the short-term outlook for these devices unclear, they will undoubtedly continue to be improved, and ultimately may prove to be a critical part of the armamentarium of devices used for rehabilitation of hearing loss.

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CHAPTER ONE HUNDRED AND FIFTY-EIGHT

Cochlear Implantation: Patient Evaluation and Device Selection

P. Ashley Wackym

Christina L. Runge-Samuelson

Key Points

- Cochlear implants are auditory prostheses designed to link an internal device interfaced with the auditory nerve to an external device that uses a specific speech coding strategy to translate acoustic information into electric stimulation.
- Prelingually deafened children acquire speech and language through central plasticity resulting from stimulation by auditory prostheses.
- Postlingually deafened children and adults, as well as those with severe to profound hearing loss, who derive marginal benefit from hearing aids, are appropriate cochlear implant candidates.
- The medical evaluation begins with a detailed collection of the patient's history including age of onset, progression, and bilaterality of the hearing loss; risk factors for hearing loss (e.g., noise exposure, ototoxicity, trauma); and ear infection and surgery.
- Congenital deafness occurs in approximately 1 in every 1000 children, and at least 60% of these children have hereditary causes of the deafness.
- The diagnosis of auditory neuropathy/auditory dys-synchrony has been specified as a hearing disorder where preserved outer hair cell function exists with abnormal auditory neural responses; some of these patients may be cochlear implant candidates.
- Preoperative imaging using CT and/or MRI is essential.
- Current adult selection criteria in the most recent clinical trials include (1) severe or profound hearing loss with a pure-tone average of 70 dB HL, (2) use of appropriately fit hearing aids or a trial with amplification, (3) aided scores on open-set sentence tests of less than 50%, (4) no evidence of central auditory lesions or lack of an auditory nerve, and (5) no evidence of contraindications for surgery in general or cochlear implant surgery in particular.
- With the benefits of binaural cochlear implantation being realized, current candidacy decisions now include whether to receive two implants rather than one.
- We suggest the following referral criteria for cochlear implant evaluation for adults: (1) unaided thresholds of 70 dB HL or poorer at 1000 Hz and above in the better ear, even if hearing levels at 250 and 500 Hz are better; (2) unaided word discrimination less than 70%; and (3) frustration on the part of the patient because of communication difficulties, even with appropriate hearing aid use.
- Cochlear implant evaluation for children can be considered with (1) unaided thresholds of greater than 90 dB HL at 2000 Hz and above in the better ear, even if hearing levels at 250 and 500 Hz are better; (2) aided thresholds in the better ear are greater than 35 dB HL, especially at 4000 Hz; (3) no response for ABR testing in both ears or no response for one ear and responses at elevated levels in the other ear; (4) parents are frustrated with their child's development of auditory and/or communication skills; (5) progressive hearing loss with detection levels at or near the profound range at 2000 Hz and above; or (6) evidence of severely impairing auditory neuropathy/dys-synchrony. There is no lower age limit for evaluation.
- Signal-processing strategies may affect device selection for a given patient (e.g., patients who are music enthusiasts may be interested in comparing aspects of fine structure strategies, whereas other patients with neurologic processing issues may benefit from having strategies that offer slower stimulation rates).

The development and improvement of cochlear auditory prostheses have radically improved the management of children and adults with profound hearing loss. Rapid evolution in the candidacy criteria and the technology itself has resulted in large numbers of individuals who have benefited from implantation. Likewise, the introduction of three device manufacturers into the U.S. marketplace has accelerated the research and development of these auditory prostheses. In this chapter, the evaluation and expectations for both children and adults are presented, as are the similarities and differences among all three available devices in the United States.

General Background

Cochlear implants are auditory prostheses designed to link an internal device interfaced with the auditory nerve to an external device that uses

a specific speech coding strategy to translate acoustic information into electrical stimulation. For the majority of causes of deafness, the auditory hair cells are lost or dysfunctional. The bipolar spiral ganglion neurons and their primary afferent dendrites remain intact, to varying degrees on the basis of etiology, and are available for direct electrical stimulation by the cochlear implant. The tonotopic organization of the cochlea is emulated by orienting the electrode contacts toward the modiolus within the scala tympani and assigning frequencies to specific electrodes along the length of the electrode array such that electrical stimulation corresponding to the highest pitches are delivered within the basal region of the cochlea while electrical stimulation corresponding to the lowest pitches are delivered within the apical region of the cochlea. The electrical impulses directly depolarize the primary afferent neurons, effectively bypassing the dysfunctional hair cells. All three device manufacturers use an external processor that encodes speech on the basis of features that are critical for word understanding in normal listeners, and these features are discussed later in this chapter. More than 70,000 individuals have received cochlear implants, and these devices are now reliably enabling speech comprehension in the vast majority of appropriate cochlear implant recipients.

Prelingually deafened children acquire speech and language through central plasticity resulting from stimulation by auditory prostheses. Some prelingually deafened adults are appropriate cochlear implant recipients but have limited central plasticity that is required for auditory pathway development and processing. Postlingually deafened children and adults, as well as those with severe to profound hearing loss, who derive marginal benefit from hearing aids, are appropriate cochlear implant candidates.

Patient Evaluation

Otologic/Medical Evaluation and Imaging

The medical evaluation begins with a detailed collection of the patient's history, followed by physical examination. The otologic history includes age of onset, progression, bilaterality of the hearing loss; risk factors for hearing loss (e.g., noise exposure, ototoxicity, trauma), and ear infection and surgery. History of possible vestibular dysfunction includes delayed walking, difficulty in riding a bicycle, or difficulty maintaining balance while walking with eyes closed or in the dark. A thorough family history is important including the age of onset, severity, and rate of progression of any hearing loss.

GENETIC HEARING LOSS. The etiology of the hearing loss is an important consideration. Profound hearing loss and deafness, although clear symptoms, have a heterogeneous group of causes. Of the genetic causes, more than 400 forms of syndromic hearing loss have been described, and the list of nonsyndromic loci now exceeds 80,[1] many of which are discussed elsewhere in this book.

Congenital deafness occurs in approximately 1 in every 1000 children, and at least 60% of these children have hereditary causes of the deafness.[2] It is estimated that 70% of all hereditary hearing losses are nonsyndromic, nearly 80% of which are inherited in an autosomal recessive fashion.[3] To date, 54 autosomal recessive, 24 autosomal dominant, and 8 X-linked loci have been characterized for nonsyndromic sensorineural hearing loss (NSHL).[1] Several mitochondrial DNA variants have also been implicated.[1] Studies indicate that up to 50% of all NSHL cases are due to a mutation in a single gene encoding connexin 26 (Cx26).[4] The gene coding for Cx26 (gap junction protein beta 2 or *GJB2*) is located at locus DFNB1 on human chromosome 13q12. The coding sequence of the protein is contained in a single exon that can be easily analyzed using sequencing methods.[5] Children with nonsyndromic genetic hearing loss, if implanted early, are typically excellent performers with their devices.

Genetic syndromal deafness represents a small proportion of all profound hearing impairment; however, there are typically other considerations to be made when these individuals are being considered for cochlear implantation. Although there are more than 400 genetic syndromes that include hearing loss, most syndromic deafness is confined to a limited number of syndromes.[6] Only two common autosomal recessive forms of syndromic deafness exist: Pendred's syndrome (deafness, wide vestibular aqueduct, and thyroid dysfunction) and Usher's syndrome (deafness, blindness due to retinitis pigmentosa, with or without vestibular dysfunction). Jervell and Lange-Nielsen syndrome (deafness and sudden death syndrome due to prolonged QT interval) occurs in families with strong histories or in population isolates. It is, however, important to consider when preparing to bring a child to the operating room when there is a family history of deafness and cardiac death. Unfortunately, the electrocardiogram (ECG) is not entirely sensitive or specific for this syndrome[7]; however, referral to a cardiologist for evaluation and treatment is essential for any deaf child with prolongation of the QT interval on an ECG, history of syncopal episodes, or a family history of prolonged QT interval. Neurofibromatosis type 2 (NF2) is usually diagnosed between the ages of 10 and 30 years, and these individuals can express the phenotype of bilateral acoustic neuromas, which is an important issue to consider when developing a management algorithm. If one of the tumors is removed while small and if the cochlear nerve is preserved, despite losing functional hearing, cochlear implantation is appropriate if a several-year interval has been observed indicating that a recidivistic tumor will not compromise the cochlear nerve. Otherwise, auditory brainstem implantation is an appropriate alternative.

The previous four syndromic disorders are not readily diagnosed at birth by history and physical examination. The most common dominant syndromes resulting in deafness are Stickler syndrome, branchio-oto-renal syndrome, and Waardenburg syndrome. When physical examination or history suggests a syndromic hearing loss, online resources have been developed to help the physician during the evaluation process.[8]

AUDITORY NEUROPATHY/AUDITORY DYS-SYNCHRONY. Over several years evidence has emerged regarding the existence of a hearing disorder that does not fit into the standard conductive, mixed, or sensorineural hearing loss categories. Relatively recently, the diagnosis of auditory neuropathy/auditory dys-synchrony (AN/D) has been specified as a hearing disorder in which present cochlear outer hair cell function is found in conjunction with absent or abnormal auditory neural responses, which is indicative of poor neural synchrony.[9] Reports on the incidence of AN/D symptoms range from 0.5[10] to 1.3%[11] of the population suspect for hearing loss, and 15% of those with absent auditory brainstem response,[11] which is otherwise consistent with severe to profound sensorineural hearing loss. Behavioral audiometric thresholds may or may not be within normal limits and can fluctuate over time, and speech perception in AN/D patients is often much poorer than the behavioral thresholds would predict. There are many possible reasons for poor auditory neural synchrony including, but not limited to, dysfunction of cochlear inner hair cells, of the inner hair cell/spiral ganglion nerve synapse, or of the auditory nerve itself.

The variety of etiologies in AN/D results in a heterogeneous population. Starr[12] reported the diagnoses from 70 patients with AN/D as fitting into the following categories: 40% hereditary, often associated with Charcot-Marie-Tooth disease; 20% with a mix of etiologies including toxic-metabolic (i.e., anoxia, hyperbilirubinemia), immunologic, and infectious; and 40% idiopathic. Transient AN/D has also been documented with temperature fluctuation in cases of severe illness.[13,14] In addition, AN/D may coexist with peripheral neuropathy, which has been observed as a loss of myelin and neural fibers in the cross section of sural nerves from some AN/D patients.[12]

Fitting AN/D patients with hearing aids may not provide sufficient benefit for communication because amplification provides increased sound intensity but does not have the capability to contribute to improved neural synchrony. After careful evaluation and when recommended, electrical stimulation with cochlear implants holds promise as a treatment option for individuals who are severely hearing impaired from AN/D,[15,16] and has been successful in our clinical experience. However, cochlear implantation may be contraindicated in cases in which neural function is significantly compromised or the auditory nerve is deficient or absent.[17]

ACQUIRED DEAFNESS. In young children, many acquired forms of deafness cannot be easily differentiated from genetic deafness. Prenatal infection with TORCH microorganisms (toxoplasmosis, syphilis,

rubella, cytomegalovirus [CMV], and herpes) is commonly associated with deafness. This spectrum of infections can result in reduced ganglion cell counts, cognitive dysfunction, and abnormal position of the facial nerve, all issues limiting the effectiveness of cochlear implants or increasing the risk of cochlear implant surgery. Prematurity and low birth weight, low Apgar scores, and hyperbilirubinemia can all be associated with deafness and, because of the central auditory processing abnormalities associated with these conditions, expectations for performance outcome following cochlear implantation should be tempered. Similarly, there can be rehabilitation needs and problems with these multiply disabled children.

Autoimmune inner ear disease (see Chapter 153) is typically rapidly progressive and often associated with highly favorable outcomes in postlingual patients receiving cochlear implants, likely due to the well-preserved primary afferent neuron population and the short duration of deafness. Although it is unusual for patients with bilateral Meniere disease to lose enough hearing to require cochlear implantation, such patients typically perform at excellent levels with an implant, likely due to significant residual hearing and auditory memory.

Many inherited or acquired diseases affect the temporal bone, which can produce severe to profound hearing loss requiring cochlear implantation. Otosclerosis, Paget disease, Camurati-Engelmann disease,[18] and meningitis with secondary labyrinthitis ossificans are a few examples of diseases that can present management challenges with cochlear implantation. Aside from the potential difficulty in electrode insertion, the reduction in bone density often leads to unwanted sequelae such as facial nerve stimulation due to current spread outside of the cochlea, affecting the postoperative programming of the device.

Although rare, bilateral temporal bone fractures resulting in deafness can be rehabilitated with cochlear implants. Early implantation should be performed to avoid cochlear fibrosis. If imaging studies suggest trauma to the auditory nerve, it is important to determine if the auditory nerve is functional using promontory electrical stimulation while recording electrically evoked auditory brainstem potentials (ABR). The use of auditory brainstem implantation in this clinical setting has been reported in Europe[19]; however, the first such application of this technology in the United States occurred only recently.

PHYSICAL EXAMINATION. All adults or children with profound hearing loss should have a complete physical examination. Clinical correlates of specific etiologies of sensorineural hearing loss are addressed in Chapters 147, 148, and 149 of this text.

CHRONIC SUPPURATIVE OTITIS MEDIA. Cochlear implantation was initially viewed as contraindicated in young children with chronic suppurative otitis media (CSOM) because of the potential risk of infection.[20] However, selective retrospective studies have shown that the prevalence and severity of OM does not increase following implantation,[21,22] leading surgeons to advocate cochlear implantation if the ear is dry at the time of implantation.

Some surgeons advocate a two-stage operative approach; the first operation involves a radical mastoidectomy (if not already performed), eustachian tube obliteration, and mastoid cavity obliteration with oversewing of the ear canal. Cochlear implantation is performed at a later time, usually 2 to 6 months postobliteration.[23] The major risk of mastoid obliteration is the formation of cholesteatoma, which must be carefully monitored on a long-term basis. Other authors advocate an individualized management strategy: (1) patients with a dry tympanic membrane perforation receive a first-stage myringoplasty followed by implantation in 3 months; (2) patients with cholesteatoma or an unstable mastoid cavity receive a radical mastoidectomy and obliteration followed months later by a second stage cochlear implantation; (3) patients with a stable cavity receive one-stage cavity obliteration and electrode implantation.[24] Finally, some practitioners advocate treating radical mastoid cavities with a one-stage operative approach that includes oversewing the external auditory canal and cochlear implantation without obliteration or reduction of the cavity.[25,26] Luntz and colleagues[27] have described a treatment algorithm with multiple steps aimed at resolving the draining ear. Using this strategy, cochlear implantation is performed at the completion of any step if the ear is dry. The existence of multiple protocols for managing cochlear implant candidates with CSOM reflects the problematic nature of this disease process. Regardless of the management protocol, all patients currently receive selected antimicrobial prophylaxis immediately before implantation.

Microbial biofilms are a common if not normal phenomena in nature; however, in the clinical arena biofilm formation is associated with increased morbidity and mortality.[28,29] Biofilms are characterized by a complex three-dimensional architecture with a network of adherent cells connected by water channels and encapsulated within an extracellular matrix.[30] Biofilms are recalcitrant to antibiotics, antiseptics, and industrial biocides. Possible mechanisms include (1) restricted penetration of drugs through the matrix; (2) phenotypic changes resulting from a decreased growth rate or nutrient limitation; and (3) surface-induced expression of resistance genes. Although there is an extensive literature on bacterial biofilms, little attention has been paid to medically relevant fungal biofilms, despite the fact that yeasts are the third leading cause of catheter-related infections, with the second highest colonization to infection rate and the highest crude mortality. Transplantation procedures, immunosuppression, use of chronic indwelling catheters, and prolonged intensive care unit stays are salient risk factors for fungal disease.[31] Biomedical devices including stents, shunts, and prostheses (voice, heart valve, knee, etc.); implants (breast, lens, dentures, etc.); endotracheal tubes; pacemakers; and various types of catheters have been shown to support colonization and biofilm formation by *Candida*.[32] Antifungal therapy alone has been shown to be insufficient for cure, requiring removal of the biomedical device.[33]

Since the advent of antibiotics in the 1940s, many authors have reported fungal overgrowth following antibacterial therapy.[34] Although bacteria usually cause CSOM, fungal infection or overgrowth is surprisingly common. One prospective study in CSOM patients reported growth of *Candida* species in 10% of ears with purulent otorrhea and in 35% of ears treated for purulence with topical ciprofloxacin for 3 weeks.[35] Furthermore, another study in which cultures were obtained from ears with ventilation tubes and otorrhea before and after a 10-day course of topical ofloxacin ear drops (Floxin) or oral amoxicillin/clavulanate demonstrated a 5% incidence of *Candida* superinfections in the amoxicillin/clavulanate group but negligible incidence in the ofloxacin group.[36] These results confirm the findings of an earlier study in which the incidence of *Candida* was significantly greater for patients treated with amoxicillin/clavulanate compared with a group treated with topical ofloxacin. We have had one case of fungal colonization of a cochlear implant with *Candida albicans*.[37] No guidelines have been proposed for dealing with episodes of otitis media in the early postoperative period. During this time interval, the physical barrier created by the fibrous sealing of the cochleostomy is in the process of being laid down, and thus the electrode array provides direct access to the inner ear. An infection of the middle ear during this period may easily extend along the electrode array, induce damage to the auditory nerve, and possibly lead to biofilm formation, requiring immediate removal of the implant. In addition, this puts the patient at higher risk for further spread of infection into the intracranial space and subsequent meningitis.[38] The high prevalence of bacterial biofilms in chronic otitis media have been recently demonstrated,[39] and bacterial biofilms have also been demonstrated in cases of infected cochlear implants that required explantation.[40]

IMAGING. Preoperative high-resolution temporal bone computed tomography (CT) scans, without contrast, should be performed on all cochlear implant candidates. Determination of intact internal auditory canals, normalcy of the cochlea, primary or secondary bone diseases affecting the cochlea, and presence of a wide vestibular aqueduct represent an important data set to complete. Many children with congenital deafness will be found to have an associated cochlear malformation, typically dilated vestibule, wide vestibular aqueduct, cochlear hypoplasia, or a common cavity.[41] When congenital or acquired narrow internal auditory canals are identified on preoperative CT scanning, primary afferent innervation may be lacking and cochlear implantation is therefore contraindicated.[18,42] Another important finding to identify is a wide vestibular aqueduct, which, when present, is an indication to perform preoperative magnetic resonance imaging

(MRI). This is an important preoperative consideration because this abnormality is associated with an abnormal communication between the cerebrospinal fluid (CSF) space and the cochlea. Clinically, this is often associated with a "perilymph gusher," and sealing of the cochleostomy with pericranium or fascia is particularly important to avoid meningitis following acute suppurative otitis media. Hypoplastic cochleas are associated with shorter length and range in character from a common cavity to an incomplete partition at the apical region of the cochlea. In children with auditory neuropathy/auditory dys-synchrony, MRI should be performed because up to 18% of these children can have small or absent cochlear nerves despite normal internal auditory canal size as demonstrated with CT.[17] Other anomalies such as the abnormal course or position of the facial nerve and round window niche occur. With the exception of an absent auditory nerve or internal auditory canal, most malformed cochleas can be implanted with a sufficient number of electrodes to provide open-set (unlimited word or sentence possibilities) speech perception.

Labyrinthitis ossificans can occur after meningitis, particularly when *Streptococcus pneumoniae* is the infecting mocroorganism.[38] Whereas temporal bone CT can show complete ossification well, MRI can provide complementary information when partial ossification has occurred. T2-weighted MRI sequences are particularly useful in determining whether a scala tympani with partial ossification or fibrosis contains perilymph.

High-resolution temporal bone CT scanning can also be helpful in sorting out issues related to device dysfunction or when unexpectedly poor outcome occurs. Figure 158-1 shows the temporal bone containing a Med-El C40+ device in a patient who has otosclerosis and the new onset of facial nerve stimulation. The reduced bone density and lucency seen around the otic capsule resulting from her advanced cochlear otosclerosis allowed current to spread from the cochlea to the facial nerve. Figure 158-2 shows the temporal bone of a young child whose performance was unexpectedly low and who was also noted to have facial nerve stimulation with cochlear implant use. After his referral to our center for evaluation, a high-resolution temporal bone CT was obtained. The CT scan showed a malformed cochlea with an incomplete partition at the apex and the electrode tip leaving the cochlea and extending into the internal auditory canal. This type of cochlear malformation is typically associated with a thin partition between the modiolus and the internal auditory canal.

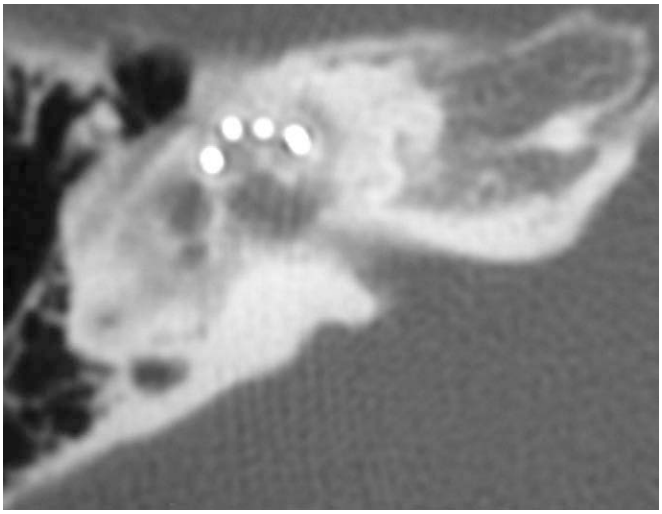

Figure 158-1. High-resolution temporal bone axial computed tomography scan using a bone window algorithm shows a right ear with a well-positioned electrode array (Med-El C40+) within a cochlea affected by otosclerosis. Note the reduced density of the otic capsule bone and the lucency surrounding the otic capsule *(center, top right).* This patient was experiencing facial nerve stimulation with cochlear implant use due to current spread through the otic capsule to the facial nerve *(Published with permission, copyright © 2009 P.A. Wackym, MD.)*

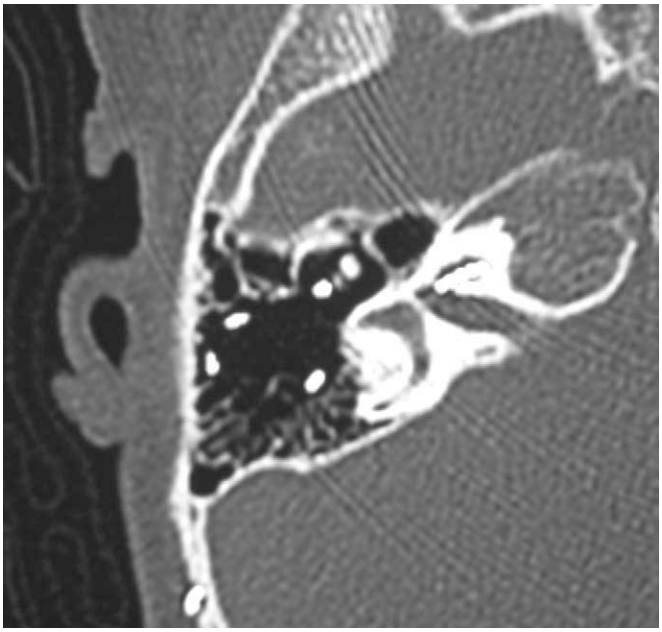

Figure 158-2. High-resolution temporal bone axial computed tomography (CT) using a bone window algorithm shows a right ear with a cochlear implant electrode array that has broken through the cochlea/modiolar wall to enter the internal auditory canal (CII Bionic Ear with HiFocus 1j electrode). The implanting surgeon, at another institution, did not recognize that the child had an incomplete partition at the apex of the cochlea. This malformation can be associated with a thin bony wall between the cochlea and the modiolus. This child was performing at a level lower than expected with his cochlear implant and had facial nerve activation with implant use, which led to the CT scan to evaluate the electrode position. The child's second side was implanted with a HiRes 90K device, and the initial device was removed and replaced with a HiRes 90K device, resolving his facial nerve stimulation problem. *(Published with permission, copyright © 2009 P.A. Wackym, MD.)*

Evaluation of Adult Cochlear Implant Candidates

The benefits of cochlear implantation have increased substantially over the past quarter century due to changes in technology and expanded candidate criteria. Consideration for cochlear implantation in adults still requires careful assessment to (1) determine preimplant hearing aid fitting and performance, (2) compare a candidate's preimplant performance with that of current implant recipients, (3) provide a recommendation for or against cochlear implantation, (4) select an ear for implantation, and (5) determine appropriate expectations that will guide the counseling of prospective patients, which is critical for user satisfaction.

Current Adult Selection Criteria

Food and Drug Administration (FDA) approved guidelines for cochlear implantation vary slightly with different clinical trials depending on the manufacturer's submission and labeling aims. Guidelines also change over time, in part, because cochlear implant recipients' average scores have been found to be higher than individuals with better hearing or word recognition. Current adult selection criteria in the most recent clinical trials include (1) severe or profound hearing loss with a pure-tone average (PTA) of 70 dB HL, (2) use of appropriately fit hearing aids or a trial with amplification, (3) aided scores on open-set sentence tests of less than 50%, (4) no evidence of central auditory lesions or lack of an auditory nerve, and (5) no evidence of contraindications for surgery in general or cochlear implant surgery in particular. Additionally, cochlear implant centers generally recommend at least 1 to 3 months of hearing aid use, realistic expectations by the patient and

family members, and willingness to comply with follow-up procedures as defined by the center.

The goal of the evaluation process is to determine whether an individual would perform as well with appropriately fit hearing aids as with a cochlear implant. In addition to comparing the candidate's performance with average cochlear implant users, it is important to compare the candidate with cochlear implant users who are matched for such factors as length of profound hearing loss or useable residual hearing, which are known factors that contribute to the variance in patient performance. In other words, if a candidate has had recent onset of profound hearing loss, it is more appropriate to compare him or her to the top 25% of cochlear implant users. Likewise, if a candidate has had no hearing aid use for 20 years and long-term deafness, it is more appropriate to compare that individual with the lower 25% of implant recipients' performance. However, even with the most educated guess of cochlear implant outcome for a given individual and the knowledge that detection levels can be improved, specific postimplant results cannot be guaranteed, and this principle must be effectively communicated to candidates.

ADULT AUDIOLOGIC PROTOCOL. For adults, sound detection and speech perception abilities are assessed to determine candidacy. Preoperatively, patients are evaluated with a battery of measures while using hearing aids, and the results are compared with the most recent average and range of cochlear implant performance. Preoperative measures are also repeated postimplant for longitudinal monitoring of patient performance. Single-subject research designs are often implemented in clinical trials in which each patient serves as his or her control, primarily due to the large variability within the population of cochlear implant candidates and users. The selection of preoperative test measures, therefore, should also take into consideration comparative postimplant measures.

Preimplant audiologic tests include unaided and aided detection thresholds for pure-tone and warble-tone stimuli, respectively. Unaided thresholds are obtained in each ear individually, and aided detection thresholds may be obtained monaurally and binaurally. Although there are no aided detection level criteria, it is helpful to determine aided levels as one aspect of appropriate hearing aid fitting and for comparison with expected postimplant sound field detection thresholds. For some patients, aided testing can also reveal recruitment (i.e., unusual sensitivity to loud sounds), which may limit benefit from amplification due to the inability to incorporate needed hearing aid gain.

Aided speech perception abilities are often assessed in both monaural and binaural conditions, depending on the use of amplification in each ear. Speech perception measures are conducted in the sound field, typically at a presentation level of 60 dB SPL and include open-set recorded presentations of words and sentences in quiet, and if appropriate, in noise. In the best-aided condition, the assessment of individual ears provides critical information for determining which ear to implant for unilateral implantation. In addition, the best-aided condition, whether it be either ear alone or both ears together, provides information about the candidate's maximum performance for comparison with cochlear implant performance.

Word and sentence recognition tests included in the Minimum Speech Test Battery for Adult Cochlear Implant Users (MSTB) are used at many cochlear implant centers to assess performance. The MSTB is a set of compact disc recordings designed to provide word and sentence tests for the preimplant and postimplant evaluation of speech recognition, regardless of implant device. The Consonant-Nucleus-Consonant (CNC) Monosyllable Word Test[43] assesses single-syllable word recognition. One CNC list contains 50 monosyllabic words presented in an open-set format. The CNC Words were among the original set of words from which the Northwestern University Auditory Test 6 (NU6) Monosyllabic Word Test[44] were taken.

The presentation of auditory-only sentence lists from the Hearing in Noise Test (HINT)[45] evaluates each patient's ability to understand sentence material in quiet or in the presence of background noise. Each HINT list is phonemically balanced and contains 10 sentences recorded by a male speaker that are equivalent in the features of length, intelligibility, and naturalness. When the sentences are presented in noise, the signal-to-noise ratio typically used is +10 dB, although this ratio can be adjusted to make the test condition more or less difficult. For patients with some open-set speech recognition for words and/or sentences preoperatively, the BKB (Bamford-Koval-Bench) Sentences[46] may be administered in an adaptive procedure (i.e., BKB SIN; sentences-in-noise). In this condition the sentences are presented at a fixed presentation level (e.g., 65 dB SPL), and the noise is varied for signal-to-noise (S/N) ratios between +20 and −5. Clinical observations suggest that, when testing adults, scores on open-set word and sentence measures, particularly in the presence of noise, are more reflective of patient satisfaction with hearing aids and more useful for determining cochlear implant candidacy than unaided and/or aided detection thresholds.

As performance with cochlear implants continues to improve because of advances in technology and broadening candidacy criteria, it is recommended that speech perception performance be assessed with measures that approximate everyday listening. Study findings by Skinner and colleagues[47] and our cochlear implant team[48] suggest that speech recognition tests be presented at 60 rather than 70 dB SPL to determine implant candidacy. These findings have resulted in the use of 60 dB SPL in U.S. clinical trials and general clinical practice across centers. Additional steps toward the use of measures that approximate everyday listening include the presence of background noise, variation in speaker gender and rate, and variation in the location of the speaker.

Following the evaluation of sound detection and speech perception, other areas of assessment may include vestibular testing, tinnitus assessment, and patient satisfaction or quality-of-life questionnaires.

OUTCOME EXPECTATIONS FOR ADULTS. Almost all patients demonstrate improved sound detection with their cochlear implants compared with their preoperative performance with hearing aids, and this is especially evident in the high-frequency range. Average postoperative sound-field detection thresholds for warble-tone stimuli are approximately 25 to 30 dB HL for frequencies 250 through 4000 Hz.[48]

When determining patient's expectations for cochlear implant performance and when counseling patients preimplant, it is important to stay abreast of both the average speech perception performance of cochlear implant recipients and the range of performance. In a recent study of 78 of adult cochlear implant users, 26 each with the Clarion, Nucleus, and Med-El device, the average CNC word scores at 70, 60, and 50 dB SPL were 42%, 39%, and 24%, respectively.[48] In this same group of subjects the mean HINT scores at 70, 60, and 50 dB SPL were 72%, 73%, and 57%, respectively. When the HINT was presented at 60 dB SPL in the presence of speech spectrum noise at an S/N ratio of +10, the average score for this subject sample was 48%. These results represent average performance; however, there was a great deal of variation in scores for individuals, ranging from 0% to 100% for most measures. In general, patients perform less well on single syllable word tests compared with sentence tests, and less well in the presence of noise than in quiet. Many cochlear implant users can understand sentences without lipreading cues and can therefore converse on the telephone. Although the primary objective of speech coding strategies is the perception of speech, some patients also enjoy music.

The majority of postlingually deafened adults demonstrate significant preoperative to postoperative improvements on open-set speech perception measures, often as early as 1 month postimplant. Compared with postlingual affected adults, some prelingually affected adults, defined as having onset of profound or severe-to-profound hearing loss at younger than 3 to 6 years of age (depending on the respective study), demonstrate open-set speech recognition, although the percentage is smaller and often the length of device use needed to achieve this is longer. Although the average postoperative scores for individuals with prelingual hearing loss are generally lower compared with those with postlingual hearing loss, there have been significant preoperative to postoperative improvements in speech perception reported for this group.[49] Therefore adults with prelingual onset of severe-to-profound hearing loss may be appropriate candidates for cochlear implantation.

Providing that older patients are enjoying relatively good health, there is presently no upper age limit for cochlear implantation. Audiologic results for cochlear implant users ages 65 to 80 years indicate significant improvements for both preoperative to postoperative comparisons[50,51] and for varied speech stimulus presentation levels.[48]

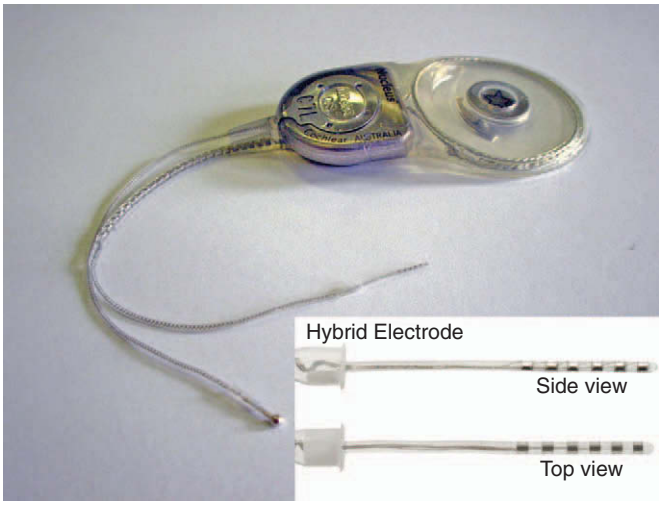

Figure 158-3. General appearance of the Nucleus Hybrid device for electroacoustic stimulation. Note the receiver/stimulator, removable magnet, loop antenna, separate ground electrode, and 10-mm electrode array. Inset shows the side and top view of the array that is designed to minimize electrode insertion trauma and preserve residual hearing. *(Published with permission, copyright © 2007 Cochlear Americas.)*

Current Trends That Affect Adult Cochlear Implant Candidacy

COMBINED ELECTRIC AND ACOUSTIC STIMULATION. For patients with more residual hearing preimplant than the average cochlear implant candidate, performance is expected to be better. In addition, some patients have considerable residual hearing in the lower frequencies (i.e., 250 and 500 Hz) but little measurable hearing for frequencies at 1000 Hz and above. In these patients it is difficult to obtain good aided benefit in the high frequencies with a hearing aid while maintaining appropriate gain in the lower frequencies where little, if any, amplification is necessary. The ability to understand speech is consequently compromised by the inability to detect and/or discriminate important high frequency sounds. Also, low-frequency sounds may be masked or distorted by the power needed in the high frequencies. These findings have led to the investigation of combined electrical and acoustic stimulation (EAS), such that the basal end of the cochlea receives electrical signals that are complemented by acoustic signals received at the apical portion of the cochlea. To use EAS, the low-frequency residual hearing must be preserved when the electrode array is inserted in the cochlea (Fig. 158-3). This is obtained by using shortened electrode arrays (20 mm for the Med-El device, and 10 mm for the Nucleus Hybrid device) inserted into the scala tympani and specific surgical techniques designed to make the electrode insertion as atraumatic as possible. These modifications include controlled opening and no direct suctioning of perilymph from the scala tympani; avoidance of perilymph contamination by blood and debris; use of nonototoxic topical antibiotics, corticosteroids, and lubricant (hyaluronic acid) during insertion; and immediate sealing of the cochleostomy after insertion using fascia. Speech perception findings reported thus far suggest improved performance in the combined EAS condition compared with either stimulation condition alone and compared with preimplant performance.[52] Additionally, recent data suggest that speech perception performance while listening in the presence of noise including multitalker babble is superior in the combined EAS condition compared with that of traditional cochlear implant users under the same adverse listening conditions.[53] It is likely that future candidacy may include patients with more low-frequency hearing, which is therefore a consideration during patient evaluation.

REHABILITATION OF ASYMMETRIC HEARING LOSS. A large number of patients who have lost hearing in one ear are not traditional cochlear implant candidates. These patients vary in the amount of hearing in their functional ear, ranging from normal hearing to severe hearing loss associated with marginal hearing aid benefit. As more experience has been gained with implantation of patients with more residual hearing and patients who benefit from hearing aid use in the nonimplanted ear,[52] the concept of cochlear implantation to rehabilitate asymmetric hearing loss is being considered.

BINAURAL COCHLEAR IMPLANTS. Historically, individuals received cochlear implants in one ear only. With the completion of clinical trials with bilateral implantation and the benefits of binaural implantation being realized, current candidacy decisions now include whether to receive two implants rather than one. Outcomes data regarding the benefits of binaural implantation continue to be published, and clear benefits in sound localization and listening in noise have been demonstrated.[54] Specifically, studies have shown that binaural implants provide a "head shadow" effect for listening to speech in the presence of other noise or competing speakers. This occurs because one ear is "shadowed" from the noise source when speech and noise come from different directions, allowing the ear with the better signal-to-noise ratio to do the listening. Other binaural advantages occur when information from both ears is combined to improve listening. Binaural summation effects have been reported whereby performance is improved in the binaural condition compared with monaural condition when speech and noise are in the front.[55] Binaural squelch effects have been reported less frequently to date, but in some cases, improvement in performance has been shown by adding the ear nearer the noise source.[56] Both binaural summation and binaural squelch effects rely on successful bilateral interaction of the brainstem and central auditory system nuclei, whereas the head shadow effect is simply a physical phenomenon created by the listener's head. We have found that presentation of more difficult auditory stimuli helps to demonstrate the improved benefit obtained by patients tested in the binaural condition compared with the benefit from their better-performing cochlear implant.[57]

Binaural implantation in adults recently completed clinical trials at a number of centers and with each of the cochlear implant manufacturers in the United States. Because results have been generally positive and the majority of bilateral recipients indicate a strong preference for bilateral over unilateral implant use, it is now the case that binaural implantation has become a part of the candidacy decision.

Recommendations for Referral for Adult Cochlear Implant Evaluation

At our center, we suggest the following referral criteria for cochlear implant evaluation for adults. Referral to a cochlear implant center does not mean that the individual is necessarily going to receive a cochlear implant, but that an evaluation is recommended to determine whether a cochlear implant would be beneficial. If the individual meets the following criteria, an evaluation is suggested. The criteria are (1) unaided thresholds of 70 dB HL or poorer at 1000 Hz and above in the better ear, even if hearing levels at 250 and 500 Hz are better; (2) unaided word discrimination less than 70%; and (3) frustration on the part of the patient due to communication difficulties, even with appropriate hearing aid use.

Evaluation of Pediatric Cochlear Implant Candidates

Cochlear implants have been available for children ages 2 to 17 years since 1990. Originally, children who were candidates for cochlear implantation typically had profound bilateral sensorineural hearing loss with pure-tone average thresholds of 100 dB HL or greater, often with corner audiograms. These children also displayed aided sound-field thresholds well below the range of average conversational speech and typical speech detection thresholds at and above 60 dB HL. During early clinical trials, pediatric candidates were not able to understand words when using their hearing alone, even with high-gain hearing aids and well-fitted earmolds. Since then, candidacy criteria have changed and technology has improved, both of which have influenced benefit. As with adults, consideration for cochlear implantation still requires careful assessment to (1) determine preimplant fitting of hearing aids and baseline performance, (2) compare a candidate's preimplant performance with that of current implant users, (3) provide a recommen-

dation for or against cochlear implantation, (4) select an ear for implantation, and (5) determine appropriate expectations that will guide the counseling of prospective families.

Current Pediatric Selection Criteria

The selection criteria for children vary slightly depending on the respective FDA-approved clinical trial and/or criteria recommended by the cochlear implant center. Generally speaking, the subject selection criteria include the following: (1) 12 months through 17 years of age; (2) profound sensorineural hearing loss (unaided PTA thresholds of ≥ 90 dB HL); (3) minimal benefit from hearing aids, defined as less than 20% to 30% on single-syllable word tests, or for younger children, lack of developmentally appropriate auditory milestones measured using parent report scales; (4) no evidence of central auditory lesions or lack of an auditory nerve; and (5) no evidence of contraindications for surgery in general or cochlear implant surgery in particular. Additionally, cochlear implant centers generally recommend at least 3 to 6 months of hearing aid use, unless cochlear ossification is noted or anticipated; realistic expectations by family members; enrollment in a postoperative rehabilitation program that supports the use of cochlear implants and the development of auditory skills; and willingness on the part of the family to comply with follow-up procedures as defined by the center.

PEDIATRIC AUDIOLOGIC PROTOCOL. As with adults, children are assessed preoperatively with a battery of sound detection and speech perception measures while using hearing aids, and this baseline is compared with the most recent average and range of cochlear implant performance. For children, speech perception measures assess a wide range of auditory skills from sound detection to recognition of words and sentences. Measures are selected that are developmentally appropriate for the child's age, language level, and auditory ability. Although the audiologic assessment will play a key role in candidacy, with children other factors may influence the candidacy decision and/or postimplant outcome, and therefore a multidisciplinary team approach is advised.

Before cochlear implant evaluation, most children will have an ABR test as an objective measure of the status of the peripheral and brainstem auditory system. With an ABR, acoustic click stimuli are presented to assess auditory sensitivity to each ear. Children who are implant candidates typically have no response to acoustic stimuli at the limits of the testing equipment, suggesting with reasonable accuracy hearing loss in the profound range. Another group of children that can display absent or abnormal ABR findings are those with auditory neuropathy.[9] In these cases of absent or abnormal ABR, comparison of positive (condensation) and negative (rarefaction) polarity stimuli will show an inversion of the peaks of the cochlear microphonic. The cochlear microphonic appears as an early latency response on the ABR waveform and is indicative of outer hair cell function. Otoacoustic emission testing can also be used as a measure of outer hair cell function. Due to the prevalence of children diagnosed with AN/AD[15] and the number of these children who have received cochlear implants,[58] our current protocols for electrophysiologic assessment include otoacoustic emission and ABR testing because these measures are sensitive to cochlear and auditory nerve function, respectively. The diagnosis of auditory neuropathy does not necessarily preclude a child from cochlear implant candidacy.

Unaided detection thresholds for pure-tone stimuli are obtained in individual ears using standard clinical procedures. Aided thresholds are obtained in the binaural condition, and if possible, the monaural conditions. For young children who are unable to participate in speech perception tasks, both unaided threshold testing and electrophysiologic measures become important criteria for cochlear implantation. Because we know the limitations of hearing aids, if we are confident in the reliability of the unaided threshold levels, we can predict with some certainty the eventual aided benefit. Using hearing aids, the measurement of sound detection levels, and when possible, speech perception abilities, can provide confirmation of the unaided thresholds. Although one criterion for pediatric candidacy is profound hearing loss, published reports and clinical experience both indicate that adults with severe hearing losses perform well with cochlear implants. Therefore we might expect the same outcome for children with similar severe hearing losses. With respect to children with AN/AD, unaided detection levels vary considerably and may not be predictive of aided levels or speech perception abilities.

Tests of speech perception assess a range of skills depending on the child's auditory abilities and language level. Closed-set measures include a small number of choices that are provided to the child either as objects or pictures (e.g., Early Speech Perception Test or ESP).[59] Monosyllable, spondee, and/or trochee words are spoken with audition alone (no visual cues), and the child is asked to select the object or picture that represents the stimulus. With open-set measures of word and sentence recognition, no choices are provided. The child repeats the words or sentences presented in quiet or in the presence of background noise. For example, using the Lexical Neighborhood Test (LNT),[60] 50 monosyllabic words are presented that are either "easy," occurring with high frequency in the English language and having few lexical neighbors, or "hard," occurring less frequently and with many lexical neighbors. For children with vocabulary levels that approximate those of a 5-year old, the Phonetically Balanced Kindergarten (PBK) Test[61] can be administered. It includes 50 words and has been in clinical use for many years. Recordings of the BKB Sentences[46] and the HINT-C Sentences[45] are typically used in the evaluation process for children who have some language and auditory experience. For children who are too young to participate in speech perception measures, parent interview scales are administered. The Meaningful Auditory Integration Scale (MAIS)[62] asks questions of parents or family members related to the child's spontaneous awareness of sound and use of audition in a meaningful way at home, school, or other natural environments.

OTHER EVALUATIONS FOR PEDIATRIC COCHLEAR IMPLANT CANDIDATES. For children, the results of speech production assessments are good indicators of hearing history and whether the child has learned to use his or her residual hearing. Language evaluations are also important because the ultimate goal of cochlear implantation is effective communication. Neither of these areas of assessment dictates candidacy, but they contribute to the confirmation of hearing levels and expected preimplant communication coincident with auditory experience. Results are also used to monitor either preimplant or postimplant performance over time and to develop rehabilitation goals for educators, clinicians, and parents.

A psychologic evaluation is obtained to assess the child's verbal and nonverbal intelligence, attention and memory skills, and visual-motor integration. When considering a child for a cochlear implant, counseling the family preimplant, and planning for possible rehabilitative needs postimplant, it is important to know the cognitive abilities of the child. If the child is gifted, for example, then expecting average cochlear implant performance may be an underestimation. Likewise, if the child has a developmental delay, this will affect rate and eventual level of performance with the implant and counseling may be directed toward more conservative expectations. Differentiating the influence of deafness and cochlear implantation from other disabilities or diagnoses such as developmental delay, autism, attention deficit disorder, or learning disabilities can be difficult. These issues are addressed in the psychologic evaluation preimplant and influence the recommendation for or against cochlear implantation, provide guidance for counseling families, and assist in rehabilitative planning.

Success with a cochlear implant can be influenced by the collaboration of individuals working with the child (parents, educators, and therapists). A team effort is best initiated during the preimplant process and sets the stage for later communication between the individuals on the implant team and the child's educators and family. Early cultivation of communication is important for a variety of reasons including confirmation of the child's test results and use of residual hearing, discussion of areas of concern, sharing effective test-taking and rehabilitative strategies, setting expectations, and identification of postimplant rehabilitation resources and goals.

OUTCOME EXPECTATIONS FOR CHILDREN. Auditory detection levels with a cochlear implant are expected to be similar to those for adults, which are approximately 25 dB HL for frequencies 250 through 4000 Hz. These detection levels allow access to information that is important for the development of auditory skills and communication.

As with adults, when determining expectations, it is important to stay informed of the average and range of pediatric cochlear implant performance.

In a publication by Geers and colleagues,[63] the results of 181 prelingual deaf children, implanted before 5 years of age who had used their cochlear implants for an average of 5 years, were reported for the outcome areas of speech perception, speech production, spoken language, total language, and reading. The average scores reported for several measures are as follows: ESP-spondee 85%, ESP-monosyllable 79%, LNT-easy 48%, LNT-hard 44%, and BKB sentences 57%. Children who were good speech perceivers were also the children who exhibited superior performance for measures of speech intelligibility, language, and reading. Half of the children were enrolled in oral communication programs, and the other half were enrolled in programs using total communication. Those children enrolled in educational environments that emphasized auditory and spoken language development had the highest scores on speech perception, speech production, and language measures. In this study, subjects were implanted between 1992 and 1994, mostly using the Nucleus 22 and SPEAK coding strategy; therefore the most recent cochlear implant technology and candidacy criteria were not represented.

Studies conducted with children indicate that earlier implantation is associated with higher performance for a given time period postimplant,[64] that preimplant unaided residual hearing influences performance and the development of speech perception skills postimplant,[65] and that there is a steady increase in performance over time that does not plateau during the first 3 to 5 years of implant use.[66]

On the basis of research studies and clinical experience, we describe in this section general expectations for children with onset of deafness of less than 1 year on the basis of their age at implantation. Expectations for children implanted at age 2 years and before include the potential for communication skill development at rates similar to normal-hearing peers, potential for speech to be easily understood by strangers, reduced or possible elimination of language delay, attendance at a neighborhood school with minimal support services by kindergarten or first grade, and increased likelihood of becoming an auditory/oral communicator. Expectations for children implanted before the age of 4 years include substantial improvement in speech perception, increased vocalizations/verbalizations at early stages postimplant, auditory behaviors evident before they can be formally measured, speech production skills reflective of auditory abilities, and language delays that are reduced. For children implanted between 4 and 5 years, expectations include improvement in speech perception with excellent closed-set performance and varied open-set abilities, improvements in speech production, use of hearing to support improvements in language, and reduced dependence on visual cues for communication. For children implanted at or after age 6 years, we expect improved auditory detection abilities, improvements in speech perception that entail good closed-set abilities but limited open-set skills, possible improvements in speech production, and continued dependence on visual cues for communication. Generally, children implanted at an older age require more time to reach their potential with the device than those implanted at younger ages.

In addition, for children with progressive or sudden onset of hearing loss, we expect excellent progress with cochlear implantation and achievement of these skills with a shorter duration of cochlear implant use. Likewise, for children with some residual hearing preimplant, we also expect higher levels of performance in relatively shorter periods of time. As discussed regarding adults, it is important to match expectations with reasonable appropriate outcomes for children on the basis of their hearing history, age at implantation, and nonaudiologic factors.

Current Trends That Affect Pediatric Cochlear Implant Candidacy

BINAURAL COCHLEAR IMPLANTS. Far beyond what has been experienced with adult patients, the majority of major cochlear implant centers are now performing bilateral cochlear implantation in the majority of children. Reports in children have followed similar trends as those for adults, with improvements in the ability to recognize speech in noise and to localize a sound source. The ability to follow large spatial changes in speaker location is a critical skill for academic learning in the classroom setting, as is the ability to follow rapid changes between speakers in a smaller space such as in a small group setting at school or during a conversation with multiple speakers at home. Bilateral implantation is desirable for young children during the critical period for the development of spoken communication. To study the observed clinical benefits reported by parents and teachers and observed by clinicians caring for these children, there are several multicenter investigations of bilateral cochlear implantation in children currently under way in North America and Europe. Due to the longer periods required for speech language development in young children, these trials are designed to extend a minimum of 5 years. On the basis of the findings in these trials, the circumstances for which we would recommend bilateral implants for children will be evident.

Factors That Affect Pediatric Cochlear Implant Performance

The most common preimplant factors that affect performance for children include age at implantation, hearing experience (age at onset of profound hearing loss, amount of residual hearing, progressive nature of the hearing loss, aided levels, consistency of hearing aid use), training with amplification (in the case of some residual hearing), presence of other disabilities, and parent and family support. Postimplant factors that contribute to performance levels include length of cochlear implant use, rehabilitative training, and family support. Communication mode is also a documented variable that affects postimplant outcome because children in programs and homes that focus on the development of spoken language perform higher than children in programs without this emphasis.[63] Children using total communication at school and home can achieve substantial levels of performance; however, this achievement will be less likely if an emphasis on auditory skill development and spoken communication is not included with the use of sign language.

Ear Selection in Pediatric Cochlear Implant Candidates

For children whose parents elect for their child to receive a single cochlear implant, the selection of the ear for unilateral implantation follows the same logic as discussed earlier for adults. At our center, the pediatric population differs from the adults in that fewer children have an etiology of progressive hearing loss (22%), compared with those with congenital bilateral hearing loss (65%) or sudden onset of bilateral hearing loss (13%). In general, this results in fewer children having ear asymmetries or patterns of change in hearing over time. Therefore fewer children have ear differences. Because we encourage the use of a contralateral hearing aid postimplant if at all possible, we select the ear for implantation that is least likely to benefit from amplification. All things being equal, we select the right ear to capture the possible advantage of contralateral, left hemisphere specialization for speech recognition.[67]

Recommendations for Referral for Pediatric Cochlear Implant Evaluation

At our center, we suggest the following referral criteria for cochlear implant evaluation for children. As mentioned previously with adults, referral to a cochlear implant center does not mean that a child is necessarily going to receive a cochlear implant, but that an evaluation is recommended to determine whether a cochlear implant would be beneficial. If the child meets one or more of the following criteria, an evaluation is suggested. The criteria are (1) unaided thresholds of 90 dB HL or poorer at 2000 Hz and above in the better ear, even if hearing levels at 250 and 500 Hz are better; (2) aided levels in the better ear poorer than 35 dB HL, especially at 4000 Hz; (3) no response for ABR testing in both ears or no response for one ear and responses at elevated levels in the other ear; (4) parents are frustrated with their child's development of auditory and/or communication skills; (5) progressive hearing loss with detection levels at or near the profound range at 2000 Hz and above; or (6) evidence of severely impairing auditory neuropathy/dys-synchrony. Evaluation has no lower age limit; age at implantation is a critical factor that influences postimplant performance, and children who may be too young for the operation are not too young for evaluation.

Device Selection

All cochlear implant systems include external and internal hardware. The external equipment includes a microphone, speech processor, and transmission system. The internal device includes a receiver/stimulator and an electrode array.

In general, an external microphone picks up sound and speech in the environment and sends the information to a speech processor, either the body-worn (BW) or ear-level type. The speech processor converts the sounds into electric signals, which are sent across the skin via radio frequency transmission to the internal receiver/stimulator. The transmission of the signal occurs when there is successful alignment of the external magnet housed in the transmitter with the internal magnet housed in the receiver/stimulator. The receiver/stimulator decodes the signals and delivers them to the electrodes positioned within the cochlea. The electrodes stimulate the auditory nerve, and the signal is sent along the auditory pathway to the auditory cortex. A description of the most recent available equipment for each cochlear implant manufacturer used by patients in the United States is provided as follows.

Internal Receiver Stimulators and Electrode Designs

NUCLEUS FREEDOM WITH CONTOUR ADVANCE ELECTRODE. The Nucleus Freedom device with Contour Advance electrode (CI24RE[CA]) consists of an internal receiver/stimulator that uses a flexible silicone housing surrounding a titanium case. The Nucleus Freedom device with the Contour Advance electrode is shown in Figures 158-4 and 158-5. The magnet is removable/replaceable and allows for MRI studies with magnets up to 1.5 tesla (T), after removal of the magnet. The electrode design is a perimodiolar electrode and is preformed to conform to the modiolus. A stylet is positioned within this electrode array and maintains the electrode in a straight configuration until its removal during the operation. The electrode array is curved, consisting of 22 half-banded platinum electrodes, variably spaced over 15 mm. The diameter of the intracochlear portion ranges from 0.5 mm to 0.8 mm. Overall, the length of the electrode array distal to the first of three silicon marker rings is 24 mm; however, the electrode is designed to be inserted 22 mm, and a platinum band is present at this position to use as a guide for depth of insertion. The half-banded electrodes face the modiolus with a width of 0.3 mm and a geometric area ranging from 0.28 mm^2 to 0.31 mm^2. Of all available electrodes on the market, this is the stiffest electrode and consequently is relatively easy to insert. The greatest disadvantage of this current electrode design is that once the stylet has been removed, it cannot be replaced. This is problematic should the electrode insertion be difficult because of anatomic variations, in which case the back-up device would be required. Manual positioning of the electrode tip within the opening of the cochleostomy is performed, and guiding the tip into this position is assisted by the use of a claw-shaped instrument held in the dominant hand. Once the electrode tip is retained within the opening of the cochleostomy, bimanual advancement of the electrode array using two claw-shaped instruments held opposing each other, as close to the cochleostomy as possible, assists advancement of the electrode array within the scala tympani. There is a white marker incorporated along the electrode that is used to determine when the electrode array should be advanced off of the stylet until complete insertion has been achieved. The Nucleus Contour electrode array has three Silastic bands outside of the electrode array that represent the proximal limit, and these should remain outside of the cochleostomy. Once this level is reached, the remainder of the stylet is withdrawn and discarded. The electrode is then maintained in a perimodiolar position.[68]

The Nucleus device also has a second electrode design, a double electrode array to be used for implantation of severely ossified cochleas (Fig. 158-6). The configuration for this includes two electrode arrays, each with 11 contacts within a length of 8.5 mm.

HiRes 90K. The Advanced Bionics Corporation system includes the HiRes 90K receiver/stimulator (Fig. 158-7) and a choice of two electrodes; the HiFocus 1j array or the Helix array. The HiRes 90K system has a removable magnet that has been approved by the FDA to allow for an MRI with a field strength of up to 1.5 T, providing that the magnet has been removed. The HiFocus 1j electrode system is shown in Figure 32-14. This electrode is "banana shaped" and curved toward the modiolus, consisting of 16 contacts, spaced every 1.1 mm over 17 mm. The length of the electrode array inserted into the cochlea is 23 mm. The electrodes face the modiolus with a width of 0.4 mm and length of 0.5 mm. The HiFocus 1j electrode system uses an insertion tube through which the insertion tool allows advancement of the electrode array. Both a metal (outer diameter of 1.5 mm) insertion tube and a Teflon (outer diameter of 2 mm) insertion tube are included, and selection is based on surgeon preference; however, the metal tube provides greater stability. Gentle pressure along a thumb-driven advancement mechanism is required to insert the electrode. Should errors occur during electrode insertion, the electrode is easily reloaded into the insertion tube, and additional electrode insertion attempts can be completed until the electrode insertion has been achieved.

The HiFocus Helix electrode system is shown in Figure 158-8. This electrode is designed to be perimodiolar in location after insertion. The array consists of 16 contacts, spaced every 0.85 mm over 13 mm.

Figure 158-4. General appearance of the Nucleus Freedom device with the Contour Advance electrode. Note the receiver/stimulator, removable magnet, loop antenna, separate ground electrode, and electrode array. *(Published with permission, copyright © 2008 Cochlear Americas.)*

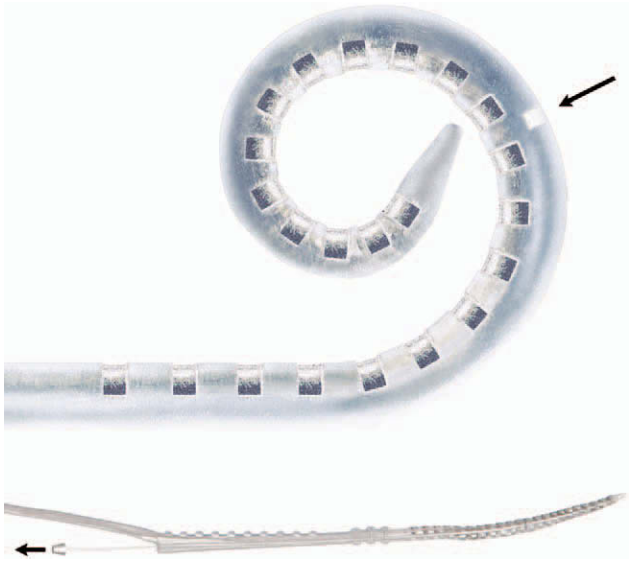

Figure 158-5. Nucleus Contour Advance electrode after *(top)* and before *(bottom)* stylet removal. The electrode array has a more linear configuration before stylet removal. The electrode is advanced until the white marker *(long arrow)* is located at the level of the cochleostomy. The electrode is then advanced off of the stylet by holding the stylet with a forceps and inserting the electrode. Removal of the stylet *(short arrow)* allows the electrode to return to the precurved configuration of the array, which places the electrode contacts in a perimodiolar position. *(Published with permission, copyright © 2008 Cochlear Americas.)*

Figure 158-6. General appearance of the Nucleus device with double electrodes for use in patients with cochlear ossification. Note the receiver/stimulator, removable magnet, loop antenna, separate ground electrode, and the dual electrode arrays, each with 11 contacts over a length of 8.5 mm. *(Published with permission, copyright © 2008 Cochlear Americas.)*

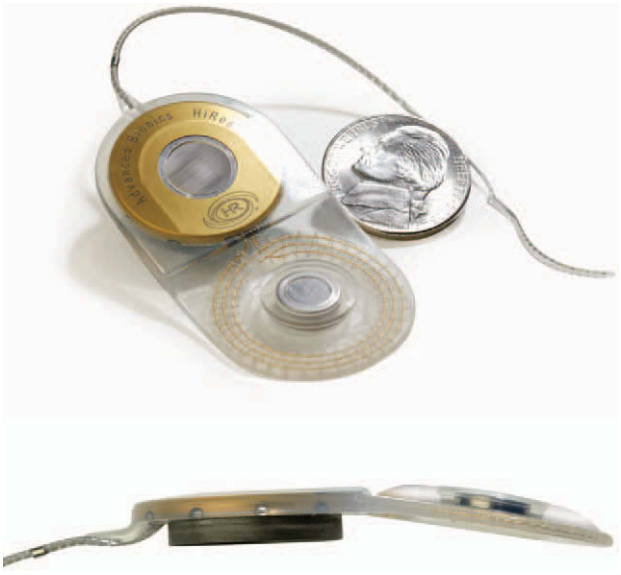

Figure 158-7. General appearance of the HiRes 90K Bionic Ear device with the 1j electrode. Note the receiver/stimulator with tapered edge at the front of the implant, removable magnet, loop antenna, and electrode array *(top)*. The side view shows the low profile of the portion of the device that is located on the surface of the skull *(bottom)*. *(Published with permission, copyright © 2008 Advanced Bionics Corporation.)*

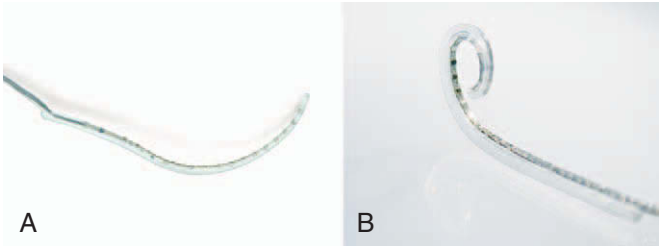

Figure 158-8. Photographs of the HiFocus 1j and Helix electrodes. **A,** The 1j electrode is banana shaped and has flat contacts oriented toward the modiolus. The raised partitions shown in the inset, between electrode contacts, are designed to reduce electrode interactions. **B,** The Helix electrode uses the same flat contact configuration with the raised partitions but is precurved to place the electrode array in a perimodiolar position after insertion. *(Published with permission, copyright © 2008 Advanced Bionics Corporation.)*

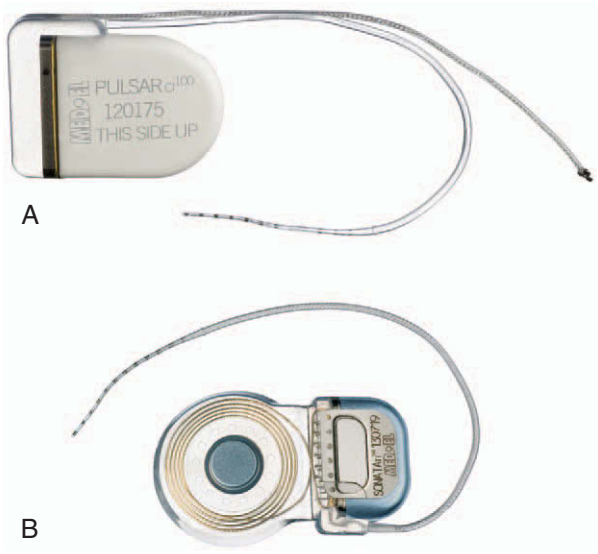

Figure 158-9. **A,** General appearance of the Med-El PulsarCI100 device. The internal device is housed in a ceramic case containing the receiver/stimulator, internal magnet, and loop antenna. **B,** General appearance of the Med-El SonataTI100 device. The internal device is housed in Silastic and has a similar configuration for the receiver/stimulator, internal magnet, and loop antenna as does the Nucleus Freedom and HiRes 90K devices. *(Published with permission, copyright © 2008 Med-El Corporation.)*

The diameter of the intracochlear portion ranges from 0.6 mm to 1.1 mm. The length of the electrode array inserted into the cochlea is 24.5 mm. The electrodes face the modiolus with a width of 0.4 mm and length of 0.5 mm. The HiFocus Helix electrode system uses a preloaded stylet assembly by which the electrode array is advanced. Should errors occur during electrode insertion, the electrode is easily reloaded into the insertion stylet assembly, and additional electrode insertion attempts can be completed until the electrode insertion has been achieved. This is in contrast to the Nucleus Contour Advance perimodiolar electrode, which cannot be reloaded after removal of the stylet.

MED-EL PULSARCI100 AND SONATATI100. The Med-El PulsarCI100 system uses a receiver/stimulator that is housed in a ceramic case (Fig. 158-9). The PulsarCI100 system has FDA approval for use with MRI at 0.2 T causing no additional risk to the patient or significant impact on the device or image quality, except for the magnet-induced artifact surrounding the internal magnet. In Europe many patients with Med-El implants have safely undergone MRI studies with 1.0 and 1.5 T scanners.[69] The Med-El system has six separate electrode designs (see Figs. 158-12 and 158-13). The standard electrode is the longest electrode available in the marketplace and is tapered in design. Twelve pairs of electrode bands are distributed over the 31.5 mm electrode array length. A FLEXeas array (20.9 mm) is also available for applications such as EAS; for cochleas that are partially ossified, a compressed electrode is available; and for severely ossified cochleas, a split electrode array is available. In July 2007 FDA approval was granted for the Med-El SonataCI100 internal device (see Fig. 158-9). The SonataCI100 Cochlear Implant contains the same electronics as the PulsarCI100 device, but the electronics are encased in a titanium housing that is smaller and thinner than the PulsarCI100 ceramic casing. All Med-El electrode arrays are compatible with the SonataTI100. The receiver coil and internal magnet are positioned outside

of the electronics package in flexible silicone, although the magnet is not removable for MRI. The SonataTI100 is also MRI compatible in the United States at 0.2 T without magnet removal.

If ossification of the cochlea is encountered during the opening of the cochleostomy, the use of the Med-El Insertion Test Device (ITD) can be helpful to determine which of their various electrode options should be used. If the ITD can be inserted to the small flanges present 17.8 mm from the tip, the standard array should be used; if less than that, the medium or compressed array should be used. The medium electrode array (PulsarCI100M) has all 12 pairs of electrodes distributed over 21 mm spaced 1.9 mm apart. The PulsarCI100 compressed electrode (PulsarCI100S) is designed with the same number of electrode contacts ($n = 12$ pairs), but arranged closer together on the apical end of the array and spaced over 12.1 mm. With ossification present, the ITD is advanced through the cochleostomy and the depth of insertion is determined. If it is apparent that insertion of the standard electrode array would result in electrodes being extracochlear in location, the compressed or medium electrode array should be used and fully inserted.

For more severely ossified cochleas, the Med-El split electrode design (PulsarCI100GB) has two compressed electrode arrays with five and seven pairs of electrode contacts, respectively (Fig. 158-10). These electrode arrays are inserted via two cochleostomies. When the two arrays are in place, the electrode contacts provide more sites of potential stimulation than a single standard array incompletely inserted into the cochlea. The sixth electrode design is for applications in patients who have a common cochlear cavity (see Figs. 158-10 and 158-11). This electrode uses the basic PulsarCI100S array with 3 to 5 mm of Silastic and a distal nonfunctional platinum ball.

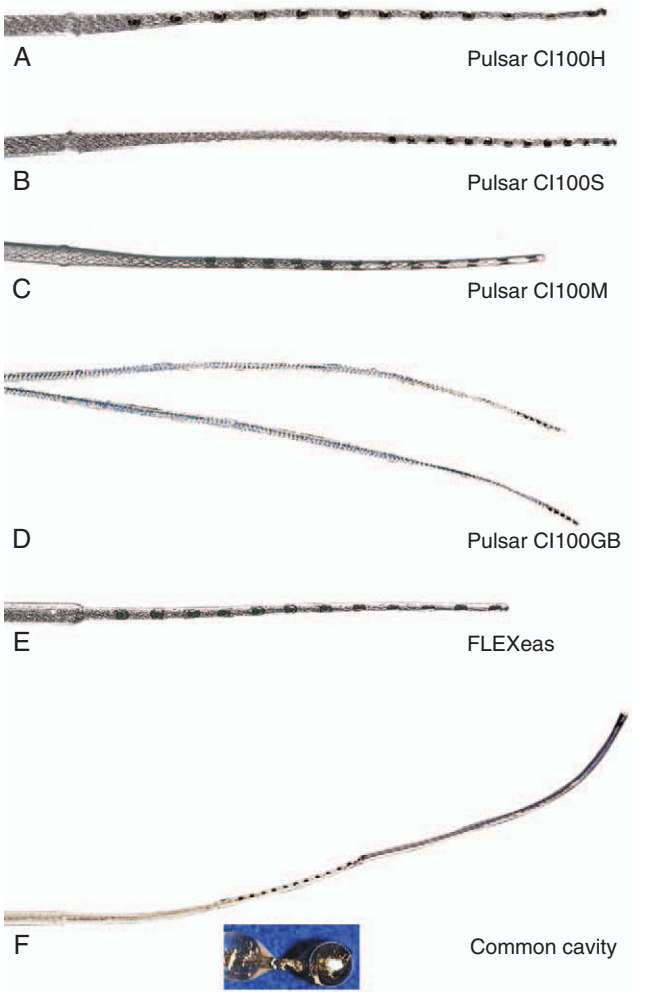

Figure 158-10. Six electrode designs available for the Med-El PulsarCI100 and SonataTI100 cochlear implants. **A,** Standard 31.5 mm electrode with the electrode contacts distributed over 26.4 mm. When ossification is encountered during creation of the cochleostomy, use of the insertion test device allows determination of whether to open the standard electrode array or one of the two shorter arrays or the split electrode array. **B,** The compressed array distributes the electrode contacts over 13 mm. **C,** The medium array distributes the electrode contacts over 21 mm. **D,** The split array has one with five pairs of electrode contacts, while the other has seven pairs of electrode contacts. **E,** For hearing preservation and application of electroacoustic stimulation, the FLEXeas electrode is designed to be thin and 20.9 mm in length. **F,** For severe cochlear malformations such as a common cavity, the custom-manufactured common cavity electrode can be used. This electrode array uses the basic compressed electrode with a nonfunctional Silastic extension terminating in a platinum ball *(inset),* which is used to place the electrode array via a double labyrinthotomy technique as shown in Figure 158-11. *(Published with permission, copyright © 2009 P.A. Wackym, MD.)*

External Speech Processors

Each manufacturer offers a body-worn (BW) and behind-the-ear (BTE) processor. The BW processors were the first wearable devices for each implant type, followed by the introduction of BTE processors, which are generally preferred by adults and some children/parents. Both BW and BTE processors have program switches, volume and/or sensitivity controls, batteries (rechargeable or alkaline), and accessories. External processor wear options vary from one device to another but may include, for example, a remote battery pack worn off the ear or a rechargeable battery pack worn on the processor at the ear. A variety of mechanisms (e.g., earhooks, indicator lights) perform functions such as alerting parents to a low battery or a disconnected headpiece. External auditory input sources can be connected to the processors such as auxiliary microphones, telephone adaptors, tape recorders, television audio amplifiers, or FM systems. Other cosmetic considerations include a variety of processor and transmission coil colors, decorative caps, processor belt clips, and harnesses or hip packs for daily wear. Because the external equipment changes regularly, the specifics for each manufacturer are reviewed at the time of device discussion and selection, which occurs once cochlear implantation has been recommended.

Current Signal Processing Strategies

Each device manufacturer provides a selection of signal processing strategies that may affect device selection for a given patient. For example, patients who are music enthusiasts may be interested in comparing aspects of fine structure strategies, whereas other patients with neurologic processing issues may benefit from having strategies that offer slower stimulation rates. Below are summaries of currently available signal processing strategies.

Temporal Strategies

CONTINUOUS INTERLEAVED SAMPLING. Continuous interleaved sampling (CIS) is a speech processing strategy that has been implemented in cochlear implant devices in recent years. One problem encountered with early speech processing strategies was interaction between electrical fields when electrodes were stimulated simultaneously, particularly with broad, monopolar stimulation. This is referred to as channel interaction, and it is thought to result in a degradation of the intended signal. CIS was introduced by Wilson and colleagues[70] as a way to minimize overlap between monopolar electric fields across stimulated electrodes, thereby preserving the integrity of the electrical signal. In CIS, biphasic pulses are delivered to electrodes with timing offsets so that none of the electrodes are stimulated simultaneously. This sequential stimulation pattern results in increased electrical channel independence, which, in addition to decreasing channel interaction, allows for the possible advantage of using more channels.

Although several versions of CIS are implemented across devices, the pulse amplitudes in CIS are generally determined by several steps. First, at a given point in time, the acoustic input signal is bandpass filtered, with the lower frequency information allocated to apical channels and higher-frequency information allocated to basal channels.

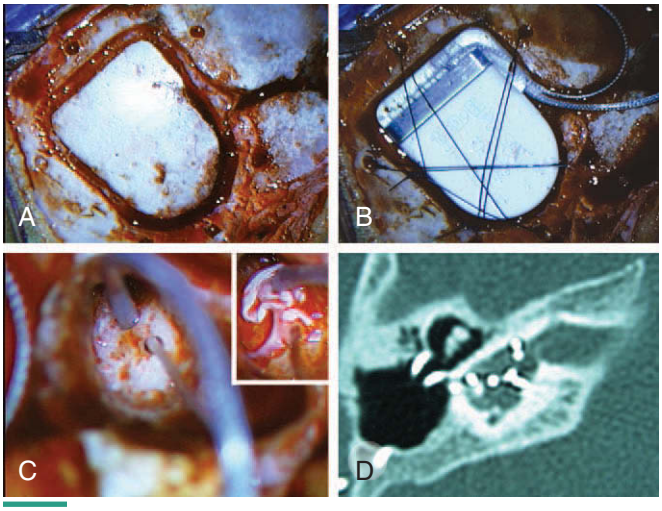

Figure 158-11. Cochlear implantation in a common cavity malformation. **A,** Craniotomy with the bone island technique. **B,** The Med-El internal receiver/stimulator secured with three 3-0 nylon sutures. **C,** the common cavity electrode was inserted via a double labyrinthotomy technique. Inset shows fascia sealing both labyrinthotomies. **D,** Postoperative computed tomography scan shows the position of the electrode array within the common cavity. *(Published with permission, copyright © 2009 P.A. Wackym, MD.)*

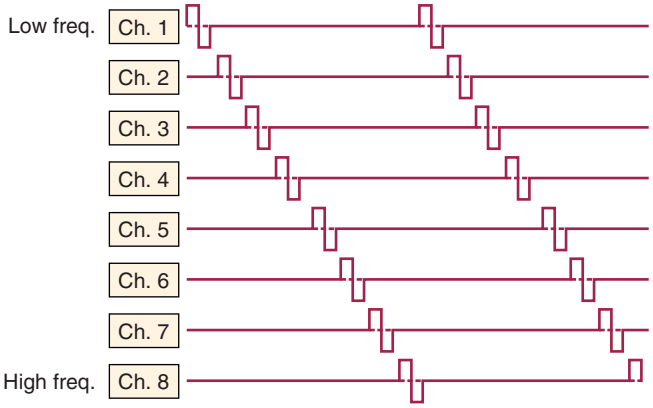

Figure 158-12. Analog stimulation. Each electrode is stimulated continuously and simultaneously. In this example, electrode 1 carries the lowest frequency information and electrode 7 carries the highest frequency information. The Simultaneous Analog Stimulation (SAS) implemented by Advanced Bionics Corporation uses a bipolar electrode configuration to reduce electrode interaction. *(Published with permission, copyright © 2008 Advanced Bionics Corporation.)*

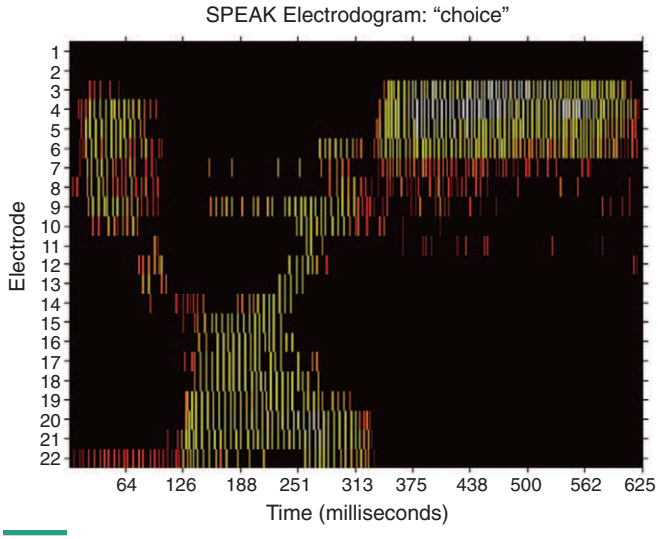

Figure 158-13. Spectral Peak Extraction (SPEAK). An electrodogram is shown for the word "choice" encoded by the SPEAK strategy. Time is plotted on the abscissa and electrode number on the ordinate, and the more intense stimuli are indicated by brighter bars. The relatively low stimulation rate of 250 Hz is apparent. *(Published with permission, copyright © 2008 Cochlear Americas.)*

Next, within each frequency band, the amplitude of the input signal is determined, and this envelope amplitude is compressed to fit into the appropriate dynamic range of electrical hearing for each channel. The compressed amplitude calculated from the input signal is used to determine the amplitude of the stimulus pulses that are sent to the designated electrodes. In this way, CIS primarily conveys temporal information from the input signal. All three devices available in the United States have a CIS strategy option.

ANALOG STIMULATION. Electric analog stimulation is a digitized representation of the original acoustic signal that is presented continuously over time and simultaneously to the different electrodes in a tonotopic manner. Preservation of the original acoustic signal would presumably be beneficial for electrical hearing, but limitations to this stimulation paradigm warrant consideration. An early analog speech processing strategy, compressed analog (CA),[71] was presented using a monopolar electrode configuration. The combination of broad current spread and continuous, simultaneous stimulation resulted in extensive channel interaction. Current spread can be reduced by changing the electrode configuration from monopolar to bipolar mode, which localizes the electric field by stimulating between a pair of electrodes on the array.[72] Using a bipolar coupling mode, the analog strategy available in the Clarion 1.2, CI Bionic Ear, CII Bionic Ear, and HiRes 90K devices is referred to as Simultaneous Analog Stimulation (SAS). An example of SAS is shown in Figure 158-12, with the low-frequency analog stimulation sent to the apical channel (channel 1 in the Advanced Bionics Corporation devices) and the highest frequency stimulation to the basal channel (channel 7).

Spectral Emphasis Strategies

SPECTRAL PEAK EXTRACTION. Spectral peak extraction, or SPEAK, is implemented in the Nucleus device.[73] SPEAK includes a bandpass filter analysis of the input signal, and the outputs selected for stimulation are those with the highest amplitude components, or the largest spectral peaks. The corresponding electrodes are activated sequentially in a basal-to-apical direction at a relatively low rate (≈250 Hz). Typically, the number of electrodes stimulated, or maxima, is 6 to 8, although it may range from 1 to 10, with the more electrodes stimulated, the slower the rate. Figure 158-13 shows an example of the stimulus output pattern for the SPEAK strategy in the Nucleus device. The plot, referred to as an *electrodogram,* shows the electrodes stimulated over time for the word "choice," with intensity indicated by the relative brightness of the lines.

ADVANCED COMBINATION ENCODER. The Advanced Combination Encoder (ACE) strategy was designed for the Nucleus device to incorporate the spectral representation benefits of SPEAK with a high rate CIS.[74] ACE provides a range of stimulation rates per channel, from 500 to 3500 pulses per second, and allows for a maxima range from 1 to 20. An electrodogram for the word "choice" processed with ACE is shown in Figure 158-14. The rapid stimulation rate and increased number of stimulated electrodes is apparent when compared with the SPEAK strategy.

Fine Structure Signal Processing

Fine structure signal processing combines both temporal and spectral cues, is typically presented using high pulse rates, and may incorporate a recently implemented "virtual channel" paradigm. The higher rate

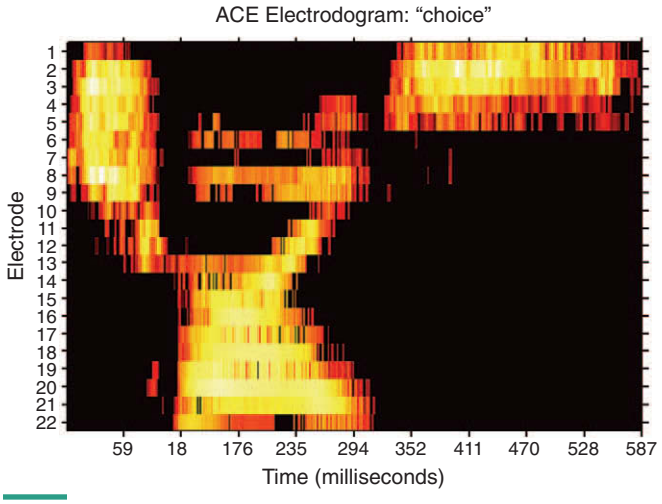

Figure 158-14. Advanced Combination Encoder (ACE). An electrodogram for the word "choice" (as plotted in Fig. 158-17) is shown for coding with the ACE strategy. Compared with SPEAK, the stimulation rate is faster and the number of electrodes stimulated is greater. *(Published with permission, copyright © 2008 Cochlear Americas.)*

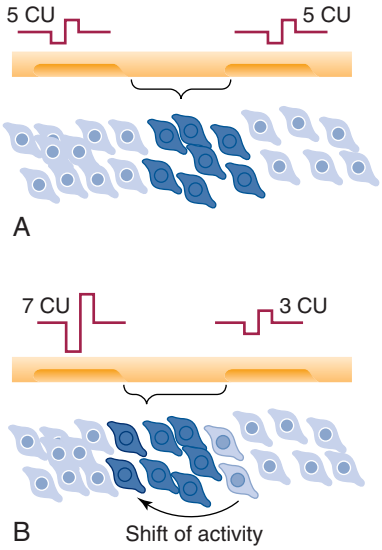

Figure 158-15. Schematic illustration of current steering between adjacent electrodes and stimulation of neural elements. **A** shows equal proportions of current presented to the electrodes, which effectively focuses stimulation halfway between the contacts. **B** shows a shift in the current proportions between electrodes and the resulting shift of activity toward the more heavily weighted contact. *(Published with permission, copyright © 2008 Advanced Bionics Corporation.)*

strategies generally use short duration pulses and increased filter update rates. It is theorized that this results in electrical stimulation that more accurately represents the input signal.

Improving delivery of spectral cue information with coding strategies has become of particular interest with advances in device design and evolving patient expectations such as music appreciation and listening in noise. Stimulation of different electrodes along the array typically elicits different pitch percepts in cochlear implant users. The number of different pitch percepts a person has reflects that individual's spectral resolution abilities. Until recently, spectral resolution with cochlear implants was limited by the number of stimulating electrodes. A method of stimulus current delivery has been developed to increase the number of pitch percepts given a finite number of electrodes. This stimulation paradigm is referred to as "current steering," and the resulting additional pitch percepts are called "virtual channels."

Current steering is accomplished when two adjacent electrodes are stimulated simultaneously, subsequently eliciting a pitch percept that falls between the pitches from each electrode when stimulated alone.[75,76] This effect has also been shown with sequential stimulation of adjacent electrodes.[77] Figure 158-15 shows a schematic example of equal proportions of current presented simultaneously to two electrodes *(top),* thus stimulating the neural population halfway between the contacts. By changing the proportion of current delivered to each electrode, the responding neural population likewise shifts (Fig. 158-15, *bottom*) and thus creates an additional pitch percept without changing the loudness.[78] Algorithms for current steering between electrodes and across the array have been developed by all three manufacturers, for use with their recent-generation devices.

Factors That Affect Device Choice

NEED FOR SPECIAL ELECTRODE ARRAYS. When individuals have hearing loss that is appropriate for cochlear implantation, it is possible that the cochlea may be malformed, depending on the etiology of the hearing loss. This includes varying degrees of Mondini malformation, in which there may be fewer cochlear turns or dehiscent cochleae. The cochlea may be ossified, to varying degrees, which may occur with meningitis, Paget disease, or otosclerosis. In addition, there are types of hearing loss that may necessitate preservation of hearing with implantation. In any of these cases, it may be necessary to have special electrode arrays available such as short, compressed, split, or custom arrays, all of which have been described earlier.

TECHNOLOGY DIFFERENCES IN SPEECH CODING STRATEGY AND ELECTRODE CONFIGURATION. Device selection is also influenced by changes in technology that may make one device more appealing than another for a given individual. For example, a speech coding strategy that emphasizes both temporal and spectral cues may be desirable for a patient who has a great love of music. Depending on an individual's work or other daily life environment, certain noise reduction features may become relevant. As discussed previously, in some cases a patient may be limited to selecting a given device on the basis of his or her cochlear anatomy or hearing status that requires the use of a particular electrode array design.

MAGNETIC RESONANCE IMAGING COMPATIBILITY. MRI is a powerful noninvasive diagnostic tool that uses magnetic fields and pulses of radio waves to generate images. The components of an MRI unit include a static magnetic field (0.5 to 4 T); magnetic fields caused by switched gradients (0 to 20 T/s at ≈ 15 Hz); and radiofrequency energy (0 to 6 kW peak at 64 MHz [for 1.5 T]).[79,80] It is an imaging modality with an already wide range of clinical applications that continues to expand. Ideally, this diagnostic tool should be available for the benefit of cochlear implant (CI) recipients. The Cochlear Corporation's CI24M, CI24R(CA), and CI24ABI devices, as well as the Advanced Bionics Corporation's HiRes 90K device, were all designed so that the internal magnet could be removed and replaced to complete an MRI study.

Studies with the Med-El Combi 40/40+ and Clarion 1.2 (Advanced Bionics) cochlear implants have delineated many of the factors in CI/MRI interactions.[81,82] The factors that have been studied include demagnetization, artifacts, induced voltages, temperature increases, torque, and force. These investigations have used both the 0.3 T and 1.5 T MRI units. The force and torque exerted by the MRI unit on the internal magnet of the cochlear implant receiver are of particular concern. The potential for a catastrophic force on the implant to fracture the inner table of skull and exert pressure on the brain demands full investigation of cochlear implant/MRI compatibility. Previous studies concluded that a 0.2 T MRI evaluation force and torque remained within "acceptable limits."[81,82] There have been several in vivo studies performed in Europe using 1.0 T MRI.[69] In this largest series of 30 patients with Med-El cochlear implants who underwent 1.0 T MRI evaluations with a variety of MRI sequences, none suffered pain, burning, auditory sensation, deterioration of their auditory abilities, or other adverse sequelae. Presently, patients with the

Med-El C40+, PulsarCI100, or SonataTI100 devices in place greater than 6 months are approved by the FDA to undergo MRI studies with a 0.2 T scanner, provided the company approves the protocol for the radiologist.

We have completed studies to determine the magnitude of force required to fracture the floor of a cochlear implant receiver bed.[83] The testing protocol was designed to create a physical worst-case scenario yet approximate the in vivo condition. Several considerations went into attaining this dual goal. Each recessed cochlear implant bed was drilled to a maximum uniform thinness rather than drilling just deep enough to accommodate the cochlear implant. A stainless steel template was chosen for impacting the specimens because the arc of its edge would closely approximate that of the cochlear implant affecting the skull in vivo. In addition, a line load system more realistically approximated the in vivo condition than a point load system. The center of the specimen was chosen for contact with the template. This placement minimized the risk of the template touching any surface other than the floor of the recessed cochlear implant bed. It also assisted identical placement of the template for each specimen. Finally, this placement allowed the template to affect the specimen at its least reinforced site, thereby providing a worst-case scenario. Since the in vivo system had the thinned bone in continuity with the native skull and it is this region that receives the force vector during the cochlear implant magnet/MRI magnet interaction, it is anticipated that the biomechanical forces required to produce failure at this interface would be much greater than those measured in the study referenced earlier.[83] In an earlier investigation of cochlear implant/MRI compatibility, 0.3 to 1.0 newtons (N) was used as an acceptable level of force exerted on a cochlear implant during MRI evaluation.[81] The researchers recommended this range because it represents the magnitude of force that a cochlear implant may experience during a regular day in the life of a cochlear implant recipient. More specifically, this is the magnitude of the force exerted on the internal magnet of a cochlear implant when the external transmitter and magnet are removed. In these prior studies, the measured force vectors ranged from 0.17 to 0.42 N. Calculations using these measured force vectors and appropriate geometry resulted in maximum forces of approximately 8 N exerted on the cochlear implant during 1.5 T MRI evaluation in a worst-case scenario. The results of our biophysics studies showed that the load-carrying capacity of a recessed cochlear implant bed drilled into fresh frozen human calvaria specimens, with bone thickness of 0.3 to 0.6 mm (S.D. 0.11 mm), is more than an order of magnitude greater than this force (mean = 134.13 *N*).[83] When a bone island with exposed dura is necessary to inset the internal device, titanium or resorbable mesh has been shown in vitro to provide even greater mechanical support beneath a cochlear implant and this approach also has the advantage of providing immediate support.[84] Moreover, we have demonstrated that no demagnetization of the internal device magnet occurs after 15 successive MRI scans in a 1.5 T unit.[85] Further studies in patients will be necessary to demonstrate the safety of this practice using cochlear implants with the internal magnet remaining in place. However, for all candidates, and particularly those who are in need of frequent MRI scans, the options and limitations of each device should be discussed so that the patient can make an informed decision.

EXTERNAL SPEECH PROCESSOR SIZE, WEIGHT AND AESTHETICS. Often, the design and aesthetics of the external components, specifically the speech processor, have a great deal of influence on device selection (Figs. 158-16 to 158-18). Individuals tend to prefer a BTE processor because it is lighter, smaller, and does not have a cord that runs down the back of the neck. For young children, it may be desirable to use a BW processor that can be worn on the child's back and out of reach. In addition, some BTE processors may be too large or heavy to stay on a child's ear. However, some manufacturers have introduced smaller, lighter BTE wear options designed specifically for children. Patients with dexterity or vision problems often select a processor with larger, more accessible controls. Color choice of the external components is also relevant. Some prefer to match hair and/or skin tone, and others like interesting designs or colors that they can change to match their clothing.

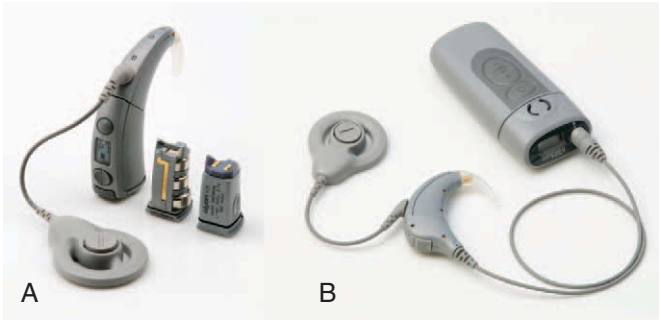

Figure 158-16. Ear-level and body-worn speech processors for the Nucleus Freedom System. **A,** Freedom behind-the-ear speech processor. Multiple colors are also available. Disposable or rechargeable batteries are used. **B,** Freedom body-worn speech processor. Note the ear hook, which contains the microphone and the magnet/transmitter coil. *(Published with permission, copyright © 2008 Cochlear Americas.)*

Figure 158-17. Harmony ear-level speech processor. Multiple colors are available, *lower right,* as well as multiple-colored accent strips. A separate body-worn battery pack is also available for infants with cochlear implants. *(Published with permission, copyright © 2008 Advanced Bionics Corporation.)*

Figure 158-18. Ear-level speech processors for the Med-El cochlear implant systems. The OPUS 1 has a modular design with two small switches, whereas the OPUS 2 has a more ergonomic switch-free design. Multiple colors are available. A separate body-worn battery pack is also available for infants with cochlear implants. *(Published with permission, © 2007 Med-El Corporation.)*

BATTERIES. The type, cost, and lifespan of batteries are important to some patients when choosing a device. Body-worn speech processors can use either disposable alkaline or rechargeable batteries. BTE processors use either disposable high power 675 hearing aid batteries or proprietary rechargeable batteries, depending on the manufacturer of the device. The specific processor, battery type, speech coding strategy, and patient programming needs each affect battery life. However, the generally expected battery life and ease of changing the batteries may cause a patient or family to choose one implant design over another.

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CHAPTER ONE HUNDRED AND FIFTY-NINE

Cochlear Implantation: Medical and Surgical Considerations

Thomas J. Balkany

Kevin D. Brown

Bruce J. Gantz

Key Points

- Diagnostic therapy, including auditory verbal therapy with appropriate hearing aids, is critical before implanting devices in children with severe to profound hearing loss.
- MRI offers numerous advantages over CT, including direct visualization of the cochlear nerve, assessment of the patency of the cochlea, and visualization of the cerebellar pontine angle and brainstem for other abnormalities.
- Children and adults should be immunized against *Streptococcus pneumoniae* according to the high-risk schedule before cochlear implantation.
- Auditory neuropathy is not a contraindication to cochlear implantation.
- Cochlear implantation in children is ideally performed before 12 months of age.
- Michel's aplasia or absence of the cochlear nerve are absolute contraindications to cochlear implantation.
- Patients who require revision implant surgery (reimplantation) generally perform as well with their second implant as with their first.
- A second cochlear implant (implanted sequentially or simultaneously) improves sound localization and speech recognition in noise over a single implant.

Cochlear implantation has become a standard medical procedure for the rehabilitation of hearing-impaired adults and children. The medical and surgical decision to undertake cochlear implantation is based on the doctor-patient relationship. Candidacy issues, device selection, and planning for postoperative habitation are more complex than for other otologic surgeries, and they require a dedicated cochlear implant team. Decisions about whether to operate and which ear and device to select are made on the basis of input from the cochlear implant team, a detailed medical history and physical examination, and laboratory and imaging studies.

The physical characteristics of receiver stimulators and electrode arrays vary among manufacturers, thus necessitating surgical techniques that are specific to the device to minimize complications.[1-4] The facial nerve monitor is recommended in all cases as an adjunct for preventing overheating or other damage to the facial nerve while working within the facial recess and the middle ear.

Cochlear implant surgery—like technology and candidate evaluation—has evolved since the mid 1980s. During that time, techniques have been developed to reduce complications, to safely place implants in children who are younger than 12 months old, to insert electrodes in ossified and dysplastic cochlea, and to replace failed devices. The implantation procedure includes elements of mastoid and middle ear surgery, as well as cochleostomy, electrode insertion, and securing of the receiver stimulator.

Medical and Surgical Evaluation

This evaluation includes all aspects of cochlear implant candidacy, including critical analysis of hearing tests, motivation of the patient and family, and status of language development (Box 159-1). It should also focus on the patient's general health, especially with regard to his or her ability to undergo general anesthesia. A complete history and physical examination is followed by appropriate laboratory tests. Imaging studies play a particularly important role in this evaluation. When necessary, consultation with appropriate specialists is indicated.

During the physical examination, special attention is paid to the ear and central nervous system. Extensive laboratory evaluations such as thyroid function studies, lipid profiles, and viral screens are expensive and have not been found to be helpful unless specifically indicated by the history and physical examination.

Hearing tests with ear-specific auditory information in both aided and unaided conditions must be obtained. It is critically important to be certain that the patient's hearing aids are appropriate for the hearing loss. In young, prelinguistically deafened children, it may not be possible to accurately assess hearing during a single session or even a series of sessions within a sound booth. In very young children, a combination of diagnostic audiometric strategies may be necessary, including auditory brainstem response (ABR), auditory steady-state response (ASSR), and behavioral observation. The ABR is limited in its ability to obtain tone-specific information (limited frequency specificity).

Box 159-1

Candidacy Criteria for Children

- Severe to profound bilateral sensorineural hearing loss
- Benefits from hearing aids less than that expected from cochlear implants
- Medical clearance to undergo general anesthesia
- Family support, motivation, and appropriate expectations
- Rehabilitation/educational support for the development of aural language, speech, and hearing in children

ASSR uses a continuous tone with a carrier frequency that is amplitude and frequency modulated. Similar to an ABR, the ASSR is recorded from scalp electrodes, but the recordings show primary energy at the carrier frequency and two sidebands separated from the carrier by the modulation frequency. Recent studies have demonstrated correlation between the degree of hearing loss measured by standard PTA and ASSR at 500, 1000, 2000, and 4000 Hz.[5]

In diagnostic therapy, the patient is fit with the appropriate hearing aids, placed in a program of auditory-verbal or auditory-oral therapy, and followed up for a period of months. During that time, it is typical to see hearing-impaired children make some gains with regard to receptive language function, and these may be compared with the expected gains that typically occur with cochlear implants.

Genetic testing continues to evolve as an important adjunct in the diagnosis of hearing loss. Approximately half of the estimated 1 in 1000 infants born with bilateral severe to profound deafness are thought to have genetic factors. There are more than 46 genes currently identified that contribute to hearing loss, but one gene, *GJB2*, which encodes the protein connexin 26 and maps to the autosomal recessive deafness gene (*DFNB1*) locus, is responsible for a significant proportion of these cases. When mutations in *GJB2* and *GJB6* (connexin 30) are screened together, the cause of 50% of bilateral severe to profound hearing loss is identified in certain populations. Four main benefits of genetic testing have been identified.[6] First, the identification of a specific genetic cause precludes further costly testing. It also defines the chance of transmission by understanding the specific genetic cause of the hearing loss and its method of inheritance. Testing also provides parental reassurance that it was nothing done during the pregnancy that contributed to the hearing loss, thus helping to prevent unnecessary guilt. It also provides prognostic information with respect to the possible development of other medical problems and can help in predicting outcomes with hearing rehabilitation such as cochlear implantation.[7]

Both high-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) may be used in the preoperative evaluation of patients with profound deafness who are candidates for cochlear implantation. HRCT may assist in the evaluation of inner ear morphology (Fig. 159-1), patency of the cochlea (Fig. 159-2), position of the facial nerve, location of large mastoid emissary veins, size of the facial recess, thickness of the parietal bone, and height of the jugular bulb (Box 159-2). MRI has been used more frequently for preimplantation evaluation in recent years. Although MRI is not as effective in visualizing the fallopian canal or the bony structure of the otic capsule, it is more effective in identifying fibrosis of the cochlea by assessing its patency, in identifying the presence and caliber of the cochlear nerve (especially on sagittal T2 imaging of the internal auditory canal), and in providing information about brainstem and cortical lesions. A study compared the ability of HRCT and MRI for identifying abnormalities of the cochlea and modiolus, and MRI was found to be superior.[8] For these reasons, it has subsequently become the preferred means for preoperative evaluation of children undergoing cochlear implantation at many institutions. It is recommended, however, that HRCT still be performed in cases in which there are malformations of the external canal, semicircular canals, or vestibule due to the higher incidence of an anomalous facial nerve.[8] Both tests may be indicated in the presence of labyrinthine anomaly.

Figure 159-1. Cochlear dysplasia, absence of modiolus and bony partition. This coronal high-resolution computed tomography scan of a child with congenital deafness demonstrates a cystic cochlea without bony partition, the absence of a partition from the vestibule, and a wide, stubby, horizontal, semicircular canal. A large oval window niche can also be seen in this view.

Figure 159-2. Coronal high-resolution computed tomography scan demonstrating nearly complete cochlear ossification. This scan demonstrates nearly complete ossification of the labyrinth. A small portion of the upper turns may remain patent. Note that ossification generally begins in the basal turn and proceeds apically.

Ear Selection

Selection of the ear to be operated on is somewhat complex and prescriptive for the individual patient. The factors to be considered include the following.

Physical Characteristics

Physical characteristics of the temporal bone that are used for ear selection include the presence of the cochlea and the auditory nerve, the degree of dysplasia, the degree of ossification, prior surgical procedures

(e.g., canal-wall-down mastoidectomy), facial nerve anomalies, and chronic otitis media.

Residual Hearing Level

At this time, the risk of losing residual hearing during electrode insertion is estimated at 50% to 70%, although recent techniques may reduce the risk to 20%.[9] Thus, if there is significant aided benefit from the better ear, the worse ear is often favored. Conversely, it is widely held that patients with more residual hearing have better outcomes from cochlear implantation. For this reason, if a patient is anacusic, the ear that has more residual hearing may be favored. Fig. 159-3 presents an algorithm that may be helpful when considering these issues.

If one ear has had profound deafness for more than 10 to 15 years, the ear with better hearing is usually selected, because duration of deafness is one of the few measures that correlate with performance outcome. If the individual can use a hearing aid for sound awareness, preserving the ear with better hearing may assist with binaural localization and may assist with competing noise.

Box 159-2

Computed Tomography and Magnetic Resonance Imaging Information

- Inner ear morphology
- Cochlear patency
- Position of fallopian canal
- Presence of cochlear nerve
- Size of facial recess
- Location of large mastoid emissary veins
- Height of jugular bulb
- Thickness of parietal bone

Vaccination for Meningitis

In 2003, a *New England Journal of Medicine* article highlighted an increased incidence of pneumococcal meningitis in cochlear implant recipients in comparison to an age-matched general population.[10] A total of 4264 children were evaluated and 26 children were identified with streptococcal meningitis, representing an incidence of 0.6% in cochlear implant recipients. This was a 30-fold increase over their age-matched convenience sample cohort. Two major limitations of the study were that, first, 11.5% of children receiving an implant have a previous history of meningitis, and these children have an increased risk of recurrence. Second, 8.5% of children receiving implants have labyrinthine dysplasia, which also places them at an increased risk for meningitis. The degree to which an increase in meningitis is due to a cochlear implant, versus high risk factors such as prior meningitis or dysplasia, requires an adequate control group of deaf children rather than normal children as used in this study.

In order to test whether this risk was theoretical or actual in nature, animal experiments were performed in rats to determine whether placement of a cochlear implant increases the risk of meningitis.[11] In this study, rats receiving a cochlear implant were at a significantly increased risk of developing bacterial meningitis when inoculated with *S. pneumoniae* by any route (intraperitoneal, middle ear, inner ear) in comparison to surgical controls. In a later companion study, vaccination with 23-valent pneumococcal capsular polysaccharide vaccine (PPV23, Pneumovax) prevented the development of meningitis in rats inoculated by an intraperitoneal route and significantly reduced the frequency of meningitis in rats inoculated by a middle ear route. There was a nonsignificant reduction in frequency of meningitis

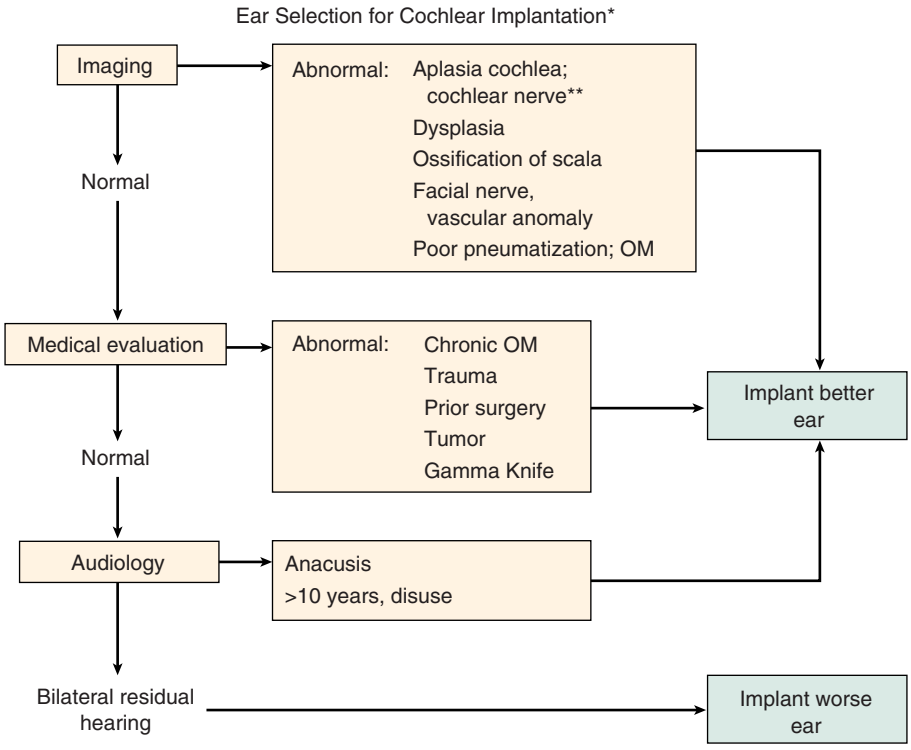

Figure 159-3. Ear selection algorithm. Selection of the ear to receive a cochlear implant is not a simple matter and must be prescribed specifically for each patient. The three general considerations are imaging, otologic history, and residual hearing level. Individual considerations such as lifestyle (driver vs. passenger), handedness (regarding ability to place the external device), and the patient's preferences must also be taken into consideration. OM, otitis media.

in rats inoculated via the inner ear. This suggested PPV23 can protect healthy rats from meningitis caused by a vaccine-covered *S. pneumoniae* serotype.[12]

There are currently two vaccines available that both generate antibodies to the polysaccharide capsule of *S. pneumoniae*. These include the PPV23 vaccine, which is a 23-valent vaccine composed of pure capsular antigen, and the heptavalent pneumococcal conjugated vaccine (PCV7, Prevnar), which contains seven pneumococcal serotypes conjugated to a nontoxic variant of diphtheria toxin. Both of these generate an antibody response, although PPV23 is not recommended for children younger than 2 years of age because of immaturity of their immune systems that may lead to a potentially poor response to pure capsular antigen.[13] It is the current recommendation of the Centers for Disease Control and Prevention (CDC) to ensure that children receiving a cochlear implant are immunized according to age-appropriate pneumococcal vaccination with PCV7, PPV23, or both according to the Advisory Committee on Immunization Practices (ACIP) schedules for persons at high risk (Box 159-3).[14]

Surgical Technique

Preparation and Draping

Under general anesthesia, the patient is placed supine with the head turned 45 to 60 degrees away from the surgeon. With very young children, care should be taken to avoid excessive rotation of the head so as to avoid subluxation of the cervical spine when the child is relaxed under general anesthesia. Long-lasting neuromuscular blockade is avoided to allow the use of the facial nerve monitor. Minimal shaving is used to reduce the psychologic impact of the procedure. The ear is prepped in a sterile manner, and a povidone-iodine–impregnated occlusive drape is used to retract the pinna anteriorly and to seal off the external auditory meatus. Using the appropriate implant guides provided by the manufacturer, the location of the implantable receiver stimulator may be marked on underlying parietal bone transcutaneously using methylene blue. A single intravenous injection of prophylactic antibiotics within 30 minutes of surgery is recommended, although this has not been subject to a prospective trial.

Incisions and Flap Design

Cochlear implant incisions have evolved over time (Fig. 159-4), but the principles of incision design remain constant. The resulting flap should cover the implant with margins of at least 1 cm in all directions, and a good blood supply should be maintained. Access to the linea temporalis, mastoid tip, and spine of Henle, without undue retraction, is necessary.

The original postauricular C-shaped incision used with single-channel implants was effective and had a low rate of complications. However, as multichannel devices came into use, the larger receiver stimulators required a larger flap. These larger postauricular C-shaped incisions were associated with a higher rate of complications—mainly device extrusion—and were subsequently replaced by an inferiorly based "inverted U" flap. This has undergone further modification (see Fig. 159-4), to an extended postauricular incision that has gradually become shortened and remains the most commonly used incision at this time. An extended endaural incision has also been used, but early experience with this incision demonstrated an unacceptably high incidence of skin breakdown at the external auditory meatus.

Box 159-3

ACIP Recommendations for Persons Receiving a Cochlear Implant

- Children younger than 24 months with cochlear implants should receive PCV7, as is universally recommended; children with a lapse in vaccination should be vaccinated according to the catch-up scheduled after the PCV7 shortage resolved.
- Children 24 to 59 months old with cochlear implants who have not received PCV7 should be vaccinated according to the high-risk schedule; children with a lapse in vaccination should be vaccinated according to the catch-up scheduled after the PCV7 shortage resolved; children who have completed the PCV7 series should receive PPV23 2 months or more after vaccination with PCV7.
- Persons 5 to 64 years with cochlear implants should receive PPV23 according to the schedule used for persons with chronic illnesses; a single dose is indicated.
- Persons planning to receive a cochlear implant should be up-to-date on age-appropriate pneumococcal vaccination at least 2 weeks before surgery, if possible.

ACIP, Advisory Committee on Immunization Practices.

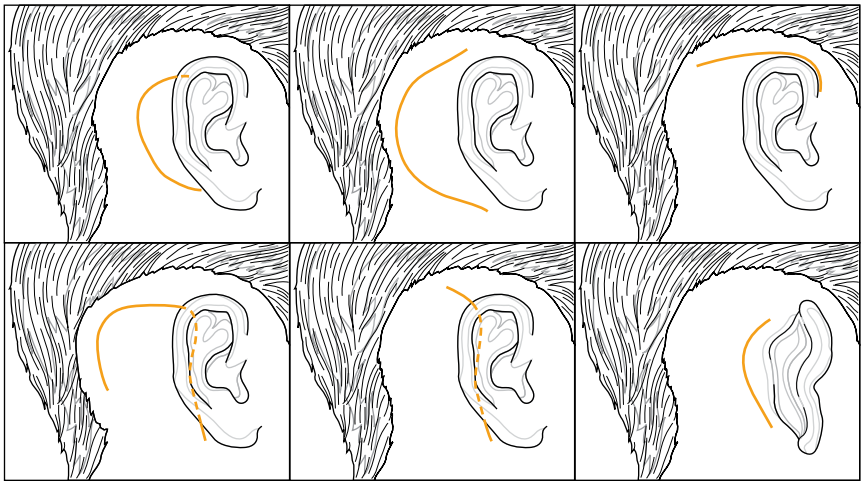

Figure 159-4. Cochlear implant incisions. Since the 1970s, a number of incisions have been used for cochlear implantation. The original small C-shaped incision was used for the relatively small, single-channel cochlear implant. When multichannel cochlear implants came into wide use in the 1980s, the C-shaped incision was simply enlarged. At that time, most complications had to do with flap breakdown. The large C-shaped incision had to be extended superiorly and inferiorly to allow for adequate arterial and venous blood supply. In response to the wound problems, an extended endaural incision was widely used in Europe, and an inferiorly based or U-shaped incision was developed in Australia. This gradually evolved into a simple extension of the standard postauricular incision. At the present time, a minimal incision is used in many centers for children and, in some centers, for adults as well.

A "minimal incision" has also been used for cochlear implantation. This incision is approximately 3 to 4 cm long and situated 1 cm posterior to the retroauricular crease. The advantages of this incision are that it requires minimal hair shaving, it heals faster and with less swelling than larger incisions, and it allows for initial stimulation at 2 weeks in most cases. Disadvantages include the need for additional skin retraction, reduced visibility, and somewhat limited access when drilling a bone seat and tie-down holes for securing the device.

Before incision, the intracutaneous infiltration of 1 to 3 mL of 1:100,000 epinephrine may be used to obtain better hemostasis. Similarly, a monopolar cautery knife may be used for both incision and flap elevation. It should be noted, however, that in cases of simultaneous or sequential cochlear implantation, monopolar cautery is contraindicated due to potential current interaction with the circuitry of the receiver-stimulator. In these cases, it is advisable to perform the approach for both sides before placing the implant (simultaneous implants)[15] to use a nonconducting means of dissection to provide hemostasis, including the bipolar, Shaw scalpel, and most recently the Plasma Knife in cases of sequential implantation.[16]

Skin Flap

The skin flap is elevated, along with subcutaneous tissue, in the plane of the temporalis fascia. By splitting the fascia, the flap may be raised in an avascular plane; this plane is most easily identified in the superior area of the flap and carried inferiorly.

Because the receiver stimulator will be situated at an angle of 30 to 45 degrees from vertical (it is more vertical in younger children), the skin and subcutaneous tissue flap are usually not elevated inferiorly to the lamdoidal suture. If dissection is carried below this point, large branches of the occipital artery and vein may be encountered, thereby causing unnecessary blood loss and delaying the procedure.

Because the external processor must transmit across the skin, the efficiency of both power and information transmission is governed by the thickness of the skin flap. The stability of the external transmitting coil, which is held in place magnetically, is similarly affected by skin thickness. Current devices require that the flap be less than 10 to 12 mm thick. Significant risk is inherent whenever a skin flap must be thinned. It is recommended to avoid thinning the skin flap to less than 0.8 cm and to prevent thinning to the level of hair follicles in all cases. When hair follicles are exposed, the risks of infection around the receiver/stimulator and of eventual extrusion are heightened.

After the skin/subcutaneous tissue flap has been elevated, a separate anteriorly based pericranial flap is then elevated. This flap extends along the linea temporalis posteriorly from a point just above the exterior auditory canal to a point that will cover at least the anterior portion of the receiver stimulator. The subcutaneous pericranial flap should be 2 to 3 cm in the cephalocaudal dimension and at least 2 cm in length. The pericranial incision is then carried inferiorly to a point just above the occipital crest and then anteroinferiorly, staying above the attachment of strap muscles, to the mastoid tip. In young children, the usual precautions to avoid the facial nerve in the absence of a mastoid tip are exercised. This flap is elevated anteriorly and retained in fishhooks or with a self-retaining retractor to expose the mastoid cortex and the area of the receiver/stimulator seat and tie-down sutures.

It is important to carry the soft tissue dissection anteriorly to expose and thin the bony wall of the posterior external auditory canal. In young children, care must be taken when placing the retractor, because it can tear the skin of the external auditory canal, thereby contaminating the surgical area.

A subperiosteal pocket for the receiver-stimulator is elevated beneath the pericranium posterosuperior to the mastoid using a periosteal elevator. The dimensions of the pocket depend on the design of the receiver-stimulator.

Bony Seat

A custom-fit bony seat and tie-down holes may be drilled into the parietal bone to recess and immobilize the receiver/stimulator; this reduces its profile and protects it from trauma as well as making it less noticeable to the patient and family. Drilling the seat and bone holes in young children often exposes dura, and care must be taken to avoid complications. Cerebrospinal fluid (CSF) leak, subdural hematoma, epidural hematoma, lateral sinus thrombosis, and cerebral infarct have all been reported.[17-19] At this time, techniques are being developed that do not require bone seats or bone tie-down holes.

The anterior edge of the receiver/stimulator should be at least 1 cm behind the skin incision. In addition, the location of the internal magnet should be far enough posterior so that the patient will not have a problem wearing an ear-level processor. Each manufacturer provides a mock implant and guide to help determine the site of the receiver-stimulator seat. Bony tie-down holes are drilled superior and inferior to the seat (Fig. 159-6). In young children, the bony fixation holes are often epidural and require that the dura be slightly elevated to avoid damage. Later, the receiver-stimulator will be secured with a single nonreabsorbable suture. The knot should be rotated into an inferior tie-down hole using two mosquito clamps.

Mastoidectomy

A complete mastoidectomy is performed, but, unlike in chronic ear surgery, the mastoid cortex is not marsupialized but rather is left slightly overhanging superiorly, posteriorly, and inferiorly to help retain and control the electrode cable. Likewise, it is not necessary to exenterate all retrosigmoid or tip cells.

The facial recess is widely opened. Care is taken to preserve a layer of bone overlying the facial nerve. It may be necessary to remove bone on the anterior medial surface of the fallopian canal just below the pyramidal process to provide adequate access to the round window. The bony external auditory canal wall should be thinned maximally, but it should never be penetrated. The chorda tympani can usually be preserved. Thinning the posterior canal wall allows the microscopic view to vector from anterolateral to posteromedial, because the round window niche is a posterior structure of the mesotympanum.

The incus bridge that separates the fossa incudis from the facial recess may be divided between the short process of the incus and the horizontal semicircular canal (Fig. 159-5). Although this requires only a few seconds with a 0.5-mm diamond burr, it allows the electrode cable to be passed under the short process into the epitympanum and firmly lodges it in position. Another benefit of this procedure is to direct

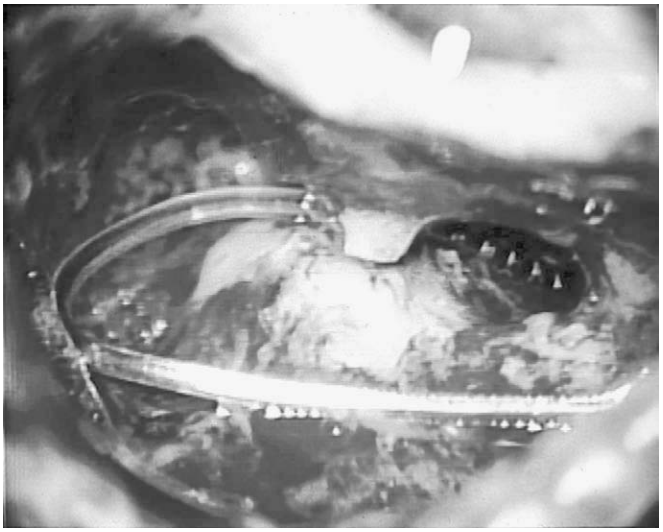

Figure 159-5. Split bridge. The incus bridge is divided using a 0.5-mm diamond burr between the short process of the incus anteriorly and the horizontal, semicircular canal. In doing this, the posterior incudal ligament is sacrificed. A cochlear implant electrode is seen after it has been placed inside the split bridge; this fixes the electrode in place, prevents extrusion, and directs the electrode away from the drill-exposed segment of the fallopian canal and the tympanic membrane (in the event that it should retract).

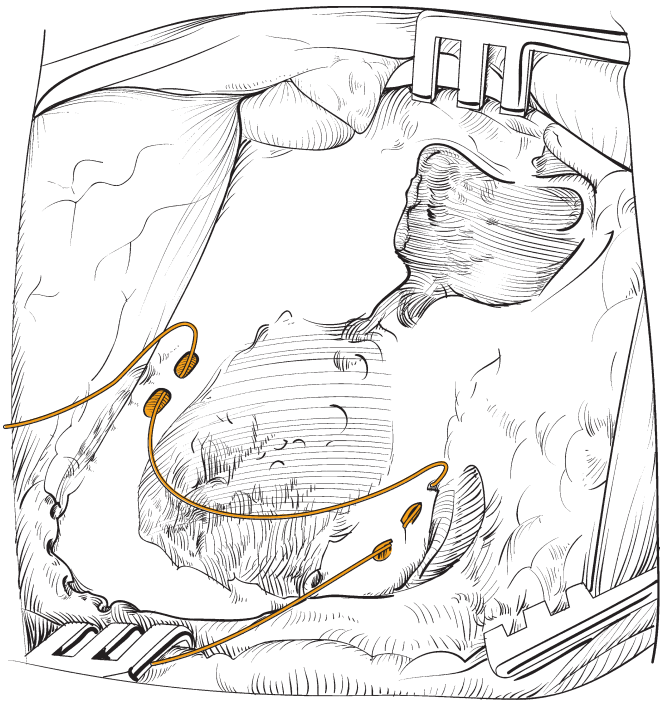

Figure 159-6. Bony seat and tie-down sutures with mastoid cavity. A custom-designed bony seat is made to recess the implantable receiver stimulator, thereby reducing its profile, providing a degree of protection from trauma, and minimizing mobility, which could result in work hardening of the electrode lead. A 2-mm diamond drill bit is used to create connecting suture holes superiorly and inferiorly, and a 2-0 nonabsorbable monofilament suture is used to secure the device into its seat. A trough is drilled to connect the seat to the mastoid cavity.

the cable away from the tympanic membrane in cases in which retraction or the need for myringotomy may arise.[20]

Cochleostomy

In the past, there have been instances in which the electrode was inadvertently placed into a hypotympanic air cell. It is important to identify the round window membrane to be certain that the cochleostomy and electrode insertion will proceed properly. The round window membrane is rarely more than 1- to 1.5-mm inferior to the stapedius tendon.

As with other aspects of the surgery, the placement and size of the cochleostomy varies somewhat depending on the implant to be used. In general terms, the cochleostomy is drilled through the promontory just anterior and inferior to the round window membrane. Care is taken to prevent bleeding into the cochleostomy by elevating the mucoperiosteum away from the selected site and using topical epinephrine on Gelfoam pledgets (Pharmacia & Upjohn Co., Kalamazoo, MI), if necessary. Good hemostasis should be obtained before opening the cochlea. If necessary, large Gelfoam pledgets may be placed in the epitympanum or mastoid cavity to prevent the drip down of blood. Bone dust should also be kept out of the cochlea.

A 1.5-mm diamond burr is used to thin the bone anteroinferior to the round window membrane. The overhanging niche is removed, if necessary, to positively identify the round window membrane. A 1-mm burr is used to remove remaining bone down to the endosteum itself. As the endosteum is approached, meticulous drilling is necessary to avoid inadvertent penetration. As a correlate, exposure of the endosteum of the scala tympani should be treated like a stapedotomy because penetration into the scala exposes the inner ear to significant acoustic trauma of up to 130 dB.[21] Endosteum is continuous with and found at the level of the round window membrane, which is used as a guide to the depth of the drilling. After this, the middle ear is carefully irrigated to remove all bone dust. It is imperative to prevent the rotating drill shaft from contacting the facial recess bone that overlies the facial nerve while drilling the cochleostomy. Overheating may result in delayed or immediate postoperative facial weakness.

The size of the cochleostomy is determined by the manufacturer and varies from 1.0 to 1.4 mm. The endosteum may be opened with a 25-gauge spinal needle, straight pick, or Beaver 59-10 cataract knife (Becton Dickinson Co., Franklin Lakes, NJ) just before insertion of the electrode.

Recent research has focused on the benefit of preserving low-frequency hearing in patients with predominantly high-frequency (speech frequencies) hearing loss by atraumatic insertion of the cochlear implant electrode. Low-frequency hearing may be preserved because the typical electrode does not extend into the distal apex of the cochlea, the frequency place of low tones. Use of a short/hybrid electrode has resulted in improved patient word understanding, particularly in noise, as well as improved music perception.[22,23] This has also been investigated using standard electrode insertion through the round window as opposed to performing the previous standard cochleostomy. In a noncontrolled case series, five of nine children were shown to have preserved low-frequency hearing after surgery, and eight of nine demonstrated a benefit of combined electric and acoustic stimulation.[24] Patients undergoing implantation by a round window approach may also have reduced postoperative vertigo.[25]

The round window approach to cochlear implant insertion has support in anatomic studies as well. Reduced damage to intracochlear structures has been directly demonstrated and/or suggested by multiple cadaveric temporal bone studies.[26-28] In addition, temporal bone studies have revealed the potential for significant acoustic trauma while drilling the cochleostomy, with up to 130 dB levels experienced by the inner ear.[21] The round window approach also is technically less difficult than cochleostomy and uses easily visible landmarks in many cases.[28]

Receiver Stimulator

The pocket for the receiver stimulator is copiously irrigated with dilute bacitracin solution, and any final hemostasis necessary is undertaken. Monopolar electrocoagulation systems are turned off and unplugged. The receiver stimulator is then placed into its bony seat/pocket and tied down with suture.

Electrode Insertion

The electrode tip is placed in the cochleostomy using specially adapted instruments or jeweler's forceps. It is important to direct the natural curvature of the electrode away from the basilar membrane and to insert it into the principal axis of the scala. Hyaluronic acid or 50% glycerine may be used to keep blood out of the scala during electrode insertion and to lubricate the electrode. Specialized instruments provided by the manufacturer may then be used to slowly and gently insert the electrode.

The electrode cable may be stabilized by placing it into the split bridge, if desired. Then, 1- to 2-mm pieces of temporalis fascia, pericranium, or muscle are used to pack 360 degrees around the electrode at the cochleostomy. Alternatively, a 3-mm piece of tissue may be buttonholed and slipped up the electrode array past all of the contacts. After near total insertion, it is then slipped back into the cochleostomy, and the electrode is advanced 1 mm farther.

The entire area is then copiously irrigated, and the incision is closed in layers. A light mastoid pressure dressing is applied overnight and removed after a wound check in the morning. Typically, drains are not used.

Special Considerations for Children

Hearing loss during the first few years of life is known to delay the development of language and to lead to serious developmental consequences. During the language-sensitive first years of life, loss of peripheral hearing has been shown to cause central auditory system abnormalities in experimental animals and to cause auditory perceptual disorders in children.[29-32] Cochlear implants, on the other hand, have shown a protective effect when electrical stimulation is delivered to the developing auditory system of deafened animals.[33-35] These issues have

led to the initial perception that the restriction of cochlear implantation to children older than the age of 2 years may limit potential development and linguistic outcomes. Children who have received implants by the age of 2 years acquire language at approximately the same rate as children without implants.[36] When implanted at this age, however, the child may not be able to overcome the original language gap caused by a lack of auditory input during the preimplant years. This has led to an increased interest in earlier implantation. A number of studies have demonstrated the safety and benefit of cochlear implantation in children younger than 12 months of age as well as the benefit to the children with respect to preverbal communication.[37-40] One study that evaluated children who had received their implants before 12 months of age revealed language comprehension and expressive development comparable to hearing peers. Their levels of language comprehension and expressive development was significantly better than those of children receiving implants between 12 and 24 months of age, thus supporting the practice of earlier implantation.[41] This has led to recommendations for implantation in appropriate candidates as young as 6 months of age. It is difficult to perform surgery much earlier, because approximately 6 months is needed for diagnostic testing, medical evaluations, and trials with hearing aids.

As the age of implantation has decreased, the acceptable levels of residual hearing of cochlear implant candidates has increased. Thus, although cochlear implants were originally restricted to children who were nearly anacusic, experience has shown that children with more residual hearing often perform better with implants. Hearing results in children with some measurable open-set speech recognition ability before implantation are better than those in children with none at all.[42-46]

Because the cochlea is full size at birth, there is no anatomic difficulty with electrode insertion in infants. However, deliberate surgical techniques for stimulator fixation and mastoidectomy and accommodation for head growth have been necessary for successful implantation. In very young children, it is often necessary to expose small areas of dura for the placement of tie-down sutures or seating of the implant. The skin incision must avoid the exposed facial nerve at the stylomastoid foramen. Redundancy of the electrode cable has been sufficient to prevent the extrusion of implants placed in very young children.

No specific complications associated with putting implants into very young children have been reported.

Otitis Media

The increased incidence of otitis media in very young children was once considered a relative contraindication to implantation. However, a number of studies have demonstrated that, after the ear infections are controlled medically or with ventilation tubes, implantation may proceed. Cochlear implantation is associated with neither increased incidence of otitis media nor complications such as labyrinthitis.[47-53] Some evidence has in fact suggested that mastoidectomy when combined with the improved ventilation of the middle ear afforded by performing a facial recess may decrease the incidence of otitis media.[54]

Otitis media should be managed aggressively to avoid delay in cochlear implantation. Treatment may require acute and prophylactic antibiotics, insertion of ventilation tubes, and in some cases, mastoidectomy with obliteration. The latter is usually performed as a staged preliminary step toward implantation in patients with chronic otitis media. It has been suggested that ventilation tubes be placed before implantation in children with unremitting otitis media with effusion and left in place for spontaneous extrusion.[55]

The recent association of meningitis and cochlear implantation has altered the thinking of some physicians regarding the management of recurrent otitis media, active otitis media with effusion, and an ear with a perforation. If severe chronic eustachian tube dysfunction is evident, a subtotal petrosectomy and closure of the eustachian tube and ear canal is advocated by some. This procedure should be performed 2 to 3 months before implantation of the internal stimulator receiver.

Auditory Neuropathy

Auditory neuropathy (AN) or dyssynchrony is associated with hearing loss in which outer hair cells function but inner hair cells or the cochlear nerve are dysfunctional. The diagnosis is made when otoacoustic emissions or cochlear microphonics are recordable (thus indicating outer hair cell function to be present) and the auditory brainstem response is absent. AN is suspected when the audiogram shows disproportionately low word recognition scores and the MRI is normal. It is critical in this population to provide an adequate trial of hearing aids and auditory verbal therapy because, despite an absent ABR, some children will have adequate benefit from hearing aids alone. Our experiences (as well as that of others) with AN implantees have been excellent in both adults and children.[56-58] The diagnosis of AN should not preclude consideration of a child for implantation. However, receipt of cochlear implants in many children has been delayed after a diagnosis of AN is made.

Meningitis and the Ossified Cochlea

Deafness caused by meningitis is associated with a reduction in spiral ganglion cells and often with ossification of the fluid spaces of the cochlea.[32] Because children who are deafened by meningitis may regain some of the hearing that was initially lost, immediate implantation is not recommended. However, fibrosis and ossification of the cochlea may occur within a few months after meningitis, and follow-up with serial MRIs performed at 2- to 3-month intervals may be done. If the perilymph/endolymph signature is lost, it indicates that fibrosis and eventual ossification may be occurring. In such cases, hearing does not return, and early implantation may be indicated. In some cases, the horizontal semicircular canal may show ossification earlier than the cochlea.

Meningitic patients generally require higher stimulation levels and more adaptive changes in their programming modes over time as compared with other patients.[59] This population has also been found to be at an increased risk of stimulation of the facial nerve (as have otosclerotic patients); however, this may be due to the higher stimulation amplitudes that are necessary, and it is usually controlled by inactivation of the offending electrodes or decreasing maximum stimulation levels. This may result in reduced performance of the implant. Nonetheless, patients with postmeningitic deafness and cochlear ossification can receive their implants via a variety of techniques,[60,61] and they can be electrically stimulated with generally good outcomes.[62] In the decade of the 1990s, approximately 3% to 9% of pediatric cochlear implant candidates had some degree of cochlear ossification, but in nearly 90% of these patients, the ossification is limited to the area that is adjacent to the round window membrane.[61] This may be drilled through to reach the open lumen of the basilar turn. When there is more extensive ossification of the scala tympani, the scala vestibuli may be patent and used for insertion. In both of these instances, a standard, full-length electrode is used, and results are similar to those of patients with no ossification.[61,63]

When both scala are ossified beyond the ascending turn of the cochlea, a complete drill out procedure or the use of a special electrode may be implemented.[64,65] Med-El Corporation (Innsbruck, Austria) manufactures a compressed electrode that has all of its contacts within a 10-mm distance for insertion into the inferior segment tunnel of the basal turn. Both Med-El and Cochlear Corporation (Melbourne, Australia) produce a split electrode array in which some contacts are placed in the inferior segment tunnel and others in the superior segment of the basal turn or in the second turn of the cochlea (see Fig. 159-7).

Labyrinthine Dysplasia

Deformities of the cochlea were once considered an absolute contraindication to cochlear implantation. However, at this time, deafness as a result of cochlear dysplasia is routinely managed with cochlear implants. Results vary directly with the degree of abnormal development. The majority of cases—including Mondini's dysplasia (incomplete partition), large vestibular aqueduct, and other, less severe forms of dysplasia—are associated with excellent results.[66,67]

The common cavity deformity, however, has highly variable results that are generally not as good as those seen in children with normal cochlea. Aplasia of the cochlea (Michel's deformity) or absence of the auditory nerve are absolute contraindications to implantation of the affected ear.

Absence of the cochlear nerve is suspected in anacusic patients with internal auditory canal (IAC) diameters of 1.5 mm or less. When a stenotic bony IAC is found, sagittal high-resolution MRI with heavily T2-weighted images is indicated to identify the presence of nerve bundles. The normal cochlear nerve may be seen coursing anteriorly toward the base of the modiolus. When facial nerve function is normal, one of the visible nerve bundles is considered to be the seventh cranial nerve. If the child has vestibular responses to calorics, another bundle may be considered the vestibular nerve; however, this nerve may be combined with the cochlear nerve. Electrical auditory brainstem responses may be performed to document the presence of the auditory nerve when there is doubt. In adults and children who are 6 years old and older, simple promontory testing may be performed in the office with topical anesthesia to obtain the same information.

CSF gushers should be expected in all cases of labyrinthine dysplasia. When a gusher occurs, implantation may proceed through the clear fluid, or the surgeon may elect to elevate the head of the table by 15 degrees and wait until no further fluid emerges. After the electrode is inserted, muscle and fascia are tightly packed into the cochleostomy to prevent further CSF leakage. A lumbar drain should not be used before sealing the cochleostomy, because it reduces the CSF pressure head, thereby making it impossible to determine whether the tissue seal is adequate.

Patients with Compromised Healing

Patients with reduced wound-healing capabilities because of underlying medical conditions or who are immunosuppressed by medications are considered to be at increased risk for postoperative infection and device extrusion. Nonetheless, in a review of patients with systemic autoimmune disorders as well as after liver and kidney transplantation, after high-dose radiation to the surgical field, or who were taking relatively high-dose immunosuppressive medications, implantation has been accomplished without significant complications.[68]

Older Patients

Some unique changes associated with aging must be considered in patients older than age 70 years. These include degeneration of all elements of the auditory system, the likelihood of prolonged duration of deafness, diminished central auditory function and communication ability, and coexisting medical and psychosocial problems.

Nonetheless, cochlear implantation in older adults has been successful, with results comparable to those in younger adults overall.[69] In our experience, patients up to the age of 87 years have obtained excellent results as evaluated by audiometric and quality-of-life measures. Nonetheless, in patients who are older than 80 years, these outcomes are not as good overall as they are in younger patients. Perioperative attention to medical and surgical details has allowed for safe insertion and a minimum of postoperative problems. Patients at this age are generally observed overnight in the hospital after surgery and are discharged the following morning.

Older patients may have difficulty understanding and recalling the information necessary for proper operation of their external device. Difficulties associated with arthritis and fine motor abilities may lead to problems changing batteries or adjusting the controls of the device. Older adults may also progress less rapidly with the use of their device if they live alone and are not exposed to verbal communication on a consistent basis.[69] Extensive counseling is required to address all of these issues and limitations. The ability to retain and use the relatively large amount of technical information by older patients must be kept in mind during counseling.

Bilateral Cochlear Implantation

The psychoacoustic literature has demonstrated improved auditory function when normal-hearing people listen with both ears and when hearing-impaired subjects use bilateral hearing aids.[70] This finding extends to bilateral implant recipients who have been clearly demonstrated to have improved speech recognition in noise compared with unilateral conditions.[15,71-74] This binaural advantage is predominantly from the head shadow effect in which speech and noise are spatially separated such that one ear is protected from the noise due to an acoustic shadow, and therefore has a better signal-to-noise ratio. Binaural summation and squelch have variable effects.[75] Because much social discourse occurs within a background of noise (classroom, party, busy restaurant), this advantage is of paramount importance to patients.

Sound localization is better in patients with bilateral implants than in patients with unilateral listening conditions. Unilateral localization accuracy has been identified between 50 and 67 degrees, whereas bilateral accuracy was determined to be between 24 and 29 degrees.[76-78] Sound localization is of critical importance in avoiding a potentially dangerous situation (e.g., locating an ambulance speeding down the street); it also permits the listener to focus on source and position of sound to improve the signal-to-noise ratio in daily situations.

In 2008, a position statement from the William House Cochlear Implant Study Group formally advocated bilateral cochlear implantation in children and adults because their review of literature supported the conclusion that both children and adults performed better with two implants than with one.[79]

Complications

Drilling the internal cochlear stimulator (ICS) seat and tie-down holes engenders the possibility of damage to the dura or the underlying dural blood vessels. Performing the mastoidectomy and opening the facial recess have the same risks as are present in other transmastoid procedures. However, because of the absence of chronic disease in most cases, the risks are somewhat reduced. Nonetheless, when operating on children with congenital deformities, there is a greater risk that the facial nerve may follow an aberrant course within the temporal bone.

Cochlear implantation also includes the insertion of a very delicate electrode, and the incidence of damaged or misplaced electrodes has declined from 1.74% to 1.18% since the late 1990s. The risk of postoperative facial paresis has also decreased from 1.74% in 1995 to 0.41%.[80,81]

Revision cochlear implantation surgery is not an uncommon occurrence after initial surgery. Reported rates of revision surgery vary, but recently revision surgery in adults has been reported at 5.4% to 7%.[81,82] The rate of revision implantation in children has typically been higher, with reports placing the rate between 8% and 12.5%.[81-83] The most common indications for revision surgery in a 2008 report was "hard failure" or device malfunction that occurred in 46% of the cases of revision surgery.[83] Medical-surgical reasons (e.g., wound healing, electrode malposition, cholesteatoma) were the second most common cause, occurring in 37% of cases. A "soft failure" (decrease in auditory performance or aversive symptoms in a device that performs within manufacturer specifications) occurred in 15% of cases. In general, patients performed as well after reimplantation as their best performance before surgery.[83,84]

Reimplantation may also be necessary when technology advances to the point that the device in use is outmoded (e.g., the transition from single-channel to multichannel implants). Studies of repeat electrode insertion depth show results that are generally equal to the original, although cases of both improved and diminished function have been reported.[84,85]

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CHAPTER ONE HUNDRED AND SIXTY

Cochlear Implants: Results, Outcomes, Rehabilitation, and Education

Charles J. Limb

Howard W. Francis

Sue Archbold

Gerard O'Donoghue

John K. Niparko

Key Points

- Performance of cochlear implants is affected by baseline factors that should be assessed as implant candidacy is considered. A multidisciplinary team enables simultaneous input from multiple perspectives, and is the most effective approach to assessing a candidate's needs and desires and the potential for an implant to meet them.
- In the 1980s, candidacy requirements for a cochlear implant required total or near-total sensorineural hearing loss as characterized by a pure-tone average of 100 dB or greater; amplified thresholds that failed to reach 60 dB; and an absence of open-set speech recognition despite the use of powerful, best-fit hearing aids. Because clinical experience has indicated that the mean speech reception scores of implant recipients generally exceed the aided results of individuals with lesser impairments, the audiologic criteria have been progressively relaxed since the early stages of multichannel implants to include a range of pure-tone averages, focusing instead on functional benefits provided by amplification.
- Although a cochlear implant facilitates sensitive hearing reliably, actual "listening" capabilities are less easily characterized.
- Speech recognition remains the standard metric of cochlear implant candidacy and performance. Speech recognition results show high variability, however, and awareness is increasing that epiphenomena surrounding implantation and the postimplant experience affect performance.
- For children, the extent to which the implant experience assists oral language development is a key reflection of the effectiveness with which developmental learning is normalized. Children with early-onset deafness lack the base of auditory memory needed to pair implant-mediated precepts with meaning. They may harbor other disabilities that may prevent instinctive language learning. Such conditions can produce a wide range of individual variability, particularly when intervention with a cochlear implant is delayed.
- In children, initial reports suggested that implantation before age 3 years provides distinct advantages over later implantation in cases of early-onset deafness. More recent data suggest that speech recognition and language skills are facilitated with implantation in earlier toddler and even infancy stages. Whether earlier implantation may yield greater benefits requires longitudinal follow-up of the development of ever younger infants undergoing implantation.
- Adults with cochlear implants exhibit a similarly wide range of results, often owing to factors outside of the device per se.
- To improve the accuracy of predicting an implant's outcome and to counsel patients effectively, comprehensive preimplant assessment is necessary.
- Screening for other handicapping conditions, particularly conditions that would impair the acquisition of receptive and productive communication skills, helps determine candidacy and direct rehabilitative strategies.
- Postimplantation rehabilitation can be important for some adult implant recipients, but is crucial for children to optimize the usefulness of an implant. It is often assumed that effective interactive skills and language comprehension directly result from the sensitivity with which sound is perceived through a cochlear implant. Hearing is not a sufficient condition for these higher skills, however, and a high priority should be placed on auditory rehabilitation to enhance fundamental skills in verbal communication.

Three decades of clinical experience with cochlear implantation suggest that notions of "success" or "failure" are highly nonspecific. There is a wide spectrum of the effects of cochlear implantation, which span a range of communication, psychosocial, and cognitive outcomes. Assessment of "success" with a cochlear implant is complex. The sense of hearing is pivotal to the phonologic awareness and processing that supports speech and language, including the development of visual language reception (reading) and production (writing), and a range of communicative behaviors and cognitive functions. This chapter examines the broad effects of cochlear implants in children and adults. We have drawn information from reports of clinic-based results and patient-based surveys. Basic assessment of physiologic response to auditory nerve stimulation, measures of receptive and productive benefit, and surveys of life effects as reflected in measures of quality of life and economic outcomes are described.

Although we characterize the effects of the implant per se, clinicians caring for hearing-impaired patients are increasingly aware that *clinical practices* related to cochlear implantation—especially practices related to candidate selection and rehabilitation—modify expectations and observed results. The most obvious effect of severe to profound sensorineural hearing loss is that there is insufficient phonologic access to encode complex information contained in speech streams. Cochlear implants seem to enable a level of phonologic access that can reliably overcome barriers to speech recognition. It has been tempting to assume that restored audition through a cochlear implant would provide sufficient input for a child to achieve a normal trajectory of developmental learning or an adult to reacquire the skills of verbal communication fully. The tasks of developmental learning and spoken communication require more than basic perceptive capacity, however.

A child or adult with an implant must attempt to process information conveyed by a prosthetic device using afferent tracts that may be altered consequent to early deafferentation. The ability to assimilate auditory information in facilitating communication tasks cannot be assumed because of well-recognized deprivation effects inherent in advanced sensorineural hearing loss. Environment and developmental experience are likely important, if not determinative, of implant benefit in some domains. Through a fuller understanding of the elements of success and failure with cochlear implants, clinicians can gain insight into criteria for candidate selection, and for the services and environments that would optimize use of an implant as a communication tool.

Results of Implantation

Factors Related to the Measurement of Auditory Performance

Auditory performance is measured at preimplant and postimplant intervals. Preimplant assessments form the basis of evaluating patient candidacy. Postimplant measures document the progress of the patient, while allowing the clinician to monitor for device-related and environmental factors that can influence long-term outcomes. Measurement variables associated with auditory testing should be standardized as much as possible. Clinicians can choose between closed-set tests (e.g., forced choice of one answer from a list of four) and open-set tests (auditory alone without context) of words or sentences. Closed-set tests are easier for patients than open-set tests, and are susceptible to "ceiling effects," reflecting high contextual information available when word and sentence material are presented.[188] The method of presentation can also affect speech perception scores.[1a] Live presentation typically produces higher rates of correct responses than taped presentations.

Trends toward higher rates of open-set speech recognition with newer implant technology and longer implant experience have prompted more stringent assessments. Increasing the difficulty of a speech perception test has the effect of limiting the "ceiling effect" that results from testing with simple, everyday phrases. To generate meaningful comparative data, increasing test difficulty normalizes distributions of scores, enabling more powerful statistical tests of differences between groups.

Tests of Implant Performance

The Minimum Speech Test Battery (MSTB) was developed for adult cochlear implant users. The MSTB is a set of high-fidelity disc recordings that provide a standardized set of comprehensive tests of preoperative and postoperative speech recognition.[2] To minimize the effects of learning and memorization, MSTB word and sentence tests have different lists for at least six testing trials. The average and range of performance of cochlear implant users are crucial to defining audiologic performance boundaries for implant candidacy.

The major components of the MSTB are the Hearing in Noise Test (HINT) and the Consonant/Nucleus/Consonant Test (CNC). The HINT[2] provides a measure of speech recognition ability for sentences in quiet and in noise. The background noise is filtered to match the long-term average spectrum of the sentences. In the MSTB, the HINT sentence lists are presented at 70 +dB in quiet and at 10 +dB signal-to-noise ratio (i.e., noise at 60 +dB). Smaller signal-to-noise ratios (e.g., 5 +dB or 0 +dB) may also be used to avoid ceiling effects. Although normal-hearing listeners can comprehend sentences effectively with signal-to-noise ratios of 3 +dB, implant recipients typically show degraded speech recognition when signal-to-noise ratios are reduced beyond 10 +dB.

The CNC consists of lists of monosyllabic words with equal phonemic distribution, with each list having approximately the same phonemic distribution as the English language.[3] Such lists provide material for performance testing that is more likely to represent daily experience with speech stimuli. These tests measure percentage of words correctly recognized. Open-set conditions for monosyllabic word recognition are considered the most difficult challenge to a listener with a cochlear implant, and such tests are useful to compare outcomes in adults.[4] Revised CNC lists[5] were developed to eliminate uncommon words and proper nouns. Ten lists of 50 words contain monosyllabic words that are employed with a frequency of greater than 4 per 1 million, as calculated in word-frequency tables. As part of the MSTB protocol, during each preoperative and postoperative evaluation, one CNC and one HINT list should be presented in quiet at 70 dB(A). In addition, if the patient performs greater than 30% under quiet conditions, HINT sentences can be presented in noise at 10 +dB signal-to-noise ratio.

Implant Performance in Adults

Improved speech perception is the primary goal of cochlear implantation. Although initial clinical series judged implant efficacy mostly on environmental sound perception and performance on closed-set tests, greater emphasis is now placed on measures of open-set speech comprehension. Speech-perception results from early clinical trials have served to guide the evolution of cochlear implantation. Gantz and colleagues[6] provided early comparative data in their assessment of environmental sound and speech perception in a large cohort of nonrandomized single-channel and multichannel implant users. Multichannel implants provided significantly higher levels of performance on all measures. Cohen and associates[7] performed the first prospective, randomized trial of cochlear implants through the U.S. Veterans' Administration hospital system. The trial provided high-quality clinical data and convincing evidence of open-set speech recognition, and established the clear superiority of multichannel over single-channel designs. The study was the first to report a low complication rate and high device reliability in individuals deafened after language acquisition from multiple centers with varying levels of prior programmatic implant experience.

Cohen and Waltzman,[8] Skinner and colleagues,[9,10] and Wilson and associates[11] assessed effects of changing external processing capabilities. They compared the performance of subjects fitted with processors designed to increase the rate of information transfer through higher rates of pulsed stimulation. Each study assessed a different processor, and study design and processing strategy also differed among studies. In each study, the use of a more sophisticated speech processor led to significantly better performance in open-set speech recognition.

Clinical observations in patients with current processors indicate that for patients with implant experience longer than 6 months, the mean score on open-set word testing approximates 25% to 40% (range 0% to 100%).[7,12-14] Results achieved with the most recently developed speech processing strategies reveal mean scores greater than 75% on words-in-sentence testing (range 0% to 100%). Although subjects perform substantially poorer on single-word testing, these mean scores

continue to improve as speech-processing strategy evolves.[10] After implantation, speech recognition by telephone[15] and music appreciation are often observed.

Benefits are enhanced through the use of more recently developed processing strategies. Spahr and colleagues[16] observed that differences in implant design affect performance, especially in difficult listening situations. Input dynamic range and the method by which compression is implemented seem to be the major factors that account for results in difficult listening situations, with greater performance associated with the expanded dynamic range offered by current processing strategies employed by the Advanced Bionics and MedEl devices.

Predictors of Benefit in Adults

Assessments of speech recognition in adults with cochlear implants offer the opportunity to develop models of benefit prediction. As investigators identify the salient predictive factors, candidacy, device and processing strategy, and the degree of postoperative auditory rehabilitation necessary, they can be better informed. The contributions of modifiers to differences in performance (multivariate analysis) have been addressed in several large studies.[6,7,12-14,17-19] The following factors have been evaluated:

- *Subject variables*: age of onset, age of implantation, deafness duration, etiology, preoperative hearing, survival and location of spiral ganglion cells, patency of the scala tympani, cognitive skills, personality, visual attention, motivation, engagement, communication mode, and auditory memory

- *Device variables*: processor, implant, electrode geometry, electrode number, duration and pattern of implant use, and strategy employed by the speech processing unit

Although the significance of the above-listed factors varies across different populations, multiple regression analysis has identified variables with high predictive value for speech comprehension. Length of implant use accounts for a high degree of variance in speech perception measured postoperatively. When length of use is controlled, preoperative hearing (particularly with respect to speech recognition) also accounts for a high degree of variance. Duration of deafness, age of implantation, cochlear patency, subject engagement with the therapeutic regimen, and processor type also carry high predictive values for speech understanding.

In addition to the factors in the list, the choice of ear to implant is a highly compelling issue. Other studies have emphasized the utility of implanting the better hearing ear.[13] At Johns Hopkins Hospital, we have long advocated the implantation of the poorer hearing ear. Although more data are needed, our studies so far reveal no significant difference in implant performance based on whether the better or worse hearing ear is implanted. Figure 160-1 shows a regression plot of the predicted postoperative word scores for each patient as modeled by the Johns Hopkins (implant poorer ear) and Iowa formulas (better ear).[17] Virtually identical scores are predicted on the basis of each patient's duration of deafness and preoperative sentence recognition scores. These data suggest that results obtained through cochlear implantation of the poorer hearing ear are statistically equivalent to results obtained through implantation of the better hearing ear. The similarity of results obtained through both methods suggests that implantation may have a beneficial effect on central auditory pathway development regardless of sidedness.

Another variable that influences speech perception is technologic sophistication of the implanted device. Improvements in speech perception have been associated with generational improvements in signal processing strategies, speech processors, and electrode arrays,[20] but may reflect clinical trends and technologic advances.[13] Criteria for cochlear implant candidacy are constantly expanding. Research has shown that patients with greater residual hearing show even more promising results. Identification of monosyllabic words for individuals using early generations of the Nucleus (Cochlear Corp., Sydney, Australia) multichannel cochlear implant averaged 16%,[6] whereas performance exceeds 50% on similar measures with current technology.[10,16] Earlier studies have contrasted performance across different manufacturers of devices. Differences in performance seem more closely related, however, to general demographic differences across patient populations, tests used, and length of experience with the devices than to differences in characteristics of like-generation devices per se.[21,22]

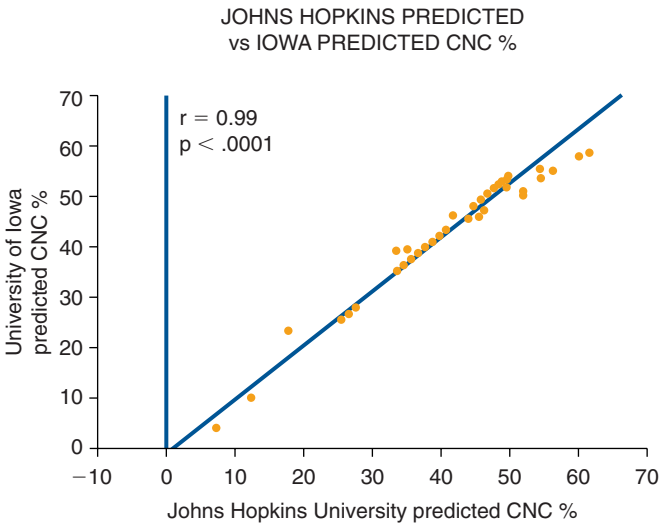

Figure 160-1. Regression plot of the predicted postoperative word scores for each patient as modeled by the Johns Hopkins (implant poorer ear) and Iowa formulas (better ear). There are virtually identical scores predicted on the basis of each patient's duration of deafness and preoperative sentence recognition scores. These data suggest that results obtained through cochlear implantation of the poorer hearing ear are statistically equivalent to results obtained through implantation of the better hearing ear. The similarity of results obtained through both methods suggests that implantation may have a beneficial effect on central auditory pathway development regardless of sidedness. CNC, Consonant/Nucleus/Consonant Test.

Cochlear Implantation with Hearing Preservation in Adults

There has been considerable interest in clinical strategies that combine residual acoustic hearing with electric hearing provided by a cochlear implant. Two strategies have been developed, depending on baseline hearing status. A *combined* mode uses a cochlear implant in one ear and a hearing aid in the other ear.[23] A *hybrid* strategy uses a hearing aid and a cochlear implant in the same ear.[24,25]

The goal of combining amplification with a cochlear implant in the opposite ear is to preserve perceptual advantages inherent in (predominantly low frequency) acoustic hearing in an attempt to capture at least some binaural cues. In fact, binaural advantages are observed in some patients.[23] Tests of speech perception in noise reveal trends toward a binaural advantage for word recognition depending on the direction of origin of noise (with advantages obviated when noise is on the hearing aid side). Localization ability improved with both devices. These data support the use of a hearing aid opposite a cochlear implant for appropriate patients.

Success with hearing preservation[26,27] in ears implanted with scala tympani electrodes has encouraged the development of hybrid modes of stimulation—electroacoustic hearing. Various surgical strategies have been adopted in attempts to limit cochlear trauma with scala tympani electrode insertion, enhancing opportunities for preserving residual (typically, <1 kHz) hearing. Hearing preservation procedures are designed to avert basilar membrane rupture and attendant spiral ganglion cell loss. Optimal preservation seems to be achieved with placement of the cochleostomy in a strategic location (away from the basilar membrane) along with cautious insertion of adapted, smaller arrays in a manner that limits impact on the endosteal and basilar membrane surfaces.[28]

Electroacoustic hearing seems to confer distinct advantages in speech perception and in music listening.[25,29] Improvements in speech-

in-noise understanding and melody recognition are linked to the ability to distinguish fine pitch differences through preserved, low-frequency acoustic hearing. There may be expanded spectral representation that more faithfully supports higher frequency hearing over time.[30] These observations suggest that the preservation of residual low-frequency hearing should be considered in selected patients. Observations of advantages in electroacoustic hearing may expand candidate selection criteria for cochlear implantation.

Although electroacoustic stimulation is a promising treatment for patients with residual low-frequency hearing, a small subset lose residual hearing despite best attempts with preservation. Such patients may obtain expected levels of benefit using the electric mode of the hybrid implant alone. For patients unable to achieve this benefit from an electroacoustic strategy after losing residual hearing, reimplantation with a standard array seems to provide higher levels of speech recognition.[31]

Implant Performance in Children

Pediatric cochlear implantation began with House-3M, single-channel implants in 1980. Investigational trials with multichannel cochlear implants began with adolescents (10 to 17 years old) in 1985 and with children (2 to 9 years old) in November 1986. Implantation of infants and toddlers younger than 2 years began in 1995.[32] Although clinical experience with cochlear implantation is shorter in children than in adults, a large body of clinical reports is now available.[33,34] Investigators have evaluated the hearing and speech receptive benefit of cochlear implants in children since 1985.

Auditory Performance Assessments for Children

Auditory performance in children is assessed with a battery of audiologic tests that can address the wide range of perceptual skills exhibited by children with severe-to-profound sensorineural hearing loss. Although substantial auditory gains are apparent in implanted children, the range of quantifiable improvement varies widely among children, and depends heavily on the duration of use of the device, preoperative conditions, and longitudinal experience and training effects. For this reason, testing should survey a range of levels of speech recognition, including simple awareness of sound, pattern perception (discrimination of time and stress differences of utterance), closed-set (multiple choice) speech recognition, and open-set (auditory only) recognition.

Methodologic variables must be considered when attempting to rate objectively the effect of cochlear implants on the development of speech perception in deaf children. Difficulties are inherent in objectively rating communication competence in very young children. Older children may exhibit advantages by virtue of greater familiarity with a test's context, independent of perceptual skills. Objective assessment mandates a structured setting that is not always conducive to eliciting a child's best cooperative effort. Investigators must also account for discontinuity in the age-appropriate measures necessary for longitudinal assessment.[34] Methodologic challenges and developmental considerations inherent in pediatric implant assessment have been examined in detail by Kirk and Diefendorf,[35] who categorized variables as relating to the following:

- *Internal variables*: the child's age and level of language and cognitive development
- *External variables*: the child's ability and willingness to respond as influenced by reinforcement and required memory task
- *Methodologic variables*: the procedure of voice presentation, the test administered, and the available options from which to choose a response

Tests of speech perceptions typically used for childhood assessment have been described in detail,[1a,35-37] and usually consist of closed-set tests that assess word identification among a limited set of options with auditory cues only, open-set tests (scored by percentage of individual words correctly repeated), and structured interviews of parents using criteria-based surveys[38] to assess response to sound in everyday situations and behaviors related to spoken communication.

Early Studies of Speech Reception in Children with Cochlear Implants

House and colleagues[39] found that children with cochlear implants obtain substantial improvement in auditory thresholds, closed-set speech recognition, and limited open-set speech recognition with the House-3M single-channel implant. Miyamoto and coworkers[40] provided systematic, well-controlled assessments of childhood cohorts and consistently showed performance advantages of multichannel over single-channel implants. Other early studies by Fryauf-Bertschy,[41] Gantz,[42] Miyamoto,[18] and Waltzman[43] and their colleagues observed that implanted children gain substantial speech perceptive capabilities for 5 years after implantation. Because many of the implanted children tracked in these studies were congenitally or prelingually deaf, there are compelling data to indicate that implantation can provide auditory access during critical developmental stages to form the early correlates of spoken language.

The studies we have cited have shown implant benefit in children with total or near-total hearing loss. An important issue for candidacy of children with lesser degrees of hearing impairment is the study of implant benefit relative to controls who have not received implants. Classification of children according to preoperative hearing levels can provide a common ground for comparison. Miyamoto and associates[44] described the following candidacy scale for stratifying children according to aided pure-tone detection thresholds: "Gold" class hearing aid users have unaided thresholds of 90 to 100 dB at two of three frequencies (0.5 kHz, 1 kHz, 2 kHz), with a mean of 94 dB. "Silver" class hearing aid users have unaided thresholds of 101 to 110 dB at two of three frequencies, with a mean of 104 dB. "Bronze" class users have unaided thresholds of greater than 110 dB at two of three frequencies, with a mean greater than 110 dB.

Hearing aid users in the "gold" category generally fall into Boothroyd's[45] category of "considerable residual hearing." In many such cases, hearing aid users that function at this level show substantial capabilities for near-normal trajectories of speech and oral language acquisition. This particular group of profoundly hearing-impaired children sets a comparative standard for speech perception performance. "Silver" category hearing aid users receive few spectral cues and rely heavily on temporal cues for speech perception. "Bronze" category users are considered "totally deaf," and receive only low-frequency percepts and restricted or no temporal cues.

Most hearing-impaired children who have received cochlear implants fell into or were eventually moved into the "bronze" category. Compared with children using amplification, children with implants have shown the following:

- After 2 years of implant experience, mean speech intelligibility scores of implanted children surpass those of "silver" category hearing aid users and approach within 10% scores of "gold" category users, particularly on more stringent tests of speech comprehension.[44,46] Longitudinal tracking of implanted children shows no evidence of a plateau effect in mean scores of speech comprehension. In conjunction with evidence based on multivariate analysis, this observation suggests that length of implant use is the primary determinant of receptive benefit.
- Trends toward continued improvement in speech reception are also associated with improved intelligibility of speech.[47] Although the measured proficiency of speech produced remains low through the first 2 years after implantation, intelligibility scores thereafter show dramatic gains and surpass those of hearing aid users in the "silver" category.[48] These observations are consistent with observations of gains in speech intelligibility in other childhood cohorts.[49,50]

More Recent Studies of Speech Reception in Children with Cochlear Implants

Between 1994 and 2004, numerous reports documented various levels of gains in speech recognition in young deaf children using multichan-

nel cochlear implants. Miyamoto and coworkers[18] noted that in 29 children with 1 to 4 years of experience with a cochlear implant, approximately one half achieved open-set speech recognition. Waltzman and Cohen[51] found that 14 children implanted before age 3 years attained high levels of speech perception performance with only 2 years of experience. Fryauf-Bertschy and coworkers[52] examined speech perception in cochlear-implanted children over 4 years, and noted significant increases in pattern perception and results of closed-set speech perception tests.

Variability in speech-perception performance across subjects is widely recognized, and is related to several variables, including age of implantation,[33,42,52-54] mode of communication,[43,55] family support,[52] and length of deafness.[56,57] Miyamoto and colleagues[40] found that duration of deafness, communication mode, age at onset of deafness, and type of processor accounted for approximately 35% of variance in closed-set testing. The length of implant use alone accounted for a larger percentage of variance on all speech perception measures. In a 5-year follow-up study, O'Donoghue and associates[53] found that age at implantation was the most significant covariant, and that mode of communication was the most significant between-individuals factor. The latter study showed that young age at implantation and oral communication mode are the most important known determinants of later speech perception in young children after cochlear implantation.

Waltzman and colleagues[43] and Brackett and Zara[58] reported improved speech reception in children implanted at age 2 to 3 years compared with children implanted at an older age. Multicenter data reported by Osberger and associates[59] indicated that implant performance of children implanted before age 2 years is significantly better than implant performance of children implanted between age 2 and 3 years. The authors also identified an important confounding variable, however, that exists in the children who receive a cochlear implant at a younger age: they are more likely to use an oral mode of communication. This, by itself, may be a predictor of higher implant performance—an observation borne out in early studies of a national childhood cohort assembled by Geers and colleagues.[55]

Osberger and coworkers[59] also found that children with more residual hearing relative to earlier cohorts were undergoing implantation. Gantz and colleagues[60] compiled data from across centers that indicate children with some degree of preoperative open-set speech recognition obtain substantially higher levels of speech comprehension. Taken together, these studies suggest the strongest potential for benefit exists with implantation at a young age, when intervention is provided early and, in the case of a progressive loss, before auditory input is lost completely.

Cheng and associates[33] performed a meta-analysis of relevant literature on speech recognition in children with cochlear implants. Of 1916 reports on cochlear implants published since 1966, 44 contained sufficient patient data to compare speech recognition results between published (n = 1904 children) and unpublished (n = 261) trials.[33] Meta-analysis was complicated by the diversity of tests required to address the full spectrum of speech reception in children with cochlear implants. An expanded format of the Speech Perception Categories[61] was designed to integrate results across studies. The main conclusions of this meta-analysis were that earlier implantation is associated with a greater trajectory of gain in speech recognition (Fig. 160-2), performance comparing deafness of congenital and acquired etiologies levels out over time, and there is an absence of reaching a plateau of speech recognition benefits over time. More than 75% of the children with cochlear implants reported in peer-reviewed publications have achieved substantial open-set speech recognition after 3 years of implant use.

Implantation of Infants

New diagnostic approaches and improved treatment options have enhanced real-life outcomes and transformed clinical approaches to the treatment of early-onset hearing loss. Universal newborn hearing screening now routinely identifies hearing loss that might have gone unnoticed in years past until a child had failed to develop language skills. Such early identification affords the opportunity to provide clinical intervention during a brief and critical growth period when neural connections develop physiologic support needed for children to achieve verbal communication.

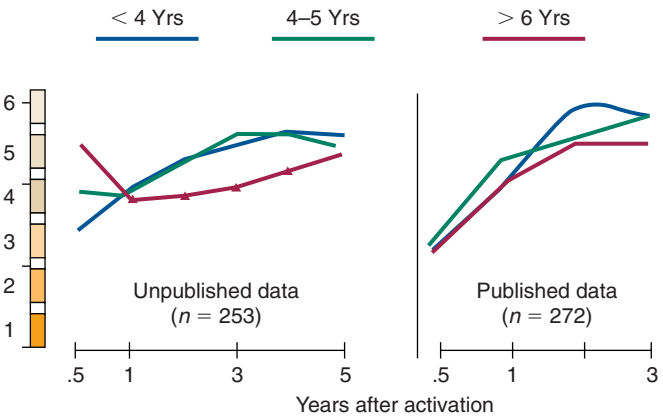

Figure 160-2. Meta-analysis of speech perception results with cochlear implantation in children, showing effects of age at implantation on speech perception. Published and unpublished data are shown. Three different ages at implantation groups are compared (<4 years, 4 to 5 years, and >6 years). The ordinal scale represents levels of speech perception: 1, detection; 2, pattern; 3, limited closed-set; 4, substantial closed-set; 5, limited open-set; and 6, substantial open-set.

A growing body of evidence supports the early application of cochlear implantation in congenitally deaf children. Meta-analyses of the effects of age at implantation have shown that children undergoing implantation at younger ages achieve greater progress in speech perception skills than children implanted at older ages.[33,62,63] Because the development of language follows the same trajectory as that reflecting speech perception, language growth is more favorable in children who receive cochlear implants early in life.[64] To the extent that higher language ability results in greater independence in school settings,[65] earlier intervention would enhance the cost-effectiveness of the cochlear implant.

Cochlear implantation has been shown to be a safe procedure in children younger than 12 months old.[66,67] The motivation to pursue implantation when a child has been deemed an appropriate candidate is supported by compelling data showing the benefits of earlier intervention. Tait and colleagues[68] showed that preverbal skills develop much more rapidly in children who receive cochlear implants before 2 years of age compared with children implanted between 2 and 3 years old, or between 3 and 4 years old. Connor and colleagues[69] examined latent growth curves and showed the value of very early implantation as it translated into more favorable outcomes. Dettman and colleagues[70] in Australia and Lesinski-Schiedat and associates[71] in Germany have convincingly shown with longitudinal assessment that the language trajectories of children implanted before age 12 months are greater than those achieved with implantation after 12 months of age.

Nicholas and Geers[72] showed that language outcomes for deaf children for whom appropriate intervention occurs within the first months of life are far superior to outcomes associated with later intervention. They noted that the first 3 years in a child's life are crucial for acquiring information about the world, communicating with family, and developing a cognitive and linguistic foundation from which all further development unfolds.

Because of the demonstrated safety of early implantation and the effectiveness of early linguistic intervention, cochlear implantation in younger children (12 months old) has been approved by the Food and Drug Administration in the United States. The current approval for implantation at age 12 months should be interpreted with caution. The intent of that approval is based on open market applications from manufacturers; delaying intervention results and the risk of prolonged auditory deprivation and adverse consequences for development should be weighed in each individual case.

Bilateral Cochlear Implantation

In an effort to expand the benefits obtained with unilateral cochlear implantation, bilateral implantation has been pursued in increasing

numbers of patients, either simultaneous or sequential. As of this writing, approximately 20% of all implant users have bilateral devices based on generally positive subjective experiences with low rates of complication. An important development within the field of cochlear implantation is to assess fully the impact of bilateral intervention.

Normal listeners possess a range of auditory capabilities owing to binaural processing, as follows:

Localization: Normal listeners are able to tell where sound is coming from in the horizontal plane (at ear level) with an accuracy of ±14 degrees.[73] The brain uses differences in intensity and time between the two ears to determine the location of a sound source. To localize sound in the vertical plane (up and down), or when time and intensity cues between the two ears are ambiguous, spectral (pitch) information is important.[74] The shapes of the outer ear and ear canal change the intensities of all of the pitches arriving at the ear (by reflecting them differently) to determine the location of sounds in the vertical plane.[75]

Head shadow: When listening to speech in noise, the head acts as a sound barrier that makes noise quieter on the side away from the speech. When one ear is close to the noise source, adding the other ear (away from the noise) provides a second ear where the speech is louder than the competing noise.

Squelch: When signals and noise come from different directions, the brain is able to separate them by comparing time, intensity, and pitch differences between the two ears. The practical effect is that the brain is able to suppress signals that the listener does not wish to hear.

Summation: When identical signals are presented to the two ears, there is an advantage when hearing with both ears instead of just one alone. The brain has a special ability to use the signals from both ears to produce this binaural advantage.

Studies of subjects with unilateral hearing loss illustrate some of the problems that a listener with only one "good" ear may encounter. Background noise often interferes with word recognition in quiet and noisy conditions even when the speech is directed to the good ear. People have reported difficulty hearing and understanding speech even in relatively quiet situations that include low-level noise (e.g., car radios, air conditioners).[76] Children with unilateral hearing loss not only have difficulty in noise,[77] but also show delays in language development and academic performance relative to their peers with normal hearing.[78]

In addition to the general advantages of binaural hearing, there may be other compelling reasons for considering bilateral implantation in very young children. Congenitally deaf children depend on their cochlear implants for learning spoken language. Children with normal hearing acquire language through incidental learning—that is, through participation in everyday communication and social experiences, which are often unintended and incidental. Although studies have shown improved language acquisition in children with unilateral implants relative to their preimplant performance with hearing aids,[64,79] children still lag behind their peers with normal hearing in mastery of more complex language structures that are requisites for academic success.[80] If a young deaf child has two implants, the rate of incidental language learning is likely to be accelerated because they would be better able to understand speech in everyday situations (most of which are noisy), and to localize to the most relevant (speech) events in their environment. The improved benefits with bilateral implants in young deaf children have important implications for language acquisition, academic success, and educational and occupational opportunities.

Providing sound input to both ears in a young deaf child ensures that sound is processed on both sides of the brain. The right and left auditory cortices can develop in a more normal sequence. If a child is implanted on only one side, the parts of the brain that would have been stimulated by the nonimplanted ear do not develop, and eventually plasticity is greatly diminished. Ryugo and colleagues[81] reported that electric stimulation of the auditory system largely prevents or reverses the synaptic abnormalities seen in congenitally deaf white cats.

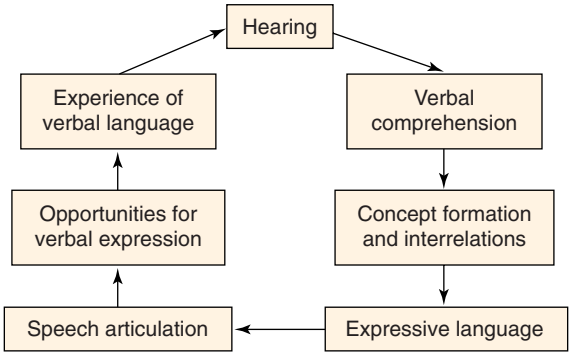

Figure 160-3. The cycle of verbal communication. Hearing is crucial to the process of verbal communication and allows for verbal comprehension. Concept formation gives rise to expressive language and speech articulation capabilities, which are applied as verbal language in appropriate situations. Successful verbal communication ultimately depends on hearing. *(Modified from the Reynell Developmental Scales Manual. Los Angeles: Western Psychological Services.)*

Reports of the bilateral benefits experienced by adult and pediatric patients with two implants continue to increase.[82-91] There are few prospective studies of children who receive two implants during early childhood, however.

Although the "era of bilateral implantation" has been introduced, there are few controlled trials to date.[92] Preliminary results reveal evidence of an expanded sound field and loudness summation, and some level of sound localization ability to most bilateral recipients. In a few patients, benefits attributable to effective squelch are noted. Such findings show central integration of electric stimulation from the two ears despite an absence of precise tonotopic matching of binaural inputs. Systems that enable integrated speech processing of inputs from the bilateral sound fields have yet to be introduced clinically. It is uncertain whether potential benefits of bilateral implantation could be expanded through such processing.

Language Development in Children

A primary goal of implantation in children is to assist comprehension and expression through the use of spoken language. Language is defined as a vehicle for shaping and relating abstractions for communication.[93] The meaning of language-mediated abstraction is independent of the immediate situation. Practical use of language is based on the assignment of a single name to various appearances and situations under varying conditions. Information exchange via spoken language involves a conversion of thought into speech. This conversion relies on mental representations of phonologic (sound) structure and syntactic (phrase) structure.

All fundamental models of language development propose that the acquisition of language is the result of progressive organization from an initially undifferentiated state. As incremental differentiation occurs, language skills become more sophisticated and hierarchically integrated. The child first must learn to form internal representations of acoustic speech patterns (Fig. 160-3). These experiences enable a child to identify consistent patterns in phonologic inputs and to develop associations between context and semantic and syntactic patterns. Through increased familiarity, these associations between spoken language and their actual counterparts build a child's semantic awareness.[94] Social cognition and emotional needs are likely to encourage such development, as supported by observations that infants become "tuned" to their language environment in the form of "perceptual maps" (Fig. 160-4),[95] and show protolinguistic behaviors with caretakers that are bidirectional.[96-98]

Early communication between infants and caregivers forms a critical foundation for development. This foundation provides a base on which cognition, affect, and social interaction may evolve.[99] If communication is hindered, development fails to proceed normally, with

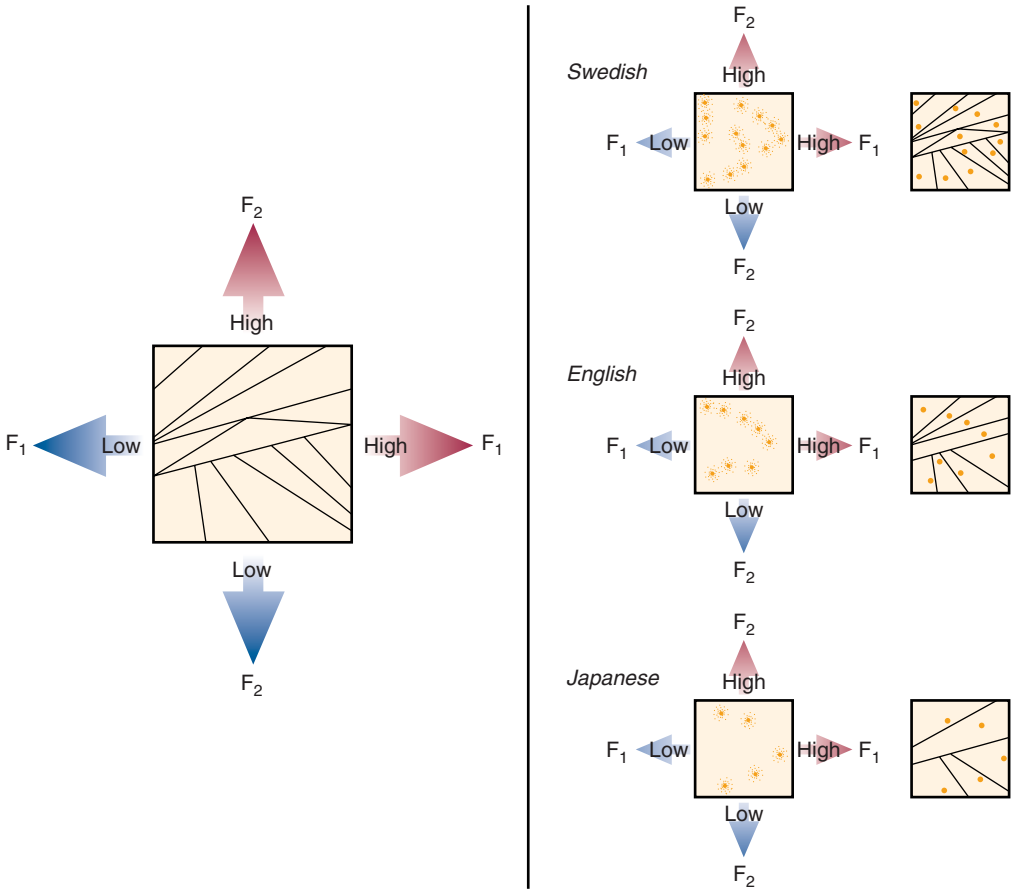

Figure 160-4. *Left,* Schematic figure shows natural auditory boundaries according to F_1 and F_2 formant frequencies. These boundaries are thought to provide a framework by which infants process incoming sound streams into gross categories. Intrinsic phonetic differences separate boundary regions from one another. *Right,* The ability to partition auditory input according to these boundaries is independent of linguistic experience, and is present throughout various languages. Examples of vowel processing in three different languages (Swedish, English, and Japanese) are shown. *(Adapted from Kuhl PK, Meitzoff A. Speech as an intermodal object of perception. In: Yonas A, ed. Perceptual Development in Infancy. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988:235-266; and Kirk KI. Challenges in the clinical investigation of cochlear implant outcomes. In: Niparko JK, ed.* Cochlear Implants: Principles and Practices. *Philadelphia: Lippincott Williams & Wilkins; 2000:225-259.)*

detrimental sequelae in terms of cognitive, behavioral, and social development. Hearing loss and subsequent obstacles to communication threaten optimal development.[100-102] Because most children who have sensorineural hearing loss are born to hearing parents, a "mismatch" may exist between child and parent[103] that prevents effective communication.[104,105] Because sign language skills in hearing parents tend to be absent or basic, such children are at further risk for developmental delay.[106,107] Additional evidence confirms that children with sensorineural hearing loss who engage in linguistic interactions with their parents show age-appropriate cognitive, social, and behavioral development.[100] More recent theories suggest the processes linking language to cognition, affect, and behavior are dynamic and bidirectional, rather than discrete or independent.[108,109]

For successful bidirectional communication to occur within the family unit, language must be linked to cognition, affect, and behavior. Visual attention, which may be reliably assessed at 4 months of age, is crucial for guiding development.[99,110] Data suggest that visual attention is highly relevant to the development of emotional bonds to caregivers, language learning, and the processing of perceptual information.[111-114] In normal development, much of this early visual attention is actually directed by sound. Infants look longer in the direction of sound and longer at visual events whose temporal rhythms match what they hear.[115,116] When sound perception is impaired, visual and auditory integration is similarly disrupted, forcing a child with sensorineural hearing loss to rely on vision for communication and cues about when and where to direct attention.[117,118] This notion has been confirmed in studies of hearing-impaired children using computerized task performance measures.[117,119,120] These impairments have been found to contribute to behavioral problems.[120] By comparison, two studies found that children with cochlear implants perform better on this computerized task than children without cochlear implants.[117,119]

In addition to visual attention, other types of preverbal communication underlie the acquisition of verbal language. Substantial gains in prelinguistic behaviors, including eye contact and turn-taking,[121] and in verbal spontaneity[122] are observed as early correlates of implant benefit, developing within 6 months of implantation in young children.[123] Tait and associates[124] found that preverbal measures obtained 12 months after implantation are predictive of late performance on speech perception tasks. They observed a significant association between the preverbal measure of "autonomy" obtained before implantation and later speech perception performance. This latter finding has important theoretic implications for understanding of language development, and suggests that intervention that promotes autonomy in adult-child interaction may lead to improved outcomes. Such intervention can be introduced as soon as deafness is discovered.

Language Acquisition in Children with Cochlear Implants

By improving auditory access, cochlear implants augment sound and phrase structure. Although difficult to characterize, benefits in receptive language skills and language production after implantation are the crucial measure by which effectiveness of implants in young children should be assessed. One approach is to compare language performance on standardized tests. The Reynell Developmental Language Scale evaluates receptive and expressive skills independently.[125] These scales

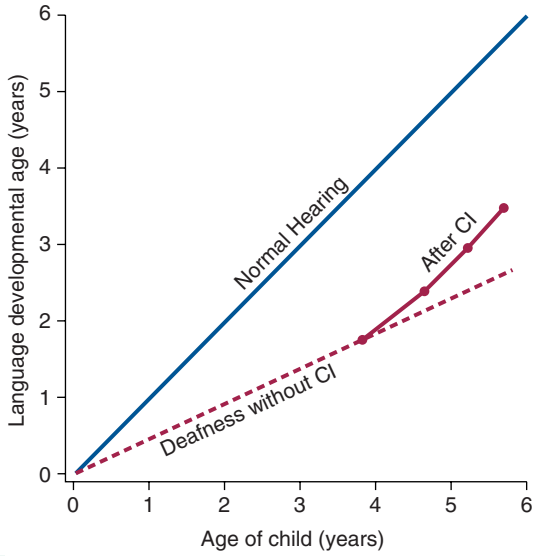

Figure 160-5. The effect of cochlear implantation (CI) in children on language development. *Solid line* depicts normal language development as it correlates to chronologic age. *Dashed line* shows the developmental delay that occurs in deafness before CI. After CI, language development progresses at the same rate as children with normal hearing. This suggests that language delay is a product of cumulative deficits acquired before CI, rather than from impaired progress after CI. *(Modified from Svirsky MA, Teoh SW, Neuburger H. Development of language and speech perception in congenitally, profoundly deaf children as a function of age at cochlear implantation.* Audiol Neurootol. *2004;9:224-233.)*

have been normalized on the basis of performance levels of hearing children in an age range of 1 to 8 years, and have been used extensively in populations of deaf children. Although deaf children without cochlear implants achieved language competence at half the rate of normal-hearing peers, implanted subjects exhibited language-learning rates that matched, on average, those of their normal-hearing peers.[125,126] In a study of 23 children who became deaf before 3 years of age, Svirsky and colleagues[126] studied language development after cochlear implantation. The average age of implantation in this cohort was approximately 4 years. These investigators found that speech development progressed at a decreased rate before implantation, but that after implantation, language development in implanted children was parallel to that of normal-hearing children (Fig. 160-5). The implication of this study is that differences in language delay between implanted and normal-hearing children could be explained by the initial period of deafness before implantation, rather than performance or progress after implantation. These findings also emphasize the importance of early implantation. Data are rapidly being gathered to confirm that earlier implantation might limit early language delays to enable more age-appropriate language acquisition.

Robbins and associates[125] noted that implantation improved language-learning rates for children in oral communication and total communication settings based on the Reynall Developmental Language Scale. Geers and coworkers,[55] also assessing language skills in implanted children enrolled in oral communication and total communication settings, found that the groups did not differ in language level, although the oral group showed significantly better intelligibility in their speech production.

Delays in receptive and expressive language among hearing-impaired children have consistently been documented in the literature, although such delays are not strongly related to degree of hearing loss.[127,128] Performance on language measures can be influenced by the child's mode of communication such that results may not directly reflect the influences of auditory perception or prosthetic intervention. Clinical findings support the hypothesis, however, that some deaf children are able to use the acoustic-phonetic cues provided by the implant in ways that may reduce the language gap between normal-hearing and deaf children.

Central nervous system processing is a primary determinant of the level of verbal language ultimately attained after cochlear implantation.[129] Pisoni[129] assessed performance in two groups of pediatric cochlear implant users: "Stars" were children whose phonetically balanced kindergarten scores placed them in the top 20%. The second group, children with scores in the bottom 20%, comprised the control group. Speech perception, spoken word recognition, speech intelligibility, and language level were compared between the two groups at preimplantation and at yearly postimplant intervals. Children in the "Stars" group did not score consistently better on all behavioral measures than children in the control group. Differences between the groups were manifest only on specific tests and task demands. Children with superior implant performance were consistently better on measures of speech perception (i.e., vowel and consonant recognition), spoken word recognition, comprehension, language development, and speech intelligibility than were the control children. The two groups did not differ, however, in their vocabulary knowledge, nonverbal intelligence, visuomotor integration, or visual attention. It was concluded that "Star performance" on measures of spoken language processing and speech intelligibility was not attributed to global differences in overall performance, but to differences specifically in the task of processing auditory information provided by the cochlear implant.

The authors also examined the differential performance on various behavioral tests of communicative ability administered after 1 year of cochlear implant use. Strength of correlation revealed a significant association between spoken word recognition, language development, and speech intelligibility for the "Stars" group, but not for the control group. "Star performance" seemed to result from an enhanced language processing ability and the development of phonologic and lexical representations.

The strong relationship between spoken word recognition and speech intelligibility for superior implant performers suggests that (1) a transfer of knowledge exists between speech perception and production, and (2) that speech perception and production share a common system of internal representation. According to Pisoni and Geers,[130] the exceptional performance of the "Stars" seems to be a result of their superior abilities to perceive, encode, and retrieve information about spoken words from lexical memory. They described the capacity for processing tasks that require the manipulation and transformation of the phonologic representations of spoken words as "working memory." Pisoni and Geers[130] then investigated the impact of working memory on measures of speech perception, speech intelligibility, language processing, and reading in implanted children with prelingual deafness. The investigators evaluated correlations between children's ability to recall lists of orally presented digits and their performance on these measures. The authors observed correlations between auditory memory and performance in each outcome area, suggesting that working memory plays an important role in mediating performance across these higher communication tasks.[130]

Promising clinical studies have generally supported wider application of cochlear implants in children. Childhood implant research has often relied, however, on case-series design, based in a single center that evaluated children who used different generations of implant technology. Few studies have examined the impact of cochlear implants on the "whole" child, particularly when one considers the importance of understanding longitudinal measures of cognitive, social, and behavioral development. There is also little information available on the perceived benefit of childhood implantation from a perspective of cost-effectiveness.

The need and significance of this information is underscored by the fact that clinical decisions to pursue early cochlear implantation are often prompted by parental choice. Parents of deaf children choose among options which have vastly different implications for the use of medical, (re)habilitative, educational, and other societal resources. A pressing issue concerns the validity of generalizing from early observations of benefit from cochlear implantation to the decision to implant younger children. Should very young infants identified with severe to profound sensorineural hearing loss undergo cochlear implantation within weeks of diagnosis?

An ongoing multicenter study is examining the clinical modifiers of postimplant developmental outcomes, including oral language acquisition, speech recognition skills, selective attention and problem-solving skills, behavioral and social development, parent-child interactions, and quality-of-life measures in children undergoing implantation in six U.S. implant centers.[131] It is hoped that a detailed assessment of communicative and psychosocial results will contribute to an understanding of the factors predicting implant-associated language use, communication competence in early childhood, and the perceived value of early cochlear implantation in light of associated costs. It is hoped that conclusions will enable an informed approach to implant candidacy when considering (re)habilitative strategies designed to enhance developmental learning in children with severe to profound sensorineural hearing loss.

Outcomes after Cochlear Implantation

Educational Placement and Support of Implanted Children

A hearing-impaired child is at substantial risk for educational underachievement.[132,133] Educational achievement by a hearing-impaired child can be enhanced by verbal communication. Traditional methods of speech instruction are more successful with children who have enough residual hearing to benefit from early devices of hearing rehabilitation.[134] Improved speech perception and production provided by cochlear implants offer the possibility of increased access to oral-based education and enhanced educational independence.

Francis[135] and Koch[136] and their colleagues tracked the educational progress of implanted children by using an educational resource matrix to map educational and rehabilitative resource use. The matrix was developed on the basis of observations that changes in classroom settings (e.g., into a mainstream classroom) are often compensated by an initial increase in interpreter and speech-language therapy. Follow-up of 35 school-aged children with implants indicated that, relative to age-matched hearing aid users with equivalent baseline hearing, implanted students are mainstreamed at a substantially higher rate, although this effect is not immediate, and requires rehabilitative support to be achieved. Within 5 years after implantation, the rate of full-time assignment to a mainstream classroom increases from 12% to 75% (Fig. 160-6).

Quality of Life and Cost-Effectiveness

Prior studies of the cost-utility of cochlear implants have assessed quality of life and health status to determine the utility gained from cochlear implants.[19,137,138] *Utility* is a concept that reflects the true value of a good or service. Cost-utility methods determine the ratio of monetary expenditure to change in utility as defined by a change in quality of life over a given period. The assessment of cost-utility is based on the following:

$$\text{Cost-utility} = \text{costs (in \$)}/(\text{quality-adjusted life-years})$$
$$= \text{costs (in \$)}/(\text{life-years} \times \text{health utility})$$

Life-years is the mean anticipated number of years of implant experience based on a life-expectancy analysis of the participating cohort. The change in health utility reflects the difference between preimplant and postimplant scores on survey instruments that have been designed and validated to reflect quality of life. In the United States, England, and Canada, health interventions with a cost-utility ratio less than $20,000 (U.S.) are generally considered to represent acceptable value for money expended (i.e., they are "cost-effective").[139-141]

Quality-of-Life Studies in Adults and the Elderly

Costs per quality-adjusted life-year (QALY) for cochlear implants in adult users were determined using cost data that account for the preoperative, postoperative, and operative phases of cochlear implantation.[19,138] Benefits were determined on the basis of functional status and quality of life. The precise cost-utility results varied among studies, mostly because of methodologic differences in the determination of benefit, level of benefit obtained, and differences in costs associated with the intervention. Nonetheless, these appraisals consistently indicated that the multichannel cochlear implant in adult populations is associated with cost-utility ratios in the range of $14,000 to $18,000/QALY, indicating a highly favorable position in terms of cost-effectiveness (Table 160-1).

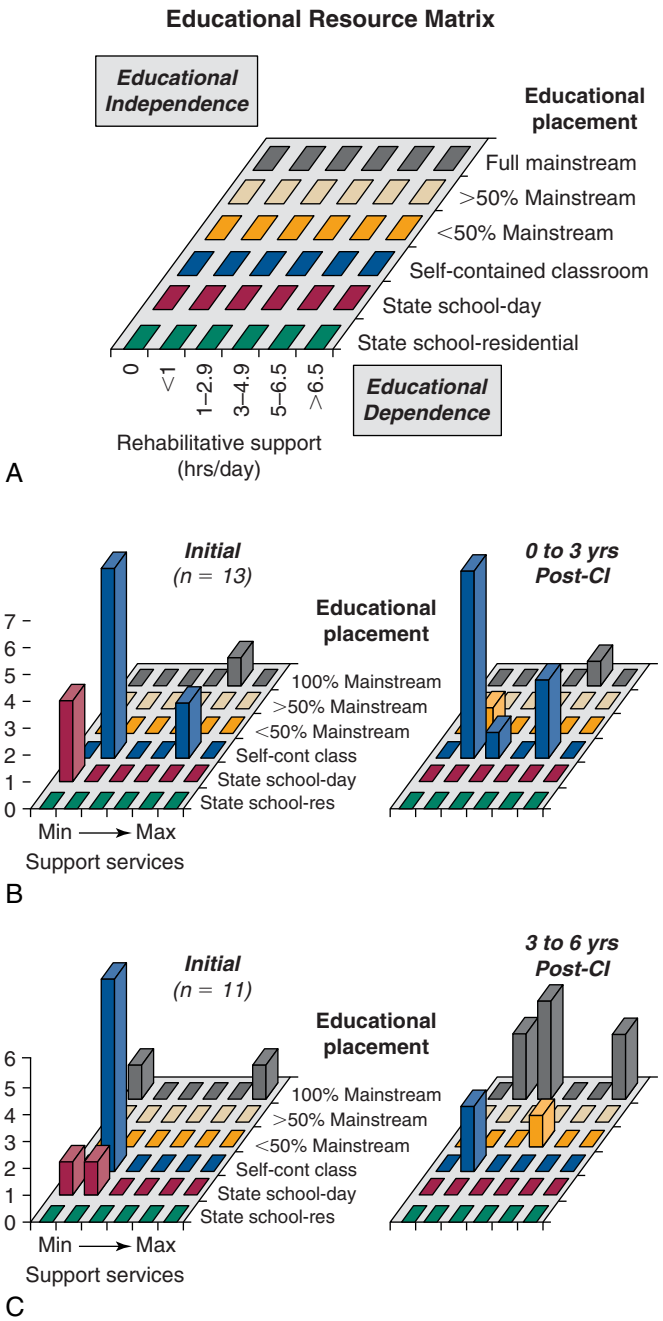

Figure 160-6. Matrix of educational resource usage by children with cochlear implantation (CI). **A,** The Educational Resource Matrix (ERM) plot classroom placement *(ordinate)* versus rehabilitative (speech-language and interpretive) support *(abscissa)*. **B,** Patterns of change in use of educational resources in a cohort of children within 3 years of CI. **C,** Patterns of change in use of educational resources in a cohort of children 3 to 6 years after CI. Note the higher levels of mainstreaming, and reduced use of support services with prolonged use of the cochlear implant. (***A,*** *From Koch ME, Wyatt JR, Francis HW, Niparko JK. A model of educational resource use by children with cochlear implants.* Otolaryngol Head Neck Surg. *1997;117:174-179;* ***B,*** *from Francis HW, Koch ME, Wyatt JR, Niparko JK. Trends in educational placement and cost-benefit considerations in children with cochlear implants.* Arch Otolaryngol Head Neck Surg. *1999;125:499-505.)*

Table 160-1

Cost-Utility Ratio of Cochlear Implantation in Adults

Source; Year	Instrument	Country	No. Patients	Health Utility Gain	Cost-Utility Ratio, S/QALY
Palmer et al; 1999	HUI	U.S.	37	+0.20	14,670
Wyatt et al; 1996	HUI	U.S.	229	+0.204	15,928
Wyatt and Niparko; 1995	VAS—without*	U.S.	229	+0.304	9,000
Summerfield and Marshall; 1995	VAS—without*	United Kingdom	105	+0.41	7,405
Summerfield and Marshall; 1995	VAS—before†	United Kingdom	103	+0.23	13,200
Harris et al; 1995	QWB	U.S.	7	+0.072	31,711
Fugain et al; 1998	VAS	France	30	+0.22	6,848
Overall			**511**	**+0.26**	**12,787**

Meta-analysis of studies of cost-effectiveness of cochlear implantation in adults. The overall cost-utility ratio was calculated to be $12,787 per quality-adjusted life-years (QALYs). In the United States, England, and Canada, a threshold of $25,000/QALY or less is considered an acceptable cost-utility ratio for a given health intervention.

*Patient rating of health utility if cochlear implant were taken away.

†Patient rating of health utility before implantation.

HUI, Health Utilities Index; QWB, Quality of Well-Being Scale; VAS, Visual Analog Scale.

Hearing impairment is one of the most common clinical conditions affecting elderly individuals in the United States.[142] Hearing loss is so profound in 10% of elderly hearing-impaired individuals that little or no benefit is gained with conventional amplification.[143] Assessing the effectiveness of cochlear implants in elderly patients requires consideration of audiologic and psychosocial factors. The social isolation associated with acquired hearing loss in elderly individuals[144] is accompanied by a significant decline in quality of life and an increase in emotional handicap.[145] The rehabilitation of hearing loss is an important goal in this vulnerable population, providing functional and psychologic contributions to quality of life.

Age-related degeneration of the spiral ganglion[146,147] and progressive central auditory dysfunction[148,149] raise potential concerns about the efficacy of cochlear prostheses in the elderly. Comparable gains in speech understanding have been reported for elderly and younger groups of implant recipients,[150] but the implications of these functional gains on the quality of life of older adults have not been well characterized. The determination of auditory efficacy and quality of life is crucial to any cost-benefit analysis in elderly patients, and may help guide clinical resource allocation, particularly in light of the high costs associated with cochlear implantation as a nonlifesaving intervention.

Reports of quality of life gains in elderly patients with cochlear implants have been favorable,[151-153] but are based on questionnaires that are difficult to correlate with function and cost-utility. Francis and colleagues[151] evaluated 47 patients with multichannel cochlear implants, 50 to 80 years old, who completed the Ontario Health Utilities Index Mark 3 (HUI3) survey and a quality-of-life survey. This study assessed preimplantation and postimplantation (6 months and 1 year after implantation) responses to questions related to device use and quality of life. A significant mean gain occurred in health utility of 0.24 (SD 0.33) associated with cochlear implantation ($P < .0001$) (Fig. 160-7). Improvements in hearing and emotional health attributes were primarily responsible for this increase in health-related quality-of-life measure. A significant increase occurred in speech perception scores at 6 months after surgery ($P < .0001$ for Central Institute for the Deaf sentence and monosyllabic word tests), and there was a strong correlation between the magnitude of health utility gains and postoperative enhancement of speech perception ($r = 0.45$, $P < .05$). Speech perception gain was also correlated with improvements in emotional status and the hours of daily implant use. The authors concluded that cochlear implantation has a statistically significant and cost-effective impact on the quality of life of older deaf patients.

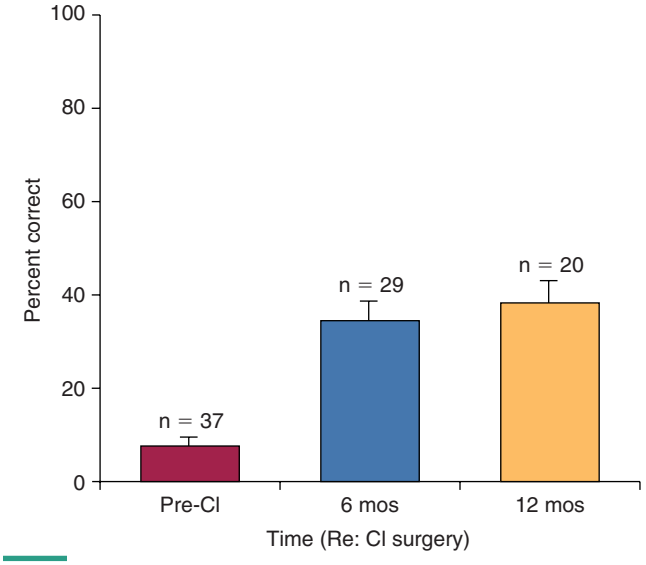

Figure 160-7. Mean monosyllabic word scores obtained in older adult subjects with postlingual hearing impairment just before cochlear implantation (CI) and at 6 and 12 months afterward (error bar = 1 SE). Monosyllabic word scores, which are generally considered one of the most difficult tests of speech perception, clearly increase during the first year after CI.

Quality-of-Life Studies in Children

Published cost-utility analyses of the cochlear implant in children have been limited by using either health utilities obtained from adult patients[19,139,154] or hypothetically estimated utilities of a deaf child.[155-158] These studies yielded cost-utility ratios that spread over a wide range ($3141 to $25,450/QALY). Utility assessments derived from adult patient surveys may not capture the impact of issues unique to childhood deafness.[33] To address this issue more rigorously, Cheng and coworkers[137] surveyed parents of a cohort of 78 children (average age 7.4 years, with 1.9 years of cochlear implant use) who received multichannel implants at the Johns Hopkins Hospital to determine direct and total cost to society per QALY. Parents of profoundly deaf children

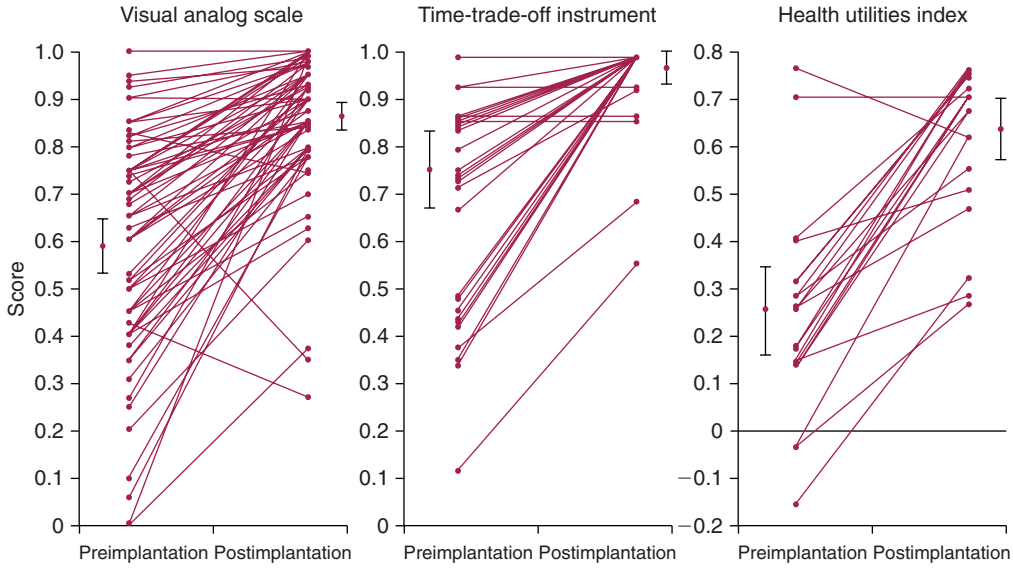

Figure 160-8. Retrospective health utility scores from parents of children with cochlear implants. Three different methods of assessing health utility scores are shown. The mean change in utility (postintervention—preintervention scores) was 0.27 for the visual analog scale, 0.22 for the time-trade-off instrument, and 0.39 for the health utilities index. The error bars on the side of each graph show mean scores with 95% confidence intervals.

($n = 48$) awaiting cochlear implantation served as a comparison group to assess the validity of recall. Using the Time-Trade-Off (TTO), Visual Analog Scale (VAS), and HUI3, parents rated their child's health state "now," "immediately before," and "1 year before" the cochlear implant. Mean VAS scores increased 0.27 on a scale of 0 to 1 (from 0.59 to 0.86), TTO scores increased 0.22 (from 0.75 to 0.97), and HUI scores increased 0.39 (from 0.25 to 0.64) (Fig. 160-8). Discounted direct medical costs were $60,228, yielding cost-utility ratios of $9029/QALY using the TTO, $7500/QALY using the VAS, and $5197/QALY using the HUI3. Including indirect costs, such as reduced educational expenses, the cochlear implant yielded a calculated net savings of $53,198 per child. Based on assessments of this cohort from a single center, childhood cochlear implantation produces a positive impact on quality of life at reasonable direct costs and results in societal savings.

The educational resource matrix used by Francis[135] and Koch[136] and their colleagues offers a basis for assessing overall cost-benefit ratios of the cochlear implant in children. Although educational costs for all implanted students remain static or initially increased, ultimate achievement of educational independence for most implanted children produces net savings that range from $30,000 to $100,000 per child, including the costs associated with initial cochlear implantation and postoperative rehabilitation. Language-related and education-related outcomes in children with cochlear implants have been supplemented with parental perspectives of quality-of-life effects to yield cost-utility ratings.[137,154] Despite conservative assumptions, results show that cochlear implantation is, relative to other medical and surgical interventions, highly cost-effective in profoundly hearing-impaired young children.

Auditory Rehabilitation after Cochlear Implantation

The uniqueness of the listening experience enabled by a cochlear implant is underscored by qualitative differences in how sound perception is elicited compared with other strategies of auditory rehabilitation. A hearing aid filters, amplifies, and compresses the acoustic signal, delivering a processed signal to the cochlea for transduction. In contrast, a cochlear implant receives, processes, and transmits acoustic information by generating electric fields. Electric hearing bypasses nonfunctional cochlear transducers by directly depolarizing auditory nerve fibers. Implant systems convey an electric code based in selected features of speech that are crucial to phoneme and word understanding in normal listeners, without the advantages of signal preparation provided by cochlear mechanisms of sound processing that render complex sounds listenable and discriminable. The listening experience with the cochlear implant also differs from normal audition in the timing of when that experience begins.

Either through a process of learning in the early, formative years in children, or by virtue of "auditory memory" in adults, capabilities for meaningful listening develop for most implant recipients. A central clinical question relates to the potential benefit to be derived from dedicated sensory training, commonly referred to as "auditory training." Can such training enable a cochlear implant user to apply latent skills and adaptive strategies to listening tasks that offset deprivation effects and the limitations of cochlear implant listening to capitalize on the device capabilities?

Exposure to conversational speech likely provides insight otherwise unavailable. Language learning may be too complex to be acquired using didactic methods alone. Consistent, frequent exposure may offer the greatest prospects of refining oral language skills. Through tracking the temporal, spectral, and intensity parameters of sound, the cochlear implant provides cues of voicing and articulation patterns that are not visually detectable. For deaf children who experience difficulty in developing their language skills, the possibilities afforded by early implantation, before the onset of changes consequent to deafferentation, seem to be substantial. The best method of achieving such outcomes are yet to be determined, however.

Efficacy of Auditory Training in Cochlear Implant Rehabilitation

Auditory training that provides real-world utility to restored audition in implant recipients is necessarily highly individualized. That is, the goals for a patient's auditory, speech, language, and cognitive development rely on a host of influences unique to the individual. Because of the need for such an individualized approach, studies of treatment efficacy of auditory training with high internal validity are difficult to construct. Carney and Moeller[159] noted that earlier efficacy studies target specific treatment areas of perceptual skill development, language development, speech production, academic performance, and social-emotional growth. Treatment goals within various treatment areas often vary, limiting the ability to assess the impact within any single category.

Prior studies have systematically assessed the development of speech perception with training in implant listeners. Watson[160] noted

that studies of the perception of complex nonspeech sounds have shown that individual parts of spectral-temporal waveforms can become more salient through selective training. One consequence of training is that the same sound can be perceived quite differently, depending on earlier experience as it affects a listener's expectancy and the psychologic mindset brought to the task. The time course of learning to identify initially unfamiliar speech sounds by normal-hearing listeners extends through months, possibly even years, before reaching a stable level of performance. If implant users are required to learn to interpret sounds as unfamiliar to them as the nonspeech sounds used in research are to normal-hearing listeners, a similar lengthy experience may be required to reach a plateau of maximum performance. Why this has not been the case in some clinical studies is a puzzle.

Watson[160] offered an explanation in that speech perception may depend heavily on abilities other than sensory acuity or tonal resolution. Studies of individual differences in auditory temporal and spectral acuity have not shown strong correlations between individual differences in those abilities and individual differences in speech perception. It is argued that one way to interpret this observation is that differences in the ability to hear speech (as by two hearing-impaired listeners with the same audiogram) may be the result of differences in the way in which central pathways generate the ability to infer an original stimulus from its fragments.

Dawson and Clark[161] tested whether the ability to use place-coded vowel formant information would be subject to training effects in a group of congenitally deafened patients with limited speech perception ability. They investigated the relationship between electrode position difference limens and vowel recognition. Young subjects were assessed with synthesized versions of the words "hid," "head," "had," "hud," "hod," and "hood." Performance during a nontraining period was compared with the change in performance after 10 training sessions. Two of four subjects showed significant gains, and improvements were consistent with their electrode discrimination ability. Difference limens ranged from one to three electrodes for these patients, and for two other patients who showed minimal to no improvements. Minimal gains shown by one subject could be partly explained by poorer apical electrode position difference limen. The authors concluded that significant gains in vowel perception occurred after training, and suggested the need for children to continue prolonged aural rehabilitation for a period after implantation. Despite intensive efforts, minimal improvements can sometimes occur, however, and such limited success is not always accounted for by limitations at the level of the auditory periphery.

Svirsky and coworkers[162] examined two possible reasons underlying longitudinal improvements in vowel identification by cochlear implant users: improved labeling of vowel sounds and improved electrode discrimination. Improvements in vowel identification were attributed to improved labeling, suggesting cortical learning effects were responsible for the observed changes, as opposed to enhanced electrode discrimination.

Rehabilitation in Adults with Cochlear Implants

After implant activation, adult users must adjust to the novel signals transmitted by the speech processor. Recipients must learn to associate electrically elicited sound patterns with perceptions that were previously meaningful sound sensations. Rehabilitative needs differ in implant recipients depending on their auditory experience before the onset of deafness. For a prelinguistically deafened implant recipient, auditory and speech (articulation) training are crucial in facilitating communication change. For a postlinguistically deafened patient, auditory training often focuses on more complex listening skills—understanding speech in noise, telephone use, and music appreciation.[163]

Auditory Training in Children with Cochlear Implants

Programs of auditory training in children with implants are often organized with a hierarchic approach by which the child learns to associate meaning with unfamiliar and possibly unnatural sounds.[122,164] After showing awareness of sounds (detection), the child is taught to determine whether sounds are the same or different (discrimination), to recognize sounds and to associate meaning with them (identification), and to respond appropriately in verbal discourse (comprehension). Expressively, the child learns to imitate phonemes and syllables and to coarticulate these sounds to produce progressively more difficult words and phrases. Imitation or approximation of speech sounds and words is a strategy used for developing an "auditory feedback loop"—the interrelated function of perception of sound and production of speech. Functional use of spoken language depends on the child's ability to produce meaningful linguistic utterances spontaneously. This process begins with a single word and progresses through sequential stages to complex phrases and entire stories.[165] Boothroyd[166] stressed the need for flexibility in guidelines for therapy sessions, noting that "the structure needs to exist in the mind of the teacher, and not be so obvious in the activities done with the child."

Boothroyd and colleagues[167] provided a model of auditory development that highlights the time course of development and identifies component skills that are crucial to effective auditory perception in children. They defined auditory perception as the interpretation of sensory evidence that is derived from sound and is reflective of objects and events that caused the sound. Similar to other perceptual events, auditory perception involves not only sensory evidence, but also contextual evidence, prior knowledge, memory, attention, and processing skills. Auditory speech perception is special because the events to be perceived are those of language. Similarly, the listener's knowledge base and processing skills must include those related to language in general and to spoken language in particular.

The normal auditory system is complete and functional at birth, but myelination continues for several years in the higher auditory pathways. Correspondingly, infants display increasingly sophisticated discrimination and recognition ability. Psychoacoustic performance does not reach adult levels for several years, however. Infants at 6 months of age show the beginnings of phonemic classification. Their capacity of performance improves during childhood, including phonetic contrast perception, phoneme recognition, perception of speech in noise, selective attention, and the use of linguistic context. Because experience plays a key role in the development of the knowledge and skills required for auditory perception in general, and for auditory speech perception in particular, intensifying that experience in hearing loss and with prosthetic devices is theoretically attractive.

Boothroyd and colleagues[167] noted that it is tempting to assume that the sensory evidence available to a developing child is determined only by the functional integrity of the peripheral auditory system, independent of auditory experience. Basic science investigations document the influence of auditory experience on the organization of auditory pathways,[168] however, and observe that better organization through experience could increase the sensory evidence made available from patterns of neural excitation produced in the cochlea.

Cochlear implants provide profoundly deaf children with a level of hearing sensitivity that enables them to perceive most of the sounds of spoken language, even when presented at low levels of intensity. Rehabilitative practices are designed to build on this level of sound awareness. In the case of a child who developed an audition-based language system before the onset of deafness, the cochlear implant restores access to spoken language—in many cases with expanded phonemic access. In the case of children who have never heard or who lost their hearing before the establishment of spoken language, access to sound provided by the cochlear implant initially lacks meaningful associations.

Current cochlear implant technology also provides the potential for deaf children to make use of generalization and incidental learning. Benefits of "hearing" extend well beyond contexts of one-on-one repartees with predictable discourse. Age of onset, degree of hearing loss, and amplification history[47] determine the quantity and quality of auditory stimulation received before implantation and readiness to interpret acoustic information. A child experienced in using residual hearing from an early age through amplification is likely to adapt to the sounds provided by the implant more quickly than a child with limited experience in listening.[167] The close scrutiny afforded by regular interaction with an auditory training therapist allows for the early detection of either the need for device reprogramming or failure of components of the implant system.

Components of auditory training in children with cochlear implants are designed to foster the development of auditory and speech skills in a manner that simulates a hearing child's acquisition of spoken language, while addressing remedial needs that arise as a consequence of auditory deprivation during early development.[169] Rehabilitative strategies related to auditory, speech, and language skills should seek to achieve overall communicative competence.[50] Ideally, rehabilitative strategies do not teach specific, isolated auditory, speech, or language subskills. Because subskills are only a means to an end that is multimodal communicative competence, training in any one individual subskill should not be given too much weight. Programs are most effective when they take an integrated approach to rehabilitation and avoid rote, drill-oriented approaches.

Maintenance of the Device

An important role in developing auditory skills and using a cochlear implant successfully is maintenance of the device itself.[155,156] This maintenance includes keeping all external parts in good functioning order, and working with an audiologist who specializes in cochlear implants on a regularly scheduled basis for device programming. In most cochlear implant centers, the audiologist serves as the case manager for the patient during the cochlear implant candidacy process and postimplantation.

Programming the device requires software and hardware from the cochlear implant manufacturer. For an adult patient, programming the cochlear implant involves numerous perception judgments, such as threshold of hearing, loudness level, loudness balancing, and in some cases pitch ranking. The patient's hearing history can determine the ease or difficulty of these tasks. Other factors, such as tinnitus, can come into consideration when establishing threshold levels of hearing with an electric stimulus. These measurements are necessary to program a patient's dynamic range of hearing with the cochlear implant. These settings are individual and can vary from patient to patient. The program that is saved to the external components is referred to as the cochlear implant map. Changes in the stimulus levels are most frequently seen in the initial stages of activation of the device. Many appointments are involved in the activation process to keep up with the physiologic changes involved with an individual learning to hear with the electric input. Through time, the stimulus levels become more stable, and primarily fine-tuning adjustments are made. Little research is available to explain the physiologic changes that induce needed map changes. Anecdotal reports are available that also suggest various program changes are needed when the patient is undergoing hormonal changes, such as pregnancy, puberty, or menopause.

If the patient is unable to participate in the judgments needed to create a cochlear implant map, some objective measures may be used. Cochlear implant manufacturers have created software that can measure an electrically evoked compound action potential through the cochlear implant: Neural Response Telemetry (NRT), by the Cochlear Corporation of Englewood, Colorado (manufacturer of the N24 device), and Neural Response Imaging (NRI), by the Advanced Bionics Corporation of Sylmar, California (manufacturer of the Clarion/Hi-Res devices). NRT measures are found at levels between threshold and maximal comfort in an individual's map. Limitations exist when using these measurements.[170,171] Although direct nerve responses seem to have value in some populations, behavioral testing is the tried and true method of programming.

Another objective measurement that has been previously used in device programming is electric acoustic reflex thresholds. Studies have found that the electric acoustic reflex threshold highly correlates with comfort levels on a cochlear implant map.[172,173] These measurements are not present in all patients, however, so this option may not always be available. If the reflex is measurable, this can provide valuable information for the audiologist when programming a child. Some children have high tolerance levels for the electric stimulus and do not react negatively if the map is created using inappropriately high levels. If the cochlear implant program is too loud, it can prevent the child from developing auditory skills or responding appropriately.

Audiograms may also be used to check the validity of a cochlear implant map. Using the audiogram has limitations, however, when determining the integrity of a cochlear implant program. The audiogram is going to show the patient's responses to the perception of soft stimuli. It does not tell you, however, whether the program is at an appropriate comfort level, or whether the sound quality of the map is good. Most cochlear implant audiograms are in the 20- to 30-dB range. It is possible to have a good audiogram with inappropriate map settings in the external device. A strength of the audiogram is that it can flag equipment malfunction or gross changes needed in the cochlear implant settings.

Intensive follow-up is required for successful outcomes after cochlear implantation. The adult cochlear implant patient should have his or her external devices reprogrammed at least annually. Pediatric patients should, at a minimum, come on a biannual basis. Many children are seen more frequently than a twice a year if any questions arise on how their listening skills are developing, and to ensure that their devices are programmed appropriately. Regularly scheduled program checks also offer an opportunity for the audiologist to track the development of the patient's speech understanding scores using the MSTB protocol explained previously. Conducting speech perception measures at regular intervals can provide the cochlear implant audiologist or therapist with valuable information on what the patient is hearing and understanding. This information can be used to change the patient's map or as an indication of where to focus therapy goals. Also, if the patient reports a sudden change in performance, this change can be documented by showing a decrease in speech perception abilities. This documentation validates the patient's concerns and assists the audiologist and therapist to help return the patient to baseline functioning.

The cochlear implant should not be considered a "fix" for severe to profound hearing loss. This device requires intensive rehabilitation to use it effectively and requires regular follow-up and maintenance. Although the learning process with the cochlear implant seems complex and unpredictable, the cochlear implant can provide an opportunity for deaf individuals to hear sounds that would never be possible with conventional amplification. This is especially true for deaf children, who can use the cochlear implant as a tool for receptive and expressive oral speech abilities and, most importantly, language learning.

Educating Children with Cochlear Implants

Deaf education has long been concerned with the necessity of overcoming the devastating effect profound deafness has on language acquisition and on educational attainments. Normally hearing children come to education and the development of literacy and numeracy skills with language already acquired through the channel of hearing in interaction with their care providers. For children deaf from birth, this normal process is disrupted with consequent effects on language acquisition. Deaf education is concerned not only with the processes of educational attainments of literacy and numeracy, but also with the processes of linguistic development and how to overcome the problem of lack of hearing in the normal communicative development.

The two major questions that have challenged educators for years have been which communication method to use (oral or sign language), and where to educate children (in special or mainstream schools). Visual means of communication were promoted, with sign language being seen as the solution by some, and oral language using visual support of lip-reading and other clues as the way forward. In 1880, the Milan conference on deaf education promulgated the opinion that oral language was "superior" to that of sign language. This statement, at a time when there was little amplification available, began the predominance of oralism throughout the world, and a polarization of views between individuals who believed that all deaf children should communicate by spoken language alone, and individuals who believed that all deaf children should communicate by sign language.

Although the oral view was held strongly in the 19th century and first half of the 20th century, reports of poor linguistic and educational attainments and speech intelligibility of deaf children began to challenge it. The increasing voice of the deaf community, wanting recognition of its own language and culture, also began to be heard. Signed methods of communication were increasingly introduced to educational systems in many countries, often taking the form of total, or simultaneous, communication, where spoken language is used with

signed support. This method does not use the grammar of sign language, however, and in the 1980s interest grew in the use of sign bilingualism, where the languages of the deaf community and the hearing community are used to varying degrees and emphases. In the United States, the term "bi-bi" is often used to describe bilingual and bicultural approaches. Although terminology may vary, communication approaches may be grouped into three broad categories:

- Oral/aural—spoken language alone
- Use of speech and sign simultaneously (total communication)
- Bilingualism

There are subcategories within each category; oral communication methods include natural oralism, the use of cued speech, and auditory verbal approaches. These subcategories make comparison of the effectiveness of differing communication choices complex, and make the appropriate communication choices challenging for parents.

Another major choice for parents pertains to the setting in which their deaf child should be educated. Historically, deaf children were educated in special schools for the deaf. These schools were often residential and in remote areas, requiring children to leave home and obtain their education away from their families. Large schools for the deaf were established in many countries in the 19th century, and deaf culture and language thrived in these institutions. During the second half of the 20th century, there was an increasing trend for children with any disability to be educated in mainstream schools with appropriate support. For deaf children, the development of more effective hearing aids and the provision of FM systems facilitated the greater possibility of participation in mainstream education.

The closure of many schools for the deaf has been a worldwide phenomenon, which may be seen by the deaf community as a threat to their culture and language. With more children in mainstream schools, a reduction in special schools may also mean greater difficulty in providing specialist educational support to deaf children, and greater difficulty in accessing individuals working with deaf children in mainstream schools for continuing professional development and attaining the knowledge and expertise they need.

The options for educational placement today are the following:

- A school for the deaf (residential or day)
- A unit or resource base in a mainstream school (with varying degrees of integration into the mainstream school)
- A mainstream school (with varying degrees of support in quality and quantity)

These situations are not mutually exclusive, but overlap to a large degree, with wide variations in practice, particularly in degree of support. This overlap makes comparisons about educational independence in varying educational settings complex, and comparing the effectiveness of differing educational settings complex. Francis and colleagues[135] produced a useful matrix of educational resource use, illustrating the continuum of support; a child in a mainstream school with full-time support in class may have less educational independence than a child in a class of 10 in a special school.

Historically, the education of deaf children has been the subject of great controversy, often fed by rhetoric rather than fact, and with few data about the comparative efficacy of various alternatives, or information about making such important choices for parents. Into this already controversial area, the advent of cochlear implantation has added another dimension.

Advent of Cochlear Implantation

The advent of cochlear implantation was hoped to ameliorate the educational challenges produced by profound deafness.[80] In providing useful hearing across the speech frequencies, cochlear implantation facilitates the development of early communication skills and spoken language through interaction with care providers. Early reports of encouraging levels of spoken language perception and production led many authors to predict that mainstream education would be the likelihood for most profoundly deaf children. The success of cochlear implantation has often been measured in terms of access to mainstream education, not least because it has been seen as a means of measuring cost-benefit from cochlear implantation.[135,154] Children with implants are attending mainstream schools in greater numbers after implantation,[174] and this has been thought to be associated with potential savings in educational costs.[154]

What are the needs of children with implants, and are they different from the needs of users of traditional hearing aids? Children with implants need the implant system working well and worn consistently, good listening conditions, and good communication opportunities. These needs are not so different from the needs of hearing aid wearers. What cochlear implants have done is enable profoundly deaf children to function as moderately deaf—and many with a unilateral loss, despite the trend to bilateral implantation. Cochlear implants provide useful hearing to enable profoundly deaf children to acquire language through hearing,[169] to hear all the grammatical features of speech, and to develop wholly intelligible speech. Cochlear implants require complex technology, which requires a surgical procedure and long-term maintenance. How to ensure that children with implants obtain the maximum benefit from this technology remains a challenge.

It has long been recognized that the long-term management of deaf children with implants is in the hands of educators, and there is a major need for educators responsible for the children on a daily basis to have training and regular updates on this complex technology and the expectations they can have. In a survey of parents, community-based implant professionals, and implant professionals in Europe,[175] the most common thread in the responses was the need for long-term support in education for the implant system and for educational services to become more flexible in meeting the needs of this growing group of children. Parents expressed great frustration that their children did not receive the support they needed particularly as they went to secondary or high school, and frustration that there were not greater links between the implant centers and the local educational services. A survey of European teachers of the deaf showed that they were highly interested in receiving information and training about cochlear implants.[176]

To be successful in mainstream education, it must be ensured that the classroom situation is appropriate, with good acoustics, and that the technology is successfully managed, with high expectations of its use. We know the educational implications of a unilateral or moderate hearing loss in the busy mainstream classroom environment[177,178]; children would mishear or misunderstand in noise and not follow the fast-moving discourse around the classroom. For some children, implants may work too well: their speech intelligibility may be such that they appear as normally hearing children, and their needs may be overlooked, and for the children themselves it is difficult to articulate their needs. In such situations, misunderstandings would continue, and children would be unlikely to realize their academic potential. For other children, the implant may not have provided the outcomes expected; the range of outcomes from implantation is large. For these children, an auditory processing disorder or a language learning difficulty may be present, which affects the development of spoken language. The educational needs of these children may not be met in mainstream provision, as had been predicted.

Educational Outcomes

With regard to these educational decisions that parents make for their children, there is evidence that cochlear implantation has had an influence. More children with cochlear implants are going to mainstream schools than to schools for the deaf compared with a group of profoundly deaf children with hearing aids of the same age.[174] These were children 5 to 7 years old; Thoutenhoofd[179] did not find such a trend long-term toward mainstream placement, and there is anecdotal evidence that children with implants are findin g challenges in managing in the secondary or high school environment. Geers and colleagues[180] also found a trend toward mainstream education, but again this was in children at the primary stage.

With regard to communication mode and choices of communication after implantation, there is varying evidence of the influence of oral and signing environments. On the whole, the trend is to support the use of oral input,[180] but the context in which this is best provided in the long-term is still debated, and the situation is complex. Archbold and colleagues[181] showed that the outcomes in terms of speech perception and production 3 years after implantation were not different in children who had begun with some form of signed input and changed to oral, and children who had used oral communication only. Further study showed that children implanted before age 3 change from using signed communication to oral communication,[182] and children implanted at a younger age change communication mode faster.[68] There is evidence that although young people with implants develop intelligible spoken language, they also value the use of sign language, or signed support.[183] If children are to develop spoken language, however, they need to be in an educational environment that values it and promotes its use.

With regard to educational attainments, Stacey and coworkers[184] and Thoutenhoofd[179] showed that children with cochlear implants had improved educational attainments compared with children with hearing aids. Increasing evidence is showing that children with implants have better reading skills than comparative groups with hearing aids,[185] and that children implanted younger are continuing to read at improved rates.[186] In providing access to the grammatical features of spoken language through hearing, cochlear implants have enabled profoundly deaf children to have a greater awareness than previously of the phonology of language before coming to the written word. Spencer and Marschark[187] stated, "Spoken language development of deaf children may be more possible today than ever before. We are poised on a threshold of what often seem like unlimited possibilities." This statement reflects the ways in which new hearing technologies, and cochlear implantation in particular, have transformed educational opportunities for deaf children.

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CHAPTER ONE HUNDRED AND SIXTY-ONE

Central Neural Auditory Prosthesis

Robert J. S. Briggs

Key Points

- The concept of auditory brainstem implantation was introduced in 1979 by House and Hitselberger at the House Ear Institute.
- The biocompatibility of direct electric stimulation of the auditory brainstem has been shown in experimental preparations and clinical experience. The electric threshold for tissue damage, relating most specifically to charge density, is typically orders of magnitude greater than the threshold for activating the auditory pathway.
- The auditory brainstem implant (ABI) is now established as an effective method of partial hearing restoration in patients with neurofibromatosis type 2 (NF2). The ABI can provide environmental sound awareness and an aid to lip reading; however, open set speech perception is achieved only rarely.
- The most common indication for ABI is in patients with NF2. The current criteria for use in the United States are NF2 patients 12 years old or older, undergoing first or second side vestibular schwannoma removal. There are no specific audiologic criteria.
- The ABI consists of a multielectrode surface array that is placed over the cochlear nucleus within the lateral recess of the fourth ventricle. Intraoperative electrically evoked auditory brainstem responses are measured to confirm and refine correct position.
- Although some pitch differentiation is achieved between electrodes on the surface array, the tonotopic orientation of cochlear nucleus neurons is unfavorable for surface stimulation. Electric stimulation from individual electrodes may activate a broad area of neurons; in addition, adjacent electrodes may activate overlapping regions of neurons, so provision of independent spectral information by electric stimulation is very limited. The cochlear nucleus comprises a variety of specialized neurons with extrinsic and intrinsic projections that are either excitatory or inhibitory in function. In addition to losing the degree of peripheral tonotopic stimulation achieved with a cochlear implant, direct stimulation of the cochlear nucleus with an ABI may mean loss of specialized neural function within the cochlear nucleus.
- Because the tonotopicity of the cochlear nucleus is not adequately accessed with a surface electrode, it is proposed that a penetrating array might allow more selective tonotopic stimulation of the cochlear nucleus. A clinical trial has been undertaken at House Ear Institute, with 10 NF2 patients implanted with a prototype penetrating ABI in combination with a surface array. The outcomes are not proving any better than the surface electrode ABI, in terms of the reliability of achieving auditory sensations or of the speech perception levels achieved. In the cases where the penetrating ABI provided little benefit, the surface electrode array was successful in providing auditory benefit.
- The inferior colliculus is an obligatory synaptic terminus in the ascending auditory system. The central nucleus of the inferior colliculus also has a clearly defined tonotopic map, and so has been proposed as an alternative site for stimulation with a penetrating electrode. Clinical trials with a prototype auditory midbrain implant electrode are currently under way.
- Improved speech perception outcomes have been shown in ABI recipients without NF2—patients with cochlear nerve avulsion or injury or cochlear ossification who cannot benefit from a cochlear implant. These improved outcomes have led to the hope that children with cochlear nerve aplasia, who are unsuitable for cochlear implants, might benefit from ABI.

Multichannel cochlear implantation is now well established as an extremely effective method of hearing restoration for congenital and acquired sensorineural hearing loss. When conditions involving the cochlear nerve make peripheral intracochlear stimulation ineffective, some patients cannot benefit from cochlear implantation. Most commonly, this situation occurs in patients with neurofibromatosis type 2 (NF2), where bilateral vestibular schwannoma growth or surgical removal results in loss of cochlear nerve function. In this situation, direct electric stimulation of the cochlear nucleus at the brainstem using an auditory brainstem implant (ABI) is possible. Although the hearing outcomes with ABIs are limited compared with cochlear implants, the ABI is currently the most sophisticated and successful central neural prosthesis.

There is now a large experience with the use of ABIs in NF2 patients. Although some auditory benefit is usually achieved, it is generally limited to perception of environmental sound and an aid to lip reading. Rarely, open set speech understanding is achieved.

More recently, there has been increased interest in the use of ABIs for conditions where cochlear implants are ineffective, in particular, postmeningitic cochlear ossification or bilateral eighth cranial nerve

injury from temporal bone fractures or avulsion. Better hearing outcomes have been observed in these patients without NF2, suggesting that NF2 is associated with intrinsic dysfunction of the cochlear nucleus. This suggestion has led investigators to attempt stimulation higher up the auditory pathway at the inferior colliculus with auditory midbrain implants (AMIs). The improved performance with ABIs in patients without NF2 has also provided hope that children with cochlear aplasia, who are unsuitable for cochlear implants, might benefit from ABIs.

Biocompatibility

Direct stimulation of the central nervous system entails unique safety concerns. The mechanisms of tissue damage resulting from the direct injection of current into brain parenchyma have been extensively studied.[1-3] Charge transfer from an electrode to biologic tissue depends on two independent electrochemical mechanisms, as follows:

1. The first mechanism is a simple capacitive mechanism of current that flows when a relatively high dielectric boundary exists between electrode and tissue. When an alternate voltage is created across the interface, charges accumulate differentially on each side of the dielectric boundary, alternating in polarity as dictated by the stimulus. Charging and discharging on either side of the dielectric boundary induces current flow in the biologic medium *without* the direct transfer of the carriers of the charge between electrode and tissue.

2. A second mechanism is one without a dielectric boundary. Charge carriers transfer between electrode and tissue as a result of reduction-oxidation reactions. Reversible reactions are confined to the electrode-tissue interface. Irreversible reactions generate new chemical species, however, which migrate into the tissue and may cause damage.

Safety thresholds of neuroprosthetic stimulation depend on several factors. Yuen and colleagues[4] have shown that the extent of neural injury with contemporary electroprosthetic materials producing direct stimulation closely correlates with the *charge density per phase*. Charge density directly relates to stimulation intensity, stimulation duration, and the effective area of the electrode terminus. The effective area of an electroprosthesis can differ from its geometric area. Brummer and Turner[5] measured the real surface area and suggested that surface roughness factors would range from 1.4 to 30.

The threshold for damage to the cerebral cortex found by Agnew and associates[6] was 320 μA, with a corresponding charge density of 3200 μcoul/cm^2/phase. Niparko and colleagues[7] found that the threshold for tissue damage within the cochlear nucleus (with a penetrating electrode) was 150 μA, a current that corresponded with a charge density of 600 μcoul/cm^2/phase. Stimulation at intensities of 150 μA and 200 μA (approximately 600 μcoul/cm^2/phase and 800 μcoul/cm^2/phase) produced significant tissue response at the site of the electrode terminus with neuronal loss, fiber necrosis, and reactive cells present. The injury threshold was found to exceed the threshold for functional activation, however, by a factor of at least five across all animals studied.

Differences between the damage thresholds determined across studies of central nervous system stimulators may relate to differences in implantation sites and variance in calculations that relate to effective versus geometric surface area. Differences also may be attributable to differences in microelectrode design (e.g., percentage of iridium) and fabrication that affect real charge densities at the electrode terminus for the same stimulation intensities.

History of Clinical Approaches

The concept of auditory brainstem implantation was introduced by House and Hitselberger at the House Ear Institute (HEI, Los Angeles, CA). In 1979, they implanted a two-ball electrode in a woman with NF2 undergoing acoustic neuroma removal. This first ABI was stimulated with a modified hearing aid, and the patient received useful auditory sensations.[8] Nonauditory stimulus occurred, which limited use of the electrode. Subsequently, this original electrode was replaced with a specially designed two-electrode surface array, which used a Dacron mesh carrier. This electrode was attached to a percutaneous pedestal connector and was stimulated by a modified 3M-House cochlear implant speech processor. This patient has continued to achieve acoustic percepts with electric stimulation, and has continued to use the device successfully 10 to 12 hours a day.[9] Between 1984 and 1992, 24 NF2 patients were implanted at HEI, with the single-channel, initially two-electrode, and subsequently three-electrode, ABI under an investigational device exemption from the U.S. Food and Drug Administration (FDA).

The first fully implantable ABI was manufactured by Cochlear Pty Ltd, based on the CI 22 mini–cochlear implant. The electrode array was modified to an eight-electrode pad, developed by HEI in collaboration with Cochlear Ltd and Huntington Medical Research Institute (Pasadena, CA). After initial trials at HEI, a multicenter clinical trial, based in North America, was undertaken. In Europe, a 21-electrode array was also developed by Cochlear Ltd and used with the same receiver stimulator.[10-13] Clinical experience from these trials led to the best features of both electrode arrays being combined to create the current Nucleus ABI electrode, a 21-electrode array connected to the CI 24M receiver stimulator (Fig. 161-1). The system functions similar to a cochlear implant with a fully implantable receiver stimulator package and an externally worn speech processor and transmitting coil. The receiver stimulator package has a removable magnet because

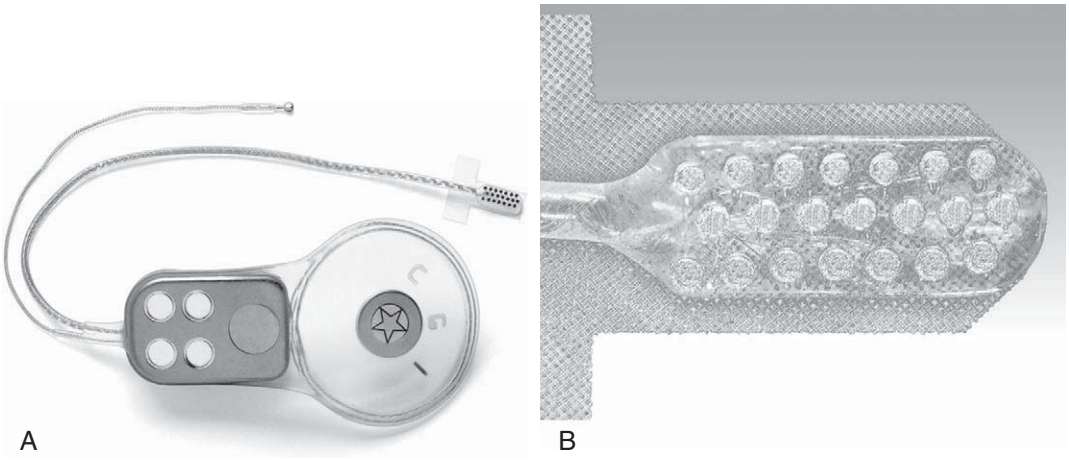

Figure 161-1. The current auditory brainstem implant (ABI) is a 21-electrode array that is stimulated similar to a cochlear implant through a transcutaneous radiofrequency transmitter and receiver. **A,** Internal component of ABI. **B,** Enlarged view of electrode array. *(Courtesy of Cochlear Ltd.)*

many recipients require repeated postoperative cranial magnetic resonance imaging examinations.

ABIs have also been produced by Med El in Europe and Advanced Bionics in the United States. The function of all these devices is the same as a cochlear implant with variation only in the size of the electrode pad and number of electrode contacts.

The Nucleus 24 ABI is the multichannel 21-electrode surface array, which remains commercially available with FDA and CME approval. Studies have been undertaken at HEI with a penetrating electrode array with limited success. The most recent development is the use of an AMI, in an attempt at inferior colliculus stimulation, either with a surface array or with a penetrating electrode.

With respect to biocompatibility, there is no clinical evidence for neuronal injury occurring as a result of chronic electric stimulation, as evidenced by the demonstrated gradual improved performance over time.

Indications

The most common indication for an ABI is in patients with NF2. In the United States, the ABI is approved only for use in NF2 patients. The current criteria for use in the United States are postlingual NF2 patients 12 years old or older, undergoing first or second side vestibular schwannoma removal. There are no specific audiologic criteria.

Auditory brainstem implantation should be considered in all NF2 patients undergoing vestibular schwannoma removal, in whom there is no expectation of ipsilateral residual hearing. ABIs are indicated particularly if contralateral hearing is absent or poor, or if there is a contralateral tumor that is likely to result in hearing loss in the foreseeable future.

Usually, the ABI is placed at the time of second side vestibular schwannoma removal, when the patient either has a preoperative profound-to-total hearing loss or will have one postoperatively. Some patients choose to have an ABI placed at the time of first side tumor removal (if hearing preservation is not attempted), as a so-called sleeper, in the expectation that the patients will not use the device while they have useful residual hearing in the contralateral ear.

An ABI can be successfully placed as a second-stage procedure after previous vestibular schwannoma surgery. There may be an advantage in delayed implantation if, at the first surgery, there is a large tumor deforming the brainstem and distorting the lateral recess anatomy and position. There is potential, however, for fibrosis and loss of brainstem landmarks occurring after initial tumor surgery that would make placement of the ABI difficult at a second procedure. Prior stereotactic radiotherapy, particularly by gamma knife, is a relative contraindication to ABI placement because of the potential for radiation necrosis of the cochlear nucleus region or fibrous tissue preventing proper device placement. There have been reports where this has been a problem, and where successful ABI use after radiotherapy was achieved.[14,15] The use of ABIs in patients without NF2 is discussed later in this chapter.

Anatomy and Surgical Approaches

Much of the early ABI research focused on gaining a better understanding of the three-dimensional anatomy of the cochlear nerve root, foramen of Luschka, and cochlear nucleus, and potential surgical approaches.[16-23] The cochlear nucleus comprises ventral and dorsal components, situated in the pons where the eighth cranial nerve enters the brainstem at the pontomedullary junction, medial to the cerebellar peduncle. The surfaces of the ventral and dorsal cochlear nuclei are exposed in the anterosuperior aspect of the lateral recess of the fourth ventricle. The ABI electrode is placed into this recess. The foramen of Luschka is the lateral opening of the recess and contains choroid plexus.

The surface landmarks for the lateral recess are the adjacent lower cranial nerves. The foramen of Luschka is situated immediately posterior to the origin of the ninth glossopharyngeal and tenth vagal nerve rootlets, inferior to the eighth nerve root entry zone and posteroinferior to the seventh nerve origin. The flocculus of the cerebellum overlies the foramen. The recess runs in a posteromedial direction from the foramen of Luschka to enter the fourth ventricle.

The translabyrinthine approach has been favored by most surgeons for ABI placement in NF2 patients undergoing tumor removal.[10] Some centers have used a retrosigmoid approach for recipients with NF2 and without NF2.[24] The translabyrinthine approach provides a more lateral view of the brainstem and better view into the foramen of Luschka. Possibly this better view assists in atraumatic electrode array placement; however, translabyrinthine and retrosigmoid approaches can be used effectively. Cerebellar retraction is reduced or avoided by the translabyrinthine approach. If a retrosigmoid or lateral suboccipital approach is used, it is important that the exposure is made as far forward and inferiorly as possible, skeletonizing and retracting the sigmoid sinus anteriorly, to allow a low anterior approach to give the most direct access to the region of the foramen, with the least cerebellar retraction.

The cochlear nucleus is identified within the lateral recess of the fourth ventricle. The cochlear nucleus is identified by following the eighth and ninth cranial nerves medially. The flocculus is retracted posteriorly, and the foramen of Luschka is identified, immediately posterior to the origin of the ninth cranial nerve. The cochlear nerve is followed medially, as it enters the lateral recess of the fourth ventricle. Dissection is carried between the eighth cranial nerve and the choroid plexus, which may need to be removed or shrunk with bipolar cautery. Within the lateral recess, as the cochlear nerve is followed medially, two prominent structures can be visualized anterosuperiorly curving around the brainstem caudally to the pontobulbar sulcus. The cranial structure is the bulging of the cochlear nucleus, and the caudal structure is the pontobulbar body. Between them, a small straight vein is a constant finding and important landmark. The taenia of the choroid plexus is a fibrous band at the entrance of the fourth ventricle. This band usually needs to be divided to allow visualization within the lateral recess and create room for the electrode array insertion. The location of the lateral recess usually can be confirmed by observing flow of cerebrospinal fluid as the anesthesiologist induces a Valsalva maneuver in the patient.

Positioning the electrode array within the lateral recess is crucial to successful auditory stimulation. If the array is too lateral, stimulation of the glossopharyngeal and facial nerves or other lower cranial nerves and cerebellar flocculus can occur. If the array is too deep, the medial electrode contacts would lie within the fourth ventricle and be ineffective. Similarly, caudal or cranial rotation of the electrode array can significantly affect position over the cochlear nucleus. Figure 161-2 shows a schematic representation of the electrode array position.

Intraoperative Monitoring

Successful positioning of the electrode array and final adjustment of position is confirmed by the use of intraoperative electric evoked auditory brainstem response (ABR) testing. The technique of intraoperative recording of short latency auditory potentials induced by electric stimulation of the cochlear nucleus was developed by Waring[25] at HEI. When the electrode array is initially positioned within the lateral recess using anatomic landmarks, electrodes within the array are stimulated, and the evoked ABR response is recorded. Initially, stimulation is performed across the entire length of the electrode array. If a response is achieved, a selection of distal, proximal, and lateral electrode combinations is used in forward and reserve polarity to differentiate stimulus artifact from real response. Presence or absence of response at different electrode combinations allows careful manipulation of the electrode array, such as deeper insertion or caudal or cranial rotation, to identify optimal position and improve the ABR responses.

Typically, either two or three wave responses are seen, as shown in Figure 161-3. The electric evoked ABR response waves are of short latency (0.7 to 3.6 ms). If large late potentials greater than 4 ms are observed, this is usually an indication of motor cranial nerve stimulation. While electric evoked ABR testing is undertaken, monitoring of cranial nerves V, VII, and IX should be continued. This monitoring helps identify inadvertent nonauditory stimulation, and may assist electrode positioning further.

Outcomes

Complications

Because the ABI is usually placed at the time of vestibular schwannoma removal, the occurrence of postoperative problems, including bleeding

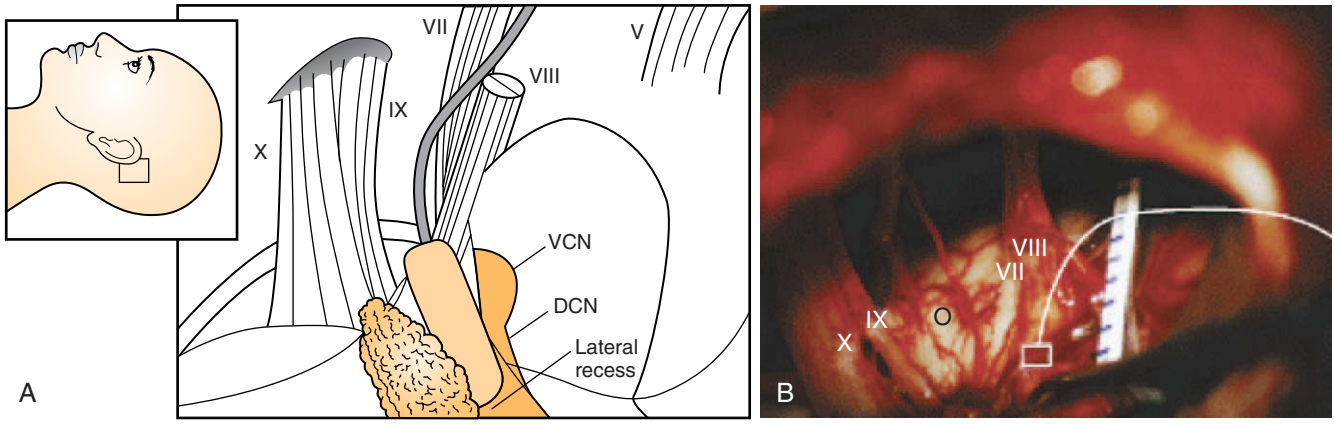

Figure 161-2. The region for placement of the auditory brainstem implant (ABI). **A,** Schematic of the left brainstem. The ABI electrode pad is being placed in the lateral recess. DCN, dorsal cochlear nucleus; VCN, ventral cochlear nucleus; V, trigeminal nerve; VII, facial nerve; VIII, cochleovestibular nerve (cut); IX, glossopharyngeal nerve; X, vagus nerve. **B,** Photograph of the left brainstem and cochlear nucleus region as seen from the lateral suboccipital approach. *Rectangle* indicates position of electrode array. O, inferior olive; VII, facial nerve; VIII, cochleovestibular nerve; IX, glossopharyngeal nerve; X, vagus nerve.

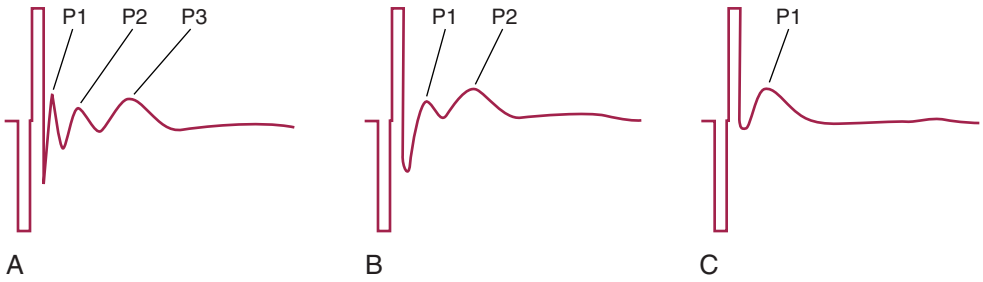

Figure 161-3. Idealized evoked auditory brainstem responses produced by electric stimulation of the cochlear nucleus. **A,** Three-wave response. **B,** Two-wave response. **C,** One-wave response.

and cranial nerve deficit, particularly facial nerve and cerebellar dysfunction, is generally attributed to the tumor removal and not specifically to the ABI placement. Similarly, postoperative cerebrospinal fluid fistula is well recognized after vestibular schwannoma surgery, and it is not thought that the presence of the electrode cable or subcutaneous receiver stimulator increases this risk. Cerebrospinal fluid fistula through the wound and the attendant risk of infection in the presence of the ABI is a potentially disastrous problem, however. As with cochlear implants, meticulous care must be taken with planning of incisions and placement of the receiver stimulator package to avoid problems with wound breakdown and infection. There have been anecdotal reports of hydrocephalus after surgery and ABI placement, possibly resulting from obstruction of cerebrospinal fluid flow through the lateral recess of the fourth ventricle by the electrode array position.

For patients without NF2, in whom there is no indication for surgery to remove a tumor, the potential risks of a craniotomy, cerebellar retraction, brainstem and lower cranial nerve manipulation, and electrode placement all need to be weighed against the potential hearing benefit with the ABI.

Long-term follow-up of ABI recipients, particularly the initial multicenter clinical trial subjects, has involved extensive neurologic examination, and no changes in neurologic status have been identified that seem to be related to the ABI electrode and electric stimulation. Probably the most specific ABI complication is the failure to achieve auditory stimulation and sensation. The normal anatomy of the fourth ventricle lateral recess allows the electrode array with its Dacron mesh backing to be held securely. Displacement of the electrode array can occur, however. This displacement is more likely when there has been distortion of the brainstem by a large tumor. The foramen of Luschka and lateral recess is often widely effaced, and so secure positioning of the array is difficult. Despite packing with fat or oxidized cellulose (Surgicel), migration of the array may occur in the early postoperative period. If there is absence of auditory perception on electrode stimulation, nonauditory stimulation, particularly of the facial, trigeminal, or lower cranial nerves, is more likely.

Even with accurate stable electrode positioning within the lateral recess, there is a high incidence of nonauditory or somatic sensations occurring with stimulation of at least some electrodes across the array. Otto and coworkers[26] reported results from a multicenter study in which 42% of all electrodes resulted in noticeable nonauditory sensations. The most commonly reported nonauditory sensations are ipsilateral facial tingling or throat discomfort or sensation of jittering of the visual field. Less commonly, discomfort or tingling occurs in the limbs or trunk, either ipsilateral or contralateral. Only rarely are motor responses (muscle twitch) in the arm or leg reported; and cardiorespiratory changes have been reported very rarely with electrode stimulation.

It is presumed that nonauditory sensation occurs from stimulation of adjacent anatomic structures, in particular (1) cerebellar flocculus (visual jitter), (2) facial nerve, (3) glossopharyngeal nerve (throat discomfort), and (4) retrograde activation of cerebellar peduncle (ipsilateral tingling and motor activation). Usually, the nonauditory sensation occurs together with an auditory percept, on a particular electrode or pair of electrodes. The nonauditory effect can usually be reduced or eliminated by increasing the pulse width of stimulus, referencing the electrode to a different stimulation ground, or turning off that electrode.[12] It has been observed that there is a decrease in nonauditory sensations over time. Possibly this decrease is due to fibrous encapsulation of the electrode array or, perhaps, alteration of brainstem shape after removal of a compressive tumor.

Auditory Performance

The auditory performance achieved with the ABI in NF2 patients has been very encouraging with similar outcomes reported from different centers and patient groups. Although useful auditory perception is usually achieved, the hearing level does not compare with that of current cochlear implant recipients. When auditory sensations are achieved with the ABI, the hearing has generally been limited to perception of environmental sound and an aid to lip reading. Ebinger and colleagues[27] reported the results of the U.S. multicenter ABI clinical trial. Of 92 subjects, 85% showed auditory sensation, of whom 93% showed improvement in speech understanding using audition with ABI and lip reading compared with the ABI alone or lip reading alone. Significant open set speech understanding in the audition alone condition (e.g., telephone use) is rare.[28] Remarkably similar outcomes have been reported from various centers in Europe and Australia.[11,29-31]

The ABI provides subjects with auditory percepts sufficient to give environmental sound awareness (as shown by the Sound Effects Recognition Test).[32] Information is also provided on the stress and rhythm in speech, which assists subjects with lip reading. Why ABI performance is limited compared with cochlear implant speech perception outcomes is unclear. On psychophysical testing, there is limited pitch variation between separate electrodes or channels on the ABI array.[33] This means limited tonotopic stimulation and limited independent channels of spectral information can be provided. The first step in mapping the ABI is the pitch ranking of the electrodes with auditory percepts. Most ABI patients exhibit a rising pitch percept from lateral to medial across the array, a few have a falling pitch pattern, and some have a variable or flattened pitch pattern.

The tonotopic orientation of neurons within the cochlear nucleus is suboptimal for surface electrode stimulation. The frequency change is from superficial to deep, rather than across the cochlear nucleus surface. Electric stimulation from individual electrodes or channels may activate a broad area of neurons; in addition, adjacent electrodes may activate overlapping regions of neurons, so provision of independent spectral information by electric stimulation is very limited.

The cochlear nucleus is composed of various specialized neurons with extrinsic and intrinsic projections that are either excitatory or inhibitory in function. In addition to losing the degree of peripheral tonotopic stimulation achieved with a cochlear implant, direct stimulation of the cochlear nucleus with an ABI may mean loss of specialized neural function within the cochlear nucleus.

Penetrating Auditory Brainstem Implant

Because the tonotopicity of the cochlear nucleus is not adequately accessed with a surface electrode, it is proposed that a penetrating array might allow more selective tonotopic stimulation of the cochlear nucleus.[34] Animal studies have shown that selective neural stimulation is possible with proximal recording in the inferior colliculus.[35]

A prototype human penetrating ABI (PABI) has been developed at HEI. There have been two generations of PABI with each being a combination of penetrating and surface arrays (Fig. 161-4). In the first, there were 8 penetrating electrodes and 14 surface electrodes. The second contained 10 penetrating electrodes and 12 surface electrodes. Placement of the PABI presents a greater surgical challenge than a surface array. The electrode needs to be accurately inserted into the cochlear nucleus for auditory stimulation to be successful. A stimulating probe has been used to generate an evoked ABR in an attempt to confirm the site of the cochlear nucleus before PABI insertion. This probe has not proven specific enough in site of stimulation to identify the cochlear nucleus definitely. The penetrating array must also be inserted rapidly to avoid any shearing effect on neural tissue because of brainstem movement during the insertion. To facilitate accurate rapid placement, a pneumatic insertion tool has also been developed.

A clinical trial has been undertaken at HEI, with 10 NF2 patients implanted with the two generations of PABI. The outcomes are not proving any better than the surface electrode ABI in terms of the reliability of achieving auditory sensations or of the speech perception levels achieved. In the cases where the PABI provided little benefit, the surface electrode array was successful in providing auditory benefit (Brackmann D, Otto S, personal communication).

Figure 161-4. Combined penetrating auditory brainstem implant and surface electrode array. *(Courtesy of Cochlear Ltd. and House Ear Institute.)*

Outcome of Auditory Brainstem Implants in Patients without Neurofibromatosis Type 2

Although the ABI has been predominantly implanted in NF2 patients, there is increasing international experience with ABI use in patients without NF2 who are unsuitable for, or have failed, cochlear implantation. Typically, these subjects have loss of eighth cranial nerve integrity because of skull base fracture or traumatic avulsion, or have severe postmeningitis cochlear ossification.

The hearing outcomes achieved in these patients are significantly better than the outcomes in NF2 patients. Some non-NF2 ABI recipients achieve speech perception at levels comparable to successful cochlear implant recipients. Colletti and colleagues[36] reported 63% open set sentence recognition in the audition alone mode in nontumor patients compared with 12% in NF2 patients. Similar outcomes have been reported Grayeli and associates.[37]

This difference in performance between the tumor and nontumor groups implies that the NF2 condition and presence of bilateral vestibular schwannomas has an intrinsic effect on cochlear nucleus function that adversely effects the speech perception achieved with electric stimulation. Colletti and Shannon[38] examined two groups of ABI recipients, 10 NF2 and 10 non-NF2 patients. Parameters studied included electric stimulation thresholds, electrode selectivity, and amplitude modulation and speech perception. These investigators showed that the NF2 patients have significantly worse modulation detection and speech discrimination than non-NF2 recipients. Both groups had similar range of pitch perception and loudness percepts, and so the investigators postulated that the poorer amplitude detection may be due to damage to a specific cell type or region within the cochlear nucleus. Possibly the chopper cells are more susceptible to damage because of their large size and large metabolic requirements. Alternatively, the small cell cap of the cochlear nucleus may be specifically damaged. These cells receive projections from the vestibular nerve root, and so may be affected by vestibular schwannoma growth or surgical removal.

It is unclear why the presence of the vestibular schwannoma has an adverse effect. It may be neural damage associated with progressive sensorineural hearing loss, brainstem distortion owing to the mass effect of a large tumor, or direct brainstem trauma or alteration in vascularity associated with surgical tumor removal. It does not seem to be simply a tumor mass effect or brainstem manipulation that limits ABI outcomes. Some NF2 patients lose hearing with only small tumors that do not contact the brainstem. In the author's experience, these patients do not perform better with an ABI than patients who had large tumors and significant brainstem compression.

Penetrating Auditory Midbrain Implant

The fact that the ABI can produce high levels of speech perception in non-NF2 patients, presumably owing to intrinsic cochlear nucleus

dysfunction, raises the possibility that stimulating the auditory midbrain proximal to the damaged cochlear nucleus may be a better alternative in NF2 patients. Lenarz and coworkers[39] suggested the central nucleus of the inferior colliculus as the potential site.

Colletti and colleagues[40] reported placement of an electrode array (Med El ABI) on the dorsal surface of the inferior colliculus in an NF2 patient. The patient was considered unsuitable for an ABI because of prior surgery and radiation therapy for vestibular schwannomas. The electrode array was placed via a median infratentorial, supracerebellar approach. All 12 electrodes on the array produced auditory sensations without nonauditory responses. Postoperatively, some electrodes apparently developed higher thresholds, presumably because of movement of the array. Seven electrodes were activated with discernible pitch differentiation, measured on only three of the seven electrodes. Apparently, the patient could discriminate multisyllabic words in a five-choice test, and achieved an aid to lip reading with audition via the AMI.

To achieve useful speech perception with multielectrode AMI stimulation, pitch differentiation between electrodes is necessary. The inferior colliculus is an obligatory synaptic terminus in the ascending auditory system.[41] It consists of the central nucleus, the external nucleus, and the dorsal nucleus. The central nucleus contains a clearly defined tonotopic map with preserved tonotopic projections to the ipsilateral auditory thalamus and cortex and to the contralateral inferior colliculus.[42] Most of the tonotopic structures of the inferior colliculus are internally oriented along a dorsolateral to ventromedial axis. A penetrating electrode array has been developed by MHH and Cochlear Limited to access the tonotopic orientation of the inferior colliculus. The penetrating AMI array is 6.2 mm long and 0.4 mm in diameter with 20 platinum ring electrodes. The array is constructed of soft silicon with a central removable stainless steel stylet to facilitate insertion into the inferior colliculus (Fig. 161-5).

Samii and associates[43] reported use of the lateral suboccipital approach for combined vestibular schwannoma removal and supracerebellar access to the inferior colliculus for insertion of the penetrating AMI. Three NF2 patients were implanted in Hannover, Germany, using this approach with intraoperative stereotactic navigation to identify the appropriate trajectory for electrode insertion. All three subjects got auditory percepts; however, postoperative imaging and the presence of nonauditory sensations showed that proper electrode placement was achieved in only one case with the other two electrodes being in the dorsal cortex of the inferior colliculus and the surface of the lateral lemniscus. Each subject showed various pitch, temporal, loudness, and directional percepts. They achieved environmental sound perception and obtained an aid to lip reading, but at 6 months did not get open set speech perception.[44] The hearing obtained apparently improves over time, as is observed in cochlear implant and ABI patients over several years.

The hearing result in the patient with accurate central nucleus inferior colliculus placement was superior to the other two. The electrophysiologic properties of the inferior colliculus neurons are different from the peripheral auditory nerve or cochlear nucleus. Modified stimulation and speech processing strategies may be necessary to activate neurons more effectively across the frequency and isofrequency dimensions of the central nucleus of the inferior colliculus and to optimize speech perception outcomes.

Alternative Strategies in Patients with Neurofibromatosis Type 2

Because the speech perception outcomes achieved with ABIs and AMIs remain limited, tumor management strategies that preserve an intact cochlear nerve should be considered. Successful cochlear implantation has been reported in patients after vestibular schwannoma removal.[45-47] Cochlear implantation after long-term vestibular schwannoma growth control by stereotactic radiation therapy can also provide open set speech perception (Briggs RJS, personal experience). Planned partial tumor removal preserving the cochlear nerve, possibly with radiation therapy if necessary, in association with cochlear implantation rather than ABI may give better hearing outcomes in selected NF2 patients.

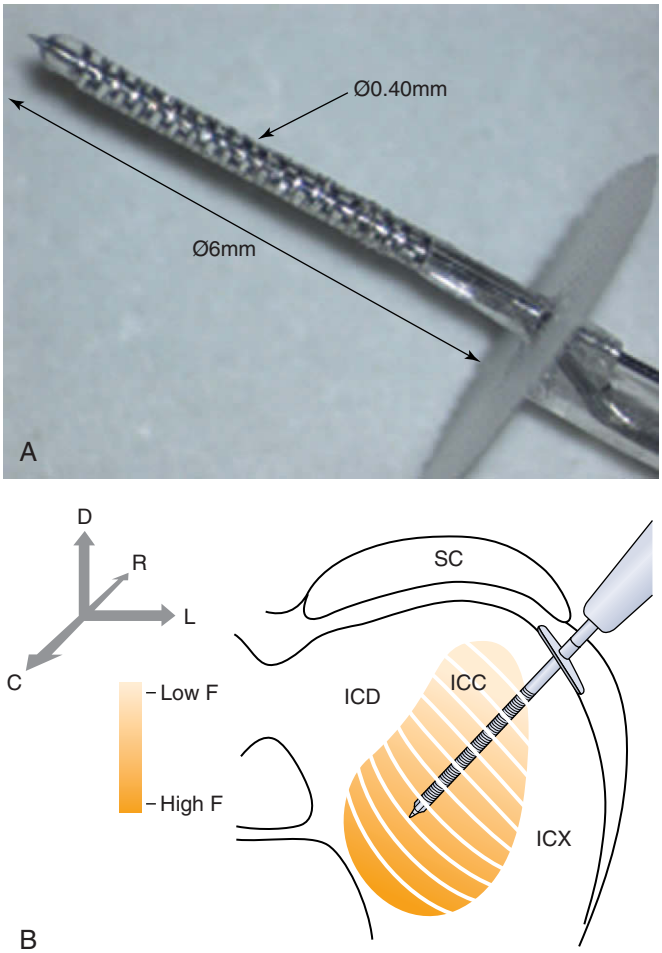

Figure 161-5. A, Image of the human prototype auditory midbrain implant (AMI) electrode array. **B,** Schematic of inferior colliculus showing AMI electrode in situ. ICC, central inferior colliculus; ICD, dorsal inferior colliculus; ICX, lateral inferior colliculus; SC, superior colliculus. *(**A,** Courtesy of Cochlear Ltd. and Medical University of Hannover.)*

Auditory Brainstem Implants in Children with Cochlear Nerve Aplasia

Because of the improved outcomes in non-NF2 ABI recipients, there is hope that the same improved level of hearing may be possible in children with cochlear dysplasia or cochlear nerve aplasia who are unsuitable for cochlear implantation. There is limited experience in numerous centers with ABI placement in children with various cochlear dysplasias and cochlear nerve aplasia or hypoplasia. Colletti and colleagues[48] showed that ABI placement is technically feasible, and that some auditory rehabilitation is possible with children showing environmental sound awareness and limited speech detection.

Although the ABI electrode array can be placed in children younger than 2 years, the subsequent programming of the ABI to achieve potentially useful sound detection is an enormous challenge. As discussed earlier, the successful use of an ABI depends on programming the device to use electrodes that produce auditory sensation without significant nonauditory stimulation, and to use pitch ranking of electrodes across the array. Although electric evoked ABR recording can give some indication of which electrodes produce an auditory response, it is extremely difficult to differentiate auditory from nonauditory responses, and virtually impossible to pitch rank electrodes in prelingual children who cannot give meaningful feedback. Device programming is undertaken on an empiric basis, using cautious and lengthy stepwise programming sessions.

Although initial reports of sound detection and device use in these children have been encouraging, it will be some time before it is shown

whether the hearing achieved is sufficient for useful speech and language development. Of three young children implanted in Manchester, one had a potentially life-threatening postoperative posterior fossa bleed, but made a good recovery and shows benefit with the ABI (Ramsden R, personal communication). Presumably, as with cochlear implantation, the younger the age of intervention, the better the hearing outcome will be; however, the potential hearing benefits need to be well shown and carefully weighed against the potential risks of such major surgery in young children.

Summary

The ABI is now established as an effective method of partial hearing restoration in patients with NF2. The ABI can provide environmental sound awareness and an aid to lip reading; however, open set speech perception is achieved only rarely. Trials of a penetrating ABI and penetrating inferior colliculus AMI have not provided improved hearing outcomes yet. Better speech perception outcomes have been shown in ABI recipients without NF2. These improved outcomes have led to hope that children with cochlear nerve aplasia, who are unsuitable for cochlear implants, might benefit from ABI.

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CHAPTER ONE HUNDRED AND SIXTY-TWO

Hearing Aids: Strategies of Amplification

Brad A. Stach

Virginia Ramachandran

Key Points

- Hearing aid technology is advancing at a rapid pace, resulting in an expansion of candidacy and enhancement in benefit from hearing aid use.
- Resulting in large part from the adaptability of modern technology, indications for successful hearing aid use relate more to a patient's communication needs and challenges than to the specifics of degree or configuration of hearing loss.
- Most modern hearing aids use digital signal processing, with high-fidelity signal reproduction and considerable flexibility for matching hearing loss and communication needs.
- Input to the hearing aid is ordinarily received by microphones with variable directionality that may change as a function of the listening environment. Signals may also be received by various wireless transmitter/receiver technologies.
- Directional microphones enhance signal-to-noise ratios, allowing for improved speech perception in noise.
- The digital amplifier allows for variable control in the frequency, amplitude, and time domains to permit programming to fit an individual's hearing loss and ability.
- Hearing aid selection involves matching hearing loss and communication needs with style, technology, and features.
- Type, degree, and configuration of hearing loss are the most important determinants of the style and type of signal processing and features that are indicated.
- Hearing aid validation is carried out by in situ measurement of speech and other signals being delivered to the tympanic membrane.
- Outcome measures provide valuable information regarding satisfaction with and benefit from hearing aid use.

The most common treatment for sensorineural hearing loss is the use of conventional hearing aid amplification. Despite substantial strides in the implementation of implantable technology, hearing aids remain the most widely used and appropriate treatment solution for most patients with hearing loss. Although hearing devices implanted worldwide during a year now number in the thousands, more than 2.4 million hearing aids were dispensed last year in the United States alone.[1]

Previously, hearing aid amplifiers used analog circuits with limited flexibility to fit a patient's hearing loss. Modern hearing aids incorporate digital signal processing (DSP), sophisticated noise and feedback reduction, adaptable directionality, and wireless connectivity. These advances permit accurate fitting over a broader range of hearing loss degree and configurations, and lead to noticeable enhancement in quality of amplified sound and listening performance. This chapter provides a general overview of hearing aids, including indications for their use; amplification technologies; and the selection, fitting, and verification process.

Indications for Hearing Aid Use

Whether a patient is a candidate for a hearing aid is determined by three primary factors and several secondary considerations. Assuming that surgical or other medical management of the hearing loss has been exhausted, candidacy is based on the interaction of degree and configuration of hearing loss, the extent of the communication disorder resulting from the loss, motivation of the patient to address the communication disorder, and attitude toward hearing aid use.[2] Generally, most patients who seek hearing aids can benefit from their use. Even in cases in which the prognosis for successful hearing aid use is guarded, an amplification solution is usually available if the patient is sufficiently motivated.

Hearing Loss Considerations

A primary consideration in successful hearing aid use is the nature, degree, and configuration of hearing sensitivity loss. Although no firm criteria exist about how much hearing loss is too little or too much to preclude successful hearing aid use, some general rules guide prognosis.

In an effort to provide a realistic view of the characteristics of hearing aid users, we evaluated data from 1860 ears of 1049 consecutive patients who were fitted with hearing aids at the Henry Ford Hospital during 2007. Patients ranged in age from 1 to 101 years old. The distribution of ages is shown in Figure 162-1. Of all patients, 81% were at least 60 years old, and 61% were 70 years or older. These percentages are typical of the hearing aid population in general. The prevalence of hearing loss is progressively greater with age, as is the use of hearing aids. Hearing aids are predominantly fitted on ears with sensorineural (88%) or mixed (11%) hearing loss. In this sample, less than 1% of

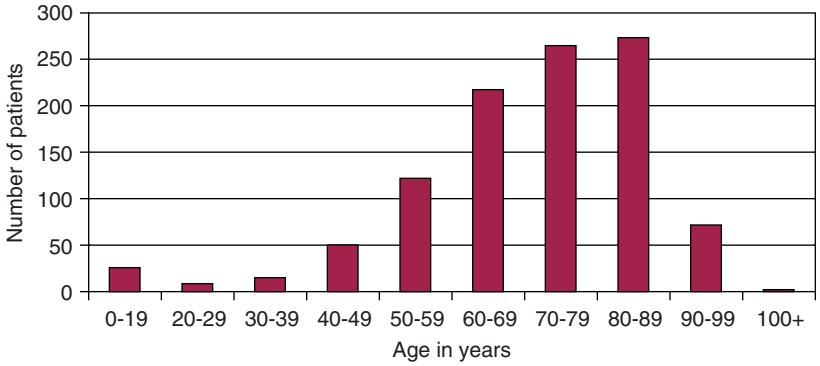

Figure 162-1. Distribution of hearing aid patients by age.

hearing aid devices were fitted on ears with pure conductive hearing loss.

Among people with hearing loss, there are significantly more individuals with mild hearing loss than severe or profound loss. Among this group of hearing aid users, most patients who choose to use hearing aids have hearing loss that is at least moderate in degree. The proportion of patients who have hearing loss and use hearing aids increases substantially with increasing severity of hearing loss. Stated the other way, the penetration of hearing aids into the potential market is low for mild hearing loss and considerably greater as hearing loss increases.

Slope of the audiometric configuration is another factor that influences hearing aid usage. Most patients have flat or sloping hearing loss—that is, hearing sensitivity that is similar across frequencies, or that is better in the low frequencies than the high frequencies. For some audiometric configurations, it is very challenging to provide appropriate amplification. One difficult configuration is a high-frequency precipitous loss, where hearing sensitivity is normal through 500 Hz and decreases dramatically at higher frequencies. There may even be dead regions in the cochlea, where hair cell loss is so complete that no transduction occurs. Depending on the frequency at which the loss begins and the slope of the loss, this type of hearing loss can be very difficult to fit effectively. The other extreme is the rising audiogram, a relatively unusual audiometric configuration in which a hearing loss occurs at the low frequencies, but not the high frequencies. Although this type of loss seldom causes enough of a communication problem to warrant hearing aid use, when it does, certain aspects of the fitting can be troublesome, and the prognosis for successful fitting is limited. In the present sample, less than 2% of ears had rising audiograms.

Although degree of loss is associated with hearing aid use, the audiogram offers only one piece of information needed to determine candidacy. Most patients with minimal to mild hearing loss do not pursue hearing aids, although some do. This fact indicates that the presence of hearing loss alone may be insufficient to compel a patient to hearing aid use, but that a mild degree of hearing loss does not contraindicate hearing aid use. Even patients with minimal hearing losses can wear mild gain hearing aids with benefit. Generally, if the hearing impairment is enough to cause a problem in communication, the patient is a candidate for hearing aids.

Some patients have too much hearing loss for hearing aid use. Severe or profound loss can limit the usefulness of even the most powerful hearing aids. In many cases of profound hearing loss, a hearing aid can provide only environmental awareness or some rudimentary perception of speech. Many patients do not consider this benefit to be valuable enough to warrant the use of hearing aids. In these cases, cochlear implantation is often the most beneficial treatment strategy.

Another audiometric consideration in hearing aid use is suprathreshold speech recognition ability. In most patients, speech recognition is commensurate with degree of hearing loss and is simply a reflection of audibility of spoken speech. In these patients, amplification of the sound that is missing can provide significant enhancement of speech recognition. In other patients, speech recognition is poorer than expected for a given hearing loss. For example, cochlear hearing loss secondary to endolymphatic hydrops can cause substantial distortion of sound, resulting in very poor speech recognition ability. If it is sufficiently poor, hearing aid amplification may contribute to audibility but will be unsatisfactory overall.

Auditory processing disorders in young children and in aging adults can also reduce the benefit from conventional hearing aid amplification. It is not unusual for geriatric patients who were previously successful hearing aid users to experience increasingly less success as their central auditory nervous systems change with age.[3] The problem is seldom extreme enough to preclude hearing aid use, but these patients may benefit more from assistive technology to complement hearing aid use.[4] Prognosis for hearing aid benefit in these patients is guarded.

Communication Disorder and Motivation

The impact of a hearing loss can vary considerably among patients and is an important factor in hearing aid candidacy. Some patients with slow onset presbycusis, of even moderate degree, perceive no difficulty with communication. Such patients effectively use communication strategies such as speech reading and manipulation of the environment to minimize the impact of hearing loss. The prognosis for successful hearing aid use is limited by the patient's lack of recognition of the hearing loss. Other patients, who have considerably less hearing loss but greater communication demands or less success with coping strategies, might perceive communication difficulties and be anxious to quantify the hearing loss for the purpose of obtaining hearing instruments.

Patient motivation is another key factor in predicting success with hearing aids. A patient who is internally motivated to hear better is an excellent candidate for successful hearing aid use. The breadth of amplification options for such a patient is substantial. In contrast, an unwilling patient who gives in to the requests of a spouse or other family members to seek hearing aid amplification often finds numerous reasons why hearing aid amplification is unsatisfactory.

Candidacy for hearing aid amplification is fairly straightforward. If a patient has a sensorineural or other nontreatable hearing loss that is causing a communication disorder, the patient is a candidate for amplification. Even when a hearing impairment is mild, if it is causing difficulty with communication, and the patient is motivated to do something about it, the patient is a candidate for hearing aid amplification and is likely to benefit from its use.

Otologic and Other Factors

Other factors can influence hearing aid candidacy, although they are more likely to influence the selection of type and style of device than to preclude its use. Although a progressive or fluctuating hearing loss does not rule out conventional hearing aid use, the selected hearing instrument must be sufficiently flexible to allow for alterations in programming to accommodate the patient's changing hearing. Patients with microtia or other anomalies may have ear canals or pinnae that prevent fitting with a conventional custom hearing instrument or the ear mold used with a behind-the-ear (BTE) hearing aid. More commonly, the size of the ear canal of a patient sometimes limits the use

of certain in-the-ear (ITE) hearing aids. Other physical and medical limitations can make conventional hearing aid use difficult. Occasionally, a patient with hearing loss has external otitis or ear drainage that cannot be controlled medically. Placing a hearing aid in such an ear can be a constant source of problems. Certain rare pain disorders may also limit access to the ear canal.

Physical and cognitive limitations may influence hearing aid candidacy. Physical limitations are primarily limitations pertaining to dexterity issues from arthritis and other conditions that affect a patient's ability to manipulate certain styles of hearing aids.[5,6] Limited cognitive ability can be a barrier to successful hearing aid use when a patient has difficulty remembering how to operate a hearing aid and its components.

Hearing Aid Technology

Evolution of Hearing Aid Technology

Hearing aid technology has advanced rapidly. Modern hearing aids use DSP for high-fidelity sound reproduction. They have adaptive directionality, feedback control, noise reduction, and low battery drain. They are readily programmable, providing substantial flexibility for precise fitting. Modern hearing aids also have advanced amplification strategies that reduce distortion and enhance listening comfort.[7]

One early step in the progress of technology was component miniaturization. Microphones, amplifier circuits, loudspeakers, and batteries all have been reduced in size. This miniaturization has allowed sophisticated signal processing circuits to be fitted into a completely-in-the-canal (CIC) style of hearing aid. It has also allowed for more technology components, such as wireless receivers, to be incorporated into smaller sized devices worn over or in the ear.

Programmability of hearing aids was a major step in the advancement of hearing aid technology. This programmability provided flexible control of hearing aid characteristics. In the recent past, a hearing aid circuit had to be matched carefully to a patient's audiogram at the time of hearing aid selection. Now hearing aids are available that can be programmed over a wide fitting range so that the matching is done at the time of hearing aid fitting, rather than at the time of selection. Programmability also provides multiple memories for a single hearing aid, allowing the potential for use of different response parameters for different listening situations.

Hearing aids have progressed since the late 1990s from analog to DSP. In analog hearing aids, acoustic signals followed an analog path that was under analog control, wherein an acoustic signal was converted by a microphone into electric energy in a continuously variable manner. In DSP hearing aids, acoustic signals are converted from analog to digital and back again, with digital control over various amplification parameters. DSP eliminated many of the barriers faced in trying to design analog circuits to fit in a small hearing aid and run on low-powered batteries. Along with flexibility inherent in enhanced programmability, modern devices provide more precise and flexible frequency shaping, more sophisticated compression algorithms, better acoustic feedback reduction, and enhanced noise reduction algorithms.[8,9] The degree of sophistication of signal processing that is used in modern hearing aids seems limited only by the conceptual framework of how hearing aid amplification should work.

The most recent technologic advance in hearing aids is the growing opportunity of wireless connectivity, permitting communication from one hearing aid to another and from hearing aids to other electronic devices and signal sources.[10]

Hearing Instrument Components

A hearing aid is an amplification device that consists of three basic components: a microphone, an amplifier, and a receiver. The power source for the amplifier is a battery. Most hearing aids also have some external controls, such as a program button or volume control on the hearing aid, or a remote control. A schematic of the basic components is shown in Figure 162-2.

The most common input transducer in a hearing aid is a microphone, which converts acoustic energy into electric energy. As a sound source vibrates, it creates pressure waves of expanding and compressing air molecules. The membrane of the microphone vibrates in response to these pressure changes, creating an electric energy flow that corresponds to the amplitude, frequency, and phase of the acoustic signal.

Sound can also be delivered to the amplifier of a hearing aid via direct audio input, wherein a sound source reaches the hearing aid directly via a wire connector or "boot" that connects to a BTE hearing aid. One of the most common alternative input transducers is the telecoil, or t-coil. A telecoil allows the hearing aid to receive electromagnetic signals directly, bypassing the hearing aid microphone. The telecoil is often used with the telephone to reduce background noise, and to minimize the potential for feedback that occurs when placing a device near the microphone. A telecoil can be activated by a manual control on the hearing aid, by remote control, or automatically when the hearing aid senses an electromagnetic field.[11]

The telecoil can also be used to provide input for remote-microphone sources. The signal from the remote microphone is transmitted in some form to a loop of wire, which transmits the signal electromagnetically to the telecoil of the hearing aid.[11] This type of technology is often used in a classroom situation, to allow the signal delivered from the remote-microphone worn by a teacher to be directly input to the hearing aid worn by the student.[12] This technology minimizes the degradation of the auditory signal caused by background noise and distance.

A hearing aid may have some other form of wireless transducer, such as a frequency-modulated (FM) receiver or Bluetooth or other modern wireless connectivity. An FM receiver can be built into a hearing aid or attached as a boot on a BTE hearing aid. The FM receiver acts like an FM radio, receiving signals from a transmitter and directing them to the amplifier of the hearing aid.[13] Increasingly, modern hearing aids are equipped with other wireless connectivity solutions, so that the hearing aid amplifier can receive signals directly from mobile phones, computers, or personal music players.[10]

The function of a hearing aid is to amplify sound. This amplification is accomplished through the power amplifier of the hearing aid. The amplifier adds gain to the level of the electric signal that is delivered to the hearing aid's transducer. The amplifier can differentially enhance higher or lower frequency and higher or lower intensity sounds. It also has a limiting function so that it does not deliver excessive energy to the ear.

The output transducer of a hearing aid is its receiver, or loudspeaker. The loudspeaker receives an amplified electric signal from the hearing aid amplifier and converts it back into acoustic energy. Hearing aid receivers have a broad, flat frequency response to reproduce accurately the signals being processed by the hearing aid amplifier.

Electroacoustic Characteristics

The acoustic response characteristics of hearing aids are described in terms of frequency gain, input-output, and output limiting. Gain is the amount of energy that is added to the input signal. The amount of gain

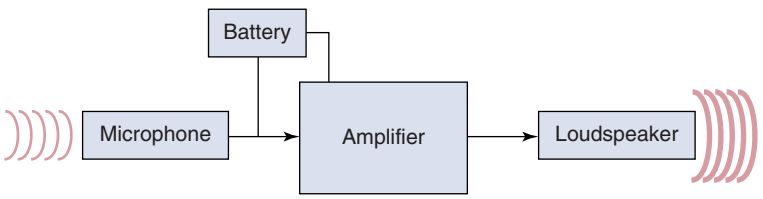

Figure 162-2. The components of a hearing aid.

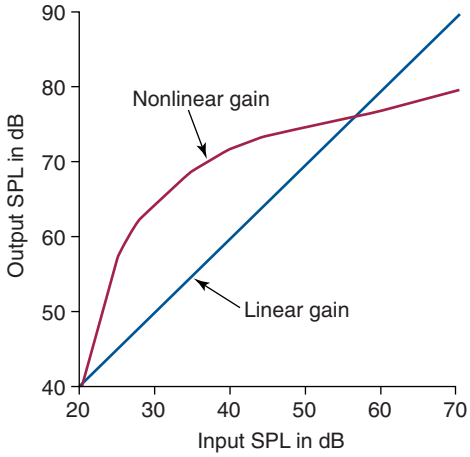

Figure 162-3. Relationship of sound input to output in linear and nonlinear hearing aid circuits. For the linear circuit, gain remains at a constant 20 dB, regardless of input level. For the nonlinear circuit, amount of gain changes as a function of input level. SPL, sound pressure level.

varies as a function of frequency to accommodate varying hearing loss configurations. The relationship of gain as a function of frequency is the frequency gain response of a hearing aid. The frequency gain response represents the gain produced by a hearing aid to a specified intensity level of a signal presented across the frequency range. It reflects the difference between the intensity level of the output of the hearing aid and the intensity level of the input. Most methods used for prescribing a hearing aid are based on providing a specified amount of gain at a given frequency, based on a patient's pure-tone audiogram.

The amount of gain also varies as a function of intensity level. The input-output characteristic of a hearing aid describes this relationship. The input-output function can be linear or nonlinear.

With linear amplification, the same amount of amplification, or gain, is applied to an input signal regardless of the intensity level of the signal so that low-intensity sounds are amplified to the same extent as high-intensity sounds. Figure 162-3 shows an example of a linear input-output function. In this example, for every dB increase in the input, there is a corresponding dB increase in the output. Fitting of linear hearing aids was a standard approach in the early years of hearing aids and remains applicable for conductive hearing loss and some mild sensorineural hearing losses. A problem with this type of amplification is that it does not address the nonlinearity of loudness growth that occurs with sensorineural hearing impairment. Many patients with sensorineural hearing loss do not hear low-intensity sounds, but can hear high-intensity sounds normally or even excessively loud owing to recruitment phenomena. Because a linear device amplifies soft and loud sounds identically, if a low-intensity sound is made loud enough to be audible, a high-intensity sound is likely to be too loud for the listener.[14]

In nonlinear amplification, the relationship between input and output is not constant, so that low-intensity sounds are amplified to a greater extent than high-intensity sounds; this is shown schematically in Figure 162-3. The overall effect is to make low-intensity sounds audible; moderate sounds comfortable; and high-intensity sounds loud, but not too loud.

Nonlinear amplification is designed to address two problems with sensorineural hearing loss: reduced dynamic range, and loudness growth that is different from that of a normal ear. *Dynamic range* in this case is a term used to describe the decibel difference between the level of a person's threshold of hearing sensitivity and the level that causes discomfort. In an individual with normal hearing, this range is 0 to about 100 dB hearing level (HL). In a patient with sensorineural hearing loss, the range is reduced. A patient with a 50-dB hearing loss and a discomfort level of 100 dB has a dynamic range of only 50 dB. Compression circuitry is used to boost the gain of low-intensity sounds so that they are audible, but to limit the gain of high-intensity sounds so that

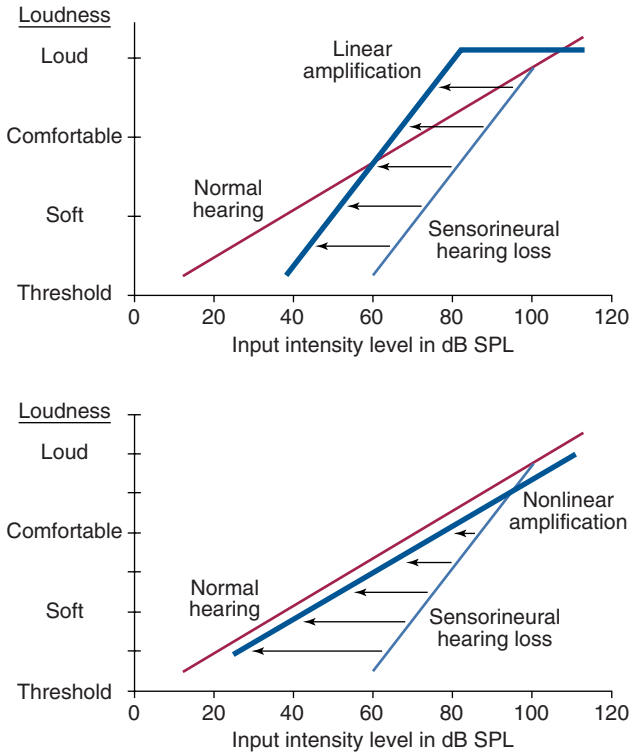

Figure 162-4. The difference between linear and nonlinear amplification in an ear with sensorineural hearing loss and nonlinear loudness growth. SPL, sound pressure level. *(From Stach B. Clinical Audiology: An Introduction. 2nd ed. Clifton Park, NY: Delmar Cengage Learning: 2010, 583.)*

they are not uncomfortable. Figure 162-4 illustrates the difference between linear output and dynamic-range compression as it relates to an ear with sensorineural hearing loss and nonlinear loudness growth.

Nonlinear amplification is achieved with compression circuitry. *Compression* is a term that is used to describe how the amplification of a signal is changed as a function of its intensity. Compression techniques are used to limit the maximum output of a hearing aid and to provide nonlinear amplification across a wide range of inputs.[14,15]

Numerous nonlinear compression strategies have been developed to address the dynamic-range issue, and they vary in approach and complexity. Some strategies are designed to provide compression over a portion of the dynamic range. Partial dynamic-range compression typically provides linear amplification for low input signals and some level of compression when the input reaches a certain level. Other strategies are designed to provide compression over a wider portion of the dynamic range. Wide dynamic-range compression has as its basis the enhanced amplification of quiet sounds and reduced amplification of loud sounds, and is designed to package speech into a listener's residual dynamic range. For most systems, dynamic-range compression can be altered in multiple frequency bands. In this way, if a patient's dynamic range is reduced in one frequency range and nearly normal in another, the compression can be tailored to the frequency band where it is needed, and the other band can act as more of a linear amplifier.[14-16]

An amplifier also contains circuitry that limits its output. It is important that the output level of a hearing aid be limited to some maximum because high-intensity sounds can be damaging to the ear and uncomfortable to the listener. The classic method of limiting output, known as *peak clipping*, does not allow the peaks of signals to exceed a certain level. This method commonly causes distortion for high-intensity inputs. Compression limiting, the current standard method of output limiting, allows the amplifier to become nonlinear as input signals reach a predetermined level, so that the amount of gain is diminished significantly near the maximum output level.[14,15]

Other Hearing Aid Features

Today's hearing aids include many features that make an important contribution to successful hearing aid fitting: directionality, noise reduction, feedback reduction, program management, automatic adaptivity, and data logging. During normal hearing, sound pressure waves reach the tympanic membrane after the acoustic signal has been modified by the resonance characteristics of the pinna, concha, and ear canal. These changes to the acoustic signal greatly aid the localization of a sound source in space, and contribute to the ability to hear in the presence of background noise.[17] With hearing aid use, sound is received by the microphone, which is removed from the location of the tympanic membrane. The signal from the microphone does not include the spatial cues provided by the ear, reducing the ability to hear in background noise.

One important strategy for restoring some of these spatial cues is the use of directional microphones. A directional microphone is one that is designed to be more sensitive to sounds emanating from one direction than another. In most listening situations, the signal of interest is in front of the listener, and background noise is separated spatially, often from behind the listener. A directional microphone is designed to enhance the signal from the front and reduce the signal from behind or from wherever else it might be detected.

In its simplest form, a microphone is equally sensitive to sounds coming from all directions, or is omnidirectional in nature. A microphone can be made to be more directional by using two ports, one on the front and one on the back of the hearing aid. Each port leads to the opposite side of the diaphragm of the microphone. The rear port of the microphone is filtered in a way that causes a phase shift, or time delay, between sounds reaching each side of the microphone. In this way, sounds emanating from behind the listener are delayed so that they arrive at the back of the diaphragm simultaneously with their arrival at the front of the diaphragm. Equal sound pressure levels at both sides of the diaphragm essentially cancel those from behind because the diaphragm cannot move. The directional response pattern can be manipulated by changing the spacing of the ports or the time delay or both.

The modern version of the directionality feature uses two or more directional microphones in an array within the hearing aid. The directionality is created by subtracting the sound at the rear microphone from that at the front. The time delay is manipulated acoustically and electronically based on the number of microphones, the physical nature of the array, and the filters used to optimize the directionality pattern.

Most hearing aids can be changed from an omnidirectional to a directional setting. Typically, omnidirectional microphones are used in quiet environments.[18] Directional microphones are beneficial in background noise so that the microphone sensitivity is focused in a desired direction. In some instruments, the directionality feature is activated manually by the patient. In other instruments, it can be activated automatically and adaptively when the hearing aid senses background noise, changing the amount of directionality based on the extent of the noise.[19]

Noise reduction circuitry is available in most modern hearing aids to reduce unwanted background noise in an effort to improve patient comfort and speech recognition. The sophistication of noise reduction strategies has advanced dramatically,[20] and a thorough description is beyond the scope of this chapter. A simple example might serve to illustrate how the problem can be approached. The frequency and intensity of ongoing speech is highly variable and of short duration, whereas some background noise is relatively constant in nature. A DSP hearing aid can easily detect the difference in time constant and reduce the gain of the hearing aid in the frequency band of constant noise. Modern strategies use increasingly sophisticated algorithms to improve comfort and audibility in noise.

Acoustic feedback occurs when the amplified sound emanating from a receiver is directed back into the microphone of the same amplifying system. Physical separation of the microphone and receiver is the most effective way to reduce feedback. Another feedback reduction mechanism is feedback suppression circuitry. With feedback suppression, the hearing aid recognizes the occurrence of feedback based on frequency, intensity, and temporal characteristics. It reduces amplification in the offending frequency range to reduce feedback or uses phase cancellation of the feedback signal to eliminate audible feedback.[21,22]

All listening situations are not equal. As a result of modern programming capabilities of hearing aids, different responses can be programmed for different situations. One hearing aid response may be appropriate for a certain acoustic environment, such as telephone use, whereas a different type of response may be more appropriate for listening in a noisy environment. Most modern hearing aids have multiple memories that contain different acoustic responses or programs. Multiple memories have the potential to make many programmed responses available in the same hearing device. These programs can be manually accessed through push-button or other types of switches to change settings, or can be changed automatically by the hearing aid as it responds adaptively to the acoustic environment.

The more recent trend in hearing aids is to reduce user control of the response in favor of adaptive control by the hearing aid itself. In such cases, the device continuously samples the acoustic environment and makes changes based on what it measures. This type of automatic control of the hearing aid is beneficial because changes can be made without users needing to monitor the environment themselves. The willingness and ability to use the various programs and features of the hearing aid effectively varies among hearing aid users. These differences can be addressed with adaptivity, as the hearing aid algorithms dictate when the acoustic environment calls for changes to the hearing aid function. In some cases, patients may choose to retain control over the hearing aid, even when adaptive features are available, owing to very specific listening requirements.

Data logging is a feature available in most modern digital hearing aids. The programming software of the hearing aid is designed to track and record user settings and changes to provide statistics that characterize hearing aid use. Commonly accrued information includes time of hearing aid use by the patient, use of automatic or manually controlled hearing aid programs and features, and classification of the listening environments of the user. Data logging is typically used for counseling of patients regarding hearing aid use. If data logging indicates that a patient has used a hearing aid only for a limited time each day, the patient can be effectively counseled regarding the benefit of consistent hearing aid use. Data logging can also be used for troubleshooting of patient complaints. In addition, based on the changes that are typically made by the user and the examination of the typical listening environments of the user, changes can be made to hearing aid programming by the provider.[23] Many data logging systems suggest changes based on listener preferences and experiences. Some data logging systems allow for changes to be automatically made to programming based on these factors and with input by the user when hearing aid characteristics are optimal for a particular listening environment.[24]

Hearing Aid Styles

Hearing aids are available in several styles and with a range of functionality. Each style type has characteristic advantages and disadvantages that must be weighed against user needs and preferences. The most common styles of hearing aids are BTE and ITE hearing aids.

Behind-the-Ear Hearing Aids

A BTE hearing aid consists of the microphone and amplifier in a case that is worn behind the ear. The receiver may be located behind the ear or in the ear canal. Amplified sound is delivered to the ear canal through a tube that leads to a custom-fitted ear mold, a standard open-canal coupler, or a receiver in the canal. External controls for patient manipulation, usually volume control or program button or both, are located on the back side. Figure 162-5 shows BTE hearing aids.

One method for delivery of sound to the ear canal is to channel sound from the ear hook through tubing that terminates in a custom ear mold that fits in the auricle. Ear molds are custom-made in a variety of styles. The resonance characteristics of the ear mold and tubing significantly alter the acoustic properties of amplified sound. The frequency gain characteristics of the hearing aid output can be modified by ear mold and tubing selection and modifications.[25]

Another method of coupling the BTE to the external canal is known as *open-fit technology* or *open-canal fittings*. With these fittings, the ear canal coupler is typically nonoccluding so that it does not completely fill the ear canal. It typically uses thinner tubing than that found with traditional custom-made ear molds, and it is usually a standard, rather than custom-made, coupler. Open-canal fittings are especially useful for high-frequency hearing loss. Low-frequency sound is free to pass through the ear canal in an unobstructed manner, permitting natural hearing in the lower frequencies.[25]

Another BTE variation is the receiver-in-the-canal (RIC) fitting. The RIC fitting can be an open-canal fit, or a conventional, occluded BTE fit. The use of the RIC fitting reduces potential for acoustic feedback by increasing the separation of the receiver from the microphone, creating opportunity for more hearing aid gain when using an occluded fit. When using an open-canal fit, the opportunity for acoustic feedback is similar to that of an open-canal fit with the receiver in the BTE.[26] With an RIC device, the tubing that is used with other BTE devices is replaced by a thin wire that directs the amplifier output to the receiver.

In-the-Ear Hearing Aids

An ITE hearing aid has all of the components contained in a custom-fitted case that fits into the outer ear or ear canal. A device that fills the outer ear concha is referred to as an ITE hearing aid. A device that is smaller and fits into the ear canal is known as an in-the-canal (ITC) hearing aid. Another device, a CIC hearing aid, is even smaller and fits deeply in the canal. Figure 162-6 shows ITE hearing aids.

Style Considerations

The choice of hearing aid style is based on several important factors. The first consideration is acoustic feedback. The higher the intensity of output, the more likely it is that sound will escape from the ear canal, and feedback will occur. Potential for acoustic feedback is lowest in BTE hearing aids, where the distance between the microphone and loudspeaker is greatest. Feedback potential is also reduced by sealing off the ear canal with a tightly fitting aid or ear mold.[27] Although electronic feedback control has reduced these problems,[22] smaller ITE hearing aids are generally restricted to milder hearing losses.

Occlusion of the ear canal creates problems in some patients, and may influence style consideration. Occlusion of the ear canal results in reduced aeration of the external auditory meatus, which may lead to problems associated with external otitis. In addition, a certain amount of hearing loss, known as *insertion loss,* occurs with occlusion of the ear canal while the hearing aid is in place. This occlusion creates hearing loss for patients who have normal low-frequency hearing. Occlusion of the ear canal also causes a phenomenon referred to as the *occlusion effect,* wherein a patient's own voice is perceived as loud and "echoing."[28]

One solution to occlusion problems is the placement of a vent. A vent is simply a passageway for exchange of air and sound around or through a hearing aid or ear mold. The acoustic characteristics of the hearing aid response can be manipulated by the size and type of vent used.[29] Low-frequency amplification can be eliminated, and natural sound can be allowed to pass through the hearing aid for patients with normal low-frequency hearing. Generally, the larger the vent, the more pronounced is the effect. A vent also creates opportunity for acoustic feedback to occur, however, because sound is more likely to escape from the ear canal and be directed into the microphone.[25] The use of an open-canal fit also reduces problems associated with occlusion,[30] with the same feedback-related challenges encountered with venting.

The choice of hearing aid style has an impact on microphone placement. Our ability to localize sound benefits from the natural influences of the auricle and concha. In addition, the auricle and concha increase high-frequency hearing by collecting and resonating sound greater than 2000 Hz. The closer the microphone is to the tympanic membrane, the more the hearing aid can benefit from these natural influences. Conversely, the farther removed the microphone, the more the hearing aid would have to make up for the elimination of these influences. CIC hearing aids can have an advantage over other styles in terms of microphone location.[17] Placing the microphone deeply in the ear canal has other practical advantages, including reduction of wind noise, ease of telephone use, and enhanced listening with headsets and stethoscopes.

Hearing aid style also affects effectiveness of directional microphones. Directional effectiveness is greatest when there is sufficient distance between the microphones located on the hearing aid. Because larger devices such as BTEs and ITEs have microphones that are farther removed from the tympanic membrane, directionality is more of a necessity. Larger devices also have more space available to accommodate optimal microphone placement, so greater directionality is more easily achieved.

An important style consideration relates to durability of the instruments. In ITE instruments, all of the electronic components are placed within the ear canal and are subjected to the detrimental effects of perspiration and cerumen. As a result, repair rates and downtime can be considerably greater for these devices. In contrast, BTE hearing aids have these components housed away from the ear canal, minimizing these effects.

Figure 162-5. Behind-the-ear hearing aids. *(Courtesy of Oticon, Inc., Somerset, NJ.)*

Hearing Assistive Technologies

Assistive technologies other than hearing aids are available for situation-specific hearing, including assistive listening devices (ALDs), alerting

Figure 162-6. In-the-ear hearing aids. **A,** Completely-in-the-canal aids. **B,** In-the-canal aids. **C,** In-the-ear aids. *(Courtesy of Oticon, Inc., Somerset, NJ.)*

and signaling devices, and telephone amplifiers. ALDs include personal amplifiers, FM systems, and television listeners. These devices are designed to enhance an acoustic signal over background noise by the use of a remote microphone. The use of a remote microphone allows the signal to be received by the listener without the degrading effects of distance and reverberation.[13]

Several groups of patients benefit from use of ALDs. Some patients with severe hearing loss do not receive sufficient benefit from hearing aids and find that supplementing hearing aid use with ALDs is necessary. Other individuals with high communication demands in their workplace or social life also benefit from ALDs. Some patients may have communication limitations only in very specific situations, so that general use of a hearing aid is not indicated. An example is a patient who notes difficulty only with watching television or attending a meeting. ALDs tailored to particular needs are often a more appropriate solution in such cases. Some patients have auditory processing disorder that is not accompanied by a loss in hearing sensitivity. Communication difficulties for such patients are characterized by difficulty understanding speech in background noise. For these patients, use of a remote microphone for enhancement of signal-to-noise ratio is more appropriate than amplification from a hearing aid.

A personal FM system is an ALD designed to minimize the effects of noise and distance with a remote microphone. The system consists of two parts, a microphone-transmitter and an amplifier-receiver. The microphone and transmitter are worn by or are close to the speaker. Some transmitters have array microphones that are designed for directionality. The signal is transmitted to the receiver via FM radio waves. The amplifier and receiver are worn by the listener, usually integrated into the hearing aid or coupled to the listener's ear via earphones.[13] Newer forms of wireless coupling of transmitter and receiver are also emerging as a solution for enhancing spatial hearing.[10]

Other assistive technologies are available to provide solutions for specific listening situations. Telephone amplifiers, which are available in several forms, increase the ability to hear on the telephone for many patients. Another commonly used assistive technology is closed captioning of television shows, which allow the viewer to see the spoken dialogue in printed form. Alerting devices, such as alarm clocks, fire alarms, and doorbells, are designed to flash a light or vibrate a bed when activated.

Selection and Fitting Process

The process of hearing aid selection and fitting usually follows this course: selection, quality control, programming, verification, and adjustment. Hearing aids are selected based on the degree and configuration an individual's hearing loss, the individual's communication needs, and other factors relating to style choice. After hearing aid selection, impressions are made of the ear canal for custom ear molds or hearing aids. When the hearing aids are received from the manufacturer, the aids are subjected to quality control of form and electroacoustic function. The hearing aids are programmed based on the patient's audiometric outcomes and needs. Verification of the frequency response is usually made by probe-microphone measurement. A small microphone is placed near the tympanic membrane, and the responses of the hearing aids to speech or speechlike sounds are determined for different levels of input. The hearing aids are adjusted so that the responses approximate the desired targets. The electroacoustic performance is verified further with formal or informal assessment of quality, loudness, or speech perception. The hearing aids may be adjusted again if perceptual expectations are not met.

Target Gain

The fundamental way to specify a starting point for determining the response of a hearing aid is to prescribe frequency-gain characteristics based on audiometric measures.[31] Numerous prescriptive rules have been developed. Some are based on hearing thresholds alone and attempt to specify gain that would amplify average conversational speech to a comfortable or preferred listening level. The half-gain rule prescribes gain equal to one half the amount of hearing loss; the third-gain rule prescribes gain equal to one third of the loss. Most prescriptive rules have this simple approach as a basis, then adjust individual frequencies based on empirically determined correction factors. One popular early threshold-based procedure, which still serves as the basis for some current approaches, is that of the National Acoustic Laboratory.[32]

Another approach is to prescribe frequency-gain characteristics based on threshold and discomfort levels.[31] One notable effort is the desired sensation level (DSL) method.[33] The DSL was originally designed for fitting hearing aids in children, and it prescribed gain based on thresholds and predicted discomfort levels. A newer alternative, the DSL[i/o], is designed to ensure audibility of soft sounds[34] and is used in many modern fitting systems.

Prescriptive procedures were also developed in response to wide-dynamic range compression amplifiers. In these approaches, targets were determined for soft, moderate, and loud sound.[35] More recent procedures combine the linear approach of the early threshold-based prescription methods with different prescription requirements for soft and loud sounds.[31,36]

Other considerations for determining targets include the type of hearing loss and whether one or both ears are being fitted. When there is a conductive component to the hearing loss, target gain is usually increased by approximately 25% of the air-bone gap at a given frequency. When the hearing aid fitting is binaural, the target gain for each ear should be reduced by 3 to 6 dB for binaural summation.[31,37]

Hearing Aid Selection

The process of hearing aid selection first involves assessment of the patient's communication needs and other patient factors that may have an impact on hearing aid use. Appropriateness of the patient for hearing aid candidacy is assessed, and the determination is made whether to pursue hearing aid amplification. This decision is followed by determination of the style and features that would be most appropriate for the patient's hearing loss and communication needs.[38]

The fitting range of a hearing aid is used to determine appropriateness of a hearing aid circuit for a patient's degree and configuration of hearing loss. The fitting range shows the general response curve of the amplifier and is used to determine the ability of a particular hearing aid amplifier to provide necessary gain. This response curve can be manipulated with software controls to reduce or enhance specific frequency ranges to provide the necessary gain for a specific hearing sensitivity. An example is shown in Figure 162-7. Newer hearing aid circuits have a more generic frequency response that can be extensively manipulated, creating a "one-size-fits-many" concept of hearing aid circuitry.

Because of the inherent flexibility of the DSP platform of modern hearing aids, a given hearing aid can be programmed to fit a wide range of degree and configuration of hearing loss. Generally, the factors that separate one hearing aid from another are related to features and processor algorithms, rather than to the frequency gain response of the hearing aid.

Ear Considerations

For most patients, it is best to fit both ears with hearing aids because of the binaural advantage. The brain relies on differences in time and intensity of signals between the ears to localize the source of a sound in the environment.[39] Binaural processing of sound enhances the audibility of speech coming from different directions,[40] and the ability to focus on a desired sound source[41] while suppressing background noise. The use of two ears also improves the perception of sound quality[42] and enhances hearing sensitivity.[37] If a patient has relatively symmetric hearing loss, he or she would benefit more from two hearing aids than from one hearing aid.[41] Evidence suggests that unilateral hearing aid fitting places the unaided ear at a relative disadvantage, which may have a long-term negative effect on the speech perception ability of the unaided ear.[43,44]

Sometimes it is impossible to fit binaural hearing aids effectively. In cases where both ears have hearing loss, but there is significant asymmetry between ears, it is generally more appropriate to fit a hearing aid on the better hearing ear than on the poorer hearing ear.[45,46] This is because fitting the better ear would provide the best aided ability of either monaural fitting. Rarely, in cases of poor speech recognition in

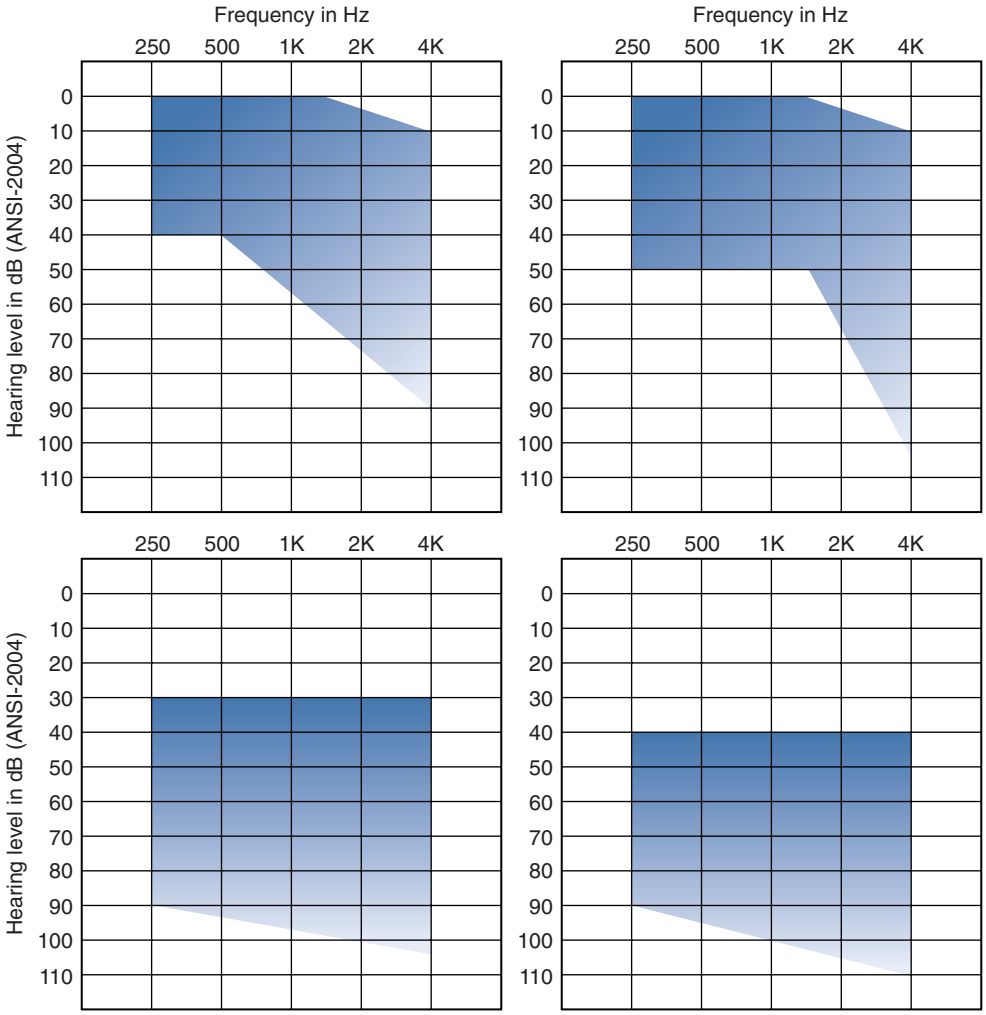

Figure 162-7. Fitting ranges for four different hearing aids, ranging from a mild gain to a power hearing device. ANSI, American National Standards Institute.

one ear, stimulation of the poorer ear can lead to a binaural interference effect, wherein speech understanding is decreased overall.[45,47]

If only one ear has hearing loss, and it can be effectively fitted with a hearing aid, a monaural fitting is indicated. If the poorer ear cannot be effectively fitted, the approach of contralateral routing of signals may be used. A microphone and hearing aid are placed on the poorer or nonhearing ear to deliver signals to the other ear either through bone conduction or via a receiving device worn on the normal-hearing ear.[48]

Other Considerations

Other factors that must be considered in the hearing aid selection process include hearing aid style, directional microphones, occlusion issues, feedback suppression, noise reduction, number and size of user controls, telecoil and other wireless options, and device costs.[38,49] Many of these factors interact with each other because hearing aid manufacturers tend to group availability of features into particular technology levels.

The selection process usually begins with a discussion of hearing aid style. In many cases, the hearing loss may dictate or at least influence this decision. The decision is also influenced by patient preference, which is often based on appearance, convenience issues, or past experience.

The feature/technology level of the hearing aid must also be determined. Grouping of hearing aid features varies among and within manufacturers. Higher levels of technology increase the financial cost of the device.

Some hearing aid selection decisions are made by the provider, and others are made by the patient. The selection of the appropriate feature/technology level involves negotiation with the patient about communication needs and the cost-effectiveness of the various solutions. The communication needs assessment plays a vital role in determination of the hearing aid characteristics that are most important for a given patient. When all of the decisions have been made, the selection is narrowed down to a set of device options. A decision is made regarding specific hearing aids for the patient by comparing these options against the knowledge of devices available from the hearing aid manufacturers.

Fitting and Verification

The general process of fitting and verification includes crafting ear impressions, quality control measures, device programming, verification of fit, and verification of function.

Fitting

The fitting process begins with making impressions of the outer ear and external auditory meatus. The impressions are used by the manufacturer to create custom-fitted ear molds or ITE hearing aids. The quality of the impression dictates the quality of the physical fit of the hearing instruments.

Impression making begins with otoscopic inspection of the ears and ear canals to ensure that they are healthy and suitable for the introduction of impression material. The ear canal is assessed for signs of external otitis and of the tympanic membranes for perforations or

inflammation. The inspection process also includes an evaluation of the amount of cerumen in the canals to ensure that they are not impacted or would not become impacted as a result of the impression-making process.

Care must be taken to protect the tympanic membrane and middle ear from impression material. Significant complications have been reported from impression material entering the middle ear space or mastoid cavity.[50,51] For protection, a foam or cotton block is placed deep into the ear canal as a barrier between the tympanic membrane and the impression material. When ear impressions are being made for CIC hearing aids or ear molds for profound hearing loss, very deep impressions of the ear canal are taken, and extra precautions may be necessary. When the blocks are in place, impression material is mixed, and the ear canals are filled. Several types of materials are available for making impressions. Impressions that are silicone-based tend to be more viscous than the powder and liquid forms. It seems likely that additional viscosity should reduce the risk of complications. After the material has set, and the impressions are removed, the ear canals are inspected again to determine that all impression material has been removed, and no trauma has occurred during the impression-making process.

If the ear molds are to be used with BTE hearing aids, decisions are made about the style of ear mold, the material to be used, and the style and size of tubing and venting. Ear mold materials vary in softness and flexibility. Some materials are nonallergenic. The decisions regarding which material and style to use are based on issues relating to comfort and feedback.[27] Decisions regarding bore size, tubing, and venting affect the frequency gain of the hearing aid.

Electroacoustic analyses of the hearing aids are made before programming to ensure that their output meets specified design parameters. This is done with the hearing aid placed in a test chamber of a hearing aid analyzer, in a 2-cc coupler, attached to a microphone. The chamber has a loudspeaker to deliver test signals to the hearing aid. The amplified signal is sent to the analyzer, which is a sophisticated sound-level meter.[52]

Hearing aid analyzers measure the acoustic output of a hearing aid according to specifications of the American National Standards Institute's Standard for Characterizing Hearing Aid Performance (ANSI S3.2-2003).[53] Standard electroacoustic analysis of a hearing aid provides information about the hearing aid's gain, maximum output, and frequency response. It also provides a measure of circuit noise, distortion, and battery drain. Results of this analysis are compared with the hearing aid specifications provided by the manufacturer to ensure that the hearing aid is operating as expected.[52]

Programming of hearing aids is accomplished via computer software that is proprietary for each manufacturer. The basic response of the hearing aid is derived from the patient's audiogram based on a prescriptive target. Manufacturers usually use proprietary targets that match the assumptions underlying their signal processing strategy. Most parameters of the response can be adjusted as indicated. Some decisions are based on patient characteristics, such as age or experience using a hearing aid. New users typically initially prefer less gain than what might be prescribed for their hearing losses after they adjust to the amplification. For experienced users, response settings may vary depending on the type of processing used in the past.

During this initial stage, preliminary decisions are made about management of programming controls. A decision is made as to whether multiple memories are to be used for a given patient, and how the programs are organized among the memories. Decisions are also made regarding the activation of manual controls, telecoil preferences, noise and feedback reduction responses, and level of sensitivity or responsiveness for adaptive technology in hearing aids. The gain response, maximum output, and prescriptive formula are evaluated to determine appropriateness for the patient. These decisions are made based on the particular characteristics of the device and patient factors, including age and cognitive abilities, degree and configuration of hearing loss, patient experience with hearing aids, and communication needs.

After programming, the physical fit of the device is assessed. Appropriateness, comfort, and security of the fit are determined, as are the absence of feedback and appropriateness of the microphone location. If the fit is inadequate, the hearing aids or ear molds can be modified. Assessment of occlusion effect is typically made by patient perception of his or her own voice, and alterations are made if necessary. The patient's ability to insert and remove the devices and manipulate controls independently is also determined.

Verification

The overall process of verifying suitability of hearing aids includes objective measurements of gain and frequency response from the hearing aids in the ear canal, adjustment of parameters to meet targets for gain and frequency response, and subjective judgments from patients regarding sound quality.

As sound leaves the hearing aid, it is modified by the resonance characteristics of the physical features of the ear canal. The methods for prescriptive gain for the hearing aid take into account the physical characteristics of average ears and must be adjusted for individual variations. The characteristics of transducers can also vary slightly across hearing aids. The output of the hearing aid in the ear canal itself must be verified with real-ear testing. This testing assesses whether the targeted gains are achieved across the frequency range for a given input to the hearing aid. The most commonly used real-ear tests are probe-microphone measurements.

Probe-microphone measurements are made using a spectrum analyzer that delivers various types of signals to a loudspeaker located near the ears of a patient. A small thin tube is inserted into the ear canal down close to the tympanic membrane. The other end of the tube is attached to a sensitive microphone that records sound from deep in the ear canal. This tube allows for measurement of the acoustic changes that occur owing to the resonance of the patient's pinna and ear canal.[54-56]

With the probe tube in place, speech or speechlike sounds are presented through the loudspeaker at a given intensity level, and measurements are made of sound in the ear canal without a hearing aid in place. This measurement is called the real-ear unaided response or gain (REUR/G). Next, the same sounds are presented with the patient's hearing aid in place and functioning. This measurement is called the real-ear aided response or gain (REAR/G). The difference between the aided response and the unaided response (REAG − REUG) is the real-ear insertion gain (REIG). The REIG provides information about the amount of sound that the hearing aid adds when it is in place in the ear. This process is typically performed for low-intensity, average-intensity, and high-intensity signals. If the response does not match the expected target, programming changes are made to the hearing aid until the target is approximated.[54-57]

Another approach to probe-microphone measurements is known as *speech mapping*. In this case, the signal presented through the loudspeaker is low-intensity, average-intensity, and high-intensity speech. The response of the hearing aid is measured near the patient's tympanic membrane, and adjustments are made to approximate targets for speech input. Live speech, such as from a spouse, can also be used to examine the audibility of a particular voice with the hearing aid programming. This process results in verification that the amplified signal being delivered to a patient's tympanic membrane meets prescriptive targets for different input levels. If the targets are correct, when the patient is wearing the hearing aids, low-intensity sounds should be audible, average sounds should be comfortable, and high-intensity sounds should be loud but tolerable.[58]

After objective verification measures, the quality of the amplified sound is assessed with some form of subjective quality judgments or functional intelligibility procedures. Perceptual verification is done in many ways, informally and formally. Strategies include speech perception judgments, loudness judgment ratings, functional gain measurement, and speech recognition measures.

Orientation, Counseling, and Follow-up

After the completion of hearing aid fitting and verification, the patient is oriented to the hearing aid and its use. Areas addressed typically include components and functioning of the hearing aids, battery use, and care and maintenance of the hearing aids. One of the most crucial aspects of the hearing aid orientation is discussion of reasonable expec-

tations of hearing aid use and strategies for adapting to different listening environments.[59] The goal of the hearing aid orientation is for the patient to learn how to use their hearing aid effectively.[60,61]

At the end of the orientation and counseling session, patients are typically scheduled for a follow-up visit. At the follow-up appointment, benefit and satisfaction with the hearing aid are assessed, and any necessary adjustments are made. It is often at this follow-up that outcome measures are made to ensure that the patient's communication needs are being met and to help in planning of any additional rehabilitative services.

Outcome Measurement

The goal of the hearing treatment process is to reduce the communication disorder imposed by a hearing loss. We generally define success at reaching this goal in terms of whether the patient understands speech better with the hearing aid, and whether the hearing aid helps to reduce the handicapping influence of hearing impairment. Outcome measures are designed to assess the impact of hearing aid use on communication. Self-assessment scales can be administered before and after amplification use to determine whether the hearing aids have had a positive impact in reducing communication disorder resulting from hearing loss.[62] Assessments may also be completed by spouses or other individuals who are affected by the hearing loss.

Patient perceptions of hearing ability and challenges are measured with self-assessment tools such as the Hearing Handicap Inventory for the Elderly (HHIE),[63] the Abbreviated Profile of Hearing Aid Benefit (APHAB),[64] and the Client Oriented Scale of Improvement (COSI).[65] Quality-of-life measures are used to determine how hearing aid amplification affects overall well-being. Measures such as the Glasgow Hearing Aid Benefit Profile (GHABP)[66] and the International Outcome Inventory—Hearing Aids (IOI-HA)[67] can help to measure the impact of audiologic treatment on quality of life.

Special Considerations Based on Patient Age

Infants and Children

Hearing aid selection and fitting for infants and children are more challenging than for adults for many reasons.[68-70] There is a smaller volume of space between the end of the ear mold and the tympanic membrane in children, owing to the smaller size of the ear canal, resulting in higher sound pressure levels delivered to the ear than in adults. Children also have different resonance characteristics than adults, which means that certain frequencies are emphasized more than others. In addition, because children are growing over time, these physical factors change, and must be regularly accounted for in hearing aid adjustments.[71]

Another major difference between hearing aid selection and fitting with children is that there is often considerably less information known about the hearing loss in a child compared with an adult.[70] This situation complicates the ability to prescribe gain in a hearing aid when fitting a child. Children are also less able to participate in the selection and fitting process and to provide useful information regarding perception of hearing aid sound quality and function.

There are important factors to consider regarding hearing aid use in children.[70] First, because children are still in the process of learning speech and language, it is crucial to provide consistent and undistorted auditory input.[72] Although adult knowledge of speech and language can fill in for missing or distorted input, children learning language through the auditory system have no linguistic basis for doing so. Second, children have less ability to control their listening environment than adults to maximize audibility. They also have less control over their hearing aids because most controls are disabled to protect against the child accidentally reducing the gain of the aid inappropriately.[71] Third, because of fluctuating hearing loss, such as that from otitis media with effusion, hearing may be more variable in young children.

Some general guidelines exist for fitting hearing aids on children. Children are always fitted with binaural hearing aids to maximize audibility, unless contraindicated by medical factors or extreme hearing asymmetry. BTE hearing aids are used in most cases because the auricle and ear canal grow in size, requiring that the custom portion of the hearing aid be changed frequently while the child is young; this is most appropriately accomplished by remaking the ear mold of a BTE, rather than an entire custom hearing aid. Soft material is used for ear molds, and the ear molds are connected to pediatric ear hooks for proper fitting.[71] BTE hearing aids are also indicated because flexibility in the fitting range of the hearing aid is necessary. Detailed information regarding the hearing loss may be incomplete at the time of the hearing aid fitting because of patient age. If the hearing loss fluctuates because of progressive hearing loss or otitis media with effusion, the BTE hearing aid allows for greater programming flexibility. Another advantage of BTE hearing aids for children is the nearly universal capacity for access to devices from remote microphones. The use of direct audio input, telecoils, and other wireless techniques are important for classroom and other listening environments to maximize the ability of the child to understand the teacher in a noisy classroom situation.[12]

The making of ear impressions can be challenging in a young child. If a child is sedated for the purpose of auditory brainstem response testing or surgical procedures, such as placement of pressure equalization tubes, this procedure can be readily accomplished at that time.

Prescriptive targets for hearing aid gain have been developed for children. An example is the DSL[i/o] approach.[34] These targets can be verified by probe-microphone measurements, which is even more important in pediatric ears because of the variability in ear canal size and its impact on the acoustic response of the hearing aid. Because of the difficulty of making real-ear measurements in children, a different measure, known as the real-ear coupler difference, is often useful. In this case, resonance characteristics of the child's ear are determined by making a single probe-tube measurement with a hearing aid in place. This measurement is compared with the resonance characteristics of a 2-cc coupler. Use of the coupler for measurement minimizes the impact of the patient's cooperation on verification procedures.[71,73,74]

Functional measures are more frequently made for pediatric patients than for adult patients to verify the appropriateness of hearing aid output.[75] Functional gain is the difference between the threshold with the hearing aid and without the hearing aid. Another useful functional measure is speech recognition with the hearing aids. Speech targets can be presented in the presence of background competition. The task of the child is to identify the correct speech stimulus, usually through a picture-pointing task. Aided results can be compared with unaided results and to expectations for normal hearing ability under similar circumstances.

Aging Patients

In some older patients, hearing loss sensitivity is compounded by changes in central auditory nervous system function. The consequence of such changes is typically reduction in speech recognition even in quiet, reduced temporal processing of auditory information, and reduced ability to hear speech in background noise because of diminished ability to use two ears to localize sound. Patients with significant changes in auditory nervous system function do not seem to benefit as much from hearing aid devices as their younger counterparts.[76] In fitting hearing aids for older patients, strategies designed to improve listening in background noise, such as the use of directional microphones,[19,77] noise-reduction processing, and use of remote microphones, are likely to improve patient benefit.

Another important consideration for fitting hearing aids in older patients is that there may be greater difficulty with physical manipulation of the hearing aid, owing to arthritis and other conditions.[6,78] Diminished vision may also be a problem.[79] Additionally, patients with cognitive decline may have difficulty remembering how to use or maintain their hearing aids effectively,[80] and in general may have greater difficulty understanding speech, even when speech is made audible with hearing aids.

Hearing Aids: Some Rules of Thumb

Most otolaryngologists encounter patients with medically intractable hearing loss on a daily basis in their clinics. Many clinicians do not have the opportunity to stay abreast of changes in hearing aid technology or fitting approaches. Patients seek their counsel about the

appropriateness of devices. Although the details may change quickly, there are some rules of thumb that have withstood the test of time, as follows:

"Two ears are better than one." Most patients hear better with binaural amplification, are more satisfied with sound quality and with hearing in noise, and find better overall benefit.

"Bigger is better." BTE hearing aids are considerably more durable than ITEs, are often less conspicuous, are easier to get a comfortable fit, have fewer feedback issues, can have more features, have a longer battery life, and are easier to manipulate.

"It's about communication not the audiogram." If a patient is having difficulty communicating because of sensorineural hearing loss and is motivated for an amplification solution, one can be found.

"If you haven't tried a hearing aid in 2 years, you haven't tried a hearing aid." There is a technology arms race out there, and the result is higher quality devices, more flexible fitting opportunities, and better quality-of-life outcomes.

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CHAPTER ONE HUNDRED AND SIXTY-THREE

Principles of Applied Vestibular Physiology

John P. Carey

Charles C. Della Santina

Key Points

- The vestibular system primarily drives reflexes to maintain stable vision and posture.
- By modulating the non-zero baseline firing of vestibular afferent nerve fibers, semicircular canals encode rotation of the head, and otolith organs encode linear acceleration and tilt.
- Stimulation of a semicircular canal produces eye movements in the plane of that canal.
- A semicircular canal normally is excited by rotation in the plane of the canal bringing the head toward the ipsilateral side.
- Any stimulus that excites a semicircular canal's afferents will be interpreted as excitatory rotation in the plane of that canal.
- High-acceleration head rotation in the excitatory direction of a canal elicits a greater response than does the same rotation in the inhibitory direction.
- The response to simultaneous canal stimuli is approximately the sum of the responses to each stimulus alone.
- Nystagmus due to dysfunction of semicircular canals has a fixed axis and direction with respect to the head.
- Brainstem circuitry boosts low-frequency vestibulo-ocular reflex (VOR) performance through velocity storage and neural integration. Failure of these mechanisms suggests a central pathologic process.
- The utricle senses both head tilt and translation, but loss of unilateral utricular function is interpreted by the brain as a head tilt toward the opposite side.
- Sudden changes in saccular activity evoke changes in postural tone.
- The normal vestibular system can rapidly adjust the vestibular reflexes according to the context, but adaptation to unilateral loss of vestibular function may be slow and susceptible to decompensation.

This chapter presents an approach to the vestibular system that provides a basis for understanding the evaluation and management of vestibular disorders described in subsequent chapters. The chapter is organized around 12 basic principles of vestibular system function, reviewing the physiologic underpinnings of each and illustrating their importance in clinical findings when appropriate. This core set of organizing principles can help clinicians quickly recognize the significance of findings on the vestibular exam and precisely localize peripheral vestibular problems to the affected end organs.

Several reviews can be consulted for further explanations of vestibular physiology.[1-4]

Principles

Principle 1: The Vestibular System Primarily Drives Reflexes to Maintain Stable Vision and Posture

Anatomic and Physiologic Basis

The vestibular system's main function is to sense head movements, especially involuntary ones, and counter them with reflexive eye movements and postural adjustments that keep the visual world stable and keep us from falling. The labyrinth of the inner ear senses head rotation and linear acceleration and sends that information to secondary vestibular neurons in the brainstem vestibular nuclei. Secondary vestibular neuron signals diverge to other areas of the central nervous system to drive vestibular reflexes. Specifically, neurons encoding head movement form synapses within the ocular motor nuclei to elicit the patterns of extraocular muscle contraction and relaxation needed for the vestibulo-ocular reflex (VOR), which stabilizes gaze (eye position in space). Other secondary vestibular neurons synapse on cervical spinal motor neurons to generate the vestibulocolic reflex (VCR), or to lower spinal motor neurons to generate the vestibulospinal reflexes (VSRs). These reflexes stabilize posture and facilitate gait. Vestibular sensory input to autonomic centers, particularly information about posture with respect to gravity, is used to adjust hemodynamic reflexes to maintain cerebral perfusion. Finally, vestibular input to the cerebellum is essential for coordination and adaptation of vestibular reflexes when changes occur such as injury to a vestibular end organ or alteration in vision (e.g., a new pair of glasses).

Vestibular signals also reach cortical areas to mediate the perception of movement and orientation. Nevertheless, the common head movements of everyday life usually go unnoticed, which is why ves-

tibular sensation is not included among the vernacular "five senses"—sight, smell, taste, touch, and hearing. Yet the loss of vestibular sensation causes distinct and often severe symptoms. This distress has perhaps been best captured in the first-hand account of J.C., a physician who lost his vestibular sense to an ototoxic aminoglycoside antibiotic: "By bracing my head between two of the metal bars at the head of the bed I found I could minimize the effect of the pulse beat that made the letters on the page jump and blur… In these corridors I had the peculiar sensation that I was inside a flexible tube, fixed at the end nearest me but swaying free at the far end."[5]

Like many other patients who have lost vestibular function, J.C. soon recovered and resumed most of his usual activities without the distressing sense of *oscillopsia*, the perception that the world is moving whenever the head is moved. This recovery is due to a combination of central adaptation to abnormal vestibular signals and the use of information from other sensory systems that provide information about movement and posture. For example, somatosensory information from proprioceptive sensors in the limbs contributes to the sense of vertical body orientation.[6] Proprioceptors in the neck mediate a cervico-ocular reflex that can augment the deficient VOR.[7,8] Likewise, postural information may be supplied by gravity receptors in the major blood vessels and abdominal viscera.[9] Because head movements may be also sensed by their impact on the retinal image, vision-based oculomotor systems can partly supplant a deficient VOR. For example, smooth pursuit is a type of reflexive eye movement that helps to stabilize images on the retina. During smooth pursuit, movement of a target image on the retina causes a conjugate following movement of the eyes to keep the target fixed on the fovea. The stimulus for this reflex is the difference between the velocity of the visual target and the velocity of the eye, which is called *retinal slip velocity*. This visual error is computed by the primary visual cortex; transmitted to the middle temporal, parietal, and frontal cortices; and forwarded to the brainstem and cerebellum to generate the oculomotor command signals. The multiple synapses involved in this reflex impose a long latency (approximately 100 msec), and the reflex breaks down at relatively modest velocities (more than approximately 50 degrees/second)[10] and frequencies (more than approximately 1 Hz).[11] Optokinetic nystagmus, which elicits eye rotation in response to optic flow of the visual scene, operates over a range of velocities and frequencies similar to smooth pursuit.[12] These limitations make these visually driven reflexes inadequate to stabilize vision during many common head movements. For example, the head pitches up and down at a frequency of approximately 2 Hz and velocity of approximately 90 degrees/second during walking, while during running head pitch harmonics may extend to 15 to 20 Hz. Voluntary head-on-body horizontal rotations can reach 800 degrees/second and can also have significant harmonics to 15 to 20 Hz.[13]

The limitations of smooth pursuit and optokinetic nystagmus illustrate the important concept that reflexive sensorimotor systems have optimal operating ranges. Smooth visual pursuit functions best for low-frequency and slow head movements. Autonomic gravity receptors function best for static and very-low-frequency conditions. These and other reflexes overlap with the vestibular system for part of its operating range, but nonvestibular systems largely break down during quick head movements. Therefore, the vestibular system is essential for gaze stabilization during *high-frequency*, *high-velocity*, and *high-acceleration* head movements.

Clinical Importance

The reflexive nature of the vestibular system is central to understanding vestibular pathophysiology. The brainstem interprets imbalances in vestibular input due to pathologic processes in the same way that it interprets imbalances due to physiologic stimuli. Therefore, the cardinal signs of vestibular disorders are reflexive eye movements and postural changes. These reflexive signs can largely be understood as the brainstem's responses to *perceived* rotation around a specific axis or *perceived* tilting or translation of the head, even though the head is still and upright. Knowing the effective stimulus for each vestibular end-organ allows determination of which end organ or combination of end organs must be stimulated to produce the observed motor output. Working backwards in this fashion, the end organs affected by pathology can usually be inferred.

In interpreting reflexive eye movements and postural changes in the search for vestibular dysfunction, an important consideration is that vestibular reflexes may be observed only in isolation under certain conditions. For many conditions, in fact, other reflexive systems can compensate for the loss of vestibular reflexes, thereby masking any deficit. For example, a patient with well-compensated, longstanding bilateral loss of vestibular function may surprisingly appear to have no problem keeping vision fixed on the examiner as the examiner rotates the patient's head slowly from side to side. In such persons, smooth pursuit, optokinetic nystagmus, and (to a lesser extent) the cervico-ocular reflex make up for the vestibular deficit. This is an example of a head movement that *can* be sensed by the vestibular system, but which is not in the range of frequencies and accelerations sensed *exclusively* by the vestibular system. However, when the examiner suddenly and rapidly rotates the head to either side, the eyes do not stay on target. The vestibular deficit can thus be unmasked by very dynamic head movements.

Principle 2: By Modulating the Non-Zero Baseline Firing of Vestibular Afferent Nerve Fibers, Semicircular Canals Encode Rotation of the Head, and Otolith Organs Encode Linear Acceleration and Tilt

Anatomic and Physiologic Basis

Sensory Transduction

The labyrinth of the inner ear houses a set of inertial sensors that detect rotary and linear acceleration. Each bony labyrinth encloses a membranous labyrinth consisting of three semicircular canals arrayed roughly at right angles to each other and two roughly orthogonal otolith organs, the utricle and saccule (Fig. 163-1). Semicircular canals primarily sense rotational acceleration of the head. The utricle and saccule primarily sense linear acceleration in horizontal and vertical (superoinferior) directions, respectively.

Sensation by semicircular canals works as follows. When the head accelerates in the plane of a semicircular canal, inertia causes the endolymph in the canal to lag behind the motion of the membranous canal, much as coffee in a mug initially remains in place as the mug is rotated about it. Relative to the canal walls, the endolymph effectively moves in the opposite direction as the head. Inside the ampulla, a swelling at the end of the canal where it meets the utricle, pressure exerted by endolymph deflects the cupula, an elastic membrane that spans a cross-section of the ampulla[14] (Fig. 163-2). Vestibular hair cells are arrayed beneath the cupula on the surface of the crista ampullaris, a saddle-shaped neuroepithelium. Hair cells are so named for tufts of stereocilia that project from their apical surfaces. These stereociliary bundles are coupled to the cupula so that its deflection creates a shearing stress between the stereocilia and the cuticular plates at the tops of the hair cells.

Stereocilia deflection is the common mechanism by which all hair cells transduce mechanical forces (Fig. 163-3). Stereocilia within a bundle are linked to one another by protein strands called "tip links" that span from the side of a taller stereocilium to the tip of its shorter neighbor in the array. The tip links are believed to act as gating springs for mechanically sensitive ion channels, meaning that the tip links literally tug at molecular gates in the stereocilia.[15,16] These gates, which are cation channels, open or close (or, more precisely, spend more or less time in the open state), depending on the direction in which the stereocilia are deflected. When deflected in the open or "on" direction, which is toward the tallest stereocilium, cations, including potassium ions from the potassium-rich endolymph, rush in through the gates, and the membrane potential of the hair cell becomes more positive (see Fig. 163-3B, C). This in turn activates voltage-sensitive calcium channels at the basolateral aspect of the hair cell, and an influx of calcium leads to an increase in the release of excitatory neurotransmitters, principally glutamate, from hair cell synapses onto the vestibular primary afferents (see Fig. 163-3D). All of the hair cells on a semicircular canal crista are oriented or "polarized" in the same direc-

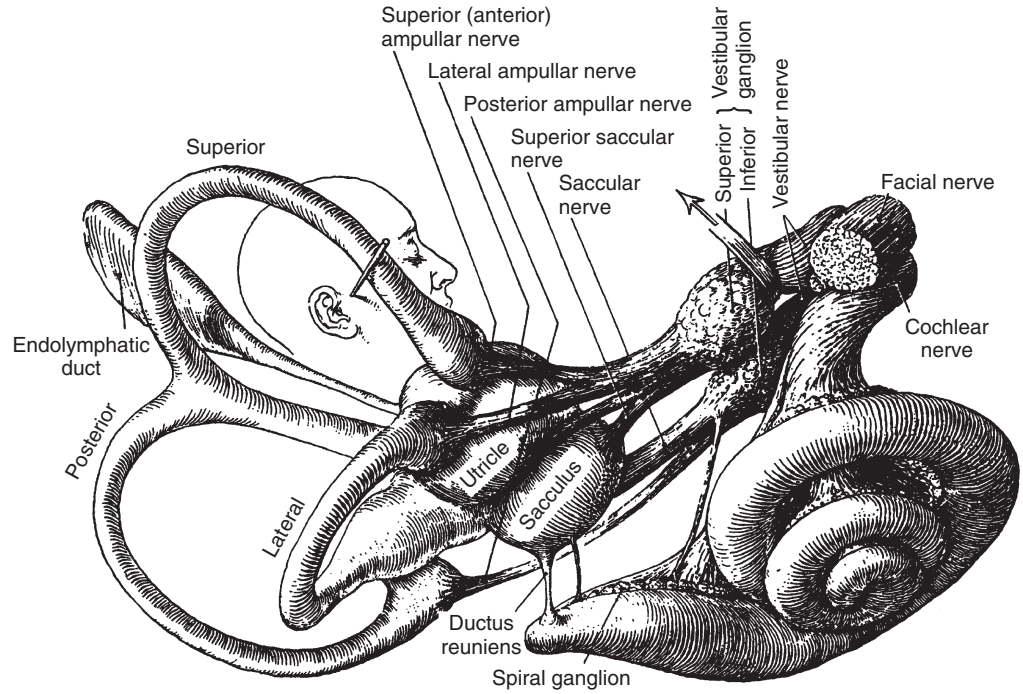

Figure 163-1. The vestibular end organs. *(From Brodel M.* Three Unpublished Drawings of the Anatomy of the Human Ear. *Philadelphia: WB Saunders; 1946.)*

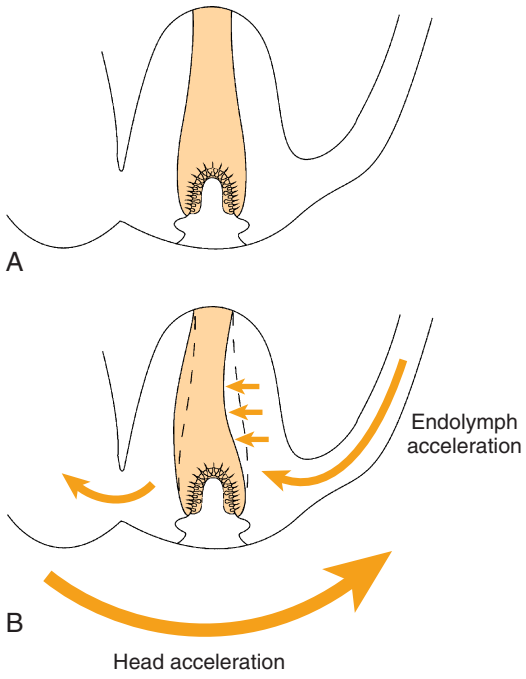

Figure 163-2. **A,** The cupula spans the lumen of the ampulla from the crista to the membranous labyrinth. **B,** Head acceleration exceeds endolymph acceleration. The relative flow of endolymph in the canal is therefore opposite to the direction of head acceleration. This flow produces a pressure across the elastic cupula, which deflects in response.

tion. That is to say that their stereociliary bundles all have the tall ends pointing the same way, so that the endolymph motion that is excitatory for one hair cell will be excitatory for all of the hair cells on that crista (Fig. 163-4).

The otolith organs sense linear accelerations. These organs contain sheets of hair cells on a sensory epithelium called a *macula* (Fig. 163-5). A gelatinous membrane sits atop the macula, and microscopic stones made of calcium carbonate, the *otoliths* (or *otoconia*), are embedded on the surface of this otolithic membrane. The *sacculus* (or *saccule*), located on the medial wall of the vestibule of the labyrinth in the spherical recess, has its macula oriented vertically. Gravity therefore tonically pulls the saccular otolithic mass inferiorly when the head is upright. The *utriculus* (or *utricle*) is located above the saccule in the elliptical recess of the vestibule. Its macula is oriented in roughly the same plane as the horizontal semicircular canal, although its anterior end curves upward. When the head tilts out of the upright position, the component of the gravitational vector that is tangential to the macula creates a shearing force on stereocilia of utricular hair cells. The cellular transduction process is identical to that described above for the crista. However, the hair cells of the maculae, unlike those of the cristae, are not all polarized in the same direction (Fig. 163-6). Instead, they are oriented relative to a curving central zone known as the *striola*. The utricular striola forms a C shape, with the open side pointing medially. The striola divides the utricular macula into a medial two thirds (polarized to be excited by downward tilt of the ipsilateral ear) and a lateral one third polarized in the opposite direction. Hair cells of the sacculus point away from its striola, which curves and hooks superiorly in its anterior portion. Each macula is essentially a linear accelerometer, with the saccular macula encoding acceleration roughly within a parasagittal plane (along the naso-occipital and superoinferior axes), and the utricular macula encoding linear acceleration roughly in an axial plane (along the naso-occipital and interaural axes). A given linear acceleration may produce a complex pattern of excitation and inhibition across the two maculas (Fig. 163-7), a pattern that encodes the direction and magnitude of the linear acceleration.[17] By contrast, each of the three semicircular canals senses just a one-dimensional component of rotational acceleration.

Modulation of neurotransmitter release from hair cells within each vestibular endorgan modulates the action potential frequency, or *firing rate*, of vestibular nerve afferent fibers (Fig. 163-8). The afferents have a baseline rate of firing, probably due to a baseline rate of release of neurotransmitter from the vestibular hair cells. Changes in vestibular nerve afferent firing are conveyed to secondary neurons in the brainstem. Baseline firing gives the system the important property of *bidirectional sensitivity*: Firing can increase for excitatory head movements and decrease for inhibitory head movements.[18] Thus, loss of one

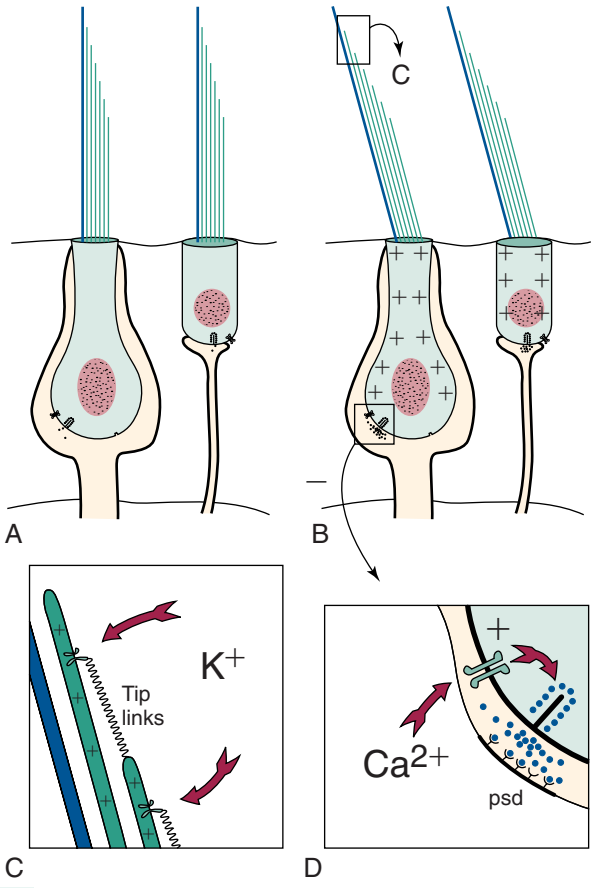

Figure 163-3. Sensory transduction by vestibular hair cells. **A,** At rest there is some baseline release of excitatory glutamate from the hair cell synapses onto the vestibular afferents. **B,** Hair cells are depolarized when the stereocilia are deflected in the "on" direction (toward the kinocilium, in dark blue). **C,** This occurs because the stretched tip links mechanically open cationic channels in the stereocilia membranes. The influx of potassium ions raises the hair cell's membrane potential. **D,** The increased membrane potential activates voltage-sensitive calcium channels in the basolateral membrane of the cell. Synaptic release of glutamate increases, and receptors in the postsynaptic (*psd*) density on the afferent increase its membrane potential, which in turn increases afferent firing rate.

labyrinth does not mean loss of the ability to sense one half of the head's movements.

Response of the Cupula

How a semicircular canal encodes head rotation can be understood using a mathematical model of a fluid-filled *torsional pendulum*.[4] Figure 163-9 depicts the mechanical forces acting on the left horizontal semicircular canal seen from above during counterclockwise head rotation through angle $H(t)$ in the plane of the canal. Head rotation carries the membranous semicircular canal along with it, whereas the inertia of the endolymph and cupula tend to keep these elements stationary in space (like the coffee in a mug as the mug is quickly turned). Nevertheless, two things act to accelerate the endolymph in the same direction that the head is turning but through the smaller angle $X(t)$. The first is the elastic or spring-like push from the distended cupula as it pushes against the endolymph (deep blue in Fig. 163-9). The second is the viscous drag exerted on the endolymph at its interface with the walls of the membranous canal.

Recall that for linear motion, Newton's Second Law states that $\sum F = ma$, where $\sum F$ is the sum of all applied forces, m is mass, and a is the resultant acceleration. For rotational motion, the analogous equation is $\sum T = I\alpha$, where T is torque, I is the moment of inertia, and α is rotational acceleration. For the rotating semicircular canal, the equation can be written

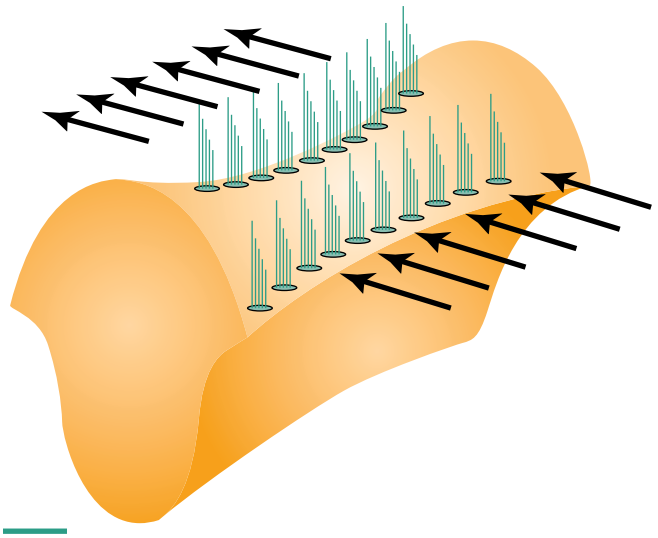

Figure 163-4. Morphologic polarization of the stereociliary bundles in the crista ampullaris. The "on" direction of deflection is always toward the kinocilium, which is next to the tallest stereocilium. Hair cells on the crista ampullaris of a given semicircular canal have all their stereocilia polarized in the same direction.

$$\sum T = T_{elastic} + T_{viscous} = I\ddot{X}(t). \qquad \text{Eq. 163-1}$$

Equation 163-1 says that the sum of the elastic and viscous torques acts on the moment of inertia I of the endolymph and cupula to accelerate the endolymph through space by $\ddot{X}(t)$. (Overdots are used to denote time derivatives, so $X(t)$, $\dot{X}(t)$, and $\ddot{X}(t)$ are endolymph rotational position, velocity, and acceleration, respectively.)

The elastic torque exerted by the cupula is proportional to the deflection of the cupula from its resting position (light blue in Fig. 163-9). That deflection is given by the difference between how far the head moves in space and how far the endolymph moves in space:

$$\Theta(t) = H(t) - X(t). \qquad \text{Eq. 163-2}$$

Thus, the elastic torque is

$$T_{elastic} = K\Theta(t). \qquad \text{Eq. 163-3}$$

The viscous torque is proportional to the velocity of the endolymph relative to the walls of the canal. Differentiation of Equation 163-2 gives this relative endolymph velocity:

$$\dot{\Theta}(t) = \dot{H}(t) - \dot{X}(t). \qquad \text{Eq. 163-4}$$

Therefore,

$$T_{viscous} = B\dot{\Theta}(t). \qquad \text{Eq. 163-5}$$

Finally, to get endolymph acceleration, $\dot{X}(t)$, we differentiate Equation 163-2 and rewrite it as

$$\ddot{X}(t) = \ddot{H}(t) - \ddot{\Theta}(t) \qquad \text{Eq. 163-6}$$

Now Equation 163-1 can be written as

$$K\Theta(t) + B\dot{\Theta}(t) = I\ddot{H}(t) - I\ddot{\Theta}(t). \qquad \text{Eq. 163-7}$$

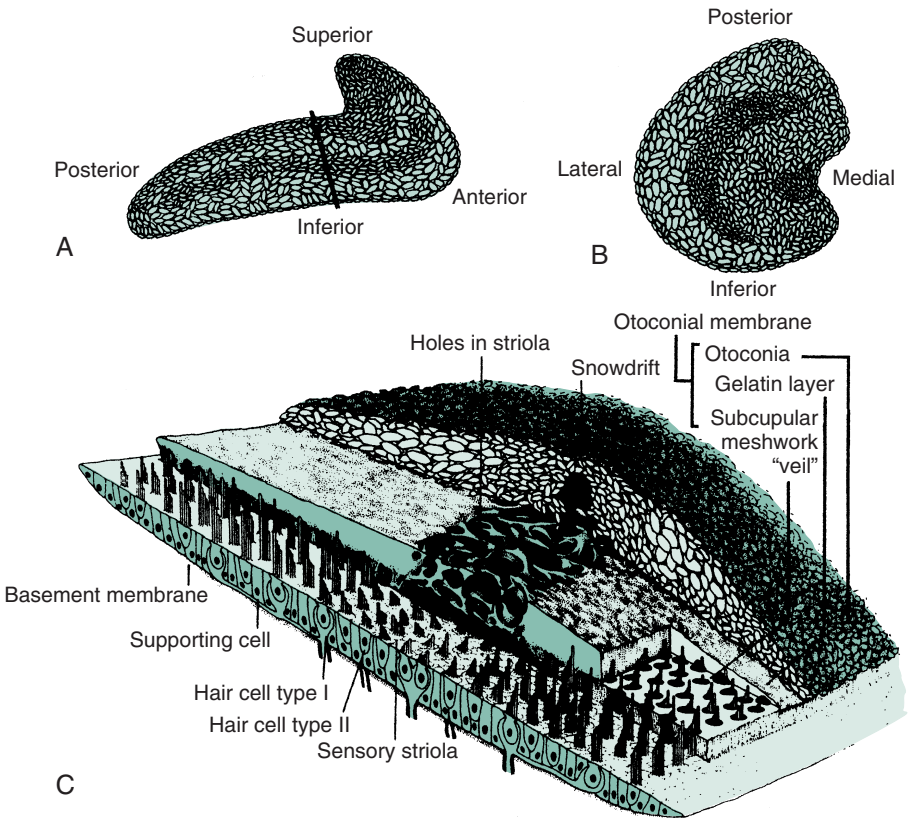

Figure 163-5. Arrangement of otoliths in the two maculae. **A,** Saccule. **B,** Utricle. **C,** Composition of the saccular otoconial membrane in a section taken at the level shown in **A.** *(From Paparella MM, Shumrick DA, eds.* Textbook of Otolaryngology. *Vol 1. Philadelphia: WB Saunders; 1980.)*

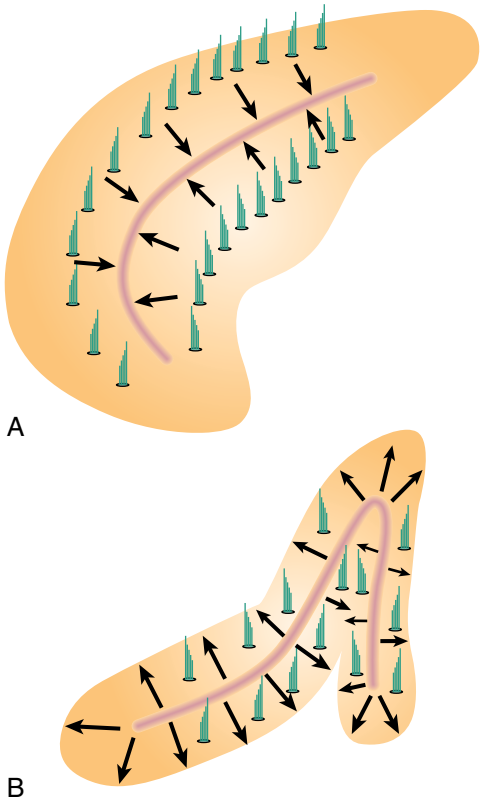

Figure 163-6. Morphologic polarizations of the stereociliary bundles in the maculae of the utricle (**A**) and saccule (**B**). The "on" direction of stereociliary deflection is indicated by the *arrows*. In the utricle (**A**), hair cells are excited by stereociliary deflection toward the striola *(curving central zone)*. In the saccule (**B**), hair cells are excited by stereociliary deflection away from the striola.

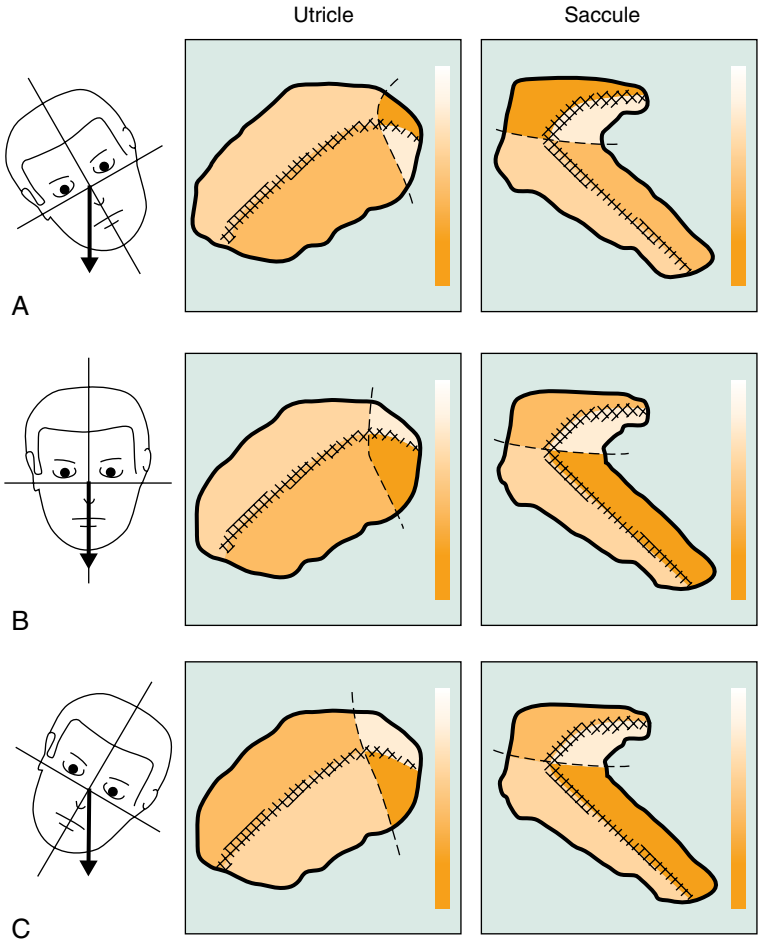

Figure 163-7. Estimated patterns of excitation and inhibition for the left utricle and saccule when the head is (**A**) tilted with the right ear 30 degrees down, (**B**) upright, and (**C**) tilted with the left ear 30 degrees down. The utricle is seen from above, and the saccule from the left side. The nidpoint of the color scale represents baseline activity, whereas dark orange and white represent depolarization and hyperpolarization, respectively. *(Modified from Jaeger R, Takagi A, Haslwanter T. Modeling the relation between head orientations and otolith responses in humans.* Hear Res. *2002;173:29.)*

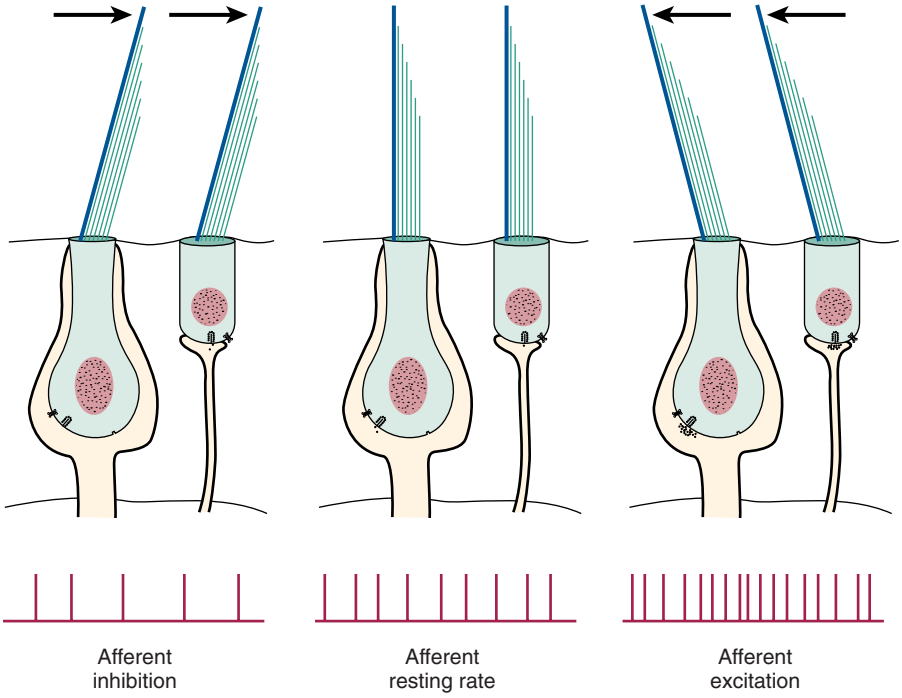

Figure 163-8. A vestibular afferent nerve fires actively at rest (*center*). Its firing rate is modulated by sensory transduction. The afferent is inhibited when its hair cells' stereocilia are deflected in the "off" direction (away from the kinocilium, in dark blue *left panel*) and excited when the stereocilia are deflected in the "on" direction (toward the kinocilium, *right panel*).

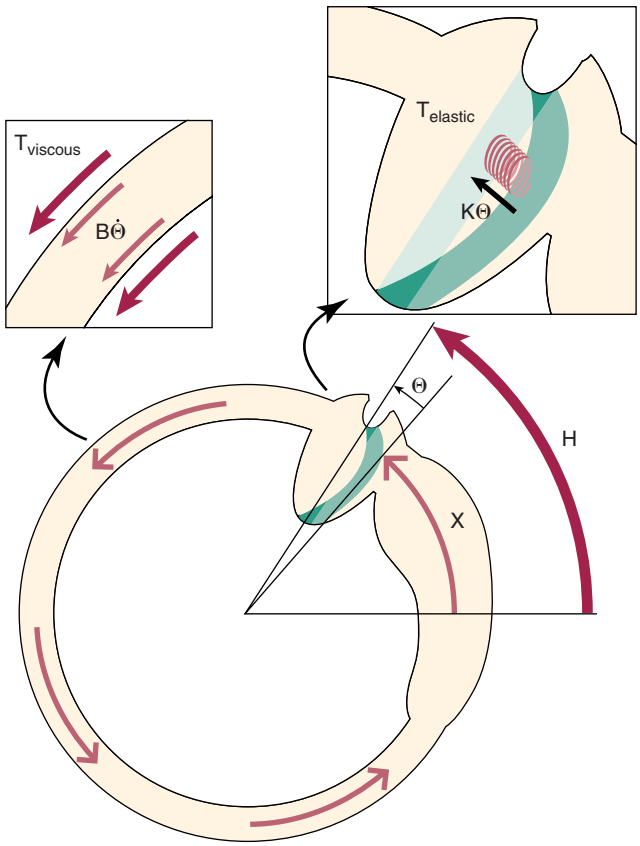

Figure 163-9. The torsional pendulum model of the mechanical forces acting on the cupula and endolymph of the left horizontal canal during leftward angular head acceleration as seen from above. As the head rotates through space over an angle *H*, endolymph inside the canal also rotates through space, but over a slightly smaller angle *X*. The difference between the angles through which the head and endolymph rotate in space is Θ, which approximates the angular deflection of the cupula. This creates an elastic torque proportional to the deflection: $T_{elastic} = K\Theta$. A viscous or drag torque is produced by the relative flow of endolymph along the walls of the canal and is proportional to the endolymph velocity relative to the canal: $T_{viscous} = B\dot{\Theta}$. The sum of these torques will equal the moment of inertia of the cupula and endolymph times their acceleration: $K\Theta + B\dot{\Theta} = I\ddot{X} = I\ddot{H} - I\ddot{\Theta}$.

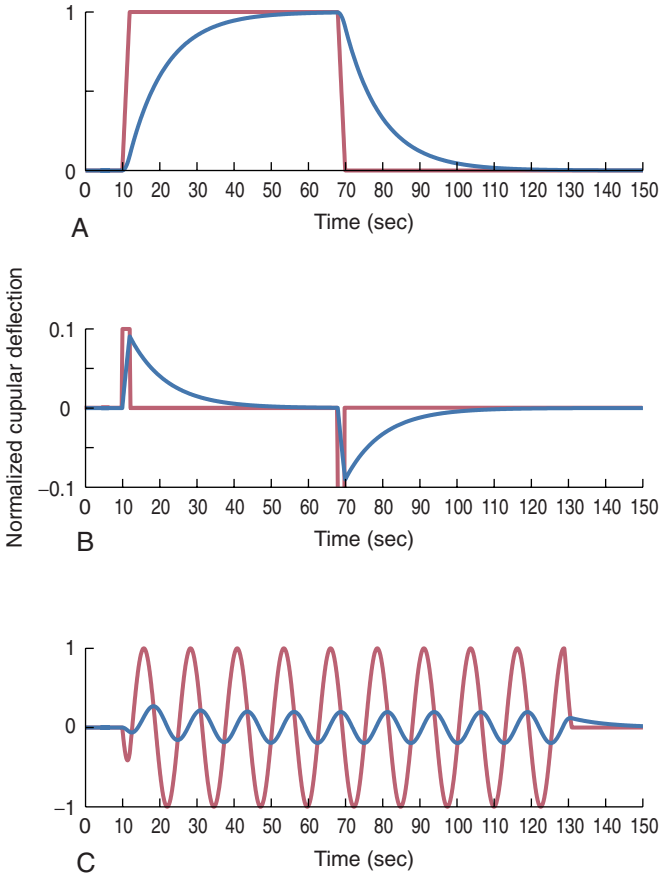

Figure 163-10. Patterns of cupular displacement in response to rotational head movements as predicted by the torsional pendulum model. **A,** A step of constant head acceleration *(red tracing)* results in a constant cupular deflection *(blue)* after an exponential increase in deflection with a time constant of about 10 sec. **B,** A step of constant velocity is produced by an impulse of acceleration in one direction followed by an impulse of deceleration in the opposite direction (acceleration impulses are shown in *red*). The cupula is transiently displaced, returning to its resting position with a decay time constant of about 10 sec. **C,** Sinusoidal *acceleration* of the head (*red*) yields a response in phase with head *velocity*.

The movement of the cupula can now be described as a function of head acceleration:

$$K\Theta(t) + B\dot{\Theta}(t) + I\ddot{\Theta}(t) = I\ddot{H}(t) \qquad \text{Eq. 163-8}$$

The full solution to Equation 163-8 is derived in the Appendix, but considerable insights can be gained without the full solution simply by inserting measured values for the physical constants in Equation 163-8 and considering the behavior under special circumstances.

For example, during a constant, low-acceleration head rotation (Fig.163-10A), cupular deflection eventually reaches a steady-state constant value. Because cupular velocity and acceleration eventually decay to zero under these circumstances, Equation 163-8 reduces to

$$K\Theta(t) \approx I\ddot{H}(t) \qquad \text{Eq. 163-9}$$

and cupular deflection (and afferent firing rate) is approximately proportional to head acceleration. The time course of cupular displacement in response to a constant acceleration approximates a single exponential growth, and the time constant with which cupular displacement reaches its maximum deflection is approximately 10 seconds, the time constant of the cupula (see Appendix). When the constant acceleration stops, the cupula returns to its zero position exponentially with the same time constant.

The same time constant governs the cupular response to very brief pulses of head acceleration. Figure 163-10B shows the predicted cupular deflection to an impulse of acceleration, which brings the head to a constant velocity plateau until an impulse of deceleration stops the rotation. Such "velocity steps" are often done as part of clinical rotary chair tests. However, the measured value of the time constant of the VOR in such testing is generally much longer than what would be anticipated by this calculated cupular response because of further processing by the brain (This is addressed later in the discussion of Principle 9.)

During sinusoidal head rotations in the range encompassing most natural head movements (approximately 0.1 to 15 Hz), viscous friction dominates the cupular response, and Equation 163-8 reduces to

$$B\dot{\Theta}(t) \approx I\ddot{H}(t) \qquad \text{Eq. 163-10}$$

This implies that

$$\Theta(t) \approx \frac{I}{B}\dot{H}(t), \qquad \text{Eq. 163-11}$$

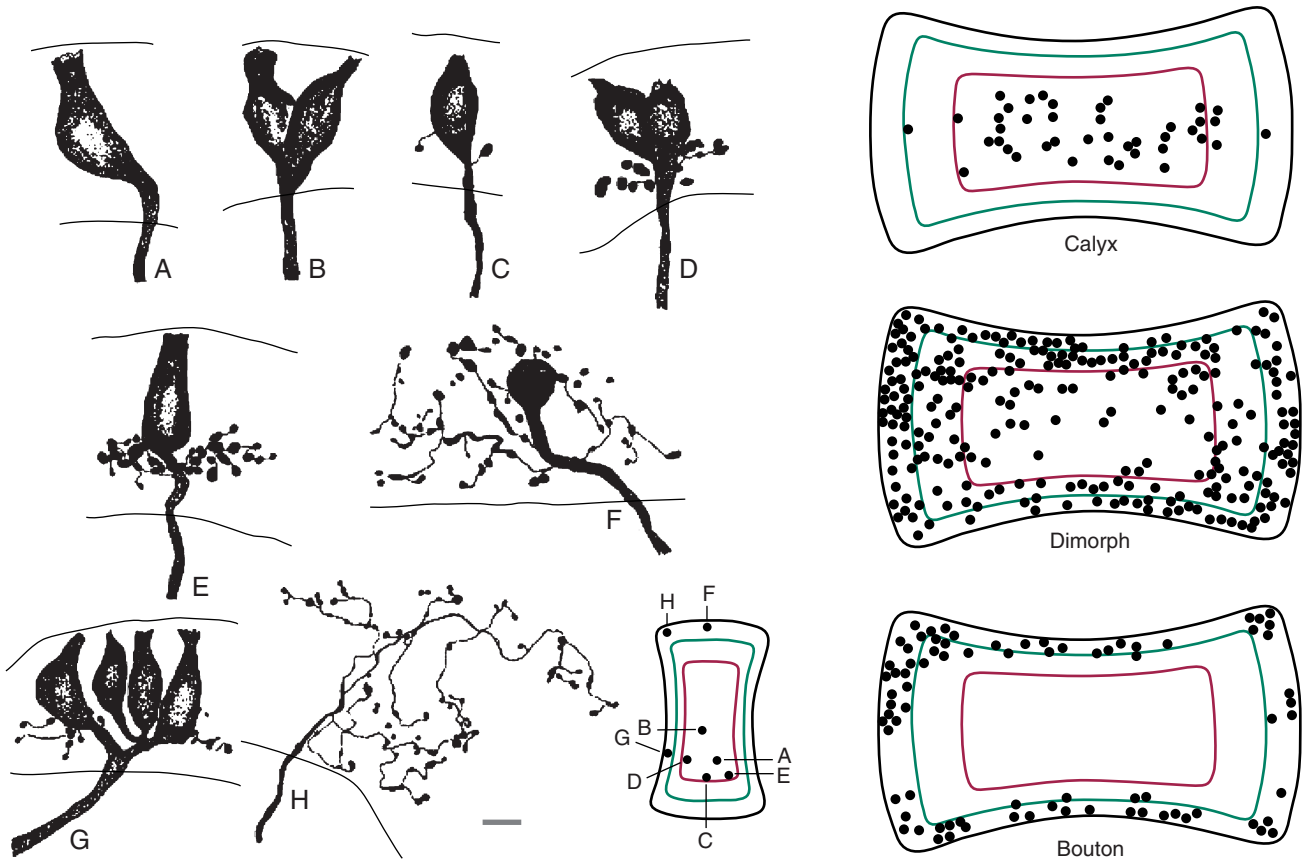

Figure 163-11. Morphology of mammalian vestibular afferents as revealed by horseradish peroxidase labeling of individual units in the chinchilla. **A,** Calyx fiber innervating a single type I hair cell. **B,** Calyx fiber innervating two type 1 hair cells. **C** to **G,** Dimorphic fibers innervate both type 1 and 2 hair cells. **H,** Bouton fiber. *Inset*: Locations of these afferents are placed on a standard map of the crista. *Right*: Three standard maps of the cristae divided into concentrically arranged central (*inside red border*), intermediate, and peripheral (*outside green*) zones of equal areas. Shown are the locations of calyx, dimorphic, and bouton fibers, with each colored dot representing a single dye-filled fiber. Dimorphic units make up 70% of the population, bouton units 20%, and calyx units 10%. *(From Fernandez C, Baird RA, Goldberg JM. The vestibular nerve of the chinchilla. I. Peripheral innervation patterns in the horizontal and superior semicircular canals.* J Neurophysiol. *1988;60:167.)*

so that cupular deflection is proportional to head *velocity*. This is demonstrated in Figure 163-10C: Note that the cupula's predicted response is not in phase with the sine wave that describes head acceleration (red). Rather, the cupula's motion appears to peak one-fourth cycle in advance of the head's motion. This 90-degree phase advance in the cupula's motion can be represented by a cosine wave, which is the integral of the sine wave. The endolymph and cupula thus act as a mechanical integrator of the input head acceleration. The integral of acceleration is velocity, so the important point here is that the cupula encodes head velocity over its physiologically relevant frequency range, even though the stimulus acting on the endolymph is head acceleration. Because of this, and because retinal image slip velocity is an important determinant of visual acuity, clinical and experimental tests conventionally report findings with respect to head velocity.

Response of the Otoconial Membrane

An approach similar to the analysis of cupular motion yields an equation relating the predicted movement of the otoconial membrane to head acceleration.[4] Unfortunately, the otoconial membrane is an inhomogeneous structure whose complexities make it difficult to estimate the physical parameters in the model that would predict its responses under different conditions. The membrane consists of the dense otoconial layer on top, a stiff mesh layer in the middle, and an elastic gel layer on the bottom.[19] At the macular surface it is presumably fixed. It is unclear how tightly otoconial displacement is coupled to the motion of the stereocilia. These uncertainties lead to models that variously predict that the otoconial membrane responds to linear acceleration or velocity, but the actual behavior remains unresolved.[17,20]

Encoding by the Afferents

Morphologically, mammalian vestibular afferents can be grouped into calyceal, bouton, and dimorphic fibers[21-23] (Fig. 163-11). Calyceal fibers (see Fig. 163-11A and B) form chalice-shaped calyx synapses on one or several neighboring type 1 hair cells. Each calyx engulfs the basolateral membrane of the enclosed type 1 hair cell(s). At the other end of the morphological spectrum, a bouton fiber (see Fig. 163-11H) forms 15 to 100 button-like synapses on multiple type 2 hair cells distributed over 25 to 75 µm. Dimorphic fibers (see Fig. 163-11C to G) include 1 to 4 calyceal synapses with type 1 hair cells and 1 to 50 bouton-type synapses with type 2 hair cells. The spatial distribution of afferent endings within the sensory neuroepithelium differs for these three different morphologic groups (shown to the right in Fig. 163-11). Calyceal afferents in the crista are found exclusively in the central zone (on the top of the crest) and in the macula exclusively in the striola. Bouton fibers mostly arborize in the peripheral zone of the crista and in the extrastriolar zones of the maculae. Dimorphic afferents innervate all regions of the vestibular sensory epithelia, and are the dominant fiber type.[22-24]

In mammals, physiologic response characteristics segregate vestibular nerve afferent fibers into two classes based on the regularity in the spacing of spontaneous action potentials[25] (as reviewed by Goldberg and Fernández[26]). *Regular afferents* (Fig. 163-12A) fire at 50 to 100 spikes/second at rest, with very little variation in resting rate for a given

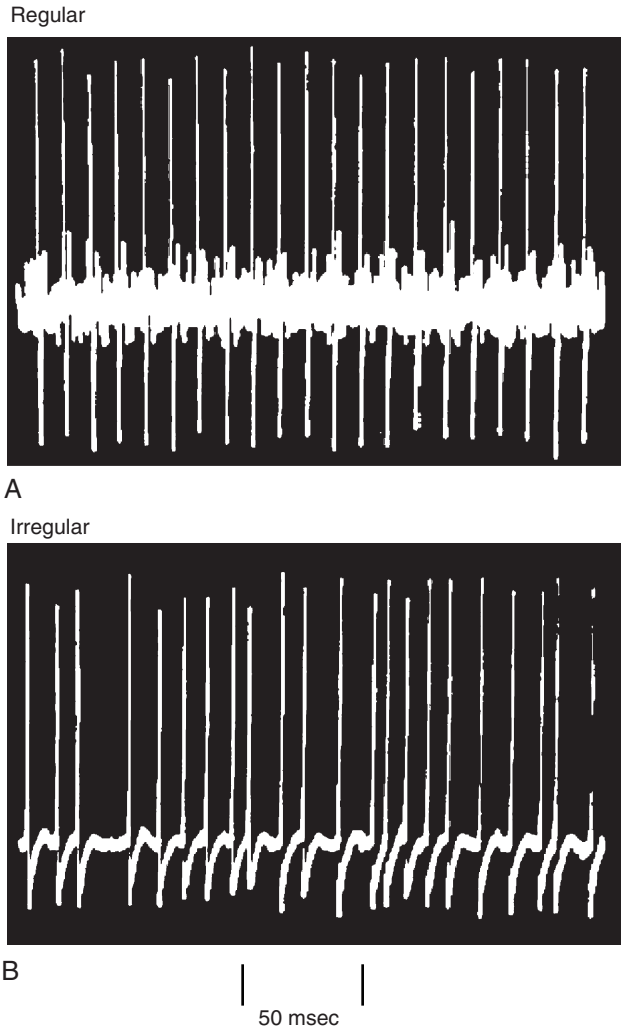

Figure 163-12. Regular (**A**) and irregular (**B**) discharge patterns in the spike trains recorded from two afferents from the superior canal crista in the squirrel monkey. *(From Goldberg JM, Fernandez C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. I. Resting discharge and response to constant angular accelerations.* J Neurophysiol. *1971;34:635.)*

fiber.[27,28] In general, they respond to vestibular stimulation with *tonic* responses. That is, their firing modulates about the baseline, going up and down in close approximation to the stimulus acting on the hair cells. For the otolith organs, the presumed stimulus acting on the hair cells is linear acceleration. The regular afferents in the macula fire in close approximation to linear acceleration.[29,30] For the semicircular canals, the effective stimulus acting on the hair cells turns out to be rotational *velocity*, not acceleration, as explained earlier and in the Appendix. Regular afferents innervating the crista respond with firing rate variations that closely approximate that head velocity signal. Regular units typically have a relatively low sensitivity (change in spike rate for a change in stimulus) to head rotation, to activation of efferent pathways, and to galvanic stimulation.[27,29,31,32] Regular afferents typically have medium or thin axons with bouton-only or dimorphic arborizations in the peripheral zones of cristae or otolithic maculae.[27,33-35]

In contrast with regular vestibular afferents, *irregular afferents* typically are thick to medium-sized axons that end in calyceal or dimorphic terminals in the central (or *striolar*) zones of vestibular endorgans.[27,32-35] Their interspike intervals are much more variable (see Fig. 163-12B). As a population, irregular afferents have a wider range of spontaneous rates than do regular fibers. Irregular units show *phasic* responses to the stimulus acting on the endorgan. That is, the response is more transient, and it approximates the rate of change of the stimulus acting on the endorgan rather than simply the stimulus itself. Thus, irregular units in the crista approximate the head's rotational *acceleration*, which is the rate of change of velocity.[27,29,31] Irregulars in the macula approximate the linear *jerk*, the derivative of linear acceleration.[29,30] Irregular units may have very high sensitivity to vestibular stimuli, except for a unique group of low-sensitivity calyx units in the crista, whose function is still unclear.[25] Sensitivities to activation by efferent pathways and to galvanic stimulation also are generally greater for irregular afferents.[26,36]

Smith and Goldberg[37] have described a model of vestibular nerve afferent spike-initiation dynamics that accounts for many of these observed differences between classes of afferent discharge (Fig. 163-13). After the peak of an action potential (caused by inward sodium currents), outward potassium currents briefly hyperpolarize the vestibular afferent membrane. The potassium conductance decays in a time-dependent manner, and the membrane potential rises again toward the threshold voltage for spike generation. Excitatory postsynaptic potentials (EPSPs) due to synaptic neurotransmitter release superimpose on this repolarization. The model assumes that variations in this potassium conductance between different afferents accounts for their regularity of discharge. In regularly discharging afferents, the model proposes that a

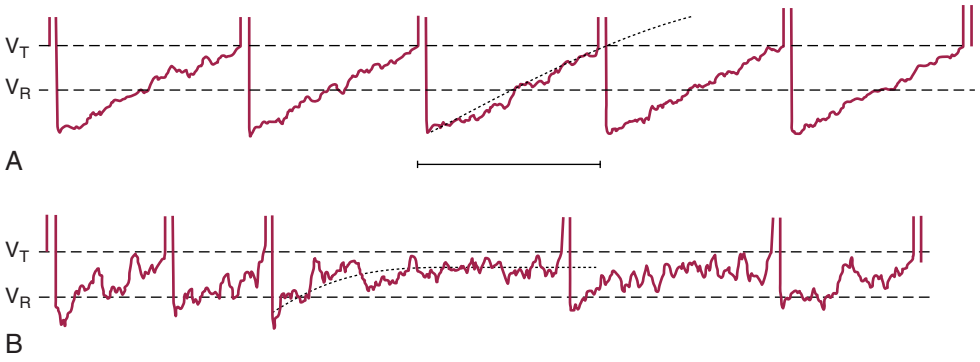

Figure 163-13. The stochastic afterhyperpolarization (AHP) model of repetitive discharge in vestibular afferents. V_R, resting potential; V_T, threshold for spike generation. Two model units are shown with their mean interspike trajectories *(dotted lines)*. **A,** The unit at the top has a regular discharge because of its deep and slow AHP and relatively small miniature excitatory postsynaptic potentials (EPSPs). **B,** The bottom unit is irregular because its AHP is shallow and fast, and its miniature EPSPs are somewhat larger than those in **A.** Note that regular discharge is associated with the mean trajectory eventually crossing V_T at regular intervals. For the irregular discharge, the mean trajectory does not cross V_T, and the actual unit potential crosses V_T only when sufficient EPSPs are added to the mean trajectory. As a result, the timing of spikes in the regular unit is largely determined by the mean trajectory, whereas timing for the irregular unit's spikes is largely determined by synaptic noise. *(Data from Smith CE, Goldberg JM. A stochastic afterhyperpolarization model of repetitive activity in vestibular afferents.* Biol Cybern. *1986;54:41.)*

large potassium conductance decays slowly but inexorably, so that the repolarization continues in a deterministic fashion until the membrane potential again reaches firing threshold (see Fig. 163-13A). The model assumes that quanta of neurotransmitter released from hair cells cause relatively little variation in the trajectory of the repolarization. This deterministic nature of the repolarization means that the membrane reaches the threshold for another spike at almost the same time for each spike. Thus, the interspike intervals are all similar, and the unit's discharge is regular. By contrast, in irregularly discharging afferents, the model assumes a potassium conductance that is high initially but decays rapidly so that it does not carry the membrane potential back up to the threshold for firing by itself (see Fig. 163-13B). These fibers sit just below threshold voltage until driven above it by the added potential due to EPSPs. Neurotransmitter release and EPSPs are quantal and random, so that the time at which the membrane reaches firing potential is highly variable from spike to spike. Thus, the unit's discharge is irregular.

These firing characteristics of the different classes of afferents may be dictated by morphologic and biochemical specializations of their membranes. The variation in discharge regularity is best correlated with the position of the afferent's endings in the neuroepithelium. Irregular units arise from the central zone of the crista or striola of the macula, and regular units arise from the peripheral zone of the crista or extrastriola of the macula. These variations may be due to regional variations in the ion channels that govern interspike intervals.[25] Alternatively, the correspondence between afferent discharge regularity and the number of hair cells with which an afferent forms synapses suggests that discharge regularity may be due in part to combining inputs from many stochastically independent synapses.[38]

Because regular and irregular vestibular nerve afferent fibers have distinct characteristics in so many respects, it seems likely that they mediate different functions.[25] One hypothesis holds that regular and irregular afferents may help compensate for different dynamic loads of the different vestibular reflexes. Regular afferents carry signals roughly in phase with head velocity, the expected output of the mechanics of the semicircular canals (as described; see also the Appendix). Irregular units with high gains have responses more in phase with head acceleration than velocity. The VOR for low-frequency head rotations requires a signal that approximates head velocity, and the regular afferents seem to provide an ideal input for this reflex.[39] By contrast, the VSRs involve very different mechanical loads and may require inputs from the labyrinth that better reflect the head's acceleration, a task to which the irregulars seem better suited.[40] Anatomically, regular and irregular afferents overlap extensively in their distributions to the central vestibular nuclei.[41-43] However, physiologic evidence suggests that there is some segregation of regular and irregular inputs between central projections to the ocular motor centers and the spinal motor centers.[44,45] Another role for the irregular afferents may be to initiate the vestibular reflexes with a very short latency for rapid head movements.[46] Finally, some evidence suggests that the dynamics of irregular afferents are better suited to provide the modifiable component of the VOR when gain must be changed rapidly. Examples are the higher gain needed when the eyes are verged on a near target,[47,48] the change needed to adapt to magnifying or "minifying" spectacles,[49,50] and the adaptation that must occur on one side when function is lost on the other side.[51,52]

In addition to more than 10,000 afferents, each labyrinth also receives efferent innervation from approximately 400 to 600 neurons that lie on either side of the brainstem adjacent to the vestibular nuclei.[53,54] Highly vesiculated efferent endings synapse onto type 2 hair cells and onto the axons of vestibular afferents.[55-57] In mammals, excitation of efferents causes an increase in the background discharge of vestibular afferents, particularly irregular ones.[26] Mammalian efferents can be activated by high head velocities.[58] In fish, vestibular efferents can be activated during behavioral arousal in which head movement would be anticipated.[36] These observations have led to the hypothesis that the efferents may serve to raise baseline afferent firing rates, particularly of irregular afferents, in anticipation of rapid head movements so as to prevent inhibitory silencing.[26,36] Yet Cullen and Minor[59] found that in alert monkeys, afferents responded identically to actively and passively generated rapid head-on-body rotations, making an efferent role in such brief movements unlikely. These investigators hypothesized that vestibular efferents may act to balance firing between the two labyrinths, a role that may be particularly important after some degree of loss of unilateral function.

Principle 3: Stimulation of a Semicircular Canal Produces Eye Movements in the Plane of that Canal

This important principle often is referred to as *Ewald's First Law*. Ewald cannulated the individual membranous canals in pigeons and observed the effects of endolymph motion on body, head, and eye movements. Although Ewald may have codified this principle on the basis of his work,[60] it is clear that earlier workers like Flourens and Mach recognized that manipulations of an isolated semicircular canal in experimental animals produced eye or head movements in the plane of that canal.[61]

Anatomic and Physiologic Basis

The anatomic basis of this principle begins with the anatomy of the semicircular canals. The arrangement of the canals places fluid motion sensors at the ends of relatively long, slender, fluid-filled, donut-shaped tubes. Each tube lies more or less in one plane. The most effective stimulus to move the fluid in such a planar semicircular tube is angular acceleration in that plane, about an axis perpendicular to the plane and through the center of the "donut hole."

The three semicircular canals of the labyrinth are roughly orthogonal to each other, so that one labyrinth can sense any rotation in three-dimensional space. Canals in the two labyrinths are arranged in complementary, coplanar pairs.[62] The two horizontal canals are roughly in one plane, which is nearly horizontal when the head is in an upright position. The left anterior canal is roughly coplanar with the right posterior canal in the *LARP* (left anterior–right posterior) plane, which lies approximately 45 degrees off the midsagittal plane with the anterior end toward the left and the posterior end toward the right. And the right anterior canal is roughly coplanar with the left posterior canal in the *RALP* (right anterior–left posterior) plane, again roughly 45 degrees off the sagittal plane and orthogonal to the LARP and horizontal planes (Fig. 163-14). These canal planes define the cardinal coordinate system for vestibular sensation.

The power of this principle goes beyond the notion that the canal planes simply provide a coordinate system for vestibular *sensation*. Canal planes also provide the coordinate system for the final *motor output* of the VOR (and for the vestibulo-colic neck reflex). The beauty of this canal-fixed (and thus head-fixed) coordinate system for eye movements is that it reduces the neural computation required for ocular motor output to exactly compensate for the head movement.

How is this coordinate system preserved in the central connections of the VOR? Figure 163-15 shows the connections from the left horizontal canal that mediate the VOR when that canal is excited. We have already seen how this movement excites the afferents from this canal; the inset demonstrates this increase in firing from the baseline rate. Secondary vestibular neurons in the ipsilateral vestibular (medial and superior) nuclei receive these afferent signals and connect to the ocular motor nuclei controlling the medial and lateral rectus muscles, which also lie roughly in a horizontal plane. Secondary vestibular neurons carry excitatory signals to the ipsilateral third nucleus and contralateral sixth nucleus to excite the ipsilateral medial rectus and contralateral lateral rectus, respectively. These muscles pull the eyes toward the right as the head turns toward the left, accomplishing the goal of keeping the eyes stable in space. Other secondary vestibular neurons carry inhibitory signals to the contralateral third and ipsilateral sixth nuclei to simultaneously relax the antagonist muscles, the contralateral medial rectus and the ipsilateral lateral rectus, respectively. This reciprocal activity is typical of the extraocular muscles, which work in contraction-relaxation pairs.[63]

Just as the extraocular muscles work in reciprocal pairs, so too do the coplanar semicircular canals. Like the left horizontal canal, the right horizontal canal is also stimulated by the horizontal head turn (Fig. 163-16). However, because the polarity of stereociliary bundles in the

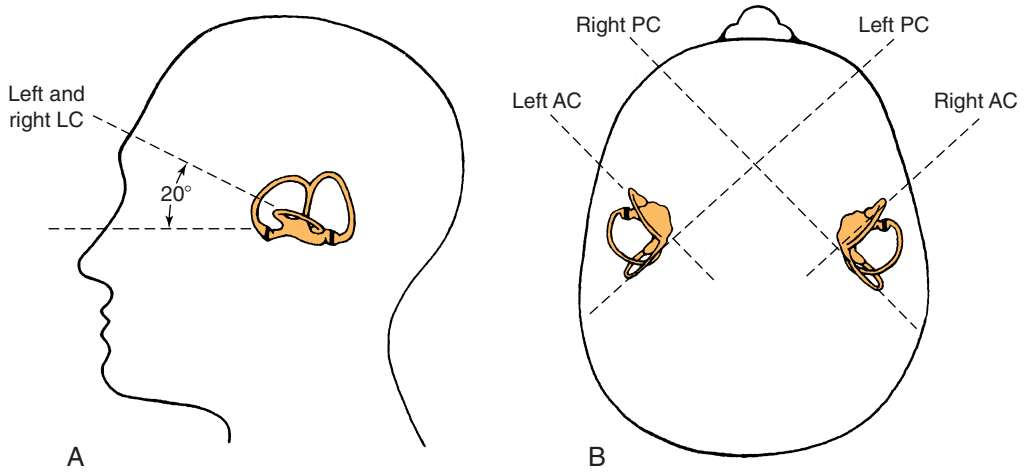

Figure 163-14. Orientation of the semicircular canals. **A,** When the head is upright, the horizontal canal (or lateral canal [LC]) is tilted approximately 20 degrees upward from the horizontal plane at its anterior end. **B,** The vertical canals are oriented in planes roughly 45 degrees from the midsagittal plane. The right anterior canal (AC) and left posterior canal (PC) lie in the same plane, the right anterior–left posterior (RALP) plane. The left anterior and right posterior canals lie in the left anterior–right posterior (LARP) plane. *(Adapted From Barber HO, Stockwell CW.* Manual of Electronystagmography. *St Louis: Mosby; 1976.)*

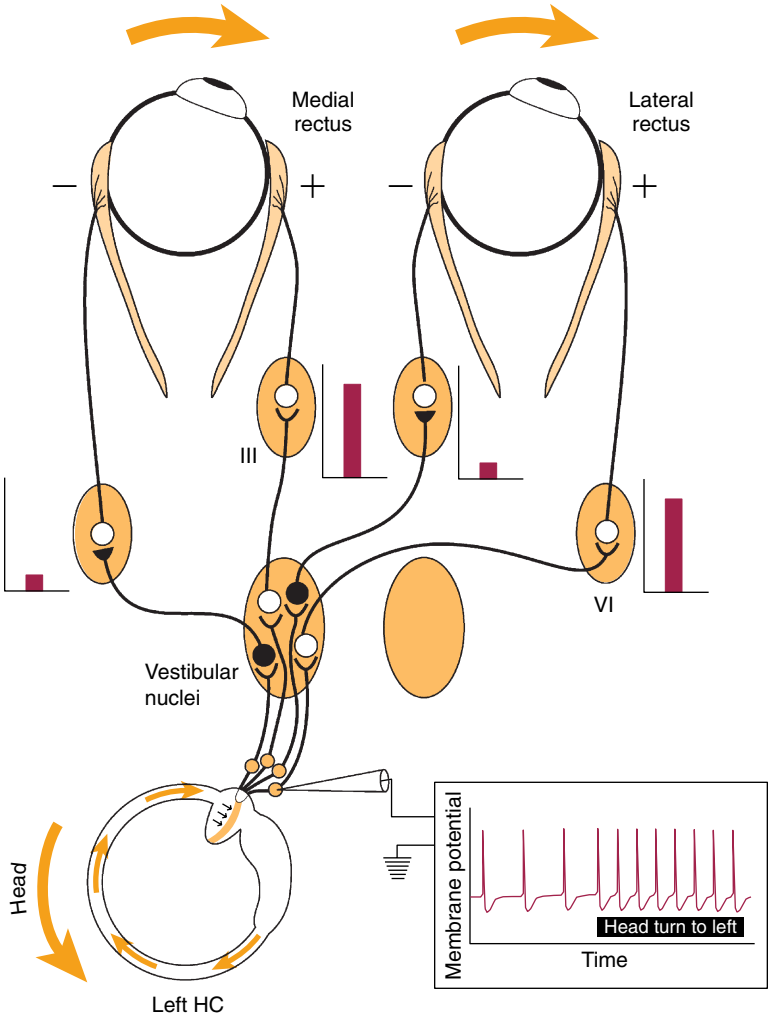

Figure 163-15. Neural connections in the direct pathway for the vestibulo-ocular reflex (VOR) from excitation of the left horizontal canal (HC). As seen from above, a leftward head rotation produces relative endolymph flow in the left HC that is clockwise and toward the utricle. The cupular deflection excites the hair cells in the left HC ampulla, and the firing rate in the afferents increases *(inset)*. Excitatory interneurons in the vestibular nuclei connect to motor neurons for the medial rectus muscle in the ipsilateral third nucleus (III) and lateral rectus muscle in the contralateral sixth nucleus (VI). Firing rates for these motor neurons increase *(mini bar graphs)*. The respective muscles contract and pull the eyes clockwise, opposite the head, during the slow phases of nystagmus. Inhibitory interneurons in the vestibular nuclei connect to motoneurons for the left lateral rectus and right medial rectus. Their firing rates decrease, and these antagonist muscles relax to facilitate the eye movement.

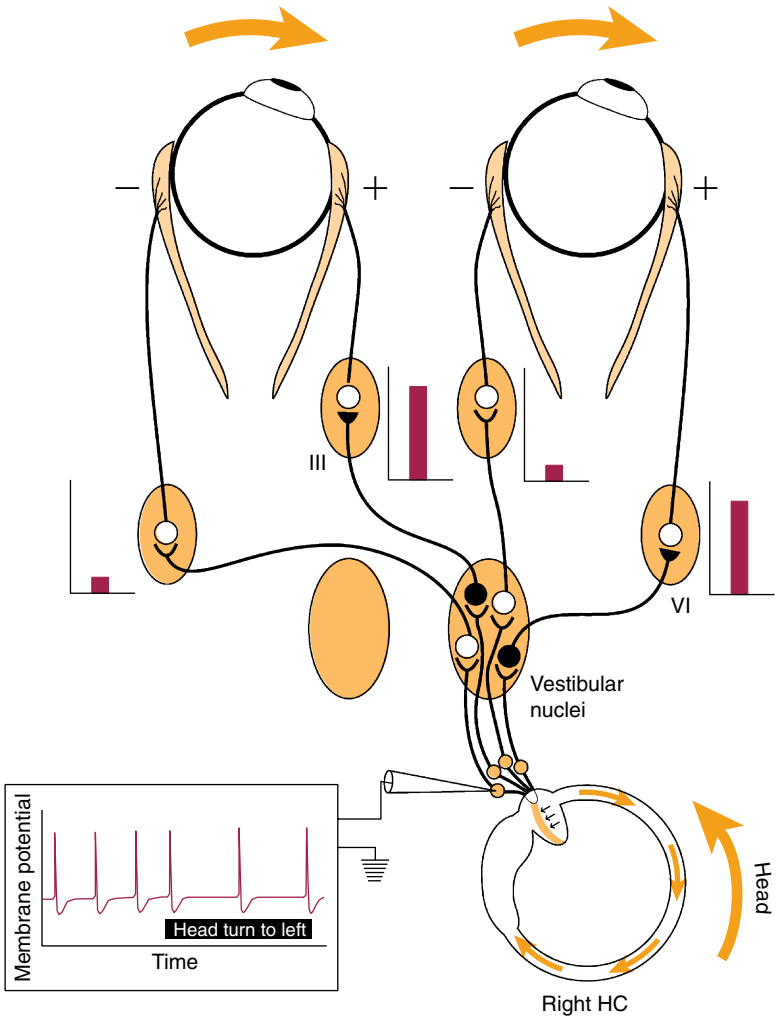

Figure 163-16. Complementary neural connections in the direct pathway for the vestibulo-ocular reflex (VOR) from inhibition of the right horizontal canal (HC). As seen from above, a leftward head rotation again produces relative endolymph flow that is clockwise in the canal. However, for the right HC, this flow is away from the utricle. The cupular deflection inhibits the hair cells in the right HC ampulla, and the firing rate in the afferents decreases *(inset)*. Inhibitory interneurons in the vestibular nuclei reverse this inhibition, sending further excitatory signals *(mini bar graphs)* to the motorneurons for the medial rectus muscle in the ipsilateral third nucleus (III) and lateral rectus muscle in the contralateral sixth nucleus (VI). The contraction of these muscles is augmented. Simultaneously, excitatory interneurons *(open circles)* in the vestibular nuclei preserve and convey inhibition *(mini bar graphs)* to motoneurons for the lateral rectus muscle in the left sixth nucleus (VI) and medial rectus muscle in the right third nucleus (III). The inhibitory signals further relax these antagonist muscles.

right horizontal canal is a mirror image of the arrangement on the left, the flow of endolymph with respect to the head, still clockwise as seen from above, has an *inhibitory* effect on the right horizontal canal afferents. Connections from the right vestibular nuclei to the ocular motor nuclei also mirror those on the left. With the inverse signals coming through this mirror-image circuit from the right side, the ocular motor nuclei receive greater excitatory stimuli for the right lateral and left medial rectus muscles, and more inhibition for their antagonists. Thus, head rotation produces an excitatory contribution to the VOR from one canal and an inhibitory contribution from its coplanar mate. This often is referred to as the "push-pull" arrangement of the canals. Thanks to the nonzero baseline firing rate of vestibular afferent neurons, both of the canals in a coplanar pair can encode rotational acceleration in that plane.

Like the horizontal canals and the lateral and medial recti, the vertical semicircular canals are linked to the vertical pairs of eye muscles, a fact that helps explain the pulling directions and insertions of the superior and inferior oblique muscles. Figure 163-17 demonstrates that the LARP plane aligns with the pulling directions of the left superior and inferior rectus muscles as well as the right superior and inferior oblique muscles. The connections from the secondary vestibular nuclei can be traced, just as shown in Figures 163-15 and 163-16. The important result is indicated by the contrast coding in Figure 163-17. Excitation of the left anterior canal (shading) and inhibition of the right posterior canal (shading) result in contraction of the muscles that pull the eyes upward in the LARP plane and relaxation of the muscles that pull them downward in that plane. Similarly, the RALP plane aligns with the pulling directions of those vertical eye muscles that move the eyes in the RALP plane.

The alignment of canal planes and extraocular muscle planes is not exact, and the excitation of a single canal pair does not solely produce activity in a dedicated pair of extraocular muscles. Other muscles must be activated to compensate for a head rotation even when it is purely in the plane of one semicircular canal. However, this arrangement between semicircular canals and extraocular muscles is remarkably constant across vertebrate species, even allowing for the shift between lateral-eyed species (e.g., rabbits) and frontal-eyed ones (e.g., humans). Because the vestibular labyrinth evolved before movable eyes,[64] extraocular muscles may have evolved to pull in the preexisting canal planes. Robinson[65] has argued that there is an evolutionary advantage to keeping the extraocular muscles aligned with the semicircular canals. Such an arrangement minimizes the brainstem processing

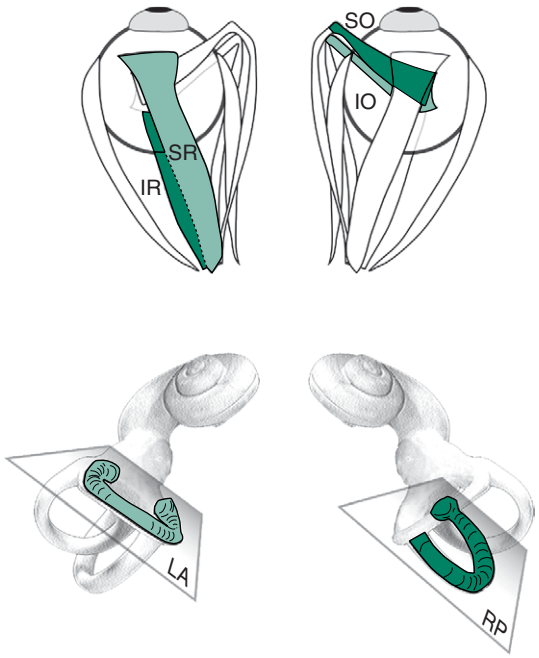

Figure 163-17. The left anterior–right posterior canal (LARP) plane aligns with the pulling directions of the left superior rectus (SR) and inferior rectus (IR) muscles, as well as the right superior oblique (SO) and inferior oblique (IO) muscles. As indicated by the shading, excitation of the left anterior canal (and inhibition of the right posterior canal) causes contraction of the left superior rectus and right inferior oblique muscles and relaxation of the darker-shaded antagonists. The result will be an upward movement of the eyes in the LARP plane. Excitation of the right posterior canal will produce the opposite effect.

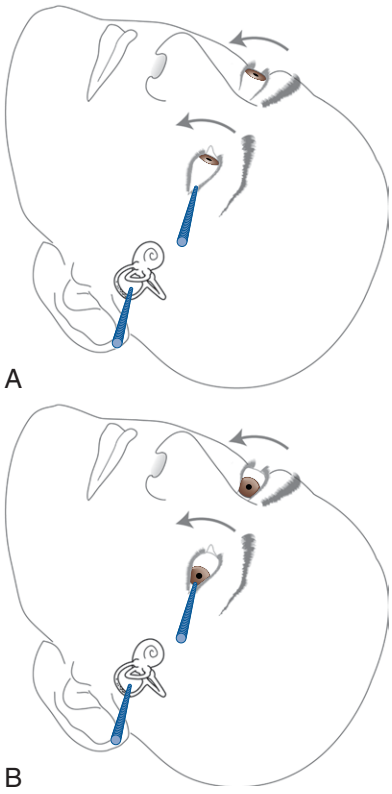

Figure 163-18. Excitation of the left posterior canal (PC) by moving canaliths in benign paroxysmal positional vertigo (PC-BPPV) causes slow phase eye movements downward in the plane of the affected PC. The eyes rotate around an axis parallel to the one going through the center of the affected PC. **A,** When gaze is directed perpendicular to the axis of eye rotation, the pupil appears to move up and down in an eye-fixed reference frame. **B,** When gaze is directed parallel to the axis of eye rotation, the pupil appears to move torsionally in an eye-fixed reference frame. In either case, the eyes rotate around the same axis when considered in a canal-fixed frame of reference.

needed to activate the appropriate ensemble of eye muscles to compensate for head movement. Minimizing the number of synapses involved in the reflex preserves its remarkably short latency of approximately 7 msec,[66] which in turn minimizes retinal image slip during very rapid head movements.

Clinical Importance

Because of the primacy of the canals in determining how the eyes move under vestibular stimulation, it is helpful to think about vestibular eye movements in a *canal-fixed frame of reference*. A good example of the power of this approach is in investigation of benign paroxysmal positional vertigo (BPPV). In the most widely accepted current model of BPPV, otolith crystals displaced from the utricular otoconial mass come to rest in one of the semicircular canals (typically the posterior semicircular canal).[67] When the patient lies down and turns the head toward the affected side, aligning the posterior canal (PC) with the pull of gravity (the left Dix-Hallpike maneuver), the otolith crystals fall toward what is now the "bottom" of the canal. As the otoliths fall, they push endolymph ahead of them, causing cupular deflection and exciting hair cells on the posterior canal crista. Nystagmus develops during the time that endolymph moves. Ewald's First Law predicts the direction of that nystagmus: It will be in the plane of the affected posterior canal, independent of pupil position or head position.

Trying to apply this principle to PC-BPPV confuses many novice examiners. They observe instead that the nystagmus seems to change direction depending on where the patient directs the gaze. When the patient looks out to the side (toward the affected ear), the examiner sees a primarily torsional movement of the eyes. When the patient looks up toward the ceiling (away from the affected ear), the eyes appear to move vertically (Fig. 163-18). With the eyes in a neutral position (straight-ahead gaze), the nystagmus is a mixture of vertical and torsional movements. How can the principle be valid if the nystagmus changes directions?

In reality, no change occurs in the direction of the nystagmus with respect to the canal planes; it is a figment of the wrong frame of reference. In examining eye movements, we are accustomed to thinking in an eye-fixed reference frame in which the line of sight (the line extending forward from the pupil) determines what is up, down, left, right, clockwise, and counterclockwise relative to that axis. But Ewald's First Law demands that we abandon this oculocentric view of eye movements and instead see them in a canal-centric view. In this view, the location of the pupil does not matter. The globe continues to rotate around the axis parallel to the one passing perpendicularly through the posterior canal that is being stimulated (shown in blue in Fig. 163-18). The pupil is simply a surface feature going along for the ride, wherever it happens to be directed. Ewald's First Law states that *the eyes will move in the plane of the stimulated canal no matter where gaze is directed*. In fact, the apparent variation in pupil movement with gaze direction during nystagmus can be used to an examiner's advantage in trying to discern which canal is affected in BPPV (or any other cause of single-canal dysfunction). By asking a patient to look parallel and perpendicular to the plane of the canal in question during periods of nystagmus, one should observe that when the pupil is in the plane of the affected canal, the nystagmus moves the pupil most obviously. This is because the pupil is at the equator of the rotating globe, where rotation will carry it the farthest. When the patient's gaze is directed perpendicular to the plane of the affected canal, the pupil is at the pole of the rotating globe, and eye movement is limited to cyclotorsion about the axis of rotation, which

can be subtle to detect. Finding these two gaze directions can identify and confirm the canal (or at least the coplanar canal pair) causing the nystagmus.

Principle 4: A Semicircular Canal Normally Is Excited by Rotation in the Plane of the Canal Bringing the Head toward the Ipsilateral Side

Anatomic and Physiologic Basis

A semicircular canal crista is excited by rotation in its plane in one direction and is inhibited by rotation in its plane in the opposite direction. Another look at Figure 163-9 shows that turning the head toward the left in the horizontal canal plane produces endolymph rotation to the left *relative to space.* But that endolymph rotation is less than the head rotation by the angle Θ. Thus, *relative to the canal*, there is endolymph rotation of Θ to the right, and the cupula is deflected toward the utricle. The pattern of afferent activation results from the polarization of the stereocilia of the hair cells on the cristae. In the horizontal canal, the taller ends of the bundles point toward the utricle. Flow of endolymph (relative to the head) toward the ampulla-ampullopetal flow (from Latin *petere*, to seek), therefore excites the horizontal canal afferents, and flow of endolymph away from the ampulla—ampullofugal flow (from Latin *fugere,* "to flee")—inhibits these afferents. Thus, relative to the head, endolymph flow toward the ampulla occurs when the head is turning in the plane of the horizontal canal toward the same side.

The vertical canals, however, have the opposite pattern of hair cell polarization. The taller ends of the bundles point away from the utricle, so that flow away from the ampulla (ampullofugal) excites their afferents. For the left anterior canal, whose ampulla is at its anterior end, turning the head down and rolling it to the left in the plane of the left anterior canal results in relative endolymph flow that is ampullofugal. For the left posterior canal, whose ampulla is at its posterior end, turning the head up and rolling it to the left in the plane of the left posterior canal moves its endolymph away from the ampulla and excites its afferents. The mirror-image rotations would pertain to the right vertical canals.

Fortunately, keeping track of ampullopetal and ampullofugal flows is unnecessary. Instead, one need only recall that a semicircular canal is excited by rotation in the plane of the canal bringing the head toward the *ipsilateral* side. For example, the right horizontal canal is excited by turning the head rightward in the horizontal plane. The right anterior canal is excited by pitching the head nose down while rolling the head toward the right in a plane 45 degrees off of the midsagittal plane. The right posterior canal is excited by pitching the head nose up while rolling it toward the right in a plane 45 degrees off the midsagittal plane. In the case of each semicircular canal on the right, the rotation exciting that canal brings the head toward the right in the plane of the canal. In the case of the horizontal canals, the nose is turned toward the right. In the case of the vertical canals, the top of the head is rotated toward the right.

It should be obvious by now that a semicircular canal is inhibited by rotation in the plane of the canal toward the opposite side. As described previously, the arrangement of canals is such that when head rotation excites one, it inhibits its coplanar mate. Thus, the rotations explained in the last paragraph would produce inhibition of the left horizontal, posterior, and anterior canals, respectively.

Clinical Importance

This principle eliminates the need to memorize the orientations of stereocilia in particular ampullae and whether ampullopetal or ampullofugal flow excites a given canal. In fact, it is easier to deduce the basic anatomy and physiology from this principle than vice versa. For example, rolling the head toward the left and bringing the nose up excites the left posterior canal according to Principle 4. As noted earlier, endolymph flows relative to the membranous canal in a direction opposite to the head rotation. Thus, the left posterior canal is excited when endolymph flows upwards and toward the right in the canal—that is, ampullofugal. The stereocilia of this canal must be polarized with the tall ends away from the utricle. A considerable amount of anatomy and physiology is condensed into this simple principle.

Principle 5: Any Stimulus That Excites a Semicircular Canal's Afferents Will Be Interpreted as Excitatory Rotation in the Plane of That Canal

Anatomic and Physiologic Basis

Perhaps because the VOR is critical to the survival of any vertebrate that needs to see and move about its environment, evolution appears to have placed a high premium on maintaining parsimonious and rapid neural connections of head rotational sensors to eye muscles. This allows for optimal performance when the system is working normally. However, by devoting dedicated lines of communication from the canals to the extraocular muscles, nature has effectively made the eyes slaves to the vestibular system. Designed, as it is, to expeditiously and reliably produce the eye movements needed to counter a sensed head movement, the system cannot help but produce those eye movements when the vestibular afferent firing rate changes from some other cause. Likewise, the systems mediating postural reflexes and perception of spatial orientation will respond to pathologic alterations in peripheral vestibular input in the same way that they do to tilting or translational movement. An important point is that the brainstem (and patient) will interpret any change in firing rate from vestibular afferents as indicating head rotation, tilt, or translation that would normally produce that same change in firing rate. Secondary vestibular neurons relay the same misinformation to other reflex control centers and higher areas of conscious sensation. This leads to autonomic and postural disturbances as well as the noxious sensation of *vertigo*, an illusion of self-motion.

A pathologic asymmetry in input from coplanar canals causes the eyes to turn in an attempt to compensate for the "perceived" head rotation. However, given the mechanical constraints imposed by the extraocular muscles, the eyes cannot continue to rotate in the same direction that the canals command for very long. Instead, rapid, resetting movements occur, taking the eyes back toward their neutral positions in the orbits. The result is *nystagmus*, a rhythmic, slowly forward–quickly backward movement of the eyes. The quick resetting movements (similar to saccades) are *quick phases* of nystagmus, and the vestibular-driven slower movements are *slow phases*. Unfortunately, convention dictates that nystagmus direction is described according to the direction of the quick phases, because these are more dramatic and noticeable. However, an important pont is that the slow phases are the *components driven by the vestibular system*. By focusing on the direction of slow phases, one reduces the number of mental inversions required to identify the pathologic canal causing an observed nystagmus.

This principle holds almost universally true for brief, unpredictable changes in afferent firing, but not necessarily for persistent stable changes. Fortunately, the nystagmus caused by sustained imbalances in afferent vestibular tone eventually abates as brainstem and cerebellar neural circuitry adapt to the imbalance, as discussed later on (Principle 12). Still, this principle's explanation of responses to brief changes in labyrinthine activity provides a powerful clinical diagnostic tool in localizing disease processes to individual canals.

Clinical Importance

Posterior Canal Benign Paroxysmal Positional Vertigo

In the example of PC-BPPV introduced above, we saw how loose otoconia and endolymph flowed in an ampullofugal direction when the affected PC was oriented vertically in the Dix-Hallpike position. From Principle 4, this direction of endolymph flow excites the PC afferents. From Principle 3, the eye movements resulting from excitation of the PC will be in the plane of that PC. Principle 5 predicts the direction of the slow phases of the nystagmus in this plane. Excitation of the PC afferents will be interpreted as an excitatory rotation of the head in the plane of the PC, and the nystagmus generated would be compensatory for the perceived rotation. For the left PC, excitatory rotation consists rolling the head toward the left while bringing the nose up. To keep the eyes stable in space, the VOR generates slow phases that move the eyes down and roll them clockwise (with respect to the patient's head).

The quick phases are opposite; they beat up and counterclockwise with respect to the patient's head.

Superior Canal Dehiscence Syndrome

In another example of a disorder causing isolated stimulation of a single semicircular canal, a young woman complains that exposure of the left ear to loud sound "makes the world flutter up and down." Applying a loud sound to the left ear through a headphone causes her to develop vertigo and nystagmus. When she is directed to look 45 degrees to her left, one observes that the slow phases of her nystagmus move her pupils up and down. When she looks 45 degrees to her right, the slow phases appear to be cyclotorsional movements of her pupils clockwise (from her perspective). As she attempts straight-ahead gaze, the nystagmus becomes a mixture of these vertical and torsional movements. The examiner must think in a canal-fixed coordinate system and recognize that in each case, the eyes rotate around the same axis, or in the same plane. In this case, the eyes are moving in the LARP plane and in the direction anticipated for excitation of the left anterior canal or inhibition of the right posterior canal. Because only the left ear is receiving the sound stimulus, the problem must lie in the left anterior canal.

This is an example of *superior semicircular canal dehiscence syndrome* causing a *Tullio phenomenon*. Tullio[68] experimented with sound as a stimulus for the labyrinth in pigeons after he fenestrated their semicircular canals. He observed that this caused eye and head nystagmus in the plane of the fenestrated semicircular canal, another example of Ewald's First Law. Huizinga[69] proposed that the fenestra created a third "mobile window" in the labyrinth, in addition to the oval and round windows. This window opens another route for sound pressure dissipation in the labyrinth. This new route is along the affected canal, so endolymph moves through the semicircular canal under the influence of sound or other pressure changes applied to the oval or round windows (Fig. 163-19A). By Principle 5, the fenestrated superior canal exposed to loud sound encodes the resulting endolymph flow as it would a head rotation in the plane of the affected canal and toward the affected side. Superior canal dehiscence syndrome was only recently discovered.[70] It was the observation of nystagmus just as described here and the line of reasoning presented by Principles 1 to 5 that led investigators to suspect that the superior canal was the source of the nystagmus, which CT scanning confirmed (see Fig. 163-19B).

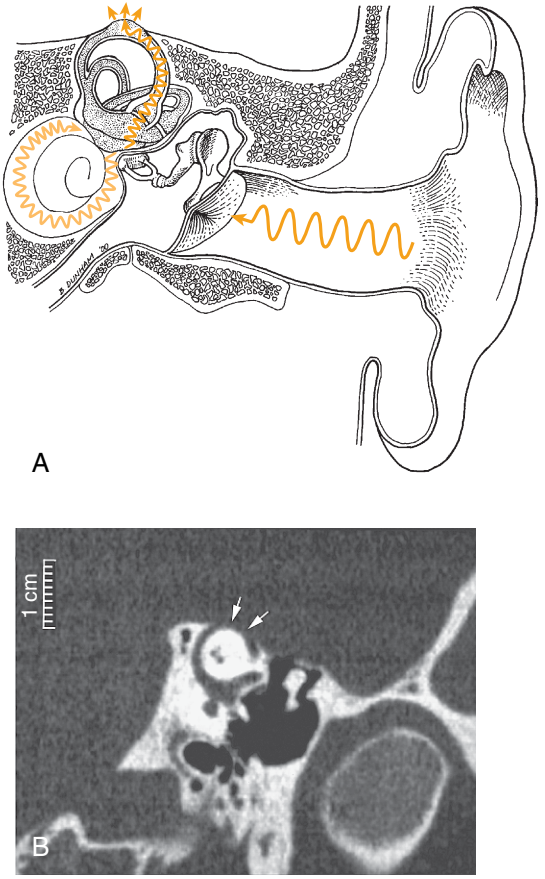

Figure 163-19. A, In superior canal dehiscence syndrome, sound waves can excite the superior canal because the "third mobile window" created by the dehiscence allows some sound pressure to be dissipated along a route through the superior canal in addition to the conventional route through the cochlea. **B,** CT scan demonstrating dehiscence *(arrows)* of the superior canal. *(Illustration courtesy of Dr. B. Dunham.)*

Nystagmus during Caloric Testing

In the caloric test, warm or cool water is irrigated in the external auditory canal. Thermal transfer across the mastoid and eardrum changes the temperature, and therefore density, of the endolymph in the lateral part of the horizontal semicircular canal. That endolymph becomes lighter (by heating) or heavier (by cooling) than the endolymph in the rest of the labyrinth. When the subject is placed supine (with the head up approximately 20 degrees) so as to bring the horizontal canal into a vertical plane, endolymph in the lateral part of the canal made lighter by warming rises toward the ampulla. This is equivalent to the movement caused by turning the head ipsilaterally in the head-horizontal plane. By Principle 4, this manuever excites that canal. By Principle 5, the compensatory eye movements, the slow phases of nystagmus, are in the horizontal canal plane and toward the contralateral side. The quick phases are directed toward the ipsilateral side. By reverse reasoning, for cool irrigation, the horizontal canal is inhibited, and the quick phases are directed toward the contralateral side. (The mnemonic COWS—*c*old *o*pposite, *w*arm *s*ame—can be used to recall the direction of the beating of the nystagmus.) A major advantage of the caloric test is that unlike rotational tests, it applies a truly unilateral stimulus. Diminished caloric responses on one side often help to localize a hypofunctional labyrinth. More details on the caloric test can be found in Chapter 164, Evaluation of the Patient with Dizziness.

Unfortunately, the caloric test has several disadvantages. Testing-predominantly stimulates the horizontal semicircular canal, and little information is provided about other canals and the otolith end organs. Judging from the nystagmus it produces, a caloric stimulus is approximately equivalent to a 5- to 10 degrees/second squared (sec^2) acceleration to a sustained horizontal rotation of approximately 50 to 100 degrees/second. The nystagmus typically persists in one direction for 120 seconds or longer. A comparable head rotation would be a half-cycle of a sine wave with a period of 240 seconds, or a frequency of 1/240 second = 0.004 Hz. This stimulus is well below the ideal operating range of the semicircular canal (see Appendix). Nevertheless, the caloric test remains one of the cornerstones of vestibular evaluation because it gives information about one labyrinth in isolation, which low-frequency rotational tests cannot do.

Principle 6: High Acceleration Head Rotation in the Excitatory Direction of a Canal Elicits a Greater Response than the Same Rotation in the Inhibitory Direction

Anatomic and Physiologic Basis

Ewald made a second important observation in his experiments in which he moved endolymph in individual semicircular canals.[60] Movement of endolymph in the "on" direction for a canal produced greater nystagmus than an equal movement of endolymph in the "off" direction. This observation, *Ewald's Second Law*, indicates an *excitation-inhibition asymmetry*. Excitation-inhibition asymmetries occur at multiple levels in the vestibular system. First, in the hair cells there is an asymmetry in the transduction process. Figure 163-20 shows that in vestibular hair cells there is a larger receptor potential response for stereociliary deflection in the "on" direction than in the "off" direction. A second asymmetry is introduced by the vestibular nerve afferents. Recall that the afferents fire even when the head is at rest, and that this firing is modulated by the hair cell responses to head acceleration after the endolymph and cupula integrate the signal to yield one representing head velocity (Principle 2). Vestibular afferents in mammals

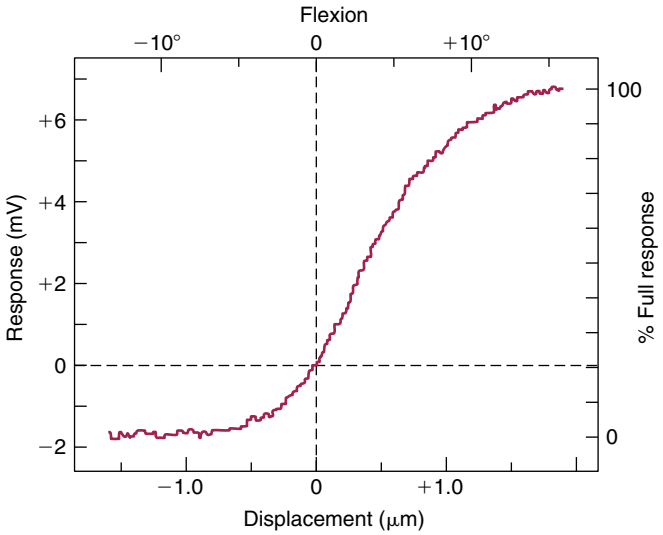

Figure 163-20. Excitation-inhibition asymmetry in the receptor potential of saccular hair cells from the bullfrog. Deflection of stereocilia in the "on" direction produces a larger change in receptor potential than does a comparable deflection in the "off" direction. *(From Hudspeth AJ, Corey DP. Sensitivity, polarity, and conductance change in the response of vertebrate hair cells to controlled mechanical stimuli.* Proc Natl Acad Sci U S A. *1977;74:2407.)*

have baseline firing rates ranging from 50 to 100 spikes/second.[25] Although these firing rates can be driven upwards to 300 to 400 spikes/second, they can be driven no lower than zero. This *inhibitory cutoff* is the most obvious and severe form of excitation-inhibition asymmetry in the vestibular system. Even in the range in which there is no inhibitory cutoff, responses for some vestibular afferents show excitation-inhibition asymmetry, with excitatory rotation causing a greater change in vestibular nerve afferent firing rate than does an equal and opposite inhibitory rotation. Using galvanic currents to stimulate vestibular afferents independent of their hair cells, Goldberg and coworkers[28] showed that this asymmetry is more marked for irregular afferents.

These peripheral asymmetries may be mostly eliminated in the central vestibular connections because of the reciprocal characteristics of signals from one side compared to another. In fact, such a combination of nonlinear sensors acting reciprocally on a symmetrical premotor system can increase the linear range of the vestibular reflexes when both sides are functioning appropriately.[72] However, nonlinearities in the VOR become pronounced when labyrinthine function is lost unilaterally.

Clinical Importance

Aw and colleagues[73] demonstrated that rapid passive rotary head movements elicit markedly asymmetrical VOR responses in humans after unilateral labyrinthectomy. These "head thrusts" are unpredictable, high-acceleration (3000 to 4000 degrees/sec^2) head rotations through amplitudes of 10 to 20 degrees. When the head is thrust in one of the semicircular canal planes so as to excite the canal on the intact side, the VOR that results is nearly compensatory for the head movement (Fig. 163-21, right panels). By contrast, when the head is thrust in one of

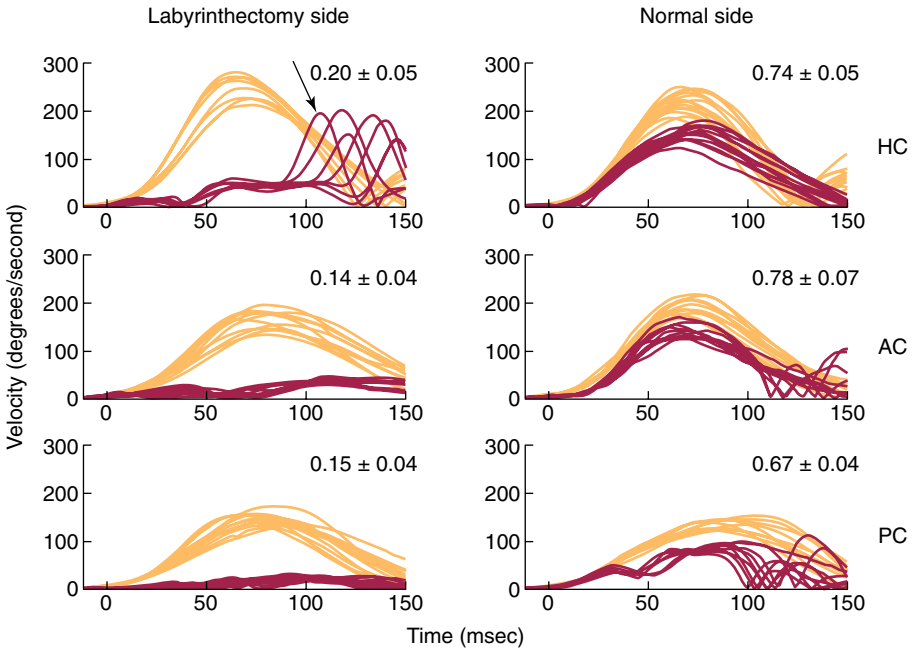

Figure 163-21. Results of head thrust testing of the angular vestibulo-ocular reflexes (aVORs) in a subject after unilateral labyrinthectomy. The examiner manually rotated the subject's head in one of the canal planes during each trial. The subject was instructed to keep his gaze fixed on a small stationary visual target 1.2 m directly in front of him. Eye and head velocities were measured with magnetic search coils. Each panel shows data for 8 to 15 trials exciting one canal. For example, the *top left panel* contains data for rotations in the plane of the horizontal canals (HCs) toward the side of the labyrinthectomy. Head velocity traces are shown in orange, and eye velocity traces are shown in red. For ease of comparison, all velocities are shown as positive values. Gain of the aVOR was defined as the peak eye velocity/peak head velocity ratio during a 30-msec window leading up to the peak head velocity. The gain (mean ± SD) for the respective canal is given in the *upper right corner* of each panel. Note that head thrusts that excited the canals on the normal side were accompanied by nearly compensatory eye movements. By contrast, head thrusts toward the labyrinthectomy side generated very minimal VORs in the period up to peak head velocity. After approximately 90 msec, the visual system registered the retinal slip and triggered a visually guided eye movement to reset gaze on the target *(arrow)*. AC, anterior canal; PC, posterior canal. *(Data from Carey JP, Minor LB, Peng GC, Della Santina CC, Cremer PD, Haslwanter T. Changes in the three-dimensional angular vestibulo-ocular reflex following intratympanic gentamicin for Meniere's disease. JARO. 2002;3:430.)*

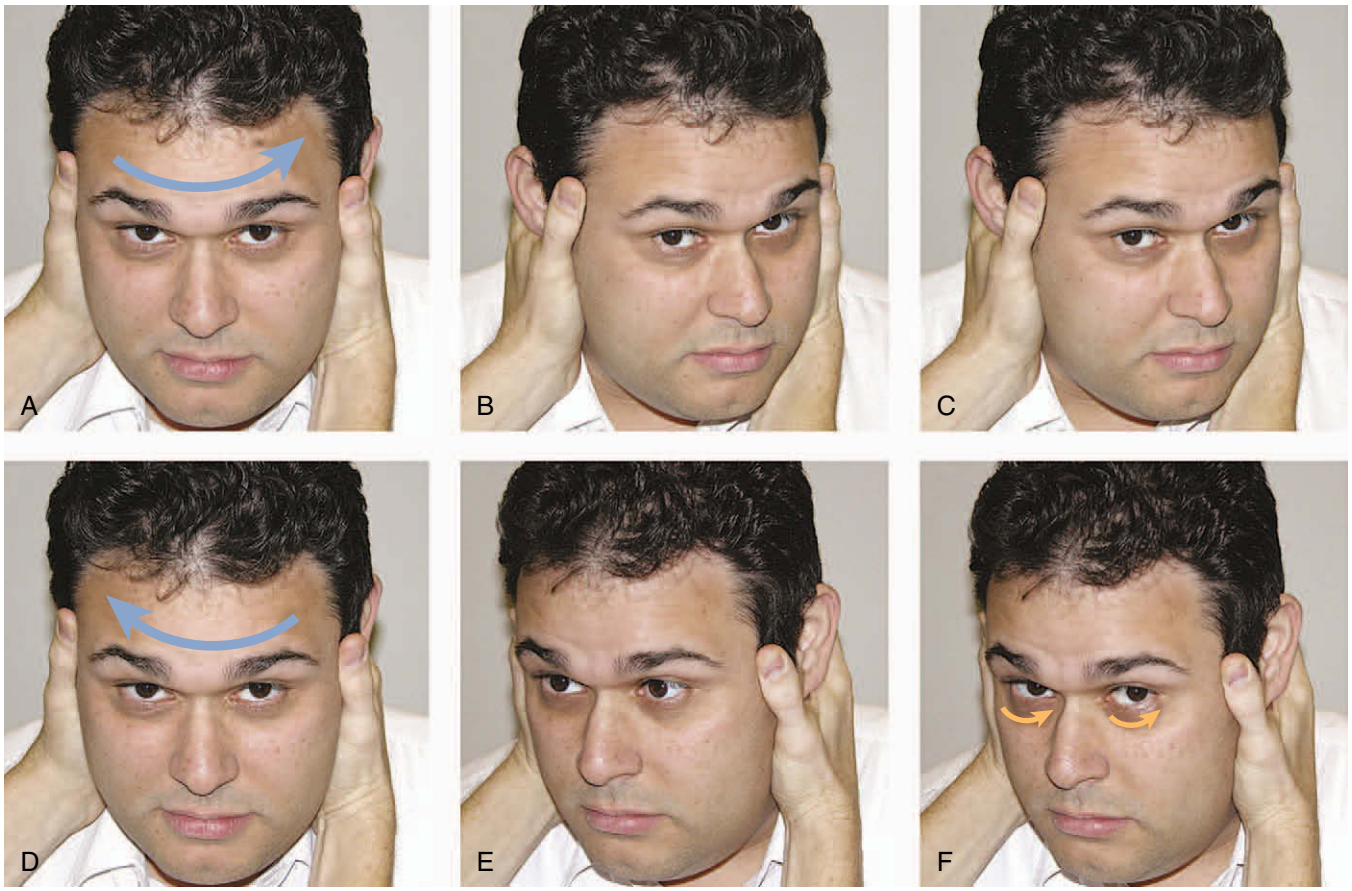

Figure 163-22. In the clinical version of the head thrust test, the examiner asks the subject to fix the gaze on the examiner's nose. The examiner rapidly turns the subject's head, but only by approximately 10 to 15 degrees; larger angles of rotation are unnecessary and may risk injury to the neck. The acceleration must be 3000 degrees/second squared (sec^2) or greater, and the peak velocity must be 150 to 300 degrees/second, meaning that the rotation must be finished in 150 msec. Photographs **A** to **C** show a head thrust to the left, exciting the left horizontal canal (HC). The eyes stay on the examiner's nose throughout the maneuver, indicating normal left HC function. Photographs **D** to **F** show a head thrust to the right, exciting the right HC. The eyes do not stay on target, but move with the head during the head thrust (**D** and **E**). A refixation saccade brings the eyes back on target after completion of the head movement (**F**). This is a "positive" head thrust sign for the right HC, indicating hypofunction of that canal.

the semicircular canal planes so as to excite the canal on the lesioned side, the VOR that results is markedly diminished (see Fig. 163-21, left panels). Although head rotation produces an excitatory contribution from the ipsilateral horizontal canal and an inhibitory contribution from the contralateral one, these contributions are markedly asymmetrical under these conditions. The inhibitory contribution from the intact canal is insufficient to drive a compensatory VOR when the head is thrust toward the lesioned side. Note that Figure 163-21 shows that there is a small VOR response for the head thrust toward the lesioned side. This is the inhibitory contribution from the intact canal. On the other hand, the excitatory contribution from the intact canal that is obtained when the head is thrust toward the intact side is almost adequate to drive a fully compensatory VOR by itself. Such a marked asymmetry may not be evident for low-frequency, low-velocity rotations, which are not dynamic enough to cut off responses in the inhibited nerve.[74]

The head thrust test (HTT) has become one of the most important tools in the clinical evaluation of vestibular function. In its qualitative, "bedside" form, the examiner simply asks the subject to stare at the examiner's nose while the examiner turns the subject's head quickly along the excitatory direction for one canal (Fig. 163-22). If the function of that canal is diminished, the VOR will fail to keep the eye on target, and the examiner will see the patient make a *refixation saccade* after the head movement is completed. If the patient has compensated well for the loss of function, the refixation saccade may even occur while the head is completing its movement, and it may take some experience to spot the saccade while the head is still in motion. By contrast, when the head thrust is in the excitatory direction of an intact canal (and nerve), the patient's gaze remains stable on the examiner's nose throughout the movement.

The HTT can localize isolated hypofunction of individual semicircular canals. Figure 163-23 shows an example of the quantitative head thrust test applied to all of the canals in a patient with a large (5-mm) dehiscence of the right superior canal. The VOR gain is reduced only for the affected superior canal, probably because large dehiscences allow the brain and dura to completely compress the membranous canal, thereby blocking endolymph motion in the canal.[75] The appearance of such a large dehiscence on computer tomographic (CT) scanning is shown in Figure 163-19B.

Principle 7: The Response to Simultaneous Canal Stimuli Is Approximately the Sum of the Responses to Each Stimulus Alone

This principle allows an intuitive approximation of the direction and magnitude of nystagmus caused by excitation (or inhibition) of any combination of semicircular canals.

Anatomic and Physiologic Basis

From Principle 3 and Principle 4, it should be clear that rotation of the head purely in one of the canal planes produces eye movements in

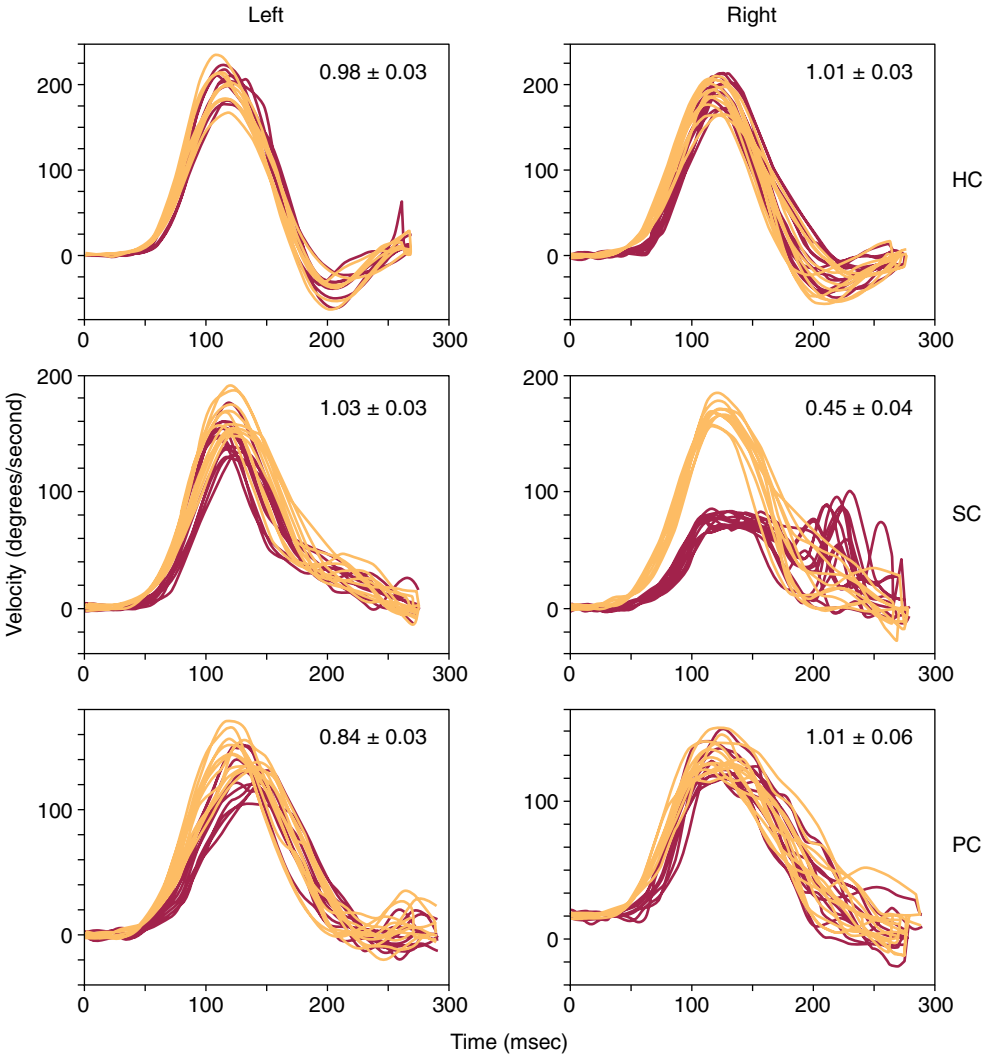

Figure 163-23. Results of head thrust testing of the aVOR in a subject with right superior semicircular canal (SC) dehiscence. Data are presented in the format described in Figure 163-21. Note the isolated loss of function in the right SC. This loss of rotary sensory function is presumably due to complete occlusion of the membranous canal by the brain and dura herniating into the lumen of the canal as shown on the CT scan *(inset)*. AC, anterior canal; HC, horizontal canal.

that canal plane. In reality, few natural head movements align solely with one canal plane, and most rotations stimulate two or even all three of the pairs of canals. How much is each canal stimulated in such a rotation? The motion of the endolymph in each canal (relative to the canal) will determine the degree to which the hair cells in that canal are stimulated. The endolymph motion in each canal is proportional to the component of the head's rotational velocity acting in the plane of that canal. A convenient way to view this is by the use of vector notation to describe the rotations.

The rotation of an object can be represented graphically with a vector that has direction and magnitude that uniquely describe the rotation. The vector lies along the axis about which the object is rotating. The direction of the vector along this axis is given by the right-hand rule (Fig. 163-24A). If the right hand were wrapped around that axis with the ends of the fingers pointing in the direction of the object's rotation, the thumb would point in the direction of the arrow of the vector. The length of the vector describes the magnitude of the rotation (e.g., degrees of angular displacement or degrees/second of angular velocity).

Using vector notation, the rotations that maximally excite each of the semicircular canals can be depicted as shown in Figure 163-24B to D. The axis of each of these rotations is perpendicular to the plane of the canal and is called its *sensitivity axis*. In the case of a head rotation that is not confined along one of these axes, the component of head velocity acting on each of the canals can be determined by graphically projecting the head velocity vector onto each of the sensitivity axes. For example, in Figure 163-24E, a head rotation to the left with the head upright mostly stimulates the left horizontal canal. The component of head rotation operating on the horizontal canal is the projection onto the horizontal canal's sensitivity axis. However, note that the projections onto the sensitivity axes of the superior and posterior canals indicate an excitatory stimulus acting on the ipsilateral superior canal and an inhibitory stimulus acting on the ipsilateral posterior canal. Mathematically, the magnitude of the stimulus projected onto the canal's sensitivity axis is the magnitude of the head velocity vector times the cosine of the angle between the axis around which the head rotates and the sensitivity axis of the canal.

Because the canal planes are approximately orthogonal to each other, the sensitivity axes are also approximately orthogonal. The pattern of activity induced in the ampullary nerves therefore effectively decomposes a head rotation into mutually independent simultaneous components along the sensitivity axes. The actions of pairs of extraocular muscles are similarly combined. The extraocular muscles are arranged in pairs that approximately rotate the eyes around axes in the orbit that parallel the sensitivity axes of the canals. Simultaneous activation of extraocular muscle pairs in proportions similar to the propor-

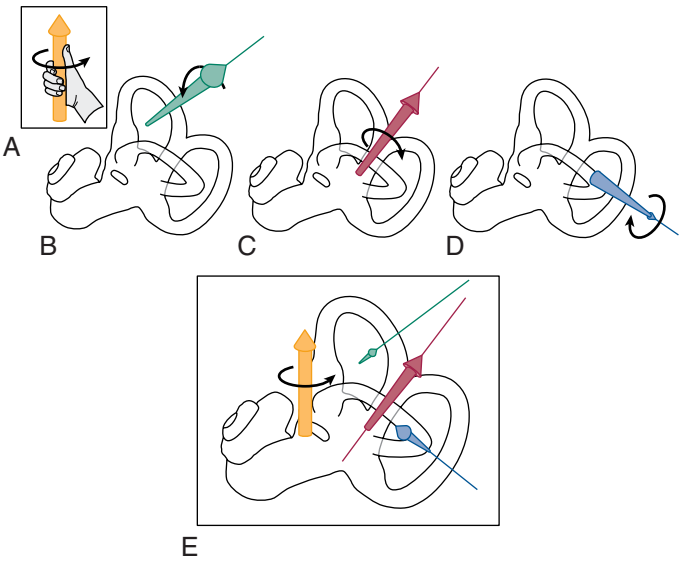

Figure 163-24. Vector representation of head velocity acting to stimulate the individual semicircular canals. **A,** The right-hand rule. The vector describing a rotation is oriented along the axis of rotation, pointing in the direction toward which the thumb of the right hand would point if the fingers wrapped around the axis and pointed in the direction of rotation. The magnitude of the vector represents a measure the rotation, either angular displacement or velocity. **B,** The sensitivity axis of the left superior canal lies perpendicular to the plane of that canal. Excitatory head rotation in that plane down and toward the left is depicted by a vector along the sensitivity axis. **C** and **D,** The sensitivity axes of the horizontal and posterior canals, each with a vector denoting the rotation that maximally excites it. **E,** The contribution of each canal in response to an upright horizontal head rotation to the left (orange vector). The bulk of the head velocity acts on the horizontal canal (HC), as shown by the projection (in red) along its sensitivity axis. The HC is not truly horizontal in this condition. Consequently, the rotation also acts on the superior canal (green vector) and posterior canal (blue vector). The SC receives a small excitatory stimulus. Note that the projection onto the PC's sensitivity axis is in its negative direction, meaning that the PC is inhibited under these circumstances.

tions of canal activation will result in eye rotation around an axis parallel to that about which the head rotates, but in the opposite direction. This, of course, is the goal of the angular VOR.

Given its ability to immediately sort incoming stimuli (head rotations) into spatially independent, minimally redundant channels of information, the labyrinth can be thought of as a "smart sensor" that not only measures stimuli but encodes them immediately in a maximally efficient way for downstream use in driving the angular VOR. In this respect, it is analogous to the cochlea, which segregates sounds into separate bins of the frequency spectrum, and the retina, which spatially maps the world into a retinotopic space.

Just as head rotations rarely stimulate only one pair of semicircular canals, labyrinthine pathology rarely affects only one canal. The brain perceives the simultaneous activation of several canals as the head rotation that would produce the same component of activation along each canal's sensitivity axis. These components are linearly combined to produce an eye movement that would compensate for the perceived head movement. By *observing the axis of the nystagmus*, the examiner can deduce which combination of canals are being excited (or inhibited). This *linear superposition* of the canal signals for simultaneous stimulation of multiple canals was confirmed in an elegant series of experiments by Cohen and associates.[63,76-78] These workers used both cineoculography of eye movements and electromyographic recordings from extraocular muscles in cats while electrically stimulating ampullary nerves alone and in combinations. They observed that even highly nonphysiologic combinations of ampullary nerve stimuli caused eye movements and extraocular muscle activity that could be predicted as the vector summation of responses to each stimulus alone (Fig. 163-25). Individual stimulation of the left semicircular canals caused eye movements that were rightward (for the left horizontal canal), upward and clockwise (for the left anterior canal), or downward and clockwise (for the left posterior canal) with respect to the animal's head. In a canal frame of reference, each of these eye movements is in the plane of the stimulated canal, as predicted by Ewald's First Law (Principle 3). Simultaneous stimulation of the left horizontal and anterior canals caused eye movements that were rightward, upward, and clockwise. In a canal frame of reference, the axis of these eye movements is a weighted vector sum of the responses of stimulated horizontal and anterior canals. Simultaneous stimulation of the left horizontal and posterior canals caused eye movements that were rightward, downward, and clockwise—that is, around an axis given by the sum of two equal vectors along the sensitivity axes of the horizontal and posterior canals. Simultaneous stimulation of the left anterior and left posterior canals caused eye movements that were clockwise, as would be expected from cancellation of the pitch (up and down) response components when vectors along the sensitivity axes of these two canals are summed. Finally, simultaneous stimulation of the all three left canals caused eye movements that were rightward and clockwise, again the prediction from a sum of equal vectors along the sensitivity axes of these canals.

Clinical Implications

This last experiment, by Suzuki and coworkers,[76] models what occurs when all of the canals on one side become excited from their baseline firing rates. The slow phase of the observed nystagmus has a horizontal component toward the contralateral side and a torsional component that moves the superior pole of the eye toward the contralateral side. The nystagmus beats to the ipsilateral side both horizontally and torsionally. There is no vertical component to this nystagmus. This *irritative nystagmus* can be seen when the labyrinth is irritated, for example, early in an attack of Meniere's disease, after stapedectomy procedures, and early in the course of viral labyrinthitis.

The same static imbalance in firing rates between sides occurs with unilateral labyrinthine hypofunction. Consider the case of left unilateral labyrinthectomy, in which case all three canals on that side are ablated. Unopposed activity of the right lateral canal contributes a leftward slow phase component. Unopposed activity of the right anterior canal contributes an upward and counterclockwise slow phase component. Finally, unopposed activity of the right posterior canal contributes a downward and counterclockwise slow phase component. These components combine, with the up and down components canceling each other, and with the net result being a leftward and counterclockwise slow phase (rightward- and clockwise-beating) nystagmus.

Quantitative application of this principle has yielded important information about the pathophysiology of vestibular neuritis. Fetter and Dichgans[79] measured three-dimensional eye movements in 16 patients with spontaneous nystagmus 3 to 10 days after the onset of vestibular neuritis. Their spontaneous nystagmus axes clustered between the direction expected from hypofunction of the horizontal canal and the direction expected from hypofunction of the anterior canal on the affected side. Hypofunction of the posterior canal did not seem to contribute to the nystagmus, and head thrusts in the plane of the ipsilateral posterior canal showed preserved function. These investigators proposed that vestibular neuritis is therefore usually a disorder of the organs innervated by the superior vestibular nerve—that is, the horizontal and anterior canals and the utricle. In support of this hypothesis is the observation that vestibular-evoked myogenic potentials (VEMPs) (a test of saccular function—see Principle 11) usually are preserved in these patients.[80] Furthermore, the frequent (approximately 21%) occurrence of ipsilateral posterior canal BPPV in these patients makes sense under this hypothesis: Function remains intact in the posterior canal, which can mediate BPPV if damage to the utricle releases otoconia into that canal.[80]

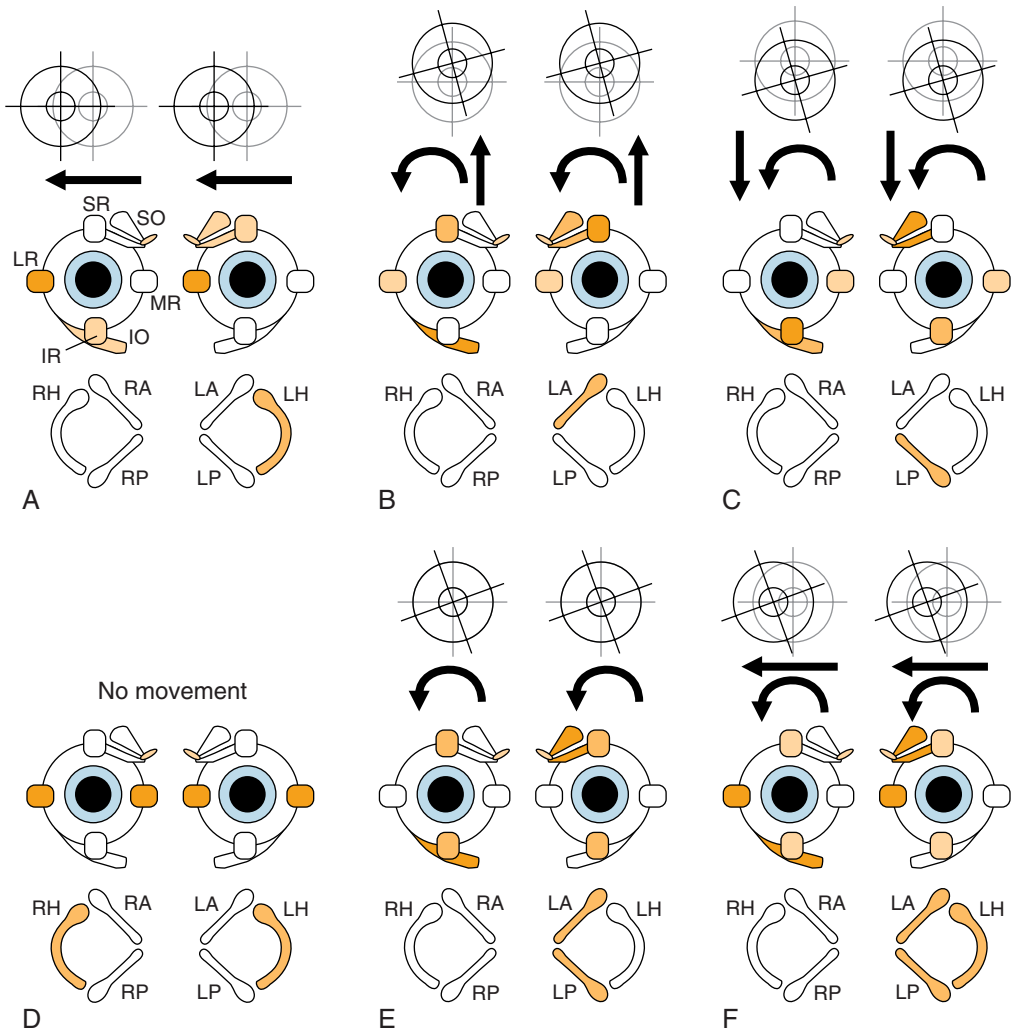

Figure 163-25. Nystagmus slow phases observed for excitation of individual semicircular canals. In the *bottom row* of each panel, *shading* indicates the excited canal(s). LA/LH/LP, left anterior, horizontal, and posterior canals; RA/RH/RP, right anterior, horizontal, and posterior canals. In the *middle row*, a cartoon of the extraocular muscles depicts which muscles are activated (darker shading indicates stronger activation). LR/MR/SR/IR, lateral, medial, superior, inferior rectus; SO/IO, superior/inferior oblique. In the *top row*, the resultant yaw, pitch, and/or roll eye movements are indicated. **A,** Excitation of the left horizontal canal causes rightward slow phases due mainly to strong activation of right LR and left MR. **B,** Excitation of the left anterior canal causes upward/clockwise (from patient's perspective) slow phases, due to combined action of the right IO and SR and the left SO and SR. **C,** Excitation of the left posterior canal causes downward/clockwise (from patient's perspective) slow phases, due to combined action of the right IO and IR and the left SO and IR. **D,** Equal stimulation of LH and RH canals elicits antagonistic contraction of MR and LR bilaterally, yielding no nystagmus. **E,** Combined equal excitation of LA and LP canals excites muscle activity that is the sum of each canal's individual effect; upward and downward pulls cancel, resulting in a purely clockwise nystagmus. **F,** Combined equal excitation of all three left canals causes a right-clockwise slow phase, the expected result of summing activity for each individual canal. *(Adapted from Cohen B, Suzuki J-I, Bender MB. Eye movements from semicircular canal nerve stimulation in the cat.* Ann Otol Rhinol Laryngol. *1964;73:153; data adjusted to human head frame of reference.)*

Principle 8: Nystagmus Due to Dysfunction of Semicircular Canals Has a Fixed Axis and Direction with Respect to the Head

Anatomic and Physiologic Basis

The concept of a fixed axis of nystagmus for stimulation of an isolated semicircular canal has already been demonstrated for posterior canal BPPV, under Principle 3. In that case, the eyes always rotated about the sensitivity axis of the affected posterior canal. Having the patient direct gaze orthogonal to and along the sensitivity axis of the posterior canal showed that there was really no change in the direction of nystagmus when considered in the canal-fixed reference frame (despite the dramatic change in the eye-fixed reference frame).

This principle extends that concept to any axis of rotation resulting from stimulation or inhibition of any combination of semicircular canals. Consider again the patient with acute unilateral hypofunction of all of the right semicircular canals. There is relative excitation of all the left canals. As demonstrated previously, the nystagmus will beat toward the left both horizontally and torsionally. Changing gaze direction does not change the leftward direction of the fast phases of this nystagmus. Thus, it is a *direction-fixed* nystagmus. In general, peripheral nystagmus has a fixed axis and direction.

Clinical Implications

This principle helps to distinguish nystagmus from a peripheral vestibular disorder from nystagmus due to a central disorder. In the case of the latter, the axis or direction of nystagmus may change depending on the direction of gaze.[81] It is important to note that the *magnitude* of the nystagmus is *not* fixed depending on gaze. The reason for this is discussed in the next principle.

Principle 9: Brainstem Circuitry Boosts Low-Frequency VOR Performance through Velocity Storage and Neural Integration; Failure of These Mechanisms Suggests Central Pathology

The description of the VOR up to this point has depicted little role for brainstem and cerebellar signal processing, other than passing on the vestibular signals to the appropriate ocular motor nuclei. This "direct pathway" is the classical three-neuron reflex arc. However, the brainstem does more than serve as a conduit for the vestibular afferent signals. An "indirect pathway" through the brainstem circuits also must account for the poor performance of the vestibular endorgans at low frequencies and the need for further integration of the incoming head velocity signal to generate fully compensatory eye movements. The brainstem accomplishes these tasks through processes called *velocity storage* and *velocity-to-position integration*. These two processes also lead to several important clinical phenomena, such as post-rotatory nystagmus, post–head-shaking nystagmus, and Alexander's Law. The last of these is another one of the cardinal signs that differentiates peripheral from central causes of nystagmus.

Anatomic and Physiologic Basis

Velocity Storage

For head rotations at frequencies below approximately 0.1 Hz, the vestibular nerve afferent firing rate gives a poor representation of head velocity (see Appendix). In response to a constant velocity rotation, the cupula initially deflects but then returns back to its resting position, with a time constant of approximately 13 seconds.[82] Thus, nystagmus in response to a constant-velocity rotation would be expected to disappear after approximately 30 seconds (see Fig. 163-10B).

In fact, the situation would be made somewhat worse because canal afferent neural responses also tend to decay for static or low frequency responses. This adaptation of afferent firing is a property of the neuron itself, and it is especially pronounced for irregular afferents. The effect of adaptation is to make afferents respond more transiently to static and low frequency cupular displacements. Thus, some canal afferents end up carrying a transient signal in response to low frequency and constant velocity rotations. This signal more closely reflects the rate of change of head velocity—that is, acceleration—than velocity itself.

Despite these tendencies for the peripheral vestibular signals to decay prematurely, experimental observations in humans have shown that the time constant of the decay of the angular VOR for constant velocity rotation is about 20 seconds, longer than would be expected based on the performance characteristics of the canals alone.[83] Neural circuits in the brainstem seem to perseverate canal signals, stretching them out in time. The important physiologic consequence of this effect (historically called *velocity storage*, because it appears to "store" the head velocity information for some period of time) is that it allows the vestibular system to function better at low frequencies. Because of velocity storage, the lower corner frequency of the system is extended to approximately 0.08 Hz. This allows sufficient overlap between the VOR and lower-frequency gaze-stabilizing systems (smooth pursuit and optokinetic nystagmus) to avoid having a region of frequency in which neither system works well.[12]

Robinson[84] proposed that velocity storage could be accomplished by a feedback loop operating in a circuit including the vestibular nuclei. Lesion studies in monkeys suggest that velocity storage arises from neurons in medial vestibular nucleus (MVN) and descending vestibular nucleus (DVN) whose axons cross the midline.[85]

Velocity-to-Position Integration

A second problem arises in matching the signals coming out of the semicircular canals to those needed to act on the eye muscles. For all eye movements, in order to move the eye, the contraction of an extraocular muscle must not only overcome the force of viscous drag (friction), which is proportional to eye velocity. It also must overcome the elastic restoring force that arises principally from stretch of the antagonistic extraocular muscle with which it is paired. This elastic restoring force is significant, even though the antagonist muscle receives an inhibitory command. This force, analogous to that produced by a spring, is proportional to the eye's displacement or position. Experimental evidence shows that the oculomotor neurons receive a signal that includes signal components for both the desired eye velocity $\dot{E}(t)$ and the instantaneous eye position $E(t)$:

$$\textit{firing rate} = kE(t) + r\dot{E}(t) \qquad \text{Eq. 163-12}^{86}$$

In making a horizontal saccade, for example, a velocity command is generated by an excitatory burst neuron in the paramedian pontine reticular formation (PPRF) (Fig. 163-26). This command is a pulse of neural activity, which is sent along a direct path to the abducens and oculomotor nuclei. Alone, it would provide only the term proportional to desired eye velocity, and the eye would slide back to its neutral position in the orbit without the ongoing pull from the muscle to overcome the elastic restoring force. The ongoing pull from the term proportional to eye position is obtained by way of an indirect path through neurons that mathematically time-integrate the pulse (a transient or phasic command) to yield a step (a tonic command). The final signal carried by the oculomotor neuron is thus a pulse-step (phasic-tonic) signal of the form of Equation 163-12.

For the VOR as well, the oculomotor neurons need to receive both an eye velocity and eye position command (Fig. 163-27). The desired eye velocity $\dot{E}(t)$ is easily obtained; it is simply equal and opposite to the head velocity $\dot{H}(t)$, a quantity approximately provided by the signals from the semicircular canals. The estimate of eye position $E(t)$ is provided by the brainstem *velocity-to-position integrator*, which integrates the velocity signal provided by the canals to give an estimate of position. All types of conjugate eye movements—the VOR, optokinetic nystagmus, saccades, and pursuit—are initiated as velocity commands that are passed both directly to the oculomotor neurons and indirectly through this shared neural integrator.[87] This brainstem integrator likely is a circuit of recurrently connected neurons in which signals reverberate and produce synaptic changes, a form of short-term memory.[88,89] For horizontal eye movements, the integrating neurons lie in the nucleus prepositus hypoglossi region of the pons.[90,91] For torsional and vertical eye movements, they lie in the interstitial nucleus of Cajal.[92]

Clinical Implications

Pre- and Post-rotatory Nystagmus

Velocity storage is responsible for the prolonged nystagmus that occurs after sustained constant-velocity rotation in one direction (Fig. 163-28). Rotation to one side generates a positive change in afferent firing on the ipsilateral side and a negative change on the contralateral side. Because of the excitation-inhibition asymmetry inherent in the semicircular canal signals (Principle 6), the net result is not zero change in the afferent firing rate sensed by the brainstem, but rather a net excitation on the ipsilateral side. The velocity storage mechanism perseverates this net excitation beyond the time that the cupula deflection has returned to zero (see Fig. 163-10B). The brainstem thus perceives that the head continues to rotate toward the same side, and it generates an angular VOR for that perceived rotation. The slow phases of nystagmus are directed toward the contralateral side, and the fast phases are directed toward the ipsilateral side. This nystagmus decays exponentially as the velocity storage mechanism discharges with the time constant of approximately 20 seconds.

Head-Shake Nystagmus

If the head is rotated side to side in the horizontal plane in normal subjects, the velocity storage mechanism is charged equally on both sides. There is no post-rotatory nystagmus as the stored velocities decay at the same rate on either side. However, nystagmus does occur after head shaking in subjects with unilateral vestibular hypofunction.[93] In the clinical head-shaking test, the examiner passively rotates the subject's head horizontally at 1 to 2 Hz for 10 to 20 cycles of rotation. Once the rotation stops, the eyes are observed under Frenzel lenses in order to prevent visual suppression of the nystagmus. As the head is shaken from the lesioned side toward the intact side, net excitation is stored by the velocity storage mechanism. In fact, the *net* excitation

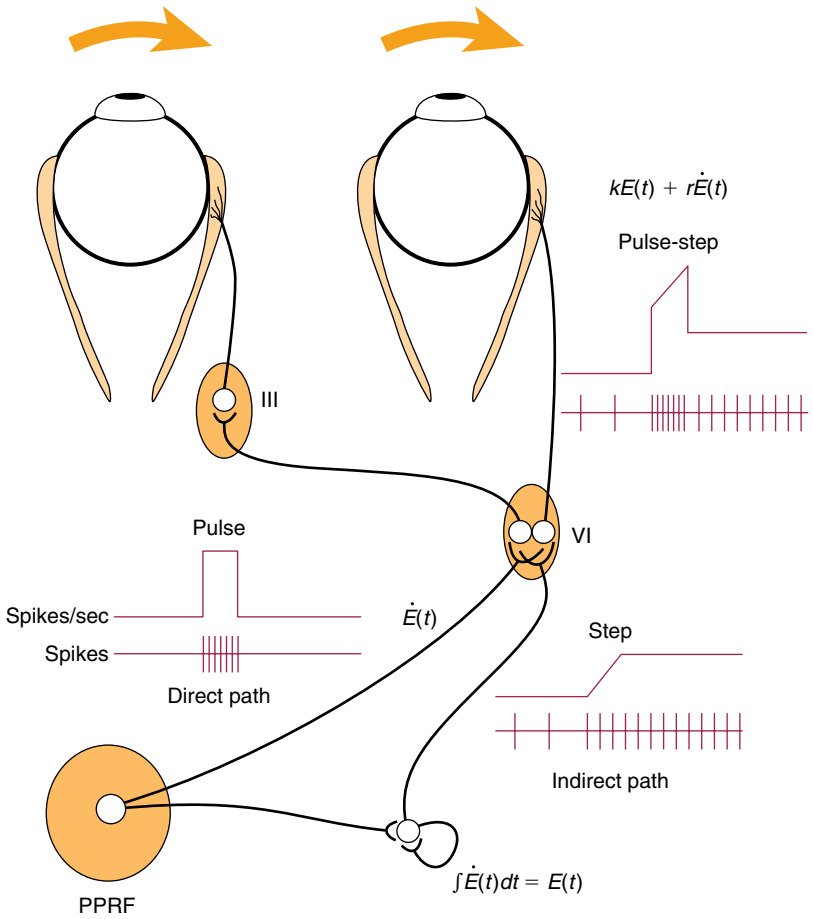

Figure 163-26. The motor command for the saccade originates in the paramedian pontine reticular formation (PPRF) as a pulse of neural firing. This activity is transmitted along a direct path to the ocular motor nuclei as a pulse. The pulse also is integrated into a step of neural discharge and transmitted to the ocular motor nuclei along an indirect path. The final motor signal is thus a pulse-step combination, as required by the dynamics of the eye muscles.

is greater than in normal subjects because there is no inhibitory signal coming from the lesioned labyrinth. When the head is turned and rotated toward the lesioned side, there is no excitatory stimulus sent to the brainstem from that side, and only a small inhibitory stimulus from the intact labyrinth. After multiple cycles of back-and-forth rotation, a marked asymmetry develops in the velocity storage mechanism, one that signals illusory continued rotation toward the intact side. As a result, when the head stops rotating, the nystagmus is as would be expected for continued rotation toward the intact side: The slow phases go toward the lesioned side, and the fast phases toward the intact side. This pattern may even reverse after several seconds, presumably because neurons affected by velocity storage adapt to the prolonged change in firing from their baseline rates.

The head shaking test provides another very useful means of localizing labyrinthine loss, one that complements the information derived from caloric testing and head thrust testing. As noted previously, caloric testing measures the function of an isolated semicircular canal at relatively low frequency. The head thrust test uses rapid, brief rotations with frequency content in the range of 3 to 5 Hz. By providing information about the function of the labyrinth at 1 to 2 Hz, the head-shaking test may provide information not available from the other two tests.

Alexander's Law

The brainstem integrator also manifests characteristic findings in vestibular pathology. In the acute period after loss of unilateral labyrinthine function, the integrator becomes dysfunctional or "leaky." In part, this may be an adaptive strategy by the brain to minimize nystagmus. As we have already seen, integration of the vestibular signal increases the drive to the extraocular muscles that pull the eye in the direction of the slow phases. By shutting down the integrator, the brain may decrease the slow-phase velocity of nystagmus. However, because the integrator is shared by other oculomotor systems, including the saccadic system, the ability to hold the eye in an eccentric position in the orbit is impaired when the integrator is leaky. As a result, the eyes tend to drift back to the center position in the orbits (Fig. 163-29). This centripetal drift has an important effect on the observed nystagmus. When the eyes look toward the direction of the fast phase of nystagmus, the drift due to the "leakiness" of the integrator adds to the slow-phase velocity due to the vestibular imbalance, and as a result the nystagmus slow-phase velocity increases. However, when the eyes look toward the direction of the slow phase, the centripetal drift due to the leaky integrator subtracts from the slow-phase velocity due to the vestibular imbalance, and the nystagmus slow-phase decreases or may disappear. This observation has come to be known as *Alexander's Law*.[94] Although occasionally seen in central lesions, peripheral types of nystagmus generally will obey Alexander's Law, making it an important neuro-otologic examination finding in distinguishing nystagmus of central origin from that of peripheral origin.

Interpreting Rotary Chair Tests

Dysfunction of the neural integrator and velocity storage can also be seen in the results of rotary chair testing. Rotary chair testing may consist of either steps of constant-velocity rotation or sinusoidal harmonic oscillations, typically from 0.01 to 0.6 Hz. Velocity steps may be delivered by suddenly starting the rotation of the chair from zero velocity to a sustained constant velocity in one direction (as in Fig. 163-8B). Alternatively, the equivalent stimulus may be obtained by braking the chair after a prolonged constant velocity rotation in the

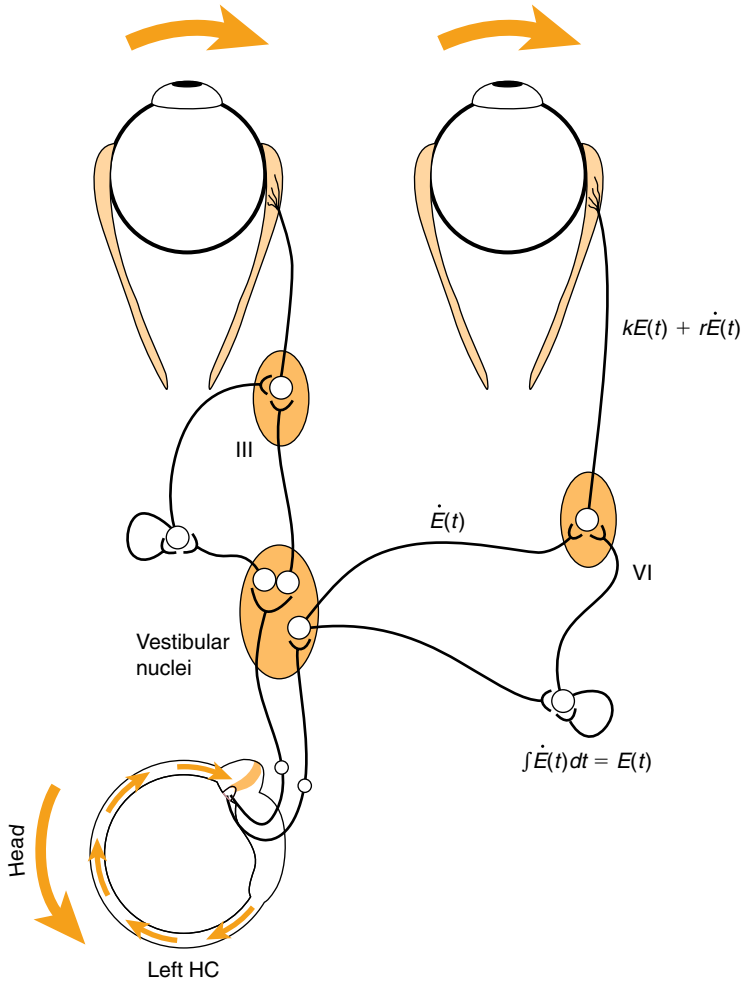

Figure 163-27. Signals from the canals also pass through direct and indirect pathways to the ocular motor nuclei. The direct excitatory pathway for the horizontal vestibulo-ocular reflex (VOR) is depicted in detail in Figure 163-15. The indirect pathway through the velocity-to-position integrator provides the final ocular motor signal with a component proportional to eye position. HC, horizontal canal.

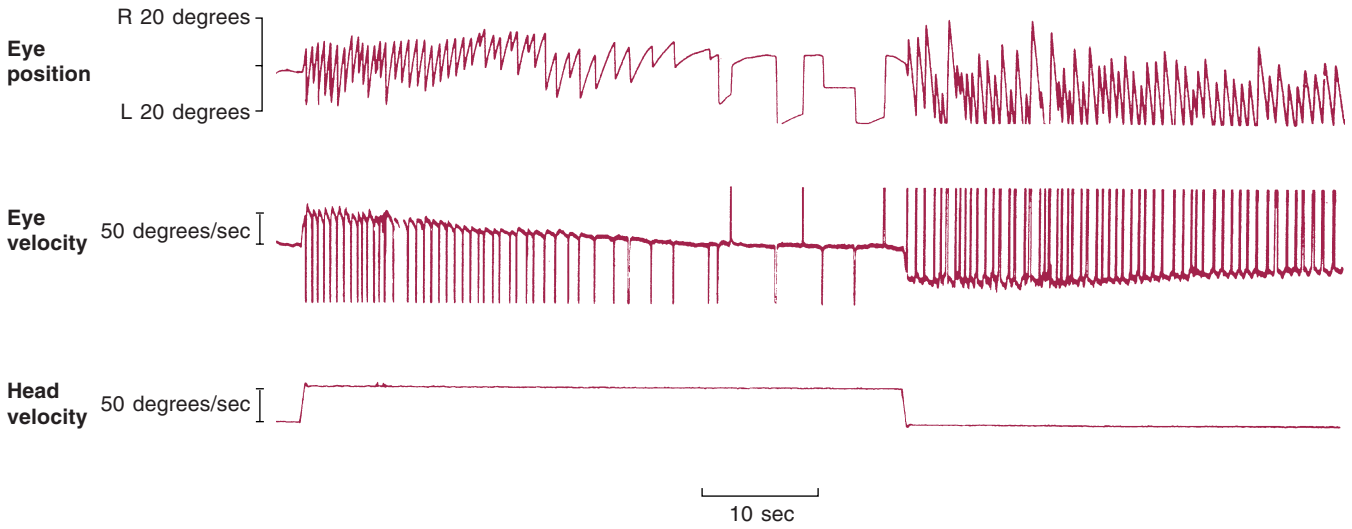

Figure 163-28. Per- and post-rotatory nystagmus in a monkey in response to a step of head velocity to 50 degrees/second. While the chair continues to rotate at 50 degrees/second constant velocity, the initial nystagmus decays more slowly than would be predicted based on the cupula's time constant. After the chair rotation stops, the nystagmus appears again but in the opposite direction. This after-nystagmus also decays more slowly than would be anticipated. The prolongation of the nystagmus after rotation is a manifestation of velocity storage. *(Modified from Cannon SC, Robinson DA. Loss of the neural integrator of the oculomotor system from brain stem lesions in monkey.* J Neurophysiol. *1987;57:1383.)*

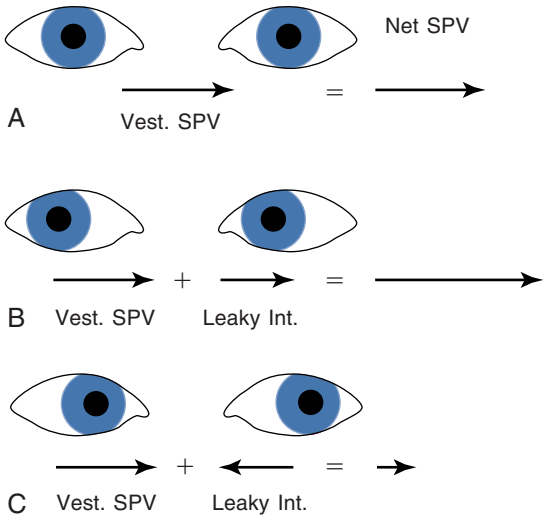

Figure 163-29. Alexander's law. The interactions of the vestibular slow phase velocity (Vest. SPV) and a leaky integrator (Int.) are demonstrated for a case of left acute vestibular hypofunction. In neutral gaze (**A**), the vestibular slow phase alone is manifest. When the gaze is in the direction of the fast phase (*right*, **B**), the leaky integrator causes the eyes to drift to the left. This drift adds to the vestibular slow-phase signal, and the net slow-phase velocity increases. When the gaze is in the direction of the slow phase (*left*, **C**), the leaky integrator causes the eyes to drift to the right. This drift subtracts from the vestibular slow-phase signal, and the net slow-phase velocity decreases.

other direction. The horizontal canals' endolymph and cupulae tend to keep moving in the direction that the chair had been moving, so that the stimulus is equivalent to a velocity step in the direction opposite to that in which the chair had been turning. In the case of unilateral loss of labyrinthine function, the magnitude of post-rotatory nystagmus in response to a velocity step expected to excite the lesioned horizontal canal may be low in comparison to that for velocity steps expected to excite the intact side. However, a decrement in nystagmus may not be detectable in subjects with compensated unilateral loss of labyrinthine function because, as explained in Principle 6, the relatively low frequencies and accelerations involved in rotary chair testing may not elicit much excitation-inhibition asymmetry. Instead, the only abnormality may be that the time constant of post-rotatory nystagmus is shortened. The impairment of the brainstem's velocity storage mechanism secondary to the loss of peripheral function decreases this time constant. For bilateral loss of labyrinthine function, nystagmus in response to steps is likely to show decreased gains and decreased time constants.

When sinusoidal rotary chair testing is performed in subjects with unilateral loss of labyrinthine function, the *gain* of the VOR (the ratio of eye velocity/head velocity; see Appendix) may be lower as the head is rotated toward the lesioned side. More commonly, however, the gain will be low bilaterally or even normal, especially once the individual has compensated for the loss of unilateral function. Often, however, the *phase* of the VOR will remain advanced relative to head velocity at low frequencies.[95] Again, this reflects the limitations of the semicircular canal in producing a response that encodes head velocity at low frequencies (see Appendix). These limitations, which are mitigated by velocity storage and neural integration, become manifest when velocity storage and integration are disrupted by a loss of peripheral vestibular function.

Principle 10: The Utricle Senses Both Head Tilt and Translation, but Loss of Unilateral Utricular Function Is Interpreted by the Brain as a Head Tilt toward the Opposite Side

Anatomic and Physiologic Basis

The utricle senses linear accelerations that are tangential to some portion of its curved surface. Most of the utricle is approximately in the plane of the horizontal canal, although its anterior end curves upward from this plane. The baseline firing of utricular afferent fibers is therefore best modulated by linear accelerations in the horizontal plane—that is, fore-and-aft or side-to-side. Hair cells in the utricle are polarized such that stereociliary deflections toward the striola excite the hair cells, and deflections away from the striola inhibit them. Because the orientations of the stereociliary bundles vary over the surface of the utricle, the organ's overall pattern of responses to a given linear acceleration can be quite complex (see Fig. 163-7). Linear accelerations in different directions probably activate unique ensembles of activity in the afferents of the utricle, with some areas being excited and others inhibited. These ensemble responses may encode the direction of head acceleration.[17]

Excitation or inhibition of *all* regions of the utricle does not occur under normal conditions of vestibular stimulation. Thus, predicting what the brain will perceive during pathologic conditions resulting in stimulation of the whole utricle is less straightforward than was the case for the semicircular canals, whose hair cells are all polarized in the same direction. However, studies in cats[96] and monkeys[97] have demonstrated a 3:1 predominance of afferents arising from the medial aspect of the utricle, which is sensitive to accelerations produced by ipsilateral tilts. Thus, the brain interprets a tonic increase in firing from the utricle on one side as a net acceleration of the otoconial mass toward the ipsilateral side. Conversely, the brain interprets a decrease or loss in firing from the utricle on one side as a net acceleration of the otoconial mass toward the contralateral or intact side.

However, the brain must still decide how to interpret this signal representing a net acceleration of the otoconial mass to one side. Such acceleration could be produced by an ipsilateral tilt or by a contralateral translational movement of the head. There is little physical difference between the shear forces acting on the hair cells of the otolith organs in these two circumstances, but the expected reflexive response of the vestibular system would be quite different depending on the interpretation. If tilt is perceived, then the appropriate compensatory reflexes would be counter rolling deviations of the eyes and head. If translation is perceived, the appropriate reflexes would be horizontal eye movements.

Just how the brain distinguishes utricular signals due to tilt from those due to translation remains one of the ongoing controversies in vestibular physiology. The equivalence of tilt and translation provides the brain a seemingly irresolvable ambiguity in the utricular afferent signals. Nevertheless, the brain is somehow able to correctly resolve the source of the ambiguous stimulus under normal conditions, so that an interaural translation produces horizontal eye movements with little or no roll movements. By contrast, when the same net acceleration acts on the utricles during tilting movements of the head, the eyes counter-roll appropriate to the tilt, but do not turn horizontally as they would for an interaural translation. One way to resolve these different stimuli might be based on the frequency content. Low-frequency or static linear accelerations acting on the otolith organs might be interpreted as gravitational accelerations resulting from tilt, whereas transient linear accelerations might be interpreted as linear translations.[98,99] An alternative hypothesis is that the central nervous system integrates information from the semicircular canals with information from the otolith organs to distinguish tilts (which also transiently activate canals) from translations (which activate only the otolith organs). In support of this hypothesis, experiments in rhesus monkeys in which the semicircular canals were inactivated by plugging demonstrated that in the absence of canal signals, modulation of otolith activity by roll tilts led to eye movements that would instead be compensatory for perceived interaural translations.[100] Thus, the brain appears to need the additional signals from the canals to distinguish tilts from translations.

Whether the brain uses the frequency content of the incoming utricular signal or the concomitant signals from the canals, the perception of a static decrease in the firing rates of utricular afferents on one side should be interpreted as tilt toward the opposite side, not translation toward the same side. From the point of view of frequency content, the static nature of the firing rate change would mimic the static (low-frequency) change due to a head tilt. From the point of view of the

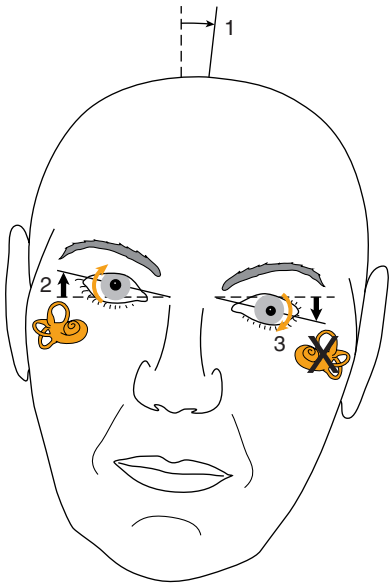

Figure 163-30. The otolith tilt reaction for loss of left utricular function consists of (1) head tilt to the left, (2) elevation of the right eye and depression of the left eye, and (3) roll of the superior pole of each eye to the patient's left.

canal signals, recall that loss of unilateral labyrinthine function leaves a relative excess of signals from the contralateral vertical canals that would be perceived as rolling of the head toward the intact side. This would be the expected concomitant canal signal for a head tilt toward the intact side. Thus, the loss of unilateral utricular function is interpreted by the brain as a head tilt toward the *opposite* side.

Clinical Importance

An isolated loss of utricular nerve activity elicits a stereotypical set of static responses called the *ocular tilt reaction*, which comprises (1) a head tilt toward the lesioned side, (2) a disconjugate deviation of the eyes such that the pupil on the intact side is elevated and the pupil on the lesioned side is depressed (a so-called skew deviation), and (3) a static conjugate counter-roll of the eyes rolling the superior pole of each eye away from the intact utricle[101] (Fig. 163-30). Each of these signs can be understood as the brain's compensatory response to a perceived head tilt toward the intact utricle. This perception arises from the excess of ipsilateral tilt information coming from the intact utricle. The ocular tilt reaction can also occur from interruption of central otolithic pathways as, for example, in multiple sclerosis.[102,103] The full ocular tilt reaction is not often observed with peripheral vestibular lesions because the brainstem compensates for some aspects very rapidly. However, the otolaryngologist will occasionally encounter the postoperative complaint of vertical diplopia after resection of an acoustic neuroma or sectioning of the vestibular nerve. By alternately covering the eyes and observing the opposite vertical shifts that occur for each eye, the skew deviation quickly becomes apparent.

Although the full ocular tilt reaction may not persist for very long after an acute lesion, the static roll of each eye toward the lesioned side may be detected for weeks to months afterward.[104,105] This can be shown with careful fundus photography, but a more practical method is with the perceptual test of subjective visual vertical (SVV) or subjective visual horizontal (SVH). Subjects with recent unilateral loss of otolith function will consistently displace a lighted line in a dark room so that it is tilted off the desired vertical or horizontal orientation toward the lesioned side. In fact, a close correlation has been noted between the absolute torsional deviation of the eyes and the angular displacement of the line from vertical or horizontal.[106] The tilt in SVV or SVH usually decreases over months after a loss of unilateral vestibular function, but for severe lesions such as vestibular nerve section some deviation persists permanently.[104]

Principle 11: Sudden Changes in Saccular Activity Evoke Changes in Postural Tone

Anatomic and Physiologic Basis

The saccule is almost planar and lies in a parasagittal orientation. Hair cells of the saccule, polarized so that they are excited by otoconial mass displacements away from the striola, can sense accelerations fore or aft (along the naso-occipital axis) or up and down. Most afferents from the saccule have a preferred up or down direction.[97] Moreover, only the sacculus can sense linear accelerations up or down, whereas naso-occipital accelerations will activate some utricular as well as saccular afferents. Thus, the sacculus has a unique role of sensing upward or downward accelerations.

When the head is upright in the gravitational field, the acceleration due to gravity (9.8 m/sec^2) constantly pulls the saccular otoconial mass toward the earth. Afferents in the inferior half of the saccule, whose hair cells are excited by this downward acceleration, have lower firing rates and lower sensitivities to linear accelerations than do those afferents in the upper half of the utricle.[97] The afferents in the upper half are excited by relative upward acceleration of the otoconial mass, such as might occur when the head drops suddenly, e.g., when one is falling. Thus, sudden excitation of hair cells across the saccular macula probably would be interpreted by the brain as a sudden loss of postural tone, as in falling. The appropriate compensatory reflex would be one that activates the trunk and limb extensor muscles and relaxes the flexors to restore postural tone. Accordingly, the saccular afferents project to the lateral portions of the vestibular nuclei, which give rise to the vestibulospinal tract, in contrast to the utricular afferents, which project more rostrally to areas involved in the VORs.[106]

Clinical Importance

Saccular excitation probably underlies the test of VEMPs. VEMPs are transient decreases in flexor muscle electromyographic (EMG) activity evoked by loud acoustic clicks or tones applied to the ear. Sufficiently loud sounds applied to the ear excite saccular afferents.[107,108] The predicted reflexive response as noted earlier would include relaxation of flexor muscles. The EMG activity averaged over multiple acoustic stimuli from a tonically contracting flexor muscle will demonstrate a biphasic short latency relaxation potential. The EMG activity can be recorded in many different flexor muscles, but the sternocleidomastoid (SCM) responses have been best described.[109] Because the saccule mediates sound-evoked VEMP responses in the normal labyrinth, absence of VEMP responses may indicate saccular dysfunction. However, transmission of the VEMP acoustic stimulus is very sensitive to any cause of conductive hearing loss in the middle ear, and VEMPs are usually absent in the presence of conductive hearing loss. Interestingly, the preservation of VEMP responses in the face of conductive hearing loss implies an abnormally low acoustic impedance of the labyrinth, such as occurs in superior canal dehiscence syndrome[110] or with enlarged vestibular aqueduct syndrome.[111]

Another example of the postural tone changes that may be related to saccular activity is the drop attack. Also known as the "otolithic crisis of Tumarkin," the drop attack is a dramatic loss of postural tone that can occur in Meniere's disease independent of other vestibular symptoms at the time of the fall.[112] It is not clear what causes the sudden loss of postural tone, but sudden deformations of the saccular macula associated with the hydropic changes of the labyrinth have been invoked.

Principle 12: The Normal Vestibular System Can Rapidly Adjust Vestibular Reflexes in Accordance with the Context, but Adaptation to Unilateral Loss of Vestibular Function May Be Slow and Susceptible to Decompensation

Anatomic and Physiologic Basis

As emphasized throughout this chapter, the vestibular system is efficiently designed to give stereotypical motor reflex outputs that compensate for the movements of the head. Yet a stereotypical output appropriate for one context may be inappropriate for another. For example, redirection of gaze is accomplished by turning first the eyes,

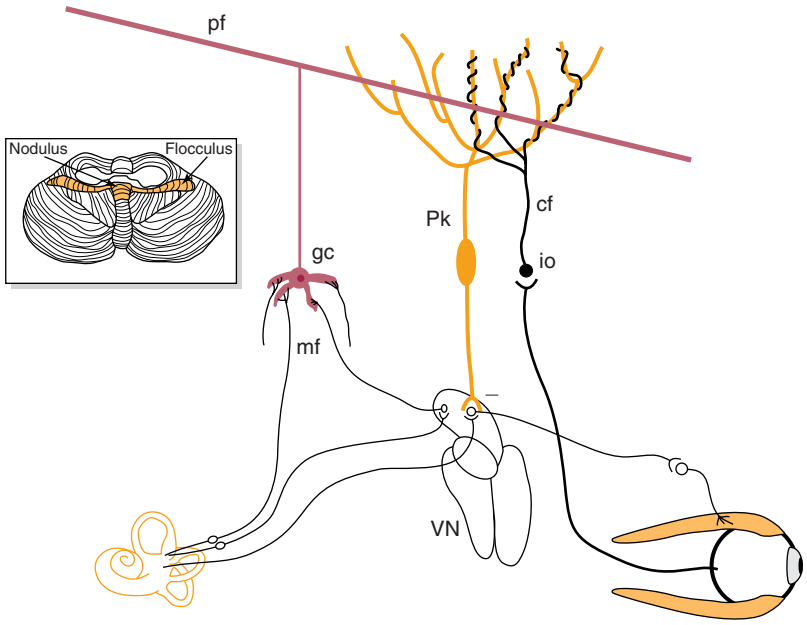

Figure 163-31. Circuitry of the cerebellum involved in modifying the vestibulo-ocular reflex (VOR). Inputs from primary vestibular afferents and secondary vestibular neurons (VN) form mossy fiber (mf) inputs to cerebellar granule cells (gc). Parallel fibers (pf) originating from these synapse weakly with Purkinje cells (Pk), causing a highly tonic inhibitory output of simple spikes from the Purkinje cells onto secondary vestibular neurons controlling the VOR. Climbing fiber (cf) input from the inferior olive (io) carries sensorimotor error information such as retinal slip. Climbing fibers make extensive and strong synapses onto Purkinje cells. Climbing fiber activity leads to complex spikes in the Purkinje cells, which can alter the efficacy of the parallel fibers' synapses onto the Purkinje cells—a form of learning.

then the head, toward a new visual target. During the gaze shift, there is a period during which both the eyes and head must move in the same direction. The VOR must actually be turned off during this period; otherwise, the eyes would stay fixed on the original target. This *cancellation* of the VOR is measurable in secondary vestibular neurons as a decrease in VOR gain when gaze is being redirected.[113,114] The mechanism by which the VOR can be canceled is not clear, but secondary vestibular neurons may receive "efference copies" of the commands going to the eye muscles. These oculomotor signals may, through inhibitory connections, decrease the responses of secondary vestibular neurons participating in the VOR reflex arc.

Under other circumstances, the VOR gain may need to be increased. For example, when the eyes are verged to view a target near the nose, they must rotate through a larger angle than that fore head rotation, in order to stay on target. In fact, as head rotation brings one eye closer to the target and takes the other eye farther away from it, each eye will require a *different* VOR gain value. Viirre and coworkers[115] showed that the VOR performs as needed under these demanding conditions to stabilize images on the retina, and it appears to do so within 10 to 20 msec of the onset of head movement—faster than could be explained by the use of any visual feedback information to correct the VOR. These investigators suggested that otolith interactions with canal signals could provide a means to constantly update an internal map of the visual target in space, allowing adjustments to the gain of the VOR for each eye.

Other contextual changes in the vestibular reflexes take place more slowly. For example, the VOR gain needs to be adjusted for changes in visual magnification when someone begins wearing spectacles. Long-term changes in vestibular reflexes, a form of motor learning, depend heavily on the cerebellum, specifically the flocculonodular lobe of the cerebellum. The basic wiring of the cerebellum as it relates to the VOR reflex arc is shown in Figure 163-31. The output of the cerebellar cortex comes from Purkinje cells, which have an inhibitory effect on their target neurons in the vestibular nuclei. Purkinje cells have two distinct patterns of activation. Simple spikes occur at high rates and are triggered by inputs from many parallel fibers. These parallel fibers arise from granule cells, which in turn receive inputs from mossy fibers. The latter convey a variety of motor and sensory signals. Input from many parallel fibers, each of which synapses weakly onto Purkinje cells, leads to a high tonic output of simple spikes from the Purkinje cells. By contrast, the climbing fibers from the inferior olive carry sensorimotor error signals—for example, retinal slip. Each climbing fiber makes numerous synapses with the dendrites of a Purkinje cell, so that one climbing fiber has a strong effect on the Purkinje cell. This effect generates complex spikes at low rates. In the classical model of cerebellar learning, repetitive and synchronous activation of climbing fiber and parallel fiber inputs causes a gradual reduction in the strength of parallel fiber synapses onto Purkinje cells—so-called long-term depression.[116] In the context of the VOR, weakening the parallel fiber input would diminish the tonic inhibition of the Purkinje cells on the secondary vestibular neurons. The VOR gain would increase as needed to correct the error signal carried by the climbing fibers. It is likely that learning in the cerebellum is much more complex than this, with changes occurring at multiple synapses. An important point is that error signals such as retinal slip may be necessary to drive the motor learning that underlies some compensatory changes in the vestibular system. This phenomenon is the basis for many physical therapy interventions for loss of unilateral vestibular function.

After unilateral loss of vestibular function (e.g., labyrinthectomy), a profound imbalance develops in the firing rates of the vestibular nuclei, with most second-order neurons on the ipsilateral side going silent.[116-125] The static imbalance results in the nystagmus and ocular tilt reaction described earlier. This static imbalance is corrected within 1 week of labyrinthectomy in alert guinea pigs[122] and within 3 weeks in the monkey.[126] Some component of the recovery of resting activity in secondary vestibular neurons is intrinsic.[127] On the other hand, subsequent lesions in other parts of the central nervous system (CNS), such as the spinal cord[128] or inferior olive,[129] can cause transient decompensation and recurrence of symptoms of static imbalance. Two important points emerge from these observations: First, an astonishing compensation for static vestibular imbalance can occur but may require a period of weeks. Second, this compensation may be disrupted by other changes in the CNS at later times, causing a recurrence of symptoms due to static vestibular imbalance. It bears repeating that despite the recovery of static central vestibular imbalance, asymmetries in dynamic responses to head movements persist, to some degree, perma-

nently, after unilateral loss of vestibular function. This is exemplified by the head thrust test discussed in Principle 6.

Clinical Implications

Vestibular compensation requires there to be a stable (although reduced) level of peripheral vestibular function over time. The compensatory mechanisms must also be presented with sensory error signals, and their ability to sense and process these signals must not be compromised. These requirements have three important clinical consequences.

Static Loss of Vestibular Function Can Be Compensated, but Fluctuating Loss Cannot

There are important clinical correlates to the observations that the vestibular system adapts slowly to loss of unilateral function and that changes elsewhere in the CNS or further changes in vestibular function can cause decompensation. Disease states that cause static, stable loss of peripheral vestibular function are typically much less debilitating than are losses than fluctuate over minutes to hours. When there is an acute, fixed loss of unilateral vestibular function, such as after labyrinthectomy, vestibular neurectomy, or some cases of viral labyrinthitis, patients typically have several days of vertigo and nystagmus. Most patients with normal contralateral function compensate for unilateral loss remarkably well over 1 to 2 weeks.[130] Spontaneous nystagmus resolves within a few days, although nystagmus induced by head-shaking and lateral gaze toward the contralesional side may persist longer (see Principle 9). Again, it should be emphasized that sudden, rapid head rotations to the ipsilateral (nonfunctioning) side will always cause transient failure of the VOR if there is not recovery of ipsilateral peripheral function (see Principle 6). Within 2 weeks after acute unilateral loss of function, most patients no longer have vertigo at rest, and can walk, although they may require assistance. By 1 month later, most are walking unassisted and returning to normal daily activities.

In contrast to the relatively benign and predictable course after a permanent total unilateral loss of vestibular function, the fluctuating function typical in Meniere's disease and BPPV can cause intense and debilitating vertigo and nystagmus with each attack. These disorders cause a fluctuating perturbation of peripheral vestibular function on an hour-to-hour or even minute-to-minute basis. The brain simply cannot complete its compensatory work in this time frame, before peripheral function returns to normal. The compensatory mechanisms are effectively faced with a "moving target."

Perhaps the least symptomatic loss of vestibular function occurs with the slow growth of vestibular schwannomas. As the vestibular nerves are slowly infiltrated or compressed, the brain compensates for the gradual loss of function imperceptibly, and patients may have no symptoms save for the occasional off-balance feeling when turning the head rapidly toward the tumor side—a natural equivalent to the head thrust test. Patients with such loss of peripheral function may have little postoperative vertigo, whereas those with preserved function up until the time that one or both vestibular nerves are cut in removing the tumor often have severe vertigo, nystagmus, and the ocular tilt reaction.[130]

The disparity between typical responses to stable and fluctuating losses underlies the rationale behind use of ablative therapies such as intratympanic gentamicin, vestibular neurectomy, and labyrinthectomy for intractable Meniere's disease. After the initial period of compensation, patients who had previously suffered frequent bouts of vertigo usually have relatively few and tolerable vestibular symptoms, so long as contralateral function is intact and stable (reviewed by Blakley[131]).

The difference between stable and fluctuating losses also has diagnostic importance. Because stable vestibular deficits generally do not cause ongoing vertigo, recurrent vertigo in the setting of a well-compensated vestibular loss should be seen as a sign of further fluctuation in vestibular function. This fluctuation may be due to a reactivation of a quiescent disease process such as Meniere's disease, or the appearance of a new labyrinthine problem. A relatively common example of the latter is occurrence of posterior canal BPPV in 15% to 30% of patients who previously had vestibular neuritis.[132,133] As noted in the clinical implications of Principle 7, vestibular neuritis usually involves the superior vestibular nerve and its endorgans, sparing the saccule and posterior canal, which are supplied by the inferior vestibular nerve. It is thought that the damage to the labyrinth can cause release of otoconia from the utricle, and that these otoconia then settle in the posterior canal, precipitating BPPV. Typical posterior canal BPPV can develop in an ear that had vestibular neuritis even months after the onset of the neuritis.

The Effect of Suppressive Drugs on Vestibular Compensation

Patients with the acute syndrome of unilateral vestibular hypofunction are commonly given medications to alleviate their distressing symptoms: benzodiazepines (e.g., diazepam), anticholinergic agents (e.g., meclizine), and antiemetic agents (e.g., promethazine). Although these drugs are invaluable for the acute relief of these distressing symptoms, they can be counterproductive to vestibular compensation if continued for too long. Recall that central adaptation is partially driven by error signals, the sensory mismatch that occurs, for example, between the vestibular signals and visual signals when the VOR fails. These sensory mismatches cause a sense of vertigo in patients with recent-onset unilateral hypofunction as they begin moving once the static symptoms have abated. Suppressing this vertigo with the continued use of some medications can prolong or even prevent vestibular compensation. Studying the effects of medications on vestibular compensation after unilateral labyrinthectomy in cats, Peppard[134] found that the commonly used vestibular symptom suppressants diazepam, scopolamine and dimenhydrinate could hinder the rate and extent of compensation. Meclizine probably has similar effects. Conversely, a combination of a stimulant (amphetamine) and a general antiemetic (trimethobenzamide) had a beneficial effect in enhancing compensation, perhaps because increased physical activity corresponded to more head movements that challenged the system and drove compensation.

The Basis of Vestibular Rehabilitation

A variety of rehabilitation regimens have been constructed around the principle that vestibular compensation is driven by sensory mismatches, particularly between the visual and vestibular systems. Not only do these mismatches drive changes in the gain of remaining vestibular reflexes, but they also engender compensatory changes in other motor systems to replace lost vestibular functions. Examples are the central preprogramming of eye movements and of postural responses, the potentiation of the cervico-ocular reflex, and modification of saccadic eye movements. Sensory substitution of visual and somatosensory cues for the lost vestibular cues may also contribute to overall compensation.[135]

Although controlled studies of vestibular rehabilitation are difficult to perform, these programs generally do improve the subjective sense of balance in persons with fixed loss of vestibular function and often improve their objective performance on balance tests, as well as returning them to many of their activities of daily living.[136-138]

Appendix

Experimental and clinical vestibular tests often employ sinusoidal head rotations at different frequencies as stimuli, and report results in terms of VOR *gain*, *phase*, and *time constant*. These terms describe the *frequency response* of the system. The concept of the frequency response of a system is familiar to anyone who has used a graphic equalizer on a stereo system (Fig. 163-32A). Setting the sliders determines how much attenuation of the incoming signal is applied to each frequency band. The resulting output can be graphically described by the *Bode plot* (see Fig. 163-32B). In the example shown in Figure 163-32, the equalizer is set up as a low-pass filter, letting through low frequencies but attenuating high frequencies. The goal of the following analysis is to derive the frequency response—the Bode plot—for the semicircular canal.

Equation 163-8, which describes the movement of the cupula, can be written as

$$\ddot{\Theta}(t) = \ddot{H}(t) - \frac{B}{I}\dot{\Theta}(t) - \frac{K}{I}\Theta(t) \qquad \text{Eq. 163-13}$$

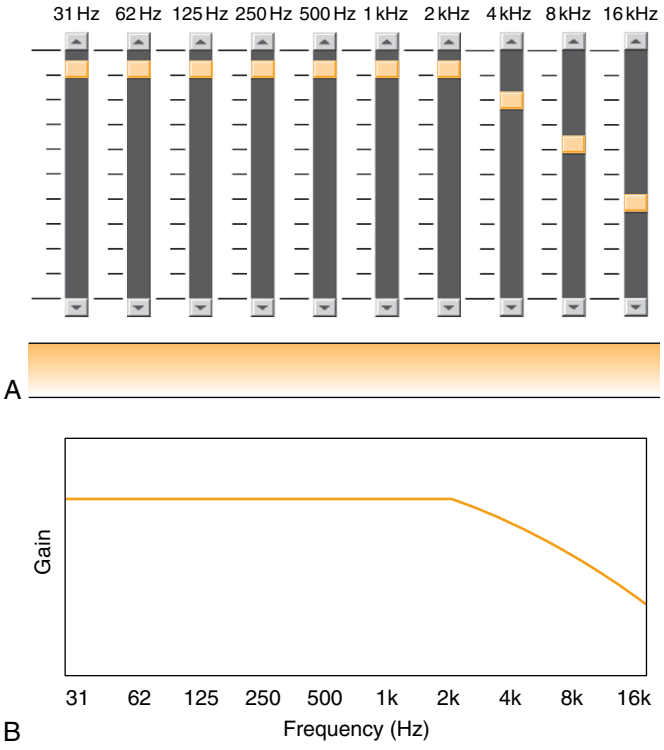

Figure 163-32. **A,** The graphic equalizer provides a means of setting signal strength (gain) across frequencies. **B,** The analytical expression of this is the Bode gain plot.

This differential equation is expressed as a function of time, or *in the time domain*. Although it can be solved as a function of time, our principal interest is to determine this system's frequency dependence. Thus, it is useful to transform this equation into the *frequency domain*. The French mathematician Laplace (1749-1827) devised a method to transform differential equations in the time domain to algebraic equations in the frequency domain. The latter are much easier to solve, and once the solution is obtained, tables can be used to look up the time-domain equivalent if it is needed. The power of Laplace's technique, however, is that it immediately gives the frequency response of the system in the form of a *transfer function* in the frequency domain. Transfer functions, which describe the input-output characteristics of systems across frequencies, are fundamental to the study of the auditory and vestibular systems.

The Laplace transform is

$$f(s) = L\{F(t)\} = \int_0^\infty e^{-st} F(t)\,dt, \text{ where } s = \sigma + j\omega. \qquad \text{Eq. 163-14}$$

The Laplace transform essentially converts signals that vary in time into those that vary in frequency by using complex exponentials. This works because most natural signals can be represented as some combination of functions that have exponential growth or decay and sinusoidal oscillations. Equations of the form $F(t) = Ae^{\sigma t}$ describe exponential growth or decay. Those of the form $F(t) = Ae^{j\omega t}$ describe sinusoidal oscillations, because

$$Ae^{j\omega t} = A(\cos\omega t + j\sin\omega t) \qquad \text{Eq. 163-15}$$

Thus, the complex exponential term $e^{-(\sigma+j\omega)t}$, encompasses most signals.

The following two features of the Laplace transform make it of such practical use in converting differential equations to algebraic ones. If $L\{Y(t)\} = y(s)$,

1. $$L\{\dot{Y}(t)\} = sy(s) - Y(0) \qquad \text{Eq. 163-16}$$

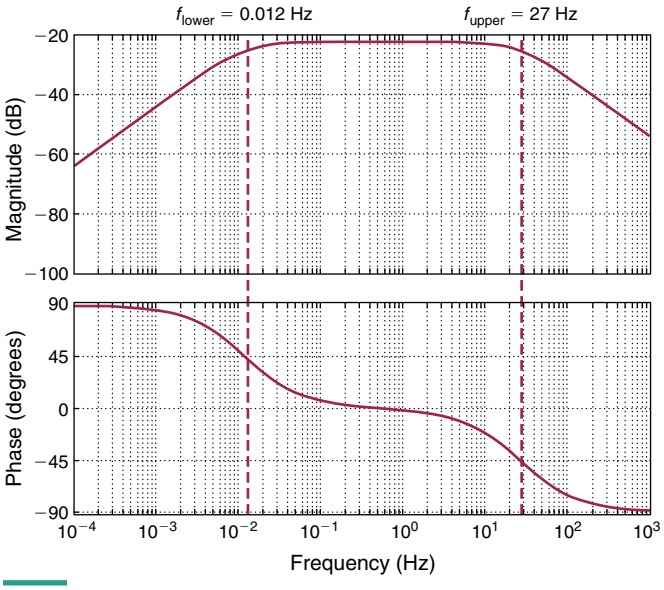

Figure 163-33. Gain (**A**) and phase (**B**) plots for the semicircular canal transfer function relative to head velocity as given in Equation 163-20. Upper and lower corner frequencies (*f*) are indicated.

That is, the Laplace transform of a derivative is just *s* times the Laplace transform of the function, minus the value of the function at time zero. The value at time zero often is 0. Thus, *differentiation* in the *time* domain becomes *multiplication* by *s* in the *frequency* domain.

2. $$L\left\{\int Y(t)\,dt\right\} = \frac{y(s)}{s} \qquad \text{Eq. 163-17}$$

That is, the Laplace transform of an integral is just the Laplace transform of the function divided by *s*. Thus, *integration in the time domain becomes division by s in the frequency domain.*

Using these features, Equation 163-13 can now be written in the frequency domain:

$$s^2\Theta(s) = s\dot{H}(s) - s\frac{B}{I}\Theta(s) - \frac{K}{I}\Theta(s) \qquad \text{Eq. 163-18}$$

or

$$\frac{\Theta(s)}{\dot{H}(s)} = \frac{s}{s^2 + s\frac{B}{I} + \frac{K}{I}} = \frac{I}{K} \times \frac{s}{\frac{I}{K}s^2 + \frac{B}{K}s + 1} \qquad \text{Eq. 163-19}$$

Combining the different constants gives

$$\frac{\Theta(s)}{\dot{H}(s)} = \frac{\tau_1\tau_2 s}{(\tau_1 s + 1)(\tau_2 s + 1)} \qquad \text{Eq. 163-20}$$

where $\tau_1\tau_2 = {}^{1}\!/_{K}$ and $\tau_1 + \tau_2 = {}^{B}\!/_{K}$. Values for these time constants have been estimated at $\tau_1 \approx 0.006$ second and $\tau_2 \approx 13$ seconds.[82]

Note that Equation 163-20 gives the desired relationship between the motion of the endolymph (output) and the head velocity (input). This input-output relationship is the transfer function of the semicircular canal. The shown or frequency response of this transfer function can be obtained by standard engineering mathematics and is shown in Figure 163-33. This plot shows that the expected endolymph motion is indeed in phase with head velocity and has a constant gain over a wide frequency range, from approximately 0.012 to 27 Hz. Thus, over this frequency range, the *semicircular canal approximately encodes head velocity*.

Although this range encompasses most natural head movements, it should be noted that the canal is not a particularly good encoder of head velocity for very low frequency rotations. For example, whereas a slow turn at 0.02 Hz is sensed with little attenuation (1.4 dB below the

flat midfrequency gain), the phase shift is approximately 32 degrees. This deficiency in the performance of the canals at low frequencies is improved by the central mechanism of *velocity storage* (see Principle 9).

Acknowledgments

We would like to thank Dr. Philip Cremer (Sydney, Australia) for the inspiration to explain vestibular physiology with a few fundamental principles. Principle 4 is directly attributed to him. We also thank Dr. Thomas Haslwanter (Linz, Austria) for comments on the manuscript.

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CHAPTER ONE HUNDRED AND SIXTY-FOUR

Evaluation of the Patient with Dizziness

Timothy E. Hullar

David S. Zee

Lloyd B. Minor

Key Points

- Imbalance can be due to dysfunction of either the peripheral or the central vestibular system.
- A careful clinical history is critical for determining the cause of imbalance; identification of symptom duration and triggers is key.
- The bedside examination often offers clues to the diagnosis, especially in patients who are asymptomatic at the time of the visit.
- Evaluation of eye movements and hearing assessment are the central parts of the physical examination.
- Laboratory tests must be used judiciously to investigate specific diagnostic entities suggested by the clinical history and bedside examination.
- Determination of treatment options depends on an accurate diagnosis.
- Specific exercises can help patients adapt to long-term balance deficits.

Background

Dizziness is the ninth most common complaint leading patients to visit their primary care physicians, rising to third among those 65 to 75 years of age and first among older patients.[1,2] Despite its frequency, symptoms of dizziness can be difficult for the patient to describe and for the physician to categorize. *Dysequilibrium*, *unsteadiness*, *vertigo*, and *lightheadedness* all are terms that patients may use to describe their sensations. Evaluation of balance signals from peripheral vestibular nerve afferents, the visual system, and somatosensory and proprioceptive receptors normally occurs below a patient's level of awareness, making symptoms particularly difficult to describe.

This chapter outlines an approach to the evaluation of patients with dizziness that builds on an understanding of the pathophysiology of dizziness to develop an organized method for history taking and physical examination leading to the identification of specific abnormalities. A description of some of the physiological and functional principles underlying the symptoms and signs of vestibular disorders is presented first. (A comprehensive description of these topics is provided in Chapter 163.) Using an approach based on these considerations, the clinical evaluation, including the history, physical examination, and quantitative tests of vestibular function, is described next. Finally, the adaptive capabilities of the vestibular system and principles of vestibular rehabilitation are reviewed.

Fundamentals of Vestibular Function

Peripheral Anatomy and Physiology

The vestibular receptors are located in the labyrinth and consist bilaterally of three orthogonally oriented semicircular canals and two otolith organs. The semicircular canals sense angular acceleration and are arranged in roughly parallel pairs: the two horizontal (also called "lateral") canals, the left anterior and right posterior canals, and the right anterior and left posterior canals. The orthogonal geometry of the semicircular canals in each labyrinth permits three-dimensional rotational head movements to be represented as the vector sum of components in each plane. Most vestibular nerve afferents have a spontaneous firing rate between 10 and 100 spikes/second. When the head is still, primary afferents in the right and left vestibular periphery discharge tonically at the same rate. During horizontal head rotation, the horizontal semicircular canal is stimulated in the ipsilateral labyrinth and inhibited in the opposite. During vigorous horizontal head rotations, many afferents and central vestibular neurons on the inhibited side are silenced.[3,4]

Over the physiologic range of head movements (0.1 to 15 Hz), the intrinsic mechanical properties of the semicircular canals integrate this acceleration signal into a velocity signal. This signal is further modified by individual afferents, providing central vestibular neurons with an array of signals carrying velocity and acceleration information. Activity in the vestibular nerve is the major source of sensory input to the vestibular nuclei, with almost 30,000 afferents projecting from each labyrinth to the brainstem in humans.[5] Neurons in the vestibular nuclei typically receive bilateral inputs from the coplanar semicircular canals (direct projections from afferent nerve fibers on the ipsilateral side and commissural projections from central vestibular neurons that cross from the contralateral side), with excitation of peripheral afferents causing increased firing rates of the neurons in the ipsilateral vestibular nucleus.

Eye Movements

Vestibular information is vital to controlling both eye movements and body posture, but eye movements are the more easily studied and the

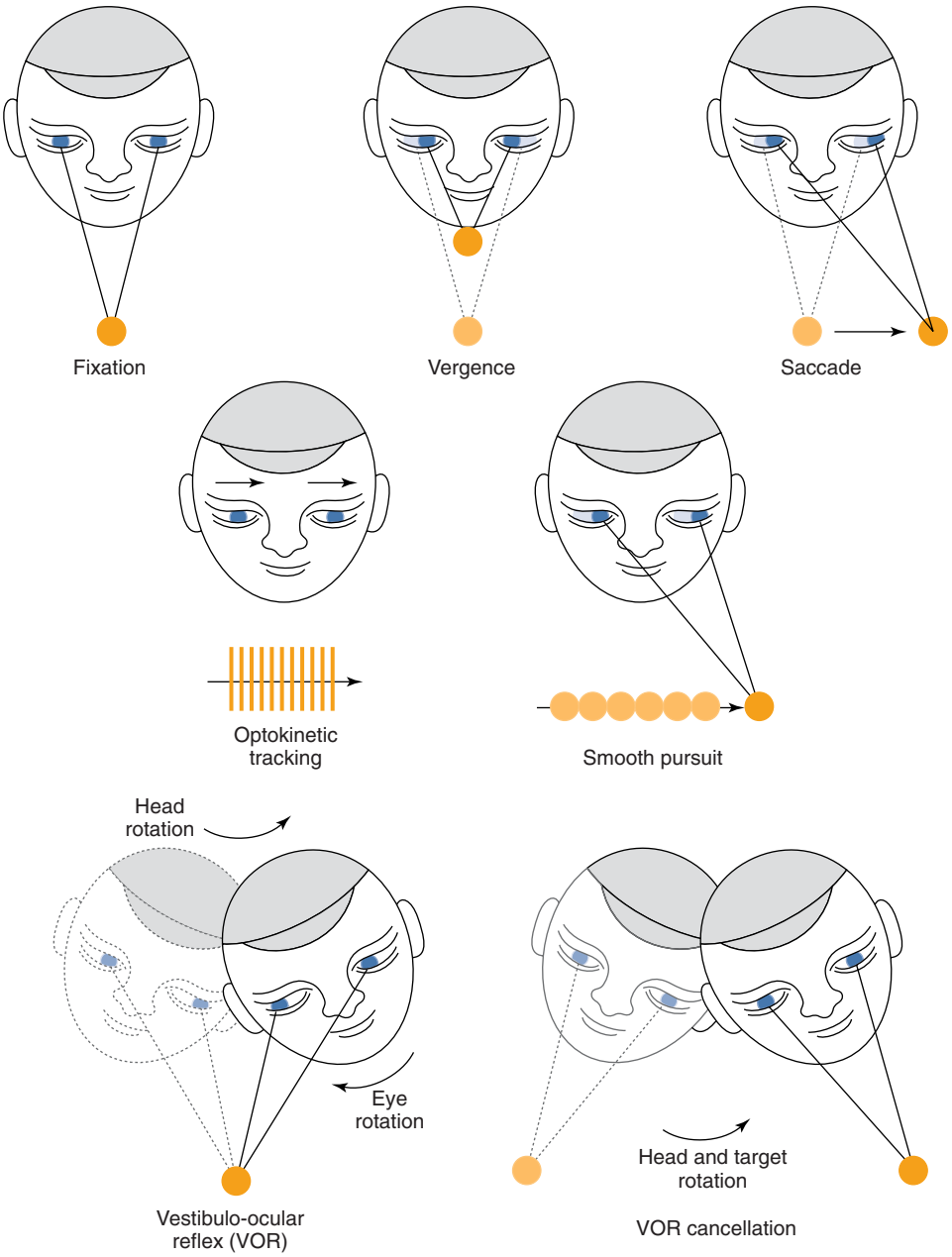


Figure 164-1. Schematic depiction of the functional classes of eye movements. Basic research in the neurophysiology of oculomotor control and clinical studies of eye movement disorders have been enhanced by the recognition of functionally distinct subsystems. Seven types of eye movements are shown.

better understood of the two. All eye movements are aimed at ensuring optimal visual acuity (Fig. 164-1). Vestibular and optokinetic eye movements work to hold eye position in space (i.e., *gaze*) constant by producing compensatory eye movements that keep images stable on the retina during head movements. Saccadic, pursuit, and vergence eye movements change gaze so that images of objects of interest are brought to or kept on the fovea, where visual resolution is highest. Saccades rotate the eye to bring an image onto the fovea, whereas pursuit maintains that image on the fovea as it moves across the visual field. Vergence movements are disjunctive, causing the eyes to move in opposite directions to place the image of an object simultaneously on both foveae during movements of the head or the object (Table 164-1).

Visual acuity is degraded if images slip across the retina even as slowly as 2 to 3 degrees/second.[6] Vestibulo-ocular reflexes (VORs) are responsible for maintaining binocular fixation and stabilizing binocular foveal images during head movements.[7] The VORs are divided into two types: angular and translational. *Angular* reflexes are initiated by activation of the semicircular canals. The canals are aligned with the pulling directions of the three pairs of extraocular muscles,[8] so that activation of a single semicircular canal (as in benign positional vertigo or canal dehiscence) leads to motion of the eyes about an axis that aligns with the axis of the semicircular canal (Fig. 164-2). The latency of the angular reflex is approximately 7 msec in humans.[9]

Translational VORs are driven by otolith afferents and can be grouped into two categories according to the eye movement responses: *tilt* responses, which compensate for lateral head tilt with respect to gravity, and *translational* responses, which produce eye movements compensatory for linear movements of the head (Fig. 164-3). Lateral head tilt produces ocular counter-rolling, a torsional movement of the eye about the line of sight. The torsional deviation of the eyes in response to 60- to 75-degree static head tilts is 6 to 8 degrees.[10] The small amplitude of eye movement produced by relatively large tilts of

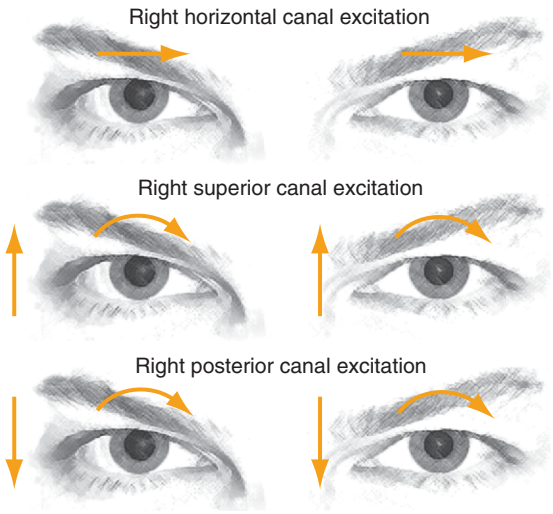


Figure 164-2. Relationship of individual canals and eye movements. Activation of individual canals leads to stereotypical eye movements. The horizontal canal is activated by head rotation in the horizontal plane, whereas pure activation of the posterior canal may be seen in benign positional vertigo, and pure activation of the superior canal is seen in superior canal dehiscence syndrome. All *arrows* represent direction of slow phase eye movements. *(From Hullar TE, Minor LB. The neurotologic examination. In: Jackler RK, Brackmann DE, eds.* Neurotology. *2nd ed. St Louis: Mosby; 2004:215-277.)*

Table 164-1

Functional Classes of Human Eye Movements

Class of Eye Movement	Main Function
Visual fixation	Holds the image of a stationary object on the fovea
Vestibular	Holds images of the seen world steady on the retina during brief head rotations
Optokinetic	Holds images of the seen world steady on the retina during sustained head rotations
Smooth pursuit	Holds the image of a moving target on the fovea
Nystagmus	The repetition of a compensatory slow phase and quick phase resetting movement of the eyes; in quick phases, gaze directed toward the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions so that images of a single object are placed simultaneously on both foveas

the head appears to indicate that ocular counterrolling is a vestigial response with little compensatory function, but during lower-amplitude sinusoidal head rolls, the torsional gain is significantly greater. Compensatory eye movements in these situations seem to result largely from canal-related reflexes, although the otolith organs also are

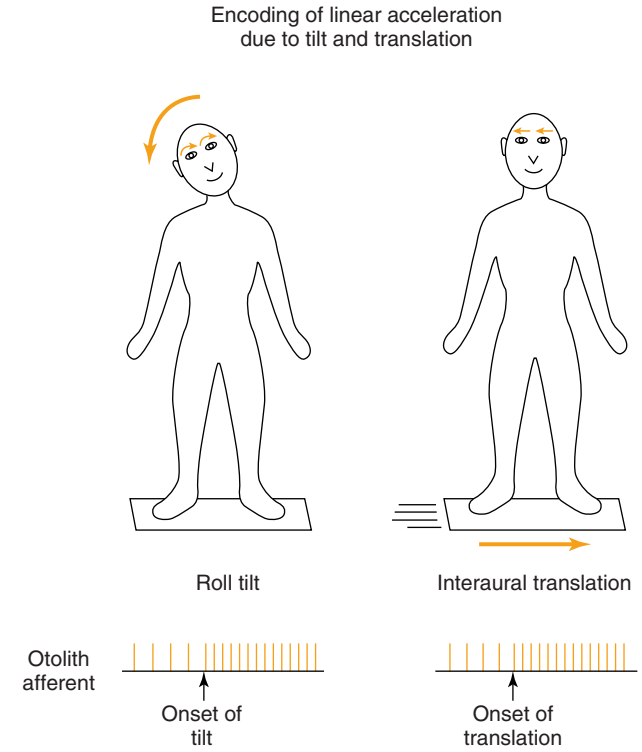


Figure 164-3. Otolith afferents respond to linear acceleration. Identical changes in otolith afferent activity can result from head movements that change the orientation of the head relative to gravity (roll tilt) and from linear translational movement (interaural translation). There is no way for otolith afferents to distinguish whether a translation or a tilt produced the modulation in otolith afferent activity. The compensatory eye movements evoked by these two types of head movements are quite different, as shown on the diagram. Central processing of signals in the brainstem must be responsible for resolution of the so-called translation-tilt ambiguity. *(From Minor LB. Physiological principles of vestibular function on earth and in space.* Otolaryngol Head Neck Surg. *1998;118:54.)*

activated.[11] Translational VORs produce eye movements that maintain the point of binocular fixation for each retina during linear head movements.

Otolith afferents cannot distinguish between tilt and translation. Information from the semicircular canals, comparison of the phasic and tonic components of modulation in otolith afferent activation, frequency-selective organization of otolith-mediated responses, or other sensory signals such as vision or proprioception must be involved in determining appropriate reflex responses. For example, tilting of the head involves both canal and otolith activation, and the combined activation of these receptors provides cues to the brain that the modulation in otolith activity is due to a tilt and not to a linear head movement. Frequency-selective filtering of otolith afferent signals provides another complementary mechanism. Head movements that change slowly with respect to gravity (frequency content less than 0.25 Hz) may be interpreted as tilt stimuli, whereas those with higher frequency content lead to responses that are directed to maintaining stable gaze during linear head movements.[12,13]

Head Movements

Compared with the relatively simple task of the six muscles moving each eye, the 20 muscles moving the neck must contend with more complicated planar relationships, the substantial inertia of the head, and the effect of stretch reflexes and muscular co-contraction. The situation is even more complicated because the trunk and lower extremities are involved in maintaining posture and upright stance. Two reflexes are important for stabilizing the head. The vestibulocollic reflex

(VCR) governs the activation of neck muscles in response to vestibular input,[14] and the cervicocollic reflex (CCR) governs the activation of neck muscles in response to stretch receptors.[15] Studies of head stability during locomotion in humans have shown that the peak velocity of these rotational head perturbations generally does not exceed 150 degrees/second, but their predominant frequency can be as high as 5 Hz, with a frequency for some components of head movements up to 15 Hz.[16-19] Studies of head movements in patients who have lost vestibular function indicate that head stability can be achieved by way of the mechanical properties of head and neck muscles, rather than neural reflexive factors.[20,21] The CCR, consisting of compensatory eye movements during head-on-body rotation caused by neck proprioception, contributes little to gaze stability in healthy people, although it may become more important if labyrinthine function is lost.[22,23]

Combinations of eye and head movements are used to acquire and track a target of interest, as well as to stabilize gaze in response to perturbations of the body. Voluntary eye-head movements can be thought of as either saccadic or pursuit in nature. During small eye-head saccades (less than 30 degrees), the shift of gaze may be achieved by superposition of an internal saccadic command and the VOR.[21] For larger eye-head saccades (more than approximately 40 degrees), the VOR appears to be "turned off" or "disconnected." Nevertheless, the vestibular signal caused by the head movement is still available so that an accurate gaze change can be achieved.[24] During smooth eye-head tracking, more than one mechanism may operate to override the VOR so that gaze follows the moving target smoothly. Evidence suggests that an internal smooth pursuit signal partly cancels the VOR, and that an additional mechanism may be reduction in the activity or partial suppression of the VOR during such eye-head tracking.[25-28] Disorders causing impairment of smooth pursuit usually, but not always, also cause deficits of smooth, combined, eye-head tracking.[29] Patients who have lost vestibular function, on the other hand, often show combined eye-head tracking that is superior to ocular pursuit.[26]

Posture

Active processes for control of the body's center of gravity are involved in maintaining postural stability in healthy subjects. The center of gravity is located in the lower abdominal area and slightly forward of the ankle joints in a healthy person standing erect. In humans, the goal of postural control is to maintain sway within the limits of stability for different body positions and activities. The limits of stability are defined by a horizontal ellipse measuring approximately 12.5 degrees from front to back. The lateral dimension of limits of stability depends on the subject's height relative to spacing between the feet. For a person 70 inches tall with feet placed 4 inches apart, the lateral dimension of the "limits of stability" ellipse is approximately 16 degrees from left to right.

Postural responses to perturbations (movement of the support surface or body) are organized into discrete patterns about the ankles and hips. The pattern(s) to be used depends on structure of the support surface and position of the center of gravity relative to limits of stability. Movements of the body about the ankle joints are the effectors of the *ankle strategy.* The ankle strategy is effective when the center of gravity moves slowly and within the limits of stability, and the support surface is longer than the feet and strong enough to resist torque about the ankles. When it is not possible to exert an adequate amount of torque around the ankle joint, healthy subjects invoke a *hip strategy*. This strategy consists of exerting a horizontal shear force on the support surface by counterphase leg and trunk movements about the hip. The hip strategy also is effective when the center of gravity moves rapidly or approaches the limits of stability.

Contributions of the Brainstem and Cerebellum

The cupula of the semicircular canal returns to neutral position with a time constant of approximately 6 seconds, but the associated decay in eye movements is closer to 15 seconds in normal humans because of the effect of a process termed *velocity storage*. The neural center responsible for this process is located in the brainstem. This mechanism improves the capability of the system to respond to low-frequency head motion[30] and to orient vestibulo-ocular responses to gravity.[31,32] Velocity storage is (transiently) lost in cases of acute unilateral vestibular loss and remains diminished in the long term.

The *neural integrator* is another brainstem mechanism vital for proper eye movements.[33] It produces a steady command to the extraocular muscles to hold the eyes eccentrically, instead of allowing them to drift back to neutral gaze position because of the elastic restoring forces of the orbital tissues. Proper function of the neural integrator also is necessary for the VOR to have the appropriate phase (timing) relationship to head rotation. The neural integrator is not able to hold gaze appropriately in cases of acute unilateral deafferentation.

The cerebellum plays an important role in immediate and long-term adaptive ocular motor control.[34] Lesions of the flocculus impair smooth pursuit and VOR cancellation, which normally allows the eyes to move with head rotations to follow a target.[35] Floccular lesions may cause horizontal gaze-evoked nystagmus, downbeat nystagmus, rebound nystagmus, increased or decreased amplitude (gain) of the VOR, and postsaccadic drift, or *glissades*.

The vestibulocerebellum also is important for ensuring that the eyes rotate in a plane parallel to head rotation so that images can be stabilized appropriately on the retina.[36] The dorsal vermis and underlying fastigial nuclei are important in the control of saccadic amplitude and smooth pursuit; lesions here produce saccadic inaccuracy (dysmetria) and impair the ability to make long-term adaptive adjustments in saccade accuracy.[37] Other "cerebellar" eye signs, which cannot be localized precisely, include square-wave jerks, defective convergence, divergence nystagmus, and alternating hyperdeviation (skew) on lateral gaze.[38]

Approach to the Patient with Dizziness

History

In many cases a specific cause for a patient's dizziness can be determined from an accurate history alone. Taking the history of a patient with a complaint related to dizziness must begin in an open-ended fashion, allowing the patient to describe the symptoms with minimal direction from the clinician. The process can be facilitated by asking the patient to complete and return a questionnaire about symptoms before the first appointment.

From the history, the clinician should have a general idea of whether the symptoms are attributable to a vestibular disorder and, if so, whether this disorder is central or peripheral in origin. An outline of diagnostic possibilities based on symptoms and signs is shown in Figure 164-4.

- Does the patient have vertigo? Vertigo is an illusory sense of motion. The patient can feel as if the motion is internal or that objects in the surroundings are moving or tilting. The sense of motion can be rotatory, linear, or a change in orientation relative to the vertical. Vertigo indicates a problem within the vestibular system, although the abnormality can be located anywhere within the system. Lightheadedness, as opposed to vertigo, may indicate presyncope. Although often related to neural factors, such as vasovagal syncope, it also can reflect cardiac disease, especially in older patients. Generalized imbalance may reflect more central processes, including mal de débarquement or migraine. Some conditions, such as migraine, can manifest with nonspecific imbalance symptoms in addition to acute vertigo.

- What happened the first time the imbalance occurred? The onset of symptoms with straining can be indicative of a disorder such as semicircular canal dehiscence or perilymphatic fistula. Straining also can lead to presyncope in a vasovagal reaction. In women, the association of symptoms with menstrual periods can indicate migraine. A correlation of symptoms with a large salt load should raise suspicion for Meniere's disease. The onset of symptoms after head trauma may indicate benign paroxysmal positional vertigo.

- Are the symptoms episodic or continuous, and if episodic, how long do they last? Most vestibulopathies cause fluctuating or episodic symptoms, although a constant sense of dysequilibrium may be

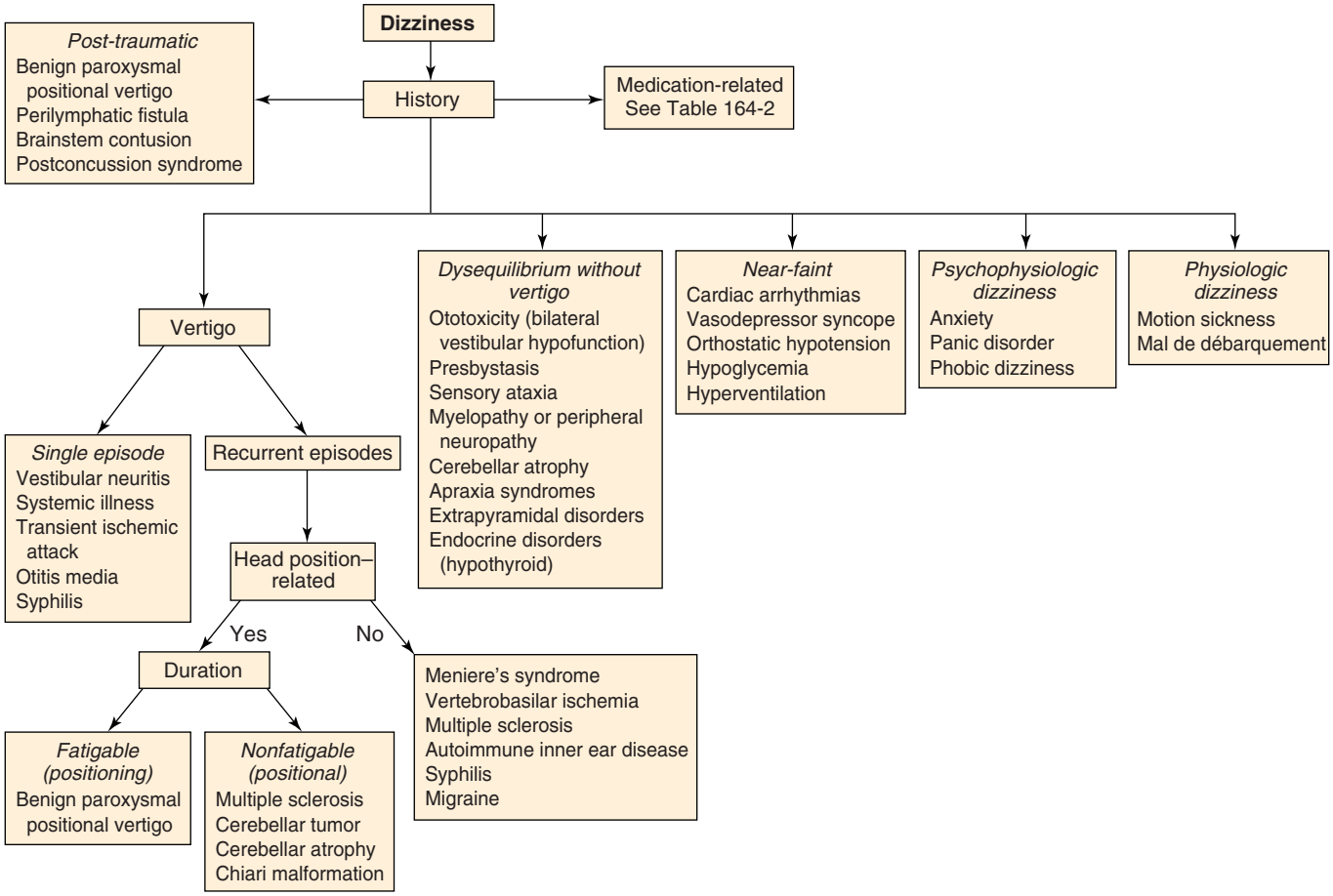


Figure 164-4. Algorithm for the differential diagnosis for dizziness, based on information from the patient's history. *(Modified from Baloh RW, Fife TD, Furman JM, Zee DS. The approach to the patient with dizziness. In: Mancall EL, ed.* Continuum: Lifelong Learning in Neurology. *Vol 2. Cleveland: Advanstar Communication; 1996:25-36.)*

present in addition to the more variable elements of the symptom complex. Migraine tends to be episodic, with each episode lasting hours to days. Benign paroxysmal positional vertigo (BPPV) is episodic but lasts a short time, although patients may note that they are "susceptible" to head motion for weeks and then not susceptible at other times. Continuous symptoms may reflect a condition such as mal de débarquement, migraine, or psychogenic dizziness.

- What brings on the problem? The diagnosis of certain vestibulopathies is strongly suggested from events or movements that trigger symptoms.
  - *Movement of the head*. BPPV of the posterior canal classically begins on rolling over in bed or tilting the head backward and toward the affected ear. BPPV of the horizontal canal can be brought on by lying with the head flat on the bed then turning it to the side. Rapid head movements may uncover vestibular hypofunction by producing a sensation of *oscillopsia* (an illusion of motion for objects that are known to be stationary). When induced by head movements, oscillopsia often is a sign of vestibular hypofunction. Brief (5 to 10 seconds) periods of vertigo, either spontaneous or sometimes induced by certain head movements, may be a sign of vascular compression of the eighth cranial nerve complex.
  - *Lifestyle*. Patients with vestibular migraine may report that certain foods such as caffeine, cheeses, wine, and other foodstuffs can bring on symptoms. The symptoms also may be induced by stress or lack of sleep.
  - *Environment*. Changes in the weather, menses, or motion stimulation such as ceiling fans or video games may bring on problems for patients who have vestibular migraine. Fluorescent lights also may cause a problem. In patients with canal dehiscence, symptoms may be brought on by loud sounds or by maneuvers that change middle ear or intracranial pressure. Changes in seasons also may provoke symptoms in patients with Meniere's disease or migraine, possibly as a result of allergy.
  - *Pressure*. Patients with semicircular canal dehiscence, perilymphatic fistula, or enlarged vestibular aqueduct may have problems with acute pressure changes such as in performing a Valsalva maneuver, coughing, or straining.
- What other signs and symptoms are associated with the dizziness or vertigo? A sensation of aural fullness and tinnitus can precede an attack of vertigo in patients with Meniere's disease. Sweating, dyspnea, and palpitations often accompany panic attacks but also may indicate a cardiogenic cause for presyncope manifesting as imbalance. Migraine-related vertigo may or may not be accompanied by an aura or headache. Other neurologic signs may indicate central mass effect or vascular pathology.
- Is there a family history of imbalance or headache? Migraine-related vertigo can run in families, and the same may be true for Meniere's disease. Otosclerosis, which can be accompanied by imbalance, also has a genetic component. Some genetic conditions, such as CHARGE syndrome (i.e., *c*oloboma, *h*eart anomalies, choanal *a*tresia, *r*etardation of growth and development, and *g*enital and *e*ar anomalies), have a prominent vestibular phenotype.
- Are there other, psychogenic disorders that may be responsible for the patient's symptoms? Anxiety disorders, panic syndromes, and agoraphobia can lead to episodic vertigo that mimics a vestibulopa-

thy. These conditions are frequent in patients with dizziness. Patients with psychogenic dizziness often describe generalized imbalance that lasts for long periods.

- Are there underlying medical problems that may cause or exacerbate the patient's symptoms? Thyroid disease, diabetes mellitus, anemia, autoimmune diseases, infections such as syphilis or Lyme disease, hypoperfusion of the brain from postural hypotension, and cardiac arrhythmias all can lead to dizziness or vertigo. Patients with migraine are more likely to experience BPPV than are those who do not have migraine. Medications also can produce symptoms that mimic vestibular disorders (Table 164-2).

Physical Exam

The physical examination is goal-directed at testing hypotheses made from the history. Each physician will develop an individual approach, with elements of the examination tailored to specific symptoms reported by the patient. A careful bedside examination, including a general otolaryngologic exam, often can be sufficient for appropriate vestibular diagnosis. In some cases, laboratory tests or quantitative methods for evaluation of vestibular function, or both, are important to help make the diagnosis or to document pathophysiologic changes or recovery during the clinical course.

Bedside Exam

No clinical test can directly measure the function of the vestibular periphery. Instead, inferences must be made about vestibular function on the basis of the performance of "downstream" processes. The most important and well-studied of these are eye movements. Use of *Frenzel lenses* (magnifying lenses that prevent the patient from using visual fixation to suppress any spontaneous nystagmus) can increase the examiner's sensitivity for nystagmus and is vital to a thorough ocular examination.

Nystagmus

Eye movements indicative of a vestibular disorder commonly take the form of nystagmus. Several different types of nystagmus are recognized (Table 164-3). The most common is *jerk nystagmus*, which consists of

Table 164-2

Type and Mechanism of Dizziness Associated with Commonly Used Drugs

Drug(s)	Type(s) of Dizziness	Mechanism(s)
Aminoglycosides, cisplatin	Vertigo, dysequilibrium	Damage to vestibular hair cells
Tranquilizers	Intoxication	Central nervous system depression
Antiepileptics	Dysequilibrium	Cerebellar toxicity
Antihypertensives, diuretics	Near-syncope	Postural hypotension, reduced cerebral blood flow
Amiodarone	Dysequilibrium and oscillopsia	Unknown
Alcohol	Intoxication, dysequilibrium, positional vertigo	Central nervous system depression, cerebellar toxicity, change in cupular and endolymphatic specific gravity
Methotrexate	Dysequilibrium	Brainstem and cerebellar toxicity
Anticoagulants	Vertigo	Hemorrhage into inner ear or brain

From Baloh RW, Fife TD, Furman JM, Zee DS. The approach to the patient with dizziness. In: Mancall EI, ed. *Continuum: Lifelong Learning in Neurology*. Vol 2. Cleveland: Advanstar Communications; 1996:25-36.

Table 164-3

Clinical Observations and Causes of Nystagmus

Observation	Cause(s)
Sinusoidal oscillation without fast phases: "pendular nystagmus"	Multiple sclerosis, toluene intoxication, or brainstem infarction with inferior olivary hypertrophy (the syndrome of palatomyoclonus)[a,b] Acquired pendular nystagmus frequently disconjugate; may even be horizontal in one eye and vertical in the other May be responsive to memantine[c]
Purely torsional nystagmus	Intrinsic brainstem involvement within the vestibular nuclei; suggestive of syringomyelia[d]
Downbeat nystagmus	Arnold-Chiari deformity or degenerative lesions of the cerebellum[e] Treated with 4-aminopyridine
Upbeat nystagmus	Lesions at the pontomedullary or pontomesencephalic junction or within the fourth ventricle[f]
Horizontal jerk nystagmus that changes direction approximately every 2 minutes: "periodic alternating nystagmus"	Lesions in the nodulus of the cerebellum[g,h] Treated with baclofen
Nystagmus on attempted eccentric gaze and with slow phases that show a declining exponential time course	Side effect of certain medications, especially anticonvulsants, hypnotics, and tranquilizers, and in patients with disease of the vestibulocerebellum or its brainstem connections in the medial vestibular nucleus and nucleus prepositus hypoglossi[i]

Table 164-3

Clinical Observations and Causes of Nystagmus—cont'd

Observation	Cause(s)
Accelerating slow phases accentuated by attempted fixation, decreased by convergence or active eyelid closure, associated with a head turn, and sometimes accompanied by "reversed" smooth pursuit: "infantile" or "congenital" nystagmus	May be related to central or peripheral deficits[j] May be associated with albinism, retinal diseases, and early visual deprivation May be responsive to neurontin or memantine[j,k]
Gaze-evoked nystagmus that may dampen and actually change direction ("centripetal nystagmus") and often is followed by rebound nystagmus (slow phases are directed toward the previous position of eccentric gaze) when the eyes return to the primary position	Peripheral vestibular lesions, drug intoxication, and cerebellar lesions[l] Rebound nystagmus associated with many cerebellar lesions, including olivocerebellar atrophy[m]
Slow phases with exponentially increasing waveforms	Congenital nystagmus and acquired lesions of the cerebellum
Nystagmus of greater intensity or present only in the abducting eye: "dissociated nystagmus"	Commonly occurs in patients with internuclear ophthalmoplegia (INO) Mechanism unknown for abducting nystagmus in INO[n]
One eye goes up and the other goes down: "seesaw nystagmus"	Midbrain lesions May be related to an imbalance of activity in structures that receive projections from the labyrinthine otolith organs[o]
Slow phases directed centrally and with retraction of the eye into the orbit: "convergence-retraction nystagmus"	Midbrain lesions May be a failure of saccades or of vergence[p] Usually coexists with upgaze paralysis (Parinaud's syndrome)
Skew deviation and the ocular tilt reaction (one half-cycle of seesaw nystagmus)	Occurs with acute peripheral vestibular (otolith organ) lesions and with lesions in the medulla, the pons, and the midbrain Often associated with head tilt[q]
Nystagmus occurring in a plane other than that of vestibular stimulation: "perverted nystagmus"	Central vestibular disorders; multiple sclerosis[r]

[a]Data from Hain TC, Zee DS, Maria BL. Tilt suppression of vestibulo-ocular reflex in patients with cerebellar lesions. *Acta Otolaryngol*. 1988;105:13-20.
[b]Data from Nakada T, Kwee IL. Oculopalatal myoclonus. *Brain*. 1986;109(Pt 3):431-441.
[c]Data from Stahl JS, Rottach KG, Averbuch-Heller L, et al. A pilot study of gabapentin as treatment for acquired nystagmus. *Neuroophthalmology*. 1996;16:107-113.
[d]Data from Noseworthy JH, Ebers GC, Leigh RJ, et al. Torsional nystagmus: quantitative features and possible pathogenesis. *Neurology*. 1988;38:992-994.
[e]Data from Baloh RW, Yee RD. Spontaneous vertical nystagmus. *Rev Neurol (Paris)*. 1989;145:527-532.
[f]Data from Ranalli PJ, Sharpe JA. Upbeat nystagmus and the ventral tegmental pathway of the upward vestibuloocular reflex. *Neurology*. 1988;38:1329-1330.
[g]Data from Leigh RJ, Robinson DA, Zee DS. A hypothetical explanation for periodic alternating nystagmus: instability in the optokinetic-vestibular system. *Ann N Y Acad Sci*. 1988;374:619-635.
[h]Data from Waespe W, Cohen B, Raphan T. Dynamic modification of the vestibulo-ocular reflex by the nodulus and uvula. *Science*. 1985;228:199-202.
[i]Data from Lewis RF, Zee DS. Ocular motor disorders associated with cerebellar lesions: pathophysiology and topical localization. *Rev Neurol (Paris)*. 1993;149:665-677.
[j]Data from Jacobs JB, Dell'Osso LF. Congenital nystagmus: hypotheses for its genesis and complex waveforms within a behavioral ocular motor system model. *J Vis*. 2004;4:604-625.
[k]Data from McLean R, Proudlock F, Thomas S, Degg C, Gottlob I. Congenital nystagmus: randomized, controlled, double-masked trial of memantine/gabapentin. *Ann Neurol*. 2007;61:130-138.
[l]Data from Leech J, Gresty M, Hess K, Rudge P. Gaze failure, drifting eye movements, and centripetal nystagmus in cerebellar disease. *Br J Ophthalmol*. 1977;61:774-781.
[m]Data from Bondar RL, Sharpe JA, Lewis AJ. Rebound nystagmus in olivocerebellar atrophy: a clinicopathological correlation. *Ann Neurol*. 1984;15:474-477.
[n]Data from Zee DS, Hain TC, Carl JR. Abduction nystagmus in internuclear ophthalmoplegia. *Ann Neurol*. 1987;21:383-388.
[o]Data from Nakada T, Kwee IL. Seesaw nystagmus. Role of visuovestibular interaction in its pathogenesis. *J Clin Neuroophthalmol*. 1988;8:171-177.
[p]Data from Rambold H, Kompf D, Helmchen C. Convergence retraction nystagmus: a disorder of vergence? *Ann Neurol*. 2001;50:677-681.
[q]Data from Parulekar MV, Dai S, Buncic JR, Wong AM. Head position-dependent changes in ocular torsion and vertical misalignment in skew deviation. *Arch Ophthalmol*. 2008;126:899-905.
[r]Data from Minagar A, Sheremata WA, Tusa RJ. Perverted head-shaking nystagmus: a possible mechanism. *Neurology*. 2001;57:887-889.

so-called slow phases, which represent vestibular signals for eye movements, and fast phases, which represent resetting actions bringing the eyes back toward the center of the orbit but are not as relevant for diagnostic purposes. The direction of nystagmus often is named for the direction of the fast phases, because the fast phases are more obvious on clinical examination. The trajectory of the slow phases should be scrutinized for the following characteristics of individual slow phases: (1) an increase in velocity, as is commonly found with congenital nystagmus; (2) a decrease in velocity, as is seen in patients with cerebellar lesions; and (3) a constant velocity, as is typical for vestibular disturbances.

Spontaneous nystagmus of vestibular origin arises from an imbalance in tonic levels of activity mediating the VOR. The spontaneous nystagmus resulting from unilateral vestibular hypofunction is a jerk nystagmus and is present when the head is still, is reduced by visual fixation, and is increased or becomes apparent only when fixation is eliminated during use of Frenzel lenses. A horizontal-torsional nystagmus typically is observed acutely after unilateral loss of vestibular function. The horizontal component beats toward the "stronger" (intact) ear, and the torsional component involves beating of the superior poles of the eyes toward the intact ear.

The characteristics of nystagmus when the eyes are directed away from center often adds additional diagnostic information. The patient is asked to maintain eccentric horizontal and then vertical positions of gaze (approximately 30 degrees from center orientation). Minimal drift normally should be encountered for periods up to 15 seconds. Nystagmus arising from peripheral lesions and some central lesions is more intense (slow-phase velocity is higher) when the eyes are turned in the direction of the quick phase.[39] This effect, known as *Alexander's law* (Fig. 164-5), is due to the combination of gaze-evoked nystagmus (caused by the initial loss of the neural integrator after a peripheral lesion) and with the vestibular nystagmus caused by the static asymmetry of the lesion itself. The two factors add on looking away from the lesion and cancel each other on looking toward it. *Bruns' nystagmus*, found in patients with cerebellopontine angle tumors, is a combination of gaze-evoked nystagmus with low-frequency, large-amplitude, fast phases on looking toward the side of the lesion and jerk nystagmus with high-frequency, small-amplitude, fast phases on looking the other way.[40] The gaze-holding component of the nystagmus may represent an adaptation to the jerk nystagmus caused by vestibular imbalance.[41] Horizontal gaze–evoked nystagmus is a hallmark of lesions in the medial vestibular nucleus and nucleus prepositus hypoglossi complex. Low-amplitude gaze-evoked nystagmus often is a side effect of many types of medications, including hypnotics, sedatives, and anxiolytics. Many healthy persons may exhibit some physiologic, horizontal, end-gaze nystagmus. It usually disappears once the target is brought back into view of both eyes (i.e., at approximately 30 degrees of eccentricity).

The effect of vergence should be noted, because it may intensify or cause a change in direction of some central forms of vestibular nystagmus or may dampen congenital nystagmus.

Skew Deviation and Ocular Tilt Reaction

Skew deviation is a vertical misalignment of the eyes that cannot be explained on the basis of an ocular muscle palsy (Fig. 164-6). It is the hallmark of an imbalance in tonic levels of activity along peripheral or central pathways mediating otolith-ocular reflexes.[42] Patients with skew deviation often complain of vertical diplopia and sometimes torsional diplopia (one image tilted with respect to the other). The *alternate cover test* is used to detect skew deviation: The examiner covers one eye of the patient with a card and then moves the cover to the patient's other eye while looking for a vertical corrective movement as an index of a vertical misalignment. A skew deviation also can be detected by covering one eye with a red glass (Maddox rod) to dissociate images seen in the two eyes and inquiring whether the patient sees one image above the other, indicating vertical misalignment. The effect of position of the eye in the orbit and of left and right head tilt on the skew also should be examined. Skew deviations tend to be relatively comitant (i.e., the degree of misalignment changes little with different direction

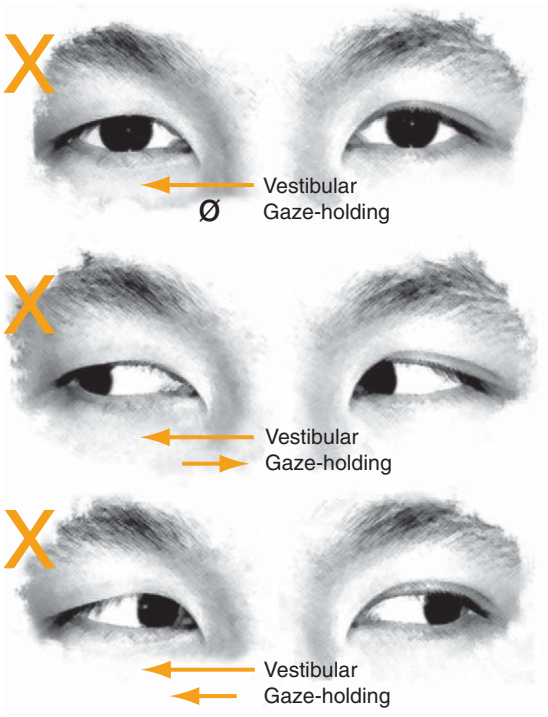


Figure 164-5. Alexander's law. With an acute deficit of the right labyrinth, vestibular input drives the eyes to the right (slow-phase component of nystagmus). A defective neural integrator (caused by the unilateral loss) tends to bring the eyes back to neutral position. With the eyes directed toward the lesion, the two effects cancel. With the eyes directed away from the lesion, they add. *(From Hullar TE, Minor LB. The neurotologic examination. In: Jackler RK, Brackmann DE, eds.* Neurotology. *2nd ed. St. Louis: Mosby: 2004:215-227.)*

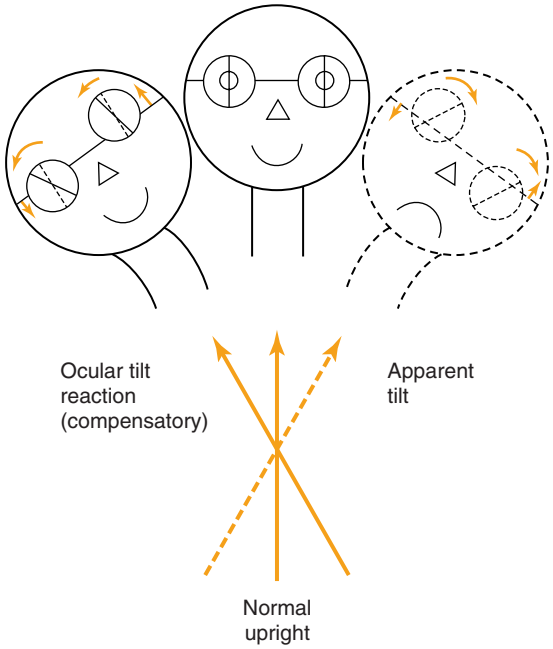


Figure 164-6. The ocular tilt reaction depicted as motor compensation to a lesion-induced apparent eye-head tile *(dashed line)*. The compensatory head tilt is in a direction opposite to the apparent head tilt *(solid line)*. Eyes and head are continuously adjusted to the orientation that the brain computes as being vertical. *(From Brandt T, Dieterich M. Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions.* Brain. *1987;110:649.)*

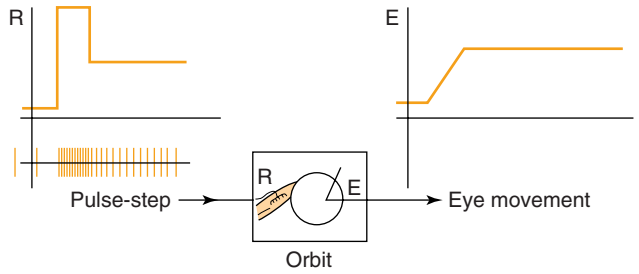


Figure 164-7. The neural signal for a saccade. At *right* is shown the eye movement: E is eye position in the orbit; the abscissa scale represents time. At *left* is shown the neural signal sent to the extraocular muscles to produce the saccade. The *vertical lines* indicate the occurrence of action potentials of an ocular motoneuron. The *graph* above plots the neuron's discharge rate (R) against time (firing frequency histogram). It shows the neurally encoded pulse (velocity command) and step (position command).

of gaze), whereas a fourth cranial nerve palsy causes a vertical misalignment that is greatest with the affected eye down and medial. The adducting eye is higher and the misalignment is greater with the head tilted toward the side of the higher eye. Skew deviations in otolith-ocular imbalance do not show such a clear relation to changes in eye and head position, although they may be decreased or disappear when the affected person is supine.[43] The lower eye is on the side of the lesion with peripheral or vestibular nucleus lesions. Otolith-ocular pathways cross at the level of the vestibular nucleus, so lesions above the decussation result in the higher eye being on the side of the lesion (such as with lesions of the medial longitudinal fasciculus causing internuclear ophthalmoplegia). The head usually is tilted toward the side of the lower eye. Skew deviations also can occur with cerebellar lesions.

Saccades

Rapid changes in gaze from one target to another are achieved by *saccades*. The neural signal for a saccade includes a *pulse* of activity, which brings the eye to its new position, and a *step*, which is a constant neural signal holding the eye at its new position in the orbit (Fig. 164-7). Saccades are examined by asking the patient to alternately fixate (with the head still) on the examiner's nose and then on the finger, held at different locations at approximately 15 degrees away from primary position. Measures of saccades such as accuracy, velocity, and stability represent the effects of the neural pulse, the step, and the match between pulse and step.[44] An error in the pulse amplitude creates overshoot or undershoot dysmetria. This is characteristic of disorders of the dorsal vermis or the fastigial nuclei of the cerebellum, although it appears with lesions in other parts of the nervous system. *Wallenberg's syndrome* produces a specific pattern of saccadic dysmetria: Saccades overshoot to the side of the lesion, undershoot away from the side of the lesion, and, with attempted purely vertical saccades, show an inappropriate horizontal component toward the side of the lesion. Lesions of the superior cerebellar peduncle produce just the opposite: Saccades overshoot when directed away from the side of the lesion.[45]

Normally, saccades follow a relatively invariant relationship between peak velocity and amplitude termed the *main sequence*.[46] A decrease in the height of the saccadic pulse causes slow saccades. Slow horizontal saccades usually imply disease of the pons such as olivopontocerebellar atrophy (spinal cerebellar atrophy type 2 [SCA2]). Slow vertical saccades usually imply disease affecting the midbrain such as progressive supranuclear palsy, Huntington's disease, or Niemann-Pick disease. A mismatch between the size of the pulse and step produces brief (several hundred milliseconds) postsaccadic drift, or glissades. Postsaccadic drift occurs with disease of the cerebellar flocculus. The combination of slow, hypometric saccades and postsaccadic drift also occurs in patients with internuclear ophthalmoplegia, oculomotor nerve palsies, myasthenia gravis, and ocular myopathies. Hypermetric saccades with macrosaccadic oscillations (large saccades about the position of the target) typically are found in patients with lesions in the midline deep cerebellar nuclei.[47] Saccadic oscillations without an intersaccadic interval (back-to-back, to-and-fro saccades) are called *ocular flutter* when they are limited to the horizontal plane and *opsoclonus* when they are multidirectional (horizontal, vertical, torsional). Either type of oscillation may occur in patients with various types of encephalitis or postinfectious immune-mediated processes, as a paraneoplastic remote effect of neuroblastoma or other tumors, or in association with toxins. Ocular flutter also may be voluntarily elicited by some normal people.[48]

The normal saccadic latency is approximately 200 msec, but this latency is increased by disorders of saccadic initiation. Impaired saccadic initiation has been reported in patients with a variety of conditions, including frontal lobe lesions, congenital or acquired oculomotor apraxia, Huntington's disease, progressive supranuclear palsy, and Alzheimer's disease. Patients with bilateral frontal lobe lesions or Parkinson's disease also have difficulty in rapidly alternating gaze between two stationary targets. Patients with Huntington's disease show a characteristic defect in initiating more voluntary, as opposed to more reflexive, saccades. They have particular difficulty in predictive tracking and are unable to suppress inappropriate saccades to the visual target.[49]

Inappropriate saccades disrupt steady fixation.[50] They include *square-wave jerks,* which are small-amplitude (up to 5 degrees) saccades that take the eyes off target and are followed within 200 msec by a corrective saccade. Square-wave jerks may occur in healthy elderly persons or in patients with cerebral hemisphere lesions but are especially prominent in patients with progressive supranuclear palsy and cerebellar disease. Square-wave jerks may be an exaggeration of the microsaccades that occur in healthy people during fixation and can be detected most easily by ophthalmoscopy when the patient is instructed to fixate on a target seen with the other eye. Macro square-wave jerks (10 to 40 degrees in amplitude, with a short intersaccadic interval) have been observed in patients with multiple sclerosis and olivopontocerebellar atrophy.

Smooth Pursuit

The tracking movements of the eyes used to follow an object moving across the field of view, caused by either motion of the object or motion of the viewer, are mediated by the smooth pursuit system. This requires that other gaze-stabilizing inputs, such as vestibular or optokinetic, be suppressed. Smooth pursuit is tested by having the patient follow targets moving no faster than 20 degrees/second. Asymmetries in horizontal tracking, as reflected by the presence of more corrective saccades in one direction, are more helpful in identification of an abnormality than is an overall symmetrical decrease in smooth tracking unless it is profound. Smooth pursuit mechanisms assist visual fixation, suppressing nystagmus from peripheral but not central lesions.

Patients with lesions affecting the temporo-occipital region have been reported to have selective defects in motion detection[24] and are unable to make accurate smooth pursuit or accurate saccadic eye movements because of this deficit.[51] Patients with posterior cortical lesions exhibit a unidirectional (ipsilateral) deficit for smooth pursuit and also a defect of motion detection in the contralateral hemifield.[51] Experimental lesions of dorsolateral pontine nuclei also cause an ipsilateral deficit of smooth pursuit tracking.[52] Lesions of frontal eye fields impair pursuit eye movements,[53] and lesions within the flocculus impair smooth pursuit, especially for ipsilateral tracking. The flocculus projects to the ipsilateral vestibular nuclei, and lesions of this area, including those associated with Wallenberg's syndrome, mainly impair contralateral smooth pursuit.[54]

In addition to the asymmetric deficits of pursuit that may occur with focal lesions, a variety of conditions may bilaterally impair smooth pursuit. A common cause of impaired smooth pursuit is the effect of medications such as anticonvulsants and sedatives. Smooth pursuit is performed less well by elderly persons and is impaired in patients with a variety of neurologic conditions such as Parkinson's disease, progressive supranuclear palsy, and Alzheimer's disease and in those with schizophrenia. In patients with congenital nystagmus, smooth pursuit may appear "reversed," with slow phases directed opposite to the motion of the target.[55] The pathomechanism for this apparent reversal of smooth pursuit is controversial.[56] Disease of the cerebral hemisphere

may produce a low-amplitude horizontal nystagmus in primary position with constant-velocity slow phases directed toward the intact hemisphere. Slow-phase velocity is not decreased by fixation. This nystagmus may result from an imbalance of pursuit tone.

Optokinetic

During sustained rotations, the vestibular signal decays and becomes a poor indicator of head motion. This effect is well known to pilots, who are trained not to trust the vestibular system during prolonged turns. The optokinetic system drives the eyes to follow the visual surround during low-frequency (sustained) head movements. Optokinetic nystagmus (OKN) is a response to motion of the entire visual field, rather than to a particular target (for which the smooth pursuit system is used), and is responsible for effects such as automatic visual tracking of a picket fence seen from a moving car. Use of a bedside optokinetic tape is a convenient way to elicit OKN. Because smooth-pursuit tracking contributes to the generation of optokinetic responses, many of the abnormalities resulting in smooth pursuit deficits also lead to impaired OKN.

Vestibulo-Ocular Reflex Cancellation

The ability of a patient to maintain steady gaze on a target moving in tandem with the head is attributable to cancellation of the VOR. The patient is instructed to fixate on an object (such as the examiner's finger) that moves with the patient's head. A deficit of VOR cancellation is interpreted in conjunction with results obtained from evaluating VOR amplitude.

Vergence

Vergence eye movements, found in frontal-eyed animals such as humans, are disjunctive (opposite direction) responses to changes in gaze. They are necessary, for example, when a target is brought nearer to the viewer and the gaze of each eye converges to keep its image aligned on both retinas. Vergence can be generated volitionally or reflexively and, with accommodation of the lens and papillary constriction, is one element of the "near triad" for close viewing. Eye movements involved in vergence are under the control of several groups of neurons near the oculomotor nuclei.[57] Insufficient vergence causing diplopia at near viewing may be due to aging, stress, or head trauma.[58] Convergence spasm (which may be functional) or divergence paralysis has been mistakenly diagnosed as bilateral sixth nerve palsy. Divergence paralysis has been described with intracranial hypertension[59] or hypotension,[60] with lesions of the midbrain,[61] cerebellum, or in association with medication.[62]

Eye-Head Coordination

Unilateral labyrinthine loss may lead to a head tilt and counterrolling of the eyes.[42] Other disorders causing instability of the head include tremors such as those caused by Parkinson's disease and abnormal postures caused by dystonia and torticollis.[63] Patients with congenital nystagmus sometimes have a head tremor. Such head tremors usually do not compensate for the ocular oscillations, and both are likely to be caused by the same underlying disorder.[64] Intermittent head tremor also is a feature of spasmus nutans, which affects infants and young children.

Other features of this condition include head tilts and turns and nystagmus. The nystagmus is characteristically intermittent, of small amplitude and high frequency, and is typically asymmetric in the two eyes.[65] Any child seen with a monocular form of nystagmus requires a complete ophthalmologic examination and consideration of imaging studies to exclude a tumor of the anterior visual pathways. Disorders of eye-head saccades include involuntary head turning associated with focal epileptic seizures[66] and paresis of voluntary head turning associated with conjugate gaze palsy secondary to an acute lesion of one cerebral hemisphere. *Ocular motor apraxia*, which is characterized by the impaired ability to make voluntary eye movements, often is characterized by thrusting head movements by which the patient is able to shift gaze. These head movements are more conspicuous in the congenital form of ocular motor apraxia, which exclusively affects horizontal eye movements.[66,67] Acquired ocular motor apraxia is associated with bilateral frontoparietal hemispheral deficits, and horizontal and vertical head movements are affected.[68] Disorders causing impairment of smooth pursuit usually, but not always, cause commensurate deficits of smooth, combined, eye-head tracking.[29] Patients who also have lost vestibular function, on the other hand, often show combined eye-head tracking that is superior to smooth ocular pursuit, because no VOR occurs to cancel.[26]

Low-Frequency Vestibulo-Ocular Reflex

An abnormal VOR is indicated by the presence of corrective (catch-up) saccades during head rotations in the light. These can be identified by oscillating the patient's head smoothly left and right (yaw), followed by up and down (pitch) and then right-ear-down to left-ear-down positions (roll) at approximately 0.5 Hz. Because visual stimuli have little ability to generate torsional slow phases, responses to rotations of the head in roll reflect primarily labyrinthine (and possibly neck afferent) stimulation. Absence of torsional fast phases in one direction of head rotation in the roll plane points to a lesion in the rostral interstitial nucleus of the medial longitudinal fasciculus.[69]

Head-Shaking Nystagmus

Head-shaking nystagmus is a test of imbalance in dynamic vestibular function. With Frenzel lenses in place, the patient is instructed to shake the head vigorously approximately 30 times horizontally. Head shaking is stopped abruptly, and the examiner looks for any nystagmus. Healthy persons usually exhibit no or occasionally just a beat or two of head-shaking nystagmus. With a unilateral loss of labyrinthine function, however, a vigorous nystagmus is typical, with slow phases initially directed toward the lesioned side and then a reversal phase with slow phases directed oppositely.[70] The initial phase of head-shaking nystagmus arises because of asymmetry of peripheral inputs during high-velocity head rotations: More activity is generated during rotation toward the intact side than toward the affected side. This asymmetry leads to an accumulation of activity within central velocity storage mechanisms during head shaking. Nystagmus after head shaking reflects discharge of that activity.

The amplitude and duration of the initial phase of head-shaking nystagmus depend on the state of the velocity-storage mechanism. Because velocity storage typically is disabled during the immediate period after an acute unilateral vestibular loss, the primary phase of head-shaking nystagmus may be absent or attenuated in these circumstances. The reversal phase of head-shaking nystagmus reflects short-term adaptation, probably originating in the vestibular nerve and central pathways,[71] and may still be present in acute loss. With unilateral peripheral lesions, vertical head shaking may lead to a low-amplitude horizontal nystagmus, with slow phases directed toward the intact ear. Central lesions (such as those caused by cerebellar dysfunction) also may lead to head-shaking nystagmus, often with a vertical nystagmus after horizontal head shaking. It also is likely that head-shaking nystagmus may result from mechanical disturbances in the labyrinth (e.g., debris adherent to the semicircular canals) or an abnormality of the cupula itself.

Vibration

Vibration-induced nystagmus has been used as a diagnostic tool for patients with superior canal dehiscence. Application of a vibrator to the suboccipital area on the side of the dehiscence can induce a prominent vertical-torsional nystagmus consistent with activation of the dehiscent canal.[72] Vibration also has been shown to induce nystagmus with fast phases toward the intact side in patients with unilateral loss due to vestibular neuropathy or Meniere's disease.[73]

Head Impulse Test

The head impulse maneuver is uniquely able to examine individual canals and to test their responses to high-acceleration, high-frequency motions, whose pathology may be significantly different in genesis and effect from that in lower-frequency losses such as those identified on caloric testing.[74] Brief, high-acceleration horizontal head impulses in the excitatory direction of each canal are applied while the patient is instructed to look carefully at the examiner's nose (Fig. 164-8). A slow phase of abnormally low amplitude will be evoked in response to head

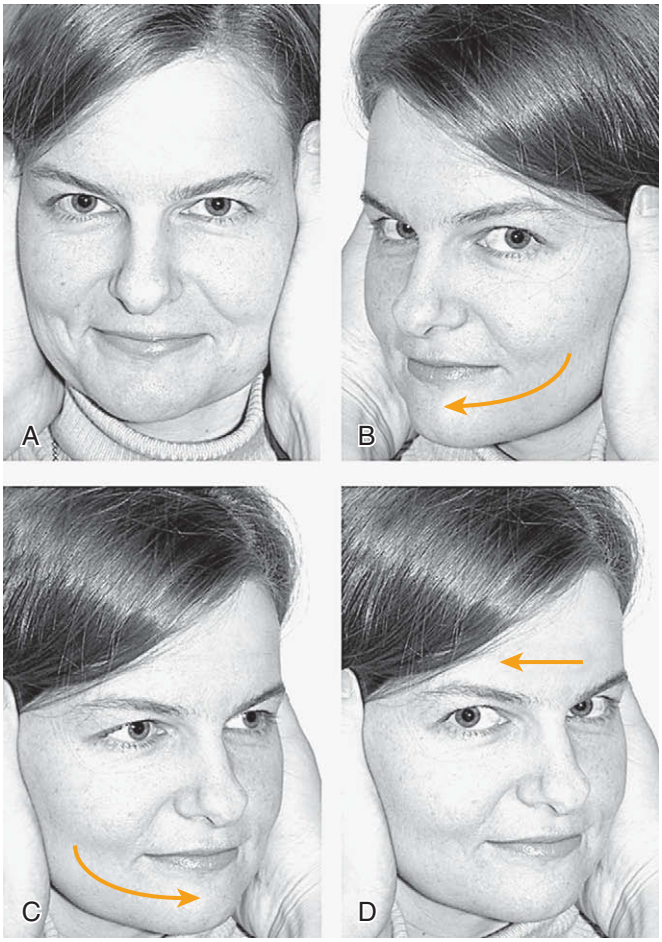


Figure 164-8. The head impulse sign. Starting from neutral position (**A**), a rapid head impulse to the right in the horizontal plane elicits compensatory eye movements to the left, and the patient's eyes remain stable on the examiner (**B**). With a similar movement to the left, a hypoactive labyrinth (**C**) results in a delayed catchup saccade (**D**) to maintain gaze. The *arrow* in **D** shows the direction of the catchup saccade. *(From Hullar TE, Minor LB. The neurotologic examination. In: Jackler RK, Brackmann DE, eds.* Neurotology. *2nd ed. St. Louis: Mosby: 2004:215-227.)*

impulse toward a lesioned or hypoactive labyrinth. A corrective rapid eye movement, required to bring the eyes back to the intended point of fixation, is seen in such cases. A full examination of the labyrinth involves head impulses in each of the three planes of the canals (horizontal, left anterior/right posterior, and right anterior/left posterior) in both directions for each plane. Detection of diminished function in the vertical canals through clinical observations on the head impulse test can be considerably more difficult than for the horizontal head impulse test.

Positional Testing

Positional (sustained) and positioning (transient) nystagmus are best observed with the patient wearing Frenzel lenses. Dix-Hallpike positioning for identification of posterior canal benign paroxysmal positional vertigo (BPPV) is performed first. The patient sits upright on an examination table. For testing to detect the presence of right posterior canal BPPV, the head is turned 45 degrees such that the chin is toward the right shoulder. The patient is then rapidly brought straight back into a right head-hanging position (Fig. 164-9). This position is maintained for at least 30 seconds. The nystagmus characteristic of BPPV begins after a latency of 2 to 10 seconds (although sometimes longer), increases in amplitude over approximately 10 seconds, and decreases in velocity over the next 30 seconds. Posterior canal BPPV results in a vertical-torsional nystagmus, with slow phases directed downward, with intorsion of the lower eye and extorsion of the higher eye. Because of the orientation of pulling directions for the oblique and vertical rectus muscles, the planar characteristics of the nystagmus relative to the orbit change with direction of gaze: on looking to the dependent ear, it appears more torsional and on looking to the higher ear, more vertical.

A horizontal canal variant of BPPV has been described. In these patients, a strong horizontal nystagmus builds up and declines over the same time course as for posterior canal BPPV. In some patients, the nystagmus beats toward the dependent ear (geotropic); in others, it beats away from the dependent ear (apogeotropic). The standard Dix-Hallpike maneuver may not elicit nystagmus in cases of horizontal canal BPPV. Such a nystagmus can be identified by bringing the patient backward into the supine, head-hanging position and then turning the head left-ear-down or right-ear-down. The nystagmus seen with horizontal canal BPPV may last longer than that seen in posterior canal BPPV. Such patients also may exhibit a small amount of spontaneous nystagmus when sitting upright, which varies as the head is pitched forward or backward. Anterior canal BPPV also has been described but is relatively rare. A sustained, usually horizontal positional nystagmus of low velocity is a common finding in patients with central or peripheral vestibular lesions and also may be present in asymptomatic human

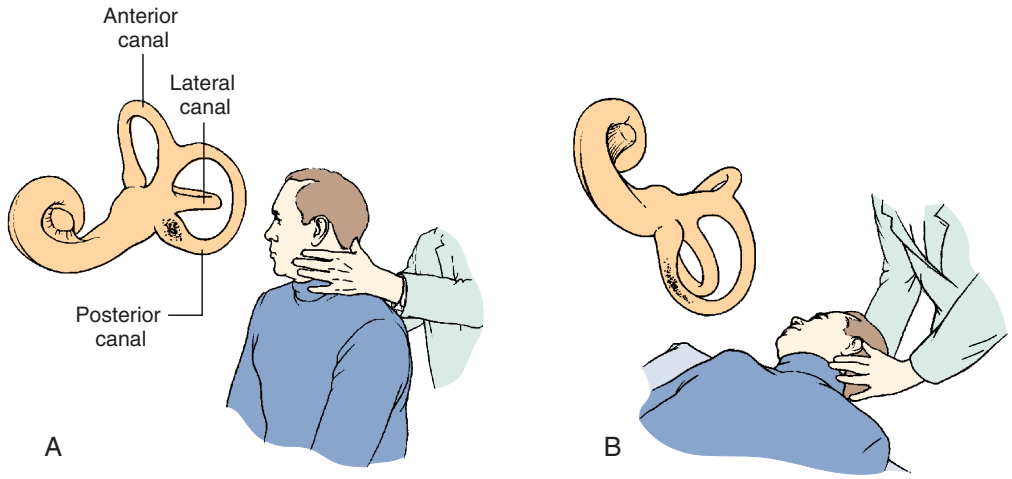


Figure 164-9. The Dix-Hallpike maneuver. Lowering the patient's head backwards and to the side allows debris in the posterior canal (**A**) to fall to its lowest position, activating the canal and causing eye movements and vertigo (**B**). *(From Hullar TE, Minor LB. Vestibular physiology and disorders of the labyrinth. In: Glasscock ME, Gulya AJ, eds.* Surgery of the Ear. *5th ed. Toronto: BC Decker; 2003.)*

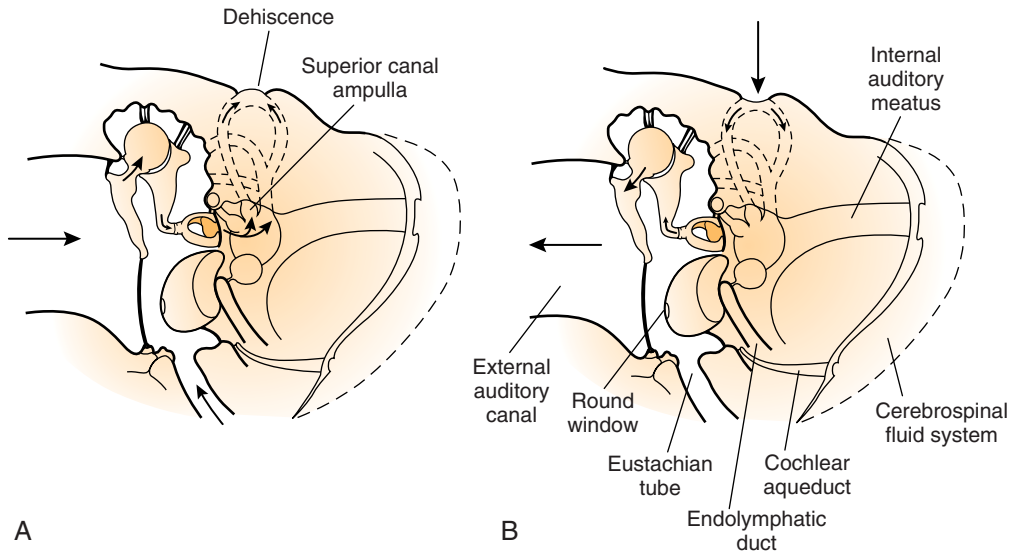


Figure 164-10. A, Pressure changes inducing eye movements in superior semicircular canal dehiscence syndrome. Positive pressure in the external auditory canal causes bulging of the membranous canal into the cranial cavity and ampullofugal flow (*arrows*). **B,** Negative pressure in the external auditory canal causes bulging of the cranial contents into the superior canal and ampullopetal flow (*arrows*). *(From Minor LB, Solomon D, Zinreich J, Zee DS. Sound- and/or pressure-induced vertigo due to bone dehiscence of the superior semicircular canal.* Arch Otolaryngol Head Neck Surg. *1998;124: 249-258.)*

subjects.[75] A central lesion is most likely when positional nystagmus is purely vertical or purely torsional or if the patient exhibits a sustained unidirectional horizontal positional nystagmus of high enough intensity to be observed without Frenzel lenses. Positional testing also may exacerbate a spontaneous nystagmus.

Dynamic Visual Acuity

Persons with normal vestibular function typically show no more than a one-line decline in visual acuity on the Snellen chart with head movement, whereas those with vestibular hypofunction (particularly bilateral hypofunction) may show up to a five-line decline in acuity with head movement.[23] To test for this effect, the patient's ability to read a Snellen chart with the head stationary is compared with acuity during horizontal head oscillations at a frequency of approximately 2 Hz. Patients with corrective lenses are instructed to wear their glasses or contact lenses during this testing. Quantitative analysis of dynamic visual acuity has revealed that retinal slip velocities of as little as 2 to 3 degrees/second result in oscillopsia and consequent loss of acuity.[6]

Vertical dynamic visual acuity also may be tested. The test can be improved by use of a computerized display, which prevents patients from seeing the Snellen chart when their head movements drop below a critical velocity at the ends of each oscillation.[76] Dynamic visual acuity also has been measured during rapid head movements and may, in some situations, serve as a useful proxy for quantitative measurement of angular VOR gain during these rapid head movements.

Eye Movements Evoked by Sound or Changes in Middle Ear Pressure

Changes in pressure in the inner ear can be induced by the Valsalva maneuver with the glottis closed (increasing intracranial pressure) and glottis open using a nose pinch (increasing middle ear pressure through the eustachian tube). In patients with superior canal dehiscence, nystagmus may be evoked by either or both maneuvers. The Valsalva maneuver with the glottis closed increases intracranial pressure and exerts force directly at the site of the dehiscence, causing deflection of the cupula of the superior canal toward the ampulla, in its "off" direction. On release of the pressure, the cupula is deflected in its preferred "on" direction, causing stimulatory nystagmus[77] (Fig. 164-10). The plane in which the eyes move during this nystagmus typically aligns with the plane of the affected superior canal. Craniocervical junction anomalies (e.g., Arnold-Chiari malformation), perilymph fistulas, and other abnormalities involving the ossicles, oval window, semicircular canals, or otolith organs also may cause vertigo with the Valsalva maneuver.

Tullio's phenomenon is the occurrence of vestibular symptoms and eye movements with exposure to sound. Motion of the tympanic membrane and ossicular chain can induce vertigo and nystagmus (*Hennebert's sign*) in patients with otic syphilis, perilymph fistula, and dehiscences of the semicircular canals. Superior semicircular canal dehiscence syndrome, caused by lack of bone covering the superior semicircular canal and arcuate eminence, may feature sound-evoked or pressure-evoked vertigo and conductive hearing loss.[78,79] If suspected, these causes should be investigated by moving the tympanic membrane with tragal compression or insufflation through a Siegle's speculum. Pure tones can be given over a range from 250 to 4000 Hz at intensities of 100 to 110 dB. The characteristic nystagmus evoked by activation of the superior canal is a vertical-torsional nystagmus with slow phases that are directed upward in the vertical plane and that involve motion of the superior pole of the eye away from the affected ear in the torsional plane. The eye movements evoked by sound or pressure stimuli in superior canal dehiscence typically are conjugate. Depending on the stimulus parameters and the effect of the dehiscence in individual patients, the evoked eye movements may be brief in duration and may not involve a sustained nystagmus.

Hyperventilation

Patients with anxiety or phobic disorders may sometimes hyperventilate and experience symptoms but usually do not show signs of nystagmus. Patients with demyelinating lesions on the vestibular nerve (such as an acoustic neuroma or compression by a small blood vessel) or with a central distribution (such as in multiple sclerosis) may show an excitatory (due to restoration of function) hyperventilation-induced nystagmus.[80] In the case of a peripheral lesion, the slow phase is away from the involved ear. Hyperventilation-induced nystagmus (usually a paretic nystagmus, with the slow phase toward the involved ear) rarely is noted in patients with pathologic conditions of the vestibular end organs alone.[81]

Vestibulospinal Function

Static imbalance in vestibulospinal reflexes is identified from Romberg testing, tandem walking, evaluation of past pointing, and the stepping test. The *Romberg test* is used to assess sway with feet together and tandem in eyes opened and closed condition. Falls during *tandem*

walking are suggestive of horizontal canal dysfunction. *Past pointing* of the arms to previously seen targets with eyes closed also may be a sign of vestibulospinal imbalance. It is best elicited by having the patient repetitively raise both arms over the head, with index fingers extended, and then bring them down, with eyes closed, toward the examiner's index fingers (but without actually touching them) located at waist level. For the *stepping test*, the patient, with eyes closed and arms outstretched, steps in place for at least 30 seconds.[82,83] A patient with acute labyrinthine asymmetry may turn to the weak side, in the direction of the slow phase of the nystagmus. This test sometimes is augmented with caloric stimulation.[84] Dynamic vestibulospinal function is assessed by observing postural stability during rapid turns or in response to external perturbations imposed by the examiner (i.e., a gentle shove forward, backward, or to the side). A complete examination of (1) gait, (2) strength, reflexes, and sensation in the legs, and (3) cerebellar function is essential for the interpretation of postural instability and dysequilibrium.

Sensory Integration

Balance relies on collection of vestibular, visual, and proprioception information and also on their appropriate central integration. The Clinical Test of Sensory Integration and Balance (CTSIB) is a simple series of bedside tests designed to evaluate these processes.[85,86] This test simulates the test conditions of dynamic computed posturography, detailed later on, with the patient standing on foam to disrupt proprioception and wearing a large paper lantern over the head, to simulate posturography's sway-reference condition. Results of the CTSIB correspond with dynamic posturography findings.[87]

Quantitative Testing

Quantitative tests of physiologic processes under vestibular control can be useful in identifying the cause of a patient's symptoms, confirming clinical findings, planning therapy, and monitoring the response to treatment.

Methods of Eye Movement Recordings

Three techniques can be used for quantitative measurement of eye movements. *Electronystagmography* (ENG) remains the most practical laboratory test to evaluate patients with dizziness or imbalance.[88] ENG can be helpful when the clinical picture suggests unilateral or bilateral vestibular hypofunction; disorders of oculomotor control such as deficits of smooth pursuit, saccades, or optokinetic eye movements; Meniere's disease or endolymphatic hydrops; BPPV; recurrent vestibulopathy; or migraine-associated dizziness. The quantitative information from ENG enables the clinician to monitor progression of or recovery from disorders affecting vestibulo-ocular control.

Electro-oculography (EOG) is based on the corneoretinal potential (difference in electrical charge potential between the cornea and the retina). The eye acts as an electrical dipole oriented along its long axis. Movement of this dipole relative to the surface electrodes produces an electrical signal corresponding to eye position. Surface electrodes are placed about each eye as shown in Figure 164-11. Horizontal eye movements typically can be resolved to an accuracy of 0.5 degree. Even under optimal recording conditions, however, the sensitivity of EOG is less than that of direct visual inspection (approximately 0.1 degree). Visual inspection of small-amplitude eye movements either directly or with the aid of Frenzel lenses or an ophthalmoscope is important for documentation of low-amplitude nystagmus. Vertically aligned electrodes sense voltage associated with eye and lid movement, so EOG cannot be used in the quantitative assessment of *vertical* eye movements. It is adequate, in most instances, for qualitative clinical assessment of vertical eye movement disorders and provides a useful monitor of eye blinks.[89] Torsional eye movements cannot be measured with EOG. For this reason, it is important for the examiner to look at the patient's eyes, either directly or with Frenzel lenses in place, during positioning testing so that the vertical-torsional nystagmus caused by posterior canal BPPV is not missed.

The *magnetic search coil technique* is based on the principle that voltage changes are induced in a coil of wire moving in an oscillating magnetic field.[89a] A minute wire is embedded in a plastic annulus that is inserted surrounding, but not actually touching, the cornea. Eye movements in three dimensions—horizontal, vertical, and torsional—can be resolved to an accuracy of approximately 0.02 degree (1-minute arc) and at speeds of up to 1000 samples per second. The technique also can be used to measure combined eye and head movements. The main disadvantage of search coil recordings is the level of expertise, in comparison with other techniques, required to set up the apparatus and conduct the recording sessions. Topical anesthetic drops are required to insert the search coil on the patient's eye. The risk of corneal abrasion is low when proper coil insertion and removal techniques are used.

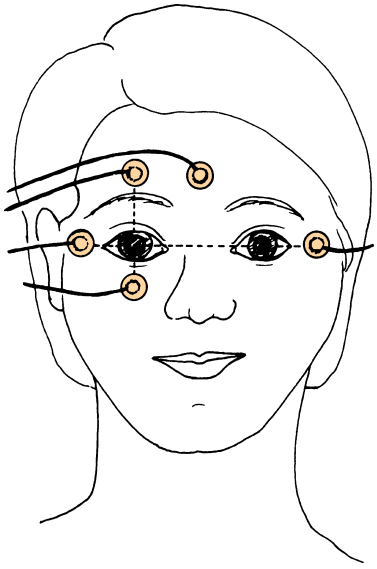


Figure 164-11. Surface electrodes are placed at outer canthi for recording horizontal eye movements and above and below one eye for recording vertical eye movements throughout the electronystagmographic procedure. A ground or reference electrode is placed on the forehead. If recordings are to be made of each eye independently, additional electrodes are placed at the inner canthus of the eye to be recorded.

Infrared video can monitor movement of the cornea or pupil. This technique can be used to record eye movements in three dimensions. Advantages are that the technique is noninvasive, requires little setup time, and is not associated with the position drifts (requiring repeated calibrations) seen with EOG. Disadvantages are that, although procedures and algorithms are improving at a rapid pace, image fitting and analysis techniques still do not work properly for some patients. The time resolution of these methods is poorer (lower sampling rates) than that available with search coil techniques.

Nystagmus

Eye movements are recorded with eyes closed and with eyes open and viewing a stationary visual target. A spontaneous nystagmus and effects of fixation suppression on this nystagmus are thereby determined. Effects of eye position on this nystagmus and the presence of gaze-evoked nystagmus are then assessed by asking the patient to look left, right, up, and down, much as in bedside testing as previously described. The recording of eye movements in darkness is a standard part of ENG testing.

Saccade Testing

The patient is instructed to fixate (with eye movements while keeping the head stationary) on a series of randomly displayed dots or lights at eccentricities of 5 to 30 degrees. Saccades typically begin with a latency of 180 to 200 msec after presentation of a target. Saccade velocity increases linearly with amplitude up to approximately 20 degrees but remains relatively constant for higher amplitudes (Fig. 164-12). Healthy persons consistently undershoot the target for saccades by more than 20 degrees. Asymmetries in saccade amplitude or peak

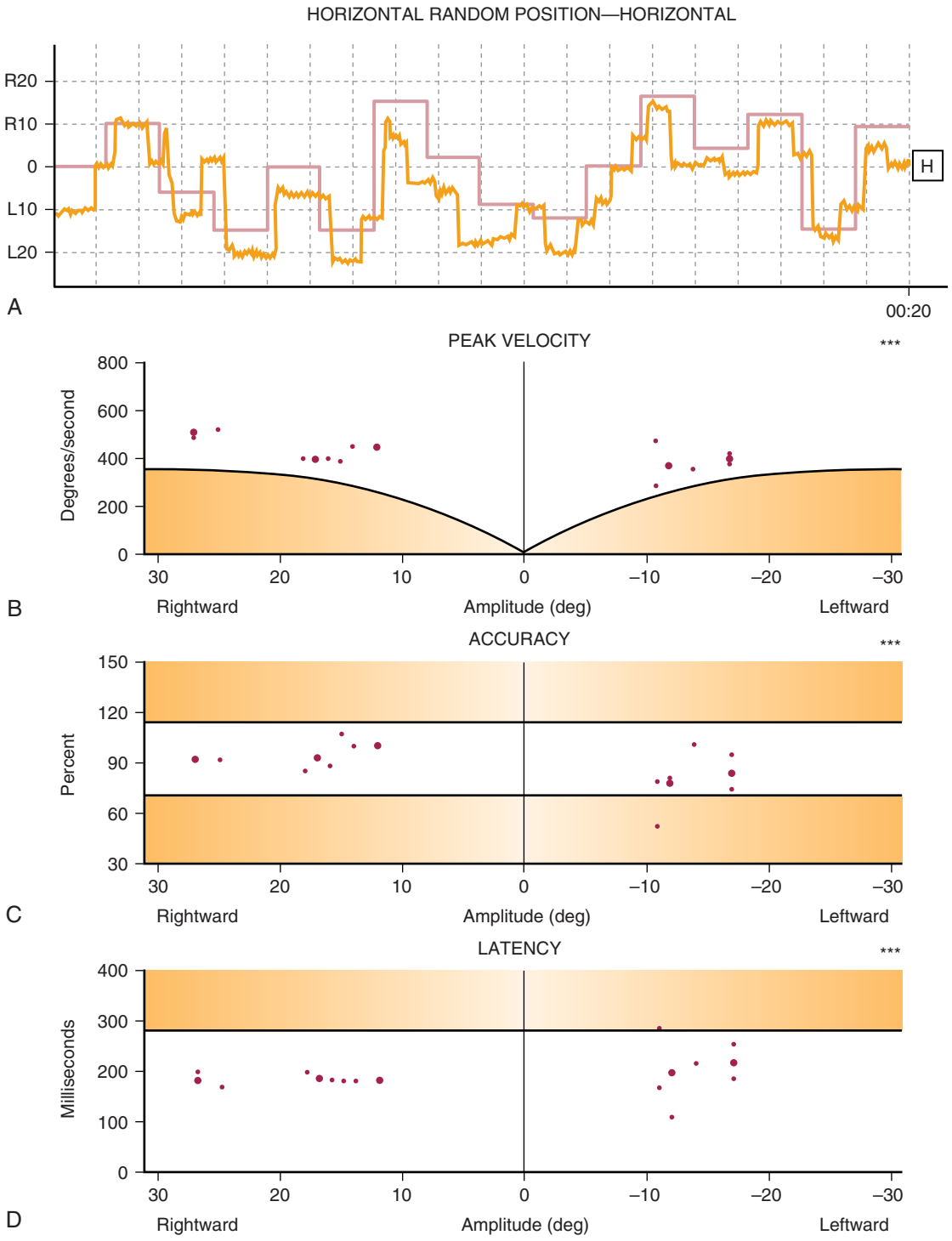


Figure 164-12. Electronystagmographic recordings of saccades. **A,** Eye tracings. **B,** Plot of speed versus amplitude. **C,** Accuracy. **D,** Latency. *Yellow* denotes areas of abnormal responses. See text for causes of inaccurate saccades.

velocity can provide localizing information. With EOG, the speed of abducting saccades seems to be lower than that of adducting saccades, although recordings with search coil and infrared techniques suggest the opposite.

Smooth Pursuit

The patient is asked to watch a target that moves horizontally in a sinusoidal fashion at a low frequency (0.2 to 0.7 Hz) with a position amplitude of 20 degrees in each direction. Inspection of the waveform of the tracking eye movement often is of greater diagnostic use than are absolute measures of gain and phase (Fig. 164-13). "Catch-up" saccades typically are seen when pursuit responses are decreased. Saccadic pursuit is characterized by the occurrence of these saccades in a "stair-step" pattern. Such patterns are seen in cerebellar disease and also may occur with the decreases in pursuit gain that occur with aging.

Optokinetic Testing

Testing is often performed with the subject surrounded by a visual scene that moves in one direction at velocities of 30 to 60 degrees/

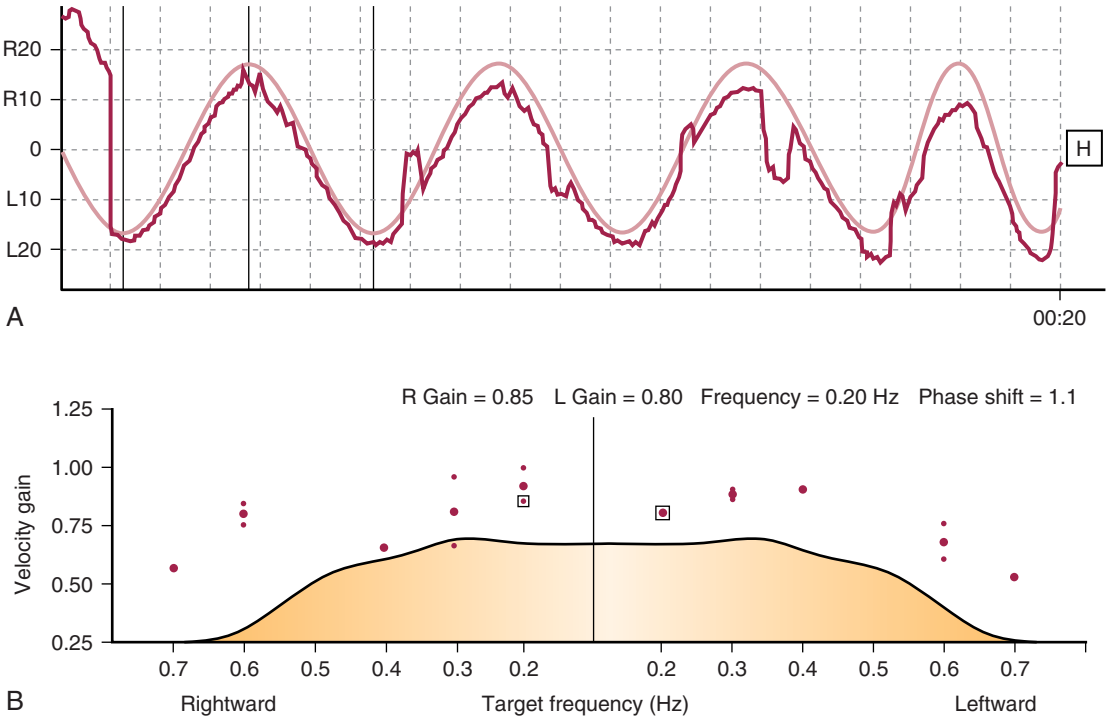


Figure 164-13. Electronystagmographic recordings of smooth pursuit. **A,** Smooth sinusoid, target motion; irregular tracing, eye movements. **B,** Gain in response to moving target at various frequencies. *Yellow shaded area* represents abnormally low responses.

second. The optokinetic tracking response is a nystagmus in the plane of motion of the visual scene. Response gain (the ratio of slow-phase eye velocity to velocity of the visual scene) is measured, and the profile of slow-fast component interaction is assessed. In general, slow-phase abnormalities on optokinetic tests parallel those detected with smooth pursuit testing, whereas fast-phase abnormalities are correlated with those detected on saccade testing. During sustained rotations, the vestibular signal decays and becomes a poor indicator of head motion. To maintain ocular fixation during low-frequency or sustained head movements, the optokinetic system drives the eyes to follow the visual surround. Optokinetic reflexes are a response to motion of the entire visual field rather than of a particular target (for which the smooth pursuit system is used) and are responsible for effects such as automatic tracking of a picket fence seen from a moving car.

Optokinetic afternystagmus (OKAN) is the perseveration of nystagmus after an optokinetic stimulus has been eliminated. OKAN is characterized by its initial eye velocity, time constant of declining eye velocity, cumulative eye position, and symmetry.[38] Velocity storage is believed to be the neural mechanism responsible for maintaining the nystagmus after an optokinetic stimulus. Because smooth pursuit tracking movements contribute to the generation of the slow phases of OKN and confound the assessment of the nystagmus response to optokinetic stimuli, OKAN is the best measure of the action of the portion of the optokinetic responses generated through the vestibular nuclei. If optokinetic reflexes are impaired, OKAN will not be generated even if smooth pursuit is preserved. Optokinetic reflexes are absent in persons with bilateral peripheral vestibular loss but also may be deficient in some normal subjects. OKAN declines with age,[90] and as with the effects of velocity storage caused by vestibular stimulation, its time constant can be reduced with repetition.[91] OKAN is modified in microgravity environments, and its duration is reduced by tilting the head, implying that the otolith organs are important to its genesis. Asymmetries in OKAN have been reported in patients with unilateral vestibular hypofunction induced by removal of an acoustic neuroma. Responses are greater in amplitude and longer in duration for stimulus and eye movement toward the side of the lesion.[92]

Caloric Testing

Caloric testing remains the most useful laboratory investigation for determining the responsiveness of the labyrinth. It is one of the few modalities that allow one labyrinth to be studied independently of the other. Caloric testing relies on stimulating (with a warm stimulus) or inhibiting (with a cool stimulus) the vestibular system by alternately changing the temperature of the external auditory canal with water or air. The horizontal canal is affected most by such temperature changes because it is located closest to the external auditory canal and is oriented in the plane of the temperature gradient that results in the temporal bone from irrigation with water.

Caloric testing causes a response in two ways. The first is a convective component, with the temperature gradient across the horizontal canal resulting in a density difference within the endolymph of the canal (Fig. 164-14). When the horizontal canal is oriented earth-vertically (by elevating the head 30 degrees from the supine position or 60 degrees backward from the upright position), the more dense fluid sinks to the lower position in the canal and the less dense fluid rises to the upper part of the canal. In the presence of gravity, a flow of endolymph occurs from the cooler (more dense) region to the warmer (less dense) region. This movement of fluid within the canal (convective flow) deflects the cupula, thereby leading to a change in the discharge rate of vestibular nerve afferents. Endolymph flows toward the ampulla (resulting in an increase in vestibular nerve afferent discharge) for warm irrigations and away from the ampulla (resulting in a decrease in afferent discharge) for cold irrigations. This effect depends on head position (Fig. 164-15).

The second component does not vary with head position and results in an excitation of the horizontal canal when the ear is warmed and in an inhibition when it is cooled. The nonconvective component may be a result of a direct temperature effect on hair cells or vestibular nerve afferents[93] or cupular displacement resulting from pressure changes in the membranous duct.[94] Direct evidence for the existence of a nonconvective component came from demonstration that a caloric nystagmus can be elicited in the microgravity environment of orbital space flight under conditions in which convection is absent.[95] The

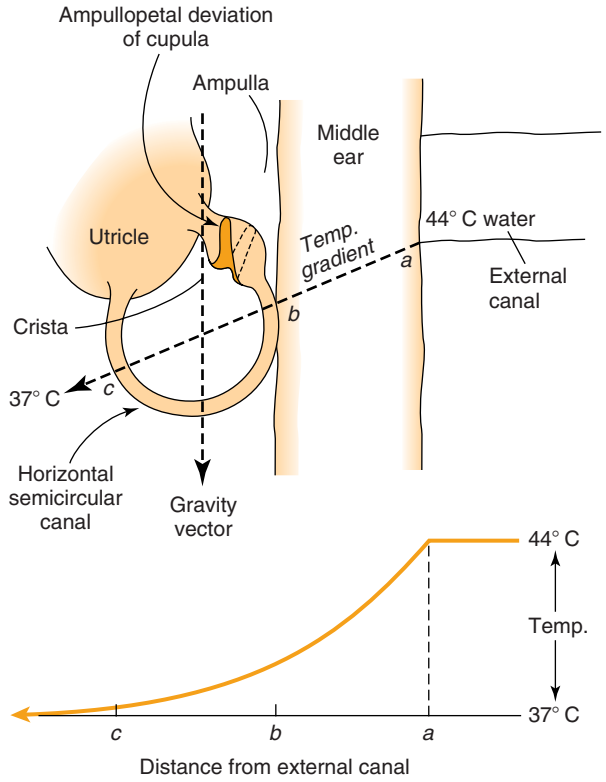


Figure 164-14. Top, Convective flow mechanism of the caloric response. Irrigation with warm or cold water (or air) results in a temperature gradient across the horizontal semicircular canal. With the horizontal canal oriented in the earth-vertical plane, gravity induces the convective flow of endolymph from the cooler area of the canal, in which endolymph is more dense, into the warmer area of the canal, in which endolymph is less dense. For the warm caloric irrigation used for this diagram, ampullopetal deflection of the cupula results from this flow of endolymph. Vestibular nerve afferents innervating the horizontal semicircular canal are excited, and a horizontal nystagmus with slow phase components directed toward the opposite ear is produced. A cold caloric stimulus results in an oppositely directed response with ampullofugal deflection to the cupula, inhibition of horizontal canal afferents, and a nystagmus with slow-phase components directed toward the ear to which the cold caloric is applied. **Bottom,** Graph showing temperature at locations *a*, *b*, and *c*, indicated above. *(From Baloh RW, Honorubia V.* Clinical Neurophysiology of the Vestibular System. *2nd ed. Philadelphia: F.A. Davis; 1990.)*

convective component accounts for 75% of the caloric response in the conventional testing position. Convective and nonconvective components are, in the squirrel monkey, affected by a position-dependent, otolith-mediated modification of velocity storage mechanisms.[96]

An otoscopic examination should be performed before caloric testing. Cerumen should be removed to obtain clear visualization of the tympanic membrane. Testing of caloric nystagmus is performed with eyes opened in darkness, behind Frenzel lenses, or in a dimly illuminated room with the patient looking at a Ganzfeld or nonpatterned background. Concentration tasks such as mental arithmetic are used to maintain alertness. EOG calibrations typically are checked after each or every other stimulus. Water calorics should be avoided in cases of tympanic membrane perforation. Improved stimulus reproducibility can be obtained by direct visualization of the position of the irrigation source within the external canal at the time of the stimulus.

Alternate binaural, bithermal caloric testing is the most commonly used testing protocol.[97] Cool water (30° C) and warm water (44° C) are administered for 60 to 90 seconds to each ear in a set order such as right warm, left warm, right cold, left cold. Such a stimulus results in a heating effect in the temporal bone that lasts for 10 to 20 minutes, although nystagmus frequently decays over a much shorter time course (2 to 3 minutes) because of the effects of adaptation.[98] The prolonged heating effect of a single temperature irrigation requires that at least 10 minutes be allowed between successive irrigations. Biphasic caloric irrigations can reduce patient nausea and shorten the wait between stimuli to approximately 2 minutes by using irrigation with water at 43.5° C for 45 seconds, 30.5° C for 65 seconds, and 43.5° C for 23 seconds.[99,100]

Eye movements are recorded for a period of several seconds before onset of an irrigation, during the irrigation, and until the nystagmus has ended. Standard computer algorithms exist for distinguishing fast from slow components of nystagmus and for determining the velocity of each slow component. A plot of slow component velocity is then formed (Fig. 164-16), and the maximum slow component is determined on the basis of three to five slow components with highest velocity. Data are interpreted in terms of unilateral weakness (UW) and directional preponderance (DP), according to formulas described by Jongkees and colleagues[101]:

$$UW = 100\% \times [(R30° + R44°) - (L30° + L44°)]/(R30° + R44° + L30° + L44°)$$

$$DP = 100\% \times [(R30° + L44°) - (R44° + L30°)]/(R30° + L44° + R44° + L30°)$$

Normative values are established for each laboratory. A UW value greater than 20% and DP value greater than 25% usually are considered significant. UW is a sign of decreased responsiveness of the horizontal semicircular canal or the ampullary nerve that provides its innervation. DP commonly is seen in patients with spontaneous nystagmus. For example, a right-beating spontaneous nystagmus will commonly lead to a DP for right-beating responses on caloric testing. The spontaneous nystagmus simply adds to or subtracts from each response to caloric irrigation depending on its direction. In the absence of spontaneous nystagmus, DP may be a central sign indicating asymmetrical sensitivities of central vestibular neurons to inhibitory-excitatory stimuli or asymmetries in the inputs from these central vestibular neurons to extraocular motoneurons. An increased warm and a diminished cold response, as can occur in an ear affected with Meniere's disease, can result in a DP. Caloric nystagmus can be suppressed with visual fixation in healthy persons. Failure of fixation suppression of caloric nystagmus can be seen in central disorders such as cerebellar disease.

Rotatory Chair Testing

Unlike caloric tests, rotational tests analyze the responses of both semicircular canals together. They require a high-torque motor-driven chair and specific software to analyze the results. Rotatory chair testing is useful in assessing vestibular function in patients with suspected bilateral vestibular hypofunction, in patients receiving vestibulotoxic medications, and in children who may not tolerate caloric testing. Clinical situations in which findings on rotatory chair testing in pediatric patients may provide useful information include determining whether a failure to achieve normal developmental milestones is based in part on absent vestibular function, evaluating vestibular function after meningitis, and determining the presence or absence of vestibular function in patients undergoing a genetic evaluation for hearing loss.

Rotational testing does not depend on delivery of a stimulus directly to the inner ear, as with the caloric test, so results are therefore not susceptible to variables such as size or shape of the external auditory canal. Rotational testing is less bothersome to some patients than is caloric testing (although nausea and vertigo associated with calorics can be decreased considerably with the use of temperature switch techniques as described). Most commercially available rotational testing systems administer low-frequency sinusoidal rotations and analyze eye movement responses to the input stimulus. The patient's head typically is aligned with the chin pitched 30 degrees nose down such that horizontal semicircular canals are in the plane of rotation. Approximately 10 cycles of the sinusoidal head velocity stimulus are recorded for five to eight test frequencies over the range of 0.01 to 0.7 Hz, with the

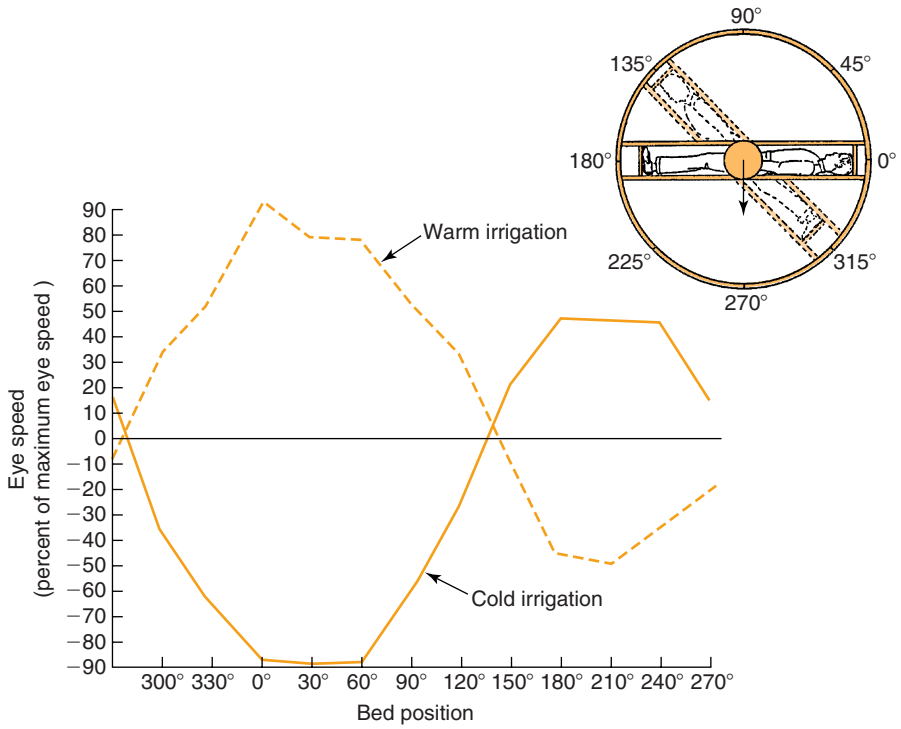
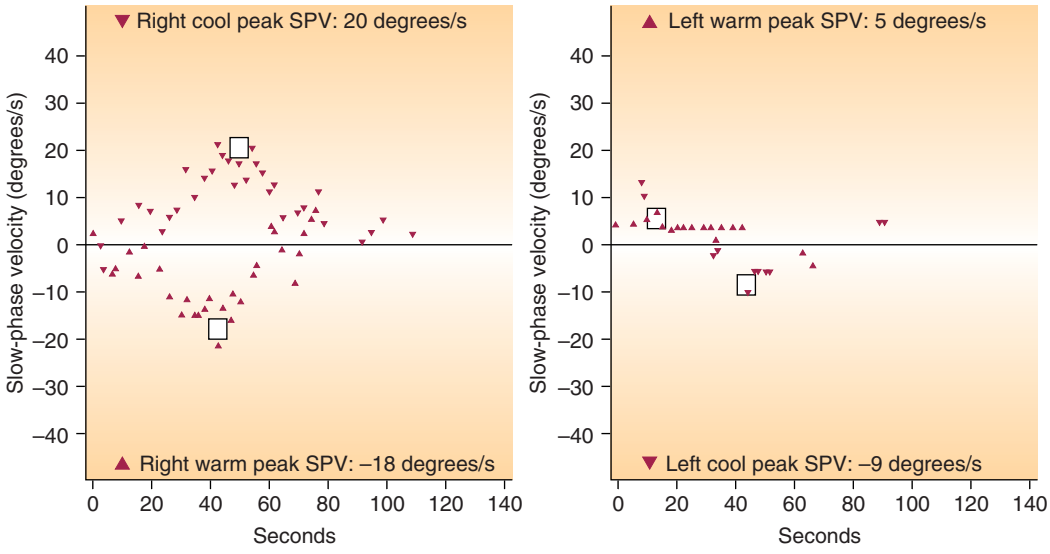


Figure 164-15. Average slow-phase eye velocity in response to warm (44° C) and cold (30° C) irrigations with subjects oriented in different bed positions. Subjects were lying on a Stryker bed that could be moved through 360 degrees in the pitch plane (see *inset*). For each subject, the percent of the maximum value in the curve (which usually occurred at the 30-degree position, at which the horizontal canal is in the earth-vertical plane) was determined at each of the positions tested. These percentages were then averaged for all subjects to obtain the composite plots shown. Four observations are apparent: (1) Caloric responses in the face-up positions are consistently greater in intensity than those in the face-down positions. (2) "Face-up" responses cover a larger segment of the 360-degree arc than the "face-down" responses. (3) The curves appear to approximate a sine function. (4) The findings are similar for warm and for cold irrigations. *(Modified from Coats AD, Smith SY. Body position and the intensity of caloric nystagmus.* Acta Otolaryngol (Stockh). *1967;63:515.)*



Caloric weakness: 46% in the left ear
Directional preponderance: 4% to the right

Figure 164-16. Caloric responses in a patient with unilateral labyrinthine hypofunction. The patient had no response in the left ear, although right ear responses to warm and cold irrigations were normal. SPV, slow component velocity.

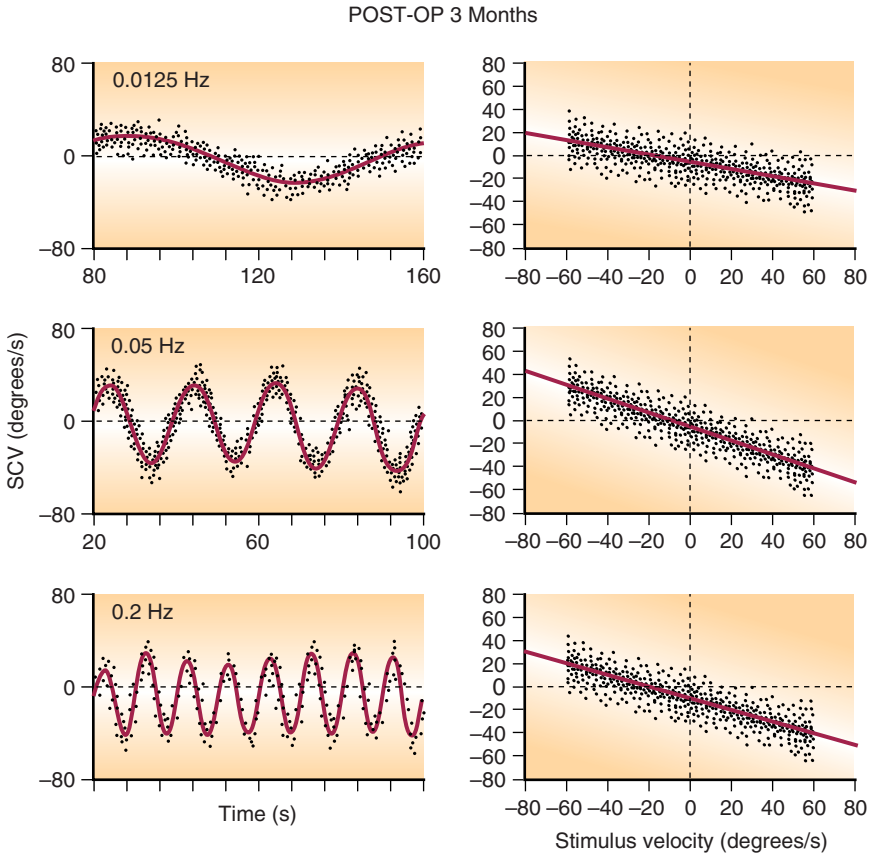


Figure 164-17. Rotational chair responses 3 months after unilateral vestibular deafferentation. Vertical axis = ocular response in degrees/second. Note that at the low frequencies tested here, the patient's responses *(dots)* closely follow the chair's movement *(solid line)*, indicating compensation from the lesion. Head impulse signs at this stage are likely to remain pathologic. The bottom stimulus-velocity curve *(lower right)* shows a slight bias (i.e., the line does not pass exactly through the origin). SPV, slow component velocity. *(From Jenkins HA. Long-term adaptive changes of the vestibulo-ocular reflex in patients following acoustic neuroma surgery.* Laryngoscope. *1985;95:1224.)*

patient in darkness. The results are averaged over successive cycles, and gain, phase, asymmetry, and bias velocity are calculated. *Gain* refers to amplitude of the maximum slow-phase eye velocity divided by amplitude of the maximum stimulus velocity. *Phase* is the temporal shift in eye velocity relative to head velocity. For a perfectly compensatory VOR, eye velocity should be equal in amplitude but opposite in direction to head velocity. This would correspond to a VOR gain of 1.0 and phase shift of 180 degrees (meaning that eye velocity would lag head velocity by 180 degrees).

Cerebellar abnormalities produce specific changes in responses that can be evaluated with rotatory chair testing. Velocity storage mechanisms that are responsible for prolonging the VOR time constant relative to that of vestibular nerve afferents are sensitive to the orientation of the head with respect to gravity. In healthy persons, tilting the head downward at the onset of post-rotatory nystagmus results in an immediate suppression of the stored velocity response, but patients with midline cerebellar lesions near the uvula and nodulus have VOR time constants that are normal in the upright position and are not affected by post-rotatory tilt.[102] Patients with cerebellar lesions such as caused by the Arnold-Chiari malformation exhibit tilt suppression intermediate between that of healthy persons and that of patients with midline cerebellar lesions. Abnormally high gain on rotational testing also has been noted in cases of cerebellar atrophy.[103] However, the presence of post-rotatory nystagmus evoked by this test is influenced by the level of vestibular function and by the status of velocity storage mechanisms, and the nystagmus can be suppressed by visual fixation. Because of the many processes involved, the test results have proved to be variable and difficult to correlate with specific pathologic processes.

Directionally dependent asymmetries can indicate relative weakness of function in one labyrinth compared with the other.[104] In the case of a patient with absence of vestibular function on the right, head rotation to the left continues to evoke a normal VOR, whereas rotations to the right may produce a weaker response, with gain decreasing as velocity increases. These asymmetries are thought to occur because vestibular neurons have an approximately three-fold higher range for excitation than for inhibition. The effects of these asymmetries are not seen when both labyrinths are functioning symmetrically, presumably because the brain is able to compensate for the loss of signals on the side being driven into inhibitory cutoff by use of signals from the excited side. The asymmetries are, however, more pronounced for rotational velocities and frequencies greater than those typically used in conventional clinical testing. Patients with compensated unilateral vestibular loss frequently exhibit normal gain and phase with minimal asymmetries on standard sinusoidal rotatory chair tests[105] (Fig. 164-17).

A further indication of unilateral deficiency of vestibular function is seen as a bias velocity in responses to sinusoidal rotations. Spontaneous nystagmus causes a bias velocity by adding the slow-phase velocity of the nystagmus to the response to sinusoidal stimulation, but such a bias also can be seen after spontaneous nystagmus has resolved. The direction of bias alone does not identify the affected ear, because both irritative lesions (such as Meniere's disease, serous labyrinthitis, labyrinthine fistulas, and acoustic neuromas) and ablative lesions can cause bias (but in opposite directions).

Step changes in head velocity can be used instead of sinusoidal rotations to identify vestibular hypofunction. The patient is seated in the rotatory chair apparatus, and eye movements are recorded with EOG. Testing is performed in darkness. The chair accelerates rapidly to the right or to the left, reaching its peak velocity (typically 60 or 240 degrees/second) in 1 second. A horizontal nystagmus is recorded. Response gain and VOR time constant are determined by the time after

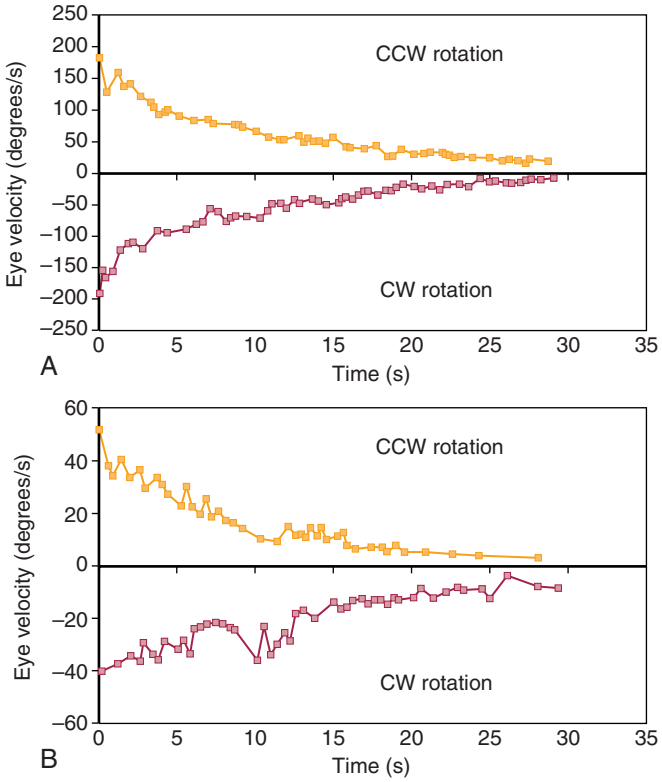


Figure 164-18. Velocity of horizontal slow-phase components of nystagmus evoked by velocity steps of 240 degrees/second (**A**) and 60 degrees/second (**B**). The subject is seated in a rotatory chair with the head positioned in approximately the horizontal canal plane (chin tilted downward 30 degrees from ambient position of the head) in **A** and in the ambient position (30 degrees upward from the horizontal canal plane) in **B.** Testing is conducted in darkness. Chair rotations in the counterclockwise (CCW) direction evoke slow phases to the right, whereas rotation in the clockwise (CW) direction evokes slow phases to the left. Gain is determined from the responses in **A** by dividing the velocity of the first slow phase in response to the stimulus by the head velocity. Gain measures approximately 0.80 in these data and is symmetrical for clockwise and counterclockwise rotations. Time constant is measured from responses to 60-degrees/second rotations as the time required for slow-phase velocity to decline by 63% of its initial value. In the data shown for CW rotation in **B,** the initial eye velocity is 40 degrees/second and falls to 15 degrees/second (a decline of 63% from the initial value) 20 seconds after the stimulus onset. The time constant of the response is therefore 20 seconds.

onset of the stimulus at which slow-phase eye velocity has decreased by 67% of its initial value (Fig. 164-18). A further procedure has been used to improve test sensitivity in identifying unilateral vestibular hypofunction: A rotation of 240 degrees/second is given with the patient's head aligned in the 30-degree chin-down position (to bring the horizontal canals into the plane of rotation) and with the head pitched 30 degrees upward.[106] The effect of the rotational stimulus on the horizontal semicircular canals varies with the cosine of the angle of the canal to the plane of rotation. Thus, the stimulus causes only approximately 60% of maximal activation with the head in the 30-degree pitched-upward position. Vertical semicircular canals are brought more into the plane of rotation in these pitched positions. In cases of unilateral vestibular hypofunction, gain asymmetries caused by the inhibitory cutoff effects are more likely to be seen with the horizontal canals aligned in the plane of rotation.

Electrocochleography

Electrocochleography (ECOG) may be useful in the diagnosis of Meniere's disease, although interpretation of the findings remains a

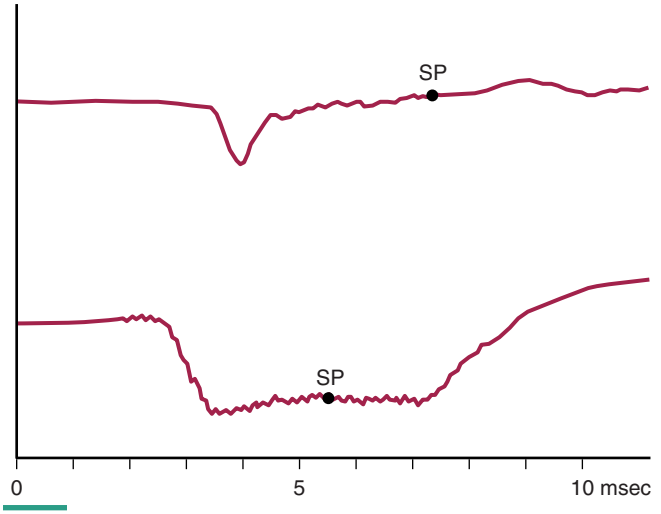


Figure 164-19. Transtympanic electrocochleography. *Top line*, Normal response to tone burst stimulus. *Bottom line*, Pathologic response, with shifted summating potential line (SP) relative to the baseline.

topic of controversy. The cochlea responds to repeated presentation of sound with auditory evoked potentials, which can be represented as an action potential (AP) and a summating potential (SP) (Fig. 164-19). A ratio between the two (SP/AP ratio) greater than 0.4 and an AP duration longer than 3 msec are indicative of endolymphatic hydrops.[107] This effect is believed to be due to the altered physical properties of the basilar membrane because of endolymphatic hydrops. ECOG can be performed with tone bursts or clicks. Recent studies regarding the safety and efficacy of transtympanic ECOG indicate that this technique may be superior to simply placing the electrode in the external canal.[108] The utility of ECOG in the identification of Meniere's disease has been questioned.

Subjective Visual Vertical

The subjective visual vertical is a useful measure of otolith function. Patients sit in a darkened area and focus on a line that they manipulate by use of a dial until they perceive it as vertical. Patients with acute utricular lesions usually leave the line tilted 10 to 15 degrees toward the side of the lesion. Deficits in subjective visual vertical also are seen in patients with brainstem infarctions.[109]

Quantitative Head Impulse Testing

Quantitative head impulse testing allows recording of responses for later analysis and detection of short-latency or small eye movements that may be missed under bedside conditions. Eye movements generally are recorded using scleral search coil technology. Quantitative head impulse testing allows accurate titration of intratympanic gentamicin treatment for intractable Meniere's disease[110,111] and to show that vestibular neuritis preferentially spares the inferior vestibular nerve serving the posterior semicircular canal.[112] These methods also have shown that plugging of the superior canal as used in the treatment of superior canal dehiscence typically causes reduction in function of the plugged canal with preservation of function in the other canals.[113]

Active Head Movement Analysis Techniques

Active head movement analysis techniques have been developed to evaluate the VOR in response to higher-frequency head rotations than those customarily used in rotatory chair testing. This broader range of stimulus frequencies is possible because the test subjects make the head movements actively, using their own neck musculature to rotate the head. In these cases, head velocity is measured by a transducer mounted directly to the head. In one of the more commonly used commercial systems (Vestibular Autorotation Test, Western Systems Research, Inc., Pasadena, California), a computer-generated metronome cues head movements for an 18-second trial period over a swept-frequency band from 2 to 6 Hz. Broad-band cross-spectral analysis is used to determine

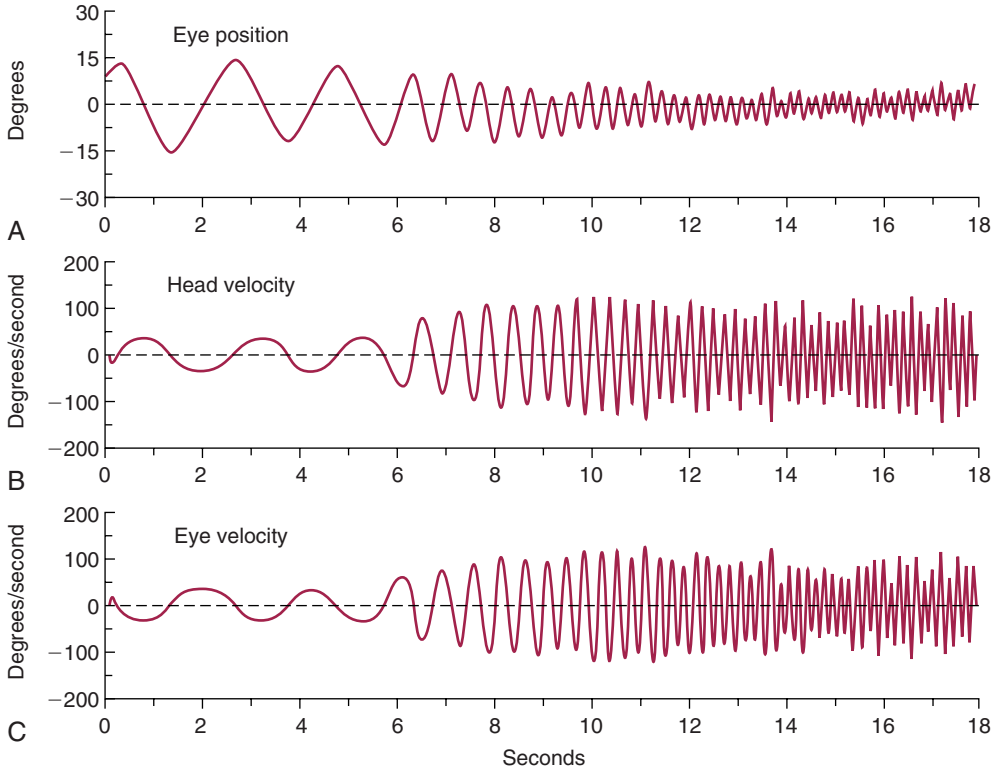


Figure 164-20. Horizontal eye position (**A**), head velocity (**B**), and eye velocity (**C**) during active head movement testing with the Vestibular Autorotation Test. *(From Fineberg R, O'Leary DP, Davis LL. Use of active head movements for computerized vestibular testing.* Arch Otolaryngol Head Neck Surg. *1987;113:1063.)*

all harmonic contributions that occur at each frequency. Results are computed and reported as gain and phase values at 12 selected frequencies over the range of 2 to 6 Hz (Fig. 164-20). Testing is performed with the room illuminated, while the patient fixates on a stationary target that does not move with the head. The range of frequencies tested exceeds that over which smooth pursuit typically is active, so responses are a result of the VOR. Normative data have been obtained for patients of various ages (see Fig. 164-20).[114,115] The vertical VOR can be evaluated in a similar fashion.

Active head movement testing of the VOR has been applied in monitoring patients receiving vestibulotoxic medications such as cisplatin.[116] Asymmetries in responses have been shown to be correlated directionally with the side of lesion in patients with unilateral labyrinthectomy and with the side of lesion in patients with acoustic neuroma.[115] Many patients with Meniere's syndrome also were noted to have abnormalities when these testing procedures were applied.[117] The sensitivity of active tests such as the vestibular autorotation test may be somewhat less than that of passive tests such as head impulse testing, because of the patient's ability to preprogram his or her eye movements during active head movements.[118]

Vestibular Evoked Myogenic Potentials

Recent studies have demonstrated that healthy subjects exhibit a relaxation of the ipsilateral sternocleidomastoid (SCM) muscle in response to auditory stimulation (100- to 200-msec rarefaction clicks, 95-dB sound pressure level [SPL] or tone bursts).[119] These cervical vestibular evoked myogenic potential (VEMP) responses are recorded with electromyelography (EMG) and occur at a short latency (12 msec) relative to onset of the click stimulus (Fig. 164-21). The responses are abolished on the side of surgery after unilateral vestibular neurectomy.[120] VEMP responses are a result of selective activation of vestibular nerve afferents innervating the sacculus. In addition to aiding in diagnosis of otolith function, patients with superior canal dehiscence syndrome also seem to have lower thresholds and increased amplitude[121] and patients with Meniere's disease may have higher thresholds for responses to VEMPs.[122]

Variants of the test include the use of a reflex hammer to produce a sharp tap on the patient's forehead. With this modification, VEMPs were evoked in a small series of patients with conductive hearing loss, while the selectivity of the test was maintained in patients with unilateral vestibular loss.[123] Bone-conducted stimulation with pure tones may be more sensitive than air-conducted sounds.[124] VEMPs also may be recorded from the extraocular musculature.[125] Ocular VEMPs may be superior to cervical VEMPs for detection of superior canal dehiscence.[126]

Posturography

Techniques for postural assessment in patients have been developed in an attempt to provide a quantitative assessment of processes involved in maintaining upright stance under static and dynamic conditions. These tests have conceptual appeal, because they provide a potential mechanism for evaluation of all sensory systems (vestibular, visual, and somatosensory) that provide information important for maintaining balance.

The most commonly used system for clinical postural assessment is computerized dynamic posturography (CDP) (e.g., Equitest, NeuroCom International, Clackamas, Oregon). The test subject stands on a computer-controlled movable platform with a movable visual surround. The platform and visual surround can be fixed or move independently or concomitantly with postural sway. Anterior-to-posterior sway of center of gravity is monitored with pressure-sensitive gauges located in each quadrant of the platform (Fig. 164-22). The standard CDP test battery includes assessment of automatic postural responses to platform movements—the motor control test—and determination of effects of manipulations of visual and somatosensory information on standing balance—the sensory organization test (SOT).

Motor Control Test

The platform administers sudden sagittal movements to the feet, and "toes-up" and "toes-down" platform rotations of 4.0 degrees in 500 msec also are presented. Strain gauges for each foot are then used to calculate the following: weight symmetry (distribution of weight over

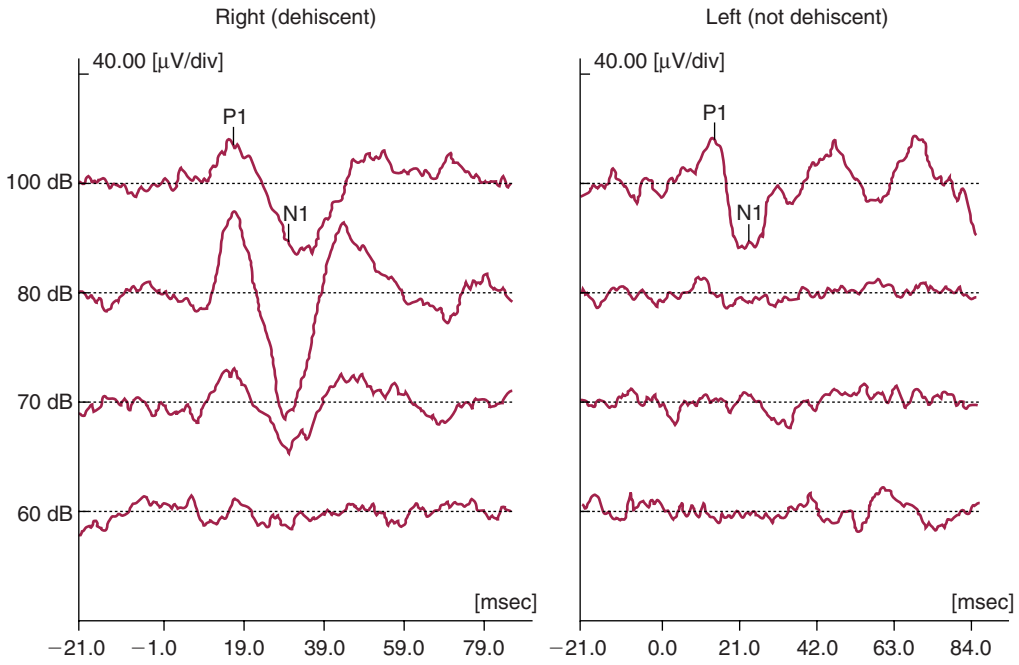


Figure 164-21. Vestibular evoked myogenic potentials (VEMPs) in a patient with unilateral semicircular canal dehiscence responding to clicks. Stimulus was presented at time = 0 msec. The evoked potential peaks at approximately 16 msec and is evident bilaterally at 100 dB *(top tracing)*. On the dehiscent side *(right)*, the potential is still present at 70 dB, but on the normal side *(left)*, no VEMP is present below 100 dB. div, division.

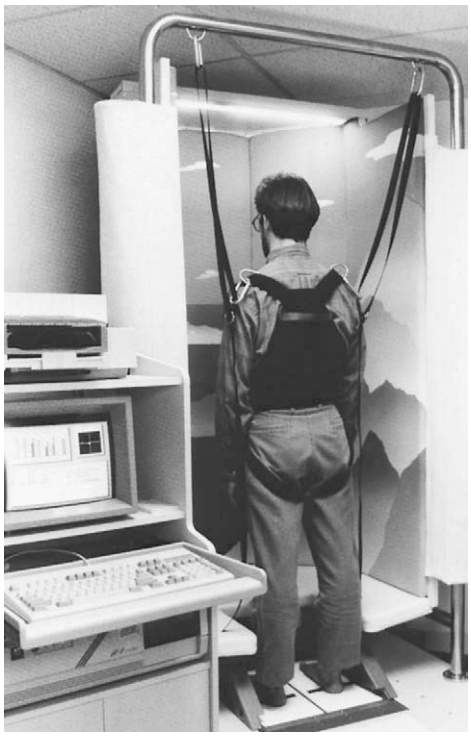


Figure 164-22. Photograph of the NeuroCom International Equitest system shows a subject standing on a platform surrounded by a visual scene. Pressure-sensing strain gauges beneath the platform surface detect patient sway by measuring vertical and horizontal forces applied to the surface. A safety harness is attached to the patient in case loss of balance occurs. The platform surface and the visual surround are capable of moving independently or simultaneously.

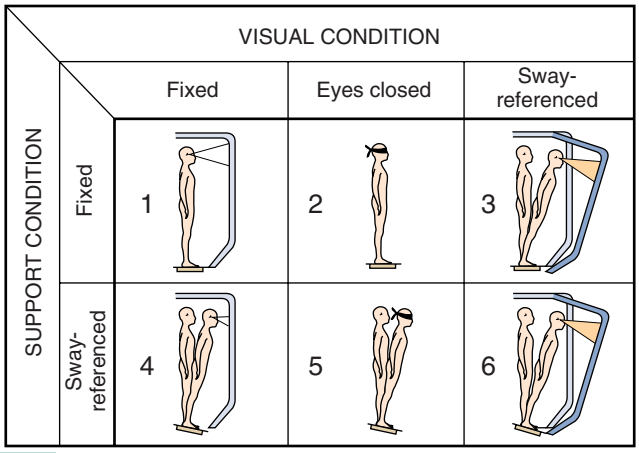


Figure 164-23. The sensory organization test protocol showing the six test conditions. *(From Nashner LM. Computerized dynamic posturography. In: Jacobson GP, Newman CW, Kartush JM, eds.* Handbook of Balance Function Testing. *St. Louis: Mosby; 1996:280-307.)*

both feet during movement), amplitude scaling (distribution of force through legs during platform movement), latency (time from onset of platform movement to discernible response and relationship to amplitude of movement), and adaptation (relationship between response amplitude and stimulus repetition).

Sensory Organization Test

Six test conditions comprise the SOT test battery (Fig. 164-23). The platform remains fixed under the first three test conditions, providing the patient with stable reference for somatosensory information. The visual surround also remains fixed in test condition 1, making this the condition for optimal stability. The patient's eyes are closed in test condition 2, and anteroposterior (AP) sway is controlled by vestibular and somatosensory information. Balance is controlled mainly by somatosensory information during this test condition, so patients with

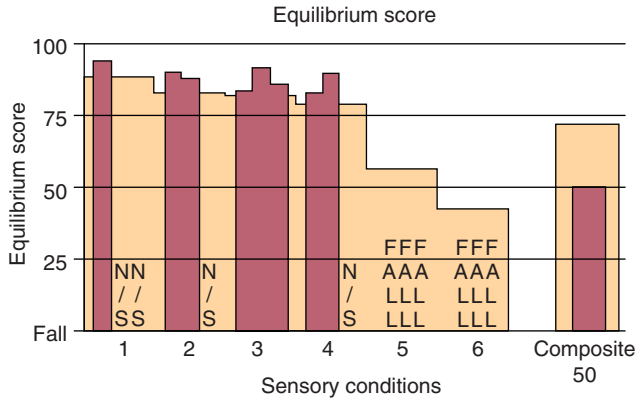


Figure 164-24. Vestibular dysfunction (5-6) pattern. Distortion of somatosensory cues (conditions 5 and 6) and distortion (condition 6) or elimination of visual cues (condition 5) force the patient to rely on vestibular information for balance and posture. This pattern can be seen with acute unilateral or bilateral vestibular lesions, in cases of poor compensation in response to peripheral vestibular lesions, and occasionally with central vestibular system disease. Patients with compensated unilateral peripheral vestibular lesions typically exhibit normal performance on the sensory organization test. During actual test conditions, a stimulus repetition may be deferred if the preceding presentation of that stimulus gives a normal response. The label FALL indicates trials in which the sway in response to the stimulus was outside the limits of stability and would have resulted in a fall had the patient not been secured with a harness. N/S, no stimulus.

deficient vestibular function typically show minimal unsteadiness on this test condition, provided that somatosensory function is normal.

The visual surround moves in reference to AP body sway in test condition 3. "Sway referencing" of the visual surround results in distorted visual inputs to systems controlling balance. Maintaining balance requires the brain to disregard these inaccurate visual inputs and select vestibular and somatosensory cues for balance. As in condition 2, somatosensory inputs are most important for postural control in these situations, so patients with vestibular deficits (but normal somatosensation) tend to do well.

The platform moves to follow the AP sway of the patient in test conditions 4, 5, and 6, thereby providing distorted somatosensory inputs to the brain. Inaccurate proprioceptive cues must be suppressed in these cases, with vestibular and visual inputs used to maintain postural stability. The visual surround remains fixed in condition 4, which permits visual and vestibular inputs to be used in maintaining balance. Patients with vestibular deficits tend to do well in this condition, provided that their vision is intact. The patient's eyes are closed in condition 5, and the platform is sway referenced. Only vestibular cues can be used to maintain balance in this condition, and patients with bilateral vestibular hypofunction or uncompensated unilateral vestibular hypofunction sway excessively. The platform and visual surround are sway referenced in condition 6. Vestibular inputs must now be selected over inaccurate somatosensory and visual cues to maintain balance in this situation. Responses are quantitatively assessed in each condition and compared with age-related norms. Balance strategies (hip or ankle) also are measured. Specific profiles for SOT findings are shown in Figure 164-24.

Use of Posturography

The role of CDP in the diagnosis and management of dizziness continues to be a topic of debate.[127] Rather than serving as a screening test for making a diagnosis in all patients with unidentified problems affecting posture or balance, CDP may be beneficial in three specifically defined clinical situations[128]:

1. *Planning and monitoring a course of postural rehabilitation*. Diagnoses for which posturography can be useful include unilateral or bilateral vestibular hypofunction, brainstem stroke, cerebellar ataxia, extrapyramidal disorders, and vestibular schwannomas and cerebellopontine angle neoplasms. Vestibular rehabilitation programs that are specifically designed for a patient's profile of deficits have been shown to be more effective at alleviating symptoms than generic physical therapy measures.[129] CDP can be useful in the selection of exercises included in a patient's rehabilitation program and in monitoring responses to the therapeutic regimen. For example, patients with dysequilibrium after a unilateral loss of vestibular function can demonstrate dependence on somatosensory or visual information to maintain balance. Patients with somatosensory reliance are given exercises that include walking on uneven surfaces to promote use of visual or vestibular cues to balance, whereas those with visual dependence do exercises that involve intermittently closing the eyes to promote use of somatosensory and vestibular cues.

   The organization of an exercise program on the basis of data obtained from posturography has been demonstrated to have a beneficial effect on functional outcome. Patients showed a significant reduction in postural sway on SOT conditions 5 and 6 in patients with peripheral vestibulopathy who received vestibular rehabilitation compared with those of a control group who only received vestibular-suppressant medication.[130] Patients with a variety of peripheral and central vestibular disorders show improvements in subjective and objective measures of functional outcome after receiving an exercise regimen organized around abnormalities on SOT.[131] Evaluation of CDP prelesion and postlesion can also be useful in defining the expected outcome and end point of vestibular rehabilitation for each patient. Patients undergoing vestibular neurectomy for intractable vertigo who showed preoperative abnormalities on CDP showed persisting abnormalities even after a postoperative recovery period, whereas patients with normal findings preoperatively returned to normal.[132]

2. *Determination of the need for high-volume cerebrospinal fluid (CSF) drainage with lumbar punctures or shunting in patients with dysequilibrium or gait disturbances caused by processes resulting in abnormal CSF pressure dynamics*. These patients develop dysequilibrium and ataxia with increased CSF accumulation. CDP is useful in quantifying their improvement after CSF draining and in predicting their response to ventriculoperitoneal shunting.[133]

3. *Documentation of postural responses when malingering, exaggeration of disability for compensation, or conversion disorder is suspected*. CDP can identify inconsistencies between symptoms and performance parameters that have been shown to indicate a functional deficit as in malingering or conversion disorder.[134,135] Patients with these disorders often show patterns on CDP that are described as aphysiologic (e.g., poorer performance on SOT conditions 1 and 2 than on 5 and 6). Identification of such patients can be useful in making recommendations about disability status and the need for psychiatric intervention.

Audiogram

Audiometric findings may indicate the cause of imbalance and guide its therapy. Sensorineural hearing loss may accompany peripheral vestibular loss caused by Meniere's disease or aminoglycoside vestibulotoxicity. A Stenger test may help identify malingering. Conductive hearing loss may accompany superior canal dehiscence and enlarged vestibular aqueduct syndrome. Auditory reflex testing helps distinguish these conditions from others, such as otosclerosis, that may have similar balance-related symptoms.

High-Resolution Temporal Bone Computed Tomography

Advances in radiologic techniques have allowed improved diagnosis of many otologic disorders. Superior canal dehiscence syndrome is characterized by sound-induced or pressure-induced vertigo or apparent conductive hearing loss, or both, due to incomplete covering of the superior semicircular canal in the arcuate eminence. In affected patients, eye movements in the plane of the superior semicircular canal often can

be induced by loud noises and by maneuvers that change middle ear or intracranial pressure. Confirmation of this diagnosis requires thin-slice computed tomography (CT) images of the temporal bone in the plane of the superior semicircular canal. Scanners with 0.5-mm slice thickness had a 93% positive predictive value, compared with only 50% with a 1.0 mm slice thickness, because of partial volume averaging in the coarser scan.[136]

Magnetic Resonance Imaging

Dysarthria, diplopia, and paresthesias may accompany the vertigo seen in cases of vertebrobasilar insufficiency. Other neurologic signs including cranial neuropathies and seizure activity may indicate a primary intracranial process.

Serologic Tests

Serologic abnormalities are rare in patients with symptoms of imbalance but in some cases may indicate severe disease. Syphilis, Lyme disease, or Susac syndrome may manifest with hearing loss or imbalance. Antiphospholipid syndrome recently has been associated with inner ear disease, and treatment may prevent significant embolic events.[137] *Cogan's syndrome* is an inflammatory condition characterized by severe visual and vestibular symptoms. In some cases, life-threatening systemic vasculitis may develop.[138] Rare paraneoplastic syndromes associated with breast cancer or Hodgkin's lymphoma may be associated with imbalance.[139]

Adaptive Capabilities of the Vestibular System

The clinician must consider adaptive changes when evaluating the results of vestibular testing. Unilateral loss of vestibular function creates two general types of deficits for which a correction is required: *static imbalance*, related to differences in the levels of tonic activity of neurons in the vestibular nuclei, and *dynamic disturbances*, related to responsiveness to motion. For the VOR, spontaneous nystagmus with the head stationary is an example of the former type of disturbance, whereas decreased amplitude and asymmetry of eye rotation during head rotation are examples of the latter. For a fixed (nonfluctuating) unilateral loss of vestibular function, resolution of static signs such as spontaneous nystagmus and the ocular tilt reaction usually occurs within days, but dynamic processes return toward baseline levels over the course of several weeks. Some processes such as the function of velocity storage and responses to high-frequency, high-acceleration head movements toward the hypoactive labyrinth may not recover.

Adaptive mechanisms are most likely to involve increasing sensitivities of central vestibular neurons to signals they receive from the intact vestibular nerve or adjustments in the level of modulation in neurons that connect the vestibular nuclei from one side to the other. Experimental evidence indicates that once acquired, these adaptive and compensatory changes require continued sensory exposure for maintenance of appropriate responses. In addition to the central mechanisms that promote normalization of vestibular processes after labyrinthine or central injuries, the brain can substitute other strategies for generating responses involved in sensing and controlling motion. These substitutions can involve other sensory inputs for driving the same motor response (e.g., substitution of the cervico-ocular reflex or the optokinetic reflex for labyrinthine-evoked VOR). Other strategies can be based on prediction or anticipation of intended motor behavior (e.g., gaze overshoots during combined eye and head movements in labyrinthine-defective persons can be prevented by preprogramming compensatory slow phases and decreasing saccade size in anticipation of a head movement). A consequence of such an adaptive capability is that a vestibular disorder reflects the "pure" effects of a lesion only when history-taking and patient examination are done immediately after change in vestibular function.

Specific vestibular rehabilitation exercises constitute the appropriate treatment for patients with unilateral or bilateral vestibular loss. These exercises are designed to assist the brain's intrinsic adaptive processes to compensate for loss of peripheral function. A successful rehabilitation program usually is carried out in partnership with a physical therapist. Some exercises are designed to increase the gain of the hypoactive vestibular system by maintaining fixation on a target while moving the head. Others attempt to habituate the patient to disturbing symptoms by mildly and repetitively provoking them. Rehabilitation is effective in patients with acute vestibular loss, as well as in patients with more chronic symptoms. Patients with bilateral vestibular loss generally enjoy less benefit from rehabilitation than that observed in patients with unilateral loss. Despite the benefits of rehabilitation, many patients will never achieve the same level of activity that they had before their vestibular loss. Some patients who do not improve after vestibular exercises may have problems such as benign positional vertigo or superior canal dehiscence that are better treated with more specific therapies.

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CHAPTER ONE HUNDRED AND SIXTY-FIVE

Peripheral Vestibular Disorders

Benjamin T. Crane

David A. Schessel

Julian Nedzelski

Lloyd B. Minor

Key Points

- The peripheral vestibular system transduces head movement, playing key roles in stabilizing vision and ambulation.
- The history of vertigo symptoms provides definitive insights into underlying diagnosis and pathophysiology; the first step is to differentiate peripheral from central vestibular disorders.
- Peripheral vestibular disorders are highly prevalent, affecting 1 in 13 people during their lifetime.
- Benign paroxysmal positional vertigo (BPPV) produces characteristic symptoms of position sensitivity and fatigability and often is effectively diagnosed with the Dix-Hallpike maneuver and treated with the Epley maneuver.
- The diagnosis of vestibular neuritis is suggested by dramatic, sudden-onset vertigo with vegetative symptoms.
- The diagnosis of Meniere's disease is based on a history of episodes of vertigo lasting up to 24 hours, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. If followed for 2 years, more than half of Meniere's patients will have a spontaneous cessation of vertigo symptoms.
- Treatments for Meniere's disease include low-sodium diet, diuretics, and intratympanic injection of dexamethasone or gentamicin. More advanced cases not responsive to initial therapy may be treated with nerve section or labyrinthectomy.
- Superior canal dehiscence syndrome is caused by absence of bone over the superior canal. Symptoms include vertigo induced by loud sound or high pressure, conductive hearing loss, pulsatile tinnitus, and autophony.
- Cogan's syndrome is characterized by interstitial keratitis, hearing loss, and vestibular symptoms. Systemic steroids are the accepted treatment.
- Perilymph fistula is a controversial diagnosis with presenting symptoms of dizziness and hearing loss.
- Bilateral vestibular hypofunction can manifest with oscillopsia and gait disturbance. Aminoglycosides are the most common cause.
- Enlarged vestibular aqueduct syndrome usually manifests with hearing loss in childhood, but vertigo often develops later in life.

Basic Principles of Peripheral Vestibular Physiology

The peripheral vestibular system depends on the sensory receptor structures, which are responsible both for sensing motion and position of the head in space and for converting this sensory stimulus into an electrical signal. These sensory signals are carried to the central nervous system (CNS) in the form of neural activity.

Vestibular receptors are organized to detect head motion in a specific direction or plane. Horizontal head rotation (yaw) produces a stimulus to the horizontal semicircular canals. Pitching of the head from front to back, as well as roll from side to side, is detected by the superior and posterior semicircular canals. Linear acceleration such as gravity as well as motion along a straight trajectory are sensed by the otolith organs located in the utricle and saccule.

All receptors are tonically active. A resting, spontaneous, continual outflow of action potentials from the vestibular portion of the eighth cranial nerve has been recognized. With head motion, this spontaneous activity is modulated up or down. For example, turning the head to the right in the upright position produces an increase in activity in the nerve coming from the right horizontal semicircular canal, whereas left turns decrease activity below the resting rate from the same canal. These paired labyrinths (one in each ear) behave in a "push-pull" fashion. The CNS compares the inputs coming from both ears. When the inputs are equal, the system is balanced, with no sense of movement. When inputs are asymmetrical, the CNS interprets this finding as a head rotation and as a result generates compensatory eye movements and postural adjustments, all of which lead to a conscious sensation relative to the perceived movement of the head.

Of great importance, the CNS is capable of rebalancing itself—that is, compensating after an injury to the peripheral receptor. This compensation is thought to occur as a result of the organism's ability to compare other sensory, visual, and kinesthetic inputs to vestibular

input and, when the inaccuracy of the latter has been recognized, to readjust the central response. As a consequence, the point of balance is reset. CNS compensation in an otherwise healthy person results in near-normal clinical recovery even if complete unilateral vestibular loss has occurred. However, compensation takes time, on the order of days.

Abrupt vestibular imbalance created by a labyrinthectomy leads to severe vertigo, nausea, and ataxia that gradually resolve over ensuing days. On the other hand, a slowly progressive lesion of the vestibular system, such as occurs with acoustic neuromas, rarely causes vertigo. Although vestibular function is destroyed, because the damage has been incurred gradually, ongoing central adaptation masks the developing asymmetry between the ears.

As opposed to acute unilateral peripheral vestibular loss, bilateral vestibular loss, exemplified in the patient who has suffered ototoxicity, results in permanent clinical disability. Because peripheral vestibular input is lacking, the CNS is unable to make the required adjustments to head movements. If the loss is simultaneous and symmetrical, no significant vertigo results. The patient complains of worsened balance, especially in the dark. Fixed objects appear to jump with any head movement (oscillopsia). The symptoms are due to a now inefficient vestibulo-ocular and vestibulospinal system. An important point is that so long as vestibular input is symmetrical, vertigo symptoms will not arise even in the case of complete absence of any vestibular activity.

Clinical Relevance

The lifetime prevalence of vestibular vertigo is 7.4%.[1] In 80% of affected persons, vertigo resulted in a medical consultation, interruption of daily activities, or sick leave. Of patients who present to emergency departments with falls of unknown cause, 80% have vestibular impairment, and 40% complain of vertigo.[2] Thus, peripheral vestibular disorders constitute a significant medical problem. The most important clinical feature in the diagnosis of peripheral vestibular dysfunction is its pattern of presentation or history.

Vertigo is the illusion of motion, either of self (subjective) or of the environment (objective). Although the thorough neuro-otologic examination is beyond the scope of this chapter, a minimum vertigo history should address the following: (1) the duration of the individual attack (e.g., hours vs. days); (2) frequency (e.g., daily versus monthly); (3) the effect of head movements (e.g., worse, better, or no effect); (4) specific position–induced (e.g., rolling onto the right side in bed); (5) associated aural symptoms (e.g., hearing loss and tinnitus); (6) concomitant ear disease (e.g., otorrhea, previous surgery, trauma).

One of the most important features of the pattern of presentation of peripheral vestibular disorders is the duration of vertigo. Based on this parameter, the following classification of peripheral vestibular disease can be used:

1. Vertigo lasting seconds (benign paroxysmal positional vertigo)

2. Vertigo lasting minutes to hours
   a. Meniere's disease
   b. Migraine-associated vertigo (covered in Chapter 166)
   c. Otic syphilis
   d. Cogan's disease

3. Vertigo lasting days to weeks (vestibular neuritis)

4. Vertigo of variable duration
   a. Inner ear fistula
   b. Labyrinthine concussion
   c. Blast trauma
   d. Barotrauma
   e. Familial vestibulopathy
   f. Superior semicircular canal dehiscence syndrome
   g. Bilateral vestibular hypofunction

Historical Background

Before the 1860s, dizziness and balance problems were thought to be exclusively central disorders, often referred to collectively as "cerebral congestion" or lumped in with epilepsy. As early as the 1820s, post-rotation nystagmus was observed in mental patients after rotation in cages as a means to subdue them. Jan E. Purkinje hypothesized that this effect was central in origin. Vertigo symptoms during this period often were treated with leaching, purging, and cupping. Around this time emerged the first hints that equilibrium may have a peripheral component. Pierre Flourens noticed that pigeons would fly in circles in the same orientation as an ablated semicircular canal.[3]

The existence of peripheral vestibular disorders was proposed by Prosper Meniere in 1861.[4] Meniere was the director of a large deaf-mute institution in Paris who probably saw patients in whom both vertigo and hearing loss developed immediately after trauma to the ear, allowing him to conclude that both symptoms have a common inner ear origin.[5] To support his conclusion he presented the results of an autopsy of a young girl in whom sudden hearing loss and acute vertigo developed after such injury. On autopsy, her brain was found to be normal but the inner ear was filled with blood. It is ironic that this patient probably had leukemia, and not endolymphatic hydrops. Because of this finding, it was commonly believed well into the 20th century that Meniere's disease was caused by hemorrhage. Before 1940, "Meniere's disease" was used as a generic term for any peripheral vertigo, especially if it involved hearing loss. The first insight into the true pathophysiology of Meniere's disease came a decade after his initial report, with Knapp's hypothesis that inner ear hydrops was similar to ocular glaucoma.[6]

Early treatments of peripheral vertigo focused on destruction of the end organ. In 1904 the techniques of both eighth cranial nerve section[7] and labyrinthectomy[8,9] were described. The concept of drainage of the endolymph was first reported by Portmann in 1926.[10] Dandy also proposed selective vestibular nerve sectioning using a suboccipital approach during the 1930s, by which he treated more than 600 patients.[11] In this early period these procedures carried a high risk of deafness and facial nerve paralysis, as well as significant mortality rates. It was not until 1938, after examination of nerve section specimens taken from two patients who died in the perioperative period, that Hallpike and Cairns were able to report dilatation of the endolymphatic system in patients with Meniere's disease. This finding was hypothesized to reflect a disruption of the resorptive mechanism.[12] This pathologic feature also was independently observed by Yamakawa.[13]

Treatment of Meniere's disease that focuses on reversing endolymphatic hydrops has continued to evolve through the present day, with several variations on the Portmann shunt being proposed, such as transmastoid decompression,[14] subarachnoid drainage,[15] and cochleosacculotomy.[16] All of these procedures have had incomplete success in treating vertigo symptoms and carry a risk of hearing loss. A randomized controlled trial has suggested that these procedures have an efficacy similar to that for the placebo effect of surgery,[17] although a more recent analysis of these data has suggested that endolymphatic shunts may have a real effect.[18] Accordingly, these procedures continue to evolve and be performed.

BPPV is the most common cause of peripheral vertigo. BPPV was first described by Bárány in 1921, and he attributed the disorder to otolith disease.[19] After Bárány's initial description, scattered contradictory and confusing reports of BPPV appeared in the literature.[20] The clinical diagnosis of this disorder was not well defined until Dix and Hallpike described the classic positioning which causes a characteristic nystagmus in 1952.[21] Like Bárány, however, they believed it was due primarily to otolith disease. It was noted that the disease could be cured by a chemical labyrinthectomy[22] and eighth nerve section.[23] Schuknecht observed granular deposits on the cupula of the posterior semicircular canal in temporal bone specimens and proposed the "cupulolithiasis" theory to explain the pathophysiology.[24] This theory provides a basis for understanding the disorder, although more recent work has shown that the disorder is more commonly due to free-floating particles in the semicircular canal ("canalithiasis"), rather than cupulolithiasis. Gacek proposed transection of only the posterior ampullary nerve for relief of BPPV, confirming the posterior canal origin.[25] In most patients, however, the Epley canalith repositioning maneuver is adequate treatment,[26] and no surgery is required.

The most recently described etiologic disorder with peripheral vertigo is superior canal dehiscence.[27] Affected patients often exhibit a

Tullio phenomenon (nystagmus with loud noise) or *Hennebert's sign* (eye movements caused by pressure on the external auditory canal). This dehiscence acts as a third window into the middle cranial fossa, which can be plugged using a middle cranial fossa approach[28] or a transmastoid approach.[29]

Tremendous progress has been made in understanding the causes of peripheral vertigo and developing treatments. However, even today, vertigo is a symptom whose cause often cannot definitely be attributed to a known single disease process. Further developments in our understanding will no doubt occur and will modify the medical and surgical treatments of peripheral vestibular disorders.

Benign Paroxysmal Positional Vertigo

The most common peripheral vestibular disorder generally is agreed to be BPPV. The hallmark of the disease is brief spells (lasting seconds) of often severe vertigo that are experienced after specific movements of the head. The head movements that most commonly cause symptoms are rolling over in bed and extreme posterior extension of the head as if looking under a sink. Current understanding of this disease has evolved such that specific therapies based on accepted theories have been developed and proved successful in controlling symptoms.

The disorder initially was described in 1921 by Bárány.[19] He recognized several of the cardinal manifestations of BPPV, including vertical and torsional components of the nystagmus, the brief duration of the nystagmus, and the fatigability of the nystagmus and vertigo. Bárány did not, however, correlate the onset of the nystagmus with the positioning maneuver. He erroneously concluded that an abnormality in the encoding of head position by the otoliths was responsible for the symptoms and signs that he had noted. In 1952, Dix and Hallpike[21] reported this entity in a large group of patients. They described their now well-known maneuver for eliciting the classic pattern of nystagmus and its associated symptoms. They recognized the important features of the nystagmus occurring in BPPV, including its latency, directional characteristics, brief duration despite maintaining the offending head position, reversibility upon returning the patient to a seated position, and fatigability from repeated testing. They correctly identified the offending labyrinth but incorrectly concluded that BPPV results from an otolithic disturbance.

Schuknecht[30] reviewed the previous studies of BPPV, including the temporal bone histology of several patients who had experienced the disorder. He noted extensive utricular destruction in these patients and damage to other structures supplied by the anterior vestibular artery. This observation and the failure of electrical stimulation of the utriculus or sacculus to produce discrete patterns of nystagmus in laboratory animals led Schuknecht to conclude that abnormal stimulation of the otoliths was not responsible for the disorder. He suggested that the posterior canal crista was the probable source of the dysfunction. According to Schuknecht, BPPV was caused by loose otoconia from the utricle that, in certain positions, displaced the cupula of the posterior canal. Deposition of otoconia on the cupula of the posterior canal, known as "cupulolithiasis," was later proposed by Schuknecht as the mechanism of BPPV.[24] However, this mechanism poorly explained the brief duration of the nystagmus and the reversal of the nystagmus on return to a sitting position.

The suggestion that the mechanism of BPPV could result from deflection of the posterior canal cupula by the movement of debris in the posterior canal was revisited by Hall and colleagues.[31] These investigators suggested that the nonfatigable form was due to fixed deposits on the cupula, whereas the fatigable form was attributed to the motion of free-floating material within the lumen of the posterior semicircular canal. In most cases, BPPV-associated nystagmus is most commonly due to motion of material in the lumen of the posterior canal.

This latter theory is consistent with the five typical features of posterior canal BPPV: (1) The canalithiasis mechanism explains the latency of nystagmus as a result of the time needed for motion of the material within the posterior canal to be initiated by gravity. (2) The nystagmus duration is correlated with the length of time required for the dense material to reach the lowest part of the canal. (3) The vertical (up-beating) and torsional (top of the eyes beating toward the lowermost ear) components of the nystagmus are consistent with eye movements evoked by stimulation of the posterior canal nerve in experimental animals. (4) The reversal of nystagmus when the patient returns to the sitting upright position is due to retrograde movement of material in the lumen of the posterior canal back toward the ampulla, with resulting ampullopetal deflection of the cupula. (5) The fatigability of the nystagmus evoked by repeated Dix-Hallpike positional testing is explained by dispersion of material within the canal.

Incidence

BPPV is the most common cause of vertigo in patients seen by the otolaryngologist, accounting for 20% to 40% of cases of peripheral vestibular disease[32]—making it almost twice as frequent as Meniere's disease. The incidence is difficult to estimate because of the benign, typically self-limited course of the disease. It is thought to range from 10.7 per 100,000 to 17.3 per 100,000 population in Japan[33] and has been reported as 64 per 100,000 in a population study from Minnesota.[34]

The mean age at onset is in the fourth and fifth decades, but BPPV also may occur in childhood.[35] In a study of pediatric patients with BPPV, an association with migraine was suggested, leading to the hypothesis that migraine-induced ischemia may be responsible for the release of otoconia in some cases.[36] Overall, the incidence increases with age,[37] and BPPV is twice as common in women.[35]

Diagnosis

History

The patient with BPPV experiences severe vertigo associated with change in head position. The most frequently cited occurrence of this symptom follows rolling over or getting into bed and assuming a supine position. Frequently a specific side is identified as being associated with symptom onset (e.g., "the dizziness comes when I roll over to my right side but not to the left"). Patients also will experience similar symptoms on arising from a bending position, looking up to take an object off a shelf, tilting the head back to shave, positioning the head in the hairdresser's chair, or turning rapidly.

Symptoms occur suddenly and last on the order of seconds but never in excess of a minute.[35] The subjective impression of attack reported by the patient frequently is longer.

Episodes of vertigo frequently are clustered in time and separated by remissions lasting months or more. The patient also may report that periods of active disease may be associated with constant feelings of lightheadedness, worsened by head movement.[38] These chronic balance problems may be worse on awakening.

In most cases of BPPV, no specific etiologic disorder can be identified. In a large survey by Baloh and colleagues, no cause was identified in 48% of cases.[35] The most common known cause was closed head injury, followed by vestibular neuritis. In our experience, BPPV will eventually develop in nearly 15% of patients suffering from vestibular neuritis. Other cited predisposing events include infections and certain surgical procedures, including stapedectomy[35] and insertion of a cochlear implant.[39] Prolonged bed rest and Meniere's disease also are predisposing factors.

Findings on Examination

The diagnosis of BPPV is made by observing the classic eye movements in association with the Dix-Hallpike maneuver, combined with a suggestive history. The *Dix-Hallpike maneuver* is carried out as follows (Fig. 165-1). The patient is positioned supine on an examination table with the head extending over the edge. The patient is lowered with the head supported and turned 45 degrees to one side. The eyes are carefully observed. If no abnormal eye movements are seen, the patient is returned to the upright position. The maneuver is repeated with the head turned in the opposite direction and finally with the head extended supine.[40]

The pattern of response consists of the following: (1) The nystagmus is a combined vertical up-beating and rotary (torsional) component beating toward the downward eye (the superior poles of the eyes beat toward the downward ear). Pure vertical nystagmus is not BPPV.[35] (2) A latency of onset of nystagmus (seconds) is common. (3) Duration

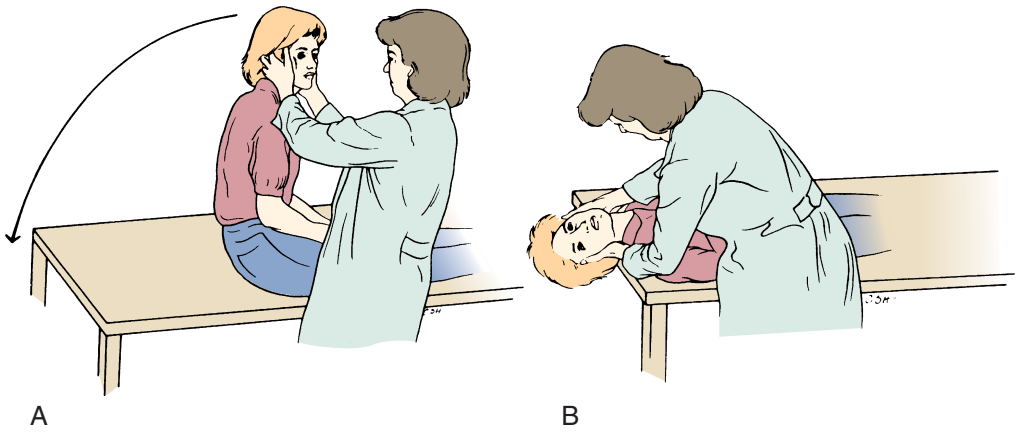

Figure 165-1. Right Dix-Hallpike maneuver for eliciting nystagmus and vertigo due to posterior canal benign paroxysmal positional vertigo (BPPV). The patient's head is first turned 45 degrees to the right (**A**). The patient's neck and shoulders are then brought into the supine position with the neck extended below the level of the examination table (**B**). The patient is observed for nystagmus and assessed for symptoms of vertigo. The patient is next returned to the upright position. *(From Herdman SJ, ed.* Vestibular Rehabilitation. *Philadelphia: F.A. Davis; 1994. Used with permission.)*

of nystagmus is short (less than 1 minute). (4) Vertiginous symptoms are invariably associated. (5) The nystagmus disappears with repeated testing (i.e., it is fatigable). (6) Symptoms often recur with the nystagmus in the opposite direction on return of the head to the upright position.[38]

Canalithiasis of the posterior semicircular canal is the most frequent cause of BPPV. Posterior canal BPPV rarely may be bilateral.[41] If the head is not positioned correctly during testing (i.e., not positioned with the head in the plane of the posterior canal during testing of the unaffected side), debris on the affected side may come to rest against the cupula, simulating an excitatory nystagmus from the unaffected ear.[42] The lateral semicircular canal has been identified as the affected structure in approximately 12% of cases, with a significant fraction of these being induced by the repositioning maneuver for posterior canal BPPV.[43] Lateral canal BPPV can be detected by a variation of the Dix-Hallpike maneuver: The patient is first brought to the supine position with the head resting on (not hyperextended below) the examining table. The head is then turned rapidly to the right so that the patient's right ear rests on the table. Eye movements are monitored with Frenzel lenses for 30 seconds. The patient is then returned to the supine position (looking upward) and the head is turned rapidly to the left so that the left ear rests on the table. Eye movements are again monitored.

The nystagmus with lateral canal BPPV is horizontal and may beat toward (geotropic) or away from (ageotropic) the downward ear. It often begins with a shorter latency, increases in magnitude while maintaining the test position, and is less susceptible to fatigue with repetitive testing than the vertical torsional nystagmus of posterior canal BPPV. The increased amplitude and duration of the horizontal nystagmus may reflect action of the central velocity storage mechanisms (which perseverate signals from the vestibular periphery, especially those arising from the lateral canal). Cupulolithiasis, arising either independently or in combination with canalithiasis, is more likely to be involved in the etiology of lateral canal BPPV than is the case for posterior canal BPPV. Cupulolithiasis can be differentiated from canalithiasis by minimal or absent latency to the onset of nystagmus. Cupulolithiaisis also can persist for minutes or even as long as the patient remains in the provocative position.[44] If the nystagmus is geotropic, the particles are likely to be in the long arm of the lateral canal relatively far from the ampulla. If the nystagmus is ageotropic, the particles may be in the long arm relatively close to the ampulla or on the opposite side of the cupula, either floating within the endolymph or embedded in the cupula.

The superior semicircular canal is affected in only 2% of cases of BPPV.[45] The nystagmus expected in cases of superior canal BPPV would be downbeat and torsional. Such a nystagmus can be elicited by standard Dix-Hallpike positioning testing. The right posterior canal lies in roughly the same plane as that of the left superior canal, and vice versa. Placement of the head into the right Dix-Hallpike position will therefore bring the left superior and right posterior canals into the plane of gravity. A nystagmus resulting from the left superior canal BPPV would, in this position, be expected to be downbeat, with a torsional component directed such that the superior part of each eye beats toward the upward ear. Note that this nystagmus is opposite in vertical and torsional direction from that resulting from right posterior canal BPPV.

Test Results

The bedside Dix-Hallpike test[21] combined with an appropriate history is key to making the diagnosis. Standard electro-oculography (EOG) and the many videonystagmography devices do not record the torsional eye movements associated with BPPV. The eye movement tracings obtained with these standard devices used for clinical testing reflect solely the associated vertical and horizontal components of the eye movements. The observation of these patterns may be facilitated by the use of Frenzel lenses.

Treatment with Repositioning

First-line therapy for BPPV is organized around repositioning maneuvers that, in cases of canalithiasis, use gravity to move canalith debris out of the affected semicircular canal and into the vestibule. For posterior canal BPPV, the maneuver developed by Epley[26] is particularly effective (Fig. 165-2). The maneuver begins with placement of the head into the Dix-Hallpike position, to evoke vertigo. The posterior canal on the affected side is in the earth-vertical plane with the head in this position. After the initial nystagmus subsides, a 180-degree roll of the head (in two 90-degree increments, stopping in each position until any nystagmus resolves) to the position in which the offending ear is up (i.e., the nose is pointed at a 45-degree angle toward the ground in this position) is performed. The patient is then brought to the sitting upright position. The maneuver is likely to be successful when nystagmus of the same direction continues to be elicited in each of the new positions (as the debris continues to move away from the cupula). The maneuver is repeated until no nystagmus is elicited. In our experience, when administered in this way, the Epley maneuver is effective in more than 90% of cases in eliminating BPPV. Medications are not usually given, but a low dose of meclizine or a benzodiazepine 1 hour before may be appropriate if the patient is unusually anxious or susceptible to nausea and vomiting with vestibular stimulation.

The Semont maneuver also is effective for posterior canal BPPV[46] but is more difficult to perform and is less effective than the simpler, more comfortable Epley maneuver.[47] The patient is moved quickly into the position that provokes the vertigo and remains in that position for 4 minutes. The patient is then turned rapidly to the opposite side, ear down, and remains in this second position before slowly sitting up.

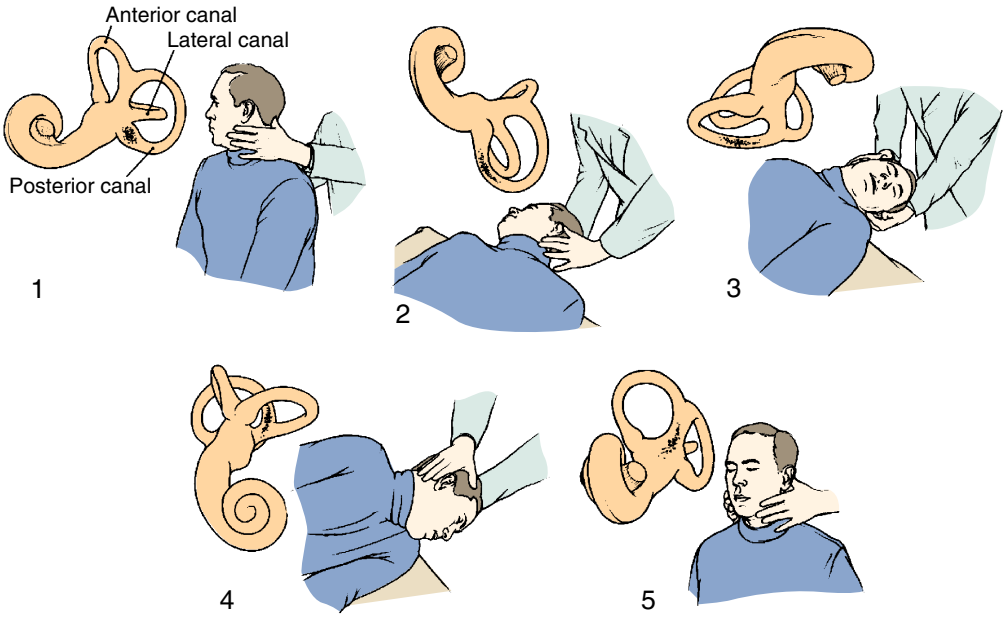

Figure 165-2. Canalith repositioning maneuver for treatment of benign paroxysmal positional vertigo (BPPV) affecting the posterior canal of the right ear. **1,** The patient's head is turned to the right at the beginning of the canalith repositioning maneuver. The *inset* shows the location of the debris near the ampulla of the posterior canal. The diagram of the head in each inset shows the orientation from which the labyrinth is viewed. **2,** The patient is brought into the supine position with the head extended below the level of the gurney. The debris falls toward the common crus as the head is moved backward. **3,** The head is moved approximately 180 degrees to the left while keeping the neck extended with the head below the level of the gurney. Debris enters the common crus as the head is turned toward the contralateral side. **4,** The patient's head is further rotated to the left by rolling onto the left side until the patient is face down. Debris begins to enter the vestibule. **5,** The patient is brought back to the upright position. Debris collects in the vestibule. *(Illustration by David Rini. From Hullar TE, Minor LB: Vestibular physiology and disorders of the labyrinth. In: Glasscock ME, Gulya AJ, eds.* Surgery of the Ear. *5th ed. Hamilton, Ontario: B.C. Decker; 2003.)*

For both Epley and Semont maneuvers, gravity is the stimulus that moves the particles within the canal, so turning the head on the body is unnecessary. En bloc movement of the head and body to the extent possible is the preferred treatment pattern. Some physicians also use a small handheld vibrator over the mastoid and claim slightly better results, although the results do not seem significantly different.[48] Mastoid vibration should be avoided in patients who have had retinal detachment or who may be susceptible to such a detachment because of high myopia. Some investigators recommend having the patient sleep with the head elevated for 1 to 2 days after the maneuver, but this has not been shown to have a significant effect.[49]

The following observations support the effectiveness of these maneuvers for treatment of posterior canal BPPV: (1) Patients who have been symptomatic for years can be cured; (2) BPPV involving one canal can convert to BPPV involving another canal as a result of treatment; (3) patients in whom the wrong side was treated and post-treatment instructions were given show no improvement; and (4) randomized trials have shown the effectiveness of the treatment maneuvers. Because BPPV commonly resolves in a few weeks to a month, a repositioning maneuver may seem to be no better than placebo in an unselected group of patients with BPPV in whom spontaneous recovery is common. In more intractable cases, however, the treatment will almost certainly be determined to be effective.

Treatment maneuvers also have been suggested for the lateral canal variant of BPPV. In cases that involve geotropic nystagmus, lying on one side with the affected ear up for 12 hours has been reported to be effective in the vast majority of cases.[50]

Treatment maneuvers for superior canal BPPV should follow the same principles. The head initially should be moved into a dependent position wherein the ampulla is superior, then rotated by 180 degrees, and then brought back to its initial position. Data on treatment of superior canal BPPV have not been reported, no doubt owing to its relative rarity.[51]

Some events that can occur during repositioning maneuvers are worthy of discussion. Posterior canal BPPV can be converted to lateral canal BPPV during the Epley maneuver. The lateral canal BPPV usually resolves in several days. Posterior canal BPPV can occasionally be converted into a presumed anterior canal BPPV (i.e., symptoms worsen when the offending ear is up). An obstruction of canalith material may occur at the common crus during the Epley maneuver, resulting in a sustained pure torsional nystagmus (both the superior and posterior canals are excited simultaneously, so the opposing vertical components cancel and the torsional components add).

Surgical Treatment

The vast majority of patients with BPPV will be cured by repositioning maneuvers, but surgical therapy remains an option for the rare patient with disabling persistent disease.

Singular neurectomy to treat refractory BPPV was proposed by Gacek.[25] During the three decades since it was described, the procedure has been performed at least 342 times, of which 252 were by Gacek himself.[52] Although the procedure generally is effective, it is technically difficult and the risk of hearing loss from the procedure may be as high as 41%.[53]

Posterior semicircular canal occlusion was introduced as a treatment for BPPV in 1990.[54] This technique blocks the canal lumen so that it becomes unresponsive to angular acceleration. At total of 97 cases have been reported in the literature. Although the procedure was associated with brief postoperative vertigo, 94 of the 97 patients were cured of their BPPV.[55] The procedure is associated with a postoperative hearing loss that usually recovers over several weeks.

Vestibular Neuritis

Vestibular neuritis typically manifests with dramatic, sudden onset of vertigo and attendant vegetative symptoms.[56] Typically, the dizziness lasts for days, with gradual, definite improvement throughout the course. Balance-related complaints, particularly caused by or related to

rapid head movements, may be present for months after resolution of the acute disease. Paroxysmal positional vertigo occurs subsequently in a small percentage of patients.[57,58] Vestibular neuritis has been known to recur, with some patients reporting similar, usually less intense attacks for years.[58] Bilateral disease has been described and must be considered in the differential diagnosis for bilateral vestibular loss. Vestibular neuritis is not associated with subjective change in hearing or with any focal neurologic complaints.[21] Although historically the terms *vestibular neuritis* and *labyrinthitis* were used interchangeably, *vestibular neuritis* is now considered the more accurate term for cases that do not involve hearing loss. The term *epidemic vertigo* has also been used historically and is synonymous with vestibular neuritis; the term reflects the observation that the vertigo often is preceded by upper respiratory infection.[58]

Subjectively, hearing remains normal. When sudden sensorineural hearing loss accompanies vertigo with a vestibular neuritis–like pattern, classification as a sudden sensorineural hearing loss should be considered. In such cases, treatment appropriate for sudden sensorineural hearing loss should be instituted and the evaluation should include evaluation for a retrocochlear lesion, such as acoustic neuroma.

A documented caloric response reduction or positive head thrust test in the direction of the involved side can be used to identify the side of involvement.[56] Head thrust testing in the canal plane may have the advantage of localizing the pathology to the inferior or superior vestibular nerve.[59] However, inferior vestibular nerve involvement is unusual, so VEMP testing is rarely useful.[60] Lateralization also has been reported with use of magnetic resonance imaging (MRI) with gadolinium enhancement.[61]

Histopathologic studies of temporal bones from patients believed to have experienced this clinical entity reveals vestibular nerve degeneration with sparing of the peripheral receptor structure.[58] Human pathologic studies also have demonstrated signs of more chronic inflammation in the rare case manifesting a more chronic or recurrent course of disease. A postinfectious syndrome has been suggested in these cases. Opinion holds that the superior vestibular nerve is more commonly involved in this disease than the inferior. It is postulated that this predilection may be secondary to the longer and narrower bony canal traversed by the superior nerve, making it more susceptible to compressive swelling.[62] It also is possible that isolated inferior vestibular nerve neuritis is not diagnosed owing to normal horizontal head thrust and caloric testing.[63]

The cause of the degeneration is not established. Infection with one of the neurotropic viruses, such as herpesvirus, is thought to be responsible. *Borellia* infection also has been noted in some instances. In most cases, the responsible virus is never identified.

Treatment has historically been supportive and symptomatic for vertigo and related vegetative symptoms. Recently, methylprednisolone and valacyclovir have been investigated as possible therapeutic agents in a placebo-controlled, double-blind study.[64] Patients given methylprednisolone experienced significantly more improvement after 1 year. Valacyclovir was not shown to have any affect. As in all acute peripheral vestibular losses, early ambulation is encouraged.

Meniere's Disease

Meniere's disease (idiopathic endolymphatic hydrops) is a disorder of the inner ear associated with a symptoms consisting of spontaneous, episodic attacks of vertigo; sensorineural hearing loss which usually fluctuates; tinnitus; and often a sensation of aural fullness. Despite this well-known symptom complex, Meniere's disease remains a controversial and often difficult condition to diagnose and treat. This is in part due to the dramatic variability that is the hallmark of this disease. This discussion concentrates on current thought concerning Meniere's disease as well as indicates some of these underlying controversies.

History

Prosper Meniere first described the symptom complex in 1861 and proposed the pathologic site to be in the labyrinth. It was Meniere along with Flourens who recognized that vertiginous symptoms could originate in the inner ear. However, hemorrhage into the inner ear, which Meniere himself believed to be the pathophysiology, has proved to be erroneous. Knapp advanced the hypothesis that hydrops was similar to ocular glaucoma,[6] although this was not histologically demonstrated until 1938.[12,13] Before that time, "Meniere's disease" was used as a generic term for any peripheral vertigo. Understanding of Meniere's disease has advanced considerably since these initial descriptions, yet the cause of the underlying hydrops remains elusive and controversial despite seventy years of active research.

Incidence

Wide variation exists in the published rates for incidence of Meniere's disease. These range from 17 per 100,000 in the Japanese population[65] to a high of 513 per 100,000 in the population of southern Finland,[66] with several studies reporting intermediate values. Some of the variation may be explained by the diagnostic criteria used and by access to health care in a population. The disease seems to be more prevalent among whites,[67] with a male-to-female ratio of approximately 1. The peak age at onset is in the fourth and fifth decades of life, although presentation can be at almost any age.

The frequency of bilateral disease is unclear, and the incidence in published reports is from 2% to 78%.[68] The rate depends on the duration of follow-up and the diagnostic criteria. The studies at the extreme ends of this range were from before 1980, when standardized diagnostic criteria were not in use. The true incidence probably is in the range of 19% to 24%.[67,68] Symptoms of bilateral disease may appear many years or decades after onset of the unilateral symptoms.[69]

Familial occurrence of Meniere's disease has been reported in 10% to 20% of cases.[70] An autosomal dominant mode of inheritance has been suggested,[71] although the mode of inheritance can be variable. Migraine is strongly associated with Meniere's disease in familial cases.[72] The incidence is elevated in persons with specific major histocompatability complexes (MHCs). Human leukocyte antigens (HLA) B8/DR3 and Cw7 have been associated with Meniere's disease.[73,74] The etiology of the disease in persons with these HLAs may be autoimmune.[75]

Pathogenesis

Meniere's disease is characterized by recurring attacks of vertigo, sensorineural hearing loss, tinnitus, and, in some affected persons, a fluctuating sense of fullness in the ear. Acute attacks are superimposed on a gradual deterioration in sensorineural hearing in the involved ear, typically in the low frequencies initially. Over time, a reduction in responsiveness of the involved peripheral vestibular system occurs.

The pathologic basis thought to underscore these findings is a distortion of the membranous labyrinth. The hallmark of this distortion is endolymphatic hydrops.[12] This condition reflects the changes in the anatomy of the membranous labyrinth as a consequence of the overaccumulation of endolymph. Such changes occur at the expense of the perilymphatic space (Fig. 165-3).

Traditional thought has held that endolymph, which is produced by the stria vascularis in the cochlea and by the dark cells in the vestibular labyrinth, circulates in both a radial and a longitudinal fashion.[76] In the case of hydrops, the underlying pathophysiology is controversial, but inadequate absorption of endolymph by the endolymphatic sac is the prevalent theory.[77] The endolymphatic duct may act as a valve to regulate endolymph homeostasis.[78] Temporal bone histologic equivalents of hydrops have been produced in animals as a consequence of disruption of the endolymphatic sac, thereby supporting the above theory of pathogenesis.[79]

Histopathologic studies of the human sac in the hydrops patient remain controversial. Some investigators have reported perisaccular fibrosis[80] and decreased endolymphatic duct size.[81] However, the underlying cause of these histologic findings is not certain.

Imaging studies in patients with Meniere's disease also identify abnormalities of the endolymphatic drainage system. Such studies suggest hypoplasia of the endolymphatic sac and duct, reflected in the decreased visualization of the vestibular aqueduct and reduction in periaqueductal pneumatization on computed tomography (CT) imaging.[82] Persons with Meniere's disease have significantly smaller and

shorter endolymph drainage systems, as measured by the distance between the posterior semicircular canal and the posterior fossa on magnetic resonance images.[83] These anatomic variations are apparent by the age of 3 years and may predispose affected persons to later development of Meniere's disease. Enhancement of the endolymphatic sac[84] (Fig. 165-4) and perilymphatic space[85] has been demonstrated on MRI after gadolinium enhancement. However, significant individual variation has been observed, so imaging studies are neither diagnostic or predictive for Meniere's disease. The main role of imaging in the diagnosis of Meniere's disease is to exclude other possible causes of dizziness and unilateral hearing loss, such as a vestibular schwannoma.

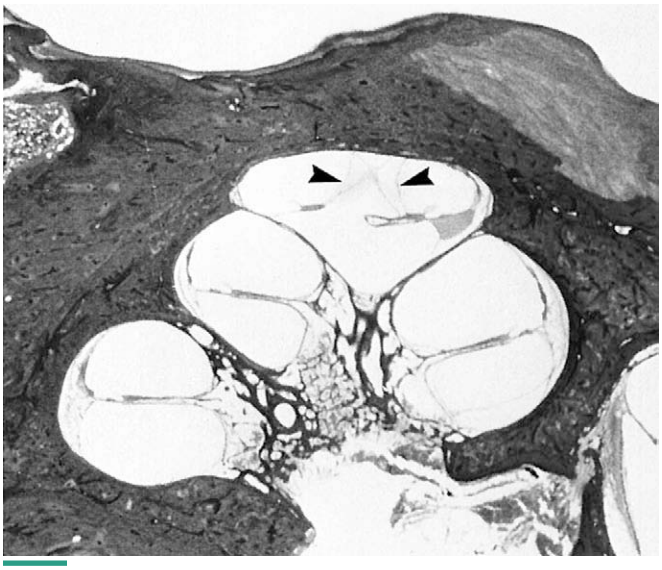

Figure 165-3. Photomicrograph of a cross section of human cochlea demonstrating endolymphatic hydrops in a patient with Meniere's disease. Note the distention of Reissner's membrane into the scala tympani in the apical turn of the cochlea *(arrowheads)*. *(Courtesy of Drs. J. Rutka and M. Hawke, University of Toronto.)*

Endolymphatic hydrops has been uniformly observed in the temporal bones from persons with Meniere's disease. However not all patients found to have hydrops, had a history of Meniere's disease.[86,87] Hydrops also is a postmortem finding after labyrinthitis, otitis media, head trauma, mumps, and meningitis. Asymptomatic hydrops also has been described.[88]

Ruptures in the membranous labyrinth of the patient with Meniere's disease are thought to be significant to the pathophysiology of the disorder. Membranous ruptures have been found in nearly all parts of the inner ear. Healed scars, presumably after rupture, also have been identified.[89,90] Their presence has supported one of the more prominent theories of the pathogenesis of Meniere's disease. Schuknecht postulated that ruptures in the membranous labyrinth allow leakage of the potassium-rich endolymph into the perilymph, bathing the eighth cranial nerve and lateral sides of the hair cells.[91] High concentrations of extracellular potassium depolarize the nerve cells, causing their acute inactivation. The result is a decrease in auditory and vestibular neuronal outflow consistent with the hearing loss and features of acute vestibular paralysis seen in a typical Meniere's attack. Healing of the membranes is presumed to allow restitution of the normal chemical milieu, with termination of the attack and improvement in vestibular and auditory function. The chronic deterioration in inner ear function presumably is the effect of repeated exposure to the effects of the potassium. This theory remains somewhat controversial, because some investigators have suggested that these ruptures rarely occur and do not adequately explain the observed symptoms.[92]

Etiology

The triad of hearing loss, tinnitus, and vertigo constitutes Meniere's syndrome. If the cause is unknown, it is defined as Meniere's disease.[93] However, if a disease entity that is known to cause endolymphatic hydrops is associated with the syndrome, the diagnosis is one of secondary endolymphatic hydrops (i.e., otosclerotic foci causing mechanical endolymphatic blockage[94]). Obstruction of the endolymphatic duct is the basis for development of hydrops in experimental animals. This is accomplished by any lesion that can produce failure of duct function, including mechanical blockage, chemical fibrosis, viral inoculation, immunologically induced inflammation, and ischemia.[95] However, these animal models cannot be interpreted to explain the actual cause of the human disease. These models also do not completely reproduce the clinical and pathologic entity experienced by humans.

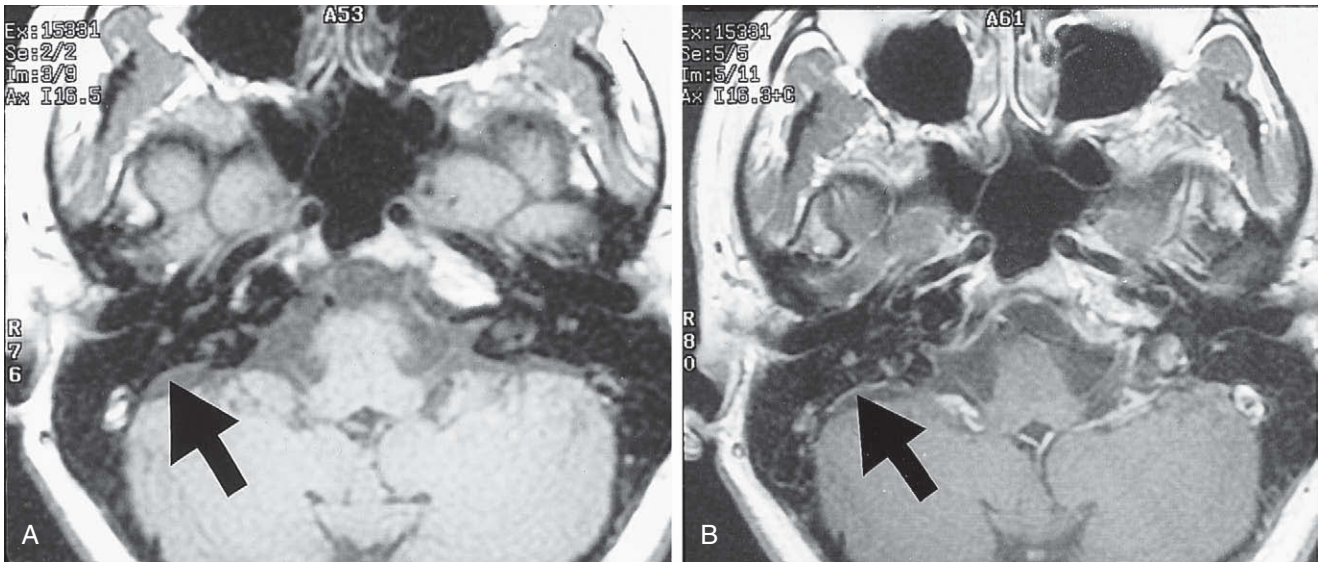

Figure 165-4. Magnetic resonance imaging for evaluating Meniere's disease. **A,** Nonenhanced axial T1-weighted image of right petrous bone demonstrating the nonenhancing endolymphatic sac *(arrow)* in a patient with Meniere's disease. **B,** Post-gadolinium T1-weighted image from the same patient. Note enhancement of the endolymphatic sac. *(Courtesy of Dr. D. Fitzgerald, Washington, DC.)*

Antibodies directed against normal inner ear elements have been suggested. Patients with Meniere's disease have an increased incidence of specific types of human leukocyte antigens.[70,96] However, most autoimmune processes, including those that affect the ear, such as Cogan's syndrome, have histopathologic findings including infiltration of white blood cells and cellular destruction. If an autoimmune mechanism is responsible, it would have to have a more indolent course or be intermittent and absent at the time of tissue sampling.

Viral infection also has been a suggested pathomechanism for Meniere's disease.[89] The observed occurrence of symptomatic hydrops many years after unexplained deafness, so-called delayed endolymphatic hydrops, suggests that subclinical viral infection could cause hydrops many decades later.[97] However, no virus has been conclusively identified, and comparison of patients with Meniere's disease with control subjects has demonstrated no difference in response to herpes simplex virus.[98]

Ischemia of the endolymphatic sac or inner ear has also been proposed as a underlying mechanism of Meniere's disease.[99] Such a common vascular mechanism may link migraine and Meniere's disease.[72,100,101]

Numerous factors have been implicated as causative for Meniere's disease. Although this lack of specificity in part reflects the current lack of understanding, it also suggests that Meniere's disease may be multifactorial or may represent the common end point of a variety of injuries or anatomic variables. A number of processes seem to be associated with the development of hydrops (e.g., trauma, acute otitis media, labyrinthitis, congenital inner ear deformity, idiopathic processes), but these are not always associated with the development of symptoms.[86] It is possible that Meniere's disease is precipitated by a variety of events such as autoimmune, viral, traumatic, or vascular or ischemic and may even be the result of congenital anatomic and molecular variations that may act as triggers for the later development of symptomatic hydrops (see Chapters 149 and 153).

Diagnosis

No single test is available to make the diagnosis of Meniere's disease. Rather, the most important aspect of the diagnostic process is a complete history, including a detailed description of the pattern of disease presentation, supported by quantitative testing. The most recent definition of the disease has been established by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) and is summarized in Table 165-1.[102]

Clinical Presentation

The typical history consists of recurring attacks of vertigo (96.2%) with tinnitus (91.1%) and ipsilateral hearing loss (87.7%).[103] Attacks often are preceded by an aura consisting of a sense of fullness in the ear, increasing tinnitus, and a decrease in hearing. The attacks may, however, be sudden in onset, with little or no warning. Acute attacks typically last from minutes to hours, most commonly 2 to 3 hours.[104] Attacks lasting longer than a day are unusual and if present should cast doubt on the diagnosis.

The classic presentation as just described is not always detailed by the patient. This is particularly true in the early phases of the disease. Often in retrospect, the disease seems to manifest with a predominance of either vestibular or auditory complaints.[105] In the series reported by Kitahara and associates, 50% of patients presented with vertigo and hearing loss together, 19% with vertigo only, and 26% with only deafness.[106] These variable initial presentations have led to the usage of the terms *cochlear* and *vestibular* Meniere's disease. These subtypes are not widely used, however, and are considered by the AAO-HNS Committee on Hearing and Equilibrium[102] to be an inappropriate application of the diagnosis.[106] Furthermore, no pathologic correlation for these subtypes has been found.[86] The terms *recurrent vestibulopathy* and *atypical Meniere's disease* have been used to describe the condition on persons with less than the classic triad of hearing loss, vertigo, and sensation of aural fullness or tinnitus.

The clinical course of Meniere's disease is highly variable. Patients often have a cluster of attacks separated by long remissions. Silverstein and coworkers[107] found that vertigo ceased spontaneously in 57% of patients in 2 years and in 71% after 8.3 years. Attacks often are clustered in time. Severity of symptoms ranges from minimal inconvenience to complete incapacitation; the AAO-HNS has provided staging guidelines[102] (Table 165-2). In addition to the incapacitating effects of the physical manifestations of Meniere's disease (vertigo, dysequilibrium, hearing loss, tinnitus, and pressure), the disease is emotionally disabling.[108]

History

Incapacitating, spinning vertigo, usually in the horizontal axis, is the most distressing complaint of the affected patient.[93] As is typical of peripheral vestibular dysfunction, the symptoms are exacerbated with any head movement. Accompanying symptoms and signs may include nausea, vomiting, diarrhea, and sweating. Between attacks, patients

Table 165-1

AAO-HNS Criteria for Meniere's Disease Diagnosis

Major Symptoms

Vertigo
- Recurrent, well-defined episodes of spinning or rotation
- Duration from 20 minutes to 24 hours.
- Nystagmus associated with attacks
- Nausea and vomiting during vertigo spells common
- No neurologic symptoms with vertigo

Deafness
- Hearing deficits fluctuate
- Sensorineural hearing loss
- Hearing loss progressive, usually unilateral

Tinnitus
- Variable, often low-pitched and louder during attacks
- Usually unilateral
- Subjective

Diagnosis

Possible Meniere's disease
- Episodic vertigo without hearing loss *or*
- Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium, but without definite episodes
- Other causes excluded

Probable Meniere's disease
- One definitive episode of vertigo
- Hearing loss documented by audiogram at least once
- Tinnitus or sense of aural fullness in the presumed affected ear
- Other causes excluded

Definite Meniere's disease
- Two or more definitive spontaneous episodes of vertigo lasting at least 20 minutes
- Audiometrically documented hearing loss on at least one occasion
- Tinnitus or sense of aural fullness in the presumed affected ear
- Other causes excluded

Certain Meniere's disease
- Definite Meniere's disease, *plus* histopathologic confirmation

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery.
From Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology–Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg.* 1995;113:181.

Table 165-2

AAO-HNS Criteria for Meniere's Disease Severity

Vertigo

a. Any treatment should be evaluated after at least 24 months.
b. Formula to obtain numeric value for vertigo: ratio of average number of definitive spells per month after therapy divided by definitive spells per month before therapy (averaged over a 24-month period) × 100 = numeric value
c. Numeric value scale:

Numeric Value	Control Level	Class
0-40	Complete control of definitive spells	A
41-80	Limited control of definitive spells	B
81-120	Insignificant control of definitive spells	C
>120		D
Secondary treatment initiated		E

Disability

a. No disability
b. Mild disability: intermittent or continuous dizziness/unsteadiness that precludes working in a hazardous environment
c. Moderate disability: intermittent or continuous dizziness that results in a sedentary occupation
d. Severe disability: symptoms so severe as to exclude gainful employment

Hearing

a. Hearing is measured using a four-frequency pure-tone average (PTA) of 500 Hz, 1 kHz, 2 kHz, and 3 kHz.
b. Pretreatment hearing level: worst hearing level during 6 months before surgery
c. Post-treatment hearing level: poorest hearing level measured 18-24 months after institution of therapy
d. Hearing classification:
   i. Unchanged: ≤10-dB PTA improvement or worsening or ≤15% speech discrimination improvement or worsening
   ii. Improved: >10-dB PTA improvement or >15% discrimination improvement
   iii. Worse: >10-dB PTA worsening or >15% discrimination worsening

In 1996, the Committee on Hearing and Equilibrium reaffirmed and clarified the guidelines, adding initial staging and reporting guidelines:

Initial Hearing Level

Stage	Four-Tone Average (dB)
1	≤25
2	26-40
3	41-70
4	>70

Functional Level Scale

Regarding my current state of overall function, not just during attacks:

1. My dizziness has no effect on my activities at all.
2. When I am dizzy, I have to stop for a while, but it soon passes and I can resume my activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
3. When I am dizzy I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
4. I am able to work, drive, travel, and take care of a family or engage in most activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.
5. I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to do. Even essential activities must be limited. I am disabled.
6. I have been disabled for 1 year or longer and/or I receive compensation because of my dizziness or balance problem.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery.
From Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology–Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg.* 1995;113:181.

may be entirely asymptomatic or may describe periods of dysequilibrium, lightheadedness, and tilt.

Sudden unexplained falls without loss of consciousness or associated vertigo occasionally are described. Tumarkin[109] attributed these events to acute utriculosaccular dysfunction—so-called otolithic crises of Tumarkin, or drop attacks. It is thought that an abrupt change in otolithic input generates an erroneous vertical gravity reference. This in turn generates an inappropriate postural adjustment by way of the vestibulospinal pathway, resulting in a sudden fall.[110,111] Attacks are so sudden that injury can occur. The patient often describes a feeling of being pushed or "the world moving." The spells are brief with little associated vertigo. Drop attacks have been reported in 2% to 6% of persons with Meniere's disease. They tend to occur in clusters and then spontaneously remit.

Lermoyez described an unusual clinical presentation in which tinnitus and hearing loss precede and worsen with the onset of vertigo. When the vertiginous episode occurs, the tinnitus and hearing loss dramatically resolve. The temporal bone studies in a patient with such attacks noted hydrops and membrane ruptures isolated to the basal turns of the cochlea and the saccule.[112]

Acute Meniere's attacks are rarely observed by physicians. Horizontal nystagmus is the cardinal finding, but the direction varies over the course of the attack, so it is not useful in determining the involved ear.

Hearing Loss and Tinnitus

The sensorineural hearing loss in Meniere's disease typically is fluctuating and progressive. It often occurs coincident with the sensation of fullness or pressure in the ear. A pattern of low-frequency fluctuating loss and a coincident nonchanging, high-frequency loss is described, resulting in a "peaked" or "tent-like" tracing on the audiogram. This peak classically occurs at 2 kHz. Over time, the hearing loss normalizes across frequencies and becomes less variable.[105] In only 1% to 2% of patients does the hearing loss progress to profound deafness.

Additional features include diplacusis, a difference in the perception of pitch between the ears (43.6%) and recruitment (56%).[93]

Tinnitus tends to be nonpulsatile and variously described as whistling or roaring. It may be continuous or intermittent. Tinnitus often begins, gets louder, or changes pitch as an attack approaches. Frequently a period of improvement follows the attack.

Investigations

Electronystagmography

Electrooculographic recordings of eye movements after caloric and rotational stimulation are a commonly available and reliable method of assessing vestibular function. The caloric test often can localize the involved ear. A significant caloric response reduction is found in 48% to 73.5% of patients with Meniere's disease.[113] Complete absence of caloric response is reported in 6% to 11% of patients.

Head Thrust Testing

The head thrust test popularized by Halmagyi is very sensitive for detection of unilateral vestibular dysfunction.[114] However, in Meniere's disease, the asymmetry is subtle and present in only 29% of the patients.[115]

Electrocochleography

The summating potential (SP), as recorded by electrocochleography in patients with Meniere's disease, is larger and more negative. This is thought to reflect the distention of the basilar membrane into the scala tympani, causing an increase in the normal asymmetry of its vibration. The most commonly used value is the ratio of amplitudes of the SP and the eighth cranial nerve action potential (AP), the SP/AP ratio. This is based on the observed variability in the amplitude of the SP, considering variables such as recording technique and electrode placement. The SP/AP ratio has been used to reduce the intertest variability, resulting in a more linear response. The SP becomes relatively larger in hydrops; accordingly, the SP/AP ratio increases.[116] It is not a definitive test, because ratios are elevated in 62% of patients with Meniere's disease and in 21% of control subjects. Because of the difficulty in obtaining reproducible recordings and the variability of the wave amplitudes noted with patient age, hearing loss, and stage of disease, as well as the availability of reliable, less invasive diagnostic methods, electrocochleography is now infrequently used for this purpose.[117,118]

Dehydrating Agents

The assumption that an increase in endolymph volume, with its effect on labyrinthine membrane behavior, produces, in part, the hearing loss and vestibular deficit in Meniere's disease has led to the administration of dehydrating agents (e.g., urea, glycerol, furosemide). The goal is to reduce the volume abnormalities in the inner ear and produce a measurable change in response. Improvement has been measured with audiometrics, reduction in SP negativity (as recorded with electrocochleography), or a change in the gain of the vestibulo-ocular response to rotational stimulation. The reported sensitivity and specificity rates for the test vary widely. Klockhoff reports a 60% sensitivity in cases of known Meniere's disease.[119] Psychological factors constitute a significant source of variability, leading some authorities to question the usefulness of the test.[117,120]

Vestibular Evoked Myopotentials

VEMPs are generated by playing loud clicks in the ear, which move the stapes footplate and stimulate the saccule. This is the start of a disynaptic pathway that passes through the vestibular nuclei and then to synapses that relax the sternocleomastoid muscle. The saccule is the second most common site affected by hydrops, which has caused VEMPs to be investigated as a potential diagnostic tool. In the normal ear, the best response is near 500 Hz. Ears affected by Meniere's disease have elevated VEMP thresholds with flattened tuning.[121] The interaural amplitude difference in the response has been implicated as a staging tool for Meniere's disease.[122] Although these tests show differences between populations, they currently have limited diagnostic value owing to the large individual variation in responses.

Treatment

Therapy of Meniere's disease is aimed at the reduction of its associated symptoms. The optimal curative treatment should stop vertigo, abolish tinnitus, and reverse hearing loss. Unfortunately, long-term hearing impairment does not seem amenable to treatment.[108] Currently, almost all proven therapies are directed at relieving vertigo, which usually is the most distressing symptom.

Evaluating treatments for vertigo in patients with Meniere's disease has been made difficult by the natural history of the disease, which includes spontaneous improvement in 60% to 80% of cases, and because many treatments have a significant placebo effect.[96,123,124] This is further supported by the 71% reduction in symptoms by patients who refused surgery,[107] and placebo-controlled studies of endolymphatic sac surgery[17,125] and medical therapy.[126] The large variety of Meniere's disease treatments reflect the extreme variability in clinical response and the inherent difficulty in assessing effectiveness.

Dietary Modification and Diuretics

Salt restriction and diuresis may be the best initial therapy for Meniere's disease.[127,128] The goal of salt restriction and diuretics is to reduce endolymph volume by fluid removal or reduced production. Despite the popularity of these treatments, neither salt restriction[129] nor use of diuretics[130,131] has had its efficacy confirmed by double-blind, placebo-controlled studies. Carbonic anhydrase inhibitors such as acetazolamide were recommended on the basis of the localization of carbonic anhydrase to the dark cells and the stria vascularis. However, these agents have not proved to be clinically more effective than other diuretics.[132] Despite the lack of hard evidence of their efficacy, we feel that a low-salt diet and diuresis constitute an appropriate and effective treatment for Meniere's disease with a low risk of side effects.

Vasodilators

In the belief that Meniere's disease was the result of strial ischemia, vasodilating agents have been used. Betahistine, an oral preparation

of histamine, is one such medication.[133] It has proved to be effective in treatment of Meniere's disease in a placebo-controlled study.[133,134] Such studies have flaws, however, which continues to raise doubts about the efficacy of betahistine over placebo.[135] The medication has become a popular treatment for Meniere's disease in Europe.[136] The drug is available through compounding pharmacies in the United States but often is not covered by insurance and is infrequently prescribed.

Symptomatic Treatment

Antivertiginous medications, antiemetics, sedatives, antidepressants, and psychiatric treatment have been reported to be beneficial in reducing the severity of the vertigo and vegetative symptoms and in improving tolerance of Meniere's symptoms.[137]

Local Overpressure Therapy

A relatively recent approach to decrease hydrops is by pulsing pressure in the middle ear. As long ago as 40 years, overpressure in the middle ear was reported to decrease Meniere's symptoms during acute vertigo attacks.[138] The mechanism of vertigo reduction is unclear, although it may facilitate endolymph absorption.[139]

Since 2000, the Meniett device has been approved for use by the U.S. Food and Drug Administration (FDA). This device is a handheld air pressure generator that the patient self-administers. The pressure is delivered in complex pulses of up to 20 cm of water, over a 5 minute period. The device requires a ventilation tube to be placed in the tympanic membrane before initiation of therapy. A randomized controlled trial demonstrated that patients using the Meniett device experienced a significant decrease in vertigo symptoms for the first 3 months of therapy but that findings afterward were similar to those with placebo.[140] The placebo device in these cases was an inactive device that did not administer pressure. Long-term treatment with the Meniett device has shown results similar to the natural course of Meniere's disease.[141]

Of note, simple placement of a ventilation tube with no additional therapy also has been reported to control vertigo symptoms in many patients with Meniere's disease.[142,143]

Intratympanic Injection

Intratympanic injection commonly is performed with either dexamethasone or gentamicin for control of vertigo symptoms. The term *chemical labyrinthectomy* often is applied to intratympanic gentamicin treatment, but it may not be an appropriate assessment of the effect of gentamicin on the labyrinth in titrated therapy. Instillation of aminoglycosides into the middle ear was described by Schuknecht in 1957 with streptomycin injection through a microcatheter placed through the tympanic membrane.[144] Control of vertigo was achieved in these patients, but severe hearing loss in the treated ear also occurred in most patients.

Gentamicin has a vestibulotoxicity that is high relative to its cochleotoxicity; accordingly, it can be used to control vestibular symptoms while sparing hearing. The gentamicin can be administered through either a tympanostomy tube or directly injected through the tympanic membrane. Peripheral vestibular deficits are evident on head thrust testing after even a single dose of gentamicin[145] (Fig. 165-5). The concentration of the medication used and frequency of injection vary by series. The risk of hearing loss also varies greatly by series, depending on the dose and frequency of treatment. Lange[146] reported elmination of vertigo in 90% of 92 patients, but the incidence of hearing loss and level of vestibular function were not specified. Beck and Schmit[147] sought to determine if complete ablation of vestibular function, as measured with ice water caloric response, was needed for vertigo control. They found that it was not, and that this end point led to severe to profound hearing loss in 58% of treated patients. Wu and Minor[148] found complete control of vertigo in 90%, with profound sensory neural hearing loss in only 3% of patients. Nedzelski and associates[149] found that control of vertigo was achieved in 83% of patients, with substantial control in the remaining subjects. A 10%

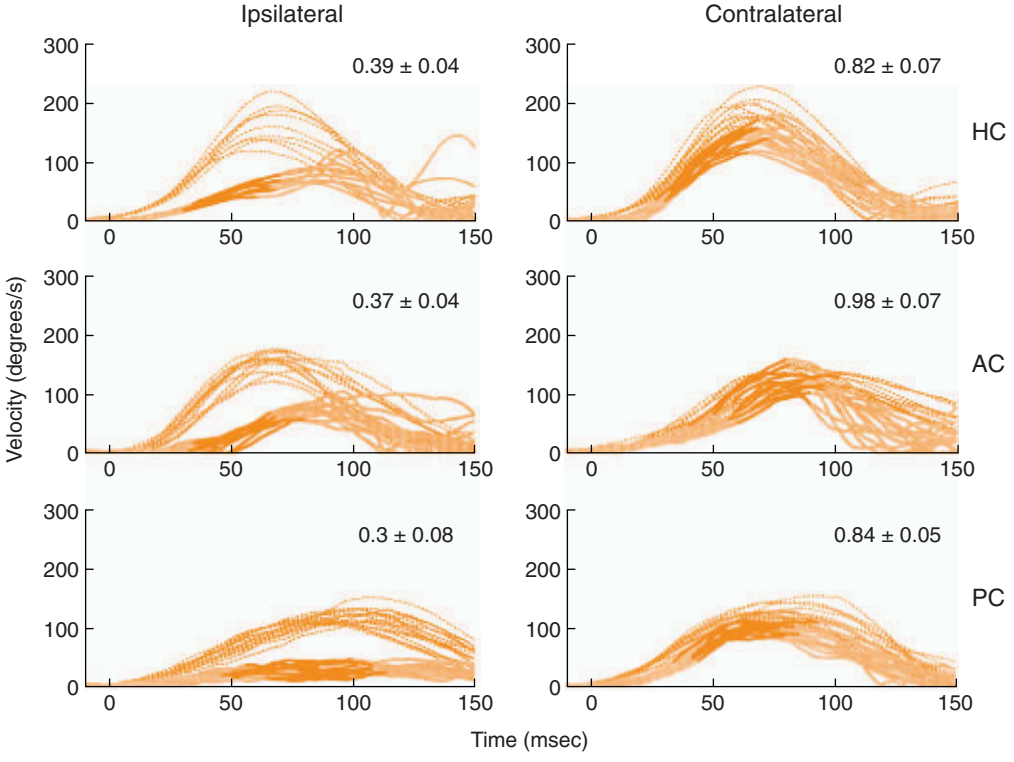

Figure 165-5. Response to head thrusts that excited each of the six semicircular canals in a typical subject measured 49 days after a single intratympanic injection of gentamicin in the right ear. AC, anterior canal; HC, horizontal canal; PC, posterior canal. *(Reproduced from Carey JP, Minor LB, Peng GC, et al. Changes in the three-dimensional angular vestibulo-ocular reflex following intratympanic gentamicin for Meniere's disease.* J Assoc Res Otolaryngol. *2002;3:430.)*

incidence of profound hearing loss in the treated ear was noted. The current trend is away from multiple doses of gentamicin and toward a single-injection regimen, with additional doses only if needed to control symptoms (so-called titration therapy). The risk of hearing loss with gentamicin using many current protocols is similar to that with the natural history of Meniere's disease.[127,148]

Intratympanic injection of dexamethasone is considered by many experts to be a reasonable procedure to offer when vertigo is intractable but the patient still has some functional hearing. The mechanism for steroid effect on vertigo symptoms is not currently clear. Some evidence suggests that Meniere's disease has an autoimmune component, which the steroids may address. Several studies have reported a beneficial effect of intratympanic injection of dexamethasone in the control of vertigo from Meniere's disease,[150,151] although the effect on hearing loss and tinnitus is minimal. The risk of hearing loss or other complications from the steroid injection appears to be low. A small randomized trial has shown complete resolution of vertigo symptoms in 82% of patients receiving dexamethasone, compared with 57% receiving saline injection.[152] Dexamethasone injections may need to be repeated every 3 months to maintain the patient free of vertigo symptoms, although the optimal dosing frequency is variable and unknown. Concentrations used have varied from 2 to 24 mg/mL.

Endolymphatic Sac Surgery

Surgical decompression of the endolymph for Meniere's disease was first described by Portmann in 1926.[10] During the more than three fourths of a century during which this technique has been practiced, numerous variations on the concept have been devised. Despite significant investigation into techniques to decompress the endolymph, the etiology of endolymphatic hydrops as part of the pathophysiology of Meniere's disease is still an active area of controversy and debate. Several theories have been proposed: release of external compression on the sac, neovascularization of the perisaccular region, allowing passive diffusion of endolymph, and creation of an osmotic gradient out of the sac.[153]

Several variations of endolymphatic sac surgery have been described. Simple decompression, wide decompression that includes the sigmoid sinus,[154] cannulating the endolymphatic duct, endolymphatic drainage to the subarchnoid space, drainage to the mastoid, and removal of the extraosseous portion of the sac[155] all have been advocated. A variety of prostheses also have been proposed, ranging from simple Silastic sheets to tubes and one-way valves designed to allow flow selectively in either the mastoid or the subarachnoid direction.

In a double-blind, placebo-controlled study by Thomsen and coworkers, a mastoidectomy alone had the same efficacy as that of an endolymphatic shunt in a group of 30 patients, with 15 randomly selected for each operation.[17] The efficacy of the procedure remains controversial, with other workers re-examining the data of Thomsen and colleagues and claiming that a significant result would have been found if a different criterion for success had been used[156] or if different statistical methods were applied.[18]

Nerve Section

Several approaches to sectioning of the vestibular nerve have been described. The earliest approach was the retrosigmoid, with the first large series accumulated by Walter Dandy in the 1930s.[11] The terms *retrosigmoid* and *suboccipital* are now used interchangeably. The middle fossa approach to the internal auditory canal and superior vestibular nerve was developed by William House[157] and later modified to include sectioning of the inferior vestibular nerve.[158] A retrolabyrinthine approach has also been described.[159]

Vestibular nerve section achieves a complete vertigo control rate of approximately 85% to 95%, with 80% to 90% of patients maintaining their preoperative hearing after the procedure.[160-162] The procedure offers much greater vertigo control rates than those reported for endolymphatic shunt procedures but also is more invasive and technically challenging. Vestibular nerve section has been argued to carry a lower risk of hearing loss when compared with gentamicin injection,[161] although the risk of hearing loss with gentamicin seems to be most significant with high-dose protocols.

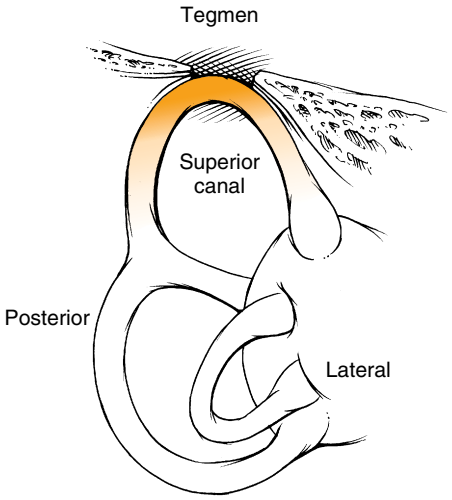

Figure 165-6. Superior canal dehiscence. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Labyrinthectomy

The most destructive procedure for treatment of Meniere's disease is labyrinthectomy, owing to the uniform destruction of hearing and vestibular function. Ideal candidates for the procedure are pateints who have no functional hearing and in whom more conservative treatments such as gentamicin injection have failed. Despite the associated morbidity, the procedure has a higher rate of vertigo control than that typical for vestibular neurectomy[163] and has been reported to improve quality of life in 98% of operated patients.[164] The procedure is most commonly performed through a transmastoid exposure but can be done using a transcanal approach.

Superior Canal Dehiscence Syndrome

Superior canal dehiscence syndrome (SCDS)[27] is the result of the absence of bone over the superior canal (Fig. 165-6). This bony dehiscence creates a third mobile window that allows the abnormal movement of endolymph during presentation of loud sounds (Tullio phenomenon[165]), tragal compression, nose-blowing, or other mechanisms for creation of a pressure gradient between the ear and middle fossa. Loud sound or increased pressure often causes nystagmus in the same plane as that of the superior canal on the affected side.[166] The nystagmus is a combination of vertical and torsional rotation aligning with the superior canal, as predicted by Ewald's first law.[167] When gaze shifts 45 degrees toward the side of the dehiscence, the pupil will move in a vertical direction. During gaze 45 degrees in the contralateral direction, the eye will rotate about an axis through the pupil. The Tullio phenomenon is not observed in all cases of SCDS. In addition to dizziness and nystagmus, SCDS may be characterized by autophony (sensation of increased loudness of the patient's own voice), conductive hearing loss that is not due to middle ear pathology, or pulsatile tinnitus.[168] High-resolution CT scans with reconstructions in the plane of the superior canal and orthogonal to that plane should be done to confirm the diagnosis.

The pathophysiology of superior canal dehiscence can be understood in terms of the effects of the dehiscence in creation of a third "mobile window" into the inner ear. Under normal circumstances, sound pressure enters the inner ear through the stapes footplate in the oval window and, after passing around the cochlea, exits through the round window. The presence of a dehiscence in the superior canal allows this canal to respond to sound and pressure stimuli. The direction of the evoked eye movements supports this mechanism. Loud sounds, positive pressure in the external auditory canal, and Valsalva maneuver against pinched nostrils cause ampullofugal deflection of the superior canal, which results in excitation of afferents innervating this canal. The evoked eye movements can include a nystagmus that has slow components directed upward with torsional motion of the supe-

rior pole of the eye away from the affected ear. Conversely, negative pressure in the external canal, Valsalva maneuver against a closed glottis, and jugular venous compression cause ampullopetal deflection of the superior canal, which results in inhibition of afferents innervating this canal. The evoked eye movements typically are in the plane of the superior canal but in the opposite direction (downward with torsional motion of the superior pole of the eye toward the affected ear) (Fig. 165-7).

The severity of a patient's symptoms and the impact of these symptoms on lifestyle are major determinants in the discussion of surgery for superior canal dehiscence.[168] Some patients are discovered to have SCDS as an incidental finding on CT scan and do not have symptoms. In other patients, only autophony or conductive hearing loss may be noted. A decision about surgical plugging of the superior canal to alleviate symptoms should be based on the impact of symptoms on a patient's lifestyle and a consideration of the risks of surgery.

Confirmation of dehiscence of bone overlying the superior canal in patients with the syndrome has been obtained with high-resolution CT scans of the temporal bones.[28,169-171] Conventional temporal bone CT scans are performed with 1.0-mm collimation, and images are displayed in the axial and coronal planes. These scans have a relatively low specificity (high number of false-positive results) in the identification of superior canal dehiscence because of the effects of partial volume averaging. The specificity and positive predictive value of these scans are improved when 0.5-mm-collimated helical CT scans are performed with re-formation of the images in the plane of the superior canal.[171] The scans also are reformatted radially around the canal in the plane perpendicular to the superior canal, so that the cross section of the canal can be evaluated (Fig. 165-8). Of note, even the best CT scan may be misleading, because very thin bone may be below the resolution of the scanner; accordingly, diagnosis should never be based on the CT scan alone.

CT studies have shown that the thickness of bone overlying the intact superior canal in a patient with unilateral dehiscence is significantly thinner than in patients without superior canal dehiscence.[172] This finding and observations from a review of 1000 histologically

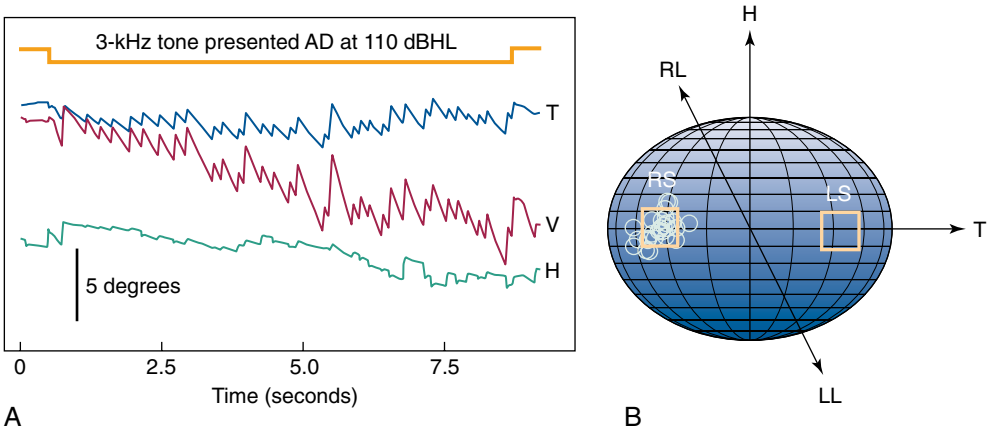

Figure 165-7. Ocular responses to sound in the superior canal dehiscence (SCD) syndrome. Nystagmus induced by a 3-kHz tone at an intensity of 100 dB in the right ear (AD [*auris dextra*]) of a 33-year-old woman with right SCD syndrome. **A,** Torsional (T), vertical (V), and horizontal (H) eye position recorded with the scleral search coil technique from the right eye. The time during which the tone was presented is indicated by the *yellow bar* at the top. Positive direction for horizontal is left, vertical is down, and torsional is clockwise (from the patient's perspective, so rotation of the superior pole of the patient's eye is to the patient's right). In response to the tone in her right ear, the patient developed a nystagmus with upward, counterclockwise slow phases consistent with excitation of the right superior canal. **B,** The axis of slow-phase eye velocity corresponded to the data plotted in **A.** The sphere represents the patient's head, as viewed from the right. The positive direction of the horizontal axis (H) travels upward from the top of the head, the torsional axis (T) straight ahead from the patient's nose, and the vertical axis (obscured by the sphere) from the patient's left ear. The anatomic axis of each of the right superior (RS), left superior (LS), right lateral (RL), and left lateral (LL) semicircular canals is shown. The box around the axis of each superior canal indicates the region (±2 SD) from the mean orientation of that axis. Each *light circle* represents the mean eye velocity axis for one slow phase of nystagmus. *(Reproduced with permission from Minor LB, Cremer PD, Carey JP, et al. Symptoms and signs in superior canal dehiscence syndrome.* Ann N Y Acad Sci. *2001;942:259-273.)*

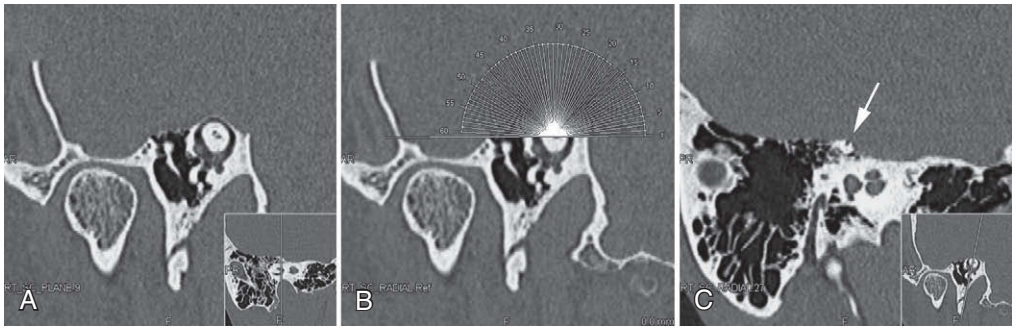

Figure 165-8. Computed tomography (CT) of the right superior semicircular canal demonstrating dehiscence. **A,** CT image is reconstructed in the plane of the torus of the right superior canal. **B,** The center of the superior canal is identified, and radial orthogonal reconstructions are performed at 3-degree intervals. **C,** The radial reconstructions are sequentially examined along the course of the superior canal, and dehiscence in the canal is identified if bone does not appear to completely cover the canal *(arrow)*. The *inset* at lower right in **A** and **C** shows the plane of section of this radial reconstruction relative to the superior canal plane.

processed temporal bones sectioned in a plane parallel to the petrous ridge[173] suggest an underlying developmental or congenital abnormality that leads to the development of the syndrome. The onset of symptoms and signs associated with this syndrome typically has been during adulthood. Patients in whom a normal thickness of bone fails to develop may then acquire the syndrome when the abnormally thin layer of bone is disrupted by trauma or is eroded over time as a consequence of the pressure from the overlying temporal lobe.

Vestibular evoked myogenic potentials (VEMP) responses have been useful in assessing for the presence of superior canal dehiscence syndrome.[174-176] In this test, short-latency relaxation potentials evoked by clicks or by tone bursts are recorded from surface EMG electrodes placed on the skin over the ipsilateral sternocleidomastoid muscle while that muscle is tonically contracted. These responses arise from the vestibular end organs, most likely the sacculus.[177,178] The threshold for eliciting the VEMP response is lower in an ear affected with superior canal dehiscence than in a normal ear.[174,176]

Some patients with the vestibular symptoms and signs indicative of superior canal dehiscence syndrome also have been noted to have auditory manifestations of the disorder. The Weber tuning fork test typically lateralizes to the affected ear, and patients also may hear a tuning fork placed on the lateral malleolus of the foot.[168,179] Patients may present with seemingly bizarre complaints, such as "hearing" their eye movements or their pulse. Bone conduction thresholds on audiometry can be below 0 dB normal hearing level (NHL). Therefore, an air-bone gap may be present even when air conduction thresholds are normal.[180] This conductive hearing loss may be caused by formation of a third window by the dehiscence, which causes a dissipation of acoustic energy transmitted through air conduction mechanisms. For some patients, autophony or a disturbing sound of their own voice can be the primary symptom.[181] The clinical manifestations of superior canal dehiscence include vestibular signs and symptoms in some patients, vestibular and auditory abnormalities in others, and exclusively auditory findings in others.

Patients who experience only mild effects of the symptoms and signs associated with superior canal dehiscence may not require any specific treatment other than avoidance of the stimuli that evoke these effects. Placement of a tympanostomy tube may be beneficial in some patients with principally pressure-induced symptoms. For patients who are debilitated by symptoms associated with the syndrome, surgical repair of the superior canal dehiscence by plugging the superior canal through a middle cranial fossa approach can be effective in alleviating or attenuating the vestibular signs and symptoms.[28,182]

Cogan's Syndrome

Cogan's syndrome was first described in 1945 and is characterized by interstitial keratitis, "low-frequency unilateral" hearing loss, and vestibular symptoms as well as nonreactive tests for syphilis.[183] The syndrome was later divided into typical and atypical forms on the basis of specific ocular findings.[184] The typical form includes interstitial keratitis, whereas the atypical form has ocular features of scleritis, episcleritis, papilledema, and retinal detachment.[185] Ten percent of patients with Cogan's syndrome have the atypical form. Multisystem involvement, including CNS manifestations and inflammatory vascular disease, is a feature of Cogan's disease. Of the two forms, systemic features are noted more commonly in atypical Cogan's disease. In the typical form, the heart and lungs are the usual site of systemic involvement, including aortitis, pleuritis, pericardial effusion, coronary arteritis, and myocardial infarction. In atypical Cogan's disease, systemic features arise from a systemic vasculitis (e.g., polyarteritis nodosa, arthritis, glomerulonephritis, gastrointestinal problems).

Ocular and inner ear changes appear concurrently or within 6 months of each other. Ocular complaints include photophobia, blurred vision, lacrimation, and pain. These symptoms and signs may be unilateral or bilateral. Onset usually is sudden, and resolution is gradual. Recurrences over years are not uncommon. Ocular pathologic changes include infiltration of the cornea with lymphocytes and plasma cells as well as corneal neovascularization.

Balance-related symptoms are similar to those of Meniere's disease and consist of sudden attacks of true vertigo with ataxia and vegetative symptoms. Progression to the complete absence of vestibular function, manifested by ataxia and oscillopsia, is common.

Hearing loss is sensorineural in type and is bilateral in 44% of patients.[186] The loss is progressive without spontaneous improvement, frequently becoming profound. In bilateral cases, hearing loss frequently begins on one side.

Cogan's syndrome is thought to be of autoimmune basis. This suspected etiology is based on lymphocyte transformation tests, migration inhibition to inner ear tissues, the association with rheumatologic diseases, and presence of lymphocytes and plasma cells in the ear and eye, as well as the clinical response to systemic steroids.

Clinically, patients often report having had an upper respiratory infection within 7 to 10 days of initial onset of Cogan's syndrome.[184] Raised IgG and IgM titers to *Chlamydia* are reported in association with active Cogan's syndrome. Furthermore, antibody titers are noted to decrease with remission of disease. For this reason, it has been suggested that an acute infection, perhaps with *Chlamydia*, promotes sensitization of the immune system to "self" and leads to immune-mediated disease.[184]

Systemic corticosteroids are the accepted treatment. An initial dose of 1 mg/kg per day of prednisone usually is recommended, followed by a slow taper. The probability of hearing improvement is thought to be better the sooner the steroids are started.[185] In addition, cyclophosphamide and methotrexate have been recommended by some authorities if systemic vasculitis is present.

Otosyphilis

Syphilis is a sexually transmitted disease that can become disseminated and affect almost any organ system. Although it is thought to be a rare condition in the modern era, the diagnosis is difficult to confirm, and many cases may be misdiagnosed as other conditions.[187] Thirty percent of patients suffering from congenital syphilis and 80% of symptomatic neurosyphilis patients experience significant hearing loss.[188]

Otologic involvement can be grouped into two categories: early syphilis, symptoms occurring within 2 years of exposure, and late otosyphilis, when the disease becomes symptomatic after 2 years. Vestibular symptoms are less frequent in early otosyphilis; they most commonly manifest as a sudden hearing loss. Late otosyphilis presents similar to Meniere's disease with episodes of vertigo combined with progressive hearing loss and tinnitus, which often is unilateral.[185,189] Late-stage otologic syphilis, whether acquired or congenital syphilis, can manifest up to 50 years or more after exposure. Systemic symptoms frequently overshadow the otologic ones and include signs of meningitis. In the case of early congenital syphilis, systemic involvement may prove to be fatal.

Interstitial keratitis is a feature of 90% of patients with late-onset otologic syphilis, whether congenital or acquired. The triad of sensorineural hearing loss, interstitial keratitis, and notched incisors—*Hutchinson's triad*—is an exclusive feature of late congenital syphilis.[188]

Hennebert's sign (nystagmus and vertigo produced by pressure change on the ear, thought to be due to deformation of a softened, gummatous otic capsule) and Tullio phenomenon (nystagmus and vertigo caused by loud noise), although often encountered in syphilis, are not pathognomonic for the disease and also are common findings in superior canal dehiscence.

The Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR) nontreponemal tests are easily performed and relatively inexpensive. Sensitivity varies with the stage of disease. In view of the fact that otologic symptoms occur in late-stage disease, nontreponemal tests detect only 70% of cases of otosyphilis.[190] These tests are useful in following therapeutic response, by change in titer and loss of reactivity. On the other hand, treponemal tests—such as free treponemal antigen absorption, FTA-ABS, and microhemagglutination *Treponema pallidum* [MHATP] assays, which detect the presence of the organism—are far more sensitive; these tests detect 95% or more of cases of late-stage disease. The FTA or MHATP and their variations are the tests of choice for the detection of otologic syphilis.[190] Lumbar puncture is not necessarily warranted because results are positive in only 5% of cases of otosyphilis.[185]

Treatment of otologic syphilis varies. Some investigators feel that in the early stages of the disease, treatment with antibiotics alone (i.e.,

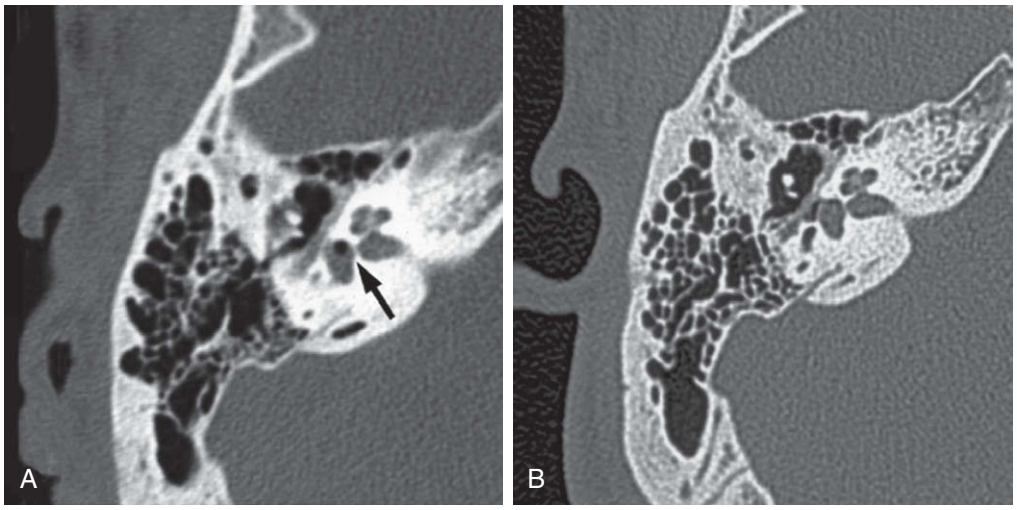

Figure 165-9. **A,** Axial CT scan of the temporal bone of a 15-year-old patient in whom pneumolabyrinth developed immediately after penetrating trauma to the left ear. This patient also presented with vertigo, a mixed hearing loss, nausea, and vomiting. The vestibular and auditory symptoms resolved with conservative management in the days after the injury, and no air was seen on a CT scan obtained 4 days later **(B)**. Within 5 months of the event, sensorineural hearing improved by 40 dB. *(Reproduced from Lao WW, Niparko JK. Assessment of changes in cochlear function with pneumolabyrinth after middle ear trauma.* Otol Neurotol. *2007;28:1013.)*

penicillin 2.4 million units IM) provides a cure, frequently resulting in hearing improvement.[188] Additional use of a 10-day course of steroids is advocated. Although consensus is lacking regarding exact drug treatment for late-stage disease, it generally is agreed that protracted therapy with both antibiotics and steroids is indicated. Difficulty in eradication of the infection, despite adequate antibiotic therapy, is ascribed to prolonged dividing time for the treponeme in late-stage disease. Antibiotic regimens of variable duration have been suggested. A recommended neurosyphilis treatment protocol consists of 1.8 million units of penicillin IM daily with 500 mg of oral probenicid four times daily for 3 weeks. It is suggested that otic syphilis and neurosyphilis are comparable with respect to response to treatment.[188] Prenisone (40 to 60 mg per day) is given for at least 2 weeks before tapering. Steroids are used in part to minimize the potential damage to the ear by the inflammatory response in the early treatment of syphilis. Improvement in hearing, particularly of speech discrimination, is noted in 35% to 50% of cases, along with resolution of vestibular symptoms.[188]

Perilymph Fistulas

Inner ear fistulas are abnormal communications between the labyrinth and surrounding structures. The labyrinth normally is covered by dense bone. Labyrinthine fistulas can be organized into three main categories: (1) leakage of perilymph from the inner ear to the middle ear, (2) disruption of the bony labyrinth by disease such as cholesteatoma, and (3) idiopathic bony dehiscence of the semicircular canals (i.e., superior semicircular canal dehiscence syndrome and posterior canal dehiscence). These disorders manifest with similar symptoms of hearing loss and episodic vertigo despite their differing etiology.[191] Idiopathic bony dehiscence of the semicircular canals creates problems of pressure transfer, as noted previously, but not fluid mixing.

The clinical presentation of inner ear fistula may range in severity from mild and inconsequential to severe and incapacitating. Sensorineural hearing losses vary from an isolated high-frequency loss to a low-frequency or flat one. Speech discrimination test results are not characteristic. Both the pure-tone threshold and speech discrimination scores have been noted to fluctuate. Isolated mild conductive losses have been noted.[192] Glasscock and colleagues, in a series of patients who had undergone surgical exploration for fistulas, were unable to identify differences in audiometric profile for patients with proven fistulas and those without.[193] Vestibular symptoms also are variable and may include episodic incapacitating vertigo (equivalent to a Meniere's disease attack), positional vertigo, motion intolerance, or occasional dysequilibrium. (Disequilibrium with increases in CSF pressure such as with nose blowing or lifting has been noted, as has Tullio's phenomenon (occurrence of vertigo during) exposure to loud noises).

Definitive leakage of perilymph from the inner ear to the middle ear can be caused by trauma[194] or may be noted after stapedectomy.[195] Spontaneous fistulas are rare except in cases of Mondini malformation and other congenital abnormalities.[196] CT may reveal pneumolabyrinth[194] (Fig. 165-9). In definitive cases of leakage, patching with a tissue graft can achieve the goal of hearing preservation and relief of vertigo, although even definitive cases can resolve with conservative management and without surgery.[194] However, many cases of vertigo or hearing loss alleged to be caused by perilymph fistula are much more ambiguous, with equivocal surgical findings.[197-199]

A fistula can be through fissula ante fenestram, or a fissure from the round window niche with the ampulla of the posterior canal may be seen. Fissures in these areas tend to be common, and their clinical significance is not clear.[200] It is difficult to ascertain whether small amounts of fluid seen during surgical exploration are truly perilymph. An assay for beta-2 transferrin (a protein unique to cerebrospinal fluid) has been suggested, but it has a low sensitivity for detection of small amounts of fluid.[201]

The absence of observed leakage during surgery has been interpreted to mean either that no fistula exists, that the fistula may be intermittent, or that the fistula may be present but too small to be detected. In cases of negative findings on exploration, it is unclear if patching of the oval and round windows is of any value. Criteria for determining when a middle ear exploration for perilymph fistula may be beneficial have been difficult to establish, because no definitive test is available to make the diagnosis and interobserver concordance is low.[202] Applying pressure in the external auditory canal to see if eye movements are evoked (Hennebert sign) has been used. Measuring postural sway during pressure to the external auditory canal also has been proposed as a diagnostic test for fistula.[202] Even if a fistula exists, spontaneous resolution may occur. Recently, many patients who initially were diagnosed with fistulas have been found to have superior canal dehiscence.[191]

Chronic ear disease can cause a bona fide fistula. Long-standing otitis media can lead to cholesteatoma formation, with consequent erosion of the dense bone around the labyrinth. Patients in whom fistulas develop usually have a multiyear history of chronic ear disease, sometimes requiring several operations. In a recent review of 375 surgical procedures done for chronic otitis media, labyrinthine fistulas were

identified in 29 cases, 25 of which involved canal-wall-down mastoidectomies.[203] The overall incidence of fistulas after canal-wall-down mastoidectomies was 13%. All of these patients experienced vertigo symptoms. However, of the 19 tested, only 14 exhibited a Hennebert sign with positive pressure. The horizontal semicircular canal was the most common site of fistula formation (76%), followed by oval window and promontory. In these cases, surgical closure of the fistula is recommended.

Trauma

Vertigo and ataxia are common sequelae of head trauma. Vestibular-related complaints can arise from cervical trauma and CNS trauma, as well as peripheral vestibular damage. Only symptoms resulting from peripheral vestibular damage are considered here. Mechanisms by which damage can be inflicted include blunt concussive trauma, penetrating trauma, explosive blast, and barotrauma. Similar lesions can result with different mechanisms of injury. Hence, labyrinthine concussion can follow blunt trauma as well as barotraumas.

Nonpenetrating Trauma

Labyrinthine Concussion

Injuries of the labyrinth that do not result in violation of the otic capsule or the intralabyrinthine limiting membranes are classified as *labyrinthine concussion*.

Vestibular-related symptoms, although variable and not well characterized, generally are thought to include mild vertigo, imbalance, visual confusion, and vegetative symptoms (e.g., nausea and vomiting). These symptoms typically are short-lived and gradually subside over a period of days to weeks. Examination of the patient with active symptoms may demonstrate nystagmus directed toward the side of the lesion acutely (i.e., over hours), followed by more typical contralateral beating nystagmus. Past pointing and falling in the direction of the slow phase of nystagmus have been reported. Vestibular testing may demonstrate a reduction in the caloric response and abnormality of vestibulo-ocular reflex gain and phase after rotational testing.[204]

Benign positional vertigo also is a common sequel of blunt head trauma.[204] Diagnosis and management of this entity are discussed earlier in this chapter.

Hearing loss and tinnitus often are reported. When present, the most common pattern of hearing loss is similar to that of a noise-induced hearing loss, with a loss most apparent at 4 kHz.[205]

Both the vestibular and the auditory complaints usually are transient, with spontaneous resolution occurring over a matter of days to weeks.[204] However, symptoms also have been reported to persist and worsen over time.

Blast Trauma

Explosive blasts can produce pressure waves greater than 200 dB sound pressure level (SPL).[206] The ear, which exists to capture and amplify this energy, frequently is injured when exposed to such a noise. Blast trauma would include that incurred by such mechanisms as an open-handed slap to the ear, as well as actual explosions. Perforation of the tympanic membrane, ossicular disruption, or both may occur; however, inner ear damage is more likely when the conductive mechanism remains intact. Auditory loss is common and often recovers spontaneously but can be permanent.[207] Dizziness is present in 15% of patients.[208]

Penetrating Trauma

Acute vertigo and sensorineural hearing loss heralds inner ear damage. Nystagmus beats in the direction of the healthy ear owing to the acute loss on the affected side. Vegetative symptoms typically are present. Vertigo will gradually subside over the ensuing days to weeks. Hearing loss, when present, can range in severity from mild and transient to profound and permanent.

Barotrauma

Damage to the inner ear resulting from pressure changes is known as barotrauma. Historically thought to be a fairly rare problem, barotrauma is now believed to be a fairly frequent injury among divers. Inner ear dysfunction can be produced by rapidly changing air pressure, as in atmospheric barotrauma, by elevated or asymmetric middle ear pressure, as in alternobaric trauma, or by bubble formation within the labyrinth or its blood supply in the case of inner ear decompression sickness and isobaric gas counter diffusion sickness.

Alternobaric vertigo is most prominent in divers during ascent to the surface and in fliers during ascent of the aircraft. Both scenarios involve decreasing ambient pressure. Vertigo is relieved by equilibration of middle ear–ambient pressure differences, as well as by repressurization (i.e., by descending several meters in the case of divers). As many as 26% of divers and 10% to 17% of pilots have admitted to experiencing alternobaric-like vertigo.[209]

Susceptibility to alternobaric vertigo is thought to be a consequence of individual variations in the pressure required within the middle ear to force open the eustachian tube. Conditions that alter eustachian tube patency (e.g., mucosal turgescence) such as upper respiratory infection are known to contribute. The effects of alternobaric trauma on the inner ear are temporary. In most cases, vertigo, hearing loss, and tinnitus are described as resolving in 10 to 15 minutes. The occurrence of alternobaric trauma can be minimized by frequent equilibration of middle ear pressure during diving, the use of topical nasal decongestants before the dive, and the avoidance of diving during periods of increased upper respiratory obstruction (e.g., upper respiratory infection, sinusitis).[210]

Atmospheric barotrauma is caused by extremes of pressure or abrupt changes in middle ear pressure, which are capable of damaging middle ear and inner ear structures. Damage to the latter is reflected by auditory and vestibular dysfunction. As opposed to alternobaric trauma, barotraumatic injury frequently is long-lasting or permanent. Hearing loss and tinnitus are universal complaints, whereas vertigo tends to be less common (35%) and rarely is the primary complaint.[211] When present, vertigo resolves within a few weeks even without treatment. The hearing loss ranges in severity from a mild, high-frequency sensorineural type to complete deafness. Suggested treatment of inner ear barotrauma is similar to that recommended for perilymph fistula. Bed rest, head elevation, and close monitoring of hearing and balance-related symptoms are suggested. Symptoms usually resolve spontaneously in a matter of hours to days with conservative management.[212]

Inner ear decompression sickness (IEDS) has become more common as a consequence of the increased use of mixed gas, oxyhelium, for deep water diving. Although damage produced by these disorders is not restricted to the inner ear, it now represents the most common decompression injury experienced by persons diving to depths greater than 100 m.[213] In a recent series it was found to account for 33% of diving-related ear injuries.[214] In IEDS, vertigo is almost always the primary symptom, and hearing loss when present usually is unilateral and often manifests later, after the vertigo begins to resolve.[211] Otologic symptoms often are the sole feature of decompression sickness, particularly in cases in which oxyhelium is used. When the inner ear is affected, vestibular and auditory dysfunction often is permanent, particularly if treatment is delayed. One study claims that significant improvement is achieved only when hyperbaric oxygen therapy is started within 68 minutes.[215] In some reports, however, improvement has been obtained when hyperbaric oxygen was started 24 hours after the injury.[211]

Familial Vestibulopathy

The rare syndrome of familial vestibulopathy with autosomal dominant inheritance is characterized by sudden attacks of vertigo followed by chronic dysequilibrium. The vertigo typically lasts on the order of minutes, with several hours of subsequent dysequilibrium. These spells recur at variable intervals for many years. Some patients have reported that spells seemed to be triggered by stress. Patients also have described the gradual onset of chronic dysequilibrium and oscillopsia due to vestibular insufficiency.[216] Auditory symptoms including tinnitus are absent. It is notable that all affected persons also experience migraine headaches, although headache was not associated with the spells of vertigo. An autosomal dominant mode of inheritance was defined.

Findings on quantitative testing in these patients include imaging results that are normal except for bilateral vestibular responses on caloric testing and low gains with shortened time constants on rotary testing—all of which are consistent with damage to the peripheral vestibular system.

In all cases, spells of vertigo were successfully terminated with the administration of acetazolamide. The mechanism of action in this case is unknown; however, in a seemingly related condition, familial periodic vertigo and ataxia, the acetazolamide effect is presumed to be that of a reduction in acidity of the brain.

More recently, another familial syndrome associated with migraine headaches, essential tremor, and vertigo was identified.[217] In this syndrome, vertigo lasts minutes to hours. As in the familial vestibulopathy already described, headaches were unassociated with the spells of vertigo. Spells were triggered by stress, exercise, and lack of sleep. The long-term progressive vestibular deficit noted in the familial vestibulopathy syndrome was not noted in this latter disease. As in the former disease, acetazolamide was proved to be effective at curtailing spells of vertigo as well as the migraines. Although clustering of migraine and episodic vertigo occurs in many families, the search for a single gene remains elusive. It is likely that multiple genes and possible environmental factors are responsible.[218]

Migraine itself may contribute to permanent damage of the vestibular end organs. (Migraine-associated vertigo is discussed in Chapter 166). However, the disorder also may have a peripheral component in some patients. Caloric paresis in patients with migraine occurs at a rate of 15% to 35%.[218,219] Vasospasm and small artery infarction have been suggested as potential mechanisms.[220]

Bilateral Vestibular Hypofunction

Bilateral loss of vestibular function leads to oscillopsia with head movements, as well as to disturbances of gait of variable severity. Hypofunction most commonly is induced by the vestibulotoxic effects of aminoglycoside medications. In 1952, a physician published a classic description of the symptoms of vestibular hypofunction that developed 2.5 months into a course of intramuscular streptomycin injections to treat sepsis of his right knee.[221] He also described oscillopsia and dysequilibrium of sudden onset and worsening over 2 to 3 days. By then he had to stabilize his head on bars in order to read, because even his pulse induced enough head motion to produce oscillopsia. His balance improved as he learned how to use visual and somatosensory information to make up for his loss of vestibular function.

It is estimated that vestibular injury develops in up to 3% of patients who receive gentamicin.[222] The vestibulotoxicity usually is not detected until the patient leaves the hospital and does not correlate with peak or trough levels or with dosage levels.[223,224] A genetic predisposition to increased sensitivity for aminoglycoside toxicity has been identified as linked to mutation of a mitochondrial ribosomal protein.[225] Thus, aminoglycosides are not recommended when an alternative is practical. If gentamicin is used, bedside tests of vestibular function including assessment of dynamic visual acuity and the head thrust test should be performed daily, when feasible, so that the medication may be stopped at the first signs of vestibulotoxicty.[226]

Other causes of bilateral vestibular loss include degenerative diseases of the cerebellum, meningitis, systemic autoimmune diseases, trauma, and bilateral Meniere's disease. No underlying cause is identified in approximately 20% of cases.[227]

Enlarged Vestibular Aqueduct

The vestibular aqueduct is an aperture in the posterior ridge of the petrous bone that contains the endolymphatic duct and sac. Enlargement of this structure probably occurs as a result of dilation of the endolymphatic duct during embryogenesis.[228] Patients usually present with hearing loss that begins in early childhood and often progresses with minor head trauma. The onset of vestibular symptoms in these patients often is delayed until adulthood, with episodes of vertigo that last between 15 minutes and 3 hours.[229] Childhood vestibular symptoms also have been described.[230] On testing, patients have been found to have impaired vestibulo-ocular reflex function and decreased VEMP thresholds.[231] Diagnosis is based on the CT finding of a vestibular aqueduct width greater than 1.5 mm at the midpoint; in most patients, this is similar to the width of the horizontal semicircular canal (Fig. 165-10). Experience in treatment of vertigo associated with enlarged vestibular aqueduct has been limited, but symptomatic and supportive treatment is suggested.

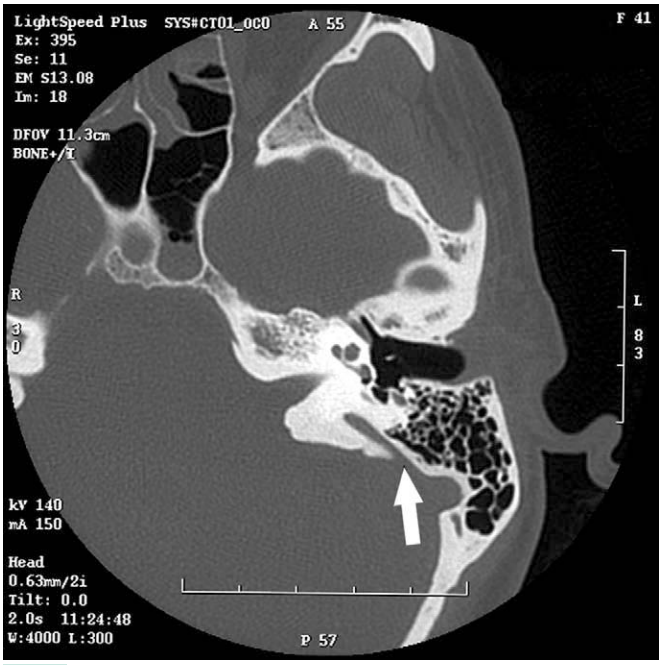

Figure 165-10. CT scan of the left temporal bone of a patient with enlarged vestibular aqueduct syndrome. *White arrow* points to the vestibular aqueduct. *(Courtesy of Dr. Howard Francis.)*

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CHAPTER ONE HUNDRED AND SIXTY-SIX

Central Vestibular Disorders

Benjamin T. Crane

Scott D. Z. Eggers

David S. Zee

Robert W. Baloh

Key Points

- Determining a central versus a peripheral origin for vertigo requires a careful assessment of symptoms and presenting circumstances, as well as physical findings.
- Appreciation of migraine as a common etiologic disorder in patients presenting with dizziness and other vestibular symptoms is essential to optimal clinical management of this highly prevalent disorder.
- The diagnosis of migraine-associated vertigo relies critically on the history and can be substantiated by monitoring the response over time to diet manipulation and medical management.
- Effective, definitive treatment of migraine-associated vertigo requires the patient's understanding of the importance of lifestyle modification to promote compliance.
- Migraine-associated vertigo is best treated with beta-blockers, tricyclic antidepressants, serotonin reuptake inhibitors, or anticonvulsants.
- Meniere's disease and benign paroxysmal positional vertigo (BPPV) are commonly associated with migraine.
- Vascular disorders are a common cause of vertigo in the elderly population.
- Several types of strokes can manifest with vertigo but almost always are associated with multiple neurologic deficits.
- Neoplasms can manifest with vertigo; vestibular schwannoma is the most likely tumor to present with this symptom, although tumors in the brain stem and cerebellum also can cause vertigo. Screening for neoplasm should be considered in patients with progression of symptoms, particularly when another cranial nerve or central nervous system disorder is present.
- Disorders of the craniovertebral junction can cause vertigo symptoms and should be considered when cervical motion is impaired or radiculopathy is suspected.
- The otolaryngologist should be aware that multiple sclerosis, normal pressure hydrocephalus, focal seizure disorders, and cerebellar ataxia syndromes can produce vertigo.

Dizziness can be classified into *vertigo* (a sense of motion, either of the person or of the visual surround), *dysequilibrium without vertigo*, *presyncope* (near-faint, lightheadedness), and *psychophysiologic dizziness* (often associated with extreme motion sensitivity, anxiety and panic, and phobic behavior). Dizziness, often with motion sickness, can occur in normal persons when they are exposed to unnatural patterns of motion—for example, during sea and car travel. Overlaid on all types of dizziness can be the psychological consequences of extremely distressing symptoms, and vice versa: Dizziness can be a symptom of a psychiatric disorder such as panic and anxiety syndromes and depression. Many conditions of central nervous system origin can cause each of these types of dizziness.

The first task of an otolaryngologist in examining a patient with dizziness is to determine if the symptom is of central or peripheral origin[1] (Table 166-1). Some central causes of acute vertigo can be life-threatening and may necessitate immediate intervention.[2] The differentiation can almost always be made by physical examination based on the type of nystagmus, result of head thrust test, severity of imbalance, and presence or absence of other neurologic signs.

Spontaneous nystagmus of peripheral origin typically is horizontal, or horizontal with a torsional component, and does not change direction with direction of gaze. Spontaneous nystagmus of central origin also can be purely horizontal but often is purely vertical or torsional and usually changes direction with changes in gaze.[1]

The *head thrust test* is performed as follows: The examiner grasps the patient's head and applies a brief, high-acceleration head rotation, first in one direction and then the other.[3] During these maneuvers, the patient fixates on the examiner's nose and the examiner watches for corrective rapid eye movements (saccades), which are a sign of decreased vestibular response (i.e., the eyes move with the head, rather than remaining fixed in space). If a "catch-up" saccade occurs after head thrusts in one direction but not in the other, a peripheral (including the labyrinth and the eighth cranial nerve on its course from the brainstem) lesion on that side is likely.

Patients with an acute peripheral vestibular lesion typically can stand but may demonstrate sway toward the side of a lesion. By contrast, patients with vertigo of central origin often are able to stand

Table 166-1

Differentiation of Central and Peripheral Vertigo

Feature	Central Origin	Peripheral Origin
Imbalance	Severe	Mild to moderate
Neurologic symptoms	Frequent	Rare
Nystagmus	Changes direction No change with fixation	Unidirectional Decreases with fixation
Hearing loss	Rare	Frequent
Nausea	Variable	Severe
Recovery	Slow	Rapid

Box 166-1

Diagnostic Criteria for Migraine

Migraine without Aura

A. At least five attacks fulfilling criteria B to D
B. Headache lasting 4 to 72 hours when untreated
C. Headache with at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe intensity, aggravation by physical activity
D. During the headach, either nausea and vomiting or photophobia
E. Not attributable to another disorder

Typical Aura with Migraine Headache

A. At least two attacks fulfilling criteria B to D
B. Fully reversible visual, sensory, or aphasic aura symptoms with no motor weakness
C. At least two of the following: homonymous positive features or unilateral sensory symptoms; for at least one symptom, gradual development over more than 5 minutes; duration of 5 to 60 minutes for each symptom
D. Headache following aura after a symptom-free interval of less than 60 minutes
E. Not attributable to another disorder

without support. Associated neurologic signs such as dysarthria, incoordination, numbness, or weakness suggest a central origin.

Dizziness and vertigo can be caused by diverse pathologic conditions of the central nervous system (CNS). Differentiation of these disorders from those of peripheral labyrinthine origin requires familiarity with the associated signs and symptoms of CNS processes, their natural history, and their appearance. Definitive diagnostic evaluation and management usually involve cooperation with neurologists or neurosurgeons. A classification of CNS disorders associated with vestibular symptoms includes intracranial complications of suppurative otitis, vascular disorders, neoplasms, disorders of the craniovertebral junction, multiple sclerosis, familial ataxia syndromes, and focal seizure disorders.

Intracranial Complications of Otitic Infections

Epidural or subdural abscesses, as well as those of the temporal bone, petrous apex, or cerebellum, can cause vestibular signs and symptoms. Such processes usually are associated with other signs of infection, such as fever or sepsis, and are rare in the modern era of antibiotics.

Migraine

Migraine is characterized by recurrent headaches associated with nausea, vomiting, hypersensitivity to light, sound, and smell.[4] This clinical entity is an important consideration in the diagnosis because patients with migraine often present with dizziness. Neurologic aura symptoms are present in one third of migraine patients. Migraine affects nearly 25% of women, 15% of men,[5,6] and 5% of children.[7] In the prepubertal period, boys with migraine slightly outnumber girls, but at puberty, migraine decreases in boys and increases in girls, so that a 2:1 female preponderance is established by adulthood.[8] Migraine typically begins in young adulthood, with onset of symptoms after the age of 40 in only 10% of sufferers.

The diagnosis and classification of migraine and other headache disorders have been a controversial issue. The most recent effort of the Headache Classification Committee of the International Headache Society (IHS)[4] sets up criteria that allow meaningful comparisons of groups of patients between centers. The IHS classifies the most common type of migraine as migraine with and migraine without aura (Box 166-1); other classified types of migraine headache have been designated but are not considered in this chapter because they will only rarely be encountered by the otolaryngologist.

The definition of migrainous vertigo also has been controversial. Neuhauser and colleagues[9] proposed criteria for *definite migrainous vertigo* as follows: (1) episodic vestibular symptoms (rotational vertigo, other illusory self or object motion, positional vertigo, head motion intolerance) of at least moderate severity; (2) migraine according to IHS criteria; (3) at least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache, photophobia, phonophobia, visual or other auras; and (4) other causes ruled out by appropriate investigations. *Probable migrainous vertigo* was the designation chosen for patients who did not meet definite criteria but were still believed to have migrainous vertigo as the most likely diagnosis. This definition requires criteria 1 and 4 from the foregoing list, plus at least one of the following: migraine according to IHS criteria; migrainous symptoms during vertigo; migraine-specific precipitants of vertigo (e.g., specific foods, sleep irregularities, hormonal changes); and response to antimigraine drugs. A diagnostic algorithm[10] for definite and probable migrainous vertigo (Fig. 166-1) has been proposed.

To elicit a history adequate to make the diagnosis, an understanding of the various components of the aura is essential. In descending order of frequency, these features are (1) scotoma or blind spots; (2) teichopsia, or fortification spectra (a zig-zag pattern in the visual field resembling a fort); (3) flashing or colored lights; and (4) paresthesias.

Vestibular Symptoms

Nonspecific Dizziness

Nonspecific dizziness occurs frequently in patients with either tension or migraine headaches and does not in itself differentiate between the two groups, although dizziness is more common and more severe in migraine sufferers.

Vertigo

Vertigo is extremely common in patients with migraine and occurred in 26.5% of Kayan and Hood's group of patients with migraine, compared with 7.8% of those with tension headache ($P < .001$).[11] Some studies have found the incidence of vertigo in classic migraine sufferers to be as high as 42%.[12] The severity of vertigo in patients with migraine tends to be greater than in those suffering from tension headaches. Vertigo severe enough for the patient to seek medical attention for relief occurred in 5% of those with migraine but in less than 1% of those with tension headache.[11]

The temporal relationship of vertiginous spells to migraine headaches is important to ascertain. Vertigo does not usually manifest as an aura immediately preceding the headache as a prodrome. Of the 53 patients with vertigo and migraine interviewed by Kayan and Hood,[11]

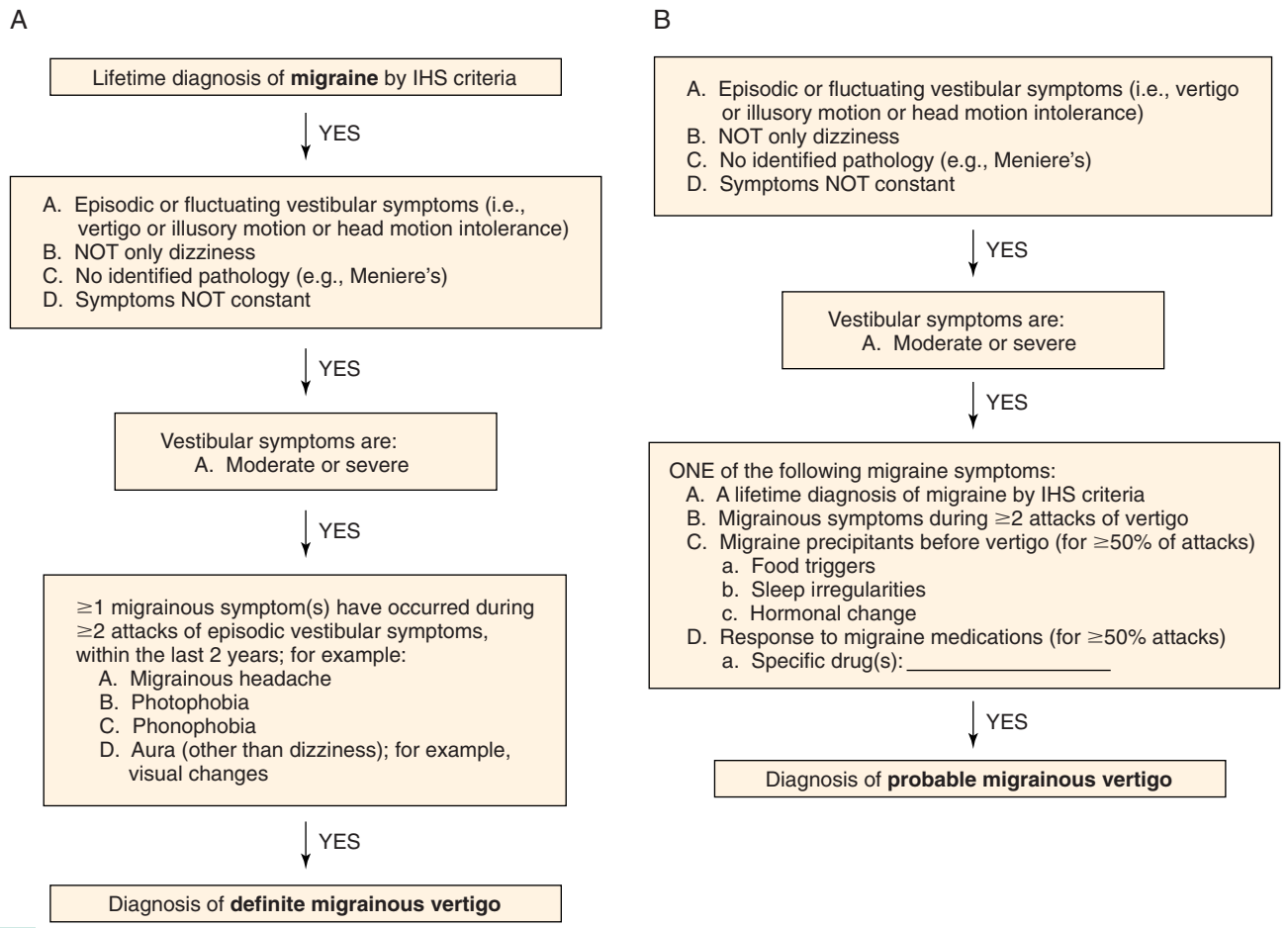

Figure 166-1. Diagnosis of definite (**A**) and probable (**B**) migrainous vertigo. "Moderate" vestibular symptoms interfere with daily activities, and "severe" vestibular symptoms prohibit daily activities. "Head motion intolerance" is the sensation of imbalance or illusory self or object motion provoked by head motion. IHS, International Headache Society. *(From Furman JM, Marcus DA, Balaban CD. Migrainous vertigo: development of a pathogenetic model and structured diagnostic interview.* Curr Opin Neurol. *2003;16:5-13. Adapted from Neuhauser H, Leopold M, von Brevern M, et al. The interrelations of migraine vertigo and migrainous vertigo.* Neurology. *2001;56:436-441.)*

the vertigo immediately preceded the headache in only 15%, whereas it occurred during the headache in 47% and during the headache-free interval in 36% of patients. In a series of 50 patients with basilar migraine, Olsson[13] and Cuttler and Baloh[14] also found vertigo to occur more often during the headache-free interval than as a prodrome before the headache.

Motion Sickness

The relationship between migraine and motion sickness is well established. In his seminal study of 9000 Swedish schoolchildren, Bille[15] matched children with more pronounced migraine to children in a similar group without migraine. Severe motion sickness was present in 49% of the children with migraine and in only 10% of the control group. Barabas and colleagues found that 45% of 60 children with migraine experienced at least three episodes of motion sickness culminating in vomiting, compared with 5% to 7% of three similar-sized control groups of subjects with non-migraine headaches, seizure disorders, and learning disabilities or neurologic perceptual impairments.[16] In adults, a similarly significantly greater incidence of motion sickness has been observed in patients with classic migraine than in patients with tension and cluster headaches.[12] In the Kayan and Hood[11] series of 200 unselected patients with migraine, 51% reported motion sickness, compared with 20% of the patients with tension headache.

A subset of migraine sufferers experience disabling motion sickness. These patients limit their head motion to a minimum, limit their daily activities accordingly, frequently rest during the day, and when symptomatic may need to remain motionless for up to an hour until symptoms abate. If they cannot avoid vestibular stimulation, a full-blown migraine attack can be triggered. Caloric responses in these patients tend to be symmetrical and very brisk, often culminating in emesis. If treatment provides a dramatic response, the patients often are surprised to recognize how much they had restricted their lifestyle. Often, neither the patient nor the physician suspects that the migraine had any relationship to the other symptoms. Patients often discuss only the vestibular symptoms and ignore or discount any effects of the underlying problem. Prophylactic migraine therapy often yields dramatic clinical improvement with a decrease in symptoms.

Auditory Symptoms

Of the patients studied by Kayan and Hood,[11] 20% complained of hearing loss, tinnitus, or pitch distortion, and one fourth of the 20% had multiple auditory symptoms. In descending order of frequency, the temporal patterns for occurrence of these symptoms were during the headache, during the headache-free interval, and immediately before the headache. The temporal relationship of these symptoms mirror the relationship of vertigo to headache in this same series.

Hearing Loss

The association of hearing loss to migraine is reported to be approximately 7%.[11] Hearing loss is a more prominent symptom in patients with basilar migraine. In Olsson's study,[13] 52% of the patients noticed a change in hearing as part of the aura immediately preceding the migraine headache and 50% had a fluctuating low-frequency sen-

sorineural hearing loss. A group of migraine patients in whom hearing loss thought to be due to vasospasm has been reported.[17]

Tinnitus

Tinnitus was experienced by 15% of migraine patients, but none with tension headache,[11] and in more than 60% of basilar migraine patients.[13]

Distortion

Although distortion was noted by only 4% of patients in the Kayan and Hood series,[11] its actual prevalence may be higher. More attention may be given to more bothersome symptoms, and auditory distortion may be ignored by physicians and patients alike as unimportant.

Phonophobia

Loud noise aversion distinguishes patients with migraine from those suffering other types of headaches. Only 12% of tension headache sufferers experienced phonophobia, but 81% of those with migraine had the symptom.[11] Olsson[13] detected phonophobia in patients with basilar migraine at a rate of 70% during headache and 76% during headache-free intervals. Furthermore, he documented an abnormal loudness discomfort level in 78% of these patients, whereas only 14% had abnormal speech reception thresholds.

Migraine Associated with Neuro-otologic Symptoms

Basilar Migraine

Bickerstaff[18] described a form of migraine ascribed to ischemia in the distribution of the basilar artery. This syndrome currently is known as *basilar migraine*, replacing "basilar artery migraine" and "posterior fossa migraine," which occasionally appear in the older literature. This subtype of migraine was similar to classic migraine in that it consisted of an aura followed by a severe headache. However, a majority of affected patients were adolescent girls, in whom the migraine attacks often occurred premenstrually. Later observers emphasized other aspects of the clinical picture such as stupor,[19] loss of consciousness,[20] neurologic symptoms,[21] hearing loss, and vertigo.[22] These symptoms are thought to be due to involvement of the brainstem, cerebellum, cranial nerve nuclei, and occipital lobe cortex.

Migraine without Headache

Migraine should not be eliminated as a cause for vertigo just because headaches are not present. Whitty[23] reported on a series of patients with symptoms typically experienced during a migraine aura but no headaches. In these patients, typical headaches sometimes developed later in life, or auras that were only intermittently related to headaches were noted. Other observers have described similar patients using the term *migraine equivalent*[24-26] or *migraine accompaniments.*[27] A history of motion sickness, premenstrual clustering of attacks, or headaches associated with some of the attacks is frequent. Personal or family history of migraine also is helpful in diagnosing these patients.

Etiology

Historically migraine headache was thought to result from dilation of intracranial and dural arteries causing stretching of pain fibers in the walls of the arteries. The complex phenomena associated with migraine cannot be fully explained by a vascular theory. More recently, neurally based spreading of depression activity has been implicated,[28,29] although the neurophysiology is far from completely understood.

A family history of migraine is present in approximately 40% to 90% of affected persons, compared with 5% to 20% of unaffected subjects. When migraine sufferers with and without aura are examined separately, patients who have migraine with aura are more likely to have affected family members. When twins are studied, conconcordance rates for migraine are only 10% to 34%, depending on the country, suggesting that both genetic and environmental factors play a role.[30]

Familial hemiplegic migraine (FHM) is a rare type of migraine that affects only 0.01% of the general population.[31] However, the underlying cellular cause is relatively well understood. Unlike most types of migraine, FHM has a clear autosomal dominant pattern of inheritance. Thus far, mutations have been found in three different genes that determine neuronal excitability.

Management

Treatment of migraine has historically been focused on headache symptoms. Management of migraine headache can be divided into two categories: symptomatic and prophylactic. Some interventions are useful in ameliorating the symptoms of the acute attack, whereas others are designed to reduce the frequency or severity of attacks. Symptomatic management includes analgesics, antiemetics, antivertiginous drugs, sedatives, and vasoconstrictors. In many patients, over-the-counter analgesics such as ibuprofen, aspirin, or acetaminophen and rest are all that is needed to relieve headache symptoms. Decreased gastric motility occurs during and between migraine attacks, which may decrease absorption of oral drugs, contributing to nausea and vomiting.[32] Metocopramide promotes normal gastric motility and may improve absorption of oral medication.

Nutrition may play a significant role in the frequency and severity of migraine headaches and migraine-associated dizziness. Riboflavin (vitamin B_2) has been shown to be more effective than placebo in reducing the frequency of migraine headache when given in a dose of 400 mg daily.[33] High-dose magnesium also has been found to have a therapeutic effect on migraine; suggested mechanisms have included inhibiting platelet aggregation, counteracting vasospasm, stabilizing cell membranes, and anti-inflammatory effects.[34] Patients suffering from migraine symptoms have been found to have lower levels of magnesium, and infusion of magnesium can relieve symptoms.[35] Magnesium given orally in a dose of 600 mg daily also has been shown to decrease headache symptoms[36]; however, diarrhea is a potential side effect at these doses.

Food sensitivity may be a migraine trigger in a significant number of patients with migraine symptoms.[34] Although some patients have observed that consuming a certain food will reliably provoke a headache, the effect of diet is more subtle. Foods that should be avoided include red wine, aged cheeses, beer, chocolate, caffeine, and yogurt.[37] Alcohol itself does not seem to be a trigger, because vodka consumption does not provoke attacks.[38] Dietary modification may be considered as first-line therapy for migraine prophylaxis (Fig. 166-2).

Vestibular migraine symptoms often are not directly related to the headache symptoms, and in some cases, dizziness as a manifestation of migraine can be present nearly continuously. Treatment of vestibular migraine has tended to mirror that of traditional migraine symptoms, and medications that alleviate headache symptoms also tend to be effective for vertigo symptoms.[39] However, because the migraine-associated dizziness often is much more frequent than the headaches, prophylaxis usually is necessary.

Sumatriptan (Imitrex), a 5HT1D receptor agonist, has become the principal drug to abort severe migraine headache. Initial trials indicate that in 90% of cases the drug effectively aborts migraine headache symptoms within an hour of their onset when it is given subcutaneously; in 70% to 85%, symptoms may be aborted within 2 hours.[40] Common side effects include sensations of heaviness and pressure in the chest, with coronary artery vasospasm more rarely reported. Although sumatriptan is remarkably effective in relief of early migraine headaches, breakthrough is common, and the drug has limited efficacy for concurrent vestibular symptoms.

Propranolol (Inderal) is the drug most commonly used for preventing migraine episodes. Approximately 50% to 70% of patients with headache symptoms derive benefit from prophylactic propranolol therapy, which also may be beneficial for vertigo symptoms.[21] The medication is contraindicated in patients with asthma, congestive heart failure, peripheral vascular disease, diabetes, or hypothyroidism. Principal side effects include fatigue, lethargy, and dizziness, which usually occurs on rising from a seated or supine position. Side effects are minimized by slowly increasing the dose from a low starting level. Doses of 80 to 180 mg per day usually are effective. The medication should be continued for at least 2 to 3 months at the highest level of tolerance before it is considered a failure. On discontinuation, the drug should be gradually tapered over several days.

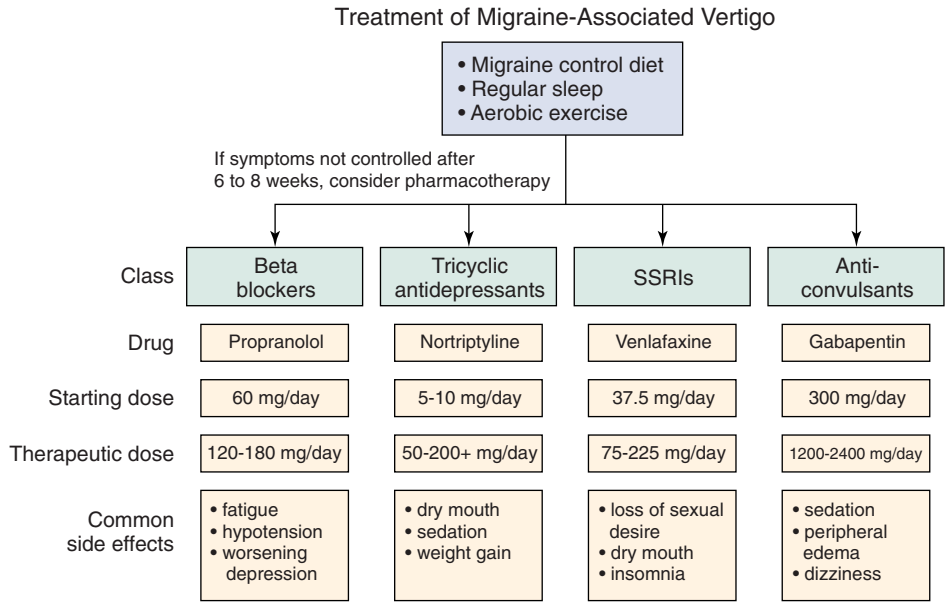

Figure 166-2. Flowchart of suggested migraine treatment. Lifestyle modification usually is a good first option because it is not associated with side effects and will provide symptomatic improvement in most patients. Pharmacotherapy should be considered if more conservative measures fail.

A variety of beta-adrenergic agents also have been used for migraine prophylaxis. Atenolol (Tenormin), metoprolol (Lopressor), nadolol (Corgard), and timolol (Blocadren) probably are as effective as propranolol. However, a number of other beta-adrenergic antagonists (e.g., acebutolol, oxprenolol, alprenolol) do not appear to be effective in migraine prophylaxis. It has been suggested that pure beta-adrenergic antagonism without intrinsic sympathomimetic activity is required for efficacy.

Calcium channel blockers (nifedipine, verapamil) also have been reported to reduce the frequency of migraine attacks, but the effect is likely to be only modest.[41] Diltiazem (Cardizem) does not seem to have any effect on migraine prevention.

Tricyclic antidepressants also have been shown to decrease the frequency and severity of migraine attacks. Amitriptyline is perhaps the most-studied drug in this category, with several studies showing its efficacy.[42] Starting doses usually are 10 to 25 mg, which usually is given at bedtime, to avoid the side effects of sedation and anticholinergic activity. Weight gain is a side effect that limits patient compliance with therapy in some populations. Therapeutic doses usually are 50 to 100 mg, with some patients who also suffer from depressive symptoms requiring doses of up to 400 mg. Nortriptyline is less sedating than amitriptyline and has a dosage profile similar to that of amitriptyline.

The role for selective serotonin reuptake inhibitors (SSRIs) for treatment of migraine remains controversial. Some evidence shows that they seem to be less effective than tricyclic antidepressants[43] for headache symptoms. However, in patients with chronic subjective dizziness as their primary symptom, SSRIs seem to be effective.[44]

Clinical trials have shown gabapentin (Neurontin) to be effective at dosages of 1200 to 2400 mg per day,[45] which usually is divided into three doses daily. Dizziness, peripheral edema, and somnolence are common side effects.

Valproic acid derivatives such as divalproex (Depakote) are effective in migraine prevention. However, the need to monitor levels and the side effect profile of these medications, which includes nausea, fatigue, weight gain, teratogenicity, hepatic toxicity, and tremor, have made them infrequently used.

Acetazolamide (Diamox) has been shown to be effective in preventing migraine headaches and episodic vertigo in families who also exhibit essential tremor.[46] However, it has not been shown to be of benefit in larger migraine headache populations.[47] It may be effective in ameliorating motion-induced vestibular symptoms in patients with migraine.

Vestibular Disorders Associated with Migraine

Benign Paroxysmal Positional Vertigo

BPPV is the most common cause of peripheral vertigo. The disorder probably is due to free-floating particles in the semicircular canal (canalithiasis), which usually collect in the posterior semicircular canal owing its low point with respect to gravity. Classic symptoms include brief episodes (lasting less than 1 minute) of vertigo when the head is tilted backwards or during rolling over in bed. An extensive discussion of diagnosis and treatment of this common disorder is outside the scope of this chapter. Of note, however, migraine and motion sickness are three times more common in patients with BPPV than in the general population, with 59% of patients having a family history of migraine.[48]

Meniere's Disease

Meniere's disease classically manifests with unilateral low-frequency fluctuating hearing loss, a sense of aural fullness, and dizziness lasting several minutes to hours.[49] However, the presence and severity of these symptoms are variable, which can overlap with those of migraine.[50] Unselected patients with migraine have a 7% incidence of hearing loss and 26% incidence of vertigo.[11] In patients with Meniere's disease, the lifetime incidence of migraine is 56%, versus only 25% in controls.[51] The frequent co-occurrence of Meniere's disease and migraine suggests a pathophysiologic link between the two syndromes.[52] Alternatively, the diseases may be separate processes that cause similar symptoms. It is likely that both Meniere's disease and migraine are not homogeneous disorders but may be caused by a spectrum of genetic and environmental influences—so both explanations may be correct: Migraine may be one of many risk factors for Meniere's disease, and vice versa.

Vestibular Disorders Related to Migraine

Benign Paroxysmal Vertigo of Childhood

Basser[53] described a clinical entity in children younger than 4 years of age that he called *benign paroxysmal vertigo*. This should not be confused with the much more common benign paroxysmal positional

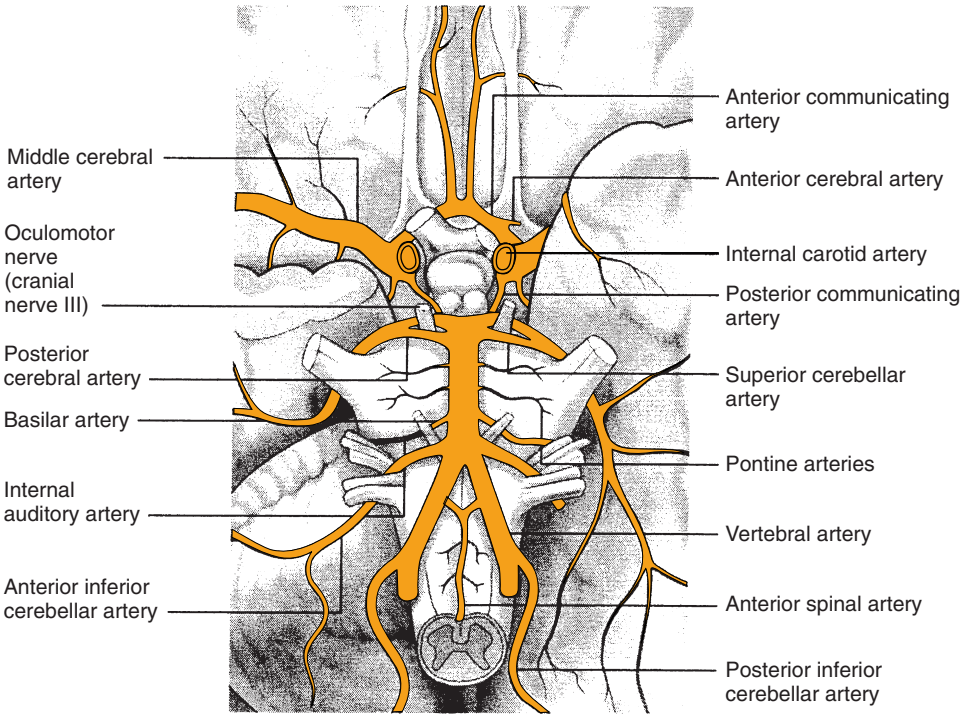

Figure 166-3. The blood vessels supplying the brain. The brainstem is supplied by branches of the vertebral arteries and basilar artery. Note that although this figure shows the internal auditory artery arising directly from the basilar artery, it more commonly branches off the anterior inferior cerebellar artery instead. *(Adapted from Kandel ER, Schwartz JH, Jessell TM.* Principles of Neural Science. *New York: McGraw-Hill; 2000:1303.)*

vertigo (BPPV), which also is referred to as benign positional vertigo. Children with this disorder usually become suddenly frightened, cry out, cling to the parent, stagger as though drunk, and exhibit pallor, diaphoresis, and frequent vomiting. Symptoms are worsened by head motion. The episodes last less than 5 minutes, after which the child is normal again. The symptoms usually manifest at the age of 2 to 3 years and gradually decrease until they resolve before age 8. When the clinical picture is clear, treatment is not needed. On long-term follow-up, classic migraine eventually developed in six of seven patients with this disorder.[54]

Paroxysmal Torticollis

Snyder[55] described a series of 12 infants who experienced recurrent attacks of head tilt before the age of 8 months. The spells lasted from a few hours to 3 days and occasionally were accompanied by pallor, vomiting, and agitation. Subsequent observers have suggested a familial occurrence[56] and that symptoms also may involve the trunk and extremities.[57] The spells usually stop spontaneously by age 5, and no treatment is needed.

Vascular Disorders

Abnormalities of blood flow to the vestibular system are relatively common causes of vestibular symptoms and often are difficult to distinguish from well-known end organ disorders. Clinical presentations vary for many reasons. Functional deficits may be restricted to one or both end organs or their structures or may involve the vestibular nuclei or other peripheral or central regions. Diverse abnormal processes can result in permanent or temporary loss of function. Permanent losses typically result from arterial occlusion or from hemorrhagic infarction. Transient effects may accompany arterial stenosis, vascular spasm, inadequate perfusion pressure, or reversed arterial flow with shunting such as in subclavian steal syndrome. Many symptom complexes are possible, but defined clinical entities are more common.

The blood supply to the inner ear, brainstem, and cerebellum arises from the vertebrobasilar system. Vertigo can occur from occlusion of any of the three major circumferential branches of the vertebral or basilar arteries: the posterior inferior cerebellar artery, the anterior inferior cerebellar artery, and the superior cerebellar artery (Fig. 166-3).

Specific Disorders

Vertebrobasilar Insufficiency

Vertebrobasilar insufficiency is a significant cause of vertigo in the elderly population.[58,59] Vertigo due to vertebrobasilar insufficiency is of abrupt onset, usually lasts several minutes, and frequently is associated with nausea and vomiting. Presentation with vertigo symptoms alone is extremely uncommon and occurs in less than 1% of patients.[60] Usually multiple symptoms are present, which often include headache, diplopia, ataxia, numbness, weakness, or oropharyngeal dysfunction. Repeated episodes of vertigo without other symptoms suggest another diagnosis.

Atherosclerosis of the subclavian, vertebral, or basilar arteries usually is the underlying cause of vertebrobasilar insufficiency. The distribution of large-artery atherosclerosis differs according to race and gender.[61] European men tend to have atherosclerosis at the origin of the vertebral arteries near the subclavian. Intercranial large-artery atherosclerosis is more common among African Americans, Asians, and women. Hypertension increases the risk of lipohyalinotic thickening of these vessels, which increases the risk of infarction.

Rarely, occlusion or stenosis of the subclavian or innominate artery just proximal to the origin of the vertebral artery results in *subclavian steal syndrome*. In patients with this syndrome, vertebral insufficiency results from siphoning of blood down the vertebral artery from the basilar system to supply the upper extremities. Vertigo and other symptoms are precipitated by exercise of the upper extremities.

If the patient is suspected to have had a stroke, a CT scan should be ordered to rule out the possibility of a hemorrhagic event. If a patient has presented within 3 hours after the onset of symptoms, the National Institute for Neurological Disorders and Stroke (NINDS) guidelines recommend administration of t-PA intravenously. However, recommendations in this area are rapidly evolving, and in the acute phase, patients should be treated by a neurologist familiar with stroke.

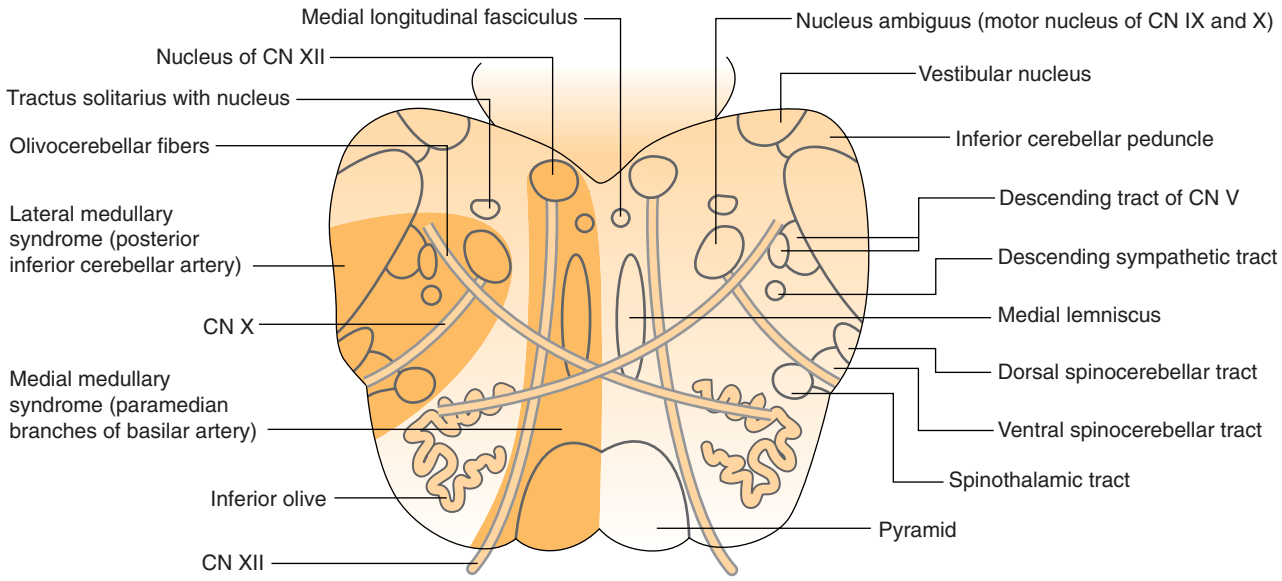

Figure 166-4. Medulla cross section with anatomic structures labeled on the *right* and vascular lesions on the *left*. CN, cranial nerve. *(Adapted from Kandel ER, Schwartz JH, Jessell TM.* Principles of Neural Science. *New York: McGraw-Hill; 2000:1303.)*

In most patients with nonacute presentations, treatment consists of controlling risk factors such as diabetes, hypertension, and hyperlipidemia. In patients with symptomatic intracranial stenosis with 50% to 99% occlusion, aspirin and warfarin are equally effective, but warfarin carries a higher risk of hemorrhagic events,[62] so aspirin is the agent of choice. Anticoagulation with warfarin should be considered if the patient has previously had an embolic stroke of cardiac origin.[58] Stenting of vertebral artery stenosis has been tried, with mixed results. Endarterectomy for extracranial vertebral artery disease also has been successfully performed, but indications for such procedures are still evolving.

Lateral Medullary Syndrome

The zone of infarction producing the lateral medullary syndrome (Wallenberg's syndrome) consists of a wedge of the dorsolateral medulla just posterior to the olive (Fig. 166-4). The syndrome usually results from occlusion of the ipsilateral vertebral artery and rarely from occlusion of the posterior inferior cerebellar artery.[63] The classic presentation includes sensory deficits affecting the trunk and extremities on the opposite side of the infarct and sensory and motor deficits affecting the face and cranial nerves ipsilateral to the infarct. Characteristic symptoms include vertigo, ipsilateral facial pain, diplopia, dysphagia, and dysphonia. Neurologic examination may reveal a ipsilateral Horner's syndrome, ipsilateral dysmetria, dysrhythmia, spontaneous nystagmus, and contralateral loss of pain and temperature sensation.

Hearing loss does not occur because the lesion is caudal to the cochlear nerve entry zone and cochlear nuclei.

Some patients exhibit a prominent motor disturbance that causes the body and extremities to deviate toward the lesion site as if being pulled by an invisible force.[64] This so-called lateral pulsion also affects the oculomotor system, producing excessively large saccades directed toward the side of the lesion and abnormally small saccades away from the lesion. Most patients with Wallenberg's syndrome have major residual neurologic deficits months or even years after the acute infarction.

Lateral Pontomedullary Syndrome

Ischemia in the distribution of the anterior inferior cerebellar artery results in infarction of the dorsolateral pontomedullary region and the inferolateral cerebellum.[65] The middle cerebellar peduncle typically is the core of the affected territory (Fig. 166-5). Because the labyrinthine artery originates from the anterior inferior cerebellar artery in 80% of patients, infarction of the membranous labyrinth is a common accompaniment. Severe vertigo, nausea, and vomiting are common initial symptoms. Other signs and symptoms include ipsilateral hearing loss, tinnitus, facial paralysis, and cerebellar asynergy. Spontaneous nystagmus is common. Contralateral loss of pain and temperature sensation may be caused by crossed spinothalamic fibers. Onset of symptoms is acute, followed by gradual improvement. Vertigo may persist for several weeks owing to damage of the central compensation mechanisms.

Cerebellar Infarction

Occlusion of the vertebral artery, the posterior inferior cerebellar artery, the anterior inferior cerebellar artery, or the superior cerebellar artery may result in infarction confined to the cerebellum without brainstem involvement[66] (Fig. 166-6). Initial signs and symptoms are severe vertigo, vomiting, and ataxia. Lack of typical brainstem signs may cause an incorrect diagnosis of an acute peripheral labyrinthine disorder. The key to the diagnosis is the presence of prominent cerebellar signs such as gait ataxia and paretic gaze nystagmus. The diagnostic modality of choice is magnetic resonance imaging (MRI). After a latent interval of 24 to 96 hours, some patients exhibit signs of progressive brainstem dysfunction caused by compression by a swelling cerebellum. Progression to quadriplegia, coma, and death may follow unless surgical decompression is performed.

Cerebellar Hemorrhage

Spontaneous intraparenchymal hemorrhage into the cerebellum causes neurologic symptoms that often rapidly progress to coma and death.[67-69] The initial manifestations are severe vertigo, vomiting, and ataxia. As with cerebellar infarction, brainstem signs may not initially be present, which may cause the condition to be confused with a peripheral vestibular problem. Modern imaging studies such as computed tomography (CT) and MRI have revolutionized the diagnosis of this condition (Fig. 166-7). Mortality rates range from as low as 20%[70] up to 74%, depending on the series. The value of and indications for surgical intervention remain controversial and probably depend on the size and location of the hematoma as well as the patient's symptoms.[67]

Evaluation and Management

Cerebrovascular disease is a primary consideration in the differential diagnosis for acute spontaneous vertigo, particularly if the patient has vascular risk factors. If the history and examination findings suggest a vascular disorder, immediate neuroimaging is necessary. CT of the brain without contrast often is the first imaging test because it is widely available and shows intraparenchymal or subarachnoid blood. Hemorrhage can mimic any of the ischemic stroke syndromes and must be

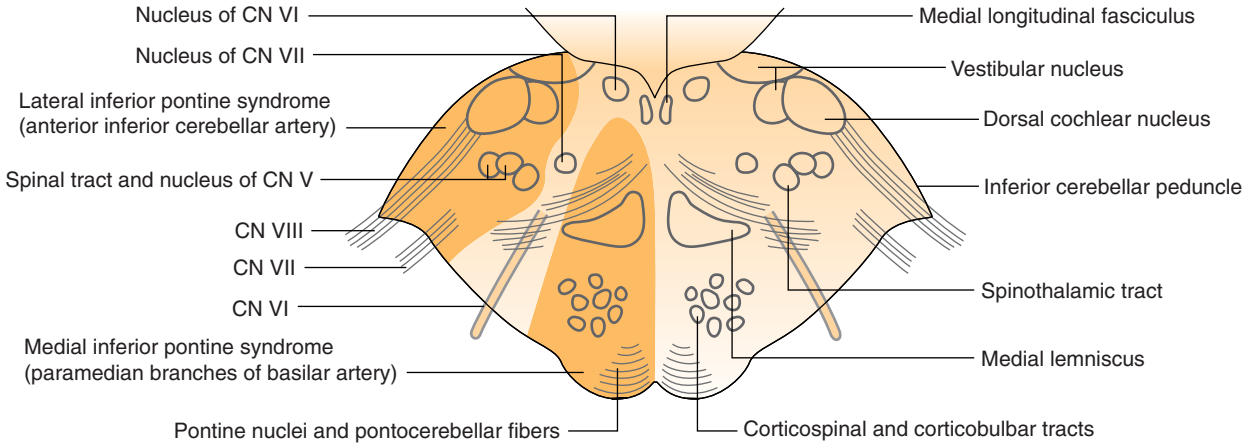

Figure 166-5. Lower pons cross section with anatomic structures labeled on the *right* and vascular lesions on the *left*. CN, cranial nerve. *(Adapted from Kandel ER, Schwartz JH, Jessell TM.* Principles of Neural Science. *New York: McGraw-Hill; 2000:1303.)*

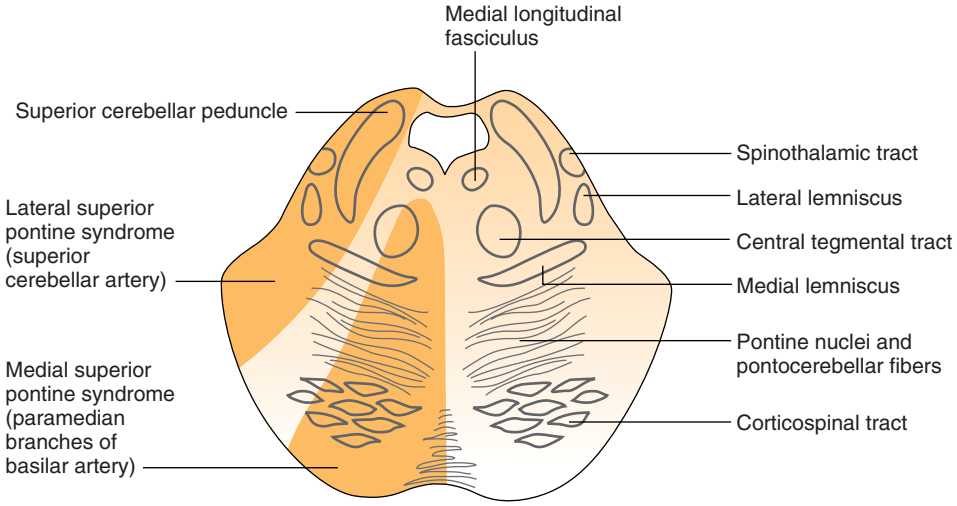

Figure 166-6. Upper pons cross section with anatomic structures labeled on the *right* and vascular lesions on the *left*. *(Adapted from Kandel ER, Schwartz JH, Jessell TM.* Principles of Neural Science. *New York: McGraw-Hill; 2000:1303.)*

excluded with thin-section CT through the cerebellum, brainstem, and fourth ventricle. MRI and magnetic resonance angiography (MRA) are superior to CT for viewing the vertebrobasilar vessels and their supplied structures, because CT scans often are normal in appearance with cerebellar or brainstem infarction. MRI, on the other hand, detects ischemic strokes in the brainstem and cerebellum early on, as well as edema. Diffusion-weighted imaging with MRI can now detect infarcts within the first hour of ischemia (Fig. 166-8). MRA has begun to replace conventional angiography in certain circumstances. Vertebral artery dissection and vertebral or basilar artery stenosis or occlusion generally can be identified with MRA of the cervical vessels performed with contrast (Fig. 166-9).

Neoplasms

Space-occupying lesions can induce vestibular symptoms by compressing or by destroying neural tissue within the temporal bone, in the cerebellopontine angle, or intra-axially within the brainstem and cerebellum. Symptoms also can be produced or increased by vascular compression.

Vestibular Schwannomas

Vestibular schwannomas can manifest with vertigo symptoms, which can be disabling in some patients,[71] although such symptoms are present in less than 20% of patients with these tumors.[72] Hyperventilation-induced vertigo also may occur in the absence of hearing loss.[73] Discussion of the diagnosis and treatment of vestibular neuromas can be found in Chapters 149 and 153.

Brainstem Neoplasms

Gliomas of the brainstem usually grow slowly and infiltrate the brainstem nuclei and fiber tracts, producing progressive symptoms and signs. The typical history is one of relentlessly progressive involvement of one brainstem center after another, often causing death with the destruction of the vital cardiorespiratory centers of the medulla. These tumors are 5 to 10 times more common in children than in adults. Vestibular and cochlear signs and symptoms occur in approximately one half of patients, but the spectrum of findings usually makes a brainstem origin clear. In the modern era, imaging studies such as CT or MRI usually are performed to investigate the initial manifestations, making the diagnosis obvious.

Tumors originating in the pons or midbrain initially are likely to cause long tract signs, cranial nerve deficits, and ataxia. Although uncommon, tumors that originate in the medulla are likely to cause recurrent vertigo and vomiting. Irradiation is the treatment of choice, because surgical resection of this area is associated with significant morbidity.

Tumors originating in the fourth ventricle and compressing the vestibular nuclei in its floor also can produce vestibular symptoms.

Medulloblastomas, occurring primarily in children and adolescents, are rapidly growing, highly cellular tumors that originate in the posterior midline or vermis of the cerebellum and invade the fourth ventricle and adjacent cerebellar hemispheres. Headaches and vomiting occur early from obstructive hydrocephalus and associated increased intracranial pressure. An attack of headache, vertigo, vomiting, and visual loss may result from a change in head position, producing transient cerebrospinal fluid (CSF) obstruction (Bruns' syndrome). Positional vertigo and nystagmus may be the presenting manifestations.[74,75] Other fourth ventricle tumors that produce a similar clinical picture include ependymomas, papillomas, teratomas, epidermoid cysts, and cysticercosis. The diagnosis of a fourth ventricular mass is made readily with MRI and CT scanning, but frequently the exact nature of the tumor cannot be determined before surgical exploration and biopsy. Complete removal of tumor should be achieved when possible. Medulloblastomas are particularly sensitive to radiotherapy.[76]

Figure 166-7. Noncontrast computed tomography scan of a cerebellar hematoma within the vermis. Surrounding edema and effacement of the superior aspect of the fourth ventricle are evident. Resulting obstruction of cerebrospinal fluid outflow may lead to hydrocephalus. *(Courtesy of K. D. Flemming.)*

Cerebellar Neoplasm

Clinical manifestations of posterior fossa tumors include dizziness in 81% and vertigo in 44% of patients.[77] One half of patients with posterior fossa tumors exhibit spontaneous nystagmus, and a third lack caloric responses. Other common symptoms and signs of cerebellar tumors include tinnitus, hearing loss, headache, nausea or vomiting, and ataxia. Gliomas of the cerebellum may be relatively silent until they become large enough to obstruct CSF circulation or compress the brainstem.[78] Positional vertigo occasionally is the initial symptom of a cerebellar tumor.[79,80] Paroxysmal positional nystagmus, when present, is atypical, because it can be induced in several different positions and is nonfatigable. Tumors that can produce these signs and symptoms include gliomas, teratomas, hemangiomas, and hemangioblastomas. Each of these tumors has a characteristic appearance on MRI and CT scans, although occasionally the exact tumor type cannot be determined before surgical biopsy.

Cervical Vertigo

Dizziness caused by disorders of the neck and cervical spine is poorly understood and relatively uncommon. Neck afferents are recognized to have a role in the coordination of eye, head, and body spatial orientation. Perception of head rotation can be driven by vestibular, proprioceptive, or visual inputs. Cervical vertigo must be by definition proprioceptive in nature, because the other inputs that cause vertigo do not exist in the neck. Laboratory experiments in humans that eliminate visual input with darkness and vestibular input by holding the head still have shown that trunk motion can produce the sensation of head turning[81]; however, this has not been shown to occur in more ordinary situations. Several studies have provided limited evidence for the existence of cervical vertigo. Unilateral local anesthesia of the cervical roots can cause ataxia and nystagmus in animals and ataxia without nystagmus in humans.[82] Patients with chronic cervicobrachial neck pain also have worse results on posturography tests.[83] These results are difficult to interpret because trauma that causes neck pain also can cause brain injury and damage to peripheral otolith organs. In clinical practice, it is necessary to exclude neurologic, vestibular, and psychosomatic disorders before a disorder of the craniovertebral junction can be given serious consideration. The diagnosis of cervical vertigo remains largely theoretical.[84,85]

Disorders of the Craniovertebral Junction

Disorders of the craniovertebral junction are poorly understood and relatively uncommon. The patients frequently are referred for

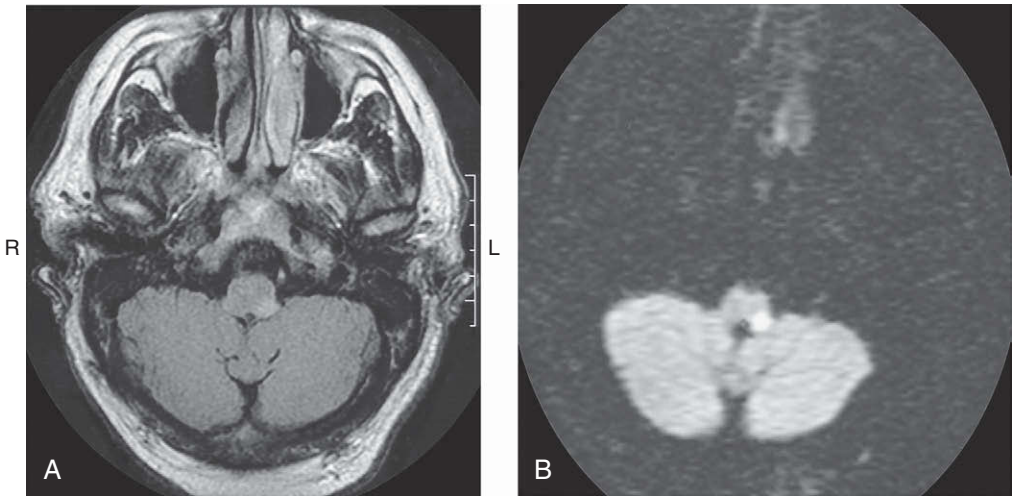

Figure 166-8. Magnetic resonance imaging of a lateral medullary infarction. **A,** Image obtained using the fluid-attenuated inversion recovery (FLAIR) sequence. **B,** Image obtained using a diffusion-weighted sequence. Both show changes of an acute infarction involving the left dorsolateral medulla. *(Courtesy of K. D. Flemming.)*

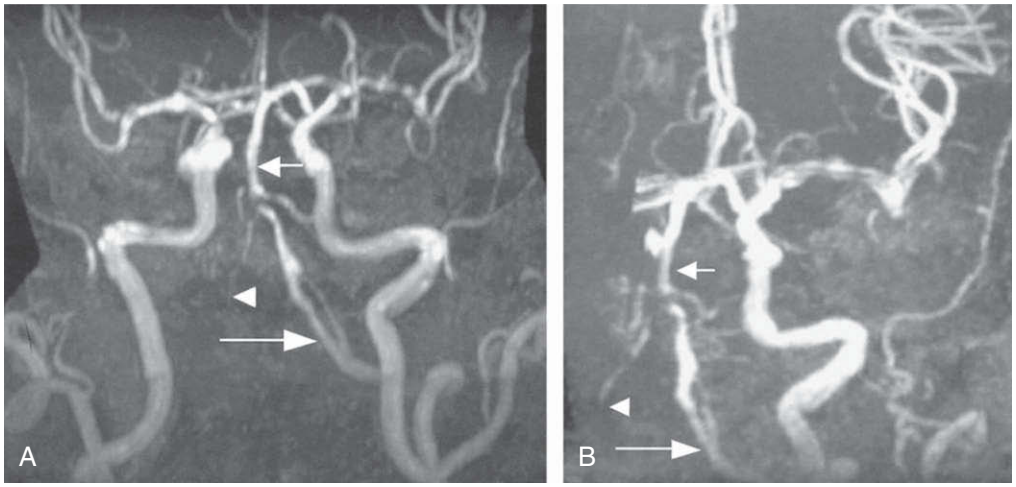

Figure 166-9. Contrast-enhanced magnetic resonance angiogram showing stenosis of the cervical vessels. **A,** Frontal view. **B,** Lateral view. Severe stenosis can be seen at the junction of the left vertebral artery *(long arrow)* and the basilar artery *(short arrow)*. The right distal vertebral artery also is occluded *(arrowhead)*. *(From Lee H. Sudden bilateral simultaneous deafness with vertigo as a sole manifestation of vertebrobasilar insufficiency.* J Neurol Neurosurg Psychiatry. *2003;74:540.)*

surgical evaluation because of brainstem or lower cranial nerve signs and symptoms such as tinnitus, vertigo, hearing loss, pharyngeal dysfunction, hoarseness, or airway obstruction. Physical examination can be difficult and misleading, and radiographic findings often are not sufficient to establish a diagnosis. An understanding of these disorders may facilitate appropriate evaluation and prevention of inappropriate management such as middle ear exploration and endolymphatic sac surgery.

Pathophysiology

The physiologic problem common to these disorders is physical compression of the CNS at the level of the upper spinal cord and medulla (cervicomedullary compression).[86-88] The rostrocaudal area of compression is variable, and the impingement can be ventral or dorsal, or (rarely) both. A second but uncommon potential mechanism is vascular insufficiency of the anterior spinal or vertebral arteries from angulation, stretching, or extrinsic obstruction.[89,90]

Classification

Basilar Impression

Basilar impression is an upward indentation or invagination of the clivus or posterior fossa floor.[86,91] This defect causes the upper cervical spine to migrate cephalad toward the brainstem, as the floor of the skull collapses under the weight of the head. The normal anatomy of the foramen magnum, first cervical vertebra (atlas), second cervical vertebra (axis), and its odontoid process (dens) can become altered by disease, trauma, or congenital deformities. When a softening of the skull base results, the skull literally descends onto the spinal column and odontoid. As the odontoid projects intracranially, it compresses the ventral aspect of the medulla.

Associated erosive changes of the occipital condyles and atlas accentuate the protrusion of the odontoid, narrow the diameter and circumference of the foramen magnum and spinal canal, and provide mechanisms for dorsal cervicomedullary compression. The odontoid not only projects above the foramen magnum but also occupies a large portion of its circumference.

Disorders known to cause basilar impression include Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, cretinism, and rickets.[86] The diagnosis is confirmed when lateral radiographic views of the skull demonstrate that the tip of the odontoid either extends above Chamberlain's line (a line extending from the posterior edge of the hard palate to the posterior lip of the foramen magnum)[92] or projects posterior to Wackenheim's clivus-canal line. The term *platybasia* has been used synonymously with *basilar artery impression* by some authors. Although the two conditions coexist, platybasia itself causes no symptoms.

Assimilation of the Atlas

Assimilation of the atlas (also called *occipitalization of the atlas*) is a bony union between the first cervical vertebra and the skull.[93] The amount of union varies, but motion between the two structures does not occur. As a result, the odontoid often impinges on the effective anteroposterior diameter of the foramen. A frequent associated finding is fusion of the axis to the third cervical vertebra. The condition is frequently developmental in origin and is found in association with abnormalities of the jaw, cleft palate, auricular deformities, cervical ribs, and urinary tract anomalies.[94] Klippel-Feil syndrome is one of the most common causes of cervical vertebral fusion.

Signs and symptoms of this syndrome are variable and typically appear fairly late and progress slowly. Symptoms may involve the brainstem, cerebellum, spinal cord, or lower cervical nerve roots or the vascular supply to these structures. These symptoms frequently precipitate a visit to a neurologist, but vertigo, facial paresis, dysphagia, hearing loss, and tongue atrophy may bring some patients to an otolaryngologist for initial evaluation. Although the disorder can be diagnosed with CT reconstructions, the key to diagnosis often is MRI, which allows direct coronal and sagittal imaging.[95]

Atlantoaxial Dislocation

During flexion and extension of the neck, congenital fusion of the occiput to the atlas increases the strain on the structures that normally restrict the motion of the atlas on the axis, especially if fusion of other cervical vertebrae also is present. The transverse ligaments that normally secure the odontoid against the anterior aspect of the arch of the atlas may weaken because of this repeated strain, and the resultant laxity allows the odontoid to move posteriorly into the lumen of the foramen magnum with neck flexion. Flexion or extension of the neck may then produce symptoms, depending on whether the predominant neural compression is anterior from the odontoid or posterior from the posterior arch of C1. When the atlas or congenital cervical fusion has been assimilated, the transverse odontoid ligament is sometimes hypoplastic, which makes laxity and atlantoaxial dislocation even more likely.

Atlantoaxial instability is associated with a number of congenital and acquired disease processes. It occurs in 10% to 30% of patients with Down syndrome when diagnosed radiographically, with an atlantodens interval of 4 to 5 mm.[96,97] The condition also is associated with spondyloepiphyseal dysplasia, Hurler's syndrome, and Morquio syndrome, and in those with achondroplastic dwarfism. A high incidence of atlantoaxial instability, resulting from destruction of the normal

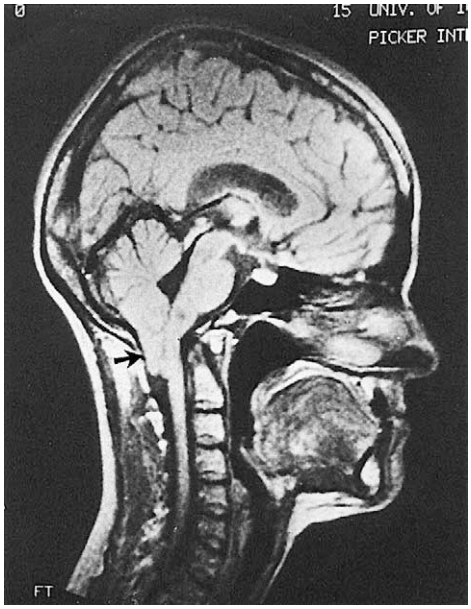

Figure 166-10. Magnetic resonance image of the head of a patient with Chiari type I malformation. Cerebellar tonsils *(arrow)* can be seen below the foramen magnum.

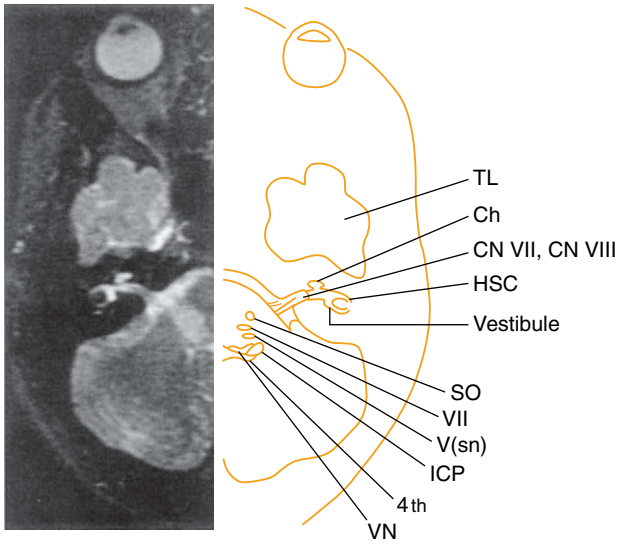

Figure 166-11. Axial T2-weighted brainstem magnetic resonance image showing high signal intensity in the region of the eighth nerve root-entry zone. Note that the vestibular nuclei appeared to be spared. Shown for comparison is a line drawing with major anatomic structures labeled. 4th, fourth ventricle; Ch, cochlea; CN VII, seventh cranial nerve; CN VIII, eighth cranial nerve; HSC, horizontal semicircular canal; ICP, inferior cerebellar peduncle; SO, superior olive; TL, temporal lobe; VII, facial nucleus; V(sn), spinal nucleus of the trigeminal tract; VN, vestibular nuclei. *(From Furman JM, Durrant JD, Hirsch WL. Eighth nerve signs in a case of multiple sclerosis.* Am J Otolaryngol. *1989;10:376-381.)*

stabilizing mechanisms by inflammatory tissue, has been reported in patients with rheumatoid arthritis.[98] Similarly, ligamentous laxity can result from inflammatory conditions affecting the retropharyngeal soft tissues or cervical bony structures, such as osteitis, retropharyngeal abscess, or lymphadenitis. Atlantoaxial instability in association with pharyngeal infection has come to be known as Grisel's syndrome.[99] It is rare in adults and associated with pain and dysphagia.

Most patients with atlantoaxial instability of developmental origin are asymptomatic, and the instability does not usually worsen with time.[97] Symptoms and signs develop in only 1% to 2% of patients with Down syndrome and usually appear between the ages of 5 and 15 years. Neck pain, sensory deficits, and difficulty with bladder control have been described; more subtle manifestations include decreased activity tolerance, changes in gait, and hyperreflexia.

Chiari Malformation

Chiari malformations are a group of developmental hindbrain and spinal cord abnormalities characterized by hernation of the contents of the posterior cranial fossa caudally through the foramen magnum into the upper cervical spine. These patients may present with symptoms related to the vestibular system such as ataxia, nystagmus, or vertigo.[100] Chiari malformation can be divided into two forms, type I and type II. The Chiari type I malformation is more common and more mild. Symptoms of Chiari type I usually are delayed until the age of 25 to 35 years. Affected persons often have subtle neurologic symptoms that are not associated with other developmental defects. Diagnosis is made by CT or MR images reconstructed in the sagittal plane, which may demonstrate deformation of the cerebellar tonsils more than 5 mm caudally through the foramen magnum (Fig. 166-10). The Chiari type II malformation manifests in the first few months of life with associated hydrocephalus and other CNS malformations such as meningomyelocele.

Classic presentation symptoms of Chiari type I malformation include upper extremity weakness, sensory loss, and pain. Occipital headaches that are exacerbated by coughing sneezing, bending over, or lifting also are a common presenting feature. Ataxia and nystagmus are reported in 24% of patients, with vertigo being a complaint in only 8%.[101] Patients also may have a vestibular test profile consistent with peripheral dysfunction but remain asymptomatic.[100] These patients also may present to the otolaryngologist with difficulty swallowing, aspiration, or hoarseness due to involvement of the lower cranial nerves (cranial nerves IX through XII).

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating CNS disorder of idiopathic origin with the onset in early adulthood. The disease affects women twice as often as men. The key to diagnosis is the presence of disseminated signs of CNS dysfunction manifested in an alternating and remitting and exacerbating course. Many symptoms can occur, depending on the location of the lesions. Vertigo is the initial symptom of MS in only approximately 5% of patients, although the symptom may be present in as many as one half of these patients at some point in the course of the disease.[102] Lesions within the vestibular nuclei and in the entry zone of cranial nerve VIII represent the most common locations for demyelinating activity to cause vertigo in patients with MS[103] (Fig. 166-11). However, benign paroxysmal positional vertigo remains the most common cause of vertigo in these patients,[104] as in the general population.

The diagnosis of MS remains a clinical one, with no definitive imaging study or laboratory tests.[105] Abnormalities in CSF can be identified in as many as 90% of patients with MS at some point in the course of the disease. Findings included increased gamma globulin level, oligoclonal banding of gamma globulin, and increased myelin basic protein. MRI demonstrates white matter lesions in more than 90% of patients, although similar lesions occasionally are seen in patients without MS.[106]

MS is treated with disease-modifying and symptomatic therapies. Intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 days is commonly used to hasten recovery from acute exacerbations. Drugs such as interferon-beta 1a and 1b and copolymer 1 are immunomodulating drugs that alter the natural history of MS. They reduce the relapse rate and the appearance of new MRI lesions and slow the progression. Other medications are used to treat symptoms of spasticity, neurogenic bladder, and fatigue.

Cerebellar Ataxia Syndromes

Recurrent or progressive ataxia is the primary neurologic deficit in several well-defined hereditary and sporadic degenerative disorders. Abnormal nystagmus is common and may be one of several categories,

including gaze paretic nystagmus and rebound nystagmus. The central nature of this symptom is almost always clear owing to the gait disturbances, dysarthria, tremor, and bradykinesias; accordingly, these patients rarely present to otolaryngologists. Impaired vestibular function usually is not symptomatic, although it may be found on clinical tests.

Friedreich's ataxia, the most common hereditary ataxia, is of autosomal recessive inheritance and usually is caused by a GAA repeat expansion in the frataxin gene. The onset of symptoms usually is before 20 years but may be as late as the sixth decade. Classically, its distinguishing features include an axonal sensory neuropathy with areflexia, Babinski sign, dysarthria, diabetes, and cardiomyopathy, although genetic testing has expanded the phenotypic range. Reduced vestibulo-ocular reflex gain is common, and saccadic intrusions (square-wave jerks) are characteristic. Rarer causes of recessively inherited ataxias include ataxia-telangiectasia, abetalipoproteinemia, and Refsum's disease. Ataxia is a feature of many other inborn metabolic and mitochondrial disorders.

Spinocerebellar atrophy encompasses a group of disorders in which cerebellar ataxia is a prominent feature. Many different genetically inherited subtypes have been identified by genetic linkage analysis.[107]

Cerebellar atrophy is characterized by gradual onset of ataxia, without other associated signs, beginning later in life. The disorder can be genetic or sporadic. Vestibular testing often reveals rebound nystagmus and spontaneous vertical nystagmus.[108]

Familiar episodic ataxia is an uncommon ataxia with a dominant inheritance pattern characterized by recurrent vertigo and ataxia. Episodes of ataxia often are triggered by stress, last minutes to hours, and begin between early childhood and early adulthood. Symptoms are markedly reduced or eliminated by acetazolamide.[109]

Paraneoplastic cerebellar degeneration (PCD) typically manifests as a subacute, rapidly progressive cerebellar syndrome. The development of anti-Purkinje cell antibodies (PCAs) in patients with undiagnosed and otherwise asymptomatic malignancies may result in the syndrome of PCD. PCD typically begins fairly abruptly and progresses rapidly through several months, with cerebellar-type ocular motor and vestibular abnormalities, dysarthria, and severe appendicular and gait ataxia. The cerebellum is not directly invaded by tumor, but the tumor produces remote effects on the cerebellum that probably are immune-mediated. It most commonly occurs in patients with carcinoma of the lung (small cell), breast, ovary, and Hodgkin's lymphoma. However, the neurologic symptoms usually appear before the cancer is identified.[110]

Focal Seizure Disorders

Vertigo can be part of an aura of a focal seizure. Smith[111] studied a group of patients with vestibular symptoms as part of their aura. The most common vestibular symptom was a sense of spinning, which occurred in 55% of these patients, followed by a sense of linear translation in 30%. However, episodes of vertigo as isolated manifestations of a seizure disorder occur rarely, if ever.

Normal Pressure Hydrocephalus

Idiopathic normal pressure hydrocephalus classically manifests with the triad of dementia, urinary incontinence, and gait or balance disturbance. However, these symptoms represent the more severe end of the clinical spectrum, and more subtle cases can manifest with only mild gait or balance symptoms.[112] Cognitive symptoms also are common but may be mild. Patients usually become symptomatic after the age of 60 years. Diagnosis requires an imaging study that demonstrates nonobstructive ventricular enlargement disproportionate to the degree of cerebral atrophy.

Physiologic Dizziness

Physiologic dizziness refers to phenomena that occur in normal persons as a result of physiologic stimulation of the vestibular, visual, or somatosensory system. Typically a mismatch among sensory signals causes disorientation, imbalance, and vegetative symptoms.

Motion Sickness

Motion sickness is a common form of physiologic dizziness. The main symptoms are dizziness, fatigue, pallor, cold sweats, salivation, and finally nausea and vomiting. It usually is caused by prolonged vestibular stimulation but also may occur with visual stimulation. The key symptom is nausea, a term derived from the Greek *naus*, "ship." Motion sickness may develop aboard a ship, in a car, on an airplane, or in space. Symptoms generally are worse when subjects are not able to visualize the movement, thereby creating a visual-vestibular conflict. Relief may be gained on a ship by standing on the deck and focusing on the horizon or land, rather than sitting in an enclosed cabin. When riding in a car, riding in the back seat or reading may make symptoms worse than sitting in front and looking off into the distance. Susceptibility among affected persons varies considerably. Patients with migraine generally are more prone to motion sickness, and bouts of motion sickness during childhood may be the first symptom of migraine.

Physical measures may help prevent motion sickness. In the long term, repeated gradual exposure to motion causes protective habituation, which may be the most effective therapeutic measure. Minimizing conflicting sensory inputs by restricting unnecessary head movement (such as pressing the head firmly against the headrest of a car) is helpful, as is minimizing any visual-vestibular mismatch, as described earlier.

Anti–motion sickness drugs are aimed at modulating the histaminic, cholinergic, and noradrenergic neurotransmitters that are thought to be important in the neural processes of motion sickness. These drugs work by blocking the emetic response, reducing the size of the sensory mismatch by promoting habituation, or blocking conflicting sensory inputs.

Mal de Débarquement Syndrome

Mal de débarquement (MDD), "sickness of disembarkment," refers to inappropriate sensations of movement after exposure to motion. Although this unusual syndrome typically follows a sea voyage, MDD may occur after extended train, air, or car travel.[113] The characteristic symptom is a sensation of persistent rocking or swaying of the body without rotational vertigo. Vague dysequilibrium or unsteadiness also may be a feature. MDD is distinguished from motion sickness in that patients with MDD are mostly symptom-free during the period of motion. Although many normal persons experience similar symptoms of "land sickness" for up to 48 hours after exposure to prolonged motion, most experts define MDD as a syndrome persisting for at least a month. During symptomatic periods, patients typically report improvement while in a moving vehicle or while walking that is lost when they stop moving, when symptoms worsen. MDD affects predominantly women, with a mean age at onset in the 40s. Symptoms may last for months to years. Some investigators have hypothesized that MDD is caused by a multisensorimotor adaptation and habituation to a new or abnormal motion environment. Benzodiazepines such as clonazepam or diazepam or amitriptyline may have a beneficial effect, but meclizine and scopolamine were ineffective.[113]

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CHAPTER ONE HUNDRED AND SIXTY-SEVEN

Surgery for Vestibular Disorders

Steven A. Telian

Key Points

- The otologist should recognize the vulnerability of patients with refractory vertigo, shelter them from nonvalidated treatments, and seek to guide them toward the most effective surgical options.
- Some operations seek to correct a pathologic process that is unique to a particular diagnosis, while preserving or restoring inner ear function. Success in this setting hinges on making an exact diagnosis and selecting procedures with proven efficacy.
- If a labyrinthine lesion is unstable or rapidly progressive in nature, central vestibular compensation is not possible unless the ear is first stabilized by medical or surgical management.
- The patient with recurrent vertigo refractory to conservative treatment is a candidate for a procedure that will ablate the residual vestibular function in the involved ear.
- Labyrinthectomy and vestibular nerve section will reliably ablate peripheral vestibular function and may be applied in the management of any unstable peripheral vestibular disorder.
- The endolymphatic sac is simply a specialized portion of the posterior fossa dura containing resorptive epithelium. Operations for decompression of the sac, with or without shunting, have a low efficacy rate but produce favorable results in some cases.
- It is not certain whether the observed benefits from sac decompression operations are due to a nonspecific effect of surgery or the decompression itself. Thus, if it is difficult to identify the sac, the prudent surgeon should never hesitate to terminate the procedure rather than risk a complication.
- Transmastoid labyrinthectomy is the gold standard procedure for surgical relief of vertigo from inner ear pathology but generally is reserved for patients who already have poor hearing in the involved ear.
- If hearing preservation is desired, selective vestibular nerve section procedures provide proven relief of vertigo for properly selected patients.
- If a patient describes a severe vestibular crisis at initial onset, without equally intense symptoms on any occasion since the original event, an uncompensated stable peripheral lesion is likely. Such patients are best treated with vestibular rehabilitation.
- Unilateral fluctuating or progressive sensorineural hearing loss is a strong indication of unstable inner ear function and is useful for lateralizing the offending ear.
- If uncertainty exists regarding which ear is causing vertigo, ablative surgery is not recommended. If the patient reports that vertigo spells are associated with auditory symptoms in the better ear, the second ear may have become involved, and surgery is ill-advised.

The otolaryngologist frequently is asked to evaluate a patient with intense vertigo or severe balance disturbance who has tried multiple medical treatments without success. Those who consider themselves disabled by their symptoms are eager, and often desperate, for relief. Although it is proper to consider surgical treatment in this setting, the physician should recognize that an unsuccessful surgical intervention may greatly aggravate the patient's discouragement regarding the disease, with the potential for alienation from the surgeon and from the medical profession in general. Recognizing the vulnerability of this patient population, the astute clinician seeks to guide the patient toward rational and effective surgical options when available, and to shelter them from nonvalidated medical or surgical treatments.

This chapter reviews the surgical procedures that are available for the management of vestibular disorders, with an emphasis on principles that promote understanding of the proper role and limitations of each procedure. Clinical application of these principles in patient selection can be expected to result in satisfactory outcomes in a high percentage of surgical procedures performed for dizziness.

Rationale for Surgery

When vertigo results from acute disturbances of the peripheral vestibular system, the patient will experience intense symptoms that gradually subside. If the lesion is self-limited and stable (e.g., acute viral labyrinthitis), it will not produce fluctuating or progressive dysfunction in the system. In this setting, the process of central vestibular compensation will reliably relieve dizziness in most patients by adjusting to the altered sensory inputs from the periphery. Similarly, ongoing vestibular compensation can minimize symptoms of vestibular loss from lesions that produce an insidious progressive deterioration, such as vestibular schwannoma. However, if the lesion is unstable or rapidly progressive in nature, central compensation is not possible unless the ear can be stabilized by medical or surgical management. Meniere's disease is the

prototypical disorder in this category, wherein the ear fluctuates between normal labyrinthine function and dramatic cochleovestibular pathology. Accordingly, vestibular system surgery is most likely to succeed when it is undertaken to stabilize an unstable ear, either by correcting a defect that underlies the disorder or by ablating function in the pathologic ear.

Certain surgical procedures are applicable only for one particular diagnosis. Some of these operations are widely accepted as both rational and effective, such as repair of a superior semicircular canal dehiscence or operations for intractable benign paroxysmal positional vertigo. Other disease-specific operations, such as endolymphatic sac surgery for Meniere's disease, repair of perilymph fistula, and microvascular decompression of the eighth nerve, continue to generate controversy. All of these operations have as their unifying feature the goal of correcting a pathologic process that is unique to the particular diagnosis, while preserving or restoring inner ear function. Success in this setting hinges on making an exact diagnosis and selecting operations with proven efficacy. On the other hand, procedures such as labyrinthectomy and vestibular nerve section are designed to ablate unilateral vestibular function and may be applied in the management of any peripheral vestibular disorder. In this setting, an etiologic diagnosis is less critical. Instead, the physician must be certain that the problem is attributable to ongoing fluctuating or rapidly progressive labyrinthine dysfunction and that the pathologic ear has been correctly identified.

Procedures for Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo (BPPV) most often affects the posterior semicircular canal. Variations of this condition affecting any of the three semicircular canals have now been recognized, as discussed in Chapters 164 and 165. BPPV seems to be caused by displaced otoconial debris within the membranous labyrinth. The original pathogenic hypothesis proposed that otoconial debris became lodged within the ampulla of the posterior semicircular canal (cupulolithiasis), rendering it sensitive to gravity. In the early 1990s, evidence accumulated to support the concept of otoconia floating freely in the membranous canal (canalithiasis).[1-3] These particles within the semicircular canal are purported to cause a transient flow of endolymph after a change in head position, producing a deviation of the cupula and triggering a change in the neural firing rate in the vestibular nerve. The brain perceives this change as rotation in the plane of the semicircular canal, with resulting vertigo and nystagmus. This theory is largely confirmed by the favorable results of particle repositioning maneuvers and the posterior canal occlusion procedure. It also better satisfies the conceptual framework for the biomechanics of BPPV originally suggested in the 1970s by McCabe and Ryu.[4] Although cupulolithiasis may certainly result in vestibular symptoms, this entity occurs much less frequently.

Before surgical procedures for BPPV are considered, it should be recognized that this condition has a high rate of spontaneous resolution and also is highly responsive to management by physical therapy interventions. Surgery is rarely required and should be reserved for refractory or multiply-recurrent cases. Nonsurgical management options[5] include traditional habituation exercises, Brandt-Daroff exercises, the liberatory maneuver of Semont, and particle repositioning techniques popularized by Epley and Parnes. A detailed discussion of these management options is provided in Chapters 163 and 165.

Singular Neurectomy

Gacek and Gacek[6] have advocated the singular neurectomy procedure for BPPV. This procedure involves selective transection of the branch of the inferior vestibular nerve innervating the posterior canal ampulla. The nerve is interrupted within the singular canal, which travels from the posterior portion of the internal auditory canal to the posterior canal ampulla (Fig. 167-1). This procedure is a highly rational choice for management of intractable posterior canal BPPV, because it is safer and more specific than a complete section of the vestibular nerve. However, this procedure is demanding technically and should not be undertaken unless the surgeon has mastered the approach in the temporal bone dissection laboratory. Gacek has performed 74% of the reported cases in the world literature, with preservation of hearing in 97% of the operated patients; other investigators report poor hearing results with this procedure.[7]

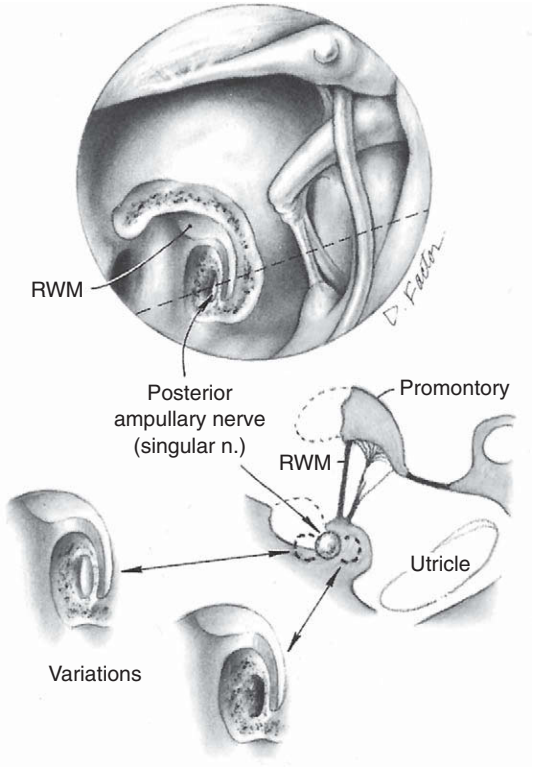

Figure 167-1. Singular neurectomy. After exposure of the round window membrane (RWM), the singular nerve is exposed inferior to the posterosuperior portion of RWM. Three variations in location of the nerve are illustrated in the vertical section taken along the broken line.

For this procedure, a tympanomeatal flap is elevated using a transcanal approach, and the bony lip of the round window niche is removed to visualize the round window membrane itself. The surgeon approaches the singular canal by drilling at a site inferior to the round window. Ideally, the nerve is transected just before its point of entry into the ampulla. The ampulla itself and the vestibule are at risk for injury during the procedure, and injury of either structure may result in severe vertigo and sensorineural hearing loss. One study suggested that the nerve measures approximately 5 mm in length and is best accessed by drilling approximately 0.7 mm posteroinferiorly to the posteromedial margin of the round window membrane after saucerization of the niche.[8] This study also found that whereas the average depth of the nerve was 1.5 mm, the posterior canal ampulla, the cochlear aqueduct, and the inferior cochlear vein were all within 2 mm of the preferred drilling point, which highlights the dangers of this approach. Another study showed that the nerve was always at least 0.7 mm from the edge of the exposed round window membrane, with an average depth of 1.3 mm.[9] Transtympanic access was believed to be straightforward in only 20% of specimens and impossible in 28%. This procedure has largely been supplanted by the technically simpler semicircular canal occlusion procedure.

Posterior Semicircular Canal Occlusion

Parnes and McClure[2] introduced the concept of surgical occlusion of the posterior semicircular canal for the relief of BPPV. Conceptually, the canal occlusion procedure is based on the assumption that otoconial debris, originally from the macula of the utricle, settles into the endolymphatic space of the posterior semicircular canal and produces the signs and symptoms of BPPV.

The surgery is conducted to obstruct the bony lumen of the dome of the posterior semicircular canal without disruption of the membra-

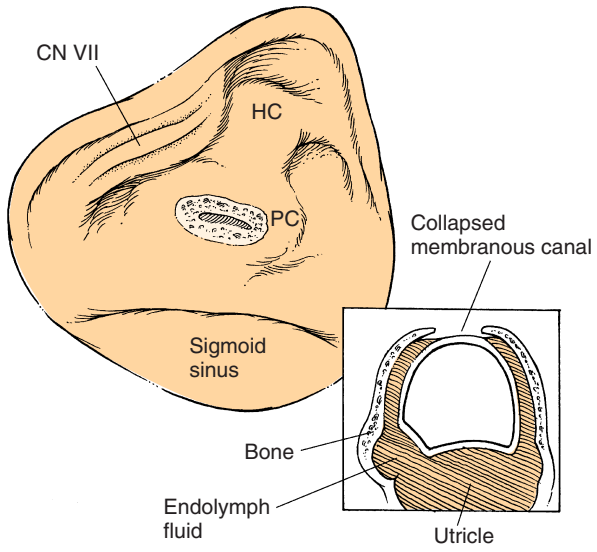

Figure 167-2. Posterior semicircular canal occlusion. After transmastoid exposure of the posterior semicircular canal, the bony lumen is opened and obstructed, with care to avoid disrupting the collapsed membranous canal (inset). CN VII, seventh cranial nerve; HC, horizontal semicircular canal; PC, posterior semicircular canal with fenestration.

nous labyrinth (see Fig. 167-2). After a complete mastoidectomy is performed, the horizontal semicircular canal is identified. The dome of the posterior semicircular canal is then identified between the horizontal canal and the posterior fossa dural plate. The lumen of the posterior canal is approached with a diamond drill until it is visible as a dark line through a thin layer of residual bone. The lumen is opened by removing the remaining thin bone over the canal lumen using delicate instrumentation, with care taken to avoid damaging the membranous canal or suctioning fluid from the perilymphatic space. The perilymph is gently removed by placing a wick of absorbent material near the labyrinthotomy site, causing the membranous semicircular canal to collapse against the deep wall of the bony canal lumen. The canal may then be occluded by placing small plugs of periosteum into the canal, one toward the ampulla and one toward the common crus. The labyrinthotomy is repaired by filling the lumen with wet bone dust harvested during the mastoidectomy. This material can be secured in position by placing bone wax or a piece of connective tissue over the dome of the canal.

The patient may have mild to moderate unsteadiness after the procedure but usually is fit for discharge from the hospital within 24 to 48 hours. A small risk of reactive labyrinthitis and sensorineural hearing loss is associated with the need to open the bony labyrinth. Approximately 15% of patients have protracted postoperative dysequilibrium, but vertigo control rates approach 100%, and hearing loss is uncommon.[10] Dizziness Handicap Inventory scores are reduced significantly, and patient satisfaction is 85%.[11]

Surgery for Superior Semicircular Canal Dehiscence

Minor[12] first described the syndrome of superior semicircular canal dehiscence (SSCD) in 2000. Further detailed characterization and recommendations for treatment have evolved since that ground-breaking report. Morphometric evidence indicates that SSCD may be associated with generalized reduction in the thickness of the squamous portion of the temporal bone,[13] which would predispose affected patients to middle fossa superior semicircular canal defects and explain the frequent association with natural dehiscences of the tegmen tympani and mastoideum. Aural pressure and unusual sensitivity to bone-conducted sounds are common complaints. Patients frequently report autophony, so this condition must be distinguished from the patulous eustachian tube. Vestibular symptoms typically are transient and are induced by loud sounds or any activity that leads to a transient increase in intracranial pressure. Some patients also report chronic dysequilibrium. Eye movements that are characteristic of superior semicircular canal stimulation may be seen in response to applied pressure stimuli—specifically, a torsional downward deviation of the eye. Vestibular evoked myogenic potential (VEMP) thresholds are reduced and amplitudes elevated in the setting of open dehiscence. Auditory findings include an apparent conductive or mixed hearing loss with a significant low-frequency conductive component. The apparent conductive hearing loss is believed to be caused by shunting of air-conducted acoustic energy away from the basilar membrance within the cochlea toward the dehiscence, which is functioning as a third mobile window.[14] It is essential to distinguish this condition audiometrically from otosclerosis by requesting testing for supranormal thresholds (often better than 0 dB) on bone conduction audiometry, and for the presence of acoustic reflexes.[15]

In cases in which clinical symptoms and test results suggest this diagnosis, high-resolution computed tomography (CT) of the temporal bone is indicated in an effort to visualize a dehiscence of the canal at the dural interface in the floor of the middle cranial fossa. These studies should be performed in a parasagittal plane orthogonal to the superior canal (Fig. 167-3). Generally, the dehiscence is repaired through a middle cranial fossa craniotomy, and evidence is mounting that disrupting the canal by obstructive plugging is superior to a simple repair ("resurfacing") of the defect.[16] Plugging of the SSCD reliably relieves vertigo symptoms and reduces the gain of the angular vestibulo-ocular reflex (VOR) by an average of 44% for the superior canal, along with a modest 10% reduction for the ipislateral posterior canal.[17] The procedure will resolve most of the auditory symptoms, but results are less predictable than those for vestibular symptoms. Care should be taken to avoid suctioning perilymph from the dehiscence during surgery; plugging may be accomplished with tissue plugs supported by bone chips or bone paté. In carefully selected patients, it may be possible to repair the dehiscence using a transmastoid approach, obviating the need for a craniotomy.[18]

Repair of Perilymphatic Fistula

Perilymphatic fistula is a controversial diagnosis that centers on the phenomenon of perilymph leaking from the inner ear into the middle ear cleft through the oval window, round window, or other abnormally patent fissures in the bony labyrinth.[19] A perilymph fistula may develop after stapedectomy surgery, penetrating middle ear trauma, head trauma, or barotrauma.[20] Uncertainty regarding the clinical criteria for the diagnosis and the inability to document the presence of a microfistula at surgery contribute to the problematic nature of this diagnosis.[21] Most authors agree that acute perilymph fistulas generally heal spontaneously, so a 2- to 3-day period of bedrest initially is appropriate. With suspected fistula after penetrating trauma, early exploration is indicated to preserve residual hearing, unless complete hearing loss is already present at diagnosis. In suspected chronic cases, a trial of vestibular rehabilitation before middle ear exploration may be appropriate if the diagnosis is uncertain, particularly if the hearing is stable.

Some investigators have attempted to use β-2 transferrin in fluids collected from the middle ear to support a clinical diagnosis of perilymph fistula, but results have been conflicting using this protein as a marker for perilymph.[22,23] Unpublished data from my laboratory suggest that assays for β-2 transferrin used for identification of cerebrospinal fluid leak are not sensitive enough to detect this protein in only 1 to 2 μL of perilymph. On the other hand, exquisitely sensitive assays will detect trace amounts that are present in serum, which could lead to false-positive results. Accordingly, use of this technique in an effort to confirm this diagnosis is not recommended.

An exploratory tympanotomy for perilymph fistula should be undertaken with use of local anesthesia and mild sedation whenever possible, so that the patient may be enlisted to perform the Valsalva maneuver to help identify perilymph leaks. After a tympanomeatal flap is elevated, bone is removed from the posterior superior wall of the bony external auditory canal until the oval window is completely visible. Likewise, it may be wise to remove any mucosal folds and the

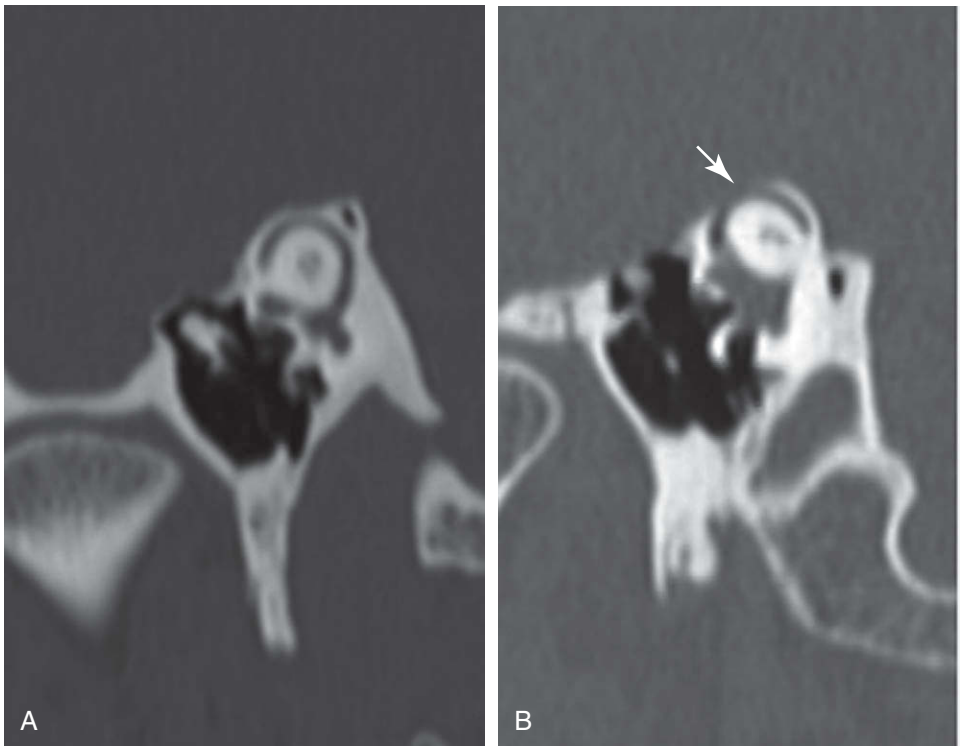

Figure 167-3. Superior canal dehiscence is best confirmed on a parasagittal computed tomography (CT) image obtained in the plane orthogonal to the superior canal. **A** shows a normal canal, with the *arrow* in **B** indicating a dehiscence.

bony overhang of the round window niche to better visualize the round window membrane. It is rare to see a dramatic defect in the oval or round window in routine perilymph fistula explorations. Fluid may be suctioned from the niche to see if it reaccumulates, although this phenomenon is common and does not verify that a perilymph fistula is present. Poe and Bottrill[24] have added credence to the suggestion that pooling of clear fluid in the oval or round window is due to transudation or to dependent accumulation of local anesthetic solutions. They performed transtympanic endoscopy of the middle ear before raising a tympanomeatal flap, and documented that fluid was not evident in the windows until after injection of the local anesthetic solution. In fact, endoscopic visualization of the middle ear could supplant formal tympanotomy for diagnosis of this disorder. The ear also should be inspected for abnormally patent fissures in the bony labyrinth, especially anterior to the oval window and inferior to the round window. Any suspicious defect should be repaired by removing surrounding mucosa and patching with connective tissue, secured by packing. My own practice is to routinely patch the round window niche in explorations with negative findings, but a more conservative approach is indicated in the oval window region to avoid the risk of an iatrogenic conductive hearing loss.

Specific Operations for Meniere's Disease

Meniere's disease is characterized clinically by the complex of recurrent episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and a subjective sense of aural fullness. If the diagnosis is uncertain, the indications for surgical procedures designed to address this specific disorder are less straightforward. The general teaching is that surgery is reserved for patients with "intractable vertigo in whom medical therapy has failed." Experience suggests that otologists differ significantly in their standards for determining medical failure. Some clinicians require that the patient experience 6 to 12 months of frequent and severe spells of vertigo before surgery is undertaken; others are willing to proceed more quickly. These differences are important to consider in evaluating uncontrolled clinical studies of surgical efficacy, especially in light of the spontaneous remissions that characterize this disorder.

A less invasive alternate treatment for Meniere's disease, intratympanic gentamicin injection, has become an accepted alternative to ablative surgery.[25-27] Uncontrolled reports of success with intratympanic corticosteroids are accumulating, but higher-quality studies of efficacy in this disorder are needed.[28] Therapy with a novel mechanical device, the Meniett device (Medtronic Xomed, Jacksonville, Florida), has demonstrated a significant reduction of episodic vertigo among surgical candidates in a placebo-controlled randomized clinical trial.[29] This therapy involves insertion of a tympanostomy tube in the affected ear, with subsequent application of intermittent pulsatile overpressure to the inner ear in 5-minute treatment cycles three times daily. Sustained remissions were typical, and only 24% elected to proceed to surgical treatment within 2 years.[30]

When a decision is made to proceed with surgery, questions arise regarding the choice of operation. Although vestibular nerve section or labyrinthectomy should reliably relieve vertigo related to Meniere's disease, these procedures ablate residual function in the affected ear. The ideal procedure for Meniere's disease would restore normal function, or at least preserve residual function, while stabilizing the ear. As discussed next, two operative procedures have been proposed to achieve this goal: cochleosacculotomy and endolymphatic sac surgery.

Cochleosacculotomy

The cochlear endolymphatic shunt procedure, usually referred to as *cochleosacculotomy*, is designed to create a permanent communication to equilibrate endolymphatic and perilymphatic pressures in the hydropic ear.[31] The goal is to create a small permanent fistula in the osseous spiral lamina within the basal turn of the cochlea. This is performed by elevating a tympanomeatal flap and exposing the round window niche. A 3-mm right-angle pick is inserted through the round window membrane and directed toward the oval window niche, hugging the lateral wall of the inner ear (Fig. 167-4), and fracturing the osseous spiral lamina. As might be expected, the operation has been associated with a 25% incidence of high-frequency sensorineural hearing loss and a 10% incidence of profound deafness.[32] Despite reports of 70% success with long-term relief of vertigo, the operation

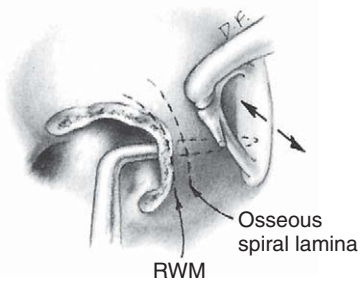

Figure 167-4. Cochleosacculotomy. Bony overhang of round window niche is removed to allow insertion of 3-mm, right-angle hook through the osseous spiral lamina of the basal end of the cochlea. Penetration of the tip of the hook can be monitored by movement of the stapes footplate. RWM, level of round window membrane.

has enjoyed only limited application. In one series of elderly patients with Meniere's disease, vertigo control was documented in almost every patient, but hearing was almost universally worse.[33] The study authors recommended that this operation be used as an alternative to labyrinthectomy in elderly patients with preexisting severe hearing loss.

Endolymphatic Sac Surgery

Although the specific physiologic defect causing Meniere's disease is unclear, many investigators report a beneficial effect in uncontrolled studies of surgical intervention directed toward the endolymphatic sac in patients with Meniere's disease. The first operative procedure on the endolymphatic sac was performed by Portmann.[34] Many modifications have been proposed, including bony decompression of the sac by Shambaugh,[35] placement of an endolymphatic-subarachnoid shunt by House,[36] and an endolymphatic-mastoid shunt by Shea.[37] Complications of endolymphatic sac procedures include hearing loss, cerebrospinal fluid leak, and facial nerve paralysis, although they are infrequent.

The efficacy of endolymphatic sac procedures has been widely questioned and debated. Some investigators suggest that the operation is ill-conceived and that the reported results may be biased or reflect a nonspecific effect of the operative undertaking or the natural history of this spontaneously remitting condition.[38,39] Evidence of a nonspecific effect of anesthesia on Meniere's disease has been provided by Gates,[40] who documented in a prospective observational trial that administration of a potent neuroleptic analgesic (Innovar) provided lasting relief of vertigo for most patients in whom medical management had failed to produce improvement. Advocates of sac surgery argue that a 50% to 70% success rate improves on the anticipated natural history in this patient population, making an endolymphatic sac procedure preferable to immediate use of an ablative procedure.[41] One uncontrolled observational study suggested that vertigo and vestibular disability could be largely corrected in 90% of patients evaluated 2 years after wide bony decompression of the sac and sigmoid sinus.[42] An important randomized clinical trial performed in Denmark during the 1970s compared endolymphatic sac decompression with a "sham" cortical mastoidectomy operation. The patients and those evaluating the outcomes were blinded to group assignment. Multiple subsequent reports were published, culminating with a 9-year follow-up report.[43] Both surgical groups demonstrated improvements that were not statistically different, and the investigators concluded that clinical improvement with decreased vertigo was attributable to a "placebo effect." The conclusions of this study have been widely debated, with proponents of sac surgery arguing that the sample size was too small to detect clinically important differences and pointing out that both groups did improve, thus arguing in favor of the operation even if the effect was nonspecific. Welling and Nagaraja[44] reanalyzed the data from this study by more sophisticated modern statistical methods. They demonstrated from the original data set that, even with the small sample size, the sac surgery group showed statistically significant reductions in postoperative vertigo, nausea and vomiting, and tinnitus compared with the mastoidectomy control group. Unfortunately, because the study did not include a nonsurgical control group, the potentially important influence of disease natural history on the reported efficacy could not be assessed. The Danish group performed another small controlled study comparing endolymphatic sac decompression and insertion of a tympanostomy tube, demonstrating that both groups had similar levels of improvement.[45] Again, a nonsurgical control group was not used.

One difficulty in performing vertigo outcome studies has been a lack of validated metrics for measuring treatment outcome. A previously validated medical quality-of-life instrument, the SF-36, has been demonstrated to correlate well with the 1995 disease reporting classification[44] proposed by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS).[46] The study showed that preoperative patients scored well below population norms, and that those achieving AAO-HNS class A or B outcomes (vertigo relief) normalized their scores. Alternative metrics have been proposed for future prospective studies that are more specific to Meniere's disease.[47,48]

In the absence of properly controlled clinical trials, the otologist should perform a critical review of the literature before recommending endolymphatic sac procedures. Several specific issues warrant consideration: Is endolymphatic sac surgery sufficiently efficacious for control of vertigo in patients who are eager for reliable results? If so, do the results deteriorate over time? Is the efficacy of sac surgery reported in uncontrolled observational studies inflated, in view of the retrospective nature of the studies? Is most of the observed benefit attributable to the placebo effect or to another nonspecific effect of surgery? The available evidence seems to indicate that endolymphatic sac surgery has not been demonstrated to be a sufficiently reliable surgical treatment for Meniere's disease. Continued uncertainty about these issues after decades of clinical experience underscores the need for properly controlled multi-institutional clinical trials to address the role of endolymphatic sac surgery in Meniere's disease.

The surgical approach to the endolymphatic sac begins with a cortical mastoidectomy. Once the antrum is exposed, it is wise to copiously irrigate the cavity and temporarily obstruct the aditus ad antrum to prevent bone dust from accumulating in the middle ear, which can result in a delayed conductive hearing loss from fixation of the ossicular chain. The bony labyrinth, particularly the posterior semicircular canal, should be positively identified before any bone is removed from the posterior fossa dura.

The endolymphatic sac is simply a specialized portion of the posterior fossa dura that contains the resorptive epithelium of the membranous labyrinth. It is connected to the vestibule by the endolymphatic duct, which travels in the vestibular aqueduct through the bony labyrinth medial to the posterior semicircular canal and then parallel to the common crus of the posterior and superior semicircular canals. The entrance of the endolymphatic sac into the vestibular aqueduct is a helpful surgical landmark in seeking to identify the sac. It is located roughly at the point where a hypothetical line parallel to the horizontal semicircular canal bisects the dome of the posterior semicircular canal (Donaldson's line). In seeking to identify the sac, this critical landmark should be remembered, because the endolymphatic sac is always inferior to this line. As indicated by my own experience performing surgical procedures after previous "endolymphatic sac decompression" failures, a not uncommon finding in such cases is that this area of the temporal bone was not previously dissected, so that the sac was never actually identified or decompressed.

The endolymphatic sac is bounded superiorly by Donaldson's line, posteriorly by the sigmoid sinus, anteroinferiorly by the jugular bulb, and laterally by the descending (mastoid) portion of the facial nerve. This region of the temporal bone may be poorly pneumatized, because there seems to be an association between Meniere's disease and underdevelopment of this portion of the mastoid process. Such an operative finding not only makes proper identification of the sac difficult but also increases the danger of injury to the facial nerve and the sigmoid sinus. To avoid injury to these structures, the surgeon should widely remove bone posterior and lateral to the sigmoid sinus. The digastric ridge should be identified inferiorly and followed toward the stylomastoid foramen. This will allow the surgeon to open any retrofacial air cell tract that is present and thus to identify the level of the facial nerve. After these structures are positively identified, the posterior

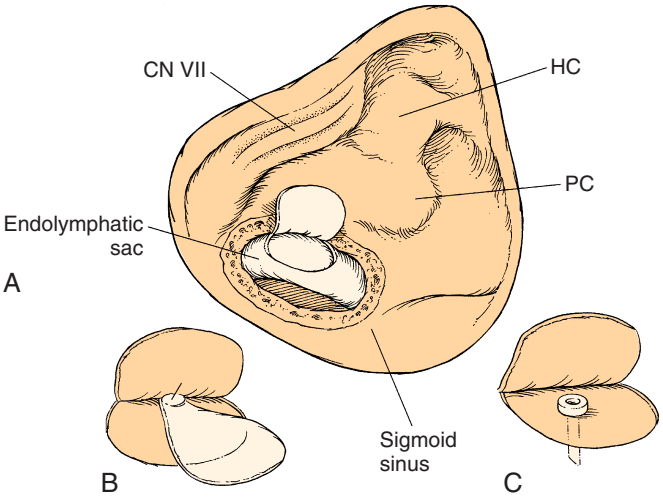

Figure 167-5. Endolymphatic sac surgery. **A,** Endolymphatic sac exposed by transmastoid approach and incised. **B,** Endolymphatic sac–mastoid shunt involves placing Silastic sheeting or a shunt into the lumen of the sac. **C,** Endolymphatic sac–subarachnoid shunt placement requires penetration of the deep layer of the sac lumen (posterior fossa dura) into the subarachnoid space. CN VII, seventh cranial nerve; HC, horizontal semicircular canal; PC, posterior semicircular canal.

fossa dura behind the sinus and the sinus itself should be decompressed with a large diamond drill. The surgeon then may retract the sinus and dissect bluntly between the bony dural plate and the presigmoid posterior fossa dura (containing the endolymphatic sac). After the sinus and the dura are safety retracted, the bony dural plate inferior to Donaldson's line can be removed down to the level of the jugular bulb. Dissection may proceed anteromedially into the retrofacial air cell tract until the site of the endolymphatic duct's entry into bone medial to the posterior semicircular canal is seen. Care should be taken not to injure the medial surface of the facial nerve or the dome of the posterior canal while drilling in this region. This portion of the dissection is greatly facilitated by the dural decompression that has already been accomplished.

Once the sac has been identified, the surgeon should decide whether to terminate the procedure, having accomplished a wide bony decompression, or to open the lumen and place a shunt. Reported series of wide bony decompression without shunting[49] compare favorably with those series that included shunt procedures. Some experts have recommended placing a pressure-sensitive valve into the endolymphatic duct after the sac lumen has been opened and followed into the duct.[50] Other surgeons have failed to achieve the positive results originally reported with this procedure.[51] It often is difficult or impossible to identify one predominant lumen of the sac, and foreign material placed into the sac has been shown to become rapidly encapsulated with fibrous tissue. Despite these considerations, most surgeons who perform endolymphatic sac surgery choose to place a shunt from the sac into the mastoid cavity (Fig. 167-5A and B). On the other hand, use of an endolymphatic sac–subarachnoid shunt[36] (Fig. 167-5C) carries a higher risk of cerebrospinal fluid leak. Beyond this consideration, the procedure seems to be conceptually flawed, because the pressure in the subarachnoid space will always exceed that in the endolymphatic space, even in an ear with significant endolymphatic hydrops. In general, the more the sac is surgically manipulated, the greater the risk of cerebrospinal fluid leak postoperatively. When it is difficult to identify the sac or its lumen, the prudent surgeon will never hesitate to terminate the procedure rather than risk a serious complication.

Patient Selection in Ablative Vestibular Surgery

The patient with recurrent vertigo that has been refractory to medical or conservative surgical treatment is a candidate to undergo a procedure that will ablate the residual vestibular function in the involved ear. In this setting, the patient willingly sacrifices the residual function in the diseased ear in order to eliminate the spontaneous episodes of vertigo that result from fluctuating inputs from the labyrinth to the central nervous system. A successful outcome hinges on the patient's ability to compensate centrally for the unilateral loss of function.

The transmastoid labyrinthectomy is the gold standard procedure for surgical relief of vertigo from inner ear pathology. Because complete loss of residual hearing is inevitable after this operation, it is reserved for those patients who have poor hearing in the affected ear. When hearing must be preserved, a selective vestibular nerve section procedure may be undertaken. Although more risky and slightly less reliable, vestibular neurectomy enjoys a proven track record in the surgical relief of vertigo in properly selected patients. Both of these procedures ideally will produce a total loss of afferent input from the offending vestibular periphery. Although these procedures are applied most often in persons with Meniere's disease, they may be effective in patients with any unstable peripheral vestibular disorder.[52,53]

The Priority of Distinguishing Poor Compensation from Unstable Labyrinthine Disease

Although the specific etiology of dizziness is at times elusive, it usually is possible to distinguish on clinical grounds those patients whose symptoms are caused by an uncompensated stable lesion from those with unstable or progressive disease in the vestibular system. It generally is believed that an operation designed to ablate unilateral vestibular function can effectively relieve vertigo caused by labyrinthine dysfunction of any cause. However, failure to recognize that the patient's symptoms result from poor vestibular compensation for a stable lesion may lead to inappropriate and fruitless surgical intervention.[54] This categorical distinction has important management implications, especially as current understanding of vestibular compensation has evolved. Before the availability of vestibular rehabilitation programs, surgery to ablate vestibular function was offered to any patient whose vestibular injuries were clearly peripheral in nature and could be lateralized to one ear. Subsequently, however, it was demonstrated that the results obtained with vestibular rehabilitation are markedly superior to those with vestibular nerve section for the control of symptoms caused by uncompensated vestibular neuritis (Table 167-1). Thus, surgery is rarely recommended for this indication today. With uncompensated lesions, both surgeon and patient should be aware that the prognosis for success is dramatically lower than that reported for disorders characterized by fluctuating or deteriorating unilateral labyrinthine function.

The methods available to help the clinician distinguish uncompensated patients with a stable vestibular lesion from those with unstable labyrinthine pathology include recognition of key features in the clinical history, the use of vestibular testing, and, when appropriate, the use of a therapeutic trial of vestibular rehabilitation.

Clues in the Clinical History

It often is argued that a complete neurotologic history is the most important component in the diagnostic evaluation of the patient with a balance disorder. This also is true in the assessment of the patient's compensation status. Certain clues in the history will suggest that the patient has incomplete compensation, despite the fact that the vestibular lesion is stable. If the patient describes a severe vestibular crisis at onset without equally intense symptoms on any occasion since that time, an uncompensated lesion is more likely, and the patient is best treated with vestibular rehabilitation. Poor compensation is particularly likely to be the cause of continuous unsteadiness or mild recurring motion-provoked vertigo after recovery from the severe crisis. However, if the current spells are just as severe or more severe than the initial insult, an unstable or progressive vestibular lesion is strongly suggested. In such cases, the patient is best treated with medical or surgical measures designed to stabilize labyrinthine function, once the possibility of a central pathologic process has been eliminated.

The documentation of fluctuating or progressive sensorineural hearing loss also provides a strong indication of unstable inner ear function. Sometimes the patient is uncertain about the nature of an

Table 167-1

University of Michigan Treatment Results in Uncompensated Vestibular Neuritis

Outcome	Vestibular Nerve Section ($n = 16$)	Vestibular Rehabilitation ($n = 59$)
Complete improvement	None	25%
Dramatic improvement	25%	47%
Mild improvement	45%	13%
No improvement	25%	15%
Worse	5%	None

associated hearing loss. A review of serial audiograms may be helpful in this setting. Occasionally, it is desirable to obtain an audiogram during an episode of vertigo to determine whether subtle changes in auditory function are occurring that may be imperceptible to the patient.

The Role of Vestibular Testing

A complete battery of vestibular tests may be helpful in assessing compensation status or in explaining poor compensation by identifying pathologic processes in the central nervous system. The specific vestibular test results that may be helpful in these distinctions are summarized in Box 167-1.

Clinically significant spontaneous nystagmus, positional nystagmus, or a directional preponderance on electronystagmography (ENG) or videonystagmography (VNG) studies provides evidence for failure of physiologic compensation in the VOR. Rotational chair phase or gain abnormalities may identify a pathologic change in the VOR but do not assess compensation within the central nervous system. However, persistent asymmetry in VOR responses strongly suggests that the peripheral lesion is physiologically uncompensated. For head rotation toward the paretic side, the maximum eye velocity induced by the VOR is reduced from normal. This fact results in the observed asymmetry of VOR gain for rightward versus leftward rotations. This asymmetry usually resolves as the compensation process proceeds, at least in the subphysiologic range tested by rotational chair technology. A persisting VOR asymmetry even in well-compensated patients may be identified using the head thrust test above frequencies of 1 Hz.

Dynamic posturography provides adjunctive functional information about the balance system. Sometimes a patient whose major complaints are related to the vestibular system will have normal findings on ENG and rotational chair testing. Posturography may help to demonstrate continued functional impairment despite relatively normal physiologic responses in both inner ears. Patient age and preoperative posturography score have been shown to correlate strongly with postoperative Dizziness Handicap Inventory score.[55] Any evidence of a malingering pattern on postural control testing also may inform the clinician of previously unsuspected psychosocial issues complicating the patient's care.

Box 167-1

Clinical Usefulness of Vestibular Test Results

Evidence for Peripheral Labyrinthine Dysfunction
Unilateral caloric weakness
Spontaneous or positional nystagmus with normal oculomotor findings
Rapid positioning nystagmus after Dix-Hallpike maneuver
Rotational chair phase or asymmetry abnormality
Reduced VOR gain on rotational chair (bilateral weakness)

Evidence for Central Nervous System Pathology
Vertical or perverted nystagmus
Oculomotor test abnormalities
Failure of visual fixation suppression of nystagmus
Motor coordination test abnormalities on dynamic posturography, without musculoskeletal disorder

Evidence for Uncompensated Status
Persistent spontaneous or positional nystagmus
Post–head-shaking nystagmus
Rotational chair asymmetry
Sensory organization test abnormalities on dynamic posturography

Evidence for Improved Compensation Status after Treatment
Resolution of nystagmus
Resolution of rotational chair asymmetry
Improved performance on posturography

VOR, vestibulo-ocular reflex.

Therapeutic Trial of Vestibular Rehabilitation

Ultimately, even with the best clinical history and vestibular test capabilities, the clinician often is faced with diagnostic uncertainty when treating patients with dizziness. As an extreme example, a head injury patient who has a mix of spontaneous and motion-provoked symptoms exhibits evidence of central and peripheral vestibular dysfunction; chronic headache, impairment of cognitive function, and reactive depression also are present. In such patients, it may be difficult or impossible to identify the primary cause of ongoing disability. In settings of diagnostic uncertainty, a program of supervised vestibular rehabilitation may be helpful from a diagnostic standpoint.[5] The patient may make outstanding progress, suggesting that the primary problem was poor compensation for a stable lesion in the vestibular system. If the patient fails to improve, or seems to be worse after 4 to 6 weeks of therapy, an unstable lesion of the labyrinth is considerably more likely. Such an outcome would add credibility to a clinical diagnosis such as post-traumatic endolymphatic hydrops or perilymphatic fistula.

Identification of the Offending Labyrinth

If if there is any uncertainty regarding the ear that is causing vertigo, ablative surgery should not be considered. Reliable lateralizing features include fluctuating or progressive unilateral sensorineural hearing loss and a consistently reproducible unilateral reduction of responsiveness to caloric irrigations. An asymmetrical hearing loss in one ear is the best indicator of the abnormal side.[56] Preexisting hearing loss of extended

duration need not dissuade the physician from incriminating the involved ear as the cause of vertigo.[57,58] To illustrate the importance of this point, one study demonstrated 100% relief of vertigo in 13 patients with delayed-onset endolymphatic hydrops beginning up to 60 years after the onset of hearing loss.[59] Less reliable features include tinnitus, subjective sense of aural fullness, direction of observed spontaneous or positional nystagmus, and rotary chair asymmetries. Although audiologic and vestibular test results usually are reliable in determining the involved ear, they should always be interpreted in light of the entire clinical presentation, to avoid a serious error in diagnosis. For example, with significant unilateral sensorineural hearing loss and a unilateral vestibular weakness on the same side, the clinician usually can be confident that the suspect labyrinth is pathologic. However, if the patient reports that the vertigo spells are associated with roaring tinnitus or hearing fluctuations in the better ear, it is most likely that the second ear has become involved. In this case, surgery would be ill advised.

Identification of Intracranial Pathology

Acoustic neuroma and other lesions of the posterior fossa may manifest with clinical features indistinguishable from those of classic vertigo syndromes.[60] Therefore, it is appropriate to perform a definitive radiographic imaging study before vestibular surgery of any type is undertaken. Magnetic resonance imaging (MRI) of the posterior fossa with gadolinium enhancement provides a reliable means of detecting tumors of any size, early stages of demyelinating disease, and subtle ischemic lesions of the brainstem.

Consideration of Other Potential Treatments

Although labyrinthectomy and vestibular nerve section may be applied in any peripheral vestibular disorder, certain patients may be effectively treated by simpler procedures. The use of transtympanically injected aminoglycosides for chemical suppression or ablation of labyrinthine function is particularly appropriate for the management of Meniere's disease in those patients who would be poor surgical candidates.

Brackmann and associates[61] performed 25 eighth nerve microvascular decompression procedures for vertigo in 20 patients over one decade. This procedure was limited to patients who did not have episodic vertigo but had disabling motion-induced dizziness unrelieved by vestibular rehabilitation exercises or conventional medications. The diagnosis was confirmed when these symptoms were associated with radiographic evidence of a vessel loop impinging the nerve. The investigators reported significant improvement in 80% of patients. This procedure offers the potential to reduce vestibular symptoms without destruction of vestibular function in properly selected patients.

Residual Hearing and Selection of Procedure

Generally, labyrinthectomy is reserved for patients with extremely poor residual hearing in the involved ear. Rather than setting a specific hearing threshold or speech discrimination score as the criterion for suggesting a vestibular nerve section instead of a labyrinthectomy, most surgeons prefer to consider each case on an individual basis. Ultimately, the patient's perception of the usefulness of the residual hearing is the most important factor. Some patients insist that they receive benefit from hearing aid use in ears that the medical community would deem useless compared with the better ear. Others fail to recognize any functional utility from an ear that should provide benefit with proper amplification. Clearly, such perceptions must influence the choice of surgical procedure. It is appropriate to perform a labyrinthectomy instead of a selective vestibular nerve section if the contralateral ear is stable, if the patient is convinced that the involved ear is functionally useless, or if the incremental risks of intracranial surgery are unacceptable. A vestibular neurectomy is appropriate when hearing in the involved ear is deemed useful by the patient, especially when the hearing in the involved ear is unlikely to deteriorate in the near future. However, because the cochlear efferent fibers travel with the vestibular nerve, it must be recognized that a vestibular neurectomy may contribute to undesirable hearing symptoms in Meniere's disease: Sound intolerance and reduced speech discrimination in noise may be evident, even if the pure-tone detection and discrimination scores in quiet are unchanged.[62]

Some investigators argue that labyrinthectomy should never be performed if any hearing remains, fearing the unlikely scenario that the better ear may develop a hearing loss greater than the current loss in the diseased ear. If this rare outcome should occur, a cochlear implant in the most recently deafened ear would almost certainly rehabilitate the patient successfully. Insisting on the preservation of minimal residual hearing in a functionally useless poorer ear is too dogmatic to be practical, especially when the additional risks of vestibular nerve section, such as intracranial hemorrhage, meningitis, and cerebrospinal fluid leak, are considered. Beyond this, the available evidence suggests that preserved hearing often will continue to deteriorate and eventually provide no benefit for the patient.[63,64]

Ablative Procedures for the Control of Vertigo

Surgery for control of vertigo symptoms is virtually always elective. Patients should decide when their vertigo has produced sufficient disability in their lifestyle to outweigh the consequences and risks of surgery. A patient who has come to this decision without coercion by family or the physician is most prepared to face the surgery and the recovery period with a positive outlook.

Labyrinthectomy

Labyrinthectomy may be performed when persistent or recurrent labyrinthine symptoms of any etiology are attributed to dysfunction in an ear with severe to profound sensorineural hearing loss. All residual hearing sensitivity is sacrificed by this procedure. The operation may be undertaken using a transcanal or transmastoid approach. The transcanal labyrinthectomy, also known as oval window labyrinthectomy, retains some popularity. It can be performed quickly by approaching the inner ear through the external auditory canal, although complete ablation of vestibular neuroepithelium cannot reliably be accomplished.[65] The procedure begins by elevating a tympanomeatal flap to enter the middle ear and then accessing the vestibule of the bony labyrinth by removing the stapes from the oval window. Some surgeons advocate removing bone from the promontory below the oval window toward the round window to improve visualization of the vestibule (Fig. 167-6A). The saccule and utricle are identified and removed. An attempt may be made to reach and remove the ampullae of the horizontal and superior semicircular canals, although this step requires blind manipulation with a long right-angled instrument medial to the facial nerve. Augmenting this procedure by a selective section of the nerve to the posterior semicircular canal ampulla should help to prevent residual posterior canal function. To accomplish this, the bony exposure of the vestibule can be extended by drilling near the round window until the nerve to the posterior ampulla is identified and divided. Because the primary shortcoming of the transcanal labyrinthectomy is the inability to visualize all neuroepithelial elements of the inner ear, many surgeons supplement their mechanical efforts by filling the vestibule with absorbable packing soaked with an ototoxic aminoglycoside antibiotic, which enhances the likelihood of success. Although this procedure reliably eliminates vertigo, postoperative imbalance is seen in more than 60% of patients, a rate almost three times higher than after transmastoid labyrinthectomy in the elderly population.[66]

Transmastoid labyrinthectomy (Fig. 167-7) is the gold standard procedure for surgical ablation of vestibular function. The transmastoid approach allows complete visualization and removal of the entire semicircular canal system, utricle, and saccule, resulting in highly reliable relief of vertigo.[67,68] Success is nearly universal and the improvement in quality of life is remarkable for properly selected patients.[69] This transtemporal procedure requires precise knowledge of the anatomy of the bony vestibular labyrinth and other structures in the temporal bone that are medial to the tympanic and mastoid portions of the facial nerve. The neurotologic surgeon who is familiar with transtemporal surgical approaches generally is very proficient operating in this region and can be expected to safely accomplish a complete labyrinthectomy by way of a transmastoid approach. Those surgeons who are less familiar with the anatomy of the temporal bone medial to the facial nerve

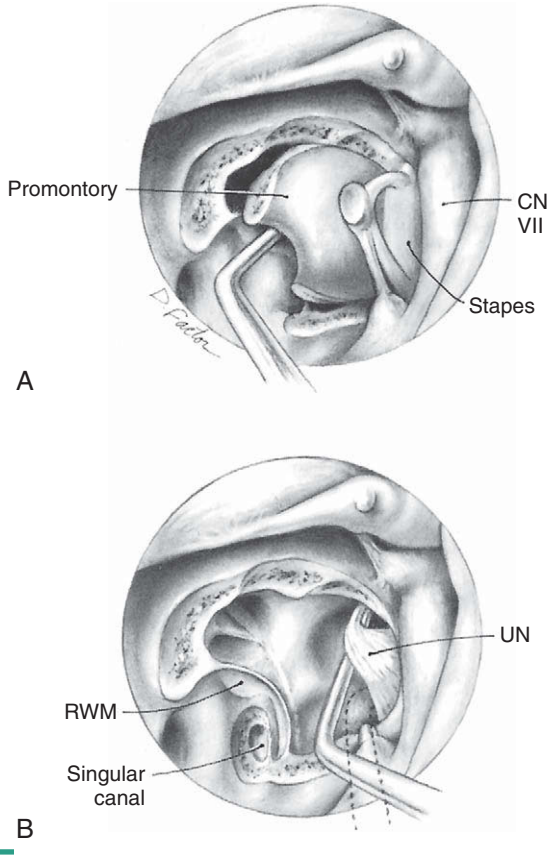

Figure 167-6. Transcanal labyrinthectomy. **A,** Removal of promontory bone and stapes provides wide exposure of vestibule. **B,** Right-angle hook is used to extract utricular neuroepithelium (UN) from the elliptical recess on the roof of the vestibule. Singular canal has been opened and the nerve to the posterior canal ampulla divided. CN VII, seventh cranial nerve; RWM, round window membrane.

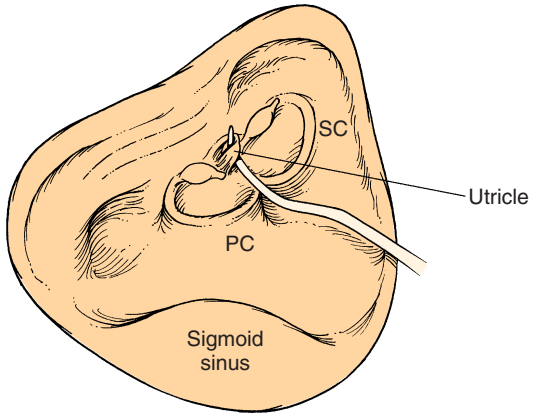

Figure 167-7. Transmastoid labyrinthectomy (left ear). Exposure of the ampullated ends of all three semicircular canals and the vestibule is accomplished, and all neuroepithelium is removed under direct vision. Care is taken to skeletonize but not expose the facial nerve. PC, posterior semicircular canal; SC, superior semicircular canal.

should familiarize themselves with this approach in the temporal bone laboratory before undertaking this procedure in the clinical setting.

The procedure begins with a cortical mastoidectomy performed through a postauricular approach. After the central mastoid air cell tract and the antrum are identified, the cavity should be widely beveled to improve exposure. Special attention should be paid to beveling the bone over the middle fossa dura and the sinodural angle; otherwise, the angle of visualization medial to the facial nerve may not be adequate to allow safe opening of the vestibule and the posterior canal ampulla. Rarely, a limited decompression of the middle fossa dura or the sigmoid sinus is required in a poorly pneumatized mastoid. After the mastoidectomy is completed, the dome of the horizontal semicircular canal is visible at the depth of the antrum. The largest burr or coarse diamond drill bit that will fit safely between the middle fossa dura and the dome of the horizontal canal (usually 4 mm) should be selected. Proper use of continuous suction-irrigation allows the surgeon to prevent injury to soft tissue structures that limit the margins of dissection, such as dura, the superior petrosal sinus, and the facial nerve. Drilling of the labyrinth should commence by deepening the "solid angle" between the three bony semicircular canals before the lumen of any canal is opened. The surgeon will then sequentially open the lumen of the bony semicircular canals, bivalving the internal surface of each canal toward the center of an ever deeper and wider bony cup that is developed as labyrinthine bone is removed.

Generally, the horizontal canal lumen is opened first and used as a landmark to protect the tympanic segment of the facial nerve. The equator of the rotating drill bit should never be allowed to come lateral to the inferior lip of the bony cup, because this would cause the drill to slip into the facial nerve. It is especially dangerous when a right-handed surgeon is operating in the right ear with the drill rotating clockwise. Some surgeons elect to reverse the direction of drill rotation for this part of the procedure in the right ear, to allow better control of the drill. After the horizontal canal lumen is identified, it is followed posteriorly toward the nonampullated end until the dome of the posterior canal is opened. This canal is then followed to the common crus, where the superior canal lumen can also be identified. By progressively deepening and widening the bony cup, it is possible to follow the superior canal toward its ampullated end. During this portion of the dissection, minor bleeding from the subarcuate artery is to be expected. Although this may be a nuisance, it is best to press ahead and completely open the arch of the superior canal and then control the vessel once in an definitive fashion, rather than stopping to address the bleeding several times.

The superior canal ampulla is adjacent to the horizontal canal ampulla, which is opened next. To approach the ampullated end of the posterior semicircular canal, the nonampullated end of the horizontal canal will have to be progressively transgressed until the posterior portion of the vestibule is open. The surgeon should stay within the cup and follow the internal surface of the posterior canal lumen as it passes medial to the second genu of the facial nerve. Care should be taken to avoid injury to the medial surface of the nerve by undercutting it with the drill. To prevent this injury, the surgeon should bevel the cup laterally over the second genu of the nerve and not allow an overhang of bone to develop that may potentially obscure visualization. It is safe and perhaps even desirable to carefully identify the nerve sheath through a thin layer of intact bone, a technique known as "skeletonizing" the nerve. This allows the surgeon to visualize and securely verify the position of the nerve. Whenever the nerve is being skeletonized, it is important to use a gentle polishing drill motion that parallels the direction of the nerve, along with copious irrigation so that the nerve can be seen through the bone before the sheath is exposed or injured. A smaller drill (usually 3 mm) is required to work safely between the skeletonized facial nerve and the posterior fossa dura. After the posterior canal ampulla has been opened, bone can be removed over the vestibule by connecting the three ampullated ends. Then sufficient access has been achieved so that all elements of the membranous labyrinth may be removed, including the cupula of each semicircular canal, the utricle, and the saccule. Care should be taken not to perforate the thin bone at the lateral end of the internal auditory canal during removal of neuroepithelium.

Disadvantages of labyrinthectomy include complete ipsilateral loss of hearing and a period of postoperative vertigo. Nystagmus usually is brisk and may persist for several days. Generally, the patient walks unassisted by the second or third postoperative day. Although vestibu-

lar compensation is mostly complete by 2 months postoperatively, further gradual improvement over 12 to 18 months may be anticipated. In some patients, significant dysequilibrium persists. Rare complications of labyrinthectomy that should be discussed with patients include facial nerve injury, cerebrospinal fluid leak, and disabling chronic dysequilibrium. In experienced hands, the overall occurrence of surgical complications is infrequent. Because the operation should not violate the dura of the posterior cranial fossa or the internal auditory canal, the risk of meningitis or cerebrospinal fluid leak is slight.

Vestibular Nerve Section

Success rates for control of vertigo by all approaches to the vestibular nerve ranges from 80% to 95%, notably poorer than with labyrinthectomy. In most cases, a vestibular nerve section procedure is selected in an effort to relieve episodic vertigo without sacrificing the patient's residual hearing. However, a complete discussion of the subject must at least mention two rarely used approaches for vestibular nerve section that, like labyrinthectomy, do sacrifice residual auditory function. These are the translabyrinthine vestibular neurectomy[70] (Fig. 167-8) and the transcochlear cochleovestibular neurectomy[71] (Fig. 167-9). Each of these operations supplements one of the two common labyrinthectomy procedures by adding an intradural dissection of the eighth cranial nerve within the internal auditory canal. The rationale used to justify adding a vestibular neurectomy after the labyrinthectomy has been completed is to accomplish division of the vestibular nerve medial to Scarpa's ganglion in the internal auditory canal. In the translabyrinthine vestibular neurectomy, a transmastoid labyrinthectomy is completed, and the internal auditory canal dura is then identified and opened, exposing the neural contents of the canal. Both the superior and inferior divisions of the vestibular nerve may then be avulsed from the lateral end of the canal and sectioned medial to the ganglion. Similarly, the transcochlear cochleovestibular neurectomy extends the transcanal labyrinthectomy to open the cochlea and the distal end of the internal auditory canal to section the cochlear nerve along with the vestibular nerve. The cochlear neurectomy is added in an effort to decrease tinnitus after the procedure. This approach currently has few adherents, because most reports of cochlear nerve section for tinnitus have shown a dismal success rate, thus failing to justify the additional risk associated with opening the internal auditory canal.

The rationale for these two extensions of labyrinthectomy procedures is dubious because of the excellent results obtained with transmastoid labyrinthectomy alone,[72] especially in view of the increased risk of cerebrospinal fluid leak and meningitis associated with intradural dissection.

Most often, vestibular nerve section is performed in an effort to eliminate disordered vestibular function while preserving useful hearing in the symptomatic ear. In this setting, selective section of the vestibular nerve is the primary goal, with intent to preserve the labyrinth, auditory nerve fibers, and cochlear blood supply. The best surgical approach for selective vestibular nerve section remains a controversial issue. The three conventional approaches that are used are the middle fossa approach, the retrolabyrinthine approach, and the retrosigmoid approach.

The middle fossa approach, popularized in the 1970s by Fisch[73] and Glasscock,[74] is the most technically demanding. It permits the most definitive section of the vestibular fibers by specifically identifying the superior and inferior vestibular nerves within the lateral portion of the internal auditory canal. In this location, they have separated anatomically from the auditory fibers of the eighth nerve (Fig. 167-10). Although this approach provides a better opportunity to avoid injury to the cochlear nerve fibers, it carries a risk for injury to the cochlear blood supply, because the labyrinthine artery ramifies in the distal portion of the internal auditory canal, in close proximity to the inferior vestibular nerve. If the surgeon elects to avoid this risk by choosing not to transect the inferior vestibular nerve, episodic vertigo may persist. In addition, this operation involves the highest rate of injury to the facial nerve among conventional approaches for vestibular neurectomy (with temporary paresis rates as high as 33%) and a significantly higher rate than in labyrinthectomy.[75,76]

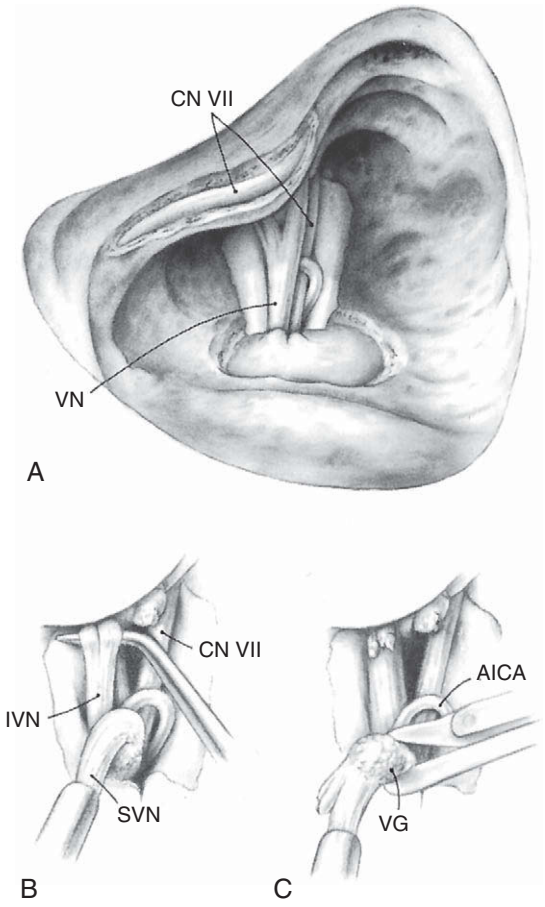

Figure 167-8. Translabyrinthine vestibular nerve transection. **A,** Nerves of internal auditory canal are exposed. **B,** Traction on the transected end of the superior division of the vestibular nerve (SVN) permits exposure of the inferior division of the vestibular nerve (IVN). **C,** Transection of the nerve trunk proximal to the vestibular ganglion (VG) completes excision of vestibular neurons. Anterior inferior cerebellar artery (AICA) is occasionally visualized. CN VII, seventh cranial nerve; VN, vestibular nerve.

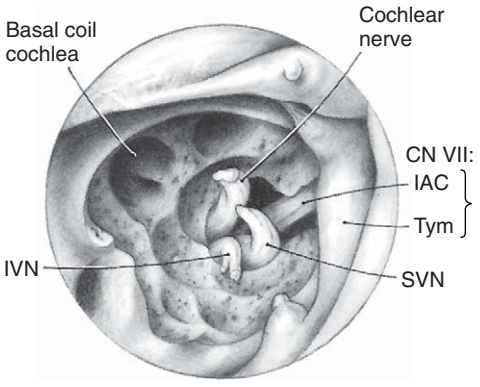

Figure 167-9. Transcochlear vestibular nerve transection. Medial wall of vestibule and lateral cochlear wall are removed to expose distal end of internal auditory canal (IAC). Cochlear and vestibular nerve branches are transected at their distal ends. SVN and IVN, superior and inferior divisions, respectively, of the vestibular nerve; Tym, tympanic segment of cranial nerve VII (CN VII).

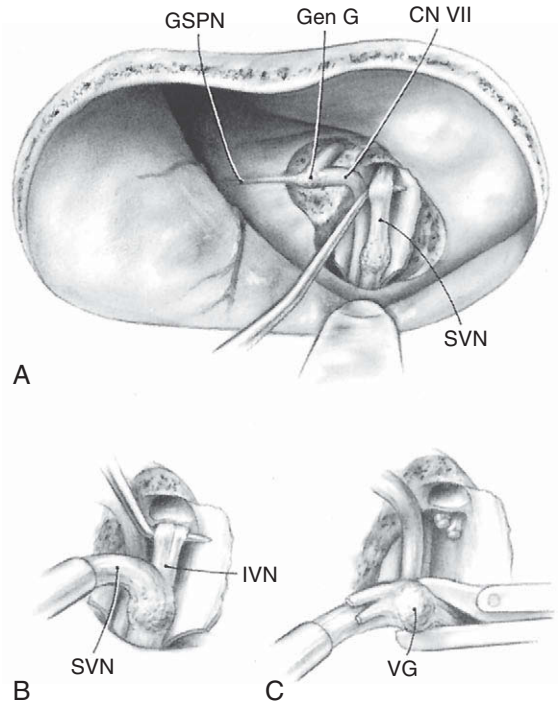

Figure 167-10. Selective transection of vestibular nerve (middle fossa approach). **A,** Vestibular and facial nerves are exposed in the superior compartment of the internal auditory canal. The superior division of the vestibular nerve (SVN) is avulsed distally with a right-angle hook. Gen G, geniculate ganglion; GSPN, greater superficial petrosal nerve. **B,** Traction on the distal end of the SVN with a suction tip permits exposure of the inferior division of the vestibular nerve (IVN). **C,** After lateral transection of the IVN, the vestibular nerve trunk is transected proximal to the vestibular ganglion (VG).

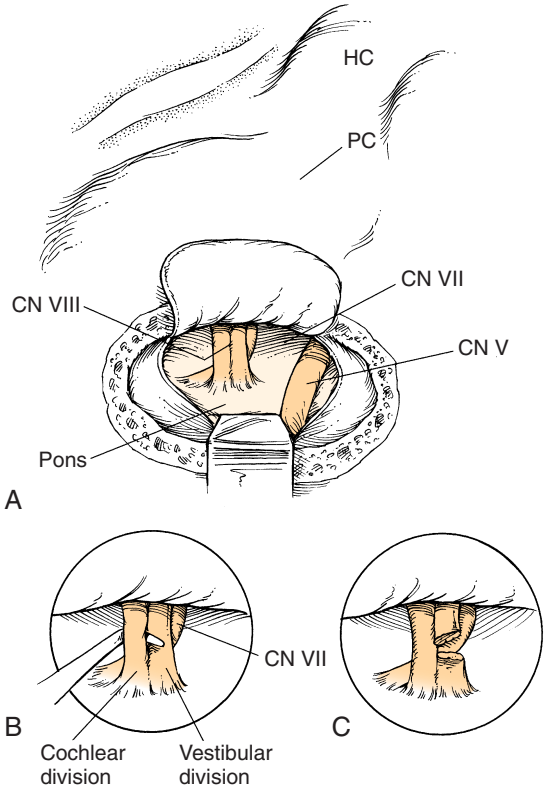

Figure 167-11. Retrolabyrinthine vestibular nerve transection. **A,** After a flap of posterior fossa dura including endolymphatic sac has been elevated, the retractor exposes the seventh and eighth cranial nerves (CN VII, CN VIII). **B,** Vestibular nerve fibers are separated from the cochlear nerve with sharp and blunt instruments. **C,** The vestibular nerve is transected. CN V, trigeminal nerve; HC, horizontal semicircular canal; PC, posterior semicircular canal.

With the middle fossa approach, the operation begins with a temporal craniotomy centered above the external auditory canal. The middle fossa dura is elevated from the surface of the temporal bone, and the temporal lobe is retracted extradurally with a specially designed retractor. Then the contents of the internal auditory canal are skeletonized, with care taken not to injure the cochlea, the superior semicircular canal, or the labyrinthine portion of the facial nerve. An effort should be made to dissect almost 180 degrees around the internal canal, so that its contents will be easily visible after the dura is opened (see Fig. 167-10A). It is not necessary to completely expose the labyrinthine segment of the facial nerve, although confirming its location will help with orientation. With continuous intraoperative monitoring of the facial nerve and auditory evoked potentials, the dura is incised, and the facial nerve is positively identified within the internal canal by electrical stimulation. The superior vestibular nerve then may be avulsed from its lateral attachments and sectioned (see Fig. 167-10B). The same procedure is repeated with the inferior division of the vestibular nerve, with care taken to avoid the cochlear blood supply and adjacent fibers of the auditory nerve that are traveling to the basal turn of the cochlea (see Fig. 167-10).

In the 1980s, several otologists reported series of retrolabyrinthine vestibular nerve section procedures, establishing this as a reliable approach with a lower incidence of hearing loss and facial nerve injury.[77-79] The retrolabyrinthine approach is also technically simpler than the middle fossa operation. The primary drawback is that the eighth cranial nerve (cranial nerve VIII) is exposed only in the cerebellopontine angle, between the porus acousticus and the brainstem, where it may be difficult to reliably separate auditory fibers from the vestibular fibers. The surgical view of cranial nerve VIII that is afforded by the retrolabyrinthine approach (Fig. 167-11) is somewhat constricted, particularly if the surgeon is not careful to follow several technical points designed to maximize exposure through the temporal bone.

The retrolabyrinthine exposure requires wide decompression of the posterior fossa dura both anterior and posterior to the sigmoid sinus. The dura should be exposed for approximately 1.5 cm posterior to the sinus to allow easy retraction. The bone anterior to the sinus then is removed until the bony labyrinth is outlined and until the entire endolymphatic sac area is exposed. The jugular bulb is the inferior limit of dissection. Because inferior bone removal is critical to satisfactory intracranial exposure, the surgeon should make every effort to open the retrofacial air cell tract and expose the sac until the jugular bulb is skeletonized. Care should be taken to prevent entry of bone dust into the middle ear while drilling, because this may lead to delayed fixation of the ossicular chain. The dura and the endolymphatic sac then are incised, and a flap of dura is retracted forward, exposing the posterior fossa. The cerebellum is gently retracted, and the cerebrospinal fluid of the cerebellopontine angle cistern is released by incising the arachnoid membrane. The trigeminal nerve and the tentorium cerebelli are identified superiorly for orientation. The eighth nerve complex then is identified inferiorly. Because the angle of vision is parallel to the posterior face of the petrous bone, the porus acousticus is not visible. If the inferior bony exposure is exceptionally good, the small multiple fibers of the intracranial portions of cranial nerves IX and X may be visible. Often, the flocculus of the cerebellum must be retracted to improve visualization of the eighth nerve. The facial nerve should be positively identified by electrical stimulation, which usually requires

minor retraction of the eighth nerve. The superior (caudal) half of the eighth nerve complex contains the vestibular fibers, which should be divided from the inferior portion and then sharply sectioned. Ideally, the vestibular component is completely divided without injury to the nervus intermedius or facial nerve. The dura then is approximated, and the closure is augmented with a piece of temporalis fascia. The aditus ad antrum is blocked with an additional piece of fascia, and the mastoid defect is filled with an abdominal fat graft. It is best to place a small bone chip harvested during the mastoidectomy between the mastoid contents and the ossicle heads to prevent prolapse of the graft material into the middle ear.

A disadvantage of the retrolabyrinthine approach is uncertainty about the plane between the cochlear and vestibular nerve bundles. Thus, this approach is associated with a risk for incomplete vestibular neurectomy and some chance that auditory neurons may be inadvertently divided. Nevertheless, use of this approach is satisfactory if the hearing results are equivalent to those reported with other methods. A slightly higher risk of cerebrospinal fluid leak has been attributed to the difficulty of reliably closing the posterior fossa dura anterior to the sigmoid sinus.

In the 1930s, two neurosurgeons, Dandy[80] and McKenzie,[81] each reported a series of cranial nerve VIII section procedures for vertigo using a lateral suboccipital craniotomy approach. Long-term follow-up evaluation of Dandy's suboccipital vestibular nerve section procedures demonstrated a 90% rate of complete relief of vertigo.[82] This approach, now commonly called the retrosigmoid approach, allows for selective sectioning of the vestibular nerve in roughly the same location encountered in the retrolabyrinthine approach. Many neurotologists prefer this approach today, because no temporal bone dissection is required to expose the eighth nerve complex, improving the speed and perhaps the safety of the procedure. In addition, because a watertight closure of the retrosigmoid dura usually can be accomplished, the incidence of cerebrospinal fluid leak presumably will be lower. Disadvantages include poorer proximity to the nerve from the depth of the wound, the need for increased intradural retraction of the cerebellum, and a significant incidence of troublesome postoperative headaches. The headache problem may be ameliorated to some degree by avoiding intradural drilling, constraining the spread of bone dust in the subarachnoid space, and making efforts to prevent postoperative attachment of the deep skull base musculature to the exposed retrosigmoid dura.

One group of neurotologic surgeons reported a modification of the retrosigmoid approach in which 60 to 90 mL of cerebrospinal fluid is removed by means of a lumbar drain to decompress the posterior fossa before the operation.[83] They were then able to perform the procedure by use of a 2-cm craniotomy and reported a short operative time, no cerebrospinal fluid leaks, and a very low incidence of postoperative headache. Some surgeons prefer the retrosigmoid approach or even a combined retrolabyrinthine-retrosigmoid approach, because these provide the opportunity to remove bone behind the internal auditory canal to better distinguish between the auditory and vestibular fibers, providing a more reliable ablation of vestibular function.[84,85]

The infralabyrinthine approach[86] for vestibular nerve section is rarely used. As the name implies, the surgeon approaches the internal auditory canal by outlining the posterior semicircular canal and working through the retrofacial air cell tract inferior to the intact bony labyrinth. This approach offers the theoretical advantages of a highly selective vestibular nerve section, facial nerve safety, and a rather limited intradural dissection confined to the distal portion of the internal auditory canal. Of note, however, this technically demanding exposure can be accomplished only in extensively pneumatized temporal bones. It also requires substantial dural decompression and sigmoid sinus retraction inferiorly, where the sinus wall may be less durable.

Although intracranial approaches for the control of vertigo all are associated with the potential for catastrophic complications, the overall complication rate is low. Stroke, subdural hematoma, facial nerve paralysis, meningitis, and wound infection have been reported. Postoperative facial nerve paralysis is infrequent, especially with posterior fossa approaches. In most series, the incidence of sensorineural hearing loss is less than 10%. Vestibular nerve section should not be expected to eliminate the auditory symptoms of ongoing endolymphatic hydrops. The addition of a concurrent endolymphatic sac decompression procedure does not appear to increase the chance of a good hearing outcome after vestibular neurectomy.[87] After vestibular nerve section, most patients return to their usual activities within 2 to 4 months. Rates of control of vertigo by all approaches to the vestibular nerve range from 80% to 95%—notably poorer than with labyrinthectomy. In cases in which a neurectomy in the posterior fossa has failed to relieve the vertigo, a middle fossa approach may theoretically be used to accomplish a more selective vestibular neurectomy in the lateral portion of the internal auditory canal. One study reported only a 55% success rate in this setting, which again emphasizes the priority of differentiating disordered residual cranial nerve VIII function from inadequate compensation.[88]

Postoperative Vestibular Compensation

After any ablative vestibular procedure, there is always a requisite period of vestibular compensation. In counseling preoperative patients, an important point is that vestibular compensation is variable and somewhat unpredictable. Not all patients will compensate fully for the loss of unilateral vestibular function, and up to 30% may be left with considerable chronic dysequilibrium or motion-provoked vertigo. The phenomenon of incomplete or delayed postoperative compensation explains many of the unsatisfactory outcomes after vestibular surgery. One study documented that although most post-labyrinthectomy patients are relieved of vertigo, only 50% return to work.[89] This suggests that functional recovery is more complex than simply achieving relief of vertigo spells. It has long been the impression of some surgeons that recovery from vestibular nerve section is more protracted and more frequently incomplete than after labyrinthectomy.[75] One study showed that post-neurectomy patients had a higher incidence of prolonged postoperative ataxia (11%) than that experienced by post-labyrinthectomy patients (2%), as well as a longer delay of return to work.[75] Eisenman and colleagues[63] compared long-term compensation 3 to 10 years after these two operations in patients who had satisfactory relief of their episodic vertigo symptoms. No differences were found between the groups in self-assessment of balance abilities or functional balance performance. Both groups showed evidence of incomplete physiologic compensation in a majority of subjects, suggesting that recovery of vestibular function after seemingly successful ablative surgery is not as comprehensive as was previously believed.

The routine use of vestibular exercises may help to optimize balance function after any operation that results in unilateral loss of labyrinthine function. It is appropriate for the rehabilitation therapist to offer counseling and instruction in a generic exercise program to all postoperative patients, and any patients who demonstrate poor progress toward recovery should be promptly referred for a customized program of therapy. Persons at particular risk for poor recovery include patients with additional sensory deficits or other complicating neurologic conditions, those using centrally sedating medications, and any who may have a poor psychological motivation for recovery. Such patients should be encouraged to pursue a customized program of vestibular rehabilitation early in the postoperative course.

If a relapse of vestibular symptoms occurs beyond the acute phase of recovery, it may be difficult to distinguish among disease progression, involvement of the contralateral ear, and central decompensation. The phenomenon of decompensation may occur after an initially satisfactory recovery from any peripheral lesion, including vestibular surgery. Early failures after labyrinthectomy are best attributed to incorrect diagnosis, incomplete surgical removal of the neuroepithelium, or inadequate initial vestibular compensation. Late failures may be a result of central decompensation, which should respond briskly to vestibular rehabilitation.[54] Failures after vestibular nerve section may be caused by an incomplete division of the vestibular fibers. A labyrinthectomy or a revision procedure to complete the neurectomy may be required in this setting. However, a therapeutic trial of vestibular rehabilitation is always appropriate before additional surgery is considered if decompensation or incomplete compensation is a possibility.

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CHAPTER ONE HUNDRED AND SIXTY-EIGHT

Vestibular and Balance Rehabilitation: Program Essentials

Neil T. Shepard

Steven A. Telian

Audrey B. Erman

Key Points

- Vestibular compensation is the normal physiologic response of a healthy central nervous system to vestibular pathology.
- In many patients with chronic imbalance and dizziness, the symptom complex is a result of incomplete compensation after a vestibular insult.
- The compensation process hinges on the neurologic phenomenon of adaptive plasticity, with reorganization of perceptual and motor output responses to altered sensory inputs.
- Patients who avoid the inciting movements that provoke sensorimotor conflicts or continually use vestibular suppressant medications are at particular risk for delayed or incomplete compensation.
- Confounding central neurologic disease or an unstable peripheral lesion also can lead to ongoing symptoms.
- Individualized vestibular rehabilitation programs constitute a safe and effective treatment option for a large percentage of patients with complaints of imbalance and dizziness.
- Referrals are based on symptomatic complaints, rather than specific etiologic diagnoses or test results.
- Benign paroxysmal positional vertigo (BPPV) is an inner ear disorder that is particularly responsive to physical therapy interventions.

Vestibular exercises were first described in the early 1940s by Drs. Cooksey and Cawthorne for the treatment of surgically induced vestibulopathies. Their simple eye, head, and body movements assist in habituation and are still in use today. Modern vestibular and balance rehabilitation therapy (VBRT) programs have evolved into multidisciplinary efforts in which physicians and therapists collaborate in a team approach, frequently in association with sophisticated vestibular testing facilities. A sufficient number of prospective, controlled studies have now been conducted to demonstrate both the efficacy and cost-effectiveness of vestibular rehabilitation.[1] Accordingly, this treatment has become widely available and is the primary management technique for a large proportion of patients with complaints of imbalance and dizziness.

The two overall goals in a VBRT program are (1) to advance the central vestibular compensation process (Fig. 168-1), resulting in reduction in symptoms under static and dynamic conditions, and improvement in the function of the vestibulo-ocular reflex (VOR); and (2) improvement in the functionality of static and dynamic balance and gait. This second goal can be a process that is achievable independent of complete central compensation.

To accomplish these goals, a variety of different exercise techniques may be used. Each has specific subgoals within the overall structure of a VBRT program. Not all available techniques are used with every patient. The various techniques and their goals are as follows:

- *Adaptation exercises*: to improve the functional performance of the VOR[2-4] (Fig. 168-2).
- *Habituation exercises*: to reduce or eliminate dysphoric responses to a specific stimulus by repeated exposure to a sensory conflict situation.[5,6]
- *Sensory substitution exercises*: to allow for the use of alternative sensory inputs or central nervous system preprogramming and motor output paths in the acquisition of control for gaze stabilization during head movements, and for postural and gait control.[7-11]
- *Balance exercises*: improved performance in both static and dynamic postural control. Practice of tai chi or similar activities may be an effective adjunct in this setting, especially for patients with complaints of continuous imbalance when standing.

- *Gait exercises*: improvement in ambulation by use of both short and long courses. As the patient progresses in the program, these gait activities are combined with habituation and adaptation exercises through the use of head rotations during walking.

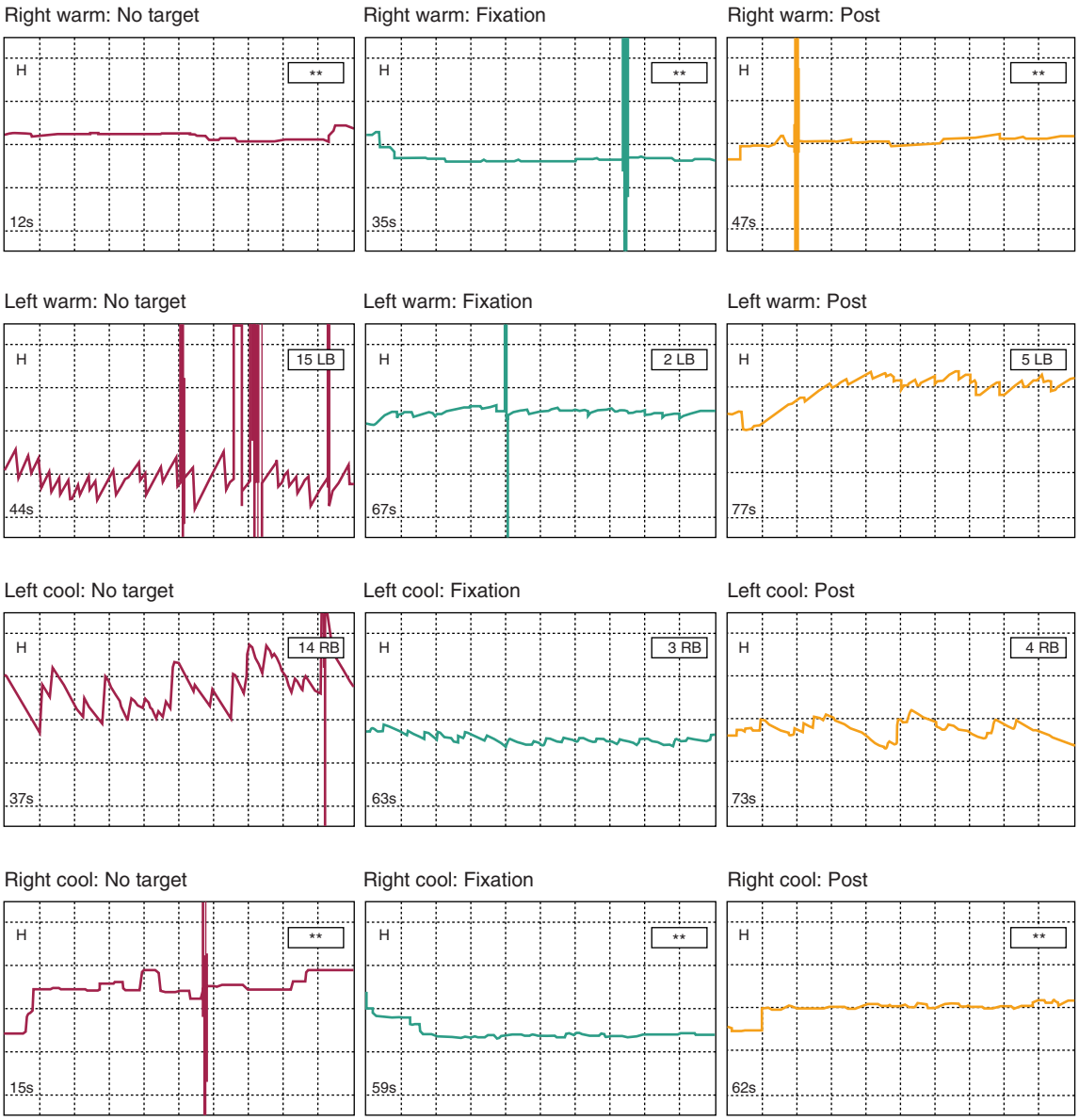
- *General conditioning*: to achieve lifestyle changes to increase activity and fitness.

- *Maintenance program*: to allow for continued exercise activity without the rigor of a formal program, yet to maintain the accomplishments achieved during the active treatment phase. This is especially important in certain central nervous system disorders.[12]

These elements form the basis for the programs discussed in this chapter. A full, in-depth discussion of all of the aspects of a VBRT program is available in Herdman's definitive work on vestibular rehabilitation.[13]

Physiologic Rationale for Vestibular and Balance Rehabilitation

A unique feature of the central nervous system is its ability to adjust to asymmetries in peripheral vestibular inputs and, to a lesser degree, to fix insults within the central vestibular pathways.[14] This adjustment process is referred to as vestibular compensation and occurs naturally after most vestibular insults, provided that the affected person resumes an active lifestyle. Such adaptive plasticity requires active neuronal changes in the cerebellum and the brainstem nuclei in response to the sensory conflicts produced by central or peripheral vestibular pathology. In most instances, this process will reliably relieve vestibular symptoms, provided that the lesion is either stable or producing only gradual progressive deterioration. The underlying physiologic components of this process are the foundations of vestibular and balance rehabilitation. At least four distinct components of vestibular compensation are recognized: *static compensation*, which occurs regardless of movement,



A

Figure 168-1. Videonystagmography test results from a patient with uncompensated right unilateral vestibular system hypofunction. **A,** Results of bithermal alternating open loop water irrigations. The *left column* shows the maximum nystagmus response to right warm, left warm, left cool, and right cool irrigations. The *center column* shows the suppression of nystagmus with a fixation target, and the *right column* shows return of nystagmus after ("post") suppression.

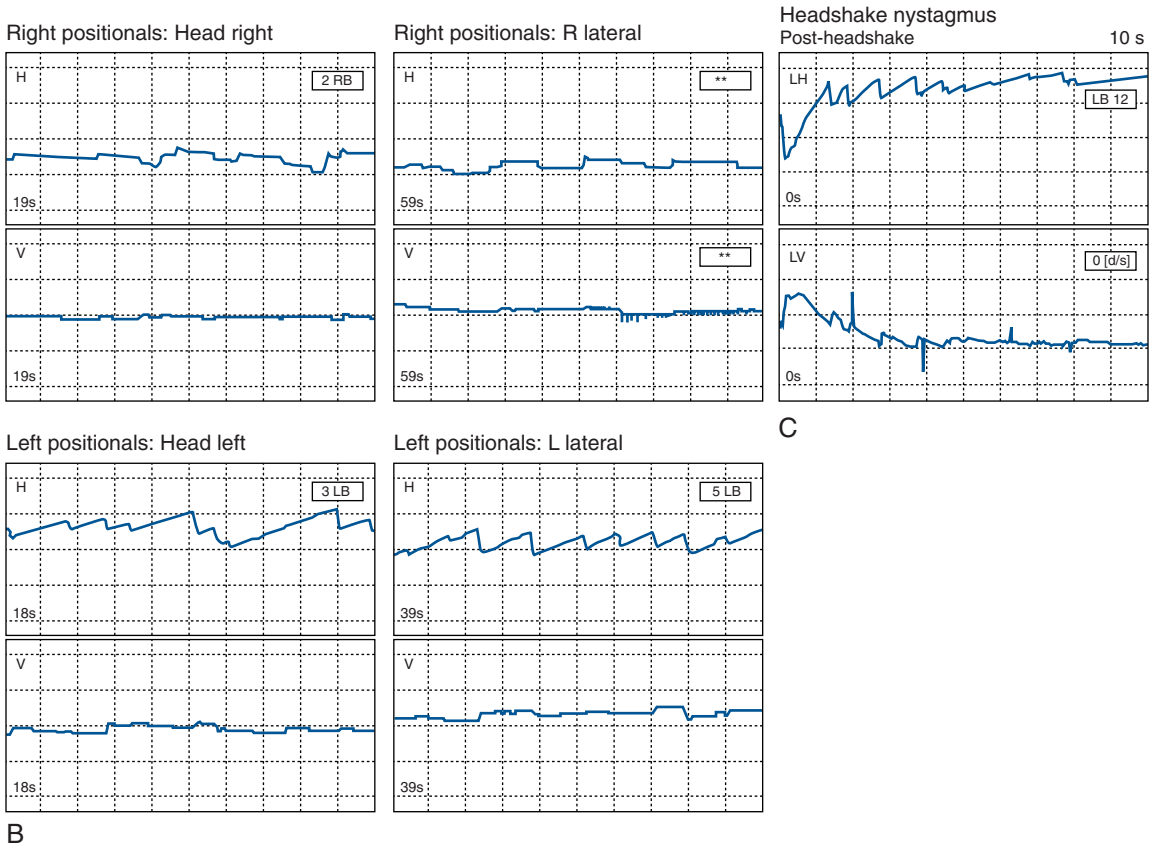


Figure 168-1. **B,** Results from positional testing. In the *top row*, the eye movement recordings for horizontal are shown in the *top box*, with vertical eye movements shown in the *lower box*, from positions of head turn right from supine and right lateral positions. In the *lower row*, the eye movement recordings are shown for the positions of head turn left and left lateral. Left-beating nystagmus ranging from 3 to 5 degrees/second slow-component eye velocity is noted, with no significant nystagmus in the head right and right lateral positions (not shown are three additional positions, also with left-beating nystagmus). **C,** Result of the post-headshake nystagmus test. The *top box* shows the significant left-beating nystagmus that resulted from horizontal headshaking. Minor up-beating nystagmus is seen in the *lower box*.

and three dynamic compensatory processes, *adaptation*, *habituation*, and *sensory substitution*, each of which is promoted by various exercise techniques targeted in VBFT.

Static Compensation for Peripheral Vestibular Lesions

Vertigo of acute onset is accompanied by nystagmus and a variety of neurovegetative symptoms, such as nausea and vomiting. This symptom complex is a result of a persistent asymmetry of vestibular input, often seen after ablative surgical procedures or with acute insults to the peripheral system. The acute or static phase of recovery is mediated by tonic rebalancing of the resting activity in the vestibular nuclei. These changes minimize side-to-side discrepancies between the tonic firing rates in the second-order neurons originating in the nuclei and occur without the need of head movement or vision.[14-18] This activity generally provides relief from the most intense symptoms of vertigo and vomiting within 24 to 72 hours. Nevertheless, the patient continues to experience considerable dysequilibrium, because the system is unable to respond appropriately to the dynamic aspects of vestibular input produced by normal head movements. Thus, even after the intense vertigo has been controlled, continued motion-provoked vertigo is common until dynamic compensation is achieved.

Dynamic Compensation

To eliminate persisting dysequilibrium and residual motion-provoked vertigo after a vestibular lesion, the system must adjust to produce accurate responses to head movements. The dynamic compensation phase seems to be accomplished by reorganization of brainstem and cerebellar pathways, without modulating the neural input to the vestibular nuclei from the peripheral system.[14] This process is much slower than static compensation and typically requires reprogramming of eye movements and postural control responses to head movements. The necessary reprogramming is accomplished by exposure to stimuli that challenge both the gaze stabilization and postural control systems. Because of the brainstem commissural pathways connecting the vestibular nuclei, appropriate central vestibular responses can be produced from inputs arriving from one functioning labyrinth. This feature of the compensation process is critical to recovery after extensive pathologic insults or ablative vestibular surgery, such as labyrinthectomy or vestibular nerve section. As discussed next, three major areas are active in the process of dynamic compensation: adaptation, habituation, and sensory substitution.

Adaptation is the neurologic mechanism that allows for long-term changes in the neuronal response to head movement-provoked gaze stabilization. The neural signals that induce the adaptation are generated primarily by "retinal slip" of the visual image on the retina. This phenomenon is generated by a disordered VOR response, when a head movement produces a perceived motion of a stable object in the visual environment. The resulting error signal can lead to fairly prompt and long-term changes in the functional performance of the VOR.[4] This process of adaptation produced by retinal slip seems to be context-dependent, so that specific adjustments must be made for movements of different frequency, directions of head movement, eye position in the orbit, and distances from the visual target.[3,19] The complexity of the adaptation process helps explain why residual symptoms are almost unavoidable even in a fairly well-compensated patient. Postural stability also is improved by reducing abnormal visual influences on postural control mechanisms secondary to retinal slip.

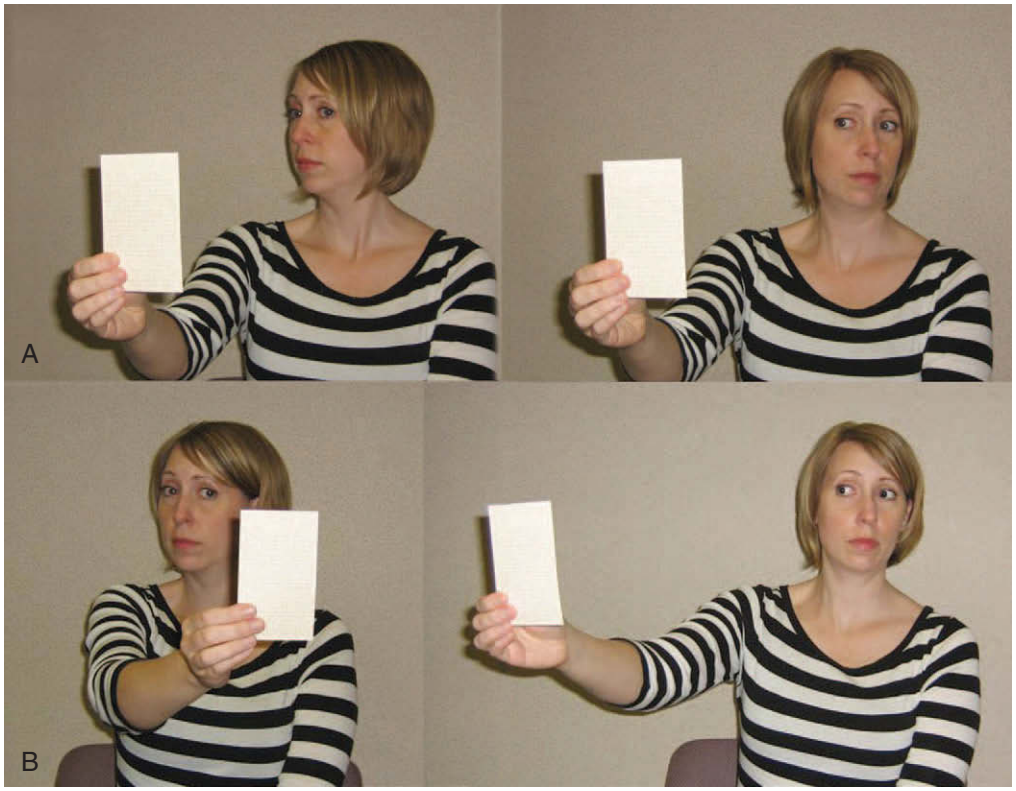


Figure 168-2. Adaptation exercises given to the patient whose videonystagmography results are shown in Figure 168-1. **A,** The "times 1" adaptation exercise. In the times 1 viewing, the target is held still and the patient focuses on a letter on the card and oscillates her head in a small arc in the horizontal plane as fast as she can while maintaining clear visual imaging of the target. **B,** Progression to a "times 2" viewing exercise. In the times 2 viewing, the task is the same, of maintaining clear visual imaging on the letter on the card; however, this time, as the head is moved to the right, the target is moved to the left, doubling the amount the eyes have to move for the same head movement shown in **A**.

Habituation is the long-term reduction of a response to a noxious stimulus resulting from repeated exposure to the stimulus.[20] This phenomenon seems to be context-dependent and does not generalize well from one head movement to another. This mechanism is essential for a variety of conditions that can produce sensitivity to head movement or motion in the visual surroundings. Although peripheral asymmetry is one common cause of these symptoms, other common causes are central lesions, anxiety disorders, and migraine disorders.[5] Although the adjustments produced by habituation are made fairly quickly and are reasonably accurate, the central system requires consistency in the inputs to use them properly for habituation. For this reason, it is essentially impossible to "compensate" for an unstable vestibular lesion such as Meniere's disease.

The primary goals of both adaptation and habituation are to produce gaze stability and postural stability in both static and dynamic situations. The response frequency ranges for gaze and postural stability are very different. To achieve gaze stability, the responsible mechanisms must function properly in a range from static position (no motion) up to movements that correlate with head motions as quick as 10 Hz. Postural stability is predominantly a task that requires responsiveness only below 4 Hz.[21,22]

In addition to adaptation and habituation, another critical component of dynamic compensation involves *sensory substitution*. This process requires the adoption of alternate strategies for gaze and postural control, in order to replace the compromised sensory function. For example, the patient with bilateral loss of peripheral vestibular function becomes dependent primarily on visual or proprioceptive inputs to maintain postural stability. Although these mechanisms may need to be fostered in a therapeutic setting, many patients will have developed some of these out of necessity before coming for evaluation. Although sensory substitution may be helpful, it may be maladaptive in some environmental settings. For example, a patient may be overly dependent on vision and therefore cannot use proprioceptive and residual vestibular inputs to successfully navigate in darkness. In addition to the common substitution of visual and proprioceptive inputs, some of the other mechanisms that may be invoked in the setting of vestibular loss include (1) activation of the cervico-ocular reflex, which is not particularly active in healthy persons[10]; (2) use of the smooth pursuit tracking system[11]; and (3) use of anticipatory or corrective saccades. Patients with both unilateral and bilateral vestibular deficits use corrective saccades to adjust for the reduction of VOR-induced eye movements after head movement. With central preprogramming through exposure to specific eye-head coordinated movements, these eye movements can be applied automatically to help maintain gaze stability when the VOR is deficient.[7,8]

Research findings suggest that initial central vestibular compensation for a peripheral lesion can be enhanced by head movement but is delayed by inactivity.[23-26] It also is hampered by central vestibular dysfunction of any cause.[27] Medications that typically are used for acute symptoms of vertigo, such as meclizine, scopolamine, and benzodiazepines, all cause sedation and central nervous system depression. Although they may provide helpful symptomatic relief during the initial stages of an acute labyrinthine crisis, their effects are potentially counterproductive with respect to vestibular compensation, especially with use over extended periods.[24,28] In addition, chronic anxiety or other psychiatric disorders may delay or disrupt the compensation process.[29,30]

Although remarkably reliable, vestibular compensation seems to be a somewhat fragile, energy-dependent process. Even after it is apparently complete, periods of symptomatic relapse may occur because of decompensation. A period of inactivity, extreme fatigue, change in medications, general anesthesia or an intercurrent illness may trigger these relapses. A relapse of vestibular symptoms in this setting does not imply ongoing, progressive, or new labyrinthine dysfunction.

These features of vestibular compensation suggest that avoidance of movements and body positions that provoke vertigo, as well as the traditional practice of prescribing vestibular suppressants, may be inappropriate. Because the stimulus for recovery seems to be repeated exposure to the sensory conflicts produced by movement, the patient's medications should be discontinued once the acute symptoms are resolved, and an active program geared toward recovery should be encouraged. For most affected persons, recovery will be rapid and nearly complete. For some, the symptoms of vestibular dysfunction may persist. Although the latter patients are candidates for vestibular rehabilitation programs, starting a formal vestibular rehabilitation program as early as possible for patients whose symptom presentation suggests a high likelihood of benefit from such programs can help to avoid the persistence of symptoms.

Assessment of Vestibular Compensation

Role of the Clinical History

A complete neuro-otologic history probably is the single most important component of the diagnostic evaluation of the patient with a balance disorder. Balance function study results must be interpreted in light of the presenting symptoms and medical history.[31] In general, the information sought should include the onset of symptoms and their characteristics at that time, the progression of symptoms over time, the nature and duration of typical spells, any predisposing factors in the medical history, and use of medications or other management strategies. Complicating features of anxiety, depression, or excessive dependence on medications should be addressed. Some effort should be extended to identify the degree of disability produced by the patient's vestibular complaints with respect to his or her professional and social activities. The stability and commitment of the patient's psychological support system also should be assessed.

Ongoing complaints after a peripheral vestibular insult indicate that compensation is incomplete. The history and presenting symptoms are used to determine whether these continuing sensations may be a result of a fluctuating or progressive labyrinthine disorder. In the case of the unstable lesion, poor compensation results because the central nervous system cannot react to unpredictable peripheral inputs. In the history, an unstable periphery is suspected if symptoms are spontaneous in onset. In the stable cases, the symptoms are much more likely to be consistently provoked by head or eye movements. It is the patients with stable lesions who are most likely to benefit from vestibular and balance rehabilitation. The patients in the group with unstable lesions may have VBRT as part of their management, but it is not likely to be the primary modality of treatment.

Role of Vestibular Testing

The most traditional purpose of balance function studies is site-of-lesion localization addressing the sensory inputs, motor output elements, and neural pathways that may be involved in producing the reported symptoms. Balance function studies also may assess the patient's functional ability to use sensory input systems in an integrated fashion, as in maintenance of stance before and after induced sway and coordination of head and eye movements during gaze activities. The third assessment goal is to evaluate, in a limited manner, the current degree of physiologic and functional compensation.[32]

Although a wide variety of studies may be used to assess the balance system in the broadest sense, tests that are used to determine the extent and site of vestibular lesions are unable to predict the type of vestibular symptoms, the magnitude of those symptoms, or the level of disability in an individual patient. When the predictive utility of the vestibular test battery is reviewed, no significant correlation is found between test results and performance of high-level activities of daily living in the chronically dizzy patient. Thus, a therapist can and must proceed with an evaluation of these factors, irrespective of the vestibular test results.

Although specific subtests within videonystagmography (VNG), rotary chair, and postural control testing can give indications of compensation status, the value of such tests is somewhat limited. Typically, the information obtained from these studies relates more to the static phase of compensation than that of the dynamic phase. Clinically significant spontaneous nystagmus, positional nystagmus, and a directional preponderance on the VNG provide evidence for failure of physiologic compensation in the control of eye movements. Rotational chair testing stimulates the horizontal semicircular canals and their afferent inputs over a broad range of frequencies and accelerations. Although this is a physiologic rather than a functional evaluation, it provides information about the vestibulo-ocular system that is not obtained from the VNG. In general, although abnormalities in the timing (phase lead) or amplitude (gain) of the eye movements produced by the VOR provide evidence for peripheral vestibular dysfunction, these physiologic measures do not assess the level of compensation within the central system.[14] On the other hand, persistent asymmetry (bias) in the slow-phase eye velocity responses produced by rightward versus leftward rotation strongly suggests that the peripheral lesion is physiologically uncompensated.

Dynamic posturography provides information about balance system function that is not available through the other vestibular testing modalities. The sensory organization portion of dynamic posturography is primarily a test of functional capabilities, rather than a site-of-lesion evaluation. By measuring the degree of postural sway under several test conditions, this test determines whether the patient is able to make proper use of sensory inputs from the visual, vestibular, and somatosensory systems for maintaining stable stance. By identifying difficulty in the use of one or more of the input informations, a quantitative estimate of functional compensation is obtained. It is not unusual to document normal sensory organization findings in patients who report motion-provoked symptoms exclusively and show no signs of pathologic nystagmus or significant asymmetry on rotational chair testing. By contrast, some patients will demonstrate significant abnormalities of postural control, reflecting inadequate functional compensation, even when the more physiologic measures (VNG and rotational chair) suggest a reasonably complete physiologic compensation process.

The movement coordination battery of dynamic posturography may be used to assess the automatic motor output responses from the central nervous system in response to perturbations of stance. Abnormalities detected may help to explain findings in the sensory organization test, especially the somatosensory and vestibular dysfunction pattern. It also may provide indications of previously undiagnosed peripheral neuropathy or biomechanical deficits resulting from known musculoskeletal conditions.[33,34] This protocol does not provide any information about the status of compensation.

Vestibular Rehabilitation: Patient Selection Criteria

Vestibular Rehabilitation as a Primary Treatment Modality

The use of VBRT in the treatment of BPPV is well accepted. The use of noncustomized programs such as Cawthorne exercises has a long and fairly successful history for the management of this problem.[19,23,35] However, for many patients, the commonly prescribed Cawthorne program is too intensive and often provokes intense vestibular symptoms, sometimes accompanied by nausea or vomiting. This discourages the patient from continuing. A preferred noncustomized program for BPPV that addresses the needs of most patients is the Brandt-Daroff program.[23] An alternate approach for the treatment of classic BPPV caused by otoconia floating free in one of the semicircular canals (canalithiasis) is to perform an appropriate particle repositioning maneuver.[36] When these techniques are insufficient to bring relief, the patient should be referred to a vestibular therapist for a customized program.[6] For a complete discussion of BPPV and particle repositioning maneuvers, please refer to Chapters 163-165.

The use of VBRT as the primary treatment recommendation is appropriate in any condition characterized by a stable unilateral peripheral or central vestibular deficit when the patient's natural compensation process is incomplete. This is a symptom-driven indication that is determined from the patient's presenting symptoms. The report of spontaneously occurring symptoms or documented fluctuations in

hearing or vestibular function suggests an unstable lesion. If the patient's evaluation reveals no evidence of a progressive or fluctuant (unstable) process, it is likely that VBRT will produce a satisfactory resolution of symptoms. This intervention is certainly preferable to the protracted use of vestibular suppressants. In most patients with stable peripheral lesions, there is no role for the use of long-term vestibular suppressants. However, they may be useful at the outset of VBRT to reduce symptoms to a level that allows the patient to perform the prescribed exercise program.[37]

The final indication for the use of VBRT as a primary treatment modality is for disorders characterized by multifactorial balance difficulties, such as those seen in the elderly.[38] This option becomes especially important when other treatment options are unavailable or have been exhausted. These patients may benefit greatly from postural control exercises and individualized conditioning programs. Frequently, the relationship with the therapist assumes a strong counseling function, and the use of assistive devices for safety in ambulation can be introduced as needed.

Vestibular Rehabilitation as an Adjunctive Modality

Several situations may require the use of VBRT interventions as an adjunctive treatment modality. The use of routine or selective VBRT is helpful in optimizing the outcome after vestibular surgery, such as vestibular schwannoma removal, labyrinthectomy, or vestibular nerve section, and after intratympanic aminoglycoside administration for Meniere's disease. When a patient with an unstable vestibular condition undergoes an ablative procedure, a more profound, yet stable, unilateral vestibular lesion is created. The process of acute and chronic compensation must begin anew. It is possible that many of the unsatisfactory outcomes after vestibular surgery can be attributed to incomplete or delayed postoperative compensation. All patients should be instructed regarding the importance of central compensation for the success of any ablative vestibular procedure. Those individuals who are at particular risk for poor recovery because of complicating central nervous system conditions, sedating medications, or poor motivation for recovery should be encouraged to pursue a customized program of VBRT early in their postoperative course.

Vestibular rehabilitation may play a role in other conditions that include a component of balance complaints.[5,39] Frequently, patients who have had head injuries have significant disability from vestibular symptoms. Because their condition often includes cognitive and central vestibular involvement, along with the peripheral labyrinthine component, VBRT techniques are best used as a supplement to a comprehensive, multidisciplinary head injury program rather than as the primary rehabilitative measure. Similarly, patients with anxiety disorders often seek management of ill-defined vestibular symptoms. After a suitable evaluation is performed, VBRT may be recommended as an adjunctive measure for the anxiety disorder. If the anxiety is mild, VBRT functions as a behavioral intervention, similar to exposure therapy for treatment of phobias. If the anxiety component is significant, and particularly if panic attacks are frequent, psychiatric intervention will be required as well. The use of VBRT can be of assistance in situations of migraine-associated dizziness, provided that appropriate treatment for migraine is given concurrently.[5,13]

Patients with Meniere's disease may complain of positional vertigo or other chronic vestibular symptoms between their definitive attacks. Although such patients are candidates for VBRT, they need to recognize that the prognosis for lasting relief of chronic symptoms is reduced if the typical severe attacks of Meniere's disease occur more than monthly. If the attacks are rare, or the Meniere's disease is inactive, the prognosis is considerably improved.

Vestibular Rehabilitation as a Therapeutic Trial

At times, the physician may be uncertain whether a patient's complaints are due to stable vestibular disease with inadequate compensation or to an unstable labyrinthine disorder, such as perilymphatic fistula. In this setting, a trial of VBRT is appropriate if the hearing is stable and may assist in the diagnosis by clarifying this important distinction. Failure to improve in VBRT lends further credibility to the diagnostic impression that the lesion is unstable or progressive. It is then advisable to proceed with appropriate surgical management, provided that the symptoms are severe enough to warrant the procedure and they are believed to emanate from the end organ. This conservative treatment course is particularly appropriate before surgical interventions are considered for controversial diagnoses such as spontaneous perilymph fistula.[40]

It is sometimes difficult to determine whether a postoperative relapse of vestibular symptoms represents disease progression or merely central decompensation.[41] Decompensation may be observed as a late sequela after initially complete compensation for any peripheral lesion, including vestibular surgery. For example, many surgeons consider transmastoid labyrinthectomy to be a definitive procedure for the control of vertigo of peripheral origin. Thus, an explanation of why failures are reported to occur is warranted. Early failures are best attributed to incorrect diagnosis, incomplete removal of the neuroepithelium at the time of surgery, or inadequate initial central nervous system compensation. Late failures have been hypothesized to result from "post-labyrinthectomy neuromas."[42,43] Although there is little reason to expect that such lesions could produce symptoms, some surgeons would advocate performing a vestibular neurectomy in this setting. An alternate explanation for these recurrent symptoms after a complete labyrinthectomy would be late central decompensation, which should respond briskly to VBRT. Instead of proceeding to additional surgery, a therapeutic trial of VBRT is suitable whenever the possibility of incomplete compensation or decompensation remains.

Inappropriate Candidates

Patients whose symptoms occur strictly in spontaneous, discrete episodes, such as are seen with Meniere's disease, are unlikely to benefit from VBRT. If no provocative movements or body positions are found to reliably produce spells and no postural control abnormalities are noted during the evaluation, the patient is best managed with alternative medical or surgical strategies. Nonetheless, such patients should be encouraged to remain active and optimize their general health through physical activities performed at a level that is appropriate for their age and general health.

Role of Balance Function Studies in Patient Selection

It needs to be recognized that VBRT is a symptom-driven treatment program. The principal features that suggest use of VBRT for primary or adjunctive management are complaints related to motion-provoked symptoms or dysfunction with balance and gait. Is there a role for the use of balance function studies for determination of which patients would be appropriate candidates for VBRT? Do these tests play any role in the monitoring of the program's outcome?

Of the main balance function studies, *dynamic posturography* has the highest likelihood of suggesting that VBRT may be appropriate and guiding the treatment prescribed by the therapist. Some patients have a symptom presentation that does not suggest the use of therapy as a management option, yet performance on dynamic posturography shows clear deficits in maintenance of upright stance during challenging conditions. Such a patient would then be a highly appropriate candidate for VBRT to improve performance and reduce the potential for falls. Dynamic postural control evaluations in patients for whom VBRT is to be used can assist in the design and monitoring of the customized VBRT program.[19,33,37]

The VNG and rotary chair studies do not provide information that assists in deciding who is an appropriate candidate for VBRT. However, if a patient is otherwise an appropriate candidate for VBRT, these studies can be used to reinforce the use of a specific form of exercise in the therapy program. Indications of deficits in the VOR provide support for the use of adaptation exercises as a means for improving the VOR gain and, thereby, the functional performance of the VOR. Neither of these studies holds any significant utility with respect to the monitoring of the progress of a VBRT program. However, if the patient is not improving as expected, repeating portions of the VNG or rotary chair protocol may be useful in determining whether the vestibular system pathology has progressed in a way that would adversely affect the patient's progress.[44]

Table 168-1

Common Techniques for Vestibular Rehabilitation

Vestibulopathy	Rehabilitative Strategy
Acute uncompensated unilateral peripheral lesion *Example*: immediate postoperative status or recent crisis	Generic vestibular rehabilitation program to start Customized program if patient does not make satisfactory progress
Stable uncompensated unilateral peripheral lesion *Example*: previous crisis with continuous symptoms	Habituation and adaptation exercises Postural control activities if abnormalities detected during testing
Bilateral peripheral lesions	Sensory substitution with visual-vestibular interaction Postural control activities if abnormalities detected Screening for other comorbid conditions that may aggravate balance problems
BPPV	Particle repositioning maneuver Habituation exercises if repositioning fails
Vertiginous migraines Anxiety-provoked symptoms Head injury	Sensory substitution activities potentially of benefit with chronic dizziness related to vertiginous migraine Vestibular rehabilitative adjuvant treatment as part of a multidisciplinary approach

BPPV, benign paroxysmal positional vertigo.

Vestibular Rehabilitation: Common Techniques

The vestibular rehabilitation therapist uses a variety of techniques when providing a program customized to the needs of the individual patient (Table 168-1). For a complete discussion of the diagnostic and therapeutic interventions that may appropriately be performed by the therapist, the interested reader is referred to other resources for further reading.[13,45] This section of the chapter reviews several general categories of exercise techniques that are used in a customized program of VBRT.

Adaptation Exercises

The principal goal of adaptation exercises is improvement in the functional performance of the VOR and accompanying gaze stability for those who demonstrate a VOR deficit physiologically and who have predictable symptoms provoked by head movements. Evidence of a VOR deficit may include a caloric response asymmetry on VNG and/or an abnormal time constant on rotary chair testing. The functional impact of a physiologic VOR deficit is realized through the use of Dynamic Visual Acuity (DVA) testing, which assesses the ability to accurately resolve a visual target while the head is in motion.[13] The activities involve primarily eye-head coordinated movements called VOR *times 1* and *times 2* viewing exercises (see Fig. 168-2), described elsewhere.[5,13] Using eye movement recordings during the head thrust, test pilot data have been able to show an actual increase in the gain of the VOR correlating with functional improvement as reflected in the DVA in patients with unilateral hypofunction. However, the gain was more consistently increased for active (patient-initiated) head thrusts than for passive (unexpected examiner-initiated) head thrusts.[46] The implication of this work is that to appreciate an actual change in physiologic gain of the system, the task must have direct relevance to the patient. This is the first study to show a mechanistic change as a result of the vestibular rehabilitation adaptation exercises. Of interest is that even though the underlying mechanism for VOR adaptation may not as yet be well understood, the prescribed exercises do result in measurable changes in the VOR functional performance.[1,13,14]

Habituation Exercises

For most patients with positionally provoked symptoms, the primary goal is to extinguish residual pathologic responses after incomplete or disordered compensation.[47] The therapist identifies the typical movements that produce the most pronounced symptoms and provides the patient with a limited but progressive program of exercises that reproduce these movements. Typically, these are performed two to three times daily, with the duration and number of repetitions varying according to the severity of nausea or dizziness they produce. Patients are counseled that symptoms are aggravated by the exercises at first but that gradual improvement will follow. Patients often are encouraged by experiencing short-term habituation at the end of an exercise session. If they can persevere with their program, most patients will begin to note dramatic relief of positional vertigo within 4 to 6 weeks.

There is obviously significant overlap between these and the adaptation activities. Differences exist in the details of the techniques relative to speed, visual target, number of movements, and repetition. The underlying principle of habituation exercises is that of brief repeated exposures. This technique also can be used to reduce sensitivity to visual motion–provoked symptoms, although that is a more difficult task.

Substitution Exercises

As the name implies, substitution exercises teach the patient to use alternative strategies and sensory inputs to make up for those that are deficient or absent. There is clearly a limit to how much vision or proprioception can substitute for the vestibular system, or how much vestibular information can substitute for proprioception. These limits are secondary to the differences in the frequency range over which each of these inputs and the various motor and perceptual outputs function.[21,22] Notwithstanding the limitations, this technique can be successful in promoting changes in performance for both gaze stability and postural control by means of the mechanism of central preprogramming.[9,48]

Postural Control and Gait Exercises

When abnormalities of postural control are detected in the assessment, these may be specifically addressed in the prescribed exercise program. Programs can be designed to correct weight-bearing asymmetries, limited mobility about the center of gravity, and sensory input selection problems. For example, if the patient is found to depend on somatosensory input despite the availability of accurate visual cues, the program may involve exercises that require balancing on thick foam. This would be performed initially with eyes open and eventually with eyes closed.

Although working on static balance is one dimension of therapy, more complex gait activities over a short course (such as a 10- to 20-foot walk) often are prescribed and combined with other, more complex movements. These may involve specific activities such as stepping over objects or incorporating reciprocal head movements. The patient also

may be asked to practice walking on different types of surfaces such as a compressible soft carpet or an irregular gravel parking lot. These activities are designed to enhance stability in daily activities. Patients with bilateral loss of vestibular function may be instructed to perform exercises that help with sensory substitution. These may include walking in progressively more challenging, dimly lit environments to facilitate somatosensory substitution and balancing on more challenging support services to facilitate visual substitution.[13]

Conditioning and Maintenance Activities

Most patients with vertigo and balance disorders have adopted a sedentary lifestyle to avoid precipitating their symptoms. Although such a response is understandable, the inactivity contributes to their ongoing disability and delays their recovery. Thus, all patients who receive customized VBRT programs also are provided with suggestions for a general exercise program that is suited to their age, health, and interests. For most patients, this would involve at least a graduated walking program. For many, a more strenuous program is suggested that may include jogging, treadmill, aerobics, or bicycling. Activities that involve coordinated eye, head, and body movements such as golf, bowling, handball, or racquet sports may be appropriate. Swimming is approached cautiously because of the disorientation experienced by many patients with vestibular dysfunction in the relative weightlessness of the aquatic environment.

Maintenance of Initial Results

Once the patient has completed the initial period of treatment, progress is assessed and adjustments are made in the program. Exercises that no longer produce symptoms are eliminated and replaced by others that were not originally included because of lower priority. This process is continued until the improvements begin to plateau. When this point is reached, it is important to provide the patient with counseling and a program of maintenance exercises to secure the benefits gained from the active treatment program. The maintenance program typically includes continuing the prescribed conditioning exercises, as well as any unique postural control activities that were required. The patient is instructed to resume exercises if a relapse of symptoms should occur. For central nervous system lesions involving the cerebellum, indications are that the active program needs to be continued indefinitely to maintain benefits.[12]

Role of Therapist in Patient Education

A key role of the therapist in the management of the patient with a balance disorder is to educate the patient about the illness.[12] The patient often has acquired considerable misinformation that must be addressed. This supportive function of the therapist is particularly essential for the management of patients with a less favorable prognosis. A patient who is well educated regarding the nature of vestibular or balance dysfunction will understand the rationale for vestibular rehabilitation. The patient will recognize that these measures are simply a management technique instead of a cure for the underlying deficits. This orientation takes the patient from a passive role toward an active role in his or her own recovery.

Vestibular Rehabilitation: Expected Results

A 2-year prospective clinical trial including all patients undergoing VBRT at the University of Michigan suggested that a reduction of symptoms can be expected in approximately 85% of cases. In this trial, 80% of patients also showed improved scores on a disability rating scale after therapy.[37] A subsequent randomized controlled clinical trial provided evidence that VBRT programs customized to the unique needs of the individual patient provided results that are superior to those obtained with generic programs of therapy.[49] A recent review from the Cochrane collaboration evaluated 21 randomized trials of vestibular rehabilitation for unilateral peripheral vestibular dysfunction. Overall, the results strongly support vestibular rehabilitation as an effective tool in the management for unilateral vestibular dysfunction over medications, placebo or sham interventions, or no intervention.[50] Whitney and Rossi[1] also have provided a useful review of multiple published studies of VBRT efficacy. In their review, they classify the works by the presence or absence of control groups and the prospective or retrospective nature of the studies. Overall, the studies reviewed demonstrate significant evidence supporting the efficacy of VBRT as a major management tool for patients with balance and vestibular disorders. This summary also demonstrates that VBRT is highly beneficial after unilateral surgical ablation of vestibular function. Similar results may be expected in treating fixed unilateral lesions such as vestibular neuritis and labyrinthitis. Treatment of canalithiasis causing classic BPPV with the particle-repositioning maneuver is effective in more than 90% of cases, but the condition may recur in up to 30% of patients. Habituation exercises have been reported to yield similar results but do not offer relief as promptly. Patients with bilateral vestibulopathy treated with VBRT show significant improvement in speed of ambulation and stair negotiation, postural stability, and reaching distance compared with control subjects.

In general, the patients who have a poorer prognosis for improvement with VBRT include those with severe bilateral peripheral lesions, combined central and peripheral vestibular deficits and headache syndromes after head injury, and those with established long-term disability. For those in whom migraine or anxiety disorders are the primary source for symptoms, VBRT can be effective if used with treatment for the primary disease process.[5] Although some elderly patients may progress poorly because of irreversible multisensory dysfunction, the overall experience with this age group has been favorable.

The concurrent use of vestibular suppressant medication or other centrally acting agents has been shown to delay the time course of recovery during VBRT. Whenever possible, these medications should be tapered to lower doses or discontinued completely. On the other hand, they may be continued if they are essential for treatment of complicating medical conditions or for relief of symptoms during the VBRT program, because their use does not seem to dramatically reduce the chances of a satisfactory ultimate outcome.

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Facial Nerve Disorders

CHAPTER ONE HUNDRED AND SIXTY-NINE

Tests of Facial Nerve Function

Rodney C. Diaz

Robert A. Dobie

Key Points

- History and physical examination are the most important tools in evaluation of facial nerve function and in diagnosis of dysfunction.
- The House-Brackmann grading system is the most commonly used method of categorizing and documenting long-term facial nerve function after insult, injury, or surgery.
- Topognostic testing correlates specific functional deficits with corresponding anatomic branch points to determine the site of the lesion along the course of the facial nerve; it has been largely superseded by electrodiagnostic testing.
- The four types of electrodiagnostic testing are the nerve excitability test (NET), the maximum stimulation test (MST), electroneuronography (ENoG) (also called electroneurography), and electromyography (EMG). Each has its advantages and disadvantages.
- Electrodiagnostic testing of the facial nerve can differentiate neurapraxia from neural degeneration, but it cannot distinguish between different degrees of neural degeneration.
- Electrodiagnostic testing can provide prognostic information regarding the likelihood of complete or good recovery versus severely incomplete or poor recovery; threshold criteria for predicting poor recovery are used by some surgeons in patient selection for surgical exploration and decompression of the facial nerve.
- Intraoperative facial nerve monitoring has been shown to be a valuable adjunct in surgery for acoustic neuroma and other tumors of the cerebellopontine angle, as well as in revision parotidectomy for recurrent pleomorphic adenoma. Multiple factors can affect accuracy and performance; therefore, responses from a monitoring device should not supplant surgical knowledge and experience in intraoperative decision making.
- Unconventional forms of facial nerve monitoring, under development, may provide additional information for evaluating facial nerve integrity intraoperatively beyond standard methods of intraoperative monitoring.

In facial paralysis, as in most medical problems, history and physical examination usually provide more useful information than laboratory tests. Sometimes, however, a more objective evaluation of facial nerve function is indicated to detect a facial nerve lesion; to measure its severity; to localize it to a particular intracranial, intratemporal, or extratemporal site; to assess the prognosis for recovery; to assist in treatment decisions; or to detect and avoid surgical injury. Quantitative tests of facial nerve function are then used.

Useful diagnostic tests add information to what is already known, influence the choice of therapy, and ultimately improve clinical outcomes.[1] This chapter discusses several tests for evaluation of the facial nerve that can be helpful—as well as several that have not been shown to be helpful—in various clinical scenarios. Intraoperative monitoring of electrical activity of muscles innervated by the facial nerve is by far the most well-established, clinically useful means of assessing facial nerve function, other than physical examination. Outpatient electrical testing of facial nerve function makes sense in clinical settings in which surgical repair or decompression is under consideration, such as after temporal bone fracture or Bell's palsy. Of note, however, most of the tests described in this chapter have very limited proven clinical usefulness.

Facial nerve imaging also is briefly discussed. Although magnetic resonance imaging (MRI) is the modality of choice when a tumor is suspected to be the cause of facial paralysis, it seems not to be useful in Bell's palsy.

Physical Examination

Facial weakness can be extremely subtle, apparent only to a trained examiner (and perhaps to the patient). Paradoxically, mild unilateral facial weakness sometimes can be more easily detected by comparison with a normal contralateral side by having the patient perform nominal rather than maximal volitional movements. Rapid repetitive blinking also can unmask a mild facial weakness, which will manifest as slowed or reduced blink frequency compared with that on the normal side. By contrast, when facial paralysis is total or near-total, the diagnosis is obvious; such impairment can be devastating to the patient on functional, social, and psychologic levels.

Attempts have been made to standardize measurement of facial function, using techniques as simple as measurements with hand-held calipers and as complex as digital photographic and videographic documentation.[2,3] Whereas caliper methods have been shown to demonstrate a high intertest variability, digital photographic methods appear to be much more reliable.[4]

Several systems of clinical measurement of facial nerve function have been devised, but since the mid-1980s, the House-Brackmann system has been most widely used and has been endorsed by the

American Academy of Otolaryngology–Head and Neck Surgery.[5] In the House-Brackmann system, grade I is normal function, grade VI is complete absence of facial motor function, and grades II to V are intermediate (Table 169-1).

The House-Brackmann system is least ambiguous at its extremes and most prone to intertest variability at its intermediate grades II to V: Multiple regional descriptors of facial movement within each scale can overlap, leading to confusion in assigning the appropriate grade. Alternatively, major functional criteria can be used to create unambiguous categories of progression of deficit correlated with each grade (Fig. 169-1).

Similarly, examiners do not always agree among themselves, even when using the same formal grading system. In two studies, each with more than 100 patients with various degrees of facial weakness, examiners unanimously agreed on the House-Brackmann grade as often as 80% (three examiners in one study) and as seldom as 33% (five examiners in the other study).[6,7] Of course, the probability of disagreement should increase as more examiners are used; the probability of any two examiners disagreeing is as low as 13%[8] (on the assumption that in all cases of three-examiner disagreement, two choose one grade and the third choose another grade) and as high as 40% (on the assumption of maximum dispersion of examiner judgments across House-Brackmann categories).[9] It would be interesting to know how much of this variability is caused by individual examiners' test-retest variability (i.e., the tendency of an examiner to assign different scores to the same patient on repeated examination) and how much is attributable to consistent differences among examiners (e.g., between "strict" and "lax" graders).

The wide acceptance of the House-Brackmann system has not prevented many others from proposing new systems. For example, Burres and Fisch[10] described a method requiring multiple measurements of movement in different parts of the face; Croxson and colleagues[6] showed the expected correlation between Burres-Fisch and House-Brackmann in 42 patients, but considerable variability of Burres-Fisch scores was observed for House-Brackmann grades III and IV. Murtry and coworkers[9] proposed and tested the Nottingham system of subjective estimation of movement at each of several points on the face. This method correlated better with House-Brackmann than did Burres-Fisch, and it was simpler to perform. Newer systems include those devised by Ross and associates at Sunnybrook (Ontario, Canada)[11] and Coulson and colleagues in Sydney, Australia.[12] both of which place particular emphasis on the degree of synkinesis in facial movement. These systems demonstrate good overall test-intertest reliability and correlation with the House-Brackmann system, but subjective evaluation of degree of synkinesis is much more variable.[12,13]

Neely and associates[14] showed the feasibility of computer-assisted image analysis for measuring facial movement. Other objective measurement systems have been proposed by Johnson[15] and Jansen[16] and their coworkers. These methods are promising, particularly for research and for the assessment of weakness affecting only a single region of the face (e.g., forehead, lower lip).

An occasionally overlooked limitation of the House-Brackmann grading system is in the evaluation of acute facial paralysis. The differentiation among House-Brackmann grades II, III, IV, and V rests partly on the presence and severity of synkinesis, contracture, hemifacial spasm, and asymmetry at rest—all sequelae of long-term facial nerve dysfunction and hence all absent in the setting of acute facial paralysis. This inherent restriction extends to most other alternative grading systems as well.

The House-Brackmann system applied in its strictest sense is well suited for evaluation of long-standing facial nerve dysfunction but not acute facial paralysis.[17] Nonetheless, this system can be informally rethought for use in the acute setting, in terms of graduated degrees of facial weakness: grade I, normal or 100% function, grade II, mild weakness or 75% to 99% function; grade III, moderate weakness or 50% to 75% function; grade IV, moderately severe weakness or 25% to 50% function; grade V, severe weakness or 1% to 25% function; and grade VI, complete paralysis or zero function. The obvious disadvantage of this technique is in the reversion to a coarse, imprecise, unweighted method of scaling facial function. However, although not canonical, this method allows for continued use of a six-scale grading system to track facial nerve function through the entire clinical course, from acute onset of the paralysis to long-term outcome.

Table 169-1

House-Brackmann Facial Nerve Grading System

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Mild dysfunction	Gross: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone Motion—Forehead: moderate to good function Motion—Eye: complete closure with minimum effort Motion—Mouth: slight asymmetry
III	Moderate dysfunction	Gross: Obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, or hemifacial spasm At rest: normal symmetry and tone Motion—Forehead: slight to moderate movement Motion—Eye: complete closure with effort Motion—Mouth: slightly weak with maximum effort
IV	Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone Motion—Forehead: none Motion—Eye: incomplete closure Motion—Mouth: asymmetric with maximum effort
V	Severe dysfunction	Gross: only barely perceptible motion At rest: asymmetry Motion—Forehead: none Motion—Eye: incomplete closure Motion—Mouth: slight movement
VI	Total paralysis	No movement

The best system would be reliable, easy to use, and correlate well with patient self-assessment. Kahn and coworkers[18] developed a 15-item questionnaire for patient self-assessment of facial paralysis; questionnaire results in 76 patients correlated fairly well with both House-Brackmann and the Sunnybrook Facial Grading System.[11] The American Academy of Otolaryngology–Head and Neck Surgery committee on facial nerve disorders has been in the process of developing a standardized grading system for facial nerve function, but this has not yet been formalized.[19] For now, House-Brackmann still seems the most reasonable and widely used choice.

Topognostic Tests

Topognostic tests were intended to reveal the site of lesion by use of a simple principle: Lesions below the point at which a particular branch

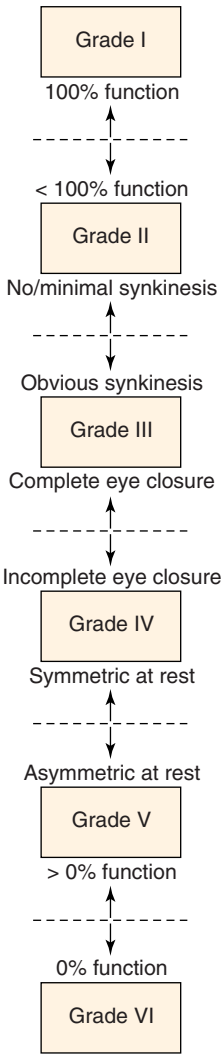

Figure 169-1. Schematic diagram of functional progression in assigning House-Brackmann grade to degree of facial paralysis.

leaves the facial nerve trunk will spare the function subserved by that branch. Accordingly, injury to the nerve in the face cannot affect lacrimation, salivation, taste, or the stapedius reflex. Conversely, the combination of facial paralysis and decreased lacrimation can theoretically be caused only by a lesion in the segment of the nerve in which voluntary motor fibers and parasympathetic fibers to the lacrimal gland run together (i.e., from the cerebellopontine angle to the geniculate ganglion).

In complete focal lesions, which often are the result of trauma, topognostic tests are reliable but usually are unnecessary, because clinical examination and imaging suffice to describe the site of lesion. Bell's palsy, on the other hand, usually is a mixed and partial lesion with varying degrees of conduction block and degeneration changes within different fibers and fascicles of the nerve trunk; therefore, topognostic tests are not expected to provide precise information about the level of the lesion. Many investigators have noted paradoxic and misleading results in applying topognostic testing principles in the evaluation of patients with Bell's palsy. In recent years, otologists use these tests only rarely.

Lacrimal Function

Schirmer's test has the advantages of simplicity, speed, and economy: The physician places a folded strip of sterile filter paper into the conjunctival fornix of each eye and compares the rate of tear production of the two sides. Normally, the portion of the filter paper in contact with the conjunctiva acts as an irritant, stimulating an increased flow of tears, which are then wicked along the filter paper strip by capillary action. The length of the wetted portion of the strip after a fixed interval (usually 5 minutes) is measured and is proportional to the volume of tears produced. A defect in the afferent (the trigeminal nerve along the opthalmic division, or V_1) or efferent (the facial nerve by way of the greater superficial petrosal nerve) limb of this reflex may cause a reduced flow. The reflex is consensual (i.e., a unilateral irritating stimulus in either eye causes tearing in both eyes, and a unilateral sensory deficit in either eye will reduce tearing bilaterally). However, unilateral corneal anesthesia reduces tearing asymmetrically, with a greater reduction on the anesthetized side; therefore, when a sensory deficit is present, presence of bilateral corneal anesthesia should be considered, and stimulation of lacrimation by other noxious stimuli (e.g., inhalation of ammonia) should be performed instead of the conventional Schirmer's test.[8]

Schirmer's test usually is considered positive if the affected side shows less than one-half the amount of lacrimation seen on the healthy side. This corresponds well to the normative data of Fisch,[20] who found that 95% of healthy persons had relatively symmetric responses (the lesser response was less than 54% of the greater response). Fisch[20] also pointed out that tearing often is reduced bilaterally in Bell's palsy (perhaps because of subclinical involvement of other cranial nerves). Thus, both the symmetry of the response and its absolute magnitude are important; a total response (sum of the lengths of wetted filter paper for both eyes) of less than 25 mm is considered abnormal.

Fisch[20] correlated the results of Schirmer's test and ENoG (see later under "Electrodiagnostic Testing") in patients with Bell's palsy and herpes zoster oticus and found that all cases with 90% or greater degeneration by ENoG had an abnormal result on Schirmer's test. However, the Schirmer's test result did not indicate degeneration earlier than ENoG and was abnormal in several cases in which ENoG correctly predicted a good spontaneous recovery.

May[21] added Schirmer's test to the salivary flow test and MST (see later under "Electrodiagnostic Testing") in a battery of prognostic tests. A decrease to 25% of normal in any of these was associated with a 90% chance of a poor recovery.

Stapedius Reflex

The nerve to the stapedius muscle branches off the facial trunk just past the second genu in the vertical (mastoid) part of the nerve. In patients with hearing loss, acoustic reflex testing is used to assess the afferent (auditory) limb of the reflex, but in cases of facial paralysis, the same test is used to assess the efferent (facial motor) limb. An absent reflex or a reflex that is less than one-half the amplitude of the contralateral side is considered abnormal.

The reflex can be elicited by ipsilateral or contralateral acoustic stimulation or, in cases of bilateral severe hearing loss, by tactile or electrical stimulation. It is absent in 69% of cases of Bell's palsy (in 84% when the paralysis is complete) at the time of presentation; the reflex recovers at about the same time as for clinically observed movements.[22] The prognostic value of this test therefore seems limited.

Taste

Because the chorda tympani carries fibers subserving taste from the anterior two thirds of the tongue, many investigators have studied abnormalities of taste in Bell's palsy. Psychophysical assessment can be performed with natural stimuli, such as filter paper disks impregnated with aqueous solutions of salt, sugar, citrate, or quinine, or with electrical stimulation of the tongue.[23] The latter modality, termed *electrogustometry* (EGM), has the advantages of speed and ease of quantification. EGM involves bipolar or monopolar electrical stimulation of the tongue, with current delivery on the order of 4 μA (−6 dB) to 4 mA (34 dB). Threshold responses are denoted by the current level's imparting a subjective sensation of one of the four cardinal tastes or of buzzing or tingling. In healthy persons, the two sides of the tongue have similar thresholds for electrical stimulation, rarely differing by greater than 25%.[24] Older studies demonstrated little usefulness of taste testing, because results were abnormal in almost all patients who were in the acute phase of Bell's palsy; accordingly, EGM could not be used to identify patients with a poor prognosis.[25,26] A newer

study suggests better predictive value for the test: Of a cohort of 50 patients with complete idiopathic facial paralysis, 18 demonstrated abnormal EGM responses (defined as no response or a threshold difference greater than 20 dB across sides), and 7 demonstrated no response on NET, all of whom were in the abnormal EGM responses group. Of these 7, 5 demonstrated incomplete recovery of facial nerve function on long-term follow-up.[23] Taste function appears to recover before visible facial movement in some cases, so if the results of electrogustometry are normal in the second week or later, clinical recovery may be imminent.

Salivary Flow Test

The salivary flow test requires cannulation of the submandibular ducts and comparison of stimulated flow rates on the two sides. It is time-consuming and unpleasant for the patient, especially if performed repeatedly; this latter drawback is one good reason it is not widely used. Reduced submandibular flow implies a lesion at or proximal to the point at which the chorda tympani nerve leaves the main facial trunk; this is variable and may be anywhere in the vertical (mastoid) portion of the nerve.

Ekstrand[27] stated that reduced salivary flow (less than 45% of flow on the healthy side after stimulation with 6% citric acid) correlates well with worse outcome in Bell's palsy. Complete or incomplete recovery could be predicted with 89% accuracy. It is unclear whether these data, all collected within 10 days of onset of paralysis, provide an earlier or more reliable indication of prognosis than electrical or other tests.

May and Hawkins[28] noted that salivary flow decreases sooner than do threshold changes in NET (see under "Electrodiagnostic Testing" later on) in idiopathic facial paralysis. These workers argued that a flow rate of 25% or less of that on the contralateral, unaffected side is an indication for surgery.

Salivary pH

At least one report[29] showed that a submandibular salivary pH of 6.1 or less predicts incomplete recovery in cases of Bell's palsy. Presumably only the duct on the affected side needs to be cannulated, because in this study, all of the control sides had pH levels of 6.4 or more. The overall accuracy of prediction was 91%. Unfortunately, the reported experience with salivary pH is very limited; it is unknown whether this test gives an earlier prognosis than other tests.

Imaging

Magnetic resonance imaging (MRI) with intravenous gadolinium contrast has revolutionized tumor detection in the cerebellopontine angle and temporal bone and is currently the study of choice when a facial nerve tumor is suspected (e.g., in a case of slowly progressive or long-standing weakness).[30] However, enhancement also occurs in most cases of Bell's palsy and herpes zoster opticus, usually in the perigeniculate portions of the nerve.[31,32] This enhancement may persist for more than 1 year after clinical recovery; can be distinguished from neoplasm by its linear, unenlarged appearance; and has no apparent prognostic significance. Computed tomography (CT) is valuable for surgical planning in cholesteatomas and temporal bone trauma involving facial nerve paralysis but probably is less useful than MRI in the investigation of atypical idiopathic paralysis. Unfortunately, even MRI fails to detect a substantial number of malignant parotid tumors.[33]

MRI shows the greatest utility in predicting location and depth of parotid gland tumors, but even in this capacity it is no better than simple manual palpation alone. The MRI appearance of tumor indistinct from surrounding parotid parenchyma has a positive predictive value for malignancy of only 0.48; accordingly, fine needle aspiration biopsy continues to be the "gold standard" modality for preoperative evaluation of parotid masses.[34]

Pathophysiology

Sunderland[35] provided a simple, five-category histopathologic classification of peripheral nerve injury based on a schematic framework proposed by Seddon[36] (Fig. 169-2). Some investigators have since expanded this classification to include a sixth category involving mixed forms of injury proposed by MacKinnon and associates.[37] This classification of

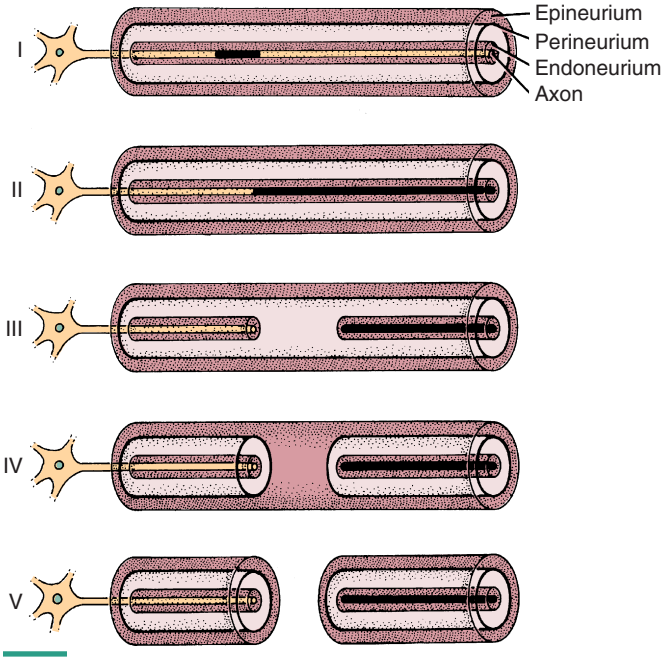

Figure 169-2. Sunderland histopathologic classification of peripheral nerve injury. Roman numerals I to V at *left* denote the Sunderland class corresponding to the degree of injury depicted in the diagram.

nerve trunk injury is helpful in understanding and interpreting the results of electrical tests.

Class I: Pressure on a nerve trunk, provided that it is not too severe, causes conduction block, termed neurapraxia by Seddon. No physical disruption of axonal continuity occurs, and supportive connective tissue elements remain intact. When the pressure or other insult (e.g., local anesthetic infiltration) is removed, the nerve can recover quickly. During conduction block, no impulses can cross the area of the lesion, but electrical stimulation distal to the lesion still produces a propagated action potential and a visible muscle twitch at all times after injury. An example of a Sunderland class I injury is the neurapraxia of an arm or leg that has "gone to sleep."

Class II: A more severe lesion, whether caused by pressure or some other insult (e.g., viral inflammation), may cause axonal disruption without injury to supporting structures. Wallerian degeneration occurs and propagates distally from the site of injury to the motor end plate and proximally to the first adjacent node of Ranvier. In a class II injury, the connective tissue elements remain viable, so regenerating axons may return precisely to their original destinations. Removal of the original mechanism of insult permits complete recovery, but this is considerably delayed, because the axon must regrow from the site of the lesion to the motor end plate at a rate of approximately 1 mm/day before function returns. A class II injury is an *axonotmesis*.

Class III: If the lesion disrupts the endoneurium, wallerian degeneration occurs as in a class II injury, but the regenerating axons are free to enter the wrong endoneurial tubes or may fail to enter an endoneurial tube at all; this aberrant regeneration may be associated with incomplete recovery, manifested as an inability to make discrete movements of individual facial regions without involuntary movement of other parts of the face—an abnormality termed *synkinesis*. Sunderland class III to V nerve injuries, in which aberrant regeneration can occur, are *neurotmesis* injuries.

Class IV: Perineurial disruption implies an even more severe injury, in which the potential for incomplete and aberrant regeneration is greater. Intraneural scarring may prevent most axons from reaching

the muscle, resulting in not only greater synkinesis but incomplete motor function recovery.

Class V: A complete transection of a nerve, including its epineurial sheath, carries almost no hope for useful regeneration, unless the ends are approximated or spanned and repaired.

Class VI: Insults to the facial nerve trunk, whether compressive, inflammatory, or traumatic in origin, can be heterogeneous in nature, with differing degrees of injury from fascicle to fascicle. Such mixed injury involving both neurapraxia and a variable degree of neurodegeneration has been advocated as an additional class of injury.

A patient with a conduction block (class I injury) cannot move the facial muscles voluntarily, but a facial twitch can be elicited by transcutaneous electrical stimulation of the nerve distal to the lesion. The twitch can be observed visually, or the electrical response of the facial muscles may be recorded. Because no wallerian degeneration occurs, this electrical stimulability distal to the site of lesion is preserved indefinitely in isolated class I injury.

In classes II to VI, once wallerian degeneration has occurred, electrical stimulation of the nerve distal to the lesion will fail to produce a propagated action potential and muscle contraction. However, before axonal degeneration, the distal segment is still electrically stimulable. Wallerian degeneration begins immediately after injury but progresses slowly. Histopathologic degeneration of the distal segment becomes apparent approximately 1 week after insult and continues for the ensuing 1 to 2 months.[38] In the case of the facial nerve, this delay in degeneration results in continued electrical stimulability of the distal segment for up to 3 to 5 days after injury.[39] Thus, during these first days after an insult, electrodiagnostic testing of any form cannot distinguish between neurapraxic and neurodegenerative injuries.

After wallerian degeneration, electrical testing can distinguish axonally intact but neurapraxic lesions (class I) from axonally disrupted and neurodegenerative lesions (classes II to V). It cannot, however, distinguish among the different classes of neurodegenerative lesions II, III, IV, and V. An important consideration in the use of such testing is its limited ability to distinguish between pure lesions associated with an excellent prognosis for perfect spontaneous recovery (class II) and those associated with a poor prognosis for useful recovery without surgical repair (class V).

It also is important to recognize that most facial nerve lesions are not pure but probably mixed, with some fibers in conduction block and others disrupted with varying degrees of connective tissue injury. Accordingly, a majority of insults to the facial nerve, whether compressive, inflammatory, or traumatic (except for complete transections), probably are class VI, with a variable threshold of electrical stimulability commensurate with the proportion of neural degeneration across the nerve trunk.

Electrodiagnostic Testing

Tests based on these two principles, electrical stimulation and recording of the electromyographic response, are useful in determining prognosis and sometimes in stratifying patients for nonsurgical versus surgical management. However, they are rarely useful in differential diagnosis. In Bell's palsy and traumatic facial nerve paralysis, electrical tests most often are used to identify patients whose nerves have begun to degenerate, because these patients may be candidates for decompression surgery. In this sense, outpatient evaluation of facial paralysis with electrical testing only needs to be performed if the physician is prepared to recommend decompression in the event that degeneration is discovered. However, intraoperative monitoring of facial nerve function (usually with electromyography) is in widespread use in many types of intracranial and intratemporal surgery.

Nerve Excitability Test

The simplest and best-known test for facial nerve degeneration is the NET introduced by Laumans and Jonkees.[40] The stimulating electrode is placed on the skin over the stylomastoid foramen or over one of the peripheral branches of the nerve, with a return electrode taped to the forearm. Beginning with the healthy side, electrical pulses, typically 0.3 msec in duration, are delivered at steadily increasing current levels until a facial twitch is noted. The lowest current eliciting a visible twitch is the threshold of excitation. Next, the process is repeated on the paralyzed side, and the difference in thresholds between the two sides is calculated.

In a simple conduction block (e.g., after infiltration of the perineural tissues with lidocaine proximal to the point of stimulation), no difference exists between the two sides; the paralyzed nerve is as easy to stimulate distal to the site of lesion as the healthy nerve. After a more severe injury (Sunderland classes II to V) in which distal axonal degeneration occurs, electrical excitability is gradually lost, over a period of 3 to 4 days—even after a total section of the nerve. Findings on the NET (and all other electrical tests involving distal stimulation), therefore, always lag several days behind the biologic events themselves.[41]

In most cases of Bell's palsy with complete paralysis, some degree of neural degeneration occurs, evolving over 1 to 2 weeks.[42] Accordingly, proponents of the NET urge frequent, even daily, examinations, so that severe degeneration can be detected as early as possible. A difference of 3.5 milliamperes (mA) or more in thresholds between the two sides has been proposed as a reliable sign of severe degeneration and has been used as an indicator for surgical decompression. With use of this criterion, complete versus incomplete recovery can be predicted with 80% accuracy.[40] Some investigators insist on conducting two consecutive tests showing differences greater than 3.5 mA to reduce the chance of test error. Lewis and colleagues[43] have reported thresholds in more than 10,000 NETs in cases of Bell's palsy, using the trunk and branches to the eye, forehead, and mouth.

The NET is useful only during the first 2 to 3 weeks of complete paralysis, before complete degeneration has occurred. This test is unnecessary in cases of incomplete paralysis, in which the prognosis is always excellent; in these cases, the test result will be normal when the segment of nerve distal to the lesion is stimulated. If the paralysis becomes total, the test can determine whether a pure conduction block exists or whether degeneration is occurring, as indicated by progressive loss of excitability. Total paralysis for longer than 1 month is almost invariably associated with total loss of excitability. Once excitability is lost and this result is confirmed by repeat testing, further excitability tests are pointless, because clinically evident recovery always begins before any apparent electrical excitability returns. This disparity results because the regenerating axons are smaller, more irregular in size, and fewer in number than before the lesion occurred. Electrical stimulation generally is ineffective in eliciting a synchronous and hence observable twitch in the early stages of regeneration. As these early fibers regenerate, they may regain electrical function individually, while group function, measured as a clinically apparent twitch on electrical stimulation, still is not evident. This phenomenon is termed *early deblocking*, or asynchronous firing of the facial nerve. Similarly, with complete paralysis, if clinical recovery begins before degeneration is noted, continuing testing is unnecessary, because recovery will be rapid and complete.

Partial degeneration and a bad outcome are not synonymous. In a Sunderland class II lesion, nearly complete recovery may occur without serious complications. Laumans and Jonkees[40] state that even patients who show degeneration (threshold difference greater than 3.5 mA) have a 38% chance for complete spontaneous recovery; in the remainder, development of complications such as permanent weakness (not total paralysis) and synkinesis is typical.

Because of relatively large intersubject variations in threshold compared with the small differences between the two sides of the face, stating NET results in proportional terms rather than in absolute threshold differences may be more appropriate. For example, Mechelse and associates[44] used as their criterion for decompression a 150% increase in threshold compared with the healthy side.

Maximum Stimulation Test

The MST is similar to the NET in that it involves visual (i.e., subjective) evaluation of electrically elicited facial movements. Instead of measuring threshold, however, maximal stimuli (current levels at which the greatest amplitude of facial movement is seen) or supramaximal stimuli (even higher current levels) are used. The electrode type and

placement and the nerve-stimulating equipment are the same as in the NET. On the unaffected side, the stimulus current intensity is increased above the threshold level incrementally—with corresponding increases in subjective facial twitch magnitude—until the maximum stimulation level is reached. Stimulation above this level does not elicit any further increase in facial twitch magnitude. This maximum stimulation level is then used to stimulate the affected side, and the degree of facial contraction is subjectively assessed as either equal, mildly decreased, markedly decreased, or without response compared with that on the normal side. With MST as performed by May and coworkers,[45] peripheral branches are the preferred site of stimulation, and the movements on the paralyzed side are subjectively expressed as a percentage (0%, 25%, 50%, 75%, 100%) of the movements on the healthy side.

The theoretic basis of the MST is that by stimulating all intact axons, the proportion of fibers that have degenerated can be estimated; this information should more reliably guide prognosis and treatment than that obtained with the NET. Unfortunately, no good data comparing these or other electrical prognostic tests in the same patients are available, so this claim has not been proved.

According to May and coworkers,[46] when MST results remained normal in Bell's palsy, 88% of patients recovered completely. Reduced movement presaged only a 27% chance of complete recovery. An absence of electrically stimulated movement was always associated with incomplete recovery.

MST is painful for some patients; Molina[47] suggests that the use of a pulse duration less than 0.4 msec (as opposed to the 1 msec proposed by May and coworkers[46]) can eliminate this discomfort, although higher currents are required in some cases.

Electroneuronography

In ENoG, the facial nerve is stimulated transcutaneously at the stylomastoid foramen, as in the NET, although a bipolar stimulating electrode is used. Responses to maximal electrical stimulation of the two sides are compared, as in the MST, but they are recorded in a more objective fashion by measuring the evoked compound muscle action potential (CMAP) with a second bipolar electrode pair placed (usually) in the nasolabial groove. A supramaximal stimulus often is used, and peak-to-peak amplitude is measured in millivolts (mV). The average difference in response amplitude between the two sides in healthy patients has been said to be only 3%.[48] The term "electroneuronography" is actually a misnomer, because it is the facial muscle CMAP that is measured and recorded. Some workers use the term *evoked electromyography* synonymously with *electroneuronography*.

Clearly, this method offers the potential advantage of an objective registration of electrically evoked responses, and the amplitude of response on the paralyzed side can be expressed as a precise percentage of that on the healthy side. For example, if the amplitude of the response on the paralyzed side is only 10% of that on the normal side, an estimated 90% of fibers are said to have degenerated on the paralyzed side. However, this method has some practical difficulties that should be mastered before reliable results can be expected.[49,50] Test-retest errors in the 20% range have been reported by Raslan and associates,[51] despite standardization of electrode positions. Most investigators require a 30% or greater asymmetry (or change over time) for results to be considered abnormal.

The use of ENoG to prognosticate in Bell's palsy has become widespread, although Gates[52] points out the lack of comparative studies showing ENoG to be superior to NET or MST. For example, Coker and coworkers[53] showed good correlation between ENoG and NET (when NET threshold differences exceeded 2 mA, ENoG amplitude on the paralyzed side usually was less than 10% of the normal side), but their study provided no data on clinical outcomes to help choose one test over the other.

The most valid data supporting the use of ENoG would have to come from studies limited to cases of complete paralysis (because incomplete paralysis is known to have an excellent prognosis). In 37 such cases, May and colleagues[45] showed that severe ENoG amplitude reductions (to less than 10% of the unaffected side) were highly correlated with incomplete recovery. Although Canter and associates[54] could find no correlation of final outcome with ENoG in 23 patients with complete paralysis, they did not specifically test the predictive value of the 10% criterion widely used by other authors. More recently, Sillman and colleagues[25] found excellent correlations between ENoG and outcome in Bell's palsy ($n = 66$) but not in traumatic facial nerve palsy ($n = 29$).

Electrical recording of the muscle response also offers the possibility of measuring latency, which is the time elapsed between stimulus and response. Only slight interest in this variable has developed; although slow nerve conduction velocities might be expected to be an early indicator of degeneration, the available data are in conflict. Joachims and associates[55] stated that increased latency in the first 72 hours (before any observable change in threshold or response amplitude) was a reliable predictor of a poor outcome. However, Esslen[48] reported that in 145 patients, latency never increased before the 5th day, and latency changes never preceded changes in evoked potential amplitude; he concluded that latency measurements were of no clinical value. Danielides[42] and Ruboyianes[56] and their coworkers also suggested that latency adds nothing to information provided by ENoG amplitude or MST.

The limitation described for the NET, namely, its inapplicability in cases of partial paralysis after the beginning of clinical recovery and after excitability has been lost, also applies to the MST and to ENoG. In acute facial paralysis, all of these tests are useful only in tracking the early course of a completely paralyzed nerve until clinical recovery begins or the nerve shows complete loss of excitability.

Esslen[48] used ENoG to study the time course of Bell's palsy, finding that the acute phase rarely exceeds 10 days. Decreases in ENoG amplitude after the 10th day were associated with substantial latency increases and were attributed to desynchronization of surviving fibers, rather than to increased degeneration. Accordingly, the time elapsed since the onset of paralysis should be taken into account in the interpretation of ENoG results. Patients reaching 95% degeneration (amplitude of response equals 5% of that on the healthy side) within 2 weeks had a 50% chance of a poor recovery, whereas patients exhibiting a more gradual decrease in ENoG amplitude had a much better prognosis.[57]

Most proponents of ENoG use it mainly to obtain an early prognosis in acute facial paralysis (Bell's or post-traumatic) or to select patients for decompression surgery. Kartush[58] pointed out that ENoG also can document subclinical facial nerve involvement by tumors, especially acoustic neuromas. Patients with acoustic tumors who had ENoG evidence of nerve involvement (despite clinically normal facial movement) were more likely to have postoperative weakness. However, because ENoG amplitude reductions were highly correlated with increasing tumor size (which also predicts poorer facial nerve outcome), it is unclear whether ENoG really adds prognostic information when tumor size is known. ENoG also has demonstrated some success in preoperative detection of facial nerve infiltration by malignant parotid tumors, even when no paresis is seen on clinical examination.[59] Table 169-2 summarizes the three versions of electrodiagnostic testing and commonly accepted threshold criteria for consideration of facial nerve decompression for complete facial paralysis.

Electromyography

EMG is the recording of spontaneous and voluntary muscle potentials using needles introduced into the muscle. Its role in the early phase of Bell's palsy is limited, because it does not permit a quantitative estimate of the extent of nerve degeneration (the percentage of degenerated fibers). However, EMG may be helpful in certain situations. Several authorities who favor decompression for Bell's palsy base their decisions for surgery primarily on the NET or ENoG, but also require confirmatory EMG[40,49]; if it shows voluntarily active facial motor units despite loss of excitability of the nerve trunk, the prognosis for a good spontaneous recovery is excellent.[25,48] This application of EMG in Bell's palsy probably is underused.

After loss of excitability, tests requiring electrical stimulation such as NET and ENoG are no longer useful. However, EMG may give prognostically useful information during this phase of the illness. After 10 to 14 days, fibrillation potentials may be detected, confirming the presence of degenerating motor units; in 81% of patients with such findings, incomplete recovery is the rule.[60] More useful are the polyphasic reinnervation potentials that may be seen as early as 4 to 6 weeks

Table 169-2

Electrodiagnostic Testing Criteria

Test	Criteria to Consider Facial Nerve Decompression
Nerve excitability test (NET)	>3.5-mA threshold difference between sides
Maximal stimulation test (MST)	No response on injured side at maximal stimulation
Electroneurography (EnoG)	>90% degeneration within 14 days

after the onset of paralysis. Presence of these potentials precedes clinically detectable recovery and predicts a fair to good recovery.[48] Grosheva and coworkers noted that EMG performed after 14 days exhibited greater prognostic value for determining good versus poor recovery, with both higher specificity and positive predictive value, than ENoG performed before 14 days using a 75% degeneration cutoff criterion; however, their study included many patients with incomplete facial paralysis.[61]

Because few surgeons advocate decompression surgery for Bell's palsy late in the course of the disease, this use of EMG is uncommon. It may be helpful in the assessment of long-standing facial paralysis, along with muscle biopsy, to determine the possible success of substitution anastomosis or cross-facial anastomosis as a mechanism of restoring facial motion. EMG also can help assess whether a nerve repair (e.g., in the cerebellopontine angle) is unsuccessful. If no clinical recovery occurs and EMG shows no polyphasic reinnervation potentials at 15 months (or at 18 months at the latest), the anastomosis should be considered a failure, and another operation should be considered (e.g., hypoglossal-facial anastomosis).

Facial Nerve Monitoring

During the 1980s, audible EMG monitoring of facial nerve function during acoustic neuroma surgery became routine in many centers, and its application has spread to other operations involving risk to the facial nerve and other cranial nerves.[62] Although it is possible for the surgeon or an associate to watch for facial movements in response to mechanical or electrical stimulation of the nerve, simple observation fails to detect many small muscular contractions and in any case demands constant vigilance. By contrast, electrodes in or near the facial muscles record EMG potentials that can be amplified and made audible with a loudspeaker. Thus, the surgeon's ears can monitor the facial nerve while the hands and eyes operate. Harner and colleagues[63] pointed out that this technique is not really new but has only recently become popular.

Facial nerve monitoring can be performed in many different ways. One approach to categorizing the type of monitoring used is to consider if it is active versus passive.[64] Having a surgical assistant visually monitor the face for twitches during parotid surgery is technically a form of facial nerve monitoring, albeit a coarse and highly variable one. By applying needle electrodes to the facial muscles and recording CMAPs, the activity of the facial nerve can be monitored in a more standardized, precise, and sensitive fashion. Both of these examples are *passive* forms of facial nerve monitoing, whereby facial muscle movement is activated only with direct mechanical, stretch, caloric, or other nonelectrical stimulation of the facial nerve. Facial nerve monitoring electrodes typically are placed in a two-channel montage including the orbicularis oculi and orbicularis oris muscles, although four-channel arrangements can be used as well.

When electrical stimulation of the facial nerve is used along with measurement of facial CMAPs, the technique is termed *active* facial nerve monitoring. Electrical stimulation is delivered by a monopolar or bipolar electrode (e.g., similar to those used for bipolar electrocautery), which is insulated except at the tips. Commercially available monopolar electrodes are flexible with blunt tips, which makes them convenient for access to cramped areas. In addition, electrified instruments with insulated shafts are available that are shaped in the form of traditional otomicroscopic dissectors such as curved needles, sickle knives, round knives, gimmicks, and other elevators. On bipolar stimulation, the current is mostly confined to the tissue between the electrified tips; with wide tip separation, the stimulation is similar to that with use of a monopolar electrode, but with the tips close together, bipolar stimulation is quite specific. Both types are satisfactory if the user understands these differences.

Electrical stimulation activates a surrounding volume of tissue commensurate in size with the delivered current intensity, and modulation of current intensity can provide the surgeon with good sensitivity for locating and mapping the facial nerve. Early in the dissection before the facial nerve has been visually identified, initial stimulation with higher current levels allows the surgeon to stimulate the nerve from afar, without the need for direct contact on the nerve. As dissection is carried closer to the nerve, lowering the current level allows for more precise determination of nerve location. As dissection is continued and the facial nerve (or its candidates) are identified, low-level current stimulation directly on the nerve provides confirmation that the nerve has been positively identified.

When the surgeon stimulates the nerve electrically, a CMAP is recorded from the monitored facial muscles and can be plotted on an oscilloscope (if visual display is being used), and the loudspeaker emits a characteristic thump. Gentle mechanical stimulation (e.g., touching the nerve with an instrument) will produce a similar sound. Tension on the nerve from mechanical stretching or caloric or thermal stimulation of the nerve from irrigation often will produce a prolonged irregular series of discharges that sounds like popcorn popping. Prass and associates[65] termed these two characteristic sounds *bursts* and *trains*, respectively. Learning to identify these sounds is easy, providing instant feedback regarding the location of the facial nerve and concomitant surgical manipulation. Bursts imply near-instantaneous nerve stimulation; trains signify ongoing stimulation of the nerve, which can be potentially more damaging.

Kartush[58] stated that excessive intraoperative train activity predicts poor outcome; Prell and colleagues correlated total train time (the summation of online monitoring time during which trains were recorded) greater than 10 seconds with a higher likelihood of immediate and long-term deterioration in facial function.[66] Hone and associates[67] disagree. Conversely, if at the end of the surgical procedure the nerve can be stimulated successfully near the brainstem with low currents (0.05 to 0.1 mA), all investigators agree that the prognosis for postoperative function is excellent.[68-72] As seen in patients with Bell's palsy or traumatic facial paralysis, patients undergoing resection of acoustic neuromas in whom facial function is intact immediately postoperatively but a delayed paralysis develops subsequently have better long-term facial function than those with immediate weakness or paralysis.[73]

As with any technical aid, a number of pitfalls have been recognized. Failure to obtain audible facial nerve responses can be caused by any of a multitude of possible errors: detached or shorted electrodes, incorrect wiring of electrodes, malfunction of a nerve monitor or stimulator, inadvertent direct anesthesia of the facial nerve from local anesthetic infiltration to the stylomastoid foramen, pharmacologic muscular paralysis from induction agents used in anesthetic management, or even simply a muted speaker, as well as many other complications (including a nonfunctional nerve). Anesthesiologists have shown that the facial musculature is less susceptible to pharmacologic paralysis than somatic musculature and that a moderate degree of paralysis[74,75] (leading to 50% reduction of hypothenar muscle potentials or even "complete" neuromuscular blockage as measured in the thumb)[76] does not necessarily interfere with facial nerve monitoring.

Stimulation of the trigeminal nerve occasionally can cause electrical confusion, or crosstalk; the facial muscle electrodes may pick up EMG signals from the nearby masseter muscle. Similarly, stimulation of the adjacent vestibular or cochlear nerves can sometimes activate the facial nerve as well, leading to a false-positive identification.

Electrode position should always be checked by voluntary movement, transcutaneous electrical stimulation, or most commonly simply

by tapping over the muscular area being monitored before the surgical site is draped. The most useful intraoperative check on the monitoring equipment is the stimulus artifact or warble tone, which is produced when the stimulating electrode touches tissue remote from the facial nerve. Standard neuromonitoring equipment can be set to produce an auditory flag such as a warble tone or a verbal phrase confirming current flow. This auditory notification confirms that the stimulator is delivering current, the electrodes are in place, and the loudspeaker is working and is to be distinguished from the audible bursts and trains indicating true facial nerve stimulation and facial muscle contraction.

The idea that audible EMG monitoring makes acoustic tumor surgery easier, faster, and probably more successful in terms of facial nerve preservation has become widely accepted anecdotally, and several investigators have shown that postoperative facial nerve function is better in patients who have been monitored (at least during operations for resection of large tumors).[77-79] These studies seem to have used historical control groups (i.e., monitoring was adopted for all patients at a particular point in time, with no monitoring for patients operated on before that time). This limitation makes it hard to be sure that some of the improvements were not caused by improvements over time in the surgeon's skill; indeed, one group acknowledged that the monitored group also had profited from evolving surgical techniques (more use of sharp dissection).[80] This finding highlights the role of the monitor as teacher; the surgeon rapidly learns to prefer medial-to-lateral over lateral-to-medial dissection and sharp over blunt dissection (when the tumor is adherent to the nerve). Although most surgeons use EMG monitoring, others have monitored facial contractions with a motion sensor connected to an electronic circuit that produces an audible signal or by the use of small bells that are sutured to facial skin.[72,81,82]

A panel discussion at a meeting of the American Otological Society produced consensus that electrical facial nerve monitoring is valuable in acoustic tumor surgery and may be useful in facial nerve rerouting in skull base surgery.[83,84] A consensus conference on acoustic tumors sponsored by the National Institutes of Health came to a similar conclusion that benefits of intraoperative facial nerve monitoring in acoustic neuroma surgery had been clearly established.[85]

Electrical facial nerve monitoring is now used by a majority of American otolaryngologists performing parotidectomies, although such monitoring has not been shown to improve postoperative facial paralysis rates after primary parotid gland surgery.[86-88] A retrospective study by Makeieff and colleagues did demonstrate an advantage in postoperative facial paralysis rates when intraoperative continuous facial nerve monitoring was used in 14 of 32 patients undergoing revision total parotidectomy for recurrent pleomorphic adenoma.[89]

In adjusting for the probabilities of facial nerve paralysis with or without monitoring, intraoperative facial nerve monitoring has been shown to be cost-effective for both primary and revision middle ear and mastoid surgical procedures, with a higher number of quality-adjusted life-years and lower average cost than for a no-monitoring strategy.[90]

Unconventional Tests of Facial Nerve Function

Acoustic Reflex Evoked Potentials

Hammerschlag and associates[91] reported a scalp-recorded potential at 12- to 15-msec latency in response to acoustic stimulation contralateral to the recording site and attributed this to facial motor pathway activation. The response persisted after paralysis during anesthesia, and these workers proposed its use for intraoperative monitoring of facial nerve function. However, the response was extremely small (much lower in amplitude than that of the auditory brainstem response), which would make it difficult and slow to record, requiring prolonged averaging. This response seems unlikely to be useful, because audible EMG monitoring gives essentially instantaneous feedback for intraoperative assessment of facial nerve function.

Antidromic Potentials

If a motor nerve is electrically or mechanically stimulated at some point between its cell body and its synapse on a muscle fiber, action potentials will be propagated in two directions: An orthodromic or antegrade impulse will travel distally toward the muscle, whereas an antidromic or retrograde impulse will travel proximally toward the cell body. The orthodromic impulse will cross the neuromuscular junction, resulting in an observable muscle contraction and a recordable compound muscle action potential. This *M-wave* is the same potential recorded in ENoG. Although the antidromic impulse will not cross a synapse, it can be recorded by electrodes on the proximal nerve (near field) or at a distance (far field). Tashima and coworkers[92] recorded electrical responses from the geniculate ganglion region in guinea pigs while stimulating the facial nerve at the stylomastoid foramen. These near-field antidromic responses were reliably altered by surgical lesions placed between the stimulating and the recording electrodes. Other modifications for improving the consistency and reliability in producing antidromic potentials involve stimulation of the buccal branch of the facial nerve through Stensen's duct, rather than percutaneous stimulation of the facial nerve branches.[93]

Far-field antidromic potentials have been recorded from the scalp after electrical stimulation near the stylomastoid foramen, in hopes that this would yield a noninvasive test of the integrity of the intratemporal or intracranial portions of the facial nerve. However, these responses are difficult to record and interpret. Metson[94] concluded, on the basis of studies in cats, that the intracranial nerve was the main generator, but Kartush and associates[95] found in dogs that the mastoid segment was primarily responsible.

As previously mentioned, the antidromic impulse will not travel farther "upstream" than the facial nucleus motor neuron, but it can be reflected back along that neuron's axon in an orthodromic direction, eventually reaching the muscle and stimulating a muscle action potential—the *F-wave*—that is delayed relative to the initial M-wave. These F-waves are unusually large in hemifacial spasm,[96] suggesting that facial nucleus hyperexcitability plays a role in that disorder. F-waves are easily disrupted by even the mildest degree of facial paresis.[97] They often are abnormal with delayed latency or decreased amplitude or are absent in patients with acoustic tumors, even when clinical examination of facial nerve function yields normal findings.[98] However, they do not predict postoperative function when tumor size is taken into consideration.[99]

Antidromic stimulation of peripheral branches of the facial nerve has been introduced into intraoperative monitoring, with continuous recording of either near-field potentials from the facial nerve near the brainstem[100] or F-waves from facial musculature.[89] Wedekind and Klug[98,101] believe that F-wave monitoring provides earlier and better prognostic information to the surgeon than that obtained with continuous EMG monitoring.

Blink Reflex

Electrical or mechanical stimulation of the supraorbital branch of the trigeminal nerve elicits a reflex contraction (blink) of the orbicularis oculi muscle, which is innervated by the facial nerve. Two studies found blink reflex abnormalities (recorded by EMG) in many patients with acoustic tumors (far more than were found by ENoG).[102,103] Although this finding suggests that subclinical facial nerve involvement is more common than has been clinically appreciated, neither study offered evidence that blink reflex testing added any prognostic information to that available from tumor size.

Magnetic Stimulation

A rapidly varying magnetic field produced by a surge of current in a coil placed over the skin will induce electrical currents in underlying tissue and can be used to stimulate nerves. This method offers two potential advantages over conventional electrical stimulation of the facial nerve: (1) the nerve can be maximally stimulated without pain or discomfort, and (2) if the coil is placed in the temporoparietal area (transcranial stimulation), the nerve seems to be stimulated in the region of the geniculate ganglion or the internal auditory canal. This functionality, when coupled with electrical stimulation of the facial nerve at the stylomastoid foramen, could obviously be useful for site-of-lesion determination, at least in the earliest phases of paralysis before electrical excitability distal to a lesion is lost.[104-108]

Patients with magnetically stimulable nerves, when tested up to 4 days after onset of Bell's palsy, had a better prognosis than those whose

responses had been lost.[109] Unfortunately, it was unclear whether this test added prognostic information once the severity of the clinically assessed paresis was taken into account. Schriefer and colleagues[109] found no response to transcranial magnetic stimulation in serial follow-up evaluations of two patients with Bell's palsy, even after rapid and complete clinical recovery (2 and 3 weeks, respectively), suggesting that this technique may not be useful for prognostic purposes after the first few days. Rösler[110] and Duckert[111] and their coworkers found that magnetic stimulation offered no unique prognostic information in acoustic tumor cases once tumor size (the best predictor of facial nerve outcome) is considered.

Optical Stimulation

Another method of stimulating the facial nerve without direct tissue contact is by optical excitation. Contact-free optical excitation provides the important potential benefit of neural stimulation without mechanical trauma. Unfortunately, early efforts at optical nerve stimulation using ultraviolet-wavelength excimer laser were successful only at energy densities comparable to the photoablation threshold.[112] Wells and colleagues demonstrated successful optical stimulation of frog and rat sciatic nerve with pulsed short- and medium-wavelength infrared laser light, with neural tissue damage occurring at energy densities 2.5 times neural excitation threshold.[113] More recently, Teudt and coworkers used short-wavelength infrared pulsed laser light to successfully stimulate the extratemporal facial nerve without neural damage seen on histologic examination.[114] Neural tissue injury occurred at an energy density similar to that reported by Wells and colleagues,[113] approximately 1.3 to 3 times that of threshold.

Such optical excitation techniques would have an obvious advantage for use in locations in which mechanical dissection of the facial nerve must be kept to a minimum, such as at the cerebellopontine angle, where the nerve does not yet have a protective layer of epineurium for support. This specific application has not yet been reported.

Transcranial Electrical Stimulation–Induced Facial Motor Evoked Potentials

Current methods of intraoperative facial nerve monitoring allow for active stimulation of the nerve at the level of the hand-held stimulator. Although this technique is beneficial in identifying and confirming the integrity of the nerve at all points distal to the dissection, it cannot test the integrity of the nerve proximal to dissection, which may be vital to know during dissection of a large cranial base tumor, when the facial nerve root entry zone is not readily identified. Antidromic stimulation and F-wave monitoring of the facial nerve can theoretically overcome this drawback. Another more recently developed method involves transcranial electrical stimulation of the cortical facial motor pathway and measurement of the corresponding facial motor evoked potentials (MEPs).

In intraoperative transcranial electrical stimulation, spiral electrodes are placed at Cz and C3/C4 overlying the facial motor cortex contralateral to the side of the lesion being removed. Electrical stimulation of these facial corticobulbar neurons is propagated across the pyramidal decussation to stimulate facial nucleus neurons on the side ipsilateral to the lesion. Lower motor neuron stimulation propagates to the facial musculature, where a muscle action potential is recorded in the standard fashion; this corticobulbar-derived CMAP is the MEP. Thus, the integrity of the entire facial motor tract is tested by this technique. MEP recordings are performed before tumor microdissection (baseline), at regular intervals intraoperatively, and immediately after completion of dissection (final). The final-to-baseline MEP amplitude ratio is calculated to determine the likelihood of an intact or disrupted facial motor tract.[115]

Transcranial excitation of the facial motor cortex is dependent on multipulse stimulation, in contrast with facial nerve stimulation, which adds to the specificity of the technique. However, application of the transcranial electrical stimulation technique is characterized by multiple constraints, including the necessity for nonvolatile anesthesia (only propofol and narcotic infusions are used for maintenance of anesthesia, as volatile agents adversely affect corticobulbar stimulability), use of high stimulus voltages (on the order of 100 to 400 V) and subsequent need to pause surgical dissection during MEP acquisition, and the possibility of epileptic discharge during cortical stimulation.[116]

Nonetheless, the technique has been used with good success by several groups.[117-119] Final-to-baseline MEP amplitude ratios greater than 50% appear to correlate well with good immediate postoperative facial function (reported as House-Brackmann grade I or II); ratios less than 50% correlate with varying degrees of worse function (reported as House-Brackmann grades III to VI). This technique is in its infancy and is likely to undergo continued refinement, with its ultimate utility to be determined.

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CHAPTER ONE HUNDRED AND SEVENTY

Clinical Disorders of the Facial Nerve

Douglas E. Mattox

Key Points

- The term *Bell's palsy* should be reserved for abrupt-onset, idiopathic facial paralysis without other identified cause.
- Progressive facial paralysis is not Bell's palsy and should prompt an investigation for neoplasm.
- The etiology of Bell's palsy is reactivation of herpes simplex virus (HSV).
- The mainstay of treatment for Bell's palsy is corticosteroids.
- Ramsay Hunt syndrome (herpes zoster oticus) is caused by varicella-zoster virus (VZV).
- Bell's palsy is common during pregnancy and is managed as for any other facial palsy, in collaboration with the patient's obstetrician.
- Bilateral facial paralysis suggests the possibility of Lyme disease.
- When facial paralysis occurs in the setting of chronic otitis media (suppurative or cholesteatoma), the first line of treatment is to resolve the ear disease; subsequent recovery from the facial paralysis is the usual outcome in this setting.

This chapter describes clinical disorders of the facial nerve (Fig. 170-1). Most of the discussion is devoted to idiopathic paralysis (Bell's palsy); however, disorders of the facial nerve associated with other diseases also are presented. The usefulness of electrodiagnostic testing and the medical and surgical management of Bell's palsy are reviewed as well.

Bell's Palsy: Spontaneous Idiopathic Facial Paralysis

The term *Bell's palsy* should be reserved for cases of facial paralysis in which signs and symptoms are consistent with the disease and in which a diligent search fails to identify another cause for the clinical findings. Every experienced otolaryngologist has seen patients whose facial paralysis was caused by malignancy, facial neuroma, intracranial tumor, infection, or some other manageable cause but was misdiagnosed by another physician. The dictum that "all that palsies are not Bell's" cannot be overemphasized.

Although older literature relegated Bell's palsy to a diagnosis of exclusion, May and colleagues[1] emphasized the diagnosis on the basis of specific clinical features. Taverner[2] outlined the minimum diagnostic criteria for Bell's palsy: (1) paralysis or paresis of all muscle groups of one side of the face; (2) sudden onset; (3) absence of signs of central nervous system (CNS) disease; and (4) absence of signs of ear or cerebellopontine angle disease. The differential diagnosis of facial palsy is shown in Table 170-1.

Incidence

The annual estimated incidence of Bell's palsy is 20 to 30 patients per 100,000 population; it was 20.2 of 100,000 per year in the United Kingdom between 1992 and 1996.[3] The incidence is greater in patients older than 65 years (59 of 100,000) and lower in children younger than age 13 (13 of 100,000).[4-6] The male-to-female ratio for Bell's palsy is approximately equal, except for a predominance in women younger than 20 years of age and a slight predominance in men older than 40 years.[4] The left and right sides of the face are equally involved. Thirty percent of patients will have incomplete paralysis on presentation, and 70% will have a complete paralysis.[7] Bilateral paralysis occurs in 0.3% of patients, and 9% have a history of previous paralysis.[4] A family history of Bell's palsy can be elicited in 8% of patients.[4]

Etiology

Proposed causes of Bell's palsy include microcirculatory failure of the vasa nervorum,[8,9] viral infection, ischemic neuropathy, and autoimmune reactions.[10,11] Of these, the viral hypothesis has been the most widely accepted[4,12]; however, no virus has ever been consistently isolated from the serum of patients with Bell's palsy.[13] Thus, the evidence for the viral hypothesis is indirect, relying on clinical observations and changes in viral antibody titers. Furthermore, although the underlying cause may be viral, the immediate cause of the paralysis itself is debated to be viral neuropathy alone or ischemic neuropathy secondary to viral infection.[14]

Acute facial paralysis can occur as part of many viral illnesses, including mumps,[15] rubella,[16] herpes simplex,[17] and Epstein-Barr virus.[18,19] A viral cause for Bell's palsy also is supported by the finding that it seems to be part of a polyneuritis syndrome in which the facial palsy is the most obvious cranial nerve involved. Careful neurologic examination will reveal other cranial nerve weaknesses in more than 50% of patients with Bell's palsy.[20,21] Adour[22,23] found several affected cranial nerves in most patients (Table 170-2).

A direct link between Bell's palsy and viral infection has been difficult to establish. Serologic studies have examined both seroconversion and prevalence of antigens to suspected etiologic agents in patients with Bell's palsy, especially HSV and VZV. The results have been conflicting and have been dependent on techniques used and popula-

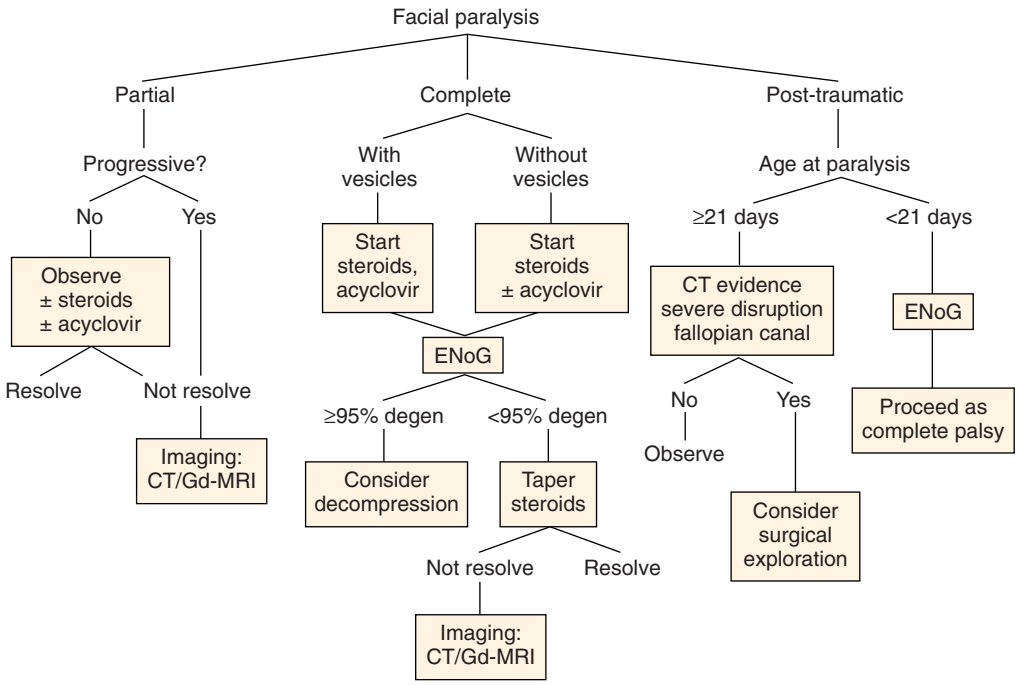

Figure 170-1. Facial paralysis: management algorithm.

Table 170-1
Differential Diagnosis of Facial Paralysis

Acute Paralysis	Chronic or Progressive Paralysis
Polyneuritis	Malignancies
· Bell's palsy	· Primary parotid tumor
· Herpes zoster	· Metastatic tumor
· Guillain-Barré syndrome	Benign tumors
· Autoimmune disease	· Schwannoma
· Lyme disease	· Glomus tumor
· Human immunodeficiency virus infection	Cholesteatoma
· Kawasaki's disease	
Trauma	
· Temporal bone fracture	
· Barotrauma	
· Birth trauma	
Otitis media	
· Acute bacterial	
· Chronic bacterial	
· Cholesteatoma	
Sarcoidosis	
Melkersson-Rosenthal syndrome	
Neurologic disorders	
· Human immunodeficiency virus infection	
· Cerebrovascular disorder—central or peripheral	

Modified from Adour KK, Hilsinger RL Jr, Callan EJ: Facial paralysis and Bell's palsy: a protocol for differential diagnosis. *Am J Otol*. 1985;Nov(Suppl):68.

Table 170-2
Polyneuropathy in Bell's Palsy

Symptom	Incidence (%)
Hypesthesia or dysesthesia of the glossopharyngeal or trigeminal nerve	80
Hypoesthesia of C2	20
Vagal motor weakness	20
Trigeminal motor weakness	3
Facial or retroauricular pain	60
Dysgeusia	57
Hyperacusis	30
Decreased tearing	17

From Adour KK: Current concepts in neurology: diagnosis and management of facial paralysis. *N Engl J Med*. 1982;307:348.

tions studied.[24,25] One reason for failure of these studies is that they sought for signs of an acute infection immediately preceding the onset of the Bell's palsy. No seasonal predilection or epidemic clustering has been documented, however, so it is much more likely that Bell's palsy is caused by reactivation of a latent virus rather than direct, communicable viral infection.

Morgan and colleagues[26,27] and Vahlne and coworkers[28] support the hypothesis that Bell's palsy is a reactivation of VZV that may be initiated by several stresses, including heterotopic viruses (viruses other than herpesviruses) or physical or metabolic stress. Activation by other agents may explain the diversity and inconsistency of the antibody titers reported in various studies, as well as the epidemicity or clustering of cases. This reactivation can occur without a measurable antibody response to HSV.

The best evidence for reactivation of HSV as the mechanism for Bell's palsy comes from several studies of the geniculate ganglion and facial nerve. Futura[29] and Takasu[30] and their coworkers have demonstrated HSV-1 DNA in both the trigeminal and geniculate ganglia of unselected autopsy specimens. Burgess and colleagues[31] reported a single of case of a patient who died shortly after Bell's palsy developed and in whom HSV-1 genomic DNA was identified in the geniculate ganglion of the facial nerve. Assay of archival control tissue for viral DNA yielded negative findings. In the most important study so far, Murakami and associates[32] looked at endoneurial fluid and postauricular muscle from patients with Bell's palsy or Ramsay Hunt syndrome and control subjects. Polymerase chain reaction (PCR) assay was used to test for HSV-1 DNA and VZV DNA, and the results were confirmed with Southern blot analysis. HSV DNA was detected in 11 of 14 patients with Bell's palsy, whereas VZV DNA was not recovered from any. Conversely, VZV DNA was recovered from all the patients with Ramsay Hunt syndrome, whereas none had HSV-1 DNA. Unaffected control subjects had neither virus DNA. This study suggests a clean distinction between Bell's palsy and Ramsay Hunt syndrome; however, other studies suggest more overlap.

Futura and coworkers[33] studied 142 patients with both clinical Ramsay Hunt syndrome and acute facial palsy. Thirteen were diagnosed as having Ramsay Hunt syndrome on the first visit, and in another eight, vesicular lesions developed subsequent to their initial evaluation. Of the 121 with nonvesicular acute facial paralysis, 35 had VZV DNA detected in their saliva or serologic evidence of VZV reactivation. Yamakawa and colleagues[34] demonstrated how technique-sensitive these studies are. Using two different PCR techniques, these investigators found high but differing rates of VZV DNA detection in patients with Ramsay Hunt symdrome.

A few animal studies also support a viral cause for Bell's palsy. Ishii and coworkers[35] induced facial paralysis in guinea pigs by inoculating the surface of the facial nerve with HSV-1. The severity of paralysis and subsequent degeneration were evaluated histologically and seemed to be worse if the epineurium was removed before inoculation. Of interest, these workers found greater extension of the virus centrally within the nerve than toward the periphery. Sugita and associates[36] induced an acute transient facial paralysis in mice by injecting HSV into the auricles and tongues of mice. The paralysis started 6 to 9 days after inoculation and resolved after 3 to 7 days. Viral antigens were detected in the facial nerve, geniculate ganglion, and facial nerve nucleus. A spontaneously recovering ischemic facial palsy also can be induced in cats by embolization of internal and external maxillary arteries. The onset of the paralysis is immediate after embolization and resolves after 2 months.[37]

Although it is likely that the underlying disease in Bell's palsy is viral polyneuropathy, an unresolved question is why such a profound effect on the facial nerve occurs, in contrast with the relatively minor and transient changes in the other cranial nerves. The major anatomic difference between the facial and other cranial nerves is in its long bony canal. Fisch[38] measured the diameter of the fallopian canal throughout the temporal bone and found that the narrowest point was at the junction of the internal auditory canal and the labyrinthine portion, which he called the *meatal foramen*. The meatal foramen averaged 0.68 mm in diameter, whereas the remainder of the fallopian canal measured 1.02 to 1.53 mm. Fisch reasoned that edema in this narrow segment of the fallopian canal could cause damming of the axoplasmic flow within the facial nerve. This site of lesion in Bell's palsy has been confirmed by clinical observation[39,40] and by intraoperative neuronography.[41,42] A similar site of lesion has been identified electrophysiologically in herpes zoster oticus.[43]

Histopathology

Fowler[16] reported autopsy findings in a patient who died shortly after Bell's palsy developed. The entire intratemporal nerve contained dilated and engorged veins and venules. Fresh hemorrhage was found within the internal auditory canal surrounding the facial nerve that extended as far as the geniculate ganglion. Fowler theorized that the ischemia resulted from microthrombi rather than vasospasm.

Reddy and associates[44] examined a facial nerve 17 days after the onset of spontaneous paralysis. The nerve showed scattered degeneration of the myelin sheaths and axons. From 10% to 30% of facial nerve fibers were surrounded by phagocytic cells. The perivascular areas also showed inflammatory reactive changes and hemorrhage.

Proctor and coworkers[45] examined a patient who died 13 days after the onset of facial paralysis. The facial nerve showed lymphocytic infiltration and phagocytosis of myelin by macrophages throughout the infratemporal course of the nerve. Initially, these findings were interpreted as evidence for a viral cause. However, when McKeever and colleagues[46] reexamined the case, they emphasized that the inflammatory cells were most prominent where the facial nerve was surrounded by bone, especially in the labyrinthine portion of the fallopian canal, but not within the internal auditory canal. These investigators theorized that the histopathologic features suggested a compression-type injury with no evidence of vascular occlusion.

O'Donoghue and Michaels[47] found degeneration of myelin sheaths and axon fibers throughout the intratemporal course of the facial nerve. The nerve was constricted at the meatal foramen, and an osteoclastic giant cell reaction caused resorption of bone around the geniculate ganglion. These workers interpreted the observed changes as consistent with a viral cause, but as pointed out by Jenkins and associates,[40] these findings do not preclude edema and constriction of the facial nerve as the final event leading to the paralysis.

Podvinec[48] found inflammatory infiltrates in the intratemporal portion of the facial nerve 6 months after the onset of the palsy, along with signs of wallerian degeneration and regeneration. He suggested that the persistence of infiltrates for this extended time may result from compromised circulation within the fallopian canal. Jackson and colleagues[49] reported the histopathologic findings from the labyrinthine segment of the facial nerve in a patient 1 year after the onset of a total facial paralysis secondary to herpes zoster. A portion of the nerve within the auditory canal was essentially healthy; however, at the meatal foramen, the nerve became a mixed fibrotic and necrotic acellular mass.

Michaels[50] described the histopathologic findings in an autopsy performed 11 days after the onset of Bell's palsy. As in other studies, histopathologic features included demyelination, compression, bone resorption, and lymphocytic infiltration in the proximal labyrinthine segment of the facial nerve. Michaels cautioned against the overinterpretation of bulging of the nerve in the distal internal auditory canal, because it was found on both the healthy and the pathologic sides.

Another approach to the histologic evaluation of Bell's palsy is with biopsy specimens obtained intraoperatively, including biopsy specimens of the chorda tympani and greater petrosal nerve. Chorda tympani specimens in acute Bell's palsy have shown degeneration of myelinated fibers but no inflammatory response.[51,52] Fisch and Felix[14] examined greater petrosal nerve specimens obtained during middle cranial fossa facial nerve decompression. Their findings included degeneration and demyelination of large axons and lymphocytic infiltration. They found these results to be consistent with wallerian degeneration starting proximal to the geniculate ganglion, probably from the meatal foramen.

In summary, most histologic studies show diffuse demyelination of the facial nerve throughout its intratemporal course, with the most severe changes in the labyrinthine segment and at the meatal foramen.

Central Nervous System Changes

Auditory symptoms, usually in the form of hyperacusis, may be present in up to 30% of patients with Bell's palsy.[53] The cause for these auditory symptoms is unknown. McCandless and Schumacher[54] did not find evidence of a lesion affecting the cochlear nerve in patients with facial paralysis. Many researchers have attributed the hyperacusis to decreased damping of sound secondary to dysfunction of the stapedius muscle. However, most investigators have not found reduced contralateral stapedius reflex thresholds, suggesting that an absence of stapedial damping is not the cause.[55]

On the basis of these observations, many investigators have concluded that the auditory dysfunction results from CNS involvement.[53] A few patients with Bell's palsy have auditory brainstem response (ABR) abnormalities compared with ABRs in age-matched control subjects. These abnormalities include an increase in the wave I to V interval and

the interaural difference for wave V. These changes usually are present bilaterally and resolve with recovery from the facial paralysis.[55] These findings suggested a brainstem abnormality associated with Bell's palsy that the study authors hypothesized is related to the reactivation of HSV. These findings should be interpreted with caution. Other investigators did not confirm the presence of such ABR abnormalities,[56,57] and the findings have not been corroborated by somatosensory evoked potentials or visual evoked potentials.

Several investigators have looked for CNS changes in acute facial paralysis by studying the cerebrospinal fluid (CSF). Again the results are contradictory. Findings of elevated levels of myelin basic protein[58] and pleocytosis[59] in the CSF support CNS involvement in Bell's palsy. Weber and coworkers[60] found a normal total cell count, total protein concentration, blood-CSF permeability, and CSF–to–serum immunoglobulin ratios in most patients with Bell's palsy. Only approximately 10% of these patients demonstrated some pathologic feature of the CSF, including a mild increase in blood-CSF permeability or pleocytosis. These workers concluded that their findings did not support the hypothesis that Bell's palsy was a part of a cranial polyneuropathy.

CNS changes in Bell's palsy also have been suggested by magnetic resonance imaging (MRI). Jonsson and associates[61] found brain or brainstem changes in 5 of 19 patients with Bell's palsy. These areas of increased signal intensity did not correlate with the facial nerve brainstem nucleus or the supranuclear pathways and were interpreted as indicative of unrelated vascular disease.

Electrophysiology and Testing

The multiple branches from the facial nerve, including the greater petrosal nerve, stapedial nerve, chorda tympani, and muscular branches, led to the development of topodiagnostic testing to localize the site of a facial nerve lesion. Schirmer's test evaluates greater petrosal nerve function by measuring the lacrimal secretions accumulating on a piece of filter paper placed under the eyelid at the medial canthus.[62] Stapedial nerve function can be evaluated with stapedial reflex testing. The chorda tympani nerve can be evaluated with taste testing or with the submandibular salivary flow test described by Magielski and Blatt.[63] Unfortunately, the accuracy of localization with topodiagnostic testing has been disappointing.[42] This is not a surprising finding in Bell's palsy, in which the lesion is a diffuse demyelination throughout the nerve. However, topodiagnostic testing also has yielded disappointing results in investigation of tumors in which a sharply defined site of lesion was expected.[64]

Electrodiagnostic tests on the motor branches of the facial nerve also have been used to assess function and predict outcome. All of these tests have a similar shortcoming: Stimulation and recording are performed only distal to the lesion, rather than on opposite sides of the site of injury.[65] Accordingly, such testing should be delayed because it will not demonstrate abnormalities until nerve degeneration has reached the site of stimulation, usually 4 to 5 days after injury.

Nerve Excitability Threshold

The use of electricity as a neurodiagnostic test was described by Duchenne in 1892 and was adapted to the facial nerve by Laumans and Jongkees.[66] Application of the Hilger nerve stimulator is the method of facial nerve evaluation most commonly used by otolaryngologists. The extratemporal portion of the nerve is stimulated with a small-amplitude, pulsed direct current. The face is observed for the lowest current to produce a visible twitch. Although a threshold difference of more than 3.5 mA between the two sides has been considered to be suggestive of nerve degeneration, Gates[67] found that with careful technique, low thresholds were obtained with percutaneous stimulation. The thresholds increased slowly with age and body weight, but nerve excitability thresholds greater than 1.25 mA in the upper division and 2 mA in the lower division were statistically abnormal.

Maximal Stimulation Test

A modification of the minimal excitability test, the maximal stimulation test, attempted to determine the difference between the strength and amount of contraction of the facial musculature caused by a supramaximal electrical stimulus.[68,69] However, the maximal stimulation test is difficult to quantitate and is more subject to interobserver variation than is the minimal stimulation test.[65]

Electroneurography

Electroneurography (ENoG), also called electroneuronography, adds recording of the facial muscle action potential with surface or needle electrodes to the stimulation tests. Esslen[70] introduced the use of bipolar surface electrodes for stimulation and recording of responses. The two electrodes are moved independently to produce the maximum amplitude of response. The response is evaluated by comparing the peak-to-peak amplitude of the maximum response obtained for the two sides of the face.

Electromyography

Electromyography (EMG) measures muscle action potentials generated by spontaneous and voluntary activity. It is distinct from other electrodiagnostic tests in which the activity is generated by active stimulation of the nerve. Denervation potentials are seen 10 days or longer after onset of the palsy; therefore, they are of limited value in determining early prognosis of facial paralysis. However, the loss of voluntary motor unit potentials within the first 3 to 4 days of paralysis suggests a poor prognosis.[65] Conversely, retention of voluntary motor activity past the 7th day suggests that complete degeneration will not occur. Sittel and Stennert[71] found that the detection of spontaneous fibrillation by needle EMG had an 80% accuracy in predicting a poor outcome 10 to 14 days after onset of paralysis. Unfortunately, this is too late to be useful in surgical decision making.

Nerve Conduction Velocity

Nerve conduction velocity can be measured between the stylomastoid foramen and the mandibular branch of the facial nerve. A strong correlation has been found between decrease in nerve conduction velocity and decrease in the compound nerve action potential measured by ENoG during the first 2 weeks after the onset of paralysis.[72] Normal facial nerve conduction velocity ranges between 37 and 58 meters/second, and conduction velocities in this range were associated with uniformly good outcomes. Conduction velocities between 20 and 30 meters/second carry a 50% chance of significant residual paresis or synkinesis, and those less than 10 meters/second were associated with poor outcomes.

Interpretation of Electrical Tests

All electrical stimulation tests have the same fundamental weakness: inferences are made on the basis of tests on the nerve distal to the site of injury within the temporal bone. Therefore, there is an inherent delay between the onset of the injury and the development of sufficient degeneration of the distal segment of the nerve to be discovered by the tests. Only intraoperative monitoring, with stimulation proximal to the lesion, provides direct information about the state of the nerve at the site of the lesion. Newer experimental techniques, including antidromic stimulation and magnetic stimulation, hold some promise for circumventing this limitation.

Excellent recovery of facial function is invariable when the decline in the compound action potential (CAP) as measured by ENoG does not reach 90%, and one half of patients in whom this level of degeneration is documented also have excellent outcomes.[73,74] The problem is how to identify patients who will not achieve a good recovery, and at least a partial answer lies in the combination of ENoG with standard EMG. For patients who maintain recordable voluntary motor potentials despite a severe depression of the CAP, the prognosis is excellent.[74] This finding may be explained by severe desynchronization of the motor units, causing a reduced or absent CAP.

Electromagnetic Stimulation of the Facial Nerve

Facial nerve testing with electromagnetic stimulation also has been explored. Benecke and colleagues[75] were able to stimulate the nerve with cortical (supranuclear) electromagnetic discharges, demonstrating that the nerve could be stimulated trans-synaptically. Direct stimulation of the facial nerve with electromagnetic stimulation also has been described. On the basis of latencies of compound muscle action

potentials from magnetic and electrical stimulation of the facial nerve, investigators concluded that the root entry zone of the facial nerve was the most likely site of excitation with magnetic stimulation.[76] These data are tantalizing because the ideal test of the facial nerve would stimulate the nerve medial to the presumed site of the conduction block in the labyrinthine segment. Meyer and coworkers[77] found an absence of electromagnetic responses to be the earliest sign of nerve conduction block in patients with Bell's palsy, and that electromagnetic stimulation could differentiate between central and peripheral nerve lesions.

It is not yet clear, however, whether magnetic stimulation will be a useful predictive test, because significant discrepancies have been noted between the response to magnetic stimulation and clinical findings. Patients with incomplete palsies may exhibit complete loss of response to magnetic stimulation.[78] Loss of response to electromagnetic stimulation occurs in more patients with Bell's palsy than does loss of electrical stimulation, and this finding may persist after facial function has clinically recovered.[75,79] Nowak and associates[80] tested 65 patients with facial paralysis with both transcranial magnetic stimulation and electrical stimulation of the facial nerve. A severe reduction in muscle action potiental response was observed in both Bell's palsy and herpes zoster and did not correlate with the clinical grade of the palsy. On the basis of current clinical information, electrical stimulation seems to add little to the diagnostic armamentarium in facial palsy.

Imaging of the Facial Nerve

Gadolinium-enhanced MRI has been used to study the peripheral facial nerve in Bell's palsy. Enhancement of the facial nerve is a common finding in healthy persons, making evaluation of facial nerve findings on MRI difficult. The most consistent area of enhancement in Bell's palsy and herpetic palsy is the distal meatal and labyrinthine segments.[81,82] Sartoretti-Schefer and associates[82] hypothesized that the gadolinium enhancement resulted from breakdown of the blood-brain barrier or from venous congestion in the epineurium. However, the location or degree of enhancement does not correlate with the recovery of facial movement.[81,83] In a recent report that used high-resolution gadolinium-enhanced MRI with surface coils, Kress and colleagues[84] were able to differentiate 3 patients with poor outcomes from 17 who recovered on the basis of the wide distribution and intensity of enhancement. The development of more detailed MRI techniques may prove useful in determining the prognosis of Bell's palsy.[85]

Prognosis and Statistics

The prognosis for most patients with Bell's palsy is excellent: 80% to 90% recover completely.[6,53] Peitersen[7] reported that none of 1505 patients followed without management had permanent complete paralysis, and that 17 had moderate to severe sequelae (contracture, synkinesis, palsy). Many large series of patients with Bell's palsy have been analyzed to identify prognostic factors that have a significant impact on outcome. The most important such factor is whether the paralysis is incomplete or complete. The prognosis for affected persons in whom complete facial paralysis never develops is excellent: 95% to 100% recover with no identifiable sequelae.[6,86]

The many reports available in the literature are difficult to compare, because they use different criteria for inclusion and evaluation of outcome. Stankiewicz[87] collated the outcomes from nine reports, including the large series of Park and Watkins[88] and Peitersen.[89] The overall results from these series were 53% complete recovery, 44% partial recovery, and only 3% no recovery. The results in the general population probably are better than those in these studies.

Other factors associated with poor outcome include hyperacusis; decreased tearing; age older than 60 years; diabetes mellitus; hypertension; and severe aural, anterior facial, or radicular pain.[4,90] Abraham-Inpijn and associates,[91] however, compared outcomes in 200 patients by use of several potential prognostic factors, including severity of the facial paralysis, mean arterial pressure, age, clinical or chemical diabetes mellitus, and history of hypertension. Only the severity of the paralysis at its maximum extent and the mean arterial pressure at presentation proved to be statistically significant. Peitersen[7] noted a correlation between sequelae (synkinesis, contracture) and the interval between paralysis and the onset of recovery.

Management

Management of Bell's palsy has had a long, complex evolution that is not yet complete. Methods currently advocated include observation, corticosteroids, surgical decompression, and antiviral agents.

The use of corticosteroids in Bell's palsy was first proposed by Rothendler.[92] Since then, corticosteroid therapy has become the most common approach to management of Bell's palsy.[93] Adour and Wingerd[94,95] stated that although prednisone does not reduce the number of patients with eventual partial denervation or contracture or synkinesis, it reduces the number of patients with eventual complete denervation, therefore making the disease less severe. Numerous prospective and retrospective studies on the effectiveness of corticosteroids in Bell's palsy have been reported. In a meta-analysis, Ramsey and colleagues[96] found two studies with sufficient numbers of patients and rigor for analysis and concluded that treated patients had a 17% better chance of complete recovery than placebo-managed or untreated patients. Their analysis of a larger number of studies concluded that the odds of recovery with steroid treatment ranged between 49% and 97%, versus 23% and 64% for untreated patients. Consensus is lacking regarding the dose or duration of steroid treatment.

The case for steroid treatment in children in less clear. Neither Prescott[97] nor Unüvar and coworkers[98] found a beneficial effect of corticosteroids for Bell's palsy in children. Salman and MacGregor[99] came to the same conclusion in their systematic review of the literature.

Patients with Bell's palsy commonly are treated with antiviral agents in addition to prednisone,[100] although once again, definitive proof of efficacy is lacking. Although initial enthusiasm was high for the use of a combination of steroids and antivirals[101,102] more recent studies have yielded negative results. Sullivan and colleagues[103] conducted a four-armed, multi-institutional trial of prednisolone, acyclovir, a combined regimen of both agents, and placebo. Significant improvement in outcome was observed in both arms containing prednisolone, but no additional benefit from antiviral treatment was found. A similar outcome was described in a study reported from Japan.[104] Current opinion does not support the use of antivirals in Bell's palsy.

Surgical therapy is more controversial, because unlike with corticosteroids, it is associated with the possibility of significant additional injury. Early enthusiasm for transmastoid decompression of the tympanic and mastoid segments of the facial nerve has waned,[105] and the procedure has been abandoned,[1] because randomized trials showed no benefit[1] and because of evidence that the site of the lesion is in the proximal labyrinthine portion of the facial nerve, which is inaccessible through the mastoid.[38]

The efficacy of surgical decompression of the meatal foramen and labyrinthine segment of the facial nerve in patients with poor prognosis as shown by ENoG testing is promising, but it has been difficult to assemble a large enough series to definitively establish its value in randomized trials. Fisch[38] compared outcomes in 14 surgical patients with 90% degeneration or greater as shown by ENoG within 3 weeks of the onset of paralysis with those in 13 similar patients who refused surgery. He found a subtle but statistically significant improvement in the long-term facial recovery in the operative group. Sillman[74] found a shift toward grade I and II recovery in patients with greater than 90% degeneration who underwent surgical decompression versus those managed with corticosteroids alone. In the most well-controlled study of middle fossa decompression of the facial nerve in Bell's palsy, Gantz and colleagues[106] evaluated the outcome when ENoG showed greater than 90% degeneration, and no voluntary motor unit potentials were found on electromyography performed within 2 weeks of onset of paralysis. Ninety-one percent of surgical patients achieved House-Brackmann grade I or II recovery, versus a 42% chance of these same results with steroids alone. Graham and Kartush[107] described six patients with recurrent facial paralysis, one of whom had Melkersson-Rosenthal syndrome. None of these patients experienced recurrent facial paralysis after total seventh nerve decompression from the stylomastoid foramen to the internal auditory canal. Thus, surgical decompression remains in the armamentarium for the management of facial paralysis, but timing and appropriate patient identification remain difficult.

Persistent synkinesis can be a problem for many patients recovering from severe degeneration of the facial nerve regardless of the cause. Chua and associates[108] performed a dose escalation study of botulinum toxin to determine the best treatment for reducing eyelid synkinesia and found the lowest dose, 40 units injected into the orbicularis oculi, to give the best reduction in synkinesia while avoiding ptosis. Borodic and coworkers[109] reported similar results with botulinum toxin in a multi-institutional study.

Special Cases of Facial Paralysis

Ramsay Hunt Syndrome

Ramsay Hunt syndrome (herpes zoster facial paralysis) differs from Bell's palsy, because it is associated with VZV infection (as shown by rising titers of antibodies to VZV) and the presence of skin vesicles on the pinna, retroauricular area, face, or mouth. Compared with Bell's palsy, Ramsay Hunt syndrome generally causes more severe symptoms, and patients are at higher risk for the development of complete nerve degeneration.[110]

Varicella, or chickenpox, is the manifestation of primary infection by VZV (HSV, varicellae) in a nonimmune host. Herpes zoster is the manifestation of this same virus infection in a partially immune host. Serologic and epidemiologic data strongly suggest that varicella-zoster represents the reactivation of a latent virus rather than reinfection. After the primary infection, the virus probably travels to the dorsal root to extramedullary cranial nerve ganglia, where it remains dormant until it is reactivated. Reactivation generally occurs during a period of decreased cell-mediated immunity. VZV infection is the second most common cause of facial paralysis. The incidence of herpes zoster in patients with peripheral facial palsy is 4.5% to 9%.[111] A Mayo Clinic study[112] estimated the annual incidence of herpes zoster as 130 cases per 100,000. The incidence increased dramatically in patients older than age 60; 10% of this population had identifiable risk factors for decreased cell-mediated immunity, including carcinoma, trauma, radiotherapy, and chemotherapy. The increased incidence in the elderly is explained by an age-related decrease in cellular immune response to VZV.[113]

The severity of the paralysis is worse and the prognosis poorer in herpes zoster oticus than in Bell's palsy. Peitersen[114] reported full recovery in only 22% of patients, and Devriese[115] found complete recovery in only 16%. As in Bell's palsy, the recovery is predicted in part by the severity of the paralysis. Complete recovery occurred in only 10% of patients after complete loss of facial function and in approximately 66% after incomplete loss.[111]

The timing of the appearance of the vestibular eruption may have prognostic significance. In most cases, eruption and paralysis occur simultaneously. In approximately 25% of cases, the eruption precedes the paralysis; these patients have a higher likelihood of recovery.[111] Patients with Ramsay Hunt syndrome also are more likely than patients with Bell's palsy to have associated cranial nerve symptoms, including hyperacusis, hearing loss, and pain.[116] Ramsay Hunt syndrome can be misdiagnosed on the basis of initial presentation. In approximately 10% of patients, the vesicular rash appears well after the initial facial paralysis, and many patients demonstrate a rise in antibody to VZV without ever exhibiting cutaneous or mucous membrane vesicles—so-called Ramsay Hunt sine herpete.

Severe ocular complications can occur with herpes zoster ophthalmicus. These complications include uveitis, keratoconjunctivitis, optic neuritis, and glaucoma and are almost always associated with involvement of the ophthalmic division of the trigeminal nerve. Herpes zoster ophthalmicus may be difficult to differentiate from the localized skin rash associated with HSV infection. Although both conditions may cause keratitis, differentiation between them is extremely important, because topical corticosteroids are used to manage herpes zoster but are contraindicated in HSV infection. Ophthalmologic consultation for biomicroscopy, staining, cytologic studies, and viral isolation studies may differentiate these two conditions.[117] Adour[94] stated that aside from concerns about ophthalmic involvement, the development of skin vesicles before or after initiation of prednisone does not contraindicate corticosteroid use.

Management of patients with herpes zoster, including cephalic zoster, consists of systemic corticosteroids.[118] A specific benefit of corticosteroid therapy is a reduction in postherpetic neuralgia. The usefulness of corticosteroids in fostering recovery from the facial paralysis is controversial; however, early institution of corticosteroids seems to relieve acute pain, reduce vertigo, and decrease the incidence of postherpetic neuralgia.[119,120]

The antiviral agent acyclovir also is recommended to treat herpes zoster facial paralysis.[121,122] Acyclovir is a nucleotide analog that interferes with herpes virus DNA polymerase and inhibits DNA replication. The drug is preferentially taken up by HSV-infected cells, making it nearly nontoxic to noninfected cells. Early return of facial function after acyclovir management has been reported by some investigators,[121,122] but no beneficial effects were reported by others.[123] At the least, treatment with acyclovir seems to lessen pain and promote resolution of the vesicles.

Box 170-1

Congenital versus Acquired Facial Paralysis

Congenital

Mononeural agenesis
Congenital facial paralysis
Congenital unilateral lower lip palsy
Facial paralysis with other deficits
Möbius syndrome (cranial nerves VI, VII; bilateral)
Hemifacial microsomia
Oculoauriculovertebral dysplasia
Poland's syndrome (agenesis of pectoralis major muscle)
Secondary to teratogens
Thalidomide
Rubella

Acquired

Birth trauma
Forceps injury
Pressure from maternal sacrum
Pressure from fetal shoulder
Intracranial hemorrhage
Idiopathic
Bell's palsy
Systemic or infectious disease
Melkersson-Rosenthal syndrome
Poliomyelitis
Infectious mononucleosis
Varicella
Acute otitis media
Meningitis

Modified from Harris JP, Davidson TM, May M, Fria T: Evaluation and treatment of congenital facial paralysis. *Arch Otolaryngol*. 1983;109:145.

Congenital Facial Paralysis

The incidence of facial paralysis in newborns has been estimated at 0.23% of live births.[124] The first dilemma in managing facial palsy in an infant or young child lies in differentiating true congenital paralysis from birth trauma. The differential diagnosis of congenital facial palsy is shown in Box 170-1. Birth trauma usually causes isolated facial paralysis and other signs of injury, including facial swelling, ecchymosis, and hemotympanum. Abnormalities of other cranial nerves or abnormalities on brainstem audiometry (prolongation of the I to III or I to V interval) suggest that the facial paralysis is congenital and not traumatic.[125]

Of facial paralysis cases in infants, 78% are related to birth trauma. These cases are equally divided between forceps deliveries and vaginal deliveries plus cesarean sections,[126,127] suggesting that intrauterine facial nerve injury can occur from pressure on the infant's face by the sacral

prominence during birth. Supranuclear palsy secondary to intracranial hemorrhage also has been reported.[128]

The mildest form of congenital facial dysfunction is congenital unilateral lower lip palsy, in which the defect is limited to an absence of depressor labii inferioris muscle activity. It is associated with a lesion of the brainstem.[129]

Möbius' syndrome represents a broad spectrum of clinical and pathologic findings ranging from isolated unilateral facial paralysis (usually associated with sixth cranial nerve paralysis) to bilateral absence of facial and abducens nerve function. Multiple other cranial nerves, including the glossopharyngeal, vagus, hypoglossal, and other extraocular motor nerves, also may be affected.[129a] Forty-three percent of children with Möbius syndrome have a history of some significant event in utero.[130] A majority of patients with Möbius' syndrome demonstrate sparing of the lower face compared with the upper face. Verzijl and coworkers[131] performed electrophysiologic testing on 11 patients with Möbius syndrome and concluded that Möbius syndrome is not a primary developmental disorder of the facial musculature but is a disorder of the rhombencephalon including both motor nuclei and transversing long tracts. MRI evidence suggests evidence of absence of the seventh cranial nerve in the internal auditory canal, implying the lower face receives aberrant innervation from other nerves, including the trigeminal, glossopharyngeal, and hypoglossal nerves.

Multiple cranial nerve palsies including facial palsy are seen in the CHARGE association (*c*olobomata, *h*eart disease, *a*tresia of choanae, *r*etarded growth, *g*enital hypoplasia, *e*ar anomalies and deafness). Of CHARGE-associated cases, 75% have at least one cranial nerve involved, and 58% have two or more cranial nerves involved. The most frequently involved are the auditory nerve in 60%, the facial nerve in 43%, and the glossopharyngeal or vagus nerve in 30%.[132]

Habilitation of the face in congenital facial paralysis usually is accomplished with temporalis muscle transfer, tarsorrhaphy, upper eyelid gold weights, and free muscle transfers. Surgical exploration and decompression of the facial nerve are rarely useful.[133]

Spontaneous Facial Paralysis in Children

Bell's palsy is uncommon in children; 8% of patients in the series by Peitersen[89] and only 2% in the series by Adour and coworkers[4] were younger than 10 years of age. Manning and Adour[134] and Prescott[97] found a female preponderance in this group.

The prognosis for children with Bell's palsy is uncertain. Peitersen,[89] Taverner,[2] and Prescott[97] reported a high rate of spontaneous recovery in children with Bell's palsy, in part related to the high frequency of incomplete paralysis. Inamura and colleagues[135] found that 97% of 58 cases recovered completely and concluded that corticosteroids had no impact on recovery. However, Alberti and Biagioni[136] and Manning and Adour[134] reported that a significant percentage of children did not recover from their facial paralysis. Jenkins and colleagues[40] and Prescott[97] argued that the prognosis was determined by the amount of nerve degeneration revealed by electrophysiologic testing and noted that children and adults with similar electrical testing results had similar outcomes.

Familial Facial Paralysis

Adour and associates[4] reported that 8% of patients with Bell's palsy had a positive family history, and Willbrand and associates[137] reported a 6% incidence. In addition, sporadic reports describe families with several affected members, usually each experiencing several attacks. Cawthorne and Haynes[138] reported the cases of two brothers, one of whom had experienced five episodes of Bell's palsy and the other, three episodes. DeSanto and Schubert[139] reported 10 cases of Bell's palsy in a family over 83 years; Wilbrand and associates[137] reported a family with 29 cases of Bell's palsy over 40 years. Samuel[140] reported a child who experienced four episodes of Bell's palsy involving both sides of the face; the child's father had six episodes of unilateral Bell's palsy. Amit[141] described a family tree in which only women (the index patient and her mother, maternal aunt, and maternal grandmother) had Bell's palsy. In three of the four, onset was during puberty, suggesting that hormonal influence may have been important. The evidence from these sporadic cases is insufficient to determine conclusively a genetic influence. In such cases, however, the paralysis often has an early age at onset and is recurrent, and the prognosis is excellent.

Recurrent Paralysis

Adour and coworkers[4] found that 9.3% of patients with Bell's palsy had a history of previous paralysis. Similarly, Hallmo and colleagues[142] reported that 10.9% of patients had a history of a previous facial paralysis (approximately equally on the ipsilateral and contralateral sides). Prescott[97] reported that 20 of 228 children (9%) with Bell's palsy who were younger than 18 years had a history of previous paralysis on the same side, and 8 had contralateral paralysis. The interval between the two attacks usually was longer than 1 year.[143] Perhaps the record for recurrent facial paralysis was set by a woman who experienced more than 50 episodes of unilateral lower facial paralysis after exposure to the disinfectant chlorocresol.[144] The age distribution for patients with recurrent facial palsy was the same as that for the overall population with Bell's palsy,[4] except for those with ipsilateral recurrent palsies, which may be associated with a younger age at onset.[143] Several reports noted a slight female predominance in recurrent facial palsy.[143,145] Diabetes mellitus was present in 39% of patients with recurrent paralysis in one study[4] but only in 4% in another.[142]

Controversy continues regarding whether the prognosis for recovery from recurrent facial palsy is better or worse on subsequent attacks. Some investigators state that the second attack is associated with a poorer prognosis and therefore constitutes a stronger indication for surgical decompression.[146] Most other workers, however, found no prognostic difference between the primary and subsequent attacks of facial paralysis and no difference whether the second attack occurred on the ipsilateral or contralateral side.[142]

Recurrence of facial palsy should prompt a careful investigation for other etiologic disorders. May and associates[1] found a tumor in 8 of 40 of patients (20%) with a second palsy on the same side.

Bilateral Facial Paralysis

Bilateral idiopathic facial paralysis is much less common than unilateral paralysis and occurs in only 0.3% to 2% of patients.[147] Bilateral facial paralysis is associated with a much higher incidence of systemic causes than unilateral palsy and should spur a diligent search for an underlying disorder.[148] The diseases most commonly associated with bilateral facial paralysis are Guillain-Barré syndrome, Bell's palsy, multiple idiopathic cranial neuropathies, brainstem encephalitis, benign intracranial hypertension, syphilis, leukemia, sarcoidosis, Lyme disease, and bacterial meningitis.[149,150] The possibility of an intrapontine or prepontine tumor also should be excluded.[150] Most of these conditions are associated with other systemic or neurologic signs that suggest the appropriate diagnosis.

Guillain-Barré syndrome is a progressive ascending motor paralysis, occurring after a viral infection, that usually affects the lower limbs. However, rare bulbar, myelitic, and cerebral forms of Guillain-Barré do not affect the limbs. Of the cranial nerves, the facial nerve is the third most commonly affected, after the glossopharyngeal and vagus.[151] The diagnosis is based on the typical clinical picture and the presence of elevated CSF protein but a normal cell count. Other conditions associated with facial diplegia include influenza,[152] infectious mononucleosis,[153] other viral infections,[154] and diabetes.[155] Heerfordt's syndrome (parotid enlargement, iridocyclitis, and cranial nerve palsy) associated with sarcoidosis also can cause bilateral facial paralysis.

The workup for a patient with bilateral facial paralysis should include a careful neurologic examination to detect other cranial neuropathies, a lumbar puncture to obtain CSF for cytologic studies, chemistry, culture, a Venereal Disease Research Laboratory (VDRL) test for syphilis. An MRI scan should exclude space-occupying lesions.[156]

The disability caused by bilateral facial paralysis is dramatically more severe than that from unilateral paralysis. Aggressive eye care with ointment, taping, or patching usually is required, but this approach significantly interferes with visual function. Bilateral paralysis of the lower lip leads to a characteristic speech impairment, oral incompetence, and drooling. In severe cases, inadequate circulation of saliva may have dental sequelae.[157] The psychologic impact can be devastating, because these patients are incapable of voluntary or emotional expres-

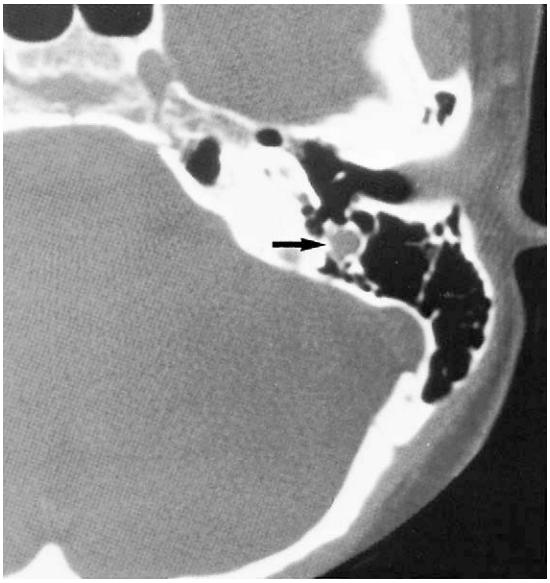

Figure 170-2. Axial CT scan of the right temporal bone shows enlargement of the mastoid segment of the fallopian canal *(arrow)* in the child with progressive facial paralysis. The lesion was a neuroma of the facial nerve.

sion.[158] Recovery in bilateral Bell's palsy is similar to that in unilateral palsy, although one side may recover before the other.[159]

Progressive Paralysis

Slowly progressive facial paralysis is not Bell's palsy. The differential diagnosis includes primary neuromas of the facial nerve (Fig. 170-2); metastases from squamous cell carcinomas and melanomas of the face and scalp; and occasionally distant metastases from kidney, breast, lung, and prostate.[160] Progressive facial paralysis also can occur from other primary temporal bone and cerebellopontine angle lesions and from carotid artery aneurysms.[161] A tumor should be excluded in all of these cases; the investigation should begin with physical examination for neuroma of the peripheral branches of the facial nerve and continue with computed tomography (CT) and gadolinium-enhanced MRI of the infratemporal and intracranial portions of the nerve. If results of these studies are negative, some authorities argue for exploration of the nerve from the peripheral branches through the temporal bone.[162] At the very least, patients with negative findings on initial evaluation require careful serial observation and imaging.

Traumatic Facial Paralysis

The most common causes of infratemporal facial nerve injury are temporal bone fracture, penetrating injuries (typically from a bullet), and iatrogenic injuries.

Injury of the facial nerve in temporal bone fractures can result from compression from bone fragments, intraneural hematomas, entrapment from compression, and loss of continuity. The distal labyrinthine segment and geniculate ganglion are the areas of the facial nerve most susceptible to injury in longitudinal and transverse temporal bone fractures[163] (Fig. 170-3). This portion of the facial nerve is particularly at risk because of its small size and lack of fibrous supporting tissue, and because of traction between the greater petrosal nerve and the geniculate ganglion caused by temporary distraction of the anterior and posterior portions of the temporal bone at the time of the injury.[163] Grobman and colleagues[164] presented a case that featured severe compression, demyelination, and edema of the facial nerve proximal to the site of the injury, with the most severe changes at the meatal foramen, in addition to direct injury to the nerve. These investigators pointed out that histologic changes in the facial nerve were similar to those in Bell's palsy, despite the fact that the initial insult to the nerve was different. High-resolution CT of the temporal bone is the most effective way to identify potential sites of injury of the facial nerve (Fig. 170-4).

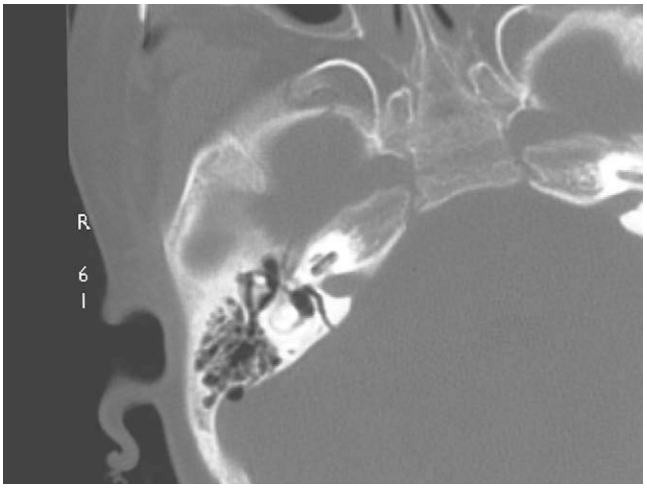

Figure 170-3. An axial CT scan of the temporal bone showing a transverse fracture of the temporal bone through the vestibule and geniculate ganglion.

Figure 170-4. A coronal CT scan of the temporal bone showing a transverse fracture of the temporal bone through the cochlea and traversing the fallopian canal in the tympanic portion of the facial nerve.

Management of facial nerve injury in temporal bone fractures has been controversial. Some authorities recommend observation and symptomatic care only. Maiman and associates[165] followed 45 patients nonoperatively. Twenty-nine had injuries severe enough to be visible on polytomography. Of the 45, 44 achieved satisfactory recovery, and 65% had complete recovery. McKennan and Chole[166] reported excellent recovery in patients with delayed-onset paralysis managed nonsurgically.

In decisions about surgical decompression in specific cases, such cases traditionally have been divided into those with immediate onset and those with delayed onset after the injury; immediate-onset paralysis is associated with severe injuries and poorer outcomes.[166] Conversely, Adegbite and coworkers[167] found the outcome was predicted by the severity of the paralysis but not the time of onset. Fisch,[73] however, advocated surgical intervention on the basis of ENoG results rather than time of onset of the paralysis. He established a criterion of greater than 90% degeneration within 6 days of onset. The timing of surgery, however, does not have to be within 6 days; in fact, some advantage may lie in delaying surgery up to 3 weeks after an immediate paralysis,

to allow resolution of edema and hematoma and to make the surgical field more discernible.[39] Chang and Cass[168] carefully reviewed the literature on surgical versus expectant management of facial paralysis after temporal bone fracture and concluded that the natural history, the appropriate timing, or reporting criteria exist to judge the true efficacy of facial nerve decompression in nonpenetrating injury of the temporal bone.

Long-standing paralysis also is a management problem, because electrical testing is not valid. In such cases, unless CT shows gross disruption of the fallopian canal, it is advisable to wait 12 months and then explore the nerve if clinical or EMG signs of recovery do not appear.

Penetrating injuries (gunshot wounds) often are accompanied by severe injuries, including dural tears, CSF otorrhea, damage of the otic capsule, and vascular injury. Evaluation includes high-resolution CT, carotid arteriography, and facial nerve electrical testing. Telischi and Patete[169] emphasize that extratemporal facial nerve blast injuries may not cause transection of the facial nerve; these workers recommend continued conservative management even if the nerve is severely hemorrhagic and contused.

Iatrogenic facial paralysis is a feared complication of ear surgery. For optimal management, the cases can be divided into those in which the integrity of the facial nerve was a concern intraoperatively and those in which the paralysis was unexpected. In the former group, the nerve should be positively identified by use of landmarks distant from the site of presumed injury. The nerve is traced to the site of injury, the local area decompressed, and disrupted nerve fibers reapposed. If loss of nerve tissue is serious, an onlay or interpositional facial graft can be used. If the landmarks are not discernible, the dissection should be terminated before further injury occurs and an appropriate colleague consulted. In the emotionally and medicolegally charged realm of iatrogenic injury, consultation is often beneficial to all involved. If the facial paralysis is unexpected, it is appropriate for the original surgeon to manage the case. Tight dressings and packing should be released immediately and time allowed for any local anesthetic effects to dissipate. If these measures do not result in recovery of function, urgent reexploration and decompression of the nerve should be performed.

Surgical exploration of the facial nerve after trauma requires the surgeon to be familiar with the entire temporal bone and to be prepared for mastoid, translabyrinthine, and middle fossa exploration and repair of the nerve. Caution is necessary for middle fossa exploration in patients with temporal bone trauma. Jones and associates[170] reported that 14 of 15 patients with CT evidence of temporal bone fracture also had MRI evidence of significant ipsilateral temporal lobe contusion.

Facial Paralysis Associated with Other Conditions

Pregnancy

The possible role of hormonal and fluid changes in the pathogenesis of Bell's palsy has been debated since Bell[171] first suggested an association between idiopathic paralysis and pregnancy in 1830. Bell's palsy is 3.3 times more frequent among pregnant women than among similarly aged nonpregnant women[172] and most commonly occurs in the third trimester or immediately post partum.[4,172] Recurrent palsy with repeated pregnancies and bilateral facial palsies during pregnancy also have been reported.[173]

In a series of 18 patients, Falco and Eriksson[174] reported that preeclampsia was six times more common among patients with facial palsy than in the general population of pregnant women. Facial palsy in pregnant women cannot be correlated with preterm labor, low birth weight, fetal congenital abnormality, or other perinatal abnormality. The prognosis and outcome compared with those in age-matched nonpregnant women are uncertain; some studies indicate no difference,[175] whereas others suggest decidedly worse results.[176] Gillman and coworkers[176] compared 77 women in whom Bell's palsy developed during pregnancy, or immediately post partum, with age-matched nonpregnant women and age-matched men. The pregnant patients had a statistically significant poorer result than either of the comparison groups.[176] Treatment with prednisone is the mainstay of management for the pregnant woman with Bell's palsy, although no significant difference in outcome with or without steroids was found in this study. Prednisone apparently poses minimal risk to the developing fetus, especially in the third trimester.[177]

Melkersson-Rosenthal Syndrome

Melkersson-Rosenthal syndrome consists of a triad of symptoms: recurrent orofacial edema, recurrent facial palsy, and lingua plicata (fissured tongue). The orofacial edema is the defining feature; lingua plicata and peripheral facial paralysis each occur in one half of the patients. The complete triad is present only in one fourth of the patients. Onset of the condition generally is in the second decade of life, and the manifestations usually occur sequentially and seldom appear simultaneously.

The major diagnostic criterion is persistent or recurring nonpitting facial edema that cannot be explained by infection, malignancy, or connective tissue disorder. The oral swelling usually involves the lips and buccal area, but the gingiva, palate, and tongue also can be affected. The swelling can extend to the supraorbital and infraorbital tissues of the cheek.[178] The edematous lips assume a chapped, fissured, red-brown appearance. The swelling usually is transient but may recur at regular intervals.

After numerous recurrences, the lips eventually become permanently deformed. They also may have chronic fissuring that is slow to heal and painful.[179] The extent of the facial swelling varies, ranging from unilateral involvement of the lower lip to bilateral total facial edema.[179] Chronic swelling constitutes a cosmetic problem and may interfere with speaking and eating. The chronic and recurrent nature of the edema distinguishes it from transient angioneurotic edema. Biopsy specimens of the lip reveal noncaseating epithelioid cell granulomas surrounded by histocytes, plasma cells, and lymphocytes.[179] The cause of Melkersson-Rosenthal syndrome is unknown. Some authorities consider it to be a variant of sarcoidosis, but others dispute this theory. Some experts suggest that it is a primary vasomotor disturbance,[180] whereas others suggest it has an allergic cause. Elevation of angiotensin-converting enzyme (ACE), seen in sarcoidosis and some other diseases, has been reported in some cases.[181]

Facial paralysis occurs in 50% to 90% of patients with Melkersson-Rosenthal syndrome, and it has an abrupt onset that is identical to that in Bell's palsy.[182] A history of bilateral sequential paralysis and relapse of paralysis after initial recovery is common. The site of the paralysis usually corresponds with the area of facial swelling.[179] Symptomatic management of the facial paralysis is indicated. No randomized trials of corticosteroids or surgery have been conducted, although cessation of the recurrent facial paralyses has been reported in several series after facial nerve decompression.[107,183]

Human Immunodeficiency Virus Infection

Acute facial palsy can occur at any stage of human immunodeficiency virus (HIV) infection. The palsy can be a direct result of or secondary to HIV disease (e.g., resulting from a secondary infection by herpes zoster virus). Most cases of facial palsy in patients with early-stage HIV infection resemble Bell's palsy in that (1) they have an abrupt onset and (2) no other cause is identifiable. These patients also are at risk for a craniocervical form of Guillain-Barré syndrome.

HIV is neurotropic and has been isolated from the CSF and neural tissues in all stages of HIV infection.[184] Acute facial palsy in acute and chronic HIV infection may result from invasion of the facial nerve or the facial ganglion by the virus.[185] Alternately, it has been suggested that acute facial palsy may be part of an acute inflammatory demyelinating polyneuropathy that occurs in other nerves in early stages of HIV.[186,187]

In later stages of HIV infection, facial nerve involvement may be related to the immunodeficiency, resulting in cephalic herpes zoster or systemic lymphoma. In addition, the facial nerve may be involved along with other nerves in a chronic peripheral polyneuropathy.[188]

The prognosis for idiopathic paralysis in patients with acquired immunodeficiency syndrome (AIDS) is similar to that in the general population.[189] The prognosis for facial paralysis from other causes in patients with AIDS depends on the underlying pathologic process.

Lyme Disease

Lyme disease (Bannwarth's syndrome in Europe) is caused by the tickborne spirochete *Borrelia burgdorferi*. The vectors for Lyme disease are several species of *Ixodes* ticks. The primary reservoirs of infection are the white-footed mouse and the white-tailed deer. The disease occurs in all parts of the United States.

Like syphilis, Lyme disease occurs in several stages. It begins with erythema migrans, an influenza-like illness, regional lymphadenopathy, and general malaise. The erythema migrans is an enlarging, annular, erythematous skin lesion, which may be multiple and is not limited to the site of the bite.[190] The second stage starts several weeks to months later when neurologic abnormalities develop, including meningitis, cranial nerve neuropathies, and other peripheral neuropathies. Early symptoms include headache, neck stiffness, and spinal pain. Stage three occurs months to years later with manifestations of chronic arthritis, neurologic deficits, recurrent meningitis, and subtle mental disorders.[191] Chronic neurologic complications occur in 18% of patients with untreated Lyme disease.[192]

Moscatello and coworkers[193] reviewed the head and neck symptoms in a large series of patients with Lyme disease. Headache, neck pain, and dizziness were the most common head and neck complaints. Facial paresis occurred in 4.5% of patients, may be unilateral or bilateral, and may be the sole neurologic abnormality. Halpern and Golightly[194] emphasized that the facial paralysis may precede serologic evidence of infection, and that facial paralysis may occur in the absence of either erythema migrans or identified tick bite.

Lyme disease is recognized as an increasingly important cause of facial paralysis, especially in children. In endemic areas, Lyme disease is responsible for one half of the cases of facial paralysis seen in children.[195] Facial weakness or paralysis usually resolves completely, although mild or, rarely, severe residual facial weakness has been described.[196] Reik and associates[197] reported the development of facial palsy in 6 of 18 patients with neurologic complications; 3 of these patints had residual weakness after 5 months. Puhakka and colleagues[198] found no difference in facial recovery between borreliosis and VZV infection.

The diagnosis of Lyme disease can be difficult.[199] Only 30% of patients have a recognized tick bite, and an erythema migrans rash fails to develop in 50%. Specific antibody tests may not yield a positive result for several weeks. MRI in children with neurologic symptoms may show hyperintense signal on T2-weighted images of the brain[200] and may be the best modality for following the effect of antibiotic therapy.[201]

Treatment of Lyme disease with neurologic symptoms is with ceftriaxone (2 g/day intravenously for 14 days).[201a] Improvement is not expected for several months after therapy, and recovery is seldom complete.[191]

Kawasaki's Disease

Kawasaki's disease, also known as infantile acute febrile mucocutaneous lymph node syndrome, is a multisystem disease occurring primarily in infants and young children. In addition to involvement of the mucous membranes, skin, lymph nodes, and cardiac system (coronary artery aneurysms), neurologic complications have been reported in up to 30% of patients.[202,203] Aseptic meningitis and irritability are the most common neurologic complications; however, facial palsy has been reported by several groups of investigators.[204-206]

In a review of 17 cases of well-documented facial palsy in the literature, Gallagher[204] reported the median age to be 13 months; no patient was older than 25 months. On average, onset of the paralysis occurred on day 16 of illness, and except for patients who died from cardiac complications, the palsy resolved in 1 to 12 weeks. Histologic examination of patients dying of Kawasaki's disease showed changes typical of arteritis,[207] leading Teresawa and associates[203] to conclude that the facial paralysis resulted from ischemia of the nerve. Treatment of Kawasaki's disease includes supportive care, appropriate management of cardiac failure, if present, and high-dose aspirin.

Sarcoid

Sarcoidosis is a chronic noncaseating granulomatous disease. Manifestations of systemic involvement usually include hilar or peripheral adenopathy (the lungs), polyarthralgias, anergy, hepatic dysfunction, and elevated serum calcium. Heerfordt's disease (uveoparotid fever), a variant of sarcoidosis, is characterized by nonsuppurative parotitis, uveitis, mild fever, and cranial nerve paralysis. Although only 5% of patients with sarcoidosis have cranial nerve involvement, the facial nerve is the most commonly affected.[208] By contrast, 50% of patients with uveoparotid fever have facial paralysis. The paralysis starts abruptly days to months after the onset of the parotitis. Paralysis is thought to be caused by direct invasion of the nerve by the granulomatous process[209] and not by pressure from the swollen parotid gland.[210] Sarcoidosis should be included in the differential diagnosis when the paralysis is bilateral.[147]

The diagnosis can be confirmed by an elevated serum ACE level, in contrast with tuberculosis, cancer, and pulmonary fungal diseases, in which ACE levels are low.[211] Sarcoidosis is treated with corticosteroids, after which the ACE levels are expected to return to normal.[212]

Otitis Media

Facial paralysis from otitis media is rare but can occur in acute or chronic cases. In a recent series, otitis media accounted for only 3.1% of acute facial palsies.[213] Of these 50 cases, only 5 were in children with acute otitis media. The remaining adult cases were divided equally between chronic purulent otitis media and cholesteatomas. Three additional cases were from tuberculous otitis.

Most paralyses were incomplete. Nearly all patients explored surgically were found to have a dehiscence of the bony canal of the facial nerve, usually in the tympanic segment, which presumably allowed spread of the inflammation from the middle ear to the nerve.

Facial paralysis associated with acute otitis media, especially in infants and children, should be treated with parenteral antibiotics and a wide myringotomy for drainage. Surgical manipulation of the facial nerve in acute otitis media is not recommended. Adour[94] also recommended the addition of a 10-day course of corticosteroids in conjunction with myringotomy and antibiotics.

Facial paralysis associated with chronic otitis media suggests a high probability of cholesteatoma, and surgical intervention is appropriate. The mechanism of facial paralysis associated with cholesteatoma may be compression or inflammation. Djeric[214] studied autopsy specimens from patients who had chronic otitis media but no antemortem evidence of facial paralysis. Two of 20 facial nerves had focal areas of demyelination, suggesting that adjacent inflammation may be more important than pressure. The most important hallmark of facial paralysis from cholesteatoma is a gradual onset, which distinguishes it from Bell's palsy. Removal of the cholesteatoma and decompression of the nerve without opening the perineurium will allow recovery from the paralysis in most cases.[215]

Barotrauma

Several investigators have described a curious phenomenon of recurrent facial paralysis with changes in barometric pressure. Woodhead[216] reported the case of a 50-year-old man who experienced repeated episodes of facial paralysis and ipsilateral loss of taste on ascending to 8000 to 10,000 feet while driving in mountainous regions or during air travel. His symptoms resolved on descent. Similar cases have been reported after commercial airline flights[217] and after scuba diving.[218,219] A brief facial palsy also has been reported after forceful nose blowing.[220] Barometric facial paralysis seems to be related to pressure changes in the middle ear transmitted directly to the facial nerve through natural dehiscences in the fallopian canal. Symptoms are relieved with placement of pressure equalization tubes or other means of improving eustachian tube function.[216]

Benign Intracranial Hypertension

The most common symptoms of benign intracranial hypertension are headache and visual disturbances, but occasionally it is associated with cranial nerve palsies, falsely suggesting a localized lesion. The abducens nerve is the most commonly involved, being affected in 10% to 60% of cases.[221] Unilateral and occasionally bilateral facial paralysis has been reported in a few cases of benign intracranial hypertension.[222] These

cranial nerve palsies tend to resolve promptly after reestablishment of normal intracranial pressure through medical means or by shunting.

Metabolic Disorders

Adour and colleagues[223] reported that 17% of patients older than 40 years of age with Bell's palsy had abnormal results on glucose tolerance testing; on this basis, these workers calculated that the development of Bell's palsy is 4.5 times more likely in a person with diabetes than in a person without diabetes. The incidence of diabetes, or at least abnormal glucose tolerance curves, in patients with Bell's palsy is reportedly 10%[95] to 56%.[224] A case-control study by Paolino and associates[225] also found abnormal glucose tolerance curves in 24% of patients with Bell's palsy, compared with 13% of control subjects ($P < .005$). These findings warrant caution in prescribing corticosteroids to patients with Bell's palsy. Reversible facial paralysis has been reported with hypovitaminosis A.[226]

Central Facial Paralysis

Central facial paralysis is caused by a lesion in the parietal motor cortex or the connections between the cortex and the facial nucleus. Lesions in these areas usually are accompanied by other neurologic symptoms referable to the CNS. A supranuclear palsy of the face most severely affects the lower half of the face and spares the forehead. Another important sign is that emotional facial reaction remains intact even though voluntary motion may be severely affected.

Hyperkinetic Disorders

Hemifacial Spasm

Hemifacial spasm is an involuntary twitching and contraction of one side of the face. The spasm usually starts around the mouth and, as the disease develops, comes to involve the entire face.[48] These uncontrollable spasms cause severe functional, social, and psychologic impairment. Although the spasms usually are painless, a rare form of the disease also involves the trigeminal nerve.

The cause of hemifacial spasm is widely debated; in the past, hemifacial spasm was thought to originate somewhere in the peripheral facial nerve. Esslen hypothesized that pressure or ischemia within the fallopian canal could generate spontaneous action potentials.[227] Jannetta[228] thought that compression of the seventh nerve by aberrant blood vessels near its exit from the brainstem (root entry zone) was the cause, although other workers disagree with this conclusion.[229]

An unusual aspect of hemifacial spasm is the lateral spread response first described by Esslen, in which electrical stimulation of one branch of the facial nerve causes a response in muscle innervated by a different branch. This response disappears at the time of vascular decompression.[230] How could vascular compression of the facial nerve cause facial spasms? Two mechanisms have been hypothesized[231]: (1) ephaptic transmission of impulses (electrical side currents allowing the depolarization of adjacent nerve fibers) at the site of the compression or (2) hyperactivity of the facial nucleus secondary to continuous irritation at the site of the compression. Experiments by Kuroki and Møller[231] suggest that a combination of demyelination and arterial compression is required for generation of the symptoms of hemifacial spasm and that the facial nerve becomes hyperactive after long-term irritation of the demyelinated portion.[231]

The best management of hemifacial spasm also has been contested. Many surgeons advocate some form of partial destruction of the peripheral facial nerve—either partial resection of the three main branches[232,233] or resection of involved branches determined by EMG.[234] However, Jannetta and coworkers[235] and Møller and Jannetta[230] advocate separation of the aberrant vessels from the nerves through a posterior fossa craniotomy. The experience of other surgeons confirms the success of microvascular decompression; Samii[236] and Moffat[237] and their colleagues report that 92% of patients were spasm-free 6 months after decompression of the facial nerve. Selection of patients for surgery is difficult, but recent studies with MRI and magnetic resonance angiography suggest that neurovascular contact with the nerve at the root exit zone is producing the associated symptoms.[238]

Blepharospasm

Blepharospasm is an idiopathic progressive involuntary spasm of the orbicularis oculi and upper face (corrugator and procerus muscles). Extension of the spasms to include the lower face is not uncommon.[239] In advanced cases, the eyes may be closed for as much as one third of the patient's waking time, rendering the patient functionally blind.[48] Blepharospasm generally is considered to be central in origin, although the exact mechanism is not yet determined.[43]

Treatment is directed toward selective destruction of the peripheral nerve branches innervating the orbicularis oculi muscles. McCabe and Boles[240] recommend exposing the upper branches of the facial nerve, confirmation with nerve stimulation, and resection of all branches to the orbicularis oculi. Success has been obtained with injection of botulinum toxin. Botulinum A toxin, a neurotoxin produced by *Clostridium botulinum* that interferes with the presynaptic release of acetylcholine, has been used in the management of many facial dystonias, especially blepharospasm. More than 90% of patients have experienced some relief of symptoms, although the average duration of the maximum improvement is only 11 to 14 weeks.[241,242] Systemic complications after administration of botulinum toxin have not been reported. Local complications usually are transient and include lid ptosis, facial weakness, corneal exposure, and diplopia.[243] Long-term improvement is prevented by regeneration of axons after treatment.[244] Periorbital myectomy also may produce acceptable long-term results.[239]

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CHAPTER ONE HUNDRED AND SEVENTY-ONE

Intratemporal Facial Nerve Surgery

Bruce J. Gantz

Jay T. Rubinstein

Ravi N. Samy

Samuel P. Gubbels

Key Points

- Appropriate management of facial nerve disorders requires a thorough knowledge of the pathophysiology of the diseases affecting the facial nerve, experience in the interpretation of findings on radiologic and electrophysiologic tests of the nerve, and expertise in multiple neuro-otologic surgical approaches to the facial nerve.
- The middle fossa craniotomy surgical approach provides access to the canalicular, labyrinthine, geniculate and proximal tympanic segments of the nerve while preserving hearing but is technically challenging. The middle cranial fossa approach can be used for facial nerve decompression in palsy, facial nerve tumor decompression or removal, and facial nerve grafting in the internal auditory canal, and to address facial nerve impingement resulting from longitudinal temporal bone fractures.
- A transmastoid approach can be used to address pathologic processes involving the tympanic and mastoid segments of the facial nerve while preserving inner ear function. Total facial nerve decompression can be achieved using the transmastoid approach in combination with a middle fossa craniotomy.
- The translabyrinthine approach provides access to the entirety of the intratemporal facial nerve for decompression, mobilization, or grafting when no usable hearing remains.
- Retrolabyrinthine and retrosigmoid approaches provide access to the cisternal segment of the facial nerve while preserving hearing and can be used for vascular decompression and combined with other approaches for facial nerve grafting at the brainstem.
- Anterior rerouting of the facial nerve from the geniculate to the extratemporal segment, as in the Fisch type A approach, can be performed with normal facial function possible postoperatively.
- The most important element of successful facial nerve repair is a tension-free anastomosis. An interposition graft, using the great auricular or sural nerve, should be used for nerve repair in all cases in which a tension-free end-to-end anastomosis cannot be achieved.
- In general, facial nerve tumors should be observed in patients with House-Brackmann grade I or II function. Surgical decompression is a management option for patients with facial nerve tumors and House-Brackmann grade II or III function. Tumor resection with facial nerve grafting is recommended for patients with House-Brackmann grade IV function or worse due to a facial nerve tumor.

Advances in surgical instrumentation and refinements in surgical strategies have enabled the otologist to expose safely the entire course of the facial nerve from the brainstem to its exit from the temporal bone. Surgical management of facial nerve disorders, however, continues to be as controversial as it was in the days of Cawthorne and Kettel. Successful treatment of the disease processes that cause facial nerve dysfunction requires thorough knowledge of the pathophysiology of the disease process and accurate assessment of the degree of nerve injury. Newer diagnostic tools, such as electroneuronography (ENoG) (i.e., electroneurography), high-resolution computed tomography (CT), and magnetic resonance imaging (MRI), provide more precise assessment and localization of nerve injuries in many disorders. This advance has allowed more accurate preoperative planning and selection of the most expeditious surgical approach to the nerve injury site when surgery is appropriate.

This chapter describes surgical approaches in detail, including the advantages and disadvantages of each.

Surgical Anatomy

Thorough knowledge of the intricate, convoluted course of the facial nerve and its anatomic relationship to other vital structures is essential to the surgeon who plans to operate in this area. The facial nerve (cranial nerve VII) exits the brainstem at the pontomedullary junction approximately 1.5 mm anterior to the vestibulocochlear nerve (cranial

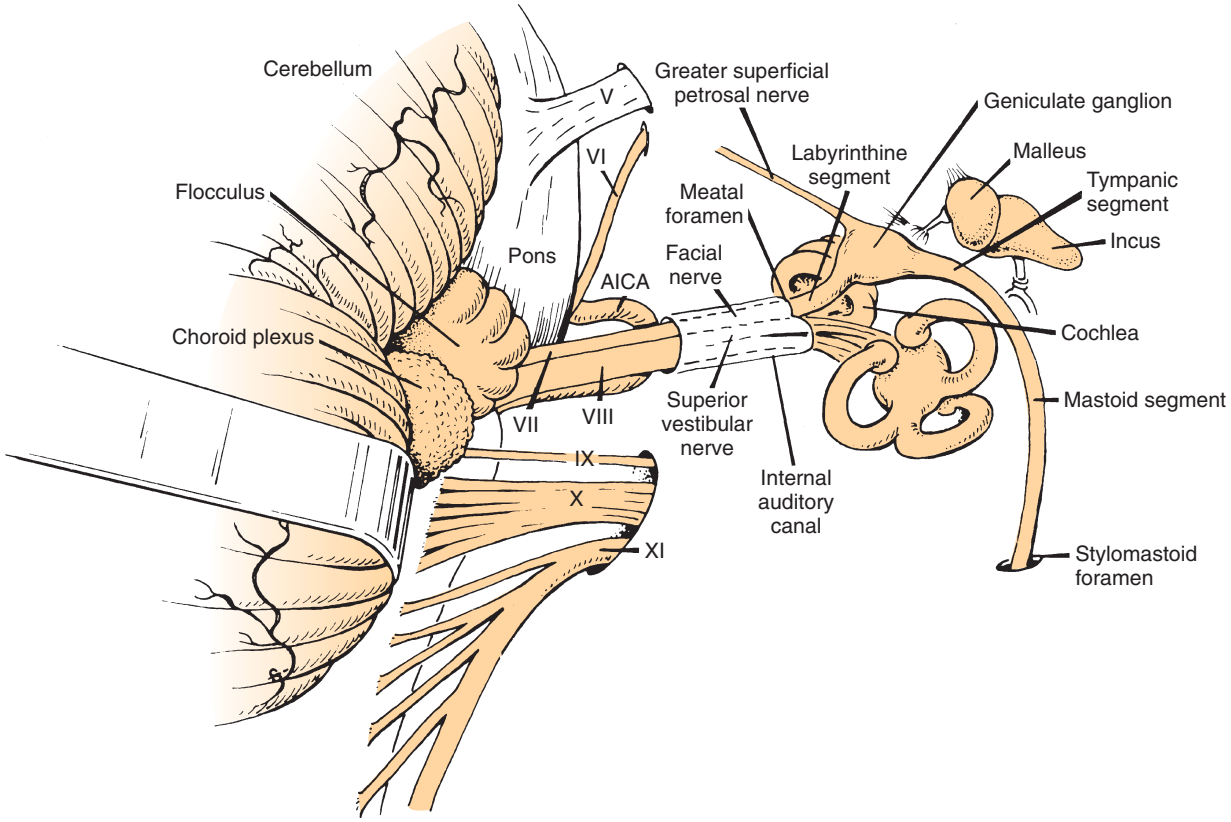

Figure 171-1. Course and relationships of the facial nerve from the pontomedullary junction to the stylomastoid foramen. AICA, anterior inferior cerebellar artery; Roman numerals designate cranial nerves.

nerve VIII). The facial nerve is smaller in diameter (approximately 1.8 mm) than the oval cranial nerve VIII (approximately 3 mm in the longer diameter). A third, smaller nerve, the nervus intermedius, emerges between cranial nerves VII and VIII and eventually becomes incorporated within the sheath of cranial nerve VII. After leaving the brainstem, cranial nerve VII follows a rostrolateral course through the cerebellopontine cistern for 15 to 17 mm, entering the porus of the internal auditory canal of the temporal bone (Fig. 171-1). Other important structures in the cerebellopontine cistern include the anterior inferior cerebellar artery (AICA) and the veins of the middle cerebellar peduncle. The AICA passes near or between cranial nerves VII and VIII; the veins are more variable in position and number. On entering the IAC, the facial nerve occupies the anterosuperior quadrant of this channel for 8 to 10 mm. Then it enters the fallopian canal at the fundus of the internal auditory canal. The internal auditory canal is anterior to the plane of the superior semicircular canal, with which it subtends an angle of approximately 60 degrees. At the entrance of the fallopian canal (meatal foramen), cranial nerve VII narrows to its smallest diameter, 0.61 to 0.68 mm.[1] Only the pia and arachnoid membranes form a sheath around the nerve at this point, because the dural investment terminates at the fundus of the internal auditory canal. Some investigators[2,3] identify the small diameter of the meatal foramen as an important contributory etiologic factor in facial paralysis associated with certain diseases, such as Bell's palsy and Ramsay Hunt syndrome.

Within its intratemporal course, the facial nerve has three distinct anatomic segments: labyrinthine, tympanic, and mastoid. The labyrinthine segment is shortest (approximately 4 mm), extending from the meatal foramen to the geniculate ganglion. This segment travels in an anterior, superior, and lateral direction, forming an anterior medial angle of 120 degrees with the internal auditory canal. Anteroinferior to the labyrinthine segment, the basal turn of the cochlea occupies a close relationship to the fallopian canal. At the lateral end of the labyrinthine segment, the geniculate ganglion is found, and the nerve makes an abrupt posterior change in direction, forming an acute angle of approximately 75 degrees. Anterior to the geniculate, the greater superficial petrosal nerve exits the temporal bone through the hiatus of the facial canal. The hiatus of the facial canal varies in distance from the geniculate ganglion. The greater superficial canal also contains the vascular supply to the geniculate ganglion region.

The tympanic segment of the nerve is approximately 11 mm long, running between the lateral semicircular canal superiorly and the stapes inferiorly, forming the superior margin of the fossa ovale. Between the tympanic and mastoid segments, the nerve gently curves inferiorly for approximately 2 to 3 mm.

The mastoid, or vertical, segment is the longest intratemporal portion of nerve: approximately 13 mm. As the nerve exits the stylomastoid foramen at the anterior margin of the digastric groove, an adherent fibrous sheath of dense vascularized connective tissue surrounds it. The stylomastoid artery and veins are within this dense sheath.

General Surgical Technique

Whenever the facial nerve is to be surgically exposed, several technical principles should be observed. First, a system for monitoring facial nerve function during the operation should be used.[4] One of the simplest monitoring methods is visual observation during critical stages of the operation. Needle electromyography also can be used if the equipment is available. No matter which monitoring technique is used, it is essential that the side of the face on which the nerve is to be exposed be draped in a manner that allows visual observation. The patient's forehead, eye, mouth, and chin should be visible. The endotracheal tube should be secured to the opposite side without taping on the side of the mouth to be observed. Towels drape the posterior, superior, and inferior margins; a fourth towel is placed along the anterior profile. An abdominal transparent plastic drape is placed over the face and operative area (Fig. 171-2). An observer can thus see the entire face during the procedure and determine whether any of the muscles move in response to surgical manipulation of the nerve. If the surgeon asks for

Figure 171-2. Plastic draping with exposure of hemiface allows visualization of facial movements in addition to electromyographic monitoring.

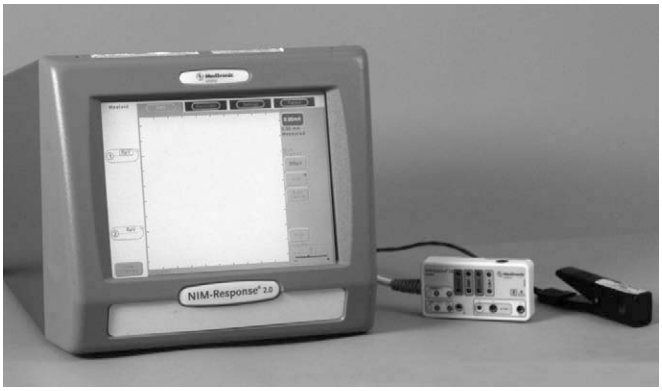

Figure 171-3. A popular commercially available nerve monitoring system. Stimulus intensity to the stimulator probe can be varied, as can the sensitivity of monitoring response.

observation during critical periods of the procedure, the circulating nurse is the best observer.

More precise intraoperative monitoring can be achieved using commercially available needle electromyographic systems (Fig. 171-3). Electromyographic needles are placed in the orbicularis oculi and orbicularis oris muscles, as shown in Figure 171-4. Stimulation of the facial nerve during the operation provides accurate localization of the nerve if the anatomy is distorted by a disease process or congenital abnormality. Constant current or constant voltage stimulators can be used. These systems allow auditory monitoring of facial nerve activity and alert the surgeon when the nerve has been stimulated. Auditory monitoring is especially useful during the removal of tumors adjacent to the facial nerve.

Instrumentation is crucial to successful exposure of the facial nerve. The largest diamond burr that the operative site can safely accommodate should be used when the operator is near the fallopian canal. Cutting burrs have a tendency to catch and jump unexpectedly, with the potential to cause severe injury to the nerve. Continuous suction-irrigation keeps the burr clean and also dissipates heat, which can induce neural damage.

The final layer of bone over the nerve should be removed by blunt elevators designed for this purpose. These instruments are thin but strong enough to remove a thin layer of bone. Stapes curettes usually are too large and can cause compression injury to the nerve. If neurolysis is to be performed, disposable microblades are available (Beaver No. 59-10). Sharp dissection is less traumatic than blunt elevation when the nerve must be lifted out of the fallopian canal. The medial surface of the nerve usually adheres to the bone and contains a rich vascular supply. Cauterization near the nerve should be performed only with bipolar electrocautery and insulated microforceps.

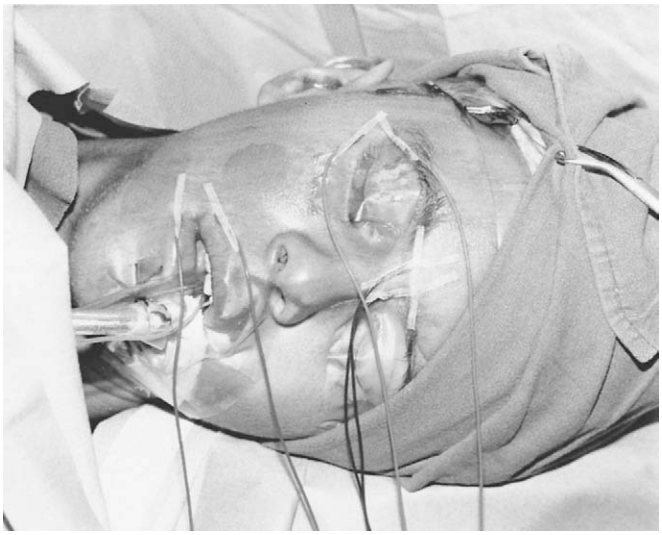

Figure 171-4. Placement of electromyographic electrodes in orbicularis oculi and orbicularis oris muscles. Ground electrodes are placed in the procerus muscle.

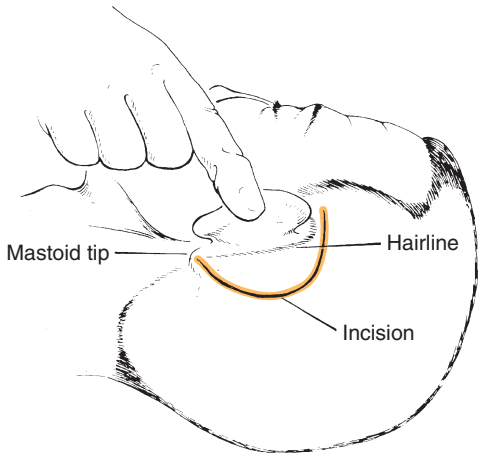

Figure 171-5. Skin incision for the retrolabyrinthine surgical approach.

Surgical Approaches

Retrolabyrinthine Approach: Brainstem to Internal Auditory Canal Porus

Technique

The patient is positioned on an operating table similar to that used for a mastoidectomy. Endotracheal anesthesia is administered, and the anesthetist is positioned at the foot of the table, allowing the surgical nurse to be opposite the surgeon. The hair is removed 4 cm superiorly and postauricularly, and the ear and the left lower abdominal quadrant (for the harvest of fat if necessary) are prepared and draped. An osmotic diuretic (250 mL of 20% mannitol) is administered intravenously at the start of the skin incision. The skin incision is made in the hairline 3 to 4 cm posterior to the postauricular crease and extended down over the mastoid tip (Fig. 171-5). Posterior placement of the skin incision provides access for occipital bone removal, which is necessary for posterior retraction of the sigmoid sinus.[5]

A complete mastoidectomy is performed. In addition, bone is removed over the sigmoid sinus from the sinodural angle to its most inferior extent. The dome of the jugular bulb also is identified. A large diamond burr and suction-irrigation are essential to prevent injury to the sinus and the posterior fossa dura. The cerebellar plate is removed

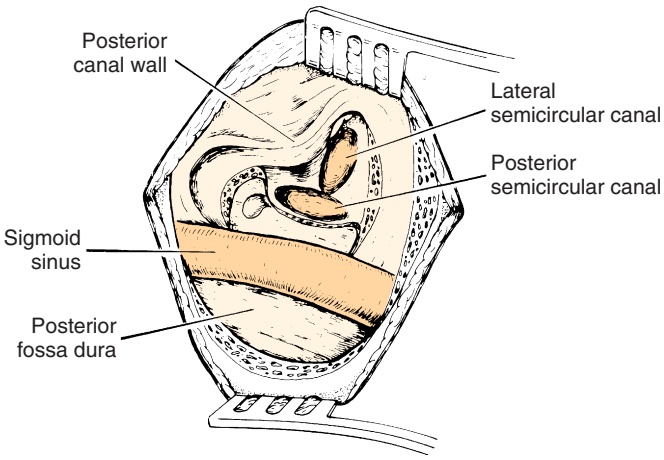

Figure 171-6. Exposure obtained through the left retrolabyrinthine approach before retraction and dural incision, as viewed by the surgeon.

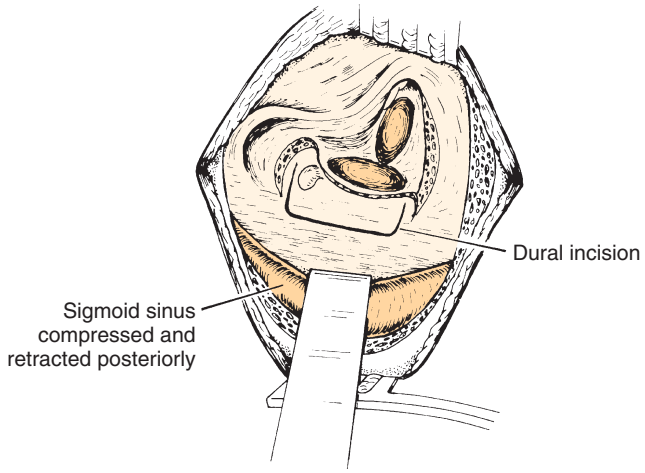

Figure 171-7. Dural incision for left retrolabyrinthine exposure.

from the tegmen mastoideum to the jugular bulb. Anteromedially, the posterior semicircular canal is identified, and inferior to the labyrinth (retrofacial area) the endolymphatic sac is exposed (Fig. 171-6). In a well-aerated mastoid, 2 to 3 mm of bone can be removed between the posterior semicircular canal and the cerebellar dura with the use of small diamond burrs. If the posterior canal is not evident, it should be blue-lined to locate its exact position.

An anteriorly based trapdoor cerebellar dural flap is fashioned with a sharp microscalpel and microscissors (Fig. 171-7). Care should be taken not to injure the small cerebellar arachnoid vessels when the dura is opened. A cuff of dura should be left adjacent to the bony margins, sigmoid sinus, and superior petrosal sinus for placement of sutures during closure. Sutures placed at the corners of the dural flap serve to retract it anteriorly. A malleable self-retaining retractor is used to retract the sigmoid sinus posteriorly. The cerebellum usually falls away from the temporal bone, and minimal, if any, retraction is required. Hyperventilation, in addition to an osmotic diuretic, is useful in obtaining brain shrinkage.

The cochleovestibular facial nerve complex is seen 2 to 3 mm inferior and parallel to Donaldson's line (a line extending posterior from the plane of the lateral semicircular canal). The arachnoid is incised sharply, releasing the cerebrospinal fluid (CSF) from the cistern. Other visible nerves are the trigeminal nerve (cranial nerve V) superiorly and the glossopharyngeal nerve (cranial nerve IX) and possibly the vagus nerve (cranial nerve X) inferiorly (Fig. 171-8). Visualization of cranial nerve VII may be completely blocked by cranial nerve VIII.

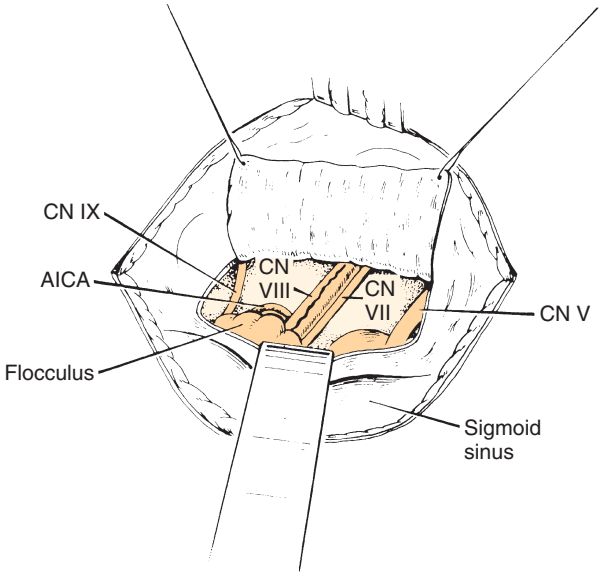

Figure 171-8. Left retrolabyrinthine exposure after retraction of the dural flap. AICA, anterior inferior cerebellar artery; CN, cranial nerve.

Cranial nerve VII usually arises 1.5 mm directly anterior to cranial nerve VIII. A Buckingham mirror aids identification of the facial nerve. The rostral division of the AICA may pass between cranial nerves VII and VIII, along with one or more veins. Approximately 15 mm of the nerve can be inspected in the cerebellopontine cistern.

At the end of the procedure, care should be taken to achieve watertight closure of the dura. Strips of abdominal fat (5 mm × 4 cm) are harvested from a lower abdominal incision, placed subdurally, and incorporated into the suture line. Braided nylon (4-0) sutures are used for closure of the dura. Fat can be placed in the mastoid but should not block the aditus or interfere with the ossicles. The subcutaneous tissues are closed in layers. A mastoid compression dressing is placed.

Retrosigmoid Approach

Technique

Another option for exposure of the facial nerve from the brainstem to the internal auditory canal is through a small retrosigmoid craniotomy. The preparation and incision are similar to those in the retrolabyrinthine approach (see Fig. 171-5). Instead of a complete mastoidectomy, the bone over the sigmoid sinus is removed to identify the posterior margin of the sinus. Bone is removed 4 cm posterior to the sigmoid sinus, exposing the posterior fossa dura (Fig. 171-9). The outline of the transverse sinus is exposed superiorly. A curvilinear incision in the posterior fossa dura is created to expose the cerebellum (Fig. 171-10). Care is taken to incise the dura without injuring the arteries and veins on the cerebellum. Cottonoid sponges lined with rubber glove strips are placed on the cerebellum. Slow, gentle retraction of the cerebellum over 5 to 10 minutes allows exposure of the posterior fossa face of temporal bone and internal auditory canal. Once the cerebellum has been slowly retracted, no external retraction is necessary. The cerebellum should fall away from the temporal bone, allowing viewing of the flocculus, choroid plexus, and the cranial nerve VII and VIII bundle (Fig. 171-11). The posterior lip of the internal auditory canal porus can be removed for additional lateral exposure, but the position of the posterior semicircular canal and its relationship to the posterior lip of the porus acusticus should be ascertained by CT.

Advantages and Uses

The retrolabyrinthine and retrosigmoid approaches provide access to the facial nerve in the cerebellopontine angle without sacrificing inner ear function. These approaches have an advantage over the routine suboccipital approach in that minimal or no cerebellar compression is needed. The procedure can be used in combination with middle fossa

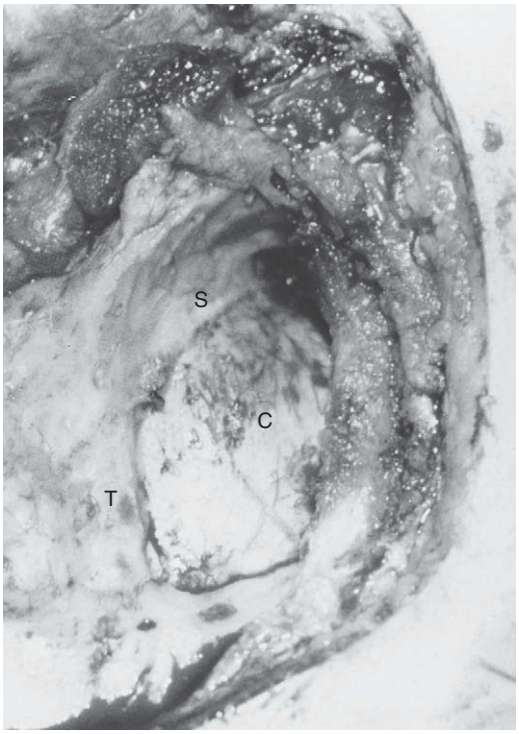

Figure 171-9. Retrosigmoid craniotomy. The skin flap is reflected anteriorly, exposing the mastoid and the cerebellar cortical bone. Craniotomy (approximately 4 × 4 cm), exposing the sigmoid sinus (S) anteriorly, transverse sinus (T) superiorly, and cerebellar dura (C).

Figure 171-10. A dural incision (2 to 3 cm long) can be linear or curvilinear. Here, 4-0 Neurolon suture retracts the anterior leaf of the dural incision.

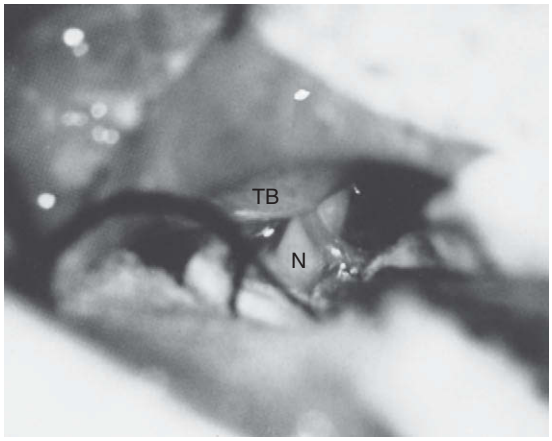

Figure 171-11. Retrosigmoid exposure. The cerebellum has been retracted from the cerebellar plate of the temporal bone (TB), exposing the neurovascular bundle (N). Cranial nerve VII is directly deep and slightly cephalic to cranial nerve VIII.

exposure for tumor removal and grafting of cranial nerve VII near the brainstem. For facial nerve surgery, the retrolabyrinthine technique is most commonly used in some practices for vascular decompression in hemifacial spasm. The AICA, posterior inferior cerebellar artery, and accompanying veins can be easily manipulated through this approach.

Limitations and Potential Complications

Visualization of the facial nerve often is hampered by the location of cranial nerve VIII. Gentle separation of the nerves with a blunt instrument can be accomplished but is associated with increased potential for hearing loss or vestibular complications. Because of the compromised exposure, management of any intracranial vascular complications is limited. If an intracranial complication occurs, rapid removal of suboccipital bone, in combination with a retrosigmoid dural opening, provides additional access.

CSF leakage is a potential problem with this approach, but careful dural reapproximation and use of subdural fat strips have decreased the incidence of this complication.

Middle Cranial Fossa (Transtemporal) Approach: Internal Auditory Canal Porus to Tympanic Segment

The middle cranial fossa approach[6] is used to expose the internal auditory canal and labyrinthine segments of the facial nerve when preservation of existing auditory function is desirable. The geniculate ganglion and tympanic portions of the nerve also can be decompressed using this approach.

Technique

The patient is placed supine on the operating table with the head turned so that the involved temporal bone is upward. The hair is shaved 6 to 8 cm above and anterior to the ear and 2 cm posterior to it. The surgeon is seated at the head of the table, with the instrument nurse at the anterior aspect of the patient's head.

A 6 cm × 8 cm posteriorly based trapdoor incision is marked in the hairline above the ear (Fig. 171-12). If exposure of the mastoid is necessary, the inferior limb of the incision can be extended postauricularly. The skin flap is elevated to expose the temporalis muscle. A 4 cm × 4 cm temporalis fascia graft is harvested for use during closure of the internal auditory canal dural defect. An anteriorly based trapdoor incision is used to elevate the temporalis muscle and periosteum. Staggering the levels of the muscle and skin incisions provides for a double-layer watertight closure at the end of the procedure.

The temporal root of the zygoma is exposed during elevation of the temporalis muscle. This landmark represents the level of the floor of the middle fossa. Stay sutures are placed in the skin and temporalis flaps to be used for retraction. A 3 cm × 5 cm bone flap centered above the temporal root of the zygoma is fashioned with a medium cutting

burr. The anterior and posterior margins of the craniotomy should be parallel to facilitate placement of the self-retaining retractor.

Branches of the middle meningeal artery are occasionally embedded within the inner table of the skull; therefore, the bone flap should be elevated in a controlled manner. Bipolar coagulation and bone wax may be necessary to control bleeding. Elevation of the dura from the floor of the middle fossa can be one of the most difficult steps. Use of blunt dissection and magnification greatly facilitates dural elevation. The dura is elevated from posterior to anterior to prevent accidental injury to an exposed geniculate ganglion and greater superficial petrosal nerve. Bipolar coagulation is used to cauterize dural reflections within the petrosquamous suture before transection with scissors.

The elevation proceeds until the petrous ridge is identified medially and the arcuate eminence, meatal plane, and greater superficial petrosal nerve are revealed anteriorly. No attempt is made to identify the middle meningeal artery and accompanying troublesome bleeding veins. The tip of a self-retaining (House-Urban) retractor is placed at the petrous ridge anterior to the arcuate eminence. A medium diamond burr and a suction-irrigation apparatus are used to identify the blue line of the superior semicircular canal. Review of a Stenvers projection radiograph obtained preoperatively will help to determine the level of the superior semicircular canal in relation to the floor of the middle fossa.

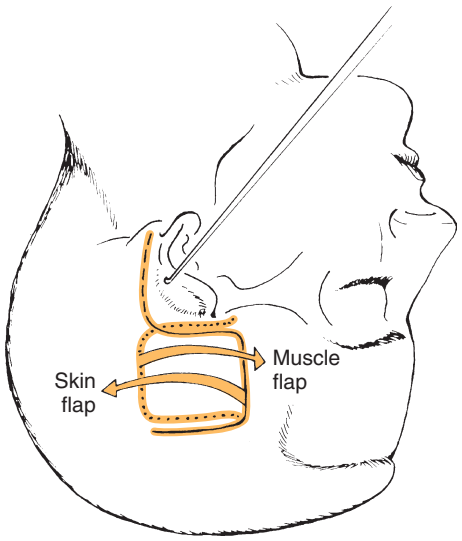

Figure 171-12. Surgical view of a skin incision *(solid line)* for the middle cranial fossa approach.Mastoid extension for total facial nerve exposure *(dashed line)* and extent of the muscle periosteal flap *(dotted line)* also are shown.

Drilling begins posterior to the arcuate eminence over the mastoid air cells and is continued until the dense yellow bone of the otic capsule is identified. Otic capsule bone is slowly removed until the blue outline of the superior semicircular canal is seen. The internal auditory canal is located by removing bone in a line 60 degrees anterior to the blue line of the superior semicircular canal and continuing until approximately 180 degrees of the canal is exposed (Fig. 171-13). Because of the close proximity of the superior semicircular canal and the basal turn of the cochlea, only approximately 120 degrees of the circumference of the internal auditory canal can be safely removed in its lateral 5 mm or more. The facial nerve occupies the anterosuperior portion of the internal auditory canal. Laterally, the vertical crest (Bill's bar) marks the division between the superior vestibular nerve and the meatal foramen.

The segment of the facial nerve at its entrance to the fallopian canal is the narrowest, most delicate portion of the nerve. At the meatal foramen, the facial nerve turns anterior and slightly superior. The basal turn of the cochlea can be within 1 mm inferiorly, and the ampulla of the superior semicircular canal can be directly posterior to the nerve. The labyrinthine segment is followed to the geniculate ganglion. The tegmen tympani is removed with care taken to avoid injury to the head of the malleus and incus. The tympanic segment is easily seen to turn abruptly posteriorly; it is followed to where it courses inferior to the lateral semicircular canal. It is advisable to leave a thin shell of bone covering the nerve until its entire course is identified. The final layer of bone is removed using small blunt elevators. The nerve is tightly confined within the labyrinthine segment of the fallopian canal; use of larger curettes should be avoided to prevent compression injury.

If the nerve is to be decompressed, neurolysis is the final step. A disposable microscalpel (Beaver No. 59-10) is used to slit the periosteum and epineural sheath.

Alternative methods to locate the facial nerve may be necessary, especially in traumatic cases. The greater superficial petrosal nerve can be traced posteriorly to the geniculate ganglion, or the tegmen tympani may be fractured to permit a view of the tympanic segment through the fracture. The tympanic segment is then used to locate the geniculate ganglion and labyrinthine segments.

At the end of the procedure, a corner piece of the bone flap is fashioned to cover the defects in the tegmen tympani and internal auditory canal (Fig. 171-14). This prevents herniation of the temporal lobe into the middle ear. The previously harvested temporalis fascia is placed over the bone plug to help seal the dural defect at the internal auditory canal. The squamous bone plug is replaced, and the temporalis muscle is closed with interrupted absorbable sutures. The skin is closed in layers. No drain is placed. A mastoid type of pressure dressing is applied.

Advantages and Uses

The middle cranial fossa approach is the only method that exposes the entire internal auditory canal and labyrinthine segment with preservation of hearing. In combination with the retrolabyrinthine and trans-

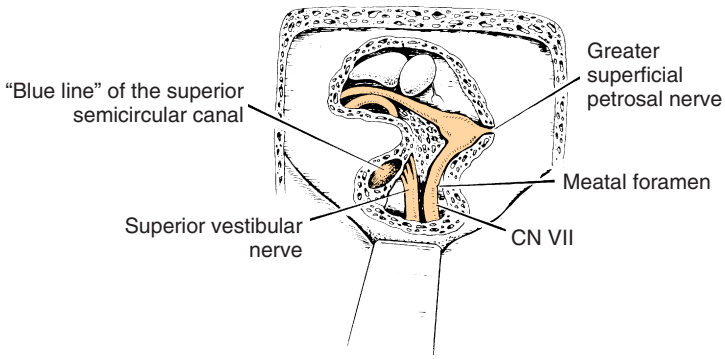

Figure 171-13. Surgical view of the left middle cranial fossa exposure after craniotomy, temporal lobe retraction, and bony exposure are complete. CN, cranial nerve.

mastoid approaches, this approach enables visualization of the entire course of the facial nerve and preserves function of the inner ear. The middle cranial fossa technique is most commonly used for decompression of the facial nerve in Bell's palsy[7,8] and with longitudinal temporal bone fractures.

Limitations and Potential Complications

The anatomy of the floor of the middle cranial fossa is variable and presents difficulty in identification of landmarks. The surgeon should have thorough knowledge of the three-dimensional anatomy of the temporal bone. Many hours in a temporal bone dissection laboratory are required to attain the delicate microsurgical skills necessary for this type of surgery.

Dural elevation can be difficult, especially in patients older than 60 years of age. The dura can adhere to the middle fossa floor and may be thin. A temporalis fascia patch should be used to repair any dural tears to prevent CSF leaks.

Conductive and sensorineural hearing losses can result from middle cranial fossa facial nerve decompression. Conductive hearing loss can be secondary to temporal lobe herniation or ossicular disruption during dissection in the attic. A free bone plug prevents temporal lobe herniation. Sensorineural hearing loss can result from direct injury to the inner ear from the drill during exposure of the cochlea or semicircular canals, or from translational injury incurred when the drill strikes an ossicle. Injury to the internal auditory vessels within the internal auditory canal also can result in loss of inner ear function. Loss of vestibular function can occur by the same mechanisms.

Persistent CSF leakage can lead to meningitis and should be controlled by a temporary lumbar drain. If CSF leakage continues despite an adequate period of lumbar drainage, surgical revision with dural repair may need to be performed.

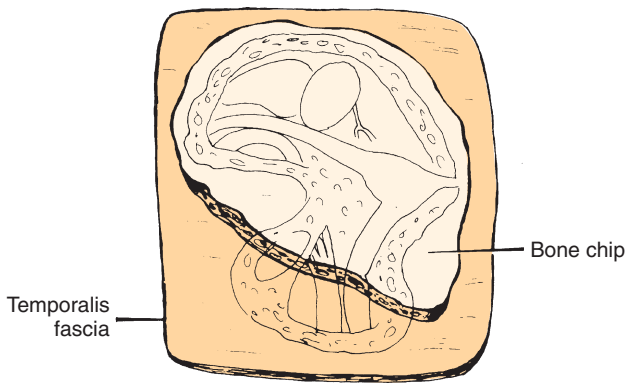

Figure 171-14. Bone chip and temporalis fascia placement for tegmen reconstruction and dural closure of the middle cranial fossa approach.

Uncontrolled bleeding or injury to the AICA poses the most serious complication during the operation. The middle cranial fossa approach does not provide adequate access to the cerebellopontine angle. The AICA and accompanying veins can loop into the internal auditory canal. Control of bleeding of these vessels may require a suboccipital exposure. Injury to the AICA results in brainstem and cerebellar infarction of variable degree, depending on the size and area of terminal arterial supply.

Results with Middle Cranial Fossa Decompression of Bell's Palsy

May and coworkers[9] showed the futility of transmastoid decompression for Bell's palsy. Only middle cranial fossa decompression of the meatal foramen, labyrinthine segment, and geniculate offers any benefit. Although the middle cranial fossa approach is used frequently for acoustic neuroma and vestibular nerve section with minimal morbidity, it is technically challenging even for experienced temporal bone surgeons and carries a significant potential for complications. A 30-dB conductive hearing loss constitutes minimal morbidity for a patient with an acoustic neuroma or intractable Meniere's disease, but it is significant for a patient who may have up to a 50% chance of spontaneous complete recovery. Thus, even with proof of efficacy, decompression is advocated only in centers experienced in the middle cranial fossa approach. As surgical series of middle cranial fossa decompression for Bell's palsy become available, honest appraisals of the statistical and clinical significance of improved facial function will be needed. Slight improvements in facial symmetry do not justify significant rates of conductive or neurosensory hearing loss or CSF leak, or the cost of the procedure and overnight postoperative stay in the intensive care unit.

In a study of middle cranial fossa decompression, Fisch[2] showed statistically significant improvements in outcome with surgery, but it is difficult to assess the degree of improvement in his subject population. Use of the House-Brackmann scale in subsequent reports will make this easier. Table 171-1 summarizes the published data available[3,10] and the experience at the University of Iowa Hospitals and Clinics through 1986 regarding outcome with middle cranial fossa decompression. All patients demonstrated more than 90% degeneration on ENoG within 14 days of onset of total paralysis and no voluntary electromyography potentials. The prognostic studies of Fisch[2] indicated, at best, a 50% rate of spontaneous satisfactory recovery when degeneration exceeded 90%.[11] Sillman and colleagues[12] and Marsh and Coker[13] studied ENoG prognostication using the House-Brackmann scale and verified Fisch's results, showing less than 50% recovery to grade I or II function when ENoG degeneration exceeded 90%.[12] Thus, patients managed with middle cranial fossa decompression are expected to return to grade I or II without surgery less than 50% of the time.

After at least a 7-month follow-up period, 23 of 26 patients returned to House-Brackmann grade I or II (see Table 171-1). Using a binomial distribution and assuming a 50% spontaneous recovery to grade I or II, this result is highly significant ($P < .00005$). No published study showed statistical significance, and none reported on morbidity

Table 171-1

Middle Cranial Fossa Decompression Outcomes in Patients with Bell's Palsy*

	No. of Patients			
House-Brackmann Grade	Iowa Cohort	Michigan Cohort[10]	Baylor Cohort[3]	Total
I	3	5	0	8
II	7	2	6	15
III	1	1	0	2
IV	0	1	0	1

*With >90% degeneration on electroneurography.

of the procedure, but all showed trends for the efficacy of middle cranial fossa decompression. Data for six of the Iowa patients appeared in a previous report.[14] With these additional cases, the Iowa patients had a highly significant recovery rate with middle cranial fossa decompression ($P < .006$). Table 171-2 shows outcome with corticosteroid management alone. Of the Iowa patients, five of eight who did not undergo prompt middle cranial fossa decompression but who met the electrophysiologic criteria for surgery did not recover to grade I or II (see Table 171-1). In the Michigan study, 14 of 25 patients who did not undergo decompression achieved grade III or IV recovery. Even if historical control subjects are not used, Iowa patients who underwent middle cranial fossa decompression improved to grade I or II significantly more often than those managed with corticosteroids alone ($P < .024$; Fisher's exact test).[15]

Table 171-2

Corticosteroid Treatment Outcomes in Patients with Bell's Palsy*

House-Brackmann Grade	No. of Patients		
	Iowa Cohort	Michigan Cohort[10]	Total
I	0	5	5
II	3	6	9
III	5	12	17
IV	0	2	2

*With >90% degeneration on electroneurography.

Transmastoid Approach: Geniculate Ganglion to Stylomastoid Foramen

Technique

A postauricular incision is used to expose the mastoid cortex. A complete mastoidectomy is performed, and the lateral semicircular canal, tegmen mastoideum, sigmoid sinus, and digastric ridge are identified. The lateral semicircular canal and digastric ridge are important landmarks for identification of the facial nerve. The tympanic segment of the nerve is immediately inferior to the lateral canal, and the anterior margin of the digastric ridge marks the location of the stylomastoid foramen. The short process of the incus is identified but should not be disturbed by an instrument or a rotating burr. The facial recess is opened with a small diamond burr (Fig. 171-15). This allows visualization of the tympanic segment of cranial nerve VII in the middle ear. With use of a medium-sized diamond burr and suction-irrigation, the fallopian canal is exposed from the lateral semicircular canal to the stylomastoid foramen. In the mastoid bone, the posterior 180 degrees of the circumference of the fallopian canal is removed. The retrofacial air cells can be removed if additional exposure is required. In the tympanum, a 1-mm diamond burr is used to remove bone to the geniculate ganglion. Again, the drill should not touch the incus. The final thin shell of bone covering the nerve is removed with blunt elevators (Fig. 171-16). Neurolysis is accomplished if desired. The wound is drained for 24 to 36 hours and closed in layers. A mastoid pressure dressing is placed.

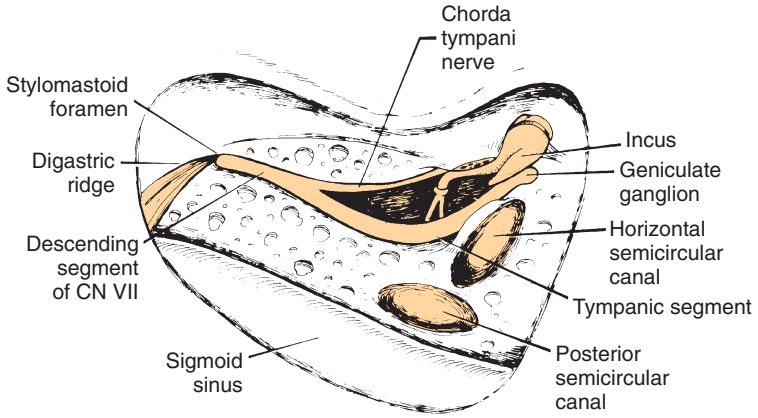

Figure 171-15. Transmastoid facial nerve exposure of the left ear after opening of the facial recess.

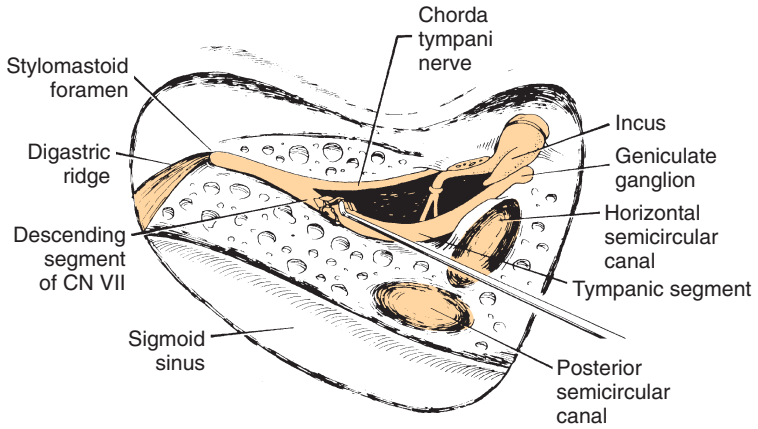

Figure 171-16. The final thin layer of bone covering the facial nerve is removed with a delicate but sturdy blunt elevator.

Advantages and Uses

Transmastoid decompression provides excellent exposure of the mastoid and tympanic segments of the facial nerve. Exposure of the geniculate ganglion requires removal of the incus, which can be replaced at the end of the operation. Conductive hearing loss may occur with this maneuver, and, in general, it is difficult to get adequate decompression of the geniculate segment without a middle fossa craniotomy. The labyrinthine segment cannot be reached through a transmastoid approach unless the ampulla of the lateral semicircular canal is sacrificed.

This route is used to explore the facial nerve when decompression is necessary for rerouting of the nerve and in cases of infection and fractures localized to the mastoid segment of the fallopian canal. Acute or chronic otitis media can induce facial paralysis. The most common sites of involvement are the tympanic segment (dehiscent in more than 25% of healthy persons) and the second genu as the nerve turns into the mastoid. With an isolated mastoid temporal bone fracture or a longitudinal temporal bone fracture that involves the distal geniculate ganglion and tympanic segments, adequate decompression can be accomplished through the mastoid. A longitudinal temporal bone fracture, however, is better managed with the improved exposure provided by a middle fossa approach. During removal of infratemporal fossa tumors, rerouting of the facial nerve frequently is required. Moving the facial nerve provides safer access to the jugular foramen and carotid canal. Transmastoid decompression is used in conjunction with middle fossa and retrolabyrinthine approaches if total facial nerve exposure is required and inner ear function is to be preserved.

Limitations and Complications

The major drawback with transmastoid exposure of the facial nerve is the limited access to the geniculate ganglion and the inability to reach the labyrinthine segment. The labyrinthine portion of the nerve commonly is the primary site of involvement in traumatic paralysis or Bell's palsy. Conductive or sensorineural hearing loss also can be a complication if the incus is removed or touched by a rotating burr during the procedure.

Translabyrinthine Approach: Total Facial Nerve Exposure

Technique

The patient is positioned on the operating table and the head and lower left abdominal quadrant are prepared and draped. An incision is made 3 cm behind the postauricular crease and carried inferiorly over the mastoid tip. Soft tissue is elevated forward off the mastoid cortex to the external auditory canal. A portion of the occipital bone posterior to the sigmoid sinus also should be exposed. An extended complete mastoidectomy is performed.

The bone over the sigmoid sinus is removed, along with 0.5 to 1.0 cm of bone posterior to this structure. The incus is removed, exposing the tympanic segment of the facial nerve inferior to the lateral semicircular canal. The facial recess is opened, further defining the position of the facial nerve in the middle ear and mastoid. A thin layer of bone should remain over the nerve while complete labyrinthectomy is performed. Inferior to the posterior semicircular canal, bone is removed, exposing the jugular bulb, posterior fossa dura, and endolymphatic sac (Fig. 171-17).

Medial to the posterior semicircular canal and lateral semicircular canal, the internal auditory canal appears blue compared with the surrounding yellow otic capsule bone. Bone is removed 180 degrees around the internal canal, exposing the porus acusticus. At the lateral margin of the internal auditory canal, the facial nerve is found medial and slightly superior to the superior vestibular nerve (Fig. 171-18). Bone is removed over the labyrinthine segment to the geniculate ganglion and then distally to the stylomastoid foramen at the anterior limit of the digastric groove. The final layer of bone is removed with blunt elevators.

The dura over the internal auditory canal and cerebellar plate can be opened to expose the cerebellopontine cistern and brainstem. Closure is accomplished with a 4 cm × 4 cm piece of temporalis fascia covering the dural defect and draped over the aditus to separate the mastoid from the middle ear (Fig. 171-19). Abdominal fat is harvested and used to obliterate the mastoid space.

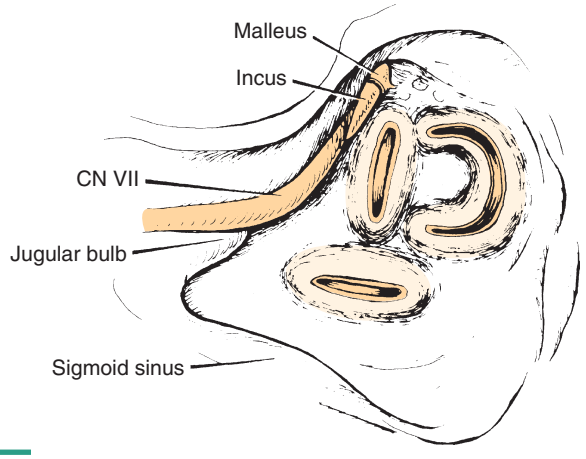

Figure 171-17. Left translabyrinthine exposure of the semicircular canals. CN, cranial nerve.

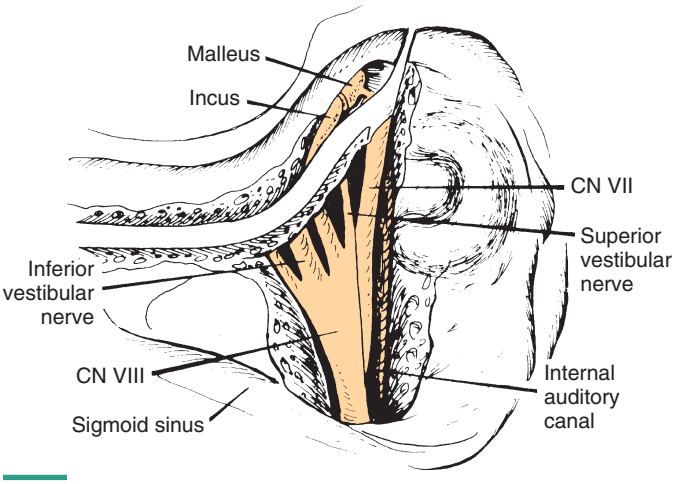

Figure 171-18. Completed left translabyrinthine exposure. CN, cranial nerve.

Advantages and Uses

The translabyrinthine exposure of the facial nerve is used primarily when the cochlear and vestibular functions have been lost preoperatively. The greatest advantage with this technique of facial nerve exposure is the ability to access the entire nerve using one approach. It most often is the approach of choice when facial paralysis has resulted from a transverse temporal bone fracture, an extensive facial neuroma, or a large congenital cholesteatoma that extends into the internal auditory canal. If an interpositional nerve graft is required, the translabyrinthine exposure provides enough working space for anastomosis at or near the brainstem.

Limitation and Complications

The greatest limitation of this procedure is that hearing and balance function must be sacrificed for total exposure of the nerve. When healthy cochlear and vestibular function exists, the surgeon should consider other approaches. Existing hearing and balance functions are destroyed, and the procedure may prevent future use of a cochlear implant device. CSF leakage and infection are the greatest risks with this operation, but the complication rate should be less than 2% if proper fascia graft and fat obliteration are performed.

Combination Approaches

It may be necessary to combine two or more of the approaches described to achieve the exposure dictated by the disease process. Occasionally, middle fossa exposure is combined with the transmastoid approach

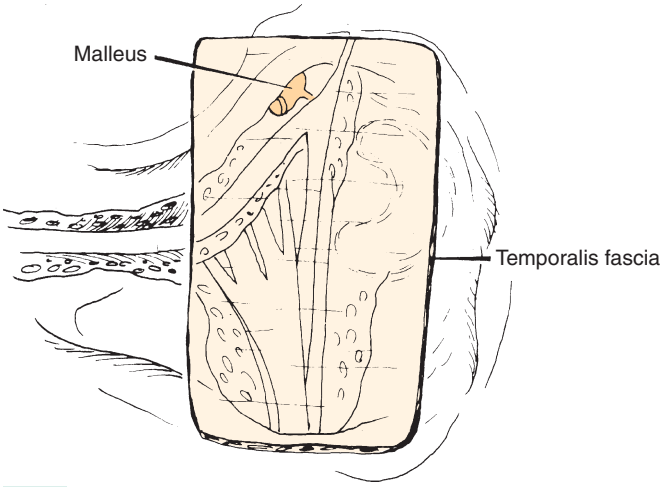

Figure 171-19. Placement of the temporalis fascia at the time of closure of the left translabyrinthine exposure.

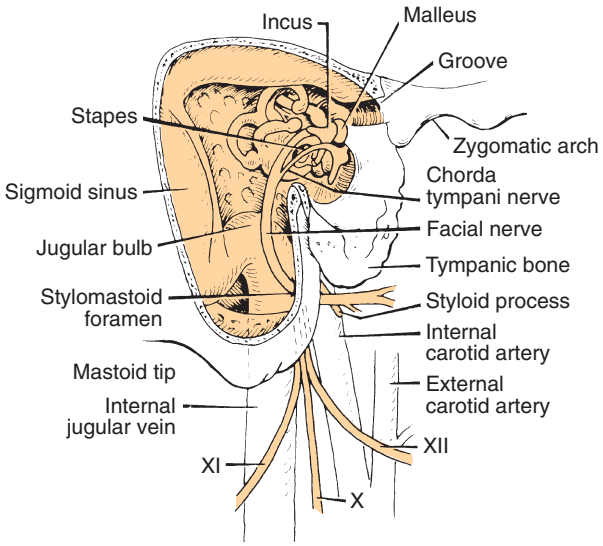

Figure 171-20. Facial nerve exposure for rerouting, as used in glomus jugulare tumor resection. Roman numerals denote cranial nerves.

when total decompression of the fallopian canal is needed. The middle fossa usually is exposed first. In most traumatic injuries, the area of facial nerve involvement is located at or just medial to the geniculate ganglion. If the injury extends distally, the lower limb of the skin incision is carried postauricularly, and a mastoid decompression is accomplished. The middle fossa retractor is left in place until the total nerve is exposed. A fascia graft is used to repair the dural defect in the internal auditory canal, and a portion of the craniotomy flap is placed over the tegmen tympani to prevent temporal lobe herniation. This combination also is useful in patients with facial nerve schwannoma and congenital cholesteatoma.

Retrolabyrinthine exposure also can be added if the disease extends medial to the porus of the internal auditory canal. During this portion of the procedure, the middle fossa retractor should be removed. Combination approaches are useful when a nerve graft is necessary and additional access is required.

Rerouting

Elevation of the facial nerve out of the fallopian canal may be necessary during nerve repair procedures and is essential for removal of sizable neoplasms in the proximity of the jugular foramen and carotid canal. Severe injury to the facial nerve at the geniculate ganglion occasionally occurs in longitudinal temporal bone fractures and can be managed by resecting the geniculate ganglion and reapproximating the labyrinthine and tympanic segments of the nerve through middle fossa exposure. Small tumors at the geniculate ganglion can be similarly managed.

To attain the necessary nerve length, the labyrinthine and transverse segments should be mobilized and elevated out of the fallopian canal. Extreme care should be taken during exposure of the labyrinthine segment of the nerve, because the basal turn of the cochlea can be less than 1 mm inferior and the ampulla of the posterior semicircular canal and lateral semicircular canal directly posterior. Small diamond burrs (0.4 to 0.8 mm) are used to remove the bone over the canal. It is safer to remove more bone anterior to the labyrinthine segment than posterior to it. The final thin layer of bone is removed with blunt microdissectors (Storz). When bone has been removed 180 degrees from the cephalic portion of the nerve, a microelevator is used to elevate the nerve gently out of the canal. Any adhesions to the bone are sharply separated with a microscalpel (Beaver No. 59-10). The tympanic segment of the nerve is mobilized in a similar manner. If the slightest tension would be necessary for reapproximation of the nerve ends, an interposition graft should be placed.

Surgical techniques have been developed to expose lesions near the jugular bulb, carotid canal, and parasellar regions.[8] The descending segment, stylomastoid foramen, and extratemporal course of the facial nerve are directly lateral to these structures. Rerouting the facial nerve greatly facilitates the surgical exposure and eliminates the need to transect the nerve in most instances. Commonly, the nerve is relocated anterior and superior to its original position, requiring the middle ear cleft to be obliterated and the posterior external bony canal to be removed.

A large, C-shaped postauricular skin incision is designed to allow exposure of the mastoid cortex and parotid gland. The skin flap is developed through the external ear canal at the bony cartilaginous junction and carried anteriorly, exposing the periparotid fascia. The extratemporal course of the facial nerve is exposed in the parotid gland in the usual fashion. The dissection of the nerve is carried distal to the pes anserinus, and the inferior division is freed from the surrounding gland for 1 to 2 cm. Additional dissection may be necessary, depending on the exposure required.

A complete mastoidectomy is performed, and the posterior external canal is lowered to the level of the lateral semicircular canal and the digastric ridge. The tympanic ring, malleus, and incus are removed. The tympanic and descending segments of the facial nerve are identified with a diamond burr (Fig. 171-20). Bone is removed 180 degrees around the nerve, leaving a thin shell that is removed with microelevators. Sharp dissection with a microscalpel frees the nerve sheath from the remaining fallopian canal.

An abundant vascular supply frequently is encountered during elevation of the nerve from the canal. Bleeding is controlled with a microtipped bipolar cautery at the lowest effective current.

At the stylomastoid foramen, a thick fibrous sheath strongly adheres to the bone. To prevent trauma to the nerve during elevation of this portion, it is suggested that the entire fibrous sheath be freed and moved with the nerve. Removal of the nerve from the sheath induces unnecessary trauma that may result in temporary paralysis. It also may be difficult to elevate the tympanic segment of the nerve because of the close proximity of the stapes superstructure. The crura and capitulum of the stapes can be removed with a crurotomy scissors. A groove that is larger than the nerve is then milled in the zygomatic root area of the epitympanum to accept the nerve as it is transposed anterosuperiorly at the level of the geniculate ganglion (Fig. 171-21).

Partial Rerouting

Partial rerouting of the facial nerve can be attempted for tumors that do not involve the protympanum, internal auditory canal, or eustachian tube. This procedure allows preservation of middle ear function. When hearing preservation is to be attempted, rerouting of only the mastoid segment of the facial nerve is more limited. The external auditory canal is transected 3 to 4 mm medial to the bony cartilaginous junction, allowing reconstruction of the external auditory canal at the end of the

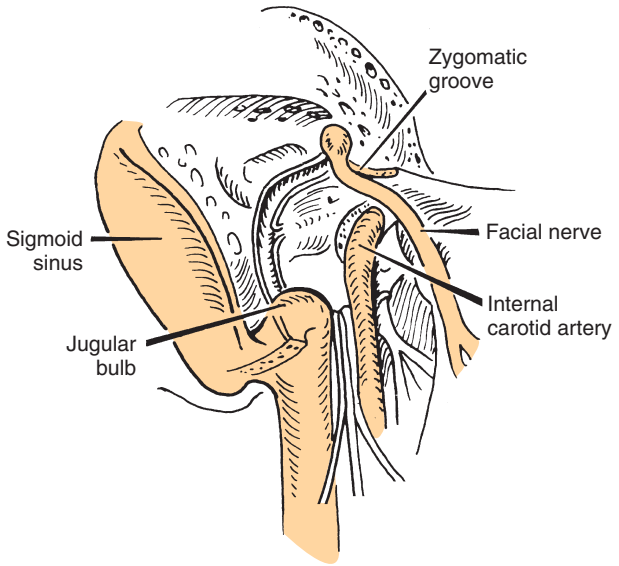

Figure 171-21. Appearance after rerouting of the facial nerve.

procedure. A canal wall-up mastoidectomy with an extended facial recess is created. In addition to thinning the posterior canal wall, the inferior wall or floor is thinned in a similar manner. The facial nerve is skeletonized to the tympanic segment and elevated out of the fallopian canal with sharp dissection. The nerve is sharply dissected with a cuff of tissue at the stylomastoid foramen, as in the total rerouting technique. The facial nerve is temporarily elevated laterally to allow exposure to the jugular foramen and the pars nervosa, containing cranial nerves IX, X, and XI. After tumor removal, the facial nerve is returned to its approximate position. A 1-mm burr is then used to create anchor holes at the lateral extent of the bony canal (one in the floor, two in the posterior wall, and one in the anterior wall). The external canal skin is secured to its position with 3-0 sutures. The sutures are placed into the thick subcutaneous tissue, rather than the skin. The canal is packed with antibiotic ointment–impregnated gauze strip for 1 week. Stenosis of the canal has not occurred in more than 30 partial rerouting procedures. Anchoring the canal skin to the bony canal prevents the formation of external canal mastoid fistula.

Nerve Repair

Whenever the continuity of the facial nerve has been disrupted by traumatic injury, iatrogenic injury, or tumor invasion, every effort should be made to restore its continuity. In some instances, an end-to-end reapproximation can be accomplished, but if any tension occurs at the anastomotic site, an interposition nerve graft confers a better chance of allowing facial movement. All nerve repair techniques produce synkinesis, but sphincteric function of the mouth and eye usually are restored. Newer microsuture techniques and instrumentation should be used to enhance return of function.

In general, the injured ends of the nerve should be freshened at a 45-degree angle. Experimental evidence has shown that cutting the nerve at this angle exposes more neural tubules, with consequently improved regrowth of the nerve.[16] In addition, a fresh razor blade induces less crush to the nerve than does a scalpel blade or scissors. Milesi[17] advocates removing a portion of the epineurium before suturing to prevent connective tissue growth at the anastomotic site. We have found that the perineurium of cranial nerve VII does not hold 10-0 sutures, and attempting to suture it increases trauma to the neural tubules. If the epineurium is cleaned from the end of the nerve for approximately only 0.5 mm, sutures can still be placed in the epineurium for reapproximating the nerve segments. Three or four sutures of 10-0 nylon are placed with jeweler's forceps or longer instruments (19-cm microforceps) for anastomosis in the cerebellopontine angle. At the brainstem, one or two sutures are placed. Within the fallopian canal, a nerve graft can be interposed without sutures if there is no chance of nerve end movement.

When an interposition graft is required, the great auricular nerve or the sural nerve is the preferred graft donor site. The great auricular nerve is readily available near the operative field if it is not involved in resection of a neoplasm and has approximately the same diameter as that of the facial nerve. It is easily located midway and perpendicular to a line drawn between the mastoid tip and the angle of the mandible. If a graft longer than 8 to 10 cm is required, the sural nerve should be used. The sural nerve has another advantage in that the peripheral portion of the nerve has many branches that can be used to reconstruct the branching pattern of the facial nerve. Little discomfort is associated with removal of the sural nerve, because it provides only a small area of sensation to the lateral lower leg. The sural nerve is found immediately posterior to the lateral malleolus, along the saphenous vein. The nerve graft should be 10% to 20% larger in diameter than the facial nerve and long enough to ensure tension-free anastomosis.

Facial Nerve Tumors

Tumors (both benign and malignant) can affect the facial nerve in the intracranial cavity, within the temporal bone, and in the parotid gland. Approximately 5% of cases of facial nerve dysfunction are due to the presence of a tumor. It is essential to differentiate intrinsic from extrinsic facial nerve tumors (e.g., a primary facial nerve tumor versus tumor contiguous with the facial nerve or metastatic disease). Extrinsic tumor involvement is much more common than intrinsic tumor involvement. Numerous benign and malignant neoplasms may occur in and around the temporal bone. Within the temporal bone itself, skull base tumors and metastases from the breast and lung are common neoplastic causes of facial paralysis in adults, whereas hematologic malignancies (leukemia, lymphoma) are common in children.[18] Management of these lesions is beyond the scope of this chapter. It is not possible to list all of the neoplasms, but common ones include facial schwannomas, congenital cholesteatomas, hemangiomas, glomus tumors, vestibular schwannomas (acoustic neuromas), squamous cell carcinomas, and parotid neoplasms. The following discussion is concerned primarily with those lesions of the facial nerve proximal to the stylomastoid foramen.

The classic symptom associated with tumors involving the facial nerve is a progressive paralysis of the face. In some benign lesions, this progression is extremely slow; months or even years may elapse before the paralysis becomes complete. The cause of a facial palsy progressive beyond 3 weeks after onset but with no return of function by 6 months is presumed to be a tumor until proven otherwise. Benign tumors produce facial paralysis by compressing the facial nerve, whereas malignant lesions invade the nerve itself. Therefore, in benign tumor removal, it is sometimes possible to dissect the mass away from the nerve without damage to the nerve itself. In dealing with malignant neoplasms, it is necessary to resect the nerve with the tumor and then perform a reconstruction of the nerve.

Early diagnosis of facial paralysis from a tumor is dependent on a high index of clinical suspicion. In addition to a slowly progressive paralysis, several other clinical features should heighten suspicion for a tumor involving the facial nerve. Twitching of the facial nerve in association with facial palsy is not seen with Bell's palsy. In addition, recurrent palsy also may be associated with a tumor. Pain, although frequently a feature of Bell's palsy or Ramsay Hunt syndrome, also is often a symptom with tumors involving the facial nerve. Involvement of other cranial nerves in addition to the facial nerve should raise concern that a neoplasm is present. A predilection for neoplasms to occur at the geniculate ganglion area, possibly owing to this area's embryologic diversity, has been suggested.[3] Evaluation for a neoplastic etiology for a facial palsy should include radiologic imaging (with both CT and MRI scans).

Acoustic neuromas are benign tumors and are the most common lesions of the internal auditory canal and cerebellopontine angle. Facial paralysis is an unusual manifestation of these tumors and generally signifies an advanced stage of tumor growth. Rarely does an acoustic neuroma actually invade the facial nerve. It also is possible for a patient with an acoustic neuroma and facial palsy to have a concomitant Bell's

palsy as the true etiology of facial nerve dysfunction. In the absence of nerve sheath invasion, the facial nerve generally appears to tolerate gradual pressure stresses well. Facial dysfunction may also occur from local vascular compromise.[19]

Nerve sheath and vascular neoplasms make up the greatest percentage of intrinsic facial nerve tumors (although they are relatively rare as a group). These tumors typically are facial schwannomas (neuromas) but also may include meningiomas, hemangiomas, and glomus tumors.[18] These tumors may manifest relatively early with facial weakness.[19] Overall, facial nerve schwannomas are uncommon, slow-growing neoplasms arising from the nerve sheath, and they may occur anywhere from the cerebellopontine angle to the peripheral branches of the facial nerve.[20] A majority of facial nerve schwannomas are intratemporal, most often involving the labyrinthine segment and geniculate ganglion.[20,21] A retrospective review demonstrated that facial nerve schwannomas were more likely to involve multiple segments than a single segment.[21] One of the largest series of facial nerve tumors to date was published by McMenomey and colleagues in 1994.[22] They reviewed their experience with 32 primary facial nerve tumors between 1975 and 1992. Preoperatively, 38% were thought to be acoustic neuromas.

A facial nerve schwannoma may be misdiagnosed as an acoustic neuroma, especially when the tumor does not enter the meatal foramen or fallopian canal and is instead confined to the internal auditory canal.[22,23] Even with high-resolution MRI, it may be difficult to distinguish preoperatively between an acoustic neuroma and a facial schwannoma. Beyond the clinical examination and clinician suspicion, no useful preoperative evaluation tools are available that can definitively identify the precise nerve of origin of intracanalicular tumors. This limitation emphasizes the need to fully inform the patient preoperatively.[23]

Treatment decisions must be made based on the patient's desires, age, degree of facial function, tumor location, and hearing status.[8,24] The goal in the management of these tumors is to maximize long-term facial nerve function while minimizing morbidity. At most centers, the most common mode of treatment is tumor resection with grafting. Observation is another option for tumors that are not producing facial paresis or are generating minimal symptoms (House-Brackmann grade II). It also is possible that with observation or expectant management, complications such as total hearing loss may occur, particularly when the tumor involves the labyrinthine and internal auditory canal portions of the nerve.[25] Unfortunately, a majority of patients undergoing resection and grafting will have additional facial nerve deficits in the immediate postoperative period, and the long-term results with grafts generally are characterized by poor recovery of forehead motion and mass motion (grade C on the Repaired Facial Nerve Recovery Scale [RFNRS][26]).

A review of the records at House Ear Institute between 1977 and 1994 showed that 93 patients were diagnosed with facial neuromas and 3031 were diagnosed with acoustic neuromas.[27] In four patients in whom the diagnosis was made during surgery, the tumor was not completely resected.[27] Two of the patients underwent decompression using an middle cranial fossa or translabyrinthine approach. Two patients underwent a retrosigmoid craniotomy, one of whom also underwent decompression; for the other, postoperative management consisted of observation of her tumor. Follow-up for these patients ranged from 24 to 62 months. In three of the four tumors, no growth was noted on the MRI scan during the follow-up period (the other showed a 6-mm growth over 5 years). In one patient (who underwent translabyrinthine decompression), facial nerve function improved from grade V preoperatively to grade II postoperatively.

The medical records of 21 patients with facial nerve tumors treated between 1982 and 2002 at the University of Iowa Hospitals and Clinics were retrospectively reviewed. The ages of the patients ranged from 13 to 76 years. Follow-up ranged from 1 month to 22 years.

In 2 of the 21 patients, the tumor was identified on an MRI scan obtained for other medical reasons. Both have normal facial nerve function (House-Brackmann grade I) and undergo periodic MRI. One has been observed for longer than 20 years and continues to have grade I facial nerve function. Twenty-one procedures were performed on the other 19 patients. Of the 21 procedures performed, 11 consisted of resection followed by interposition grafting. Patients in this group presented with conditions classified as House-Brackmann grade IV or worse. All grafting was done using the greater auricular nerve. The other 10 procedures involved decompression, debulking, or both. *Decompression* included removal of the bony confines of the facial nerve either in the internal auditory canal or in the fallopian canal at the site of the tumor and some distance proximal and distal to the tumor. *Debulking* involved removal of portions of the tumor, with the use of intraoperative facial nerve monitoring to reduce the likelihood of inadvertent damage to normal facial nerve fibers.

Table 171-3

Repaired Facial Nerve Recovery Scale (RFNRS)

Score	Function
A	Normal facial function
B	Independent movement of eyelids and mouth, slight mass motion, slight movement of the forehead
C	Strong closure of eyelids and oral sphincter, some mass motion, no forehead movement
D	Incomplete closure of eyelids, significant mass motion, good tone
E	Minimal movement of any branch, poor tone
F	No movement

Facial nerve function was graded using the House-Brackmann scale for the observation and decompression-debulking group. However, owing to the limitations and inadequacies of this grading scale for nerve resections, a different scale, the RFNRS, was used to grade nerve function in the resection and grafting group (Table 171-3). A majority of the tumors in this series were facial nerve schwannomas. All 10 of the tumors in the decompression-debulking group were schwannomas, whereas 7 of the tumors in the resection group were schwannomas. Tumors in the resection group also included 3 hemangiomas and 1 meningioma. In the decompression-debulking group, five patients had grade I function. Three patients had grade II function, one patient had grade III function, and one had grade IV function. None of the patients in this group have had grade V or VI function.

In the resection and grafting group, the best facial function noted postoperatively was grade C, which is roughly equivalent to House-Brackmann grade III, in six patients. Three patients had grade D function. One patient had grade E function and one grade F function. Of significance, none of these patients achieved a preferred grade A or B function.

Observation of intrinsic facial nerve tumors is a possible management approach, especially for patients with House-Brackmann grade I or II facial function. Surgical decompression is an option for patients with House-Brackmann grade II or III facial function. Resection with grafting is recommended for those with grade IV function or worse. Conservative management with either observation or decompression often is an appropriate option, because the best facial nerve function result after resection and grafting is grade C on the RFNRS, owing to the presence of mass motion. Nonetheless, treatment is individualized.

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CHAPTER ONE HUNDRED AND SEVENTY-TWO

Rehabilitation of Facial Paralysis

James M. Ridgway

Roger L. Crumley

Jason H. Kim

Key Points

- Paramount to the rehabilitation of facial nerve paralysis is a complete understanding of the nature of the injury, extent of the defect, viability of remaining facial nerve segments, integrity of potential donor nerves and tissues, and the overall patient's health status as well as personal desires and expectations for rehabilitation.
- A detailed history and physical examination should include a description of the mechanism of the injury, time of onset, duration of symptoms, previous surgery or radiation therapy, speech and swallowing function, and previous treatment and rehabilitation.
- Division of the face into upper, middle, and lower thirds allows for a more precise characterization of nerve defects and potential therapeutic options.
- Management of facial paralysis is dependent on the specific cause of the paralysis. Options for facial nerve rehabilitation include spontaneous nerve regeneration (observation), facial nerve neurorrhaphy, facial nerve cable graft, nerve transposition, muscle transposition, microneurovascular transfer, and static procedures.
- EMG is indispensable in determining the existence of denervation atrophy or subclinical innervation. EMG is the single most important test for determining the type of operative procedure to be performed.
- An operative electric nerve stimulator may be used only in acute injuries to identify severed distal nerve segments. Wallerian degeneration with impairment of nerve conduction has occurred by 72 hours after injury, and the surgeon is left to rely on visual identification after this point in time.
- The most desired source for rejuvenation of the paralyzed face is the ipsilateral facial nerve.
- Early protection of the eye in the setting of facial nerve paralysis is of the highest priority, because failure to recognize and treat eyelid dysfunction will result in devastating ocular complications that are entirely preventable.
- Tension-free repair of the facial nerve is critical to the success of nerve anastomosis. When operative circumstance does not permit such an end-to-end anastomosis, cable or interposition nerve grafting is the desired surgical approach to facial muscle reinnervation.
- When grafting to the proximal facial nerve segment is not an option in rehabilitation, attention is then shifted to the muscle (masseter or temporalis) or nerve (hypoglossal) transfer procedure.
- Static techniques are best used in debilitated patients with limited prognostic survival and in those for whom nerve or muscle is not available for dynamic procedures.
- Patients with incomplete recovery from facial nerve paralysis typically present with hyperkinetic, uncoordinated mass facial movements known as synkinesis. Botulinum toxin has dramatically improved the management of this condition and is the current first-line therapy.

Dealing with the consequences of unilateral facial paralysis usually is a devastating emotional ordeal for the patient. The ability to restore symmetry and motion to patients afflicted with facial paralysis is one of the most rewarding skills of the well-trained reconstructive surgeon. This chapter discusses rehabilitation of facial nerve injuries. Many of the diagnostic considerations and surgical techniques described are applicable to otogenic paralyses (intratemporal), as well as injuries and diseases that affect the parotid and facial portions of the facial nerve.

The facial nerve, once damaged, rarely attains full recovery of function. Given the challenges to the patient, counsultations regarding facial nerve paralysis require a clinician's fullest thought and compassion. A realistic approach yields the rewards of patient compliance, understanding, satisfaction, and acceptance of reality. A recent review of all state and federal civil trials alleging malpractice and facial nerve paralysis demonstrates the importance of careful explanation and documentation, as well as the importance of good patient rapport and bedside manner in preventing lawsuits.[1]

Patient Assessment

Complete patient assessment is critical to attain optimal rehabilitation of facial paralysis. It is critical to properly understand the nature of the injury and the resulting defect, to know the viability of the proximal

and distal facial nerve segments, to properly assess the viability of potential donor nerves and facial musculature, and to thoroughly assess both the patient's health status and personal desires for rehabilitation.

An outline of assessment of facial nerve paralysis is presented in Box 172-1.

Box 172-1

Assessment of Facial Nerve Paralysis

History

Type of injury
Time since injury
Age, overall health, and life expectancy
Radiation therapy (past or planned)
Nutritional factors
Previous operative report

Physical Examination

Previous incisions and scars
Integrity of trigeminal, vagal, and hypoglossal nerves
Facial motion (e.g., complete versus partial paralysis)
Status of eye (e.g., lagophthalmos, ectropion)
Facial tone, structure (e.g., habitus)

Testing/Imaging

Electromyography: indicated in all patients who have had paralysis for more than 1 year
Computed tomography and magnetic resonance imaging of temporal bone and parotid: indicated if there is any question about the cause of paralysis

Assessment of the Deformity

Physical examination includes complete head and neck examination with attention to cranial nerve function and the presence of functional masseter and temporalis muscles. The degree of facial nerve function is recorded using the House-Brackmann Facial Grading System[2] (Table 172-1). A number of facial nerve grading scales have been developed, but the House-Brackmann scale was adopted by the Facial Nerve Disorders Committee of the American Academy of Otolaryngology–Head and Neck Surgery in 1985 because of its reproducibility and ease of use.[2] This scale is useful for evaluation of overall function, but it is insufficient for precise assessment of defects affecting one or more branches of the facial nerve, and it does not allow precise measurement of effectiveness of treatments isolated to one region of the face. Therefore, the examination should assess deformity of the upper, middle, and lower thirds of the face independently. This approach allows more precise characterization of defects, aids the decision-making process for rehabilitation, and allows more precise assessment of treatment results. Facial tone also is noted, as is the presence of any reinnervation. Thorough assessment of the eye also is performed. Visual acuity, corneal integrity, eyelid closure, tearing, Bell's phenomenon, lagophthalmos, lower lid laxity, position of the lacrimal puncta, and eyebrow position are noted. Nasal examination focuses on the position of the ala and nasal septum and the presence or absence of nasal obstruction. Oral competence and height and position of the lower lip are carefully reviewed. In long-term paralysis (of more than 1 year's duration), electromyography (EMG) of the facial muscles is performed before reinnervation procedures. Occasionally, muscle biopsy provides additional information about the presence of viable muscle for innervation. If nerve fibrosis is suspected, nerve biopsy occasionally is indicated.

Another important component of the assessment is evaluation of the patient's smile pattern. The smile is created by the muscles of the lips, and smile patterns can be classified into one of three types.[3] The "Mona Lisa" smile is the most common smile pattern (67%). It is

Table 172-1

House-Brackmann Grading System

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Slight	Appearance: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone Forehead motion: moderate to good function Eyelid closure: complete with minimal effort Mouth motion: slight asymmetry
III	Moderate	Appearance: obvious but not disfiguring weakness between the two sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm At rest: normal symmetry and tone Forehead motion: slight to moderate movement Eyelid closure: complete with effort Mouth motion: slightly weak with maximal effort
IV	Moderately severe dysfunction	Appearance: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone Forehead motion: none Eyelid closure: incomplete Mouth motion: asymmetric with maximal effort
V	Severe	Appearance: only barely perceptible motion At rest: asymmetric Forehead motion: none Eyelid closure: incomplete Mouth motion: slight movement
VI	Total	No facial function

From House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg*. 1985;93:146.

dominated by action of the zygomaticus major muscle: The corners of the mouth move laterally and superiorly, with subtle elevation of the upper lip. The canine smile (31%) is dominated by levator labii superioris action, appearing as vertical elevation of the upper lip, followed by lateral elevation of the corner of the mouth. The least common smile is the full denture smile (2%), or "toothy smile," produced by simultaneous contraction of the elevators and depressors of the lips and angles of the mouth. Knowledge of facial muscle anatomy and the smile pattern exhibited by the patient is important in considering rehabilitation techniques other than nerve grafting to recreate a balanced facial appearance at rest and the simulation of a symmetric smile.

Considerations in Facial Nerve Rehabilitation

A number of factors come into play in designing a management plan for the patient with facial paralysis. In clinical situations requiring facial reanimation, the technique used often depends on the availability of a viable proximal facial nerve.

Tumor ablation with facial nerve sacrifice (as in radical parotidectomy for parotid malignancy) dictates immediate facial nerve restitution, usually by cable grafting. When the nerve's continuity and viability are in question, however, as may be seen during and after cerebellopontine angle surgery, it is wise to wait 9 to 12 months before an extratemporal facial nerve operative procedure is undertaken. Hence, no modality is universally appropriate for all afflictions of facial nerve function. Static procedures generally are used when no viable reinnervation options exist but also can be integrated with dynamic procedures to provide immediate restoration of facial symmetry.

Generally, however, the order of preference for rehabilitation procedures is as follows:

1. Spontaneous facial nerve regeneration (observation)
2. Facial nerve neurorrhaphy
3. Facial nerve cable graft
4. Nerve transposition
5. Muscle transposition
6. Microneurovascular transfer
7. Static procedures

Time since Transection

A chronic, long-standing paralysis with complete muscle degeneration poses several problems with regard to eventual reinnervation surgery. The facial muscles may undergo denervation atrophy. Severe atrophy renders the reasonably normal muscles incapable of reinnervation and contraction. Such severe atrophy may occur after 18 months of complete denervation, although in some clinical situations, muscles have been known to persist inexplicably for many years without incurring such atrophy.[4] EMG is the most helpful method for assessing facial muscle atrophy and is therefore a preoperative prerequisite for all reanimation candidates if the paralysis is of more than 12 months' duration. The presence of nascent, polyphasic, or normal voluntary action potentials in a patient with facial paralysis indicates the occurrence of reinnervation. If more than 12 months have passed since the facial nerve injury, the situation can be assumed to be stable, and an attempt at surgical reanimation may be warranted. Within the first 12 months, however, the presence of potentials may mean that reinnervation is occurring and that facial movements may return in the next few months. Reanimation surgery should therefore be postponed. Fibrillation or denervation potentials mean that the EMG electrode is positioned in denervated muscle. This is an optimal situation for cable nerve grafting or, when no viable proximal facial nerve is available, for hypoglossal-facial anastomosis.

One of the most significant EMG findings is electrical silence, reflecting denervation atrophy of the facial muscles. The surgical implication is that nerve grafting or transfer is futile and therefore contraindicated. If the facial muscles are absent or atrophied, muscle transfers are indicated.

Another effect of time includes endoneural scarring within distal nerve segments. It is not known whether endoneural scarring acts as an impediment to nerve regeneration, but when associated with muscular atrophy, it probably further precludes nerve grafting or transfer.

Presence of Partial Regeneration

Partial regeneration often is overlooked but is extremely important in determining which operation to perform. If the facial nerve has undergone enough regeneration to permit a few axons to reach the facial muscles, this partial innervation may be sufficient to preserve the muscles for many years, even though they may be totally paralyzed. In these clinical circumstances, results with hypoglossal-facial anastomosis, which generally is preferable to muscle transfer, will be optimized.

Status of the Proximal and Distal Facial Nerve

The optimal source for rejuvenation of the paralyzed face is the ipsilateral facial nerve. Anastomosis or grafting to the ipsilateral nerve has no donor consequence (other than the minor hypesthesia or anesthesia from the harvesting of a nerve graft) and facilitates natural voluntary and involuntary control. Exceptions to this general rule are those cases in which the patient needs prompt relief from corneal exposure or drooling, and a tissue transfer or sling technique may be preferred because its effects are immediate.

Accordingly, the integrity of the proximal facial nerve is critical. As with other motor nerves, no reliable electrical tests exist to confirm the viability of the proximal nerve when it is discontinuous with its distal portion. Factors that affect proximal nerve viability and are therefore important considerations in the clinical evaluation include (1) nature of the nerve injury (e.g., clean transection versus crush), (2) location of injury (proximal versus distal), (3) age (younger nerves tend to regenerate more quickly and fully), (4) nutritional status (which directly affects nerve regeneration), and (5) history of irradiation (which may impede neural regeneration).

The facial nerve distal to the injury site serves as a conduit for neural regeneration to the facial muscles after neurorrhaphy, grafting, or hypoglossal-facial anastomosis. With acute injuries (incurred less than 72 hours previous), the electrical stimulator may be used to identify the distal nerve and the muscular innervation of distal branches. After this "golden period," however, the surgeon must rely on visual identification of the divisions and branches of the distal nerve, because the capability of being stimulated electrically generally is lost after approximately 72 hours. For this reason, transected nerve branches in trauma or tumor cases should be tagged for identification by placing a small colored suture around or adjacent to each nerve branch. Any anatomic or surgical landmarks should be precisely dictated in the operative note. If no suture markers are available, and the golden period has elapsed, careful surgical searching (preferably with use of loupes or an operating microscope) may reveal each of the divisions or branches of the facial nerve. A topographic map is essential in guiding the dissection. A review by Bernstein and Nelson[5] describes the variability with which these branches are placed. The following landmarks are helpful (Fig. 172-1).

- The pes anserinus can be found 1.5 cm deep to a point 1 cm anterior and 2 cm inferior to the tragal cartilage.
- The superior division courses from the pes anserinus to the lateral corner of the eyebrow, convex posterosuperiorly (see Fig. 172-1). Bernstein and Nelson[5] stressed that these temporal branches may be multiple and reach as far posteriorly as the superficial temporal vessels.
- The buccal branch courses superiorly and then anteromedially, passing 1 cm inferior to the inferior border of the zygomatic arch (see Fig. 172-1).
- The marginal mandibular branch passes from the pes anserinus directly over the angle of the mandible and then under the inferior

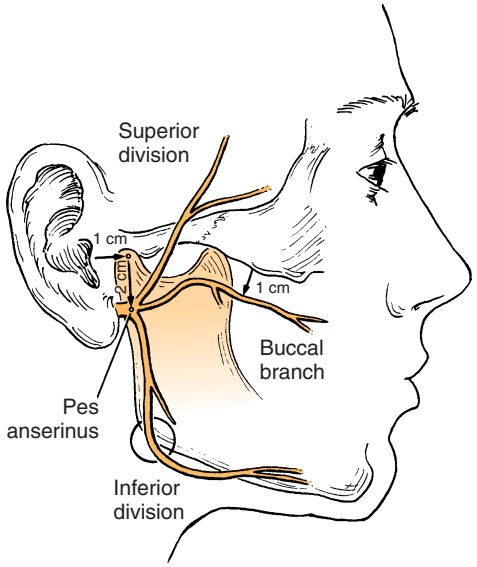

Figure 172-1. Topographic map of distal facial nerve anatomy, useful as a guide in finding nonstimulatable nerve branches for grafting. Pes anserinus is 2 cm inferior to a point 1 cm anterior to tragus. Marginal mandibular branch courses from the pes anserinus to the angle of the mandible: buccal branch parallels the zygomatic arch 1 cm below its inferior border. Superior division arcs from pes anserinus toward lateral end of the eyebrow, under a line that is convex superiorly. *(From House JW, Brackmann DE. Facial nerve grading system.* Otolaryngol Head Neck Surg. *1985;93:146.)*

border of the mandible for approximately 3 cm. It then crosses above the mandible at the level of the facial vessels. Any of several anatomic variations may exist, necessitating ingenuity in nerve grafting. When the facial nerve trunk and pes anserinus are intact, a cable graft (or hypoglossal nerve) should be sutured to that portion of the main nerve trunk. However, certain injuries and surgical procedures may sacrifice important individual portions of the nerve, requiring selective routing of reinnervation to specific divisions. The order of priority for reinnervation of facial nerve branches is as follows: (1) buccal and zygomatic branches (equal), (2) marginal mandibular, (3) frontal, and (4) cervical (the last may be disregarded or excluded).

As an example of selective routing, when a parotid tumor operation results in excision of the pes anserinus and the proximal facial branches, a branched nerve graft may be placed to reinnervate the zygomatic and the buccal branches, excluding unimportant branches. Fisch[6] advises clipping branches of cervical branches in order to route innervation to the more important portions of the face. Data confirming the efficacy of this technique, however, are very limited.

If no nerve branches are found, and EMG shows that denervated facial muscles are present, the nerve graft may be sutured directly to the muscles targeted for reinnervation (muscular neurotization). In these instances, the most important muscles are those of the midface (zygomaticus major and minor, levator labii superioris) and orbicularis oculi muscles. Reinnervation will not be as complete as in routine nerve grafting because the regenerating axons must form new connections to the old motor endplates, or they must create their own.[7]

Viability of Facial Muscles

Four types of EMG responses are observed[8]:

Normal voluntary action potentials indicate that functioning motor axons have connections with and are stimulating motor units of facial muscle.

Polyphasic potentials are seen during reinnervation and may precede visible evidence of reinnervation.

Denervation or *fibrillation potentials* indicate that otherwise normal denervated muscle exists.

Electrical silence, with no potentials seen, indicates atrophy or congenital absence of muscle, provided that the electromyographer has positioned the electrode correctly.

Donor Consequences

Many surgical procedures designed for facial reanimation borrow neural elements or signals from other systems (i.e., the hypoglossal and trigeminal systems). The consequences of sacrificing the donor nerve (known as donor deficit) are most important in planning for the overall needs of the patient. Certainly, the surgeon must assess the donor nerve preoperatively in all cases. The hypoglossal nerve must be tested for strength and vitality before it is transected and anastomosed to the distal facial nerve. Similarly, the trigeminal nerve must be intact and functional when its muscles, either masseter or temporalis, are considered for transposition into the facial muscle system.

The donor effects of facial reanimation surgery may be quite detrimental to the patient's welfare. For example, a patient with previous hypoglossal nerve injury on the opposite side could become an "oral cripple" if the remaining hypoglossal nerve were to be transected for use in a XII-VII anastomosis.

The ideal reanimation procedure is one that yields the following results: (1) no donor deficit; (2) immediate restitution of facial movement; (3) appropriate involuntary emotional response; (4) normal voluntary motion; and (5) facial symmetry. No currently available operative procedure satisfies all of these parameters. In fact, even with a bacteriologically sterile and precise surgical transection and immediate microsurgical repair of the facial nerve, completely normal neurologic function cannot be restored. Therefore, the surgeon must have a clear understanding of all operations available, including potential outcomes and sequelae.

Status of Donor Nerves

The hypoglossal nerve is the most frequently used nerve source for transfer. Reflex and physiologic similarities between the hypoglossal and facial nerves have been described.[9] The integrity of the hypoglossal nerve must be determined before it is transferred for reinnervation. Irradiation of the brainstem, lesions of the skull base and hypoglossal canal, and surgical procedures of the upper neck may affect the integrity and function of this nerve.

The trigeminal nerve has been used for facial reanimation in many ways. The methods currently used most often involve masseter or temporalis muscle transfer (necessitating that the motor portions of the trigeminal nerves be intact). Palpation of the muscle during jaw clenching confirms whether the muscle is functional.

The cross-face nerve graft procedure (faciofacial anastomosis) initially was thought to be the most appropriate and ingenious facial reanimation procedure.[10,11] The procedure is unique in that it borrows appropriate neural input from the contralateral normal side and routes it to the paralyzed side. Such a procedure requires a fully intact (contralateral) facial nerve.

Age

The proximal neuron's ability to regenerate declines with time because of denervation and aging-related changes. The etiologic mechanism probably involves diminishing regenerative vitality of the perikaryon (cell body), although peripheral scarring may play a role. The clinical implication is that facial reanimation surgery should always be performed as soon as possible, provided that the operative procedure does not interfere with or injure existing innervation or ongoing reinnervation.[12]

Health Status

Among patients with diabetes, regeneration of injured nerves is notoriously poor. Microangiopathy is an additional factor that may affect the grafted segment. These factors do not preclude a nerve graft procedure in a diabetic patient, but when combined with radiation, advancing age, and other factors, they may cause the surgeon to con-

sider muscle transfer or a suspensory operation, rather than a neural anastomosis.

Prior Radiotherapy

Radiotherapy, a necessary component of treatment for certain salivary gland malignancies, appears to have a deleterious effect on reinnervation through facial nerve grafts. McCabe[13] demonstrated satisfactory muscle reinnervation from grafting despite irradiation in animals. These investigators subsequently have documented return of facial function in nine patients who received post-grafting radiotherapy. McGuirt and McCabe[13] and Conley and Miehlke[14] have published reports indicating that facial nerve grafts function well even though irradiated, and that nerves are among the most radioresistant tissues of the human body. Pillsbury and Fisch[15] found that radiotherapy reduced the average outcome from 75% to 25% of nerve function recovery in a review of 42 grafted patients. Irradiation probably affects the neovascularization of the nerve graft by decreasing vascularity of the tissue bed and probably injures the proximal and distal segments of the nerve as well. The most radiosensitive portion of the nerve—the pontine nucleus—should be assessed to determine whether it was present in the field of irradiation.

Congenital Paralysis

In a series of 95 infants with neonatal paralysis, Smith and associates[8] found 74 of the cases to be secondary to intrauterine injury or birth trauma, whereas 21 were thought to be congenital. These infants should be studied with nerve excitability and EMG testing early in life to ascertain the status of nerves and muscles. Most patients with injury-related neonatal paralysis recover rapidly, whereas the paralysis associated with other congenital anomalies (such as Möbius syndrome) is permanent. Nerve exploration or transfer generally is futile in the latter cases.

Early Care of Facial Nerve Injury

Failure to recognize and treat acute eyelid dysfunction will result in devastating ocular complications. The ability to prevent, diagnose, and treat paralytic eyelid sequelae before major complications occur is essential in the management of any patient with facial paralysis. An important point is that the outcome of the eyelid paralysis is directly related to patient education and compliance.

Eye Protection: Evaluation and Treatment of Eyelid Paralysis

Paralysis of the orbicularis oculi results in exposure and drying of the cornea. Patients at increased risk for exposure keratitis may be identified by applying the acronym BAD—*a*bsence of Bell's phenomenon, corneal *a*nesthesia, and history of *d*ry eye. An inability to protect the cornea is the result of incomplete eye closure, preventing effective distribution of the tear film across the surface of the eye, and ectropion occurs because the atonic lower lid and lacrimal punctum fail to appose the globe and bulbar conjunctiva. This causes faulty eyelid closure and improper distribution of tears across the cornea.

Epiphora may result from failure of tears to enter the lacrimal punctum, secondary to pooling of tears due to ectropion and the loss of the orbicularis oculi tear-pumping mechanism. The response to abnormal corneal sensation may be reflex tear hypersecretion, which will further increase the epiphora.

Any patient with facial paralysis who demonstrates a poor Bell's phenomenon is at risk for the development of exposure keratitis. Eye pain may herald the onset of keratitis. In patients with diminished corneal sensation, however, exposure keratitis may asymptomatically progress to corneal ulceration. Accordingly, all patients with diminished orbicularis oculi function require ophthalmologic consultation.

Initial eye care is directed toward moisturizing the dry eye and preventing exposure. It is important to communicate to the patient the potential consequences of failure to protect the eye, in hopes of improved compliance. If the eyelid paralysis is temporary or partial, these local measures may be all that are necessary to adequately protect the eye. Regular use of artificial tears commonly is the first-line method used to keep the eye moist. Ointments also may be used, but they are less practical in the daytime because they tend to blur vision.

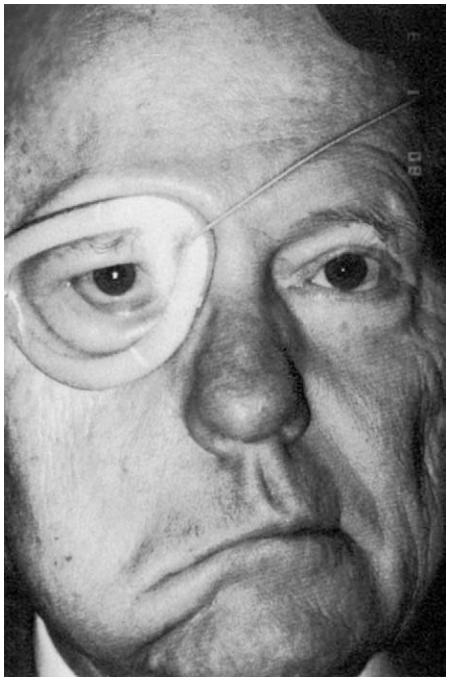

Figure 172-2. Occlusive bubble worn by a patient after acoustic neuroma surgery. The appliance has a foam rubber skin contact surface that is firmly attached to a thin Plexiglas lens. In our experience, patient compliance is relatively high with this type of device. *(Courtesy of Moisture Chamber, Pro-optics, Palatine, Illinois.)*

Lacriserts, contact lenses, and occlusive bubbles commonly are used, although patient compliance may be problematic[16] (Fig. 172-2). The eyelids frequently are patched or taped, but if incorrectly used, these methods may result in corneal injuries. Tape should not be placed vertically across the eyelashes, but applied horizontally above the eyelashes on the upper eyelid, or supporting the lateral canthal portions of the lower eyelid.[17] When an eye patch is used, care must be taken to ensure that the eye cannot open, because this would allow contact between the patch and the cornea.

Procedures to Treat Paralysis of the Lower Lid (Ectropion)

Tarsorrhaphy

The temporary lateral tarsorrhaphy is an expeditious and effective method for protecting the eye in patients with mild lagophthalmos and mild corneal exposure. A horizontal mattress suture of 7-0 silk or nylon is placed laterally to approximate the gray line (mucocutaneous junction) of the upper and lower lids. Tarsorrhaphy sutures will remain effective longer if they are placed through bolsters made of rubber (Robinson) catheters.

For longer-lasting protection, the lid adhesion tarsorrhaphy is preferred. The lid margin (gray line) of each lid is denuded 4 to 6 mm from the lateral canthus, and a similar suture technique is used to approximate the denuded mucocutaneous junctions of upper and lower lids (Fig. 172-3). Like the temporary lateral tarsorrhaphy, this procedure can be reversed if function returns. The cosmetic deformity of tarsorrhaphy and the availability of improved, alternative techniques to rehabilitate the eyelids have reduced the use of tarsorrhaphies.

Wedge Resection and Canthoplasty for Paralytic Ectropion

Wedge resection of all layers of the lower lid is a simple and expeditious procedure, but it can result in notching of the eyelid margin. A more effective option for lower lid laxity is the lateral canthoplasty, which is more reliable, with a less noticeable defect. Several techniques have been described for lid shortening and resuspension. They share the goal of

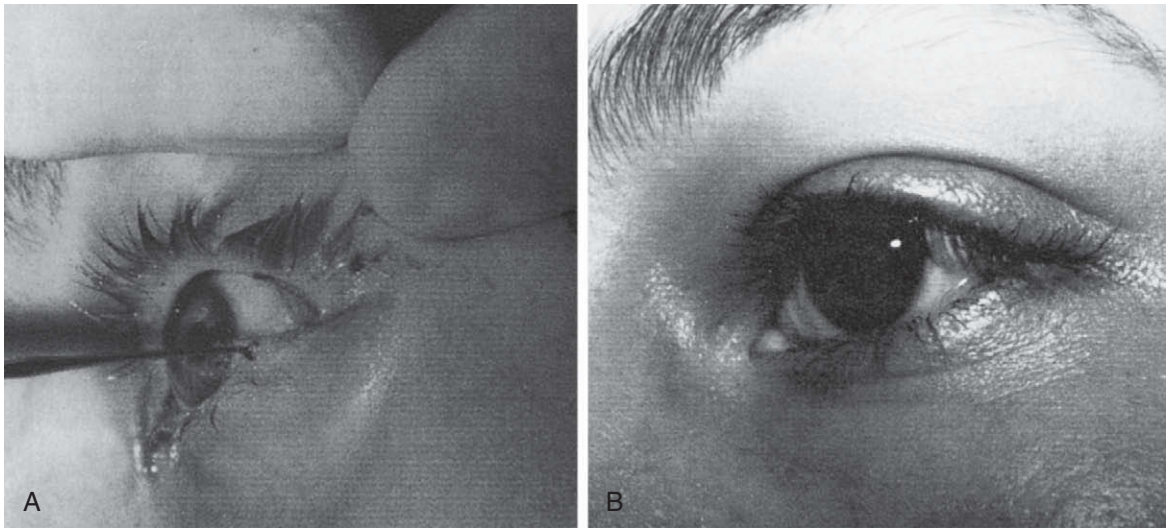

Figure 172-3. **A,** Tiny single skin hook being used to evert the lower lid for denuding of "gray line" (mucocutaneous junction). Note that a gray line of upper lid has been denuded. **B,** Healed tarsorrhaphy at 4 months. Increased eye closure may be achieved by extending the denudation and sutures medially.

eliminating laxity of the lateral canthal tendon by shortening or resuspending (or both) the tendon posteriorly behind and above Whitnall's tubercle.

The modified Bick procedure consists of lateral canthotomy and inferior cantholysis, followed by conservative resection of the lateral canthal tendon and fixation to the medial aspect of the lateral orbital wall above and posterior to Whitnall's tubercle.

The tarsal strip procedure described by Anderson and Gordy[18] modifies the previously described technique by denuding the conjunctiva over the lateral tendon and separating the posterior lamella and the tendon from the anterior lamella. The isolated tarsal strip is then suspended to the lateral orbital rim. In cases of severe ectropion, the lower lid punctum may be everted and displaced laterally after lateral canthoplasty. In these instances, a medial canthoplasty is used to restore the physiologic relationship of the punctum to the globe.[19,20] The lower lid also may be augmented with auricular cartilage to address inadequate support of the medial tarsal plate in cases not amenable to lateral tendon suspension alone.[21]

Procedures to Treat Paralysis of the Upper Lid (Lagophthalmos)

Weights, Springs, and Slings for Lagophthalmos

Gold weight insertion is extremely effective and very popular because of its reliability, minimal cosmetic deformity, and relative ease of insertion. The implant weight used is determined preoperatively by taping a weight to the upper eyelid and assessing eyelid closure. The smallest weight that allows comfortable eyelid closure and does not cause fatigue of the levator muscle is selected.

Under local anesthesia, an incision is made extending equally between the medial and middle thirds of the supratarsal crease, and the skin is elevated to the superior border of the tarsus. A pocket is formed immediately superficial to the tarsus to accommodate the dimensions of the weight. The weight is placed so that its inferior border is parallel to and just above the eyelash line. It is important to create a pocket directly on the tarsal plate, with care taken to preserve a thin cuff of tissue at the lid margin to prevent inferior extrusion of the implant. The implant is secured with clear nylon sutures superior and inferior to the tarsal plate, the orbicularis-levator complex is reapproximated, and the skin is closed.[16]

Gold weights have some disadvantages. A very low incidence of extrusion has been documented with their use even when they are inserted properly. In addition, weights depend on gravity and therefore do not effectively protect the cornea when the patient is supine, so a nighttime ointment is often required. If the weight is placed too far superior, it can result in paradoxical opening of the eye when the patient is in the supine position. Finally, the gold weight can occasionally be noticed by the casual observer as a bump in the eyelid.

Palpebral springs and silicone (Silastic) slings as described by Morel-Fatio and Lalardrie[22] and Arion,[23] respectively, also have been used for lagopththalmos. Silastic slings are used less frequently and are complicated by lateral ectropion.[24] Both types of implants share the disadvantage of extrusion, and they are more difficult to place than eyelid weights. Currently, titanium chain link implants are being used with greater frequency and with excellent results. These implants may be camouflaged to obtain a better cosmetic result, because they conform to the shape of the eyelid. Additionally, the titanium implants have been shown to result in less corneal astigmatism or cornea-altering effect on the globe itself than that typical with gold weights.[25]

Facial Nerve Grafting

Use of cable or interposition nerve grafts frequently is the desired approach to facial muscle reinnervation. The most common setting for this procedure is likely to be in combination with radical parotidectomy and facial nerve sacrifice. The clinical uses of interposition grafts are as follows: (1) radical parotidectomy with nerve sacrifice; (2) temporal bone resection; (3) traumatic avulsions; (4) cerebellopontine angle tumor resection; and (5) any other clinical situation in which viable proximal nerve can be sutured and distal elements of facial nerve can be identified. Tension-free repair is a critical element of successful nerve anastomosis. When tension-free apposition cannot be achieved using existing nerve ends, cable grafts are used.

Facial nerve grafting for acute causes such as parotid malignancy requires the surgeon to customarily identify the distal facial nerve trunk divisions or branches for the distal anastomosis. Nerve restitution should be performed at this time unless extenuating circumstances (e.g., anesthetic complications, intraoperative emergencies) rule out immediate grafting.[26] If grafting is not undertaken at the time of nerve sacrifice, it should be completed within 72 hours thereafter, so that the facial nerve stimulator may be used to identify the distal branches. Conversely, the nerve ends can be tagged for identification at a later time. When grafting is not done, the distal branch becomes nonstimulatable and thus much more difficult to locate and identify.

Surgical Planning

In planning the surgical procedure, the proximal site of nerve transection frequently is found to be in the intraparotid portion proximal to the pes anserinus. This location may present technical difficulties

because the proximal stump may not be adequate for technical ease in suturing. In other instances, the nerve may be transected at the stylomastoid foramen. If it is seen to be transected at the stylomastoid foramen, a mastoidectomy should be performed. Distal to the mastoid portion, the nerve's sheath merges with periosteum of the stylomastoid foramen and temporal bone, making this portion difficult to dissect free for suture. This difficult region exists roughly from 1 cm above to 1 cm below the stylomastoid foramen. Use of the mastoid portion of the facial nerve may require use of the longer sural or medial antebrachial cutaneous nerve, rather than the greater auricular nerve, for a cable graft.

Distally, several situations may be encountered that require some ingenuity in effecting reanimation. When the distal anastomotic site is at or proximal to the pes anserinus, a simple nerve-to-nerve suture will suffice. More frequently, however, after resection for parotid malignancy, several branches or divisions may require anastomosis. In such cases, priority must be given to the zygomatic and buccal branches, sometimes to the exclusion of other, less important facial nerve branches. Frequently, a two-branch graft can be prepared from the greater auricular nerve or the sural nerve. This situation favors suturing of one branch of the nerve graft to the buccal branch and the other graft branch to the zygomatic branch or superior division. This technique will direct innervation to the important orbicularis oculi muscle and the muscles of the buccal-smile complex (Fig. 172-4).

Choosing a Donor Nerve

Four of the nerves most commonly used are the greater auricular nerve, the sural nerve, cervical plexus, and the medial antebrachial cutaneous nerve. Each has distinctive advantages and limitations; the reconstructive surgeon should be familiar with each.

When harvesting the greater auricular nerve, tumor considerations mandate that the ipsilateral nerve not be used. Consequently, the opposite neck should be prepped and draped for harvesting the contralateral nerve in parotid malignancy cases. The nerve is easily identified, arising from the posterior surface of the sternocleidomastoid muscle at Erb's point and traveling obliquely along the sternocleidomastoid muscle toward the ear. The surgical landmarks are well defined: a line drawn from the mastoid tip to the angle of the mandible is then bisected by a perpendicular line that crosses the sternocleidomastoid muscle from inferoposterior to anterosuperior, passing toward the parotid gland. A small horizontal incision in an upper neck skin crease is made along the path of the nerve. The nerve is identified in the subcutaneous tissues and followed superiorly to the parotid gland dissecting each of the three branches, and inferiorly to the posterior border of the sternocleidomastoid muscle. The greater auricular nerve has several advantages: its size and fascicular pattern are similar to the facial nerve, it is easily harvested in familiar anatomy, and it has a favorable distal branching pattern for facial nerve grafting. Unfortunately, the nerve is limited to a maximum of 10 cm for grafting.

In patients who have undergone neck dissection or parotidectomy and in whom the greater auricular nerve is not a viable grafting option, the cervical plexus is the next ideal donor nerve. The cervical plexus can be harvested in the similar fashion to the greater auricular nerve, but requires a longer neck incision. The nerve plexus can be located just posterior and deep to the sternocleidomastoid muscle.

The sural nerve is also commonly used for facial nerve grafting. In contrast to the greater auricular nerve, the sural nerve is the longest donor nerve available, with up to 70 cm of graft available when all branches are dissected into the popliteal fossa. The donor site is located distant from the surgical resection, allowing a second team to simultaneously harvest nerve tissue. Donor site morbidity is low. However, caution should be exercised when working with diabetics or patients with peripheral vascular disease as ischemic pressure necrosis could result in the area of sensory deficit along the lateral aspect of the foot. The sural nerve is of larger diameter than the greater auricular nerve or the facial nerve, and it has more prominent connective tissue than the greater auricular nerve or medial antebrachial cutaneous nerve.

The sural nerve is formed by the junction of the medial sural cutaneous nerve and the peroneal communicating branch of the lateral sural cutaneous nerve between the two heads of the gastrocnemius muscle. The nerve lies immediately deep to and behind the lesser saphenous vein with multiple nerve branches arising near the lateral malleolus. A pneumatic tourniquet should be applied to the thigh and a transverse incision made immediately behind the lateral malleolus. "Stair-step" horizontal incisions along the course of the nerve provide appropriate exposure during the harvesting procedure. The nerve should be harvested immediately before grafting and placed in physiologic solution after débriding away any small pieces of fat or other soft tissue that might interfere with graft revascularization. At all times care is taken to avoid stretching the nerve.

The medial antebrachial cutaneous nerve has been described in the orthopedic literature for peripheral nerve repairs and is used in situ with forearm microvascular flaps for sensory innervation in head and neck cancer reconstruction. This nerve has several properties that warrant consideration for use in facial nerve reconstruction[27]: It has a consistent anatomy, traveling in the bicipital groove immediately adjacent to the basilic vein. Nerve diameter and branching pattern are similar to those of the facial nerve, and donor site morbidity is minimal with nerve harvest. Cheney[27] has described the relevant anatomy in detail.

All of the aforementioned donor nerves are sensory nerves used to lead motor nerve regeneration. This is important as harvesting a motor nerve for grafting material would certainly incur some degree of morbidity to the donor area or muscle. Although there may be theoretic difference between using a sensory nerve versus a motor nerve, further investigation is required to determine if this is of any biologic implication.

Surgical Technique

For the surgical technique of neurorrhaphy, interrupted sutures using 9-0 or 10-0 monofilament nylon are preferred. A straight and a curved pair of jeweler's forceps as well as a Castroviejo needle holder are satisfactory instruments for performing the anastomosis. Both ends of the nerve graft and the proximal and distal stumps should be transected cleanly with a fresh sterile blade.[13] For nerve trunk anastomosis, four simple epineural sutures will usually coapt the nerve ends accurately. However, obvious discrepancies in size or other epineural gaps should be closed with additional sutures. The needle should pass through epineurium only to avoid injury to the fascicular neural contents. The nerve graft should lie in the healthiest possible bed of supporting tissue, with approximately 8 to 10 mm of extra length for each anastomosis. Thus, the graft should lie in a somewhat "lazy S" configuration (see Fig. 172-4), which appears to minimize tension during healing. Suction drainage systems should be placed away from any portions of the nerve graft.

When one division is excised or injured and other portions of the nerve remain intact, it may be desirable to graft from a fascicle within the pes anserinus to a distal branch. To accomplish this, fascicular dissection is performed in parallel and along the plane of the nerve fascicles with curved jewler's forceps into the pes anserinus (Fig. 172-5). The distal buccal branch often has several small filaments, so it may be necessary to select the larger of these for distal anastomosis.

Approximation of the nerve ends using an acrylic glue has been described (Histacryl or cyano-butyl-acrylate)[28] with subsequent investigators revealing that neural anastomosis with tissue adhesive yields results similar to nerve suture. This technique is most helpful in the confined surgical considerations of the temporal bone rather than in distal facial anastomosis.[29] Others have described using biodegradable nerve tubules.

Following temporal bone resection, the nerve may be routed from the tympanic or the labyrinthine portions directly to the face through a bony window near the posterior root of the zygomatic arch. This will shorten the necessary length of the nerve graft. However, when using this technique it is important to ensure the nerve graft's protection from trauma at the temporomandibular joint if the joint is preserved. Conley and Baker[30,31] have reported excellent results using similar techniques.

Millesi[32] introduced interfascicular nerve repair, reasoning that the exact microsurgical approximation of nerve fascicles or fascicle groups may minimize synkinesis or mass movement. It is well known

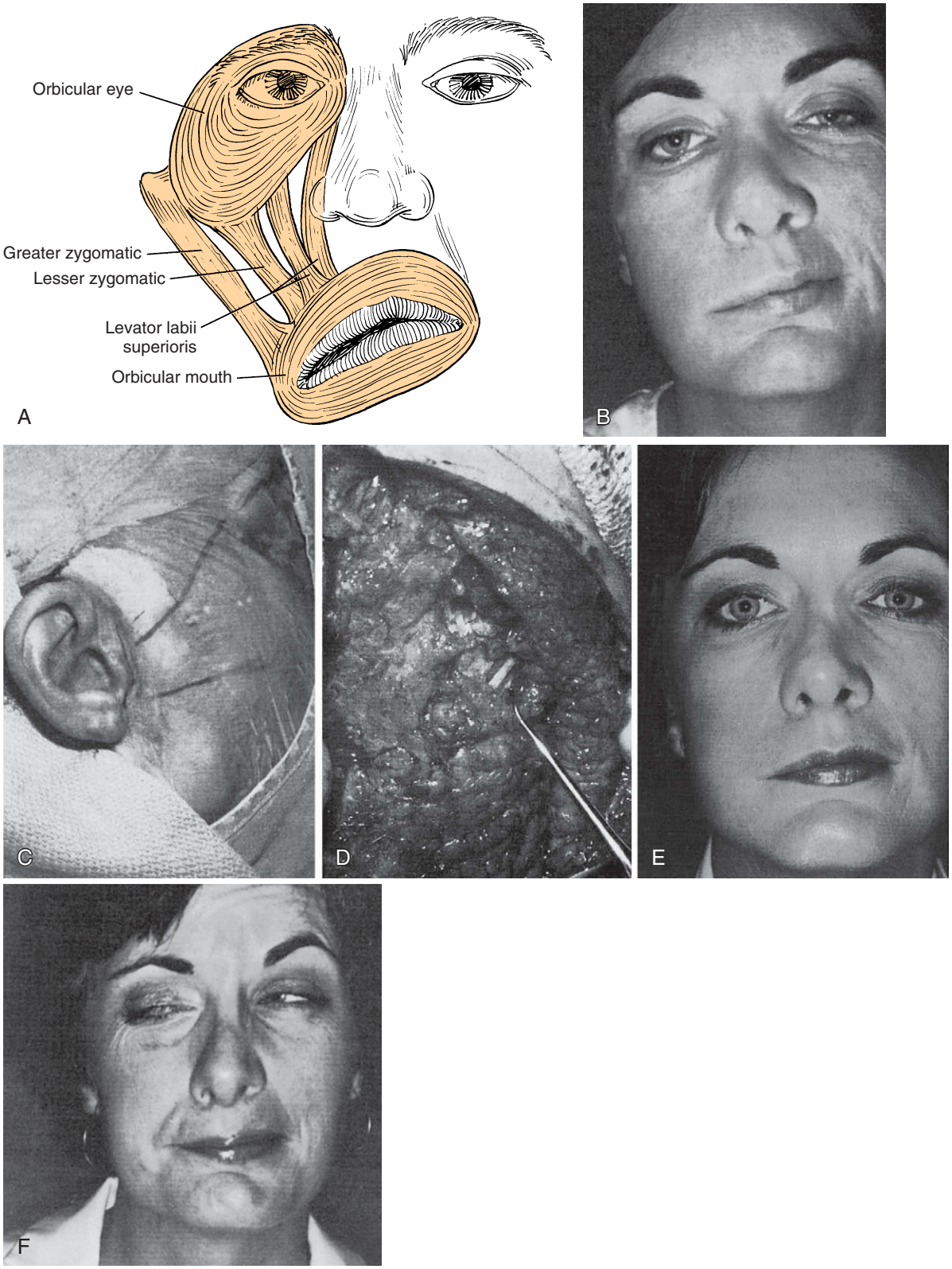

Figure 172-4. Facial muscles. **A,** The most important muscles for reanimation: The levator labii superioris, along with the lesser zygomatic muscle, probably is the most significant muscle for elevation of the upper lip. The greater zygomatic muscle also is critical as the strongest elevator of the oral commissura. **B** to **F,** Example of a delayed nerve graft in a patient in whom a parotid malignancy was removed without immediate reconstruction (because of intraoperative anesthesia considerations). **B,** The patient was referred for nerve grafting after 9 months elapsed. Note elongation of the buccal-smile complex of muscles (greater and lesser zygomatics, levator labii superioris) and paralysis of orbicular eye muscle. **C,** Preoperative surface markings for nerve branches. Nerve stimulator cannot be used to locate distal branches after 9-month time lapse. Markings are for the superior division and buccal branch, based on landmarks described in Figure 172-1 and the previous operative report. **D,** Superior division is found; it is ready for transection and anastomosis to sural graft (from midmastoid nerve segment). **E,** Result at 1 year after operation—typical for a delayed nerve graft. Orbicular eye and buccal branch muscle function is improved, but the muscles are not normally or completely reinnervated. **F,** Voluntary motion in both zygomatic and buccal branches, with synkinesia. This result also is typical for most nerve grafts in that the temporal branch (to occipitofrontal muscle) shows no reinnervation. Note the hairstyle designed to camouflage occipitofrontal muscle paralysis.

that this type of repair is preferred in nerve injuries in the extremities; however, such repairs have not been universally accepted for use in the facial nerve. Several reasons underlie this limited acceptance. The tympanic and, in many cases, the mastoid portions of the nerve have only one or two fascicles, and the intraneural topography is questionable. Few, if any, sensory fibers are present in the extratemporal portion of the facial nerve, so performing sensory-to-sensory fascicular repair is not of value.

Along with May and Miehlke, we have reported (independently) that discrete, spatially oriented fascicles are present in the nerve near the stylomastoid foramen.[33-35] Other authors, notably Sir Sidney Sunderland[36] and Tomander and colleagues,[37] have reported conflicting data demonstrating that various portions of the face are represented in a random fashion in the proximal nerve. At present, it probably is best to perform fascicular repair when the injury obviously lends itself to the technique (e.g., clean lacerations through the pes anserinus and branch nerve grafts that require fascicular dissection in the pes). Basic research has yet to reveal the exact neural topography of the more proximal portions of the nerve.

Cross-Face Nerve Grafting

Overview

The creative and physiologic method of cross-face nerve grafting provides the possibility for facial nerve control of previously paralyzed facial muscles. It is the only procedure with the theoretic capability for specific divisional control of facial muscle groups (e.g., the buccal branch controlling the buccal branch distribution, the zygomatic branch innervating the orbicularis oculi). Originally described by Scaramella[10] and Smith[11] in independent reports in 1971, the technique has not proved to be as advantageous as was first thought. Anderl[38] subsequently described his own results as good in 9 of 23 patients, whereas Samii[39] reported that only 1 of 10 patients had good movement as a result of this technique. A more recent update by Ferreira[40] indicates that those patients operated on within the first 6 months of the paralysis did better than those operated on at a later date. In some of these patients, however, partial spontaneous reinnervation may have occurred, because they appeared to have had lesions without total palsy, and the traditional waiting period of 1 year was not allowed to elapse.

Surgical Technique

The operative technique of cross-face grafting begins with transection of several fascicles, usually of the buccal branch, on the nonparalyzed side through a nasolabial fold incision. One to three sural nerve grafts are approximated to these normal contralateral branches. The nerve grafts are then passed through subcutaneous tunnels, usually in the upper lip. Cross-face grafts for the eye region often are passed above the eyebrow.

As described by most authors, this first surgical stage is performed during the first 6 months of paralysis. Surgery, of course, is not advised unless the paralysis is of known permanence. Tinel's sign often may be elicited after several months of neural ingrowth, because sensory fibers accompany the motor fibers through the cross-face graft. Anastomosis with the paralyzed facial nerve branches is performed by most surgeons during a second stage, 6 to 12 months after the first. At this time, the cross-face graft is explored and sutured to the appropriate branches of the paralyzed side. The approach is through a parotidectomy-rhytidectomy incision and usually is performed within the parotid portion of the paralyzed side.

The cross-face technique suffers from a lack of sufficient axon population and neural excitatory vitality. It is of marginal value when

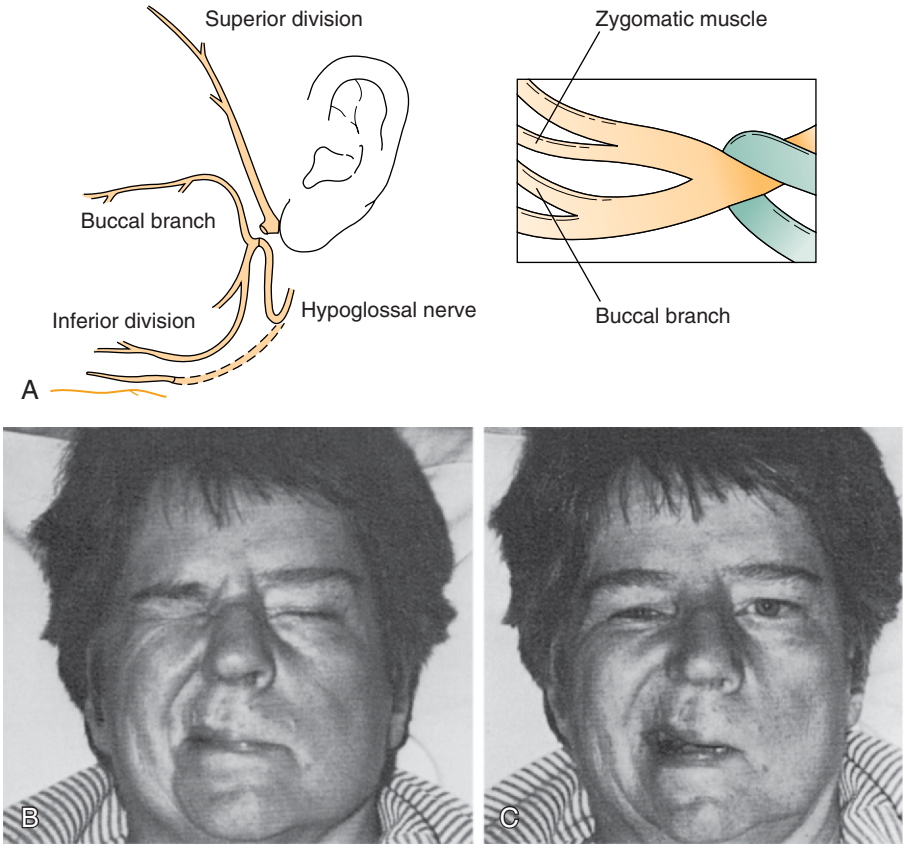

Figure 172-5. **A,** Hypoglossal-facial anastomosis showing selective reinnervation of the inferior division, leaving the superior division innervation intact. *Inset* shows fascicular dissection before anastomosis (see **D** and **E**). **B** and **C,** Preoperative photographs of patient with long-standing segmental paralysis of inferior division of facial nerve. Zygomatic branch to orbicular eye muscle shows preservation of innervation.

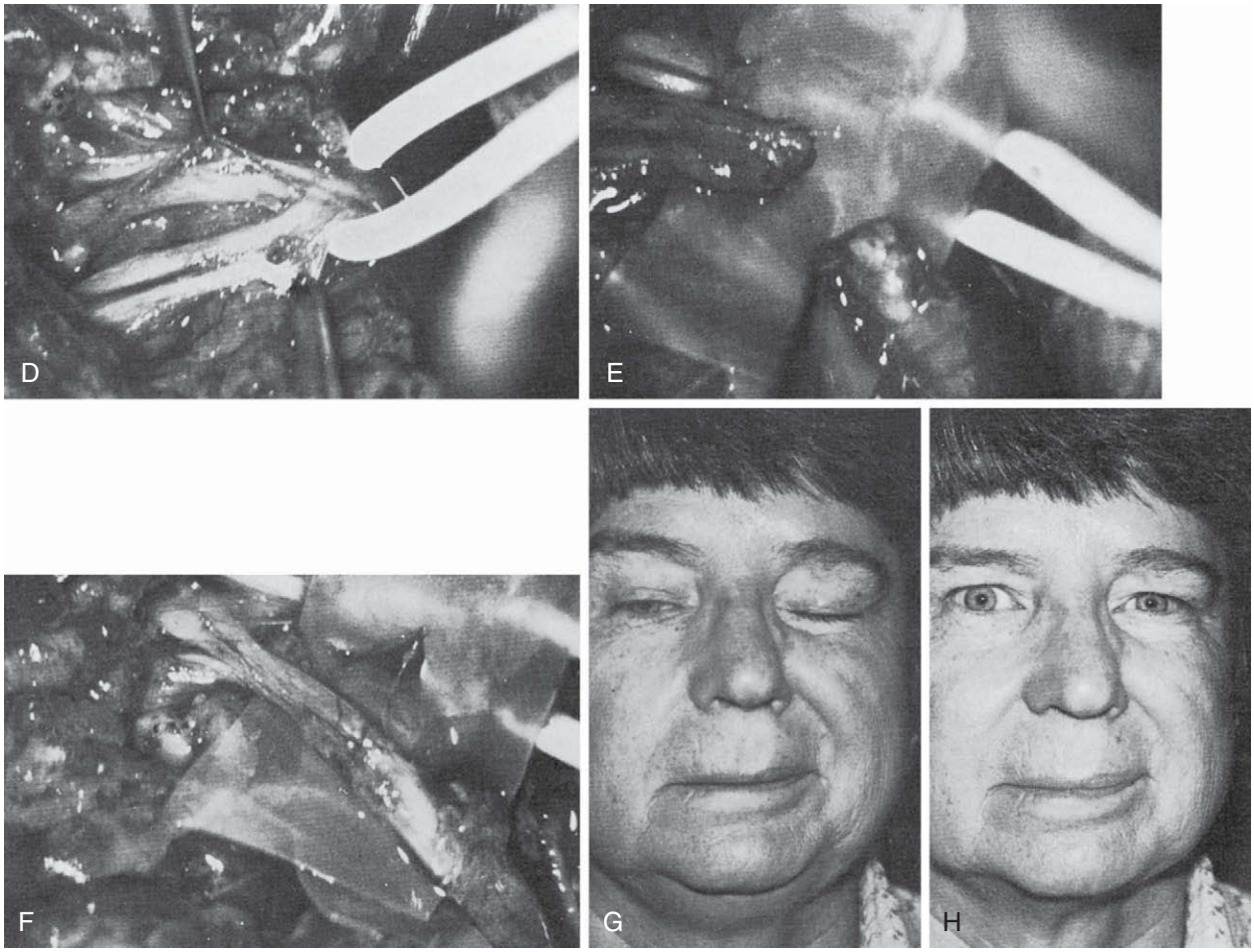

Figure 172-5, cont'd. **D to F,** Intraoperative photographs. **D,** Perineural dissection of pes anserinus reveals fascicles destined for zygomatic and buccal branches (see **A**). **E,** Buccal branch and inferior division transected. Neurosurgical loop protects intact superior division under background piece of polymeric silicone (Silastic). Hypoglossal nerve (at *lower right*) is ready for anastomosis. **F**, Completed anastomosis of hypoglossal nerve to the buccal branch and inferior division of the facial nerve. The superior division is intact and in continuity with proximal facial nerve. **G** and **H,** Strong reinnervation to entire face, 1 year after operation. **G,** Patient uses hypoglossal innervation to buccal branch muscles to enhance eye closure. **H,** Upward movement of oral commissura mediated by hypoglossal nerve, without associated or synkinetic eye closure.

used alone, but when combined with microvascular transfer of muscle (see below), it can provide suitable innervation. Conley[41] and Conley and Baker[42] have discussed the shortcomings and unproven status of cross-face grafting. Cross-face grafting currently is used only in conjunction with free muscle transfers. Reinnervation of paralyzed facial muscles has not been proved to be sufficient to justify use of this procedure without muscle transfer.

Nerve Transposition

Reinnervation by connecting an intact proximal facial nerve to the distal ipsilateral facial nerve generally is the preferred method for facial paralysis rehabilitation. Only when a proximal facial nerve stump is not viable or available should attention be turned to other strategies, such as muscle or nerve transfer.

Hypoglossal Nerve Transfer

Of the various nerves available for anastomosis with the facial nerve, the hypoglossal nerve is preferred, because an anatomic and functional relationship exists between the facial and the hypoglossal nerves. They both arise from a similar collection of neurons in the brainstem, and they also share similar reflex responses to trigeminal nerve stimulation.[9] In addition, the hypoglossal nerve is in close anatomic proximity and is readily available during other operations on the facial nerve. Hypoglossal nerve transection results in less donor disability than that typical with sacrifice of the spinal accessory, phrenic, or other regional nerves that have been used for facial reanimation. The most common criticism of hypoglossal nerve transfer is that it results in a lack of voluntary emotional control. Although this is true, ipsilateral facial nerve anastomosis often is associated with a similar drawback: Mass movements and spasms preclude any voluntary control of eye closure, smiling, or other emotional movements. In our practice, we have used hypoglossal nerve transfer for reanimation of the upper or lower division selectively by performing fascicular dissection in the pes anserinus to identify the specific fascicles that required reinnervation (see Fig. 172-5).

May and coworkers[43] attempted to decrease morbidity from tongue atrophy by performing partial transection of the hypoglossal nerve with use of a jump graft from the partially transected nerve to the distal facial nerve. Decreased effectiveness of partial transection with jump graft has been reported by some investigators.[44]

Recently, "pure" end-to-side anastomosis of the facial nerve or a jump graft into the donor hypoglossal nerve has been rediscovered[45] and reported in a small series of patients.[46] The study investigators performed anastomosis of facial nerve either mobilized from the mastoid or bridged by interposition graft into the intact hypoglossal nerve, without removal of epineurium or perineurium. This technique relies on the presumed axon sprouting across intact epineurium of the hypoglossal nerve. Some evidence indicates lateral axonal growth after

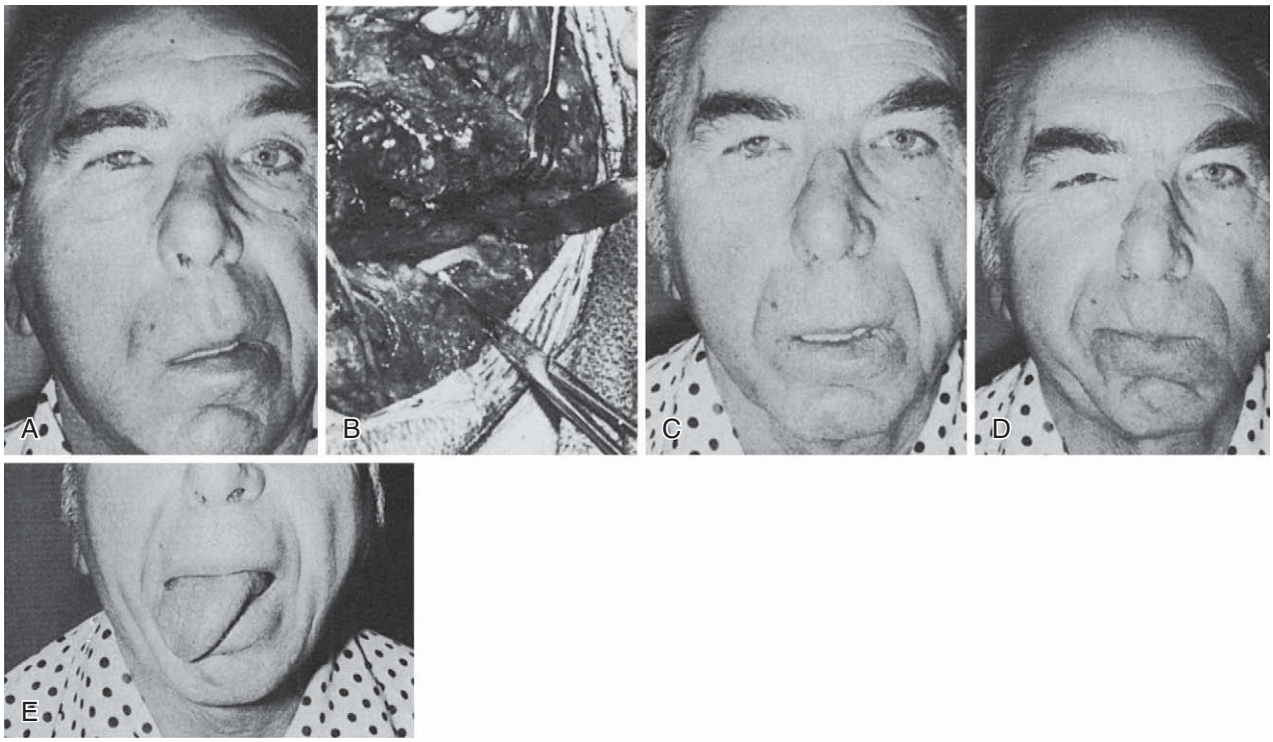

Figure 172-6. **A,** Patient with facial paralysis after acoustic neuroma excision. Lateral tarsorrhaphy is in place. **B,** Exposure of hypoglossal nerve. Note exit of ansa cervicalis branch at *lower right*. This may be transected and sutured to the distal hypoglossal, although preservation of tongue innervation usually is weak with this technique. **C,** Repose. Note elevated commissura and reconstitution of nasolabial fold. **D,** Movement instigated by pushing tongue tip against lingual aspect of mandible in canine region. This maneuver usually results in strongest facial movement after anastomosis of cranial nerves XII and VII. **E,** Typical lingual deviation after the procedure.

end-to-side nerve anastomosis occurs. Rat studies demonstrate axonal penetration of endoneurium, perineurium, and epineurium.[47-49] Whether this technique will be applicable in humans who have decreased nerve regenerative capacity and much thicker perineurium and epineurium than in the rat remains to be seen. It may be more effective to remove an epineurial window and perform the anastomosis without disruption of nerve fibers yet still induce enough axonal regrowth to provide tone and function. Further animal and human studies will be necessary to determine the usefulness and role of end-to-side neurorrhaphy for facial rehabilitation.

Surgical Technique

A modified facelift or parotidectomy incision with an extension made inferiorly toward the hyoid bone usually is used in hypoglossal nerve transfer. The parotid gland is dissected forward from the sternocleidomastoid muscle, and the facial nerve is identified in its trunk–pes anserinus region. The posterior belly of the digastric muscle is then identified, and the hypoglossal nerve is dissected free immediately medial to the tendon of the muscle. The ansa hypoglossi should be identified and dissected free so that, if desired, it may be sutured to the distal hypoglossal stump for reinnervation of the strap musculature. The hypoglossal nerve should be transected as far distally as possible to provide extra length for the anastomosis. After the nerve ends are prepared carefully under high power using a blade, four to eight epineural sutures of 10-0 monofilament nylon complete the anastomosis.

The procedure for the hypoglossal-facial nerve jump graft is similar to that for pure hypoglossal-facial nerve transfer. A greater auricular nerve graft is harvested for use as a jump graft. The facial nerve is transected on the main trunk. The hypoglossal nerve is incised in beveled fashion to expose approximately 30% of the nerve fibers. The jump graft is secured to the proximal edge of the hypoglossal nerve and to the distal end of the transected facial nerve. If the facial nerve is mobilized proximally from the mastoid, it can be directly anastomosed to the partially transected hypoglossal nerve, avoiding placement of a jump graft.

Results

In the largest series to date, involving 137 patients, approximately 95% regained satisfactory tone in repose and regained some mass facial movement.[50] Of these patients, 15% demonstrated hypertonia and excessive movement in the middle third of the face; however, none of these patients requested that the transferred nerve be reoperated. This excessive movement was found to decrease gradually over 10 to 20 years. However, Dressler and Schonle[51] and Borodic and coworkers[52] have had success treating facial hyperkinesia with selective injection of botulinum toxin. Seventy-eight percent of the patients had moderate to severe tongue atrophy, whereas 22% showed minimal atrophy; this wide variability in response of the tongue to hypoglossal nerve transection has been confirmed in other series[53] (Fig. 172-6). Use of the interpositional jump graft with partial hypoglossal nerve preservation preserved tongue function in a majority of patients and provided satisfactory function. In a series of 20 patients, good facial tone and symmetry were observed at follow-up evaluation in all patients, and 13 had "excellent" restoration of facial movement, with development of 12th nerve deficits noted in only 3 patients.[43]

Other Nerve Transfers

The spinal accessory nerve was used before the hypoglossal nerve in nerve transposition techniques. Drobnik performed the first anastomosis of cranial nerves XI and VII in 1879.[9] The phrenic nerve has been similarly used, but this technique causes paralysis of the diaphragm and induces undesirable involuntary inspiratory movements in the facial muscles.[54] The technique is now obsolete.

The neuromuscular pedicle technique described by Tucker transfers a branch of the ansa hypoglossi nerve and a small muscle bloc directly to paralyzed facial muscles. According to Tucker,[55] this proce-

dure is valuable only for the perioral, depressor anguli oris, and zygomaticus muscles. The procedure is described as transferring innervated motor endplates to the denervated facial muscles without the usual delay period seen with free nerve grafts and nerve transfers. The technique allows limited reanimated strength because of the small number of axons present in the donor nerve. In addition, sound electrophysiologic confirmation that the technique produces reinnervation is somewhat lacking, despite a report by Anonsen and colleagues on this topic.[56] Until physiologic data are presented and confirmation by other surgeons is obtained, the procedure has potential but remains unproved.

Neurotropic Factors

With several growth factors known to promote neuronal survival, application and delivery of the these factors constitute an attractive therapy for nerve injury and surgical repair. The trophic effects of nerve growth factor (NGF), glial cell–derived neurotropic factor (GDNF), brain-derived neurotropic factor (BDNF), and insulin growth factors I and II all are under current investigation.[57] In ongoing rat experiments, embryonic stem cells are used to provide the trophic support factors to the host motor neurons in restitution of the neuromuscular junction.[58] These preliminary findings provide a model for motor unit restoration and a potential therapeutic intervention in the treatment of paralysis. However, these studies are limited to the rat model and require further basic and clinical investigation.

Muscle Transfers

Masseter Transfer

Although masseter and temporalis muscle transfer techniques are effective, generally they should be used only if ipsilateral cable nerve grafting is not possible. For most patients with viable facial muscle endplates, a nerve transfer such as hypoglossal facial anastomosis also is preferable to muscle transposition. However, when the proximal facial nerve and the hypoglossal nerve are unavailable, or when facial muscles are surgically absent or atrophied, new contractile muscle must be delivered into the face. A large group of patients who fit into this category are those whose complete paralysis has lasted 2 years or more. These patients usually are characterized by severe denervation atrophy as documented by EMG. In these situations, muscle transfer is the preferred technique of reanimation.

Since the masseter was first used for facial reanimation in 1908, many modifications have been described.[59] Many authors, notably Conley and Baker, prefer the masseter muscle for rehabilitation of the lower face and midface.[30]

The masseter transfer procedure generally is performed for rehabilitation of the sagging paralyzed oral commissure and the buccal-smile complex of muscles. The masseter's upper origin from the zygomatic arch allows a predominantly posterosuperior pull on the lower midface. Transfer of the muscle can be accomplished externally through a rhytidectomy-parotidectomy incision, or intraorally using a mucosal incision in the gingivobuccal sulcus lateral to the ascending ramus of the mandible (Fig. 172-7). The masseter's blood supply is medial and deep, and its nerve supply passes through the sigmoid notch between the condylar and the coronoid processes of the mandible to reach the upper deep surface of the muscle. The nerve supply then ramifies and courses distally and inferiorly, terminating near the periosteal attachments on the lateral aspect of the mandibular angle and body. In general, the external approach is preferred, insofar as the intraoral approach is associated with somewhat limited access, poorer muscle mobilization, and less vascular control.

A generous parotidectomy incision is made and extended inferiorly below the mastoid tip. The parotid gland and masseteric fascia are exposed. The posterior border of the muscle is freed from the mandible's ascending ramus and at the lower border of the mandible. The nerve supply courses along the deep surface approximately midway between the anterior and the posterior borders of the muscle (see Fig. 172-7). It is advisable to preserve the deep fascial layer in dissecting the muscle free from the mandible. Mobilization of the periosteal attachments along the inferior border will provide secure tissue for anchoring sutures and will provide greater length of the transposed muscle.

Dissection is then carried forward to the nasolabial fold in the subcutaneous plane using large Metzenbaum or rhytidectomy scissors. The external incisions are made at or just medial to the nasolabial fold, the lateral oral commissure, and the vermilion cutaneous junction of the lower lip. Each of these incisions is connected to the cheek tunnel, allowing transfer of the masseter muscle. The muscle may be divided into three slips for attachment at these sites, or the entire periosteal end of the muscle may be used to suture the remnants of the orbicularis oris muscle from the lateral upper lip to the commissure and below. These muscle slips are sutured to the dermis and the orbicularis oris muscle using 3-0 clear nylon sutures. The best results depend on gross overcorrection with hyperelevation of the oral commisure, preservation of masseteric nerve supply, secure suture stabilization of the transposed muscle, supportive tape dressing to maintain overcorrection of the oral commissure, and nasogastric feedings to minimize masseteric movement.

Results from the masseteric procedure are quite gratifying and usually yield a high degree of facial symmetry. However, the masseter's arc of rotation will not allow for rehabilitation around the orbit. For this reason, the temporalis transfer can be combined with masseter transfer, or the reanimation of the orbital region can be approached separately with such procedures as canthoplasty and gold weights.

Temporalis Transfer

Although Gillies[60] usually is given credit for introducing the temporalis procedure, Rubin[61,62] deserves much credit for refining the goals of the procedure and the operative technique in the United States. Like the masseter transfer, the temporalis transfer procedure requires an intact ipsilateral V_3 nerve. The nerve supply to the temporalis lies along the deep surface of the muscle. The blood supply comes from the deep temporal vessels from the external carotid artery. Thus, with total parotidectomy, extensive neck dissection, or infratemporal fossa dissection, the neurovascular supply may be tenuous at best. The upper origin of the temporalis muscle is fan-shaped and arises from the periosteum of the entire temporal fossa. The muscle belly converges on a short tendinous portion deep to the zygomatic arch and inserts on the coronoid process. The muscle is best exposed through an incision that passes above the ear, slightly posteriorly, and then in an anteromedial arc. This will expose the entire upper portion of the muscle (Fig. 172-8). A convenient aponeurotic dissection plane exists lateral to the temporalis fascia.

In Rubin's technique, the muscle is dissected free from the periosteum and attached to fascial strips, which are turned down inferiorly to reach the oral commissure and eyelid area. If these fascial strips are omitted, the transposed muscle's length will be insufficient to reach the lateral oral commissure. More recently, Rubin[62] refined his temporalis transfer technique by including a slip of masseter muscle that is sutured to the oral commissure and lower lip. The resulting masseteric pull improves results by providing more posterior and lateral vectors to the oral commissure.

We prefer to use the technique described by Baker and Conley,[50] who describe retaining the integrity of the upper muscle and its overlying fascia. The latter is dissected free and then turned inferiorly for suturing to the oral commissure.

A tunnel at least 1 to 1.5 inches wide must be made over the zygomatic arch to allow the muscle to turn inferiorly and eliminate an unsightly bulge. The attachment of the strip should be just medial to the nasolabial fold so that the natural crease is reproduced by the muscle pull. As with the masseteric procedure, a marked overcorrection is necessary on the operating table. A soft silicone block or a temporoparietal fascia flap may be used to fill the temporal hollow. A modification of this technique by Sherris[63] is performed by extending the transfer into the midregion of the upper and lower lips, to reduce stretching and thinning of the lips over time.

Several modifications of the temporalis transfer have been reported in attempts to avoid folding of the temporalis muscle over the zygomatic arch. Labbé and Huault[64] describe partial inferior mobilization of the temporalis muscle from the skull by elevation of the posterior and superior attachments of the muscle. The coronoid attachments of the muscle are detached, and the muscle is inferiorly mobilized toward the upper lip. The coronoid insertion of the inferiorly displaced muscle is secured to the perioral musculature.

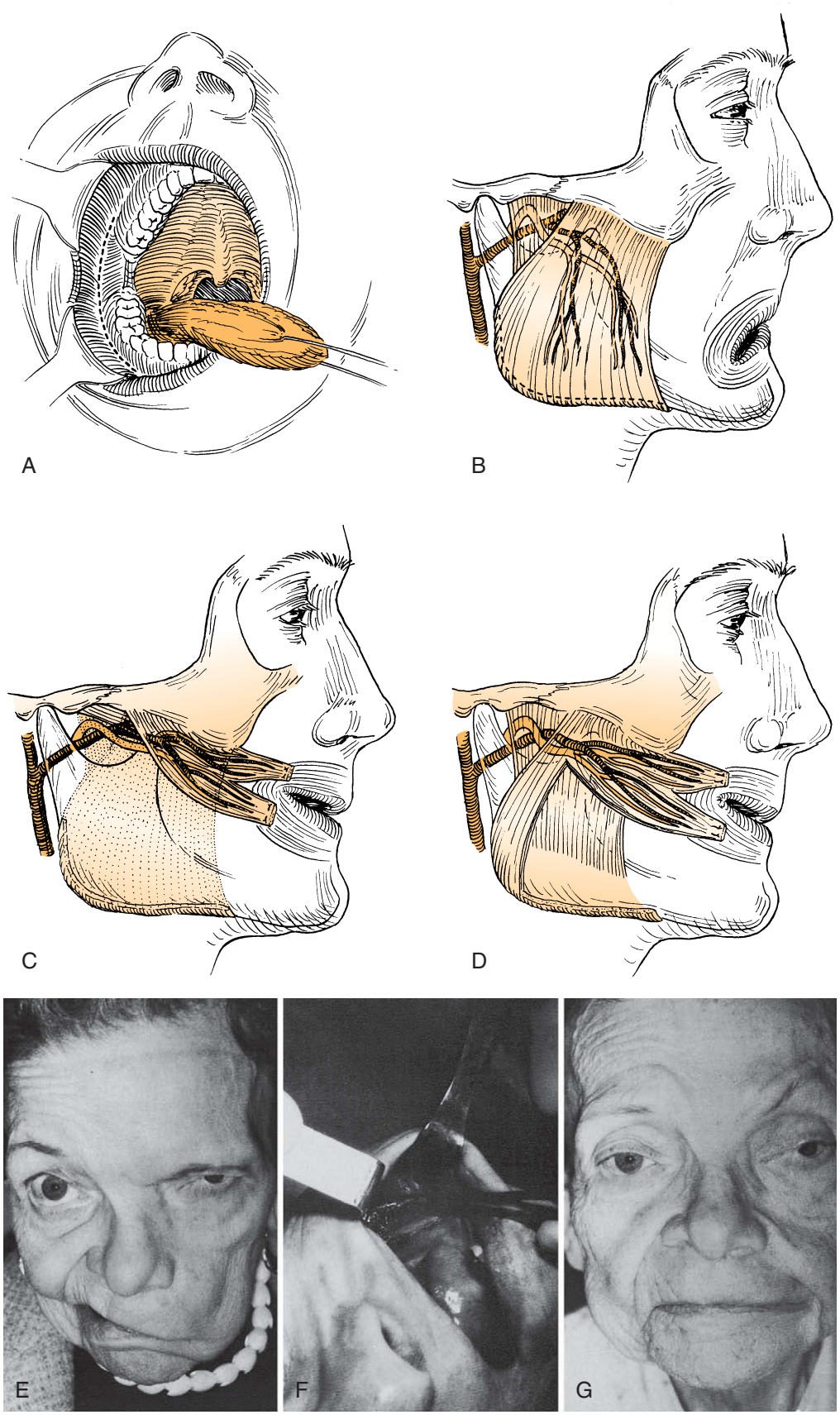

Figure 172-7. Masseter transfer procedure. **A** to **D,** Schematic depiction of key surgical principles. **A,** Intraoral approach to masseter. The procedure is more difficult when performed in this manner; an external approach is preferred. **B,** Correct incisions in muscle and periosteum. Periosteum must be incorporated in the lower portion of the muscle flap to leave the tissue secure for suturing to the lip region. **C** and **D,** Entire muscle, rather than only anterior elements, is transposed, so that the masseteric nerve supply is transferred intact with muscle belly. **E** to **G,** Use of intraoral masseter transfer for correction of complete left peripheral facial paralysis in an elderly woman. **E,** Note severe brow ptosis, medial tarsorrhaphy, and severe redundancy of cheek, paranasal, and lateral lip tissues on the left. **F,** Intraoperative photograph showing intraoral masseter transfer. Large Kelly clamp is used to grasp the inferior portion of the masseter, which will be passed through the cheek tissues to a nasolabial fold incision (see **A** through **D**). **G,** Photograph taken after browlift procedure (tarsorrhaphy has been left for eye safety). Masseter transfer has successfully raised the corner of the mouth and the nasolabial fold. The patient declined further excision of the nasolabial fold for improved cosmesis.

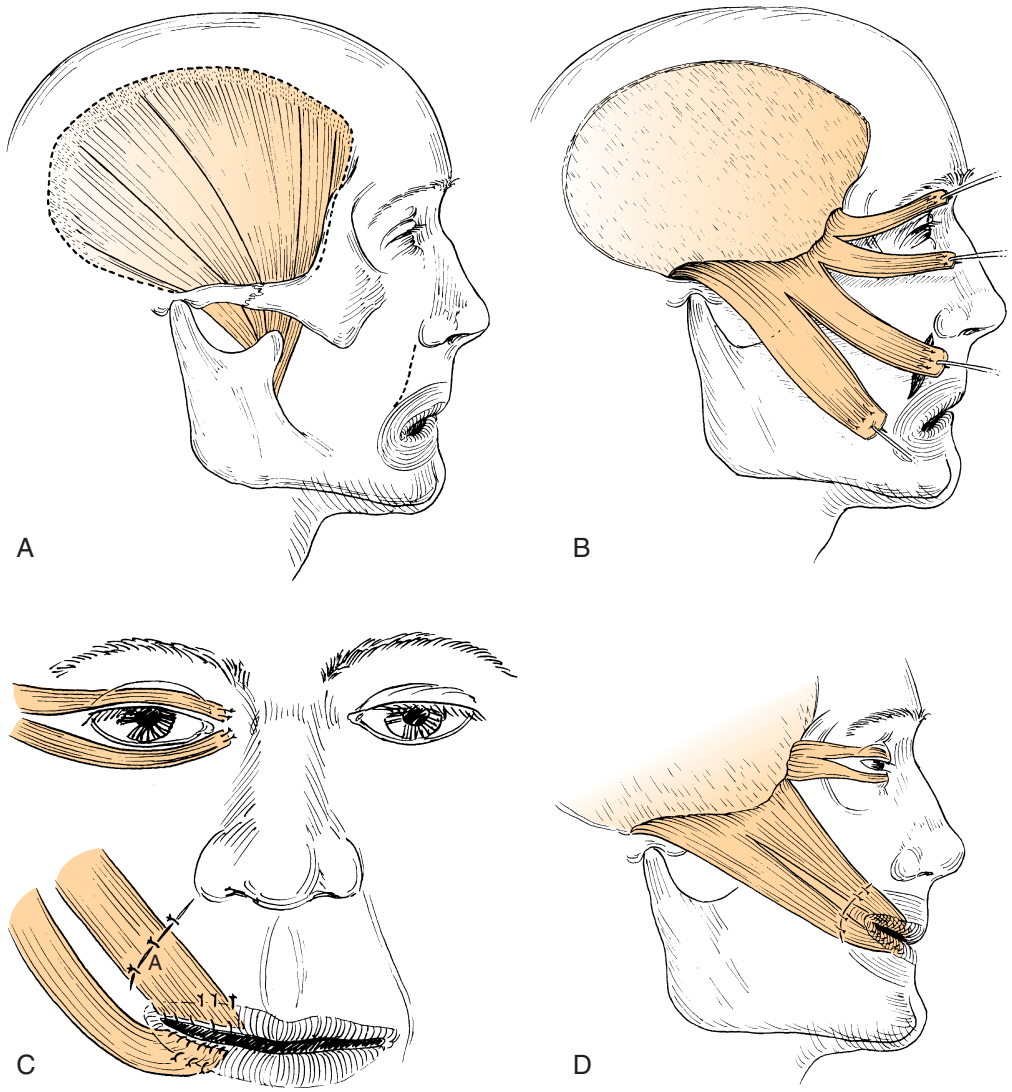

Figure 172-8. Temporalis muscle transposition. **A,** *Dotted line* illustrates the incision in the pericranium peripheral to the edge of the muscle. This results in strong periosteum to hold sutures in the transposed position. Nerve supply on deep side of muscle is not shown. **B,** Temporalis muscle divided into four slips. Note pericranium at the end of the slips sutured to the muscle to reinforce the suture site. Temporal fascia superficial to the muscle can be used in the same way. **C,** Transposed slips sutured to perioral muscles. Creativity and compulsivity are crucial during this portion of procedure. Overcorrection is mandatory. Sutures (A) must be placed in subdermis inferior to incision or in the submucosal portion of the wound deep to the orbicularis oris muscle. **D,** Completed procedure. Wide tunnel over the zygomatic arch precludes an unsightly bulge of muscle, which would otherwise be produced. Superior pull of temporalis muscle is somewhat preferred to posterolateral pull of masseter muscle (see Fig. 172-7).

Although the gold weight–canthoplasty technique often is preferred, the temporalis muscle can be used for orbital rehabilitation. The anterior third of the temporalis muscle is turned laterally into the eyelids (see Fig. 172-8). Subcutaneous tunnel dissection between the paralyzed orbicularis oculi and the eyelid skin allows passage of the fascial strips medially through both eyelids to the medial canthus, where they are sutured. As with any reconstructive procedure, adjustments and suture revisions should be checked carefully on the operating table to ensure proper eyelid contour.

With both masseter and temporalis transfer, facial muscle activation originates from the trigeminal nerve. Patients need to learn, through videotape, biofeedback, or similar methods, the proper way to contract the muscles by chewing or biting. Some younger patients may actually learn how to incorporate these movements into their own facial expressions (e.g., smiles, grimaces). However, patients should be told preoperatively that muscle transfer procedures will not allow any emotional or involuntary reanimation. When performed in the best hands, these techniques provide symmetry and tone in repose, with some learned and induced movements on attempted chewing.

Microneurovascular Muscle Transfer

Microneurovascular muscle transfer was popularized in the 1970s and has been combined with cross-face nerve grafting to restore some facial movement.[65] Because facial movements are highly complex and interrelated, enthusiasm for free muscle transfer was stimulated by the potential to use muscles that may provide isolated or independent segmental contractions, such as for superior elevation of the oral commissure. In patients with absence of facial musculature (such as those with congenital paralysis as in Möbius syndrome), microneurovascular muscle transfer seems to have strong potential.

A number of muscles and their respective nerve supply have been used for microneurovascular transfers. The most popular muscles include the gracilis, latissimus dorsi, and pectoralis minor muscle flaps.[66] Ideally, the proximal stump of the ipsilateral facial nerve is used, but this often is not possible. Traditionally, reinnervation has been

accomplished in two stages, with a preliminary cross-face nerve graft performed approximately 1 year before muscle transfer. Neural ingrowth within the grafted nerve is monitored by recording progression of Tinel's sign along the path of the graft. When reinnervation of the graft has occurred, microvascular muscle transfer is then performed. One-stage procedures using long neurovascular pedicles connected directly to the contralateral facial nerve have been described.[67-70] A recent comparison study found favorable outcomes with the one-stage reconstruction compared to the more traditional two-stage reconstruction.[70] Muscle preservation using implantable intramuscular stimulators is under investigation and may allow preservation of facial muscles while reinnervation occurs.[71] This technique shows promise in management of peripheral nerve injuries, and exploratory studies on the facial nerve have been initiated. When facial nerve input is not available, alternative nerves can be used for input, including the masseteric branch of V_3, ansa hypoglossi, or the hypoglossal nerve.[66,72]

Composite tissue allograft procedures have gained considerable interest over the last 10 years. Devauchelle[73] and Dubernard[74] and their colleagues detailed the preliminary functional improvements of the first human partial face transplant, with the return of light touch, heat and cold perception, and mouth closure. These functional milestones were obtained by 10 months postoperatively; a normal smile was observed at 18 months. As with all tissue transplantation, however, immunosuppression is an essential adjunct and not without consequence. After transplantation, the patient suffered two episodes of acute rejection, two infectious complications (type 1 herpes simplex virus infection and molluscum contagiosum), renal failure, moderate thrombotic microangiopathy, and hemolytic anemia. These preliminary findings reveal a new dimension of reconstructive surgery while also underscoring the inherent benefits of native tissues in facial reconstruction.

Significant advances in microvascular techniques and one-stage microneurovascular facial rehabilitation have greatly improved the functional outcome for appropriately selected patients. These techniques are complex, requiring expertise in both microvascular techniques and facial reconstruction. In general, patients with absent distal facial nerve fibers or intact facial musculature who are motivated to attain dynamic function are potential candidates for these procedures.

Static Procedures

Although reinnervation techniques and dynamic slings (muscular transfers) generally provide the best functional outcomes, a number of static procedures still constitute an appropriate option for selected patients. Use of static techniques is indicated in debilitated persons with poor prognosis for survival and in those for whom nerve or muscle is not available for dynamic procedures. The primary benefit of static procedures is immediate restoration of symmetry in the midface. Success depends on mastering several techniques and selective application using sound clinical judgment. Static suspension relies on elevation and positioning the soft tissues of the oral commissure or nasal ala (or both), most commonly by attaching graft materials, which are elevated and secured to the temporal-zygomatic region. Several major benefits arise from the use of static slings. First, facial symmetry at rest can be achieved immediately. Second, better control of problems associated with ptosis of the oral commissure (e.g., drooling, disarticulation with air escape, difficulty with mastication) is achieved. Finally, nasal obstruction caused by alar soft tissue collapse can be dramatically relieved by resuspension and fixation of the nasal alar complex.

Several materials have been used for static suspension. The most common have been fascia lata[75] and acellular human dermis (Alloderm).[76] In the past, expanded polytetrafluoroethylene (PTFE) (i.e., Gore-Tex) has been used more frequently.[77] The acellular dermis preparation and PTFE have the advantage of avoiding donor site morbidity, but use of foreign materials carries a small risk of infection, which is of greater concern in persons undergoing radiation therapy.

Static Facial Sling

Technique

The implant can be placed through a preauricular or temporal incision. In patients with a well-developed contralateral nasolabial fold, a nasolabial incision may be used instead. Additional incisions are made at the vermilion border of the upper and lower lips, adjacent to the commissure. A subcutaneous dissection plane is created to connect the temporal region to the oral commissure. In selected patients with nasal alar collapse and nasal obstruction from soft tissue ptosis, the dissection is extended to include the midface immediately adjacent to the nasal ala. A single strip of implant material is adequate for the procedure. This is cut to appropriate size and can be split near the end to include slips for attachment to the upper and the lower lips. Permanent sutures are placed to secure the implant to the orbicularis oris muscle and deep dermis. Resorbable sutures are placed in the deep dermis to secure the material just medial to the proposed nasolabial fold. Similar fixation is performed for a strip to the ala if desired. The sling is then suspended and secured with permanent suture to the temporalis fascia, or to the periosteum of the zygoma or zygomatic arch. If fascia lata or acellular human dermis (AHD) is used, overcorrection of the smile is achieved before fixation. Current interest has been developed in the suspension of implant materials along the nasolabial fold with suture anchoring to the deep temporal fascia.[78] In similar fashion, mimicking of the contralateral crease is achieved through suture tension along various points.

Adjunctive Procedures

A number of adjunctive procedures are available to "fine-tune" the results in persons undergoing facial rehabilitative procedures. Optimizing the care of patients with facial paralysis requires a full range of techniques in the surgical armamentarium. Although reinnervation techniques and measures to protect the eye take precedence, a number of options allow "fine-tuning" of results for the patient with facial paralysis. These can be broadly subdivided into procedures to rehabilitate the upper, middle, and lower thirds of the face. Finally, synkinesis can be a major concern, and treatment options for synkinesis are available as well.

Procedures for Upper Third of the Face

Paralysis of the upper third of the face produces significant functional and cosmetic deformities. Brow ptosis may cause superior visual field deficits as well significant facial asymmetry. This asymmetry may be further accentuated after procedures to address the lower face. Browlift techniques to manage paralytic ptosis are the same as for a cosmetic browlift, the only significant technical difference being exercise of restraint to avoid further compromising eyelid closure. Direct, midforehead, endoscopic, and indirect browlifts are all effective. When not overdone, a browlift in conjunction with lid loading or lower eyelid tightening, or both, generally produces satisfactory cosmetic and functional results. Brow ptosis associated with normal aging may be accentuated unnaturally by a unilateral lift, and in older patients, improved results are seen when bilateral browlifts are performed.[79]

Many patients with facial paralysis, particularly older persons, will express interest in additional adjunctive procedures in the periocular region. In patients with excessive redundant eyelid skin, conservative blepharoplasty can decrease superior visual field defects while cosmetically addressing brow ptosis and excessive tissue folds. Extreme caution is necessary in performing blepharoplasty in conjunction with browlift procedures. The risk of further impairing eye closure mandates a conservative approach. A maneuver to help assess the amount of skin to be safely removed consists of manually holding the paralyzed brow in the normal position with observation for impairment of eyelid closure. Similarly, it also is helpful to pinch together the excessive eyelid skin to be resected while holding the brow superiorly and observing its effect on eye closure.

Procedures for Middle Third of the Face

The middle third of the face is most commonly rehabilitated using reinnervation techniques, dynamic slings, or static slings. A number of additional procedures are available to fine-tune the results obtained with these procedures, and selection of the appropriate procedure(s) is determined by both the defect and the desires of the patient.

Nasal obstruction after facial paralysis can occur because of collapse of the alar sidewall from adjacent soft tissue ptosis and loss of intrinsic dilator naris tone. As described, a properly designed static

Figure 172-9. Result with static rehabilitation techniques in a patient with right facial paralysis:. Preoperative **(A)** and postoperative **(B)** photographs. Patient underwent direct browlift, lateral transorbital canthopexy, alloderm facial sling repair, and gold weight placement.

sling may alleviate this problem. Alar batten grafting also may provide relief.

Midface soft tissue laxity and sagging, characteristic of the aging midface, is abnormally pronounced in the paralyzed face. In older patients with significant skin laxity, performing a facelift enhances the results of other treatments for midface deformity. Facelifts can be performed concurrently with other procedures, whether dynamic or static, and some patients will benefit from and prefer a bilateral facelift (Fig. 172-9).

Like the aging patient, the patient with facial paralysis acquires ptotic palpebral-malar and nasojugal sulci, producing a hollowed-out appearance to these areas. The lower eyelid fat may bulge, and the suborbicularis oculi fat (SOOF) and midface complex descend, producing a "double convexity" sign on lateral view. In the youthful patient, the suborbicularis oculi fat typically lies at the inferior orbital rim between the orbicularis oculi muscle and the periosteum. The midface lift repositions the SOOF and associated midface soft tissue superior to its preexisting position. The lift has become a popular technique in facial rejuvenation surgery, and also has shown utility in the treatment of facial paralysis. The midface lift can be performed through a transconjunctival incision, with a lateral canthotomy and inferior cantholysis. The periosteum is incised near the orbital rim and is elevated down to the inferior maxilla, where it is released. It also is important to release the attachment to the masseter muscle. Care is taken to avoid injury to the infraorbital nerve. The periosteum and overlying soft tissue are then elevated and secured superiorly to the deep temporal fascia.

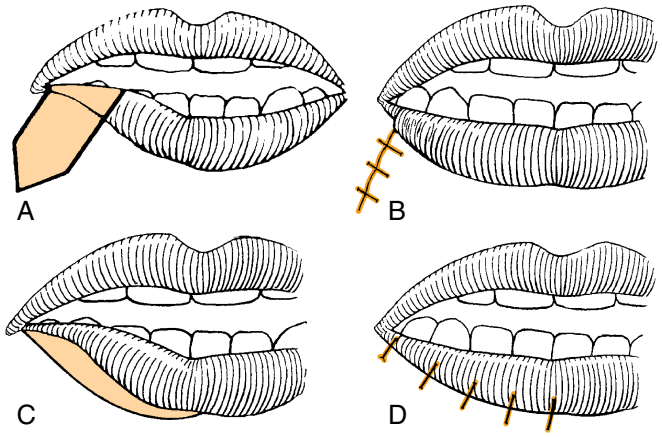

Figure 172-10. Lip wedge excision and cheiloplasty. **A,** Outline of incisions for lip wedge excision. Excision tightens the lower lip and removes part of the denervated muscle. **B,** Appearance after lip resection. Note the intentional asymmetry of vermilion border during closure to evert the lower lip. **C,** Outline of incisions for cheiloplasty. **D,** Appearance of cheiloplasty after resection. Note lowering and outward rotation of the lower lip *(Adapted from Glenn MG, Goode RL. Surgical treatment of the "marginal mandibular lip" deformity.* Otolaryngol Head Neck Surg. *1987;97:464-465.)*

Procedures for Lower Third of the Face

The functional deficits with paralysis of the lower face are dominated by manifestations of oral incompetence. Drooling, air escape with speech, and difficulty with mastication may be present. The asymmetry also produces a significant aesthetic deformity. This is due to the lack of a smile (loss of zygomaticus function) as well as the lack of depressor anguli oris (marginal mandibular nerve) function. These defects can be worsened by performance of static procedures on the middle third of the face, which can produce a troublesome gap in the region of the commissure from elevation of the upper lip.

Reinnervation, free tissue transfer, dynamic slings, and to some degree even static slings assist in repositioning the oral commissure to re-create a more symmetric smile. The asymmetry of depressor function, the so-called "marginal mandibular lip," is more troublesome and difficult to improve. The most commonly used procedures are wedge resection and transposition of the posterior belly of the digastric muscle. The wedge resection, with or without supplemental cheiloplasty technique to improve symmetry and oral competence, has been described by Glenn and Goode.[80] A 2- to 2.5-cm full-thickness excision is performed 7 to 10 mm lateral to the commissure (Fig. 172-10).

The most common dynamic technique for depressor dysfunction is the digastric transposition, first described by Conley and colleagues.[81] The digastric tendon is identified using a submandibular approach. It is released from the hyoid bone, transected near the mastoid tip, transposed superiorly, and attached to the orbicularis oris

through a separate vermilion border incision. Care is taken to preserve the mylohyoid nerve innervating the anterior belly of the digastric muscle. The anterior belly of the digastric muscle may not be available after extirpative cancer surgery, however.[82]

Management of Synkinesis

Patients with incomplete recovery from facial paralysis typically are troubled by both weakness and hyperkinesis, or synkinesis. Synkinesis develops in many patients after facial paralysis of any cause. These uncoordinated mass movements may begin within weeks after paralysis as regeneration occurs. Although the classic description of synkinesis places the etiologic mechanism in aberrant axonal regeneration, it is now known that the sites of pathology are multiple. Synaptic stripping also occurs in the facial nucleus of the brainstem, and ephaptic (non-synaptic) transmission among axons contributes to synkinesis. Future efforts to prevent or treat synkinesis will require addressing each of these areas. Synkinesis ranges in severity from a mild, barely noticeable tic to painful and debilitating mass facial movements.

Careful assessment of each region of the face is performed. It is esssential to identify the patient's most troublesome symptoms and then determine which symptoms result from decreased function and which from synkinesis. The treatment plan can then be individualized to address the patient's needs.

Traditionally, neurolysis has been a mainstay in the management of synkinesis, but it has been largely abandoned as safer and more conservative yet effective techniques have evolved. Such techniques include chemodenervation with botulinum A toxin injections and selective myectomies to target affected muscles.

Botulinum A Toxin

Botulinum A toxin is the most potent poison known to humankind, yet it has been used effectively for more than 2 decades to treat a variety of hyperfunctional disorders including torticollis,[52] blepharospasm,[83] spasmodic dysphonia,[84] strabismus,[85] hyperhidrosis,[86] hyperdynamic skin creases,[87] palatal myoclonus,[88] hemifacial spasm,[89] and facial synkinesis.[90,91] Botulinum toxin causes paralysis by blocking the presynaptic release of acetylcholine at the neuromuscular junction. This typically results in paralysis of the treated muscle for approximately 3 to 6 months. Systemic weakness can occur with doses greater than 200 units. The lethal dose is approximately 40 units/kg.[92]

Botulinum toxin has dramatically improved the management of patients with facial movement disorders. It is now a first-line agent for treatment of facial synkinesis. In most persons, surgical treatment is not necessary or desired. Synkinesis after facial nerve injury can occur in any region of the face, and botulinum toxin can be used to denervate specific muscle groups. The location of the injections is targeted to the muscles causing synkinesis. Typically, 1 to 5 units is injected per site. Initial treatments use conservative doses, which subsequently can be titrated upwards. No anesthesia generally is necessary, but many patients prefer pretreatment of the area with ice or a topical anesthetic. Drug effects are first seen several days after the injection, with a maximal effect observed at 5 to 7 days. Additional toxin can be injected after this time if the initial effect is insufficient.

Adverse effects can occur, related to the diffusion of toxin into surrounding muscles. An example is the development of ptosis after periocular injection. This problem is uncommon, occurring in perhaps 5% of cases. It can be treated with apraclonidine 0.5% drops administered to the affected eye three or four times a day until the ptosis resolves.[93] Apraclonidine causes contraction of Müller's muscle to elevate the upper eyelid. Other complications from botulinum toxin treatment of the face include diplopia, further impairment of eyelid closure, lower eyelid ectropion, brow ptosis, and drooling.

In some patients, the effectiveness of botulinum toxin decreases over time. This diminishing effect may be the result of resprouting of motor endplates or the development of neutralizing antibodies and cannot be overcome with increased doses of the toxin.[94] Patients who do not benefit from botulinum toxin treatments or demonstrate the development of resistance, or who desire a more permanent solution, may be candidates for selective myectomy.

Selective Myectomy

The development of botulinum toxin has significantly expanded the options available to the surgeon caring for a patient with synkinesis. Some patients, however, will prefer something more permanent or may exhibit unsatisfactory results with botulinum toxin injection. These patients may be candidates for selective myectomy.

Neurolysis was for many years the procedure of choice for these patients. Although Fisch[95] reported excellent results, others did not have the same success.[96] Paralytic ectropion, lagophthalmos, lip paresis, oral incompetence, blunted facial expression, and other complications from neurolysis have been reported.[97,98] Myectomy has been offered as a safer, more specific procedure for permanent resolution of synkinesis after facial paralysis.[96] Myectomy results in a more predictable result because the removed muscle does not regrow, a phenomenon that can be seen with neurolysis. In patients desiring no further treatment with botulinum toxin, or for whom botulinum toxin was ineffective, a myectomy may be performed. Selective myectomies can be performed on synkinetic facial muscles.

Summary

A variety of techniques are available for facial nerve rehabilitation after paralysis. The surgeon should know the advantages and disadvantages of the various techniques to apply them properly in each clinical situation. Thorough knowledge of neuromuscular pathophysiology also is important in the understanding of how time affects the available rehabilitative procedures. When properly informed of the limitations of these operative procedures, most patients can be rehabilitated and many of their symptoms can be alleviated.

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CHAPTER ONE HUNDRED AND SEVENTY-THREE

Surgical Anatomy of the Lateral Skull Base

Oswaldo Laércio M. Cruz

Key Points

- The temporal bone articulates with five other cranial bones and forms many sutures and foramina through which pass critical neural and vascular structures.
- Along with the greater wing of the sphenoid and a portion of the parietal bone, the temporal bone forms the lateral boundary of the middle cranial fossa.
- The petrous bone is a key element of the osseous anatomy of the middle and posterior cranial fossae.
- Medial and posterior to the foramen ovale the middle meningeal artery enters the middle cranial fossa through the foramen spinosum, and the greater superficial petrosal nerve is located medial to the middle meningeal artery.
- From superior to inferior, the greater superficial petrosal nerve, the tensor tympani muscle, and the eustachian tube all proceed in a similar anteroposterior plane.
- The greater petrosal nerve, the geniculate ganglion, and the labyrinthine segment of cranial nerve VII form an obtuse angle of approximately 120 degrees. The cochlea is embedded in the bone subtended by that angle.
- The cerebellopontine angle is traversed by the intracranial segments of cranial nerve V (superiorly) to cranial nerve IX (inferiorly) and by the premeatal, meatal, and postmeatal segments of the anterior inferior cerebellar artery (AICA).
- The medial aspect of the internal auditory canal is occupied by its four main neural components: the facial nerve (superior and anterior), the superior vestibular nerve (superior and posterior), the cochlear nerve (anterior and inferior), and the inferior vestibular nerve (posterior and inferior).
- The jugular foramen is located at the petro-occipital region and contains several vital neural and vascular components.
- The infratemporal fossa communicates with the orbit through the inferior orbital fissure, with the middle cranial fossa through the foramen spinosum, and with the pterygopalatine fossa through the pterygomaxillary fissure.

The lateral skull base presents a complex and conceptually challenging anatomy. The temporal bone, occupying a central and strategic position in supporting central nervous system (CNS) structures, articulates with five other cranial bones and forms many sutures and foramina through which pass critical neural and vascular structures. Familiarity with this complex anatomy is mandatory for an understanding of pathologic processes arising in the temporal bone and the middle and posterior cranial fossae, and for safe execution of skull base procedures.

This chapter is divided into four sections, on osseous anatomy of the lateral skull base, anatomy of the middle cranial fossa, anatomy of the posterior cranial fossa, and anatomy of the infratemporal fossa.

Osseous Anatomy of the Lateral Skull Base

The temporal bone occupies a central position at the lateral skull base, being the most important anatomic landmark in the lateral skull base anatomy.[1,2]

On lateral view, the squamosa presents a shape reminiscent of an open wing of a bird (Fig. 173-1). From its middle and caudal portions it contributes to the zygomatic arch and forms the superior wall of the external auditory canal. Its articulation with the tympanic bone in the anterosuperior external auditory canal forms the tympanosquamous suture. The zygomatic bone portion contributes to the roof of the glenoid fossa and the anterior part of the tympanic bone forms its posterior wall.

Along with the greater wing of the sphenoid and a portion of the parietal bone, the temporal bone forms the lateral boundary of the middle cranial fossa (Figs. 173-2 and 173-3). This medial aspect of the squamous bone forms the petrosquamous suture, which joins the caudal portion of the squamosa and the lateral superior portion of the petrosa. Anteriorly, at the articulation of the sphenoid with the squamous bone, is located the foramen spinosum, through which passes the middle meningeal artery into the cranium. The sulcus of this artery is easily identified on the medial surface of the squamosa (see Figs. 173-2 and 173-3).

The tympanic bone lies just inferior to the squamous portion and anterior to the mastoid and forms the tympanosquamous and tympanomastoid sutures with them (see Fig. 173-1). It is common for one edge of these suture lines (especially the tympanosquamous suture) to project as a spinous process exteding 1 to 3 mm into the lumen of the external auditory canal.[1,3,4]

The tympanic bone forms the anterior and inferior walls and a portion of the posterior wall of the external auditory meatus and is primarily responsible for the size and shape of the external auditory

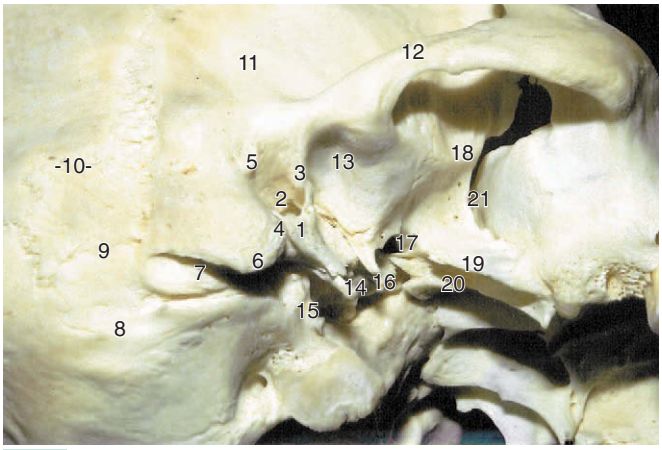

Figure 173-1. Cranium, lateral inferior view (right side): 1, tympanic bone; 2, external auditory canal; 3, tympanosquamous suture; 4, tympanomastoid suture; 5, suprameatal spine; 6, mastoid tip; 7, digastric sulcus; 8, occipital bone; 9, occipitomastoid suture; 10, parietomastoid suture; 11, squamous portion of the temporal bone; 12, zygoma; 13, glenoid fossa; 14, styloid process; 15, jugular foramen; 16, carotid canal; 17, sphenopalatine foramen; 18, greater wing of the sphenoid bone; 19, lateral pterygoid process; 20, medial pterygoid process; 21, pterygomaxillary fossa. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

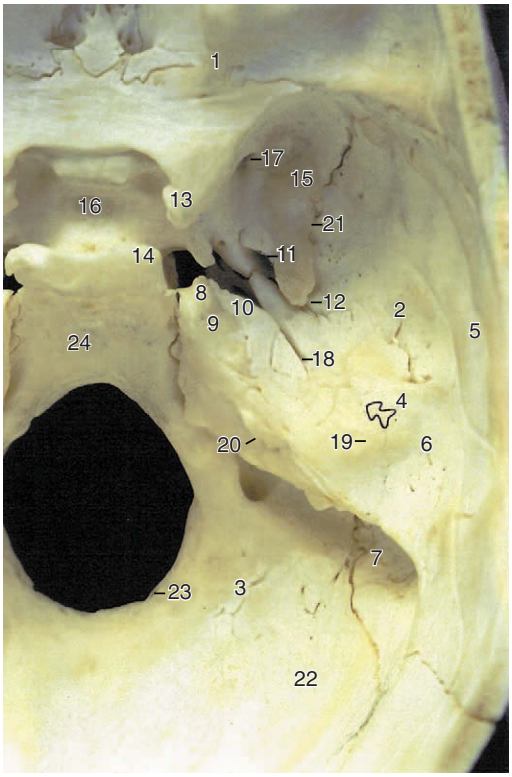

Figure 173-2. Superior view of anterior, middle, and posterior fossae, with the projection of petrous portion of temporal bone: 1, anterior fossa; 2, middle fossa; 3, posterior fossa; 4, petrous bone projection *(arrow)*; 5, squamous portion of the temporal bone; 6, mastoid tegmen; 7, sigmoid sinus impression; 8, petrous apex; 9, trigeminal depression (Meckel's cave); 10, foramen lacerum region; 11, foramen ovale; 12, foramen spinosum; 13, anterior clinoid process; 14, posterior clinoid process; 15, greater wing of sphenoid; 16, sphenoid bone and sella; 17, foramen rotundum; 18, greater petrosal nerve impression; 19, arcuate eminence; 20, internal auditory canal region; 21, petrosphenoid suture; 22, occipital bone; 23, foramen magnum; 24, clivus. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

canal. As mentioned, it also composes the posterior wall of the glenoid fossa (see Fig. 173-1).

At the medial extension of the external auditory canal, the tympanic bone ends at the tympanic sulcus or annular sulcus, into which the tympanic membrane inserts (Figs. 173-4 and 173-5; see also Fig. 173-1). On its inferior surface, the tympanic bone articulates with the petrous bone, forming the petrotympanic suture. It also contributes to the formation of the internal carotid artery canal (ascending portion) (see Figs. 173-4 and 173-5). Also, on its inferior aspect and lateral to the carotid canal, the tympanic bone forms the styloid process (see Fig. 173-1). Slightly posterior and medial to this process is the stylomastoid foramen, through which the seventh cranial nerve emerges (see Fig. 173-5).

The osseous anterior wall of the external auditory canal abuts the temporomandibular joint and is of variable thickness. The bony inferior wall is thick and related to the anterior aspect of the jugular bulb (posteriorly) and carotid canal (anteriorly) (Fig. 173-6; see also Figs. 173-1, 173-4, and 173-5). The posterior wall separates the external auditory canal from the mastoid cells and the descending portion of the facial nerve (see Fig. 173-6).[3,5]

The mastoid is a pneumatized bony process located at the most posterior and inferior part of the temporal bone that, in reality, can be considered an extension of the squamosa and a lateral projection of the petrous portion (see Figs. 173-1 and 173-2). It has a somewhat triangular form, with the vertex directed inferiorly and the base superiorly.

Anteriorly, the mastoid process forms the tympanomastoid suture as it joins the posterior portion of the tympanic bone. Above and lateral to the tympanomastoid suture is the suprameatal spine, an osseous elevation of variable size that anchors the nonosseous portion of the external auditory canal and auricle. Immediately posterior to this spine and inferior to the temporal line is a slightly depressed region called the cribriform plate, a multiperforated region that serves as a landmark for surgical access to the mastoid antrum (see Fig. 173-1).

Posteriorly, the mastoid portion presents a relationship with the parietal bone superiorly and the occipital bone inferiorly, forming the parietomastoid and occipitomastoid sutures. These two sutures join the occipitoparietal suture at a point called the asterion, an important surgical landmark for craniotomies to achieve posterior fossa access.

Medial to the mastoid tip, the posterior belly of the digastric muscle at its insertion forms an osseous depression or sulcus, running anterior to posterior. At its anterior termination, this sulcus is a land-

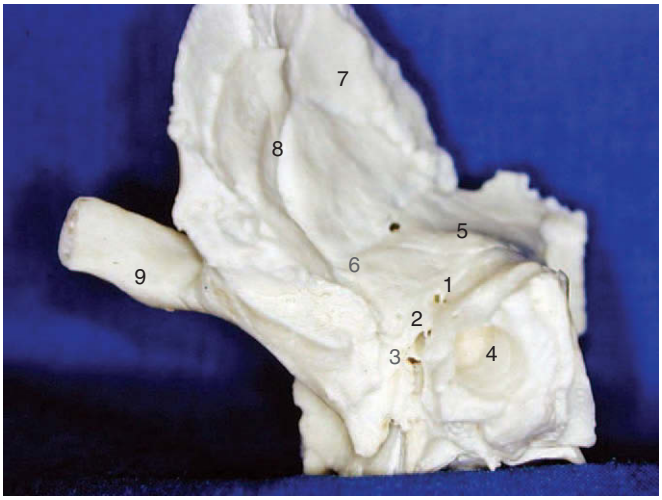

Figure 173-3. Anterior view of temporal bone (right side): 1, facial hiatus; 2, semicanal of the tensor tympani muscle; 3, osseous portion of the eustachian tube; 4, carotid artery canal (end of the horizontal portion); 5, arcuate eminence; 6, petrosquamous suture; 7, squamous portion of the temporal bone; 8, middle meningeal artery sulcus; 9, zygoma. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

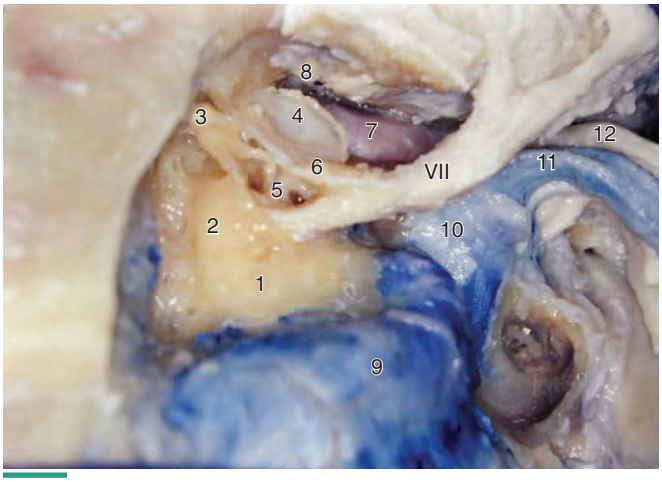

Figure 173-4. Lateral view of right temporal bone after resection of tympanic bone and mastoid and exposure of carotid artery and jugular foramen: 1, posterior semicircular canal; 2, lateral semicircular canal; 3, incus-malleus articulation; 4, tympanic membrane; 5, facial recess with view of round window niche, pyramidal eminence, stapes tendon, and incus-stapes articulation; 6, chorda tympani nerve; 7, carotid artery (ascending portion); 8, eustachian tube opening; 9, sigmoid sinus; 10, jugular bulb; 11, jugular vein (upper cervical portion); 12, cranial nerves X and XI emerging from neural intrajugular compartment of the jugular foramen; VII, facial nerve (seventh cranial nerve). *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

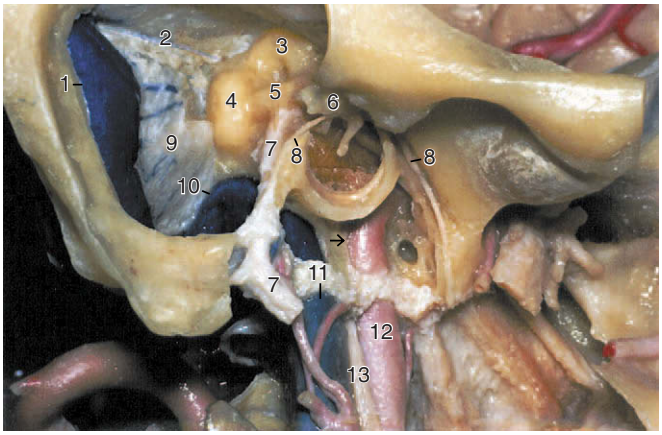

Figure 173-5. Lateral view of right temporal bone with mastoidectomy and resection of the tympanic bone, tympanic membrane, and glenoid process: 1, sigmoid sinus; 2, superior petrous sinus; 3, superior semicircular canal; 4, posterior semicircular canal; 5, lateral semicircular canal; 6, ossicular chain; 7, facial nerve; 8, chorda tympani nerve; 9, Trautmann's triangle—posterior fossa dura; 10, jugular foramen bulb; 11, jugular vein; 12, internal carotid artery: ascending portion and anterior turn or knee *(arrow)*; 13, cranial nerve IX. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

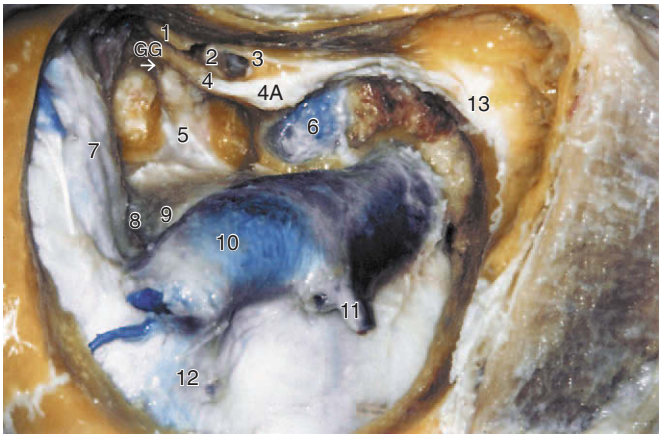

Figure 173-6. Lateral view of a right temporal bone with wide mastoidectomy, resection of the semicircular canals and exposition of the internal auditory canal: 1, incus; 2, stapes; 3, chorda tympani nerve; 4, tympanic portion of facial nerve continuing with mastoid segment (4A); 5, dura of the posterior wall of the internal auditory canal; 6, jugular foramen; 7, middle fossa dura; 8, superior petrosal sinus; 9, Trautmann's triangle (posterior fossa); 10, sigmoid sinus; 11, emissary vein; 12, transverse sinus; 13, digastric groove; GG, geniculate ganglion at the end of the labyrinthine segment of the facial nerve *(arrow)*. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

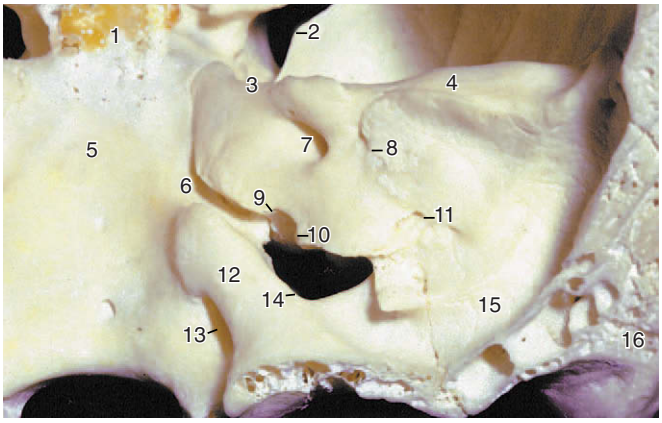

Figure 173-7. Medial view of lateral posterior fossa wall (right side): 1, sella; 2, superior orbital fissure; 3, trigeminal impression; 4, superior petrosal sinus impression; 5, clivus; 6, petro-occipital sulcus; 7, internal auditory canal; 8, subarcuate fossa; 9, cochlear aqueduct; 10, jugular process; 11, vestibular aqueduct; 12, jugular tuberculum; 13, hypoglossal nerve canal; 14, jugular foramen; 15, sigmoid sinus impression; 16, mastoid bone. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

mark for the descending portion of the facial nerve and the stylomastoid foramen (see Figs. 173-1 and 173-6).

Viewed from above and from inside the cranium, the petrous bone is a key element in the osseous anatomy of the middle and posterior fossae. It has a configuration of a three-sided pyramid (see Fig. 173-2). The base of the pyramid constitutes its lateral surface and articulates with the squamous, tympanic, and mastoid portions of the temporal bone (Fig. 173-7; see also Fig. 173-2). Two sides of the pyramid are clearly recognized as medial projections: one superior, which forms much of the floor of the middle cranial fossa, and the medial surface, which faces the posterior cranial fossa, forming most of its lateral wall. The third and inferior side articulates with the occipital bone (see Figs. 173-2 and 173-3). The anterior medial limit of the pyramid (petrous apex) reaches the greater sphenoid wing laterally, the body of the sphenoid medially and superiorly, and the clivus portion of the occipital bone medially and inferiorly (see Figs. 173-2 and 173-3). The petroclival sutures lie on either side of the midline within the circumference of the foramen magnum.

The superior surface of the petrosa forms the major portion of the middle fossa floor and presents key anatomic landmarks for otoneurologic surgery (Figs. 173-8 and 173-9; see also Figs. 173-2 and 173-3). At the most anterior medial portion (apex) is the foramen lacerum, through which passes the end of the horizontal portion of the carotid

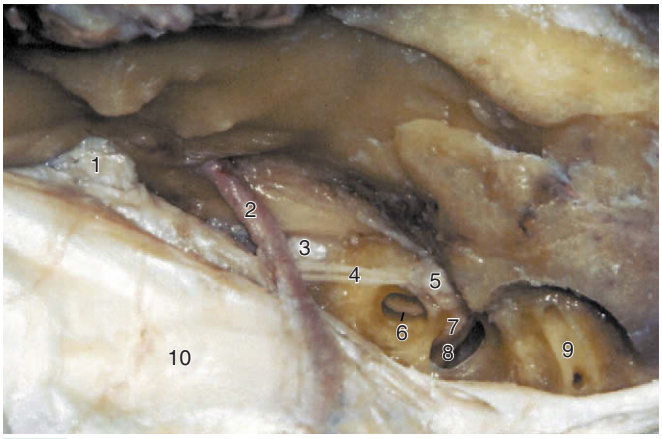

Figure 173-8. Right side view in middle cranial fossa surgical approach. The dura is detached from the temporal bone and the bone from the horizontal portion of carotid artery, cochlea, internal auditory canal, and the superior semicircular canal removed. 1, V_1 entering the foramen ovale; 2, middle meningeal artery coming from the foramen spinosum; 3, horizontal portion of the internal carotid artery; 4, greater superficial petrosal nerve; 5, geniculate ganglion; 6, cochlea; 7, facial nerve in the medial portion of the internal auditory canal; 8, superior vestibular nerve; 9, superior semicircular canal; 10, middle fossa dura. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

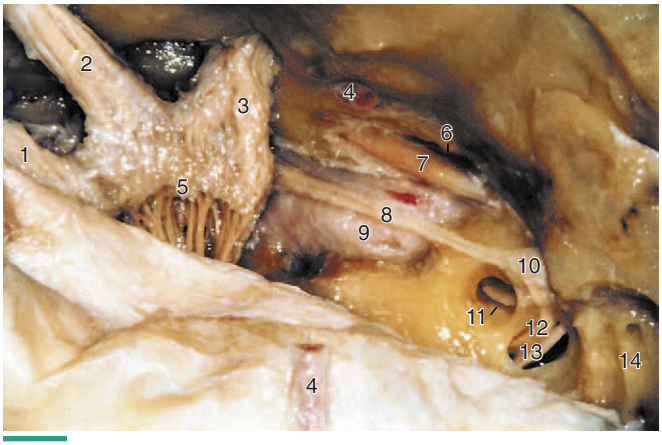

Figure 173-9. Surgical anatomy of the middle fossa approach after gasserian ganglion dissection, middle meningeal artery section, and eustachian tube and tensor tympani muscle exposure. 1, V_1: ophthalmic division of the trigeminal nerve; 2, V_2: maxillary division of the trigeminal nerve; 3, V_3: mandibular division of the trigeminal nerve; 4, middle meningeal artery; 5, gasserian ganglion; 6, eustachian tube; 7, tensor tympani muscle; 8, greater superficial petrosal nerve; 9, internal carotid artery; 10, geniculate ganglion; 11, cochlea; 12, facial nerve; 13, superior vestibular nerve; 14, superior semicircular canal. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

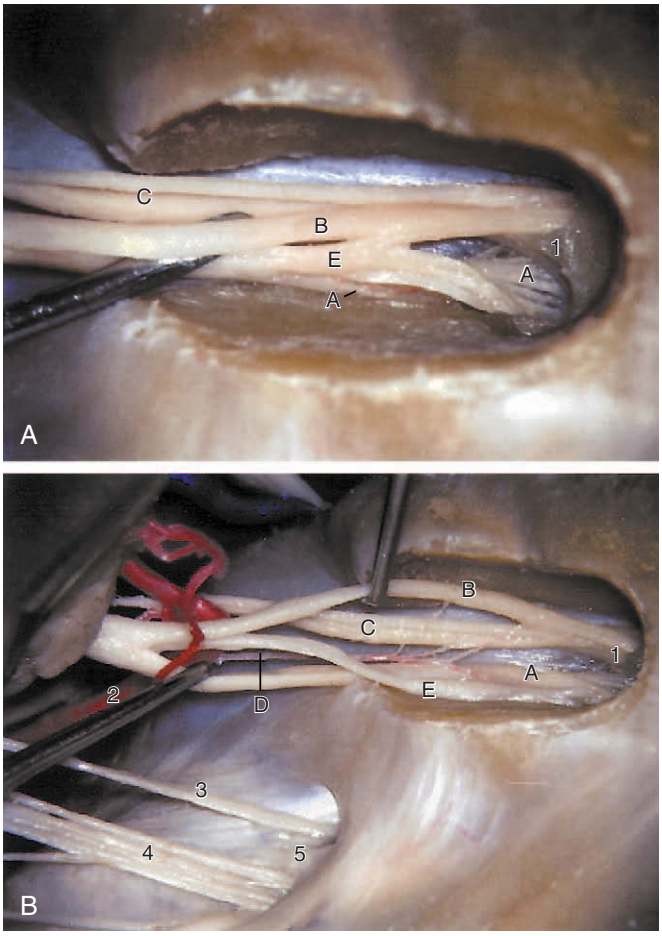

Figure 173-10. **A,** Closeup posterior view of the nerves in the internal auditory canal (right side). **B,** Close posterior view of the midface showing the petrous bone and internal auditory canal with nerve dissection. 1, transverse crest; 2, AICA (anterior inferior cerebellar artery); 3, cranial nerve IX (glossopharyngeal nerve); 4, cranial nerve X (vagus nerve); 5, dural septum; A, cochlear nerve; B, superior vestibular nerve; C, facial nerve and nervus intermedius (of Wrisberg); D, internal auditory artery; E, inferior vestibular nerve. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

artery on its way to the cavernous sinus. Medial to the foramen lacerum there is a depression in the bone border (trigeminal impression), where cranial nerve V fibers pass on their way to the Meckel's cave and gasserian ganglion. Lateral and slightly anterior to the ganglion and cave, at the junction to the sphenoid greater wing, is the foramen ovale, through which the third division of the trigeminal nerve (cranial nerve V_3) exits the cranium for the infratemporal fossa (see Figs. 173-2, 173-8, 173-9, and 173-15).

The foramen spinosum is lateral and posterior to the foramen ovale and transmits the middle meningeal artery. The facial hiatus is 10 to 15 mm medial to the foramen spinosum, a bony sulcus that receives the fibers of the greater petrosal nerve coming from the geniculate ganglion (see Figs. 173-2 and 173-3). Posterior and medial to the facial hiatus is the arcuate eminence, related to the most superior aspect of the superior semicircular canal. It is usually, but not always, elevated above the surrounding bone, and the mastoid and tympanic teguments are positioned laterally to it (see Figs. 173-2 and 173-3). The neural and vascular structures of this region are reviewed in the next section, "Anatomy of the Middle Cranial Fossa."

The medial or cerebellar surface of the temporal bone forms the anterolateral wall of the posterior fossa (see Figs. 173-2 and 173-7). Where the superior margin of the medial surface meets the medial margin of the superior surface, a bony sulcus accommodates the superior petrosal sinus on its course between the cavernous sinus and the transition zone between the lateral sinus to the sigmoid sinus. The inferior margin of the medial surface contains another sulcus at the petro-occipital junction for the inferior petrosal sinus, connecting the cavernous sinus and the jugular foramen.

The prominent structure of the petrosa's medial surface is the internal acoustic pore (porus acousticus), which represents the medial limit of the internal auditory meatus (see Fig. 173-7). The meatus ends laterally at the medial wall of the vestibule and the inferior surface of the modiolus and basal cochlear turn (Fig. 173-10; see also Figs. 173-6 and 173-7). A horizontal bony ridge located at the lateral limit divides the meatus into two compartments, superior and inferior. The upper

compartment also is divided into anterior and posterior portions by a small vertical bony crest, commonly known as "Bill's bar" in honor of William House, who first drew attention to its presence and surgical importance. These bony ridges divide the fundus of the internal auditory canal into four quadrants, each carrying its own cranial nerve: an anterior-superior quadrant with the facial nerve, an anterior-inferior quadrant with the cochlear nerve, and posterior-superior and posterior-inferior quadrants occupied by the superior and the inferior vestibular nerves, respectively[6] (see Fig. 173-10A and B).

Posterior to the superior limit of the porus of the internal auditory canal and inferior to the arcuate eminence is the subarcuate fossa, which contains a channel to the subarcuate artery and veins (see Figs. 173-7 and 173-11). Posterior and caudal to the subarcuate fossa is a small bony fissure or depression that indicates the opening of the vestibular aqueduct and the position of the endolymphatic sac in the posterior fossa (see Fig. 173-7).

The inferior surface articulates with the occipital bone forming the petro-occipital suture which is in near continuity with the occipitomastoid suture and the sulcus of the sigmoid sinus. In this region lies the butterfly-shaped jugular foramen with its lateral margin formed by the petrous bone and its medial limits by the occipital bone (see Fig. 173-7). Immediately anterior to the jugular foramen is the petro-occipital sulcus, which contains the inferior petrosal sinus. The inferior petrosal sinus enters the jugular foramen in its anterior compartment.

Cranial nerves IX, X, and XI also exit the cranial cavity through the anterior compartment of the jugular foramen and are completely separated from the venous components by a dural septum and fibrous vascular tissue (as described later under "Anatomy of the Posterior Cranial Fossa") (see Figs. 173-4, 173-5, 173-13, and 173-14). The fossa of the jugular bulb lies superior to the posterior compartment and varies greatly in size (see Figs. 173-4, 173-5, and 173-13). The funnel-shaped opening of the cochlear canaliculus is at the superior border of the anterior compartment (see Fig. 173-7). Just inferior to the anterior compartment is the opening of the hypoglossal canal, through which cranial nerve XII leaves the cranium (see Fig. 173-7).

Lateral and anterior to the anterior component of the jugular foramen is the ascending portion of the carotid artery canal at the petrosa's junctions with the tympanic bone (see Figs. 173-4 and 173-5). Within it are the internal carotid artery and the venous and sympathetic nerve plexuses. Here the carotid artery pursues a cephalic course along the anterior wall of the tympanic cavity, parallel to the anterior portion of the tympanic bone and the glenoid fossa (see Figs. 173-4 and 173-5). Just medial to the tympanic ostium of the eustachian tube and immediately anterior to the cochlea, the carotid canal bends horizontally, forming the carotid "knee," and follows a horizontal course in the middle fossa toward the petrous apex and foramen lacerum (see Figs. 173-5, 173-9, and 173-15).

From an anterior perspective, two small openings are visible lateral to the carotid canal. The superior opening is the canal for the tensor tympanic muscle, and the inferior is the osseous portion of the eustachian tube (see Fig. 173-3).

When viewed from a lateral inferior perspective, the jugular foramen lies posterior and medial to the styloid process, and posterior and lateral to the carotid canal, formed by the medial-inferior aspect of the petrous bone and the occipital bone (see Fig. 173-1).

Anatomy of the Middle Cranial Fossa

This section describes relevant anatomy for the middle cranial fossa surgical approach. After a squamosal craniotomy, the temporal lobe dura is elevated, exposing the floor of the middle fossa (see Fig. 173-8).

The gasserian ganglion is located at the anterior aspect of the petrous apex (see Fig. 173-9). The mandibular division of the fifth cranial nerve (trigeminal nerve), V_1, passes anteriorly through the superior orbital fissure. The maxillary division, V_2, passes through the foramen rotundum, and the ophthalmic division, V_3, through the foramen ovale. Medial and posterior to the foramen ovale, the middle meningeal artery enters the middle cranial fossa through the foramen spinosum (see Figs. 173-2, 173-8, and 173-9). The greater superficial petrosal nerve is located medial to the middle meningeal artery. It is the principal surgical landmark for middle cranial fossa procedures because of its consistency and its intimate relationship with nearby structures[2] (see Figs. 173-2, 173-8, and 173-9).

Lateral to the greater petrosal nerve, semicanal to the tensor tympani muscle lies medial to the middle meningeal artery (see Figs. 173-3 and 173-9). The osseous portion of the eustachian tube parallels the course of the tensor tympani muscle laterally. Thus, from superior to inferior, the greater superficial petrosal nerve, the tensor tympani muscle, and the eustachian tube all proceed in a similar anteroposterior plane (see Fig. 173-3).

The horizontal portion of the carotid artery follows a course just inferior and medial to greater petrosal nerve and inferior to the gasserian ganglion on its way to the foramen lacerum and the cavernous sinus (see Figs. 173-8 and 173-9).

The posterior termination of the greater petrosal nerve is the geniculate ganglion. That ganglion is covered by a thin lamina of bone that is absent in 16% of cases. Medial and posterior to the geniculate ganglion is the labyrinthine segment of the facial nerve emerging from the internal auditory canal. After the superior wall of the internal auditory canal is removed, the facial nerve can be seen in the anterior superior portion of the canal and the superior vestibular nerve in the posterior superior portion (see Fig. 173-9). The greater petrosal nerve, geniculate ganglion, and labyrinthine segment of cranial nerve VII form an obtuse angle of approximately 120 degrees. The cochlea is embedded in the bone subtended by that angle (see Figs. 173-8 and 173-9).

The tegmen tympani and tegmen mastoideum are lateral to the geniculate ganglion. If they are partly removed, the epitympanum, the tympanic segment of the facial nerve, and the incudomalleolar joint are seen anteriorly and the mastoid antrum and the three semicircular canals are seen posteriorly. The groove for the superior petrosal sinus at the superior medial ridge of the petrosa marks the medial limit of the middle fossa approach. The opening of the superior petrosal sinus allows access to the posterior cranial fossa.

Anatomy of the Posterior Cranial Fossa

The cerebellopontine angle is traversed by the intracranial segments of cranial nerves VII and VIII. The posterior fossa also contains many other crucial neural and vascular structures, as shown in Figures 173-11 and 173-12. Also, the posteromedial aspect of the temporal bone contains the internal auditory canal and the jugular foramen, and familiarity with their relationships is essential.

Cerebellopontine Angle

The cerebellopontine angle is delimited as follows[2,6]:

- Anteriorly, by cranial nerve VI and the lateral aspect of the clivus
- Laterally, by the medial surface of the petrosa
- Medially, by the middle cerebellar peduncle, the pons, and the ventral surface of the cerebellum
- Superiorly, by cranial nerve V
- Inferiorly, by cranial nerves IX, X, and XI
- Posteriorly, by the cerebellar floccules

Contained within this space are cranial nerves VII and VIII; the premeatal, meatal, and postmeatal segments of the AICA; and the porus of the internal auditory canal. When cranial nerves VII and VIII leave the brainstem at the bulbopontine sulcus, cranial nerve VII lies 1 to 2 mm anterior to cranial nerve VIII. Both nerves follow a lateral and ascending course to enter the internal auditory canal (see Figs. 173-11 and 173-12). From its origin to the most lateral aspects of the internal auditory canal, cranial nerve VII occupies a more anterior and superior position in relation to cranial nerve VIII (see Fig. 173-10).

Internal Auditory Canal

The internal auditory canal develops a lateral and posterior path in relation to the medial surface of the temporal bone. Its length is 1.2 to

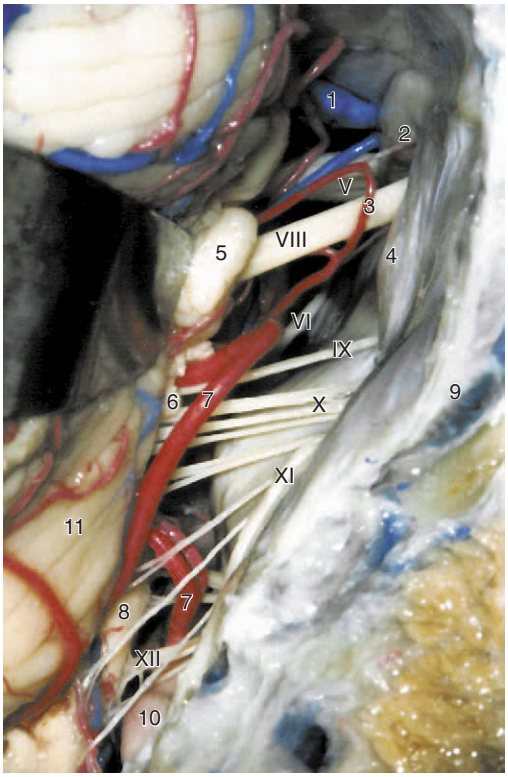

Figure 173-11. Posterior fossa and the middle surface of temporal bone relationships: posterior view as in the retrosigmoid approach (right side). 1, superior petrosal vein; 2, subarcuate artery; 3, anterior inferior cerebellar artery (AICA); 4, internal auditory artery; 5, cerebellar floccules; 6, choroid plexus; 7, posterior inferior cerebellar artery (PICA); 8, cerebellar olive; 9, sigmoid sinus; 10, vertebral artery; 11, cerebellar hemisphere. Roman numerals denote cranial nerves: V, trigeminal nerve; VI, abducens nerve; VIII, vestibulocochlear nerve; IX, glossopharyngeal nerve; X, vagus nerve; XI, spinal accessory nerve; XII, hypoglossal nerve. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

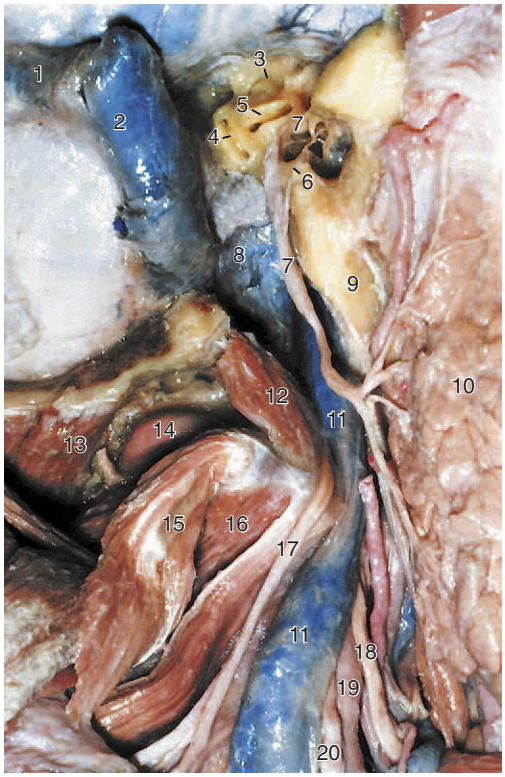

Figure 173-13. Lateral view of the lateral cranial base and the jugular foramen region. Posterior fossa and middle fossa craniotomies were performed, along with extensive mastoid resection and facial nerve exposure. 1, transverse sinus; 2, sigmoid sinus; 3, superior semicircular canal; 4, posterior semicircular canal; 5, lateral semicircular canal; 6, chorda tympani nerve; 7, cranial nerve VII (facial nerve); 8, jugular foramen; 9, tympanic bone; 10, parotid gland; 11, jugular vein; 12, rectus lateralis muscle; 13, rectus capitis major muscle; 14, vertebral artery; 15, superior oblique muscle; 16, inferior oblique muscle; 17, cranial nerve XI (accessory nerve); 18, cranial nerve XII (hypoglossal nerve); 19, internal carotid artery; 20, cranial nerve X (vagus nerve). *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

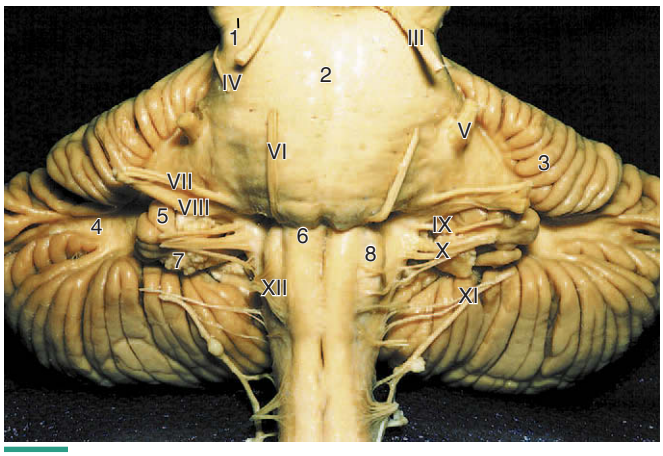

Figure 173-12. Anterior (rostral) view of the brainstem and the cerebellar hemispheres: 1, pontine-mesencephalic sulcus; 2, pons; 3, quadrangular cerebellar lobule; 4, cerebellar horizontal fissure; 5, cerebellar floccules; 6, bulbopontine sulcus; 7, choroid plexus of the IV ventricle; 8, cerebellar olive. Roman numerals denote cranial nerves. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

1.4 cm from the porus to the fundus, where it enters the inner ear[6] (see Figs. 173-6, 173-7, 173-9, and 173-10).

The lateral portion of the internal canal is divided into superior and inferior compartments by the falciform or transverse crest (see Fig. 173-10A and B). The superior compartment is further divided into anterior and posterior portions by the vertical crest (Bill's bar). Those four quadrants are occupied by the four main neural components of the internal auditory canal contents: the facial nerve (superior and anterior), the superior vestibular nerve (superior and posterior), the cochlear nerve (anterior and inferior), and the inferior vestibular nerve (posterior and inferior).

The inferior compartment does not have a bony division for the cochlear and inferior vestibular nerves, but the cochlear nerve leaves the internal auditory canal through a multiperforate osseous plate to enter the cochlear modiolus (see Fig. 173-10A). Posteroinferiorly, a small multiperforated region reflects the emergence of the inferior vestibular nerve fibers from the saccular macula, and a short distance away is the singular foramen that transmits the posterior ampullary nerve (singular nerve) from the ampulla of the posterior semicircular canal.

Jugular Foramen

The jugular foramen is located in the petro-occipital region and contains several vital neural and vascular structures (Fig. 173-13 and 173-14; see also Figs. 173-1, 173-3, 173-6, 173-7, and 173-11). The vascular structures include the sigmoid sinus, superior and inferior

Figure 173-14. Lateral view of the posterior cranial base and the jugular foramen region. The dura of the posterior fossa has been opened, permitting an excellent view of sigmoid sinus position. The lateral aspect of jugular foramen (sigmoid portion) was removed after ligation of the jugular vein and section of the lateral wall of the sigmoid sinus. 1, sigmoid sinus; 2, semicircular canals; 3, facial nerve, anteriorly displaced; 4, medial wall of the jugular foramen with an opening for the inferior petrosal sinus *(arrow)*; 5, cranial nerve IX; 6, cranial nerve XII; 7, cranial nerve XI; 8, cranial nerve X; 9, jugular vein (with ligature); 10, internal carotid artery; 11, superior laryngeal nerve; 12, cervical branch of cranial nerve XII. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

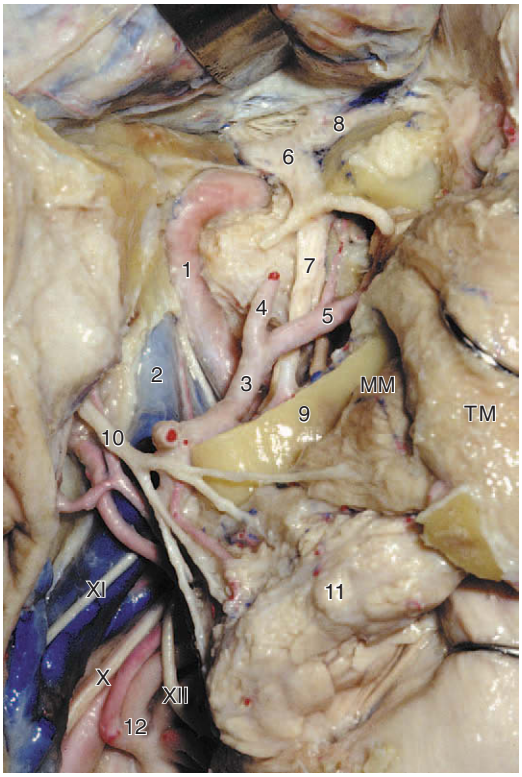

Figure 173-15. Lateral view of the infratemporal region after resection of the superior portion of the ascending ramus of the mandible. The parotid gland and the facial nerve were displaced inferiorly, as were the masseter and temporalis muscles. The lateral pterygoid muscle was resected to allow visualization of the mandibular nerve (V_3). 1, internal carotid artery; 2, jugular vein; 3, external carotid artery; 4, middle meningeal artery; 5, internal maxillary artery entering the pterygomaxillary fossa; 6, gasserian ganglion; 7, V_3 (mandibular nerve); 8, V_2 (maxillary nerve); 9, mandible (ascending ramus); 10, facial nerve, main trunk and divisions at parotid gland; 11, parotid gland; 12, inferior aspect of the external carotid artery; MM, masseter muscle; TM, temporalis muscle. Roman numerals denote cranial nerves. *(Courtesy of Oswaldo Laércio M. Cruz, Helder Tedeschi, and Albert Rhoton.)*

petrosal sinuses, jugular bulb, and meningeal branches from the ascending pharyngeal and occipital arteries. The neural components include cranial nerves IX (glossopharyngeal nerve), X (vagus nerve), and IX (spinal accessory nerve) and their respective ganglia. The jugular foramen also receives the opening of the cochlear aqueduct and is in close proximity to the hypoglossal canal and to cranial nerve XII (see Figs. 173-7, 173-11, and 173-14).

Traditionally, the jugular foramen has been divided into two parts: the larger posterior *pars venosa* and the smaller anterior *pars nervosa*. More recently, anatomic division into three compartments has been proposed[7]:

Sigmoid compartment: posterior and receiving the sigmoid sinus

Petrous compartment: anterior and receiving the inferior petrosal sinus

Neural intrajugular compartment: located between the two others and receiving the neural and arterial components

Cranial nerve IX penetrates a dural opening in the neural compartment and courses anteriorly and inferiorly near the opening of the cochlear aqueduct. Within the jugular foramen, cranial nerve IX forms two ganglia. The inferior ganglion gives rise to the auricular branch (Jacobson's nerve), which ascends across the promontory to form a sensory plexus and the lesser superficial petrosal nerve.

Cranial nerves X and XI penetrate the neural compartment inferior to cranial nerve IX and are separated from it by a dural septum. Cranial nerve X also forms a ganglion as it leaves the cranial cavity; the auricular branch of the vagus nerve (Arnold's nerve) arises from it. Arnold's nerve courses superiorly to emerge at the tympanomastoid fissure and provide sensory innervation to the posterior wall of the external auditory canal. Cranial nerve X leaves the jugular foramen and descends vertically posterior to the carotid artery and anterior to the jugular vein, parallel to and in close relationship with the cervical segment of cranial nerve XII immediately after it has left the cranial cavity (see Figs. 173-4, 173-5, 173-13, and 173-14).

Anatomy of the Infratemporal Fossa

The infratemporal fossa is a space delimited as follows (Fig. 173-15; see also Fig. 173-1):

- Anteriorly, by the posterior surface of the maxilla and the inferior orbital fissure
- Posteriorly, by the mastoid and tympanic portions of the temporal bone
- Superiorly, by the inferior surfaces of the greater wing of the sphenoid and the squamous portion of the temporal bone

- Medially, by the pterygoid process of the sphenoid, lateral portion of the clivus, first cervical vertebra, and inferior surface of the petrous portion of the temporal bone
- Laterally, by the zygomatic arch and ascending ramus of the mandible
- Inferiorly, by the the superior limit of the posterior belly of the digastric muscle and the angle of the mandible

The infratemporal fossa communicates with the orbit through the inferior orbital fissure, with the middle cranial fossa through the foramen spinosum, and with the pterygopalatine fossa through the pterygomaxillary fissure (see Figs. 173-1 and 173-15). The lateral and medial pterygoid muscles lie within the infratemporal fossa. The lateral pterygoid muscle is divided into superior and inferior parts. The superior portion arises from the roof of the infratemporal fossa, and the inferior arises from the lateral aspect of the lateral pterygoid process. Both portions insert onto the temporomandibular joint. The medial pterygoid muscle originates from the medial portion of the lateral pterygoid process and inserts on the medial surface of the angle of the mandible and the ascending ramus.

The infratemporal fossa also contains the mandibular division of the trigeminal nerve (V_3) and its branches (see Fig. 173-15), which provide motor innervation to the temporalis, masseter, and medial and lateral pterygoid muscles, as well as sensory innervation through the auriculotemporal, alveolar, lingual, and buccal nerves.

The chorda tympani nerve originates in the mastoid segment of the facial nerve (cranial nerve VII) midway in the descending portion, pursues a course anterior and superior to the posterior superior quadrant of the mesotympanum, passes through the tympanic cavity, and reaches the chorda tympani canaliculus in the petrotympanic fissure. It then passes forward and descends vertically and medially to the lateral pterygoid muscle to join the lingual nerve (see Figs. 173-4, 173-5, and 173-6).

The maxillary artery leaves the external carotid artery posterior to the ascending ramus of the mandible and enters the infratemporal fossa lateral to the lateral pterygoid muscle. It follows a trajectory anterior to the pterygomaxillary fissure and the pterygopalatine fossa (see Fig. 173-15). It divides within the infratemporal fossa. Its principal branches are the middle meningeal artery, the inferior alveolar artery, the deep temporal artery, branches to the pterygoid muscles, the auricular artery, and the anterior tympanic artery.

The venous drainage of the infratemporal fossa occurs by way of the pterygoid venous plexus, which drains posteriorly into the maxillary vein and anteriorly into the facial vein. The plexus also anastomoses with the cavernous sinus, ophthalmic veins, and pharyngeal venous plexus. Infection within the infratemporal fossa thus carries the risk of spread by hematogenous extension, especially to involve the contents of the orbit and cavernous sinus.

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CHAPTER ONE HUNDRED AND SEVENTY-FOUR

Surgery of the Anterior and Middle Cranial Base

Colin D. Pero

Frank Culicchia

Rohan R. Walvekar

Bert W. O'Malley, Jr.

Daniel W. Nuss

Key Points

- Advances in oncologic and reconstructive surgery, anesthesiology, radiology, and other related fields have made surgery of the cranial base both technically feasible and therapeutically effective. As a result, surgical resection can be considered the primary management modality for many cranial base lesions previously considered inaccessible or inoperable.
- Symptoms from anterior and middle cranial base lesions may range from headache to impaired cranial nerve and central nervous system functions. These disorders are insidious in that they cause few symptoms until they have reached advanced stages and impinge on cranial nerves, major vessels, or the brain. This paucity of early symptoms makes early diagnosis difficult.
- Operative planning for the removal of lesions of this anatomically complex region requires that laboratory testing, imaging, and vascular interventional procedures be used to their fullest potential to guide the surgical and anesthetic teams, as well as the patient's expectations.
- Operative approaches should attempt to meet principal aims of (1) optimizing exposure, (2) preserving neurovascular structures, (3) implementing the use of image guidance and endoscope assistance to enhance the resection while limiting incision length and removal of normal tissue, and (4) planning surgical techniques that optimize functional and aesthetic reconstruction.
- Postoperative complications may entail serious morbidity and mortality; limiting postoperative neurologic and other complications requires anticipation of potential risks and an aggressive approach to their prevention and management.

The cranial base often is conceptually divided into three anatomic regions that are named for their intracranial relations to the overlying cranial fossae: anterior, middle, and posterior (Fig. 174-1). From a diagnostic and therapeutic point of view, it is useful to consider the anterior and middle cranial base regions together, for several reasons. They contribute to what is commonly referred to as the craniofacial junction, where the neurocranium and the viscerocranium meet (Fig. 174-2). Both share anatomic relationships with the orbits, the nasal airway, and the paranasal sinuses, and they are therefore affected by similar pathologic processes. The anterior and middle cranial base regions have traditionally been approached using craniofacial disassembly techniques, however, endoscopic approaches to the skull base have assumed a growing role in selected cases while minimizing surgical morbidity. Additionally, robotic-assisted surgery has been investigated and holds promise for the future of anterior and middle cranial base surgery. The posterior and lateral cranial base are clinically regarded as a separate region, often approached with combined neurotologic and neurosurgical approaches (Chapters 127, 173, 176, and 177). This chapter focuses on the surgical management of lesions that affect the anterior and middle cranial base.

Surgical Anatomy

Anterior Cranial Base

The anterior cranial base can be defined as that portion of the skull base adjacent to the anterior cranial fossa. It is bounded anteriorly by the frontal bone, which contains two surgically important structures: the frontal sinus and the supraorbital foramina (Fig. 174-3). The anatomy of the anterior cranial base is described in detail in Chapter 175, and briefly reviewed here. The supraorbital foramina, which may be incomplete (and therefore referred to as supraorbital notches), transmit the supraorbital nerves and vessels. These vessels supply the galea and the pericranium of the frontal region, and their preservation facilitates subsequent use in reconstructing anterior cranial base defects.

Superiorly, the anterior cranial base is formed by the frontal, ethmoid, and sphenoid bones (Fig. 174-4). An important visible land-

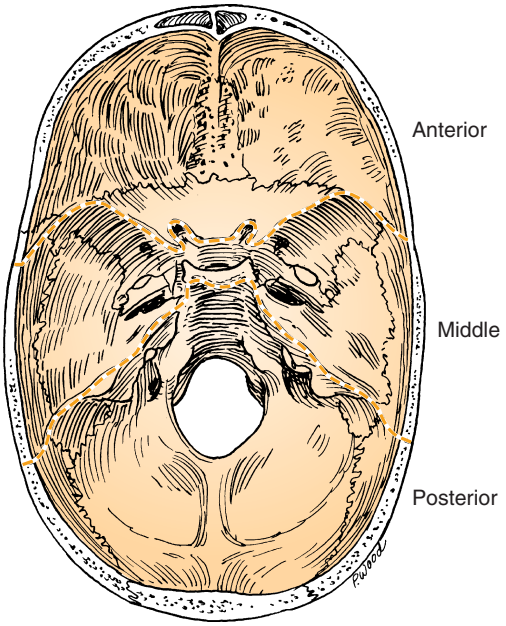

Figure 174-1. Intracranial view of cranial base showing boundaries of anterior, middle, and posterior divisions.

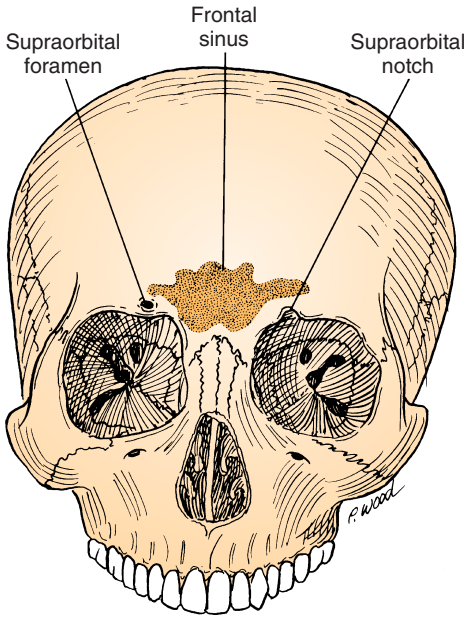

Figure 174-3. Anterior perspective of the anterior cranial base showing the outline of the frontal sinus *(shaded)* and the position of the supraorbital neurovascular pedicle exiting the supraorbital foramen *(left)* and the supraorbital notch *(right)*.

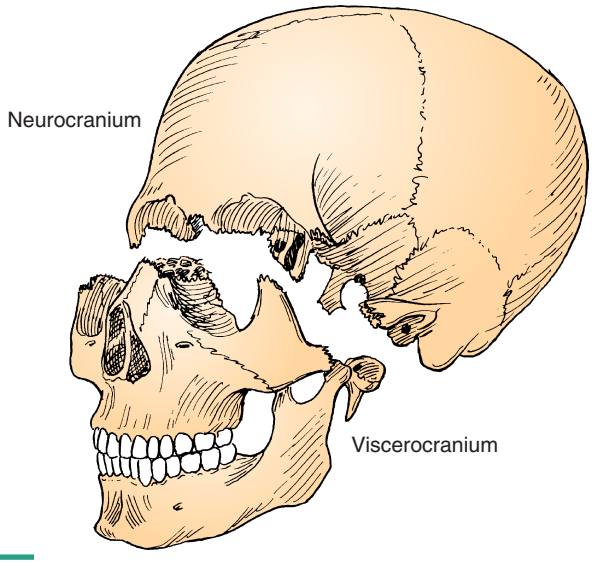

Figure 174-2. Disarticulated skull showing the junction of the neurocranium with the viscerocranium (craniofacial junction). The anterior cranial base forms the roof of the orbits and the nasal cavities, and the middle cranial base makes up the roof of the intratemporal fossa, the pterygopalatine fossa, and the nasopharynx. Operative approaches to the anterior and middle cranial base regions often traverse the viscerocranium.

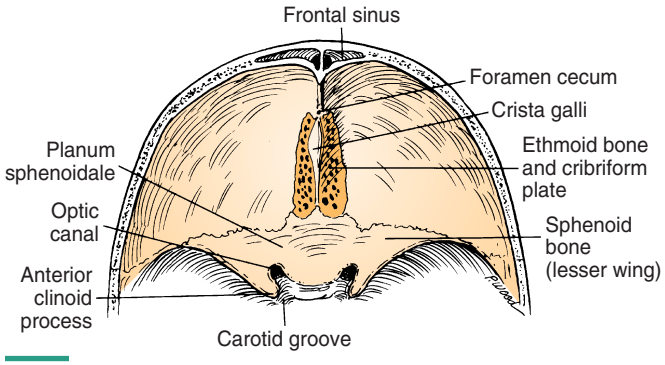

Figure 174-4. Intracranial view of the anterior cranial base and important landmarks.

mark is the foramen cecum, which is the site of a communication between veins of the nasal cavity and the origin of the superior sagittal sinus. The next landmark, the crista galli, protrudes upward from the midline to provide attachment for the falx cerebri. On either side of the crista are the openings of the cribriform plate, through which olfactory nerves are transmitted. Just posterior to the last of these olfactory foramina is a smooth-surfaced area known as the planum sphenoidale; it forms the roof of the sphenoid sinus when the sinus is well pneumatized. The anterior clinoid processes and lesser sphenoid wings delineate the most posterior limit of the anterior cranial base and delineate its boundary with the middle cranial base. Between and slightly below the clinoids are the optic canals and the internal carotid arteries (ICAs).

Extracranially, the anterior cranial base is related to the nasal cavity, the ethmoid and sphenoid sinuses, and the orbits (Fig. 174-5). The floor of the anterior cranial fossa is uneven, with the relatively flat orbital roofs sloping downward as they join the roof of the ethmoid sinuses medially. Thus, the ethmoid roof is lower than the orbital roof. The downward slope becomes even more exaggerated as the ethmoid roof joins the cribriform area (the roof of the nasal cavity), near the midline, which usually is the lowest point of the anterior skull base. The relative relationship of the height of the cribriform plate to the roof of the ethmoid is variable and has been classified by Keros into three categories: class 1, 1 to 3 mm; class 2, 4 to 7 mm; and class 3, 8 to 16 mm.[1]

This nonplanar arrangement of the cribriform area is important during transethmoid extracranial approaches to lesions of the anterior skull base. For example, an axial plane of dissection that is safe along the roof of the ethmoid may risk injury to the dura and frontal lobes if extended medially to encompass the cribriform plate territory.

The orbits contain several landmarks that can help surgical orientation during cranial base operations (Fig. 174-6). The superior orbital fissure transmits the oculomotor, trochlear, ophthalmic, and abducens

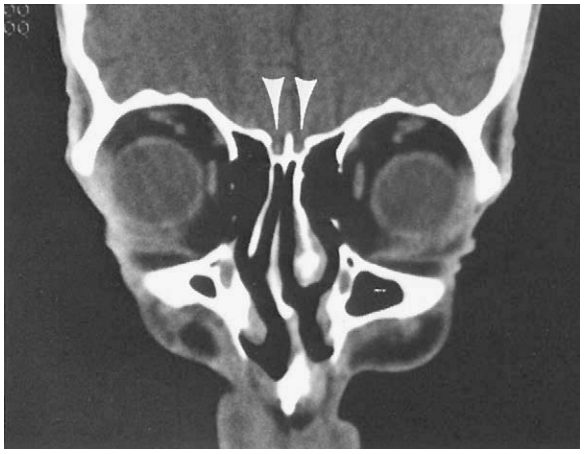

Figure 174-5. Coronal computed tomography scan through the anterior cranial fossa, orbits, and ethmoid region, showing the relationship of the anterior cranial fossa floor with the underlying orbits and sinuses. The cribriform area *(arrows)* is significantly lower than the ethmoid roof and the orbital roof. Extracranial approaches to this region should respect this anatomy to avoid injury to the dura and brain.

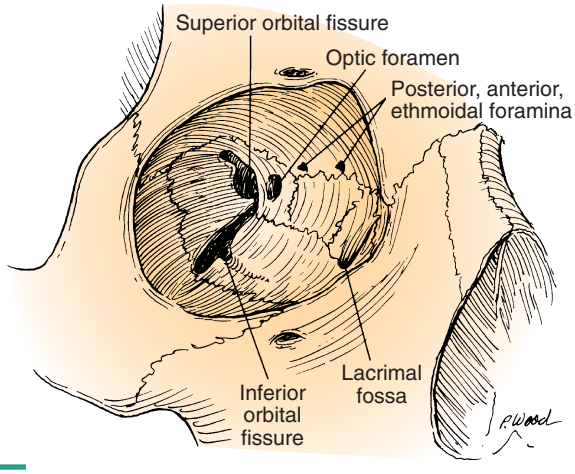

Figure 174-6. Important surgical landmarks of the orbital skeleton.

nerves (cranial nerves III, IV, V1, and VI) and the ophthalmic vein, and it communicates with the middle cranial fossa. The inferior orbital fissure contains the maxillary nerve (V2) and communicates primarily with the pterygopalatine fossa; the lateral end of this fissure is an important landmark for the placement of lateral orbital osteotomies. The optic canal transmits the optic nerve and the ophthalmic artery. The anterior and posterior arteries transmitted through ethmoid foramina should be controlled to reduce intraoperative bleeding in the nasal vault region. More important, these ethmoid foramina mark the position of the frontoethmoid suture line, a valuable guide to the level of the ethmoid roof and the anterior fossa floor. The posterior ethmoid foramen is of additional significance because of its consistent relationship with the optic canal, found 4 to 7 mm posteriorly.

Middle Cranial Base

The middle cranial base forms the floor of the middle cranial fossa. From the intracranial perspective (Fig. 174-7), the middle cranial base begins anteriorly at the posterior edge of the lesser sphenoid wing; posteriorly it ends at the posterosuperior edge of the petrous part of the temporal bone. The intracranial surface of the middle cranial base is formed by the greater wing and body of the sphenoid bone and the petrous and squamous portions of the temporal bone. As such, it forms the roof of the infratemporal fossa, middle ear, mastoid, and condylar fossa and the lateral wall of the sphenoid sinus.

Foramina along the floor of the middle fossa beginning anteriorly are the superior orbital fissure, optic canal, and foramen rotundum (representing the intracranial end of the inferior orbital fissure). Next, the foramen ovale delivers the mandibular nerve (V3) to the infratemporal fossa below, and the foramen spinosum transmits the middle meningeal artery.

The superomedial boundary of the middle cranial base is marked by the petrous part of the temporal bone containing the horizontal petrous ICA and the foramen lacerum. This foramen receives the greater superficial petrosal nerve (GSPN) (parasympathetic fibers from the facial nerve to the lacrimal gland) and conducts it to the pterygopalatine fossa inferiorly. Recognition of this relationship among the GSPN, the foramen lacerum, and the carotid canal often is helpful during surgery because the GSPN, which is readily identifiable, can be followed medially to the distal petrous ICA.

From an extracranial viewpoint, the middle cranial base extends from the posterolateral walls of the maxillary sinuses anteriorly to the petro-occipital sutures posteriorly (Fig. 174-8). It is formed by the greater wing and body of the sphenoid bone and by the temporal bone, including the condylar fossa. As on its intracranial surface, this region also contains numerous openings for major nerves and blood vessels, including the foramina ovale, spinosum, and lacerum and the stylomastoid foramen (cranial nerve VII), the jugular foramen (internal jugular vein, inferior petrosal sinus, cranial nerves IX, X, and XI), and the carotid canal (entrance of ICA into the temporal bone).

Operative approaches in this region often traverse the infratemporal fossa. Here, the muscles of mastication—the temporalis, masseter, and medial and lateral pterygoids—receive their blood supply from branches of the internal maxillary artery, which should be preserved if, for example, the versatile temporalis muscle is to be used as a flap for reconstruction. Both the lateral and medial pterygoid muscles originate in part from the lateral pterygoid plate (of the sphenoid bone), which serves as an excellent landmark owing to the following features: (1) it is a palpable guide for surgical orientation; (2) it can be easily exposed by dissection carried out medially along the greater sphenoid wing; and (3) it is easily identified on radiographic imaging studies, especially computed tomography (CT). The root of this lateral pterygoid plate is situated immediately posterior to the foramen rotundum and anterior to the foramen ovale. It can be used as an index to the positions of the maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve (Fig. 174-9). After the foramen ovale is identified, the foramen spinosum (transmitting the middle meningeal artery) will be found just posterior to it. This leads to the next critical landmark: the spine of the sphenoid.

The sphenoid spine, which is situated just medial to the condylar fossa, serves as a palpable, radiographically identifiable landmark that is important because of its location immediately lateral to the carotid canal (see Fig. 174-8). It helps the surgeon locate the highest portion of the cervical ICA, which can be followed distally to expose and mobilize the petrous ICA. Because the sphenoid spine is just medial to the condylar fossa, the mandibular condyle often is displaced anteroinferiorly or resected to enhance exposure of the ICA as it enters the cranial base.

A thorough and detailed understanding of the regional anatomy of the cranial base is best achieved through the correlative study of dry skulls, cadaveric dissections, and radiographic images.

Preoperative Considerations

The principles of the clinical evaluation of presenting symptoms and physical findings (Chapter 175) and diagnostic imaging[2] (Chapter 135) are considered in detail elsewhere in this book.

Angiography

In many cases, it is important to have information about the vascularity of a given cranial base lesion and the possible involvement of major neighboring blood vessels. For this reason, cerebral angiography often is part of the diagnostic imaging sequence. This type of angiography permits the identification of the blood supply to the lesion and its own vascular pattern while simultaneously clarifying whether the ICA or other major vessels are compromised.

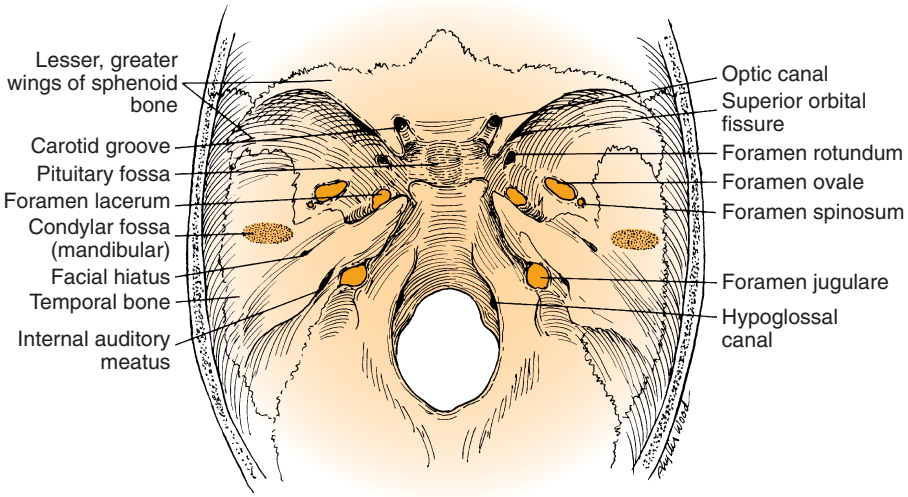

Figure 174-7. Intracranial view of the middle cranial base.

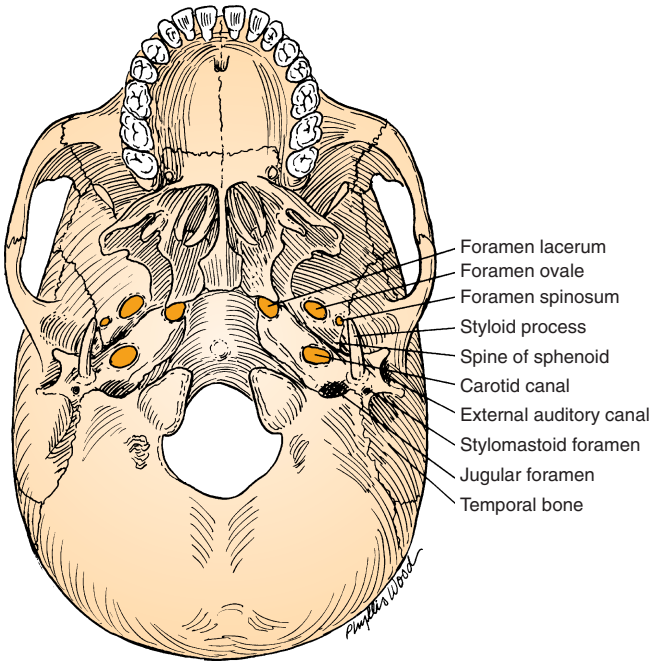

Figure 174-8. Extracranial aspect of the middle cranial base.

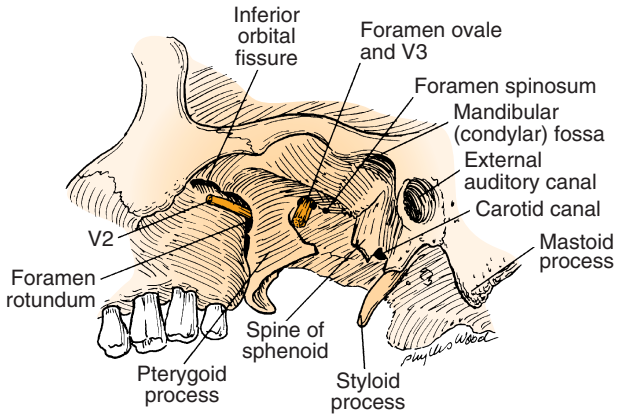

Figure 174-9. Lateral view of the pterygoid process of the sphenoid bone (pterygoid plate), showing the relationship of the foramina rotundum and ovale with associated structures. V2, maxillary nerve; V3, mandibular nerve.

Angiography also gives anatomic information about the integrity of the circle of Willis, existing collateral circulation to the cerebral hemispheres, and other possible anomalous blood supply patterns that may dictate the approach or prudent use of embolization.[3]

Angiography alone, however, does not give sufficient physiologic information about the adequacy of the circle of Willis or other collaterals with regard to supplying circulation to the brain.[4] To obtain detailed physiologic information, cerebral blood flow studies are performed.

Computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and three-dimensional reconstructive technology have added relatively noninvasive options and adjuncts to conventional imaging and angiographic methods. One drawback to these modalities is the inability to incorporate interventional techniques including balloon occlusion and embolization as preoperative workup and adjunctive procedures (as discussed next).

Cerebral Blood Flow Evaluation

If a cranial base lesion involves or impinges on the ICA or if it will be necessary to manipulate the ICA during surgery, cerebral blood flow studies should be considered. These studies give a physiologic index of the adequacy of the circulation to the brain in a quantitative way and are useful for predicting whether a patient can tolerate occlusion of the ICA without major neurologic consequence.[5-8]

The test begins with a temporary occlusion of the ICA by means of a balloon-tipped catheter inflated within the vessel. The catheter is placed percutaneously through the femoral artery and guided into the cervical portion of the ICA under fluoroscopic control, just as is done for routine cerebral angiography. This is performed with the patient awake, and serial neurologic assessments are done during the 15-minute ICA occlusion. If a neurologic deficit develops during this part of the test, occlusion is immediately discontinued. A patient demonstrating such a deficit is considered to have failed the test and is presumed to be highly dependent on the flow in that ICA; thus, the risk for stroke is increased if the carotid is compromised at surgery. If the patient tolerates 15 minutes of ICA occlusion without the development of neurologic deficit, further study uses a quantitative test in which stable xenon gas is inhaled. The inhaled xenon is distributed throughout the circulation and into the brain, where it is visible on CT scanning; this gives a picture of cerebral blood flow distribution (Fig. 174-10). This xenon-enhanced CT scan is performed with the balloon inflated and deflated in the ICA. The uptake of xenon within both cerebral hemispheres is quantitated using the digitized data from the CT scan (when xenon CT is not available, single-photon emission computed tomography [SPECT] imaging can give similar blood flow imaging, although it is not quantitative).

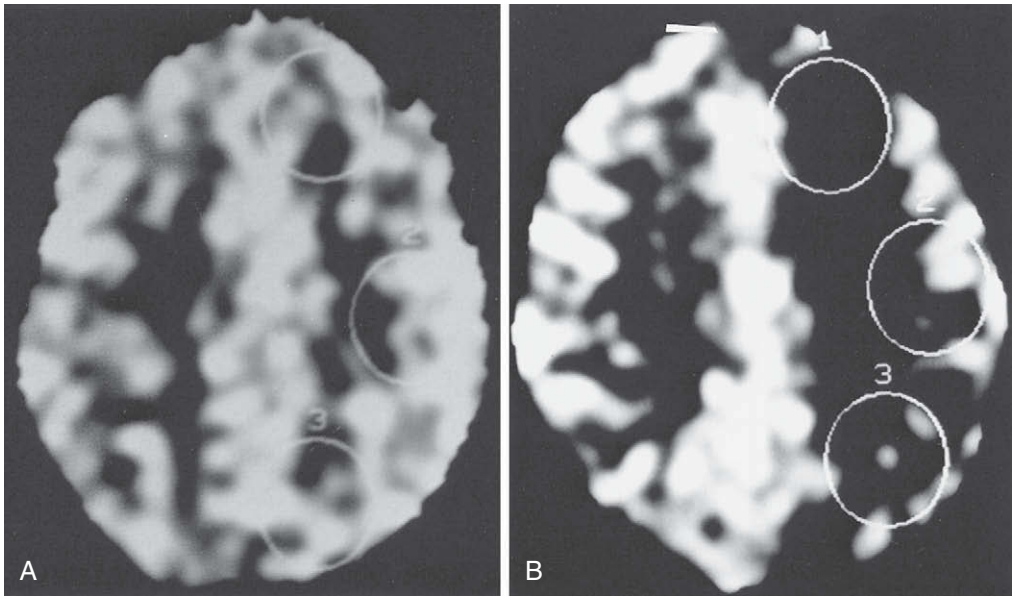

Figure 174-10. Axial slices, xenon-enhanced computed tomography scan through the level of the cerebral hemispheres. **A,** Normal cerebral blood flow distribution with symmetrical bilateral xenon uptake (*dark areas* within each hemisphere represent lateral ventricles). **B,** Significantly decreased hemispheric xenon uptake (on the right side of photograph) after inflation of a balloon within the ipsilateral internal carotid artery. From these xenon studies, cerebral blood flow in specific regions of interest *(circles)* can be quantitated. Such information is useful for predicting the patient's ability to tolerate occlusion of the internal carotid artery at surgery.

The patient who has a significant ipsilateral decrease in hemispheric xenon uptake during ICA occlusion (despite no clinically apparent neurologic deficit during the test) is considered to be at moderate risk for the development of neurologic sequelae should the ICA be occluded during surgery. Such patients would be candidates for extracranial-to-intracranial arterial bypass to enhance the intracranial circulation. Patients who have no drop in xenon uptake during balloon occlusion of the ICA are believed to be at low risk for postoperative stroke, even if the ICA is resected or permanently occluded.

Preoperative Embolization

Another advantage of preoperative angiography is the possibility for elective embolization of vascular tumor beds to help reduce intraoperative bleeding. In addition, the ICA may be electively embolized using detachable intra-arterial permanent balloons if the decision is made preoperatively that the ICA will have to be sacrificed. This is sometimes done to permit the resection of malignant tumors. These procedures are considered in more detail in Chapter 136.

Other Evaluations

For lesions near the orbits, visual acuity should be assessed quantitatively and measurements of the visual fields performed. For lesions near the temporal bone, audiologic and vestibular testing, electronystagmography, and facial electromyography (EMG) should be performed as indicated. These evaluations may help to uncover and quantify cranial nerve dysfunction in some patients. It may also help predict the degree of postoperative cranial nerve morbidity.

For lesions near the pituitary fossa, a complete endocrine evaluation should be performed. It is especially important to identify patients who preoperatively have syndrome of inappropriate antidiuretic hormone, diabetes insipidus, or hypothyroidism, because these conditions can lead to postoperative morbidity if not corrected. Also, abnormal levels of prolactin, growth hormone, or gonadotropins may be of diagnostic significance as indicators of tumors of the pituitary gland. Metastatic workup is conducted in patients with specific malignant tumors.

Pathology and Management Planning

Many disorders can affect the cranial base. Disorders in which surgery has played a significant therapeutic role include basicranial trauma; craniofacial anomalies; congenital syndromes (e.g., hypertelorism, Crouzon's syndrome); spontaneous cerebrospinal fluid fistulas; vascular problems (e.g., petrous carotid artery aneurysms); infectious diseases (e.g., petrositis, malignant external otitis); and neoplasms. Perhaps the widest acceptance and application of cranial base surgery has been in the management of neoplasms, in which the effectiveness of other modalities is limited.

Benign tumors and related lesions affecting the skull base have been reviewed by several authors and are summarized in Box 174-1.[9-11] In general, benign cranial base neoplasms are managed surgically. The surgical technique often involves "piecemeal" removal, with careful progression from one surgical landmark to the next, to permit the maximal preservation of functionally important structures. For larger tumors or those for which removal carries a high risk of damage to neighboring structures, incomplete resection with postoperative irradiation may be indicated.[12]

Malignant skull base lesions are listed in Box 174-2.[10] With some notable exceptions (i.e., leukemia, lymphoma, myeloma, metastases), malignant neoplasms are managed surgically, although in most cases surgery will not be used as the sole modality. Adjuvant management with radiation (by external beam, implantation, or brachytherapy) or chemotherapy is usually included in the therapeutic plan. Single-modality radiation therapy, including sterotactic radiotherapy, has been recommended by some investigators for certain smaller lesions.[13] Malignant lesions are surgically removed en bloc, with margins of uninvolved tissue after broad circumferential exposure whenever possible.[14]

When surgery is considered for tumors and tumor-like disorders of the cranial base, the first question that should be answered involves the biologic behavior of the lesion. As mentioned, an accurate clinical diagnosis often can be made on the basis of information obtained from the history, physical examination, and imaging studies. Whenever possible, this should be supplemented by a histologic diagnosis before definitive management is carried out.

When tumor is present within the nose, paranasal sinuses, middle ear, mastoid, oral cavity, pharynx, or neck, direct biopsy can be performed using standard techniques. When direct biopsy is not feasible, CT-guided needle biopsy may be done in selected cases (e.g., tumors of the infratemporal fossa). Occasionally a tumor may be inaccessible by either of these routes, or biopsy without adequate skull base exposure may be judged to be unsafe because of concerns about injury to nearby

Box 174-1

Benign Lesions of the Skull Base

Extracranial
Inverted papilloma
Angiofibroma
Salivary gland tumor
Paraganglioma (glomus)
Mucocele
Cholesteatoma

Intracranial
Pituitary adenoma
Craniopharyngioma
Meningioma
Schwannoma
Aneurysm
Arteriovenous malformation

Primary Basicranial
Fibrous dysplasia
Osteoma
Osteoblastoma
Chondroma
Chordoma*
Congenital
Cholesteatoma
Dermoid
Encephalocele

*Histologically benign but clinically malignant behavior.
Modified with permission from Dickins JRE. Approach to diagnosis of skull base lesions. *Am J Otol*. 1981;3:35.

Box 174-2

Malignant Lesions of the Skull Base

Extracranial
Squamous cell carcinoma
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Malignant mixed tumor
Leukemia
Lymphoma
Rhabdomyosarcoma
Neurogenic sarcoma
Undifferentiated carcinoma
Hemangiopericytoma
Synovial sarcoma
Adenocarcinoma
Basal cell carcinoma

Intracranial
Esthesioneuroblastoma
Malignant schwannoma

Primary Basicranial
Chondrosarcoma
Osteogenic sarcoma
Multiple myeloma
Histiocytosis X
Chordoma*

Metastatic
Breast
Lung
Kidney
Prostate
Melanoma

*Histologically benign but clinically malignant behavior.
Modified with permission from Dickins JRE. Approach to diagnosis of skull base lesions. *Am J Otol*. 1981;3:35.

critical structures or because of vascularity of the lesion. In these situations, the surgeon should proceed with an operative approach to the skull base that is designed to provide access to the tumor for safe biopsy before any irreversible ablative steps are taken. Then, if the frozen-section biopsy result contraindicates resection or is questionable, an alternative management plan may be made. On the basis of histologic criteria, extirpative surgery is usually not performed when one of the following conditions is present: (1) a malignant lesion is metastatic from a distant source; or (2) a malignancy is of a type that responds well to other management modalities (e.g., lymphoma).

Anesthesia

Anesthetic management is crucial for determining the outcome of cranial base operations. Techniques of neuroanesthesia are used, with the primary goals of maximal neuronal preservation and simultaneous facilitation of a controlled surgical environment.[15] Maintenance of hemodynamic factors is key in this scheme, because cerebral blood flow cannot be allowed to drop below critical levels for any significant length of time. Thus, close monitoring of arterial pressure, central venous pressure, cardiac function, and urine output is of paramount importance.

Electrophysiologic monitoring, including somatosensory-evoked potentials to assess cortical function and EMG to assess motor cranial nerve function, is another key element for the achievement of neuronal preservation. Appropriate selection of anesthetic agents and limited use of neuromuscular blocking drugs will enhance the reliability of such monitoring.

Cerebral edema, which is a common problem in intracranial surgery, can be minimized with the intraoperative use of colloids (albumin, plasma) rather than crystalloid fluids. It can be minimized by controlled hyperventilation, which, by virtue of decreasing arterial carbon dioxide tension (P_{CO_2}), causes mild cerebral vasoconstriction and a corresponding reduction in intracranial volume. Generally, P_{CO_2} between 25 and 30 mm Hg is desirable for this purpose. Lower arterial CO_2 levels significantly reduce cerebral perfusion and are not recommended. Another technique that is helpful for reducing brain swelling is the preoperative placement of an indwelling lumbar drain, which decompresses the subarachnoid space by removing cerebrospinal fluid (CSF). Lumbar drains also are important postoperatively in selected cases, because short-term CSF decompression can decrease the possibility of CSF fistula formation. Such drains are not used in patients who have major intracranial space-occupying lesions because of the risk of brainstem herniation. Cerebral edema may be lessened with timely use of corticosteroids and diuretics, an especially helpful adjunct if edema is present preoperatively as a result of a mass lesion.

The anesthesia team also is responsible for the infusion of blood products to replenish surgical blood loss, which can be considerable in some cranial base procedures. Dilutional thrombocytopenia and other coagulopathies can occur after multiple transfusions of stored blood. These problems can be successfully managed with the replacement of clotting factors (in the form of fresh-frozen plasma) and platelets in proportion with erythrocyte transfusion. Related issues include the advance donation of autologous blood for transfusion and the use of "cell saver" devices to collect blood intraoperatively and reinfuse it. With concerns surrounding blood transfusion–related infectious diseases, these techniques are becoming increasingly important. One limitation of the cell salvage technique is that it should not be used when there is a risk of reinfusing tumor cells from the operative field.

The anesthesiologist is essential to the success of surgery for cranial base lesions. Optimal anesthetic management depends on close communication between the anesthesiologist and the surgeon before, during, and after the operation.

Operative Techniques

General Considerations

As the field of skull base surgery has evolved, more and more lesions previously thought to be unreachable or unresectable are now able to be addressed surgically. The contraindications to skull base surgery for malignancy as outlined by Donald[16] include anatomic, tumor, and patient factors. Absolute anatomic contraindications include involvement of the brain stem, portions of the cerebrum, superior sagittal sinus, both internal carotid arteries, both cavernous sinuses and certain vital bridging veins. Tumor factors representing contraindications to resection usually include distant metastic disease; although some authors advocate significantly prolonged survival in those with isolated distant metastases after resection of the primary tumor, this has not been well demonstrated in skull base tumors. Certain malignancies typically display aggressive behavior despite treatment, which must be considered before extensive resection. Patients should be well informed and motivated and without medical contraindications to the operation as well.[16]

Overview of Approaches

Surgical treatment of lesions involving the anterior skull base, nasal cavity, and paranasal sinuses has evolved into a single category of craniofacial approaches. A myriad of surgical approaches have been developed for exposure of the anterior and middle cranial base regions; these range from purely intracranial to purely extracranial. However, most approaches for dealing with lesions of the skull base use combined intracranial and extracranial methods. For anterior cranial base lesions, the most commonly used approaches combine frontal craniotomy with some form of transfacial (transnasal, transmaxillary, or transorbital) exposure. Most commonly, a team of neurosurgeons and otolaryngologists performs this procedure resulting in a bifrontal craniotomy from above and a transfacial approach from below. The transfacial approach often involves midfacial degloving, and facial disassembly, requiring facial incisions and facial osteotomies. Lateral rhinotomy, removal of the frontonasal unit, Le Fort I and II osteotomies, and splitting of the maxilla have been described as means of accessing lesions of the anterior cranial base. Janecka and coworkers[17] described the facial translocation approach, which also involves an extensive facial incision and facial disassembly for access to tumors in the anterior cranial base, cavernous sinus, clivus, and infratemporal fossa.

Since the 1990s, endoscopic sinus surgery has virtually replaced the conventional open techniques used by otolaryngologists in treating sinonasal disorders and is discussed in detail in Chapter 175. Use of the endoscope as a supplement to the surgical approaches can alleviate the need for some facial incisions by allowing the surgeon to observe areas hidden from the field of view of the microscope. For those tumors that invade the anterior cranial base, the endoscope may be utilized as an adjunct to the standard bifrontal craniotomy by allowing visualization of paranasal extension into the sphenoid, ethmoid, frontal, and maxillary sinuses. From nasal or maxillary portals, the endoscope allows visualization of all of the paranasal sinuses. As the technology of endoscope optics and video systems improves, the role of endoscopic cranial base surgery will augment and supplement current microsurgical techniques. Intraorbital lesions may be approached by frontal craniotomy or subcranial approaches, often combined with transfacial approaches.[18]

For middle cranial base lesions, access is most often provided by combining temporal or frontotemporal craniotomy with infratemporal fossa dissection, transfacial exposure, or transtemporal techniques. In addition, endoscope-assisted and image-guided navigational approaches are increasingly being applied (see Chapter 177). In anterior and middle cranial base approaches, craniofacial disassembly techniques have been widely used.

Implicit in the term *craniofacial disassembly* is the concept of the systematic, stepwise dissection of cranial and facial soft tissues on the basis of the knowledge of regional vascular territories and functional anatomy, followed by osteotomies and dismantling of the craniofacial skeleton. Some of these techniques, which were developed originally by plastic and reconstructive surgeons for the correction of congenital craniofacial deformities, are of major importance in cranial base surgery, because they allow wide exposure of the skull base through temporary displacement of the viscerocranium.[19,20] The enhanced exposure of the skull base from below the neuraxis significantly reduces the need for brain retraction and therefore helps minimize postoperative neurologic dysfunction. It also allows the surgeon greater oncologic precision during the extirpative phase, with preservation of the functional and aesthetic units of the face for reconstruction.[58]

Box 174-3

Goals of Cranial Base Surgery

1. Extirpation of disease
2. Protection of vital structures
3. Restoration of critical anatomic barriers
4. Functional and aesthetic reconstruction

Planning the Operative Approach

Whether the surgery is being performed for a benign tumor, a malignancy, or other indications (e.g., inflammatory or vascular lesions, CSF fistula), the approach should be planned and executed to accomplish the four specific goals that are applicable to all cranial base operations, summarized in Box 174-3.

GOAL 1. The approach should provide adequate exposure to allow extirpation of the disease process. To a large extent, the degree of needed exposure is based on information obtained from the physical examination and imaging studies.

GOAL 2. The approach should be designed to protect critical structures near the lesion. Traditionally, the safest way to protect critical structures has been to achieve surgical access beyond the boundaries of the lesion itself to allow for direct visualization and control over the structures of interest. For example, surgical exposure around a tumor would be broadened to identify, dissect, and perhaps displace nearby cranial nerves or the carotid artery. Although obtaining this additional exposure may increase the operative time, it can be a major factor in the reduction of postoperative morbidity.

More recently, the introduction and increased application of two major technical advances have given the surgeon additional options for the protection of critical structures, often without the need for increased surgical exposure: image-guided computer-assisted surgery and endoscopic surgery.

Image-guided (stereotactic) computer-assisted surgery has become a very useful alternative—or adjunct—to wide surgical exposure in selected cases.[21-26] Such "navigational surgery" employs one of a variety of referencing systems that can assimilate preoperative imaging studies into a computer-based algorithm that allows image reformatting in three dimensions (The preoperative reference images may be CT- or magnetic resonance imaging [MRI]-based, or they may be a "fusion study" that takes advantage of both types of studies). The reformatted images then serve as the basis for intraoperative navigation, which involves the use of an interactive probe that transmits spatial-orientation information back to the computer via transmitters; these can be either electromagnetic or optical. The computer screen then displays the appropriate preoperative images with the location of the probe superimposed, thus "targeting" the area of interest (Figure 174-11). With navigational systems, structures that are anatomically fixed (i.e., orbital walls, carotid canal, optic canal) can be precisely located, and the risk of injury can be minimized.

Reported uses of image-guided surgery include primary and revision endoscopic sinus surgery, osteoplastic frontal sinusotomy, transsphenoidal hypophysectomy, endoscopic cerebrospinal fluid leak and encephalocele or meningocele repair, endoscopic skull base tumor resection, orbital surgery, and endoscopic pterygomaxillary fossa biopsy.[27,28]

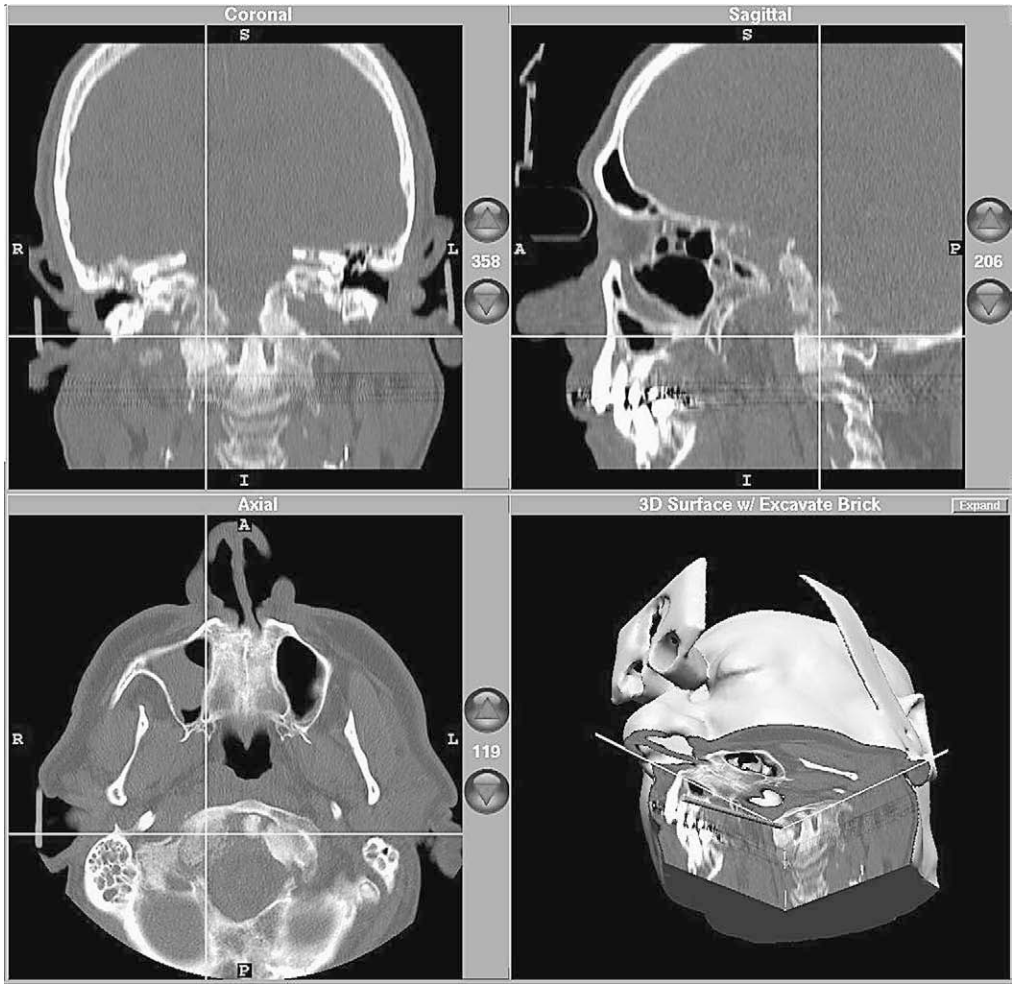

Figure 174-11. Navigational images as seen on intraoperative computer display. The patient's computed tomography images are displayed in the coronal *(top left)*, axial *(bottom left)*, and sagittal *(top right)* planes, and a three-dimensional cutaway view *(bottom right)* also is shown. On each image, the intersection of the crosshairs indicates the position of the navigational probe. As the probe is moved within the operative field, the images change to reflect the probe's precise location. In this case, a lesion that was both osteoblastic and osteolytic and that involved the occipital condyle was approached endoscopically through the nasal cavity without the need for an extensive disassembly approach. The lesion turned out to be a metastasis from a previous renal cell carcinoma.

The American Academy of Otolaryngology–Head and Neck Surgery endorses use of computer-aided surgery for the following specific procedures or conditions[29]:

- Revision sinus surgery
- Distorted sinus anatomy of development, postoperative, or traumatic origin
- Extensive sinonasal polyposis
- Pathology involving the frontal, posterior ethmoid, and sphenoid sinuses
- Disease abutting the skull base, orbit, optic nerve, or carotid artery
- CSF rhinorrhea or conditions that feature a skull base defect
- Benign and malignant sinonasal neoplasms

Intraoperative MRI or CT also has been proposed as a useful adjunct in skull base surgery. Proponents advocate the improved ability to detect residual tumor and evaluate for intraoperative complications, however, limitations of time and cost have prevented its widespread use outside of certain academic centers.[30]

Although large, multi-institutional prospective studies are yet to be accomplished, smaller studies and anecdotal reports demonstrate the efficacy of endoscope-assisted approaches for the treatment of selected skull base problems, most notably sinonasal neoplasms, pituitary tumors, and CSF leaks.[31-37]

Stamm[38] classifies endoscopic skull base approaches as follows:

1. Transnasal direct
2. Transethmoidal
3. Transseptal
4. Transplanum
5. Transsphenoidal-transpterygoid
6. Transsphenoidal-transclival
7. Transnasal-transpharyngeal (cranial-cervical junction)
8. Combined

The location and suspected pathology dictate the selection of approach.

Endoscopy-based approaches to the nasal cavity, olfactory groove, nasopharynx, ethmoid roof (anterior skull base), orbit and orbital apex, sphenoid sinus and sellar and parasellar areas, clivus, cavernous sinus, optic chiasm, pterygopalatine and infratemporal fossae, parapharyngeal space, craniocervical junction, petrous apex, and jugular foramen all have been described. In short, access to the central skull base from the frontal sinus to C2 and from the sella to the jugular foramen is now possible using the expanded endonasal approach.[39-43]

The endoscopic approach to the orbital apex and optic canal for orbital decompression in fibrous dysplasia, Graves' orbitopathy, compressive or traumatic optic neuropathy has been described. Of note, decompression is indicated only in patients with fibrous dysplasia with continuous deterioration of vision or undergoing removal of neighboring bone, but not as a prophylactic procedure.[44,45] This approach also is used in the management of clival lesions, anterior skull base tumors, and vascular malformations of the skull base.[46,47]

Kassam and associates described an approach to identify the petrous portion of the carotid artery following identification and retrograde dissection of the vidian artery. They found this to be a consistent landmark radiographically and intraoperatively.[48]

Endoscopic approaches to pituitary surgery offer benefits of improved cosmesis, decreased recovery time, and fewer complications. Three approaches exist: transnasal-transethmoid, transnasal-transseptal, and direct transnasal. The direct transnasal approach has been touted because of the advantages of avoiding the ethmoid complex, decreased operative time, and improved visualization.[2] Although endoscopic skull base surgery has been more extensively described for the anterior cranial base, endoscopic-assisted approaches to the middle cranial base also have been described.[49]

The protection of critical structures at the cranial base also is enhanced by the appropriate use of electrophysiologic monitoring, including intraoperative somatosensory evoked potentials, auditory brainstem evoked response, and EMG.[14] The injection of low-dose intrathecal fluorescein has been shown to be a useful adjunct intraoperatively to decrease the CSF leak rate and, when appropriate medication is provided, has been proven safe and without significant adverse effects.[50]

GOAL 3. The approach should be designed so that, at the completion of the extirpative phase, critical barriers between the neurocranium and viscerocranium can be reliably restored. These barriers, particularly the dura and subjacent soft tissues, normally serve to effectively insulate the intracranial contents and the ICA from exposure to the aerodigestive tract below, including the nasal cavity, sinuses, eustachian tube, and pneumatic spaces within the temporal bone. After they have been disturbed, the barriers should be restored to reduce the potential for such consequences as CSF fistula, meningitis, and septic carotid artery rupture. Also, an approach should respect the vascular territories of local tissues (i.e., the temporalis muscle, galea, and pericranium), which can then be used for the reconstruction.

Such vascularized local flaps are preferable to free flaps or nonvascularized grafts when available, however others have displayed excellent closure rates with materials ranging from acellular dermis to free microvascular transfers.[51,52] In general, smaller defects (less than 2 cm) are less likely to require vascularized tissue to achieve closure.[53,54]

Robotic endoscopic skull base surgery and transoral robotic surgery have been advocated by some researchers for the advantages of improved visualization, access, precise technique, and improved watertight closure following endoscopic skull base surgery. Although promising, more clinical investigation is needed before widespread acceptance of these techniques.[55,56]

GOAL 4. The choice of operative approach should reflect consideration for functional and aesthetic reconstruction, and it should include the placement of incisions within natural skin lines that respect aesthetic units of the face. The soft tissue closure should follow plastic surgery principles. Excellent skull base exposure usually can be achieved by elective osteotomies and the temporary removal of craniofacial bone segments, which are subsequently replaced, thereby preserving facial contour.[17,51,57-59] Even in cases in which aesthetically important segments should be removed for oncologic reasons, acceptable cosmesis can usually be accomplished through the judicious use of bone grafts and soft tissue flaps or through surgical closures designed to support alloplastic or prosthetic materials.

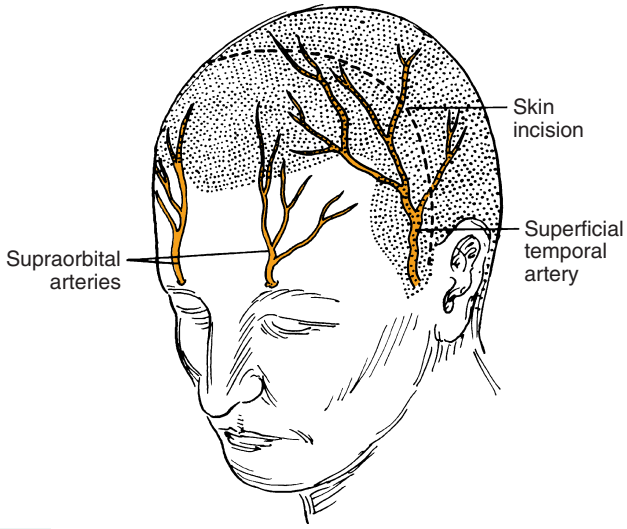

Figure 174-12. Bicoronal incision shown from the patient's left and demonstrating proper placement to allow for preservation of anterior branches of the superficial temporal artery. This incision design permits the use of a long pericranial or galeal flap (based on supraorbital vessels), which is important for the reconstruction of anterior cranial base defects.

Anterior Cranial Base Approaches

Surgical approaches to the anterior cranial base include methods that are purely extracranial and those that use combined extra- and intracranial exposures. The extracranial techniques—external ethmoidectomy, frontal sinusotomy, and intranasal ethmoidectomy—are suitable only for the management of discrete, well-localized lesions, such as CSF fistulas and some very limited benign anterior cranial base tumors. These procedures are well described elsewhere.[60,61]

Most of the remaining anterior cranial base lesions are best managed using the combined intracranial and extracranial techniques, of which there are basically two types: the classic anterior craniofacial resection and the basal subfrontal approach. Both of these approaches require bifrontal craniotomy for obtaining intracranial exposure. Except in special circumstances (e.g., in the presence of scars from previous surgery or trauma), the most utilitarian incision for surgery of the anterior cranial base is the bicoronal incision.

Technical Note: The Bicoronal Incision

The bicoronal incision should be in the true coronal plane at the level of the top of the helix of the ear or slightly anterior to it (Fig. 174-12). A short, forward-directed, preauricular extension can be made on both sides to enhance scalp flap rotation. This coronal placement of the incision preserves the anterior branches of the superficial temporal artery, enhancing viability of the scalp flap. In addition, it substantially increases the length of vascularized galea and pericranium available for reconstruction as compared with incisions along the anterior hairline, the midforehead crease, or the brow. Additional length can be gained by back-elevating the scalp flap before division and elevation of the pericranial flap.

The central portion of the anterior scalp flap (i.e., the portion between the two superior temporal lines) is elevated in the subgaleal plane if a pericranial flap may be used and in the subperiosteal (subpericranial) plane if not. Lateral to the two superior temporal lines, it is elevated in the plane just above the deep temporal fascia. Therefore, at the temporal lines, the pericranium should be sharply incised to separate it from the origin of the deep temporal fascia (see Fig. 174-15). The pericranium is divided far enough posteriorly to provide sufficient

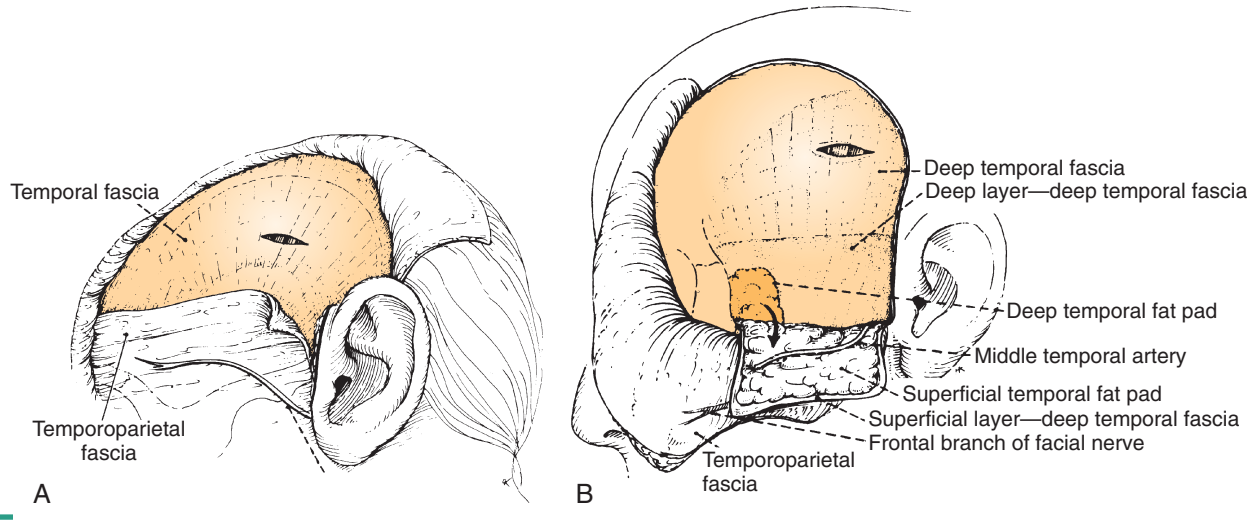

Figure 174-13. Relationship of the frontal branch of the facial nerve to layers of the temporal fascia. **A,** Anatomic dissection showing superficial temporal fascia (temporoparietal fascia), through which the nerve courses; attempts at surgery to elevate this relatively thin fascial layer alone may injure the nerve. **B,** Surgical dissection showing a deeper plane of fascial elevation that is less likely to cause injury to the frontal branch of the facial nerve. *(From Stuzin JM, Wagstrom L, Kawamoto HK, Wolfe SA. Anatomy of the frontal branch of the facial nerve: the significance of the temporal fat pad.* Plast Reconstr Surg. *1989;83:265-271.)*

length to the flap; then the dissection is carried forward in the subperiosteal plane as described earlier.

This deep temporal fascia begins to split into superficial and deep layers, beginning at approximately the level of the superior orbital rim.[62] These fascial layers diverge to envelop the lateral and medial surfaces of the zygomatic arch inferiorly; between the layers is the temporal fat pad. The frontal (temporal) branches of the facial nerve course just superficial to the zygoma along the superficial temporal fascia (temporoparietal fascia) and are prone to injury if the dissection is done at that level (Fig. 174-13A). Often these injuries can be avoided by maintaining the plane of dissection at the level of the deep layer of the deep temporal fascia (i.e., at the surface of the temporalis muscle itself). This deep plane of exposure essentially elevates the fat pad along with the superficial fascia and the superficial layer of the deep temporal fascia, thereby protecting the facial nerve branches (see Fig. 174-13B).[63,64] After the dissection reaches the level of the zygomatic arch, the arch is palpated, and its superior surface is directly exposed by sharply incising the fat pad and periosteum.

Further medially, flap elevation proceeds down the frontal area toward the supraorbital rims. Care should be taken to preserve the supraorbital supply of the galea and pericranium. This is best performed with elevation of the supraorbital rim periosteum that begins laterally and proceeds medially. A fine elevator is used first to palpate the supraorbital foramen (or notch) and then to expose its margins. If the pedicle is completely surrounded by bone, a 3-mm osteotome is used to fracture the inferior margin of the foramen, thereby liberating the pedicle and allowing it to be elevated intact, along with the remaining pericranium and underlying periorbita (Fig. 174-14). If the entire scalp flap is difficult to rotate inferiorly, the preauricular parts of the incision can be extended to as low as the tragus (without danger to the facial nerve trunk) or anteriorly (as far as the temporal hairline) to further enhance flap rotation.

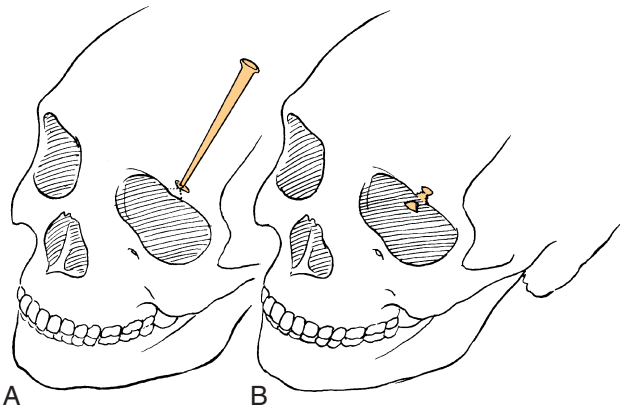

Figure 174-14. Technique for preserving the supraorbital neurovascular pedicle. **A,** After the foramen has been identified, a 3-mm osteotome is inserted along its lower border. **B,** A small segment of bone along the inferior rim of the foramen is fractured to liberate the nerve and vessels, which are reflected downward, along with soft tissues of the bicoronal flap.

Anterior Craniofacial Resection

Anterior craniofacial resection (Fig. 174-15) combines bifrontal craniotomy with transfacial exposure of the nasal cavity, ethmoid, maxillary, and orbital areas, usually by modifications of lateral rhinotomy, midfacial degloving, or other transfacial approaches.[65-67] Anterior craniofacial resection most often is used for removal of neoplasms that originate in the sinonasal tract and invade the anterior cranial fossa floor, such as squamous cell carcinoma, esthesioneuroblastoma, and adenocarcinoma. For cases in which tumor frankly invades the soft tissues of the orbit, the approach is extended to include orbital exenteration.[68]

The operation begins with transfacial exposure, which is followed by bifrontal craniotomy performed by the neurosurgeon. If the patient has a large frontal sinus, an osteoplastic flap may be elevated to avoid burr holes in the forehead area, which could later become aesthetically unsatisfactory. In such cases, the thin posterior table of the frontal sinus is opened with a diamond burr to expose the dura and then removed. If the frontal sinus is small, a frontal bone flap is developed using a guarded craniotome introduced through burr holes placed above the hairline or in the temporal areas. Near the midline, care is taken to separate the dural fold containing the sagittal sinus away from the bone to protect it before the craniotome is allowed to cross the sagittal plane. The lower horizontal bone cut should be kept low (within 1 cm of the superior orbital rims) to lessen the need for subsequent brain retraction. Withdrawing 25 to 50 mL of CSF from the lumbar subarachnoid catheter, lowering P_{CO_2} through controlled hyperventilation, and occasionally administering mannitol or corticosteroids will further reduce the need for mechanical frontal lobe retraction.

Next, the frontal lobes are elevated from the anterior cranial fossa floor by incising the dura and severing the olfactory nerves at the cribri-

form plate. This always results in some leakage of CSF, which is controlled by direct dural suture or a dural patch (from temporal fascia, fascia lata, or pericranium). The dural closure should be as watertight as possible. Dura is further elevated to expose the orbital roofs and planum sphenoidale and finally the base of the anterior clinoid processes.

If disease extirpation mandates the removal of the planum, the intracranial portions of the optic nerves should be exposed through the unroofing of the optic canal to protect them from injury at the time of sphenoid osteotomy.[14] If the disease is confined to the cribriform area, however, the planum may be entered with a cutting burr or osteotome[66] to establish the posterior bony margin without optic nerve decompression. This completes the intracranial portion of the exposure for anterior craniofacial resection.

The transfacial exposure often involves modifications of a lateral rhinotomy incision, which may transect the upper lip; this depends on whether a total maxillectomy will be done in conjunction with the resection. The periosteum is elevated from the nasal bone and from the medial and inferior surfaces of the orbit, and the nasolacrimal duct is identified and transected distally. The anterior and posterior ethmoid arteries are identified and cauterized or clipped. In most cases, it is necessary to perform a complete en bloc ethmoidectomy. For this purpose, a contralateral Lynch incision is made to elevate the contralateral periorbita, cauterize the anterior and posterior ethmoid vessels, and make the appropriate osteotomies using a sagittal saw. If preoperative imaging studies or intraoperative observations confirm the presence of tumor within the soft tissues of the orbit, then orbital exenteration may be performed after extending the skin incision laterally to include a portion of the eyelids. Depending on the nature and extent of the tumor, osteotomies also may be made to include part or all of the maxilla.

At this point, a reciprocating saw or cutting drill bit is used to create the osteotomies of the cranial floor. The frontal lobes are retracted or protected from the cutting instrument by inserting an appropriate malleable retractor. The reciprocating saw or cutting drill bit is introduced through the nasal and ethmoid exposures, and, under direct

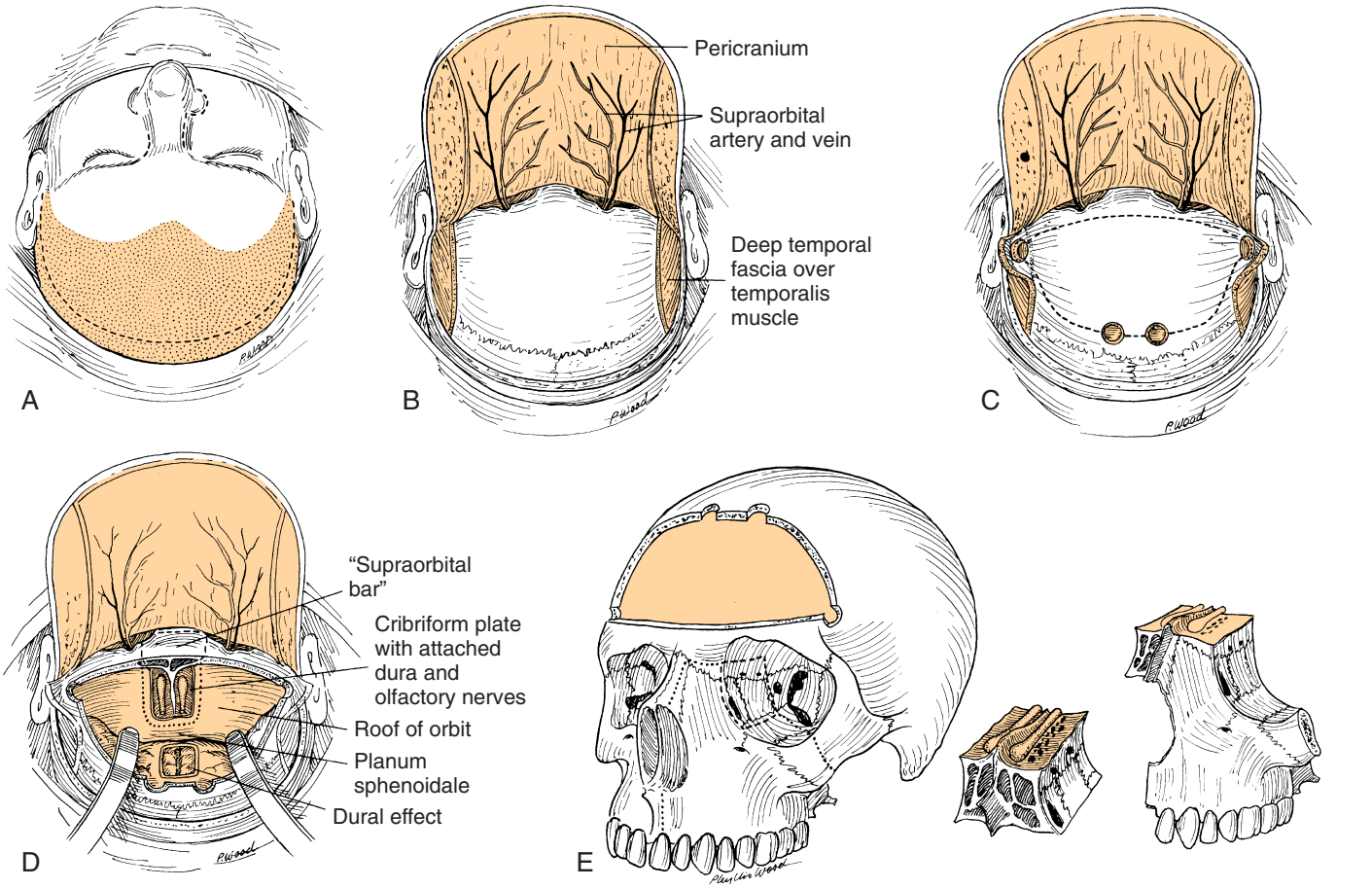

Figure 174-15. Anterior craniofacial resection. **A,** Incisions. High bicoronal incision preserves the optimal length of the galea and the pericranium for use as a reconstructive flap. Facial incisions usually include lateral rhinotomy and contralateral Lynch incisions, but these may be modified to suit the clinical situation. **B,** Elevation of the bicoronal scalp flap. The pericranium has been incised bilaterally at the superior temporal lines to separate it from the deep temporal fascia. Supraorbital vessels have been released from the supraorbital foramina to allow for the exposure of the superior orbital rims (zygomatic arches may be exposed using bicoronal incision by dissecting further laterally, as may be required for extended anterolateral craniofacial resections). **C,** Bifrontal craniotomy. *Dashed lines* represent the outline of the planned craniotomy. Temporalis muscles have been partially elevated so that burr holes may be placed below the temporal lines; superior burr holes are placed above the level of the frontal hairline. Such placement helps minimize postoperative cosmetic deformity. Paramedian positioning of superior burr holes aids in protection of superior sagittal (venous) sinus while the bone flap is being cut. **D,** Intracranial exposure. The frontal lobes have been retracted, and the dura has been incised, thereby leaving olfactory nerves and the margin of the dura to be resected en bloc, along with the cribriform plate and the ethmoid labyrinth *(dotted line)*. The amount of dura and anterior cranial fossa floor resected will depend on the extent of tumor. To enhance exposure and direct visualization, the supraorbital bar *(dashed lines)* may be included in the resected specimen; after resection margins have been verified, this portion of bone is detached from the tumor-bearing part of the specimen and replaced. **E,** Osteotomies as seen from transfacial exposure. *Dashed lines* illustrate bone cuts used for en bloc ethmoidectomy, which result in the obtaining of a specimen *(left)*. *Dotted lines* indicate additional osteotomies to be used when total maxillectomy (with or without orbital exenteration) also is performed, thereby resulting in the obtaining of a specimen *(right)*. In both cases, resection encompasses part of the anterior cranial fossa floor. The extent of anterior fossa floor resection varies and should be modified as required by the extent of tumor.

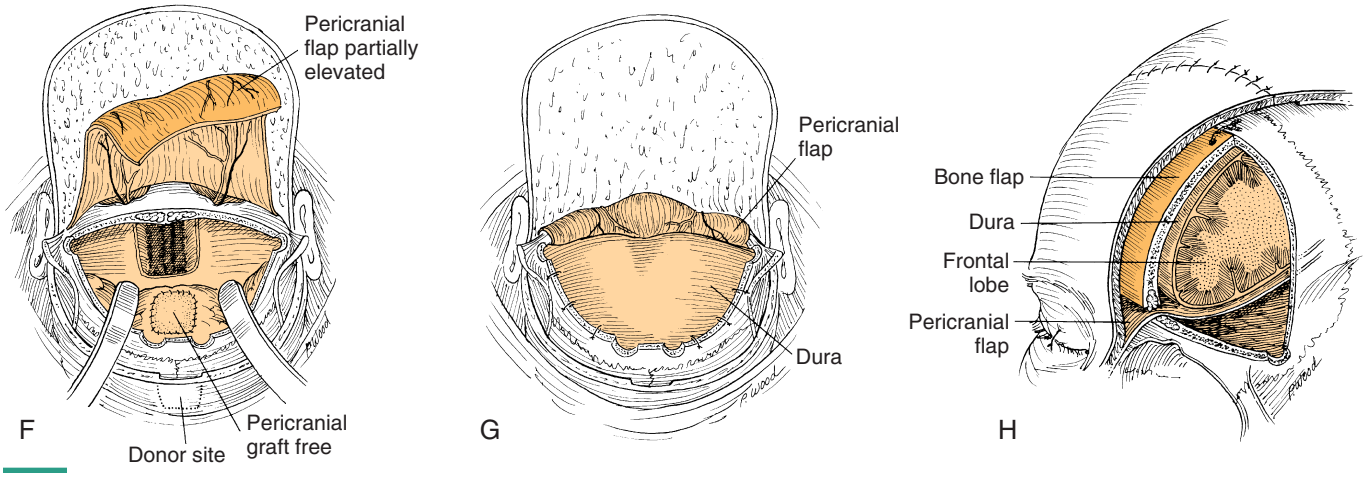

Figure 174-15, cont'd. **F,** Operative defect and preparation for closure. Large communication between the anterior cranial fossa and nasal cavity is closed by an inset of vascularized pericranial flap (shown here partially elevated from the galea). A dural defect created by resection of the olfactory nerves and surrounding dura has been closed with free graft of the pericranium taken from the posterior scalp *(dotted lines)*. Frontal sinuses have been stripped of mucosa and filled with autogenous fat after obliterating the frontonasal ducts. **G,** Cranial base defect repaired. A pericranial flap has been turned intracranially to line the anterior cranial fossa floor. Release of the frontal lobe retraction and clamping of the spinal drain have allowed for reexpansion of the brain and obliteration of the epidural dead space. The frontal bone flap is replaced and secured, with care taken to avoid compression of the pericranial flap. **H,** Cutaway view of final closure, showing the position of the pericranial flap relative to the brain and the cranial base. *(**A** to **G,** Adapted from Schramm VL. Craniofacial resection. In: Sasaki CT, McCabe BF, Kirchner JA, eds.* Surgery of the Skull Base. *Philadelphia: JB Lippincott; 1984.)*

vision, osteotomies are created from the planum sphenoidale, along the ethmoid roof, and forward to the front of the cribriform plate. These osteotomies may or may not include the supraorbital bar of bone, which is a portion of the frontal bone between the supraorbital rims (see Fig. 174-15D). If the tumor extends anteriorly to a significant degree, this supraorbital bar is removed with it as a single specimen, which can be closely inspected. If the supraorbital bar is not actually involved by tumor, it may be detached from the specimen and replaced for reconstruction at the completion of the operation.

After the resection margins have been verified by frozen section and are negative, reconstruction begins. As mentioned, it is critical that the dura be closed in a watertight fashion. This usually involves the placement of a patch of pericranium, temporal fascia, or fascia lata, followed by the placement of a vascularized pericranial flap over the defect in the floor of the anterior cranial fossa. The pericranial flap is developed by sharp dissection from the previously reflected scalp flap (see Fig. 174-15F).[69] Elevation of this flap of pericranium is continued down to the level of the glabella, with care taken to not injure its vascular pedicles. It is then rotated intracranially and positioned to form a bridge of soft tissue across the orbital roofs and back to the planum sphenoidale. If necessary, the distal end of the pericranial flap may be sutured to the dura over the planum for security; this provides a vascularized tissue barrier between the dura above and the nasal cavity below (see Fig. 174-15G and H). Unless a large amount of anterior cranial fossa bone has been resected and concern for brain herniation exists, it is usually not necessary to place a bone graft across the bony defect. Also, it is not necessary to place a skin graft on the undersurface of the pericranium (facing the nasal cavity), because this tissue mucosalizes readily on its nasal surface. After the pericranial flap is in place, the spinal drain is clamped so that no further intraoperative CSF decompression will take place. This will allow the gradual reexpansion of the brain to make contact with the pericranial flap, thereby obliterating any residual dead space. Because the pericranial flap traverses the frontal sinus, it is necessary to obliterate the frontonasal ducts and to remove all mucosa from within the sinus. A small amount of fat or free muscle may be packed into the ducts to obliterate any dead space inferiorly. The flap covers the frontonasal duct orifices and sinus floor. If the sinus is small, it may be obliterated by packing it with abdominal fat. If the sinus is large, however, removing the posterior table completely and allowing the brain and dura to expand and fill the space (cranialization of the frontal sinus) may be advisable.

In closing the facial incision, the medial canthal ligament is identified and secured to the remaining medial orbital wall. The upper and lower lid canaliculi may be intubated with a canalicular stent to prevent dacryostenosis. Before further closure, several tacking sutures are placed to secure the frontal dura to the margins of the craniotomy site; this will help in the prevention of postoperative epidural fluid and blood collections. The bifrontal craniotomy bone flap is then replaced and secured according to the surgeon's preference; this may be done with wires, plates, or sutures.

Basal Subfrontal Approach

The basal subfrontal approach or transbasal approach (Fig. 174-16)[14,70] is in many ways similar to the anterior craniofacial resection operation, except that the transfacial exposure is less extensive. Because the target area in this approach is more posterior (sphenoid and clivus) than that in the anterior craniofacial resection (ethmoids and cribriform), the craniotomy bone flap generally is somewhat larger and the orbital bone cuts are broader. This approach is used for lesions that primarily or secondarily involve the bony cranial base in the regions of the sphenoid body and upper clivus (e.g., meningiomas, fibrous dysplasia, chordomas, chondrosarcomas, ossifying fibromas).[63]

This approach also begins with a bicoronal incision. After exposing the orbital rims, periorbita is elevated from beneath the orbital roofs and medial walls in preparation for osteotomy. The anterior and posterior ethmoid arteries are identified bilaterally as landmarks, but they need not be divided because the axial ethmoid osteotomy can be made just above this level. Bifrontal craniotomy is then performed, and dura is elevated from above the orbital roofs and cribriform areas, as described. Using malleable retractors to protect the orbital contents and the brain, the reciprocating saw is used to create osteotomies that result in the temporary removal of both orbital roofs and the supraorbital bar (see Fig. 174-16A).

The coronal osteotomies along the posterior orbital roof should be made as far posteriorly as possible to simplify reconstruction, to conserve orbital contour, and to prevent postoperative pulsatile exophthalmos. These orbital cuts can be made as far back as the posterior ethmoid foramen but should be made only under direct vision from intra- and extracranial perspectives. With the use of these osteotomies, a very broad and basal exposure of the entire anterior cranial base is achieved (see Fig. 174-16B).

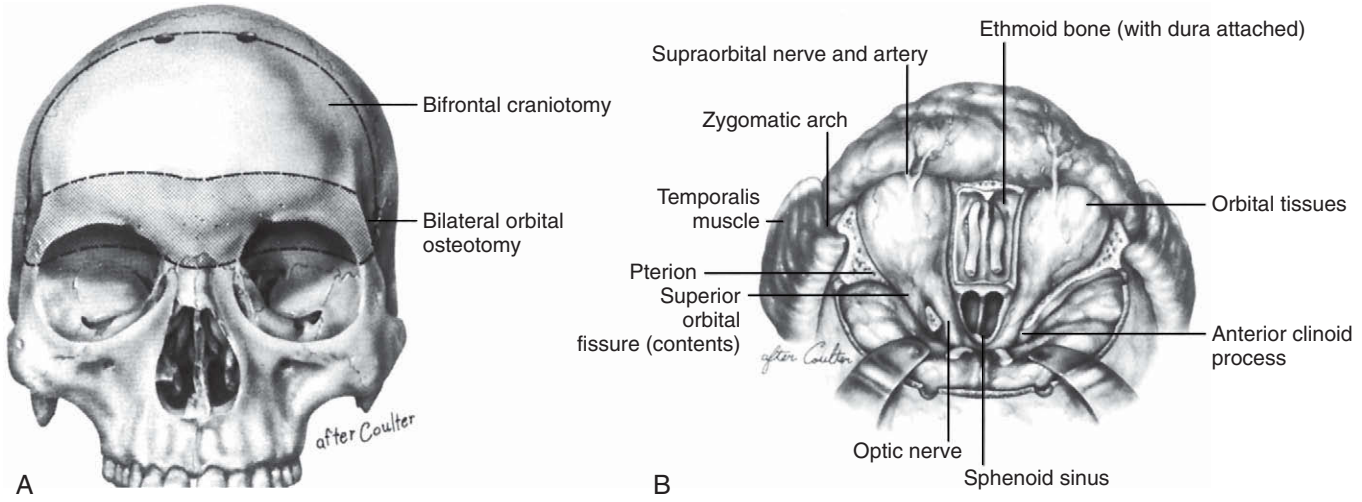

Figure 174-16. Basal subfrontal approach to the cranial base. **A,** Outlines of bifrontal craniotomy and bilateral orbital osteotomies. **B,** Surgeon's view from above after the removal of cranial and orbital bone segments. Olfactory nerves have been transected to allow sufficient brain retraction for exposure of the anterior fossa floor and decompression of the optic nerves. The sphenoid sinus has been widely opened. *(From Sekhar LN, Janecka IP. Intracranial extension of cranial base tumors and combined resection: the neurosurgical perspective. In: Jackson CG, ed.* Surgery of Skull Base Tumors. *New York: Churchill Livingstone; 1991.)*

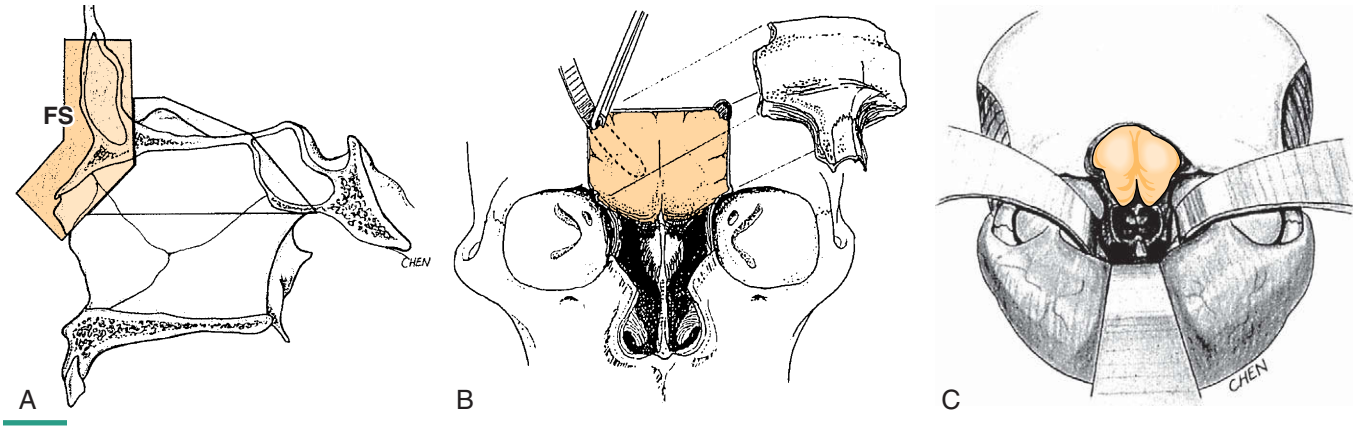

Figure 174-17. Subcranial approach to the anterior cranial base as described by Raveh.[71-73] **A,** Sagittal schematic showing the osteotomized frontonasal segment (FS), which is removed to allow access to deeper structures and then later replaced. **B,** Initial exposure afforded by the removal of the frontonasal bony segment; note the protection of the dura by a malleable retractor. **C,** Extent of exposure after lesion extirpation, with sphenoid sinus, sella, and orbital apices visible at the depth of the wound. Note that the bicoronal scalp flap has been elevated quite extensively along the lateral and medial orbital rims and nose to permt the frontonasal osteotomies and to compensate for the very low plane of access to the anterior cranial base while avoiding facial incisions *(see text)*. *(From Raveh J, Laedrach K, Ilzuka T, et al. Subcranial extended anterior approach for skull base tumors: surgical procedure and reconstruction. In: Donald PJ, ed.* Surgery of the Skull Base. *Philadelphia: Lippincott-Raven; 1998. With permission.)*

Working with the aid of the microscope, the approach is completed by rongeuring or drilling a small amount of bone remaining posteriorly to unroof the optic nerves, the superior orbital fissures, and the sphenoid sinus. Extirpation proceeds as required by the tumor and is followed by reconstruction, which is similar to that done for anterior craniofacial resection.

Raveh and colleagues[71-73] have described and refined an approach, now generally referred to as the subcranial approach, that offers significant advantages over the traditional anterior craniofacial resection and the basal subfrontal approach while combining elements of each. In the subcranial approach, facial incisions are not used; instead, the bicoronal scalp flap is reflected much further inferiorly to more completely expose both orbits and the nasomaxillary bony framework (Fig. 174-17). Extensive access along the entire anterior cranial base is possible as far back as the sella, the orbital apices, and the upper clivus. Advantages of the subcranial approach include minimal brain retraction, wide exposure, and the absence of facial scars.

Middle Cranial Base Approaches

In contrast with the anterior cranial base, surgical approaches to the middle cranial base are numerous and varied. This reflects the anatomic complexity of the region and the diversity of lesions found there. This discussion reviews several approaches and presents examples of those that have been found to be most useful.

Division into Central and Lateral Compartments

When considering surgical approaches to the middle cranial base, it is helpful to subdivide the region into a single central compartment and paired lateral compartments (Fig. 174-18).[74] When viewing the skull from the inferior perspective, the central compartment may be defined as that area between two parasagittal lines drawn from the medial pterygoid plate to the occipital condyle on each side. These lines correspond approximately to the pathways of the ICAs through the skull base. Thus, the central compartment consists of the pituitary fossa, the sphenoid rostrum and lower sphenoid sinus, the nasopharynx, the pterygopalatine fossa, and the lower portion of the clivus. (The lower

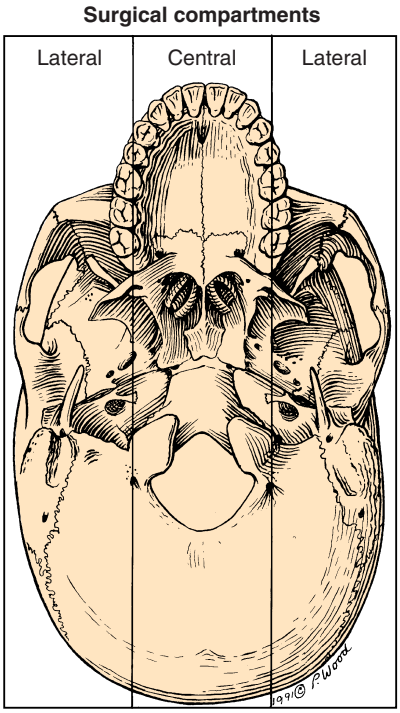

Figure 174-18. Compartments of the middle cranial base. The pathways of the internal carotid arteries as they traverse the middle cranial base region divide the region into one central and two lateral compartments. *(From Krespi YP, Sisson GA. Transmandibular exposure of the skull base.* Am J Surg. *1984;148:534-538.)*

clivus actually is part of the occipital bone and not technically part of the middle cranial base. However, the surgical approaches to this area and also to the craniovertebral junction and upper cervical spine are essentially extensions of the approaches to the central compartment.)

The lateral compartment includes the entire infratemporal fossa, the parapharyngeal space, and the petrous portion of the temporal bone. This area is important because of the high density of neural and vascular structures within, including, extratemporally, the ICA; the internal jugular vein; the maxillary nerve (V2); the mandibular nerve (V3); the facial nerve (VII); cranial nerves IX, X, XI, and XII; the sympathetic nerves; and major branches of the external carotid artery, and, intratemporally, the cochlea, the vestibule, and cranial nerve VIII.

These distinctions between central and lateral compartments are valid in the sense that limited lesions within their respective boundaries will clearly be more amenable to resection using one type of approach vs another. However, it is not unusual for advanced lesions to extend beyond the line that separates the central from the lateral compartment; therefore, the surgical approach should be tailored to suit each clinical situation.

Approaches to the Central Compartment

The major surgical approaches to the central compartment of the middle cranial base are listed in Table 174-1, along with the anatomic areas for which they provide useful exposure. Except for pituitary surgery, these approaches are used primarily for the management of extradural lesions along the skull base.

Although most central compartment approaches in the literature can give access to the sphenoid sinus, not all are suitable for pituitary or parasellar surgery because of indirect exposure or oblique angle of entry into the sinus, which increases the risk of injury to adjacent neurovascular structures. When lesions are limited to the sphenoid sinus or the pituitary fossa, the transethmoidal sphenoidotomy (Fig. 174-19)[75,76] and the transseptal sphenoidotomy (Fig. 174-20)[77,78] are

Table 174-1

Surgical Approaches to the Middle Cranial Base: Central Compartment

	Anatomic Area(s) Exposed								
Approach	**SS**	**Sella**	**Clivus**	**NP**	**PPF**	**Maxilla**	**Ethmoid**	**C spine**	**ACB**
Transseptal sphenoid	+	+	–	–	–	–	–	–	–
Transethmoidal sphenoid	+	+	–	–	–	–	+	–	+
Lateral rhinotomy	+	NR	±	+	+	+	+	–	+
Transantral	+	+	±	+	+	+	+	–	–
Midfacial degloving	+	+	+	+	+	+	+	–	+
Le Fort I osteotomy	+	+	+	+	+	+	±	+	–
Transpalatal	+	–	+	+	–	–	–	+	–
Transoral	–	–	+	+	–	–	–	+	–
Mandibulotomy	–	–	+	+	–	–	–	+	–
Extended maxillotomy	+	±	+	+	+	+	+	+	–
Midfacial split	+	+	+	+	+	+	+	+	+
Intratemporal fossa	+	±	+	+	+	±	–	–	–
Facial translocation	+	+	+	+	+	+	+	–	+

ACB, anterior cranial base; C spine, cervical spine; NP, nasopharynx; NR, not recommended; PPF, pterygopalatine fossa; SS, sphenoid sinus; ±, exposure possible but limited.

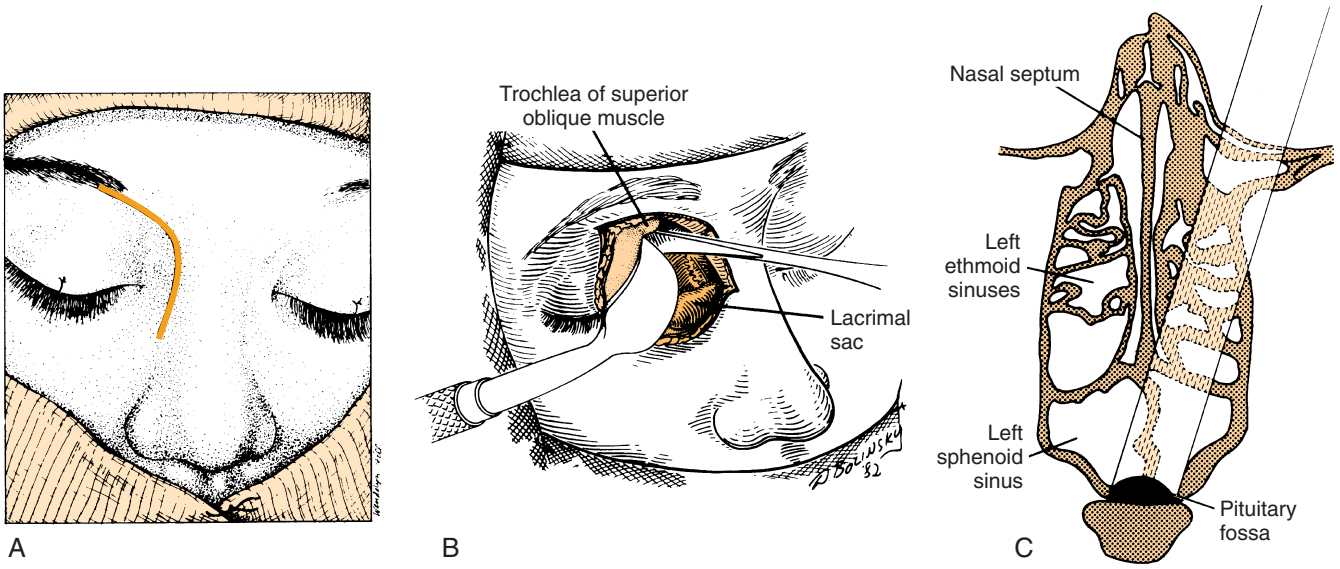

Figure 174-19. Transethmoidal-transsphenoidal approach to the cranial base. **A,** Incision. **B,** Retraction of orbital contents exposes the ethmoid labyrinth. **C,** Axial section at the level of the ethmoid and sphenoid sinuses. Progressive removal of ethmoidal air cells allows for entry into the sphenoid sinus and pituitary fossa. *(**A** and **C,** From Sasaki CT. Pituitary ablation for carcinoma of the breast: transethmoidal approach to the sella.* Otolaryngol Clin North Am. *1981;14:391; **B,** from Kirchner JA. Transethmoidal approach to the sella. In: Sasaki CT, McCabe BF, Kirchner JA, eds.* Surgery of the Skull Base. *Philadelphia: JB Lippincott; 1984.)*

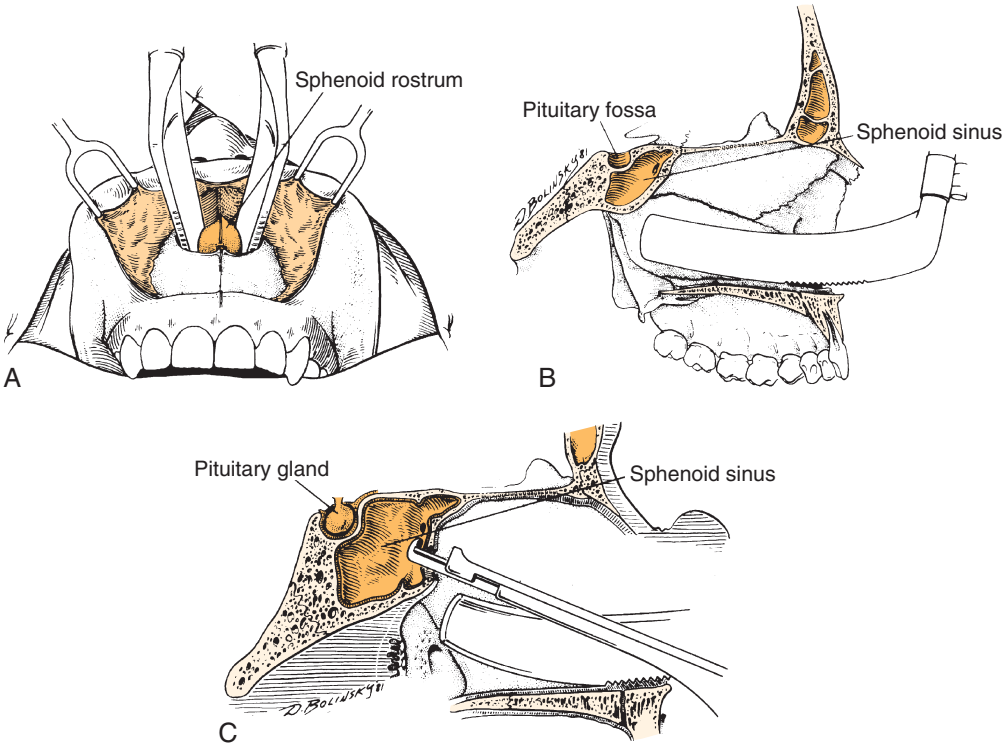

Figure 174-20. Transseptal-transsphenoidal approach to the cranial base. **A,** A sublabial incision is used to gain access to the premaxilla and to the nasal septum, which is exposed from the anterior nasal spine to the sphenoid rostrum in the subperichondrial-superiosteal plane. **B,** Lateral view of exposed area, showing a self-retaining speculum in position at the sphenoid rostrum. **C,** Sphenoid sinus is opened. A transseptal-transsphenoidal approach may be used for pituitary fossa surgery, for the removal of limited lesions of sphenoid region, or for the biopsy of tumors that involve the area. *(From Sasaki CT. Transseptal-transsphenoidal approach to the sella. In: Sasaki CT, McCabe BF, Kirchner JA, eds.* Surgery of the Skull Base. *Philadelphia: JB Lippincott; 1984.)*

usually satisfactory, safe, and effective. These approaches are useful for obtaining biopsy specimens of more extensive lesions that involve that region. For larger lesions that involve adjacent areas, however, the exposure is inadequate, because the operative field is deep and narrow, thus requiring the use of the operating microscope in most cases.

With trends toward less invasive surgical techniques, endoscopic procedures are gaining popularity as primary or adjuvant approaches in cranial base surgery. For tumors of the pituitary gland, endoscopic transnasal-transsphenoidal resection is another valuable option. Proponents of endoscopic pituitary surgery report fewer complications of facial swelling, septal perforations, nasal septal deviation or synechia formation, and numbness of the upper incisors; they also report a shorter hospital stay.[79,80] The surgery is performed with the patient under general anesthesia in the supine position with the head elevated 10 degrees. In most cases, the operation can be performed through one nostril, the choice of which depends on the width of the nasal cavity and the laterality of the pituitary tumor. The nose is decongested topically, and further vasoconstriction is achieved by infiltrating the mucosa over the rostrum of the sphenoid, the middle turbinate, and the posterior septum with lidocaine hydrochloride 1% with epinephrine 1 : 100,000.

Using a rigid zero-degree endoscope, the sphenoid ostium is identified, and its position may be confirmed by the use of C-arm fluoroscopy or image-guided navigation. The middle turbinate can be outfractured or removed to provide increased exposure to the sphenoid rostrum. The sphenoid ostia are identified and fractured inferomedially. Kerrison rongeurs or Hardy punches are used to widen the sphenoidotomy and to remove the sphenoid rostrum. The posterior septum may be rongeured to provide wide visualization, including that of the contralateral sphenoid sinus cavity. The 30-degree endoscope is inserted into both sides of the sphenoid sinus for identification of the optic and carotid protuberance, the opticocarotid recess, the clival indentation, and the anterior wall of the sella[81] (Fig. 174-21). After removal of the intersinus septum, the sella and dura are exposed and entered in the standard fashion. For resection of macroadenomas, insertion of the 30-degree endoscope allows the surgeon to follow intrasellar and extrasellar extension of the tumor and to identify and preserve the arachnoid membrane[81] (Fig. 174-22). The ability to directly visualize tumor and healthy pituitary gland through the endoscope is a major advantage over the operating microscope. This increased visualization may allow

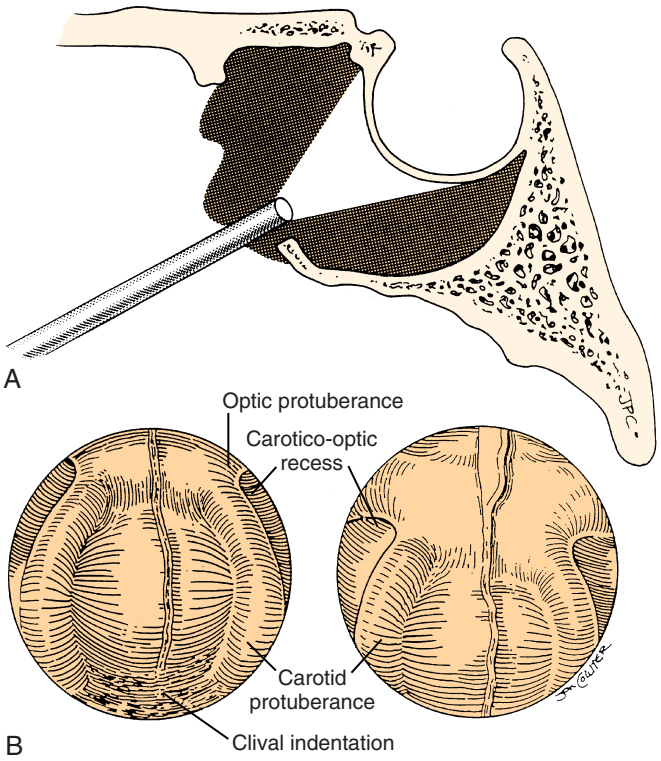

Figure 174-21. **A,** Endoscopic view of the sphenoid sinus after the completion of anterior sphenoidotomy and resection of the sphenoidal septum. **B,** *Left*: View with a zero-degree endoscope reveals the carotico-optic recesses, carotid protuberances, and clival indentation to the anterior wall of the sella. *Right*: A 30-degree endoscope provides a better panoramic view of the optic protuberances, the carotico-optic recesses, the carotid protuberances, and the upper portion of the anterior wall of the sella. *(From Jho HD, Carrau RL, Ko Y. Endoscopic pituitary surgery. In: Rengachary SS, Wilkins RH, eds.* Neurosurgical Operative Atlas. *Vol 5. Park Ridge, Ill: AANS; 1996. Copyright by the American Association of Neurological Surgeons.)*

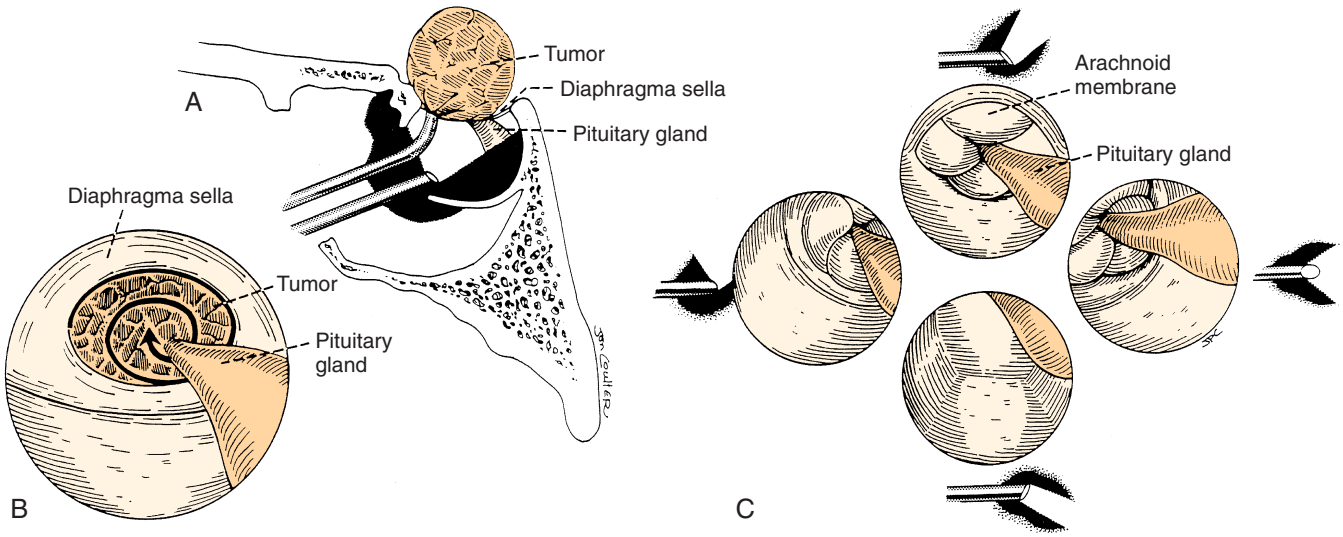

Figure 174-22. **A,** Sagittal view of the sella. **B,** 30-Degree endoscopic view of the suprasellar tumor. The suprasellar portion of the tumor is removed with a curved suction cannula beginning around the edge of the diaphragma sella circumferentially and heading toward the center of the tumor gradually. The healthy pituitary gland tissue is preserved, if possible. **C,** The arachnoid membrane will herniate down gradually when the suprasellar portion of the tumor has been completely removed. The center of the flower-shaped arachnoid membrane will be the pituitary stalk. Any healthy-looking pituitary gland tissue is preserved. When the 30-degree–angled endoscope placed inside the sella is rotated, it will reveal the suprasellar region superiorly, the lateral wall of the sella laterally, and the floor of the sella inferiorly. Residual tumor is removed from all corners by rotating the 30-degree endoscope. *(From Jho HD, Carrau RL, Ko Y. Endoscopic pituitary surgery. In: Rengachary SS, Wilkins RH, eds.* Neurosurgical Operative Atlas. *Vol 5. Park Ridge, Ill: AANS; 1996. Copyright by the American Association of Neurological Surgeons.)*

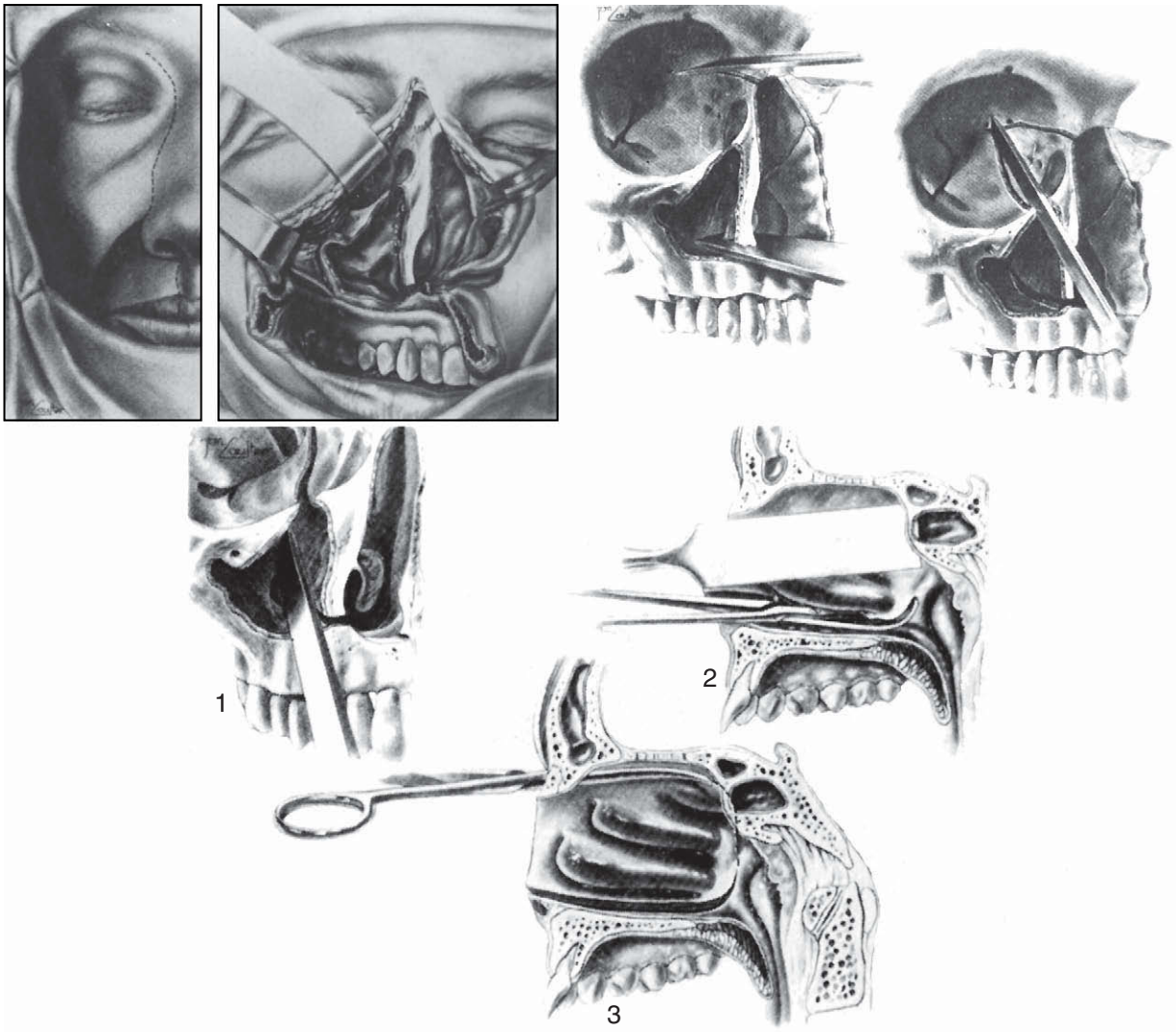

Figure 174-23. Lateral rhinotomy. *Top left,* Incision and soft tissue exposure followed by maxillary antrostomy. *Top right,* Osteotomies of the orbit and maxilla. *Bottom,* Anterior (1) and sagittal (2 and 3) views of posterior osteotomies and soft tissue cuts to remove medial portions of the orbit and maxilla. Such exposure can provide access to the face of the sphenoid, nasopharynx, pterygopalatine fossa, and ethmoid regions. *(From Schramm VL, Myers EN. "How I do it"—head and neck. A targeted problem and its solution. Lateral rhinotomy.* Laryngoscope. *1978;88:1042-1045.)*

for more complete tumor resection, while limiting the potential complications associated with blind curettage of the superior and lateral sella contents.

The lateral rhinotomy (Fig. 174-23)[82] and transantral (Fig. 174-24)[83] procedures afford wider access to the anterior sphenoid and adjacent nasopharynx, the pterygopalatine fossa, the maxilla, and the ethmoid regions. However, they generally are unsatisfactory for extirpation of any but the smallest lesions situated in the sphenoidal-clival area. The midfacial degloving approach (Fig. 174-25)[84] is more suitable for dealing with larger central compartment lesions, because it allows for improved midline access through the nose and both maxillary sinuses. Medial maxillectomy and resection of the ascending process of the palatine bone are included, if necessary, giving the surgeon good visualization of the nasopharynx and the adjacent skull base. The Le Fort I osteotomy (Fig. 174-26)[85,86] can be an alternative method for reaching these areas from a slightly more inferior angle, or it may be used as an adjunct to midface degloving, offering additional access to the oronasopharynx and clivus by displacing the hard and soft palate inferiorly.

For lesions of the clivus that also involve the upper cervical vertebrae (the craniovertebral junction), mandibulotomy (Fig. 174-27)[74,87,88] will afford a paramedian route to reach the lower areas of extension. The transpalatal (Fig. 174-28)[89,90] and transoral (Fig. 174-29)[91,92] approaches are also used for the management of lesions at the craniovertebral junction and may be used concomitantly with mandibulotomy, if necessary. A significant benefit of such a combined approach is that, with mandibulotomy, it is also possible to expose the parapharyngeal space and therefore to safely dissect along the ICA from the neck up to its entrance into the temporal bone.[74,87,88] This advantage is important when removing tumors that arise primarily in the central compartment but that have extended laterally. Conversely, for lesions that originate in the lateral compartment and extend centrally, the infratemporal fossa approach or one of its modifications can be used.[93] These approaches and the facial translocation approach,[17] which is suitable for lesions in both compartments, will be discussed in the following section.

An alternative approach for the removal of extensive lesions of the clivus and craniovertebral junction is the extended maxillotomy operation or its modification, the subtotal maxillectomy (Fig. 174-30).[94] In general, these innovative techniques combine the advantages of many approaches. They afford wide exposure of the central compartment by unilaterally displacing or resecting the hemimaxilla.

For very extensive clival and craniovertebral junction tumors, when bilateral transmaxillary access is needed, the midfacial split approach (Fig. 174-31) can be used.[51,57] This approach provides access to the entire central skull base in a unified surgical field that can extend

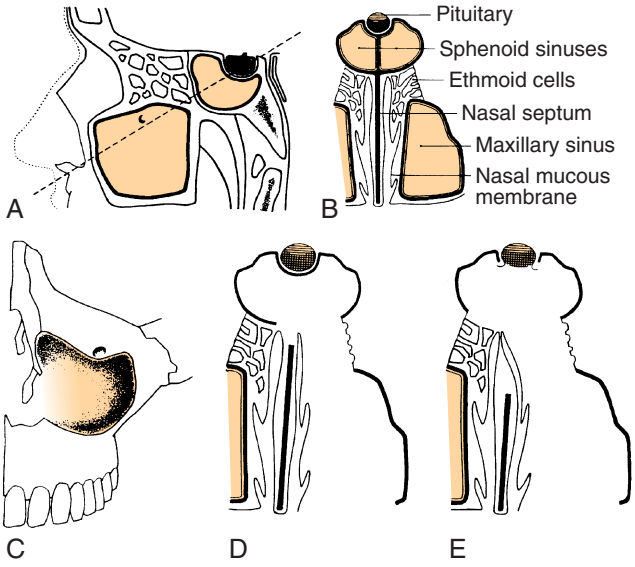

Figure 174-24. Transantral (transantrosphenoidal) approach to the cranial base as used for hypophysectomy. **A,** Near-sagittal section through the skull base and midface showing surgical route to the sphenoid region via the maxillary antrum. **B,** Oblique section in plane of the *dotted line* shown in **A** demonstrating the relationship among the maxillary sinus, the ethmoid air cells, and the sphenoid sinus. **C,** Partial medial maxillectomy performed to facilitate access. **D,** Ethmoidectomy and removal of the anterior wall of the sphenoid sinus. **E,** Exposure within the sphenoid sinus and pituitary fossa after partial submucous resection of the nasal septum. *(From Hamberger CA, Hammer G, Norlen G, Sjogren B. Transantrosphenoidal hypophysectomy.* Arch Otolaryngol. *1961;74:2-8.)*

Figure 174-25. Midfacial degloving approach. Intranasal and sublabial incisions are used to elevate skin and soft tissues from the anterior facial skeleton (degloving). Subsequent bone removal and skull base exposure are similar to that shown for lateral rhinotomy, with an added benefit of bilateral access. *(From Casson PR, Bonanno PC, Converse JM. The midface degloving procedure.* Plast Reconstr Surg. *1974;53:102-103.)*

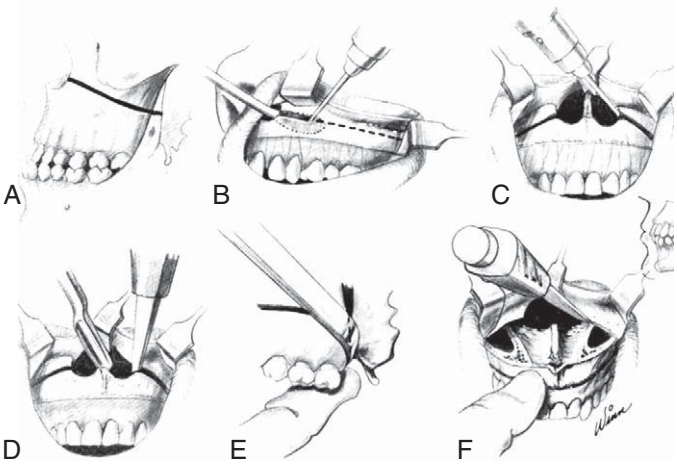

Figure 174-26. Le Fort I osteotomy approach. **A,** Lateral view of proposed osteotomy site just above the level of the nasal floor. **B** and **C,** Incisions and bone cuts along the anterolateral maxillary surface. **D,** Separation of the nasal septum with an osteotome. **E,** Separation of the maxilla from the pterygoid plate with a curved osteotome. **F,** Down-fracture of the maxilla to allow access to the maxillary sinuses, nasopharynx, and adjacent skull base. *(From Bell WH. Le Fort I osteotomy for correction of maxillary deformities.* J Oral Surg. *1975;33:412-426.)*

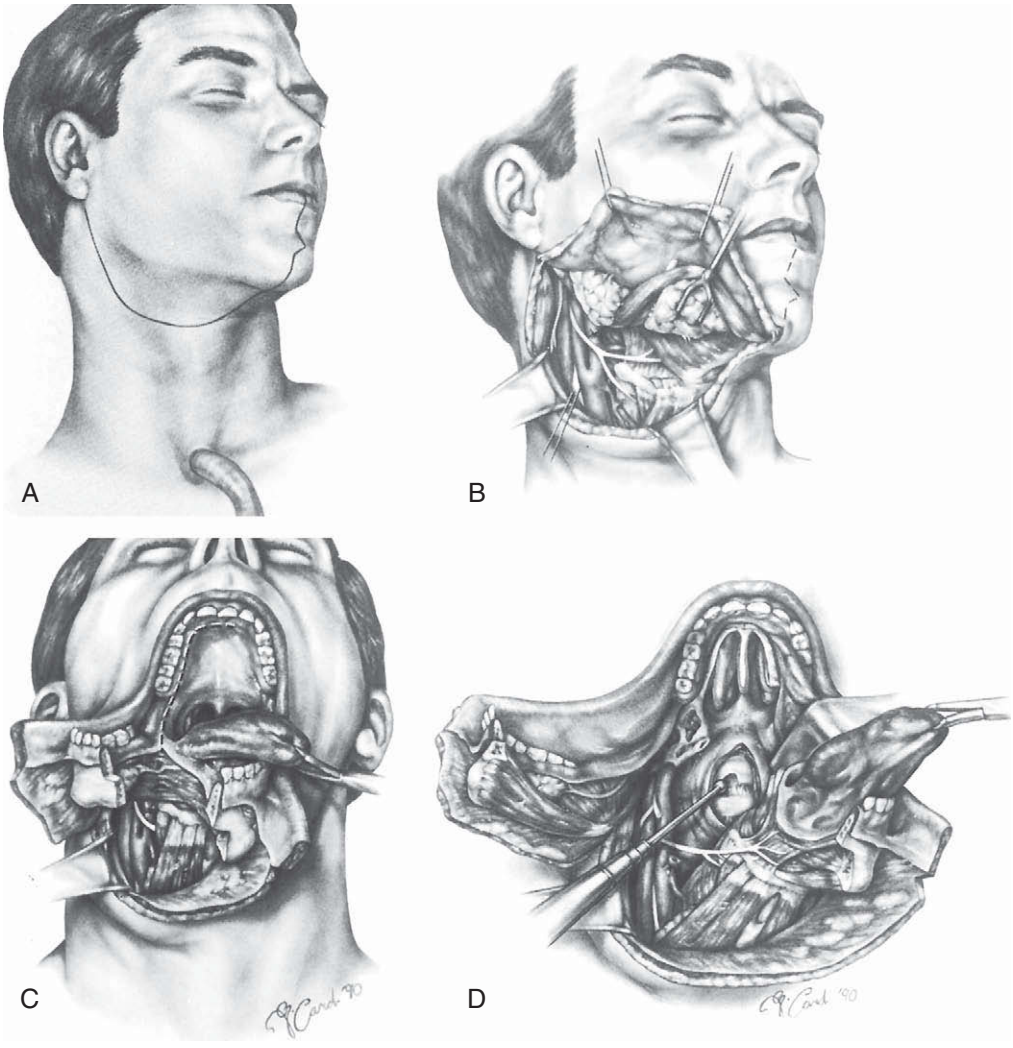

Figure 174-27. Mandibulotomy or transmandibular approach to the cranial base. **A,** Incision. **B,** Identification of major vessels and nerves in the neck. **C,** Paramedian mandibulotomy and intraoral incisions of the gingivolingual and palatal areas. **D,** After retraction of the mandible, tongue, and suprahyoid structures, major vessels may be dissected up to the skull base. Hard and soft palates are displaced to expose the nasopharynx and clivus, and upper cervical vertebrae are likewise accessible. Such an approach is useful for the management of tumors of the parapharyngeal space and the craniocervical junction. *(From Krespi YP, Cusumano RJ. Transpalatal and transmandibular approaches to the skull base. In: Jackson CG, ed.* Surgery of Skull Base Tumors. *New York: Churchill Livingstone; 1991:185-193.)*

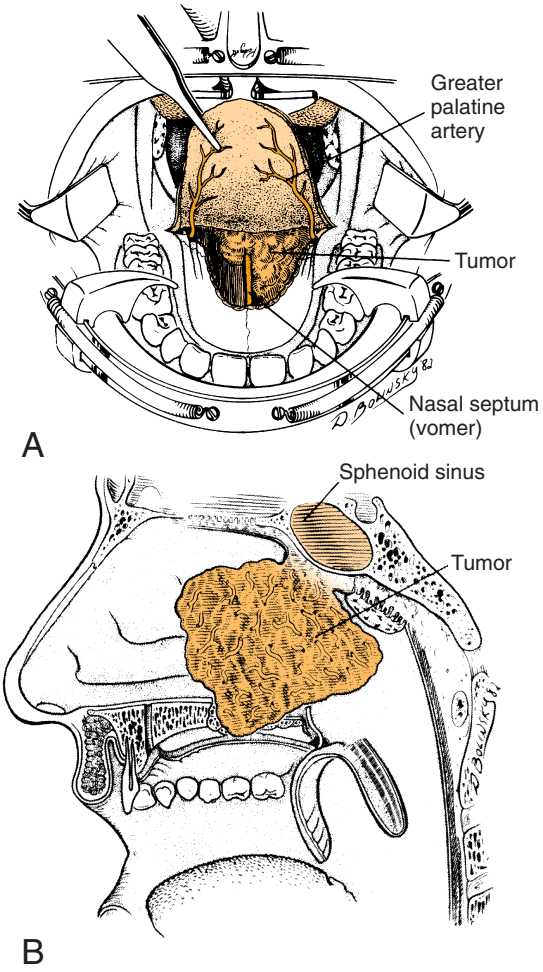

Figure 174-28. Transpalatal approach to the cranial base. **A,** A U-shaped incision has been made in the palatal mucoperiosteum, which has been elevated with care taken to preserve the greater palatine arteries bilaterally. The posterior portion of the bone of the hard palate has been removed to expose the nasal cavity and the tumor within. **B,** Sagittal view of the exposure obtained with a transpalatal approach. *(From Jenkins HA, Canalis RF. Transpalatal approach to the skull base. In: Sasaki CT, McCabe BF, Kirchner JA, eds.* Surgery of the Skull Base. *Philadelphia: JB Lippincott; 1984.)*

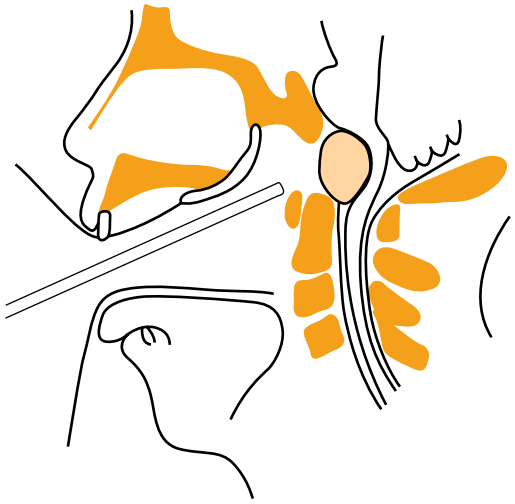

Figure 174-29. Transoral approach to the cranial base, showing access to the craniocervical junction through the open mouth, with retraction of the soft palate. *Light orange* represents a tumor of the clivus, with concomitant compression of the brainstem. *(From Crockard HA, Bradford R. Transoral transclival removal of a schwannoma anterior to the craniocervical junction. Case report.* J Neurosurg. *1985;62:293.)*

vertically from the anterior fossa floor to the level of the second cervical vertebra (and lower, if combined with mandibulotomy) and horizontally from jugular fossa to jugular fossa. This exposure is achieved using craniofacial disassembly to completely displace the midfacial skeleton, including both maxillae, the orbital floors, and the palate. It is especially useful for the management of large tumors that originate in the central compartment and that have also involved the adjacent anterior cranial base, the craniovertebral junction, or the lateral compartment.

Approaches to the Lateral Compartment

Numerous approaches have been developed and advocated for obtaining surgical access to the lateral compartment of the cranial base. Despite this apparent diversity of techniques and the sometimes confusing terminology by which they are described, considerable overlap exists. Most of the currently used approaches arrive at the cranial base through one (or more) of four main avenues: transtemporal, infratemporal, transfacial, or intracranial. These avenues refer to the primary direction or orientation from which the surgical exposure is ultimately achieved. In most cases, this orientation will influence the usefulness and morbidity of the operation. The cranial base surgeon should be familiar with the advantages and limitations of each of these four routes. For extensive lesions, it often becomes necessary to combine approaches.

Transtemporal Approaches

The transtemporal routes include the transcochlear,[95] translabyrinthine,[15,96] presigmoid, retrolabyrinthine,[2] and combined[97] approaches. These are lateral, primarily extradural techniques that traverse the mastoid and petrous portions of the temporal bone to provide exposure of lesions of the petrous apex, the clivus, and the cerebellopontine angle. The anterior limit of purely transtemporal approaches is the intrapetrous course of the ICA, and these approaches therefore give only limited access to the middle cranial base. Accordingly, they more often are used for the management of tumors of the posterior cranial base (e.g., acoustic neuromas, petroclival meningiomas, aggressive cholesteatomas), and they will therefore be discussed in more detail in Chapter 177. With respect to the middle cranial base, the transtemporal approaches are useful mainly as adjunctive techniques in combination with craniotomy, infratemporal, or transfacial approaches. They can be used to enhance exposure of advanced lesions of the middle cranial base that have secondarily extended into or beyond the petroclival region and posterior to the course of the ICA. Postoperative consequences include permanent unilateral deafness with or without disequilibrium caused by functional loss of the middle or inner ear structures and facial paralysis of variable degree and duration caused by seventh nerve decompression or transposition.

Infratemporal Approaches

The infratemporal routes to the lateral compartment include the infratemporal fossa, lateral transparotid, extended rhytidectomy, lateral transtemporal-sphenoid, lateral facial, and subtemporal-infratemporal approaches.

The infratemporal fossa approach of Fisch and colleagues[93,98,99] encompasses three variations for use in specific clinical situations (Fig. 174-32). The type A approach provides exposure between the sigmoid sinus and the condylar fossa, and it is designed to reach to the petrous apex and infralabyrinthine areas. It is most useful for the management of cholesteatomas, meningiomas, and glomus tumors of those regions. The type B approach allows access from the sigmoid sinus to the petrous tip (including exposure of the horizontal ICA and foramen ovale) to reach lesions of the clivus, such as chordomas, meningiomas, and extensive apex cholesteatomas. The type C approach expands this access to include the parasellar region, the cavernous sinus, the foramen

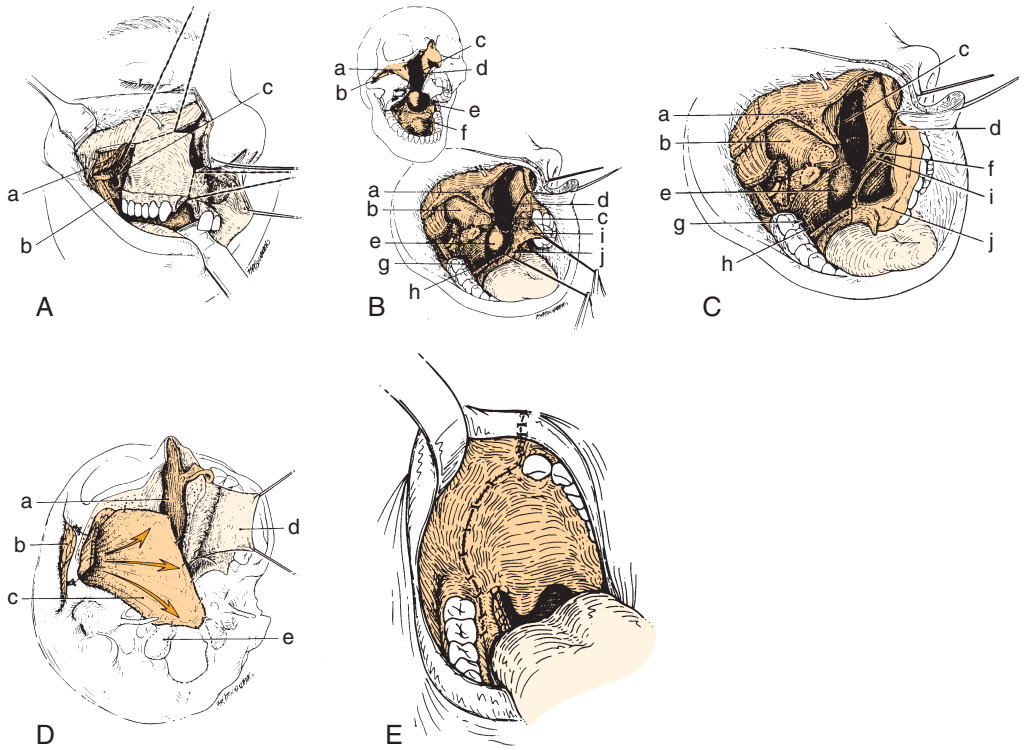

Figure 174-30. Extended maxillotomy; subtotal maxillectomy approach to the cranial base. **A,** Maxillectomy variation. Modified Weber-Fergusson incision followed by osteotomies to remove the hemimaxilla: a, masseter muscle divided; b, coronoidectomy defect; c, lateral pterygoid plate. **B,** Maxillectomy; defects: a, maxillary roof; b, infratemporal fossa; c, sinonasal defect; d, nasal septum; e, clivus tumor; f, C1 vertebra; g, lateral pharyngeal wall; h, pharyngeal wall incision; i, mucoperiosteum of hard palate; j, soft palate. **C,** Maxillotomy variation in which the hemimaxilla (j) is preserved but temporarily translocated, based on mucoperiosteum of the hard palate. See key in **B** for other lettered structures. Exposure is otherwise similar to that shown for maxillectomy. **D,** Temporalis muscle transferred into operative defect for reconstruction: a, sinonasal defect; b, fat graft; c, temporalis muscle flap; d, mucoperiosteum of hard palate; e, occipital condyle. **E,** Closure of the oral cavity and lip after subtotal maxillectomy. *(From Cocke EW Jr, Robertson JH, Robertson JT, Crook JP Jr. The extended maxillotomy and subtotal maxillectomy for excision of skull base tumors.* Arch Otolaryngol Head Neck Surg. *1992;116:92-104.)*

rotundum, and the foramen lacerum. Removal of the pterygoid plates in this approach also facilitates access to the nasopharynx. This approach is used in the resection of small nasopharyngeal carcinomas, adenoid cystic carcinomas, and angiofibromas. All three variations of the infratemporal fossa approach involve mastoidectomy, facial nerve dissection (and transposition), and obliteration of the eustachian tube, middle ear, and external auditory canal with resultant permanent conductive hearing deficit. Thus, types A, B, and C infratemporal fossa approaches share some features of the basic transtemporal approaches and yet extend the field of access anteriorly to reach the middle cranial base by virtue of exposing and controlling the petrous ICA (see Chapter 176).

For lesions of the middle cranial base that involve the infratemporal fossa, the upper pterygomaxillary space, the lateral orbit, and the orbital apex, the lateral facial approach[100] (Fig. 174-33) and the lateral transtemporal sphenoid approach[101] (Fig. 174-34) have been described. These procedures reach the infratemporal fossa from a slightly more superior direction by displacing the zygomatic arch inferiorly and reflecting the temporalis muscle. The greater wing of the sphenoid is followed to the lateral pterygoid plate, which is used as a surgical landmark, as outlined earlier. These approaches also incorporate partial removal of the greater wing of the sphenoid, which means that they include subtemporal craniectomy and extradural dissection. The advantages of these procedures are that they require no facial nerve dissection (the temporal branch of cranial nerve VII is retracted inferiorly with the skin flap), and they allow some access to the cranial base from both intracranial and extracranial perspectives.

The lateral facial approach is useful as a straightforward approach to a limited area of the middle cranial base that is technically simple to perform (after the anatomy is well understood) and that incurs relatively little morbidity. It is applicable in the management of small- to medium-sized benign tumors with limited intracranial extension, such as that which occurs with some angiofibromas. The similarly oriented lateral transtemporal sphenoid approach can be extended so that it is significantly more complex than the lateral facial approach but affords additional exposure, thus making it useful for the management of lesions in the clivus, the parasellar region, the nasopharynx, the petrous apex, and the infratemporal fossa. As the name implies, the lateral transtemporal sphenoid approach is a combination of techniques. It is similar to the infratemporal fossa approaches of Fisch except that it does not usually result in permanent conductive hearing loss, and it does not require rerouting of the facial nerve.

The subtemporal-preauricular infratemporal approach (Fig. 174-35)[14,102] is a combination of the transparotid and lateral transtemporal sphenoid procedures in addition to temporal craniotomy. It provides excellent exposure of much of the middle cranial base and allows for improved access for intracranial dissection when necessary. The orientation of the exposure begins laterally and progresses medially so that it is useful for the management of lesions of the greater sphenoid wing, the petrous apex, and the middle and lower clivus. This approach is used extensively for the resection of tumors such as meningiomas, chondrosarcomas, chordomas, and petrous apex cholesteatomas. It illustrates many important techniques used in surgery of the middle cranial base.

A hemicoronal or curved temporal incision is extended into the preauricular and cervical regions to expose the temporalis muscle, the zygomatic arch, the parotid gland, and the upper neck. (As discussed in the description of the bicoronal incision, the temporal fascia and fat

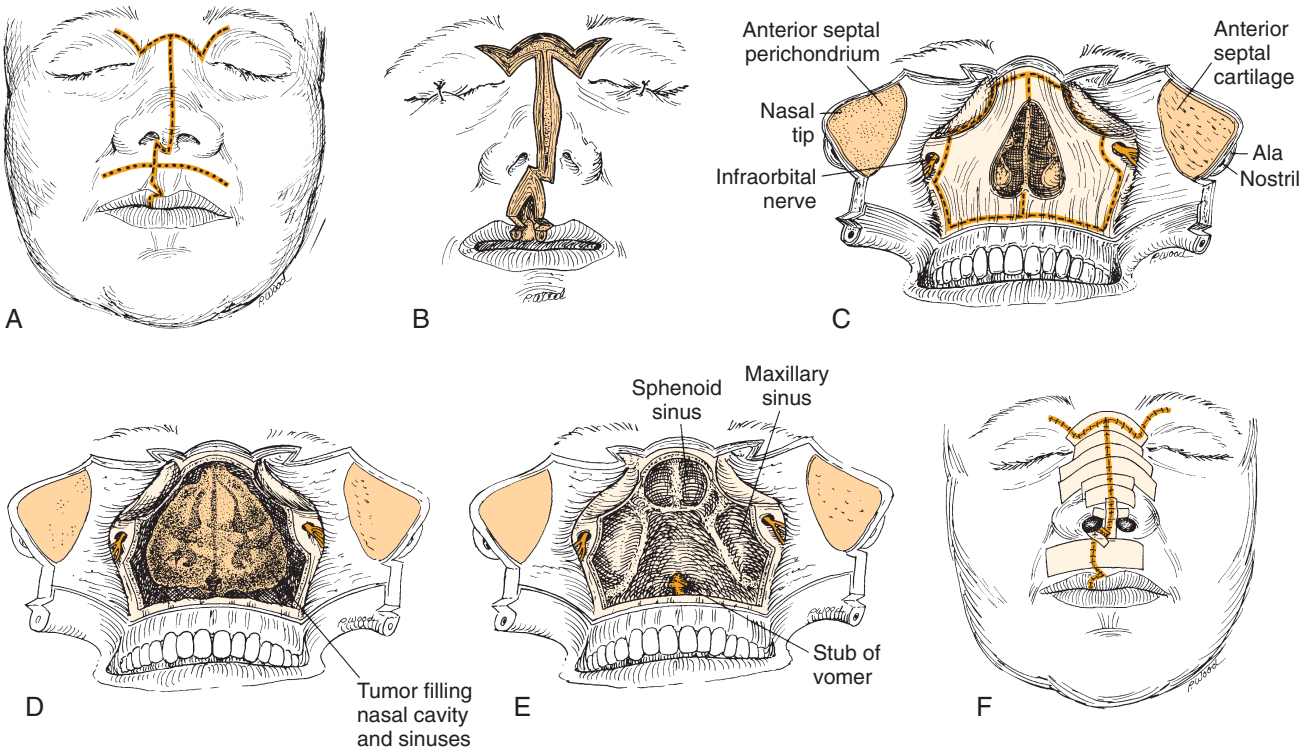

Figure 174-31. Midfacial split approach to the cranial base. **A,** Incisions. Horizontal incision across the nasion allows access to the upper orbits. Midline nasal incision divides skin and separates upper and lower lateral cartilage to expose septum; it is carried inferiorly along one side of the philtrum, splitting the upper lip. Gingivolabial incision *(dotted line)* facilitates exposure of the maxilla bilaterally. **B,** Partially developed facial soft tissue flaps, with attached nasal cartilages. **C,** Soft tissue flaps fully developed and reflected laterally to expose the orbitonasomaxillary skeleton. Proposed osteotomy sites are indicated by *dotted lines*. **D,** Midfacial exposure after osteotomies and temporary removal of bone segments, including portions of the medial and inferior orbital walls, the anterior maxilla, and the nasal bones. When necessary, osteotomies also may include the hard palate, which gives additional access to the oropharynx, the nasopharynx, and the clivus. In this example, tumor fills the posterior nasal cavity and nasopharynx and extends into the sphenoid sinus. **E,** After removal of the tumor, which included the nasal septum, the medial maxillae, and the sphenoid rostrum. **F,** Final closure. Orbitonasomaxillary bone segments are replaced and secured using microplates, and soft tissues are primarily repaired. Adhesive strips are applied, and silicone nasal stents are used for 1 week postoperatively.

pad are elevated with the skin flap, thereby protecting the frontal branch of the facial nerve). The cervical extension is used to gain access to the ICA, the internal jugular vein, and cranial nerves IX through XII, and to help identify the facial nerve extratemporally. The parotid gland is mobilized away from the sternocleidomastoid muscle, and the underlying styloid complex is divided, revealing the high cervical ICA, the internal jugular vein, and cranial nerves IX to XII. Next, the zygomatic arch is osteotomized with a reciprocating saw and removed temporarily, thereby allowing the temporalis muscle to be reflected inferiorly to expose the greater wing of the sphenoid and the underlying infratemporal fossa. In cases in which the lesion also involves the orbit (e.g., sphenoid wing meningiomas), the lateral orbital wall and rim may also be osteotomized and removed along with the zygoma. The condyle of the mandible may be retracted or resected to expose the spine of the sphenoid and its nearby structures, including the middle meningeal artery, cranial nerve division V3, and the ICA at its entrance into the carotid canal. More medially, V2 can be identified just anterior to the lateral pterygoid plate.

A low temporal craniotomy is performed, and, by extradural dissection, the temporal lobe is elevated off of the middle fossa floor, thereby revealing the intracranial landmarks: the GSPN, the middle meningeal artery, and cranial nerve divisions V2 and V3.

By progressive removal of the greater wing of the sphenoid, cranial nerve divisions V3 and V2 may be completely unroofed. If necessary, the sphenoid sinus may be opened by removing the bone between V2 and V3 and the base of the pterygoid plates. The superior orbital fissure may be unroofed in the same way.

The intrapetrous course of the ICA may be exposed, beginning at the infratemporal opening of the carotid canal and extending to just above the foramen lacerum (where the ICA enters the cavernous sinus). This is accomplished with a high-speed drill and a diamond burr using a technique analogous to that used for facial nerve decompression. To facilitate this exposure, the middle meningeal artery and the GSPN should first be divided, and the high cervical ICA with its fibrous periosteal sheath should be rendered accessible by removal of the styloid process and the surrounding bone. The ICA may be displaced forward out of its bony canal; this is useful whenever the lesion involves the clivus medial to the ICA or the petrous part of the temporal bone posterior to the ICA. The inferior aspect of the cavernous sinus may also be approached from this exposure.[7]

The sequence and extent of exposure at the skull base depend on the nature of the lesion to be extirpated. Certain steps in the procedure may be eliminated or modified to suit the needs of the particular case. For example, it is only necessary to dissect the neck if the procedure will benefit from proximal control of the ICA or from low exposure of the internal jugular vein or cranial nerves IX through XII. Otherwise, the cervical extension may be avoided.

After the lesion has been extirpated, the wound is irrigated with antibiotic solution and carefully inspected. Any dural openings are meticulously repaired primarily or by using grafts of pericranium, temporalis fascia, or fascia lata. In addition to repairing dura, every effort is made to reconstitute a functional barrier between the intracranial compartment and the visceral spaces of the head and neck. Usually this does not include any attempt to rebuild the bony basicranium. Instead,

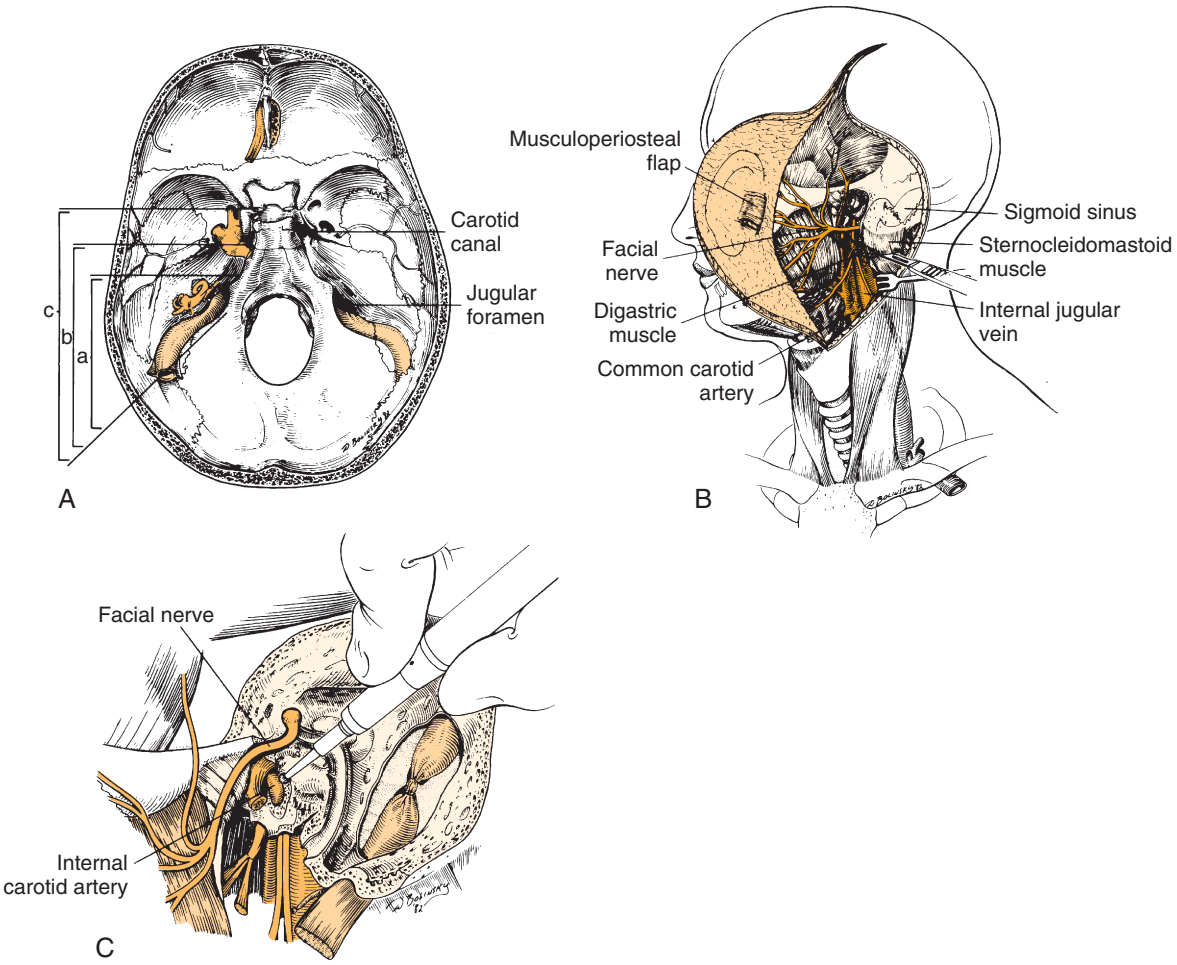

Figure 174-32. Infratemporal approach to the cranial base. **A,** Areas of the skull base accessible by each of the variations of the infratemporal approach: a, jugular foramen and petrous apex; b, clivus; c, parasellar and parasphenoid compartments. **B,** Postauricular incision with extensions into the scalp and neck. Sternocleidomastoid and digastric muscles have been divided at the mastoid tip, thereby allowing access to the carotid artery and the internal jugular vein. The facial nerve has been identified extratemporally. The external auditory canal has been closed by turning the musculoperiosteal flap. **C,** Radical mastoidectomy has exposed the sigmoid sinus (which has been ligated) and the middle fossa dura. The tympanic membrane and ossicles have been removed. The facial nerve has been unroofed and transposed anteriorly. By progressive drilling, the internal carotid artery can be traced distally through its petrous course to reach the cavernous sinus. Similarly, additional bone removal anteriorly will allow access to the parasellar region and the nasopharynx. *(From Fisch U, Pillsbury HC, Sasaki CT. Infratemporal approach to the skull base. In: Sasaki CT, McCabe BF, Kirchner JA, eds.* Surgery of the Skull Base. *Philadelphia: JB Lippincott; 1984.)*

efforts are focused on the interposition of reconstructive soft tissues—vascularized tissues, whenever possible—into the surgical defect.

Any communications with the aerodigestive tract are identified. These most often include the sphenoid sinus, the nasopharynx, and the eustachian tube. If the sphenoid sinus has been opened, its mucosa is removed, and it is obliterated with autogenous fat or by the transfer of vascularized temporalis muscle medially. If the eustachian tube has been entered, it is denuded of mucosa, packed with fat or muscle, sutured closed, and covered with vascularized temporalis muscle. If the nasopharynx has been violated, the opening is filled with a temporalis muscle flap or a free microvascular flap (e.g., rectus abdominis), depending on the size of the defect. Special care is taken to ensure that the ICA is covered with vascularized tissue throughout its course, particularly in cases in which the nasopharynx has been entered. Failure to protect the ICA in this way may result in continued exposure of the artery to bacterial contamination from the upper aerodigestive tract, with subsequent carotid rupture.

Finally, the zygomatic and craniotomy bone segments, which were previously displaced by osteotomy, are returned to their anatomic positions and secured appropriately. If the temporalis muscle has not been used as a reconstructive flap, it is returned to the temporal fossa. If a temporalis flap has been used, the temporal fossa may be filled with autologous fat from the abdomen or thigh to minimize the temporal fossa depression. Soft tissue closure then follows.

Transfacial Approaches

Transfacial exposure of the cranial base, particularly of the lateral compartment (middle cranial base region), is not a new concept. Operative procedures for the removal of neoplasms from this region were described by several authors in the 1960s.[103,104] These early procedures, which were used initially for the radical resection of malignant tumors, resulted in unacceptably high morbidity and mortality rates and considerable deformity, largely because methods to adequately reconstruct major cranial base defects were not yet available. With the introduction of craniofacial disassembly techniques and vascularized reconstructive flaps, it has become possible to dismantle the facial skeleton, to extirpate deep-seated lesions, and to perform functional reconstruction to a greater extent than ever. Accordingly, lesions of the lateral and central compartments are more amenable to surgery.

A transfacial approach to this region is desirable because it eliminates the viscerocranial skeleton as an obstacle to exposure, thereby opening up the entire infratemporal fossa and the nasal cavity, the

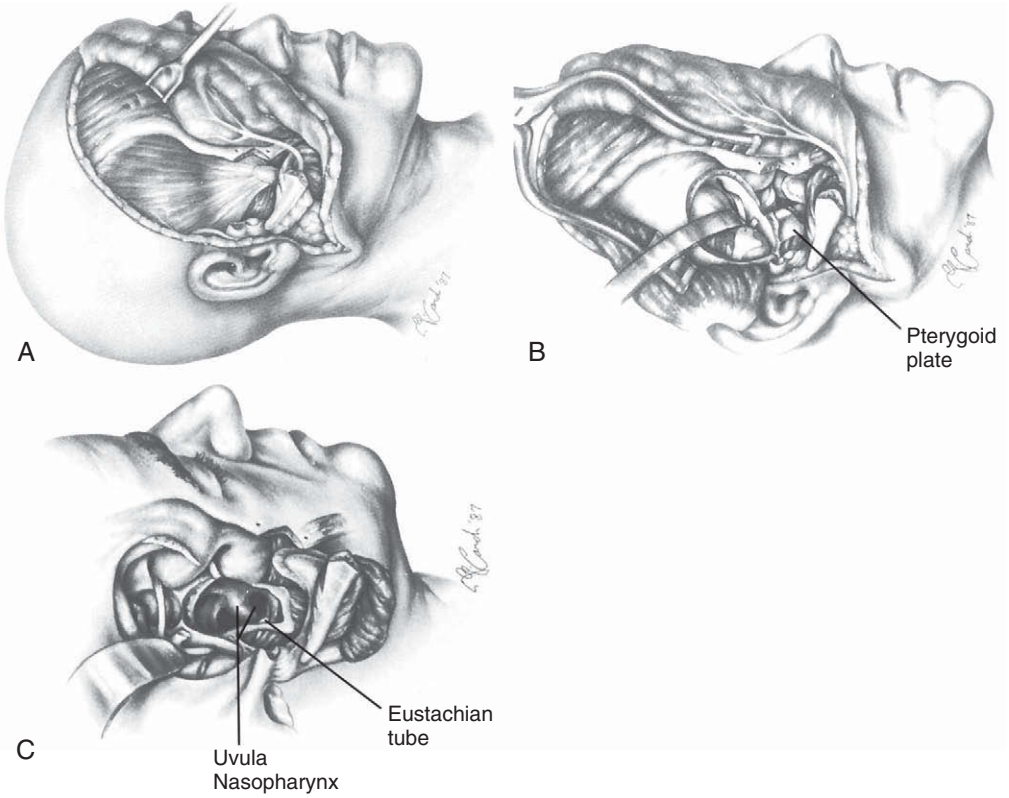

Figure 174-33. Lateral facial approach to the cranial base. **A,** A temporal and preauricular incision is used to expose the temporalis muscle and the zygomatic arch. The zygoma is sectioned to allow access to the insertion of the temporalis at the coronoid process. The frontal branch of the facial nerve is preserved within the skin flap. **B,** With the temporalis muscle retracted, the greater wing of the sphenoid is partially removed (subtemporal craniectomy). Retraction of the temporal lobe dura reveals branches of the trigeminal nerve and attachment of the pterygoid plate at the base of the sphenoid bone. **C,** Division of the maxillary nerve (V2) and resection of the pterygoid plate expose the nasopharynx. *(From Gates GA. The lateral facial approach to the nasopharynx and infratemporal fossa.* Otolaryngol Head Neck Surg. *1988;99:321-325.)*

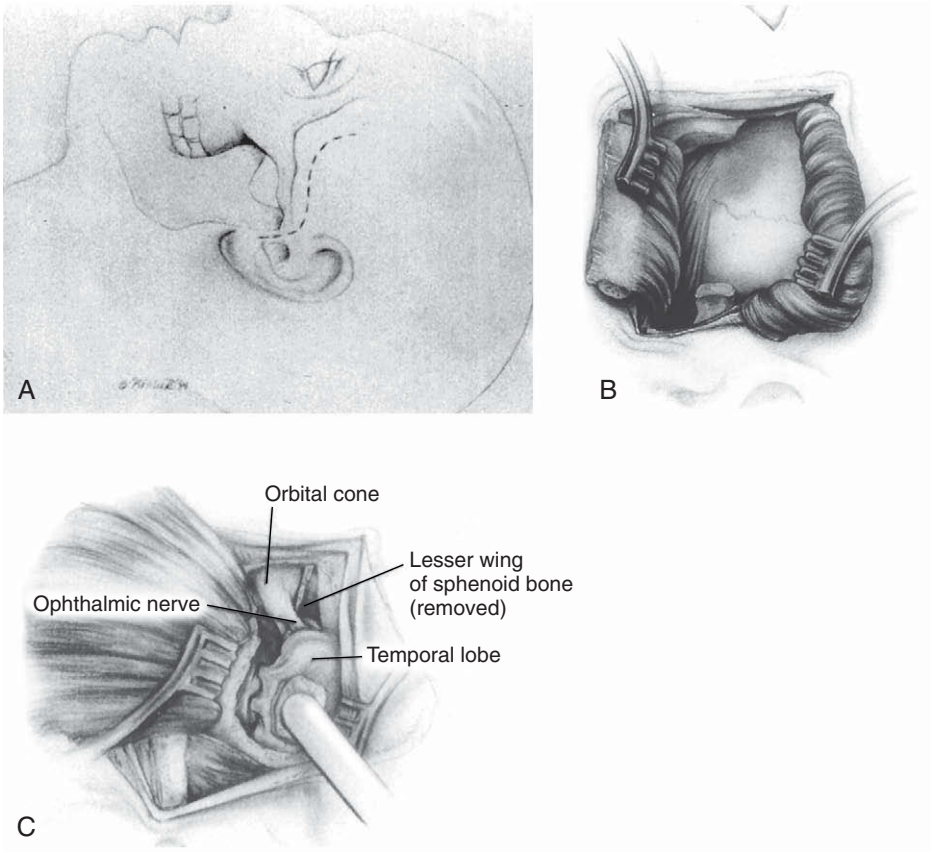

Figure 174-34. Lateral transtemporal sphenoid approach to the cranial base. **A,** Incision. **B,** Retraction of the temporalis muscle to expose the greater wing of the sphenoid. This muscle should be preserved intact and reflected inferiorly if muscle flap reconstruction of a skull base defect is anticipated. The zygomatic arch has been temporarily removed. **C,** Subtemporal craniectomy exposes the orbital apex and the floor of the middle cranial fossa. *(From Holliday MJ. Lateral transtemporal-sphenoid approach to the skull base.* Ear Nose Throat J. *1986;65:153-162.)*

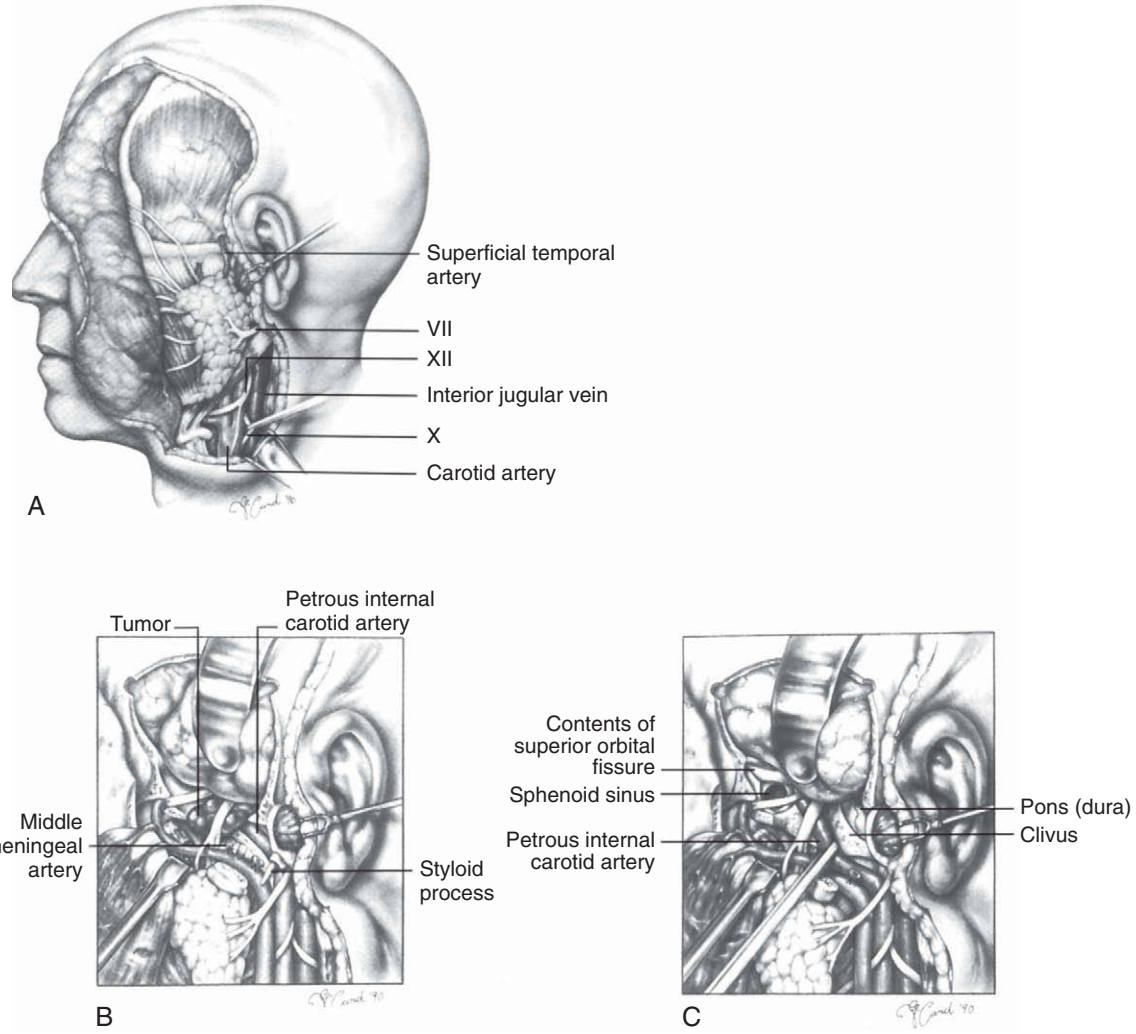

Figure 174-35. Subtemporal-preauricular and infratemporal approach to the cranial base. **A,** Initial exposure. Distal branches of the facial nerve are for demonstration only; in most cases they are not dissected. The frontal branch is included with the skin flap and retracted inferiorly. **B,** The temporalis muscle has been reflected inferiorly *(bottom left)* after temporarily removing the zygomatic arch, the mandibular condyle has been resected, and a subtemporal craniectomy has been performed. After dividing the styloid complex, the carotid artery is traced distally through part of its course within the temporal bone to separate it from the tumor. The facial nerve need not be transposed, and the conducting mechanism of the middle ear remains undisturbed in this approach. **C,** Progressive dissection exposes the clivus, the sphenoid sinus, the superior orbital fissure, and the adjacent neural and vascular structures. *(From Sekhar LN, Janecka IP. Intracranial extension of cranial base tumors and combined resection: the neurosurgical perspective. In: Jackson CG, ed.* Surgery of Skull Base Tumors. *New York: Churchill Livingstone; 1991.)*

nasopharynx, the pterygopalatine fossa, and the sphenoid region to direct access all at once. The facial translocation approach (Fig. 174-36)[17] is such a procedure.

Incisions are made in the face and scalp as shown in Figure 174-36A. The horizontal incision connects a lateral rhinotomy with a hemicoronal incision to create superior and inferior soft tissue flaps. (At this stage, the frontal branches of the facial nerve are identified using evoked EMG, tagged, and divided to be reconnected later on during the procedure. This horizontal incision is a key element in the exposure because it allows a single, unified surgical field that is unhampered by the need to work alternatively from separate cranial and facial incisions that limit the surgeon's ability to develop three-dimensional exposure at the cranial base.) The soft tissue flaps are then elevated in the subperiosteal plane from the zygoma and maxilla. Periorbita is likewise elevated from the lateral, inferior, and medial orbital rims and walls. A reciprocating saw is used to create osteotomies, and the orbitozygomaticomaxillary skeletal segment is temporarily removed.

After the temporalis muscle is reflected inferiorly, the subtemporal skull base is fully exposed, and further dissection proceeds as dictated by the lesion, using the same skull base landmarks as for other approaches. Intracranial exposure is readily obtained, if needed, by subtemporal craniectomy or by frontal or temporal craniotomy. Similarly, the pterygoid plates and muscles may be removed, thus revealing the nasopharynx, the sphenoid sinus, and the clivus. As mentioned previously, facial translocation may therefore be used as an approach to the central compartment of the middle cranial base; it provides a unified surgical field with access to both compartments.

At the completion of the extirpation, reconstruction follows the same principles as discussed. After dural repair, the temporalis muscle is used to fill the skull base defect. Because of its appreciable soft tissue bulk, the muscle also is useful for obliterating the maxillary sinus space. There it serves as a vascularized tissue bed for the orbitozygomaticomaxillary bone segment, which is replaced and secured as a free bone graft. Bony stabilization is achieved with sutures or miniplates. If it has not been resected for oncologic reasons, the infraorbital nerve (which was transected during the development of the lower facial soft tissue flap) is rerouted through its maxillary canal and reconnected to its distal trunk by suture neurorrhaphy. The frontal branches of the facial nerve also are repaired. The nasolacrimal system is stented to prevent dacryostenosis, and the medial canthal ligament is secured to the lacrimal

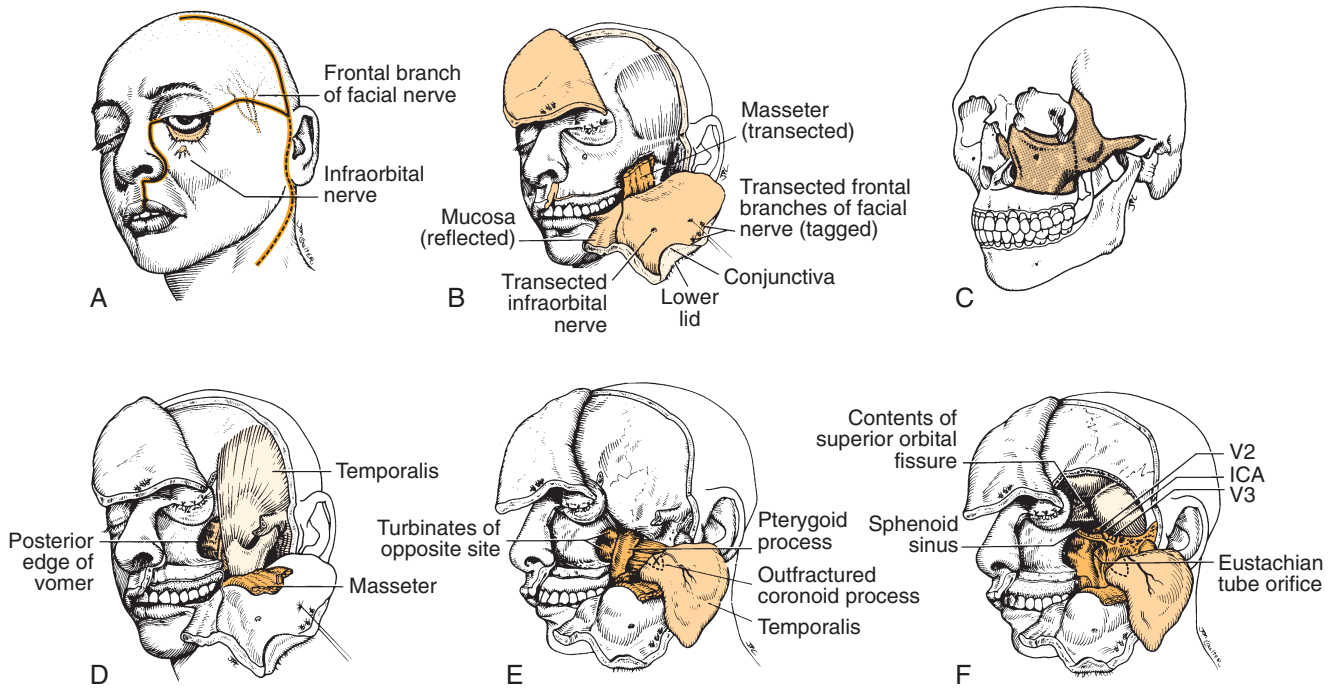

Figure 174-36. Facial translocation approach to the cranial base. **A,** Incisions. Infraorbital portion of an incision is made in the inferior fornix of the conjunctiva. The lip-splitting portion may be omitted in many cases in which low maxillary exposure is not needed. **B,** Facial soft tissue flaps fully developed and reflected to expose the craniofacial skeleton. **C,** Outline of osteotomies of the orbitozygomaticomaxillary skeleton. **D,** Exposure after temporary removal (translocation) of the orbitozygomaticomaxillary segment. **E,** Inferior reflection of the temporalis muscle—enhanced by outfracture of the coronoid process—gives access to the pterygoid region and the nasopharynx. **F,** Subtemporal craniectomy allows exposure of the middle fossa floor, the sphenoid sinus, and the adjacent neural and vascular structures. ICA, internal carotid artery. *(From Janecka IP, Sen CN, Sekhar LN, Arriaga M. Facial translocation: new approach to cranial base.* Otolaryngol Head Neck Surg. *1990;103:413-419.)*

crest. Temporary tarsorrhaphy helps support this repair during the early postoperative period. Closure of skin incisions completes the procedure.

Postoperatively, tarsorrhaphy sutures may be removed within 1 week; nasolacrimal stents remain in place for 6 to 8 weeks. In most patients, infraorbital sensation returns within 3 to 6 months, and frontalis muscle function resumes in 6 to 9 months.

The facial translocation technique is valuable for obtaining the broad exposure needed when managing large or advanced lesions of the lateral and central compartments of the middle cranial base, especially those in which much of the lesion is extracranial. Because of its modular nature, it also can be applied in various scaled-down versions that are tailored for dealing with smaller cranial base lesions.

Intracranial Approaches

Temporal craniotomy is the traditional, standard neurosurgical method for gaining access to the middle cranial fossa. For intradural lesions within the temporal lobe or for extradural lesions along the lateral convexity of the middle fossa, it is the most direct approach.[105] For lesions at the cranial base, however, temporal craniotomy alone is often less than ideal, because it requires (by virtue of its superolateral-to-inferomedial orientation) significant retraction or, in some cases, resection of the brain to reach a target area. Such brain manipulation can result in intraoperative and postoperative cerebral edema; temporal encephalomalacia; deficits of speech, memory, and cognition; and long-term risk of seizure disorder. These risks increase as the location of the lesion becomes more medial and more temporal lobe retraction is required.

Still, temporal craniotomy alone is useful for some limited lesions of the lateral compartment–middle cranial base region, such as meningiomas of the sphenoid wings. Risks of intracranial complications can be minimized by designing the craniotomy bone flap as low as possible, thereby giving a more basal and direct access to the skull base, with less need for brain retraction. The limiting factors are the petrous ridge of the temporal bone and the zygomatic arch. When preoperative imaging suggests that these structures will impede adequate exposure, a wider approach should be chosen, such as the subtemporal-infratemporal, lateral facial, or transtemporal sphenoid approach.

The middle fossa approach of House[106] involves the use of temporal craniotomy as a preliminary step to reach the IAC by the removal of bone from the superior surface of the petrous portion of the temporal bone. Because most lesions in these areas originate in relation to the seventh and eighth cranial nerves, this approach is considered in more detail in Chapters 171, 176, and 177.

When the skull base is involved only to a minimal extent and the lesion is mostly infracranial, a subtemporal craniectomy may be performed (see Figs. 174-33 and 174-36). In this procedure, only a limited area of cranial bone is removed, generally as a safe means of establishing a superior margin in resecting, for example, the base of the pterygoid plates and surrounding soft tissue. Subtemporal craniectomy may be performed by inserting a Kerrison or a similar rongeur extradurally inside the foramen ovale and gradually removing bone in the direction of the foramen rotundum. The resulting bone window allows for the protection of the middle fossa dura under direct vision while the subjacent lesion is removed.

For many lesions of the lateral compartment of the middle cranial base, temporal craniotomy and subtemporal craniectomy are used in combination with transtemporal, infratemporal, or transfacial exposure. These intracranial approaches provide added control over the neural and vascular structures in the region. As is true for all transcranial operations for cranial base lesions, close cooperation between the otolaryngologist and the neurosurgeon is essential.[107]

Reconstruction

As stated previously, use of locoregional vascularized flaps is the primary reconstructive method for skull base defects; however, support is growing for microvascular reconstruction of these defects, especially

large ones, or in revision surgery, when locoregional flaps may be unavailable.[53,54,108]

In a retrospective study, Newman and associates found a 95% success rate in reconstructing anterior and middle skull base defects. Despite a 30% overall complication rate, no cases of intracranial complication or CSF leak or deaths were associated with this reconstruction.[109] Other authors have experienced higher rates of complications including flap failure and intracranial problems (cerebrovascular accident [CVA], syndrome of inappropriate antidiuretic hormone [SIADH], meningitis, seizure, pneumocephalus, CSF leak), although most reported series have been smaller with a retrospective study design.[110]

The progression of expanded endoscopic approaches has also necessitated the development of nonvascularized materials to repair skull base defects. Acellular dermis, hydroxyapatite cement, free abdominal fat, autologous cartilage and bone grafts may be used to match each defect. Of importance, hydroxyapatite cement must not be allowed to contact the sinonasal mucosa, to avoid infection and failure.[2,111]

Postoperative Concerns

Initial Postoperative Care

All patients initially are admitted to an intensive care unit that is staffed by nurses who are experienced in neurosurgical and head-and-neck surgical care. Consultants in critical care medicine, internal medicine, and other specialties actively participate in management, when appropriate. Typically, patients will have a continuous recording of the electrocardiogram, oxygenation status (monitored by pulse oximetry), and systemic blood pressure (monitored by arterial catheter). In specific circumstances, Swan-Ganz catheters or central venous lines are used to assess cardiovascular status and fluid balance. These parameters are crucial for maintaining optimal intravascular volume, cardiac output, and cerebral blood flow.

Given the complexity of intraoperative fluid and electrolyte management, close monitoring of hematologic and chemical parameters is essential (i.e., hemoglobin; hematocrit; platelets; prothrombin and partial thromboplastin times; sodium, potassium, calcium, magnesium, and phosphorus concentrations; and serum osmolality). The appropriate replacement of blood components maintains oxygen delivery (erythrocytes) and prevents coagulopathy (platelets, plasma). Electrolyte balance is especially important, because deviation from physiologic norms can lead to confusion, agitation, stupor, or seizure activity, which may be otherwise mistaken for surgery-related neurologic insults.

Pharmacologic therapy plays an important role in the prevention of complications. Antibiotics are routinely given, beginning just before surgery and for a duration of 24 to 48 hours afterward. Inhibitors of gastric acid secretion are given postoperatively to reduce the chance of stress ulceration and gastrointestinal bleeding, and they are continued until the patient is tolerating adequate enteral nutrition. Anticonvulsants are used to prevent seizures whenever significant frontal or temporal lobe manipulation is necessary. Once instituted, anticonvulsant therapy should be periodically monitored using serum drug levels and should be continued for at least 6 to 12 months after surgery. Analgesic therapy is limited in most cases to the judicious use of intramuscular codeine, which has a mild, predictable (and reversible) effect on mental status and respiratory drive. Stronger narcotics and benzodiazepines and related sedatives generally are avoided because of their more profound and less predictable influences on these functions, potentially confounding accurate neurologic assessment.

For most procedures in which the cranial vault has been opened, a CT scan is obtained on postoperative day 1. This scan serves as a baseline study for comparison with any subsequent studies performed to investigate neurologic complications if they arise.

Prophylaxis against deep vein thrombosis and pulmonary embolism includes the intraoperative and postoperative use of dynamic compression stockings. In addition, patients are mobilized as soon as feasible after surgery.

Complications

Many of the most serious complications of cranial base surgery are related to the brain,[14] and their prevention and management demand neurosurgical expertise. First, brain manipulation, especially by excessive retraction, can lead to cerebral edema, subdural hematoma, and acute brain dysfunction specific to the anatomic site involved. In the long term, it may cause encephalomalacia and deficits of speech, memory, and cognitive and intellectual functions. Brain injury (by contusion) also may predispose the patient to seizures, especially when the temporal lobe is affected. These problems are best prevented by obtaining adequate surgical exposure through basal bone removal and craniofacial disassembly (thereby limiting the need for significant brain manipulation) and by intraoperative brain relaxation through the use of subarachnoid CSF drainage, hyperventilation, and corticosteroids.

Pneumocephalus may occur as a sudden event during the early postoperative period, after a patient attempts (against advice to the contrary) to blow his or her nose, thereby inadvertently insufflating air through the dural closure. This rapid-onset pneumocephalus may cause intracranial mass effect (tension pneumocephalus), with confusion, obtundation, and progressive neurologic deterioration. Pneumocephalus also may develop more slowly as a result of the overdrainage of CSF from a lumbar spinal drain, which can cause a siphon effect, drawing air upward from the nasal cavity. Preventive measures therefore include the following: (1) keeping patients intubated or tracheotomized until they are alert enough to follow instructions; and (2) judiciously using spinal drainage at a conservative rate and for a short duration. In most patients after cranial base surgery, the lumbar catheter is allowed to drain 25 to 50 mL every 8 hours and is removed after 24 to 72 hours. When pneumocephalus is suspected, prompt CT assessment is necessary. Small collections of air may be observed, whereas larger ones may require decompression by needle aspiration (through an osteotomy site or burr hole) or by reexploration and reinforcement of the reconstruction. In cases of acute-onset pneumocephalus, the administration of 100% oxygen is a useful adjunctive measure to enhance resorption of the intracranial air. Lumbar subarachnoid CSF drainage should be discontinued in the presence of any significant pneumocephalus.

CSF fistula is another brain-related complication that is important because of its association with meningitis. It usually manifests as rhinorrhea, but it also may cause the patient to experience a salty taste in the throat. If the nature of nasal discharge is doubtful, the β_2-transferrin assay may be used to confirm or rule out the presence of CSF.[112] For small-volume leaks, which are the most common, observation and continued spinal drainage (or serial lumbar spinal taps) usually suffice. For high-volume leaks (grossly apparent rhinorrhea) or those that are persistent, careful sinonasal endoscopy or CT cisternography can be used to localize the fistula site (i.e., frontal, ethmoid, sphenoid, eustachian tube, temporal bone), after which operative repair frequently is needed. A CSF fistula may manifest as otorrhea or as wound discharge; the management principles are similar in either case. In some situations, the original repair simply needs to be revised; in others, additional vascularized tissue may be needed to obliterate the fistula site. Such tissues may include temporalis muscle, galeal, or free microvascular flaps (e.g., rectus abdominis, omentum). In selected cases, the closure may be augmented by the judicious use of free autogenous fat grafts or fibrin glue. The risk of reconstructive failure is substantially decreased if the original repair is performed using vascularized local tissue.[69]

CNS infections, including meningitis and brain abscess, also may occur. These complications can lead to extreme neurologic morbidity or death. Preventive measures include the use of perioperative antibiotics, strict adherence to sterile technique, the minimization of dural exposure to the aerodigestive tract, and meticulous attention to reconstruction, as outlined earlier. Management consists of antimicrobial drugs (given intravenously and sometimes intrathecally) and surgical exploration when necessary to drain abscesses or to obliterate sources of continued bacterial contamination.

Cerebrovascular complications are of major concern during the perioperative period. These events may have several causes. Carotid rupture may occur as a result of infection (and pseudoaneurysm) or excessive adventitial dissection. This complication is often sudden and fatal, but it may sometimes be preceded by a sentinel bleed, which, if recognized as such, can provide time for prompt intervention (i.e., reexploration and bypass or permanent ICA occlusion). Thrombotic

ICA occlusion or embolism into distal vessels can cause stroke and death. The strict maintenance of systemic blood pressure intraoperatively and postoperatively avoids hypotension, which can precipitate ICA thrombosis. Careful surgical technique when working in the vicinity of the ICA and cautious postoperative anticoagulation in high-risk patients may decrease embolic phenomena. Although the incidence of stroke in cranial base surgery is low, stroke is a source of considerable morbidity when it does occur; this morbidity can usually be lessened when the cranial base team adopts a vigorous approach to intervention and rehabilitation. Intervention after stroke should include the tight control of the hemodynamic factors that affect cerebral blood flow to prevent extension of the infarct. It also should include measures to ensure optimal homeostasis, such as control of the airway and oxygenation, maintenance of fluid and electrolyte balance, and nutritional support. Rehabilitation of stroke patients (and of patients with neurologic deficits from other causes) is greatly facilitated by input from professionals in rehabilitation medicine, physical and occupational therapy, and speech therapy.

Cranial nerve deficits deserve special consideration because of their profound impact on postoperative recovery and quality of life. The sacrifice of olfactory nerves (cranial nerve I) often is regarded as a minor disability, but it can contribute to significant malnutrition in some patients who, because of anosmia, no longer enjoy eating. Deficits of cranial nerves II, III, IV, and VI lead to visual disability of variable degree, depending on the extent of surgical trauma and nerve involvement by the disease process itself. Dense palsies of the extraocular muscles seldom recover completely. Patients in whom such deficits are predictable should therefore be prepared for the loss of binocular vision before surgery is undertaken. Extraocular muscle surgery by the ophthalmologist can sometimes help to compensate for such deficits. The loss of visual acuity is a potential complication of anterior cranial base surgery, but it is unusual unless the optic nerves are compromised preoperatively. In these patients, recovery of optic nerve function is difficult to predict.[63]

Deficits of the fifth and seventh nerves are dangerous, mainly because of loss of sensation (V1) or protection (VII) of the cornea. Tarsorrhaphy and careful attention to ocular lubrication are important means of preventing keratitis and visual loss in these cases. Fifth nerve dysfunction, in addition to the obvious sensory deficits, may also cause significant problems with mastication (and with nutrition) because of the loss of motor innervation to the pterygoid, temporalis, and masseter muscles (V3). Seventh nerve paralysis can be a tremendous social and emotional handicap and should be rehabilitated aggressively whenever possible. Eighth nerve deficits, although rarely reversible, usually can be compensated for (when unilateral) by audiologic and vestibular training.

Deficits of cranial nerves IX, X, and XII are potentially life-threatening, especially when they occur together, because of aspiration and dysphagia with subsequent pneumonia and malnutrition. Management of patients in whom these deficits are present preoperatively or expected postoperatively should include tracheostomy and gastrostomy at the time of the cranial base surgery or very soon thereafter, before complications compromise the patient's recovery. Laryngoplasty or injection of collagen or fat into the unilaterally paralyzed larynx also may be beneficial. Patients who have multiple bilateral deficits of cranial nerves IX, X, and XII are extremely difficult to rehabilitate. Management of these cases nearly always involves permanent tracheostomy and gastrostomy and, sometimes, laryngotracheal separation.

Many complications of cranial base surgery are not brain related (Table 174-2) and can affect any physiologic system. Despite the relatively less invasive appearance of endoscopic skull base surgery, these procedures carry many of the same risks of more traditional open skull base procedures. CSF leaks remain the most common complication, and additional serious complications including damage to cranial nerves, meninges, blood vessels, and venous sinuses can present in the immediate postoperative period. Delayed complications include meningitis, brain abscess, and tension pneumocephalus, anosmia, and synechia formation. Visual loss or changes may result from damage to the optic nerve or chiasm or orbital contents, including extraocular musculature. Damage to the pituitary stalk also may result with transsphenoidal approaches.[38] Postoperative diabetes insipidus rates are reported to be as much as 50% lower in endoscopic cases.[113]

Table 174-2

Non-neurologic Complications in Cranial Base Surgery

Type of Complication	Examples
Cardiovascular	Myocardial infarction Hypotension Congestive heart failure
Respiratory	Pulmonary embolism Pneumonia Aspiration Respiratory distress syndrome Pulmonary edema
Hematologic	Post-transfusion coagulopathy Anemia Deep venous thrombosis
Renal	Acute tubular necrosis Drug-induced nephropathies
Infectious	Pneumonia Sepsis Thrombophlebitis Wound infections Viral hepatitis Urinary tract infections
Gastrointestinal	Malnutrition Stress ulcer Gastrointestinal bleeding
Metabolic	Derangements of serum sodium, potassium, calcium, phosphorus, magnesium, and other minerals
Endocrine	Diabetes insipidus Syndrome of inappropriate antidiuretic hormone Hypopituitarism
Hepatic	Drug-induced hepatitis Cholestasis

Outcomes

Although the many technical advances and multispecialty approaches in cranial base surgery have expanded the ability to achieve complete and safe tumor resection, the question remains regarding the extent that patients benefit from these invasive procedures. A 1995 review of 40 years of cranial base surgery for carcinomas and sarcomas provided some insight into the answer to this question.[114] Three general eras of major advancement in the field were analyzed for survival outcomes and trends in morbidity.

From the 1960s to the 1970s, surgical pioneers achieved 3- and 5-year survival rates of 52% and 49%, respectively. The application of skull base approaches was limited, and tumors were designated as inoperable if they extended intracranially or into the pterygopalatine fossa. Morbidity rates were significant, with overall infection rates of 54% and CSF leaks occurring in 31% of cases. From the 1970s to the 1980s, the number of cranial base cases and the number of surgeons

performing these cases increased. The major advancement was that patients with tumors previously designated as inoperable underwent attempts at complete tumor resection. Reports included tumors that extended intracranially and intracerebrally and into the pterygopalatine fossa. The 3-year survival rates rose slightly from 57% to 59%, with only limited reports of 5-year survival rates in the range of 49%. Infection rates ranged from 4% to 48%, but the incidence of CSF leaks dropped from 3% to 19%. From the 1980s to the 1990s, a multispecialty approach to cranial base surgery was introduced. Complications dropped significantly, with infection rates ranging from zero to 28% and CSF leaks diminishing from 2% to 4%. Another significant factor is that local disease control improved greatly. The 3-year survival rate increased from 67% to 74%, and the 5-year survival rate increased from 56% to 70%.[114] A recent multi-institutional study of patients undergoing craniofacial resection revealed 5-year overall, disease-specific, and recurrence-free survival rates of 48%, 53%, and 45%, respectively. Poor prognostic indicators included positive surgical margins and intracranial and orbital involvement. Melanoma and undifferentiated carcinoma carried the worst outcomes and esthesioneuroblastoma and low-grade sarcoma the best.[115]

In a large multi-institutional study of craniofacial resection patients, postoperative complications occurred in 36%. Increased risk of postoperative complications was found with the following factors; comorbid illness, previous radiation therapy, and tumor extension. Overall wound complication rates were less than 20%.[116]

Although reports in the literature are encouraging,[117-119] a need for controlled investigations and prospective clinical trials remains. This undertaking will prove to be very difficult. Unlike head and neck cancer, in which most cases are squamous cell carcinoma, cranial base tumors are less common and more varied in histologic type. Compounding the problem of broad histologic variation is the lack of uniformity of location and patterns of invasion of tumors in this complex anatomic region. When these factors are taken into consideration, investigations with adequate patient numbers to yield an accurate reflection of outcomes become nearly impossible. Multi-institutional studies may be required to circumvent these difficulties and to provide important information about the value of cranial base surgery. Such collaborative efforts may help establish the consistent use of primary and adjuvant therapies for tumors of the cranial base.

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CHAPTER ONE HUNDRED AND SEVENTY-FIVE

Transnasal Endoscopic-Assisted Surgery of the Anterior Skull Base

Aldo Cassol Stamm

Shirley S. N. Pignatari

Key Points

- Effective and safe treatment of lesions involving the anterior skull base and brain depends on several factors, including a careful clinical history, preoperative evaluation and imaging studies, familiarity with regional anatomy and cerebrovascular physiology, and refined surgical technique.
- Technologic advances such as image-guided systems and enhanced endoscopic surgical techniques and equipment have facilitated approaches to the anterior skull base and brain, optimizing the surgical exposure and reducing the risk of complications while avoiding extensive brain retraction and nerve damage.
- Use of a multidisciplinary team approach has increased survival and decreased complication rates from skull base surgery, and this type of surgery is contraindicated without such a team. The multidisciplinary team should include neurosurgery, otolaryngology, anesthesiology, pathology, endocrinology intensive care, and paramedical staff, familiar with the care of patients at risk for significant neurologic sequelae.
- The development of new reconstruction techniques for closing dural defects has been assisted by the use of pedicled nasal septal flaps and has enabled more extensive resections and reduced complication rates. However, infection, cerebrospinal fluid leakage, and difficulty controlling intradural bleeding still present a challenge, and a frank discussion of the risk of these problems is essential for the patient to give informed consent.

The past decade has brought about technologies and insights that have revolutionized our strategy in treating patients with lesions involving the skull base, orbit, and optic nerve. Our work developed from microscopic anterior skull base approaches that aimed to avoid nerve and brain retraction and were developed along two basic anterior midline routes, the transoral and the transnasal.[1-3] We have expanded the scope of the surgery we perform through these approaches and have expanded our armamentarium in achieving postresection reconstruction. Effective and safe treatment of lesions involving the skull base still presents significant challenges, however, because although we have improved postresection reconstruction, the expanded scope of surgery has added risks to the procedures.

Surgical Anatomy

Anterior Cranial Fossa

The anterior cranial fossa is composed of the orbital portion of the frontal bone anteriorly, the cribriform plate of the ethmoid bone centrally, and the lesser wing and body of the sphenoid bone posteriorly (Fig. 175-1A). The cribriform plate is located in a midline depression between the orbital roofs and separates the anterior cranial fossa from the nasal cavity. It has 15 to 20 small foramina that transmit the olfactory nerves from the superior nasal mucosa to the olfactory bulb. The crista galli projects upward at the median anterior portion of the cribriform plate and serves as the site of attachment of the falx cerebri. Between the crista galli and the frontal crest, the foramen cecum in the frontoethmoidal suture transmits an emissary vein to the superior sagittal sinus. The anterior and posterior ethmoidal branches of the ophthalmic artery exit the orbit by passing through the ethmoidal foramina to enter the cranium at the anterolateral and posterolateral edges of the cribriform plate, respectively (see Fig. 175-1B). Posteriorly, the cribriform plate articulates with the sphenoid body, which from anterior to posterior is the site of the planum sphenoidale, limbus sphenoidale, chiasmatic sulcus, tuberculum sella, pituitary fossa, and the dorsum sella. The planum sphenoidale forms the roof of the posterior ethmoid sinus and the anterior part of the sphenoid sinus and borders on the optic canals posterolaterally.[4]

Nasal Cavity

The nasal cavity is wider below than above and is bounded superiorly by the anterior cranial fossa, laterally by the orbits and the maxillary sinus, and inferiorly by the hard palate. This cavity is divided sagittally

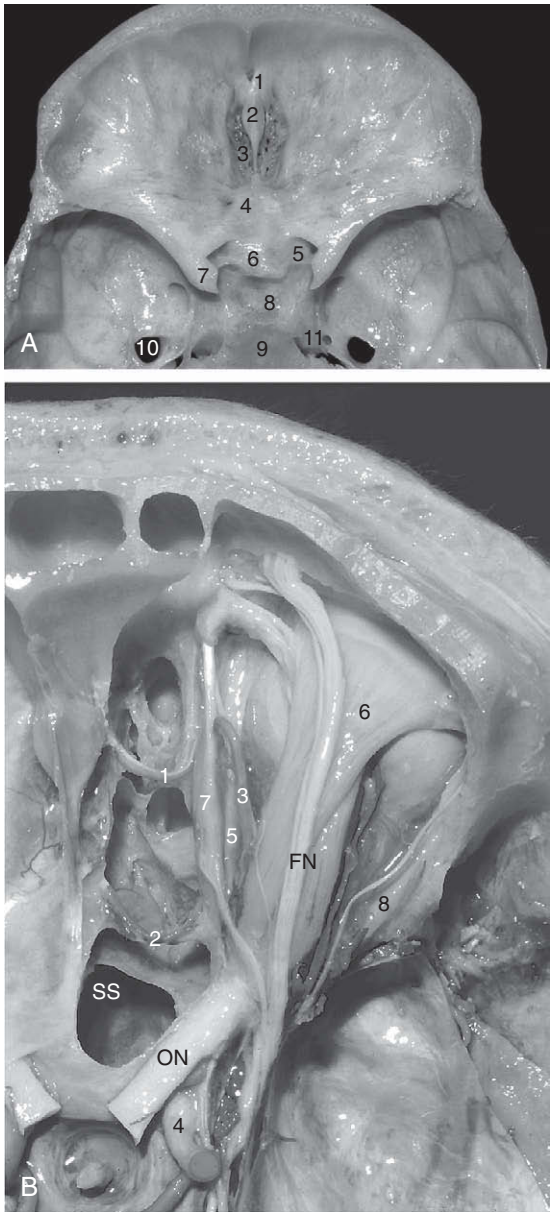

Figure 175-1. **A**, Cranial view of the skull base: 1, foramen cecum; 2, crista galli; 3, cribriform plate; 4, planum sphenoidale; 5, optic canal; 6, chiasmatic sulcus; 7, anterior clinoid process; 8, pituitary fossa; 9, dorsum sellae; 10, foramen ovale; 11, foramen lacerum. **B,** Cranial view of the skull base after removal of the floor of the anterior cranial fossa: 1, anterior ethmoidal artery; 2, posterior ethmoidal artery; 3, ophthalmic artery; 4, internal carotid artery; 5, medial rectus muscle; 6, superior rectus muscle; 7, oblique rectus muscle; 8, lateral rectus muscle. FN, frontal nerve; ON, optic nerve; SS, sphenoid sinus.

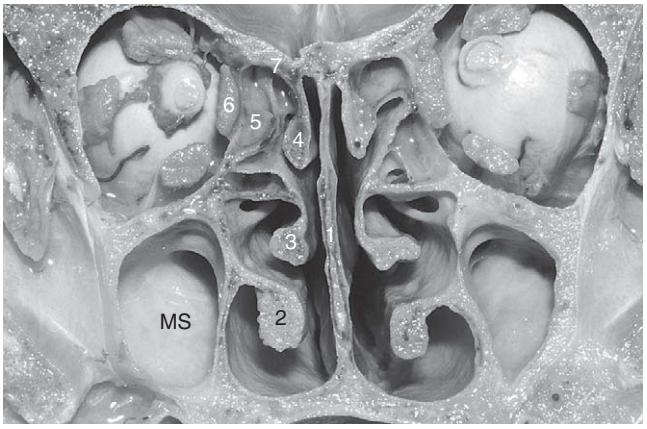

Figure 175-2. Posterior view of a coronal section of the nasal cavity and paranasal sinuses: 1, nasal septum; 2, inferior nasal turbinate; 3, middle turbinate; 4, superior turbinate; 5, ethmoid sinus; 6, medial rectus muscle; 7, fovea ethmoidalis. MS, maxillary sinus.

Figure 175-3. Lateral nasal wall, right side: 1, nostril; 2, inferior meatus; 3, inferior turbinate; 4, middle meatus; 5, middle turbinate; 6, superior meatus; 7, superior turbinate; 8, sphenoid sinus; 9, pharyngeal opening of the eustachian tube.

by the nasal septum, which is formed anteriorly and superiorly by the perpendicular plate of the ethmoid bone, posteriorly and inferiorly by the vomer, and anteroinferiorly by septal cartilage (Fig. 175-2). The nasal cavity opens anteriorly onto the face through the pyriform anterior nasal aperture and is continuous posteriorly with the nasopharynx at the posterior nasal apertures.

Each posterior nasal aperture measures approximately 25 mm vertically and 13 mm transversely and is bordered above by the anterior aspect of the sphenoid body that contains the sphenoid sinus, below by the posterior margin of the hard palate (horizontal plate of the palatine bone), medially by the nasal septum (vomer), and laterally by the medial pterygoid plate of the sphenoid.

The lateral nasal wall usually has three medially directed projections: the superior, middle, and inferior nasal turbinates or conchae (Fig. 175-3). The airway passages below these turbinates are termed the superior, middle, and inferior nasal meatuses, respectively. The paired sphenoethmoidal recesses are located above and behind the superior turbinate and in front of the upper anterior aspect of the sphenoid body. They are the sites of the paired sphenoid ostia that form the communication between the nasal cavity and the sphenoid sinus (Fig. 175-4). The upper half of the lateral nasal wall corresponds to the medial orbital wall. From anterior to posterior, it is composed of the frontal process of the maxilla, the lacrimal bone, and the orbital plate of the ethmoid bone (lamina papyracea), each separated from the next by a vertical suture. The extremely thin lacrimal and ethmoid bones contain the ethmoid air cells that separate the nasal cavity from the orbit. The nasolacrimal groove and canal (the site of the lacrimal sac and nasolacrimal duct, respectively) pass downward in front of the anterior end of the middle turbinate and open into the inferior nasal meatus. The frontoethmoidal suture is located at the level of the roof of the nasal cavity and the cribriform plate.

The anterior and posterior ethmoidal foramina transmit the anterior and posterior ethmoidal arteries and nerves and are located in, or just above, the frontal ethmoidal suture. These arteries and nerves exit the ethmoidal foramina and enter the anterior cranial fossa at the lateral

Figure 175-4. Oblique view of the right lateral nasal wall and sphenoid sinus region after removal of the nasal septum and the anterior wall of the sphenoid sinus: 1, ethmoid sinus; 2, sphenoid ostia; 3, sphenoid sinus; 4, anterior sella wall; 5, internal carotid artery; 6, trigeminal nerve; 7, superior arch of the choana.

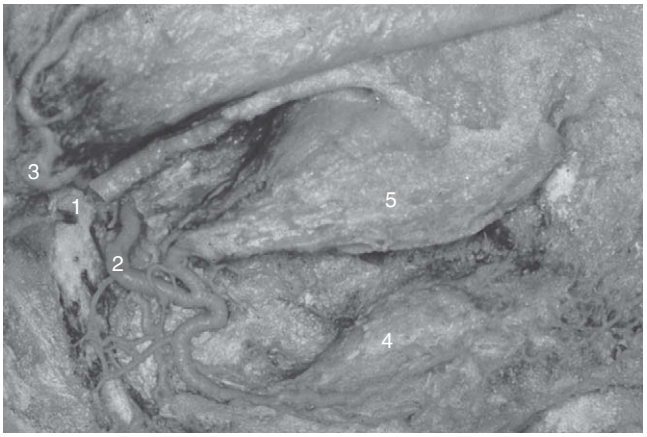

Figure 175-5. Lateral nasal wall demonstrating the terminal branches of the maxillary artery: 1, sphenopalatine foramen; 2, posterior lateral nasal artery; 3, septal artery; 4, inferior turbinate; 5, middle turbinate. *(Courtesy of Prof. Joao Navarro.)*

edge of the cribriform plate. The anterior ethmoidal artery is a terminal branch of the ophthalmic artery and supplies the mucosa of the anterior and middle ethmoid air cells and the dura covering the cribriform plate and the planum sphenoidale. The posterior ethmoidal artery usually is smaller than the anterior and is absent in nearly 30% of persons.[5] It supplies the mucosa of the posterior ethmoid cells and the dura of the planum sphenoidale. The distance from the anterior lacrimal crest of the maxilla's frontal process to the anterior ethmoidal foramen is 22 to 24 mm; the distance between the anterior and posterior ethmoidal foramina is 12 to 15 mm, and that between the posterior ethmoidal foramina and the optic canal usually is 3 to 7 mm. In the midline transfacial procedures, these ethmoidal arteries can be divided in a subperiorbital plane along the medial orbital wall. Care should be taken to prevent damaging the optic nerve, which sometimes is located immediately behind the posterior ethmoidal foramen (see Fig. 175-1B).

The inferior half of the lateral nasal wall comprises part of the medial wall of the maxillary sinus. It is formed anteriorly by the maxilla and posteriorly by the perpendicular plate of the palatine bone. The base of the middle turbinate attaches to the lateral nasal wall near the junction of the orbit and the maxillary sinus. Thus, the medial wall of the maxillary sinus is made up of the lateral wall of the middle and inferior nasal meati and the inferior turbinate. The maxillary sinus communicates with the middle nasal meatus through an opening located in the medial wall just below the roof of the sinus.[4]

The pterygopalatine fossa is situated between the posterior wall of the maxillary sinus anteriorly and the pterygoid process of the sphenoid posteriorly. The pterygopalatine fossa contains the pterygopalatine ganglion, which receives the nerve of the pterygoid canal (vidian nerve), the maxillary nerve just as it leaves the foramen rotundum, the internal maxillary artery (one of the two terminal branches of the external carotid artery), and the maxillary artery's two terminal branches, the posterior lateral nasal artery and the septal artery. Both of these terminal branches enter the nasal cavity through the sphenopalatine foramen just above the caudal aspect of the bony end (not the soft tissue end) of the middle turbinate. The septal artery courses along the roof of the nasal cavity toward the sphenoid rostrum and divides into a number of vessels that extend to the septum and the superior nasal walls. In the lateral wall of the nasal cavity, the posterior lateral nasal artery divides and provides nourishment to the turbinates and meatal spaces[6] (Fig. 175-5).

Paranasal Sinuses

The paranasal sinuses are the frontal, ethmoid, sphenoid, and maxillary. The frontal sinus consists of two large cells separated by an intersinus septum. The anatomic relationships of the sinus are mainly with the roof of the orbit, agger nasi cells, and the anterior cranial fossa. It drains

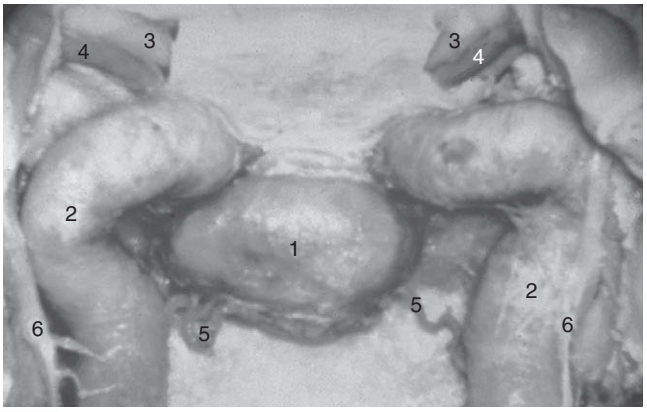

Figure 175-6. Frontal view of the central skull base after removal of the walls of the sphenoid sinus and the dura: 1, pituitary gland; 2, internal carotid artery; 3, optic nerves; 4, ophthalmic arteries; 5, inferior hypophyseal arteries; 6, sympathetic nerves. *(Courtesy of Drs. I. Inoue and A. Rhoton.)*

through the frontal recess into the middle meatus. The ethmoid sinus is composed of two groups of air cells: The anterior air cells drain into the middle meatus and the posterior group into the superior meatus.

Posterior ethmoid cells can become pneumatized far laterally and to some degree superiorly to the sphenoid sinus, in which case they are called *sphenoethmoid cells* (Onodi cells). The optic nerve and carotid artery may project into these cells, where they can be damaged during a surgical procedure. The ethmoid sinus is in intimate relation with the medial orbital wall and the floor of the anterior skull base.

The sphenoid sinus varies in shape and size and is asymmetrically divided into two parts by an irregular septum. When the sphenoid sinus is well developed, its thin lateral wall is the medial wall of the cavernous sinus. The intracavernous portion of the internal carotid artery is the most medial structure within the cavernous sinus, and in well-developed sphenoid sinuses it produces a serpiginous bony elevation in the lateral wall of the sinus called the *carotid prominence*. The carotid prominence is divided into presellar, infrasellar, and retrosellar segments.[11] The presellar segment corresponds to the anterior vertical segment and the anterior bend of the intracavernous portion of the internal carotid artery. The infrasellar segment corresponds to the short horizontal portion of the carotid, and the retrosellar segment reflects the posterior bend and posterior vertical segment (Fig. 175-6).

The optic canal often is partially encircled by the sphenoid sinus and creates a bony bulge in the superoanterior portion of its lateral wall.

The bony depression between the optic canal and the presellar segment of the carotid prominence is called the *opticocarotid recess*; it extends a variable distance into the optic strut. The bony lateral sphenoid sinus wall over the internal carotid artery and the optic nerve usually is very thin and may be absent in some areas. Although Lang[7] observed that the canal of the optic nerve was dehiscent in 6% of cases, Seibert[8] found that 57% of the optic nerves bulged into the sphenoid sinus and 1% had no bony canal. Seibert[8] also noted that the horizontal portion of the intracavernous carotid artery extended prominently into the sphenoid sinus in 67% of cases and that its bony covering was dehiscent in 6%. In his series, the maxillary nerve was prominent in the sphenoid sinus in 48% of specimens and dehiscent in 5%, and the pterygoid nerve (vidian nerve) was prominent 18% of the time.

Just below the tuberculum sellae, where they are closest to each other, the average distance between the left and right internal carotid arteries is 13.9 mm (range, 10 to 17 mm). At the anterior wall of the sella, the carotid arteries are separated by 20 mm (range, 13 to 26.5 mm), and at the level of the clivus, the distance between them is 17.4 mm (range, 10.5 to 26.5 mm).[9]

The maxillary sinus has thin walls that face the lower nasal cavity medially, the orbit superiorly, the infratemporal fossa posterolaterally, the pterygopalatine fossa posteromedially, and the soft tissue of the cheek anterolaterally. The maxillary sinus provides a transantral avenue for extending a midline surgical approach for more extensive lateral exposures of the cavernous sinus and the infratemporal fossa.[4]

Nasopharynx

The nasopharynx is situated behind the posterior nasal apertures where the septum and the inferior turbinate end. It is partially separated from the oropharynx below by the soft palate. The roof of the nasopharynx is formed by the mucoperiosteum of the upper clivus. The posterior nasopharyngeal wall is formed in successive layers by the mucosa, the superior pharyngeal constrictor muscle, the prevertebral fascia, and the longus capitis muscle. It abuts the mid- to lower clivus, the anterior aspect of the foramen magnum, and the anterior arch of the atlas (see Fig. 175-3). The pharyngeal tubercle is a small bony elevation located in the midline at the junction of the middle and lower clivus approximately 1 cm above the foramen magnum and serves as the site of attachment of the pharyngeal raphe of the superior pharyngeal constrictor muscle. The longus capitis muscles are attached to the clivus lateral to the pharyngeal tubercle on each side.

The eustachian tube, also termed the pharyngotympanic or auditory tube, opens into the lateral wall of the nasopharynx immediately posterior to the medial pterygoid plate. The fossa of Rosenmüller (pharyngeal recess) is located at the junction of the lateral and the posterior walls of the nasopharynx and projects laterally just behind the orifice of the eustachian tube. At the posterolateral depths of the fossa of Rosenmüller, only a thin layer of fibroconnective tissue separates the mucosa from the cervical internal carotid artery. The horizontal segment of the internal carotid artery in the petrous portion of the temporal bone is located immediately medial and posterior to the eustachian tube.[4]

Clivus

The clivus separates the nasopharynx from the posterior cranial fossa. It is composed of the posterior portion of the sphenoid body (basisphenoid) and the basilar part of the occipital bone (basiocciput), and it is further subdivided into upper, middle, and lower thirds. The upper third of the clivus is at the level of the sphenoid sinus and is formed by the basisphenoid bone including the dorsum sella. The middle clivus corresponds to the rostral part of the basiocciput and is located above a line connecting the caudal ends of the petroclival fissures. The lower third of the clivus is formed by the caudal part of the basiocciput. The intracranial surface of the upper two thirds of the clivus faces the pons and is concave from side to side.

The extracranial surface of the clivus gives rise to the pharyngeal tubercle at the junction of the middle and lower clivus. The upper clivus faces the roof of the nasopharynx, which extends downward in the midline to the level of the pharyngeal tubercle (Fig. 175-7).

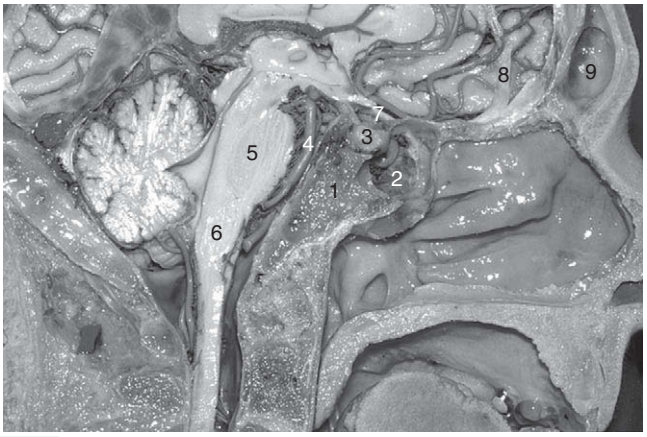

Figure 175-7. Midline sagittal section of the cranium: 1, clivus; 2, sphenoid sinus; 3, pituitary gland; 4, basilar artery; 5, pons; 6, medulla; 7, optic nerve; 8, frontal lobe; 9, frontal sinus.

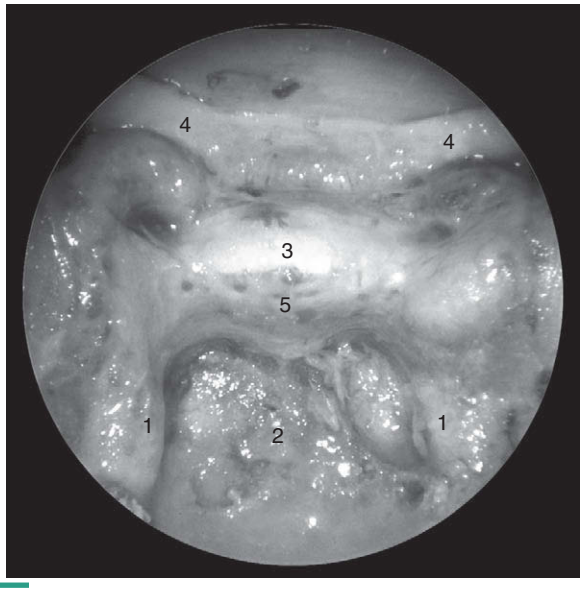

Figure 175-8. Endoscopic view of the posterior wall of the sphenoid sinus: 1, prominence of the internal carotid arteries; 2, clivus; 3, anterior sellar wall; 4, optic nerves; 5, intercavernous sinus.

The upper and middle clivus are separated from the petrous portion of the temporal bone on each side by the petroclival fissure. The basilar venous plexus is situated between the two layers of the dura of the upper clivus and is related to the dorsum sella and the posterior wall of the sphenoid sinus. It forms interconnecting venous channels between the inferior petrosal sinuses laterally, the cavernous sinuses superiorly, and the marginal sinus and epidural venous plexus inferiorly. The basilar sinus is the largest communicating channel between the paired cavernous sinuses.

Retroclival Region

When all the bone of the posterior and lateral walls of the sphenoid sinus has been removed, only periosteum covers the underlying anatomy (Fig. 175-8). The tectorial membrane protects the clival dura in the middle and lower clivus. When the external layer of the dura is opened, the basilar venous plexus and cranial nerve VI (the aducens nerve) on each side can be seen. The average distance between the two abducens nerves at the dural emergence is 19.8 mm.[10]

On opening the inner layer of the clival dura, the view through the 0-degree endoscope reveals the vertebral arteries, basilar artery and its branches (superior cerebellar arteries, anterior inferior cerebellar

Figure 175-9. Endoscopic view of the posterior fossa after the removal of the posterior wall of sphenoid sinus and upper clivus: 1, basilar artery; 2, internal carotid arteries; 3, optic nerves and chiasm; 4, pituitary gland and pituitary stalk; 5, brainstem.

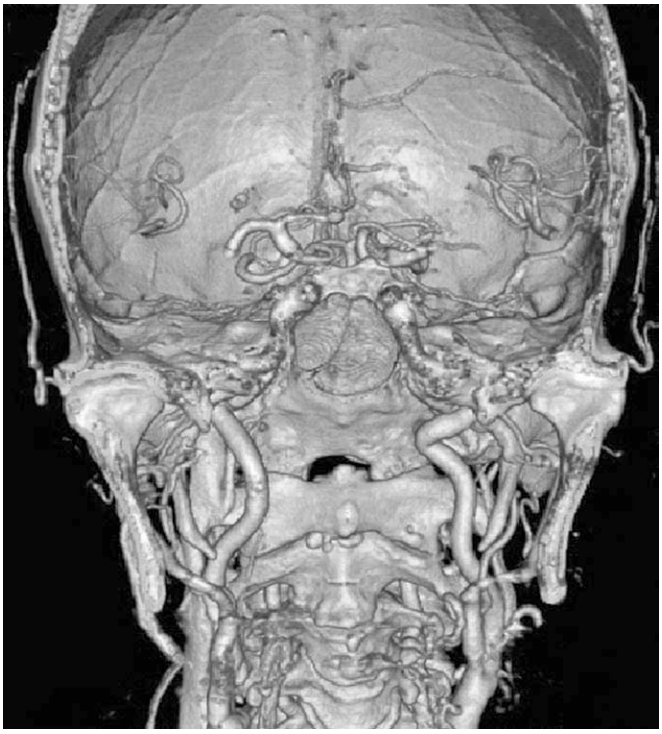

Figure 175-10. Coronal projection, computed tomographic angiography of the head and neck, showing the main vessels of the skull base region. Note the course of the internal carotid arteries and its division.

arteries), posterior cerebral arteries, brainstem, mammillary bodies, and the intradural pathway of cranial nerves III, IV, V, and VI. Just above the pituitary gland, the pituitary stalk, optic nerves, and optic chiasm can be seen. By introducing a 30-degree or 45-degree angled endoscope, it also is possible to view the cerebellopontine angle and cranial nerves VII and VIII, as well as the lower cranial nerves and the retrosellar region (Fig. 175-9).

Preoperative Assessment

The success of any skull base procedure depends on several factors, including a thorough clinical history, a careful preoperative evaluation, a well-developed surgical plan, and physician-patient conversations that include a frank discussion of the diagnosis, surgical plan, possible complications, and the roles of both the physician and the patient in the anticipated postoperative care plan.

Physical examination includes endoscopic assessment of the nasal cavity performed with the patient in a semisitting position. The nasal cavity is prepared with a topical anesthetic solution containing a vasoconstrictor. The examination is performed with rigid 4.0-mm 0-degree, 30-degree, and 70-degree endoscopes. In children, the flexible 3.2-mm endoscope is preferable, and occasionally a straight 2.7-mm endoscope is used.

Appropriate radiographic imaging studies always include diagnostic computed tomography (CT) and are essential in the assessment of all skull base lesions. CT permits assessment of critical anatomic information important during surgery including the presence and extent of erosions of the skull base; integrity of the medial orbital wall; position of the anterior skull base vessels; integrity and degree of aeration of the paranasal sinuses (particularly the sphenoid sinus); location and presence of intersinus septa; position of the internal carotid arteries, optic nerves, and cavernous sinuses; relationships between the ethmoid sinuses and the orbits and optic nerves; relationship between the roof of the ethmoid sinuses and the cribriform plate; and the presence of an Onodi cell. In assessing the frontal sinus, it is important to verify the presence of the intersinus septum and the relationship between the frontal sinus and the supraorbital ethmoid cells, the distance between the anterior and posterior sinus walls, and any bony erosions of the orbit, anterior wall, or posterior wall (anterior cranial fossa).

If the image-guided system is to be used, a multislice helical CT study is mandatory and should be performed as close as possible to the day of surgery. The images are stored on a compact disc and are used at surgery to provide a three-dimensional reconstruction of the patient's skull base region.

CT angiography is a robust technology that allows simultaneous visualization of bony and vascular structures. Venous and arterial structures can be visualized separately in the venous and arterial phases, or seen together. "Angio-CT" is especially useful in assessing the internal carotid and vertebrobasilar systems. Venous structures of particular interest include the cavernous sinus, the inferior aspect of the superior intercavernous sinuses, and the basilar venous plexus. This technology allows us to better plan surgical procedures[11] (Fig. 175-10).

Magnetic resonance imaging (MRI) is important to demonstrate the morphology of the soft tissues and the presence of liquid, but it is not helpful in assessing bony architecture. It helps to differentiate between neoplastic or inflammatory tissue and retained secretions, and to assist in clarifying the diagnosis of skull base malformations when meningoencephalocele, meningocele, or nasal glioma is suspected. MRI also is valuable to demonstrate erosion of the lateral sphenoid wall.

Magnetic resonance angiography (MRA) assesses the structure of medium-sized to large arteries and should be considered in patients with erosion of the lateral and posterior sphenoid walls to visualize the relationship between the basilar and internal carotid arteries.

Although conventional angiography is not routinely performed, it can provide essential information in some specific situations. If a lesion is suspected to involve, impinge on, or displace the internal carotid artery, the surgeon must have accurate preoperative knowledge of the position of the internal carotid artery and its relationship with the lesion, especially when the transnasal-transsphenoidal approach is contemplated (accessing the skull base through the posterior and lateral walls of the sphenoid sinus). Angiography also is helpful to verify the functional integrity of the circle of Willis and the extent of any carotid artery narrowing or occlusion, and to differentiate an aneurysm from tumor.

Operative Technique

The patient is prepared in the usual fashion for transnasal endoscopic-assisted surgery. The patient lies in a supine position on the operating

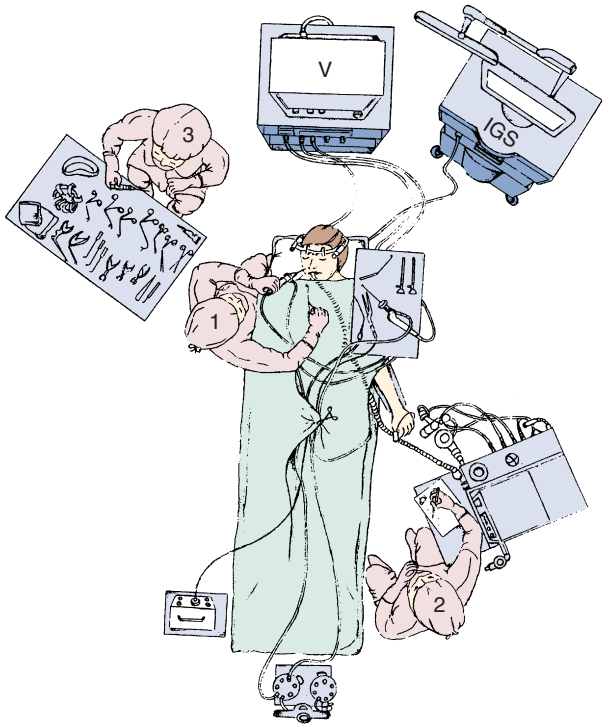

Figure 175-11. Surgical team setup in the operating room: 1, surgeon; 2, anesthesiologist; 3, nurse. IGS, image-guided system; V, video system.

table with the dorsum elevated 30 degrees, and with the head slightly extended and turned toward the surgeon. Head fixation is used when the navigation guidance system is required.

Transnasal endoscopic-assisted surgery of the skull base is performed with the patient under general controlled hypotensive anesthesia (Fig. 175-11). Compressed-rayon surgical sponges (Cottonoids) containing epinephrine, 1:2000 concentration, are placed in the nasal cavity, especially over the areas of surgical access. These Cottonoids are left in place for approximately 10 minutes before the surgical procedure is begun. If the surgical access is through the nasal septum, the septum is infiltrated with lidocaine and epinephrine, 1:100,000. When the surgery includes the pterygopalatine and zygomatic fossae and the sphenoid, the region of the sphenopalatine foramen is infiltrated with approximately 2.0 mL of the same concentration solution with an angulated 25-gauge spinal needle after first aspirating. If necessary, epinephrine-soaked Cottonoids are used for hemostasis during the surgery. If a CSF fistula is suspected, intrathecal fluorescein can be introduced at the beginning of the surgical procedure to facilitate its precise location.[12] If the use of the image-guided system is contemplated, the head frame is set up for calibration.

Instrumentation

Most skull base surgical procedures are performed with the endoscope attached to an endocamera and a video monitoring system. Endoscopes angled 0 degrees, 45 degrees, and 70 degrees can be used. In conjunction with KARL STORZ Endoscopy-America, Inc. (Culver City, California), we are developing a 5-mm wide-angle 0-degree telescope for these procedures to increase the field of view and illumination.

Although conventional surgical instrumentation also can be used, most of the microendoscopic surgical instruments for these cases are slightly longer and thinner, but just as strong or stronger. Most have an articulation located at the edge, allowing adequate visualization of the operative field. Extra-long handpieces for the surgical drill are essential and are used almost exclusively with diamond burrs of various sizes. Suction cannulas should have a blunted edge to avoid unnecessary trauma and mucosal bleeding. We recommend a micro-Kerrison punch to remove thin delicate bony plates such as those of the ethmoid air cells near the medial wall of the orbit and the bony canal of the optic nerve.

Monopolar and bipolar electrocautery can be used to control bleeding intraoperatively. Bleeding originating from branches of the anterior and posterior ethmoid arteries is more safely controlled by bipolar coagulation. Bleeding from the basilar venous plexus is not coagulated. Compression with oxidized cellulose (Surgicel) packing and obliteration of involved bony channels by diamond burrs are helpful measures.

Powered instrumentation was developed initially for soft tissue shaving and represents a major advance in transnasal endoscopic-assisted surgery. These instruments—microsurgical débriders, or "microdébriders"—have multiple functions, including suction, cutting, and irrigation. At present, newer instruments with curved blades and burrs are able to remove bone such as ethmoidal cells, drill out the frontal sinus, and debulk some tumors. The newer microsurgical débriders also produce a more precise cut of the diseased tissue, avoiding mucosal stripping, and are provided with continuous irrigation, which improves visualization and diminishes blood loss.

The new-generation image-guided systems are precise and have been very helpful in some cases of skull base surgery. These three-dimensional navigation systems provide important information about the location of anatomic structures in the operative field and create an individual anatomic map generated from a preoperative helical CT study. The advantage of this system lies in diminishing the chances of surgical complications, because it delineates the exact anatomic location of an instrument. On the basis of our experience in skull base surgery with such image-guided systems (Evolution computerized image-guided tracking system, Medtronic-Xomed, Jacksonville, Florida), we believe that they are very safe and precise and can be particularly helpful for surgery in patients who have unusual or high-risk anatomic variations, who have diseases involving the frontal sinus recess or sphenoid sinus that put the carotid artery and the optic nerves at risk, or who have recurrent or extensive disease.[13] The navigation system currently in use in our practice allows visualization of CT or magnetic resonance images or both simultaneously. This greatly improves the surgeon's ability to identify the extradural and intradural extent of the various lesions.

Transnasal Surgical Approaches to the Skull Base

Several transnasal approaches to the skull base have been described. The choice of the appropriate transnasal technique for each patient depends on the nature, location, and extent of the lesion. We currently are using the following extended transnasal surgical approaches:

- Transsphenoidal: transsellar and parasellar, transclival, and petrous apex
- Transcribriform
- Transtuberculum-transplanum
- Transmaxillary/transpterygoid/infratemporal
- Craniocervical junction

The transsphenoidal approaches (transsellar and parasellar, transclival, and petrous apex) require previous sphenoidectomy, which can be accomplished by several ways as briefly described below: direct transnasal access, transseptal access, transseptal transnasal access, and transethmoidal access. Regardless of the chosen expanded approach, the first step of the surgical procedure is the creation of a large pedicled septal flap originating at and based on the vascular pedicle of the sphenopalatine foramen. The extent of this flap is determined by the chosen approach. A vertical incision is made approximately 1 to 2 cm from the caudal edge of the nasal septum, followed by two horizontal incisions, one parallel to and just above the floor of the nasal cavity and the other approximately 0.8 cm to 1.0 cm beneath the upper limit of

the nasal septum. The inferior incision borders the superior edge of the choana toward to the sphenopalatine foramen. The flap should be subperichondrial and subperiosteal, preserving the vascular pedicle. During the procedure, the flap can be safely placed into the maxillary sinus cavity through a large middle meatus antrostomy. This maneuver avoids any obstruction of the surgical field by the flap.[14]

Transsphenoidal Approach

The great majority of the transnasal endoscopic skull base operations directly involve the sphenoid sinus, which is the focal point for several of the surgical approaches. Although the operative lesion may involve the sella or parasellar region, the clival region, or the petrous apex, the specific nature and location of the lesion will determine the technique to access the sphenoid sinus. Choices include the direct transnasal, transseptal (anterior incision, posterior incision), transseptal-transnasal (binostril approach), and transnasal plus transethmoidal (middle turbinate removal) approaches. The direct transnasal approach is used for removal of lesions involving the roof of the nasal cavity without involvement of the ethmoid sinus, lesions of the nasopharynx, and some lesions involving the sphenoid sinus. The transseptal approach is used primarily for removal of lesions involving the sphenoid sinus and sella such as pituitary adenomas.[15] The transethmoidal approach is useful for disease localized to the ethmoid sinus, the roof of the ethmoid sinus, the orbits, or lesions involving both the ethmoid and sphenoid sinuses.

Direct Transnasal Access

With direct transnasal access, the procedure is carried out through one nostril. If the nasal cavity is very narrow and the passage of the endoscope and operating instruments is limited because of a septal deviation, septoplasty is done first. After identification of the middle and superior turbinates, the posterior region of the nasal septum, and the choanal arch, the ostium of the sphenoid sinus is probed with the seeker-palpator. If diseased tissue such as polyps obstructs the access to the sphenoid recess, a microsurgical débrider can be helpful. To improve access, the superior turbinate is identified and removed with a through-cutting forceps. When the surgical access is very narrow, the posterior portion of the middle turbinate also can be removed by means of microscissors.

The initial opening of the sphenoid sinus is made with a micro-Kerrison punch, beginning at the ostium. The sphenoidotomy is enlarged inferiorly, with care taken to avoid damaging or cauterizing the septal artery that crosses the anterior wall of the sphenoid sinus in that region. If both sphenoid sinuses are to be surgically exposed, the mucoperiosteum of the anterior wall and the sphenoid rostrun are displaced laterally. The anterior wall, rostrum, and all intersinus septa are resected by semicutting or diamond burrs, giving wide exposure of the sinus (Figs. 175-12 and 175-13).

Transseptal Access

Thetransseptal approach was conceived to provide a midline access to the sphenoid sinus region through the nasal septum, avoiding damage to the structures in the nasal cavity and avoiding the lateral wall of the sphenoid sinus and the nearby carotid artery and optic nerve. This approach has been particularly useful for obtaining access to the clivus, sella, and parasellar regions, because they are midline structures.

The surgeon first performs a submucoperichondrial and submucoperiosteal infiltration with lidocaine (2%) and epinephrine (1:100,000), producing a hydraulic dissection that facilitates surgical elevation. A vertical hemitransfixion incision is made at the caudal edge of the septal cartilage, and septal flaps are elevated as in performing a septoplasty. Disarticulation of the osseocartilaginous junction (septal cartilage, ethmoid plate, and vomer) is performed with the suction elevator, with preservation of the uppermost part of the osseocartilaginous junction to avoid postoperative dorsal nasal saddling. The posterior attachment of the septum to the perpendicular lamina of the ethmoid is fractured. The posterior part of the septal bone, which obstructs access to the sphenoid rostrum, is resected with a Jansen-Middleton forceps. The mucoperiosteum of the anterior wall of the sphenoid sinus is elevated until the sinus ostia on both sides are visualized. At this point, a self-retaining speculum is introduced between the two leaves of septal mucosa, and the anterior wall of the sphenoid sinus is entirely exposed. The anterior wall is then opened with a chisel and is enlarged with a micro-Kerrison punch (Fig. 175-14). The sphenoidotomy is made large enough to allow easy simultaneous introduction of a 4-mm endoscope and a surgical instrument. Once the septum is

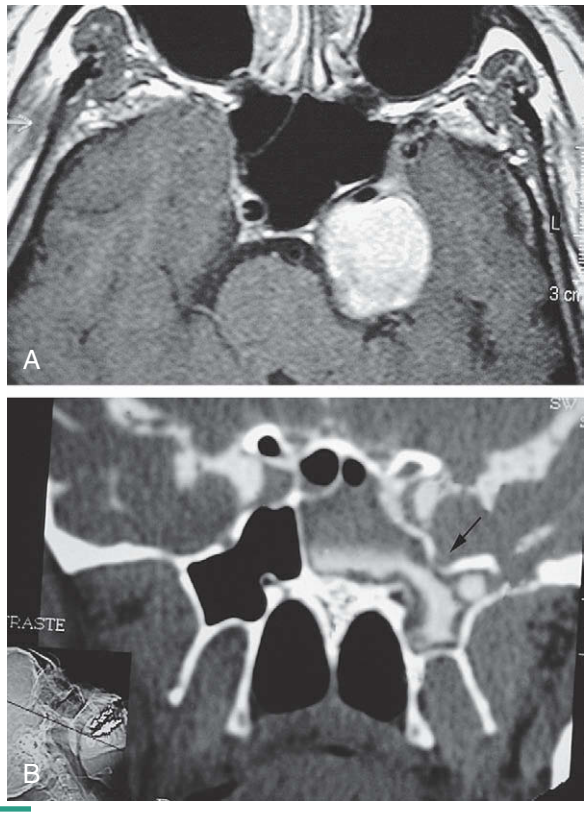

Figure 175-12. A, Axial view, magnetic resonance imaging, of a petrous apex cholesterol granuloma. **B,** computed tomography cisternogram showing a cerebrospinal fluid fistula at the lateral wall of the sphenoid sinus *(arrow)*.

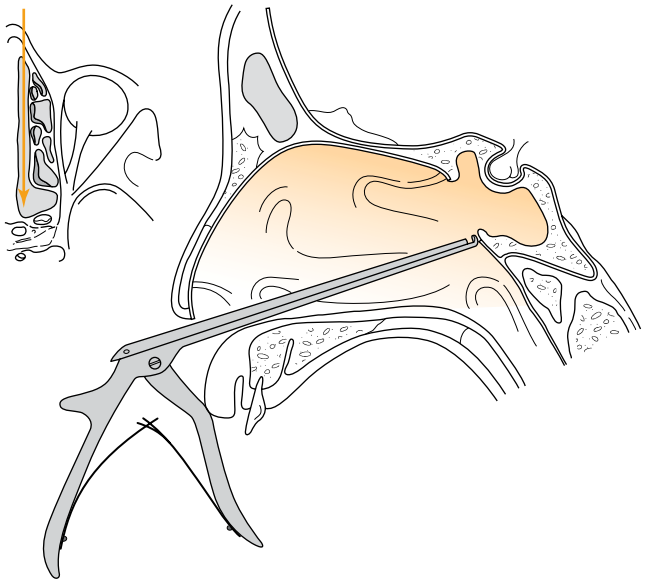

Figure 175-13. Opening of the sphenoid sinus anterior wall by means of a micro-Kerrison punch through a direct transnasal approach (*arrow* on *inset*).

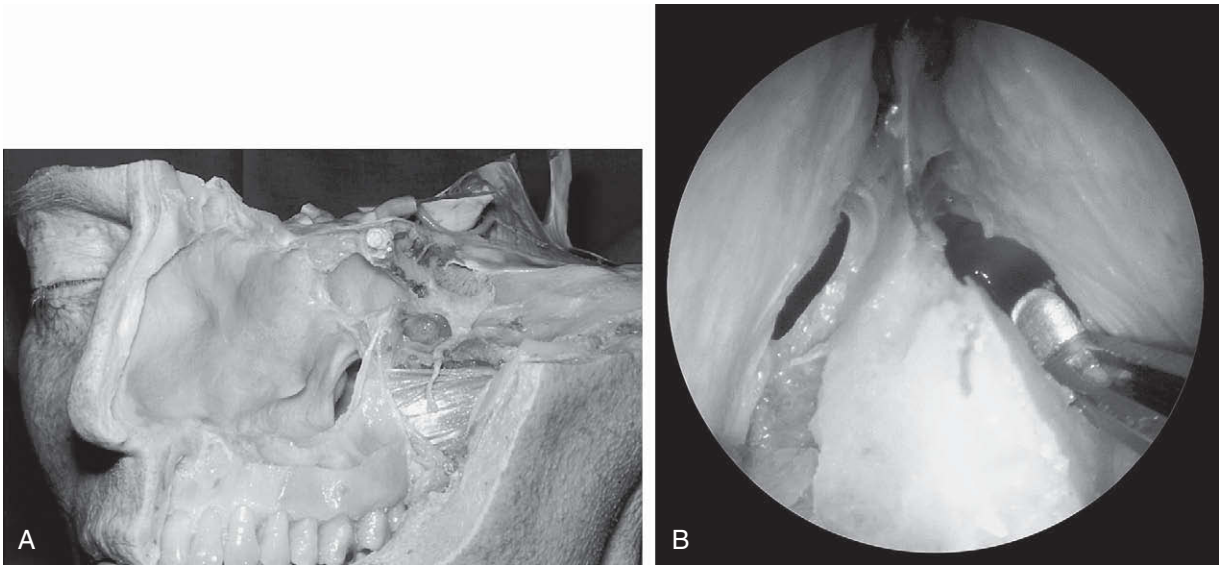

Figure 175-14. **A,** Anatomic oblique view of the nasal septum and its relation with the sphenoid sinus. **B,** Endoscopic view of the sphenoid rostrum being removed by a micro-Kerrison punch.

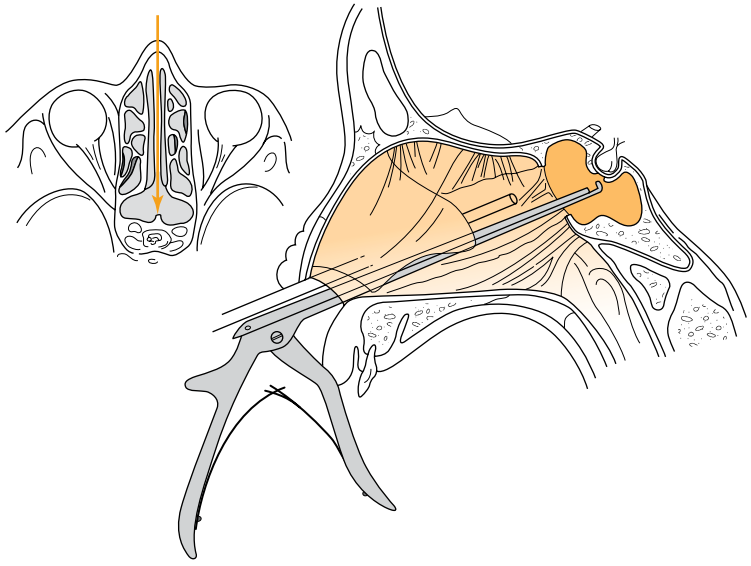

Figure 175-15. Schematic drawing of the transseptal approach (*arrow* on *inset*) to the sphenoid sinus and sellar region.

resected and the two septal flaps are displaced, the self-retaining speculum can be removed, and the surgeon can work exclusively with an endoscope and the instruments (Fig. 175-15).

Transseptal-Transnasal Access

For the transseptal-transnasal (binostril) approach (Fig. 175-16), a classic anterior septoplasty incision is made. A submucoperichondrial-mucoperiosteal dissection is performed on both sides. The posterior portion of the nasal septum is removed, with preservation of the inferior portion as a landmark for the midline. The sphenoid rostrum and anterior wall of the sphenoid sinus are exposed. The next step is the creation of a nasal septal mucosal flap on one side. Three incisions are made: vertical, superior horizontal, and inferior horizontal. These incisions can be completed with scissors or other sharp instruments as necessary, creating a mucosal flap that is displaced onto the nasal floor. This nasal septal flap preserves a posterolateral pedicle containing the sphenopalatine neurovascular bundle. Multiple modifications in length and width are possible, and the flap should be designed in accordance with the size and shape of the anticipated skull base defect. This approach has several advantages: It allows two surgeons to simultaneously manipulate surgical instruments using both nostrils; it has a very robust tissue pedicle to help in the closure of skull base defects; and it preserves the nasal septal mucosa on one side, avoiding nasal septal perforation (see Fig. 175-16).[16]

Transethmoidal Access

Transethmoidal surgical access usually is indicated for cases in which lesions extend into or involve the ethmoid and sphenoid sinuses. The most common of these lesions are hemangiopericytoma, inverted papilloma, schwannoma, meningoencephalocele, meningocele, and malignant tumors. CSF fistulas also commonly affect this area.[17]

First, an ethmoidectomy is performed beginning with the resection of the uncinate process and followed by resection of the ethmoid bulla and the remaining ethmoid cells. During the resection of the posterior ethmoid cells, the surgeon must correlate direct observation and intraoperative review of the CT scan to determine whether an Onodi cell is present, and, if so, to recognize its relationship to the optic nerve canal and the internal carotid artery.[18,19]

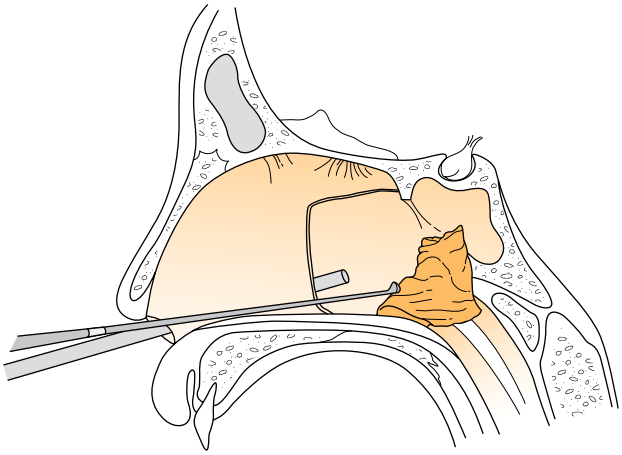

Figure 175-16. Nasal septum mucosal flap. Surgical instrument enters through one nostril and the endoscope through the septum; contralateral septal mucosa is intact and preserved.

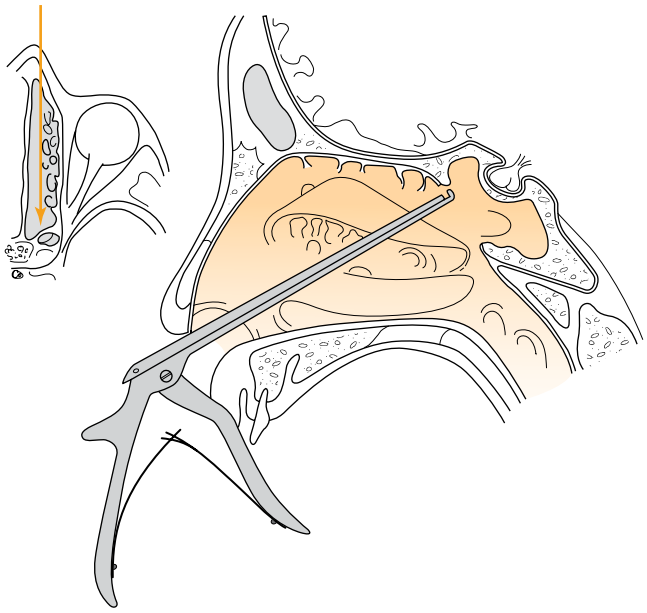

Figure 175-17. Transethmoidal approach (*arrow* on *inset*) to the sphenoid sinus.

Next, the posterior ethmoid artery is identified anterior to the front wall of the sphenoid sinus, which makes an angle of approximately 90 degrees with the roof of the ethmoid sinus. The initial opening of the sphenoid sinus is made with a delicate curette or with an atraumatic aspirator medially and inferiorly. The sphenoidotomy is then enlarged with a micro-Kerrison punch, incorporating the natural ostium into the opening (Fig. 175-17). Figure 175-18 shows a fracture of the optic nerve canals. Removal of the middle turbinate may be necessary when the lesion is located in the roof of the ethmoid sinus or the cribriform plate, as occurs in some cases of inverted papilloma, osteoma, or schwannoma. When the middle turbinate is removed, its mucoperiosteum can be used as a free graft to repair dural defects that were created by the lesion or its removal. Figure 175-19 shows removal of a schwannoma by this technique.

Transsellar and Parasellar Approaches

After the opening of the sphenoid sinus, the next step consists of opening the pituitary fossa. The anterior wall of the sphenoid sinus must be largely exposed, to facilitate the identification of the principal anatomic structures of this region, such as the prominence of the internal carotid artery canals, optic nerve canals, clivus, planum sphenoidale, and also the floor of the sella. Any intersinus and or intrasinus septa are resected by means of a strong through-cutting forceps. The mucoperiosteum of the sphenoid sinus covering the floor of the sella is displaced laterally and preserved for use in reconstruction. The next step consists of wide resection of the sellar bone, exposing the dura from one internal carotid artery to the opposite internal carotid artery and from the planum sphenoidale to the clivus. This usually is performed with a diamond burr and a micro-Kerrison punch. Thereafter, a quadrangular dural incision is made very carefully, with an attempt to visualize the precise localization of the cavernous sinus and the superior and inferior intercavernous sinuses, and of both internal carotid arteries through the exposed dura (Fig. 175-20).

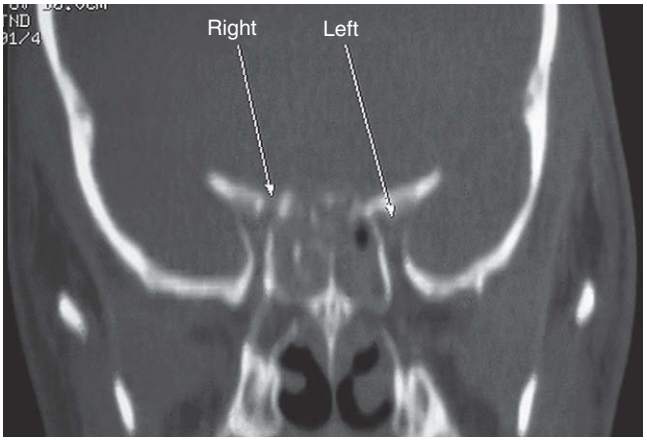

Figure 175-18. Coronal computed tomography scan showing bilateral fracture of the optic nerve canals.

These structures represent the anatomic limits of the dural opening. The dura mater, along with any attached fragments of tumor, is removed and sent for histopathologic examination. Resection of the tumor begins laterally with a 45-degree angled endoscope and curved suction tube, first identifying the angle between the arachnoid and the ICA. The arachnoid is the limit of the superior and posterior dissection (classically known as the diaphragma sella). When a complete removal is accomplished, the arachnoid frequently descends to fill the space occupied by the tumor. This can partially obstruct the surgical field of view and is one factor in incomplete tumor removal. In pituitary adenoma surgery, disection is more important than the use of the curette. Occasional bleeding is carefully controlled by application of warm saline solution, Surgicel packing, and other measures as appropriate.

If no fistula is present, the mucoperiosteum of the sphenoid sinus is replaced and secured with fibrin glue. In the presence of a CSF leak, the defect is sealed with fascia lata, fat, and mucoperiosteum of the sphenoid sinus. Fibrin glue completes the sealing process. In larger defects with high fluid flow, in addition to the previous steps, we use a pedicled flap originating from the mucoperiosteum of the posterior nasal septum to cover the region of the sella. Packing of the sphenoid sinus and nasal cavity for 5 to 7 days is recommended.

Transclival Approach

Approach to the Clivus and Cavernous Sinus

The transsphenoidal-transclival approach is used for lesions involving the clivus or retroclival region. Anterior approaches to the craniovertebral junction and clivus originally were proposed in the 1960s for the treatment of neoplasms and vertebrobasilar aneurysms.[20-23] Anterior procedures include the transseptal, transsphenoidal,[24,25] transmaxillary,[26,27] transpalatal and transoral-transpalatal,[28,29] transmandibular,[30] transmaxillary-transnasal,[31] and facial translocation approaches.[32]

Despite the fact that anterior approaches offer a more direct anatomic approach to the structures beyond the clivus, the risks of CSF leakage and infection limit most of the aforementioned approaches to extradural lesions, especially those approaches that traverse a nonsterile

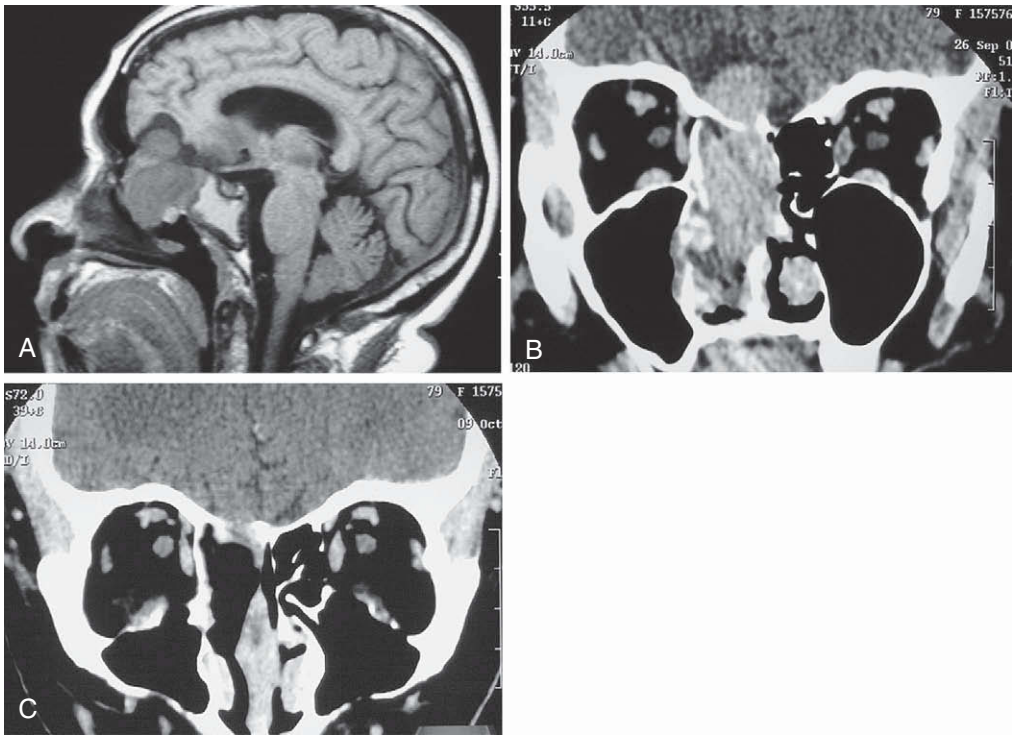

Figure 175-19. Schwannoma of the ethmoid region, with intradural extension, in a 68-year-old woman. **A,** Sagittal view, magnetic resonance imaging. **B,** Coronal reconstruction, computed tomography (CT), showing the extent of the lesion. **C,** Postoperative CT appearance, coronal reconstruction.

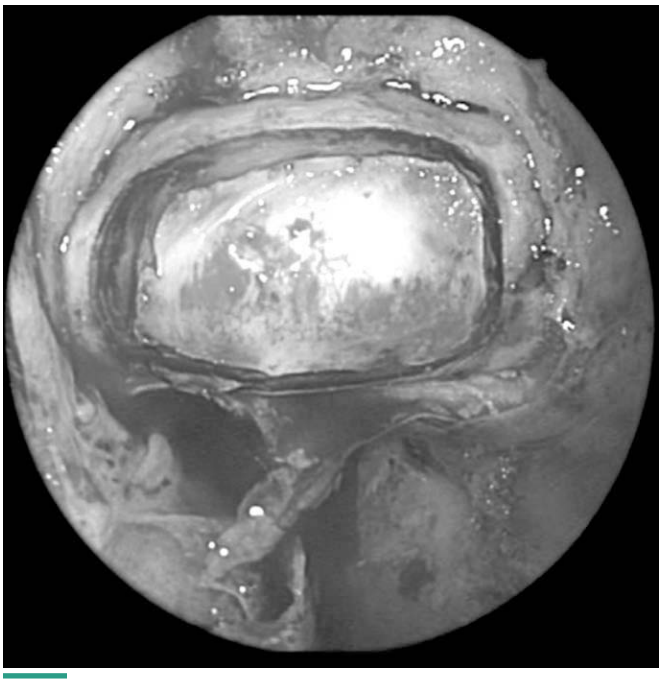

Figure 175-20. Quadrangular incision area in sellar dura.

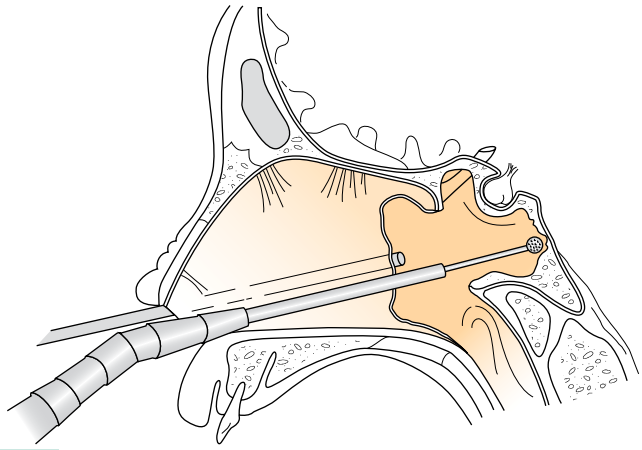

Figure 175-21. Schematic drawing showing a modified transseptal approach to the posterior sphenoid sinus wall (clivus). A surgical drill with a long handpiece and a diamond burr is used to remove the bone of the upper clivus.

operative field.[10] The major advantage of the midline transfacial approaches is the direct anterior surgical access through the large spaces of the nasal cavity, nasopharynx, oral cavity, and paranasal sinuses. However, these midline routes are restricted by critical neurovascular structures such as the internal carotid artery, optic nerve, cavernous sinus, cranial nerves, and the orbital contents.[4]

The transnasal endoscopic-assisted surgical technique begins with one of the surgical approaches to the sphenoid sinus (transnasal direct, transethmoidal, or transseptal). A wide opening of the anterior sphenoid sinus wall is obtained with a micro-Kerrison punch. The floor of the sella, the two carotid protuberances, the medial aspect of the optic canals, and the upper clivus are visualized. The sinus mucosa that lines the clival area is reflected carefully, exposing the clival bone. The bone removal initially is done with a drill system that uses a diamond burr and continued carefully with a micro-Kerrison punch if necessary (Fig. 175-21). The limits of clival bone removal are the floor of the sella superiorly, the foramen magnum inferiorly, and the bony canals of the sixth cranial nerves, the internal carotid arteries, and the occipital condyles laterally. To obtain an intradural exposure, the external layer of the dura is first incised, and the basilar venous plexus and cranial nerve VI are encountered. Bleeding in the plexus cannot be cauterized safely but usually can be controlled with small pieces of Surgicel. Large lesions

Figure 175-22. Surgical endoscopic view during a transseptal transclival approach: 1, basilar artery and branches; 2, anterior inferior cerebellar artery; 3, vertebral artery; 4, superior cerebellar artery; 5, posterior cerebral arteries; 6, intradural course of cranial nerve III; 7, brainstem; 8, mammillary bodies.

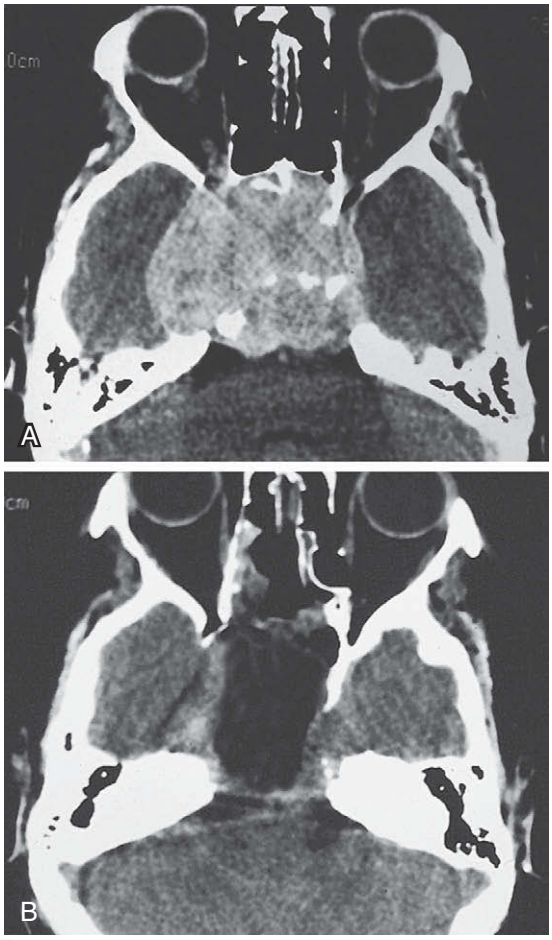

Figure 175-23. Preoperative **(A)** and, postoperative **(B)** axial computed tomography images of the operated region in a patient with clivus chordoma. An endoscopic-assisted combination transnasal, transsphenoidal, transclival surgical approach was used.

often encroach on and obliterate much of the plexus, but if the lesion is not large or if the plexus is not completely compressed, profuse and intense venous bleeding can occur. Judicious packing, time, patience, and experience are required to control such bleeding.

The opening of the internal layer of the dura at the level of the middle and superior clivus must be accomplished with great care to avoid injury to the underlying basilar artery. Once the dura is opened, minor bleeding is stopped with bipolar coagulation, and it is finally possible to introduce the endoscope carefully into the intradural space and to identify the major vessels of the posterior fossa (basilar artery and branches, anterior inferior cerebellar arteries, vertebral arteries, superior cerebellar arteries, and posterior cerebral arteries); the intradural course of cranial nerves III, IV, V, and VI; the brainstem; and the mammillary bodies. The cerebellopontine angle, cranial nerves VII through XII, and the retrosellar regions are best visualized by use of endoscopes angled 30 degrees, 45 degrees, or 70 degrees (Fig. 175-22).

Dural repair at the clivus region is difficult. If the defect is large, we occlude it with abdominal fat first and then cover the defect with grafts of fascia lata or synthetic dura (Duraform, Duragen). These grafts are covered by a large pedicled nasal septal flap, as described previously, secured in position with fibrin glue and pieces of surgical gel (Gelfoam). For small defects, the nasal cavity is packed with Merocel for 5 to 7 days, whereas for larger ones, the packing is made with gauze embedded in antibiotics for 10 to 14 days. Broad-spectrum antibiotics are given for 10 to 14 days.

The main advantages of the transsphenoidal-transclival approach with removal of the posterior nasal septum are the avoidance of cerebral retraction and a decreased incidence of injury to the lower cranial nerves. In addition, the approach is direct without external incisions, is relatively quick, and best preserves the anatomic structures. Even though endoscopes do not allow a three-dimensional perspective, they do provide a close view of the operative field from different angles. However, this technique requires working in a narrow operative field limited by critical neurovascular structures, such as internal carotid arteries, optic nerves, cavernous and basilar sinuses, and the pituitary gland. The risks of major intradural bleeding, CSF leakage, and meningitis are not to be taken lightly. Figure 175-23 illustrates this approach in a patient with a clivus chordoma.

Petrous Apex Access

This type of surgical access can be useful for biopsy and drainage purposes. It can be particularly helpful in selected cases of cholesterol granuloma of the petrous apex because complete excision is unnecessary (see Fig. 175-14). Although surgical drainage is usually accomplished through the temporal bone, the transsphenoidal endoscopic approach may be indicated when the lesion abuts against the posterior and lateral wall of the sphenoid sinus. In these cases, the use of an image-guided system can be very helpful, especially to precisely identify the internal carotid artery, optic nerve, and the lesion.

The clival region is completely exposed, and both carotid canals are identified. When the anatomy is clearly apparent, these canals are easily recognized. If the canals are difficult to identify, use of diamond burrs with suction-irrigation can help identify the vertical segment, particularly at the junction of the cavernous and petrous portions of the internal carotid artery.

The transmaxillary-transpterygoid access also permits approaching the petrous apex by exposing completely the pterygopalatine and infratemporal fossae. First, the vidian nerve canal, foramen rotundum and superior orbital fissure, and V_2 are dissected along their entire extradural extent. The early identification of the vidian canal is very important, because this can be an excellent guide to the identification of the canal of the internal carotid artery between its petrous and paraclival portions.[34] After exposure of the lateral recess of the sphenoid sinus and the lateral portion of the cavernous sinus, a diamond burr is used laterally and inferiorly, exposing the petrous apex. The petrous part of the internal carotid artery must be identified after careful dissection and resection of its bony canal. By mobilizing the artery laterally, a complete exposure of the petrous apex can be accomplished.

Transcribriform Approach

The transcribriform approach is indicated to remove lesions involving the olfactory groove, hypophysis, or crista galli; it can be performed unilaterally or bilaterally. Among the most common lesions treated using the transcribriform surgical approach are CSF leaks, meningoencephaloceles, encephaloceles, meningiomas, esthesioneuroblastomas, and malignancies.

Transcribriform Unilateral Access

The unilateral transcribriform approach is designed to remove the cribriform area and to preserve the crista galli, with or without resection of the dura mater. The procedure begins with a wide middle meatal antrostomy. The middle turbinate is removed to the level of the skull base and a complete sphenoethmoidectomy is performed, including removal of the lateral wall of the orbit, exposing the periorbita. Next, the frontal recess and frontal sinus are exposed. The anterior and posterior ethmoid arteries are then identified, coagulated, and divided. The bone of the roof of the ethmoid sinus is removed, completely exposing the dura. The medial dissection is accomplished by removing the posterior and superior portions of the ipsilateral nasal septum. Perichondrium and periosteum of the contralateral side are preserved to be used in the reconstruction.

Especially in cases of malignancy in which the lesion presents intradural extension, the dura is then removed. Reconstruction of the dural defect is achieved with one or two layers of fascia lata, covered by the contralateral septal flap. These layers are kept in place with fibrin glue and nasal packing. Lumbar drainage usually is not necessary. This endoscopic-assisted unilateral transnasal approach preserves the olfactory area on one side, which represents a great advantage over the classic craniofacial approach.

Transcribriform Bilateral Access

In cases with bilateral involvement, intradural extension of the lesion is very commom. The procedure is performed in the same way on both sides as decribed above. In such cases however, it is necessary to make a large aperture of the frontal sinus through a Draf III surgical access. Depending on the extent of the lesion, and especially in malignant tumors, the upper part of the nasal septum is also removed.

The limits of the dissection are as follows: laterally, the medial wall of the orbit; anteriorly, the frontal sinuses, and posteriorly, the sphenoid sinuses. The anterior and posterior ethmoid arteries of both sides are identified and coagulated with a bipolar cautery.

Next, complete removal of the skull base bone in this region is performed with a drill system and suction irrigation. The dura mater within the aforementioned limits is then resected. The opening of the dura is initiated with a surgical knife with a No. 11 blade after bipolar cauterization and is completed with microscissors on both sides of the falx. The falx is coagulated and the sagittal sinus packed with Surgicel, if necessary. The falx is transected and detached from the crista galli. When the lesion has a subpial extension, the dissection must be performed extremely carefully, with special attention directed at possible bleeding from branches of the anterior cerebral artery, such as the frontopolar artery. The dural defect may be large, necessitating meticulous reconstruction using two layers of fascia lata (one intradurally and another between the dura and the bone). The nasal flap, including mucoperiosteum-mucoperichondrium, is used to cover the grafts. If this flap is not available because the tissues are involved by a malignant lesion, a mucoperichondrial flap from the floor of the nasal cavity can be used (Fig. 175-24).

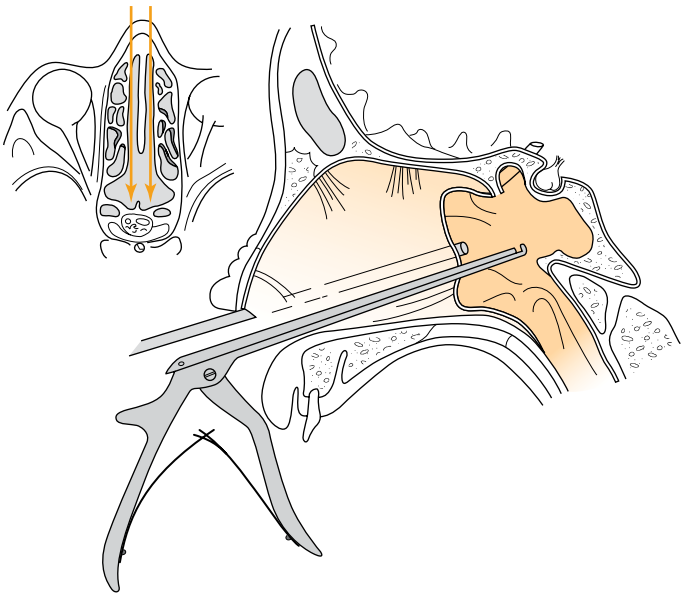

Figure 175-24. Schmatic drawing of a modified transseptal approach (*arrows* on *inset*) to the sphenoid and parasphenoid sinus regions.

Transtuberculum-Transplanum Approach

We use the transtuberculum-transplanum approach for removal of lesions involving the planum sphenoidale and tuberculum sella, most typically meningiomas. It also is useful to remove lesions that compromise the suprasellar cistern region and pre– and post–optic chiasma lesions such as pituitary microadenomas, craniopharyngiomas, Rathke's pouch cysts, and even optic nerve gliomas.

The first step in the procedure is the development of a nasal mucoperichondrial flap pedicled on the sphenopalatine foramen to be used for reconstruction at the end of the procedure. The surgical access portion of the procedure consists of a wide sphenoidotomy with resection of the posterior part of the nasal septum and the intersinus septum. To obtain adequate exposure, it also is necessary to perform bilateral posterior ethmoidectomies and to resect both middle turbinates.

The ethmoidectomies remove all cells laterally to both medial walls of the orbits and anteriorly to the level of the posterior ethmoid arteries, in order to avoid damaging the neuroepithelium. All bone in the region of the planum sphenoidale is exposed by using a high-speed drill with irrigation, continuing until the bone is as thin as an egg shell. The final layer is removed carefully with a micro-Kerrison punch.

We are especially careful not to damage the optic nerves by excessive heat generated by the use of the drill, and use shorter periods of drilling and copious irrigation. The eggshell bone over the internal carotid arteries in the parasellar region also is removed with a micro-Kerrison punch.

After the dura mater from the sellar region to the anterior portion of the planum and laterally to the lamina papyracea is exposed completely, the superior intercavernous sinus is cauterized using a bipolar system and transsected. The posterior ethmoidal arteries are coagulated and sectioned. Then the dura mater is opened carefully avoiding any damage to the attached vessels.

The intradural dissection is critical, and it is imperative to identify the internal carotid arteries in the paraclinoid region, the anterior cerebral arteries (A_1 and A_2), the anterior communicating artery, and the recurrent artery of Heubner. The optic nerve and chiasm must be identified more superiorly and also the pituitary stalk. Dissection in the arachnoidal plane is highly recommended whenever possible, as is the avoidance of excessive coagulation and traction, in order to reduce the possibility of minor surgical trauma to neurovascular structures.

Reconstruction is begun with a double layer of fascia lata, which is then covered with the pedicled nasal septal mucosal flap. We secure these with fibrin glue and place nasal packing, to remain for 7 to 10 days. We do not use external lumbar drainage.

Transmaxillary-Transpterygoidal-Infratemporal Approach

The transmaxillary approach is excellent for removing lesions that involve the medial portion of the maxillary sinus, and for larger lesions in the pterygopalatine, zygomatic, or infratemporal fossa such as angiofibromas. This approach also can be extended to gain exposure to the cavernous sinus.

The procedure begins with an anterior ethmoidectomy and continues with a wide middle meatus antrostomy to give maximal exposure

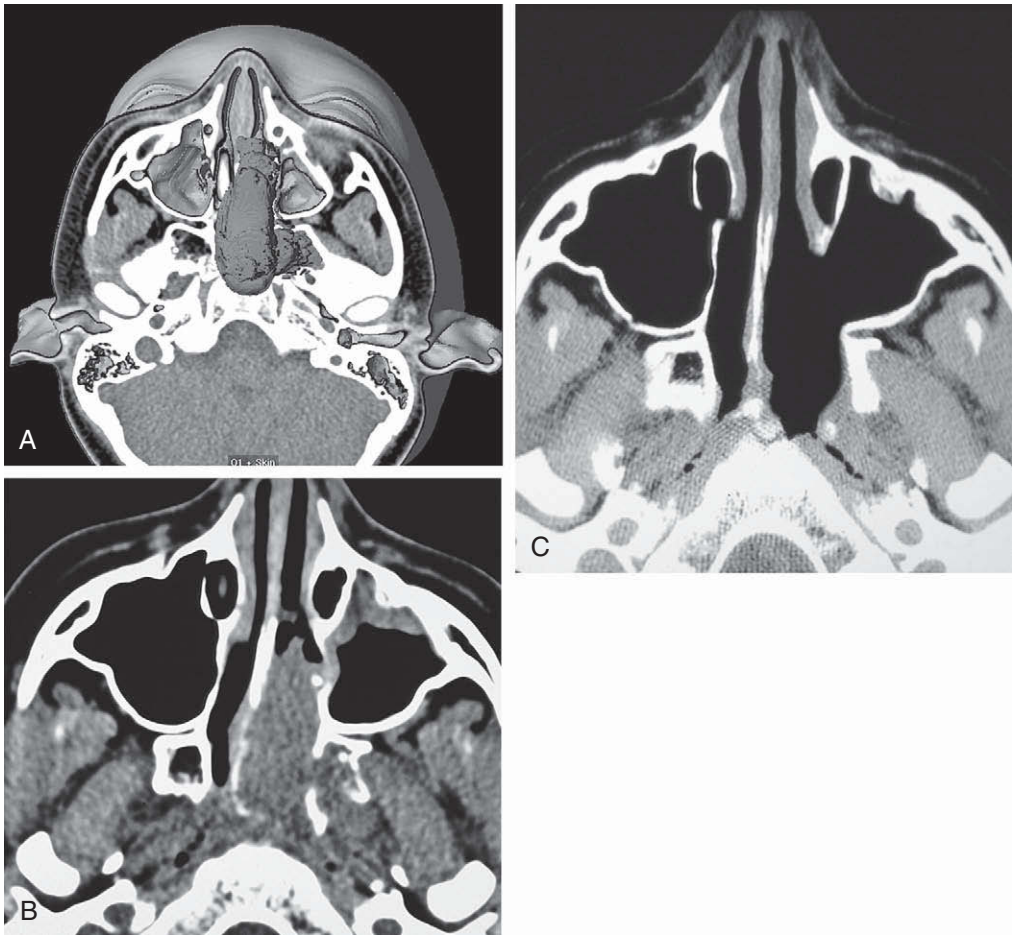

Figure 175-25. Angiofibroma in a 13-year-old boy. **A,** Axial three-dimensional computed tomography (CT) reconstruction. **B,** Preoperative axial CT scan. **C,** Postoperative axial CT scan.

of the posterior maxillary sinus wall. Sometimes it is necessary to remove the inferior turbinate, entirely resecting the medial wall of the maxillary sinus to obtain adequate exposure of the posterior and posterolateral portions of the wall of the sinus. During removal of the inferior turbinate, special care must be taken to avoid injuring the terminal branches of the maxillary artery at the sphenopalatine foramen and the second division of the trigeminal nerve.

The amount of posterior wall bone to be removed depends on the location and extent of the lesion as determined by preoperative image studies or by information from the image-guided system at the time of surgery. The posterior wall of the maxillary sinus can be opened by enlarging the sphenopalatine foramen with a micro-Kerrison punch and exposing the periosteum of the pterygopalatine, zygomatic, and infratemporal fossae. It is important to try to preserve the integrity of the periosteum and avoid fat protrusion into the operative field. If fat does protrude into the sinus, it is reduced by bipolar electrocoagulation, which also is used to control any bleeding. This technique is particularly useful in removing angiofibroma, when early identification of the feeding vessels is essential. Figure 175-25 illustrates removal of an angiofibroma using this technique.

The transpterygoid and infratemporal approaches are extensions of the transmaxillary access. In the transpterygoid approach, lateral extensions of the sphenoid sinus (pterygoid recess) and lesions involving the pterygopalatine fossa and zygomatic fossa can be accessed. This may require removal of the medial and sometimes lateral pterygoid processes in order to achieve access to the lateral and pterygoid regions of the sphenoid sinus. A wide sphenoidotomy is performed at the beginning or during the surgical operation. This access allows treatment of lesions involving the cavernous sinus that are lateral to the paraclival internal carotid artery.

The infratemporal access adds a medial endoscopic maxillectomy, including section of the nasolacrimal duct (a dacryocistorhinostomy is needed afterward). In this surgical access, we resect the posterior wall and sometimes the lateral wall of the maxillary sinus, particularly in situations with lateral expansion of the lesion.

Craniocervical Junction–Odontoid Approach

The most common indication for craniocervical junction–odontoid access is an extradural compressive lesion, the basilar invagination, which may be secondary to rheumatoid arthritis, exostosis, osteotoma, or other disorders (Fig. 175-26). Foramen magnum meningiomas, clivus chordomas with inferior extension, metastasis (especially in the odontoid process) also can be approached in this manner.

The procedure consists of the following sequence: general exposure, osseous exposure, removal of the lesion, and reconstruction. The otolaryngologic surgeon is responsible for the exposure of and access to the lesions. The surgery procedure usually is accomplished through both nostrils (four-hand technique), to permit use of multiple surgical instruments such as suction tubes, drills, and navigation system devices. The drill system must be thin, delicate, and long enough to allow its passage through the nose but without interfering with endoscopic vision. The image guide system is very helpful in these cases.

A panclival exposure creates a single cavity that extends from the sphenoid sinus to the level of the fossa of Rosenmüller. To expose the odontoid and the foramen magnum, additional soft tissue removal is required. The nasopharyngeal mucosa is cautherized with monopolar eletrocautery and then resected from the sphenoclival junction to the level of the soft palate. The longus capitis and longus colli muscles are exposed and partially resected to expose the ring of C1. Care should be taken to stay medial to the eustachian tube, especially during use of

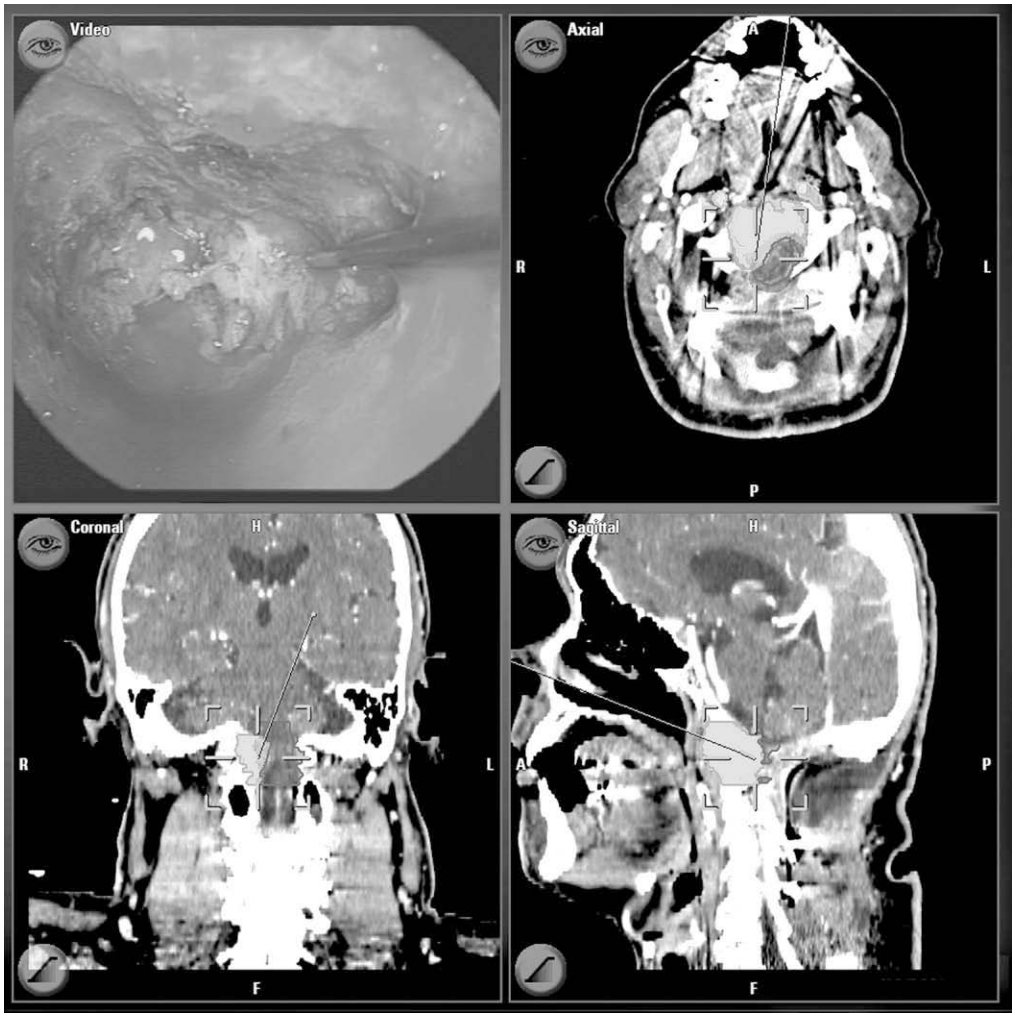

Figure 175-26. A surgical image-guided system was used to identify an osteoma located at the craniocervical junction.

electrocautery, because the parapharyngeal internal carotid artery is directly posterolateral to the eustachian tube. At the completion of the procedure, the nasopharyngeal tissues do not need reapproximation, and the surgical defect is covered with fibrin glue. The nasal passages are cleared of blood, and Silastic septal splints are inserted to minimize the risk of postoperative synechia formation.

Combined Approaches

Unfortunately, many lesions do not respect the anatomic boundaries for which the previously outlined approaches are ideal. In many instances, it is necessary to combine some of the previous approaches—for example, the transnasal direct with the transethmoidal or the transmaxillary with the transethmoidal.

Reconstruction

Reconstruction of the skull base after transnasal endoscopic surgery remains a major challenge, particularly when the dural defects are large and located at the posterior fossa.

The basic principle in sealing the dural defect is based on the use of several layers of tissue for the closure. We use fascia lata and free mucoperiosteum grafts from the floor of the nasal cavity or the middle or inferior turbinates. More recently we have used a septal flap pedicled at the region of the sphenopalatine foramen arteries. All of these layers are kept in position with fibrin glue.

If a large free space remains between the cerebral tissue and the dura, it is filled with fat (abdominal or from the thigh where the fascia was previously removed) before the first layer of fascia lata. The first layer of fascia lata is placed in a circumferential fashion, as an underlay graft between the dura and the nervous tissue. The second layer is then positioned between the dura and the bony skull base margins. The fascia lata can be substituted by artificial dura such as the collagen matrix graft (Duragen, Duraform). The third layer consists of vascularized mucoperiosteum-perichondrial flap pedicled at the region of the sphenopalatine foramen arteries. Fibrin glue is used to give support to these layers. When the septal flap is not large enough or is unavailable because of previous surgery, free mucosal grafts from the nasal floor, septum, and turbinates constitute an option. In this situation, they are ultimately covered by pieces of Gelfoam and supported by sponge packings (Merocel). When the dural defect is very large, gauze soaked in antibiotics is preferable to Merocel; over the gauze, a Foley catheter balloon is inflated to keep the tissues in position and to avoid displacement of the nasal packing into the nasopharynx. The balloon must be positioned under direct vision and inflated with no more than 10 mL of saline solution. It is left for approximately 5 days; the packing can remain for 10 to 14 days, depending on the extent of the reconstruction.

Postoperative Care

The goal of surgical treatment is to ensure the complete removal of the disease and the best possible functional result. A satisfactory postoperative result depends on both appropriate operative technique and meticulous postoperative care.

Wide-spectrum antibiotics are given during the operation and for 10 days postoperatively or until the nasal packing is removed. Adequate postoperative care of the operative site requires appropriate instrumentation, including 4-mm 0-degree, 45-degree, and 70-degree angled

endoscopes, straight and curved atraumatic aspirators, and straight and curved microforceps.

For extended endoscopic skull base and brain surgery, the nasal cavity packing can remain in place as long as 2 weeks, depending on the type of procedure and dural reconstruction grade. The operative cavity is carefully suctioned, and any residual bone fragments are removed. The patient is instucted to peform frequent nasal irrigations with 0.9% or 3% saline solution. Nasal vasoconstriction with oxymetazoline is peformed by the patient until postoperative day 5. If the procedure includes repair of a dural defect, the patient is instructed to refrain from moderate or intense physical activity, straining, nose blowing, and sneezing for approximately 30 days. To prevent constipation, a high-fiber soft diet and laxatives are recommended.

The patient returns for postoperative visits every 2 weeks. At each visit, the operated nasal cavity is cleaned of crusts, granulation tissue, clots, and secretions. Imaging exams are performed when the cavity is well healed; the timing varies with the clinical course.

Complications

Every skull base surgical procedure has potential to cause complications. For example, a U.S. survey conducted in 1997 addressed complications of transsphenoidal surgery for pituitary gland lesions and documented carotid artery injury in 1.1% of cases, central nervous system injury in 1.3%, loss of vision in 1.8%, CSF fistula in 3.9%, and meningitis in 1.5%. The estimated mortality rate was 0.9%. These data were derived from several centers that used different transnasal approaches for only one surgical site but illustrate that serious complications do occur.[33] In the experience of Kassan and colleagues,[34] the incidence of neurovascular complications in 700 patients who underwent an expanded endonasal endoscopic approach was approximately 1.0%.

Prevention of the complications of transnasal endoscopic-assisted surgery of the skull base begins with an adequate preoperative evaluation of the patient, including history of the use of medications and previous operations. High-resolution CT in coronal and axial projections with sagittal reconstruction, MRI, and sometimes angiography are essential to plan the procedure and to execute it safely with the lowest possibility of complications.[35]

Complications can be classified by severity as minor or major and by time of appearance as immediate or delayed. Minor complications are associated with little morbidity and do not compromise the life of the patient, although they may be annoying and troublesome. Most resolve with time and conservative treatment. However, major complications are the cause of significant morbidity and increased risk of death. Most orbital complications stem from direct injury to the optic nerve or the extraocular muscles or from arterial or venous bleeding within the rigid bony orbit. These injuries can result in diplopia, hematoma, proptosis, and decreased visual acuity or blindness (which can be temporary or permanent). Blindness secondary to orbital hematoma can be reversible, mandating prompt hematoma evacuation to relieve the increased pressure compromising the blood supply to the retina or the optic nerve. Direct or indirect damage to the optic nerve usually occurs at the superolateral sphenoid sinus wall or in the posterior ethmoid cells.

Intracranial complications can result from direct injury to brain, cranial nerves, meninges, blood vessels, or venous sinuses. The resulting deficits reflect the loss of function of the damaged structures in the case of brain and cranial nerves, or the effects of loss of vascular supply to critical areas (stroke), or the mass effects of a resulting hematoma. Also, CSF leakage can cause symptoms directly, as well as predisposing the patient to the development of meningitis, and air entering the brain (pneumocephalus) can cause mass effect symptoms.

Bleeding is a risk in any surgical procedure, but seldom are so many important vessels susceptible to injury. The transnasal approaches outlined previously visualize and put at risk the anterior and posterior ethmoid arteries; the sphenopalatine and maxillary arteries and their branches; the internal carotid, anterior cerebral, basilar, and vertebral arteries and their branches; and the venous sinuses of the skull base: the cavernous sinus, basilar venous plexus, and the anterior intercavernous sinus.[36]

Immediate complications occur during surgery. The most frequent of these are CSF leakage, intraoperative bleeding, orbital hematoma, brain injury, and intrasellar complications, which can include injuries of the diaphragma sella, arachnoid membrane, pituitary stalk, intra-arachnoid vascular structures, and the hypothalamus, optic nerve, and chiasm and the vessels surrounding them. Injuries to cranial nerves III and VI are uncommon except in transsphenoidal-transclival approaches.

Delayed complications include progressive loss of vision or smell, meningitis, bleeding, synechia, and infection. The surgeon also must be aware of the possibility of transitory or permanent endocrinologic complications that can result from manipulation, compression, or traction of the pituitary stalk. The surgeon must be able to diagnose acute anterior pituitary insufficiency and be able to manage the condition or have available appropriate consultants who can do so.

Summary

Dramatic improvements in technology have made it possible to extend endoscopic surgical procedures well beyond the sinuses to all three cranial fossae, as well as to the orbit and pterygopalatine, zygomatic, and infratemporal fossae. Visualization is superior, morbidity is lower, and complications of endoscopic skull base and brain surgery, particularly vascular and neurologic lesions, CSF leak, and infection, are the same as after open procedures.

Despite all of the technologic and surgical advances, extensive dural defect repair remains a considerable challenge. Even with the dazzling technical advances, surgical success depends more on other factors: The surgeon must have a perfect knowledge of the involved anatomy, extensive endoscopic surgical training and experience, good surgical skills and judgment, and a highly skilled neurosurgical colleague. Only then can transnasal endoscopic-assisted surgery of the skull base reach its full potential.

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CHAPTER ONE HUNDRED AND SEVENTY-SIX

Temporal Bone Neoplasms and Lateral Cranial Base Surgery

Michael Marsh

Herman A. Jenkins

Key Points

- Patients with encasement of the internal carotid artery by tumor, contour irregularity on angiography, or anticipated internal carotid artery resection should undergo preoperative temporary balloon test occlusion (BTO) with neurologic monitoring with or without quantitative cerebral blood flow (CBF) assessment. When preoperative BTO reveals neurologic deficit or CBF is less than 30 mL/100 g per minute, definitive resection is not an option, unless extracranial-intracranial bypass can be accomplished beforehand. The decision regarding revascularization versus permanent balloon occlusion optimally is made preoperatively.
- The minimal procedure for treatment of carcinoma of the external auditory canal usually is a lateral temporal bone (LTB) resection. If radiation therapy is anticipated postoperatively, the cavity should be obliterated, in view of the high risk of osteoradionecrosis in irradiated open cavities.
- Carcinomas of the external auditory canal extending to the mesotympanum are optimally treated with a subtotal temporal bone resection and postoperative radiation therapy.
- High-grade malignancies of the temporal bone with extension outside the petrous bone to the petrous apex, extensive dural involvement, frank parenchymal involvement, gasserian ganglion involvement, or invasion along the skull base portend a poor outcome in nearly all cases. Palliation should be strongly considered.
- Aneurysms of the upper cervical and petrous internal carotid artery can be managed by endovascular stenting, balloon trapping, or surgical resection with or without revascularization or extracranial-intracranial bypass, as indicated by angiography and BTO assessment findings.
- Glomus tympanicum tumors whose borders are clearly seen through the tympanic membrane can be removed transtympanically; otherwise, an extended facial recess approach is indicated.
- Glomus jugulare tumors are best removed through a Fisch type A infratemporal approach. Staging may be necessary with significant intracranial extension. Preoperative embolization may greatly lessen intraoperative blood loss.
- Radiotherapy for glomus jugulare tumors may be indicated for recurrences or unresectable lesions, or in the presence of a medical contraindication to surgery.
- Jugular foramen schwannomas that are primarily intracranial are most easily approached suboccipitally. Jugular foramen schwannomas that are intraforaminal or combination tumors are removed in the safest manner using an infratemporal fossa approach with (Fisch type A) or without facial nerve transposition.
- The classic history of facial nerve schwannomas is one of a slowly progressive facial paralysis over months to years, not days to weeks, although sudden onset of paralysis, fluctuating paresis, and facial tic may occur. It is recommended to wait for facial function to deteriorate to House-Brackmann grade IV before surgical resection, because this may be the best expected outcome with facial nerve resection and reanastomosis.
- Drainage of cholesterol granulomas can be performed through the perilabyrinthine pathways or transsphenoidally using endoscopic image guidance techniques.
- Surgical management of a congenital cholesteatoma involving the petrous apex requires either complete removal of the cholesteatoma matrix or permanent exteriorization.
- Chordomas of the clivus can be resected using postauricular (Fisch type B) or preauricular lateral temporal bone techniques. Transnasal endoscopically assisted approaches also may result in complete extirpation, with greatly reduced morbidity compared with lateral skull base or facial translocation anterior techniques.

Lateral approaches to the skull base require numerous manipulations of intervening structures to gain access to the various regions of the skull in and around the posterior and middle cranial fossae. Advances in preoperative assessment, surgical techniques, and perioperative care have permitted removal of tumors previously regarded as unresectable. Concomitantly, the morbidity and mortality rates associated with these procedures have decreased significantly. A cohesive skull base team affords the patient the best possible preoperative assessment, planning, and surgical execution. The team requires the expertise of an otolaryngologist or neurotologist working with the neurosurgeon, neuroradiologist, interventional arteriographer, and anesthesiologist. The reconstructive surgeon may play a major role, especially if free flaps are required. This chapter reviews pertinent anatomy, various approaches to the lateral skull base, and selected pathologic entities.

Benign and malignant lesions (Box 176-1) involving the middle ear and temporal bone are located in one of the most inaccessible areas of the body. Although a variety of histologic types of tumor are found in these areas, each is uncommon, and clinical experience in their diagnosis and management is not easily acquired. Surgical approaches to the skull base are difficult, and the risks of neurologic deficit are significant. The major arteries and veins supplying the brain, intracranial structures, and all of the cranial nerves either exit through or are contiguous with the temporal bone. Modern surgical technique strongly stresses the minimization of cosmetic or neurologic loss in the management of benign and malignant lesions of the temporal bone. Through the years, collaborative approaches to the temporal bone have been developed for treatment of benign lesions and are being expanded to encompass malignant lesions as well. Nevertheless, considerable knowledge of temporal bone anatomy and adequate temporal bone-drilling laboratory experience are essential in adapting these approaches for each patient. Many histologic types are encountered only rarely, accounting for isolated case reports in the literature. Dividing tumors into benign and malignant categories, in combination with knowledge of the particular tumor biology and meticulous preoperative planning, greatly facilitates selection of the appropriate surgical approach and successful outcome.

Skull Base Anatomy

An overview of skull base anatomy may be found in Chapters 127 and 173. With lateral approaches to the skull base, anatomic structures are approached from a vantage point different from that presented in classic anatomic texts in terms of the course of dissection, in that such approaches are designed to enhance exposure while preserving neurovascular structures. The superior boundary of the infratemporal fossa as described by Grant[1] consists of the greater wing of the sphenoid the temporal fossa containing the temporalis muscle. The medial limit is

Box 176-1

Temporal Bone Neoplasms

Primary Benign Tumors
- Paraganglioma
- Neurofibroma/schwannoma
- Meningioma
- Adenomas
  - Ceruminous adenoma
  - Eccrine cylindroma
  - Pleomorphic adenoma
- Mesenchymal
  - Chondroma
  - Chondroblastoma
  - Chondromyxoid fibroma
  - Hemangiomas
  - Lipoma
  - Myxoma
  - Fibro-osseous tumors
    - Ossifying fibroma
    - Fibrous dysplasia
  - Giant cell granuloma
  - Aneurysmal bone cysts
  - Osteoblastoma
  - Osteoma/exostosis
  - Unicameral bone cyst
  - Teratoma
- Dysontogenic tissue
- Choristoma
- Glioma

Metastatic Tumors
- Prostate
- Breast
- Gastrointestinal
- Renal cell
- Lung
- Multiple myeloma
- Lymphoma
- Leukemia (chloroma)

Primary Malignant Tumors
- Epidermal carcinomas
  - Squamous cell carcinoma
  - Verrucous carcinoma
  - Basal cell carcinoma
  - Melanoma
- Adenocarcinomas
  - Ceruminous adenocarcinoma (low-grade and high-grade)
  - Adenoid cystic
  - Mucoepidermoid
  - Sebaceous cell
  - Papillary cystadenocarcinoma
- Mesenchymal
  - Rhabdomyosarcoma
  - Fibrosarcoma
  - Chondrosarcoma
  - Osteosarcoma
  - Liposarcoma
  - Dermatofibrosarcoma protuberans
  - Fibrohistiocytoma
  - Angiosarcoma
  - Osteoclastoma
  - Chordoma
- Plasmacytoma

Contiguous Tumor Invasion
- Neuronal structures
  - Meningioma
  - Gliomas
  - Neurofibroma/schwannoma
  - Choroid plexus papilloma
- Parotid gland neoplasm
- Pituitary tumors
- Craniopharyngioma
- Chordoma
- Scalp tumors
- Nasopharyngeal carcinoma

the lateral pterygoid plate, and the lateral limit is the mandibular ramus and condyle. The posterior wall of the maxillary sinus marks the anterior limit, and posteriorly and inferiorly, the infratemporal fossa opens into the parapharyngeal space, where fascial bands and ligaments subdivide the enclosed spaces.[2-4]

The facial nerve exits the stylomastoid foramen to enter the parotid gland and then emerges from the gland distally encased in the superficial muscular aponeurotic system fascia.[5] The glenoid fossa may limit superior exposure in lateral approaches.

As low-pressure, valveless channels, the venous system in the skull base is pivotal in lateral approaches. The torcular Herophili is the confluence of the transverse sinus (lateral sinus), superior longitudinal sinus, straight sinus, and occipital sinus. Bisaria[6] found that this confluence of sinuses was missing in 24.5% of 110 cadaver dissections. Ligation of the transverse sinus may lead to massive cerebral edema if the torcular Herophili is absent.[7] The vein of Labbé, or inferior anastomotic vein, connects the superficial middle cerebral vein with the transverse sinus, draining the superficial posterior temporal and inferior parietal lobes. It occurs on the right 66% of the time and on the left 77% of the time.[8] When present, it empties into the transverse sinus just proximal to the sigmoid sinus. Interruption of the vein of Labbé may lead to temporal lobe edema and infarction, unless good collateral drainage is present.[7,8] The superior petrosal sinus runs along the posterosuperior edge of the petrous bone from the cavernous sinus to the junction of transverse and sigmoid sinuses, receiving tributaries from the tympanic cavity and from the cerebellar and inferior cerebral veins.[9] The jugular bulb, averaging 15 mm in width, usually is separated from the tympanic cavity by bone but has been reported to be dehiscent in 6% of temporal bones.[10] The inferior petrosal sinus courses between the jugular bulb and cavernous sinus in the petrooccipital fissure, receiving tributaries from the internal auditory canal, pons, medulla, and inferior cerebellum.[9] The inferior petrosal sinus, occasionally the vein of the cochlear aqueduct, and the occipital sinus drain into the jugular bulb. Cranial nerves IX, X, and XI pass through the anterior medial portion of the jugular foramen and may be compressed during maneuvers to obtain hemostasis of the inferior petrosal sinus.[11]

The internal carotid artery ascends deep to the digastric and styloid muscles to enter the carotid siphon medial to the styloid process, ascending through vertical and horizontal segments. In the vertical segment near the genu, the artery is just deep to the eustachian tube orifice, posteromedial to the glenoid fossa. The osseous eustachian tube orifice is separated from the internal carotid by, on average, 1.5 mm of bone and may have dehiscences.[12,13] The midportion of the vertical arterial segment is anteromedial to the basal turn of the cochlea. The distance to the cochlea averages approximately 1.34 mm.[14] The average length of the vertical segment is approximately 10 mm (range, 5 to 15 mm).[12,15] The horizontal segment travels obliquely in a lateral to medial direction from the genu to the intracranial entry of this vessel at the superior aspect of the foramen lacerum. Its average length is 20 mm (range, 14.5 to 26 mm).[12,15] Relevant lymphatic anatomy includes the preauricular and parotid lymphatics that drain the external ear, with more medial aspects of the external auditory canal draining into deep jugular and postauricular nodes. The mucosa of the middle ear and mastoid drains into channels surrounding the eustachian tube, which then drains into the deep superior jugular and retropharyngeal nodes.[16]

Evaluation of Skull Base Lesions

Accurate diagnosis and evaluation of tumor extent of the middle ear space and temporal bone require appropriate physical examination and audiologic, vestibular, and radiologic assessment. Tumors of the middle ear space frequently can be seen on physical examination. The combination of the frequency of certain lesions and their classic presentations often suggest the tumor type. Tumors of the lateral skull base often manifest with cranial nerve deficits, including hearing loss, pulsatile tinnitus, and eustachian tube dysfunction. A thorough history and physical examination with special attention to the cranial nerves should be undertaken. Audiometry is useful in surgical planning, particularly when removal of the labyrinth will be necessary. Radiographic evaluation provides information regarding location, extensions, surrounding structural relationships, and probable histologic findings.[17-25]

Computed Tomography and Magnetic Resonance Imaging

Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) are indispensable to modern skull base surgery (see Chapter 135). Hirsch and Curtin[26] noted that MRI and CT are "complementary and not competitive in the initial evaluation of skull base lesions." Modern CT affords exquisite bony detail and fairly good soft tissue information. The strength of CT lies in delineating the effect of the tumor on the bone of the skull base. Soft tissue–soft tissue discrimination is still limited because of the narrow range of electron densities in soft tissues of interest. More soft tissue discrimination is available with CT if iodinated contrast material is administered intravenously. The advent of MRI with its superb soft tissue sensitivity has resulted in fewer indications for use of iodinated contrast CT techniques. Although MRI is able to evaluate alterations in bony structure, it does so only indirectly, because cortical bone has few mobile water protons and hence nearly no intrinsic signal. For this reason, MRI is inferior to CT in the evaluation of subtle bony changes. Such features are important findings in temporal bone masses. The fine soft tissue discrimination of MRI is improved by the intravenous infusion of the MRI contrast medium gadolinium. Another advantage of MRI is its ability to display numerous imaging planes without repositioning the patient, which makes it easier to acquire coronal, sagittal, and even off-axis oblique images. For these reasons, MRI is superior to CT in defining brain or meningeal effects from temporal bone lesions. Because of potentially dangerous magnetic effects, MRI cannot be used in patients with certain cardiac pacemakers or valves, ferromagnetic cerebral aneurysm clips, some vena cava filters, and ferromagnetic intraocular foreign bodies.

The usual evaluation of a potential temporal bone mass begins with noncontrast temporal bone CT. This study will immediately show large lesions and usually suggests the presence of smaller lesions. Even though results of temporal bone CT may be negative, follow-up MRI may be indicated if clinical findings strongly suggest a mass. Like CT, MRI is focused to the region of interest instead of just providing thick-slice imaging of the entire head. Temporal bone MRI almost always is performed without and with gadolinium. Many practitioners choose to bypass CT if they believe the disease is retrocochlear. CT then can be added after the MRI study if precise bone detail is required.

Both CT and MRI are computerized imaging techniques. For this reason, either can be reformatted in any desired digital display. A popular type of reformatted display is a three-dimensional image. Three-dimensional displays may assist the surgeon by making it easier to understand the extent of the lesion, but they almost never provide diagnostic information that was not available on the standard axial or coronal slices. Moreover, three-dimensional displays are heavily post-processed. Significant image information can be lost in such processing. At present, three-dimensional images are used almost exclusively as supplemental displays, as dictated by the preference of the practitioner.

Preoperative Carotid Artery Assessment

In extirpation of skull base tumors, appropriate management of the internal carotid artery remains paramount (Fig. 176-1). The morbidity associated with carotid artery occlusion is well known. The first documented carotid ligation, for a sword injury, performed in 1585 by Paré, resulted in stroke.[27] Literature review reveals that unselected abrupt sacrifice of this vessel resulted in 26% (65 of 254) cerebral infarctions, with a 46% fatality rate (30 of 65).[28] Gradual occlusion, as with a Silverstone clamp, does not seem to alter morbidity. Berenstein and associates[29] noted that a significant reduction of blood flow or pressure does not occur until a cross-sectional area less than 2 mm^2 is attained, regardless of the diameter of the vessel. Late-onset complications from cervical internal carotid artery ligation may result after several hours, as a result of stasis with distal thrombosis and embolic phenomena.

Four-Vessel Arteriography

All patients considered for extensive lateral skull base surgery should undergo a four-vessel carotid angiogram with venous phase (see

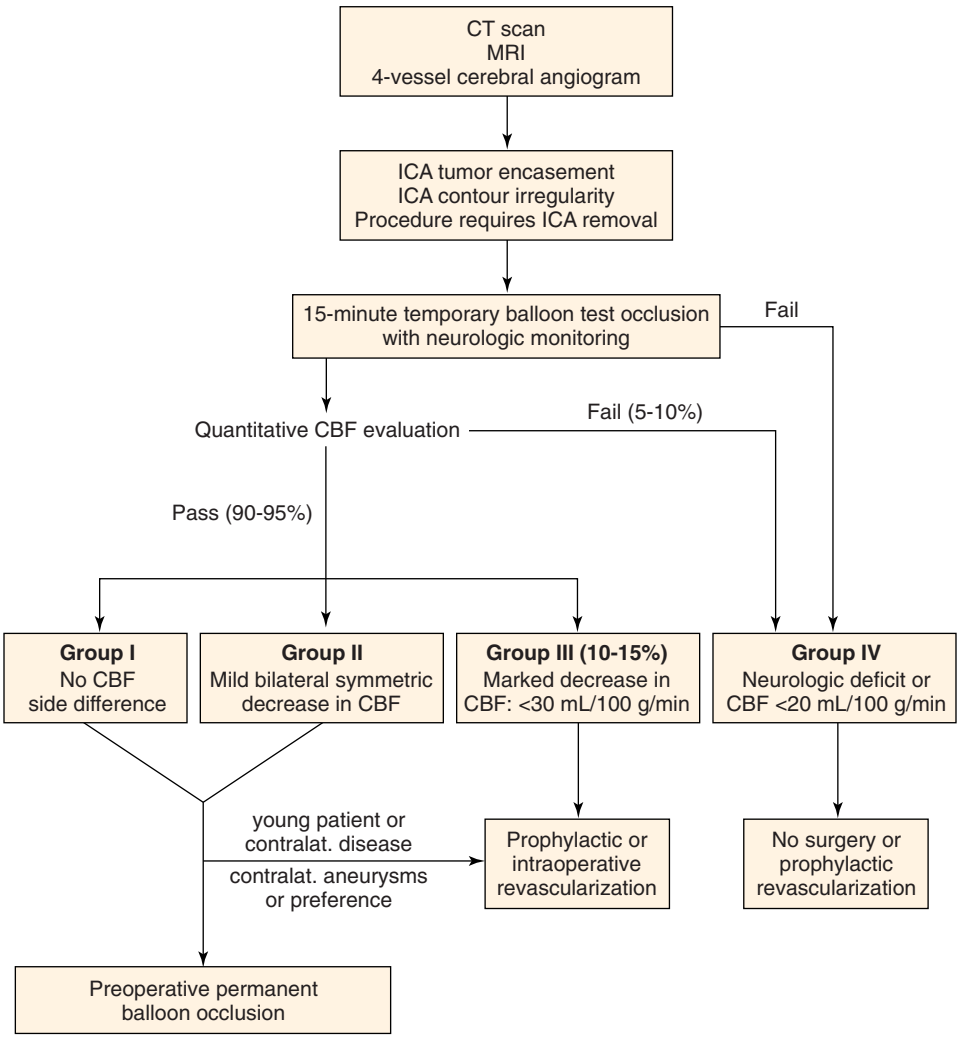

Figure 176-1. Algorithm for preoperative internal carotid artery (ICA)/cerebral blood flow (CBF) evaluation. CT, computed tomography; MRI, magnetic resonance imaging.

Chapters 135 and 136). Angiography is only qualitative but may provide critical information (Fig. 176-2).

According to Fisch and colleagues, angiographic evidence of ICA contour irregularity or stenosis at the level of lesion should prompt consideration of elective preoperative ipsilateral carotid balloon occlusion.[30] Intraoperative carotid occlusion is associated with a higher rate of permanent neurologic sequelae.

The venous phase provides critical information regarding collateral venous drainage, should ligation of the transverse sinus or the vein of Labbé be required.

Cerebral Blood Flow Assessment

Some understanding of cerebral blood flow (CBF) is essential to carotid artery management. Normal CBF approximates 50 mL/100 g per minute.[31] In alert humans, CBF less than 20 mL/100 g per minute produces failure of brain function, resulting in at least temporary hemiparesis or hemiplegia.[32] At this point, electroencephalography (EEG) usually reveals changes reflecting synaptic transmission failure.[31] As CBF decreases below 15 mL/100 g per minute, electrical activity is lost.[33] Jones and coworkers[34] found that long-lasting ischemia in monkeys from local CBF less than 17 to 18 mL/100 g per minute resulted in infarction. The time course of irreversible neuronal damage at various CBF levels in humans is unknown.

Functional assessment of CBF is required in the following clinical circumstances:

1. En bloc resection of a malignant tumor necessitating resection of the internal carotid artery
2. Tumor encasement of the internal carotid artery as seen on MRI or CT
3. Angiographic contour irregularity or stenosis at the level of the tumor

Qualitative Cerebral Blood Flow Evaluation

Various methods have been proposed to assess functional collateral circulation in the circle of Willis. Simplest is the Matas test, in which the ipsilateral carotid artery is compressed against a vertebral transverse process while the examiner observes for deterioration of neurologic function.[35] Cross-compression carotid arteriography will give a qualitative feel for ipsilateral CBF.[36] Direct intraoperative carotid stump pressures can estimate collateral circulation. A back-pressure of 50 mm Hg has been considered to be indicative of adequate CBF,[37] but stump pressures have been shown to be unreliable.[38,39] Ocular plethysmography and transcranial Doppler velocitometry of the middle cerebral artery[40] have similar theoretic limitations. In a series of patients undergoing carotid surgery, intraoperative EEG revealed no change in 18% to 56% of those with CBF levels less than 20 to 24 mL/100 g per minute, depending on the anesthetic used.[41] EEG, therefore, may be too insensitive for detection of CBF abnormality in patients who experience prolonged occlusions of the internal carotid artery.

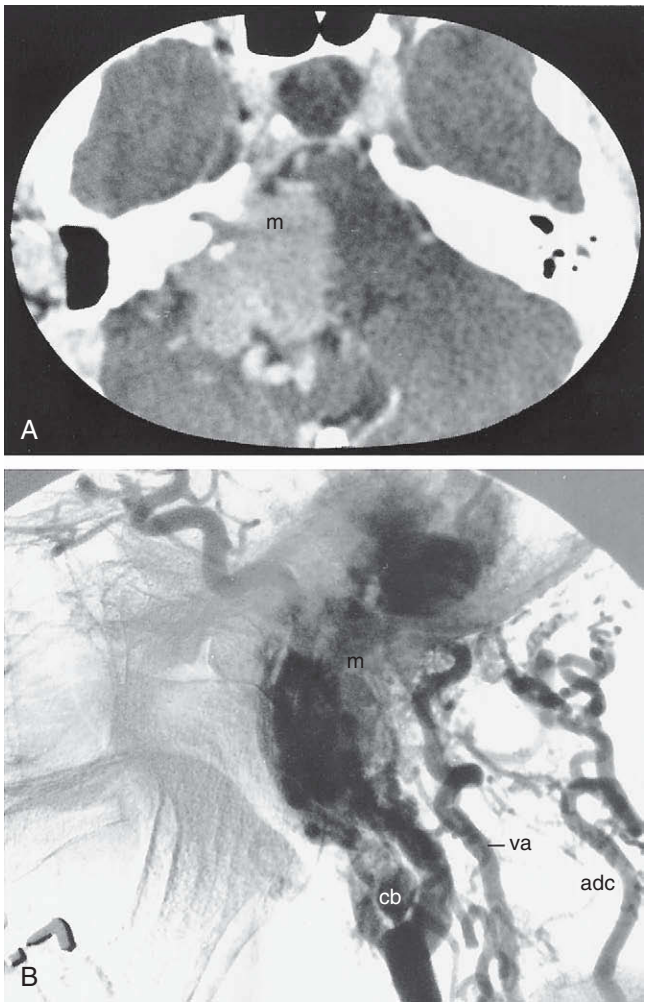

Figure 176-2. Two right-sided paragangliomas in a 61-year-old woman. **A,** Axial view, computed tomography after administration of intravenous contrast. A dense, pathologically contrast-enhancing mass (m) with tortuous dilated vessels is demonstrated. This lesion has ascended from the glomus jugulare up into the cerebellopontine angle cistern. It covers the internal auditory canal. **B,** Innominate artery angiogram, lateral subtraction view centered at the craniocervical junction. The wildly hypervascular nature of the paraganglioma is demonstrated. The tumor has parasitized the vertebral artery (va) and is ascending the deep cervical arteries (adc). These vessels have dilated and become tortuous because of the increased flow demanded from them. Besides the large glomus jugulare paraganglioma (m), the patient has a small carotid body paraganglioma (cb).

Generally accepted evaluations of CBF all involve the interventional radiologic technique of balloon test occlusion (BTO). The assessment of CBF will be either qualitative or quantitative with BTO with neurologic monitoring. Fisch uses qualitative BTO as the sole method to assess collateral CBF, with the neuroradiologist making an experienced, qualitative judgment regarding which patients should undergo permanent occlusion.[30] The collateral circulation may be stressed during BTO with pharmacologically induced hypotension or acetazolamide. Other qualitative techniques for CBF evaluation, such as single photon emission computed tomography (SPECT) and magnetoencephalography, attempt to "quantify" CBF.[42-45]

Quantitative Cerebral Blood Flow Evaluation

The impetus for quantitative evaluation of CBF is to identify the 10% to 25% subset of patients who "pass" BTO (as described next under "Carotid Management Algorithms") but are still at moderate to high risk of irreversible neurologic damage in the event of internal carotid artery occlusion. Quantitative methods of CBF evaluation during BTO include (1) positron emission tomography (PET), (2) MRI techniques, (3) cerebral perfusion CT, and (4) xenon CT or xenon 133 nuclear studies.

PET has the advantage of measuring CBF and metabolic parameters simultaneously.[46] Of the tests mentioned, PET provides the most accurate knowledge regarding cerebral hemodynamics, although it requires expensive infrastructure, is not widely available, and is time consuming.

New advances show that functional MRI (fMRI) has the potential to supplant xenon flow studies.[47-51] Such MRI studies have been used to evaluate CBF preoperatively and postoperatively for extracranial-intracranial bypass procedures.[52] The potential advantage of fMRI lies in that it requires only software upgrades to current MRI scanners. Disadvantages include the need for transport away from the vascular suite and for special equipment tolerant of the highly magnetic field.

Cerebral perfusion CT with or without acetazolamide challenge can be performed quickly on any standard helical (spiral) CT scanner with perfusion maps generated by software.[53,54] Further studies are needed to validate perfusion CT as a quantitative technique comparable to xenon CT.

Xenon 133 scintillation shows excellent correlation with quantitative assessments of CBF in a defined region with a scintillation counter on the scalp[41] and also may be used intraoperatively.

Xenon CT blood flow mapping is the best studied clinical, quantitative measure of CBF.[28,42,55-58] Inhaled xenon acts as a contrast agent, whose uptake and diffusion from cerebral tissue is proportional to blood flow. CBF distribution is estimated with specialized computer software before and after BTO of the internal carotid artery during serial CT scans and from which a blood flow map is calculated. An algorithm for carotid artery management has been proposed on the basis of preoperative xenon CT blood flow mapping with temporary carotid balloon occlusion (see Fig. 176-1). Group 3 patients (see Fig. 176-1), although "passing" BTO, have CBF values between 20 and 30 mL/100 g per minute and are thought to be in hemodynamic decompensation without neurologic deficit but entirely dependent on systemic blood pressure.[56] As is well recognized, intraoperative or postoperative blood pressure fluctuations after ICA occlusion may send these patients over the precipice. It is estimated that 90% of group 3 patients will have a major stroke after permanent occlusion of the internal carotid artery.[59]

Carotid Management Algorithms

A decision regarding management of the internal carotid artery is best made preoperatively. Intraoperative carotid occlusion usually is performed to control massive bleeding under suboptimal circumstances, resulting in a higher neurologic complication rate. Intraoperative balloon occlusion or intra-arterial shunt placement may be required if the carotid is lacerated and control is difficult.[60-62]

After preoperative functional evaluation of the internal carotid artery, either qualitative or quantitative, decisions about management of the carotid are dependent on the following factors:

- Results of the functional evaluation
- Young age
- Contralateral skull base tumor or vascular disease

Vein graft reconstruction, instead of sacrifice of the artery, may be a consideration regardless of the BTO result, especially in young patients and in cases in which contralateral involvement is a possibility, to restore physiologic circulation and reduce risk of late intracranial aneurysms.[33,42] The rationale for preservation of an ICA encased by benign tumor when this is possible, or revascularization when preservation is not possible, is valid.[63]

Opinion differs further regarding algorithms for management of the internal carotid artery based on functional evaluations, just as opinion differs regarding what constitutes an adequate evaluation in

the first place. The results of temporary BTO can be classified as either "pass" or "fail," as follows:

Pass: no neurologic deficit and CBF greater than 30 mL/100 g per minute (if quantitative evaluation has been performed)

Fail: neurologic deficit or CBF less than 30 mL/100 g per minute (if quantitative evaluation has been performed), or both

For patients with BTO results in the "fail" category, definitive resection may not be possible; alternatively, extracranial-intracranial bypass antecedent to the resection procedure should be considered.[42,64-66]

Patients who "pass" are further subclassified depending on whether qualitative or quantitative testing has been done. Fisch[30] using qualitative BTO, recommends permanent occlusion of the internal carotid artery preoperatively if the neuroradiologist confirms adequate cross-circulation and no neurologic deterioration occurs during the test. In a series reported by Zane and colleagues, only 5% (2 of 46 patients, 1 preoperatively and 1 postoperatively) had permanent neurologic sequelae after occlusion when this algorithm was used.[30] If quantitative testing has been performed, transarterial permanent balloon occlusion may be considered for operative candidates in groups 1 and 2 (CBF greater than 30 mL/100 g per minute) (see Fig. 176-1) for the same indications as those that occasioned functional CBF testing. If the decision for occlusion of the internal carotid artery is reached preoperatively, permanent balloon occlusion should be performed 1 to 4 weeks before the resection to lessen thromboembolic sequelae. Placement proximally at the level of the carotid bifurcation and distally just before the ophthalmic artery minimizes late thromboembolic sequelae.[67] The long-term sequelae of carotid occlusion are unknown, although xenon CT blood flow mapping after BTO correlates well with medium-term neurologic outcome.[28] Direct vein graft reconstruction is indicated to allow complete tumor resection (see Fig. 176-1) in patients assigned to group 3 by quantitative CBF assessment (CBF less than 30 mL/100 g per minute), those with bilateral lesions, and young patients with benign tumors, according to Sen and Sekhar.[64] Intraoperative revascularization is associated with increased operative time, graft occlusion, need for transfusion, and potential for postoperative blowout.[30] Risk of graft occlusion is especially high among patients with long grafts.

Disregarding the surgeon's preference for revascularization or permanent balloon occlusion, the decision optimally is made under controlled circumstances preoperatively.

Surgical Approaches

Although the biologic behavior of tumors involving the skull base may vary, certain general principles should be followed in their extirpation. It is essential, if possible, to determine preoperatively whether the lesion is benign or malignant. Small, benign lesions in the middle ear space whose borders are clearly visible through the tympanic membrane can be removed through the external auditory canal. When removing the tumor, the surgeon should clearly differentiate it from vascular anomaly, because injury to the internal carotid artery in its intratemporal portion is hazardous and may require ligation of the artery for control of bleeding. Benign tumors limited to the mesotympanum whose borders are not visible through the tympanic membrane may be approached through a combined transcanal and facial recess or through an extended facial recess approach. Occasionally, the facial recess is narrow, necessitating removal of all or part of the bony posterior wall of the external auditory canal. Basic surgical approaches to the mastoid and mesotympanum are described in Chapters 127 and 142. Malignancies are best removed en bloc, whereas benign lesions may be extirpated piecemeal, although depending on biology, resection may require establishing a cuff of normal tissue. Surgical approaches to lesions deeper within the temporal bone should be chosen either to provide adequate exposure for complete excision or to allow easy access to an exteriorized cavity, to preserve useful residual hearing if possible, to preserve facial nerve and other cranial nerve functions when possible, to avoid injury to the brainstem and internal carotid artery, and to provide for wound closure without cerebrospinal fluid (CSF) leak.

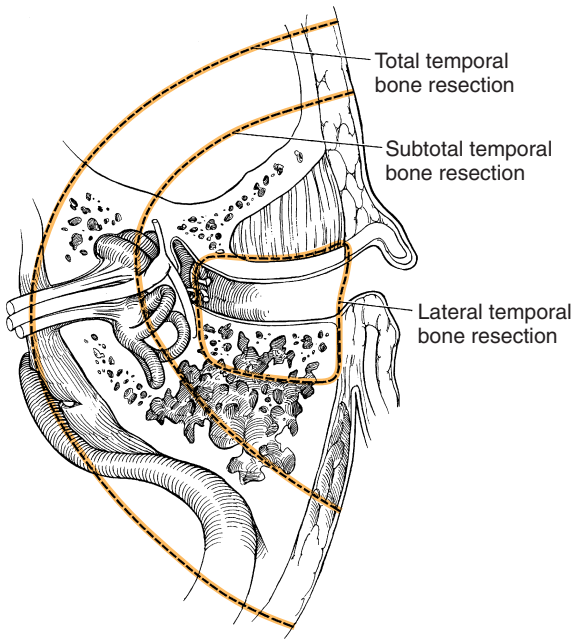

Figure 176-3. Margins of resection for lateral temporal bone, subtotal temporal bone, and total temporal bone resections.

The operative approach and intraoperative technique should maximize safe exposure and minimize morbidity. Surgeons should be well versed in all methods of exposure for various regions of the skull base. Circumferential exposure of tumor margins for benign tumors and en bloc technique for malignant lesions, minimization of blood loss by preoperative selective embolization and intraoperative selective vessel ligation, proximal and distal control of the internal carotid artery around the tumor, and preservation of cranial nerves facilitated with intraoperative monitoring by electromyography (EMG) (see Chapter 178) whenever necessary are essential to a successful outcome.

Sleeve Resection of External Auditory Canal

A sleeve resection of the external auditory canal removes the cartilaginous portion and some or all of the bony canal wall skin circumferentially without bone removal. Split-thickness skin grafts are used in the conchal bowl and external auditory canal. Some surgeons include the tympanic membrane as a medial margin to a sleeve resection, although this type of procedure generally is reserved for malignancies localized to the cartilaginous portion of the canal. Malignancies localized to or involving the osseous portion require at least a lateral temporal bone resection.

Lateral (Partial) Temporal Bone Resection

A lateral temporal bone resection[68-71] removes en bloc the entire osseous and cartilaginous portions of the external auditory canal and tympanic membrane using the extended facial recess approach (Fig. 176-3). This procedure is indicated for patients with malignant neoplasms localized to the osseous canal with no encroachment on the medial mesotympanum. Parotidectomy, neck dissection, and mandibular condylectomy are performed as adjunctive surgical procedures if indicated by preoperative radiologic or intraoperative findings. Intraoperative facial nerve monitoring is useful in this procedure.

Incisions

A soft tissue cylinder is designed to include the tragus and conchal bowl. The incision is taken vertically downward, posterior and superior to the temporal bone. The external auditory canal is sutured shut. A postauricular incision is created approximately a fingerbreadth behind the postauricular sulcus (Fig. 176-4A). It may be extended inferiorly into a neck crease for parotidectomy as required. Retractors then are placed.

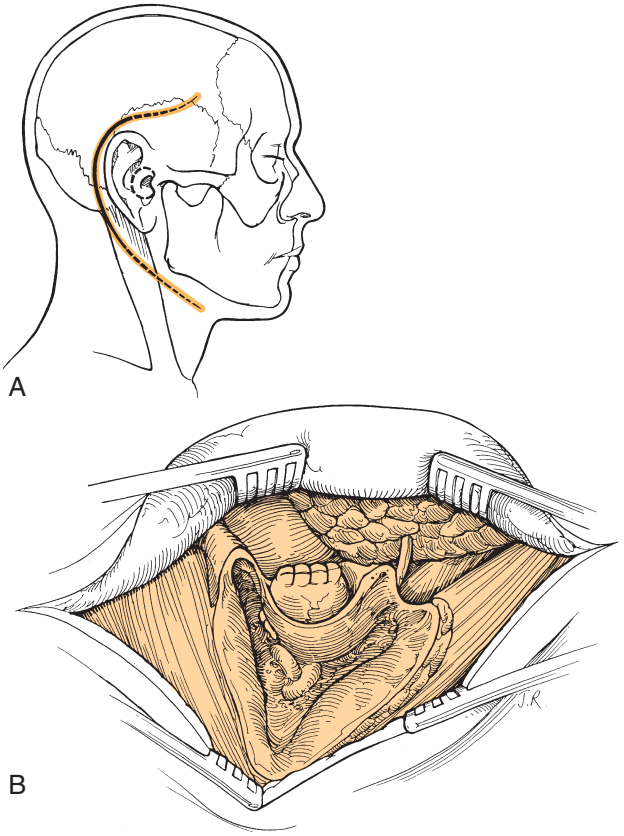

Figure 176-4. Lateral temporal bone resection: incision and initial exposure. **A,** Incisions include a central external auditory canal core, which is sutured closed. Extend incision as needed for neck dissection or temporal muscle rotation flap. Note that the tragus can be preserved for better cosmesis. **B,** Canal closure, mastoidectomy, and epitympanic dissection have been completed.

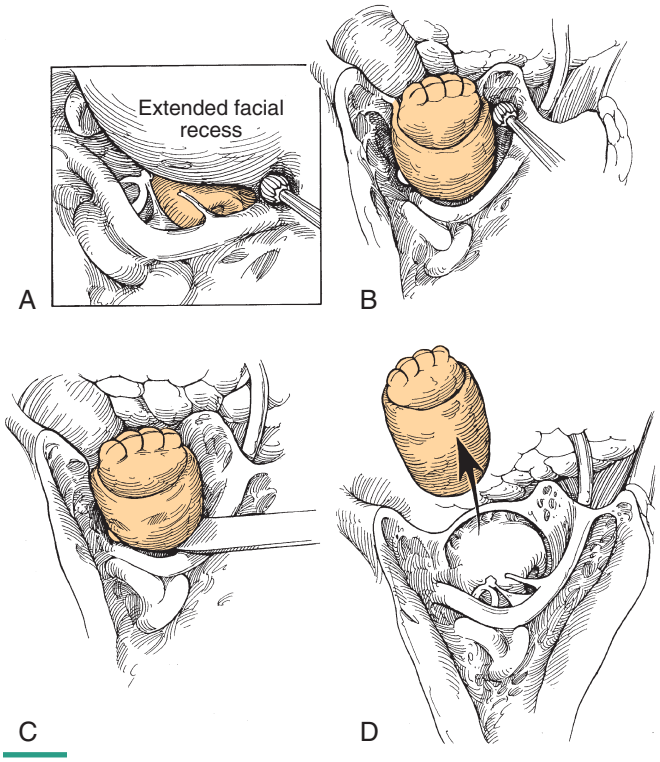

Figure 176-5. Lateral temporal bone resection: specimen delivery. **A,** Extended facial recess dissection. **B,** Hypotympanic dissection. **C,** Specimen fractured with osteotome. **D,** Specimen separated from soft tissue.

A modified neck dissection, total parotidectomy, and partial mandibulectomy may be performed if indicated by perioperative radiologic studies or intraoperative findings.

Mastoidectomy and Facial Recess Approach

A complete mastoidectomy is performed. The superior mastoid dissection is carried to the root of the zygoma, with care taken not to penetrate the osseous portion of the external auditory canal or the tegmen. Epitympanic dissection in an anterior direction should extend into the temporomandibular joint, as depicted in Figure 176-4B. An extended facial recess approach is then performed by "eggshelling" the vertical segment of the facial nerve from the second genu to the stylomastoid foramen (Fig. 176-5A). The incudostapedial joint is separated, and the pillar of bone between the facial recess approach and the fossa incudis also is removed. The tensor tympani tendon is cut with Bellucci scissors. Hypotympanic dissection is performed by extending the facial recess approach through the chorda tympani nerve. Drilling with either a diamond or cutting burr is continued along the inferior aspect of the hypotympanum medial to the annulus and lateral to the jugular bulb and carotid canal until soft tissue is reached, with care taken not to injure the intraparotid facial nerve (see Fig. 176-5B).

Removal of Specimen

Continuity between the hypotympanic dissection and the anterior epitympanic dissection is established by drilling along the anterior mesotympanum into the temporomandibular joint or by fracturing with a curved osteotome (see Fig. 176-5C). Either cautery or sharp dissection is used to separate the bony anterior canal wall from soft tissue of the temporomandibular joint and the superficial lobe of the parotid. The specimen then is sent en bloc for histopathological examination (see Fig. 176-5D).

Closure

If ancillary procedures such as parotidectomy or mandibular resection are not performed and if postoperative radiotherapy is not anticipated, creation of a large mastoid cavity is acceptable. The eustachian tube orifice should be obliterated with temporalis fascia as in a radical mastoidectomy. The mesotympanum and facial ridge may be covered with temporalis fascia graft to facilitate healing. Further conchal bowl cartilage may need to be removed to create a large meatoplasty. A split-thickness skin graft is then sutured to the edges of the conchal bowl and anterior facial skin or tragal skin and allowed to drape into the mastoid cavity and anterior cavity soft tissue. The skin graft then can be tacked into place with absorbable sutures along the soft tissue areas. Use of a graft will minimize postoperative meatal stenosis.[72] Absorbable gelatin then can be placed on the medial aspect of the mastoid cavity, followed by packing with gauze strips.

If postoperative irradiation is anticipated, the mastoid cavity should be obliterated to avoid osteoradionecrosis.[73] This may be achieved with use of abdominal fat and rotation of a temporalis graft to cover the defect. Alternately, a superiorly based sternocleidomastoid muscle flap based on the occipital artery may be rotated by incising the sternocleidomastoid muscle at the clavicle. A skin graft then is sutured to the conchal bowl margins and tacked down to underlying muscle.

Subtotal Temporal Bone and Total Temporal Bone Resections

A subtotal temporal bone resection[70,74-84] essentially allows en bloc resection of the medial surfaces of the mesotympanum, leaving the air cells of the petrous apex and portions of the bony labyrinth (see Fig. 176-3). This type of resection is indicated for patients with malignancies involving the middle ear.

A total temporal bone resection involves an en bloc resection of the temporal bone, including the petrous apex and the sigmoid sinus

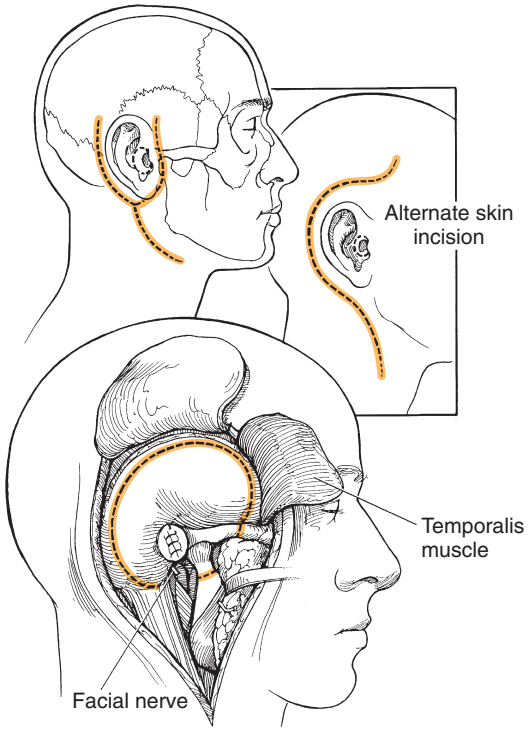

Figure 176-6. Subtotal temporal bone resection. Incisions include a central external auditory canal core, which is sutured closed. Note the tragus can be preserved for better cosmesis. Temporal craniotomy for subtotal temporal bone resection is smaller than for a total temporal bone resection. Parotid gland with main trunk of facial nerve has been elevated from masseter muscle.

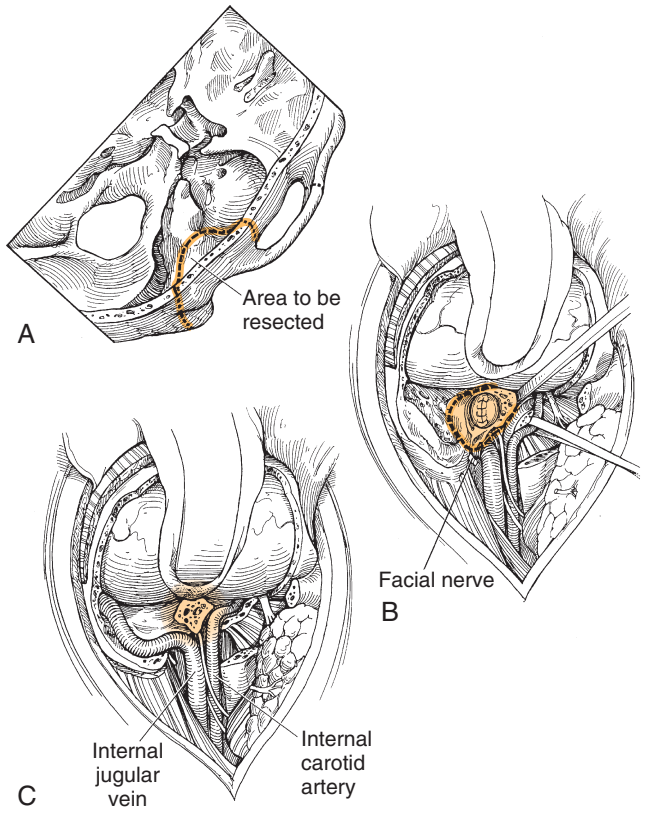

Figure 176-7. Subtotal temporal bone resection. **A,** Bird's-eye view of proposed resection. Note the facial nerve can be exposed for clean sectioning in the labyrinthine segment. **B,** Osteotome at carotid canal first genu directed at internal auditory canal fundus. **C,** Specimen removed showing remaining petrous apex and otic capsule. Roman numerals denote cranial nerves.

(see Fig. 176-3). The petrous internal carotid artery may be included in this resection. Total temporal bone resection is of questionable added benefit if a high-grade tumor involves the petrous apex or internal carotid artery or extends outside of the petrous bone intradurally or toward the cavernous sinus. Total resection may be indicated for low-grade malignancies.[83]

Incision

A large C-shaped postauricular incision or Y-shaped incision can be designed with a central island removed (Fig. 176-6). Alternately, a preauricular incision may be used for cases with involvement of the external auditory canal. In performing the incision, care should be taken to preserve the greater auricular nerve, because this nerve may be used for facial nerve interposition grafting. Also, care should be taken in elevating the flap off the zygoma, so as to not injure the peripheral frontal branch of the facial nerve.

Facial Nerve Management

With parotid involvement or involvement of the facial nerve, the distal branches or main trunks of the facial nerve may be identified and transected and marked for future interposition grafting. If no such involvement is present, the facial nerve is identified at the stylomastoid foramen and transected. The parotid is carefully dissected off the masseter. Proximal facial nerve management is considered later.

Proximal Vascular Control, Neck Dissection

If preoperative imaging indicates lymphadenopathy, a supraomohyoid modified neck dissection can be performed. Regardless of lymph node involvement, proximal vascular control of the carotid artery and internal jugular vein can be obtained, and vascular loops are placed around these vessels. The lower cranial nerve, internal carotid artery, and internal jugular vein can be followed superiorly. The sternocleidomastoid muscle is separated from the mastoid tip, as is the digastric muscle.

Infratemporal Fossa Dissection

The masseter attachment to the zygoma is detached. A mandibular osteotomy is performed from the mandibular notch to the angle of the mandible. The mandibular condyle is separated from the glenoid fossa, detaching the lateral and medial pterygoid musculature, with care taken not to injure the internal maxillary artery. Should the internal maxillary artery be injured, brisk back-bleeding would indicate good blood flow from the pterygoid plexus, presaging a viable temporalis muscle useful for reconstruction. The temporalis muscle is elevated off the skull in a subperiosteal fashion and reflected inferiorly, still attached to the coronoid process. A superior infratemporal fossa dissection should allow identification of the foramen spinosum and foramen ovale.

Temporal Craniotomy

A temporal craniotomy is performed to allow exposure of the superior surface of the petrous bone. A larger craniotomy is performed for a total temporal bone resection. The dura is elevated off the petrous bone, proceeding from posterior to anterior.

Subtotal Temporal Bone Resection

The vertical petrous portion of the internal carotid artery is identified (Fig. 176-7). This resection is performed by drilling with diamond burrs through the glenoid fossa and across the eustachian tube orifice. Mobilization of the carotid is just distal to the first genu. The distal eustachian tube orifice should be either sutured or closed with autologous tissue.

Delineation of the Sigmoid Sinus and Jugular Bulb

Presumably, if a subtotal temporal bone resection has been selected, the mastoid air system is not involved in patients with carcinoma. A mas-

toidectomy is performed, removing the mastoid cortex with cutting burrs. The sigmoid sinus and jugular bulb are carefully delineated with diamond burrs, and the jugular bulb is carefully dissected from the temporal bone, with recognition that the inferior petrosal veins enter it inferomedially. The sigmoid sinus may require ligation or extradural packing for vascular control later in the procedure.

Proximal Facial Nerve Management

Although an osteotomy may be performed at this point, with sectioning of the proximal facial nerve during an often bloody dissection, it probably would cause further stretch injury to the facial nerve. If grafting of the facial nerve is desired, further stretch injury is best avoided. The facial nerve may be delineated from the labyrinthine segment to the internal auditory canal as with routine middle cranial fossa nerve decompression or may be identified by a translabyrinthine approach (see Fig. 176-7A). Nonetheless, clean sectioning of the facial nerve facilitates interposition grafting and later facial nerve function.

Osteotomy

A groove may be drilled along the floor of the middle fossa connecting the glenoid fossa area, lateral internal auditory canal, and posterosuperior mastoid. An osteotome is inserted into the carotid canal just distal to the first genu and pointed toward the internal auditory canal (see Fig. 176-7B). The temporal bone specimen is brought out (see Fig. 176-7C), which often will result in inferior petrosal sinus bleeding, requiring intraluminal packing of the inferior petrosal sinus with oxidized cellulose or control of the jugular bulb and sigmoid sinus.

Total Temporal Bone Resection

The internal carotid artery is dissected to the foramen lacerum (Fig. 176-8). The vessel may have been permanently occluded perioperatively in accordance with the surgical plan. The internal jugular vein is ligated and cut. A suboccipital craniotomy is performed, extending over the transverse sinus and lateral posterior fossa. The dura is divided over the cerebellum, and the transverse sinus is ligated between the vein of Labbé and the superior petrosal sinus. The tentorium is divided from the lateral sinus across the superior petrosal sinus to the inferior edge of V_3 with continued dural incision along the floor of the middle cranial fossa laterally. Cranial nerves VII and VIII and the labyrinthine artery are divided at the internal carotid artery. Cranial nerves IX, X, and XI are divided intradurally. The inferior dural incision along the clivus extends from Meckel's cave caudal to the lower cranial nerve to the postsigmoid dural edge. An osteotome is inserted just posterior to the foramen ovale and directed slightly posteriorly to avoid entering the foramen lacerum. This will release the temporal bone specimen, with the occasional need for osteotomy just above the jugular bulb to separate the petro-occipital synchondrosis.[84,85] Alternatively, a groove is drilled under direct vision through the posterior fossa to connect to an externally drilled groove posterior to the petrous internal carotid artery.[83]

Reconstruction

The facial nerve and other appropriate cranial nerves can be cable grafted. Dural defects are closed as needed with fascia or pericranium. The temporalis muscle can be rotated and sutured to surrounding soft tissue. Alternately, regional or free flaps are used. Craniotomy bone and zygoma are secured with wire or miniplates. A closed suction drain then is placed before skin closure.

Infratemporal Fossa Approaches

Attacking various problems of the skull base through a lateral approach transgresses the temporal bone and infratemporal fossa. The postauricular infratemporal fossa approaches as described by Fisch[61,86-88] and the preauricular[89-92] approaches offer the best access to the jugular bulb, internal carotid artery, petrous apex, clivus, pterygomaxillary fossa, and nasopharynx. Proponents of these approaches have written extensively on the subject, and the techniques described here have been adapted from their work. Anatomic maneuvers may be added as needed to facilitate tumor exposure and extirpation.[93,94]

Postauricular Approaches to the Infratemporal Fossa

Fisch[61] has been the primary innovator of these techniques and should be credited for his work. He has divided these techniques into three basic approaches: *Type A* dissection entails radical mastoidectomy, anterior transposition of the facial nerve, exploration of the posterior infratemporal fossa, and cervical dissection permitting access to the jugular bulb, vertical petrous carotid, and posterior infratemporal fossa. *Type B* dissection explores the petrous apex, clivus, and superior infratemporal fossa. *Type C* allows exposure of the nasopharynx, peritubal space, rostral clivus, parasellar area, pterygopalatine fossa, and anterosuperior infratemporal fossa.

Incisions and Skin Flaps

The planned incision should allow for further extensions without devascularization of the elevated skin flap (Fig. 176-9A). Cervical exposure to a variable extent and anterior extension for dissection toward the clivus and parasellar area should be permitted. Keeping the inferior limb of the incision in a posterior location over the mastoid tip allows extension into the cervical area for dissection while protecting the marginal mandibular nerve. Similarly, extending the incision anterosuperiorly into the frontal area permits elevation over the zygoma to the orbital rim.

The flap should be elevated superficially to the temporalis and postauricular muscles, leaving a periosteal flap based on the external auditory canal (see Fig. 176-9B). The canal is transected with care to protect the branches of facial nerve anterior to the canal.

The plane of dissection in an anterior direction is in the subcuticular tissue over the temporal, parotid, and cervical areas. In the type A approach, the tertiary branches of the facial nerve are identified and protected, whereas in the type B and type C approaches, the frontal branch is exposed and protected near the lateral orbital rim.

Closure of the External Auditory Canal

The external auditory canal is closed in a watertight blind sac. The cartilaginous canal skin is undermined to approximately the level of the conchal bowl with tenotomy scissors. The cartilaginous canal skin then is everted and sutured with absorbable sutures and reinforced medially with the periosteal flap elevated off the mastoid cortex (see Fig. 176-9C to F).[96]

Removal of External Auditory Canal Wall Skin and Tympanic Membrane

The skin of the osseous portion of the external auditory canal wall is elevated circumferentially down to the annulus. With an operating microscope, the tympanic annulus is elevated, the incudostapedial joint is separated, the tensor tympani tendon is cut, and the neck of the malleus is nipped, allowing total removal of the canal wall skin, tympanic membrane, and attached manubrium (Fig. 176-10).

Cervical Dissection

Cervical dissection is done as needed to expose the inferior margins of the tumor. This part of the procedure is not required in most type B and type C approaches, except to gain cervical control of the vascular structures if needed. The greater auricular nerve should be sectioned as distally as possible in the parotid for potential use as an interposition graft if needed. Major structures, including the common, external, and internal carotid arteries, the internal jugular vein, and cranial nerves IX to XII, are identified (Fig. 176-11). Division of the posterior belly of the digastric near the mastoid facilitates identification of these structures up to their entrance in the skull base. Ligation of the occipital artery and ascending pharyngeal artery is indicated when these vessels prove to be the vascular supply to the tumor on arteriography. Transection of the glossopharyngeal nerve often is necessary to follow the carotid artery into the skull base. Vascular loops are placed around the internal carotid artery and jugular vein for quick identification and control in the event of bleeding (see Fig. 176-11).

Extratemporal Facial Nerve Dissection

The extratemporal facial nerve may be located deep to the midpoint of a line between the tragal pointer cartilage and the mastoid tip. After

release of parotid tissue from the sternocleidomastoid muscle, the tragal cartilage is dissected medially, identifying the facial nerve just inferior to the pointer. The facial nerve is dissected out to tertiary branches by cutting overlying the parotid gland and freeing it from the underlying parotid tissues. This exposure is required for anterior transposition in the type A approach (see Fig. 176-11). In the type B and type C approaches, facial nerve transposition is not required; only the frontal branch is followed distally to allow its preservation when the zygoma is transected. The parotid gland is bluntly dissected off the masseteric fascia to reduce traction on the facial nerve when the mandible is retracted.

Radical Mastoidectomy

The radical mastoidectomy removes the air cell tracts lateral and adjacent to the otic capsule (Fig. 176-12A). Exenteration of all tracts is important to prevent long-term complications after cavity obliteration.[96] The stapes suprastructure is removed to prevent inner ear trauma. The facial nerve is skeletonized in preparation for transposition. The eustachian tube is obliterated with bone wax impregnated with bone dust and a muscle plug. Removal of the external auditory canal, tympanic membrane, ossicles, and air cells of the temporal bone lateral to the otic capsule constitute the radical mastoidectomy.

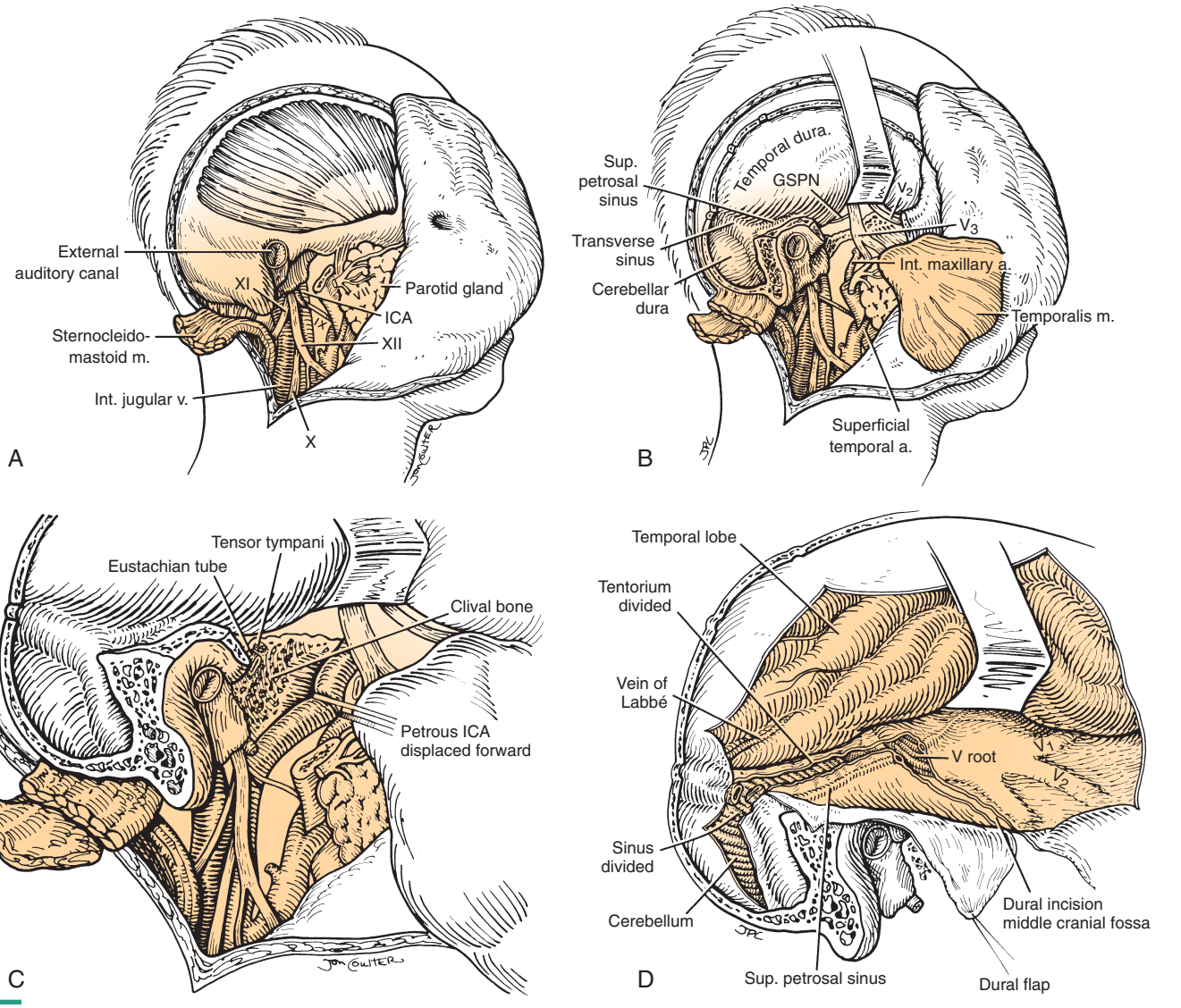

Figure 176-8. Schematic depiction of total temporal bone resection. Roman numerals denote cranial nerves. **A,** The frontotemporal-retroauricular-cervical skin flap is rotated forward. The external ear canal has been transected. The facial nerve has been transected just beyond the stylomastoid foramen. The temporomandibular joint has been opened and the mandibular ramus resected. Cranial nerves IX through XII and the jugular and carotid vessels are exposed to the neck. **B,** A temporal and suboccipital craniotomy has been extended over the transverse sinus and lateral posterior fossa. A zygomatic osteotomy and a partial mastoidectomy have been performed. The osseous middle fossa floor has been partially resected to expose second (V_2) and third (V_3) divisions of the cranial nerve V and the greater superficial petrosal nerve (GSPN). The middle meningeal artery has been transected. **C,** Continuing resection of the osseous middle fossa floor; the eustachian tube and the tensor tympani muscle have been transected. The ascending and transverse segments of the petrous ICA have been unroofed, and the ICA has become mobilized anteriorly. **D,** The temporal and retrosigmoid portions of the dura have been opened. The lateral sinus has been ligated at its junction with the sigmoid; the tentorium has been opened along the inferior edge of the mandibular nerve, trigeminal ganglion, and roof, with the interruption of the superior petrosal sinus. If the superior petrosal sinus is uninvolved, its drainage into the transverse sinus may be preserved by changing the dural incision lines. The dura has been cut over the cerebellum; the transverse sinus has been ligated and transected, and a dural flap has been brought down from over the temporal lobe. The tentorium has been divided from the transverse sinus transection, alongside and behind the petrous ridge, and anteromedially across the sinus. This cut has been connected to an incision in the dura on the middle cranial fossa floor anterior to the petrous base. The outline of the trigeminal ganglion and roots can be seen through the middle fossa dura.

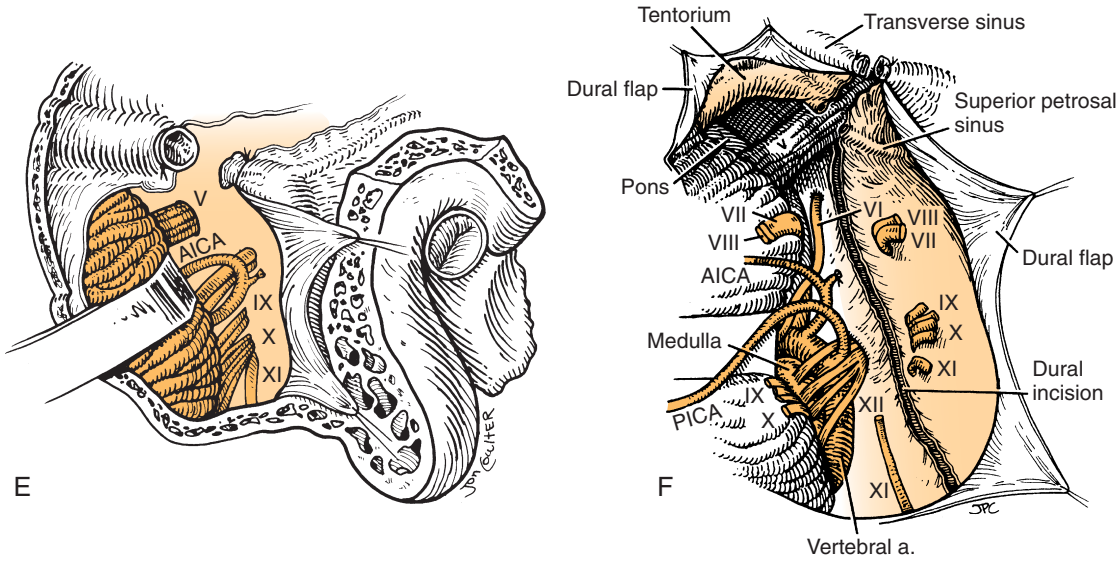

Figure 176-8, cont'd. **E,** With the cerebellum retracted medially, cranial nerves V and VII through XI can be seen. The labyrinthine (internal auditory) artery has been transected at its origin from the anterior inferior cerebellar artery (AICA). **F,** Cranial nerves VII through XI have been transected, and the underlying dura has been incised as the posterior border of the en bloc resection of the petrous bone. The petrous bone specimen then is disconnected from any remaining attachments and removed. ICA, internal carotid artery; PICA, posterior inferior cerebellar artery. *(Used with permission from Sekhar LN, Pomeranz S, Janecka IP, Hirsch B, Ramasastry S. Temporal bone neoplasms: a report on 20 surgically treated cases.* J Neurosurg. *1992;76:578-587.)*

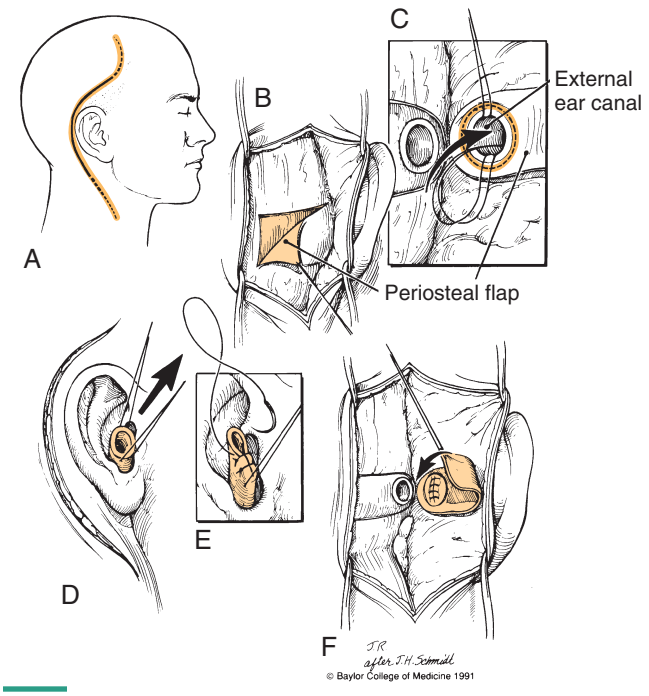

Figure 176-9. **A,** Skin incision for Fisch type A infratemporal fossa dissection. **B,** Anteriorly based periosteal flap elevation. **C** to **E,** Cartilaginous canal skin elevated, everted, and blind sac closure of external canal. **F,** Blind sac closure reinforced with periosteal flap.

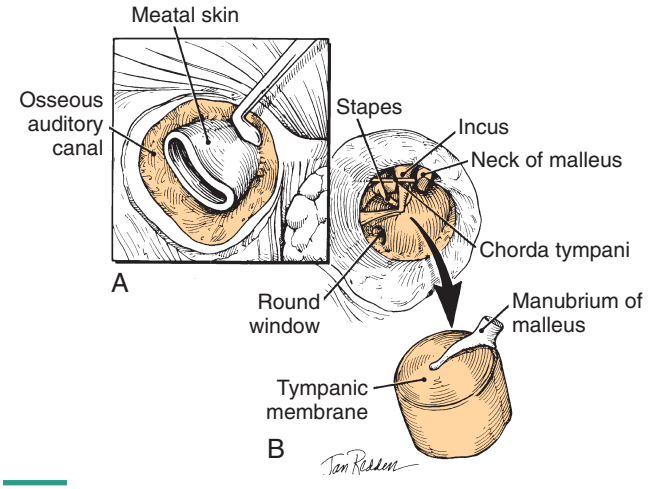

Figure 176-10. **A,** Skin of osseous external auditory canal elevated to annulus (note that lateral skin is already removed). **B,** Removal of canal skin, tympanic membrane, and attached manubrium.

Type A Approach

FACIAL NERVE TRANSPOSITION. The facial nerve should be skeletonized and freed of its bony canal 180 degrees circumferentially from the geniculate ganglion distal to the stylomastoid foramen. The horizontal semicircular canal is in jeopardy at the second genu, and bone should be removed only on the tympanic side of the facial nerve. The air cells of the mastoid tip are exenterated lateral to the digastric ridge; the cortical shell is removed with a rongeur after incising the attached digastric muscle. At the stylomastoid foramen, the facial nerve is densely adherent to the surrounding fibrous tissue, and these tissues are elevated as a unit to prevent devascularization and stretch injury to the nerve. A new bony canal is drilled in the anterior wall of the epitympanum to receive the nerve. The facial nerve is elevated carefully from the geniculate ganglion to the pes anserinus and is transposed into the new groove and secured within the parotid soft tissue (see Fig. 176-12B).

Meticulous handling of the facial nerve decreases the risk of permanent facial nerve dysfunction after transposition. Use of the operating microscope, diamond burr, and constant irrigation minimizes direct trauma. The epineurium is kept intact. The stapedius nerve, the soft tissue of the stylomastoid foramen including periosteum and enclosed facial nerve, and all medial attachments to the nerve should be sharply dissected to prevent stretch injury.

Intraoperative facial nerve monitoring with EMG is of great benefit during transposition in preventing injury (see Chapter 178).[80]

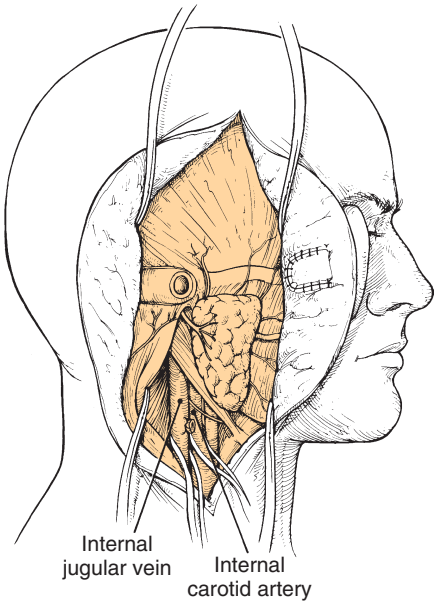

Figure 176-11. Preparatory dissection with flap elevation and proximal vascular control.

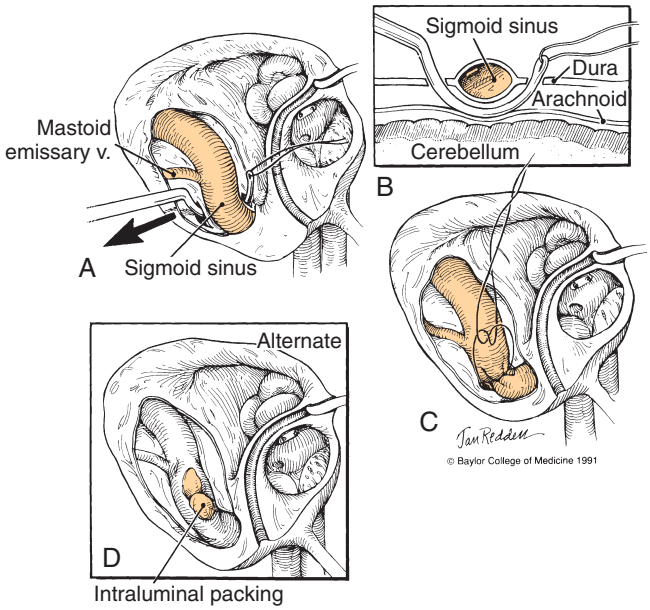

Figure 176-13. **A** to **C,** Ligation of the sigmoid sinus below the mastoid emissary vein. **D,** Alternate method of sigmoid sinus occlusion with intraluminal absorbable packing.

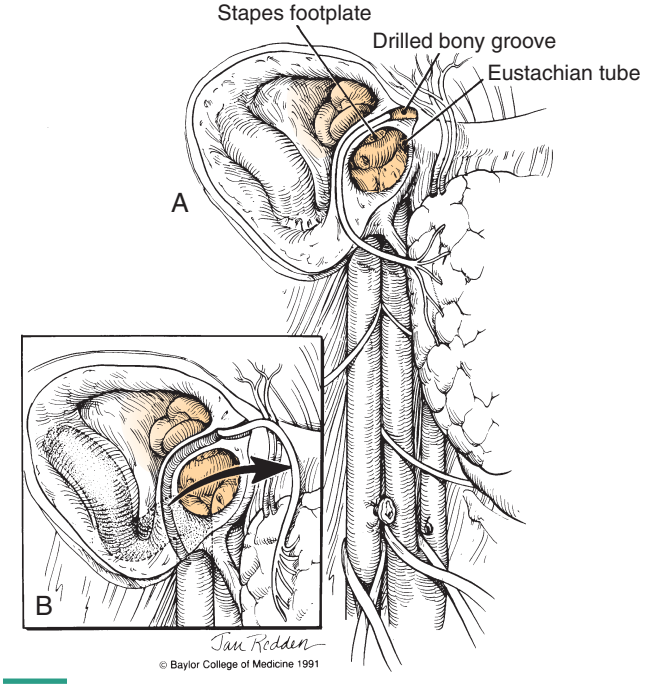

Figure 176-12. **A,** Radical mastoidectomy with facial nerve skeletonization. **B,** Anterior transposition of the facial nerve.

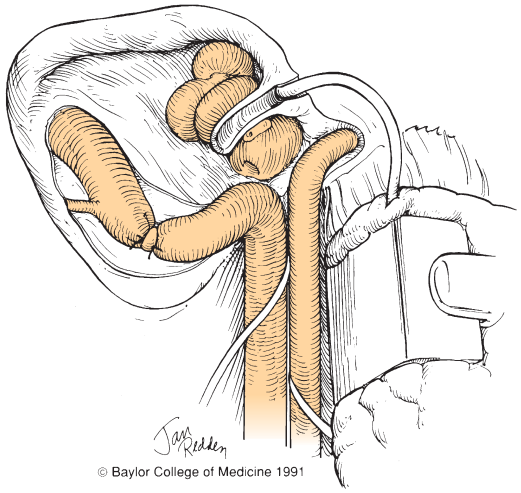

Figure 176-14. Fisch type A infratemporal fossa exposure and vascular control completed by removal of bone over carotid artery and jugular bulb.

Immediate feedback is available to the surgeon during manual manipulations, helping prevent direct trauma and stretch injury, the latter being the most common reason for postoperative dysfunction. With feedback monitoring, the surgeon can remove bone over the facial nerve more aggressively.

OCCLUSION OF THE SIGMOID SINUS. Bone is removed over the posterior fossa dura anterior and posterior to the sigmoid sinus to allow ligation. The mastoid emissary vein is left undisturbed, and ligation is performed below it if possible. Dural vessels are coagulated; the dura is elevated with dural hooks, incised in front of and behind the sigmoid sinus, and a blunt-tipped aneurysm needle is used to pass a double 2-0 silk ligature (Fig. 176-13A to C). A small CSF leak may occur and is easily controlled with a sutured muscle plug. Other methods of sigmoid sinus interruption, involving intraluminal absorbable packing (see Fig. 176-13D), are used by Jackson[97] and Holliday[98] and their coworkers.

EXPOSURE OF JUGULAR BULB AND INTERNAL CAROTID ARTERY. A clamp is passed medial to the styloid process to protect the internal carotid artery while the process is fractured and removed with the attached muscles. The parotid gland is dissected from the tympanic bone, and a modified self-retaining laminectomy retractor (Karl Storz, D-7200, Tuttlingen, Germany) is placed behind the ramus of the mandible to effect anterior subluxation. The facial nerve EMG activity is monitored to avoid stretch injury or compression of branches in the parotid gland. Exposure of the posterior infratemporal fossa now permits isolation of the vertical intrapetrous segment of the internal carotid artery. With removal of bone over the carotid artery and beneath the otic capsule, the jugular fossa is exposed for tumor removal (Figs. 176-14 and 176-15).

TUMOR REMOVAL. After exposure and distal control of the internal carotid artery are accomplished, the tumor may be carefully

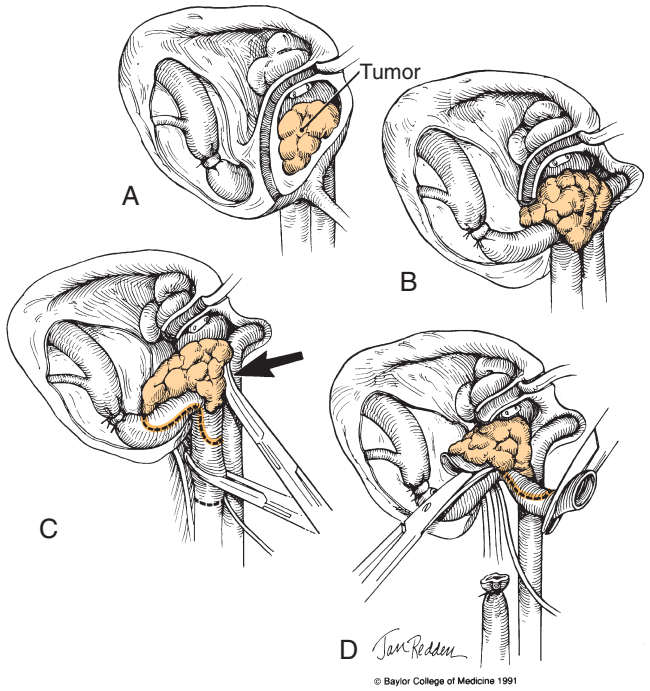

Figure 176-15. **A** to **D,** Removal of paraganglioma of the jugular bulb using the Fisch type A infratemporal fossa approach.

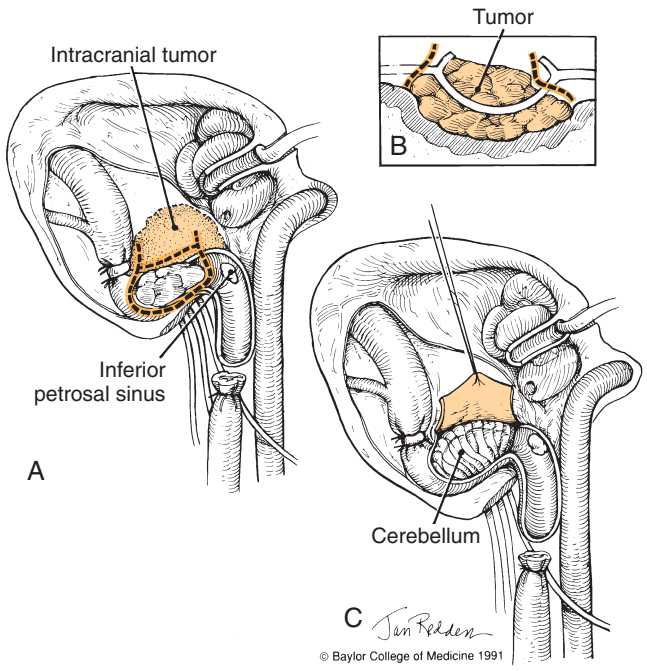

Figure 176-16. **A** and **B,** Intracranial paraganglioma extension into posterior fossa. **C,** Intracranial paraganglioma removed.

removed.[95,99] The jugular vein is ligated to prevent tumor and air embolism. Dissection begins by freeing the internal carotid artery and rotating the tumor posteriorly (see Fig. 176-15C). The lateral wall of the sigmoid sinus is removed along with intraluminal tumor (see Fig. 176-15D). The medial wall forms the barrier to the CSF. The inferior margin of the tumor is elevated, and the extracranial tumor is removed (see Fig. 176-15D). If the tumor extends intracranially, it is amputated sharply at this point. Profuse bleeding may occur from the entrances of the inferior petrosal sinus into the jugular bulb. Control is achieved by surgical packing.

After hemostasis is obtained, the posterior fossa dura is opened, and the intracranial portion of the tumor is excised (Fig. 176-16) at the same setting for intracranial tumors smaller than 2 cm. Larger tumors may be staged and removed at a later time.[100,101] Care should be taken to preserve the blood supply to the brainstem.

CLOSURE OF WOUND. The dura usually is left with a defect too large for primary closure. Fascia lata provides the best material for reconstruction, although lyophilized dura can be used to seal the defect. Abdominal fat is used to obliterate the dead space of the temporal bone, and the temporalis muscle is rotated inferiorly for reinforcement of the wound (Fig. 176-17). The skin is closed routinely, and a bulky pressure dressing is applied for a minimum of 5 days to prevent leakage of CSF.

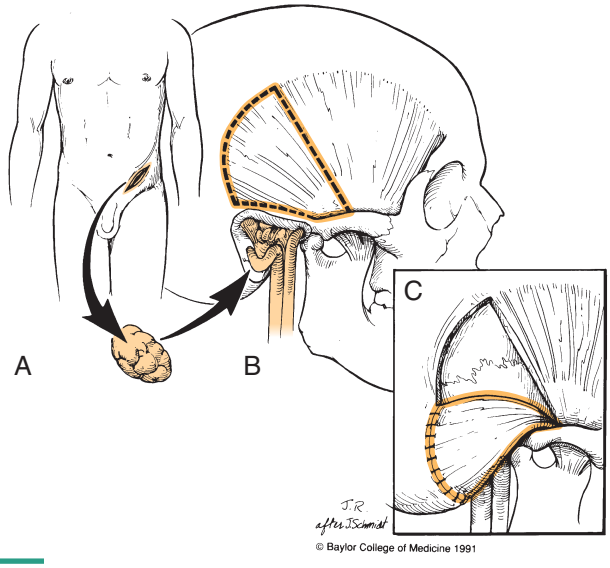

Figure 176-17. **A** to **C,** Obliteration of wound defect with abdominal fat and rotated temporalis muscle.

Type B Approach

The type B approach differs from the type A approach with respect to the facial nerve in that transposition of the nerve usually is not required. The steps up to transposition are identical to those for the type A approach. Reflection of the temporalis muscle still attached to the coronoid process and the zygoma allows the retractor to expose the superior infratemporal fossa (Fig. 176-18, A to C). Monitoring of facial nerve EMG activity during mandibular displacement helps prevent stretch injury. The limits of operative exposure in the type B approach are defined by the middle cranial fossa floor, mandibular condyle, and reflected temporalis muscle (see Fig. 176-18D).

Thinning bone under the MCF dura improves exposure. The middle meningeal artery and V_3 branch of the trigeminal nerve require bipolar cauterization and transection, respectively, thereby giving exposure to the superior 4 cm of the infratemporal fossa. The carotid artery may be uncovered from its vertical segment to its anterior limit at the foramen lacerum after separation from the soft tissues around the eustachian tube (Fig. 176-19A). The geniculate ganglion of the facial nerve and cochlea may be prone to injury if not properly recognized.

Petrous apex lesions, such as cholesteatoma or low-grade chondrosarcomas, may be removed at this point with careful anterolateral retraction of the internal carotid artery. The artery can be elevated from the foramen lacerum to the canalis caroticus to permit temporary transposition of the vessel (Fig. 176-20B). This maneuver may easily result in hemorrhage and should be performed with care. Extensive benign lesions involving the petrous apex and perilabyrinthine area may require a transotic approach combined with posterior facial nerve transposition, accomplished by cutting the greater superficial petrosal nerve and by liberating the facial nerve from the porus acusticus to the stylomastoid foramen (see Fig. 176-20).[102,103] In addition, the middle fossa

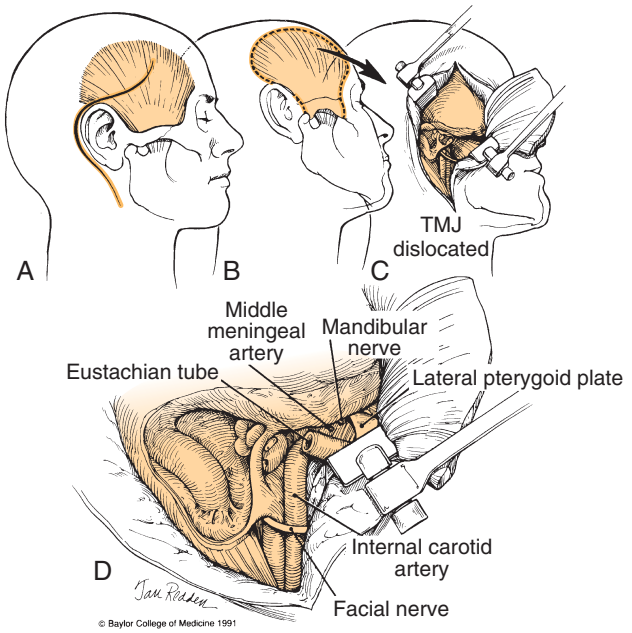

Figure 176-18. Fisch type B or C approach, incorporating the steps of the type A approach, as shown in Figures 176-9 through 176-12A. Note, however, that the intratemporal facial nerve is *not* skeletonized.) **A** to **C,** Dissection also includes transection of zygoma, elevation of the temporalis muscle and periosteum of skull base, and self-retaining retractor dislocation of the mandible inferiorly. **D,** Bone is removed to identify the middle meningeal artery and V_3 (transected here). TMJ, temporomandibular joint.

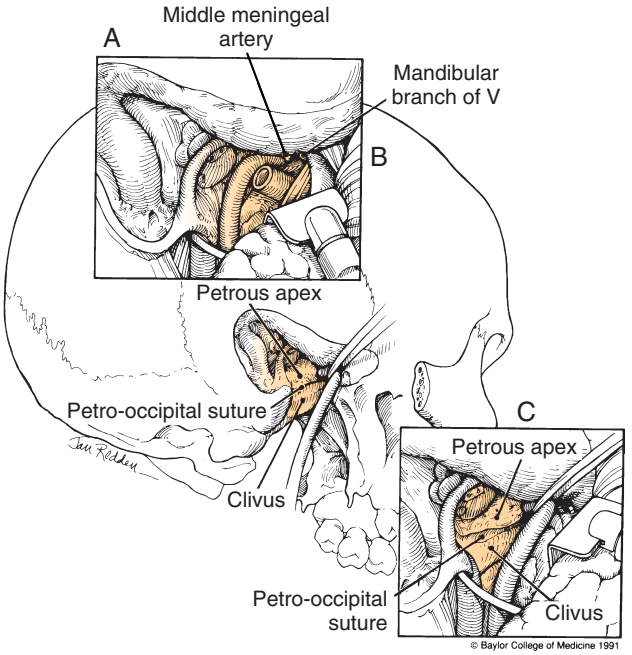

Figure 176-19. **A,** Removal of the eustachian tube permits access to the internal carotid artery up to the foramen lacerum. **B** and **C,** Elevation of the carotid artery permits additional access to the petrous apex and clivus.

may easily be accessed through a temporal craniotomy (see Chapter 174). Exposure of the clivus can be obtained by sharp incision of the fibrous attachments at the petro-occipital fissure. Tumors of the clivus, such as chordomas, up to the parasellar area may be removed through the type B approach (see Fig. 176-19C). Removal of the mandibular

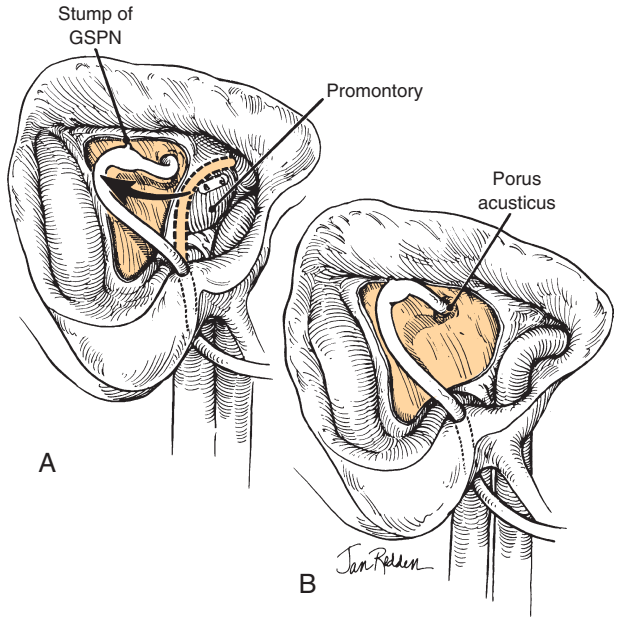

Figure 176-20. Transcochlear approach to the petrous apex. **A,** Posterior translocation of the facial nerve. GSPN, greater superficial petrosal nerve. **B,** Subtotal petrosectomy with removal of the otitic capsule.

condyle may give better exposure to the inferior clivus and upper cervical vertebrae. With inferior extension of the tumor, the facial nerve may be transposed as in a type A approach. Tumors located superior or medial to the horizontal portion of the internal carotid artery may require further mobilization of the cervical and vertical petrous carotid or the addition of a middle cranial fossa craniotomy. The superior and inferior petrosal sinuses may require removal in these extended dissections.

Type C Approach

The type C approach is an anterior extension of the type B approach. The type C infratemporal fossa approach permits posterolateral access to the rostral clivus, cavernous sinus, sphenoid sinus, peritubal space, pterygopalatine fossa, and nasopharynx and to the areas exposed by the type B approach. The type C infratemporal fossa approach, in essence, permits access anterior to the foramen lacerum up to the posterior aspect of the maxillary sinus and nasopharynx.

The base of the pterygoid process is removed to approach the sphenoid sinus and cavernous sinus (Fig. 176-21). Removal of the pterygoid base uncovers V_2 in the foramen rotundum and the inferior orbital fissure. Removal of bone from the pterygoid base permits better visualization of the sphenoid sinus; with the sinus exposed, the floor of the sella turcica can be visualized. The cavernous sinus is exposed by thinning the bone of the middle cranial fossa floor anterior to the V_2 stump. The middle cranial fossa dura may be retracted, giving an inferolateral view of the cavernous sinus.

To enter the lateral nasopharyngeal cavity, the lateral and medial pterygoid processes are removed, and the buccopharyngeal fascia and nasopharyngeal mucosa are incised. Separation of the pterygoid muscles from the mandible allows en bloc removal of the lateral nasopharyngeal wall, peritubal space, and superior infratemporal contents when needed for tumor extirpation (Fig. 176-22).

Tumors involving the pterygopalatine space require resection of the pterygoid process and a portion of the greater wing of the sphenoid with sacrifice of the maxillary branch of the trigeminal nerve. A portion of the posterior maxillary wall may be removed for further access.

Preauricular Infratemporal Approach

The preauricular approaches to the skull base described by various investigators, including Sen and Sekhar and colleagues,[90-92,104] can

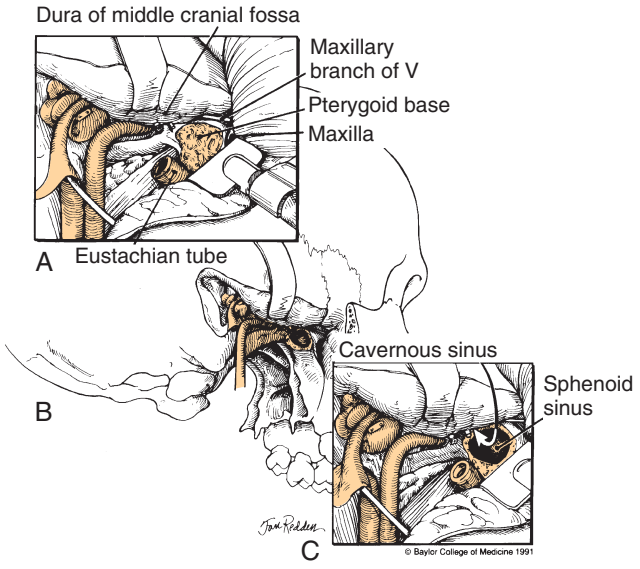

Figure 176-21. Fisch type C approach. **A,** Pterygoid base dissected with exposure of V_2. **B** and **C,** Sphenoid sinus entered.

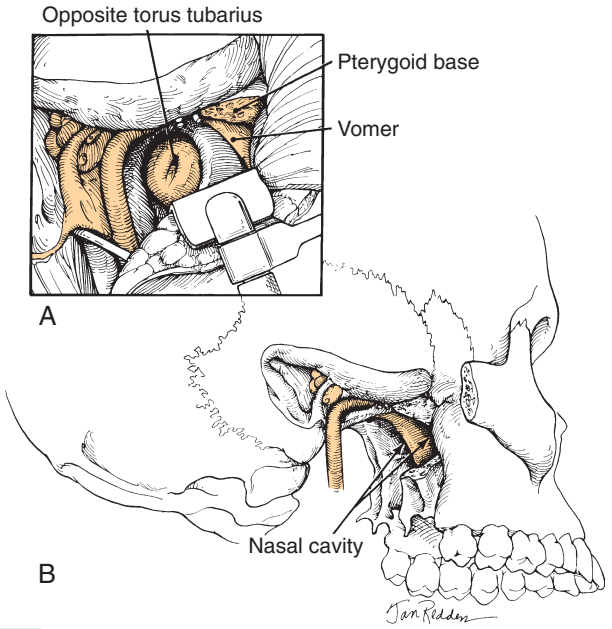

Figure 176-22. Fisch type C approach to nasopharyngeal exposure. **A** and **B,** Removal of pterygoid process and lateral wall of the nasopharynx exposing the opposite torus tubarius.

expose the upper cervical segment (without facial nerve transposition) and the intrapetrous segment of the internal carotid artery. These infratemporal dissections expose virtually the same areas as in the Fisch type B and type C approaches, albeit from a purely lateral vector of exposure. The preauricular approach permits access to the petrous apex, clivus, and superior infratemporal fossa and may be extended to include the nasopharynx, parasellar area, pterygopalatine fossa, and anterior infratemporal fossa. A frontotemporal craniotomy may be included for intracranial extension.[105] The petrous bone may be entered for access to the internal carotid artery, but the external auditory canal is not removed, and the tympanic cavity is not obliterated; therefore, the middle ear function is preserved, although the eustachian tube may be sacrificed, resulting in permanent serous otitis media. Although resecting the mandibular condyle in the preauricular approach facilitates the exposure of the internal carotid artery, such resection usually is not required in the postauricular approaches, because a posterior vector of orientation improves access.

The preauricular incision may be extended into the frontoparietal and upper cervical areas to expand exposure into the anterior infratemporal fossa (Fig. 176-23A). Identification and control of vascular structures in the neck are similar to those with the postauricular approaches. The superior cervical dissection is hindered by the facial nerve exiting the stylomastoid foramen to enter the parotid gland. Retraction of the mandible anteroinferiorly permits exposure of the upper cervical segment of the internal carotid artery (see Fig. 176-23B). Constant EMG monitoring during application of retractors greatly reduces the risk of facial nerve injury. Reflection of the temporalis muscles and zygoma as previously described for Fisch type B and type C approaches permits dissection of the anterior infratemporal fossa (see Fig. 176-23C).

The added time required for performance of a subtotal petrosectomy followed by obliteration is a disadvantage of the Fisch approach. Conductive hearing loss is inevitable, although transposition of the facial nerve, required in the type A approach, provides better access to the jugular fossa and the internal carotid artery at the skull base. The primary disadvantage of the preauricular approach is the inability to resect lesions extending into the temporal bone or posterior fossa.

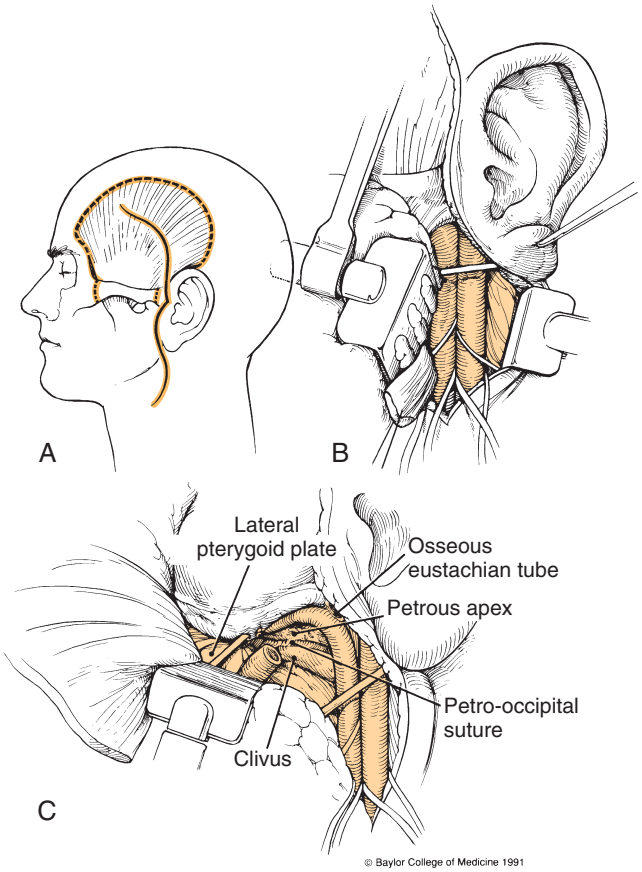

Figure 176-23. Preauricular lateral skull base approach. **A,** Incision for approach to infratemporal fossa. **B,** Exposure of major vessels to the skull base. **C,** Exposure of the infratemporal fossa.

Selected Problems

Rhabdomyosarcoma

A rhabdomyosarcoma is the most common childhood middle ear and mastoid malignancy. The recent spectacular improvement in 5-year

survival rates in patients with this disease has been achieved by several continued refinements of combined therapy: more accurate staging of parameningeal disease, adjustments of chemotherapeutic agents and dosage schedules, and advances in radiotherapy techniques.[95,106,107] Although total tumor removal is the surgical goal when possible, surgical debulking is an important concept in this disease. Gross total removal with preservation of the dura, otic capsule, and neurologic and vascular structures is performed, followed by postoperative chemotherapy and radiotherapy.

Carcinomas of the External Auditory Canal and Temporal Bone

Carcinomas and benign tumors of the external auditory canal and temporal bone are uncommon. Squamous cell carcinoma is by far the most common malignant tumor of the external auditory canal, followed by basal cell carcinoma and adenoid cystic carcinoma.[35,108-123] Carcinomas of the external auditory canal usually occur in persons 40 to 60 years of age, with some reports of carcinomas originating from cerumen glands somewhat earlier.

Pertinent Anatomy

The outer third of the cartilaginous portion of the external auditory canal contains all cerumen glands, which are modified sweat glands and sebaceous glands. The cartilage of the cartilaginous canal is J-shaped, being absent posteriorly. Anteriorly, the cartilage has small dehiscences known as the fissures of Santorini. The junction of the cartilaginous and osseous canal also permits radial spread.[124] The cartilaginous canal thus facilitates radial tumor extension. The osseous or medial two thirds of the external auditory canal for the most part is devoid of glandular tissue. The epithelium has no underlying subcuticular tissue and is closely adherent to the periosteum. The bone provides resistance to radial spread, so longitudinal spread toward the tympanic membrane is an early phenomenon. Radial spread through Huschke's foramen, a developmental defect in the tympanic ring, may permit anterior extension into the parotid. The tympanic membrane is thought to act as a barrier to longitudinal spread, although McCabe[125] has warned that microscopic extension around the annulus into the mesotympanum may occur even when the tympanic membrane is intact or grossly uninvolved. Entry of tumor into the middle ear space permits a myriad of paths of least resistance through air cell tracts and the eustachian tube.[126]

Symptoms and Signs

Carcinoma of the external auditory canal and temporal bone often will masquerade as chronic external otitis or chronic otitis. The frequency of these complaints in "routine" clinic patients has led to an average 6-month delay in diagnosis. Persistence of external otitis, despite adequate management by routine treatment measures, should increase suspicion for carcinoma and inflammatory processes as potential etiologic disorders, leading to biopsy. Persistent pain that is inordinately severe for the abnormality or a change in pain pattern with a chronically painful ear should precipitate further investigation. Some adenoid cystic carcinomas have been preceded by ear pain for several months before any abnormality is noted; therefore, serial examinations are important.

Squamous cell carcinoma may appear as a meaty or polypoid lesion in the external auditory canal. Adenoid cystic carcinoma usually is epithelium-covered and may appear as a small pimple, accompanied by complaints of significant pain. Basal cell carcinoma may exhibit serpiginous ulceration, with absence of the typically pearly edges because of characteristics of the thin, adherent canal epithelium. Hearing loss usually is conductive, from obstruction of the canal. Cochlear hearing loss and vertigo indicate labyrinthine involvement and an aggressive, advanced lesion. A parotid mass, cranial nerve paresis, and cervical lymphadenopathy also are late signs portending a grave prognosis. It is important to assess the nasopharynx to ascertain that a tumor does not originate from this area. Carcinomas of the external auditory canal should prompt close evaluation of the parotid gland, because the tumor may have originated from the parotid gland.

Figure 176-24. Squamous cell carcinoma of the right external acoustic canal in a 73-year-old woman: Axial view, computed tomography (CT) with bone algorithm. Only a focused bone algorithm CT scan would reveal the subtle bone erosion *(arrows)* associated with this carcinoma.

Staging

Planning management depends critically on preoperative evaluation. Thin-slice temporal bone CT, with soft tissue and bone protocols with intravenous contrast, will delineate the medial extent of disease and provide evidence of osseous erosion and some soft tissue detail[127] (Fig. 176-24). With extensive lesions or CT evidence of osseous erosions or soft tissue extension, MRI with gadolinium enhancement of the temporal bone, parotid gland, and upper neck will provide further soft tissue detail around the canal and intracranial involvement. Four-vessel carotid angiography and functional CBF assessment may be useful if extensive resections are indicated. An appropriate workup for metastatic disease also should be performed.

A system for staging carcinoma of the external auditory canal has been described by investigators from the University of Pittsburgh. Arriaga and Janecka[124] proposed a primary tumor–regional nodes–metastasis (TNM) staging system based on clinical examination, preoperative imaging studies, and intraoperative findings (Box 176-2). Of note, imaging may understage soft tissue extension seen intraoperatively. Other investigators have supported the clinical usefulness of this staging system.[128,129]

Management

In treating these carcinomas, the clinician should heed the admonition of Jesse and colleagues[130]: "One factor becomes painfully obvious, that the first treatment is the only one that has a chance of curing the patient, while subsequent treatment is simply palliative." For this reason, initial treatment by whatever modality chosen should be radical enough to eliminate the cancer. Consensus regarding management of carcinomas of the external auditory canal and temporal bone is not easily found in the literature, mainly because of the rarity of these lesions. Most series have one or two cases per year, extending over 2 decades or longer. Some of the larger series represent evolution of management philosophy, making critical analysis difficult. Authors often lump together all malignancies of the external auditory canal, regardless of histology, involvement of the middle ear, or other signs of advanced disease.

En bloc surgical resection of external auditory canal malignancies is considered by almost all investigators to be the primary therapy, with an adjunctive role for radiotherapy. Most recurrences are local. Positive

Box 176-2

University of Pittsburgh Tumor–Lymph Node–Metastasis Staging System Proposed for Neoplasms of the External Auditory Canal

T Status

- T_1 Tumor limited to the external auditory canal without bony erosion or evidence of soft tissue extension
- T_2 Tumor with limited external auditory canal bony erosion (not full-thickness) or radiographic finding consistent with limited (less than 0.5 cm) soft tissue involvement
- T_3 Tumor eroding the osseous external auditory canal (full-thickness) with limited (less than 0.5 cm) soft tissue involvement, or tumor involving middle ear or mastoid, or patients presenting with facial paralysis
- T_4 Tumor eroding the cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or with extensive (greater than 0.5 cm) soft tissue involvement

N Status

Involvement of lymph nodes is a poor prognostic finding and automatically places the patient in an advanced stage (i.e., stage III [T_1, N_1] or stage IV [T_2, T_3, and T_4, N_1] disease).

M Status

Distant metastasis indicates a poor prognosis and immediately places the patient in the stage IV category.

margins, despite postoperative radiotherapy, have an almost uniform fatal result.[131] Advanced lesions involving the middle ear and medial structures can be handled with combined therapy or palliatively, depending on clinical factors.

An algorithm for the management of high-grade carcinomas of the external auditory canal and temporal bone is presented in Figure 176-25.

"Local" resections in rare circumstances may be appropriate but in general are to be condemned. T_1 tumors localized to the cartilaginous canal can be appropriately managed with sleeve resection of the external auditory canal with frozen section sampling of medial margins. Such cases are rare. Lateral temporal bone resection (or en bloc removal of the canal and tympanic membrane) is the minimum operation for patients with carcinoma of the osseous portion of the canal (T_1 and T_2 tumors) and with carcinomas abutting the chondro-osseous junction. Moore and coworkers[132] argue that "canal wall down" mastoidectomy technique with anterior canal drillout (i.e., not en bloc) is equal in efficacy to an en bloc lateral temporal bone resection. Spector[133] suggests that all patients should receive postoperative radiotherapy after en bloc resections. Other workers believe that postoperative radiotherapy should not be used unless aggressive clinical or pathologic features are noted, such as soft tissue extension, metastatic lymphadenopathy, or any osseous or cartilaginous invasion on pathologic examination. If postoperative radiotherapy is likely, the mastoid cavity should be obliterated at the time of the operation to prevent osteoradionecrosis.[73]

These operations yield complex surgical specimens, and it is incumbent on the surgeon to orient the pathologist and request information regarding osseous or soft tissue invasion to gain maximum benefit for the patient. Temporal bone laboratory techniques have been advocated.[134] However, temporal bone laboratory techniques may not provide clinically pertinent information in a timely manner.

Extension into the mesotympanum, stage T_3 disease, gives rise to several other therapeutic options. The least aggressive option includes a lateral temporal bone resection plus subtotal petrosectomy followed by postoperative radiotherapy (for a 28.6% 5-year survival rate),

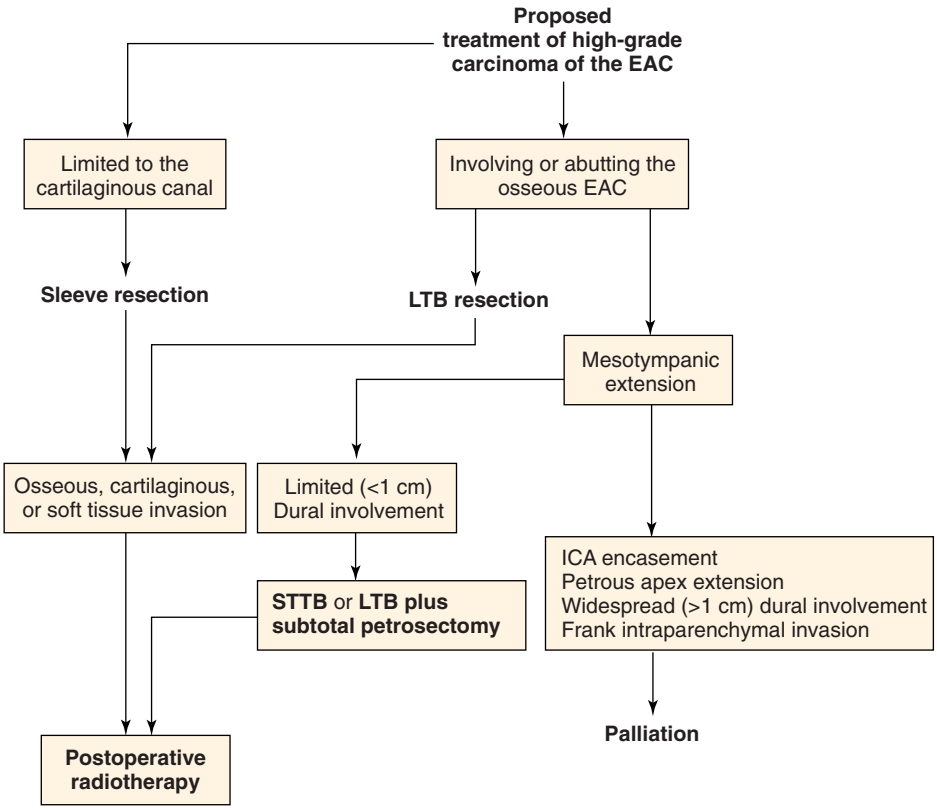

Figure 176-25. Algorithm for management of high-grade malignancies of the external auditory canal (EAC) and temporal bone. ICA, internal auditory canal; LTB, lateral temporal bone; STTB, subtotal temporal bone.

although this modality has been shown on literature analysis to be inferior to subtotal temporal bone resection (associated with a 41.7% 5-year survival rate).[84,85] Although it is uncertain whether postoperative radiotherapy provides added benefit after subtotal temporal bone resection,[84,85] we recommend subtotal temporal bone resection followed by postoperative radiotherapy. T_4 lesions with transdural extension generally have been thought to be inoperable. However, Moffat and associates[135] have successfully treated well to moderately differentiated T_4 tumors with limited temporal lobe involvement. A study by Ducic and colleagues,[136] supported by the International Study of Cranial Facial Surgery,[137] involving high-grade carcinomas of the anterior cranial fossa addressed issues of dural and intraparenchymal involvement. If dural involvement is limited (less than or equal to 1 cm) and frank intraparenchymal involvement is not apparent intraoperatively, the disease-free survivial or locoregional control shows no statistical difference with respect to dural involvement, but a dramatic decline in survival is associated with parenchymal invasion. Preoperative MRI may show dural or parenchymal involvement when none is found at surgery, possibly due to edema or inflammation. However, if overt intraparenchymal involvement is noted on frozen section, the procedure is abandoned, because as noted by Ganly and coworkers, "resection margin can still be achieved when either bone or dura is involved, but less likely when brain parechyma is involved."[137] The morbidity associated with subtotal temporal bone resection includes stroke, meningitis, and that due to sacrifice of the audiovestibular nerve and facial nerve, with a 5% perioperative mortality rate.

Total temporal bone resection also results in further morbidity from additional sacrifice of cranial nerves IX, X, and XI. Total temporal bone resection extends a subtotal resection by including the petrous apex and the entire mastoid air cell system. High-grade malignancies of the temporal bone with extension outside the petrous bone or to the petrous apex, extensive dural involvement, frank parenchymal involvement, gasserian ganglion involvement, or invasion along the skull base portend a poor outcome in nearly all cases. Palliation should be carefully and strongly considered. Patients with low- to medium-grade malignancies or extensive benign tumors, T_3 or T_4, may benefit from total temporal bone resection.[138]

Aneurysms of the Upper Cervical and Petrous Internal Carotid Artery

Primary lesions of the upper cervical and petrous segments of the internal carotid artery are decidedly rare. They include those lesions with a congenital aberrant course,[139,140] aneurysms, spontaneous and traumatic dissections, and lacerations. Aneurysm types include congenital, infectious (mycotic), pseudoaneurysms (traumatic), atherosclerotic, luetic, and fibromuscular dysplasia. Although upper cervical carotid aneurysms are associated with a high incidence of ischemic attacks and strokes, reports of rupture are unusual.[141-146] Petrous internal carotid artery aneurysms are associated with a high risk for cranial nerve dysfunction and aural hemorrhage.[147] In light of the natural history, observation is undesirable in most patients with internal carotid artery aneurysms unless other medical exigencies take precedence. Cervical carotid occlusion carries a high risk of cerebrovascular complications.

BTO aids in management decision-making (see Fig. 176-1).[148] CBF greater than 30 mL/100 g per minute carries a low risk for postocclusion infarction, thereby permitting surgical or endovascular trapping or occlusion. Surgical or permanent balloon trapping or occlusion, consisting of proximal cervical ligation or occlusion and supraclinoid internal carotid artery clipping or occlusion proximal to the ophthalmic artery, avoids late thromboembolic phenomena. Neurologic change observed on BTO or CBF less than 30 mL/100 g per minute necessitates some form of revascularization if the internal carotid artery is to be trapped or occluded. Transarterial detachable balloon trapping and cervical internal carotid artery occlusion preceded by extracranial-intracranial arterial bypass have been used.[29,149]

Preservation of internal carotid artery patency is desirable. Endovascular stenting has been performed for a petrous carotid pseudoaneurysm, preserving patency of the vessel and occluding the pseudoaneurysm with detachable coils,[150] as well as for extracranial aneurysms and dissections of the artery.[151,152] When surgical intervention is feasible or necessary, internal carotid artery reconstitution with direct reanastomosis or saphenous vein interposition grafting is preferable. A preauricular approach as described by several investigators[89,142,143,145,153] may be used to expose upper cervical carotid aneurysms, although these approaches are hindered by the facial nerve, mandible, styloid process, and tympanic bone. Lateral mandibulotomy may give access to upper cervical lesions.[154] For extension of the aneurysm to the skull base or vertical petrous internal carotid artery, the postauricular (Fisch type A or B) approach gives maximal vascular control with good distal exposure of the vessel[100,155] (Figs. 176-26 and 176-27) or routing a saphenous graft from the external carotid artery to the horizontal petrous internal carotid through a retroauricular groove.[153] Aneurysms involving the horizontal petrous segment may be approached through a Fisch type B or preauricular approach as described by Sekhar and coworkers.[91] Inadequate exposure and distal control of the horizontal petrous segment may lead to uncontrolled entry into these aneurysms. Some form of trapping with or without extracranial-intracranial bypass should be considered in patients with poorly accessible lesions.

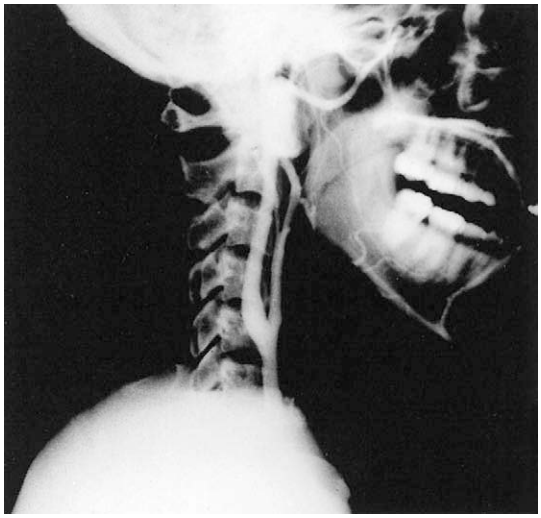

Figure 176-26. Preoperative angiogram of an upper cervical internal carotid aneurysm at the skull base.

Jugular Foramen Tumors

Tumors of the jugular foramen primarily include glomus jugulare (paraganglioma) and schwannomas of cranial nerves IX, X, and XI. The Fisch type A approach with transposition of the facial nerve and the Farrior approach[156] with limited mobilization of the vertical segment of the facial nerve both allow adequate exposure of the jugular bulb area. Donald and Chole[76] advocate a transcervical-transmastoid technique to gain access to the jugular fossa without transposing the facial nerve. This procedure, although technically feasible, provides less exposure and more limited vascular control but has the advantage of absence of facial nerve morbidity. Use of this technique is more desirable in cases in which extensive retrofacial air cells are present.

Schwannomas of the Jugular Foramen

Schwannomas originating from cranial nerves IX, X, and XI at the jugular foramen are decidedly uncommon, with only slightly more than 100 cases reported in the world's literature.[157] These tumors may be intracranial, intraforaminal, or cervical, or a combination thereof.[158] For removal of intracranial tumors, the suboccipital approach clearly is the most direct and effective route. Intraforaminal and combination tumors are removed in the safest manner through the infratemporal fossa approaches described by Fisch. These tumors originate anatomically from the pars nervosa of the jugular foramen and are situated anteromedial to the jugular bulb and internal jugular vein and posterior to the upper cervical and petrous internal carotid artery. Transposition of the facial nerve, as in the Fisch type A approach,[159] is helpful for

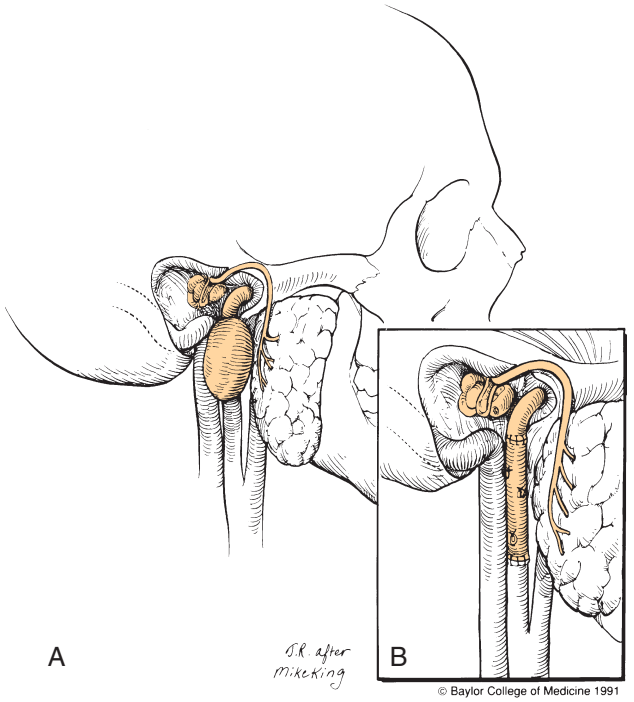

Figure 176-27. **A** and **B,** Saphenous vein repair of the aneurysm shown in Figure 176-26 with a Fisch type A infratemporal fossa approach.

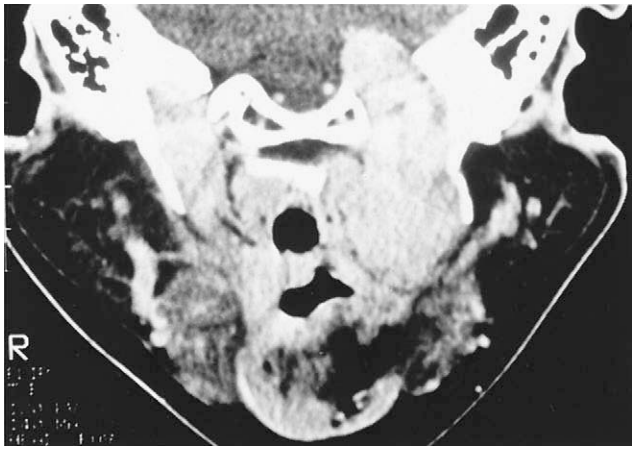

Figure 176-28. Coronal computed tomography scan revealing a jugular foramen schwannoma with a small intracranial extension removed by way of a Fisch type A infratemporal fossa approach.

control of these vascular structures and tumor exposure (Fig. 176-28). Farrior's limited approach also may have a role in small tumors.[160] Pellet[161] gave consideration to the use of an extended transcochlear route, in which a Fisch type A dissection is performed followed by sacrifice of the labyrinth to gain access to large tumors extending into the cerebellopontine angle. Oghalai and colleagues[162] describe a "transjugular craniotomy" whereby the facial nerve is not mobilized but left in a bridge of bone between an extended facial recess approach and a presigmoid craniotomy. These workers have used this technique for removal of intracranial glomus jugulare tumors.

Paragangliomas of the Temporal Bone

The glomus tumor of the temporal bone is the most frequently encountered neoplasm after the acoustic neuroma. Glomus tumors are divided into two broad categories on the basis of their site of origin: glomus tympanicum and glomus jugulare. Several classification systems have described paragangliomas of the temporal bone.[61,97,163,164] The classifications are similar and allow clinicians to communicate and compare findings and results.

Symptoms

Alford and Guilford[163] thoroughly described the signs, symptoms, and classification of glomus tumors of the temporal bone. The glomus tympanicum most frequently manifests with pulsatile tinnitus of insidious onset and a conductive hearing loss, although it also may be an incidental finding on routine physical examination.[165,166] The glomus jugulare tumor originates within the dome of the jugulare bulb and commonly appears late, after considerable growth and bony destruction. It may cause dysfunction of cranial nerves passing through the jugular bulb (cranial nerves IX to XII), facial nerve paresis caused by tumor extension into the mastoid, or sensorineural hearing loss caused by bony erosion of the labyrinth. Occasionally, either a glomus tympanicum or a glomus jugulare tumor may erode the tympanic membrane and appear as a bleeding mass in the external auditory canal.

Diagnostic Evaluation

Accurate diagnosis and evaluation of the extent of a glomus tumor of the temporal bone require appropriate physical examination and radiologic assessment.[167] The physical examination infrequently differentiates between the two kinds of glomus tumors. Only if all borders of the tumor are visible through the tympanic membrane can it be assumed that it is a glomus tympanicum tumor. If all of the borders are not visible behind the tympanic membrane, the tumor may be either a large glomus tympanicum tumor or a much larger glomus jugulare tumor that extends from the jugular bulb into the hypotympanum. If cranial nerve abnormalities are associated with a lesion, it is more likely to be a glomus jugulare tumor.

Although physical examination helps deduce the extent of a paraganglioma, radiologic evaluation is required to precisely define the lesion. CT and MRI usually are used for this evaluation (Fig. 176-29; see also Fig. 176-2). Glomus jugulare tumors require four-vessel angiography, for reasons previously discussed. Paragangliomas are vascular neoplasms. Arteriography is required if preoperative embolization of the lesions is desired. Such embolization takes place through specialized intra-arterial catheters and can lead to a marked reduction in vascularity of these masses, which reduces intraoperative blood loss and hemorrhage-related complications. The glomus jugulare paraganglioma, the most common of these tumors, causes somewhat selective erosion of the pars vasculosa portion of the jugular foramen. It also frequently destroys the bony septum between the internal carotid artery and the internal jugular vein. This bony septum is a distinctive structure whose absence is easily seen. Confounding lesions include schwannomas of cranial nerve IX, X, or XI, because these lesions also destroy the jugular foramen (Fig. 176-30). These lesions, however, usually destroy the more medial portion of the pars vasculosa or, if originating from cranial nerve IX, the pars nervosa.

At times, the paraganglioma manifest only after becoming large and eroding nearly all of the jugular foramen. Simple differentiation by the localization of bone erosion is not possible in such cases. MRI is helpful in defining these lesions, but results should be interpreted carefully. The complex flow characteristics of venous blood result in the presence of many signal artifacts in and about the jugular vein. Although experienced practitioners have become used to these artifacts, errors can still be made, and careful attention to the precontrast and postcontrast-enhanced MRI or fMRI is necessary so that the flow-related signal artifacts are not interpreted as a vascular lesion. Vasoactive peptides are produced by 1% to 3% of these tumors; therefore, patients should be screened with quantitative urine vanillylmandelic acid and hydroxyindoleacetic acid assays.

Surgical Approach

Only small glomus tympanicum tumors whose borders are clearly visible through the tympanic membrane can be removed through the external auditory canal. In radiologically proven glomus tympanicum tumors whose borders are not entirely visible through the tympanic

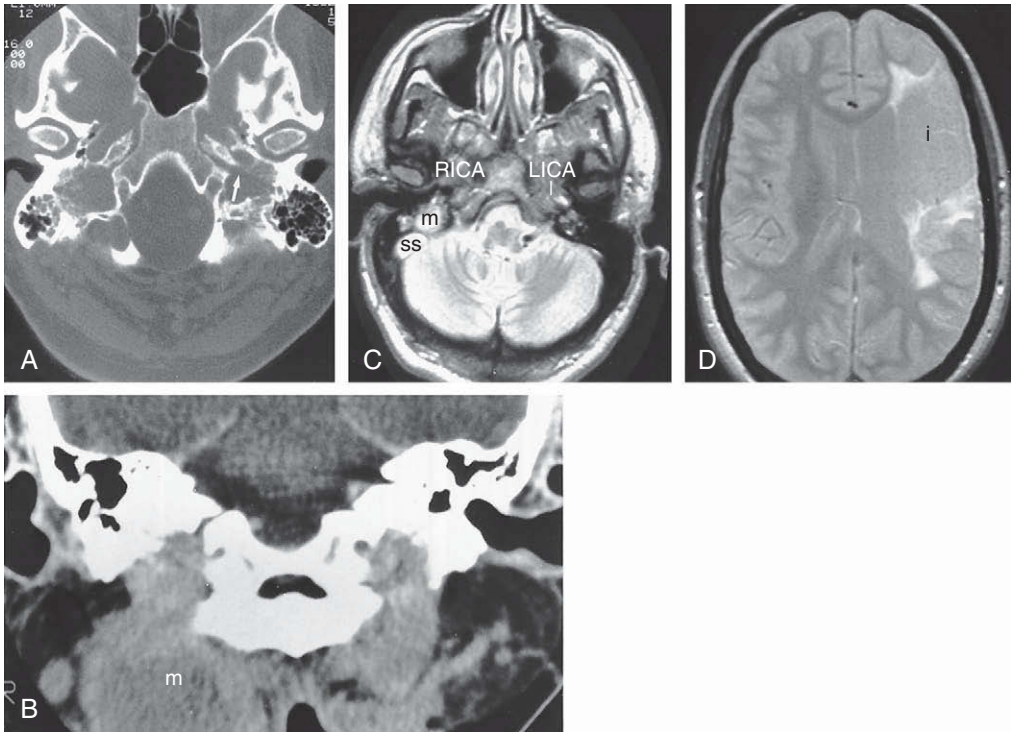

Figure 176-29. Familial paragangliomas in a 53-year-old woman.The tumors included bilateral glomus jugulare paragangliomas, a right-sided glomus vagale paraganglioma, and bilateral carotid body paragangliomas. **A,** Axial view, computed tomography (CT), bone algorithm. This CT study is performed with a small field of view and a bone algorithm to increase the resolution of bone edges. The bilateral glomus jugulare paragangliomas are destroying bone from the pars vasculosa laterally. On the left side, the lesion is destroying the septum between the internal carotid artery and the internal jugular vein. These are common findings in a glomus jugulare paraganglioma *(arrow)*. **B,** Coronal view, CT with intravenous contrast. Both glomus jugulare paragangliomas extend into the neck. However, another large mass can be seen on the right, a glomus vagale paraganglioma (m). **C,** Axial view, T2-weighted magnetic resonance imaging (MRI). The high-signal-intensity lesion, a glomus jugulare paraganglioma (m), has occluded the sigmoid sinus, which shows high-intensity signal (ss). The left internal carotid artery (LICA) shows signal of pathologic high intensity. This vessel has been occluded by a large paraganglioma in the neck *(not shown)*. Compare the signal intensity of this vessel with the normal dark black appearance of internal carotid artery flow on the right (RICA). Although MRI cannot provide the fine bony resolution of CT (see **B**), it gives more information about vascular patency. **D,** The LICA occlusion has resulted in a middle cerebral arterial distribution infarct (i).

membrane, the extended facial recess approach is recommended.[166] Occasionally, the facial recess is narrow, requiring removal of all or part of the bony posterior external auditory canal.

Glomus jugulare tumors are best approached by the Fisch type A route. Alternatively, Oghalai and colleagues[162] advocate a "transjugular craniotomy," which does not involve facial nerve transposition and its attendant morbidity. Staging may be necessary with those large tumors with extensive intracranial extension (Fig. 176-31). Bleeding intraoperatively remains a major problem in removal of glomus tumors. The efficacy of preoperative embolization of glomus tumors in reducing intraoperative blood loss is debated.[97] Some studies suggest major reduction in intraoperative blood loss and operative time after embolization.[50,67,168,169] Intraoperative ligation of the feeding vessels, such as the ascending pharyngeal, stylomastoid, caroticotympanic, internal maxillary, and superior tympanic arteries, before extirpation may lessen bleeding, although ancillary blood supply from various other sources may mitigate this result.[50] Piecemeal tumor removal, as in acoustic neuroma surgery, is impractical for management of these vascular tumors and often will result in hemorrhage, obscuring anatomic landmarks.

Lack of cranial nerve dysfunction is not a reliable indicator of intraoperative nerve integrity in patients with these tumors.[170] Cranial nerves VII and IX to XII may be involved at the skull base. In superficial involvement, segmental removal of involved epineurium may clear the tumor. Neural invasion requires segmental neurectomy. Paragangliomas often invade the periosteum of the carotid canal but rarely involve the adventitia itself.[60] Good preoperative angiographic assessment is of absolute necessity. A subperiosteal plane of dissection is developed intraoperatively. If the adventitia is involved, surgical manipulation may result in a large laceration of the carotid artery. Preoperative transarterial permanent balloon occlusion of the internal carotid artery should be considered in those tumors with infiltration of the wall of the horizontal petrous segment of the artery or with intracranial extension receiving significant blood supply from the artery and for reasons identified in Figure 176-1. If the status of the internal carotid artery is not appreciated preoperatively, several options are possible. Lacerations may be sutured directly. Saphenous vein interposition grafting may be performed with or without shunt placement.[48] The internal carotid artery may be transarterially balloon-occluded intraoperatively with or without angiographic confirmation, depending on the urgency of the situation.[60,61,169]

Radiotherapy

Although radiotherapy is not the modality of choice for treatment of surgically resectable glomus tumors of the temporal bone, tumor reductions after radiotherapy have been recorded.[171-173] Glomus tumors have been shown to have nonuniform responses, and tumor sterilization by radiotherapy is infrequent. Radiotherapy is useful for management of recurrences and unresectable lesions.

Facial Nerve Schwannomas

Schwannomas may involve the facial nerve along its intracranial, intratemporal, or extratemporal course. Altmann[174] presented the first comprehensive description of a facial nerve schwannoma and believed that its symptoms were sufficiently pathognomonic for the facial nerve schwannoma to be diagnosed clinically. These reported cases generally

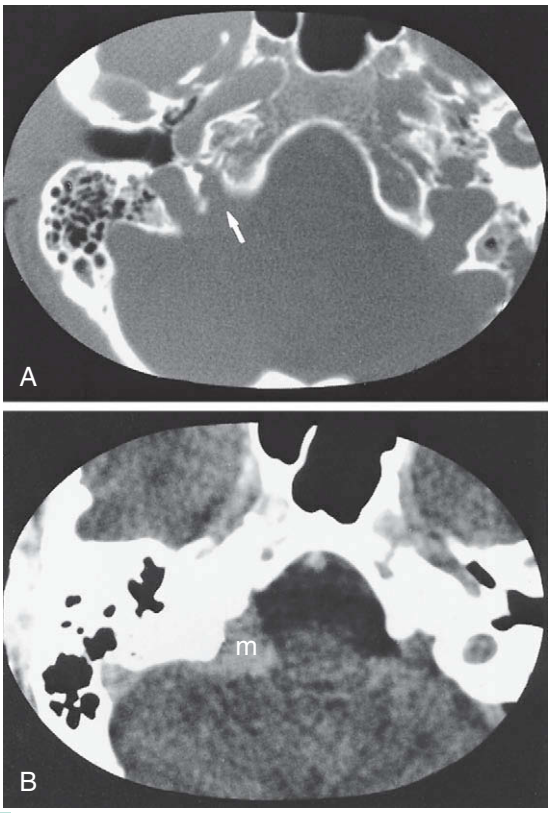

Figure 176-30. Right glossopharyngeal schwannoma in a 50-year-old woman **A,** Axial view, computed tomography bone algorithm. The neoplasm has focally expanded and destroyed the pars nervosa portion of the jugular foramen *(arrow)*. This is a helpful finding in this type of schwannoma. **B,** Axial view, computed tomography brain algorithm. This patient's neoplasm is large. It has ascended past the cochlear aqueduct toward the internal acoustic canal. If only this level were viewed, the mass (m) could simulate a vestibular schwannoma.

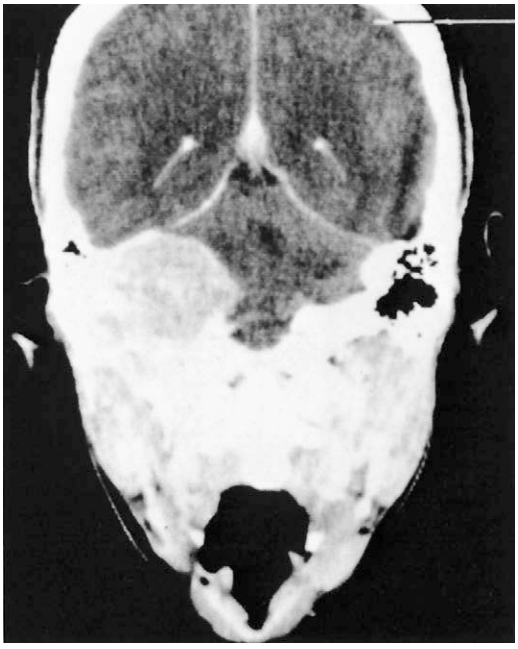

Figure 176-31. Paraganglioma of the jugular bulb with intracranial extension. The tumor was removed in one stage using a Fisch type A infratemporal fossa approach.

were diagnosed late; the patients presented with long-standing facial nerve paralysis and obstruction of the external auditory canal with tumor. More recently, with the increased awareness of this clinical entity and improved neurotologic diagnostic methods, earlier diagnosis is possible.

Diagnostic Evaluation

Facial weakness has been the most common presenting symptom in a number of series.[175,176] The classic history is one of slowly progressive facial paralysis over months to years, not days to weeks, although sudden onset of paralysis, fluctuating paresis, and facial tic may occur.[177] Hearing loss is the second most common presenting manifestation.[178] Conductive hearing loss may occur with middle ear involvement caused by tumor expansion and pressure on or disruption of the ossicular chain. In such cases, a gray-white polypoid mass frequently can be seen behind the posterosuperior tympanic membrane. Sensorineural hearing loss may result from erosion into the labyrinth or tumor compression on the cochlear nerve.

An intratemporal facial nerve schwannoma generally extends along the course of the facial nerve for a greater distance than that anticipated from the clinical or radiologic findings. The schwannoma visualized in the middle ear may extend intracranially into the internal auditory canal and cerebellopontine angle or extratemporally into the parotid gland. Preoperative radiologic assessment addresses this potential spread, but the surgeon should be prepared for more extensive nerve involvement than that suggested by clinical or radiologic testing. Topographic testing of facial nerve function, including tearing, stapedius reflex, taste, and salivation, may be helpful, but it is not definitive in the evaluation of the extent of facial nerve neuroma. Definitive assessment of facial canal alterations is made with axial and coronal temporal bone CT. The entire bony path of the facial nerve can be traced with certainty. In the normal structure, seldom is much variation observed in this path from side to side. Hence, it is simple to compare right and left to determine abnormality. The most common abnormality seen in patients with facial schwannomas is simple enlargement of the fallopian canal by a soft tissue mass. These lesions usually follow the exact path of the facial nerve. One great mimic of facial schwannomas is the facial nerve hemangioma. This uncommon lesion probably originates from arteriovenous plexus around the geniculate ganglion, internal auditory canal, or vertical segment of the facial nerve near the chorda tympani takeoff.[179] Differential diagnostic imaging characteristics include calcification-based higher CT attenuation in a hemangioma compared with a schwannoma. MRI is superior to CT in delineating a soft tissue mass along the facial nerve, especially when MRI contrast material is used. This material provides such sensitivity that the arteriovenous plexus along the fallopian portion of the facial nerve is visualized. This plexus normally can enhance in a spotty fashion, making it possible for inexperienced practitioners to identify this abnormality. In addition, inflammatory lesions of the facial nerve also will result in contrast enhancement. Accordingly, facial nerve enhancement on MRI should not be considered to be indicative of neoplasm unless a soft tissue mass is present. The clinical, CT, or MRI findings should be correlated before diagnosis of a facial nerve neoplasm. If this correlation is not definite, later follow-up imaging evaluation after a clinically appropriate amount of time has passed should resolve the issue.

In some patients with facial paralysis, radiologic evidence for tumor is lacking. Surgical exploration of all progressive facial palsies that occur over an extended period of time or facial palsies that show no return of tone or function after 6 to 12 months has been recommended, and facial schwannomas occasionally are discovered.

Management and Surgical Approach

Timing of intervention requires extensive discussion with the patient, especially if facial function is intact. McMonagle and coworkers advocate observation with serial scans until facial function deteriorates to House-Brackmann grade IV.[180] The management goals of facial nerve neuroma surgery are complete removal of the tumor with preservation of hearing and restoration of facial nerve function.[181,182] Most commonly, the transmastoid and middle cranial fossa approaches are

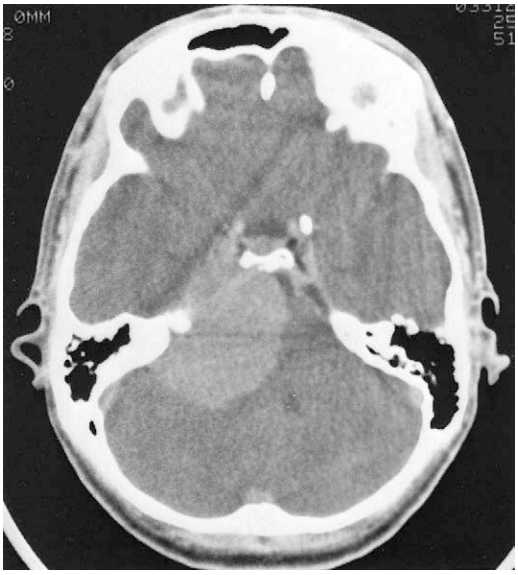

Figure 176-32. Computed tomography scan of a large posterior fossa meningioma with petrous apex involvement. The tumor was removed through a retrosigmoid craniotomy with petrosectomy, with posterior facial nerve transposition.

adequate for exposure of neuromas of the intralabyrinthine facial nerve segments. In patients with no serviceable hearing, a translabyrinthine exposure of the facial nerve may be indicated. Surgical removal and cable grafting of the facial nerve with frozen section histologic control is indicated in most patients. The nerve graft usually is placed in the fallopian canal, and its ends are approximated and stabilized with packing. Approximation of the cable graft to the facial nerve stump in the internal auditory canal is difficult. When the involved segment of nerve is limited to less than 1 cm, a facial nerve transposition and primary anastomosis sometimes can be performed. If primary anastomosis or cable grafting fail, hypoglossofacial anastomosis may be necessary (see Chapters 171 and 172).

Petrous Apex Lesions

Primary tumors of the petrous apex, either benign or low-grade neoplasms, such as cholesteatoma, schwannoma, chondroma, meningioma, chordoma, and low-grade sarcomas, are best removed totally to prevent recurrence.[183-185] The infratemporal fossa approaches to the petrous apex (i.e., Fisch type B or perhaps type A approach) give better exposure and control of the internal carotid artery and may be combined with the middle cranial fossa, retrosigmoid, transcochlear, or translabyrinthine routes as needed (Fig. 176-32). In patients with serviceable hearing, the petrous internal carotid artery may be temporarily transposed to gain access to the petrous apex with major risk of hemorrhage. The combination of the transcochlear or translabyrinthine route with posterior translocation of the facial nerve offers the best access to the petrous apex (see Figs. 176-20 and 176-32). Total temporal bone resection also is an option for low grade maligancies.

Benign cystic lesions such as cholesterol granulomas or cephaloceles are generally not extirpated. Drainage of cholesterol granulomas can be performed through the perilabyrinthine pathways[186] (see also Chapters 139 and 140) or transsphenoidally using endoscopic imaging guidance.[187-189] Symptomatic petrous apex cephaloceles can be either marsupialized intracranially using a posterior fossa approach or obliterated through a middle cranial foassa approach.[190]

Congenital Cholesteatoma

Congenital cholesteatomas of the temporal bone may be divided into four anatomic groups: middle ear, perigeniculate area, petrous apex, and cerebellopontine angle. These cholesteatomas originate from epithelial rests and should be distinguished from acquired cholesteatomas and from congenital auditory canal cholesteatomas associated with congenital atresia of the external auditory canal.

Diagnostic Evaluation

The clinical presentation of a congenital cholesteatoma varies, depending on its location. Middle ear cholesteatomas originally were described by House,[191] and clinical series have been reviewed by House and Sheehy[59] and Curtis.[192] Conductive hearing loss and a bulging whitish mass behind an intact tympanic membrane are common findings in patients with middle ear congenital cholesteatomas.[193] One half of all patients present with recurrent otitis media, and the lesions may fistulize through the tympanic membrane. The lesions also may be discovered incidentally at the time of a myringotomy or routine physical examination in children. Perigeniculate and petrous apex cholesteatomas usually present with insidious or rapidly progressive facial nerve paralysis.[194,195] Sensorineural hearing loss from labyrinthine or internal auditory canal erosion is common, but a conductive hearing loss also may result from cholesteatoma extension into the middle ear or blockage of the eustachian tube. Facial twitching may occur in the presence of congenital cholesteatomas and with facial nerve neuromas. Vestibular dysfunction may complete the symptom complex. On occasion, the cholesteatoma may erode into the middle or posterior fossa and expand markedly before producing symptoms. Preservation of hearing despite extensive destruction of the labyrinth has been reported.[45,74]

Radiologic evaluation of the temporal bone is essential in the evaluation of a congenital cholesteatoma (Fig. 176-33). Only the largest lesions will show on plain radiographs. High-resolution, focused CT of the temporal bone is ideal in this evaluation, because any alteration in normal bony structure can be seen. At times, the normal asymmetry in aeration, inflammatory, or passive effusion and bone marrow deposition in the petrous apices can cause diagnostic difficulties. These difficulties usually are resolved by clinical correlation; if the findings are problematic, MRI will provide further definition, because congenital cholesteatomas almost always will have a slightly higher signal intensity than that of spinal fluid on T1-weighted images, with moderately high signal intensity on T2-weighted images. By contrast, bone marrow fat will have a high signal intensity on T1-weighted images and then go on to fade dramatically on T2-weighted images. Typical effusions will have a low signal intensity on T1-weighted sequences, with high signal intensity on T2-weighted sequences. Giant cholesterol granulomas can be difficult to separate from congenital cholesteatomas of the petrous apex (Fig. 176-34), although giant cholesterol granulomas, but not congenital cholesteatomas, tend to show capsular enhancement.

Surgical Approach

Surgical management of a congenital cholesteatoma requires either complete removal of the cholesteatoma matrix or permanent exteriorization. The isolated middle ear cholesteatoma may be removed transtympanically. At surgery, it is essential to visualize clearly the complete extent of the cholesteatoma in the middle ear, particularly on the medial aspect of the tympanic membrane. Routine middle ear reconstructive techniques may be used if ossicles are eroded or removed or if the tympanic membrane is sacrificed. Removal of congenital cholesteatomas of the perigeniculate area or petrous apex may be accomplished by the transmastoid, middle cranial fossa approach,[196] the transsphenoidal approach,[197] or by a combination of these procedures.[94] Frequently, a cholesteatoma must be dissected from the facial nerve, and occasionally, the intralabyrinthine portion of the nerve must be mobilized to allow complete removal of a perigeniculate cholesteatoma. This maneuver may require sectioning of the greater superficial petrosal nerve and transposition of the facial nerve posteriorly at the geniculate ganglion. The cholesteatoma also may insinuate itself between the dura and the middle fossa floor and may extend for a considerable distance along this plane. Petrous apex cholesteatomas may act similarly and erode the bony labyrinth or internal auditory canal. Only by careful and often tedious dissection can injury to these structures be prevented. Cholesteatomas of the petrous apex may be exteriorized into the mastoid cavity or the sphenoid sinus, although frequent cleansing of debris from

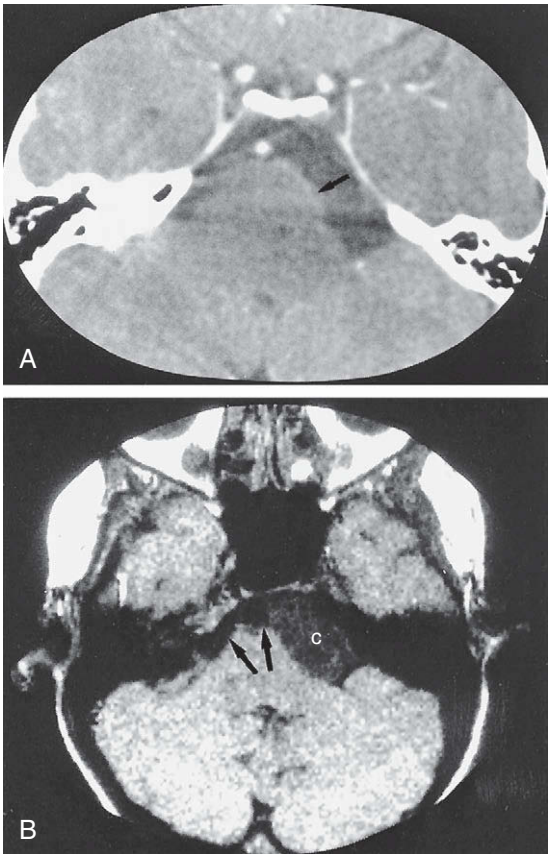

Figure 176-33. Left cerebellopontine cistern congenital epidermoid cyst in a 36-year-old man. **A,** Axial view, computed tomography (CT). Displacement of the pons to the right *(arrow)*. This displacement seems to be caused by cerebrospinal fluid (CSF) attenuation material. Accordingly, this could be an arachnoid cyst. **B,** Axial view, T1-weighted noncontrast magnetic resonance imaging. The cystic lesion (c) is now clearly seen to have higher-intensity signal than the CSF in the right cerebellopontine angle cistern *(arrows)*. This slightly higher signal intensity on T1-weighted images is helpful in separating epidermoid cysts from arachnoid cysts. This relative hyperintensity is caused by lipid, mostly cholesterin. The lipid is not seen on the CT scan as low attenuation because higher-attenuation keratin is mixed with the cholesterin. The sum of these two components balances out to nearly CSF attenuation.

the cholesteatoma cavity is required to prevent inspissations and subsequent infection.[198]

Encephalocele and Cerebrospinal Fluid Leaks

Postsurgical and postinfectious encephaloceles herniating through the tegmen tympani and tegmen mastoideum are well-recognized complications in otology.[199-201] Temporal bone herniation of the mastoid cavity is a result of loss of bony and dural support. Subsequent management should deal with CSF leakage, herniation of the brain into the mastoid cavity, and skin and cholesteatoma matrix in the middle ear and mastoid. Less frequently recognized is a spontaneous congenital encephalocele associated with CSF otorrhea or rhinorrhea.[202-207]

Diagnostic Evaluation

The appearance of postsurgical encephaloceles may occur early or late in the postoperative course. Early occurrences generally are associated with maceration of exposed brain and CSF leakage. Late occurrences are associated with pulsatile tinnitus and/or progressive prolapse of skin-covered brain into the mastoid cavity. Spontaneous congenital encephalocele may manifest as serous otitis media, CSF rhinorrhea, or CSF otorrhea through a tympanic membrane perforation or pressure-equalizing tube. Occasionally, prolapsed brain can be present as a mass behind the tympanic membrane. Because small and often multiple bony defects can be involved, carefully focused CT in the axial and coronal planes is needed to find these fenestrations. If necessary, the subarachnoid space can be opacified with myelographic contrast material, and the actual flow of the contrast-opacified spinal fluid through the fenestrations can be observed. Occasionally, encephaloceles also may be discovered as an intraoperative surprise.

Surgical Approach

Temporal bone encephaloceles and CSF leaks may be surgically approached either transmastoidally or through the middle cranial fossa intradurally or extradurally. Although transmastoid repair of the defect frequently is successful, repair through the middle cranial fossa allows greater visualization. Techniques for repair of the tegmen defect through the mastoid approach have included intracranial placement of reconstructive material (i.e., fascia, cartilage, or prosthetics) from the mastoid combined with obliteration of the mastoid with flaps or free tissue.[200,204,205,207,208] A fascia (banked)-bone-fascia technique incorporating use of a modified radical cavity, with neurosurgical consultation, followed by postoperative lumbar drainage, has been used successfully on several occasions by one of us (MM). A middle cranial fossa approach for repair provides greater visualization and can be either extradural or intradural.[209,210] A variety of closure techniques, including primary dural repair and fascia-bone-fascia, bone, cartilage, or synthetic supports, have been used. The bony and dural defects in spontaneous encephaloceles are routinely small and multiple.[211] Frequently, an encephalocele exists in the anterior epitympanum, where visualization may be inadequate and surgical repair through the transmastoid approach is difficult without ossicular disruption. Although transmastoid exposure defines the defect, repair may be better accomplished through the middle cranial fossa. The bony defects usually are small and do not require repair. The dural defects can be sealed by wide coverage of the middle cranial fossa with temporalis fascia and bone or cartilage as necessary.

Approaches to the Clivus

Clival tumor extirpation, both planning and execution, is perhaps the most difficult of skull base surgical procedures. Surrounding neurovascular structures of the brainstem and both internal carotid arteries are at risk during surgery. House and Hitselberger[103] reported use of a transcochlear route to the petrous tip and midclivus, sacrificing ipsilateral cochlear and vestibular function. This approach may be useful in removing tumors that are not intrinsic (primary) neoplasms of the clival bone itself, such as cholesteatoma and meningioma, because only the dorsal midclivus is exposed. The Fisch type B approach is useful for removal of tumors involving the midclivus with extension to the petrous apex.[61] Tumor extension medial and superior to the horizontal segment of the internal carotid artery in the petrous apex requires temporary transposition of the artery. Adding a middle cranial fossa subdural dissection may circumvent this problem.

A transcochlear dissection added to a Fisch type B approach also may improve access to the clivus. Tumor of the posterior clinoid (retrosellar) is not accessible through this route, but an intradural middle cranial fossa approach may be of benefit.[212]

With the preauricular approaches,[92,105] limitations are similar to those for techniques already discussed, but the transcochlear route cannot be used for further exposure in combination with the preauricular approach. Numerous anterior approaches to the clivus also have been described (see also Chapter 173).[124,213-217] Transnasal endoscopically assisted approaches also may result in complete extirpation with greatly reduced morbidity compared with lateral skull base or facial translocation anterior techniques (see also Chapter 174).[218] Hanna and colleagues have begun exploring robotic endoscopic surgery of the anterior and central skull base.[219]

Lesions Involving the Cavernous Sinus

The cavernous sinus is a small plexus of veins enclosed by leaves of dura on either side of the sella turcica.[220] In the cavernous sinus lie the internal carotid artery, sympathetic nerves, and cranial nerves III, IV,

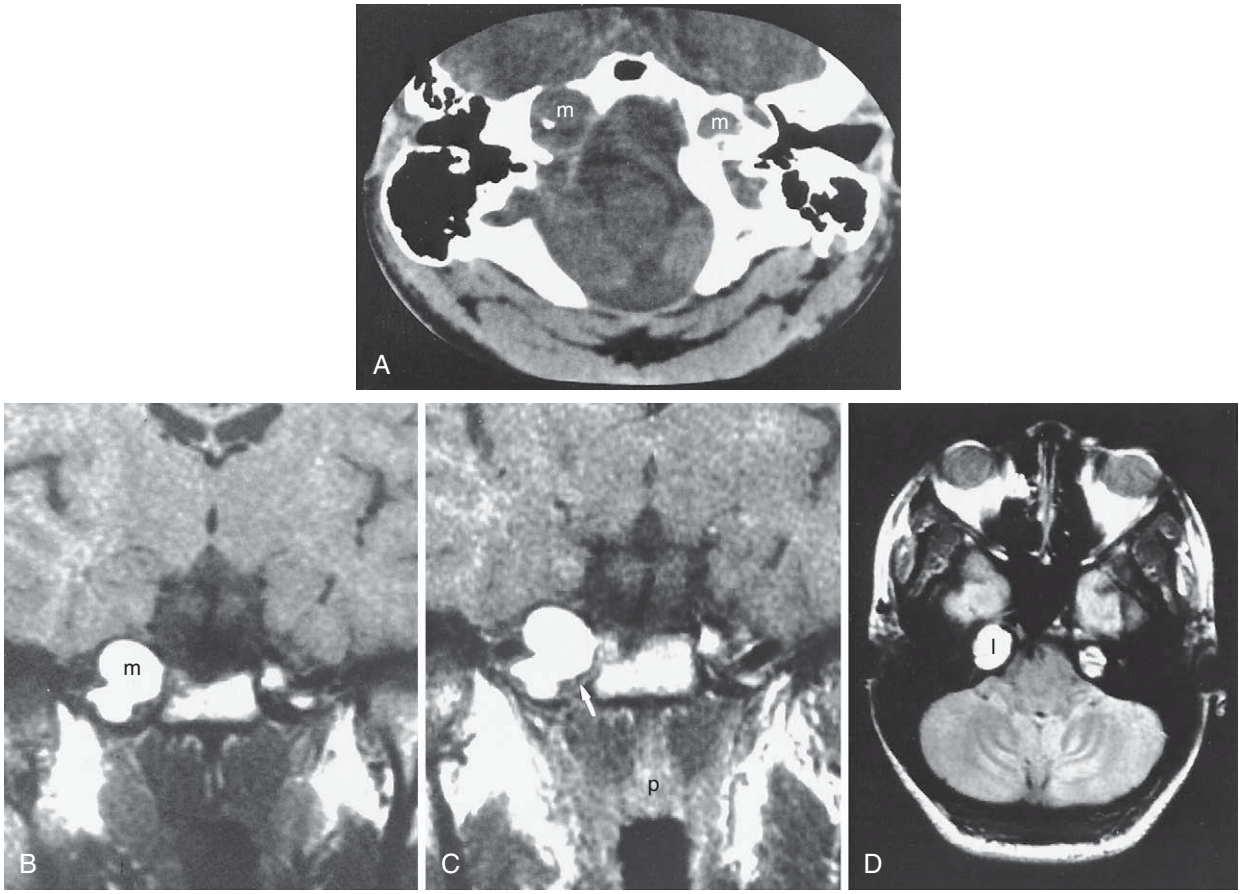

Figure 176-34. Cholesterol cysts in a 21-year-old woman. **A,** Axial view, computed tomography (CT) with intravenous contrast. Expansile, slightly low-attenuation masses (m) are seen in both petrous apices. **B,** Coronal view, T1-weighted sequence on noncontrast magnetic resonance imaging (MRI). High signal intensity is evident within both petrous apices, more pronounced in the larger, right-sided mass (m). **C,** Coronal view, T1-weighted sequence on MRI after administration of intravenous gadolinium contrast material. The edges of the lesion show enhancement *(arrow)*. The larger high-signal-intensity portion does not change. Notice the increased signal intensity in the pharyngeal mucosa (p). This is a normal finding after gadolinium administration. **D,** Axial view, T2-weighted MRI. The right-sided lesion (l) shows extremely high signal intensity. The left-sided lesion is similar but intensty increase is less marked. There is only slight inhomogeneity in this signal reflected by small patches of lower signal intensity. The combination of the CT appearance with extremely high signal intensity on T1- and T2-weighted sequences is distinctive for a cholesterol cyst. The slight inhomogeneity in the lesions is due to bone fragments, calcification, and small hemorrhages of varying ages.

VI, V_1, and sometimes V_2. Primary tumors of the cavernous sinus commonly include meningiomas or schwannomas,[89] but this region usually is invaded secondarily. Operations involving the cavernous sinus are fraught with potential complications, including bleeding, cranial nerve deficits, and carotid injury. Palliative therapy such as with conventional irradiation or gamma knife techniques may be warranted for patients with lesions in this location.

Chordoma

Cranial chordomas originate from the clivus and progressively destroy the skull base[202,204,206] (Figs. 176-35 and 176-36). They may extend ventrally into the nasopharynx, nose, or sinuses and cause obstruction. Headache, loss of vision, and cranial nerve deficits with involvement of the abducens, trigeminal, facial, and acoustic nerves are common presenting complaints. Because of the inaccessibility of the tumor site, surgical exposure and tumor removal may be difficult. Surgical debulking of the tumor followed by high-dose radiotherapy is historically the treatment of choice and may afford good palliative results. More recently, skull base surgeons have become more aggressive, tailoring surgical approaches to individual lesions to ensure complete removal. Because of the difficult accessibility, surgical control of chordoma is a unique challenge to the skull base surgeon and lends itself to creative surgical approaches (see Chapter 173). Anterior, endoscopic approaches rather than lateral skull base approaches are being pioneered to resect these difficult tumors, with great promise (see also Chapter 174).[218]

Tumors of the Parapharyngeal Space

Tumors involving the infratemporal fossa or parapharyngeal space at the skull base and extending into the temporal bone or middle cranial fossa require lateral skull base techniques. For tumors confined to the parapharyngeal space, a cervical approach, often with mandibular transection, may be indicated. Radical en bloc procedures for malignancy may require removal of the mandibular ramus and condyle.[221,222] A labiomandibulotomy[223,224] or extraoral mandibulotomy will give improved access to the tumor within the middle to upper infratemporal fossa. Reflection of the temporalis muscle and zygoma provides improved access to the superior infratemporal fossa. Retracting the mandibular condyle or resecting it may obtain further exposure. Middle cranial fossa approach may be added for superior extension (Fig. 176-37).

Approaches to the Nasopharynx

In patients with extensive benign tumors of the nasopharynx (e.g., juvenile angiofibromas), a lateral approach may be indicated. These approaches may be combined with any of the anterior approaches as the situation warrants. The Fisch type C (see Fig. 176-22) and Sekhar lateral approaches to the nasopharynx provide similar exposures, and either approach may be extended to include removal of tumor from the sphenoid sinus or pericavernous sinus area. Transmaxillary endoscopic approaches also may provide adequate exposure while minimizing operative morbidity (see Chapter 175).

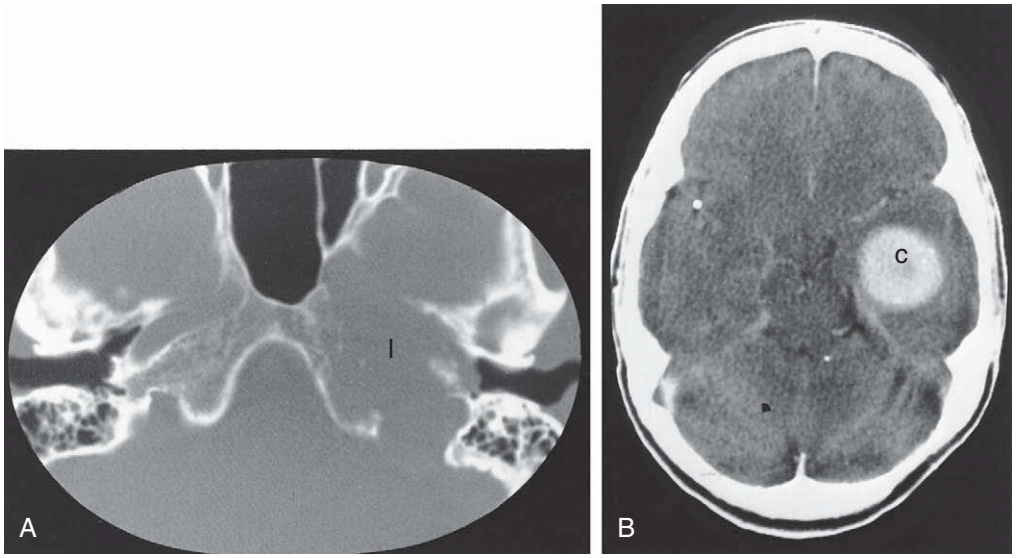

Figure 176-35. Massive petrous apex chordoma on the left in a 57-year-old man. **A,** Axial view, bone algorithm computed tomography (CT). Off-midline destructive changes characteristic of this lesion (I). Whereas most chordomas are midline, some can be quite far lateral. **B,** Axial view, brain CT with intravenous contrast. The chordoma (c) was so large that it extended up into the left temporal lobe.

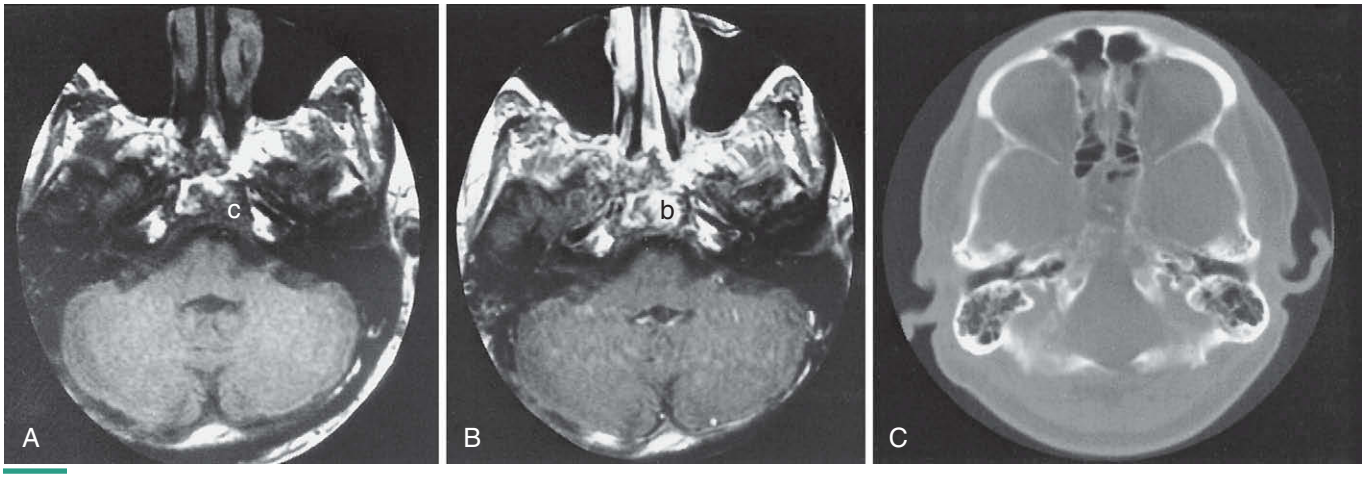

Figure 176-36. Clivus chordoma in a 59-year-old man. **A,** Axial view, T1-weighted magnetic resonance imaging (MRI). Subtle permeative changes can be seen extending into the clival bone marrow. The chordoma (c) is the darker area (of lower signal intensity) invading the brighter area (high-signal intensity) normal bone marrow fat. **B,** Axial view, T1-weighted MRI, after administration of intravenous gadolinium contrast material. The area of low signal intensity on the previous scan demonstrates markedly increased intensity (b). However, it is difficult to assess the degree of bone destruction with MRI. **C,** Standard computed tomography (CT), bone windows. Even on this nonfocused CT scan, the gross destructive changes associated with this clivus chordoma are visible. MRI is less sensitive than CT in showing bone destruction.

Excision of malignant lesions of the nasopharynx is fraught with controversy. Wang[225] has shown that patients with recurrent squamous cell carcinoma of the nasopharynx staged T_1 to T_3 may have improved survival rates if the lesions are excised. Fisch type C approach and Sekhar's approach permit en bloc removal of the lateral nasopharyngeal wall with the pterygoid and tubal musculature for persistent or recurrent tumor postradiation.

Complications

Intraoperative Complications

Intraoperative complications result mostly from lack of vascular control or coagulopathy. Management of unexpected blood loss from an internal carotid artery laceration is facilitated by proximal and distal control before repair. A lack of exposure may result in the need for emergency intraoperative balloon occlusion and ligation when hemorrhage occurs. Bleeding from the cavernous sinus can be massive, and an air embolus may occur, although this bleeding can be stopped with patient application of oxidized cellulose hemostatic strips (Surgicel). Carotid spasm may require termination of the procedure.[97]

Coagulopathy may occur as a result of massive transfusions of packed erythrocytes from citrate-induced hypocalcemia, depletion of clotting cascade proteins, hypothermia, thrombocytopenia, disseminated intravascular coagulopathy, or incompatible blood. When massive transfusion is necessary, 2 units of fresh frozen plasma and platelets should be given for every 10 units of packed erythrocytes.[226] Vasoactive glomus tumors or concomitant pheochromocytomas may lead to unexpected hypertension intraoperatively. For this reason, patients with glomus should be screened preoperatively with urine vanillylmandelic acid and hydroxyindoleacetic acid assays to rule out vasoactive tumors.

Figure 176-37. Intracranial-extracranial trigeminal schwannoma: Coronal view, magnetic resonance imaging. Excision through a preauricular approach with extraoral transection of mandible and temporal craniotomy.

Postoperative Complications

CSF leakage is one of the more common postoperative complications from infratemporal fossa surgery when the dural space must be entered. The risk of meningitis with high attendant morbidity rate is increased, as is length of hospital stay. Postoperative lower cranial nerve deficits leading to aspiration and subsequent coughing increases CSF pressure, adding another adverse variable to the management equation. Most CSF collections beneath flaps may be managed with compressive dressings, head elevation, and repeated aspirations. A lumbar subarachnoid drain best manages leakage of CSF through the wound or persistent otorhinorrhea.

In patients with large tumors and intracranial extension, the subarachnoid space should be entered for tumor exposure and extirpation. Jackson and associates[97] secured autogenous fascia to existing bone or dural margins for small to medium dural defects with temporalis muscle rotations for reinforcement. Obliteration with fat is not used. For larger defects, Gulya and coworkers[227] have used an infant-size ventriculocardiac shunt from the wound bed to the jugular stump to the right atrium, to allow continuous drainage. Lumbar subarachnoid drains combined with pressure dressings usually suffice to control leakage for large dural defects.

Cranial Nerve Deficits

The invasive nature of glomus tumors, especially those extending into the posterior fossa, has led historically to rather high rates of postoperative paralysis. Aside from intraoperative electrophysiologic monitoring,[80] the proximal identification of cranial nerves IX, X, XI, and XII in the posterior fossa and distal identification at the skull base should improve preservation of these nerves.[101] Unfortunately, these cranial nerves often are encased in tumor extending transdurally into the posterior fossa toward the root entry zones, making their preservation extremely difficult.

Most preoperative cranial nerve deficits persist postoperatively if they result from tumor invasion rather than compression. Creation of new cranial deficits, although necessary for complete tumor removal, can result in a prolonged rehabilitative phase and substantially reduce the quality of life. The patient's age and cardiopulmonary status should be carefully weighed against the tumor pathology, extent of disease, and natural course of the disease. Responses to other forms of therapy, such as radiotherapy or chemotherapy, should be considered before extensive skull base surgery is attempted. Younger, healthier patients, in general, tolerate new cranial deficits better than older patients do. Patients with marginal cardiac output are at high risk for myocardial infarction or congestive heart failure when subjected to prolonged surgery and recovery; those with compromised pulmonary function have poor tolerance for the problems created by lower cranial nerve deficiency (i.e., aspiration and decreased cough).

The oculomotor nerve can potentially be injured in cavernous sinus surgery or orbital apex. Neurapraxia or axonotmesis usually leads to a good functional recovery in 2 to 8 months, respectively. Functional recovery with reanastomosis after transection has been reported.[228] Loss of the trochlear nerve is reported to be associated with minimal functional disability. Good recovery with reanastomosis has been reported.[175] The abducens nerve has the longest intracranial course and is most prone to injury, especially in surgery for tumors of the clivus, petrous apex, or cavernous sinus. Good functional return should be expected with stretch injury, because this is a purely motor nerve.[228]

Prevention of facial nerve paresis already has been mentioned. If transection is required and the site optional, it is best to section the nerve at tertiary branches to limit synkinesis. In order of reconstructive preference for the facial nerve, options include direct reanastomosis, interposition grafting, and cranial nerve XII to VII crossover. Ocular care, with prevention of exposure keratitis, especially if the V_2 branch has been sacrificed, is of paramount importance postoperatively if the facial nerve has been injured. A lateral tarsorrhaphy affords the best protection to the eye for a combination deficit involving cranial nerves V and VII.

The approaches by Fisch to the infratemporal fossa by definition preserve cochleovestibular function. Inadvertent stapes subluxation or tumor invasion of the otic capsule may lead to sensorineural hearing loss. Exposure of the upper cervical internal carotid commonly entails loss of the glossopharyngeal nerve. Sequelae from its loss are infrequent, except when such loss is combined with other lower cranial nerve defects involving X and XII. Intraoperative reanastomosis of a vagal nerve is not indicated because of an association with paradoxic vocal cord motion. High vagal injuries can lead to a prolonged rehabilitative period. Not only are the quality of voice and protective sphincter function breached, but deglutition also is impaired through disruption of the pharyngeal plexus; when combined with losses of cranial nerves IX and XII, its loss may be debilitating. Persistent aspiration will lead to pneumonia. Tracheostomy is indicated if paresis of this combination of nerves is expected. Vocal cord medialization with endoscopic polytetrafluorethylene (Teflon) or surgical gel (Gelfoam) injection may be considered to protect the airway. Modified barium swallow may help in the decision regarding the need for a temporary feeding gastrostomy when aspiration persists.

Injury to the spinal accessory nerve usually is well tolerated in skull base procedures, because C2 and C3 ventral roots supply some motor innervation to the trapezius muscle. The suprascapular muscle also has a role in shoulder girdle stabilization. Nevertheless, reanastomosis or interposition grafting should be performed, if possible. Physical therapy and exercise instruction often are helpful in preventing persistent shoulder dysfunction.

The hypoglossal nerve often is involved with tumors of the clivus or jugular foramen. Because use of the hypoglossal nerve is an important reanimation option in facial nerve injury, its preservation is of added importance. Unilateral hypoglossal nerve loss usually is well tolerated unless combined with cranial nerve IX and X paralysis. Reconstruction of a transected hypoglossal nerve can lead to good functional recovery.[228]

Cerebrovascular Complications

The extensive manipulation of the internal carotid artery required by lateral skull base techniques understandably may lead to stroke. Preoperative angiographic evaluation and collateral circulation studies are mandatory. Anesthetic techniques such as increasing blood pressure, hypervolemia, pharmacologic vasodilation, calcium channel inhibitors, hemodilution, hyperosmolarity, and anticoagulation (when the carotid is occluded) theoretically reduce the risk.[229]

Cerebral edema or venous stroke is a concern, especially if a connection at the torcular Herophili is absent or if the vein of Labbé is interrupted.[7,8] Ligation of the sigmoid sinus is potentially more hazardous than extracranial jugular vein ligation. Collateral drainage through the superior and inferior petrosal sinuses may not be present. Presumably, the vertebral venous system compensates for posterior fossa outflow, and cerebral edema from venous occlusion is uncommon. At present, no good preoperative tests to predict this risk are available. Therefore, anastomotic veins, such as the superior petrosal sinus, inferior petrosal sinus, and mastoid emissary vein, should not be indiscriminately sacrificed.

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CHAPTER ONE HUNDRED AND SEVENTY-SEVEN

Neoplasms of the Posterior Fossa

Derald E. Brackmann

Moisés A. Arriaga

Key Points

- Extra-axial neoplasms of the posterior cranial fossa have distinguishing imaging characteristics.
- Vestibular schwannomas and meningiomas are the most common lesions. Although both enhance with gadolinium on T1-weighted MRI, meningiomas tend to be eccentric to the porus acusticus, have enhancing dural "tails," and often demonstrate adjacent hyperostosis or intralesional calcifications on CT.
- Epidermoids and arachnoid cysts both are nonenhancing lesions hypointense to brain on T1-weighted and hyperintense on T2-weighted MRI studies. They are distinguished from one another on intermediate spin sequences and diffusion-weighted imaging (DWI) sequences, with arachnoid cysts exhibiting CSF characteristics and epidermoids demonstrating restricted diffusion (bright) on DWI.
- Vascular imaging studies including traditional angiography, magnetic resonance angiography (MRA), magnetic resonance venography (MRV), and CT angiography (CTA) are useful for demonstrating the proximity of these lesions to important vascular structures.
- Treatment of extra-axial neoplasms is individualized, with consideration of patient factors, tumor size, and tumor type. The treatment objectives are patient safety and functional preservation of cranial nerves.
- Treatment strategies include observation with serial imaging, stereotactic radiosurgery or radiotherapy, and surgical removal. Total surgical removal of these lesions usually is curative.
- Neuro-otologic surgical approaches are team therapies including the translabyrinthine approach, retrosigmoid approach, middle fossa approach, extended middle fossa approach, petrosal approach, and a series of petrous apex drainage approaches. Each strategy must be considered in the context of tumor size and location, patient symptoms and overall health, and short- and long-term outcomes.

With the evolution of advanced audiovestibular testing, sensitive imaging technologies, and modern skull base surgical teams, diagnosis and management of extra-axial posterior fossa neoplasms constitute a consideration in the daily practice of otolaryngology. This chapter reviews diagnostic issues and surgical management.

Approach to Diagnosis of Neoplasms of the Posterior Fossa

Cerebellopontine angle (CPA) lesions are the predominant skull base neoplasms that affect the posterior fossa. Although acoustic neuromas account for most primary neoplasms in this category, many other lesions should be considered in the differential diagnosis.

The diagnostic evaluation begins with a thorough neuro-otologic history and physical examination. Any suspicious neuro-otologic finding should be evaluated thoroughly, because these lesions produce minimal signs and symptoms until they are far advanced. As noted, acoustic neuromas are the most common posterior fossa skull base tumors; less common lesions usually can be diagnosed accurately with the application of modern audiologic and imaging modalities and a systematic approach to evaluation of their differing characteristics. Today's improved diagnostic capabilities facilitate routine detection of tumors smaller than those detectable previously.

Posterior fossa skull base neoplasms may be grouped into common CPA lesions, including lesions of the internal auditory canal; petrous apex lesions; rare CPA lesions; and intra-axial lesions. The signs, symptoms, and diagnostic procedures for tumors within the designated categories (Box 177-1) are described next.

Common Cerebellopontine Angle Neoplasms

In published series of CPA neoplasms, acoustic neuromas are the most common tumors, accounting for more than 90%. The remaining primary tumors were meningiomas (3%), primary cholesteatomas (2.5%), and facial nerve schwannomas (1%), with less common tumors composing the remaining lesions.[1] When secondary tumors also are considered, paragangliomas constitute up to 10% of CPA neoplasms.[2]

Acoustic Neuroma

Acoustic neuroma refers to a benign schwannoma of the eighth cranial nerve. These lesions are relatively common and account for 8% to 10% of all intracranial tumors. Acoustic neuromas arise principally from the vestibular division of the nerve. The superior and inferior divisions are equally affected; intraoperatively, the nerve of origin usually is difficult to determine. The 1992 National Institutes of Health Consensus Conference made *vestibular schwannoma* the official nomenclature term for these lesions. Acoustic neuromas are slowly growing neoplasms that

Box 177-1

Skull Base Neoplasms Involving the Posterior Fossa

Common Cerebellopontine Angle Lesions
Acoustic neuroma
Meningioma
Epidermoid
Nonacoustic neuroma
Paraganglioma
Arachnoid cyst
Hemangioma

Petrous Apex Lesions
Cholesterol granuloma
Epidermoid
Asymmetric pneumatization
Retained mucus or mucocele
Petrous carotid artery aneurysm

Uncommon Cerebellopontine Angle Lesions
Metastatic tumor
Lipoma
Dermoid
Teratoma
Chordoma
Chondrosarcoma
Giant cell tumor

Intra-axial Tumors
Hemangioblastoma
Medulloblastoma
Astrocytoma
Glioma
Fourth ventricle tumor

originate in the nerve sheath and consist of schwannoma cells in a collagenous matrix. They typically are circumscribed, grossly encroaching on and displacing neural structures without direct invasion. Consistency varies, ranging from firm and dense to soft with large cystic spaces.

In the past it was taught that acoustic neuromas usually arise near the myelin-glia junction near the porus acusticus. However, no published histopathologic study has confirmed this assertion. These lesions usually arise within the internal auditory canal; however, they occasionally develop in the CPA medial to the porus. Because acoustic neuromas produce symptoms by exerting pressure on surrounding neurovascular structures, auditory and vestibular symptoms develop earlier with tumors of the internal auditory canal than with tumors of the CPA.

Of the 2000 to 3000 acoustic neuromas diagnosed annually in the United States, more than 95% occur as unilateral and nonhereditary lesions. The remaining acoustic neuromas are manifestations of the neurofibromatoses, which consist of at least two distinct genetic disorders.

Neurofibromatosis type 1 (NF1), or von Recklinghausen's disease, is a relatively common disorder of autosomal dominant inheritance with variable penetrance and an incidence of 1 in 4000 live births. The gene responsible for NF1 has been localized to chromosome 17. NF1 neuromas occur throughout the body, arising both intracranially and extracranially from the Schwann cells of any nerve; however, acoustic neuromas develop in less than 5% of patients, and bilateral acoustic neuroma is not a part of the syndrome.

Type 2 neurofibromatosis, NF2, is the central form of the disease, characterized by bilateral acoustic neuromas in up to 96% of patients. Schwannomas of the other cranial nerves, meningiomas, and ependymomas also are observed much more commonly in patients with NF2.[3]

Figure 177-1. On T2-weighted fast spin echo magnetic resonance imaging, this axial reconstruction shows a 5-mm intracanalicular tumor on the *left*.

The precise frequency of NF2 is unknown, but it is far less frequent than NF1. The gene responsible for the condition encodes a membrane protein (merlin or schwannomin) and is located on chromosome 22. Acoustic neuromas in NF2 are characterized by an onset early in life, often before the age of 21 years, as opposed to unilateral lesions, most of which are diagnosed between the ages of 40 and 60 years. Thus, acoustic neuromas appearing before the age of 30 years mandate particularly close evaluation of the contralateral ear. Although the acoustic neuromas in NF1 and NF2 resemble the lesions in nonhereditary acoustic neuromas, they are technically more challenging to remove because of a tendency to adhere to nearby structures. The clinical presentation of acoustic neuroma in neurofibromatosis is identical to that of unilateral acoustic neuroma.

Malignant schwannomas may rarely occur. They often are associated with neurofibromatosis, but they also may occur with solitary schwannomas. Another very uncommon variant is a pigmented schwannoma.[4]

Natural History

The growth rate of acoustic neuromas is extremely variable. These tumors generally are slow-growing, with average reported growth rates of 0.2 cm per year; however, growth rates in excess of 2 cm per year have been documented. Acoustic neuromas that are not treated are potentially lethal. Gradual enlargement can lead to indentation of the brainstem, increased intracranial pressure, and death during a course of 5 to 15 years.[5]

Growth of acoustic neuromas generally occurs in three phases: internal auditory canal, cisternal, and brainstem compression (Figs. 177-1, 177-2, and 177-3). Growth within the internal auditory canal results in acoustic and facial nerve compression and attenuation. Displacement of the seventh cranial nerve, the acoustic (eighth) nerve, and the anterior inferior cerebellar artery occurs just medial to the porus acusticus (cisternal portion). Medial tumor growth augments the blood supply of the tumor with bridging vessels from the brainstem surface. Fourth ventricle shift often occurs when the CPA component reaches 2 to 3 cm and total ventricle obstruction with resulting hydrocephalus occurs with continued tumor growth. Trigeminal compression occurs at approximately the 3-cm stage, which permits the superior portion of the tumor to abut the fifth cranial nerve. Massive tumor growth with hydrocephalus, brainstem compression, and cerebellar tonsil herniation may occur even with modern imaging. The otolaryngologist should remain vigilant for signs and symptoms suggestive of retrocochlear pathology.

Signs and Symptoms

Sensorineural hearing loss (SNHL), tinnitus, dysequilibrium, and facial hypesthesia are, in descending order, the most common symptoms of

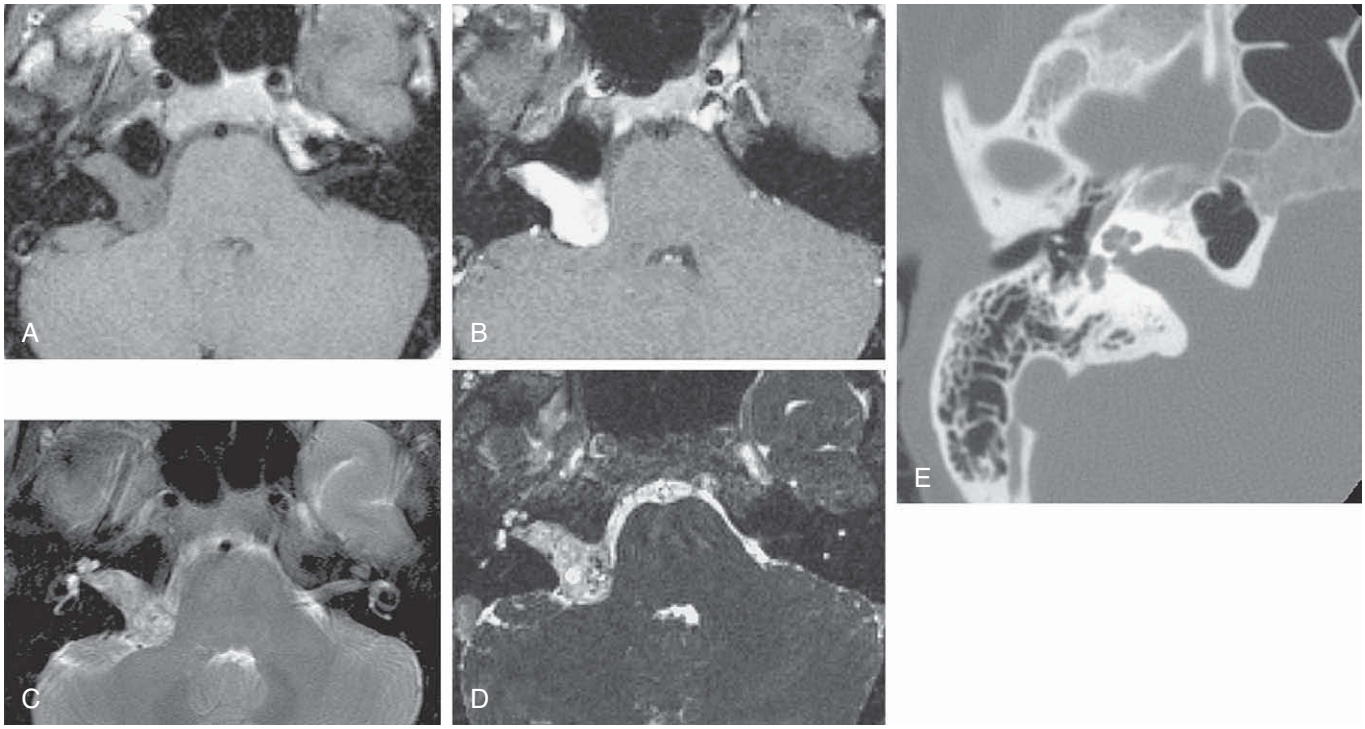

Figure 177-2. A medium-sized vestibular schwannoma, demonstrated by magnetic resonance imaging **(A** to **D)** and computed tomography **(E)**. **A** and **B,** T1-weighted images before and after intravenous administration of gadolinium contrast The tumor in the right internal auditory canal (IAC), which is mushrooming into the cerebellopontine angle and enlarging the canal, is isointense to mildly hypointense to the cerebellum and enhances markedly with contrast. **C** and **D,** T2-weighted and constructive interference in steady-state (CISS) images. The tumor is moderately hyperintense on the T2-weighted images. CISS images precisely demonstrate the cochlea, cystic, and calcified components of the tumor and surrounding vascular structures. **E,** CT bone windows. Note the enlargement of the IAC. *(Adapted from Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245.)*

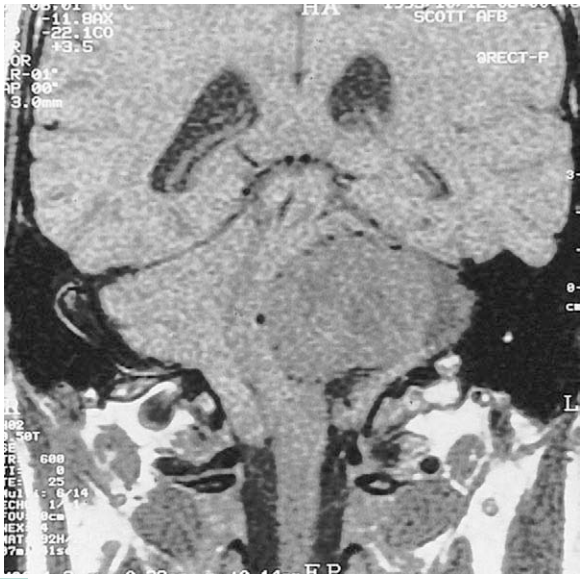

Figure 177-3. Noncontrast coronal T1 magnetic resonance image of a large acoustic neuroma with hydrocephalus, brainstem shift, and cerebellar tonsil herniation.

acoustic neuroma. Although progressive unilateral SNHL is the most common symptom, loss of speech discrimination is characteristic of retrocochlear dysfunction of the cochlear nerve presumably from pressure on the auditory nerve. The symptoms usually are slowly progressive, with a median duration of 2 years in one series.[6,7] However, up to 20% of affected patients experience sudden SNHL, although complete recovery of hearing has been reported.[8] Overall, only 1% of patients with sudden SNHL are found to have acoustic neuroma, whereas up to 5% of patients with acoustic neuroma have normal hearing.[9] Thus, any patient with asymmetric or sudden hearing loss (even after total recovery) should be considered for further evaluation for a possible retrocochlear lesion.

The dysequilibrium associated with acoustic nerve tumors usually is a mild balance disturbance, which often is so minor that the patient does not mention it and only careful questioning elicits it. Rotatory vertigo is far less common.

Diminished facial sensation or corneal reflex results from compression of the fifth cranial nerve, which is more likely with medium-sized and large tumors. As large acoustic neuromas compress the fourth ventricle and brainstem, long tract signs, ataxia, and findings of increased intracranial pressure (e.g., headaches, nausea) are produced.

Diagnostic Studies

Two categories of studies are performed in the diagnosis of acoustic neuroma. Auditory and vestibular studies assess the functional integrity of the audiovestibular system, whereas imaging studies are performed for the definitive anatomic diagnosis.

Audiometry

Routine air, bone, and speech discrimination studies may suggest the possibility of an acoustic neuroma. Asymmetric SNHL or impairment of speech discrimination disproportionate to the pure tone loss requires specific investigation for a retrocochlear lesion. In the past, an extensive audiometric test battery was necessary for timely tumor diagnosis.[6,10] In the magnetic resonance imaging (MRI) era, specialized audiometric tests are not sensitive or specific enough to detect small acoustic neuromas consistently.[11]

Auditory Brainstem Response Testing

Until recently, auditory brainstem (evoked) response (ABR) testing was considered the most sensitive modality for the detection of even small tumors, with detection rates of 95% to 100%.[12] The brainstem response to an 83-dB broadband click is recorded while the contralateral ear is masked by 78-dB white noise.[13] The latency for detection of wave V for the two ears is compared, and an adjusted interaural latency for wave V greater than 0.2 msec is considered abnormal. An approximately 10% false-positive rate has been reported for patients with SNHL who do not have a CPA tumor. Since the advent of gadolinium-enhanced MRI, however, the ABR false-negative rate (missing tumor diagnosis) has been 18% to 30% for intracanalicular tumors.[14] The possibility of false-negative results with intracanalicular acoustic neuromas has lessened the role of ABR testing for routine screening.[15] Stacked ABR testing is a modified ABR technique that offers improved sensitivity for detection of intracanalicular acoustic neuromas. It consists of testing the audiometric spectrum in a frequency-specific fashion followed by temporal alignment of the results; amplitude changes thus detected are much more sensitive for diagnosing small acoustic tumors than with routine ABR.[16,17] Nonetheless, the technique has not yet been verified in widespread clinical practice.

Vestibular Tests

Vestibular testing is not a useful screening test for acoustic neuroma. Electronystagmography (ENG) and infrared video caloric testing are helpful in defining whether the tumor arises from the superior or the inferior vestibular nerve.[18] Such information is valuable when hearing preservation surgery for acoustic neuromas is under consideration, because theoretically better results may be obtained with resection of tumors of the superior vestibular nerve.

Imaging

Computed tomography (CT) and MRI with the paramagnetic intravenous contrast agent gadopentetate (gadolinium-DTPA) are the principal imaging modalities for CPA lesions. Lo[19] proposed a scheme for the CT or MRI differential diagnosis of CPA lesions by anatomic location (extra-axial, extradural, or intra-axial) and by incidence (rare or common) (Table 177-1). In adults and teenagers acoustic neuromas, meningiomas, and epidermoids are the three most common lesions. Acoustic neuromas are very rare in children. Instead, brainstem gliomas (which can enlarge the internal auditory canal) are the most common CPA lesion in younger children.[20] Distinguishing among the three most common CPA lesions is based on specific imaging characteristics on CT and MRI (Table 177-2).

Although CT revolutionized the diagnosis of CPA tumors, gadolinium contrast MRI is sensitive and specific for detection of acoustic neuroma and is the diagnostic imaging technique of choice for the evaluation of acoustic neuroma and other CPA lesions (see Fig. 177-2).[21,22] Acoustic neuroma images on MRI are isointense or mildly hypointense to brain on T1-weighted images and mildly hyperintense to brain on T2-weighted images.[19] MRI for investigation of possible acoustic neuroma should be performed with intravenous contrast. Gadolinium increases the diagnostic sensitivity of MRI on T1-weighted images, and detection of lesions as small as 3 mm has been reported.[21] In addition to improving sensitivity in diagnosing acoustic neuromas, MRI is noninvasive, and the patient incurs no radiation exposure.

Before MRI, CT was the principal study for CPA lesions. Now the role of CT is to provide adjunctive information regarding the osseous structures surrounding a CPA lesion. It also can be the primary imaging modality in patients who cannot undergo MRI because of medical reasons (e.g., cardiac pacemaker or cochlear implant) or unmanageable phobic reactions. The CT finding characteristic of an acoustic tumor is an ovoid lesion centered on the internal auditory canal with moderate enhancing qualities. The tumor often is not homogeneous, exhibiting areas of lesser and greater enhancement. Approximately 85% of acoustic neuromas show acute angles at the bone-tumor interface, in contrast with meningiomas, in which the interface is obtuse in 75% of tumors.[19]

Intravenous contrast CT can fail to detect acoustic neuromas smaller than 1.5 cm in greatest dimension. Oxygen cisternography has been used to diagnose small, mainly intracanalicular lesions. In this technique, 4 mL of oxygen was introduced into the subarachnoid space through the opening afforded by a lumbar puncture, to highlight the structures of the internal auditory canal. This technique was very sensitive for detection of small lesions; however, it was limited by a false-positive rate of 5% and the need for a lumbar puncture.[23]

The improved availability of MRI has led to the development of MRI-based internal auditory canal screening protocols, which in many centers are comparable in cost to ABR-based internal auditory canal screening.[11] Special T2-weighted fast-spin echo sequences may achieve the accuracy of T1-weighted sequences with gadolinium without the need for contrast (see Fig. 177-1).[24] Although the software for these special sequences is not generally available, initial findings with this technique are very encouraging.

Table 177-1

Differential Diagnosis of Cerebellopontine Lesions by Imaging Location* and Incidence

Location	Incidence	Type
Extra-axial	Most common	Acoustic neuroma
	Common	Meningioma
	Common	Epidermoid (and other cysts: arachnoid, cysticercal, dermoid)
	Rare	Nonacoustic neuromas (cranial nerves V, VII, IX, X, XI, XII)
	Rare	Vascular lesions (loops, aneurysms, malformations)
Extradural	Common	Paraganglioma (glomus jugulare, glomus vagale)
	Rare	Bone lesions (benign or malignant; primary or metastatic)
Intra-axial	Rare	Astrocytoma, ependymoma, papilloma, hemangioblastoma, metastasis

*Computed tomography or magnetic resonance imaging.
Adapted from Lo WM. Tumors of the temporal bone and cerebellopontine angle. In: Som PM, Bergeron RT, eds. *Head and Neck Imaging*. St Louis: Mosby; 1991:420-445.

Meningiomas

Meningiomas represent up to 18% of all intracranial tumors and approximately 3% of CPA tumors.[25] The cells lining the arachnoid villi are the cells of origin. These cells are distributed throughout the intracranial space predominantly in relation to veins and dural sinuses. Meningiomas are benign but locally aggressive tumors, which occur at different anatomic sites in the following order of frequency: parasagittal region, falx, convexity, olfactory groove, tuberculum sellae, sphenoid ridge, petrous face (CPA), tentorium, lateral ventricle, clivus, and others.[26]

The gross appearance typically is that of a globular mass firmly adherent to the dura mater, with characteristic speckles scattered throughout the tumor that correspond to the microscopic psammoma bodies. The tumor displaces but does not invade adjacent neural tissue and has a thin investing capsule. Meningiomas can invade bone without destruction by extension along haversion canals. Adjacent bone is hyperostotic in 25% of cases.[26]

Many histopathologic classifications have been proposed, but a single, widely used system distinguishes among syncytial, transitional, fibrous, angioblastic, and sarcomatous types.[27] The specific histopathologic subtypes and growth characteristics are reviewed elsewhere.[28] In

Table 177-2

Imaging Features of the Three Most Common Cerebellopontine Angle Lesions

Feature	Acoustic Neuromas	Meningiomas	Epidermoids
Location	Centered on the internal auditory canal	Eccentric to the internal auditory canal	Anterolateral or posterolateral to brainstem
Bone changes	Most enlarge the internal auditory canal	Occasional hyperostosis	Occasional erosion
Shape	Spherical or ovoid, acute bone-tumor angle	Hemispherical, rarely plaquelike; may herniate through tentorium; obtuse bone-tumor angle	Variable—tends to dumbbell into middle fossa or contralateral cerebellopontine angle
Computed tomography density	Mostly isodense	Slightly hypodense; some calcified	Mostly hypodense; occasional peripheral calcium
Computed tomography enhancement	Moderate to marked; often inhomogeneous	Marked and homogeneous	Nonenhancing
T1-weighted magnetic resonance imaging	Isointense or hypointense	Isointense or hypointense	Hypointense
Gadolinium enhancement	Marked	Moderate	Nonenhancing
T2-weighted magnetic resonance imaging	Isointense or hypointense	Variable	Hyperintense

Adapted from Lo WM: Tumors of the temporal bone and cerebellopontine angle. In: Som PM, Bergeron RT, eds. *Head and Neck Imaging*. St Louis: Mosby; 1991:420-445.

the posterior fossa, meningiomas usually arise on the posterior surface of the petrous bone, away from or at the edge of the internal auditory canal, or along the sigmoid sinus. Because they usually arise outside of the canal, these tumors may become large before producing signs and symptoms of cranial nerve VIII compression. Most meningiomas eventually involve cranial nerve VIII.

Signs and Symptoms

Audiovestibular symptoms usually are the first indication of a posterior fossa meningioma. Among patients presenting to neurosurgeons, a higher proportion first experienced symptoms referable to the trigeminal nerve.[29] The signs and symptoms of meningiomas are similar to those of acoustic neuromas. Small tumors produce hearing loss, tinnitus, and imbalance. Larger tumors also produce signs and symptoms of involvement of other cranial nerves and hydrocephalus.

Diagnostic Studies

Audiovestibular Testing

It is impossible to distinguish acoustic neuromas from meningiomas on the basis of audiovestibular testing. Because meningiomas cause cranial nerve VIII compression, auditory and vestibular test findings become abnormal in a pattern similar to that with acoustic neuromas. Because meningiomas usually do not arise within the internal auditory canal, the sensitivity of audiometric and vestibular testing is lower with meningiomas than with acoustic neuromas. For instance, only 75% of patients with meningiomas exhibit an abnormal ABR.

Imaging

Table 177-2 summarizes features of meningiomas that assist in differentiating them from acoustic neuromas. Unlike acoustic neuromas, meningiomas usually are eccentric to the porus. Whereas acoustic neuromas seldom herniate into the middle fossa, approximately 60% of meningiomas extend to the middle fossa.[19] Meningiomas usually are hemispheric because of their broad-based attachment to the posterior petrous wall, accounting for the obtuse bone-tumor angles in 75% of meningiomas. Unlike the site of origin of acoustic neuromas, that of posterior fossa meningiomas is varied (Figs. 177-4 and 177-5).

On CT, approximately two thirds of meningiomas are hyperintense relative to the brain. Unlike acoustic neuromas, meningiomas are homogeneous and occasionally calcified. They show homogeneous enhancement with iodine infusion, which usually permits differentiation from acoustic neuromas. Hyperostosis of adjacent bone is infrequent but characteristic of meningiomas when present.

On MRI, meningiomas are of extremely variable intensity on T2-weighted images and isointense or slightly hypointense to brain on T1-weighted images. The different signal intensities among meningiomas correspond to different histopathologic subtypes.[27] Surface flow voids on MRI correspond to marginal pial blood vessels, and arborizing flow voids represent active feeders to the tumor. Calcification and cystic foci cause heterogeneity on MRI images of meningiomas.

Primary Cholesteatomas

Primary cholesteatomas (epidermoids) consist of a stratified squamous epithelial lining surrounding desquamated keratin, which originates from epithelial rests within the temporal bone or CPA. These lesions usually are slow-growing, and symptoms often do not become apparent until the second to fourth decades of life. As the lesions expand, compression and irritation of surrounding structures produce the signs and symptoms.

Primary cholesteatomas arise adjacent to the brainstem. Because they expand into the area of least resistance, primary cholesteatomas have variable shapes with irregular surfaces. They may burrow into crevices on the surface of the brain or extend in a dumbbell pattern into the middle fossa.

Signs and Symptoms

Although primary cholesteatomas produce pressure on cranial nerves VII and VIII with continued growth, these lesions can become quite large without producing any symptoms. Facial twitching is a distinguishing clinical manifestation of primary cholesteatomas. Progressive

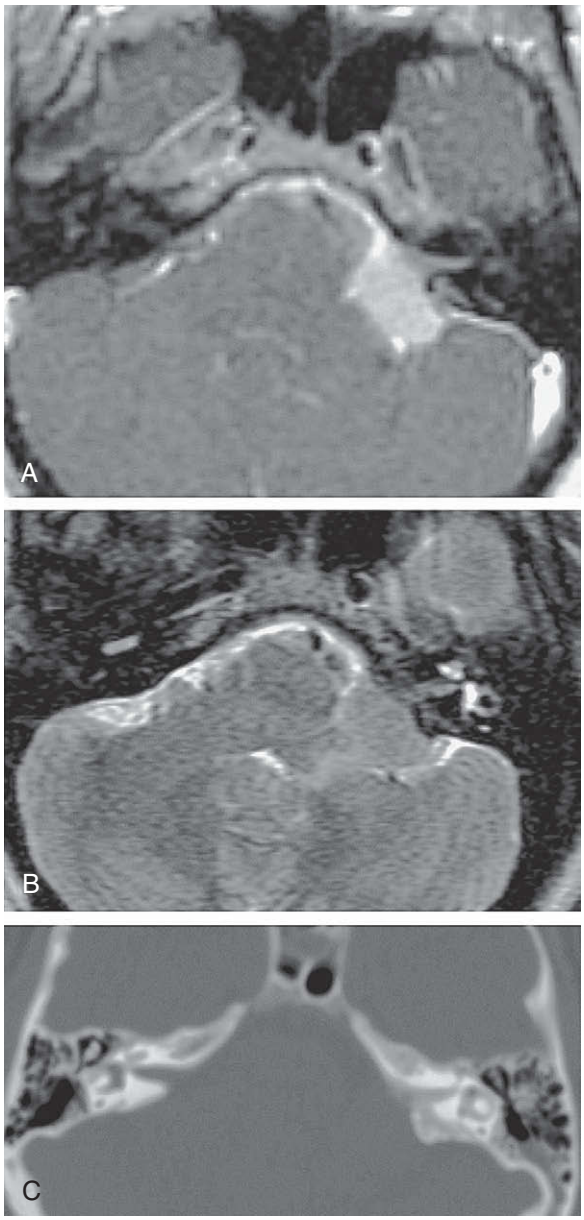

Figure 177-4. Cerebellopontine angle meningioma with classic features on magnetic resonance imaging (MRI) and computed tomography (CT). **A,** Post-gadolinium T1-weighted MRI: The tumor is eccentric to the internal auditory canal (IAC) and broadly dura-based, with obtuse angles at the bone-tumor interface. This hemispherical tumor shows uniform enhancement. Note the lack of IAC involvement. **B,** T2-weighted MRI: The tumor is homogeneously isointense to gray matter. **C,** CT bone windows. The tumor shows extensive hyperostosis underlying the dural base. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

facial paralysis is more common with these lesions than with schwannomas.

Diagnostic Studies

Auditory Testing

Auditory testing does not show any distinguishing features. As with other retrocochlear lesions, speech discrimination is poorer than would be expected from the degree of pure-tone loss. ABR also is frequently abnormal in primary cholesteatomas.[30]

Imaging

CT and MRI are useful to differentiate primary cholesteatomas from other lesions. Epidermoids originating in the CPA should be distinguished from arachnoid cysts, and epidermoids in the petrous apex should be distinguished from the much more common cholesterol granulomas. This distinction affects therapy because adequate management for primary cholesteatoma requires excision, whereas drainage is sufficient for cholesterol granulomas and arachnoid cysts.

On CT, primary cholesteatomas are less dense than brain (having a density approximating that of cerebrospinal fluid [CSF]) and exhibit no enhancement with intravenous contrast. These lesions have irregular margins and are eccentric to the porus acusticus. Enhancing components suggest an associated malignancy.[31] With MRI, primary cholesteatomas are inhomogeneous and hypointense to brain on T1-weighted images, and homogeneous and isointense or hyperintense to brain on T2-weighted images (Fig. 177-6). Schwannomas, meningiomas, and chondromas are similar to primary cholesteatomas by intensity criteria; however, epidermoids are differentiated because they are nonenhancing.

Arachnoid cysts of the CPA are difficult to distinguish from epidermoids on CT and MRI. Both lesions are of CSF density and nonenhancing; compared with primary cholesteatomas, however, arachnoid cysts have smoother surfaces, and special MRI sequences such as diffusion-weighted images (DWIs) may differentiate the intensity of the epidermoid from the CSF intensity of the arachnoid cyst (Fig. 177-7).

Facial Nerve Neuroma

Facial nerve neuromas (schwannomas) are uncommon benign neoplasms of Schwann cells that may arise anywhere along the course of the facial nerve.

Signs and Symptoms

Symptoms associated with these tumors depend on the portion of the nerve affected by the neoplasm. Peripheral involvement can manifest as a parotid mass, middle ear involvement can produce conductive hearing losses, and internal auditory canal or CPA involvement may result in SNHL. Unlike hemangiomas of the facial nerve, schwannomas do not produce facial weakness until they become very large. Sometimes a facial nerve tic is evident, which helps distinguish facial neuromas from acoustic neuromas but not from primary cholesteatomas. Of note, intratemporal lesions, with the possibility of neural entrapment, are more likely than CPA lesions to result in facial paralysis.[32]

Diagnostic Studies

Auditory Testing

The mechanisms for conductive hearing impairment and SNHL have already been described earlier in this chapter. Impedance testing may reflect motor fiber impairment on ipsilateral reflex testing or cranial nerve VIII involvement on contralateral reflex testing. ABR testing of tumors arising in the internal auditory canal shows abnormalities similar to those seen with acoustic neuroma.[13]

Electroneurography

Electroneurography, also known as electroneuronography (ENoG), measures the muscle response to a maximal bipolar stimulation of the facial nerve near the stylomastoid foramen. ENoG potentials may be reduced in facial nerve neuroma even when no facial weakness or tic is present, whereas ENoG findings remain normal in acoustic neuroma until the tumor becomes very large. Some reports suggest that the value of preoperative ENoG in patients with acoustic neuroma lies in predicting whether the lesion actually represents a facial nerve tumor.[33,34]

Imaging

Intratemporal facial nerve lesions may produce bone destruction. Because the clinical presentation and audiometric study findings in facial neuroma are not distinct, CT and MRI constitute the mainstays of diagnosis.

Because facial nerve neuromas are histologically identical to acoustic neuromas, they have the same enhancement characteristics. It

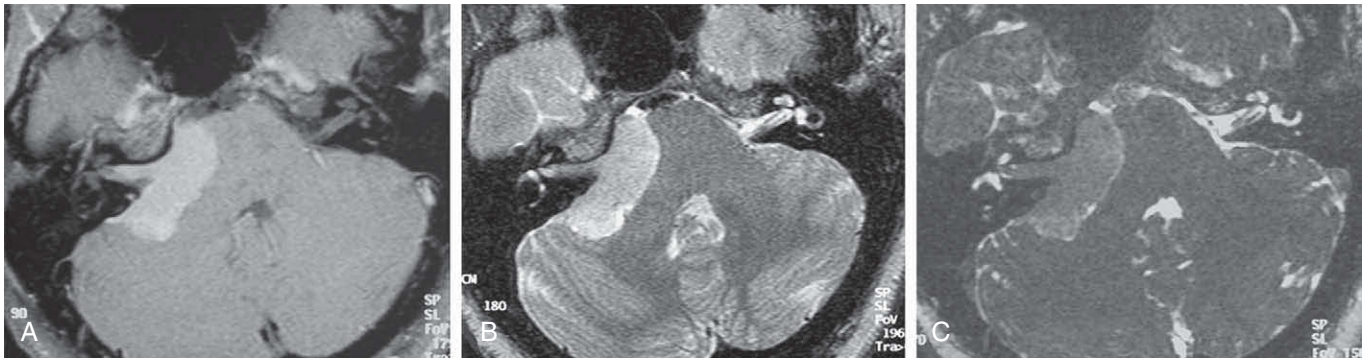

Figure 177-5. Cerebellopontine angle meningioma with intracanalicular extension, demonstrated by magnetic resonance imaging. **A,** Post-gadolinium T1-weighted image. Typical hemispherical tumor with intracanalicular extension. The dural tail of the tumor extending posteriorly is best seen on post-gadolinium images. **B,** T2-weighted image demonstrates the cerebrospinal fluid spaces and clefts surrounding the tumor. **C,** Constructive interference in steady-state (CISS) image. The internal auditory canal extension and margins of the tumor are better delineated on CISS images than on T2-weighted images. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

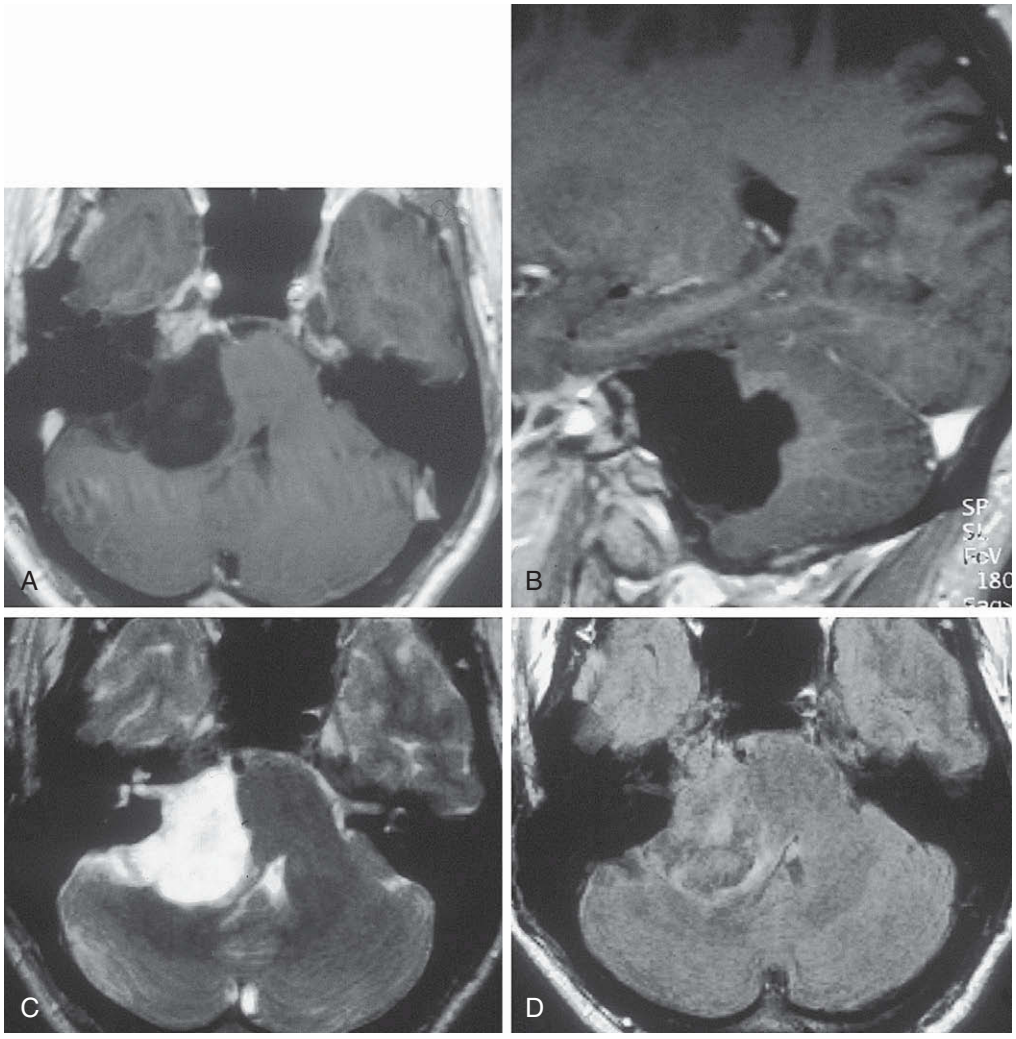

Figure 177-6. Cerebellopontine angle (CPA) epidermoid, demonstrated by magnetic resonance imaging. **A** and **B,** T1-weighted axial and sagittal images after gadolinium administration. The CPA mass extending to the prepontine cistern is isointense to cerebrospinal fluid (CSF) and shows no enhancement. **C,** T2-weighted image. The tumor, with irregular, cauliflower-like margins, is isointense to CSF, as in T1-weighted images, and is compressing the fourth ventricle. The internal auditory canal is normal. **D,** On this fluid-attenuated inversion recovery (FLAIR) sequence image, the epidermoid has heterogeneous hyperintense foci, enabling differentiation of an epidermoid from an arachnoid cyst in this case. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

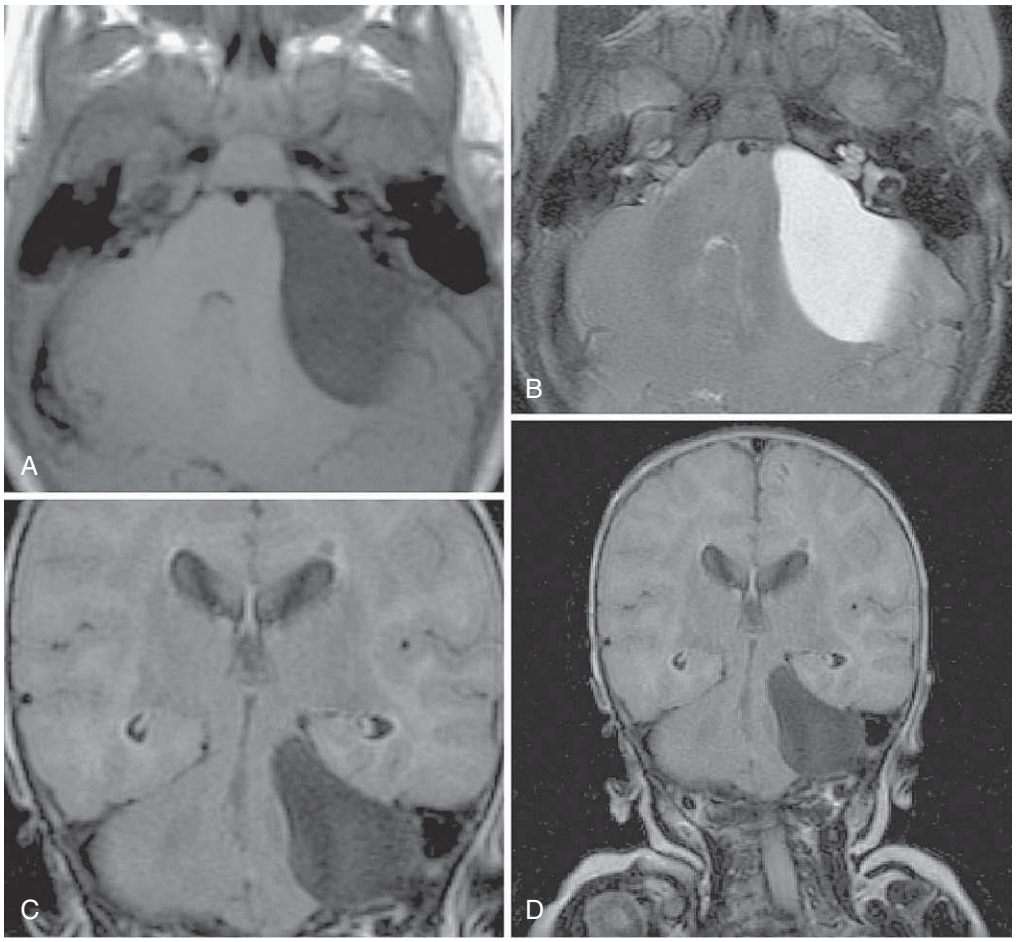

Figure 177-7. Cerebellopontine angle arachnoid cyst, demonstrated by magnetic resonance imaging. **A,** T1-weighted image. **B,** T2-weighted image. **C** and **D,** T1-weighted coronal and axial images, respectively. The cyst is isointense to CSF on all sequences. It is homogeneous, with a smooth surface, which can be helpful in differentiating it from an epidermoid. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

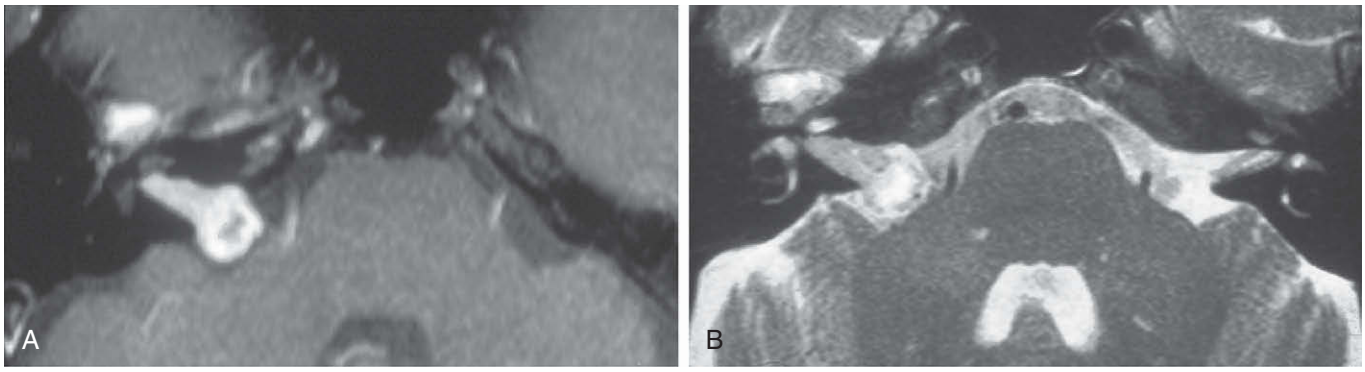

Figure 177-8. Facial schwannoma of internal auditory canal, demonstrated by magnetic resonance imaging. **A** and **B,** Post-gadolinium T1-weighted and T2-weighted images. The patient presented with progressive sensorineural hearing loss, with later development of facial palsy. The enhancing intracanalicular tumor is indistinguishable from an acoustic schwannoma. Note also the extension of the tumor to the geniculate ganglion. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

usually is impossible to identify these lesions using CT. Anterosuperior erosion of the internal auditory canal or erosion of the labyrinthine facial nerve canal if present may be the only diagnostic clue.[19] More distal tumors enlarge the geniculate ganglion and fallopian canal.

As with CT, MRI of facial neuroma produces imaging characteristics identical to those of acoustic neuromas (Fig. 177-8). The preoperative diagnosis of intracranial facial neuroma is difficult. Early facial nerve symptoms are an obvious warning that a CPA lesion may rarely be a facial nerve neuroma. Patients diagnosed with CPA neuromas should be warned preoperatively of a 1% risk of facial nerve neuroma. This possibility is emphasized if findings on preoperative ENoG are abnormal on the tumor side. In some tumors, the lesion may extend

Figure 177-9. Cystic trigeminal schwannoma, demonstrated by magnetic resonance imaging. **A,** T1-weighted image. **B,** Gadolinium T1-weighted image. **C,** T2-weighted image. The bulk of the tumor lies in the posterior fossa, with a small middle cranial fossa component enlarging the left Meckel's cave *(arrow)*. Note the similarity of the tumor to an arachnoid cyst (see Figure 177-7) on the noncontrast images (**A** and **C**). The tumor is nearly of CSF intensity because of the predominance of the intratumoral cystic components. *(From Jackler RK, Brackmann DE, eds.* Neurotology. *St Louis: Mosby; 1994.)*

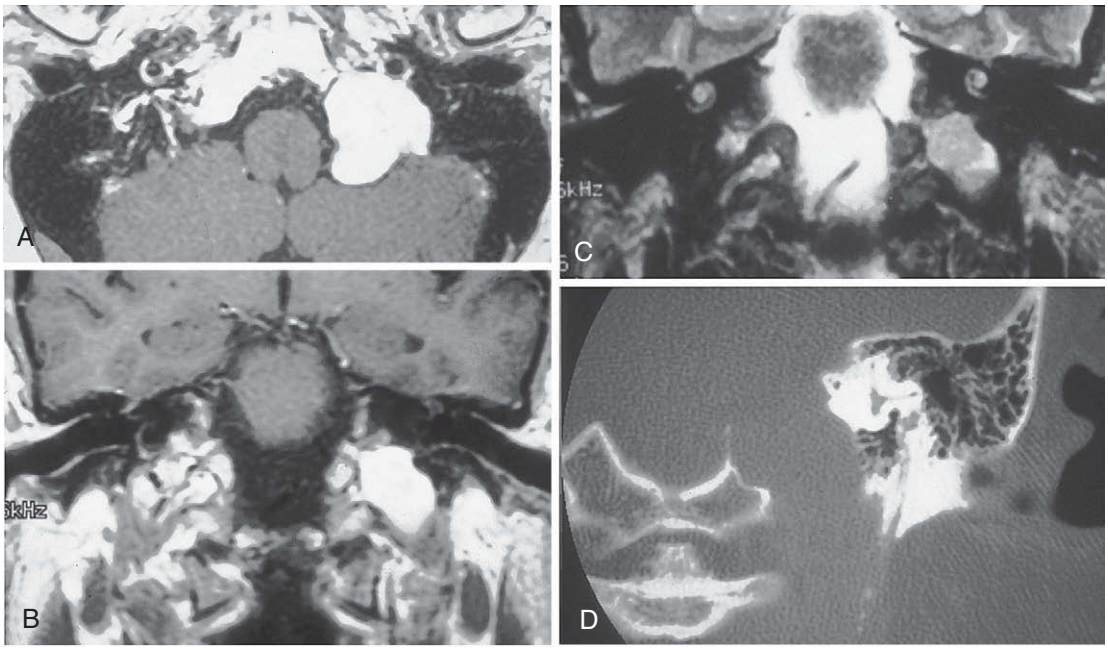

Figure 177-10. Jugular foramen schwannoma, demonstrated by magnetic resonance imaging (MRI) and computed tomography (CT). **A** and **B**, Axial and coronal T1-weighted post-gadolinium images. The large tumor in the left jugular fossa is extending inferiorly. It shows avid enhancement. **C,** Coronal T2-weighted image depicts the extracranial portion of the tumor, which is hyperintense to gray matter. **D,** CT bone windows, coronal image. Expansion of the jugular foramen is symmetric, and the margins are well defined. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:245-250.)*

from the CPA through the temporal bone course of the nerve to the extratemporal nerve in the parotid gland.

Other Cranial Nerve Neuromas

Neuromas may arise on any other cranial nerve in the posterior fossa. On imaging studies, nonacoustic neuromas have the same characteristics as those of acoustic neuromas except for their location. Overall, acoustic neuromas represent 95% of intracranial schwannomas, and trigeminal neuromas are the next most common; however, schwannomas also have been reported on cranial nerves IX, X, XI, and XII. These lesions are distinguished by their different location and by symptoms of dysfunction of the cranial nerve of origin.

Trigeminal neuromas arise intradurally, from the nerve root in the CPA and Meckel's cave, and extradurally, from the gasserian ganglion in the middle cranial fossa.[35] Typically these lesions enlarge Meckel's cave and produce hypesthesia of the face (Fig. 177-9).

Neuromas of cranial nerves IX, X, and XI produce smooth enlargement of the jugular foramen and classically cause hypesthesia and weakness of the palate, vocal cord, and shoulder, respectively (Fig. 177-10). If they arise in the posterior fossa, these tumors may grow to a large size before producing predominantly acoustic or cerebellar signs. Accurate preoperative differentiation of these tumors from acoustic neuromas is important because residual hearing is more likely to be preserved with lower cranial nerve neuromas. Hypoglossal neuromas produce motor hemiatrophy of the tongue and enlargement of the hypoglossal canal on radiography.

Glomus Tumors

Glomus tumors (paragangliomas) are discussed in detail in Chapter 176. Because glomus jugulare tumors and glomus vagale tumors may extend into the posterior fossa, they constitute an important consideration in the differential diagnosis of skull base neoplasms.

The first symptom often is pulsatile tinnitus, after which a conductive hearing loss develops. Involvement of the nerves of the jugular foramen and the hypoglossal nerve causes progressive neurologic deficits related to those nerves.

The characteristic appearance on CT with bone windows is irregular destruction of the jugular foramen, as compared with jugular

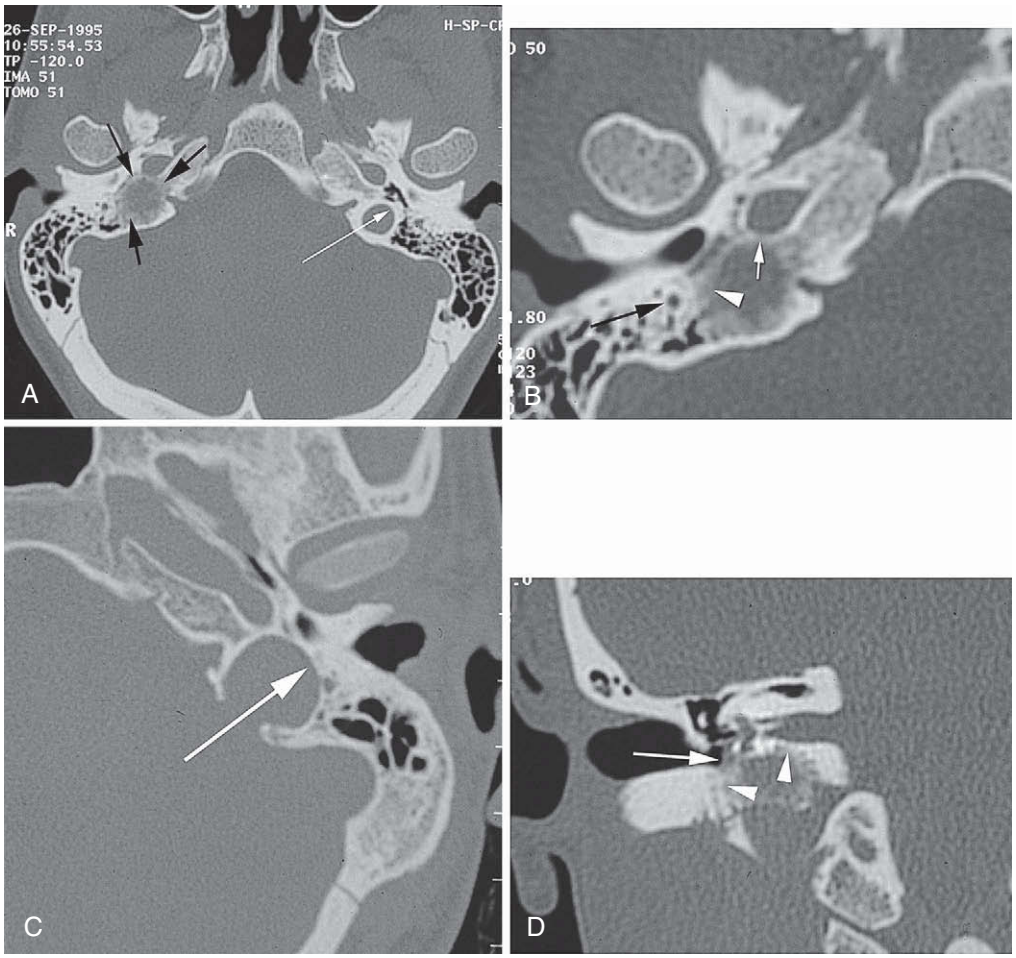

Figure 177-11. Glomus jugulare tumor, demonstrated by computed tomography. **A,** Axial image shows demineralization of the bony margins of the jugular foramen on the right side *(black arrows)*. There is demineralization of the fine cortical line usually demonstrated along the lateral aspect of the vascular portion of the jugular foramen. Compare with intact cortical plate on the opposite side *(white arrow)*. Note the demineralization of the bony wall separating the carotid canal from the jugular foramen. **B,** Enlarged axial image shows the demineralization of the lateral cortical plate *(arrowhead)*, as well as slight demineralization of the bony plate between the carotid canal and the jugular foramen *(white arrow)*. Note the proximity of the demineralized bone to the vertical section of the facial nerve canal *(black arrow)*. **C,** Axial image enlarged through the normal side shows the intact white cortical line *(arrow)* along the lateral aspect of the jugular foramen. The integrity of this line essentially excludes a glomus jugulotympanic tumor. **D,** Coronal image shows demineralization of the margins *(arrowheads)*, as well as the soft tissue of the intratympanic portion of the tumor *(arrow)*. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

foramen schwannomas, which produce smooth enlargement (Fig. 177-11). The vascular pattern of paragangliomas on angiography is characteristic (Fig. 177-12), and biopsy of these lesions is not indicated.[36] Diagnostic angiography should be performed concomitantly with preoperative embolization when surgical resection is planned.

MRI produces a unique salt-and-pepper mixture of intensities on T1- and T2-weighted images. Arborizing flow voids reveal the prominent tumor vessels of this lesion. Lo[19] described two limitations of MRI in evaluating paragangliomas: (1) bone changes and the relation of tumor to bone landmarks are not visualized; and (2) distinguishing tumor from bone marrow is difficult, especially on gadolinium-enhanced T1-weighted images. Thus, MRI may provide complementary information about infralabyrinthine and intracranial tumor extensions, but bone algorithm CT is the cornerstone of imaging evaluation in paragangliomas.

The combination of CT, MRI, and angiography can provide extensive information about involvement of the internal carotid artery. Magnetic resonance angiography (MRA) is an adjunct to intra-arterial catheterization and formal angiography (see Fig. 177-12). Angiography is a necessary step in preoperative embolization of glomus tumors; however, it is unlikely that MRA can replace direct intravascular angiography in glomus tumor management. For resection of skull base neoplasms involving the posterior fossa, if surgical resection requires manipulation of the artery, preoperative assessment of the adequacy of collateral flow by way of the circle of Willis is necessary. Temporary balloon occlusion of the carotid artery in combination with radioisotope imaging or xenon-enhanced CT can accurately quantify collateral blood flow.[37]

Arachnoid Cysts

Arachnoid cysts are thin-walled sacs that contain yellow, entrapped CSF. The current theory is that these lesions represent congenital developmental anomalies.[38] Symptoms are produced by the mass effect of the cyst on surrounding structures and may be similar to the symptoms of acoustic neuromas. These patients may experience mild to profound hearing loss with a retrocochlear pattern.[39]

These lesions have CT and MRI characteristics similar to those of epidermoids. Enlargement of the internal auditory canal often is noted but is not characteristic of these lesions. The typical appearance is that of a smooth-surfaced lesion, which on CT approximates CSF and is nonenhancing and on MRI exhibits isointensity or hypointensity to brain on T1-weighted images and hyperintensity to brain on T2-weighted images (see Fig. 177-7). In most patients, no direct inter-

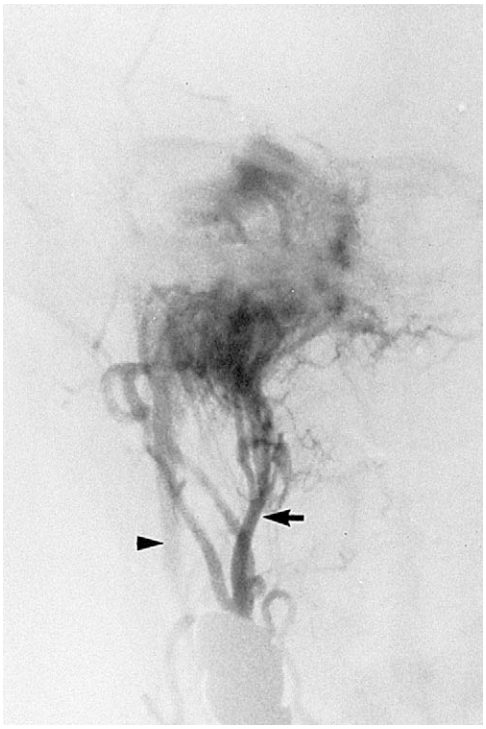

Figure 177-12. Glomus jugulare tumor. As seen on this selective external carotid angiogram, the characteristically hypervascular tumor is supplied by the hypertrophic ascending pharyngeal artery *(arrow)*. Note the early draining vein *(arrowhead)* seen during the midarterial phase. Considerations in the differential diagnosis include other hypervascular tumors such as metastatic hypernephroma, metastatic pheochromocytoma, and myeloma. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

vention is necessary. When treatment is necessary to control symptoms, management of these lesions is not total resection. Instead, surgical drainage by way of retrolabyrinthine exposure is the usual recommended therapy; however, diuretic therapy provides symptomatic relief in a few patients.

Hemangiomas

Hemangiomas are hamartomatous neoplasms originating from blood vessels. Although benign, they produce symptoms by compression of adjacent structures. Hemangiomas are capillary or cavernous.

Capillary hemangiomas typically arise in the area of the geniculate ganglion in association with a perigeniculate capillary plexus.[40] The lesion is characterized by a progressive facial weakness despite being much smaller than facial nerve neuromas. The expanding lesion with the production of pulsatile tinnitus may expose the upper basal turn of the cochlea. CT shows a smooth enlargement of the geniculate ganglion and enlargement of the labyrinthine portion of the fallopian canal by a soft tissue mass. Although capillary hemangiomas are enhancing, they produce facial weakness at such an early stage that only subtle findings may be apparent on CT, and a very small enhancement in the area of the labyrinthine segment may be the only finding. Other CT findings include honeycomb bone, irregular and indistinct bone margins, and intratumoral bone spicules (Fig. 177-13). These findings contrast with those in facial nerve neuromas, which are larger, more obvious lesions with sharp bone margins.

Cavernous hemangiomas are the second type of hemangioma. These lesions arise in the internal auditory canal and produce symptoms typical for an acoustic neuroma. Although they tend to produce symptoms more rapidly than do acoustic neuromas, these two tumor types are identical on CT. However, on MRI, cavernous hemangiomas tend to be slightly more hyperintense than the typical acoustic neuroma.

Table 177-3

Imaging Features of Petrous Apex Cystic Lesions

Features	Cholesterol Granuloma	Epidermoid	Mucocele
Computed tomography density	Isodense	Hypodense	Hypodense
T1-weighted MRI appearance	Hyperintense	Hypointense	Hypointense
Gadolinium contrast MRI appearance	Nonenhancing	Nonenhancing	Rim enhances; mass is nonenhancing
T2-weighted MRI appearance	Hyperintense	Hyperintense	Hyperintense
Borders of lesion	Smooth	Scalloped	Smooth

MRI, magnetic resonance imaging.
Adapted from Lo WM: Tumors of the temporal bone and cerebellopontine angle. In: Som PM, Bergeron RT, eds. *Head and Neck Imaging*. St Louis: Mosby; 1991:420-445.

Petrous Apex Lesions

Petrous apex lesions constitute an important category of skull base neoplasms that may involve the posterior fossa. Some of the specific lesions have been described earlier under "Common Cerebellopontine Angle Neoplasms." The critical distinction in diagnosis of petrous apex lesions is between cholesterol granulomas, which require drainage procedures, and mass lesions, which generally require complete excision.

Cholesterol Granulomas

A cholesterol granuloma arises in the pneumatized spaces of the temporal bone presumably as a result of occlusion of the air cell system. Hemorrhage into the air cells results in a foreign body reaction and progressive granuloma formation. An expansile lesion of the temporal bone results, with extension into the CPA and resultant signs and symptoms of cranial nerve VIII dysfunction. A recent theory suggests that exposed bone marrow may hemorrhage into the pneumatized petrous apex air cells, producing the foreign body reaction and granuloma formation.[41] This newer concept more adequately explains the presence of cholesterol granuloma in well-pneumatized temporal bones.

The CT and MRI findings with this lesion are distinguishable from those with the other common lesions of the petrous apex (Table 177-3). On CT, the lesions result in a punched-out appearance of the temporal bone with an isodense mass of the petrous apex that does not enhance; however, rim enhancement is evident with intravenous contrast. On MRI, T1- and T2-weighted images are hyperintense with respect to brain (Fig. 177-14). Primary cholesteatomas are the main lesions from which cholesterol granulomas should be distinguished. Cholesterol granulomas are much more common and occur 20 times more frequently than epidermoids. Overall, cholesterol granulomas are relatively uncommon compared with acoustic neuromas. Only 1 cholesterol granuloma is identified for every 35 acoustic neuromas diagnosed. Imaging distinguishes petrous apex epidermoids from petrous apex cholesterol granulomas. On CT, epidermoids show rim enhancement. With MRI, cholesterol granulomas are hyperintense on T1- and T2-weighted images, whereas epidermoids are hyperintense only on T2-weighted images.

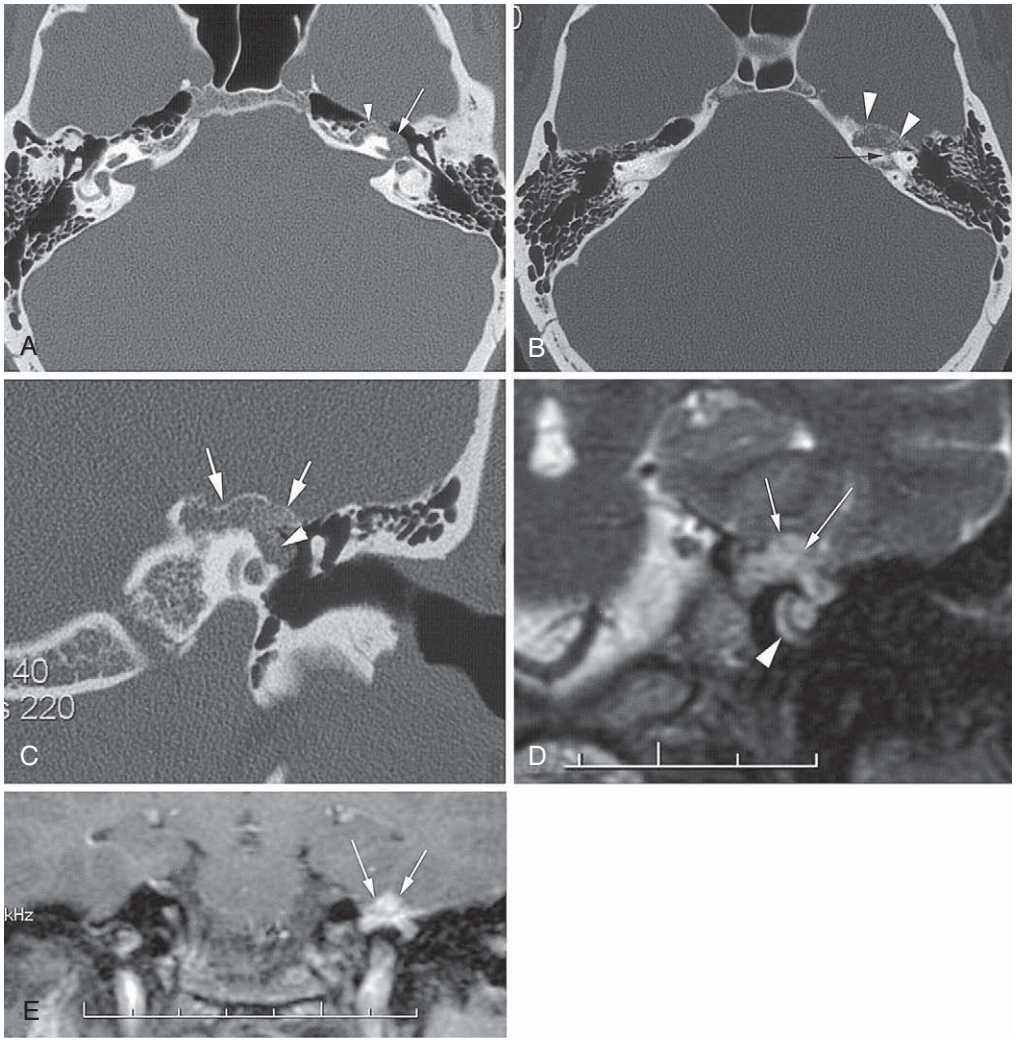

Figure 177-13. Intratemporal vascular tumor in the region of the geniculate ganglion, demonstrated by computed tomography (CT) and magnetic resonance imaging. **A,** CT image through the region of the geniculate ganglion shows expansion of the facial nerve *(arrow)*. Irregular bone is seen extending medially toward the petrous apex *(arrowhead)*. **B,** In this CT image, at a level slightly superior to **A,** demineralization is evident in the region of the labyrinthine segment of the canal *(black arrow)*. Note that the lesion *(arrowheads)* contains small spicules of bone. **C,** Coronal CT image shows the demineralized bone *(arrows)*. The abnormality extends inferiorly to enlarge the FNC *(arrowhead)* and involve the facial nerve. **D,** Coronal T2-weighted image shows the relatively high signal *(arrows)* of the vascular lesion. The fluid within the cochlea *(arrowhead)* is noted for comparison and orientation. **E,** Coronal postcontrast gadolinium T1-weighted magnetic resonance image shows the enhancement *(arrows)* of the lesion. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

Total excision of cholesterol granulomas usually is unnecessary. Drainage may be achieved by a transmastoid or transcanal infralabyrinthine approach with preservation of cranial nerve function. The transcanal, infracochlear, hypotympanotomy approach is preferred because it affords dependent drainage and the possibility of revision, if necessary, through a myringotomy.[42] In cases with unfavorable anatomy for infracochlear or infralabyrinthine drainage, middle fossa drainage is an option. Suprisingly, long-term follow-up imaging has demonstrated that middle fossa catheter drainage to the mastoid remains patent.[43]

Asymmetric Petrous Apex Pneumatization

Although asymmetric pneumatization of the petrous apex does not represent a true neoplasm, this condition can be confused with and should be distinguished from true neoplasms. The fat content of bone marrow in a nonpneumatized petrous apex can produce a hyperintense appearance on T1-weighted noncontrast MRI (Fig. 177-15). The lack of bone destruction or expansion on CT, absence of contrast enhancement with gadolinium, and hypointensity on T2-weighted images distinguish this condition from a neoplasm.

Mucocele, Mucus Retention Cysts, and Petrous Apex Effusion

Petrous apex air cells may become obstructed, resulting in retained secretions as a mucus retention cyst in the petrous apex (Fig. 177-16) or an expansile mucocele (Fig. 177-17). CT reveals a nonenhancing lesion limited to the petrous apex air cell system. The MRI appearance is consistent with a mucus-filled lesion (hypointense on T1-weighted and hyperintense on T2-weighted images). A symptomatic mucocele behaves like chronic mastoiditis, with pressure symptoms that require drainage for relief. Occasionally, retained petrous apex fluid also can cause symptoms even without mucocele. Medical treatment as for a middle ear effusion or surgical drainage usually is therapeutic.[43]

Petrous Carotid Artery Aneurysms

Although aneurysms of the horizontal carotid artery are rare, they may appear as expansile, well-defined masses (Fig. 177-18). Their preoperative identification is critical for obvious reasons. Carotid aneurysms may be confused with chondrosarcomas on the basis of radiologic appearance.

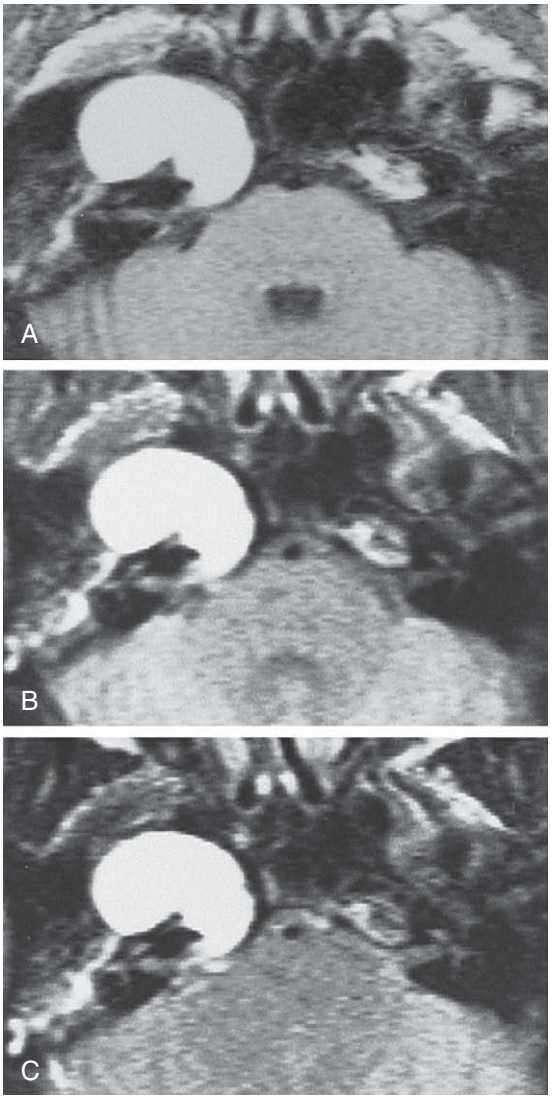

Figure 177-14. Petrous apex cholesterol granuloma, demonstrated by magnetic resonance imaging. **A** to **C,** T1-weighted, proton density, and T2-weighted images, respectively. The lesion is hyperintense on all three images. Note the hypointense rim medial to the lesion accentuated on **B** and **C**, attributable to a hemosiderin deposit or chemical shift artifact. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

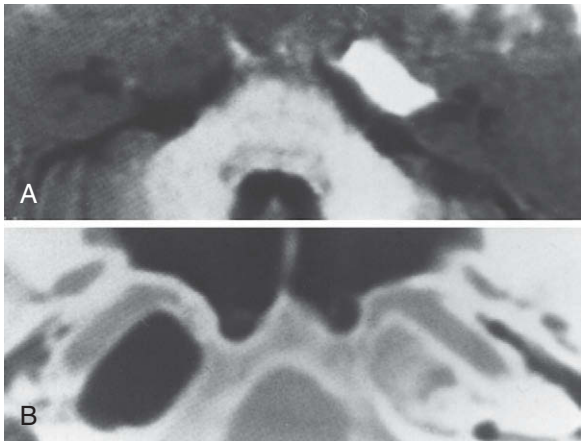

Figure 177-15. Asymmetric pneumatization of the petrous apex, demonstrated on an axial T1-weighted image **(A)** and an axial computed tomography (CT) scan **(B)**. Note that the area of hyperintensity on the T1-weighted image could be confused with a neoplasm. The CT scan reveals extensive pneumatization on the contralateral side and limited pneumatization on the side with hyperintense signal on magnetic resonance imaging.

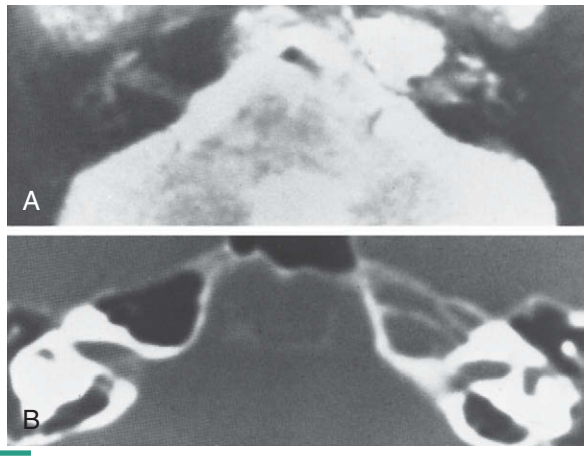

Figure 177-16. Retained mucus in petrous apex air cells, demonstrated on an axial T2-weighted magnetic resonance image **(A)** and an axial computed tomography (CT) scan **(B)**. Note that the mucus is hyperintense on the T2-weighted image, and the CT scan identifies fluid density within the petrous apex air cells.

Giant Cell Tumors

Giant cell tumors are extremely rare primary neoplasms of the temporal bone. They originate from undifferentiated cells of the supporting connective tissue and consist of multinucleated giant cells in a background of spindle-shaped stromal cells. Patients with this unusual condition demonstrate retrocochlear signs and symptoms. CT typically shows a diffuse lesion of the temporal bone compressing the contents of the internal auditory canal.

Miscellaneous Cerebellopontine Angle Lesions

Metastatic Tumors

Tumors may metastasize to the CPA from other sites, including lung, breast, prostate, oropharynx, and skin (i.e., cutaneous melanomas).[44] Tumors from these sites are distinguished by their rapid progression of symptoms and associated neurologic signs, in addition to hearing loss and dizziness. Associated lytic lesions in the petrous apex constitute another distinguishing feature of metastatic tumors. Rapid impairment of hearing, other cranial neuropathies, and brainstem dysfunction suggest malignant neoplasms of the posterior fossa, especially in a patient with a history of another malignancy.

Chordomas

Chordomas are dysontogenetic neoplasms that arise in remnants of the embryonic notochord. Although more than one half of these tumors arise in the sacrococcygeal region, more than one third occur at the skull base in the region of the clivus or, less commonly, the upper cervical vertebrae.[45] The prominent clinical characteristics are extensive bone destruction and progressive cranial nerve palsies. Extension of clivus chordomas to the petrous apex, sphenoid, or CPA is not unusual. Although fronto-orbital headache and vision complaints (e.g., limited visual fields, diplopia, loss of acuity) are more common, occasionally the initial symptoms reflect extension into the CPA. On CT, the bone destruction is readily apparent, and the masses are homogeneous with moderate enhancement and a greater density than that of bone

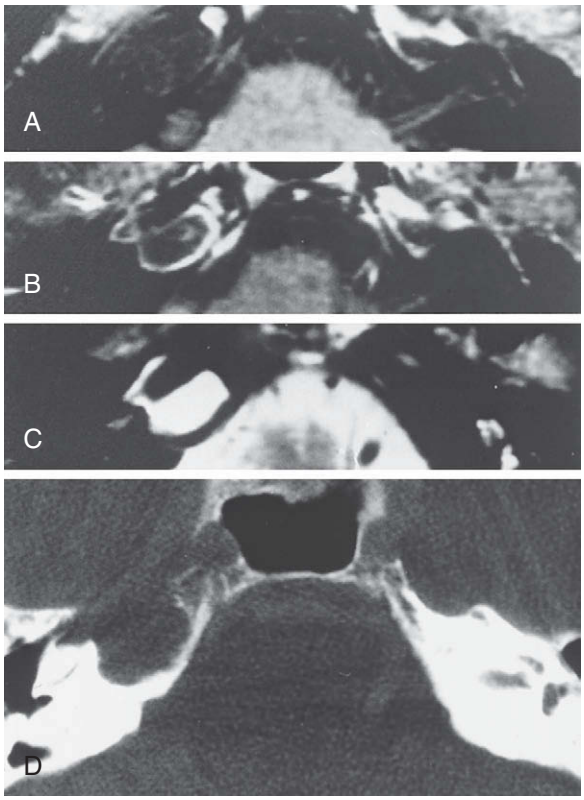

Figure 177-17. **A** to **C,** Axial magnetic resonance images of a petrous apex mucocele: T1-weighted without gadolinium **(A),** T1-weighted with gadolinium **(B),** and T2-weighted **(C).** The lesion is hypointense on the T1-weighted image and shows only rim enhancement with the addition of gadolinium. Note the hyperintensity of the mucocele on the T2-weighted image. **D,** Axial computed tomography scan of the same lesion. Note that the expansile lesion has eroded the petrous apex.

(Fig. 177-19). MRI reveals isointensity on T1-weighted images and hyperintensity on T2-weighted images (Fig. 177-20).

Chondrosarcomas

Chondrosarcomas of the skull base also may arise in the CPA. They are clinically indistinguishable from chordomas except that they are centered more laterally. CT shows characteristic bone destruction and invasiveness. MRI shows this lesion well, which is hyperintense on T2-weighted images in the area of bone destruction in the skull base (Figs. 177-21 and 177-22).

Lipomas

Lipomas are hamartomas that are thinly encapsulated and poorly delineated. They appear as soft, multilobular masses of typical adult adipose tissue. Lipomas within the internal auditory canal can produce symptoms typical of an acoustic neuroma. Although on CT these lesions are less dense than neuromas, MRI is diagnostic. The lesions are hyperintense on T1-weighted images, nonenhancing with gadolinium, and hypointense on T2-weighted images (Fig. 177-23). Fat-suppression techniques with T1-weighted sequences are confirmatory because the previously identified lesion that was hyperintense on nonenhanced T1-weighted images is rendered hypointense with fat suppression (Fig. 177-24).

Dermoid Tumors

A dermoid is a skin-lined cystic tumor containing dermal and adnexal structures. The lining of the cyst is mature, stratified squamous epithelium. A dermoid is a slowly expanding lesion that produces symptoms similar to those of a primary cholesteatoma. It may be differentiated

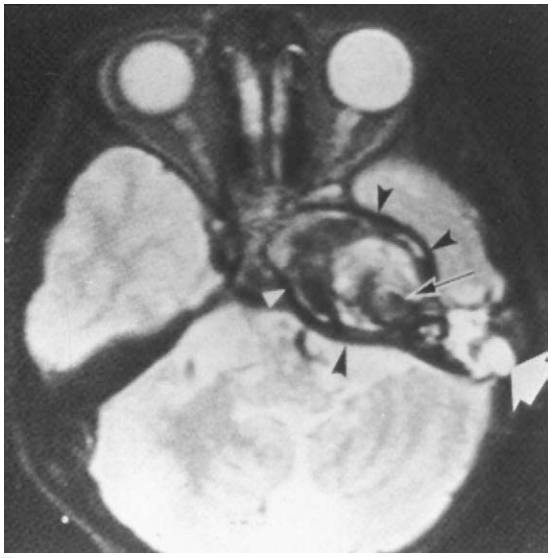

Figure 177-18. Axial T2-weighted magnetic resonance image of a petrous carotid aneurysm. The lesion is heterogeneous and shows decreased signal intensity within the thrombus. The circumscribing areas of low signal intensity *(arrowheads)* probably represents hemosiderin. The lumen *(long thin arrow)* has intermediate signal intensity as a result of slow flow as noted on the arteriogram *(not shown)* and is difficult to distinguish from thrombus. High-signal-intensity fluid is seen in multiple mastoid air cells *(short wide arrow).* *(From Tsuruda JS, Halbach VV, Higashida RT, Mark AS, Hieshima GB, Norman D. MRI evaluation of large intracranial aneurysms using cine low flip angle gradient-refocused imaging.* Am J Neuroradiol. *1988;9:418.)*

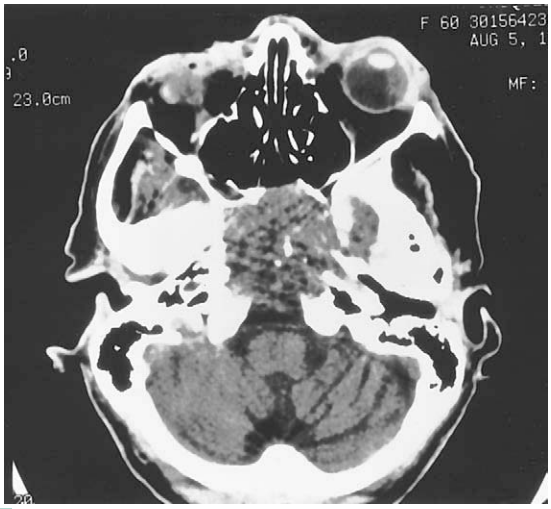

Figure 177-19. Axial computed tomography scan shows a large midline chordoma involving the petrous apex bilaterally.

on CT as a nonhomogeneous cystic mass that contains calcium but that is otherwise less dense than brain.

Teratomas

Teratomas arise from multipotential cells that differentiate into various tissues, representing more than one germ layer. They contain ectodermal, mesodermal, and endodermal tissues. Carcinomatous or sarcomatous changes occur in 10% to 35% of these tumors. When malignant degeneration occurs, symptoms progress rapidly; otherwise, slow progression is the rule, making the lesions indistinguishable from other benign CPA tumors. CT shows a nonhomogeneous lesion of less density than brain without enhancing characteristics.

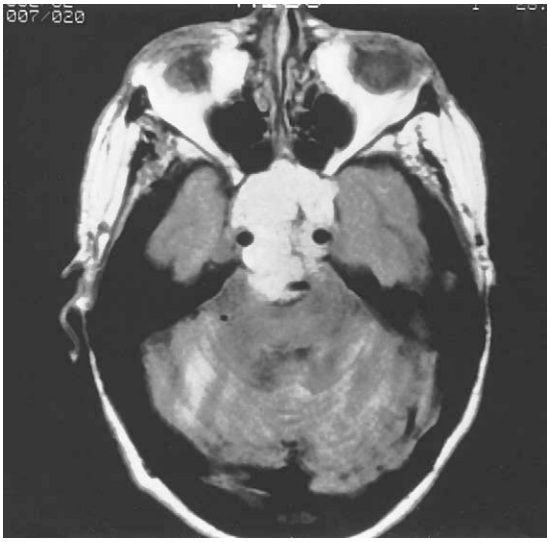

Figure 177-20. Noncontrast T1-weighted axial magnetic resonance image of the same chordoma as in Figure 177-19.

Intra-axial Tumors

Intra-axial tumors may occasionally be confused with CPA tumors as a result of extension to the CPA or compression of CPA structures. Intra-axial tumors may arise from the brainstem (gliomas), the cerebellum (medulloblastomas from the vermis or astrocytomas from the peduncles), or the fourth ventricle (choroid plexus papillomas and ependymomas). Although such lesions are highly unusual, the possibility cannot be ignored. In children, brainstem gliomas are reportedly the most common CPA neoplasms. Intra-axial tumors usually are isointense on T1-weighted MRI and hyperintense on T2-weighted images.[20,21]

Hemangioblastomas

Hemangioblastomas are tumors of blood vessel origin occurring primarily in the cerebellum. They also may occur in the cerebral hemispheres and in association with a similar retinal tumor and may be multicentric. Although histologically benign, hemangioblastomas may produce major neurologic dysfunction by compression of the brainstem.

Rapidly progressive signs and symptoms of cerebellar dysfunction are characteristic of this tumor. Hearing and balance are likely to remain normal. Imaging studies identify a tumor intrinsic to the cerebellum that may extend into the CPA.

Medulloblastomas

Medulloblastomas arise from the cells of the external granular layer of the cerebellar folia. They may appear as exophytic masses on the cerebellum with extension into the CPA. Symptoms are produced by destruction of cerebellar tissue and mass effect of the tumor on the CPA's adjacent structures.

Medulloblastomas are characterized by a rapid development of symptoms. In addition to hearing loss and dizziness, associated neurologic findings include facial weakness, dysmetria of speech and hand motion, perverted nystagmus, and abnormal peripheral reflexes. Temporal bone imaging findings are normal, but CT and MRI show a lesion intrinsic to the cerebellum.

Brainstem Gliomas

Exophytic gliomas may arise on the surface of the pons and grow into the CPA. Gliomas also may be intrinsic to the brainstem. Exophytic gliomas may produce signs and symptoms similar to those of acoustic neuromas, whereas the intrinsic variety produces predominantly long tract signs.

Patients with exophytic lesions may be diagnosed preoperatively to have acoustic neuromas. Long tract signs in association with characteristic brainstem distortion on imaging make preoperative diagnosis possible in the patients with intrinsic lesions.

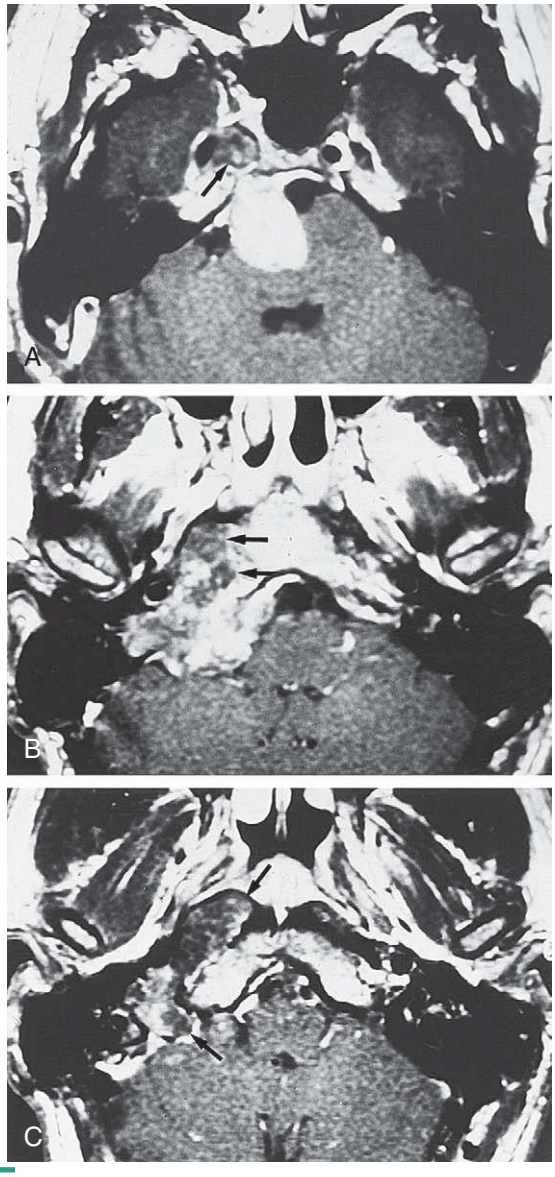

Figure 177-21. Right petrous apex chondrosarcoma. **A** to **C,** On gadolinium T1-weighted magnetic resonance imaging, the mass is markedly but inhomogeneously enhancing, with components containing small, poorly enhancing or nonenhancing foci in Meckel's cave (*arrow* in **A**) and in the petrous apex (*arrows* in **B**), as well as involvement of the longus colli muscle and jugular fossa (*arrows* in **C**). Note the markedly enhancing transdural components in the posterior fossa and the dural "tail" in **A** and **B**. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

Tumors of the Fourth Ventricle

Malignant Choroid Plexus Papillomas and Ependymomas

Choroid plexus papillomas and ependymomas arise from the fourth ventricle and cause CPA symptoms by growing through the foramen of Luschka. In this location, they produce early signs of cranial nerve VIII dysfunction. In malignant choroid plexus papillomas, CT shows a mass with enhancing characteristics of a schwannoma (Fig. 177-25). These tumors are distinguishable from an acoustic schwannoma by being separate from the internal auditory canal. Ependymomas may

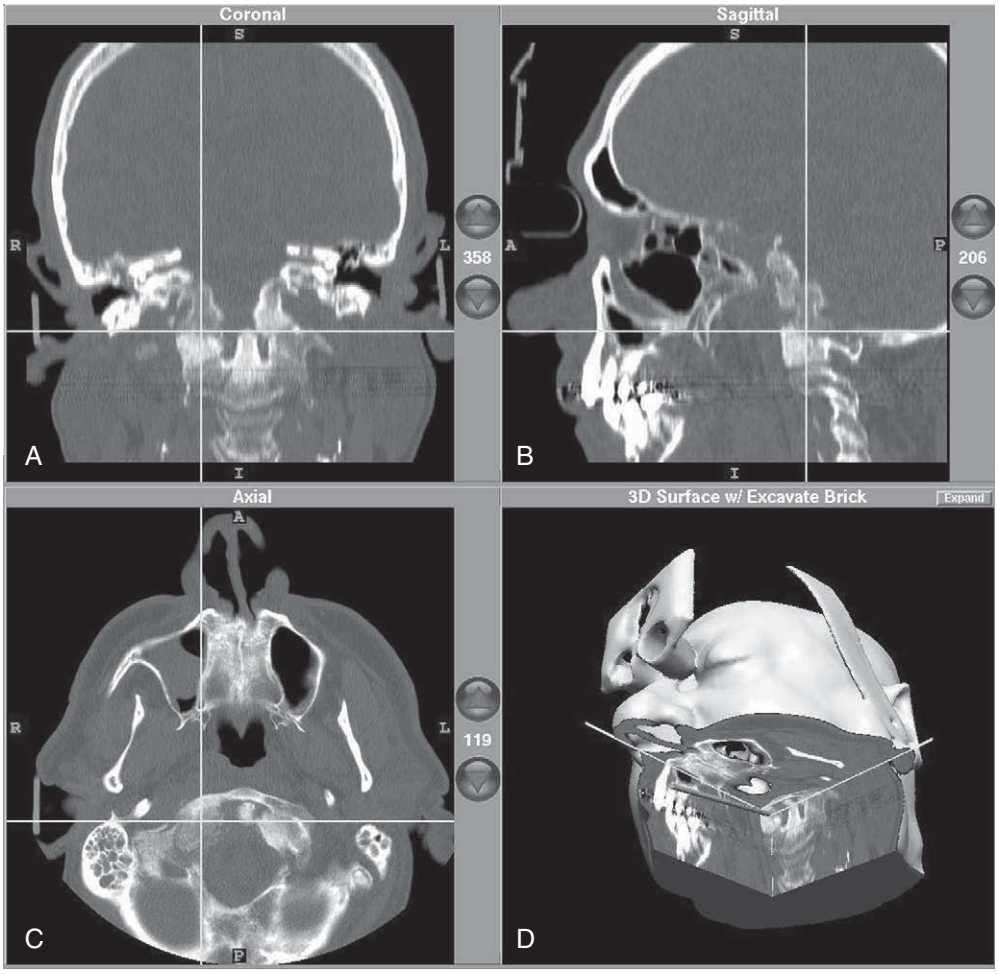

Figure 177-22. Skull base chondrosarcoma, demonstrated by magnetic resonance imaging. **A** and **B,** Axial T1-weighted pre- and postgadolinium images. **C,** Axial T2-weighted images. **D,** Coronal T1-weighted image after gadolinium enhancement. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

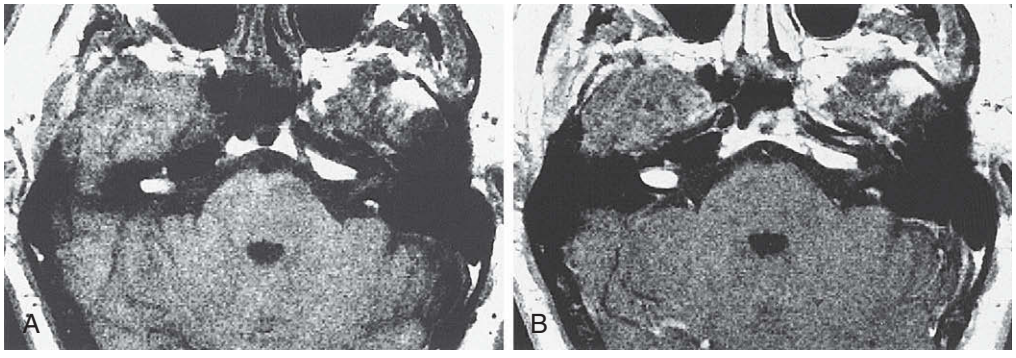

Figure 177-23. Lipoma of the right internal auditory canal, demonstrated by magnetic resonance imaging. **A,** T1-weighted image without gadolinium enhancement. **B,** Postgadolinium T1-weighted image. The lipoma has high signal intensity without gadolinium, which does not change after administration of contrast. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

calcify, and those portions have variable imaging characteristics. At MRI, both lesions are isointense to brain on T1-weighted images and mildly hyperintense to brain on T2-weighted images (Fig. 177-26). Malignant ependymomas require multimodality therapy. The role of surgery is for biopsy, brainstem decompression, and management of hydrocephalus.

Surgery of the Posterior Cranial Fossa

This section addresses surgical management of extra-axial lesions of the posterior cranial fossa and internal auditory canal. Adequate exposure for skull base neoplasms involving the posterior fossa requires precise management of the temporal bone. The modern era for skull base surgery and transtemporal techniques began in 1961, when House

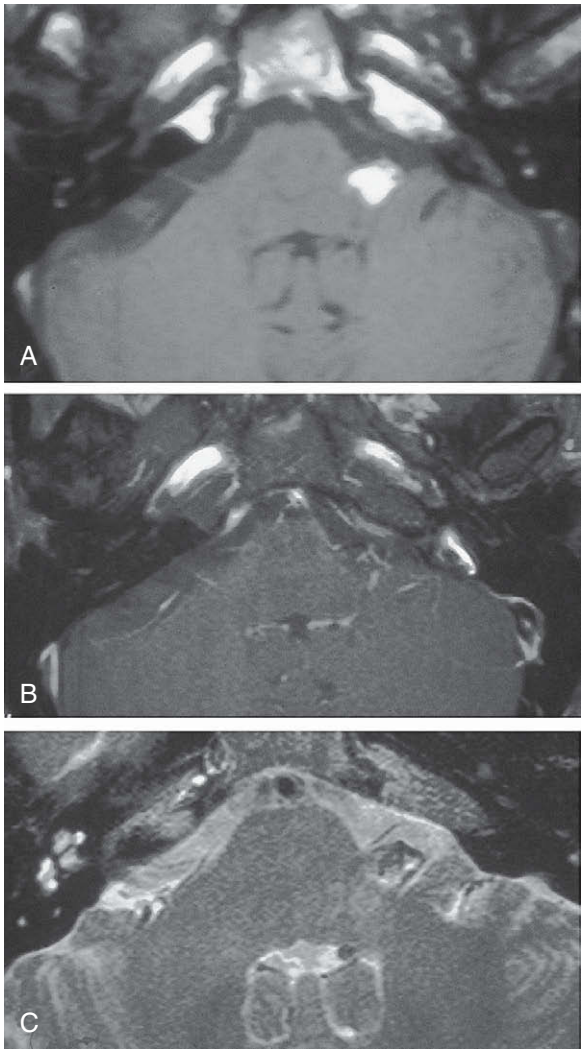

Figure 177-24. Cerebellopontine angle lipoma, demonstrated by magnetic resonance imaging. **A** and **B,** T1-weighted and fat-saturated post-gadolinium images. The signal intensity of the tumor is similar to that of bone marrow. Note the signal loss of the tumor and fatty bone marrow on the fat-saturated images. No enhancement of the lesion is seen. **C,** T2-weighted image. The lipoma typically is moderately hypointense and is seen with surrounding signal void vessels. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

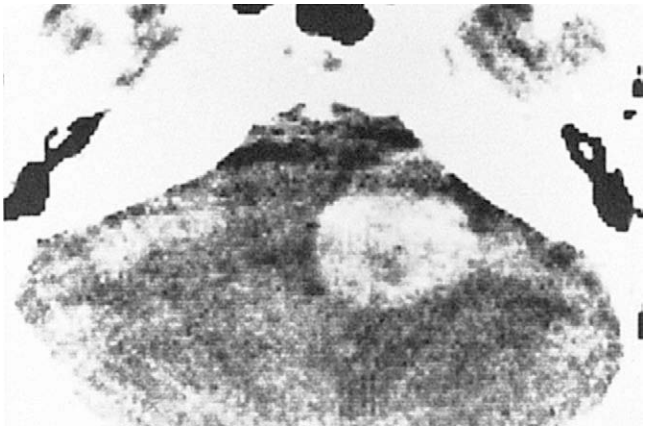

Figure 177-25. CPA choroid plexus papilloma, demonstrated by contrast computed tomography. The tumor is located at the foramen of Luschka. It is more sharply defined than an ependymoma. Like a giant aneurysm, it is detached from the petrous bone, in contrast with schwannomas and meningiomas. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003.)*

introduced the operating microscope and multidisciplinary team surgery for removal of acoustic neuromas. With the vastly reduced mortality and excellent facial nerve preservation rates of the translabyrinthine approach for acoustic neuromas, House established the translabyrinthine approach as the procedure with which all other microsurgical approaches to the CPA are compared.[46] Subsequently, multiple approaches to the CPA have been developed, each with its own advantages and indications.

Thus, the modern skull base surgical team can choose from among various approaches for resection of posterior fossa neoplasms. The procedure should be tailored to the individual patient's pathology and physiologic status. Realistic counseling of patients is critical for informed decisions concerning surgical approaches and possible cranial nerve sequelae. Skull base surgery is a team endeavor, and the full array of experts familiar with the specific needs of these patients is necessary for a successful outcome.

This section details the basic approach, specific indications, techniques, and special features of the translabyrinthine, retrosigmoid, suboccipital, retrolabyrinthine, transcochlear, transotic, middle fossa, extended middle fossa, and petrosal approaches for skull base neoplasms involving the posterior fossa. Table 177-4 summarizes the basic indications for and drawbacks of the various approaches for resection of these tumors.

In addition, the surgical approaches for skull base lesions that are adequately managed by drainage also are reviewed. A method for selecting the surgical approaches for removal of acoustic neuromas suitable for hearing preservation is presented, and general principles of patient management and management of complications of posterior fossa tumor surgery are outlined.

Translabyrinthine Approach

Basic Approach

A transmastoid labyrinthectomy and skeletonization of the sigmoid sinus and posterior fossa dura permit identification of the facial nerve with wide exposure of the internal auditory canal and CPA (Fig. 177-27).

Indications

The translabyrinthine approach is the principal neuro-otologic approach for all lesions of the CPA and internal auditory canal. This technique is ideal for removal of medium-sized and large acoustic neuromas, because hearing preservation is unlikely by any approach in tumors larger than 2 cm and because this approach carries the highest rate of preservation of facial nerve function. Small acoustic neuromas in patients without serviceable hearing also are removed by the translabyrinthine approach.

The approach is suited for removal of any neoplasms requiring exposure of the CPA, including meningiomas, nonacoustic neuromas, gliomas, chordomas, and skull base chondrosarcomas. In addition, if serviceable hearing is not present, the translabyrinthine approach is useful for complete facial nerve decompression and vestibular neurectomy.

Technique

The following discussion details patient positioning, preparation, monitoring, and tumor removal for the translabyrinthine approach. The same techniques are used for the other approaches except when otherwise specified.

The patient is positioned supine with the head turned to the opposite side. Head-holding pins or supports are not used. Electromy-

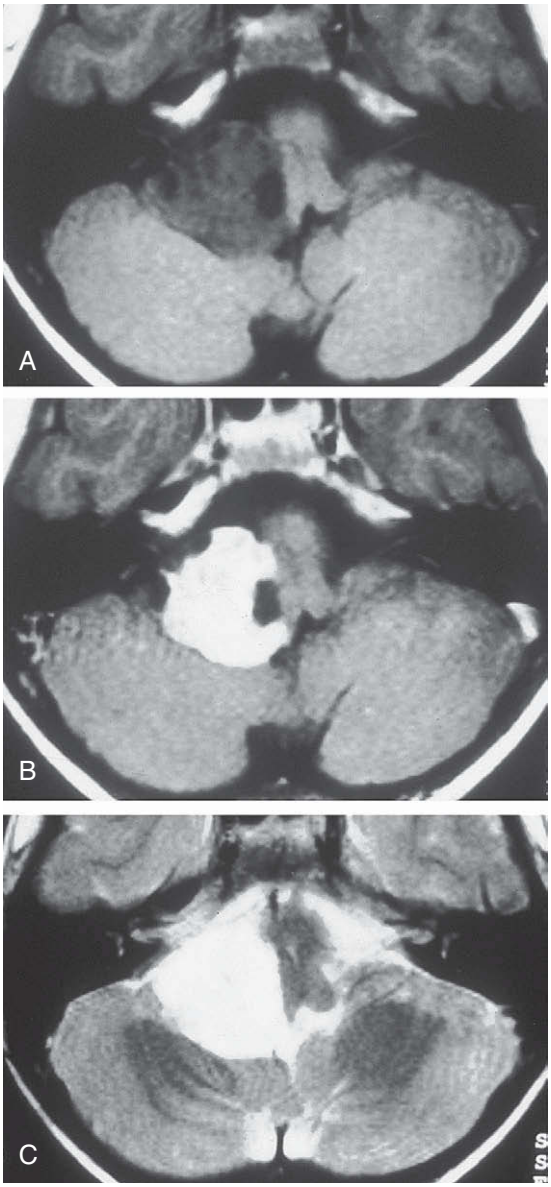

Figure 177-26. CPA ependymoma, demonstrated by magnetic resonance imaging. **A** and **B,** Pre- and postgadolinium images. The mass protruding into the right CPA from the foramen of Luschka shows clear demarcation and strong enhancement. **C,** T2-weighted image. The tumor is hyperintense and does not extend into the IAC. *(From Maya MM, Lo WWM, Kovanlikaya I. Temporal bone tumors and cerebellopontine angle lesions. In: Som PM, Curtin HD, eds.* Head and Neck Imaging. *4th ed. Philadelphia: Mosby; 2003:240-250.)*

ography (EMG) electrodes for intraoperative facial nerve monitoring are inserted into the orbicularis oris and orbicularis oculi. Intravenous antibiotic is administered when the patient arrives in the operating room. Antibiotic also is used in the irrigation solution. Hyperventilation usually is sufficient for brain relaxation.

The curved postauricular incision is made with the apex 3 cm posterior to the postauricular crease. The soft tissue and periosteum are elevated from the mastoid and adjacent occipital bone, and self-retaining retractors are inserted.

The bone removal is accomplished in four stages and is performed using the operating microscope, a high-speed drill, and continuous suction-irrigation.[5] Most of the drilling is performed with cutting burrs; however, diamond burrs are used when drilling is performed on the dura or venous sinuses. The *first stage* is a complete mastoidectomy.

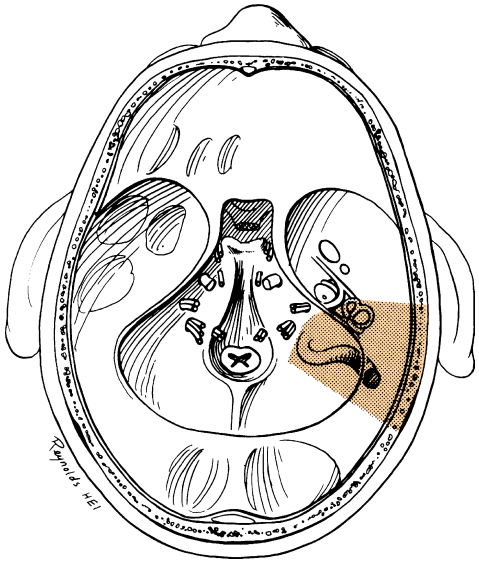

Figure 177-27. Surgical exposure in the translabyrinthine approach to the cerebellopontine angle (CPA). This approach permits direct access to the CPA without retraction of the cerebellum.

Posteriorly, the bone is removed beyond the sigmoid sinus, and the sinus is skeletonized. The extent of bone removal posterior to the sinus and decompression of the posterior fossa depends on the size of the tumor. Greater posterior removal provides greater exposure of the CPA. Superiorly, the middle fossa plate is identified and thinned. Anteriorly, the facial nerve is identified in its vertical segment but left covered with bone for protection against inadvertent burr trauma.

The *second stage* is complete labyrinthectomy. The horizontal, superior, and posterior semicircular canals are systematically removed. Particular care is required in working along the inferior border of the horizontal canal because of the proximity of the facial nerve, and along the ampulated end of the posterior canal because this end lies medial to the facial nerve.

The *third stage* of bone removal consists of actual decompression of the middle and posterior fossa dura and removal of bone around the internal auditory canal. The bone overlying the posterior fossa is removed with cutting and diamond burrs, except for an island of bone over the sigmoid sinus ("Bill's island"). The mastoid emissary vein should be transected to permit retraction of the sinus and posterior fossa dura. Accordingly, bleeding from the emissary should be controlled with sutures, cautery, or bone wax. The petrous ridge, which is the junction between the middle fossa dura and the posterior fossa dura, should be removed. The superior petrosal sinus, which lies under the petrous ridge, is sometimes adherent to the bone. The resulting bleeding is controlled with bipolar cautery or extradural packing with oxidized cellulose strips (Surgicel). The entire middle fossa dura and posterior fossa dura adjacent to the mastoid are exposed.

The *final stage* of bone removal consists of skeletonization of the internal auditory canal. The orientation of this structure is roughly parallel to the external auditory canal. Thus, the fundus of the canal is just medial to the floor of the vestibule, which was exposed during the labyrinthectomy. By contrast, identification of the porus requires extensive bone removal as the internal auditory canal is dissected medially. The basic principle of exposing the internal auditory canal is that all bone removal should be accomplished before the dura is opened, and complete bone removal requires decompression of 270 degrees around the circumference of the canal to avoid obscuring any ledges of bone. By completing bone removal before opening the dura, the risk of accidental injury to the nerves of the internal auditory canal is minimized. The inferior border of the canal is skeletonized first. This edge of the canal is identified by gradually enlarging a trough between the inferior edge of the vestibule and the jugular bulb. The cochlear aqueduct

Table 177-4

Surgical Approaches for Resection of Posterior Fossa Skull Base Neoplasms: Indications, Advantages, and Disadvantages

Approach	Indications	Advantages	Disadvantages
Translabyrinthine	Large, medium-sized, or small cerebellopontine angle tumor	Wide exposure not limited by tumor size; facial nerve identified at the cerebellopontine angle and fundus of the internal auditory canal; immediate repair of facial nerve is possible; bone removal is extradural; limited cerebellar retraction	Total hearing loss
Retrosigmoid (suboccipital)	Cerebellopontine angle tumors without extensive internal auditory canal involvement	Hearing preservation possible; wide exposure; familiarity to most neurosurgeons	Internal auditory canal fundus not exposed in hearing preservation cases; cerebellar retraction may produce hydrocephalus; intradural drilling may result in severe headaches
Retrolabyrinthine	Selected cerebellopontine angle lesions without internal auditory canal involvement, biopsy of cerebellopontine angle lesions	Hearing preservation possible; bone removal is extradural; no cerebellar retraction	Limited exposure
Transcochlear	Extensive lesions of petrous apex and clivus	Wide exposure of skull base with access to clivus and vertebral and basilar arteries and full exposure of petrous carotid artery	Temporary facial nerve paralysis; total hearing loss
Transotic	Same as for transcochlear; some advocate use in acoustic neuromas with unfavorable venous anatomy	Same as for transcochlear; no facial nerve transposition	Facial nerve in the internal auditory canal and mastoid segments limits exposure; total hearing loss
Middle fossa	Intracanalicular tumors with minimal cerebellopontine angle involvement and good hearing	Hearing preservation possible	Small tumors only; temporal lobe retraction
Extended middle fossa	Petroclival lesions involving posterior and middle fossa with good hearing	Hearing preservation possible	Extensive temporal lobe retraction
Petrosal	Large petroclival lesions with good residual hearing	Widest posterior and middle fossa exposure available	Cerebellar and temporal lobe retraction

usually is identified as the dissection proceeds anteromedially. This structure becomes the inferior limit of the dissection, thereby protecting the lower cranial nerves from injury. After the inferior border of the internal auditory canal has been identified, the bone overlying the porus acusticus is thinned with cutting and diamond burrs. The superior border of the canal is identified last, because the facial nerve is more susceptible to injury in this area. A burr size that will fit between the middle fossa dura and the superior border of the internal auditory canal is used to expose the superior border. The entrance of the facial nerve into the canal can be positively identified just medial to a vertical crest of bone, "Bill's bar," along the superior aspect of the fundus. At this point, the bony exposure has been completed, and tumor removal can begin (Fig. 177-28).

Tumor Removal

With small lesions, opening the dura of the internal auditory canal exposes the tumor. Attention is focused on the fundus of the canal, and an angled hook placed lateral to Bill's bar is used to reflect the superior vestibular nerve inferiorly and then transect it. This maneuver protects the facial nerve and identifies the lateral plane between the facial nerve and the tumor. Sharp and blunt dissection can proceed with scissors and angled hooks from lateral to medial, but without actually placing traction on the facial nerve. With some small tumors, the dissection can be completed entirely without debulking.

With large tumors, CPA exposure is necessary. Intracapsular tumor debulking is completed before the tumor is dissected directly from the facial nerve. In essence, a large tumor is reduced to a small tumor. The dural flaps are developed carefully to avoid injury to the underlying petrosal vein or even branches of the anterior inferior cerebellar artery that can reach the dura. The incision is placed midway between the sigmoid sinus and the porus acusticus. The incision is carried directly to the porus and then continued in a curve around the porus.

Debulking should be accomplished to allow positive identification of the facial nerve medial to the tumor and to complete dissection of the tumor from the brainstem. Vessels that do not actually enter the tumor are reflected away, and the posterior aspect of the tumor is incised. Intracapsular debulking is accomplished with small dissection

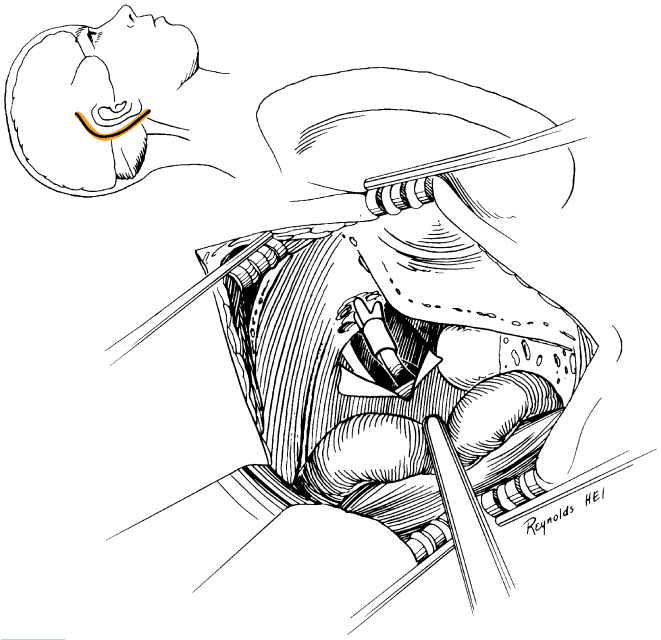

Figure 177-28. Surgical exposure in the translabyrinthine approach to the cerebellopontine angle (CPA). This approach permits positive identification of the facial nerve in its bony canal at the fundus of the internal auditory canal and at the brainstem. *Inset* shows skin incision in relation to the CPA.

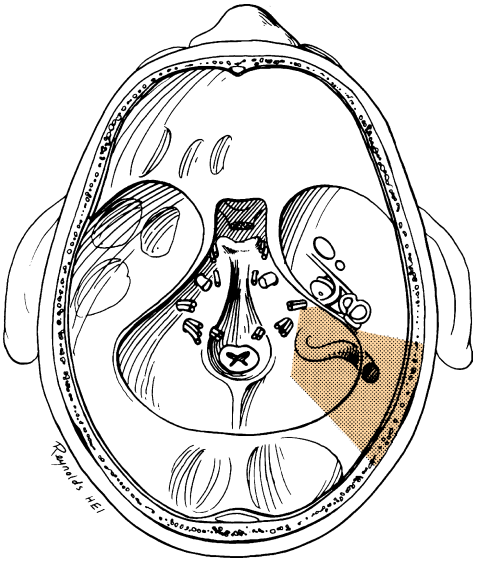

Figure 177-29. Surgical exposure in the retrosigmoid approach to the cerebellopontine angle (CPA). This approach permits wide access to the CPA; however, the cerebellum is between the surgeon and the CPA. Thus, cerebellar support (retraction) is required to permit complete visualization of the CPA.

forceps, scissors, or a rotatory dissector (e.g., House-Urban dissector) or one of the power dissectors used in endoscopic sinus surgery. Some surgeons prefer to use the laser or ultrasonic aspirator for debulking. Such intracapsular debulking permits the tumor to collapse onto itself for easier manipulation during its dissection from the facial nerve. The arachnoid sheath that binds the tumor to the nerve anteriorly is released with small hooks.

In tumor dissection, it is important to avoid pushing the tumor medially into the CPA, because this maneuver stretches the nerve at its lateral fixed bony attachment. The tumor and capsule are removed by separating them completely from the facial nerve. Once tumor debulking is completed and the facial nerve is identified medially, attention is focused on the fundus of the internal auditory canal. Final tumor dissection proceeds as for a small tumor. In this manner, most of the tumor has been removed, while the facial nerve has been protected in the dura of the internal auditory canal.

After tumor removal, eustachian tube closure is achieved by removing the incus, transecting the tensor tympani tendon, and filling the eustachian tube with Surgicel. The temporalis muscle closes the eustachian tube. By opening the facial recess during drilling, the surgeon obtains wide exposure for eustachian tube occlusion. The edges of the dura are approximated with sutures, and the mastoidectomy defect is filled with strips of abdominal fat. The ends of the strips are placed through the dural defect to plug the dural opening. Cranioplasty with use of hydroxyapatite cement or titanium mesh is a useful technique to reduce the incidence of CSF fistula postoperatively and to enhance long-term wound healing and the cosmetic result.[47,48] The wound is closed in layers, and a compressive dressing is applied.

Special Features

The translabyrinthine approach provides wide and direct access to CPA tumors with minimal cerebellar retraction. The versatility of this approach for large and small tumors makes it the most common approach for resection of acoustic neuromas.

The fundamental advantage of the translabyrinthine approach, particularly in medium-sized and large tumors, is that it permits positive identification of the facial nerve, laterally at the fundus and medially at the brainstem. Thus, the tumor can be dissected from either direction with optimal control of the facial nerve. Such medial and lateral identification of the nerve has permitted anatomic preservation of the facial nerve in greater than 98.5% of 759 acoustic neuromas removed in one large surgical series.[49] Furthermore, if the facial nerve is transected, as occurs in cases of CPA facial nerve neuroma, the tympanic and mastoid portions of the nerve are available for rerouting and reanastomosis or grafting.

Properly performed, with wide exposure of the middle and posterior fossae, the translabyrinthine approach provides exposure of the CPA as good as with any other neurosurgical approach; however, the direct route of exposure of the CPA eliminates the need for cerebellar support (retraction).

The disadvantage of this approach is that hearing cannot be preserved. In a series of 300 consecutive cases of acoustic neuromas diagnosed before the advent of gadolinium-enhanced MRI, only 5% of patients, using the broadest criteria, could be considered candidates for hearing conservation surgery.[50] The advent of gadolinium-enhanced MRI resulted in an increased percentage of acoustic neuromas among those detected, which are diagnosed at a small size before hearing is affected. Thus, hearing conservation procedures are becoming a more frequent consideration.

Retrosigmoid (Suboccipital) Approach

Basic Approach

Transmastoid decompression of the sigmoid sinus and a retrosigmoid craniotomy permit access to CPA tumors without disturbing the labyrinth. Intradural removal of the posterior wall of the internal auditory canal permits direct access to the medial two thirds of the canal (Fig. 177-29).

Indications

Because the principal advantage of this approach is hearing preservation, this technique is excellent for removal of acoustic neuromas of the CPA in patients with serviceable hearing and limited involvement of the internal auditory canal. Nonacoustic neoplasms of the CPA that do not involve the internal auditory canal, such as meningiomas, can be approached in this fashion with an opportunity for hearing preservation.

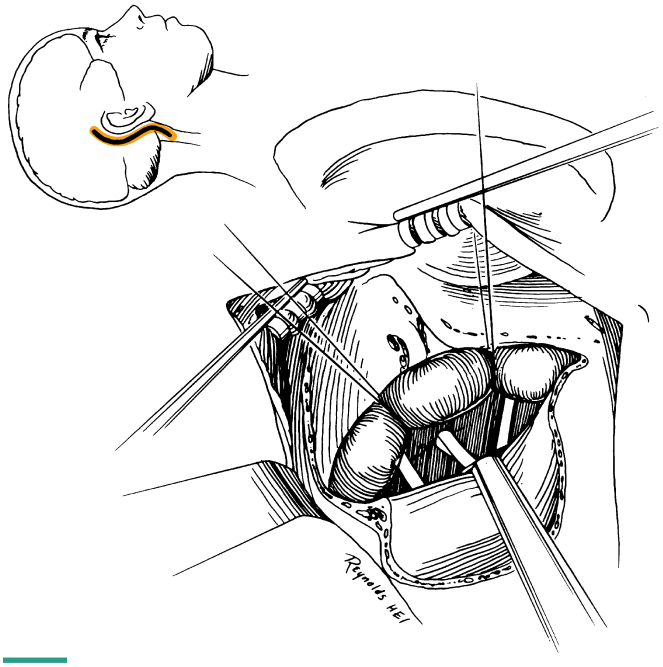

Figure 177-30. Surgical exposure in the retrosigmoid approach to the cerebellopontine angle (CPA). The mastoidectomy in conjunction with the retrosigmoid exposure permits anterior retraction of the sigmoid sinus, which improves anterior exposure. The mastoidectomy also allows positive identification of the posterior semicircular canal, which facilitates removal of the posterior lip of the internal auditory canal. *Inset* shows skin incision in relation to the CPA.

Technique

The soft tissues of the ear are reflected anteriorly and the muscles are widely reflected from the retromastoid region. Complete mastoidectomy is performed, and the sigmoid sinus is skeletonized and decompressed. The posterior semicircular canal also is skeletonized, and the posterior fossa dura up to the posterior semicircular canal is exposed. This area of exposed dura identifies the location of the posterior semicircular canal if the posterior lip of the internal auditory canal needs to be removed later in the procedure. A bone flap is removed posterior to the sigmoid sinus with the otologic drill. This flap can be preserved for replacement at the conclusion of the procedure. Alternatively, in cases with favorable venous anatomy, a craniectomy with skeletonization of the dura and sinus can be performed without entering the presigmoid mastoid air cells.

The dura is incised posterior to the sigmoid sinus, with care taken to avoid injury to the underlying vessels that may be adherent to the dura. Adequate drainage of CSF is necessary to minimize the need for cerebellar retraction. The cerebellum is exposed and supported with retractors to allow visualization of the tumor in the CPA. The neurosurgical techniques for tumor removal at the brainstem are the same regardless of the approach chosen. If the tumor is too large to permit proximal identification of the facial nerve, debulking of the tumor is performed. Once the debulking has been accomplished, the tumor is dissected from the facial nerve toward the porus acusticus (Fig. 177-30).

If the tumor extends into the internal auditory canal, the posterior lip of the canal is removed with diamond burrs. A dural flap is created lateral to the porus and reflected medially. Drilling of the posterior lip of the canal is continued until the lateral extent of the tumor is visualized. The anatomic limit for exposure of this posterior lip that will preserve hearing is the posterior semicircular canal. Attention to the area of dura previously exposed just posterior to the posterior semicircular canal will direct the surgeon to the precise location of the posterior canal when the posterior lip of the internal auditory canal is removed. Once the lateral limit of the tumor has been identified, tumor removal is accomplished in the same manner as with the translabyrinthine approach.

Unlike in the translabyrinthine approach, in which Bill's bar permits definitive identification of the facial nerve at the fundus, in the retrosigmoid approach the surgeon relies primarily on the facial nerve monitor for identifying the nerve laterally in the internal auditory canal. Once the location of the nerves is known medially and laterally, the tumor usually can be removed with preservation of the facial nerve. With surgery attempting hearing preservation, the cochlear nerve also should be preserved. Particular care is taken to preserve the blood supply to the internal auditory canal, because hearing preservation depends on an intact blood supply.

After tumor removal, the edges of the dura are reapproximated, and the mastoid and the internal auditory canal are obliterated with abdominal fat. The bone flap is replaced and the wound is closed in separate layers. A compressive dressing is applied. Alternatively, fat with hydroxyapatite cement or titanium can be used.

Special Features

The retrosigmoid approach, in selected cases, offers an opportunity for hearing preservation, with success rates ranging from 30% to 65%, depending on the selection criteria used for hearing preservation surgery.[51-53] This approach is particularly useful for removal of CPA tumors smaller than 2 cm in patients with good hearing and limited involvement of the internal auditory canal. The principal limitation of this approach is that the fundus of the canal is not directly visualized. This approach is being used more frequently as small tumors of the CPA are diagnosed with enhanced MRI and minimal auditory symptoms.

Extension of tumor to the fundus is a relative contraindication to use of the retrosigmoid approach for hearing preservation. With the retrosigmoid approach, tumor removal in the fundus is accomplished by "feel" with hooks or indirect visualization with mirrors and endoscopes. This approach risks leaving residual tumor.

Bill's bar in the fundus of the internal auditory canal cannot be used to identify the facial nerve laterally in the retrosigmoid approach. Thus, this step is more difficult in the retrosigmoid approach and relies more heavily on the nerve monitor. Although the rates of facial nerve preservation are comparable for the translabyrinthine and the retrosigmoid techniques, in our experience, facial nerve preservation rates are better with the translabyrinthine approach because it allows positive identification of the facial nerve in medial and lateral directions.[52,54,55]

A 10% incidence of severe postoperative headaches has been reported with this approach.[56] This symptom may be related to the intradural spread of bone dust, which occurs as a result of drilling the posterior lip of the internal auditory canal. Unlike in the translabyrinthine approach, drilling should be intradural in the retrosigmoid approach. Replacing the retrosigmoid bone flap with microplates or cranioplasty with synthetic materials has reduced the incidence of headaches with retrosigmoid surgery, suggesting that scar and muscle adherence to the dura also is an important factor.

Another objection to use of this approach has been the need for cerebellar retraction. Skeletonizing the sigmoid sinus and reflecting it anteriorly can minimize cerebellar retraction. However, medium-sized and large lesions require significantly more cerebellar retraction than is necessary with the translabyrinthine approach. Nonetheless, the retrosigmoid approach offers the most panoramic view of the posterior fossa.

Middle Fossa Approach

Basic Approach

A temporal craniotomy permits exposure of the internal auditory canal after identification of the superior semicircular canal and geniculate ganglion (Fig. 177-31).

Indications

The middle fossa approach is ideally suited for resection of intracanalicular acoustic neuromas. It provides limited exposure for surgery of lesions involving the CPA. CPA involvement beyond 1 cm is a relative contraindication to this approach. Decompression of the internal audi-

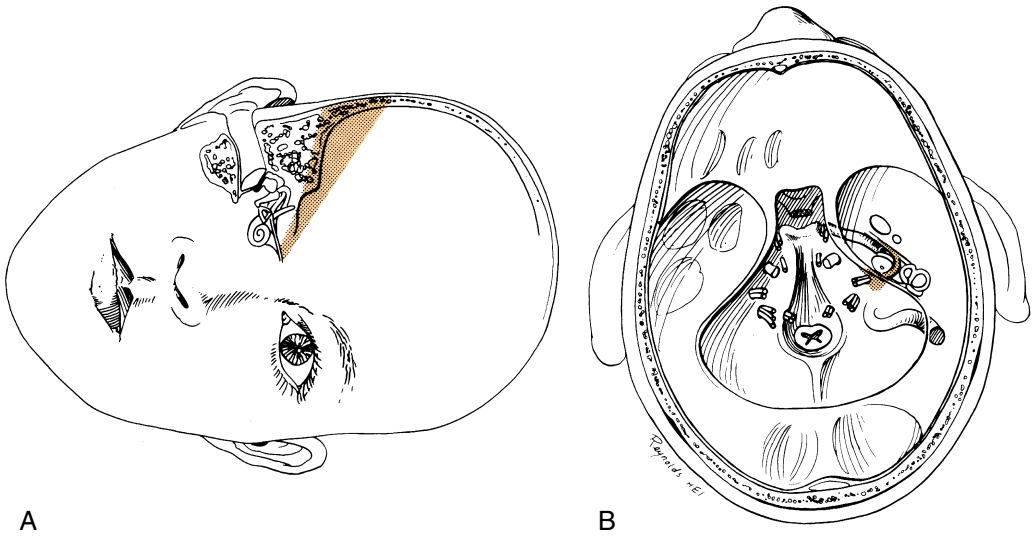

Figure 177-31. **A,** Coronal view: surgical exposure in the middle fossa approach to the cerebellopontine angle (CPA). A temporal craniotomy permits retraction of the temporal lobe and access to the floor of the middle fossa and internal auditory canal (IAC). **B,** Axial view: surgical exposure in the middle fossa approach to the CPA. The *shaded area* indicates the area of bone removal on the floor of the middle fossa. Note that although wider exposure is possible at the porus, limited space is available between the cochlea and the superior semicircular canal as the surgeon approaches the fundus of the IAC.

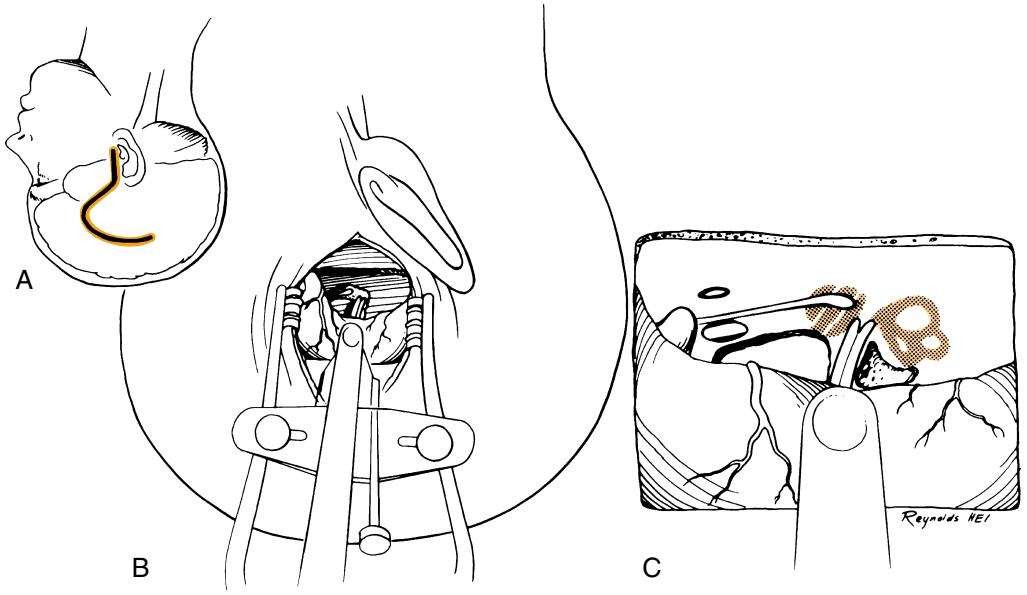

Figure 177-32. **A,** Skin incision for the middle fossa approach. Although the traditional vertical incision is used in middle fossa facial nerve decompression, the larger flap facilitates bony exposure for tumor removal. **B,** Surgeon's view of the internal auditory canal (IAC) via the middle fossa approach. Note the temporal lobe retractor in position. The proximity of the cochlea, labyrinth, and labyrinthine portion of the facial nerve at the fundus of the IAC requires precise identification of anatomic landmarks in this approach. **C,** Surgeon's view of the extended middle fossa approach. The anterior limit of bone removal is the carotid artery and the posterior limit is the labyrinth. In the illustration, the middle meningeal artery at the level of the foramen spinosum has been transected, and the horizontal carotid artery is identified coursing parallel to the greater superficial petrosal nerve and medial to the foramen ovale. Continued dissection anteromedially permits access to the cavernous sinus.

tory canal in cases of acoustic nerve tumors in only hearing ears can be accomplished in this fashion.[57]

Technique

The basic surgical exposure is illustrated in Figure 177-32A and B. Mannitol and furosemide are used in addition to hyperventilation for brain relaxation. A lumbar drain placed at the beginning of the procedure can facilitate dural elevation before open drainage of the cerebrospinal fluid. A preauricular incision is extended along the temporal region. The temporalis muscle may be reflected inferiorly or split and retracted to expose the squamosa of the temporal bone. A 5 cm × 5 cm craniotomy is centered over the zygomatic root.

The floor of the middle fossa is exposed by dissecting and elevating the dura from posterior to anterior to avoid injury to the geniculate ganglion, which can be dehiscent in up to 15% of patients. The principal landmarks for orientation are the greater superficial petrosal nerve

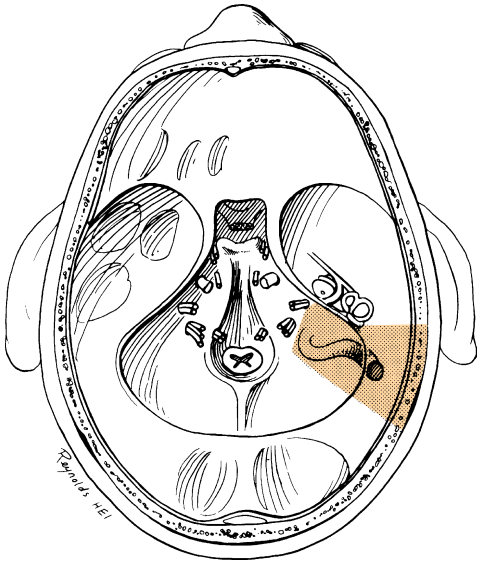

Figure 177-33. The retrolabyrinthine approach to the cerebellopontine angle (CPA). Although the exposure is limited anteriorly, removal of the bone posterior to the sigmoid sinus permits wide access to the CPA.

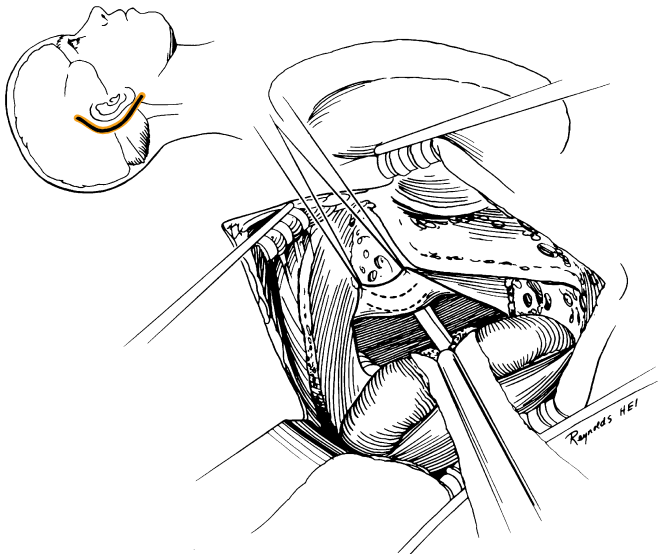

Figure 177-34. Surgeon's view of the cerebellopontine angle (CPA) with the retrolabyrinthine approach to the internal auditory canal. The dura is incised around the endolymphatic sac and reflected anteriorly. Wide posterior bone removal permits access to the CPA without a brain retractor, although suction is used to maintain the exposure. *Inset* shows skin incision in relation to the CPA.

and the arcuate eminence; however, these can be deceptive. Antidromic stimulation of the greater superficial petrosal nerve with the facial nerve stimulator can be helpful for orientation.[58] In addition, preoperative coronal CT can reveal the extent of pneumatization over the internal auditory canal and labyrinth.

Surgeons should be familiar with all techniques for identifying the internal auditory canal in middle fossa surgery, but some prefer to begin drilling medially near the porus acusticus. In this fashion, the cochlea and superior semicircular canal are not approached until the internal auditory canal has been identified. Wide skeletonization of this canal can be performed medially; however, the proximity of the cochlea and superior semicircular canal only permit unroofing the internal auditory canal laterally.

The dura is opened along the posterior aspect of the internal auditory canal. The facial nerve is freed from the tumor, and dissection proceeds in a medial to lateral direction. The canal is sealed with abdominal fat or temporalis muscle and the bone flap is replaced.

Special Features

Intracanalicular tumors, particularly those in the lateral portion of the internal auditory canal, are amenable to removal using the middle fossa approach in cases suitable for attempted hearing preservation. Because use of the approach has been limited to small lesions, the theoretic problem of limited access to the posterior fossa in case of bleeding has not been an issue.

The success of hearing preservation in selected patients is more than 70%; however, the limiting factor is the cochlear blood supply.[59] Just as in retrosigmoid hearing preservation cases, the rate of cochlear nerve preservation is substantially higher than that of actual hearing preservation. The approach is not usually recommended in patients older than 65 years because in this age group, the dura is more adherent and fragile.

Retrolabyrinthine Approach

Basic Approach

A wide mastoidectomy with skeletonization of the posterior semicircular canal permits access to the CPA with preservation of the seventh and eighth cranial nerves (Fig. 177-33).

Indications

The principal indication for the retrolabyrinthine approach is vestibular nerve section for intractable vertigo or for neurotomy in tic douloureux.[60] With posterior fossa neoplasms, the retrolabyrinthine approach affords adequate exposure and hearing preservation in selected cases of arachnoid cysts, meningiomas, and metastatic lesions of the CPA. In situations in which tissue diagnosis is required before proceeding with definitive surgery, the retrolabyrinthine approach permits wide exposure with minimal morbidity for exploration of lesions of the CPA.

Technique

The incision and soft tissue exposure for the retrolabyrinthine approach are identical to those for the translabyrinthine approach. Mannitol and furosemide are used for brain relaxation. A complete mastoidectomy is performed. The fossa incudis and the lateral and posterior semicircular canals are identified. The facial nerve is skeletonized but kept covered with bone.

Because exposure with this approach depends on collapsing the sigmoid sinus posteriorly, bone is completely removed from the sigmoid sinus and the suboccipu posterior to the sinus. Extensive exposure of the retrosigmoid dura is necessary for adequate exposure with this approach. The middle fossa dura is exposed and the petrous ridge is removed to increase the exposure.

The dura is opened as a flap that begins just medial to the sigmoid sinus and preserves the endolymphatic sac. The flap is held anteriorly with sutures and tumor dissection can be performed in the posterior fossa (Fig. 177-34). Once the CPA is entered and CSF is released, the cerebellum falls away. Accordingly, cerebellar retractors are not necessary to expose the cranial nerves in the CPA. Instead, the sigmoid is collapsed posteriorly with fenestrated suction.

When tumor removal is completed, the dura is closed with sutures. The defect is obliterated with abdominal fat with the optional use of hydroxyapatite cement or titanium mesh. Closure is performed in layers, and a compressive dressing is applied.

Special Features

The indications for the retrolabyrinthine approach in tumor removal are limited. If exposure of the internal auditory canal is not needed for a small neoplasm of the CPA, however, this approach can preserve hearing and avoids the greater degree of cerebellar retraction required for the retrosigmoid approach.

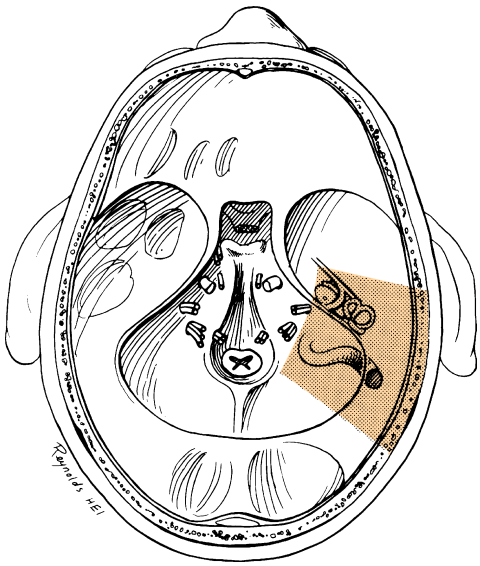

Figure 177-35. The transcochlear approach to the cerebellopontine angle petrous tip and clivus. Removal of the cochlea and anterior portion of the petrous bone permits wide visualization of the clivus and skull base.

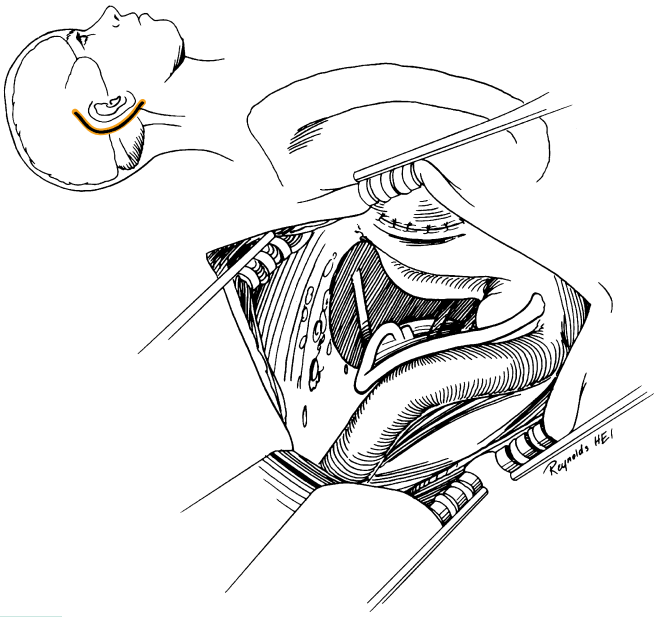

Figure 177-36. Surgeon's view of the skull base with the transcochlear approach. The external auditory canal is transected and sutured closed. Posterior transposition of the facial nerve permits unobstructed visualization from the superior petrosal sinus to the inferior petrosal sinus, anteriorly to the carotid artery, and medially to the clivus. *Inset* shows skin incision in relation to the cerebellopontine angle.

Transcochlear Approach

Basic Approach

As an extension of the translabyrinthine approach, the transcochlear approach affords additional exposure of the skull base. This is obtained by displacement of the facial nerve and removal of the cochlea to provide surgical access to lesions of the petrous tip and clivus (Fig. 177-35).

Indications

Petroclival meningiomas and epidermoids of the petrous tip are the principal lesions for which the transcochlear approach has been applied.[61] However, extensions of this approach have been used with glomus jugulare tumors, temporal bone carcinomas, and extensive nonacoustic neuromas of the CPA.

Technique

The incision, soft tissue exposure, complete mastoidectomy, labyrinthectomy, posterior and middle fossa dura decompression, and skeletonization of the internal auditory canal are performed as in the translabyrinthine approach.

The facial nerve is decompressed from the stylomastoid foramen to the geniculate ganglion. After sectioning of the chorda tympani nerve using an extended facial recess approach and transection of the greater superficial petrosal nerve, the facial nerve can be transposed posteriorly. Transposition of the nerve removes the obstacle to extending the exposure anteriorly. The transcochlear approach has been modified to include transection of the external auditory canal and two-layered closure of the meatus. This modification permits removal of the posterior wall of the external auditory canal, thus allowing wider anterior exposure in the areas of the jugular bulb and internal carotid artery. Next, the incus and stapes are removed. The cochlea is removed, thereby exposing the carotid artery anteriorly, the jugular bulb and inferior petrosal sinus inferiorly, and the superior petrosal sinus superiorly. The bony exposure leaves a dura-covered window extending from the superior petrosal sinus to the inferior petrosal sinus and reaching the clivus medially (Fig. 177-36).

The same principles of tumor removal are used as with the other approaches to the CPA. However, the position of the facial nerve in relation to the tumor and the proximity of the basilar artery make certain aspects of tumor removal with the transcochlear approach different from other approaches to the CPA. Unlike acoustic neuromas, tumors of the petrous apex and clivus often have the facial nerve on their posterior surface. Thus, the nerve should be dissected free of the tumor and protected. The position of the vertebrobasilar arterial system should be considered. As tumor dissection proceeds medially, the basilar artery will be anterosuperior and the vertebral artery will be posteroinferior. Extensive tumors that cross the midline are removed by reflecting the vessels posteriorly from the tumor capsule. Particular care is taken to preseve small perforating vessels that supply the brainstem, because their damage could be fatal. The surgical defect is filled with abdominal fat (often with hydroxyapatite or titanium mesh, or both), the wound is closed in layers, and a compressive dressing is applied.

Special Features

The transcochlear approach provides direct access to the base of implantation and blood supply of tumors arising from the petrous tip and petroclival junction. Temporary facial nerve paralysis occurs uniformly with the posterior transposition of the facial nerve required by this approach. Such paralysis is most likely to be the consequence of devascularization of the perigeniculate segments of the nerve caused by transection of the greater superficial petrosal nerve and its accompanying vessels. Because partial recovery of facial nerve function is the rule (to House-Brackmann grade 3/6 or 4/6), the approach has limited application except for removal of the most extensive life-threatening lateral skull base lesions such as malignancies or vertebrobasilar aneurysms.

Transotic Approach

Basic Approach

The transotic approach is similar to the modified transcochlear approach, in which the external auditory canal is closed and the posterior wall of the external auditory canal is removed. The distinction is that with the transotic approach, the facial nerve is skeletonized but left in its bony canal in the surgical field.

Indications

The transotic approach is indicated for removal of lesions of the CPA extending inferiorly into the jugular foramen or anteriorly into the

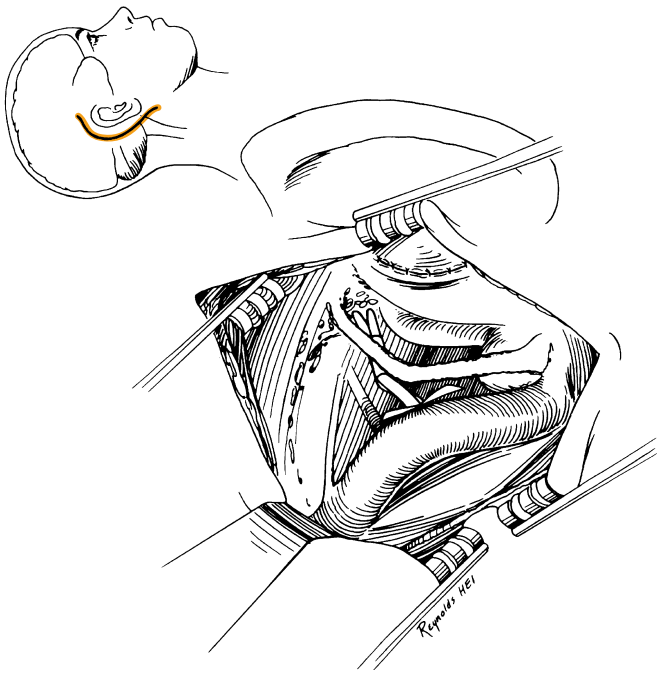

Figure 177-37. Surgeon's view of the transotic approach to the skull base. Note that the approach is identical to the transcochlear approach except that the facial nerve is not transposed. Instead, the nerve is left in its bony canal suspended across the surgical field. The in situ facial nerve limits the exposure in its internal auditory canal and mastoid segments (compare with Fig. 177-36). *Inset* shows skin incision in relation to the cerebellopontine angle.

clivus. Some proponents of this approach use the additional exposure anteriorly in cases of high jugular bulbs or anteriorly placed sigmoid sinuses in small to medium-sized acoustic neuromas.[62] The translabyrinthine approach with wide decompression of the sigmoid sinus and posterior fossa dura provides adequate exposure of the internal auditory canal and CPA, even with large acoustic neuromas with unfavorable venous anatomy.

Technique

Through a postauricular incision, the ear is reflected anteriorly, and the external auditory meatus is transected and closed in two layers. Essentially the same procedure as that described for the transcochlear approach is performed, with the exception that the facial nerve is not completely freed from the fallopian canal. Rather, the nerve is skeletonized and left in its canal. At the conclusion of the exposure, the facial nerve is suspended, traversing the surgical field with a bony cover. The tympanic ring is removed, with systematic exposure of the jugular bulb, jugular foramen, and carotid canal. By working around the facial nerve, the surgeon has access to lesions of the internal auditory canal, CPA, clivus, and jugular foramen (Fig. 177-37). Closure is performed with obliteration of the defect with abdominal fat and optional placement of hydroxyapatite cement or titanium mesh.

Special Features

The transotic approach combines the added exposure provided by removal of the tympanic ring and access medial to the facial nerve with the added safety of the avoidance of transposing the facial nerve. This approach also offers an alternative strategy for management of the anterior sigmoid or high jugular bulb in cases of CPA tumor removal in which hearing preservation will not be attempted. Leaving the facial nerve in situ is an attractive means of avoiding excessive manipulation of the facial nerve; however, leaving the nerve without transposition requires added vigilance by the surgeon as dissection proceeds medial to the plane of the facial nerve. Furthermore, exposure is limited at the brainstem because the labyrinthine segment of the facial nerve and the contents of the internal auditory canal are not transposed.

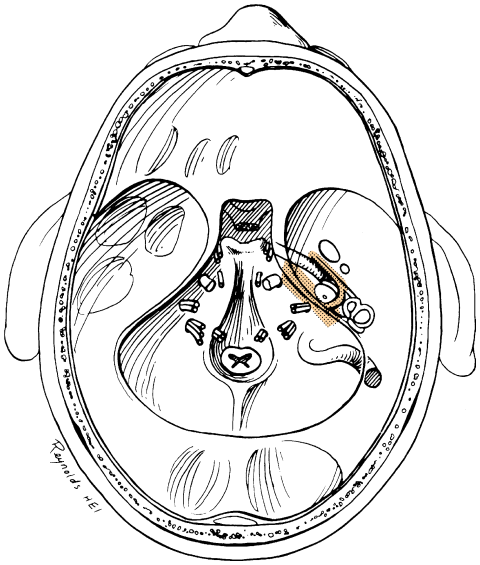

Figure 177-38. Schematic view (axial) of the extended middle fossa approach to the skull base. By removing the bone posterior and medial to the labyrinth and medial to the carotid artery, the exposure of the middle fossa approach is extended to lesions of the cerebellopontine angle that have spread beyond the tentorium or even into the cavernous sinus.

Extended Middle Fossa Approach

Basic Approach

For the extended middle fossa approach, the skull base surrounding the otic capsule is carefully removed through a wide temporal craniotomy. This approach exposes lesions extending from the posterior fossa through the tentorium and incisura and anteriorly up to the region of foramen lacerum and the posterolateral aspect of the cavernous sinus (Fig. 177-38).

Indications

The extended middle fossa approach is indicated in extensive petrous ridge and petroclival lesions involving the temporal bone that have serviceable hearing. Petrous ridge lesions with extension through the tentorium into the middle fossa are especially amenable to removal using this approach.

Technique

The patient is positioned in the supine position with the head turned to the side. Mannitol, furosemide, and hyperventilation are used for brain relaxation. After performing a wide temporal craniotomy, the temporal lobe is progressively retracted to permit identification of the middle meningeal artery anteriorly, the petrous ridge posteriorly, and the petroclival junction medially. The internal auditory canal is uncovered using the standard middle fossa technique as described. The extension in the exposure is accomplished by removing the petrous ridge and posterior aspects of the temporal bone up to the labyrinth. Anteriorly, the temporal bone is removed up to the foramen lacerum and the internal carotid artery (see Fig. 177-32C). The area of Meckel's cave is clearly identified, and the posterolateral portions of the cavernous sinus are accessible.

Special Features

The extended middle fossa approach permits safe removal of extensive lesions (especially meningiomas) of the middle and posterior fossa that have not directly involved the otic capsule or internal auditory canal. Preservation of hearing and the facial nerve is possible with this technique despite wide access to the lesion.

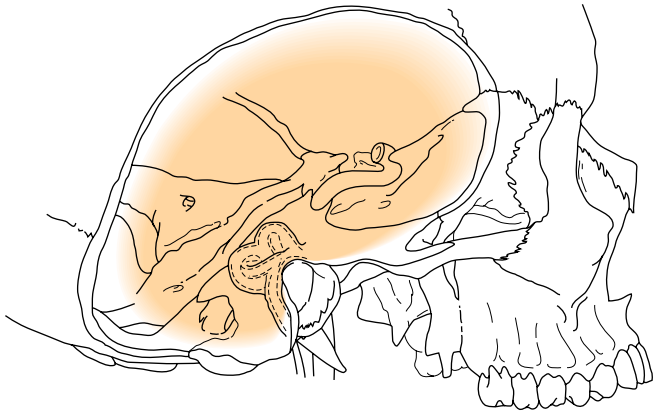

Figure 177-39. Combined petrosal approach uses the extended middle fossa, retrolabyrinthine, and retrosigmoid exposure while preserving the labyrinth.

Combined Techniques (Petrosal Approach)

Basic Technique

The previously described techniques for access to posterior fossa lesions may be combined to provide superior and posterior exposure.

Indications

Lesions involving the posterior and middle fossae or extensive lesions of the clivus are amenable to removal using combined approaches, especially if the patient retains serviceable hearing.

Technique

The usual procedures in the petrosal approach combine extended middle fossa exposure with full retrosigmoid and retrolabyrinthine exposure[63] (Fig. 177-39). The middle cranial fossa, internal auditory canal, posterior fossa, and clivus all are exposed while the otic capsule is preserved. By contrast, the translabyrinthine or transcochlear approach also can be combined with the extended medial fossa approach to provide the widest possible exposure.

Special Features

The petrosal approach provides wide exposure of the skull base from foramen magnum to the cavernous sinus while retaining the possibility for hearing preservation. The wide bone removal maximizes surgical exposure and minimizes the need for brain retraction. If hearing preservation is not a realistic expectation, the addition of otic capsule removal provides even wider surgical exposure.

Experimental Approaches

Attempted hearing preservation with partial or complete labyrinthine resection has been reported. McElveen[64] and Molony[65] and their colleagues reported systematic sealing of the vestibule during labyrinthectomy with successful hearing preservation after translabyrinthine tumor removal. To expose the lateral internal auditory canal with the retrosigmoid approach, Arriaga and Gorum[66] reported posterior semicircular canal resection with successful hearing preservation and total tumor removal in two of three enhanced retrosigmoid procedures. In extensive skull base lesions, labyrinthine procedures can be converted to partial labyrinthine resection procedures with concomitant opportunity for preserved hearing.[67]

Although these findings are promising, such techniques are currently experimental, and further investigation is necessary for such approaches to be offered routinely in clinical practice.

Approaches for Skull Base Lesions Requiring Drainage

As described earlier in this chapter, cholesterol granulomas are nonneoplastic lesions that may expand the petrous apex and produce symptoms related to the nerves of the posterior fossa. Similarly, mucoceles of the petrous apex may produce symptoms by their expansion. Both lesions are adequately managed by surgical drainage.

Translabyrinthine Approach

If hearing and vestibular function are absent, the translabyrinthine approach provides the most direct route for aeration from the mastoid through the surgical defect to the petrous apex.[68] Usually, however, this approach is inappropriate because patients often have excellent hearing despite large cholesterol granulomas.

Middle Cranial Fossa Approach

The middle cranial fossa approach permits hearing preservation but requires temporal lobe retraction for exposure. Placing a catheter from the mastoid tegmen to the apex facilitates drainage, and despite its relatively long course, the catheter remains patent, with radiologic follow-up confirmation of aeration.[43]

Infralabyrinthine Approach

After a complete mastoidectomy, the sigmoid sinus is decompressed, the posterior semicircular canal and jugular bulb are identified, and the infralabyrinthine air cells are followed into the petrous apex. The cyst is incised, drained, and stented open into the mastoid[68] (Fig. 177-40). This approach may be technically impossible in a patient with a high jugular bulb. Furthermore, although reexploration is possible in the face of an occluded stent, revision surgery requires formal reexploration of the transmastoid approach.

Transcanal Infracochlear Approach

The external auditory canal is transected and a superiorly based tympanomeatal flap is elevated. The bony external meatus is widened, and the air cell tract between the jugular bulb and carotid artery is followed into the petrous apex (Fig. 177-41). This approach permits dependent drainage of the petrous apex into the middle ear (see Fig. 177-14). If the drainage tube becomes obstructed, it may be revised through an office myringotomy. The principal disadvantages are the prolonged healing time required for the external auditory canal and the need for direct exposure of the petrous carotid artery.[42]

Selection of Surgical Approach

The rationale for selecting a particular surgical approach for acoustic neuromas is similar to that for other posterior fossa neoplasms. The principal goal is tumor removal with minimal postoperative morbidity. Accordingly, the surgical approach should be tailored to the patient's specific pathology and functional status. The notion that a single approach should be used with all lesions of the posterior fossa is counterintuitive and subjects patients to unnecessary morbidity. In patients without serviceable hearing, the translabyrinthine approach provides wide and direct access to the CPA, with maximal facial nerve safety, minimal cerebellar retraction, and a low incidence of severe postoperative headache.

Patients with small tumors and good hearing have three options for surgical removal: the translabyrinthine approach, which destroys hearing; the middle fossa approach in young patients with small, mainly intracanalicular tumors; and the retrosigmoid approach in small tumors of the CPA that do not extend to the fundus of the internal auditory canal. In general, the best hearing and functional outcomes result from individualizing the surgical approach to patient and tumor characteristics.[69]

Realistic patient counseling is necessary regarding hearing conservation procedures. Gardner and Robertson[51] rigorously reviewed the literature on hearing preservation in acoustic neuroma surgery. Of 621 reported cases of attempted hearing preservation, the success rate was 33%. Reported successful hearing preservation rates often refer only to measurable hearing. The rate is far lower if useful hearing (speech reception threshold [SRT] greater than 30 dB and speech discrimination less than 70%) or serviceable hearing (SRT greater than 50 dB and speech discrimination less than 50%) is considered. Furthermore, long-term follow-up studies reveal that 56% of patients experience significant loss of the preserved hearing over time.[59]

After a discussion of the risks and benefits of the various surgical approaches, many potential candidates for hearing preservation choose

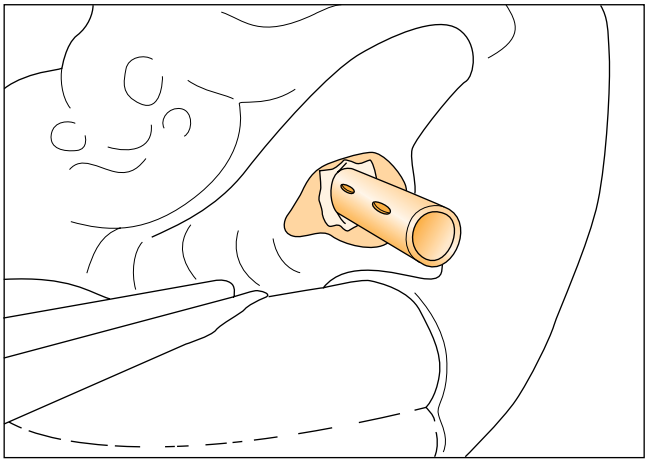

Figure 177-40. Surgeon's view of the completed transmastoid infralabyrinthine drainage of a cholesterol granuloma. The dissection is performed medial to the facial nerve and inferior to the level of the labyrinth. The drainage tube permits aeration of the cholesterol granuloma.

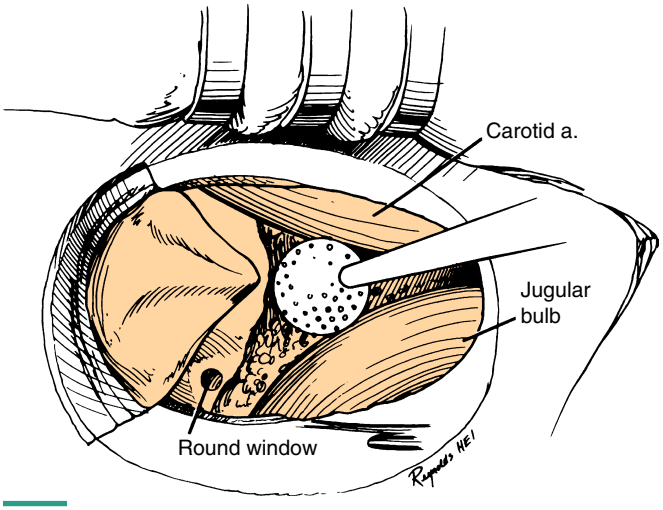

Figure 177-41. Surgeon's view of the transcanal infracochlear approach to the petrous apex. After transection of the ear canal, a superiorly based tympanomeatal flap is elevated. Diamond burrs are used to expose widely the hypotympanum, jugular bulb, and petrous carotid artery. The infracochlear cell tract is followed between the carotid artery and jugular bulb. *(From Giddings NA, Brackmann DE, Kwartler JA. Transcanal infracochlear approach to the petrous apex.* Otolaryngol Head Neck Surg. *1991;104:29.)*

the translabyrinthine approach, with its slightly higher rate of facial nerve preservation, rather than hearing conservation procedures.

With meningiomas and tumors that do not affect the internal auditory canal and have not impaired hearing, the extended middle fossa approach is used if posterior and middle fossa exposure is necessary. The retrolabyrinthine approach is used for removal of limited lesions of the CPA only, whereas the retrosigmoid approach would be applicable for resection of more extensive lesions of the posterior fossa. Extensive anteromedial exposure is needed with lesions of the clivus. Hearing preservation usually is not feasible in treatment of such lesions, and the transcochlear or transotic approach may be used.

Patient Management and Surgical Complications

Comprehensive management of patients with skull base neoplasms of the posterior fossa requires a team of specialists familiar with the particular needs of this patient group. In addition to neuro-otologists and neurosurgeons, designated internists, anesthesiologists, radiologists, ophthalmologists,[70] and critical care nurses are essential members of the team for optimal care of these patients with very specialized needs.

Preoperative Management

Preoperative antibiotics are routinely used even in uncomplicated cases. Osmotic agents and diuretics for brain relaxation usually are not used in the translabyrinthine approach; however, the retrolabyrinthine, retrosigmoid, middle fossa, and extended middle fossa approaches require such techniques to minimize the need for retraction.

Intraoperative Monitoring

Facial nerve monitoring is used routinely in all cases of posterior fossa neoplasm surgery. Continuous monitoring is performed with EMG electrodes and monitoring equipment with instantaneous visual and loudspeaker output. An audiologist assists with interpreting monitoring signals and stimulating the facial nerve when required to identify nerves intraoperatively.

Although ABR monitoring often is used in hearing preservation cases, this modality provides only delayed feedback to the surgeon and cannot affect intraoperative decision-making or tissue manipulation in a meaningful way. The advent of direct eighth nerve recording systems and electrocochleography (ECoG) modifications may make a practical real-time feedback system available to the surgeon in hearing preservation cases.[71]

Postoperative Care

The compression mastoid dressing applied in the operating room is left in place until the fourth postoperative morning if hydroxyapatite or titanium mesh was not employed. The patient is observed in the neurologic intensive care unit for 1 day and then transferred to the general ward. Limited activity is begun on the first postoperative morning, and ambulation usually resumes on the second postoperative day, with discharge home on postoperative day 3 or 4.

Complications

Anteroinferior Cerebellar Artery

Tumor manipulation at the brainstem may result in changes in vital signs. Such changes are related to ischemia, which usually is in the distribution of the anterior inferior cerebellar artery. Manipulation is stopped temporarily until vital sign changes have resolved. Vital sign alterations that do not resolve or that recur with any tumor manipulation constitute an indication to terminate the procedure. Complete interruption of this vessel may result in Atkinson's syndrome, infarction of the lateral tegmental pons, which often is fatal.[72] This complication can occur in a nonfatal form if branches of the anterior inferior cerebellar artery are transected.

Cerebrospinal Fluid Leaks

In the translabyrinthine approach, CSF leakage through the wound is rare with meticulous closure. The incidence of CSF rhinorrhea is less than 5%, and the leak usually responds to replacement of the compression mastoid dressing. The routine obliteration of the eustachian tube has nearly eliminated this problem. In the rare case of persistent leakage, spontaneous sealing of the leak can be expected after 3 days of lumbar CSF drainage. However, surgical closure of the ear canal with direct obliteration of the eustachian tube is promptly effective. Hydroxyapatite cement and titanium mesh cranioplasty techniques have been highly effective in reducing the leakage rate.

In the retrosigmoid approach, the mastoidectomy defect also is obliterated with fat. In some institutions, the mastoid is not routinely entered, and fluid communication is possible through exposed air cells, which ultimately permit fluid leakage through the eustachian tube. Aggressive application of bone wax over mastoid air cells is necessary to avoid leaks. In cases of persistent leakage, additional fat obliteration of the mastoid plus waxing of air cells usually is successful.

Meningitis

Any procedure that exposes the subarachnoid space can be complicated by postoperative meningitis. The diagnosis is suspected in a patient with a toxic appearance including stiff neck, recent headache, and fever. Appropriate CSF studies will confirm the diagnosis. The mean time to onset of meningitis in patients with acoustic neuroma is 8 days postoperatively. Aggressive medical management of this complication successfully avoids any serious complications from meningitis, other than a delayed hospital discharge.[73]

Facial Nerve Injury

Facial nerve transection ideally is managed by immediate repair or with an interposition graft.[74] In the translabyrinthine approach, access to the middle ear and mastoid portions of the nerve can provide a longer distal segment to ensure a tension-free anastomosis.[75] In cases in which direct repair is impossible or in which an intact nerve does not resume function within 1 year, the facial hypoglossal anastomosis provides reliable facial reanimation.[76] Temporalis muscle transfer is an alternative technique for reanimation of the paralyzed face that offers the benefit of immediate effects.

Ophthalmologic Considerations

The combination of facial paralysis and corneal insensitivity, which is more likely with surgery of large tumors, predisposes the cornea to significant trauma. Patients who are expected to have prolonged facial paralysis (6 months) are managed with a brow lift and placement of eyelid springs or gold weights. In cases of partial facial weakness or when the paralysis is expected to be short term, aggressive medical management including a regimen of lubricating drops or ointments, use of contact lenses, moisture chamber protection, and nightly taping of the affected eye is undertaken.[26] In some centers, gold weight implantation in the upper lid is the preferred technique for managing corneal exposure.

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CHAPTER ONE HUNDRED AND SEVENTY-EIGHT

Intraoperative Monitoring of Cranial Nerves in Neuro-otologic Surgery

Yasmine A. Ashram

Charles D. Yingling

Key Points

- Effective neurophysiologic recordings to guide the neurotologic surgeon rely on consistent protocols of neural stimulation and arrangement of the recording montage.
- In particular, a well-developed literature now demonstrates the effectiveness of monitoring facial nerve activity during vestibular schwannoma surgery by recording spontaneous and mechanically evoked activity. Recorded electrophysiologic activity reflects both nerve integrity and nerve responsivity.
- Similar methods are applicable to monitoring cranial nerves during other types of procedures, including resection of glomus jugulare tumors and prepontine tumors, microvascular decompression, parotidectomy, and tympanomastoidectomy.
- Other motor nerves—the third, fourth, motor portion of fifth, sixth, tenth, eleventh, and twelfth nerves—also can be monitored by placement of electrodes in appropriate target muscles.
- The cochlear nerve can be monitored by use of auditory brainstem response (ABR) or direct nerve action potential recordings.
- Numerous studies have confirmed that cranial nerve monitoring both reduces the incidence of postoperative deficits and can provide valuable prognostic information.
- Anticipated future developments, including the use of transcranial motor evoked potentials for continuous facial nerve stimulation, are expected to further enhance the utility of monitoring techniques.

The advent of sensitive diagnostic techniques and the refinement of microsurgical procedures have brought about a marked reduction in mortality rates for posterior fossa surgery; accordingly, increasing emphasis has been placed on preservation of cranial nerve function. This goal has in turn stimulated the development of techniques for monitoring cranial nerves during surgery. Seventh nerve monitoring during acoustic neuroma surgery has now become routine at most major medical centers, and anatomic preservation of the facial nerve has been achieved in more than 95% of the cases in some series.[1] Although facial motility often is compromised in the immediate postoperative period, the long-term prognosis is good if the nerve can be electrically stimulated after tumor removal. Preservation of hearing has been more difficult to achieve because of the more intimate relationship of such tumors with the cochleovestibular nerve but is now often achieved in smaller tumors with the aid of eighth nerve monitoring. Furthermore, the techniques developed for facial nerve monitoring are now readily adapted for monitoring other cranial motor nerves. We have reviewed these topics in greater detail elsewhere.[2]

The emphasis in this chapter is on the practical aspects of instrumentation, electrode placement, different neurophysiologic techniques used, artifact identification, types of responses encountered, and the relationship between intraoperative recordings and clinical outcome. Somatosensory evoked potential (SEP) recording[3] is not treated here, although SEP monitoring can be useful in monitoring large posterior fossa tumors with significant brainstem compression; discussions of SEP monitoring can be found in textbooks by Nuwer[4] and Møller.[5] This chapter is based primarily on the experience of the senior author with more than 700 posterior fossa procedures, as well as a review of the literature through 2007; also described are the methods currently available for cranial nerve monitoring, emphasizing facial and cochlear nerve monitoring during acoustic neuroma surgery but also including extension of these techniques to other nerves encountered in a variety of skull base procedures.

Neurophysiology in the Operating Room

Personnel

Successful intraoperative monitoring requires more than simply bringing another piece of equipment into the operating room (OR). The OR, unlike the typical clinical neurophysiology laboratory, presents a time-pressured and electrically hostile environment. Providing technically adequate recordings in the OR requires the services of professional

personnel with specialized skills and experience despite the additional costs incurred. Attempts to monitor without such personnel may result in failure, or, even worse, inadequate monitoring, with inaccurate and misleading feedback to the surgeon. Accordingly, a new specialty field of intraoperative neurophysiologic monitoring has evolved, with its own professional organization, the American Society of Neurophysiological Monitoring (ASNM).

Professional certification for surgical neurophysiologists is now offered by two national organizations in the United States. At the technologist level, the American Board of Registered Electrodiagnostic Technologists (ABRET) offers a Certification in Neuro-physiological Intraoperative Monitoring (CNIM). The American Board of Neurophysiologic Monitoring (ABNM) offers board certification to monitoring professionals holding advanced degrees and with a minimum of 3 years' experience and 300 cases monitored. Because the demand for monitoring services is growing rapidly, there is a growing need for training programs to ensure an adequate supply of qualified personnel.

Technical Considerations

Instrumentation

The basic instrumentation requirements for cranial nerve electromyography (EMG) monitoring are an isolated electrical stimulator that can be precisely controlled at low levels; several low-noise EMG amplifiers; a multichannel display; and an audio monitor with a squelch circuit to mute the output during electrocautery. A system that provides multiple channels is recommended to allow simultaneous monitoring of multiple divisions of the facial nerve independently as well as other cranial nerves.

Auditory brainstem response (ABR) monitoring requires a system that includes high-gain (100 to 500,000 K) differential amplification with multiple band-pass filtering capabilities, acoustic stimulus intensity ranging from threshold to at least 70- to 80-dB hearing level (HL), signal averaging with real-time display of the evolving averages and the input signal, and permanent disk storage with hard copy printout capability.

For complex surgical cases requiring additional EMG monitoring channels or increased ABR averaging capability, or both, several commercial multichannel systems have been developed for intraoperative use. Currently available systems allow multiple independent time bases and functions to operate simultaneously; for example, some channels may be devoted to free-running EMG at slow sweep speeds and others to stimulus-triggered EMG at a faster sweep, and still others can be used for collection of averaged ABRs.

Recording Electrodes: Type and Placement

The most commonly used recording electrodes are the platinum or stainless steel subdermal needles designed for EEG; these have a larger uninsulated surface than that of electrodes designed for single-fiber EMG and thus are more likely to detect activity arising anywhere in the monitored muscle. Disposable, presterilized electrodes are available from several sources, and their use is highly recommended.

Intramuscular hook wire electrodes, which are inserted with a hypodermic needle, also have been used.[6] These are more delicate and have higher impedance, so the simpler needle electrodes are preferred, except in situations in which the electrodes cannot be easily fastened with tape, as in procedures involving the tongue, or when the use of insulated needles is desirable to avoid crosstalk from overlying muscles. An example of the latter case is recording from extraocular muscles, for which the electrodes must pass through the orbicularis oculi muscle and will therefore respond to facial nerve activity as well.

For monitoring the facial nerve, it is desirable to place the electrodes in at least two different muscles supplied by the nerve. Mechanical trauma to the seventh nerve often causes sustained EMG activity that can make identification of the facial nerve with electrical stimulation difficult. With two or more close-spaced bipolar channels, at least one often will be quiet enough to allow responses to stimulation to be identified without signal averaging even with high tonic EMG activity.

For recording the ABR in hearing conservation procedures, one electrode is placed in the ipsilateral ear canal and another on the forehead or vertex. The placement of the second electrode is not critical so long as it is near the midline. The best electrode option for the ear canal is the Nicolet Tiptrode, which is a compressible foam insert covered with gold foil. The acoustic signal is delivered through a tube in the center of the foam, which provides an acoustic seal, and the foil provides the electrical contact for recording.

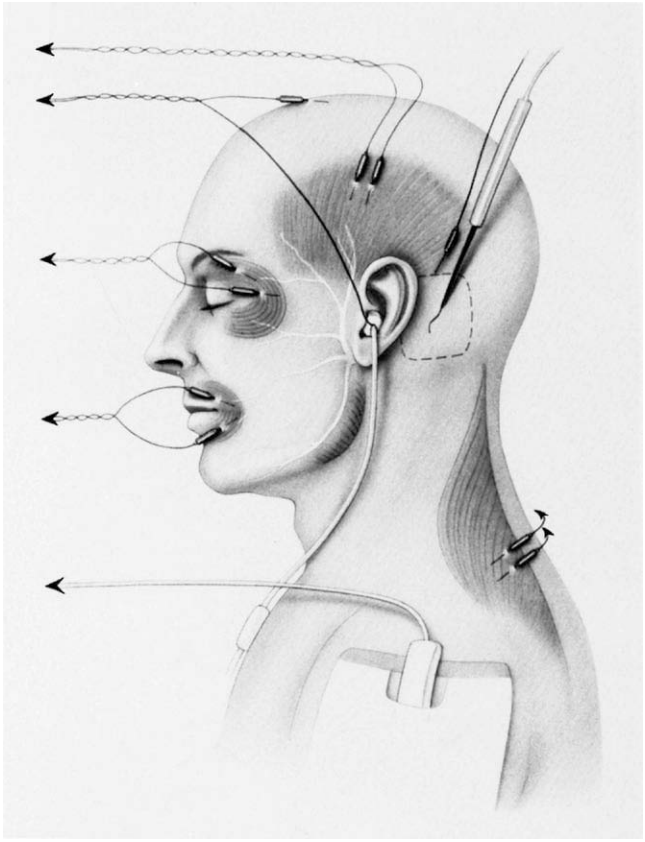

Figure 178-1. Diagrammatic representation of electrode placement for monitoring acoustic neuroma surgery with attempted hearing conservation. Pairs of needle electrodes are placed in the following muscles: temporalis (supplied by V3m), orbicularis oculi and orbicularis oris (supplied by the seventh nerve), and trapezius (by the eleventh nerve). Note that wires are twisted together to reduce 60-Hz pickup. Broadband click stimuli from a small transducer on the chest are fed through plastic tubing into the ipsilateral ear through a foil-covered sponge insert that also serves as a recording electrode and referred to a needle electrode on the forehead or vertex. An electrocautery ground pad is placed on the arm or shoulder as a signal ground. A flexible-tipped probe is used to stimulate cranial motor nerves, with a needle electrode as the stimulator ground placed in the margin of the craniotomy. *(From Yingling CD. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackmann DE, eds.* Neurotology. *St Louis: Mosby; 1994:967).*

Figure 178-1 shows the positioning of recording electrodes for a middle fossa or retrosigmoid craniotomy for acoustic neuroma resection with a goal of hearing preservation. For a translabyrinthine approach, the same configuration is used, with the exception of the earphone and electrodes for ABR recording, because hearing conservation is not possible with this approach. Two channels are devoted to the facial nerve itself, with electrode pairs placed in orbicularis oculi and orbicularis oris muscles. One of the electrodes in the orbicularis oculi pair is placed at the lateral canthus, where it also will record volume-conducted activity in the lateral rectus muscle (from the sixth cranial nerve). One channel is used to record from the masseter or temporalis muscle (V3m) using hookwire electrodes, rather than subdermal needles, to reduce crosstalk, and the fourth channel is connected

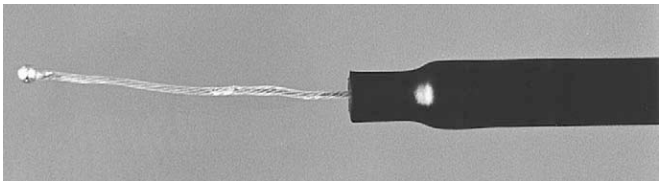

Figure 178-2. Close-up view of flexible-tipped probe used for intracranial stimulation. The entire probe and the flexible wire are insulated, except for the 0.5-mm ball on the end, to achieve localized stimulation.

to electrodes in the ipsilateral trapezius muscle (eleventh nerve). The latter two channels serve two functions: First, larger tumors may expand to involve these nerves, so monitoring may help in their identification and preservation. Second, even with smaller tumors, the extra channels serve as a control for nonsurgical causes of increased EMG activity, particularly light anesthesia.

Stimulating Electrodes

Both monopolar and bipolar stimulating electrodes have been used for intraoperative electrical stimulation. In theory, a bipolar electrode can provide more precise localization, with less current spreading from the electrode to adjacent structures. In practice, however, the threshold for bipolar stimulation depends strongly on the orientation of the two contacts with respect to the axis of the nerve.[7] Maintenance of a specific bipolar orientation is difficult in the close confines of the posterior fossa. Furthermore, if the stimulus intensity is near the threshold level (see later), a spatial resolution of less than a millimeter is easily obtained even with monopolar stimulation. Monopolar electrodes are therefore more commonly used; however, Schekutiev and Schmid[8] and Dankle and Wiegand[9] have described coaxial bipolar electrodes that may eliminate the problem of orientation.

The monopolar electrode should be connected to the cathode of the stimulator; the anodal return usually is a needle inserted into the periphery of the wound, preferably on the posterior margin of the incision to minimize stimulus artifact. This is particularly important in recording from extraocular muscles, which yield small-amplitude and short-latency responses that can easily be swamped by electrical artifacts. Several types of monopolar electrodes are available. Prass and Lüders[10] developed a malleable electrode, with the insulation continuous to a flush-tip that could be bent so that only the central portion of the tip contacted the desired tissue. They showed that this design minimized the spread of current to adjacent structures. Yingling and Gardi[11] developed a probe with a flexible platinum-iridium tip, insulated except for a 0.5-mm ball on the end (Fig. 178-2). This electrode can be used to stimulate within dissection planes or even behind the tumor, out of the surgeon's view, without concern for inadvertently damaging unseen neural or vascular structures (Fig. 178-3). With this probe, the facial nerve frequently can be located electrically even before it can be seen; dissection can then proceed in the most advantageous manner to avoid neural damage. Kartush and coworkers[7] developed a set of Rhoton-type dissecting instruments that are insulated except at the cutting surface, allowing simultaneous dissection with constant stimulation. These "stimulus dissectors" are particularly useful for removing the last portions of tumor capsule that are closely adherent to a nerve.

Stimulation Criteria

Little agreement has been achieved regarding the appropriate stimulation parameters to be used in cranial nerve monitoring, which vary considerably from one center to another. Our preference is to use a monopolar constant-voltage stimulator delivering pulses 0.2 ms in duration at a rate of 5 to 10 per second. In our experience, this is an effective and reliable choice that usually evokes a response from normal nerves at a threshold ranging between 0.05 and 0.2 V and averaging approximately 0.1 V.

Although the issue of whether constant-current or constant-voltage stimulators should be used has been a source of continuing controversy, there is no clear advantage of one method over the other. In many cases, however, the features of available equipment will limit the type of stimulation. Whether constant current or constant voltage is used, the more important issue is what actual level of stimulation is most appropriate. Rather than adhering to a simple "set it and forget it" approach, more useful information can be gained by varying the stimulation intensity in different surgical contexts, such as locating a nerve in relation to a tumor or testing the responsiveness of an already identified nerve.

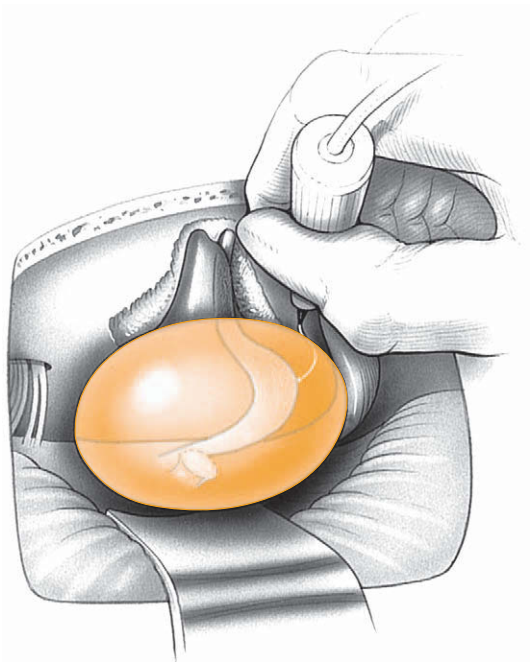

Figure 178-3. Surgical view of large acoustic neuroma (retrosigmoid approach) showing use of flexible-tipped probe to locate the facial nerve on the medial surface of the tumor out of direct view. Early identification of the facial nerve "around the corner" on the ventral surface of the tumor helps speed the procedure by allowing rapid removal of the remaining capsule. Tumor is drawn as if transparent to show details of anatomy on the hidden surface. *(Adapted from Yingling CD, Gardi JG. Intraoperative monitoring of facial and cochlear nerves during acoustic neuroma surgery.* Otolaryngol Clin North Am. *1992;25:413.)*

Anesthesia

Cortical evoked potentials are notoriously sensitive to many anesthetic agents, so careful adjustment of anesthesia levels is necessary in applications such as spinal cord monitoring with SEPs. Fortunately, the ABR and EMG responses that are used for cranial nerve monitoring are essentially unaffected by any commonly used anesthetics. The major anesthetic consideration is a contraindication to the use of muscle relaxants, because blockade of the neuromuscular junction interferes with monitoring of EMG activity. A few reports[12-14] have suggested that partial blockade can be used to prevent patient movement without blocking the ability to elicit EMG responses with facial nerve stimulation. However, in our experience, although electrically evoked EMG is relatively preserved, both spontaneous and mechanically elicited EMG activity tends to be suppressed by these agents. Therefore, *no paralytic agents should be used during surgery with cranial nerve monitoring*, other than short-acting agents such as succinylcholine given to facilitate intubation. Because the ABR and EMG are not significantly affected by routine concentrations of common anesthetics, no other constraints on anesthetic technique generally are necessary.

Finally, if local anesthetic is used at the incision site, care must be taken to avoid injection near the stylomastoid foramen to avoid anesthetizing the facial nerve. Alternatively, epinephrine 1 : 100,000 without any local anesthetic may be used to aid hemostasis.[15]

Facial Nerve (Seventh Nerve) Monitoring

Acoustic Neuroma and Other Cerebellopontine Angle Tumors

Facial nerve (seventh nerve) monitoring is routinely used in procedures to remove acoustic neuromas and other cerebellopontine angle tumors. Several techniques for facial nerve monitoring have been developed, including the use of sensitive detectors mounted on the face to detect facial nerve activity,[16-19] intraoperative EMG, recording of compound nerve action potentials (CNAPs) from the facial nerve,[20-22] intraoperative recording of nasal muscle F-wave,[23,24] and video analysis to detect facial movements.[25,26]

Electromyography

Because of its higher sensitivity[6,7,11,16,27-46] and easy application, EMG has by far overshadowed the other aforementioned methods and has become the most widely used modality for routine facial nerve monitoring. EMG recordings are used for monitoring cranial motor nerve activity in two distinct ways. First, intracranial electrical stimulation is used to identify and map the course of the nerves with evoked EMG activity and to determine the functional integrity of a nerve. Second, spontaneous EMG activity is continuously monitored to detect changes related to mechanical, thermal, or electrical irritation of the nerves by intraoperative maneuvers such as retraction,[47] tumor dissection, use of electrocautery or lasers,[48,49] or ultrasonic aspiration.

Activity Evoked by Electrical Stimulation

Use of Stimulation to Identify and Map Nerves in Relation to Tumor

Electrical stimulation is used in two main ways: (1) to rule out the presence of a nerve in a region to be dissected (using suprathreshold stimulation levels, i.e., 1 V) and (2) to map the precise locations of cranial nerves and determine their functional integrity, using stimulation levels at or just above threshold (i.e., 0.05 to 0.3 V).

Before electrical stimulation begins, correct functioning of the stimulating and recording system must be confirmed as soon as possible to avoid potentially catastrophic false-negative results. The presence of a stimulus artifact is not an unequivocal test; it is possible to have a stimulus artifact with only one lead (either the anodal return or the cathodal stimulator) connected. However, the absence of any artifact usually indicates an open circuit somewhere in the system. To avoid any ambiguity, it is preferable to confirm the operation of the entire system before beginning tumor dissection. In a retrosigmoid approach, the eleventh nerve usually can be stimulated at the jugular foramen as soon as the dura has been opened and the cerebellum retracted; an EMG response in the trapezius muscle confirms that the system is operating correctly. This confirmatory maneuver usually is possible before tumor resection begins, except in operations involving very large acoustic tumors. If the eleventh nerve is not visible at the outset, the stimulating electrode can be placed directly on a muscle and a direct muscular response obtained, although muscle requires higher stimulation levels than those effective in nerve. In translabyrinthine procedures, the facial nerve can be stimulated within the mastoid bone in the course of the labyrinthine dissection (before the tumor is exposed), although the threshold will be higher (usually 0.6 to 1.0 V, although up to 2 V may be needed), depending on the thickness of the overlying bone.

Once system function has been verified, an attempt is made to locate and stimulate the facial nerve. In smaller tumors (cerebellopontine angle component of 1 cm or less), the nerve usually can be located at its brainstem entry and an electrical response confirmed before dissection begins. Once a threshold has been established, the voltage is increased to at least three times the threshold value, and the stimulator is swept across the exposed surface of the tumor to confirm the absence of facial nerve fibers before dissection is begun. With larger tumors, the location of the facial nerve may not be immediately apparent. In such cases, we start with 0.3 V and map the accessible region, and if no response is obtained, we repeat the search at 0.5 and 1.0 V. If no response is obtained at 1.0 V, it can be safely assumed that the facial nerve is not on the exposed surface, and dissection can proceed.

During dissection, the stimulator is used repeatedly to scan the operative field for the presence of facial nerve fibers as the tumor is mobilized, using suprathreshold stimulus intensities as described previously. Once a response is obtained, stimulus intensity is reduced to 0.1 to 0.2 V, and the responsive region is narrowed. When the nerve is in sight, the electrode is placed directly on the nerve, and a threshold is obtained by slowly increasing the stimulus level from zero until a response is obtained. Further stimulation for mapping the location of the nerve is carried out at approximately three to five times this threshold, which should be periodically rechecked as dissection proceeds.

The spatial resolution of electrical mapping with monopolar stimulation is determined by stimulus intensity. For the most accurate localization, the stimulus is kept at a low level. At just suprathreshold levels, the spatial resolution is less than 1 mm, allowing the facial nerve to be easily distinguished from the adjacent vestibulocochlear complex. Conversely, to confirm that the nerve is not in an area about to be cut or cauterized, higher levels of stimulation (up to 1.0 V) are used to reduce the likelihood of false-negative results. As more and more tumor is removed, the course of the facial nerve can be mapped from brainstem to internal auditory canal. Although the nerve may be relatively cylindrical at each end, it frequently is compressed by the tumor in the cerebellopontine angle and may be seen as a broad, flat expanse of fibers splayed across the surface of the tumor. Frequently, the only way to identify the nerve and distinguish it from arachnoid tissue is with electrical stimulation; the nerve may be literally invisible to photons and visible only with electrons!

Assessment of Functional Status of Nerves after Tumor Removal

The primary use of intraoperative stimulation is in localizing and mapping the course of cranial nerves in relation to cerebellopontine angle tumors. However, electrical stimulation also is used to determine changes in the functional status of these nerves and is a useful predictor of postoperative function. In general, facial EMG responses elicited by low-threshold stimulation of the seventh nerve at the brainstem after total tumor resection constitute a good but not infallible predictor of postoperative function, because transient or delayed-onset facial palsies may be seen even when a low threshold is obtained at the end of the operation.[50-53] Conversely, a substantially elevated threshold or the inability to elicit a response with stimulation up to 1 V carries a significant likelihood of postoperative facial dysfunction, particularly in the short run.[51]

Methods based on measurement of the compound muscle action potential (CMAP) amplitude after tumor removal also have been used to quantify the functional status of the seventh nerve.[32,54] Absolute amplitude is quite variable between patients, however, and may be partially determined by nonspecific factors such as precise electrode placement, amount of subcutaneous fat,[29] facial nerve dimensions, and muscle mass.[55] These variations have led some investigators to use ratios rather than absolute values for assessment of postoperative facial nerve function. Taha and associates[56] measured the ratio of CMAP amplitudes to stimulation at the brainstem proximally and at the internal auditory meatus distally after tumor excision and found that proximal-to-distal amplitude ratios greater than 2:3 were associated with excellent outcome. Similarly, Isaacson and colleagues[57] analyzed proximal-to-distal amplitude ratios and reported that a higher ratio reflected good immediate postoperative facial nerve function. Lin and coworkers[55] used the ratio between proximal amplitude measurement after tumor dissection and supramaximal amplitude measurement in response to transcutaneous facial nerve stimulation and found that a CMAP ratio greater than 50% of maximum had a 93% positive predictive value when measured at 0.3 mA.

Prediction of long-term rather than short-term facial nerve function is the surgeon's major concern, because this would allow for better patient counseling and planning of rehabilitative treatment.[58] It has been suggested that low threshold recorded at the brainstem after tumor resection is a good predictor of long-term facial nerve function[50,59-61]; however, the ability of threshold to accurately predict long-term function has been questioned by some.[62,63] Neff and colleagues[64] evaluated a combination of threshold and amplitude and found that a minimum threshold of 0.05 mA together with a CMAP amplitude greater than

240 μV predicts a good postoperative outcome 1 year postoperatively. Fenton and associates[65] concluded that a more reliable predictor of long-term facial nerve is the clinical grade of early postoperative facial function. They also demonstrated that all patients with a recordable EMG response to proximal stimulation after tumor dissection, irrespective of the threshold or amplitude, recovered to a follow-up grade III or better facial nerve function. Although this correlation has been previously reported,[53,54,61,66,67] its importance has gone unnoticed. Therefore, it is now accepted that whenever a recordable response to electrical stimulation of whatever amplitude or threshold can be demonstrated, the facial nerve is most likely to show signs of improvement with follow-up, and intervention is therefore not recommended within the first year.[65] On the other hand, the absence of response to stimulation at the end of surgery does not doom the patient to a bad outcome. If the nerve is anatomically preserved, even with an immediate postoperative palsy, there is still a good possibility of eventual return of function as functional nerve fibers regenerate. Partial recovery of function in patients with unrecordable responses after surgery has been previously reported.[68] The earlier the onset of recovery, the better its quality; however, ifevidence of recovery is lacking at 12 months, then it is unlikely to occur.[69]

Intraoperative Identification of the Nervus Intermedius

Anatomic identification of the nervus intermedius during cerebellopontine angle surgery is important in order to prevent confusing this nerve with the facial nerve itself. Electrical stimulation of the nervus intermedius during cerebellopontine angle surgery was found to produce a characteristic response in the orbicularis oris channel only: long latency, low amplitude, and higher in threshold than the facial nerve response[70] (Fig. 178-4). Initial confusion between the nervus intermedius and a facial nerve strand at the time of stimulation is possible, because the entire course of the facial nerve may not be visually apparent to the surgeon as it passes anterior to the tumor—most common surgical approaches are from the posterior. Furthermore, tumor growth causes the facial nerve to be stretched and widened, so it often cannot be identified as a solitary trunk but rather is seen as a wide ribbon. The surgeon must recognize that stimulation of the nervus intermedius can cause EMG activity in the facial nerve monitoring channels (at least the orbicularis oris) but that the main trunk of the facial nerve may lie in an entirely different location within the cerebellopontine angle (Fig. 178-5). To protect this critical structure, it is imperative for the surgeon to locate the facial nerve itself by stimulation.

Spontaneous and Mechanically Evoked Activity

EMG responses to intracranial stimulation are the most specific indicators of cranial nerve localization and functional status. However, spontaneous EMG activity and EMG responses related to intraoperative events also are useful in preserving neural function. Some patients, particularly those with significant preoperative facial deficits,

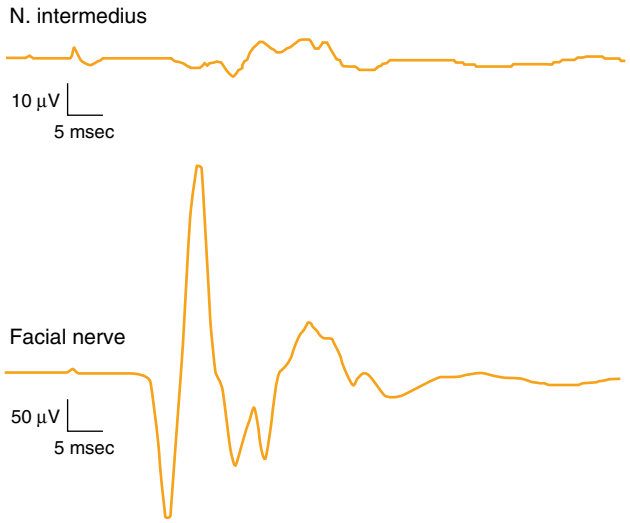

Figure 178-4. Responses in orbicularis oris to stimulation of nervus intermedius *(top)* and facial nerve *(bottom)*. Note smaller scale in nervus intermedius response, which is smaller, of longer latency, and seen only in the lower facial nerve channel. *(From Ashram YA, Jackler RK, Pitts LH, Yingling CD. Intraoperative electrophysiological identification of the nervus intermedius.* Otol Neurotol. *2005;26:274.)*

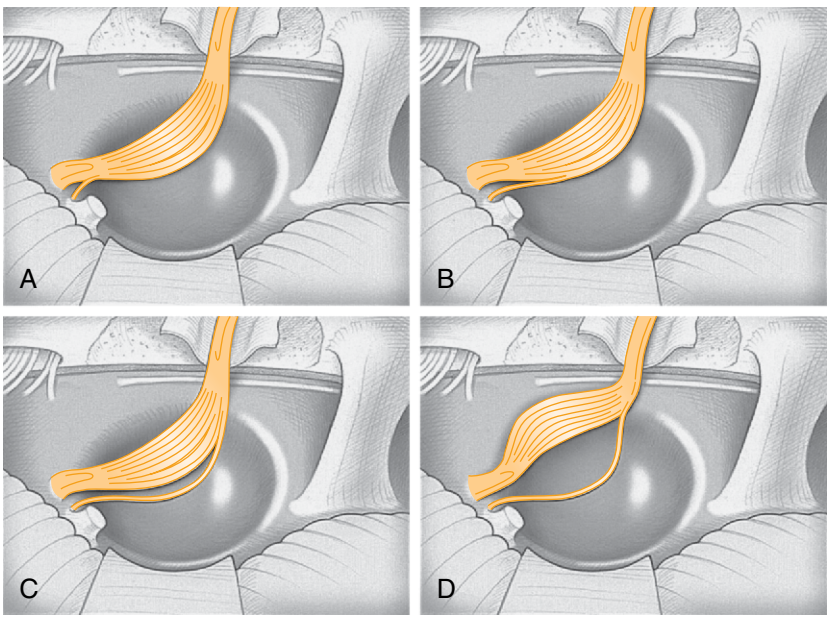

Figure 178-5. Anatomic variants in relationship between the nervus intermedius and the facial and vestibulocochlear nerves. **A,** Nervus intermedius joining nerve VII-VIII complex near brainstem root entry zone. **B,** Nervus intermedius joining nerve VII-VIII in mid-cerebellopontine angle. **C,** Nervus intermedius joining nerve VII-VIII near the porus acusticus. **D,** Nervus intermedius taking a separate course through cerebellopontine angle, where it can be misidentified as the facial nerve unless its unique response characteristics are recognized. *(From Ashram YA, Jackler RK, Pitts LH, Yingling CD. Intraoperative electrophysiological identification of the nervus intermedius.* Otol Neurotol. *2005;26:274.)*

demonstrate baseline tonic facial EMG activity; this often decreases as the nerve is decompressed with opening of the dura and draining of CSF. Virtually all patients exhibit some mechanically evoked facial EMG activity during tumor dissection, retraction, irrigation, or other intraoperative maneuvers. An increase in EMG activity associated with a particular surgical maneuver often is the earliest indicator of the location of the facial nerve. When such activity is elicited, the stimulator should then be used to search the area in question to positively identify the nerve if possible. Frequently, operative manipulations elicit EMG activity, even if the nerve is not in the immediate area, because of transmission of traction or pressure from the tumor to the nerve. In such cases, a negative response to electrical stimulation indicates that dissection can proceed. In other cases, stimulation after mechanically elicited activity results in identification of the nerve, which can then be precisely localized as described previously.

Finally, ongoing EMG activity often is an indirect indicator of depth of anesthesia, which is of particular concern when no muscle relaxants can be used. A simultaneous increase in spontaneous EMG activity on all channels is unlikely to result from localized dissection. When such a generalized increase occurs, the anesthesiologist should be notified immediately, because overt patient movement often occurs within a few seconds.

Patterns of Mechanically Evoked Electromyographic Activity

Prass and Lüders[6] distinguished two types of EMG activity associated with intraoperative events: *burst* and *train* activity. These investigators suggested that the phasic "burst" pattern, characterized by short, relatively synchronous bursts of motor unit potentials, corresponded to a single discharge of multiple facial nerve axons, and was associated with direct mechanical nerve trauma, free irrigation, application of pledgets soaked with lactated Ringer's solution over the facial nerve, or electrocautery. When burst activity occurs, it usually indicates that the facial nerve is being stimulated enough to result in depolarization and production of EMG response but not necessarily to the point of injury.[71] It generally is accepted that the occurrence of burst activity of small amplitude (less than 500 μV in amplitude) is not of major concern, and accordingly, the surgeon need not be warned each time such activity occurs.[72,73] On the other hand, the occurrence of large-amplitude burst activity (greater than 500 μV in amplitude) during the critical stages of dissection or final stages of drilling usually indicates a degree of facial nerve injury, the extent of which differs with the force and number of impacts.

As described by Prass and Lüders,[6] the second pattern, tonic or "train" activity, consisted of episodes of prolonged asynchronous grouped motor unit discharges that lasted up to several minutes. These episodes were most commonly associated with facial nerve traction, usually in the lateral to medial direction. The investigators further divided such train activity into higher-frequency trains (50 to 100 Hz), dubbed "bomber potentials" because of their sonic characteristics, and lower-frequency discharges (1 to 50 Hz), which were more irregular and had a sound resembling popping popcorn. The onset and decline of "popcorn" activity were more gradual than the more abrupt onset and decline of "bomber" activity.

Subsequently, Romstock and coworkers[72] classified train activity into three distinct patterns: A, B, and C trains. *A trains* are characterized by a sinusoidal symmetrical sequence of high-frequency and low-amplitude signals that have a sudden onset; *B trains* are regular or irregular sequences of repeated spikes or bursts with maximum intervals of 500 msec; and *C trains* are characterized by continuous irregular EMG responses that have many overlapping components. Although B and C trains did not correlate with postoperative function, the authors suggested a relation between the occurrence of A trains and poor postoperative facial nerve function.

Nakao and colleagues[74] classified train activity that occurred during the last stage of tumor resection into an *irritable* pattern with frequent EMG responses to the slightest stimuli, a *silent* pattern with few or no EMG responses, a *stray* pattern with persistent train responses up to 20 minutes despite temporary discontinuance of surgical manipulation, and an *ordinary* pattern related to mechanical stimulation of the nerve but not easily elicited. These workers found an association between the occurrence of silent or stray EMG patterns and poor postoperative outcome. The occurrence of train activity does not always imply an impending nerve injury but indicates the proximity of the facial nerve to the region of dissection and thus should be considered a reassuring sign denoting an intact and responsive nerve.[71] However, train activity of large amplitude (greater than 500 μV in amplitude) has been linked to postoperative nerve injury of variable degree,[75,76] and such events require prompt warning to the surgeon. The absence of large-amplitude train activity, on the other hand, does not always mean safe dissection, especially with large tumors producing significant facial nerve compression. The nerve axons become stretched, partially damaged, and less responsive than healthy ones, generating little EMG activity despite significant manipulation.[77] Therefore, spontaneous EMG activity may not be a reliable warning sign in large tumors, and the frequent use of electrical stimulation is important to map the tumor surface and measure any change of threshold from baseline to assess the condition of the nerve. Figure 178-6 shows representative samples of different types of EMG activity often encountered in vestibular schwannoma removal.

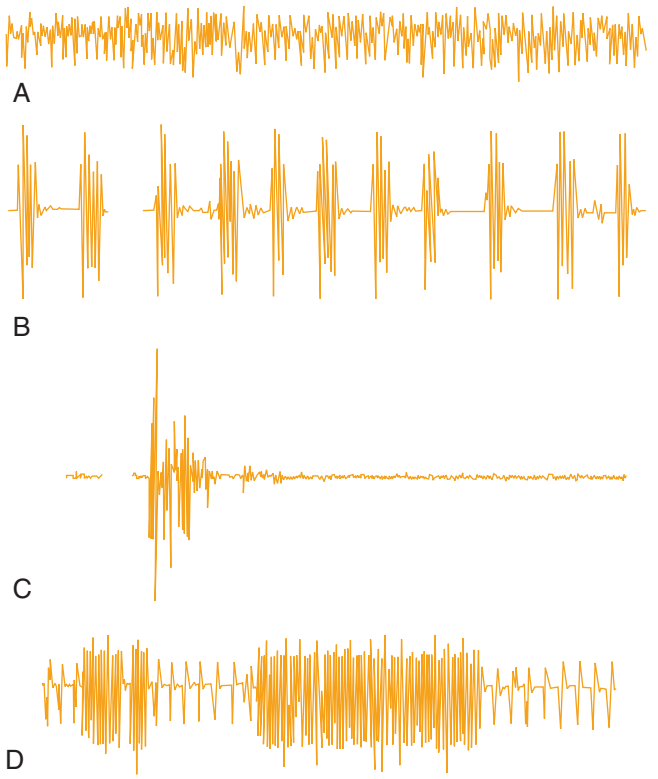

Figure 178-6. Illustrative examples of three types of electromyographic activity often seen during vestibular schwannoma surgery. **A,** Dense tonic (sustained) activity, often associated with nerve stretch and demonstrating a sinusoidal pattern. **B,** Lower tonic activity, called popcorn activity. **C,** Phasic (transient) burst activity typically associated with direct contact with the nerve. Such events are not of major significance unless they involve large-amplitude trains and occur during critical stages of dissection. **D,** Burst activity superimposed on ongoing small-amplitude train; it is important not to overlook such events overlapping on background activity, because they may pass unnoticed despite their significance. *(From Yingling CD, Ashram YA. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler R, Brackmann DE, eds.* Neurotology. *2nd ed. Philadelphia: Elsevier; 2005:958.)*

Limitations of Electromyographic Monitoring

Despite the wide use of intraoperative EMG monitoring, it still has its limitations. A major problem with EMG monitoring is its relatively low specificity. EMG channels can easily pick up artifacts, and the distinction between them and true EMG activity may sometimes be

difficult. An example is artifacts produced by bimetallic potentials as a result of contact between surgical instruments made of different metals; because these may be associated with intraoperative events similar to those producing true EMG responses, they can be difficult to recognize. Some useful criteria include the fact that artifacts typically are higher in frequency content than EMG activity and thus sound more "crackly" than true EMG activity, which has more of a "popping" sound; and the tendency for artifacts to appear simultaneously on several channels, which is unlikely for EMG activity (Fig. 178-7). Experienced monitoring personnel are in an optimal position to make such decisions, rather than surgeons, who are focused on the operative field. Another limitation of EMG monitoring is that it is virtually useless during electrocautery, when the facial nerve is potentially at high risk. Attempts to reduce the artifact from bipolar cautery have met with limited success, because such devices generate high-amplitude, broadband noise that is difficult to filter out. Techniques based on detection of motion, which are not subject to electrical interference, such as video monitoring, may provide an important adjunct to EMG monitoring despite their relatively lower sensitivity. In our experience, the practical way to deal with this problem is to use electrical stimulation before bipolar electrocoagulation to confirm that the area to be cauterized is free from facial nerve fibers. The absence of a response to higher levels of electrical stimulation (up to 1 V) in an area about to be cauterized is an indication that electrocautery can proceed safely.

Another problem with EMG monitoring is that facial nerve integrity with stimulation cannot be assessed unless the nerve is accessible in the surgical field. However, with large tumors, the facial nerve is at risk of being traumatized before it is visually apparent to the surgeon and may not be responsive to mechanical manipulation. In this situation, the facial nerve location can be anticipated by use of a flexible-tipped probe to stimulate within dissection planes or even behind the tumor, out of the surgeon's view, without concern for damaging unseen vascular or neural structures. However, the development of continuous facial nerve monitoring methods that do not rely on visual identification of the nerve remains one of the major challenges for future research.

Microvascular Decompression

Microvascular decompression procedures for treatment of trigeminal neuralgia and hemifacial spasm involve potential damage to cranial nerves in the posterior fossa; therefore, EMG and ABR monitoring frequently are used with such procedures,[78] with the same techniques described elsewhere in this chapter.

In the specific case of microvascular decompression for hemifacial spasm, however, Møller and Jannetta[40] described a different technique. This method is based on the finding of abnormal muscle response in patients with hemifacial spasm, in whom muscles innervated by one branch of the facial nerve respond when another branch is stimulated. This response is due to abnormal spread of activity from one branch of the facial nerve to another on the affected side. Because it is not suppressed by anesthesia, it can be recorded intraoperatively so long as the patient is not paralyzed.

For a typical procedure, recording electrodes are inserted into the mentalis muscle (innervated by the marginal mandibular branch of the seventh nerve) and the orbicularis oculi (temporal branch). Subdermal needle electrodes also are inserted adjacent to the marginal mandibular and temporal branches of the seventh nerve for stimulation. Of note, the stimulation voltage required will be higher (4 to 20 V) than for direct stimulation of the nerve intracranially. Intracranial stimulation as described previously can, of course, also be used to ensure the integrity of the facial nerve in decompression procedures for hemifacial spasm. Figure 178-8 shows typical results with such a procedure.

If the abnormal response is not seen at the outset, it generally can be triggered by a brief train of stimuli at a high frequency (50 Hz). The amplitude of the abnormal response typically is lower than that of the normal response and may drop even further after the dura is opened, presumably because of a shift in the relation of the vessel to the nerve. Nevertheless, an abnormal response at some amplitude generally can be seen until the nerve is decompressed. Møller and Jannetta[40] recommend that the decompression be carried out until no abnormal response can be elicited. They state that the abnormal response disappears immediately when the offending vessel is removed from the nerve, a finding also reported by Halnes and Torres,[30] although in our experience, it may take a few minutes for the abnormal response to disappear completely. Debate continues over the association between the persistence or disappearance of the abnormal muscle response and ultimate clinical outcome. Kong and associates[79] found that long-term outcomes were

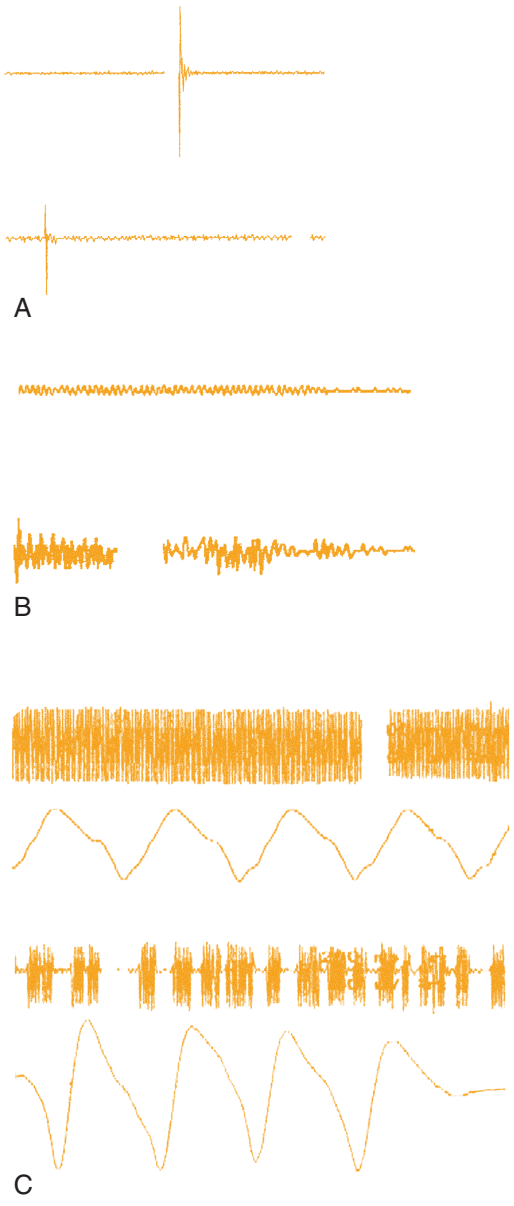

Figure 178-7. Electromyography (EMG) activity versus artifacts. **A,** *Upper trace*: Artifact produced by contact of different metallic instruments in surgical field. Note sharp edges on waveforms with exponential decay (may be confused with spike activity). *Lower trace*: Single electromyographic spike with a low-amplitude EMG background and no exponential decay. **B,** *Upper trace*: Regular sinusoidal artifact produced during drilling of the internal auditory canal (IAC). *Lower trace*: Irregular EMG activity while drilling IAC. **C,** *Upper two traces*: Regular artifact with two time scales, 200 msec/cm and 5 msec/cm. *Lower two traces*: EMG activity on the same two time scales. At 200 msec/cm, it may be difficult to differentiate between true EMG and artifact. However, with the faster 5 msec/cm time base, trace 2 shows that the artifact waveform is regular and synchronized, whereas trace 4 reveals the irregularities that characterize true EMG activity. *(From Yingling CD, Ashram YA. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler R, Brackmann DE, eds.* Neurotology. *2nd ed. Philadelphia: Elsevier; 2005:958.)*

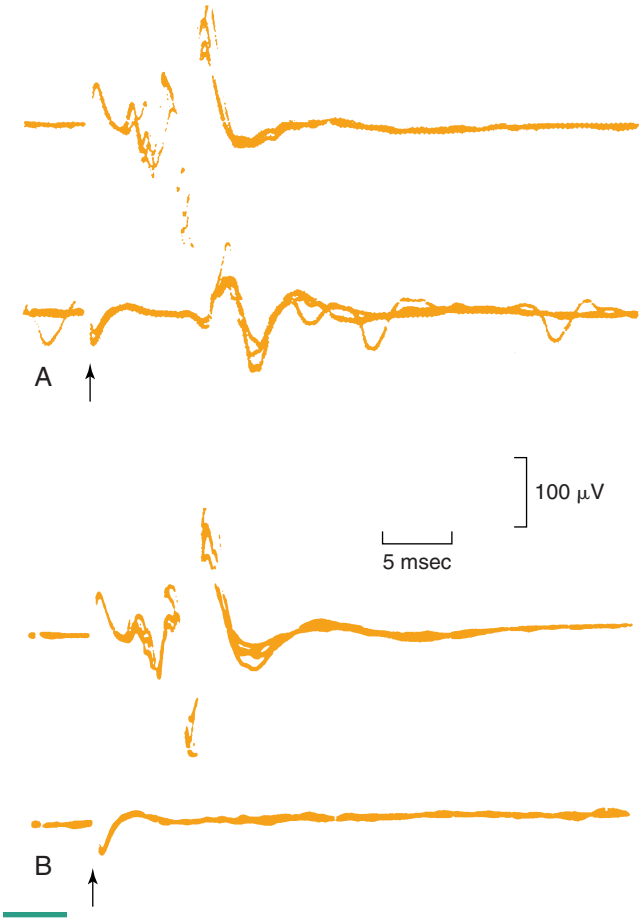

Figure 178-8. Responses during intraoperative monitoring of microvascular decompression for hemifacial spasm. Stimulating electrodes in temporal branch of facial nerve; recording channels orbicularis oculi *(top)* and mentalis *(bottom)*. **A,** *Before decompression*: The normal response in the orbicularis oculi to stimulation of the temporal branch is seen in the upper channel. The lower channel shows the abnormal response at prolonged latency in mentalis to stimulation (at time indicated by *arrow*) of temporal branch. **B,** *After decompression*: Abnormal response in mentalis no longer seen, normal response in orbicularis oculi unchanged. *(From Yingling CD. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackmann DE, eds.* Neurotology. *St Louis: Mosby; 1994:967.)*

significantly better in patients whose abnormal response disappeared completely after decompression than in those with a persistent abnormal response; however, other investigators failed to prove this association.[80] More work is still necessary to elucidate the prognostic significance of the abnormal muscle response.

Parotid Surgery

Facial nerve monitoring during parotidectomy is similar to facial nerve monitoring in cerebellopontine angle surgery, except that the seventh nerve generally is the only nerve at risk. Thus, rather than using multiple EMG channels to monitor several nerves, all available channels can be used to monitor different branches of the facial nerve, which divides within the parotid gland (pes anserinus). Our typical four-channel montage includes closely spaced bipolar electrode pairs in the frontalis muscle (temporal branch of the seventh nerve), lower orbicularis oculi (zygomatic), upper orbicularis oris (buccal), and mentalis (marginal mandibular). The pattern of responses obtained with electrical stimulation can be used to determine which branch is being stimulated. EMG activity in a single channel indicates activation of a single branch of the nerve distal to the pes, activity in two or three channels generally indicates a location within the pes, and a response on all channels indicates activation of the main trunk of the nerve between the pes and the stylomastoid foramen. This is true both for mechanically elicited activity and for responses to electrical stimulation. The methods for recording both mechanically elicited activity and responses to electrical stimulation are similar to those used intracranially; of note, however, because the intracranial portion of the facial nerve lacks the thick epineurium found distally, thresholds for direct stimulation of the nerve within the parotid gland will typically be somewhat higher than those in the posterior fossa.

Other Otologic Surgery

Facial nerve monitoring also may be useful in many otologic procedures. For example, congenital aural atresia may be associated with an anomalous course of the facial nerve or may require rerouting of the nerve to expose the oval window. Surgery for chronic otitis media and cholesteatoma also may benefit from facial nerve monitoring, particularly when preoperative findings include preexisting facial dysfunction or computer tomographic (CT) evidence of fallopian canal erosion. Revision tympanomastoidectomies carry a higher risk of facial nerve injury because landmarks may be obscured by scar tissue. However, monitoring is not necessarily indicated in every routine case. There is no simple rule for determining when monitoring is indicated; a number of factors must be taken into consideration, including preexisting deficits, size and location of lesions, previous surgery, and the surgeon's experience. Besides serving as a guide to drilling, dissection, and verifying the integrity of the nerve, monitoring also is useful in detecting facial nerve dehiscence.[81,82] Noss and associates[81] suggested that the electrical stimulation threshold of the facial nerve is more reliable than surgical observation alone in identifying risk for injury secondary to dehiscence. These workers found that a facial nerve stimulation threshold less than 1 V identifies a nerve that is electrophysiologically dehiscent and thus should be considered at increased risk for injury.

Other Motor Nerve Monitoring

Third, Fourth, and Sixth Nerve Monitoring: Extraocular Muscles

Monitoring of the oculomotor (third), trochlear (fourth), and abducens (sixth) nerves, which innervate the various extraocular muscles, frequently is necessary in surgery for more anterior skull base lesions. These may include, for example, cavernous sinus tumors, prepontine tumors, and petrous apex lesions with significant anterior or medial extension. Although the basic principles are the same as for facial nerve monitoring, the relative inaccessibility of the target muscles causes special difficulties.

Paired hookwire electrodes are now preferred for monitoring of extraocular muscles, because they are flexible and thus less likely to traumatize the eye. The hookwire electrodes are inserted through the eyelids into proximity with the tendons of the target muscles, where they pick up volume-conducted activity from the muscles themselves (Fig. 178-9).

The oculomotor nerve (third nerve) is the easiest from which to obtain specific responses, because it innervates all of the extraocular muscles except for the lateral rectus and superior oblique. Placement of an electrode at the infraorbital margin, roughly one third of the distance out from the inner canthus, will result in pickup of activity from the inferior oblique or inferior rectus muscle, both of which are innervated by the third nerve (see Fig. 178-9). Similarly, activity in the lateral rectus muscle, innervated by the abducens (sixth) nerve, can be detected by an electrode inserted from the lateral canthus. The trochlear nerve (fourth nerve) is the most difficult to monitor, because the superior oblique muscle does not connect to the eyeball in the same straightforward fashion as for the other extraocular muscles. We have described these procedures in greater detail elsewhere.[2]

The latency of responses in the extraocular muscles to stimulation of the third, fourth, or sixth nerve typically is 2 to 3 msec, much shorter than that of responses to seventh nerve stimulation. This short latency helps prevent confusion of true third, fourth, or sixth nerve responses with seventh nerve activity, which is a common contaminant of recordings from these muscles (Fig. 178-10).

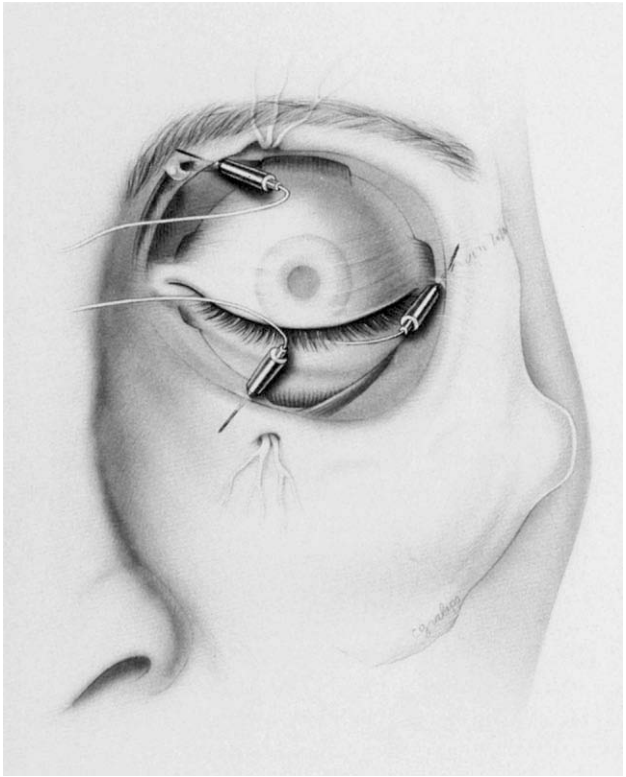

Figure 178-9. Placement of electrodes in extraocular muscles for monitoring cranial nerves III, IV, and VI. Electrodes are inserted through closed eyelids (drawn as if transparent), against inner surface of bony orbit, to record from inferior rectus/inferior oblique (third nerve), superior oblique (fourth nerve), and lateral rectus (sixth nerve). The illustration shows monopolar needle electrodes; flexible bipolar hookwire electrodes are now preferred for recording from extraocular muscles (see text for details). *(From Yingling CD. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackmann DE, eds.* Neurotology. *St Louis: Mosby; 1994:967.)*

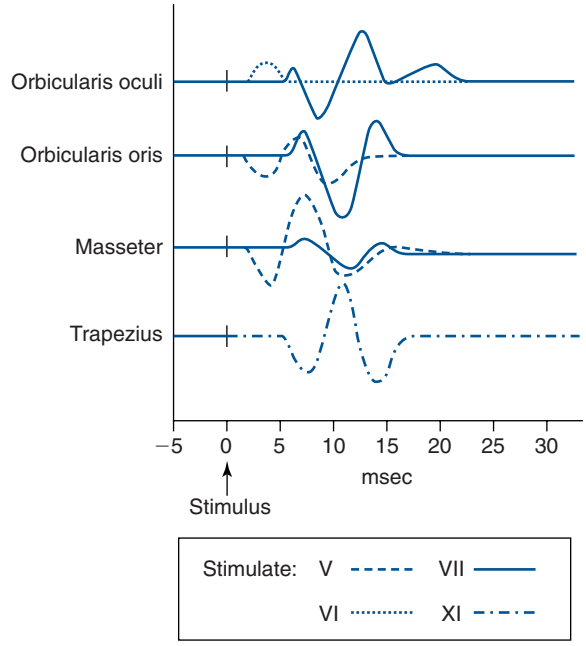

Figure 178-10. Schematic representation of responses obtained in four-channel montage (see Fig. 178-1) with intracranial stimulation of different motor nerves. Despite crosstalk in fifth and seventh nerve channels, these nerves can be clearly distinguished by the shorter latency of the responses to fifth nerve stimulation. Stimulation of the sixth nerve produces a short latency response localized to the orbicularis oculi channel because of volume conduction from the lateral rectus to the electrode at the outer canthus; stimulation of the eleventh nerve produces response restricted to the trapezius (see text for details). *(From Jackler RK, Pitts LH. Acoustic neuroma.* Neurosurg Clin N Am. *1990;1:199.)*

Complications (other than transient bruising) from monitoring of extraocular muscles are fortunately rare. It should be kept in mind, however, that the placement of electrodes near the globe is not without risk. In one of our patients, placement of an electrode near the superior oblique muscle resulted in bleeding and increased intraocular pressure, complicated by obstructed venous drainage due to compression of the posterior orbit by a neoplasm. Fortunately, this was detected before draping; the surgery was aborted and a lateral canthotomy was performed to relieve the excessive intraocular pressure. The tumor was removed a few days later, without further attempt to monitor fourth nerve function. Furthermore, diagnostic ocular EMG has been associated with rare occurrences of ecchymoses of the conjunctiva, subcapsular hemorrhage, and exposure keratitis, all of which clear without sequelae. Of greater concern is inadvertent perforation of the globe, which is more likely to occur in the presence of undetected glaucoma.[83]

Trigeminal Motor Branch Monitoring

Most efforts at intraoperative monitoring of the fifth nerve have concentrated on the motor portion (V3m), which is a branch of the third division of the nerve. There have been very few attempts to monitor the sensory branches, largely because of the technical problems encountered in overcoming stimulus artifact in trigeminal SEP recording, which is due both to the short latency of trigeminal SEPs and the proximity of the stimulation and recording sites.[84,85] However, Soustiel and coworkers[86] obtained good results with use of alternating-polarity stimuli to cancel the stimulus artifact.

The principles of monitoring V3m are the same as for seventh nerve monitoring. In practice, however, crosstalk between channels complicates the situation. Stimulation of V3m can produce large-amplitude CMAP responses that will be recorded by electrodes in masseter or temporalis and transmitted to facial muscles. Similarly, activity in facial muscles may be seen in the masseter or temporalis channels, creating the possibility of crosstalk in both directions. This overlap may pose a problem in interpreting the origin of mechanically elicited EMG activity. To minimize crosstalk, the V3m recording electrodes should be located where they will be minimally affected by facial muscle activity. We currently use hookwire electrodes placed in the temporalis muscle underneath the zygomatic arch, unless this is not possible because of the surgical approach (i.e., subtemporal or middle fossa); in such cases, the electrodes must be placed in the masseter.

Crosstalk presents less of a problem with the use of electrical stimulation because it is possible to distinguish between V3m and the seventh nerve by the latency of responses. Stimulation of the seventh nerve produces CMAP with an onset latency that typically ranges between 6 and 8 msec, depending on the exact site of stimulation, although it may be as short as 5 msec with stimulation in the far lateral internal auditory canal or delayed to as long as 20 msec if the nerve has been severely compromised by the tumor. On the other hand, stimulation of V3m produces responses of significantly shorter latency, ranging from approximately 3.5 to 5 msec. (Taken together, these findings suggest a useful mnemonic: "fifth nerve less than 5, seventh nerve approximately 7.") The differential pattern of responses seen in a typical acoustic neuroma case is shown in Figure 178-10.

Monitoring of Lower Cranial Nerves: Ninth, Tenth, Eleventh, and Twelfth Nerves

Larger acoustic neuromas with a significant inferior extension may involve the lower cranial nerves, and intraoperative monitoring of these nerves will be beneficial. More commonly, cranial nerves IX and XII are involved by tumors of the posterolateral cranial base, such as glomus

jugulare tumors, meningiomas, or schwannomas of the ninth, tenth, or eleventh nerve. The morbidity associated with removal of tumors in this region is due primarily to neural damage, which may result in deterioration of voice, swallowing difficulties, or weakness and pain in the shoulder. These nerves can be monitored with EMG techniques analogous to those already described, with appropriate placement of recording electrodes.[87-89]

The glossopharyngeal (ninth nerve) nerve primarily mediates sensation to the upper pharynx and taste to the posterior third of the tongue. The only muscle innervated by this nerve is the stylopharyngeus, which is not easily accessible for insertion of EMG recording electrodes. However, electrodes in the posterior part of the soft palate ipsilateral to the tumor will pick up volume-conducted activity from the stylopharyngeus (Fig. 178-11; see also Fig. 178-13). The electrodes are inserted intraorally after intubation and are best sutured in place to prevent accidental dislodgement.

In contrast with other lower cranial nerves, mechanical stimulation of the ninth nerve during dissection typically produces little EMG activity, so it is the nerve for which function most commonly is lost. Fortunately, the deficits produced by isolated ninth nerve damage are relatively minor. Electrical stimulation of this nerve produces EMG responses at a latency of approximately 5 to 7 msec, which generally are of low amplitude, because recording electrodes are not placed directly in the stylopharyngeus. Similar responses often are seen with stimulation of the tenth nerve; however, it is easy to distinguish between the ninth and tenth nerves with multichannel recordings, because stimulation of the tenth nerve, but not the ninth nerve, also produces responses in the vocalis muscle (see later).

The vagus (tenth) nerve is one of the most complex cranial nerves, with myriad functions affecting the cardiac, respiratory, and gastrointestinal systems, as well as providing motor innervation to pharyngeal and laryngeal musculature. The vagus nerve commonly is monitored using an endotracheal tube with integral EMG electrodes (Medtronic-Xomed, Jacksonville, Florida), so that bipolar recordings can be obtained from both left and right vocalis muscles without additional electrodes (Fig. 178-12A).

Laryngeal surface electrodes (RLN Systems, Jefferson City, Missouri), which are inserted intraorally, posterior to the larynx, after intubation with a standard endotracheal tube also have been used (see Fig. 178-12B). They have a flat contact surface that records from the posterior cricoarytenoid muscle. The large contact surface may provide more stable recordings and greater reliability than are achievable with other methods.[90] Another laryngeal surface electrode is the bipolar electrode, which wraps around and adheres to a standard endotracheal tube and is positioned between the vocal cords as the tube is inserted (Neurovision Medical, Ventura, California). Finally, Leonetti and coworkers[91] have described a method for transcricothyroid membrane placement of bipolar hookwire electrodes in the vocalis muscle.

The latency of EMG responses to electrical stimulation of the tenth nerve varies with the site of stimulation. Intracranial stimulation in the posterior fossa or jugular foramen produces response latencies ranging from roughly 4 to 6 msec. Stimulation of the recurrent laryngeal nerve in the neck, as during thyroid surgery, produces a much faster response (2 to 3 msec latency). Another important consideration with stimulation of the vagus nerve is cardiac effects; bradycardia and even asystole have been documented with traction on the tenth nerve in both the posterior fossa and jugular foramen regions. (In such circumstances, however, the total heart rate in the OR generally remains constant, because that of the anesthesiologist rises in compensation!) Fortunately, this effect generally is not seen with threshold-level electrical stimulation; however, during surgery in this region, the anesthesiologist should be prepared to administer anticholinergic agents on short notice if necessary.

Monitoring of the eleventh nerve with electrodes in the trapezius muscle (Fig. 178-13) has already been briefly considered earlier, because activity of this muscle is the most readily observable marker for identifying the nerves of the jugular foramen in removal of large acoustic neuromas or other cerebellopontine angle tumors. During monitoring for tumors of the jugular foramen region itself, it also may be useful to place electrodes in the sternocleidomastoid muscle if extra channels are

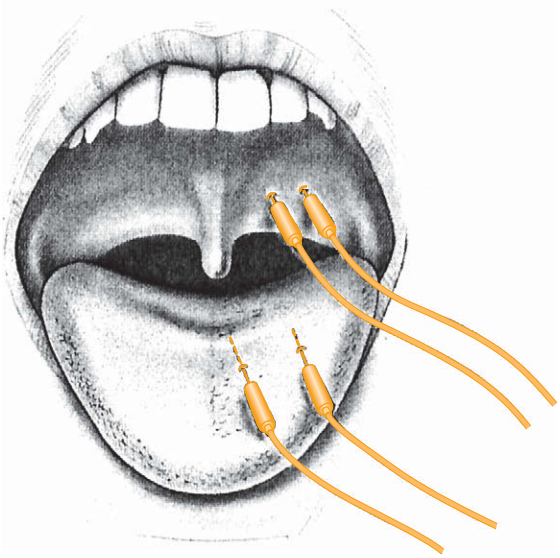

Figure 178-11. Placement of paired needle electrodes in the soft palate for monitoring the ninth cranial nerve and in the tongue for monitoring the twelfth cranial nerve *(From Lanser M, Jackler R, Yingling C. Regional monitoring of the lower (ninth through twelfth) cranial nerves. In: Kartush J, Bouchard K, eds.* Neuromonitoring in Otology and Head and Neck Surgery. *New York: Raven Press; 1992.)*

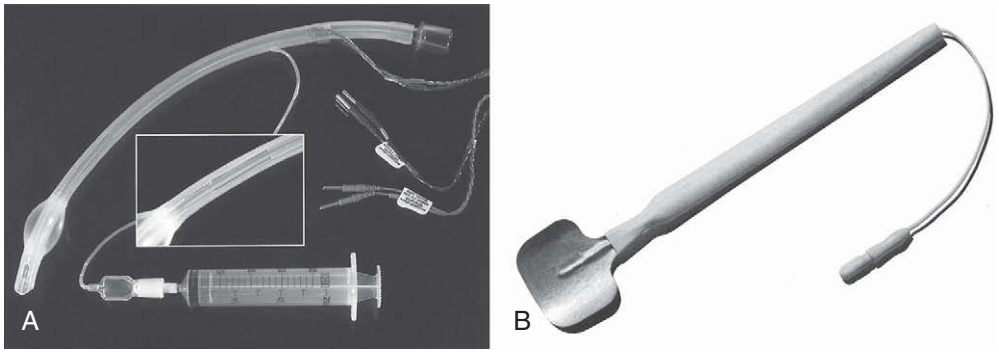

Figure 178-12. A, Electromyography (EMG) endotracheal tube. Two pairs of wires contact vocalis muscles bilaterally to record EMG activity resulting from activation of the recurrent laryngeal nerve, a component of the tenth cranial nerve **B,** Laryngeal surface electrode. The electrode is inserted into the postcricoid space after intubation with a standard endotracheal tube to record from the posterior cricoarytenoid muscles (tenth cranial nerve). *(**A,** Courtesy of Xomed-Treace, Jacksonville, Florida; **B,** courtesy of RLN Systems, Jefferson City, Missouri.)*

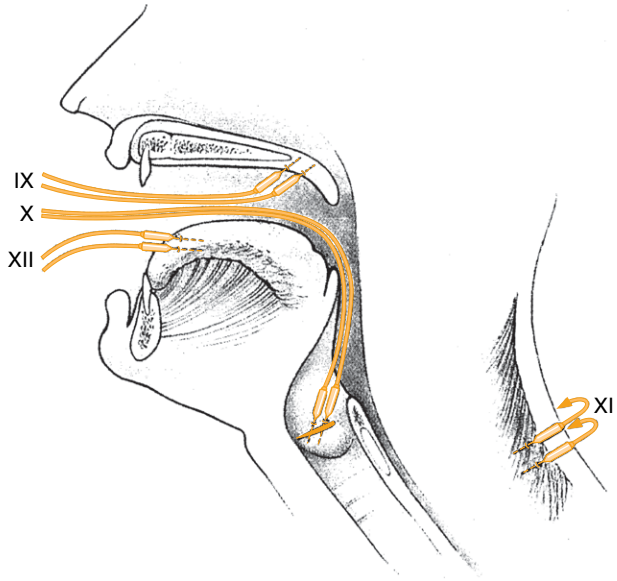

Figure 178-13. Sagittal view of placement of needle electrodes into the muscles used for lower cranial nerve monitoring. Needle electrode pairs are placed into the soft palate (ninth nerve), false vocal cord (tenth nerve), trapezius (eleventh nerve), and tongue (twelfth nerve). The electrodes placed in the false cord are unnecessary if one of the electrodes shown in Figure 178-12 is used instead. *(From Lanser M, Jackler R, Yingling C. Regional monitoring of the lower (ninth through twelfth) cranial nerves. In: Kartush J, Bouchard K, eds.* Neuromonitoring in Otology and Head and Neck Surgery. *New York: Raven Press; 1992.)*

available, especially if preoperative findings include preexisting eleventh nerve deficits and wasting of the trapezius. Because excessive movement from activation of trapezius muscles can be dangerous during surgery, stimulation of the eleventh nerve should be carried out at as low an intensity as feasible.

Finally, the twelfth cranial nerve provides motor innervation to the muscles of the tongue. Damage to this nerve produces the well-known sign of ipsilateral deviation seen on protrusion of the tongue, because of the predominance of the genioglossus muscle on the intact side, but in isolation does not usually produce major functional problems. However, damage to this nerve can lead to problems with chewing and swallowing, particularly in combination with deficits involving the eleventh and tenth nerves. This should be taken into account when facial reanimation with twelfth to seventh nerve anastomoses is under consideration in patients with lower cranial nerve deficits. The twelfth nerve can be monitored readily by insertion of electrodes into the lateral aspect of the anterior third of the ipsilateral tongue, with the electrodes sutured into place to prevent accidental dislodgement (see Figs. 178-11 and 178-13).

Cochlear Nerve (Eighth Nerve) Monitoring

The cochlear nerve is one of the most fragile of the cranial nerves and usually is much more intimately involved with acoustic tumors than the facial nerve. Thus, preservation of hearing generally is more difficult and less likely to be achieved than preservation of facial nerve function. However, recent advances in surgical and monitoring techniques have made preservation of hearing an attainable goal in removal of many smaller acoustic neuromas. Furthermore, the cochlear nerve is at risk in many other posterior fossa procedures, including resection of meningiomas and other nonacoustic tumors, vestibular neurectomies, and microvascular decompression of the fifth or seventh nerve. The most commonly used method for cochlear nerve monitoring has been intraoperative recording of the ABR.[2,11,38,55,93-110] ABR recording from the contralateral ear may be useful in cases with brainstem compression from large tumors, even if there is no hearing on the operated side.[92] More recently, direct eighth nerve action potentials,[11,38,45,49,77,111-114] electrocochleography (ECoG),[11,38,45,112,115-117] and recordings from the surface of the cochlear nucleus[118] also have been used. Finally, the use of evoked otoacoustic emissions, a more recently developed diagnostic technique, has been proposed as a potential method for monitoring cochlear nerve function.[119,120]

Auditory Brainstem Response Recording in the Operating Room

Since the ABR was first described in 1971,[121] ABR testing has become one of the most common neurophysiologic diagnostic modalities because of its ease of administration, relatively low cost, and ability to localize lesions in the peripheral auditory pathway.[122] The methods used in the OR are similar to those used clinically, with slight modifications.

Stimulus and Recording Parameters, Electrodes, and Placement

In clinical settings, stimuli for eliciting the ABR typically are delivered at rates of approximately 10 to 15 per second. For OR use, higher rates of 20 to 30 per second may be desirable to reduce averaging time. Stimulus intensity is maintained at a high level, usually at 95-dB peak sound pressure level (SPL) or higher, to obtain the best possible signal-to-noise ratio (SNR) (this is at least 60 dB above subjective click threshold levels). Although this is a high level for continuous stimulation, it does not seem to pose a problem; we are not aware of any reports of compromised hearing traceable to ABR recording over extended periods. Nevertheless, it is prudent to set the stimulus intensity at the lowest level that produces consistent waveforms.

It is necessary to use miniature earphones that do not compromise the surgical field. Møller[123] has successfully used small in-the-ear transducers designed for use with portable audio cassette players. Higher-quality transducers such as Etymotic Tubephones (Etymotic Research, Elk Grove Village, Illinois), which duplicate the frequency response of standard audiometric earphones, offer a more consistent, although expensive, alternative. For OR use, the main concern is obtaining clear definition of wave I, which often is the only useful ABR component in patients with acoustic neuroma. Any earphones that meet this criterion can be used with good success.

To minimize stimulus artifact, plastic tubing is used to conduct sound into the ear from a transducer placed a few inches away. The tube is terminated with a foam plug covered with a conductive gold foil (Tiptrode, Nicolet, Madison, Wisconsin), which also serves as one of the recording electrodes. In addition to providing acoustic isolation, this electrode provides improved definition of wave I over that obtainable with an earlobe or mastoid placement because of its closer proximity to the distal eighth nerve, the generator of wave I. The other electrode is placed at the vertex (Cz) or any point along the midsagittal plane between midforehead (Fpz) and vertex.

Because most of the power in the ABR is concentrated between 400 and 1400 Hz,[124] relatively narrow filter settings (i.e., 300 to 1500 Hz) produce more stable waveforms than wider settings (10 to 3000 Hz) typically used in the clinic, thereby facilitating rapid data collection. It also is desirable to collect a control ABR from the contralateral ear at the same time as that from the operated ear. This can be done by delivering stimuli alternately to each ear and separately averaging the left and right ear trials. Immediate comparison of the ABR from the operated side with that obtained from the contralateral ear provides a useful control for detection of nonspecific effects from factors such as anesthesia or temperature change. Of note, both ears must not be stimulated *simultaneously*, because the response from the contralateral ear could mask the loss of a response on the operative side.

Reducing Electrical and Acoustic Interference

It is imperative to take whatever steps are possible to minimize both electrical and acoustic artifacts. Electrical artifacts, which are of concern in both EMG and ABR monitoring, have already been covered. In addition, acoustic interference becomes a significant problem when either ABR or direct eighth nerve CNAPs are recorded. Drilling of the temporal bone to open the internal auditory canal can pose serious

obstacles to auditory nerve monitoring because of acoustic masking, which can degrade or even obliterate the ABR or CNAP.

Unfortunately, the cochlear nerve, as well as the inner ear itself, is at great risk during this period in typical retrosigmoid approaches. It may therefore be necessary to deliberately halt drilling periodically to obtain valid readings. Alternately, the neurophysiologist can manually start and stop the averaging process to collect data during intervals in the drilling—for example, when changing drill burrs.

Because time is a major concern, efforts have been made to develop monitoring techniques that greatly reduce data collection times. The two major approaches that have been advocated are (1) emphasizing near-field recording techniques obtained from an electrode placed directly on the cochlear nerve and (2) the use of digital in addition to analog filtering.[123-125]

Interpretation of Responses in Surgical Context

ABRs are relatively unaffected by the level of anesthesia or the type of anesthetic agents used, provided normal brain temperature is maintained. Above 32° C, ABR absolute and interpeak latencies increase as a function of decreasing temperature at a rate of approximately 0.17 to 0.2 msec/° C.[126,127] Even though core temperature is maintained at near-normal values, brainstem temperature may still decrease, especially in tissue bordering the exposed cerebellopontine angle, and especially if it is irrigated with saline that is cooler than body temperature. If core temperature is not maintained, recording ABRs from the contralateral ear can help determine whether any changes are systemic or localized.

Another factor that typically affects the ABR is the craniotomy itself. New pathways for current flow caused by the craniotomy, changes in the local environment of the cochlear nerve with removal of CSF, and exposure of the nerve to air or insertion of metallic retractors into the opening all create differences in the relationship between the sites of ABR generation in the eighth nerve and brainstem and the recording electrodes. These changes are of no clinical significance but can lead to shifts in ABR amplitude, latency, and waveform that may be as large as those associated with intraoperative events that significantly affect auditory pathways. Fortunately, most of these changes occur in the early stages of the procedure before the cochlear nerve is in serious jeopardy; it is, however, important to obtain a new intraoperative baseline after opening and placement of retractors, rather than relying on the pre-incision baseline.

In most acoustic neuroma surgeries, ABR recordings from the operated side progressively deteriorate over the course of surgery, Cerebellar retraction, trauma from dissection, acoustic trauma, decreased local temperature, and disruption of cochlear perfusion may all affect ABR peak I, III, and V amplitude and latency values.[93,106] Retraction of the cerebellum, particularly in the medial to lateral direction,[102] is thought to be one of the principal maneuvers responsible for significant ABR deterioration.[93,94] Every effort should be made to reverse such effects by adjustment of the cerebellar retractor, by temporarily halting dissection, or by attempting dissection from a different angle or direction.[100] Occasionally, wave I amplitude will be acutely enhanced, possibly because of mechanical trauma to auditory efferent (inhibitory) fibers, which travel with the vestibular nerve. This enhancement often is followed by a rapid decrease in amplitude, suggesting disruption of the blood supply to the cochlea. Figure 178-14 shows typical ABR results from three patients undergoing surgical removal of acoustic neuroma.

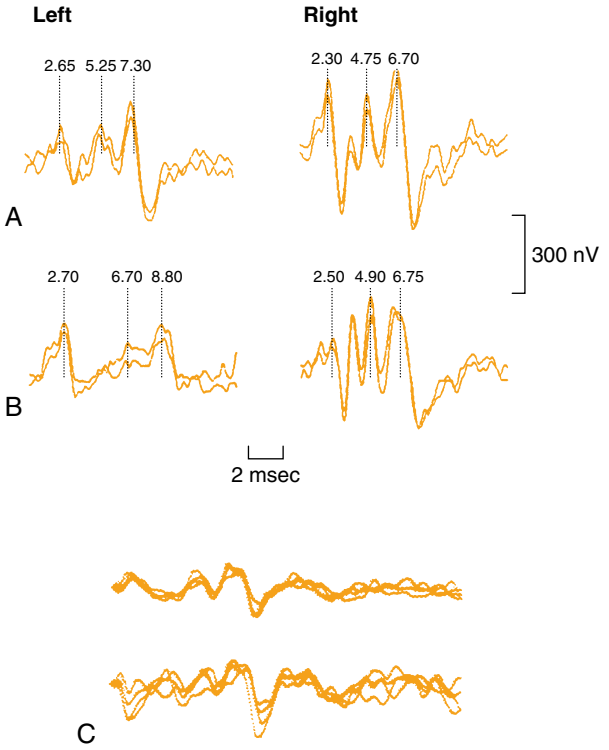

Figure 178-14. Representative examples of intraoperatively recorded auditory brainstem responses (ABRs) from three patients undergoing surgery for removal of acoustic neuroma. **A,** A 0.8-cm left-sided tumor in a 38-year-old woman with mild high-frequency hearing loss and speech discrimination scores of 92% for the left ear and 100% for the right ear. Pre-incision baseline shows well-defined ABRs on both sides. Note differences in interpeak latencies between left and right ears. **B,** A 1.8-cm tumor in a 52-year-old woman with moderate to moderate-severe sloping hearing loss and speech discrimination scores of 56% for the left ear and 90% for the right ear. Note that wave V is desynchronized and reduced in amplitude and that wave III is absent on the left side. Stimuli were alternating-polarity 100-msec clicks, presented at 80 dB above normal hearing level (nHL), 33.3/sec; 0.9-msec acoustic delay; averaged responses (N = 4000) were recorded from ipsilateral ear canal to vertex. Duplicate averages are overlaid. **C,** Intracanalicular right-sided tumor in a 48-year-old woman with nearly normal hearing, operated on by means of the middle fossa approach. *Top traces* are pre-incision baseline; *bottom traces* show preservation of auditory brainstem response after total removal of tumor, although a slight increase in latencies of waves IIII and V can be seen. Alternating-polarity 100-msec clicks, 80 dB above nHL, 21/sec; 0.9-msec acoustic delay; averaged responses (N = 1024) recorded from ipsilateral ear canal to midforehead. Four consecutive averages are overlaid. *(**A** and **B,** From Yingling CD, Gardi JG. Intraoperative monitoring of facial and cochlear nerves during acoustic neuroma surgery.* Otolaryngol Clin North Am. *1992;25:413; **C,** from Yingling CD. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackmann DE, eds.* Neurotology. *St. Louis: Mosby; 1994:967.)*

Correlation of Intraoperative Auditory Brainstem Response with Postoperative Auditory Function

If ABR wave V is found to be intact after the tumor has been completely removed, preservation of useful hearing usually is achieved.[128] However, even with such favorable intraoperative findings, hearing may still be lost. Sometimes, hearing is present in the immediate postoperative period but disappears within 2 or 3 days. The mechanism of this delayed loss is unclear, but it may involve vasospasm of the cochlear artery.[129] If only wave I of the ABR is intact, preservation of useful hearing is much less likely. In several cases, we have recorded an intact wave I for more than an hour after the cochlear nerve was transected at the brainstem, an event that is unlikely to be compatible with hearing preservation! Furthermore, transient changes in wave I and the cochlear microphonic potential, even if the response returns over the course of surgery, may reflect pathogenic changes to the nerve with poor long-term prognosis.[38,112]

Most studies with intraoperative ABR recording agree that if waves I and V are preserved, the chances of hearing preservation are excellent,[109,130,131] although exceptions have been noted.[95,109] Conversely, if waves I and V are lost, there is little or no chance of hearing preservation,[42,109,128,131] although rare exceptions have been reported.[94,132] Therefore, the surgical decision to transect the cochlear nerve, even to facilitate tumor removal, should not be based solely on ABR findings.

Matthies and Samii[133] reported that loss of wave V, although the most definite sign of postoperative hearing loss, is the least helpful in hearing preservation, because its occurrence is a late indication of compromise of hearing. Relying on earlier warning criteria would seem to be more practical, such as a wave V latency increase by 0.5 msec[134] and observation of wave III for change. Wave III is the earliest and most sensitive sign of cochlear nerve affection; change or loss of wave III is an early sign that usually is followed by wave V loss. Wave III changes therefore warrant special attention to permit prompt warning to the surgeon.

Direct Eighth Nerve Action Potentials

Placement of Electrodes

To provide more rapid feedback on the functional status of the cochlear nerve, the rate of data acquisition can be enormously speeded up by recording near-field auditory CNAPs with an electrode placed directly on the cochlear nerve near the brainstem root entry zone.[11,45,111,135,136] With this configuration, clear averages can be obtained with 64 to 128 trials or less, compared with the 1000 or more usually required to record a reproducible ABR. The averaging time is thereby reduced from nearly 1 minute to approximately 5 seconds, permitting virtually on-line feedback to the surgeon, provided that the averaging computer can be programmed to automatically collect sequential averages and display the results so that changes can be readily identified. We have described this technique in detail elsewhere.[2]

Stimulus and Recording Parameters

The same stimuli used to elicit the ABR (brief clicks of fixed or alternating polarity) also are suitable for CNAP recording. Because the direct signal from the nerve is of higher amplitude than that of the ABR, however, the amplifier gain should be 5 to 10 times lower than for ABR recording; filter settings can remain the same. Usually 64 to 128 trials per average will produce an adequate waveform; at a stimulus rate of 20 per second, a new average can thus be obtained in approximately 5 seconds. An automated protocol for collecting sequential averages becomes important in this context to reduce the time to begin a new average after the previous one finishes.

Detection and Interpretation of Changes

It is important to determine the inherent amplitude and latency variability of the CNAP before operative manipulations that may potentially affect the cochlear nerve are undertaken, because this variability forms the background against which meaningful changes must be assessed. With an accurate and stable placement of the recording electrode on the nerve, the response can be quite repeatable from one average to the next. However, if the electrode position changes slightly, the variance may increase substantially. Unfortunately, some of the manipulations that may jeopardize the cochlear nerve (e.g., movement of a retractor) also are among the most likely to move the electrode. Figure 178-15 shows an example of a typical reversible change in CNAP amplitude.

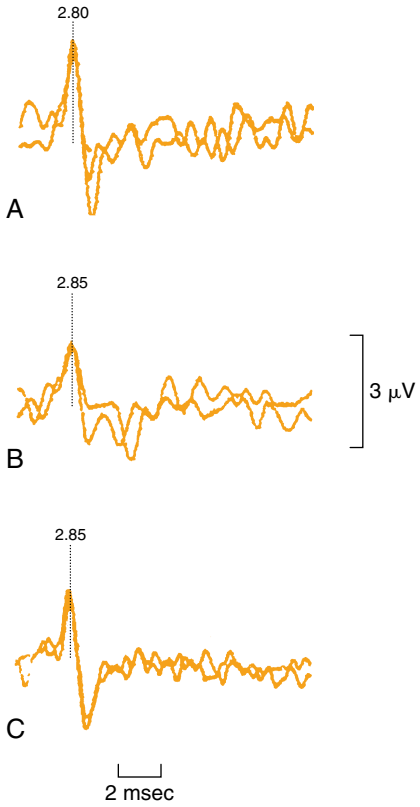

Figure 178-15. Representative changes in cochlear nerve compound action potentials during removal of a 0.6-cm intracanalicular acoustic neuroma. **A,** Just before mobilization of tissue adherent to cochlear nerve. **B,** Mobilization of tumor caused a sharp reduction (approximately 50%) in compound nerve action potential amplitude. **C,** Partial recovery of response after release of traction on nerve. Stimuli as described for Figure 178-14; 100 trials/average, duplicate averages are overlaid. (***A*** *to* ***C,*** *From Yingling CD, Gardi JG. Intraoperative monitoring of facial and cochlear nerves during acoustic neuroma surgery.* Otolaryngol Clin North Am. *1992;25:413.)*

Relation of Monitoring to Outcome

Facial and Other Motor Cranial Nerve Preservation

Several studies have evaluated postoperative facial nerve function in series of cases with and without facial nerve monitoring.[31,32,36,37,43,51,137-139] As a result of these studies, it can now be generally accepted that although monitoring results in a small increase in the proportion of subjects with good outcomes (grade I or II), the main effect of monitoring has been to greatly decrease the incidence of poor outcomes (grade V or VI). This finding undoubtedly reflects the relative ease of locating and preserving the facial nerve in smaller tumors, coupled with a greater impact of monitoring with resection of larger tumors, when the nerve is more likely to be stretched and distorted and thus more difficult to identify by anatomic criteria alone.

The National Institutes of Health (NIH) consensus conference on vestibular schwannoma[140] concluded: "The benefits of routine intraoperative monitoring of the facial nerve have been clearly established. This technique should be included in surgical therapy for vestibular schwannoma." Facial nerve monitoring for vestibular schwannoma surgery is therefore now clearly established as the standard of care. Although less formal data are available concerning monitoring of other cranial motor nerves, the techniques and applications are virtually identical and should achieve similar benefits. The same NIH consensus panel concluded: "Routine monitoring of other cranial nerves should be considered." Accordingly, it is unequivocally recommended that EMG monitoring with as many simultaneously recorded channels as necessary be used during any skull base surgery in which cranial motor nerves are at risk.

Cochlear Nerve Preservation

No such unequivocal consensus has emerged concerning the usefulness of cochlear nerve monitoring. In studies in which tumor size was restricted to less than 2.0 cm, useful to adequate hearing preservation was maintained in approximately 30% to 45% of patients, as determined by preoperative and postoperative pure tone audiometry and speech discrimination testing.[42,109,131,141-144] At present, conservation of hearing is more a function of diagnostic (gadolinium-enhanced magnetic resonance imaging [MRI] detection of smaller tumors) and surgical (increased use of middle fossa approach) factors than of intraoperative monitoring. It is hoped that improved methods for rapid detection of intraoperative changes in cochlear and cochlear nerve function will help eighth nerve monitoring to contribute more substantially to improving clinical outcome.

Attempts to compare CNAP and ABR monitoring techniques during vestibular schwannoma surgery have revealed that although both

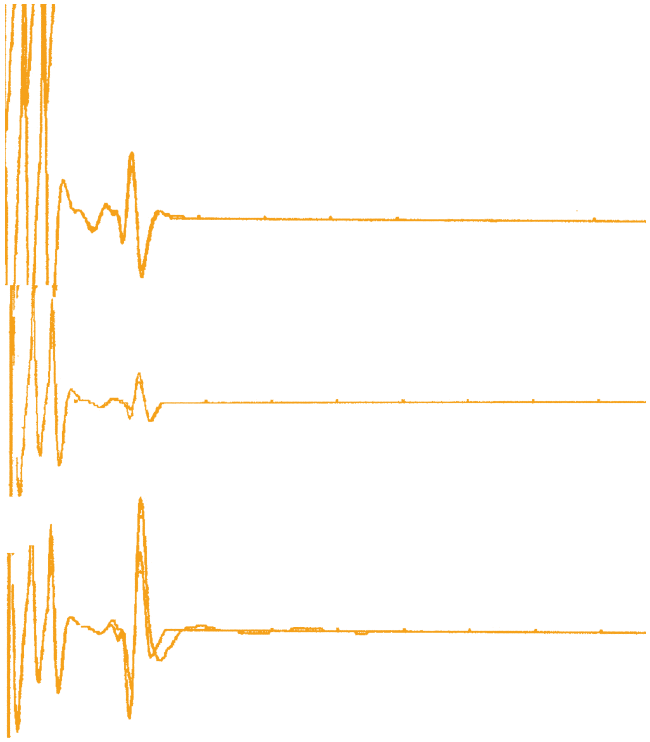

Figure 178-16. *Top*, Blink reflex recorded intraoperatively. *Middle*, Ipsilateral (R1) response recorded from orbicularis oculi after three-pulse train stimulus to supraorbital nerve. *Bottom*, Habituation of reflex response after repeated train stimulation. Restoration of reflex amplitude (dishabituation) after train stimulation of contralateral supraorbital nerve. *(From Yingling CD, Ashram YA. Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler R, Brackmann DE, eds.* Neurotology. *2nd ed. Philadelphia: Elsevier; 2005:958.)*

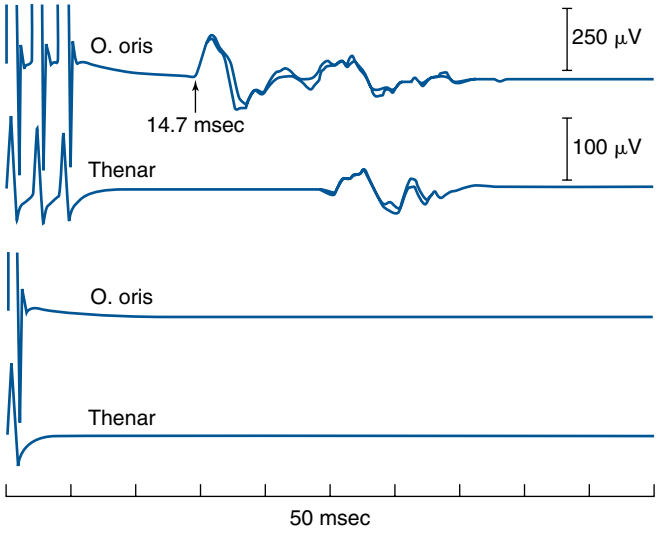

Figure 178-17. Intraoperative recordings of transcranial motor evoked potentials (tcMEPs). An example of facial MEP recorded from the left orbicularis oris (O. oris) muscle. The facial MEP response *(top trace)* is 300 mV in amplitude, generated by transcranial electrical stimulation of 3 pulses, 2-msec interstimulus interval, and 150 V. During stimulation, the anode was at M4 and the cathode at Mz. A simultaneous thenar muscle response also is shown *(second trace)*. Note the absence of same-intensity single-pulse responses *(third and fourth traces)* and the facial MEP onset latency of 14.7 msec, which indicate a central origin. Whether the apparent dispersion of the facial MEP relative to the expected duration of standard facial compound muscle action potentials (CMAPs) reflects preoperative facial nerve damage or normal temporal dispersion of facial motor neuron depolarization with pulse trains cannot be clearly determined without comparable normative data. *(From Dong CCJ, Macdonald DB, Akagami R, et al. Intraoperative facial motor evoked potential monitoring with transcranial electrical stimulation during skull base surgery.* Clin Neurophysiol. *2005;116:588.)*

ABR and CNAP are useful for predicting postoperative hearing, CNAP is more frequently obtainable, and CNAP monitoring is associated with a higher chance of hearing preservation.[145] Furthermore, CNAP monitoring is possible in patients with unrecordable ABR waveforms and may minimize cochlear nerve trauma.[146]

Colletti and associates[134] compared the value of ABR, ECoG, and directly recorded CNAPs in detecting damage to auditory structures during acoustic neuroma surgery. These investigators found that CNAPs had the highest predictive score for postoperative hearing. In particular, when a permanent loss of CNAPs occurred, sensitivity and specificity were 100%. These workers noted that ECoG activity was recorded in patients with lost CNAPs. This discrepancy was attributed to disconnection of the ear from the central auditory pathways associated with cochlear nerve damage,, with persistence of peripheral auditory function without propagation of the neural input. ABR monitoring was highly sensitive in detecting auditory damage, but its prognostic usefulness was marred by its poor specificity.

Future Directions and Conclusions

It is clear that facial nerve monitoring has had a marked impact on preservation of function in acoustic neuroma surgery. Although published data for other cranial motor nerves are more limited, the benefits are likely to be similar, because the principles are identical. The impact of monitoring on hearing preservation is less clear-cut, although the results thus far are improving and promising.

Equally clear is that much room for improvement remains. It is hopeful that the next decade will see improved techniques in a variety of areas, including better methods for automatic identification and rejection of artifacts; procedures for quantification of ongoing EMG activity; development of more sensitive non–EMG-based methods; and, perhaps most important, development of a technique for continuous assessment facial nerve integrity without direct electrical stimulation, analogous to continuous ABR recordings for assessing cochlear nerve function. This would be especially important with larger tumors, in which the nerve may be inaccessible for stimulation until extensive dissection has been done.

A possibility is to use the well-studied blink reflex,[83] which is elicited by stimulation of the supraorbital nerve (trigeminal afferents) and consists of an early ipsilateral EMG response (R1) and a later bilateral response (R2), both mediated by the facial nerve; it is the R1 response that can be recorded intraoperatively. Despite the usefulness of the blink reflex in clinical testing, it has not yet been reliably elicited in surgery because of the suppression of reflex activity by general anesthetics. It may become possible to overcome this problem by greater reliance on intravenous anesthetics, such as propofol, together with repetitive train stimulation (Fig. 178-16).

Another potentially valuable development is adapting the transcranial motor evoked potential (tcMEP) technique, now commonly used in spinal surgery, to facial nerve monitoring.[147-149] This technique entails placing a pair of stimulating needle electrodes on the scalp over the face motor area with the anode placed contralateral to the side of surgery.[150] The cortex is stimulated by multipulse constant-voltage stimulation, and EMG responses are recorded from appropriate facial muscles. The technique has some limitations, including the potential for excessive patient movement, which may not be appropriate for delicate intracranial surgery, generation of large stimulus artifact, and the possibility of extracranial current spread with peripheral facial nerve excitation; however, these limitations can be reduced by use of suitable electrode configuration and stimulation parameters.[148] Figure 178-17 shows intraoperative MEP recording from the orbicularis oris channel after multipulse transcranial electrical stimulation.

Finally, much is still to be learned about the relationship between intraoperative recordings and long-term clinical outcome. More con-

trolled studies, with carefully characterized patient populations and standardized monitoring techniques with quantification of response parameters, are needed to address many of the issues discussed previously. The only certainty is that improvements in monitoring techniques and routine inclusion of professional monitoring personnel in the surgical team, coupled with advances in early diagnosis and microsurgical techniques, will continue to improve the prognosis for preservation of cranial nerve function in patients undergoing skull base surgery.

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CHAPTER ONE HUNDRED AND SEVENTY-NINE

Stereotactic Radiation Treatment of Benign Tumors of the Cranial Base

D. Bradley Welling

Mark D. Packer

Key Points

- Stereotactic radiation therapy demonstrates good short-term control for many benign cranial base tumors.
- Short-term quality of life outcomes favor stereotactic radiation therapy over conventional surgical management.
- Radiation-induced cranial nerve injury has been reduced as lower doses of radiation have come into use.
- Long-term control and radiation-induced malignancy risk will be known in the next decade with further study.

Stereotactic radiation therapy is an option for the treatment of most benign cranial base tumors including vestibular schwannomas. The literature to date, however, consists of retrospective studies, with their inherent biases. The same also is true of the alternative treatments, including surgical and observational protocols. Long-term prospective outcome studies with blinded independent observations are needed as a strong supplement on which to base clinical treatment.

Since the late 1990s, stereotactic radiation therapy has become an increasingly popular treatment for benign tumors of the cranial base, including vestibular schwannomas. After its introduction for clinical use in 1967 by Lars Leksell, the initial acceptance of this modality waned as early complications included brainstem radiation damage, hydrocephalus, and cranial neuropathies.[1] However, as delivery has become more precise through improved stereotactic guidance, and as the tolerance levels of cranial nerves for radiation have become better elucidated, the technique has gained popularity and now offers an alternative to surgical intervention or observation for many cranial base tumors. Additionally, the combined use of radiation and surgical treatment may be considered for tumors for which incomplete excision may be planned to reduce the danger to adjacent cranial nerves. The goal of stereotactic irradiation for the treatment of benign tumors generally is considered to be growth arrest.

This chapter summarizes the principal advantages, disadvantages, and areas needing further research related to this technique. When possible, standardized definitions of tumor control and hearing preservation are specified, but this is not possible for all studies reviewed.

Principles of Stereotactic Radiation Therapy

In general, *stereotactic radiation therapy* denotes the application of any kind of ionizing radiation in a precise dosing mechanism to a target while limiting radiation exposure and damage to the adjacent surrounding tissues. Several delivery techniques for stereotactic irradiation have been developed.

With gamma knife radiotherapy techniques, well-collimated beams of radiation from 201 cobalt-60 sources are directed through ports in a semispherical helmet, allowing the beams to converge and deliver a much higher dose to the target than to the surrounding structures. The precise delivery of the beam is increased by direct fixation of a head frame attached with surgical pins to the cranium (Fig. 179-1). Although the procedure commonly is referred to as stereotactic "radiosurgery," this is a misnomer, because the therapy is accomplished by the delivery of external radiation without a surgical incision. Today most teams are composed of neurosurgeons or neuro-otologic surgeons, a radiation oncologist, and a radiation biologist. The advantage of gamma knife techniques at present is the capability for highly controlled delivery of radiation by way of multiple isopoints to the tumor target. Additionally, newer units have more fully automated coordinate adjustments, allowing more rapid dosing. A disadvantage is that tumors located much below the level of the cranial base are not readily accessible for stereotactic radiation delivery by the gamma knife. Rigid fixation of the skull to a metal frame that locks into the radiation chamber allows precise, submillimeter stereotactic radiation delivery, but the gamma knife does not lend itself to multiple fractionated treatments.[2]

An alternative to the gamma knife was developed through the application of linear accelerators (LINACs). Instead of multiple sources aimed at a central designated target, the LINACs rotate the treatment beam of the unit around the target in a variable number of rotational arcs.[3] Although the tumor margin doses are similar to those achieved with the gamma knife, LINAC delivery typically uses fewer isocenters, and the dose to the tumor may be less precisely applied. Thermoplastic molded mask systems to limit positional variation in the radiation delivery allow for the potential of fractionated schedules without the placement of pins into the skull but may not restrict movement of the target as surely as rigid fixation. Controversy exists regarding the potential benefit of fractionated stereotactic radiation protocols. Some inves-

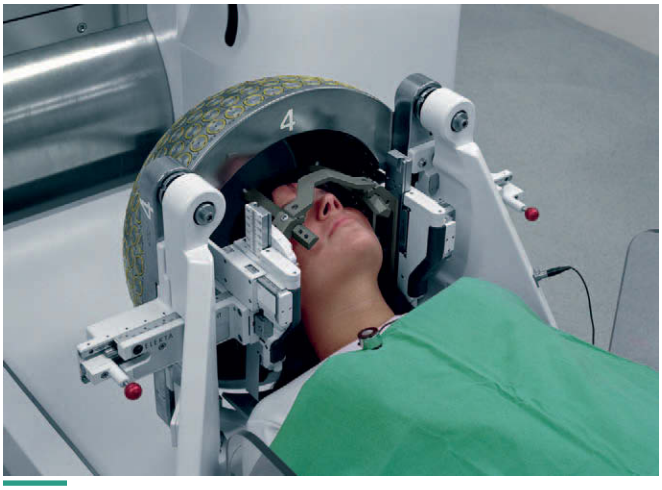

Figure 179-1. The gamma knife helmet. *(Courtesy of Elekta, Inc.)*

tigators maintain that a fractionated regimen, given over days or weeks, takes advantage of radiobiologic principles to reduce late toxicity while maintaining tumor control. However, in the case of vestibular schwannomas, both the tumor and the surrounding cranial nerves are late-reacting tissues; therefore, fractionating theoretically reduces the post-irradiation complications to the surrounding cranial nerves but also reduces the likelihood of desired tumor damage, DNA disruption, and apoptotic cell death.

Radiobiology

The therapeutic role of ionizing x-rays and gamma rays lies in their ability to alter and compromise DNA and other important biologic molecules of the cells targeted. Specifically, ionizing radiation excites electrons, which cause free radical damage of the involved cell structures. DNA damage prevents entering into the cell cycle and can lead to programmed cell death (apoptosis). Radiation damage to the phospholipids of the cell membrane also may lead to cell death. Ionizing radiation comes in two general varieties—electromagnetic, which consists of photons or packets of energy, and particulate radiation. X-rays and gamma rays are forms of electromagnetic radiation resulting when a photon indirectly transfers its energy to a target tissue. In an x-ray, a collision between an electron and the target tissue occurs, whereas gamma rays are produced when the contents of the nucleus of an atom return to their initial energy state from an excited level, a process known as gamma decay. As the electromagnetic waves pass through the tissues, they are absorbed, producing electron recoil and tissue damage as they lose their strength.

Protons are heavy charged particles that cause damage directly. They are positively charged and of a much higher mass than electrons. When a proton beam strikes its target, it delivers almost all of its energy at its delivery range, which results in a rapid dropoff of energy level, thereby limiting tissue damage past the target of interest. This characteristic is exploited to deliver a high dose of radiation directly to the target tissues with sparing of tissues deep to the delivery area. Dose inhomogeneity may increase the risks of complications for large target volumes treated with stereotactic radiation when the target area is less than a perfect match for the radiation delivery field. Complications were fewer with conformal multiple-isocenter gamma knife treatment plans than with less elaborate two-isocenter LINAC stereotactic radiation plans, which were associated with a higher risk of complications, with possible high-dose overlap regions extending into normal tissues.[4] The newer, more precise delivery systems are less likely to expose tissues out of the target regions to high doses of radiation.

Imaging

Typically, a lesion is diagnosed and confirmed by magnetic resonance imaging (MRI). On the day of the planned radiation treatment, a second MRI study is performed to precisely plan the radiation delivery after the patient's head has been fixed in the head frame. Post-irradiation MRI scans are obtained at 6 months and then yearly thereafter to observe the effect of the stereotactic radiation. Because of the long-term potential for delayed growth of the tumors and also because of the potential for malignant change, at present we recommend that yearly follow-up MRI scans be obtained.

Dose Selection

Dose selection in stereotactic radiotherapy has been evolving over the past decade as experience has been gained. Early animal studies by Kondziolka and associates[4a] demonstrated that xenograft vestibular schwannomas in the renal capsule of athymic mice showed significant reductions in tumor volume following stereotactic radiation with 40 Gy at 2 weeks and after 1 month in a 20-Gy group. Tumor vascularity was reduced in the 20- and 40-Gy groups respectively, but not in the 10-Gy group at 3-month follow-up evaluation. In humans today, however, in order to decrease facial nerve neuropathies, 17 Gy or less is delivered to the 50% isodose line (Fig. 179-2). Also, the auditory portion of the eighth cranial nerve appears to have a tolerance for approximately 11 Gy, with an 50% hearing preservation rate.[4b] Simply put, the lower the dose, the lower the complication rate—but the lower the likelihood of tumor control over the long-term follow-up period of observation.

Benign Tumors of the Cranial Base: Vestibular Schwannoma

Vestibular schwannomas have increasingly been treated with stereotactic radiation. Some centers favor this therapy over conventional surgical techniques or observation. In reporting the outcomes with gamma knife, LINAC, and fractionated stereotactic irradiation, "tumor control" has been defined in two ways. Some investigators define tumor control as no growth, whereas others report the percentage of tumors that required no further treatment. The latter definition may overestimate the true control rate, because cases in which tumors may have been growing but not requiring surgical intervention would be counted as those with successful outcomes. The most useful information that can be gleaned from the literature at this time is a compilation of reported outcomes. The lack of well-controlled studies has been duly noted. The longer the follow-up, the more valuable the study. Outcomes data extracted from the recent literature, including reports on tumor control, facial nerve function, hearing preservation, and trigeminal neuralgia, are summarized in Tables 179-1 to 179-3.

Fractionation versus Nonfractionation

Considerable debate is ongoing regarding whether or not fractionated stereotactic radiation is more favorable than single-dose stereotactic radiation for cranial nerve functional preservation in vestibular schwannoma treatment. Although fractionated radiation may give less immediate damage to the surrounding cranial nerves, damage to the slowly growing schwannoma cells also is less likely, thereby increasing the likelihood of growth. Flickinger[4c] argues that the available data in the literature are simply inadequate to allow definitive conclusions regarding which of the two delivery plans is better for cranial nerve preservation and tumor control; carefully planned, prospective controlled longitudinal studies are needed to address this concern. Indeed, the data shown in Tables 179-1 to 179-3 seem to confirm his opinion.

Traditionally, in our own practice, stereotactic radiation has been reserved for a select patient subset for the treatment of vestibular schwannoma. Elderly patients with small to medium-sized tumors with proven growth or those not fit for a surgical resection have been recommended to receive stereotactic radiation treatment. Chen, reporting data for three 5-year periods between 1990 and 2005, noted that vestibular schwannomas were being diagnosed at statistically higher ages, at smaller sizes, and in a greater proportion of patients older than 65 years of age.[5] During these periods, the frequency of observation as a treatment choice for vestibular schwannoma rose from 12% to 37%, microsurgery was performed in 59% of patients, and frequency of use of stereotactic radiation therapy rose to 4% of cases. As life expectancy

Table 179-1

Gamma Knife–Based Irradiation Protocols and Outcomes

Study	No. of Patients	Follow-up	Tumor size (cm^3)	Marginal Dose (Gy)	Isodose (mean)	Post-irradiation				
						Tumor Control	Hearing Preserved	FN Weakness	TrN Toxicity	Other
Mathieu et al, 2007[18]*	62 NF2 (74 tumors)	53 mo	5.7	14	50%	5 yr: 85% 10 yr: 81% 15 yr: 81%	1 yr: 73% 2 yr: 59% 5 yr: 48%	8%	4%	Volume/ dose-related†
Hempel et al, 2006[20]*	123	8.2 yr	1.0	13	40-85% (55%)	97%	47% 18% drop 73% audio	0	5.8	Tinn 4% Vert 13% hc 2.4%
Chung et al, 2005[14]	187	31 mo	4.1	13 11-18	50-94% (57%)	7 ya: 95%	60%	1.4%	1.1%	Blood-brain barrier disruption in 45% at <6 mo‡
Hasegawa et al, 2005[11]	317	7.8 yr 77: >10 yr	5.6	13.2	40-80% (51%)	5 ya: 93% 10 ya: 92%	68% audio/tele	1%	2%	Malignancy: 7% hc§
Huang et al, 2005[21]	45	25 mo	4.5	11.5		96%	77%	0	2%	
Paek et al, 2005[22]	25/pros	45 mo	3.0	12	50%	92%	52% 36% no loss	0	5%	Cochlear dose‖
Wowra et al, 2005[23]*	111 10 NF2	7 yr	1.6	13	45-85%	6 ya: 95%	Mean loss 10 dB (range +20 to −75)	0	12%	Tumor expansion¶
Lunsford et al, 2005[9]*	829 62 NF2	252: >10 yr	2.5	13 10-20	50%	97%	70%, 5 ya	<1%	<3%	
Landy et al, 2004[25]	34	43.4 mo		10-14	45-70%	97%	100% subjective	0	0	Arachnoid cyst
Inoue et al, 2005[26]	13	>6 yr	15.2	10-12		100%	4/5 tele	0	0	
Total	1758	>25 mo	>1.6	10-14	40-85%	81-97%	47-100%	0-8%	0-4%	

*Some studies used the same subject population: The series of Mathieu et al was the same as the NF2 subpopulation in the series of Lunsford et al; Hempel et al and Wowra et al also studied the same patients.
†Dose and volume were predictive of hearing deficit.
‡14.5% of irradiated tumors showed high signal intensity on T2-weighted sequences in peritumoral regions, consistent with disruption of the blood-brain barrier.
§One malignant transformation occurred at 48 months, resulting in death. Tumor volumes greater than 15 cm^3 were significant for treatment failure.
‖Higher doses to cochlear nucleus were deemed significant for hearing loss.
¶39% showed transient tumor expansion. Hearing loss associated with increased age and tumor expansion.
audio, audiometric data; FN, facial nerve; hc, hydrocephalus; NF2, neurofibromatosis type 2; pros, prospective; tele, telephone data; Tinn, tinnitus; TrN, trigeminal nerve; Vert, vertigo; ya, years of actuarial data.

is increasing, it seems likely that vestibular schwannomas under expectant management will be more likely to show growth when observed over longer periods of time, as demonstrated by Charabi and associates.[6] Smouha and colleagues, in a retrospective meta-analysis of patients managed without intervention, demonstrated that 43% of 1244 vestibular schwannomas showed growth over a mean follow-up period of 3.2 years.[7] Hearing loss occurred in 51% of 347 patients. Only 20% of 1001 patients from 15 studies eventually failed observation, showing growth sufficient to warrant active treatment. Smouha's data are similar to our own prospective findings, which demonstrated that 66% of tumors grew more than 15% when measured volumetrically after a mean follow-up period of 3.8 years.[8]

Outcome Assessment

Advocates of the use of stereotactic irradiation as a primary treatment for vestibular schwannomas without first documenting growth must bear in mind that over the short term, many tumors do not demonstrate growth. This calls into question whether or not post-irradiation stability of a nongrowing tumor should be considered to represent treatment success. In fairness, many patients in whom tumors are removed surgically are not followed to determine growth before treatment either. However, a fundamental difference remains between outcome assessments of the different treatment modalities. The key anatomic measure of outcome in surgery—absence of tumor or a residual of a small portion of the original tumor—typically

Table 179-2
LINAC-Based Stereotactic Irradiation Protocols and Outcomes

						Post-irradiation				
Study	No. of Patients	Follow-up	Tumor size (cm^3)	Marginal Dose (Gy)	Isodose (mean)	Tumor Control	Hearing Preserved	FN Weakness	TrN Toxicity	Other
Radu et al, 2007[27]	22	18 mo	1.85	12		100%	71% (grades I, II)	4.5%	9%	
Rutten et al, 2007[28]	26	49 mo		10-14	80%	5 yr: 95%	96%	0	8%	Volume/ dose-related
Roos et al, 2006[13]	65 4 NF2	48 mo	22 (mm)	12	85% 70-90%	95%	47%	6.1%	10.8%	Enlarging tumor: 17%* hc 1.8%
Combs et al, 2006[29]	26 2 NF2	110 mo	15 (mm)	13 11-20	80%	5 ya: 96% 10 ya: 91%	9 yr: 55%	5.2%	8%	
Chung et al, 2004[65]	27 3 NF2	27 mo 26 mo	2.6 2.4	12	80%	5 ya: 87%	1 yr: 85% 2 yr: 57%	11.8%	9.5%	SRT changes†
Friedman et al, 2006[30]	390/ pros	40 mo 63 >5 yr	2.2	12.5 10-22.5	70-80%	1 ya: 98% 2 ya: 98% 5 ya: 90%	Not reported	4.4%	3.6%	
Total	556	18-49 mo	1.9-2.6	10-14	70-90%	87-96%	47-96%	0-12%	4-11%	

*17% enlarge an average of 4 mm within the first year.
†Pre-reatment SRT was 20 dB; post-treatment SRT increased to 38 dB in 59%.
FN, facial nerve; hc, hydrocephalus; NF2, neurofibromatosis type 2; SRT, speech reception threshold; TrN, trigeminal nerve; ya, years of actuarial data.

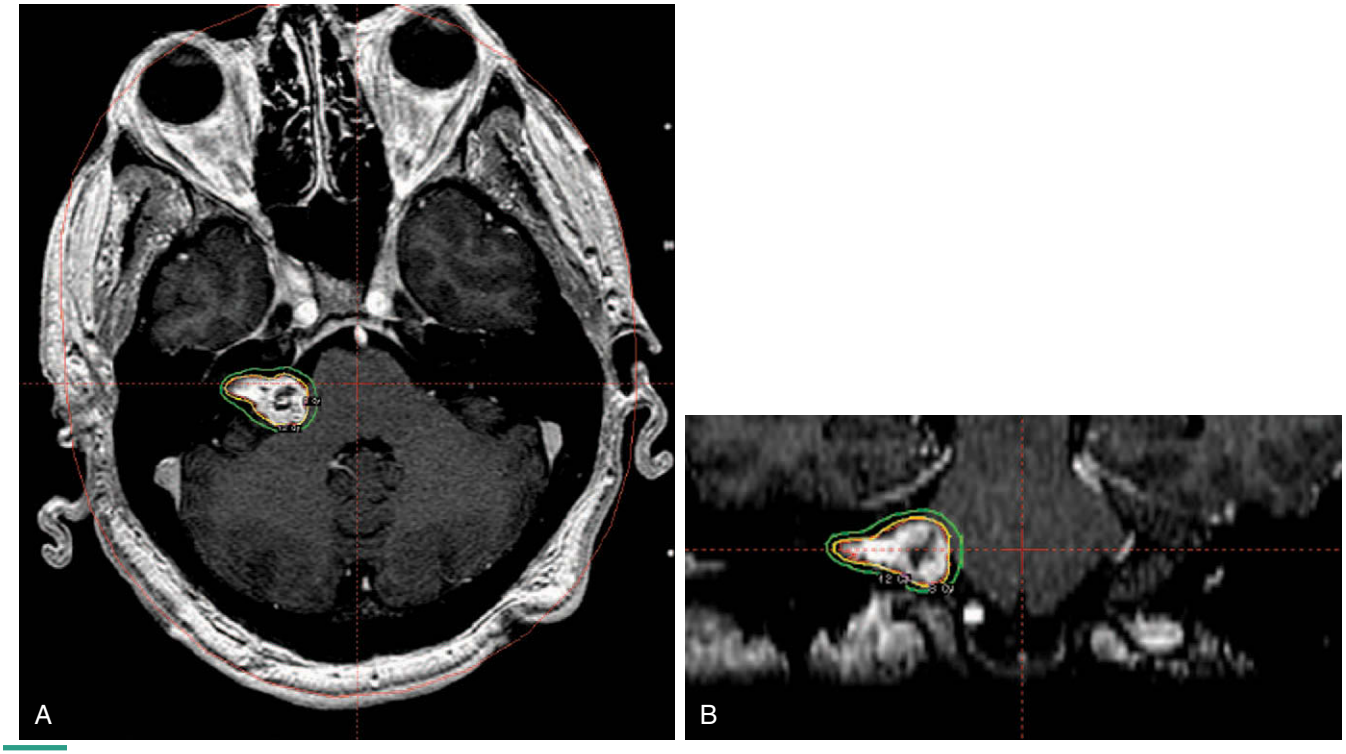

Figure 179-2. Axial (**A**) and coronal (**B**) images of radiation dose plan for a vestibular schwannoma. Multiple shots can be arranged within the tumor at various radiation doses to give homogeneous exposure to the tumor while avoiding unnecessarily high levels of radiation to adjacent structures.

Table 179-3

Fractionated Irradiation Protocols and Outcomes

						Post-irradiation				
Study*	No. of Patients	Follow-up (mo)	Tumor Size	Total Dose (Gy)	Fraction/ Isodose	Tumor Control	Hearing Preserved	FN Weakness	TrN Toxicity	Other
Thomas et al, 2007[33]	34/pros	37	1.1 cm^3	45	25 90%	2ya: 100% 4ya: 96%	2yr: 63% 3yr: 63%	6%	0	Cochlear dose†
Horan et al, 2007[34]	42 5 NF2	19	21.5 mm	50	30	2-5ya: 97%	100% useful 73% drop**	3.2%	0	
Koh et al, 2007[35]	60	32	4.9 cm^3	50	25 95-100%	5ya: 96% 5y: 93%	77.3%	0	0	GBM‡
McClelland et al, 2008[67]	20	22	2.1 cm^3	54	30 90%	100%	100% useful 44% drop**	0%	10%	
Maire et al, 2006[32]	45	80	31 mm	51	28	5ya: 86%	77.8%	0	0	MPNST§
Combs et al, 2005[36]	106/pros 14 NF2	49	3.9 cm^3	57.6	32 90%	3ya: 94% 5ya: 93%	5yr: 94%	2.3%	3.4%	29/65 audio††
Chan et al, 2005[31] XKnife‡‡	70 11 NF2	45	2.4 cm^3	54	30 95%	3ya: 100% 5ya: 98%	3/5yr: 84%, tele	1%	4%	>8 cm^3 significant‖
Chang et al, 2005[66] Cyberknife	61	48	18.5 mm	18-21	NR	98%	74%	3.3%	ND	
Selch et al, 2004[37]	50	36	2.51 cm^3	54	30 90%	100%	5 ya: 92% tele	2.1%	2.1%	Vertigo¶
Dhanachai et al, 2004[38]	5 NF2	19	5.4 cm^3	44-60 (8 pts) 30 (2 pts)	25-33	90%	40%	0	0	
Total	493	19-48	1.1-5.4 cm^3	54	25-32 >90%	86-100%	63-100%	0-6%	0-4%	

*Radiation source stated if known.
†Cochlear doses predicted hearing losses.
‡One malignant transformation occurred at 5.8 years after fractionated radiotherapy, resulting in death. 45% treated without tumor progression.
§One malignant transformation occurred at 18 years after fractionated radiotherapy, resulting in death.
‖Tumor volume larger than 8 cm^3 was predictive of hearing loss. No differences were noted in the patients with NF2.
¶Post-treatment ataxia and vertigo developed in 30%.
**100% reported having retained useful hearing, although hearing level or speech discrimination (function) dropped in 27% (73% retained current level). McClelland showed 100% retained useful functional hearing, even though 44% dropped some function.
††29 of 65 patients received audiograms.
‡‡XKnife (Integra Radionics, Burlington, MA) is a software package for 3D radiation therapy planning using LINAC = based radiotherapy units.
audio, audiometric data; FN, facial nerve; GBM, glioblastoma multiforme; hc, hydrocephalus; MPNST, malignant peripheral nerve sheath tumor; NF2, neurofibromatosis type 2; NR, not reported; pros, prospective; pts, patients; tele, telephone data; TrN, trigeminal nerve; y, years of progression-free control; ya, years of actuarial data.

differs from the growth of persistent tumor after stereotactic irradiation.

Information on outcomes pertaining to the therapeutic use of stereotactic radiation treatment is expanding. Moreover, although debate continues regarding the optimal treatment of vestibular schwannomas, a growing consensus is that focal radiation therapy, delivered in single- or fractionated-dose regimens, has an important role in the treatment of selected skull base tumors.

Because stereotactic radiation treatment of vestibular schwannomas is still evolving, results are not easily comparable on a study-to-study basis, nor are they easily grouped to add power to institutional reporting by meta-analysis. Dosing parameters have changed over time and differ among patients, among doctors, and among institutions within studies.[9-11] This variability in retrospective studies is problematic, making optimal dosing parameters difficult to discern. Dose planning is enhanced with improved imaging shot selection, and blocking strategies that safeguard neural structures. Automation in delivery systems and better understanding of the biologic effect of radiation also should result in improved outcomes.[10,11]

Because the goal of stereotactic irradiation differs from that of microsurgery and with observation, outcomes are difficult to compare. In most cases, microsurgery results in complete tumor removal. Imaging

assessment gives an immediate quantifiable result. Imaging assessment of stereotactic radiation outcomes is subject to the inherent variability of the tumor response to treatment, the quality and resolution of the imaging, the examiner's judgment, the accuracy of post-imaging software, and interobserver comparison of imaging at different time points. The definition of success is not standardized at present but appears to be moving toward a crterion of progression-free survival. Since the objective of stereotactic radiation is tumor control rather than eradication of disease, criteria for success should be objectively compared to the natural progression of these slow-growing benign tumors.

After irradiation, tumors show signs of treatment effect by loss of central enhancement within the first 6 to 12 months.[12,13] Approximately one fourth (23%) will show *expansion*, or transient tumor swelling (on average 2 to 4 mm but as much as 10 mm) generally 6 to 24 months after treatment, but swelling can be seen up to 5 years after treatment. This temporary expansion may take 6 months to 5 years to resolve.[2] Fifty percent of these tumors will undergo a loss of central contrast enhancement that may correlate histopathologically with tumor necrosis.[14] Eventually, residual tumors show return of enhancement and possibly further shrinkage. Few show peritumoral edema. More recent studies recognize these signs of radiation effect, and continued observation often validates eventual stability or regression.[2] This understanding alone has prevented surgery for what was thought to be tumor progression in earlier studies and is manifested in improved control rates in newer data. Tumors that were excised, possibly for mistaken post-irradiation progression, have shown histopathologic evidence of radiation-induced vascular changes, including intimal thickening, perivascular inflammation, and focal hemorrhage.[14] Profuse interstitial fibrin deposits also were seen. Schwannomas surgically removed after stereotactic radiation failure also have shown typical and viable schwannoma cells with increased vascularity, as well as other foci showing delayed radiation changes such as nucleolar and cytoplasmic enlargement, proliferation of endothelial cells, and necrosis.[15-17]

In 2006, Weil and colleagues published a thorough review of the English language literature regarding single-fraction stereotactic radiation.[10] Similarly, Backous and Pham and Likhterov and associates reviewed the current literature and summarized the stereotactic irradiation data, including outcomes of fractionated stereotactic radiation protocols, through 2005.[2,3] Tables 179-2 and 179-3 present outcomes data from these reviews, along with those from the most recent studies on stereotactic irradiation.[10,12,14,15,18-39] Studies with fewer than 15 patients or less than 12 months of follow-up were excluded.

Tumor Control

Current data show that after irradiation, 1% to 2% of vestibular schwannomas resolve completely; however, tumor control is achieved in 74% to 100% over varied durations of follow-up. The definition of tumor control has not been consistent. Control in some series is considered no radiographic enlargement over some set parameter (e.g., 2 mm in tumor diameter or 10% change in tumor volume). Failure in others is considered progression requiring microsurgical resection. Some centers do not consider repeat stereotactic irradiation or neurosurgical relief of radiation-induced or tumor-related hydrocephalus by ventriculoperitoneal shunting to represent treatment failure, whereas other centers do. Outcomes in patients in earlier series may have been counted as failures before recognition of the phenomenon of transient tumor expansion, thereby falsely lowering control rates in those studies. A more recent trend in reporting tumor control is to provide actuarial data. Few studies have data to report beyond a median follow-up period of 48 months. To make up for this shortcoming, probable data are generated from the few leading patients in each study to provide Kaplan-Meier survival curves with confidence intervals predicting progression-free statistics. Considering the foregoing caveats, for the studies reviewed, the weighted summary of the 5-year-progression-free tumor control was 95% for single-dose stereotactic irradiation and 94% for fractionated regimens.

Hearing Outcomes

Hearing outcomes have steadily improved since the early 1980s as a result of decreasing marginal doses, improved conformality and shielding of important structures, or better patient selection, or a combination of these factors. Dose tolerances of the cochlea, cochlear nerve, and cochlear nucleus are still under investigation.[2,22,33] In a prospective follow-up study of 34 patients, Thomas and colleagues found the cochlear dose to be the only variable that was statistically predictive of hearing preservation.[33] These investigators showed that if the percentage volume of the cochlea exposed to 90% of the total treatment dose was less than 73.3%, the median hearing loss was 10 dB, compared with 25 dB for the cochleas exposed more than 73.3%. Paek and coworkers found that treatment doses to the cochlear nucleus below 10 Gy were the only statistically significant prognostic indicator for hearing preservation in their study of primary gamma knife therapy in a select group of 25 patients with pretreatment Gardner-Robertson hearing of grade I or II.[22] Chopra and colleagues have shown that hearing outcomes improve when the marginal dose to the tumor is reduced to 13 Gy or less. Increased age, tumor swelling, radiation exposure to greater lengths of the cochlear nerve, and increased dose to the cochlear nucleus also have been associated with poorer hearing outcomes.[40] Massager and colleagues analyzed the radiation doses delivered to the cochlea during gamma knife stereotactic irradiation and concluded that the cochlea received significantly higher radiation doses in patients with worsening of hearing after treatment. The cochlear dose was significantly associated with the intracanalicular dose of radiation delivered.[41,42]

Table 179-4

Gardner-Robertson Scale*

Hearing Grade		Pure Tone Average (dB)	Speech Discrimination (%)
Grade I	(good to excellent)	0-30	70-100
Grade II	(serviceable)	31-50	50-71
Grade III	(nonserviceable)	51-90	5-49
Grade IV	(poor)	91-max	1-4

*If pure tone average and speech do not correlate, the lower grade is assigned.

Hearing status and hearing outcomes are not universally evaluated and have not been examined in a standardized fashion if included, causing difficulty in comparing data.[10,31] Because fewer patients have serviceable hearing than the already low number of patients in some series, the power of reporting hearing outcomes in these studies is compromised. The timing of audiometric follow-up testing is not always clear and does not necessarily match the duration of tumor control surveillance. Few studies offer serial data on the hearing data they collect. Thomas and colleagues reported the only prospective series of outcomes encountered.[33] Not all studies rely on objective audiometric data for reporting, and some include the use of telephone or survey information with the hearing outcomes. When audiometric data are used, the definition of serviceable hearing has varied, using either hearing levels or speech discrimination, or a combination. The Gardner-Robertson classification of hearing is most commonly used today as a scale to gauge useful hearing (Table 179-4). Class I or II hearing, or speech reception thresholds better than 50 dB and speech discrimination better than 50%, is considered to be serviceable hearing for a majority of studies (see Table 179-4). That being said, preservation of any sound perception is important and useful for lip reading and voice modulation when the contralateral hearing is compromised, as in cases of neurofibromatosis type 2 (NF2).

After stereotactic irradiation, hearing loss becomes evident over the ensuing 6 to 24 months. Hearing levels decline by 15 to 20 dB on average after treatment. Hearing continues to decline with the duration of follow-up.[2,20] A profile of progressive loss is similar to that in natural history trends derived from tumor observation data but presumably is

related to radiation effect. Tumor size may impede attempts at hearing preservation. Prasad and associates showed that useful hearing was retained in 75% of patients with tumors smaller than 1 cm^3, whereas 57% of those with tumors larger than 1 cm^3 demonstrated a hearing level of Gardner-Robertson class I or II.[43]

Hempel and coworkers documented an average drop of 18 dB with treatment.[20] These workers reported standardized follow-up data for 123 patients for a mean of 8.2 years after stereotactic gamma knife irradiation of median 1.6-cm^3 vestibular schwannomas treated with a mean marginal dose of 13 Gy. Pre- and post-treatment audiometric data were available for analysis in 63 patients. Post-treatment audiograms were obtained 1 to 24 months after treatment; in 46 of the patients (73%), audiometry was not performed until more than 5 months after treatment. Hearing declined an average of 18 dB, moving the group from a 42% pretreatment slight to moderate hearing difficulty level, on average, to 60% post-treatment moderate to high-grade hearing loss. No audiometric hearing loss occurred in 17 of 63 patients (29%), and subjectively, 53 patients (47.3%) reported that their hearing had not changed with treatment.

Thomas and colleagues, using fractionated stereotactic irradiation, conducted a prospective follow-up study in a select group of 34 patients with small tumors and good hearing and reported standardized hearing results at a median of 36.5 months.[33] Patients received doses of 50 Gy in 25 fractions to the 90% isodose line, treating median tumor volumes of 1.06 cm^3. As assessed using the Gardner-Robertson grading scale (see Table 179-4), 28 patients had grade I hearing levels before treatment, 5 had grade II hearing, and 1 had grade III hearing but was included in this select group because he felt subjectively that his hearing was serviceable. Speech reception thresholds were 20 dB on average before treatment and 40 dB after. Twenty patients (59%) retained serviceable hearing and 12 (35%) retained their pre–irradiation course Gardner-Robertson grade. Actuarial hearing preservation rates at 2, 3, and 5 years were 63%, 63%, and 56%, respectively.

Overall, reported hearing preservation rates range from 33% to 100% with gamma knife irradiation, from 47% to 96% with LINAC-based irradiation, and from 46% to 100% with fractionated protocols. The weighted average of pooled gamma knife data for more than 100 patients over more than 36 months showed a hearing preservation rate of 68%. No studies with single-dose LINAC-based protocols with more than 100 patients reported hearing outcomes; however, fractionated protocols showed a weighted hearing preservation rate of 69%.

Facial Nerve Outcomes

Stereotactic irradiation continues to offer excellent results in regard to function of the facial nerve. Improved outcomes were achieved by reducing the marginal tumor dose to less than 16 Gy, which decreased the rate of facial neuropathies to 15%. At 13 Gy or less, persistently improved facial nerve outcomes are achieved. Today, facial nerve injury is rare and usually transient. Improved outcomes are further enhanced by better conformality of treatment planning and limiting the irradiation field to the minimum length of nerve necessary for adequate tumor treatment. Tumor volume is debatable as a predictive factor for cranial neuropathy.[31,44] Reported rates of facial nerve injury in the low-dose era of treatment (12 to 14 Gy) range from 0% to 10.3% after gamma knife irradiation with up to 5.2% permanent injury, 0% to 11.8% with up to 8% permanent with LINAC-based radiotherapy, and 0% to 6% with up to 6% permanent for fractionated protocols. Facial synkinesis and spasm are sometimes discussed separately; according to the available evidence, they occur at similar rates.

Trigeminal Nerve Outcomes

Trigeminal nerve toxicity is seen in a low number of patients treated by stereotactic irradiation. Reported symptoms range in severity from trigeminal neuralgia to mild hypesthesia. The incidence ranges from 0% to 16% after gamma knife irradiation but more consistently falls between 2% and 5%. Single-dose LINAC protocols produce injury in 0.7% to 18% but more commonly in 7.5% to 10.8%. Fractionated protocols show trigeminal nerve injury in up to 14%, and routinely in up to 5% (see Tables 179-1 to 179-3).

Neurofibromatosis 2–Related Vestibular Schwannoma

In patients with the burden of multiple intracranial and spinal tumors, an effective method of treatment less invasive than surgical removal would be of great value. Concern arises, however, over irradiating benign tumors in young patients who have an inherited predisposition to tumor formation from loss of the NF2 tumor suppressor gene. In a retrospective study by Vachhani and Friedmann[45] of stereotactic radiation treatment of 14 NF2-related schwannomas, with a mean follow-up period of 38 months, no growth was noted in the radiation-treated tumors in 92% at 2 years and in 92% at 5 years. In the untreated tumors, 78% showed no growth at 2 years and 21% at 5 years.[45] Mathieu and colleagues reported the University of Pittsburgh experience, which included stereotactic radiation treatment of 74 schwannomas in 62 patients with NF2. These workers found tumor volume to be a significant predictor of local control. Actuarial control rates were 85%, 81%, and 81% at 5, 10, and 15 years, respectively. The actuarial serviceable hearing preservation rate for the 35% of patients presenting with serviceable hearing was 73% at 1 year, 59% at 2 years, and 48% at 5 years after gamma knife radiation treatment.[18]

Cystic Schwannomas

Debate is ongoing regarding the effectiveness of stereotactic radiation control of cystic vestibular schwannoma. Pendl and colleagues initially advised caution in recommending stereotactic irradiation to patients with cystic vestibular schwannoma.[46] These recommendations were based on a series of treatment failures that manifested as progressive neurologic symptoms after treatment with a mean dose of 13.8 Gy to the tumor margins. Surgical intervention was required in five of the six patients. Shirato and colleagues also claim that patients with cystic vestibular schwannomas are at significant risk for experiencing subacute expansion of the cyst after fractionated-dose stereotactic irradiation and reported that 45% showed growth in the 3-year actuarial follow-up period.[47]

In an effort to characterize the phenomenon of tumor expansion, Hasegawa and colleagues reported that of 254 vestibular schwannomas treated with high-dose irradiation between 1991 and 1998, 42 tumors (17%) continued to grow.[12] Of the 42 expanding tumors, 14 were characterized by central necrosis, 16 were solid tumors, and 12 demonstrated cystic formation or expansion. Of the 14 patients whose tumors demonstrated central necrosis, 3 required further salvage treatment. Of the 16 patients with solid tumors, 7 required additional treatment (including treatment for the malignant transformation of one tumor). All of the 12 patients in whom cysts developed or expanded eventually required craniotomy. The investigators concluded that patients shown to have cyst enlargement with neurologic deterioration after irradiation or those with new cyst formation will require surgery.

Delsanti and Régis showed only a 6.4% treatment failure rate for stereotactic irradiation of these tumors.[48] It is possible that these discrepancies are due to the low proportions of vestibular schwannoma that are cystic, or to the selection bias inherent in retrospective analysis. It is likely that truly cystic vestibular schwannomas do not respond as well as solid vestibular schwannoma to treatment by stereotactic irradiation. Further prospective studies of this variety of vestibular schwannoma are necessary before firm recommendations can be made.

Hydrocephalus

Hydrocephalus occurs in a low percentage of patients after stereotactic irradiation. Theoretically, this problem could be due to post-irradiation tumor or tissue swelling, or to new cyst formation with consequent obstructive hydrocephalus, radiation-induced fibrosis, or hemorrhage resulting in cerebrospinal fluid malabsorption and communicating hydrocephalus. Treatment by ventriculoperitoneal shunting resolves this problem in most situations, but salvage microsurgery for failed tumor control or to remove new cyst formation sometimes is necessary. Hydrocephalus occurs in 0.8% to 8% of cases with gamma knife treatment, 0% to 7.5% of LINAC single-dose protocols, and 0% to 12% of fractionated protocols, although more commonly 0% to 4%. See Tables 179-1 to 179-3.

Treatment of Stereotactic Radiation Failures

Fortunately, in most patients treated by stereotactic irradiation for vestibular schwannoma, tumor control is achieved, and follow-up with careful observation constitutes adequate management. Surveillance protocols vary, but follow-up imaging should be carried out indefinitely, or until longer-term follow-up studies in adequate numbers of patients treated at current dosing levels show this to be unnecessary. Stereotactic irradiation failure is defined as progression of tumor volume or diameter beyond the expected post-treatment expansion, progressive neurologic symptoms from active growth, or threatened brainstem compression. Although most failures manifest within 3 years of treatment, reports of failures beyond 5 years also are seen.[11,32,35,42]

Tumor volume has been shown to be a predictor of treatment failure. Hasegawa and colleagues showed actuarial 10-year progression-free control rates of 57% for tumors larger than 15 cm^3 and 95% for those smaller than 15 cm^3.[11] These workers also reported two occurrences of failures more than 5 years after stereotactic irradiation. One case involved new cyst formation, presumably secondary to intratumoral hemorrhage at 69 months, and the other involved malignant transformation of a vestibular schwannoma at 51 months. Chan and colleagues saw a similar statistical difference in progression-free survival. The 5-year actuarial rates of freedom from any neurosurgical intervention was 97% for patients with tumor volume less than 8 cm^3 and 47% for patients with tumor volume of at least 8 cm^3.[31]

The outcomes with microsurgical treatment of radiosurgical failures are unclear. Friedman and associates compared data for resection of 38 tumors after radiosurgical failure with those for resection of 38 matched primary tumors.[15] The mean follow-up period was 3.3 years. These workers noted moderate to severe adherence to the facial nerve in 89% of radiation failures, compared with 63% of primary resections. House-Brackmann grade I or II facial nerve outcomes were obtained in 37% of irradiated cases, compared with 70% of primary treatment cases. Limb and colleagues found similar difficulty for resection of radiosurgical failures compared with matched controls.[49] They also described increased operative time and uncertainty about the completeness of tumor removal. Shuto and colleagues reported data for 12 patients operated on after failed stereotactic irradiation.[50] Four also had had a previous microsurgical dissection. These investigators described difficult identification and dissection of the facial nerve and resorted to subtotal resections in order to preserve its integrity. They also found difficulty dissecting the tumor from the brainstem owing to adhesions. Hearing was sacrificed in all cases. Bleeding was scant, possibly as a result of the irradiation. Shuto's group recommend subtotal excision in revision cases and showed that growth of the residual tumor was rare.

The ultimate failure of stereotactic irradiation would be the transformation of a benign process into a malignant disease. The risk at present appears to be on the order of 0.01% to 0.3% for non–NF2-associated vestibular schwannomas.[35,51] Malignant change of a schwannoma has been reported up to 18 years after radiation treatment. Such extensive follow-up has been achieved in only a few patients.[30,52] Malignant transformation usually is a fatal event and may take more than 30 years to develop, as indicated by data on the treatment of other benign disease processes and from occupational exposure to radiation sources. The peak occurrence takes place approximately 15 years after low-dose radiation exposure, but the relative risk remains elevated well past 40 years.

The current literature does not have adequate numbers of procedures to be predictive of long-term risk. Actuarial data, although often quoted, are of no value in predicting malignant changes. Evans and colleagues as well as Ron and colleagues note an 18.8-fold increased relative risk of schwannoma induction and a 9.5-fold increased relative rate of meningioma induction after radiation doses of 2.5 Gy for the treatment of tinea capitis, adenotonsillar disease, and capillary hemangiomas.[53,54] The radiobiologic effect was dose-dependent, similar to the tissue effect and tumor growth response observed in post–World War II Japan.[55] Preston and colleagues showed that vestibular schwannomas were the most abundant intracranial tumors encountered, with a high propensity for Schwann cell mutation in response to radiation damage.[55] Overall, the risk of radiation-induced tumors appears to be approximately 0.1% to 3% after 30 years.[51,53] In light of the 33% to 40% lifetime risk of malignancy in the general population, Evans and colleagues feel that the benefits of single-dose radiation treatment for vestibular schwannoma is justified for patients with documented tumor growth who refuse surgery, or for the elderly or infirm. However, patients with NF2 in particular are the disproportionate recipients of radiation-induced malignant tumors. In a series of 829 subjects with vestibular schwannomas, 62 (7%) had NF2; yet in a review of the documented cases of malignant changes induced by stereotactic irradiation of vestibular schwannomas, 50% occurred in NF2 patients. Evans and colleagues strongly caution against the use of radiation treatment for benign tumors in childhood and in tumor-prone conditions such as neurofibromatosis.[53] We concur.

Quality of Life

In treatment of a benign disease with a natural history of general slow progression, the patient's satisfaction with the treatment outcomes is highly relevant. Quality of life measurements are useful tools for obtaining such information. Pollock and colleagues have reported the only prospective quality of life assessment to date.[56] They matched 36 microsurgical (suboccipital 69%, middle cranial fossa 6%, or translabyrinthine 25%) patients with 46 patients that underwent stereotactic irradiation. The surgical therapy group was composed of statistically older patients and showed a trend to larger tumor size when compared with the radiation therapy group. Outcomes were measured by a health status questionnaire, dizziness handicap inventory (DHI), and a tinnitus and headache survey. The questionnaires were evaluated at 3 months, 1 year, and the last follow-up. The mean follow-up period was 48 months. Responses showed statistically significant decline in the health status questionnaire parameters for the microsurgical group that resolved with follow-up. The parameters of bodily pain and mental health remained significantly different from the stereotactic irradiation group, although scores for both groups were elevated from baseline. The stereotactic irradiation group had lower DHI scores than those for the microsurgery group at last follow-up evaluation.

Myrseth and coworkers retrospectively looked at 168 patients, using the SF-36 questionnaire and the Glascow Benefit Inventory (GBI) as a measure of subjective quality of life.[57] Patients in the microsurgical therapy group (retrosigmoid 38%, translabyrinthine 62%) were significantly younger (mean age of 48.2 years, vs. 53.9 years). A larger group was lost to follow-up because of death in the stereotactic therapy group (16 vs. 8). Data were obtained by subject response for 83.3% of the patients over a 1-year follow-up period. The investigators concluded that the SF-36 did not bring out the differences between the two cohorts as well as the GBI, which showed that at 1 year, the score for the "general" category was significantly lower in the microsurgery group, although the two cohorts did not differ significantly on the "physical" and "social" scales.

Sandooram and associates also used the GBI as a quality of life measure.[58] This retrospective study, based on an 80% response from 165 subjects, included 102 patients managed with microsurgery and 10 with stereotactic irradiation. No significant age or tumor size difference was found between patients choosing microsurgery (49% retrosigmoid, 51% translabyrinthine) or stereotactic irradiation. The patients in the microsurgery group were followed for a median period of 4.8 years, whereas those in the stereotactic irradiation group were followed for a median 1.8 years. Patients in both groups showed decline in their GBI scores, although the decrease in the stereotactic irradiation group did not reach significance. A minimum follow-up period of 3 years should be sought for quality of life studies.[9] Longer follow-up is recommended for the following clinical reasons: (1) the natural progression of vestibular schwannoma shows nonlinear growth; (2) the progression of vestibular schwannoma growth in observed patients in our series was 66% at 3.8 years; and (3) the long-term failure rate for stereotactic radiation therapy is yet unknown. These considerations reinforce the need to standardize surveillance protocols and reporting definitions and measures so that future recommendations can be based on actual evidence.

No truly prospective randomized study with sufficient power or duration of follow-up that would give sufficient power has been conducted to compare the results of stereotactic irradiation. Meta-analysis

Table 179-5

Stereotactic Irradiation Protocols and Outcomes for Treatment of Glomus Jugulare Tumors

Study with Radiation Source	No. of Tumors	Local Control Rate	Hearing Preservation	Cranial Neuropathy		Dose*
				Facial Nerve	Cranial Nerves IX, X, XI	
Sharma et al, 2008[61] Gamma knife	15 primary, 9 secondary; 10 patients with follow-up	100% at 24 mo in 10 patients	NR	NR	15/24 (62%)	16.4 Gy
Lim et al, 2004[62] Cyberknife plus LINAC	16	100% at 41 mo	1 transient loss	NR	1/16 (6%)	14-27 Gy
Eustacchio et al, 1999[63] Gamma knife	10 primary, 9 recurrent	95% at 46 mo	NA	NA	NA	13.5 Gy in a 91-year-old patient who died 9 months later
Liscak et al, 1999[64] Gamma knife	30 primary, 24 recurrent	100% at 24 mo	11/14	NA	5%	16.5 Gy
Pollock, 2004[60] Gamma knife	19 primary, 23 recurrent	98% at 44 mo	81% at 4 yr	11% 43%	3%	14.9 Gy

*Mean marginal dose of 16.4 Gy.
LINAC, linear accelerator (stereotactic irradiation); NR, not reported; NA, not available.

of retrospective data can be helpful, but a meta-analysis by Weil and colleagues in 2006 concluded that current studies are subject to a number of confounding factors, are not sufficiently statistically powered, and present limited long-term actuarial outcome data.[10] These investigators did not provide sufficient confidence to support the claim that low-dose stereotactic radiation is as effective as higher doses. Hearing results also are shown to decline over time. This also is true in patients with untreated tumors under observation. Weil's group noted that the small size of patient cohorts and the small proportion of patients at 5 years provide for large confidence intervals with considerable uncertainty. Furthermore, a recent study with longer follow-up suggests worse actuarial tumor control in patients treated with a marginal dose less than 12 Gy, compared with doses of 12 Gy or higher.[14]

Despite these difficulties in comparing reports, the short-term efficacy of stereotactic irradiation for treatment of vestibular schwannoma is impressive. Stereotactic irradiation is a valuable option for treatment of sporadic vestibular schwannomas in elderly patients. It may be useful in limiting the morbidity of microsurgery or stereotactic irradiation alone when used as an adjunct to subtotal resection of tumors with large volumes. Caution is still warranted in considering its application for tumors with undocumented growth, or in younger or tumor-prone patients.

Jugular Foramen Schwannomas

Martin and associates reported results of stereotactic irradiation in 34 patients with 35 jugular foramen schwannomas treated with gamma knife protocols between 1990 and 2005.[59] Twenty-two patients had undergone previous surgical resection, and 13 patients, in whom the diagnosis was based on imaging studies, underwent primary stereotactic irradiation. One or more cranial nerve deficits were present before stereotactic irradiation in all 34 patients. The marginal dose ranged from 12 to 18 Gy, and the dose to the maximum range was 21 to 36 Gy. Follow-up periods ranged from 1.5 to 14 years, with a mean or median of 7 years. These workers reported that 33 of 35 lesions decreased in volume or were stable at 5 years. When the lower motor cranial nerves (glossopharyngeal, vagus, spinal accessory, and hypoglossal) were considered as a group, a total of 105 ipsilateral nerves were affected at the time of stereotactic irradiation; 35 were intact, with no associated symptoms. Improvement of the affected cranial nerves was noted in 22 (20%), whereas 81 (77%) remained stable and only 2 were worse. All 35 unaffected cranial nerves remained unaffected.

Paraganglioma

Paraganglioma treatment reports in the literature have fewer numbers and shorter follow-up than those for vestibular schwannomas, but reported control rates are similarly encouraging (see Table 179-5).[60-64] A summary of five representative studies in the recent literature follows. In a report by Pollock, 42 patients underwent gamma knife surgery as the primary management (19 patients) or for recurrent glomus jugulare tumors (23 patients).[60] Facial weakness and deafness were more common in patients with recurrent tumors than in those in whom primary gamma knife stereotactic irradiation was performed (48% compared with 11%). The mean tumor volume was 13.2 cm^3; the mean tumor margin dose was 14.9 Gy. The mean follow-up period for the 39 patients in whom evaluation was possible was 44 months (range, 6 to 149 months). After gamma knife surgery, 12 tumors (31%) decreased in size, 26 (67%) were unchanged, and one (2%) grew. The patient whose tumor grew underwent another course of stereotactic irradiation. Progression-free survival after gamma knife surgery was 100% at 3 and 7 years and 75% at 10 years. Six patients (15%) experienced new deficits (hearing loss alone in three, facial numbness and hearing loss in one, vocal cord paralysis and hearing loss in one, and temporary imbalance or vertigo in one). In 26 patients in whom hearing could be tested before stereotactic radiation therapy, hearing preservation was achieved in 86% and 81% at 1 and 4 years after treatment, respectively. No patient suffered a new lower cranial nerve deficit after one stereotactic radiotherapy session.

Other studies evaluating stereotactic irradiation for paragangliomas similar to Pollock's are summarized in Table 179-5. The difficulty in preserving the lower cranial nerves with the excision of glomus jugulare tumors makes stereotactic irradiation an attractive alternative if the long-term results are as good as the reported short-term results, and if the cranial nerve preservation rates with these irradiation protocols are better than the surgical salvage rates.

Conclusions

Stereotactic radiation therapy is a useful addition to the armamentarium for the treatment of benign cranial base tumors. Good short-term and mid-term outcomes with quick recovery times have been shown in largely retrospective studies. The literature to date, on both the surgical and radiation treatments for these lesions, is marked by the biases inherent in the retrospective study design, and the evidence presented is at best level 4—not strong enough on which to base dogmatic opinions regarding critical clinical decisions. Therefore, the patient's personal preference often is the deciding factor, after a thorough discussion of the advantages and disadvantages of all the possible treatment options. Long-term prospective outcome studies with blinded independent observations are necessary to obtain high-quality of data to advance clinical care in this area.

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CHAPTER ONE HUNDRED AND EIGHTY

General Considerations in Pediatric Otolaryngology

J. Scott McMurray

Key Points

- Children are physiologically different from adults. Familiarity with these differences is required for safe management of their medical and surgical problems.
- Providing optimal pediatric care requires attention to the child as patient and the adult guardians.
- Involving the child in play may alleviate anxiety regarding procedures in the physical examination.
- With practice, physical examination can be conducted in expedient fashion and will be relatively painless for the child, yet complete for the surgeon.
- Management of the pediatric otolaryngology patient often requires a multidisciplinary team approach.

For many practitioners, there is no greater reward than helping children afflicted with illness. Pediatric otolaryngology has developed as a subspecialty within otolaryngology as a bridge between the surgical discipline and pediatric medicine. Nearly every otolaryngologist will treat children during his or her professional career. An estimated 25% to 50% of a general otolaryngologist's practice may be related to pediatric problems. Pediatric otolaryngology has therefore become an important part of all training programs in this field.

As the saying goes, children are not simply little adults. Often unique approaches are required for their evaluation, diagnosis, and management. Although the child is of prime concern, the parents—as the child's guardians, who must make decisions regarding the ultimate treatment options—also must be kept informed and must be approached with compassion. This is obvious to nearly all persons who have had to make medical decisions for a loved one but may not be as obvious to those who have not. The love for and emotional bond with a child may make even the most calm and rational person unable to comprehend events and medical explanations. It is up to the surgeon to monitor and modify his or her approach and explanations to both the child and the parent. This is not always an easy task but one that is highly rewarding.

Smaller and more premature neonates are surviving and sicker children are recovering from significant illnesses as neonatal and pediatric intensive care units, as well as the skills of the physicians who care for them, continue to advance. This development has led to a demand for practitioners well versed in the management of disorders encountered in this population—namely, intubation trauma, bronchoesophageal processes, infectious disease, tumors, and congenital malformations. A multidisciplinary approach often is required. Agreement among the pediatric specialists and with the general pediatrician is important, raising a third layer of communication that is required for successful treatment of the child and family.

Physiologic differences among infants, children, and adults have occupied major research efforts and constitute the subject of complete textbooks. This chapter outlines basic differences relevant to the practice of otolaryngology, along with some related considerations. In the following discussion, the material presented for each of the major body systems is intended as a general introduction, to be used as a starting point for further investigation.

Respiratory System

Control of Ventilation

Emergence from an underwater world, in which the child relied on placental exchange of gases and nutrition, induces tremendous changes in the neonate's physiology and anatomy. Some of these changes occur rapidly at birth; others proceed more slowly. These significant changes can complicate interpretation of the neonate's problems. In particular, the assessment of the control of ventilation in the neonate may be difficult. Interventions used to obtain measurements, such as placement of a facemask or insertion of a laryngotracheal tube, may induce significant changes in ventilation. Measurements of ventilation to assess respiratory drive also depend on the assumption that the respiratory muscles are capable of converting this drive into work—which is not always the case in infants and neonates.

Muscle fibers have been found to fall into two categories. *Type I* fibers are slow twitch, highly oxidative, and fatigue resistant. *Type II* fibers are fast twitch and are easily fatigable. Newborns have a paucity of type I muscle fibers but develop them shortly after birth. The muscle fibers in the diaphragm of a preterm infant are composed of less than 10% of type I fibers. The muscle fibers of a full-term infant may be 30% type I fibers. The percentage of type I fibers increases to 55%, the expected adult level, during the first year of life. Preterm infants are more prone to respiratory fatigue; this predilection disappears as they reach maturity.

Other subtle differences in sleep patterns also affect control of ventilation. Preterm infants spend as much as 50% to 60% of their sleep state in the rapid eye movement (REM) state. During REM sleep,

the intercostal muscles are inhibited, as are most of the other skeletal muscles. This places a greater burden on the diaphragmatic activity. Much of this activity may be wasted, because the chest wall can move paradoxically in the very young. This purposeless movement readily leads to hypoventilation, increased respiratory drive, and diaphragmatic fatigue.

Biochemical and reflex controls of ventilation are similar but incompletely developed in full-term neonates when compared with adults. Neonates have a higher basal metabolic rate than that in adults. This is reflected in higher ventilatory rates relative to body mass at any given partial pressure of carbon dioxide. Increases in ventilation are proportionately similar, however, in infants and adults with an increased partial pressure of carbon dioxide. This concordance in response is not seen in preterm infants. Their response to increases in partial pressure of carbon dioxide is blunted when compared with that in full-term infants and adults. Differences also are seen in the response to partial pressure of oxygen between premature infants and full-term infants and adults. The administration of 100% oxygen decreases ventilation in the very young, suggesting the existence of chemoreceptor activity not generally seen in adults.

Gestational age, postnatal age, body temperature, and sleep state modify the ventilatory response of newborns to hypoxia. Preterm and full-term infants less than a week old who are awake and euthermic usually demonstrate biphasic breathing patterns. They often experience tachypnea followed by hypoventilation. Hypothermic infants demonstrate a blunted response to hypoxia with respiratory depression, but they do not have the initial hyperpnea. The central effects of hypoxia on the respiratory center may cause depression of ventilation. Active peripheral chemoreceptors are unable to maintain a significant influence over this response. REM sleep also may decrease the response to hypoxia in these infants. Sleep states other than REM are associated with an increase in the ventilatory response to hypoxia. Arousal from sleep during hypoxia is not seen in newborns but develops during the first few weeks of life. In these slightly older infants, further maturation of the chemoreceptors increases their ventilatory drive to hypoxia. Of interest, a decreased response to hypercarbia associated with hypoxia also occurs in newborns but not in older infants and adults.

Reflexes arising from the lung and chest wall probably are more important in maintaining ventilation in newborns and in determining the respiratory tidal volume. Periodic breathing is common in preterm and full-term infants. These periods of alternating rapid ventilation followed by apnea may be common and can be considered normal. Periodic breathing is thought to result from dyscoordination of the feedback loops controlling ventilation. During the apneic part of periodic breathing, partial pressure of carbon dioxide may increase, but changes in heart rate do not. Generally, no serious physiologic consequences are seen. This response often ceases by the age of 6 years. Some preterm infants, however, may demonstrate serious and potentially life-threatening episodes of apnea. These episodes may last longer than 20 seconds and are accompanied by bradycardia. Apneic episodes may represent a failed response to hypoxia. Because these episodes are more commonly seen during REM sleep, ventilatory fatigue, as well as impaired chemoreceptor response to hypoxia, may be the cause. Usually, stimulation is all that is required to terminate the apneic event. Aminophylline treatment generally decreases the apneic episodes through central stimulation. Continuous positive airway pressure (CPAP) also may be helpful to decrease apneic episodes by modifying the lung and chest wall reflexes.

Laryngospasm

The primary function of the larynx is to protect the lungs from aspiration. Hence, the laryngeal adductor response is a very strong reflex. The robustness of the reflex has been shown to change with age and maturity in animal models. It is strong enough to be lethal in some instances. When laryngeal adduction is coupled with tachycardia, hypertension, and apnea, it is termed the *laryngeal chemoreflex* (LCR). The LCR can be induced by laryngeal exposure to acid, base, and pressure, but it is most sensitive to water and is ablated by saline. This may have implications for sudden infant death syndrome (SIDS). Evolving responses with age to hypoxia, hypercarbia, and the laryngeal stimulation that causes the LCR may explain the age pattern seen with SIDS. Deaths attributed to SIDS have dramatically decreased as a result of a change in the recommended sleep position of children—from prone to supine. Elimination of hypercarbia from rebreathing may be the mechanism behind the decrease in SIDS deaths. Hypercarbia is a known potentiator of the LCR. An increased awareness of and more aggressive stance toward the treatment of infant reflux also may have decreased a potential stimulus for the LCR. Decreased bolus size, increased feeding frequency, frequent burping, and positioning to discourage regurgitation have been helpful to decrease the incidence of reflux in infants and perhaps the incidence of apneic spells and infant breathing issues.

Lung Volumes

In proportion to body size, the total lung capacity, functional residual capacity, and tidal volume are roughly equivalent in adults and in infants. In the full-term infant the total lung volume is approximately 160 mL, with functional residual capacity at one half of this volume. Tidal volume is approximately 16 mL and dead space is approximately 5 mL. In comparison with adults, however, any increase in dead space is much more significant in infants, related to their small lung volumes. In contrast with static lung volumes, however, alveolar ventilation is proportionately much greater in newborns (100 to 150 mL/kg of body weight) than in adults (60 mL/kg of body weight). This higher alveolar ventilation in infants results in a higher alveolar–functional residual capacity ratio, 5:1, compared with 1.5:1 in adults. Consequently, the functional residual capacity is much less of a buffer in infants, so that changes in the concentration of inspired gases are much more rapidly reflected in alveolar and arterial levels. This explains why induction of anesthesia using inhalational techniques is easier in infants than in adults. Along with the higher metabolic rate for body weight seen in infants, this differnce also explains why the ventilatory reserve in infants is not as great as in adults. The time from apnea to oxygen desaturation is much shorter in infants than in adults. Accordingly, surgical maneuvers that require short apneic periods may pose more of a challenge in infants than in adults.

The total surface area of the air-tissue interface of the alveoli in infants is small (2.8 m^2). When this relatively small gas exchange area is combined with the higher relative metabolic rate, infants have a reduced reserve capacity for gas exchange. This difference is of increased importance when congenital defects interfere with lung growth and development or if the lung parenchyma becomes damaged. The remaining healthy lung may not be adequate to sustain life.

Respiratory Rate

The most efficient respiratory rate for newborns has been calculated to be around 37 breaths per minute. This rate is close to that observed for average newborns. Full-term infants are similar to adults in requiring approximately 1% of their metabolic energy to maintain ventilation. The cost of breathing is then 0.5 mL/0.5 L of ventilation. In preterm infants, this nearly doubles to 0.9 mL/0.5 L of ventilation. The cost of respiration also dramatically increases if the lung parenchyma is diseased or damaged by processes other than prematurity. In either case, the result is higher caloric and nutritional demands. Respiratory rate can directly affect the infant's ability to complete the suck-swallow-breathe cycle as well. If gas exchange is poor, ventilation rates may increase. This increase in respiratory rate may not allow adequate time for the suck-swallow portion of feeding. Caloric intake decreases precipitously as the infant chooses breathing over feeding. This vicious circle can eventuate in failure to thrive.

Ventilation-Perfusion Relationships

Ventilation and perfusion are imperfectly matched in the neonatal lungs. Some persistent anatomic shunts in the newborn circulatory system, as well as a relatively high closing volume in the lungs, cause this mismatch. The normal arterial oxygen tension in a newborn breathing room air is 50 mm Hg. This increases dramatically during the first 24 hours of life with changes in fetal circulation and maturation of lung parenchyma. It continues to change slowly during the ensuing months and years (Table 180-1).

Table 180-1

Arterial Oxygen Tension (Pao_2) in Healthy Infants and Children

Age	Pao_2 in Room Air (mm Hg)
0-1 week	70
1-10 months	85
4-8 years	90
12-16 years	96

Table 180-2

Normal Heart Rate for Children by Age

	Heart Rate (beats/minute)	
Age	Average	Range
Newborn	120	100-170
1-11 months	120	80-160
2 years	120	80-160
4 years	100	80-120
6 years	100	75-115
10 years	90	70-110

Cardiovascular System

Newborn Heart and Cardiac Output

The heart of a healthy neonate is much different from that of an adult. The thickness of the right ventricle exceeds that of the left, as seen by the normal right axis deviation on the neonatal electrocardiogram. Shortly after birth and with closure of the fetal circulation, the left ventricle enlarges disproportionately. By the age of 6 months, the adult right-left ventricular size ratio is established.

The newborn myocardium is significantly different from the adult myocardium as well. The newborn myocardium contains fewer contractile fibers and more connective tissue. Consequently, neonatal ventricles are less compliant at rest and generate less tension during contraction. The usual Starling curves of contractility for adult cardiovascular physiology do not hold true for the neonatal heart. Cardiac output is rate-dependent in the neonatal heart. Bradycardia invariably equates with reduced cardiac output. Because of the differences in compliance and contractility in the neonatal heart, the increased contractility necessary to maintain cardiac output during bradycardia is not possible. The low compliance of the relaxed ventricle limits the size of the stroke volume; therefore, increases in preload are not as important in neonatal physiology as is heart rate. This distinction is extremely important to recognize during surgical and anesthetic procedures, which may induce bradycardia. Autonomic innervation also is incomplete in the neonatal heart, with a relative lack of sympathetic elements. This relative underdevelopment may further compromise the ability of the less contractile neonatal myocardium to respond to stress.

Heart rate is crucially important in the very young. The normal range for the newborn is 100 to 170 beats per minute. The rhythm is regular. As the child grows, the heart rate decreases (Table 180-2). Sinus arrhythmia is common in children, but all other irregular rhythms should be considered abnormal. The average newborn systolic blood pressure is 60 mm Hg; the diastolic pressure is 35 mm Hg.

Blood Volume

Intravascular blood volumes vary tremendously during the immediate postnatal period, related to the amount of blood transferred from the placenta to the child. "Stripping" the cord after birth or delays in clamping the umbilical cord may increase the blood volume by more than 20%, resulting in transient fluid overload and respiratory distress. Conversely, fetal hypoxia during labor causes vasoconstriction and a shift of blood to the placenta. Thus, fetal hypoxia may lead to hypovolemia after birth.

Because the total blood volume of an infant is small, significant blood loss can accompany relatively minor surgical blood loss. It has been observed during exchange transfusions that withdrawal of blood parallels a decline in systolic blood pressure and cardiac output. This decline is reversible to normal parameters with replacement of the same blood volume that was removed. Changes in arterial blood pressure with normal heart rates are thus proportional to the degree of hypovolemia. A newborn's ability to adapt the intravascular volume to the available blood volume is limited because of less efficient control of capacitance vessels and to immature or ineffective baroreceptors.

In the infant, systolic arterial blood pressure is closely related to circulating blood volume. Blood pressure is then an excellent guide to the adequacy of blood or fluid replacement during anesthesia, a fact that has been confirmed by extensive clinical experience.

Response to Hypoxia

Because of the relatively high metabolic rate typical of neonates and the relatively low reserve for gas exchange as described earlier in this chapter, hypoxemia can develop rapidly in neonates, in whom the first sign is bradycardia. During surgery, any unexplained episode of bradycardia should be initially treated with oxygen and increased ventilation. During hypoxemia, pulmonary vasoconstriction and hypertension occur more dramatically in the neonate than in the adult. Such changes can shift the infant back into fetal circulation, compounding the problem. Changes in cardiac output and systemic vascular resistance also differ from those in older children and adults. During hypoxemia in adults, the principal response is systemic vasodilation that, together with an increase in cardiac output, helps to maintain oxygen transport to the tissues. Fetuses and some neonates respond to hypoxemia with systemic vasoconstriction. In the fetus, hypoxemia shifts blood to the placenta to improve gas exchange and oxygenation. After birth, however, hypoxemia may lead to decreased cardiac output, thereby further limiting oxygen delivery and increasing cardiac work. In infants, early and pronounced bradycardia may result from myocardial hypoxia and acidosis.

Neonates exposed to hypoxemia suffer pulmonary and systemic vasoconstriction, decreased cardiac output, and bradycardia. Rapid recognition and intervention are necessary to prevent cardiopulmonary collapse, cardiac arrest, and death.

Blood Volume and Oxygen Transport

Neonatal blood volume is approximately 80 mL/kg at term and 20% higher in preterm infants. The hematocrit is 60% and the hemoglobin content is 18 g/100 mL. The values vary by infant, depending on when the umbilical cord is clamped. Little change in these values occurs during the first week of life, after which the hemoglobin level declines. The hemoglobin level change occurs more rapidly in preterm infants.

Approximately 70% to 90% of the hemoglobin in a full-term infant is the fetal type. Fetal hemoglobin has a higher affinity for oxygen than that of adult hemoglobin. It combines with oxygen more readily but also releases oxygen less efficiently at the tissue level than does adult hemoglobin. The increase in hemoglobin content in neonates is required to overcome this higher affinity of fetal hemoglobin for oxygen. A concentration less than 12 g/100 mL constitutes anemia. Correction of anemia by blood transfusion is indicated if the infant requires oxygen or is experiencing apnea.

Table 180-3

Ideal Electrolyte Composition for Infants

	Na^+ (mEq/L)	K^+ (mEq/L)
Intracellular	10	150
Extracellular	140	4.5

Table 180-4

Expected Fluid Losses in Children

System	Fluid Loss (mL/100 cal/day)
Sensible Losses	
Kidneys	55
Insensible Losses	
Lung	15
Skin	30
Total	100

Table 180-5

Children's Maintenance Fluid Intake Calculated by Weight

Weight (kg)	Estimated Fluid Intake (mL/hour)
0-10	4 mL/kg/hour
11-20	40 mL/hour (2 mL/kg/hour)
>20	60 mL/hour (1 mL/kg/hour)

During the first weeks of life, the hematocrit drops as a result of early suppression of erythropoiesis. The fetal type of hemoglobin is replaced with the adult type of hemoglobin with more optimal oxygen-carrying capacity. This physiologic anemia reaches its nadir at 2 to 3 months with a hemoglobin content of 9 to 11 g/100 mL. Provided that nutrition is adequate, the hemoglobin level will then gradually rise over several weeks to 12 to 13 g/100 mL, which is maintained throughout childhood.

Fluids and Fluid Management

As in adults, preoperative, intraoperative, and postoperative fluid management is extremely important in children. Some of the physiologic differences outlined earlier in this chapter make fluid administration even more critical. Because of their small intravascular volume (70 to 80 mL/kg), infants who experience small changes in fluid balance can easily become either dehydrated or overloaded with fluid. Extreme vigilance, early recognition, and tight control are required in managing fluid balance in children. Compartmentalization of total body water changes with age, but intracellular and extracellular electrolyte composition remains stable (Table 180-3). Calculating the maintenance fluid requirements for a child can be based on relatively simple formulas that vary according to metabolic and physical activity. The calculation of water loss per calorie is described in Table 180-4. The correspondence of necessary fluid intake proportional to weight is described in Table 180-5.

Complex fluid and electrolyte deficits are beyond the scope of this discussion. In most such cases, consultation with pediatric medical specialists is advised.

Pain Management

The management of pain in infants and children has undergone tremendous advances in recent years. It had been commonly believed that infants and newborns did not perceive pain because of their immature nervous system and that they do not have memory of pain if it occurs. Direct physiologic consequences have been observed in infants as a response to pain. Changes in heart rate, blood pressure, and respiration rate have been documented in infants experiencing painful stimuli. These changes can be physiologically as well as emotionally deleterious to the child.

The perception of pain depends on both sensory and emotional experiences that may be altered by various psychological factors. These factors may be specific for each individual patient, based on his or her expectations and past experiences. Efforts to reduce stress, anxiety, and fear will help decrease the apprehension and perception of pain during procedures in the office or in the operating room. In patients of the appropriate age, relaxation techniques such as guided imagery, deep breathing, and hypnosis may diminish the emotional component of pain. An adequate and age-appropriate explanation of expectations also will reduce anxiety, increase cooperation, and decrease perceived pain. The caregiver or parent also should be coached regarding expectations, because children often look to the psychological state of their parent for cues. An anxious parent often increases the anxiety of the child. Conversely, a calm and collected parent can help calm the child during uncomfortable procedures.

Non-narcotic analgesics are helpful for pain management. Acetaminophen in doses ranging from 10 to 15 mg/kg every 4 hours is useful. Other nonsteroidal anti-inflammatory medications also are excellent for pain management. They often inhibit platelet function, however, and should be used only at the discretion of the surgeon.

Narcotic analgesics are indicated for moderate to severe pain in all age groups. Optimal use requires consideration of the needs of the individual patient. Neonates require special observation during the administration of narcotics. As noted previously, ventilatory responses to hypoxia and hypercarbia are diminished in this age group. Narcotics may further decrease these responses to potentially life-threatening levels. The metabolism and half-life of narcotics are different in neonates from those in older children and adults. The permeability of the blood-brain barrier also may be increased in neonates. The use of intravenous, intramuscular, and oral narcotics is safe in the appropriately monitored setting and with the proper dose. Unlike adults, who usually self-administer and therefore self-regulate narcotic analgesics, pediatric patients often rely on caregivers to administer pain medication, which can lead to underdosing, as well as overdosing.

Sedation

More often today, professional certification and credentialing for pediatric sedation are required at institutions caring for children. The development of sedation teams, often staffed by pediatric intensivists, has increased safety and monitoring for these patients. Otolaryngologists can participate in the team effort by assessing the airway of the patient referred for sedation. Occasionally, a general anesthetic procedure with a secured airway is required for the proper level of safety for a sedated patient. Although the otolaryngologist can accomplish assessments of airway safety, the professionals on the sedation team have the final word on whether they are willing to sedate a child. The requirements for certification, the makeup of the sedation team, and the success of the interaction as measured by family satisfaction and patient outcome are dependent on the institution involved. It is important to adhere to the guidelines of the institution and to work together as a team.

Referral Sources

Unlike adults, most pediatric patients have a primary caregiver—the pediatrician or family practice physician. School-aged children require

vaccinations and usually will have a physician who provides this level of care. In turn, most pediatric patients seeking help for problems related to the ears, nose, and throat will be referred to the specialist by their primary care physician. Pediatric medicine is a specialty that legitimately considers its practitioners to be advocates for their patients. The child's primary care physician is responsible for his or her overall health and well-being. This physician can serve as a tremendous ally to help identify and refer problems early on, as well as to help translate the complex problems related to surgical management when adequate communication lines have not been established. Although every patient encounter requires an element of trust building and rapport development, a long-term relationship usually has already developed between the child's doctor and the family.

Pediatric medicine and its interface with surgery have a slightly different culture from its counterpart in the typical adult world. Often a multidisciplinary approach is used in the perioperative period. Although this approach can enhance the care of the patient, clear delineation of duties and responsibilities and open lines of communication are essential.

Although all parties involved must understand that the surgeon is ultimately responsible for the care of any patient undergoing surgery, a decision to proceed should always be accepted by the parents, as well as the referral source. Occasionally, expectations for surgery are initiated before the evaluation by the otolaryngologist. In such cases, how a decision is made must be explained clearly and logically. The surgeon makes the final recommendations for or against surgical management of a problem. All parties must clearly understand the steps leading to a logical decision.

Finally, pediatric otolaryngologists often direct their educational efforts directly to the families of the patients they treat. Education of their colleagues, specifically the primary care physicians caring for these patients, also is very important. Keeping these practitioners up to date through small education forums will maximize their ability to help with perioperative management, as well as increasing the visibility of the otolarygologist's contributions.

Patients

Although the entire family is involved in the care of a child, the child is the patient. Children experience the same fears of pain and discomfort as in adults but may lack the maturity and skills to overcome these fears. Delayed gratification is not often a concept familiar to a child. Whereas adults often bring themselves to the doctor and therefore have made the first hurdle toward obtaining medical care, children are brought by their parents and often have no idea why they are there. Establishing rapport with the child is important for myriad reasons. Not only will this put the child at ease, but it will often put the parents at ease when they see that the physician has a genuine interest in the well-being of their child. Children take cues from their parents. If the parent is apprehensive, the child will often be as well. It is important to explain not only to the parent what is to be expected during the history and physical examination but also to the child—on a level he or she may understand. Procedures that may be uncomfortable are best left to the end of the examination and are performed quickly but thoroughly.

Quickness and experience allow for a brief, but relatively complete, physical examination without undue stress on the child or the parent. Restraining an older child who may have been traumatized by a previous forceful examination is wrong and could be dangerous. In these cases, sedation or a general anesthetic is appropriate to complete the required examination.

Parents

Parents can find themselves in an uncomfortable position. They must make decisions for their sick child, decisions that may include treatment that may carry some discomfort and risk. It is important for the surgeon to be open and honest regarding the options and risks involved. Alternative treatment plans often are possible, and all of the options, with their set of risks and benefits, as well as expected outcomes, should be explained to the family. Finally, a single best option may exist, and the reasons that a surgeon considers one option better than others should be explained. Parents often have questions that may be biased by previous experiences or the advice of other family members or friends, or by exposure to the media. Time must be allotted to answer these questions.

Often, families have been referred by the primary care physician, who usually has answered many of the relevant questions. Having been referred to a specialist, the parents often identify the otolaryngologist as a person with expertise and added ability. It is important not to be placed in the situation of persuading parents to proceed with surgery. If they continue to have difficulties deciding after all of their questions have been answered, it may be suggested that they contact their primary care physician for another view. Finally, it may be more comfortable for families to make decisions regarding surgery at home with the understanding that they can call if more questions arise and will schedule an appointment if they wish to proceed.

Congenital Anomalies

Children with developmental or hereditary abnormalities often require a health care professional team approach for optimal treatment. As an example, for children with craniofacial anomalies, a craniofacial team consisting of at least an otolaryngologist, a craniofacial surgeon, dentist, geneticist, audiologist, speech-language pathologist, and social worker will bring the greatest benefit. It is important that a unified voice come from the specialists at hand. Conflicting information will only confuse the often devastated parents. Guilt regarding inheritable defects may be overwhelming to the parents. Counseling should be available from specialists in genetics when needed.

The goal of caring for children with congenital anomalies or developmental delays is to maximize their individual potential. It is important to know what difficulties a child may have from a particular disorder and then to offer advice or techniques proven to help such families cope with or manage the disability. This will be different for each child, family, and situation.

At one time, genetic counseling was routinely advised for families of all children with congenital abnormalities. The feeling today is that genetic counseling should be offered only to parents who desire it. Other than speaking in general terms of the inheritable nature of sensorineural deafness, cleft palate, or other problems, the clinician should not force the parents to face information they do not wish to acknowledge. The denial phase is related to their eventual acceptance of their child's problem. Once they have adapted to the child's abnormality, the parents are much more receptive to genetic counseling.

History

In treating children, several sources are available for historical data. A referral letter from the primary care physician often will accompany the child. This aspect of the history is important but does not replace the history taken from the parents or the child. Historical data from the primary physician give the added advantage of allowing the specialist physician to verify that the information provided by others and the data gathered during the examination are in agreement. The parents often give the history. They usually are very astute regarding their child's behaviors or symptoms and should therefore be listened to carefully. The child can be questioned as well, although he or she may not understand or be able to identify a problem. Often, chronic symptoms are not seen as problems to the child because such symptoms have been lifelong. The child, not ever having experienced life any other way, does not recognize his or her symptoms as abnormal. The difficult part for the pediatric otolaryngologist is to synthesize sometimes conflicting data into a coherent story.

Occasionally, admission to the hospital for observation is required. This allows for further collection of historical data. Symptoms described by the caregiver can be documented and perhaps better understood. Further testing also may document whether the child's safety is compromised because of symptoms or the severity of potential problems.

It also is very important to obtain a general family history, as well as a history of any diseases or illnesses affecting the child's siblings. Information regarding the pregnancy and delivery of the child also is important. Insight into any family stresses or school problems that may influence the child's psychosocial development also is helpful.

Physical Examination

Physical examination of a child can be done in a nonthreatening and calm manner. Rapport and trust are the key elements. Engaging the child as an active participant often leads to more cooperation. One technique is to let the child hold or examine the instruments before they are used. This often reduces the child's anxiety. Because many well child examinations are accompanied by vaccinations, children unfortunately often equate any visit to the doctor with a shot. The resulting apprehension and perhaps an attempt at maintaining independence or control of the self may underlie seemingly irrational behavior during an examination.

Most of the head and neck examination should be painless. Otoscopy generally is managed without difficulty. Pneumatic otoscopy can be performed but should be explained before proceeding so as not to surprise the child. Explanations build a child's trust in the examining physician. The use of a head mirror or headlamp light during the examination is the surgeon's choice. Things that cover the examiner's face often frighten children, which may decrease cooperation. Nasal endoscopy can be performed with the otoscope and a larger speculum, thereby eliminating the need to introduce a new instrument to the child. Oral examination often can be accomplished without a tongue depressor, although occasionally use of a depressor may be required to view the posterior pharynx. Palpation of the neck can be accomplished without any significant discomfort to the child, and masses or tenderness can be documented.

During the examination, further observations of the child's facial features can be made. It is important to ensure that the ears look normal, without pits or fistulas. The eyes also should be symmetrical in shape and alignment, without apparent hypertelorism or heterochromia. The nasal airway should be assessed for chronic mouth breathing and to help identify any abnormality of the palate. Listening to the child breathe, for the sounds of stridor or stertor, can help identify the level or site of potential airway obstruction. Auscultation of the neck and chest also generally is performed. The otolaryngologist will concentrate the physical examination on the particular area of interest, which is the head and neck. A general physical examination should be performed in a brief but complete manner, however.

Special Considerations

Microscopic Examination of the Ear

Otomicroscopy is an invaluable tool for assessing the ears. Children can have anxiety about this portion of the examination, however. Often, allowing the child to look through the microscope at the examiner's thumb will show that the microscope is simply a tool to obtain a magnified view of the ear. The parent can assist in reminding the child to hold still for the examination while cerumen or debris is removed from the ear canal. With the parent reclined on the examination chair or table, the child may lie on the parent like a table. The parent can then hug the child, to hold the arms and body still, while an assistant helps steady the head. Use of a papoose is possible in smaller children but often is not successful in older children. Sedation usually is not necessary but may be used in certain cases, in accordance with the sedation policies of the institution. Occasionally a general anesthetic is required to permit a complete and thorough examination.

Although usually not painful, suctioning is loud and can be frightening. The suction device is a very useful tool to quickly clean away debris and drainage. Some clinicians prefer to use cotton-tipped applicators instead. It is important to have a number of techniques in reserve and to use the one that will quickly and effectively accomplish the required task without undue stress and discomfort to the child.

Flexible Endoscopy

Nasopharyngoscopy is an invaluable tool for the otolaryngologist. With advances in technology, smaller-caliber endoscopes are being developed with improving optics. Although the mirror examination is useful, the fiberoptic endoscope allows for a dynamic examination of the nose, vellum, pharynx, hypopharynx, and larynx. When combined with videotaping, slow-motion replay is possible—an important option if only brief glimpses are obtained in a child who is not able to cooperate fully with the examination.

As in adults, topical anesthesia and nasal decongestion, with lidocaine gel or Pontocaine (tetracaine) spray and oxymetazoline, is very useful. Use of cocaine in young children is not advisable because of variable absorption rates. In infants, cocaine can produce unwanted irritability and nervousness. The parents should be counseled that after the topical anesthetic, the child should not eat or drink for approximately 30 minutes. Sedation generally is not necessary for this examination.

Complications from nasopharyngoscopy are rare. An emergency cart for airway management and the skills to use it are important to have on hand. Nasal bleeding, if it occurs, often is self-limiting or requires little intervention.

Needle Biopsy

Fine-needle aspiration (FNA) can be performed in children to obtain a biopsy specimen for histopathologic examination. Ideally, a cytopathologist should be available for interpretation of results. Many of the typical masses of the head and neck are very different from those encountered in adults and may be more difficult to characterize. This does not make FNA less useful, however. Children usually are very frightened of needles or sharp objects. EMLA cream (Astra Pharmaceuticals, Westborough, Massachusetts) or other anesthetic creams that are topically applied can render the introduction of the needle painless.

The site is prepared in a sterile manner. The 22- or 23-gauge needle, attached to a 10-mL syringe, is then placed into the mass while suction is applied. The sample obtained within the needle core is then applied to a glass slide and is placed in a fixative. It is optimal if the cytopathologist can attend or perform the procedure to provide immediate feedback regarding the adequacy of the specimen. If the specimen is inadequate and the child appears able to tolerate another attempt, FNA may be repeated using the same anesthetic. An adhesive bandage is applied when the procedure is done. FNA should be no more traumatic than obtaining a blood sample and should be explained in those terms to the parent.

Audiology

Every child can be tested for hearing loss. Pediatric otolaryngologists can help to accomplish this goal by educating the families and especially the primary care physicians of their patients. It has been shown that in children with hearing loss, early detection and treatment lead to dramatic increase in language ability later in life. Audiologists interested in pediatric screening generally are able to test children as young as 6 months of age with visual response audiometry. Visual response audiometry in experienced hands can be very reliable. Other techniques for younger children or children who are unable to conform to the demands of the task include otoacoustic emissions and auditory brainstem response (ABR) testing.

Early detection of hearing loss is extremely important to the speech and language development of the child. Currently, newborn hearing screening programs with automated ABR testing are being set up nationwide. If a screening test identifies the infant as requiring further investigation, it is essential for the otolaryngologist to provide any necessary referrals and follow-up evaluations. If no action is taken once a child has been diagnosed with hearing impairment, the test is useless and does not benefit the child or the family.

Preparation for Hospitalization and Surgery

Once the decision to proceed with hospitalization or surgery has been made, the child and parents should be readied emotionally to achieve a successful outcome. The details and expectations should be reviewed with the family by persons familiar with the process. Some institutions and most children's hospitals have programs to introduce the family to the hospital, operating room, and operating room procedures. A sense of familiarity and an understanding of what to expect will be helpful to all involved. Children can then role-play before hospital admission or surgery. With a clear understanding of what is expected, parents also are less apprehensive and help calm the child.

It is important to clarify arrival times and nothing-by-mouth requirements to the family. Special films and booklets are valuable tools for education. The parents must be encouraged to be truthful, to the best of their ability, about preparation for the upcoming surgery. It also is important that the surgeon communicate directly with both parents and child so that all questions are answered completely.

Hospital

A dedicated children's hospital is the preferred venue for pediatric otolaryngologic surgery, providing a team of physicians, nurses, and other professionals who can best handle a hospital stay or surgical procedurefor the pediatric patient. Children's hospitals constitute an important medical resource, and every surgeon involved in the care of children should support them. Unfortunately, not every community has one. In such instances, it is important to identify the best facilities in the community in which the physical plant, physicians, nurses, and support staff are capable of and enjoy caring for children. Ensuring an optimal environment for pediatric treatment will encourage the best outcomes and lead to the greatest satisfaction among patients and their families.

The concept of a team of professionals who deal strictly with pediatrics is not new; moreover, a team approach is becoming increasingly accepted as the standard of care. When complications arise, as they inevitably do in the course of even the best medical care, having the support facilities and the personnel available to handle any need promptly is vital for the best outcome possible.

Selecting Anesthesia

Pediatric anesthesia is a subspecialty in itself. Reaching a degree of proficiency to deliver an anesthetic to children of all ages requires considerable training and experience. The younger the patient, the more complex the problems encountered. As in all aspects of medicine, this subspecialty includes practitioners with special interests and expertise in particular fields. Those with expertise in safely delivering anesthesia to children should be sought when their assistance is required. Reliance on these specialists benefits both the patient and the surgeon.

With practice and special expertise, the interested clinician can devise techniques to safely and effectively perform nearly any technique. Local anesthesia as a primary anesthetic technique for pediatric surgery is possible but requires a cooperative child and an adept surgeon. Generally, local anesthetics are used for immediate postoperative pain management after surgery performed with the patient under general anesthesia. Young children generally do not understand the need for painful injections and have short attention spans, making it difficult for them to sit still for the procedure. The use of sedation for extended periods is not recommended unless support personnel are available to monitor the child during the sedation process. Many institutions have strict guidelines and require a certification process for the use of conscious sedation in children. Most invasive or painful procedures require a general anesthetic.

Postoperative Management

Probably the most important part of postoperative management is preoperative teaching. If the parent and the child are adequately prepared about the effects of surgery, they are more capable of handling the postoperative period in terms of decreased stress and optimal adherence to the postoperative regimen. Detailed teaching about the expected clinical course and unexpected possibilities is important. Providing written instructions, along with contact telephone numbers if the parents should have questions, also is very helpful. Knowing what to expect is the single most important factor in uneventful recovery from a surgical procedure without multiple phone calls and excessive concern from both patient and physician.

If a child must be hospitalized, it has been shown that the presence of a parent makes the stay less fearsome and stressful for the child. Whenever possible, parents should be encouraged to stay with the child while in the hospital. Arrangements should be made for this to be possible if it is not the norm at the hospital where the child will stay.

More often, short-stay and outpatient procedures are being performed. It is helpful for the child to return to the home setting as soon as possible. Safety is the main concern, however, and monitoring in the hospital should be done as long as necessary.

An awareness that modifications in surgical technique may be required in the management of pediatric problems is important. Dressing changes, suture removal, and postoperative manipulations should be kept to the required minimum so as not to provoke fear and discomfort in children who must undergo minor procedures. Sometimes sedation or a general anesthetic for packing or suture removal, not often required for adults, may be necessary in children. It is reasonable to plan ahead at the time of surgery to use absorbable suture material and dressings that need infrequent changing.

A Rewarding Experience

The care of children is an extremely rewarding experience. Children may become ill quickly but often recover just as quickly if put on the right pathway. Watching children grow and develop makes for lasting memories and personal satisfaction. For many clinicians, helping children with chronic illness to overcome disabilities and difficulties and watching them reach their full potential as they grow to adulthood have no match for reward.

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CHAPTER ONE HUNDRED AND EIGHTY-ONE

Anatomy and Developmental Embryology of the Neck

Daniel O. Graney

Kathleen C. Y. Sie

Key Points

- Anatomy of the neck is predictable. A detailed understanding of neck anatomy is critical for the otolaryngologist–head and neck surgeon.
- Congenital anomalies of the neck are related to the embryology of the neck.

Most descriptions of the neck divide the anatomy, for discussion purposes, into triangles. The use of triangles is simply an organizational approach to manage the volume of anatomic detail in the neck by parceling it into reasonable study units. When an incision is made over the carotid triangle, surgeons can thereby predict the structures they will encounter in precise order. Similarly, the embryologic correlates of the triangles are important in understanding the development and differential diagnosis of masses in the various triangles of the neck.

This chapter begins with descriptions of the posterior triangle and the subdivisions of the anterior triangle. Also presented is a description of the root of the neck that relates the anatomy of the two major triangles to the radical neck procedure. The chapter concludes with a discussion of the embryology of the branchial arches and the pharyngeal pouches and their contribution to various masses in the neck.

Strictly speaking, the term *triangle* connotes a planar form (i.e., a flat structure). The "triangles" in the neck, however, are three-dimensional spaces that should be visualized as shallow triangular boxes. These boxes have not only three sides but also a roof (top) and a floor (bottom). Most of the triangles are three-dimensional spaces bounded by bone and muscles, with distinct fascial layers forming the roof and floor of the space. In general terms, the triangular space contains blood vessels, nerves, lymphatic vessels, and lymph nodes. Using this somewhat contrived schema, the organization of the neck can be greatly simplified.

Posterior Triangle of Neck

The posterior triangle is bordered by the sternocleidomastoid muscle, the anterior border of the trapezius muscle, and the middle third of the clavicle (Fig. 181-1). Specific layers of deep fascia form the floor (medial wall) and roof (lateral wall) of the triangular box. An understanding of the fascial relationships in the neck is important not only because of the boundary relationships but also because fasciae form planes that provide routes of surgical access or pathways for hemorrhage and infection. For this reason, a brief discussion of the fascial planes is necessary before proceeding with the anatomy of the posterior triangle.

Fascia of Neck

One of the earliest lessons in anatomy is that there are two types of fascia in the body: the superficial and the deep. In the region of the abdominal wall, superficial fascia consists of two layers—a fatty layer (Camper's fascia) and a deeper, membranous layer (Scarpa's fascia). The deep fascial layer of the abdominal wall is not subdivided but simply envelops the abdominal muscles. In the neck the superficial fascia is very thin and is not divided into layers, whereas the deep fascia is divided into three layers.[1] The names of these layers vary with different authors, resulting in a somewhat chaotic terminology. Regardless of the terminology used, the divisions are arbitrary at best. A simple approach can provide a workable solution for either the anatomist or the surgeon.

Superficial Layer of Cervical Fascia

As just noted, the superficial layer of cervical fascia is a single layer of fascia underlying the skin. It usually is thin, except in the obese person, in which case it is thickened by adipose tissue. Its primary surgical significance is that it provides a fascial pad that protects underlying structures when a skin incision is made. In exceptionally lean people, however, the paucity of this layer may not protect underlying structures, such as the accessory nerve, so the surgeon should be wary when operating on such patients.

Deep Fascia

The deep fascia is divided into three layers, demonstrated best when the neck is viewed in cross section (Fig. 181-2). These are the external, middle, and internal layers of the deep cervical fascia. The external layer of deep fascia underlies the platysma muscle and completely invests or encircles all of the superficial neck structures. For these reasons, the external layer is also known as the superficial layer, or investing layer, of deep fascia. In the region of the sternocleidomastoid and trapezius muscles, it splits and envelopes the individual muscles. A middle layer of the deep cervical fascia encloses the visceral structures of the neck (the trachea and esophagus). Hence the synonym for the middle layer is the *visceral fascia*.

The third, or internal, layer of the deep cervical fascia surrounds the deep muscles of the neck and cervical vertebrae (Fig. 181-3). This

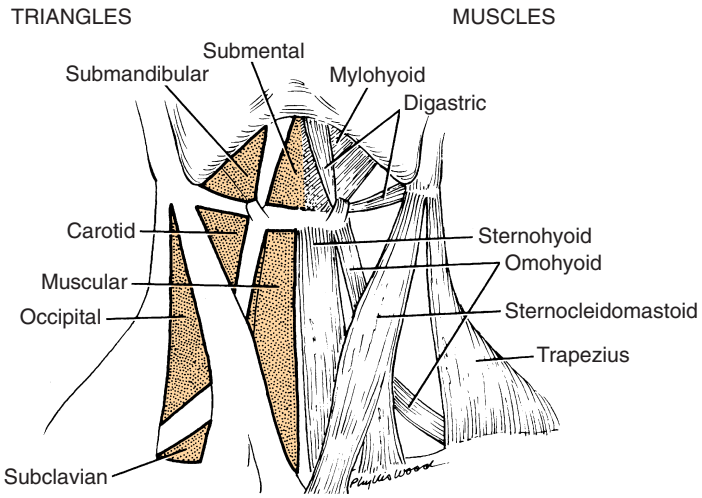

Figure 181-1. The triangles of the neck and their boundaries.

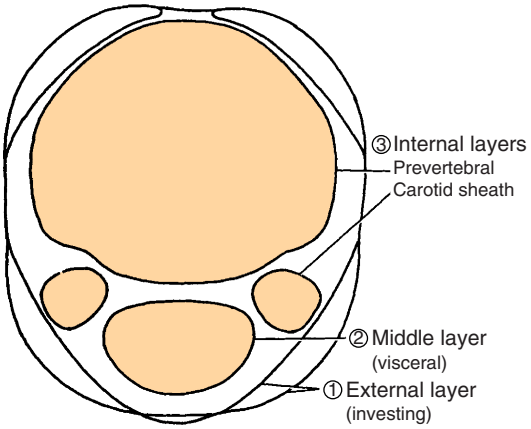

Figure 181-2. Divisions of the deep cervical fascia seen in transverse section at the level of cranial nerve VII.

layer also is known by its descriptive term *prevertebral fascia* (although "paravertebral fascia" would have been more appropriate). The muscles enclosed by the prevertebral fascia include the deep muscles of the neck (the cervical part of the erector spinae); the levator scapulae; the scalenus anterior, middle, and posterior muscles; and the longus colli and longus capitis muscles, which lie on the anterior aspect of the cervical vertebrae. The last-named pair of muscles serve as flexors of the vertebrae; the longus capitis also assists in flexion of the skull. The scalenus group underlies the prevertebral fascia in the region of transverse processes of the cervical vertebrae. The anterior tubercles of the transverse processes provide origin for the scalenus anterior muscle, whereas the posterior tubercles provide the origin for the scalenus medius and posterior muscles. Continuing posteriorly, in order, are the levator scapulae and deep cervical muscles already noted.

The internal layer of deep fascia is described by some authors as enveloping the carotid and jugular vessels. Hence, the carotid sheaths are included as part of the definition of the internal layer of deep fascia. An effective means of visualizing the spatial relationships of these layers of fascia is to examine a cross section of the neck. This view not only is informative in defining the three layers of deep fascia but also serves to relate them to the posterior triangle of the neck (see Fig. 181-2). Placing a finger over the middle of the posterior triangle (i.e., between the trapezius and sternocleidomastoid muscles) will clarify that the roof (lateral wall) of the triangle is formed by the superficial layer of deep fascia. Palpation deeper into the triangle will bring the tip of the finger into contact with the prevertebral fascia that forms the floor of the posterior triangle and invests the prevertebral muscles. If the superficial layer of the deep fascia is incised, a finger inserted into the space, exploring anteriorly between the sternocleidomastoid and prevertebral muscles, will encounter the carotid sheath. This is a surgical approach to the retropharyngeal area or to the carotid vessels for vascular surgery.

Contents of Posterior Triangle

The major contents of the posterior triangle are the cutaneous branches of the cervical plexus, the accessory nerve (cranial nerve XI), two arterial branches of the thyrocervical trunk, and an abundant number of lymph nodes associated with the veins of the region.

Cutaneous Branches of Cervical Plexus

The sensory branches of the cervical plexus contained within the posterior triangle are four cutaneous nerves, which supply the skin of the head and neck from the area of the posterior scalp to the supraclavicular region. These cutaneous nerves are the (1) lesser occipital, (2) great auricular, (3) anterior, and (4) supraclavicular (Fig. 181-4). The first three of these nerves contain cervical segments C2 and C3 and the supraclavicular nerves C3 and C4. The topographic relations of these nerves and their distribution to the skin are illustrated in Figure 181-5. The important landmark for the cervical nerves is the accessory nerve at the point where it enters the posterior triangle from under cover of the sternocleidomastoid muscle. If this point is viewed as the center of a clock face, the cervical nerves mimic the hands pointing in different directions (see Fig. 181-4, inset). For instance, on the right side, the lesser occipital nerve is approximately at the 11 o'clock position, the great auricular is at the 12 o'clock position, and the anterior cutaneous nerve of the neck can be found at the 3 o'clock position. The supraclavicular nerves consist of three or four bundles of filaments scattered between the 5 and 7 o'clock positions on the clock's face. Continuing this analogy, the accessory nerve can be seen to traverse the posterior triangle along the line of the 8 o'clock position until it enters the deep surface of the trapezius muscle. Viewed in this manner, the accessory nerve serves as a focus for organizing the pathways of the cutaneous nerves, as well as for emphasizing cranial nerve XI as a motor nerve in the posterior triangle.

Accessory Nerve

The accessory nerve supplies both the sternocleidomastoid and trapezius muscles; however, in the posterior triangle, the only fibers remaining in the nerve are those destined for the trapezius. The accessory nerve should be preserved whenever possible because paralysis of the trapezius muscle produces devastating effects on shoulder joint function. The range of shoulder abduction is diminished by at least 50 degrees when scapular rotation is impaired because of a trapezius palsy.

The accessory nerve is the only motor nerve in the posterior triangle as just defined. However, if the prevertebral fascia is incised, it is possible to encounter the motor nerves of the deep cervical muscles,

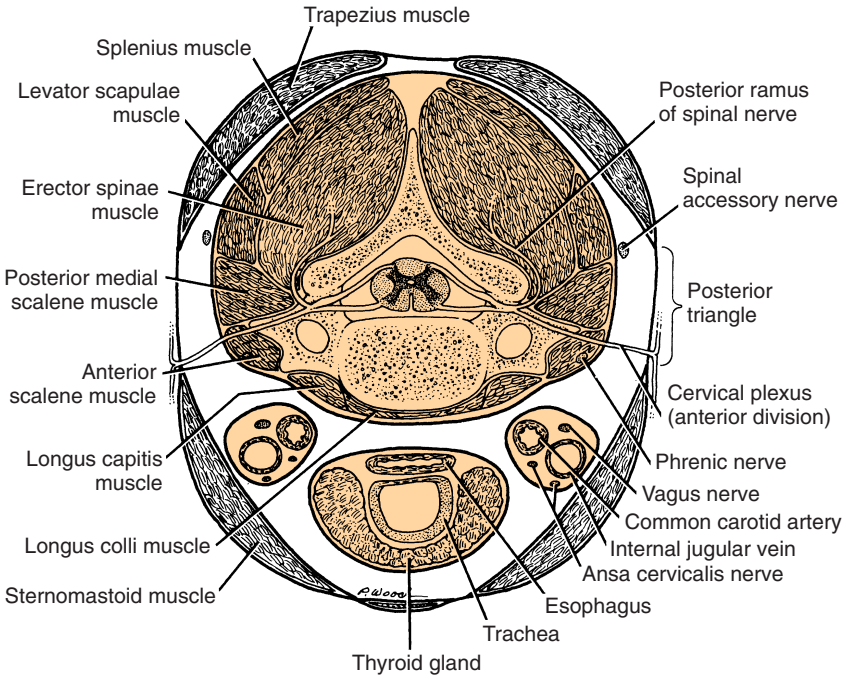

Figure 181-3. Structures contained by the deep cervical fascia seen in transverse section at the level of the cranial nerve.

the phrenic nerve, or the brachial plexus. With regard to its innervation of the sternocleidomastoid and trapezius muscles, cranial nerve XI is in fact a spinal nerve. Cell bodies of motor neurons innervating these muscles lie near the ventral horn in the upper cervical spinal cord, in the region of segments C2 through C4. The axonal fibers exit the anterior lateral portion of the cord as a series of fine filaments before becoming bundled as a nerve fiber within the subarachnoid space of the vertebral canal. The nerve ascends in the subarachnoid space, enters the posterior fossa through the foramen magnum, and joins with the cranial root of the accessory nerve before exiting the skull through the jugular foramen on the deep surface of the internal jugular vein. As the nerve descends the neck adjacent to the carotid sheath, motor or sensory filaments may join the nerve directly from segments C2 through C4.[2] After crossing the deep surface of the sternocleidomastoid muscle, the nerve enters the posterior triangle, as already described.

Arterial Branches

The major arteries of the posterior triangle are the suprascapular and transverse cervical arteries, located in the supraclavicular fossa near the base of the triangle. The arteries are derived from the thyrocervical trunk of the subclavian artery at the medial border of the scalenus anterior muscle. These arteries cross the muscle and the fossa transversely to course deep to the sternocleidomastoid muscle. Ascending and descending branches of the transverse cervical artery are usually described. The descending branch is of interest because it divides into a superficial branch that parallels the accessory nerve and a deep branch that parallels the nerve to the rhomboid muscle. The suprascapular artery, after crossing the fossa, is directed toward the suprascapular notch, where it supplies the posterior scapular muscle.

In addition to transverse cervical and suprascapular veins that parallel the course of the arteries, the posterior triangle contains the external jugular vein. It enters the triangle after crossing the superficial aspect of the sternocleidomastoid muscle in company with the great auricular nerve. The vein courses inferior to the base of the supraclavicular fossa, where it may anastomose with small vessels before entering the subclavian vein near the junction with the internal jugular vein.

Anterior Triangle of Neck

The anterior triangle of the neck is complementary to the posterior triangle and is bounded by the sternocleidomastoid muscle, the body of the mandible, and the midline of the neck. This space can be further subdivided into smaller triangular units, such as the submandibular triangle, and carotid and muscular triangles, which are included in this discussion (see Fig. 181-1).

Carotid Triangle

The carotid triangle is bordered by the posterior belly of the digastric muscle, the superior belly of the omohyoid muscle, and the midportion of the sternocleidomastoid muscle. The roof (lateral wall) of the carotid triangle is bounded by the superficial layer of deep fascia, whereas the floor (medial wall) is formed by the prevertebral fascia of the vertebral column and the visceral fascia covering the pharynx and larynx.

The contents of the carotid triangle are the carotid sheath structures. These include the common carotid with its internal and external branches, the last four cranial nerves (cranial nerves IX, X, XI, and XII), and the ansa cervicalis. In the carotid triangle, only a small branch of cranial nerve IX is left to supply the carotid sinus, because its main portion exits the sheath to enter the posterior third of the tongue. Cranial nerve XI, which also is in the upper portion of the carotid sheath, enters the sternocleidomastoid muscle at the apex of the carotid triangle, where the posterior belly of the digastric crosses the sternocleidomastoid muscle. The vagus nerve travels the entire length of the carotid sheath between the internal jugular vein and the carotid artery. Whereas the cranial nerves just mentioned lie in the posterior aspect of the carotid sheath, cranial nerve XII lies on the lateral and anterior aspect of the carotid sheath. At the level of the hyoid bone, cranial nerve XII courses anteroinferiorly to pass deep to the posterior belly of the digastric onto the surface of the hyoglossus muscle before entering the substance of the tongue.

The major focal point of the triangle is the bifurcation of the common carotid artery (Fig. 181-6). The internal carotid artery ascends the neck without branching. The external carotid artery provides several branches, many of which are important landmarks. The external carotid artery has anterior, posterior, and terminal branches.

Three anterior branches are common. In ascending order, they are the superior thyroid, lingual, and facial arteries. In some persons, the lingual and facial arteries form a common linguofacial trunk. Another important variation is the origin of the superior thyroid from the common carotid rather than the external carotid. The latter variation is important, because the external carotid occasionally is ligated (for

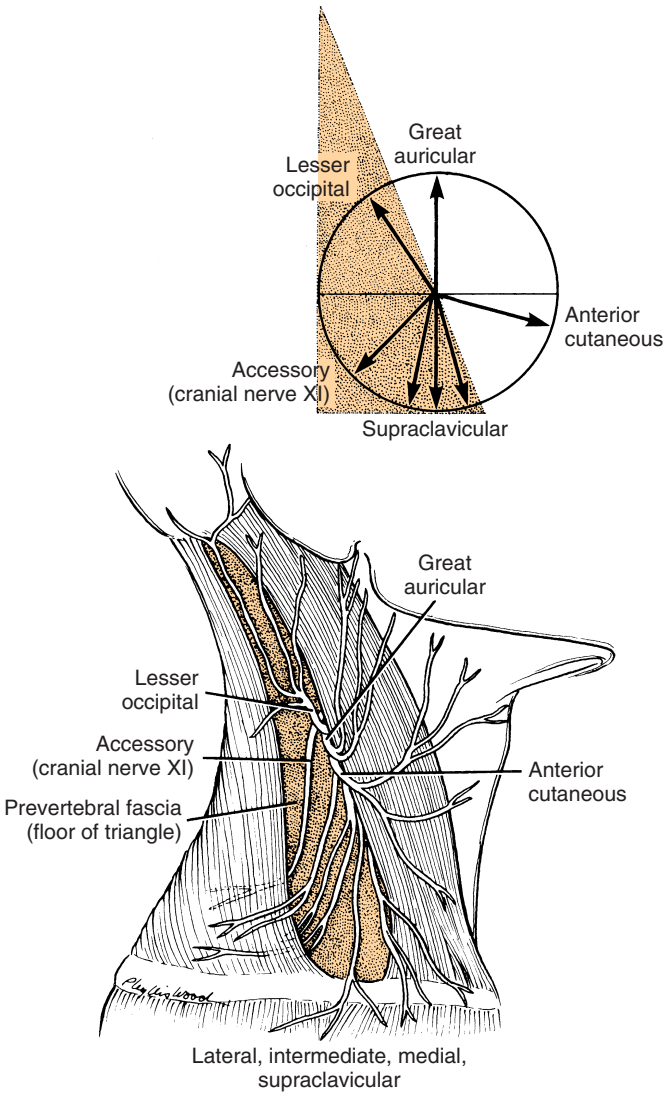

Figure 181-4. Nerves of the posterior triangle seen on the right side of the neck.

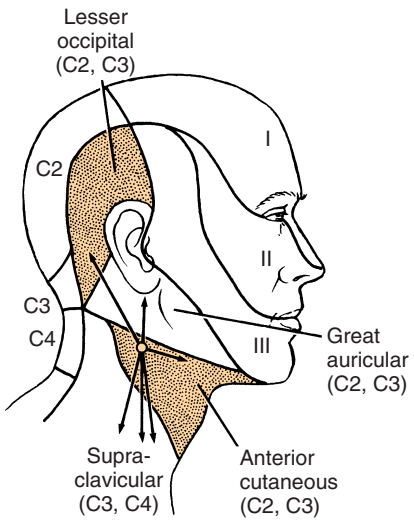

Figure 181-5. Distribution of the cutaneous branches of the cervical plexus.

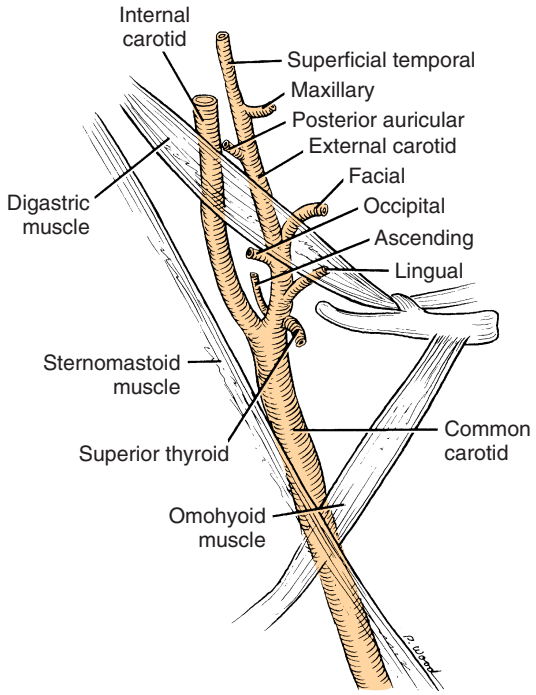

Figure 181-6. Arterial branches of the carotid triangle.

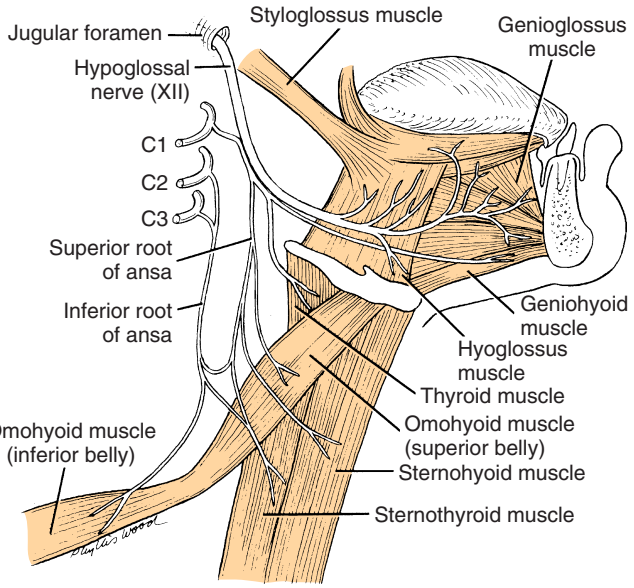

Figure 181-7. Distribution of the ansa cervicalis and the hypoglossal nerve (cranial nerve XII).

chronic epistaxis) at its origin from the common carotid. If the superior thyroid artery is used as a landmark in patients with this particular anatomic variation, it is possible to ligate the common carotid inadvertently instead of the external carotid.

The posterior branches of the external carotid are the occipital and the posterior auricular. The occipital is noteworthy for its small sternocleidomastoid branch, which supplies the sternocleidomastoid muscle. The origin of this small artery hooks cranial nerve XII as it courses anteroinferiorly and prevents it from ascending further in the neck. Thus, the sternocleidomastoid artery can be used to trace the position of cranial nerve XII. Similarly, the sternocleidomastoid artery enters its muscle near the point of cranial nerve XI, thereby also providing a means of locating the accessory nerve.

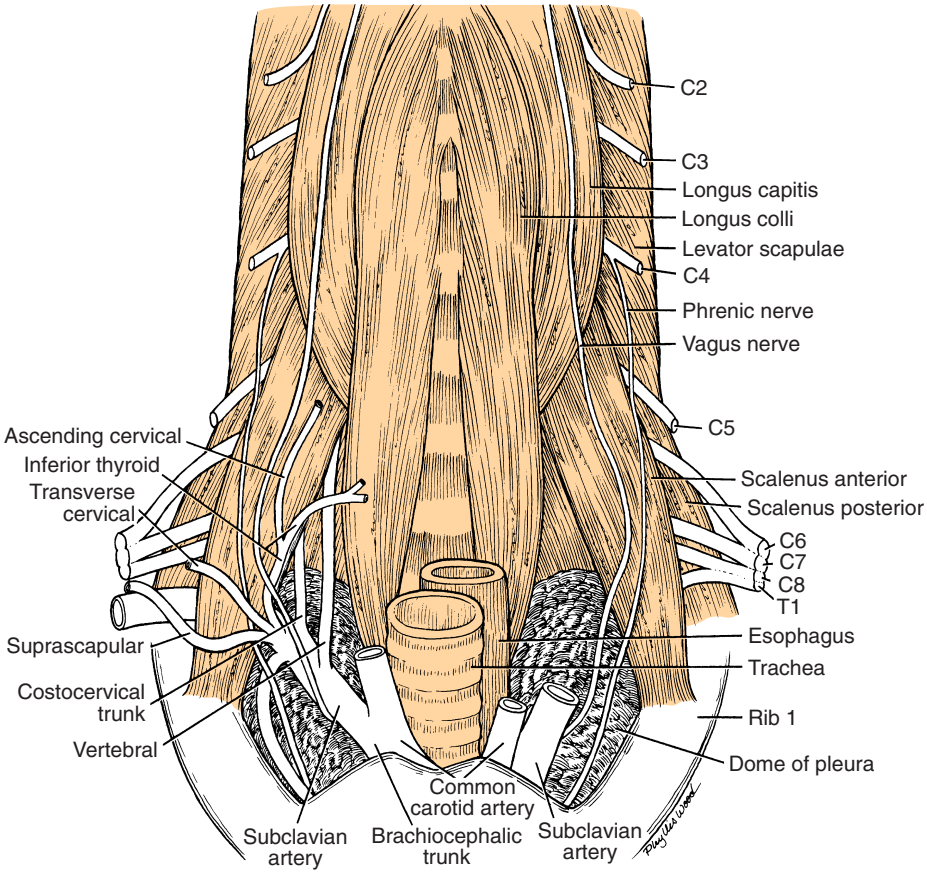

Figure 181-8. Root of the neck and subclavian artery. T1, first thoracic root; Rib 1, first rib.

Ansa Cervicalis

The ansa cervicalis is part of the cervical plexus. Its essential role is to supply the infrahyoid muscles: the sternohyoid, sternothyroid, and omohyoid muscles (Fig. 181-7). C1 fibers, which descend the neck, enter the hypoglossal nerve and travel as far as the occipital artery. At this point the hypoglossal nerve curves anteroinferiorly, but C1 fibers descend the neck to form the branch of cranial nerve XII, termed the superior root of the ansa. Fibers from C2 and C3 form an inferior root, which descends the carotid sheath on the surface of the internal jugular vein before turning anteroinferiorly to join the superior root. The ansa cervicalis is thus formed by the union of the two roots of the ansa. Three muscles are supplied directly by the ansa: the sternohyoid, sternothyroid, and omohyoid. At the origin of the superior root of the ansa, some C1 fibers do not follow the superior root but rather continue in the hypoglossal nerve transversely across the neck, before leaving cranial nerve XII to supply either the thyrohyoid muscle or the geniohyoid muscle (see Fig. 181-7). In summary, all four of the infrahyoid muscles are supplied by the ansa. In addition, one suprahyoid muscle, the geniohyoid muscle, also is supplied by the C1 fibers that have continued en route with the hypoglossal nerve. Except for proprioceptive fibers carried within the ansa, it is a motor nerve.

Thus far, two major groups of nerves of the cervical plexus have been discussed: the ansa cervicalis (principally motor) and the sensory (or cutaneous) branches of the posterior triangle. The cervical plexus comprises two other groups of fibers. One group of fibers is composed of motor filaments from cervical roots 3 and 4, supplying the levator scapulae muscle and located deep to the prevertebral fascia. The other group of fibers constitutes the phrenic nerve, derived from cervical segments C3, C4, and occasionally C5. This nerve not only is motor to the diaphragm but also supplies sensory fibers to the region of the central tendon of the diaphragm.

Root of Neck

The boundaries of the root of the neck are somewhat ill defined. The base of it is the plane of the thoracic inlet and can be traced from the manubrium laterally along the first ribs and then posterosuperiorly to the transverse process of C6 (Fig. 181-8). It contains the neck viscera and vessels. For the purposes of this discussion, it is divided unilaterally by the midline into a pyramidal space—bounded laterally by the scalenus anterior muscle, inferiorly by the first rib, and medially by the tracheoesophageal tract and midline.

The contents of the root of the neck include the great vessels emerging from the mediastinum, principally subclavian and common carotid arteries, brachiocephalic vein, vagus nerve, sympathetic trunk, and thoracic duct. As the great vessels traverse the thoracic inlet from the mediastinum, their course is divided by the scalenus anterior muscle. The subclavian vein crosses anterior to the muscle, whereas the subclavian artery courses between the cleavage plane of the scalenus anterior and scalenus medius muscles. In this region the subclavian vessels usually divide into three parts: the first part proximal to the scalenus, the second part posterior to the scalenus anterior muscle, and the third part between the lateral border of the scalenus and the lateral edge of the first rib.

A majority of the vascular branches arise from the first portion of the subclavian artery. The first branch of the subclavian artery normally is the vertebral artery, which ascends the root of the neck between the scalenus anterior and longus colli muscles to enter the foramen processus transversus of C6. The next is the thyrocervical trunk, which normally has four described branches. The first is a small ascending cervical, which supplies the prevertebral muscle region. The second branch of the thyrocervical trunk is the inferior thyroid artery coursing to the inferior pole of the thyroid gland. The inferior thyroid artery commonly supplies both the superior and inferior parathyroid glands. The third and fourth branches are the transverse cervical artery and the

suprascapular artery, already described in relation to the posterior triangle of the neck. Two branches arise from the inferior surface of the subclavian artery: the costocervical trunk and the internal thoracic artery, which descends over the suprapleural fascia into the mediastinum and anterior chest wall. Multiple variations of these vessels have been described, as detailed by Daseler and Anson.[3]

The thoracic duct ascends into the root of the neck on the left side, anterior to the thyrocervical trunk. The thoracic duct empties chyle into the venous system at the junction of the left internal jugular and subclavian veins.

Other important relationships of this region are those involving the major nerves. On the right side, the vagus nerve lies in the posterior aspect of the carotid sheath and gives off its recurrent laryngeal branch at the level of the first rib. The recurrent branch circles the lateral aspect of the subclavian artery to cross medially and enter the tracheoesophageal groove. On the left side, the recurrent nerve arises from the vagus at the aortic arch and hooks posteriorly around the ligamentum arteriosum. It enters the tracheoesophageal groove, ascending the mediastinum and neck until it enters the larynx at the level of the cricothyroid membrane.

In the most posterior part of the root of the neck, against the longus colli muscle, the sympathetic trunk ascends from the mediastinum, following the prevertebral space to the level of C2, where the superior cervical sympathetic ganglion is located. The inferior cervical ganglion lies close to the level of C7, and sometimes a middle sympathetic ganglion is described at approximately the level of C4. Injury to the cervical sympathetic chain may result in Horner's syndrome, consisting of ptosis, miosis, and anhydrosis.

This region is of particular importance during radical neck surgery, because the deep dissection usually is begun by detaching the sternocleidomastoid muscle from its attachments to the manubrium and clavicle. This exposes the carotid sheath and its contents and opens up the posterior and anterior triangles. As the dissection proceeds, the internal jugular vein is mobilized, exposing the carotid and its branches, which have been left in place. Because the en bloc mass of the internal jugular vein and sternocleidomastoid muscle is mobilized superiorly, it is important to leave the prevertebral fascia intact. With this precaution, the fascia willprovide a protective veil over the brachial plexus, phrenic nerve, sympathetic trunk, and motor nerves to the deep cervical muscles. When the prevertebral fascia is exposed, two muscles—the scalenus anterior and the longus capitis—serve as important landmarks for the spinal nerves. As the nerves emerge from the intervertebral foramina, they lie in a groove on the transverse process of the cervical vertebrae. If the vertebrae and prevertebral muscles are envisioned as being enclosed in a cylinder of prevertebral fascia, the logical conclusion is that the spinal nerves must penetrate this fascia to reach superficial structures in the neck (see Fig. 181-3). With these guidelines it is possible to identify cervical nerves C1 through C4 at the lateral border of the longus capitis, and the roots of C5 through T1 can be identified at the lateral edge of the scalenus anterior (see Fig. 181-8).

At this point in the radical neck dissection, the cutaneous nerves of the posterior triangle are encountered at their origin from the spinal nerves, and the surgeon has returned to the anatomic relationships of the posterior triangle, as discussed at the beginning of this chapter.

Lymphatic Drainage of Head and Neck

Earlier in this chapter the deep cervical fascia was described as having external, middle, and internal layers. This same rule can be applied to the lymphatic drainage of the head and neck. This plan is similar to one described by Last.[4] The external layer can be thought of as an outer circle of superficial or regional lymph nodes, the middle layer as a visceral layer of nodes draining the viscera of the neck such as the larynx and pharynx, and the internal circle of nodes composed of the paired carotid sheaths containing the internal jugular vein and deep cervical lymph nodes. The deep cervical lymph nodes are tributaries for both the superficial and visceral circles of lymph nodes.

Superficial Lymph Nodes

The superficial nodes may be thought of as a circle of nodes beginning on the face and extending posteriorly to the occipital area of the scalp. The efferent lymphatics of these nodes drain inferiorly along the major veins of the face and scalp. On the anterior face, buccal nodes in the cheek and facial nodes along the path of the facial vein drain inferiorly across the mandible, into the submandibular triangle, and to submandibular nodes. Inferior to the mandible, the superficial circle is composed of submandibular and anterior cervical lymph nodes. Sublingual nodes adjacent to the tongue receive afferent lymphatics from the anterior part of the face, particularly the lower lip and tip of tongue, and then drain superficially on the neck to deep cervical nodes approximately at the level of the omohyoid. The lymphatics from these nodes then enter the plexus of lymphatics in the carotid sheath, follow the internal jugular vein, and connect with other deep cervical nodes.

In the more posterior portion of the face (in the region of the parotid), afferent lymphatics begin in the scalp along the path of the superficial temporal vessels and drain inferiorly to parotid nodes in the superficial aspect of the parotid gland. Efferent lymphatics from parotid nodes course inferiorly along the common facial vein and thence to deep cervical nodes. Posterior to the ear, retroauricular nodes and occipital nodes follow their major channels to the deep cervical nodes of the internal jugular vein.

The general rule is that in the more anterior regions of the face, lymphatic drainage to the lower portion of the neck is more rapid, because it occurs along a sparser chain of nodes before proceeding to the deep cervical nodes. By contrast, in the deeper and more posterior portions of the face, the chain of lymphatic nodes and channels usually is more complicated, so that drainage requires more time before reaching the jugular lymph chain.

Deep Cervical Lymph Nodes

The deep cervical lymph nodes are a series of nodes that parallel the course of the internal jugular vein from the base of the skull to its terminus at the brachiocephalic junction. Most of the nodes are closely associated with the vein within the carotid sheath and lie deep to the sternocleidomastoid muscle. Two particular areas are notable. One is the region in which the posterior belly of the digastric crosses the internal jugular. This region usually is the site of one or more palpable lymph nodes termed the jugulodigastric nodes. Similarly, another large node or series of small nodes exists at the junction of the superior belly of the omohyoid and sternocleidomastoid muscles, which are termed the jugulo-omohyoid nodes. Efferent lymphatics from the deep nodes drain into the internal jugular trunks, which ultimately enter the venous system at the jugulosubclavian angle.

Lymphatic Drainage of Pharynx and Larynx

The upper portion of the pharynx, the nasopharynx, drains directly to the upper deep cervical lymph nodes along the jugular chain. The oropharynx and, particularly, the tonsil drain through the parapharyngeal spaces to the region of the midportion of the jugular and particularly the jugulodigastric nodes. In some descriptions, the jugulodigastric nodes are referred to collectively as the tonsillar node. The region of the hypopharynx and larynx drains principally along the vascular pedicles of the hypopharynx and larynx. The upper portion of the larynx from the false cord drains along the superior laryngeal vessels to deep cervical nodes on the internal jugular vein near the bifurcation of the common carotid artery. The lower half of the larynx (from the true cords proceeding inferiorly) drains along the interior laryngeal vessels to nodes about the pretracheal region and eventually to deep nodes near the base of the internal jugular vein.

Classification of Cervical Lymphatics

Nomenclature of the cervical lymphatics historically has been inconsistent. As the focus of oncologic surgery has shifted from radical extirpation to functional preservation, it has become more important to standardize the classification system for the cervical nodes. The American Academy of Otolaryngology–Head and Neck Surgery, along with the American Society of Head and Neck Surgery, has developed a standardized classification system for the cervical lymphatic system and for neck dissections.

The groups of lymph nodes are designated as levels I to VI. *Level I* includes nodes in the submental and submandibular triangles. *Level*

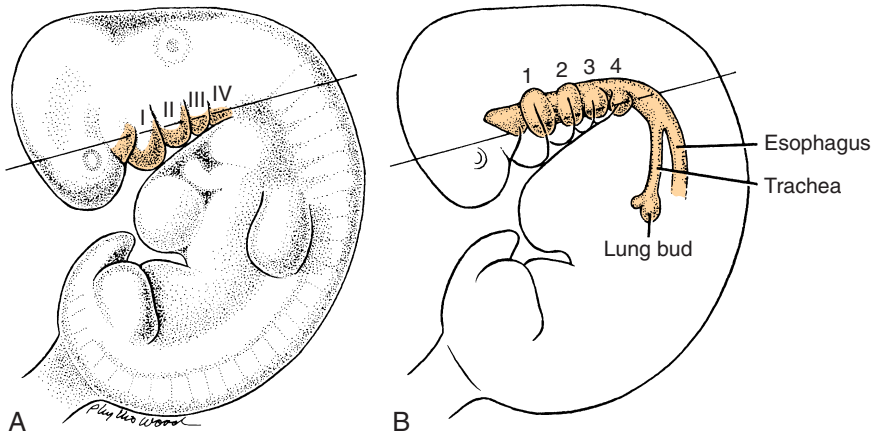

Figure 181-9. **A,** Branchial arches. **B,** Pharyngeal pouches.

II includes the upper jugular nodes located around the superior one third of the jugular vein and spinal accessory nerve extending from the carotid bifurcation or hyoid, inferiorly, to the skull base, superiorly. The anterior and posterior boundaries of this nodal group are the lateral border of the sternohyoid and the posterior border of the sternocleidomastoid muscle, respectively. *Level III* includes the middle jugular nodes around the middle third of the jugular vein, extending from the carotid bifurcation, superiorly, to the omohyoid (or cricothyroid notch, inferiorly). The anterior and posterior boundaries are the same as for level II. *Level IV* includes the lower jugular group surrounding the jugular vein from the omohyoid to the clavicle. The anterior and posterior borders are the same as in levels II and III. *Level V* is the posterior triangle group, consisting of the nodes surrounding the lower half of the spinal accessory nerve and the transverse cervical artery, including the supraclavicular nodes. The anterior boundary of level V is the posterior border of the sternocleidomastoid muscle and the posterior boundary is the anterior border of the trapezius muscle. *Level VI* includes the anterior compartment group surrounding the visceral structures of the neck from the hyoid, superiorly, to the sternal notch, inferiorly. The lateral boundary on either side of level VI is the medial aspect of the carotid sheath. This space crosses the midline and includes the perithyroidal, paratracheal, and precricoid nodes, as well as the nodes along the recurrent laryngeal nerve.[5] The terminology for neck dissection is discussed in Chapter 116.

Embryology of Head and Neck

The development of many structures in the head and neck is intimately related to either the branchial arches or the pharyngeal pouches (Fig. 181-9). These are transient embryonic structures that undergo substantial remodeling so that their original embryonic form is essentially unrecognizable by the time the infant is born. The derivatives of these structures nevertheless are important to adult morphology: Aberrations in branchial arch development may produce significant malformations.

Embryology of Branchial Arches

At 5 weeks of gestation, the area of the future face and neck of the embryo consists of five or six pairs of fingerlike masses of tissue named the *branchial arches*. Prominent in lateral profile (see Fig. 181-9), these masses are aligned in transverse orientation to the plane of the neck and are separated by clefts, termed the *branchial clefts*. The surface of the arches and clefts is lined by ectoderm, with mesodermally defined tissues contained within the branchial arches. The tissues underlying the region of the clefts are thin because of the close approximation of outpouchings from the foregut region called *pharyngeal pouches* (see Fig. 181-9). The derivatives of the arches and pouches are different because of the embryonic germ layers contained within the branchial arch (the mesoderm), whereas the pharyngeal pouches are composed of endoderm. Because of the differences in the embryonic germ layers, the following generalization can be made: In the adult, the derivatives of the branchial arch will be structures composed of muscle, bone, or similar mesodermal derivatives; the derivatives of the endodermal pharyngeal pouch will be glandular or associated with the digestive tract.

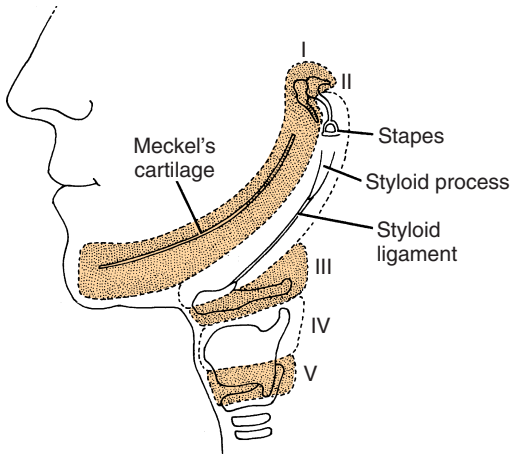

Figure 181-10. Skeletal derivatives of the branchial arches.

Derivatives of Branchial Arches

In the early phase of branchial arch development, the mesodermal mass of the arch forms a bar of cartilage, which remodels into bone, cartilage, or other connective tissue elements in the adult. Similarly, the adult musculature of the face and neck also develops from the mesoderm of the arches. The development of these structures is considered separately.

Skeletal Derivatives

The first branchial arch is the proximal part of the first arch cartilage (Meckel's cartilage), which is remodeled and contributes to the formation of the ramus of the mandible (Fig. 181-10). The distal part of the cartilage withers, and the body of the mandible is formed from intramembranous bone. Other structures formed by the proximal part of the cartilage are the sphenomandibular ligament, anterior malleolar ligament, malleus (except for the manubrium, which is from the second arch), and incus (except for its long process, which is from the second arch).

The second branchial arch is the cartilage of the second branchial arch (Reichert's cartilage), which forms bony structures proximally and distally. Its central portion withers, leaving a fibrous band—the stylohyoid ligament. Proximally, it forms the styloid process, the manubrium of the malleus, the long process of the incus, and the stapes suprastructure. The stapes footplate is mostly derived from the otic capsule.[6,7] Distally (anteroinferiorly), the second arch cartilage forms a portion of the body of the hyoid and the lesser cornu of the hyoid bone.

In the adult, it is possible to trace the path of the embryonic second arch cartilage from the styloid process, to the stylohyoid ligament, ending at the lesser cornu of the hyoid bone (see Fig. 181-10).

The third branchial arch composes the remaining portions of the hyoid bone (i.e., the body and greater cornu).

The fourth through sixth branchial arches comprise the cartilaginous elements. These arches contribute to the formation of the thyroid, cricoid, arytenoid, corniculate, and cuneiform laryngeal cartilages.

Muscular Derivatives

In the first branchial arch, the muscles formed by mesodermal elements include the muscles of mastication: the temporalis, masseter, and medial and lateral pterygoid muscles. In addition, the tensor tympani, tensor veli palatini, anterior belly of the digastric, and mylohyoid muscles also are derived from first arch mesoderm.

In the second branchial arch, the muscles formed from mesoderm include all of the muscles of facial expression from the region of the scalp, inferiorly, to the platysma muscle in the neck. In addition to those muscles, grouped as the muscles of facial expression, the posterior belly of the digastric, the stylohyoid, and the stapedius muscles also are derived from second arch mesoderm.

In the third branchial arch, only one muscle is formed from mesoderm—the stylopharyngeus muscle, a small muscle that aids in elevating the pharynx during swallowing.

In the fourth through sixth branchial arches, the muscles include the muscles that form the pharynx and larynx. Pharyngeal muscles include the superior, middle, and inferior constrictor muscles. In addition, the mesodermal elements from these branchial arches also form the striated muscle composing the upper half of the esophagus. The inferior part of the esophagus usually is composed of smooth muscle derived from the splanchnic mesoderm of the primitive foregut.

The laryngeal muscles are also formed from mesodermal elements in the fourth, fifth, and sixth arches. These include the extrinsic muscle of the larynx and the cricothyroid, as well as all of the intrinsic muscles associated with movement of the arytenoid cartilage and true and false vocal folds.

Innervation

Because of the proximity of the developing branchial arches to the brainstem, each branchial arch receives motor or sensory innervation from an adjacent cranial nerve. A comparable parallel to this pattern occurs in the trunk, where a muscle is derived from the myotome region of a somite and receives its innervation from the adjacent segmental spinal nerve. In both cases, regardless of where the primordial muscle cell migrates, it retains its primary embryonic innervation. After each arch receives its cranial nerve innervation, then the adult pattern is established, regardless of its future migration onto the back of the head or base of the neck.

The nerve of the first branchial arch is the trigeminal nerve, which supplies motor innervation to all of the muscles derived from the first arch. In addition, sensory innervation is provided not only over the region of the mandible by the third division of the trigeminal but also over the maxillary process of the first arch and the frontal nasal process by the second and first divisions of the trigeminal nerve.

The nerve of the second branchial arch is the facial nerve, which supplies motor innervation to all of the muscles derived from this mesoderm. Other than a small sensory branch of cranial nerve VII, which may supply part of the external auditory meatus, sensory distribution of cranial nerve VII to ectoderm is absent.

Cranial nerve IX supplies the single muscle derived from the third arch—the stylopharyngeus muscle. As described later on, however, it also supplies sensory innervation to parts of the pharynx associated with this region.

The vagus nerve and the cranial part of the accessory nerve supply the muscles derived from branchial arches 3 through 6. Originating in the nucleus ambiguus of the medulla, the axonal processes of these nerves descend in the vagus nerve after exiting the skull through the jugular foramen. Specifically, the pharyngeal constrictors are supplied by the pharyngeal branch of the vagus and the transitional portion of the pharynx and esophagus by its recurrent laryngeal branch. The superior laryngeal nerve supplies sensation to the larynx by its internal branch and motor innervation to the cricothyroid muscle by the external branch. The recurrent laryngeal nerve supplies the intrinsic muscles of the larynx.

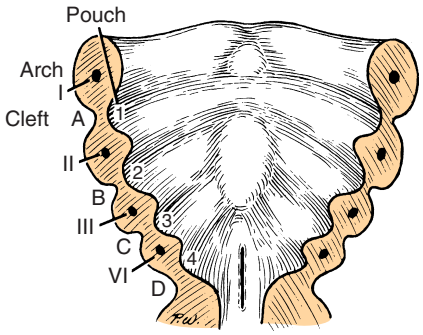

Figure 181-11. Relationships of the pharyngeal arches, clefts, and pouches in the floor of the mouth: stage I.

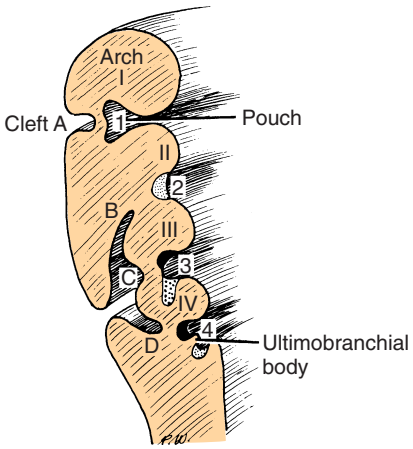

Figure 181-12. Derivatives of the pharyngeal pouches and formation of the cervical sinus: stage II.

Embryology of the Pharyngeal Pouches

The pharyngeal pouches are lateral outpouchings of the foregut or region of the primitive pharynx (see Fig. 181-9). At the extreme lateral wall of each pharyngeal pouch, the endodermal lining contacts the ectodermal epithelium of a branchial cleft (Fig. 181-11). Thus, the branchial clefts are named in relation to the pharyngeal pouch with which they are apposed. The endodermal epithelium lining of either the branchial arch or the pharyngeal pouch contributes to the formation of specific elements of the pharynx in the adult.[8]

First Pharyngeal Pouch

The first pharyngeal pouch becomes elongated and incorporated into the temporal bone and forms the epithelial lining of the middle ear (Fig. 181-12). The most lateral portion of the pouch, along with the first closing plate of the first branchial cleft, forms the tympanic membrane (see Fig. 181-12). From this relationship, it is clear that the external auditory canal is nothing more than a remodeling of the first branchial cleft (Fig. 181-13).

Second Pharyngeal Pouch

The endodermal layer of the second pharyngeal pouch forms the epithelial lining of the palatine tonsil, whereas underlying mesenchymal elements contribute to the formation of the tonsil itself (see Figs. 181-12 and 181-13).

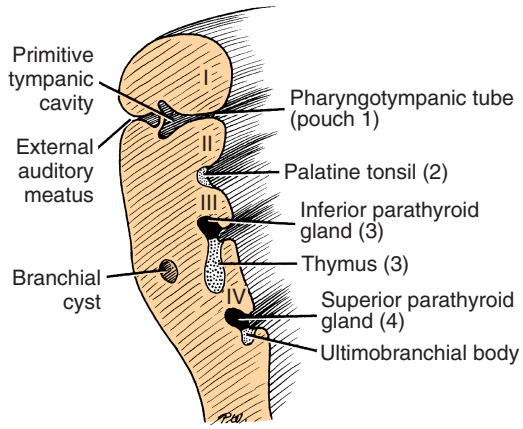

Figure 181-13. Maturation of the pharyngeal pouches: stage III.

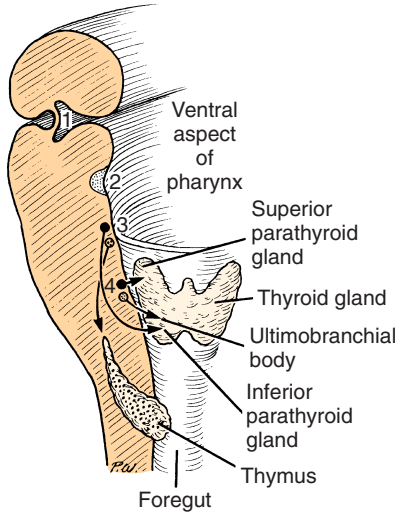

Figure 181-14. Migration of the pharyngeal derivatives into the neck: stage IV.

Third Pharyngeal Pouch

The region of the third pharyngeal pouch is subdivided into superior and inferior portions. The superior portion forms cells that eventually differentiate into the inferior parathyroid (see Fig. 181-12). The inferior portion of the third pouch becomes thymic tissue, which eventually migrates in the neck and mediastinum to form the thymus (Fig. 181-14).

Fourth through Sixth Pharyngeal Pouches

The endoderm of the fourth pouch forms the superior parathyroid gland. The adjacent area is variably named as the fifth or sixth pouch or the ultimobranchial body (see Fig. 181-13). Subsequently, the ultimobranchial body is infiltrated by cells migrating from the neural crest region. These cells eventually are incorporated into the thyroid gland and become the parafollicular cells (C cells) responsible for the secretion of calcitonin.[9,10]

Craniofacial Syndromes Related to Branchial Arch Structures

Hemifacial microsomia is thought to be related to a vascular injury in the region of the stapedial artery, resulting in microtia and mandibular hypoplasia.[11] Patients with this defect often have associated aural atresia. Mandibulofacial dysostosis, or Treacher Collins syndrome, is related to abnormalities of the first and second branchial arches. This syndrome is characterized by lid colobomata, down-slanting palpebral fissures, hypoplastic zygoma and mandible, and malformations of the external ear.[12] Other syndromes related to dysmorphogenesis of the first and second branchial arches include oculoauricular vertebral dysplasia (i.e., Goldenhar's syndrome) and branchio-oto-renal syndrome.

Branchial Cleft Remnants

The first branchial cleft becomes part of the external auditory canal, but the remaining branchial clefts are remodeled and normally do not form derivatives identifiable in the adult. However, the complicated morphodynamics of the branchial arch region seem to predispose this area to abnormalities, ranging from minor cysts to major orofacial malformations. The clinical terminology of the various branchial abnormalities is confusing. Part of the confusion results from the clinical spectrum of these anomalies—they may manifest as cysts, sinuses, or fistulae. A *cyst* has no communication with the body surface; a *sinus* communicates with a single body surface, either the skin or pharynx; and a *fistula* communicates with two body surfaces. A cystic dilation of the tract may be associated with either a sinus or a fistula. The terms *branchial cleft* and *branchial pouch* often are used interchangeably, although they refer to distinct structures. Occasionally, *groove* is used instead of *pouch* or *cleft*.

Abnormalities of First Branchial Cleft

Aberrant development of the first branchial cleft may lead to the formation of a cervical cyst or sinus in the region of the ear. Work[13] and Aronsohn and colleagues[14] emphasized the difference in the embryogenesis of preauricular cysts versus cysts of the first branchial cleft. Preauricular cysts or pits occur anterior to the external auditory canal, usually superior to the region of the tragus. In essence, they are inclusion cysts related to fusion of the ectodermal hillocks from the first and second branchial arches during formation of the auricle.[15]

By contrast, true first branchial cleft abnormalities are duplications of the membranous part of the external auditory canal, and they manifest clinically as cysts, sinuses, or fistulas. Work[13] has classified these into two types: type I, of ectodermal origin, involving only the membranous part of the canal; and type II, involving both ectoderm and mesoderm, in which duplication of cartilage also is a feature. As cystic masses or sinus tracts they may involve the parotid gland and cranial nerve VII (this particularly true of type II) or lie inferior to the ear, in the superior neck.

Abnormalities of Second through Fourth Branchial Clefts and Pouches

During closure of the cervical sinus lying between the second branchial arch and the epipericardial ridge, ectoderm may become trapped, resulting in an inclusion cyst at a later time (see Figs. 181-12 and 181-13). These are the more familiar branchial cleft cysts or sinuses, which lie on the lateral neck anterior to the sternocleidomastoid muscle. As such, they may overlie the carotid or muscular triangles of the neck. The fistulous forms of these abnormalities are surgically challenging because they may extend from the superficial area of the neck near the clavicle, superiorly, to the bed of the palatine tonsil. The course of the tract through the deep part of the neck usually lies between the internal and external carotid arteries. The pathway of this tract is easily explained on an embryologic basis. The medial wall of the cervical sinus is the region of closing plates 2 to 4 (see Fig. 181-12). A fistulous pathway breaking through into the pharynx will penetrate one of these closing plates and thereby enter either into the tonsillar bed (the second), the thyrohyoid membrane (third), or pyriform sinus or cricothyroid membrane (fourth).

Third branchial cleft sinuses, which communicate with the pharynx, travel deep to the carotid artery system in their superior extent. Thymopharyngeal cysts represent third branchial cleft remnants. As congenital cystic lesions of the neck, these are easily confused with lymphatic malformations. Remnants of the fourth branchial pouch, or pyriform sinus fistulas, may manifest as recurrent suppurative thyroiditis and usually are located on the left side.[16,17] These lesions may be associated with parathyroid, thymic, or thyroid tissue.

Isolated branchial arch remnants may manifest as subcutaneous cartilaginous tags along the anterior border of the sternocleidomastoid muscle.

Midline Lesions of the Neck

Thyroglossal duct cysts and dermoids are the most common midline lesions of the neck in children. These often are difficult to recognize clinically. The thyroglossal duct cyst derives from persistence of the embryonic thyroglossal duct, anywhere between the foramen cecum and the thyroid gland. Because of the attachments to the base of tongue, thyroglossal duct remnants will move superiorly in the neck when the patient protrudes the tongue. The thyroglossal duct remnant may contain ectopic thyroid tissue. Occasionally the cyst contains all of the functioning thyroid tissue. Because of the potential for permanent hypothyroidism after surgical excision, many investigators advocate routine preoperative assessment of the thyroid.[18,19] Ultrasound examination of the neck provides information regarding consistency of the cystic lesion and also can be used to assess for the presence of thyroid tissue in its normal position lower in the neck. Ultrasound examination is easily tolerated by children but does not give functional information. Radionuclide thyroid scans provide functional information regarding thyroid tissue (e.g., the possibility of malignancy within these lesions). Surgical excision is the treatment of choice. Thyroglossal duct remnants often involve the central part of the hyoid, necessitating removal of the midportion of the hyoid to minimize the risk of recurrence.[20]

Another midline developmental abnormality of the neck is the midline cleft. The clinical presentation varies, ranging from an area of subcutaneous absence of midline tissue, manifesting as a bluish area in the midline of the neck, to a midline vertical band. The vertical band becomes more restrictive with growth of the child and may interfere with mandibular excursion. Treatment involves excision of the band and Z-plasty.

Summary

The otolaryngologist–head and neck surgeon must be familiar with the developmental anatomy of the neck. A working knowledge of neck anatomy and embryology is critical in diagnosing and treating patients effectively.

SUGGESTED READINGS

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CHAPTER ONE HUNDRED AND EIGHTY-TWO

Anesthesia in Pediatric Otolaryngology

Veronica C. Swanson

Heike Gries

Jeffrey Koh

Key Points

- When anesthetic risk is correlated with age, children younger than 1 month of age are at the highest risk for adverse events during the procedure. The greatest improvements in patient safety have been in reducing the frequency of respiratory events. Elective procedures should be deferred until after the age of 6 months, when appropriate.
- The anesthetic plan is tailored to the patient's age—for physiologic differences as well as differences in psychological development.
- Preoperative preparation that includes patient education leads to greater satisfaction with the overall hospital experience for both child and parent.
- Routes of premedication and induction of anesthesia include oral, intranasal, intramuscular, intravenous, and inhalational.
- Decisions regarding deep versus awake extubation require careful consideration of clinical factors: Awake extubation is always the appropriate choice in patients who have difficult airway anatomy or full stomach physiology.
- Postoperative nausea and vomiting are best treated with multimodal therapy; a second dose of antiemetic agent in the same class of drug already given is rarely effective.
- Effective pain assessment and management are mandated by The Joint Commission for institutions to receive accreditation.
- Multimodal therapy for pain relief, with or without opioids, is now accepted as a more balanced approach to pain management in surgical patients. Such therapy aims to decrease the dose of any single agent, thereby improving antinociception and reducing side effects.
- Anesthetizing patients in locations outside the operating room minimizes interference with surgical needs and contributes to efficient delivery of care.
- Medical conditions with particular impact on aesthetic implications include upper respiratory infections, asthma, cystic fibrosis, diabetes mellitus, and congenital heart disease.
- The 2007 American Heart Association guidelines for the prevention of infective endocarditis in patients with congenital heart disease seek to minimize unnecessary exposure to antibiotics using evidence-based practices.
- Management of patients for bronchoscopy, adenotonsillectomy, and laryngeal surgery requires careful planning preoperatively and clear communication between surgeon and anesthesiologist throughout the procedure.

Because of the inherent complexity of the structure-function relationship in otolaryngology, pediatric otolaryngologists and anesthesiologists must work together closely in the operating room to provide optimal care to the patient. This chapter focuses on anesthesia topics that are relevant for the pediatric otolaryngologist, beginning with the safety of anesthesia for children, followed by preoperative assessment of pediatric patients. Perioperative management, including choice of drug and technique to match the situational demands, is described next. Finally, the anesthetic implications of specific diseases and the anesthetic considerations in commonly performed pediatric otolaryngology procedures are reviewed.

Anesthesia for Children

Anesthesia carries increased risk in children as compared with adults, as reported more than 50 years ago.[1] Work from the 1960s correlated this increased risk with age less than 1 year.[2] Nowadays children younger than 1 month of age are recognized as being at the highest risk,[3] which suggests that the risk of adverse events with anesthesia induction in infants is inversely proportional to age. In view of the physiologic changes that occur during the first year of life, this is not surprising. Respiratory control is immature in infants; carbon dioxide (CO_2) response curve is lower than it is in older children and adults, and hypoxia may induce apnea rather than hyperventilation.

Box 182-1

Intraoperative Monitoring Standards

Continuous presence of qualified anesthesia personnel in the operating room

Continuous evaluation of the following:

- Oxygenation
- Inspired oxygen concentration with an oxygen analyzer
- Blood oxygenation with a pulse oximeter
- Ventilation

Qualitative assessment, including chest excursion, observation of the reservoir bag, and auscultation of breath sounds

Quantitative assessment with end-tidal CO_2 analysis

A low-pressure disconnect alarm when mechanical ventilation is used

Circulation

Continuous electrocardiogram

Arterial blood pressure at least every 5 minutes

At least one of the following:

- Palpation of pulse
- Auscultation of heart sounds
- Intra-arterial blood pressure monitoring
- Ultrasound peripheral pulse monitoring
- Pulse plethysmography

Body temperature

Cardiovascular responses also are immature: The myocardium is poorly compliant, so cardiac output is rate dependent. Similarly, responses to anesthetic agents differ in accordance with patient age. Preterm and full-term newborns require lower concentrations of inhaled anesthetics than those needed in older children or adults. Inhalational agents may cause more depression of cardiac output in infants and may have a more profound effect on baroreflexes. Pharmacokinetic parameters of volume of distribution, hepatic clearance, and renal clearance differ profoundly from those in older children, affecting the dose of nearly every drug.

These differences in physiology and pharmacology are reflected in the types of anesthetic mishaps that tend to occur in newborns and infants. Inadequate ventilation and anesthetic overdose have been the most frequent sources of anesthetic morbidity and mortality in the 1980s.[4] Changes in anesthetic practice, such as improvement in monitoring (e.g., pulse oximeters and CO_2 monitors) and use of different drugs (e.g., sevoflurane instead of halothane) have decreased respiratory events and shifted the number of anesthesia-related cardiac arrests in infants toward cardiovascular causes of cardiac arrest.[5,6]

Adherence to the American Society of Anesthesiologists (ASA) monitoring standards[7] is basic to all anesthesia care performed by an anesthetist and has reduced the incidence of intraoperative complications.[8] The components of these standards are presented in Box 182-1. Most anesthesiologists consider pulse oximetry to be an indispensable part of the intraoperative monitoring armamentarium, although it has been difficult to document improvement in outcome as a result of this technique, even in a very large series.[9,10] The use of pulse oximetry alone or in combination with capnography has reduced the relative frequency of adverse respiratory events as compared with adverse cardiovascular events, perhaps because pulse oximetry and capnography are more effective for preventing respiratory events than cardiovascular events.[11]

Elective procedures should be deferred until the infant is at least 6 months to 1 year old, when anesthetic risk is likely to be lower. This is particularly true in infants who were born prematurely, because they have an increased risk of postoperative apnea until approximately 55 weeks of postconceptual age (see following). The use of trained subspecialty pediatric anesthesiologists for the care of infants and children has been suggested to be associated with improved outcomes,[12] although this contentious claim is difficult to prove.[13] More recent concern has been raised about the potential for neuronal damage in the developing brain caused by anesthetic agents. The available data are still preliminary, and no definitive human studies proving this concept have been performed. The United States Food and Drug Administration (FDA) recently launched the first phase of SAFEKIDS (Safety of Key Inhaled and Intravenous Drugs in Pediatrics), an initiative to provide seed funding for several clinical projects.[13a] Pediatric practitioners should be aware that more information probably will be presented in the coming years and may influence decisions about what age is safe to perform elective procedures.[14]

Current estimates of anesthetic mortality vary widely, depending on the definition of anesthetic death. However, mortality in healthy pediatric outpatients as the result of an anesthetic-related cause is very rare, with rates perhaps as low as 0.36 in 10,000 cases.[6,15] Accordingly, parents of otherwise healthy children can be reassured that outcomes in modern-day pediatric anesthesia are excellent.

Preoperative Assessment

Today's emphasis on cost containment has forced many changes in the practice of pediatric anesthesia. More and more patients with complex medical problems are having procedures as outpatients, which forces the preoperative contact between the anesthesiologist and the patients and family into a very few minutes. In addition, efficiency pressures have forced institutions to search for ways to maximize patient flow in surgery areas and to minimize unexpected delays or cancellations. Preoperative anesthesia clinics have developed in response to these changes.

A visit to the preanesthesia clinic before the day of surgery affords the opportunity for taking an anesthetic history; performing a physical examination; obtaining necessary laboratory tests; and informing the family about the anticipated procedures, including times for restriction of oral intake to nothing by mouth (i.e., NPO [*nil per os*]) status), premedication, anesthetic induction and maintenance, and postoperative pain management techniques. It also allows confirmation that all necessary paperwork, such as consent and surgical history and physical, is present in the medical record. An attending anesthesiologist is available for consultation for more complicated cases or to address specific clinical questions. Anesthetic risk can be discussed with patients and their families, with ample time allowed for them to ask questions. In addition, the clinic nurse can take this opportunity to educate the patient and family about the impending surgical visit and to identify fears and concerns of the parents and child.

A preoperative medical assessment includes a review of body systems and the patient's response to previous anesthetics, current medications, allergies, recent illnesses (including upper respiratory infections), and family history of problems with anesthesia. The physical examination concentrates on airway anatomy, including the mouth, jaw, teeth, and neck, and includes chest and heart auscultation to confirm the absence of significant cardiorespiratory disease. Laboratory tests are obtained as indicated by the child's condition and type of surgery planned, rather than as a routine component of the assessment.[16] Identification of clinical problems at a preanesthesia visit also allows appropriate evaluation or referral before surgery, thereby avoiding delay or cancellation on the day of surgery.

Preparation for Anesthesia

Behavioral Preparation

The days and hours leading up to surgery can be an anxious time for both children and parents. Fears about hospitalization are common among children, including fear of separation, pain, loss of control, and even death. Many of these fears are dependent on the child's age[17] (Table 182-1). Awareness of these developmental stages allows the anesthesiologist to better anticipate the needs of most children. In addition, understanding the impact of parental anxiety on a child's anxiety can help in the selection of interventions that will be helpful to both the child and the parents.

Details of the anesthetic and surgical experience should be presented in age-specific language for children of appropriate age.[18] Children who are given specific information before surgery have been shown to be less anxious than children who are given only general information.[19] Movies or videotapes can help children and parents cope with

Table 182-1

Age-Specific Concerns of Children

Age	Specific Concerns
Infant (6-18 months)	Separation anxiety
Toddler (1-2 years)	Fear of strangers, loss of mastery of the environment
Preschool (2-5 years)	Separation anxiety; difficulty distinguishing reality from fantasy; fear of pain, mutilation
School age (6-12 years)	Fear of the unknown, pain, mutilation, loss of control, autonomy
Adolescent (13-18 years)	Precarious sense of self; fear of pain, mutilation, loss of control, autonomy

From Orr RJ, Lynn AM. *Curr Rev Clin Anesth*. 1991;12:29.

the mysteries of hospital routines.[20] Comprehensive preoperative preparation programs have been shown to be helpful for reducing preoperative anxiety and enhancing coping behavior in children.[21] This may be especially important for children who will require repeated procedures, allowing them to learn coping strategies and to develop a better understanding of the environment in which they will receive their care. Parents also should be involved in these programs, because decreasing their anxiety is likely to provide the added benefit of decreasing the child's anxiety further.[22] These efforts are important even if pharmacologic agents will be used to decrease anxiety, because the combination of psychological and pharmacologic interventions can produce synergistic effects.[23]

Premedication

The choice of premedication is based on the age and specific needs of the patient. The usual goals of premedication are to reduce anxiety and to ease separation from parents. Because most children fear needles, the oral administration of sedatives has become the standard of care at many institutions. Children who are younger than 8 months of age generally do not need premedication and separate easily from their parents. Children between 8 months and 8 years of age often experience enough preoperative anxiety that preoperative medication may be helpful. Midazolam (0.5 to 1.0 mg/kg up to a maximum of 20 mg), mixed in flavored syrup and administered orally 10 to 20 minutes beforehand, usually smoothes the separation from the parents and induction of anesthesia, and has become the most popular agent for preoperative sedation for children.[24] Midazolam usually is well tolerated, although a rare decrease in oxygen saturation or blood pressure may be observed. In addition, intravenous flumazenil (10 µg/kg, administered over 1 minute, repeated as needed for a total of 5 doses; maximum 0.2 mg/dose, and 1 mg total dose) can be administered to reverse adverse effects such as oversedation, paradoxical effect, or emergence delirium.

Older children may be willing to have an intravenous line started preoperatively, especially if a topical anesthetic cream such as EMLA (eutectic mixture of local anesthetics) or ELA-Max (Ferndale Laboratories, Ferndale, Michigan) is used. EMLA cream is a mixture of lidocaine and prilocaine that penetrates intact skin and, when applied for 60 minutes or more, significantly decreases the pain associated with an intravenous insertion.[25,26] EMLA should be used with caution in children younger than 3 months of age or in children who are receiving other medications that may induce methemoglobin because of the risk of methemoglobinemia.[27] Plasma concentrations of lidocaine and prilocaine achieved with topical application are well below the toxic level,[27] but they may be higher in children with traumatized or inflamed skin. Another effect of EMLA that may be problematic is vasoconstrictive blanching, which makes the identification of potential intravenous insertion sites difficult for some practitioners. ELA-Max is an alternative to EMLA, and it contains only lidocaine in a liposomal matrix that allows for effective absorption across intact skin.[28] ELA-Max has been shown to provide equal topical anesthesia to EMLA, and it has a quicker onset of 30 minutes.[8,29] ELA-Max also produces less blanching than that seen with EMLA. If an intravenous line is placed, midazolam or another sedative can be titrated intravenously until the desired effect is achieved. Although the topical anesthetic creams are the most frequently used, alternative methods for providing topical anesthesia may be standard in some institutions.

Younger children may not accept oral premedication well, making this method of administration as anxiety-provoking as separating the child from his or her parents without any premedication. Alternative methods do exist. Intranasal administration of midazolam (0.2 to 0.3 mg/kg) using either an atomizer or simply a needle-less tuberculin syringe is easy in a patient small enough to be held or restrained.[30] This agent begins acting immediately after dosing and reaches peak concentrations by 14 minutes, having the advantage of increased bioavailability with minimal first-pass metabolism in the liver.[31] Intramuscular administration of premedication becomes necessary in larger children with behavioral issues that limit patient cooperation—autism, for instance. Because intramuscular injection is technically easier than intravenous line placement, this technique can be achieved quickly, and the child then be allowed some time with the parent, to minimize the trauma from the encounter. Intramuscular ketamine at a dose of 2 to 5 mg/kg or a combination of intramuscular ketamine and midazolam causes sedation and dissociation from the environment, making the patient more approachable for procedures, anesthesia induction, and so on. Larger doses of ketamine administered intramuscularly (up to 10 mg/kg) can induce general anesthesia (see following discussion). Anticholinergic agents may be desirable when copious airway secretions (commonly seen with ketamine) are a concern, or when vagal tone from airway manipulation produces decreases in heart rate and cardiac output. Halothane, an inhalation agent used only in a few countries outside of the United States, is more likely to cause bradycardia and a significant reduction in cardiac output in children younger than 6 months of age, than in in older children. The routine use of anticholinergic agents with halothane in these younger patients can prevent these changes.[32] Atropine (0.02 mg/kg) or glycopyrrolate (0.01 mg/kg) given intravenously at the time of induction can obviate the pain of an intramuscular injection.

Nothing-by-Mouth Orders

To minimize the risk of the aspiration of gastric contents during the induction of anesthesia, an adequate period of fasting must be maintained. Traditionally, both food and fluids have been withheld after the midnight before surgery. However, a prolonged period of fasting is uncomfortable for children, is unpleasant for the family, and risks hypovolemia. It has recently been recognized that the administration of clear liquids to children up to 2 to 3 hours before induction does not increase gastric residual volume or acidity as compared with a more prolonged fast.[33,34] In addition, morbidity and mortality rates for aspiration of gastric contents in children are exceedingly low.[35] Thus, fasting guidelines have been liberalized in recent years, and they are shown in Table 182-2. There is some debate about whether breast milk should be considered a solid or clear liquid, with many institutions allowing breastfeeding within the same guidelines as clear liquids. Nevertheless, in giving these instructions to parents, it is important to emphasize the safety issues involved to maximize compliance and avoid unnecessary delays in the start of the procedure.

Anesthetic Induction

Anesthesia can be induced by mask inhalation of a potent anesthetic agent in oxygen with or without nitrous oxide (inhalation induction), by injection of a sedative-hypnotic agent through an intravenous catheter (intravenous induction), or by intramuscular injection. As much as possible, the choice of technique is given to children; younger children tend to fear needles and prefer an inhalation induction, whereas

Table 182-2

Recommended Preoperative Fasting Guidelines for Children

Ingested Material	Minimum Fasting Period (hours)
Clear liquids	2
Breast milk	4
Infant formula	6
Light meal*	6

*A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time.
Adapted from Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologists Task Force on Preoperative Fasting. *Anesthesiology*. 1999;90:896-905.

older children and teenagers usually accept an intravenous induction. Inhalation induction will take longer in teen aged and older patients than in younger patients because of age-related physiologic differences. This prolonged time to effect must be taken into consideration if an inhalation induction is selected in this age group but does not preclude such an induction. Certain clinical factors (e.g., obesity, severe gastroesophageal reflux, full stomach) also may influence the choice of induction technique toward intravenous.

Parental Presence

With increasing frequency, parents are expressing a desire to be present at the time of their child's anesthetic induction.[36] Although parents' motives vary, most hope that the child's anxiety will be lessened by the emotional comfort of their presence. Some hospitals have induction areas outside of the sterile envelope of the operating room. If not, parents can be dressed in cover gowns and escorted into and out of the operating room for the induction.

Studies examining the impact of parental presence have had variable results, with some showing no significant impact,[37] some showing a decrease in patient anxiety,[38,39] and others showing an increase in patient anxiety.[40] Parents with a high anxiety level seem to have a negative impact on their child, whereas calm parents seem to have a positive impact on their anxious child during induction.[41] One survey reported that a majority of anesthesiologists are in favor of the practice of having parents present during induction,[42] and many hospitals tend to support this request as a mechanism to improve patient and parent satisfaction. Thus, it is likely that the trend will continue. Parents should be thoroughly educated about what to expect and how they can best help their child. They must agree to leave the induction area immediately when instructed to do so, and one member of the care team must be identified to help them during the induction. Highly anxious parents should be encouraged not to participate.

Inhalation Induction

For many years, halothane was the agent of choice for inhalation induction because of its lack of pungency relative to other agents. A more recently developed alternative, sevoflurane, is even less pungent than halothane and has fewer cardiovascular side effects, making it the current pediatric inhalational induction agent of choice. A small amount of favorably scented liquid (e.g., bubble gum flavor, for instance) applied to the inside of the mask disguises the odor of the anesthetic agent and improves the patient's acceptance of the technique.

Many anesthesiologists will begin the induction with the patient breathing 50% to 70% nitrous oxide (which is odorless) before introducing sevoflurane, thus making the addition of the sevoflurane less distressing. Noise in the room should be kept to a minimum during anesthesia induction, and the anesthesiologist often tells the child an entertaining story to direct the child's thoughts away from the reality of the situation. As the concentration of the anesthetic agent is increased, most children lose consciousness in less than 1 minute. The parents, if present, can be ushered out at this point, and an intravenous catheter can then be placed.

Intravenous Induction

Intravenous induction requires the presence of an intravenous catheter and thus is reserved for older children or teenagers, children with a preexisting intravenous catheter, children who need a rapid-sequence induction because of a full stomach, or children who object to an inhalation induction. Owing to slower uptake of inhaled anesthetic agents, inhalational induction takes much longer in older, heavier children, with consequently higher risk for laryngospasm and bronchospasm. An intavenous induction is therefore also the preferable method in this patient group.

The most common agent for intravenous induction is propofol, an alkylphenol that is formulated as a 1% solution in a white soybean oil, egg lecithin, and glycerol emulsion. Propofol is highly lipophilic and rapidly redistributes throughout body compartments, with a distribution half-life of approximately 2 minutes and an elimination half-life of approximately 30 minutes. The dose for the induction of anesthesia varies with age[43]: Infants 1 to 6 months of age require approximately 3 mg/kg, whereas older children require approximately 2.5 mg/kg. The major advantages of propofol are a rapid, clear-headed recovery with minimal associated nausea and vomiting. This has made it the intravenous induction agent of choice for outpatient procedures. The major disadvantage is pain on injection, particularly into small veins.[44] Lidocaine (0.5 to 1.0 mg/kg) administered intravenously before or during propofol injection may decrease the incidence of pain. Propofol may cause hypotension, apnea, and desaturation. Propofol also can be used for anesthesia maintenance as an intravenous infusion of 100 to 200 µg/kg per minute. This technique can be very useful for patients who have a history of severe postoperative nausea or who are undergoing procedures in which postoperative nausea is especially common (e.g., tympanoplasty). Many pediatric anesthesiologists use a propofol infusion to provide anesthesia during bronchoscopy, because it provides a reliable, stable method of administering anesthesia with spontaneous ventilation while sharing the airway and decreases the exposure of the surgeon to unscavenged anesthetic gases.

An alternative intravenous agent for induction is thiopental, an ultrashort-acting barbiturate that produces sleep in healthy, unpremedicated children; a dose of 4 to 6 mg/kg induces sedation within 1 minute of administration.[45] This drug can produce hypotension through both vasodilating effects and direct myocardial depression and must be used with caution in hypovolemic patients or patients with poor myocardial contractility. It also can produce prolonged sedation as a consequence of accumulation in fat stores if higher doses or repeated doses are given.

Rapid-Sequence Induction

Patients with a full stomach are at increased risk for the aspiration of stomach contents during the induction of anesthesia. Patients who require full stomach precautions include those who have not fasted for an adequate period, those with gastrointestinal obstruction, trauma patients whose gastric motility is depressed, or those who are at a mechanical predisposition for aspiration (e.g., patients with ascites). It is mandatory that these patients have an intravenous induction. Patients are preoxygenated with 100% oxygen by mask and then given an induction dose of a hypnotic and a rapid-acting muscle relaxant—either succinylcholine (2 mg/kg) or rocuronium (1.2 mg/kg). Application of manual pressure over the cricoid (known as the Sellick maneuver) can be performed in an attempt to seal the esophagus and to prevent passive regurgitation.[46] Pressure is not released until the endotracheal tube is in place, proper position is confirmed, and the cuff, if necessary, is inflated. At the end of the procedure, these patients should be allowed to emerge completely before extubation, to ensure adequate airway protection.

Intramuscular Induction

Ketamine is a derivative of phencyclidine with potent analgesic and amnestic properties. Anesthetic induction can be achieved with the recommended dose of 1 to 3 mg/kg intravenously or 5 to 10 mg/kg intramuscularly. As noted previously, ketamine is very useful as an intramuscular induction agent in children who are combative or unable to cooperate with a standard inhalation or intravenous induction, often because of intellectual disabilities and behavioral disorders. Ketamine is an excellent choice for anesthetic induction in hypovolemic patients because of its sympathomimetic properties; it rarely causes hypotension in these patients. Ketamine may be the intravenous induction agent of choice in patients with reactive airways[47] because it increases circulating catecholamines and causes the relaxation of tracheal, bronchial, and alveolar smooth muscle.

Ketamine tends to produce copious secretions and should be accompanied by the administration of atropine or glycopyrrolate. Nystagmus and diplopia are common side effects and will resolve as the drug is cleared from the patient's circulation. Intraoperative and postoperative dreams and hallucinations have been reported,[48] more often in older than in younger children, and less often when other sedative-hypnotic agents are used in conjunction with ketamine. If this agent is given preoperatively with the parents still present, they should be informed to expect these side effects.

Anesthesia Maintenance

Inhalational Agents

Nitrous Oxide

Nitrous oxide is a widely used inhalational induction agent in children. Its popularity is a result of its low solubility, which results in rapid uptake and distribution. Nitrous oxide also is odorless and does not cause cardiovascular depression. Although nitrous oxide allows the delivery of lower concentrations of other anesthetic agents, nitrous oxide itself is not a very potent anesthetic agent. Consequently, it must be delivered in high concentration to have an analgesic and hypnotic effect, thereby limiting the concentration of oxygen that can be delivered; it is not useful for patients who require high concentrations of oxygen and should be avoided in patients with pulmonary hypertension as it may aggravate it. Because of the lack of potency and the controversial increased incidence of postoperative nausea and vomiting (PONV), it has been used less and less for anesthesia maintenance. A 34-fold difference has been noted in the blood-gas coefficients of nitrogen (0.013) and nitrous oxide (0.46); thus, nitrous oxide will enter air-filled cavities faster than nitrogen can leave. In a fixed cavity such as the middle ear, the result is an increase in pressure. During tympanoplasty, the middle ear pressure generated by nitrous oxide can lift off the tympanic membrane graft. Therefore, nitrous oxide usually is avoided entirely during those procedures.[49] Nitrous oxide use also may present a hazard for patients with previous reconstructive middle ear surgery.[50]

Sevoflurane

Sevoflurane has completely taken the place of halothane in pediatric institutions in the United States. It is a valuable addition to the anesthesiologist's armamentarium for several reasons. First, it is less pungent than halothane, and it is even better tolerated during inhalation induction. Second, it has a blood-gas partition coefficient similar to that of nitrous oxide, so induction and emergence times are shorter than with halothane. Third, it has fewer cardiovascular effects than halothane.

Sevoflurane has several disadvantages: Its offset is so rapid that without adjunctive administration of narcotics, the perception of and response to pain may be accentuated.[51] There are reports in the literature of a significant incidence of emergence excitement associated with cases in which sevoflurane was used.[52] For these reasons, sevoflurane has assumed a role as an induction agent and a maintenance agent for very short procedures, but it often is replaced by isoflurane or desflurane after induction, depending on case type and anesthesiologist preference. Like all halogenated inhalational agents, it is a potential trigger agent for malignant hyperthermia and should be avoided in susceptible patients.

Isoflurane

Isoflurane has been used for many years as a standard maintenance inhalational agent for children and adults. In practice, it offers no clear advantage for the pediatric otolaryngology patient. It is more pungent and not nearly as well accepted by children during inhalation induction as sevoflurane. Isoflurane does increase rather than decrease heart rate. It also causes decreases in blood pressure, but unlike with halothane, the mechanism is peripheral vasodilation rather than direct myocardial depression.[53]

Desflurane

Desflurane is the newest inhalational agent to be introduced into clinical practice. Its principal advantage is its quicker time to recovery as compared with sevoflurane.[51] It appears to be well tolerated as a maintenance anesthetic, because it provides stable hemodynamics and respiratory parameters during its use. Similar to sevoflurane, desflurane has been associated with increased agitation and emergence delirium.[44] However, this effect does not seem to occur frequently enough to avoid its use in children.

Desflurane does have an irritant effect on the airway, making it contraindicated for inhalational induction or for use during airway procedures such as bronchoscopy. However, many centers have adopted a practice of inducing anesthesia with sevoflurane and then switching to desflurane to take advantage of its quick recovery time while avoiding its airway effects during induction. It also has been suggested that this agent may be particularly useful in neonates and formerly premature babies, in whom residual anesthesia effects may increase the risk of apnea postoperatively.[54]

Intravenous Agents

Opioids

Fentanyl

Fentanyl is the most commonly used supplement to anesthesia in children. Although the usual intravenous dose is 1 to 2 µg/kg, doses in excess of 100 µg/kg have been given to cardiac surgery patients with minimal cardiovascular depression.[55] An initial peripheral vasodilation occurs, but tachyphylaxis to this side effect occurs with additional dosing. Preterm and full-term newborns have variable and prolonged clearance, probably related to reduced hepatic blood flow.[56] In addition, they are extremely sensitive to the effects of fentanyl on chest wall rigidity. In neonatal patients who are not intubated, fentanyl should be given only in small increments.

The effect of low-dose fentanyl is terminated largely by redistribution, thereby resulting in a rapid reduction in clinical effect. Because fentanyl is highly lipophilic, however, higher or repeated doses result in drug accumulation. Clearance then becomes dependent on metabolism,[57] and the clinical effect, including respiratory depression, may last for hours. Chest wall rigidity has been reported after rapid fentanyl administration, although the etiology of this problem is unclear. Bradycardia may occur as a result of increased vagal tone, especially when given with other agents that may have a similar effect.

Morphine Sulfate

Overall, morphine is the most frequently used opioid in children. It can be used in the operating room to supplement inhalational agents and to provide postoperative analgesia. The usual intravenous dose is 0.05 to 0.1 mg/kg as part of a balanced anesthetic technique, although higher doses may be used for a narcotic-based technique. The dose may need to be reduced in critically ill children or young infants. The half-life after intravenous administration is approximately 3 hours in older children but is significantly longer in infants as a result of diminished clearance.[58] The major side effect is respiratory depression, which results in diminished minute ventilation, with a greater effect on respiratory rate than tidal volume. Many believe that newborns are at higher risk than older children for respiratory depression, although it is unclear whether this reflects a difference in pharmacokinetics or pharmacodynamics. Infusions of morphine at rates of 10 to 30 µg/kg per hour have been described in small infants without significant respiratory depres-

sion.[59] Appropriate monitoring for apnea should occur in premature infants and those neonates with a history of apnea and bradycardia. Histamine release is also common with the administration of morphine, and it most commonly results in a localized or generalized rash. Bronchospasm and hypotension have been reported, but they are much less common.

Hydromorphone

Hydromorphone has become a commonly used alternative to morphine. It is approximately five to seven times more potent than morphine, with the usual intravenous dose ranging from 0.015 to 0.02 mg/kg. Its half-life is similar to that of morphine, and it has a similar duration of action. Hydromorphone may be useful in patients with renal failure, because its metabolic by-products are less active than morphine's are. In addition, hydromorphone may be a good alternative for those patients who suffer side effects (e.g., itching, nausea, hallucinations) with morphine. As with other opioids, respiratory depression is the most concerning side effect, but it is rare with appropriate dosing.

Meperidine

The use of meperidine has dramatically decreased due to its unique side effect profile and the availability of equianalgesic alternatives. The principal metabolite of meperidine is normeperidine, a compound that can cause neurologic excitation manifested as tremors, irritability, or seizures. This side effect is especially pronounced with prolonged use or in patients with hepatic or renal dysfunction. Meperidine's superiority over other opioid agonists in the treatment of postoperative shivering probably is related to its kappa receptor activity and the one reason that it has not become entirely obsolete.

Alfentanil

As a short-acting analog of fentanyl, alfentanil commonly is used for short outpatient procedures. It is approximately one-fourth as potent as fentanyl and has one-third the duration of action. It has a very fast onset of action (1 minute) and a short elimination half-time (1.5 hours). It is less lipophilic than fentanyl, and the dose range is 10 to 20 μg/kg, given intravenously. Renal failure does not alter the clearance of alfentanil. Besides the opioid-related side effects, thorax rigidity and bradycardia may be seen.

Remifentanil

Remifentanil has the same analgesic potency as that of fentanyl. The key feature of remifentanil is the ester side chain hydrolysis by blood and tissue esterases, resulting in rapid metabolism (elimination half-time is 10 to 20 minutes). This results in zero order kinetics, meaning that its offset of action is 10 to 20 minutes after discontinuation of the infusion, regardless of the duration of the infusion. Said differently, it does not accumulate. It does have a rapid onset, and because of its short duration of action, it usually needs to be administered as an continuous intravenous infusion at the rate of 0.05 to 1 μg/kg/min for neonates and up to 2 μg/kg/min for older children. Pharmacokinetic parameters of remifentanil are unchanged by hepatic or renal disease. Disadvantages are the high cost and the lack of postoperative analgesia, which can be overcome with application of longer-acting opioids at the end of surgery.

Muscle Relaxants

Succinylcholine

Succinylcholine is the only depolarizing muscle relaxant. With the advent of intermediate-acting nondepolarizing relaxants, the use of succinylcholine for routine surgical procedures is declining, primarily as a result of side effects that relate to its depolarizing mode of action (see later). However, it remains the most rapid-acting of all muscle relaxants, and it is still indicated for use in rapid-sequence inductions and in the treatment of laryngospasm. Intravenous administration of 1.5 to 2.0 mg/kg achieves 95% twitch depression in 40 seconds,[60] resulting in excellent intubating conditions. Succinylcholine also can be given intramuscularly (4 to 5 mg/kg) if the intravenous route is unavailable, although the clinical effect is delayed in onset, depending on perfusion to the area of deposition.

The side effects of succinylcholine are numerous. Some degree of increase in masseter muscle tone is common and, in some cases, is extreme enough to mimic true trismus.[61] This is an important distinction to make, because as many as 50% of patients with trismus after succinylcholine are biopsy positive for susceptibility to malignant hyperthermia.[62] Succinylcholine can also cause bradycardia as a result of an increase in vagal tone; this effect is especially prominent in younger children and infants. The decline in heart rate usually is transient and, if not, is responsive to intravenous atropine; occasionally, asystole is seen. Hyperkalemia can be seen as a result of depolarization of the myoneural junction; increases of serum potassium of 0.5 mEq/L occur even in normal children.[63] Life-threatening hyperkalemia after succinylcholine administration can occur in children with burns, tetanus, paraplegia, encephalitis, crush injuries, and neuromuscular disease.[63] Myoglobinemia occurs in approximately 40% of children anesthetized with halothane who are given succinylcholine; this effect can be partially attenuated with a previous dose of a nondepolarizing agent to prevent fasciculations. A series of cardiac arrests were reported in boys who were given succinylcholine, with subsequent development of massive muscle breakdown and potassium release. The presumed etiology was previously undiagnosed muscular dystrophies.[64] In 1994, in response to these reports, the manufacturer placed a warning on the package insert cautioning the practitioner about the routine use of succinylcholine. As a result, many pediatric anesthesiologists have abandoned the routine use of succinylcholine except for rapid-sequence inductions and to treat laryngospasm. Succinylcholine may soon be replaced in that role by rocuronium, which has an onset of action of less than a minute, making it suitable for a rapid sequence induction. The disadvantage of rocuronium has been the long time to reversal after an intubating dose has been given. This makes it suboptimal and perhaps contraindicated for patients with a difficult airway. Sugammadex**,** a selective relaxant-binding agent, is in phase 3 trials. If approved, it would make rocuronium rapidly reversible and thereby make the risks of succinylcholine unnecessary. Sugammadex is not yet available for use in the United States.

Of note, 90% of an intravenous dose of succinylcholine is rapidly hydrolyzed in the plasma by pseudocholinesterase. Patients with deficient or reduced levels of pseudocholinesterase exhibit a prolonged effect from succinylcholine.

Nondepolarizing Muscle Relaxants

A variety of nondepolarizing muscle relaxants are available. These agents vary in dose, speed of onset, and duration of action. As shown in Table 182-3, the pharmacologic properties of these drugs may be different in infants from those in older children. The choice generally is based on the duration of the surgical procedure. As noted, rocuronium has been shown to produce good intubating conditions, but with a slightly longer onset of action (less than 1 minute) than with succinylcholine (less than 30 seconds).

Total intravenous anesthesia (TIVA) is a continuous titration of intravenous drugs for maintenance of anesthesia. Drugs used often are a propofol-remifentanyl or propofol-alfentanil combination. This technique provides malignant hyperthermia–safe anesthesia in the malignant hyperthermia–suscepctible patient; it often is used in patients with severe postoperative nausea and vomiting and is also the technique of choice in some airway cases (see later on).

Emergence from Anesthesia

The decision of whether to extubate a patient while he or she is awake or under surgical planes of anesthesia (deep extubation) depends on a number of factors. Deep extubations are smoother and facilitate rapid turnover. Considerations in making this decision include the patient's age, airway anatomy, underlying disease, the presence of blood or secretions in the airway at the time of extubation, the presence of a full stomach preoperatively, the ability of the postanesthesia care unit staff to manage an obstructed airway, and the immediate availability of an individual skilled in reintubation should it be required. Deep extubation is preferred in patients with asthma or in those for whom coughing would be contraindicated. Factors that favor awake extubation include a full stomach at the start of the procedure, age younger than

Table 182-3

Intubation Doses, Onset Times, and Recovery Times for Commonly Used Muscle Relaxants

	Intubating Dose (mg/kg)			
	Adults	Children	Onset Times* (min)	Recovery Times in Infants (min)
Mivacurium	0.3	0.2-0.3	1.5-2	15-20
Atracurium	0.5	0.5	2	40-60
Cisatracurium	0.1	0.1-0.2	2.5	53
Vecuronium	0.07-0.1	0.1	2.4	35
Rocuronium	0.5-1.0	0.6-1.2	1.3	42
Pancuronium	0.1	0.1	2.5	50

*Time to maximal blockade.

6 months, difficult airway anatomy for either masking or intubating, copious blood or secretions in the airway, and a predisposition to apnea. Systematic comparisons of awake versus deep extubation have revealed that patients extubated while awake have lower oxygen saturations (probably because of coughing during emergence), but there is no difference in overall morbidity or mortality.[65,66] Either technique can be performed safely; the anesthesiologist should have both approaches in his or her armamentarium and, using clinical judgment, choose the one that best fits the situation.

Postoperative Management

Nausea and Vomiting

Nausea and vomiting can result in an unpleasant recovery from surgery and anesthesia as well as a delayed discharge from the postanesthesia recovery unit and an increase in overall cost. In the pediatric population, the incidence is variable and depends on the type of surgery, the type of anesthetic used, gender, age, history of motion sickness, and adequacy of hydration.[67] Although the overall incidence is lower in children younger than 2 years of age, children older than 3 years have an average vomiting incidence of more than 40%. Procedures such as tonsillectomy and middle ear surgery may be associated with an incidence of vomiting as high as 70%. The use of narcotics, halogenated inhalational agents, and perhaps nitrous oxide increases the risk of nausea and vomiting. By contrast, propofol reduces the incidence of vomiting as compared with that with halothane in children undergoing adenotonsillectomy.[17]

Therefore, antiemetics often are given prophylactically for children at risk for PONV and a multimodal approach has been shown to be the most effective one.[68] The use of intravenous ondansetron (50 to 100 µg/kg up to 4 mg), intravenous dexamethasone (150 to 500 µg/kg up to 8 mg), and intravenous droperidol (50 to 75 µg/kg up to 1.25 mg) is evidence-based for prophylaxis for patients at risk for PONV and for treatment of patients with PONV.

Serotonin (5-hydroxytryptamine$_3$)-receptor antagonists, such as ondansetron, have shown efficacy and safety in prophylaxis and therapy of PONV, having a greater antivomiting than antinausea effect.[69] When prophylaxis with serotonin receptor antagonist fails, a rescue therapy with serotonin receptor antagonists is not recommended within the first 6 hours of surgery because it confers no additional benefit.[70]

Another drug that has been shown to help control PONV during the 24 hours after surgery is dexamethasone. Children who receive a single intraoperative dose of dexamethasone were two times less likely to vomit during the first 24 hours than children who received placebo. Routine use in four children would be expected to result in posttonsillectomy emesis experienced by one fewer patient. Additionally, children receiving dexamethasone were more likely to advance to a soft to solid diet on posttonsillectomy day 1 than were those children receiving placebo.[71]

Droperidol is an antidopaminergic antiemetic. While effective in the treatment of PONV, its sedating and extrapyramidal side effects should be considered when choosing it.[72] In 2001, the U.S. FDA issued a black box warning against the use of this drug due to concerns of serious cardiac arrhythmias secondary to QT prolongation. Since that time, the restriction has been lifted. However, it has never returned to the prevalent use that was seen prior to the ban. An overwhelming majority of anesthesiologists surveyed (92%) did not consider the ban warranted, as torsades de pointes was seen mostly when the drug was administered in very high doses or when there were confounding factors. Still, prudence would limit its use to cases in which patients do not have underlying cardiac disease, other classes of antiemetics have been exhausted, and the maximum total pediatric dose is less than 100 µg/kg or 2.5 mg total.[73]

Finally, an inexpensive but effective method of reducing the incidence of nausea and vomiting is to withhold oral fluids during the postoperative period until the child asks for them, because forced oral fluids increase the incidence of vomiting and delay discharge.[67,74,75] This can be safely done by generously hydrating the patient with intravenous fluids intraoperatively. Nontraditional treatment methods such as acupressure are being studied and thus far confirm their effectiveness in the prevention of PONV; they are useful adjuncts, especially in view of the total absence of side effects.[76]

Postintubation Croup

In children up to approximately 8 years of age, the subglottis is the narrowest portion of the airway, and it may be the source of postoperative airway obstruction secondary to mucosal swelling. A reduction in the reported incidence of postintubation croup from 1%[77] to 0.1%[78] may be obtained with use of proper-sized, non–tissue-reactive tubes that allow an air leak around the tube at 25 cm H_2O or less.

Racemic epinephrine (0.5 mL of 2.25% in 2.5 to 3.0 mL of normal saline for children weighing 15 kg or more) nebulized in oxygen is the management of choice for postintubation croup; the effect is thought to result from the vasoconstriction of the subglottic mucosa. (The dose varies, ranging from 0.2 mL for infants weighing less than 5 kg, 0.3 mL for 5- to 10-kg infants, and 0.4 mL for 10- to 15-kg infants.) Because symptoms can recur within 2 to 4 hours, the child should be observed for 4 hours after treatment before being sent home. If frequent and repeated treatments are necessary, hospital admission should be considered. Dexamethasone (0.3 to 0.5 mg/kg) also may be tried,[79] although its effect is slow in onset if it occurs at all.

Pain Management

The theory that children, particularly neonates, perceive pain less acutely and therefore do not need pain medication is no longer accepted.[80] As a result, since the early 1990s there has been a significant change in how pediatric pain is approached. Perhaps the most powerful sign of this change was that the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations [JCAHO]) added pain management to its accreditation review in 2000. Areas that now must be addressed by accredited institutions include pain assessment, pain treatment, and education about pain management.[81]

Pain assessment can be challenging in children. Assessing the degree of pain in preverbal children is problematic, although several observational scales have been developed to assist with this population.[82] Children 4 to 8 years of age have been shown to be capable of giving a self-report with simplified tools, and older children can use the same scales as those for adults.[83] Patients in the intensive care unit setting (immediately postoperatively) and cognitively impaired children remain populations to be studied in the area of pain assessment.

Intravenous opioids—whether given by bolus, infusion, or patient-controlled analgesia—are the mainstay of therapy for severe pain.[84] Children 8 years of age and older (and some mature 6- to 7-year-old children) do well with patient-controlled analgesia, tend to use less total drug, and have a better feeling of control than with traditional methods of administration. Younger children requiring intravenous opioids may benefit from administration accomplished using parent- or nurse-controlled analgesia. Appropriate parent education is a necessary prerequisite to parent-controlled analgesia.

Milder degrees of pain can be handled with nonopioid analgesics. Acetaminophen (10 to 15 mg/kg every 4 to 6 hours to a maximum of 4 g every 24 hours), alone or with oxycodone (0.1 to 0.15 mg/kg), is useful for children who can take oral medications. Rectal acetaminophen can also be given, although doses of 20 to 40 mg/kg are necessary to achieve serum levels equivalent to those obtained with 10 to 15 mg/kg given orally.[85] Ketorolac (0.5 mg/kg IM or IV every 6 hours for up to 48 hours) is a nonsteroidal anti-inflammatory agent that has potent analgesic properties; these may be equivalent to those of morphine[86] but without the respiratory depression or nausea associated with opioids. However, ketorolac requires 30 to 45 minutes for onset, has a 12% incidence of nausea, and may be associated with a higher incidence of bleeding because of effects on platelet function.[87] Nonopioid analgesics also are a good adjunct to opioid and other pain medications: multimodal therapy has been shown to be most effective in the treatment of pain, especially in difficult-to-treat cases.

Codeine, often used as a first-line oral opioid, seems to be a weak analgesic. Essentially a prodrug of morphine, it needs to be converted to its active form in the liver. Approximately 10% of the population lack the enzyme CYP2D6 and will not achieve pain relief from codeine. Accordingly, a more rational approach is to use a stronger oral analgesic as a first-line agent, especially after significantly painful procedures. As with all opioids, nausea and vomiting are potential side effects and may be more prevalent with use of codeine.

Sedation and Anesthesia Outside of the Operating Room

Over the past 10 years, an increasing number of procedures have been performed outside of the operating room. Reasons for this development include physician time constraints, reimbursement changes, new technology for procedures that cannot be done in the operating room, and the development of new anesthetic agents. This practice has been recognized to be accompanied by a risk of adverse events potentially greater than that for operating room procedures, as a result of monitoring variation, poor presedation evaluation, inadequate training, and lack of adequate recovery procedures.[88] More recently, a greater degree of scrutiny has been given to the practice of sedation for children outside of the operating room. In an effort to improve safety, the Joint Commission has been instrumental in forcing institutions to develop policies to improve the care of children and adults who are receiving sedation, as part of overall accreditation efforts. In addition, specialty organizations have developed policy statements about this topic.[89-91] In many institutions, this has meant that pediatric anesthesiologists are more directly involved with this activity than in the past.

A large number of procedures that are performed in hospitals may require use of sedation or analgesia, especially in children. Painful procedures (e.g., lumbar puncture, bone marrow biopsy, chest tube placement) are obvious examples. Other procedures, such as magnetic resonance imaging or gastrointestinal endoscopy, also may require sedation or anesthesia because of the distressing nature of one or more aspects of the examination or the need for immobility. In the context of otolaryngology, the most common candidates for out-of-the-operating-room or clinic procedures may be patients requiring the removal of pressure equalization tubes, nasal ciliary biopsy, fine-needle aspiration, or the removal of sutures. One report suggests that these procedures can be performed in the clinic safely and with less cost using intravenous sedation as compared with general anesthesia in the operating room.[92]

In general, a pediatric sedation service oversees sedation or anesthesia for a majority of out-of-the-operating-room procedures performed at our institution. All children scheduled for procedures receive a phone call before their appointment to identify any significant medical problems and to provide NPO instructions. On the day of the procedure, the patient arrives approximately 30 minutes before the planned time of the procedure for application of topical anesthesia cream. A sedation nurse then starts an intravenous line, after which the pediatric anesthesiologist provides intravenous sedation or anesthesia. After the procedure is completed, the sedation nurse oversees the patient's recovery until he or she is ready for discharge. For less invasive procedures in cooperative patients, the sedation nurse may provide conscious sedation with oral, intravenous, or intranasal medications rather than use the method described previously.

Another option is for the otolaryngologist to provide the sedation, often with oral or intravenous midazolam, possibly combined with fentanyl. Even with this type of conscious sedation, practitioners should be aware of their institution's policy about sedation. A preprocedure evaluation should be documented, monitoring should be performed during the procedure and documented, and appropriate recovery procedures should be followed. Documentation of NPO status also may be relevant, depending on the depth of sedation planned.

Medical Conditions with Anesthetic Implications

A number of medical conditions may modify preoperative preparation and intraanesthetic or postanesthetic management.

Upper Respiratory Infection

The decision of whether to anesthetize a child with an upper respiratory infection (URI) is recurrent in pediatric anesthesia. In making this decision, it is helpful to know the risks involved. Deterioration in pulmonary function is typical during a URI, including a decrease in flow rates such as forced expiratory volume in 1 second (FEV_1),[93] a decrease in mucociliary clearance,[94] and an increase in airway reactivity.[95] Resolution of these abnormalities can take up to 6 weeks after the resolution of symptoms.

These changes in pulmonary function have other clinical correlates. McGill and colleagues[96] reported on 11 cases (no denominator) of intraoperative atelectasis identified by chest radiography in children anesthetized within 4 weeks after a URI. Children with a URI may be at increased risk for postoperative desaturation,[97] croup, laryngospasm, airway obstruction, and reactive airway disease. Another prospective study evaluated adverse respiratory events in 1078 children with URIs undergoing elective surgical procedures. This study identified a significantly higher incidence of respiratory events among children with URIs, although none of these events was associated with long-term sequelae. Risk factors associated with adverse events included a history of prematurity, a history of reactive airway disease, parental smoking, and surgery involving the airway.[98,99] Conversely, a prospective study of a series of nonintubated children undergoing myringotomy failed to

show a difference in perioperative complications between asymptomatic children and children with URI symptoms.[100]

Other factors also must be considered. Do the symptoms result from allergy rather than infection? How severe is the URI? A child with fever, cough, malaise, and myalgias may be at higher risk than a child with mild rhinorrhea. How elective is the surgery? How much inconvenience would result for the family from cancellation or postponement? Is an escalation in care likely from proceeding with the surgery at that time? How often is the child symptom-free? In view of the frequency of URIs in some children and the time required for the resolution of pulmonary function abnormalities, it may be difficult to find a disease-free interval.

Frequently, the decision seems to involve more art than science. In equivocal cases, a leukocyte count and a chest radiograph may be helpful.[98] Measurement of hemoglobin saturation in a patient breathing room air may identify some at-risk children, but it is not very sensitive. Unfortunately, no combination of historical features, physical findings, or laboratory tests can identify the child at risk. A discussion of the potential risks and benefits with the parents will allow them to participate in the decision-making process. Good communication between the anesthesiologist and the otolaryngologist is essential for establishing some consistency in approach.

Premature Infants

In the early 1980s, a high incidence of apnea was reported after the administration of general anesthesia during the first few months of life to children who had been born prematurely (at 37 weeks of gestational age or before).[101,102] The risk probably extends to approximately 55 weeks of postconceptual age, with the curve approaching but never reaching a zero percent risk, and is inversely related to both postconceptual and postgestational age and hematocrit.[45]

Although the etiology of apnea is unknown, most episodes are central in origin; however, nearly one third are associated with airway obstruction.[103] Halogenated inhalation anesthetics blunt the ventilatory response to CO_2 and hypoxia, even in subanesthetic concentrations,[29] thereby accentuating preexisting abnormalities of respiratory control that may result in an apneic event. Although apnea has been reported after general, spinal,[104] and caudal[105] anesthesia, one prospective series has suggested that the incidence is lower after regional techniques without adjunctive sedation than after either general or regional anesthesia with intravenous sedation.[106] Administration of caffeine intraoperatively also may lessen the incidence of postoperative apnea.[107]

Elective procedures should be postponed until premature infants reach 55 weeks' postconceptual age, at which time the incidence of apnea is less than 1%.[45] Children at risk for postoperative apnea should have cardiorespiratory and pulse oximetry monitoring for a period of time after surgery. There is some institutional variability in the exact duration of monitoring; however, most will monitor for a period of 4 to 24 hours, depending on the infant's actual postconceptual age, history of apnea, and overall health status.

Asthma

A history of asthma in a child is important to the anesthesiologist, because good preoperative preparation and careful intraoperative anesthetic management can usually prevent serious episodes of bronchospasm. History of severity (e.g., current medication, recent wheezing history, past need for emergency department visits or hospitalization) correlates well with intraoperative risk. For children with a history of frequent asthma attacks, consultation with the child's primary care provider can help ensure that treatment is maximized before surgery. A thorough physical examination that includes chest auscultation is necessary to rule out active bronchospasm. Elective surgery should not be performed in the presence of active wheezing. In a child with active wheezing, pulmonary function testing (especially FEV_1) may be useful for documenting the extent of obstructive disease and the potential for reversal with bronchodilators. Improvement in expiratory flow rates after a trial of bronchodilators suggests that adjustments in bronchodilator therapy before elective surgery may be beneficial.[108] A variety of bronchodilator compounds are available for preoperative and intraoperative use, including β_2-agonists, corticosteroids, and anticholinergics.[108] Nebulized β_2-agonists such as albuterol are the most commonly used agents during the perioperative period because of ease of administration, good efficacy, and low incidence of side effects. Preoperative administration of albuterol may be helpful for decreasing the incidence of intraoperative bronchospasm.

The most common cause of bronchospasm in susceptible patients is instrumentation of the airway under light planes of anesthesia.[109] Both general and regional anesthetic agents can be used to obtund airway reflexes. Lidocaine (1 to 2 mg/kg) can be sprayed into the trachea or given intravenously to prevent reflex-induced bronchospasm.[110] All inhaled halogenated anesthetics prevent or ameliorate bronchospasm by increasing bronchial caliber and pulmonary compliance, decreasing pulmonary resistance, and improving gas exchange during active bronchospasm.[111,112] Ketamine also acts as a bronchodilator and may be useful as an induction agent in patients with active wheezing. Extubation of the trachea while the patient is under surgical planes of anesthesia, followed by a slow, smooth emergence, minimizes the risk of bronchospasm. However, careful attention must be paid to airway patency until the child is awake.

Cystic Fibrosis

Early diagnosis and antibiotic treatment, management of chronic pulmonary disease and malabsorption have improved the health and survival of children with cystic fibrosis (CF); currently, nearly 50% of affected patients are older than 18 years of age.[112a] Pansinusitis develops in more than 90% of children with CF, and nasal polyps in 20%; the latter may require surgery. The child with CF presents a significant challenge to the pediatric anesthesiologist; malnutrition, dehydration, and pulmonary insufficiency are all potential concerns. One series reported that 13% of patients with CF had some anesthetic complication.[113]

Preoperative evaluation of patients with CF is important for minimizing postanesthetic morbidity. The severity of pulmonary disease can be quantitated with historical features (e.g., degree of exercise intolerance, amount of sputum production) and a thorough physical examination (e.g., respiratory rate, work of breathing, quality of breath sounds, skin color). Patients with evidence of significant disease should have oximetry and perhaps arterial blood gas analysis. Electrocardiogram and echocardiogram also should be considered to screen for right ventricular dysfunction (cor pulmonale). If the patient is cooperative, pulmonary function tests may help to quantitate the degree of pulmonary compromise and serve as a baseline to assess the impact of preoperative therapy. Consultation with the pulmonologist caring for the patient also may provide important information about baseline condition and medical therapy.

In patients with significant pulmonary disease, a preoperative "tune-up" may help prevent perioperative complications. A regular program of chest physiotherapy includes chest percussion and postural drainage. Sputum samples are sent for culture and sensitivity, and antibiotic therapy may be indicated. The patient should be well hydrated to avoid inspissation of secretions. Patients not taking oral vitamin K supplements are given enteral vitamin K. If premedication is required, a benzodiazepine can be given with minimal risk of respiratory depression. An anticholinergic can be given if desired; the concern about excessive drying of secretions has not been a significant clinical problem. General anesthesia can be maintained with inhalational agents, because they are potent enough to allow for the administration of high-concentration oxygen, and they provide bronchodilation. The shorter-acting inhalational agents (e.g., sevoflurane) may be of particular benefit because of their shorter recovery time. An endotracheal tube usually is placed to deal with the most commonly reported complications, which include copious secretions, airway irritability, and compromised oxygenation.[103] Ventilation usually is assisted or controlled, to prevent intraoperative loss of lung volume and subsequent atelectasis. All delivered gases are humidified, and intravenous hydration is maintained to facilitate the clearance of secretions. Tracheal suctioning is performed as necessary, with emphasis on maximal pulmonary toilet before extubation. At the end of the procedure, the trachea is extubated after the patient is awake and breathing spontaneously.

Diabetes Mellitus

The key to the successful anesthetic management of a child with diabetes mellitus is careful administration of dextrose and insulin and frequent monitoring of blood glucose. Knowledge of the patient's daily insulin type and amount and the resulting blood glucose is important to the development of an anesthetic plan. A normal diet and insulin regimen should be maintained up to the day of surgery. Diabetic children should be scheduled for the first surgical procedure of the day when possible, because this timing usually simplifies their glucose management.

One of several approaches to the management of glucose and insulin can be taken[114]:

1. On the morning of surgery, half of the usual morning insulin dose is given as regular insulin (onset in 30 minutes; peak effect in 2 to 4 hours; duration of action of 6 to 8 hours) after an intravenous infusion of 5% dextrose in 0.45% normal saline is established at 1500 mL/m^2 per day. Serum glucose levels are monitored frequently before and after surgery and are maintained between 100 and 200 mg/dL, with a sliding scale of regular insulin given until the patient is eating and can resume the usual insulin regimen.

2. On the morning of surgery, a continuous infusion of insulin and glucose is initiated (1 or 2 units of insulin per 100 mL of 5% dextrose). Adjustments can be made in the ratio to maintain blood glucose in the desired range.

3. For procedures that are brief and will allow oral intake in the recovery room (e.g., myringotomy), no insulin and no glucose are given. These cases should be scheduled as the first of the day. When oral intake is reinitiated, 40% to 60% of the usual daily insulin dose is given subcutaneously, and blood glucose is monitored carefully.

The appropriate use of short-acting anesthetic agents and nonsedating antiemetics will allow this group of patients to return to oral intake as soon as possible. Preoperative endocrinology consultation may be helpful for patients with poorly controlled blood glucose.

Congenital Heart Disease

Patients with congenital heart disease are seen by many other surgical specialists for management of congenital abnormalities associated with a specific syndrome, as well as for treatment of other diseases found in children without heart disease. Some will have had their defect already repaired (e.g., neonatal coarctation of the aorta). Some will have received surgical palliation and thus have achieved a state that is physiologically better tolerated but does not represent series circulation (e.g., hypoplastic left-sided heart syndrome in a patient who has had a stage 1 Norwood procedure). Some will not yet have had the defect repaired because it is of secondary priority to more urgent problem (e.g., a patient with an atrial septal defect who has a foreign body in the airway). In each of these situations, an in-depth understanding of the patient's anatomy and physiology will dictate anesthetic goals.

The first issue is whether the patient requires antibiotics for subacute bacterial endocarditis (SBE) prophylaxis. In 2007, the American Heart Association, in collaboration with a number of interested medical organizations, published revised evidence-based guidelines for the prevention of infective endocarditis. Of the underlying principles from which the previous (1997) guidelines had been formed, whether antimicrobial prophylaxis was effective in humans was called into question by the committee. The new guidelines pointed toward use of infective endocarditis prophylaxis in significantly fewer patients[115] (Tables 182-4 and 182-5). If given orally, the antibiotics should be administered 1 hour before the procedure. If given intravenously or intramuscularly, they should be administered within 30 minutes before the start of the procedure (Table 182-6). For recommendations outside the scope of otorhinolaryngology, appropriate practice guidelines should be consulted.

Premedication is the next consideration in this group of patients. In general, cardiac patients tolerate premedications well. We routinely give 0.7 to 1.0 mg/kg of oral midazolam 10 to 30 minutes before taking the patient to the operating room. In patients for whom this premedication has been insufficient in the past, we may add 5 to 10 mg/kg of oral ketamine, with the recognition that this will prolong recovery time. If an intravenous line has already been established, the usual doses of intravenous premedication agent is given. The relative exceptions are the patient with pulmonary hypertension and the patient in whom an increase in pulmonary vascular resistance (PVR) will cause right-to-left shunting—specifically cyanotic patients. Elevation in CO_2 as a result of hypoventilation from premedication causes this shift. With this patient population, an anesthesiologist should be in close proximity should the premedication not be well tolerated and control of the airway and ventilation becomes necessary. Monitoring is always indicated in these patients for administration of premedication.

For patients with a pacemaker, the child's electrophysiology cardiologist should be consulted about intraoperative recommendations, because all pacemakers are different. In most cases, the recommendation will be to have a magnet available that, when placed over the pacemaker, puts it into an asynchronous mode. In this case, it will fire

Table 182-4

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for which Prophylaxis Is Recommended

Prosthetic cardiac valve
Previous infective endocarditis
Congenital heart disease (CHD)* • Unrepaired cyanotic CHD, including cases in which palliative shunts or conduits have been placed • Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months afte the procedure† • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)
Cardiac transplant recipients in whom cardiac valvulopathy develops

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.[114]

Table 182-5

Ear, Nose, and Throat Procedures and Subacute Bacterial Endocarditis Prophylaxis

Prophylaxis	Procedures
Recommended	Tonsillectomy, adenoidectomy Surgical procedures that involve respiratory mucosa Rigid bronchoscopy
Not recommended	Endotracheal intubation Flexible bronchoscopy Tympanostomy tube insertion

Table 182-6

Prophylactic Regimens for Oral and Respiratory Tract Procedures[115]

Regimen/ Patient Factors	Drug	Dosage
Standard		
Oral dosing	Amoxicillin	50 mg/kg PO up to 2.0 g
No oral dosing	Ampicillin *or*	50 mg/kg IM or IV up to 2.0 g
	Cefazolin *or*	50 mg/kg IM or IV up to 1.0 g
	Ceftriaxone	50 mg/kg IM or IV up to 1.0 g
Penicillin-allergic		
Oral dosing	Cephalexin *or*	50 mg/kg PO up to 2.0 g
	Clindamycin *or*	20 mg/kg PO up to 600 mg
	Azithromycin *or*	15 mg/kg PO up to 500 mg
	Clarithromycin	15 mg/kg PO up to 500 mg
No oral dosing	Cefazolin *or*	50 mg/kg IM or IV up to 1.0 g
	Ceftriaxone *or*	50 mg/kg IM or IV up to 1.0 g
	Clindamycin	20 mg/kg IV up to 600 mg

Table 182-7

Factors Influencing Pulmonary Vascular Resistance and Systemic Vascular Resistance

Vascular Resistance	Increases	Decreases
Pulmonary	PEEP, high airway pressure	Low airway pressure
	Low Fio_2	High Fio_2
	Acidosis, high $Paco_2$	Alkalosis, low $Paco_2$
	High hematocrit	Low hematocrit
	Sympathetic stimulation	Anesthesia
	Hypoxia	Drugs (e.g., NO, sildenafil)
	Atelectasis	
Systemic	Vasoconstrictors	Vasodilators
	Direct manipulation	Potent inhalation agents

Fio_2, inspired oxygen concentration; NO, nitric oxide; $Paco_2$, arterial carbon dioxide concentration; PEEP, positive end-expiratory pressure.

Table 182-8

Diagnosed Disorders by Age Group in Children Undergoing Bronchoscopy for Airway Obstruction

Diagnosis	Frequency (%) by Age Group		
	Younger than 1 Year	1 to 3 Years	Older than 3 Years
Congenital defects*	43	8	3
Acquired defects†	12	13	15
Normal findings	4	1	1
Total	69	22	19

*Laryngomalacia, tracheomalacia, bronchomalacia, vocal cord paralysis, vascular ring, hemangioma, cysts.
†Subglottic stenosis, papillomatosis, infection (e.g., tracheitis, epiglottitis).
Modified from Wiseman NE, Sanchez I, Powell RE. Rigid bronchoscopy in the pediatric age group: diagnostic effectiveness. *J Pediatr Surg*. 1992;27:1294.

without sensing (VOO mode). This is rarely necessary, because most (but not all) implanted pacemakers will do this automatically when faced with prolonged periods of electromagnetic interference. Finally, the grounding pad for the electrocautery should be placed as far away from the pulse generator as possible so that the path from electrocautery to grounding pad does not cross the mediastinum.

In managing the anesthetic procedure, it is important to prevent the administration of air bubbles in the intravenous fluids. Many of these patients have shunts that may allow air to pass from venous to systemic circulations, thereby increasing the risk for stroke, myocardial ischemia, renal ischemia, and so on.

For classification of the anatomy and circulation, the clearest view of the anatomy is obtained by visualizing a red blood cell traveling through the circulation, including all points at which a shunt may exist. Adopting this scheme makes it easier to sort out the anesthetic goals. Regardless of how the anatomy is arranged, it features a pulmonary circulation and a systemic circulation. With an understanding of their relationship to each other, the clinician can manipulate the resistances of the respective circulations and, in so doing, influence the degree and direction of shunting within the boundaries of what the anatomy will allow (Table 182-7). Poor ventricular function will dictate choice of an anesthetic that relies more on narcotics and less on inhalation agents.

In patients with cyanotic heart disease, polycythemia develops as a compensatory state to improve oxygen delivery in the long term. Hematocrit should therefore be measured early as a baseline and should be kept near 40 to support oxygen delivery. However, blood flow becomes sluggish when the hematocrit rises above 60. In these patients, phlebotomy may be considered to prevent ischemia resulting from stasis. The patient's cardiologist should be consulted if phlebotomy is considered as a therapeutic option.

Patients with congenital heart disease have very special needs. Except for the most severely ill of them, they tolerate noncardiac surgery quite well. However, their care needs to be optimized by an anesthesiologist who is familiar with the care of this patient population; understanding their physiology and anatomy is critical.

Anesthetic Considerations for Specific Procedures

Rigid Bronchoscopy

Anesthesia for rigid bronchoscopy presents a significant challenge for the pediatric anesthesiologist, for several reasons. First, bronchoscopy most often is indicated for the diagnosis and management of children younger than 1 year of age, predominantly because of congenital defects[116] (Table 182-8); this is relevant because anesthetic risk appears to be highest in this age group.[2,3] Second, patients who require bronchoscopy often present with difficult airway anatomy or with compromised oxygenation and ventilation; these factors may predispose them to intraoperative problems. Finally, the need to share the airway with the endoscopist demands effective two-way communication and coordination to ensure a smooth anesthetic and to prevent complications. Thus, the importance of communication between anesthesiologist and endoscopist during preoperative planning and intraoperative management cannot be overstated. Preparation should include assessment of

the bronchoscope to facilitate a connection between the bronchoscope and the anesthesia circuit.

Anesthetic technique may be modified in accordance with the child's age and the suspected diagnosis, the underlying impairment of oxygenation and ventilation, the estimated duration of the procedure, and the training and experience of both the endoscopist and the anesthesiologist. The choice of anesthetic agents and techniques often is driven by the diagnosis. In evaluating a patient with stridor or other evidence of a compromised lumen, spontaneous breathing allows for the dynamic assessment of the pathophysiology that is critical for appropriate diagnosis. Anesthesia can be induced with either intravenous (sodium thiopental, ketamine, or propofol) or inhalation (sevoflurane) agents with oxygen. Inhaled rather than fixed agents are preferred when high-grade obstruction of the upper airway is suspected, because their effect is more readily reversed, and they more reliably preserve spontaneous ventilation during induction. In either case, after induction of anesthesia, total intravenous anesthesia (as with an infusion of propofol and alfentanil, for instance) avoids the disadvantageous situation of nonscavenging of inhaled anesthetics, with exposure of inhaled anesthetics to the health care team. Nitrous oxide must be used with caution in patients with compromised oxygenation, and it is contraindicated in patients with air trapping because of the risk of lung overinflation. Heliox, a low-density gas mixture that contains 70% helium and 30% oxygen, seems to be effective for improving the respiratory condition of infants with acute bronchiolitis or croup by increasing laminar gas flow through the narrowed bronchioles, thereby improving gas delivery and reducing accompanying tachycardia and tachypnea.[117]

After the patient is adequately anesthetized, the airway can be sprayed with 4% lidocaine, which provides local anesthesia to the larynx and trachea and reduces the total requirement of anesthetic agents. Lidocaine doses up to 7 mg/kg have been proved to be safe if they are administered over 15 minutes.[118] Intravenous lidocaine (1 to 2 mg/kg) is helpful,[119] but it is not as effective as the properly administered topical agent.

Use of a pediatric bronchoscope and rod lens telescope permits good visualization of the airway while oxygen with or without an inhaled anesthetic is delivered by way of the side-arm attachment. Use of the 2.5-, 3.0-, and 3.5-mm internal-diameter bronchoscopes, however, is associated with increased resistance to breathing. In combination with anesthetic agents that depress respiration, this increased resistance may result in compromised ventilation and oxygenation during spontaneous breathing.[120] The telescope should be removed periodically to allow the child to breathe without the resistive load. Constant communication between the anesthesiologist and the endoscopist is essential.

When spontaneous ventilation is not necessary, the adjunctive administration of short-acting muscle relaxants can allow the use of lighter planes of anesthesia. Propofol can be used adjunctively with airway topical anesthesia and a muscle relaxant or narcotic. Propofol has the advantage that it can be given continuously during the procedure, thereby resulting in a more constant level of anesthesia than can be achieved with inhalational agents, the delivery of which may be interrupted repeatedly. The choice of muscle relaxant can be made on the basis of the anticipated duration of the procedure. In practice, most bronchoscopic procedures are performed without any muscle relaxant; paralysis is the exception rather than the rule. Infusion of a short-acting narcotic (e.g., alfentanil, remifentanil) may be an alternative to a muscle relaxant, thereby allowing for adequate depth of anesthesia without muscle relaxation. Another advantage of total intravenous anesthetic is that the health care professionals in the room are not exposed to the inhalational gases that cannot be scavenged effectively using the side arm of a bronchoscope.

During the removal of a foreign body, close communication between the anesthesiologist and the endoscopist is essential. A joint decision should be made about maintaining spontaneous ventilation versus using positive-pressure ventilation. Adequate relaxation of the upper airway and glottis reduces the risk that the foreign body will be lost when it is pulled out of the airway with the grasping forceps and the bronchoscope.

In 1967, Sanders described a system in which oxygen at 50 to 60 psi was directed down the bronchoscope in intermittent bursts.[121] With this system, duration of bursts is determined by balancing chest rise with estimated airway pressures. Exhalation is then passive and depends on the recoil of the chest wall musculature. Although the device usually is successful for both oxygenating and ventilating patients, a number of potential problems exist. Because room air is entrained by the Venturi effect, hypoxemia may be seen in some patients. Peak inflation pressures and flow rates are influenced by the driving pressure, the diameter and shape of the bronchoscope, the diameter and length of the injector, and the angle from the axial line of the bronchoscope. Because of the smaller diameter of pediatric bronchoscopes, flow rates tend to be lower and inflation pressures to be higher than with use of adult bronchoscopes. Tidal volumes may be low in patients with poor lung compliance. Because of the higher inflation pressures, pneumothorax or pneumomediastinum may occur.[122] Finally, blood, infectious, or particulate matter in the airway may be forced distally by high-pressure bursts.

Hypoxemia and CO_2 retention are the most frequent complications of bronchoscopy. Early detection and prompt intervention usually result in resolution without incident. Pulse oximetry monitoring is mandatory. Monitoring of ventilation with capnography is impossible during bronchoscopy because of dilution of expired gas with high fresh gas flows, making observation of chest wall movement essential. A precordial stethoscope also is useful to auscultate breath sounds. Pneumothorax, although rare, must be kept in mind if acute deterioration of ventilation and oxygenation occurs, particularly if accompanied by a decrease in lung compliance and blood pressure. A portable chest radiograph should be obtained if the index of suspicion is high. Ventricular premature beats can occur in the presence of hypercarbia and light levels of anesthesia. Normal sinus rhythm usually returns promptly with a reduction in the CO_2 tension, an increase in the anesthetic depth, the administration of intravenous lidocaine (1 mg/kg), or a change to another anesthetic agent.

Bronchospasm can also occur during bronchoscopy, particularly in patients with a history of reactive airway disease or active inflammation of the airway. Frequently, bronchospasm results from instrumentation of an inadequately anesthetized airway, particularly if the bronchoscope is in contact with the carina. Removal of the instrument and deepening the anesthetic topically or systemically usually will resolve the problem. If these measures do not, administration of a β-sympathomimetic agent such as aerosolized albuterol (0.05 to 0.15 mg/kg in 5% solution) is indicated.

When the examination is complete, the bronchoscope is removed, and bag-and-mask ventilation with 100% oxygen is instituted. An endotracheal tube may be inserted if the patient is apneic; if bleeding, presence of secretions, or difficult anatomy makes the airway tenuous; or if the patient has a full stomach. Otherwise, the patient may be awakened without an endotracheal tube so long as close observation by qualified personnel can be provided until airway reflexes have returned.

Adenotonsillectomy

Adenotonsillectomy has become a less common procedure during the past decades, because the indications for this surgery have changed. With more effective antimicrobial therapy, the percentage of patients with recurrent infection as the indication for surgery has declined, and the percentage of patients with obstructive symptoms has increased; today, 75% of tonsillectomies are performed to remove obstructions.[123] With this change has come a greater appreciation that adenotonsillar hypertrophy may lead to obstructive sleep apnea (OSA) (Box 182-2) and, in the extreme, to cor pulmonale (see Chapter 183, Obstructive Sleep Apnea Syndrome). Because of the need to prevent cor pulmonale in patients with OSA, the adenotonsillectomy population has become younger; 60% of children operated on for obstruction are younger than 8 years of age.[124] Of children younger than 3 years who require tonsillectomy, 81% have an obstruction.[124] A careful history of coagulation disturbance in either the patient or a family member should be elicited preoperatively, with appropriate laboratory workup performed only for positive histories.

Box 182-2

ICSD-2 Criteria for Pediatric Obstructive Sleep Apnea

1. Parent or caregiver report of snoring, labored breathing, or other obstructive symptoms during sleep
2. Parent or caregiver report of at least one associated symptom:
   Paradoxical chest wall motion during inspiration
   Movement arousals
   Excessive perspiration
   Unusual sleeping positions (e.g., neck hyperextension)
   Daytime symptoms: hyperactivity, aggressive behavior, or sleepiness
   Impaired growth
   Headache on waking
   Secondary enuresis
3. Polysomnograph (PSG) documents at least one scoreable respiratory event lasting at least two respiratory cycles in duration per hour of sleep (criteria subject to revision as additional data become available)
4. PSG demonstrates either—
   At least one of the following findings:
   i. Frequent arousals associated with increased respiratory effort
   ii. Oxygen desaturation with apneic events
   iii. Hypercapnia in sleep
   iv. Excessively negative esophageal pressure fluctuations
   Periods of abnormal gas exchange during sleep (hypoxemia, hypercapnia, or both) with snoring, paradoxical chest wall motion, and at least one of the following:
   i. Frequent arousals during sleep
   ii. Excessively negative esophageal pressures swings
5. The disorder is not better explained by other sleep disorders, medical or neurologic conditions, or by medication or substance use

From American Academy of Sleep Medicine. *The International Classification of Sleep Disorders*. 2nd ed. Westchester, Ill: American Academy of Sleep Medicine; 2005.

Sedative premedication should be used with caution in children with OSA, because these patients are sensitive to both the sedative and the ventilatory depressant effects of sedative-hypnotic drugs. An inhalation induction is most commonly used, with careful monitoring and attention to airway patency, which often can be improved with jaw thrust, insertion of an oral airway, or the addition of continuous positive airway pressure during spontaneous breathing.

Intubation can be accomplished either with the patient under deep inhalational anesthesia or after the administration of a short- or intermediate-acting nondepolarizing muscle relaxant. An oral Ring-Adair-Elwyn (RAE) tube generally is used because of the low profile it provides under the self-retaining mouth gag. Careful monitoring of breath sounds is necessary, because the tube can become obstructed or dislodged during placement, insertion of and removal of the mouth gag.

Recently, the flexible laryngeal mask airway (LMA) has begun to be used as an alternative to intubation for adenotonsillectomy.[125] The flexible LMA has tubing that is much more flexible than that of the original LMA, thereby allowing use of the mouth gag without fear of dislodging the LMA from its proper position. Reports thus far suggest that the LMA is safe and reliable for managing the airway during this procedure,[113,126] and its use has become more common. Factors that may contraindicate the use of the LMA include full stomach, inability to ventilate adequately through the LMA, and surgeon preference. One study has directly compared LMA with the endotracheal tube for tonsillectomy, with results suggesting that the use of the LMA resulted in inferior surgical access.[127]

Anesthesia usually is provided with a volatile agent, most often sevoflurane, combined with nitrous oxide and oxygen. Delivered oxygen concentration should be measured at less than 50% before the initiation of electrocautery to prevent airway fires. Muscle relaxants may be used, but they generally are not necessary. Titration of supplemental narcotics helps provide a smooth anesthetic and emergence, but this must be done cautiously in patients with OSA. Because these patients have down-regulation of their mu receptors, their increased sensitivity dictates the use of short-acting narcotics, and in lower-than-usual doses. Once the child awakens, postoperative pain should be appropriately treated, but the total dose of narcotic usually is lower than in patients without OSA for reasons of this down-regulation. The decision regarding timing of extubation is left to clinical judgment, as previously discussed. Patients with OSA usually are extubated while awake, whereas patients without OSA can be extubated deep. If a deep extubation is chosen, thorough pharyngeal suctioning, placement of an oral airway, and lateral head-down positioning allows blood and secretions to drain cephalad.

Occasionally, reoperation is required for persistent hemorrhage; this occurs most commonly during the first 24 hours after the operation or at 7 to 10 days after the operation. Careful assessment of volume status and hematocrit are mandatory, and so is intravenous rehydration before anesthesia induction. Patients requiring reoperation have full stomachs and are candidates for rapid-sequence induction. Awake intubation should be considered if airway anatomy is distorted.

Most adenotonsillectomies can be performed on an outpatient basis, so long as the patient is monitored closely for at least 6 hours postoperatively.[128] Historically, most anesthesiologists have recommended overnight hospitalization after adenotonsillectomy in patients with OSA. However, a study that found improvements in polysomnograms in patients with mild OSA the night after adenotonsillectomy suggests that hospitalization is necessary only for high-risk patients.[129] At particular risk are children with OSA who are younger than 3 years of age, because the incidence of airway complications and delayed oral intake is higher in this age group. Other conditions that increase risk include cerebral palsy, seizure disorders, congenital heart disease, definitive syndromes, and prematurity.

Laryngeal Surgery

Like bronchoscopy, laryngeal surgery is challenging for the anesthesiologist, because the airway is shared with the surgeon and because the surgery often is performed on infants with congenital laryngomalacia, laryngeal clefts or webs, vocal cord disorders, or laryngeal tumors. Other common indications are acquired subglottic stenosis and recurrent laryngeal papillomatosis.

Several techniques allow the surgeon and the anesthesiologist to occupy the airway simultaneously. One such technique is the spontaneous ventilation technique, which is useful when the surgeon needs to assess airway dynamics.[130-132] If inhalation technique is used, the delivered concentration of agent must be high enough to prevent coughing or laryngospasm but not so high as to cause significant cardiovascular depression or apnea. Because this balance is difficult to achieve, especially with short-acting inhalation agents, adjunctive agents (e.g., propofol, narcotics) may be used to reduce the need for high concentrations of inhalational agent. Thorough topical anesthesia with 4% lidocaine (delivered either by atomizer or by syringe with a metal or plastic introducer needle) provides additional anesthesia and also may reduce systemic anesthetic requirements. As noted previously, a continuous infusion of propofol may be used instead of an inhalational agent to reduce operating room pollution and to provide a stable anesthetic level.

The spontaneous ventilation technique has been very useful for children with recurrent papillomatosis. The anesthetic technique for these children is basically the same as that described for bronchoscopy. Many of these children become psychologically sensitized by frequent needs for laser surgery, making good behavioral support important.

Premedication usually can be used in this population, unless the airway is particularly marginal. Child life or similar services have behavioral support programs that can also be especially helpful for these children. Often just the sight or smell of the anesthesia mask or inhalational agent can be quite anxiety-provoking for these children. An acceptable alternative to mask induction may be EMLA cream application followed by an intravenous start (sometimes with a butterfly needle) and then a propofol induction.

The apnea technique may be preferred if spontaneous ventilation is not necessary and if the anesthesiologist is uncomfortable with the unprotected airway. Anesthesia is provided with a combination of a muscle relaxant, high-concentration oxygen, and halothane or propofol. Topical anesthesia of the airway is accomplished before intubation. After the suspension laryngoscope is set up, the tube is removed, and the surgeon proceeds while the patient is apneic. The tube is replaced when the pulse oximeter indicates decreasing saturation, with a threshold established by the team. Repeated reintubation and ventilation are performed until the procedure is completed. The potential for CO_2 retention is high, particularly if only short periods of ventilation are used between periods of extubation and apnea.

Supraglottic jet ventilation incorporates the use of an intravenous anesthetic such as propofol with a muscle relaxant. After topical anesthesia is provided to the airway, the suspension laryngoscope is introduced, and a jet-ventilating device is attached. The characteristics and potential risks of this technique are the same as those for rigid bronchoscopy.

Finally, it is possible to place a small endotracheal tube around which the surgeon works, although this frequently proves to be awkward. With the availability of small-cuffed endotracheal tubes, older children can be more effectively ventilated with these smaller-diameter tubes.

SUGGESTED READINGS

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CHAPTER ONE HUNDRED AND EIGHTY-THREE

Obstructive Sleep Apnea Syndrome

Laura M. Sterni

David E. Tunkel

Key Points

- Obstructive sleep apnea syndrome (OSAS) is a common medical condition that can lead to significant morbidity in children.
- Sequelae of OSAS in children include poor growth, learning and behavior problems, and cardiovascular complications, with potential long-term consequences.
- The definitive diagnosis of OSAS in children is made using overnight polysomnography. Adult criteria for the scoring and interpretation of polysomnographic data cannot be applied to children.
- First-line therapy for OSAS in most children is adenotonsillectomy, with improvement expected in many. Children with severe OSAS or with significant risk factors for OSAS beyond adenotonsillectomy may require further evaluation and therapy.
- Children with OSAS at risk for postoperative respiratory compromise may be identified preoperatively. Risk factors include age younger than 3 years, severe OSAS documented by polysomnography, and abnormalities of upper airway tone or structure, as may be seen in children with neuromuscular disease, craniofacial anomalies, or obesity.
- Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) are the most commonly used nonsurgical modalities for management of OSAS and can be applied safely and successfully in children.

The stupid-lazy child who frequently suffers from headaches at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes up with a dry mouth in the morning, is well worthy of the solicitous attention of the school medical officer.

—W. Hill, 1889[1]

More than 100 years ago, clinicians began to recognize the manifestations of sleep-related breathing obstruction in children. Today, the obstructive sleep apnea syndrome (OSAS) is recognized as a common and important pediatric health problem. Sleep-related upper airway obstruction can lead to a variety of nighttime and daytime symptoms in children. If diagnosis and treatment are delayed, the consequences of OSAS can be severe.

Classification of Sleep-Related Upper Airway Obstruction

Snoring is the common feature of three clinical syndromes of sleep-related upper airway obstruction in children. The diagnoses of primary snoring, upper airway resistance syndrome (UARS), and OSAS separate patients according to the severity of their sleep-related upper airway obstruction and resulting clinical complications.

Primary Snoring

Approximately 10% of children snore during sleep on most or all nights, and the majority of these children have primary snoring.[2-5] *Primary snoring* has been defined as snoring during sleep without associated apnea, gas exchange abnormalities, or excessive arousals.[6] The factors that predispose children to primary snoring are similar to those described for OSAS and are discussed in detail later in this chapter. Major risk factors for snoring in otherwise healthy children are obesity, decreased nasal patency (rhinitis, septal deviation, nasal obstruction), and adenotonsillar hypertrophy.[7,8] Snoring in 6- to 13-year-old children also has been strongly associated with parental cigarette smoking.[4,7]

Primary snoring does not appear to progress to OSAS in young children and may resolve over time. Investigators have performed polysomnography in children 1 to 3 years after their diagnosis of primary snoring and found no significant difference in the apnea index or nighttime gas exchange.[9,10] Ali and coworkers found that 50% of children who were described by their parents as habitual snorers at 4 years of age had stopped snoring without treatment at a 2-year follow-up evaluation.[2]

In the past, primary snoring was considered a benign condition; however, more recent studies have challenged this assumption. O'Brien and colleagues found that primary snoring was associated with an increased probability of neurobehavioral deficits in children.[11] Daytime symptoms such as sleepiness, inattention, aggressiveness, and hyperactivity are reported commonly in habitual snorers and children with OSAS.[3,12-15] Disrupted microsleep architecture has now been demonstrated in children with primary snoring, providing a possible link between neurocognitive dysfunction and habitual snoring in children.[16,17]

Upper Airway Resistance Syndrome

Children with UARS snore and have partial upper airway obstruction that leads to repetitive episodes of increased respiratory effort ending in arousals and sleep fragmentation. Daytime symptoms similar to those seen with OSAS may exist.[18-20] Children with UARS have no evidence

Table 183-1

Childhood versus Adult Obstructive Sleep Apnea Syndrome

Feature	Adults	Children
Presentation		
Excessive daytime sleepiness	Main presenting complaint	Infrequent complaint
Associated obesity	Majority of patients	Minority of patients
Underweight/failure to thrive	Not seen	Frequent finding
Daytime mouth-breathing	Not seen	Frequent finding
Gender	Male/female = 2:1	Male/female = 1:1
Enlarged tonsils and adenoids	Rarely seen	Frequent finding
Sleep Pattern		
Obstructive	Obstructive apnea	Obstructive apnea or obstructive hypoventilation
Arousal with obstruction	Common	May be less frequent
Disrupted	Common	Not often seen
Management		
Surgical	Minority of patients with inconsistent results	Definitive in many
Medical (positive pressure)	Most common management	Only in selected patients

Adapted from Carroll JL, Loughlin GM. Diagnostic criteria for obstructive sleep apnea syndrome in children. *Pediatr Pulmonol*. 1992;14:71.

of apnea, hypopnea, or gas exchange abnormalities on polysomnography. The diagnosis of UARS currently is made with the use of esophageal pressure monitoring to identify increased respiratory effort with related arousals. When polysomnography is performed without esophageal pressure monitoring, snoring with marked paradoxical breathing movements or repetitive arousals may be suggestive of UARS. Treatment options for UARS are identical to those for OSAS and are discussed later in the chapter. The incidence of UARS in children is unknown, but some centers believe it may be more common than OSAS.[19]

Obstructive Sleep Apnea Syndrome

Approximately 1% to 3% of all children will have OSAS, and as many as 40% of snoring children referred to a sleep clinic or otolaryngologist may have OSAS.[21-25] Childhood OSAS has been defined as episodes of upper airway obstruction during sleep that usually are associated with a reduction in oxyhemoglobin saturation or hypercarbia, or both. Sleep-related upper airway obstruction in children may manifest as obstructive apnea or obstructive hypoventilation.[26] Obstructive hypoventilation results from continuous partial airway obstruction, which leads to paradoxical respiratory efforts, hypercarbia, and often hypoxemia. This pattern may be more common in children, who are less prone than are adults to collapse of the upper airway.[27] Diagnosis of obstructive hypoventilation in children requires end-tidal CO_2 monitoring during polysomnography. Despite the absence of complete airway obstruction during sleep, children with obstructive hypoventilation are at risk for all of the reported complications of OSAS.

Obstructive hypoventilation generally is not seen in adults with OSAS. A number of other important differences between adults and children with OSAS are detailed in Table 183-1.

Symptoms and Signs of Childhood Obstructive Sleep Apnea Syndrome

Children with OSAS almost always present with a history of snoring and difficulty breathing during sleep.[23,28,29] Parents often report nighttime sweating, restlessness, and unusual sleeping positions in their affected children. Chest retraction, use of accessory muscles, and paradoxical rib cage motion during inspiration are seen during episodes of upper airway obstruction. Paradoxical breathing (inward movement of the thorax during inspiration) can be normal during sleep in infants and toddlers. During rapid eye movement (REM) sleep, the tonic and phasic activity of the intercostal muscles disappears, and the infant chest wall becomes more compliant. The negative intrathoracic pressures generated during inspiration result in the paradoxical inward movement of the thorax. Paradoxical breathing decreases with age and is rare in healthy children older than 3 years of age.[30] Paradoxical respirations in older children are almost always the result of upper airway obstruction.

Enuresis has been associated with OSAS in children but is not a consistent finding.[29,31,32] Enuresis associated with OSAS may be related to disrupted, restless sleep patterns that affect arousal. Several studies have reported resolution of nocturnal enuresis after adenotonsillectomy in children with symptoms of nocturnal upper airway obstruction or polysomnography that is diagnostic for OSAS.[33-35]

Daytime symptoms associated with OSAS include mouth breathing, nasal obstruction, and hyponasal speech. Morning headaches have been associated with nighttime breathing obstruction, but controlled studies comparing children with OSAS with children with normal polysomnography results have found no significant difference in the frequency of this symptom.[29,31,36] Adults with OSAS often present with excessive daytime sleepiness, but this complaint is less frequent among children with OSAS.[23,31,32,37] OSAS can lead to significant cardiopulmonary complications, poor growth, and problems with learning and behavior. These important sequelae are discussed next.

Complications of Childhood Obstructive Sleep Apnea Syndrome

Growth Impairment

Failure to thrive was commonly described in early reports of children with OSAS.[28,29,36] Although overt failure to thrive is now seen less frequently, as a result of earlier diagnosis and management of OSAS, children with OSAS often grow poorly. Improved growth has been reported in childhood OSAS after treatment with adenotonsillectomy.[38-40] Marcus and colleagues reported decreased growth in children with even mild OSAS that appeared to be related to the increased work of breathing during sleep. After adenotonsillectomy, the patients had improved growth and decreased energy expenditure during sleep.[38] Nocturnal growth hormone secretion also appears to be decreased in children with sleep-related upper airway obstruction.[41] OSAS should be considered in the differential diagnosis for failure to thrive or impaired growth that is unexplained by other conditions.

Behavior and Learning Problems

Sleep-related breathing obstruction in children can lead to significant neurocognitive and behavioral complications. A comprehensive review

of available data shows that pediatric OSAS is associated with shortfalls in academic performance, deficits in behavior and emotional regulation leading to problems such as hyperactivity and aggressiveness, difficulty with sustained and selective attention, and decreased alertness.[42] It also has been suggested that childhood OSAS may lead to problems with memory, intelligence, and executive functioning, but findings are inconclusive to date. Although the exact cause-and-effect relationships are unknown, both sleep fragmentation and intermittent hypoxia are emerging as likely components in the pathophysiology of neurobehavioral morbidity associated with sleep-disordered breathing.[43-45] Gozal and associates found that a group of children with OSAS and neurocognitive abnormalities had significantly increased levels of morning C-reactive protein when compared with children with OSAS and no cognitive dysfunction and with control subjects (i.e., children without OSAS).[46] This finding suggests that the greater the inflammatory response elicited by OSAS, the greater the risk of neurocognitive dysfunction, possibly secondary to neuronal injury.

In an encouraging trend, several studies have documented posttreatment improvement in children with OSAS who exhibited preoperative disturbances in behavior and cognition.[39,47-50] In one study of 12 children with moderate to severe OSAS, a significant reduction in inattention, aggression, and hyperactivity was seen after treatment, as assessed by the Conners Parent Rating Scale. The study authors also noted an improvement in vigilance on a continuous performance task.[47] Owens and colleagues found modest improvement after treatment in a small group of children with mild to moderate OSAS who had behavioral problems and mild deficits in executive functioning, attention, and motor skills.[50] Gozal reported evidence of learning difficulties in children with OSAS by documenting an increased incidence of snoring and nocturnal gas exchange abnormalities in a group of 297 first-grade children who were in the lowest 10th percentile of their class.[48] Of perhaps greatest interest, the children with sleep-associated gas exchange abnormalities who received treatment showed an improvement in academic performance in the second grade, whereas no academic improvements were seen in the affected children whose parents did not seek therapy.

Mitchell and Kelly assessed behavioral abnormalities in children with OSAS using the Behavioral Assessment System for Children before adenotonsillectomy, and again within 6 months after surgery and 9 to 18 months after surgery.[51] These investigators found improvements in behavioral measures after adenotonsillectomy that seemed to persist during long-term follow-up, although to a lesser degree than seen shortly after surgery. Similarly, Chervin and coworkers found that children undergoing adenotonsillectomy for any clinical indication (most often, suspected sleep-disordered breathing in this study) had increased difficulty with hyperactivity, inattention, and daytime sleepiness and were more likely to be diagnosed with attention deficit–hyperactivity disorder than control children undergoing other surgical procedures.[49] At 1 year after adenotonsillectomy, improvements were seen in all measures.

Clearly, sleep-disordered breathing, even in the mild to moderate range, carries a risk for significant and at least partially reversible neurobehavioral morbidity. It is not clear, however, if the cognitive and behavioral complications of OSAS are completely reversible. Gozal and Pope reported that children with lower academic performance in middle school were more likely to have snored loudly and frequently and to have required an adenotonsillectomy for snoring during early childhood.[52] These investigators suggested that the neurocognitive effects of sleep-related upper airway obstruction in young children may be only partially reversible and lead to a "learning debt" that adversely influences subsequent school performance. The diagnosis of OSAS should be considered in children with learning and behavior disorders. Although the ultimate prognosis remains uncertain, early recognition and therapy may help reduce possible life-long neurobehavioral limitations.

Cardiopulmonary Complications

Severe untreated OSAS can lead to pulmonary hypertension and cor pulmonale (Fig. 183-1).[28,29] Pulmonary hypertension results from the recurrent, severe, nocturnal hypoxemia, hypercarbia, and acidosis that occur during obstructive hypoventilation and apnea. Cor pulmonale generally is reversible with treatment for OSAS, but perioperative precautions are required in these high-risk patients. Amin and colleagues found that OSAS in children led to structural changes and hypertrophy of both right and left ventricles.[53] Most notably, the left ventricular hypertrophy seen in their OSAS patients was related to the degree of severity of the OSAS. These workers noted that left ventricular hypertrophy is a known risk factor for future cardiovascular disease. A follow-up study in children demonstrated a "dose-dependent" decrease in left ventricular diastolic function with increasingly severe OSAS.[54] Systemic hypertension, a frequent complication of adult OSAS, also has been reported in children with OSAS.[29,55-57] Pediatric OSAS has been shown to be associated with an increased systemic inflammatory response thought to increase the risk for atherosclerotic disease, as demonstrated by elevated levels of C-reactive protein and changes in levels of proinflammatory and anti-inflammatory cytokines.[58-60] Improvement in these inflammation indicators was noted after adenotonsillectomy, supporting the importance of early diagnosis and treatment of OSAS to avoid long-term cardiovascular morbidity.[58,59]

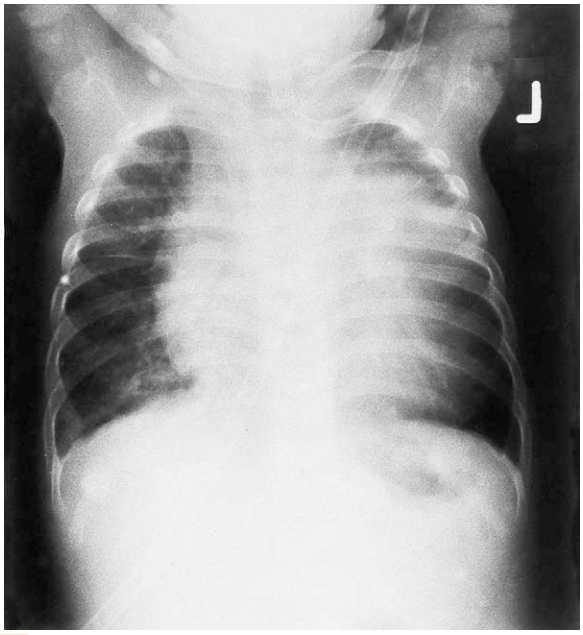

Figure 183-1. Chest radiograph of a child with cor pulmonale secondary to obstructive sleep apnea syndrome.

Pathophysiology of Obstructive Sleep Apnea

The upper airway is a collapsible muscular tube that includes the nasopharynx, oropharynx, and hypopharynx. Patency of the upper airway is determined by the tonic activity of the pharyngeal dilating muscles, as well as phasic contraction of these muscles in response to negative upper airway pressure (inspiration). Skeletal and soft tissue structures such as the tonsils and adenoids affect upper airway diameter and resistance and are important in determining airway patency. During sleep, reduced upper airway inspiratory muscle tone and diminished reflex dilation lead to airway narrowing. These effects are most pronounced in REM sleep, leading to increased obstructive events in predisposed patients.

In otherwise healthy children, adenotonsillar hypertrophy is a significant risk factor for OSAS.[36] However, no strict correlation has been found between size of the lymphoid tissues and the presence or severity of sleep-related breathing obstruction.[61-63] One child with significantly enlarged tonsils and adenoids may be asymptomatic (i.e., have no difficulty with sleep-related upper airway obstruction), whereas another with only moderate adenotonsillar hypertrophy will have severe OSAS. Furthermore, OSAS develops in only a small percentage of children with adenotonsillar hypertrophy. It is likely that a combination of structural factors and neuromotor abnormalities must be present for OSAS to occur.

Marcus and associates demonstrated that the pediatric upper airway behaves as a Starling resistor.[64] In the Starling resistor model, maximum inspiratory flow through the collapsible upper airway is determined by upstream (nasal) pressure and the pressure surrounding the collapsible segment. When airway collapse occurs, flow is independent of the downstream (tracheal) pressure. Airway collapse occurs when the pressure surrounding the airway becomes greater than the pressure within the collapsible segment. The pressure outside the airway is dictated by structural factors, as well as activity of the airway dilator muscles. These investigators found that children with OSAS had greater airway collapsibility than those with primary snoring. Although airway collapsibility was reduced after adenotonsillectomy in children with OSAS, it remained greater than in the patients with primary snoring.

Structural factors other than adenotonsillar hypertrophy may play a role in OSAS in otherwise healthy children. Arens and colleagues used magnetic resonance imaging to study the airway of children with OSAS and found a smaller upper airway volume than in control subjects.[65] In a second study, Arens' group found that the upper airway of children with OSAS was restricted along the upper two thirds, with greatest narrowing in the region of overlap of the tonsils and adenoids.[66]

Isono and associates studied children with OSAS who were given neuromuscular blockade under general anesthesia. These researchers found that the closing pressure of children with OSAS was positive and greater than that of normal children.[67] Collapsibility of the retropalatal and retroglossal segments was significantly increased in their OSAS subjects. They also determined that the cross-sectional area of the narrowest segment of the airway was significantly smaller in children with OSAS.

It appears that children with OSAS have subtle abnormalities in upper airway structure or neuromuscular control, in addition to adenotonsillar hypertrophy.

High-Risk Groups

Adenotonsillar hypertrophy is the leading cause of childhood OSAS. A number of other medical conditions also are strongly associated with OSAS in children, as listed in Table 183-2. Close follow-up is indicated in children in these high-risk groups to look for the development of signs and symptoms that may suggest sleep-related airway obstruction. Such signs and symptoms warrant polysomnographic testing to assess for the presence and severity of OSAS.

Obesity

Obese children are at risk for sleep-related breathing obstruction.[68,69] Deposition of adipose tissue within the muscles and soft tissues surrounding the upper airway in combination with external compression from the neck and jowls leads to upper airway narrowing in these patients.[70] Upward displacement of the diaphragm by the obese abdomen when the affected child is supine and decreased chest wall compliance lead to lower lung volumes during sleep, decreased oxygen stores, and increased risk of desaturation with obstructive events. Obese children are at increased risk for persistent OSAS after adenotonsillectomy. Mitchell and Kelly studied 30 obese children with OSAS and found a decrease in respiratory disturbance index (RDI) (see later under "Polysomnography") from a mean of 30 preoperatively to a mean of about 12 after adenotonsillectomy.[71] Although all children had an improved quality of life as defined by a validated questionnaire, OSAS was decreased in severity but not cured in these obese children.

Craniofacial Abnormalities

Children with craniofacial anomalies often have a multifactorial etiology for OSAS. Evaluation is directed toward examination of craniofacial issues such as skull base shape, maxillary size and shape, tongue size and support, and mandibular size and shape. Concomitant central nervous system abnormalities can affect pharyngeal tone, and any coexisting laryngotracheal anomalies should be evaluated. OSAS in such children may persist after adenotonsillectomy, and additional surgical and nonsurgical therapies may be necessary. Infants with craniofacial anomalies can be difficult to treat and may require tracheotomy.

Children with skeletal dysplasias such as achondroplasia may have mixed apnea syndromes. Compression of the brainstem at the craniocervical junction may cause abnormalities of ventilatory drive and central apnea. Cervicomedullary compression also can affect upper airway control, leading to airway obstruction during sleep. Adenotonsillar enlargement and the craniofacial features seen in these patients may also contribute to the development of OSAS.[72] Sisk and associates diagnosed OSAS in 38% of children with achondroplasia.[73] Adenotonsillectomy usually is effective, but additional therapy with continuous positive airway pressure (CPAP) or tracheotomy may be needed in such complicated cases.[74] Craniocervical decompression has been used in some patients with achondroplasia, but the effects on OSAS remain controversial.[75]

Table 183-2

Medical Conditions Associated with Obstructive Sleep Apnea Syndrome*

Achondroplasia and similar skeletal dysplasias
Apert's syndrome
Beckwith-Weidemann syndrome
Cerebral palsy
Choanal stenosis or atresia
Cleft palate after repair
Crouzon syndrome
Cystic hygroma
Down syndrome
Goldenhar syndrome/hemifacial microsomia
Hallermann-Streiff syndrome
Hypothyroidism
Klippel-Feil syndrome
Mucopolysaccharidosis
Obesity
Osteopetrosis
Papillomatosis (oropharyngeal)
Pierre Robin sequence
Pfeiffer's syndrome
Pharyngeal flap surgery
Prader-Willi syndrome
Sickle cell disease
Treacher Collins syndrome

*Other conditions not listed also may be associated with this syndrome.
Adapted from Marcus CL, Carroll JL. Obstructive sleep apnea syndrome. In: Loughlin GM, Eigen H, eds. *Respiratory Disease in Children: Diagnosis and Management*. Baltimore: Williams & Wilkins; 1994:475-499. Used with permission.

Neuromuscular Disease

Cerebral palsy in children is associated with decreased pharyngeal tone, resulting in OSAS. Adenotonsillectomy is a useful initial procedure for OSAS associated with pharyngeal hypotonia.[76] These children are at high risk for respiratory complications or persistent OSAS after adenotonsillectomy.[77-79] When pharyngeal hypotonia is marked, tracheotomy may be necessary to relieve OSAS. Aggressive craniofacial and pharyngeal surgical approaches have been used to avoid tracheotomy in neurologically impaired patients with OSAS.[80] Primary muscular diseases such as Duchenne muscular dystrophy also have been associated with the development of OSAS secondary to loss of upper airway muscle tone.[72]

Patients with Down syndrome have a high incidence of OSAS. A study of OSAS in these patients found that adenotonsillectomy alone was not adequate therapy for more than 60% of the patients.[81] It was concluded that the generalized hypotonia and anatomic abnormalities such as obesity, macroglossia, and midfacial and mandibular hypoplasia all contribute to nocturnal airway obstruction in these patients. Lefaivre and coworkers described a multilevel surgical approach to the manage-

ment of OSAS in children with Down syndrome, using a combination of facial and mandibular bony advancement and pharyngeal soft tissue surgery to achieve improvement in sleep-related upper airway obstruction.[82] Merrell and Shott described the use of lateral pharyngoplasty (plication of the tonsillar pillars), along with adenotonsillectomy, in children with Down syndrome but found polysomnographic abnormalities in 75% of these children after adenotonsillectomy with or without this modification.[83]

Mucopolysaccharidoses

Mucopolysaccharidoses, such as the Hunter and Hurler syndromes, are associated with severe progressive OSAS in affected children. The head and neck manifestations in these syndromes include short neck, depressed nasal dorsum, macroglossia, adenotonsillar enlargement, and craniofacial abnormalities.[84] Bredenkamp and colleagues reported upper airway obstruction in 17 of 45 patients (38%) with mucopolysaccharidoses, 7 (16%) of whom required tracheotomy.[85] Leighton and associates found OSAS in more than 90% of patients with mucopolysaccharidoses, with the most severe OSAS found in the Hurler and Hurler-Scheie types.[86] Laryngeal tissues can be infiltrated and tracheal size decreased from mucopolysaccharide deposition, leading to airway obstruction at multiple levels.[87] Adenotonsillectomy and tracheotomy may be part of the surgical treatment of OSAS in such complicated cases.[88] Although its clinical applications are far from clear, enzyme replacement therapy may stabilize mild OSAS in children with Hurler syndrome and may improve upper airway size.[89]

Acute-Onset or Rapidly Progressive Obstructive Sleep Apnea Syndrome

Abrupt onset or rapid progression of OSAS in children suggests rapid enlargement of lymphoid tissue in the pharynx or other lesions rapidly growing near the airway. Viral syndromes can be associated with marked lymphoid hyperplasia and severe OSAS in children, the common example being infectious mononucleosis secondary to Epstein-Barr virus infection. Acute OSAS associated with Epstein-Barr virus infection is treated with a nasopharyngeal airway and steroids until the lymphoid hyperplasia resolves.[90]

Malignant and benign tumors of the head and neck may cause sleep-related upper airway obstruction, as discussed later on. A full head and neck examination should be directed at a search for intrinsic and extrinsic masses causing airway compromise. Biopsy, when clinically indicated, should be performed to direct additional therapy.

Diagnosis

Early diagnosis and treatment of OSAS in children will result in decreased morbidity. A study by Richards and Ferdman found that the mean period between onset of symptoms and treatment of OSAS in a group of 45 children was 3.3 years.[91] Delays in treatment were related to physician, parent, and third-party factors. Early diagnosis also may be cost-effective: Children with OSAS have been shown to have a 226% increase in health care utilization when compared with control subjects during the 1 year before they receive evaluation and treatment.[92] A clinical practice guideline on the diagnosis and management of OSAS in children released by the American Academy of Pediatrics has recommended that all children be screened for snoring as part of routine health care maintenance.[93] If snoring is reported, a more detailed evaluation is recommended.

History

Numerous studies have demonstrated that OSAS cannot be distinguished from primary snoring in children, based on clinical history and physical examination alone.[23,25,36,94-96] In one report, 89% of parents of children with OSAS observed the child struggling to breathe during sleep, as did 58% of parents of children with primary snoring.[23] A majority of parents of children with both disorders were frightened by their child's nighttime breathing, often staying up nights to watch the child breathe. Goldstein and associates evaluated 30 snoring children referred to a pediatric otolaryngology clinic using a focused history and physical examination in addition to a review of audiotaped breathing of the children during sleep.[25] In only one half of the 18 children believed to have definite OSAS clinically was polysomnography diagnostic for OSAS. In a systematic literature review, Brietzke and coworkers found that 11 of 12 articles in the literature concluded that clinical assessment is inaccurate in the diagnosis of childhood OSAS.[97] Although the clinical history may not be diagnostic, a thorough evaluation of daytime and nighttime symptoms is helpful in planning subsequent studies and interpreting the findings.

Physical Examination

The diagnosis of childhood OSAS is suggested by the patient's history and confirmed by polysomnography. The physical examination should note height and weight, because growth may be impaired by OSAS. Cardiopulmonary abnormalities associated with OSAS should be identified. A full otolaryngologic examination of the head and neck should establish the likely site or sites of dynamic or static airway obstruction.

Tonsil and adenoid size should be assessed in children with symptoms of nocturnal airway obstruction. Signs of adenoidal hypertrophy include decreased nasal airflow with an adequate nasal airway on rhinoscopy, a hyponasal speech pattern, and an open mouth breathing posture. Nasal examination should be focused to exclude obstructive septal deformity, intranasal masses, and mucosal or turbinate swelling within the nose. The oral examination should center on tonsil size and symmetry, pharyngeal dimensions, palate shape and size, and tongue size and motion.

Routine oral and nasal examination can be supplemented with fiberoptic nasal endoscopy to assess nasal patency, adenoid size, and effect of tonsil size and anatomy on awake respiration.[98] Croft and associates used fiberoptic endoscopy to evaluate the site of obstruction in children with polysomnogram-proven OSAS.[62] These workers identified distinct adenoidal, adenotonsillar, tongue base, and laryngeal sites of obstruction based on fiberoptic endoscopy and planned successful surgical therapy based on these findings.

The physical examination of children with craniofacial anomalies is directed at craniofacial structure, jaw size and position, and tongue size and position. Assessment of pharyngeal and laryngeal tone is necessary in children with neuromotor diseases such as cerebral palsy or muscular dystrophy. When sleep-disordered breathing is accompanied by daytime airway symptoms such as stridor or hoarseness, laryngotracheal examination with flexible or rigid endoscopy should be performed.

Polysomnography

Overnight polysomnography in a sleep laboratory is the "gold standard" method for diagnosing childhood OSAS. An accurate diagnosis of OSAS will ensure that appropriate treatment is provided when needed and will avoid unnecessary surgery in patients with primary snoring. The quantitative data obtained from polysomnography also can help predict which children are at risk for perioperative complications. Severe OSAS on polysomnography has been shown in several studies to be an important risk factor for postoperative respiratory compromise after adenotonsillectomy.[78,79]

Pediatric sleep laboratories should involve clinicians with expertise in pediatric respiratory disorders or sleep medicine to ensure that the studies are performed and the findings interpreted appropriately for this age group. Overnight polysomnography is recommended. Although a nap study that is positive for obstructive sleep apnea correlates well with the presence of obstructive apnea on an overnight study, a negative nap study result does not exclude the diagnosis of OSAS.[99] Nap studies are limited by the short recording time and the possible absence of REM sleep periods. The use of sedatives and sleep deprivation are not recommended because both may increase upper airway obstruction artifactually.[100,101]

In children, end-tidal CO_2 should be monitored to detect obstructive hypoventilation. The consensus statement adopted by the American Thoracic Society, Standards and Indications for Cardiopulmonary Sleep Studies in Children, also recommends measurement of (1) respiratory effort, as assessed by movement of the chest wall and abdomen; (2) airflow at the nose or mouth; (3) measurement of arterial oxygen saturation (Sao_2) by pulse oximetry; (4) electrocardiographic recording to monitor cardiac rate and rhythm; (5) electromyography performed

Table 183-3

Polysomnography for Obstructive Sleep Apnea Syndrome in Children

Sleep State
Electroencephalogram
Electro-oculogram (right and left)
Electromyogram (submental)

Respiratory Variables
Abdominal and chest wall movement (strain gauges, inductive plethysmography)
Oronasal airflow (thermistor)
End-tidal CO_2
Arterial oxygen saturation with pulse oximetry

Nonrespiratory Variables
Electrocardiogram
Electromyogram (tibial) to document movements and arousals

Recommended but Not Required
Audiovideo recording

in the anterior tibial region to monitor arousals; and (6) appropriate electroencephalography, electro-oculography, and electromyography measurements for sleep staging[102] (Table 183-3).

Sleep-related upper airway obstruction is diagnosed in children who have more than one obstructive apneic episode per hour or show evidence of significant obstructive hypoventilation. In adults, obstructive apnea is considered abnormal only if the episode lasts more than 10 seconds. Significant obstructive apneic episodes in children often are shorter than 10 seconds. Because of the higher oxygen consumption in children and the fall in functional residual capacity during sleep, Sao_2 may fall after only a few seconds of upper airway obstruction in the infant or toddler. Obstructive apneas or hypopneas lasting two or more consecutive breaths generally are considered abnormal in children. *Obstructive apnea* is defined as near-complete cessation of airflow despite ongoing respiratory effort. *Obstructive hypopnea* is diagnosed when partial upper airway obstruction results in a greater than 50% reduction in airflow associated with either an arousal or a desaturation of 3% or greater from baseline. Generally, obstructive apneas and hypopneas are combined to provide the apnea-hypopnea index (AHI), which reflects the number of discrete obstructive events per hour. Many laboratories may refer to this index as the respiratory disturbance index (RDI), whereas other laboratories will use the RDI to report the number of all scored respiratory events, including central apneas, per hour. Normal children have more frequent central apneas when compared with adults. Only an obstructive event index should be used to make the diagnosis of OSAS.[103]

Obstructive hypoventilation is diagnosed when peak end-tidal CO_2 is greater than 50 mm Hg for 25% or more of total sleep time in the presence of paradoxical respirations or snoring and in the absence of lung disease.[104] *Hypoxemia* is defined as an Spo_2 less than 92% and is correlated with the child's baseline readings and respiratory events. Sleep architecture is examined as well, because an adequate study should contain at least one REM period. Sleep efficiency and frequency of arousal from sleep in association with respiratory events also are analyzed.

Data correlating polysomnographic parameters with clinical outcomes in children are lacking, and no standard guidelines exist for classifying the severity of OSAS. OSAS and obstructive hypoventilation are diagnosed when polysomnographic parameters associated with upper airway obstruction fall outside the values that are currently accepted as normal.[105-107] In our laboratory, we classify children as having either mild, moderate, or severe OSAS based on the clinical

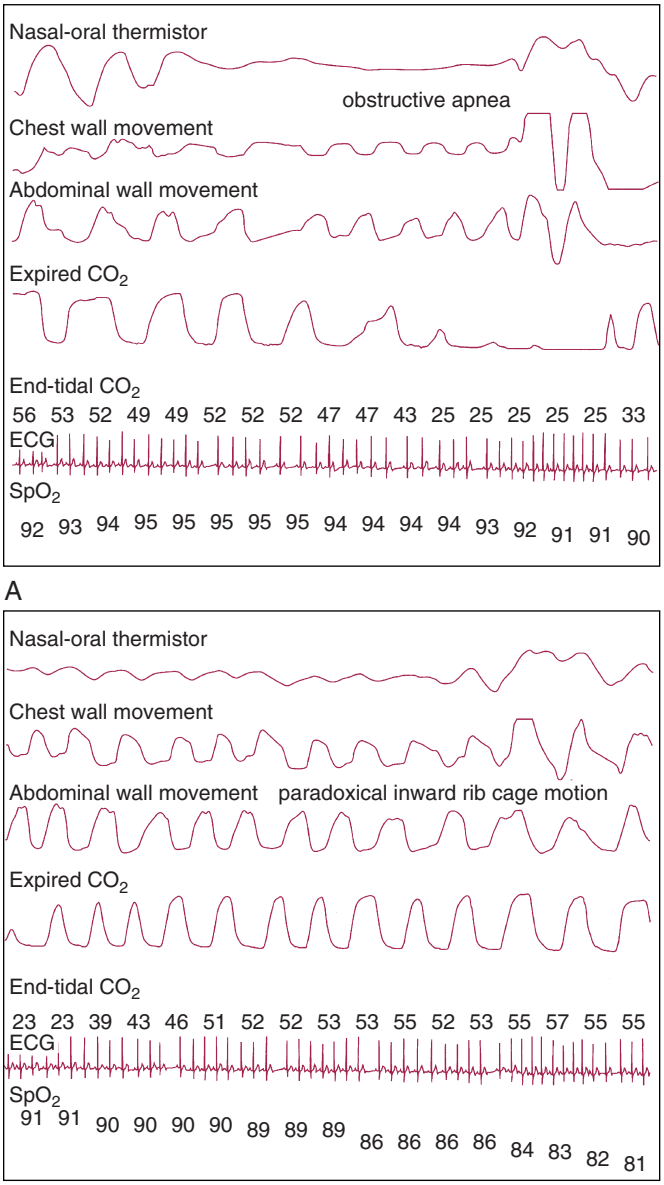

Figure 183-2. Typical polysomnographic recordings. **A,** Obstructive apnea. **B,** Obstructive hypoventilation. Evidence of paradoxical inward rib cage motion is seen in both tracings. In **A,** nasal-oral thermistor and expired CO_2 tracings flatten during the obstructive apneic episode, while respiratory efforts continue. Note the fall in arterial oxygen saturation (specifically, peripheral oxygen saturation [Spo_2]) measured by pulse oximetry that occurs shortly after the approximately 10-second event. In **B,** continuous partial airway obstruction results in elevated end-tidal CO_2 readings and a fall in Spo_2.

picture, number of obstructive events per hour, peak end-tidal CO_2 pressure ($PetCO_2$) or duration of elevated end-tidal CO_2 measurements, and frequency and severity of oxygen desaturation. We classify OSAS as severe if the patient has an obstructive event index of 10 or greater per hour because of the increased risk of respiratory compromise after adenotonsillectomy.[78] Representative polysomnographic tracings from pediatric patients are shown in Figure 183-2.

Other Studies

Because full polysomnography in children may be difficult to obtain, expensive, or inconvenient, screening methods to diagnose OSAS have been investigated. Having medical personnel directly observe a child

experiencing apnea, retractions, and paradoxical respirations during sleep may allow the diagnosis of OSAS.[102] Making a diagnosis by observation, however, does not allow characterization of the severity of the OSAS, which may be important in determining management. Videotapes, audiotapes, and continuous pulse oximetry have been helpful in predicting OSAS when results are positive but unfortunately do not rule out OSAS when results are negative.[108-110] Therefore, children with negative results on screening studies should undergo a more comprehensive evaluation. Likewise, positive results on daytime nap studies have been shown to predict OSAS, whereas negative study results do not exclude the possibility of finding OSAS on an overnight study.[99,111] Questionnaires with emphasis on the symptoms and potential health outcomes of sleep-disordered breathing in children have not been shown to have sufficient sensitivity and specificity to diagnose OSAS in individual patients.[23,31,112,113] Reports from one center suggest that evaluation for sleep-disordered breathing may be accomplished with unattended home polysomnography.[114,115] The home test performed included measurement of oxygen saturation, ventilation, and video recordings. These tests are not widely available, and additional validation of unattended home sleep studies is needed.

Other diagnostic tests may be useful when evaluating a child for OSAS. A chest radiograph, electrocardiogram, and echocardiogram should be considered for any child with symptoms or signs of cardiovascular complications, such as congestive heart failure or hypertension. Children with multiple or lengthy episodes of hypoxemia or extremely severe hypoxemia on polysomnography may require formal cardiopulmonary evaluation as well. Children with these cardiovascular complications of OSAS should have repeat polysomnography after therapy to confirm resolution of OSAS.

Although airway radiographs, cephalometric studies, and computed tomography scans may assist in designing the treatment plan for high-risk children with OSAS caused by unusual anatomic abnormalities, these studies are of limited use in the diagnosis of OSAS in otherwise healthy children. Li and coworkers determined a ratio of tonsil size and pharyngeal depth on lateral radiographs that correlated with severity of OSAS, even though clinical measurements of tonsil size did not.[116] Jain and Sahni were able to predict OSAS based on a ratio of adenoid size to nasopharyngeal depth on lateral radiographs, although clinical tonsil size measurements were not helpful.[117] Sleep fluoroscopy has been described by Gibson and associates for evaluating children at risk for upper airway obstruction at multiple levels.[118] Although dynamic assessments of airway anatomy and function using endoscopy or imaging such as cine-magnetic resonance imaging during sleep have been used in adults with OSAS and in some children with OSAS within a complex clinical picture, these techniques require additional investigation before they can be recommended for widespread use in children.[119,120]

Indications for Polysomnography

Polysomnography remains the gold standard modality for diagnosing sleep apnea in children, because clinical assessment alone is sensitive but not specific for OSAS. The controversies regarding the use of polysomnography in otherwise healthy children with suspected OSAS are reviewed by Messner, who recognizes both the need for this test to diagnose childhood OSAS and the impracticalities of mandatory use before adenotonsillectomy.[121] Children who undergo adenotonsillectomy for recurrent pharyngeal infection may have obstructive symptoms as well. These children do not require polysomnography on a routine basis. Polysomnography is recommended to invetigate concerns that the patient also may have severe OSAS requiring intensive postoperative monitoring. The use of preoperative polysomnography is most controversial in healthy children with obstructive adenotonsillar hypertrophy and no other surgical indication. Historically, adenotonsillectomy has been used to manage obstructive symptoms in healthy children without preoperative polysomnography. In fact, in a recent survey of otolaryngologists and pediatric otolaryngologists by Kay and associates, history alone remains the most common method of establishing OSAS as a surgical indication for adenotonsillectomy in children.[122] Weatherly and colleagues estimated that less than 5% of children with sleep-disordered breathing undergo laboratory-based polysomnography before adenotonsillectomy.[123] An important point is that this practice will lead to potentially unnecessary tonsillectomy in some children with obstructive symptoms but without OSAS.

The use of polysomnography to both diagnose OSAS and assess perioperative risk is recommended in children with suspected sleep-related upper-airway obstruction prior to adenotonsillectomy by both the American Academy of Pediatrics and the American Thoracic Society. The use of preoperative polysomnography is especially important in high-risk patients, including those with craniofacial anomalies, neuromotor disease, or associated medical conditions that may complicate surgical management of OSAS. Baseline preoperative polysomnography is useful to assess postoperative improvement in such high-risk patients. Polysomnography also is useful in the evaluation of children for whom information from the history or physical examination may be inconsistent. Follow-up polysomnography is recommended for children who exhibit persistent snoring or other symptoms of sleep-related upper airway obstruction 4 to 6 weeks after surgery. A follow-up sleep study also should be considered for patients with significant complications from OSAS (e.g., cor pulmonale, failure to thrive), patients with severe OSAS on an initial sleep study, or patients who are very young (younger than 1 year of age) to ensure resolution of nighttime breathing abnormalities.[102]

Surgical Management

Tonsillectomy or Adenoidectomy

Tonsillectomy, adenoidectomy, or adenotonsillectomy is the most common surgical treatment for childhood OSAS. Adenoid and tonsillar hyperplasia appears to be a key element in the compromise of airway patency during sleep in otherwise healthy children with OSAS.[124,125] Brodsky and coworkers demonstrated that children undergoing adenotonsillectomy for obstruction had decreased lateral oropharyngeal dimensions compared with children undergoing adenotonsillectomy for chronic infection.[126] These investigators suggest that decreased oropharyngeal size, in addition to adenotonsillar hyperplasia, may contribute to OSAS in children. Removal of enlarged lymphoid tissue in Waldeyer's ring is curative for most of these children.[39,127-129] Adenotonsillectomy can be recommended for initial treatment of medically complicated children with complex OSAS as well, because this surgical procedure may be curative in appropriately selected children.[130]

Perioperative management of children undergoing adenotonsillectomy for OSAS should be individualized, with the recognition that these children have more frequent postoperative complications and the potential for serious respiratory compromise.[78,79] Children younger than 3 years of age, children with severe OSAS documented by polysomnography, and children with craniofacial anomalies or neuromotor impairment are at greatest risk for perioperative respiratory compromise.[77,78,131-133] Preoperative risk assessment centers on the severity of sleep disturbance as documented by polysomnography. A recent report noted the predictive value of polysomnography in identifying children at risk for respiratory compromise after adenotonsillectomy. The study investigators suggested that preoperative nocturnal oximetry may have similar value.[134] Patients with severe OSAS may be treated with CPAP before adenotonsillectomy if surgery is to be delayed or if significant cardiovascular complications are present. Children with OSAS should undergo routine assessment of hemostatic factors and anesthetic risk for adenotonsillectomy.[135,136]

Preoperative sedation should be used judiciously in children with documented or suspected severe OSAS. Cultrara and coworkers reported on a series of 65 children who were sedated with oral midazolam before adenotonsillectomy for OSAS, diagnosed either clinically or by polysomnography.[137] No adverse respiratory events were seen in any of these patients. In a similar prospective study of 70 children with OSAS, Francis and associates noted brief self-limited respiratory events in only two children after sedation with oral midazolam before adenotonsillectomy.[138] These results should be interpreted with some caution, owing to small numbers in these studies and heterogeneity of the sample population, including variability in the severity of OSAS.

Adenotonsillectomy is performed using standard techniques, with attention to minimizing edema in children at risk for postoperative obstruction. A majority of children who undergo adenotonsillectomy

for mild OSAS experience immediate improvement as shown by sleep studies performed on the first postoperative night.[139] However, children with severe OSAS or complicating anatomic or neuromotor disorders often have a prolonged recovery or incomplete relief of OSAS.[77-79]

Radiofrequency tonsil reduction is a new technique that has been introduced as a potential treatment, in combination with surgical adenoidectomy, for OSAS in children. A pilot study of this technique demonstrated less pain when compared with conventional tonsillectomy and improvement in several clinical and polysomnographic parameters of OSAS.[140] Intracapsular subtotal tonsillectomy using several different surgical methods also has been introduced as a method of reducing perioperative morbidity in children being treated for OSAS.[141-143] Powered intracapsular tonsillectomy and adenoidectomy can reliably achieve at least short-term cure of moderate OSAS as documented by polysomnography in otherwise healthy children.[143a] The long-term efficacy of these techniques, as compared with conventional adenotonsillectomy, needs to be demonstrated in future studies.

Inpatient postoperative management, along with cardiorespiratory monitoring and pulse oximetry, is necessary for high-risk children who have moderate to severe OSAS.[78,133,144] Recovery should occur in an area in which signs of respiratory depression and airway swelling can be recognized and prompt intervention can be instituted.[136] Narcotics should be used judiciously, and postoperative oxygen supplementation should be used with careful monitoring for signs of depression of ventilatory drive. Several studies have demonstrated increased sensitivity to narcotics with regard to analgesic effects and respiratory depression in children with OSAS.[145,146] Steroids often are administered perioperatively, and nasopharyngeal airways are used in high-risk patients to support the airway after surgery. CPAP or bilevel positive airway pressure (BPAP) can be used for children with obstructive symptoms after adenotonsillectomy, including those necessitating airway support in the immediate postoperative period.[147-149]

Expected Results of Adenotonsillectomy for Obstructive Sleep Disorders in Children

Several authors have documented the clinical effectiveness of adenotonsillectomy for nocturnal upper airway obstruction in children.[128,150] Helfaer and colleagues performed polysomnography on otherwise healthy children with mild OSAS on the first night after adenotonsillectomy.[139] The number of apnea events decreased and oxygen saturation during sleep improved immediately after surgery in these children.

In some children, OSAS may persist after surgical treatment. Suen and coworkers reported that children with severe OSAS (RDI greater than 19.1) on preoperative polysomnography were likely to have residual OSAS after surgery.[95] Mitchell and Kelly found persistent OSAS in the majority of children with severe OSAS, as defined by a preoperative RDI 30 or greater, although most were improved by polysomnographic and quality of life measures.[151] In a large cohort of children diagnosed with OSAS by polysomnography, adenotonsillectomy resulted in significant relief of sleep and respiratory abnormalities found preoperatively but resulted in complete cure (defined as as obstructive apnea index of 1 or less) in only 25%.[152] In this study, 29% of the patients had an obstructive event index of 5 or higher after surgery. Children with high preoperative AHI and obese children were the least likely to be cured by surgery. Rapid relief of obstructive symptoms can be expected after adenotonsillectomy in children with mild OSAS, but OSAS may persist in severe cases or in children with significant risk factors for OSAS including obesity.

Brietzke and Gallagher performed a meta-analysis of available literature to try to determine the cure rate for adenotonsillectomy perfomed for childhood OSAS.[153] They identified 14 studies, all case series, and found a post-surgery reduction in AHI by approximately 14 events per hour. The summary success rate was 83%. Gozal and Kheirandish-Gozal reported a cure rate of 77% in a recent review but noted residual OSAS in up to 45% of children after adenotonsillectomy in their own prospective study.[154]

Of interest, more snoring and increased inspiratory effort during sleep were noted in teenagers studied 12 years after adenotonsillectomy.[155] This finding emphasizes the need for long-term study of both the natural history of and treatment outcomes for OSAS in children.

Quality of life improves for children after adenotonsillectomy for sleep apnea. De Serres and colleagues reported the results of a multicenter study of quality of life changes after adenotonsillectomy in children who had adenotonsillectomy for treatment of obstructive sleep disorders.[156] Large changes in quality of life were documented in almost 75% of children, with the most improved domains being sleep disturbance, caregiver concerns, and physical suffering. The OSA-18 is a well-validated quality of life instrument that has been useful in assessing the outcomes of patients treated for sleep-disordered breathing in several studies.[157] Using the OSA-18, Goldstein and associates found similar improvements in quality of life, again with the most significant improvements seen in the domains of sleep disturbance, caregiver concerns and physical discomfort, with concomitant improvements in behavior after adenotonsillectomy.[158] Mitchell and coworkers have documented more long-term quality of life improvements in children at 9 to 24 months after adenotonsillectomy.[159]

Other Pharyngeal Surgery

Resection of palatal and pharyngeal tissue in children as management of OSAS is almost always performed in combination with or subsequent to adenotonsillectomy. Uvulopalatopharyngoplasty (UPPP) is not widely used for the management of children with OSAS. It is used primarily for children at high risk for persistent obstruction because of neuromuscular dysfunction after adenotonsillectomy.[160] Seid and associates reported on the use of UPPP in combination with adenotonsillectomy in 10 children with obstructive apnea and mental retardation with neuromotor disease of diverse causes.[131] Only two patients required additional surgery to relieve OSAS, and one 15-month-old patient with cerebral palsy required subsequent tracheotomy. Tracheotomy was avoided in nine patients, but postoperative sleep studies were not performed.

Kosko and Derkay noted similar favorable results with UPPP combined with adenotonsillectomy in neurologically impaired children with OSAS, with 12 of 15 children showing improvement on pulse oximetry or formal polysomnography.[161] Donaldson and Redmond and also Strome have successfully used UPPP as part of the surgical management of OSAS in children with Down syndrome.[162,163] Kerschner and coworkers treated a diverse group of neurologically impaired children with OSAS with UPPP and adenotonsillectomy.[164] These workers noted long-term improvement in two thirds of their 15 patients but emphasized the need for close follow-up, because one third of their patients had recurrent or persistent upper airway obstruction severe enough to recommend tracheotomy. Potential postoperative velar dysfunction and voice alteration should be considered in the decision-making process for management of such high-risk children with OSAS. Fiberoptic endoscopy of velopharyngeal anatomy may be useful before UPPP is considered, especially in children with poor pharyngeal tone secondary to neuromotor disease.

Tongue reduction surgery has been proposed for the management of macroglossia in conjunction with OSAS, such as is seen in Beckwith-Wiedemann and Down syndromes.[165] Anterior tongue reduction probably improves cosmesis more than airway function, because the central and posterior tongue size may be more critical to airway patency. Rimell and colleagues noted that children with Beckwith-Wiedemann syndrome often required tracheotomy when airway obstruction occurred during the neonatal period.[166] These investigators also found that adenotonsillectomy probably was more beneficial than tongue reduction for managing OSAS in these children with macroglossia. Central tongue reduction has been reported to relieve symptoms of OSAS in children with Down syndrome and other craniofacial disorders.[167,168]

Obstructive sleep apnea has been described in children who have undergone pharyngeal flap surgery for correction of velopharyngeal incompetence.[169,170] Sleep-associated airway obstruction usually is most pronounced in the immediate postoperative period, and obstructive symptoms subside as the flap atrophies during the next several months. In a subset of these children, chronic OSAS may develop that may require flap revision or takedown. Predisposing anatomic factors may include tonsillar or adenoidal hypertrophy, micrognathia, or abnormalities of pharyngeal tone. OSAS after pharyngeal flap surgery appears to be more common in children born with the Pierre Robin

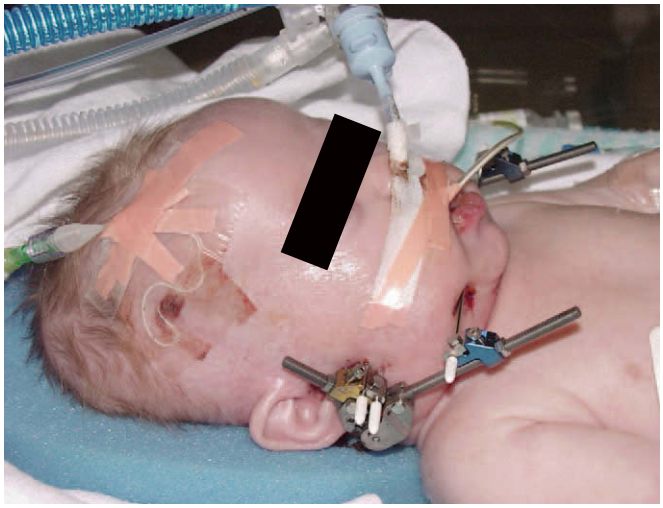

Figure 183-3. Neonate with mandibular distraction device to correct retrognathia.

sequence.[171,172] The need for close follow-up of children after pharyngeal flap surgery is emphasized by Liao and associates, who reported that 90% of children had abnormalities on polysomnograms done 6 months after flap surgery. This group used the strictest criteria for diagnosing OSAS in children: anRDI of 1 or greater.[173] Modifications of the pharyngeal flap technique, including the use of a shorter, more superiorly based flap in a procedure performed several months after planned first-stage adenoidectomy, can reduce the risk of OSAS in syndromic children.[174] Fortunately, when flap division is required for treatment of children with OSAS that persists, the speech and voice benefits of the flap surgery usually are preserved.[175]

Craniofacial Surgery

A variety of surgical procedures have been proposed to manage OSAS in children with complex craniofacial disorders or neuromotor disease. Burstein and associates successfully used mandibular advancement, tongue reduction, tongue-hyoid suspension, and other nasal and pharyngeal procedures to manage children with OSAS with abnormal craniofacial anatomy with or without neuromuscular disease.[167] Tracheotomy was avoided in 90% of this heterogeneous group of children with complex OSAS, including children with hemifacial microsomia, Down syndrome, and cerebral palsy.[176]

Children with severe OSAS and micrognathia may benefit from mandibular advancement or tongue suspension. Tracheotomy often is required in neonates and infants with these conditions to secure the airway until craniofacial growth and neuromotor maturation relieve the sleep-disordered breathing. Tomaski and coworkers have noted that children with isolated Pierre Robin sequence usually can be managed conservatively with nasopharyngeal tube placement and positioning, whereas syndromic children with associated anomalies often require tracheotomy for relief of airway obstruction.[177]

The principles of distraction osteogenesis have been used to treat children with OSAS from isolated mandibular hypoplasia.[178] Mandibular distraction has been used in children with more complex craniofacial conditions such as Treacher Collins syndrome or hemifacial microsomia, both to avoid tracheotomy and to achieve early decannulation.[179,180] A recent study documented dramatic improvement in polysomnographic measures in 10 syndromic children with upper airway obstruction after treatment with mandibular distraction.[181] Lin and associates documented the long-term benefits of mandibular distraction by performing polysomnography 4 years after surgery for neonatal upper airway obstruction[182] (Fig. 183-3). Four children had no evidence of residual or recurrent OSAS, whereas one child had severe OSAS requiring treatment. Midface distraction has been used to achieve decannulation in two patients with achondroplasia and OSAS.[183] Long-term follow-up of these children with complex OSAS-causing conditions is essential after such surgery, especially because relapse of upper airway obstruction after initial improvement has been observed in some children after mandibular distraction.[184]

Tracheotomy

Tracheotomy is indicated for the management of severe OSAS in children with complicated anatomic or neuromotor issues. A review of the literature on pediatric tracheotomy indicated that tracheotomy is now performed more often for dynamic airway issues such as severe OSAS than for fixed airway lesions.[185] Tracheotomy bypasses the areas of airway obstruction during sleep.

Tracheotomy should be considered for patients with severe OSAS associated with neuromotor disease. Tracheotomy can be avoided in some cases by UPPP, pharyngeal surgery, craniofacial surgery, or CPAP.[78,161,167] Although tracheotomy is almost always successful in relieving upper airway obstruction, the decision to perform tracheotomy must be made in the context of underlying medical conditions in the child with OSAS and the recognition of the detrimental effects of tracheotomy on the quality of life.[186]

Other Surgical Management

OSAS may be caused or worsened by nasal abnormalities or nasopharyngeal masses. Choanal atresia or stenosis can cause OSAS in neonates, and transnasal and transpalatal approaches for surgical repair are described earlier in this chapter. Nasal septal deviation as an isolated finding rarely causes childhood OSAS. Septoplasty and turbinate reduction have been used to relieve nasal obstruction and improve nocturnal breathing in adults.

Intranasal masses can cause snoring or OSAS in young infants, and removal usually is curative. Obstructive intranasal masses in children include foreign bodies, inflammatory polyps, mucoceles, and congenital masses such as nasolacrimal duct cysts.

Benign and malignant tumors of the head and neck can manifest with symptoms of OSAS. Supraglottic or parapharyngeal lymphangiomas (cystic hygroma) can cause symptoms of obstructive sleep apnea. Excision of such masses can relieve airway symptoms.[187] Nasopharyngeal carcinoma, juvenile nasopharyngeal angiofibroma, lymphoma, and rhabdomyosarcoma can manifest with obstructive symptoms when nasal or pharyngeal patency is affected. Appropriate oncologic treatment using combinations of surgery, chemotherapy, and radiotherapy can relieve airway symptoms, but airway support may be necessary until tumor regression occurs.

Nonsurgical Management

Children who fail to respond to or are not candidates for surgical intervention often can be managed successfully with nasal CPAP or BPAP.[148,149,188,189] Both modalities are safe, efficacious, and well tolerated by children. The level of positive pressure required to eliminate obstructive apneas and normalize ventilation and nighttime oxygen saturation must be determined in the sleep laboratory. Studies have demonstrated the need for serial evaluation and adjustment of CPAP in growing children, because their pressure requirements will change with time.[148,190]

Complications of CPAP or BPAP usually are minor. Local discomfort or irritation may result from poor mask fit. Regular follow-up to assess mask fit is important. Nasal symptoms such as congestion or rhinorrhea also are common. Nasal steroids or humidification of the delivered air can help relieve nasal obstruction. Hypoventilation and increased central apneas can be seen in children using CPAP or BPAP ventilators.[149] In these children, bilevel ventilation with a back-up rate can be employed. Potentially serious complications of CPAP and BPAP ventilation, including pneumothorax and clinically significant reductions in cardiac output, have not been reported in children treated for OSAS. One case report described the development of midface hypoplasia in a 15-year-old boy treated with nasal CPAP for 10 years for OSAS.[191] With long-term use of a nasal mask in children, regular evaluation of maxillomandibular growth and development is warranted.

Poor compliance is the greatest limitation to the use of CPAP and BPAP in the management of OSAS.[148,192] Pediatric centers have

estimated compliance at 50% to 100%, with adolescents being the least compliant.[148] Rains improved compliance with CPAP therapy in four developmentally delayed children with OSAS by using intensive behavioral interventions including parent training, modeling, and desensitization.[193] In many cases, compliance problems are attributable primarily to the parent or caregiver rather than to the child.[148,192] With careful attention to training of caregivers and children, prompt and aggressive treatment of minor side effects, and close follow-up, the vast majority of families can be trained to successfully use CPAP or BPAP ventilation.

Nocturnal oxygen supplementation has been studied as a temporary treatment for hypoxemia associated with OSAS until definitive therapy can be provided.[194,195] Supplemental oxygen therapy in patients with OSAS may suppress hypoxic ventilatory drive, decrease upper airway tone, and worsen OSAS.[196] Aljadeff and coworkers administered supplemental oxygen to 16 children with OSAS secondary to adenotonsillar hypertrophy and found a decrease in apneic events, lessened paradoxical breathing, increased REM sleep, decreased arousals during sleep without hypoventilation, and increased central apneas.[194] Marcus and colleagues, however, noted significant hypercarbia in 2 of 23 children with OSAS when breathing supplemental oxygen.[195] In most cases, supplemental oxygen therapy will improve oxygenation during sleep without exacerbating sleep-disordered breathing. However, nocturnal oxygen therapy for children with OSAS should be initiated only under monitored conditions. Despite normalization of oxygen saturations, patients with OSAS treated with supplemental oxygen continue to have upper airway obstruction with resulting increased work of breathing, arousals and hypercapnia. Therefore, definitive therapy must still be pursued to prevent the long-term complications of OSAS.

Corticosteroids have been used with some success to treat obstructive symptoms in acute conditions that increase adenoid and tonsil size, such as infectious mononucleosis. A 5-day course of oral prednisone was not effective in treating children with OSAS from chronic adenotonsillar hypertrophy.[197] A few studies have demonstrated a beneficial response to topical intranasal steroids in pediatric patients with OSA. In one small trial, nasal fluticasone given for 6 weeks led to modest improvement in polysomnographic parameters in the treatment group.[198] Many patients, however, continued to have an abnormal apnea index after treatment and a significant number eventually had surgery. In a second study, a 4-week course of nasal budesonide led to an improvement in the mean AHI (from 5.2 to 3.2) and a mean symptom score. The improvement in the symptom score was sustained for several months after discontinuation of therapy.[199] Leukotriene receptor antagonists also have been examined in the treatment of children with OSAS. A small group of children with mild OSAS treated for 16 weeks with daily montelukast were found to have significant reductions in adenoid size and improved breathing during sleep documented by polysomnography.[200] Leukotriene receptor antagonists in combination with intranasal steroids were studied in 36 children with mild residual OSAS after adenotonsillectomy. After 12 weeks of therapy, children in the treatment group had improved AHI, higher nadir oxygen saturation, and decreased respiratory arousals compared with control subjects.[201] Both topical intranasal steroids and leukotriene receptor anatagonists may have promising roles in the management of OSAS, particularly mild OSAS, in children. However, further studies to evaluate effectiveness and appropriate dosing and duration of therapy are needed.

The use of orthodontic devices in the treatment of OSAS in children also appears encouraging in early studies. Rapid maxillary expansion (RME) is an orthodontic treatment that widens the palate and nasal orifices. The use of RME in children with OSAS described as having maxillary contraction has led to resolution of OSAS in this select group.[202,203] Use of orthodontic devices designed to advance the mandible also has led to improvements in sleep-related upper airway obstruction.[204,205] Again, further studies are needed to define the indications and candidates for and the effectiveness of orthodontic treatment in children with OSAS.

As in adults, weight loss is an important component of the management of OSAS in obese children.[206-209] Because weight loss will also lead to other significant health benefits, nutritional counseling with aggressive follow-up is necessary for these patients.

Summary

Obstructive sleep apnea in children is an important and common medical condition that can lead to significant morbidity. The diagnosis of obstructive sleep apnea in children requires clinical suspicion supplemented with the use of specific diagnostic tests. Polysomnography remains the key to diagnosis and helps assess the need for treatment, the risk for perioperative respiratory compromise, and the likelihood of persistent OSAS after treatment. Adenotonsillectomy is the mainstay of treatment, although children with complex medical conditions affecting upper airway anatomy and tone may require additional treatment.

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CHAPTER ONE HUNDRED AND EIGHTY-FOUR

Characteristics of Normal and Abnormal Postnatal Craniofacial Growth and Development

Frederick K. Kozak

Juan Camilo Ospina

Key Points

- All theories of facial growth control mechanisms are speculative, and none is fully satisfactory.
- In Moss's functional matrix hypothesis, regulation of growth of cartilage and bone is exerted by the functional matrix surrounding them.
- The craniofacial complex can be divided into three regions: neurocranium, nasomaxillary complex, and mandible.
- Asymmetry is recognized as an intrinsic facial characteristic.
- Ionizing radiation negatively affects developing bone and soft tissue, causing several side effects and facial alterations, both functional and cosmetic.
- The correlation between animal and human experiments regarding the effects of nasoseptal and sinus surgery on craniofacial growth remains unclear.
- Effects of functional endoscopic sinus surgery (FESS) on facial growth are yet to be consistently proven.
- The use of resorbable hardware systems is highly recommended in pediatric craniofacial surgery.
- Debate is ongoing regarding the correction of nasal septal deformity or deviation in neonates and older children. A conservative approach may be warranted until more definitive data are available.
- Controversy exists in the literature regarding the role that nasal or nasopharyngeal obstruction plays with regard to dentofacial growth and development.
- Robin sequence can appear as an isolated entity or as part of several craniofacial syndromes.
- Craniofacial surgery in patients with mandibulofacial dysostosis (Treacher Collins syndrome) using osteotomies and advancement techniques appears to assist in the orientation of subsequent growth in a more normal direction and to enlarge the airway at the same time.

Volumes of literature have been written on facial growth and development, and entire academic careers have been spent researching various concepts and theories. Searching through the published literature can be overwhelming. This chapter provides a place to begin the study of facial growth and development and reviews major changes in growth from birth to late adolescence. *Growth* refers to an increase in size, whereas *development* indicates an increase in complexity of structure and function.

An understanding of the abnormal first requires comprehension of the normal. Accordingly, this chapter is divided into two parts: A brief review of the main theories of postnatal craniofacial growth and the characteristics of normal postnatal facial growth and development is presented first. Subsequently, abnormal facial growth and development are examined through several clinical examples of relevance in pediatric otolaryngology. Embryology of the head and neck is covered in Chapter 181.

Theories of Craniofacial Growth

Postnatal facial growth appears to be a complex, multifactorial phenomenon. It is clear from the resemblance of children to their parents in both facial structure and soft tissue development that genetic factors play a significant role in basic facial pattern. However, "environmental" factors most certainly influence facial growth as well. These factors can range from intercellular influences to biomechanical forces (i.e., physical forces acting on bone). This essentially is Wolff's law (1870), which states that "changes in the function of a bone are attended by alterations in its structure."[1] Bone is a tissue that responds to the stresses placed on it. Bone remodels.

The genetic and environmental control mechanisms of postnatal facial growth and development are poorly understood. The three main theories of postnatal facial growth control are the genetic preprogrammed theory, the cartilage-mediated growth theory, and the functional matrix hypothesis. Following is a brief review of these theories, none of which is fully satisfactory.

Genetic Preprogrammed Theory (Growth Sites)

Early theorists believed that the sizes and shapes of bones were genetically determined within their cells and that sutural patterns were therefore predetermined. Because bone size and shape are defined by sutures in the head, these pioneers theorized that the position of sutures limits and controls the expansion of bones. Baume[2] described "growth centres" as places of endochondral ossification with tissue-separating force, resulting in an increase in skeletal mass, and "growth sites" as regions of periosteal or sutural bone formation and modeling resorption that are adaptive to environmental influences.[3] The cells of the sutures grew into the void left as the bone segments pulled apart from the tissue-separating force. In other words, growth sites are where growth literally takes place, and growth centers are areas in which genetically predetermined growth takes place. This theory was tested by experiments involving suture removal and transplantation, and the conclusion was that sutures are not primarily responsible for growth.[4] This theory is no longer accepted as correct.

Cartilage-Mediated Growth (Scott)

In 1953, Scott theorized that the cartilage of the nasal septum "is an extension of the cartilage of the cranial base."[5] In its growth, the cartilage of the nasal septum separates the facial bones from one another and from the cranial portion of the skull and allows growth to take place at the sutures by the ordinary mechanism of surface deposition. He held that the nasal septum and also the mandibular condyles and synchondroses (otherwise known as cephalic cartilages) are growth centers. As the nasal septum grows, it puts tension on the sutures of the nasomaxillary complex, thereby displacing it forward and downward, with resultant growth occurring at pressure-related growth sites. Tension occurring in the maxillary sutures causes new bone growth when the sutures are pulled apart. Therefore, suture growth is passive and secondary.

Latham[6] theorized that a septomaxillary ligament (connection between the septum and maxilla) in the fetus causes the maxilla to be pulled forward by the septum as the maxilla grows. It is unknown whether this ligament plays a role in postnatal growth, and experimentation related to the role of the nasal cartilage in this concept is unknown. Animal experimentation involving removal of septal cartilage shortly after birth[7] or secondary to trauma seems to result in midface hypoplasia, but such experiments cannot clearly prove that the cartilage removal causes the growth deficiency. Cartilage seems to play some role that has not yet been precisely determined.

The Functional Matrix Hypothesis (Moss)

The most fundamental dictum of the functional matrix hypothesis was stated by Moss,[8,9] as follows:

> The origin of all skeletal units, all of their subsequent changes in size, shape and location and their subsequent maintenance and being, are always, and without exception, secondary, compensatory and mechanical obligatory responses to the morphogenetically and temporally prior and primary alterations of the operational (functional) demands of their specifically related functional matrices. Put more succinctly, "Bones do not grow, they are grown."[10]

The basic premise of this theory is that bone and cartilage do not regulate their own growth. This theory proposes that craniofacial bony growth occurs as a reaction to—or in response to—the functional matrix surrounding it. A functional matrix consists of the cells that comprise muscle, soft tissue, teeth, glands, and nerves, as well as the functioning volumes of various cavities associated with the head and neck region (e.g., nasal, orbital, oral, pharyngeal, and neurocranial). A feedback system exists between the functional matrix and the bone and cartilage involved. Growth of cranial size occurs in response to growth of the brain, growth of the bony orbits occurs in response to the size of the orbit, and growth of the facial bones occurs in response to growth of the surrounding soft tissues. The resultant enlargement of the associated cavities of the head and neck occurs because of the functional demands of the airway, breathing, and eating "spaces." The craniofacial bones are in a dependent relationship with the surrounding soft tissues. Critics state that Moss's theory explains *what* happens during growth but does not explain *how* it happens. Moss's theory is quite useful in clinical practice because it allows separate assessment of each functional unit in the craniofacial skeleton (i.e., brain = cranium, eye = orbit, jaws (mandible) = mastication, nasomaxillary complex and associated airways = respiration, and the ear = temporal bone). The functional matrix operates within the genetic constraints of the cells and tissues involved.

Facial growth involves intimate morphogenic and biomechanical relationships among all of its component tissue parts, each influenced by and in turn influencing the other. A fundamental principle is that no part is developmentally independent or self-contained.[11]

At this time, all theories of growth control mechanisms are speculative, with strengths and faults in each. Further research is required before any definite conclusion can be made.

Bone Growth Concepts

Osteogenesis

A review of bone formation is required for a discussion of craniofacial growth. The initial step in osteogenesis is the laying down of primary or woven bone. *Primary bone* is immature bone defined by random orientation of collagen fibers and is temporary, except in a few locations such as the tooth sockets and sutures of the cranial bones. Primary bone generally either becomes secondary (lamellar) bone or is removed to leave bone marrow cavities. *Secondary bone* differs from primary bone in that its collagen has an orderly pattern and it has an increased number of osteoblasts. Osteogenesis occurs through intramembranous ossification in mesenchyme and endochondral ossification in preexisting cartilage.

Intramembranous Bone Formation

During intramembranous bone formation, mesenchymal cells differentiate into osteoblasts and accumulate in the area where bone is laid down. The osteoblasts begin to produce osteoid, which consists of collagenous fibers and a homogeneous matrix that is primary bone. Secondary bone replaces the primary bone through ossification of the osteoid.

Endochondral Bone Formation

In endochondral bone formation, simultaneous removal of cartilage and subsequent formation of bone occur. Endochondral bone formation is more complex than intramembranous bone formation. Various zones exist in active endochondral bone formation, including the zones of reserve cartilage, proliferating cartilage, hypertrophic cartilage, calcified matrix, and resorption. The hypertrophic cartilage cells enlarge, and the surrounding matrix becomes calcified. A separate collar of bone forms around the circumference of the center of this cartilage bar. This is periosteal or, more precisely, perichondral bone. A vascular bud migrates into the cartilage and a primary marrow cavity forms. Meanwhile, activity at the various zones continues. Erosion of the cartilage takes place at the two ends of the expanding primitive marrow cavity, and bone forms on the spicules of the cartilage at the erosion front. The epiphyseal plate of long bones allows simpler visualization of this process (Fig. 184-1).

This descriptive review of bone formation can be supplemented by a molecular view of bone formation.[12]

Remodeling and Displacement

Enlow and Hans[11] described the two basic types of growth movement: remodeling and displacement. This concept pertains to both bone and

the surrounding soft tissues in the craniofacial complex. *Remodeling* involves changes in the size and shape of bone, the joining of separate bones and how they fit together, the adaptation intrinsically and extrinsically of these newly joined bones, and finally the relocation of these bones—each influenced by their overall enlargement. *Displacement* is the process whereby a space is created between bones as they enlarge. Resorption and deposition are ongoing in bones throughout the craniofacial complex during growth as part of the remodeling and displacement processes.

According to Rodan, "bone formation and bone resorption are finely regulated processes, controlled by local and systemic factors, carried out by a family of different interacting cells which communicate via cytokines, cell contacts, and elaboration of matrix which feeds back on cellular behavior."[13]

Figure 184-1. Endochondral bone formation at an epiphyseal plate.

Facial Changes during Normal Growth and Development

General

The faces of infants and children clearly differ from those of adults. Matching an infant's photograph with that of the corresponding adult photograph is challenging because of the changes that occur with growth and development of the craniofacial region. A baby's face is pudgy and round, relatively wide, and vertically short; the nose is small; the eyes appear relatively far apart; and there is a prominent forehead.

Infants have a large head relative to their body size. Their facial complex, which includes the nasomaxillary complex and mandible, is much smaller than the calvaria and basicranium (Figs. 184-2 through 184-4). With growth and development of the facial complex come changes in the size ratio of the cranium to the face. In infants the cranium-to-face ratio is approximately 3:1; whereas in adults it is approximately 2:1 (see Fig. 184-4).

With growth, increasing demands are made on the respiratory and masticatory systems. As part of the growth of the facial complex, the nose, mandible, and maxilla increase in size—resulting in the larger, coarser features of the adult face in comparison with the child's (see Fig. 184-3). The facial complex increases in size relative to the cranium. Similarly, body size increases relative to head size, to result in normal adult body and head proportions (Fig. 184-5).

Craniofacial Regions of Growth

The craniofacial complex can be divided into three regions: (1) the neurocranium, which is further divided into the calvaria and basicranium; (2) the nasomaxillary complex; and (3) the mandible. Figures 184-2 and 184-3 show the changes that occur in the craniofacial complex from birth to adulthood. The embryonic human skull has 110 ossification centers, many of which fuse, to result in 45 bones in the neonatal skull and ultimately 22 bones in the young adult skull.[1] Table 184-1 summarizes the changes in size of various anatomic sites that take place during growth and development from infancy to adulthood.[1,14-25]

Neurocranium (Calvaria = Roof and Basicranium = Floor)

Calvaria

The calvaria comprises the frontal, parietal, and parts of the temporal, occipital, and sphenoid bones. These bones are formed by intramembranous ossification, with the exception of noncalvarial parts of the occipital, temporal, and sphenoid bones, which are formed through endochondral ossification. These bones initially are separated by fontanelles, which develop into sutures early and then finally fuse in adult life (Fig. 184-6).

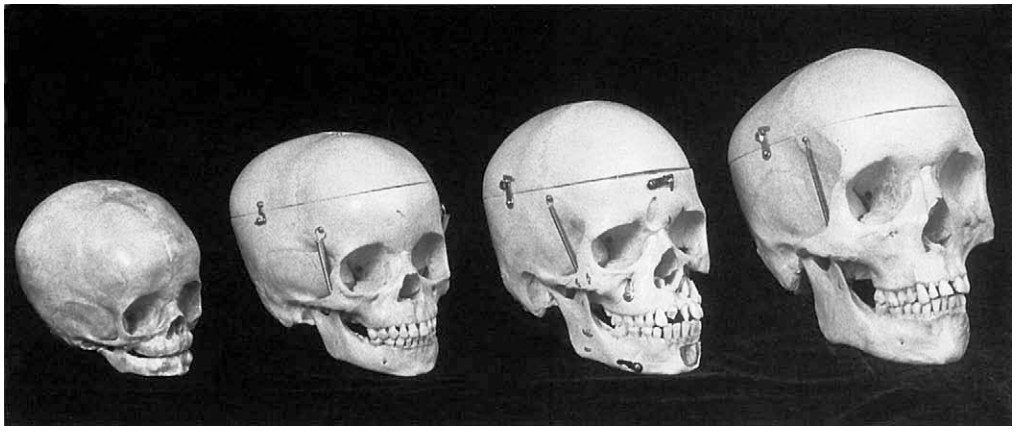

Figure 184-2. The skulls of an infant (approximately 8 months of age), a 5- to 6-year-old, a 10- to 12-year-old, and an adult. Note the bony craniofacial changes with increasing age.

Figure 184-3. Photographs of two siblings from birth to adulthood, demonstrating changes in the craniofacial complex with growth and development. The girl is shown at birth, 10 months, 2.5 years, 6 years, 10 years, 14 years, and 18 years of age, with the last photo in adulthood at 25 years of age. Her brother male is shown at birth, 7 months, 2 years, 5 years, 9 years, 15 years, 19 years, and 25 years of age.

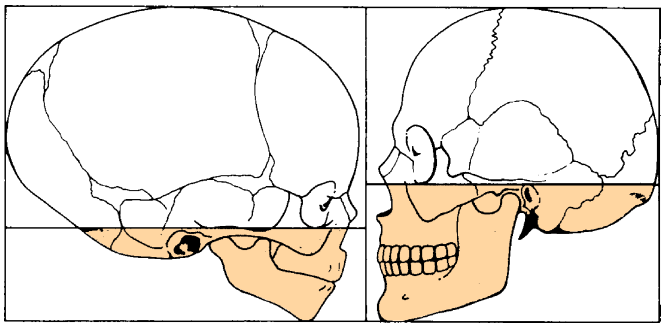

Figure 184-4. The size ratio of the cranium to the face changes considerably during growth and development. In the newborn, the cranium/face ratio is approximately 3:1, whereas in adults, this ratio is approximately 2:1. *(From Proffit WR.* Contemporary Orthodontics*. 2nd ed. St Louis: Mosby; 1993.)*

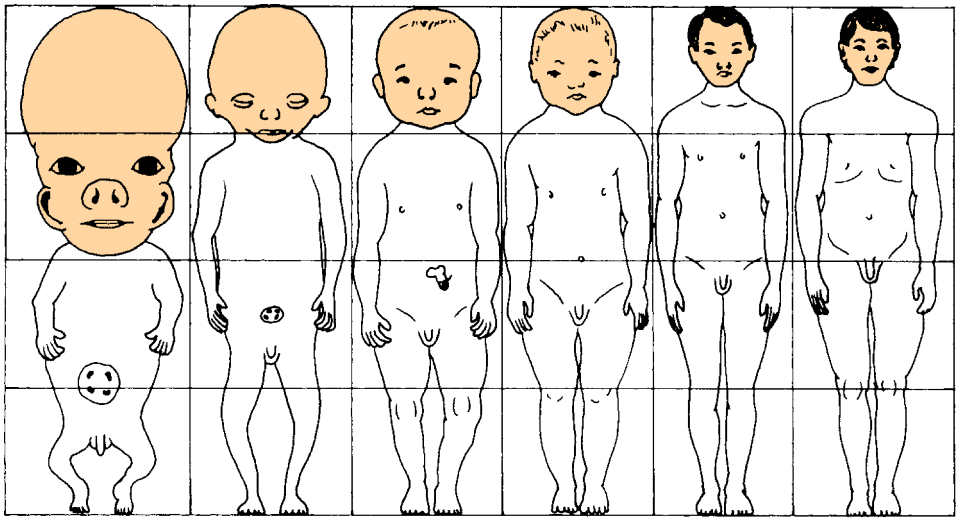

Figure 184-5. Schematic drawing showing the changes in body proportions during normal growth and development. *(From Proffit WR.* Contemporary Orthodontics*. 2nd ed. St Louis: Mosby; 1993.)*

Table 184-1

Normal Craniofacial Growth and Development

Growth Aspect	Age/Development
Neurocranium growth	Birth/25% of ultimate growth 6 months/50% of ultimate growth 2 years/75% of ultimate growth 10 years/95% of ultimate growth
Facial skeletal growth	10 years/65% of ultimate growth
Neurocranium/face size ratio	Birth/8:1 2 years/6:1 5 years/4:1 Adult/2.1:1 to 2.5:1
Brain size	Birth to adulthood/3.5∞ increase
Fontanelle closure	3 months after birth/anterolateral Second year of life/posterolateral 2 months after birth/posterior Second year of life/anterior
Orbits	2 years/50% of ultimate growth 7 years/100% of ultimate growth
Inner ear	6 months of fetal life/full adult size
Brain weight	Full-term infant/25% of eventual weight 6 months/50% of eventual weight 2 years/80% of eventual weight 10 years/almost eventual weight
Postnatal brain growth	1 year/60% of ultimate growth 2 years/80% of ultimate growth 8 years/95% of ultimate growth Minimal growth continues to at least age 25 years
Facial height (males)	Birth/40% to 61% of ultimate growth
Upper facial height	1 year/63 to 86% of ultimate growth 3 years/72 to 90% of ultimate growth 5 years/82 to 100% of ultimate growth (mean, 89%)
Total facial height	Birth 38% to 45% of ultimate growth 1 year/50 to 66% of ultimate growth 3 years/66 to 78% of ultimate growth 5 years/68 to 82% of ultimate growth (mean, 77%)
Facial dimension	3 months/equivalent to 40% of adult size 2 years/equivalent of 70% of adult size 5 years/equivalent of 80% of adult size
Nasal height and nasal bridge length	Fully mature in boys at age 15, girls at age 12
Nasal tip protrusion	Boys age 15, females age 13
Upper and lower nasal dorsum	Males age 14, females age 12
Anterior and posterior nasal depth	Males age 14, females age 12
Foramen magnum	1 year/80% of transverse adult size 1 year/74% of sagittal adult size
Skull base (basion = nasion)	Birth/56% of adult length 2 years/70% of adult length 10 years/90% of adult length Prechordal part contributes 75% of the postnatal length and parachordal (basioccipital) contributes to 25%
Dentition eruption	8 months-2.5 years/primary teeth 6 years-20 years/permanent teeth
Maxillary antrum height	Birth/20% 7 years/50% 10 years/55%
Bizygomatic width	Birth/60% 3 years/80% 5 years/82% 10 years/85%
Cranial width	Birth/65% 3 years/85% 5 years/92% 10 years/95%
Cranial length	Birth/60% 3 years/85% 5 years/90% 10 years/95%

Data from references 1, 14-25.

As the child's brain grows, the calvarial bones are displaced. This displacement theoretically results in the deposition of new bone on the sutural edges. Growth of bone is seen on both the internal and external tables of the calvaria. This also results in an expanded medullary space. Significant thickening occurs from infancy to adulthood. The ascendancy (dominance) of the neurocranium over the facial complex during the early stages of life is clearly related to the inordinately early development of the brain.[21] The major portion of calvarial growth is completed by the age of 4 years (Fig. 184-7).

Basicranium

Growth of the cranial base creates space for the enlarging brain and oronasal structures with their associated airway. The basicranium grows more slowly than the neurocranium. At birth and at 10 years of age, the cranial base exhibits 63% and 95%, respectively, of its ultimate size.[21] The basicranium comprises parts of the occipital, temporal, sphenoid, and ethmoid bones. The occipital, temporal, and sphenoid portions form through endochondral ossification. The ethmoid and inferior nasal concha form solely by intramembranous bone formation.

In the midline, synchondroses are present (Fig. 184-8). These synchondroses remain after the chondrocranium (cartilage precursor of the basicranium) has ossified. During childhood, the spheno-occipital synchondrosis is the principal growth cartilage of the basicranium, and its growth persists into early adolescence.[3,11] Other synchondroses of the basicranium are the sphenoethmoidal, intersphenoidal, sphenofrontal, and frontoethmoidal synchondroses, all of which play a minimal

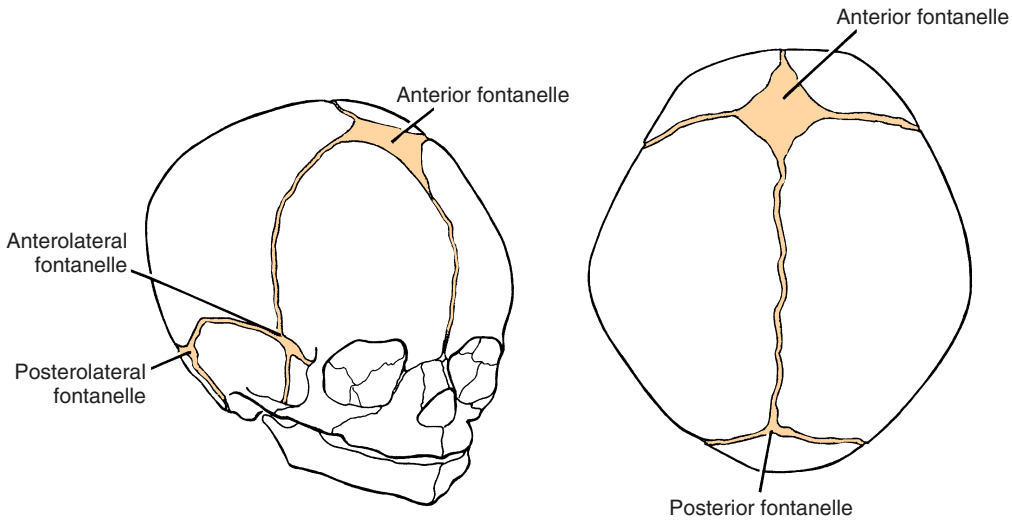

Figure 184-6. Newborn skull fontanelles.

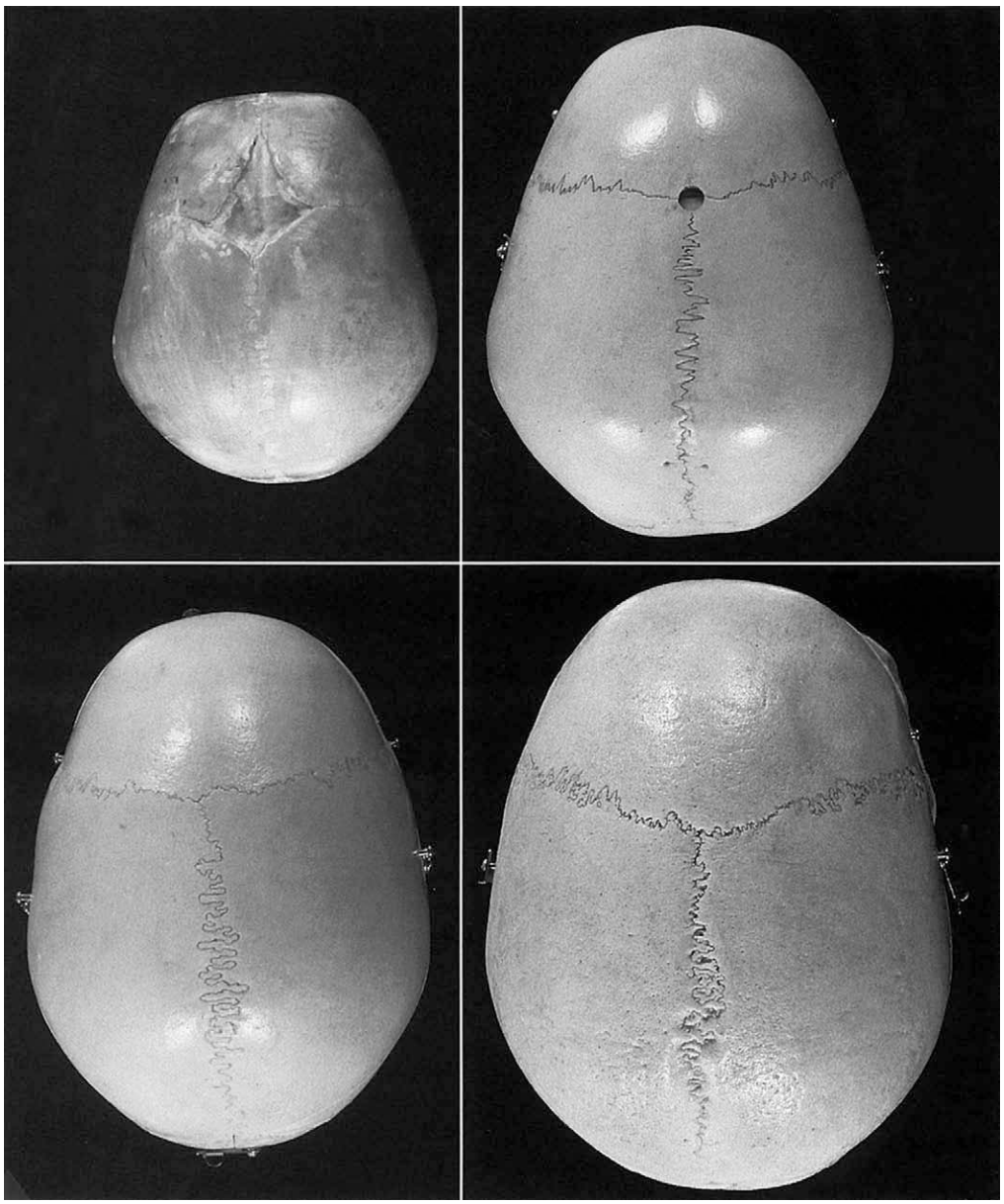

Figure 184-7. Top view of skulls showing the shape change that occurs from infancy to adulthood. Shown are infant (approximately 8 months of age), 5- to 6-year-old, 10- to 12-year-old, and adult skulls.

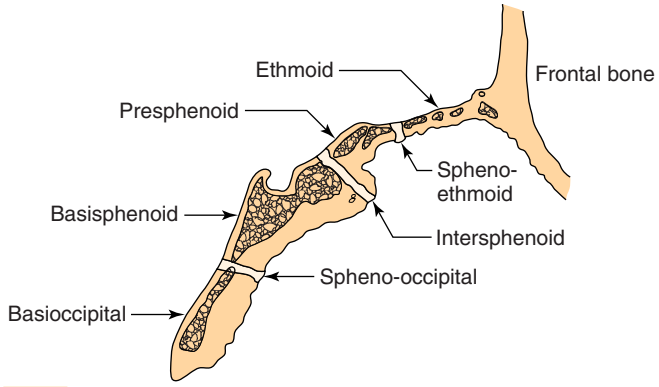

Figure 184-8. Diagrammatic representation of the synchondroses of the cranial base, showing the location of these important growth sites. *(From Proffit WR. Contemporary Orthodontics. 2nd ed. St Louis: Mosby; 1993.)*

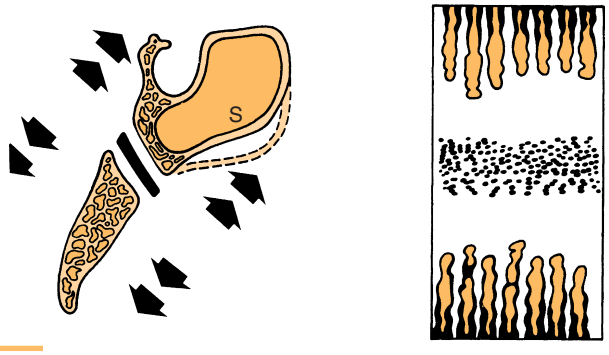

Figure 184-9. Diagrammatic representation of growth at the intersphenoid synchondrosis. A bank of immature proliferating cartilage cells is located at the center of the synchondrosis, whereas a band of maturing cartilage cells extends in both directions away from the center. Endochondral ossification occurs at both margins. Growth at the synchondrosis lengthens this area of the cranial base. S, sphenoid sinus. *(From Proffit WR. Contemporary Orthodontics. 2nd ed. St Louis: Mosby; 1993.)*

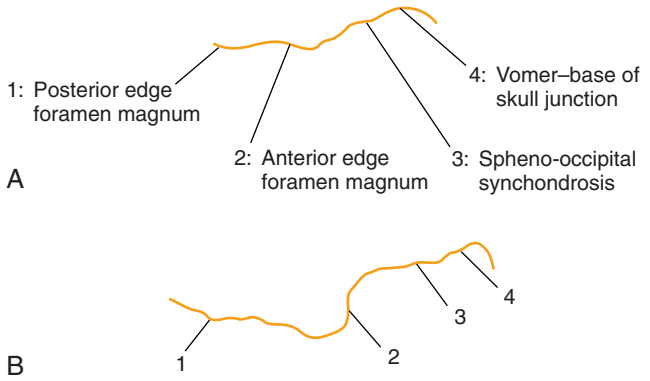

Figure 184-10. Flexion of the cranial base. With growth, a more convex superior or flexed appearance develops from infancy to adulthood. **A,** Infant. **B,** Adult.

role in postnatal growth. The synchondroses have zones similar to those in the epiphyseal cartilage of long bones. However, growth occurs in two directions, resulting in elongation of the basicranium until its ultimate ossification is completed (Fig. 184-9).

The development of ossification center sutures and synchondroses in the chondrocranium throughout childhood hase been chronicled by means of computed tomography (CT). These data can provide standards for skull base maturity. In addition, postnatal normal CT variants and magnetic resonance imaging (MRI) assessment of the cranial base have been characterized.[26,27]

In newborns and infants, the cranial base is quite flat. With growth into childhood, a more convex superior or flexed appearance emerges, with further enlargement during adolescence and adulthood. The spheno-occipital synchondrosis becomes more flexed as the maxillary portion of the nasomaxillary complex moves toward the foramen magnum and moves under the anterior cranial fossa (Fig. 184-10). Components of the cranial base can be seen more clearly in older pediatric skulls than in infant skulls. The foramen magnum approaches adult size and the primary dentition has erupted by 3 years of age. By 8 years of age, the occipital bone has fused around the foramen magnum, and the secondary dentition is erupting. The major difference between the adolescent and adult skull is fusion of the spheno-occipital synchondrosis. Fusion of this synchondrosis begins at approximately 15 years of age for boys and at 12 or 13 years of age for girls on the cerebral surface. Ossification on the external aspect is complete by age 20[1] (Fig. 184-11). The chondrocranium-basicranium is a junction between both the neurocranial and facial complex bones. Its alteration affects not only neurocranial and skull growth but also facial morphology.[3]

Nasomaxillary Complex

The nasomaxillary complex develops through intramembranous ossification. It includes the nasal, lacrimal, maxillary, zygomatic, pterygoid, and vomer bones.

The nasomaxillary complex is displaced forward and downward from the cranial floor (basicranium) as a result of growth of the associated soft tissues. New bone growth occurs at sutural contact surfaces on both sides of the suture, with a resultant increase in the size of both bones involved (Fig. 184-12). Bone is added at the frontal maxillary, zygomaticotemporal, zygomaticosphenoidal, zygomaticomaxillary, ethmoidomaxillary, frontoethmoidal, nasomaxillary, nasofrontal, frontolacrimal, palatine, and vomerine sutures. Interaction between the basicranium and the nasomaxillary complex constantly occurs. Rotatory displacement is caused by the downward and forward growth of the middle cranial fossa, resulting in greater or lesser amounts of displacement and remodeling growth in the posterior and anterior parts of the maxilla, depending on the biomechanical forces involved.[11]

The anterior surface of the maxilla is an area of significant resorption (Fig. 184-13). Even though bone is being resorbed here, the maxilla is still growing forward. This is a good example of remodeling and displacement (Fig. 184-14). Growth and development of the nasomaxillary complex are shown in Figure 184-15. Vertical nasomaxillary growth occurs at the frontomaxillary, frontozygomatic, frontonasal, ethmoidomaxillary, and frontoethmoidal sutures as a result of orbital and nasal growth.

The orbits, which are linked to cranial growth, are quite large at birth because of their relationship with the globe. Orbital remodeling is quite complex—50% of postnatal orbital growth is achieved by the age of 2 years, and it is almost complete by age 7 years.[21] The superior aspect of the orbit in toddlers is similar to that in adults, although the inferior aspect differs. The floor of the nose is almost at the level of the inferior orbital rim in infants; then the distance progressively increases so that the floor is significantly lower in adults. The eyes in the adult face are not much farther apart than those in a child's. According to Enlow and Hans,[11] however, "because of the larger nose, higher nasal bridge, increase in the vertical facial dimension and the widening of the cheekbones, the eyes of the adult appear much closer together." The main contribution to the widening face is from the lateral expansion of the zygomaticomaxillary sutures and the intermaxillary suture growth. Eruption of the primary and secondary teeth results in an increase in the size of the maxilla. As the maxilla moves downward and forward and secondary teeth erupt, the maxillary sinuses increase in size as well.

Sinuses

At birth, the maxillary sinus is large enough to be seen radiologically. Relatively rapid growth occurs between ages of 1 and 4 years; by age

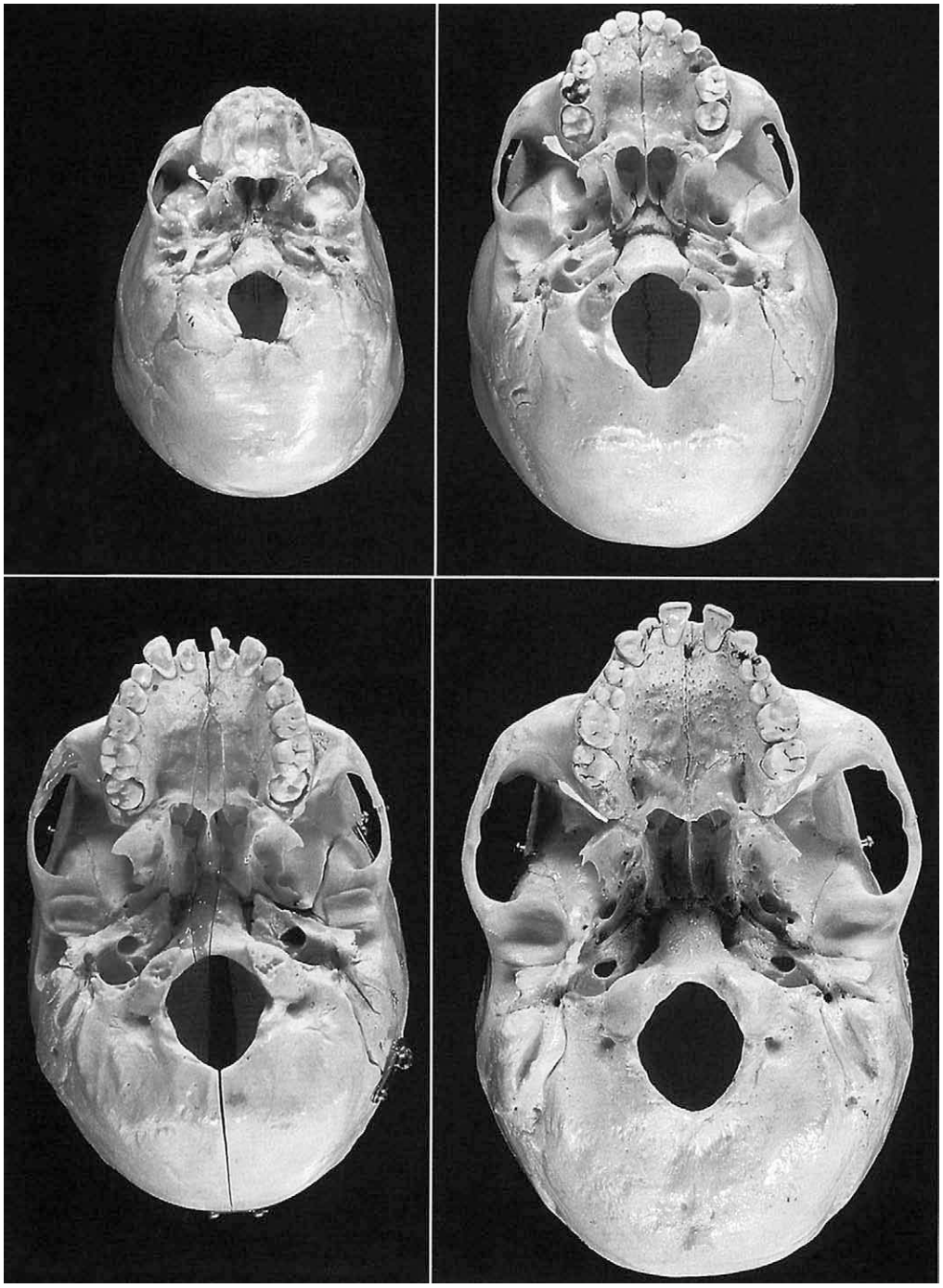

Figure 184-11. Basal extracranial views of the skulls of an infant (at 8 months of age), a 5- to 6-year-old, a 10- to 12-year-old, and an adult. Components of the cranial base are more clearly seen in the older skulls. Note the open spheno-occipital synchondrosis in the 5- to 6-year-old skull and that the most posterior molar on the right side of the photograph is not the patient's—it was inserted.

5, the sinus has started to expand laterally beyond the infraorbital foramen, although its floor does not extend below the nasal cavity. As the permanent dentition erupts, there is growth inferiorly of the floor of the sinus. By the age of 16 years, the maxillary sinus reaches full size (Fig. 184-16). The ethmoid sinuses are present at birth and have attained adult size by the early teens. The frontal sinus distinguishes itself from the ethmoids around age 5 and demonstrates a variable growth rate until reaching adult size in late puberty. The sphenoid sinus is the last to develop and is present radiologically at approximately age 6. Growth of the sphenoid sinus continues well past puberty into the early adult years.[28]

Shah and coworkers reviewed 91 CT scans in 66 patients (16 obtained serially over time) between the ages of 0 and 12 and demonstrated periods of significant growth in the paranasal sinuses in children. The ethmoid sinuses were the first to fully develop, followed by the maxillary, sphenoid and frontal sinuses.[29]

Mandible

The mandible forms in relation to the first branchial cartilage, otherwise known as Meckel's cartilage. Meckel's cartilage is interesting in that it is not replaced by bone. Instead, membranous bone forms lateral to Meckel's cartilage, and Meckel's cartilage then disappears[30] (Fig.

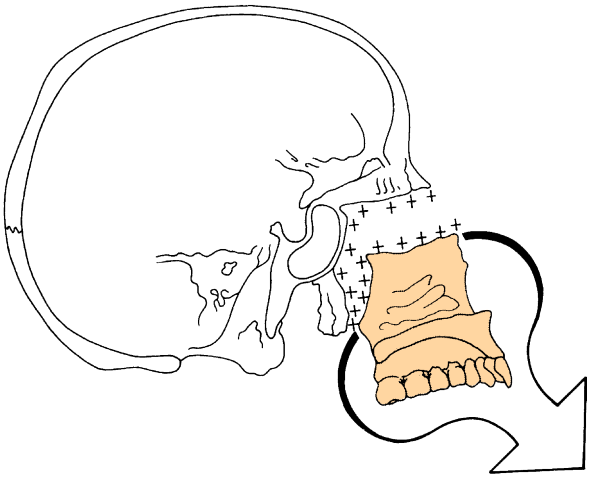

Figure 184-12. As growth of the surrounding soft tissues translates the maxilla downward and forward, opening space at its superior and posterior sutural attachments, new bone is added on both sides of the sutures. *(From Proffit WR.* Contemporary Orthodontics. *2nd ed. St Louis: Mosby; 1993.)*

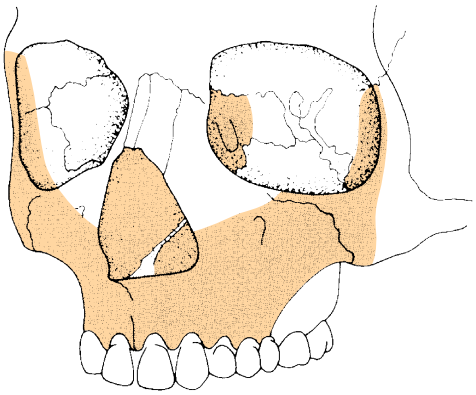

Figure 184-13. As the maxilla is carried downward and forward, its anterior surface tends to resorb. Resorption surfaces are shown in *gold*. Only a small area around the anterior nasal spine is not affected. *(From Proffit WR.* Contemporary Orthodontics. *2nd ed. St Louis: Mosby; 1993.)*

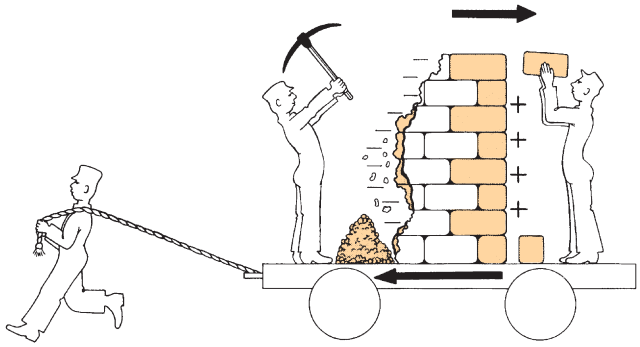

Figure 184-14. Surface remodeling of a bone—in the direction opposite that in which the bone is being translated by growth of adjacent structures—creates a situation analogous to that depicted in this cartoon. The wall is being rebuilt to move it backward at the same time the platform on which it is mounted is being moved forward. *(From Proffit WR.* Contemporary Orthodontics. *2nd ed. St Louis: Mosby; 1993.)*

184-17). At birth, the mandible comprises two bones with the symphysis menti between them. This suture closes by the age of 1 year, after which the major portion of mandibular growth occurs posteriorly.

Resorption occurring anteriorly and deposition occurring posteriorly result in the overall growth of the mandible (Fig. 184-18). Although the condyles are a major site of growth, they are not a master growth center, as was previously thought.

Variation of endochondral bone growth occurs at the articular contact portion of the condyle. The main contribution of condylar cartilage is to provide regional adaptive growth by maintaining the condylar area in a proper anatomic relationship with the temporal bone as the whole mandible is simultaneously being carried downward and forward.[11] The mandible grows by enlarging and widening in response to the increase in size of the muscles of mastication and an enlarging oropharynx, which accommodates the concomitant growth of the nasomaxillary complex. The ramus grows posteriorly and at the same time increases the inter-ramal dimension along with the laterally expanding cranial floor. The coronoid processes grow superiorly and buccally, with the anterior edges of the rami being continually resorbed in the process. The condyles grow posteriorly, superiorly, and laterally (Fig. 184-19). Even though it is a single bone, Sperber[1] described the mandible functionally as six skeletal subunits. These subunits are the alveolar, coronoid, and angular bones, the condylar process, and the chin, all of which are attached to the "body" of the mandible. Moss's concept of functional matrices then influences the growth of each subunit (teeth: alveolar unit; action of the temporalis muscle: coronoid process; masseter and medial pterygoids: angle and ramus; lateral pterygoid–condylar process, perioral muscles, tongue, and expanding oropharyngeal cavity: entire mandible).

The infant mandibular arch is U-shaped; whereas the adult arch is more V-shaped (Fig. 184-20). The gonial angle (the angle between the ramus and the body) is more obtuse in infants than in adults (Fig. 184-21). Mandibular growth takes place in two specific growth spurts, the first between the ages of 5 and 10 years and the second between ages 10 and 15 years.[31] Growth in mandibular width is completed during early adolescence. Growth in mandibular length is complete 2 to 3 years after menstruation in females and approximately 4 years after attainment of sexual maturity in males. Growth in mandibular height is complete in the late teens in females and early twenties in males (see Fig. 184-21).

Internal and external rotational changes of the mandible occur during growth and, of course, in conjunction with rotational changes in the maxilla (Fig. 184-22). Bjork and Skieller[32] described this in detail using metallic implants. Miller and Kerr[31] supported their findings but used a digitizer program for longitudinal follow-up with cephalograms in a number of patients. Overall mandibular growth is not uniform and steady, because corpus length and ramus height grow in an irregular pattern.[25,34] Jaw rotation influences the degree of tooth eruption.

Craniofacial cephalometric and anthropometric studies are abundant in the literature, and normative data are available. A review of these topics is beyond the scope of this chapter; however, these measurements may be used to assist in the interpretation of optimal growth and development in the clinical situation.[35-42]

Abnormal Facial Growth and Development

Asymmetry of the human face is well recognized as a normal finding and in fact is an intrinsic facial characteristic. According to Ferrario and colleagues, "the skeletal structures show a greater degree of asymmetry than their soft tissue drape."[43] Age is certainly one factor that influences asymmetry. Melnik[44] found that the left side of the face was larger at the age of 6 years, whereas the right side of the face was larger at age 16. Disagreement exists in the literature regarding the degree, side, and localization of normal facial asymmetry, although some researchers believe that this is because of methodologic differences.[43] Normal facial asymmetry involves many subtle differences that are not readily apparent to the viewer. Conversely, abnormal facial asymmetry typically is quite obvious.

Our culture is obsessed with physical attractiveness, which to a large extent is based on facial symmetry and what is perceived to be "normal." Langlois[45] found that the preference for attractive persons is

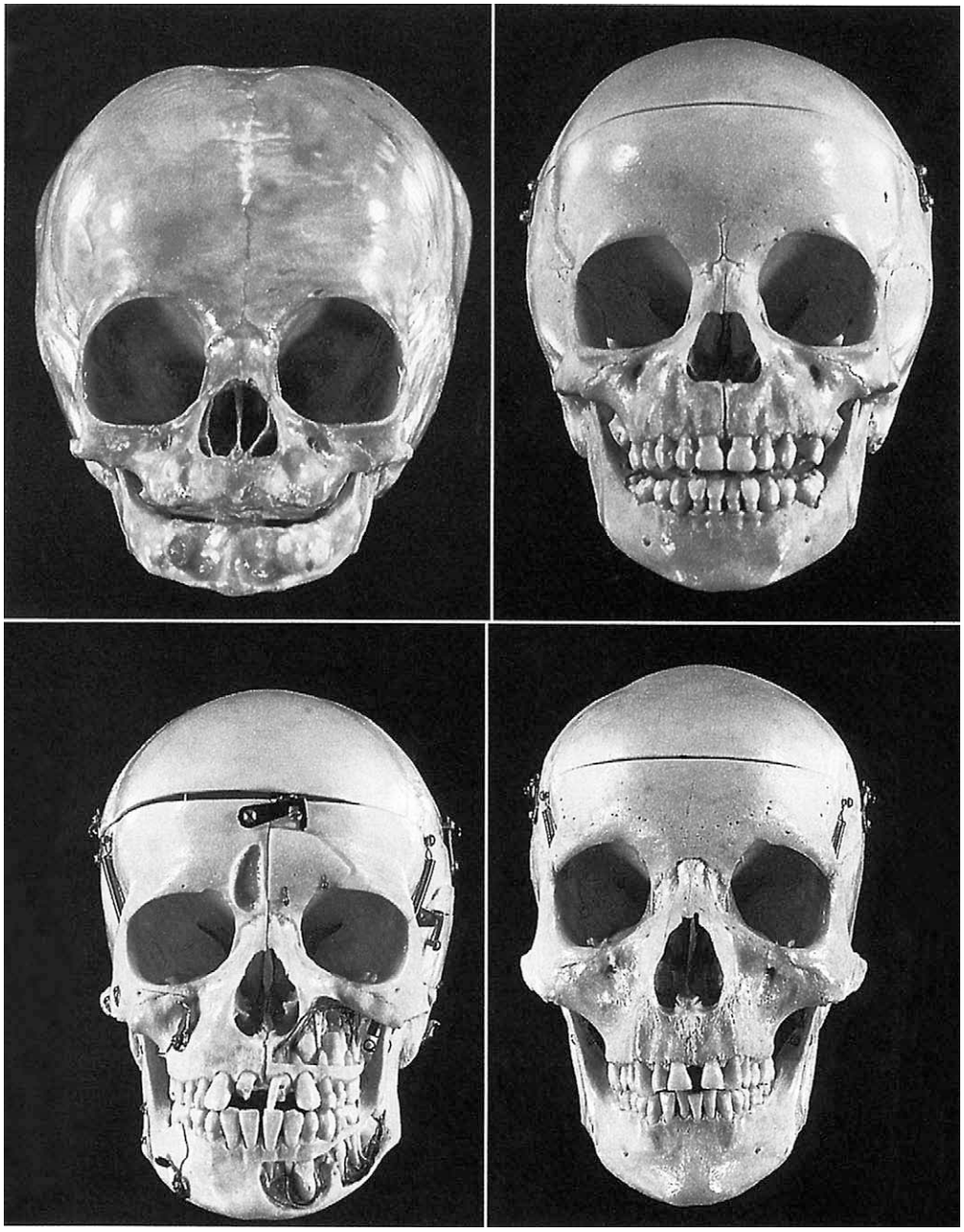

Figure 184-15. Anterior view of the skulls of an infant (8 months of age), a 5- to 6-year-old, a 10- to 12-year-old, and an adult. Note the overall change of skull shape and the facial complex/cranium ratio, the relationship of the orbits to the floor of the nose, nasomaxillary and mandibular growth, and dental changes.

evident early in life and involves all age groups and races. As a result, people whose appearance is divergent from the "norm," with or without intellectual impairment, are viewed differently in our society.

Abnormal facial growth and development may be of iatrogenic, traumatic, mechanical, or genetic etiology: Radiotherapy, functional endoscopic sinus surgery (FESS), internal fixation, nasoseptal trauma and surgery, and nasal obstruction related to dentofacial growth, as well as genetic conditions, all have been recognized as causes. Some etiologic categories relevant to pediatric otolaryngology are reviewed next.

Radiotherapy

Ionizing radiation is widely recognized as detrimental to the growth of developing tissue. In a majority of cases, this consequence is a result of the application of full doses to radiosensitive tumors.[46] Rhabdomyosarcoma and undifferentiated sarcomas constitute the most common type of malignant tumor of soft tissue of childhood. Of these sarcomas, 35% are found in the head and neck region. Retinoblastoma is the most frequent malignant ocular tumor in childhood and is a frequent indication for radiotherapy in the pediatric population.[47,48] Multimodal therapy (radiotherapy and chemotherapy) has been effective in the treatment of these tumors with a 3-year relapse-free survival rate of between 70% and 100%.[49-52] The value of radiotherapy has not been questioned given its success rate,[53] but as more children have been cured of cancer and the survival rates have increased, concerns about the long-term side effects of these therapeutic regimens (alone or in combination) have arisen.[50,51]

The effects of radiation therapy on facial growth, as well as radiation's collateral effects, are detailed in Table 184-2. Virtually 100% of children who have received radiotherapy suffer from alterations in the development of facial soft tissues, and in more than 60% of these

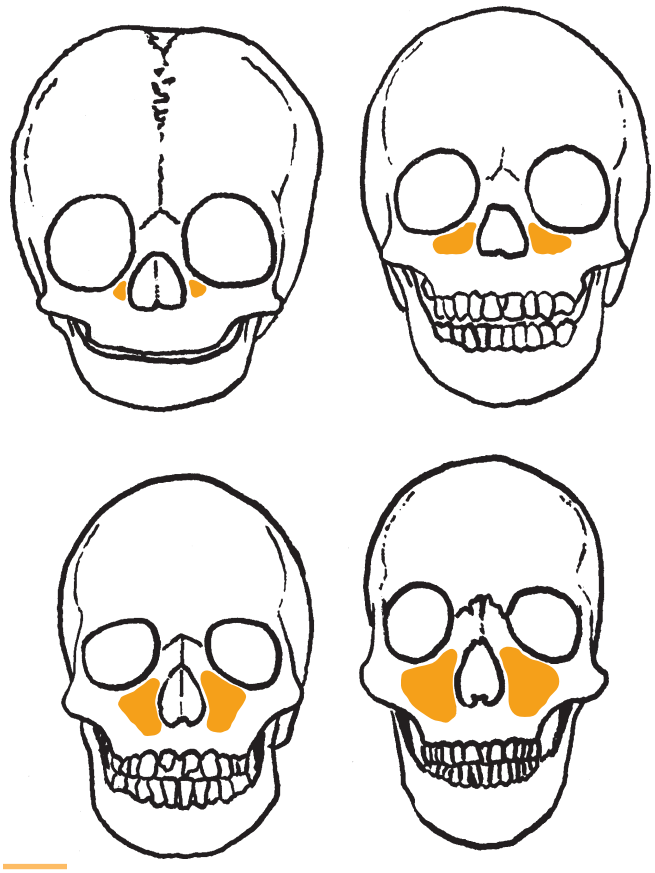

Figure 184-16. Maxillary sinus growth in an infant (8 months of age), a 5- to 6-year-old, a 10- to 12-year-old, and an adult. Drawings from x-ray images of skulls.

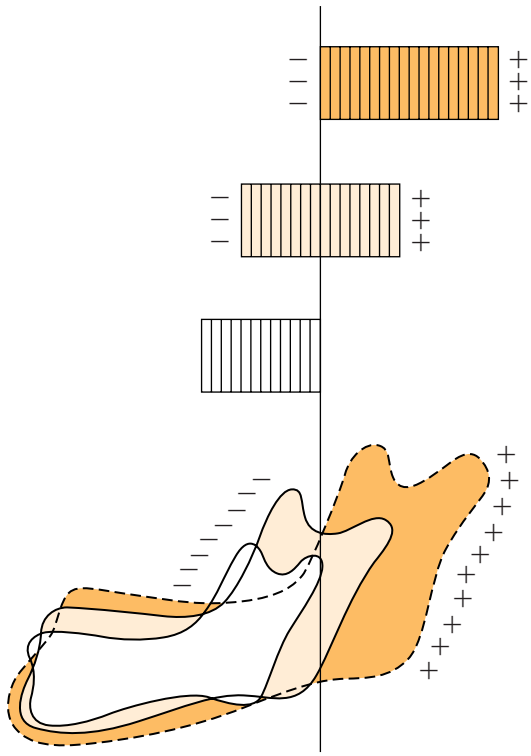

Figure 184-18. As the mandible lengthens, the ramus is extensively remodeled—so much so that the bone at the tip of the condylar process at an early age can be found at the anterior surface of the ramus some years later. Given the extent of surface remodeling changes that occur, it is an obvious area to emphasize endochondral bone formation at the condyle as the major mechanism for growth of the mandible. *(From Proffit WR. Contemporary Orthodontics. 2nd ed. St Louis: Mosby; 1993.)*

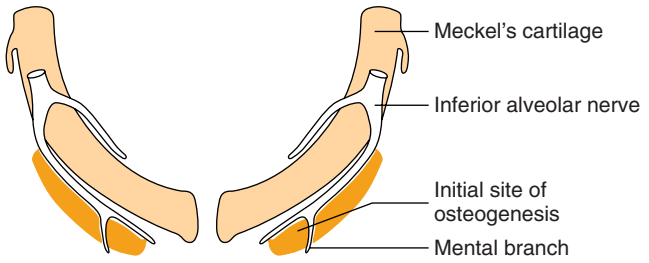

Figure 184-17. Diagrammatic representation of the relation of the site of initial bone formation in the mandible to Meckel's cartilage and the inferior alveolar nerve. Bone formation begins just lateral to Meckel's cartilage and spreads posteriorly along it without any direct replacement of the cartilage by the newly forming bone of the mandible. *(From Proffit WR. Contemporary Orthodontics. 2nd ed. St Louis: Mosby; 1993.)*

children, the facial bones are affected.[47,54] The younger the patient at the time of irradiation, the greater the effects on craniofacial development.[51,55,56] These side effects are more frequent and more severe within the first 10 years after irradiation.[54]

It has been difficult to determine the safest dose of irradiation that keeps side effects on growing tissue to a minimum but at the same time is effective in eradicating the cancer.[46,53,54] Techniques for radiotherapy administration have changed during the past 20 years. The principal aim is to achieve a balance between cure and late toxicity of the treatment.[54] Changes to minimize undesirable effects include radiotherapy with megavoltage, hyperfractionation, three-dimensional therapy, intensity-modulation, and conformal radiation with multiple fields.[47,55] In all children undergoing radiotherapy of the head and neck, it is mandatory that multidisciplinary follow-up be part of the ongoing management.

Functional Endoscopic Sinus Surgery

FESS has become the standard of care in the surgical management of chronic sinusitis and other sinus disorders in the pediatric population. Its effectiveness has been accepted when clear indications for surgery are established.[57,58] However, concerns have arisen regarding potential negative effects on the growth and development of paranasal sinuses and the nasomaxillary complex in the pediatric patient.[59]

A knowledge of sinus anatomy during different stages of development, as well as of pathologic circumstances such as chronic sinusitis, is imperative in decisions regarding FESS in the pediatric population.[28,60-62]

The absolute and relative indications for FESS in the pediatric population varied during the 1990s and into the millennium. These changes were related to the evolving definitions of sinus disorders and short- and long-term outcome measures.[60,63-68] This topic is covered in Chapter 195.

Although the relationship between nasal breathing and sinus development remains unclear, it is generally accepted that the development of the paranasal sinuses is linked to the growth of the nasomaxillary complex. A reasonable assumption, therefore, is that any intervention at this level, either an endoscopic technique or a Caldwell-Luc procedure, on a growing patient will have negative effects on the normal process of remodeling, expansion, and pneumatization.

Results of animal studies have varied depending on the species and the intervention. Kraut and Kronman examined 36-day-old New Zealand White rabbits and unilaterally filled their maxillary sinuses with polyhydroxyethylmethacrylate without adverse effect on

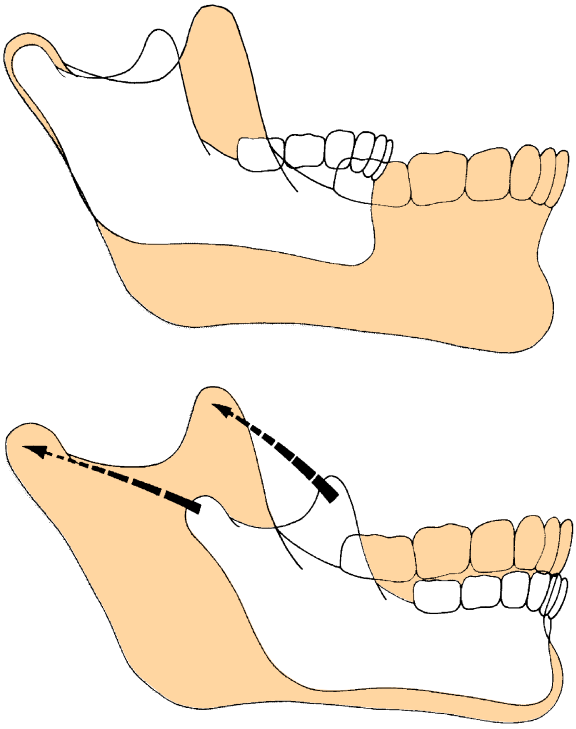

Figure 184-19. Mandibular growth as viewed from the perspective of vital staining dyes. Note the minimal changes in the body and chin area, whereas exceptional growth and remodeling occur in the ramus, moving it posteriorly. The correct concept of mandibular growth is that the mandible is translated downward and forward and grows upward and backward in response to this translation, maintaining its contact with the skull. *(From Proffit WR.* Contemporary Orthodontics. *2nd ed. St Louis: Mosby; 1993.)*

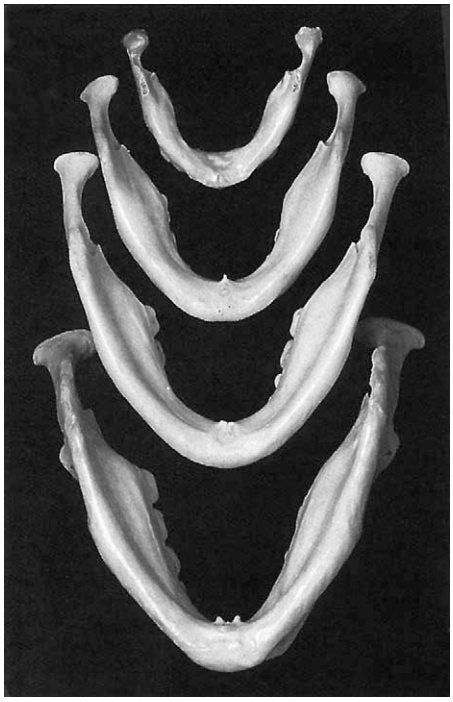

Figure 184-20. With mandibular growth, the U shape of the infant mandible *(top)* changes to more of a V shape, as seen in the adult *(bottom)*.

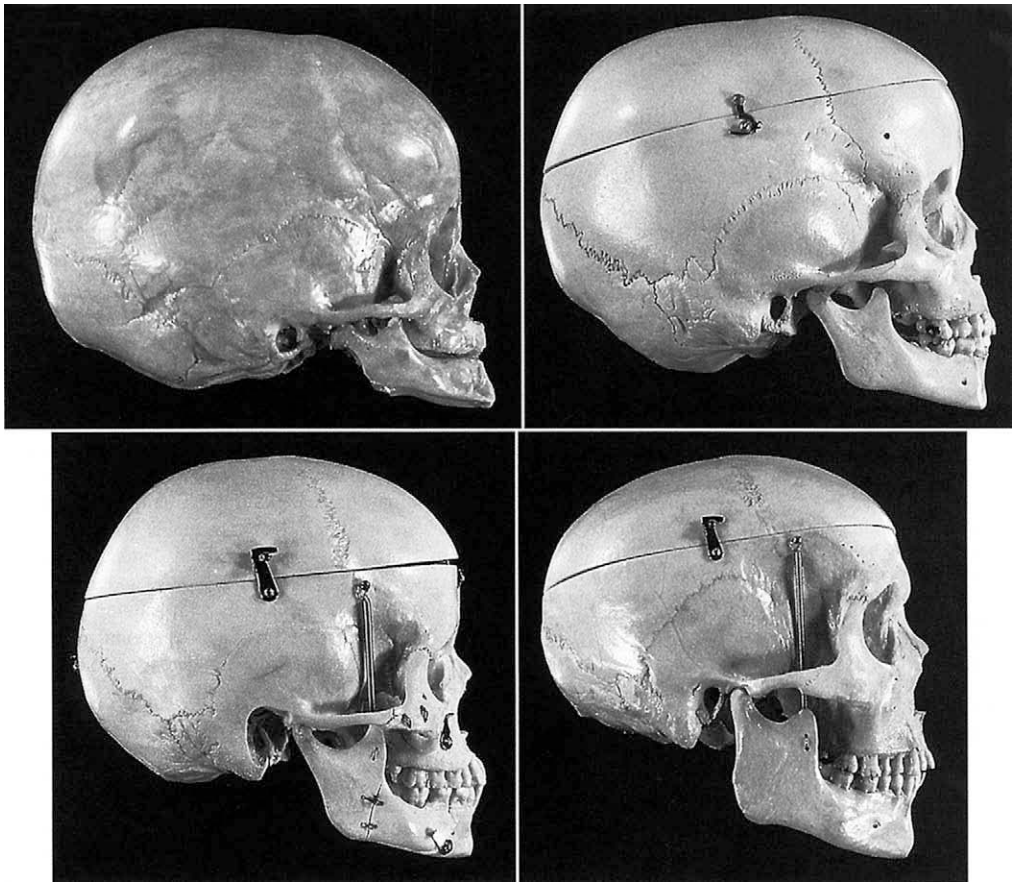

Figure 184-21. Lateral view of the skulls of an infant (at 8 months of age), a 5- to 6-year-old, a 10- to 12-year-old, and an adult. Note that the gonial angle of the mandible is more obtuse in the infant. The overall change in size of the mandible through time is dramatic.

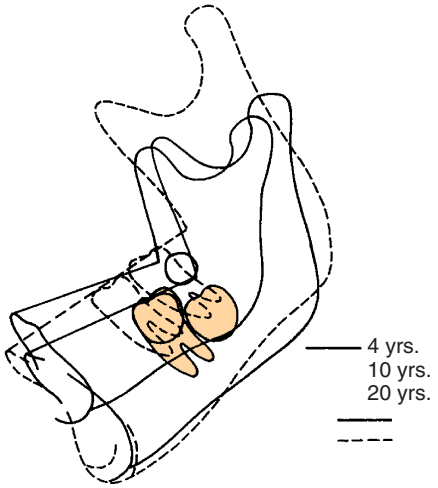

Figure 184-22. Superimposition on implants for a patient with a normal growth pattern showing surface changes in the mandible from ages 4 to 20 years. For this patient, there was a –19 degree internal rotation but only a –3 degree change in the mandibular plane angle. Note dramatic remodeling in the area of the gonial angle, with a net resorption during this period. This surface remodeling or external rotation compensates for, and conceals the extent of, the internal rotation. *(From Bjork A, Skiller V. Normal and abnormal growth of the mandible: a synthesis of longitudinal cephalometric implant studies over a period of 25 years.* Eur J Orthod. *1983;5:1.)*

craniofacial growth.[69] Mair and coworkers studied eight newly weaned piglets subjected to unilateral FESS. The researchers examined the piglets 6 months after surgery, noting significant reduction of the facial growth and maxillary-ethmoidal sinus development on the operated side.[70] Carpenter and associates found significant restrictive effects on piglet facial skeletal development after FESS.[71] Verwoerd-Verhoef and Verwoerd demonstrated that controlled resection of the bony sinonasal wall and partial resection of anterior ethmoid did not affect later development of nasal bones and maxilla on 20 young New Zealand White rabbits.[72]

Several studies in children have been undertaken. Mair and coworkers analyzed the uncinate processes and ethmoids of 84 children (mean age of 6 years; age range, 1 to 18 years) who previously had undergone FESS. In children younger than 9 years of age, woven and lamellar bone were present, in contrast with the presence of exclusively lamellar-mature bone in the children older than 9 years of age. These results suggest that the safest age at which a pediatric patient should be operated on is 9 or older.[70] Kosko and colleagues in 1996 presented five cases of children (mean age of 30 months) who had undergone bilateral FESS for refractory chronic sinusitis. At mean postoperative month 42, four children showed unilateral maxillary hypoplasia and one child showed bilateral hypoplasia without apparent changes in facial symmetry.[59] Sinus hypoplasia can be from primary causes related to individual development or secondary causes associated with a response to facial trauma, chronic sinusitis, or FESS, which has affected the activation of bone formation factors or the removal of growth centers.[59,61,73] In 2000, Senior and associates did not find long-term significant differences in sinus volumes in eight patients (age range, 2 to 14 years) who had required FESS after unilateral orbital complications of acute sinusitis, but the age range was so wide they could not determine any age-related association.[74] In a 2002 retrospective study, Bothwell and coworkers reported no evidence of facial growth disruption 10 years after FESS in 67 children between 2 and 4 years of age.[63]

Lusk and colleagues reported results of a 10-year retrospective follow-up study in children (aged 2 to 5 years) treated with FESS for chronic rhinosinusitis. Parental satisfaction regarding nasal symptoms was significantly higher in the surgically managed group than in the medically treated group. The study focused on six symptoms: day cough, night cough, irritability or crankiness, headaches, nasal airway obstruction, and purulent rhinorrhea. In comparisons of individual symptoms, no statistically significant difference was found between the two groups. However, when the mean was controlled for baseline symptom severity and CT severity, additional analysis noted a statistically significant decrease in nasal airway obstruction and in rhinorrhea in the surgical treatment group.[75]

In a small series of 14 patients with cystic fibrosis ranging in age from 9 to 28 years, Van Peteghem and Clement found no impact on the outcome of facial growth in comparison with their control group of 5 patients with cystic fibrosis who did not require surgery.[76]

In view of the small sample sizes in several studies and the lack of prospective studies, concerns still remain regarding FESS in the pediatric population. Unless the patient has an acute complication of sinus origin, FESS for chronic sinusitis should ideally be delayed until maximal medical therapy has been undertaken in order to avoid potential negative effects on facial growth.[58,77] It is recommended that one be prudent regarding the timing and extent of FESS in children and that clear indications for surgery be followed. If FESS is performed, conservative treatment preserving as much as possible of the normal mucosa, periosteum, and bone is recommended.[59,64,70,71] Further prospective studies in both animal and humans are required to clarify the role of FESS in the facial growth of children.

Internal Fixation and Facial Growth

Midface skeletal maturity is complete by approximately age 12 years. An important point is that any trauma or reconstructive surgery before this age may adversely effect facial growth.[78] However, according to Singh and Bartlett's review of data for surgically treated children for craniofacial fractures, a majority of cases had a favorable outcome with regard to facial growth and development on long-term follow-up, except for isolated condylar fractures and patients with complex centrofacial trauma.[79] There were significant limitations to this retrospective descriptive paper.

Some basic principles should be followed in planning the management of these patients. Complete clinical and image-guided assessment, early repair of fracture and soft tissue injury, minimal but sufficient surgical exposure, and correct technical application of fixation devices are required to achieve good bone stability without disrupting long-term facial growth.[78,80-83]

The direct effect of plates and screws on facial skeletal development has been studied. Lin and associates found significant growth retardation in a craniofacial segment in kittens that underwent osteotomies in conjunction with different fixation systems.[84] However, Mooney and coworkers did not find significant effects in rabbits.[85] These workers suggested, along with Carinci and colleagues, to avoid crossing sutures with plates and screws, because of the risk of synostosis.[86] Yaremchuk and coinvestigators found that osteotomy and fixation in the infant rhesus monkey affected craniofacial growth.[87] Growth deformity in selected craniometric parameters was greater when the complexity of fixation (longer plates and more screws) were used.[87,88] Courtemanche and associates found that the use of rigid internal fixation in the growing skull of piglets resulted in a contour deformity of the calvaria, and that the microplate and screw became completely incorporated into the bone. These workers suggested that this type of fixation not be used in the infant craniofacial skeleton.[89] Salyer and colleagues concluded that absorbable materials did not disrupt bone growth in canine puppies, but in this study, osteotomies were not performed.[90] In 1996, Canady and coworkers designed an animal model using conventional vitallium hardware after osteotomies without the restriction from routine rigid fixation. This system permitted more normal growth of the rabbit head compared with the rigid fixation system.[91,92] Laurenzo and associates concluded in 1995 that experimental osteotomies cause severe bony restriction in rabbits, regardless of the use of rigid plate fixation, supporting the theory that trauma itself affects growth and development.[93] However, the validity of studies using animal models has been criticized because of the lack of full applicability in humans.[87]

Imola and colleagues published a 2001 retrospective study of patients treated with resorbable plate fixation systems, concluding that this method is safe, with results comparable to those with use of metal

Table 184-2

Side Effects of Radiotherapy

Category	Manifestations
Skin	Dryness, abnormal pigmentation, telangiectasis, malignant degeneration, atrophy, alopecia, sebaceous cysts
Mucosa	Xerostomia, atrophy, fibrosis
Soft tissues	Atrophy, hypoplasia, sensitivity to infections
Facial bones	Growth retardation, hypoplasia, dysplasia, appositional growth restriction, weak resistance to infections, loss of cortical bone density, atrophy of alveolar process, micrognathia, facial asymmetry, condylar hypoplasia, "bird face," abnormal occlusion
Teeth	Failure to erupt, disturbed eruption, damage to tooth buds, anodontia, hypodontia, pseudoanodontia, mineralization, caries, root foreshortening, enamel dysplasia, atypical root morphology
Orbit	Bone and soft tissue hypoplasia, persistent infections.
Eyes	Cataracts, xerophthalmia, retinopathy, corneal lesions, loss of vision, keratoconjunctivitis, dryness of globe, enophthalmos, stenosis of lacrimal duct
Head and neck muscles	Atrophy, trismus, fibrosis
Risk of second malignancy	Osteogenic sarcoma, soft tissue sarcomas usually within radiation fields, thyroid, breast, acute myeloid leukemia, histiocytoma
Brain	Cerebral function damage
Middle ear	Serous otitis media, chronic otorrhea
Paranasal sinuses	Bone hypoplasia, chronic sinusitis
Audiology	Sensorineural or conductive hearing loss
Speech	Velopharyngeal incompetency
Hormonal	Growth retardation, growth hormone deficiency
Psychologic	Psychologic disorders
Cosmetic	Bone or soft tissue hypoplasia, facial asymmetry, severe neck fibrosis, nuchal asymmetry
Various	Nutritional and vitamin deficiency

Data from references 46-48, 50, 51, 53; and from Berkowitz RJ, Neuman P, Spalding P, Novak L, Strandjord S, Coccia PF. Developmental orofacial deficits associated with multimodal cancer therapy: case report. *Pediatr Dent*. 1989;11:227; Larson D, Kroll S, Jaffe N, Serure A, Goepfert H. Long-term effects of radiotherapy in childhood and adolescence. *Am J Surg*. 1990;160:349; Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. *Acta Paediatr Suppl*. 1999;88:1; and Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia. A comparison of three treatment modalities. *Cancer*. 1990;66:2645, 1990.

plates, but without the negative effect on the growth and development of the facial skeleton, because of its resorptive capacity once the fracture is healed.[94]

As more data over time are acquired regarding internal fixation and facial growth in the pediatric population, clarity regarding long-term outcome is sure to be achieved.

Nasoseptal Trauma and Surgery

It has long been suggested that nasal trauma or surgery has a detrimental effect on the nasofacial development of growing children. The literature notes that in adults with a deviated nasoseptal complex, up to 65% had sustained trauma in childhood.[95] It is important to recognize that nasoseptal deformities are a result of a complex interaction of factors, including trauma, surgery, inheritance, and individual growth patterns. Surgical correction of nasoseptal deformities during childhood remains very controversial because of potential adverse functional or aesthetic long-term sequelae.[96-98]

Animal Studies

Historically, various animal models of nasal septal trauma have been analyzed in attempts to find a valid correlation with humans. Sarnat and Wexler reported that in 1858 Flick removed septal cartilage from several different types of newly weaned animals and found significantly shortened hard palates on autopsy specimens suggesting that palatal growth depended on the growth of the nasal septum. They also reported that the degree of snout deformity was proportional to the amount of septum and perichondrium resected from rabbits.[99] Wexler confirmed these findings in a follow-up study.[100] Moss and colleagues wrote that the septum played a passive role in the development of the midface, acting only as a support structure in guinea pigs.[101] Hartshorn had similar findings after septectomies in puppies.[102] Stenstrom and Thilander studied guinea pigs, noting that in this species the septum is not the primary structure determining facial growth.[103]

Beginning in the 1970s, experimental models changed because the animal procedures to date frequently had been carried out in a destruc-

tive fashion and not as they would have been carried out in humans. Bernstein did not find growth retardation in dogs after conservative septoplasties in which the mucoperichondrium was preserved and the removed cartilage was reinserted but not sewn in.[104] Nordgaard and Kvinnsland noted severe deformities in rats after septoplasty, regardless of whether there was preservation of the mucoperichondrium.[105] Verwoerd and associates reported that the basal portion of cartilage, the perpendicular lamina, and the junction between cartilage and the premaxilla and cartilage with the sphenoid were the key areas in nasal development in rabbits.[106] Cupero and colleagues found that septal surgery preserving mucoperichondrium did not affect facial development in ferrets.[107] However, concerns persisted in the literature because of the lack of clear correlation between animals and humans.

Human Studies

In human studies it is difficult to differentiate the proportion of long-term sequelae on nasofacial growth and development attributable to trauma alone or in combination with surgery. A number of authors have theorized on the growth centers of the septum[106,108-111] (Fig. 184-23). Clinical cases such as that seen in Figure 184-24 invite researchers to question the role the septum plays in nasal growth. In the case depicted, a septal abscess developed at the age of 1 year. Serial photographs of the patient follow nasal growth at ages 1, 7, and 12 years. Nasal size appears to be smaller than expected; however, until the patient goes through a facial growth phase as an adolescent, it is difficult to comment on what the final proportion of his nose to the rest of his face will be. Clinically, he also has nasal obstruction secondary to a significantly deviated septum.

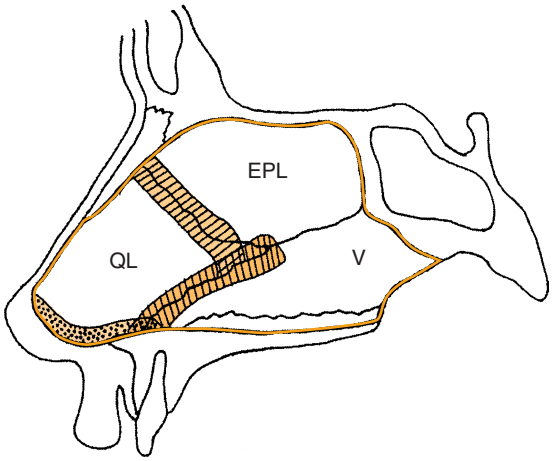

Figure 184-23. Proposed growth centers of the septum. EPL, ethmoid perpendicular lamina; QL, quadrangular lamina; V, vomer.

Alpini and colleagues examined 423 newborns, finding pyramid deformities with septal dislocation and columella deviation, assumed to be related to labor trauma with vaginal delivery. No infant delivered by cesarean section had a pyramid deformity. Septal deviation and subluxation were postulated to be related to developmental defects, and findings were essentially the same in the vaginally delivered and cesarean section–delivered infants.[112]

Traditionally, it has been accepted that nasoseptal surgery in children should be delayed until nasal maturity has been reached, at approximately the age of 15 years in boys and 12 years in girls. Parameters for the male and female such as facial maturity (15 and 12 years, respectively), near complete projection of the nasal tip (16 and 14 years, respectively), and the completion of growth spurts at ages 1 to 6 years and 12 to 16 years have been used to justify delay of surgical correction.[14,98,113] Akguner and coworkers, after analyzing anthropometric studies of 140 boys and 140 girls (age range, 11 to 17 years), concluded that the safest age for a septorhinoplasty in children was 15 years for boys and 13 for girls.[14] El-Hakim and associates compared 11 anthropometric variables in children who had undergone open rhinoplasty and found no long-term sequelae, although Béjar and colleagues previously had found a trend in growth retardation in the dorsum length (length from nasion to pronasale), which was not statistically significant.[96,114]

As noted by Pirsig, several clinical trials and studies with children were published during the early to mid-twentieth century: Krieg (1900), Freer (1902), Killian (1908), Metzembaum (1929), Cottle (1939, 1964). Those studies suggested that septoplasty be undertaken at the age of 16 years.[115] Farrior and Connolly postulated that a preadolescent could undergo conservative septoplasty in cases of severe deformity or impairment of nasal function.[116] In Pirsig's series of 261 children 4 to 14 years of age who underwent septoplasty, 80% achieved positive functional and aesthetic long-term outcomes, whereas 15% did not.[115] Pirsig, as well as other investigators, classified failures as the following anomalies found after trauma or surgery or both: mucosal atrophy, soft tissue scars, resorption or regeneration of cartilage (frequently ectopic) resulting in septal redeviation, bony resorption, fibrosis, hypoplasia (after septal hematoma or abscess), or hyperplastic changes (resulting in humps or crests).[95,115] Ortiz-Monasterio and

Figure 184-24. **A,** Septal abscess in a 1-year-old boy. **B1** and **B2,** Nasal profile in the same patient at ages 1 and 7 years, respectively. **C,** Nasal profile in the same patient at age 12.

Olmedo demonstrated no long-term negative outcomes in 44 children (8 to 12 years of age) after formal rhinoplasty including medial and lateral osteotomies. In this series, 65% of patients underwent septoplasty with limited dissection of mucoperichondrium and minimum cartilage excision and, when indicated, cartilage was crosshatched and replaced. Patients were followed up with preoperative and postoperative photographic and anthropometric studies.[117]

Surgical Timing and Approach

Timing of nasal surgery depends on when the injury or traumatic event has taken place and the amount of time to presentation to the surgeon. Some investigators have addressed the possibility of intervention in neonates with septal deviations secondary to delivery related injuries. Emami and Sooknundun and their coworkers advocate closed reposition or reduction of anterior septal nasal deformities and subluxations within the first few days of life in order to avoid future deformities.[118,119] However, many deviated noses of the newborn, both externally and internally do resolve on their own over several days to weeks. Kawalski and Spiewak concluded that anterior septal deviations caused by birth injuries are likely to resolve spontaneously within the first 3 days of life, suggesting that any intervention should be considered only for older children.[120]

Hippocrates (fifth century BC) described in detail the technique of nasal fracture reduction.[121] Pirsig suggested that the best time to correct nasal fractures in the pediatric population was between 6 and 10 days after injury.[95] He also felt that open reduction 2 to 3 weeks after injury was possible in cases of "massive pathologic signs." Many surgeons advocate waiting a period of 7 to 10 days after injury for the optimal time frame for fractures requiring closed reduction. Timing for surgery in patients presenting long after the traumatic event is more varied in the literature. Farrior and Connolly believed that it was wise to delay the procedure until achieving complete facial maturity, except in cases of severe functional impairment, in which it was important to do a limited resection, with proper reposition of cartilage. Alar or dorsum procedures were recommended to be delayed as long as possible.[116] It should be noted that much of the literature is anecdotal or lacks a scientific basis for the recommendations and opinions expressed.[122]

Different surgical approaches have been proposed. Loh and Chang described the basic septoplasty technique in children, with no noteworthy differences from adults, except for the conservative excision of cartilage and bone.[123] For severe deformities, Jugo proposed open rhinoseptoplasty, excising, and replacing the septum, without violating the K point (i.e., the junction between nasal bones and upper lateral cartilages on the nasal dorsum), neither cutting the septospinal ligament nor dissecting inferior tunnels. In less severe cases, a conventional Cottle's septoplasty is advised.[124] Koltai and colleagues agreed with this.[125] Crysdale's group proposed two approaches in children 6 years of age and older. When the deviation is located caudally and posterior to an imaginary line from the anterior nasal spine to the anterior aspect of the nasal bones, a hemitransfixion incision and limited excision of cartilage, maxillary crest, and vomer is indicated. If the deviation is anterior to this line, they suggested an open approach removing the whole quadrilateral cartilage and replacing it using its posterior edge, creating a "new" septal midline.[96,98,114,126,127]

In conclusion, rhinoseptoplasty in children remains a controversial topic.[127-130] It would appear impossible not to interfere to some degree with the growth pattern in operating on a developing nose. Farrior and Connolly in 1970 counseled prudence in this regard:

> There has not been adequate documentation by anatomic sections, embryologic study, and clinical verification of just what components of the nasal structure should not be disturbed or removed and what portions of these various structures should be either removed or preserved. The actual rates of growth of each component and what precisely located surgical trauma would do to future development have not been well studied. In any event, conservatism and repositioning without removal of tissue, or with minimal tissue disturbance, seems to be the wise approach.[116]

Although further study has taken place since Farrior and Connolly's delineation of the problem, questions remain regarding timing of and approach to this not uncommon reconstruction. Therefore, these procedures should be performed conservatively and, when possible, delayed until facial maturity is attained. However, should severe deformities be present, corrective procedures are indicated. A second surgical repair may be required once facial growth is completed or nearly completed, depending on the age of the child at the time of the initial procedure. Before proceeding to surgery, the child's functional, aesthetic, and psychologic parameters must be considered, and it is paramount that these considerations be discussed fully with the patient and the family.

Nasal Obstruction and Dentofacial Growth

Genetic factors clearly play a role in dentofacial growth in humans. Controversy exists in the literature regarding the role that nasopharyngeal obstruction plays with regard to dentofacial growth and development. Two schools of thought prevail: (1) that nasal obstruction plays a role and (2) that it does not.[131,132]

Nasal obstruction results in increases in both nasal flow resistance and nasal power (rate of energy required to move air through the nose), such that the child may be forced to switch to mouth breathing. When mouth breathing, the child has an open-mouth posture (OMP)—the mandible and tongue are displaced downward and backward and the head is tilted backward. It has been hypothesized that OMP affects the direction of jaw growth and the interaction of the teeth both horizontally and vertically. Stress from the suprahyoid muscles and the platysma is thought to influence growth on the lower aspect of the mandible. Sperber[1] makes reference to Moss's functional matrix hypothesis, noting that the nasal cavity also may influence growth of the face. Enlarged adenoids in young children are one of the most common causes of nasal obstruction, potentially resulting in the typical "adenoid facies" (narrow, increased facial height, protruding teeth, OMP, short upper lip and larger lower lip, small nose, high-vaulted palatal arch, and the appearance of a vacant or dull facial expression (Fig. 184-25). However, the cause-and-effect relationship of nasal obstruction and this facial morphology has not been substantiated. Heredity also may be involved to some degree.[1]

It should be noted that the term *mouth breathing* is in fact a misnomer, because most persons identified as using this mode of breathing are in fact oronasal breathers. Complete mouth breathing is unusual, and Ung and colleagues reported only 2 of the 49 children they studied to be 100% mouth breathers.[133] In fact, the accurate determination of respiratory mode (oral, nasal, or oronasal breathing) remains elusive, leading to significant difficulties in researching the effect of nasal obstruction on facial growth. The nasal valve area also may play a significant role in nasal obstruction. Ung's group found that the breathing modes of growing children varied on different days of testing. Hairfield and associates concluded that "the variation in respiratory mode we observed may make it impossible to identify clear cause-and-effect relationships regarding upper airway function on facial development."[134] The lack of normative data on nasorespiratory breathing and problematic measurement of respiratory mode must be kept in mind in reviewing the literature regarding implications of nasal obstruction on facial growth and development.

Open Mouth Posture

OMP in children may result from nasal obstruction secondary to enlarged adenoids, from significant allergic disease, from habit developed during previous nasal airway blockage, or from lack of encouragement from adult caregivers to maintain closed-mouth posture. However, oral respiration and OMP are quite common in children and may be unrelated to nasal airway obstruction. Indeed, it may be a normal part of development for some children. Warren and coworkers found that, before the age of 8 years, the proportion of nasal breathers and that of oral breathers were roughly equal. After 8 years of age, a majority of

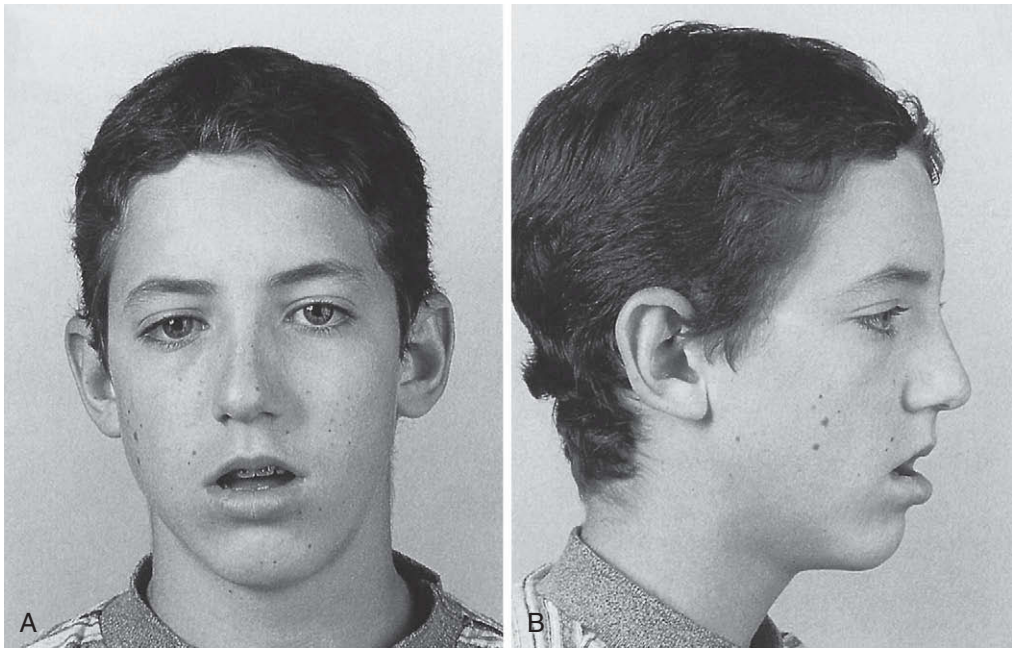

Figure 184-25. **A** and **B,** Typical "adenoid facies" in a 14-year-old boy. Note the long face, open mouth posture, short upper lip, larger lower lip, small nose, and dull facial expression.

children were nasal or predominantly nasal breathers.[135] Black children appear to abandon OMP more quickly over time at a faster rate than that noted in white children.[136] In evaluating children for chronic mouth breathing, OMP does not necessarily imply significant nasal obstruction, because some children will have OMP but are nasal breathers. In their study of children with severe nasopharyngeal obstruction, Woodside and colleagues found that 80% converted to nasal breathing after adenoidectomy.[137] The remaining 20% of their study population did not convert to nasal breathing following adenoidectomy. Soft tissue components of the oral cavity also may contribute to OMP (e.g., the tongue, by means of tongue thrusting).

Review of the Literature

Several studies have considered the specific effect of nasal airway obstruction on dentofacial growth. Complete nasal obstruction appears to alter dentofacial growth.[138] Paul and Nanda[139] and Gross and coworkers[136] found that children with OMP had less growth of the maxillary arches compared with children with closed-mouth posture. Brodie postulated that in some patients, the force of the buccinator muscle and its attachment may result in poor maxillary arch expansion.[140] A narrow maxillary arch frequently is associated with skeletal open bite and anterior crossbite.[22,141] Oulis and associates[142] found that the presence of posterior crossbite was high in children with severe upper-airway obstruction. Linder-Aronson summarized the conclusions of several studies[143-146]:

1. Monozygotic twins are more alike in mandibular growth direction than dizygotic twins, indicating some genetic influence.

2. Children with enlarged adenoids resulting in nasopharyngeal obstruction and subsequent mouth breathing have a longer total and longer lower anterior facial height. They also have an inclination toward a retrognathic mandible in comparison with unaffected children. Children with enlarged adenoids experience subsequent alteration of the dentofacial structures, resulting in an increase in the incidence of open bite, posterior crossbite, and narrower upper maxillary arches.

3. Children with enlarged adenoids and malocclusion, at 5-year follow-up after adenoidectomy, were found to have an increase in maxillary arch width and a decrease in lower facial height and mandibular plane angle. Affected girls demonstrated more horizontal mandibular growth.

4. Some children may undergo partial reversal of dental and skeletal anomalies after relief of nasal obstruction. Specifically, after adenoidectomy some children have shown evidence of a "partial recovery" from abnormal facial growth direction of the mandible and a decrease in lower facial height.

5. Changes in specific tooth positioning (incisors) after adenoidectomy have been noted.

In their study of 38 children observed over 5 years after adenoidectomy, Woodside and others[137] concluded that mandibular growth was greater in both males and females at the chin than in control subjects and that midface growth was greater in males, although no change in maxillary growth direction was observed for either gender.

Extended head posture is characteristic with mouth breathing and reverses when normal nasal breathing is resumed.[141] Studies in primates with obligatory oral breathing have shown that partial recovery of lower facial height and mandibular steepness occurred when normal respiration was resumed.[147,148] Extrapolation of primate studies on nasal obstruction and growth to humans is not clear. Houston[149] postulated that "growth in anterior face height is determined primarily by growth in the length of the cervical column and the associated stretch of the cranio-cervical fascia and musculature." Muscular influence in this area is supported by the primate studies noted previously.

In many of these studies the differences in measurements were statistically significant but not greatly so. In comparing "long face" and "normal face" adolescents, Fields and colleagues[150] showed data suggesting that decreased nasal respiration may add to a long face phenotype but is not the only cause. Although a large proportion of oral breathers are represented in the long face population, a significant number of long face persons do not have nasal obstruction.[22] Ung and coworkers[133] found a weak association of maxillary and mandibular incisors and class II malocclusion with retroclination. These workers questioned the clinical significance, even though the correlation was statistically significant. In addition, the association between dentofacial variables and respiratory pattern was weak in establishing generalizations about causal relationships when assessed subjectively and objectively. Mahony and associates, in their study of 80 children (45 with

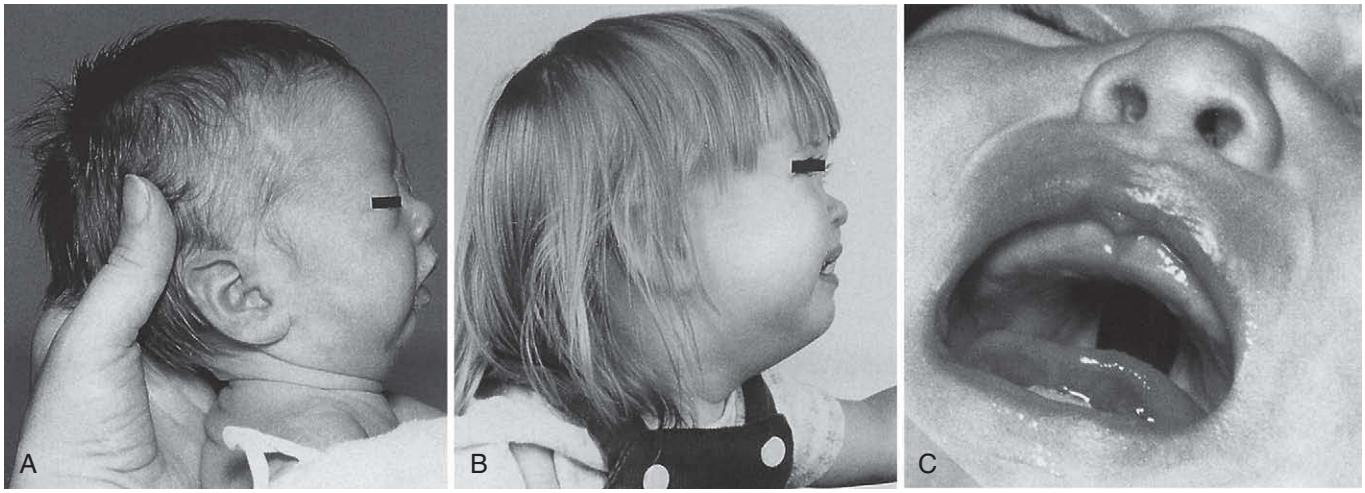

Figure 184-26. **A,** A newborn with Robin sequence. **B,** The same child at 2 years of age. Note the partial mandibular catch-up growth. **C,** U-shaped cleft palate in a patient with Robin sequence.

nasal obstruction who received an adenoidectomy and 35 age- and sex-matched controls), concluded that the changes in the dentoalveolar heights of the maxillary molars and the ratio of the upper and lower anterior face heights seem to be associated with the change in mode of breathing from mouth to nose breathing after adenoidectomy.[151] Hartgerink and Vig[152] could find no significant correlation between the respiratory and morphologic features studied, although they described associations among lip posture, lower anterior facial height, and nasal resistance.

Perhaps there is a period in facial growth and development during which a decrease in nasal breathing and an increase in oral breathing critically influence dentofacial growth. If so, then the timing of intervention would be important to alleviate or lessen the adverse aspects of the ultimate facial result.[133]

Rapid maxillary expansion (RME) with and without surgery has been shown to decrease nasal resistance and increase repiratory area. The study investigators advocate that the pubertal or prepubertal age period is the most suitable age for this intervention in patients with both maxillary constriction and a posterior cross-bite.[153] RME improved obstructive sleep apnea by changing the anatomic structure (widening of the nasal fossa and release of the septum) in 42 patients reported by Pirelli and colleagues; however, this study did not include a control group.[154]

Taking into account the research conducted in this area, the role that breathing patterns and modes play in dentofacial growth is still open to debate. Although the evidence is not entirely clear and the exact mechanisms remain unknown, it appears that craniofacial changes occur in persons with significant nasal obstruction secondary to adenoidal hypertrophy. This has led some researchers in the field to say that adults should watch for OMP in children and encourage them to "maintain appropriate lip seal posture" because of the high incidence of OMP in the orthodontic population. In the event that closed mouth posture cannot be maintained, the clinician should search for a treatable cause of OMP, such as an adenoidectomy.

Variations in response to the relief of nasal obstruction occur in patients, and it may be difficult to decide who would benefit from an adenoidectomy. Although the literature contains a growing body of data that nasal obstruction influences facial characteristics and that reversal may occur under certain conditions, this is still open to debate.

Hartgerink and Vig[152] concluded that "neither orthodontists nor otolaryngologists can predict or accurately diagnose nasal airway impairment from the patient's facial proportions or lip separation at rest." The prudent otolaryngologist should review in detail the findings in a specific case before embarking on a surgical procedure to possibly alter or reverse dentofacial growth.

Craniofacial Abnormalities

Robin Sequence (Pierre Robin Syndrome)

The combination of micrognathia, cleft palate, and glossoptosis is known as the Robin sequence (Fig. 184-26). Previously known as Pierre Robin syndrome, this entity is now recognized to demonstrate etiologic heterogeneity; thus, it does not meet the criteria for a syndrome, with a single identifiable etiology. Cohen[155] proposed that "etiologic heterogeneity suggests pathogenetic heterogeneity in Robin sequence."

There are various definitions of the Robin sequence, including the presence or absence of a cleft palate, glossoptosis, and airway difficulty. This variability has caused confusion in the literature. The Robin sequence can be classified as either isolated (nonsyndromic) or in association with a syndrome (syndromic). Shprintzen[156] found that approximately 20% of patients had isolated Robin sequence, with the remaining 80% of cases associated with various syndromes. The primary clinical implications of this condition are airway obstruction and feeding difficulty. Anatomically, the larynx is under the base of the tongue in patients with micrognathia and glossoptosis, making direct laryngoscopy or intubation difficult and occasionally impossible.[157] Cleft palate and respiratory difficulty can hamper feeding and contribute to failure to thrive.

Whether the Robin sequence is isolated or associated with a syndrome has very significant implications with respect to mandibular growth. A common error made by physicians is to convey to the family of a newborn with Robin sequence that the child's mandible will reach relatively normal size within a couple of years.[158] If the Robin sequence is associated with a known syndrome (primary error or nondeformational cause), such as Treacher Collins or Stickler syndrome, mandibular hypoplasia will persist throughout the patient's life unless surgical intervention is undertaken. In these cases, postnatal catch-up growth does not occur.

If the Robin sequence is isolated, however, with the etiologic pathogenesis related to deformation, then catch-up growth does occur. Pruzansky[159] believed that postnatal growth potential should be included in the analysis of differences between malformed mandibles and that "some mandibles are capable of considerable postnatal recuperations."

It was formerly thought that once affected patients were full-grown, their mandibles would be of essentially normal size. Pruzansky[159] noted that the mandible in such patients differed from the normal mandible in that "the gonial angle was more obtuse, the condyle extended distally from the ramus, and ramus-to-body proportions were deviant because of the greater reduction in body length." He also noted that these features persisted from infancy into adulthood. The mandible appears to grow faster than normal in such patients during the first

few months of life, resulting in alleviation of breathing problems and feeding difficulty in many. Not all patients are so fortunate, however, and numerous measures have been advocated to address these issues: positioning, subperiosteal tongue release, and tracheostomy, among others.[156,157,160-163]

Even in the isolated Robin sequence, full or complete catch-up growth does not occur (see Fig. 184-26A and B). Figueroa and associates[164] performed a retrospective longitudinal cephalometric study analyzing size, growth, and the relation of the mandible, tongue, and airway in isolated nonsyndromic Robin sequence infants. These investigators found that the increased mandibular growth rate in these infants was significant but did not reach values seen in healthy infants. Craniofacial variables were significantly different between healthy patients and those with the Robin sequence. This study supported the concept of "partial mandibular catch-up growth." The investigators also discussed an unpublished study from their institution in which adolescent patients with Robin sequence were compared with healthy children. Results indicated that craniofacial dimensions, including the maxilla, mandible, and airway, were smaller in Robin sequence patients. Laitinen and Ranta[165] and Laitinen[166] found the dental arches at birth of patients with Robin sequence (isolated or possibly syndromic) and those of patients with isolated cleft lip and palate to be equal. By the age of 6 years, the dental arches in patients with Robin sequence were smaller than isolated cleft palate arches, which in turn were smaller than those in children without clefts.

The U-shaped cleft palate in Robin sequence and its mode of development are different from those of the usual V shape seen in primary defects (see Fig. 184-26C). Hanson and Smith[167] hypothesized that with micrognathia, the posteriorly displaced tongue is interposed between the palatal shelves. The palatal shelves do not close, resulting in less posterior growth of the soft palate and subsequently the U-shaped cleft palate. That is, the small mandible causes the tongue to be placed abnormally in the posterior portion of the oral cavity, in between the palatal shelves, and the subsequent lack of closure and growth of the palatal shelves and the lack of growth of the soft palate result in the U-shaped defect.

Robin sequence is relatively common, occurring in approximately 1 in 8500 births. Prevalence is confusing, however, because of the isolated versus syndromic differentiation. The most important issue in these patients is first to ensure an adequate airway and feeding; and then to determine whether there is an associated syndrome in order to communicate to the family the degree of intervention that is likely to be needed.

Down Syndrome (Trisomy 21)

Down syndrome (trisomy 21) is the most common malformation syndrome (Fig. 184-27). It occurs in approximately 1 in 650 live births, and the prevalence is greater with increasing maternal age. Affected persons, who have an extra copy of the genetic material on chromosome 21, have a highly characteristic appearance.[168,169] More than 100 different physical signs can be present with Down syndrome. The main features, in addition to intellectual deficit, are the craniofacial physical characteristics listed in Box 184-1. These characteristics make persons with Down syndrome appear significantly different from the rest of the population. Pueschel and Pueschel[170] extensively reviewed the biomedical concerns of Down syndrome patients, including growth and devel-

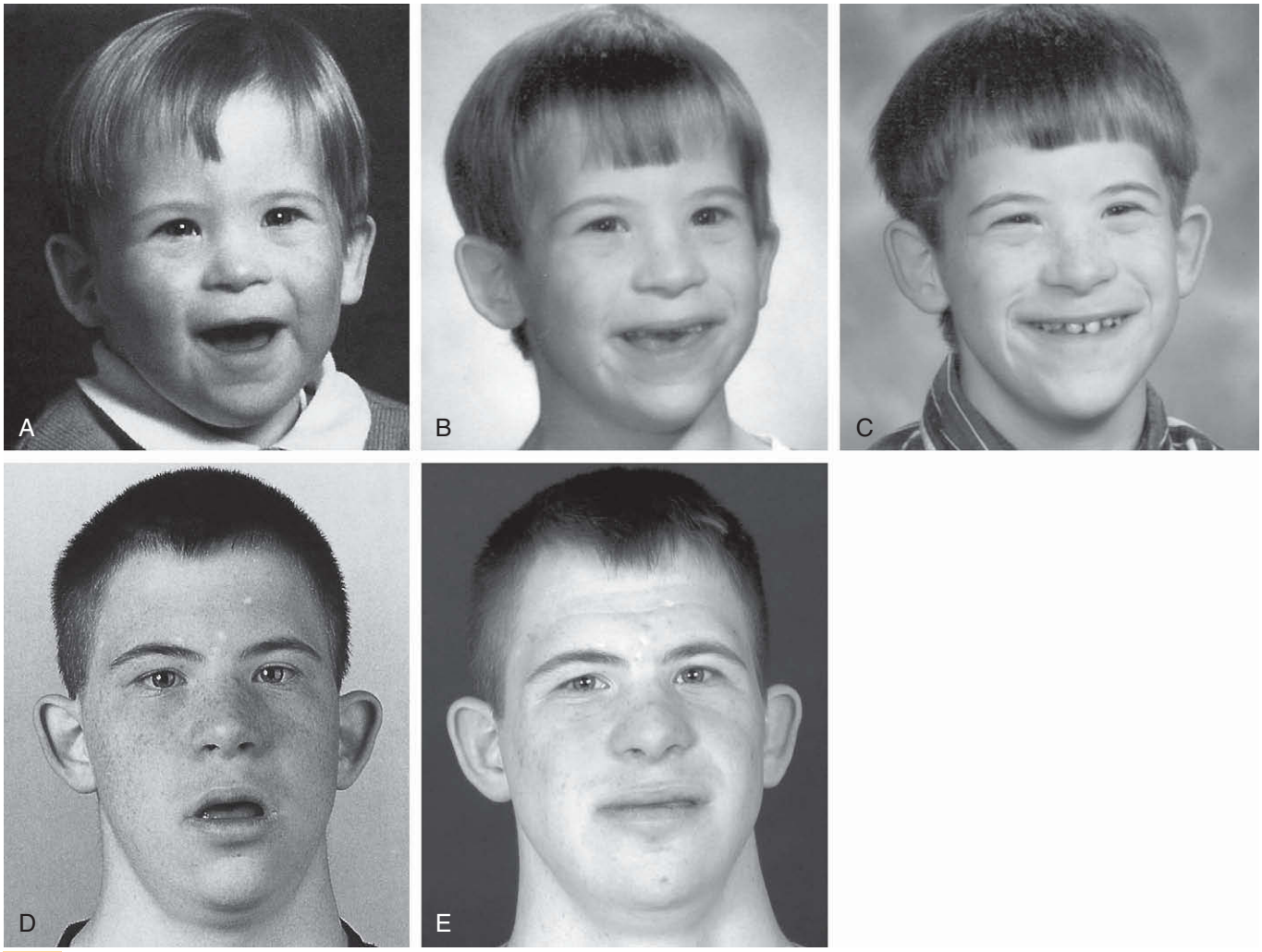

Figure 184-27. **A,** A 2-year-old boy with Down syndrome (trisomy 21). **B,** At age 5. **C,** At age 11. **D,** At age 14. **E,** The patient at age 20.

Box 184-1

Craniofacial Features of Down Syndrome

Brachycephaly
Flat occiput
Upward-slanting palpebral fissures
Epicanthic folds
Short, small nose
Abnormal small ears
Short neck
Midface hypoplasia
Large fissured lips
Large fissured tongue
Dental abnormalities

opment. The specific dysmorphic facial features of Down syndrome, outlined in Box 184-1, can be further classified into five main regions: skull, midface, mandibular and oral, ears, and eyes. The growth changes in each of these regions are reviewed next.

Skull

A majority of patients with Down syndrome have brachycephaly. Head breadth (the largest lateral diameter of the head) and head length (measured from the nasion to the largest length across the occiput) were found to be essentially normal in the first 6 months of life when compared with healthy children.[171,172] At 6 months and 1 year, however, the mean values were less by 1 SD for head breadth and 2 to 3 SDs for head length. The greater difference in head length versus head breadth suggests that cranial growth is more reduced at the cranial base than in the area of the calvaria. In 1979, Hamill and associates[173] determined that head circumference is smaller in persons with trisomy 21; however, this reduction from the norm is thought to be a reflection of overall body size. When head circumference is plotted against body/length ratios, these values are found to be within normal range. Head circumference is related to intracranial or brain growth; whereas cranial base growth probably is under the same control as for total body growth. The occiput also is found to be flat, which is especially noticeable in the profile view. Allanson and colleagues[174] obtained 21 craniofacial anthropometric measurements from patients with trisomy 21 between the ages of 6 months and 61 years of age. Their data were compared with normal known standards and were in agreement with previous studies involving craniofacial findings in Down syndrome. These investigators specifically mention brachycephaly, round face, and small ears but add that underdevelopment of the maxilla in comparison with the mandible also occurs. More recently, computerized anthropometry has been used in patients with trisomy 21 and compared with normal reference data. Several differences have been noted, particularly related to midfacial hypoplasia, decreased nasal protrusion, and a lower facial third region (mandible).[175] Allanson's group found that as age increases, maxillary growth is reduced in comparison with mandibular growth, resulting in a change from the usual round face seen in infants to the more oval shape seen in older patients (see Fig. 184-27).

Sperber[1] indicated that the reduced cranial base results in an increased angulation because of the loss of the flattening effect of the growth of the spheno-occipital synchondrosis. In a skull of normal or reduced capacity, an increase in the basal angle is highly suggestive of Down syndrome.[176] This results in a "dish" deformity of the midface, accentuated by the large neurocranium. The anterior fontanelle is late to close, and the so-called third fontanelle, an open sagittal suture in the region of the parietal bone, is present.[177] A metopic suture is quite common in Down syndrome patients.

Midface

Benda[178,179] noted a deficiency in postnatal development of the nasal bones, the ethmoid, and the maxilla that results in continuance of the fetal proportions of the face in persons with Down syndrome. He also noted that hypoplastic or even absent paranasal sinuses also contribute to midface hypoplasia. Shapiro and associates[180] found that Down syndrome patients have narrower and shorter palates. The deficiency in palatal length, in comparison with that in healthy persons, was so great in the patients from their study (age range, 7 to 18 years) that they could distinguish between a Down syndrome patient and a healthy person on the basis of this dimension alone. Palatal vaults previously were thought to be abnormal (higher-arching) in patients with trisomy 21, but Shapiro's group confirmed that they are within the normal range.[180] Smaller nasal bones appear to contribute to the saddle nose–small nose of these patients.[1] Interorbital distance is reduced, and the mandible is more obtuse.[181] The angle between the base of the skull and the hard palate is less acute than normal in patients with trisomy 21, and the nasopharynx generally is small because of soft tissue encroachment. Although limited by a small sample size, another study compared rapid maxillary expansion in 13 children and no intervention in 13. Acoustic rhinometry measured nasal patency; those children undergoing expansion showed a significant increase in the total nasal volume. The investigators also noted that the widening of the maxillary bones also gives more space for the tongue in the oral cavity and that there is positive dental improvement. However, these two areas were not reviewed objectively in this article.[182]

Sperber[1] theorized that the neural crest tissues involved in facial bone formation, (including the nose) either "may be deficient in number, may not complete migration to their destination, or fail in their inductive capacity or cytodifferentiation." The generalized retardation in midface growth, along with the underdevelopment of the sinuses in patients with trisomy 21, results in the overall poor development and flat facial profile of the midface.

Ears

Persons with Down syndrome have long been recognized to have small ears. The ears are frequently small and boxlike and can be low-set with abnormal overlapping or folding of the helix. Aase and colleagues[183] noted that "of all the anthropomorphic measurements studied, the longitudinal dimensions of the pinna fell furthest below the expected norm at all age levels studied." This finding usually was greater than 2 SDs below the norm in newborns to 1-year-olds and 1 SD in patients older than 1 year of age. External ear canal narrowing is extremely common, and middle ear abnormalities exist.[184,185] The mastoid abnormalities in Down syndrome are mainly hypoplasia and sclerosis.[186] These abnormalities may have an inflammatory etiology from increased problems of middle ear pathology secondary to eustachian tube dysfunction. Generalized hypotonia in Down syndrome may affect the tensor veli palatini muscle, resulting in eustachian tube dysfunction.

Mandible and Oral Manifestations

The oral manifestations of Down syndrome are outlined in Box 184-1. Thickened and fissured lips as the patient advances in age, a large, fissured tongue (possibly related to a relatively small oral cavity), and various dental abnormalities are very common in these patients.[170,187-191] After the age of 16 to 18 years, progressive mandibular prognathism may occur and is believed to be related to the large tongue in a small oral cavity.[192]

Eyes

Using radiographic methods, Gerald and Silverman[181] described narrowing of the interorbital distance in patients with Down syndrome and concluded that this orbital hypotelorism is the skeletal substrate for the characteristic face in these patients. Cohen and associates[193] agreed that ocular hypotelorism is true when measured; however, they also noted that the hypertelorism may appear to be more pronounced in these patients because of the characteristic epicanthic folds and low nasal bridge. Other factors that contribute to the illusion of extreme hypertelorism include exotropia, narrow palpebral fissures, dystopia canthorum, and widely spaced eyebrows. In Down syndrome, epicanthic folds appear to result from underdevelopment of the nasion.[178] An alternative theory is that the epicanthic folds result from an abnormal distribution of the orbicularis oculi muscle, with some fibers passing

circularly in front of the tendon rather than inserting wholly into the ligament.[23]

Abnormal and Poor Growth in Down Syndrome

No specific gene or genes on chromosome 21 have been identified to contribute to the current understanding of how the many phenotypic findings arise in Down syndrome. However, it is postulated that a dosage effect occurs because of the extra chromosome. No growth-regulating genes have been mapped on chromosome 21, but Pueschel and Pueschel[170] postulate that "gene coding for growth-regulating proteins may play a part in the growth retardation observed in individuals with Down syndrome." According to this theory, the extra chromosome 21 is responsible for the abnormal embryogenesis of the fetus with Down syndrome, and somehow the balance in the growth process is altered. Further studies in the molecular biology of growth and development will ultimately delineate this unknown.

Achondroplasia

Achondroplasia is the most common of the chondrodysplasias. A full description of this disorder of bone formation can be found in the works of Jones[169] and Gorlin and colleagues[168] and in the Online Mendelian Inheritance in Man (OMIM) database.[194]

Achondroplasia is an autosomal dominant disorder, with a majority of cases representing a new mutation. Bone formed from cartilage is abnormal because of a mutation in the fibroblast growth factor receptor-3 gene, *FGFR3*, which is located at 4p16.3.[195,196] Two different point mutations have been found in *FGFR3* in patients with achondroplasia, and both lead to the substitution of an arginine residue for a glycine at position 380 of the mature protein, which is in the transmembrane domain of *FGFR3*.[194] In addition to expression of the receptor in cartilage, *FGFR-3* transcripts are present in fetal and adult brains, which have the highest levels of any tissue. This finding may indicate that the effects of the gene involve calvarial content as well as skeletal cartilage, leading to true megalencephaly.[194,197] The exact process leading to the phenotypic appearance is unclear.

Persons affected by this disorder have short stature secondary to rhizomelic shortening of the limbs, as well as abnormalities of a number of other bones, including the lumbar spine, carpals, metacarpals, phalanges, and pelvis (Fig. 184-28A and C). The characteristic facial appearance of achondroplasia results from early spheno-occipital closure, a short cranial base, a small foramen magnum, and resultant megalocephaly with frontal bossing, sunken bridge of the nose, and midface hypoplasia (see Fig. 184-28B and D). In addition, the eustachian tube is shortened. Head growth normally is rapid in the first 6 months of life in patients with achondroplasia.[198]

It is postulated that the genetic defect in achondroplasia leads to reduced growth of the occipital bones, resulting in the small foramen magnum.[19] Premature fusion of the associated synchondroses could also explain the abnormal foramen magnum configuration. Measurement of the foramen magnum may identify affected persons at risk for possible neurologic complications in achondroplasia. Basilar kyphosis is present, with the angle between the ethmoidal plane and clivus reduced to 85 to 90 degrees (normal angle, 110 to 120 degrees).[199] The clivus is vertical, and the sphenoid sinus frequently extends into it.[200] The sella may be small and abnormally J-shaped.[201] The petrous portion of the temporal bone is very distorted, and the internal and external acoustic meatus and labyrinths are abnormally oriented. Of interest, balance is not affected in these patients. Mastoid development is minimal.[200] The chondrocranium is short and narrow, as noted earlier. Dorst[16] observed that the midface is recessed in profile because the facial bones "hang down" from the chondrocranium. Articulation is normal.[199] The mandible is not affected by the genetic mutation but appears disproportionately large. Class 3 dental occlusion is common. Surgical correction using standard craniofacial procedures and nasal bone grafting improves the cosmetic appearance if this is desired.[201,202]

Mandibulofacial Dysostosis (Treacher Collins Syndrome, Franceschetti-Klein Syndrome)

Mandibulofacial dysostosis (MFD), also known as Treacher Collins syndrome, is a rare malformation syndrome associated with a very characteristic appearance,[203] as shown in Figure 184-29. The craniofacial abnormalities in mandibulofacial dysostosis are outlined in Box 184-2,[168,169] and the syndrome is covered in detail elsewhere.[168,169,204]

Box 184-2

Craniofacial Findings in Mandibulofacial Dysostosis (Treacher Collins Syndrome)

Eyes
- Downward-slanting palpebral fissures
- Lower lid coloboma
- Partial to total absence of lower eyelashes

Ears
- Auricular malformations with or without tags and preauricular blind fistulas
- Stenosis or atresia of the external ear canals
- Middle ear and ossicular abnormalities

Face
- Malar hypoplasia (hypoplastic zygomatic bones) and nonfusion of the zygomatic arches
- Flat frontal nasal angle
- Hypoplastic supraorbital rims and ridges
- Narrow nares and hypoplastic alar cartilages
- Tongues of hair onto cheeks

Mandible and Oral Cavity
- Mandibular hypoplasia and severe hypoplasia of the mandibular condyle
- Microstomia
- High-arched, narrow, or cleft palate
- Dental abnormalities

Data from Gorlin RJ, Cohen MM Jr, Levin LS, eds. *Syndromes of the Head and Neck*. 3rd ed. New York: Oxford University Press; 1990; and Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation*. 5th ed. Philadelphia: WB Saunders; 1997.

Mandibulofacial dysostosis is a rare autosomal dominant condition with complete penetrance and variable expression. Sixty percent of cases are the result of spontaneous new mutations. The gene was first localized to 5q32-33.1 by linkage analysis and was subsequently identified by positional cloning.[205] The identification of mutations in the *TCOF1* gene (also referred to as the *TREACLE* gene) in five different families confirmed the causative nature of this gene in MFD. Its function is unknown. At present, linkage analysis or mutational analysis can be undertaken to identify affected family members who may exhibit only mild phenotypic features of this syndrome.

Marsh and colleagues[21,206] provide an exhaustive, outstanding review of the cranial dysmorphology in mandibulofacial dysostosis, deriving their data both from the literature and from three-dimensional reformation imaging from CT scans. From a clinical standpoint, pharyngeal hypoplasia in affected persons is significant because it makes these patients prone to airway difficulty both early in life and later in life. Pharyngeal hypoplasia existed in all 11 patients with mandibulofacial dysostosis reviewed by Shprintzen and coworkers.[207] In fact, patients with a mild or incomplete phenotype were equally at risk. Shprintzen's group recommended nasopharyngoscopy and anterior posterior roentgenography to aid in the diagnosis. With growth, there is an increase in basilar kyphosis exacerbating the problem. MFD patients reported in the literature have responded to craniofacial surgery to alleviate their apnea.[208,209]

Patients with MFD have an abnormal acute cranial base that is 2 to 3 SDs below normal.[156] Peterson-Falzone and Figueroa[210] reviewed the longitudinal measurements of cranial base angulation in 24 patients with mandibulofacial dysostosis. These investigators showed an increase

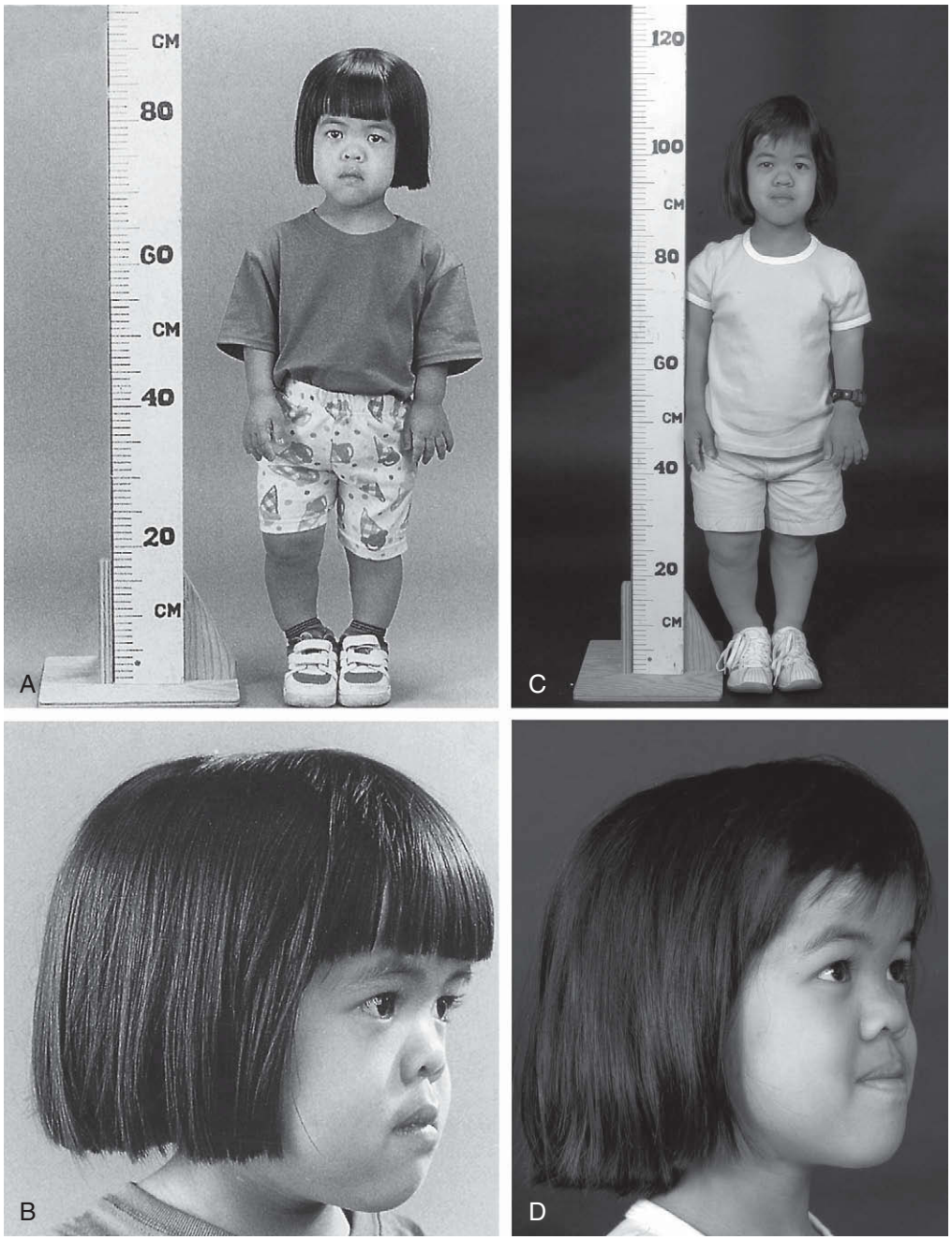

Figure 184-28. **A,** A 6-year-old girl with achondroplasia. **B,** The child manifests the characteristic facial appearance of achondroplasia: frontal bossing, sunken bridge of the nose, and midfacial hypoplasia. The normal mandible appears larger than usual. **C** and **D,** At age 12 years.

in the flexure of the cranial base angle over time, with more than 50% of cases falling into the kyphotic range, confirming previous reports of this finding in the literature. The investigators attribute the increasing flexion to intracranial resorption and extracranial bony apposition as described by Hans[11] and Enlow.[17] They speculate that the increased flexion may be greater in mandibulofacial dysostosis because the clivus resorbs to a greater degree during cranial base development. This may be because of a disproportion between normal brain mass in persons with mandibulofacial dysostosis and the reduction in facial height and the association with the anterior cranial base.

Deficient growth of the spheno-occipital and intersphenoidal synchondroses also plays a role in the formation of the abnormal cranial base. Kreiborg and Dahl[211] studied craniofacial growth in two children with MFD. Progressive basilar kyphosis occurred in both children, and the researchers hypothesized that bending took place at the sphenofrontal suture. They believed that this, along with abnormal growth of the mandible, led to impairment of the airway, that the calvaria appeared to rotate backward and downward in relation to the anterior cranial base, and that the sphenofrontal suture acted as a joint. Kreiborg and Dahl also concluded that the abnormal growth of the mandible occurred at the condyle, which is in agreement with Enlow and Hans' work.[11,17] This study also is consistent with previous findings of hypoplasia of the greater wings of the sphenoid and pterygoid plates.

The mandible in mandibulofacial dysostosis is hypoplastic. The gonial angle (ramus to body angle) is obtuse. The condyles are hypoplastic or completely absent. Antegonial notching (the concavity on the inferior border of the mandible anterior to the ramus-body junction) has been described as characteristic of mandibulofacial dysostosis, distinguishing it from other syndromes that involve the mandible. These features have been presented from studies of lateral cephalograms, longitudinal roentgen cephalometric analyses using metallic implants, and a review of dry skulls.[212-214] Grayson and coworkers[215] disputed this

Figure 184-29. **A,** Characteristic facial appearance of a 10-month-old child with mandibulofacial dysostosis (Treacher Collins syndrome). **B,** Oblique view of same patient. Note the absent external ear canal, which is bilateral, and the headband, which holds bone conduction hearing aids. **C** and **D,** At age 6.

conclusion, although their methods did not employ classic cephalographic landmarks. They believed that complex craniofacial deformities require assessment from more than just conventional methods of measurement.[216]

Moss's functional matrix theory involves the concept that the mandible exhibits plasticity as it relates to the functional matrix with which it is involved, namely the anatomic features related to respiration and feeding. To know what the relationship is between the abnormal mandible—seen in mandibulofacial dysostosis and its functional matrix (respiration and feeding) in the context of Moss's functional matrix hypothesis in experimental form—would be helpful to better understand how the abnormal mandible functions in affected patients.[4,7-10]

Arvystas and Shprintzen[35] used 12 patients, ranging in age from 3 to 22 years (mean age, 10 years 4 months), as a sample population of mandibulofacial dysostosis. A number of cephalometric analyses were undertaken. These workers concluded that the characteristic appearance of the face in Treacher Collins syndrome (i.e., mandibulofacial dysostosis) is a product of the distinctive relationship among the abnormal basicranium, the dysmorphic mandible, and anomalous maxillary-malar complex. The anterior displacement of the temporomandibular joint, the short ramus, short mandibular body, synthesis distortion, and displaced maxilla all result in the characteristic appearance in this syndrome.[35]

Craniofacial surgery for patients with Treacher Collins syndrome is mandatory when problems with the airway become life threatening or are so severe as to compromise the individual. Previously, onlay techniques and soft tissue augmentation were used. However, craniofacial surgery using osteotomies and advancement techniques appears to assist in the orientation of subsequent growth in a more normal direction and to enlarge the airway at the same time. This results in both cosmetic and functional improvement.

As patients with MFD grow, their abnormally formed bones also grow, maintaining their original anatomy. "As they are malformed, so shall they grow."[217] Some researchers believe that the facial appearance of MFD individuals may improve during childhood growth.

Other Conditions and Syndromes

Numerous other syndromes and conditions may result in abnormalities of craniofacial growth and development. Cleft lip and palate and the craniosynostoses are two complex conditions resulting in abnormal

craniofacial growth and development. These conditions cannot be given justice in a brief review, and the reader is directed to the significant body of literature covering these topics.

Conclusions

Craniofacial growth and development are extremely complex. Despite the voluminous amount of literature on this topic, little is known about the control mechanisms involved, even though the current understanding has increased because of the genetic revolution. The latter part of this chapter has described craniofacial growth in several genetic conditions from a primarily anatomic perspective, because at present this is all that is known.

Genetic predetermination is involved to a certain extent in facial growth and development, and many studying the field of craniofacial growth support the concept of Moss's functional matrix hypothesis and its interaction within the genetic constraints of the cells and tissues involved. As some critics have stated, however, Moss's theory explains *what* happens during growth but does not explain *how* it happens. The same can be said in describing abnormal facial growth and development. The cellular interaction within and between craniofacial regions remains unknown. It also seems likely that genes related to craniofacial growth and development are related to neurodevelopment. In the mid-1990s, an understanding of molecular genetics and craniofacial malformations began to emerge.[218,219] Although much progress has occurred in the study of genes for growth factors and signaling factors, much more is still to be learned.[220]

Acknowledgment

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CHAPTER ONE HUNDRED AND EIGHTY-FIVE

Craniofacial Surgery for Congenital and Acquired Deformities

Jonathan Z. Baskin

Sherard A. Tatum, III

Key Points

- Craniofacial anomalies are relatively common deformities, many of which can treated by the otolaryngologist–head and neck surgeon with pediatric and/or facial plastic training.
- Craniofacial defects are often part of a larger syndrome affecting many functional systems.
- Appropriate care is best rendered by a clinically diverse team.
- The underlying pathology is etiologically diverse and heterogeneous.
- Craniofacial skeletal anomalies can be treated surgically with techniques that are reliable and reproducible.
- The application of craniofacial surgical principles, developed to treat congenital problems, also serves well for tumor extirpation and trauma repair.
- Several materials are currently available to reconstruct the craniofacial skeleton, but there is wide effort to develop more biomimetic bone substitutes.

Craniofacial surgery is a broad and continually growing field that addresses a wide array of congenital and acquired deformities. Much of the growth in this field has occurred in the last few decades, thus it is a relatively young discipline that is still actively evolving. This medical and surgical subspecialty includes a set of approaches and techniques developed in the last 50 years that allow for safe, reliable manipulation of the craniofacial skeleton. Although the field is focused primarily on congenital problems, the techniques can be broadly applied to trauma and tumor surgery of the craniofacial structures. *Craniofacial anomaly* refers to any malformation that involves the face, cranium, and cranial base. In the pediatric population the field is more commonly concerned with congenital anomalies, whereas in adults the more commonly encountered applications relate to trauma and neoplasm.

Congenital craniofacial deformities commonly occur as isolated defects and less often as part of a syndrome. The Committee on Nomenclature and Classification of Craniofacial Anomalies of the American Cleft Palate Association has organized craniofacial malformations into the following five categories: (1) facial clefts/encephaloceles and dysostoses; (2) atrophy/hypoplasia; (3) neoplasia/hyperplasia; (4) craniosynostosis; and (5) unclassified. Clinical entities such as orbital hypertelorism often exist with a syndrome that clearly fits into one of the aforementioned classifications.[1] Hypoplasia of the midface and micrognathia would be incorporated into the second category. In children, hematologic disorders and overly aggressive cerebrospinal fluid (CSF) shunting can result in secondary craniofacial disorders, which can be put into the third or fifth category. Acquired deformities of the craniofacial complex also include those inflicted by means of a traumatic event. Neoplasm (third category) and its treatment are classified as acquired deformities.

As is plainly evident, the field of craniofacial surgery is large with many and varied subfields. The objective of this chapter is to provide an overview of craniofacial surgery. The pathophysiology of major craniofacial anomalies is discussed in order to provide a framework for an understanding of the important clinical issues. The focus of the discussion is on cranial vault and craniofacial bony defects. Those disorders of first and second branchial arch derivatives that give rise to known craniofacial anomalies are briefly described. Trauma and neoplasm are important contributors to craniofacial disease and are examined briefly in this chapter but discussed in greater detail elsewhere in the text. Facial and palatal clefting is a very important subject in craniofacial surgery and is briefly discussed from a basic perspective. A clinical discussion of these defects, however, is the focus of another chapter.

Epidemiology

Craniofacial anomalies have been reported to constitute approximately one third of all congenital defects. The incidence of assorted individual deformities and syndromes varies. However, the overall incidence is considered to be 0.2 to 0.5 per 1000 births.[2] Interestingly, some craniofacial deformities occur at a uniform rate across racial and ethnic populations, whereas others occur at a frequency that varies as a function of race and ethnicity.

Several craniofacial malformations appear to have a genetic etiology. Several familial types have been well documented, and transmission can occur via autosomal dominant or recessive modes. With occasional exceptions males and females tend to have similar incidences for most anomalies. Craniofacial anomalies have been reported to occur as part of a genetic condition in about 20% of cases.[2] However, with the discovery of new syndromes and the recognition that "isolated defects" often have a genetic etiology, the 20% figure is probably an underestimate. Furthermore, as discussed here, the pathogenesis of craniofacial anomalies is complex, and generally it is most accurate to describe their etiology as multifactorial.

Mechanisms of Postnatal Facial Growth

It was once thought that craniofacial growth (like all other growth) was regulated, to a large extent, by the central nervous system. It is now understood to be much more complex. On a cellular level, the signal-sensitive membranes of the many types of cells respond to several different cues. On a developmental level, the functional needs of a particular structure and its relationship to adjoining structures strongly influence patterns of growth. Craniofacial bony growth is secondary to neural tissue growth and expansion. The brain as an organ mass develops early in embryogenesis. The developing brain highly influences the morphology of the basicranium, which in turn functions as a template for subsequent facial growth. The face can be viewed as a series of stratified vertical levels or fields that are strongly affected by growth of the brain and basicranium.[3]

Physiologically, there are two primary forces at play during the growth of individual craniofacial bones and structures, displacement and remodeling (Fig. 185-1). Growth does not indicate uniform enlargement of a structure; rather, it refers to a combination of displacement and remodeling. Displacement occurs when the bone is pushed away from its articulation with other bones (by the combined effects of growth of the surrounding soft tissue and growth center/sutural activity). Remodeling occurs by resorption and deposition of new bone that result in a net vector of growth. It is in this way that the correct tissue mass is achieved and that enlargement occurs proportionally and in the appropriate direction.

In the craniofacial complex the basicranium (along with the related soft tissues) influences the naso-orbito-maxillary complex and the ramus of the mandible, which conform through continual remodeling. Growth of the naso-orbito-maxillary complex displaces the maxillary dento-alveolus. This displacement together with growth of the mandibular ramus then affects growth of the corpus (body) of the mandible. The importance of soft tissues in growth is demonstrated in such clinical manifestations as the "adenoid face." The entire system is plastic and in flux throughout the growing period (even after periods of growth, albeit to a far lesser extent). It is for this reason that rigid nonbiologic implants such as those of titanium have the potential to interfere with normal growth if used during active development; they lack the plasticity that is so vital to dynamic growth.[4-6]

Throughout the period of craniofacial growth an overriding homeostasis exists among the different fields of growth. Small aberrations in one field can be counterbalanced by compensatory growth in another, resulting in constant equilibrium. This is very important for the physician to bear in mind when planning surgical or orthodontic intervention. Treatment failure or relapse is likely if that equilibrium is significantly disrupted.[7] Generally, interventions are more likely to succeed if the cause of the abnormality is addressed during periods of rapid growth. In contrast, the effect of the abnormality is more successfully treated during periods of slow growth.[3]

Craniofacial synostosis, or premature closure of a suture, is a good example of the morphologic consequence of defective skeletal growth. It also illustrates the importance of homeostasis in craniofacial development. The causes of craniosynostosis are likely multifactorial and the source of some controversy.[8,9] It has been shown to be associated with abnormalities in sutural biology, various biomechanical forces,[10] and defects in the primary growth centers of the involved bones. Sutural growth is also affected by surrounding tissue interactions. The contacting dura, for instance, influences the continued patency of sutures and helps regulate its closure.[11-14]

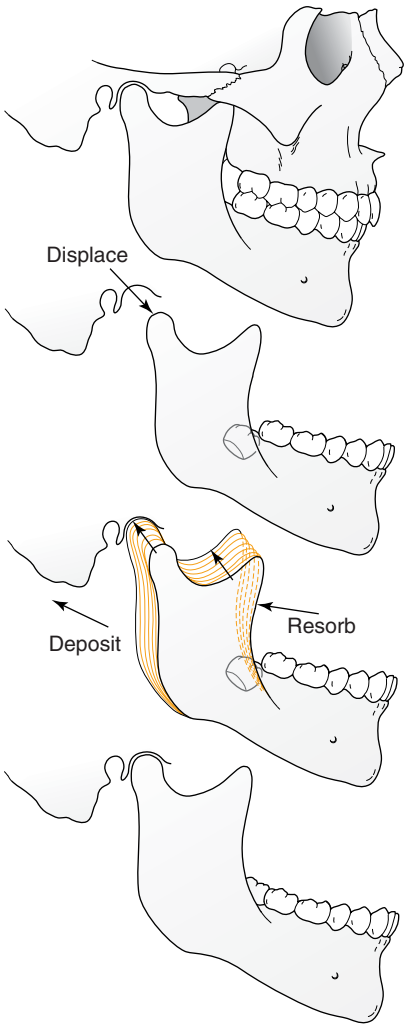

Figure 185-1. Schematic representation of displacement and remodeling in the mandible. Remodeling occurs through a combination of resorption and deposition. *(From The facial growth process. In Enlow: DH (ed). Facial Growth. 3rd ed. Philadelphia: WB Saunders; 1990.)*

Regardless of the underlying etiology, the morphologic cause of the defect is premature closure of the suture, and this disruption in normal growth upsets the homeostasis inherent to the process. Consequently, compensatory growth occurs elsewhere as a means of achieving a new homeostasis. If the synostotic suture is treated early in life (while craniofacial growth is still quite active) the normal homeostasis can be restored by releasing the synostotic suture and thereby addressing the cause of the problem. If it is treated later in life, when active growth is largely complete, the morphologic results of the defect (including the anatomy associated with the compensation) have to be addressed because the sutural growth is no longer relevant.

Fusion of the facial processes during embryogenesis is another fundamental aspect of facial growth that is critical to normal development. Orofacial clefting results from a defect in this process. For opposing facial processes to fuse in the midline, the contacting epithelia must be eliminated so that the underlying mesenchymal tissue can become continuous. In the palate this elimination has been shown to occur through apoptosis, epithelial to mesenchymal cell transdifferentiation, or cell migration.[14-17] Underdevelopment of the mesenchyme of the involved subunits might preclude proper fusing, as can excessive apoptosis. Inadequate migration or proliferation of neural crest ectomesenchyme might have the same result. Facial clefting can also result from constricting anatomic defects. In the case of stunted mandibular growth, a Pierre Robin sequence can ensue whereby the palatal shelves are prevented from fusing in the midline.

Pathophysiology

As previously mentioned, the etiology of congenital craniofacial disorders is most often multifactorial and incompletely understood. A diverse and heterogeneous group of factors can contribute to abnormal craniofacial development. Various genetic defects have been implicated in the development of craniofacial anomalies. This field of study has yielded an enormous amount of information in the last few decades. In addition, numerous metabolic diseases are known to interfere with bone growth and suture function. Environmental factors have also been shown to exert important influences on embryologic craniofacial development.

Molecular Genetics

Several genetic defects have been identified that are directly associated with various craniofacial defects (Table 185-1). The products of these genes tend to fall into one of the following categories:

- Growth factor receptors: fibroblast growth factor receptors (FGFRs) 1, 2, and 3; tumor growth factor-β receptors (TGFβRs) 1 and 2; PTC and FGDY gene products
- Ephrins: membrane-anchored ligands for Eph receptor tyrosine kinases
- Transcription factors: MSX2, ALX4, GLI3, MITF, PAX3, RUNX2, TWIST
- Connective tissue structural proteins: type II and XI collagen, fibrillin-1 (FBN1)

These genetic defects have been linked to syndromes as well as isolated defects. For instance, defective FGFRs have been identified as the etiologic basis of some types of craniosynostosis as well as various syndromes (see Table 185-1).[18-45]

FGFRs are transmembrane receptors for fibroblast growth factors (FGFs). FGFs are involved in regulating cell proliferation, differentiation, and migration through a number of pathways. The receptor is made up of an extracellular domain (receptor-ligand binding), a transmembrane domain, and an intracellular tyrosine kinase enzymatic domain (Fig. 185-2A). There are several variations of the FGFR protein—all with important cell growth functions. Signaling via FGFR1, for instance, has been shown to facilitate neural crest migration, and a defective receptor has been linked to midline facial clefting in mice.[45] Defects in FGFR1 have been found to cause Kallmann's syndrome 2, which can include cleft lip and palate (see Fig. 185-2B).[46] Defects in FGFR1 and FGFR2 have been linked to syndromes such as Pfeiffer's syndrome (in which both receptors are defective) and to conditions of which craniosynostosis is a feature.[38,47] Defects in FGFR2 alone have been found in Apert's syndrome,[20,48] Jackson-Weiss syndrome,[28] Crouzon's syndrome,[29] and Beare-Stevenson cutis gyrata syndrome.[49] A defective FGFR3 protein is responsible for Crouzonodermoskeletal syndrome (Crouzon's syndrome with acanthosis nigricans),[30] for Muenke-type craniosynostosis,[32] and also for the disease process seen in achondroplasia.[50] In this disease the epiphyseal growth plates in long bones prematurely fuse. There are gross and histological similarities of long bone growth plates to the synchondroses of the calvaria. This work has led to the understanding that FGFR3 is involved in regulation of skeletal growth. In FGFR3 knockout mice (mice in which the gene that encodes this protein has been eliminated), there is severe retardation of skeletal maturation.[48,51-53]

The link between known syndromes or anomalies and genetic defects, however, can be complex and difficult to characterize. Defects in each of the three domains (in different FGFRs) have been discovered in association with craniofacial abnormalities, yet defects in the same domain of one FGFR type can cause two separate syndromes. For instance, identical mutations have been discovered in patients with Crouzon's, Pfeiffer's, and Jackson-Weiss syndromes, suggesting the involvement of other factors in the ultimate phenotypic expression.[38] Conversely, as is evident in Figure 185-2B, mutations in several distinct domains on one particular FGFR can result in the same phenotype.

As previously mentioned, defects in transcription factors and connective tissue proteins are also implicated in the pathogenesis of craniosynostosis. MSX2 is a homeobox gene that encodes a DNA binding transcription factor. It has been associated with nonsyndromic craniosynostosis (Boston type),[24,54] and ALX4, another homeobox gene, has been linked to parietal foramina.[34] Most cases of Saethre-Chotzen syndrome are caused by haplo-insufficiency of the TWIST gene, which appears to encode a transcription factor.[41] The GLI-3 gene and the transcription factor that it encodes are defective in Grieg's cephalopolysyndactyly (a rare syndrome that can include craniosynostosis).[31,55]

Genetic defects encoding several different extracellular matrix constituents can lead to anomalies of the craniofacial complex. Defective collagen, such as that seen in osteogenesis imperfecta, is clearly associated with bony abnormalities, although this disease only occasionally affects the craniofacial skeleton. Defective fibrillin (encoded by FBN1) results in Shprintzen-Goldberg syndrome with craniosynostosis and maxillary/mandibular hypoplasia.[43] The defective genes responsible for Stickler's syndrome are *COL2A1* and *COL11A2*, which encode types II and XI collagen, respectively.[56,57]

Metabolic Disorders

Several metabolic derangements are known to interfere with craniofacial development. The best known is the group of disorders known as the *mucopolysaccharidoses*. This group of disorders is characterized by a deficiency of lysosomal enzymes that results in a buildup of mucopolysaccharides. Although there are several clinical entities, patients with some of the more severe variations of the disease have large and dolichocephalic (long and narrow) skulls with premature closure of the sagittal suture and poorly developed mastoids and paranasal sinuses. Mucolipidosis, hyperthyroidism, and rickets are also known causes of craniosynostosis.[58,59]

Intrauterine Causes

In utero environmental contributors to craniofacial maldevelopment fit into the following four general categories: teratogenic, infectious, nutritional, and mechanical. Fetal alcohol syndrome can involve a wide range of defects, including holoprosencephaly. Tobacco use during critical periods of embryogenesis has also been shown to adversely affect craniofacial development. Medications such as hydantoin, phenytoin, valproic acid, and isotretinoin (a vitamin A derivative used in the treatment of acne) can exert deleterious effects on embryogenesis, as can toluene, the environmental contaminant dioxin, and ionizing radiation.[14,60,61]

Viral infections during pregnancy have been shown to cause cleft lip/palate via mutations in PVRL1 and IRF6.[62,63] Nutritional intake is also clearly linked to craniofacial development. Sonic hedgehog signaling, which is important in mediating parts of craniofacial development, is modulated by cholesterol. Therefore diets and medications that profoundly influence cholesterol levels can cause craniofacial malformations.[64,65] The link between a diet deficient in folic acid and neural tube defects has been well documented and has led to the widespread supplemental addition of folic acid to many processed foods throughout the developed world.

Finally, intrauterine constraint can cause deformation of the craniofacial skeleton. Factors that have been associated with intrauterine constraint include breech presentation, persistent fetal lie, early pelvic engagement of the head, oligohydramnios, prima gravidity, multiple gestations, uterine malformations, amniotic bands, and defects in fetal neuromuscular development.[66,67]

Acquired Craniofacial Deformities

Several postnatal conditions predispose an infant to disrupted craniofacial growth. Hematologic diseases such as thalassemias, sickle cell anemia, congenital hemolytic icterus, and polycythemia vera are known to cause craniosynostosis. Hyperplasia of the bone marrow leads to bony overgrowth in the skull. This in turn can cause the calvarial sutures to fuse prematurely.[68] Iatrogenic craniofacial anomalies can occur in patients who require ventricular shunts. If the shunt volumes in such patients are excessive, there is a lack of tension across the

Table 185-1

Craniofacial Anomalies with Phenotype and Known Gene Mutation

Condition	Craniofacial Phenotype	Gene*	OMIM Code†	Chapter Reference(s)
Aortic aneurysm, arterial tortuosity, hypertelorism, cleft palate/bifid uvula, craniosynostosis	Craniosynostosis, cleft palate, hypertelorism	TGFβR1 TGFβR2	190181 190182	19
Apert's syndrome	Craniosynostosis (brachycephaly); wide midline defect closes by coalescence of bony islands; midface malformations; dental crowding; cleft or narrow palate with swellings	FGFR2	101200	20-22
Beare-Stevenson cutis gyrata syndrome	Craniosynostosis (kleeblattschädel)	FGFR2	123790	23
Boston-type craniosynostosis	Craniosynostosis (kleeblattschädel), forehead retrusion, frontal bossing	MSX2	123101	24
Cleidocranial dysplasia	Delayed suture closure, frontal parietal bossing, wormian bone(s), hyperdontia, tooth eruption defects	RUNX2	119600	25
Craniofrontonasal syndrome	Craniosynostosis (brachycephaly), central defect between frontal bones, hypertelorism, divergent orbits	EFNB1	304110	26
Craniolacuna and pansynostosis	Multiple rounded calvarial bone defects, widespread craniosynostosis, hydrocephalus	FGFR2		27
Crouzon's syndrome	Craniosynostosis (brachycephaly), pronounced digital impressions of skull, midface hypoplasia, shallow orbits	FGFR2	123500	28, 29
Crouzonodermoskeletal syndrome	Craniosynostosis	FGFR3	134934	30
Grieg's cephalopolysyndactyly	Craniosynostosis in small percentage of cases, frontal bossing, sagittal ridging, hypertelorism	GLI3	175700	31
Muenke-type craniosynostosis (nonsyndromic)	Craniosynostosis (brachycephaly)	FGFR3	602849	32, 33
Parietal foramina	Symmetric parietal bone defects, cleft lip/palate	MSX2 ALX4	168500 605420	34-36
Parietal foramina with cleidocranial dysplasia	Symmetric parietal bone defects	MSX2	168550	37
Pfeiffer's syndrome	Craniosynostosis (brachycephaly)	FGFR1 FGFR2	101600	38-40
Saethre-Chotzen syndrome	Craniosynostosis (especially brachycephaly), flat forehead, low hairline	TWIST	101400	41, 42
Shprintzen-Goldberg (marfanoid) syndrome	Craniosynostosis (especially lambdoid and sagittal sutures), maxillary and mandibular hypoplasia, palatal abnormalities	FBN1	182212	43
Thanatophoric dysplasia II	Craniosynostosis (cloverleaf skull)	FGFR3	187601	44

*Gene abbreviations that have not been defined/spelled out are not acronyms or abbreviations.
†Online Mendelian Inheritance in Man database; available at www.ncbi.nlm.nih.gov/omim/
EFNB1, ephrin-B1; FBN, fibrillin; FGFR, fibroblast growth factor receptor; TGF-βR, tumor growth factor-β receptor
Adapted from Rice DP. Craniofacial anomalies: from development to molecular pathogenesis. *Curr Mol Med.* 2005;5:699-722.

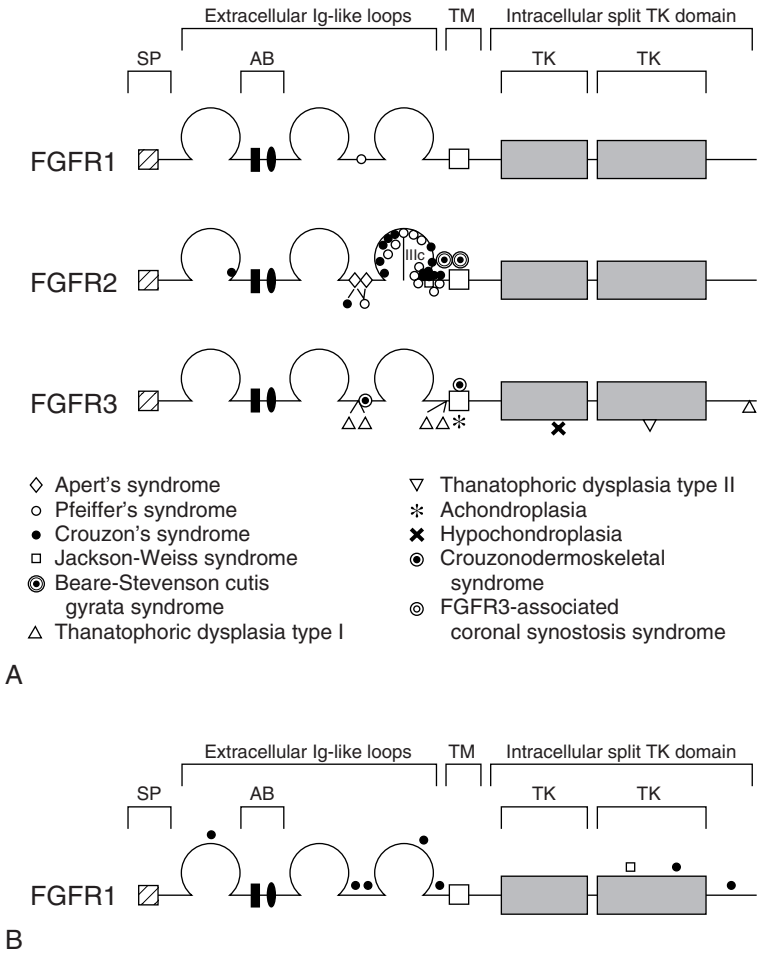

Figure 185-2. DNA mutations lead to several known defects in the fibroblastic growth factor receptor (FGFR) protein. **A,** Depicted are three receptors with defects involving different domains. Two phenotypically distinct syndromes can be caused by genetic mutations in the same functional domain of the same receptor type. **B,** Several different mutations of FGFR1 (*circles* refer to missense mutations, and *square* refers to a frameshift mutation) widely distributed along several distinct domains of the receptor that have been associated with one recognizable phenotype, Kallmann's syndrome. AB, acidic box; Ig, immunoglobulin; SP, signal peptide; TK, tyrosine kinase; TM, transmembrane domain. (**A** from Cohen MM Jr, Maclean RE. *Craniosynostosis: Diagnosis, Evaluation and Management.* 2nd ed. New York: Oxford Press; 2000. **B** adapted from Trarbach EB, Costa EM, Versiani B, et al. Novel fibroblast growth factor receptor 1 mutations in patients with congenital hypogonadotrophic hypogonadism with and without anosmia. *J Clin Endocrinol Metab.* 2006;91:4006-4012.)

sutures, which produces an environment that mechanistically resembles the one seen in microcephaly. In these conditions there is an increased risk of secondary craniosynostosis.[58] Etiologically, trauma and neoplasm can cause acquired craniofacial deformity, although they do so rarely.

Clinical Manifestations

Congenital Craniofacial Abnormalities

Craniofacial anomalies range from mild functionally asymptomatic defects (certain single-suture craniosynostoses) to severe anomalies that are not compatible with life (forms of holoprosencephaly). Typically, the pediatrician consults the craniofacial surgeon about a neonate who has an abnormally shaped head or unusual appearance. A fundamentally important point is to suspect the deformity to be part of a wider syndrome and to initiate a comprehensive examination in search of other abnormalities. However, the majority of cases of craniosynostosis are isolated with no associated anomalies.[69] Descriptions of some of the more common craniofacial abnormalities follow.

Craniosynostosis

Craniosynostosis refers to premature closure of the involved bony suture. The consequence is that growth is inhibited in the direction perpendicular to the suture line (Fig. 185-3). Ensuing developmental growth occurs in a compensatory pattern that permits, to the extent possible, continued expansion of the intracranial content in unrestricted directions. It must be stressed that the compensatory growth that occurs is the normal biologic response to sutural constraint. The functional and aesthetic imbalance that occurs is, in part, a byproduct of normal physiology. The various types of craniosynostosis are as follows.

Scaphocephaly

Scaphocephaly is the most common of cranial synostotic conditions. The sagittal suture, or part of it, prematurely fuses (Fig. 185-4). This anomaly prevents calvarial growth in the transverse dimension. The compensatory growth occurs in the anteroposterior (AP) direction, leaving the patient with decreased biparietal and bitemporal dimensions. The resulting head shape is long and narrow. There are several variations ("saddle deformity," "football deformity"), depending on the extent of premature sagittal fusion and also on whether the metopic suture is involved.

Trigonocephaly

Trigonocephaly refers to a triangular forehead (as viewed from above) and is associated with metopic suture synostosis. There is a decrease in bifrontal diameter. It is a mild form of craniosynostosis with rare func-

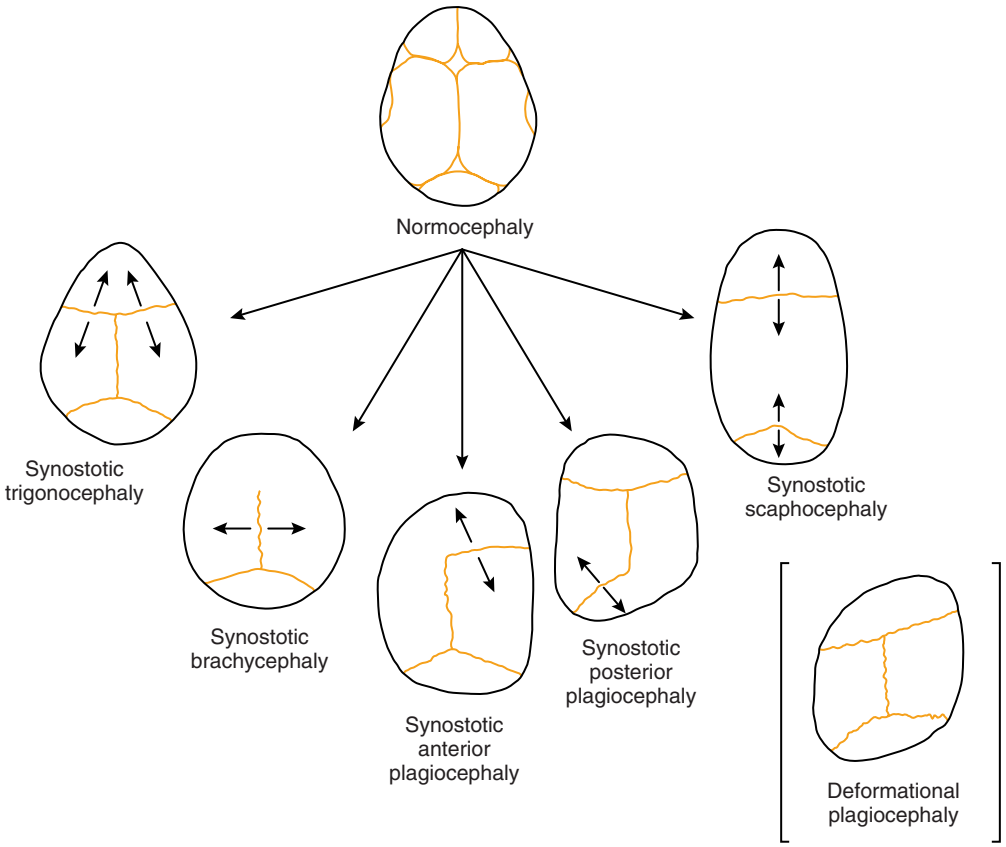

Figure 185-3. In craniosynostosis, growth is prevented from occurring across the fused suture. *Arrows* demonstrate compensatory growth that occurs across open sutures with continued intracranial expansion. (From Cohen MM Jr, Maclean RE. *Craniosynostosis: Diagnosis, Evaluation and Management*. 2nd ed. New York: Oxford Press; 2000:122.)

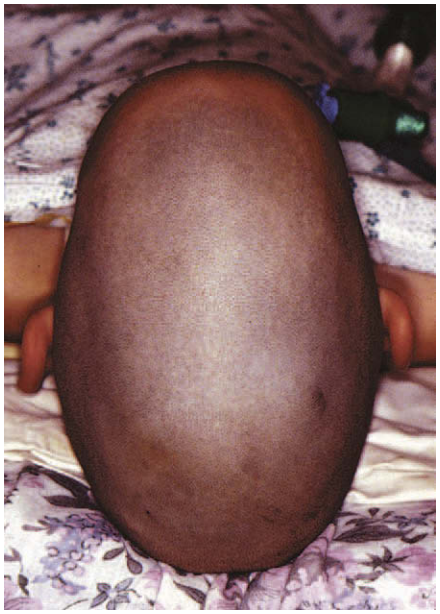

Figure 185-4. Sagittal suture synostosis without premature metopic closure resulting in scaphocephaly.

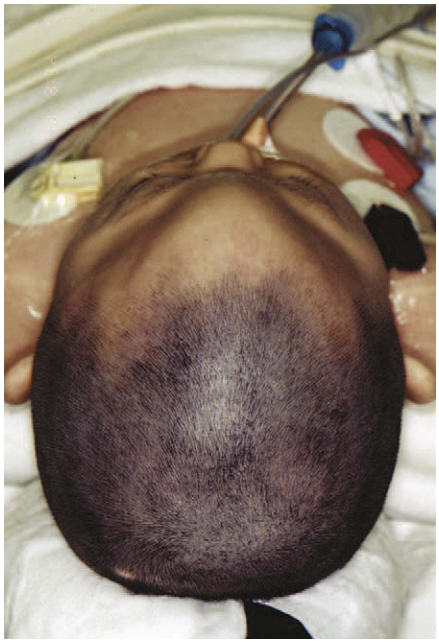

Figure 185-5. Metopic suture synostosis resulting in trigonocephaly.

tional consequences (Fig. 185-5). The suture area is thickened, resulting in an anterior midsagittal ridge. This appearance has been described as resembling the keel of a ship. There can be associated hypotelorism. In mild cases there may be only suture ridging without significant forehead deformity.

Plagiocephaly

In *plagiocephaly,* the head is asymmetric, flattened in one or more regions. It can be either synostotic or deformational and can be anterior or posterior. *Synostotic plagiocephaly* refers to either unilateral coronal (Fig. 185-6) or lambdoid synostosis. In coronal synostosis the forehead

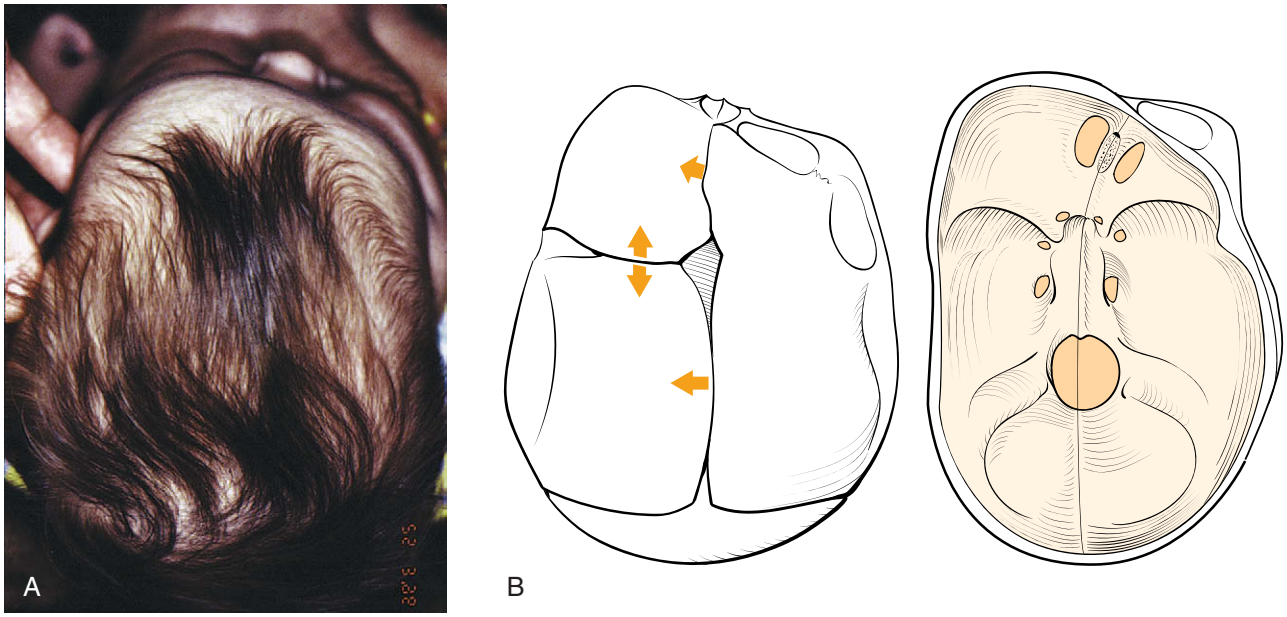

Figure 185-6. **A,** Unilateral coronal synostosis resulting in plagiocephaly. Note that the cranial vault irregularities are not confined to those ipsilateral to the defect. Compensatory growth has resulted in frontal bossing on the contralateral side. **B,** A schematic representation of plagiocephaly.

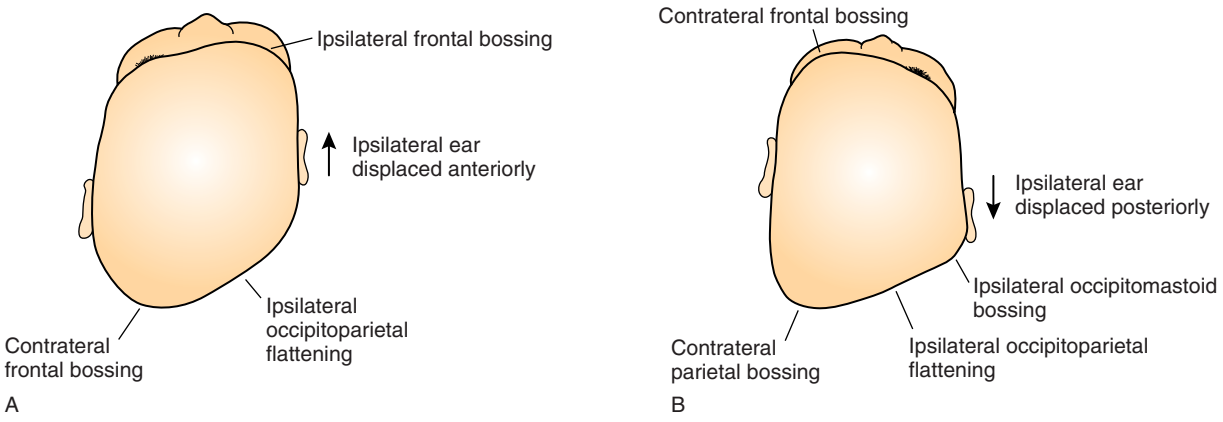

Figure 185-7. Deformational and synostotic plagiocephaly give rise to different characteristic head shapes. **A,** Posterior deformational plagiocephaly results in a parallelogram shape to the head with an anteriorly displaced ipsilateral ear. **B,** Unilateral lambdoid synostosis gives rise to contralateral posterior and occasional anterior bossing. The ipsilateral ear is displaced posteriorly. *(From Cohen MM Jr, Maclean RE.* Craniosynostosis: Diagnosis, Evaluation and Management. *2nd ed. New York: Oxford Press; 2000:128.)*

of the affected side is flat whereas the supraorbital rim is elevated and displaced posteriorly. The rim lies at or posterior to the plane of the cornea although it should normally be about 1 cm anterior to the cornea. The nasal root can be deviated to the side of the defect. The contralateral forehead is bossed, and the supraorbital rim can be pushed down. The ipsilateral auricle is anteriorly displaced but the occiput is minimally affected.

In unilateral lambdoid synostosis, there is an occipital flatness on the affected side. The ipsilateral auricle is posteriorly displaced, but the forehead is not typically affected. True lambdoid synostosis is a rare entity. Lambdoidal synostosis is frequently confused with posterior deformational plagiocephaly.

Deformational plagiocephaly is far more common and can be influenced by the previously noted intrauterine constraint factors, hypotonia, and prematurity. It is further compounded by sleeping in the supine positioning, with a predilection of the infant to sleep on one side owing to a prominent occiput and poor head control. This phenomenon has increased since the American Academy of Pediatrics, in an effort to reduce sudden infant death syndrome (SIDS), issued its recommendations to place sleeping infants in the supine position.[58,69] Additionally, persistent fetal lie, vertebral anomalies, muscular disorders, ocular abnormalities as well as assorted other conditions, can cause torticollis, further aggravating sleep position problems. The sutures in deformational plagiocephaly remain open so there is no ridging. The differences in head shape between synostotic and deformational plagiocephaly are illustrated in Figure 185-7.

Brachycephaly

Brachycephaly is the term used for bilateral coronal synostosis (Fig. 185-8). It is often accompanied by turricephaly (tall head) or acrocephaly (pointed head). As a result of this sutural synostosis, the skull is unable to expand in the AP dimension. In order to accommodate the expanding intracranial content, the skull grows in the lateral and superior dimensions. The neonate's cranium, therefore, has a smaller AP distance and greater lateral dimensions. The forehead comes right off the nose with a low hairline, and the glabellar depression is absent.

Figure 185-8. Bilateral coronal suture synostosis resulting in brachycephaly.

Figure 185-9. Coronal and sagittal suture synostosis in this child with Apert's syndrome resulted in acrocephaly.

Acrocephaly

Acrocephaly (also known as oxycephaly and turricephaly) consists of a skull that is high and conical (Fig. 185-9). This abnormality can develop as a result of progressive postnatal involvement of both the sagittal and coronal sutures. Compensatory growth occurs through the anterior fontanel.

Kleeblattschädel

Kleeblattschädel is also known as cloverleaf skull (Fig. 185-10). It results from synostosis of all the sutures previously discussed except for the metopic suture. The bone overlying the sutures is very thick but the intervening bone is thin. The expanding intracranial content tends to cause a ballooning of the thin bone between the sutures. This compensatory growth, in addition to expansion through the remaining open sutures, gives the characteristic lobular appearance of a cloverleaf. The skull growth falls drastically short of the needs of intracranial expansion, giving rise to neurologic impairment, increased intracranial pressure (ICP), and, often, secondary hydrocephalus. These patients exhibit exorbitism and therefore are at risk for globe exposure, and their optic nerves can also be at risk for damage. This anomaly requires prompt surgical attention to release the binding skull.

Figure 185-10. Premature fusion of all the cranial sutures except for the metopic and squamosal sutures results in kleeblattschädel or cloverleaf skull. (From Cohen MM Jr, Maclean RE. *Craniosynostosis: Diagnosis, Evaluation and Management.* 2nd ed. New York: Oxford Press; 2000.)

Facial Clefts

Facial clefts make up a large category of facial anomalies. A facial cleft is classified on the basis its position relative to the midsagittal plane. Although rare, facial clefts can present uniquely challenging problems to the surgeon. A further discussion of facial clefts is beyond the scope of this chapter.

Encephalocele

An *encephalocele* is a protrusion of intracranial content through a defect in the craniofacial skeleton (Fig. 185-11). It is classified according to its position in the skull. If the protruding content contains meninges, it is referred to as a *meningocele*. If it contains meninges and brain, it is called a *meningoencephalocele*, and if the protrusion additionally contains ventricle, it is known as a *meningoencephalocystocele*.[70]

Syndromes

The syndromes that cause craniofacial anomalies are quite varied in their clinical presentation. Because craniofacial anomalies frequently manifest as part of these syndromes, a familiarity with some of the well-described syndromes is important. This knowledge leads to more focused examination. Once a full survey is done, the proper consultations can be sought. Brief descriptions of several syndromes follow.

Crouzon's Syndrome

Crouzon's syndrome is an autosomal dominant condition that exhibits complete penetrance and variable expressivity. It often results in brachycephaly, but multiple sutures can also be affected. The calvarial suture defects can occur prenatally or throughout the first 5 years of life. There is associated midface (maxillary) hypoplasia, which leads to a class III malocclusion (the mandible is typically near normal). Exorbitism occurs as a result of decreased bony orbital volume (in contrast to exophthalmos, which results from greater intraorbital content). Intelligence is usually normal if patients are appropriately managed.

Apert's Syndrome

Apert's syndrome resembles Crouzon's syndrome in several ways. Most cases of Apert's syndrome arise sporadically through new mutations, although some familial cases with autosomal dominant transmission have been reported.[71] The disorder is characterized by brachycephaly

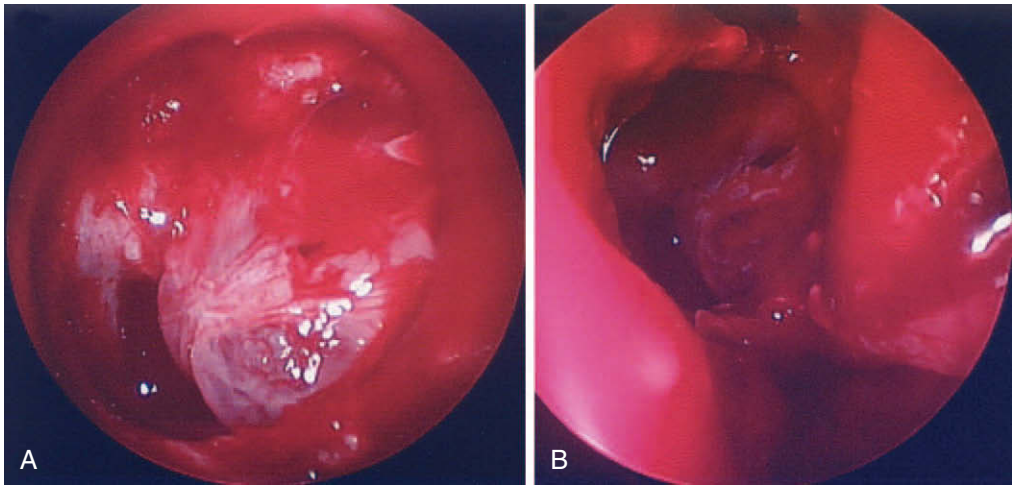

Figure 185-11. An endoscopic view of a meningoencephalocele protruding through the lateral wall of the sphenoid sinus. This was associated with a cerebrospinal fluid leak and a history of bacterial meningitis. **A,** An endoscopic view of the sphenoid ostium, which has been widened to allow sufficient access to the skull base defect. **B,** After mild (intrathecal) decompression but prior to endoscopic repair, the dural defect is clearly seen.

(with resultant turricephaly) and midfacial hypoplasia (with associated orbital and dental issues). Unlike patients affected with Crouzon's syndrome, patients with Apert's syndrome have symmetric syndactyly of the hands and feet as well as other axial skeletal abnormalities. The palate frequently has a high arch and may be cleft. The defects in Apert's syndrome are present at birth, and intelligence is often decreased.

Pfeiffer's Syndrome

Pfeiffer's syndrome is an autosomal dominant disorder that features craniosynostosis. The coronal sutures are frequently involved, giving rise to brachycephaly, but the sagittal and lambdoid sutures can also be involved. Affected patients can have midface hypoplasia (with associated orbital and dental issues) as well as enlarged thumbs and big toes.

Jackson-Weiss Syndrome

Jackson-Weiss syndrome is an autosomal dominant disorder with high penetrance and variable expressivity that resembles Pfeiffer's syndrome. Brachycephaly is common, the big toes are abnormally wide, but the thumbs are typically normal. Midfacial hypoplasia is more common than in Pfeiffer's syndrome. Jackson-Weiss syndrome was originally identified in an Amish population but can affect other individuals as well.

Saethre-Chotzen Syndrome

Saethre-Chotzen syndrome is an autosomal dominant disorder with full penetrance. Affected patients have craniosynostosis (often brachycephaly) with a low hairline, ptosis, brachydactyly, and a high arched palate with occasional palatal clefting. Midface hypoplasia is not common.

Carpenter's Syndrome

Carpenter's syndrome is a rare syndrome that is autosomal recessive. Patients affected by this syndrome usually suffer from craniosynostosis that can involve the sagittal, lambdoid, and coronal sutures. Midfacial hypoplasia can be a component but is usually mild. Other features are preaxial polysyndactyly of the feet and other syndactyly. Children with Carpenter's syndrome generally have developmental delays.

Stickler's Syndrome

Stickler's syndrome, also known as arthro-ophthalmopathy, is an autosomal dominant syndrome and is one of the more common syndromes, affecting about 1 in 10,000 people. It is caused by mutations in genes that encode type II collagen, type XI collagen, or both. This connective tissue disorder has ocular, orofacial, skeletal, cardiac, and auditory manifestations. The phenotypic orofacial expression is characterized by occasional midface underdevelopment, mandibular hypoplasia, and cleft palate. Stickler's syndrome is the most common syndrome to be associated with Pierre Robin sequence. It has been estimated that between 30% and 40% of patients diagnosed as having the Pierre Robin sequence (micrognathia, cleft palate, and glossoptosis) in fact have Stickler's syndrome. Given its variable expressivity, this syndrome, in its mild forms, often goes unrecognized.

Velocardiofacial Syndrome

Velocardiofacial syndrome is autosomal dominant with variable expressivity and penetrance and may be the most common syndrome after Down syndrome. There are numerous associated anomalies aside from the well-documented craniofacial, cardiac, and vascular malformations. The craniofacial anomaly broadly consists of a more open angle of flexion in the basicranium. This has an impact on the appearance of the midface and lower face (mandible). Clefting of the secondary palate can be overt or can take the form of an occult cleft that is apparent only on nasopharyngoscopy.[72] Velocardiofacial syndrome can easily be overlooked because affected patients are often not obviously abnormal in appearance.

Mandibulofacial Dysostosis

Mandibulofacial dysostosis, also known as Treacher Collins syndrome, is an autosomal dominant disorder with variable penetrance and expressivity. It involves numerous bilateral developmental abnormalities in structures that derive from the first and second branchial arches. Clinical features include zygomatic hypoplasia, micrognathia, dysplastic ears, antimongoloid slants to the eyes, colobomas of the lower eyelids, and deficient eyelashes in the medial two thirds of the lower eyelids. Mandibulofacial dysostosis is associated with Pierre Robin sequence and palatal clefting in 35% of cases. Severe obstructive apnea secondary to the micrognathia and glossoptosis often requires medical intervention.

Facio-Oculo-Auriculo-Vertebral Spectrum

Facio-oculo-auriculo-vertebral spectrum (FOAVS) refers to a group of anomalies that originate from unilateral defects in the first and second branchial arches. Most cases are sporadic, although familial cases have been reported. There is evidence that this syndrome results from a unilateral hemorrhagic event involving the stapedial artery during early craniofacial development.[73] FOAVS (also known as hemifacial microsomia), which includes Goldenhar's syndrome, can be quite diverse in terms of severity and scope. It is a rare disorder (1/5600 live births) that is present at birth. It involves the unilateral soft and skeletal tissues of the face and external and middle ear. It can manifest as temporal, zygomatic (malar), maxillary, and mandibular hypoplasia, hypoplastic

facial musculature, and cleft lip and palate. It involves a wide variety of external and middle ear deformities related to structures that derive from the first and second branchial arch. Atresia of the external auditory canals and preauricular skin tags can all exist in FOAVS. The eye can be involved, with the occurrence of colobomas, epibulbar choristomas, blepharophimosis, and strabismus. Vertebral anomalies include fusion of vertebrae, spina bifida, and other more specific abnormalities. A variety of other, non-craniofacial abnormalities are associated with FOAVS.

Trauma

The basic concepts of craniomaxillofacial trauma and treatment are similar in the pediatric and adult populations. The differences mostly concern patterns of fracture in young children and how repair of fractures affect subsequent craniofacial growth. The pattern of facial fractures in children is influenced by several factors. The facial bones are not fully mineralized and are therefore more pliable and elastic, resulting in more "greenstick" fractures. Tooth buds replace much of the bone of the dental arches, creating a different stress-strain curve in the mandible and maxilla. Depending on the patient's age the sutures may not be fused, and there is a higher proportion of cancellous bone with thinner cortices. The face is also much smaller relative to the cranial cavity with minimal aeration of the sinuses, and the buttress system is not fully developed. In adolescence the face has matured sufficiently so that patterns of facial fractures more closely resemble those seen in the adult.

The incidence of facial fractures in the pediatric population has been estimated to range from 1% to 14.7%, and head injuries are frequently associated with them. The group least likely to suffer from facial trauma is children younger than 5 years. The preponderance of injuries in children has been reported to occur in boys, though some studies have found no gender predilection. According to some reports motor vehicle accidents are responsible for these injuries in up to 80% of cases. However, in the last 20 years, with the wider use of seatbelts and federally approved child-safe car seats, the incidence has significantly declined. Injuries that do result in pediatric maxillofacial trauma are usually quite severe and therefore are frequently accompanied by other systemic injuries.[74,75]

In general, fractures involving the forehead, frontal sinus, naso-orbital-ethmoid complex, and optic canals, as well as Le Fort fractures are managed through the craniofacial techniques similar to those developed for congenital anomalies. Facial trauma that is best managed via craniofacial techniques is usually severe but fortunately also rare. Complex midface fractures including Le Fort fractures are uncommon. (Although the Le Fort system is used to describe complex midface fractures in children, later classification systems tend to be functional and are based on the force of the impact and the resultant extent of bony disruption.) Fronto-orbital fractures and other fractures of the upper face occur with an even lower frequency.

Neoplasm

Craniofacial or skull base tumors are fortunately rare occurrences in the pediatric population. Head and neck tumors account for about 5% of all childhood cancers, and those involving the skull base are a small proportion of that figure. Of the solid nonhematologic lesions, brain tumors are the most common, followed by neuroblastoma and rhabdomyosarcoma, non-rhabdomyosarcoma sarcomas, salivary gland tumors, and teratomas. Benign tumors in the craniofacial region are also rare; they include fibrous dysplasia (Fig. 185-12), angiofibromas, granulomas, pituitary adenomas, and other unusual lesions.

Patient Evaluation

Craniofacial Team

Given the complexity of the problems found in the patient with a craniofacial disorder, the principle that care must be delivered by a clinically diverse and highly trained team has become the standard of care. Careful timing and coordination of procedures maximize benefits while minimizing trauma to the patient and family. In addition to the craniofacial surgeon, a typical team might consist of a pediatrician, neurosurgeon, ophthalmologist, dentist, orthodontist, oral surgeon, prosthodontist, geneticist, nurse, speech pathologist, audiologist, anthropologist, psychologist, and nutritionist. The emphasis is on taking a comprehensive approach to the health care of the individual. This approach is based on the recognition that these abnormalities, as well as their treatment, can affect many different functional systems. Open and unimpeded communication among the different members of the team is essential for full realization of the benefit of this approach.

History and Physical Examination

At the initial evaluation, a personal, family medical, and genetic history must be obtained. It is prudent to suspect that any defect of the craniofacial complex is part of a larger syndrome, so a full body survey is performed. All anomalies are noted, with an attempt to group them into a known syndrome. The head shape should be observed from front, rear, sides and vertex. The forms and positions of the eyes and ears are examined. The head is evaluated by palpation of the sutures and fontanelles to detect not only patency but also ICP. There should be no sutural ridging, and the fontanelles should not be bulging. The head circumference, the AP, bifrontal, bitemporal, and biparietal diameters, and the vertical height of the skull from the supraorbital border are all measured. In normal children the posterior and anterior fontanelles close at approximately 3 and 18 months, respectively, and the cephalic index (the ratio of the greatest width of the head to its greatest

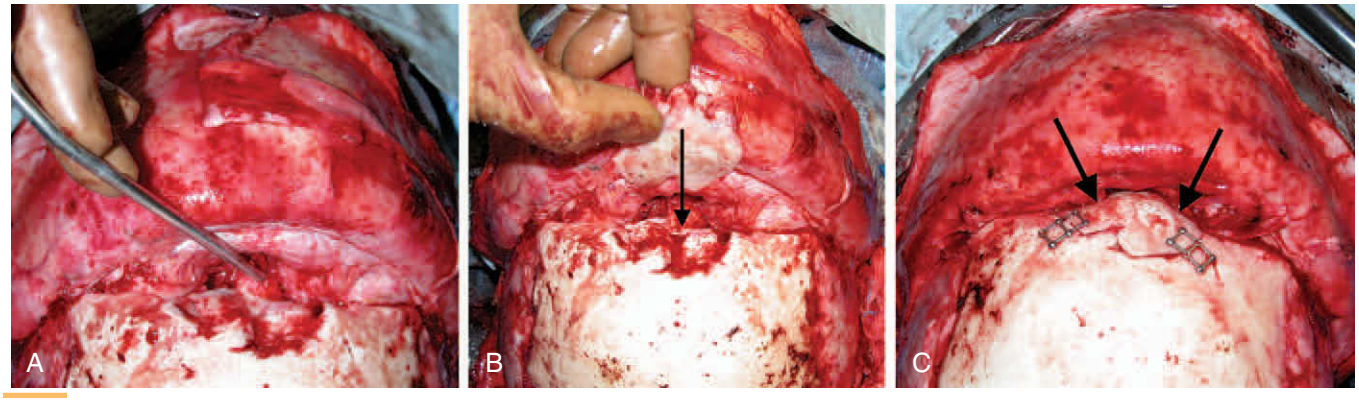

Figure 185-12. Operative images of a patient with fibrous dysplasia involving the anterior skull base who initially presented in her teenage years. Earlier endoscopic attempts at removal had failed and left the patient with strabismus, a mucocele of the frontal sinus, and exposed dura. **A,** A subcranial approach was utilized to remove the fibrous dysplasia. The suction tip is pointing to the lesion. **B,** The lesion has been removed, and the *arrow* is pointing to the area of dural exposure. The bone flap is shown. **C,** The bone flap has been replaced. *Arrows* are pointing to the pericranial flap that has been placed under the bone flap and used to seal the dural defect and obliterate the frontal sinus.

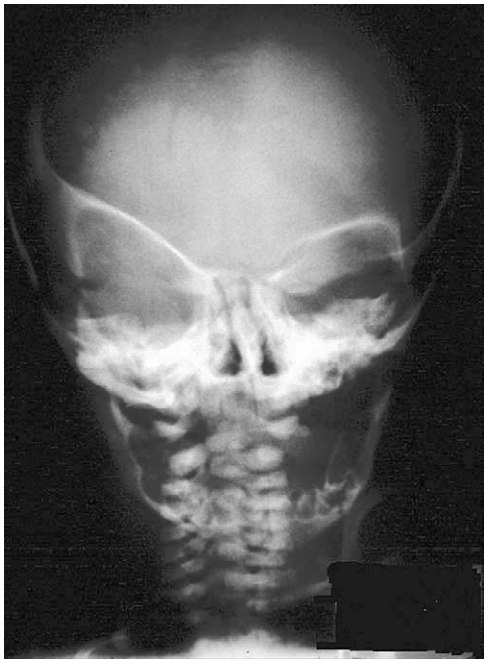

Figure 185-13. Skull film demonstrating the "harlequin mask" appearance seen in patients with unilateral coronal suture synostosis.

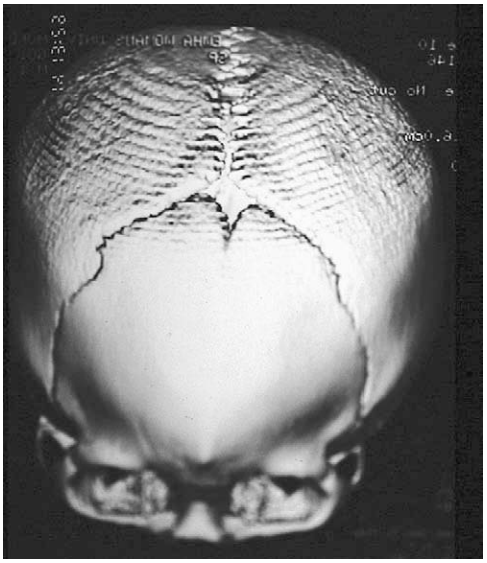

Figure 185-14. Three-dimensional computed tomography reconstruction demonstrating trigonocephaly.

length multiplied by 100) is 75 to 80. Although occlusion cannot be evaluated in the neonate, the relative dimensions of the mandible and midface are noted. The symmetry and range of motion of the neck must be examined as well.

Imaging

Plain radiographs can be useful in certain circumstances. The absence of normal sutural lucency may indicate synostosis. In plagiocephaly and brachycephaly, premature fusion of the frontoethmoid and frontosphenoid sutures causes elevation of the lesser wing of the sphenoid, producing the harlequin mask appearance (either unilateral or bilateral) on a plain AP film of the skull (Fig. 185-13). The hammered-copper or thumb-printing appearance of the inner table of the skull on cranial radiographs is associated with increased ICP and craniosynostosis; although its presence is easily detected, its clinical significance has been questioned.[76] Lateral and AP cephalometric radiographs continue to be useful, especially for evaluation of the progress of craniofacial growth.

However, for most defects computed tomography is the ideal modality for evaluation. Given its ubiquity and declining costs it has largely replaced plain radiography. Additionally, the software for three-dimensional reconstruction is widely accessible and provides detail of the bony anatomy that is unsurpassed (Fig. 185-14). Various cephalometric and volumetric analyses can be easily achieved. If necessary, a stereolithographic model based on three-dimensional studies can be built that provides an accurate template of the patient's craniofacial skeleton. Sophisticated software is also available to help in planning reconstruction (Fig. 185-15). Planning software is particularly helpful when one is preparing to reconstruct unilateral or some asymmetric defects. Although valuable information about the central nervous system can be obtained with computed tomography, magnetic resonance imaging is usually the modality of choice for evaluating the brain.

Indications for and Timing of Intervention

When one is considering treatment for craniofacial diseases and anomalies, it is helpful to stratify a patient into one of the following three categories based on the nature of the problem: life-threatening issues, functional impairments, and aesthetic issues. Issues classified as life-threatening include upper airway obstruction. An example is a neonate with severe Pierre Robin sequence. Another example is severe syndromic craniosynostosis affecting multiple sutures with dangerous ICP elevations. The second category, functional impairment, includes a broad spectrum of problems that range from visual impairment to neurocognitive problems as the child reaches school age. The third category is that of a mild deformity that results in what society might consider an abnormal aesthetic appearance.

The treatment algorithm for life-threatening problems is usually straightforward. The neonate with upper airway obstruction is treated either by distraction of the mandible (discussed in greater detail later) or a tracheotomy. The patient with kleeblattschädel requires urgent release of the binding skull by total cranial vault remodeling, and the child with dangerously high ICP is often treated with a ventriculoperitoneal shunt. The algorithm becomes more complex, however, for neonates with functional impairment.

The complexity arises because the consequences of not intervening or of the intervention itself are not always fully understood. Significant fronto-orbital retrusion is at the more severe end of the spectrum, as it may portend serious functional, neurologic, or ophthalmic problems. The presence of more than one synostosis is often associated with neurocognitive compromise. Anomalies of the maxilla and mandible not only affect appearance but also can impact the airway, dentition, and speech and therefore frequently require therapeutic intervention. Hypertelorism and other orbital dystopias can manifest as significant visual issues, in which case surgical reconstruction is necessary. Nonsyndromic single-suture craniosynostosis (SSC) is particularly difficult to classify because the association between the anomalies and functional sequelae is controversial. The incidence of increased ICP and neurocognitive deficiencies in nonsyndromic single-suture craniosynostosis is still debated, and further investigation of this issue is warranted.[77-79]

When the neonate has the mildest of craniosynostoses, such as some types of single-suture craniosynostosis or partial synostosis, positional plagiocephaly, mild FOAVS, and other mild craniofacial anomalies, the problem can be classified as aesthetic in nature. In such cases the craniofacial team and the involved family members must weigh the severity of aesthetic deformity against the risks of surgical intervention. The temptation to develop a strict algorithm based on the defect alone has to be resisted, as demonstrated by metopic suture synostosis. This deformity manifests with a wide range of severity in fronto-orbital malposition and hypotelorism, and the metopic suture closes earlier than previously thought.[80] The implication that prior standards used to guide the surgeon in deciding when to intervene surgically are not quite as relevant. In the case of positional plagiocephaly, the treatment does tend to be more clear-cut. Changing sleep position, treating causes

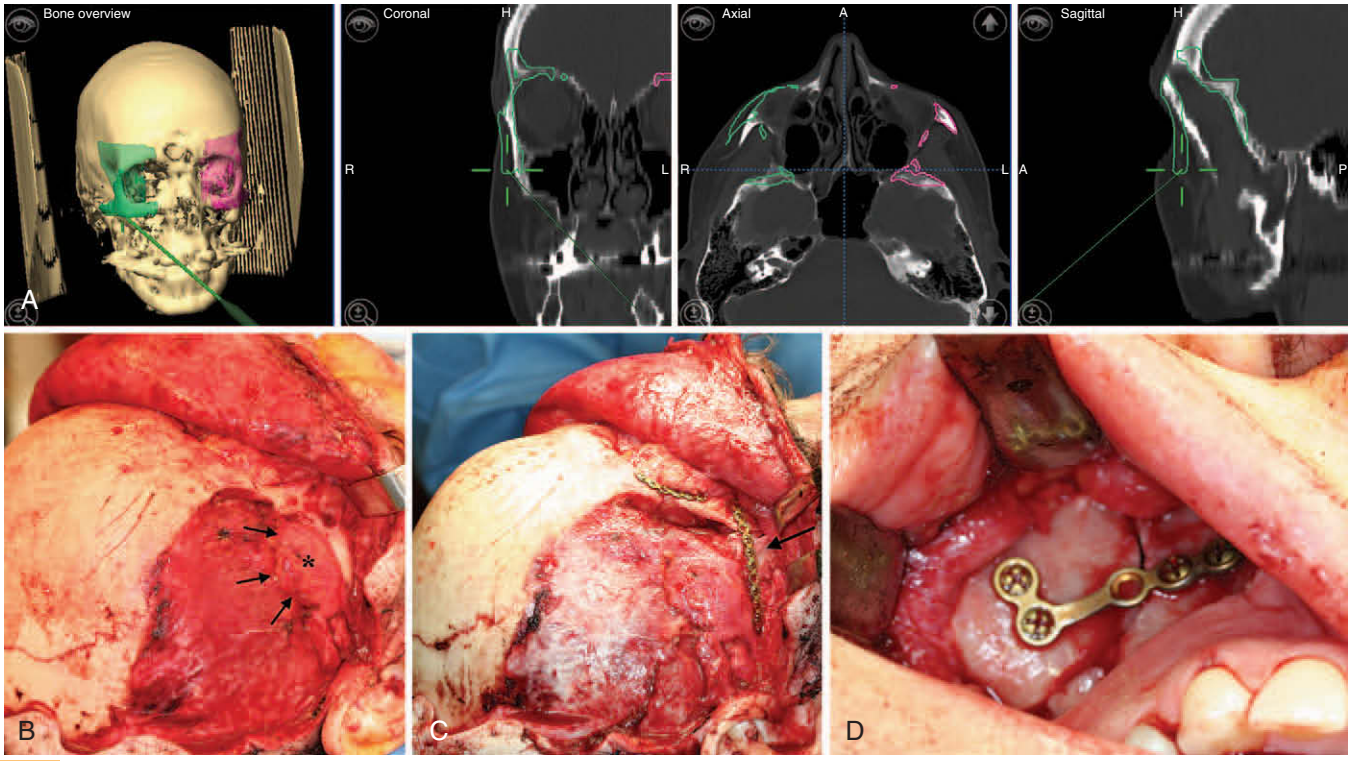

Figure 185-15. Images of a patient who had suffered from traumatically displaced fractures of the orbit and zygomatico-maxillary complex (ZMC) about a half year prior to presentation. Because of the delay in treatment, the skeletal segments healed in a malunion, resulting in a facial deformity as well as orbital dystopia. **A,** With the use of planning cranio-maxillo-facial software, the facial skeleton is displayed in the coronal, axial, and sagittal planes. The *green line* in the upper left image of the skull refers roughly to the planes in which the other three slides are shown. **B,** A bicoronal flap has been elevated to expose the orbit and ZMC. *Arrows* indicate where the superficial layer of the deep temporalis fascia has been incised at the temporal line of fusion and elevated to expose the temporal fat pad (indicated by *asterisk*). This is necessary to gain wide exposure to the zygomatic arch, which had been fractured in multiple places. **C,** Appropriate osteotomies have been made, and the displaced segment mobilized. Using the reconstructed image generated by the planning software the image guidance system helps in the proper placement of the osteotomized segment, which is fixed in place with titanium plates (this patient is old enough to allow for nonresorbable fixation). *Arrow* indicates calvarial bone grafting that was used to buttress the new construct (harvest not shown). **D,** A sublabial incision is necessary to make the inferior cut and apply the fixation.

of torticollis, and cranial molding orthotics can all be used quite effectively when appropriately applied.

The age at which surgical correction is appropriate depends on the particular anomaly, the extent of functional compromise, and the overall health of the patient. Pediatric anesthesia has greatly improved in the last several years, making surgery in infants significantly safer. This issue is particularly important in craniofacial surgery because many of the procedures are easier to conduct in young patients. Patients younger than 1 year have remarkable bony regenerative capacity. The bone is also thinner and more pliable, making it easier to cut and contour. Of course, with younger patients, there are risks that must be considered, such as intolerance to even mild blood loss.

Neonates suffering from airway obstruction are treated immediately if extubation fails. In the case of kleeblattschädel, multiple synostectomies must be performed within the first few weeks of life to prevent severe functional deficits and even death. Early intervention is also indicated for increased ICP and corneal exposure. Simple synostectomies (in treating scaphocephaly, for example) are often performed in patients 2 to 6 months old. The authors generally perform frontoorbital advancement and cranial vault remodeling procedures in infants 6 to 9 months old. Monobloc surgery of the forehead, orbits, and midface is often done at 3 to 4 years, although with distraction osteogenesis, the tendency is toward earlier intervention. Whole orbit movements are typically done while patients are 2 to 4 years old. Surgery effecting change in the occlusal relationships is often delayed until the teenage years. Depending on the severity and scope of the deformities, multiple procedures may be required to maximize the correction.

Surgical Techniques

Congenital Craniofacial Abnormalities

Because much of the surgery for craniofacial anomalies is performed on very young patients, special attention needs to be given to tightly monitoring and regulating the patient's vital functions. Infants have such a small blood volume blood that transfusion is often required in lengthy craniofacial procedures. Young patients also have decreased thermoregulatory capacity, so the room temperature is kept relatively high, especially during induction of anesthesia. Venous and arterial lines are inserted, as is a bladder catheter, preferably with a core temperature sensor. In a combined extracranial-intracranial procedure, antibiotics and steroids are routinely given. Shaving of the scalp for the incision is optional and based on the surgeon's preference. The scalp is scrubbed with a soap solution and povidone-iodine solution, and the face is generally also prepared with antiseptic scrub. The oral and nasal cavities should be irrigated if there is a likelihood that they will be part of the surgical field.

The eyes are protected by gentle application of ophthalmic ointment followed by covering with a clear plastic dressing. If access to the eyes is necessary, no taping is applied. Corneal shields are avoided when a bicoronal flap is elevated because the flap, when turned on itself, can often exert a fair amount of pressure on the shields, which could lead to eye damage. If necessary, a tarsorrhaphy suture can be used to protect the eyes.

Given that the head position is frequently altered during these procedures, it is very important to properly secure the endotracheal

tube to the patient and, if necessary, bring part of the tube into the field. If access to the maxilla is necessary, then the tube must be secured to the mandible. Although prone and sphinx positions are preferred by some surgeons, we prefer to perform most craniofacial procedures with the patient supine and the head flexed. In orthognathic procedures it is generally necessary to intubate the patient nasally. The tube must be draped in such a way so as to make it easily accessible to the anesthesia team if inspection of the ventilatory circuit is necessary. During draping of the patient, it is best to leave as much of the face (including the ears) in the field as possible. This exposure is helpful to maintain orientation. Prior to incision, a vasoconstricting agent can be injected into the skin, but doses must be carefully titrated in the young pediatric population. An epinephrine solution of 1 : 200,000 or 1 : 400,000 is recommended.

Although the coronal incision is the most widely used approach for gaining access to the craniofacial skeleton, other, smaller incisions are used for different applications. For cases of mild to moderate sagittal synostosis, an endoscopic approach can be used or a midsagittal (wavy) incision can be employed to gain access to the synostotic portion of the suture. However, whenever access to the supraorbital bar is necessary, the bicoronal incision is necessary.

Coronal Incision

The coronal incision can extend pre- or postauricularly. When extended into the postauricular area, the incision is hidden, and adequate exposure of the cranium and the upper and part of the middle thirds of the face can still be obtained. The incision is designed as a wavy line that extends across the vertex of the head (Fig. 185-16).[13,81] The overall incision can be rotated more anteriorly to allow more anterior/inferior retraction of the flap. Some surgeons sharply zigzag the incision so as to make multiple V-Y closures possible if the advancement is so significant as to preclude normal closure of the coronal flap. The flap can then be elevated in a subperiosteal or subgaleal plane over the calvarium. The dissection is continued to the deep temporalis fascia elevating the temporal-parietal fascia. Dissection in this plane enables the frontal branch of the facial nerve to be elevated in the flap. If access to the zygomatic arch is required, the superficial layer of the deep temporalis fascia is elevated starting at the temporal line of fusion (see Fig. 185-15). This maneuver has the added advantage of adding an extra layer of tissue in between the dissection and the facial nerve branch. In some types of cranial vault remodeling, it is necessary to elevate the temporalis muscle as well, but this step is performed independent of the scalp elevation.

Sagittal Synostosis

Sagittal synostosis requires that the skull be allowed to expand in the transverse dimension and reduced in the AP dimension. There is a spectrum of procedures for scaphocephalic correction. Mild cases treated before 3 months of age may be managed with strip craniectomy alone (Fig. 185-17). A strip craniectomy is performed by removing sagittal or parasagittal sections of bone. Severe cases and patients treated after 9 to 12 months may require total cranial vault remodeling. In these cases coronal and lambdoid osteotomies can be made, and the parietal bones out-fractured. In severe cases the frontal bone can be significantly bossed and often has to be reshaped or transposed to improve the contour of the forehead. This requires a coronal incision (Fig. 185-18).

Fronto-Orbital Advancement

Centrally, the dissection exposes the supraorbital bar in the subperiosteal plain (if the dissection was done in a subgaleal layer, the periosteum is incised 2 cm above the supraorbital rims). The supraorbital rims and frontonasal region are fully exposed, with preservation of the supraorbital neurovascular bundles, which can be quite small in the neonate. In the very young patient this structure rarely exits via a foramen; rather, it lies in a groove in the medial half of the supraorbital rim, generally over the pupil. If there is a foramen, the inferior rim must be osteotomized in order to dissect and mobilize the neurovascular bundle. Progressing medially, the lacrimal crests can be exposed, if necessary, after separation of the medial canthal ligaments from their bony attachments and elevation of the lacrimal sac. In the midline the

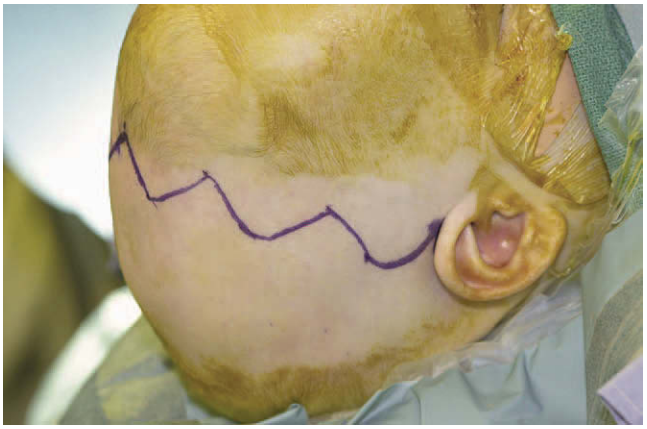

Figure 185-16. A wavy-line bicoronal incision that extends postauricularly is well concealed once the hair has grown in sufficiently.

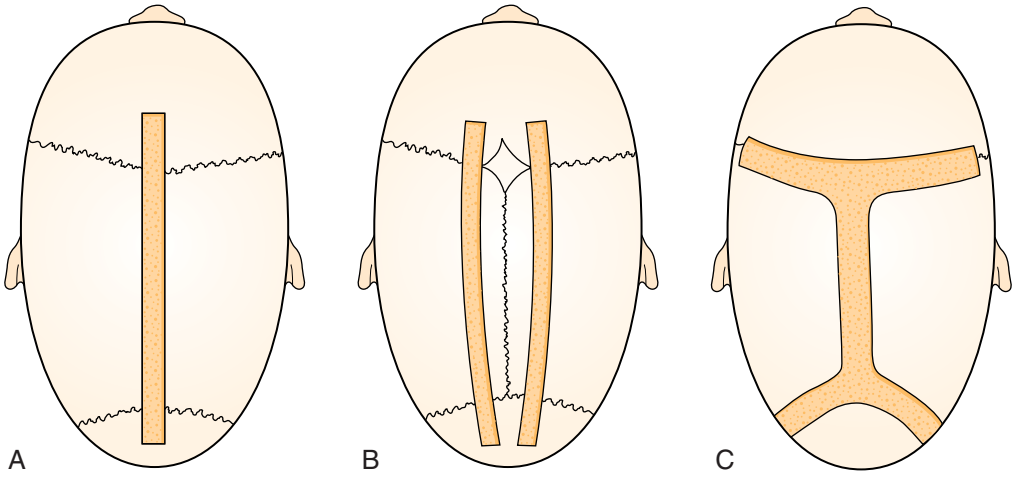

Figure 185-17. A range of surgical treatments can be employed for repair of scaphocephaly, depending on the severity. **A,** Removal of the suture. **B,** Strip craniectomies. **C,** Removal of the suture as well as coronal and lambdoid cuts. The latter is frequently combined with out-fracture of the parietal bones.

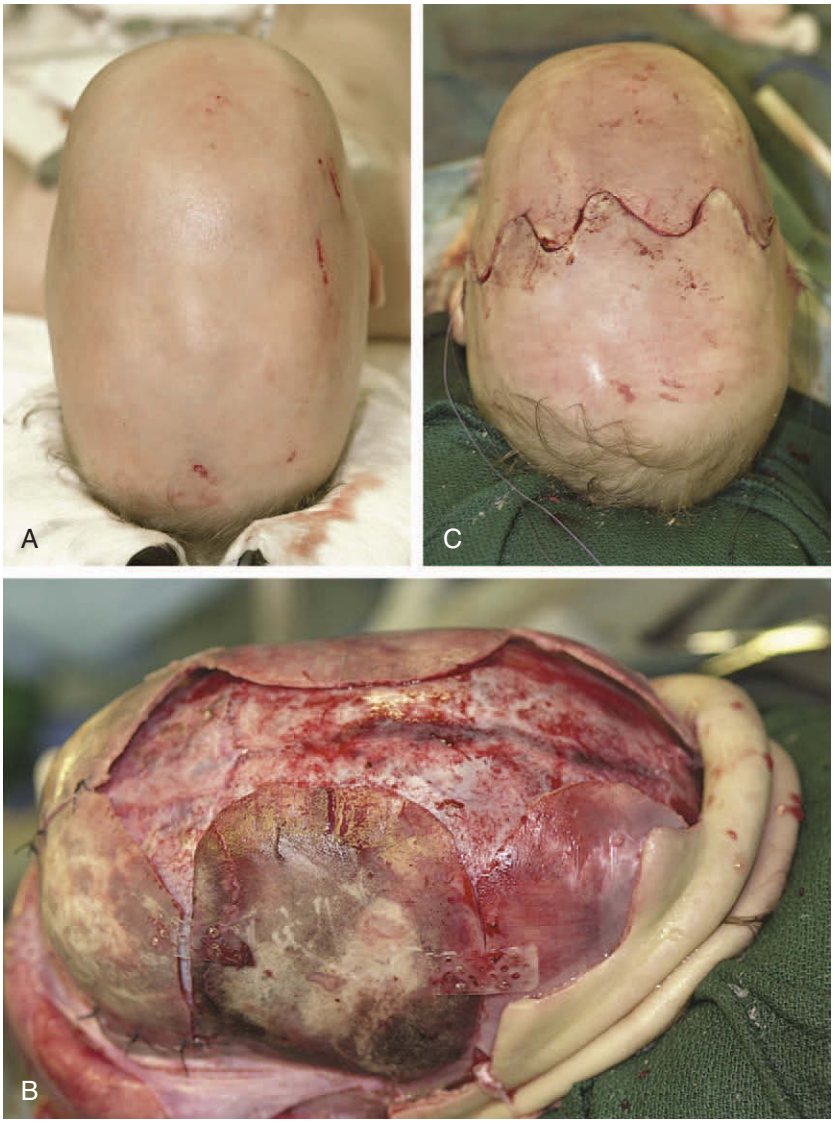

Figure 185-18. Scaphocephalic repair. **A,** Preoperative view of severe scaphocephaly. **B,** Repair required total cranial vault remodeling—the temporal-parietal complex was out-fractured on each side. Note the combined use of resorbable sutures and plates to achieve a stable construct. **C,** Postoperative view.

dissection is carried just past the nasofrontal suture. Laterally, exposure is extended from the zygomatic arch medially to the body of the zygoma. Fronto-orbital procedures generally require inferior exposure only to the level of the frontozygomatic suture. The lateral orbital rim is then exposed, and this dissection is connected to that of the supraorbital bar. The orbital roof is carefully dissected in the subperiosteal layer. The lateral orbital walls are exposed by elevation of the anterior aspect of the temporalis muscle from the temporal fossa.

Once the dissection is complete, intended osteotomy sites for both the supraorbital bar and the bifrontal craniotomy are marked. A side-cutting power craniotome is typically used once strategic bur holes have been drilled. The bifrontal craniotomy (Fig. 185-19) is done initially, with care taken to leave a transverse bar of bone above the supraorbital rims that is between 10 and 15 mm in width. The dura is freed from the anterior aspect of the anterior cranial fossa but left adherent over the cribriform plate. The supraorbital bar or bandeau is then marked for osteotomy. The superior osteotomy for the supraorbital bar was created by the bifrontal craniotomy. If a strip of bone was left over, the sagittal sinus it is cut from the bandeau. Laterally, the superior bandeau osteotomy is extended into the squamous portion of the temporal bone. Inferiorly, the central transverse osteotomy is made at or just above the

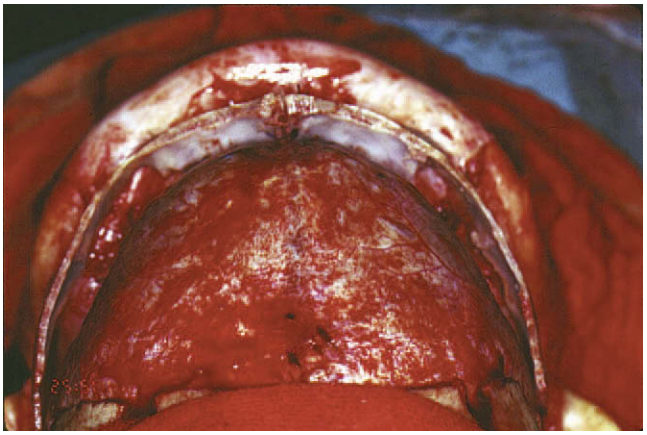

Figure 185-19. A bifrontal craniotomy has been performed. Note the elevation of the dura from the anterior cranial fossa in preparation for removal of the bandeau.

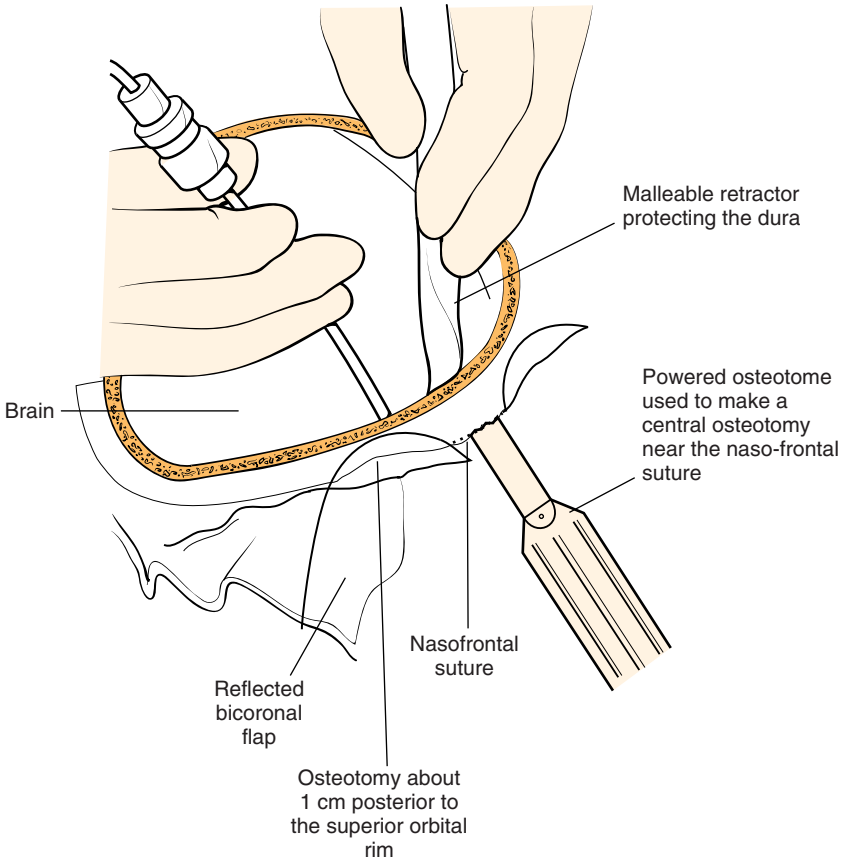

Figure 185-20. The central cut of the bandeau is illustrated. This cut is made above the nasofrontal suture. It is extended into the anterior cranial fossa anterior to the crista galli while protecting the brain with a malleable retractor. This way olfaction is preserved, and the barrier between the intracranial and nasal cavities is left intact. *(Adapted from Salyer K.* Techniques in Aesthetic Craniofacial Surgery. *New York; Gower Medical; 1989:35.)*

frontonasal suture (Fig. 185-20). This cut extends directly to the anterior cranial fossa at a point anterior to the crista galli. This location preserves olfaction as well as the barrier between the brain and the nasal cavity. The osteotomy is then carried into the medial orbit just above the lacrimal fossa. The osteotomy turns superiorly 5 to 10 mm inside the orbital rim, traverses the orbital roof around 10 mm posterior to the superior orbital rim, and extends down the lateral orbital wall to the level of the zygomaticofrontal suture. The lateral orbital rim is cut at the suture, and that cut extends posteriorly into the greater wing of the sphenoid and the squamous portion of the temporal bone parallel to and 10 to 15 mm inferior to the previous cut into this region. This site corresponds intracranially with the junction of the anterior and middle cranial fossae near the pterion. Enough length of the temporal portion of the bandeau will allow a tongue-and-groove action at this lateral point in order to increase the bony contact once the advancement has been completed. This maneuver facilitates bony stability. Removal of the bandeau is frequently hindered by incomplete osteotomy at the trifurcation (of the anterior extent) of the middle cranial fossa, the lateral orbital wall, and the greater wing of the sphenoid. The anterior tip of the temporal lobe must be protected while this cut is completed.

Once the bony segments are removed, they are reshaped on a separate table. The supraorbital bar can be reshaped to the extent required by the deformity (Fig. 185-21). Bone is removed as needed in thickened areas to facilitate bone bending. In unilateral synostosis (plagiocephaly) the central angle of the forehead is mildly affected, and only small alterations are necessary to increase the central angle to 150 to 170 degrees. Although only one side is affected in plagiocephaly, minor changes are required on the unaffected side because of compensatory frontal bossing. More drastic measures might be required for trigonocephaly, in which the central angle of the forehead can be as acute as

Figure 185-21. The bandeau following removal.

90 degrees. It is sometimes necessary to split the bandeau in the midline and add a bone graft in order to widen the central angle (Fig. 185-22). The components are then fixed to one another with absorbable plates, sutures, or both. Just above the lateral orbital rims, the angle between the supraorbital rim and the temporal fossa is adjusted to between 100 and 110 degrees. The orbital bar is then replaced in an advanced position.

The extent of advancement obviously depends on the nature of the anomaly. In trigonocephaly and plagiocephaly, the orbital advancement is predominantly lateral, with the medial portion advancing little if any. In brachycephaly the entire bandeau is usually advanced, but the movement is still greater laterally than medially (Fig. 185-23). Maintaining contact between the supraorbital bar and the root of the

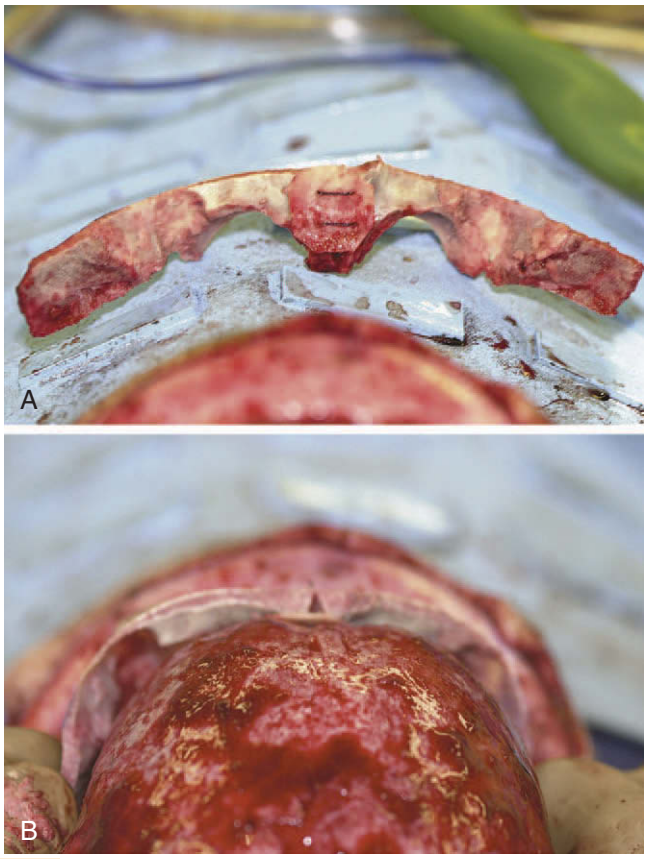

Figure 185-22. **A,** The bandeau can be split and a graft used to stabilize the new supraorbital construct. **B,** The bandeau is in place.

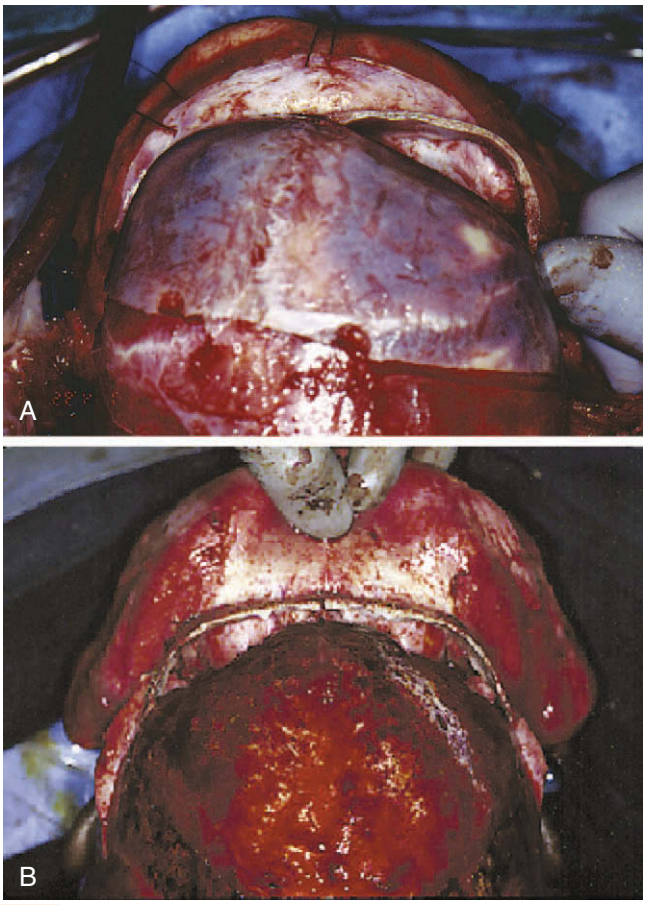

Figure 185-23. **A,** In this plagiocephalic repair, the lateral advancement of the bandeau is dramatic, whereas centrally little advancement was necessary. **B,** In this brachycephalic repair, there is more central advancement relative to the plagiocephaly repair but still far less than the lateral advancements.

nose is also important from the perspective of frontal sinus development, which later enhances central forehead projection.[82] It is important to establish symmetry with the advancement. Both rims should be about 1 cm anterior to the cornea. In severe cases the bandeau can be advanced as much as 2 cm, but bone grafting may be necessary. The supraorbital bar is fixed to the skull with absorbable plates, sutures, or both at the nasion and laterally (Fig. 185-24).

Lambdoid synostosis is repaired in much the same way as coronal synostosis. However, instead of removing and reshaping a supraorbital bar, the surgeon removes an occipital bar and advances it posteriorly and the occipitoparietal complex is reshaped to create posterior symmetry. Other types of cranial vault remodeling, including severe scaphocephaly, are also done via the coronal incision.

Resorbable plate technology represents a breakthrough in this treatment.[83] It offers dependable rigid fixation without the use of metallic plates.[84] Resorbable plates are less likely to interfere with craniofacial growth and development the way that titanium plates can, and they also rarely require removal.[85] The problem of intracranial plate migration with growth is avoided as well—typically the plates lose a large proportion of their strength within the first 6 months and are resorbed in less than 18 months. The calvarial bone flaps are then reshaped to provide normal contour to the head. Sometimes it is necessary to further osteotomize the flaps. The various components can be replaced in different positions to give the best contour. The bones are then fixed to the surrounding skull with absorbable plates or sutures. Maintaining large pieces of bone that are bent to the desired conformation, rather than creating small segments of bone with many osteotomies, provides for a more stable construct with less fixation than would be required if the bones were cut into smaller pieces.

Because of the advancement, there will be defects in the bone at various places. In patients younger than 1 year, bony defects are generally not of major concern because of bone regeneration. However, in older children and adults, large defects must be addressed. The orbital roofs represent a clear example. If there is a persistent communication between the orbit and the brain, pulsatile ophthalmopathy can develop. Therefore, these defects must be repaired with bone grafts (Fig. 185-25). Calvarial defects in the child or adult can be repaired with bone grafts or other bone replacement materials.

When the skeletal reconstruction is complete, attention is directed to a multilayer and precise closure. If the temporalis muscle has been elevated, it must be advanced to the lateral orbital rim and sutured. If this step is not performed, temporal hollowing occurs, creating an unaesthetic appearance. The muscle can be sutured to holes drilled in the lateral orbital rim or to one of the fixation plates. The galea aponeurosis is reapproximated with absorbable suture. The skin can then be closed with permanent or absorbable suture. We prefer to avoid suture removal in young children, so we perform a subcuticular closure with absorbable suture. In older children, skin staples can be used. If a sharp zigzag incision was used and the skin cannot be easily approximated (particularly in repair of severe brachycephaly), cutaneous closure can be performed, with use of the V-Y technique at each peak of the zigzag. We avoid using drains, especially in young patients. A gentle pressure and occlusive dressing is placed over the head.

Monobloc Advancement

Older children (>2-4 years) who present with fronto-orbital retrusion in conjunction with midface retrusion are potential candidates for a one-stage procedure. The (frontofacial) monobloc advancement originally described by Ortiz-Monasterio and colleagues[86] combines a fronto-orbital advancement with a Le Fort III level facial advancement (Fig. 185-26). The procedure is performed through the coronal inci-

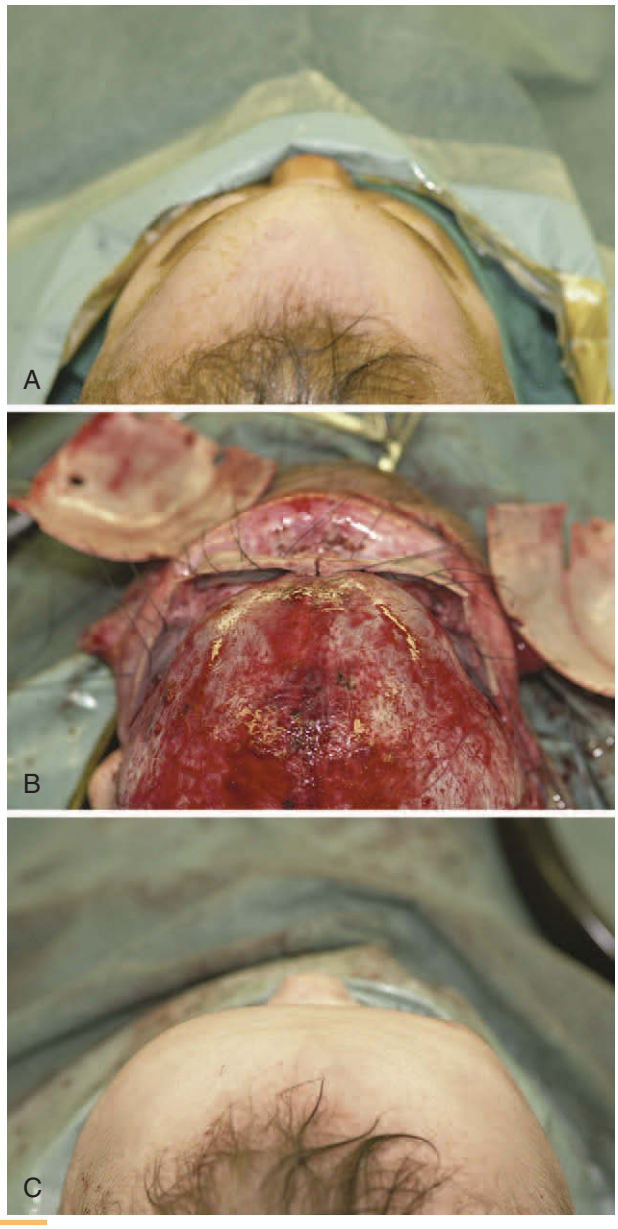

Figure 185-24. Trigonocephalic repair. **A,** Preoperative view. **B.** Intraoperative view. **C,** Postoperative view.

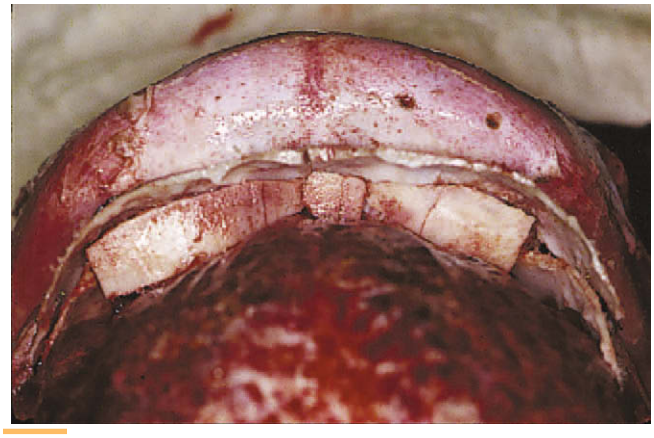

Figure 185-25. Bone grafts are placed between the orbit and the anterior cranial fossa in an effort to reconstitute the orbital roof.

sion. The craniotomy is similar to the one performed in a fronto-orbital advancement. The zygomatic arches are cut. The frontal bar is included with the Le Fort III segment. Circumferential orbital bony cuts are made with use of both extracranial and intracranial approaches. The lateral and inferior orbital walls are osteotomized starting in the inferior orbital fissure. The medial wall is cut just posterior to the posterior lacrimal crest. The orbital roof osteotomy is made intracranially. The nasal septum is cut via the frontoethmoid osteotomy. Finally, through the infratemporal fossa or the mouth, the maxilla is separated from the pterygomaxillary junction. The monobloc segment is then advanced and rigidly fixed with use of absorbable or titanium plates.

In some craniofacial deformities, such as those commonly seen in patients with Apert's syndrome, hypertelorism is present in association with maxillary deformities. Facial bipartition is a technique used to simultaneously correct hypertelorism and maxillary arch abnormalities (Fig. 185-27). Bone grafts are used to help maintain the advancement. Pericranial flaps and tissue glues are also used to create a seal between the anterior cranial fossa and the nasal cavities.

Although combining the two corrections into one procedure, has an obvious advantage, it is also associated with a higher rate of infection, presumably because of an incomplete seal of the central nervous system from the nasal cavities. It is for this reason that patients must be carefully selected for such a procedure. In situations in which the monobloc advancement is clearly the procedure of choice, distraction (in place of craniofacial advancement during the operation) may offer a safer way to achieve the desired results (see Fig. 185-26). The approach and the osteotomies are no different from the en bloc advancement just described.

Orbital Hypertelorism and Dystopia

In the correction of orbital hypertelorism, the approach is similar to that used in a fronto-orbital advancement, except that circumferential periorbital elevation is required. A bifrontal craniotomy is performed; however, a 1- to 1.5-cm strip of bone is left intact just above the orbital rims and below the bifrontal craniotomy. The anterior cranial fossa is exposed but the cribriform plate and crista galli are left intact to preserve olfaction. The periorbita is freed up to the infraorbital fissure. Four (box) osteotomies are made to encircle the entire bony orbit. The cuts outside the supraorbital, lateral, and medial rims can be made via the bicoronal exposure; however, the inferior cuts are facilitated by either a transconjunctival or subciliary incision. The bony orbits are mobilized by making a second set of circumferential osteotomies inside the orbit (using the inferior orbital fissure as a landmark) to separate the anterior part of the orbit from the posterior part. Upon mobilization of the orbits, a central bony block is osteotomized from the naso-ethmoid complex. The anterior ethmoid fovea and air cells are often removed in this maneuver. The cribriform plate, along with the olfactory fibers and mucosa, are left intact. The bony orbits are then translocated to more medial positions. Vertical or rotational dystopia can be addressed at this point by addition or removal of bone in the appropriate areas to achieve proper orbital position. The bony segments are then fixed in their new positions with either resorbable or metallic plates. Closure proceeds as previously discussed. Because of instability of the mobilized orbit in the very young child, this type of correction is typically deferred until after age 2 years.

Distraction Osteogenesis

Distraction osteogenesis has been employed in the long bones for just under a century now. It was first applied to the craniofacial skeleton more than 80 years ago[87] but has come into widespread clinical use only in the last 25 years.[88] *Distraction osteogenesis* refers to creation of a controlled fracture in a bony structure followed by separation of the bony segments in a controlled and gradual manner. This process induces the formation of new bone in between the distracted segments. The advantages of using distraction osteogenesis in the craniofacial skeleton are numerous. It allows for skeletal lengthening and advancement in three dimensions. The process is a gradual one that allows the skin–soft tissue envelope to adapt to and accommodate skeletal movement.[89] It is also safer than many of the traditional skeletal techniques. Distraction osteogenesis is less involved and requires less operative time

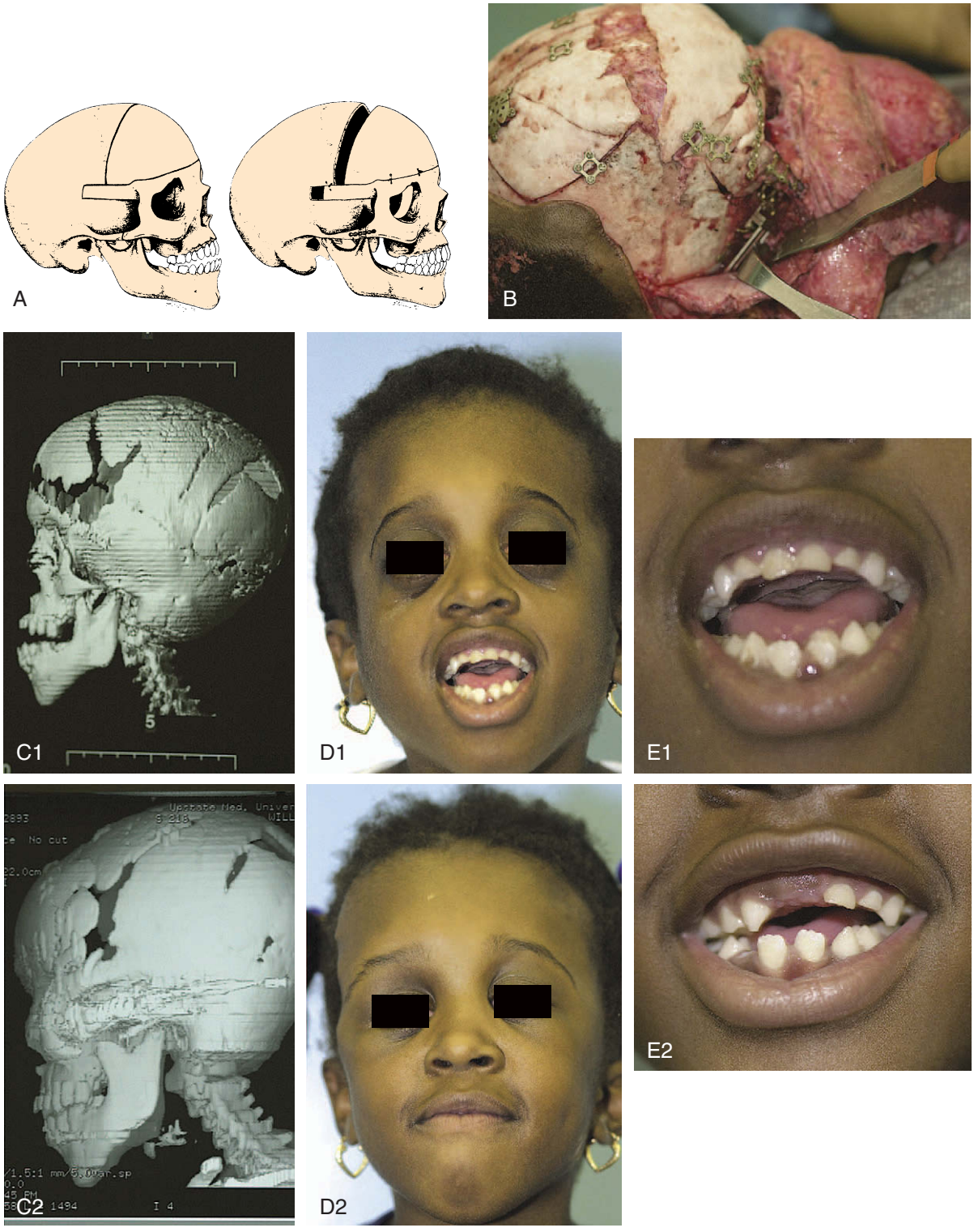

Figure 185-26. **A,** The monobloc advancement: Le Fort III osteotomies are performed in concert with a bifrontal craniotomy and mobilization of the bandeau. Fronto-orbital as well as midfacial advancements are then performed. **B,** Monobloc advancement with an internal distractor used to gradually advance the facial segment. (Note the right internal distractor device at the end of the retractors.) **C,** Preoperative (C1) and postoperative/postdistraction (C2) three-dimensional computed tomography scans. **D,** Preoperative (D1) and postoperative/post-distraction (D2) frontal photographs. **E,** Preoperative (E1) and postoperative/post-distraction (E2) dental/occlusal photographs.

(generating less blood loss) than the techniques it has replaced. As a result it is an attractive treatment alternative for children and infants with some craniofacial anomalies.

Distraction osteogenesis can be carried out with internal or external devices (Fig. 185-28). Internal devices have the advantage of not requiring big and bulky hardware protruding from the face and can, at times, be applied intraorally. The extent of control over the vectors of distraction is limited with internal devices. The external devices allow for three-dimensional distraction and better control of the vectors of distraction (see Fig. 185-28). The disadvantage lies in their bulkiness.

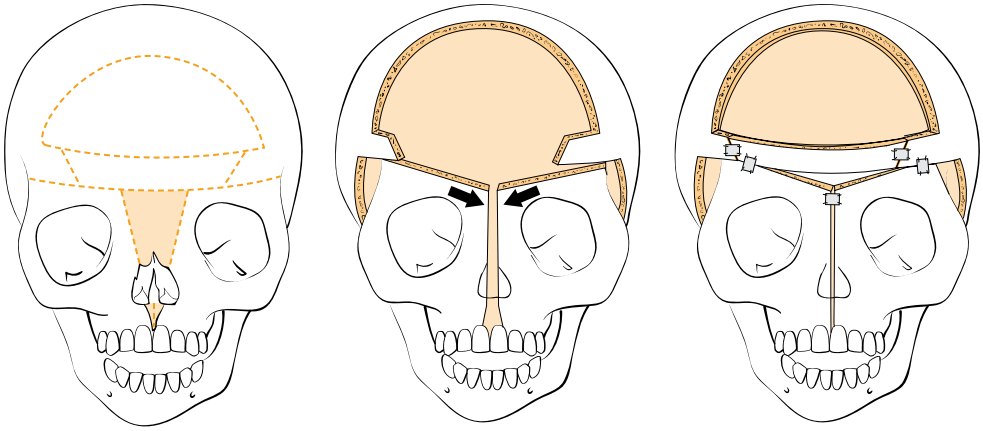

Figure 185-27. Facial bipartition can be used to move the orbits into more medial positions and narrow maxillary width as well. An inverted triangular wedge of bone is removed from the midline extending from the supraorbital ridge to the maxillary arch. The skeletal segments are then rotated, bringing the orbits into closer alignment and also reducing an open bite deformity. This procedure is also employed in the repair of some midfacial clefts. *(From Salyer K.* Aesthetic Craniofacial Surgery. *Philadelphia; Lippincott; 1989:67.)*

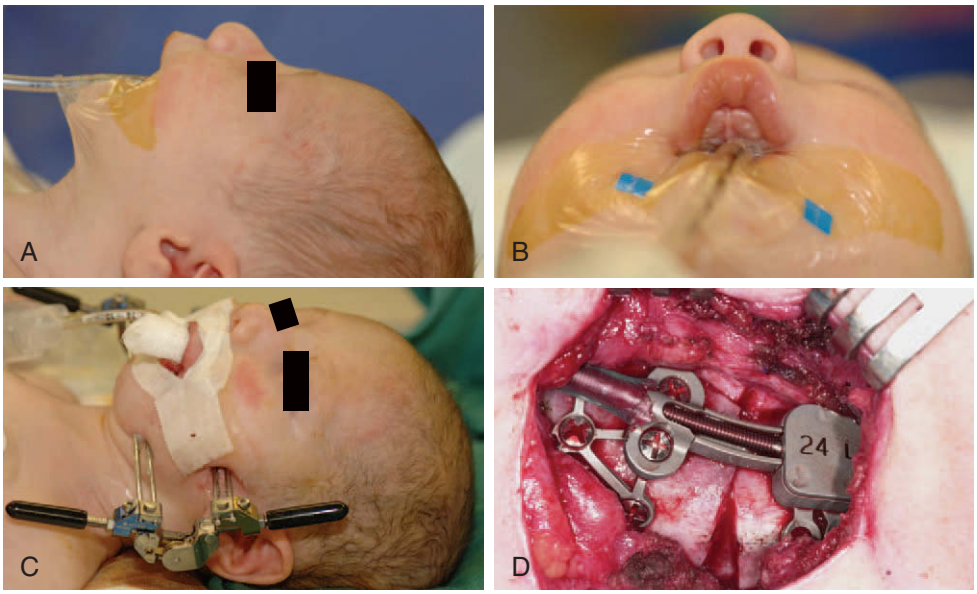

Figure 185-28. Distraction osteogenesis of the mandible. Profile view **(A)** and base view **(B)** of a neonate with Pierre Robin sequence. This patient could not achieve adequate ventilation without mechanical respiratory support. **C,** External distractors were placed after bilateral intra-oral osteotomies were created. The patient's mandible was ultimately distracted more than 1 cm, eliminating the need for any respiratory assistance. **D,** Internal distraction in a different patient. The distractors were applied after osteotomies were created through extra-oral incisions.

Pin migration scars can be significant as well. However, this is a rapidly evolving technique, and new devices are constantly being introduced. As the internal devices become more sophisticated, their roles will continue to expand.

The most common application of distraction osteogenesis in the craniofacial skeleton is the mandible. It is used for maxillary advancement and in the upper face and cranial vault as well. The process consists of several phases. At the time of surgery, the skin or mucosa and soft tissue are incised to expose the part of the facial skeleton that is to be distracted. The periosteum is incised directly over the intended site of osteotomy, which is marked out. The appropriate holes are drilled for fixation of the distraction device before the controlled osteotomy is made. In the mandible, the cortical cuts are made carefully to protect dental and neurovascular structures. Full mobility about the osteotomy sites must be confirmed to ensure total disunion of the bony segments; any bony continuity would hinder or prevent distraction. The distraction hardware is then put into place. Placement involves anchoring the device on both sides of the osteotomy with screws for an internal device or percutaneous pins for an external device. Some devices are borne by teeth or a dental implant. Distraction osteogenesis has a place in alveolar bone reconstruction and dental restoration as well.

A latency period is observed following osteotomy and placement of the device before actual distraction is begun. During this time the healing process commences with callus formation. The duration of the latency period depends on the age of the patient. In very young patients it can be as short as 24 hours, and in adults it can be as long as 1 week. It is more detrimental to wait too long than to begin too early, for premature fusion would render the distraction difficult or impossible. The beginning of distraction initiates what is termed the *distraction phase*. During this period, new immature bone is laid down between the osteotomized bony edges. The rate of distraction and the frequency with which it is done depend on the nature of the defect and the age of the patient. These variables are the subject of some debate, although the rate of distraction typically varies between 1 and 3 mm/day in one to three installments.

In the period subsequent to the distraction phase, the bone remodels and matures in what is known as the *consolidation phase*. The distraction hardware is left in place for a variable time. The rule of thumb we use is to allow consolidation to occur for a period that is at least twice the duration of distraction period. During the consolidation phase, the regenerate mineralizes and the soft tissue continues to change its shape and orientation so as to achieve balance with the new position of the bone. After several months the new bone is similar in volume to the native bone but with somewhat reduced mineral content and strength.

Trauma

The goal of treatment is the restoration of function and three-dimensional architecture. For severe and displaced fractures, internal fixation is often necessary.[90] The window of time in which fractures can be repaired is shorter in children as a result of the rapidity of their healing time. Many surgeons advocate using resorbable plates and screws for internal bony fixation, although others prefer using small titanium plates, arguing that complications from permanent (mini)plates are minimal.[75,85,91-93]

Neoplasm

Approaches to the skull base for tumor extirpation also require an intimate understanding of craniofacial anatomy because normal anatomy is often effaced. Several craniofacial approaches have been described in the pediatric population that can be used to gain access to tumors of the anterior and middle cranial fossae.[94] Historically, tumors of the anterior skull base were approached with a frontal craniotomy combined with a facial incision such as a lateral rhinotomy with or without a Weber-Ferguson facial incision. However, tumors of the anterior cranial fossa can be adequately exposed with a subcranial (subfrontal) approach without facial incisions (see Fig. 185-12). As previously mentioned, this latter exposure involves removal of the frontonasal complex. The extent of frontal and orbital rim bone removal is determined by the size, location, and nature of the lesion. In an extended subcranial approach, large sections of the bony orbit can be removed.[95]

The middle cranial fossa can be approached through a variety of techniques. The endoscopic transnasal-transsphenoidal approach can be effective in resection of midline tumors associated with the sella turcica, sphenoid cavity, and posterior nasal cavity. Figure 185-11 demonstrates repair of a sphenoid sinus encephalocele via this endoscopic approach. Even malignant or locally destructive lesions are occasionally accessible via this approach. Le Fort I, transpalatal, and midfacial degloving techniques can be used to gain limited access to lesions of the skull base.[96] More aggressive lesions that are off the midline (such as petroclival lesions) can be approached via the infratemporal fossa (or a modified version) or other transbasal approaches.[97] The cranio-orbito-zygomatic and transcondylar approaches provide excellent exposure of the infratemporal fossa. A frontotemporal craniotomy extends the exposure to the middle cranial fossa and the petrous internal carotid artery as well as other petroclival structures. When a lesion involves the middle cranial fossa, the infratemporal fossa, and the nasopharynx, a wider exposure is frequently necessary. The facial translocation procedure provides very wide exposure to lesions in this area and is well suited for malignancies, for which a margin of healthy tissue must be removed as well. It involves extended facial incisions as well as transection of facial nerve branches that are later reanastomosed. A maxillary-zygomatic bony segment is removed in order to gain access to the necessary extracranial lesion. A subtemporal craniotomy then provides intracranial exposure. In reconstruction of the bony framework, the same principles must be followed as for any other craniofacial procedure.

Biomaterials in Skeletal or Cartilaginous Defect Repair

When selecting materials for reconstituting craniofacial skeletal defects, the surgeon must recognize that no one material fills all needs. Several materials are available, reflecting the reality that there is no truly superior product in the field. The craniofacial surgeon starts the process of selecting a material by identifying a specific clinical need and a tissue substitute that will fill as much of that need as possible. Three types of factors are primarily responsible for outcomes of the use of bone substitute material, host factors, surgical technique, and the features of the material.

Host factors are of fundamental importance whenever a graft or implant is to be used. They include any systemic conditions, such as autoimmune illness, as well as the local environment. The local environment is profoundly influenced by anything that alters its vascularity, such as radiation therapy. The functional demands of the tissue being replaced are carefully considered. A calvarial defect, for instance, has different requirements from those of a mandibular defect, which has much greater load-bearing requirements. The extent of soft tissue coverage and mobility to which the implant is exposed are also key factors. Implants that work in the malar eminence might not work in the ear or nose.

Surgical technique can also play an important role in how well an implant is tolerated. Intra-oral approaches carry an increased risk of infection if closure is not executed with meticulous attention. For all approaches, appropriate handling of the soft tissues and the periosteum (when available) can be critical to success. Material preparation, such as pretreatment with an antimicrobial agent, can also be important in improving the likelihood of success.

The third factor is the material itself. On a general level a material that is nontoxic, noncarcinogenic, and nonimmunogenic to biologic systems is said to be *biocompatible*. Inflammation, which in previous discussions of the subject was considered a negative quality, can actually be advantageous as long as it is resolvable. The concept of biocompatibility, however, is more complex than even this definition implies. As previously discussed, a material that is biocompatible in one area may not be so in another. The use of expanded polytetrafluorethylene (ePTFE) is an excellent example. ePTFE has been successfully used for many years in vascular surgery,[98] but the use of Proplast, a closely related material, in reconstruction of the temporo-mandibular joint produced disastrous complications.[99] In some applications and locations, a material that causes a local but temporary reaction is desirable, whereas in others, a totally inert material is required. On the basis of this analysis, it is more precise to include application and local factors in the definition of biocompatibility.

Furthermore, it is most useful to think of biocompatibility as a broad spectrum with autogenous grafts on one end and alloplastic (synthetic) materials on the other. Allografts (homografts) and xenografts fall in the middle of that spectrum. Autogenous materials represent the "gold standard," but this category is not homogeneous. Cancellous bone grafts are quite different from cortical grafts. Cortical grafts can be further subclassified as endochondral or intramembraneous bone, with functional differences between the two.[100-102] Although there is a vast and successful experience with autogenous grafting,[103] this method still has its limitations. Donor site morbidity should not be taken lightly. In a prospective study evaluating iliac crest donor site pain, Sasso and colleagues[104] reported that a significant proportion of patients still had donor site pain 2 years after surgery. In addition, incomplete resorption and remodeling of cortical bone occurs in autogenous grafts, and unpredictable remodeling can be an issue as well.[105,106]

Allografts can be used in place of autogenous grafts. Demineralized bone matrix and irradiated cadaveric bone are examples of allografts currently used by some surgeons. Xenografts are also used; they include various collagen preparations that are employed as bone substitutes. The final category is synthetic biomaterials or alloplasts. This category consists of metals, ceramics, polymers, and biomimetic materials. This final subcategory refers to materials that mimic bone structurally or biologically and includes tissue-engineered constructs.

The metal most commonly used for craniofacial reconstruction is titanium. This metal not only has some osteoconductive properties but also has a modulus of elasticity that approaches that of bone. This feature results in less stress shielding than observed with stainless steel or Vitallium, both of which are rarely used today. Gold is inert, and its high density has made it useful in some applications, such as facial reanimation.

Polymers include a diverse set of materials some of which are nonresorbable and some resorbable. They have a successful track record for use in facial augmentation.[107] Methacrylates are nonresorbable and

have been widely used for calvarial reconstruction since World War II. High-density porous polyethylene is a straight-chain aliphatic hydrocarbon that is inert and also nonresorbable. It has been used successfully in some craniofacial applications. The primary problem with these materials is associated with their risk for infection or extrusion during the life of the recipient. Implants fabricated from polylactic acid and polyglycolic acid are resorbable and have sufficient strength for some load-sharing applications. This material has been promising as a means of bony fixation without the use of a permanent material.

Ceramics include calcium phosphates such as hydroxyapatite and bioglass. Hydroxyapatite, which has the advantage of being closely related to the carbonated apatite found in bone, has been shown to be reasonably effective in animal models and has proven clinical efficacy in some applications.[108,109] However, in the sintered and cement forms, it is not entirely accessible to the remodeling activities of osteoclasts. Its osteoconductivity and osteoinductivity are often less than ideal.[106,110,111] Bioglasses are very osteoconductive, but some of their properties, such as stiffness and elasticity, render them inappropriate for many craniofacial applications.

The final subcategory is synthetic biomimetic materials. They are designed to replicate bone on a structural and biologic level. They are often composites and can include bioactive factors such as bone morphogenic proteins or cells in a tissue-engineered material. This field is very promising in offering the hope of an off-the-shelf material that can simulate bone and stimulate the bone remodeling cycle—so that it is resorbed via osteoclastic remodeling coupled with osteoblastic bone deposition. Biomimetic biomaterials are theoretically replaced with normal lamellar bone. Given the pace of research in this field, a true bone substitute material of this nature is certainly on the horizon.

Conclusion

The field of craniofacial surgery is a rapidly developing and complex field. Appropriate care can best be rendered by a multimember team with diverse and in-depth training. The craniofacial defects encountered are often part of a larger syndrome affecting many functional systems. The underlying pathology is etiologically diverse and heterogeneous. The application of craniofacial principles developed to treat congenital problems also serves well for tumor extirpation and trauma repair. Several materials are currently available to reconstruct the craniofacial skeleton, but there is also a wide effort to develop more biomimetic materials.

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CHAPTER ONE HUNDRED AND EIGHTY-SIX

Cleft Lip and Palate

Oren Friedman

Tom D. Wang

Henry A. Milczuk

Key Points

- Cleft lip and palate deformities constitute the most common congenital defect of the head.
- The etiology of clefting is multifactorial. Its prevalence varies among ethnic groups and within families. Syndromes are common, especially among patients with cleft palate.
- Surgical decisions should be based on careful analysis of the defects. The goals are restoring function (e.g., lip closure, nasal airway, normal speech, eustachian tube function, useful dental occlusion) and maximizing lip, nose, and midface symmetry.
- Numerous surgical (and medical) approaches have been developed, and different teams use various management strategies for patients with clefting.
- Patients with cleft lip or cleft palate are best managed using a multidisciplinary approach. A coordinated medical and surgical care plan provides optimal long-term outcomes. The patient's medical and surgical needs change over time.

Cleft lip and cleft palate are among the more common congenital deformities. Patients with these deformities often may have associated problems including otologic disease, speech and language problems (delayed onset, articulation disorders, velopharyngeal incompetence or insufficiency), dental deformities (e.g., malocclusion; missing, malformed, or supernumerary teeth), facial growth deficiencies, and psychosocial issues. Some children have associated genetic syndromes or chromosomal abnormalities.

This chapter discusses some of these problems and their treatment strategies for the child with cleft lip or palate, or both, with emphasis on the need for a well-coordinated multidisciplinary approach to management.

Classification of Cleft Lip and Palate

A variety of classification systems have been proposed, but few have found wide acceptance. The embryologic development of the lip and palate serves as the foundation for a number of cleft classification systems. Some useful terms and concepts for cleft classifications are described in this section.

The incisive foramen divides the palate into the primary palate and the secondary palate. The secondary palate develops after completion of development of the primary palate, and extends from the incisive foramen anteriorly to the uvula posteriorly. The primary palate, which has the incisive foramen as its posterior border, consists of the premaxilla, lip, nasal tip, and columella.[1]

Cleft lip is classified as unilateral or bilateral, and its extent may be classified as complete or incomplete. A complete cleft involves the entire vertical thickness of the upper lip, and is often associated with an alveolar cleft, because the embryologic origins of the lip and primary palate are the same (Fig. 186-1). An incomplete cleft lip involves only a portion of the vertical height of the lip, with a variable segment of continuity across the cleft region. The variable continuous segment may present as a simple muscular diastasis with intact overlying skin or as a wide cleft with only a thin band of skin crossing the region of the cleft (Fig. 186-2). *Simonart's band* is the bridge or bar of lip tissue, of variable size, that bridges the cleft gap. Simonart's band usually consists of skin only, although some histologic studies have shown some muscle fibers to lie within the band.[2] Unilateral clefts of the lip should include a designation of whether the right or the left side is involved.

Palatal clefts also are described as being unilateral or bilateral, and their extent may be classified as complete or incomplete. In addition, cleft palates are classified according to their location relative to the incisive foramen. Clefts of the primary palate occur anterior to the incisive foramen, and clefts of the secondary palate involve the segment posterior to the incisive foramen. A unilateral cleft of the secondary palate is defined by a cleft in which the palatal process of the maxilla on one side is fused with the nasal septum (Fig. 186-3). A bilateral complete cleft of the secondary palate has no point of fusion between the maxilla and the nasal septum (Fig. 186-4). A complete cleft of the entire palate involves both the primary and secondary palate, including one or both sides of the premaxilla/alveolar arch, and frequently involves a cleft lip. An isolated cleft palate usually involves the secondary palate only, and has varying degrees of severity. The least severe incomplete cleft is the submucous cleft palate (SMCP) in which the underlying palatal musculature is deficient and inappropriately attached. Associated features include a bifid uvula, a zona pellucida (bluish midline region representing the muscle deficiency), and a notch in the posterior hard palate[3] (Fig. 186-5). All three elements are not required for the diagnosis of SMCP, however.

Embryology

For full appreciation of the variety of anatomic deformities that may be encountered in the patient with cleft lip and palate, an understanding of the normal embryologic development of the lip, palate, and nose

Figure 186-1. A patient with complete unilateral cleft of lip and palate. *Arrow* marks the junction of the nasal septum with the noncleft side of the palate.

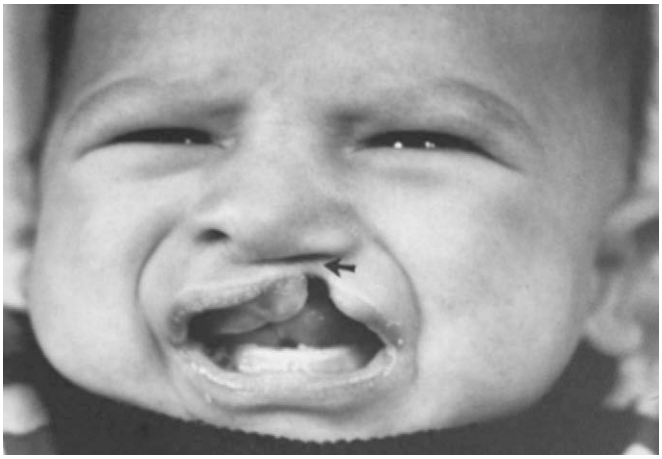

Figure 186-2. *Arrow* indicates Simonart's band connecting two sides in a patient with incomplete cleft lip.

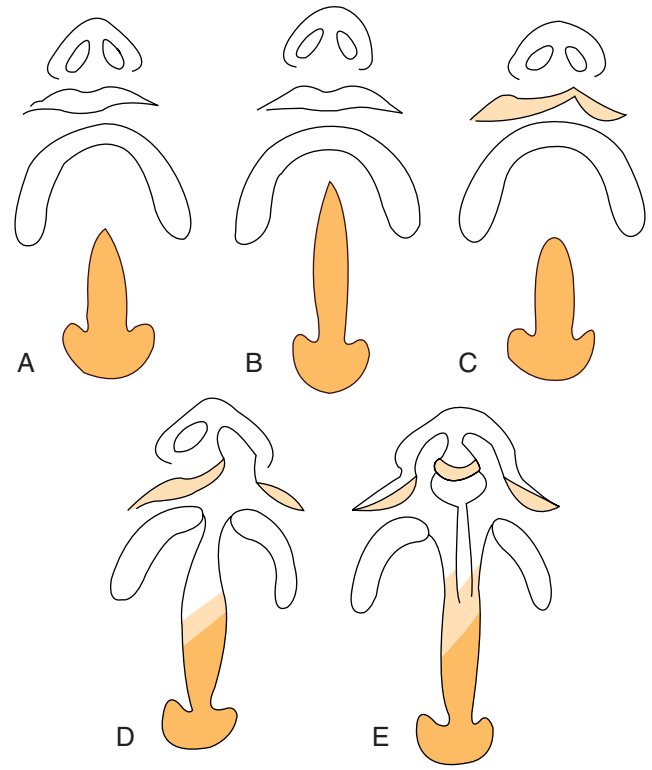

Figure 186-3. Classification of cleft palate. The division between primary palate (prolabium, premaxilla, and anterior septum) and secondary palate is the incisive foramen. **A,** Incomplete cleft of the secondary palate. **B,** Complete cleft of the secondary palate (extending as far as the incisive foramen). **C,** Incomplete cleft of the primary and secondary palates. **D,** Unilateral complete cleft of the primary and secondary palates. **E,** Bilateral complete cleft of the primary and secondary palates. *(After Kernahan and Stark, 1958. From McCarthy JG, Cutting CB, Hogan VM. Introduction to facial clefts. In: McCarthy JG, ed.* Plastic Surgery. *Vol 4. Philadelphia: WB Saunders; 1990:2443.)*

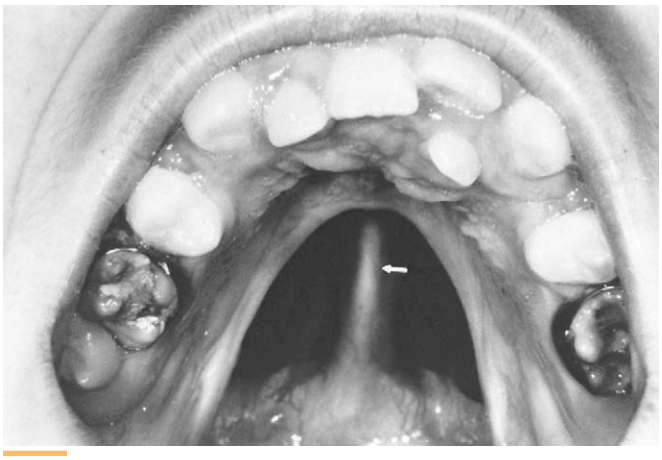

Figure 186-4. A patient with bilateral complete cleft palate. *Arrow* marks the nasal septum, which is not connected to either palatal shelf.

is essential. At the end of the fourth embryonic week, the neural crest–derived facial prominences appear from the first pair of pharyngeal arches. The maxillary prominences are found laterally (Fig. 186-6). The frontonasal prominences, formed by the proliferation of mesenchyme ventral to the forebrain, form the upper border of the stomodeum. On either side of the frontonasal prominences are local thickenings of surface ectoderm which form the nasal placodes.[1]

During the fifth week of embryonic development, the nasal placodes invaginate to form the nasal pits. This invagination process creates a ridge of tissue around the pit, called the lateral nasal prominences laterally, and the medial nasal prominences medially (Fig. 186-7).

Over the next 2 weeks, the paired maxillary prominences grow medially and approximate the paired medial nasal prominences (Fig. 186-8). Over time, fusion of the paired medial nasal prominences and paired maxillary prominences occurs, thereby forming the upper lip. The medial nasal prominences fuse to form the philtrum, medial upper lip, nasal tip, and columella. The maxillary prominences form the lateral aspects of the upper lip. The lateral nasal prominences are not involved in the formation of the upper lip, but form the nose (Fig. 186-9).[1,3]

The nose is formed from five facial prominences: The frontonasal prominence forms the bridge, the fused medial nasal prominences form the tip and columella, and the lateral nasal prominences form the nasal alae (Table 186-1).

Palatogenesis begins at the end of the fifth week, with complete fusion occurring by 12 weeks of development. As the maxillary prominences grow and push the medial nasal prominences medially, the medial nasal prominences fuse not only at the surface but also at deeper levels (Fig. 186-10). Thus, the intermaxillary segment, or primary palate, which includes the central maxillary alveolar arch that houses the four incisor teeth and the hard palate anterior to the incisive

foramen, is formed by the deeper levels of fusion of the two medial nasal prominences. Once the primary palate is completely developed, the secondary palate begins to develop.[1,3]

The secondary palate makes up the major portion of the palate. It is formed from the palatine shelves, which are two shelflike outgrowths of the maxillary prominences. In the sixth week of embryonic development, the palatine shelves are directed obliquely downward on either side of the tongue (Fig. 186-11). By the seventh week, the palatine shelves migrate inferomedially to lie horizontally above the tongue. It is in this horizontal position that the palatine shelves fuse in the midline to form the secondary palate (Fig. 186-12). The palatine shelves fuse with the previously formed primary palate anteriorly, and the nasal septum fuses with the newly formed secondary and primary palate. Palatal fusion occurs from anterior to posterior, beginning at the incisive foramen at 8 weeks of gestation and reaching completion by week 12 with uvular fusion (Fig. 186-13). The degree of clefting noted clinically is a consequence of the point in fetal development when the fusion process is interrupted.

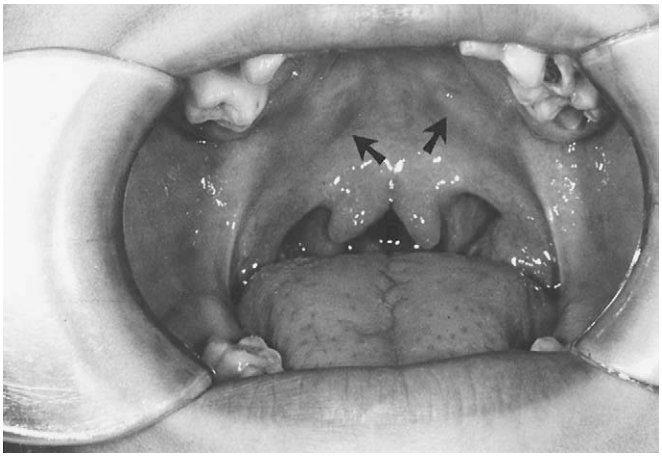

Figure 186-5. Submucous cleft palate with bifid uvula and muscular diastasis *(arrows)*.

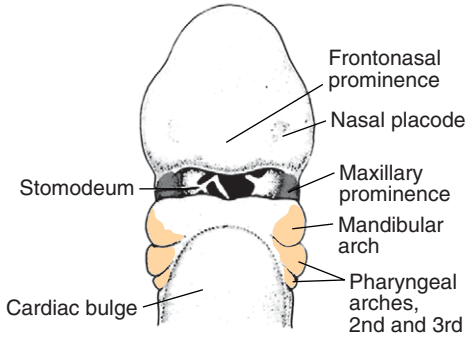

Figure 186-6. Lateral view of an embryo at the end of week 4, showing the position of the pharyngeal arches. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:315.)*

Diagnosis

Prenatal Diagnosis

The advent of ultrasonography for use in prenatal care and improvements in imaging now permits antepartum diagnosis of cleft lip and palate[4,5] (Fig. 186-14). Routine prenatal ultrasonography is now the standard practice in most communities. More reliable prenatal diagnosis can be made of cleft lip than of cleft palate.[6] Diagnostic accuracy is improved if two-dimensional ultrasonography is combined with three-

Table 186-1

Structures Contributing to the Formation of the Face

Prominence	Structures Formed
Frontonasal*	Forehead; bridge of the nose, medial and lateral nasal prominences
Maxillary	Cheeks, lateral portion of the upper lip
Medial nasal	Philtrum of the upper lip, crest and tip of the nose
Lateral nasal	Alae of the nose
Mandibular	Lower lip

*The frontonasal prominence represents a single unpaired structure, whereas the other prominences are paired.
From Sadler TW. Head and neck embryology. In: Sadler TW, ed. *Langman's Medical Embryology*. 6th ed. Baltimore: Williams & Wilkins; 1990:315.

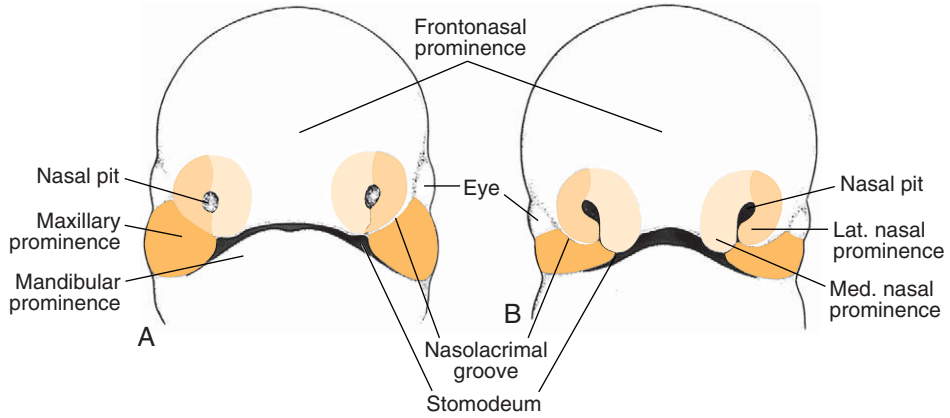

Figure 186-7. Frontal aspect of the face. **A**, Five-week embryo. **B**, Six-week embryo. The nasal prominences are gradually separated from the maxillary prominence by deep furrows. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:315.)*

dimensional ultrasonography.[7] The diagnosis can be made as early as 18 weeks, although the accuracy improves with the age of the fetus.[8] It is estimated that 12% of these fetuses will have other anomalies.[5] The parents frequently will want additional information and often are referred to cleft teams for counseling. Most families find antenatal counseling helpful in planning for care of the child with an orofacial cleft.[9]

Molecular Genetics of Orofacial Clefts

Clefts of the lip and/or palate are influenced by both genetic and environmental factors. Monozygotic twins demonstrate a concordance rate of 40% to 60% for clefting. Failure to reach 100% concordance in monozygotic twins suggests that genetics alone does not determine orofacial clefts. Embryology and genetics suggest that clefts of the primary palate, those that involve the lip with or without the remaining palate (CLP), arise from a different mechanism from that operative with clefts involving the secondary palate only (CP).[10] Currently, approximately 70% of CLP patients are thought to be nonsyndromic, whereas 50% of CP patients are nonsyndromic.[11] Syndromic clefts may be the result of a single gene transmission as occurs in autosomal dominant, autosomal recessive, or X-linked heredity. Facial clefting is a possible association in more than 200 syndromes.[12] The most common syndrome associated with cleft lip is van der Woude syndrome. Lower lip pits and CLP are the characteristics features of this syndrome, although CLP and isolated CP can be seen in the same

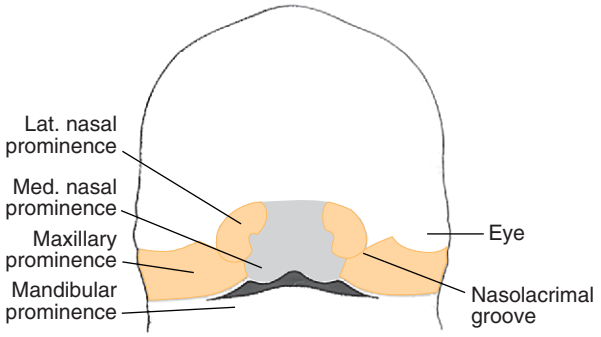

Figure 186-8. In a 7-week embryo, the maxillary prominences have fused with the medial nasal prominences. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:316.)*

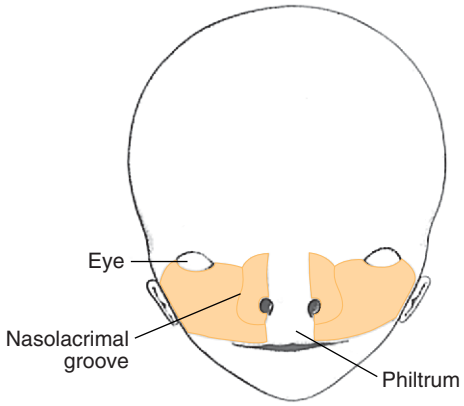

Figure 186-9. In a 10-week embryo, the maxillary prominences have formed the lateral lip and the medial nasal prominences have formed the philtrum. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:316.)*

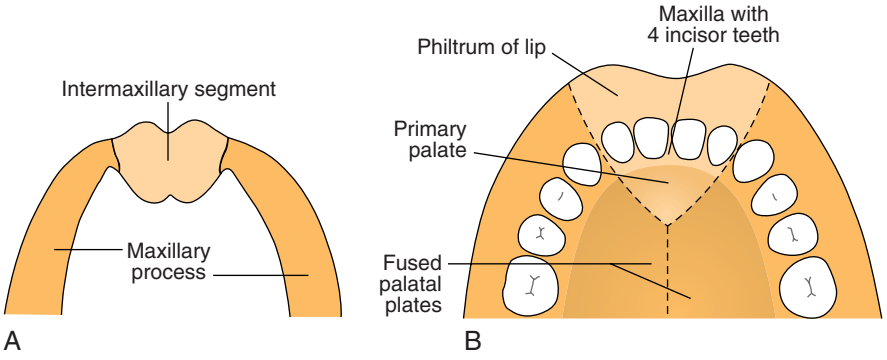

Figure 186-10. **A**, Schematic drawing of the intermaxillary segment and maxillary processes. **B**, The intermaxillary segment gives rise to the philtrum of the upper lip; the median part of the maxillary bone and its four incisor teeth; and the triangular primary palate. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:317.)*

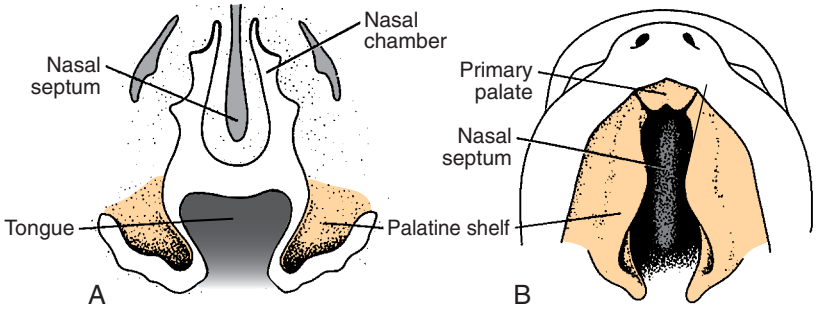

Figure 186-11. **A**, Frontal section through the head of a 6-week embryo. The palatine shelves are located in the vertical position on each side of the tongue. **B**, Ventral view of the palatine shelves after removal of the lower jaw and the tongue. Note the clefts between the primary triangular palate and the palatine shelves, which are still in a vertical position. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:317.)*

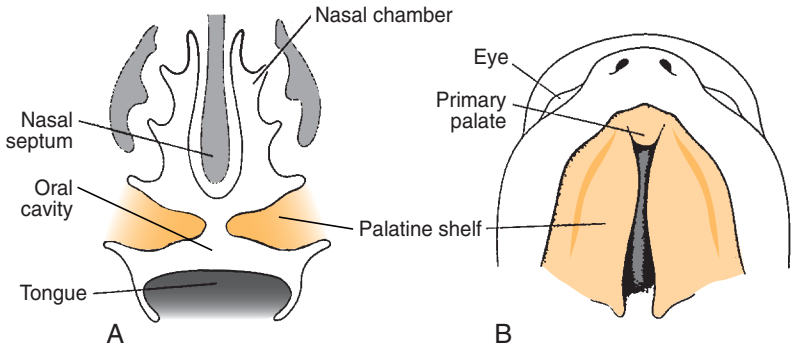

Figure 186-12. **A**, Frontal section through the head of a 7-week embryo. The tongue has moved downward, and the palatine shelves have reached a horizontal position. **B**, Ventral view of the palatine shelves after removal of the lower jaw and tongue. The shelves are in a horizontal position. Note the nasal septum. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:318.)*

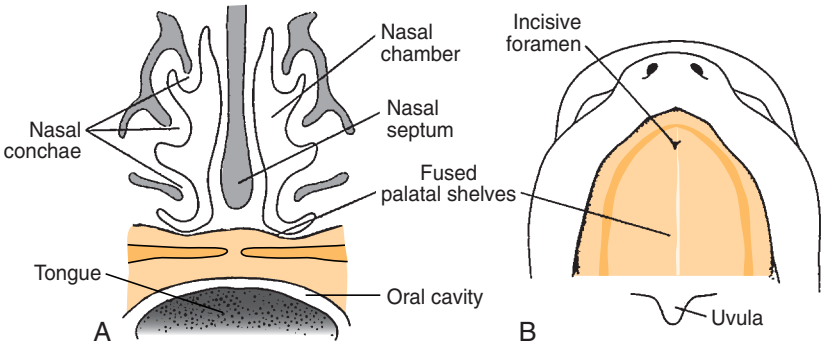

Figure 186-13. **A**, Frontal section through the head of a 10-week embryo. The two palatine shelves have fused with each other and with the nasal septum. **B**, Ventral view of the palate. The incisive foramen forms the midline landmark between the primary and the secondary palate. *(From Sadler TW. Head and neck embryology. In: Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:318.)*

Figure 186-14. Surface-rendered three-dimensional ultrasound image of a 24-week fetus with isolated unilateral left cleft lip. *(Courtesy of Roya Sohaey, MD, Portland, Oregon.)*

family and lip pits are not found in 10%. Genetic studies indicate that the gene responsible for this autosomal dominant disorder is on chromosome 1.[13] A number of signaling molecules, transcription factors, and growth factors have been identified that are particularly important to the development of the lip and palate.[14] Mutations to the gene, delay in expression of the gene product, or exposure to an environmental factor affecting the gene or its product may result in a cleft.

Several teratogens have been implicated in cleft development. These include alcohol,[15] tobacco smoke,[16] phenytoin,[17] and retinoic acid.[18] Meta-analysis did not find maternal age to be a factor.[19] Multivitamin supplements lower risk for CLP and possibly isolated CP.[20] Whether preconceptual folic acid supplementation alone can reduce clefting is controversial.[21,22] Potential mechanisms of genetic, environmental, and biochemical interactions have been suggested and reviewed.[20,23] Human teratogen studies should be interpreted with caution due to the potential for confounding variables and recall bias.

Genetic linkage studies have suggested a number of potential loci for clefts,[24,25] though only loci on chromosome 6p have consistently demonstrated linkage to CLP.[26,27] Linkage studies are limited by small numbers of families available for study. Transgenic mouse models and mouse strains with spontaneous clefts have identified candidate genes that may also affect human clefting. Mice deficient in the *Msx1* gene, implicated in signaling between tissue layers during embryogenesis, all developed clefts of the secondary palate.[28] Another putative mediator of orofacial clefting is transforming growth factor beta-3 (TGF-β_3). Knockout of the TGF-β_3 gene in mice results in clefts, but the addition of TGF-β_3 to embryonic murine tissue culture stimulates palatal shelf adhesion.[29] Studies of South American children with CLP suggest and

interaction between *Msx1* and TGF-β_3 loci increasing cleft susceptibility.[30] Transforming growth factor alpha also is considered to be a factor modulating CLP in humans.[31]

Epidemiology

Cleft lip and palate deformities are thought to be the most common congenital anomalies of the head and neck. Cleft lip with or without cleft palate must be distinguished from isolated cleft palate deformities because of different embryologic, etiologic, and epidemiologic factors.[32] Cleft lip occurs in 1 in 1000 live births in the United States, whereas cleft palate deformity occurs in 1 in 2000 live births. Cleft lip deformities occur with the highest incidence among Native Americans (3.6 in 1000 births), Asians (2.1 in 1000), and whites (1 in 1000) and with the lowest incidence among blacks (0.41 in 1,000).[12] By contrast, the incidence of cleft palate does not differ among ethnic groups, being reported as 0.5 in 1000 live births. Cleft lip occurs more commonly in boys than in girls, whereas cleft palate occurs more commonly in girls than in boys. Fusion of the palatine shelves 1 week later in girls than in boys is thought to be responsible for the higher frequency of cleft palate in girls.[1]

Recurrent risk rates for cleft lip with or without cleft palate and for isolated cleft palate have been determined and may be useful in counseling parents about the risk of cleft in future pregnancies.[32] Two unaffected parents with one child affected with a cleft have a 4.4% chance of having another child with a cleft lip and palate and a 2.5% chance of having a child with isolated cleft palate. One parent affected with a cleft has a 3.2% chance of having a child with cleft lip and palate and a 6.8% chance of having a child with isolated cleft palate. Presence of a cleft in one parent and in one sibling is associated with a 15.8% chance that the next child will have a cleft lip or palate, and a 14.9% chance that the next child will have a cleft palate.[32]

Multidisciplinary Cleft Team

Comprehensive care of the child with cleft palate is best done within a team of health care professionals trained in the care of various disorders that accompany and develop as a result of the cleft lip or palate.[33-35] This approach recognizes that no single discipline possesses all of the expertise needed for proper management of the many problems of these patients. The cleft team also will focus on the needs of the patient and family. Standards have been recommended by the American Cleft Palate–Craniofacial Association.[36] Specialties that often make up a cleft care team are listed in Box 186-1. Members should meet face to face to discuss patient care at least six times a year. Continuing education for the care of patients with cleft deformities should be an integral part of membership in a cleft team.

Team care begins when an infant is identified as having a cleft. The nursing staff or the pediatrician, within the context of a cleft care team approach, monitor feeding, growth, and development of the child. Parents are provided counseling, genetic information as needed, and verbal and written instructions regarding care plans. Most teams develop protocols for the management of children with cleft lip and palate deformities. These algorithms for care are based on the experience of the team members and assign care for anticipated needs of the child. A sample management protocol is outlined in Table 186-2. The otolaryngologist carries the roles of airway management, otologic care, and evaluation of velopharyngeal insufficiency and, in some teams, serves as the facial reconstructive surgeon.

Box 186-1

Specialty Members of a Cleft Care Team

Reconstructive surgeon
Otolaryngologist
Plastic surgeon
Oral maxillofacial surgeon
Speech-language pathologist
Orthodontist
Pediatric or prosthodontic dentist
Developmental or general pediatrician
Genetics counselor
Audiologist
Nurse
Social worker
Psychologist

Adapted from the American Cleft Palate–Craniofacial Association.

Nursing Care

Special problems that are encountered in nursing care of the patient with a cleft deformity include initial feeding, postoperative airway and feeding management, and family care issues centered on frequent medical and surgical needs. Nurses often provide an additional and, for some parents, more secure source of information regarding treatment

Table 186-2

Example Protocol for Multidisciplinary Approach to Care of Patients with Cleft Lip and Palate

Age Range	Intervention
Prenatal	Refer to Cleft Palate Team Medical diagnosis Genetic counseling Address psychosocial issues
Neonatal (0-1 month)	Same as above Provide feeding instructions Monitor growth Hearing screening
1-4 months	Monitor feeding and growth Repair cleft lip Monitor ears and hearing
5-15 months	Monitor feeding, growth, and development Repair cleft palate Monitor ears and hearing; consider ear tubes Instructions in oral hygiene
16-24 months	Assess speech and language development Monitor ears and hearing; ear tubes if indicated Monitor development
2-5 years	Monitor speech and language development; manage velopharyngeal insufficiency Monitor ears and hearing; ear tubes if indicated Assess development and psychosocial needs Consider lip/nose revision before child reaches school age
6-11 years	Monitor speech and language; manage velopharyngeal insufficiency Orthodontic evaluation and treatment Alveolar bone graft Monitor school and psychosocial needs
12-21 years	Monitor school and psychosocial needs Orthodontics and restorative dentistry Genetic counseling Rhinoplasty (if needed) Orthognathic surgery (if needed)

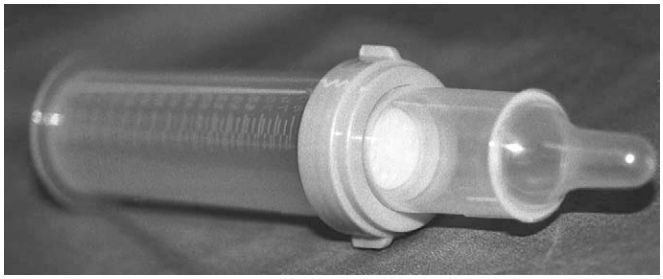

Figure 186-15. Haberman feeder.

Figure 186-16. Mead-Johnson feeder.

plans. Parents may feel more comfortable revealing their concerns or frustrations related to their child to nursing staff. The participation of dedicated and skilled nurses is valuable within the cleft care team.

Infants with a cleft palate are limited in their ability to suck. The common cavity between the nose and the mouth permits air to leak as the infant tries to suck. Cleft lip alone usually does not cause feeding problems. Accordingly, a number of strategies have been devised and different feeders have been created for feeding the infant with a cleft palate. Generally, breast feeding is ineffective. Alternately, expressed (pumped) breast milk can be delivered using one of the specialized feeders. The three most commonly used cleft palate feeders are the Mead-Johnson, Haberman, and Pigeon bottles (Figs. 186-15 to 186-17). Each allows for parent-controlled delivery of the meal (expressed breast milk or formula). Parents and caregivers need to be taught how to properly use the feeder and observed for the first feed to insure proper use of the feeder.[37,38] Trial and error may be needed to discover the best technique and feeder for the infant. Children with cleft palate generally swallow much more air during feeds. Frequent burping often is necessary; this should be explained to parents. Attention should be paid to the child's growth. Following weight and length gains using standardized growth charts is very useful to ensure that the infant stays on the appropriate growth curves.

Nurses can help families find the best position and technique for feeding after surgery. Oral and facial wounds affect placement of a feeding nipple. Often, the same cleft feeder can be used as before surgery, although the feeding technique may need to be modified owing to pain and swelling. Wound care also can be taught by nursing staff. Fresh lip wounds should be kept clean (with soap and water) and moist with ointments. Often, padded elbow restraints that prevent flexion of the elbow but permit other arm and hand motion are placed after surgery. Children are discouraged from placing fingers or other things into the mouth that may potentially disrupt the suture line. Restraints also may be used after palatoplasty. The restraints are left on until the intraoral wounds have epithelialized. Close monitoring by nursing staff will facilitate return to normal activities after surgery.

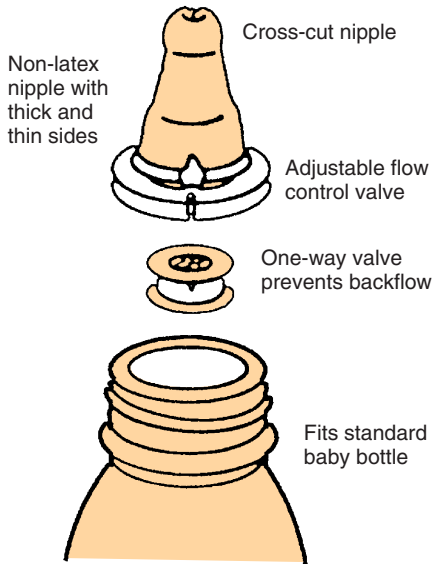

Figure 186-17. Pigeon feeder.

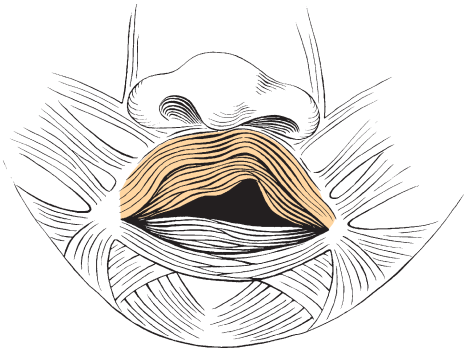

Figure 186-18. Muscle abnormality in an incomplete cleft lip that involves less than two thirds of the lip. Lower muscle fibers insert into tissue at the cleft margins; upper muscle fibers in the medial and lateral segment connect over the top of the incomplete cleft, forming a partial oral sphincter.

Anatomy

Anatomy of the Cleft Lip Deformity

The normal upper lip is divided into red and white components. The red lip is a mucous membrane, whereas the white lip is a cutaneous structure. The mucocutaneous junction at the vermilion border between the red and white lips is an important anatomic boundary that must be reconstructed meticulously in cleft lip repair for a natural-looking result. Failure to do so will draw attention to the irregularity at the vermilion border and create a poor cosmetic result.[3,39,]

In unaffected persons, the orbicularis oris muscle forms a complete sphincter around the oral cavity, providing the substrate for proper form and function of the lips and mouth. All patients with cleft lip deformities have muscular deficiencies and irregularities of varying degrees, leading to the abnormal appearance and function of the lip and mouth (Figs. 186-18 and 186-19). For proper correction of cleft lip deformities, it is essential not only to create symmetry of the lip superficially, at the skin level, but also to re-create the complete orbicularis muscular sling, for long-lasting cosmetic and functional results, and to re-establish complete mucosal coverage to ensure optimal healing and prevent distorting wound contracture. The muscle fibers in cleft lip deformities run in an inferior-to-superior direction along the margins of the cleft. They insert into the columella medially and along the nasal ala laterally. These fibers must be detached from their

Figure 186-19. Abnormal direction and insertion of muscle fibers of medial and lateral segments of the cleft into the cleft margin, the area of the ala nasi (laterally), and the base of the columella (medially). *Dark line* indicates arterial supply.

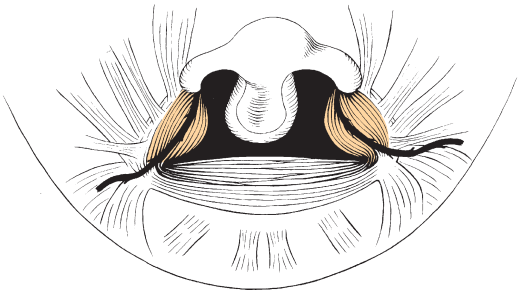

Figure 186-20. Abnormal muscle anatomy of a complete bilateral cleft. Both lateral muscle segments insert into the alae nasi, with the prolabium completely devoid of muscle tissue. Arterial supply is indicated by a *dark line*.

insertions and reoriented in a horizontal direction to bridge the cleft and create a complete muscular sling around the entire circumference of the oral cavity.[3,39]

Bilateral clefts also have abnormally oriented muscle fibers that run along the edges of the lateral aspect of the cleft (Fig. 186-20). Typically, the prolabial segment does not contain any useful muscle but is filled with connective tissue. In addition to the muscle and cutaneous irregularities, patients with bilateral cleft deformities have premaxillary and alveolar protrusion relative to the nasal septum. The premaxillary bony deformity may push the lip so far anteriorly and superiorly toward the nasal tip that the columella is severely diminished in strength and height and may even be obliterated completely (Fig. 186-21). There is often inadequate length to the medial crura; consequently, there is inadequate columellar skin. One of the major challenges in bilateral cleft repair is columellar reconstruction.[3,39]

The anatomic characteristics of the unilateral cleft lip nasal deformity include irregularities of the tip, columella, nostril, alar base, septum, and skeleton[40] (Fig. 186-22). The nasal tip is deflected toward the noncleft side, with a relatively short medial crus and long lateral crus on the cleft side. In addition, the lateral crus of the lower lateral cartilage is caudally displaced on the cleft side. The columella is shorter than normal on the cleft side, and the columella lies on the non-cleft side due to the unopposed action of the intact orbicularis oris muscle. The nostril on the cleft side is horizontally oriented rather than the normal vertical orientation.[17] Similarly, the nasal septum is deflected to the noncleft side. The alar base on the side of the cleft is displaced laterally, inferiorly, and posteriorly. Finally, there is a deficiency of maxillary bone on the cleft side, with the nasal floor often being absent.

The bilateral cleft lip nasal deformity differs from the unilateral deformity in several aspects other than laterality. The degree of nasal deformity relates to the severity of the cleft lip deformity—whether the cleft lip is complete or incomplete. It also is affected by the degree of

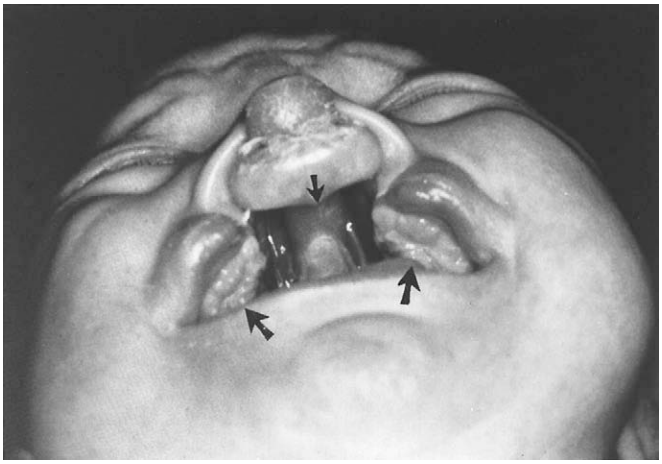

Figure 186-21. A patient with complete bilateral cleft lip and palate: *Top arrow*, protruding premaxilla; *bottom arrows*, collapse of alveolar arches.

Figure 186-22. Classic nasal deformity associated with the unilateral cleft lip.

premaxillary protrusion. Bilateral cleft lip nasal deformities are symmetrical, making the repair of the nose somewhat simpler with regard to gaining tip symmetry. The challenging aspect of the bilateral cleft lip nasal deformity is the lack of adequate columellar tissue. This lack of tissue includes deficiencies in the length of the lower lateral cartilages, as well as deficiency of skin overlying these shortened cartilages. The tip usually is broad and flat, and the alae are laterally displaced, with resultant horizontally oriented nostrils.[40]

Cleft Palate Deformity

Various degrees of deformity involving all tissue layers are seen in cleft palate. With soft palate cleft, deficiencies of the muscle and mucosal layers also are characteristic.

Five muscle pairs contribute to the soft palate. Normally, the levator veli palatini muscle has a transverse orientation, occupying the midportion of the soft palate, thereby creating a muscular sling for the velum.[41] This muscular sling is the principal structural component in closure of the nasopharynx during speech and swallowing. Other muscles that contribute to the velopharyngeal sphincter include the palatopharyngeus, superior constrictor, and musculus uvulae. The musculus uvulae runs beneath the nasopharyngeal musculus and extends from the tensor aponeurosis to the base of the uvula.[42] During speech, its contraction increases the midline bulk of the posterior edge of the soft palate. Deficiency of the musculus uvulae like that seen in

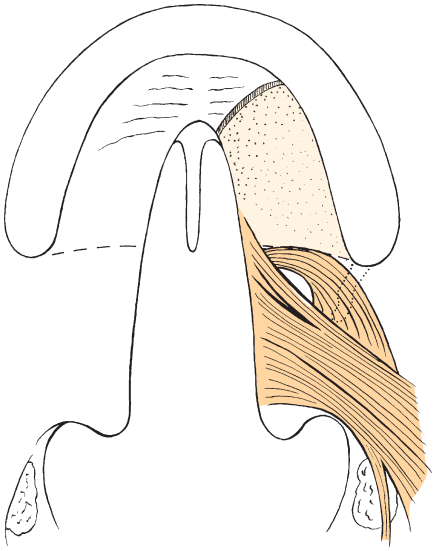

Figure 186-23. Abnormal muscle insertion into the posterior margin of the hard palate in a patient with clefting. Muscles are directed along the margins of the cleft, rather than across the soft palate as occurs normally.

submucous cleft palate may lead to velopharyngeal insufficiency and speech disorders (see Chapter 187, Velopharyngeal Dysfunction). The tensor veli palatini (TVP) muscle runs from its origins at the skull base and eustachian tube, wraps around the hamulus, and inserts into the posterior edge of the hard palate and forms an aponeurosis in the anterior midline of the soft palate.[43] Its functions are dilation of the eustachian tube and support for the soft palate during contraction.

In patients with cleft palate, the muscles of the soft palate may be hypoplastic,[44] in addition to exhibiting misdirection and abnormal insertions into the posterior hard palate (Fig. 186-23). Mucosa that envelops these muscles is deficient, except in the case of a submucous cleft palate. If the cleft involves the hard palate, then a midline bony deficiency of variable degree will extend toward the incisive foramen. The vomer usually is unattached in isolated cleft palate but may or may not be attached if there is a cleft lip. Abnormal muscle insertions combined with tissue absence or hypoplasia lead to palatal dysfunction. Palatoplasty aims to restore function by reorienting the muscles and reconstructing the continuity of the tissues.

Cleft Lip Repair and Cleft Rhinoplasty

The timing of cleft lip repair varies among surgeons. Some have suggested that lip repair be performed within 48 hours of the child's birth to prevent a separate hospitalization and to allow the parents to leave the hospital with a healthy-appearing newborn. Others prefer to delay surgery to allow for more tissue availability for the repair, more time for parent-child bonding, and more time for the parents to gain a better understanding and acceptance of the infant's congenital deformity. Commonly, the "rule of 10s" is applied, which suggests that surgery proceed when the infant is at least 10 weeks old, weighs 10 pounds, and has a hemoglobin level of 10 g/dL. We typically perform cleft repair during the child's second to third month of life, to gain the advantages just described.

Definitive Unilateral Lip Repair

Probably the most common technique for cleft lip repair is the Millard technique. Other techniques have been described, but this chapter focuses on only the Millard technique. The Millard rotation advancement closure for unilateral cleft lip repair entails the downward and lateral rotation of the medial segment of the cleft lip combined with the medial advancement of the lateral cleft segment into the defect. All cleft lips have a discrepancy between the vertical height of the lip from the Cupid's bow peak to the columellar base on the cleft and noncleft sides of the lip (philtral ridge height). The design and length of the rotation flap and the degree of back-cut required will depend on the difference in vertical height between the two sides. Advancement of tissue from the lateral segment of the cleft medially not only closes the tissue defect to bridge the gap but also serves to maintain the rotation flap in position and thus to maintain the amount of vertical height gained by the rotation flap and back-cut.[3,44]

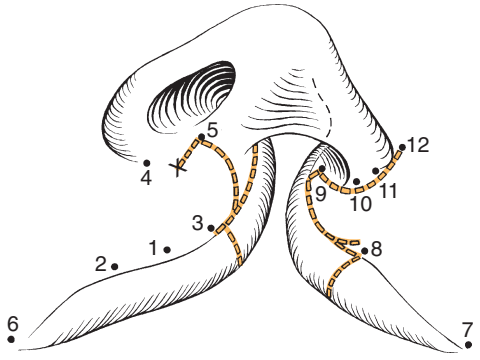

Figure 186-24. Rotation advancement technique: landmarks and incisions. See text for details.

The procedure begins with the skin markings, as shown in Figure 186-24. Skin markings are made with a 30-gauge needle and methylene blue dye. Extreme care should be paid to the measurements and placement of the skin markings, because these serve as the foundation for the surgical repair and provide stable anatomic landmarks in a changing surgical field.[31] The first marking, labeled 1 on the figure, is a point made at the mucocutaneous junction at the exact low point of Cupid's bow, which marks the central point of the upper lip. A second point (2) is placed at the height of Cupid's bow on the noncleft side of the upper lip. The distance between points 1 and 2 is measured—it normally is between 2 and 4 mm—and is used to establish the location of point 3, which represents the height of Cupid's bow on the cleft side of the upper lip. Thus, the distance from point 1 to point 2 is equal to the distance from point 1 to point 3. Point 4 marks the alar base on the noncleft side, and point 5 marks the columellar base on the noncleft side. Point 5 represents the superiormost extent of the vertical portion of the rotation flap, as discussed further later on. Point x, the back-cut point, is made at a variable distance from point 5 and is determined by estimating the amount of tissue needed to create symmetrical philtral ridges and to make up for the discrepancy in vertical height of the lip at the philtral ridge. Point x should never cross the philtral ridge on the noncleft side but should lie medial to it, so that the back-cut of the rotation flap runs parallel and medial to the normal philtral ridge on the noncleft side. This helps to maintain a scar-free philtral ridge on the noncleft side and improves the ultimate cosmetic result of cleft lip repair.

Point 6 marks the noncleft oral commissure, and point 7 marks the oral commissure on the cleft side. Point 8 marks the peak of Cupid's bow on the cleft side. It is placed at a distance from the commissure on the cleft side (distance from points 7 to 8) equal to that for the point placed at the peak of Cupid's bow on the noncleft side relative to the commissure on the noncleft side (distance from points 2 to 6). Point 9 is the medialmost point of the advancement flap and is placed at a distance from point 8 that is equivalent to the distance between point 3 and point 5 + x. Thus, the philtral ridge is formed by the union of the cleft edge on the side of the advancement flap (line 8-9) and the cut edges of the rotation flap on the non-cleft side (line 3-x). Point 10 is the cleft side alar base, point 11 is along the alar-facial crease, and point 12 is placed at the estimated lateralmost aspect of the advancement flap.

Surgical Technique—Rotation Flap

The normal philtral ridge height is 10 mm, and the rotation flap is designed to create a 10-mm-long segment for use in establishing philtral ridge symmetry. The rotation incision starts at point 3 and extends toward point 5, following a gentle curve and providing 4 to 5 mm of

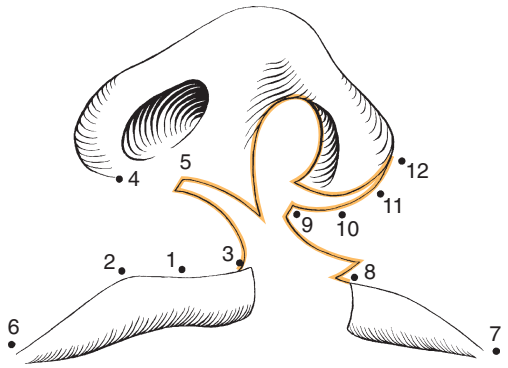

Figure 186-25. Rotation advancement technique: flaps incised and elevated. See text for details.

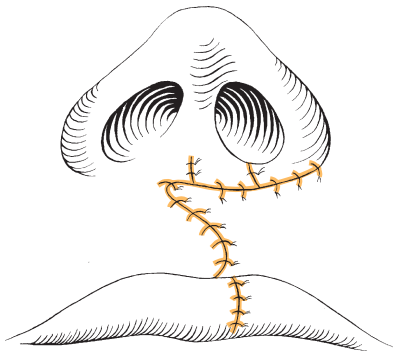

Figure 186-26. Rotation advancement technique: final suturing.

length toward the goal of 10 mm (Fig. 186-25). At the columellar base, the rotation flap incision follows a gentle curve and hugs the base of the columella, passing through point 5. This curve along the base of the columella adds an additional 3 mm of length toward the 10-mm goal. The final discrepancy in vertical height is compensated for with a back-cut to point x, using a stab incision with the No. 11 blade. The extension to the back-cut adds 2 to 3 mm of additional height that will be used to create philtral ridge symmetry. The back-cut is made at a 90-degree angle to the curved incision at the columellar base, to run parallel to rather than crossing the uninvolved philtral ridge. The rotation incisions are carried through the entire thickness of the orbicularis muscle and oral mucosa, to allow a complete release of the medial aspect of the cleft. Undermining along the edges of the rotation flap incision is continued for 1 to 2 mm on the cutaneous and mucosal surfaces, to permit eversion of the wound edges during skin closure.[32]

After completion of the rotation flap cuts, a "c" flap remains, which is a segment of skin that ran between the cut edge of the rotation flap and the edge of the cleft. The "c" flap may be used to add tissue length to the columella, which typically has a tissue deficiency.

Surgical Technique—Advancement Flap

The advancement flap starts with an incision from point 8 to point 9, creating the lateral edge of the new philtral ridge, which will be sutured to the edge of the previously created rotation flap (see Fig. 186-25). Thus, the length of line 8-9 is equal to the length of line 3-x. Release of the advancement flap is then achieved by continuing the incision horizontally along the alar base. Similarly, release of the gingivobuccal sulcus mucosa is performed with sharp dissection, to permit greater mobility. All incisions are carried down to the face of the maxilla, and blunt dissection along the face of the maxilla with scissors is performed, allowing the lateral lip segment freedom of mobility with minimal tension on the closure. Undermining the cutaneous and mucosal surfaces will allow eversion on wound closure.[3,32,45]

Closure—Rotation Advancement Flap

Once the rotation and advancement flaps are developed, approximation of the flaps is achieved with the help of skin hooks, followed by suturing of the flaps to one another to complete the lip reconstruction (Fig. 186-26). Four-0 Vicryl suture is used for all deep muscle stitches and oral mucosal stitches, and 6-0 fast-absorbing gut is used for the skin closure. The first key stitch attaches the muscle at the tip of the advancement flap to the muscle at the rotation flap back-cut point x. The next throw attaches the muscle layers of the advancement and rotation flaps at the level of the vermilion border. It is essential to align this stitch precisely in order to give a natural-appearing vermilion. Additional 4-0 Vicryl stitches are then used to reinforce the muscle layer of closure along the length of the philtral ridge. The mucosa is closed with 4-0 Vicryl suture placed in simple interrupted fashion. Skin closure is achieved with simple interrupted stitches of 6-0 fast-absorbing gut suture. The skin at the vermilion is closed with great precision to provide optimal cosmesis.[3,45]

Primary Rhinoplasty

The cleft lip deformity is always associated with nasal abnormalities. The extent of the nasal abnormality is related to the severity of the cleft lip. Nasal deformities associated with incomplete cleft lips are less severe than those associated with complete lip clefts. The goals of primary rhinoplasty include closure of the nasal floor, repositioning the lower lateral cartilages, and repositioning the alar base. These goals may be achieved through the same incisions that are used for the cleft lip repair, so that no additional incisions are required if the nasal deformity is addressed at the time of cleft lip repair.[40,46] Once the lip incisions are made, the muscle and soft tissue attachments of the ala are separated from the maxilla. Subsequently, through the same incisions, the lower lateral cartilages are freed from the overlying nasal skin along the entire nasal tip. Suturing of the lateral crura to the septum or to the ipsilateral dome helps to reposition the crura and alar base medially, increases tip projection, and creates greater symmetry between the two sides. Although secondary rhinoplasty frequently is still needed, the patient achieves greater social acceptance in the formative years when primary rhinoplasty is performed.

Bilateral Cleft Lip Deformities

The primary difference between the unilateral and bilateral cleft deformities lies in the position and characteristics of the premaxilla and prolabium. The lateral segments of the bilateral cleft lip deformity are similar to the lateral segments of the unilateral deformity. The difference lies in the medial segment of the cleft, the premaxilla. In bilateral deformities, the premaxilla is either partially or completely detached from both maxillae. The premaxilla and prolabium protrude anteriorly and superiorly and generally are unrelated to the maxilla itself. The columella is most often shorter than normal. Moreover, it may not be evident on surface inspection, though medial crura of the lower lateral cartilages are present. The prolabial soft tissue, though relatively scarce, should be used to form the full vertical length of the lip. The prolabial vermilion is used for the intraoral lining. The central vermilion is built up with vermilion-muscle flaps created from the lateral lip segments, and the vermilion ridge comes from the lateral lip segments. It may be helpful to use preoperative orthodontics to rotate the premaxillary segment posteriorly and rotate the lateral maxillary segments medially in order to increase the soft tissue available for closure and reduce the tension on the repair.[47] The repair we prefer for bilateral clefts is the single stage approach described by Millard, in which the orbicularis is advanced across the cleft, and straight vertical closure lines along the skin lie in the newly created philtral ridges[48] (Fig. 186-27A to F).

Cleft Palate Repair

All palatoplasty techniques share the same goals. These include separation of the nasal cavity from the oral cavity, creation of a competent velopharyngeal valve for both swallowing and speech, preservation of midface growth, and development of functional occlusion.

Controversy surrounds timing of cleft palate repair. Improved speech outcomes are seen when the soft palate is repaired early. Dorf and Curtin[49] demonstrated a 10% occurrence of articulation errors when palatoplasty was completed by 1 year and an 86% incidence of

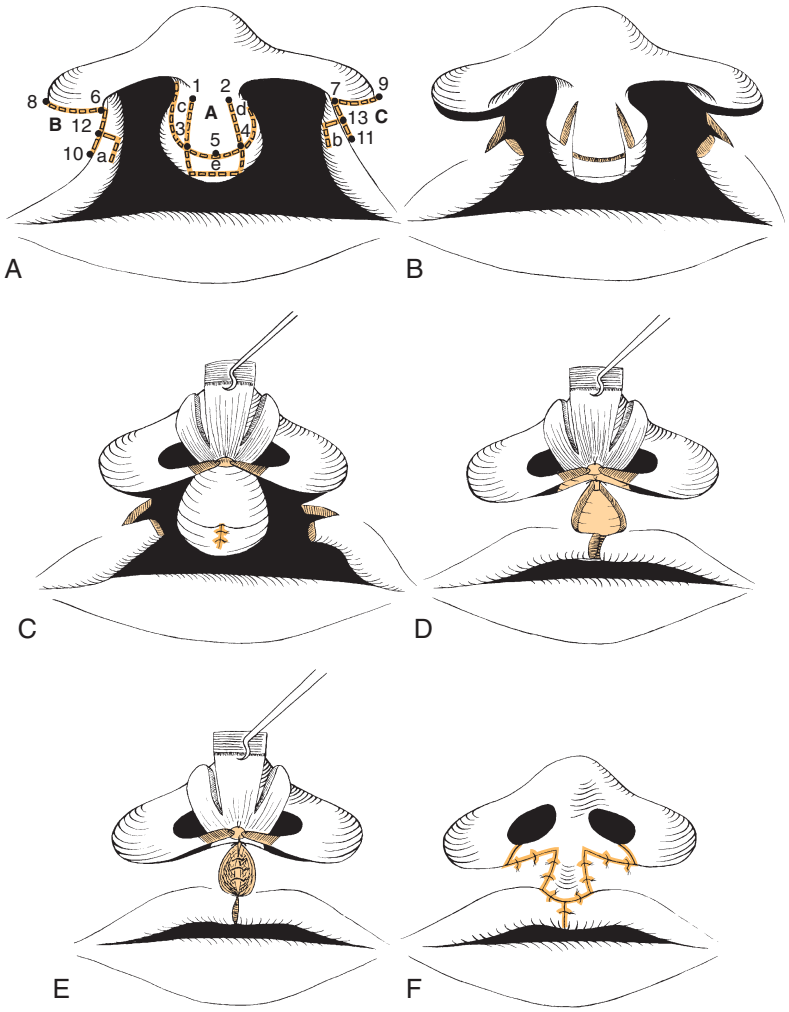

Figure 186-27. **A**, Bilateral cleft lip repair: landmarks and incisions. Prolabium provides philtral flap, A; forked flaps, c and d; and tubercle-reinforcing flap, e. Lateral lip provides flaps B and C and midline vermilion flaps a (within B) and b (within C). **B**, Bilateral cleft lip repair: flaps incised and elevated. **C**, Tips of the ala nasi de-epithelialized and sutured medially at the base of the prolabium. Excess prolabial mucosa provided the medial lining of the labial sulcus. **D**, Tips of the flaps sutured medially beneath the prolabium. **E**, Bilateral cleft lip repair: orbiuclaris oris muscle and mucosal approximation. **F**, Placement of forked flaps in the nasal sill and final suturing. Flap e (see **A**) may be used to reinforce the tubercle from behind.

articulation errors when repair was completed after 1 year. Similar results were found comparing early and late palatoplasty in isolated cleft palate. Haapanen and Rantala[50] compared three groups of children whose palatoplasty was done at mean ages of 12.9 months, 18.5 months, and 22.1 months. Significantly fewer children in the groups undergoing repair before 18 months had hypernasal speech or articulation errors or required secondary surgery to correct speech. Most surgeons and speech pathologists believe that soft palate repair should be done before the age of 12 months in order to minimize speech disorders.

Palate surgery during childhood may adversely affect facial growth. Case studies of adults with unrepaired clefts demonstrate normal midface development.[51,52] Animal studies suggest that disruption of the hard palate mucoperiosteum inhibits maxillary growth.[53] To preserve growth potential, some centers prefer a staged approach: early repair of the soft palate, obturation of the hard palate, then later surgical closure of the hard palate.[54,55] However, others have not found significant difference in maxillary development between patients who have single-stage palatoplasty versus two-stage repair.[56,57] Other factors that need to be considered are the type and severity of clefting. It appears that inherent growth deficiencies are associated with different cleft types.[58] More severe tissue deficiencies at birth in unilateral cleft lip and palate patients predict more growth retardation after cleft repair.[59] Given that this controversy over timing and staging of cleft palate repair has continued for several decades, prospective, multicenter clinical trials will be required to resolve many of the issues.

Palatoplasty Techniques

Preparation for palatoplasty requires analysis of abnormal anatomy. Knowledge of different techniques in palate repair will allow for an individualized surgical approach. The basic surgical techniques include primary veloplasty (Schweckendiek palatoplasty), bipedicled flap palatoplasty (von Langenbeck), V-Y pushback palatoplasty, unipedicled two-flap palatoplasty, and the double-opposing Z-plasty (Furlow) palatoplasty. Although credit is given to the original description of a palatoplasty technique by creating an eponym, it is important for the cleft surgeon to document the details of the technique used. Over time, many modifications have been advanced for each procedure. Important considerations for each technique are closure with minimal tension, layered closure, and reconstruction of the levator sling. The two most common techniques for palate closure are outlined next.

Two-Flap Palatoplasty

The two-flap palatoplasty is a commonly used technique for cleft palate repair and involves incisions that extend to the alveolar portion of the cleft or to the incisive foramen (Fig. 186-28). The nasal cavity can be

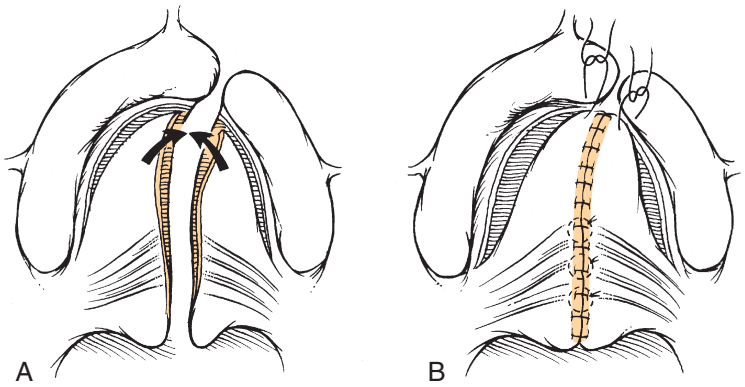

Figure 186-28. Two-flap palatoplasty. **A**, Incisions used to create unipedicled palate flaps. *Arrows* demonstrate rotation of bilateral flaps. **B**, The levator sling is reconstructed and closure is complete. In many cases, the hard palate mucoperiosteum can be reapproximated to the medial edge of the gingival incisions. This can minimize exposure of palate bone, which is believed to inhibit maxillary growth.

reconstructed by elevating vomer flaps, thereby creating four flaps used for reconstruction (not shown in Fig. 186-28). Vomer flaps are rotated laterally to unite with the mucosa at the medial edge of the nasal floor. The mucoperiosteal flaps are then rotated medially to close the cleft. The alveolar cleft is not closed using this method, nor is the palate lengthened unless a double-opposing Z-plasty (described next) is used to reconstruct the soft palate. This latter technique often is used for repair of complete primary and secondary cleft palate.

Furlow Palatoplasty (Double-Opposing Z-plasty)

The double-opposing Z-plasty palatoplasty was first described by Furlow in 1986.[60] This technique lengthens the soft palate and reconstructs the muscle sling. The two flaps containing muscle are rotated posteriorly and the two mucosa-only flaps are transposed anteriorly. It is more difficult to perform, especially in wide clefts. It can be combined with a unipedicled closure of the hard palate.[61] It also is commonly used to correct velopharyngeal insufficiency in patients with submucous cleft palate.[62] Speech outcomes are improved compared with those achieved with other palatoplasty techniques.[63,64]

Surgical Technique

Basic Principles

The patient should not have any active medical problems (other than otitis media). A family history of bleeding warrants an evaluation for a coagulopathy. Plans for airway management, especially for patients with Robin sequence, should be discussed with the anesthesiologist. A reinforced oral endotracheal tube should be used, to minimize kinking and ventilation problems while the mouth gag is in place. Most surgeons prefer the Dingman mouth gag for exposure of the oral cavity and pharynx. This mouth gag can exert significant pressure on the tongue.[65] If the mouth gag is then suspended from a Mayo stand, the exerted pressure may exceed arterial perfusion pressure to the tongue. Postoperative tongue edema risks airway obstruction and prolonged intubation. To minimize this risk, periodic release of the mouth gag during palatoplasty is recommended. Perioperative steroids (dexamethasone sodium phosphate 0.25 mg/kg) lower postoperative airway distress[66] and can reduce length of hospitalization[67] after primary palatoplasty. Perioperative antibiotics also may reduce the risk of infection. Injection of a topical anesthetic containing epinephrine into the planned incision and dissection sites and, if possible, into the greater palatine foramen helps reduce intraoperative blood loss.

Two-Flap Palatoplasty

Once general anesthesia has been achieved and the patient is in a supine position, the margins of the cleft at the junction of the nasal and oral epithelium are identified. The margins are incised sharply with a scalpel, separating the mucosa. Lateral releasing incisions are made medial to the alveolus and down to bone, and care is taken to avoid injury to the tooth buds and the neurovascular pedicle at the greater palatine foramen. This lateral incision is carried posteriorly just into the retromolar area and through mucosa only at this point (Fig. 186-29).

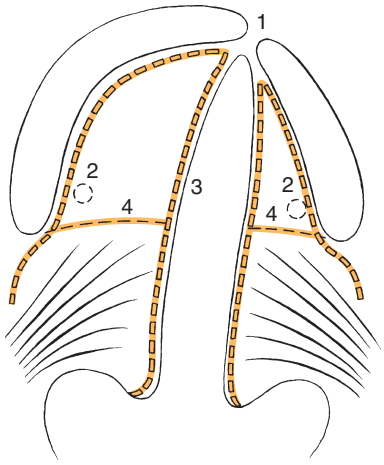

Figure 186-29. Two-flap palatoplasty. Landmarks are as follows: 1, alveolar cleft; 2, neurovascular bundle at the greater palatine foramen; 3, vomer; 4, posterior edge of hard palate. Incisions are indicated by the *dotted lines*.

Dissection begins with the separation of the soft palate muscle from the nasal mucosa. At least 3 mm of mucosa is elevated sharply. To perform an intervelar veloplasty, the muscle should be freed from most of its nasal mucosa attachments laterally. This dissection is technically difficult, because the muscles adhere tightly to the nasal mucosa. In similar fashion, the oral mucosa is elevated from the soft palate muscles.

Next, the mucoperiosteum of the hard palate is elevated using a periosteal elevator. Anteriorly, this dissection is easy, but caution is taken posteriorly near the greater palatine foramen. Once the neurovascular bundle is identified, the surrounding fibrous attachments are carefully dissected from the bone. This maneuver will provide additional medial displacement of the flaps and minimize tension during repair. On the cleft side, the medial edge of the mucoperiosteal flap is released from the nasal mucosa. On the noncleft side, the mucoperiosteum is elevated from the vomer. Continuity is maintained between the vomerine mucoperiosteum and the nasal mucosa of the soft palate on this side. The soft palate muscles are then released from their abnormal attachments at the posterior edge of the hard palate (Fig. 186-30).

Rotating the flaps medially with forceps tests mobility of the flaps. If additional mobility is needed, then several other maneuvers can be used. A back-cut at the posterior edge of the vomer will allow easier closure of the nasal cavity. Extension of the relaxing incision posteriorly

Figure 186-30. Two-flap palatoplasty: flaps incised and elevated.

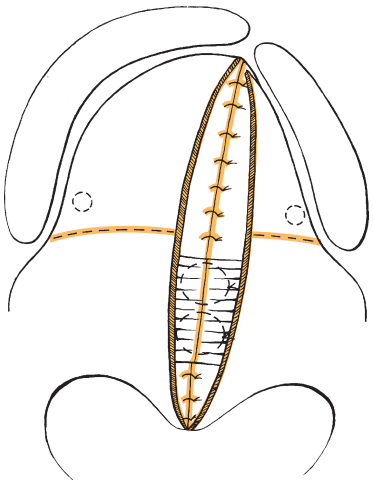

Figure 186-31. Two-flap palatoplasty: nasal mucosa and mucoperiosteum closed and levator reconstructed.

combined with blunt dissection between the pterygoid process and the superior constrictor muscle (space of Ernst) will further mobilize the anterior soft palate region. Wide clefts may require medial fracture of the hamulus, thereby releasing tension on the TVP, although concern about the potential adverse effect on eustachian tube function has been raised.[42]

Repair of the palate is done in three layers. Absorbable suture is used throughout. The nasal surface is closed with 4-0 or 5-0 suture. Tension usually is greatest at the junction of the hard and soft palate. In patients with wide clefts, primary closure of the nasal surface at this junction may not be possible. Clark and associates[68] report using acellular dermal grafts (LifeCell, Branchburg, New Jersey) placed between the nasal and oral surfaces to provide a biologic surface for healing by secondary intention. Several buried sutures placed using a horizontal mattress technique are used to repair the soft palate muscles and to reconstruct the levator sling (Fig. 186-31). The oral surface is closed first along the cleft edge. Mattress sutures help evert the edge of the mucoperiosteum. Simple sutures are used to close the oral mucosa. Laterally, closure is completed by reapproximating the mucoperiosteum to the medial alveolus; only sutures that do not increase tension along the cleft edge should be used (Fig. 186-32). If there is exposed bone or tissue (for example, the stippled area in Fig. 186-32), usually in the region of the hamulus and posterior hard palate, then microfibrillar collagen (Avitene; Bard, Salt Lake City, Utah) is packed into the open wounds to optimize hemostasis.

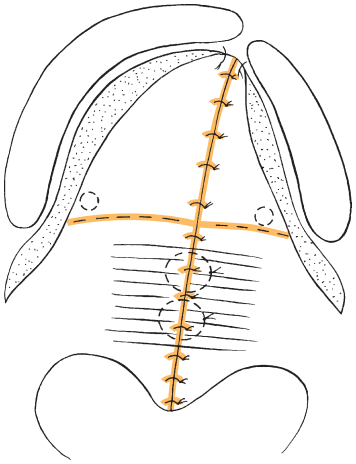

Figure 186-32. Two-flap palatoplasty: oral layer closed.

Double-Opposing Z-plasty Palatoplasty (Furlow Palatoplasty)

The double-opposing Z-plasty palatoplasty (Furlow palatoplasty) applies specifically to the repair of the soft palate and reconstruction of a levator sling. If the patient has a cleft involving the hard palate, closure of the hard palate is the same as for a two-flap palatoplasty. It is recommended that the soft palate dissection be completed before the incisions and elevation of flaps that are performed on the hard palate. By keeping the hard palate tissues intact, tension is provided to enable easier dissection of the soft palate needed for the Furlow palatoplasty. Elevation of the muscles from the nasal mucosa is technically challenging and is easier if the instruments are handled using a "forehand" grip and movements. For a right-handed surgeon, this means dissecting the muscles from the left aspect of the soft palate. Handedness then determines the types of flaps created elsewhere in the soft palate. A left-handed surgeon would perform the double-opposing Z-plasty in a mirror image of what is described next.

Incisions are first made sharply along the left cleft margin separating the oral and nasal mucosa. (If a double-opposing Z-plasty palatoplasty is being performed for repair of a submucous cleft palate, the midline incision should go only through the oral mucosa and leave the nasal mucosa intact until later.) A second incision is made from the apex of the cleft or 3 mm posterior to the junction of the hard and soft palate to just posterior to the hamulus. This incision parallels the posterior margin of the hard palate. It is important to leave at least 2 mm of mucosa posterior to the bony margin. Care must be taken not to tear or cut through the nasal surface. Dissection proceeds to the lateral pharyngeal wall from just superior to the tonsillar fossa to beneath the hamulus. The levator veli palatini muscle is released from the posterior edge of the hard palate using electrocautery (Fig. 186-33).

An anteriorly based oral mucosa flap is then created on the right soft palate. Incisions are made along the cleft margin and from the base of the uvula to just posterior to the hamulus. The mucosa and submucosa, a fatty layer that contains several unnamed feeder vessels, are elevated sharply from the muscle layer. This dissection plane is indistinct. By maintaining tension between the mucosa and muscle, thin muscle fibers are identified at the inferior edge of the muscle bundle. The oral mucosa flap is elevated to the posterior edge of the hard palate and over the hamulus (Fig. 186-34).

The right soft palate muscle is released from the posterior edge of the hard palate. Care must be taken to maintain at least 3 mm of nasal mucosa posterior to the edge of the hard palate. If this incision is too close to the bony edge, then suture closure becomes quite difficult once the left mucosa flap is transposed. The fourth flap is created from the left nasal mucosa. Scissors are used to incise from the base of the uvula to beneath the hamulus (Fig. 186-35). If a hard palate cleft repair is needed, the mucoperiosteal flaps are raised after creating the four flaps from the soft palate.

These four flaps are transposed so that the mucosa-only flaps are rotated anteriorly and the muscle-containing flaps are rotated posteri-

orly. Suturing is done with 4-0 or 5-0 absorbable suture. Use of a small needle with a high degree of curvature (P-2 needle; Ethicon, Somerville, New Jersey) often is necessary for closure along the posterior edge of the hard palate incisions. The nasal layer is closed before the oral layer (Fig. 186-36). It is helpful to first suture the apex of the flap into the recipient corner, thereby stretching the flap. Any length discrepancy between incisions can be accounted for during closure. The uvula should be reconstructed. Contracture of the oral mucosa-muscle flap may restrict its advancement during the oral closure. Occasionally, a short V-Y advancement can be done at the right anterior corner to facilitate watertight closure of the oral surface.

Complications

During palatoplasty, hemostasis should be secured with pressure and electrocautery. Typically, less than 50 mL of blood is lost if epinephrine is used during initial injections and careful hemostasis is maintained. Postoperative bleeding is rare unless open wounds exist. After removal of the mouth gag and before extubation, the floor of mouth and tongue should be inspected for signs of edema. Prolonged tongue ischemia may result in edema with the potential for airway obstruction. Periodic

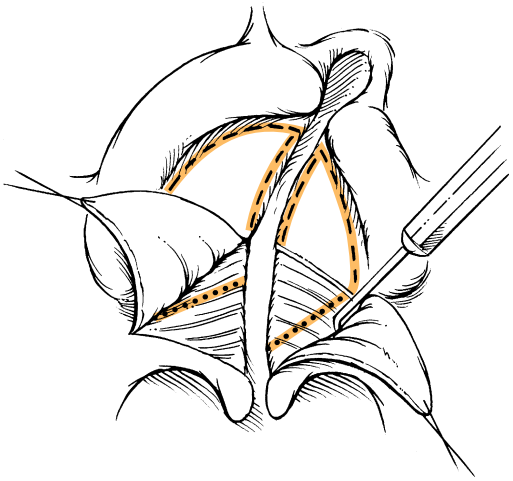

Figure 186-34. Oral mucosa flaps fully elevated. Soft palate muscles are seen on the right, and only the submucosa of the nasopharynx is exposed on the left. The *dotted lines* indicate where the incisions are planned for the next two flaps on the soft palate. *Dashed lines* on the hard palate indicate where incisions are to be made.

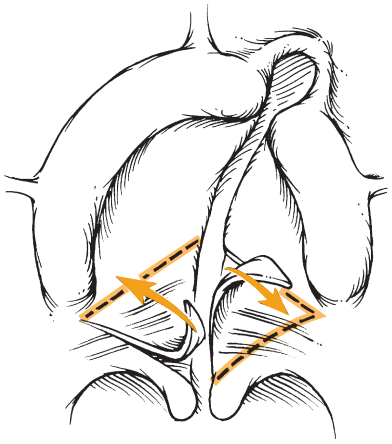

Figure 186-33. Double-opposing Z-plasty (Furlow) palatoplasty for a unilateral left complete cleft palate. Initial incisions and elevation of the first two flaps are indicated by the *arrows*. The left flap consists of oral mucosa and soft palate muscles. The right flap consists of oral mucosa and submucosa (perspective shown is that of a right-handed surgeon).

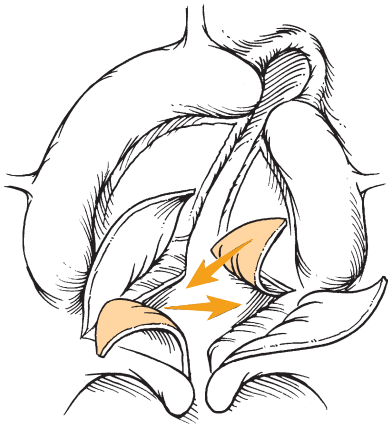

Figure 186-35. The nasopharyngeal mucosa flap from the left is transposed anteriorly. The flap containing soft palate muscle and nasopharyngeal mucosa from the right is transposed posteriorly.

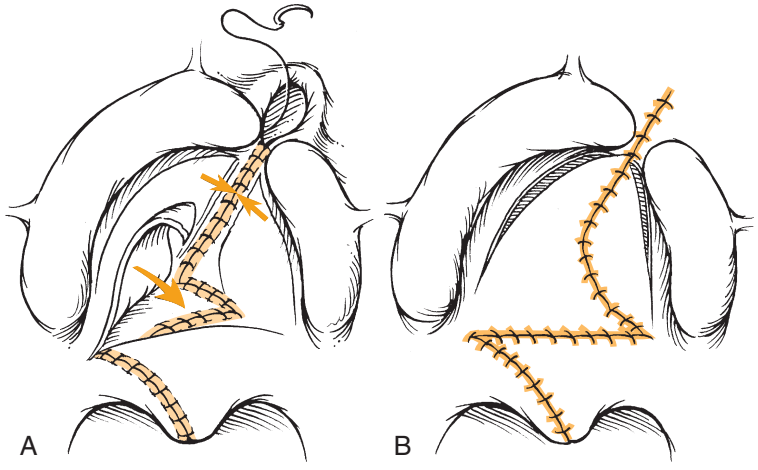

Figure 186-36. **A,** Closure of the oral surface of the soft palate. The muscle-mucosa flap from the right has been transposed and the oral mucosa is rotated anteriorly *(single large arrow)*. Nasal closure for double-opposing Z-plasty (Furlow) palatoplasty in a unilateral left complete cleft palate is also shown *(opposing smaller arrows)*. Nasal mucosa has been released along the cleft edge. Mucoperiosteal flaps were elevated bilaterally and pedicled from the greater palatine foramen *(not shown)*. **B,** Closure of the oral mucosa of both the hard and soft palate has been completed. If the incisions medial to the alveolus can be closed without substantially increasing tension, this is now performed.

release of the mouth gag during surgery should help prevent tongue ischemia.[65] Before extubation, a heavy silk suture typically is placed around the tongue tip. This "tongue stitch" may be used in lieu of an oral airway to aid postoperative airway management. This suture often is removed once the child is fully aware in the postanesthesia care unit but may be left until a safe airway is secure.

Historically, high rates of oronasal fistula formation have been reported after palatoplasty. When only fistulas that occur in the areas after primary repair (i.e., not intentional) are considered, the frequency of oronasal fistula is 8.7% to 23%.[69-71] Severity of clefting and type of cleft were the main risk factors identified. Recurrence rates after fistula repair range from 25% to 33%. Sites of fistulization typically are the anterior hard palate and the junction of the hard and soft palate.

The most common complication after palatoplasty is velopharyngeal insufficiency. Surgical technique may be a factor, with lower rates reported for double-opposing Z-plasty than for more traditional methods.[72] This topic is fully discussed in Chapter 187, Velopharyngeal Dysfunction.

Special Considerations in Patients with Cleft Palate

Robin Sequence

First described in 1923 in his native France and subsequently reported in the English literature in 1934, the Robin sequence is named for Dr. Pierre Robin, who highlighted the importance of the combination of micrognathia, glossoptosis, and cleft palate.[73,74] In the absence of other congenital abnormalities, the triad is considered a sequence because the micrognathia is the primary cause of the glossoptosis and cleft palate. However, the Robin sequence often is found associated with other abnormalities.[75,76] In such cases, the term "syndromic Robin sequence" has been used. Associated abnormalities are found in 52% to 83% of patients with Robin sequence. Stickler syndrome is the most common syndrome in children with Robin sequence, seen in 14% to 34% of cases. Sensorineural hearing loss and myopia are common findings in infants with Stickler syndrome. It is recommended that all children who present with features suggestive of Robin sequence have early hearing and vision screening. In nonsyndromic Robin sequence, it is unclear whether compensatory or "catch-up" growth occurs in the first years of life. The work of some investigators suggests that mandibular growth may be stimulated by tongue activity and oral motor development.[77,78] However, other work has shown that growth of the mandible in patients with Robin sequence is not significantly different from that in control subjects.[79-81]

Glossoptosis is an important factor that contributes to the upper airway obstruction commonly seen in Robin sequence. Retrodisplacement of the tongue into the oropharynx and inadequate support from the genioglossus muscle are the consequences of specific anatomic deficiencies of the mandible in these patients: a small body and short ramus. Negative pressure within the pharynx during inspiration and swallowing, combined with the anatomic and physiologic limitations imposed by micrognathia, frequently result in an unstable airway and dysphagia.[82-84] Severity of obstruction can be assessed by clinical evaluation, pulse oximetry, or polysomnography.[85]

Several strategies have been advocated for treating the airway obstruction in patients with Robin sequence.[82,83] These include prone positioning, which allows the tongue to fall away from the posterior pharyngeal wall.[82] If this strategy is ineffective in maintaining airway patency, a nasopharyngeal airway can help.[86] Maintenance of the nasopharyngeal airway can be challenging, as the tube requires suctioning and changing periodically. Oral feeding in this setting is made difficult owing to the frequent reflux of the meal through the tube. Gavage feeding may be needed in such cases.[87] Other centers will perform a glossopexy or lip-tongue adhesion in infants in whom positioning fails to maintain airway patency.[88-90] High success rates are reported when patients are selected on the basis of nasopharyngoscopy findings of an anterior-to-posterior collapse by the tongue, causing occlusion of the airway.[88] Complications of glossopexy include dehisence, which has been reported as high as 56%.[91]

Tracheostomy has traditionally been used for those patients with Robin sequence who also have severe airway obstruction or synchronous airway lesions, or in those infants in whom airway management by other methods has been unsuccessful.[82,83,92,93] Tracheostomy establishes an airway distal to the pharyngeal obstruction, and it has minimal impact on oropharyngeal swallowing mechanics. Another advantage of the tracheostomy is that it can be used during subsequent surgical procedures such as palatoplasty. A secure airway during palatoplasty is important, because airway problems occurring immediately after palatoplasty were most commonly seen in children with Robin sequence.[94] Nearly all patients with isolated Robin sequence who have tracheostomy performed to relieve airway obstruction can be decannulated after palatoplasty.[93] However, tracheostomy is not without difficulties in management and risks of serious complications.

Mandibular distraction osteogenesis is another method used to address the inadequate airway in infants with Robin sequence. First described in children in 1992,[95] the procedure is now advocated as primary treatment to relieve upper airway obstruction in these patients.[96,97] Bilateral mandibular osteotomies are performed and a distraction device is placed on either side of the osteotomy. Over the next several weeks, the distraction and subsequent consolidation across the osteotomy sites act to regenerate bone of the mandible, thereby lengthening the body or the ascending ramus. This in turn advances the tongue away from the posterior pharynx. In one series, all patients were successfully extubated or decannulated using this technique.[97] Selection criteria for mandibular distraction versus other airway management strategies have not been established.

Velocardiofacial or Microdeletion Chromosome 22 Syndrome

Velocardiofacial syndrome (VCFS) encompasses numerous phenotypic manifestations. It is the most common syndrome associated with isolated patients with isolated cleft palate.[98] It has become increasingly recognized in cleft palate patients and patients who present with velopharyngeal insufficiency (see Chapter 187, Velopharyngeal Dysfunction).[99,100] In one large series, 9% of patients had cleft palate and 32% had velopharyngeal insufficiency.[101] The palatal evaluation may reveal overt, submucous, or occult submucous clefting. Its phenotypic expression overlaps with DiGeorge syndrome and conotruncal anomaly face syndrome.[102] Because of the phenotypic overlap among these three syndromes, each a result of a deletion in the long arm of chromosome 22, the name "22q11 deletion syndrome" has been suggested.[103] More than 100 anatomic and functional abnormalities have been described in patients with VCFS.[101,104] The incidence of this deletion is estimated at 1 in 3000 to 1 in 4000 children.[105] Fluorescence in situ hybridization probes are available to identify patients with this deletion. The prevalence of patients with the phenotypic diagnosis of VCFS who test positive for the deletion is 68% to 81%.[102,106] Although its transmission is as an autosomal dominant trait, most cases represent a de novo deletion.[101,107]

The head and neck manifestations of VCFS are numerous. Facial dysmorphism can be subtle and several different findings are described. These include an elongated midface ("adenoid facies"), a shortened midface with malar hypoplasia, broad nasal base, low-set ears, thickened helical rims, mandibular micrognathia, and microcephaly.[108-110] Dysphagia is common and may present during infancy.[111] The dysphagia may be independent of cleft palate or cardiac involvement and may persist beyond infancy. Pharyngeal hypotonia and poor oral phase of swallowing are both felt to contribute to the dysphagia. Middle ear disease is common, with reports of 22% to 88% of patients affected.[108,109] Conductive hearing loss and chronic suppurative otitis media may result. These patients may require repeated tympanostomy tube placement. Adenoidectomy should be carefully considered in patients with VCFS, because a high incidence of postoperative velopharyngeal insufficiency has been described.[99] In addition to the high frequency of clefting seen in these patients, other factors may contribute to the eustachian tube dysfunction. An abnormally flattened basisphenoid has been described in patients with VCFS,[112] and palatal muscle dysplasia also is seen (Fig. 186-37). Medialized carotid arteries are found in some patients with VCFS, increasing risk for injury during pharyngeal

Figure 186-37. Magnetic resonance image of the soft palate in a patient with velocardiofacial syndrome. Note the increased signal intensity of this T1-weighted image, suggesting increased fat composition within the soft palate as compared with the surrounding facial and pharyngeal muscles.

surgery.[113] Imaging of the pharynx using magnetic resonance angiography is suggested,[114] although spontaneous resolution has been described.[115] Searching for pulsations along the posterior pharyngeal wall during nasendoscopy is recommended for this population. Velopharyngeal insufficiency is common in VCFS; the evaluation and management of this problem are covered elsewhere (see Chapter 187, Velopharyngeal Dysfunction). Vocal cord nodules may be found. Patients with velopharyngeal insufficiency may compensate by using glottal stops. Anterior laryngeal web also may be seen in these patients.[101]

Submucous Cleft Palate

A bifid uvula, a notch in the posterior hard palate due to the absence of the posterior vomerine spine, and a translucent zone in the midline of the soft palate constitute the classic findings with submucous cleft palate (SMCP) (see Fig. 186-5). Large population-based studies suggest a prevalence for SMCP of 1 in 1250.[116] An occult SMCP, not evident on oral examination, occurs when only the muscularis uvulae is dehiscent.[117] The diagnosis of occult SMCP is made during nasendoscopy for evaluation of velopharyngeal insufficiency[118] (see Chapter 187, Velopharyngeal Dysfunction).

The cause for the palatal dysfunction seen in patients with SMCP may involve several factors. Abnormal insertion of the levator palatini into the posterior margin of the hard palate and diathesis of the muscularis uvulae may result in the inability of the posterior margin of the soft palate to fully contact the pharyngeal wall. Histologic analysis of surgical specimens from patients with SMCP revealed increased fibrosis, especially within muscle fascicles; fascicular disorganization; and hypoplastic myocytes.[44] However, there does not appear to be differences in craniofacial morphology between symptomatic and asymptomatic children with SMCP.[119] Longitudinal studies indicate that more than 50% of patients with SMCP will develop speech disorders requiring surgery.[120,121] These studies were conducted in tertiary referral cleft clinics, thus the actual frequency of symptomatic patients with SMCP may be lower. SMCP appears more frequently in association with other craniofacial abnormalities. Occult SMCP is the most common palatal abnormality associated with VCFS, seen in 67% to 69% of affected patients. Overt SMCP may be found in another 24% of patients with this syndrome.[108,109] The soft palate should be diligently inspected and palpated prior to adenoidectomy because of the high prevalence of SMCP in cleft lip–only patients. The relationship between SMCP and otitis media is unclear. Higher rates of recurrent otitis media or need for tympanostomy tube placement in the first year of life were found in children with bifid uvula, but the difference was not significant. This difference was not seen at 3 years.[122] Similarly, no difference in effusions was found between surgical patients with and without bifid uvula.[123] Whether bifid uvula–only is an adequate marker for other deficiencies in SMCP is unknown. The discovery of SMCP in infancy or early childhood requires follow-up evaluation through adolescence. Because many children remain asymptomatic, surgical correction of the palatal deformity is indicated only when clinical problems are refractory to medical therapy.

Ear Disease

It has been recognized for some time that children with cleft palate have a very high frequency of middle ear disease compared with the noncleft population. Paradise and colleagues[124] first reported that all children with cleft palate examined by pneumatic otoscopy and otomicroscopy showed effusions. Muntz[125] reported that 96% of children with cleft palate required tympanostomy tube placement. Nearly 50% of these children required repeat tympanostomy tube placement. Complications in this group included chronic tympanic membrane perforation in 13%, chronic suppurative otitis media in 6%, and cholesteatoma in 1%. Dominguez and Harker[126] revealed the importance of routine follow-up care by an otolaryngologist to minimize complications of ear disease. The rates of cholesteatoma formation were reduced from 9% to 3% when a coordinated team approach to care of the CLP patient was instituted.

Otitis media with effusion develops within the first months of life in a child with cleft palate. In a prospective study, Dhillon[127] found middle ear effusions by aspiration in 97% of ears at 4 months of age. This study also demonstrated that eustachian tube function did not return within 2 years after palatoplasty in 80% of patients. Other prospective studies support poor eustachian tube function and otitis media as problems that persist during the first few years after palatoplasty.[128,129] It should be noted that in each of these studies, a "traditional" palatoplasty was performed. The potential effect that the type of palatoplasty has on otologic outcomes is unknown.

Frequency of otitis media decreases with increasing age of the child with cleft palate. Smith and colleagues[130] used audiology and tympanometry to determine that the average recovery time for eustachian tube function was 6 years after palatoplasty. Among children followed for at least 6 years, 70% of ears had normal eustachian tube function. More than 90% of the ears that recovered eustachian tube function were able to maintain normalcy. Tympanoplasty results were similar for patients with cleft palate (including SMCP) and children without cleft deformity with regard to postoperative air-bone gap, graft survival, and need for postoperative ventilation tube.[131]

Abnormalities of the cartilage and muscles surrounding the eustachian tube are responsible for the high prevalence of otitis media associated with cleft palate. Paratubal cartilage abnormalities have been described that may contribute to dysfunction in patients with cleft palate. Hypoplasia of the lateral cartilage relative to the medial cartilage was found in infants with cleft palate.[132,133] The curvature of the eustachian tube lumen, as determined by the shape of the surrounding cartilage, also was found to be abnormal when compared with noncleft specimens. Cephalometric data suggest that the width and angulation of the skull base with respect to the eustachian tube are different in patients with cleft palate.[134] Abnormal insertions of the TVP and levator veli palatini muscles into the cartilages and skull base also may adversely affect their role in eustachian tube function. Matsune and

colleagues[135] studied temporal bone specimens from patients with cleft palate and compared them with those from non-cleft control subjects. No insertion of the TVP muscle to the lateral paratubal cartilage was found in 40% of CP specimens. All normal specimens demonstrated an insertion of the TVP to the lateral cartilage. Moreover, the length of TVP muscle inserted into the cartilage was reduced in CP specimens. Huang and coworkers[43] dissected fresh cadavers of normal adults. Their detailed analysis of the anatomy of the TVP and levator veli palatini muscles suggests that the TVP opens the eustachian tube directly by traction on the lateral cartilage. The levator veli palatini may open the eustachian tube by displacement of the medial cartilage. Some studies have identified the muscle fibers inserting into the lateral cartilage as a distinct muscle, the dilatator tubae.[136,137] It remains unclear to what degree the altered anatomy of the paratubal muscles directly affects eustachian tube dysfunction, because the levator veli palatini muscle is more severely affected by cleft palate.

Insertion of ventilation tubes is the standard treatment for otitis media in patients with cleft palate. Controversy surrounds the timing of ear tube placement. Otitis media with effusion is known to decrease hearing thresholds. Decreased hearing at a very young age may affect future speech and language development, especially in this high-risk group of patients. However, high rates of otorrhea from ears with ventilation tubes placed before palatoplasty have been reported; excessive compliance of the eustachian tube before palatoplasty has been suggested as the etiologic basis.[138] Chronic otorrhea resolved only after palatoplasty in four children who had early ear tube placement.[139] No long-term studies have been conducted to determine whether early placement of ventilation tubes, and correction of hearing loss, affect speech outcomes in patients born with cleft palate. Newborn hearing screening can provide an early indication of auditory function and help with treatment decisions such as when ear tubes should be placed.

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CHAPTER ONE HUNDRED AND EIGHTY-SEVEN

Velopharyngeal Dysfunction

Harlan Muntz

Marshall E. Smith

Cara Sauder

Key Points

- Velopharyngeal inadequacy refers to any type of dysfunction and may be categorized as insufficiency, incompetence, and mislearning.
- "Phoneme-specific" velopharyngeal dysfunction (VPD) is diagnosed when one or more phonemes are abnormally produced with increased resonance while the rest of the speech is normal. The increased resonance most often is noted with /s/, /sh/, and /z/, and rarely, /f/ phonemes.
- Recommendations for management of VPD are best made jointly by a team that includes the surgeon, speech-language pathologist, and dentist or prosthodontist if needed.
- Compensatory articulation errors that are a result of VPD alone do not frequently occur with oral motor weakness. Therefore, oral motor exercises are not appropriate unless there is evidence of oral motor weakness in addition to VPD.
- The Furlow palatoplasty reorients the levator while also thickening and lengthening the palate.
- All surgical corrections of VPD may lead to airway obstruction.
- It is helpful for the otolaryngologist, speech-language pathologist, and other team members to take a "transdisciplinary" approach to the management of VPD.

In the English language, only three phonemes normally are produced with nasal air escape—/n/, /m/, and /ng/. All of the other sounds are produced with oral air flow. In speech production, the velopharynx is considered an articulator, as are the jaw, tongue, lips, pharynx, and larynx. These articulators work together to produce the various sounds of speech. Normal velopharyngeal function varies according to the sounds of speech produced. Factors that affect velopharyngeal valving include vowel height, consonant type, proximity of nasal sounds to oral sounds, utterance length, speaking rate, and tongue height. For vowels, velar position is higher for vowels with a high pharyngeal constriction such as /i/ and /u/ than for low-pharyngeal-constriction vowels such as /a/. The velar port generally is closed for vowels, except when the vowel is in proximity to a nasal consonant. The velopharyngeal port therefore changes its relatively open and closed states depending on the balance of oral versus nasal consonants occurring in the speech stimuli. Velar movement may vary widely in velocity and displacement with the tasks of the particular speech, particularly speaking rate.

If the velopharynx is not functioning correctly or if a defect in the palate allows the oral sound to resonate through the nose, speech may be perceived as abnormal. Incompetence of the velopharyngeal mechanism leads to increased hypernasality, nasal turbulence, or nasal emission. If an obstruction to nasal airflow is present, the resonance is hyponasal. Speech intelligibility is determined primarily by articulation; however, abnormal speech resonance distorts speech production, impairs overall speech quality, and can adversely affect intelligibility.

Functional Anatomy

The velopharyngeal port closes as the velum moves in a posterior-to-superior direction. The lateral pharyngeal walls may move medially. Occasionally, anterior movement of the posterior wall will be seen. The muscles of the velopharynx contribute to this closure (Table 187-1).

The elevation and posterior motion of the velum are attributed to the levator veli palatini (LVP). This is the main muscle mass of the velum.[1] Variation in the angle of insertion to the base of skull may change the elevation.[2] The palatoglossus and palatopharyngeus muscles pull the palate down, opposing the LVP. The palatopharyngeus muscle pull tends to stretch the velum laterally, thereby increasing the velar area and altering the shape of the contact.[2] This muscle can make subtle changes to velar height, especially when the velum is in the elevated position.[3] The musculus uvulae adds bulk to the dorsal side of the velum.

Lateral wall motion varies from person to person and depends on speech context. The greatest movement usually is below the levator eminence at the level of the full length of the velum and hard palate.[4] This movement is attributed to selective movement of the uppermost fibers of the superior constrictor. Because of the relationship between the lateral fibers of the superior constrictor and the palatopharyngeus, it has been suggested that this muscle is involved in the lateral wall motion as well.[5]

Passavant's ridge is a posterior wall feature seen in some persons during speech or swallow. It has been associated with lateral wall motion and is thought to be caused by a similar movement of the uppermost fibers of the superior constrictor and palatopharyngeus.[6] It may be involved in velopharyngeal closure in as many as one third of patients in whom Passavant's ridge is observed.[7,8] Its movement also can be seen below the level of the velopharyngeal port and therefore does not assist in the closure.

Table 187-1

Muscles of the Velopharynx

Muscle	Origination	Attachment	Function	Innervation
Tensor veli palatini	Vertical portion arises from the scaphoid fossa at the base of the internal pterygoid plate, from the spine of the sphenoid, and from the outer side of the cartilaginous portion of the eustachian tube	Terminates in a tendon that winds around the hamular process	Tenses the soft palate; opens the auditory tube during swallowing	Mandibular branch of the trigeminal nerve
Levator veli palatini	Arises from the undersurface of the apex of the petrous portion of the temporal bone and from the inner surface of the cartilaginous portion of the eustachian tube; found to occupy the intermediate 40% of the length of the soft palate*	Fibers spread out in the soft palate, where they blend with those of the opposite side	Acts as a sling when contracted to pull the velum in a posterosuperior direction[4]; major elevator of the velum[13]; positions the velum†	Pharyngeal plexus derived from the glossopharyngeal and vagus nerves and the facial nerve‡; course of the facial nerve is through the greater petrosal nerve§
Musculus uvulae	Palatal aponeurosis in a circumscribed area posterior to the hard palate‖	Inserts into the uvula	Adds bulk to the dorsal surface of the soft palate	Pharyngeal plexus; pharyngeal plexus derived from the glossopharyngeal and vagus nerves and the facial nerve‡
Palatoglossus	Has a fan-shaped attachment from the anterior surface of the soft palate¶	Courses through loose connective tissue within the anterior faucial pillar and has a tapering termination in the side of the tongue¶	Elevates the tongue upward and backward to constrict the pillars and probably lowers the velum**; positions the velum†	Pharyngeal plexus composed of branches from the glossopharyngeus and vagus cranial nerves and from the sympathetic trunk
Palatopharyngeal	Arises from the soft palate	Inserts with the stylopharyngeus into the posterior border of the thyroid cartilage	Adducts the posterior pillars, constricts the pharyngeal isthmus, narrows the velopharyngeal orifice, raises the larynx, and lowers the pharynx††; positions the velum†	Pharyngeal plexus
Superior constrictor	Arises from the lower third of the posterior margin of the internal pterygoid plate and its hamular process	Inserts into the median raphe	Medial movement of the lateral aspects of the pharyngeal walls[4]; high levels of activity are related to laughter[13]; may function to draw the velum posteriorly[13]; pulls the posterior wall and posterolateral angle	Pharyngeal plexus derived from the glossopharyngeal and vagus nerves and the facial nerve‡

*Data from Boorman JG, Sommerlad BC. Levator palati and palatal dimples: their anatomy, relationship and clinical significance. *Br J Plast Surg*. 1985;38:326.
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Approach to Diagnosis and Management of Velopharyngeal Dysfunction

Evaluation of velopharyngeal dysfunction (VPD) requires an understanding of the causes of the condition to make an appropriate diagnosis. Assessment includes an accurate study of the degree and nature of velopharyngeal function and its impact on speech production. This information is then used to formulate management recommendations, which generally include speech therapy, surgical intervention, or prosthetic obturation. These management options are reviewed later in the chapter.

Causes of Velopharyngeal Dysfunction

Velopharyngeal dysfunction refers to abnormal function of the velopharyngeal sphincter mechanism. However, it does not identify the cause. Perceptually, this dysfunction is considered a dysphonia because it affects the sound quality of the voice. The cause of the dysphonia needs to be identified. Campbell and associates[9] reported on 427 children referred to a pediatric voice and resonance clinic for voice problems. Of those children, 16% were actually found to have velopharyngeal, rather than laryngeal dysfunction. Different terminology has been used to describe the causes of VPD, and relevant terms and concepts are used inconsistently throughout the medical literature. In this chapter, we use the definitions summarized by D'Antonio and Crockett.[10] *Velopharyngeal inadequacy* refers to any type of VPD and can be divided into three etiologic categories: insufficiency, incompetence, and mislearning. Velopharyngeal *insufficiency* encompasses structural defects that result in insufficient tissue to accomplish closure—a well-known example being cleft palate. *Incompetence* describes impairment of motor control secondary to neurologic dysfunction, such as paresis or paralysis. Causes of incompetence include the sequelae of skull base surgery and tumors around the jugular foramen and vagus nerve, or central nervous system (CNS) impairment from brainstem stroke. *Mislearning* is the result of etiologic factors that are independent of structural defects or neuromotor pathology.

Congenital anatomic conditions affecting velopharyngeal function most commonly are attributable to clefting of the palate. VPD in the absence of an overt cleft palate also occurs. Affected children may have other anatomic abnormalities or functional disorders causing velopharyngeal insufficiency. These include congenital short palate, palatopharyngeal disproportion, a less overt palate deficiency called occult submucous cleft palate (absence of the musculus uvulae), and longitudinally oriented levators. Hypertrophic tonsils occasionally can cause insufficiency by impeding palate closure. Neurogenic causes of velopharyngeal incompetence include muscular dystrophies, myasthenia gravis, traumatic brain injury, Down syndrome, and velocardiofacial syndrome (22q11 deletion). An adenoidectomy can create or unmask VPD in any of these settings. In velopharyngeal insufficiency, a large adenoid can compensate for a short palate. In velopharyngeal incompetence, adenoidectomy can compensate for a poorly mobile palate. With removal of the adenoidal tissue, the mechanism of compensation is eliminated. Velopharyngeal inadequacy has been reported to occur after 1 in 1500 adenoidectomies.[11,12]

Assessment

Perceptual Speech Analysis

Most otolaryngologists will encounter children with VPD in their practice. In taking the history of a child referred for a voice or speech problem, the clinician should listen carefully to input from the parent or caregiver, who typically spends the most time hearing the child speak. Then, attention needs to be paid to the speech of the child, who often is shy and does not speak voluntarily. Playing games or asking direct questions can stimulate the child to begin spontaneous speech. This perceptual evaluation will provide the clinician with a sense of the language level, articulation, and the nasal resonance as the child is speaking. The possibility of a diagnosis of VPD should be considered even in children referred for other concerns.

If VPD is suspected, a few easy tests will further elucidate the problem. Many of these tests are quickly and easily performed in the office setting with a reasonably cooperative patient. These include nasal occlusion and mirror fogging tests during the child's production of various phonemes or phrases selected to provoke the symptoms.

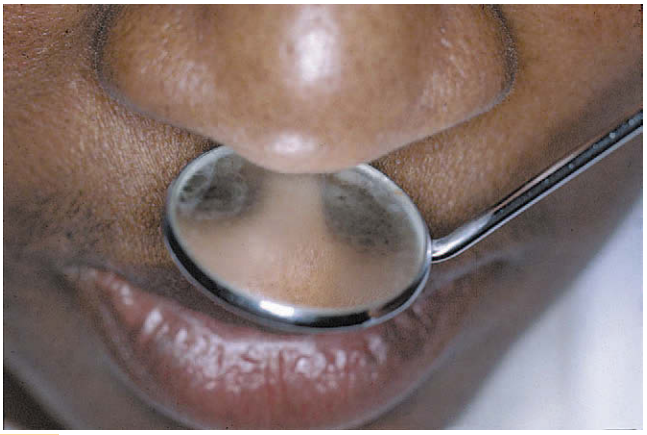

Figure 187-1. Mirror technique; note the fogging with nasal air escape.

Table 187-2

Examples of Tasks to Evaluate

Nasal Consonants	
Ma ma	Money
Na na	Monkey
Momma made lemon jam	Nancy is a nurse

Hyponasal resonance is most noted in the sounds /m/, /n/, and /ng/. These nasalized consonants will be altered with decreased nasal airflow. The /m/ will be changed to sound like /b/, the /n/ changed to sound like /d/, and the /ng/ to a hard /g/. Humming the /m/ sound will not change with nose plugging if the nose is already occluded. In addition, the examiner will not feel nasal vibrations. Normally, a mirror held under the nose should fog with voicing of the nasal consonants (Fig. 187-1). If the voice quality is the same with or without occlusion of the nose, then nasal or nasopharyngeal obstruction is present. Hyponasal resonance can be described as that quality of speech associated with the congestion of a common cold. Large adenoids or congested nasal turbinates also may be seen. Repetition of words or sentences that are loaded with nasal consonants will aid in documentation of this abnormality (Table 187-2). The velopharynx continues to be active during production of words and phrases with nasal consonant sounds but will be between a relaxed and a closed state.

Hypernasality or increased nasal resonance will be noted with production of non-nasal phonemes (Table 187-3). Because most sounds (vowels and consonants) in the English language are non-nasal, there are many phonemes to work with. The early phonologic repertoire usually includes the bilabial plosives /p, b/ and lingua-alveolar phonemes /t, d/. Using phonemes—words and sentences loaded with these sounds—allows the listener to assess speech resonance (normal or hypernasal). Plugging the nose while the child repeats the /p, b, t, d/ sounds or during sustained production of /s/ or /sh/ will result in noticeable change in resonance if there is hypernasality on these sounds. The use of a mirror beneath the nose during speech tasks also will assist in the detection of the nasal air escape (see Fig. 187-1). Fogging of the mirror typically is observed only for production of nasals and nasalized vowels. Increasing the complexity of the tasks (i.e., sounds to words to phrases to sentences) may document deterioration of the velopharyngeal competence. The degree of openness is determined by the phonetic environment. Some children will do less well if nasal and non-nasal phonemes are mixed. Repetition of tasks during a period of minutes

Table 187-3

Examples of Tasks to Evaluate

Non-Nasal Consonants		
Pa pa pa	Daddy did it	Sustain "s"
Baby	Too tight	Sustain "sh"
Puppy	Go get an egg	Count from "sixty to seventy"
Puffy	Forty-four fat fish	Baby bib
Daddy	Sissy saw it	Get it out

may unmask velopharyngeal fatigue, as seen in myasthenia gravis. Velar height or elevation is most pronounced during the "high" vowels of /i/ and /u/[13] and the fricative /s/.[14] Even if velopharyngeal function is improving, production of these sounds may remain difficult.

The clinician also may encounter "phoneme-specific" VPD, or mislearning. In this entity, one or more phonemes are produced abnormally with increased resonance, while the rest of the speech is normal.[15] It most often is noted with production of /s/, /sh/, /z/, and rarely, /f/ phonemes. A nasal fricative substitution is characteristic. Because these are predominant sounds in the English language, the patient often is believed to be globally hypernasal. Because other non-nasal sounds demonstrate no air escape, however, the velopharynx should be recognized to be otherwise functional. Appropriate articulation therapy usually will correct this abnormality.

The diagnosis of hypernasality may be confounded by concomitant dysphonia or hyponasality. Hoarseness will distort the sound enough that mild VPD may be overlooked. More than 40% of children with VPD also have dysphonia.[16] The use of the mirror test helps separate VPD from laryngeal pathology.

Children with VPD also may have nasal or pharyngeal airway obstruction that affects the nasal consonants. In such cases, both hyponasality and nasal air escape on production of non-nasal phonemes can occur. The abnormality is described as "mixed."

The presence of velopharyngeal insufficiency has a significant impact on the child's and the family's quality of life. Emotional and communication aspects are primarily affected. Parents seem to be an appropriate proxy in determining the impact of the altered speech on the child's quality of life.[17]

When VPD has been suspected on clinical examination, further testing is indicated. There are a number of techniques used for evaluation. Indirect measures to assess for VPD include nasometry and pressure-flow measurements. Imaging studies of the VP mechanism include lateral cephalometrics, speech videofluoroscopy, and speech endoscopy. Further specific resonance-related articulation assessment also is an important component in assessment of these patients.

Nasometry

Nasometry is an objective standardized assessment that measures the ratio of sound intensity between the nose and the mouth. This typically is done with voicing of standard phrases and passages. Standardized values exist for specific tasks. Calculation of the number of standard deviations from normative values for each phonemic set yields a measure of the severity of the resonance pattern. Nasometry can be used in the initial evaluation to document the degree of dysfunction. Perhaps more important, it is used in assessing progress during speech therapy or in following other interventions.[18] A discrepancy may exist between nasal scores and the perceived degree of hypernasality.[19] Figure 187-2 shows the Kay Elemetrics headgear used for this test.

Pressure Flow

Pressure and airflow measurement is another method of assessing velopharyngeal function during speech.[20-22] The nose is covered with a small mask to permit accurate measurement of nasal airflow. A probe is placed into the mouth to measure oral pressure. In the child with normal velopharyngeal function, no airflow will be detected during production of non-nasal phonemes. Oral pressure will be present if nasal air escape is detected during non-nasal sounds. An advantage to the pressure-flow technique is the ability to determine the timing of the air escape.[14] The pressure-flow technique also is used to calculate the cross-sectional nasopharyngeal airway area from the pressure-flow measures.

Figure 187-2. Nasometer apparatus in position.

Imaging Studies

An imaging study of the velopharyngeal mechanism is indicated when speech therapy is not progressing, if speech evaluation reveals significant hypernasality, if a diagnostic dilemma is present, or when surgery is under consideration. Lateral cephalometric x-ray studies were done in the past but are limited by a sagittal plane view and do not provide information on dynamic movement of the velopharyngeal mechanism. Current methods of imaging velopharyngeal function include speech videofluoroscopy and speech nasal endoscopy. Endoscopy has largely supplanted videofluoroscopy in most clinics today. Children older than 3 years of age most often will cooperate with the evaluation. The speech nasal examination may not be useful, however, in the child with significant developmental delays. If the child cannot produce appropriately articulated phonemes, the study will not give adequate speech information. The accuracy of articulation has a direct effect on the closure.[23] Velopharyngeal closure on swallow does not yield information regarding speech.[6] To be of value, the assessment requires appropriate articulation of phonemes.

Speech Videofluoroscopy

Videofluoroscopic evaluation has been a standard tool in assessment of the speech mechanism.[24] Generally, a speech-language pathologist attends this examination with a radiologist in the hospital imaging department, as is done for modified barium swallow studies. A small amount of barium is introduced through the nose to coat the velopharynx and improve visualization. While under fluoroscopy, the child repeats or reads a set of phoneme-specific speech tasks. Because the velopharyngeal sphincter functions in several planes of movement, accurate analysis will require at least two and preferably three views. The lateral view demonstrates the length, thickness, anterior-posterior, and superior motion of the palate, as well as the anterior movements of the posterior pharyngeal wall (Passavant's ridge). The anterior-posterior view assesses the lateral wall motion. An en face view (e.g., Towne's or submental vertex view) will look down the velopharynx and demonstrate lateral wall, velar, and posterior wall motion.

Videofluoroscopy has some limitations. Because of the radiation exposure, the speech sample may need to be shortened. Cooperation of the patient is still needed. Interpretation of the radiographs requires experience with analysis of the images. The examining team must include both a radiologist and a speech therapist with experience in this

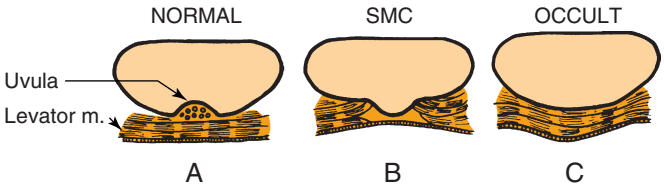

Figure 187-3. Muscle orientation of normal (**A**), submucous cleft (**B**), and occult submucous cleft (**C**). SMC, submucous cleft.

area of practice. With videofluoroscopy, closure patterns can be well defined and the level of Passavant's ridge and its participation in closure can best be assessed. Nevertheless, this assessment may still miss small fistulas and intermittent closure patterns. In addition, it is difficult to evaluate postsurgical changes. Many teams are moving toward the use of endoscopy as the standard first-line assessment tool.[25,26]

Speech Endoscopy

Speech endoscopy is now considered the most useful tool for evaluation.[27] Many otolaryngologists and some speech-language pathologists are experienced in the use of this minimally invasive diagnostic test. Ideally, the test is conducted with both the physician and speech-language pathologist in the room at the same time. If this is not possible, the examination can be video recorded for review. After topical anesthesia of the nose has been accomplished, a flexible nasopharyngoscope is introduced into the velopharynx.

The best image is obtained with the scope positioned higher in the nasopharynx to reduce parallax and fish-eye distortions. Passing the flexible scope in the middle meatus region (rather than along the floor) of the nose facilitates this optimal positioning. As with speech videofluoroscopy, a series of words, phrases, and sentences are spoken while the endoscopic images are recorded. It is important to use a microphone and record the voice, not just the video images. Endoscopy allows assessment of the static anatomy such as the nasal septum, eustachian tube orifice, adenoid pad, and structure of the musculus uvulae. Absence of the musculus uvulae is seen with occult submucous clefting (Fig. 187-3).

During speech tasks, the examiner observes velar and lateral wall motion and looks for Passavant's ridge. Incomplete closure can be documented by viewing the unclosed port or bubbling of mucus in the velopharynx. Contribution of the adenoid pad to closure, adenoid or posterior wall irregularities, and interference by the tonsils can be seen. There is no restriction on the duration of the speech sample, as constrained by the speech videofluroscopy. A clear and specific assessment can be made of both structure and function.

Four primary velopharyngeal closure patterns have been observed, as depicted in Figure 187-4.[28] These can be seen in both endoscopy and speech videofluoroscopy. These patterns are best understood in terms of the residual gap orientation on incomplete closure of the velopharynx.

The *coronal* closure pattern has a coronally oriented gap (seen in 55% of the population). The palate (velum) moves posteriorly without much contribution from the lateral walls or posterior wall. The *sagittal* closure pattern (seen in 10% to 15% of the population) leaves a gap oriented in a sagittal plane, because the major contribution to closure is from the lateral walls. The *circular* closure pattern has significant motion of the velum and the lateral walls, leaving a circular central gap (seen in 10% to 20% of the population). If the closure is *circular with Passavant's ridge*, then there is motion of the velum and lateral walls with additional presence of Passavant's ridge (seen in 15% to 20% of the population). Passavant's ridge may be present without contributing to closure.

The closure pattern may assist in prescribing surgical or prosthetic intervention. Knowing where the "gap" is should allow the clinician to decide how best to obturate that gap, as discussed next.[29-31]

Treatment

Management of VPD generally involves speech therapy or prosthetic or surgical treatment of the velopharyngeal defect, or combinations of

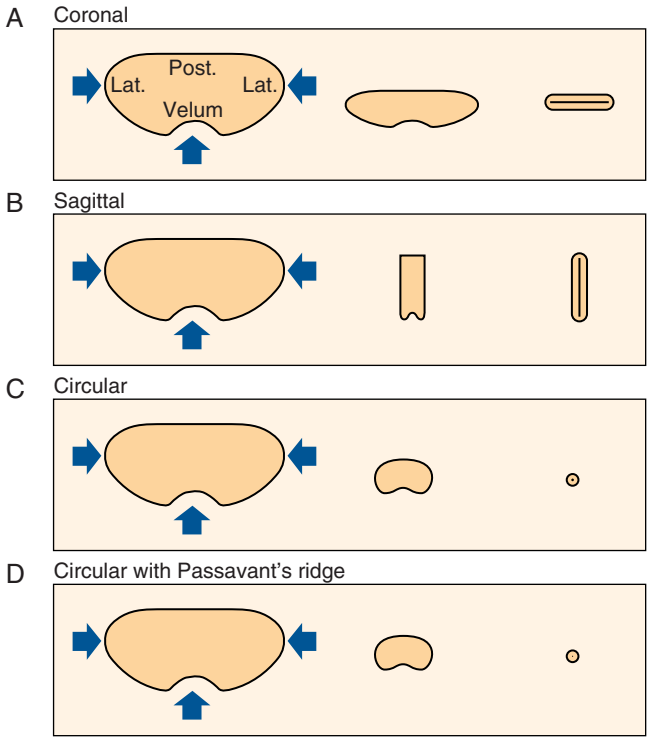

Figure 187-4. The closure patterns in the velopharynx. The pattern is based on the shape of the gap as it closes: **A,** coronal; **B,** sagittal; **C,** circular; **D,** circular with Passavant's ridge.

these approaches. Recommendations for each child generally are made jointly by a team that includes the surgeon, speech-language pathologist, and dentist or prosthodontist if needed.

Speech Therapy

Candidacy for and timing of speech therapy for children with VPD need to be examined closely by an experienced speech-language pathologist and the otolaryngologist. Speech therapy will not repair a deficiency in structure of the mechanism. Therefore, candidacy for therapy generally is limited to the following clinical circumstances: mild VPD in a child in whom appropriate stimulation yields improvement, inconsistent VPD, VPD occurring only when the child is fatigued, VPD with inappropriate articulation, VPD associated with oral-motor dysfunction, and failure of compensatory misarticulation to resolve spontaneously after surgical correction has been done. For patients who are candidates for speech therapy, the time of initiation of these services and the types of therapy recommended will depend on age, etiology, severity of VPD, cognition, hearing, phonetic inventory, expressive vocabulary, and the child and family's ability to participate in a therapeutic program.

Development of maladaptive articulations is common in children with VPD.[32,33] Excellent results from surgery can eliminate VPD, but impaired articulation may remain and greatly affect intelligibility. These abnormal articulation patterns include backing patterns, pharyngeal fricatives, glottal stops, and impaired sibilants. Speech intelligibility often is affected more by the presence of these articulation errors than by the resonance itself. If the maladaptive articulation is habituated, it may be difficult to reverse. Children who maintain articulation errors despite correction of VPD require speech therapy.[34] For children who receive surgical intervention of a structural deficit such as cleft palate, early intervention is recommended if stop oral consonants are not observed 6 to 8 weeks after surgery.[35] Phoneme-specific audible nasal air emissions can be present in children without VPD as well. Although appropriate referrals are important to rule out VPD, these children demonstrate an articulation disorder necessitating speech therapy as a primary means of treatment.

Articulation

Efficacy data regarding specific types of speech therapy techniques used to address articulation and resonance impairments in children with VPD are largely lacking. Correcting the placement and manner of articulation and adding additional phonemes to children's repertoires are primary goals of articulation therapy. Targets are selected on the basis of age appropriateness, impact on intelligibility, function, and stimulability. Careful evaluation of dentition to ensure that articulation errors are not a direct result of a structural problem also is required before initiation of therapy. The approach to articulation therapy does not vary significantly as a result of the presence or absence of VPD. However, glottal and nasal substitutions generally are considered atypical articulation disorders, so clinicians may have less experience in treating these types of substitutions. A generally recognized example of an articulation approach used to eliminate glottal stops involves repeating a stop plus vowel production first with a whisper and then gradually increase the voicing component.[36] Audible nasal air emissions that are phoneme-specific also are considered to be errors of articulation. Nasal air emissions generally occur during production of fricative, affricates, and sibilants. Clinicians frequently have the patient shape these sounds by increasing airflow during /t/ productions or use other voiceless stops with the same place of articulation as the targeted sound to establish correct productions. Nares-occluded oral productions of phonemes, syllables, words, and sentences also may be effective. Auditory, tactile, and visual training and feedback with respect to placement and manner of articulation as well as voicing components have demonstrated improvement in articulation of children with VPD as well.[37] Although some of the biofeedback techniques reported in the literature are not clinically relevant, they provide rationale for the use of auditory, visual, and tactile feedback during correct and incorrect productions of phonemes. Of note, compensatory articulation errors that are a result of VPD alone do not frequently occur with oral motor weakness. Therefore, oral motor exercises are not appropriate unless there is evidence of oral motor weakness in addition to VPD.

Resonance

It is unclear whether increasing strength or control of the muscles required for velopharyngeal closure by means of behavioral intervention is possible. Speech therapy generally is considered to be appropriate only when VPD is mild or inconsistently present, or if the affected child appears to fatigue throughout the day. Previous investigations of exercises to increase strength of the muscles needed for velopharyngeal closure have yielded poor results. Sucking, gagging, swallowing, and blowing exercises and electrical stimulation demonstrated no direct impact on improved velopharyngeal closure during speech tasks.[38-40] Attempts to train improved or more consistent velopharyngeal closure using speech therapy in children with mild hypernasality or intermittent closure rely heavily on auditory feedback. It is presumed that the ability to hear the difference between nasal and non-nasal productions is an important aspect of training production. Microphones, accelerometers, and tubing to assist with perception of airflow through the nose often are used. Resonance therapy and nasal occlusion with subsequent imitation of resonance without nares occluded are also commonly used to assist with auditory awareness and improve resonance. Visual feedback using the nasometer, which measures nasal and oral acoustic energy, is common instrumentation in many cleft palate and craniofacial settings. Some evidence supports its usefulness in reducing nasality with visual feedback.[14] However, long-term carryover has not been documented to the same degree.

Other forms of biofeedback, including Seescape, nasal stethoscope, and endoscopic feedback,[41,42] all have been used with some degree of success. Therapy techniques may include oral-motor awareness, continuous positive airway pressure (CPAP), and biofeedback techniques. Children with an inconsistent closure or those who on evaluation demonstrate minimal VPD may benefit from nasal CPAP. Nasal CPAP is used during speech tasks and resistance exercises performed to strengthen the velopharyngeal muscles. The exercises can be done at home. Although the reported results were variable, it may be helpful in some children for whom traditional therapy approaches do not result in significant improvement.[43]

Compensatory Strategies

Children who have undergone surgical repair of VPD but continue to demonstrate hypernasality often are referred for speech therapy to determine if altering speech production may improve speech to within socially acceptable limits. Strategies often include increasing breath support or loudness to increase sentence length, using increased jaw opening, and modifying pitch or breathiness of voice quality. Listener ratings of these changes either have not been studied in a systematic way or have yielded varied results.[44] Therefore, these therapy techniques generally are recommended on a trial basis.

Prosthetic Management

Prosthetic treatment has been used for many years and has been shown to be effective.[45] A palatal lift is created that pushes the palate up and back to contact the posterior pharyngeal wall (Fig. 187-5). If the palate is not too short, this maneuver will allow resolution of the VPD. Alternatively, an obturator (speech bulb prosthesis) is a round piece of acrylic that can be placed into the velopharynx so that with movement, the walls of the velopharynx will achieve closure as they contact the obturator (Fig. 187-6). "Weaning" from the obturator (bulb reduction therapy) subsequent to improved lateral wall and velar movement has been described.[46] Another study of clinical outcomes with the lift prosthesis did not seem to confirm this possibility.[47]

Prosthetic intervention is used in cases in which airway limitation is significant. The prosthesis can be removed at night to avoid obstructive apnea. It also is very useful in the case of stroke or central nervous system trauma[48] when there is a possibility of recovery. Older

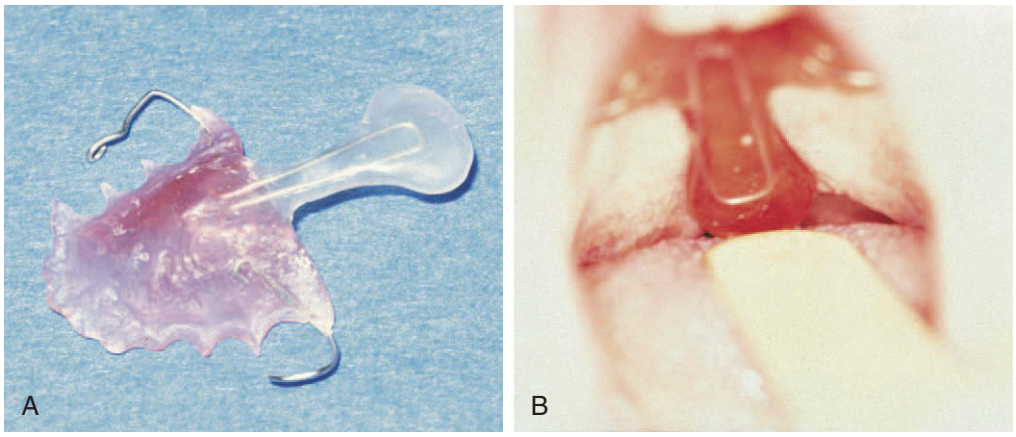

Figure 187-5. A palatal lift is shown out of the mouth **(A)** and in position **(B)**.

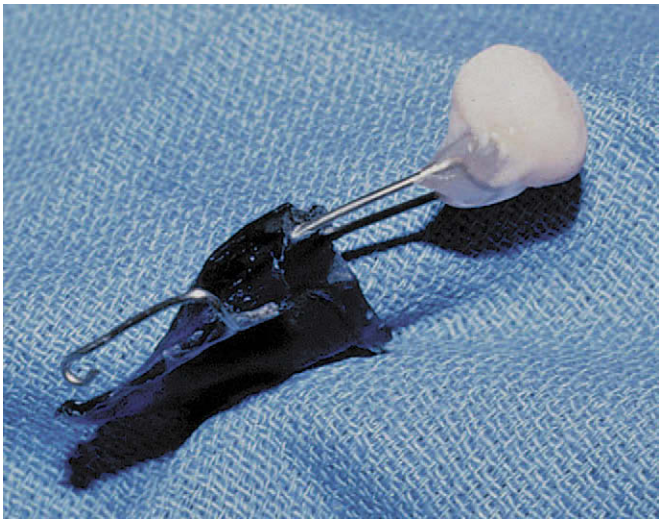

Figure 187-6. A palatal bulb obturator.

children and adults may be the most suitable candidates for this approach.

Prosthetic management has several limitations. First, an experienced prosthodontist is required for the fabrication, fitting, and maintenance of the appliance. Adequate maxillary dentition is mandatory, because the prosthesis is "hung" on the maxillary teeth. During the loss of deciduous teeth, keeping the prosthesis in place may not be possible. Similarly, during the rapid expansion of the maxilla in preparation for bone grafting, retention of the prosthesis is nearly impossible. The child must be cooperative with dental care. Finally, the prosthesis must be maintained with removal, cleaning, and repair. The inconvenience of this limits its widespread use and makes surgical options more desirable for long-term management in children.

Surgical Intervention

If a structural problem in velopharyngeal function exists, or speech therapy alone is ineffective, surgical intervention is a consideration. Options include intravelar veloplasty, Furlow double-opposing Z-plasty, sphincter pharyngoplasty, and superiorly based pharyngeal flap operations. The intravelar veloplasty and Furlow Z-plasty attempt to improve function by reorienting the levator sling. The (sphincter) pharyngoplasty borrows lateral wall tissue to obturate the lateral and posterior walls. The pharyngeal flap borrows tissue from the posterior wall to obturate the middle portion of the velopharynx.

Levator Repositioning

If the levator veli palatini muscle is oriented longitudinally, such as in a submucous cleft palate or after a palatoplasty, velar motion may be improved by reorienting the levator musculature. The traditional approach to this is an intravelar veloplasty. This operation dissects the levator muscles from their posterior attachment to the hard palate and nasal and oral mucosa to achieve a more anatomic transverse orientation. Although this is intuitively sensible, the results are not always satisfactory.[49] It has, however, been used with some success in "re-repair" of the palate if VPD follows a palatoplasty that did not include levator repositioning.[50]

The intravelar veloplasty can be done at the initial palate repair or as a secondary operation. An initial repair technique that can be slightly altered in revision surgery is described next.

After induction of general anesthesia and the securing of the endotracheal tube, a mouth gag is placed. This device secures the endotracheal tube against the tongue while retracting it out of the way with epinephrine. The greater palatine neurovascular bundle is injected with a small amount of local anesthetic. The palate will blanch, demonstrating a good local block. The soft palate is then additionally infiltrated to achieve further hemostasis.

The hard palatal flaps are elevated to the neurovascular bundle. Care is taken to dissect this without injury to the vascular supply. The lateral incision allows dissection around the hamulus. This maneuver will assist in freeing enough oral mucosa to allow closure.

The levator muscle inserts into the posterior border of the hard palate. This alignment makes the muscle nonfunctional. As the muscle is dissected from the posterior hard palate border, care is taken to avoid injuring the thinner nasal mucosa. The muscle is then freed from the oral mucosa and nasal mucosa. The dissection is best carried back to the hamulus and the levator followed toward the skull base. Debate is ongoing regarding the advantage of fracturing the hamulus to increase the mobility of the muscle bundle.

The palate is then closed in three layers. Nasal mucosa is closed with everting simple and mattress sutures from anterior to posterior. Absorbable sutures such as chromic are used. Uvular reapproximation, though not essential, is ideal. The muscle bundle often is attenuated. It is best closed with mattress sutures across the midline and may be tacked in this anatomic position. The oral mucosa is then closed as well.

Double-Opposing Z-plasty Palatoplasty

A current trend has been toward the use of the double-opposing Z-plasty originally described by Furlow (see Chapter 186).[38,51-54] This method reorients the levator while also thickening and lengthening the palate. The Furlow double-opposing Z-plasty also can be used as a primary closure, a repair of a submucous cleft palate, or a secondary procedure if the levators are longitudinally oriented. The Z-plasty is a well-known technique for lengthening a scar. The reorientation of the flaps also builds bulk in the posterior palate to aid contact of the posterior pharyngeal wall.

The Furlow double-opposing Z-plasty is done with the patient under general anesthesia. The mouth gag is used as well. After injection for hemostasis, as described earlier in the discussion of intravelar veloplasty, the four flaps are designed. The two myomucosal flaps are always posteriorly based and two mucosal flaps anteriorly based. A right-handed surgeon may find the elevation of the myomucosal flap on the patient's left more easily done, but this is not required.

If the palate is intact, it is divided in the midline. An incision is made on the left hemipalate, just posterior to the hard palate edge, leaving a small margin for ease of closure. This incision is carried through the muscle layer to the submucosal layer of the nasal mucosa. Care must be taken not to injure the thin nasal mucosa. The dissection is then carried posteriorly toward the free margin of the palate.

The oral mucosa is elevated from the muscle layer on the right hemipalate. This is based anteriorly. The incision is made just anterior to the free margin of the right hemipalate.

The right myomucosal flap is then developed by incising the muscle and nasal mucosa from the posterior edge of the right hard palate from medial to lateral. A cuff of tissue is left at the hard palate to facilitate closure.

The nasal mucosal flap on the left hemipalate is developed. An incision is made beneath the left myomucosal flap near the posterior edge of the soft palate toward the eustachian tube. This also creates a flap based anteriorly on the hard palate.

These four flaps are then repositioned to allow closure. The closure proceeds first with the nasal suture line repair, followed by the oral suture line closure. The left nasal mucosal flap is rotated across midline to the right hard palate margin. Everting sutures are tied with the knot toward the nose. The right myomucosal flap is then rotated to the left to insert into the left hemipalate. This maneuver brings the muscle bundle across the midline. The tension is not in the midline but lateral, reducing risk of fistula formation. The rotated flap is positioned so that the midline incision is now sewn to the posterior edge of the soft palate. The incision line that was at the hard palate is now sewn to the free edge of the nasal mucosal flap.

The oral mucosal flap from the right hemipalate is now rotated to the left, past the midline. The right oral mucosal flap is sutured to the incision at the posterior hard palate. The left myomucosal flap is

then rotated to the right across the midline. The once-medial edge will be sutured to the posterior soft palate edge. The muscular flaps thus overlap each other, which thickens the soft palate. The lateral incision will be closed to the free margin of the oral mucosal flap. The uvula is reapproximated.

Pharyngeal Flap

For years, the pharyngeal flap operation has been the mainstay of management for VPD when performed as a secondary procedure in patients with cleft palate. Many surgeons have excellent success with this operation.[29,55-59] Although both inferiorly and superiorly based flaps can be designed, the superiorly based flap is in more common use.[60] This flap places posterior wall tissue in the center of the velopharynx, leaving a lateral port on either side. With use of lateral port control with an appropriately sized catheter, airway problems are reduced.[58] Because of the midline obturation, the pharyngeal flap is ideal for a sagittal or circular pattern with good lateral wall motion. It may be altered as a secondary procedure to improve results.[61,62] Lateral wall motion is necessary for closure, but some evidence suggests that the lateral wall motion will improve after the procedure.[57]

After induction of general anesthesia and endotracheal intubation, the Dingman mouth gag is introduced. Palatal injection is performed as described earlier. The posterior pharyngeal wall is injected as well.

The flap is designed based on previously obtained endoscopic or videofluoroscopic results. The width and length will be key. Care must be taken to avoid elevating the flap too far into the hypopharynx, to reduce scarring and postoperative dysphagia.

Lateral incisions are made to the prevertebral fascia. The flap is undermined. Division in the inferior aspect can be left until the palate is opened. It is important to recognize that the flap will shrink once the inferior cut is made. Adequate length is important, but little advantage accrues to creation of an exceptionally long flap.

This procedure may be done using a palatal split technique, with the nasal mucosa used to cover the raw surface of the flap. Alternatively, the flap may be introduced into a bivalved palate. Flap width can vary because of the vagaries of scarring.

If the bivalve or fish-mouth technique is chosen, the palate is retracted to expose the nasal surface. An incision is made just anterior to the free margin on the nasal side. The oral mucosa is then dissected from the muscle layer through this incision, creating a pocket. The width of the pocket is based on the preoperative assessment on the needed width of the flap.

The superiorly based flap is then released from its inferior connection. The flap is inserted into the pocket so that the raw surface is in contact with the raw surface of the pocket. Sutures are brought from the oral surface of the palate through the pocket. These are then placed from the raw surface of the flap through the mucosa about 1 cm from the tip. The suture is then placed back through the mucosa of the flap and brought through the pocket to come out on the oral mucosal surface. As these sutures are tied, the flap pulls itself into the pocket, with raw surface to raw surface and mucosa to mucosa. Lateral port control is helpful. The mucosa also can be removed from the distal end of the pharyngeal flap so that the sutures can be placed at the distal end of the flap. The denuded flap is inserted into the pocket. This technique, in one report, yielded inconsistent results when compared with others.[30]

If the surgeon prefers, a palatal split approach can be used. The palate is divided in the midline. The hemipalate sections are retracted laterally. Back-cuts are made through the nasal mucosa at the posterior margin of the hard palate to elevate a laterally based nasal mucosal flap from the soft palate. The pharyngeal flap is sutured to the midline at the soft-hard palate junction and laterally to the mucosal edge of the back-cut. Lateral port control is maintained by the placement of catheters. The size of the port is determined by how far laterally the flap is sewn to the back cut. The laterally based nasal mucosal flaps are then sewn over the pharyngeal flap, to reduce scar contracture and narrowing of the flap. The nasal mucosal incision is closed in the midline. The cut edges of the muscular layer are reapproximated. The oral mucosa is then closed.

The posterior wall defect can be partially closed to assist in the postoperative healing, but can also be left open to heal secondarily. Excessive closure narrows the pharynx, which can cause airway obstruction and consequent sleep apnea.

Pharyngoplasty

The sphincter pharyngoplasty is commonly used for treatment of VPD.[6,63-67] This procedure is a popular choice because of a perceived decrease in risk of postoperative airway obstruction and a high percentage of coronal and circular closure patterns. Bilateral myomucosal flaps are elevated from the lateral pharyngeal wall to be inserted into an incision on the posterior nasopharyngeal wall at the level of greatest closure. This obturates the posterior and lateral portions of the velopharynx. Movement of the palate to the flap accomplishes closure.[66,67] Sphincter pharyngoplasty is ideally suited for a coronal closure but also is useful in the circular closure if the palate has reasonable motion. This procedure is called a sphincter operation because it was felt that active movement of the myomucosal flap was possible. Although active motion of the flap occasionally is seen, it is not constant.[66,67] There seems to be improved palatal motion after this procedure.[67] The width, length, and degree of overlap of the myomucosal flaps determine the "tightness." Alterations in these three factors can compensate to some degree for limitation of palatal motion seen preoperatively.

The sphincter pharyngoplasty preparation is similar to the previously discussed palatal operations. Because no incisions are made in the palate, injection for hemostasis is only in the lateral pharyngeal wall and posterior nasopharynx.

The palate is retracted with a uvula retractor or red rubber catheters. Preoperative endoscopy or speech videofluoroscopy allows estimation of the amount of obturation needed and the level of maximal palatal excursion. The width of the lateral myomucosal flaps can be altered and the position of the incision for nasopharyngeal insertion decided, as needed. Adjustability is an advantage of this procedure. Even unilateral sphincter pharyngoplasty may be used on occasion.

A posterior incision is made at the level of the maximal palatal excursion. The flap placed at this level will allow the most closure during speech. The incision is carried bilaterally to the posterior limb of the outlined lateral flap. It is not carried through the deep fascia.

The lateral flaps are superiorly based myomucosal flaps. They may include the palatopharyngeal muscle (posterior tonsillar pillar) but can be taken directly from the constrictors.

Many variations are available on the placement of the flaps. Rotation into the velopharynx and suturing to the horizontal incision are necessary. The posterior border of the left flap can be sutured to the superior border of the horizontal incision in the nasopharynx. The right flap is rotated so that the anterior border is sutured to the inferior border of the horizontal incision. The two flaps are then sutured together at the remaining free edge.

The degree of overlap will determine the tightness of the sphincter, the degree of obturation, and obstruction. If vigorous movement of the palate is seen preoperatively, a narrow flap can be taken and secured with less overlap. If little preoperative palatal motion is possible, a wider flap is harvested and the overlap should be maximal.

In the postoperative period, all of these procedures warrant concern related to airway obstruction.[56,68-70] Close monitoring of the patient through the immediate postoperative period for acute obstruction is necessary. Chronic obstruction can manifest as obstructive sleep apnea. The use of CPAP can be helpful to allow resolution of edema and scar maturation. Some children can then "outgrow" the obstruction over time as the dimensions of the pharynx increase with growth.

Posterior Wall Augmentation

In the child who has a very small posterior midline "gap" that causes VPD, augmentation of the posterior pharyngeal wall may be tried. Although many materials have been used, including hyaluronic acid,[71] fat,[72] Teflon,[73] Proplast,[74] and cartilage,[75] most have achieved limited long-term success. A recent animal study looked at the duration of injectable micronized acellular dermal matrix in a submucosal area. Even after only 30 days, little of the injected material remained.[76] Gray and colleagues reported lasting improvement using a "rolled" posterior

pharyngeal flap for autologous posterior wall augmentation.[77] In this procedure, a superiorly based pharyngeal flap is rolled or folded on itself and sutured to make a ridge in the posterior nasopharynx. Success may be variable, however: Durability of the obturation was not seen in a similar study using this technique.[78]

The autologous posterior wall augmentation uses the superiorly based pharyngeal flap. Lateral incisions are made, and the flap is elevated along the deep fascial plane. The flap is folded on itself. The distal end of the flap is secured at the base of the elevated flap into the deep fascia. This creates a mass effect on the posterior velopharyngeal wall. Preoperative endoscopy or speech videofluoroscopy can assist in determining the correct level for positioning the "rolled" flap. As in the pharyngeal flap operation, the posterior wall defect can be partially closed.

Choice of Surgical Intervention

Although basing selection of the surgical intervention on the gap seen at speech videofluoroscopy or endoscopy seems like a reasonable approach, alternative views have emerged. In one series, no difference was seen between superiorly and inferiorly based pharyngeal flaps.[79] A prospective multicenter study randomizing the patients to undergo either sphincter pharyngoplasty or a pharyngeal flap operation suggested no difference in outcomes.[63] Indeed, in centers that use pharyngeal flap operations as the mainstay of management for children with VPI, excellent results are obtained even though the most common closure pattern is coronal.[55] One protocol suggests that the initial decision be based on the orientation of the levators. A Furlow Z-plasty is done if they are suspected not to be horizontally placed. If that fails or if the orientation is normal in a child without a cleft deformity or if the cleft repair included this, a sphincter pharyngoplasty is used.[80]

Fortunately, most reported series do show very good results in the overwhelming majority of the patients. To that end, surgeons should consider maximizing competency in a particular technique and continuing to develop the skills for that technique. An important point is that although the velopharyngeal incompetence can be surgically eliminated, speech therapy may still be needed to correct the articulation errors, especially those that are maladaptive.

Conclusions

The diagnosis, assessment, and management of VPD involve a variety of diagnostic options, assessment tools, and management options. It is helpful for the otolaryngologist, speech-language pathologist, and other team members to take a "transdisciplinary" approach, in which each is thoroughly knowledgeable about the various disciplines involved in the care of children with these problems.[36] Identifying the need for speech therapy and the timely inclusion of surgical management, if needed, demand an understanding of the velopharyngeal mechanism and its relation to phonologic and articulation development, as well as awareness of the various surgical and prosthetic options and their short- and long-term consequences for the child.

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CHAPTER ONE HUNDRED AND EIGHTY-EIGHT

Congenital Malformations of the Nose

Ravindhra G. Elluru

Christopher T. Wootten

Key Points

- Most congenital nasal lesions relate to developmental errors in one of three embryologic zones: (1) anterior neuropore; (2) central midface; (3) nasobuccal membrane.
- Encephaloceles, gliomas, and dermoids share a common embryologic origin and frequently manifest as midline nasal masses that require surgical management.
- Appropriate preoperative imaging with CT or MRI, or both, and use of careful intraoperative dissection techniques are required to determine whether a dermoid extends intracranially. In such cases, optimal management consists of a combined approach involving otolaryngology and neurosurgery.
- The most common congenital nasal disorders of the central midface relate to cleft lip deformities. The typical appearance of the nose features a flattened, retracted nostril and a broad nasal tip.
- Congenital nasal pyriform aperture stenosis is associated with holoprosencephaly and a central maxillary megaincisor in a majority of cases. Pituitary abnormalities are also common.
- Up to 30% of infants are born with nasolacrimal duct obstruction, but only those with nasal obstruction and feeding difficulties secondary to nasolacrimal duct cysts require marsupialization.
- Choanal atresia is a relatively common cause of congenital nasal obstruction and more frequently is unilateral in presentation.
- Choanal atresia without a bony component does not exist. Transnasal approaches are the most popular technique. Mucosa-sparing techniques are associated with the best outcomes.

Overview

Congenital malformations of the nose and paranasal sinuses are rare manifestations of disordered development located at the origin of the aerodigestive tract. Clinical presentations range from subtle cosmetic deformities to life-threatening acute upper airway obstruction and feeding difficulties in neonates. This chapter focuses on the most common congenital lesions in the nose and paranasal sinuses. These lesions are considered within the framework of possible developmental errors in specific anatomic zones: (1) errors at the anterior neuropore, (2) errors of the central midface, and (3) errors of the nasobuccal membrane. Mesodermal and germline malformations not unique to the nose and paranasal sinuses also are discussed.

Developmental Errors of the Anterior Neuropore

The anterior neuropore persists medial to the optic recesses in the third week of life, and around it the skull base develops as the frontal, ethmoidal, and nasal bones. Behind the nasal bones but in front of the nasal and septal cartilages lies a potential space, the prenasal space. The foramen caecum forms a defect in the anterior skull base at the apex of the prenasal space, where the cribriform plate ultimately condenses. This structure is closed by its fusion with the fonticulus frontalis, a fontanelle between the inferior aspect of the frontal bones and the developing nasal bones. During the third through the eighth weeks of development, a projection of dura extends through the foramen caecum, traverses the prenasal space, and apposes ectoderm at the tip of the nasal bones (the future rhinion). As the foramen closes, the dural diverticulum detaches from the overlying ectoderm and retracts into the cranium. Irrevocably apposed ectoderm may be pulled posterosuperiorly toward and even through the foramen caecum, giving rise to a dermoid fistula, cyst, or sinus. Faulty or premature closure of the foramen may enable persistence of neural tissue in the nasal cavity as isolated heterotopic glial tissue (glioma) or as a patent central nervous system (CNS) communication (meningocele or encephalocele) (Fig. 188-1). The latter can occur in a paramedian position, as a nasoethmoidal encephalocele, or, more laterally through a medial orbital wall defect, as a naso-orbital encephalocele. Basal encephaloceles herniate posterior to the cribriform plate. Similar errors may occur above the developing nasal bones at the fonticulus frontalis. Intracranial contents may herniate through the patent fonticulus frontalis until the eighth week. If the fonticulus also closes abnormally, the result may be persistence of an extranasal path, leading to nasofrontal meningoceles or encephaloceles or gliomas[1] (Fig. 188-2).

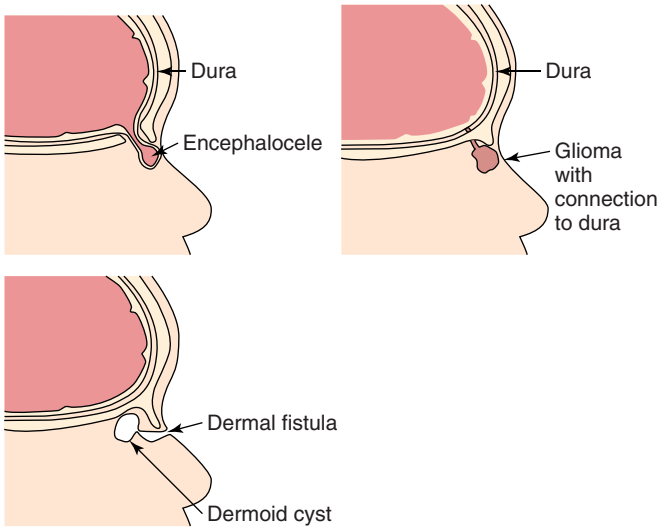

Figure 188-1. Schematic view of the common midline nasal masses.

Figure 188-2. Sincipital encephalocoele. A soft, bluish compressible mass protruding from the glabellar region.

Encephaloceles

An *encephalocele* is an extracranial herniation of cranial contents through a defect in the skull. When the encephalocele includes meninges only, it is termed a *meningocele*; if it includes both brain and meninges, it is termed a *meningoencephalocele*. Estimates of the incidence of these lesions vary considerably, ranging from 1 in 3000 to 1 in 30,000 live births in North America and Europe. The incidence in Asian populations is higher, with a reported incidence of 1 in 6000 live births. Encephaloceles have no familial tendency or gender predilection. Approximately 40% of affected patients have other associated anomalies.[2-4]

Encephaloceles are divided into occipital, sincipital, and basal types (Tables 188-1 and 188-2). Occipital encephaloceles will not be discussed in this chapter as they occur outside the nose. *Sincipital* encephaloceles account for 25% of all encephaloceles, and they are further classified according to their location. Nasofrontal encephaloceles manifest as glabellar masses, causing telecanthus and inferior displacement of the nasal bones. Nasoethmoidal lesions manifest as dorsal nasal masses, causing superior displacement of the nasal bones and inferior displacement of the alar cartilages. Naso-orbital lesions manifest as orbital masses, causing proptosis and visual changes.[1] The anatomic course of each of these sincipital encephalocele presentations is shown in Table 188-1. *Basal* encephaloceles are less common, arising

Table 188-1

Sincipital Encephaloceles

Type	Course	Clinical Features
Nasofrontal	Through bone defect between orbits and forward between nasal and frontal bones to the area superficial to the nasal bones	Glabellar mass Telecanthus Inferior displacement of nasal bones
Nasoethmoidal	Through foramen caecum deep to the nasal bones, turning superficially at the cephalic end of the upper lateral cartilage to expand superficial to the upper lateral cartilage	Mass on the nasal dorsum Superior displacement of nasal bones Inferior displacement of the alar cartilages
Naso-orbital	Through the foramen caecum deep to the nasal and frontal bones through a lateral defect in the medial orbital wall	Orbital mass Proptosis Visual changes

Table 188-2

Basal Encephaloceles

Type	Course	Clinical Features
Transethmoidal	Through the cribriform plate into the superior meatus medial to the middle turbinate	Most common type Nasal obstruction Hypertelorism Broad nasal vault Unilateral nasal mass
Sphenoethmoidal	Passes through a bony defect between the posterior ethmoid cells and sphenoid	Nasal obstruction Hypertelorism Broad nasal vault Unilateral nasal mass
Transsphenoidal	Through a patent craniopharyngeal canal into the nasopharynx	Nasopharyngeal mass Nasal obstruction Associated with cleft palate
Spheno-orbital	Through the superior orbital fissure and out the inferior orbital fissure into the sphenopalatine fossa	Unilateral exophthalmos Visual changes Diplopia

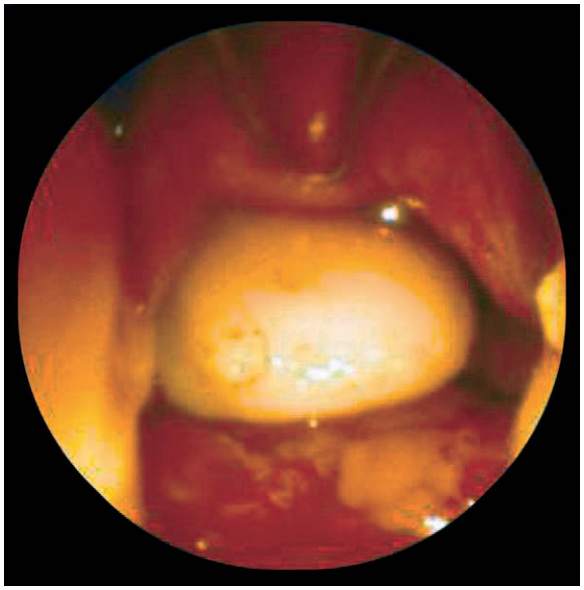

Figure 188-3. Basal encephalocele seen in nasopharynx with a 120-degree angled telescope.

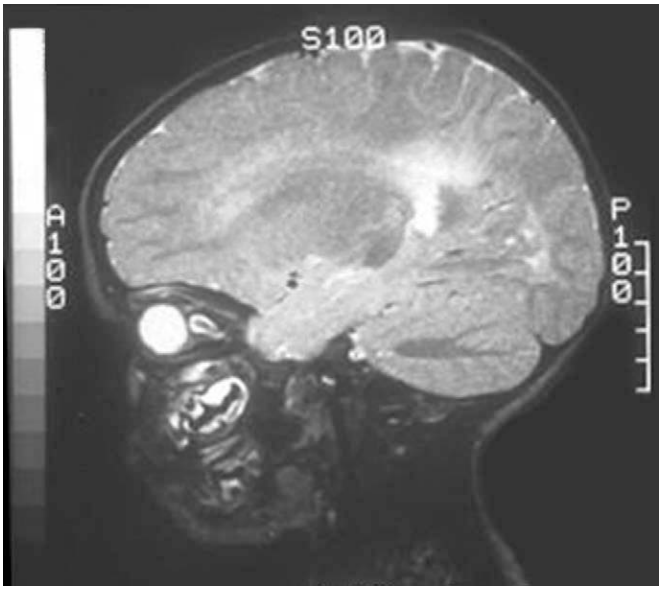

Figure 188-4. Sagittal magnetic resonance image of a basal meningoencephalocele protruding into the nasopharynx.

between the cribriform plate and the superior orbital fissure or posterior clinoid fissure and manifesting as an intranasal mass (Fig. 188-3). These masses may not manifest until later in childhood, when they cause nasal obstruction and drainage. Sincipital and basal encephaloceles appear as pulsatile, bluish compressible lesions that transilluminate. Classically, these lesions expand with crying, straining, or compression of the jugular veins.

On histopathologic analysis, sincipital and basal encephaloceles have a glial component, with astrocytes surrounded by collagen, submucosal glands, and sometimes nasal septal cartilage or calcification. When it is difficult to differentiate between gliomas and encephaloceles, the presence of ependymal tissue is consistent with an encephalocele.[5]

High-resolution computed tomography (CT) or magnetic resonance imaging (MRI) delineates encephaloceles and additionally helps to exclude associated anomalies such as agenesis of the corpus callosum and hydrocephalus.[5] CT outlines the bony cartilaginous defect, whereas MRI provides complementary information regarding the soft tissue characteristics of the mass (Fig. 188-4). MRI also differentiates meningoceles from meningoencephaloceles. Sagittal reconstructions and contrast enhancement are particularly advantageous for identifying an intracranial connection.

Once the diagnosis of encephalocele has been made, management is surgical. Most authorities advocate intervention in the first few months of life[2] to minimize the risk of meningitis and cosmetic deformity, but the risk of meningitis is not decreased with prophylactic antibiotics while surgery is being planned. Additionally, early intervention makes the identification of the intracranial connection technically easier and allows more complete repair of the dural defect.[2] Small lesions with minimal skull base defects may be managed endoscopically. Larger lesions require a combined approach with a craniotomy to resect condemned dura and cerebral tissue with concomitant endoscopic removal of the residual nasal tumor. The skull base defect can then be reconstructed using a pericranial flap or split-thickness calvarial bone graft.[5] The most commonly encountered postoperative complications are cerebrospinal fluid (CSF) leak, meningitis, and hydrocephalus. Postoperative neurologic function reflects the patient's preoperative performance. Encephalocele recurrence rates of 4% to10% have been reported.[6]

Gliomas

Gliomas consist of heterotopic glial tissue that lacks a patent CSF communication to the subarachnoid space; however, 5% to 20% of gliomas maintain a fibrous affiliation (see Fig. 188-1). Nasal gliomas are rare and show nonfamilial inheritance. They occur more commonly in males (in a ratio of 3:2). These benign masses manifest as extranasal (60%), intranasal (30%), or combined (10%) lesions.[7] *Extranasal* gliomas are smooth, firm, noncompressible masses that occur most commonly at the glabella, although they may arise along the side of the nose or the nasomaxillary suture line.[2] *Intranasal* gliomas are polypoid pale masses that may protrude from the nostril. The nasal fossa on the involved side may be obstructed. Intranasal gliomas most often arises from the lateral nasal wall near the middle turbinate and occasionally from the nasal septum.[7] Nasal gliomas rarely may extend into the orbit, frontal sinus, oral cavity, or nasopharynx. Because they lack a patent CSF connection, gliomas do not change in size with crying or straining and do not transilluminate.

Pathologically, gliomas are better termed nasal glial heterotopias, nasal cerebral heterotopias, or congenital nasal neuroectodermal tumors. Histologic analysis shows dysplastic, neuroglial, and fibrovascular tissue. Ependymal tissue is not found in gliomas, a distinction that allows differentiation from encephaloceles.

Diagnostic evaluation should include a CT scan to assess the bony anatomy of the skull base, an MRI study to accurately image soft tissue connections to the CNS, and nasal endoscopy to assess the location, origin, and extent of the nasal mass. As with encephaloceles, sagittal reconstructions and contrast enhancement are useful imaging adjuncts.

Proper management of gliomas requires surgical extirpation using a multidisciplinary approach involving otolaryngology and neurosurgery. Delaying intervention may lead to distortion of the septum or nasal bones, or infection. With cosmesis kept in mind, surgical access should provide exposure of the lesion and possible exploration of the skull base. For resection of extranasal gliomas, options include lateral rhinotomy, external rhinoplasty, transglabellar subcranial, bicoronal, and midline nasal approaches.[8] Except in the case of large glabellar lesions, the external rhinoplasty approach provides adequate surgical exposure while minimizing the use of facial incisions.[5] When a fibrous stalk is present that extends deep to the nasal bones toward the base of the skull, a nasal osteotomy is recommended to improve exposure. Following the stalk in its entirety is crucial in determining the possible presence of an intracranial extension. As a result of advancements in surgical instrumentation, image guidance, and surgical techniques, most intranasal gliomas can be removed endoscopically.[9,10] Reported recurrence rates are between 4% and 10%.[11]

Nasal Dermoids

Nasal dermoids are frontonasal inclusion cysts or tracts related to embryologic errors localized to the anterior neuropore. Congenital

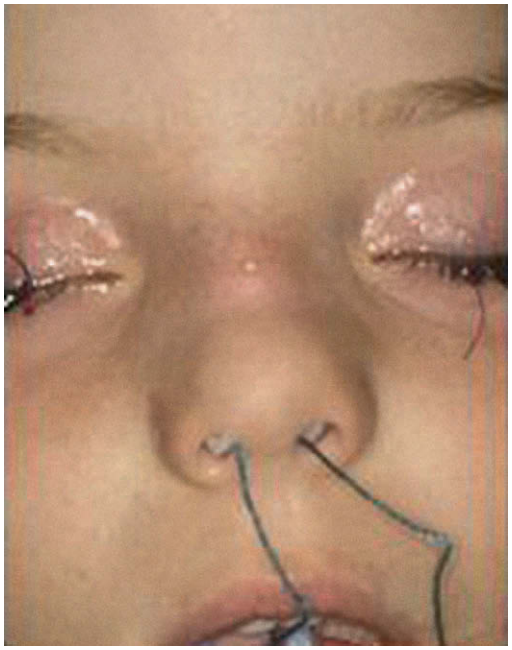

Figure 188-5. Nasal dermoid manifesting as a firm midline nasal swelling associated with a sinus opening.

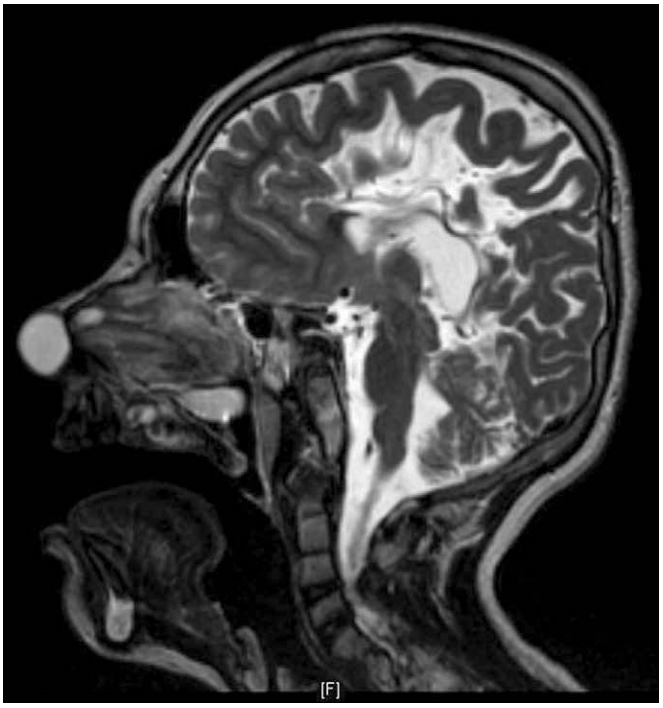

Figure 188-6. Sagittal magnetic resonance image of a nasal dermoid, evident as a region of signal hyperintensity in the anterior nasal septum as a hyperintense lesion.

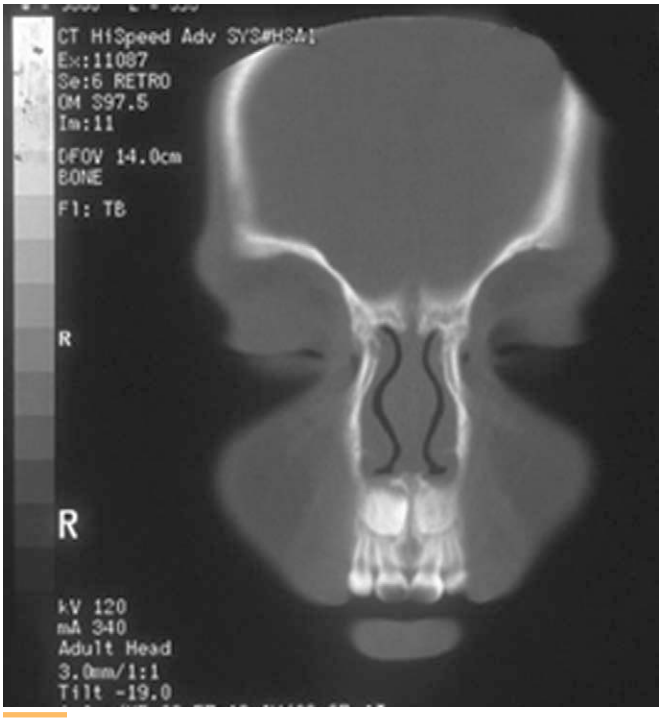

Figure 188-7. Coronal computed tomography scan showing a bifid crista galli and an enlarged foramen caecum.

midline nasal masses occur in 1 in 3000 to 1 in 40,000 live births, and dermoids are by far the most common.[12] Nasal dermoids account for 1% to 3% of all dermoids and approximately 10% to12% of head and neck dermoids. Most dermoid cysts occur sporadically, with a slight male preponderance,[13,14] although familial associations have been reported. Nasal dermoids may accompany aural atresia, pinna deformity, mental retardation, hydrocephalus, branchial arch anomalies, cleft lip and palate, hypertelorism, and hemifacial microsomia in 5% to 41% of presentations.[13]

Nasal dermoids usually manifest as a midline pit or mass. In approximately 50% of clinical presentations, a dimple is present at or near the rhinion, along with a widened nasal bridge; however, the true spectrum of disease includes cysts, sinuses, or fistulas that may occur anywhere along the embryologic line from the nasal tip into the cranial space. Mass lesions are firm, lobulated, and noncompressible and may be associated with a sinus opening (Fig. 188-5) with intermittent caseous discharge or infection. Although a protruding hair is seen in only a minority of patients, it is pathognomic for a nasal dermoid. A lesion within the nasal septum will cause nasal obstruction. Intracranial extension rates range from 4% to 45%.[13] Recurrent meningitis with typical skin flora may indicate an intracranial tract. Nasal dermoids do not enlarge with crying or straining and do not transilluminate.

Unlike teratomas, which contain all three embryonal germ layers, congenital dermoids contain only ectodermal and mesodermal embryonic elements. The latter include hair follicles, sebaceous glands, and sweat glands that are found in the wall of the cyst and thus differentiate these masses from simple epidermoid cysts. Keratin debris is another prominent feature on histologic examination, and dermoids also lack the glial features of encephaloceles and gliomas.

CT and MRI provide complementary information in the radiologic evaluation of nasal dermoids. Thin-slice (1 to 3 mm) CT scans with intravenous contrast are recommended to differentiate the dermoid from the surrounding nasal mucosa and to define the bony anatomy of the nose and anterior skull base (Fig. 188-6). Unique findings with intracranial dermoids include a bifid crista galli (Fig. 188-7) and an enlarged foramen caecum; a normal crista galli and foramen caecum may be used to exclude intracranial extension.[15] Multiplanar, thin-section contrast-enhanced MRI is used to depict the soft tissue anatomy of the anterior skull base, and contrast-enhanced MRI distinguishes the nonenhancing dermoid from enhancing lesions such as hemangiomas and teratomas. The neonatal crista galli does not contain marrow fat, so high signal intensity on T1-weighted images is suggestive of an intracranial dermoid.

As with other congenital anterior neuropore lesions, the management of nasal dermoids is surgical. Because aspiration, incision and drainage, curettage, and subtotal excision are associated with high recurrence rates, these management approaches generally are not advocated. Assessing the degree of intracranial extension is crucial, and in

patients with features suggestive of intracranial extension, a combined intracranial-extracranial approach should be planned with the participating neurosurgeon. Extracranial access should fulfill four criteria: (1) excellent access to the midline; (2) access to the base of the skull; (3) adequate exposure for reconstruction of the nasal dorsum; and (4) an acceptable scar.[16] Several different extracranial approaches have been described. The external rhinoplasty incision generally gives the best cosmetic result and is therefore the most widely used approach. This approach also gives access to the skull base and allows for exposure of the nasal dorsum; nevertheless, it provides limited access to lesions in the glabellar region. Alternative approaches include lateral rhinotomy and midline vertical incisions, both of which provide excellent access.[13] For lesions in the glabellar area without a sinus tract, a transglabellar subcranial approach, a paracanthal incision, or a bicoronal approach is an acceptable alternative. Glabellar lesions with a sinus opening require an elliptic incision to excise the ostium, despite the possibility of a widened scar.

For lesions that extend into the cranial cavity, a multidisciplinary effort is required to perform a frontal craniotomy. This usually is carried out through a coronal incision using a combined intracranial-extracranial approach with a large frontal craniotomy; however, anterior small window craniotomies have been described.[17] Sessions[18] has suggested that craniotomy may be avoided altogether and the tract sutureligated if it is devoid of epidermal and adnexal structures at the skull base. This information can be obtained by intraoperative frozen-section analysis of the tract. A number of investigators[13,15] agree with this approach. Other workers[19] have suggested that epidermal elements may be staggered along the tract and thus postulate that a single biopsy site may provide false-negative information regarding the presence of an intracranial extension of the dermoid tract. The overall recurrence rate after adequate excision is low; however, long-term follow-up is essential to diagnose the occasional late recurrence.

Developmental Errors of the Central Midface

Eruption of nasal pits into the choana, fusion of the palatal shelves, and growth of the nasal septum and soft palate coincide with the development of the lateral nasal wall and primitive sinus anatomy. For normal nasal and paranasal growth to occur, all of these rapid changes must take place with complete precision.[1]

Normal nasal development occurs between weeks 4 and 12 of life. During this time, neural crest cells migrate from their origin in the dorsal neural folds around the eye to form the first and second branchial arch–derived facial prominences surrounding the stomodeum. The stomodeum is surrounded by the frontonasal prominence superiorly, the maxillary processes laterally, and the mandibular processes inferiorly. The nasal placodes, which are two small thickenings in the frontonasal prominence, begin to burrow, forming nasal pits. This invagination process in the fifth week creates ridges of tissue around the pit; these are called the lateral nasal prominences laterally and the medial nasal prominences medially. Nasolacrimal duct development begins as a thickening of the ectoderm that becomes buried in the mesoderm of the nasal pits between the lateral nasal prominence and the maxillary process. This buried ectoderm canalizes from superiorly to inferiorly postnatally. The lateral and medial prominences finalize interaction with the developing maxillary process, creating the philtrum and medial lip (from the fused medial nasal prominences) and the lateral upper lip (from the maxillary prominences). The lateral nasal prominences form the nasal alae (Fig. 188-8).

Errors in central midface development underlie a host of congenital anomalies. Arhinia (congenital absence of the nose) may result from (1) abnormal migration of neural crest cells; (2) failure of fusion of the medial and lateral nasal processes; (3) overgrowth and premature fusion of the medial nasal processes; or (4) lack of resorption of the nasal epithelial plugs.[20] Similarly, polyrhinia probably results from incomplete development of the frontonasal process, which subsequently allows separation of the developing lateral portions of the nose.[1,21,22] The medial nasal processes and the septum continue to develop as scripted and are duplicated, thereby forming a "double nose."[1,2,11,23] Proboscis lateralis may result from mesodermal proliferation errors in the frontonasal and maxillary processes adjacent to the forming nasal pits. Epidermal breakdown then occurs, leaving the lateral nasal process sequestered as a tube arising in the frontonasal region. Also, because of this breakdown, the nasolacrimal duct is not formed.[1] Independent of proboscis lateralis, failure of the nasolacrimal ectodermal tract to canalize postnatally may result in formation of a nasolacrimal duct cyst in an otherwise normal patient.

Midline and paramedian fusion errors produce midfacial clefting. This may be isolated to the midface or occur as a part of cephalic clefting (Robert's syndrome) or holoprosencephaly. Errors in fusion of the medial nasal prominences with the medial aspect of the maxillary process produce a cleft lip, with its accompanying congenital nasal deformity. Finally, deficient development of the primary palate and bony overgrowth of the nasal process of the maxilla[24] are responsible for congenital nasal pyriform aperture stenosis. A developmental deficiency of the incisive os could explain the occurrence of a triangular plate, the narrow inferior portion of the nasal cavity, and the associated central maxillary mega-incisor, which is seen in 60% of cases[25] (Fig. 188-9). The term *holoprosencephaly* was introduced by DeMyer and coworkers to describe median facial anomalies and the brain morphology associated with these anomalies.[26] Holoprosencephaly is a failure of the embryonic forebrain to cleave sagittally into cerebral hemispheres, transversely into a diencephalon, and horizontally into olfactory and optic bulbs. This failure is associated with a spectrum of facial anomalies including (1) cyclopia (single eye and single orbit with arhinia and proboscis); (2) ethmocephaly (extreme hypertelorism, separate orbits, and arhinia; (3) cebocephaly (hypertelorism and proboscis-like nose without cleft lip); (4) median cleft lip (orbital hypertelorism and flat nose); and (5) median philtrum-premaxilla anlage (hypertelorism, bilateral cleft lip, and a median process representing the philtrum-maxilla anlage).

Complete Agenesis of the Nose (Arhinia)

Arhinia is part of the holoprosencephaly spectrum. This malformation is extremely rare, with approximately 30 cases described in the literature (Fig. 188-10). In the few reported cases, arhinia generally is sporadic in inheritance and may occur either as an isolated defect or in association with other facial and cerebral abnormalities.[27] Associations with genetic disorders such as trisomy 10, trisomy 13, and trisomy 21, as well as chromosome 9 inversion and translocation of chromosomes 3 and 12, also have been reported.[3,27,28]

The features of arhinia include absence of the external nose and nasal airways, hypoplasia of the maxilla, a small high-arched palate, and hypertelorism. Affected infants display respiratory distress and cyanosis associated with feeding. Older children may gulp food between breaths. Speech is characteristically hypernasal, and patients demonstrate evidence of hyposmia. Physical examination reveals an absence of the external nose, nasal septum, and sinuses. Rare associated abnormalities of the eye include anophthalmia and hypoplasia of the orbits.

Early management of arhinia focuses on nutrition. A cleft palate feeder or a gastrostomy tube is required. A prosthetic nose may be used until the child is older and can undergo definitive surgical repair. Vertical distraction osteogenesis of the midface has been reported to increase midfacial height, maximizing bone and soft tissue for later reconstruction.[29] Re-establishing the nasal passageway requires removing the incisors, creating an airway through the maxilla, and releasing the high-arched palate. The nasal passage is then lined with split-thickness skin grafts and maintained with long-term stenting. Restenosis is common, and serial dilations are required. Reconstruction of the external nose is a multistage procedure that requires the use of tissue expanders, bone, cartilage or prosthetic grafts, and local or regional skin flaps, with concomitant dacrocystorhinostomy to prevent recurrent conjunctivitis resulting from absence of the nasolacrimal ducts.[30]

Polyrhinia and Supernumerary Nostril

Polyrhinia (double nose) and supernumerary nostril (accessory nostril) are extremely rare anomalies, with only four reported cases of each.[21] These deformities may occur in isolation or in association with pseudohypertelorism. Patients with polyrhinia generally present with anterior (septal duplication, duplicated nasal passageways) and posterior (choanal atresia) nasal defects. The primary step in surgical

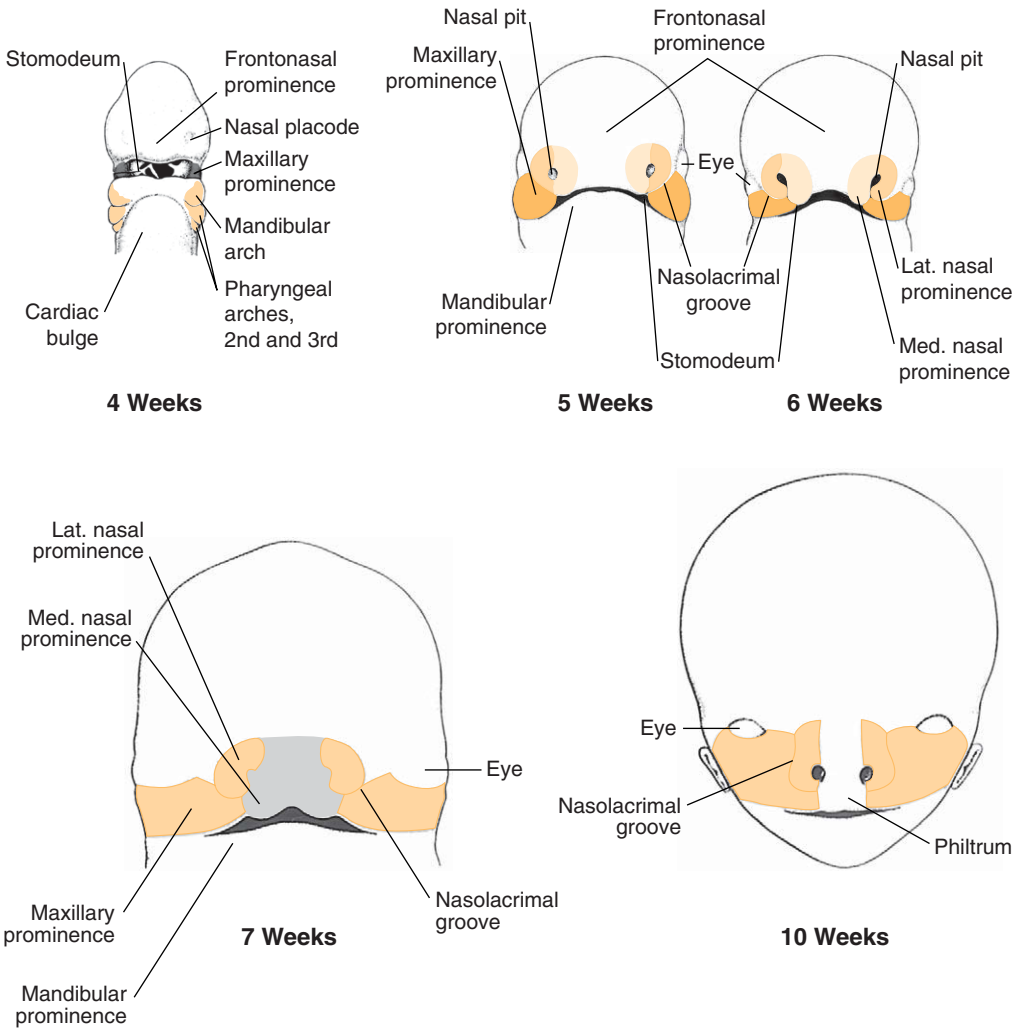

Figure 188-8. Embryo at weeks 4, 5, 6, 7, and 10, showing the developing nasal structures. *(From Sadler TW. Head and neck embryology. In Sadler TW, ed.* Langman's Medical Embryology. *6th ed. Baltimore: Williams & Wilkins; 1990:315-316.)*

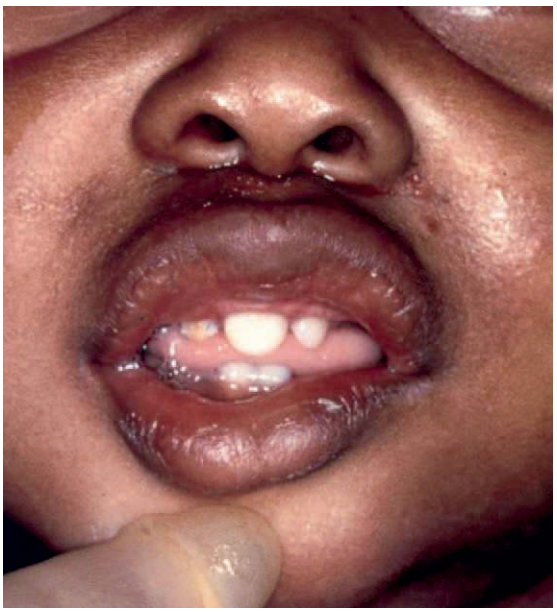

Figure 188-9. Maxillary mega-incisor in association with CNPAS.

Figure 188-10. Congenital arhinia.

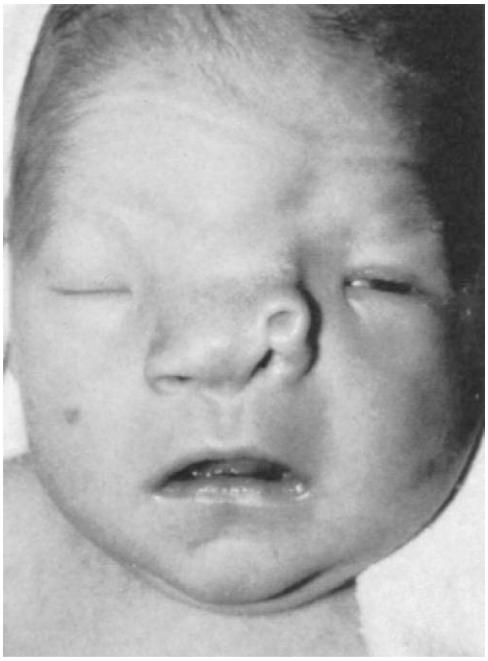

Figure 188-11. Proboscis lateralis. *(From Hengerer AS, Wein RO. Congenital abnormalities of the nose and paranasal sinuses. In: Bluestone CD, Stool SE, Alper CM, et al, eds.* Pediatric Otolaryngology. *4th ed. Philadelphia: Saunders; 2001:988.)*

management is correction of the choanal atresia. The nasal deformity is later corrected by removing the medial portions of each nasal passage and anastomosing the lateral portions in the midline.[2] The result is a broad flat nose with a depression in the midline, which can be corrected later on by medial in-fracture of the nasal bones and additional rhinoplasty techniques.

Supernumerary nostril manifests with the external appearance of a small accessory nasal orifice with surrounding redundant soft tissue. The orifice may be lateral, medial or superior to the nose. With a true fistula, a discharge from this orifice may occur. Treatment entails excision of the supernumerary nostril and primary closure of the defect or closure with the assistance of local flaps.[21]

Proboscis Lateralis

Proboscis lateralis is a rare disorder that manifests as a tubular sleeve of skin attached to the inner canthus of the orbit and heminasal aplasia on the affected side (Fig. 188-11). This deformity is thought to be secondary to fusion of the maxillary process on the affected side with the contralateral developing nasal process. Approximately 30 cases have been reported in the recent literature. Proboscis lateralis is associated with other CNS abnormalities and congenital ocular lesions, such as microphthalmus, coloboma, and arachnoid cysts. The diagnosis is made by physical examination, nasal endoscopy, and CT scanning. Treatment is delayed until facial growth is complete, and a prosthetic device is worn until reconstructive efforts begin. Reconstruction involves the use of bone and cartilage grafts and surrounding skin, including the tube of anomalous lateral nasal skin. Restenosis is common, and serial dilations with stenting often are required.[2]

Craniofacial Clefts

Craniofacial clefts are exceedingly rare and generally are not encountered in routine clinical practice. The hallmarks of this disorder are ocular hypertelorism; a broad nasal root; lack of formation of the nasal tip; anterior cranium bifidum occultum; median clefting of the nose, lip, and palate; and unilateral orbital clefting or notching of the nasal ala.[1,31] DeMyer[32] noted an association among hypertelorism, cephalic anomalies, and mental deficiency. The Tessier classification of cranial clefts[23] is the most widely used. This classification is based on specific axes (0 to 14) along the face and cranium. Because the orbit is common to the face and cranium, it distinguishes cranial clefts (9 to 14) from facial clefts (0 to 8).

There is a large degree of variability in the severity of median nasal clefts. This deformity, also known as bifid nose and internasal dysplasia, can range from a simple median scar at the cephalic end of the nasal dorsum to a completely split nose, forming separate halves with independent medial nasal walls. Disparate associations have been reported in the literature. A median cleft lip is a frequent associated anomaly.[33] The airway usually is adequate despite the cosmetic appearance. Before surgical reconstruction, it is important to rule out a possible dermoid cyst or encephalocele within the nasal-septal area. Surgical reconstruction requires the cooperative efforts of a multidisciplinary team, and treatment outcomes depend largely on the severity of the midline dysraphia.

Lateral nasal clefts are rare anomalies that involve defects of the lateral nasal wall or ala. They range from scarlike lines in the ala to triangular defects extending into the inner canthal fold and affecting the nasolacrimal apparatus. As with median nasal clefts, lateral nasal clefts require surgical reconstruction using a multidisciplinary approach.

Cleft Lip Nasal Deformity

Cleft lip deformity is among the most common congenital abnormalities of the head and neck. A complete cleft lip extends into the floor of the nose, whereas an incomplete cleft extends only partway through the upper lip. Cleft lip deformity shows a male predilection. Overall, the incidence of cleft lip and palate, singly or in combination, is between 1 in 1000 and 1 in 4000 live births. One half of these demonstrate cleft lip and palate, whereas 20% involve cleft lip alone. The distribution of left, right, and bilateral cleft lip deformities is approximately 6:3:1.

All complete clefts and many incomplete clefts involve the nose. The most severe defects are those associated with a bilateral complete cleft. Children with a bilateral deformity have a flattened nasal tip and a shortened columella. They also may have bilateral maxillary hypoplasia and relative prognathism. Less severe deformity is seen in children with unilateral clefting. In these children, the nasal ala on the side of the cleft is more laterally based, giving the appearance of a flat, retracted nostril. The caudal septum also is displaced to the cleft side. The maxilla on the cleft side is hypoplastic, and the nasal tip has a bifid appearance.

Treatment options for nasal deformities associated with cleft lip include both primary and secondary rhinoplasty. Many surgeons undertake redraping of the skin–soft tissue envelope over the lower lateral cartilages at the time of initial cleft lip repair within the first year of life. The flattened appearance of the nostril may be corrected by anchoring the skin–soft tissue envelope more medially on the lower lateral cartilage. This correction also adds definition to the tip subunit. Later, during a second procedure, a laterally based chondrocutaneous sliding flap procedure is performed to reposition the alar base; this often is combined with a columellar strut or shield graft placement to project the foreshortened columella. The secondary operation often is divided into stages. Stage 1, performed at the ages of 4 to 6 years, aims at providing cosmetic improvement. Stage 2, performed at ages 8 to 12 years, follows orthodontic correction and has the goal of making available an optimal skeletal framework. More definitive rhinoplasty is delayed until skeletal growth is completed. Accordingly, it is performed at the ages of approximately 16 to 18 years.[34] Both open and closed rhinoplasty techniques have been used.

Congenital Nasal Pyriform Aperture Stenosis

Congenital nasal pyriform aperture stenosis (CNPAS) is a rare anomaly that occurs secondary to bony overgrowth of the nasal process of the maxilla and typically manifests in the first few months of life. The stenosis may occur in isolation, or the patient may present with a central mega-incisor and the holoprosencephaly spectrum of congenital midline lesions. Hypertelorism, a flat nasal bridge, and the central mega-incisor are clinical features of the premaxillary dysgenesis associated with holoprosencephaly. Pituitary disorders and dental and facial anomalies also are part of this spectrum.

The pyriform aperture is the narrowest part of the nasal cavity, and small changes in the cross-sectional area significantly affect airflow by increasing nasal airway resistance. Newborns present with symptoms

Figure 188-12. Congenital nasal pyriform aperture stenosis, as seen on anterior rhinoscopy.

Figure 188-13. Axial computed tomography scan showing pyriform aperture stenosis secondary to overgrowth of the nasal process of the maxilla, causing reduction in the width of the piriform aperture.

similar to those of choanal atresia, and failure to pass a nasopharyngeal catheter may result in a misdiagnosis of choanal atresia. In older infants and children, nasal obstructive symptoms may be triggered by an upper respiratory infection, which further compromises the already narrow airway.

The diagnosis of CNPAS is established by physical examination and is best confirmed by CT, which shows that the width of the pyriform aperture, the cross-sectional area of the nasal cavity, and the width of the choana all are reduced. By contrast, the height of the nasal cavity and cross-sectional area of the choana are not altered (Figs. 188-12 and 188-13). Belden and colleagues[35] found the most helpful CT measurement to be the width of the pyriform aperture, defined as the distance between the medial aspects of the maxillae at the level of the inferior meatus, as measured on images in the axial plane. These workers reported that the width was never greater than 8 mm in their CNPAS group and never less than 11 mm in their control group. It is prudent for patients with a central maxillary incisor to undergo further investigation, to include central imaging for evaluation of CNS malformations, chromosomal analysis, and pituitary function testing.[36]

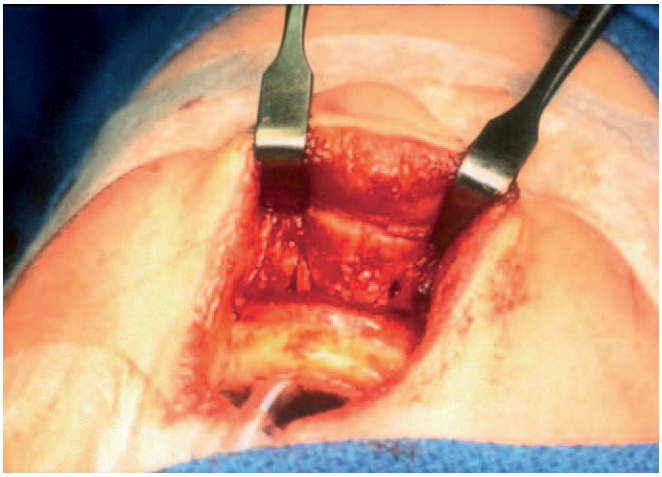

Figure 188-14. Sublabial approach to the piriform aperture. A gingivobuccal sulcus incision is made and a mucoperiosteal flap is raised to expose the piriform aperture.

Operative management is not always necessary for patients with CNPAS. Nonoperative management with nasal tubes and topical vasoconstrictive drops may be all that is required until growth results in increased nasal airway size. In patients who require surgery, repair is best accomplished through a sublabial approach, exposing the inferior and lateral pyriform aperture (Fig. 188-14). An otologic drill is used to widen the bony lateral and inferior margins. Brown and associates[24] recommend the use of nasal stents for up to 4 weeks.

Nasolacrimal Duct Cysts

Nasolacrimal duct cysts (dacrocystoceles) are uncommon abnormalities of the inferior meatus. These abnormalities may lead to nasal obstruction, respiratory distress, and epiphora. Although approximately 30% of all neonates have distal nasolacrimal duct obstruction at birth, formation of symptomatic cysts occurs only rarely in these children. The duct begins canalization at its lacrimal end and progresses inferiorly. In addition to producing nasal obstructive symptoms, the presence of a nasolacrimal duct cyst also makes neonates susceptible to aspiration and feeding difficulties. Infants with bilateral dacrocystoceles are the most severely affected. In most affected children, obstruction spontaneously resolves by 9 months of age.

The diagnosis of nasolacrimal duct cysts is made by anterior rhinoscopy or nasal endoscopy, which demonstrates a cystic mass in the inferior meatus (Fig. 188-15). This can be confirmed on a CT scan. The classic features evident on imaging are a dilated nasal lacrimal duct, an intranasal cyst, and cystic dilation of the lacrimal sac.[37]

Operative management is indicated for infants who have feeding problems, infection, or respiratory obstruction. The cyst is marsupialized endoscopically into the inferior meatus, opening the lesion with a curette or microsurgical débrider. This is best accomplished by a multidisciplinary team that includes an ophthalmologist, who may need to perform nasolacrimal duct probing and possible placement of nasolacrimal duct stents.

Developmental Errors of the Nasobuccal Membrane

During the third and fourth weeks of development, paramedian ectodermal nasal placodes appear. The nasal placodes, which are two small thickenings in the frontonasal process, begin to burrow, forming nasal pits. As these pits develop into the pouches of the nose and paranasal sinuses, the nasal pouches come to lie above the oral and buccal cavity. The nasobuccal membrane separates the nasal and oral or buccal spaces, and choanal atresia probably derives from failure of the nasobuccal membrane to rupture in the fifth and sixth weeks of development. An alternative theory suggests that abnormal migration of neural crest cells

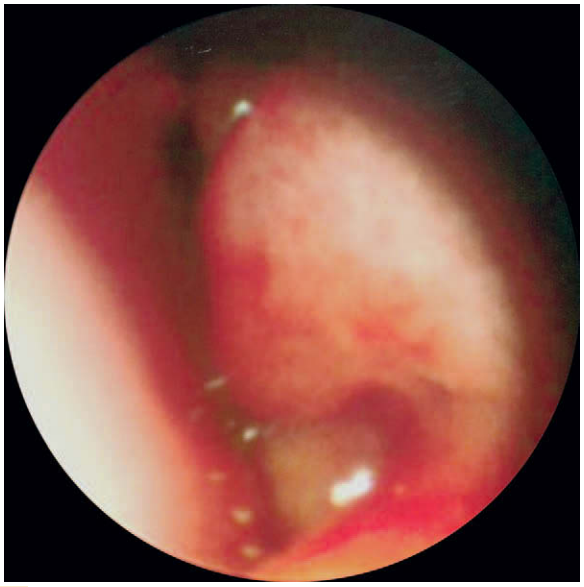

Figure 188-15. Left nasolacrimal duct cyst in the inferior meatus, as seen on anterior rhinoscopy.

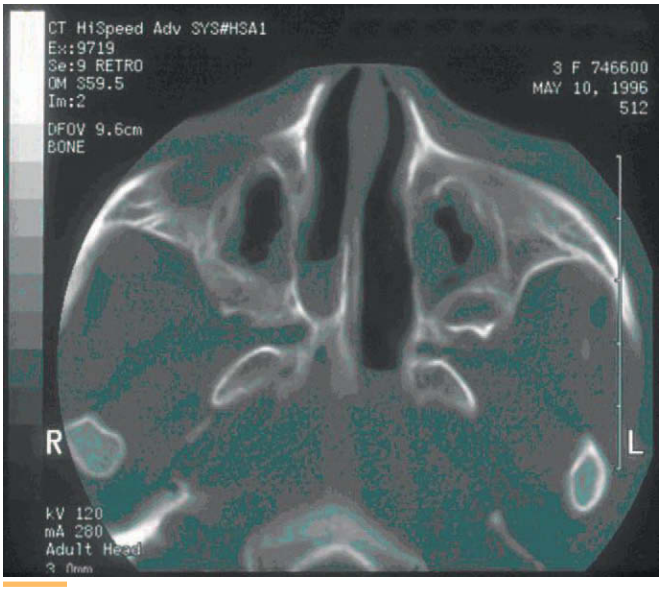

Figure 188-16. Axial computed tomography scan of unilateral choanal atresia, with a complete bony atretic plate and associated soft tissue.

results in choanal atresia. This theory is supported by the high incidence of choanal atresia in patients with mandibulofacial dysostosis (Treacher Collins syndrome), which is associated with abnormal neural crest migration.

Choanal Atresia

Choanal atresia occurs when the posterior nasal cavity fails to communicate with the nasopharynx.[1] This anomaly has a reported incidence ranging from 1 in 5000 to 1 in 8000 live births.[38] Up to two thirds of cases are unilateral, with atresia most commonly occurring on the right side.[1] Fifty percent of all patients with choanal atresia and up to 75% of patients with bilateral disease have other associated congenital anomalies.[2] These anomalies include CHARGE syndrome (*c*oloboma, *h*eart defects, *a*tretic choana, *r*etardation of growth and development, *g*enitourinary disorders, and *e*ar abnormalities); polydactyly; nasal, auricular, and palatal deformities; Crouzon's syndrome; craniosynostosis; microcephaly; hypoplasia of the orbit and midface; cleft palate; and hypertelorism.[39,40] The anatomic features that characterize choanal atresia include (1) a narrow nasal cavity; (2) lateral bony obstruction by the pterygoid plates; (3) medial obstruction caused by thickening of the vomer; and (4) membranous obstruction.[41-43] In a study conducted by Brown and associates,[41] the incidence of pure bony atresia was found to be 29%, whereas that of mixed bony-membranous atresia was 71%. No patients were found to have a purely membranous atresia.

The clinical presentation of choanal atresia varies between unilateral and bilateral disease. Patients with unilateral disease present later in life with rhinorrhea and nasal obstruction. On anterior rhinoscopy, the occluded nasal cavity is typically filled with thick, tenacious secretions. Patients with bilateral choanal atresia typically present as newborns with cyanotic events. An event begins with increasing efforts to breathe, tight mouth closure, and chest retractions followed by cyanosis. The cycle is broken by crying. A variant of bilateral choanal stenosis presents later in life with mouth breathing, recurrent sinusitis, chronic rhinorrhea, otitis media, failure to thrive, and defects of speech.

The diagnosis of choanal atresia is made clinically by failure to pass a 6F catheter through the nose into the nasopharynx (a distance of approximately 32 mm). CT is used to confirm the diagnosis and reveal the nature and thickness of the atresia.[44] Suctioning and pharmacologic vasoconstriction before imaging will improve resolution (Figs. 188-16 and 188-17). CT scanning also differentiates between complete atresia and stenosis. A diagnosis of choanal stenosis is made

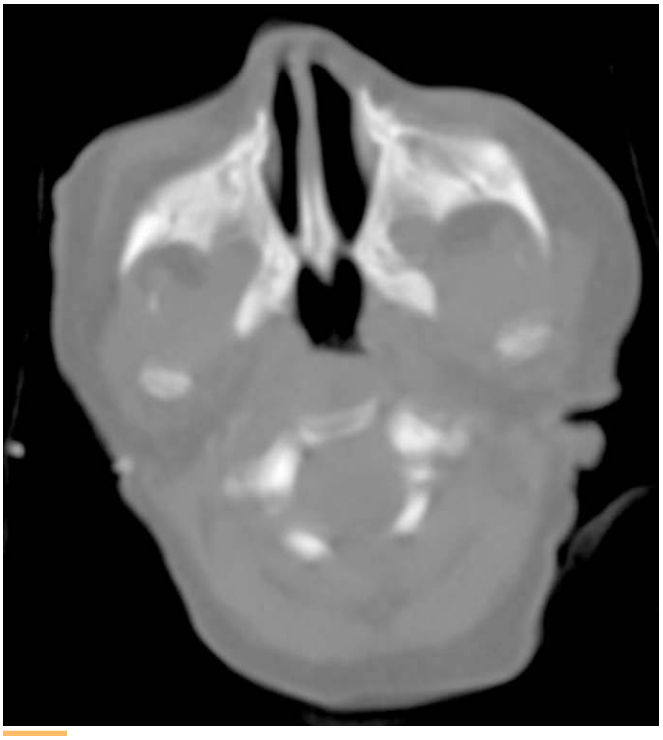

Figure 188-17. Axial computed tomography scan showing bilateral chonal atresia with soft tissue.

with recognition of a narrowed yet patent choana. Derkay and Grundfast[45] more specifically define this entity as a choanal space less than 6 mm across. This diagnosis should be confirmed by endoscopic evaluation (Fig. 188-18).

Unilateral atresia does not constitute an emergency. Treatment is delayed for several months, allowing for growth of the nose, which enhances the ease of surgery and reduces the risk of postoperative complications and restenosis. Bilateral atresia requires an initial intervention to establish an oropharyngeal or orotracheal airway and gastric feeding before definitive surgery. The timing of surgery is variable, and it may be preferable to wait several months until adequate facial growth has occurred (similar to the timing of cleft lip repair). In patients with

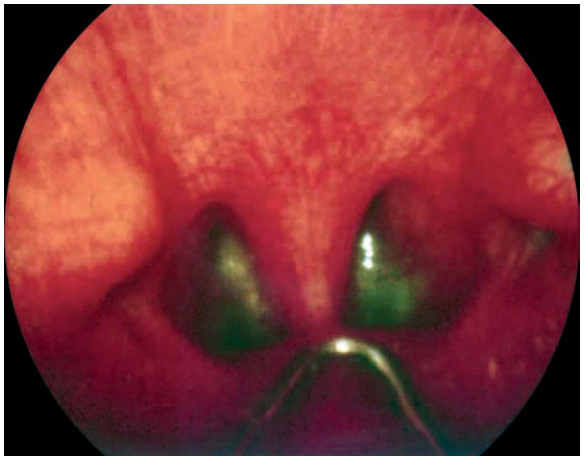

Figure 188-18. A view of bilateral choanal atresia through a 120-degree nasopharyngoscope.

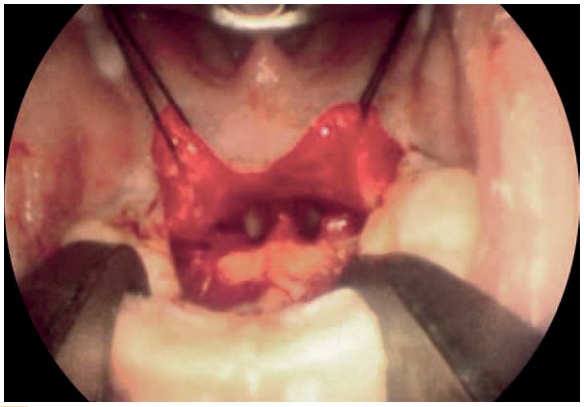

Figure 188-19. Transpalatal approach to choanal atresia repair. A pedicled hard palate mucoperiosteal flap based on the greater palatine artery is elevated to expose the choanae.

additional indications for tracheotomy, a surgical airway is obtained and definitive atresia repair is often delayed, allowing for facial growth. A shift has occurred in the surgical philosophy over the last few decades away from transpalatal (Fig. 188-19) and toward transnasal surgery. This shift can be attributed to reports citing a lower risk of dental and facial growth abnormalities associated with the latter approach. Most techniques begin the repair by perforating the atretic plate at its thinnest portion, using a urethral sound or suction instrument. A 0-degree transnasal endoscope or a 120-degree nasopharyngoscope is used for visualization (see Fig. 188-14). Subsequently, a backbiting forceps, a microsurgical débrider, a laser, and a drill are used as necessary to remove choanal soft tissue and bone. The posterior tip of the middle turbinate is a useful anatomic landmark. Restricting surgical maneuvers to remain inferior to this structure reduces the risk of intracranial injury.[46] The importance of stenting, as well as the use of fibroblast inhibitors (mitomycin C) and the preservation of mucosal flaps, remains controversial. Regardless of the techniques used, most studies[47,48] report significant recurrence rates, necessitating revision surgery. The lowest recurrence rates are seen in older children (with unilateral atresia), nonsyndromic patients, and patients who have undergone surgical procedures that minimize mucosal trauma.

Other Mesodermal and Germline Malformations

Mesodermally derived lesions such as hemangiomas and lipoblastomas may occur in the head and neck, although they rarely occur in the nose. These lesions present unique management challenges to the otolaryngologist or facial plastic surgeon. Similarly, germline malformations such as teratomas rarely localize to the nasopharynx. These foci may be remnants of normal embryologic structures that break off or fail to migrate along well-defined pathways to their normal destination.[49] The management of cutaneous hemangiomas follows principles detailed elsewhere in this text; the unique presentation and management of nasopharyngeal teratomas are described in this section.

Intranasal Hemangiomas

Infantile hemangiomas are discussed more fully elsewhere in this text. As suggested by Waner and colleagues, glucose transporter isoform 1 (GLUT1)-positive infantile hemangiomas have a predilection for embryonic fusion planes on the central face.[50] Thus, deep midface infantile hemangiomas may involve or distort the nasal lining. More typically, the intranasal hemangiomas described in the literature are lobular capillary hemangiomas and reparative cavernous hemangiomas. These noninfantile hemangiomas are GLUT1-negative and have been noted on the septum, the middle and inferior turbinates, and the lateral nasal wall.[51] These lesions frequently manifest with epistaxis and nasal obstruction. On examination, the hemangiomatous masses are friable, sessile or pedunculated, and reddish-purple in color. MRI shows high signal intensity on T2 sequences and enhancement with gadolinium on T1 sequences. CT may show associated bony remodeling. Whereas true infantile hemangiomas are amenable to both surgical and nonsurgical management, lobular capillary hemangiomas and cavernous lesions are treated by wide local excision of the lesion using endoscopic or open (midface degloving, open rhinoplasty, lateral rhinotomy) approaches.[51,52] Preoperative angioembolization has been described for larger lesions. The prognosis is excellent with complete excision.

Nasopharyngeal Teratomas

Teratomas are the most common germ cell tumors of childhood and are almost always benign. These lesions comprise representative tissues from each of the three embryonic germ layers (ectoderm, endoderm, and mesoderm) and generally contain tissues foreign to the anatomic site of origin. Teratomas occurring in infancy and early childhood generally are extragonadal, whereas those manifesting in older children more commonly occur in the ovary or testis.[53] Teratomas of the head and neck account for less than 5% of all teratomas. These rare neoplasms, which reportedly occur in 1 in 20,000 to 1 in 40,000 live births, may be located in the brain, orbit, oropharynx, nasopharynx, or cervical region.

Clinically, nasopharyngeal teratomas may be sessile or pedunculated and often protrude through the mouth. Anencephaly, hemicrania, and palatal fissures are associated with these lesions. The newborn usually presents with severe acute respiratory distress requiring endotracheal intubation or tracheotomy. In patients with smaller lesions, feeding difficulties may be the only presenting symptom.[54]

The diagnosis of congenital nasopharyngeal teratoma begins in utero. Maternal clinical characteristics may include polyhydramnios due to impaired swallowing and elevated α-fetoprotein levels. Larger lesions often are diagnosed by prenatal ultrasound examination. Such early detection enables planning for an EXIT (ex utero intrapartum treatment) procedure to secure the infant's airway before division of the maternal-fetal circulation. For lesions manifesting postnatally, fine needle aspiration may be used to assist in establishing the diagnosis.[54] Imaging is confirmatory. Lesions are seen as cystic and solid areas of fat density on CT and MRI (Fig. 188-20). Areas of bone and tooth formation may be present. Most nasopharyngeal teratomas are well encapsulated and demonstrate no intracranial connections.

The management of nasopharyngeal teratomas is surgical, and the approach depends greatly on the size of the lesion. Lesions can be excised through a transoral approach with or without endoscopic assistance. This approach may require splitting of the soft palate or palatal resection. Endoscopic assistance may obviate the need for palatal division or resection.[49] External approaches using a lateral rhinotomy incision or a transcervical incision also are used. If an intracranial component is present, a craniofacial approach is necessary. Outcomes generally are good, and α-fetoprotein levels are periodically measured to monitor for recurrence.

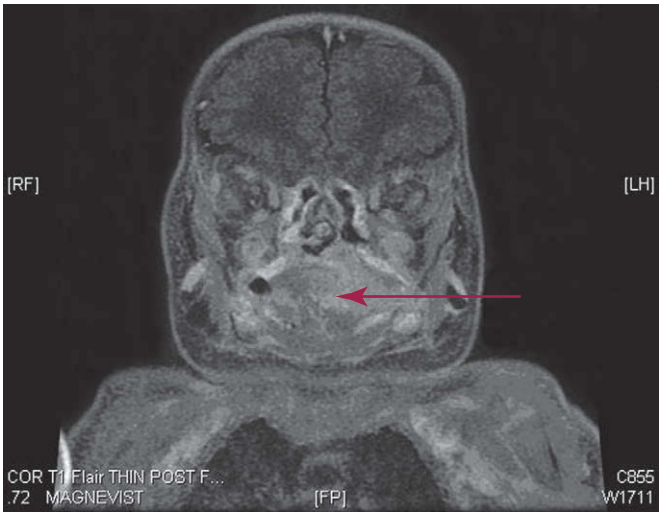

Figure 188-20. Nasopharyngeal teratoma on a coronal magnetic resonance image with characteristic heterogeneous signal intensity *(arrow)*.

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CHAPTER ONE HUNDRED AND EIGHTY-NINE

Pediatric Facial Fractures

Paul R. Krakovitz

Peter J. Koltai

Key Points

- After the first month of life, trauma is the number one cause of pediatric deaths and a major contributor to long-term morbidity.
- Nasal fractures in children are the most common fractures of the facial bones in this age group. Mandible fractures are the most common facial fractures in children requiring hospitalization.
- Pediatric facial fractures often are complicated by associated neurocranial injury.
- Owing to rapid changes in facial dimensions with growth, patterns of fractures differ significantly among various pediatric age groups and between children and adults.
- Fractures to the developing body and ramus of the mandible are less likely to cause growth disturbance.
- Fractures to the developing mandibular condyles and the midface often lead to developmental deformities.
- Rigid fixation with plates and screws is avoided in the management of pediatric fractures unless the original features cannot be restored by simpler, less invasive means. These materials should be used in short segments so that crossing more than one osseous suture line is avoided. Use of resorbable plating systems is confined to non–load-bearing bone.
- After septal hematoma initially is ruled out in the evaluation of a child with a nasal injury, reexamination 3 to 5 days later is indicated to allow time for the resolution of edema. An accurate diagnosis can then be made in regard to a displaced nasal fracture, which if present necessitates reduction. Occult nasoethmoidal fracture is suspected when the clinical findings include marked flattening of the nasal dorsum.
- With internal fixation of fractures of the mandible or maxilla in children younger than 13 years, an understanding of the position of unerupted tooth buds is crucial. In regard to the mandible, monocortical miniplates are drilled in the lowermost margin.
- Maxillomandibular fixation is limited to 2 to 3 weeks and is followed by 6 to 8 weeks of use of guiding elastic bands.
- Delayed periorbital hematoma suggests fracture of the orbital roof.
- With extensive fractures of the orbital floor or demonstrable muscle entrapment, early surgery is appropriate. With more isolated injuries, waiting 7 to 10 days may prevent an unnecessary operation.

After the first month of life, trauma is the number one cause of pediatric deaths and a major contributor to long-term morbidity.[1,2] Nearly 15,000 children die and 100,000 others are disabled worldwide each year from trauma resulting from motor vehicle crashes, sports injuries, falls, altercations, and abuse.[2] More than $15 billion is spent annually in the United States for the treatment of childhood injuries.[1,3] Despite this epidemic of injuries, facial fractures in children remain uncommon.

Reconstruction of pediatric facial fractures requires an understanding of craniofacial development and of the consequences of injury for future growth. The patterns of facial fracture differ significantly not only between adults and children but also among pediatric age groups. Although some of the treatment strategies for facial fractures in adults and children are similar, children need to be considered in a different management algorithm because the repair of bony injuries is best accomplished by techniques that may adversely affect craniofacial development. This dilemma renders the treatment of facial fractures in children controversial. It is not possible to resolve all of the issues related to treatment; however, a rational approach to treatment that yields consistently excellent results can be formulated.

Epidemiology

Pediatric maxillofacial injuries account for approximately 5% of all facial fractures, although the incidence is reported as being between 1.5% and 15%.[4-18] Children younger than 5 years of age account for only 0.9% to 1.2%, whereas those 6 to 14 years of age account for 4% to 6% of all cases of maxillofacial trauma.[19,20] Bamjee and colleagues[19] found that 7% of pediatric traumatic injuries occur in children younger than 6 years, whereas 70% befall those between 13 and 18 years of age, indicating the increased vulnerability of the maturing face as well as the greater risk-taking behavior of a growing child.

In children, males are more prone to maxillofacial fractures than females, with an overall ratio of 1.5:1 to 2.3:1.[18,21-24] In children younger than 8 years, no difference between genders has been noted.[25] With approaching adolescence and greater involvement in sports and violence, the male-to-female ratio approaches 4.5:1.[25] In South Africa,

male children are three times more likely to be involved in violence resulting in facial fractures; however, other types of injuries resulting in facial fractures are gender-neutral.[19] Nasal fractures are the most common fractures of the facial bones in children. Because most nasal fractures are treated in an office setting, precise statistics on their frequency are difficult to determine. Limited studies have reported the incidence to be between 45% and 60% of all facial fractures.[26,27]

Mandible fractures are the most common facial fractures in children requiring hospitalization. Depending on whether nasal fractures are included, mandible fractures account for between 5% and 50% of reported pediatric facial fractures.[1,16,21] The condyle is the most common site, accounting for 40% to 70% of mandibular fractures.[11,18,22,28] Mandibular body (0 to 20% of fractures, depending on the series), angle (3% to 17%), ramus (3% to 10%), and symphyseal fractures (2% to 30%) occur less frequently in young children.[9,12-14,22,25-27,29-37] As adolescence approaches, the incidence of fractures of the arch and body of the mandible reflects a more adult pattern.[38] Dentoalveolar fractures, like nasal fractures, often are treated in an office setting; hence, it is difficult to gauge their true frequency, which probably is higher than the 14% incidence reported in one large study.[29]

Complex facial fractures are rare in children. The literature shows a wide range of anatomic distribution. Reported incidence rates for orbital fractures range from 0.2% to 30%; for zygomatic complex fractures, 2.7% to 13.5%; and for Le Fort type fractures, 0 to 16%.[9,17,26,27,39,40] The sporadic distribution of midface injuries, especially among preadolescent children, highlights their uniqueness and emphasizes how limited a particular surgeon's experience can be with these complex injuries.

Associated injuries are a common feature of childhood maxillofacial trauma. In the pediatric age group, intracranial, intra-abdominal, and orthopedic injuries are associated with more severe types of facial fractures in 30% to 60% of the cases.[8,9,38,41] Temporal bone and soft tissue injuries also are commonly associated with facial fractures.[9] In young children, up to 86% of orbital roof fractures are associated with frontal skull fractures and concomitant intracranial injuries.[7,42] In 30% of orbital fractures, there are other associated facial injuries.[43] These statistics emphasize the importance of a complete initial assessment in children with facial trauma and highlight the dilemma of the timing of repair when medical instability conflicts with the limited period during which optimal reconstruction is best accomplished.

Etiology

In considering the cause of pediatric facial fractures, it is important to understand both the types of traumatic events that result in injury and the unique anatomic features of the child's face. These combined factors predispose children to patterns of injury that are different from those seen in adults.

Motor vehicle collisions constitute the main cause of serious pediatric facial trauma.[4-15,17,18] Fortunately, less than 1% of traffic accidents result in pediatric facial bone fractures.[44] The risk of injury is 1.6 times higher for children who are inappropriately restrained in the vehicle, and children seated in the front seat have nearly twice the risk of fracture as those sitting in the rear seat.[44] Air bags have been shown to decrease the mortality rate in the adult population; however, children younger than the age of 10 years have a 34% increased risk of dying in frontal crashes with air bag deployment.[45] The current recommendations for protection during motor vehicle travel by the American Academy of Pediatrics and the National Highway Traffic Safety Administration are use of child restraints for children weighing less than 40 lb, belt-positioning booster seats for children from 40 to 80 lb and up to 57 inches in height, and lap-shoulder belts for children weighing more than 80 lb and more than 57 inches tall, and placement of children younger than 13 years in the rear seat.[46-48]

Although a majority of serious pediatric facial fractures are incurred in motor vehicle collisions, childhood play is the most common cause of facial trauma (15% to 30%) when all forms of fractures are considered, including orbital, nasal, and dentoalveolar fractures.[49] Bicycle accidents remain an important cause of injury to children, and although wearing helmets has greatly reduced midfacial and intracranial injuries, the current designs of helmets do not protect against mandibular and dentoalveolar injury.[50-53] Other causes include falls (20% to 30%), aggravated assault (8% to 30%), and sports injuries (2% to 30%).* An uncommon cause of facial fracture is trauma from dog bites.[56,57] Isolated orbital fractures most commonly are seen in sports, with violence recognized as a significant risk among those 12 years and older.[43,58] Child abuse deserves special mention. Facial fractures, in particular, of the mandible, can be the result of child abuse.[8,14,33,59] It is important to consider the possibility of child abuse, especially in cases of facial injury among children younger than 5 years, because this is the age group at highest risk for battering.

Both social and anatomic differences account for the disparity in the incidence and in the nature of facial fractures between adults and children. Falls are frequent but generally occur from low heights and involve low speeds, so the likelihood of serious fractures is diminished. Children generally are in a more protected environment than adults that further reduces the risk of major injuries.

Understanding the difference in the patterns of fractures between children and adults requires familiarity with the development of the facial skeleton. At birth, the craniofacial ratio is 8:1, with the face located in a recessed position relative to a large skull. The cranium and forehead effectively shield the smaller lower and middle thirds of the face from injury. By the age of 2 years, the cranium has achieved 80% of its mature size. Facial growth also is rapid during this period, but it is only after the second year that facial growth outpaces cranial growth. Brain and ocular growth are near completion by age 7; however, facial growth continues into the second decade of life.[60,61] In adults, the craniofacial ratio is 2:1.[61,62] The consequence of the higher craniofacial ratio is that the cranium, especially the prominent forehead overhanging the face, absorbs the major portion of the impacting force. This accounts for the higher proportion of pediatric skull fractures relative to facial fractures and the rarity of serious midface fractures in young children, in whom the force necessary to cause major maxillary disruption often results in brain injury and death.[14,35]

Another resilient feature of young children is the makeup of the face with thick soft tissue, lack of sinus pneumatization, and elasticity of the bones. The greater proportion of cancellous to cortical bone explains the higher incidence of "greenstick" fractures in children.[63] The presence of unerupted and mixed dentition in the maxilla and mandible increases the resistance to fracture, although fractures can occur through developing tooth crypts. As the child enters adolescence and adulthood, the concomitant pneumatization of the paranasal sinuses, maturation of the dentition, hardening of bone, and thinning of the facial soft tissues, synchronized with higher-energy injuries associated with increased risk-taking behavior, all lead to a higher risk of fracture.[29,60,64-66]

Emergency Management

The first step in evaluating pediatric facial trauma is to follow the basic principles of trauma management. A primary survey must be made of the child's airway, breathing, and circulation. Airway-securing algorithms should be closely followed. In most cases of isolated facial trauma, careful posturing of the child is adequate. The oral cavity should be cleared of loose teeth and bone fragments, with suctioning of blood and secretions as necessary. In case of mandibular displacement, a midline traction suture on the tongue can help maintain a patent airway.

Orotracheal intubation is necessary in patients with concomitant cranial trauma, severe bleeding associated with midfacial fractures, or oropharyngeal obstruction and posterior retrusion of the mandible. Orotracheal intubation ideally is accomplished after the cervical spine is secured. Optimally, when oropharyngeal or laryngeal injuries are present, intubation is performed in the operating room with rigid instrumentation. "Crash" tracheotomy and particularly cricothyrotomy in the emergency department are ideally avoided in favor of orotracheal intubation. Once the airway is secured, elective controlled tracheotomy can be performed in the operating room when deemed necessary by the extent of injury. In one series of 73 patients with mandibular frac-

*References 12-14, 19, 21, 22, 25, 27, 32, 34, 36, 39, 54, 55.

tures, only one patient required airway control for obstruction; a tracheotomy was not necessary.[14] However, a controlled tracheotomy is a safe option in patients with panfacial fractures and associated major systemic trauma.[38]

Hypovolemic shock can result from the blood loss with injuries to the highly vascular face of a child. This blood loss may be a double threat if the bleeding is into the airway. Standard volume replacement practices should be implemented, along with transfusion of blood products as indicated.

The secondary survey of the head and neck is conducted in an orderly fashion, beginning with the neurologic assessment and proceeding to evaluation of the neck and cervical spine, inspection of the eyes, otoscopy, rhinoscopy, and finally, examination of the face and oral cavity.

Clinical and Physical Evaluation

If at all possible, an accurate history should be obtained, with the focus on the mechanism of injury as well as the energy and direction of the impact. An injury that appears inconsistent with the reported history should raise suspicion of child abuse.

Although cooperation may be limited in young children, the examination of the facial skeleton should begin with inspection followed by manual palpation in an orderly and systematic manner. Suggestive signs of facial fracture can include facial asymmetry, edema, ecchymosis, Battle's sign, "raccoon eyes," periorbital swelling, conjunctival chemosis, epistaxis, trismus, and malocclusion.

Bimanual examination of the facial skeleton begins over the zygomatic arches and systemically proceeds down the face. The examiner feels for asymmetry, tenderness, and crepitation. The forehead, malar eminences, orbital rims, and nasal bones are palpated. The premaxilla should be grasped with one hand and the head stabilized with the opposite hand to check midfacial stability. Further information can be obtained by intraoral digital examination of the maxillary buttresses.

The manual examination of the mandible begins with the palpation of the temporomandibular joints and the external auditory canals with opening and closing of the jaw. The entirety of the mandible is palpated both intraorally and extraorally. The oral examination includes inspection of the hard and soft palate, tongue, floor of the mouth, and dentition. The gingiva is closely examined for ecchymosis and lacerations; the occlusion is inspected.

A complete neurologic examination is important with evaluation of the level of consciousness (using the Glasgow Coma Scale) and of cranial nerve integrity. Particular attention to the sensory function of the fifth cranial nerve and the motor function of the seventh cranial nerve is essential. Ophthalmologic evaluation is important to rule out optic nerve injury, intraocular trauma, and ophthalmoplegia. This should include visual assessment (if possible), ophthalmoscopy, and tests for range of motion, diplopia, and pupillary reflexes. Forced duction testing should be performed with the patient under anesthesia whenever orbital trauma is suspected. The anterior external ear canal wall is inspected for lacerations from a condylar fracture; a hematotympanum may suggest a temporal bone fracture. Anterior rhinoscopy is valuable for evaluation for septal injury, septal hematoma, or cerebrospinal fluid (CSF) rhinorrhea.

Radiologic Examination

Computed tomography (CT) is invaluable in the evaluation of pediatric trauma. Axial and coronal cuts allow for a complete survey of the craniofacial, intracranial, orbital, and facial skeleton. Orbital injuries should be evaluated with 1.5- to 3.0-mm coronal and axial cuts. When the stability of the cervical spine is in question, and in the case of an uncooperative child, coronal cuts may be unobtainable. However, coronal reconstructions are universally available with the software of contemporary CT scanners, and these allow for appropriate preoperative assessment and surgical planning. Three-dimensional CT reconstructions also are routinely available to permit a more global understanding of the injury. Intraoperative findings generally correlate well with radiologic images.

The "gold standard" imaging study for displaying the mandible is the panoramic radiographic view (Panorex). This can be difficult to obtain in a multiply injured or uncooperative child. Alternatively, a plain film such as Towne's view is specific for the condyles. The lateral oblique view displays the condyle, coronoid, ramus, angle, and body. Intraoral projections can be helpful for symphyseal, parasymphyseal, and dentoalveolar fractures. In our experience, the axial CT scans of the mandible are the most useful for documenting mandible fractures in a multiply injured child and are best obtained when cranial and upper facial CT scanning is being performed.

Routine x-ray evaluation for isolated pediatric nasal trauma is rarely useful. Standard nasal radiographs frequently are inaccurate, especially in children whose nasal bones are not fully fused. However, when significant flattening or deformity of the nasal dorsum has occurred, both axial and coronal CT scans should be obtained.

Facial Growth and Trauma

Craniofacial bone growth is a complex process that is incompletely understood, and even less is known about the effects of trauma on this process.[67] See Chapter 184 for a detailed review of facial growth.

It is clear that facial growth is a complex process. What is unclear is the mechanism of control and coordination responsible for overall growth.[68] Practical concepts for the repair of facial fractures in children are based on the known effects of trauma in the growing face, as well as on an understanding of the operational mechanics of facial development (see Chapter 185, Craniofacial Surgery for Congenital and Acquired Deformities). The mandible appears to be generally resistant to abnormalities of growth as a result of trauma, unless its function is altered as a result of injury in or near the TMJ. Early return of mandibular mobility is desirable to facilitate the restorative bony changes that result from normal function.

The nose, nasoethmoidal complex, and maxilla are more prone to growth abnormalities resulting from trauma. This susceptibility probably stems from the minor restorative functional movement to which these bones are subject, the physiologic derangements that result from the fractures, the importance of the septum as a regional growth site, and the vulnerability of the multiple suture sites to scar formation. These factors suggest that basic tenets should be followed in the interfragmentary repair of pediatric fractures:

- Careful restoration of injured soft tissue, particularly the periosteum
- Close attention to septal injuries, with an emphasis on realignment rather than resection
- Reduction of fractures into their stable anatomic locations
- Correct realignment of suture lines
- Minimal periosteal elevation
- Three-dimensional, stable fixation of complex fractures
- Use of bone grafts in rigid fixation as a substrate for growth in areas of bone loss

Rigid Fixation

Controversy still exists over the use of rigid fixation in the developing face. See Chapter 184 for detailed discussion of rigid fixation in children.

With the current state of knowledge, plate fixation should be considered only for children with complex three-dimensional injuries that cannot be repaired by simpler means. Such caution is appropriate for several reasons: Access for plating often requires surgical trauma to facial soft tissues and extensive periosteal elevation, both important factors with potential for adverse alteration of facial growth. Bone is deposited at facial sutures as a result of tension fields across them. Plating across a suture line could potentially convert the sites to compressive fields, resulting in bony absorption. Plate and screw fixation also risks injury to maxillary tooth buds.

Nevertheless, with the recognition that each reconstructive technique has its strengths and its weaknesses, the use of rigid fixation is

Table 189-1

Physical Properties of the Common Monomeric Polymers Currently Used in Fabricating Bioresorbable Plates and Screws

			In Vivo Degradation Time	
Monomer	**Glass Transition Temperature (° C)**	**Flexural Strength (MPa)**	**Strength**	**Mass**
Polyglycolic acid	35-40	320	4-6 wk	6-12 mo
Poly L-lactic acid	60-65	190	6 mo	1-6+ yr
Poly DL-lactic acid	55-60	150	8-12 wk	12-16 mo
Polydioxanone	16	120	4-6 wk	6-12 mo

Adapted from Imola MJ, Hamlar DD, Shao W, Chowdhury K, Tatum S. Resorbable plate fixation in pediatric craniofacial surgery: long-term outcome. *Arch Facial Plast Surg*. 2001;3:79-90.

highly desirable in complex fractures in which the original features are difficult to restore. The alternative of no correction is unacceptable, and the use of interfragmentary wires requires tedious surgery and can lead to reconstruction of uncertain stability. As Rahn[69] has written, "Open reduction of a fracture may sometimes appear to be an aggressive approach. It can be justified when late reconstruction and secondary surgery is avoided. Thus an approach that appears initially to be more aggressive may be more conservative."

Permanent versus Resorbable Plating Systems

As noted, controversy is ongoing regarding the use of permanent plates and screws in the developing face. Although these techniques are excellent for fixation, leaving a metallic foreign body in a growing child has several drawbacks: Transcranial migration of metallic plates is a well-recognized problem.[70-72] Growth disturbances in both animal and human studies have been shown with use of permanent rigid fixation.[41,73-75] Metal hypersensitivity, potential for bone atrophy, interference with CT and MRI, allergy, and palpability all are potential problems with use of metallic plates. Accordingly, many surgeons routinely remove plates once the fracture line is well healed, especially in children.[76-80] However, others suggest that watchful waiting is appropriate and have found the need to remove plates for the aforementioned reasons in approxiamtely 8% of the pediatric population.[81] Of interest, in a rabbit study, Connelly and Smith[82] found that the removal of rigid plate fixation had a more deleterious effect on growth than if the rigid fixation was left in place. An alternative solution to this quandary is the use of absorbable plates and screws, the safety and efficacy of which have been shown by extensive animal research and subsequent use in craniofacial surgery and facial trauma reconstruction.[72,76,83-95] A study using resorbable copolymer in infant minipigs looked for local reaction as well as the complication of passive intraosseous translocation of plates. The investigators found the tissue reaction to be minimal and demonstrated that although the plates were embedded in the growing bone, this did not hinder degradation of the plates or screws.[95] Bioabsorbable plates are reasonable in cost and clinically safe. With experience in their application, resorbable systems are comparable in efficiency to metal plating systems.

The most commonly used craniofacial bioabsorbable materials are high-molecular-weight polyalphahydroxy acids: polylactic acid (PLA), polyglycolic acid (PGA), and polydioxanone (i.e., the suture material PDS) and their copolymers. Lactic acid has two enantiomeric forms: L-lactic acid (PLLA) and D-lactic acid (PDLLA). PLA and PGA are metabolized into carbon dioxide and water and are eliminated by respiration; the degradation products of PDS are excreted primarily in the urine.[93] The absorption occurs initially by hydrolysis and is completed by phagocytosis.[96] The physical properties of the polymers are outlined in Table 189-1.[90] Pure polymers have been shown to have disadvantages in strength, time to degradation, or local tissue reaction.[86,93,96] PGA has the best initial strength properties, equal to those of stainless steel.[97] PGA's mechanical properties are lost in 6 weeks, and resorption is complete within 1 year.[49,57] However, the use of pure PGA has resulted in adverse reactions in up to 60% of cases, including swelling, draining fistulas, and osteolysis.[98,99] In vivo sheep studies have shown that PLLA takes 5 years to resorb.[94] Reports on pure PLLA have demonstrated late tissue responses up to 4 years after implantation.[100]

Current resorbable plating systems take advantage of copolymers of PLA and PGA, which allow for variable duration of adequate mechanical strength and biodegradation time. LactoSorb was the first absorbable system approved by the U.S. Food and Drug Administration (FDA) in 1996, and at present there are five commercially available resorbable plating systems with different properties based on their individual polymer chemistry, as outlined in Table 189-2.[90] Because each plating manufacturer uses slightly different mixtures of copolymers, plate strength, absorption, and ease of handling will differ between the systems. Ideally, the plate used will retain full strength for 4 to 6 weeks, the time it takes for facial fractures to ossify.[101] The absorbable plates currently on the market maintain 60% to 90% of their strength through the 3-month mark.[96]

Complications with resorbable systems are comparable with results with metal plates, with the exception of the potential for long-term translocation with metal implants.[20,90,93,102-104] The most common adverse reactions are transient peri-implant edema and a high rate of temporary visibility or palpability of hardware, both of which resolve with time. Foreign body reaction in the surrounding tissue typically is minimal.[96] To date, the long-term studies on absorbable plating systems have exclusively used LactoSorb, which has a faster resorption time than some of the more recently released systems. Studies have shown that the available resorbable plating systems (1.5- and 2.0-mm screw diameters) provide flexural and tensile strength comparable with that of the microplate titanium systems (1.0- to 1.3-mm-diameter screws).[105] Definitive long-term studies in facial trauma have yet to conclude whether resorbable plates cause problems with growth restriction.

At this time, absorbable plates are not recommended for all types of pediatric facial fractures. As indicated by preliminary data on sagittal split osteotomy plated with absorbable systems, excellent results were obtained without the use of maxillomandibular fixation (MMF) in a 15-month follow-up study.[93] However, the use of absorbable plates in the mandible and "load-bearing" bone is still investigational in children, and long-term results are limited.[90,92] At this time, the indications for the use of absorbable systems in pediatric trauma are in non–load-bearing regions in the upper and middle thirds of the craniofacial skeleton.

From a practical point of view, the main difficulties we have found with use of resorbable plates are in complex midfacial fractures with

Table 189-2

Commercially Available Craniomaxillofacial Resorbable Plating Systems and Their Properties

System with Manufacturer and Date Introduced	Polymer Composition	In Vitro Time	
		Remaining Strength	Complete Resorption
LactoSorb W. Lorenz Surgical Inc., Jacksonville, Florida February 1996	PLLA 82%, PGA 18%	*8 wk*: 70% *12 wk*: 30%	6-12 mo
Macropore Medtronic, Minneapolis,Minnesota July 1998	PLLA (70%, PDLLA 30%	*6 mo*: 90% *12 mo*: 50%	1-3 yr
Bionx Bionx Implants Inc., Bluebell, Pennsylvania December 1998	PLLA 70%, PDLLA 30%	*8 wk*: 90% *6 mo*: 30%	1-2 yr
Resorbable Fixation System Synthes, Paoli, Pennsylvania February 2000	PLLA 70%, PDLLA 30%	*8 wk*: 68% *6 mo*: 30%	1-6 yr
DeltaSystem Stryker-Leibinger, Kalamazoo, Michigan March 2000	PLLA 85%, PDLLA 5%, PGA 10%	*8 wk*: 81% *6 mo*: 50%	1.5-3 yr

PDLLA, poly-DL-lactic acid; PGA, polyglycolic acid; PLLA, poly-L-lactic acid.
Adapted from Imola MJ, Hamlar DD, Shao W, Chowdhury K, Tatum S. Resorbable plate fixation in pediatric craniofacial surgery: long-term outcome. *Arch Facial Plast Surg*. 2001;3:79-90.

marked comminution or "cornflaking" of the bone. In such cases, the relatively large size of the resorbable instrumentation (especially the screws) makes fixation of multiple small fragments awkward and often impracticable. For similar reasons, problems with use of these devices also are on the infraorbital rim and in the nasoethmoidal area. Further evolution of resorbable plates and screws toward smaller, more refined sizes should improve their practicability for the rare highly comminuted midfacial injuries.

Maxillomandibular Fixation

In decisions regarding techniques to achieve MMF, primary considerations include the age and development of the teeth. In children who lack teeth or in whom the poor retentive shape of the deciduous teeth makes the use of arch bars and interdental wiring impractical, alternative methods of MMF need to be considered. Fortunately, 2 to 3 weeks of mandibular immobilization in children younger than 12 years is adequate.[38,106]

One approach is the use of an overlay acrylic mandibular splint held in place by circum-mandibular and transnasal wires. The splint's occlusal surface is placed in normocentric relation to the maxilla, and immobilization is accomplished by suspending a wire from the piriform aperture and tightening it around the mandibular midline wire that is holding the splint to the mandible (Fig. 189-1).

An alternative technique that adds more interocclusal stability is the placement of resorbable screws in the symphysis at the inferior border as well as that of the zygoma. The monofilament suture is tied between the two screws, thus avoiding the need for a circum-mandibular suture. The use of this MMF method in teenagers and adults is not advised, owing to the higher forces generated by the masticatory muscles.[107]

In children between the ages of 2 and 5 years, the deciduous incisors have firm roots, and if the deciduous molars have formed, they can be used for cap splints or arch bars. In general after age 10, the development of permanent teeth provides for safe anchors.[29] However, children develop at different rates, and the strength of the teeth should be carefully examined before the placement of any type of MMF instrumentation.

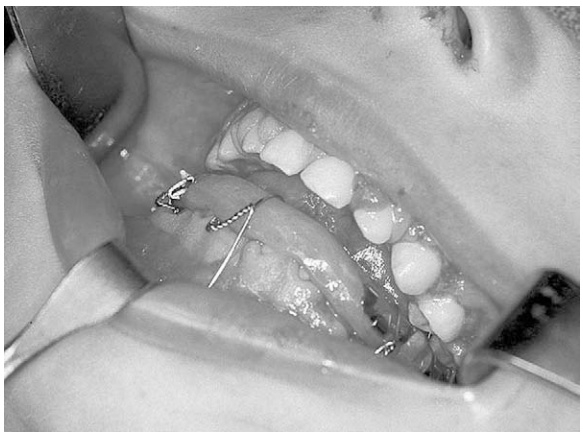

Figure 189-1. Circum-mandibular wires holding an acrylic splint in place in a 3-year-old child with a fracture of the body of the mandible, right side.

Surgical Approaches

Miniplate and microplate screw fixation systems have made open reduction with internal fixation (ORIF) the preferred method of treatment for midface fractures. The entire facial skeleton can be accessed and reconstructed using a combination of six incisions, which allows for rigid interfragmentary fixation of the entire midface[108] (Figs. 189-2 to 189-6). The *bicoronal* incision provides exposure of structures of the upper third of the face, including the zygomatic arches; lateral, medial, and superior orbital rims; and the nasoethmoidal region. The bicoronal

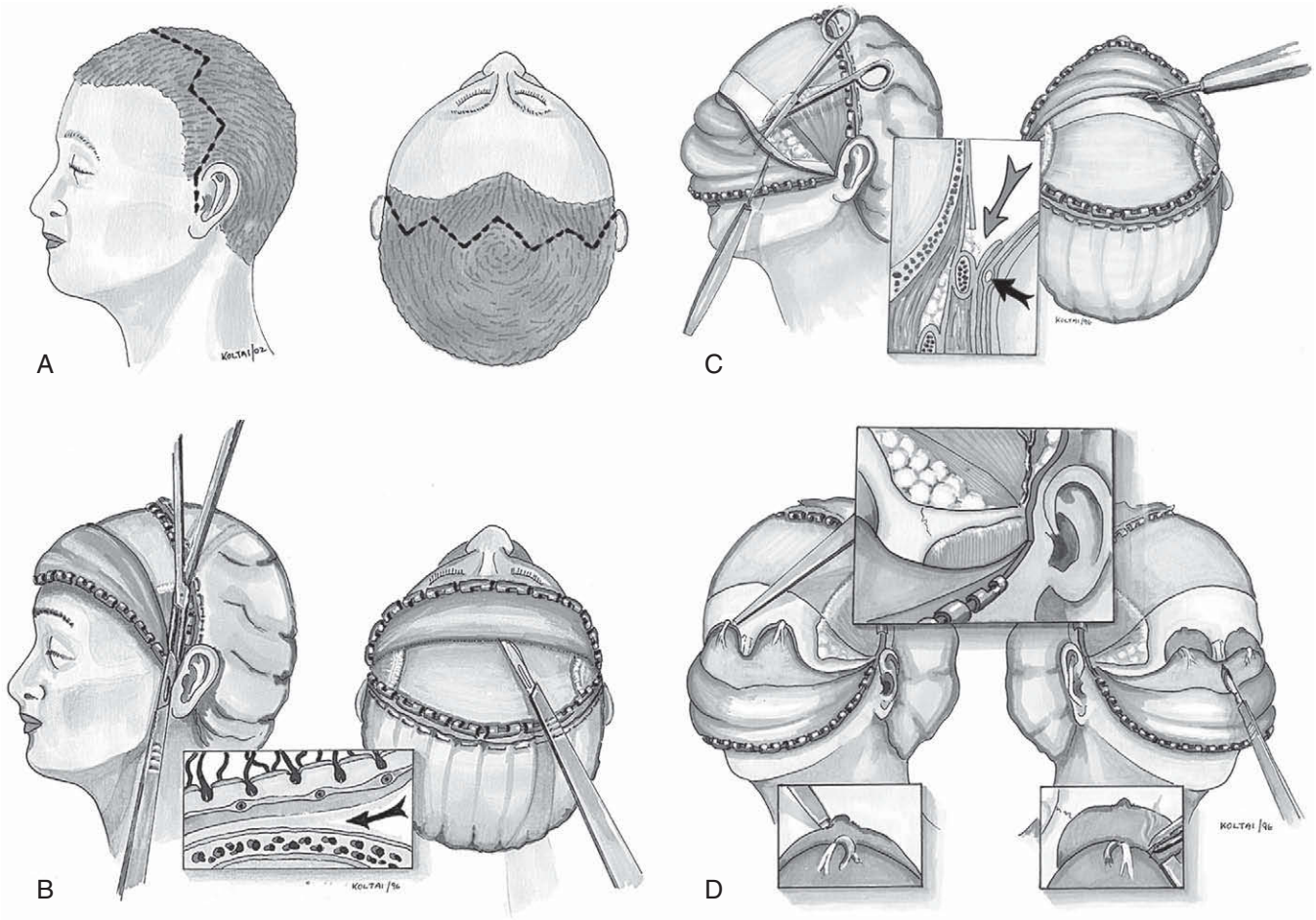

Figure 189-2. **A,** The incision line for coronal exposure begins in the preauricular crease above the tragus, enters the hairline above the attachment of the helix, and traverses the cranium 4 to 6 cm behind the hairline. The "stealth" modification of the traditional coronal incision leaves a broken-line, less visible scar. This technique also avoids parting of wetted hair along the incision line, a common postoperative complaint after repair using the traditional approach. **B,** The incision is carried down to the calvarial periosteum medially, which is contiguous with the deep temporal fascia laterally. The flap is elevated with a knife or blunt finger dissection in the subgaleal plane *(inset)*. Over the temporalis muscle, blunt dissection with a hemostat or scissor is used to develop the plane between the fascia and scalp. The scalp is incised over the instrument to prevent penetration of the deep temporal fascia, which will result in bleeding. **C,** Medially, the subgaleal dissection ends 2 cm above the supraorbital rims. The periosteum is incised, and dissection continues subperiosteally. Laterally, the temporal fat pad can be seen under the deep temporal fascia. The fascia is incised and dissection proceeds between the fascia and the fat pad, protecting the frontal branch of the facial nerve (*black arrow* on *inset*), which lies within the overlying temporoparietal fascia. **D,** The superior surface of the zygoma is exposed through sharp dissection of the periosteum, beginning at the temporal root of the arch *(upper inset)*. Medially, the supraorbital neurovascular bundle is released from its foramen using an osteotome or drill *(lower left inset)*. The medial orbit is exposed with blunt dissection and the anterior ethmoid neurovascular bundle, if still intact, is divided after bipolar cauterization *(lower right inset)*. A relaxing incision of the periosteum over the nasal dorsum allows for greater exposure. *(Reprinted with permission.)*

approach, which is subperiosteal over the cranium and subfascial over the temporalis muscle, permits access to the superior and medial orbital rims. Orbital roof and nasoethmoid exposure can be obtained by mobilizing the supraorbital neurovascular bundle. Detachment of the temporalis fascia from the lateral orbital rim and zygomatic arch reveals the bones of the entire upper face from the zygomatic root on one side completely around to the other. The exposure provides a means to realign and rigidly fix the frontozygomatic suture, the entire zygomatic arch, and the nasal bones. It also allows for harvesting of cranial bone grafts for orbital reconstruction and cantilever nasal reconstruction in complex nasoethmoid fractures. The inferior orbital rims and floor can be exposed by either a subciliary or transconjunctival incision. The medial orbit and apex can be exposed by a *transcaruncular* approach. The *gingivolabial sulcus* approach provides access to the entire maxilla, laterally to the malar bone and zygoma, anteriorly to the infraorbital nerve, and medially up to the lacrimal fossa. The exposure provides for the reestablishment of both the lateral zygomaticomaxillary buttress and the medial nasomaxillary buttress. The entire nasoethmoidal region can be exposed by a *midfacial degloving* incision.

The sequencing of procedures for repair of severe midfacial fractures, especially when the mandible is fractured, is important. Reestablishing occlusion by MMF and repair of the mandible establishes a solid base for upper face reconstruction. Different strategies with respect to the sequencing of maxillary fractures have evolved (Fig. 189-7). Traditionally, the external frame of the face is realigned, and then the work proceeds toward the central core. This approach emphasizes control of the facial width and projection, which is the function of the zygomatic arch.

Other reconstructive strategies emphasize the use of the anterior cranial base as a template for the midfacial reconstruction. This sequencing begins with reconstruction of the frontal bone to which the relations of the nasoethmoidal regions, orbit, and outer facial frame are reestablished. Reconstruction is then completed by connection of the midface to the occlusal unit at the Le Fort I level.

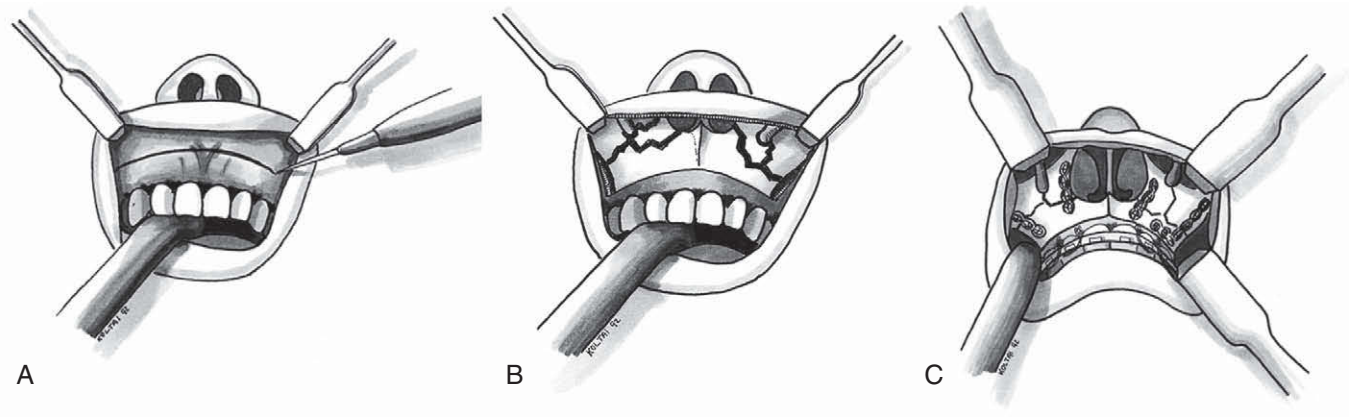

Figure 189-3. **A,** Using needle cautery, a maxillary gingivolabial sulcus incision is created, leaving a 3-mm cuff of tissue on the gingival side to facilitate closure. **B,** Fractures of the anterior and lateral buttresses have been exposed. **C,** The buttresses have been reduced and plated. *(Reprinted with permission.)*

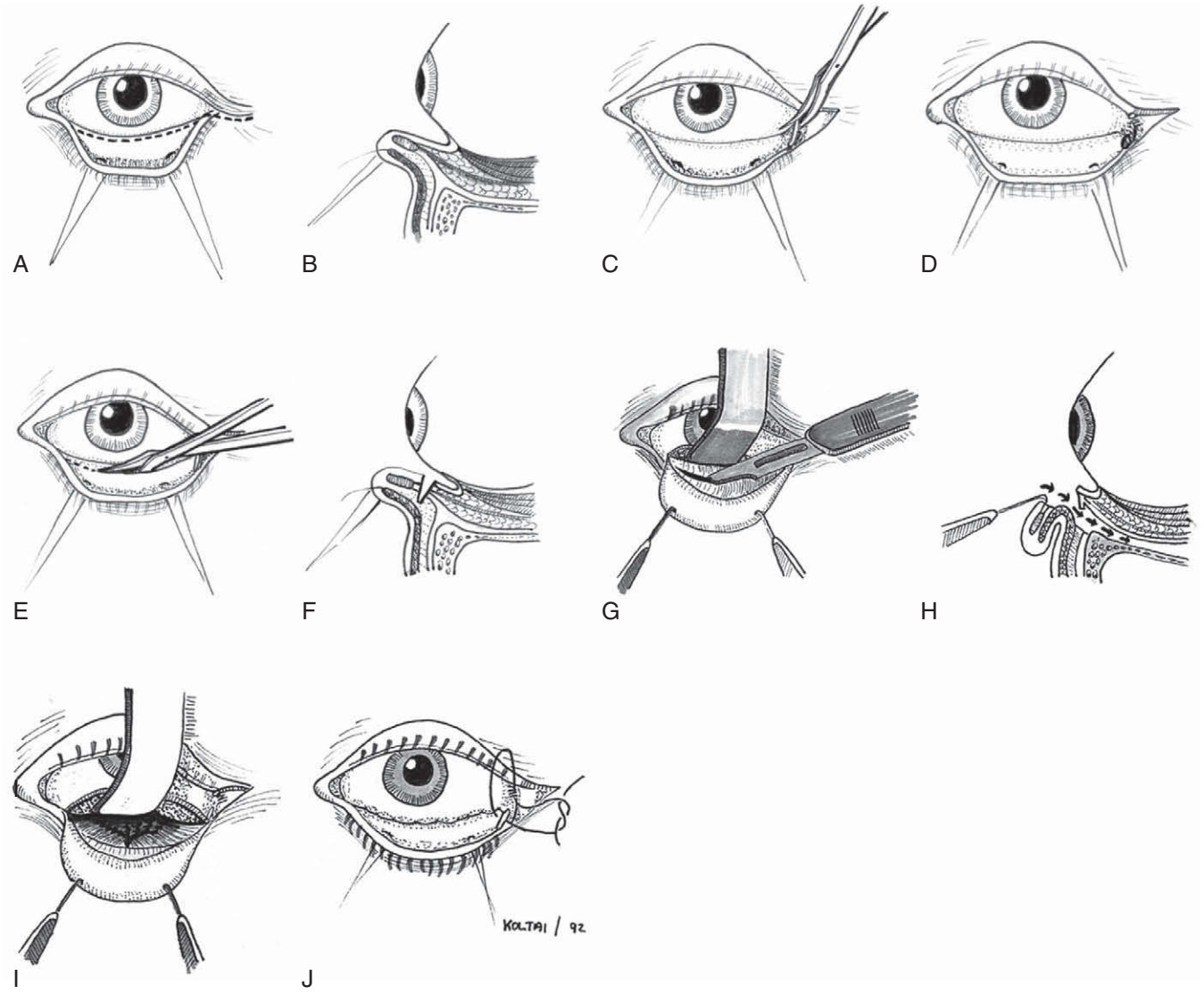

Figure 189-4. **A** to **F,** After traction, sutures are placed in the lower lid, and a lateral cantholysis is performed. Through the lateral canthotomy, sutures are introduced in the subconjunctival plane and blunt dissection proceeds inferior to the tarsal plate and medially up to, but not past, the lacrimal punctum. The conjunctiva is then incised below the tarsal plate **(E)**. The dissection can proceed in a preseptal or postseptal plane. **G** to **J,** The periosteum on the orbital rim is exposed and incised, allowing access to the floor. The procedure for closure consists of placement of running sutures of 6-0 chromic for the conjunctiva and 5-0 polydioxanone for repair of the cantholysis. *(Reprinted with permission.)*

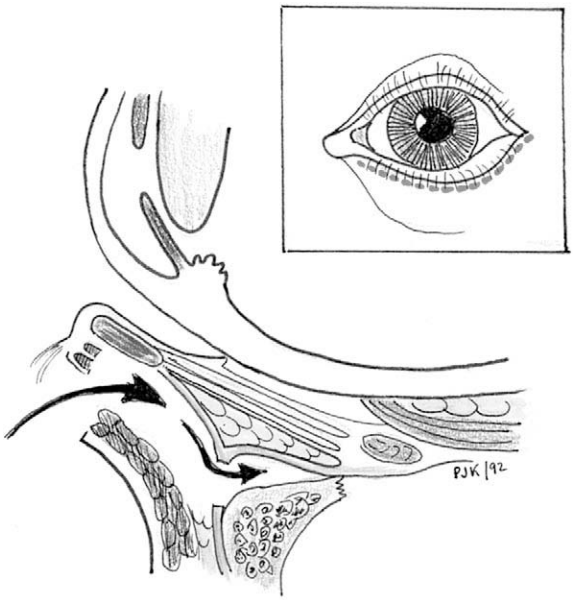

Figure 189-5. The subciliary incision is made 1 to 2 mm inferior to the lashes, through the skin and the orbicularis muscle. The plane of dissection is between the orbicularis muscle and the orbital septum. The periosteum is incised at the orbital rim, and the floor of the orbit is exposed. *(Reprinted with permission.)*

Our own approach to pediatric injuries is based on the recognition that the face is composed of component units connected by their associated buttresses and that the most prominent and most challenging aesthetic unit is the nasoethmoidal area. First, occlusion is established, and if necessary, the mandible is repaired. The central core is then reconstructed, followed by positioning of the orbits and the outer facial frame to the central core (Fig. 189-8).

Surgical Reconstruction

Fracture of the Mandible

Bicycle accidents, motor vehicle collisions, and falls are the most common source for mandibular fractures in children.[109] Greenstick injuries are more frequent in young children because of the presence of unerupted teeth, which increases density of bone, and a higher percentage of cancellous bone, which increases the elasticity.[110] Fractures through developing tooth crypts risk the maldevelopment as well as the devitalization of the respective teeth.[111]

The technical goal of repair in pediatric mandibular fractures is to restore the underlying bony architecture to its preinjury occlusion, tempered by the age-specific development of the mandible and the variable dentition. Before the age of 2 years, the eruption of the deciduous teeth is incomplete. From 2 to 5 years of age, the deciduous incisors and molars have firm roots. In children 5 and 9 years of age, resorption of the deciduous roots and incomplete eruption of the secondary dentition are characteristic. After 10 to 12 years of age, most children have a healthy complement of secondary dentition.

Complications of pediatric mandibular fractures include infection, nonunion, malunion, malocclusion, and TMJ dysfunction. Injuries to teeth in the fracture line account for 7% to 50% of all mandibular fractures.[18,112,113,] Post-traumatic ankylosis of the condyle is a rare but significant complication associated with injury in children younger than 3 years and those in whom MMF was prolonged.[122] One study showed a significant decrease in the vitality of teeth in proximity to fractures of the mandible treated by plates, which the investigators speculated was due to periosteal elevation and increased manipulation of bony fragments.[114] Several adult studies have shown an increased infection rate when teeth in the line of fracture are extracted during open repair.[115-119]

Condylar Fracture

Condylar fractures can be classified into three anatomic types. The first two are intracapsular and include crush-type fractures of the condylar head and high condylar fractures through the neck above the sigmoid notch. Before the age of 6 years, there is a preponderance of intracapsular fractures.[109] The third and most common type is a low or subcondylar fracture, often of the greenstick variety (Fig. 189-9). This fracture type is extracapsular and occurs from the sigmoid notch back toward the posterior ramus. The age discrepancy probably is related to anatomic development. When an injury occurs in a young child, the thickness of the condylar neck and the flexibility of the mandible direct the force toward the condylar head. Furthermore, children younger than 6 years are more likely to have other, systemic injuries concurrent with a mandible fracture.[14]

The condyle is an important site of mandibular growth, and controversy exists in the literature about the long-term issues surrounding preadolescent condylar fracture.[38] Lindahl and Hollender[120] showed that remodeling of the condyle after fracture resulted in normal anatomy in children aged 3 to 11 years but occurred to a lesser extent in adolescents and was minimal in adults. These findings have been the basis for the theory that younger children have fewer long-term problems.[10] However, more than one third of patients with arrested condylar development have a history of facial trauma.[121] Although most children heal without functional impairment,[122,124-126] multiple studies have demonstrated that between 5% and 20% of children with condylar fractures subsequently have some degree of functional or radiologic deformity.[13,16,32,122-124,127-129] Therefore, prolonged follow-up is mandatory, and orthodontia may be an important adjunct in the long-term management of condylar fractures.[38]

Clinical and experimental observations support a conservative, closed approach to the management of most pediatric condylar fractures. Although open surgical treatment is advocated by some experts, the primary decision is not whether to perform open reduction of the fracture but whether the child will need immobilization with MMF. Most unilateral and some bilateral condylar fractures will manifest with normal occlusion and mobility. A soft diet and movement exercises are all that is needed. Condylar fractures manifesting with an open bite, mandibular retrusion, or movement limitation are best treated with 2 to 3 weeks of immobilization. Early and persistent movement with an elastic jaw exerciser generally prevents the development of ankylosis and aids in restoring function (Fig. 189-10).

The indications for an open surgical approach to repair of pediatric condylar fractures are quite limited, and the procedure is reserved for the displacement of the condyle into the middle cranial fossa or interference with jaw mobility.[122] These circumstances are best approached with either a preauricular or submandibular approach, depending on the location of the fracture (Fig. 189-11).

Symphyseal and Parasymphyseal Fractures

Approximately one third of condylar fractures will have an associated symphyseal fracture.[109] With symphyseal and parasymphyseal fractures, the submental musculature exerts a downward and retrusive force, causing displacement of the fractured segments. These fractures with minimal to moderate displacement often can be realigned with careful manual manipulation of the patient under anesthesia and immobilized by the methods described for pediatric MMF.

The decision to treat with soft diet, MMF, or ORIF is best made on the basis of the degree of disruption in the fracture and the extent of occlusion change. The problem with MMF is that reducing the fracture on the side of the dentition (tension surface) often will result in distraction of the lower border (compression surface) of the mandible. To better reduce serious displacement, ORIF of the fragments is required. These midline areas are readily exposed using an intraoral approach. The lower border can then be reduced by wire fixation or by monocortical reconstruction with miniplates (Fig. 189-12). With both techniques, great care must be exercised in drill hole placement to prevent injury to the developing tooth buds (Fig. 189-13). Once preinjury occlusion has been established, a minor degree of osseous gap at the fracture site is of less consequence in the bony healing of pediatric mandibular fractures.[38] With both miniplate reconstruction and inter-

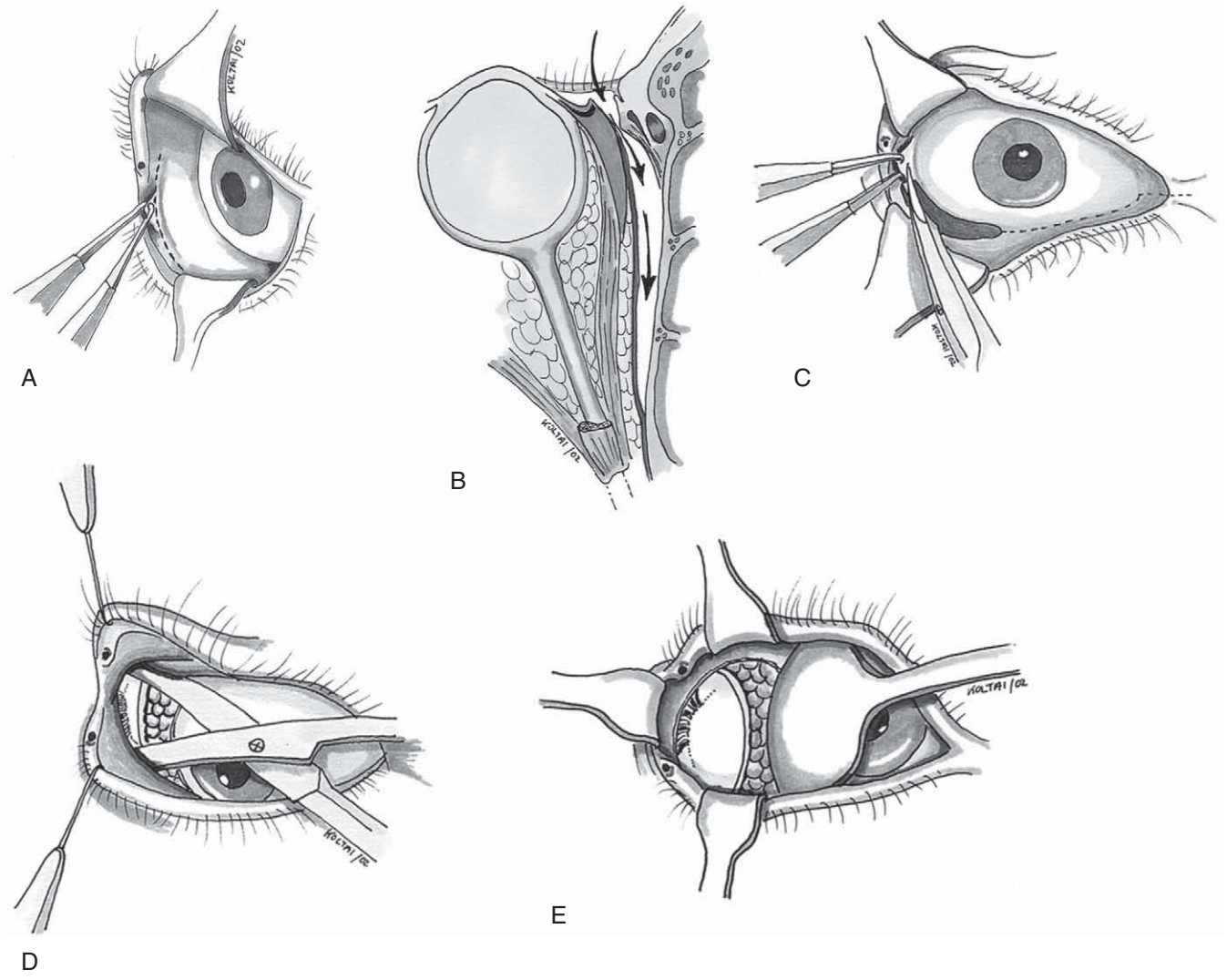

Figure 189-6. Transcaruncular approach. **A** and **B,** After retraction of the medial lid margins, the caruncle is incised along with the medial aspect of the superior and inferior conjunctival fornices. The incision can be continued into a transconjunctival approach with lateral canthotomy to expose the entire medial, inferior, and lateral orbit (*dotted line* in **A**). **C,** Blunt dissection in the plane between Horner's muscle medial and the orbital septum laterally is carried to the posterior lacrimal crest (*dotted line*). **D,** The periorbita is incised behind the posterior lacrimal crest; wide subperiosteal elevation exposed the medial orbital wall. **E,** Superior view of the orbit demonstrates the plane of dissection to gain wide exposure of the medial orbit to the apex. *(Reprinted with permission.)*

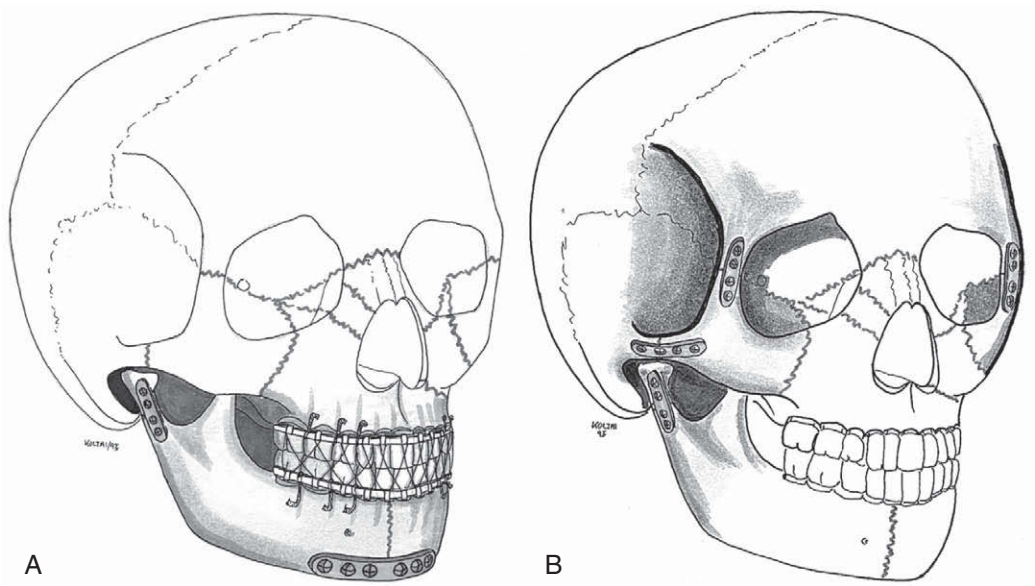

Figure 189-7. **A,** Bottom-up approach. Traditional sequencing begins with reconstruction of the occlusion and the mandible, which then serves as a template for the upper face. **B,** Outside-in approach. The outer facial frame is reconstructed with emphasis on the zygomatic arches, to narrow and project the face. *(Reprinted with permission.)*

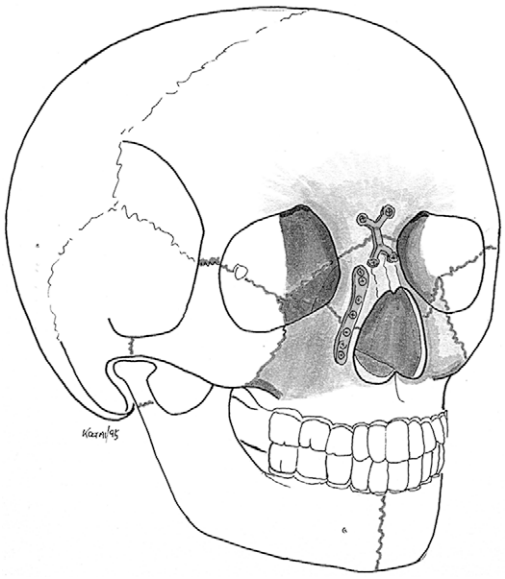

Figure 189-8. Inside-out approach. Reconstruction begins with the central core of the face, using the anterior skull base as the template, with the goal of improving the accuracy of the repair of the aesthetically most significant component of the face. *(Reprinted with permission.)*

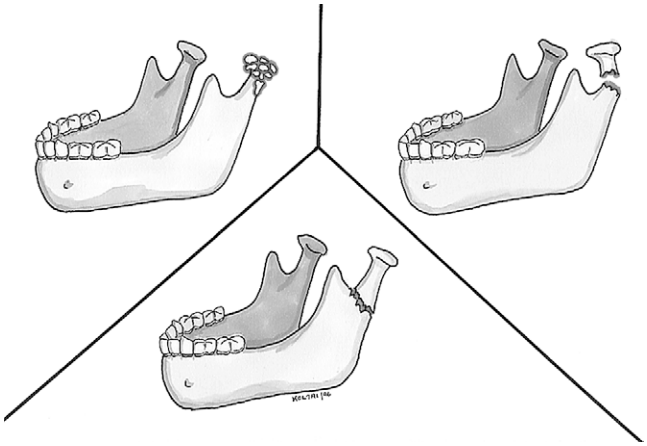

Figure 189-9. Three types of condylar fractures in children: crush injuries of the condylar head, high condylar fractures of the neck, and low subcondylar fractures. *(Reprinted with permission.)*

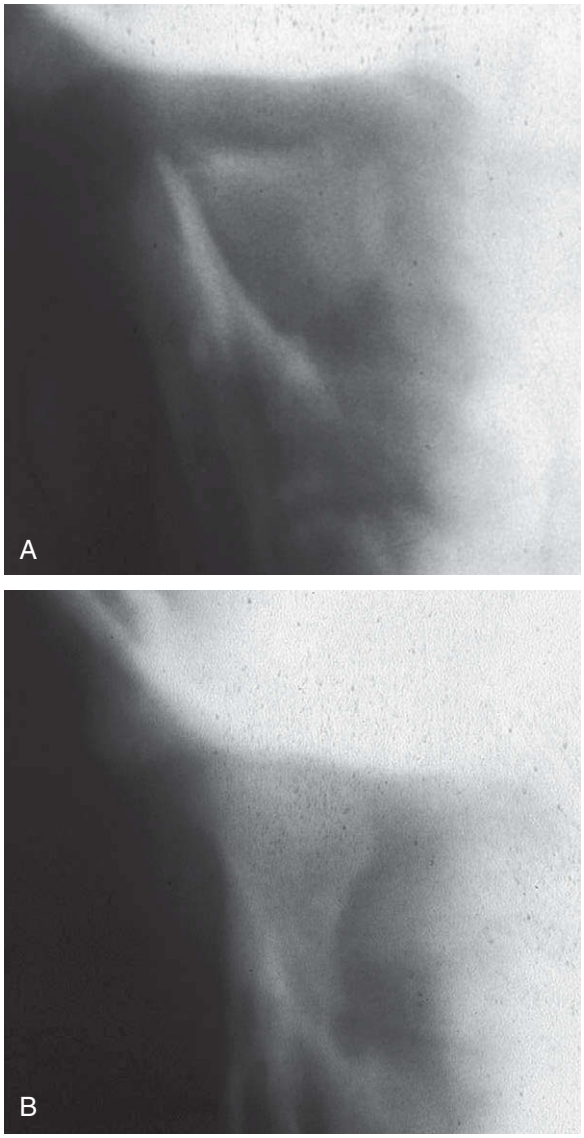

Figure 189-10. **A,** Polytomogram obtained in a 5-year-old child with a right subcondylar fracture, showing medial displacement of the condyle into the infratemporal fossa. The child was minimally symptomatic and treated only with analgesics, a soft diet, and range-of-motion exercises. **B,** Polytomogram obtained in the same child 6 months later, with the condyle restored to its normal position.

osseous wiring, a brief period of 2 to 3 weeks of MMF is required. In children with full, permanent dentition, the principles of bicortical, compression plate reduction are applicable.

Currently, absorbable plating systems in pediatric mandible fractures are not routinely used, nor are they FDA approved for this application.[90]

Angle and Body Fractures

Fractures of the body and angle frequently are monocortical greenstick fractures. Children with these injuries typically have normal occlusion and jaw movement. Treatment with soft diet, analgesics, and observation is appropriate. When the fracture components are displaced, treatment will depend on the availability of dentition, the directions of muscle pull, and the degree of distraction. For distracted body fractures, MMF with elastic traction usually is adequate. However, if misalignment of the lower border cannot be controlled in a conservative manner, then ORIF and the placement of monocortical miniplates will be necessary. The open reduction of posteriorly placed body fractures may require an external approach. However, the transcutaneous sleeve with improved plate holding instrumentation has made intraoral reduction technically simpler (Fig. 189-14).

Dentoalveolar Fracture

Falls and play accidents are the most common cause of dentoalveolar injury.[130,131] These fractures constitute dental emergencies because salvage of the traumatized bone segment and teeth requires prompt reimplantation. Isolated loss of the deciduous teeth without bone is not a problem; however, identification of tooth type, particularly during a period of mixed dentition, is difficult for practitioners unfamiliar with pediatric dentition. The maxillary incisors are the most commonly injured primary and permanent teeth, accounting for approximately 85% of dental injuries[130] (Fig. 189-15). Tooth luxation and concussion are more common in younger children, whereas crown fractures with dentin exposure are more common in children with permanent dentition.[131] Treatment is directed at arranging for immediate, definitive care of the child by a dentist. In the interim, the tooth is gently cleansed

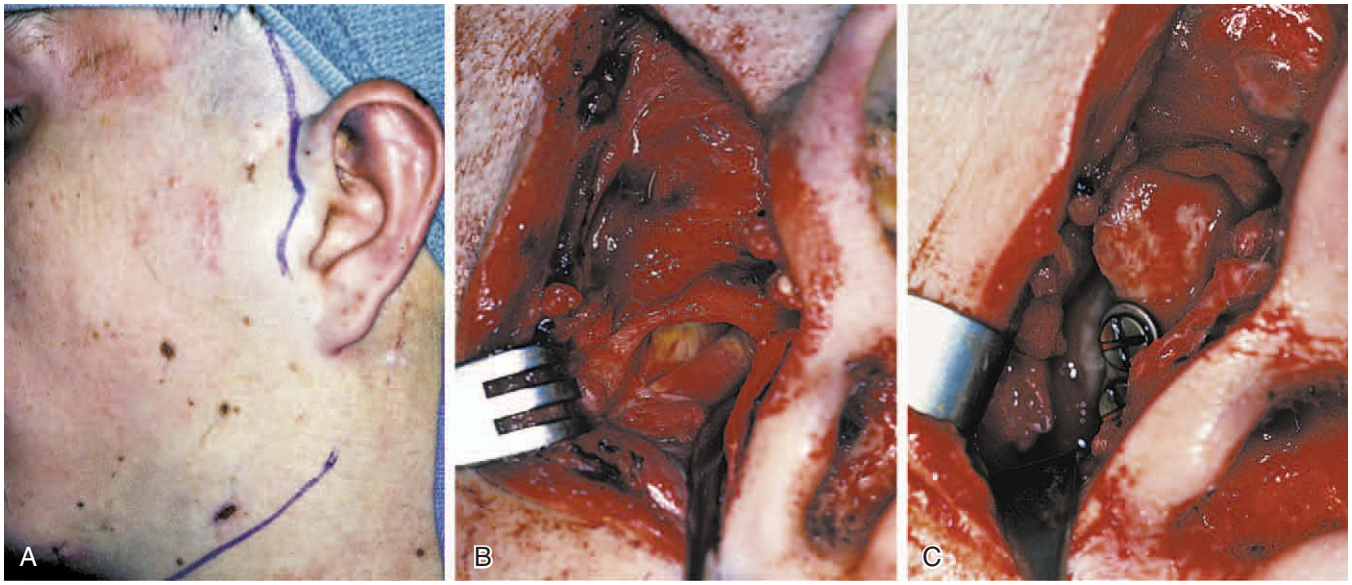

Figure 189-11. **A,** Surgical approach to a left subcondylar fracture in a 14-year-old adolescent male. **B,** Exposure of the temporomandibular joint with an empty glenoid fossa due to medial displacement of the condylar head. **C,** Open reduction and internal fixation of the condyle with titanium plates and screws.

with saline and handled by the crown. If possible, the tooth is replaced in the socket. However, if the child is uncooperative, then the tooth should be kept in saline-soaked gauze or a bowl of milk until a dentist can reimplant and stabilize the tooth. Every effort should be made to have the tooth reimplanted within 1 hour; beyond this time, tooth viability is less likely.

When an alveolar fracture is associated with a tooth fracture, treatment is more problematic. Tanaka and colleagues[15] found that dentoalveolar fractures were associated with the highest incidence of subsequent malocclusion among pediatric fractures. The problem often involves avulsed teeth, fractured roots, and displaced bone. Proper repositioning of the fragments can be very difficult, although reduction should be attempted. Prolonged periods of MMF often are required to maintain these fragments. Occasionally, stabilization with miniplates can be of some help if the bone is large enough to accept screw fixation and surgical space is adequate to avoid injuring healthy surrounding roots. A common outcome is loss of all of the components of a dentoalveolar fracture, despite aggressive measures.

Midface Fracture

Midface fractures in all age groups are described by the Le Fort classification. *Le Fort I fractures* separate the palate from the maxilla, extending through the floor of the nose, maxillary sinus, and the pterygoid plates. *Le Fort II fractures* separate the central midface from the cranium, extending through the pterygoid plates, along the lateral and anterior maxillary walls, the medial orbital wall, and the nasofrontal suture. *Le Fort III* fractures separate the entire face from the cranium extending through the zygomatic arch, frontozygomatic suture, lateral orbital wall, medial orbital wall, nasofrontal suture, septum, and the pterygoid plates.

Le Fort I fractures are rarely seen until approximately the age of 10 years, when the maxillary sinuses are well developed and the permanent teeth begin to descend.[132] In our experience, fractures in children rarely follow the typical Le Fort patterns of injury. Palatal fractures are more common in the pediatric midface injury due to incomplete fusion at the midline suture.[133] Manson[49] and Koltai[134] and their colleagues proposed a classification of midface fractures that is a simple and accurate preoperative tool. The classification, based on the energy of the impacting force, confirms that CT accurately defines the pattern of fracture and generally is the best guide for the extent and intensity of the reconstruction. Type I injuries are minimally displaced; type II fractures are moderately displaced, with some comminution; and type III fractures are severely displaced, with multiple comminution of the buttresses, resulting in a highly unstable injury that requires three-dimensional reconstruction and bone grafting.

Midface fractures in children are rare and manifest clinically with severe facial edema, prominent orbital ecchymosis, and malocclusion. Concomitant neurocranial injuries are frequent, because a force great enough to fracture the midface often will be transmitted intracranially. Axial and coronal CT scanning is indispensable for properly assessing the severity and degree of bony displacement and in developing a surgical plan. A team approach for care, including the expertise of pediatric intensivists, neurosurgeons, ophthalmologists, and anesthetists, is essential. Early operative intervention is ideal; however, this may not be possible owing to the medical condition of the child. Significant fracture displacement should be reduced within 10 days because of the high osteogenic potential of the periosteum and the growth centers; otherwise, rapid interfragmentary healing makes late correction difficult.[135] Acute reduction should be considered when fractures are accessible through open wounds.

The goals of therapy are to reestablish facial symmetry, appropriate occlusion, and normal three-dimensional proportions. Injuries with minimal or no displacement do not require correction. Active intervention is necessary when displacement has altered form or function (Fig. 189-16).

Zygomaticomalar Complex Fractures

Zygomaticomalar complex fractures correspond to the maxillary sinus pneumatization and are uncommon in children younger than 5 years. The frontozygomatic suture tends to be weak in children and easily displaced. Compared with those in adults, zygomaticomalar complex fractures in children tend to involve the lateral wall and orbital floor more extensively.[133,136] It is important to recognize orbital symptoms, including diplopia with ocular restriction and enophthalmos, signaling the possibility of an orbital floor fracture. Zygomaticomalar complex fractures can be classified by the patterns seen on CT scans, which generally correlate with the energy of the impacting force. Greenstick fracture with minimal displacement from the suture lines is typical with lower-force injuries. High-impact injuries lead to various degrees of disruption and comminution of the infraorbital rim, anterior

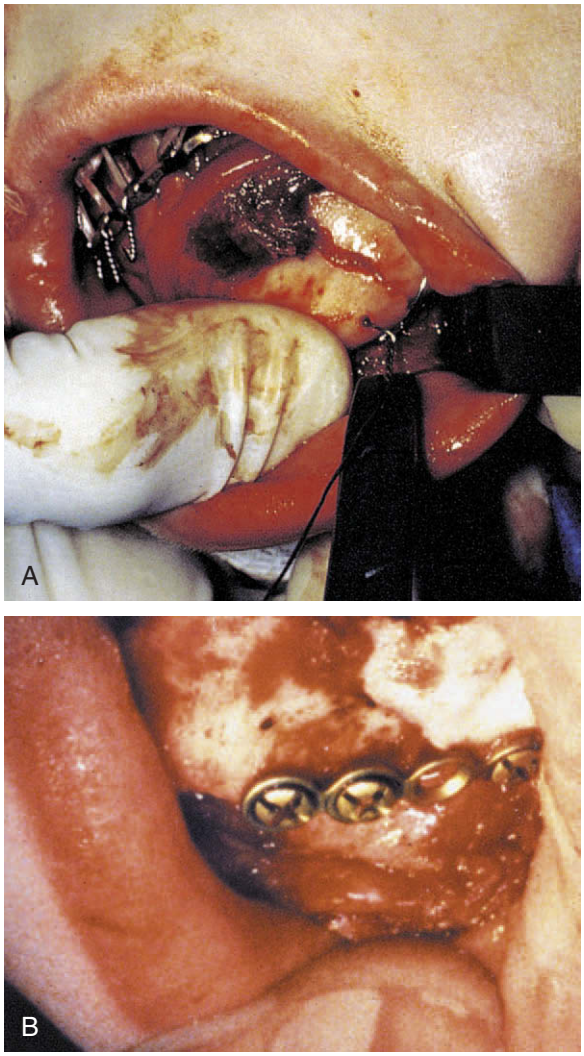

Figure 189-12. **A,** Basket-wire osteosynthesis of left parasymphyseal fracture in a 10-year-old boy. Note the proximity of the wire reduction to the lower mandibular margin. **B,** Monocortical miniplate osteosynthesis of a right parasymphyseal fracture in a 6-year-old boy. Note the proximity of the plate to the lower mandibular margin.

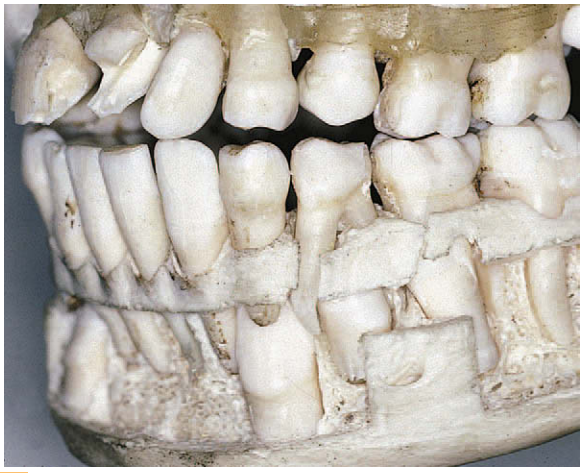

Figure 189-13. Cadaver preparation from an 11-year-old child. Note the proximity of the unerupted left lower canine tooth to the lower mandibular margin.

maxillary buttresses, and orbital wall and floor defects (Fig. 189-17). When the malar fragment has been laterally displaced, the fracture probably is unstable and will require fixation. The most severe injuries often are associated with Le Fort III fractures, again requiring rigid fixation.

The fracture typically involves the frontozygomatic suture, the infraorbital rim, the zygomaticomaxillary buttress, and the zygomatic arch, seen to be separated at the zygomaticotemporal suture. Minimally displaced fractures can be treated conservatively. A Gille's approach or transcutaneous bone hook can be used to reduce greenstick-type injuries, which frequently will not require internal fixation for stability. When simple reduction techniques result in unstable or nonanatomic reduction, ORIF is indicated.

Surgical correction involves adequate control of the frontozygomatic suture, the infraorbital rim, and the lateral buttresses. In most type I fractures, control of the infraorbital rim and the frontozygomatic suture can be accomplished with external palpation, and open visualization is necessary only for identification of the zygomaticomaxillary buttress through an intraoral gingivolabial sulcus incision. For type II fractures, open visualization can be accomplished through a brow, subciliary, or transconjunctival incision with lateral canthotomy, together with an upper buccal sulcus incision. For type III fractures for which significant reconstruction of the zygomatic arch also is required, a hemicoronal approach is necessary. Once exposure is achieved, most injuries can be reconstructed by one-point fixation of the zygomaticomaxillary buttress, or by two-point fixation with microplates at the frontozygomatic suture and infraorbital rim. Severe fractures will require three-point fixation of all of the buttresses. Zygomatic arch deformities usually can be repositioned by elevating through a brow or lateral canthotomy incision. When indicated, orbital floor exploration should be performed.

Nasal Fractures

The child's nose differs significantly from that of the adult. The soft, compliant cartilages that constitute the anterior projection of the nose bend easily during blunt trauma. The force causing the trauma is therefore dissipated across the maxilla and its buttresses, resulting in a broad area of edema. Rarely, the external cartilages can be dislocated from the bony framework. The septum is more rigid and thus likely to be fractured.

Several types of injury can affect the septum: Its perichondrial covering may become detached in response to the deformation of the cartilage during impact. This creates a potential space for the development of a septal hematoma. The septum also can be torn from its bony attachments or fractured in a vertical, horizontal, or stellate fashion. This can result in immediate or subsequent obstruction, delayed twisting deformities, and growth disturbances.

In young children, the nasal bones are rarely fractured because of minimal projection, but when they occur, fractures typically are of the greenstick type or occur along suture lines. When the blow is directly to the midline, an "open book" fracture can result, with central depression, lateral flaring, and splayed nasal bones over the frontal process (Fig. 189-18). With fractures of the nasal skeleton, a high index of suspicion should be maintained for more extensive but occult nasoethmoidal and orbital injuries. Fortunately, with isolated nasal fracture, growth retardation is rarely seen.[21,40]

The initial examination of a child with a suspected nasal fracture often is of limited value with regard to the external deformity because of edema. Several days may be required for the swelling to go down before the true extent of the deformity can be appreciated. However, immediate intranasal examination is essential to evaluate for septal injury, particularly septal hematoma. Nasal obstruction is the hallmark of septal hematoma and can be observed on anterior rhinoscopy as an obvious purple bulge on one side of the nose. The bulge is compressible but does not shrink with topical vasoconstriction. Septal hematoma is a serious complication and, left untreated, can result in a thick fibrotic and obstructive septum. The hematoma also can become infected, resulting in loss of cartilage and subsequent saddle nose deformity or septal perforation (Fig. 189-19). These injuries should be treated immediately with evacuation. In most cases this will require

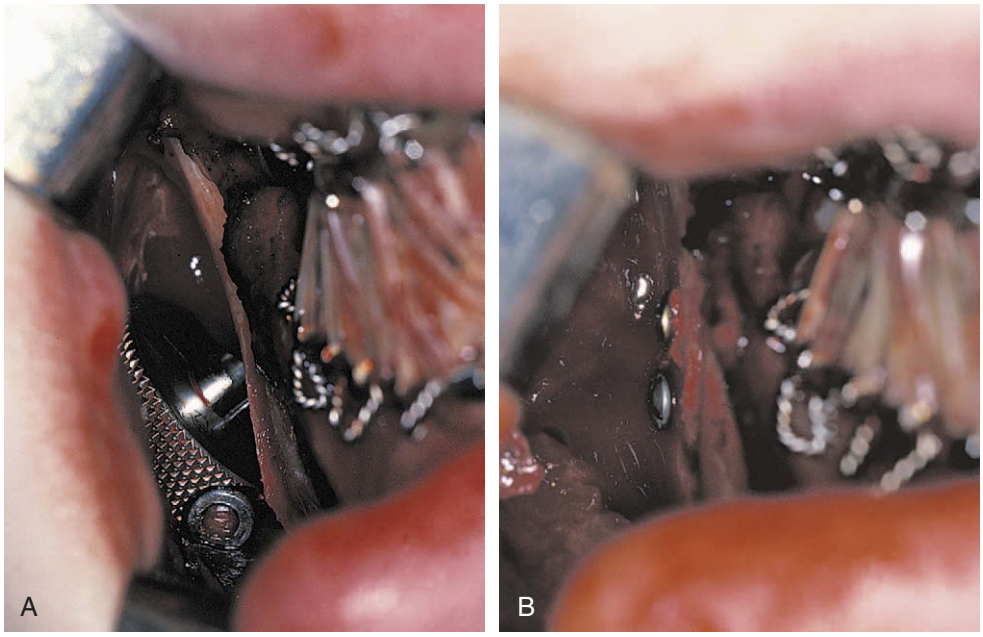

Figure 189-14. **A,** Transcutaneous instrumentation for intraoral reduction of a right-angle fracture in a 13-year-old girl. **B,** Open reduction and internal fixation of the fracture with lag screws.

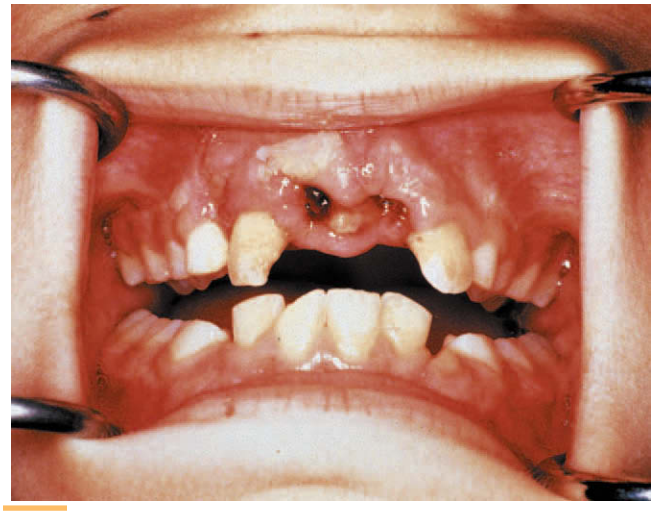

Figure 189-15. Avulsed central upper incisors in a 6-year-old boy.

Figure 189-16. Clinical appearance of a 13-year-old boy with a nasoethmoidal fracture. Note the leftward displacement and upward rotation of the entire nasoethmoid complex.

general anesthesia. The use of a Killian septal incision allows for both drainage of the hematoma and investigation and suture reduction of any displaced septal fragments. After exploration has been completed, the mucoperichondrial leaflet is sewn back to the cartilage with a through-and-through suture. Septal splints and packing should be used for 2 to 3 days to prevent re-formation of the hematoma. Prophylactic oral antibiotics should be instituted. While the patient is under anesthesia, the bony nasal pyramid is examined, and if it is found to be dislocated, closed reduction can be accomplished.

If a septal hematoma has been ruled out and the possibility of nasal fracture is still a concern, the child is asked to return in 5 days, allowing time for the facial edema to subside. If a bony or septal fracture is present, resulting in a cosmetic deformity or a fixed nasal obstruction, then definitive surgical management is undertaken. Closed reduction of the bony fracture can be performed with intranasal instrumentation and bimanual external manipulation. Greenstick fractures may not always reduce into the desired position and sometimes require small osteotomies for proper alignment of the fragments. If significant dislocations are present or if the injury is more than 2 weeks old, open reduction may be necessary. The timing of open reduction is a subject of some debate; often, waiting is the best approach.

Newborn Nose

An occasional problem in newborn infants is an asymmetrical tip deformity. These infants typically have a flattened nasal tip off to one side, with the septum tilted in the same direction. The bony dorsum is invariably straight. Some controversy has arisen regarding whether this type of deformity is caused by birth trauma or by prolonged intrauterine positional pressure. Some surgeons advocate immediate surgical reduction of these deformities by straightening and relocating the septum.[137] In our experience, however, these deformities generally straighten over time despite lack of intervention, without late sequelae. The best approach with these children is to reassure the parents that the nose will straighten out in time. It is possible that such a displace-

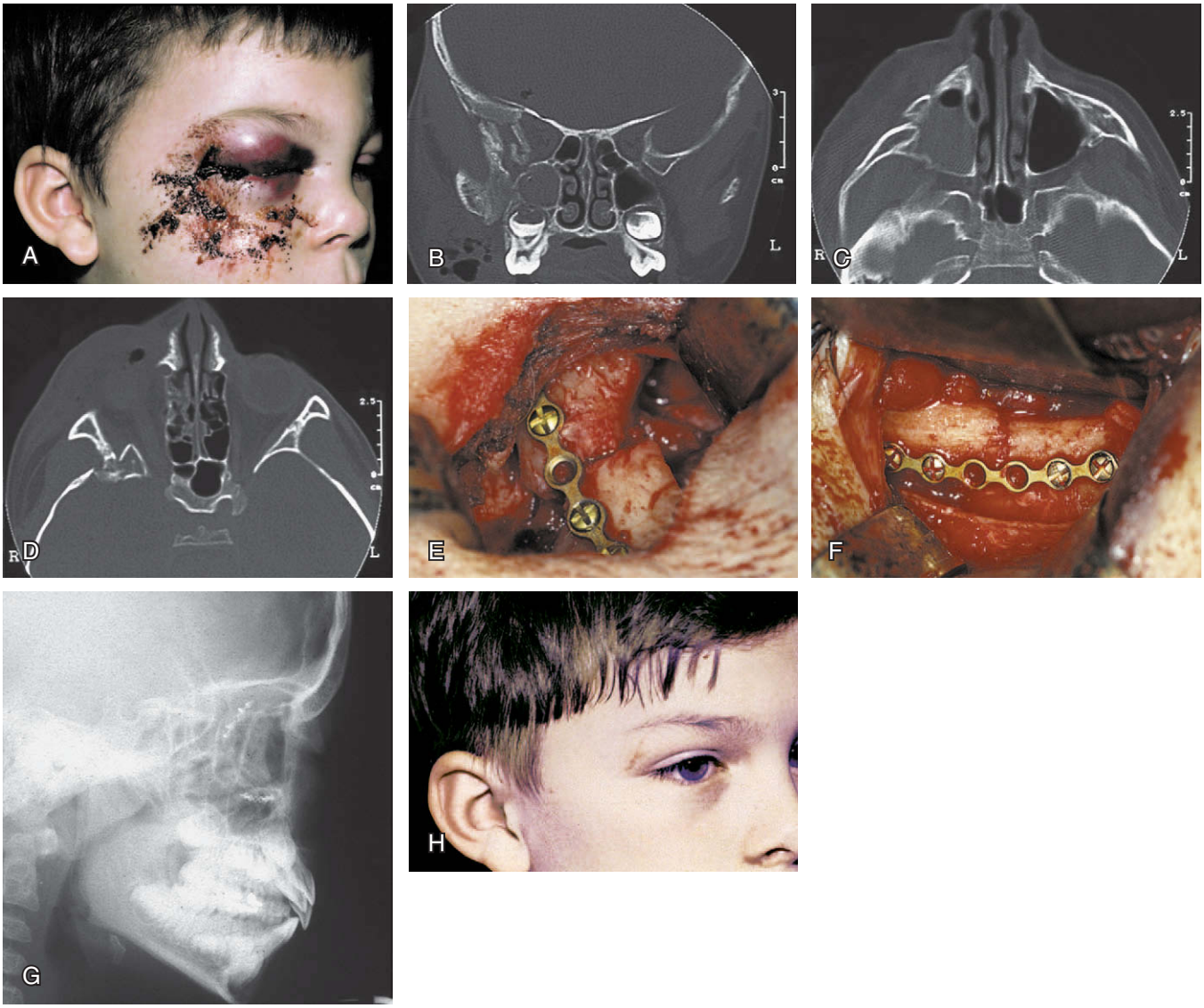

Figure 189-17. **A,** Clinical appearance of a 6-year-old boy with a right zygomaticomalar complex fracture. **B,** Coronal CT scan showing the medial rotation of the malar fragment. **C,** Axial CT scan showing the fractured zygomatic arch. **D,** Axial CT scan showing the buckling of the lateral orbital wall. **E,** Open reduction and internal fixation of a frontozygomatic fracture. **F,** Open reduction and internal fixation of an infraorbital rim fracture. **G,** Postoperative x-ray image of the reduction. **H,** Appearance at 1 year after reduction.

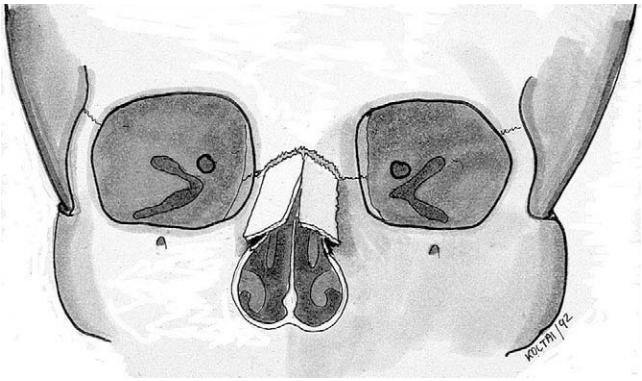

Figure 189-18. When the blow is directly to the midline, an "open-book" fracture can result, with central depression, lateral flaring, and splayed nasal bones over the frontal process.

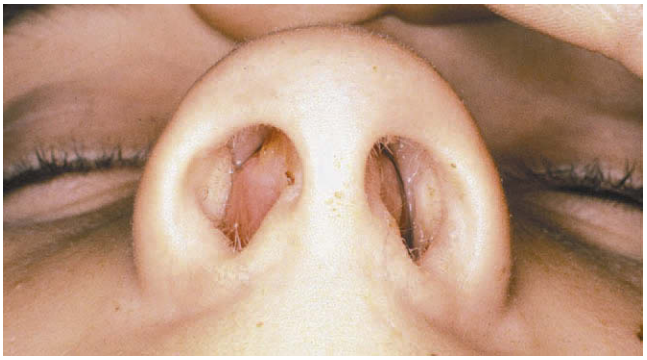

Figure 189-19. Bilateral septal hematoma in a 6-year-old child. Obstruction is present on both sides of the nose. There was no response to vasoconstriction.

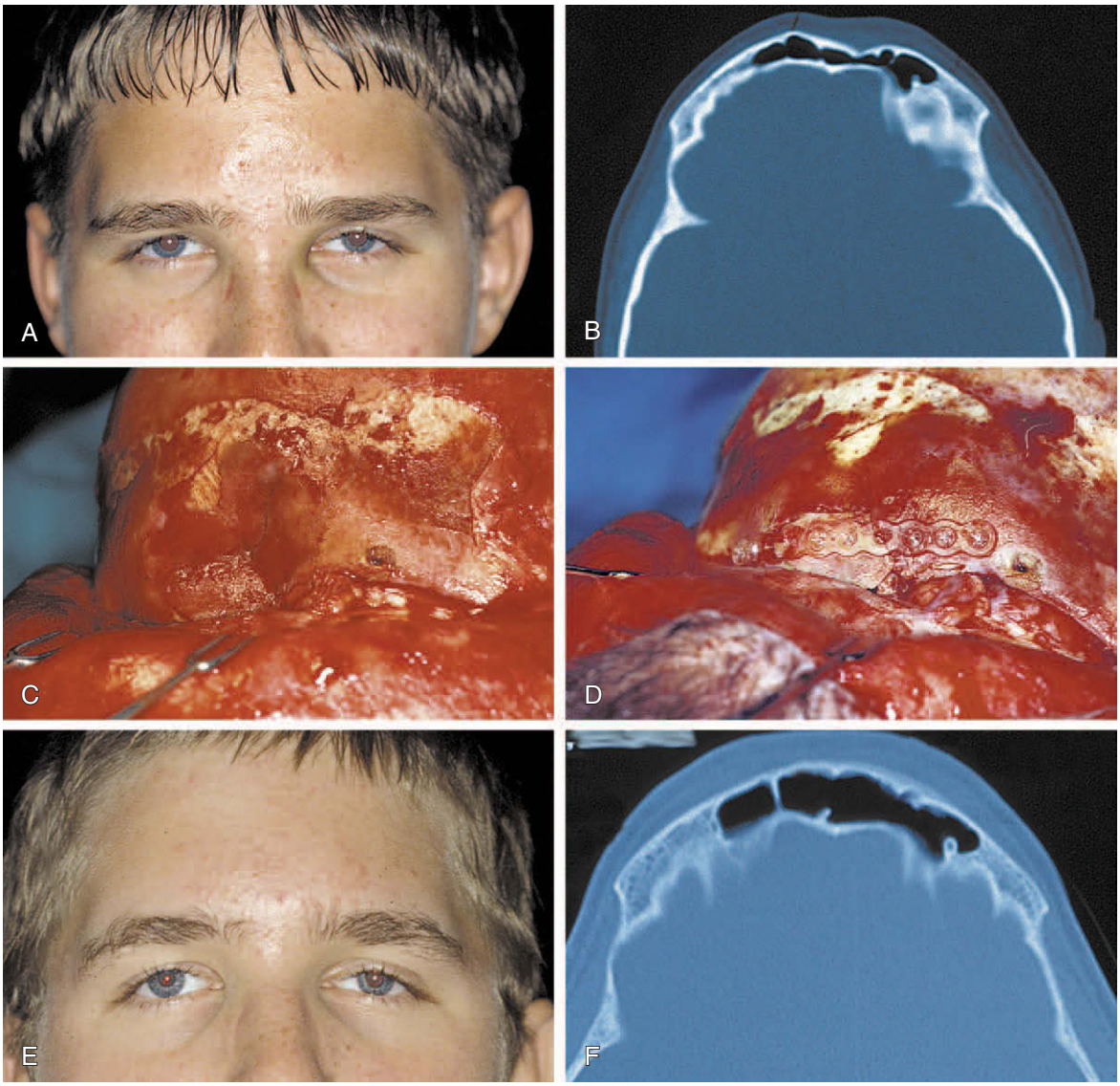

Figure 189-20. **A,** Clinical appearance of a 14-year-old boy with an anterior table frontal sinus fracture. Note the depression over the left brow. **B,** Axial CT scan demonstrates the left anterior table fracture. **C,** Surgical exposure of the depressed anterior table. **D,** Open reduction and internal fixation with resorbable plate. **E,** Postoperative view at 6 months shows resolution of the forehead depression. **F,** Axial CT scan at 6 months demonstrates normal anterior table contour.

ment can cause airway obstruction in a neonate who is an obligate nose breather, and in such cases, relocation of the septum is indicated.

Frontal Sinus Fracture

The frontal sinus is the last of the paranasal sinuses to develop in children and is therefore not prone to injury until adolescence. However, when fractures of the frontal sinus occur, 70% involve the posterior table, and the rate of CSF leak is 18%—nearly double that found in the adult population.[138] Management of pediatric frontal sinus fractures is similar to that of fractures in adults. When forehead deformity is present in a child with an anterior table fracture, it needs to be reduced (Fig. 189-20). The nasofrontal duct should be investigated both by direct visualization of the sinus floor and endoscopically. Posterior table fractures require open reconstruction, and severe comminution warrants neurosurgical consultation. Most posterior fractures are associated with anterior fractures, which can be repaired concurrently. The need for sinus obliteration is based on the same criteria as for adults. Long-term sequelae include CSF leak, intracranial abscess, and mucopyocele formation. It is important to maintain long-term follow-up with periodic imaging.

Fractures of the supraorbital rim can be treated as part of the neurosurgical repair and be approached either by extension of overlying laceration or through a coronal incision. Occasionally, a brow incision will be sufficient. Once frontal pneumatization has occurred, supraorbital rim fracture becomes more likely. Frontal sinus injury in this type of injury is common, and the approach is the same as for the adult.

Orbital Fracture

Injuries to the orbit and nasoethmoidal region can leave children with significant functional and cosmetic defects. The scope of these injuries is related to the magnitude of the force causing the injury and can vary, with injuries ranging from relatively minor fractures, such as "blowout" of the orbital floor, to complex fractures. Associated facial fractures occur in 30% of orbital fractures.[43]

Orbital fracture patterns in children tend to be age-specific. The two distinct factors in facial growth that affect the patterns of pediatric orbital fractures are craniofacial geometry and expansion and growth of the paranasal sinuses.[139] The ethmoid air cells steadily expand, reaching 70% of the interorbital width by the age of 7 years.[140] At birth, the maxillary sinus is medial to the globe, with the alveolar margin in close

Figure 189-21. Periorbital edema, ecchymoses, and subconjunctival hemorrhage are indicative of orbital injury in this 13-year-old boy with lateral orbital wall and orbital floor fractures.

Figure 189-22. Left orbital apex fracture resulting in blindness, ophthalmoplegia, and ptosis in a 14-year-old girl.

proximity to the inferior orbital rim. By age 7, the maxillary sinus has widened past the midpupillary line to occupy one half of the lateral nasal wall. Also at this age, the slowly expanding frontal sinus begins to reside above the supraorbital rim.[141] Before the age of 7 years, the large cranium is more vulnerable to trauma than the face.

There are two proposed mechanisms of orbital wall fractures.[142] The first mechanism, called the *bone conduction process*, stipulates that force applied to the orbital rim is transmitted to the walls, which then fracture.[143] The second mechanism, called the *hydraulic process*, stipulates that the force applied to the globe causes an increase in intraorbital pressure, which then results in fracture of the walls. Both mechanisms probably are operational, although bone conduction accounts for most fractures.

Suspected orbital trauma warrants an ophthalmologic evaluation. Periorbital edema, ecchymoses, and subconjunctival hemorrhage are indicative of orbital injury. Propagation of the orbital wall buckling deformation can result in optic nerve injury without apex fracture; accordingly, the first priority is an assessment of visual acuity.[156] The position of the globe, often obscured by edema, is inspected for exophthalmos, enophthalmos, and vertical dystopia. Intraocular pressures are measured. The extraocular musculature is tested for voluntary range of motion and, if necessary, with forced duction with the patient under anesthesia. Intercanthal distance and the length of the palpebral fissures are measured, and the locations of the medial canthal ligaments are identified. The rims are palpated for disruption. Cranial nerve V is tested for sensitivity (Fig. 189-21).

The orbit has three anatomically distinct regions classified by fracture patterns.[144] The *anterior* component is the hard bone of the orbital rim and is divided into three subsections. The first is the supraorbital rim, a portion of the frontal bone. Second is the infraorbital rim, which is part of the zygomaticomalar complex. The third is the medial rim, to which the medial canthal tendons attach, and is part of the nasoethmoidal complex. The *middle* component consists of the thin lamellae of bone forming the roof, the floor, and the medial and lateral walls. The *posterior* component consists of the orbital apex, including the orbital fissures and the optic canal.

Some orbital fractures in children can be treated successfully by traditional closed or limited open techniques. However, for the severe injuries that require open reduction with rigid internal fixation, the development of hidden extended incisions for complete exposure has been a major advance.

Orbital roof fractures rarely require repair. However, if ocular mobility has not improved within 7 to 10 days of injury, repair should be performed. Permanent exophthalmos, vertical dystopia, and encephaloceles can result from unattended fractures. Reconstruction is best accomplished using basicranial exposure or a combined neurosurgical-maxillofacial approach, with intracranial exposure of the orbital roof. Timing of these repairs is based on implementation of any necessary neurosurgical intervention.

Orbital Apex Fracture

Orbital apex injuries in children are exceedingly rare in clinical practice, probably because the force required is lethal.[4,12,17,40,110] Fractures of the apex usually are due to posterior extensions of complex craniofacial injuries. Blindness is the greatest concern, potentially occurring as a result of optic nerve injury and vascular injury to the ophthalmic artery. Loss of visual acuity and afferent pupil defect are the hallmark findings for an optic neuropathy. Initial treatment is with high-dose steroids. If visual acuity does not improve, optic nerve decompression should be considered using either a transsphenoidal, intracranial, or endoscopic approach. Injury to the neurovascular structures entering the superior orbital fissure can result in ophthalmoplegia, ptosis, and fifth nerve hypesthesia. Treatment is expectant, and long-term deficits are common[144] (Fig. 189-22).

Orbital Floor Fracture

Orbital floor fractures are the most common injuries of the middle component of the orbit.[145-148] In children, the occurrence of these injuries parallels the pneumatization of the maxillary sinus, and they generally are not seen before the age of 5 years. They occur as isolated blowout fractures or in conjunction with zygomaticomalar or Le Fort–type fractures.

Isolated orbital floor fractures typically present with diplopia, infraorbital hypoesthesia, periorbital ecchymosis, and edema. "Trapdoor" and "saucer" fractures are the two major types of blowout or orbital floor fractures seen in the pediatric population. Serious ocular injury with blowout fractures occurs in less than 5% of cases.[149,150]

The *trapdoor fracture* is a pure orbital floor fracture, linear in form and hinged medially, that allows herniation of orbital contents through the fracture and then entraps these herniated contents.[149,150] It usually is a consequence of low-velocity blunt trauma and is seen most commonly in the pediatric population, probably as the result of a greenstick fracture phenomenon.[151-153] The trapdoor fracture, also known as the white-eyed fracture, can be subtle on presentation. The degree of orbital edema tends to be relatively minor in trapdoor cases and insufficient to explain the significant reduction in supraduction motility.[7,151,154-158] Furthermore, the trapdoor fracture frequently is associated with nausea and vomiting.[58,151] Trapdoor fractures are believed to cause tissue ischemia and necrosis, particularly of the inferior rectus and oblique muscles.[7,154-158] Failure to relieve the pressure on the muscle results in persistent diplopia.[153] With lid edema, the diagnosis can be difficult. It is therefore imperative to maintain a high index of suspicion for trapdoor fractures. CT scans classically show a trapdoor fracture along the canal of the infraorbital nerve.[153] However, entrapment is a clinical diagnosis, so CT scanning should be used to aid in the diagnosis. Severe limitation on forced duction testing is diagnostic for these fractures[155,157] (Fig. 189-23).

The second type of orbital floor rupture is the *saucer fracture*, characterized by a depressed crack in the orbital floor, resulting in enophthalmos. These fractures are more likely to cause enophthalmos

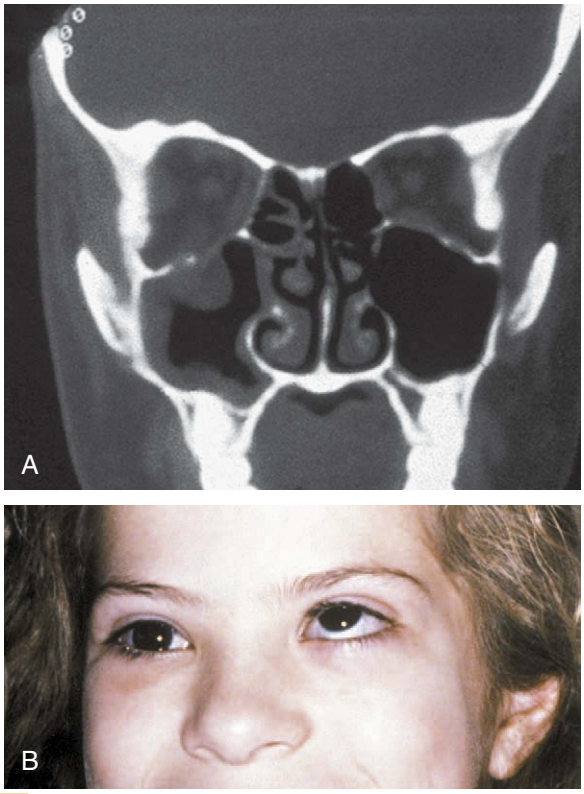

Figure 189-23. "Trapdoor" fracture of the right orbital floor in a 10-year-old child with entrapment of the inferior rectus muscle. **A,** CT scan demonstrating entrapment. **B,** Clinical photograph demonstrating the limitation of upward gaze on the right side. This problem resolved with exploration and freeing up of the entrapped muscle.

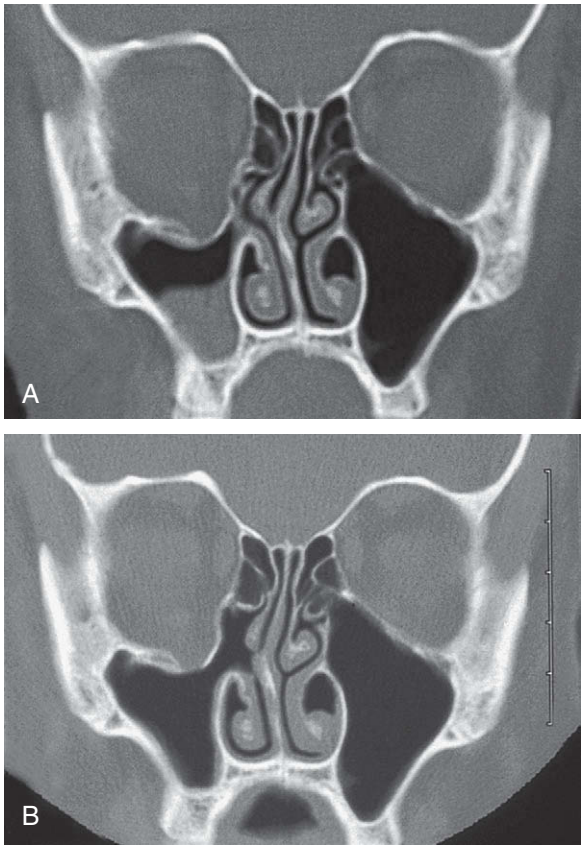

Figure 189-24. **A,** CT scan demonstrating unrecognized "saucer" fracture of the right orbital floor in a 15-year-old adolescent, causing obstruction of maxillary sinus outflow tract resulting in chronic maxillary sinusitis. **B,** Resolution of sinusitis after endoscopic maxillary antrostomy. Despite the obvious expansion of orbital volume noted on this coronal CT scan, the patient had only 1 mm of measurable enophthalmos and did not wish to have it repaired.

without significant duction deficits.[58] Because larger fractures tend not to impinge the muscle, they are less apt to cause muscle ischemia and can therefore be addressed after the resolution of edema (Fig. 189-24).

Differentiating between the two types of floor fractures is important, although management remains unnecessarily controversial. Relatively few studies evaluating the characteristics and management of internal orbital fractures in the pediatric population have been published. Putterman and colleagues popularized observation and a nonsurgical approach to all orbital blowout fractures, and for many years this was the trend in treatment.[159] However, failure to treat can lead to permanent gaze restriction, diplopia, and enophthalmos.[160,161] Accordingly, the practice of observation for all floor fractures has been challenged, with recognition of a role for surgery in some cases.

Indications for surgical intervention after an internal orbital fracture include significant (greater than 2 mm) enophthalmos, extraocular muscle restriction with positive results on forced duction testing (greater than 30 degrees), symptomatic diplopia, or CT findings of large orbital wall defect (involving more than 50% of the floor or orbital wall).[151,156,157,162,163] It is crucial that pseudoentrapment conditions such as orbital soft tissue swelling, extraocular muscle contusion, and cranial nerve injuries be distinguished from true muscular entrapment, because patients with the former conditions can be managed with observation only. The timing of surgery also is controversial. Patients with minimal diplopia, good ocular motility, absence of evidence of significant fracture or herniation on CT scans, and no significant enophthalmos can be managed by close observation over weeks.[164] However, some studies have demonstrated tight restriction of extraocular muscles. Patients with true muscle incarceration have an increased chance of ocular motility recovery with early intervention, preferably within 48 hours.[7,151,153-158,165,166]

The orbital floor can be exposed through a transconjunctival or subciliary approach. The orbital contents are gently teased back into the orbit, and bony fragments are reduced if possible. If a small defect or weakness persist, an implant of absorbable gelatin film (Gel-film) usually is adequate in children. Larger defects in children can be grafted with split calvarial bone.

Orbital Roof Fracture

Orbital roof fractures occur primarily in younger children, as a consequence of the proportionally larger cranium and the lack of frontal sinus pneumatization.[129,167] With aging, the orbital floor thins as the maxillary sinus enlarges. Consistent with maturation, the pattern of orbital fractures changes from roof fractures to the lower orbit around the age of 7 years.[8]

A history of a blow to the brow from a fall or blunt object associated with a late-developing periorbital hematoma should alert the clinician to the possibility of a roof fracture. Proptosis or dystopia can occur but may not be immediately evident (Fig. 189-25). In older children, orbital roof fractures occur as a component of more extensive craniofacial fractures, usually the result of high-velocity injuries. Up to 86% of all orbital roof fractures are associated with intracranial injury.[42,168] The orbit and globe rarely sustain long-term damage, so surgical repair is rarely necessary.[8] Fracture fragments that are displaced into the orbit will require combined intracranial and extracranial exploration with cranial bone graft reconstruction of the deficit to correct dystopia and exophthalmos and to prevent development of encephaloceles. Orbital encephaloceles have been reported as late sequelae, manifesting with vertical dystopia, axial proptosis, and pulsation of the globe.[26] Therefore, long-term follow-up with periodic imaging is important.

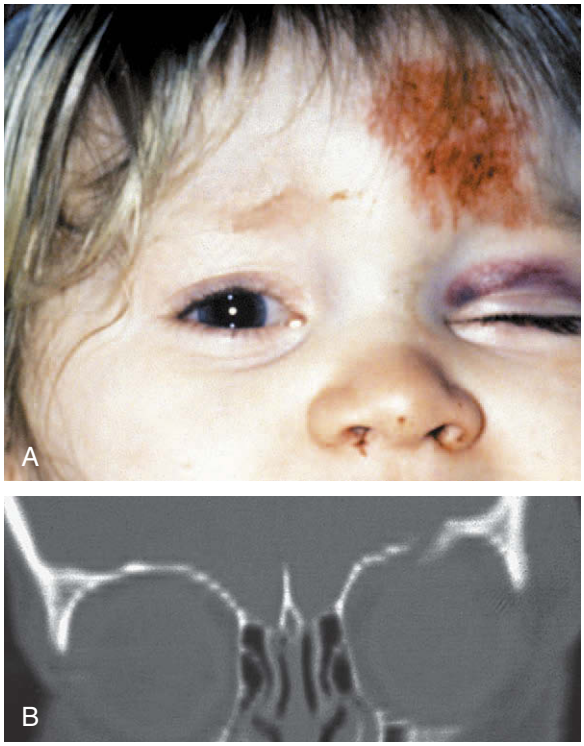

Figure 189-25. Left orbital roof fracture in a 3-year-old child from a blow to the left forehead. **A,** Note the upper eyelid hematoma. **B,** Coronal reconstruction CT scan shows the buckling of the orbital roof.

Lateral/Medial Orbital Wall

Pure fractures of the lateral and medial walls of the orbit are rare.[122,125,] When they do occur, orbital emphysema is commonly seen on CT scans. Surgical correction is necessary only for isolated injuries with nonresolving or fixed enophthalmos and entrapment within the ethmoid sinus. Surgical exposure can be accomplished using either a transcaruncular approach or through an external ethmoidectomy incision. The advantage of the transcaruncular approach is camouflage of the incision, with the small risk of medial fornix scarring[98,169,170] (Fig. 189-26).

Naso-orbitoethmoid Fractures

Fractures of the naso-orbitoethmoid (NOE) complex can vary in severity, ranging from minimal dislocations to highly comminuted compound fractures that extend into the surrounding frontal bone, orbits, and maxilla. The four-sided NOE fracture is anatomically defined by fractures of the nasofrontal suture, nasal bones, medial orbital rim, and infraorbital rim. This complex makes up the "central fragment" core of the midface.[144] Presence and degree of comminution of this core will determine the severity of the fracture and the complexity of surgery to achieve optimal cosmetic and functional results (Fig. 189-27).

CT scan is invaluable in the assessment of the NOE fracture. Evaluation of the medial canthal ligaments is mandatory and best performed with the patient under anesthesia by inserting a hemostat in the nose up toward the medial orbital rim (Fig. 189-28). Traumatic hypertelorism is evaluated by intercanthal distance, which is difficult owing to the lack of standard reference data and the great variation between males and females and among those of differing ethnic backgrounds. Nevertheless, the average intercanthal distance in children at the age of 3 years is approximately 25 mm; by age 12, it is 28 mm, and by adulthood, 30 mm.[140] An additional 5 mm of soft tissue widening above the age-adjusted average is suggestive of displaced fracture of the NOE complex, with 10 mm of displacement being diagnostic.

Most NOE fractures are best treated with ORIF. Although this is technically difficult, overcorrection of the NOE fracture is aesthetically superior to undercorrection.[171] Exposure is best obtained through preexisting lacerations or coronal incisions, with mobilization of the globes along the orbital roof to expose the nasal dorsum. The major fragments and the medial canthal ligaments are identified. Care is taken to preserve the attachment of the ligament to the bony insertion. To facilitate interfragmentary reduction and transnasal wiring, the central fragment is mobilized (Fig. 189-29).

Resetting the intercanthal distance is aesthetically the most important step for optimal results. Interorbital growth is nearly complete by the age of 8 years. It is crucial in children to set the intercanthal distance narrower than anticipated. In medial canthal reconstruction, a drill hole is made in the anterior lacrimal crest just above the insertion of the anterior limb of the tendon. A second drill hole is made in the posterior lacrimal crest just behind the insertion of the posterior limbs. Contralateral drill holes are made, and 28-gauge, stainless steel wire is passed transnasally between the two fragments and tightened in an effort to overcorrect the deformity. An alternative technique is to use a small screw as the anchor for the transnasal wires. Interfragmentary wiring is completed and, if the repair is unstable, further supported by plate fixation of the medial orbital rim[65,144] (Fig. 189-30).

The final step is reconstruction of the nasal dorsum, which often loses its support. A cantilever calvarial bone graft can be used to correct this deformity. It is best to place these grafts rigidly in hopes of limiting reabsorption. The tip of the graft should be deep to the upper border of the lower lateral cartilages (Fig. 189-31).

Direct injury to the lacrimal drainage system is uncommon in NOE fractures. Nevertheless, the lacrimal sac, duct, and canaliculi should be examined, and if injured, definitive repair with stents should be performed to prevent epiphora.

Conclusion

Children sustain severe maxillofacial injuries that require appropriate repair. The primary factor that distinguishes the management of pediatric fractures from that of adult fractures is facial growth. Trauma to the mandible is well compensated and growth disturbances are uncommon with appropriate treatment. Inadequate treatment of upper and midfacial injuries may result in serious alterations of facial growth. CT scanning, craniofacial exposure, bone grafting, and the advent of resorbable rigid fixation facilitate the reconstruction of the most complex three-dimensional disfigurements. These techniques have solid theoretic and practical applications in severe facial trauma.

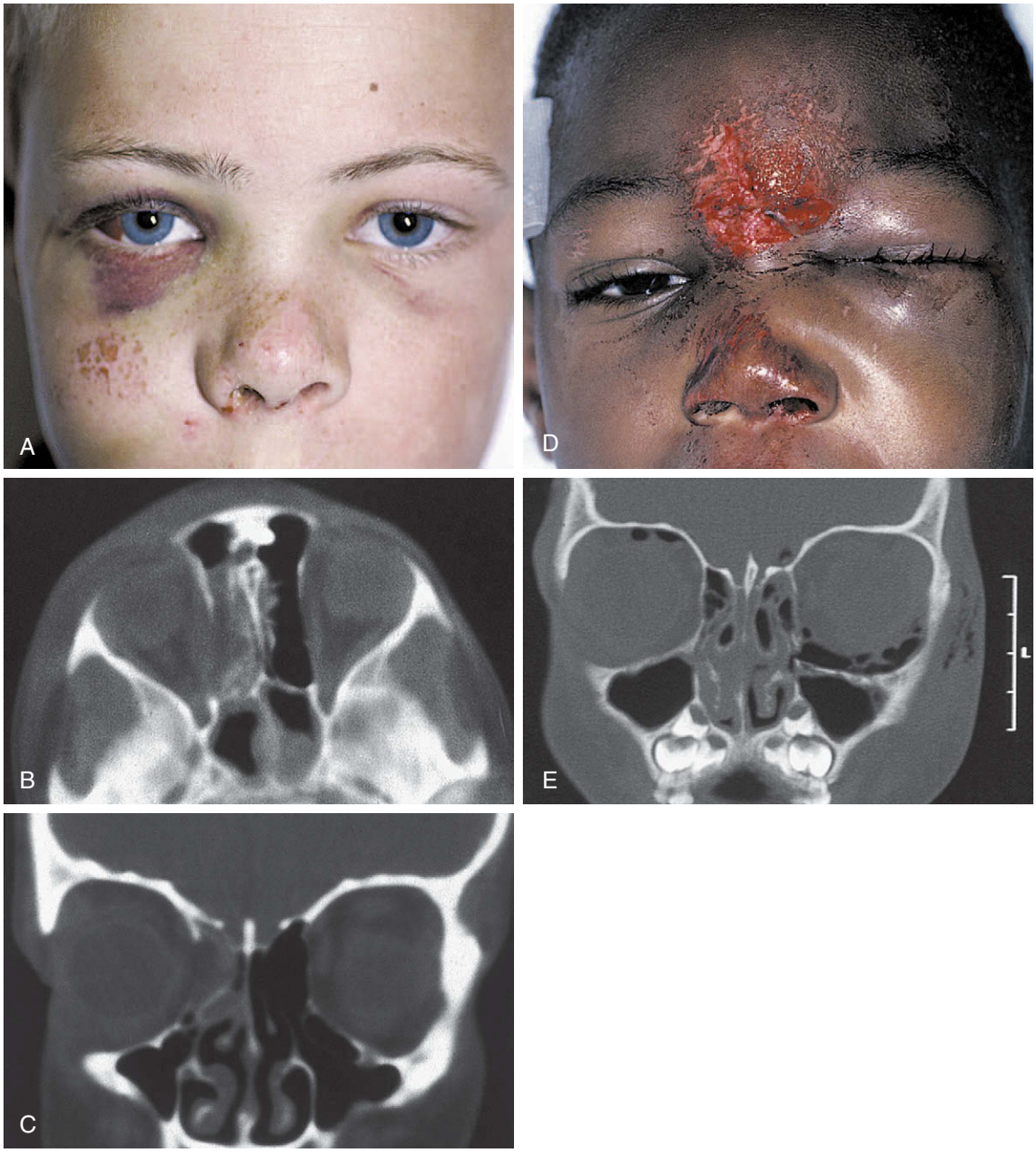

Figure 189-26. **A to C,** Right medial orbital wall fracture in a 9-year-old child. **A,** Note the lower eyelid and subconjunctival hematoma. **B** and **C,** Axial and coronal CT scans showing the medial displacement of the lamina papyracea. **D** and **E,** Nondisplaced bilateral medial orbital fractures in a 4-year-old child from a blow to the nasoethmoidal region and forehead. **D,** Clinical photograph. **E,** Coronal CT scan demonstrating orbital emphysema from the nondisplaced medial wall fractures. *(**B** and **C**, courtesy of Linda Brodsky, MD.)*

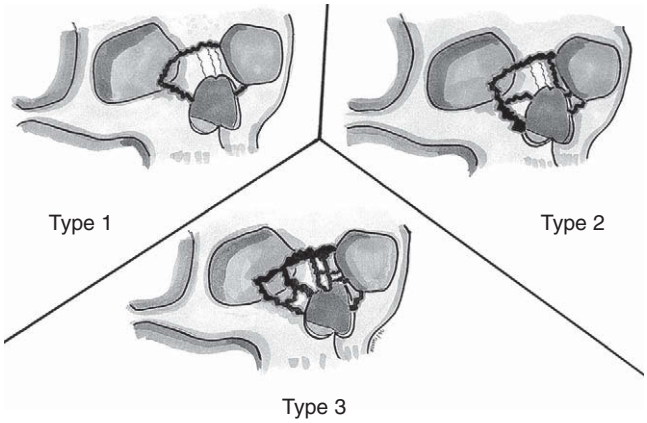

Figure 189-27. Classification of nasoethmoidal fractures. In type 1 fractures, the "central fragment" is intact as a single fragment of bone. In type 2 fractures, the central fragment is comminuted, but the fracture does not extend deep to the anterior lacrimal crest. In type 3 fractures, the comminution extends deep to the anterior lacrimal crest.

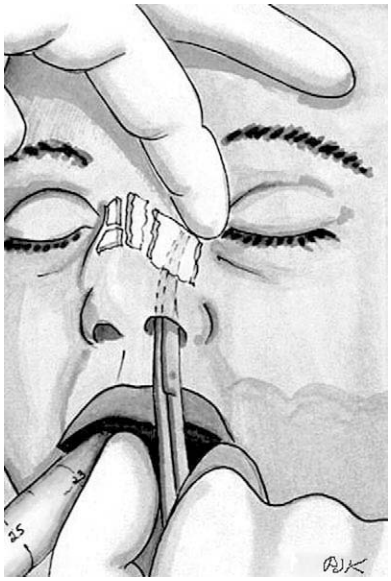

Figure 189-28. Bimanual test for medial canthal displacement. A hemostat is placed intranasally underneath the canthal bearing bone while the examiner's finger palpates the medial canthal tendon. The mobility of the canthal tendon-bearing fragment is an indication for medial canthopexy.

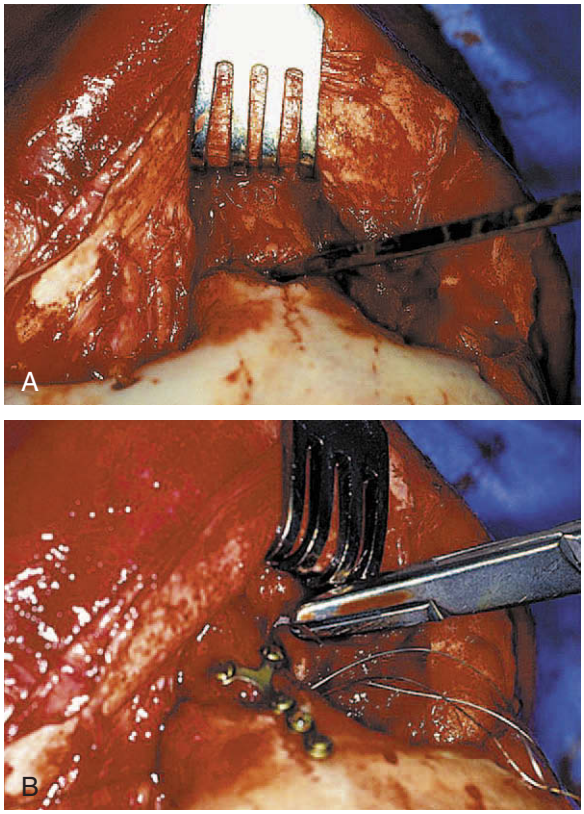

Figure 189-29. Repair of a nasoethmoidal fracture in a 3-year-old child was delayed for 3 weeks owing to concomitant neurocranial injuries, by which time the injury had begun to heal. **A,** At surgical repair, the fracture fragments required remobilization. **B,** Open reduction and internal fixation of the "central fragment" has been completed by suspension from the frontal bar by a "Y" plate. Medial canthopexy with transnasal wiring is demonstrated.

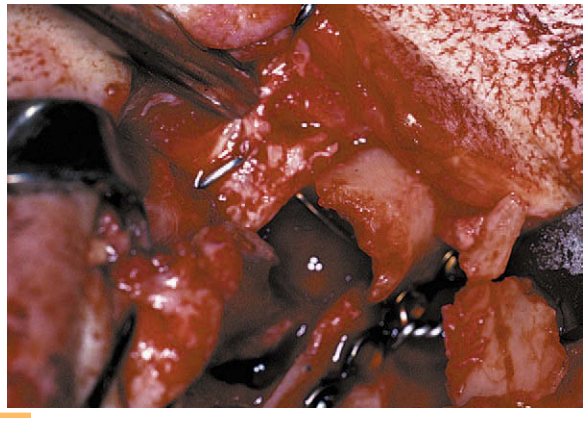

Figure 189-30. Repair of a comminuted compound type 3 nasoethmoidal fracture with bone loss in a 15-year-old adolescent. Medial canthopexy with transnasal wiring is shown.

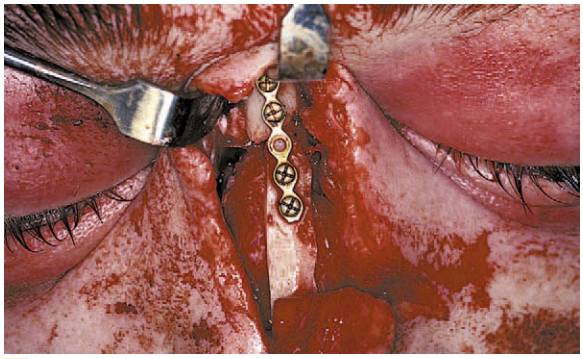

Figure 189-31. Cantilever calvarial bone graft has been used for reconstruction of the nasal dorsum.

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CHAPTER ONE HUNDRED AND NINETY

Early Detection and Diagnosis of Infant Hearing Impairment

Susan J. Norton

Prabhat K. Bhama

Jonathan A. Perkins

Key Points

General

- Hearing loss may lead to delayed language development and poor school performance.
- Universal newborn hearing screening allows for earlier detection and intervention in infants with hearing loss, which may result in improved language development in affected children.
- Estimated rates of congenital sensorineural hearing loss (SNHL) range from 1 per 1000 to 3 per 1000 live births, depending on the degree of hearing loss.

Principles and Techniques of Newborn Hearing Assessment

- Screening outcomes are either "pass" (no further testing indicated) or "refer" (infant is at risk for hearing loss and requires diagnostic hearing evaluation).
- The auditory brainstem response (ABR) measures action potential responses of the eighth cranial nerve to an auditory stimulus.
- Evoked otoacoustic emissions (EOAEs) measure sound waves generated by the outer hair cells of the cochlea after an auditory stimulus.
- Most newborns with hearing loss do not have obvious abnormalities on physical examination, but ophthalmologic examination is warranted in these patients because of the high incidence of ocular defects in patients with severe to profound hearing loss.
- A strong association between hearing loss and impaired vestibular function in infants and children has been documented.
- Newborns who fail initial hearing screening tests should undergo careful otomicroscopic examination, because middle and external auditory canal problems are a frequent cause of such results.
- Diagnostic audiology (or visual reinforcement audiometry for infants unable to understand verbal instruction) is indicated by the age of 3 months for all infants not passing a newborn hearing screening test.
- Standardized laboratory tests in infants failing initial screening are not necessary or cost effective.

History of Infant Hearing Screening

The importance of early identification of hearing loss has been recognized for many years.[1-3] Undetected hearing loss present from an early age can impede acquisition of speech, language, cognitive, and social-emotional development.

Joint Committee on Infant Hearing

The Joint Committee on Infant Hearing (JCIH), of which the American Academy of Otolaryngology–Head and Neck Surgery is a founding member, was established in 1969 with the goal of developing more accurate and efficient methods of identifying neonatal hearing impairment. In 1972, the JCIH recommended the use of a High-Risk Registry (HRR) to identify neonates at higher-than-normal risk for hearing loss. It recommended these infants be referred for audiologic testing within the first 2 months of life. In 1982,[4] 1990,[5] and 1994[6] the JCIH issued updated high-risk criteria. The 1994 HRR included family history of hereditary childhood sensorineural hearing loss, in utero infection (e.g., toxoplasmosis, other viral infections, rubella, cytomegalovirus infection, and herpes simplex [TORCH]), craniofacial anomalies, birth weight less than 1500 g, hyperbilirubinemia severe enough to necessitate an exchange transfusion, ototoxic medications including but not limited to use of aminoglycosides in multiple courses or in combination with loop diuretics, bacterial meningitis, Apgar scores of 0 to 4 at 1 minute or 0 to 6 at 5 minutes, mechanical ventilation lasting 5 days or more, and presence of stigmata or other findings associated with a syndrome known to include sensorineural or conductive hearing

loss. However, the JCIH recommended HRR use only if universal newborn hearing screening (UNHS) was unavailable. Only 2% to 5% of neonates with one or more risk factors exhibit a moderate to profound hearing loss. Conversely, 95% to 98% of neonates with one or more risk factors have normal hearing.[7] Furthermore, 50% of children with moderate to profound congenital hearing loss exhibit no risk factors for hearing loss.[8] This means that use of the HRR alone, as an indication for hearing testing, would leave at least 50% of infants with congenital hearing loss undiagnosed. In 2007, the JCIH recommended hearing screening for all newborns, with formal audiologic assessment in those who fail the initial screening test by 3 months of age, followed by intervention by 6 months of age for children with significant hearing loss.[9]

Delay in Identification

A significant delay exists in the identification and intervention of hearing impairment for infants without risk factors. For infants with mild to moderate hearing loss, a 1996 survey showed that parents of high-risk infants first suspected the loss when their infants were at a median age of 8 months. By contrast, the parents of infants without risk factors first suspected their infant had a hearing loss when the child was 15 months old.[10,11] Hearing loss was confirmed in infants without risk factors at 22 months of age, compared with 12 months of age for infants with risk factors, and infants were enrolled in intervention at 28 and 18 months, respectively. Ages of suspicion (7 to 8 months), diagnosis (12 to 13 months), and intervention (18 to 19 months) were essentially the same for infants with severe to profound hearing loss, regardless of whether risk factors were present. Recent retrospective studies indicate that infants with hearing loss enrolled in appropriate early intervention by 6 months of age incur significantly fewer delays than those who enroll after 6 months of age.[10,12] These findings are for children with all degrees of hearing loss, as well as for children with other handicapping conditions.

Universal Newborn Hearing Screening

In 1993, the National Institute for Deafness and Other Communicative Disorders (NIDCD) Consensus Conference on Early Identification of Hearing Loss recommended UNHS for infants within the first 3 months of life, preferably before hospital discharge.[13] Subsequently, several organizations and government agencies have endorsed UNHS as the best way to ensure early detection and habilitation of hearing loss. These groups include the Academy of Otolaryngology–Head and Neck Surgery, American Academy of Pediatrics, American Speech-Language-Hearing Association, American Academy of Audiology, and others. Despite considerable disagreement concerning the relative merits of specific measurement approaches for neonatal hearing screening and whether UNHS is even appropriate at this time,[14] universal newborn and infant hearing screening statutes have been passed in 41 states (legislation is pending in two states), and all states have implemented newborn hearing screening programs.[9] The goals of the U.S. Department of Health and Human Services' initiative Healthy People 2010 include UNHS by 1 month of age, diagnostic confirmation of hearing loss by 3 months of age, and enrollment in appropriate early intervention for children with hearing loss and their families by 6 months of age.[15] The Newborn Infant Hearing and Screening Intervention Act of 1999 provided funding to help states reach this goal. In 2008, the U.S. Preventive Services Task Force published a grade B recommendation to screen for hearing loss in all newborn infants.[16]

Prevalence of Sensorineural Hearing Loss in Children

Estimates of congenital sensorineural hearing loss (SNHL) vary, ranging from 1 per 1000 to 3 per 1000 live births, depending on the degree of hearing loss. Bilateral severe to profound hearing loss (70 dB HL or greater) occurs in 1 per 1000 live births. When the results of several studies are averaged, approximately 3 per 1000 infants have a hearing loss of 30 dB or greater.[17-21] The incidence of significant hearing loss is 10 times greater for infants with one or more risk factors than for those with no risk factors.

Progressive, late-onset, and acquired hearing loss in childhood is a continuing challenge. In its survey of deaf and hard-of-hearing school-aged children, Gallaudet Research Institute found a prevalence of significant hearing loss of 1.8% in children 3 to 17 years of age.[22] This figure is six times higher than the incidence of hearing loss in the neonatal period. Similarly, van Naarden and colleagues[23] reported that the average point prevalence of hearing losses 40 dB or greater increased with age from 0.67% at 3 years of age to 1.38% at 10 years of age. It is important that hearing, speech, and language development be monitored because of the occurrence of progressive, late-onset, and acquired hearing loss in early childhood.

Increase in Early Identification

In those states with UNHS, the average age of identification of congenital hearing loss has dramatically decreased. Rhode Island mandated UNHS in 1993. In 1998, Vohr and colleagues[24] reported that the average age at confirmation of permanent hearing loss in Rhode Island infants was 3 months. By contrast, in the absence of UNHS, the average age at diagnosis of permanent hearing loss in children was 31.25 months. In its 1999 Policy Statement, the American Academy of Pediatrics noted: "Reliance on physician observation and/or parental recognition has not been successful in the past in detecting significant hearing loss in the first year of life."[25] Long-term prospective studies of deaf and hard-of-hearing children identified through newborn hearing screening programs are needed to determine if in fact educational and vocational outcomes are significantly better for these children. A recently published controlled trial in the United Kingdom demonstrated that UNHS increased the proportion of 7- to 9-year-old children with permanent hearing loss who were identified before 6 months of age.[26] Strong data illustrating improved speech and language development from early interventions are lacking, but one controlled trial found that early detection of childhood hearing impairment leads to higher language scores (but not speech scores) in mid-childhood.[27]

Principles and Techniques of Newborn Hearing Assessment

Testing Protocols

The goal of newborn hearing screening is to identify those infants who need diagnostic hearing evaluations because they are at risk for significant hearing loss. With current technology, screening outcomes are either "pass" or "refer" (Fig. 190-1). "Pass" indicates the infant is not at risk for significant hearing loss and needs no further testing at this time. "Refer" indicates the infant is at risk for hearing loss and requires a diagnostic hearing evaluation. It is important to emphasize to parents and health care providers that "refer" does not mean that the baby has a hearing loss; this designation indicates only that the child has a greater risk of having hearing loss.

For many years, a primary barrier to UNHS was the lack of affordable, reliable, easy-to-use methodology. A hearing screening test has several requirements. First, the response being measured must be robust, specific to the peripheral auditory system, and present in all normal-hearing newborns. Second, the response criteria must be objective, based on scientific data, and applied consistently. Third, the measurement procedures must be noninvasive, rapid, reliable, and easy to use, with capability for separate testing of each ear. Behavioral methods do not meet these requirements. At present, one of two physiologic measures of auditory system status is used singly or in combination in most UNHS programs. Current technology uses automated protocols and pass-refer criteria. Such algorithms allow the use of less experienced testers, thereby reducing the cost of screening and removing some of the variability in test administration.

Auditory Brainstem Responses

The auditory brainstem response (ABR) is a series of scalp-recorded electrical potentials generated in the auditory nerve and brainstem during the first 10 to 20 ms after the onset of a transient stimulus. For the purposes of a hearing screening, responses typically are elicited by air-conducted clicks presented at a level that is thought to produce a response in ears with normal hearing and to produce no response in ears with

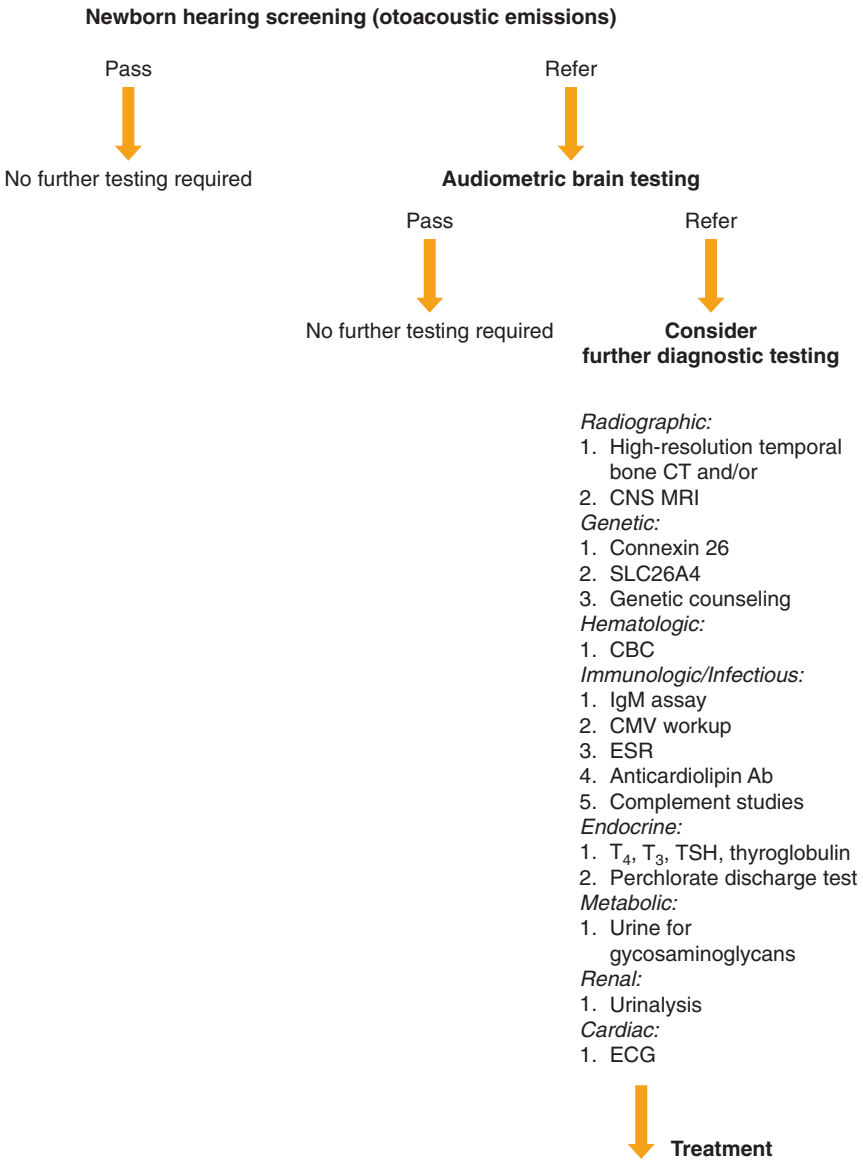

Figure 190-1. Algorithm for newborn hearing screening. Ab, antibody; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; MRI, magnetic resonance imaging; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

hearing loss (30 to 35 dB normal hearing level [nHL]). Surface electrodes record the synchronized time-domain averaged response to the click.

In response to a click stimulus of known intensity, ABR latency and morphology are highly predictable for infants of a given age. This evoked potential is present in human neonates as early as 25 weeks of gestational age and is unaffected by sleep, attention, or sedation. ABR morphology changes rapidly with age during infancy because of maturation of the central nervous system (CNS). Therefore, it is important to use age-appropriate latency-intensity norms in judging the quality of ABR. ABR is affected by external and middle ear, cochlear, auditory nerve, and brainstem status. Middle ear disease or anomaly reduces the stimulus intensity, thus increasing the latency and decreasing the amplitude of the ABR. Cochlear abnormalities affect the quality and morphology of the ABR in many different ways. Response amplitude may be reduced, latency may be increased, or waveform morphology altered, depending on the degree and configuration of the hearing loss. Brief stimuli such as clicks have a broadband frequency spectrum. Click-evoked ABR is not frequency-specific. Any region of normal hearing can generate the response if there is sufficient energy in the stimulus at that frequency. ABR also is abnormal in the presence of eighth cranial nerve and lower brainstem abnormalities even if peripheral hearing loss is not present.

ABR has been used for many years to screen infants in the neonatal intensive care unit (NICU) before hospital discharge.[28-32] Recent advances have resulted in the development of automated ABR detection algorithms.[33-37] These systems replace the subjective impression of the tester as to the presence or absence of an ABR, with an objective statistical estimate of the likelihood or probability of a "response" distinct from the background "noise."

Evoked Otoacoustic Emissions

Evoked otoacoustic emissions (EOAEs) are also used widely for newborn hearing screening. EOAEs are acoustic signals generated by the cochlea in response to auditory stimulation. They are a physiologically vulnerable indicator of cochlear status, specifically outer hair cells. EOAE generation is independent of neural activity, so EOAE testing measures cochlear status independent of CNS status. Transient evoked otoacoustic emissions (TEOAEs) occur after a brief click stimulus.[38] TEOAEs provide information over a broad frequency range (approximately 500 to 6000 Hz). Distortion product otoacoustic emis-

sions (DPOAEs) occur in response to simultaneous presentation of two pure tones with the appropriate frequency and amplitude ratios and provide frequency-specific information across a broad range of frequencies.[39]

Almost immediately after the first otoacoustic emissions (OAEs) reports by Kemp and Ryan[40] and Kemp, several investigators suggested that one of the potentially most useful clinical applications of OAE is assessment of cochlear status in infants.[41,42] In theory, OAEs were thought to (1) take less time to measure than an ABR, because OAEs do not require electrode attachment, (2) provide information over a broader frequency range than click-evoked ABR, and (3) provide cochlear-specific information unaffected by neurologic pathology.

Data from several groups of investigators indicate that robust, broadband TEOAEs can be measured in neonatal ears in the absence of external or middle ear pathology.[40,43,44] Likewise, data indicate that DPOAEs are robust in neonates and infants.[45-49]

Concerns about OAE-based neonatal hearing screening include difficulty testing in noisy environments, and the effects of vernix and other debris in the ear canal, as well as collapsing ear canals during the first 24 hours after birth.

Comparison of Otoacoustic Emissions and Auditory Brainstem Responses

In summary, technologic advances now make it possible to assess auditory function in neonates and infants. These electrophysiologic and acoustic responses can be safely applied without reliance on a behavioral response. However, neither OAE nor ABR tests evaluate hearing or describe how a particular person will use available hearing. OAE and ABR are physiologic responses related to peripheral hearing status but constitute indirect measures of hearing.

To predict hearing status in children 8 to 12 months of age, a multicenter longitudinal study compared the accuracy of click-evoked ABRs, TEOAEs, and DPOAEs. The results indicated no significant differences among the three measures.[48] However, a recent study comparing two-step TEOAEs and ABRs found that ABR was more effective for UNHS because it yields fewer false-positive results and a lower referral rate compared with TEOAE, resulting in a smaller percentage of infants lost during follow-up.[50]

Typically, a simple pass-refer criterion is chosen for a screening tool. Many studies and these programs assume a priori that all infants who "passed" the screen had normal hearing. To determine the true accuracy of neonatal tests, however, it is necessary to follow all infants evaluated during the neonatal period, regardless of neonatal test outcome.[48] Because the true hearing status of those infants who pass the screening test is not known, true sensitivity cannot be calculated. Errors made among infants with normal hearing can be known because these false-positive results are evaluated with additional testing. The fact that the "passes" may include infants with hearing loss will have little or no influence on the true-negative rate or specificity of the test, because the vast majority of infants have normal hearing. However, the errors among ears with hearing loss (false-negative results) cannot be known if only those infants failing the newborn hearing test are followed. This is because misses are not followed up. Assigning a "pass" to even a small number of babies with hearing loss can have a large effect on test sensitivity because of the small total number of those with hearing loss.

The sensitivity and specificity of ABR, TEOAE, and DPOAE testing alone or in combination depend on the target degree of hearing loss, the test parameters, and response criteria. For example, Hyde and associates[51] reported ABR sensitivity of 98% and specificity of 96% if the average target hearing loss is 40 dB nHL at 2 and 4 kHz. If the target degree of hearing loss is 30 dB nHL, sensitivity and specificity were 100% and 91%, respectively. Norton and coworkers held specificity at 80% and determined sensitivity for TEOAE, DPOAE, and ABR alone and in combination for a target loss of 30 dB nHL. Sensitivity ranged from 80% to 90%. If those infants with known progressive hearing loss were excluded, sensitivity improved.[48]

Because it is impossible for hospital-based screening UNHS programs to follow all infants screened regardless of test outcome, it is important to remember that no test is perfect. Click-evoked ABR often misses hearing losses in which hearing is normal at some frequencies. For example, a baby with a low-frequency hearing loss with normal thresholds at 2000 Hz and above will pass an ABR screening test. Likewise, a baby with high-frequency hearing loss with normal hearing at lower frequencies may pass an ABR screen. High-frequency hearing losses are relatively common and may have significant effects on speech and language development.

OAE testing may miss inner hair cell and eighth cranial nerve hearing losses. OAEs are generated by the outer hair cells and are independent of neural status. Recently, there are concerns about auditory dyssynchrony,[52] defined as robust OAEs and abnormal or absent ABR. This is an extremely heterogeneous population whose behavioral hearing status ranges from normal hearing to profound hearing loss. Good incidence data of this disorder in the neonatal population are scarce.

Physicians and parents must include regular monitoring of hearing, speech, and language milestones even for those infants who pass a newborn hearing screening test whether it is TEAOE, DPOAE, or ABR.

Common UNHS protocols include OAE testing before discharge followed by an outpatient OAE re-screen for inpatient referrals, OAE inpatient screen and ABR re-screen, OAE and ABR inpatient screens, and ABR inpatient and ABR re-screens. Outpatient re-screens help minimize the number of infants referred for diagnostic audiologic testing and hence costs. Persistent re-screening is inappropriate. Infants should be referred for diagnostic follow-up evaluation after two failed screenings.

Some hospitals implement two-stage screening, in which OAE is used as the preliminary screening test. Infants failing this test are then screened with the automated ABR (AABR). Those who fail the AABR undergo more diagnostic testing to evaluate for permanent hearing loss, but infants who pass the AABR are not tested further. A multicenter evaluation of the two-stage screening revealed that many infants with hearing loss may be missed, because infants who pass only the AABR are not referred for further testing.[53]

Diagnosis and Treatment of Hearing Loss in Infants

History

In infants who fail hearing screening tests, a directed history to identify potential sources of hearing loss is appropriate.[54] A careful family history looking for hearing loss, ocular abnormalities, congenital cardiac problems in first- and second-degree relatives, and any associated syndromes is essential. Prenatal history for possible maternal infection (i.e., TORCH), gestational diabetes, and hypothyroidism can help direct the evaluation. Maternal use of alcohol should be sought, because fetal alcohol syndrome is associated with auditory dysfunction. Other maternal illnesses and social habits (e.g., drug use and smoking) should be sought. Risk factors for hearing loss in the perinatal period are well known, as discussed earlier in this chapter.[6,55]

Physical Examination

A majority of newborns with hearing loss do not have abnormal physical features.[56] Nevertheless, a complete physical examination is essential. Presence of abnormal iris color, skin tags, anterior cervical neck pits, goiter, cleft palate, skull shape, abnormal numbers of digits, areas of hypopigmentation, and café au lait spots are potential signs of a syndromic disorder. Such a diagnosis, such as Wardenburg's or branchio-oto-renal syndrome, may explain hearing loss identified through infant hearing screening. Alternatively, these physical signs may prompt careful follow-up investigation and imaging to identify progressive sensorineural hearing loss or conductive hearing loss, which may occur in neurofibromatosis or craniosynostosis. Pendred's syndrome may be associated with goiter development. Stickler's syndrome has characteristic eye and facial features, along with cleft palate. Patients suspected of having possible branchio-oto-renal syndrome need a renal ultrasound examination. Those patients identified with severe to profound sensorineural hearing loss and neurologic and ocular abnormalities should

have serial ophthalmologic evaluations to evaluate for retinitis pigmentosa. Electroretinography may uncover early forms of this abnormality, allowing early identification of Usher's syndrome. At this point the exact indications for this testing modality are unclear, but some investigators recommend electroretinography in all cases of undetermined bilateral severe to profound sensorineural hearing loss.[57] In any case, ophthalmologic examination is warranted, because up to one half of children with severe to profound hearing loss have ocular defects.[58]

Vestibular Function Assessment

When hearing loss is identified, careful attention to vestibular function is necessary.[59] A strong association exists between hearing loss and impaired vestibular function in infants and children. Neurologic and developmental milestones are important to record. Signs of peripheral vestibular dysfunction can occur with delayed motor development. Evaluation for the presence of nystagmus (i.e., spontaneous or head shaking type) can be done in infants. When nystagmus is present, further testing may be warranted.

Otomicroscopy

Infants who fail hearing screening tests should have careful middle and external auditory canal examinations with the otomicroscope, because a problem with the middle and external auditory canals is the most common source of failed initial hearing screening.[60] This type of examination allows careful cleaning of the ear canal and identification of external auditory canal stenosis or atresia.[61,62] Additionally, assessment of middle ear function may be possible with this method by assessing the thickness and character of the tympanic membrane, as well as its motion. In older children, tympanometry and pneumatic otoscopy by experienced examiners both measure middle ear status accurately, but in infancy (0 to 6 months of age) both measures can miss detection of middle ear effusions.[63]

Middle Ear Effusions

When persistent middle ear effusions are identified as a potential source of an abnormal hearing screening, observation is essential when there is no evidence of acute inflammation. The incidence of middle ear effusions in the first year of life is quite high and in infancy it is estimated to be as high 61%.[64] In our practice, we usually wait 2 to 3 months for spontaneous resolution of the middle ear effusion. If the effusion persists after that time, ABR testing is still performed to determine whether there is a response to sound. No clear guidelines for medical therapy have been developed for infants with persistent middle ear effusions. Oral steroid therapy can be given to clear the effusion, but in infancy the risks of this treatment must be weighed against its benefits.[65] If the child has acute otitis media, antibiotic therapy is necessary along with observation for effusion resolution. Tympanostomy tube insertion is done for persistent middle ear effusion. Usually the recommendations for treatment of persistent otitis media with effusion in children between 1 and 3 years of age as outlined in 1994 by the Agency for Health Care Policy and Research also are used in young infants.[66,67] However, no outcomes studies have been conducted to demonstrate the most effective therapy for middle ear effusions in children younger than 1 year of age.

Diagnostic Audiology

As mentioned earlier in this chapter, all infants not passing a newborn hearing screening should be referred for diagnostic audiology by 3 months of age. Diagnostic follow-up investigation for infants referred from newborn hearing screening programs should include threshold frequency–specific ABR and OAE testing. Frequency-specific ABR thresholds have good agreement with behavioral thresholds[68] and can be used to fit appropriate amplification and guide intervention. Air and bone conduction should both be evaluated using tone-pip ABR. A significant air-bone gap in ABR thresholds is indicative of external or middle ear pathology, just as with pure-tone audiometry. EOAE should always be obtained with ABR testing to rule out auditory neuropathy and other neural losses. Tympanometry using a probe-tone frequency of 1000 Hz or higher can provide information about middle ear status. In children younger than 4 months of corrected age, traditional tympanometry—using a 226-Hz probe tone—is invalid because of the characteristics of the neonatal ear canal.[69]

Visual Reinforcement Audiometry

Visual reinforcement audiometry (VRA) is a modification of standard audiometric testing, designed for infants who are unable to understand verbal instruction. In VRA, operant conditioning techniques are used to reward a natural orienting response of the infant by providing an enjoyable event to reinforce the likelihood of continued responses. An infant's natural response to sound is a head turn in the direction of the sound source. When that response is rewarded by the activation of a lighted, animated toy, the infant may continue to respond for a sufficient number of stimulus trials to obtain an audiogram.[70]

VRA thresholds for infants as young as 6 months of age have been shown to be within 10 dB of adult hearing thresholds. VRA thresholds have been shown to be comparable to thresholds obtained by play audiometry in children of preschool age.[71-74] Good agreement between VRA and tympanometry indicates that the method is sensitive enough to detect even slight threshold elevations, such as those due to middle ear effusion. VRA is not restricted to sound field testing. Numerous reports indicate that VRA testing can be done reliably under earphones. Infants born prematurely who have spent time in the NICU tend to perform better if testing is delayed until 6 to 8 months corrected age. By 12 months of age, infants have been shown to need fewer conditioning trials, be less variable in responses near threshold, and yield fewer false-positive responses in comparison with infants who are 6 months of age; however, older infants tend to reject earphones more frequently than younger ones.[73-76]

Ancillary Testing

Ancillary Laboratory Testing

No evidence shows that standardized batteries of laboratory tests in infants failing initial hearing screening are necessary or cost effective.[56] All testing in these infants should be directed by hearing testing results and patient age, history, and physical examination.[77] These tests usually exclude specific causes of hearing loss but on occasion can confirm a diagnosis. Routine blood chemistry and complete blood count are unhelpful in evaluating hearing loss in infancy. If there is a family history of hematologic disease, such as thalassemia or sickle cell disease, screening can be performed for these disorders.[78,79] Diseases with platelet abnormalities that usually appear later in life (e.g., Fechtner or Epstein-Barr syndrome) can be discovered.[80] Such diseases are associated with sensorineural hearing loss.[12,38] Similarly, Alport's syndrome can be suspected when laboratory evidence for renal dysfunction is present with hearing loss. Autoimmune-induced hearing loss can occur in children but is not routinely suspected in infants.[63] Metabolic disorders, such as mucopolysaccharidoses, are associated with both conductive and sensorineural hearing loss and should be tested for when assessment reveals a family history of metabolic disorders, with hearing loss or physical features consistent with this diagnosis.[81,82] When the family history includes syncopal episodes and hearing loss, an electrocardiogram should be obtained to look for evidence of Jervell and Lange-Nielsen syndrome.

Guidelines for Genetic Testing

Deafness in infancy is believed to be at least 50% genetic in origin, with the remaining 50% being acquired or of unknown etiology.[83] Of the cases of genetic deafness, 75% to 80% are autosomal recessive, 15% to 20% are autosomal dominant, and 1% to 2% are X-linked. A few patients acquire hearing loss through mitochondrial inheritance. Of note, newborn hearing screening does not identify progressive hearing loss, which does occur in preschool-aged children. It is estimated that 15% to 20% of young children identified with SNHL have progressive hearing loss. Among children with SNHL in infancy, chromosomal karyotyping is recommended for those with a maternal history of multiple miscarriages and an unrecognizable constellation of anomalies. Additionally, if there are any associated neurologic or cardiac defects, chromosomal karyotyping is essential. Rapid advances in

molecular genetics ensure that many new diagnostic methods for detection of the genetic basis for hearing loss will become available by the next decade.

Screening for Connexin 26 Mutation

In the late 1990s and early in the millennium, the autosomal recessive inheritance of hearing loss was linked to mutations at *GJB2*.[84,85] This gene codes for connexin 26 and is believed to be responsible for up to one half of all cases of autosomal recessive congenital hearing loss. The 35delG deletion is responsible for 70% of all connexin 26 mutations. The autosomal recessive non-syndromic hearing loss mutation in connexin 26 is known as DFNB1 (in genetic notation, the prefix DFNB signifies autosomal recessive hearing loss).[86] DFNB1 is associated with prelingual nonprogressive bilateral sensorineural hearing loss without evidence of temporal bone computed tomography (CT) anomalies or vestibular abnormalities. The hearing loss associated with this deletion can range from mild deficits to profound deafness. Considerable interfamilial variation in degree of hearing loss is recognized among affected families. Because the 35delG mutation involves a single base pair, screening tests for this deletion are available. It is estimated that the connexin 26 deletion is responsible for 50% of the cases of autosomal recessive sensorineural hearing loss.[87] Within this family of connexins, however, 60 different allele variations exist and therefore the hearing loss may not always be simply a result of the 35delG mutation.[88] When a child is born homozygous for the 35delG mutation, the chance of recurrence is 25%. The same chance of occurrence is present in a heterozygous patient. Siblings of affected persons have a 66% chance of carrying the deletion while having normal hearing.[89] Therefore, when testing for the 35DelG mutation is performed, genetic counseling should also be available.

Testing for Pendred's Syndrome

Genetic testing can be performed when Pendred's syndrome is suspected.[86] Pendred's syndrome represents 10% of the cases of syndromic hearing loss and is the most common cause of syndromic hearing loss. It is associated with a dilated vestibular aqueduct on temporal CT scanning.[90] Screening for mutations at *SCL26A4* (*DFNB4*) is done in the research setting.[85] Results of thyroid function tests usually are normal, with the exception of thyroglobulin levels, which can be elevated. The perchlorate discharge test is nonspecific and difficult to perform in young children.

Temporal Bone Imaging

Noncontrast temporal bone CT scanning is the imaging test most commonly used for all children with SNHL. Increasingly, T2-weighted MRI is being used as new techniques have enhanced its capability to delineate anatomy. (See also Chapter 191 in this text.) The timing of the imaging is debated and is beyond the scope of this chapter to discuss. It should definitely be performed at any age in all patients with progressive SNHL or craniofacial anomalies. These clinical signs are the best predictive factors for abnormalities within the temporal bone.[91] As mentioned earlier, the dilated vestibular aqueduct is associated with Pendred's syndrome.[92] A dilated vestibular aqueduct is defined as one with a diameter greater than 1.5 mm at its middle third or greater than 2.0 mm anywhere along its length. When a dilated duct is discovered, testing for Pendred's syndrome should be initiated, along with serial audiologic examinations to detect progressive hearing loss. Mondini dysplasia reflects abnormal development of the cochlea and is associated with both Pendred's and branchio-oto-renal syndromes.[93] Abnormalities of the semicircular canals also are seen on temporal bone imaging and are associated with a well-recognized constellation of manifestations: coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary problems, and ear abnormalities—the CHARGE association.[94] Superior semicircular canal dehiscence also can be identified radiographically and has been associated with conductive hearing loss in children, albeit in rare cases.[95]

Identification of internal auditory canal stenosis and possible eighth cranial nerve aplasia is associated with hereditary deafness. This X-linked form of deafness (DFN3) is associated with conductive loss at birth, followed by SNHL at a later age. Magnetic resonance imaging (MRI) scanning can be used to visualize the acoustic nerve, exclude aplasia, and rule out inner ear destruction secondary to infectious causes.[96] In cases in which infection or neoplasia is suspected, MRI with contrast is favored.[97] Accurate imaging of the seventh and eighth cranial nerve complex may be necessary before consideration for cochlear implantation.[98] Functional MRI scanning may help elucidate the exact nature of SNHL found in infancy.[99,100] Additionally, central auditory processing may be further clarified with this modality.[101] Because of its soft tissue detail,[102] some investigators feel that MRI should be performed in cases of pediatric unilateral or asymmetrical SNHL in which CT findings are negative, to rule out a CNS cause of hearing loss.[103] MRI also is indicated in patients who may have neurofibromatosis type 2. If CT results are negative but hearing loss is progressive, or if audiologic testing reveals a possible retrocochlear pathology, MRI also may be warranted.[104]

Screening for Maternally Transmitted Infection

Other laboratory evaluations may include specific immunoglobulin M (IgM) testing for suspected intrauterine infection. IgM does not cross the placenta and, if present in the infant's blood, may suggest congenital cytomegalovirus (CMV), syphilis, or rubella infection. Further testing to elucidate these potential sources of hearing loss may include cultures for CMV in blood, urine, or saliva. Congenital CMV infection is a frequent congenital infection that can have significant neurologic sequelae.[12] Hearing loss can be the only manifestation.[105] The virus persists in infected infants and can be detected in the first 3 months of life. When the virus is detected, early treatment may lessen the severity of neurologic sequelae. With congenital syphilis, the fluorescent treponemal antibody absorption (FTA-ABS) test indicates intrauterine transmission of syphilis.[106] Congenital toxoplasmosis is present in 0.6% of newborns. Hearing loss is present in 10% to 15% of these newborns and usually is associated with other abnormalities (i.e., chorioretinitis, intracerebral calcification, and microcephaly). Early identification of the potential for this infection suggests that treatment may reduce the level of hearing impairment. Herpes simplex type 2 usually is transmitted through contact with vaginal lesions at the time of delivery and is associated with a low incidence of hearing loss. On the other hand, herpes simplex type 1 is associated with hearing loss in transplacental transmission.[107] Detection of IgM antibodies to this virus raises this infection as a possible source of hearing loss. Congenital rubella can be detected through serologic testing. Although the incidence of this infection has significantly decreased in recent times, it still is present, particularly in underdeveloped countries, and hearing loss is estimated to be the only sign of this infection in 50% of cases.[83]

Intervention Strategies

Surgical Therapy for Conductive Hearing Loss

Newborns with conductive hearing loss most commonly have middle ear effusions. If the actual hearing threshold needs to be established, then tympanostomy tube insertion is necessary. Other types of surgery to correct conductive hearing loss are beyond the scope of this discussion and are not usually attempted in infancy.

Bone Conduction Amplification

Hearing aids should be considered for any child who demonstrates a permanent bilateral hearing loss—both conductive and sensorineural—exceeding 20 dB HL between 1000 and 4000 Hz.[108] Even children with minimal hearing losses are at risk for experiencing educational difficulty.[109,110] A bone conduction hearing aid is fitted when the child is unable to wear air conduction hearing aids as a result of atresia, stenotic ear canals, or recurrent draining middle ears. Bone-anchored hearing aids are not approved by the U.S. Food and Drug Administration (FDA) for children younger than 5 years of age.

Amplification

Hearing aids should be fitted as soon as possible after confirmation of a hearing loss. As infants are identified earlier as a result of UNHS, audiologists face many challenges in fitting hearing aids, including size

of the head and ear canal, poor head control, behavior, and rapid growth. Children younger than 7 years of age should be fitted with either behind the ear (BTE) hearing aids or bone conduction hearing aids.[108] Smaller styles of hearing aids, such as in the ear (ITE) and completely in canal (CIC) aids, are inappropriate for infants and young children whose ear canals are constantly increasing in size. Increasing ear canal size means that new ear molds must be made frequently to ensure proper amplification. ITE and CIC hearing aids would necessitate recasting, leaving the child without amplification during this process. Furthermore, ITE and CIC hearing aids pose a significant safety issue.

Hearing aid evaluation and selection involve determination of the appropriate circuitry and processing algorithm based on the child's degree, configuration, and type of hearing loss, plus the child's developmental needs and family resources. A selection and fitting technique designed for infants should be employed. The most widely used procedure involves measurement of the real-ear-to-coupler (RECD).[109-111] In addition, a technique such as the desired sensation level (DSL) method should be used to ensure audibility of the amplified speech, regardless of input level or vocal effort.[112,113]

Infants, particularly those with hearing losses of 55 dB and above, should be fitted with personal wireless frequency modulation (FM) systems to improve the speech-to-noise ratio. A receiver attaches to the child's hearing aid, and the caregiver wears a microphone and transmitter. Use of an FM system also reduces the feedback problems often encountered with infants, who have poor head control and mobility.

Regular follow-up appointments with the audiologist are critical for optimal fitting and usage of amplification devices for infants. Generally, infants are seen for follow-up appointments at least every 3 months during their first year. Ear molds may need to be remade even more frequently for some children. Other important considerations for children include tamper-resistant battery doors and controls, clips to secure the hearing aid to the child's clothing to prevent loss, listening tubes for parents, and extended warranties for loss and damage. Orientation for parents and other caregivers should include care and use of the hearing aid and FM system including wearing schedules, insertion, removal, storage, cleaning, and basic troubleshooting.

Sound field–aided testing often is used to confirm audibility. Aided testing provides information about how the child uses the signal provided by the hearing aid. That is, RECD and DSL are used to select, fit, and verify proper hearing aid function and audibility, whereas sound field testing provides information about how the child is using his or her hearing. Misleading information may be obtained in cases of severe to profound hearing loss or minimal hearing loss, or when nonlinear signal processing or digital noise reduction circuitry is used.[112]

Cochlear Implantation

A discussion of all aspects of cochlear implantation in children is beyond the scope of this chapter. Some general considerations are presented here.

When SNHL is identified and hearing aid amplification is applied with success, consideration for cochlear implantation is entertained. It is our practice to carefully evaluate each patient to establish candidacy for this procedure. As time has gone on, the indications for implantation have broadened and continue to evolve. Several studies indicate that the younger the age at which children with severe to profound hearing loss receive a cochlear implant, the better their auditory oral speech and language skills, and the more likely they are to be mainstreamed with their normal-hearing age peers. The FDA has approved cochlear implants for infants with profound hearing loss at 12 months of age and at 18 months of age for those with severe hearing loss. Increasingly, infants younger than 12 months of age are receiving cochlear implants. The key component of all treatment is identification of the type and extent of the hearing loss. Once this has been established, appropriate rehabilitative measures can be initiated, which eventually may include cochlear implantation. Several temporal bone abnormalities that may preclude this intervention are cochlear ossification and vestibular nerve aplasia. Enlarged vestibular aqueduct (EVA) syndrome has been thought to be a contraindication to implantation in the past, but not at present. Postmeningitic deafness is associated with cochlear ossification, and early implantation is recommended by some investigators to avoid the difficulties encountered when the cochlea is ossified. If the vestibular nerve is nonexistent, implantation will not help.

Early Intervention

Hearing loss in infants is primarily a communication problem, limiting the child's access to spoken language. Hearing loss happens to the family, not just the child. Providing the infant with full access to communication is the primary goal of early intervention. In addition to the use of assertive listening devices, parents learn to accommodate their baby's communication needs. The Individuals with Disabilities Education Act (IDEA) mandates early intervention services for children 0 to 3 years of age.[114] These programs are administered by individual states. Physicians should consult with local agencies to learn more about the services in their home state. Services for infants with hearing loss and families are generally home-based. There may be play groups and parent groups, but IDEA specifies that a majority of services be delivered in natural environments (i.e., where infants without disabilities are found). Because of the unique language and communication needs of deaf and hard of hearing (D/HOH) children, it is critical that services be provided by professionals with expertise in childhood hearing loss and early childhood education.

Historically, controversies in the education of D/HOH children have focused on communication methodology. Three broad categories exist: American Sign Language (ASL), simultaneous communication using spoken and signed English, and auditory-oral only. The history and nuances of this issue are beyond the scope of this discussion. Parents of children with hearing loss repeatedly stress that they want full unbiased access to information about their options, that they want to talk to other parents and not just to professionals, and that they are in charge of making decisions about their baby's communication needs.

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CHAPTER ONE HUNDRED AND NINETY-ONE

Congenital Malformations of the Inner Ear

Robert K. Jackler

Key Points

- In congenital SNHL, approximately 20% of inner ears demonstrate a radiographically detectable abnormality.
- Many patterns of deformity appear to result from disturbance in the embryogenesis of the inner ear during the first trimester.
- Enlargement of the vestibular aqueduct is most common, followed in frequency by semicircular canal and cochlear deformities.
- The imaging patterns of cochlear anomaly include aplasia, hypoplasia, incomplete partition, and common cavity.
- Semicircular canals may be absent (aplastic) or deformed (dysplastic).
- The eighth nerve may be aplastic or hypoplastic, especially when the internal auditory canal is narrow.
- Congenital ear malformations may be a feature of syndromes such as Pendred's and Usher's syndromes, the CHARGE association, and various trisomies.
- High-resolution T2-weighted MRI is superior to CT because it shows the endolymphatic sac and eighth nerve.
- Hearing in milder deformities is variable but tends to worsen over time.
- Pseudoconductive hearing loss may be present, with a high risk for dead ear and occurrence of CSF "gusher" at stapes surgery.
- Predilection for stapes gusher, due to modiolar defects, may be inherited in an X-linked pattern.
- Head trauma may cause sudden decrease in hearing.
- May be associated with transotic CSF leak and recurrent meningitis.
- Surgery on the endolymphatic sac or middle ear windows has not been shown to improve or stabilize hearing.
- Cochlear implantation usually is successful but carries a heightened risk for CSF leak, meningitis, and facial twitch.

Development of the inner ear begins early in embryogenesis. By the end of the eighth week, the membranous labyrinth has assumed its characteristic convoluted shape.[1] Gradual ossification of the otic capsule develops around the membranous labyrinth and is essentially complete by birth.[2] Maturation of the sensory epithelium occurs long after formation of the membranous labyrinth, during the late second and early third trimesters. By weeks 26 to 28 of gestation, hair cell and auditory neural development are largely complete. Thus, the normal human fetus may be able to hear 2.5 to 3 months before birth.

Most inner ear malformations arise when formation of the membranous labyrinth is interrupted during the first trimester of pregnancy.[2] This interruption may be either a result of inborn genetic error or a consequence of a teratogenic exposure during the period of inner ear organogenesis between the fourth and eighth weeks of gestation. Genetic errors may be either dominant or recessive and may manifest as sensorineural hearing loss (SNHL) alone or be associated with any of a number of syndromes.[4] A partial list of syndromes associated with radiologically detectable inner ear malformation includes Pendred's, Usher's, Waardenburg's, Wildervanck's (cervico-oculoacoustic), branchio-oto-renal, and Alagille's sundromes.[5-8] Nonsyndromic familial inner ear malformations have also been described.[9,10] Teratogenic influences known to affect inner ear organogenesis include in utero viral infection (e.g., rubella, cytomegalovirus infection), chemical teratogens (e.g., thalidomide), and radiation exposure.[11] Abnormalities in otic capsule structure and deficiencies in the organ of Corti appear to arise as secondary effects of the earlier error in development of the membranous labyrinth. Derangement of the otic capsule ossification process alone does not appear to be a major mechanism in congenital hearing loss. Ossification of the labyrinthine lumen, however, is a common finding in early acquired deafness, typically arising as a consequence of meningitis.

Developmental damage to cochlear structure and function is not restricted to agents that cause gross structural malformations. Even in doses below those that would be ototoxic in the adult, aminoglycoside antibiotics administered in the animal equivalent of the human first trimester of pregnancy cause severe hearing loss in several species.[12] This time frame corresponds to the maturation of the outer hair cells and initiation of the cochlear potentials. Human studies also document this. In 35 of the infants delivered by 72 women who received streptomycin prophylaxis for tuberculosis during the first 4 months of pregnancy, auditory deficits ranging from minor high-frequency threshold elevations to severe bilateral SNHL were noted.[13]

The risk is not restricted to the first trimester. Even at low doses, slighter hearing losses were noted when aminoglycoside antibiotics were administered during the human equivalent of the last two trimesters of pregnancy, which has obvious implications for use of these drugs in pregnant women and in premature infants who have not yet reached functional cochlear maturity.

Congenital anomalies of the inner ear may be considered in two broad categories: malformations with pathologic changes limited to the

membranous labyrinth and malformations that involve both the osseous and membranous portions of the labyrinth. This division has been chosen because of its clinical relevance. Only patients with malformed otic capsules exhibit abnormalities on inner ear radiographs and therefore may be diagnosed during life. By inference, children with congenital SNHL and radiographically normal inner ears may be assumed to possess anomalies limited to the membranous labyrinth or neural pathways. Although several types of membranous deformities have been described, their classification is not yet of clinical use because differentiation requires histopathologic examination. Among the deformities that affect the otic capsule, a variety of morphologic patterns may be recognized radiographically, and classification may have prognostic and even therapeutic importance.

Incidence

Most children with congenital sensory hearing loss, with the possible exception of auditory neuropathy, would have detectable abnormalities in their inner ears if they could be examined histologically. Because most children with profound bilateral SNHL have radiographically normal inner ears, it can be inferred that malformations limited to the membranous labyrinth predominate. The incidence of malformations reported varies, depending on the hearing level of the study population, the sophistication of imaging used, and the definition of abnormality used by the observer. As a rule of thumb, approximately 20% of cases of congenital SNHL will demonstrate inner ear malformation with modern imaging technology. In a series of 234 children who had SNHL of varying degrees of severity, Reilly[14] found cochlear anomalies in only 4% of those evaluated by high-resolution computed tomography (CT). With improvements in CT imaging technology and greater awareness of inner ear deformities, Antonelli and colleagues found anomalies in 31% of 157 children with SNHL of variable degree.[15] In another CT study, anomalies were found in 17% of 185 ears of children with SNHL and none in the ears of 309 children without SNHL.[16] A large Korean study found 22% incidence of anomalies on radiologic imaging in 590 ears with profound SNHL.[17]

The incidence of deformities of the semicircular canals (SCCs) and inner ear aqueducts has been less well studied than that of cochlear deformities. In a series of patients with radiographically detectable malformations of the inner ear, the cochlea was involved in 76%, the semicircular canals were involved in 39%, and the vestibular aqueduct (VA) was affected in 32% of ears.[3] The total is more than 100%, because many cases demonstrate abnormalities of more than one portion of the inner ear. In recent years, a heightened awareness of VA enlargement, combined with the greater sensitivity of axial CT scans in demonstrating this deformity, has led to a substantial increase in its detection. The rapid accrual of cases by clinicians interested in inner ear malformations suggests that enlargement of the VA will ultimately prove to be the most common radiographically detectable inner ear anomaly.[6]

Among deaf children with radiographically normal inner ears, histopathologic studies indicate that cochleosaccular dysplasia (Scheibe's dysplasia) is by far the most common deformity.[18] Because of the paucity of pathologic specimens available for examination, it is impossible to estimate the relative frequency of the various membranous malformations.

Classification

The traditional nomenclature used to describe congenital anomalies of the inner ear involves a confusing array of eponyms that stem from the first reports of the various morphologic patterns, usually by 18th or 19th century authors. In this chapter, a descriptive classification system is used, along with the traditional eponymous terminology, to make this topic more logical, easier to learn, and more clinically relevant (Box 191-1). In membranous malformations, this classification is based on histopathologic changes in the inner ear; in combined osseous-membranous deformities, radiographic appearance is used to distinguish among the various entities.[3] Correct use of the terminology of pathoembryology is important, although these terms frequently are applied imprecisely in the earlier literature. Key terms are *aplasia* (complete lack of development), *hypoplasia* (incomplete development), and *dysplasia* (aberration in development). The classification scheme used in this chapter has proved to be of practical clinical use and has been employed in most published studies in recent years. Other classification schema that categorize observed anomalies have been proposed.[19]

Box 191-1

Classification of Congenital Inner Ear Malformations

Malformations Limited to the Membranous Labyrinth

- Complete membranous labyrinthine dysplasia
- Limited membranous labyrinthine dysplasia
  - Cochleosaccular dysplasia (Scheibe)
  - Cochlear basal turn dysplasia

Malformations of the Osseous and Membranous Labyrinth

- Complete labyrinthine aplasia (Michel)
- Cochlear anomalies
  - Cochlear aplasia
  - Cochlear hypoplasia
  - Incomplete partition (Mondini)
  - Common cavity
- Labyrinthine anomalies
  - Semicircular canal dysplasia
  - Semicircular canal aplasia
- Aqueductal anomalies
  - Enlargement of the vestibular aqueduct
  - Enlargement of the cochlear aqueduct
- Internal auditory canal anomalies
  - Narrow internal auditory canal
  - Wide internal auditory canal
- Eighth nerve anomalies
  - Hypoplasia
  - Aplasia

Malformations Limited to the Membranous Labyrinth

In malformations limited to the membranous labyrinth, which account for more than 90% of cases of congenital deafness, the bony labyrinth is normal.[20-23] In its most severe form, membranous dysplasia involves the entire labyrinth, including the cochlea, semicircular canals (SCCs), utricle, and saccule. A limited form of membranous labyrinthine dysplasia, involving only a portion of the inner ear, also has been described.

Complete Membranous Labyrinthine Dysplasia

Complete membranous labyrinthine dysplasia was first described by Siebenmann and Bing[24] and is extremely rare. It has been reported in association with cardioauditory (Jervell and Lange-Nielsen) and Usher syndromes.[25]

Limited Membranous Labyrinthine Dysplasia

Cochleosaccular Dysplasia (Scheibe's Dysplasia)

Incomplete development of the pars inferior is the most frequent histopathologic finding in congenital deafness. It was first described by Scheibe[26] and commonly is known as *cochleosaccular dysplasia*. The spectrum of pathologic findings in this anomaly, which is confined to the cochlea and the saccule, has been well described.[22,27-30] The organ of Corti is either partially or completely missing. The cochlear duct usually is collapsed, with Reissner's membrane adherent to the limbus. Less commonly, the duct is distended, presumably as a result of endolymphatic hydrops. The stria vascularis typically is degenerated and may contain colloidal inclusions. Schuknecht[31] described characteristic

strial changes consisting of aplasia alternating with regions of hyperplasia and gross deformity. Cochlear changes may be severe in the base turn and gradually lessen in intensity toward the apex, or they may be severe throughout. The saccule usually is collapsed and has degenerated sensory epithelium. In cochleosaccular dysplasia, the SCCs and utricle are normal. Auditory neuronal survival is variable but may remain normal into adulthood, at least in some cases. Cochleosaccular dysplasia also has been demonstrated in a number of animal species, including the deaf white cat, Dalmatian dogs, and various mouse mutants.[32]

Cochlear Basal Turn Dysplasia

Dysplasia limited to the basal turn of the cochlea may be related to familial high-frequency SNHL. No description of membranous labyrinthine dysplasia limited to the pars superior was found in an extensive review of the literature. This outcome is not surprising, because affected persons probably are minimally symptomatic. They would have normal hearing and presumably would have compensated for their congenital vestibular deficit.

Malformations of the Membranous and Osseous Labyrinth

Congenital anomalies of the inner ear that deform the otic capsule are of special interest to the clinician because they may be recognized and differentiated during life through radiographic imaging. As discussed previously, only approximately 20% of congenitally deaf people demonstrate radiographically anomalous inner ears. The clinical manifestations and natural history of these deformities are highly variable. Although some patients are deaf from birth, most maintain some residual hearing into adulthood. Slowly progressive deterioration of hearing during childhood, with eventual stabilization, is common. Sudden decrements in hearing are frequent and may appear to be spontaneous or may be triggered by head trauma, even minor in nature. Presumably, most of these cases are due either to internal fistulization secondary to membrane rupture within the cochlea, with admixture of perilymph and endolymph, or to external fistulization to the middle ear. Fluctuant hearing loss is unusual in these patients, and endolymphatic hydrops is an atypical finding. In some patients, hearing may be best preserved in very high frequencies (greater than 8000 Hz), which are not measured by conventional audiometry.[33] Residual ultra-audiometric hearing should be suspected in hearing-impaired children who manifest substantially better auditory function than would be predicted by pure tone results in the speech frequencies.[34] Occasionally, malformation of the inner ears may be associated with normal hearing.[35,36] This is especially the case for semicircular canal anomalies.[37] Vestibular symptoms, which occasionally are severe, are present in approximately 20% of patients.[3] Retardation of motor development has been documented in some children with malformed inner ears, particularly those in whom semicircular canals are absent.[38] A few patients experience vertigo when exposed to loud sounds—the so-called Tullio phenomenon.[39]

A wide variety of morphologic patterns of inner ear malformation has been observed radiographically and may involve the cochlea, SCCs, or vestibular aqueduct[3,40-45] (Fig. 191-1). Similar diversity has been observed on histologic analysis.[21,46-50] A majority of combined osseous and membranous malformations appears to arise from a premature arrest in the development of one or more components of the inner ear (Fig. 191-2). The strongest evidence for this theory comes from the resemblance of most malformed inner ears to the appearance of the inner ear during embryogenesis, particularly between the fourth and eighth weeks of gestation. As a general rule, the earlier the developmental arrest, the more severe the deformity and the worse the hearing will be.

Other anomalies cannot be explained by a premature arrest in development alone and appear to arise from an aberrant embryologic process. An example of this type of anomaly is a cochlea of normal length but abnormal size or coiling geometry.[46] In humans, the inner ear is of adult size at birth and shows strikingly little variation in size among individual patients. Pappas and colleagues[51] suggested that some children with congenital SNHL and apparently normal inner ear morphology on CT possess subtle abnormalities in the dimensions of inner ear structures. These investigators propose that such dimensional variations arise from a teratogenic insult during the second or third trimester, after the membranous labyrinth has formed but before it has reached adult size. Further study is needed to determine the clinical relevance of these observations.

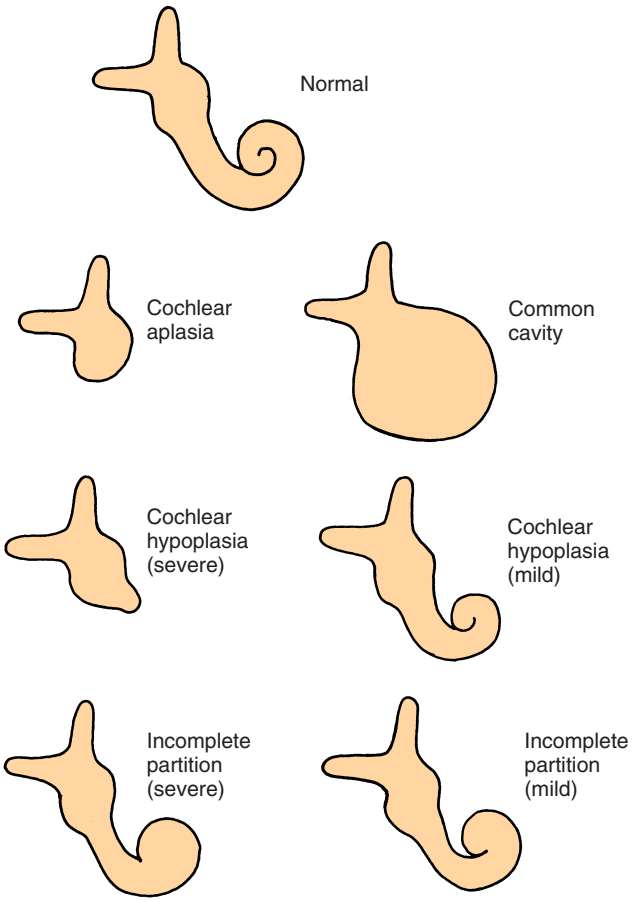

Figure 191-1. Cochlear malformations. Drawings were made from coronal computed tomography scans. *(From Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis.* Laryngoscope. *1987;97[Suppl 40]:2.)*

Whereas some inner ear malformations involve only one portion of the inner ear, many patients have a combination of anomalies involving more than one component. Between the fourth and fifth weeks of development, the spheric otocyst develops three buds that ultimately form the cochlea, SCCs, and VA (see Fig. 191-2). An inner ear malformation may be limited to one of these anlages, may involve a combination of two, or may even affect all three.

The frequent coexistence of deformities involving the cochlea, SCCs, and VA has several possible explanations: (1) the anomaly is genetically predetermined; (2) an insult to the embryo occurred before the fifth week; or (3) each of the buds was susceptible to some teratogenic influence at a later stage of development. A majority of inner ear malformations are bilateral and symmetrical. In cases in which radiographs detect an anomaly on only one side, the opposite "normal" inner ear has a hearing loss in approximately 50% of cases.[3]

Before the evolution of high-resolution imaging technology, clinicians and histopathologists alike tended to lump these malformations together under the term *Mondini's dysplasia*, after the first report by Carlo Mondini. We are indebted to the late Dr. Peter Phelps and Latin scholar Gordon Hartley for an English translation of Mondini's original article.[52] Before the Academy of Sciences of the University of Bologna, Mondini described the inner ear findings in a deaf 8-year-old boy who was struck on the foot by a wagon and later died of gangrene.[53]

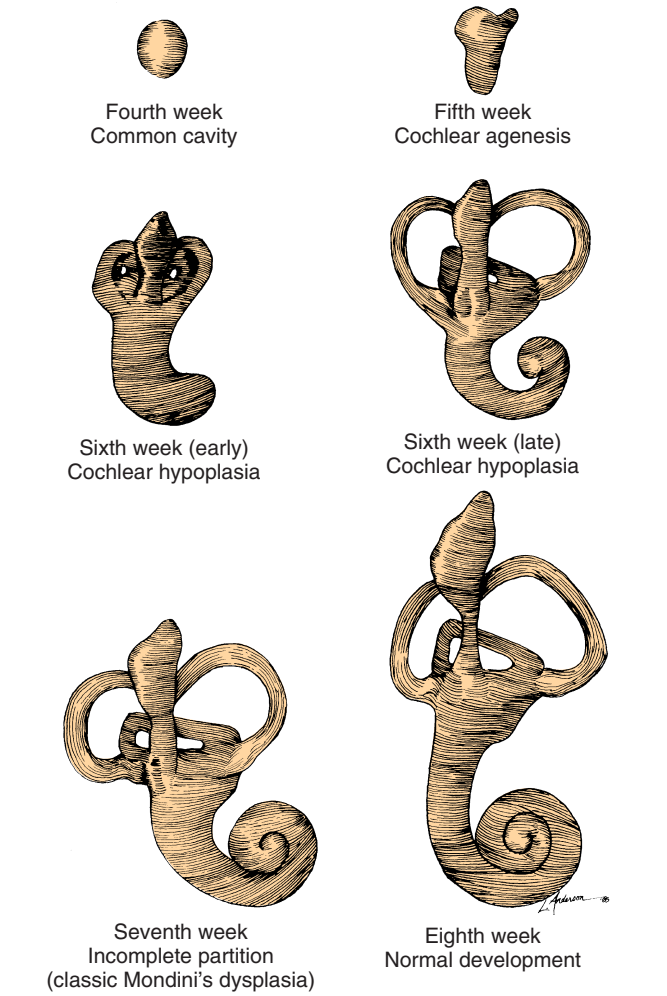

Figure 191-2. Embryogenesis of cochlear malformations. *(From Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis.* Laryngoscope. *1987;97(Suppl 40):2.)*

Table 191-1

Relative Incidence of Cochlear Malformations

Malformation	Incidence (%)
Incomplete partition (Mondini's dysplasia)	55
Common cavity	26
Cochlear hypoplasia	15
Cochlear aplasia	3
Complete labyrinthine aplasia (Michel's aplasia)	1

The cochlea possessed only 1.5 turns and had a hollow apical cavity. An enlarged vestibule and VA also were noted. This deformity is the most common form of cochlear anomaly (Table 191-1). Although numerous other distinct anatomic patterns of inner ear malformation are discernible radiographically and histologically, many workers continue to use the term Mondini's dysplasia to describe them all. To avoid a confusing and overly broad nomenclature system, this designation is best reserved for the particular subtype of cochlear malformation first described by Mondini, whether or not it is associated with other inner ear malformations.

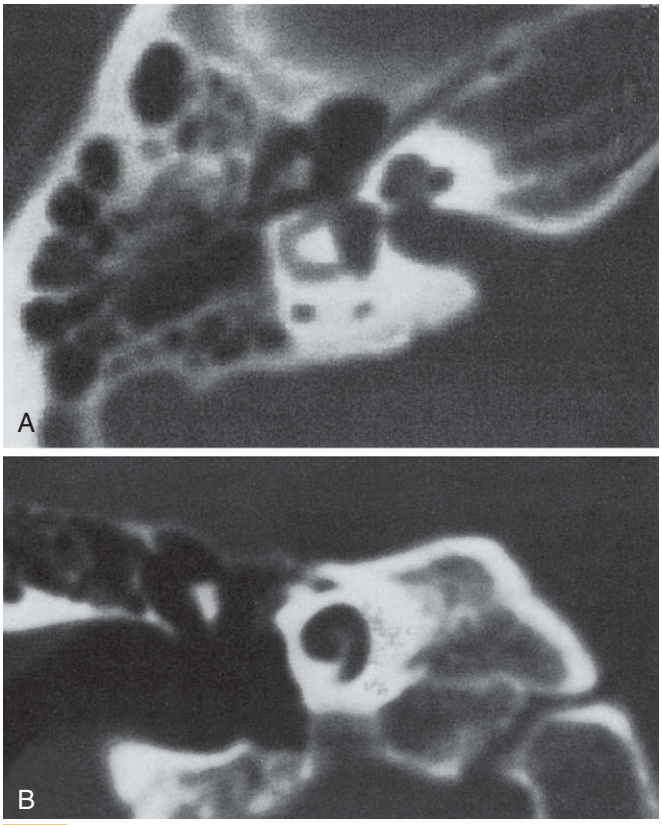

Figure 191-3. Radiographically normal inner ear as seen on axial (**A**) and coronal (**B**) high-resolution computed tomography scans. Note that the normal cochlea appears to have only 1.5 turns on the coronal scan, as a result of the oblique angle of section in relation to the axial scans of the modiolus.

Complete Labyrinthine Aplasia (Michel's Aplasia)

The most severe deformity of the membranous and osseous labyrinth, complete labyrinthine aplasia, was first described by Michel.[54] This malformation is exceedingly rare. Presumably, a developmental arrest occurs before the formation of an otic vesicle, resulting in a complete absence of inner ear structures. Complete labyrinthine aplasia has been reported in association with anencephaly and thalidomide exposure.[21,55] An association with external ear abnormalities also has been reported.[56] A purported case of Michel's aplasia actually described a cystic inner ear of the common cavity type.[57] This is but one example of the inaccurate use of traditional eponyms—a frequent occurrence in the literature. The incidence of complete labyrinthine aplasia is overestimated in the radiographic literature because it is confused with labyrinthine ossification. In the latter condition, which usually is acquired during life, a sizable and dense otic capsule is evident radiographically. In complete labyrinthine aplasia, the otic capsule is entirely absent[58] (Figs. 191-3 to 191-5). Such ears are, of course, uniformly deaf.

Cochlear Anomalies

Cochlear Aplasia

In cochlear aplasia the cochlea is completely absent, presumably as a result of an arrest in the development of the cochlear bud at the fifth week of gestation (see Fig. 191-1). This morphologic pattern is rare. Radiographically, only a vestibule and SCCs (usually deformed) are present. To differentiate this anomaly from labyrinthine ossification, it is necessary to assess the amount of otic capsule bone anterior to the internal auditory canal (IAC). In cochlear aplasia, the otic capsule is

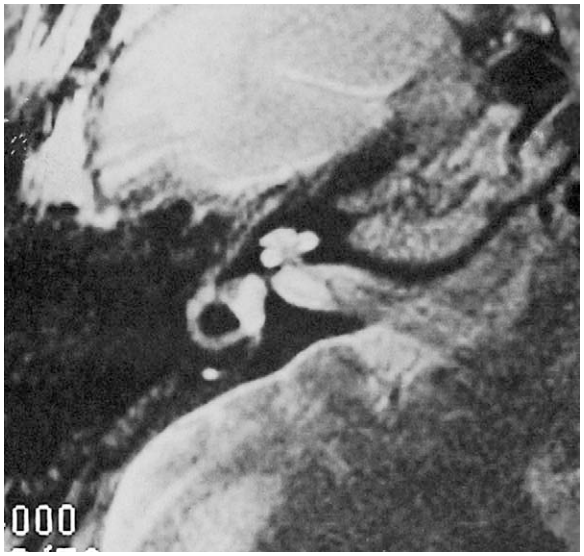

Figure 191-4. Axial high-resolution T2-weighted magnetic resonance image (fast spin echo) of a normal inner ear at the level of the mid- and apical cochlea and lateral semicircular canal. Note the internal detail of the cochlea, which includes visualization of the scalar partitions and the modiolus. The seventh and eighth cranial nerves can be seen in the internal auditory canal outlined by cerebrospinal fluid.

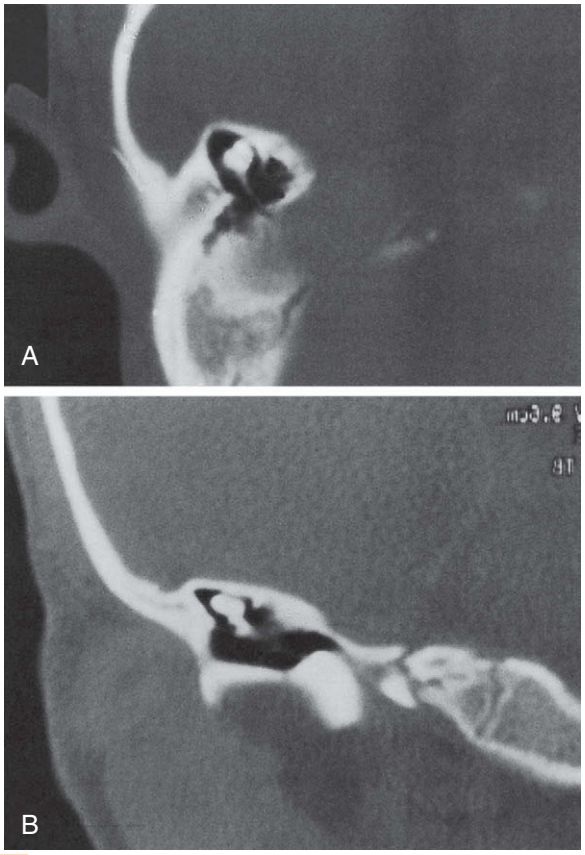

Figure 191-5. Complete labyrinthine aplasia as seen on axial (**A**) and coronal (**B**) computed tomography scans. Note the presence of an ear canal and middle ear but complete absence of the otic capsule. *(Courtesy of Joel Swartz, MD.)*

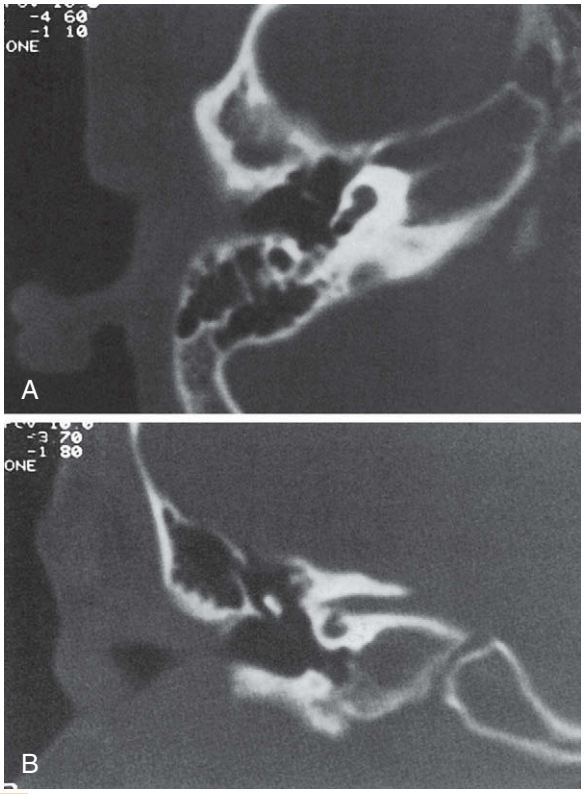

Figure 191-6. Cochlear hypoplasia as seen on axial (**A**) and coronal (**B**) computed tomography scans. The cochlea consists of only a small bud off the vestibule.

absent, whereas in osseous obliteration, it is dense and of normal dimensions. Ears with cochlear aplasia are devoid of auditory function.

Cochlear Hypoplasia

An arrest during the sixth week of gestation results in a hypoplastic cochlea consisting of a single turn or less. This deformity comprises approximately 15% of all cochlear anomalies. Radiographically, a small bud of variable length (usually 1 to 3 mm) protrudes from the vestibule (Fig. 191-6). The vestibule frequently is enlarged, with accompanying semicircular malformations in approximately one half of the cases. Small cochleas lacking a modiolus or other internal architecture have been described histologically.[27,50,59] Hearing is variable in these ears and may be remarkably good in view of the minute size of the cochlea. The variability of hearing presumably is accounted for by the degree of membranous labyrinthine development within the truncated cochlear lumen.

Incomplete Partition (Mondini)

Arrest at the seventh week of gestation yields a cochlea that has only 1.5 turns. This is the most common type of cochlear malformation, accounting for more than 50% of all such deformities. Radiographically, the cochlea is smaller than normal and partially or completely lacks an interscalar septum (Figs. 191-7 and 191-8). Although the cochlea usually measures 8 to 10 mm vertically, it is typically in the 5- to 6-mm range in incomplete partition deformity. Care must be exercised in counting the number of cochlear turns radiographically because this may be difficult to determine even using high-resolution CT. The radiographic diagnosis depends more on cochlear size and the absence of a scalar septum than on the number of cochlear turns perceived. Histologically, incomplete partition appears to be the radiographic correlate of classical Mondini's dysplasia (Fig. 191-9). In numerous reported cases, a small cochlea with 1.5 turns possessing an apical scala communis secondary to deficiency in the osseous spiral lamina has been described.[27,46,48] Sennaroglu and Saatci have subtyped the incomplete partition deformity into three variants[60] (Fig. 191-10).

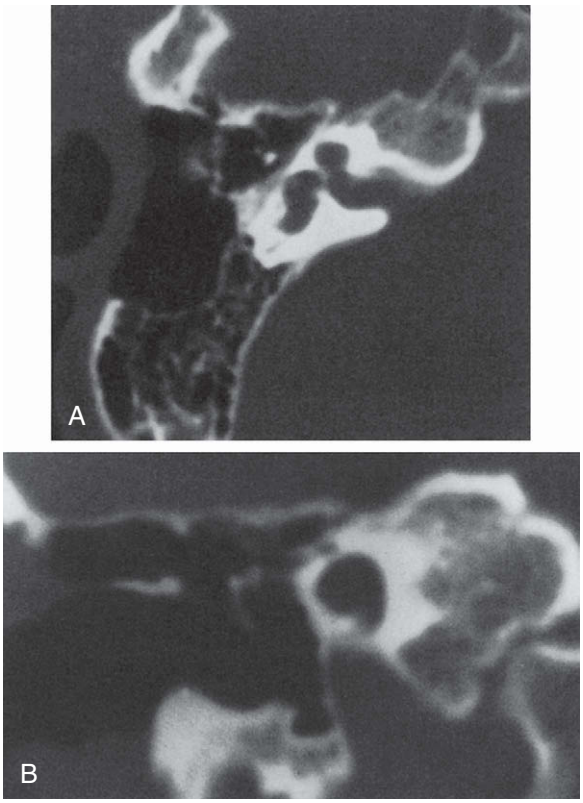

Figure 191-7. Incomplete partition as seen on axial (**A**) and coronal (**B**) computed tomography scans. Note the absence of an interscalar septum, which is more evident on the coronal scan.

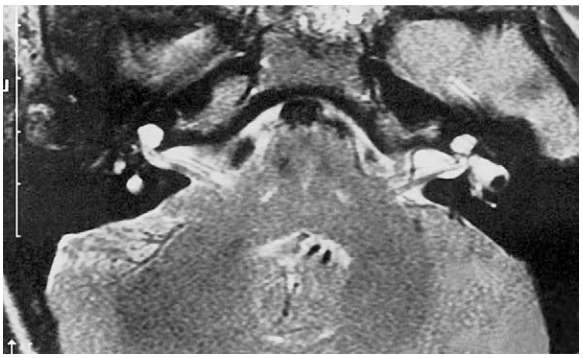

Figure 191-8. High-resolution T2-weighted magnetic resonance image (fast spin echo) of an incomplete partition deformity. Note the absence of intracochlear septation.

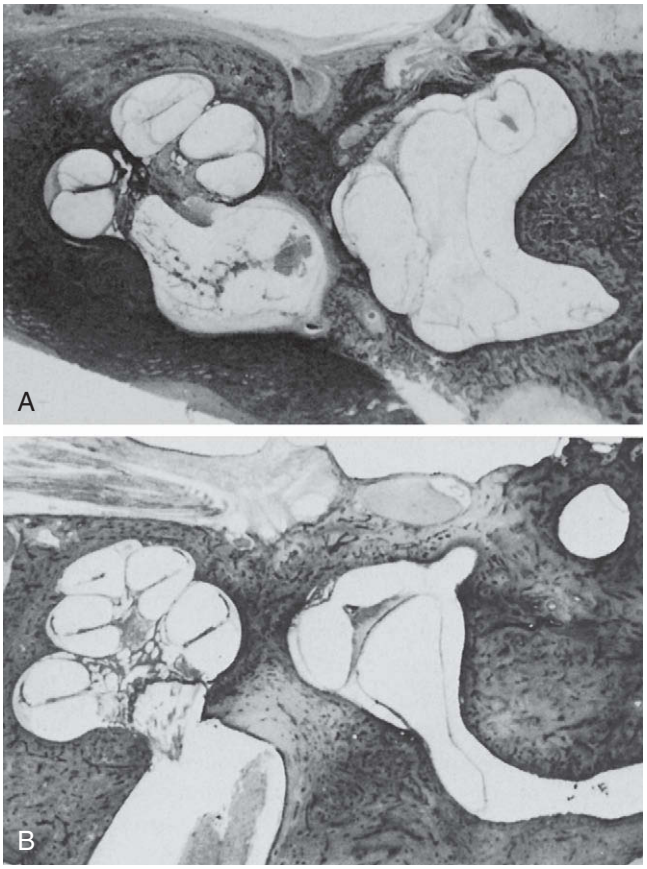

Figure 191-9. **A,** Photomicrograph of a malformed cochlea with the typical features of Mondini's dysplasia. The cochlea has 1.5 turns and an apical scala communis. **B,** Midmodiolar section through a normal cochlea for comparison. *(From Monsell EM, Jackler RK, Motta G, Linthicum FH Jr. Congenital malformations of the inner ear: histologic findings in five temporal bones.* Laryngoscope. *1987;97[Suppl 40]:18.)*

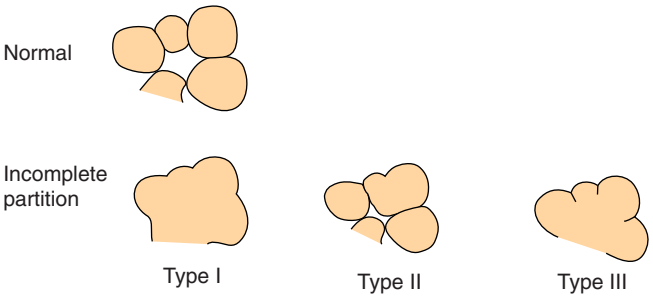

Figure 191-10. Subtypes of the incomplete partition deformity proposed by Sennaroglu and Saatci. *(From Sennaroglu L, Saatci I. Unpartitioned versus incompletely partitioned cochleae: radiologic differentiation.* Otol Neurotol. *2004;25:520.)*

Type I lacks the entire modiolus and interscalar septa and demonstrates a cystic appearance. Type II has a normal base turn but a cystic apex ("Mondini type"). Recently Sennaroglu has proposed a type III variant with deficient modiolus and partial interscalar septation at the cochlea's periphery (L. Sennaroglu, personal communication, 2007). Organ of Corti development is variable, as is the auditory neural population. As might be expected, auditory function also is variable, ranging from normal to profound SNHL. The mean hearing threshold (three-tone average) in a group of 41 ears with incomplete partition was 75 dB.[3] SCC deformities accompany incomplete partition of the cochlea in approximately 20% of cases.

Common Cavity

A deformed inner ear in which the cochlea and vestibule are confluent, forming an ovoid cystic space without internal architecture, may be explained by an arrest at the week 4 otocyst stage. Alternatively, this deformity may result from aberrant development at a later stage. An empty ovoid space typically longer in its horizontal dimension is seen radiographically. Although the size of the cyst may vary, it averages 7 mm vertically and 10 mm horizontally. It is quite easy to misdiagnose a dysplastic lateral SCC as a common cavity deformity. The key to differentiating between the two is that a common cavity cochlea lies predominantly anterior to the IAC on axial-plane CT, and a dysplastic vestibular system lies posterior to it. Histologically, an ovoid or spherical smooth-walled cystic cavity containing primordia of the membranous labyrinth has been described.[48,50,55] Sensory and supporting

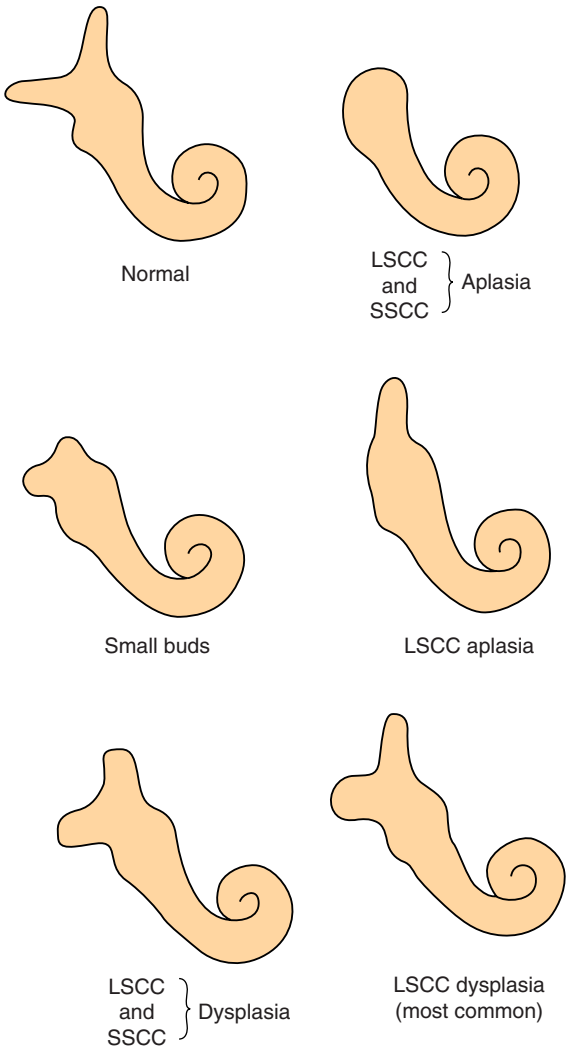

Figure 191-11. Semicircular canal malformations. LSCC, lateral semicircular canal; SSCC, superior semicircular canal. *(From Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis.* Laryngoscope. *1987;97[Suppl 40]:2.)*

cells may be differentiated into recognizable organs of Corti that are scattered peripherally around the walls of the cyst. Neural population usually is sparse or absent. Hearing is usually, but not invariably, poor.

Cochlear Hyperplasia

First reported in 2006, three temporal bones with a extra half apical turn have been described histologically.[61] Neither the clinical features nor the radiographic appearance of this anomaily has yet to be reported.

Labyrinthine Anomalies

Semicircular Canal Dysplasia

Dysplasia of the lateral SCC is a common type of inner ear malformation (Fig. 191-11). Approximately 40% of ears with a malformed cochlea will have an accompanying dysplasia of the lateral SCC.[3] Occasionally, dysplasia of the lateral SCC exists as the sole inner ear malformation. During the sixth week of development, the budding SCC normally forms a semicircular evagination from the vestibular anlage. The central portion of the pocket-shaped protrusion adheres, leaving a peripheral semicircular tube. When this central adhesion fails to occur, SCC dysplasia results (Fig. 191-12; see also Fig. 191-2). SCC dysplasia occasionally takes the form of a small bud, rather than the more common half-disk shape, presumably because of a slightly earlier timing of the developmental insult. The lateral SCC is deformed more often than the posterior or superior SCC, apparently because it forms earlier in embryogenesis. The typical radiographic appearance of SCC dysplasia is that of a short, broad cystic space confluent with the vestibule (Fig. 191-13).

Numerous histologic descriptions of SCC dysplasia exist in the literature.[46-50] The half-disk shaped cavity may contain a rudimentary crista ampullaris. The utricle and saccule may be distended, collapsed, or entirely absent. Caloric responses in SCC dysplasia are functionally absent or reduced in most cases, but a few may have normal responsiveness.[3] Ears with malformations limited to the vestibular system often have normal or near-normal hearing. When the cochlea also is abnormal, sensory hearing levels tend to be impaired, to a variable degree.[62] SCC dysplasia appears to have an association with conductive hearing loss, presumably because of inner ear micromechanical factors rather than stapes fixation.[63]

Semicircular Canal Aplasia

SCC aplasia is only one-fourth as common as SCC dysplasia.[3] It is usually associated with cochlear anomalies.[29] Presumably, SCC aplasia

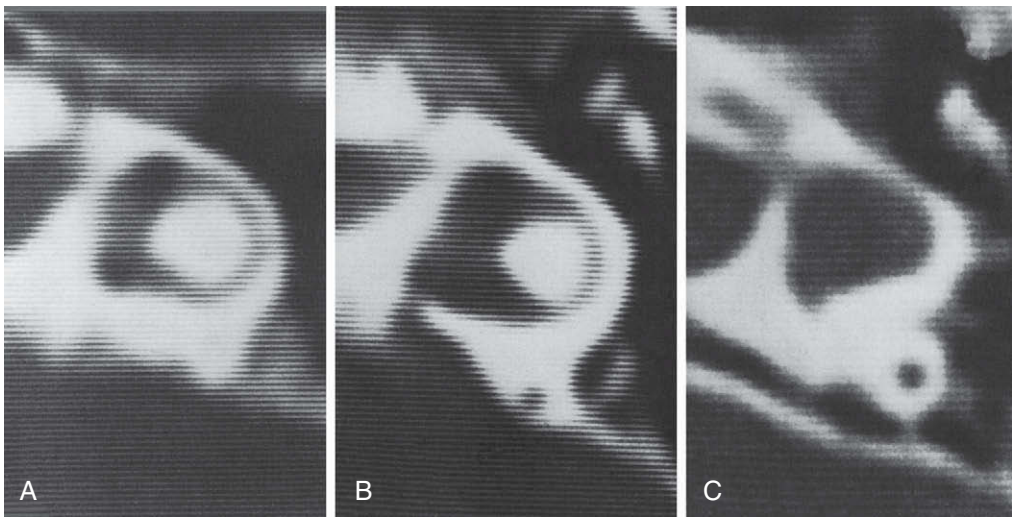

Figure 191-12. **A,** Lateral semicircular canal dysplasia as seen on an axial computed tomography scan. The normal appearance should be contrasted with that in mild, and severe dysplasia, in **B** and **C,** respectively. These images illustrate how semicircular canal dysplasia may arise from a failure of adhesion of the central region of the vestibular evagination during development. *(From Jackler RK, Luxford WM, House WF. Congenital malformations of the inner ear: a classification based on embryogenesis.* Laryngoscope. *1987;97[Suppl 40]:2.)*

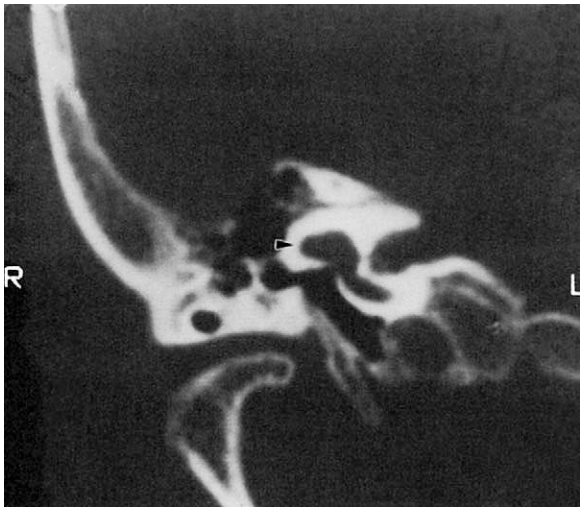

Figure 191-13. Lateral semicircular canal dysplasia *(arrowhead)* as seen on a coronal computed tomography scan. Note that the canal appears short, broad, and confluent with the vestibule.

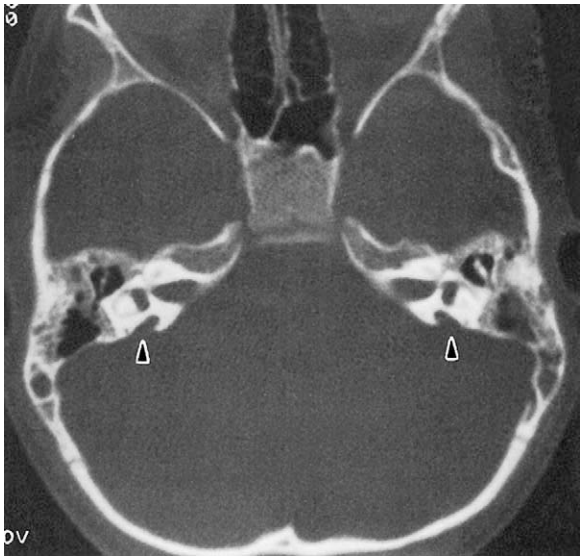

Figure 191-14. Bilateral enlargement of the vestibular aqueducts *(arrowheads)* as seen on an axial computed tomography scan.

arises from a failure in the development of the vestibular anlage before the sixth week of gestation. Most cases are syndromic, with a predominance of the CHARGE association (*c*oloboma, *h*eart defects, *a*tresia of the choanae, *r*etardation of growth and development, *g*enital, and *e*ar abnormalities or hearing loss).[64,65]

Malformations of the Vestibular and Cochlear Aqueducts

Enlargement of the Vestibular Aqueduct

Experience suggests that enlargement of the VA is the most common radiographically detectable malformation of the inner ear.[57,66-71] In earlier literature its incidence was underestimated, partly because of a lack of awareness but mostly because enlargement of the VA could be visualized only by lateral polytomography at a time when most studies were confined to the anteroposterior plane. The advent of high-resolution CT in the axial plane has made assessment of the VA much easier. The diameter of a normal VA, when measured halfway between the common crus and its external aperture, is between 0.4 and 1 mm. Enlargement of the VA is diagnosed when its diameter exceeds 2 mm, although enlarged VAs may exceed 6 mm in width. Whereas the VA is well visualized on axial CT (Fig. 191-14), the dilated endolymphatic sac is better seen with T2-weighted magnetic resonance imaging (MRI)[72,73] (Fig. 191-15). The sac often is seen to be enormously enlarged on MRI, sometimes measuring 2 cm or more in diameter.[74] In many cases, VA enlargement accompanies malformation of the cochlea or SCC. It also may be the sole radiographically detectable abnormality of the inner ear in a child with hearing loss. This condition is commonly referred to as the large VA syndrome, after Valvassori and Clemis's first descriptions.[75,76]

The VA derives from a diverticulum formed in the wall of the otocyst during the fifth week of gestation. It begins as a short, broad pouch but gradually elongates and thins until it achieves its characteristic J shape of adulthood (see Fig. 191-2). A premature arrest in development would be expected to produce a VA that is abnormally short and broad. However, an increasing body of evidence suggests that VA enlargement does not stem from an early arrest of sac development, but rather is an acquired deformity. Histologically, the sac and aqueduct are thin-walled and lack both vascularity and the rugose features thought to be important for physiologic function. Three observations suggest that a large VA stems from an abnormal communication between the subarachnoid space and the fluid chambers of the inner ear. The bone surrounding the VA may show signs of erosion, a finding that is inconsistent with a stable congenital deformity.[77] Serial MR images show variability in both the size and signal characteristics of the enlarged sac.[78] Presence of cerebrospinal fluid (CSF) under pressure,

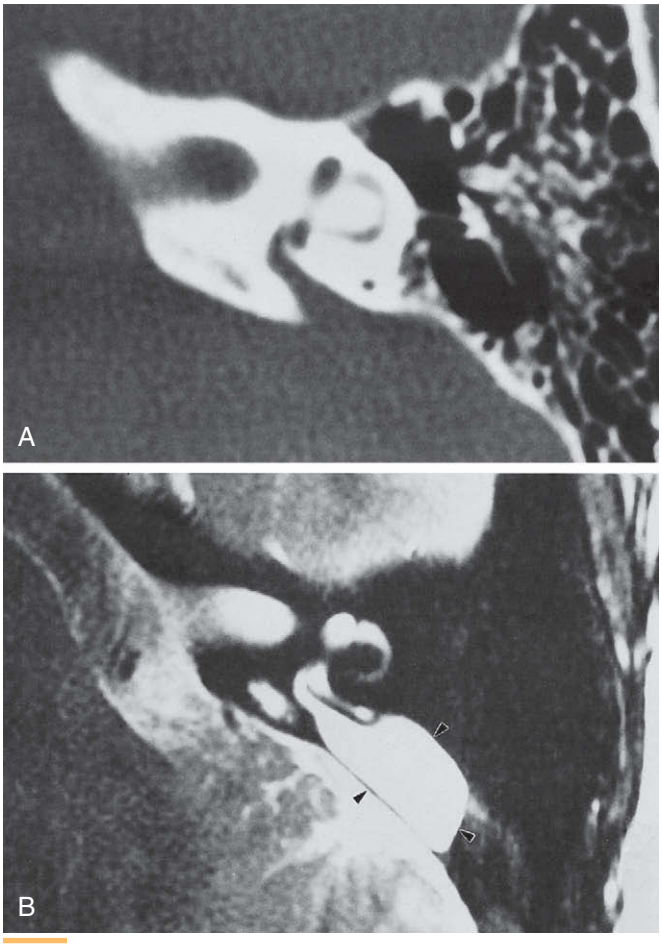

Figure 191-15. A comparison of computed tomography (**A,** axial scan), and magnetic resonance imaging (**B**), T2-weighted, fastspin echo sequence, of a large vestibular aqueduct deformity. Note that only the magnetic resonance image delineates the extent of the enormously enlarged endolymphatic sac *(arrowheads)*. *(Courtesy of Joel Swartz, MD.)*

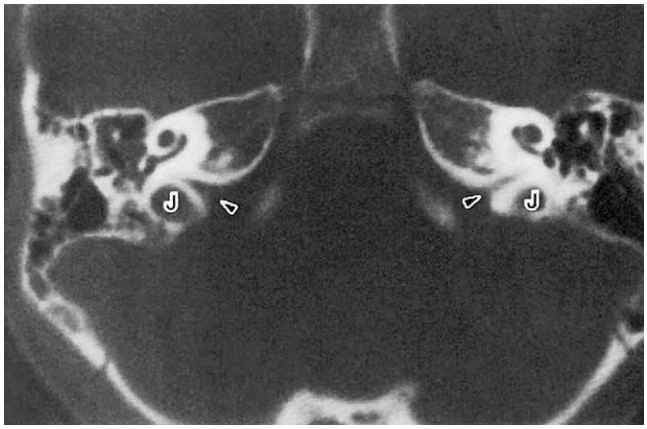

Figure 191-16. Axial computed tomography scan demonstrating a normal cochlear aqueduct bilaterally *(arrowheads)*. The external aperture typically lies inferior to the internal auditory canal and just above the jugular bulb (J).

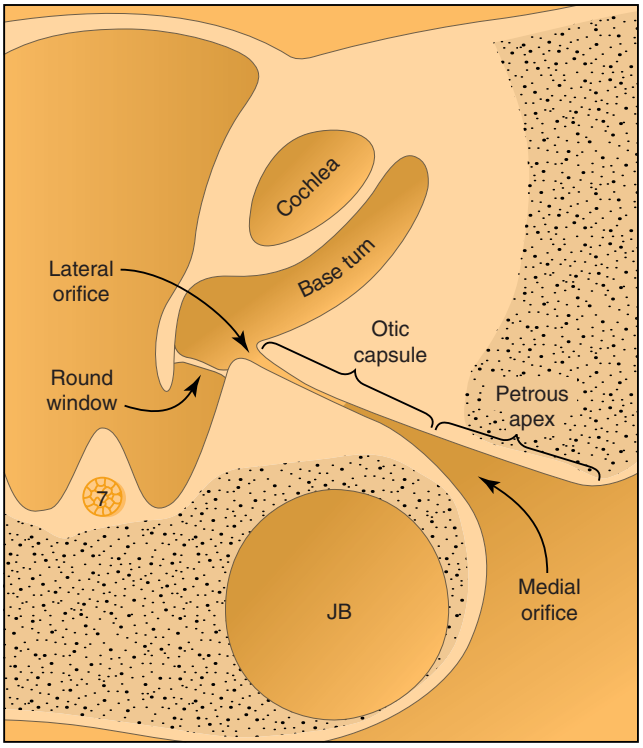

Figure 191-17. Illustration of the cochlear aqueduct in the axial plane. The diameter of the medial orifice is highly variable but often is wide (as depicted here) in normal-hearing persons. By contrast, the otic capsule portion typically is very narrow in both healthy and congenitally deaf persons. *(Adapted from Jackler RK, Hwang PH. Enlargement of the cochlear aqueduct: fact or fiction?* Otolaryngol Head Neck Surg. *1993;109:14.)*

with consequent "gusher," within the inner ear has been observed in ears with large VAs during both cochlear implantation and stapedectomy.[31,79] Furthermore, the existence of abnormal CSF in the inner ear pathway frequently has been observed with CT or MRI. This anomaly typically consists of a defect of the cochlear modiolus at the distal end of the IAC.[12,73] For CSF to become confluent with the endolymphatic space, the CSF fistula (subarachnoid space to perilymph compartment) must be accompanied by a second fistula joining the endolymph and perilymph spaces.

The large VA syndrome typically is bilateral. Affected children usually are born with normal or mildly impaired hearing that gradually deteriorates through childhood into adolescence and early adulthood. Hearing levels are variable, although at least 40% eventually develop profound SNHL.[80] As with other inner ear malformations, there is a tendency to suffer sudden decrements of hearing, particularly after head trauma. Conductive hearing loss may be present but is likely to be from intracochlear micromechanical disturbances rather than from impairment of ossicular mobility. Stapes surgery is best avoided because of the risk of CSF otorrhea.[79] Vestibular complaints in these patients have frequently been reported.[81,82] Large VA syndrome has been observed to occur in familial clusters.[10]

Surgical manipulation of the endolymphatic sac has been attempted in patients with large VAs. In a sizable series of shunt procedures, there was a high incidence of postoperative hearing loss.[67] Furthermore, a comparison of the operated and contralateral unoperated ears revealed no evidence of hearing stabilization after surgery. Recently, surgical obliteration of the enlarged endolymphatic sac with muscle and fascia has been advocated.[83] Results in a multicenter study indicated that the procedure not only lacks efficacy but actually injures one half of the operated ears.[84] Cochlear implantation has been quite successful in both adults and children with large VAs.[85,86]

Enlargement of the Cochlear Aqueduct

Enlargement of the cochlear aqueduct (CA) frequently is mentioned in the otologic literature because of its purported association with stapedectomy gusher and transotic CSF leak. Despite an active interest in the field and an extensive review of published radiographic images, I have never seen a radiograph that convincingly demonstrated CA enlargement.[87] Most cases presented as enlargement of the CA are misinterpretations of the wide internal funnel that opens into the posterior fossa.[88,89] In healthy subjects, the radiographic diameter of this aperture averages 3 to 4 mm but ranges from radiographically invisible to more than 10 mm[46,90-92] (Figs. 191-16 and 191-17). For enlargement of the CA to be diagnosed radiographically, the intraosseous portion coursing toward the vestibule must be enlarged beyond 1 mm, the practical resolution limit of contemporary CT scanners. If criteria analogous to those for enlargement of the VA are used, then an enlarged CA must have a diameter exceeding 2 mm throughout its course between the inner ear and the posterior fossa.

The preponderance of evidence suggests that the human CA usually is functionally patent.[92-94] In most persons, however, it can neither transmit sudden large pressure changes to the inner ear nor allow free flow of spinal fluid in any significant quantity (e.g., with outflow of perilymphatic fluid from perilymphatic fistula or an open vestibule). This observation reflects two anatomic features of the aqueduct: a narrow diameter of the bony channel and the presence of a fibrous tissue meshwork occupying and baffling the lumen. Schuknecht and Reisser[95] evaluated more than 1400 temporal bones in the Massachusetts Eye and Ear Infirmary collection and found no CA that exceeded 0.2 mm at its narrowest point. This series included 29 congenitally malformed inner ears. Of note, the CA was absent or nonpatent in 21 of these dysmorphic ears.

Some persons have less than normal or no fibrous tissue within the lumen, and the bony diameter is wider than normal. An opportunity may then exist for free flow of CSF from the oval window through the CA. According to Poiseuille's law, fluid flow through a tube varies with the fourth power of the radius, suggesting the possibility of free flow in an individual with a large-diameter unimpeded channel, as discussed by Allen.[96] Several histologic studies of congenital inner ear malformations have detected slightly larger CAs, particularly at their lateral orifice at the vestibule.[24,49] Even in these malformed inner ears, however, the aqueduct diameter remained well in the submillimeter range. From a clinical standpoint, a CA less than 1 mm in diameter is undetectable radiographically. Despite the theoretical possibility that a widely patent CA may cause a stapedectomy gusher, abnormal connections between the IAC and the vestibule appear to be etiologic in a majority of cases.[9,89,97,98]

Figure 191-18. Axial computed tomography scan of a bulbous internal auditory canal (IAC). Note the minimal separation between the lateral end of the IAC from the vestibule *(arrowheads)*. Such an ear may be prone to spontaneous cerebrospinal fluid leakage and to "gusher" during stapes surgery.

Figure 191-19. A pathologically narrow internal auditory canal (IAC) as seen on an axial computed tomography scan *(arrowheads)*. When the IAC is less than 3 mm in diameter, incomplete auditory nerve development is probable.

Developmental Anomalies of the Internal Auditory Canal

Wide Internal Auditory Canal

Unlike congenital narrowness of the IAC, a congenitally large canal may be an incidental finding in healthy individuals (Fig. 191-18). When a large IAC (larger than 10 mm in diameter) accompanies a malformation of the inner ear, it does not, as an independent variable, correlate with the level of hearing.[3] One report suggests that a wide IAC may be correlated with hearing loss.[99] The primary importance of detecting enlargement of the IAC is its association with spontaneous CSF leak and the occurrence of gusher during stapes surgery.[97] Because hearing after stapedectomy complicated by CSF gusher (often erroneously called "perilymph gusher") frequently is poor, a CT scan should be obtained before stapedectomy to address congenital fixation is undertaken. Dilation of the IAC, especially when the partition between the lateral end of the canal and inner ear appears deficient, should contraindicate stapedectomy.

Narrow Internal Auditory Canal

A narrow IAC may indicate a failure of eighth cranial nerve development. When a patient has normal facial function and an IAC less than 3 mm in diameter, it is likely that the bony canal transmits only the facial nerve (Fig. 191-19). A narrow IAC may accompany inner ear malformations or may be the sole radiographically detectable anomaly in a deaf child. A narrow IAC has been considered a relative contraindication to cochlear implantation, because it suggests that the eighth nerve may be insufficiently developed to conduct an auditory signal.[50] After cochlear implantation, some patients with narrow IACs have experienced facial pain and twitching without useful auditory sensation.

Anomalies of the Eighth Nerve

Hypoplasia and aplasia of the eighth nerve are often, but not inevitably, associated with congenital narrowness or even absence of the IAC. Similarly, although eighth nerve maldevelopment frequently accompanies malformation of the inner ear, the presence of a normal cochlea and semicircular canals does not guarantee normal development of the audiovestibular nerve.[100] High-resolution, thin-section MRI with T2-weighted sequences currently is the best means of assessing the fine anatomy of the eighth nerve in the IAC.[101,102] Such a study is warranted before cochlear implantation when the bony IAC is narrow on the CT scan, with severe types of inner ear malformation, and in syndromes known to be associated with maldevelopment of the eighth nerve (e.g., the CHARGE association, Möbius's syndrome).[103] Unilateral cochlear nerve aplasia, sometimes familial, is increasingly recognized as an important cause of congenital unilateral profound SNHL.[104,105] The internal auditory canal frequently is normal.[106] Increasingly refined MR techniques may reveal hypoplasia of the auditory nerve as more common than previously recognized.[107]

Syndromic Correlations and Familial Patterns

Inner ear malformations have been described in an increasing number of recognized syndromes associated with SNHL. Some of the more common examples are reviewed briefly next.

In Waardenburg's syndrome type I, absence of all three semicircular canals (17%) and cochlear hypoplasia (8%) have been reported.[108] In Waardenburg's syndrome type II, maldevelopment of the posterior semicircular canal has been described.[109] Semicircular canal agenesis or hypoplasia also has been noted in CHARGE syndrome.[110,111] In branchio-oto-renal syndrome, hypoplasia of the cochlea, sometimes accompanied by large VA, has been reported.[7,112,113] In Pendred's syndrome, large VA is a common feature, sometimes accompanied by modiolar deficiency.[114,115] Otic capsule anomalies also have been described in trisomy E and Usher's syndrome.[5,8] Down syndrome (trisomy 21) is associated with semicircular canal dysplasia and a variety of other inner ear malformations.[116]

Nonsyndromic familial patterns of inner ear malformation also have been identified.[9,10] An autosomal recessive pattern of Mondini's dysplasia has been reported.[117] In familial Mondini's dysplasia, genetic analysis has identified a deletion in locus DFN3.[118] Inherited complete labyrinthine aplasia (Michel's aplasia) has been described with a probable autosomal recessive inheritance pattern.[119] Familial lateral semicircular canal malformation has been described in association with anomalies of the external and middle ear.[120] Nonsyndromic familial occurrence of large VA has been associated with the Pendred gene.[121]

Cerebrospinal Fluid Leakage and Meningitis

Congenitally malformed inner ears may be a source of CSF otorhinorrhea.[122,123] For CSF leakage to occur, two abnormal connections must be present: one between the subarachnoid space and the inner ear and a second between the inner ear and middle ear. The most common pathologic interconnection between the subarachnoid space and the inner ear is through the fundus of the IAC. Histologically, large defects in the modiolar end of the IAC have been shown to exist in 10% of dysplastic ears.[95] Leakage may occur less often around the facial nerve at the lateral end of the IAC[124-126] (Fig. 191-20). The junction between the IAC and the inner ear may be evaluated with CT (Figs. 191-21 and 191-22). A well-defined bony plate normally partitions the distal IAC from the labyrinthine lumen. In a number of well-documented

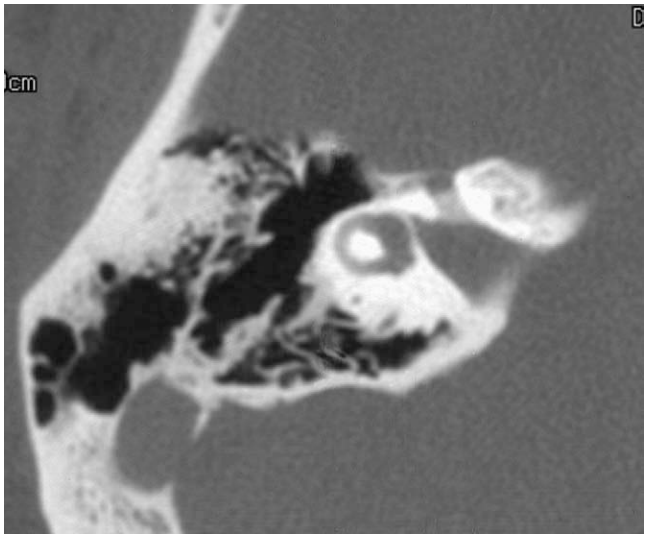

Figure 191-20. Dilated labyrinthine section of the fallopian canal associated with cochlear hypoplasia. This may serve as a conduit for cerebrospinal fluid leakage.

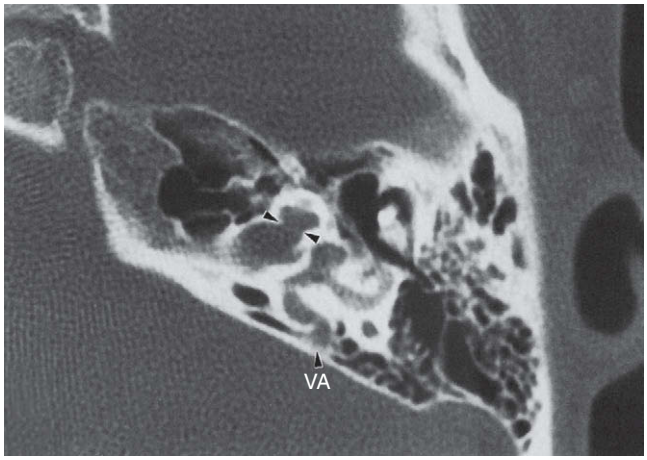

Figure 191-21. Axial computed tomography scan of an abnormal interconnection between the lateral end of the internal auditory canal and the cochlea. Note the absence of the modiolus *(arrowheads)* and the large vestibular aqueduct (VA).

Figure 191-22. Axial computed tomography scan of an abnormal interconnection between the lateral end of the internal auditory canal (IAC) and a dysplastic vestibular system. Note the junction between the IAC and the dilated vestibule *(arrowheads)*.

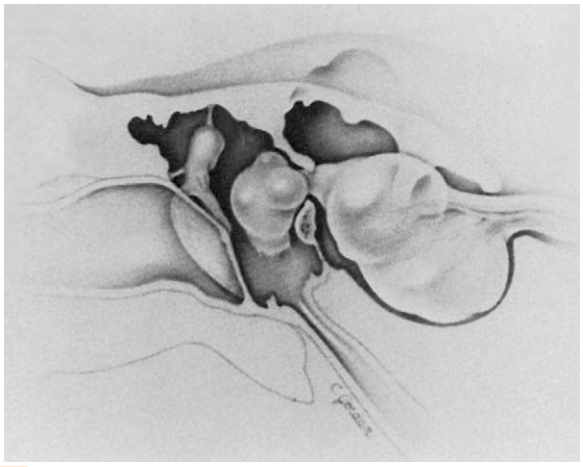

Figure 191-23. Drawing of a dural hernia protruding through the oval window in a child with cochlear hypoplasia, chronic cerebrospinal fluid leakage, and recurrent meningitis. *(From Herther C, Schindler RA. Mondini's dysplasia with recurrent meningitis.* Laryngoscope. *1985;95:655.)*

cases of CSF leakage, radiopaque contrast placed into the cerebellopontine angle cistern could be traced through the IAC into the inner ear.[122,124,127-129] The propensity of a dysplastic inner ear to leak CSF depends on its morphologic type. The common cavity deformity appears to be at particularly high risk. By contrast, Phelps and coworkers[130,131] maintain that the incomplete partition deformity (Mondini's dysplasia) is not associated with a heightened risk of CSF leakage. In ears with CSF fistulas, the SCCs usually are severely deformed. Although enlargement of the VA is a sign that CSF pressure is present within the inner ear, it does not necessarily imply the existence of an external leak into the middle ear. Rarely, transotic CSF leakage may be accompanied by a second congenital fistula in the anterior skull base.[132]

A second potential pathway between the subarachnoid space and the inner ear is the CA. As discussed previously in this chapter, there is little evidence to suggest that this pathway is a source of vigorous CSF leakage. In one published report, a CT metrizamide cisternogram was said to demonstrate a large CSF leak occurring through the CA; however, the published image showed the defect to be far anterior and superior to the region of the CA.[122]

A direct route between the subarachnoid space and middle ear, bypassing the inner ear, may exist in rare cases. Hyrtl's fissure, a congenital cleft that runs between the hypotympanum and posterior cranial fossa passing in proximity to the jugular bulb, has been reported to be a source of CSF leakage.[125] It is interesting that a diligent search of the historical literature has failed to find a publication on this subject by Hyrtl, despite his long eponymic association with this deformity.[133] In the interest of clarity, the descriptive term *tympanomeningeal fissure* is preferable.

The pathologic interconnection between the inner ear and middle ear most frequently is at the oval window. Numerous reports have described defects in the central portion of the footplate with a protruding membrane, most probably arachnoid[123,124,134-137] (Fig. 191-23). In other cases the defect is adjacent to the footplate, particularly just

anterior to it. Much less frequently, leakage may occur through the round window or a fissure on the promontory.[123] Schuknecht and Reisser[95] evaluated the oval and round windows in 29 ears with congenital malformations of the inner ear. On histologic examination, the stapes were absent in 4, fixed in 6, and normal in 15 cases. In 4 cases the footplates were noted to have defects that were bridged by thin membranes only. The round windows were normal in 28 cases and abnormal in only 1 (bony closure). No deficiencies in the round window membranes were noted.

The primary clinical importance of CSF leakage is the risk of meningitis. There have been numerous reports of meningitis complicating congenital malformation of the inner ear.[122-124,134,136-138] Recurrent bouts of meningitis are typical, and recognition of the inner ear as the source frequently comes only after several episodes have occurred. Acute otitis media appears to be the bacterial source in most cases. All children with recurrent meningitis without an obvious cause should undergo CT of the inner ear to exclude inner ear malformation.[139] Even children with a single episode of meningitis should have a postrecovery audiogram followed by CT if unilateral or bilateral SNHL is discovered. The causative organisms in a review of 24 reported cases have been *Streptococcus pneumoniae* (in 71% of the cases), *Haemophilus influenzae* (in 33%), and β-hemolytic streptococci (in 8%). The total exceeds 100% because of the incidence of polymicrobial infection.

Surgical closure of transotic CSF leakage may be attempted at four anatomic levels: (1) the posterior cranial fossa; (2) the dysplastic inner ear; (3) the middle ear windows; and (4) the eustachian tube. In an ear with residual hearing, tympanotomy and overlay grafting of the site of leakage with a connective tissue graft is indicated as a first attempt. Unfortunately, recurrent leakage is common. When this technique fails and a useful amount of hearing persists, posterior fossa craniotomy with placement of a muscle plug in the IAC or connective tissue graft over the fistulous tract may prove to be successful and spare hearing.[122] When the hearing is poor, a direct approach to the dysplastic inner ear is indicated. After tympanotomy and removal of the footplate, an oversized piece of muscle may be used to obliterate the vestibule.[18,25,123,140] If the anatomy is unfavorable for this maneuver, a postauricular translabyrinthine approach to the IAC should prove to be effective. Farrior and Endicott[141] proposed a hypotympanic approach to ablation of the CA. However, this aqueduct has never been convincingly demonstrated to cause a high-volume CSF leak. The final option, closure of the eustachian tube, is not a good choice for children. After this procedure, the anomalous CSF pathway is still open to the middle ear—a disadvantageous situation at an age when acute otitis media is common. Subsequent to the repair of any CSF leakage, the patient is placed on bed rest with the head elevated 30 degrees for several days. Acetazolamide (Diamox) is administered to reduce CSF production, and fluids are restricted. Placement of a lumbar drain is a useful adjunctive measure, although it may be difficult to insert and maintain in young children.[90]

X-Linked Stapes Gusher Syndrome

A form of hereditary mixed conductive and sensory hearing loss associated with CSF gusher during stapes surgery has recently been described.[142] Inherited hearing loss follows an X-linked pattern.[143] The characteristic inner ear deformity may be seen radiographically.[144,145] On CT, the cochlear modiolus is deficient and the lateral portion of the IAC often is bulbous (see Fig. 191-21). These observations provide strong evidence that the abnormal interconnection between the subarachnoid space and the inner ear is by way of the lateral terminus of the IAC. The labyrinthine segment of the fallopian canal may be dilated. In the vestibular system, the posterior semicircular canal often is deformed, and the VA may be enlarged.

The occurrence of stapes fixation in X-linked gusher syndrome is questionable. It has been proposed that the observed air-bone gap may be accounted for by alteration in cochlear micromechanics rather than dysfunction of the conducting system.[146] Results of acoustic reflex testing and auditory evoked responses are more consistent with a pure sensory hearing loss than a mixed form. The outcome of stapes surgery in these patients usually is poor, with anacusis in the operated ear a frequent result. When surgery is contemplated for a congenital conductive hearing loss, preoperative imaging is advisable to screen for inner ear malformation.

Perilymphatic Fistula

In contrast with CSF leakage, a perilymphatic fistula requires only one abnormal pathway: an interconnection of the inner ear with the tympanic cavity. In all probability, perilymph fistula and CSF leak are part of a spectrum of related disturbances of inner ear fluid homeostasis. Although separation of the two topics may be artificial pathophysiologically, it can be justified by the different clinical settings of the two problems. With CSF leakage, the cardinal clinical issues are gross fluid leakage and recurrent meningitis; with perilymph fistulization, sudden or progressive hearing loss and vertigo are the primary manifestations.

Much controversy surrounds the diagnosis and management of perilymphatic fistula in children. The candidate group for exploratory tympanotomy consists of children with progressive or sudden SNHL. CT of the inner ear may demonstrate pneumolabyrinth, although this finding is rare (Fig. 191-24). Conservative surgeons have advocated exploration only in children with radiographically abnormal inner ears who have a clear antecedent event of head trauma or barometric pressure change.[147] Other workers have espoused the notion of surgical exploration in all children with unexplained SNHL.[14,148,149] Great variability exists in the number of fistulas "confirmed" at surgery. Pappas and colleagues[147] found only 4 fistulas in 36 ears (11%) explored for progressive SNHL during childhood. Of note, 50% of these ears had radiographically malformed inner ears. By contrast, Parnes and McCabe[148] found fistulas in 20 of 26 children's ears (77%), only 6 of whom had inner ear anomalies radiographically. A high incidence of fistulas among children with sensory hearing loss (64%), both with and without inner ear malformation, has been reported.[150,151] Furthermore, one group of investigators claim to have objective verification of the presence of perilymph in the middle ear through evaluation of β_2-transferrin levels in surgical aspirates.[152] An important point is that considerable doubt exists regarding whether this test is valid. A recent study in which perilymph samples were directly obtained during either stapedectomy or cochlear implant surgery failed to detect β_2-transferrin in this fluid.[153]

In exploration of a perilymph fistula, it is important to perform provocative maneuvers to render subtle perilymph flows more visible. Such maneuvers include performing a Valsalva maneuver, using the Trendelenburg position, and compressing the jugular veins. Many surgeons are either missing subtle or intermittent perilymphatic fistulas during explorations or overdiagnosing them by misinterpreting middle ear secretions or local anesthetic as perilymph. Attempts to make a

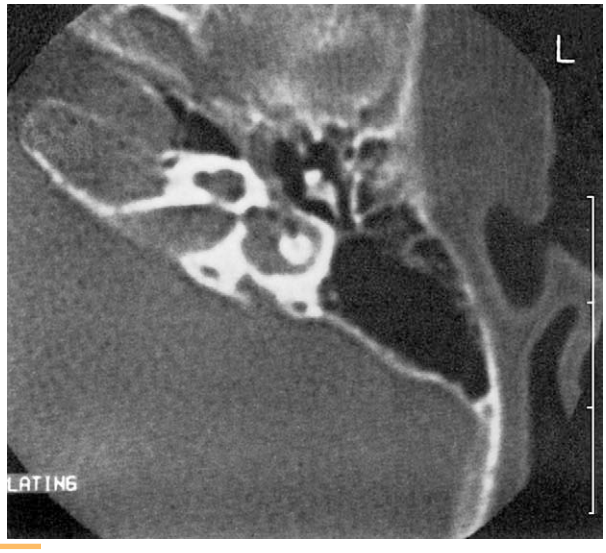

Figure 191-24. Air bubbles in the inner ear (pneumolabyrinth) in a congenitally deaf child with a perilymphatic fistula.

practical biochemical test for the presence of perilymph or CSF in the middle ear—through either assay of β_2-transferrin or intrathecal fluorescein administration—have not yet proved useful.[154,155] Most surgeons patch both oval and round windows with connective tissue whether or not a perilymphatic fistula was identified during exploration.

Rather than dwell on the controversy about how many fistulas are found, the critical observer should judge the effectiveness of the therapeutic intervention by analyzing its outcome relative to the natural history of the disease. In this regard, results of perilymphatic fistula exploration in children have been disappointing. In one series of 36 patients, hearing was better in 3, unchanged in 21, and worse in 12.[147] Similar results have been obtained in other childhood perilymphatic fistula series. It would be difficult to argue that these data represent a significant improvement over the natural history of the inner ear disease. Congenital progressive SNHL often is characterized by long periods of stability interspersed with periods of rapid deterioration. Even a relative improvement in hearing may occur after an episode of sudden loss. It is apparent that most children with sudden or progressive SNHL have suffered from cochlear diseases other than perilymphatic fistula. Examples are hereditary progressive loss, viral labyrinthitis (e.g., measles, mumps, cytomegalovirus), autoimmune inner ear disease (e.g., Cogan's syndrome), and endolymphatic hydrops. Even in the most suggestive clinical situation—sudden loss triggered by head trauma in a child with radiographically malformed inner ears—only a minority of patients demonstrate oval or round window fistulization. Many of these children probably lose hearing as a result of internal fistulization between the endolymphatic and perilymphatic space because of deficiencies of the osseous spiral lamina, rather than because of external fistulization to the middle ear. A minority of children with sudden or progressive SNHL have prominent vestibular symptoms. Results of perilymphatic fistula repair in the relief of vertigo have been quite good, although spontaneous recovery from vestibulopathy is common in this age group.

Inner Ear Malformations in Congenital Aural Atresia

Development of the external and middle ears is embryologically distinct from that of the inner ear. Anomalies of the lateral portion of the temporal bone typically result from derangement of the first or second branchial arches. Despite their embryologic separateness, congenital aural atresia may coexist with malformation of the inner ear.[156] In one study of patients with atresia, 12% (8 of 66) had a radiographically detectable inner ear abnormality.[157] In this group, SCC abnormalities were most common, including some ears with normal bone-conduction hearing. Cochlear anomalies were present in 5% (3 of 66) of these patients, all of whom had poor bone conduction hearing. It is an embryologic enigma that one patient with unilateral atresia had a malformed inner ear only on the contralateral side. In another polytomographic study of atretic ears, 8% (4 of 48) had SCC anomalies, and 2% (1 of 48) had a deformed cochlea.[158] As indicated by a comprehensive review of the relevant literature, approximately 5% of patients with atresia have cochlear deformities, whereas 10% have malformed SCCs. As a general rule, surgical reconstruction of atretic ears should not be attempted when they are associated with malformation of the inner ear. The deformed cochlea is more vulnerable to injury from vibratory trauma, and the risk of inducing a sensory hearing loss is increased. This surgery also carries a heightened risk of CSF leakage.

Imaging

During the 1980s and 1990s, CT was the gold standard imaging modality for investigation of patients suspected of having an inner ear malformation. In the early 21st century, new MRI techniques are capable of producing images superior to those obtained with CT. In contrast to CT, which depicts otic capsule bone, MRI displays inner ear morphology by imaging inner ear fluids. High-resolution, thin-section, T2-weighted sequences (e.g., fast-spin echo) provide exquisite detail of inner ear anatomy (see Fig. 191-4).[159] MRI is superior to CT in a number of ways. MRI can distinguish between a cochlea filled with fluid and one occluded by soft tissue. CT is unable to make this distinction—an observation of great importance in assessing scala tympani patency before cochlear implantation. MRI provides more information about large VAs than that provided by CT.[72,73,160] It displays not only the dilated osseous canal but also the dimensions of the often impressively expanded endolymphatic sac. Direct visualization of the eighth nerve in the IAC, where it appears as a linear filling defect outlined by CSF, is yet another advantage of MRI. This capability is important in certain severe deformities in which neural agenesis may be found. Three-dimensional renderings of inner ear malformations have been produced using both CT and MRI.[161,162]

In assessing images for possible inner ear malformation, it is important to measure the size of structures and not merely look for anomalous patterns. Normative data of inner ear dimension have been published to aid in this determination.[163] Quantitative measurement has been shown to increase diagnositc yield in cochlear hypoplasia (less than 4.4 mm cochlear height on coronal images) and semicircular canal dysplasia (bony island width on axial projection) even for experienced neuroradiologists.[164]

In addition to inner ear malformation, numerous causes of acute and chronic SNHL in children are recognized. Whereas either CT or MRI findings would be normal in the great majority of these, a few disorders can be visualized only by MRI. The obvious category is lesions of the cerebellopontine angle (e.g., tumors) and brainstem (e.g., adrenoleukodystrophy). On noncontrast T1-weighted MRI, acute hemorrhage results in hyperintensity of the inner ear. On gadolinium-enhanced studies, acute inflammation (e.g., viral infection) results in high signal intensity in the inner ear or along the course of the eighth nerve.

When selecting MRI as an imaging study to screen for inner ear malformation, it is important for the physician to be aware that standard MRI protocols designed to screen for central nervous system abnormalities provide only limited information concerning the inner ear. To be useful in screening for inner ear anomalies, specially designed protocols are needed.[159] One disadvantage of MRI is the difficulty young children have in tolerating the confined spaces of the magnet. In addition, fast-spin echo MRI requires considerably longer scan time than does CT. Whereas simple sedation usually is sufficient for CT, acquiring high-quality magnetic resonance images may require use of general anesthesia in pediatric patients. Accordingly, despite the numerous advantages of MRI (including the absence of ionizing radiation), CT is the pediatric examination of choice in many centers for this important practical reason.

Evaluation and Management

High-resolution CT or MRI of the inner ears is recommended for all children with suspected congenital malformation of the inner ear, including those with otherwise unexplained SNHL, regardless of whether it has existed from birth or occurred later. Scans usually are obtained when hearing impairment is first recognized. Use of thin slices of 1- or 1.5-mm thickness with 0.5-mm overlap will adequately image the minute inner ear structures.[59] If only one plane of view is to be obtained, the axial orientation is preferred because it provides superior images of the VA, a frequently malformed structure that is difficult to visualize on coronal scans. When possible, both axial and coronal views should be obtained, because certain subtle deformities, such as deficiency of the interscalar septum, are best seen in the coronal orientation. It is important to examine thoroughly all portions of the inner ear, because anomalies frequently are multiple (Fig. 191-25).

No medical or surgical therapy has been shown to prevent the progressive hearing loss associated with congenital malformation of the inner ear. After a sudden decrease in hearing, a short course of an oral corticosteroid (e.g., prednisone) is administered. Although no studies have assessed the efficacy of corticosteroids in children with inner ear deformities, studies of idiopathic sudden SNHL in adults suggest some benefit. Furthermore, autoimmune mechanisms may play a role in a few children with rapid hearing deterioration, a possibility that justifies a therapeutic trial. Of course, many patients experience spontaneous partial recovery after sudden losses, even without therapeutic intervention.

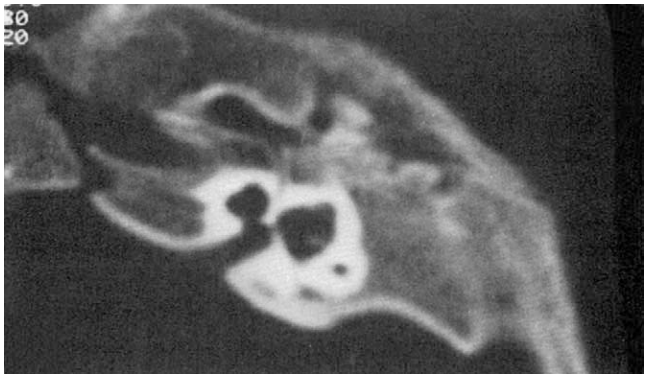

Figure 191-25. Axial computed tomography scan demonstrating a cochlear deformity (incomplete partition) as well as dysplasia of the lateral semicircular canal. Many congenitally malformed inner ears have abnormalities in more than one portion of the inner ear.

Few patients with congenitally malformed inner ears have a fluctuating pattern of hearing loss suggestive of endolymphatic hydrops. When fluctuations are encountered, however, a low-salt diet and diuretics are prescribed. Surgical intervention is indicated in a few well-defined circumstances. Obviously, CSF leakage and meningitis require intervention. Exploration for perilymphatic fistula is reserved for patients with radiographically abnormal inner ears who have suffered a sudden hearing deterioration temporally related to a precipitating event such as head trauma, rapid barometric pressure change, vigorous exercise, or sneezing. As discussed previously, even in these patients, only a minority have a fistula, and those who do frequently continue to lose hearing despite repair. House[165] and later others advocated endolymphatic sac surgery for congenital malformations of the inner ear[166-168]; however, a careful analysis of the outcome in a large series revealed no benefit of this surgery in terms of hearing stabilization.[169] In fact, nearly 30% of the patients suffered significant postoperative hearing deterioration. Patients with large VAs appear to be at particularly high risk for poor outcome after sac surgery. Surgical obliteration of the endolymphatic sac with muscle and fascia has been advocated in patients with enlargement of the VA.[83] Unfortunately, a multicenter study showed that this procedure not only fails to stabilize hearing but is associated with a 50% rate of sensorineural hearing deterioration.[84]

Preventive measures are important in the management of patients with congenitally malformed inner ears. The risk of CSF leakage may be estimated by CT or MRI of the inner ear. Anatomic features of concern include a wide IAC, deficient partitioning between the IAC and inner ear, and enlargement of the vestibule in the horizontal plane. Parents should be made aware of the risk of meningitis and instructed in recognizing its early symptoms and signs. Because most episodes of meningitis associated with inner ear malformation are pneumococcal, use of the pneumococcal vaccine is recommended.[170] Children with malformed inner ears should avoid head trauma and rapid barometric pressure changes, because these risk provoking a sudden hearing loss or even CSF leakage. Activities such as contact sports and scuba diving are discouraged. Finally, establishing a prognosis for future auditory function in a hearing-impaired child serves as a guide for educational and rehabilitative efforts. Recognizing an inner ear malformation on CT may be helpful, because certain morphologic patterns have more favorable prognoses than others.

Cochlear Implantation

Electrical stimulation of the auditory nerve has proved useful in many forms of sensory deafness, including those associated with congenital malformations of the inner ear. The fundamental premise of cochlear implantation is that some of the cochlear neural population survive despite the absence of hair cells. In congenital malformations of the inner ear, the auditory nerve population typically is less than with other forms of sensory deafness. The normal human spiral ganglion cell count usually is 25,000 to 35,000. In eight congenitally dysplastic ears, Schmidt[171] reported cell counts ranging from 7677 to 16,110, with an average of only 11,478. By contrast, ears with profound sensory hearing loss from ototoxicity, otosclerosis, or mechanisms of sudden loss have ganglion cell populations in the range of 18,000 to 22,000. This observation suggests that malformed inner ears could be electrically stimulated but that improvements in speech discrimination would fall below average for the deaf population at large. A narrow IAC on pre-implantation CT (less than 3 mm in diameter) is a strongly adverse predictor of neural survival.[23]

Cochlear implantation in deformities that involve both the membranous and osseous labyrinth raises several special considerations. Cochlear implantation in malformations limited to the membranous labyrinth is equivalent to implantation in the prelingually deaf child (see Chapter 159). Results of implantation with short, single-channel devices in patients with cochlear hypoplasia, common cavity, and incomplete partition deformities appear in the literature.[36,172,173] In successful cases, sound detection levels are similar to those in other prelingually deaf children.[174,175] Implantation of deformed cochleas with multichannel devices also has proved to be valuable in a majority of cases but is associated with a higher rate of complications.[31,176-179] Performance varies widely and appears, on average, to be somewhat below that realized in most other forms of deafness. The design of multichannel electrodes makes certain assumptions about the geometry of the scala tympani that affect the anticipated orientation of stimulating electrodes to neural elements. Although standard electrodes are not optimized for dysplastic cochleae, fabrication of custom electrodes for each malformed cochlea is not feasible with current technology. The degree of electrode insertion varies, in large part because of variability in size and geometry of the deformed cochlea.[180] Only partial insertion may be realized, particularly in hypoplastic cochleas, whereas complete insertion is more common with milder deformities such as incomplete partition.

One complication of unpredictable electrode positioning is stimulation of the facial nerve at current levels lower than the threshold for auditory perception. Cross-stimulation of the facial nerve has been reported with both single-channel and multichannel designs and has prevented some patients from using the device. Multichannel systems have a distinct advantage in this regard because the offending electrode pair or pairs may be programmed out of the stimulation map, thereby preserving the ability to provide auditory stimulation. The presence of a dysplastic inner ear may be a warning that the facial nerve is malpositioned.[181] An anomalous facial nerve course has been reported to occur in 16% of malformed inner ears.[176] In one patient with cochlear hypoplasia, an anomalous facial nerve was injured immediately above the round window niche, a highly vulnerable location during implant surgery.[31] Use of electrophysiologic facial nerve monitoring during implantation in patients with malformed inner ears is advisable. It also is possible for a persistent stapedial artery to traverse the round window region, thereby precluding implantation.[182]

Another complication of implantation in malformed cochleas is facial twitching consequent to inadvertent penetration of the IAC by the electrode.[179] When such a malpositioned electrode is activated, vigorous facial twitching may occur at an extremely low stimulation threshold. To avoid this complication, post-implantation CT is advisable before stimulation is undertaken to assess electrode position after implantation in a malformed cochlea.

CSF leak also has been a frequent complication during implantation of the malformed cochlea, occurring with an incidence of approximately 40%.[176] The leak typically is evident immediately on opening the round window and presumably occurs as a result of deficiencies in the partition between the modiolus and the dural envelope at the lateral end of the IAC. Leaks have been successfully handled by packing connective tissue around the electrode, but temporary CSF diversion may be required to obtain a lasting seal.[183] Multichannel cochlear implants, especially certain varieties designed to approximate the modiolus, have been associated with an increased long-term incidence of meningitis.[184] The incidence may well be higher in patients with malformed inner ears.[185]

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CHAPTER ONE HUNDRED AND NINETY-TWO

Microtia Reconstruction

Craig S. Murakami

Vito C. Quatela

Kathleen C. Y. Sie

Joseph Shvidler

Key Points

- The auricle is formed from the branchial arches starting at approximately 5 weeks of gestation.
- The auricle grows rapidly in the first 3 years of life and then grows more slowly until approximately 13 years of age for boys and 12 years of age for girls. Normal adult ear height ranges from 5.5 to 6.5 cm.
- The etiology of microtia most commonly is sporadic, possibly as the result of a vascular injury in the distribution of the stapedial artery. Other causes include teratogenic exposures and syndromic associations.
- Type I microtia is used to designate ears with mild deformity. Type II includes ears that have all major structures present to some degree. Type III deformities have few or no recognizable landmarks of the auricle, although the lobule usually is present and positioned anteriorly. Anotia is the complete absence of auricle and lobule.
- Options for microtia management include observation, prosthetic management, and reconstruction with autologous rib graft or Medpor implant with temporoparietal fascial flap.
- Observation is recommended until the child is at least 5 to 8 years old. This allows both growth of the donor rib cartilage and development of the contralateral normal ear. In general, microtia repair should precede atresia repair.

Microtia occurs with an overall frequency of approximately 1 to 3 cases per 10,000 population,[1] although certain ethnic groups, such as Navaho Indians in Mexico and the Japanese, may have higher incidence of microtia.[2] Microtia deformities appear to be more common on the right side and affect boys more often than girls at roughly a 2.5:1 ratio; unilateral cases outnumber bilateral cases by 4:1. Surgical management of microtia remains one of the greatest reconstructive challenges for an otolaryngologist.[3-6] Auricular reconstruction of the microtia deformity is a complex and labor-intensive process that requires careful preoperative planning, surgical skill, and artistry. This chapter provides a basic overview of clinical issues in children with microtia and reconstruction with autologus rib cartilage. Discussion of aural atresia is presented elsewhere.

Embryology

The inner ear begins as the otic placode at approximately the third week of gestation, and it then forms into the otic pit and otic cyst. The external ear begins to form in the fifth week of gestation. The auricle begins as six small buds of mesenchyme, classically known as the hillocks of His, surrounding the dorsal end of the first branchial cleft.[7-10] On either side of the first branchial cleft are the first (mandibular) and second (hyoid) branchial arches. Hillocks 1 through 3 arise from the first branchial arch, and hillocks 4 through 6 arise from the second branchial arch. Conventional teaching holds that the first hillock forms the tragus, the second and third form the helix, the fourth and fifth form the antihelix, and the sixth forms the antitragus. The majority of the central ear is derived from hillocks 4 and 5, and the lobule appears to be one of the last parts of the ear to develop (Fig. 192-1). It has been estimated that the hyoid arch forms about 85% of the auricle.[5] The exact embryology of each of these hillocks remains unclear. The position of the auricular complex begins at the anterior neck region. As the mandible develops during gestational weeks 8 through 12, the auricular complex moves in dorsal and cephalic directions. The etiology of microtia remains unknown in most cases, although the inciting event that arrests development of the ear must occur during the first trimester, and may be related to abnormal neural crest cell migration.

Known teratogens, such as the retinoic acid derivative isotretinoin (Accutane; Roche, Nutley, New Jersey), can produce forms of microtia in conjunction with craniofacial, cardiac, thymic, and CNS anomalies, a condition commonly known as retinoic embryopathy.[11] Thalidomide and mycophenolate mofetil also have been reported to be associated with microtia.[12,13] Microtia is associated with other anomalies about 50% of the time. Microtia is most commonly associated with other regional anomalies related to the first and second branchial arches, i.e., facioauriculovertebral syndrome. Within the facioauriculovertebral spectrum are malformations and syndromes that affect the first and second branchial arch derivatives, such as Goldenhar's syndrome (preauricular nodes, epibulbar dermoids, mandibular hypoplasia), hemifacial microsomia,[14] and oculoauricular vertebral dysplasia (microtia, cervical spine anomalies, and epibulbar dermoids).[15,16] It may be that Goldenhar's syndrome, hemifacial microsomia, oculoauriculovertebral dysplasia, and microtia are simply variants of the same entity.[4] Microtia also may be seen in syndromes such as Treacher Collins syndrome, which has an autosomal dominant inheritance pattern.

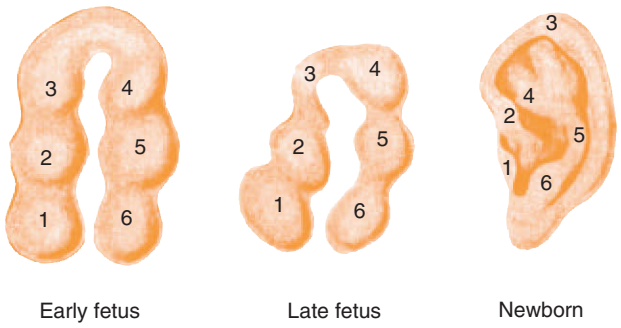

Figure 192-1. Embryonic development. The ear develops from six hillocks of His. Hillocks 1 through 3 are from the first branchial arch, and hillocks 4 to 6 are from the second branchial arch. Hillock 1 forms the tragus, hillock 2 forms the root of the helix, and hillock 6 forms the antitragus. Hillocks 2 through 5 appear to form the helix and antihelix.

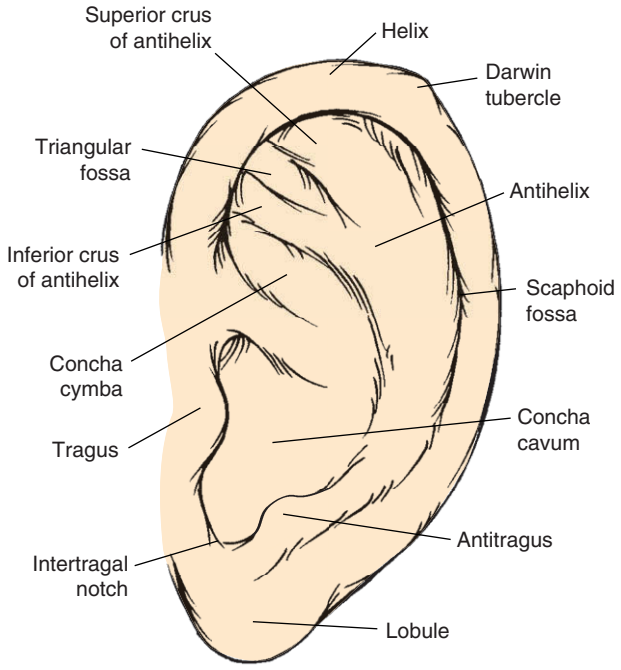

Figure 192-2. Normal anatomic landmarks of the ear.

Ear Anatomy

The anatomic contour of the normal ear must first be reviewed in order to understand the nature and extent of microtic ear deformities (Fig. 192-2). The auricle is an aesthetic sculpture of complex convexities, concavities, and curved lines such as the helix and the antihelix, which are smooth and uninterrupted. The elastic cartilage framework of the auricle is usually pliable yet structurally strong and extraordinarily resistant to trauma. The skin of the ear is fibrofatty and loose over the lobule and the margin of the helix but thin and fixed over the remaining cartilage framework.

Normal adult ear height ranges from 5.5 to 6.5 cm, which is typically attained by 13 years of age in boys and 12 years of age in girls. The ear goes through rapid growth between 2 and 3 years of age and reaches 95% of its adult size by about age 5. Thereafter it grows at a modest rate until it reaches its adult size during early teenage years. The horizontal width of the ear is achieved at a much earlier age. Protrusion of the ear from the surface of the mastoid should be 1.5 to 2.0 cm, thereby creating an angle between 15 and 20 degrees.[17] The superior margin of the helix is at the level of the tail of the eyebrow in 85% of people. Because the tail of the eyebrow is also quite variable, the level of the upper eyelid also may be used as a landmark if the patient has bilateral microtia.[18] The ear inclination is the angle formed by the vertical axis of the face and the longitudinal axis of the ear with the patient in the Frankfort horizontal position. This is approximately 24.8 degrees, with a standard deviation of 6.2 degrees.[19] Therefore, the longitudinal axis of the ear is not quite parallel with the dorsum of the nose (as is commonly thought), because the ear is in a slightly more vertical orientation.

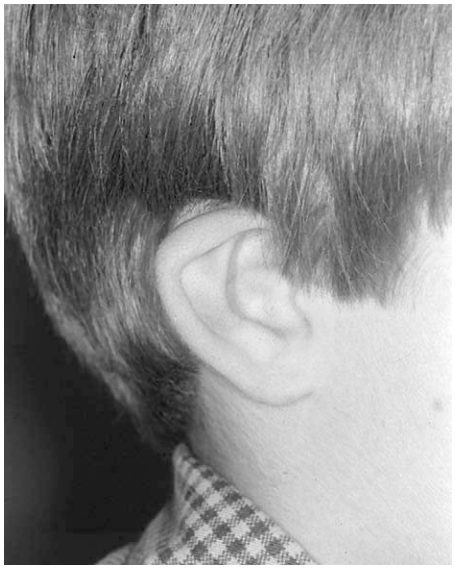

Figure 192-3. Type I microtia. A constricted ear with minimal tissue deficiency.

Microtia

Microtia deformities come in various shapes and sizes, and unfortunately, there is currently no universal, precise, and accurate classification scheme that is clinically useful. Classification schemes are further complicated if the status of the external auditory canal (EAC) and middle ear contents and the presence or absence of an associated syndrome are included.[5,20] Classification usually is simplified by evaluating the external auricular deformities alone. Perhaps *dysplasia* is a better term than *microtia* to use in describing ear deformities. Dysplasia deformities typically are divided into three broad and simple categories that have a great deal of overlap.[21] *Type I* (Fig. 192-3) is used to designate ears with mild deformity. All major structures are present to some degree, and reconstruction does not require additional tissue. *Type II* (atypical microtia) dysplasia (Fig. 192-4A to C) includes ears that have all major structures present to some degree. There is a deficiency of tissue, and surgical correction requires the addition of cartilage and skin. Mini-ear and severe cup-ear deformities are included in this category. The external auditory meatus is present, but it may demonstrate some degree of stenosis. *Type III* (classic microtia) dysplasia (Fig. 192-5A to C) deformities have few or no recognizable landmarks of the auricle, although the lobule usually is present and positioned anteriorly (see Fig. 192-16). *Anotia* is the complete absence of auricle and lobule. Reconstructive surgeons may find it more useful to simply note the status of the helix and antihelix, the conchal bowl, the lobule, the tragus, and the EAC, because these landmarks dictate the stages of ear reconstruction and the degree of surgical difficulty.

Evaluation

Children with microtia typically present to an otolaryngologist early during infancy because of the visible anomaly and parental concerns related to the child's hearing. The parents are usually concerned with the short- and long-term effects of monaural hearing on the child's speech development and the possibility of learning disabilities. Physical examination should focus on the mandibular shape and excursion, mouth, maxilla, eyes, and neck to rule out mandibular asym-

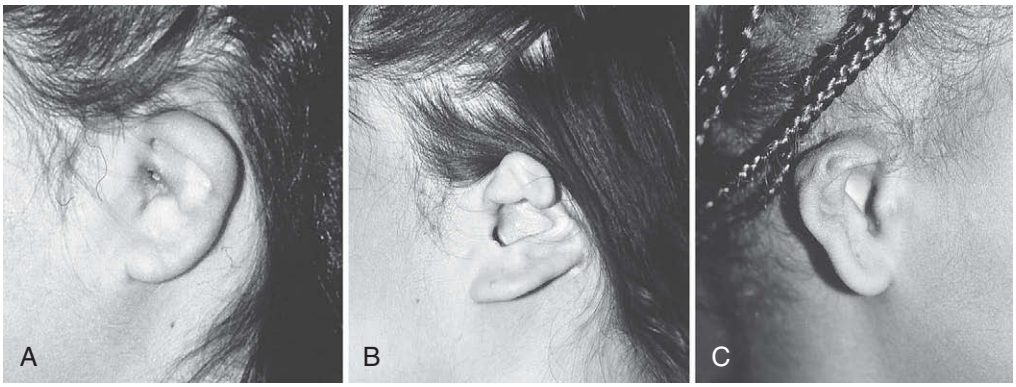

Figure 192-4. Type II microtia. **A,** A patient with type II microtia demonstrating a slight deformity with a small helix and missing antihelix. This patient also demonstrated canal stenosis. **B,** More extensive loss of the helix and antihelix, with a relatively normal canal and conchal cavum. **C,** A patient with loss of the superior crus of the antihelix and a constricted helix.

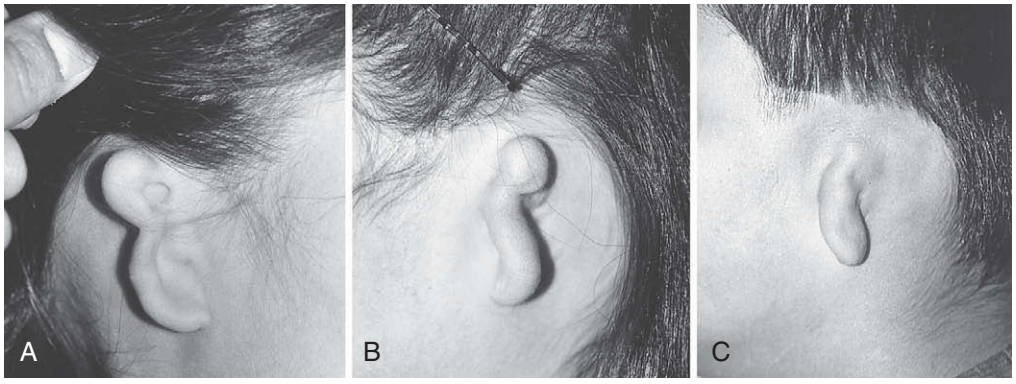

Figure 192-5. Type III microtia. **A** and **B,** Ears with moderate deformity and a few remaining visible landmarks of the helix. **C,** No recognizable landmarks of the auricle or canal are apparent, but the lobule is preserved.

metry, maxillary asymmetry, epibulbar dermoids, coloboma, and vertebral anomalies, which may indicate that the microtia is part of a syndrome.

Although patients with microtia typically have normal hearing in the contralateral ear, all patients with unilateral microtia should have age-appropriate hearing assessment. Hearing should continue to be monitored and eustachian tube dysfunction in the patent ear should be treated. Radiologic evaluation should include high-resolution computed tomography (CT) scan of the temporal bones to assess degree of atresia; cervical spine films to rule out vertebral anomalies; renal ultrasound to rule out congenital renal malformations; and panoramic (Panorex) films to assess the status of the mandible. If multiple anomalies are found, the child is referred to a multidisciplinary craniofacial team for more comprehensive evaluation.

Planning

Early evaluation by an otologist who is familiar with aural atresia is generally recommended. In most cases of unilateral microtia with aural atresia and a contralateral normal-hearing ear, canal reconstruction is controversial because speech development is expected to be normal. However, children with unilateral hearing loss predictably will have difficulties with sound localization and speech discrimination in a noisy setting. Careful review of the middle ear status, ossicular mass, position of the facial nerve, formation of the cochlea, and vestibular structures on CT scan helps the otologic surgeon determine candidacy for atresia repair.

If the patient is considered to be a favorable candidate, atresia repair should be performed after completion of microtia reconstruction. Patients with bilateral microtia and normal bone conduction thresholds may benefit from bone conduction hearing aids. Bone-anchored hearing aids may be considered in children older than 5 years of age.

With regard to the pinna, the patient and family are presented with three options: observation; prosthetic management, either adhesive- or implant-retained; and reconstructive options including staged reconstruction with autologous rib graft, and reconstruction with linear high-density polyethylene (Medpor) surgical implant material and temporoparietal fascial flap. Generally, observation is recommended until the child is at least 5 to 8 years old. This allows both growth of the donor rib cartilage and development of the contralateral normal ear, which will act as a template for the microtic side. Waiting until the child is older may reduce the risk of the development of a thoracic deformity as a result of harvesting of cartilaginous rib graft, although we feel this risk is minimal.[22] Finally, waiting until the child is school-aged allows the child to participate in these important decisions. We feel that it is important for the child to understand the options and participate in the decision making. The general health of the child is assessed, with particular attention paid to growth, maturation, and lung function. It is important to assess lung function, because the risk of pneumothorax and postoperative atelectasis and pneumonia is significant. This assessment usually is performed by the child's pediatrician. It is important to question the child about his or her personal concerns and to inquire about the effects of the microtia on social interaction with friends and classmates. Each child and parent will have different concerns that should be explored preoperatively.

During the planning stage of reconstruction, the surgical benefits, risks, and alternatives are discussed with the patient and the parents (Table 192-1). Complications such as infection, bleeding, scarring, graft loss, displacement or resorption, asymmetry, and pneumothorax should be discussed in detail. The possibility of a less-than-optimal aesthetic result also is discussed, and the expectations of the patient, parents, and surgeon must be realistic and clearly defined. Providing postoperative photographs of previous patients often is

Table 192-1

Overview of Treatment Options for Microtia

Treatment	Details	Advantage(s)	Disadvantages
Observation		No risk	Cosmesis Psychosocial issues
Prosthesis	Adhesive retained	Appearance	More difficult to incorporate atresia repair Requires removal of prosthesis at night and replacement in the morning Cost of prosthesis and maintenance
	Implant retained	Secure retention Appearance	Requires two surgical procedures that include removal of the microtic remnant Daily maintenance of implant site Appearance of implant site Cost of prosthesis and maintenance Eliminates possibility of reconstruction in the future
Reconstruction	Autogenous rib	Autogenous tissue Minimum maintenance More easily accommodates atresia repair	Appearance Donor site morbidity Multiple surgical procedures
	Medpor	Less donor site morbidity Less variability in carving	Foreign body More challenging to do atresia repair Increased risk of exposure of the framework

helpful to patients if the pictures depict a realistic result of a similar deformity.

One alternative for older children or adults may be the use of an auricular prosthesis. In some institutions, placement of a permanent auricular prosthesis with osseointegrated implants is recommended as the primary management modality. The aesthetic appearance often is excellent. However, most reconstructive surgeons discourage the use of osseointegrated implants for younger patients as a primary modality for several reasons: The implant sites will require daily care to maintain the health of the soft tissue surrounding the percutaneous osseointegrated implants. The prosthesis needs to be removed at night and replaced in the morning. The patient may unnecessarily avoid situations that may accidentally dislodge the ear and cause embarrassment. The placement of the osseointegrated implants requires removal of the soft tissue with skin grafting to bone to create nonmobile skin surrounding the posts. This eliminates the possibility of reconstructive surgery in the future. Furthermore, the prostheses are expensive and often not covered by third-party payers, leaving the patient at risk for having the osseointegrated implants in place without a prosthesis to wear in the future.

Finally, other materials for auricular reconstruction should be mentioned as part of a thorough informed consent, even if your institution may not offer these types of reconstructions. Implantable materials such as Medpor are used as alternatives to autogenous cartilage. Use of synthetic frameworks eliminates the need to harvest and carve the rib. However, the likelihood of extrusion and the lifelong risk of infections may outweigh their benefit. Stem cell technology is still emerging, and stem cell–derived implants may someday replace the need for rib graft harvesting. To date, no reliable cartilage implant created from stem cells is available.

Autogenous Costochondral Reconstruction

The use of rib cartilage in auricular reconstruction was pioneered by Tanzer[23] and refined by the meticulous work and accomplishments of Brent.[24,25] Reconstruction using the standard rib-grafting technique requires three to four stages, each separated by 2 to 6 months, beginning when the patient is approximately 6 to 8 years old.

The surgeon must develop carving and sculpting skills before undertaking a microtia reconstruction on a patient. For obvious reasons, fresh cadaveric rib cartilage is the best material with which to practice carving and harvesting grafts. If this cannot be obtained, carving the basic auricular framework can be practiced using soap or potatoes.

The surgical procedure described next is appropriate for reconstruction in patients with the most common class III dysplasia, or "peanut" ear.

Classic Microtia Reconstruction

Stage I: Cartilage Implantation

The first stage of microtia reconstruction is undoubtedly the most tedious and crucial of the entire process.[24] One of the most important objectives during the first stage is to place the auricular framework in a position that achieves the best symmetry for the patient's face. Placement of the reconstructed ear is determined by the position of the normal ear, and we do not alter this position to accommodate future reconstruction of the canal atresia or a low-lying hairline. If the hairline is low, the initial ear reconstruction is destined to have hair along the helix that will require depilation or excision at a later date. Preoperative tissue expansion to increase the amount of non–hair-bearing skin is not recommended, because the expanded skin capsule does not contour well over the implanted cartilaginous framework.

Three templates are made using radiographic film: a positioning template, a sizing template, and a carving template. The positioning template is made by carefully tracing the contour of the normal ear. It has the outline of the normal ear, with the landmarks of the lateral palpebral fissure and the lateral oral commissure for reference points. The landmarks are etched onto the radiographic film with an 18-gauge needle or scalpel to avoid losing these reference points (Fig. 192-6). The distance from the lateral palpebral fissure to the root of the helix is also measured on the template and should approximate 6.5 cm, or the length of the normal ear. The sizing template, which is a tracing of the entire ear, is used to test the size of the skin pocket in which the cartilaginous framework is placed. The carving template is drawn from the sizing template to include the landmarks of the antihelix, the triangular fossa, the scaphoid fossa, the medial aspect of the helix, and the antitragus. It is drawn 1 to 2 mm smaller than the sizing template to compensate for the thickness of the overlying skin. It is also used to determine the best donor site during rib harvesting and as a template

for sculpting the cartilaginous framework. After the landmarks are permanently etched, the templates are autoclaved. The entire head and neck region is prepared so that the contralateral normal side can be easily visualized to evaluate symmetry. The eyes and mouth are covered with a transparent drape to allow visualization of the lateral palpebral fissure and the lateral commissure and to facilitate placement using the positioning template. The recipient ear site is injected with lidocaine with epinephrine to assist with hemostasis, and the incision is drawn along the anterior and superior margin of the rudimentary lobule. The contralateral side of the chest is prepared, because the contralateral rib graft has better contour characteristics. The chest incision is drawn just superior to the margin of the rib cage.

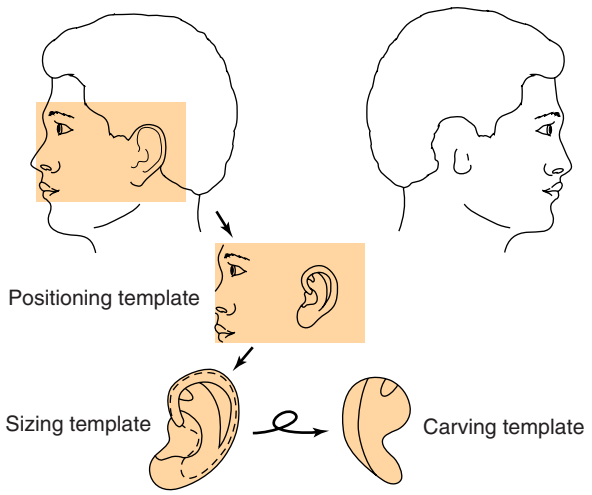

Figure 192-6. Templates for reconstruction. The positioning template, which is drawn with reference landmarks, is used to create the sizing and carving templates. The sizing template is drawn to match the exact size of the normal ear. The carving template is slightly smaller than the sizing template to compensate for the thickness of the skin flap.

We generally use two surgical teams to reduce operating time. The donor site incision is made on the contralateral side of the chest, and the inferior margin of the rib cage is exposed. We have refined a minimally invasive technique, using a 2-cm skin incision (Fig. 192-7A). Two cartilaginous segments are required: a segment of free-floating cartilage to create the helical rim and a portion of synchondrosis to create the auricular framework.

The floating eighth rib is isolated, and dissection is continued posterolaterally to the bony-cartilaginous junction. Ideally this segment is 8 to 9 cm in length. Then the synchondrosis, usually between sixth and seventh ribs, is exposed. The carving template is used to determine the best donor site for the synchondrosis (see Fig. 192-7B to D). The rib cartilage is harvested with the superficial perichondrium intact. After removal of both segments, the donor site is checked for violation of the pleura. The chest wound is filled with saline and the anesthesiologist is asked to deliver positive-pressure ventilation to sustain a pressure of 40 cm H_2O. If a defect in the pleura is identified, a red rubber catheter is introduced into the pleural space and placed on continuous suction. The catheter is removed during positive-pressure ventilation, and the wound is closed with an airtight closure. A suction drain is placed in the subcutaneous space after closure of the rectus muscle. Intercostal bupivacaine blocks are placed at the end of the procedure to reduce postoperative pain.

All incision planning should take into consideration future stages of reconstruction. The recipient incision is made vertically along the anterosuperior margin of the lobule. This incision site will be used for the second-stage lobule transfer. The rudimentary cartilage segment is meticulously removed, with great care taken to avoid perforating or traumatizing the skin flap. The recipient pocket is elevated over the

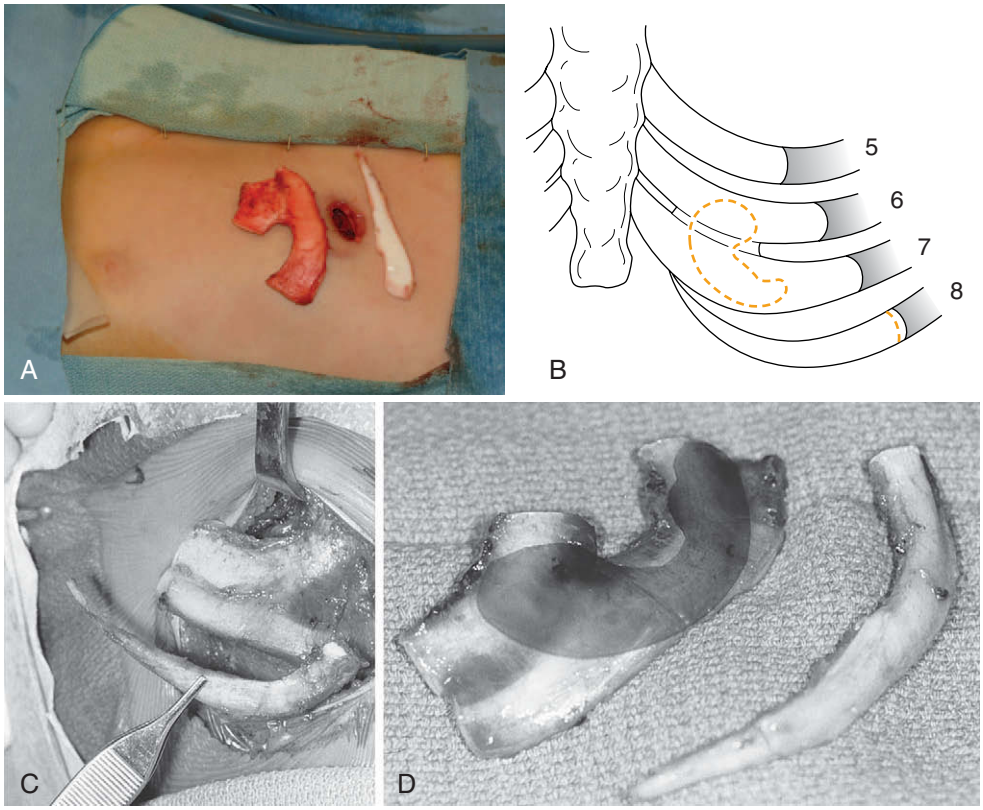

Figure 192-7. The donor site. **A,** A minimally invasive 2-cm incision is used to harvest rib segments. **B** to **D,** The contralateral chest is chosen for the donor site. The sixth, seventh, and eighth ribs and the synchondrosis between the sixth and seventh ribs are depicted. (The longer incision depicted in **C** is rarely necessary.) The donor sites of the auricular framework and the helical rim are indicated.

mastoid in a subcutaneous plane. The flap is thinned to a uniform thickness. In the hair-bearing region, the skin is thicker, because it becomes continuous with the scalp and contains a layer of galea. Dissection must be superficial to this layer of galea so that the flap remains uniformly thin and pliable. The sizing template is used to ensure that the pocket is large enough to accommodate the framework. The sizing template reduces the number of times that the reconstructed cartilage framework is transferred in and out of the pocket while adjustments are made; this helps reduce the amount of unnecessary handling and the risk of fracturing the framework.

The framework and helix are carved using Nos. 10, 11, and 15 scalpel blades. The 6700 Beaver blade can also be used (Fig. 192-8). As much perichondrium as possible is left intact over the lateral surface to enhance revascularization and tissue fixation. Suture or wire fixation is needed occasionally to reinforce the synchondrosis and to provide additional support to the framework. Additional cartilage grafts can be sutured to the posterior surface of the synchondrosis for more rigidity. The helix is carved from the eighth rib using the thicker part of the graft for the root of the helix and the thin distal tip of the graft for the caudal helix. The graft is carefully thinned until it is pliable enough to bend around the framework, and it is sutured into position with 4-0 clear nylon sutures. Additional thinning of the scaphoid and triangular fossa can be done after the helix is adequately fixated (Fig. 192-9A to C).

The reconstructed framework with attached helix is then placed into the pocket in a rotational manner, beginning with the root of the helix and then rotating the framework clockwise for the right side and counterclockwise for the left. If the pocket is excessively tight and the overlying skin remains blanched with poor vascular refill, the implant is removed and the pocket enlarged. After the graft is properly positioned, a small round suction drain is placed deep to the framework and brought out through the skin in the hairline. After the wound is sealed, the skin should conform to the framework, and the details of the helix and antihelix should be clearly visible (Fig. 192-10). The concavities of the ear are packed with petroleum gauze and secured with 4-0 chromic bolster sutures. A Glasscock dressing is applied using fluffed gauze to avoid unnecessary pressure. The drains are placed on intermediate suction. One of us (CSM) prefers continuous suction for 24 hours before placing the drains on bulb suction; another (VQ) recommends the continuous use of butterfly drains connected to vacuum-sealed red rubber–topped tubes.

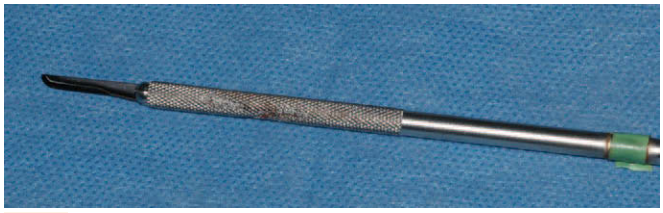

Figure 192-8. A 6700 Beaver blade is used to carve the framework.

A chest radiograph is obtained in the recovery room to rule out the possibility of pneumothorax. These patients are admitted for 48 hours for pain control, and intravenous antibiotics. The chest drain is removed on the first postoperative day, and the ear drain is removed after 2 to 3 days when there is little or no drainage. The vascularity of the skin overlying the helix is inspected on a regular basis, and the mastoid dressing is removed at 24 to 48 hours. A Glasscock dressing is then applied for the next 2 weeks to protect the ear. The patient must refrain from strenuous activity for 4 to 6 weeks, and the patient is not allowed to participate in contact sports for 1 month to avoid injuring the donor rib site.

Stage II: Lobule Transfer

The second surgery is performed 2 to 3 months after the first stage. A transposition flap is designed to move the vertically oriented lobule to the tail of the framework. After the incisions are made, a pocket is created within the lobule to accommodate the tail of the framework. The tail is elevated from the mastoid cortex so that the lobule can be wrapped around the posteroinferior margin of the cartilage framework. Care is taken to evert the wound margins in an attempt to avoid a stepoff at the junction of the lobule and framework. One to two Z-plasties are performed across the transverse portion of the incision (Fig. 192-11A to F).

Stage III: Creation of Postauricular Sulcus

This procedure is performed approximately 3 months after stage II (Fig. 192-12A to D). An incision is made around the helical rim. However, if there is hair on the helix, the incision is made slightly lower on its lateral surface to minimize the hair-bearing skin over the framework. The non–hair-bearing auricular skin is advanced 2 to 3 mm superiorly over the helical rim, and absorbable tacking sutures are placed between the subcutaneous tissue and the cartilaginous framework. The ear is released by dissecting into the postauricular sulcus and leaving the perichondrium intact to protect the cartilage graft. The postauricular skin over the mastoid is undermined and advanced into the postauricular sulcus, to help project the ear laterally away from the mastoid. After the postauricular skin is advanced and secured, the remaining defect is measured. It usually measures approximately $4 \times 8\,cm^2$. An elliptical thick split-thickness graft is harvested freehand from the left groin. The donor site is closed primarily. The graft is secured into the newly created postauricular sulcus with 5-0 chromic sutures. A bolster is secured into the sulcus with a 4-0 nylon. The ear is covered with a Glasscock dressing for protection for 1 to 2 weeks. The bolster is removed after 5 to 7 days, and the skin graft is kept moist for 2 to 3 weeks.

For some patients, the contralateral ear is prominent, contributing to the asymmetrical appearance of the ears. Otoplasty of the normally formed ear can be combined with this procedure, and the skin excised for the otoplasty can be used for grafting of the newly created postauricular sulcus of the microtic ear.

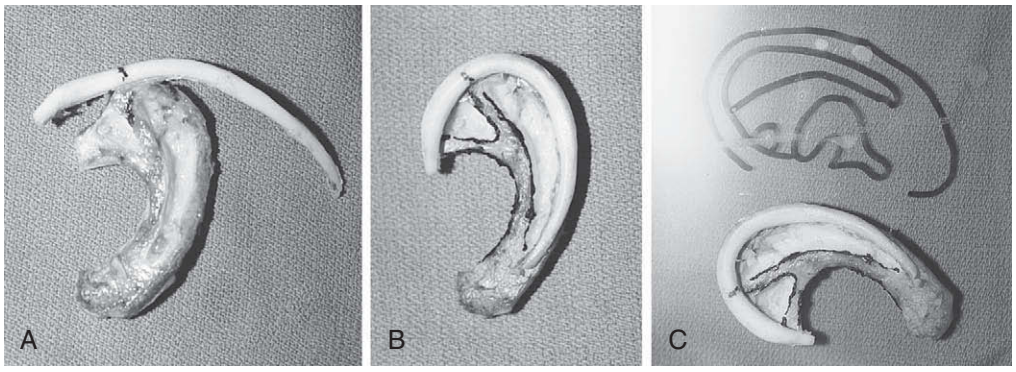

Figure 192-9. Construction of the implant. **A,** The framework is carved from the sixth and seventh ribs. The helix is carved from the eighth rib and is bent gently around the framework. **B,** The helix is secured with 4-0 clear nylon or wire. **C,** The implant is compared with the template.

Figure 192-10. Placement of the implant. The implant is placed into the pocket and positioned using the positioning template. One drain is placed over the surface of the implant as one is placed deep to the implant. The drains are then placed on suction. Note the contouring of the skin over the cartilaginous framework, with the drain traversing over the antihelix and into the scaphoid fossa.

Stage IV: Tragus Reconstruction

The fourth stage of reconstruction is to form a tragus and conchal bowl. If the conchal bowl is well defined, a composite graft can be used to reconstruct the tragus. An elliptical composite graft is removed from the concha cymba of the contralateral ear. An incision is made along the posterior border of the future tragus, and the composite graft is placed on the posterior surface to give the tragus some projection. The shadowing effect gives the illusion of an external auditory meatus. If the conchal bowl is not defined, an incision is made along the posterior border of the future conchal bowl, and an anterior-based cutaneous circular flap is created. The conchal bowl is then debulked of scar tissue and any rudimentary skin and cartilage that might remain. Because of facial nerve anomalies, a facial nerve monitor is recommended. The flap is folded onto itself to create a tragus that is then reinforced with a small piece of auricular or rib cartilage, and the surface of the conchal bowl is covered with a small skin graft (Fig. 192-13A to C). The bolster is removed in 3 to 5 days. Occasionally, an additional operation is needed to further elevate the reconstructed ear away from the mastoid using grafts of cartilage implanted medial to the framework.

Atypical Microtia Repair

Second-degree dysplasia or atypical microtia presents a more difficult surgical challenge. As previously discussed, many components of the auricular structure are recognizable, but there is a distinct tissue deficiency that necessitates the transportation of cartilage and skin. The additional structure often eliminates the necessity for complete framework insertion. When the vertical height difference between the two ears is greater than 20 mm, consideration is given to using a rib framework. When the difference is less than 20 mm, the result is achieved by

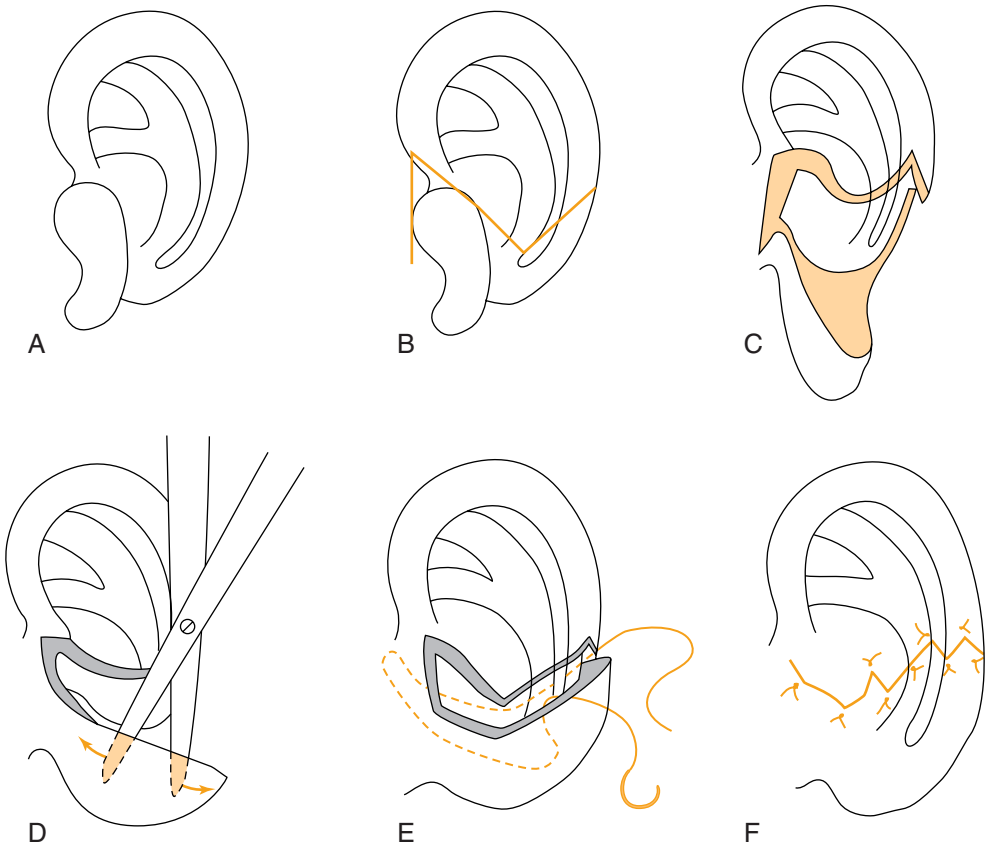

Figure 192-11. Stage II lobule transfer. **A,** Preoperatively, the lobule is noted to be malpositioned anteriorly. **B,** A lobule transposition flap incision is drawn. **C,** Lobule is elevated and posteroinferior margin of the framework is dissected out. **D,** A pocket is dissected within the lobule, and the lobule is transposed over the posteroinferior margin of the graft. **E,** Suture is placed from the pocket in the lobule to mastoid periosteum in order to reduce the flare of the lobule. **F,** Several mini Z-plasties are created along the incision to break up the scar and prevent contracture. Incisions are closed with mattress sutures.

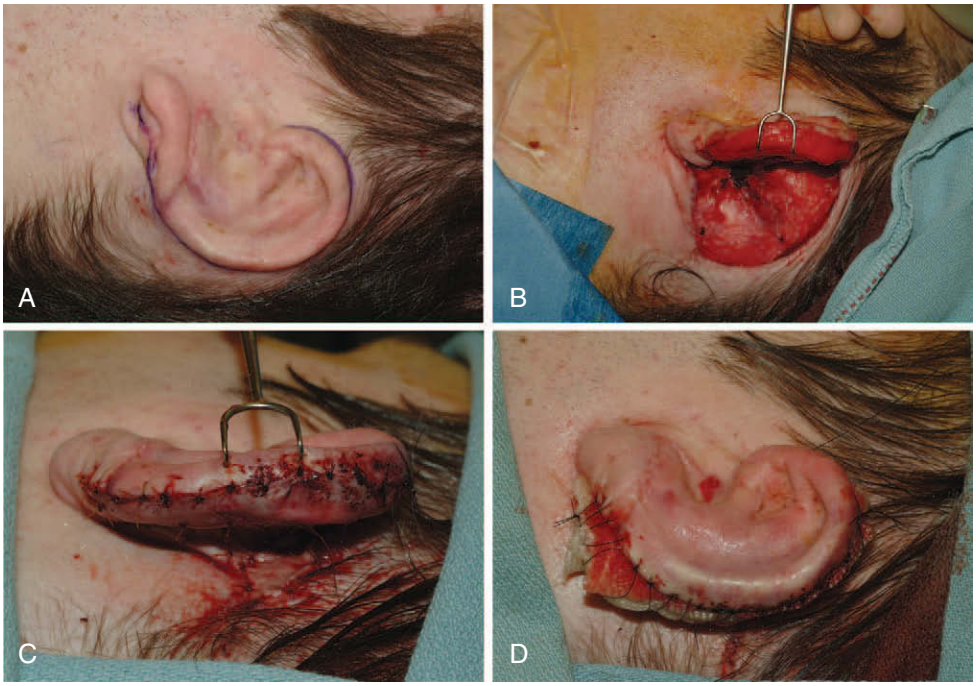

Figure 192-12. Stage III skin grafting. **A,** Before the procedure. **B,** Release of the skin, leaving the perichondrium intact. Dissection is carried into the postauricular sulcus, and postauricular skin is advanced. **C,** Skin graft in place. **D,** Skin graft secured with a soft bolster.

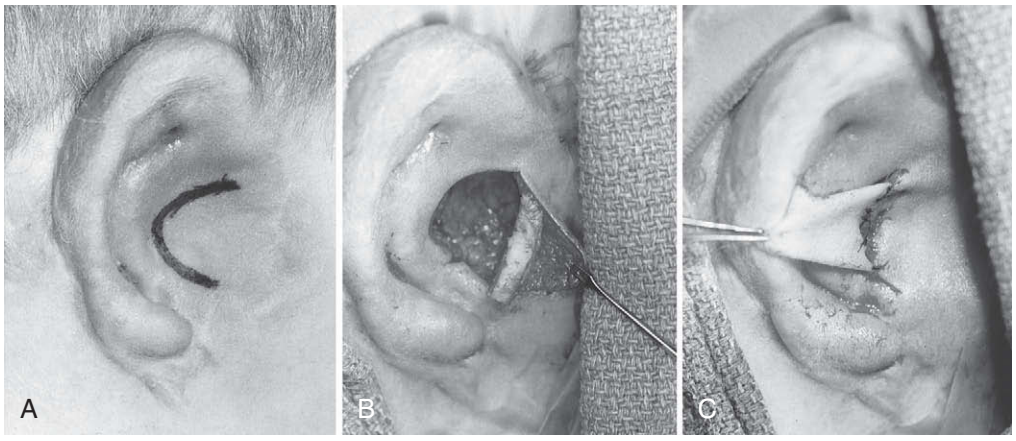

Figure 192-13. Stage IV tragus reconstruction. **A,** In bilateral microtia, tragal reconstruction is more difficult, because both ears are reconstructed; thus, normal concha cymba is not available for composite grafting. A longer flap must be elevated to provide both medial and lateral tragal lining. **B,** A free cartilage graft is placed to prevent contraction and is lined by the skin flap. **C,** The conchal bowl is deepened and lined with a skin graft. *(From Quatela VC, Goldman ND. Microtia repair.* Facial Plast Surg. 1995;11:257. Used with permission.)

expanding the existing structure; this is done by a combination of unfurling, uncupping, and increasing the vertical height with the use of cartilage composite grafts (Fig. 192-14A to H).[26] The helical root can also be advanced in a V-Y fashion into the helix to help augment the vertical height. Unlike classic microtia reconstruction, the use of vestigial remnants as a main framework does not lead to consistent results. Figure 192-15A to F shows a child with atypical microtia with an undeveloped lobule that was reconstructed by placing a cartilage implant that was harvested from the contralateral conchal bowl. This reconstruction was followed by a staged skin graft with an advancement flap of postauricular skin.

Complications

Major complications are rare. However, seemingly minor complications may lead to loss of the graft if they are not treated expeditiously. Immediate postoperative complications include pneumothorax and hematoma formation. Short-term complications include skin flap necrosis and infection. If a graft becomes exposed postoperatively secondary to breakdown of the overlying skin flap, the patient is placed on antibiotics that provide coverage for *Staphylococcus* and *Pseudomonas* infections, and the exposed site is covered with moist continuous dressings. If the exposure is small (1 to 2 mm) and the perichondrium is intact, the wound may granulate with local wound care. If the perichondrium is gone and the cartilage exposed, the framework may become devitalized, desiccated, and infected. Early coverage of the site with a local flap or a temporoparietal fascia flap with an overlying skin graft should be considered. Prolonged antibiotic therapy after flap coverage is necessary to avoid progression of the infection and eventual collapse and resorption of the graft.

Minor complications include malpositioning, scar contracture or hypertrophy, and poor contouring. Generally, problems with scar formation and poor contouring resolve with time if the cartilage has not

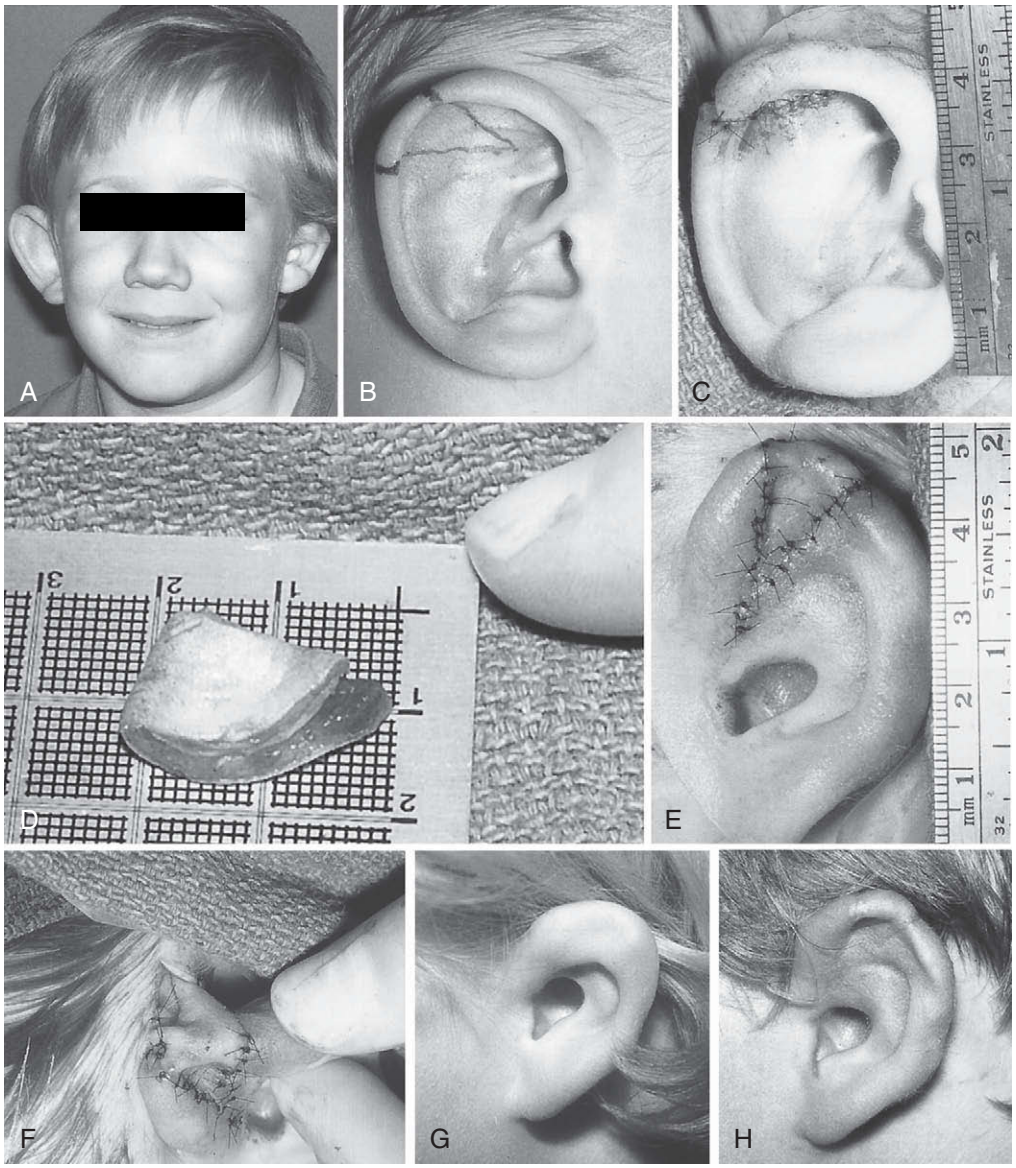

Figure 192-14. Atypical microtia reconstruction. **A,** A congenital defect of the ear with more than 20 mm of vertical height than in the contralateral healthy ear. **B,** The donor site composite graft is harvested to equal to one-half the size of the recipient defect, thereby reducing the disparity. The donor site is closed primarily, with the only resultant deformity being shortened vertical height, which is desirable in this patient's ear. **C,** The donor ear is shortened by 1 cm but retains good form. **D,** The composite graft. **E,** The composite graft sutured into position; vertical height is increased by approximately 1 cm. **F,** Epithelium is removed from the medial aspect of the composite graft, and the graft placed into a postauricular subcutaneous pocket. The medial skin is still attached at the rim as a hinge flap. The medial perichondrium is in contact with the retroauricular soft tissue; this will ensure maximum recipient contact for graft survival. Release is accomplished 2 weeks later, using the hinge flap skin for medial resurfacing. **G,** Before surgery. **H,** The final result at 1 year.

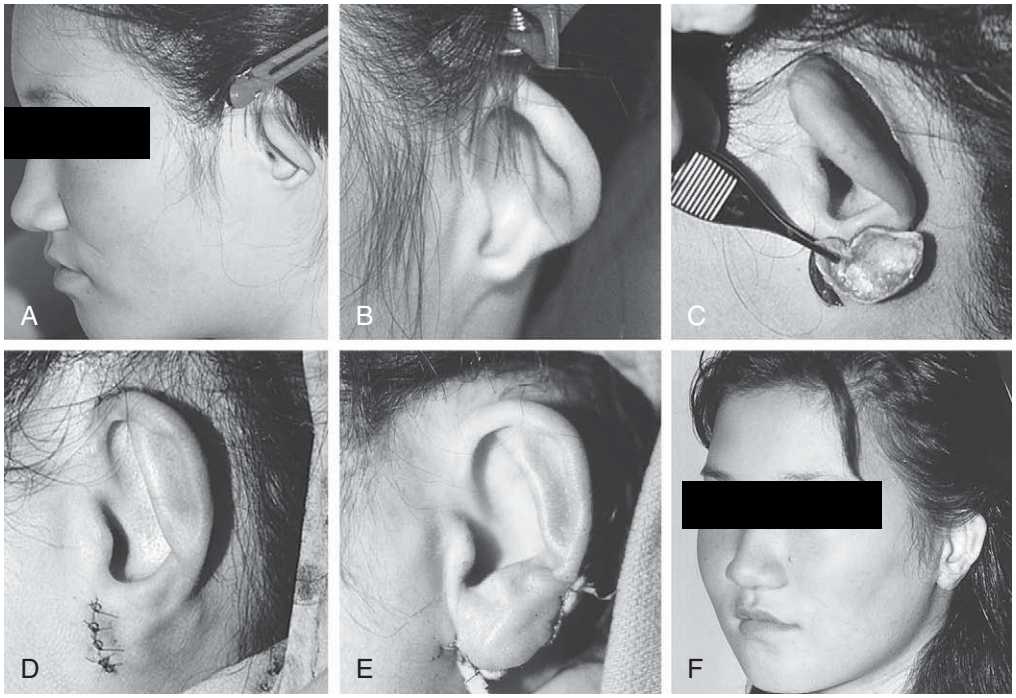

Figure 192-15. **A** and **B,** Type II atypical microtia with a missing lobule and a dysmorphic helix and antihelix. **C** to **E,** Two-stage reconstruction required placement of a conchal cartilage graft followed by delayed release of the lobule, advancement of postauricular skin, and placement of a full-thickness skin graft that was secured with a bolster dressing. **F,** Final postoperative result at 1 year.

Figure 192-16. **A,** Type III microtia with anteriorly positioned lobule. **B** to **F,** At 2 years after completion of microtia reconstruction. Note the height symmetry and angle of the auricle in relation to Frankfurt horizontal plane.

become infected or undergone resorption. Minor scar revisions may be necessary when indicated, and the surgeon should be careful not to expose the cartilage graft. Problems with malposition are usually minor if proper template techniques were used, and they are commonly related to preexisting lobule asymmetry or generalized facial asymmetry caused by hemifacial microsomia. Major malposition problems are usually related to poor preoperative planning.

Conclusions

Managing patients with microtia can be a rewarding experience for both the patient and the surgeon if proper training, preparation, and planning are done. Each patient and each ear deformity are unique, thus making the management of these patients a humbling, challenging, and perpetually stimulating problem. In many respects, microtia surgery is similar to rhinoplasty, in which the surgeon continually strives to achieve the elusive "perfect" aesthetic and functional result through meticulous planning and attention to detail.

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CHAPTER ONE HUNDRED AND NINETY-THREE

Reconstruction of the Auditory Canal and Tympanum

Antonio De la Cruz

Karen B. Teufert

Key Points

- Atresiaplasty aims to create a patent, skin-lined external auditory canal and to achieve a postoperative air-bone gap within 20 to 30 dB.
- In bilateral or unilateral cases of congenital atresia, auricular reconstruction and atresiaplasty are recommended at 6 years of age. Reconstruction with porous high-density polyethylene (Medpor) can be done at an earlier age. In unilateral cases, atresiaplasty is indicated only in minor deformities.
- The microtia repair is performed first because of the need for an excellent blood supply to cover the autologous rib graft, and the hearing restoration surgery is performed 2 months after the last step of the microtia repair.
- There are two requirements for planning surgery in congenital aural atresia: radiographic three-dimensional evaluation of the temporal bone and audiometric evidence of cochlear function.
- The following four anatomic parameters as seen radiographically are crucial for surgical planning: the status of the inner ear, the extent of pneumatization of the mastoid, the course of the facial nerve (both the relationship of the horizontal segment to the oval window and the location of the mastoid segment), and the presence of the oval window and stapes footplate.
- Ideal surgical candidates display a well-developed mastoid and a good oval window/footplate–facial nerve relationship.
- Ossicular reconstruction with the patient's own ossicular chain is preferred to the use of a prosthesis.
- Complications of atresiaplasty include lateralization of the tympanic membrane, stenosis of the meatus, sensorineural hearing loss, and facial nerve palsy.
- Graft lateralization is the most common delayed cause of a poor hearing outcome, usually occurring in the first 12 months after surgery.
- Polymeric silicone sheets, hydroxylated polyvinyl acetate wicks, absorbable gelatin film disks, and tabs in the fascia graft have helped lower the incidence of tympanic membrane lateralization by keeping the tympanic membrane graft in position.
- The incidence of stenosis has been significantly reduced with the use of one-piece split-thickness skin grafts covering all exposed bone, and polymeric silicone sheets and hydroxylated polyvinyl acetate wicks in the external auditory canal.
- It is important that drilling on the ossicular chain be minimized when it is dissected away from the atretic bone to reduce the risk of noise-induced sensorineural hearing loss.
- Intraoperative facial nerve monitoring is essential in all cases because there are often no clearly identifiable landmarks in atretic ears.
- Bone-anchored hearing aids are an alternative to atresiaplasty for rehabilitation of hearing loss resulting from congenital aural atresia, particularly in patients who are not good candidates for surgery.

Congenital aural atresia (CAA) represents aplasia or hypoplasia of the external auditory canal (EAC) resulting from failed or aborted development and is often associated with other malformations of the temporal bone, including external, middle, and inner ear deformities. CAA is unilateral more often than bilateral (occurring at a ratio of 3:1), preferentially affects males and the right side, and occurs in 1 in 10,000 to 1 in 20,000 live births.[1] Bony atresia occurs more frequently than membranous atresia. Fusion of the malleus and incus is the most common associated middle ear deformity, whereas the stapes footplate is usually normal.[2] Microtia is common in patients with CAA, and generally the severity of the external deformity correlates with the extent of middle ear deformity.[3-5] As opposed to middle ear malformations, the incidence of inner ear abnormalities in patients with CAA is relatively low, reflecting the earlier and independent embryonic development of the inner ear. The facial nerve typically lies in a normal position but may be displaced anteriorly and laterally in the vertical segment. Atresiaplasty aims to create a patent, skin-lined EAC and to achieve a postoperative air-bone gap within 20 to 30 dB. Surgical success depends on the appropriate selection of candidates for surgery and on proficient application of all modern tympanoplasty techniques,

including meatoplasty, canalplasty, tympanic membrane grafting, and ossicular reconstruction.

Embryology

Knowledge of normal ear development aids understanding of the potential combinations of malformations possible in ears with CAA. This understanding helps physicians select appropriate surgical candidates and avoid complications during surgery. Because the inner ear, middle ear, and external ear develop independently, deformity of one does not necessitate deformity of another. Fortunately, inner ear structure and function are usually normal in ears with outer and middle ear abnormalities.[6]

The external auditory meatus develops from the first branchial groove. During the second month, a solid core of epithelium extends inward from the primary meatus to the primitive tympanic cavity forming the meatal plate.[7,8] During the 21st week, this core resorbs and canalizes, forming the precursor to the EAC. Failure of resorption and canalization accounts for most cases of CAA. Subsequent posterior and inferior development carries the middle ear and facial nerve to their normal locations. By the end of the third gestational month, the primitive auricle has formed from six hillocks derived from the first and second branchial arches.

The eustachian tube, tympanic cavity, and mastoid air cells derive from the first branchial pouch, and the tympanic membrane forms from the plaque of tissue where this pouch meets the epithelium of the EAC.[7,8] Pneumatization of the middle ear and mastoid occurs late in fetal development, is usually present by birth, and continues to expand postnatally. Meckel's cartilage (first branchial arch) gives rise to the neck and head of the malleus and the body of the incus, whereas Reichert's cartilage (second branchial arch) forms the long processes of the malleus and incus as well as the stapes superstructure. The stapes footplate has a dual embryologic origin, developing from the second arch and from the otic capsule. The ossicles achieve their final shape by the fourth month and are covered with a mucous membrane from the expanding tympanic cavity by the end of the seventh to eighth month.

The facial nerve is the nerve of the second branchial arch. Its general course is established by the end of the embryonic period; however, its ultimate intraosseous course depends on later bony expansion of the tympanic ring and cavity.[9] The auditory placode on the lateral surface of the hindbrain gives rise to the membranous inner ear during the third to the sixth week. The surrounding mesenchyme transforms into the bony otic capsule.

Classification Systems

In atresiaplasty, surgery classification systems that help in the identification of best candidates and in comparison of outcome and multiple schemes have been developed. The De la Cruz classification divides abnormalities into "minor" and "major" categories (Box 193-1).[2] The clinical importance of this classification is that surgery in cases of minor malformations has a good possibility of yielding serviceable hearing, whereas cases of major malformations are best treated with the bone-anchored hearing aid (BAHA) system.

The point-grading system for preoperative assessment of the best candidates for hearing improvement developed by Jahrsdoerfer and colleagues[10] assigns points on the basis of preoperative temporal bone CT scan findings of mastoid pneumatization, presence of the oval and round windows, facial nerve course, status of the ossicles and mesotympanum, and presence of the stapes, as well as on the external appearance (Table 193-1). Each parameter receives 1 point except for the presence of the stapes, which receives 2 points. A score of 8 or higher predicts the best chance of surgical success (greater than 80% success). A score of 7 implies a fair result, a score of 6, a marginal result; and a score less than 6 indicates that the patient would have poor results from atresiaplasty.

Ishimoto and colleagues[11] evaluated the relationship between hearing level and temporal bone abnormalities in patients with microtia, using the Jahrsdoerfer scoring system and high-resolution CT (HRCT) scans of the temporal bone.[11] The hearing level in microtic ears best correlated with the formation of oval/round windows and ossicular development but not with the degree of middle ear aeration, facial nerve aberration, or severity of microtia.

Box 193-1

De la Cruz Classification of Congenital Aural Atresia

Minor Malformations

- Normal mastoid pneumatization
- Normal oval window footplate
- Good facial nerve–footplate relationship
- Normal inner ear

Major Malformations

- Poor pneumatization
- Abnormality or absence of oval window/footplate
- Abnormal course of the facial nerve
- Abnormalities of the inner ear

Adapted from De la Cruz A, Linthicum FH Jr, Luxford WM. Congenital atresia of the external auditory canal. *Laryngoscope*. 1985;95:421-427.

Table 193-1

Jahrsdoerfer Grading System of Candidacy for Atresiaplasty

Parameter	Points
Stapes present	2
Oval window open	1
Middle ear space	1
Facial nerve normal	1
Malleus-incus complex present	1
Mastoid well pneumatized	1
Incus-stapes connection	1
Round window normal	1
Appearance of external ear	1
Total available points	10

Total Score	Type of Candidate
10	Excellent
9	Very good
8	Good
7	Fair
6	Marginal
≤5	Poor

Modified from Jahrsdoerfer RA, Yeakley JW, Aguilar EA, Cole RR, Gray LC. Grading system for the selection of patients with congenital aural atresia. *Am J Otol.* 1992;13:6-12.

Other classifications systems have been developed by Altmann,[12] Chiossone,[13] and Schuknecht.[14] Congenital cholesteatoma occurs in 14% of patients with CAA and is not included in any of the grading systems because these systems are used only for predicting hearing results in patients undergoing elective procedures.

Initial Evaluation

Several issues should be addressed in infants presented with CAA. In addition to the malformations of the temporal bone, other congenital abnormalities may be present and should be excluded. Evaluation of auditory function with auditory brainstem response (ABR) audiometry should be performed during the first few days of life in patients with either unilateral or bilateral atresia, because ipsilateral and contralateral inner ear abnormalities may be associated with CAA. Occasionally, a patient with unilateral atresia has a total sensorineural hearing loss (SNHL) on the side of the normal-looking ear. To maximize speech and language development, proper hearing amplification must begin promptly. For the patient with bilateral CAA, a bone conduction hearing aid should be applied as soon as possible, ideally at 3 or 4 weeks of age. Hearing amplification is not necessary in the patient with unilateral atresia if hearing is normal in the contralateral ear.

Parents of a child with sporadic, nonsyndromic CAA are counseled that the possibility of CAA in their subsequent children is no greater than that for the general population. Options regarding future auricular reconstruction are also reviewed with the parents, and the need for proper hearing rehabilitation is stressed. Early enrollment in special education enhances speech and language development. Children with CAA in association with other syndromes (e.g., hemifacial microsomia, Treacher Collins or Crouzon's syndrome, Pierre Robin sequence) are poor surgical candidates for whom long-term bone-conduction aids or BAHAs offer the best rehabilitation.

The two requirements for elective atresiaplasty are (1) audiometric evidence of cochlear function and (2) radiographic three-dimensional evaluation of the temporal bone. As noted, audiometric evaluation should occur within the first few days of life; however, radiologic evaluation with HRCT of the temporal bone is deferred until age 5 or 6 years. A patient with CAA may experience an infected or draining ear or acute facial palsy with or without a congenital cholesteatoma. In such a case, resolution of the infection and removal of the cholesteatoma, if present, take priority, and HRCT scanning may be indicated before age 5 or 6 years.

Timing of Ear Reconstructive Surgery

Auricular reconstruction precedes hearing restoration surgery by at least 2 months to optimize the blood supply for the autologous rib graft and complex flaps.[15] For patients with binaural or unilateral atresia, microtia repair and atresiaplasty are recommended at 6 years of age. By this age, mastoid pneumatization is complete and the costal cartilage has developed sufficiently for auricular reconstruction. Auricular defects can be rehabilitated with an osseointegrated percutaneous mastoid implant prosthesis, with or without bone-conduction aids such as a BAHA.[16] Alloplastic materials have been used for microtia repair in the past, but a high risk of extrusion is associated with their use. However, new materials, such as porous high-density polyethylene (Medpor), seem to be very well tolerated.[17,18] Medpor reconstruction can be done before or after atresiaplasty because intact blood supply is not indispensable to its success.

In unilateral cases, atresiaplasty surgery may be indicated in a patient who has "minor" unilateral atresia with normal middle ear, ossicles, and facial nerve and excellent pneumatization. In such a patient, atresiaplasty may be offered in childhood with the parents' consent. An adult with unilateral atresia commonly requests atresiaplasty when presbycusis develops in the normal ear.

Preoperative Evaluation and Patient Counseling

Palpation of the mastoid tip, suprameatal spine of Henle (if present), condyle, and zygomatic arch provides a reasonable clinical estimate of the size of the mastoid. This is a useful measure because the new ear canal will be created at the expense of the mastoid air-cell system. The preoperative imaging study is HRCT of the temporal bone in both axial and coronal planes (Fig. 193-1). The surgeon and the radiologist should both review the HRCT scans. Particular attention is given to the following elements, which are the most critical for surgical planning: (1) the status of the inner ear, (2) the extent of temporal bone pneumatization, (3) the course of the facial nerve, with emphasis on the relationship of the horizontal portion to the footplate and the location of the mastoid segment, and (4) the presence of the oval window and stapes footplate. The ideal surgical candidate displays a well-developed mastoid and a good oval window/footplate–facial nerve relationship. In addition to the elements mentioned, HRCT also delineates the thickness and form of the atretic bone, the soft tissue contribution to the atresia, the size and status of the middle ear cavity, and the presence or absence of congenital cholesteatoma. These factors are less critical for the repair.

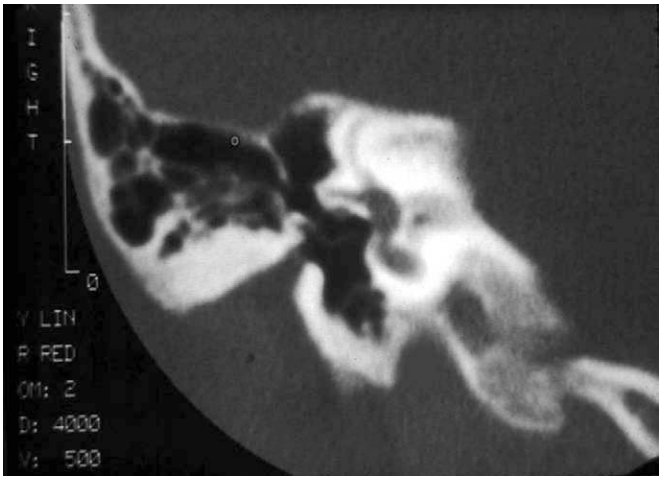

Figure 193-1. Congenital aural atresia, right ear. Coronal high-resolution computed tomography demonstrates atretic external auditory canal and normally developed mastoid system, with normal inner ear.

Poor pneumatization is the most common cause of inoperability in CAA. Fortunately, the majority of patients have normal pneumatization. A facial nerve overlying the oval window may prevent ossicular reconstruction and hearing improvement. If the oval window is absent, it is possible to fenestrate the lateral semicircular canal to improve hearing. However, hearing results are generally poorer in such cases and there is increased risk of SNHL. Patients with these findings are usually best rehabilitated with hearing amplification. Atresiaplasty carries potential for facial nerve injury. The nerve often lies more laterally than usual and may assume a more acute angle than its usual 90 to 120 degrees at the mastoid genu (Fig. 193-2). Even in patients in whom the facial nerve follows a normal course, the distances between the nerve and the temporomandibular joint and between the nerve and the posterior wall of the tympanic cavity are significantly reduced.

Preoperative patient and parent counseling carefully considers reasonably expected surgical results and the potential risks and complications.[19-25] Patients who have minor malformations or a score of 8 or better on the Jahrsdoerfer grading scale are given a greater than 80% chance of significant hearing improvement. Of surgical patients, we find that 50% achieve a long-term postoperative air-bone gap of 30 dB or less.[26] The risk of graft lateralization is less than 4%, the risk of high-tone SNHL is approximately 7%, and the risk of facial nerve palsy is less than 1%. Other risks and complications are comparable to those for other tympanomastoidectomy procedures. Patients and parents are reminded that frequent postoperative visits are critical in the early postoperative period and that a split-thickness skin graft will be taken from the low abdomen to line the new ear canal.

Surgical Approach

Although three approaches to drilling the new ear canal have been described, we have used only an anterior approach for the past 25 years,

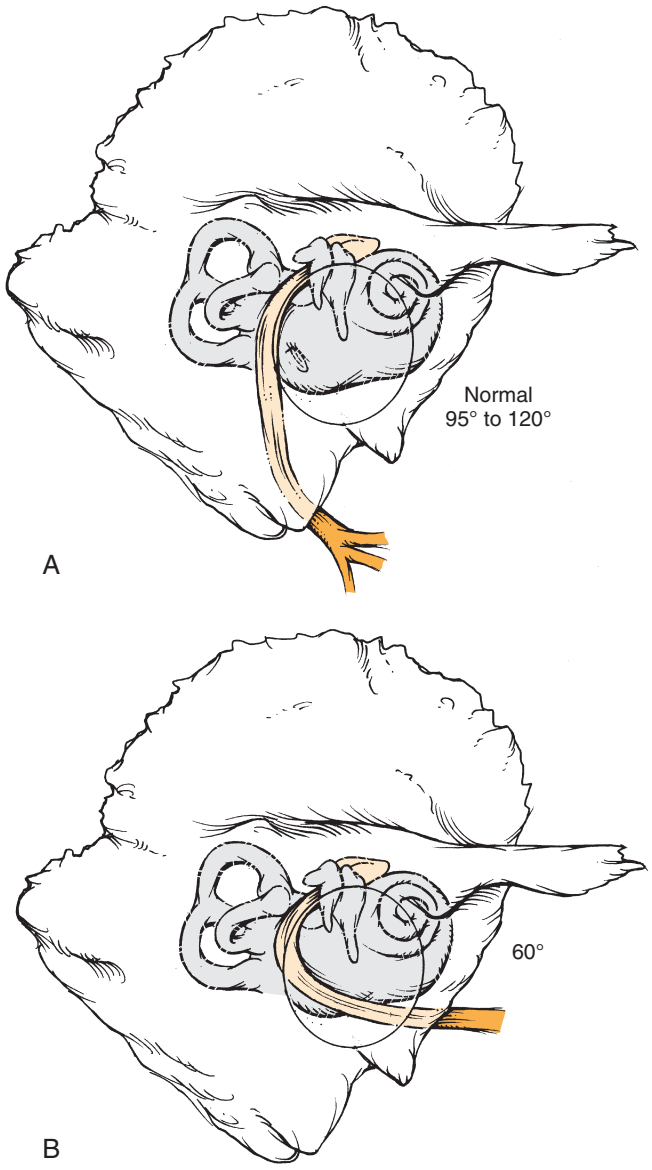

Figure 193-2. The facial nerve in congenital aural atresia. **A,** Normal intratemporal facial nerve anatomy. **B,** Intratemporal facial nerve anatomy in congenital aural atresia. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

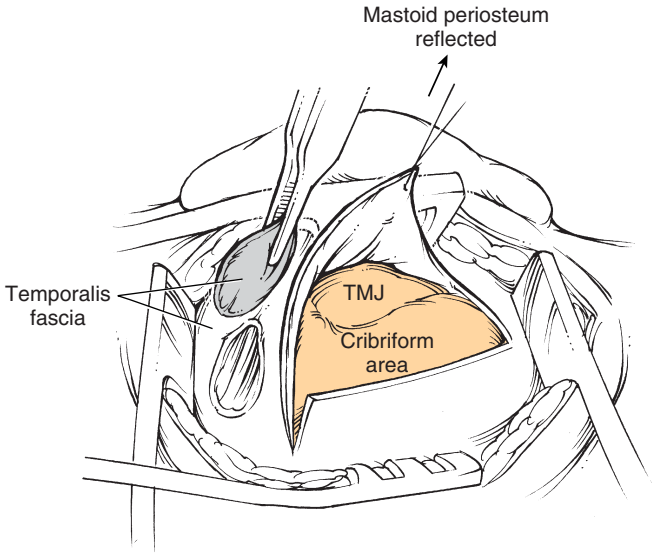

Figure 193-3. Incision, harvesting temporalis fascia, T incision, and elevation of periosteum. TMJ, temporomandibular joint. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

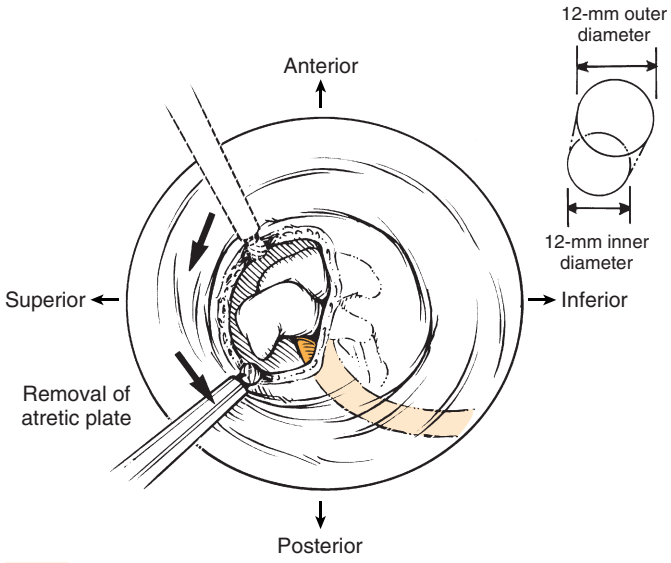

Figure 193-4. Anterior approach: Removal of atretic plate and adhesions, exposing the ossicles, and drilling for the new ear canal. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

and only this standard approach is described here.[27] Under general endotracheal anesthesia, the patient is placed in the otologic position with the head turned away. Facial nerve monitoring electrodes are placed, and muscle relaxants are avoided. The postauricular area is shaved, and the auricle and postauricular area are prepared with povidone-iodine and then draped. The lower abdomen is similarly prepared for the skin graft donor site.

The approach in all cases is through a postauricular incision. In patients with prior auricular reconstruction, care is taken not to expose the grafted costal cartilage. A T-shaped incision is made in the periosteum, and the subcutaneous tissue and periosteum are elevated anteriorly to allow identification of the glenoid fossa (Fig. 193-3). The temporomandibular joint space is gently explored to ensure that an anomalous facial nerve or tympanic bone remnant is not lying within it. Temporalis fascia is harvested and dried.

If a remnant of tympanic bone is present, drilling for the new ear canal begins at the cribriform area. If no such remnant exists, drilling of a 12-mm cylindrical canal begins at the level of the linea temporalis, just posterior to the glenoid fossa. Dissection proceeds anteriorly and medially, taking into consideration the lack of landmarks in atretic bone. The middle fossa plate is identified and followed to the epitympanum, where the fused malleus head–incus body mass is identified (Fig. 193-4). Care is taken to avoid exposure of the temporomandibular joint space or to avoid opening an excessive number of mastoid air cells. A radical mastoidectomy–like approach is to be avoided. Once the ossicular mass is identified, the atretic bone is removed with diamond micro-drills and curettes to completely expose the ossicles (Fig. 193-5A). It is important to minimize drilling on the ossicular mass because transmission of high-speed drill energy to the inner ear may result in high-tone SNHL. An argon laser is used to free the malleus-incus complex from its soft tissue attachments to reduce potential drill trauma to the inner ear. The ossicular mass in the epitympanum is meticulously dissected free of the atresia plate and left intact. Although the temporomandibular joint often limits anterior dissection, particular effort is made to try to create a space of 2 mm or greater

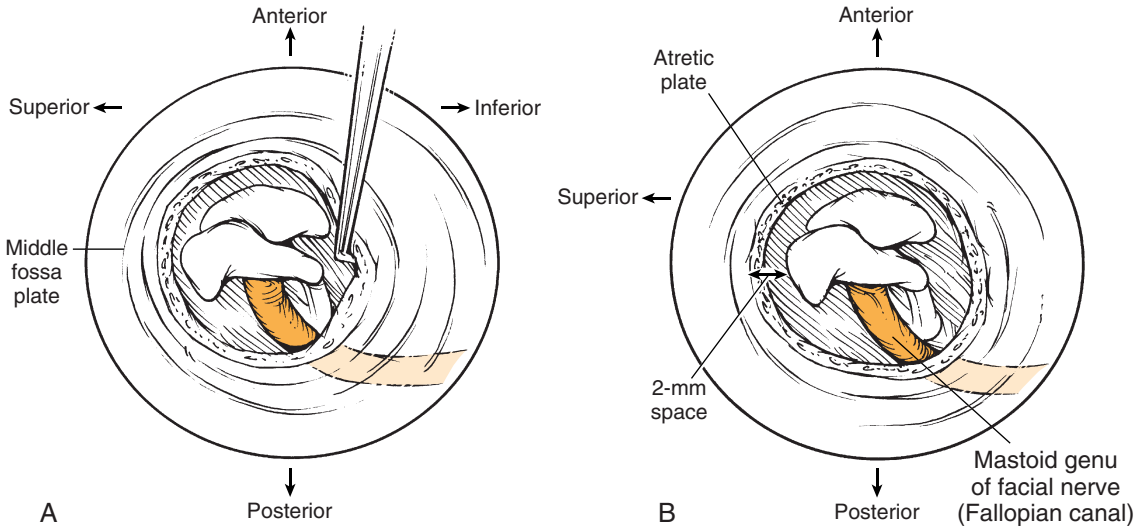

Figure 193-5. **A** and **B,** Anterior approach: The ossicular mass is dissected free of the atretic plate, and a 2-mm space is created around the ossicles. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

anterior to the ossicular mass (Fig. 193-5B). The horizontal facial nerve always lies medial to the ossicular mass. During dissection of the inferior and posterior aspects of the canal, an aberrant facial nerve may be encountered as it passes laterally through the atretic bone. Drilling for the new ear canal continues until it measures about 12 mm. This circumference is most difficult to achieve medially, where the facial nerve, temporomandibular joint capsule, and middle fossa plate limit larger exposure.

Reconstruction with the patient's own ossicular chain is performed in almost all cases, even if the ossicular chain is deformed. Therefore, if the ossicular chain is intact, it is left in place and used for ossicular reconstruction. When this is not possible, a total or partial ossicular reconstruction prosthesis to either a mobile footplate or the stapes head is used for reconstruction. If access to the oval window footplate is impossible because a dehiscent facial nerve obliterates the window, hearing restoration can be accomplished with the use of a BAHA.[28-30]

Drilling continues to create an external auditory canal. It must be one-and-one-third times the size of a normal canal (12 mm vs. 9 mm) to allow for contracture healing in the postoperative period. During creation of the external auditory canal, care is taken not to enter the temporomandibular joint or unnecessarily open mastoid cells.

A dermatome is used to obtain a 0.008-inch thick, 6 × 6-cm split-thickness skin graft (STSG) from the hypogastrium. Pressure with a gauze sponge wet-soaked in 1% lidocaine with epinephrine 1 : 100,000 and thrombin solution aids hemostasis of the donor site. When dry, the donor site is dressed with a sterile wound dressing such as a Tegaderm dressing (3M, St. Paul, MN). This step reduces most of the pain associated with other methods of donor site care. One edge of the skin graft is cut in a zigzag fashion to create four or five triangular points (Fig. 193-6). To facilitate inspection of the skin graft in the final stages of the procedure, the tips of each point and the two corners on the opposite edge are colored with a skin marker.

The dried temporalis fascia is trimmed to size, ideally a 20 × 15-mm oval, and a small (4-mm) "tab" is cut into the anterior-inferior aspect of the graft in an attempt to prevent lateralization. (Lateralization is the most common delayed cause of a poor hearing outcome, usually occurring in the first 12 months after surgery. Once the graft starts lateralizing, it pulls away from the ossicles, and the original good hearing results slowly deteriorate.) Thirty minutes before grafting begins, nitrous oxide administration is discontinued. The fascia is placed over the ossicular chain medial to the malleus, if present, or over the cartilage that covers the prosthesis (Fig. 193-7). The tab of the graft is placed medially into the protympanum to help prevent lateralization of the new eardrum.

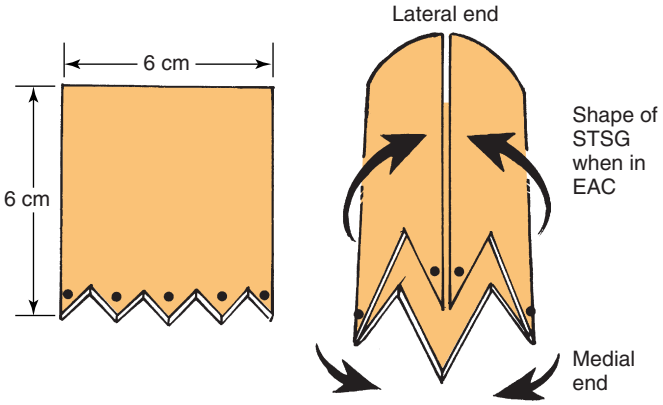

Figure 193-6. Split-thickness skin graft (STSG) used to line new external auditory canal (EAC). *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Next, the new ear canal is circumferentially lined with the STSG so that all the bone is completely covered (Fig. 193-8). The triangular corners of the skin graft are placed medially and partially overlap the fascia. The previous coloring of the points helps ensure that no skin lies folded on itself and that the entire width of the graft is used. A single layer of antibiotic-soaked absorbable gelatin sponge (Gelfoam; Pfizer Inc, New York) holds the fascia and skin graft in place. To reproduce the anterior tympanomeatal angle, a disk of absorbable gelatin film (Gelfilm; Pfizer Inc) is placed over the fascia and skin graft. After the fascia and skin graft are in proper position, three 0.020-inch polymeric silicone (Silastic; Dow Corning Corporation, Midland, MI) strips are placed to line the skin (Fig. 193-9). This step helps prevent adhesions between the skin graft and the ear canal packing and ensures good contact between the skin graft and ear canal bone. A 9 × 15-mm hydroxylated polyvinyl acetate sponge wick (Merocel; Medtronic USA, Inc., Jacksonville, FL) is placed in the bony canal.

A 12-mm meatus is created, with the anticipation that a third of its diameter will diminish through normal healing. Before the meatoplasty is begun, the ear is turned back and the periosteum is brought back in place with one absorbable suture at the superior level of the new ear canal. This maneuver stabilizes the pinna and helps ensure that the meatus is at the same level as the new ear canal. Skin, subcutaneous tissue, and cartilage are removed in a 12-mm-diameter core over the new meatus. An attempt is made to avoid exposing the grafted cartilage

or other materials used for auricular reconstruction. The lateral edge of the STSG is brought through the meatoplasty, and the lateral portion of the new ear canal and the meatus are packed with a large 15 × 25-mm Ambrus Merocel Ear Wick (Medtronic Xomed Surgical Products, Jacksonville, Fla.). This packing applies diffuse pressure over the entire lateral skin graft and widely packs the meatoplasty. Five tacking sutures of 5-0 Ti-Cron (Covidien, Mansfield, MA) attach the lateral edge of the skin graft circumferentially to the meatal skin. Finally, 6-0 fast-absorbing plain gut is used in a running manner between each Ti-Cron sutures (Fig. 193-10). The periosteum is sutured back into position. The postauricular incision is closed using absorbable sutures (3-0 polyglactin 910 [Vicryl; Ethicon, Inc, Somerville, NJ]). Steri-Strip surgical skin closures (3M) cover the incision, a mastoid dressing is applied, anesthesia is reversed, monitoring equipment is removed, and the patient leaves the operating room.

Silastic sheets and Merocel wicks have helped decrease both the incidence of TM lateralization by keeping the TM graft in position and the incidence of postoperative EAC stenosis by covering all exposed areas of bone that may cause granulation tissue formation.[26] The Merocel wicks that are now available in many sizes for canal stenting help prevent postoperative infection and granulation tissue by allowing administration of topical antibiotic medication to the entire external auditory canal.

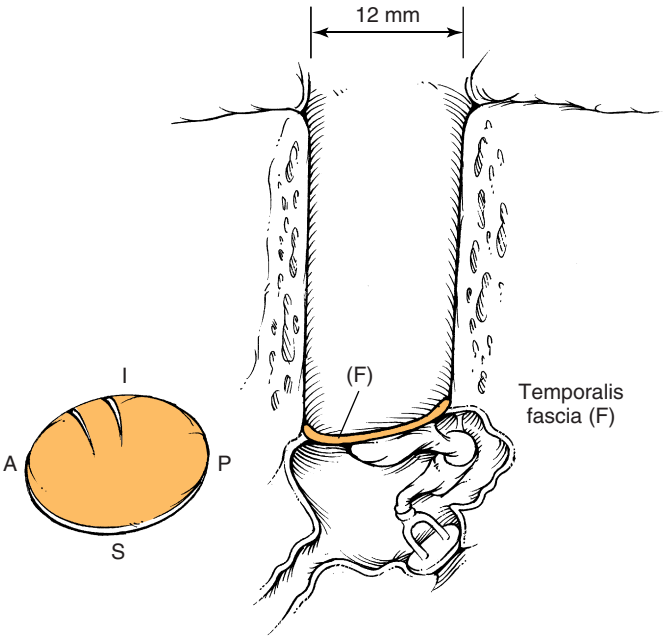

Figure 193-7. Temporalis fascia graft with tabs used over an ossicular mass or a partial ossicular replacement prosthesis and cartilage. A, anterior; I, inferior; P, posterior; S, superior. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

Postoperative Care

The mastoid dressing is removed on the first postoperative day. The Tegaderm dressing remains over the STSG donor site for at least 3 weeks to allow epithelialization to occur under the plastic. The patient is seen 1 week after surgery, at which time the tacking Ti-Cron sutures at the meatus and the postauricular Steri-Strips are removed. Any dried blood or crusting on the lateral end of the meatus pack should be trimmed. The postauricular site can now be washed, but water precautions continue for the ear canal. We continue to see the patient on a weekly basis. At 2 weeks, the Merocel packs and Silastic sheet are removed, and the meatus is repacked with antibiotic-soaked Gelfoam. At this point, the patient or parent(s) should apply antibiotic suspension to the packing in the ear canal twice a day for 8 to 12 weeks. Usually by 3 weeks, the abdominal donor site has completed the initial re-epithelialization, and the Tegaderm dressing may be removed.

By 6 to 8 weeks postoperatively, nearly all of the Gelfoam is usually gone and the canal is healing well. The first postoperative

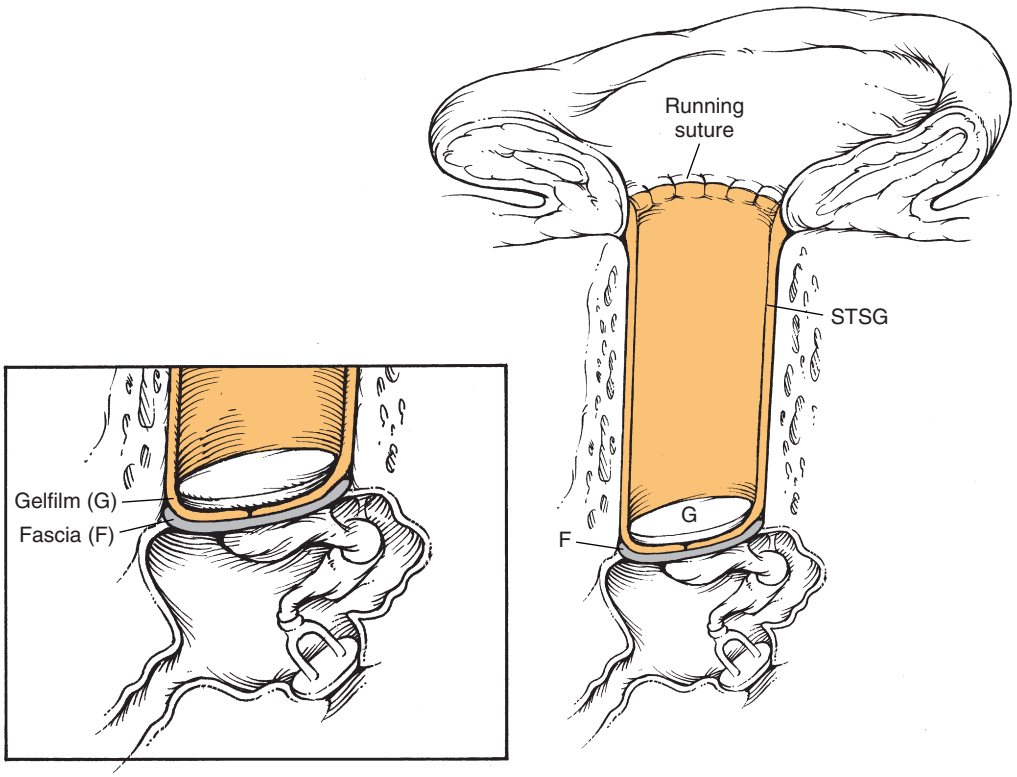

Figure 193-8. Two views of a split-thickness skin graft (STSG) in place over fascia, lining new external auditory canal, and disk of Gelfilm over fascia and skin graft. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

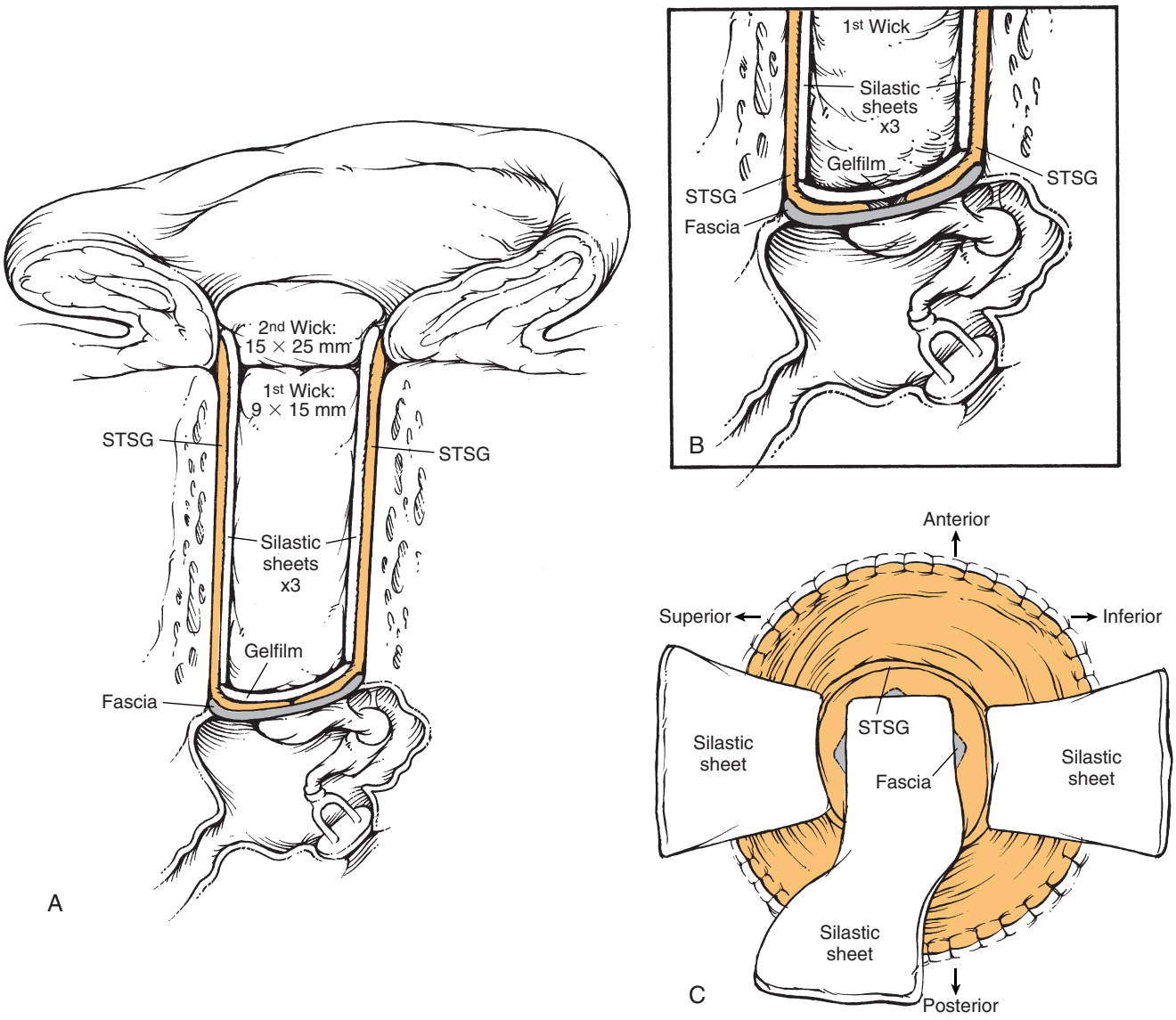

Figure 193-9. Split-thickness skin graft (STSG) and Silastic (polymeric silicone) strips with ear wicks to maintain contact with bony external auditory canal, and wide meatus. *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

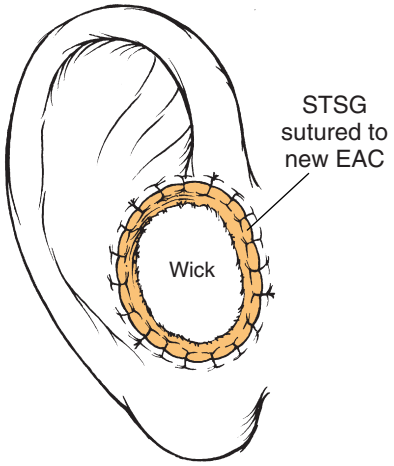

Figure 193-10. Split-thickness skin graft (STSG) sutured into place at meatus, to new external auditory canal (EAC). *(© 2008 by Johns Hopkins University, Art as Applied to Medicine.)*

audiogram is obtained at that time, and audiography is repeated in 6 months, in 1 year, and yearly thereafter.

Avoidance of Complications

Complications of atresiaplasty include lateralization of the tympanic membrane in 3.4% of patients, stenosis of the meatus in 3.8%, high-tone SNHL in 7.5%, and facial nerve palsy in less than 1%.[26,31] Other investigators have reported meatal stenosis in 7% and tympanic membrane lateralization in 18% of their cases.[32] Attention to intraoperative measures helps minimize graft lateralization: Nitrous oxide should be discontinued 30 minutes before grafting. The graft should be anchored medially to the malleus and the tab should be placed into the protympanum. Use of an accurately sized Gelfilm disk attempts to recreate an anterior tympanomeatal angle and keeps the graft in position. Silastic sheets and Merocel wicks placed in the EAC also help minimize the incidence of graft lateralization. The patient must be followed carefully for at least 24 months, because lateralization has been known to occur up to 12 months postoperatively.

The incidence of stenosis has been significantly reduced with the use of one-piece STSGs covering all exposed bone, and Silastic sheets and Merocel wicks in the EAC.[26] Of equal importance to surgical

technique are consistent postoperative follow-up and office care. Patients or their parents should understand beforehand that they must strictly follow the postoperative instructions and that they must keep all scheduled postoperative visits. We check the circumference of the pack each week to ensure that there is no ingrowth of grafted skin into the pack. If the meatus appears to be narrowing, usually at the third month, it should be dilated every 2 weeks and restented with the large Merocel wick for several months to 2 years. This measure usually avoids the need for reoperation. Early identification and treatment of infection are also necessary to prevent graft failure and canal stenosis.

High-tone SNHL occurs in up to 7.5% of cases.[26,31] To reduce the risk of noise-induced hearing loss, it is critical to minimize drilling on the ossicular chain while it is being dissected away from the atretic bone, but noise transmission during creation of the ear canal cannot be completely avoided. Use of the laser helps minimize manipulation when the surgeon is trying to free the malleus-incus complex from the atretic plate. With better imaging techniques, oval window problems can be identified preoperatively, and problems of SNHL due to oval window drill-out are avoided. Likewise, patients with computed tomography evidence of severe malformations are likely to have poor surgical results and so are best fitted with conventional bone-conduction hearing aids or BAHAs instead.

Intraoperative facial nerve monitoring is essential in all cases because there are often no clearly identifiable landmarks in atretic ears. If the monitor is off transiently because of the use of electrocautery, the surgeon can monitor the facial nerve manually by placing a hand on the patient's face. It is also important to remember that in a poorly pneumatized temporal bone, the otic capsule may be difficult to distinguish, and care must be taken to avoid "blue lining" (or worse) of the semicircular canals.

Surgical Alternatives to Atresiaplasty

BAHAs provide a good alternative to atresiaplasty for rehabilitation of hearing loss resulting from CAA.[28,33] BAHAs are especially suitable for patients with bilateral CAA and who, because of the severity of the malformations, would have poor results with atresiaplasty. The BAHA is a better alternative than a conventional bone hearing aid. Conventional bone hearing aids have the following drawbacks: discomfort because of constant pressure from the steel spring, worse sound quality because of higher-frequency attenuation by the skin, and poor aesthetics and insecure positioning of the device. The BAHA works without pressure on the skin and provides direct bone transmission without air interface.

Surgery for the BAHA can be performed under local or general anesthesia and is a one-stage procedure. To implant the BAHA, a small titanium abutment is implanted behind the ear, where it osseointegrates to the mastoid bone. After a 3-month healing period the BAHA processor can then be connected.

Audiologic indications for the BAHA include a pure-tone average bone-conduction threshold better than or equal to a 45-dB hearing level (average of 500, 1000, 2000, and 3000 Hz). A maximum speech discrimination score better than 60% for use of the PB word lists is recommended. From an audiologic point of view, the side with the better cochlear function (the better bone-conduction threshold) should be used. Patients with a bone-conduction threshold of 25 to 45 dB hearing level will be expected to improve but may not achieve levels in the normal range. Patients with a bone-conduction threshold of less than 25 dB hearing level can be expected to experience hearing improvements that restore hearing levels to normal ranges. Patients must be able to maintain the abutment/skin interface of the BAHA. Careful consideration must be given to the patient's psychological, physical, emotional, and developmental capabilities to maintain hygiene. Titanium implants can be installed in most patients because allergy to titanium is extremely rare. Alternative treatments should be considered for patients with a disease state that might jeopardize osseointegration.

In general, we do not recommend implantable hearing aids in young children, because the surgical scars may preclude any future microtia repair. However, the BAHA titanium implant is ideally placed 5 to 6 cm behind and 3 cm above the ear canal in a hair-bearing area. This placement seems to allow for the possibility of future microtia repair that would transplant costal cartilage to an area with unscarred skin. On the other hand, the titanium implants for a bone-anchored ear epithesis are ideally placed 18 to 20 mm behind the (future) ear canal. This site would interfere with the skin of a future auricle, if reconstruction is contemplated.

Summary

The treatment of congenital aural atresia represents a challenging, complex problem. Early identification, appropriate hearing amplification, and speech and language therapy are crucial in patients with bilateral disease. Surgical coordination with the auricular reconstruction surgeon allows for the best aesthetic and functional success. Strict radiologic and clinical criteria are necessary to appropriately identify atresiaplasty candidates. Classification of patients into those with minor and major malformations provides prognosis for hearing improvement and potential risks of surgery. A thorough understanding of the embryologic development of the ear and adherence to the surgical principles of tympanoplasty, canalplasty, and facial nerve surgery enable optimal and safe hearing restoration. Maintenance of good initial surgical results and avoidance of late complications requires diligent postoperative office care. BAHAs provide a good alternative for patients in whom atresiaplasty results would be poor.

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CHAPTER ONE HUNDRED AND NINETY-FOUR

Acute Otitis Media and Otitis Media with Effusion

Margaretha L. Casselbrant

Ellen M. Mandel

Key Points

- The presence or absence of signs and symptoms and findings on the otoscopic examination provide the basis for diagnosis of the different types of otitis media.
- Proper treatment depends on differentiation between acute otitis media and otitis media with effusion.
- The highest incidence of otitis media occurs between the ages of 6 and 11 months and decreases with age. Risk factors include both host and environmental factors.
- Prevention of disease through use of vaccines and risk factor reduction is desirable.
- For children 2 years of age or older with nonsevere acute otitis media, published guidelines have given the option of observing rather than treating with antibiotics immediately.
- Antihistamines and steroids are ineffective for the treatment of otitis media.
- Tympanostomy tube insertion is effective in reducing recurrent episodes of otitis media and persistent middle ear effusion.
- Adenoidectomy *is not* recommended for the initial surgical treatment of otitis media unless nasal obstruction is present but *is* recommended for children in whom a repeat surgical procedure is needed.
- Careful follow-up is needed to identify complications and sequelae of otitis media as well as of its treatment.

Otitis media is not only a disease of modern times. It has been a major health problem in many societies. In the 8th century, the most common approach to healing was water from wells named after various saints.[1] Otitis media is in general a childhood disease, and in most children it resolves with anatomic and physiologic changes with growth. Until the condition has resolved, it may affect balance, hearing, and speech and language development and cause poor school performance. This disease affects not only the child but the whole family, from an economic as well as a societal standpoint. It is more than the cost for medicine or visits to the doctors; passing sleepless nights due to a crying child, having to take off from work to stay home with the child, and taking the child to the doctors can be very stressful for the family. The cost for medical and surgical therapy for otitis media in children 5 years of age or younger is estimated at $5 billion annually in the United States.[2]

Diagnosis

Definition/Symptoms and Signs

Although considered to constitute a continuum of disease, otitis media can be subclassified into *acute otitis media* (AOM) and *otitis media with effusion* (OME) on the basis of signs and symptoms. Because the treatments for AOM and for OME differ, it is important to accurately diagnose the two conditions. AOM generally is characterized by rapid onset of signs and symptoms of inflammation in the middle ear accompanied by middle ear effusion (MEE). Signs of inflammation include bulging or fullness of the tympanic membrane (TM), erythema of the TM, and acute perforation of the TM with otorrhea. Symptoms include otalgia, irritability, and fever. OME, on the other hand, is defined as MEE without signs and symptoms of acute inflammation as found in AOM.

Physical Examination

In addition to the examination of the ears, a proper head and neck examination is invaluable, because it may identify conditions that may predispose the patient to otitis media. Facial features should be assessed for craniofacial anomalies such as those of Down syndrome and Treacher Collins syndrome, because they are associated with increased incidence of otitis media. Examination of the oropharynx may show a bifid uvula or a cleft palate. Hypernasality indicates velopharyngeal insufficiency, whereas hyponasality may be caused by obstructing adenoids or nasal obstruction due to nasal polyposis or deviated septum.

Pneumatic otoscopy is the primary diagnostic tool to evaluate the status of the middle ear, because it allows assessment of the TM and its mobility. The normal TM is translucent and concave and moves briskly with application of positive and negative pressure. A visible landmark is the handle (manubrium) of the malleus, which is attached to the TM, with the umbo in the center of the TM. To adequately visualize the TM, the external ear canal must be cleared of cerumen and debris. The assessment of the TM should note *position*, *color*, *degree of translucency*, and *mobility*. To ascertain the mobility of the TM, a good airtight seal must be obtained between the speculum and the ear canal. The largest speculum that fits comfortably should be used. A bulb through which air is puffed should be attached to the otoscope, allowing for visualization of TM mobility. Reduced or no mobility of

the TM indicates loss of compliance of the TM, either as a result of effusion in the middle ear or from increased stiffness due to scarring or increased thickness of the TM. Total absence of mobility of the TM may also be due to an opening in the TM either as a perforation or a patent tympanostomy tube. Other features, such as fluid levels or bubbles, may be more easily discerned with movement of the TM. The position of the TM ranges from severely retracted to bulging. Mild to moderate retraction indicates negative pressure, MEE, or both, whereas a severely retracted TM usually is associated with effusion. Fullness and bulging of the TM are caused by increased pressure or fluid, or both, in the middle ear. Opacification of the TM may be caused by thickening or scarring or presence of MEE. A red but translucent TM is a typical finding in a crying or sneezing infant, secondary to engorgement of blood vessels in the TM. On the other hand, a "red" TM that is full or bulging often is a sign of AOM. A pink, gray, yellow, or blue retracted TM with reduced or no mobility usually is seen with OME. Myringitis is inflammation of the TM without fluid in the middle ear. Use of an operating microscope may clarify features seen on otoscopy, and visualization of scarring and atrophy of the TM may be enhanced.

Immittance Testing (Tympanometry)

Immittance testing is an excellent adjunct to the assessment of middle ear status and the management of otitis media. When otoscopic evaluation is inconclusive or difficult to perform, tympanometry can be very useful in evaluating ear disease in children older than 6 months of age. It is easy to perform and most often is well accepted by the patient. It has been used for school screening as well as in pediatricians' offices. It also is valuable for documentation of middle ear status over time with repeat testing. A small probe, which emits a tone, is placed in the ear canal with an airtight seal. The tympanogram is obtained by plotting the immittance (acoustic energy of the reflected tone) of the middle ear as a function of the pressure in the external ear canal, which varies, ranging from −400 to +200 daPa (decapascals). The instrument provides measures such as peak compensated (static) admittance, tympanometric peak pressure, acoustic reflex, and tympanometric width (TW) (a measure of gradient). The following set of criteria uses TW to categorize middle ear status[3]:

TW less than 150 daPa = no OME

TW greater than 350 daPa = OME

TW 150-350 daPa = presence or absence of OME is determined by otoscopy

A flat or rounded pattern (TW greater than 350 daPa) with a small ear canal volume indicates MEE, whereas a flat pattern with a large ear canal volume suggests a perforation or a patent tympanostomy tube. In a normal air-filled middle ear with equal pressure on both sides of the TM, the peak pressure of the tympanogram is 0 daPa. Algorithms have been developed to determine the presence or absence of MEE, some combining pneumatic otoscopy and tympanometry. Other methods of ascertaining middle ear status have been investigated, including spectral gradient acoustic reflectometry[4,5] and ultrasound evaluation,[6] but they have been found to have limitations, although they may be useful for screening.

Audiometry

MEE usually results in a mild to moderate conductive hearing loss. The assessment of hearing is essential to management, because hearing impairment can predispose the affected child to delays in speech and language development and may later affect school performance. Audiometry should be used to determine specific management strategies, with a more aggressive approach considered in children with significant hearing impairment.

Behavioral audiometry requires cooperation of the child with the examination and the test is adapted to the age of the child. *Visual reinforcement audiometry* is used for children 6 months to 2 years of age and involves presentation of a sound stimulus in the sound field with observation of the child's conditioned head turn response. This reaction is rewarded with a visual reinforcement such as an animated toy. *Play audiometry*, for children older than 2 years, is similar to *conventional audiometry* (for children over 5 years of age), but the child places toys in a bucket rather than raising a hand to acknowledge hearing the sound. Hearing thresholds in the sound field or ear-specific are determined at 0.25, 0.5, 1, 2, 4, and 8 kHz, depending on the age of the child.

Auditory brainstem audiometry (ABR) and *transitory otoacoustic emissions* (TOAE) are excellent methods for testing children who do not cooperate with behavioral hearing evaluation because of very young age or developmental delay. Except for infants, sedation or general anesthesia is usually necessary for ABR testing in younger children. Three electrodes are placed (forehead and each mastoid process) to record the response to clicks of 2000 to 4000 Hz or pure tone burst. The ABR consists of five to seven vertex-positive waves. Waves I to III presumably reflect activity of the auditory centers in the eighth nerve fibers and pons, waves IV and V reflect auditory centers in mid- to rostral pons and caudal midbrain, respectively; activity from waves VI and VII is less certain. The ABR reflects auditory neural electrical responses that are adequately correlated to behavioral hearing thresholds. However, a normal response on the ABR suggests only that the auditory system up to the midbrain level is responsive to the stimulus employed. Thus, it does not guarantee normal hearing.

Otoacoustic emissions (OAE) testing measures cochlear function (outer hair cells) and is a means of objective assessment of auditory function. It commonly is used for newborn hearing screening because it is fast and easy to perform. It is excellent for testing children who do not cooperate with behavioral testing. MEE may confound the results. Therefore, if the OAEs are absent, immittance testing should be performed to assess the middle ear. For children who "fail" OAE testing, follow-up audiologic testing must be done to assess type and degree of hearing loss.

Pathophysiology and Pathogenesis

The pathophysiology of otitis media is multifactorial, with various overlapping factors (Fig. 194-1).

Eustachian Tube Function

The eustachian tube in the infant is shorter, wider, and more horizontal than in the adult, which accounts for the high rate of otitis media in infants and children. By the age of 7 years, when the tube has a more

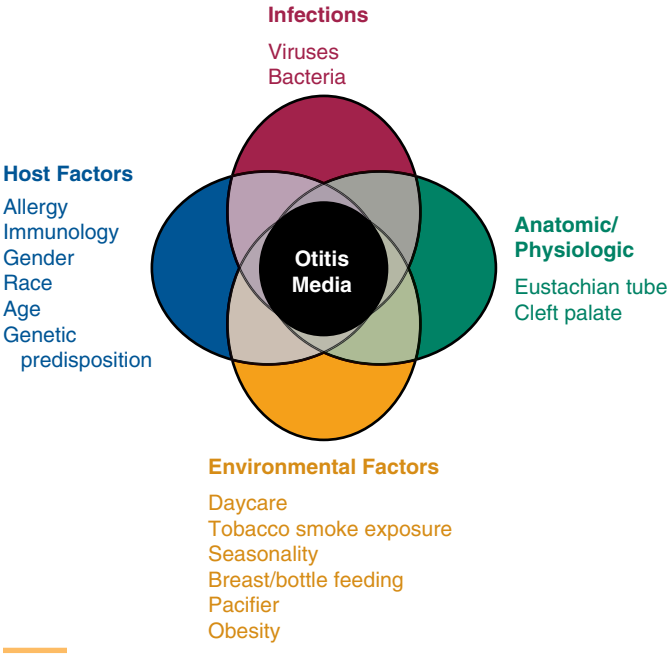

Figure 194-1. Various factors interact in the pathogenesis of otitis media.

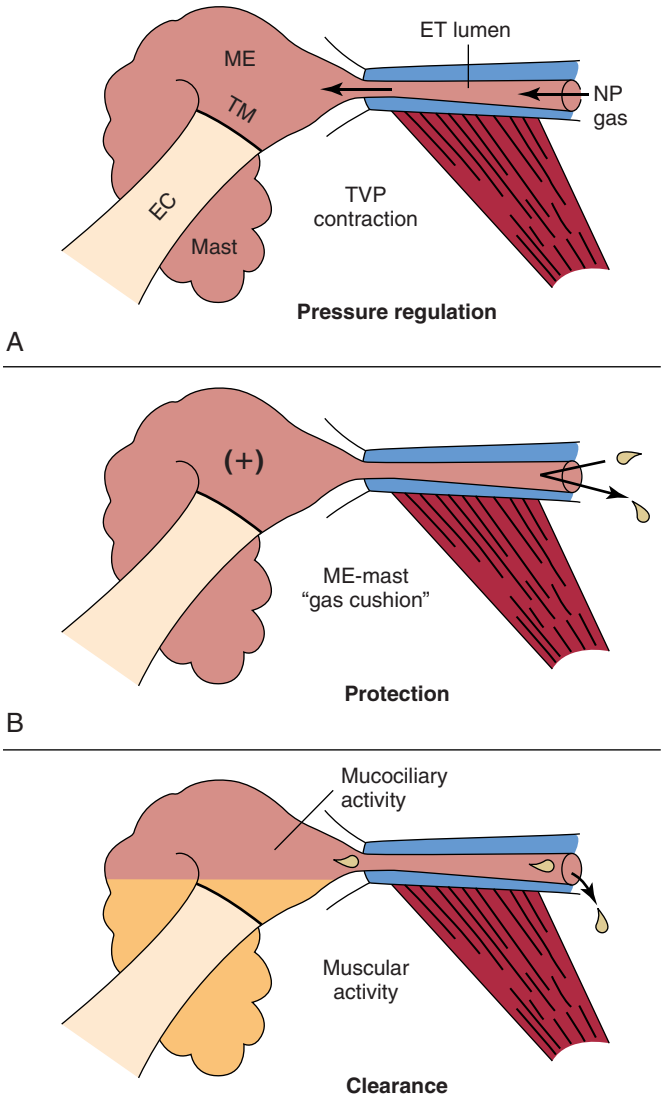

Figure 194-2. Functions of the eustachian tube (ET)-middle ear (ME)-mastoid (mast) gas cell system. **A,** Pressure regulation function is related to active dilation of the tube by contraction of the tensor veli palatini muscle (TVP). **B,** Protective function is dependent in part on an intact middle ear and mastoid gas cells to maintain a gas cushion. **C,** Clearance function is enhanced by mucociliary activity and muscular activity during tubal closing. EC, external canal; NP, nasopharynx; TM, tympanic membrane. *(Adapted from Bluestone CD.* Eustachian Tube: Structure, Function, Role in Otitis Media. *Hamilton, Ont: BC Decker; 2005:51.)*

adult configuration, the prevalence of otitis media is low.[7] The three physiologic functions of the eustachian tube are (1) *pressure regulation* (ventilation), (2) *protection*, and (3) *clearance* (drainage). Of these three functions, pressure regulation is the most important[8] (Fig. 194-2). Middle ear pressure is equilibrated to atmospheric pressure through active intermittent openings of the eustachian tube caused by contraction of the tensor veli palatini muscle during swallowing, jaw movements, and yawning. If active function is impaired, negative pressure will develop in the middle ear. Pressure regulation can be impaired by failure of the opening mechanism (*functional obstruction*) or anatomic (*mechanical*) obstruction. Using a pressure chamber, Bylander and associates evaluated eustachian tube function in children and adults who were considered otologically normal with intact TMs.[9] Although only 5% of the adults were not able to equilibrate negative middle ear pressure, as many as 35.8% of the children could not equilibrate negative pressure. Children 3 to 6 years of age performed worse than children 7 to 12 years of age. These studies indicate that in even apparently otologically normal children eustachian tube function is worse than in adults, but it does improve with age. The improvement in the eustachian tube function parallels the decrease in the incidence of otitis media. Stenström and colleagues tested eustachian tube function in 50 otitis-prone children and 49 children with no history of AOM (control group) using a pressure chamber.[10] The otitis-prone children had significantly poorer active tubal function than the normal control subjects, suggesting that recurrent AOM is the result of functional obstruction of the eustachian tube.

In ears with normal eustachian tube function, the eustachian tube is collapsed when at rest. This arrangement protects the middle ear from nasopharyngeal sound pressure and reflux of secretions from the nasopharynx.

The clearance of secretions produced within the middle ear into the nasopharynx is provided via the mucociliary system and through the "pumping action" of the eustachian tube during closing. The passive closing of the tube is initiated at the middle ear end of the eustachian tube and progresses toward the nasopharyngeal end, facilitating removal of the secretions.

Infection

Bacteriology

Before the year 2000, studies in the United States reported that *Streptococcus pneumoniae* was the single most common bacterial pathogen in AOM, followed by *Haemophilus influenzae* and *Moraxella catarrhalis*; *Streptococcus pyogenes* and other miscellaneous bacteria accounted for just a few cases. From ears with chronic OME, *H. influenzae* was the single most common pathogen, with *S. pneumoniae*, *M. catarrhalis*, and other bacteria accounting for a small percentage of cases each. Data obtained during the 1980s from a single institution is shown in Figure 194-3.[11] There was great hope that the introduction and subsequent use of the heptavalent conjugated pneumococcal vaccine (PCV7) for infants and young children, licensed in the United States in 2000, would lead to a substantial decrease in AOM. However, data from vaccine trials conducted in California[12] and Finland[13] revealed only a 7.8% and a 6% relative risk reduction, respectively, in AOM. Casey and Pichichero examined the experience of children in a suburban Rochester, New York, practice in the years 2001 to 2003 (after the introduction of PCV7) compared with the years 1995 to 2000 and reported a 24% decrease in persistent AOM and AOM treatment failures.[14] These investigators also reported a decrease in recovery of *S. pneumoniae* from the ears of such children and an increase in *H. influenzae*. McEllistrem and coworkers looked at middle ear cultures obtained between 1999 and 2002 at five institutions.[15] They reported that the percentage of AOM episodes due to non-PCV7 serogroups increased after 2000, from 12% in 1999 to 32% in 2002, and the nonvaccine serotypes were more frequent in those who received more than one dose of vaccine. The frequency of penicillin nonsusceptible strains in the vaccine and nonvaccine serotypes remained unchanged.

Nasopharyngeal carriage also was examined. Pelton and associates enrolled 275 infants and children 2 to 24 months of age in a surveillance study in which nasopharyngeal swabs or nasal washes were obtained at all well-child visits and at visits for AOM.[16] From 2000 to 2003, these workers noted a decrease in vaccine serotypes with an increase in nonvaccine serotypes. Tracking antimicrobial susceptibility, they found that the MIC50 and the MIC90 for amoxicillin were stable until the 6-month period from October 2002 to March 2003, when they both increased significantly. Jacobs and associates examined the nasopharyngeal flora in children undergoing tympanostomy tube placement in March 2004 to March 2005 and also found a decrease in vaccine serotypes with a concomitant increase in nonvaccine serotypes, many of which were antibiotic-resistant strains.[17]

These data point to a changing bacteriology and the need for continued surveillance. A remarkable decrease in serious disease has occurred with the use of the newer pneumococcal vaccines, but the impact on otitis media continues to evolve.

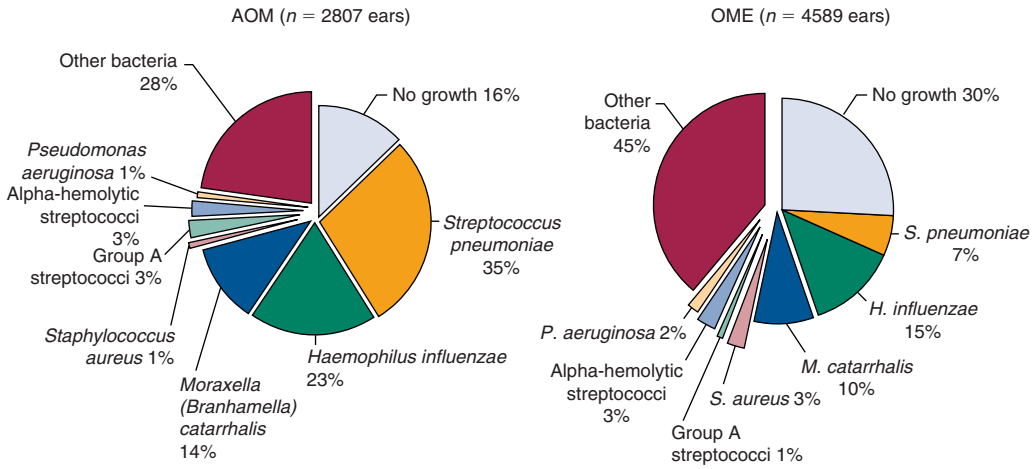

Figure 194-3. Comparison of distribution of isolates in 2807 effusions from patients with acute otitis media (AOM) and 4589 effusions from patients with otitis media with effusion (OME) at the Pittsburgh Otitis Media Research Center, 1980 to 1989. Total percentages are greater than 100% because of multiple organisms. *(Adapted from Bluestone CD, Klein JO.* Otitis Media in Infants and Children. *4th ed. Hamilton, Ont: BC Decker; 2007:103.)*

Biofilms

Bacterial biofilms are sessile communities of interacting bacteria attached to a surface and encased in a protective matrix of exopolysaccharides rather than living in a motile "planktonic" or free-floating state. The exopolysaccharide matrix provides protection from phagocytosis and other host defense mechanisms due to lack of accessibility by immunoglobulins and complement. The reduced metabolic rate of bacteria in the biofilm renders them resistant to antimicrobial treatment. The bacterial community relies on a complex intracellular communication system that provides for organized growth characteristics known as "quorum sensing." Biofilms have been known to exist on hard surfaces such as metal pipes or teeth. However, recent animal and human studies have suggested that biofilms can also be isolated from the middle ear. Post and coworkers, using polymerase chain reaction (PCR) methodology, found evidence of bacteria in 48% of culture-negative MEE specimens from children undergoing tympanostomy tube insertion for chronic OME.[18] Hall-Stoodley and colleagues obtained confocal laser scanning microscopy images from the middle ear mucosa of 26 children scheduled for tympanostomy tube insertion for recurrent or persistent otitis media and 8 control subjects (3 children and 5 adults) who underwent cochlear implantation.[19] Generic stains and species-specific probes for *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* were used to evaluate biofilm morphology. Mucosal biofilms were visualized in 92% of the mucosa from children with chronic and recurrent otitis media but were not observed in any of the 8 control subjects. The investigators suggested that the findings supported the hypothesis that chronic middle ear disease is biofilm-related. Biofilms also have been identified in the nasopharynx of children with otitis media, and it was suggested that the biofilm may act as a reservoir for bacterial pathogens resistant to antibiotics. The mechanical débridement of the nasopharyngeal biofilms may explain the observed clinical benefit associated with adenoidectomy in subsets of pediatric patients.[20]

Viruses

Until the introduction of PCR, viruses were not considered a major factor in the etiology of otitis media, probably because of the technical difficulties in isolating the viruses. Using PCR techniques, however, it has been possible to identify respiratory syncytial virus (RSV), influenzavirus, adenovirus, parainfluenza virus, and rhinoviruses in MEE.[21,22] There is strong evidence that viruses have a crucial role in the development of AOM.[22] In a majority of children, viral infection of the upper respiratory tract mucosa initiates the whole cascade of events that finally leads to the development of AOM, and AOM may be regarded as a complication of a preceding or concomitant viral infection. In a study of 60 children (in 24 families) who were followed from October 2003 through April 2004 by daily parental recording of illness signs, weekly pneumatic otoscopy and viral PCR analysis of nasal secretions collected during "colds" or when MEE was noted, or from enrolled siblings without these conditions, one or more viruses were identified from 73% of secretions collected during a cold but only 18% collected at a time without a cold.[23] Of 93 episodes of otitis media, 70% occurred during a cold, and nasal secretions from 77% of children at the time of these episodes were positive for virus.

Allergy and Immunology

Even though allergy is considered in the pathogenesis of otitis media, the causal mechanism is not understood, and well-controlled studies to prove the efficacy of anti-allergic medication in the treatment of OM are lacking. Several mechanisms by which allergy may cause otitis media have been suggested: (1) the middle ear is a "shock organ" (target); (2) allergy may induce inflammatory swelling of the eustachian tube mucosa; (3) allergies produce inflammatory obstruction of the nose; and (4) bacteria-laden allergic nasopharyngeal secretions may be aspirated into the middle ear. The last three mechanisms involve an association between allergy and abnormal eustachian tube function. Prospective studies have reported a relationship between upper respiratory tract allergy and eustachian tube obstruction in a series of provocative, intranasal allergen–inhalation challenge studies.[24]

Recent studies focus on the analysis of the inflammatory markers in MEE to determine the role of allergy. Both TH1 and TH2 inflammatory patterns in helper T cells have been found in OME. TH1 cytokines antagonize allergic inflammation and play a key part in the defense against viruses and intracellular pathogens, whereas TH2 cytokines promote IgE production, eosinophil growth, and mucus production.[25] The chemoattractant cytokine RANTES (*r*egulated upon *a*ctivation, normal *T* cell–*e*xpressed and *s*ecreted) and eosinophilic cationic protein (ECP), signs of a TH2 process, were assessed in MEE samples from 25 children with allergy and 20 nonallergic children who were 5 to 11 years old at the time of tympanostomy tube insertion.[26] RANTES and ECP levels were significantly higher in the MEE samples from children with allergy than in children without allergy ($P < 0.01$ and < 0.05, respectively). A positive correlation also was found between RANTES and ECP in MEE ($P < 0.01$) in children with allergy, which suggests that allergy is a contributing factor in the pathogenesis of otitis media.

Children with major immune deficiencies may have recurrent otitis media as part of their overall clinical picture, but most otitis-prone children may have only a subtle immunologic abnormality that predisposes them to recurrent infections.[27] The three major pathogens of otitis media—*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*—frequently colonize the nasopharynx. There are many strains of these

organisms, and among the different strains are heterologous surface (strain specific) antigens and conserved antigens. Conserved antigens induce broadly protective antibodies while strain-specific antigens induce limited protection. Otitis-prone children may display strain-specific immunity but fail to develop a broadly protective antibody response, which makes them susceptible to recurrent and persistent otitis media.[28]

Recurrence of bilateral OME after tympanostomy tube insertion was more likely in children with poor eustachian tube function and low IgA or low IgG2 and decreased levels of mannose-binding lectin than in children with poor tubal function and high IgA and IgG2 measured at the time of tube insertion.[29] This suggests that an interaction between various immune factors may increase the risk for the development of otitis media.

Gastroesophageal Reflux

In 2002 Tasker and associates reported finding pepsin/pepsinogen, using enzyme-linked immunosorbent assays, in 90.8% of 65 MEE samples obtained at the time of myringotomy in children.[30] The pepsin-pepsinogen levels ranged from 0.8 to 213.9 µg/mL, which is 1000 times higher than serum levels. He and colleagues, using a sensitive and specific pepsin assay, detected pepsin activity in 14.4% of 152 subjects undergoing tympanostomy tube insertion.[31] The levels of pepsin ranged from 13 to 687 ng/mL. Crapko and associates also identified pepsin activity in the middle ear fluid in 60% of 20 subjects also undergoing tympanostomy tube insertion.[32] In this group of children the pepsin levels ranged from 80 to 1000 ng/mL. The latter studies have shown that pepsin is identified less frequently and at lower levels of pepsin, which may be due to differences in methodology. However, it may be concluded from these studies that gastroesophageal reflux may be a causative factor in otitis media, with a potential role for antireflux therapy in the treatment of otitis media in some children, but adequate controlled trials have not been done.

Epidemiology

Incidence and Prevalence

Otitis media is considered a worldwide pediatric health care problem. The Early Childhood Study—Birth Cohort (ECLS—B), a nationally representative longitudinal study of more than 8000 children born in 2001, showed that otitis media was diagnosed in 39% of children by 9 months and 62% of children by 2 years of age.[33] Although the highest incidence of otitis media is in young children, it also occurs in older children, adolescents, and adults. The Oslo Birth Cohort enrolling infants born in a 15-month period in 1992 to 1993 found that 13% of 10-year-olds had at least one episode of otitis media in the previous 12 months.[34] Approximately 3% to 15% of patients with otitis media referred to otolaryngology clinics are adults.[35]

Acute Otitis Media

Most children experience at least one episode of AOM during their childhood. The cumulative incidence of the first episode of AOM based on studies from various countries ranges from 19% to 62% by age 1 year and 50% to 84% by 3 years of age[36-42] (Fig. 194-4). In a majority of these studies, the peak incidence of AOM was during the first 6 to 12 months of life.[39] The incidence decreases with age, and by the age of 7 years, few children experience episodes of AOM. Recurrent episodes of AOM are common in young children. By 6 months of age, 20% have had two or more episodes.[43] Occurrence of three or more episodes of AOM by the ages of 1, 3, 5, and 7 years has been documented in 10% to 19%, 50%, 65%, and 75% of children, respectively.[39] Occurrence of six or more episodes of AOM was documented in 39% of children by the age of 7 years.

Otitis Media with Effusion

It may be difficult to determine the "true" incidence of OME because, by definition, OME is asymptomatic. Furthermore, most screening studies determine the presence of MEE without differentiating between AOM and OME. Also, a short time between observations is needed for precise assessment of the onset and time to resolution of each new episode of OME, because approximately 65% of OME episodes in children 2 to 7 years of age resolve within 1 month.[44] Monthly examinations with otoscopy and tympanometry in 2- to 6-year-old children in a day care center in Pittsburgh revealed MEE at least once in 53% to 61% of the children. Lous and Fiellau-Nikolajsen found an incidence of MEE of 26% in 7-year-old children followed monthly for 1 year using tympanometry.[45]

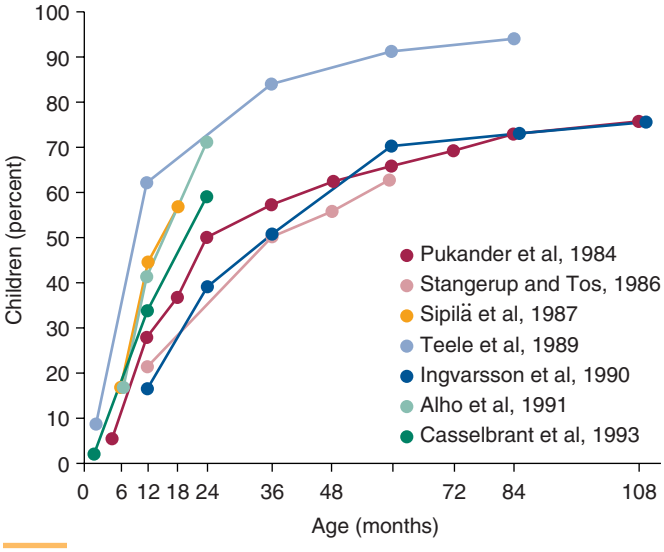

Figure 194-4. Cumulative incidence of first episode of acute otitis media. *(Reproduced from Casselbrant ML, Mandel EM. Epidemiology. In: Rosenfeld RM, Bluestone CD, eds.* Evidence-Based Otitis Media. *2nd ed. Hamilton, Ont: BC Decker; 2003:147.)*

The point prevalence of MEE from different countries shows a wide variation, depending on the age of the child, season of the year, and type of assessment. Thus, it must be emphasized that comparison of outcomes between studies will require careful evaluation of study methodology, as well as caution in drawing conclusions. However, nearly all children had experienced at least one episode by the age of 3 years.[46]

Trend over Time

Even though otitis media remains a major problem in the United States, several recent studies point to a trend toward reduction in the burden of otitis media. Grijalva and associates compared the national rates of outpatient visits for pneumonia and otitis media in children in 1994 to 1999 to those in 2002 to 2003 using the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.[47] The results showed that otitis media visit rates declined by 20% in children younger than 2 years of age while there was no significant decrease in outpatient visit rates for pneumonia or other respiratory infections in children in this same age group. The second study compared the risk of developing frequent otitis media or having tympanostomy tubes inserted in four birth cohorts (1998 to 1999, 1999 to 2000, 2000 to 2001, and 2001 to 2002).[48] The study population included all children at birth in TennCare or selected upstate New York commercial insurance plans as of July 1998 and followed them for 5 years. When comparing the 2000-2001 cohort to the 1998-1999 cohort frequent otitis media declined by 17% and 28% and tympanostomy tube insertion declined by 16% and 23% for Tennessee and New York cohorts, respectively. The decline may be the result of infant immunization, catch-up doses in older children, and herd immunity after introduction of the heptavalent pneumococcal conjugate vaccine in the United States in 2000. In a comparison of the 2000 to 2001 and 2001 to 2002 birth cohorts, frequent otitis media and tympanostomy tubes remained stable in New York but increased in Tennessee. The investigators attributed this to several possible factors including increase in disease due to nonvaccine serotypes and change in medical care utilization.

A decline in the incidence of otitis media also has been reported from several European countries. Kvaerner conducted a study in Norway of hospital admissions for AOM from 1999 to 2005 among children aged 7 years or younger.[49] Hospitalization for AOM was less frequent but the incidence of acute mastoiditis remained stable at approximately 6 per 100,000 children over time. The consultation rates to the general physicians in the Netherlands for otitis media during 1995 to 2003 in children from birth to 13 years of age were assessed using the research database of the Netherlands University Medical Center Utrecht Primary Care Network.[50] The overall consultation rates decreased by 9% for AOM and 34% for OME. In children aged 2 to 6 years and those aged 6 to 13 years, the rate of AOM declined by 15% and 40%, respectively; the rates of OME declined by 41% and 48%, respectively. In children younger than 2 years of age, however, the rates of AOM and OME increased by 46% and 66%.

Data from the General Practitioner Database in the United Kingdom were analyzed for events classified as AOM or "glue ear" in the years 1991 to 2001.[51] Total consultations for AOM and glue ear in children aged 2 to 13 years had changed from 105.3 to 34.7 and 15.2 to 16.7 per 1000 per year, respectively.

Further surveillance is needed. As noted previously, disease rates must continue to be monitored to determine the effects of vaccines and changes in treatment on the epidemiology of otitis media.

Risk Factors

Risk factors can be host-related (age, gender, race, prematurity, allergy, immunocompetence, cleft palate and craniofacial abnormalities, genetic predisposition) as well as environmental (upper respiratory infections, seasonality, day care, siblings, tobacco smoke exposure, breastfeeding, socioeconomic status, pacifier use, and obesity) and are considered important in the occurrence, recurrence, and persistence of middle ear disease.

Host-Related Factors

Age

The highest incidence of AOM is between 6 and 11 months of age,[39] and onset of the first episode of AOM before 6 months[39] or 12 months of age is a powerful predictor of recurrence.[52] The risk of persistent MEE after an episode of AOM is inversely correlated with age,[39] and children who experience their first episode of MEE before 2 months of age are at a higher risk for persistent fluid during their first year of life than are children who have their first episode later.[53]

Sex

Most investigators have reported no apparent sex-based difference in the incidence of OME.[46] Paradise and coworkers, in a study involving more than 2000 infants, found males had more time with MEE, although the difference was not large.[54] Some studies have found a significantly higher incidence of AOM in males as well as more recurrent episodes than in females, but others have not found this.[46]

Race

Earlier studies have suggested a lower incidence of otitis media in African-American children than in white children. More recent studies in which the children were followed prospectively from infancy to age 2 years with routine examinations of the ears every 6 weeks showed no difference between the African-American and white children in their experience with otitis media.[54,55] A third study, part of an American population-based sample survey evaluating schoolchildren 6 to 10 years of age with tympanometry, reported no difference between African-American and white children. However, the prevalence of OME was significantly higher in Hispanic children compared with white children.[56] In another study of more than 11,000 infants followed only from the ages of 1 through 6 months at two urban and one suburban location in the United States, non-Hispanic white children had significantly higher rates of otitis media after multivariant adjustment than non-Hispanic black or Asian children. There was no difference between Hispanic and non-Hispanic children.[57]

Prematurity

Some studies have shown a possible association between low birth weight and prematurity and otitis media, but others have not. In many of these studies, however, the sample sizes have been relatively small. A recent study analyzing data from more than 10,000 births showed some relationship between very low birth weight (less than 1500 g) and frequent otitis media, but no increased risk was found for recurrent otitis media and moderately low birth weight (1500 to 2499 g). In a prospective cohort study of 136 children treated with tympanostomy tubes, a positive but nonsignificant association was documented between low birth weight or low gestational age or history of incubator care and recurrent OME.[58]

Allergy

There is still controversy regarding the role of allergy in the pathogenesis of otitis media. Allergy is a common problem in children, occurring at a time when respiratory infections and otitis media are common. Most, but not all, of the epidemiologic studies have supported an association. Pukander and Karma followed 707 children with AOM and found that in children with atopic manifestations, persistence of MEE for 2 months or longer was more common than in children without allergy.[59] In another study, however, atopic diathesis was not found to predispose affected children to the development of AOM.[60] The Japanese investigators Tomonaga and associates determined that allergic rhinitis was present in 50% of 259 patients (mean age of 6 years) in whom OME had been diagnosed, and OME was present in 21% of 605 patients (mean age of 9 years) in whom allergic rhinitis had been diagnosed.[61] Among 108 children 5 to 8 years of age (mean age of 6 years) in whom neither condition had been diagnosed, the occurrence rates for allergic rhinitis, OME, and both of these conditions were 17%, 6%, and 2%, respectively. Another investigative group (Kraemer and coworkers) compared risk factors for persistent MEE among 76 children hospitalized for bilateral myringotomy with tube insertion (M&T) and 76 control subjects matched by age, gender, and season of admission for a general surgical procedure.[62] Results showed a nearly fourfold increase in the risk of persistent MEE in children who had atopic symptoms for more than 15 days per month. In another study, Bernstein and Reisman determined the allergy status of a group of 200 children who had undergone one or more M&T procedures.[63] These workers diagnosed allergy in 23% of the entire group but found that the frequency was 35% among the 88 children with multiple myringotomies with tube insertions. The frequency of allergy in these patients was higher than that reported for children of similar age in the general population. The foregoing studies generally found a higher frequency of OME in allergic children than in age-matched nonallergic children, as well as higher frequencies of allergy in children with OME than in children without OME.

Immunocompetence

Children with recurrent otitis media as well as other recurrent infections may have a defect in the immune system such as a defect in phagocyte function, humoral immunity, local immunity, or other immune defects.[8] Children infected with the human immunodeficiency virus (HIV) demonstrate a significantly higher recurrence rate than in normal children or children who have seroconverted.[64]

Cleft Palate/Craniofacial Abnormality

Otitis media is considered "universal" in infants younger than 2 years of age with unrepaired cleft palate.[65] After surgical repair of the palate, the occurrence of otitis media is reduced, probably because of improvement in eustachian tube function. However, many children continue to have problems up into the teens. Otitis media also is common in children with other craniofacial abnormalities or Down syndrome, also due to anatomic or functional eustachian tube abnormalities.[66] In children with Down syndrome, low resistance of the tube, in addition to poor active eustachian tube function, predisposes them to reflux of nasal secretions into the middle ear.[67]

Genetic Predisposition

The frequency of the occurrence of one episode of otitis media is so high that a genetic predisposition is highly unlikely. However, a pre-

disposition to recurrent episodes of otitis media and chronic MEE may have a significant genetic component. The etiology of otitis media is multifactorial, involving environmental as well as genetic factors. A large number of genes may be involved, each contributing to a particular increase in disease risk.

Twin and triplet studies have been used to assess the heritability of otitis media. Two retrospective studies using questionnaires have been published. The first study, using 2750 Norwegian twin pairs, estimated the heritability at 0.74 in females and 0.45 in males.[68] In the second study, the estimated heritability was, on average, 0.57 at the ages of 2, 3, and 4 years.[69] In a prospective twin-triplet study from Pittsburgh with monthly assessments of middle ear status, the heritability estimate for otitis media at age 2 years was 0.79 in females and 0.64 in males.[70] Heritability is a population statistic used to ascertain if a trait is heritable, and linkage and association studies may identify genetic regions or specific genes influencing the particular trait or disease. Daly and coworkers, using genome-wide linkage analysis, have suggested that chromosomal regions on 19q and 10q contain genes contributing to the susceptibility to chronic OME or recurrent AOM.[71] Subsequent fine mapping of both regions further strengthened the evidence for this linkage.[72] In addition, evidence for an association between polymorphisms in *FBXO11*, the human homolog of a mouse model gene for chronic otitis media, and chronic OME/recurrent AOM (COME/ROM) has been reported.[73]

Environmental Factors

A study was conducted to assess the variation in environmental risk factors for otitis media across Western countries, including European countries, the United States, Canada, and Australia.[74] The main risk factors for otitis media were day care atendance, number of siblings, tobacco smoke exposure, breastfeeding, birth weight, socioeconomic status, and air pollution. However, the results indicated large variations in rates across the various countries: day care at ages 1 to 3 years: Sweden 75% versus Italy 6%; breastfed at 6 months: Norway 80% versus Poland 6%; and women smoking: Germany, France, and Norway 30% to 40% versus Portugal less than 10%.

Upper Respiratory Infection/Seasonality

Both epidemiologic evidence and clinical experience strongly suggest that otitis media frequently is a complication of an upper respiratory infection (URI). The incidence of AOM is highest during the fall and winter months and lowest during spring and summer months, which parallels the incidence of URI.[44] This correlation supports the hypothesis that an episode of URI plays an important role in the etiology of otitis media. Rhinovirus, RSV, adenovirus, and coronavirus have been detected in MEE during episodes of AOM.[21,75] Upper respiratory tract infections with RSV, influenzavirus, and adenovirus often precede an episode of AOM.[22] In a prospective study of Finnish children, 54% of ensuing AOM episodes were diagnosed by day 4 after the onset of URI symptoms.[76]

Day Care/Home Care/Siblings

Almost universally, day care center attendance remains a very important risk factor for development of otitis media. For example, prevalence of high negative ME pressure and flat tympanograms (type B), indicative of MEE, have been shown to be highest in children cared for in day care centers with many children, intermediate in children in family day care with fewer children, and lowest in children cared for at home.[77] Children attending day care centers also have been shown to be more likely to have tympanostomy tubes inserted than children cared for at home.[78]

Birth order has been shown to be associated with episodes of otitis media and percentage of time with MEE.[55] First-born children had a lower rate of episodes of AOM and less time with MEE during the first 2 years of life than children with older siblings. Also, having more than one sibling was significantly related to early onset of otitis media.[59]

The increased morbidity among children in day care centers and in children with older siblings may be related to the greater opportunity for exposure to viral URI, which may cause eustachian tube dysfunction, leading to the development of otitis media.

Tobacco Smoke Exposure

An association between otitis media and passive exposure to smoking has been reported by many investigators while others have not been able to demonstrate such an association. In most studies the information regarding smoke exposure has been obtained from the parents. A few recent studies have measured cotinine, a metabolite of nicotine, in blood, urine, or saliva of the child and have been able to more accurately determine the association between otitis media and smoke exposure.[43,79] More information about the pathogenesis and duration and intensity of exposure is needed to clarify this association. Two recent studies have shown an association between middle ear status and parental smoking. In children exposed to parental smoking, tympanostomy tubes stayed in place for 59 weeks, compared with 86 weeks in children who were not exposed to smoking.[80] Also, myringosclerosis was more prevalent in children with two smoking parents compared with those with no smoking parents (64% versus 20%) and maternal smoking was associated with a highly increased risk of recurrent otitis media after insertion of tympanostomy tubes.[81]

Breastfeeding/Bottle Feeding

Currently, most national and international authorities, including the American Academy of Pediatrics and the American Academy of Family Physicians, the World Health Organization (WHO), and the United Nations Children's Fund, recommend 6 months of exclusive breastfeeding. In 2004, Kramer and Kakuma published a comprehensive review of the world literature to determine health benefits of exclusive breastfeeding for 6 months compared with 3 to 4 months.[82] They reported a decrease in the risk for gastrointestinal infection even in developed areas. It had not been shown previously that exclusive breastfeeding for 6 months or longer compared with 4 to less than 6 months in the United States provided greater protection against respiratory infections. Therefore, a secondary analysis of data from the National Health and Nutrition Examination Survey III, a population-based cross-sectional home survey conducted from 1988 to 1994, was undertaken.[83] After adjustment for demographic variables, child care, and smoke exposure, the data revealed statistically significant increased risk for both pneumonia (odds ratio [OR]: 4.27; 95% confidence interval [CI]: 1.27-14.35) and three or more episodes of otitis media (OR: 1.95; 95% CI: 1.06-3.59) in those children breastfed 4 to less than 6 months. These findings further support the current recommendations that infants receive breast milk exclusively during the first 6 months of life.

Socioeconomic Status

Socioeconomic status and access to health care are factors that may affect the incidence of otitis media. It has been generally thought that otitis media is more common among persons in the lower socioeconomic strata as a result of poor sanitary conditions and crowding. Paradise and colleagues followed 2253 infants for 2 years in the United States and found an inverse relationship between the cumulative proportion of days with MEE and socioeconomic status.[84] However, many studies have not revealed any correlation between socioeconomic status of the child's family and the incidence of MEE.

Pacifier Use

Niemelä and associates reported that pacifier use increased the annual incidence of AOM and calculated that pacifier use was responsible for 25% of AOM episodes in children younger than 3 years.[85] They reported the results of an intervention trial in which parents in various well-baby clinics were taught that pacifier use was harmful and should be limited, and parents in other clinics were not provided with this information. This led to a 29% decrease in AOM in the group provided with pacifier information. Pacifier use has been theorized to contribute to the development of otitis media, possibly due to the sucking action of the child propelling nasopharyngeal secretions into the middle ear or by the pacifier acting as a fomite. However, Brook and Gober cultured the surface of pacifiers from children with AOM but found no pathogens typical of AOM.[86] The role of pacifier use in AOM remains unclear.

Obesity

Recent studies have indicated a possible association between otitis media and body mass index (BMI). Tympanostomy tube insertion and overweight were studied in two cohorts of children followed from birth to 2 years of age.[87] Weight-for-length and BMI-for-age were calculated using well-child visit data. In the cohort of predominantly white children, a history of tympanostomy tube insertion significantly predicted risk of BMI index beyond the 85th percentile at the age of 2 years. In the other cohort of American Indian children, a history of recurrent AOM increased the likelihood of weight-for-length index beyond the 95th percentile. Further studies are needed to clarify the association.

Prevention of Disease

Prevention and modification of risk factors and vaccine development are two recommended strategies for the prevention of disease.

Management of Environmental Factors

Promotion of breastfeeding in the first 6 months of life, avoidance of supine bottle feeding and pacifier use, and elimination of passive tobacco smoke may be helpful in reducing the risk of development of otitis media. Alteration of child care arrangements such that the child is exposed to fewer children may also be of benefit.

Vaccines

The three most common bacteria isolated from the middle ear are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. At present, the *S. pneumoniae* vaccines (Pneumovax and Prevnar) are the only bacterial vaccines available for otitis media. Although respiratory viruses, such as RSV, influenzavirus, adenovirus, parainfluenza virus, and rhinovirus, have been isolated in MEE using PCR, influenza vaccine is the only available recommended viral vaccine today that may have an impact on otitis media.

Bacterial Vaccines

Streptococcus pneumoniae *Vaccine*

Pneumovax is a 23-valent polysaccharide vaccine that is not efficacious in children 2 years or younger because of poor antigen production in this age group. Prevnar is a conjugated vaccine in which pneumococcal polysaccharides are conjugated to a nontoxic mutant of diphtheria toxin. The 7-valent vaccine (PCV7), which includes serotypes 4, 6B, 9V, 14,18C, 19F, and 23F, was licensed for use in the United States in 2000 and recommended for use in children younger than 6 years of age by the American Academy of Pediatrics.[88] Infants are immunized at the ages of 2, 4, 6, and 12 to 15 months. For previously unimmunized children 7 to 23 months of age, a reduced number of doses is recommended, and for children 24 to 59 months of age and children at high risk at any age, two doses of PCV7 and one dose of the 23-valent vaccine are recommended.

The efficacy for AOM of the conjugated vaccine has been evaluated in several randomized clinical trials. The trial from Northern California Kaiser Permanente enrolling 37,868 children randomly assigned to either pneumococcal conjugate vaccine or a meningococcal type C conjugate vaccine and followed prospectively, reported an overall reduction of episodes of otitis media of 7%.[12] However, children with recurrent otitis media benefited from the vaccine with a reduction in otitis media episodes ranging from 9.3% to 22.8%, increasing as the frequency of episodes of AOM increased. In addition, immunized children were 20.1% less likely to require tube placement than control subjects. The PCV7 vaccine demonstrated a much higher efficacy (greater than 80%) in reducing invasive pneumococcal disease than in reducing the burden of otitis media. Additional follow-up of the study subjects continued to demonstrate a modest amount of protection against episodes of AOM and need for tympanostomy tube insertion.[89] In a Finnish study of 1662 children randomized to receive either PCV7 vaccine or a hepatitis B vaccine, with follow-up to the age of 24 months, a bacterial diagnosis was made based on a culture of the middle ear fluid, in addition to the clinical assessment of episodes of AOM.[13] The vaccine reduced the number of AOM episodes from any cause by 6%, the number of culture-confirmed pneumococcal episodes by 34%, and the number of episodes due to the vaccine serotypes by 57%. The number of episodes attributed to serotypes that were cross-reactive with those in the vaccine was reduced by 51%, whereas the number of episodes due to all other serotypes increased by 33%. The modest response in reducing number of episodes of AOM was due to a decrease in vaccine efficacy against serotype-specific infections as well as an increase in AOM episodes due to nonvaccine serotypes. A second trial was conducted in Finland using a 7-valent pneumococcal polysaccharide–meningococcal outer membrane protein complex conjugate vaccine (PncOMPC) in 1666 children who were followed for 24 months.[90] This trial showed no reduction in overall number of AOM episodes. The reduction in number of AOM episodes due to any culture-confirmed pneumococci was 25% and to vaccine serotype pneumococci, 56%—results similar to those with the PCV7. This vaccine failed to show protection against cross-reactive serotypes. An increased rate of carriage of nonvaccine serotypes was noted among infants vaccinated with the pneumococcal conjugate vaccine.

With use of the vaccine, pneumococcal colonization in the nasopharynx has changed as the vaccine has caused a reduction in the carriage rate of vaccine serotypes and replacement with nonvaccine serotypes.[17,91] It should be noted that a reduction in nasopharyngeal carriage of vaccine serotypes and an increase in nonvaccine serotypes has also been seen in children younger than 7 months of age.[16]

In the United States and Finland, the initial immunization with PCV7 is at age 2 months based on the results from the clinical trials. However, the question of whether or not the results obtained in the Finnish and U.S. trials could be extrapolated to older children who already had a history of recurrent episodes of AOM was addressed by Dutch and Belgian trials.[92,93] Seventy-eight and 383 children with documented histories of recurrent AOM were enrolled in the Belgian and Dutch studies, respectively. In both trials children between 1 and 7 years old were immunized at entry with PCV7 followed by a booster immunization with a 23-valent pneumococcal polysaccharide vaccine 7 months later and followed up for a total of 18 months in the Dutch trial and 26 months in the Belgian trial. The results from these two studies did not lend any support to the use of pneumococcal conjugate vaccine to prevent AOM in previously unvaccinated toddlers and children with a history of recurrent AOM. The differences in outcome between the studies in older children and those in healthy infants may be caused by differences in age at immunization. In the infant studies the PCV7 immunization may prevent or delay nasopharyngeal colonization of the most frequent pneumococcal serotypes and consequently delay pneumococcal episodes of AOM until a later age. In older children, who already are carriers of pneumococci, there is rapid replacement of pneumococcal vaccine serotypes with nonvaccine serotypes.

An 11-valent polysaccharide pneumococcal serotype vaccine conjugated to *H. influenzae*–derived protein D was evaluated in a clinical trial conducted in the Czech Republic enrolling a total of 4968 children, who were followed to the end of the second year of life.[94] Middle ear fluid was cultured when episodes of AOM were diagnosed. The vaccine reduced the overall incidence of AOM episodes by 33.6%. Vaccine efficacy was 57.6% for episodes of AOM caused by pneumococcal serotypes included in the vaccine and 66% for vaccine-related cross-reactive pneumococcal serotypes. There was no significant change in number of AOM episodes due to other nonvaccine serotypes. Of great interest is that there was 35.3% efficacy against AOM episodes caused by nontypeable *H. influenzae*. These results indicate that using the *H. influenzae*–derived protein D as a protein for conjugation of pneumococcal polysaccharides not only allowed for protection against pneumococcal otitis, but also against otitis media due to nontypeable *H. influenzae*. The use of the *H. influenzae*–derived protein D and the two additional pneumococcal serotypes probably explains the 33.6% reduction in numbers of all types of AOM episodes by the vaccine, which is significantly better than in the previously mentioned trials.[12,13]

Maternal Immunization

Infants immunized with PCV7 are unlikely to elicit protective serum antibody concentrations during the first 4 to 6 months of life, when

recurrent AOM begins. Maternal immunization with pneumococcal vaccine is another approach that is currently being studied in animals as well as in humans.[95,96] A randomized clinical trial was conducted to evaluate the immunogenocity and reactogenicity of the 23-valent pneumococcal polysaccharide vaccine among pregnant women in the Philippines. A significant rise in antibody to polysaccharides varying from 3.3- to 9.1-fold for individual serotypes between pre- and postvaccination was seen in the immunized mothers relative to that in the control subjects. The level of polysaccharide-specific antibody in cord blood was also significantly higher in the immunized group, indicating transfer from mother to infant to provide enhanced protection. Adverse reactions were mild and required no treatment. Healy and Baker, reviewing the subject of maternal vaccination, found strong evidence that maternal immunization would be a feasible approach, particularly for providing early protection to children at high risk.[97] The main concerns with maternal immunization appear to be the fear of risk of birth defects.

Haemophilus influenzae *Vaccine*

Because nontypeable *H. influenzae* is the second most common bacterial pathogen isolated from middle ear fluid in AOM, much effort has been channeled into developing an effective vaccine. Many different approaches using animal models have been used to develop vaccine antigens for nontypeable *H. influenzae*–induced otitis media, including the following proteins: outer membrane protein (OMP) P5, 26, P2, P6, Htr protein, protein D, phosphorylcholine (ChoP), detoxified lipo-oligosaccharides (dLOSs), and type 1V Pili. For the first time, however, it was possible to demonstrate an effective *H. influenzae* antigen for otitis media in a clinical trial using an 11-valent vaccine with the pneumococcal capsular polysaccharides conjugated to protein D, an outer membrane protein of *H. influenzae*, as previously mentioned.[94] Although the efficacy was only 35.3%, the results indicate that it would be feasible to develop an effective vaccine for *H. influenzae*.

Moraxella catarrhalis *Vaccine*

Moraxella catarrhalis is considered the third most common bacterial pathogen isolated from the middle ear. Although the frequency of *M. catarrhalis* infections has previously been rather modest, recent studies have indicated that the frequency of nasopharyngeal colonization with *M. catarrhalis* in children with otitis media increased with the widespread use of the pneumococcal conjugate vaccine.[98] Therefore, for the greatest impact on reducing otitis media episodes, the development of a vaccine that contains *M. catarrhalis*, as well as *S. pneumoniae* and *H. influenzae* antigens, is necessary. Very little progress has been made in defining the protective immune response in *M. catarrhalis*. However, recently, protective immune responses to *M. catarrhalis* in adults with chronic obstructive pulmonary disease have been identified.[99,100] Candidate *M. catarrhalis* vaccine antigens that have been shown to induce potentially protective responses include outer membrane protein OlpA, CopB, filamentous hemagglutinin (FHA-like protein), and lipo-oligosaccharides (LOSs).

Viral Vaccines

Based on evidence regarding the role of viruses in the pathogenesis of AOM, the development of viral vaccines should be strongly promoted.[22] It should be recognized that bacterial vaccines only prevent the bacterial complications of a viral infection, while viral vaccines act at an earlier stage in the pathogenesis of AOM. Thus, viral vaccines have the potential to prevent viral upper respiratory infections, thereby potentially preventing the development of AOM as a complication of bacterial colonization of the nasopharynx.

Influenza Vaccine

The only commercially available viral vaccine today used for prevention of otitis media is the influenza vaccine, which is recommended for all children 6 to 59 months of age and older children with high-risk conditions by the American Academy of Pediatrics.[101] Currently, two types of influenza vaccine are available. Trivalent inactivated influenza vaccine (TIV) contains killed viruses and is given intramuscularly to children 6 months and older and adults. Live-attenuated influenza vaccine (LAIV) contains live virus, is given intranasally, and currently is licensed by the U.S. Food and Drug Administration (FDA) for healthy persons 2 through 49 years of age.

A prospective study in children 13 years or younger was conducted during two respiratory seasons in Finland.[102] The average annual rate of influenza was highest (179 cases/1000 children) among children younger than 3 years of age. AOM developed as a complication of influenza in 39.7% of children younger than 3 years. For every 100 influenza-infected children younger than 3 years, there were 195 days of parental loss of work (mean 3.2 days). The investigators concluded that vaccination of children younger than 3 years of age may be beneficial for reducing the direct and indirect costs of childhood AOM.

Two recent clinical trials have addressed the efficacy of inactivated influenza vaccine in preventing otitis media. Hoberman and coworkers conducted a randomized double-blind, placebo controlled 2-year clinical trial in 786 children 6 to 24 months of age in Pittsburgh, Pennsylvania.[103] The investigators did not identify any significant reduction in the burden of AOM from administration of inactivated trivalent influenza vaccine. However, in the first year of the study, the efficacy of the vaccine against culture-confirmed influenza was 66%, whereas in the second year of the study the efficacy was −7%. The low efficacy rate in the second year may be explained by the fact that the attack rate of influenza virus in the second year did not reach epidemic proportions, in contrast with the first year (3.3% versus 15.9% in the placebo group). The second study was single-blinded and evaluated the efficacy of inactivated influenza vaccine in preventing otitis media. The study was carried out in 119 children 6 to 60 months of age attending day care in Turkey. Efficacy rates for the vaccine against AOM, OME, and otitis media were 51%, 18%, and 18%, respectively.[104]

A multicenter study enrolled and randomly assigned 8475 children 6 to 59 months of age in a double-blind fashion to intranasal trivalent live-attenuated influenza vaccine or trivalent inactivated influenza vaccine intramuscularly to assess the efficacy and safety of the vaccines.[105] The live-attenuated vaccine was overall superior to the inactivated vaccine in preventing influenza episodes. There were 54.9% fewer cases of culture-confirmed influenza episodes in the group that received the live-attenuated vaccine ($P < 0.001$). The superior efficacy of the live-attenuated vaccine was observed for both antigenically well-matched and drifted viruses. Rates of wheezing and hospitalization were higher in the youngest children who received the live-attenuated vaccine than in those given the inactivated vaccine. In 2007 the FDA approved the use of this vaccine for children 2 years of age and older without a history of recurrent wheezing or asthma. Additional studies to assess the safety of the vaccine in the youngest children need to be done.

Respiratory Syncytial Virus Vaccine

The seriousness of RSV infection in infants and children and the need for an RSV vaccine are widely recognized. In addition to causing lower airway infections, the RSV virus is one of the major viruses contributing to the development of AOM.[75] Only live-attenuated vaccines have been investigated. Karron and associates developed a recombinant live-attenuated RSV vaccine that was attenuated in RSV-seropositive children and was well tolerated and immunogenic in RSV-seronegative children.[106] Further studies are needed to assess the clinical efficacy.

An alternative approach to preventing RSV infection is maternal immunization. Munoz and colleagues conducted a study to assess safety and immunogenicity of an RSV purified fusion protein 2 (PFP-2) subunit vaccine in 35 pregnant women in their third trimester and the effect on the offspring.[107] The infants were followed during their first RSV season. Seventy-five percent of the immunized infants had a response to the PFP-2 by Western blot analysis, compared with none of the control subjects. The transplacental transfer of vaccine-induced maternal antibodies was efficient, and no increase in frequency or severity of respiratory tract infections was observed in the immunized infants. The infants were born healthy, and no adverse events related to maternal immunization were documented.

Treatment

The treatment of otitis media involves medical and surgical therapies.

Acute Otitis Media

Observation

In an effort to reduce antibiotic use and stem increasing bacterial resistance, observation without use of antibiotics is listed as an option for selected children with AOM in the guidelines document published by the American Academy of Pediatrics and American Academy of Family Physicians in 2004.[108] Children for whom this is an option are to be selected on the basis of diagnostic certainty, age, illness severity, and access to medical care. Severe disease is defined as moderate to severe otalgia, fever with temperatures higher than 39° C (102° F) orally or 39.5° C rectally, or a toxic-appearing child. Children younger than 6 months of age should be treated with antibiotics regardless; children 6 to 23 months, if the illness is nonsevere, may be observed if the diagnosis is uncertain, but if AOM is certain or severe, the child should be treated with antibiotics; children 24 months or older may be watched if the diagnosis is uncertain or disease is nonsevere but treated if AOM is severe.

Already a popular method of management in several countries outside the United States, observation, or "watchful waiting," is predicated on the results of several earlier studies showing a high spontaneous cure rate for AOM.[109-114] Wald, however, cited problems with the earlier studies: The definition of AOM used in the various studies may have allowed for the inclusion of subjects with asymptomatic OME; children younger than 2 years of age were not included in some studies and were underrepresented in others; the sickest children often were not selected for these studies; and the antibiotic selected may have been inappropriate and the doses used were often insufficient, all of which would make the efficacy of antimicrobial treatment appear lower.[115] A meta-analysis of studies of AOM with an observation group found that children younger than 2 years of age and those with bilateral AOM were more likely to have prolonged symptoms when not given antimicrobial treatment.[116]

Nonetheless, the practice of not treating AOM immediately with antibiotics, often giving a "backup" prescription in case of persistence of symptoms, is undergoing further scrutiny in this country and elsewhere. McCormick and associates reported their randomized trial of immediate antibiotics plus symptom medication versus symptom medication only in 223 subjects with "nonsevere" AOM, of whom 57% were younger than 2 years of age.[117] At day 12, 69% of TMs and 25% of tympanograms were considered to be normal in the antibiotic group, compared with 51% of TMs and 10% of the tympanograms in the nontreated group; 66% of the watchful-waiting group completed the study without antibiotics. Nasopharyngeal cultures at day 12 of the study revealed that *S. pneumoniae* was eradicated in most of the antibiotic-treated subjects, but the strains that were cultured were more likely to be antibiotic-resistant. Parental satisfaction with the assigned "treatment" was the same in both groups. Spiro and associates randomly assigned children 6 months to 12 years of age diagnosed with AOM (definition left to discretion of physician) to receive either immediate antibiotic treatment or a "wait-and-see" prescription, to be filled if the child was not improving or was worse at 48 hours.[118] In this study, performed in an emergency department population, the mean age of subjects was 3.2 years; approximately 84% had unilateral AOM. The investigators found that 62% of the group given instructions to delay filling the prescription did not fill the prescription, compared with 13% given the instructions to start the medication immediately ($P < 0.001$). The presence of fever or otalgia was associated with filling the prescription.

Vernacchio and coworkers surveyed physicians in a national practice-based pediatric research network regarding their preferred management of AOM.[119] Despite the studies showing that the use of observation or delayed prescribing may allow for spontaneous recovery in many children and the option of observation was offered in the AOM guidelines, they found that although 83% considered observation a "reasonable option," it was used only in a median of 15% of cases.

Medical Treatment

Antibiotics

Many antibiotics are available, but according to American Academy of Pediatrics–American Academy of Family Physicians guidelines,[108] amoxicillin is still the first-line antibiotic for non-severe episodes of AOM and, at 90 mg/kg per day in two divided doses, is recommended to provide coverage for *S. pneumoniae*, including resistant strains. For severe episodes of AOM, amoxicillin–clavulanic acid (amoxicillin 90 mg/kg per day and clavulanic acid 6.4 mg/kg per day in two divided doses) is recommended and will provide coverage for beta-lactamase–producing *H. influenzae* and *M. catarrhalis*. According to these guidelines, cephalosporins should be considered as accepted first-line treatment only for patients with penicillin allergy. Macrolides should be prescribed for patients with penicillin and cephalosporin allergies. Treatment failure is defined as persistence or recurrence of symptoms and signs 48 to 72 hours after institution of initial treatment. In such cases, the diagnosis should then be reassessed and antibiotics started if not given previously or changed to a broader-spectrum agent if antibiotics were previously prescribed (amoxicillin–clavulanic acid if amoxicillin failed to produce improvement and ceftriaxone for 3 days if amoxicillin–clavulanic acid was not effective). Tympanocentesis should always be considered if the child does not respond to the antibiotic treatment, in order to identify the bacteria in the MEE and to select an appropriate antibiotic.

Duration of Treatment

Ten days of antibiotic treatment has been the standard, but in an effort to reduce cost and the incidence of antibiotic resistance, the efficacy of shorter courses has been investigated. Studies have found the 10-day course has resulted in fewer early treatment failures in younger children,[8] in children recently treated for AOM,[120] and in those presenting with spontaneous perforation of the TM,[121] compared with a 5-day course. The recent U.S. guidelines recommend the standard 10-day course of therapy for younger children and for children with severe disease, and for those 6 years of age and older with mild to moderate disease, a 5- to 7-day course may be used.[108] Several short courses of antibiotics have been approved by the FDA for use in AOM. Cefpodoxime proxetil and cefdinir have been approved for a 5-day course; azithromycin may be given for 1-, 3-, and 5-day courses; one dose of IM ceftriaxone may be given, although results for penicillin-resistant *S. pneumoniae* are better with a 3-day course.[122]

Longer courses of antibiotics have also been proposed. In a randomized, double-blind trial of 10 days of amoxicillin versus 20 days of amoxicillin or 10 days of amoxicillin with an additional 10 days of amoxicillin-clavulanate, no advantage in treatment failure or duration of MEE was found with the longer courses.[123]

Decongestants/Antihistamines

A meta-analysis of studies of decongestant-antihistamine preparations for AOM found no benefit of these agents for early cure, symptom resolution, or prevention of surgery or complications. Although some benefit of the combination was found in number of subjects with persistent AOM at the 2-week endpoint, the 5- to 8-fold risk of side effects, along with the fact that finding benefit was inversely correlated with study quality, led the authors to not recommend the routine use of decongestant-antihistamine agents for AOM.[124] In 1994, Chonmaitree and associates reported increased levels of histamine in middle ear fluid from children with AOM and speculated that antihistamine may be clinically beneficial in reducing inflammation.[125] However, in a recent trial for AOM, antihistamine administered with an antibiotic did not result in improved clinical outcome and prolonged the duration of effusion.[126] At this point, neither decongestants or antihistamines, nor their combinations, are recommended for the treatment of AOM.

Steroids

Studies in rats suggested that steroid given with antibiotic reduced inflammatory changes in the middle ear mucosa to a greater extent than treatment with antibiotic alone.[127] McCormick and coworkers found no reduction in histamine or leukotriene B4 in children treated with

oral antibiotic and steroid compared with children receiving antibiotic alone but did find a lower rate of treatment failure during the first 2 weeks and a shorter duration for MEE in those treated with steroids.[128] When a larger sample of subjects was studied, however, the same group of workers found that corticosteroid (2 mg/kg given for 5 days) administered with antibiotic did not provide any improvement in clinical outcome.[126]

Recurrent Acute Otitis Media

Antibiotic Prophylaxis

Many studies have examined the efficacy of antibiotics in preventing AOM in children with frequently recurrent episodes. Many antibiotics have been studied, particularly amoxicillin and sulfisoxazole, used at one-half of their recommended daily dose and given once per day for months. Studies generally have concluded that antimicrobials are effective in preventing disease.[129] This method of managing children with recurrent AOM is not recommended, however, because of the potential for increasing resistant organisms. Rather than daily medicine given for months at a time, treating intermittently at the time of upper respiratory tract symptoms has been tried, but efficacy is less than with continuous medication.[130]

Surgical Treatment

Myringotomy/Tympanocentesis

For episodes of AOM, a myringotomy or tympanocentesis is helpful for relief of pain and allows samples to be obtained for culture to identify the pathogen and to guide in the selection of antibiotics, but provides no advantage in duration of effusion or recurrence of episodes of AOM.[111]

Myringotomy with Tympanostomy Tube Insertion

When preventive and medical treatments for recurrent AOM have failed, tympanostomy tube insertion is recommended. Two recent randomized studies have assessed the efficacy of tympanostomy tube insertion for recurrent AOM. A randomized clinical trial to evaluate the efficacy of myringotomy with tympanostomy tube insertion (M&T) versus sulfisoxazole prophylaxis versus placebo enrolled 65 children 4 years or younger with recurrent AOM and followed them for 6 months or longer.[131] Treatment failure was defined as two episodes of AOM or otorrhea in less than 3 months. Five of 22 children in the M&T group experienced treatment failure, compared with 12 of 20 children in the placebo group ($P = 0.02$) and 8 of 21 children in the prophylaxis group. In a similar study to determine the efficacy of amoxicillin prophylaxis versus M&T versus placebo, 264 children 7 to 35 months of age with recurrent AOM were randomized to one of the three treatment arms and followed for 2 years.[132] The average proportion of time with OM (AOM or otorrhea) was 10% in the amoxicillin, 15% in the placebo, and 6.6% in the tube groups (placebo versus tube; $P < 0.001$). Rates of new episodes of any type per child was 0.6 in the amoxicillin, 1.08 in the placebo, and 1.02 in the tube groups (amoxicillin versus placebo; $P < 0.001$). The low rate of new episodes must be viewed in light of the fact that the study subjects proved not to be at as high risk for AOM as had been anticipated. However, in comparison with children who received placebo, children with tympanostomy tubes spent less time with OM. It should be kept in mind that episodes of otorrhea with tympanostomy tubes usually are less severe, without fever and otalgia, and in most cases resolve with ototopical drops and do not require oral antibiotics.

For children with recurrent episodes of AOM, usually defined as three or more episodes of AOM in 6 months or four or more episodes in 12 months, insertion of tympanostomy tubes is an option.

Adenoidectomy with and without Tonsillectomy

Two parallel randomized clinical trials compared the efficacy of adenoidectomy and adenotonsillectomy in 461 children 3 to 15 years of age with persistent or recurrent otitis media who had not previously undergone tympanostomy tube placement.[133] Children without recurrent throat infections were randomized to undergo adenoidectomy, adenotonsillectomy, or no surgery (no adenoidectomy or adenotonsillectomy), and children with recurrent throat infections, to undergo adenotonsillectomy or no surgery. A majority of children (91%) had a history of recurrent AOM. The benefit of surgery in both trials was modest and limited mainly to the first follow-up year. The largest difference was in the three-way trial between adenotonsillectomy and no surgery, with a mean annual AOM rate of 1.4 versus 2.1 ($P < 0.001$) and mean estimated percentage of time with otitis media of 18.6% versus 29.9% ($P = 0.002$). Based on the short-term efficacy of adenoidectomy and adenotonsillectomy as well as the morbidity rate and cost of these procedures, it was suggested that neither should be considered as the initial surgical procedure.

In a randomized clinical trial assessing the efficacy of adenoidectomy versus placebo versus long-term antimicrobial prophylaxis in preventing episodes of recurrent AOM, 180 children 10 to 24 months of age were enrolled and followed for 24 months. No significant difference was observed between the groups in the numbers of episodes of AOM, visits to doctors, antibiotic prescriptions, and days with symptoms of respiratory infection. The investigators concluded that adenoidectomy cannot be recommended as the primary treatment in this age group.[134]

Hammarén-Malmi and colleagues conducted a clinical trial in children 12 to 48 months of age with recurrent AOM (three or more episodes in 6 months or five or more episodes in 12 months) to evaluate the efficacy of adenoidectomy in children receiving tympanostomy tubes.[81] The children were randomized to undergo tympanostomy tube insertion (i.e., bilateral myringotomy with tube insertion) with or without adenoidectomy. During the follow-up period of 12 months, the mean number of AOM episodes was 1.7 for children in the adenoidectomy plus tube insertion group, compared with 1.4 in children in the tube insertion–only group. Adenoidectomy at time of tympanostomy tube insertion does not significantly reduce the incidence of AOM in otitis-prone children younger than 4 years of age.

Adenoidectomy may provide modest improvement in children with recurrent AOM but is not recommended as a first-line procedure unless indicated for airway obstruction. Tonsillectomy, in conjunction with adenoidectomy, provides no significant advantage over adenoidectomy alone, and the risks outweigh the benefits.

Otitis Media with Effusion

Observation

For children not at risk for speech and language or learning disabilities, "watchful waiting" may be appropriate. Hearing testing should be done if MEE persists for 3 months or longer or at any time that language delay, learning difficulties or significant hearing loss is suspected. If the average hearing level is below 20 dB, watchful waiting is suggested, but if it is greater than 40 dB in the better ear, surgery is recommended. For children with hearing levels in the better ear between 21 and 39 dB, management is based on the duration of effusion and severity of symptoms. For children not at risk, examination at 3- to 6-month intervals until the fluid has resolved, hearing loss, language, or learning delays are identified or there are suspected structural abnormalities of the ear drum, is recommended.[108]

Medical Treatment

Decongestant/Antihistamine

Decongestant with or without antihistamine was a popular treatment for OME, but clinical trials found no efficacy of these medications.[135-138] In studies of OME at the Children's Hospital of Pittsburgh, no efficacy was found for an oral decongestant-antihistamine combination given either alone[139] or with an antimicrobial agent.[140]

Antibiotics

Antibiotics came into prominence as treatment for OME toward the end of the 1970s and beginning of the 1980s, when studies showed the ineffectiveness of decongestant-antihistamine combinations. In addition, although effusions were thought to be sterile, studies showed that specimens from asymptomatic children with MEE contained bacte-

ria.[11,141] Mandel and associates reported the results of their double-blind, randomized trial in which 518 children with OME of varying durations were divided into three treatment groups: (1) amoxicillin (40 mg/kg/day) for 14 days plus a decongestant/antihistamine combination for 28 days; (2) amoxicillin for 14 days plus placebo for decongestant/antihistamine for 28 days, or (3) placebo for both amoxicillin and decongestant/antihistamine.[140] At 4 weeks, the rate of resolution of MEE was twice as high in those treated with amoxicillin, with or without a decongestant-antihistamine agent, as those who received placebo (percentages of effusion-free: 31.6%, 28.8%, and 14.1% in the amoxicillin plus decongestant-antihistamine, amoxicillin alone, and placebo groups, respectively); the addition of the decongestant-antihistamine made no difference. Recurrence of effusion occurred in most subjects within 3 months after completion of treatment. Other antibiotics, including amoxicillin-clavulanate, ceftibuten, and penicillin, have been tested in clinical trials to determine whether all antibiotics had the same efficacy, but none has been clearly shown to have any long-term advantage over the others.[142-144] Mandel and associates compared the efficacies of cefaclor and erythromycin-sulfisoxazole to that of amoxicillin.[145] Besides not being better than placebo, cefaclor and erythromycin-sulfisoxazole showed no increased efficacy at 2 and 4 weeks after starting treatment compared with amoxicillin. Antibiotic used in prophylactic doses (generally half the total daily dose used for AOM, given once daily for months) has also been examined in the treatment of OME, but its efficacy is linked more to preventing AOM than treating OME.[146] Despite short-term efficacy, antibiotics are not recommended for routine treatment of OME, due to lack of long-term efficacy, the high spontaneous cure rate, and concern about overuse of antibiotics.[129,147]

Steroids

Theoretically, glucocorticoids should be efficacious in the treatment of OME: Anti-inflammatory properties are due to inhibition of phospholipase A_2, which then inhibits formation of arachidonic acid and the subsequent synthesis of inflammatory mediators; up-regulation of transepithelial sodium transport promotes fluid removal from the middle ear; and decreasing mucin production by suppressing MUC5AC.[148] In clinical trials, systemic steroids have demonstrated an advantage over placebo in resolving MEE, but owing to the high recurrence rate after treatment, steroids are not recommended for long-term management.[149]

Because of the side effects with use of systemic steroid, especially for prolonged courses of treatment, other routes of administration have been investigated. Tracy and colleagues used prophylactic antibiotics with and without (both an untreated group and a placebo group) intranasal beclomethasone to treat 59 children with chronic OME and recurrent AOM.[150] Although all groups improved initially, no difference in OME resolution was observed by the 12-week visit. Cengel and Akyol found, in a nonblinded, randomized (every other subject assigned to active treatment with nasal mometasone spray for 6 weeks, with the remaining subjects assigned to no treatment) study of patients with documented MEE of at least 3 months' duration, 42.2% of treated subjects resolved at 6 weeks, compared with 14.5% of untreated subjects ($P < 0.001$); no long-term follow-up was reported.[151]

Autoinflation

Popularized by Politzer more than 100 years ago, devices to insufflate air through the eustachian tube have been tried for the treatment of OME. However, studies using a number of devices have failed to show consistent efficacy,[152-155] so autoinflation is not recommended for routine use at this time. In their meta-analysis, Perera and associates concluded that because of its low cost and absence of adverse effects, autoinflation might be considered for use while awaiting spontaneous resolution of the effusion.[155]

Surgical Treatment

Myringotomy

Myringotomy alone has been shown to be ineffective for long-term management and is not recommended for chronic OME.[156,157] Laser-assisted myringotomy has been described as an alternative to the standard myringotomy in children with chronic OME, and the procedure can be done using local anesthesia and is considered safe. However, the mean time to closure of the perforation is only 2 to 3 weeks.[158,159]

Myringotomy with Tympanostomy Tube Insertion

In children with persistent MEE, the decision of whether to insert tympanostomy tubes is based on the child's hearing status and risk for developmental problems. Several randomized clinical trials have demonstrated evidence-based indications for the use of tympanostomy tube insertion for chronic OME.

The efficacy of M&T for the management of OME has been the subject of many studies. Mandel and coworkers reported the results of a 3-year clinical trial of 109 children, 7 months to 12 years of age, with OME of 2 months' duration or longer who were unresponsive to medical management and who were randomly assigned to receive myringotomy alone, M&T, or no surgery.[160] During the first year, over 50% of subjects in the myringotomy-only and the no surgery groups met preset treatment failure criteria and underwent M&T. A second study designed to correct some of the design flaws of the first study and to extend the time until treatment failure involved 111 children with OME for at least 2 months and whose pure-tone averages bilaterally were 35 dB or less.[157] This study also found high rates of treatment failure in children in the myringotomy-only group (70%) and the no surgery group (56%). The percentages of time with MEE during the first year in the myringotomy-only, M&T, and no surgery groups were 61%, 17%, and 64%, respectively ($P < 0.001$). From these studies, it was concluded that myringotomy offered no advantage over no surgery in regard to percentage of time with effusion, number of AOM episodes, and number of repeat surgical procedures, and M&T provided more disease-free time and better hearing than myringotomy only or no surgery.

Gates and associates studied the effects of various surgical treatments in children 4 to 8 years of age with chronic OME; 127 children were randomly assigned to undergo myringotomy and 150 were assigned to undergo M&T.[156] Compared with myringotomy only, M&T provided less time with effusion and more time with better hearing, and necessitated fewer surgical retreatments.

The previously mentioned studies[157,160] were performed at a time when it was considered "unethical" to allow a child to have MEE for more than 2 to 3 months because of the associated hearing loss and the possible detrimental effects on speech and language development. A more recent study by Paradise and colleagues randomly assigned 429 children younger than 3 years of age with persistent or recurrent OME either to prompt M&T or to M&T up to 9 months later.[84] Eighty-five percent of children in the promptly treated group and 41% of children in the late treatment group had undergone M&T by 6 years of age. On developmental testing at 6 years, there were no significant differences between the groups on 30 measures. Of interest, in both the randomized clinical trial and in children randomly selected from those followed in the study but who did not meet criteria for randomization, sociodemographic variables seemed to be the most important factors influencing developmental outcomes.

Adenoidectomy

A study by Maw enrolling children 2 to 11 years of age with chronic OME showed that adenoidectomy alone and M&T alone provided better results than no surgery, but the combination of the two surgical procedures provided better results than either alone.[161] The addition of tonsillectomy to adenoidectomy provided no additional benefit for middle ear fluid resolution. In the previously discussed study by Gates and associates,[156] the children randomly assigned to the adenoidectomy-myringotomy and the adenoidectomy-M&T groups both had a lower percentage of time with effusion than those who received M&T alone. Thus, on the basis of these results, Gates and associates recommended adenoidectomy-myringotomy as the first-line procedure.[156]

Paradise and colleagues studied 213 children 1 to 15 years old with recurrent AOM or OME who had previously had M&T.[162] Children were randomly assigned to undergo adenoidectomy or no ade-

noidectomy; M&T was also performed at the same time for specific indications. Among the 99 subjects who were randomized, a significant reduction in time with otitis media during the first 2 years was observed in the children who underwent adenoidectomy, in comparison with those who did not. For the remaining children, whose parents chose not to allow random assignment, the results favored adenoidectomy over no adenoidectomy.

A clinical trial enrolling 98 children ranging in age from 24 to 47 months who had bilateral OME for 3 months or longer, or unilateral OME for 6 months or longer, or recurrence of effusion after extrusion of previously placed tympanostomy tubes, randomized the subjects to undergo M&T versus adenoidectomy and myringotomy with and without insertion of tubes.[163] Adenoidectomy with M&T provided no advantage over M&T alone (11.9% versus 18.1%; $P = 0.12$) in regard to mean percentage of time with MEE during the 18-month follow-up period. However, the mean percentage of time with MEE in the adenoidectomy-myringotomy alone group (35.7%) was significantly higher than in both the M&T and the adenoidectomy-M&T groups ($P < 0.001$ and $P = 0.003$, respectively). Also, in the adenoidectomy plus myringotomy group, 25% of the children subsequently needed an additional procedure (M&T), compared with less than 10% in the two groups with initial M&T.

Several retrospective studies have looked at the efficacy of adenoidectomy in addition to M&T. Boston and associates evaluated risk factors for additional tube insertion in 2121 patients undergoing bilateral M&T.[164] In 19.9% of the children, two or more tube insertions were performed. After the initial tube insertion, as many as 45.1% of the patients needed an additional surgical procedure (tube insertion, adenoidectomy, or tonsillectomy with or without adenoidectomy). Patients younger than 18 months at the initial procedure were significantly more likely to have a second procedure (26.3% versus 15.9%; $P < 0.001$). Adenoidectomy was performed at the time of the initial tube insertion in 527 patients (24.5%). This reduced the probability of needing a second set of tubes (0.08 versus 0.24; $P < 0.001$). Also, the probability of needing a third set of tubes was reduced when adenoidectomy was performed at or before placement of the second set of tubes (0.15 versus 0.40; $P < 0.001$). The presence of craniofacial abnormalities and a family history of adenoidectomy, tonsillectomy, or tube insertion increased the likelihood of need for subsequent tube insertions ($P < 0.001$). Sex and race were not risk factors for subsequent tube insertion.[164]

Another retrospective study evaluated the effect of adjuvant adenoidectomy or adenotonsillectomy at time of tympanostomy tube insertion on the rate of reinsertion of tubes and re-hospitalization for otitis media–related conditions in 37,316 Canadian children (≤19 years) for whom tube insertion was their first surgical procedure.[165] Compared with tube insertion alone, adenoidectomy was associated with a reduction in the likelihood of reinsertion of tubes (relative risk [RR]: 0.5; 95% CI: 0.5-0.6; $P < 0.001$), as was adenotonsillectomy (RR: 0.5; 95% CI: 0.5-0.6; $P < 0.001$). Performing adenoidectomy or adenotonsillectomy at the time of the initial tympanostomy tube insertion substantially reduced the likelihood of additional hospitalization and operations related to otitis media among children 2 years of age or older.

A third large retrospective study assessing the benefits of adjuvant pharyngeal surgery (adenoidectomy, adenotonsillectomy and tonsillectomy) at the time of tympanostomy tube insertion examined the records of 51,373 children less than 10 years of age.[166] Twenty-nine percent of the children had pharyngeal surgery at the time of the first tube insertion. The study authors concluded that having adenoidectomy or adenotonsillectomy at the time of first or subsequent tube insertion was associated with reduced risk of further tube insertion.

Guidelines

In 2004 a revised Clinical Practical Guidelines for OME was published jointly by the American Academy of Family Physicians, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Academy of Pediatrics.[108] The guidelines were evidence-based, and the quality of the evidence was assessed. The recommendations reflected the quality of the evidence and the balance between benefit and harm that is anticipated when recommendations are followed. The guidelines apply to children 2 months through 12 years of age with and without developmental disabilities or underlying conditions that predispose to OME and its sequelae. The decision regarding surgery for OME depends largely on hearing status, associated symptoms, the child's developmental risk, and the anticipated chance of timely spontaneous resolution of the effusion. Surgical candidates are children with (1) OME lasting 4 months or longer with persistent hearing loss or other signs or symptoms; (2) recurrent or persistent OME associated with increased risk of developmental problems regardless of hearing status; and (3) OME and structural damage to the TM or middle ear.

Tympanostomy tube insertion is the initial preferred procedure. Adenoidectomy should not be performed except for a specific indication (i.e., nasal obstruction, chronic adenoiditis). Repeat surgery consists of adenoidectomy plus myringotomy with or without tympanostomy tube insertion. Tonsillectomy alone or myringotomy alone should not be used to treat OME.

Quality of Life Assessment

The first validated quality of life (QOL) outcome study for otitis media used the OM-6 instrument developed by Rosenfeld and associates, representing six domains: physical stress, hearing loss, speech impairment, emotional distress, activity limitation, and caregivers' concerns.[167] Large, moderate, and small improvements after tympanostomy tube insertion were documented in 56%, 15%, and 8% of children, respectively, using this instrument.[168] Trivial changes were noticed in 17% of children and 4% of children had a poor outcome after tube insertion. The results indicate that tympanostomy tube insertion produces large short-term improvement in QOL for most children.

A QOL outcome study assessed the parents' appreciation of their child's general condition using the OM-6 scale before, after, and retrospectively before tube insertion in a group of Dutch children 12 to 36 months of age.[169] The results from the retrospective assessment of the child's general condition prior to tube insertion indicated that the parents underestimated the effects of otitis media before surgery. In particular, after tube insertion, parents were able to appreciate the extent of presurgical hearing loss.

Surgical Issues

Tympanostomy Tube Placement

Rationale

Myringotomy and tympanostomy tube insertion is currently the most common surgical procedure in children that requires general anesthesia. Insertion of a tympanostomy tube promotes ventilation of the middle ear and drainage through both the eustachian tube and the tympanostomy tube. Also the aeration of the middle ear may promote normalization of the middle ear mucosa. The removal of MEE restores the conductive hearing loss. However, reflux of nasopharyngeal secretions may occur in an ear with a tympanostomy tube, causing otorrhea due to loss of the middle ear air cushion effect.

Procedure

In most children insertion of tympanostomy tubes is performed under general mask anesthesia. In older children who are cooperative tympanostomy tube insertion could be performed using topical anesthesia such as phenol or lidocaine delivered by iontophoresis.

The procedure should be performed using a binocular operating microscope. After satisfactory removal of cerumen and debris the entire TM should be inspected to rule out any abnormalities. The myringotomy incision is performed in the anterior-superior or anterior-inferior quadrant of the pars tensa. A radial incision is made small enough to prevent premature tube extrusion but large enough that the tube can be easily inserted using an alligator forceps. If MEE is present, it should be aspirated. When the effusion is purulent or mucopurulent, it should be aspirated into a Juhn trap or Alden-Senturia trap and sent for culture (Fig. 194-5). If the MEE is too thick to be aspirated through the myringotomy incision with a large suction tip, a counterincision is

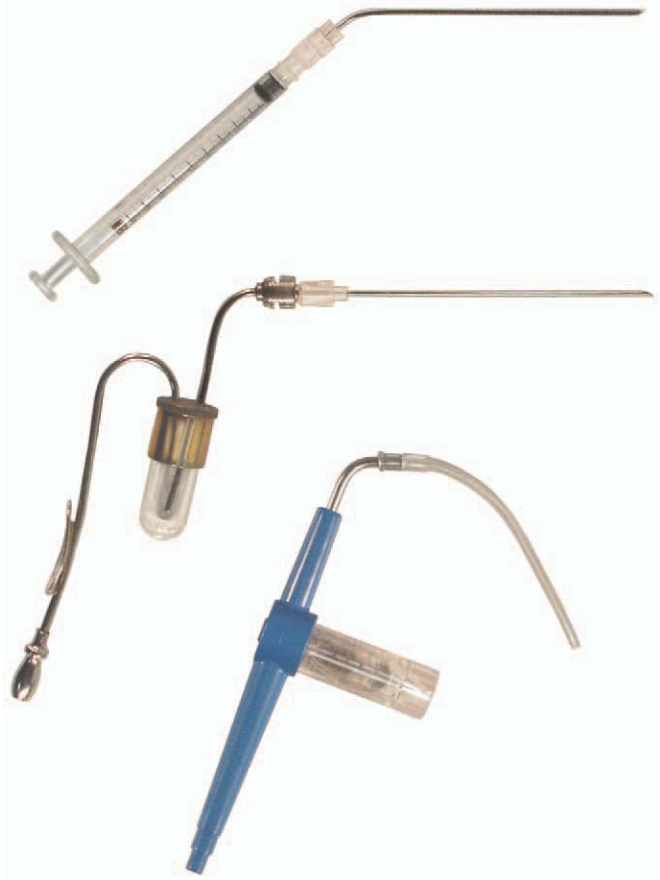

Figure 194-5. Collection vehicles for aspiration of middle ear effusions. *Top to bottom*: Syringe with spinal needle; Alden Senturia trap; Juhn Tym-Tap.

made in the inferior part of the tympanic membrane or sterile saline is placed in the canal or through the myringotomy to enhance the aspiration of the viscous fluid. There is still controversy regarding the best place to insert the tympanostomy tube. The anterosuperior quadrant is associated with a longer clincial tube life; however, a persistent perforation in that area is somewhat more difficult to repair.

Selection of Tympanostomy Tubes and Indications

Many different tympanostomy tubes have been developed, but most tympanostomy tubes are variations of the grommet or the T-tube. The duration of time before extrusion is shorter for grommet tubes than for T-tubes. Weigel and associates performed a randomized prospective trial of four different types of tympanostomy tubes in 75 children.[170] During the first 2 years, 93% of Shepard tubes, 80% of Armstrong tubes, 66% of Reuter-Bobbin tubes, and 31% of Goode T-tubes had extruded. In studies from Pittsburgh, the clinical life of the Armstrong-type tube was approximately 1 year; 50% had extruded by 12 months, and 75% by 18 months.[157] The time to extrusion is a function of the size, shape of the medial flange, absence of a lateral flange, and the material of the tube. Also, the coating of the tube may affect the time to extrusion, because it may prevent infections.[171,172]

In a young child with a history of recurrent or persistent otitis media, a tympanostomy tube that remains in place for at least a year is preferable. If the child has recurrent otitis media after the tubes have become nonfunctional or extruded, a similar type of tube should be recommended. Grommets with shorter duration are recommended in older children, who may not continue to have problems after the then current season. T-tubes or long-term tubes are recommended for older children with persistent problems due to poor eustachian tube function. These tubes also are recommended for children who have an atrophic TM after going through multiple sets of tympanostomy tubes, because a regular grommet tube may be very quickly extruded.

Perioperative and Postoperative Ototopical Drops

In an effort to reduce early postoperative otorrhea and tube blockage, use of ototopical antimicrobial drops at the time of surgery has been recommended, especially if MEE is present.[173,174] Only FDA-approved ototopical agents such as ofloxacin (Floxin) and ciprofloxacin (Ciprodex) should be considered.

Postsurgical Follow-up

All patients should return for a follow-up visit a few weeks after the surgery for an otoscopic examination to assess the status of the tympanostomy tube. Patients with a hearing loss documented preoperatively should have a repeat hearing evaluation postoperatively. Patients who did not have a preoperative hearing test should be examined postoperatively to document that the hearing is normal. Patients usually are evaluated 6 to 12 months after the insertion of the tubes and every 6 months thereafter, or when problems occur, to assess the status of the tubes and the TM.

Complications and Sequelae

Otorrhea

Otorrhea through a tube or perforation is a common problem after tympanostomy tube insertion and has been recorded in as many as 50% of children with tympanostomy tubes.[175] Transient otorrhea occurred in the postoperative period in 16% (range, 8.8 to 42.0) and later in 26% (range, 4.3 to 68.2) of patients; recurrent otorrhea occurred in 7.4% (range, 0.7 to 19.6), and chronic otorrhea in 3.4% (range, 1.4 to 9.9) of patients.[176] If untreated, acute otorrhea can develop into chronic suppurative otitis media. Pathogens typical of AOM (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes*) were found in 42% and *P. aeruginosa* and *S. aureus* in 44% of all episodes of acute otorrhea in 246 children with tympanostomy tubes followed prospectively.[175] The typical AOM pathogens were more common in children under 6 years of age than in older children (50% versus 4.4%; $P < 0.001$). *P. aeruginosa* was more common in children 6 years of age or older than in the younger children (43.5% versus 20.5%; $P = 0.052$). Roland and colleagues obtained 1309 isolates from 956 acutely draining ears and identified *S. pneumoniae* in 17%, *H. influenzae* in 18%, *S. aureus* in 13%, *P. aeruginosa* in 12%, and fungus in 5%.[177] Several clinical trials have demonstrated that ototopical agents such as ofloxacin otic solution and ciprofloxacin-dexamethasone otic suspension are effective when acute otorrhea occurs through a tympanostomy tube or perforation, even when no systemic antibiotic is given.[178] In a child who has severe systemic symptoms, a systemic antibiotic should be added. The ciprofloxacin-dexamethasone combination has been shown to be superior to ofloxacin in resolving granulation tissue.[179] The use of other ototopical agents in ears with a nonintact TM has not been approved by the FDA, because they can be ototoxic, especially those that contain aminoglycoside. If the drainage does not resolve in 7 to 10 days, suctioning of the ear canal should be performed and a culture specimen from the opening of the tube should be obtained to determine the causative pathogen. If yeast is the predominant organism, treatment with a topical antifungal drop such as clotrimazole should be initiated. Repeated aural toilet is a very important part of the treatment. Compliance with a regimen of frequent suctioning may be difficult for both the child and the parent, however. If aural toilet and topical treatment fail to produce improvement and the organisms are not sensitive to oral antibiotics, then intravenous antibiotics, removal of the tube(s), or simple mastoidectomy should be considered. CT scan of the temporal bones should be obtained before possible mastoidectomy, to look for complications such as coalescent mastoiditis. In older children with recurrent episodes of otorrhea, removal of the tubes is the treatment of choice, because in these children the eustachian tube may have matured and secretion from the nasopharynx may be refluxing into the middle ear. Also, the tube occasionally may act as a foreign body, causing a foreign body reaction with granulation tissue formation and infections.

Recently, biofilms were identified on a tympanostomy tube removed from a child with a chronic draining ear.[180]

Tympanosclerosis, Atrophy, and Retraction Pockets

A meta-analysis reviewing 134 articles estimated the incidence of TM sequelae after tube extrusion and reported that tympanosclerosis occurred in 32% (range, 7.2 to 64.3), focal atrophy in 25% (range, 1.6 to 75.0), and retraction pockets in 3.1% (range, 0 to 22.7) of ears.[176] The type of tube (short-term versus long-term) had no significant impact on these rates.

The sequelae of tympanostomy tube insertion in children with chronic OME followed for 8 years was reported by Daly and associates.[181] One hundred thirty-eight children (275 ears) followed for 3 years and 84 of these children (167 ears) followed for 8 years were evaluated in regard to TM myringosclerosis, atrophy, retraction pockets or perforations, hearing loss, and static admittance. In general, the annual incidence of sequelae was greater at the 4- to 5-year follow-up than at the 6- to 8-year follow-up. Although atrophy developed in 67% of the ears, myringosclerosis in 40%, and perforation in 3% between the 3- and 8-year follow-up evaluations, the annual risk of new sequelae declined considerably throughout the 3- to 8-year follow-up period for most sequelae studied. However, atrophy and pars tensa or pars flaccida retraction were present in 55% of ears at the 8-year follow-up evaluation, which may put children at risk for continuing middle ear problems during adolescence and adulthood. These results support the need for long-term follow-up in selected patients.

In reporting the incidence of TM abnormalities in children in the previously cited trial[84] of prompt versus delayed tube insertion, Johnston and associates noted that in children who underwent intubation, segmental atrophy and tympanosclerosis at age 5 years were more common than in children who did not receive tubes.[182] These workers found no significant relationship between hearing levels at 6 years of age and the presence or type of TM abnormalities.

Persistent Perforation

The incidence of persistent perforation after extrusion of tympanostomy tubes has been estimated at 4.8% (for short-term tubes, 2.2% [range, 0 to 12.3%]; for long-term tubes, 16.6% [range, 0 to 47.0%]).[176] Also, long-term tubes increased the relative risk of perforation by 3.5 (95% CI: 2.6 to 4.9) over that for short-term tubes. The perforations caused by tympanostomy tubes usually are small; consequently, hearing loss is very mild. The perforations are easily managed with a simple fat graft or surgical gel (Gelfoam), paper patch, or Steri-strip myringoplasty. Sckolnick and associates recently found that the success rate with Gelfoam myringoplasty was higher than with fat graft or paper patch.[183] Before closing the perforation, it is important to ensure that eustachian tube function is good; otherwise, there is a risk of nonclosure or reaccumulation of fluid in the middle ear. As a rule, the TM in the opposite ear should be intact and free of infection for 1 year.

Cholesteatoma

For all types of tubes, the combined incidence of cholesteatoma is 0.7%, but for short-term tubes, the incidence is 0.8% (range, 0 to 6.5) and for long-term tubes 1.4% (range, 0 to 3.0).[176] Any of several mechanisms may be responsible for the development of cholesteatomas. Tympanostomy tubes may be inserted to prevent the development of cholesteatoma in a retraction pocket. However, cholest atoma may result from ingrowth or transplantation of keratinized epithelium into the middle ear cleft around a tympanostomy tube. Also, an intratympanic cholesteatoma may develop after surgical manipulation of the TM. Patients with tympanostomy tubes require regular follow-up during the time the tubes are in place and after extrusion to assess the TM and middle ear for cholesteatoma development.

Early Extrusion

Premature extrusion of tubes occurs in approximately 3.9% of ears.[176] This is most likely due to infection in the middle ear that pushes the tube into the external ear canal. The tube may not have been properly inserted, especially if the TM is thickened owing to an infection at the time of tube insertion. An atrophic TM also may allow early tube extrusion.

Tube Blockage

The lumen of the tympanostomy tube may become obstructed from dried blood or mucus, granulation tissue or a polyp caused by infections in the middle ear. The incidence of plugging of the tube is 6.9% (range, 0 to 37.3) of ears.[176] The tube sometimes can be unplugged using a pick, suction, a Rosen needle or ototopical drops for 10 to 14 days. If the blockage cannot be resolved but the middle ear is effusion-free with normal middle ear pressure, the tube can be left in place and watched until extrusion. On the other hand, if fluid has accumulated in the middle ear or recurrent infections continue, replacement of the tube may be indicated.

Tube Displacement into the Middle Ear

The incidence of displacement of a tympanostomy tube into the middle ear is 0.5% (range, 0 to 1.3).[176] It occurs most commonly at the time of surgery, but it can also be seen later due to infection or trauma, which is very rare. If the tube is displaced into the middle ear during surgery, attempts should be made to retrieve the tube at the time of surgery. However, if a tube is visualized behind an intact TM, risks versus benefits have to be assessed, because a child would require general anesthesia and an incision of the TM to retrieve the tube. A tympanostomy tube displaced behind an intact TM rarely causes problems.

Retained Tympanostomy Tubes

A tympanostomy tube usually is not removed surgically, because most tubes extrude spontaneously. In some children, however, the tube remains in place in the TM and has to be removed surgically. Indications for removing a tympanostomy tube include the following clinical scenarios:

- Retention of one tube after extrusion of the other tube if the middle ear has been free of disease for 1 year or longer in a child 5 to 6 years old or older
- Bilateral retained tubes in an older child with good eustachian tube function
- Chronic or recurrent episodes of otorrhea that are not able to be managed medically, especially in an older child who previously has not had recurrent episodes of otorrhea, because this could be a sign of reflux of secretions from the nasopharynx due to maturation of the eustachian tube
- Blockage of a tympanostomy tube that has become embedded in granulation tissue

In children, most retained grommet, short-term tubes usually are removed with the patient under general anesthesia. After the tube has been removed, a paper patch or Gelfoam myringoplasty is performed. Soft long-term T-tubes may be removed in the office in older cooperative children. In these children, follow-up is esssential to see if the perforation closes spontaneously or requires myringoplasty.

Water Precautions

Several studies have been published, including two meta-analyses[184,185] demonstrating no increase in episodes of otorrhea in patients with tympanostomy tubes not using water precautions over the number of episodes of otorrhea in those using water precautions. In a clinical trial to assess the need for water precautions after insertion of tympanostomy tubes, 201 children, 6 months to 6 years of age, were randomized to swimming and bathing with and without ear plugs and evaluated monthly for 1 year and whenever an episode of otorrhea occurred.[186] At least one episode of otorrhea was documented in 47% of children who used ear plugs, compared with 56% in children with no ear plugs ($P = 0.21$). The mean rate of otorrhea per month for children who used ear plugs was 0.07, versus 0.10 for children not using ear plugs ($P = 0.05$). Although children who do not use ear plugs have a higher inci-

dence of episodes of otorrhea, the clinical impact of using ear plugs is small, and their use should be individualized, rather than recommended on a routine basis.

A clinical survey was conducted in the Pacific Northwest to determine the recommendations given to parents and patients regarding water precautions for swimming with tympanostomy tubes.[187] A total of 263 physicians returned the survey (23.5% response rate). As indicated by the survey findings, most primary care physicians (83%) and approximately one half of the otolaryngologists (47%) still recommend water precautions for swimming with tympanostomy tubes.

Adenoidectomy

Rationale for Adenoidectomy

The rationale for removal of the adenoids in children with otitis media is that the enlargement of the adenoids may cause obstruction of the nasopharynx and blockage of the eustachian tube, preventing ventilation of the middle ear–mastoid system.[188] Also, the adenoid tissue in children with otitis media has been found to have increased bacterial colonization, which may predispose to recurrent infections.[189] Coticchia and associates have demonstrated that the adenoids are covered with biofilm, which may act as a reservoir for bacteria causing middle ear disease.[20] This may explain the clinical improvement obtained after mechanical débridement of the adenoids. The effect of adenoidectomy for children with otitis media is independent of the size of the adenoids.[156,162]

Procedure

Adenoidectomy requires general anesthesia accomplished by either endotracheal intubation or laryngeal mask anesthesia (LMA) and is performed using many different techniques, including curettage, electocautery, microsurgical débridement, or coblation to remove the midline adenoid tissue. The adenoidectomy is completed when the choanae are completely opened and the nasopharynx has a smooth, level contour. Care should be taken to avoid injury to the torus tubarius, which may potentially result in stenosis and eustachian tube dysfunction. In children with submucous cleft palate without airway obstruction, adenoidectomy is not recommended for otitis media because of the risk of velopharyngeal insufficiency. If obstruction exists, partial superior adenoidectomy should be performed, leaving an inferior strip of adenoid tissue for palate closure. Other complications include bleeding, respiratory distress, and atlantoaxial subluxation, which are rare.

Complications and Sequelae of Otitis Media

Complications and sequelae of otitis media are *intratemporal* (extracranial, i.e., temporal bone or neck) or *intracranial* (within the cranial cavity). The intracranial complications are rare in developed countries but are still common in developing nations.

A judicious approach to the use of antimicrobial therapy, including observation without antimicrobials for AOM, has been promoted by guidelines in many different countries owing to the development of increased bacterial resistance to the most common antibiotics. However, delaying antimicrobial therapy may increase the risk for development of complications. Schilder and coworkers compared the national prescription rate of antibiotics for AOM and the national incidence rate of acute mastoiditis across countries.[190] The study showed a slightly higher incidence rate of acute mastoiditis in children (i.e., approximately 4 per 100,000 person–years) in the Netherlands, where only 31% of patients with AOM receive antibiotics, as compared with 2 per 100,000 person-years in the United States, where almost all cases of AOM are treated with antibiotics. More recent studies have shown that use of antibiotics to treat AOM in children may not influence the subsequent development of acute mastoiditis.[191] Also, there is no difference in the proportion of pediatric mastoiditis caused by *S. pneumoniae* in the preconjugated pneumococcal vaccine era versus the postvaccine era.[192]

Intratemporal Complications

The intratemporal complications of otitis media include hearing loss, vestibular and balance problems, acute perforation of the TM, mastoiditis, petrositis, labyrinthitis, and facial paralysis. The intratemporal sequelae include chronic suppurative otitis media, atelectatsis of the middle ear, adhesive otitis media, cholesteatoma, cholesterol granuloma, tympanosclerosis, and ossicular discontinuity and fixation with hearing loss.

Hearing Loss and Balance Problems

Most children with MEE have hearing loss that can be fluctuating or persistent. It usually is a mild to moderate conductive loss averaging between 20 and 30 dB.[193] Rarely, a permanent sensorineural hearing loss may result from AOM or OME, possibly as a result of spread of the infection through the round or oval window or a suppurative complication. Behavioral hearing thresholds in the high frequencies (12 to 20 kHz) are significantly higher in children with a history of otitis media when the middle ear was effusion free.[194]

During an episode with MEE, balance and vestibular function seem to deteriorate, and when the effusion resolves or tympanostomy tubes are inserted, these functions improve.[55] Also, children with otitis media may be more visually dependent as a result of the deterioration of vestibular function causing excessive reliance on other nonvestibular sensory cues to maintain balance.[195] Children may have delayed development of motor coordination skills, such as walking or manipulating their environment; the resultant "clumsiness" may make them more accident-prone. Stenström and Ingvarsson reported that Swedish otitis-prone children were seen more often in the orthopedic and general surgery departments compared with children who were not otitis-prone.[196]

Speech-Language and Child Development

Many studies have investigated the association between otitis media and child development. Some studies have found an association, whereas others have failed to do so. In a recent article, Paradise and coworkers reported that there was no difference between children with otitis media with early versus late tympanostomy tube insertion with regard to hearing, speech-language, and developmental testing.[197] As indicated in the OME Guidelines,[108] however, it is recommended that children with OME undergo hearing testing every 3 to 6 months and be assessed for tympanostomy tube placement if they are at risk for any developmental difficulties due to otitis media, such as significant speech delay.

Mastoiditis

Mastoiditis remains the most common suppurative complication of AOM. Mastoiditis without periosteitis or osteitis most likely represents a continuation of the middle ear inflammation as the mastoid air cell system is in continuity with the middle ear. In acute mastoiditis with periosteitis the infection has spread to the periosteum covering the mastoid process. The spread from the mastoid cells to the periosteum usually is through the mastoid emissary veins. In acute mastoiditis with osteitis with and without subperiosteal abscess the infection can cause destruction of the mastoid cells, leading to "coalescence" of the cells (i.e., mastoid empyema), and present as a subperiosteal abscess. The infection also may spread medially to the petrous bone (petrositis), the labyrinth (labyrinthitis), and neck (Bezold's abscess) and involve the facial nerve or extend into the intracranial cavity.

The diagnosis is made by physical examination and imaging studies such as CT scans and MRI. In the early stage, there are no specific signs and symptoms of mastoid infection with later progression to erythema and tenderness over the mastoid area, to edema or a subperiosteal abscess with displacement of the pinna inferiorly and anteriorly and obliteration of the postauricular crease. The CT scan in the early stage most frequently shows a cloudy mastoid; the inflammatory process may progress and develop into osteitis, with destruction of mastoid bone. Mastoiditis with and without periosteitis often responds to medical treatment and tympanocentesis or tympanostomy tube insertion, whereas mastoiditis with osteitis and bone destruction usually requires cortical mastoidectomy.

Intracranial Complications

The middle ear and the mastoid air cell system are close to the intracranial cavity, and infection can spread to the intracranial structures. Suppurative intracranial complications due to AOM include meningi-

tis, epidural abscess, subdural empyema, focal otitic encephalitis, brain abscess, lateral sinus thrombosis, and otic hydrocephalus. These are serious conditions and potentially life-threatening. The signs and symptoms are persistent headache, lethargy, malaise, irritability, severe otalgia, fever, and nausea and vomiting, as well as signs of intracranial complications including stiff neck, focal seizures, ataxia, blurred vision, papilledema, diplopia, hemiplegia, aphasia, dysdiadochokinesia, intention tremor, cranial nerve deficits other than of the facial nerve, dysmetria, and hemianopia. Any child with an intracranial infection such as meningitis or brain abscess should be evaluated for middle ear disease.

Meningitis

Hematogenous spread is the most common route of spread of infection from the middle ear to the meninges. It also may occur by direct extension through a preformed pathway or retrograde thrombophlebitis. Meningitis as a complication of otitis media is treated with high doses of broad-spectrum antibiotics; the dose is then adjusted according to the cerebrospinal fluid (CSF) culture results. Tympanocentesis or tympanostomy tube insertion should be done urgently to obtain material for culture to identify the causative agent of the otitis media. Surgery such as cortical mastoidectomy or tympanomastoidectomy may be necessary when the patient is stabilized.

Subdural Abscess and Subdural Empyema

Subdural abscess usually results when cholesteatoma or infection destroys bone next to the dura and there is an accumulation of granulation tissue and purulent material. A subdural empyema is an accumulation of purulent material between the dura and the arachnoid membrane. Treatment consists of broad-spectum antibiotics as well as surgical drainage by a neurosurgeon and otolaryngologist.

Brain Abscess

An otogenic brain abscess can develop directly from an acute or chronic middle ear infection or from the development of an adjacent infection such as a lateral sinus thrombophlebitis, petrositis or meningitis. The diagnosis is based on presence of clinical signs and symptoms and on CT and MRI findings. The CSF may be culture-negative if the abscess is deep. Treatment includes broad-spectrum antimicrobial agents and surgical treatment of the primary focus. Treatment for the brain abscess may consist of only long-term parenteral antibiotic therapy.

Lateral Sinus Thrombosis

Lateral and sigmoid sinus thrombophlebitis arises from an adjacent mastoid infection in contact with the sinus wall through inflammation of the adventitia and is followed by penetration of the venous wall. A thrombus is formed after the infection has spread to the intima; the mural thrombus may become infected and may occlude the lumen. Embolization of the thrombus may cause additional disease. Treatment includes parenteral broad-spectum antimicrobial agents; anticoagulants are recommended by some experts, but consensus is lacking on this issue. Surgical treatment may include tympanostomy tube insertion alone or with tympanomastoidectomy. There is also controversy regarding opening the lateral sinus and removing the thrombus or ligating the jugular vein in the neck if the patient experiences repeated episodes of formation of septic emboli.

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CHAPTER ONE HUNDRED AND NINETY-FIVE

Pediatric Chronic Sinusitis

Rodney P. Lusk

Key Points

- Pediatric sinusitis is of primarily infectious origin secondary to immaturity of the immune system and small developing sinuses.
- Allergy, immunodeficiency, and GERD may be important associated diseases.
- Imaging is not required for medical management in children. Plain films are not useful in children. CT scans should be obtained only if ethmoidectomy is being contemplated.
- Medical management consists primarily of parental education regarding the frequency of upper respiratory tract infections and medical management but also may include broad-spectrum oral antibiotics as indicated, topical nasal steroid sprays if the patient is allergic, and appropriate management of GERD.
- Surgical management is considered in patients in whom medical management has failed and who have infections outside the norm. Options include endoscopic anterior ethmoidectomy and conservative maxillary antrostomy, adenoidectomy (to rid the nasopharynx of possible contamination secondary to biofilms), and rarely, sphenoidotomy.
- Surgical intervention has not been shown to interrupt facial growth in children and, in appropriately selected patients, is very successful.

The diagnosis of acute and chronic sinusitis is a common primarily clinical diagnosis. It is associated with significant morbidity. In a quality of life assessment, Cunningham[1] and colleagues found that sinusitis had a more significant impact on children and their families than asthma, juvenile rheumatoid arthritis, and other chronic disorders.

Pediatric sinusitis is estimated to complicate approximately 5% to 10% of upper respiratory infections in early childhood.[2] Because children average six to eight upper respiratory illnesses per year, sinusitis is a very common problem.

Etiology

Age is clearly one of the most significant etiologic factors in pediatric sinusitis.[3] Because of their immature immune system, children are more likely to develop upper respiratory tract viral infections and associated acute sinusitis. A strong association has been recognized between sinusitis and respiratory viral infections. Viral infections are thought to cause significant ciliary dysfunction by decreasing the ciliary beat frequency or destroying the ciliary blanket.[4] These changes result in inflammation and edema that obstructs the ostium and increases the chance of establishing a bacterial infection of the sinuses. The ciliary dysfunction and edema will interrupt the drainage in the osteomeatal complex, predisposing the patient to the development of acute and possibly chronic sinusitis. As the ciliary function improves, the sinuses clear and the infection resolves in 80% of patients. The role of allergy in chronic sinusitis remains controversial. Rachelefsky[5] and coworkers[6] were the first to point out an association between allergic symptoms and sinusitis in children. The allergic reaction also will be associated with edema, and the same pathophysiology may be present. Huang[7] studied this issue for 5 years in children with perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR). Huang found that the prevalence of sinusitis was significantly higher among patients with PAR than among those with SAR, regardless of age or season. The patients with mold allergy PAR had a higher risk than those with nonmold allergies. Huang concluded that mold allergy is an important risk factor for sinusitis.

According to Ponikau and colleagues,[8] allergic fungal sinusitis may be an important factor in polypoid disease in adults. A strong correlation does appear to exist between the allergic response and fungal infections in some patients. The presentation of pediatric patients with allergic fungal sinusitis is different from that of adults. Children have more malleable bones and therefore incur a higher incidence of obvious abnormalities of their facial skeletons. Obstruction and the disease appear to be more unilateral.

The incidence of sinusitis and that of seasonal allergic symptoms do not, however, show a high degree of correlation. Numerous studies show that approximately 50% of children with sinusitis also have allergies; however, cause and effect have not been definitively demonstrated. A long-standing association among asthma, allergies, and chronic sinusitis is recognized. Dixon and associates[9] found a strong correlation between asthmatics and patients with rhinitis or sinusitis. In a recent study, Riccio and coworkers[10] found that allergic asthmatic children with chronic rhinosinusitis have a typical Th2 cytokine pattern. Nonallergic asthmatic children share a similar pattern. Riccio's group postulated that these findings suggest the existence of a common pathophysiologic mechanism shared by upper and lower airways, consistent with the concept of unified airway disease. This concept of unified airway disease has been increasingly recognized.[11]

Gastroesophageal reflux disease (GERD) may be associated with chronic sinusitis.[9] The incidence of GERD in children is not known, but Bothwell and associates are convinced that GERD is present in a majority of children with chronic sinusitis and effective treatment of the reflux can prevent sinus surgery.[12] Chambers and colleagues[13] found that GERD was the only reliable historical symptom that predicted a bad outcome in adults. There is, however, conflicting information in the literature. Suskind and coworkers[14] studied patients undergoing

antireflux surgery and who had failed medical management. In this very young group of patients (younger than 2 years), only two patients (14%) had severe chronic sinusitis and otitis media. Yellon and colleagues[15] also found an incidence of sinusitis in only 10% of patients with esophagitis proved by biopsy. These two studies lead one to conclude that sinusitis is not associated with GERD. Without a doubt, some children have sinusitis associated with GERD. Reflux may be intermittent and cannot be identified with a 24-hour pH probe study. If present, the GERD should be treated with a proton pump inhibitor, which could possibly prevent the need for surgery. Some investigators have recommended empirical therapy with a proton pump inhibitor before proceeding with surgical management.[16]

Without a doubt, the bacteria causing sinusitis are becoming more resistant to antibiotics, especially *Streptococcus pneumoniae*, which has made medical management of chronic sinusitis more difficult. The aerobic pathogens in pediatric chronic sinusitis include bacteria typical of acute sinusitis and organisms more characteristic of chronic disease, such as *Staphylococcus aureus*. These resistant strains have a significant effect on the usefulness of available antibiotic regimens for medical management.

Imaging

It is now clear that plain films do not adequately image the pediatric sinuses.[17] In the setting of acute sinusitis, Gwaltney and associates[18] showed a high incidence of opacification of the anterior ethmoid and maxillary sinuses with acute rhinovirus infections. For assessing the status of sinuses, the coronal CT study remains the imaging method of choice. Plain films do not reveal the true status of sinusitis in children.[19] In general, sinusitis is a clinical diagnosis, and radiographic imaging is not necessary in children for confirmation. This is in contrast with adults, for whom most otolaryngologists (73%) feel that a CT scan is required to confirm the diagnosis.[20] CT scans should be obtained when both the parents and the surgeon feel that surgical intervention is warranted. The CT scan is used primarily to look for anatomic abnormalities that would increase the risk of surgical complications and to help document the presence of disease. The CT scan should be obtained after a trial of maximum medical management that would include broad-spectrum antibiotics and topical nasal steroid sprays for at least 3 to 4 weeks. The CT scan should be obtained at the end of this course of management. It is difficult to assess the meaning of positive findings on a CT scan that has been obtained without prior medical management. It also is important to avoid being forced by an anxious or frustrated parent into operating on a child whose CT scan shows minimal disease. The best way to prevent this is to warn the parents, before obtaining the CT scan, that a small amount of disease does not necessarily require surgical intervention.

Treatment

Irrigation of the nose has been found to be efficatious; however, in the child, compliance can be a significant issue. Irrigation with saline has been found to be as effective as use of topical vasoconstrictors.[21] If the child can cooperate, irrigations should be included as a primary modality.

In general, cultures of the nasal cavity have not been readily used in the pediatric population. In fact, many laboratories will not run routine cultures of the nose. The literature is mixed regarding the efficacy of directed cultures. Jiang and coworkers[22,23] have shown that the bacteriology of the middle meatus was different from that found in the ethmoid bulla. They therefore concluded that the bacteriologic findings in the middle meatus may not reflect the real bacteriology in chronic sinusitis. Other studies have shown that bacteriologic findings in the middle meatus have a high correlation with antral punctures.[24] In the cooperative patient, endoscopically directed cultures of the middle meatus may be very useful, particularly in communities with increased resistance. If the patient is uncooperative, then broad-spectrum antibiotics would be appropriate.

Medical Management

Because antibacterial therapy most often is empirically chosen to treat the disorder, knowledge of the typical etiologic agents, as well as awareness of the antibacterial susceptibility profiles in a given community, is of paramount importance.

Much is unknown about antibiotic therapy and chronic sinusitis. Recent advances, however, include recognition of the importance of nontypable *Haemophilus influenzae* unresponsive to first-generation cephalosporins and of tetracycline-resistant gram-positive cocci and the increasing emergence of beta-lactamase–positive respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis*. These realities now mandate the more conservative use of antibiotics in upper respiratory tract infections and the use of newer therapeutic agents for acute and chronic sinusitis.

One subject on which most authors have agreed in recent publications on pediatric sinusitis is that patient expectations for antibotic usage need to be altered. Currently, antibiotics often are used to treat viral upper respiratory tract infections, even though they usually are ineffective. This frequent inappropriate antibiotic use contributes to the emergence of drug-resistant bacterial pathogens. It is frequently difficult to assess whether the infection is viral or has been complicated by a bacterial infection and would subsequently improve with antibiotic therapy. Reviews in the literature emphasize the need for primary medical, not surgical, management of sinusitis. In the most resistant cases, however, surgery can have a significant therapeutic role, as outlined later in this chapter.

Chronic sinusitis is best treated with broader spectrum antibiotics. For the most resistant strains of pneumococci, File and colleagues[25] found the newer form of amoxicillin-clavulanate (2000 mg-125 mg) and the fluoroquinolones[26] to be highly active against these cultured isolates from patients with community-acquired respiratory tract infection. These drugs, however, should be saved for the most resistant infections.

There are proponents of the use of long-term, low-dose therapy with erythromycin in patients who do not respond to aggressive medical management.[27] Don and associates have recommended intravenous antibiotic therapy as an alternative to endoscopic sinus surgery.[28] They believed this was warranted because of the risk of interference with facial skeletal growth and complications of endoscopic sinus surgery. Conclusive evidence now shows that endoscopic sinus surgery does not interfere with facial growth,[29] and the risks of endoscopic sinus surgery are small. Don and associates[28] found that 89% of the patients had complete resolution of symptoms after intravenous therapy with selective adenoidectomy; the remaining 11% failed to respond to intravenous therapy and required endoscopic surgery. In this study, the criteria for performing selective adenoidectomy are not clear, and significant complications were reported with intravenous therapy as well. Intravenous therapy is, however, a potential modality of therapy in resistant cases and can be used for complications of acute or chronic sinusitis.

Some investigators have recommended topical aerosolized antibiotics, but others have found them to be ineffective.[12] At this time, a firm recommendation about the use of topical aerosolized antibiotics cannot be made.

Prospective studies are lacking in the use of antihistamines and decongestants. In theory, decongestants would decrease the amount of edema and open the ostia. Topical steroids have been shown to decrease edema within 2 weeks and may be of modest benefit. Topical steroids have been shown to be safe and not to interrupt growth.[30]

Some investigators have used intravenous immune globulin (IVIG) to treat patients who do not have immune deficiencies but have chronic sinusitis.[31] They concluded that IVIG was successful in improving the medical management of chronic sinusitis. They also thought the mechanisms by which IVIG may be helpful are probably not based on the concept of immune replacement therapy, but more likely as an immune or inflammatory modulating agent.

Surgical Management

There is little doubt that chronic sinusitis–like symptoms occur in children with large obstructive adenoid pads (Fig. 195-1). If the obstructive adenoid pad is not removed, the nasal cavity cannot become healthy. Several studies indicate that adenoidectomy improves the signs and symptoms of sinusitis.[32,33] The efficacy of the treatment

Figure 195-1. Endoscopic view of enlarged adenoid pad causing nasal obstruction and symptoms compatible with obstructive sleep apnea (OSA).

Figure 195-2. Endoscopic view of mucosa intact over the lamina papyracea and basal lamella.

appears to be independent of the size of the adenoid pad. Recently, biofilms have been discovered covering the adenoid tissue in children with chronic sinusitis.[34,35] Such biofilms may constitute a repository for bacterial seeding of the middle meatus; this theory is supported by the efficacy of adenoidectomy regardless of the size of the adenoid pad. Certainly more work needs to be performed in this area before a firm correlation can be established. Good prospective studies assessing the efficacy of adenoidectomy in well-documented cases of sinusitis have yet to be performed. Overall, adenoidectomy can be expected to help relieve the symptoms of chronic sinusitis in approximately 50% of patients. A majority of pediatric otolaryngologists perform an adenoidectomy as the initial step in surgical management of chronic sinusitis.[36]

Some investigators believe that endoscopic surgery is rarely indicated. Endoscopic sinus surgery has become, however, a primary method of surgical therapy for chronic sinusitis after adenoidectomy. The indications for endoscopic sinus surgery remain controversial. The Consensus Panel[37] preferred to divide its indications into absolute and possible indications:

Absolute indications include (1) complete nasal airway obstruction in cystic fibrosis due to massive polyposis or closure of the nose by medialization of the lateral nasal wall; (2) antrochoanal polyp; (3) intracranial complications; (4) mucoceles and mucopyoceles; (5) orbital abscess; (6) traumatic injury to the optic canal; (7) dacryocystorhinitis due to sinusitis and resistant to medical treatment; (8) fungal sinusitis; (9) some meningoencephaloceles; and (10) some neoplasms.

Relative or possible indications, which are present in the vast majority of patients, include chronic rhinosinusitis that persists despite optimal medical management and after the exclusion of any systemic disease. Optimal management includes 4 to 6 weeks of adequate broad-spectrum antibiotics and treatment of any concomitant diseases.

According to the Consensus Panel,[37] only a small fraction of all children suffering from chronic sinusitis will require functional endoscopic sinus surgery (FESS), but these children account for a majority of surgical patients, and the procedure has gained popularity. Reported success rates, defined mainly on the basis of improvement over preoperative symptoms, have been encouraging and ranged between 71% and 93%. Hebert and Bent[38] performed a meta-analysis that revealed a success rate of 88.4% with surgical management in children in whom medical management had failed to effect improvement. With more experience, many surgeons have modified their techniques to be less aggressive, with the aim of preservation of mucosa. Advances in instrumentation, including the advent of the microsurgical débrider and sharp through-biting instruments, also have contributed to realization of this goal. It is now possible to preserve mucosa over the lamina papyracea, middle turbinate, and basal lamella (Fig. 195-2). Extensive sphenoethmoidectomy usually is not justified in children unless they have symptomatic polyps secondary to cystic fibrosis or allergic fungal sinusitis (Fig. 195-3).

Most surgeons perform a limited procedure that involves an anterior ethmoidectomy and maxillary antrostomy.[36] The size of the maxillary antrostomy continues to be controversial. Many surgeons have become more conservative in the size of their antrostomy. The mucosa in the area of the root of the middle turbinate should not be removed. It is important to leave mucosa in this area to prevent scarring in the frontal recess. If the ostium can be seen with a 30-degree telescope, then it does not need to be enlarged. If, however, there is evidence of a polypoid mucosa in the ostium or if it is edematous and can only be identified with a seeker, then it may be enlarged posteriorly into the fontanelle, with through-biting instruments. On occasion, usually less than 30% of the time, the posterior ethmoid sinuses will need to be entered. In unusual circumstances, less than 10% of the time, the sphenoid sinus or frontal sinuses will need to be entered. The frontal recess in children is the source of the frontal sinuses, and frontal sinuses are not developed in children. Therefore, instrumentation of this area should be performed very carefully.

When the procedure was originally performed, a second-look operation that included cleaning of the cavity was believed to be necessary. In the pediatric population, this meant a second general anesthetic procedure. Ramadan[39] found that treatment with intravenous dexamethasone during endoscopic sinus surgery was safe and was helpful in reducing scarring and swelling noted during the second-look procedure. Use of corticosteroids was particularly helpful in children with asthma, lower CT scores, no exposure to smoking, and older than 6 years of age. Walner and associates[40] found that avoiding a second look did not increase the incidence of revision surgery. Fakhri and coworkers[41] concluded that second-look endoscopy did not decrease the incidence of revision surgery; therefore, the second look was of no benefit after routine FESS. It has now become more common practice to use some type of absorbable stenting material in children, to omit the second look. Most surgeons do not perform a second-look operation.[36]

Many areas of surgical management of sinusitis need further investigation but none is more important than the impact on facial growth. In two studies in animal models, piglets showed interruption of facial growth on the side of endoscopic surgery, but the animals clinically did not show evidence of abnormal growth.[42,43] Lund and associates[44] have

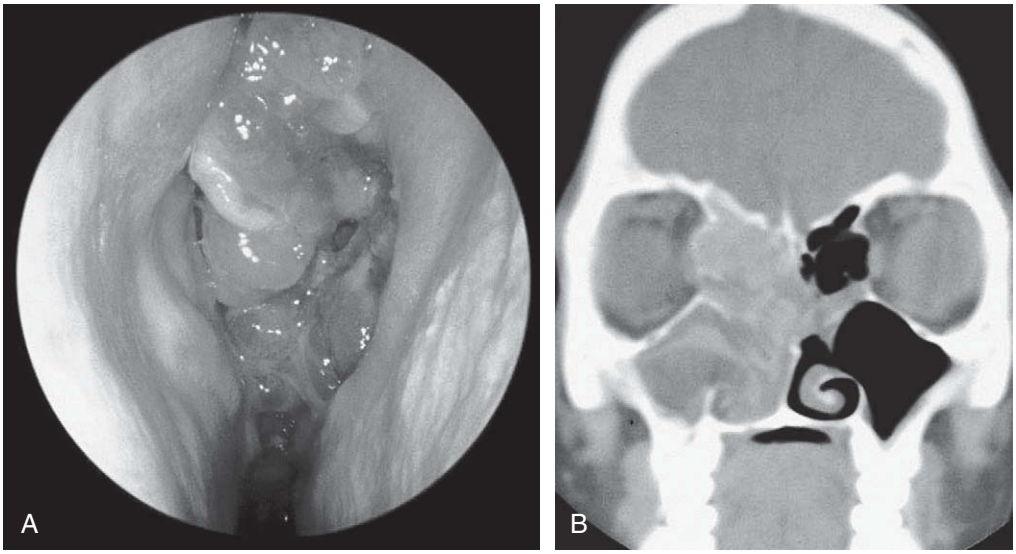

Figure 195-3. **A,** Endoscopic view of polyps secondary to fungal sinusitis. **B,** Computed tomography scan of a patient with fungal sinusitis.

evidence that very aggressive surgical management of midface lesions is not associated with interruption of facial growth. Wolf and colleagues[45] did not note any evidence of interruption of facial growth. However, these two studies did not perform accurate measurements of the facial skeleton.

Bothwell and associatess[29] sought to determine whether FESS performed in children with chronic rhinosinusitis alters facial growth. They evaluated 67 children with a mean age of 3.1 years at presentation. The patients were evaluated for facial growth 10 years later, at a mean age of 13.2 years. In this series, 46 children underwent FESS and 21 children did not undergo FESS and acted as a control group. Quantitative anthropomorphic analysis was performed using 12 standard facial measurements on both groups. A facial plastic surgery expert performed blinded qualitative facial analysis on standardized photographs. Both quantitative and qualitative analyses showed no trends or statistical significance in changes of facial growth between children who underwent FESS and those who had chronic sinusitis but did not undergo FESS. The data also showed no deviations, or trends toward deviation, from the standard norms in children. Bothwell's investigators concluded that evidence for an adverse effect of FESS on facial growth in children was lacking.

Large clinical studies are necessary to further elucidate the pathophysiology and medical and surgical management of chronic sinusitis. These studies will be difficult to perform because of the large numbers required.

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CHAPTER ONE HUNDRED AND NINETY-SIX

Pharyngitis and Adenotonsillar Disease

W. Peyton Shirley

Audie L. Woolley

Brian J. Wiatrak

Key Points

- An understanding of the anatomy, embryology, and physiology of Waldeyer's ring is important to learning how to diagnose and treat disease in this region.
- The physician must be familiar with and be able to diagnose a wide range of infections that may be seen in Waldeyer's ring. Once the diagnosis is made, the physician needs to know the treatment options and the potential complications that may result from pharyngitis and adenotonsillar disease.
- Adenotonsillar hypertrophy is a common cause of upper airway obstruction in children that has a wide range of clinical manifestations and complications. Newer research suggests that upper airway obstruction potentially leads not only to harmful physiologic alterations but also to pathologic changes in behavior and neurocognitive development.
- Proper preoperative assessment is crucial. A good history and thorough physical examination are the most important part of appropriate treatment of adenotonsillar disease. The physician must be familiar with and know how to optimally use all the available diagnostic tests and procedures. Finally, the surgeon must have a thorough understanding of the proper indications for adenotonsillectomy.
- Many techniques have been and continue to be used to perform adenotonsillectomy. The physician must have knowledge of all the surgical options available and must make an informed choice about the method. Whatever technique is chosen, careful surgical technique is important as well as an awareness of potential complications. The surgeon must be able to handle the potential complications but, more important, know how to avoid them.

Infectious and inflammatory diseases involving the pharynx, tonsils, and adenoids account for a significant proportion of childhood illnesses and pediatric health care expenditures. They often result in two of the most common surgical procedures of childhood, tonsillectomy and adenoidectomy (Fig. 196-1). Clinical research has now helped illuminate this vast area of pediatric otolaryngology, including the effects of adenotonsillar hypertrophy on obstructive sleep apnea and the many possible sequelae of obstructive sleep apnea, the microbiologic flora of the tonsils and adenoids and their role in chronic adenotonsillar hypertrophy, the relationship between adenotonsillar hypertrophy and craniofacial growth, and new techniques for adenotonsillectomy with improved management of perioperative morbidity. This chapter reviews the current understanding of pharyngitis and adenotonsillar disease processes.

History

Celsus was the first to report removal of the tonsils.[1] Describing his surgical technique, Celsus indicated that "the tonsils are loosened by scraping around them and then torn out."[1] Hemostasis was obtained using a vinegar mouthwash and painting the tonsillar fossa with a medication to reduce bleeding.[2] Aëtius of Amida on the Tigris described a technique for tonsillectomy in the first half of the sixth century, in which a hook was used to snare the tonsil and a knife was used for amputation. He warned of the severe dangers of hemorrhage when excision was too deep.[3] Subsequent surgical techniques were described by Paul of Aegina in 625, and Physick described a forceps to facilitate extirpation of the tonsil, which became the forerunner of the modern tonsil guillotine.[1,4] Mackenzie improved on the Physick tonsillotome and popularized its use for surgery of the tonsils in the late nineteenth century.[5]

The adenoids were first described by the Danish physician Meyer. In his 1868 paper "Adenoid vegetations in the nasopharyngeal cavity," Meyer described in detail his technique of posterior rhinoscopy to diagnose adenoid hypertrophy and recommended removal of adenoid tissue with the aid of a ring knife.[6] In 1885, Gottstein described the first adenoid curette.[6]

Crowe and colleagues[7] reviewed 1000 consecutive tonsillectomies performed between 1911 and 1917. In the study "Relation of tonsillar and nasopharyngeal infection to general systemic disorders," they provided a detailed description of a meticulous surgical technique by sharp dissection and described using the Crowe-Davis mouth gag. The low complication rate they described compares favorably with rates in modern reports of tonsillectomy.

Anatomy

Waldeyer's Ring

Together, the lingual tonsils anteriorly, the palatine tonsils laterally, and the pharyngeal tonsils (adenoids) posterosuperiorly form a ring of lymphoid or adenoid tissue around the upper end of the pharynx known as Waldeyer's tonsillar ring. All the structures of Waldeyer's ring have similar histology and, presumably, similar functions.

Palatine Tonsil

The palatine tonsil represents the largest accumulation of lymphoid tissue in Waldeyer's ring and, in contrast to the lingual and pharyngeal tonsils, constitutes a compact body with a definite thin capsule on its deep surface.[8] Tonsillar crypts, blind tubules from the epithelium on the surface of the tonsil that are lined with stratified squamous epithelium, extend deep into this tissue.

The tonsillar capsule is a specialized portion of the pharyngobasilar fascia that covers the surface of the tonsil and extends into it to form septa that conduct the nerves and vessels.[8] The tonsil is not, therefore, easily separated from its capsule, but the capsule is united largely by loose connective tissue to the pharyngeal muscles. One can easily dissect the tonsil from its normal position by separating the capsule from the muscle through this loose connective tissue.

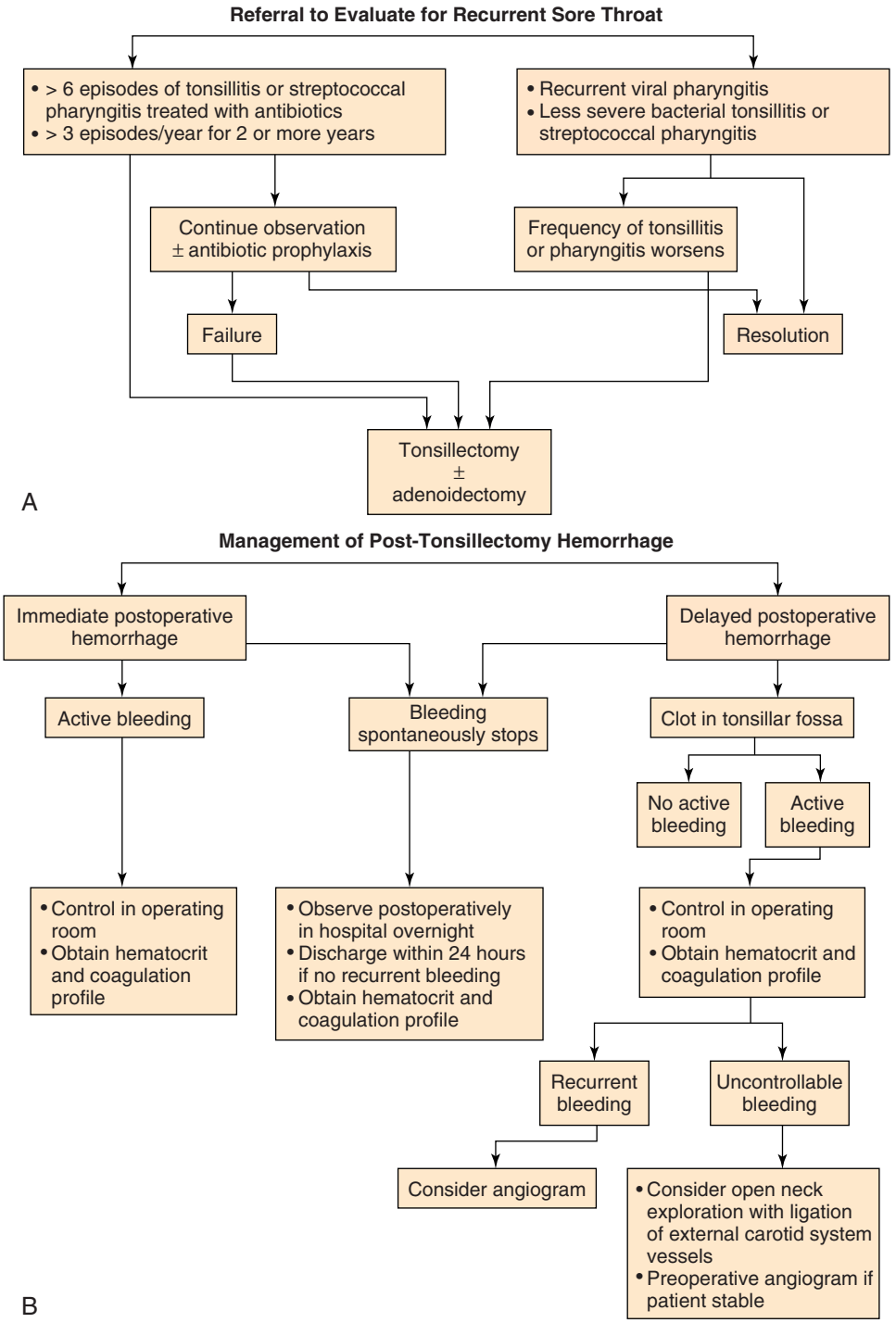

Figure 196-1. Management algorithms for pediatric pharyngitis and adenotonsillar disease. **A,** Algorithm for evaluation of a patient referred for recurrent sore throat. **B,** Algorithm for management of post-tonsillectomy hemorrhage. *Continued*

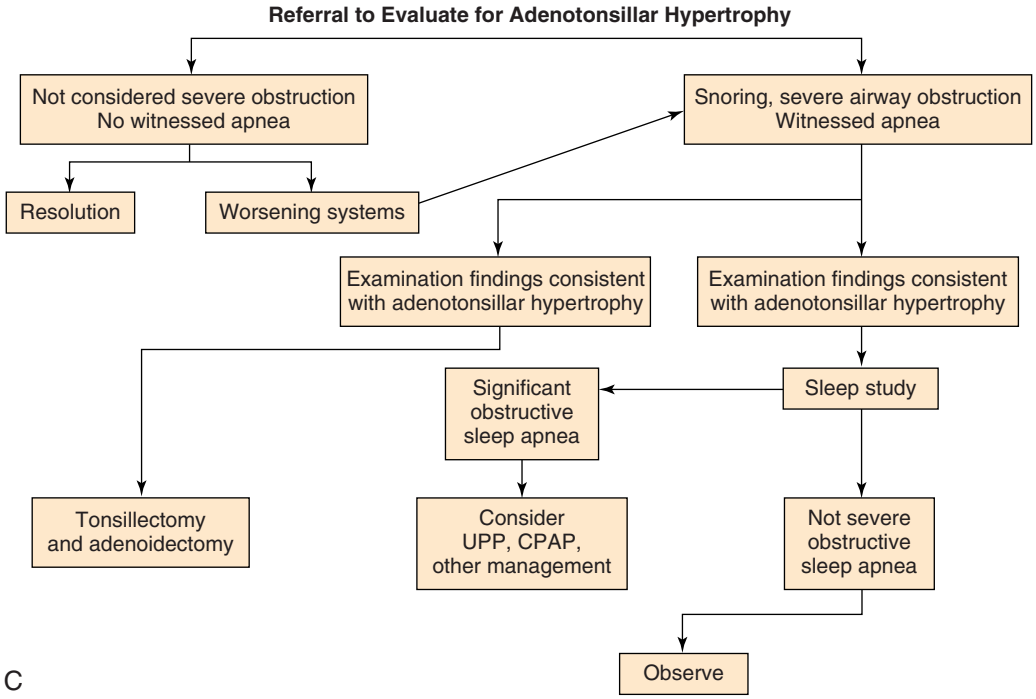

Figure 196-1, cont'd. **C,** Algorithm for evaluation of a patient referred for adenotonsillar hypertrophy.

The tonsillar fossa is composed of three muscles: the palatoglossus muscle, which forms the anterior pillar; the palatopharyngeal muscle, which is the posterior pillar; and the superior constrictor muscle of the pharynx, which forms the larger part of the tonsillar bed.[8] The muscular wall is thin, and immediately against it on the outer wall of the pharynx is the glossopharyngeal nerve. This nerve can be easily injured if the tonsillar bed is violated, and not uncommonly the nerve is temporarily affected by edema after tonsillectomy, which produces both a transitory loss of taste over the posterior third of the tongue and referred otalgia.

The arterial blood supply of the tonsil enters primarily at the lower pole, with branches also at the upper pole. There are typically three arteries at the lower pole: the tonsillar branch of the dorsal lingual artery anteriorly, the ascending palatine artery (a branch of the facial artery) posteriorly, and the tonsillar branch of the facial artery between them that enters the lower aspect of the tonsillar bed.[8] At the upper pole of the tonsil, the ascending pharyngeal artery enters posteriorly, and the lesser palatine artery enters on the anterior surface. The tonsillar branch of the facial artery is the largest. Venous blood drains through a peritonsillar plexus about the capsule.[8] The plexus drains into the lingual and pharyngeal veins, which in turn drain into the internal jugular vein.

The nerve supply of the tonsillar region is through the tonsillar branches of the glossopharyngeal nerve about the lower pole of the tonsil and through the descending branches of the lesser palatine nerves, which course through the pterygopalatine ganglion.[8] The cause of referred otalgia with tonsillitis is through the tympanic branch of the glossopharyngeal nerve. Efferent lymphatic drainage courses through the upper deep cervical lymph nodes, especially the jugulodigastric or tonsillar node located behind the angle of the mandible.[8]

Adenoids

The adenoid or pharyngeal tonsils form the central part of the ring of lymphoid tissue surrounding the oropharyngeal isthmus. The adenoid is composed of lymphoid tissue, with its apex pointed toward the nasal septum and its base toward the roof and posterior wall of the nasopharynx. The adenoid is covered by a pseudostratified ciliated columnar epithelium that is plicated to form numerous surface folds. The adenoid develops as a midline structure by the fusion of two lateral primordia that become visible during early fetal life, are fully developed during the seventh month of gestation, and continue to grow until the fifth year of life, often causing some airway obstruction.[6,9] Thereafter, the adenoid gradually atrophies, the nasopharynx grows, and the airway improves.[10]

The blood supply and drainage are from the ascending pharyngeal artery, the ascending palatine artery, the pharyngeal branch of the maxillary artery, the artery of the pterygoid canal, and contributing branches from the tonsillar branch of the facial artery.[9] Venous drainage is to the pharyngeal plexus, which communicates with the pterygoid plexus and then drains into the internal jugular and facial veins. The nerve supply is from the pharyngeal plexus. The efferent lymphatic drainage of the adenoids is to the retropharyngeal and pharyngomaxillary space lymph nodes.[9]

Immunology of the Adenoids and Tonsils

The adenoids and tonsils are predominantly B-cell organs; B cells account for 50% to 65% of all adenoid and tonsillar lymphocytes.[11] Approximately 40% of adenoid and tonsillar lymphocytes are T cells, and 3% are mature plasma cells. Conversely, 70% of the lymphocytes in peripheral blood are T cells.[12] The immunoreactive lymphoid cells of the adenoids and tonsils are found in four distinct areas: the reticular cell epithelium, the extrafollicular area, the mantle zone of the lymphoid follicle, and the germinal center of the lymphoid follicle.[11]

Ample evidence shows that the adenoids and tonsils are involved in inducing secretory immunity and regulating secretory immunoglobulin production. They contain a system of channels covered by specialized endothelium that can mediate antigen uptake much like Peyer's patches of epithelium in the bowel.[13] Both the adenoids and tonsils are favorably located to mediate immunologic protection of the upper aerodigestive tract as they are exposed to airborne antigens. Both organs, specifically the tonsils, are particularly designed for direct transport of foreign material from the exterior to the lymphoid cells.[11] This is in contrast to lymph nodes, which depend on antigenic delivery through afferent lymphatics. The tonsillar crypts are covered by stratified squamous epithelium. There are 10 to 30 of these crypts in the tonsils, and they are ideally suited to trapping foreign material and transporting it to the lymphoid follicles.[11]

The tonsils and adenoids rank among the secondary lymphatic organs. Intratonsillar defense mechanisms eliminate weak antigenic

signals. Only when additional higher antigenic concentrations are presented does proliferation of antigen-sensitive B cells occur in the germinal centers.[11] Low antigen doses effect the differentiation of lymphocytes to plasma cells, whereas high antigen doses produce B-cell proliferation. The generation of B cells in the germinal centers of the tonsils is considered by Siegel to be one of the most essential tonsillar functions.[14]

Immunoglobulins (Igs) produced by the adenoid include IgG, IgA, IgM, and IgD.[11] IgG appears to pass into the nasopharyngeal lumen by passive diffusion.[11] The tonsil produces antibodies locally as well as B cells, which migrate to other sites around the pharynx and periglandular lymphoid tissues to produce antibodies.

T-cell functions, such as interferon-γ production and, presumably, production of other important lymphokines, have been shown to be present in tonsils and adenoids.[11] The role played by tonsillar and adenoid T cells in tumor response is still unknown.

The human tonsils are immunologically most active between ages 4 and 10 years. Involution of the tonsils begins after puberty, resulting in a decrease of the B-cell population and a relative increase in the ratio of T to B cells.[11,15] Although the overall Ig-producing function is affected, considerable B-cell activity is still seen in clinically healthy tonsils even at age 80 years.[16] The situation is different in disease-associated changes, such as when recurrent tonsillitis and adenoid hyperplasia are observed. Inflammation of the reticular crypt epithelium results in shedding of immunologically active cells and decreasing antigen transport function with subsequent replacement by stratified squamous epithelium.[17] These changes lead to reduced activation of the local B-cell system, decreased antibody production, and an overall reduction in density of the B-cell and germinal centers in extrafollicular areas.[17] In contrast to recurrent tonsillitis, the changes are less pronounced in adenoid hyperplasia, in which the immunoregulatory conditions necessary for maintenance of the B-cell population are well preserved. The reason is most likely that the reticular epithelium is less affected in inflammation of adenoids than of tonsils.

Reports conflict regarding the immunologic consequences of tonsillectomy and adenoidectomy, yet it is clear that no major immunologic deficiencies result from these procedures.[16,18] Ogra[19] showed a three- to fourfold drop in titers in children previously immunized with live poliovirus vaccine. Attempts to vaccinate seronegative children subjected to tonsillectomy and adenoidectomy have resulted in delayed and lowered nasopharyngeal secretory immune responses as measured by IgA antibodies to the poliovirus.[19] Fortunately, poliovirus epidemics are no longer an annual threat. Serum IgA levels in patients who had undergone tonsillectomy were lower than in age-matched controls, but this immunologic change did not appear to be clinically significant. Some studies actually point to improved immunologic activity after tonsillectomy. One study showed better neutrophil chemotaxis after tonsillectomy, and another demonstrated increased IgG and IgM production, possibly as a result of unblocking of the suppression that the immune system was subject to before tonsillectomy.[20,21] One large study, with a cohort of 1328 children, showed no higher incidence of atopic disease (asthma, allergic rhinitis, and eczema) in children who had adenotonsillectomy prior to age 8 than in those who had not undergone surgery.[22]

It is clear that the adenoids and tonsils are active immunologic organs that generally reinforce the mucosal immunity of the entire upper aerodigestive tract. The immunologic role of these organs should be considered before a patient undergoes adenoidectomy or tonsillectomy; nonetheless, clinical consideration still forms the actual basis of surgery.

Bacteriology

Establishment of normal flora in the upper respiratory tract begins at birth. *Actinomyces*, *Fusobacterium*, and *Nocardia* are acquired by age 6 to 8 months.[23] Subsequently, *Bacteroides*, *Leptotrichia*, *Propionibacterium*, and *Candida* are also established as part of the oral flora.[24] *Fusobacterium* populations reach high numbers after dentition and reach maximal numbers at 1 year of age.[23] The ratio of anaerobic to aerobic bacteria in saliva is approximately 10:1,[24] because of variations in oxygen concentration throughout the oral cavity.

Healthy children up to 5 years of age can harbor known aerobic pathogens. Ingvarsson and colleagues[24] reported that *Streptococcus pneumoniae* was recovered in 19% of healthy children, *Haemophilus influenzae* in 13%, group A *Streptococcus* in 5%, and *Moraxella (Branhamella) catarrhalis* in 36%. The frequency of pathogens decreases with age, possibly because of greater immunity. Changes in the pharyngeal bacteria flora noted during viral illnesses are thought to be a result of the increased adherence of *Staphylococcus aureus* as well as gram-negative enteric organisms.[25] Oral pharyngeal colonization during illness-free periods was found to vary from 12% to 18% for gram-negative enteric organisms and from 5% to 14% for *S. aureus*.[26] During an episode of viral upper respiratory tract infection, the colonization rates for gram-negative organisms and *S. aureus* increased to 60% and 43%, respectively.

Brodsky and Koch[27] found substantive differences between the types and numbers of aerobic bacteria found in nondiseased and diseased adenoids. The core samples of normal adenoids showed that 75% of children who were relatively free of upper respiratory disease, otitis media, and symptoms of adenoid obstruction had either no bacterial growth on culture or bacteria that are considered part of the normal flora and not pathogenic. Core samples in adenoids of only 45% of children who had chronic adenoid infection and 39% who had obstructive adenoid hypertrophy had no bacteria growth or only normal flora; the bacteria found in these children were more likely to be β-lactamase producers.

Infections of Waldeyer's Ring

Many organisms can induce inflammation of Waldeyer's ring. These include aerobic as well as anaerobic bacteria, viruses, yeasts, and parasites. Some of the infectious organisms are part of the normal oral pharyngeal flora, and others are external pathogens. Because the oropharynx is colonized by many organisms, most infections of Waldeyer's ring are polymicrobial. These organisms work synergistically and can be demonstrated in mixed aerobic and anaerobic infections.[28]

Another feature of mixed infections is the ability of organisms resistant to an antimicrobial agent to protect an organism susceptible to that agent by the production of an antibiotic-degrading enzyme that is secreted into the tissues.[29] Because of the polymicrobial nature of most infections around Waldeyer's ring, it is often difficult to interpret data derived from clinical samples obtained from mucosal surfaces and to differentiate between organisms that are colonized and those that are invaders.

Viruses

The classic "common cold" is the most frequent cause of otolaryngologic infection in children. A multitude of offending viral pathogens have been implicated in causing pharyngitis, including rhinovirus, influenzavirus, parainfluenza virus, adenovirus, coxsackievirus, echovirus, reovirus, and respiratory syncytial virus. Viral pharyngitis is usually mild in manifestations, with patients complaining of a sore throat and dysphagia. Most patients have a fever with erythema of the pharyngeal mucosa. The tonsils may be enlarged but frequently there is no associated exudate.

Herpangina caused by coxsackievirus is characterized by small vesicles with erythematous bases that become ulcers and are spread over the anterior pillar tonsils, palate, and posterior pharynx (Fig. 196-2). Herpes simplex virus commonly causes the well-known "cold sore." This virus can also cause exudative or nonexudative pharyngitis, mainly in older children and young adults. In younger children, the herpesvirus may induce gingivostomatitis.

Management of viral infections is nonspecific and symptomatic. Antibiotics are helpful in cases of secondary bacterial infection.[30]

Epstein-Barr Virus

One particular type of viral infection that deserves special attention is the Epstein-Barr virus (EBV). EBV induces the mononucleosis syndrome, which consists of high fever; general malaise; large, swollen, dirty-gray tonsils (Fig. 196-3); sore throat; dysphagia; and odynophagia. Petechiae located at the junction of the hard and soft palate are highly

Figure 196-2. Viral ulcer on the right tonsil consistent with coxsackievirus infection.

Figure 196-3. Tonsillar hypertrophy and mononucleosis with significant airway obstruction.

suggestive of EBV infection, although not pathognomonic. Often patients with EBV infection have hepatosplenomegaly with resultant liver damage. The most common method of transmission is oral contact.

Diagnosis of EBV is confirmed by laboratory studies. A differential blood count showing 50% lymphocytosis with 10% atypical lymphocytes is characteristic of EBV infection. Serologic studies include monospot and other serum heterophil antibody titer measurements. Results of these tests may be negative initially, and repeat testing in 1 to 2 weeks is warranted if clinical suspicion of EBV infection is strong. The heterophil antibody titers are detected by the Paul-Bunnell-Davidsohn or ox-cell hemolysis test. If the heterophil antibody agglutination test result is negative, the disease may still be present. Only 60% of patients with infectious mononucleosis have a positive result within the first 2 weeks after onset of the illness; 90% have a positive result 1 month after onset.[31] EBV-specific serologic assays have become the method of choice for confirmation of acute or convalescent EBV infection. Figure 196-4 shows the serologic response time. Management of this condition is symptomatic. Recovery may take weeks, and antibiotics are used to treat secondary bacterial infections. Ampicillin should be avoided because a rash may occur despite previous intake without similar reactions. Upper airway obstruction from severely enlarged tonsils can be life-threatening and should be managed promptly with the insertion of a nasopharyngeal airway and short-term high-dose steroid therapy. If the obstruction is severe and unrelieved by these measures, a tonsillectomy or tracheotomy may be necessary.

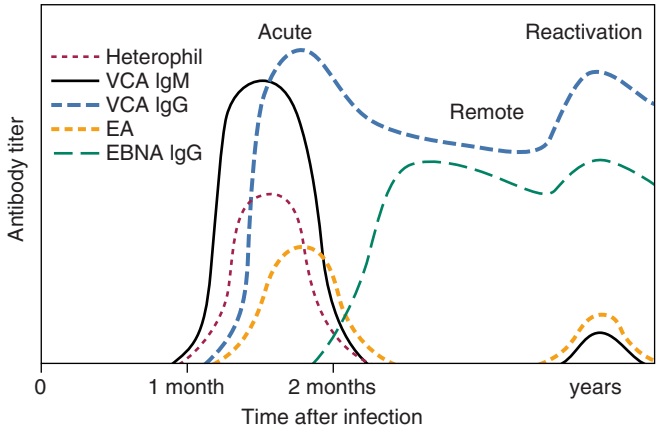

Figure 196-4. Serologic response time in diagnosis of EBV infection. EA, early antigen; EBNA, EBV nuclear antigen; Ig, immunoglobulin; VCA, viral capsid antigen. *(From Gulley ML. Molecular diagnosis of Epstein-Barr virus-related diseases.* J Mol Diagn. *2001;3:1-10.)*

Candida

Candidiasis can result in severe pharyngitis, particularly in patients who are immunocompromised or who have been undergoing treatment with antimicrobial agents. It is a fairly unmistakable syndrome consisting of coherent white plaques on the oral pharyngeal mucosa. Removal of these plaques may reveal a raw, bleeding surface. Management is with nystatin or, in refractory cases, fluconazole.

Neisseria

Pharyngitis as a result of *Neisseria gonorrhoeae* is common in homosexual men. It has been detected in 6% of adolescents with acute pharyngitis.[32] Although the infection is often asymptomatic, it can result and persist after treatment. Acute exudative tonsillitis is a manifestation of gonococcal pharyngitis. The clinical syndrome may range from an asymptomatic to an exudative pharyngitis, but most cases tend to fall toward the exudative pharyngitis end of the spectrum. Nonetheless, disseminated gonococcemia can result even from mild or asymptomatic infection. Penicillin and tetracycline are the most effective therapeutic agents.

Vincent's Angina

Vincent's angina is secondary to *Spirochaeta denticulata* and Vincent's fusiform bacillus *Borrelia vincentii* (*Treponema vincentii*). This condition arises slowly, manifesting both mild local and systemic symptoms. The infection arises most commonly in overcrowded conditions. Patients present with complaints of high fever, headache, sore throat, and physical findings of cervical lymphadenopathy and a membrane on the tonsil that, when removed, reveals an ulcer that remains confined to the surrounding tissue and usually heals in 7 to 10 days.[33] Management consists of penicillin therapy. Local treatment in the form of oral hygiene is helpful. This condition may be confused with trench mouth, which is caused by the same organisms but in which oral cavity ulcers include the gums and oral mucous membranes.[34]

Syphilis

Treponema pallidum infections in both the primary and secondary stages of syphilis can be associated with oral pharyngeal lesions. In primary syphilis, oral chancres appear about 3 weeks after exposure. Grayish superficial mucous membrane patches surrounded by an erythematous border are generally found in patients with secondary syphilis.

Corynebacterium diphtheriae

The incidence of *Corynebacterium diphtheriae* infection has declined markedly since the introduction of diphtheria vaccination. This organism causes an early exudative pharyngotonsillitis with a thick pharyngeal membrane. Infection can then spread to the throat, tonsils, palate, and larynx.[35] *C. diphtheriae* organisms also produce a lethal exotoxin

that can damage cells in distant organs. Today only 200 to 300 cases of diphtheria occur in the United States each year, usually—but not exclusively—in people who have not been immunized.[36] The organism is a gram-positive pleomorphic aerobic bacillus that can be identified in a routine throat culture, particularly when the microbiologist is made aware of a clinical suspicion of this diagnosis. Only toxigenic strains infected with a bacteriophage can cause diphtheria.[30] Laryngeal inflammation combined with an exudative, necrotic, gray pharyngeal membrane may result in airway obstruction. Removal of this membrane causes bleeding. Early diagnosis is critical, and the goal of therapy is neutralization of unbound toxin with antitoxin. Myocarditis and neurologic sequelae resembling features of Guillain-Barré syndrome or poliomyelitis may result.[35,36] The organism is identified by fluorescent antibody studies. The presence of Klebs-Löffler bacillus in the membrane can be diagnosed with Gram staining.[34] Because diphtheria is an emergency condition, antitoxin must be given in the first 48 hours of onset to be effective. Airway obstruction should be managed with tracheotomy. Penicillin in high doses should be administered.

Streptococcal Tonsillitis-Pharyngitis

Group A *Streptococcus* is the most common bacterial cause of acute pharyngitis.[37] The public health importance of this infection lies not only in its frequency but also on the fact that it is a precursor of two serious sequelae, acute rheumatic fever and poststreptococcal glomerulonephritis. Although the incidence of rheumatic fever has decreased, all groups of β-hemolytic streptococci have been associated with rheumatic fever.[23]

Acute streptococcal tonsillitis is a disease of childhood, with a peak incidence at about 5 to 6 years of age, but can occur in children younger than 3 years and in adults older than 50 years.[34] Outbreaks may arise in epidemic forms in institutional settings such as recruit camps and daycare facilities. Acute tonsillitis manifests as a dry throat, malaise, fever, fullness of the throat, odynophagia, dysphagia, otalgia, headache, limb and back pain, cervical adenopathy, and shivering. Examination reveals a dry tongue, erythematous, enlarged tonsils, and yellowish white spots on the tonsils. In severe cases, a tonsillar or pharyngeal membrane or purulent exudate may exist along with jugulodigastric lymph node enlargement.[34]

The diagnosis of acute tonsillitis is made mainly on clinical grounds. The clinical manifestations of streptococcal and nonstreptococcal pharyngitis overlap so broadly that it is often impossible to make the diagnosis with certainty. For this reason, most authorities recommend that the diagnosis of group A β-hemolytic streptococcal (GABHS) pharyngitis be verified or ruled out by microbiologic tests in patients who appear likely, on the basis of clinical and epidemiologic considerations, to have this illness.[37,38] The time-honored method of diagnostic confirmation is the throat culture. This is a simple and extremely useful test but sampling must be skillfully performed by swabbing the posterior pharynx and tonsillar areas.[37] The specimen must also be appropriately processed and read. Such selective use of throat cultures represents good medical practice.

One of the major problems in the use of throat cultures in everyday medical practice has been the delay in obtaining results. The delay can range from 18 to 48 hours, which holds up the start of appropriate management but does not increase the likelihood of development of rheumatic fever. Nevertheless, it can be difficult for physicians to persuade parents of the wisdom of withholding antibiotics until results are known, especially if their children are cranky and febrile. If group A streptococcal pharyngitis is treated early in the clinical course, the period of communicability is reduced.[39] Management is thus initiated before culture results are available and unfortunately may not be terminated even when negative results are obtained. Development of rapid strep detection tests for the detection of the group A streptococcal antigen has therefore represented a useful advance.

Several rapid tests to detect group A streptococcal antigen in the pharynx have been developed. They employ either latex agglutination or enzyme-linked immunosorbent assay (ELISA) methods to extract the antigen from a swab. The streptococcal group A carbohydrate may be detected within a matter of minutes. The test kits are suitable for use in a physician's office. Although the rapid detection tests are highly specific, they are unfortunately not as sensitive as routine throat culture.[37,40,41] A negative rapid detection test result may prompt the practitioner to withhold antibiotic therapy while awaiting culture results. Most guidelines suggest that throat cultures should be performed when the body temperature is greater than 38.3° C or when the illness is characterized exclusively by a sore throat.[42] The most accurate and cost-effective method to diagnose acute GABHS infection is the use of the rapid strep test. This is followed by standard throat culture in patients with a negative rapid strep test result and a strong suspicion of streptococcal tonsillitis.

Even optimally obtained and processed, throat cultures are not without flaws. Throat culture cannot reliably differentiate acute from chronic infection. The treatment of all patients who have positive culture results leads to over-management. There are occasional false-negative results (approximately 10% of cases), although one report has found that patients with false-negative results are most likely carriers who do not require treatment.[37] Studies have reported that a single throat culture is 90% to 97% sensitive and 90% specific for GABHS growth.[43] The carrier state can be elucidated by serologic testing. A true infection is demonstrated by a positive throat culture result and at least a two-dilutional rise in the antistreptolysin-O titer.[44] A GABHS carrier without acute infection has a positive culture result with no change in dilution titer.[45] Excluding the diagnosis of group A streptococcal pharyngitis is quite important because the majority of patients with acute pharyngitis do not have "strep" throat.

Therapy has usually been directed at the aerobic pathogens traditionally associated with tonsillitis (e.g., GABHS). Penicillin is still the agent of choice in most cases. However, anaerobic bacteria play a major role in the complications associated with tonsillitis, so they are probably also involved in recurrent tonsillitis. One study has documented the prevalence of *Bacteroides* cultured from chronically inflamed tonsils.[46] Anaerobes also have been implicated in acute tonsillitis.[23] Clinical failure of penicillin should lead to the suspicion of β-lactamase–producing organisms. The reason for the treatment failure could be that these organisms either act as pathogens themselves, so-called direct pathogens, or protect susceptible pathogens from the effects of β-lactamase antibiotics, making them so-called indirect pathogens. In such cases, the patient complains of sore throat that never resolves completely despite penicillin management. An alternative to the use of penicillin is to use a penicillin plus a β-lactamase inhibitor such as clavulanic acid (e.g., amoxicillin/clavulanic acid). Other alternatives are clindamycin and a combination of erythromycin and metronidazole. Institution of antibiotic therapy within 24 to 48 hours of symptom onset will result in decreased symptoms associated with sore throat, fever, and adenopathy 12 to 24 hours sooner than without antibiotic administration. The use of antibiotics also minimizes the chance of suppurative complications and diminishes the likelihood of acute rheumatic fever.[47,48] Ten full days of therapy is necessary, as eloquently demonstrated by Schwartz and colleagues,[49] who showed that children receiving 10 days of therapy have lower clinical and bacteriologic recurrence rates than children receiving only 7 days of therapy.

There appears to be no need for further management for asymptomatic carriers because the carrier state does not lead to suppurative or nonsuppurative complications nor is the patient likely to spread the disease to others.[50] Although asymptomatic patients need neither culture nor management if results of follow-up culture are positive, certain high-risk situations should be approached differently. For example, if a family member had rheumatic fever or if a family has been experiencing recurrent streptococcal illness, another course of antibiotics would be recommended for the carrier. Patients who become symptomatic after an appropriate course of therapy may indeed represent true management failures for which a second course of therapy would also be justified.[50]

Tonsillar Concretions/Tonsilloliths

Tonsillar concretions or tonsilloliths (Fig. 196-5) arise from retained material and bacterial growth in the tonsillar or adenoid crypts and may exist in patients with or without a history of inflammatory disorders in either the tonsils or adenoids.[51] The clinical presentation of fetor oris (halitosis) and sore throat as well as the presence of whitish, expressible,

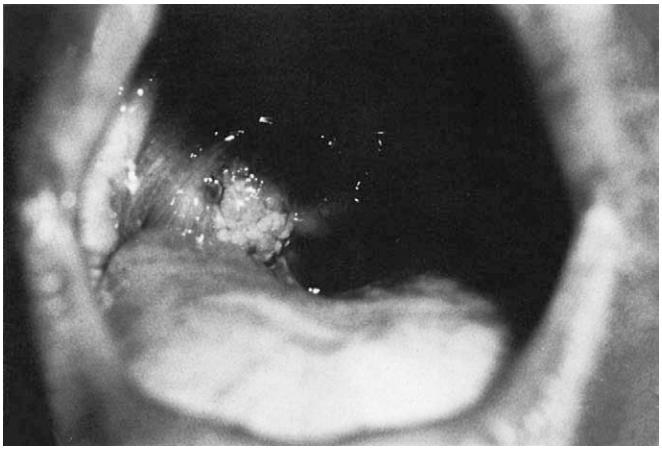

Figure 196-5. Tonsillolith of the right tonsil.

foul-tasting, and foul-smelling cheesy lumps from the tonsils characterizes the tonsillar concretions in many patients. Local management involves simple expression of the concretions by the patient, the use of pulsating jets of water to clean the pockets of debris mechanically, or application of topical silver nitrate to the tonsillar crypts in an effort to chemically cauterize and obliterate them. Persistent problems with pain, halitosis, foreign body sensation, or otalgia may require surgical removal of the tonsils as definitive therapy.

Complications of Tonsillitis

The complications of tonsillitis can be broken down into nonsuppurative and suppurative complications. Nonsuppurative complications include scarlet fever, acute rheumatic fever, and poststreptococcal glomerulonephritis. Suppurative complications are the result of abscess formation and include peritonsillar and parapharyngeal abscess development.

Nonsuppurative Complications

Scarlet fever is secondary to acute streptococcal tonsillitis or pharyngitis with production of endotoxins by the bacteria.[33] Manifestations include an erythematous rash; severe lymphadenopathy with a sore throat; vomiting; headache; fever; erythematous tonsils and pharynx; tachycardia; and a yellow exudate over the tonsils, pharynx, and nasopharynx. The membrane that is present over the tonsils is usually more friable than that seen with diphtheria. A strawberry tongue with a rash and large glossal papillae is a good diagnostic sign. Diagnosis of scarlet fever is made by culture and positive result of the Dick test, which is an intradermal injection of dilute streptococcal toxin.[34] Management of this condition involves intravenous administration of penicillin G. Otologic complications may include necrotizing otitis media with complete loss of the tympanic membrane and ossicles.

Fortunately, acute rheumatic fever is an uncommon illness in the United States today. The incidence of rheumatic fever following sporadic streptococcal infection is approximately 0.3%.[50] A patient with rheumatic fever who does not comply with penicillin prophylaxis should have a tonsillectomy and adenoidectomy because patients who have undergone surgery have a lower infection rate with β-hemolytic streptococcus.[52]

Poststreptococcal glomerulonephritis may be seen after both pharyngeal and skin infections. The incidence is approximately 24% after exposure to nephrogenic strains, but these strains account for less than 1% of the total pharyngeal strains.[50] Typically, an acute nephritic syndrome develops 1 to 2 weeks after a streptococcal infection. The infection is secondary to the presence of a common antigen of the glomerulus with the streptococcus. Penicillin management may not decrease the attack rate, and there is no evidence that antibiotic therapy affects the natural history of glomerulonephritis. A tonsillectomy may be necessary to eliminate the source of infection.

Suppurative Complications

Peritonsillar Infections

Peritonsillar abscess most commonly occurs in patients with recurrent tonsillitis or in those with chronic tonsillitis that has been inadequately treated. The spread of infection is from the superior pole of the tonsil with pus formation between the tonsil bed and the tonsillar capsule.[33] This infection usually occurs unilaterally and the pain is quite severe, with referred otalgia to the ipsilateral ear a few days after the onset of tonsillitis. Drooling is caused by odynophagia and dysphagia. Trismus is frequently present as a result of irritation of the pterygoid musculature by the pus and inflammation. There is gross unilateral swelling of the palate and anterior pillar with displacement of the tonsil downward and medially with reflection of the uvula toward the opposite side. Cultures of the peritonsillar abscess usually show a polymicrobial infection, both aerobic and anaerobic.[53]

Needle aspiration may be used to obtain a test aspirate and identify the site of the abscess. If pus is found on needle aspiration, the abscess may be opened with a long-handled scalpel to incise the mucosa over the abscess and a blunt-tip hemostat to spread and break up the loculi, draining as much pus as possible. If there has been a previous history of tonsillitis, a Quinsy tonsillectomy may be quite effective. This removes the possibility of recurrent infections and allows swift improvement of the patient's condition. This procedure is particularly favored in younger patients in whom further tonsillar infections are more likely and because of the difficulty of needle aspiration or surgical drainage in children under local anesthesia. Care must be taken to avoid abscess rupture and pus inhalation during the induction of anesthesia and endotracheal intubation.

Cellulitis should be differentiated from abscess in the management of peritonsillar infections. Some abscesses may be clinically obvious, whereas others are less obvious. When there is extension of infection of the peritonsillar abscess, computed tomography (CT) with contrast enhancement may be indicated (Fig. 196-6).

The choice between needle aspiration and incision and drainage in the management of peritonsillar abscesses is controversial. Traditional management has consisted of incision and drainage, with tonsillectomy 4 to 12 weeks later. Some surgeons advocate immediate tonsillectomy or Quinsy tonsillectomy as definitive management to ensure complete drainage of the abscess and to alleviate the need for a second hospitalization for an interval tonsillectomy.[54] Each therapeutic modality has advantages in certain situations. If incision and drainage or needle aspiration fails to drain an abscess adequately, a Quinsy tonsillectomy is indicated. In patients with a prior history of recurrent peritonsillar abscess or recurrent tonsillitis severe enough to warrant tonsillectomy, a Quinsy tonsillectomy should be considered. Quinsy tonsillectomy is particularly favored in children because they are likely to experience further episodes of tonsillitis, and needle aspiration or incision and drainage with a child under local anesthesia is often difficult or impossible.

Parapharyngeal Space Abscess

An abscess can develop in the parapharyngeal space if infection or pus drains from either the tonsils or from a peritonsillar abscess through the superior constrictor muscle.[33] The abscess is located between the superior constrictor muscle and the deep cervical fascia and causes displacement of the tonsil on the lateral pharyngeal wall toward the midline. Involvement of the adjacent pterygoid and paraspinal muscle with the inflammatory process results in trismus and a stiff neck. The thickness of the overlying sternocleidomastoid muscle often prevents the detection of fluctuance by palpation.

Patients with parapharyngeal space infections characteristically exhibit fever, leukocytosis, and pain. Progression of the infectious process of the abscess may spread down the carotid sheath into the mediastinum. As with most soft-tissue infections of the neck, lateral pharyngeal space infections are polymicrobial and usually reflect oropharyngeal flora. Intraoral examination reveals swelling of the lateral pharyngeal wall, especially behind the posterior tonsillar pillar. Anteromedial tonsil displacement is present. Clinically this may be confused with a peritonsillar abscess, so if indicated, a CT scan with contrast

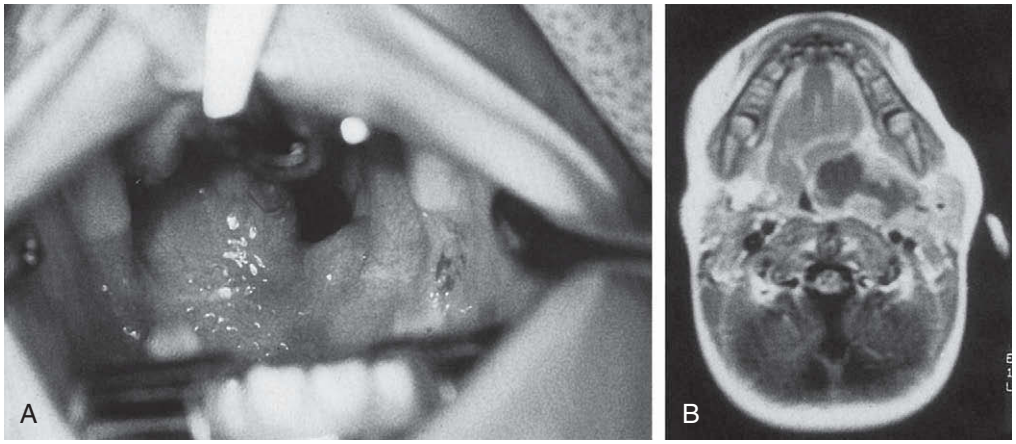

Figure 196-6. **A,** Left peritonsillar abscess in an 18-month-old child. **B,** Magnetic resonance image of the peritonsillar abscess in the same patient, showing extension of the abscess into the retropharyngeal space.

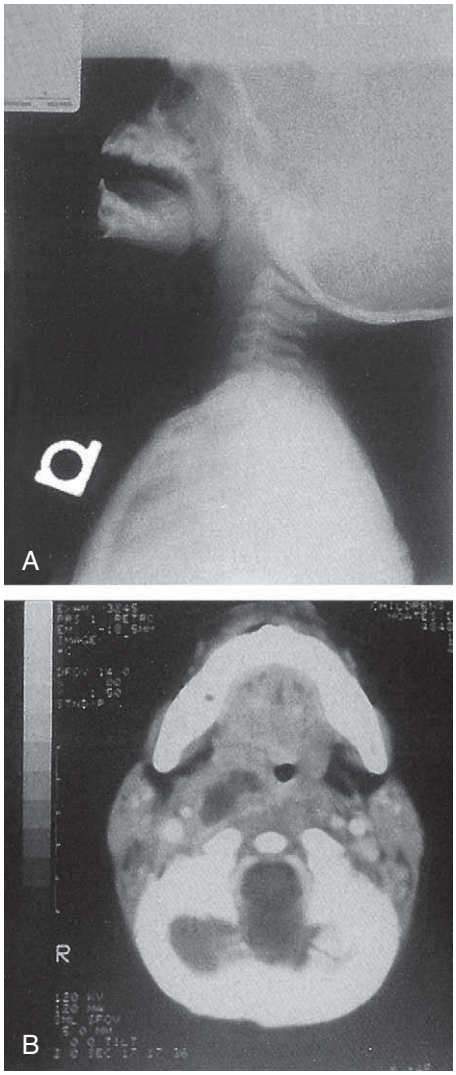

Figure 196-7. **A,** Lateral neck radiograph showing a retropharyngeal abscess. **B,** Computed tomography scan of the same patient.

Figure 196-8. Tonsillar hypertrophy with significant pharyngeal obstruction.

enhancement should be obtained. Neurologic deficits involving cranial nerves IX, X, and XII may occur.

Initially, lateral pharyngeal space infections should be managed with aggressive antibiotic therapy, fluid replacement, and close observation. Surgical intervention is often required to bring about resolution of these infections. Intraoral approaches should be confined to management of peritonsillar abscesses and should not be used in true lateral pharyngeal space abscesses because of inadequate exposure if severe bleeding arises. An external approach to the parapharyngeal space usually consists of a transverse submandibular excision approximately 2 cm inferior to the mandibular margin, which extends from the anterior limits of the submandibular gland just past the angle of the mandible. The submandibular gland is freed inferiorly and posteriorly by sharp, blunt dissection, and access to the space is achieved by dissection between the tail of the submandibular gland and the anterior aspect of the sternocleidomastoid muscle. With this approach, the skull base can easily be explored.

Retropharyngeal Space Infections

The superior limit of the retropharyngeal space is the cranial base. Inferiorly, the retrovisceral space extends into the mediastinum to approximately the level of the tracheal bifurcation. The buccal pharyngeal fascia is adherent to the prevertebral fascia in the midline, so that infection in the retropharyngeal space is unilateral. Lateral neck radiography, CT, or ultrasonography may help ascertain whether there is cellulitis or a true abscess (Fig. 196-7). The source of the retropharyngeal abscess is a chain of lymph nodes present on either side of the midline in the retropharyngeal space. These lymph nodes

receive drainage from the nose, paranasal sinuses, pharynx, and eustachian tube.

Retropharyngeal space infections occur most commonly in children younger than 2 years. Children with infection in the retropharyngeal space usually present with irritability, fever, dysphagia, muffled speech, noisy breathing, stiff neck, and cervical lymphadenopathy. Physical examination usually shows unilateral posterior pharyngeal swelling, which is visualized on inspection of the child's pharynx.

A transoral approach is recommended for incision and drainage of retropharyngeal space abscesses. If the abscess extends inferiorly below the hyoid bone (shown on the CT scan), an external approach should be used. The patient must undergo oral intubation, which can be done safely by introduction of the tube on the side opposite the abscess to avoid aspiration of purulent material. The patient must be positioned in the head-down Trendelenburg position, and packing should be placed around the endotracheal tube inferiorly. Gram staining, culture, and antimicrobial sensitivity staining should be performed on the purulent material. A small vertical incision is made in the lateral aspect of the posterior pharyngeal wall at a point between the junction of the lateral one third and medial two thirds of the distance between the midline of the pharynx and the medial aspect of the retromolar trigone.[55] The space is gently probed with a hemostat to break up the loculations and drain the abscess. A drain is not used because of the possibility of aspiration if swallowed postoperatively. If the abscess extends laterally to involve the parapharyngeal space, it should be drained through an external approach.

Chronic Adenotonsillar Hypertrophy

Etiology

Chronic adenotonsillar hypertrophy—manifesting as various degrees of airway obstruction in children—has become the most common indication for adenotonsillectomy in the United States.[56] Typically, the tonsils and adenoids are very small at birth and progressively enlarge over the first four years of life as a result of increased immunologic activity (Figs. 196-8 and 196-9). Brodsky and colleagues[27,57] reported that hypertrophied and chronically infected tonsils and adenoids had greater loads of pathogenic bacteria, especially β-lactamase producers, than nondiseased tonsils and adenoids.[57,58] These studies were based on core samples that were believed to be more accurate than surface cultures of the tonsils and adenoids. It is possible that equilibrium exists between the normal flora of the adenotonsillar tissue and their local immunologic response and that this equilibrium can become disrupted with recurrent acute viral or bacterial infections or colonization with pathogenic bacteria, resulting in hypertrophied lymphoid tissue.[27]

In addition to chronic bacterial infection, exposure to secondhand smoke has been implicated as a cause of adenotonsillar hypertrophy in children.[8]

Airway Obstruction

Obstructive sleep apnea is the most common indication for tonsillectomy in the pediatric population. Pediatric obstructive sleep apnea, confirmed by polysomnography, is reported to have an incidence of 1% to 3%.[59-61] The obstructive apnea is almost always associated with hypertrophy of the tonsils and adenoids. The tonsil and adenoid tissue, when large, fills the area of the oropharynx and nasopharynx, obstructing airflow. This obstruction is worse when the patient is supine and asleep owing to the effects of gravity and the relaxation of surrounding nasopharyngeal and oropharyngeal soft tissue. The obstruction can result in a mildly compromised airway, which leads to snoring, and most children with airway obstruction related to adenotonsillar hypertrophy have a history of significant snoring at night.[28,31,59,62,63] The obstruction may lead to intermittent complete airway obstruction with subsequent apnea and oxygen desaturation. The apnea typically is short and usually associated with a brief arousal wherein the patient repositions himself or herself and opens the airway. However, if the apnea is prolonged, oxygen desaturation can occur. Such desaturation episodes put stress on the cardiovascular system.

Before the syndrome of obstructive sleep apnea was widely recognized, children sometimes presented with pulmonary hypertension and cor pulmonale, failure to thrive, and developmental delay.[64] Such severe consequences rarely occur now, but the sleep disturbance manifests as multiple clinical symptoms that are commonly seen. Some of the more common symptoms that occur during the sleep of affected children are loud "heroic" breathing, diaphoresis, apnea, gasping, mouth-breathing, restless sleep, enuresis, drooling, night terrors, and sleepwalking. During the day affected children may suffer from daytime sleepiness, morning headache, dry mouth, halitosis, swallowing difficulty, behavioral difficulties and hyponasal speech, or, rarely, hypernasal speech (rhinolalia aperta) caused by enlarged tonsils impinging on normal palatal movement.[63] Behavioral difficulties include hyperactivity, inattentiveness in the classroom, problems with academic performance, and rebellious or aggressive behavior. The aforementioned behavioral difficulties are also clinical manifestations of the most commonly diagnosed psychiatric diagnosis in children—attention deficit–hyperactivity disorder (ADHD).

Today obstructive sleep apnea and its consequences are widely recognized, and for that reason it is the primary indication for tonsillectomy in this country.[65] There is no debate about the existence of the obstructive sleep apnea syndrome or that adenotonsillectomy is the treatment of choice. However, there is considerable debate about the methods of diagnosis and therefore considerable discussion about exactly how large a group of children is affected by the syndrome (see Chapter 183 for a full discussion).

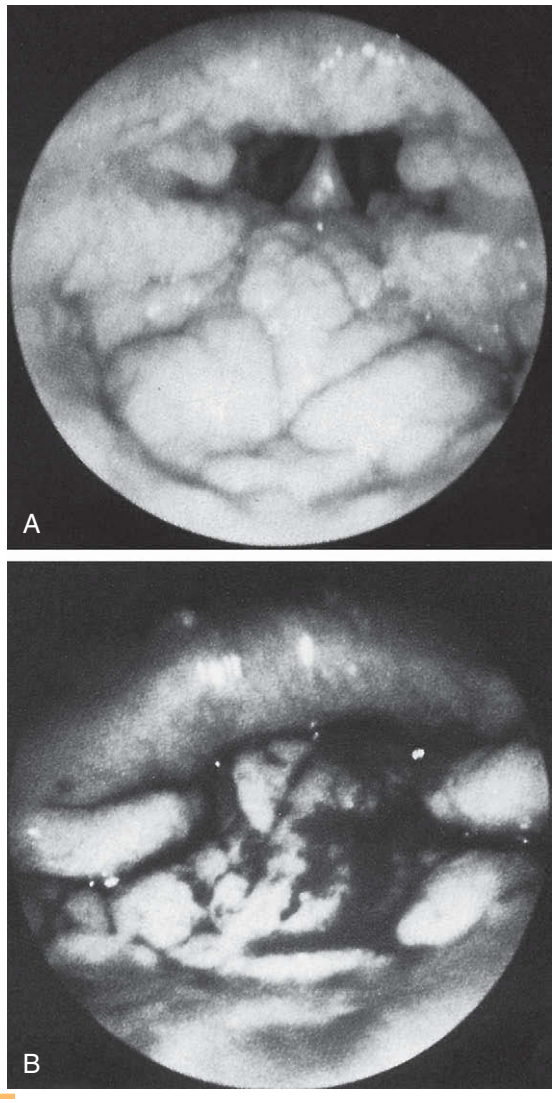

Figure 196-9. A, Endoscopic view of mild adenoid hypertrophy. **B,** Severe adenoid hypertrophy with total choanal obstruction.

Attention Deficit–Hyperactivity Disorder

As previously noted, inattention and hyperactivity are some of the daytime symptoms shown to have a relationship to pediatric sleep-disordered breathing (SDB). This relationship has been demonstrated in studies of children in whom obstructive sleep apnea syndrome has been documented by formal sleep study. However, an increased incidence of inattention and hyperactivity has also been found in children with significant snoring but with negative sleep study results, as well as in groups of snoring children without any formal sleep testing.

Numerous articles in the literature have shown a significant relationship between sleep-disordered breathing and the symptoms of ADHD. One study investigated 996 children aged 4 to 5 years seen consecutively in a community health clinic. Of the 782 for whom the questionnaires were completed, 95 or 12% of the children were found to snore on most nights. A group of 66 children considered at high risk for sleep disturbance was selected from these 95 children and compared with a control group who had no symptoms of sleep disturbance. The study used a modified version of the Conner's behavioral scale to assess symptoms of hyperactivity. These 66 children were studied with overnight oximetry and video monitoring. According to results of the overnight study, only 7 of the 66 children in the high-risk group had documented obstructive sleep apnea syndrome, but all the children in this high-risk group had significantly higher scores on parental and teacher reports of hyperactive behavior.[60]

Another study looked at the relationship between the symptoms of sleep-disordered breathing and problem behavior including hyperactivity and inattention. The study enrolled 3019 5-year-old children. The researchers used a questionnaire to evaluate for symptoms of sleep-disordered breathing as well as problems with behavior, and had a subset of 219 children's families complete the Revised Conners' Parent Rating Scale as a means of validating the results obtained with limited initial questioning. Symptoms of sleep-disordered breathing were present in 25% of the children. A strong association was found between parent-reported sleep problems and the parent-reported incidence of inattention, hyperactivity, and aggressiveness. Interestingly, a dose-response effect on problem behaviors was seen for both snoring frequency and snoring loudness. These results remained significant even when data were adjusted for sex, race, maternal education level, maternal marital status, household income, and respiratory history. Such adjustments had not been made in previous reports on the link between SDB and ADHD.[66]

A different study evaluated 2076 children and found 71 with behavioral or academic problems. These children had significantly more problems with snoring and difficulty breathing. This association was found to be strongest with children who had academic problems or in children whose specific behavioral problem was consistent with ADHD.[67]

Other studies have examined this issue from the opposite direction, evaluating a group of children diagnosed with neuropsychological problems and searching for signs and symptoms of SDB. These studies show that children with neuropsychological problems have a higher percentage of sleep problems than normal controls. Marcotte and associates looked at 200 children referred for psychiatric evaluation for possible ADHD; 79 children were diagnosed with ADHD, learning disability, or combined ADHD–learning disability. Through parent questionnaires, the investigators found a high incidence of reported sleep problems at night in comparison with the incidence in a control group of children. They did not find any difference in the reported length of sleep. Thus, the effect seems to depend on quality, not quantity, of sleep.[68]

Another study surveyed a group of parents at a child psychiatry unit and a group of patients at a general pediatric clinic. Children at the psychiatry clinic with the diagnosis of ADHD had a 33% incidence of habitual snoring, compared with 11% of the other children at the psychiatry clinic and 9% in those at the general pediatric clinic. Higher snoring scores derived from the validated pediatric sleep questionnaires were associated with higher levels of inattention and hyperactivity, again pointing to an apparent dose-response relationship.[69]

The pathophysiology of ADHD is unknown, but there are suggestions that an abnormal sleep pattern may be one causal factor. It has long been known that stimulants improve behavior in patients with ADHD. Stimulants are believed to work because ADHD is a disorder caused by hypovigilance rather than hypervigilance.[70] If hypovigilance is indeed the mechanism, it makes sense that a child with decreased or poor sleep secondary to obstructive sleep apnea syndrome would be much more likely to suffer from symptoms of ADHD. Consequently, if the sleep obstruction was removed, it should follow that the quality of sleep would improve and therefore symptoms of ADHD would diminish.

One small article in the European literature did show that symptoms of ADHD diminished after adenotonsillectomy.[71] At this point, however, no large prospective studies have looked carefully at this issue. This is an area of active research in the literature and one that receives a lot of attention, but still more work must be done to better clarify the cause-and-effect relationships.

Neurocognitive Development

Sleep is an important part of a child's growth and development, particularly during periods of brain maturation. Among different species, greater sleep requirements have been seen in maturing as opposed to fully mature individuals. Sleep, particularly in children, can be a very active process and may play a key role in proper brain maturation.

Multiple studies have indicated that children with a childhood history of snoring and SDB may have alteration in normal neurocognitive development. One study evaluated 297 first-grade children whose school performance was in the lowest 10th percentile in their class ranking. With both a parental questionnaire and overnight pulse oximetry monitoring and transcutaneous monitoring of partial pressure of carbon dioxide, the group was screened for signs and symptoms of a sleep disorder. The researchers found that 54 (18.1%) of these children had sleep-associated gas exchange abnormalities. Parents of these children were all offered surgical treatment, and 24 underwent tonsillectomy and adenoidectomy; parents of the remaining 30 refused surgical treatment. The group undergoing surgical treatment had a significant improvement in school scores the following year, whereas, the group refused treatment and a control group had no change in year-to year scores.[72]

In another study, the author sent questionnaires to the parents of seventh and eighth graders whose test scores placed them in either the top 25% or bottom 25% of the class. These students were matched for age, gender, race, address, and schools. The parents were sent questions related to their child's sleeping habits from age 2 to 6 years, in which the primary indicators of sleep disturbance were snoring frequency and loudness. Only those with reported loud frequent snoring during childhood years were included in the group with suspected sleep disorder. The few children with current snoring were excluded. The investigators ultimately had 800 students in each group and found that frequent and loud snoring was reported in 12.9% of the low-performing students, but in 5.1% of the high-performing children.[73] To the investigators, these results indicated that a significant sleep disturbance during the early important years of neurocognitive development may create deficits that cannot be overcome later in life, after the sleep disturbance has resolved.

One study compared the results of neurocognitive testing between 16 snoring children and 13 normal controls aged 5 to 10 years. Of the snoring children, 13 completed polysomnograms and none had clinically defined obstructive sleep apnea. The researchers found that the snoring children had lower attention, memory, and intelligence scores. They concluded that the impact of clinically mild SDB may be greater than suspected and may significantly affect future development of the child.[74]

Another study looked at a large community sample of 5-year-old children. The investigators screened the children for SDB and found that those with symptoms of SDB had significantly lower scores on a wide range of neurocognitive studies. These studies included assessments of executive function, memory, and general intellectual ability. All the test results were adjusted for any potentially confounding sociodemographic or health issues.[66] This study found that the differences in cognitive function were present even if the children with polysomnography-confirmed obstructive sleep apnea were excluded. Thus, even in children with what has been referred to as "primary snoring" were shown in this study to have measurable neurocognitive deficits.

The mechanism underlying possible cognitive deficits remains unclear. Three major processes occur during the sleep of children with upper airway obstruction—episodic hypoxia, repeated arousal leading to sleep deprivation or sleep fragmentation, and periodic or continuous alveolar hypoventilation combined with intermittent hypercapnia. Which of these sequelae or in what proportion they may be responsible for cognitive impairment is not known.[73] Central nervous system development is an ongoing process from infancy to adolescence, and developing neural elements are most likely more susceptible to injury. Neurocognitive deficits in children affected with SDB may be more prominent in the area of the prefrontal cortex because these areas do not finish development until adolescence.[75]

The National Institutes of Health–sponsored 2003 National Sleep Disorders Research Plan states, "In recent years it has become apparent that SDB and snoring are not as innocuous as previously thought." The report continues that failure to diagnose and treat such disorders in a timely manner may lead to long-lasting residual consequences. "However, the point of transition between what constitutes pathology and what is normal has yet to be defined."[76] In an editorial, one researcher active in this area discussed the accumulating evidence of a causal relationship between pediatric SDB and neurocognitive deficits. He concluded his thoughts, "The remaining but complex challenge will be to define at what age, and by what means, intervention will be required to prevent long-term neurocognitive dysfunction."[77]

An article by Garetz[78] offers a good review of the literature surrounding the issues of behavior and cognition associated with SDB. She discusses the need for further research while pointing out that none of the studies in this area has been randomized, and few studies have addressed well how ethnicity and obesity may play a role in these areas. Clearly, many questions are left unanswered at this point. First, we do not know what the dose-response relationship is between SDB and neurocognitive impairment. How long should a child be allowed to snore before treatment is recommended? We know snoring resolves spontaneously in many children, so how long do we allow a child's snoring to persist before we have concern that cognitive function will be affected? Is the tolerable length of time related to the age of the child—is a child more sensitive to the effects of sleep disturbance at 3 years or 7 years, and thus should we wait less time in a 3- year-old with significant SDB? These are all questions that further research must address.

Enuresis

Enuresis is another indicator of severe underlying airway obstruction in children. Weider and associates[79] described enuresis related to chronic adenotonsillar hypertrophy and significant airway obstruction that was relieved by adenotonsillectomy. In this study, all patients with secondary enuresis (developed later during childhood) showed response to adenotonsillectomy, whereas 24 patients with primary enuresis (congenitally present) showed no response to surgery, possibly as a result of other neurologic factors. A proposed cause of enuresis is poor nocturnal regulation of antidiuretic hormone release that is related to disorders of rapid eye movement (REM) sleep.

Growth Problems

Children with chronic adenotonsillar hypertrophy and airway obstruction may also present with failure to thrive.[64,80] A review of the literature further confirmed this apparent relationship between SDB secondary to adenotonsillar hypertrophy and the risk of growth failure in children.[81] This relationship may be related to abnormal regulation of growth hormone. During rapid eye movement sleep, growth hormone may be severely disrupted in children with obstructive sleep apnea.[80] Several studies have confirmed a postoperative increase in circulating insulin-like growth factor and its binding proteins in children with obstructive sleep apnea secondary to adenotonsillar hypertrophy.[82,83]

Cardiopulmonary Complication

Severe cases of sleep obstruction may result in cor pulmonale, pulmonary vascular hypertension, and alveolar hypoventilation, all of which may be reversed by adenotonsillectomy (Fig. 196-10).[19,84,85] The etiology of cor pulmonale is related to chronic upper airway obstruction, which leads to pulmonary ventilation-perfusion abnormalities and chronic alveolar hypoventilation. The result is chronic hypercapnia and hypoxia with respiratory acidemia, pulmonary artery vasoconstriction, and right ventricular dilation. Eventual cardiac failure may occur.[31,86,87] Relief of upper airway obstruction by adenotonsillectomy will eventually reverse this condition. However, increased partial pressure of carbon dioxide (P_{CO_2}) values may persist after relief of the obstruction, occasionally requiring prolonged endotracheal intubation and mechanical ventilation until P_{CO_2} values return to normal.

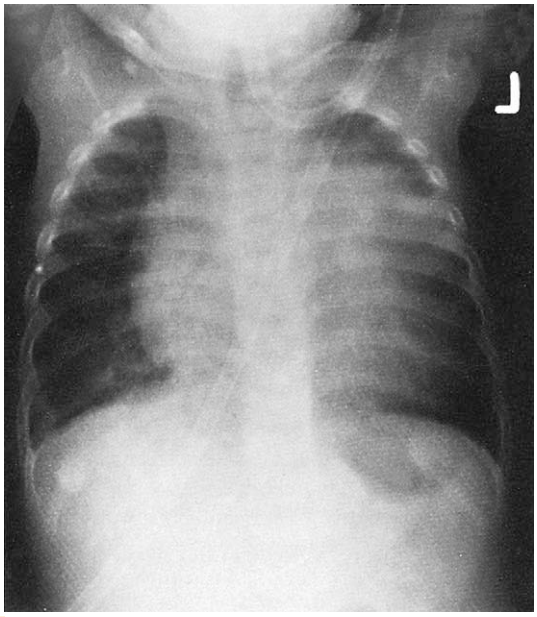

Figure 196-10. Posteroanterior chest radiograph of a patient with adenotonsillar hypertrophy, severe airway obstruction, pulmonary vascular hypertension, and cor pulmonale.

Craniofacial Growth and Adenotonsillar Hypertrophy

Chronic mouth-breathing secondary to adenotonsillar hypertrophy and upper airway obstruction has been shown to affect craniofacial growth patterns in children. As early as 1872, Tomes[88] reported that children who were chronic mouth-breathers secondary to adenoid hypertrophy displayed evidence of malocclusion and maxillofacial growth abnormalities. Mouth-breathing leads to downward and backward displacement of the mandible and tongue and potential postural changes of the head and neck that may secondarily affect dental occlusion and jaw growth.[89] Numerous animal and human studies have demonstrated the effect of chronic nasal obstruction on maxillofacial growth patterns. Harvold[90] showed that chronic nasal obstruction may lead to narrow maxillary dental arches in rhesus monkeys. Linder-Aronson and colleagues[91] demonstrated the classic stigmata of adenoid facies in children with chronic nasopharyngeal obstruction from adenoid hypertrophy. These consisted of longer total anterior face height with a tendency toward a retrognathic mandible in comparison with controls.

Adenotonsillectomy has been shown to reverse some of these findings.[91,92] Other investigators have confirmed the relationship between chronic nasal obstruction, adenotonsillar hypertrophy, and increased facial height.[93,94] A later study showed a significant correlation between adverse cephalometric data and adenotonsillar hypertrophy in a group of children 4 to 12 years old.[95] Although there is significant support in the literature for the effect of upper airway obstruction and adenotonsillar hypertrophy on craniofacial growth, other studies have been less conclusive about this relationship.[94,96,97] Maxillofacial growth disturbances in children who are mouth-breathers may also be multifactorial in etiology.[98] As a result of this apparent relationship among upper airway obstruction, adenotonsillar hypertrophy, and craniofacial

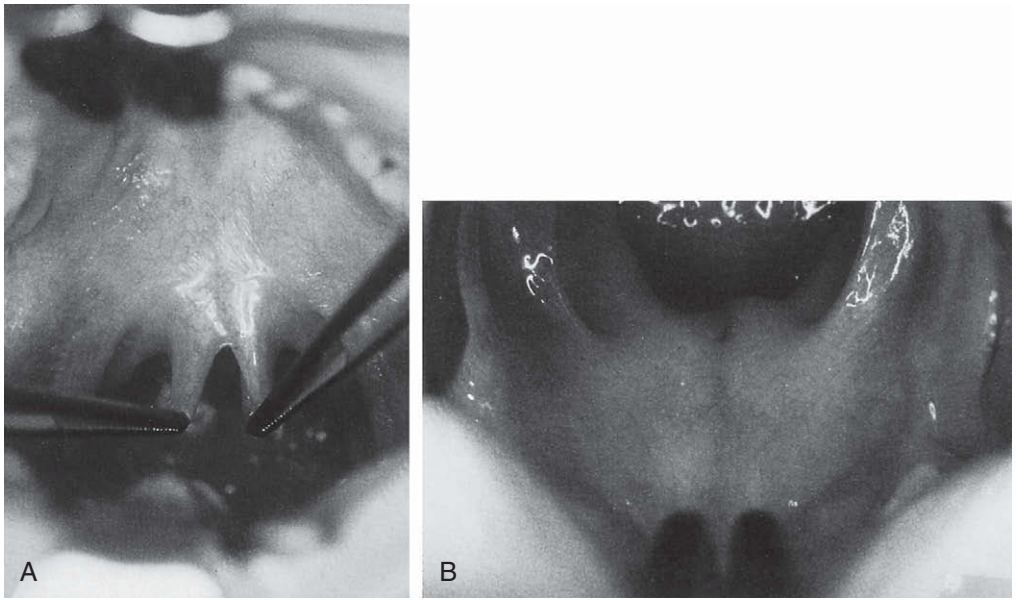

Figure 196-11. **A,** Bifid uvula in a patient with a submucous cleft palate. **B,** Submucous cleft palate.

growth disturbance, an otolaryngologic evaluation may be warranted in children undergoing orthodontic procedures for malocclusion who show evidence of adenotonsillar hypertrophy and mouth-breathing.

Diagnostic Assessment of the Tonsils and Adenoids

The physical examination of patients with suspected adenotonsillar disease should include a thorough head and neck examination to rule out manifestations of chronic adenotonsillar hypertrophy (i.e., the craniofacial stigmata of chronic nasal obstruction, which includes open-mouth breathing, an elongated face, dark circles under the eyes, and evidence of dental malocclusion). Other possible causes of nasal obstruction and these findings (e.g., turbinate hypertrophy secondary to allergic rhinitis) should also be evaluated. It is important to listen to the patient's speech to assess the presence of hyponasality. Having the child repeat words such as "Mickey Mouse," which emphasize nasal emission, and "baseball," which does not, better illuminates the presence of hyponasality.[4]

Brodsky and coworkers[57] described an assessment scale for tonsillar hypertrophy. In this scale, 0 indicates that the tonsils do not impinge on the airway; 1+ indicates less than 25% airway obstruction; 2+ indicates 25% to 50% airway obstruction; 3+ indicates 50% to 75% airway obstruction; and 4+ indicates more than 75% airway obstruction. It is also important to assess the palate on oral examination. Patients with evidence of overt or submucous cleft palate are at increased risk for the development of velopharyngeal insufficiency (VPI) after adenoidectomy. Submucous cleft palate may manifest only as a bifid uvula. However, notching of the posterior hard palate may be palpable, and an obvious translucent line through the mid–soft palate may be evident (Fig. 196-11). Although diagnostic assessment of the tonsils is apparent with oral examination, evaluation of adenoid tissue is much more difficult because it is not easily accessible on physical examination.

Lateral neck radiography may be helpful in assessing adenoid hypertrophy (Fig. 196-12). Fujioka and associates[99] determined that the adenoid-nasopharyngeal ratio, measured by lateral neck radiography, closely correlated with clinical symptomatology related to adenoid hypertrophy. This conclusion has been confirmed by other reports.[100] However, physiologic variations during nasal and oral breathing may affect these nasopharyngeal dimensions as measured by lateral neck radiography.[101] Furthermore, during an upper respiratory or sinonasal infection, significant nasopharyngeal secretions and purulence can obscure the nasopharynx and give the false impression of adenoid obstruction.

Figure 196-12. Lateral neck radiograph demonstrating significant adenoid hypertrophy and nasopharyngeal obstruction.

Lateral neck radiography is not necessary for the evaluation of all patients with suspected adenoid hypertrophy. Patients with significant obstructive symptomatology and obvious tonsillar hypertrophy most likely require surgical intervention, and findings on lateral neck radiography would not alter the decision to proceed with surgery. Patients with significant nasal obstruction and insignificant tonsillar hypertrophy should undergo radiographic assessment of the nasopharynx. Patients with significant nasal obstruction and evidence of allergic rhinitis may have concurrent underlying adenoid hypertrophy and would benefit from lateral neck radiography.

Flexible endoscopic nasopharyngoscopy may also be valuable in the assessment of adenotonsillar disease. With appropriate topical anesthesia, pediatric endoscopes, and reassurance from the physician, children generally tolerate this procedure well. The presence of adenoid tissue obstructing the posterior nasal choana will be apparent with this technique. The degree of hypopharyngeal extension of tonsillar hyper-

trophy may also be apparent. Sometimes tonsils that do not appear significantly large on oral examination can be seen to impinge upon and actually push back the epiglottis when viewed from above with the flexible laryngoscope. VPI secondary to tonsillar hypertrophy limiting palatal movement will be apparent on nasopharyngoscopy. The presence of adenoiditis may also be diagnosed from the presence of purulent secretions covering the adenoid pad. Wormald and Prescott[102] and Wang and others[103] demonstrated the greater efficacy of flexible nasopharyngoscopy in comparison with lateral neck radiography and clinical symptomatology in the assessment of adenoid hypertrophy in children. Rhinomanometry has also been demonstrated to correlate with the presence of nasal obstruction secondary to adenoid hypertrophy; however, this test is not well tolerated by children, is difficult and time-consuming to administer, and is probably not of clinical benefit in its current form.[104]

The role of polysomnographic testing in children has been previously reported.[64,80,105] Because of the high cost of polysomnography, it is important for the otolaryngologist to be selective in referring patients for this diagnostic modality. Furthermore there are few dedicated pediatric sleep laboratories and the wait for a study can often be very long. Patients with obvious symptoms related to adenotonsillar hypertrophy confirmed by physical examination most likely do not require polysomnographic testing. Patients with significant symptomatology—suggesting sleep apnea or a significant sleep disturbance without evidence of significant adenotonsillar hypertrophy on examination—should undergo polysomnographic testing to determine the severity of the sleep disturbance. Children with significant comorbidities that may increase surgical risk are also candidates for a polysomnogram to help in the preoperative risk-benefit assessment of surgical intervention. A polysomnogram may also help in the evaluation of the neurologically compromised child, in order to differentiate between obstructive and central apnea, because surgery is not likely to improve the latter. Screening chest radiography and electrocardiography are also recommended in the preoperative assessment of severe cases.

Preoperative Assessment

Preoperative assessment in patients undergoing adenotonsillectomy is crucial and may reveal problems that could complicate either surgery or the patient's postoperative course. It is crucial to detect the existence of any coagulation abnormalities. A family history of coagulation disorders or easy bruising may be a warning sign of an underlying bleeding disorder that warrants further hematologic evaluation. Routine evaluation of coagulation parameters before surgery in patients undergoing adenotonsillectomy is controversial. Manning and colleagues,[106] examining the records of 994 of 1050 consecutive patients undergoing tonsillectomy, adenoidectomy, or adenotonsillectomy, determined that evidence of coagulation disorders in patients with no clinical history of or findings consistent with a hematologic disorder was extremely low, thereby not justifying routine preoperative coagulation studies. This conclusion was confirmed by Close and associates,[100] who suggested that excessive bleeding associated with tonsillectomy was usually not the result of an identifiable coagulation disorder.

Conversely, Kang and coworkers[107] studied the risk of postoperative hemorrhage in 1061 children undergoing adenotonsillectomy. In this study, 2.5% of the children had at least one abnormality on preoperative coagulation screening, which consisted of determinations of prothrombin time, partial thromboplastin time, bleeding time, and platelet count. These researchers suggested that, although hematologic disorders were diagnosed infrequently by preoperative coagulation screening, the coagulation profile may detect patients who are more likely to bleed postoperatively.[107] This suggestion is consistent with the findings of Bolger and colleagues,[108] who demonstrated abnormal initial coagulation screening results in 11.5% of patients undergoing adenotonsillectomy. It is apparent that patients who have an obvious family or clinical history of excessive bleeding or an underlying hematologic disorder require close monitoring of coagulation profiles and consultation with a hematologist. Use of preoperative coagulation screening should be left to the discretion of the surgeon until its role is better clarified by further study.

Box 196-1

Surgical Indications for Tonsillectomy

Infection

- Recurrent, acute tonsillitis (more than 6 episodes per year or 3 episodes per year for 2 years or longer)
- Recurrent acute tonsillitis associated with other conditions:
  - Cardiac valvular disease associated with recurrent streptococcal tonsillitis
  - Recurrent febrile seizures
- Chronic tonsillitis that is unresponsive to medical therapy and is associated with:
  - Halitosis
  - Persistent sore throat
  - Tender cervical adenitis
- Streptococcal carrier state unresponsive to medical therapy
- Peritonsillar abscess
- Tonsillitis associated with abscessed cervical nodes
- Mononucleosis with severely obstructing tonsils that is unresponsive to medical therapy

Obstruction

- Excessive snoring and chronic mouth-breathing
- Obstructive sleep apnea or sleep disturbances
- Adenotonsillar hypertrophy associated with:
  - Cor pulmonale
  - Failure to thrive
  - Dysphagia
  - Speech abnormalities
  - Craniofacial growth abnormalities
  - Occlusion abnormalities

Other

- Suspected neoplasia–asymmetric tonsillar hypertrophy

Patients with obvious severe airway obstruction secondary to adenotonsillar hypertrophy may require polysomnography, chest radiography, electrocardiography, and, possibly, cardiology consultation. Patients with cor pulmonale and hypercapnia may need postoperative intensive care monitoring with mechanical ventilation to avoid postobstructive pulmonary edema. If the severity of airway obstruction is not clear from history supplied by the parents, polysomnography may be warranted.

Patients with other medical conditions may require further testing or preoperative consultation. Patients with a history of significant bronchospasm may require pulmonary medicine evaluation and management in the perioperative period. Black patients should be screened for sickle cell disease preoperatively, and girls of reproductive age should undergo a preoperative serum β-human chorionic gonadotropin test to rule out pregnancy. Velocardiofacial syndrome may require preoperative angiography to determine the presence of abnormally medially displaced carotid arteries, which may be at risk during tonsillectomy.[109]

Adenotonsillectomy

The technique of adenotonsillectomy has evolved significantly over the past 2000 years, and various techniques are used today for extirpation of the tonsils and adenoids. Multiple tonsillectomy techniques exist, including the sharp dissection initially described by Crowe and associates[7]; various electrocauterization techniques; lasers (including potassium-titanyl–phosphate [KTP][110] and CO_2[52]); the tonsil guillotine; as well as newer technologies and techniques such as Coblation (ArthroCare Corporation, Austin, TX), the Harmonic Scalpel (Ethicon Endo-Surgery, Inc., Cincinnati, OH), and the Microdebrider (Medtronic Xomed, Inc., Jacksonville, FL). The number of adenotonsillectomies

Box 196-2

Surgical Indications for Adenoidectomy

Infection

Purulent adenoiditis

Adenoid hypertrophy associated with:

- Chronic otitis media with effusion
- Chronic recurrent acute otitis media
- Chronic otitis media with perforation
- Otorrhea or chronic tube otorrhea

Obstruction

Adenoid hypertrophy associated with excessive snoring and chronic mouth-breathing

Sleep apnea or sleep disturbances

Adenoid hypertrophy associated with:

- Cor pulmonale
- Failure to thrive
- Dysphagia
- Speech abnormalities
- Craniofacial growth abnormalities
- Occlusion abnormalities
- Speech abnormalities

Other

Suspected neoplasia

Adenoid hypertrophy associated with chronic sinusitis

performed in the United States appears to have peaked in the 1940s and 1950s.[56] In 1959, 1.4 million tonsillectomies were performed. This number decreased to 500,000 in 1979 and fell even further to 340,000 in 1985.[50,56] In the past 30 years there has been a significant decrease in the number of adenotonsillectomies performed in the United States, as well as a change in the preoperative indications for surgery. Whereas chronic infection was the primary surgical indication for adenotonsillectomy in the 1950s and 1960s, airway obstruction and obstructive sleep apnea have now become the most common preoperative indications for surgery.[56] Apparent drops in the number of adenotonsillectomies performed in the United States reflect a higher degree of selectivity by otolaryngologists and referring primary care physicians.

Indications

The current indications for tonsillectomy and adenoidectomy are shown in Boxes 196-1 and 196-2. Generally, the indications for adenotonsillectomy can be related primarily to chronic upper airway obstruction in conjunction with adenotonsillar hypertrophy, which manifests as snoring, obstructive sleep apnea, or chronic infectious conditions such as chronic recurrent tonsillitis.

Upper Airway Obstruction

Patients with airway obstruction related to adenotonsillar hypertrophy typically present with excessive snoring and sometimes with witnessed brief apneic events. The severity of the condition can often be elicited with a history supplied by the parents. However, there may often be no indications of airway obstruction other than loud snoring. It has been demonstrated that patients who snore loudly at night may manifest significant sleep apnea on polysomnographic testing when no significant parental history of witnessed apnea has been noted.[111] Patients who have obvious adenotonsillar hypertrophy on physical examination, a significant history of loud snoring with the associated symptoms of restless, disturbed sleep, or daytime somnolence do not necessarily need preoperative polysomnographic testing. If the parent is unclear about the severity of airway obstruction or if the physical findings and history are not consistent, preoperative polysomnographic testing is warranted to demonstrate the severity of airway obstruction.

Chronic Infections

Patients with chronic recurrent tonsillitis or chronic tonsillitis may benefit from tonsillectomy and possibly adenoidectomy. In 1995, the American Academy of Otolaryngology–Head and Neck Surgery Clinical Indicators Compendium stated that patients who have three or more infections of the tonsils and/or adenoids per year despite adequate medical therapy are candidates for tonsillectomy and adenoidectomy.[112] Other indications are chronic tonsillitis unresponsive to medical therapy that results in a persistent foul taste or halitosis and recurrent tonsillitis associated with the streptococcal state that has not responded to β-lactamase–resistant antimicrobial therapy.[112] The efficacy of elective tonsillectomy for recurrent sore throats has been demonstrated by numerous investigators.[113,114] The efficacy of elective tonsillectomy has also been shown in children with recurrent throat infections, including GABHS.[114]

In a study by Paradise and associates,[114] 187 children participated in a randomized clinical trial. Inclusion criteria for the study were seven or more sore throat episodes in the preceding year that were treated with antibiotics; five or more sore throat episodes in the 2 preceding years; or three or more episodes in each of the 3 preceding years. Elective tonsillectomy or adenoidectomy resulted in better status than that in a control group of children who were managed nonsurgically. Factors that should be taken into account in the consideration of surgery for recurrent throat infections in children are (1) the severity of each episode, (2) how well infections have responded to medical therapy, and (3) quality of life issues (e.g., number of school days missed).

Tonsillectomy and adenoidectomy should be considered in patients with recurrent tonsillitis, as well as other medical conditions such as cardiac valvular disease with recurrent streptococcal tonsillitis, a history of febrile seizures, poorly controlled diabetes, and, possibly, ventricular peritoneal shunts. Systemic infections in these situations could become life-threatening.

Tonsillectomy is the management of choice for peritonsillar abscess in children who do not tolerate needle aspiration. Peritonsillar abscesses that have been successfully drained by needle aspiration are not necessarily absolute indications for tonsillectomy. However, tonsillectomy is definitely indicated in cases of recurrent peritonsillar abscess.[54,115-117]

Although diphtheria is currently unusual, tonsillectomy may be warranted in patients who are diphtheria carriers and have not shown response to antibiotic therapy. Finally, patients with chronic halitosis related to debris in the tonsillar crypts or secondary to chronic tonsillitis are candidates for tonsillectomy.

Adenoidectomy

Indications

Adenoid hypertrophy or chronic adenoiditis may cause significant problems requiring adenoidectomy in situations in which the tonsils themselves are not diseased and are not contributing to symptomatology. Patients with chronic adenoid hypertrophy causing craniofacial morphology problems, excessive snoring, or, possibly, quality of life issues (e.g., poor olfaction) are candidates for adenoidectomy.[118] Adenoid hypertrophy may be confirmed by flexible nasopharyngoscopy or lateral cervical radiography.

Patients with a history of chronic recurrent sinusitis may also benefit from adenoidectomy. Patients with chronic sinusitis and significant adenoid hypertrophy may initially benefit from adenoidectomy rather than undergoing more extensive sinus surgery.[119] In addition, patients with chronic purulent rhinitis secondary to chronic adenoiditis may also have response to adenoidectomy if their rhinitis has not responded well to appropriate medical therapy. Evidence now points to a possible reason for the efficacy of adenoidectomy in these situations. Coticchia and colleagues[120] showed that biofilms were prominent in the adenoids of children with chronic sinusitis. The group compared pediatric adenoids removed for chronic sinusitis with those removed for obstructive sleep apnea. In the sinusitis-related adenoids, 94.9% of the mucosal surface was covered with dense mature biofilms, compared with just 1.9% of the surface in the hypertrophy-only adenoids. This

study suggests that the biofilms may be a natural reservoir for resistant bacteria and that their removal during adenoidectomy may be the reason for the observed benefit of the procedure.

Patients with hyponasal speech (rhinolalia clausa) are also candidates for adenoidectomy. Hypernasal speech (rhinolalia aperta) is a contraindication to adenoidectomy. However, in unusual cases, excessive tonsillar hypertrophy may impede palatal movement, which may improve after tonsillectomy.[121]

Although surgical intervention should be considered in cases of severe nasal obstruction related to adenoid hypertrophy, there is evidence that alternative medical therapy exists to manage adenoid hypertrophy. Demain and Goetz[122] demonstrated that aqueous nasal beclomethasone therapy led to significant improvement of nasal obstruction secondary to adenoid hypertrophy, which was confirmed by pre- and post-management flexible nasopharyngoscopy. In addition, patients with underlying inhalant allergies may benefit from antihistamine therapy and, possibly, from allergic immunologic desensitization therapy.

Conservative adenoidectomy should be performed in patients with a cleft palate or submucous cleft palate, leaving the lower portion of the adenoid pad intact to decrease the risk of postoperative VPI.

Adenoidectomy and Otitis Media

The role of the adenoids in the etiology of otitis media has been controversial. However, several investigations have demonstrated that appropriate management of the adenoids plays an important role in the diagnosis and management of chronic otitis media in children. Numerous reports have demonstrated that adenoidectomy alone or in conjunction with myringotomy tube placement may reduce the incidence of future episodes of otitis media and possibly reduce the necessity for future ventilation tubes.[123,124] Gates and colleagues[123] randomly assigned 578 children between the ages of 4 and 8 years to four management groups; group 1 underwent bilateral myringotomy and no ventilation tube placement; group 2 underwent placement of ventilation tubes; group 3 underwent adenoidectomy alone; and group 4 underwent adenoidectomy and placement of ventilation tubes. They demonstrated with statistical significance that patients who underwent adenoidectomy in conjunction with bilateral myringotomy had significantly lower postmanagement morbidity, as measured by hearing loss secondary to middle-ear effusion and the number of subsequent placements of ventilation tubes. Paradise and associates[124] randomly studied 213 children who had previously received ventilation tubes that had since extruded. These patients were randomized into two groups, those undergoing adenoidectomy and those who did not (control group). The adenoidectomy group had statistically significant less otitis media than control subjects. Another, large study further demonstrated the effectiveness of adenoidectomy in this regard. Kadhim and associates,[125] evaluating data on 50,000 children younger than 10 years who had undergone myringotomy tube placement, found that adenoidectomy at the time of tube placement decreased the odds of needing subsequent tube placement regardless of whether or not the child was having adenotonsillar disease. The actual mechanism by which adenoidectomy affects the course of otitis media in children is unclear. Surgical extirpation of the adenoids may remove a nasopharyngeal nidus of contaminated tissue that secondarily acts as a source of infection in the middle ear, or adenoidectomy may simply remove an anatomic obstruction of the eustachian tube. The actual size of the adenoid pad has not necessarily been implicated in the etiology of chronic otitis media with effusion. Many studies have been unable to determine the relationship between adenoid size and chronic otitis media with effusion.[126-129]

On the basis of current evidence, adenoidectomy should be considered in children undergoing primary ventilation tube placement who have symptomatology suggestive of chronic nasal obstruction or adenoid hypertrophy that is confirmed by nasopharyngoscopy or nasopharyngeal radiography. Patients who require subsequent sets of ventilation tubes also may be candidates for adenoidectomy, regardless of adenoid size or symptomatology. If surgery is elected, proper technique is important, as Bluestone[115] and McKee[130] reported that surgical manipulation of the eustachian tube during adenoidectomy may predispose children to eustachian tube malfunction and the subsequent development of otitis media with effusion.

Adenotonsillectomy: Surgical Technique

Many surgical techniques have been described for extirpation of the tonsils and adenoids. Crowe and associates[7] described the first meticulous surgical dissection technique with use of sharp instrumentation. More recently, however, dissection with electrocautery has become the most popular and common technique. Other current techniques are the Coblator (ArthroCare Corporation), the Microdebrider, the ultrasonic Harmonic Scalpel, bipolar electrocautery, and, less frequently, CO_2 or KTP laser tonsillectomy.[62,110,131-135] A 2007 survey of pediatric otolaryngologists showed monopolar cautery to be by far the most common method of tonsillectomy, favored by 53% of the respondents. Coblation at 16% was the second most common method, cold dissection combined with electrocautery was third at 10%, followed by bipolar electrocautery at 6%.[136] Evidence also suggests that sharp dissection may lead to slightly less postoperative pain. However, there may be less intraoperative blood loss with electrocautery techniques.[132,137,138] Guillotine tonsillectomy techniques are still used and have been shown to have a low complication rate.[140-141] In China, the technique of guillotine tonsillectomy in children without anesthesia has been described.[142]

Of the new technologies, Coblation tonsillectomy has received possibly the most attention and acceptance. Coblation technology utilizes a system of radiofrequency bipolar electrical current that passes through a medium of normal saline, which results in the production of a plasma field of sodium ions. These energized ions are able to break down intercellular bonds and effectively vaporize tissue at a temperature of only 60° C. This vaporization theoretically results in effective dissection with less postoperative pain from thermal injury.[143,144] The technique can be utilized for complete tonsillectomy or for intracapsular tonsillectomy, otherwise known as tonsillotomy, in which the tonsil is debulked, leaving a small amount of lymphoid tissue to cover the inferior constrictor muscle. Multiple newer studies suggest decreased pain and recovery time with Coblation than with electrocautery and the Harmonic Scalpel.[145-147] These studies report no higher incidence of postoperative hemorrhage with this technique. Some researchers, however, have found a higher bleeding rate with the Coblator, and this issue remains a concern for some writers.[148-150]

The Coblator consists of a hand piece with a suction irrigation tip that transmits the radiofrequency current and dissects tissue and also has a cautery capability for hemostasis. With the Coblation technique, a separate suction cautery device is theoretically not necessary, because adenoidectomy can be performed with the Coblator. The blade can be bent to allow placement into the nasopharynx to allow Coblation of adenoid tissue with use of mirror visualization. This technique may work adequately for small adenoid pads; however, it may not be as efficacious for large obstructive adenoid pads. Research is ongoing to improve the Coblator to enhance its capabilities to perform adenoidectomy.

The Harmonic Scalpel utilizes ultrasonic technology to cut and coagulate tissues, resulting in minimal tissue damage from thermal trauma. The device converts electrical energy from a generator into mechanical vibration through a transducer that consists of piezoelectric ceramics, generating a back-and-forth vibration of the blade at a frequency of approximately 55.5 kHz. The device can cut tissue on low- and high-power settings and can also coagulate bleeding tissue. Initially, the Harmonic Scalpel found its use in laparoscopic surgery in the field of pediatric and general surgery. However, its use in tonsillectomy has been reported to have encouraging results.[103,151] Wiatrak and Willging[151] reported on a prospective study consisting of 117 patients undergoing either traditional electrocautery technique or Harmonic Scalpel surgery. They found a trend toward decreased postoperative pain over the first 3 postoperative days and a significant increase in the ability to sleep comfortably through the first three postoperative nights in children undergoing Harmonic Scalpel surgery. The duration of the procedure was longer for the Harmonic Scalpel than for electrocautery. The complication rates were equivalent in the two groups. At this time the Harmonic Scalpel cannot be utilized for adenoidectomy, so other techniques must be used for that operation. A concern about its use is higher costs incurred for each blade utilized for tonsillectomy. Other studies

have shown the Harmonic Scalpel to be an effective instrument for tonsillectomy but have not found it to have a significant advantage over electrocautery.[152]

Subtotal tonsillectomy has become a more popular technique over the last several years. The concept of partial intracapsular tonsillectomy or tonsillotomy is not new to otolaryngology.[153] This procedure can be performed using any of the described instruments but is now most commonly performed with powered instrumentation.[154,155] Ideally in this technique, the only tissue manipulated and dissected is the tonsil itself. No mucosal cuts are made, the peritonsillar capsule is not dissected, and there should not be any direct cauterization of the peritonsillar fascia and underlying pharyngeal musculature. All of the preceding features are thought to make the postoperative pain and discomfort much less with this technique. With use of a microsurgical debrider, the hypertrophied tonsils are sequentially shaved behind the levels of the anterior and posterior tonsillar pillars. Exposure is obtained by retraction of the anterior tonsillar pillar with a Herd retractor. Hemostasis is obtained with suction cautery. Multiple studies point to a reduced need for pain medicine and more rapid return to normal activity and normal diet with subtotal microsurgical debrider tonsillectomy.[156-158] The incidence of postoperative bleeding is not increased with this technique and may actually be slightly less than with traditional electrocautery.[159] However, at least one study did not show a significant difference in return to normal activity and pain resolution between these two methods.[160] The indications for this technique are controversial, with some advocating this technique as appropriate for all indications in all ages and others stating that it should be performed only in children without a history of tonsillitis, owing to the concern about persistent tonsillitis in the residual tonsil tissue. Cost is a factor in the use of disposable microsurgical debrider blades for partial intracapsular tonsillectomy. At this point there is little evidence that the residual tissue is associated with recurrent tonsillitis as the child ages, but more long-term data are needed for confirmation. The most significant concern with this technique is the possibility of regrowth and the subsequent recurrence of obstructive symptoms. In one series of 278 patients, the incidence of regrowth was 3.2%.[161] This event is rare but does occur, and the patient's parents must be made aware of this possibility during the informed consent discussion for this procedure.

The microsurgical debrider can be effective for performing adenoidectomy. Koltai and others have reported on and shown the safety and efficacy of this technique.[155,162-165] Koltai, Chan, and Younes[166] report that the utilization of power-assisted adenoidectomy allows more precise, rapid, and safe removal of adenoid tissue. This technique is especially useful in removing adenoid tissue that extends through the choanae and into the nasal cavity. However, the cost of microsurgical debrider blades continues to be an issue related to its use. Stanislaw and coworkers,[167] in a prospective evaluation of power-assisted adenoidectomy or curette adenoidectomy in 90 children, found that power-assisted adenoidectomy was 20% faster, involved 27% less blood loss, and provided a more complete resection and better control of depth of reception. It also had higher surgeon satisfaction.

Technique Description

Electrocautery tonsillectomy using a meticulous dissection technique and low electrocautery wattage results in very minimal intraoperative blood loss and acceptable postoperative discomfort. This technique is described in detail. Instrumentation is shown in Figure 196-13.

Patients should not eat solid foods for 8 hours before surgery. If the patient is closely supervised, he or she may drink clear liquids until 3 hours before surgery. Preoperative sedation with midazolam hydrochloride (0.5 to 1 mg/kg) approximately 30 minutes before surgery may be necessary for patients with excessive preoperative anxiety. Anesthesia is typically induced by mask ventilation, with subsequent intravenous access after the anesthetic has taken effect. Patients usually receive intravenous antibiotics such as ampicillin (20 mg/kg; maximum dose, 1 g). Telian and colleagues[168] demonstrated that intravenous antibiotics followed by a 1-week course of postoperative oral antibiotics significantly decreased morbidity after tonsillectomy.

Patients who have a significant history of obstructive sleep apnea or are younger than 3 years receive intraoperative corticosteroids, most commonly dexamethasone (0.5 mg/kg). Catlin and Grimes[169] reported that one dose of intraoperative intravenous corticosteroids improved

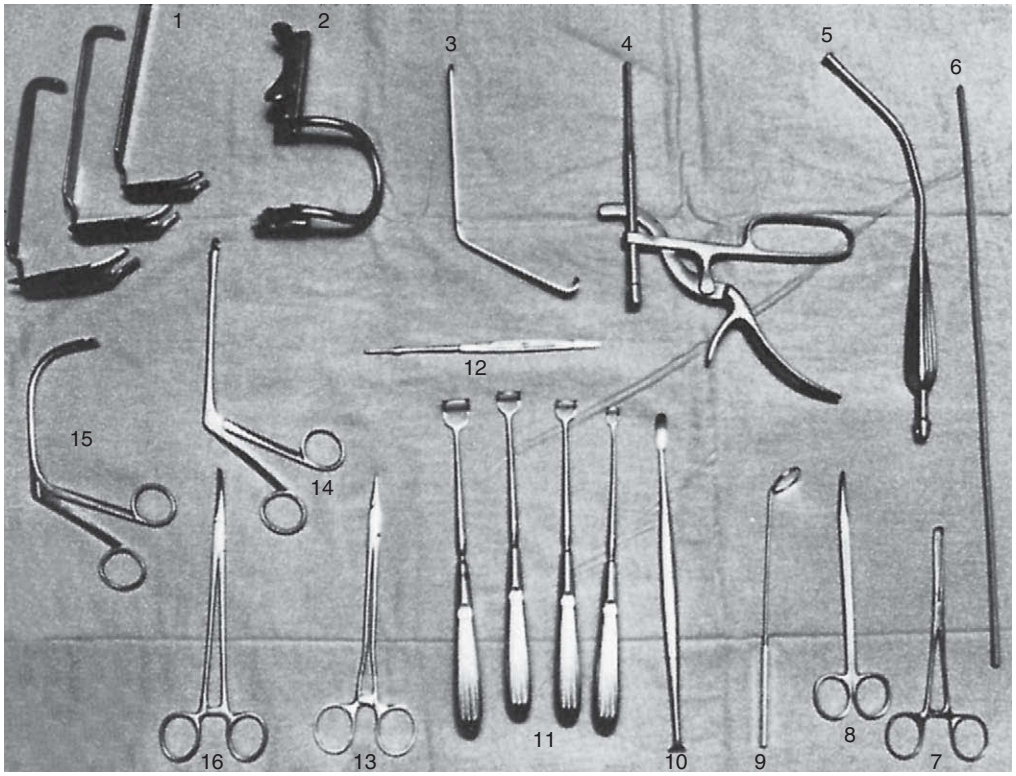

Figure 196-13. Instrumentation used in tonsillectomy and adenoidectomy procedures.

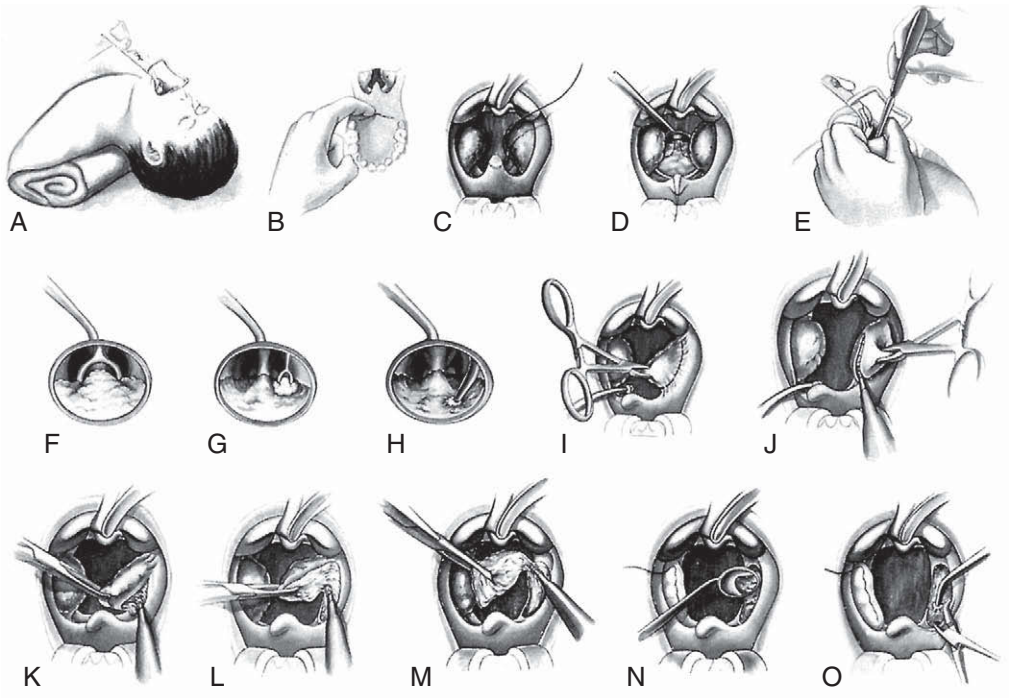

Figure 196-14. Adenotonsillectomy technique. **A,** Patient placed in Rose's position. **B,** Palate inspected for presence of submucous cleft. **C,** Nylon suture placed through uvula for retraction. **D,** Nasopharynx inspected with mirror. **E** and **F,** Positioning of curette for adenoid removal. **G,** Removal of adenoid remnants with small curette. **H,** Removal of adenoid remnants and control of bleeding with suction cautery. **I** and **J,** Grasping of right tonsil and incision of mucosa using cautery. **K** to **M,** Dissection of tonsil with cautery. **N,** Inspection of superior pole with mirror. **O,** Control of bleeding with suction cautery.

recovery time in children following tonsillectomy. However, Ohlms and associates[170] and Volk and coworkers[171] demonstrated no significant effects on recovery time of a single dose of intravenous steroids. We use corticosteroids to potentially reduce airway edema in patients who are more susceptible to airway complications after tonsillectomy. Although we do not routinely use peritonsillar infiltration with local anesthetic agents, numerous reports have described short-term benefit of this procedure with regard to postoperative pain in the immediate recovery period after tonsillectomy.[172-174] Peritonsillar infiltration with local anesthesia may also decrease intraoperative blood loss in patients undergoing sharp-dissection tonsillectomy.[172]

After induction of general anesthesia and placement of an endotracheal tube, the patient is placed in Rose's position (Fig. 196-14A) and a Crowe-Davis mouth gag is placed for exposure of the oropharynx. A red rubber catheter is placed through the right nares, brought back out through the oral cavity, and clamped with a Kelly clamp to retract the soft palate for better visualization of the nasopharynx. At this point the hard and soft palate are examined by visual inspection and palpation for evidence of a submucous cleft palate. Adenoidectomy should not be performed in the presence of an occult submucous cleft palate unless absolutely necessary. Conservative adenoidectomy should be considered in these situations. The Microdebrider is especially useful in this rare situation.

Adenoidectomy in the United States is still most commonly performed with adenoid curettes, which have either straight or curved handles.[175] The LaForce adenotome also has been described as an instrument for adenoid extirpation.[176] The nasopharynx is inspected with a nasopharyngeal mirror to assess the size of the adenoid pad and guide placement of the curette. The curette is placed high in the nasopharynx so it abuts the posterior aspect of the nasal septum. The adenoid pad is then carefully curetted, with care taken not to penetrate deeply into the prevertebral region. Care must also be taken during use of the curette not to extend too far laterally and thus potentially risking damage to the torus tubarius and eustachian tube orifice. Small curettes may be used to remove residual adenoid tissue in the posterior choanal region. This step entails removal of the superior portion of the adenoid pad and preservation of the inferior aspect with cautery or curettes. Packs are placed into the nasopharynx to obtain hemostasis.

With use of the Microdebrider, the exposure is the same. The instrument is set to oscillate at a maximum of 1500 rpm. With the nasopharyngeal mirror, the adenoids are débrided, with protection of the eustachian tube opening and care taken to not débride too deeply. When all the desired adenoid tissue has been removed, the nasopharynx is packed.

After tonsillectomy has been performed, the nasopharynx is reexamined, and hemostasis is obtained with suction electrocautery. It is important to remember that the mouth-gag tongue blade places pressure on the base of tongue and should be released intermittently to allow blood circulation in the tongue and possibly aid in reducing postoperative pain. A throat pack may be used to prevent blood and secretions from entering the esophagus. Swallowing of blood and secretions may lead to postoperative nausea and vomiting. In addition, blood oozing around the endotracheal tube may form a laryngeal clot, which may lead to postextubation airway obstruction. Children undergoing adenotonsillectomy typically have an uncuffed endotracheal tube, which may allow leakage of air around the tube with positive-pressure ventilation. Fires and endotracheal tube explosions have been reported during tonsillectomy, presumably related to oxygen leaking around uncuffed endotracheal tubes.[177]

At this point, the tonsillectomy is performed with electrocautery. The tonsil is grasped with an Allis clamp or tenaculum. It is then retracted medially, and the superior pole is incised with the electrocautery; the surgeon identifies the tonsillar capsule and carefully dissects the avascular plane between the capsule and the tonsillar bed. When sharp dissection is used, the superior mucosal incision may be made with a knife, and blunt dissection may be used to separate the tonsil from the tonsillar bed with a Thompson dissector or a Fischer knife. With the electrocautery, the tonsil is carefully dissected down to its inferior extent, where it is amputated. With sharp dissection, a tonsil snare can be used to amputate the tonsil at the inferior pole. If bleeding is noted at this point, a pack may be placed in the tonsillar fossa, and the other tonsil is then excised in the same manner. Care must be taken

to preserve the mucosa and muscle in the posterior pillar, especially superiorly. Extensive cauterization and tissue loss of the posterior pillar may predispose the patient to postoperative nasopharyngeal stenosis. If electrocautery is being used, great care must be taken that other metal instrumentation in the oropharynx (e.g., the mouth gag or Yankauer suction) not touch the electrocautery blade, so as to avoid burning the oropharynx and lips. In addition, the electrocautery blade should be guarded with a nonconducting material.

After removal of the tonsillar fossa packs, residual bleeding may be controlled with electrocautery on a low-wattage setting. Significant bleeding vessels may have to be clamped and ligated. Great care should be taken in the use of suture ligatures in the tonsillar fossa. The external maxillary and lingual arteries may inadvertently be ligated in the region of the inferior tonsillar pole, thus leading to sloughing and severe hemorrhage. In addition, the internal carotid artery, which is in close proximity to the tonsillar fossa, may be damaged inadvertently, resulting in complications such as pseudoaneurysm formation and excessive hemorrhage.[52] After hemostasis has been obtained in the oropharynx and nasopharynx, the oral and nasal cavities are thoroughly irrigated. The hypopharynx is suctioned to evacuate all secretions and potential blood clots, and the stomach is also suctioned at this point. The patient is then awakened and extubated.

In general, accepted practice is to admit for overnight admission patients who have a significant history of obstructive sleep apnea, those younger than 3 years, and those with other medical problems or extenuating circumstances. If they are taking oral fluids adequately, all patients undergoing outpatient surgery are discharged after an observation period of approximately 2 to 4 hours. Intravenous fluids are administered according to deficit replacement and maintenance until oral intake resumes satisfactorily; lactated Ringer's solution or 0.5 normal saline is used. Acetaminophen with or without codeine is given for analgesia. A 1-week course of oral antibiotics is also prescribed. The patient's diet advances from clear liquids on the day of surgery to a soft diet the following day and then solid foods subsequently as tolerated. Soft foods are generally well tolerated. However, patients with unrestricted diets have not been shown to have significant complication rates postoperatively.[6,58,178] Patients or their parents are instructed to return immediately to the emergency room if there is any evidence of bright red bleeding from the nose or oral cavity.

Inpatient versus Outpatient Procedures

It has been clearly demonstrated in the literature that adenotonsillectomy in appropriately selected children may be performed on an outpatient basis.[14,25,105,179,180] It is important that patients are observed postoperatively and that they obtain significant postoperative intravenous rehydration. Postoperative observation times discussed in the literature vary from 136 minutes to 6 to 8 hours.[133,181] Although short-stay outpatient tonsillectomy has been demonstrated as a safe and cost-effective procedure, it is important preoperatively to identify outpatients who are at risk for postoperative complications and who may benefit from longer observation periods following surgery.

Numerous writers believe that children younger than 3 years should be admitted for observation after surgery because they are at increased risk for postoperative complications, most of which are airway-related.[94,180,182-185] The ultimate decision for postoperative admission lies with the surgeon. Other patients who may warrant admission after adenotonsillectomy include those with (1) a history of an abnormal bleeding disorder or abnormal preoperative coagulation profile, (2) evidence of severe obstructive sleep apnea, (3) underlying craniofacial abnormalities such as Down syndrome, and (4) systemic disorders such as cardiopulmonary disease or asthma. Postoperative admission also should be considered for patients undergoing tonsillectomy for peritonsillar abscess, for patients who live a long distance from the hospital (>60 miles or 1 hour driving time), or for patients whose home situation is not consistent with close postoperative observation.[116,117,186]

Complications

Serious postoperative complications secondary to surgery of the tonsils and adenoids are primarily related to pain, hemorrhage, airway obstruction, postoperative pulmonary edema, VPI, nasopharyngeal stenosis, and death.[187] Meticulous attention to surgical technique and technical advances in modern anesthesiology have significantly reduced the number of complications related to adenotonsillectomy. Paradise reported an overall complication rate of 14%; all of these complications were self-limiting.[124] Richmond described a series of 794 patients undergoing adenotonsillectomy, of whom 4.2% had variable degrees of postoperative bleeding and 1.3% had self-limiting postoperative airway obstruction. In 9409 pediatric patients undergoing adenotonsillectomy, Crysdale and Russel[188] reported an overall hemorrhage rate of 2.15%, with only 0.06% of patients requiring a second general anesthetic for hemostasis. For reasons other than the hemorrhage (including fever, airway distress, pneumonia, inadequate oral intake, vomiting, and pain), 0.6% of the patients required delayed hospitalization. The incidence of serious surgical complications has been reported to be approximately 15 cases per 1000.[189] Pulmonary abscess, although dreaded in the past, is now extremely rare. However, this complication may still be encountered, as may other rare complications, including Horner's syndrome, optic neuritis, meningitis, brain abscess, paralysis of the glossopharyngeal and recurrent laryngeal nerves, salivary fistulas from the submandibular gland to the tonsillar fossa, and mediastinal emphysema.[187,190,191]

Chronic postoperative pain related to fibrosis and calcification of the stylohyoid ligament (Eagle's syndrome) may be encountered occasionally. Pain referred to the ipsilateral ear may be diagnosed by palpation of the tonsillar fossa and from demonstration by radiographic studies of an elongated styloid process. Aspiration of foreign bodies (e.g., dislodged teeth, sponges, and lymphoid tissue) may also be encountered. If a tooth aspiration is suspected, a radiographic study should be obtained immediately. If a permanent tooth has been dislodged, a dental consultation should be obtained. A thorough investigation, including endoscopy, must be performed when a suspected foreign body has been aspirated.

Postoperative Hemorrhage

Postoperative hemorrhage is the most common serious complication of adenotonsillectomy. Reported postoperative hemorrhage rates range from 0.5% to 10%, although variable rates have been reported with different surgical techniques.[188,192-195] Meticulous attention to surgical technique and intraoperative hemostasis, regardless of the technique used, will lead to acceptable postoperative hemorrhage rates. Detection of underlying coagulation disorders by history and physical findings or through preoperative screening in appropriately selected patients will help avert significant intraoperative blood loss. Appropriate preoperative and intraoperative measures are taken in conjunction with a hematology consult. Certain analgesics (e.g., ketorolac tromethamine) have been associated with increased hemorrhage rates when given in the perioperative period and should be avoided in patients undergoing adenotonsillectomy.[63,196]

The extensive blood supply of the tonsillar fossa is composed of a complex network of anastomosing arteries primarily arising from the ipsilateral external carotid artery system. However, there are contributions from the internal carotid and vertebral arteries, and contralateral vessels circulate through the circle of Willis.[197] Therefore, extensive intraoperative or postoperative hemorrhage may not always cease after ligation of the external carotid artery. In rare, severe cases, ligation of other branches (e.g., the maxillary, facial, lingual, or superior thyroid artery) may be necessary.[192]

The arterial blood supply of the nasopharynx and adenoids arises from both the internal and external carotid arterial system. However, bleeding in this region can be controlled most commonly with compression and electrocautery. In severe cases, application of caustic agents (e.g., tannic acid, bismuth subgallate) or hemostatic agents (e.g., Avitene) may be beneficial. Aberrant arterial vessels in the oropharynx and nasopharynx may be damaged intraoperatively (Fig. 196-15). McKenzie and Wolfe[97] reported an aberrant carotid artery arising in Rosenmüller's fossa that was injured during adenoidectomy, necessitating subsequent ligation of the common carotid artery with resultant transient hemiplegia.

Bleeding can be intraoperative, immediately postoperative (within 24 hours), or delayed (after 24 hours). Intraoperative hemorrhage may

Figure 196-15. Computed tomography scan with contrast enhancement demonstrating an aberrant artery in the left retropharyngeal region.

be related to an underlying coagulopathy or possibly to major arterial damage in severe cases. Steps to control major intraoperative hemorrhage include use of suction cautery or ligation or, possibly, placement of a pack in the tonsillar fossa and over-suturing of the tonsillar pillars to provide constant compression of the fossa. Suture ligatures may damage underlying arterial vessels, thereby worsening the bleeding or possibly leading to delayed postoperative hemorrhage and should be placed with extreme care if they are used.[87,198] In severe cases, ligation of larger arteries through an open-neck exploration may be necessary. However, this should be an extremely uncommon step. Persistent hemorrhage from the nasopharynx after adenoidectomy is often related to residual remnants of adenoid tissue that should be completely removed to best obtain hemostasis.

Immediately postoperative bleeding after adenoidectomy may be controlled initially with topical decongestant nose drops. However, patients with severe bleeding should be taken back to the operating room for examination of the nasopharynx and definitive hemostasis, in which the clots are suctioned, adenoid remnants are removed, and the nasopharyngeal pad is definitively cauterized.

Delayed postoperative bleeding, although typically not as dangerous as intraoperative or immediately postoperative bleeding, may be fatal if not managed appropriately. Patients or parents should be well informed before discharge about the possibility of delayed postoperative hemorrhage and should be told to return for immediate evaluation if there is any evidence of bright red bleeding from the nose or mouth. The most common time for delayed postoperative bleeding is between the fifth and seventh postoperative days. When hemorrhage occurs, patients should be returned to the operating room for immediate hemostasis if active bleeding is confirmed on physical examination. If no active bleeding is apparent and a blood clot is evident in the tonsillar fossa, it should not be disturbed. However, if the surgeon cannot determine whether active bleeding is taking place, the clot should be suctioned to allow better examination. Blood clots often hide bleeding vessels and may prevent appropriate coagulation as a result of fibrinolysis.[199] Patients with delayed hemorrhage who are not actively bleeding and have a blood clot present in the tonsillar fossa should at least be admitted for overnight observation. A coagulation profile and hematocrit measurement should be obtained.

Airway Obstruction and Pulmonary Edema

Postoperative airway obstruction may occur after adenotonsillectomy, especially in children younger than 3 years.[58,182] Edema of the tongue, nasopharynx, and palate may necessitate temporary replacement of a nasal trumpet and also may require intravenous corticosteroid therapy. Dislodging of pharyngeal clots may obstruct the larynx postoperatively, resulting in death.[200] Therefore, all clots should be evacuated from the pharynx before termination of the procedure.

Postoperative pulmonary edema may arise in patients with long-term upper airway obstruction related to adenotonsillar hypertrophy, often necessitating prolonged mechanical ventilation. Patients with a prolonged history of obstructive sleep apnea—as documented by polysomnography and evidence of cor pulmonale—should be observed closely after surgery with pulse oximetry in a monitored setting. Patients with persistent hypercapnia may require planned postoperative mechanical ventilation until P_{CO_2} values return to normal.

Velopharyngeal Insufficiency

Velopharyngeal insufficiency (VPI), or hypernasality, is a relatively unusual complication primarily related to adenoidectomy. In patients with excessively large tonsils and preoperative VPI, the velopharyngeal insufficiency may actually improve after the obstructive tonsils have been removed. Patients with a history of cleft palate or evidence of an occult submucous cleft palate on physical examination (see Figure 196-11) should not undergo adenoidectomy unless it is absolutely necessary. In these situations conservative or partial adenoidectomy should be performed. The actual incidence of VPI after adenoidectomy in otherwise healthy children has been estimated to be between 1 in 750 and 1 in 1459.[189,201] It is important to determine preoperatively whether there is a family history of VPI or whether the patient had a prior history of hypernasal speech or nasal regurgitation as an infant. These signs may herald the development of postoperative VPI. If an underlying speech abnormality exists preoperatively, speech therapy evaluation should be performed. It also is important to determine whether reported hyponasal speech is truly related to a nasal obstruction or is actually related to hypernasal speech, which can be misinterpreted by parents.

Patients in whom postoperative VPI develops should be evaluated and managed initially by a speech pathologist. Most cases are transient and will resolve with time. However, severe cases may require surgical intervention, such as formation of a pharyngeal flap, sphincteroplasty, or, possibly, posterior pharyngeal wall augmentation. Reconstructive surgery should be considered in patients with persistent VPI that has not responded to speech therapy for at least 1 year. *Habit palsy* is transient postoperative VPI that develops secondary to pain when the patient has altered pharyngeal muscle control during speech and swallowing. If it is not resolved shortly after surgery, speech therapy is usually successful.

Nasopharyngeal Stenosis

Nasopharyngeal stenosis is an extremely difficult management problem that requires surgical intervention for satisfactory resolution. This situation may arise from excessive cauterization with extensive mucosal destruction involving the nasopharynx, lateral nasopharyngeal wall, and superior tonsillar pillar along with excessive resection of posterior tonsillar pillar tissue. Other predisposing factors are performance of surgery during an acute episode of pharyngitis or purulent sinusitis, revision adenoid surgery with removal of lateral pharyngeal bands, and keloid formation.[202] Figi[203] described 37 cases of nasopharyngeal stenosis, 22 of which were secondary to adenotonsillectomy.[109] Guggenheim[204] reported 18 cases of nasopharyngeal stenosis secondary to adenoidectomy caused by stripping of the lymphoid tissue from the torus tubarius, Rosenmüller's fossa, and the lateral nasopharynx.[205]

Numerous techniques have been described for surgical repair using a combination of skin flaps, local mucosal flaps, stents, skin grafts, and scar incisions.[206] Cotton[207] described a technique using incision of the stenosis with rotation of a laterally and inferiorly based pharyngeal flap to reline the nasopharynx. Occasionally, second-stage repair is necessary. Physical findings in patients with nasopharyngeal stenosis

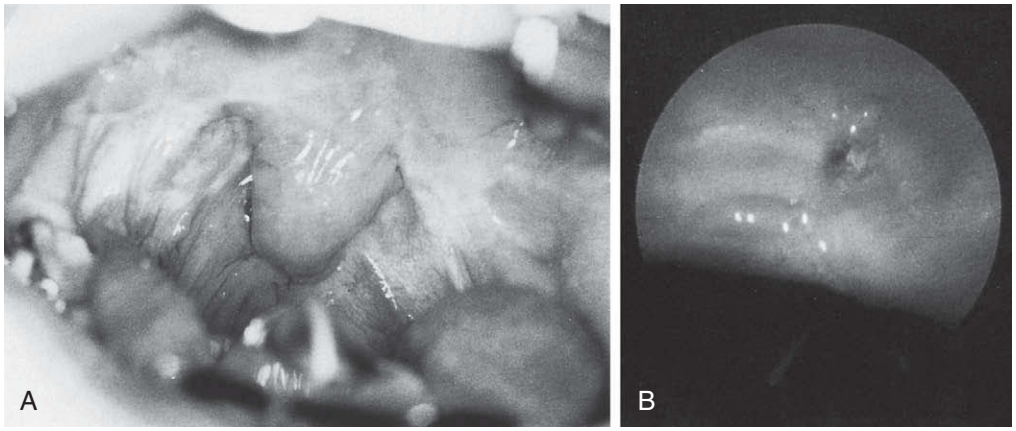

Figure 196-16. **A,** Oropharyngeal view of postadenotonsillectomy nasopharyngeal stenosis. **B,** Endoscopic view of nasopharyngeal stenosis by means of a 120-degree rod-lens telescope.

typically consist of scarring of the uvula down to the posterior pharyngeal wall with possibly a small opening visible on mirror examination or flexible nasopharyngoscopy (Fig. 196-16). The majority of the scarring is based laterally in the region of the posterior tonsillar pillars. This results in partial or complete obstruction of the nasopharyngeal airway and can be extremely debilitating.

Cervical Spine Complications

A rare complication of adenoidectomy or tonsillectomy is atlantoaxial subluxation (Grisel's syndrome). Although up to 10% of patients may report neck pain after adenoidectomy, patients with Grisel's syndrome have decalcification of the anterior arch of the atlas and laxity of the anterior transverse ligament between the atlas and axis.[63,208] This leads to complaints of stiff neck with spasm of the sternocleidomastoid or deep cervical muscle. The patient holds the head to one side with slight rotation toward the opposite side. Radiographic evaluation in suspected cases should include anteroposterior and lateral cervical spine radiography in addition to flexion-extension radiographs, which may detect mild subluxation. In severe cases, CT and possibly magnetic resonance imaging may demonstrate evidence of decalcification, which may be associated with cervical spine osteomyelitis. Most cases of atlantoaxial subluxation are related to infection or trauma and only rarely are secondary to adenotonsillectomy.[209] Patients with Down syndrome are more prone to traumatic atlantoaxial subluxation following adenotonsillectomy. Great care should be taken in cervical spine manipulation during surgery in patients with Down syndrome.[104]

Management of atlantoaxial subluxation after adenoidectomy or adenotonsillectomy should be individualized according to the duration and the symptoms present. Intravenous antimicrobial therapy and possibly cervical traction may be necessary. In the presence of cervical osteomyelitis, long-term (4-8 weeks) intravenous antimicrobial therapy, coupled with cervical stabilization, will be necessary.[209] Retropharyngeal abscess after adenoidectomy has also been reported.[190]

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CHAPTER ONE HUNDRED AND NINETY-SEVEN

Infections of the Airway in Children

Newton O. Duncan

Key Points

- The diagnosis of pediatric airway infections requires astute clinical acumen and judicious use of laboratory testing and imaging techniques.
- Prompt and evidence-based management of these potentially life-threatening infections provides reliable, successful outcomes.
- Viral croup, or laryngotracheitis, is the most common airway obstructive infection in children with well-defined diagnostic criteria and clinically documented management schemes.
- Supraglottitis or epiglottitis has become a rare clinical entity, but its diagnosis and management should not be forgotten.
- Bacterial tracheitis, or exudative tracheitis, is also uncommon, but prompt diagnosis and management may be lifesaving.
- Retropharyngeal cellulitis and abscesses are common airway infections in children and a high index of suspicion may be needed for diagnosis. Well-defined CT imaging results can help determine where surgical management is appropriate.

Children may experience a variety of infections involving the upper respiratory tract and surrounding structures. Some infections occur commonly, some may be self-limited, and some may be relatively inconsequential. However, other infections, some of which are more rare, may be life threatening. The astute clinician can often identify the various airway infections by an accurate clinical history and targeted physical examination. Radiologic imaging, laboratory studies, or airway endoscopy may also be helpful for accurate diagnosis. Nevertheless, a keen understanding of the various signs and symptoms of airway infections is important. The signs and symptoms of the various airway infections may have many similarities because the anatomic structures and tissues involved are close in proximity. These similar airway findings also can be present in children with acute tonsillitis, infectious mononucleosis, diphtheria, peritonsillar abscess, congenital airway anomalies, subglottic stenosis of any etiology, and in those with airway foreign bodies. Therefore great familiarity with the spectrum of childhood airway disease entities can be extremely important in their prompt diagnosis and management. This chapter emphasizes the current recognition and management of croup (laryngotracheitis), supraglottitis (epiglottitis), bacterial tracheitis, and retropharyngeal abscesses.

Croup (Laryngotracheitis)

The term *croup* is from the ancient Scottish language that refers to the harsh, barking cough that may be present in those with a number of different acquired or congenital disorders.[1,2] Several terms have been used synonymously with croup, leading to confusion about the exact nature of the disease. These terms include *croup, viral croup, laryngotracheitis, laryngotracheobronchitis, pseudomembranous croup, spasmodic croup,* and *postintubation croup.* This infectious disease primarily involves the vocal folds or glottis and the subglottis. Because viruses predominantly cause this entity, the most descriptive and widely used terms are either viral croup or, more properly, viral laryngotracheitis. Viral laryngotracheitis, or croup, is the most common form of infectious upper airway tract obstruction in children. It is estimated that this condition accounts for 90% of infectious airway obstructions and that 3% to 5% of children have at least one episode of croup. This condition can be recurrent in approximately 5% of children.[3] Most children with croup have mild-spectrum symptoms but some children (1.5% to 15%) with more severe spectrum croup require hospital admission for airway obstructive symptoms, and during hospitalization 1% to 5% may require intubation.[4] Parainfluenza viruses 1 and 2 primarily are implicated in this disease (up to 75%), but influenza A and B, respiratory syncytial virus, measles, adenovirus, varicella, and herpes simplex virus type 1 all have been isolated.[5] Measles involvement in those with croup historically leads to an aggressive form of the disease.[6] More recently, influenza viruses and herpes simplex viruses have both been implicated in more severe or prolonged courses of croup.[7,8]

Children are most commonly affected when they are between 6 months and 3 years of age, with a peak incidence at 18 to 24 months of age. Boys are more likely affected, by more than a 2 : 1 ratio. Although croup can occur at any time of the year, there is a strong seasonal occurrence in late autumn and winter. Croup may be called atypical if it occurs in infants younger than 6 months of age, lasts more than 7 days, or does not respond to appropriate treatment. Other etiologies besides acute viral laryngotracheitis should be considered in these atypical cases.

Viral croup transmission occurs by direct contact and exposure to nasopharyngeal secretions.[9] The incubation period before onset of clinical symptoms is 2 to 6 days for parainfluenza virus type 1, and children may continue to shed the virus for up to 2 weeks.[10] After acquisition, the viral infection involves the nasopharynx, producing nasal symptoms. Local spread to the larynx and trachea ensues. The mucosa of the vocal folds and subglottis become erythematous and swollen. Lymphocytes, histiocytes, and polymorphonuclear leukocytes infiltrate the lamina propria, submucosa, and adventitia. In addition, generalized mucosal edema is present. The duration of illness usually is from 3 to 5 days. The crucial factor in those with viral croup is the amount of swelling in the subglottic area. The subglottis is the narrowest portion of the upper respiratory tract and, because of the complete cartilaginous cricoid ring, any edema that occurs in the subglottis does so at the expense of the airway lumen. Because stridor does not occur until there is already significant airway obstruction and because any decrease in cross-sectional area is proportional to the square of the radius of the airway lumen, any further decrease in airway size caused

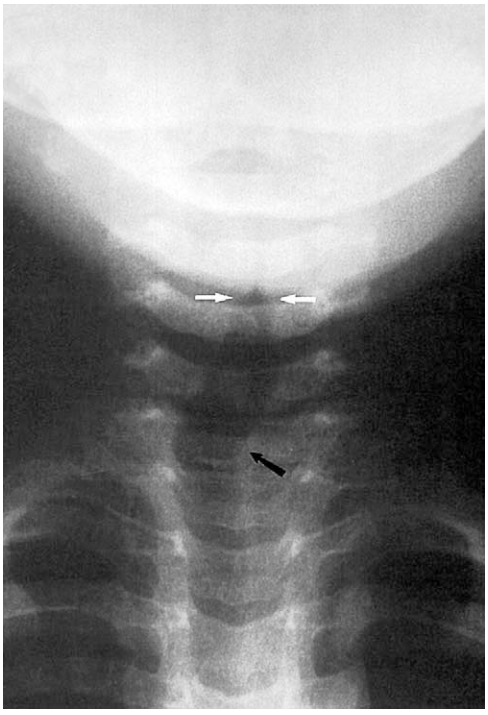

Figure 197-1. Normal anteroposterior radiographic view of the soft tissues of the neck demonstrating the normal shouldering contours of the proximal trachea *(white arrows).* Many children will show slight angulation of the trachea, which is a normal variant *(black arrow).*

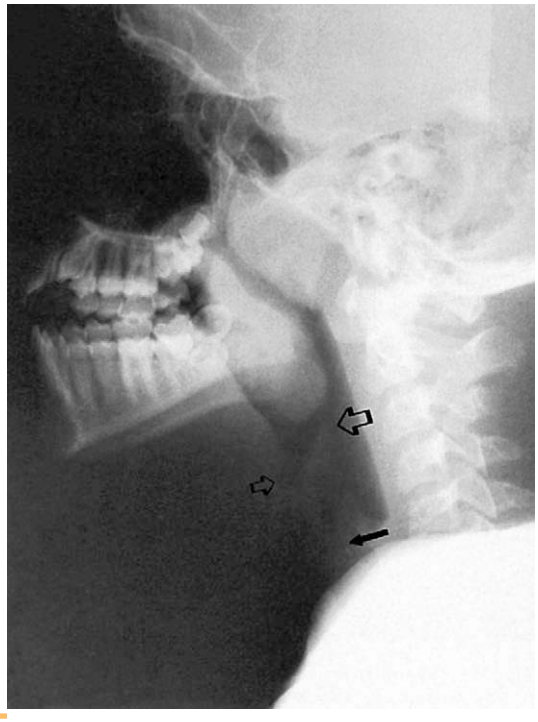

Figure 197-2. Normal lateral soft tissue radiograph of the airway with normal epiglottis *(large open arrow)* and well-defined vallecula *(small open arrow).* The *black arrow* shows the laryngeal ventricle.

by mucous plugging or crusting may lead to rapid and complete airway obstruction.

Clinical Features

Characteristically, children with viral croup have a history of prodromal upper airway infection. Low-grade fever may be present. There also may be leukocytosis, although the leukocyte count in most patients is normal. Inspiratory stridor, hoarseness, and a barking cough are cardinal symptoms of viral croup. This cough is invariably present and may help distinguish croup from other illnesses. The presence of biphasic stridor, retractions, high respiratory rate, or oxygen desaturations indicates severe airway obstruction.

Viral croup may present with only mild symptoms of airway obstruction, but it also can be severe with life-threatening airway obstruction. Many different schemes have been developed to assess the spectrum and severity of croup in an effort to assist in determining how to best manage the different presentations of croup.[1,5,10] Regardless of the scheme used, it is important to consider the following parameters when evaluating children with croup or airway obstruction in general: (1) stridor—inspiratory versus expiratory; (2) respiratory rate; (3) chest retractions; (4) air entry into the chest by auscultation (decreased with severe obstruction); (5) anxiety or restlessness; (6) color or cyanosis; (7) oxygen desaturation by pulse oximetry; and (8) level of consciousness.

Diagnosis

The diagnosis of croup is highly suggested by history and physical examination alone. Detailed questioning about possible foreign body ingestion should be made, along with any previous intubation history. Radiographic imaging of the airway traditionally has been helpful in evaluating those with airway disorders (Figs. 197-1 and 197-2). The diagnosis can be confirmed radiographically by anteroposterior (AP) and lateral (high kilovoltage) films of the upper airway. The frontal AP view classically shows a "steeple sign" in the subglottic area, whereas the lateral view is characterized by haziness of the same area (Figs. 197-3 and 197-4). Flexible fiberoptic laryngoscopy occasionally may be helpful in establishing the correct diagnosis of viral croup. This procedure should be performed with utmost care if there are moderate-to-

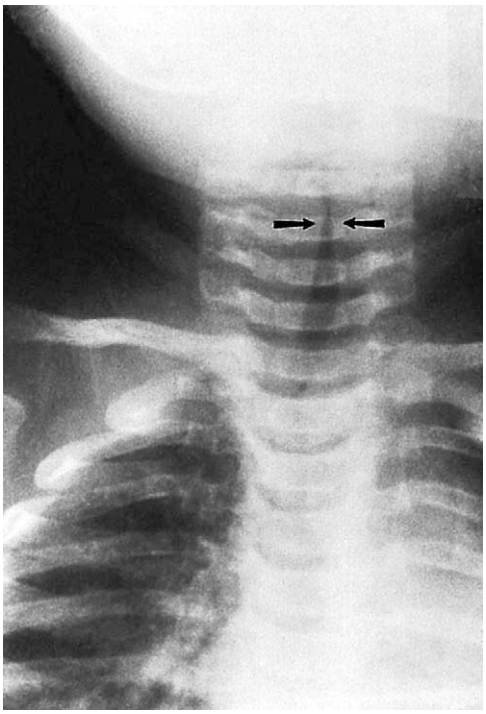

Figure 197-3. Narrowed subglottis in viral croup *(arrows)* in the anteroposterior radiographic view.

severe airway obstructive symptoms. In patients with severe airway obstruction, the diagnosis may be confirmed by direct laryngoscopy at the time of intubation (Figs. 197-5 and 197-6).

Differential Diagnosis

The most important differential diagnosis to consider in children with suspected croup is supraglottitis (Table 197-1). Thereafter, the possible

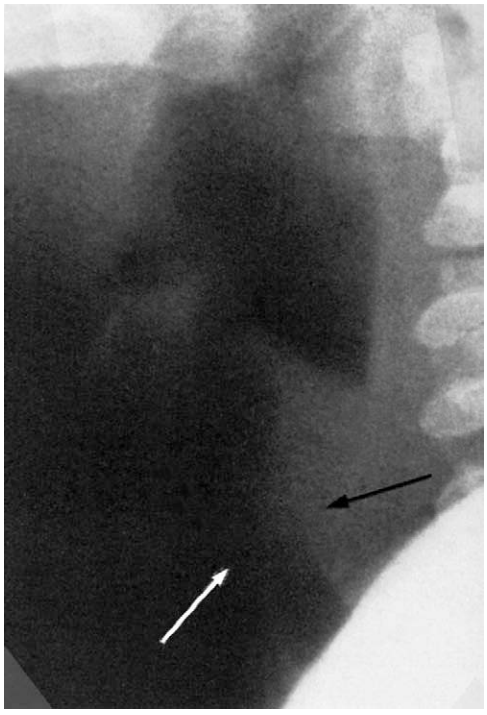

Figure 197-4. Hazy subglottis in the lateral radiographic view *(arrows)* seen in viral croup.

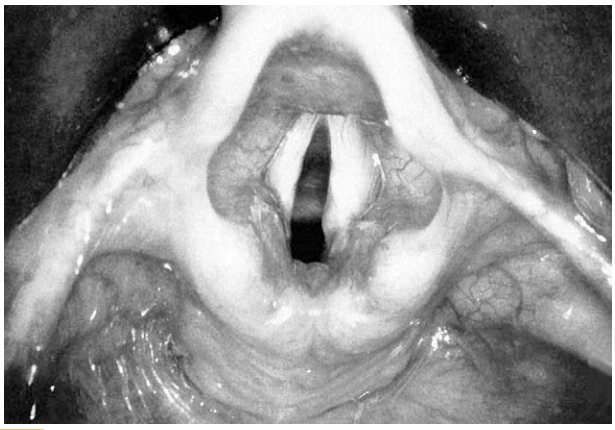

Figure 197-5. Normal child larynx with crisp vocal folds and widely patent subglottis visualized by a rigid rod telescope.

presence of any airway foreign body, particularly in the larynx or subglottis, must be considered. Subglottic hemangiomas may have similar symptoms in infants younger than 6 months of age. Recurrent episodes of a crouplike illness may occur not only in those with congenital subglottic narrowing, but also in children with acquired subglottic stenosis. Therefore a history of intubation may be important. Viral croup in the presence of any preexisting laryngeal or subglottic narrowing may lead to early or recurrent stridor and symptoms of croup. Atypical or recurrent symptoms of croup always demand close attention for other etiologies of airway compromise in addition to viral croup. Gastroesophageal reflux also may be a contributing cause of recurrent croup.[11] When viral croup is not responding to appropriate therapy and when children exhibit an increasingly febrile or toxic appearance, bacterial superinfection in the subglottis or trachea should be suspected. This may occur in 10% to 15% of patients hospitalized with more severe croup. Bacterial tracheitis actually may originate as a complication of viral croup.[12]

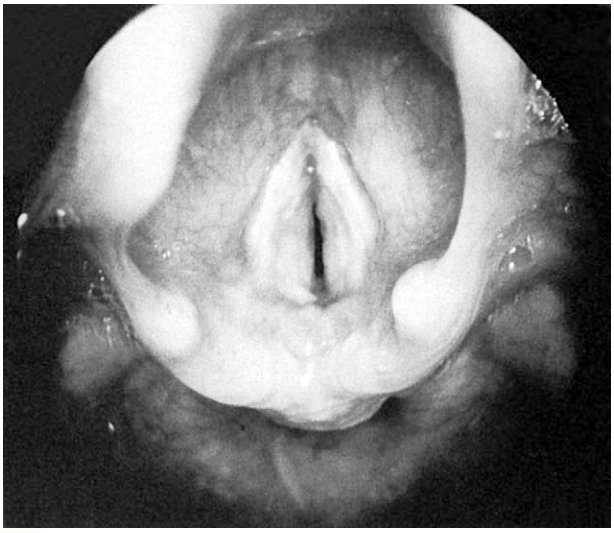

Figure 197-6. Viral croup with severe vocal fold and subglottic edema as seen with a rigid rod telescope.

Spasmodic Croup

Spasmodic croup is a poorly understood entity that is manifested by the sudden onset of stridor, usually at night, in a healthy child between 1 and 3 years of age with no concomitant upper respiratory tract infection. A barking cough and dyspnea accompany the stridor. These episodes may be recurrent in nature and usually resolve spontaneously or with cool humid air within several hours. The vocal folds may be involved with spasm, and mild, pale transient vocal fold and subglottic edema may be present. Some of the same viruses that cause viral croup may be involved with causing spasmodic croup. An increasing body of evidence suggests an association between spasmodic croup and recurrent croup with nonspecific bronchial hyperactivity, asthma, and allergic disease.[13-16] Spasmodic croup and viral croup also may well represent two ends of a broad spectrum in the clinical presentation of a single disease.[17]

Management

Most children with viral croup have symptoms within the mild spectrum of the illness and do not require a physician visit. The illness usually is self-limited, peaking in severity through 3 to 5 days with no specific treatment required at home. A quiet environment and parental comforting or support is universally important in the treatment of children with croup. Any stimulus or disturbance promotes crying and an increased respiratory rate. The airway is stabilized with less mucosal dryness when the child is quiet and when anxiety or crying is diminished.

Management strategies for viral croup have included glucocorticoids, racemic epinephrine, heliox, and mist. Although viral croup is the most common form of airway obstruction in young children, many controversies remain and there is no consensus regarding optimal treatment. Recently, croup clinical pathways have been devised to promote consistent, safe, and effective management that might result in reduced hospital admissions and earlier hospital discharge.[18]

Overwhelming evidence is present to support the use of glucocorticoids in both outpatient and inpatient settings in the management of moderate to severe decrease in croup.[19-22] Segal and others[23] have documented an 86% decrease in hospital admissions for treatment of croup when steroids were used. The exact mechanism of action of glucocorticoids in croup is unknown, but they probably decrease endothelial permeability, thus leading to decreased mucosal edema. This effect commonly takes at least 3 hours. In mild to moderate cases, oral prednisolone 2 mg/kg/day in two divided doses may be used in the outpatient setting or home for approximately 3 days. This regimen is particularly useful in milder, recurrent cases of croup, with parents keeping prednisolone at home to use when symptoms occur.

Table 197-1

Differential Diagnosis of Upper Airway Infections in Children

	Laryngotracheitis (Viral Croup)	Supraglottitis (Epiglottitis)	Bacterial Tracheitis	Retropharyngeal Abscess
Age	6 mo to 3 yr	1-8 yr	6 mo to 8 yr	1-5 yr
Onset	Slow	Rapid	Rapid	Slow
Prodrome	URI symptoms	None or mild URI	URI symptoms	URI symptoms
Fever	Variable or none	High	Usually high	Usually high
Hoarseness/barky cough	Yes	No	Yes	No
Dysphagia	No	Yes	Yes	Yes
Toxic appearance	No	Yes	Yes	Variable

URI, upper respiratory infection.

In the emergency center, dexamethasone has been extensively used in doses from 0.15 mg/kg to 0.60 mg/kg, with maximum doses of 1 mg/kg for moderate to severe croup.[22,24] Oral administration is as effective or better than intramuscular injection or nebulized therapy.[15,22] Nebulized budesonide has also been compared with dexamethasone but has had no clear clinical advantage.[24] If the symptoms of croup are severe enough to warrant the use of racemic epinephrine, then glucocorticoids are helpful in preventing any associated mucosal rebound edema 2 to 3 hours later. Glucocorticoids have had a significant impact in the outpatient setting but have also greatly decreased the severity of symptoms and the duration of hospitalization.[22,25,26] At this point it appears that an initial dexamethasone dose of 0.60 mg/kg orally is preferred because of its low dose and ease of administration.[27] Further doses of prednisolone (2 mg/kg/day) or dexamethasone (1 mg/kg/day) in divided doses may be used to sustain the glucocorticoid effect in either inpatients or outpatients. Intravenous administration is preferable in serious inpatient disease. Prolonged use of glucocorticoids should be monitored carefully, particularly when antibiotics may be used, to prevent candida overgrowth in the subglottis or trachea.[28] In the absence of clinical evidence of an emerging bacterial process, there is no support for the use of antibiotics in the management of viral croup.

Racemic epinephrine in an equal mixture of the d- and l-isomers of epinephrine has been used in the United States and Canada since 1971[29] but has become available and accepted in other countries as well. It has been shown that l-epinephrine is at least as effective as racemic epinephrine, is readily available worldwide, has no increased side effects, and is less expensive than d-epinephrine.[30] The α-adrenergic effects of epinephrine cause mucosal vasoconstriction, leading to decreased edema in the subglottic region. Using 0.5 mL of a 2.25% solution of racemic epinephrine diluted in 3 mL of saline delivered by a nebulizer results in rapid clinical improvement of moderate to severe respiratory distress within 10 to 30 minutes.[17,31] Alternatively, 5 mL of a 1:1000 solution of l-epinephrine produces equivalent results. This effect wanes and disappears by 2 hours after administration, with rebound mucosal edema in some patients. Because of this temporary effect and possible rebound, children should be observed closely after administering racemic epinephrine for 2 to 3 hours. Recent reports document the safe use of racemic epinephrine in an outpatient setting. These children were observed for at least 2 to 3 hours, were significantly improved, could easily return to the hospital if needed, and were closely followed as outpatients.[32-35] Racemic epinephrine has become widely used in outpatient settings for moderate to severe croup within similar observation criteria described in the studies. In an intensive care setting it can be used every 30 minutes, but it is usually spaced every 3 to 4 hours in a regular hospital unit. Glucocorticoid administration is important in any setting to prevent or diminish the mucosal rebound potential of racemic epinephrine. Racemic epinephrine should be used with great caution in patients with tachycardia or cardiac anomalies such as tetralogy of Fallot or idiopathic subaortic stenosis.

Heliox, a helium-oxygen mixture, may be helpful in severe croup. It decreases the work of breathing by promoting laminar flow through the partially obstructed airway. One study has shown similar improvement in croup scores with heliox administration when compared with patients given epinephrine.[36] Heliox may be used as an adjunct to all other medical therapy for croup.

Humidified air or mist has historically been used to treat croup before other medical therapy was available. Humidifiers or steam showers at home and mist tents or blow-by mist in hospital settings presumably moisten secretions, make for easier expectoration, and prevent drying or crusting that may further compromise a narrow airway. There may also be soothing of the involved mucosa, making children more comfortable and less likely to increase submucosal inflammation by vigorous coughing. However, only several studies have investigated the effectiveness of moist air in the management of croup and have demonstrated no benefit over control patients.[22,26,37,38] Furthermore, the issue of warm versus cool mist has not been settled. Despite the lack of objective benefit, strong anecdotal experience may support the continued use of mist, particularly in severe hospitalized cases of viral croup or in low-humidity environments. Mist tents should be avoided or used with caution because they may provoke more anxiety in children and therefore blow-by mist may be a better alternative. Well-designed studies are necessary to define the role of mist in the management of viral croup.

When medical therapy fails to alleviate respiratory distress, endotracheal intubation (nasotracheal or orotracheal) may be necessary. A tube at least a half size smaller than estimated for the child's size or age should be used. When possible, intubation should be done in a controlled situation in the operating room with an inhalation agent, while the child is spontaneously breathing. This also may allow for airway endoscopy at the same time. Optical rigid rod telescopes should be used to assess the airway, and rigid bronchoscopes should be avoided if possible to prevent further airway mucosal injury. Extubation can be performed when an air leak is detected. If no air leak is detected after 5 to 7 days, thorough airway endoscopy is indicated. Airway endoscopy also is important in recurrent, prolonged, or atypical cases of croup. Ideally, endoscopy should be performed 3 to 4 weeks after the acute episode has resolved so that acute inflammatory changes can be differentiated from previous existing anatomic abnormalities. A thorough evaluation of the larynx, subglottis, and trachea with rigid rod telescopes then should be performed.

Supraglottitis (Epiglottitis)

Since Michel's original description of "angina epiglottidea anterior" in 1878,[39] acute epiglottitis, or *supraglottitis* as it is more correctly called, has become recognized as a rapidly progressive, life-threatening airway

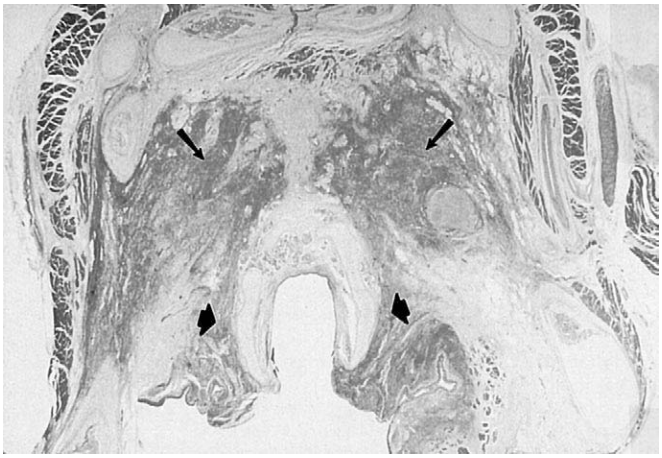

Figure 197-7. Histologic section of a larynx (postmortem) in supraglottitis showing posterior curling of the epiglottic cartilage *(arrowheads)* and severe inflammatory edema of the lingual surface of the epiglottis *(arrows)*.

emergency. Supraglottitis predominantly affected children in what may be termed the prevaccine era. A precipitous decline in supraglottitis in children has occurred since the introduction of the Haemophilus influenzae type b (HIB) vaccine.[40-42] Before widespread use of the HIB vaccination, the incidence of HIB among children ranged from 6 per 100,000 in Canada[43] to 34 per 100,000 in Switzerland.[44] In 1988 conjugated HIB vaccine was introduced with recommendations for universal use in children by 2 years of age in 1990 and immunized levels of at least 90% by 1995. Invasive HIB disease, primarily supraglottitis and meningitis, has declined nationally in the United States by 95%.[45] Immunization works by producing antibodies to the polysaccharide capsule of HIB. Supraglottitis may infrequently occur even when immunization has occurred because of failure of antibody production.[45] Acute supraglottitis remains a rare infection. Its importance lies in its high mortality if the diagnosis is not made promptly.

Supraglottitis is a cellulitis of all the supraglottic structures (not just the epiglottis) that may completely obstruct the airway. As the supraglottic edema increases, the epiglottis curls posteriorly and inferiorly as a result of diffuse inflammatory infiltration of the lingual surface of the epiglottis (Fig. 197-7). The aryepiglottic folds are also affected. With the airway partially occluded, mucus can easily complete obstruction of the airway. Diffuse infiltration of polymorphonuclear lymphocytes and inflammatory edema are seen histologically. Progress is rapid, in terms of hours rather than days. The disease classically occurred in children 2 to 6 years of age; however, it may occur at any age including in newborns.[28,46] A higher incidence may be seen in the winter or spring, although the disease may occur at any time of the year. Supraglottitis may be more commonly seen in older children and adults in today's HIB vaccine era.[23]

The causative organism most commonly identified in more than 90% of supraglottitis in the prevaccine era was *H. influenzae* type b (HIB).[40,47] This bacterial species may be part of the normal nasopharyngeal flora, or it may be acquired by respiratory transmission from other intimate contact. These bacteria may become blood borne and subsequently seed the epiglottis, meninges, facial skin, lungs, or joints. As the frequency of HIB disease has decreased in the HIB vaccine era, the epidemiology of supraglottitis has shifted.[48] Group A β-hemolytic streptococci comprise the majority of cases.[21,49] Other pathogens such as staphylococcus,[50] pneumococcus,[51] klebsiella,[52] Haemophilus parainfluenzae,[53] pseudomonas,[54] viruses,[53,55-57] and candida[58] have been isolated. Other rare causes including crack cocaine,[59] Kawasaki disease,[60] thermal epiglottitis caused by hot food or drink,[61,62] and post transplant lymphoproliferative disorder[63] have been reported. With the appearance of the human immunodeficiency virus (HIV), chronic epiglottitis associated with lymphoid hyperplasia within the epiglottis of an HIV-infected child has been reported.[64]

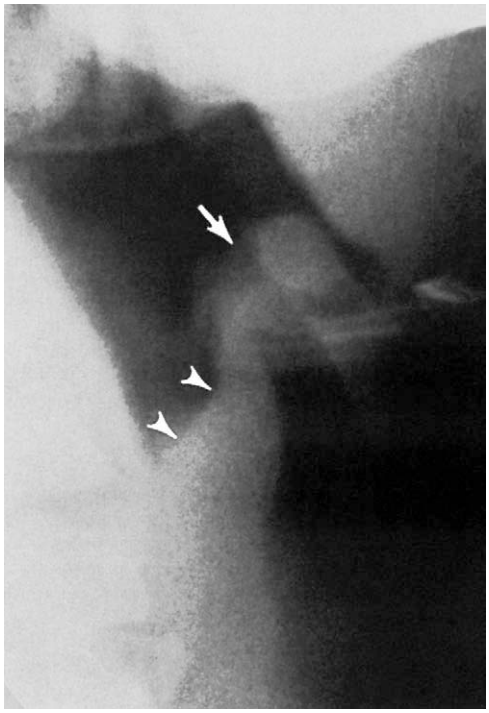

Figure 197-8. Supraglottitis seen on lateral soft tissue radiograph with a rounded epiglottis *(arrow)*, thickened aryepiglottic folds *(arrowheads)*, and distention of the hypopharynx.

Clinical Features

Due to the rarity of supraglottitis in the HIB vaccine era, the diagnosis may be more challenging. Regardless of the age at presentation, the three most common signs of supraglottitis are fever, difficulty breathing, and irritability. Children are toxic in appearance and have clinical evidence of major upper airway obstruction. The child exhibits shallow respiration, inspiratory stridor, retractions, and drooling. There is severe throat pain and dysphagia. Speech is limited because of pain. A cough or hoarseness is usually not present, but the voice may be muffled. Stridor occurs late when airway obstruction is almost complete. Activity is minimal, and the patient usually prefers sitting or leaning forward. The child may assume a "tripod" position (i.e., seated, with the hands braced against the bed and the head held in the sniffing position to maximize airflow through a narrowed laryngeal inlet). Sudden laryngospasm may occur with aspiration of secretions into an already compromised airway and produce respiratory arrest. Some of the atypical causes of supraglottitis may have a more protracted presentation.

Diagnosis

Prompt recognition of this acute airway emergency is essential to prevent airway obstruction. The diagnosis of acute epiglottitis is made by direct inspection of the supraglottic structures in a controlled environment, usually in the operating room. In a cooperative patient with no imminent complete airway obstruction, the pharynx may be visualized without a tongue blade to rule out acute tonsil or peritonsillar infection. Attempts to visualize the epiglottis in the office or emergency department without the ability or equipment to manage an obstructed airway are strongly discouraged.

The need for radiologic studies is controversial. Although there is no question that supraglottitis can be diagnosed on a lateral neck radiograph, the question arises whether this is a safe and necessary procedure. Most radiology suites lack the facilities to handle an obstructed pediatric airway. A child presenting with the previous signs and symptoms probably should forego radiologic testing and proceed directly to the operating room. If there is any question as to the correct diagnosis and if the child is not in respiratory distress, radiologic examination can confirm

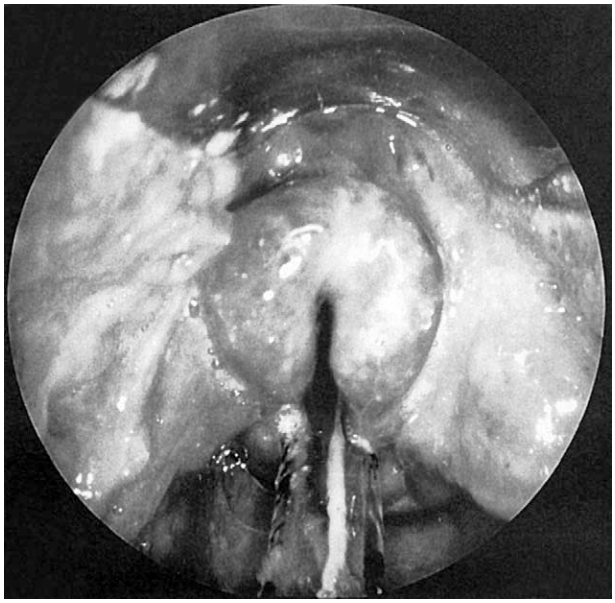

Figure 197-9. Supraglottitis just after intubation, visualized by a rigid rod telescope.

the diagnosis and exclude other causes of acute airway obstruction. Among the different diagnoses to be excluded are foreign bodies, retropharyngeal abscesses, and viral croup or laryngotracheitis.

Lateral neck radiographs in those with epiglottitis reveal swelling and rounding of the epiglottis with thickening and bulging of the aryepiglottic folds and distention of the hypopharynx (Fig. 197-8). In addition, the subglottic airway will appear normal on AP radiographs. In the operating room, examination of the supraglottis reveals an edematous, erythematous epiglottis with variable degrees of obstruction of the airway (Fig. 197-9). The cartilaginous landmarks are often obscured. Mucosal changes range from erythema to frank ulceration or sloughing. Rarely, an abscess can be found in the lingual surface of the epiglottis. The differential diagnosis of inpatients with possible supraglottitis includes viral croup or laryngotracheitis, bacterial tracheitis, uvulitis, acute tonsillitis, retropharyngeal or peritonsillar abscess, and diphtheria. Diphtheria is a rare infection seen only in certain areas with nonimmunized patients. A history of diphtheria immunization and the absence of pharyngeal membranes make the diagnosis unlikely. Foreign body aspiration in a child with an acute upper respiratory infection also may mimic supraglottitis.

Management

Close cooperation among the otolaryngologist, pediatrician, and anesthesiologist is paramount in the management of supraglottitis. If the diagnosis of acute supraglottitis is suspected, care should be taken to avoid stimulating the child. The child will naturally assume a posture and breathing pattern that maximizes ventilation. Any intervention may convert a functional—albeit unstable—airway into a nonfunctional, acutely obstructed airway. Anything that causes the child to cry may precipitate obstruction. Therefore drawing blood, throat examination, establishing an intravenous line, restraining for a radiograph, undressing the child, or even separating from a parent may cause distress and lead to airway obstruction. Any of these procedures should wait until a stable airway has been established.

Once the diagnosis of acute supraglottitis is made, survival is closely related to the establishment of an artificial airway. For many years, this meant a tracheotomy was performed when the diagnosis was made. Since the 1970s, the safety of intubation has been established, and now endotracheal intubation by nasal or oral routes has become the standard method of managing acute supraglottitis. The rationale for this change is based on the rapid response of the infectious process to appropriate antibiotic therapy. The edema of the supraglottic larynx usually subsides within 48 to 72 hours, allowing safe removal of the endotracheal tube.[65] Despite this observation, if personnel skilled in endotracheal intubation will not be available postoperatively or if the airway can only initially be secured with a rigid bronchoscope, then a tracheotomy still may be the most appropriate choice.

If supraglottitis is suspected, the patient should be taken to the operating room, accompanied by personnel experienced in the establishment of an emergency airway including tracheotomy. Once in the operating room, the patient undergoes gentle, slow, inhalational induction of general anesthesia with a nonirritating inhalation agent. Muscle relaxants should be avoided until an airway is established. Only after adequate anesthesia is obtained should blood samples be taken or intravenous lines be established. A small rigid rod telescope with an endotracheal tube threaded over it may also be useful in patients in whom the glottic airway cannot be visualized. The telescope is advanced through the larynx, and then the endotracheal tube is advanced over the telescope into the trachea. A rigid bronchoscope of the appropriate size and one size smaller should be available. In addition, equipment for a tracheotomy should be at hand. The larynx is examined by the otolaryngologist, and the diagnosis is confirmed. Temporary orotracheal intubation is performed. Cultures are taken from the surface of the epiglottis, and simultaneous blood cultures are drawn. Blood cultures are almost always positive for HIB when this is the causative organism. Orderly nasotracheal intubation can be performed in most patients with removal of the orotracheal tube. Nasotracheal intubation is preferred because there is less motion and resultant irritation of the subglottis. Adequate sedation or restraint is essential to prevent accidental self-extubation.

Appropriate antibiotic therapy is begun with the first dose given in the operating room. Ceftriaxone, cefotaxime, or ampicillin-sulbactam are all appropriate choices even in the HIB-vaccine era. Vancomycin may be used if the child is sensitive to cephalosporins. Adjustments in antibiotics can be made on the basis of culture results. The duration of antibiotic therapy depends on the clinical response of the child. Oral antibiotics indicated by culture results can be used to complete a 7- to 10-day course of therapy as soon as extubation has been accomplished and adequate oral intake is present. Adjunctive treatment with corticosteroids is controversial. Antibody levels to HIB should be measured if there is a history of HIB vaccine administration.

Extubation generally can be accomplished within 48 hours.[65] Criteria for extubation include decreased erythema and swelling of the epiglottis on laryngoscopy and the development of an air leak around the endotracheal tube or after an empirical 48 hours of intubation. Visualization of the supraglottis offers the best guide to extubation. When there is no air leak at 48 hours, flexible fiberoptic laryngoscopy or even direct laryngoscopy can be performed safely and quickly in the intensive care unit in an effort to determine when extubation is safe and to shorten the duration of intubation.

Complications

Although the airway compromise in supraglottitis itself is a life-threatening illness, other infections may occur simultaneously, which may have an equally deleterious effect. In the era of HIB supraglottitis, there was a 90% to 95% rate of positive blood culture for HIB.[66] Therefore it was not surprising that hematogenous dissemination of the disease occurred. The most common infectious complication was pneumonia. Other concomitant HIB infections included meningitis, cervical adenitis, pericarditis, septic arthritis, and otitis media.[66-68] Meningitis may be difficult to diagnose in a sedated patient, and therefore one must be cognizant of this manifestation of HIB disease. The dose of antimicrobial agent ordinarily given may be below that which is recommended for managing meningitis.

Noninfectious complications may also occur in patients with supraglottitis. Any patient with complete airway obstruction and respiratory arrest can suffer hypoxic damage of the central nervous system and other organ systems. Even patients who have had appropriate management of their airway obstruction can become hypoxic. The sudden relief of upper airway obstruction can result in postobstructive pulmonary edema with subsequent hypoxia.[69] This potential complication should be anticipated before the placement of an artificial airway, especially in those patients exhibiting a high degree of airway obstruc-

tion. Appropriate levels of positive end-expiratory pressure after endotracheal intubation can provide a protective mechanism against the development of pulmonary edema.

Bacterial Tracheitis (Exudative Tracheitis)

Bacterial tracheitis, perhaps better known as *exudative tracheitis,* has also been termed bacterial laryngotracheobronchitis, membranous laryngotracheobronchitis, and pseudo-membranous croup. It is a rare but potentially life-threatening disease. The disease was certainly described by C. L. Jackson in 1945, but it was not until 1979 that it was redescribed in detail.[70-72] Since then, there has been a growing consensus of opinion that bacterial tracheitis represents a secondary or complicating bacterial infection of viral croup or laryngotracheitis.[12,73] The secondary bacterial pathogen most often described is *Staphylococcus aureus,* but a more recent report found *Moraxella catarrhalis* to be the most frequently implicated pathogen followed by *S. aureus.* This series and others also suggested an epidemiologic change to a slightly less morbid condition.[74,75] Other pathogens include *Streptococcus pyogenes, H. influenzae,* and more rarely gram-negative enteric bacteria.[3]

Bacterial tracheitis primarily occurs during the respiratory virus seasons of autumn and winter, similar to viral croup. It may be seen in a wider range of ages than typical croup, with a mean age of 7.9 years.[72] The infectious inflammatory process involves the subglottis and trachea with marked edema in the subglottis as in those with viral croup. Diffuse mucosal ulceration and pseudo-membrane formation follow, with sloughing of these membranes into the tracheal lumen further contributing to airway obstruction. A purulent exudate is commonly present in copious amounts throughout the trachea and main bronchi as well. Blood cultures are usually negative, but tracheal cultures reliably reveal the bacterial pathogen.[3]

Clinical Features

The onset of bacterial tracheitis is variable. Some children become acutely ill and have severe respiratory distress within hours of the onset of illness. In other children there is a several-day prodromal period of stridor, barky cough, and hoarseness typical of viral croup that precedes the rapid, dramatic onset of higher fever, increasing respiratory distress, and toxic appearance. These patients often do not respond to racemic epinephrine because the disease rapidly progresses. High fever, cough, and stridor occur almost simultaneously over several hours. The rapid onset of the illness is similar to supraglottitis, but there usually is no dysphagia or drooling. Leukocytosis often is prominent in those with bacterial tracheitis.

Diagnosis

The diagnosis may be suspected on the basis of signs and symptoms, but it is confirmed by endoscopic examination of the airway. Plain radiographic imaging of the upper airway will show a "steeple" sign of the upper trachea or subglottis in anterior views, similar to viral croup, but it is the lateral view that can be most helpful. Diffuse haziness is present in the tracheal air column, along with soft tissue irregularities within the lumen, indicating pseudo-membrane detachment (Fig. 197-10).

No clinical, radiologic, or laboratory feature alone or in combination is a reliable predictor of bacterial tracheitis. The only diagnostic procedure that distinguishes bacterial tracheitis promptly and accurately from other acute upper airway disease is airway endoscopy.[76]

Management

Airway endoscopy is not only diagnostic of bacterial tracheitis but also is therapeutic at the same time. Children should be taken to the operating room, where induction of anesthesia with spontaneous ventilation is similar to that in children with supraglottitis. Direct laryngoscopy then is performed with careful examination of the larynx, subglottis, trachea, and main bronchi with a rigid rod telescope (Fig. 197-11). A rigid bronchoscope may be necessary along with the rigid rod telescope to adequately suction and remove the copious secretions and pseudomembranes. Cultures and a Gram stain should be obtained from the tracheal secretions. Orotracheal or nasotracheal intubation then can be performed to secure the airway, if necessary. When rigid bronchoscopy is performed, this may induce further mucosal injury and edema in the subglottis, requiring a longer period of intubation. Tracheotomy is rarely necessary.

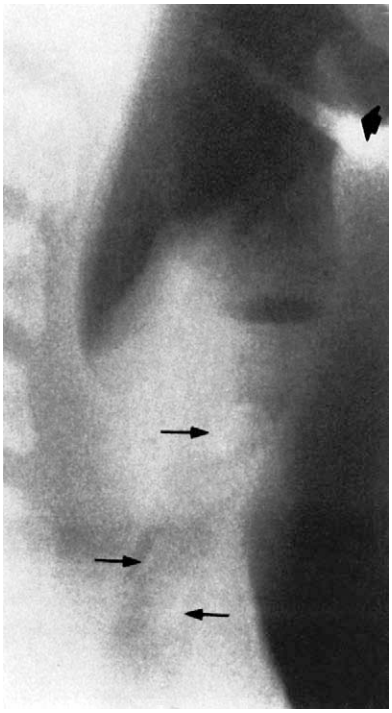

Figure 197-10. Bacterial tracheitis in a lateral soft tissue radiograph with obscured tracheal airway caused by sloughed mucosa *(arrows).* The epiglottis *(arrowhead)* is normal.

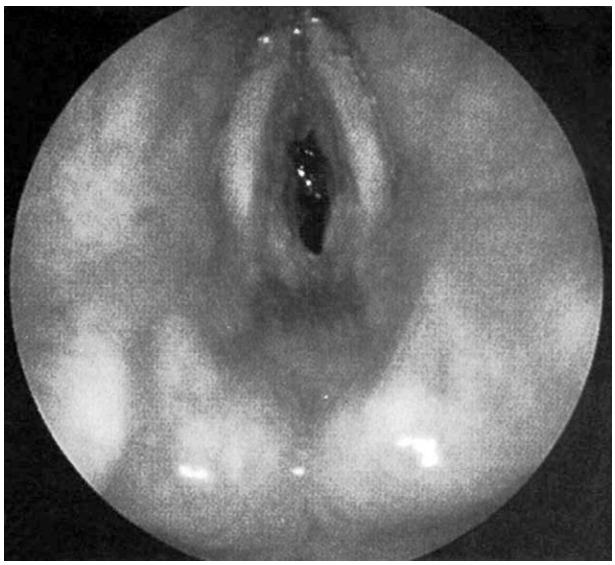

Figure 197-11. Bacterial tracheitis with severe glottic and subglottic edema with sloughed mucosa in the lumen.

Historically, the majority of patients (up to 80%) with bacterial tracheitis required intubation and ventilatory support.[44,72] More recent reports again suggest a milder illness with only 53% needing intubation.[75] While intubated, meticulous airway care with frequent saline administration and suctioning of the trachea should be performed to evacuate the thick and copious secretions. Occasionally, repeat rigid bronchoscopy may be necessary to handle unusually tenacious secretions. Initial parenteral antibiotic therapy should include vancomycin—because of the rise in resistant *S. aureus* organisms—along with cefotaxime or ceftriaxone for gram-negative organisms or mixed flora.

Gram's stain, culture results, and sensitivity results will direct ultimate antibiotic choices. Nafcillin, ampicillin-sulbactam, and cefuroxime may be good secondary antibiotic choices when culture and sensitivity results are known. Parenteral antibiotics should be continued beyond extubation when the child has undergone major clinical improvement. Extubation can be safely performed when the child's temperature has returned to normal, when a leak is present around the endotracheal tube, and when the secretions have markedly decreased. Oral antibiotics then can be used to complete a 10- to 14-day course of therapy. Intubation may be necessary for 6 to 7 days in more severe cases with a mean hospitalization of 10 days, which usually is longer than that of those with viral croup.[3]

The most common complication of bacterial tracheitis is pneumonia, occurring in about 50% of children. Severe hypoxia with death has occurred after respiratory arrest in severe cases of airway obstruction.[77]

Retropharyngeal Abscess

Retropharyngeal abscesses occur primarily in children, but they can be seen in adults where it is an entirely different disease associated with direct extension from adjacent structures, penetrating trauma, granulomatous disease, and cervical spine osteomyelitis. In children, retropharyngeal abscesses have been described since antiquity, but they have become less common as a result of antibiotic use since the 1950s.[78] However, Kirse and Roberson,[79] in a large review, reported a dramatic increase in the incidence of retropharyngeal abscess in 2001. Because of its anatomic location, a retropharyngeal abscess can still be a life-threatening illness that requires prompt diagnosis and treatment.

The retropharyngeal space extends from the skull base into the mediastinum as far as T6. It is limited posteriorly by the prevertebral fascia; anteriorly by the buccopharyngeal fascia, pharyngobasilar fascia over the three pharyngeal constrictor muscles, and the esophagus; and laterally by the carotid sheath. The space communicates directly with the parapharyngeal space anterolaterally. Within the retropharyngeal space are two vertical paramedian chains of lymph nodes that drain potential infections in the nasopharynx, oropharynx, paranasal sinuses, and possibly middle ear.[3] These lymph nodes are common in childhood, but they undergo atrophy by puberty. Suppuration of these nodes leads to abscess formation within the retropharyngeal space. Other sources of infection in this space include penetrating foreign bodies, endoscopy or intubation trauma, pharyngitis, pyogenic or mycobacterial vertebral body osteomyelitis, petrositis, and dental procedures.[80]

Retropharyngeal abscesses are most common in early childhood, with 70% of patients younger than 6 years of age and 50% younger than 3 years of age.[79,81] Coulthard and Isaacs[82] reported that 55% of their cases were younger than 1 year of age, and 10% presented in the neonatal period. Boys are more likely to be affected than girls by a 2 : 1 margin.[79]

Clinical Features

The symptoms of retropharyngeal abscess often, but not always, begin insidiously after an antecedent mild upper respiratory infection. Children usually present with fever, sore throat, progressive dysphagia, and drooling. Neck stiffness and mild torticollis may be present and may be suggestive of the diagnosis, distinguishing it from supraglottitis. Stridor is more prominent in younger children and increases as the abscess increases in size. Examination of the pharynx may reveal asymmetric swelling of the posterolateral oropharyngeal wall, but this may be difficult to assess in an uncooperative child with pooling of pharyngeal secretions. Cervical adenopathy also is common. Because of the presence of nonspecific signs and symptoms, a high degree of suspicion is required to ultimately make the diagnosis of retropharyngeal abscess.

Diagnosis

When there is clinical suspicion of retropharyngeal abscess, a complete blood count with differential and a lateral soft tissue radiograph of the neck should be obtained. The neck should be extended, and the radiograph should be taken on inspiration. The diagnosis of retropharyngeal cellulitis or abscess is suggested when the retropharyngeal space at the level of C2 is twice the diameter of the vertebral body (Fig. 197-12).[10]

Figure 197-12. Retropharyngeal cellulitis and abscess seen on a lateral radiographic view with widened soft tissue in the retropharynx compared with the adjacent vertebral bodies.

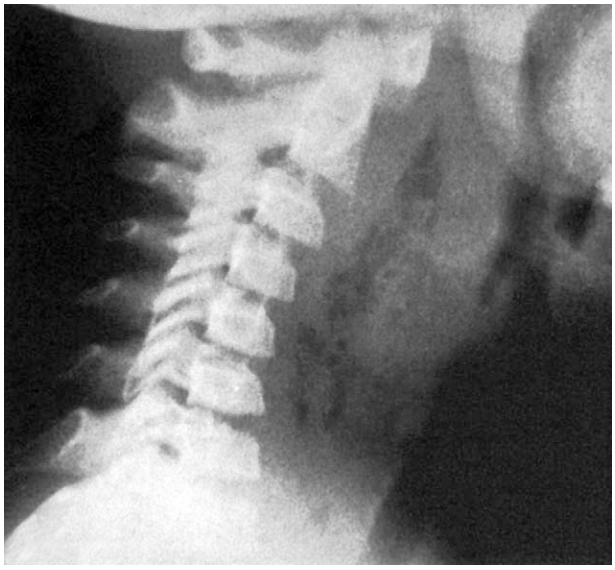

Figure 197-13. Retropharyngeal abscess in a lateral view with gas production within the soft tissues of the retropharynx.

This criterion has a sensitivity of nearly 90%.[82] The lateral radiograph also may reveal gas caused by gas-producing bacteria within the widened retropharyngeal tissues (Fig. 197-13). The normal cervical spine lordosis may be lost or even reversed, and the radiograph should be examined carefully for vertebral or intervertebral disease. The radiographic technique is extremely important because retropharyngeal thickening may be seen when the neck is flexed or when the view is taken on expiration. A chest radiograph should also be performed to exclude mediastinitis or aspiration pneumonia.

When the lateral neck radiograph reveals widened retropharyngeal soft tissues or there are equivocal findings with a strong clinical suspicion of retropharyngeal abscess, computed tomography (CT) of the neck with contrast is extremely helpful in differentiating an abscess from retropharyngeal cellulitis or phlegmon (Fig. 197-14). If there is no airway compromise, the child may be sedated for the CT scan, but, when significant obstruction is present, intubation may be necessary

Figure 197-14. Axial computed tomography showing a hypodense area in the left retropharynx with early ring enhancement, indicating a retropharyngeal abscess *(arrow)*.

with the involvement of anesthesia and otolaryngology specialists. Scans should be obtained from the skull base to the thoracic inlet with delayed imaging at least midway through the intravenous contrast injection. Round, central hypodense nodes without clear ring enhancement suggest edematous nodes or phlegmon. When central hypodensity is associated with clear ring enhancement and irregular or scalloped walls, this is most suggestive of an abscess.[79] Using these criteria, CT imaging should accurately delineate abscess from cellulitis in more than 75% of cases. Roberson and colleagues[83] described a comprehensive practice guideline for diagnosis and management of retropharyngeal abscesses with standardized care and good outcomes. The CT scan also defines the exact abscess location and any possible extension into other anatomic areas such as the parapharyngeal space. This is most valuable information when incision and drainage of the abscess is performed.

Management

As in other airway infections, the airway should be secured in severe cases of respiratory distress before ever performing diagnostic procedures. Once the diagnosis is confirmed, initial antibiotic therapy is directed empirically toward aerobic and anaerobic flora of the nasopharynx. Aerobic species include Streptococcus, S. aureus, and Haemophilus. Group A β-hemolytic streptococci have emerged as important organisms either alone or in polymicrobial infections. Bacteroides, Peptostreptococcus, and fusobacteria are the most commonly encountered anaerobes.[79,80] Initial antimicrobial therapy should include clindamycin or ampicillin-sulbactam. An aminoglycoside or third-generation cephalosporin may also be necessary in neonates to provide management for gram-negative enterics.

When CT suggests only a phlegmon or cellulitis, a trial of intravenous antibiotics is warranted. If after 48 hours the child is clinically well, then outpatient antibiotic therapy is appropriate. If the clinical course is worrisome, however, a repeat CT scan or surgical intervention should be considered.

With the availability of CT imaging to distinguish retropharyngeal cellulitis from abscess formation, the surgeon can best determine those children who will require abscess incision and drainage. When an abscess is found or suspected, incision and drainage should be performed in most cases because this may greatly expedite resolution of this disease. Very small abscesses in children who are clinically improving may be treated medically. The transoral approach is indicated in almost all children, except in those rare cases when there is extension or involvement lateral to the great vessels. The vessels should be well examined on the imaging study to rule out the rare possibility of vascular wall compromise. Careful oral intubation should be performed to avoid abscess rupture and possible aspiration of purulent material. The pharyngeal incision is made over the most prominent bulging area, which is almost always located on one side of the posterior pharynx near the lateral pharyngeal wall. Blunt dissection may reveal thin secretions in early abscess formation but thicker mucopurulent secretions in a more defined abscess. Needle aspiration may be helpful in localizing a purulent collection. A drain is not required. When a child presents with a major inflammatory lateral neck mass and a large parapharyngeal space abscess, in addition to retropharyngeal involvement, a lateral cervical incision and drainage procedure is indicated with drain placement. Cultures of the purulent drainage from either approach will help direct antibiotic therapy. When the child is afebrile, asymptomatic, and swallowing well, appropriate oral antibiotics (e.g., amoxicillin–clavulanic acid or clindamycin) can be used to complete a 10- to 14-day course of therapy.

Complications

Complications that should be considered in children with retropharyngeal abscesses include airway obstruction, spontaneous abscess perforation, aspiration pneumonia, mediastinitis, and sepsis. More rarely, retropharyngeal abscess can result in chest empyema, thrombosis of the internal jugular vein, erosion of the carotid artery, and atlantoaxial dislocation.[10,80] With early suspicion of the clinical possibility of a retropharyngeal abscess, along with CT imaging, good anesthesia, and prompt surgical drainage, complications should be extremely low with near zero mortality.

Acknowledgments

I want to gratefully acknowledge the support of my mentor Dr. Bruce N. P. Benjamin, Sydney, Australia, in collecting the endoscopic airway photographs in this chapter; Dr. Lynn Trautwein, Texas Children's Hospital, Houston, for helping assemble the radiographs and imaging views; and Ms. Nancy Turner for manuscript editorial assistance.

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CHAPTER ONE HUNDRED AND NINETY-EIGHT

Differential Diagnosis of Neck Masses

Ralph F. Wetmore

William P. Potsic

Key Points

- The two major categories of neck masses in children are congenital and acquired lesions. Congenital cysts make up the majority of the congenital lesions, whereas infectious masses comprise a majority of the acquired ones.
- A good history and physical are essential to narrow the differential diagnosis of a pediatric neck mass. Computed tomography (CT), magnetic resonance imaging (MRI), and neck ultrasound are the major radiologic studies that help in the evaluation of a neck mass.
- Most branchial cleft cysts are either second or third branchial derivatives. Thyroglossal duct cysts develop within the embryonic thyroid descent tract.
- Hemangiomas are proliferative lesions, rather than neoplastic, and typically begin to involute at 18 to 24 months of age. Vascular and lymphatic malformations are also congenital lesions but do not involute.
- Most infectious lymphadenopathy is viral, but streptococcal or staphylococcal organisms may cause suppurative lymphadenopathy.
- Lymphoma is the most common neck malignancy in children and presents as an enlarging neck mass with or without systemic symptoms of fever, weight loss, night sweats, or fatigue. Malignant neck lesions tend to occur most commonly in either the posterior cervical or supraclavicular regions.

The presentation of a neck mass in a pediatric patient has many diagnostic possibilities not normally encountered in an adult (Fig. 198-1). Neoplastic disease, especially malignant, is the primary consideration in the evaluation of a neck mass in an adult. In contrast, diagnosis of a pediatric neck mass can be categorized, depending on the location, growth factors, and the child's age. The possibility of malignancy should always be considered in the differential diagnosis in pediatric patients; however, it is not as overriding a concern as in adults.

The two major categories of pediatric neck masses include congenital and acquired lesions. Congenital masses have a high incidence (>50% in some series),[1] which initially differentiates them from acquired masses. The primary type of acquired masses is inflammatory (acute and chronic), which further narrows the differential diagnosis. Benign and malignant lesions are rare in the pediatric patient.

The approach to the child with a neck mass depends on the history and physical examination. Radiographic and laboratory studies may prove helpful, but some masses require surgical biopsy to establish the diagnosis. Thus the pediatric neck mass often poses a challenge to the surgeon.

History

In the evaluation of a pediatric patient with a neck mass, a detailed history alone can often exclude many lesions in the differential diagnosis. Consideration of temporal relationships can often prove helpful. A history of infection elsewhere in the patient or recent travel or exposure to farm animals may suggest an infectious origin. Preceding trauma may signal a hematoma, whereas an increase in the size of the mass or pain with eating may point to a salivary gland problem. Exposure to drugs such as phenytoin may also be contributory.

The growth characteristics of the neck mass are important. Slow growth suggests a benign process, whereas rapid enlargement occurs with infectious or malignant lesions. Some masses fluctuate in size (e.g., hemangiomas increase in size with straining and crying). Fever, weight loss, night sweats, or fatigue suggest a malignant process.

Physical Examination

In the evaluation of a child with a neck mass, comprehensive head and neck examination is essential. Clues to the pathogenesis of the neck mass may be found anywhere in the head. Likewise, a total physical examination should be performed with special attention to other lymph node groups such as the axillae and groin. Palpation for an enlarged spleen should always be attempted.

Infants frequently have small palpable lymph nodes in the posterior cervical region, whereas older children have palpable nodes in the anterior cervical, posterior cervical, and submandibular regions. Any node greater than 2 cm in diameter falls outside the range of these normal hyperplastic nodes and should be evaluated further.

In examination of abnormal lymph nodes or a neck mass, the location is important for determining the site of the precipitating infection or the primary source of a malignant neoplasm. For example, infection in the nasopharynx tends to drain into the posterior cervical

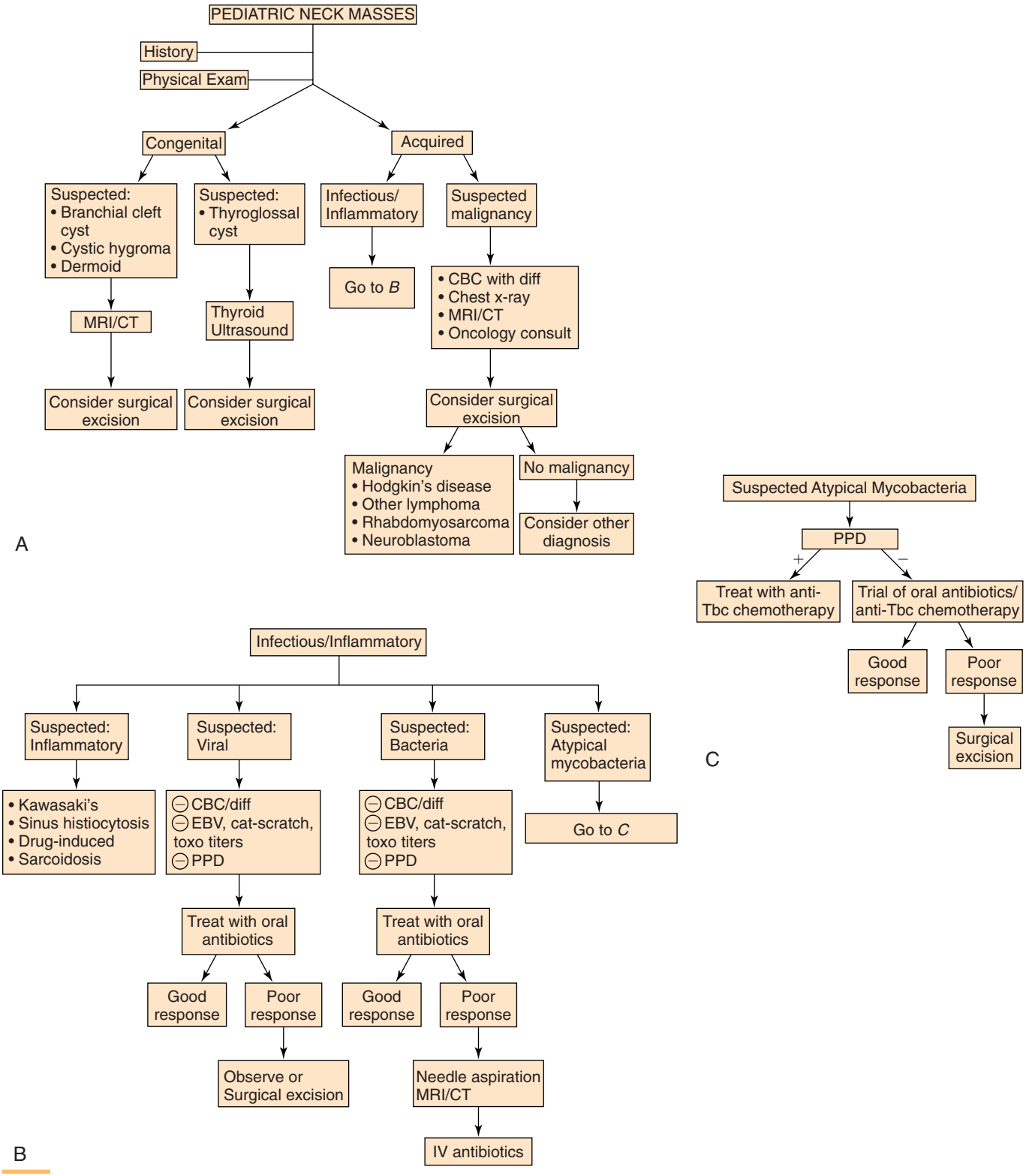

Figure 198-1. **A** to **C**, Algorithms for the differential diagnosis of neck masses.

region, whereas tonsillitis may cause enlargement in the anterior cervical region. Moussatos[2] and Putney[3] noted an increased incidence of malignancy in the posterior cervical triangle; in contrast, Torsiglieri and colleagues[1] reported an increased incidence in the supraclavicular region.

The consistency of a neck mass is frequently helpful in categorizing the mass. For example, hard masses tend to occur with infection or a malignant process. Fixation of a mass to the skin or deeper structures of the neck suggests a malignancy. A fluctuant mass tends to occur with abscess formation or a cyst.

Radiologic Studies

Depending on the clinical impression of a neck mass from the history and physical examination, selected radiographic studies may help narrow the differential diagnosis. Chest radiography is helpful if a malignancy, sarcoidosis, or pulmonary tuberculosis is suspected. In the

evaluation of the nasopharynx, cervical spine, or retropharyngeal region, lateral neck radiography may show an abnormality. Likewise, a sinus series may show evidence of an infection or neoplasm in the paranasal sinuses.

In cases of infection in the neck, computed tomography (CT) with contrast may differentiate cellulitis that may respond solely to antibiotic therapy from an abscess with rim enhancement that may necessitate surgery. CT with contrast also helps identify vascular masses such as hemangiomas. Magnetic resonance imaging (MRI) provides even better detail of soft tissue. When combined with contrast, MRI is also useful in the evaluation of vascular lesions.

Ultrasound of the neck is most helpful in differentiating a cystic structure from a solid mass. It should be included as part of the evaluation of any thyroid mass. Before excision of a thyroglossal duct cyst, ultrasound can confirm the presence of a thyroid gland in its normal position, ruling out the possibility of ectopic thyroid. Use of ultrasound in these cases is easier and more economical. Thyroid scanning remains essential in the evaluation of any thyroid mass.

Laboratory Studies

As with radiography, selected laboratory studies may be useful in the evaluation of the pediatric neck mass. A complete blood count with differential is indicated if a malignancy or systemic infection is suspected. Serologic testing for Epstein-Barr virus (EBV), cytomegalovirus, toxoplasmosis, syphilis, or cat-scratch disease may be diagnostic. An elevated serum calcium level is highly suggestive of sarcoidosis, whereas thyroid function studies are necessary in the evaluation of most thyroid masses. Urinary collection for vanillylmandelic acid (VMA) is helpful when neuroblastoma is suspected. Although not as accurate as a culture of infected tissue, skin tests, if available, remain a reliable indicator of mycobacterial disease.

Surgical Diagnosis

Although fine-needle aspiration of a suspected malignancy is not as reliable in children as in adults, fine-needle aspiration of a neck infection decompresses the mass and provides material for culture. In some cases, especially when the diagnosis of malignancy is considered, an incisional or excisional biopsy is indicated. Advantages of a biopsy include inspection of the lesion, providing a cuff of healthy surrounding tissue and tissue for frozen and permanent section, electron microscopy, and tumor markers.

Congenital Masses

Branchial Cleft Cysts

Although the definitive mechanism for the development of branchial cleft cysts is unclear, it is suspected that these congenital masses result from the cervical sinus of His becoming entrapped without an external or internal opening. An epithelium-lined cyst results. Others suggest that these cysts develop from epithelial rests of tissue from Waldeyer's ring.[4] Branchial cleft cysts are relatively common; in one series, they comprise one third of congenital neck masses.[1]

Branchial cleft cysts typically are seen as nontender, fluctuant masses that may become inflamed and abscess during an upper respiratory infection (Fig. 198-2). First branchial cleft cysts, although rare, typically present near the angle of the mandible (Fig. 198-3). Second branchial cysts are found high in the neck and deep to the anterior border of the sternocleidomastoid muscle. Third branchial cleft cysts, also rare, are seen near the upper pole of the thyroid gland. Other symptoms, depending on the size of the cyst, include dysphagia, dyspnea, and stridor.

Radiologic evaluation of a branchial cleft cyst may include ultrasound, CT, and MRI. Ultrasound shows a fluid-filled cyst and can differentiate cystic lesions from solid masses. CT and MRI also confirm the cystic characteristics of the mass and, more importantly, delineate the relationship of the cyst to surrounding structures (Fig. 198-4).

Management of branchial cleft cysts is surgical excision. It is advisable, if possible, to manage an infected cyst with antibiotics, allowing the inflammation to resolve before excision is attempted.

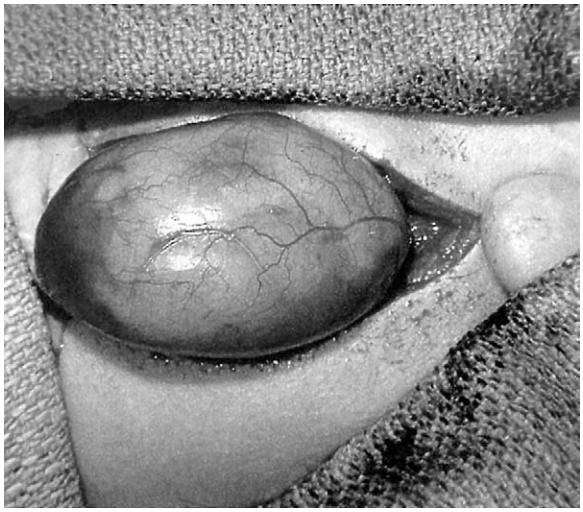

Figure 198-2. A typical branchial cleft cyst is an epithelium-lined cyst filled with mucoid material. This cyst presents along the anterior border of the sternocleidomastoid muscle.

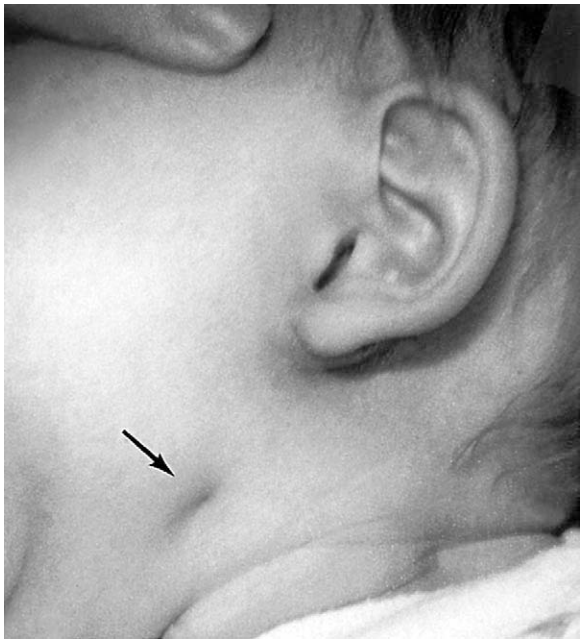

Figure 198-3. First branchial derivatives present as a pit or a mass near the angle of the mandible *(arrow)*. They frequently originate in or near the external canal and, during their course, involve the facial nerve.

Thyroglossal Duct Cysts

Thyroglossal duct cysts form in a persistent thyroid descent tract that begins as an elongation of the thyroid diverticulum. Beginning at the foramen caecum of the tongue, this tract may extend to the thyroid gland itself, where some tissue may persist in the region of a pyramidal lobe. These remnants are cysts and are not associated with a cutaneous sinus or fistula tract unless surgically drained and inadequately excised. They comprise approximately one third of congenital neck masses in children.[1]

Most thyroglossal duct cysts are seen in the midline near the level of the hyoid bone because the tract passes just anterior to the hyoid bone (Fig. 198-5). Some cysts may present laterally and are not infrequently found superior to the hyoid or as low as the level of the thyroid gland. Thyroglossal duct cysts that occur off the midline may be

Figure 198-4. Axial computed tomography of the neck shows a branchial cleft cyst in the hypolucent area *(arrow)*.

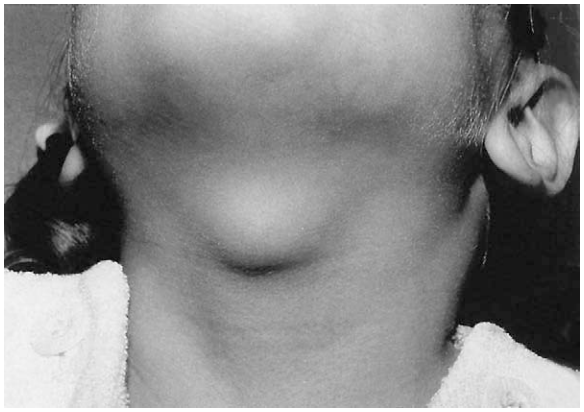

Figure 198-5. Thyroglossal duct cysts are often found in the midline of the neck at or near the hyoid bone.

difficult to differentiate from branchial cleft cysts, an important factor in their surgical excision. Other unusual presentations of thyroglossal duct cysts include formation on either side of the hyoid bone as dumbbell-shaped lesions and, rarely, as cystic lesions in the larynx. Thyroid tissue is found in surgical specimens in up to 45% of cases.[5]

A thyroglossal duct cyst usually presents as an asymptomatic mass but may be associated with mild dysphagia. Not infrequently, presentation of these cysts may be accompanied by infection, causing rapid enlargement that may produce significant dysphagia and choking.

In cases in which a thyroglossal duct cyst is suspected, it is important to differentiate ectopic thyroid from a cyst. Although only 10% of ectopic thyroid is found in the neck, it may represent the only thyroid tissue in 75% of patients.[6] Children with ectopic thyroid may be mildly hypothyroid; however, excision of this tissue necessitates hormone replacement for the remainder of the patient's life. Thyroid ultrasound and radionucleotide scanning can differentiate ectopic thyroid from a thyroglossal duct cyst; ultrasound is easier to perform, less expensive, and does not use radioisotopes.

The Sistrunk operation is the standard method of thyroglossal duct cyst excision. The cyst is excised along with a cuff of tissue including the center portion of the hyoid bone. Incision and drainage of an infected cyst should be avoided because violation of the cyst capsule may invite recurrence. Recurrence rates of nearly 10% have been reported in children who have undergone uncomplicated Sistrunk operations.[1]

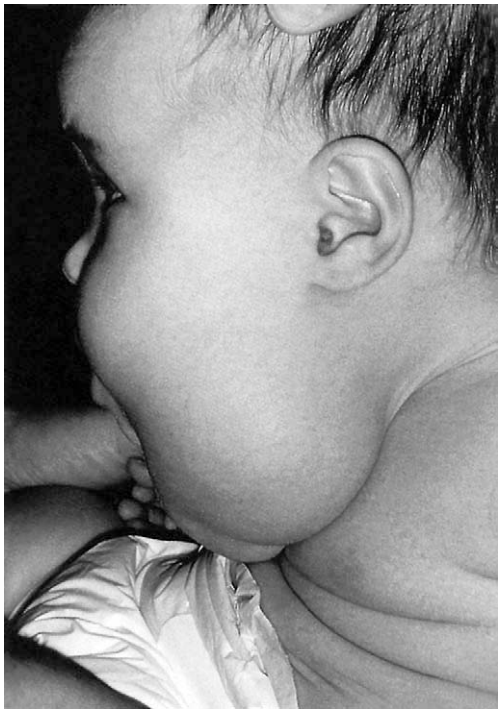

Figure 198-6. Lymphangiomas of the neck may cause significant cosmetic deformity and may impair respiration or alimentation.

Lymphatic Malformations (Lymphangiomas)

The term *lymphatic malformation* is a better definition of the lesion that was previously termed *lymphangioma.* Lymphatic malformations are congenital malformations of lymph tissue that result from the failure of lymph spaces to connect to the rest of the lymphatic system. Lesions containing both lymphatic and venous components may be labeled combined venolymphatic malformations. Macrocystic lymphatic malformations (previously termed *cystic hygroma*) contain large thick-walled cysts that have less infiltration of surrounding tissue. Microcystic lymphatic malformations have more extensive infiltration of the soft tissue structures of the head and neck, especially in the tongue and floor of mouth, making their excision difficult.

A lymphatic malformation presents as a soft, smooth, nontender mass that is compressible and can be transilluminated (Fig. 198-6). Typically, lymphatic malformations fluctuate in size as a result of infection or hemorrhage. They mostly impact the cosmetic appearance of the child. Depending on the size and location of the mass, there may be respiratory compromise and difficulty in feeding.

Radiographic evaluation with MRI or CT is invaluable for diagnosis and determination of the extent of the lesion. Radiography shows fluid-filled spaces with surrounding connective tissue. Because these malformations lack a capsule and extend along the lymphatic channels, MRI or CT is essential in defining normal anatomic structures that should be preserved when surgical excision is performed.

The goals of surgery are to improve cosmetic appearance and to counter impaired breathing or eating. Because of the infiltrative nature of these malformations, complete surgical excision is often difficult; debulking of the mass often accomplishes these goals.

Some experts recommend staging of surgical excision in extensive cases.[7] Management with radiotherapy has not been effective.[8] Macrocystic lesions can be treated with sclerotherapy using alcohol. An experimental lyophilized streptococcal compound, OK-432, has been used successfully to sclerose macrocystic lesions.[9]

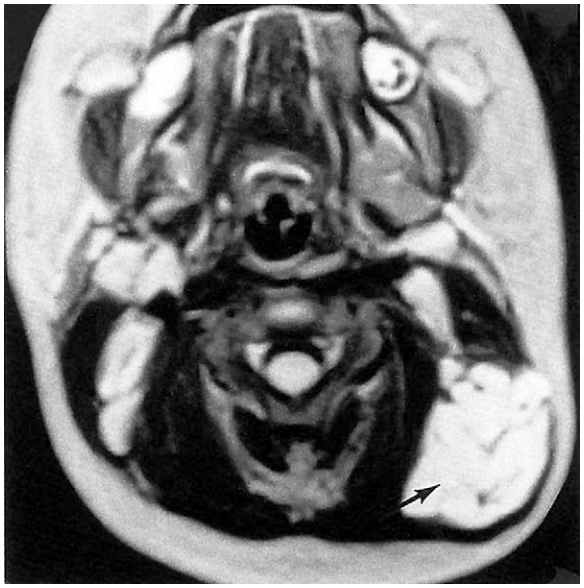

Figure 198-7. Magnetic resonance imaging with contrast shows an enhancing vascular lesion in the posterior neck consistent with a hemangioma *(arrow)*.

Hemangiomas

Hemangiomas are proliferative endothelial lesions rather than true neoplasms. Hemangiomas present at birth, grow rapidly during the first year of life, and begin to slowly involute at 18 to 24 months of age. Hemangiomas occur in up to 10% of children with a female-to-male ratio of 2:1.[10]

Hemangiomas are seen as red or bluish soft masses that frequently have a skin component. Typically, these masses are compressible and increase with straining or crying. With large hemangiomas, a bruit may be heard over the lesion. CT or MRI with contrast often confirms the diagnosis of a vascular lesion (Fig. 198-7).

Because hemangiomas typically involute after several years, the usual management is observation, unless there is functional impairment, bleeding, skin necrosis, or a coagulopathy caused by thrombocytopenia. Use of systemic corticosteroids may be helpful in the management of complications such as skin ulceration, dysphagia, dyspnea, thrombocytopenia, or cardiac failure.[11-14] Surgical excision or laser therapy may be helpful in cases of incomplete involution or when mild functional or cosmetic abnormalities remain. Management with radiotherapy may lead to malignant transformation, and the use of sclerosing agents and cryotherapy has produced poor results.[8,15]

Teratomas

Teratomas in the head and neck are rare, comprising only 3.5% of all teratomas in one series.[16] Although there is a female-to-male preponderance of 6:1 in other body regions, the female-to-male ratio is equal in the head and neck.[17] Teratomas arise from pluripotential cells and consist of tissues foreign to the site from which they arise. A history of maternal polyhydramnios has been noted in up to 18% of neonates who have a cervical teratoma (Fig. 198-8).

Most teratomas present as firm neck masses. With large teratomas, there may be symptoms of respiratory compromise caused by tracheal compression. Intrinsic calcifications may be seen on CT or MRI, a finding that may assist diagnosis. Management is by surgical excision; failure of complete excision may result in recurrence.

Dermoid Cysts

Similar to teratomas, to which they are pathologically related, dermoid cysts arise from epithelium that has been entrapped in tissue during embryogenesis or by traumatic implantation. Dermoid cysts consist of epithelium-lined cavities filled with skin appendages (e.g., hair, hair follicles, sebaceous glands). They are found at other sites in the head and neck including the orbit, nose, nasopharynx, and oral cavity.

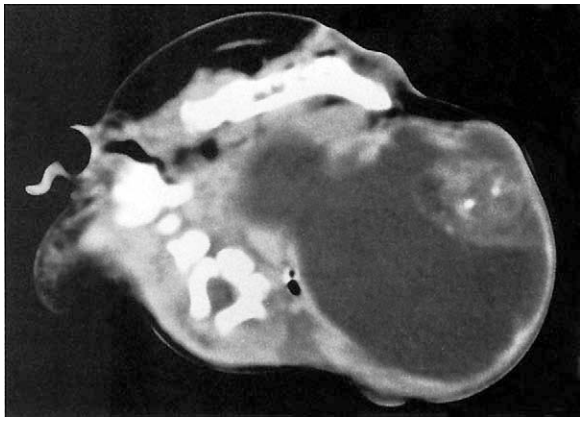

Figure 198-8. Computed tomography shows a large teratoma cyst in a newborn that severely compromised the respiratory tract and required a tracheostomy.

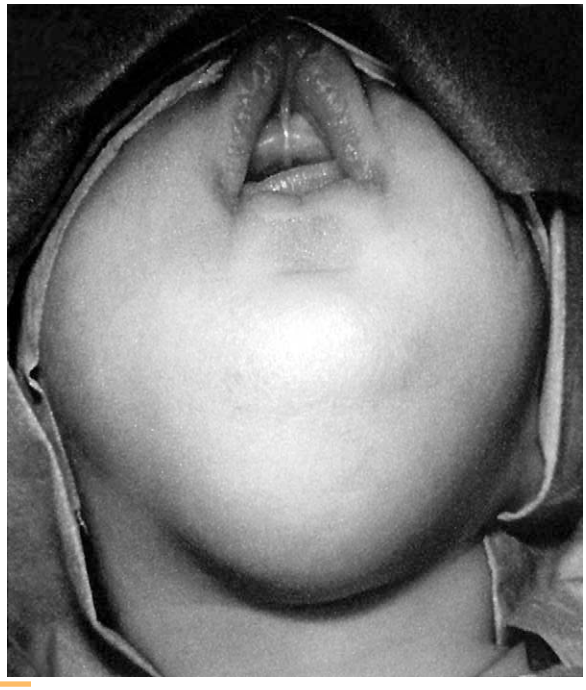

Figure 198-9. A large dermoid cyst presents in the midline of the submental region.

Typically, dermoid cysts are seen in the midline of the neck, usually in the submental region (Figs. 198-9 and 198-10). They are attached to and move with the overlying skin and are painless unless infected. Management is by complete surgical excision.

Laryngoceles

A laryngocele is an abnormal dilation or herniation of the saccule of the larynx. If this dilation lies within the limits of the thyroid cartilage, the laryngocele is internal. If it extends beyond the thyroid cartilage in a cephalad direction to protrude through the thyrohyoid membrane, the laryngocele is external. Some laryngoceles present with internal and external components. Laryngoceles are rare in infants and children but may present congenitally in newborns. Clinical differentiation of air-filled laryngoceles from fluid-filled saccular cysts may be impossible.[18]

Hoarseness, cough, dyspnea, and dysphagia suggest a laryngocele. CT may be helpful in diagnosis, especially in delineating the extent of the lesion and differentiating the laryngocele's air-filled space from the

Figure 198-10. Magnetic resonance imaging (sagittal view) shows a large dermoid cyst in the submental region just deep to the tongue *(arrow)*.

fluid of a saccular cyst. Surgical excision through an external approach is the management of choice.

Thymic Cysts

The thymus develops from the third pharyngeal pouch and descends into the chest. An implant of thymic tissue along this descent tract anywhere in the neck may result in a thymic cyst. Thymic cysts may be more common than suggested by several reports in the literature.[19] Almost all are unilateral (most commonly on the left side of the neck), and 90% are cystic.[20]

Typically, a thymic cyst presents as an asymptomatic mass, but it may be painful if infected or if there is a rapid increase in its size. CT or MRI may help differentiate a thymic cyst comprising a single cystic lesion from a cystic hygroma that has multiple large cysts within the mass. The preferred management is surgical excision. Diagnosis is confirmed by histologic identification of Hassall's corpuscles.

Vascular Malformations

Vascular malformations can be divided into two groups depending on blood flow. Slow-flow lesions include capillary malformations and venous malformations, whereas arterial and arteriovenous malformations are typically fast-flow lesions. Vascular malformations represent congenital structural anomalies, grow at the same rate as the child, and do not involute.

Venous anomalies of the external jugular vein may occasionally present as a neck mass.[21] Typically, the external jugular vein empties into the subclavian vein, but it may empty into the internal jugular vein outside the carotid sheath, forming a venous plexus. Jugular malformations present as soft, compressible masses along the anterior border of the sternocleidomastoid muscle. Management is by ligation or excision of the anomaly.

Sternocleidomastoid Tumors of Infancy

Neonates with sternocleidomastoid tumors present with neck masses that are usually not apparent at birth but appear at 1 to 8 weeks of age. Pathologically, the mass is characterized by dense fibrous tissue and the absence of normal striated muscle (Fig. 198-11). As the mass resolves, the remaining muscle continues to degenerate into fibrous tissue. The etiology of this disorder, also known as *congenital torticollis,* is unclear; however, birth trauma, ischemia of the muscle, and intrauterine positioning have been implicated.

Most patients are firstborn[22]; siblings are rarely affected.[1] Congenital torticollis presents as a firm, painless, discrete, fusiform mass within the sternocleidomastoid muscle that slowly increases in size for 2 to 3 months and then slowly regresses for 4 to 8 months (Fig. 198-12). Because the mass disappears in more than 80% of cases,[23] conservative management with physiotherapy (passive and active motion) prevents the development of restrictive torticollis. In resistant cases, surgical section of the sternocleidomastoid muscle may be required.

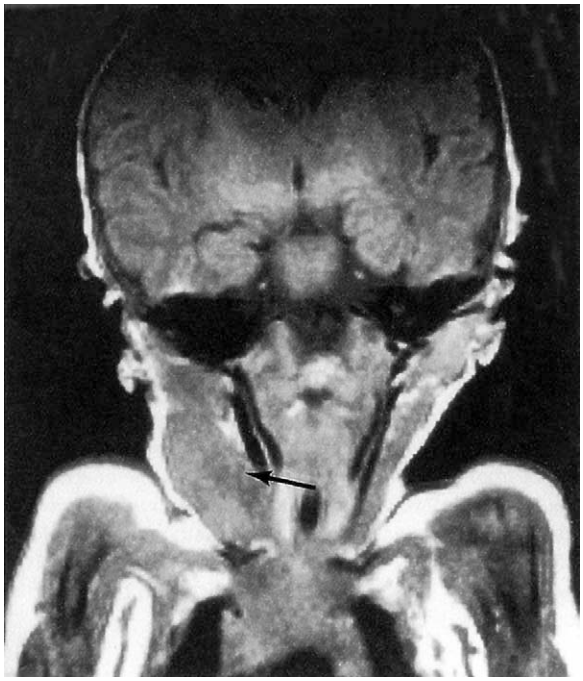

Figure 198-11. Magnetic resonance imaging of an infant with congenital torticollis shows enlargement of the sternocleidomastoid muscle *(arrow)*.

Figure 198-12. A firm mass in the midportion of the sternocleidomastoid muscle is seen in an infant with congenital torticollis.

Acquired Masses

Viral Lymphadenopathy

Reactive lymph nodes result from viral upper respiratory tract infections such as adenovirus, rhinovirus, or enterovirus (coxsackievirus A and B). EBV often presents with massive lymphadenopathy in addition

to enlargement of other lymphoid tissue (e.g., tonsils, spleen). On pathologic examination, there is a proliferation of normal cells; however, in contrast to neoplastic disease, the nodal architecture is intact.

Reactive lymphadenopathy is frequently bilateral and is associated with symptoms of the underlying respiratory infection. Management is observation, although not infrequently these nodes are biopsied because their consistency mimics lymphoma and their regression in size is often slow.

Unlike most cases of viral lymphadenopathy, human immunodeficiency virus (HIV) infection may result in acquired immunodeficiency syndrome (AIDS) whose associated findings, aside from generalized lymphadenopathy, include hepatosplenomegaly; weight loss; susceptibility to viral, bacterial, and fungal infections; and fevers. Pediatric AIDS should be suspected in cases in which multiple neck nodes are involved with bacterial infection and in cases that fail to respond to adequate antibiotic therapy.

Cervical lymphadenopathy is also a manifestation of posttransplantation lymphoproliferative disease (PTLD). PTLD is associated with an Epstein-Barr infection in patients who have undergone either solid organ or bone marrow transplantation. Histologic examination of a biopsied node and Epstein-Barr titers are essential in the diagnosis of this disorder.[7,24]

Bacterial Lymphadenopathy

Suppurative Lymphadenopathy

Staphylococcus aureus and group A β-*Streptococcus* are the most common causative organisms of suppuration in the neck, although other bacteria such as *Haemophilus* and *Moraxella* species have been implicated. Brodsky and colleagues[25] found a 19% incidence for anaerobic bacteria versus 67% for aerobic bacteria. Brook[26] reported a similar anaerobic incidence and β-lactamase-positive organisms in 34%. In neonates the offending organisms may be *Staphylococcus* or *Streptococcus,* but *Pseudomonas* and other gram-negative bacteria have also been reported.[27,28] Several studies have documented a rising incidence of methicillin-resistant *S. aureus* (MRSA) as the pathogen in community-acquired pediatric cervical neck infections.

No major differences between the *Staphylococcus* and *Streptococcus* groups are evident when demographic factors and occurrence of symptoms are compared. Frequently, the neck mass develops in the submandibular region, but it may occur in the anterior and posterior cervical triangles (Fig. 198-13).[29] Associated symptoms include a history of upper respiratory infection, sore throat, earache, and skin lesions.[29] Initial management is with antibiotic therapy, either orally or intravenously, depending on the severity of the infection. Failure to respond to medication may indicate the need for fine-needle aspiration or incision and drainage.

Cat-Scratch Disease

Most cases of cat-scratch disease occur in patients younger than 20 years,[30] and males are affected more frequently than females.[31] More than 90% of patients have a history of feline contact, and there is a fall and winter prevalence. Although the symptom complex of cat-scratch disease has been recognized for almost 50 years, only recently has the bacterium *Bartonella henselae* been implicated as the etiologic agent.[32] Serologic testing by indirect fluorescent antibodies for *Bartonella* DNA has a high sensitivity and specificity. Typically, affected children are seen with lymphadenopathy associated with mild fever and other symptoms of malaise. Antibiotic therapy with azithromycin, an aminoglycoside, or ciprofloxacin is usually curative.[32] Rarely is the infection severe enough to require surgery.

Toxoplasmosis

Infection with *Toxoplasma gondii* is usually contracted through the consumption of poorly cooked meat or ingestion of oocytes excreted in cat feces. Symptoms include fever, malaise, sore throat, and myalgias. Cervical adenitis occurs in greater than 90% of cases.[33] Complications of toxoplasmosis include myocarditis and pneumonitis. The diagnosis is confirmed by serologic testing, and management is with pyrimethamine or sulfonamides.

Figure 198-13. Computed tomography with contrast shows a neck abscess in the submandibular triangle *(arrow).* Abscess formation is characterized by hypolucency and rim enhancement.

Mycobacterial Infection

Most atypical mycobacterial infections are caused by a variety of mycobacteria including *Mycobacterium avium-intracellulare, Mycobacterium scrofulaceum, Mycobacterium kansasii, Mycobacterium fortuitum,* and *Mycobacterium haemophilum.* In the past few years, the reemergence *of Mycobacterium tuberculosis* has been noted; *M. tuberculosis* as a cause of cervical adenopathy is associated with pulmonary tuberculosis in endemic areas of the United States. In a series on the cause of mycobacterial neck infections, Hawkins and colleagues[35] showed a 59% incidence for atypical mycobacteria compared with 29% for *M. tuberculosis.*

Skin tests for *M. tuberculosis* and atypical mycobacteria are available[34] and were positive in 95% of cases in the series by Hawkins and colleagues.[35] Mycobacterial infection is definitively diagnosed by culture, which frequently takes weeks.

The most common site of mycobacterial infection in the neck is the anterior superior cervical region, followed by the posterior cervical, middle cervical, supraclavicular, and submental regions. Atypical mycobacterial infection is not infrequently found in the preauricular region (Fig. 198-14). It tends to occur unilaterally, whereas *M. tuberculosis* is more diffuse and frequently bilateral.[35] A painless, firm, enlarging mass in the face of antibiotic therapy suggests the diagnosis. The overlying skin is frequently discolored with atypical mycobacterial infection. In patients with *M. tuberculosis* infection, weight loss, fever, and anorexia may also be present.

The current management of *M. tuberculosis* infection is with antituberculous chemotherapy, usually including two drugs, although lymph nodes infected with atypical mycobacteria are best managed by surgical excision or incision and curettage. Hawkins and colleagues[35] showed resolution of neck masses in 4 of 18 cases of atypical mycobacterial infection with chemotherapy alone.

Fungal Infections

Fungal infections of the neck typically present in immunocompromised patients with symptoms and signs that suggest viral or bacterial infection. The usual pathogens include *Candida, Histoplasma,* and *Aspergillus.* The diagnosis is made by serology or fungal smear and culture.

Figure 198-14. Atypical mycobacterial infection frequently involves the submandibular triangle and preauricular regions.

Management of fungal lymphadenopathy requires intravenous amphotericin B.

Sialadenitis

The salivary glands are susceptible to viral and bacterial infection and, at times, may resemble infection of surrounding lymph nodes. Although rare since the development of a vaccine, mumps is a paramyxoviral infection that may cause orchitis, meningitis, or sensorineural hearing loss. One or both parotid or submandibular glands may be involved. Management includes supportive measures such as analgesics and hydration.

In addition to viral infection, dehydration and generalized disability of patients often predispose to bacterial infection of the salivary glands. The causative organisms include *S. aureus, Streptococcus* species, and *Haemophilus influenzae.*

Children with sialadenitis have a rapid onset of pain and swelling of the affected glands. Fever, chills, and malaise may also occur. Examination of the oral cavity may reveal purulent discharge from the ducts of the involved glands (Stensen's or Wharton's). Management of bacterial sialadenitis is hydration and oral or intravenous broad-spectrum antibiotic therapy.

Noninfectious Inflammatory Disorders

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease is an acute multisystem vasculitis of unknown etiology that tends to affect children younger than 5 years of age.[36] To confirm this diagnosis, the patient should have fever persisting for 5 days and four of the following features: (1) acute, nonpurulent cervical lymphadenopathy that is usually unilateral; (2) erythema, edema, and desquamation of the hands and feet; (3) polymorphous exanthem; (4) bilateral painless conjunctival infection; and (5) erythema and infection of the lips and oral cavity.

Associated findings in the acute stage include thrombocytosis and cardiac signs of pericardial effusion.[37] In the subacute stage, coronary artery aneurysms may develop in 15% to 20% of cases.[36] The goal of management is to reduce the inflammatory response with aspirin and γ-globulin therapy.

Sinus Histiocytosis (Rosai-Dorfman Disease)

Children with sinus histiocytosis have massive nontender cervical lymphadenopathy that is similar to infectious mononucleosis or lymphoma. The disease is thought to represent an abnormal histiocytic response to some precipitating cause, possibly either a herpesvirus or EBV.[38] Biopsy shows dilated sinuses, many plasma cells, and marked proliferation of histiocytes. In addition to massive adenopathy, fever and skin nodules may be present. Management of this disorder is expectant.

Drug-Induced Lymphadenopathy

Although phenytoin is the most well-known cause of drug-induced lymphadenopathy, pyrimethamine, allopurinol, and phenylbutazone have also been implicated.[39] Typically, the adenopathy resolves when drug therapy is discontinued; however, long-term use of phenytoin has been reported to progress to a premalignant pseudolymphomatous state.

Sarcoidosis

The etiology of sarcoidosis is unknown, but clusters of cases tend to suggest an infectious or toxic origin. It is found most commonly in the second decade of life, and men and women are affected equally. Patients typically have lymph node enlargement, fatigue, and weight loss. Depending on the sites of involvement, there may also be cough, dyspnea, hoarseness, bone and joint pain, visual symptoms, headaches, fever, and skin rash. Abnormalities on chest radiography help suggest the diagnosis, which is confirmed by finding noncaseating granulomas on biopsy of involved tissue. Management is expectant, although corticosteroids may be helpful in acute settings.

Benign Neoplasms

Lipomas

Lipomas are benign encapsulated fatty tumors found in subcutaneous tissue. In general, they rarely occur in the head and neck. The usual management is surgical excision.

Thyroid Adenomas

A thyroid adenoma presents as an isolated mass that is palpable within the thyroid gland. On ultrasound, an adenoma appears as a solid mass in contrast to a thyroid cyst. On thyroid scanning, an adenoma appears as a cold nodule; however, some adenomas take up radionucleotide and show function, although not as much as that seen with typical hyperfunctioning nodules. Thyroid adenomas usually require excision to differentiate them from thyroid carcinomas.

Neurofibromas

Neurofibromas are circumscribed tumors that arise from small cutaneous nerves and are composed of Schwann cells, nerve fibers, and fibroblasts. They may be solitary or more rarely occur as multiple neurofibromas (e.g., in von Recklinghausen's disease). Management is excision, taking care not to injure nearby anatomic structures.

Pleomorphic Adenomas

Pleomorphic adenomas are salivary gland tumors that typically arise in the lateral portion of the parotid gland. They present as slow-growing painless masses that show no evidence of nerve or skin involvement. A superficial parotidectomy is necessary for surgical excision.

Malignant Neoplasms

Lymphomas

Lymphomas are the most common neck malignancy in large pediatric series.[1,40] They may be divided into two histologic categories, Hodgkin's and non-Hodgkin's, which have different clinical courses and prognoses.

Rye classified Hodgkin's disease into four histologic types: nodular sclerosing, mixed cellularity, lymphocyte predominant, and lymphocyte depleted. Males of any age are more commonly afflicted with Hodgkin's disease than females, although the incidence is nearly equal during the teenage years.[41] Hodgkin's disease often presents as an asymptomatic cervical or supraclavicular mass (Fig. 198-15). Fever is commonly associated with cough, night sweats, and weight loss. After confirmation of cell type by biopsy, management consists of chemotherapy or radiotherapy, depending on the histologic findings and staging.

Non-Hodgkin's lymphoma is more likely to be disseminated and extranodal. Histologic types include lymphoblastic, large cell, and undifferentiated. The liver, lung, and bone marrow are the most common sites of extralymphatic involvement. In the neck, non-Hodgkin's lymphoma is less common than Hodgkin's disease.[42] Weight

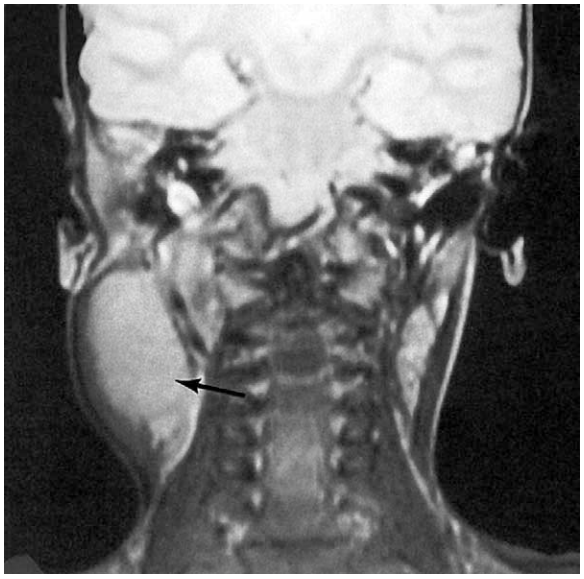

Figure 198-15. Magnetic resonance imaging of the neck shows Hodgkin's disease presenting in the posterior cervical region *(arrow)*.

loss, night sweats, and fever are common, especially when disease is more disseminated. Chemotherapy is the mainstay of management of non-Hodgkin's lymphoma.

Rhabdomyosarcomas

Soft tissue sarcomas comprise a small percentage of all childhood malignancies. Rhabdomyosarcoma is the most common soft tissue sarcoma; because it occurs most commonly in the head and neck, it comprises a significant percentage of malignant neck masses in series of pediatric patients.[43] The peak incidence of rhabdomyosarcoma occurs at 2 to 5 years, with another peak between 15 and 19 years of age.[44] White children are affected more often than children of other races, and there is a slight male predominance.[44] Embryonal rhabdomyosarcoma is the most common cell type, followed by alveolar and pleomorphic.[45]

Predominant sites of rhabdomyosarcoma in the head and neck include the orbit, nasopharynx, paranasal sinuses, ears, and oral cavity. Primary involvement of the neck occurred in 89% of cases in one series.[46] Metastatic disease from one area of the head to the neck is rare.[47]

Management of rhabdomyosarcoma includes a combination of surgery, radiotherapy, and chemotherapy. The role of surgery, biopsy, debulking, or radical excision depends on the site, extent, and presence of recurrence. Radiotherapy to the primary site is given at 5000 to 6000 cGy in children older than 3 years of age and lesser doses in younger children. Two thirds of patients experience long-term survival or cure.[43,9]

Thyroid Carcinoma

Thyroid carcinoma is uncommon in the pediatric age group but has been associated with exposure to low-dose ionizing radiation.[48] Female children are more commonly affected but less so than female adults. The usual histology is papillary or mixed papillary-follicular. Involved patients have a solitary mass in the anterior neck. More worrisome signs include rapid growth of the mass, hoarseness, dysphagia, and fixation of the mass to the surrounding structures. Metastases, when present, are found in regional lymph nodes and the lungs or bones. Ultrasound or thyroid scanning is helpful in diagnosis, although frozen section at the time of surgical excision is definitive. Because almost all thyroid carcinoma in children is papillary, management should be subtotal or total thyroidectomy with neck dissection if there is nodal involvement. Thyroid suppression is often used to prevent recurrence, and radioactive iodine helps eliminate unresectable tumor.

Salivary Gland Malignancies

Mucoepidermoid and acinic cell carcinomas of the salivary glands account for approximately 60% of malignant epithelial neoplasms in children.[49] With mucoepidermoid carcinoma, local invasiveness, regional metastasis, and prognosis depend on histologic differentiation; the behavior of acinic cell carcinoma does not correlate with histology. Mucoepidermoid and acinic cell carcinomas present as solitary firm masses that grow painlessly, usually in the parotid gland. Both tumors tend to be low grade and are seldom fatal.[49] Depending on which gland is involved, initial management is by superficial parotidectomy or submandibular gland excision. The use of adjuvant therapy including neck dissection or radiotherapy depends on cell type and tumor growth characteristics.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma may present with a mass in the neck associated with a nasopharyngeal mass, unilateral otitis media, rhinorrhea, and nasal obstruction. In advanced cases, there may be one or more cranial nerve palsies. There is an increased incidence of nasopharyngeal carcinoma in black and Asian teenagers.[50,51] Titers of EBV types 2 and 3 have been elevated in patients with nasopharyngeal carcinoma.[6] Although the diagnosis is confirmed by biopsy, CT and MRI may help determine the extent of tumor involvement. Bone or liver metastasis may be identified with a bone scan or CT of the abdomen. Management depends on clinical staging and includes radiotherapy with or without chemotherapy.

Neuroblastomas

Neuroblastomas are malignant neoplasms that originate from primitive neuroblasts and neural crest cells. Only 2% to 4% of neuroblastomas originate in the neck.[52] In the neck, these masses may be associated with an ipsilateral Horner's syndrome.[53] Because systemic involvement is common, evaluation of the patient should include MRI and CT of the neck, chest, and abdomen, looking for metastatic spread. Elevated urinary VMA found on 24-hour collection strongly suggests neuroblastoma. Management depends on the extent of involvement and may include surgical excision, radiotherapy, and chemotherapy.

Summary

A neck mass may provide a diagnostic challenge to the clinician and a source of anxiety to the parents. Systematic evaluation, paying particular attention to important details in the history and physical examination, can narrow the differential diagnosis and allow selection of appropriate radiologic and laboratory studies when indicated. In children, congenital and inflammatory masses are most common, but malignancy should be considered, especially if the mass continues to grow after appropriate therapy.

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CHAPTER ONE HUNDRED AND NINETY-NINE

Vascular Anomalies of the Head and Neck

Jonathan A. Perkins

Eunice Y. Chen

Key Points

- The most common types of head and neck vascular tumors are hemangioma of infancy (HOI), whereas the most common head and neck vascular malformations are lymphatic malformations.
- HOIs are absent at birth, occur in infancy, proliferate up to the age of 9 to 10 months, and variably involute or shrink over years.
- HOIs and lymphatic malformations each have unique endothelium that distinguishes them from other types of vascular tumors and malformations.
- Periocular hemangiomas of infancy can cause deprivation amblyopia and astigmatic amblyopia.
- Superficial HOIs and other red, cutaneous vascular lesions can be treated with a pulsed dye laser.
- Surgical excision of focal hemangiomas can be done to both prevent complications and improve treatment outcomes.
- Lymphatic malformations are classified by stage and radiographic appearance as macrocystic or microcystic or a combination of both.
- Lymphatic malformations occur in utero and manifest at birth or in association with an infection or trauma later in life. Most malformations manifesting at birth or later in life are associated with a normal karyotype.
- Macrocystic lymphatic malformations can resolve spontaneously or be treated with either surgery or sclerotherapy. Microcystic suprahyoid lymphatic malformations are difficult to treat with any modality and frequently cause macroglossia.
- Venous malformations are associated with tyrosine-kinase type 2 receptor dysfunction, which causes abnormal venous structure. Histologically, venous malformations are a combination of both blood vasculature as well as lymphatic vasculature.
- Kasabach-Merritt phenomenon is most commonly associated with the vascular tumors kaposiform hemangioendothelioma and tufted angioma.
- Arteriovenous malformations are high-flow venous malformations that occur in any area of the head and neck and frequently require a combination of embolization and surgical therapy for treatment. Medical therapy is ineffective.

Vascular anomalies encompass vascular tumors and malformations and involve the head and neck 70% to 80% of the time. Clinical and radiographic findings, and occasionally histologic evidence, are used to distinguish among various vascular anomaly subtypes. A vascular anomaly classification system has been developed based on these factors[1,2] (Table 199-1). Hemangiomas of infancy (HOIs) were the first vascular lesions to be distinguished from other vascular anomalies, based on their natural history.[3] HOIs, unlike other vascular anomalies, are absent at birth, appear during infancy, grow rapidly within the first year of life, and then undergo a variable period of involution. Numerous recent discoveries have further solidified the distinction between vascular tumors and vascular malformations.[4-6]

Vascular tumors usually are benign, have neoplastic characteristics, and represent disordered angiogenesis.[4] Radiographically these tumors can be characterized by describing lesion size, blood flow, and location.[7,8] Certain clinical conditions, such as Kasabach-Merritt phenomenon and PHACES syndrome (*p*osterior fossa abnormalities, *h*emangiomas, *a*rterial anomalies, *c*ardiac anomalies, *e*ye abnormalities, *s*ternal or abdominal clefting), are associated with vascular tumors and not vascular malformations.[9-11] Vascular malformations often contain all vessel types—arterial, venous, and lymphatic—and seem to represent disordered vasculogenesis. Most vascular malformations are present at birth and demonstrate growth parallel to the child's growth. These lesions have a distinct radiographic appearance in their location, size, and blood flow—in particular, that through the lesion. Additionally, certain types of vascular malformations are characterized on the basis of the radiologic architecture of the lesion. This characterization has been most useful in identifying lymphatic malformations. These malformations also are associated with either local tissue or bony overgrowth (Fig. 199-1). Since the original distinction of hemangiomas from other types of vascular tumors and malformations, molecular characteristics as well as radiographic features of individual vascular anomaly subtypes have allowed further distinction between various types of vascular anomalies. This chapter outlines these distinctions and

explains how these distinctions have led to treatment improvements, potentially leading to better clinical outcomes.

A genetic and molecular basis for some vascular anomalies is being investigated.[12-14] The most apparent link between genetic defect and disease is seen in inherited venous malformations, in which a mutation in the protein receptor for tyrosine kinase (Tie2), which normally allows endothelial–smooth muscle communication essential for venous morphogenesis.[15] Defects in the smooth muscle layer of vessels with venous malformations result from this mutation. Similarly, vascular malformations in hereditary hemorrhagic telangiectasia types 1 to 3 are associated with gene mutations that adversely affect endothelial function.[16] Familial HOIs are linked to defects in the fifth chromosome.[17] Sporadic HOI endothelium is clonal.[18,19] Glomangiomas have defective "glomulin" function, distinguishing them from other venous malformations.[20] Ateriovenous malformations occurring with atypical capillary malformations have been linked to a gene *RASA1*.[21] Hypertrophy of tissues near vascular malformations has been linked in certain syndromes to a mutation in the *PTEN* tumor suppressor gene.[22,23] This information creates a basis for understanding the mechanisms behind the pathogenesis of vascular anomalies.

Table 199-1

Vascular Anomaly Classification*

Vascular Malformation	Vascular Tumor
Single-Vessel Type	Hemangioma
Capillary	Hemangioma of infancy
Venous	Congenital hemangioma
Lymphatic	Rapidly involuting congenital hemangioma (RICH)
Combined/Complex	Noninvoluting congenital hemangioma (NICH)
Malformations	Lobular hemangioma (pyogenic granuloma)
Arteriovenous	Vascular Neoplasm
Lymphaticovenous	Kaposiform hemangioendothelioma
Capillary-venous	Angiosarcoma
Capillary-lymphaticovenous	Hemangiopericytoma
Capillary-arteriovenous	Miscellaneous
	Tufted angioma

*Binary classification system adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996.

Vascular Tumors

Hemangiomas of Infancy

HOIs are absent at birth and appear in infancy; they proliferate for 6 to 9 months and then involute partially or completely over several years[24-26] (Fig. 199-2). Vascular lesions not following this pattern should be considered for alternative diagnoses.[6] In addition to clinical diagnosis, HOI diagnosis can be further confirmed through molecular staining and imaging.[27,28] HOI endothelium has several unique surface markers detected by immunohistochemistry. The first marker for HOI described was glucose transporter-1 (GLUT-1); others have since been described. GLUT-1 detection separates HOIs from other vascular anomalies and congenital hemangioma.[28] Improvements in image acquisition with both computed tomography (CT) scanning and magnetic resonance imaging (MRI) allow differentiation between HOIs and other vascular anomalies[8,29,30] (Fig. 199-3).

Clinical Presentation

At birth, HOI can be completely absent or may be present as a slight redness or pallor in the area in which a HOI subsequently appears.[24] In the first several months of life, HOIs grow rapidly and can involve any area of the head and neck. Often multiple hemangiomas are present in areas outside the head and neck. Two thirds of HOIs occur in girls. HOIs are more prevalent in premature infants and infants born to mothers of advanced maternal age, with a history of chorionic villus sampling. Terminology to describe types of HOIs and their appearances and locations[31] are illustrated in Figure 199-4. Segmental HOIs usually are superficial, variably involve cutaneous dermatomes, and have more associated morbidity than focal HOIs. These lesions are thought to occur in embryologic prominences that are related to neural crest cells, which influence vascular patterning.[32] In the head and neck, focal HOIs occur in identifiable patterns that are thought to be associated with lines of embryonic tissue fusion.[31,32] Building on the concept of embryonic fusion planes, several groups of investigators have observed that midface HOIs do not predictably involute.

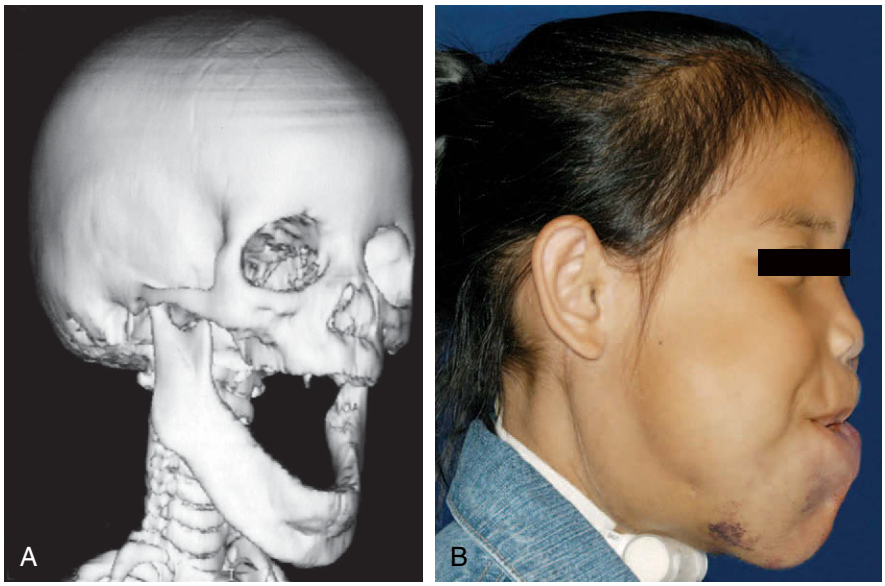

Figure 199-1. Mandibular overgrowth associated with lymphatic malformation. **A,** Three-dimensional computed tomography reconstruction in infancy. **B,** Clinical photograph of same patient at a later age.

Figure 199-2. Segmental hemangioma appearance. **A,** Initial appearance in infancy. **B,** Late proliferative stage. **C,** Beginning involutional phase.

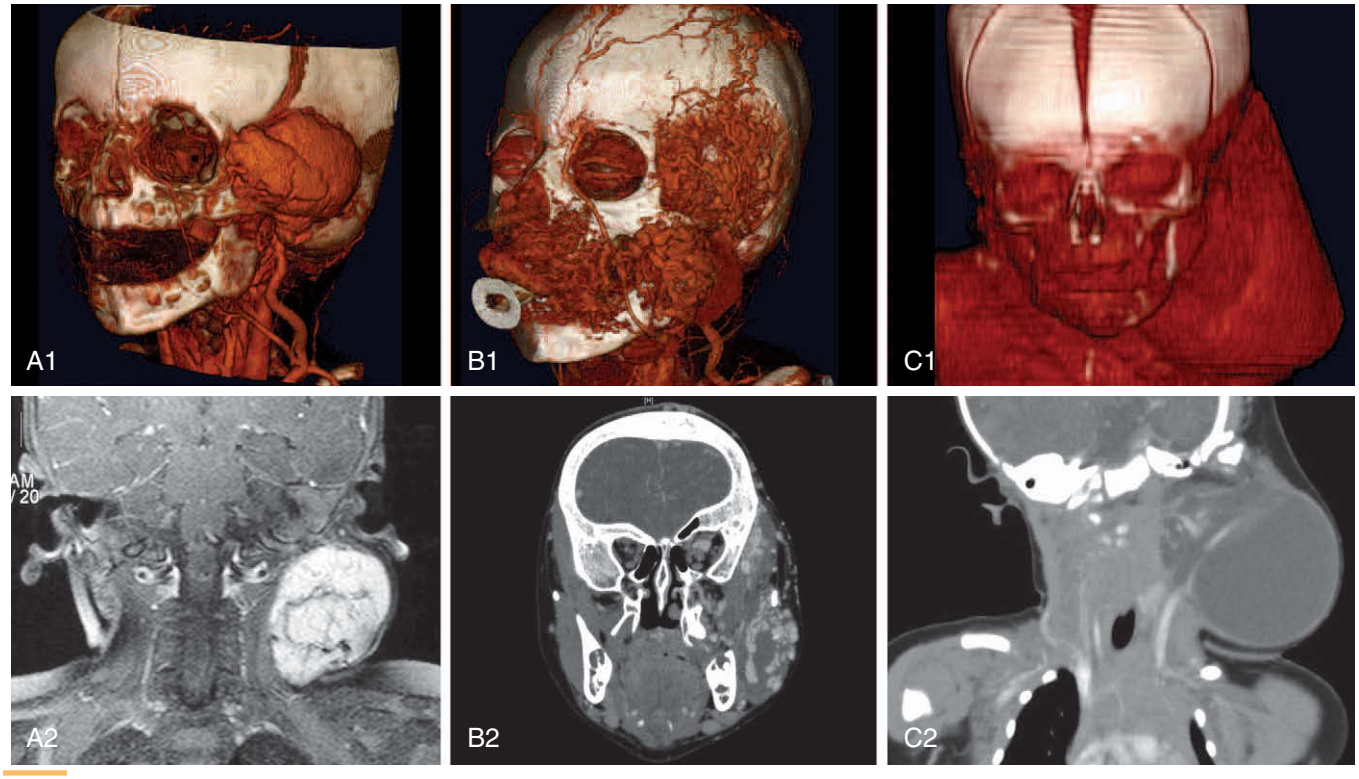

Figure 199-3. Vascular anomaly imaging. **A,** Three-dimensional CT angiography (A1) and coronal CT scan (A2) of deep hemangioma of infancy. **B,** Three-dimensional CT angiography and coronal CT scan of venous malformation. **C,** Three-dimensional CT angiography and coronal CT scan of lymphatic malformation.

PHACES Syndrome

An association between some HOIs and ventral clefting, congenital cardiac malformations, intracranial malformations, and ocular abnormalities has been described; the specific manifestations collectively make up the PHACES syndrome[11] (Fig. 199-5). Central nervous system symptoms include developmental delays, seizures, and congenital stroke. Patients suspected to have PHACES syndrome should undergo head imaging, ophthalmologic examination, and cardiac evaluation. Some clinicians recommend antiplatelet therapy for patients with abnormal cerebral vasculature, to prevent congenital stroke.[33,34] Further analysis of HOI biology is necessary to elucidate these associations.

Other Types of Vascular Tumors

Congenital Hemangioma

High-flow vascular tumors manifesting at birth that are histologically identical to HOIs except for positive GLUT-1 staining are called *congenital hemangiomas*.[73,74] There are two types of congenital hemangiomas—those that rapidly resolve over the span of a year and those that persist. Accordingly, they are named *rapidly involuting congenital hemangioma* (RICH) and *non-involuting congenital hemangioma* (NICH), respectively. These lesions often are difficult to distinguish from HOIs unless a careful history is taken and histologic analysis is performed. Often the diagnosis remains uncertain until the clinical behavior of a given lesion is observed (Fig. 199-6). Medical therapy is ineffective for congenital hemangiomas. Treatment for RICH usually is limited to observation, whereas NICH may require laser or surgical therapy.

Kaposiform Hemangioendothelioma and Tufted Angioma

Most nonhemangioma vascular tumors are benign. These tumors occur rarely in the head and neck. The two most common tumors are kaposiform hemangioendothelioma (KHE) and tufted angioma (TA). KHEs occur anywhere in the head and neck and have a significant lymphatic component in addition to blood vascular endothelium.[75] Clinically,

Figure 199-4. Hemangioma of infancy, types. **A,** Superficial focal hemangioma; forehead. **B,** Mixed segmental hemangioma; midface, lip, forehead. **C,** Deep focal hemangioma; malar region. **D,** Mixed focal hemangioma; malar lower eyelid. **E,** Mixed segmental hemangioma; cheek, malar region.

Figure 199-5. Clinical appearance in PHACES syndrome. **A,** Segmental hemangioma involving the lips, nose, left upper and lower face. **B,** Segmental hemangioma involving the lips, nose, left upper and bilateral lower face. **C,** Segmental lower lip hemangioma with sternal cleft. **D,** Focal lower lip hemangioma with sternal cleft.

KHEs appear as violaceous cutaneous nodules extending into deep tissues locally (Fig. 199-7). Their radiographic appearance is one of diffuse infiltrative vascular process (see Fig. 199-7). Careful assessment through imaging and diagnostic biopsy should guide KHE therapy. TAs are more localized and may or may not involve the skin. Treatment for both KHE and TA is centered on proper diagnosis, prevention of complications, and tumor control. Diagnosis requires an incisional biopsy with possible immunohistochemical staining. Curative surgical resection is possible and advisable for some localized tumors, but for large lesions, surgery may not be curative. With extensive KHEs or TAs that are causing pain, loss of function, or significant disfigurement, antiangiogenic chemotherapy may be necessary. The natural history of these lesions in the head and neck often is unclear; therefore, treatment needs to be individualized.

Figure 199-6. Appearance of noninvoluting congenital hemangioma.

Common Complications of Vascular Tumors

Because most vascular tumors are HOIs, which proliferate rapidly, complications occur most frequently with these lesions. HOI complications occur primarily from lesion-induced functional compromise and cutaneous ulceration. Breathing can become compromised and obstructed from airway HOI. HOI can cause biphasic stridor by narrowing the infant's subglottic airway[35] (Fig. 199-8). Obstruction of the visual axis by a proliferating HOI occurs with eyelid lesions, inducing deprivation amblyopia[36] (Fig. 199-9). Deformation of the eye from lesion compression or periocular tissue distortion before the age of 6 months induces astigmatic amblyopia.[37] Proliferating HOI located in places of repetitive skin trauma such as the lips and neck skinfolds can ulcerate, resulting in scarring. The reasons for ulceration are unclear, but when present, ulcerations begin as brown crusts, become painful, bleed, and require local wound care for healing. Extensive ulcerations of the hemangioma can become infected and result in tissue loss, further complicating healing and treatment[38] (Fig. 199-10). Ulceration involving the lip often makes oral feeding challenging because of pain and hemangioma-induced lip distortion. Large, deep head and neck HOIs involving the parapharyngeal and scalp regions often are associated with high-output cardiac failure, due to the increased blood flow in these vascular lesions.[39] The psychosocial consequences of HOI for the family and patient are important to consider in treatment planning.[40]

Unusual Conditions Associated with Vascular Tumors

Kasabach-Merritt Phenomenon

Kasabach-Merritt phenomenon is the occurrence of profound thrombocytopenia in association with vascular tumors. For unknown reasons, KHE and TA, not HOI, are the vascular tumors most frequently associated with Kasabach-Merritt phenomenon.[9,10,76] This occurs in infancy and requires extensive chemotherapy to reduce the risk of bleeding associated with thrombocytopenia. The mechanisms leading to thrombocytopenia are unknown. Before the capability of histologic distinction between the endothelium of KHE, TA, and HOI, many vascular tumors were called simply "hemangiomas," and Kasabach-Merritt phenomenon was associated erroneously with HOI. Newly described vascular entities, not classified as vascular tumors, also are associated with thrombocytopenia. The spectrum of this phenomenon as it relates to vascular anomalies is still being defined.[77]

Figure 199-7. Kaposiform hemangioendothelioma, clinical and radiographic appearance. **A,** Cutaneous nodules. **B,** Deep lesion extending to the skin. **C,** Coronal computed tomography scan of lesion shown in **B.**

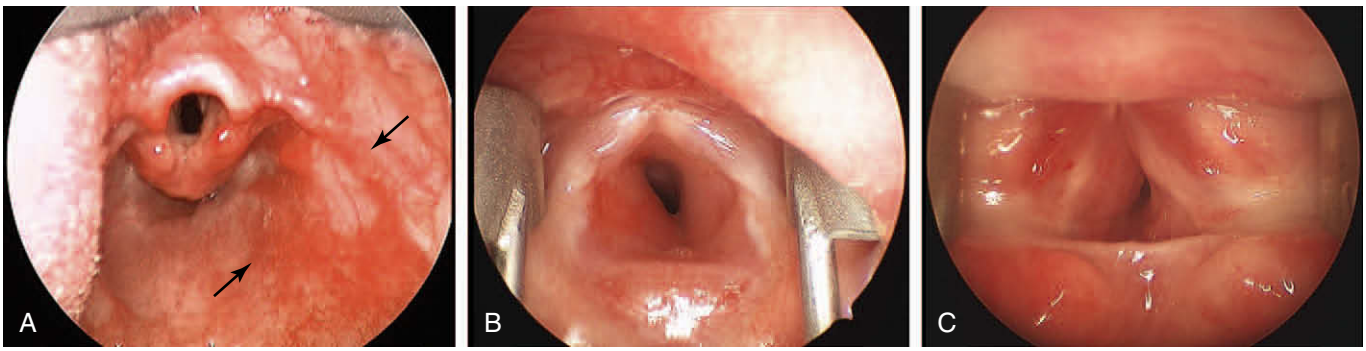

Figure 199-8. Endoscopic appearance of airway hemangioma of infancy. **A,** Diffuse hypopharyngeal mucosal involvement *(arrows)*. **B,** Unilateral posterior focal hemangioma; left subglottis (see also Fig. 199-16A and B). **C,** Circumferential, segmental hemangioma; subglottis (see also Fig. 199-16C and D).

Figure 199-9. Deep focal hemangioma of infancy, upper eyelid, impinging visual axis.

Bone Resorption

Bone resorption can occur in association with KHE, resulting in localized osteopenia. The mechanisms for bone resorption are unknown. When bone loss occurs, chemotherapy has not been shown to change outcome.

Treatment Overview

Analysis and Treatment of Facial Hemangiomas

A complete discussion of all aspects of facial hemangioma treatment is beyond the scope of this chapter.[72] Some general concepts and principles useful in management decisions follow:

1. Societal attitudes and recognition of treatment possibilities for HOIs that involve the face are changing. Lesions that formerly were allowed to "involute," followed by delayed treatment of residual skin changes, are being managed more aggressively in early childhood (Fig. 199-11).

2. HOIs in certain areas of the face are prone to complications and noninvolution. This is especially true of midface lesions. Recognition of the varied natural history of facial HOI is essential to treatment planning and family counseling.

3. HOIs distort involved tissue by creating tissue excess and sometimes inducing adjacent bone and soft tissue hypertrophy (Fig. 199-12). This hypertrophy creates surgical and reconstructive challenges that differ from usual tissue deficits associated with facial tumor resection.

4. Large facial HOIs require more intensive monitoring and treatment planning than smaller lesions. Often the treatment of these lesions requires combined modalities and occurs in multiple stages over several years (Figs. 199-13 and 199-14).

5. An understanding of the medical, laser, and surgical treatment implications and options associated with HOI type and facial location is essential in planning treatment of these lesions.

Medical Therapy

Medical therapy for proliferating HOI is directed at stopping angiogenesis and decreasing peritumoral inflammation; in contrast, medical therapy for nonproliferating HOI is ineffective.[4,41,42] Although controversial, the mainstay of medical therapy has been systemic corticosteroid administration, which is antiangiogenic and anti-inflammatory.

Figure 199-10. Hemangioma of infancy, lip. **A,** Ulcerated hemangioma during proliferation. **B,** Lip appearance after several pulsed dye laser treatments and ulcer healing.

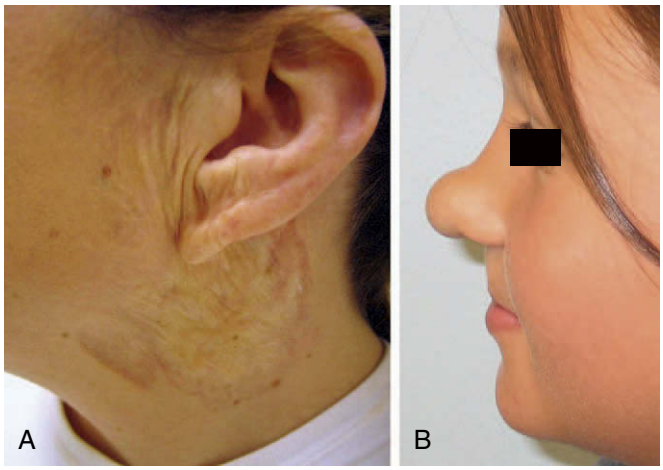

Figure 199-11. Persistent tissue changes from hemangioma of infancy. **A,** Fibrofatty skin changes from involuted mixed parotid hemangioma of infancy in adult. **B,** Enlargement of nasal tip from persistent deep focal hemangioma of infancy in adolescent.

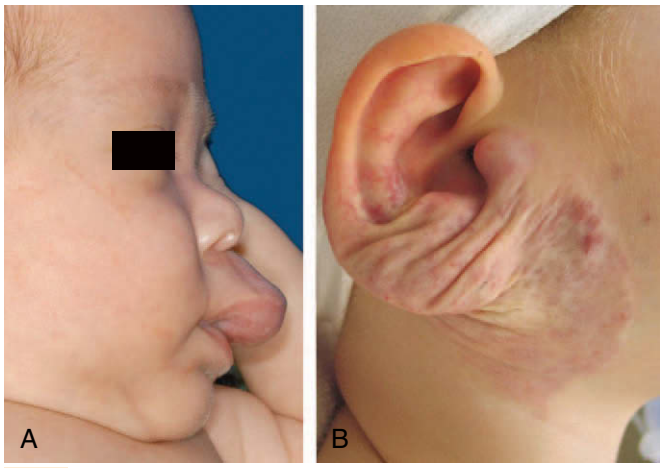

Figure 199-12. Tissue expansion and hypertrophy associated with hemangioma of infancy. **A,** Focal upper lip hemangioma: Lateral view demonstrating increased lip height and width. **B,** Mixed parotid-ear hemangioma: Lateral view demonstrating enlargement of lower third of the auricle.

Figure 199-13. Combined laser and surgical treatment of large nasal tip mixed focal hemangioma of infancy. **A,** Before treatment. **B,** After residual deep hemangioma excision via external rhinoplasty approach.

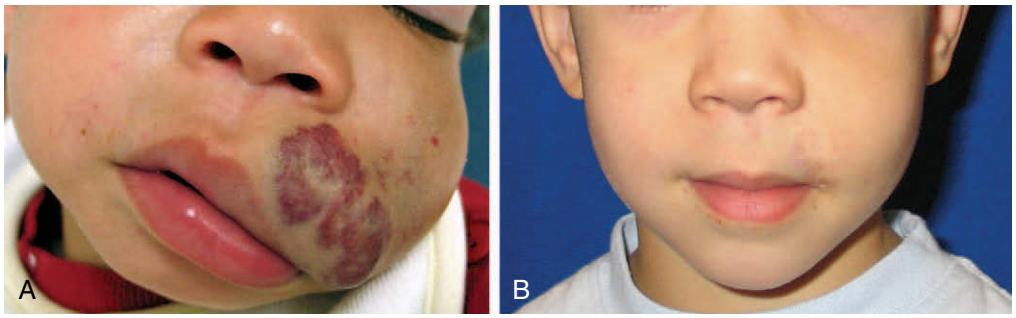

Figure 199-14. Combined laser and surgical treatment of large upper lip–cheek mixed segmental hemangioma of infancy. **A,** Before treatment. **B,** After laser treatment and deep hemangioma excision.

Figure 199-15. Laser treatment of superficial hemangioma. **A,** Pretreatment appearance. **B,** Appearance after three pulsed dye laser treatments.

The major indication for corticosteroid use depends on the presence of HOI complications or the attempt to prevent such complications, which occur more frequently with extensive segmental lesions.[26] For extensive proliferating HOI, prednisolone is given orally with doses ranging from 1 to 5 mg/kg/day in treatment courses that begin with an empirical burst at a high dose and then a slow 4- to 6-week taper off the medication. In theory, this minimizes the systemic side effects of steroid usage, but no long-term efficacy studies have been done.[43] Effectiveness of therapy is monitored throughout therapy; live vaccine administration is avoided, and blood pressure is monitored. Focal HOI of the head and neck can be injected with corticosteroids to localize drug delivery.[44,45] This practice is controversial and specialty specific, owing to the risk of blindness, training differences, and uncertain efficacy. Despite this, it is frequently done under general anesthesia for eyelid HOI while directly visualizing the retina.[36,46] In this location steroids are very effective in reducing HOI size, thereby decreasing the risk of HOI-induced visual impairment, but intralesional steroid injections can induce measurable adrenal suppression.[46] The role of topical medications to treat hemangiomas is being defined.[47] Other forms of antiangiogenic chemotherapy, such as interferon, have been used to treat HOIs.[48,49] The initial optimism for interferon as an effective agent for treatment of extensive HOI was subdued by the realization that before the age of 1 year, the central nervous system appears to be sensitive to this medication; neurologic complications such as spastic dysplegia were frequent.[50] For this reason, interferon is not used without serious consideration. However, it is still used in selected patients during times of rapid HOI proliferation. The proper dose of interferon is controversial, because previously reported complications were attributed to inappropriately high interferon dosing. More recently, vincristine has been investigated as a medication that can be used safely for treatment of extensive HOI.[51,52] Trials are under way to determine its efficacy in comparison with corticosteroids. Most recently, propranolol has been found to have an effect on reduction of HOI size. Further study is necessary to refine its use in the treatment of HOI.[78]

Laser Therapy

Superficial HOIs are red; the pulsed dye laser with a cooling device can reduce and even remove this skin redness, while the epidermis overlying the HOI is preserved.[53,54] The pulsed dye laser does not reduce HOI volume. This device is advantageous because it spares the superficial epidermis and allows for treatment of cutaneous redness without scarring (Fig. 199-15). However, when this device is used in patients younger than 6 months of age, when the HOI is actively proliferating, it can induce epithelial disruption, ulceration, and scarring.[55] For this reason, most clinicians recommend waiting to use the pulsed dye laser until after the age of 6 months. Often, reducing HOI redness is the only therapy necessary, because the deep portion of the lesion resolves with involution.

Surgical Therapy

When HOIs cause functional compromise of vision or breathing and are unresponsive to medical therapy, surgical excision may be necessary to preserve function.[56-58] HOIs that partially involute may leave significantly abnormal fibrofatty skin changes, requiring surgical resection.[59] A variety of techniques for HOI removal and reconstruction have been described. In most cases, waiting until the HOI has stopped proliferating is advisable.[60,61] When the HOI is causing airway or visual compromise, surgery during proliferation may be necessary. HOI occurring on the face can be significantly disfiguring and may be best treated with surgical excision.[62] When this type of lesion is mixed, with a larger superficial component, staged treatment with pulsed dye laser induces skin and dermal thickening, allowing HOI excision with minimal skin loss and tension-free closure of the defect (see Fig. 199-13).[63]

Assessment and Treatment of Airway Hemangiomas

One of the conditions associated with HOI that warrant the direct involvement of the otolaryngologist is an airway hemangioma. HOIs can occur anywhere in the upper and lower airways.[35] Usually the lesion is asymptomatic, involving the superficial mucosa. When a parapharyngeal HOI is large and abuts the pharynx, extrinsic compression of the airway can occur, particularly during sleep. Symptoms of sleep-disturbed breathing may arise during HOI proliferation or inflammation. Laryngeal involvement with HOI frequently manifests during infancy in the proliferative phase in association with an upper respiratory infection, or later in life with recurrent croup.[64] This clinical

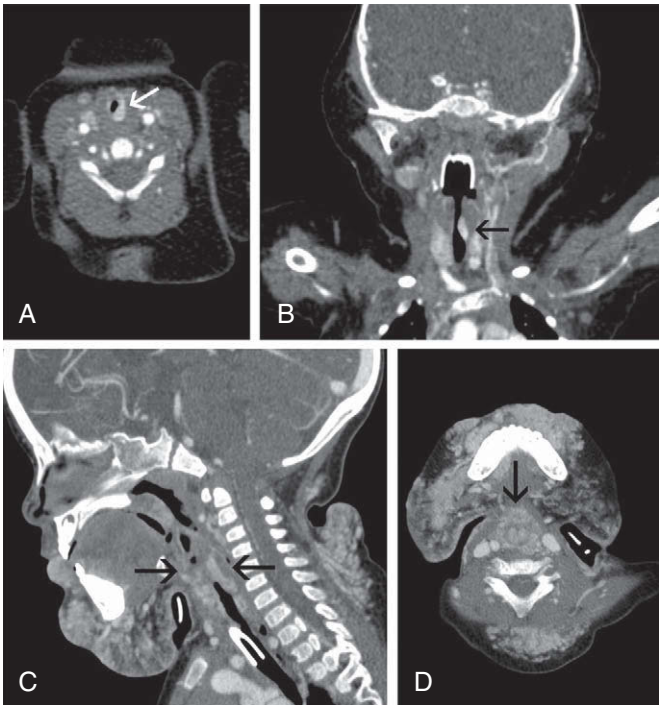

Figure 199-16. Computed tomography (CT) assessment of airway hemangioma of infancy. **A** and **B,** CT appearance of focal airway hemangioma of infancy. **A,** Axial scan; **B,** coronal scan. Compare endoscopic photograph of the same patient in Figure 199-8B. **C** and **D,** CT appearance of segmental airway hemangioma of infancy. **C,** Sagittal scan; **D,** axial scan. Compare endoscopic photograph of the same patient in Figure 199-8C.

feature is different from those of other types of hemangiomas, such as a lobular hemangioma (also known as a pyogenic granuloma).[65] Because the subglottic airway is the narrowest portion of the pediatric airway, HOIs in this area induce the greatest degree of respiratory embarrassment. Assessment of a stridorous infant must include the possibility of an airway hemangioma, especially if a cutaneous HOI is present. Segmental HOIs in the lower face are associated with airway lesions in at least 50% of cases.[66] Stridor in association with this type of HOI should prompt hospital admission, fiberoptic laryngoscopy, and even operative endoscopy if the initial evaluation is nondiagnostic. Advances in CT imaging techniques enable accurate assessment of HOI extent, to include evaluation of airway lesions (Fig. 199-16). Along with careful endoscopy, such imaging will reveal a pattern of HOI in the airway that can be described as similar to cutaneous HOI. In other words, there can be focal HOIs located only in the subglottis or segmental HOIs that are transglottic and extend into the soft tissues surrounding the airway.

Treatment of airway HOI is aimed at preventing the need for a tracheotomy. Initial treatment with high-dose oral corticosteroids usually improves the respiratory status within 24 hours. Empirical use of steroids in any patient with cutaneous HOI and new-onset stridor can be used as a diagnostic assessment. If rapid improvement occurs, then presence of an airway HOI is likely. If no improvement is obtained, some other problem exists. Airway protection, when necessary, can be accomplished with endotracheal intubation using a small uncuffed endotracheal tube. This option allows safe transfer to a facility capable of comprehensive HOI care and avoids using a tracheotomy for immediate airway protection. Chemotherapy has been used to treat these lesions, but safety of this management method is controversial.[67] Numerous methods of operative interventiont have been used successfully for many airway hemangiomas.[56,57,68-70] Several themes have emerged from analysis of airway hemangiomas over several decades. "Focal" lesions that involve one side of the subglottis are successfully treated with steroid injection, laser ablation, or surgical excision. Larger circumferential "segmental" lesions are more difficult to treat and may necessitate tracheotomy management. Frequently, these lesions respond temporarily to steroid treatment. Laser use for circumferential lesions is done only on one side of the larynx at a time, necessitating multiple treatments that can result in airway scarring and stenosis.[71] Surgical excision as initial treatment for extensive airway HOI is being done more routinely and successfully, but careful case selection is imperative.[56] In all airway hemangiomas, use of oral corticosteroids, intermittently and long-term, usually is necessary until the HOI stops proliferating. Analysis of treatment outcomes for airway hemangiomas is in its infancy, owing to ongoing changes in the current understanding of HOI biology.[35]

Vascular Malformations

Lymphatic Malformations

In our experience, lymphatic malformations are the most common vascular malformation affecting the head and neck in children.[79,80] Seventy-five percent of all lymphatic malformations occur in the head and neck. The etiology of lymphatic malformations remains unknown. Histologically, they consist of abnormally dilated lymphatic channels. Most lymphatic malformations are present at birth, although some appear later in childhood when they enlarge in response to infection or trauma. Unlike the detection of nuchal thickening and lucency in utero, the postnatal presence of these malformations is not associated with chromosomal abnormalities.[81-83] Up to 60% of all lymphatic malformations are detected by ultrasound examination in utero.[84] It has been suggested that the sporadic occurrence of lymphatic malformations is due to de novo somatic mutations.

Diagnostic Evaluation

Diagnosis and characterization of lymphatic malformations can be accomplished with either MRI or CT scanning.[7] On MRI, T1-weighted images show nonenhancing muscle signal intensity, whereas T2-weighted images demonstrate nonenhanced high signal intensity without any feeding or draining vessels. CT scans show nonenhancing fluid density areas.[8] Either modality is useful for classifying the lesion as macrocystic (cystic spaces measuring 2 cm or larger), microcystic, or mixed.[85] Additionally, the prominent venous component of microcystic suprahyoid malformations is demonstrated with CT. Prenatal ultrasound examination can be used not only to detect the malformation but also to determine if there is a possibility of airway compromise at birth.[86] If further information regarding the lesion is required, a prenatal MRI study also can be used. With this information, delivery procedures that protect the infant airway while maintaining maternal-fetal circulation can be planned.[87]

Clinical Assessment and Behavior of Lesions

Clinical understanding of lymphatic malformation behavior and treatment outcome has improved through better diagnostic imaging and head and neck staging systems[88] (Fig. 199-17). Macrocystic malformations in the posterior neck, without septations, that are infrahyoid can resolve without treatment.[89] In general, macrocystic malformations in any location in the neck can be obliterated with sclerotherapy or surgery.[90-92] By contrast, bilateral suprahyoid lesions, which tend to be microcystic or mixed, respond poorly to any treatment and are more often associated with complications.[92-94] These lesions frequently involve the oral and pharyngeal mucosa, with consequent recurrent tongue swelling, persistent tongue hypertrophy, mucosal bleeding, speech difficulty, and airway compromise. In general, lymphatic malformations lateral to the lateral canthal line tend to be macrocystic, whereas medial midfacial lesions tend to be more mixed. Midface involvement is uncommon and usually is completely microcystic[95,96] (Fig. 199-18). The larger and more extensive suprahyoid malformations have the most unpredictable clinical behavior and cause the most problematic dysfunction of the upper aerodigestive tract.

Associated Conditions

Lymphatic malformations are associated with unique problems that complicate treatment. Repeated episodes of malformation swelling

Figure 199-17. Head and neck lymphatic malformation stages. **A,** Stage 1, unilateral infrahyoid. **B,** Stage 2, unilateral suprahyoid. **C,** Stage 3, unilateral supra- and infrahyoid. **D,** Stage 4, bilateral suprahyoid. **E,** Stage 5, bilateral supra- and infrahyoid.

Figure 199-18. Microcystic lymphatic malformation involving left upper lip.

in association with presumed infection or trauma frequently occur, especially in suprahyoid microcystic or mixed lymphatic-venous malformations with oral mucosal involvement.[97] Mucosal inflammation can trigger intermittent aggravation of airway and feeding issues. These inflammatory-infectious episodes are treated effectively with appropriate broad-spectrum antibiotics with or without systemic corticosteroids.[80] Patients with transmural tongue involvement by malformation benefit significantly from this treatment both acutely as well as prophylactically. What triggers inflammation of lymphatic malformations is unknown, but in some cases recurrent or persistent inflammation may be related to immune dysfunction. Patients with large bilateral or microcystic lymphatic malformations can have significant lymphocytopenia involving T, B, and natural killer (NK) cell subsets.[98] This lymphocytopenia is not related to lymphocyte sequestration within the malformation, as was previously thought. Large bilateral or microcystic lesions involving the oral mucosa require more intensive treatment in lymphopenic patients than in patients without lymphocytopenia.[99]

Lymphatic malformations frequently involve and can distort the facial skeleton. This distortion is most evident in the mandible in association with large bilateral suprahyoid lesions[93] (Fig. 199-19; see also Fig. 199-1). The reasons for skeletal overgrowth are unknown. Early surgical excision of the soft tissue lymphatic malformation does not appear to change the rate or incidence of bony involvement. When the mandible is enlarged by malformation, mandibular reduction surgery may be indicated. In rare cases, large lymphatic malformations near the skull and skull base may be associated with bone resorption and more widely disseminated lymphatic growth, which can be fatal.[78] Bone loss also occurs with some lymphatic malformations. Gorham syndrome (disappearing bone disease) is the most striking manifestation of lymphatic vessels overtaking bony structures.[99a]

Treatment Options: Sclerotherapy versus Surgery

Favorably staged lymphatic malformations, such as unilocular macrocystic posterior lateral malformations, can be observed over time. If problems such as infection do not occur during observation, the lesion may regress spontaneously[89] (Fig. 199-20). A decision for intervention usually is triggered by concerns for airway, feeding, speech, infection, and appearance.

Sclerotherapy

Sclerotherapy for macrocystic (cysts larger than 2 cm in diameter) malformations is no longer new, but popularity for this intervention appears to be on the rise, even though it is infrequenly used according to some reports.[100,101] Sclerotherapy with all reported agents is usually ineffective for microcystic lesions.[102] Sclerotherapy involves percutaneous needle aspiration of macrocystic spaces under fluoroscopic guidance

Figure 199-19. Facial asymmetry in parotid lymphatic malformation. **A,** Swollen lymphatic malformation before treatment. **B,** Persistent facial asymmetry after treatment; asymmetry involves both soft tissue and bone.

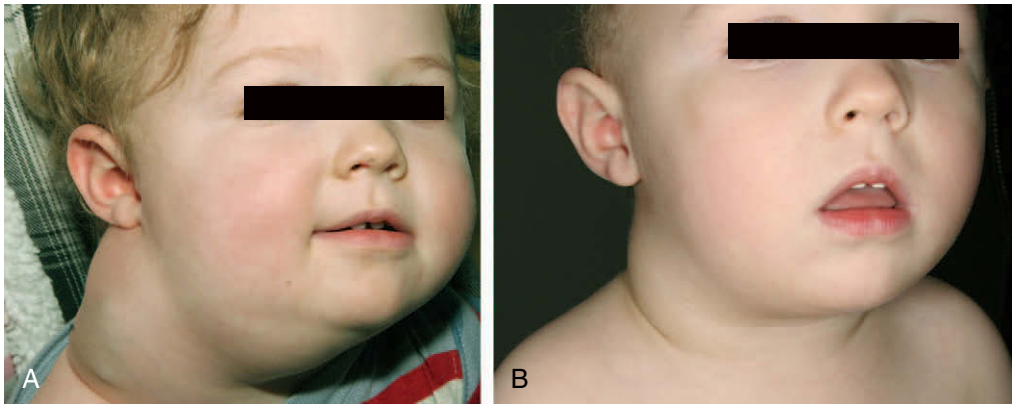

Figure 199-20. Spontaneous resolution of macrocystic posterior cervical lymphatic malformation. **A,** Initial appearance, before the age of 6 months. **B,** Complete resolution by the age of 1 year.

with subsequent injection of the sclerosing agent. Use of OK-432 (Picibanil, Chugai Pharmaceutical Company, Tokyo) as a sclerosant, because of its decreased toxicity and scarring risks, has led to increased interest in sclerotherapy. OK-432 is not commercially available in the United States, but published reports show promising results for macrocystic lesions after multiple treatments.[102,103] Similar efficacy for treatment of macrocystic lesions has been reported for doxycycline, bleomycin, ethanol, and sodium tetradecyl sulfate.[104,105] Major toxicity issues, including pulmonary fibrosis with bleomycin and permanent nerve injury with ethanol, are rare. Other rare complications include sepsis, shock, stroke, and seizures. Minor issues such as skin blistering and loss, fever, and erythema and pain at the injection site are more common.

Surgery

Surgical excision, the traditional treatment of choice for most types of lymphatic malformations, is still the most common treatment modality.[100] Excision of localized macrocystic lesions in the posteroinferior neck and parotid and submandibular regions generally has a high rate of complication-free surgical success.[80] However, in some reports, the complication rate, especially for large mixed suprahyoid lesions, is high.[93] Complications include cranial nerve or great vessel injury, tongue edema requiring tracheotomy, bleeding, and infection.

Surgical goals should be total excision with preservation of vital structures, when possible. Subtotal excision, not surprisingly, results in more postoperative persistent problems but may be necessary to preserve vital structures.[95] Lymphatic malformations are infiltrative and involve nerves, vessels, and muscles. It is common in large facial malformations to have facial nerve branches weave back and forth in the cyst walls and within the lesion, resulting in unusual nerve location and greater nerve length.[106] Intraoperative electromyographic nerve mapping can aid in these difficult dissections (Fig. 199-21). For bilateral suprahyoid lesions with mucosal involvement, waiting as long as possible before surgery and doing one side at a time (staged excision) may reduce the potential for permanent tongue enlargement. When the tongue becomes enlarged, surgical reduction may be indicated[107] (Fig. 199-22). Postoperative drainage of the surgical site is essential after resection, because significant lymphorrhea can occur.[108]

Figure 199-21. Preoperative facial nerve mapping before lymphatic malformation excision.

Figure 199-22. Microcystic lymphatic malformation, mucosa and deep tongue involvement.

Treatment Option Conclusions

New consensus views regarding treatment of lymphatic malformations appear to be emerging. The practice of waiting for the possibility of spontaneous resolution for unilocular or nearly unilocular lesions, especially if they are located in the posteroinferior neck, is becoming more common. Most vascular anomaly centers are treating macrocystic disease with either sclerotherapy or surgery. Systemic steroids, in addition to antibiotics, are used to treat severe acute inflammation and infection, although controlled studies are lacking and immune surveillance is necessary. Anecdotal evidence has led many clinicians to delay surgery, if necessary, as long as possible and to perform surgery for large suprahyoid lesions in stages to reduce complications (e.g., tongue edema). Little consensus exists regarding treatment to reduce mandibular and other facial overgrowth.

Venous Malformations

Venous malformations consist of tangled abnormal blood vessels filled with slow flow blood. Some of these lesions have been associated with a receptor tyrosine kinase (Tie2) dysfunction.[13] Other molecular mechanisms may be involved in the disordered vasculogenesis associated with these lesions.[109] These lesions frequently are present in muscle tissue, are compressible, enlarge with Valsalva maneuver or dependent positioning, and give a bluish hue under involved skin or mucosa[110] (Fig. 199-23). Occasionally, intracranial and skull base extension can occur, particularly with periorbital lesions.[111] Histologically, many of these lesions comprise blood and lymphatic vascular elements.[112] They usually are present at birth, slowly enlarge over time, and may become inflamed and painful during puberty and with trauma.[113] Diagnosis can be made clinically with radiographic confirmation. Duplex scanning shows slow blood flow, and lesions have a bright signal on T2-weighted sequences on MRI.[7] CT scans frequently demonstrate calcified phleboliths. Treatment consists of symptom management and malformation ablation or excision in selected lesions. Pain from enlargement is thought to be due to adjacent nerve irritation from the malformation and may be related to the intralesional consumptive coagulopathy present in some patients.[112,113] This coagulopathy can be detected through elevated D-dimers and low fibrinogen. Antiplatelet and anti-inflammatory agents can help control symptoms. In extreme situations, low-dose heparin may be necessary in conjunction with hematology consultation. Venous malformation ablation can be achieved with complete surgical excision if possible. Careful preoperative assessment is essential to detect any evidence of a subclinical coagulopathy. Combined therapy with sclerosis and surgery usually is necessary to minimize blood loss and morbidity.[110,114] When excessive intraoperative bleeding occurs, novel hemostatic measures have been used effectively.[115] For lesions that are amenable to sclerotherapy, intralesional sclerosants or laser can be utilized[116-118] (Fig. 199-24). Often, periodic treatments are necessary.

Arteriovenous Malformations

Arteriovenous malformations are high-flow vascular malformations that can manifest as enlarging masses throughout the head and neck, most frequently involving the cheek or auricle.[119] Some arteriovenous malformations are found with cutaneous capillary malformations and are associated with gene abnormalities.[21] Functionally, these congenital lesions arise from a nidus of blood vessels that have abnormal precapillary communication from arteries to veins. This creates the arteriographic diagnostic finding for arteriovenous malformations of "early venous filling." By contrast, arteriovenous fistulas are a solitary abnormal communication between arteries and veins that usually are acquired secondary to trauma. Diagnosis of arteriovenous malformations requires imaging with MR or CT angiography[29,120] (Fig. 199-25). Occasionally, interventional angiography also is necessary, but usually this can be done in conjunction with embolization, immediately before surgical treatment. The natural history of these malformations often is unclear, but four clinical stages—dormancy, expansion, destruction, and heart failure—have been described and correlated with treatment outcome.[119] In the dormancy stage, these malformations can be mistaken for other vascular anomalies. In some patients, enlargement and growth can occur during adolescence. Treatment of arteriovenous malformations includes nonintervention or intervention with a combination of preoperative embolization followed by surgical excision of the nidus.[121] Lesions contained within bone can be managed with embolization alone, but once the lesion involves adjacent soft tissue, surgery may be necessary.[122] These lesions recur commonly, so treatment decisions must be carefully planned.

Capillary Malformations

Skin capillaries that are persistently dilated form malformations commonly known as *port-wine stains*.[123] These capillary malformations frequently are seen in the mid- and upper face. In the upper face and eyelid region, they are associated with Sturge-Weber syndrome.[124] This condition is characterized by capillary malformations involving the eye, skin, and leptomeninges. Capillary malformations in the upper face warrant concomitant evaluation with brain MRI and ophthalmologic examination to rule out this syndrome. These lesions progressively darken and thicken throughout life and are associated with local tissue hypertrophy and hamartomatous nodule formation that may require

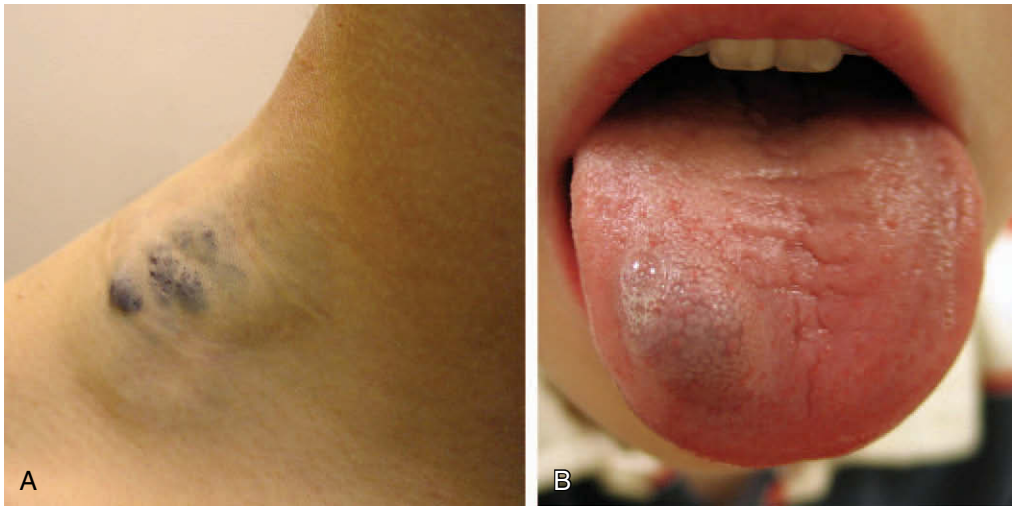

Figure 199-23. Venous malformation appearance. **A,** Skin. **B,** Tongue.

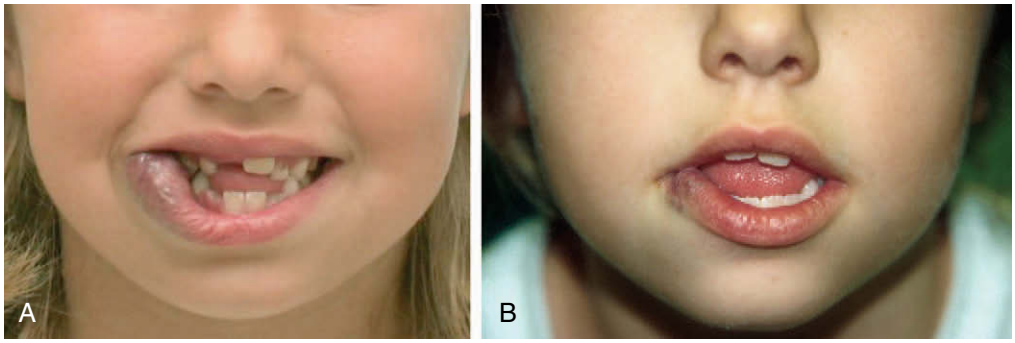

Figure 199-24. Venous malformation treatment with interstitial laser. **A,** Lip before treatment. **B,** Lip after two laser treatments.

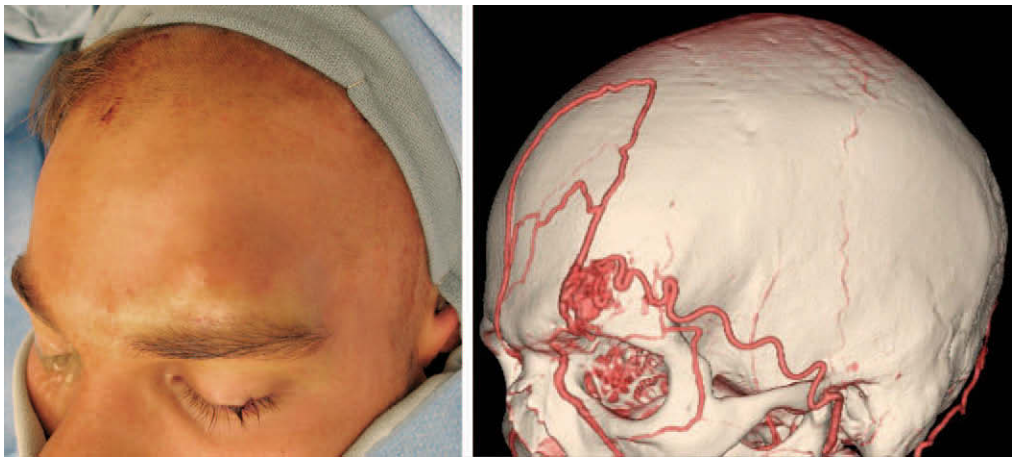

Figure 199-25. Computed tomography angiography and clinical appearance of quiescent arteriovenous malformation nidus, left brow.

treatment[125] (Fig. 199-26). The superficial component of these lesions can be managed with serial pulsed-dye laser treatments.[126] Some malformations are resistant to this therapy, and other laser modalities can be used.[127] No therapy is curative.

Summary

Current understanding of vascular anomalies is evolving with new advances in molecular, genetic, diagnostic, disease staging, and therapeutic outcomes research. As a field of clinical medicine, the management of these anomalies crosses traditional boundaries between medical and surgical disciplines. This overlap necessitates a multidisciplinary approach, in order to optimize patient care and treatment outcomes. It is anticipated that future diagnostic and treatment modalities will be more effective in predicting the clinical course and preventing complications of these common and benign yet problematic lesions.

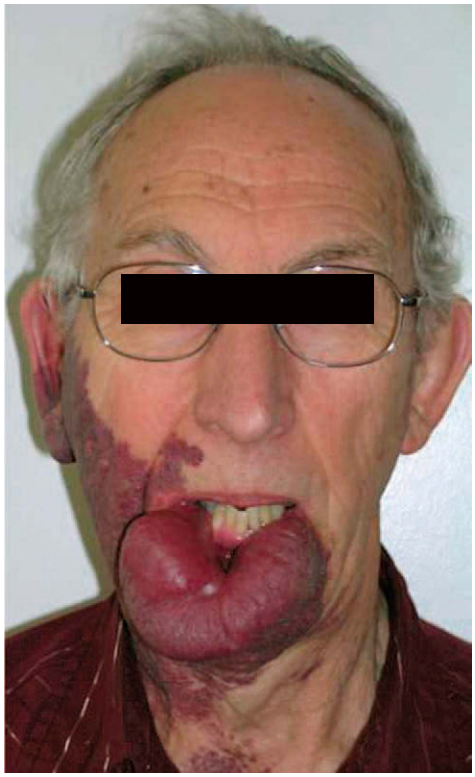

Figure 199-26. Capillary malformation of lower face and lip. The lip hypertrophy was related to the capillary malformation. *(Courtesy of Dr. J. Gruss.)*

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CHAPTER TWO HUNDRED

Pediatric Head and Neck Malignancies

Carol J. MacArthur

Richard J. H. Smith

Key Points

- Each year in the United States, cancer is diagnosed in 1 of every 7000 children 0 to 14 years of age.
- Although accidents are the leading cause of death in children, malignancies remain the most common cause of death from disease in the 1- to 14-year-old age group.
- Unlike adults, most childhood tumors are mesenchymal or neuroectodermal in origin.
- Nearly one third of pediatric malignancies are leukemias, and an additional 12% are lymphomas. Nonhematologic solid tumors account for the remaining 55%.
- Every child with suspected leukemia-lymphoma or neuroblastoma should have a workup to evaluate for gene translocations, antigen expression, and gene amplification. Critical to this histopathologic workup is the delivery of fresh tissue to the pathologist for proper handling.
- Pediatric head and neck cancer treatment is guided by the guidelines developed in accordance with collaborative, multimodality therapeutic protocols, such as the Intergroup Rhabdomyosarcoma Study Groups Committee (IRSC).
- Because of the high rate of metastatic disease in pediatric cancers, combined therapy usually is required (surgical biopsy or excision, chemotherapy, radiation therapy if needed for local control).
- With increasing numbers of long-term survivors of pediatric head and neck cancer, ongoing management of sequelae from treatment is essential, including attention to development of secondary malignancies 1 to 2 decades after treatment.

Each year in the United States, cancer is diagnosed in 1 of every 7000 children 0 to 14 years of age. In 1998, the diagnosis of cancer was given to 8700 children before their 15th birthday and to 3700 young adults between 15 and 20 years of age in the United States.[1] Data collected by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) between 1972 and 1990 suggested that these numbers were on the rise. In 1972, 12 cancers were diagnosed per 100,000 children under the age of 15 years; by 1990, that number had increased to nearly 14 per 100,000.[2,3] However, the rates have been stable since 1990.[4] Among malignancies of the head and neck, the incidence rate increased from 1.1 to 1.49 per 100,000 person–years.[5] During this same period, cancer-related mortality rate decreased. Therefore, the changes in incidence probably coincided with earlier diagnosis because of advances in central nervous system (CNS) diagnostic imaging such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), and not a true increase in rates of disease.[4] However, malignancies remain the most common cause of death from disease in the 1- to 14-year-old age group. Childhood cancers are exceeded only by accidents as the leading cause of death in children older than 1 year of age.

Certain populations of children are at a higher risk for developing childhood malignancies. Down syndrome (DS) patients have a 20-fold increased chance of developing leukemia over the normal population. Post-transplantation pediatric patients and children who have received chemotherapy or radiotherapy are at increased risk for development of a second malignancy, most commonly non-Hodgkin's lymphoma or leukemia. Beckwith-Wiedemann syndrome and hemihyperplasia (previously termed hemihypertrophy) is linked with an increased risk of Wilms' tumor and hepatoblastoma. Patients with Bloom's syndrome, ataxia-telangiectasia, X-linked hypogammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency syndrome, severe combined immunodeficiency syndrome, X-linked lymphoproliferative disorder, selective IgA deficiency syndrome, and autoimmune diseases are all at increased risk for development of lymphoma, leukemia, and solid tumors.

The types and relative frequencies of childhood cancers are vastly different from those of cancers in adults. Most childhood tumors are mesenchymal or neuroectodermal in origin, whereas adult tumors are usually epithelial in origin. Nearly one third of pediatric malignancies are leukemias, most commonly acute lymphocytic leukemia, and an additional 12% are either Hodgkin's lymphoma or non-Hodgkin's lymphoma. Nonhematologic solid tumors comprise the remaining 55%. Of all solid tumors in children younger than 15 years of age, brain tumors are most common, followed in frequency by neuroblastoma, Wilms' tumor, non-Hodgkin's lymphoma, Hodgkin's disease, and rhabdomyosarcoma.

Impressive gains have been made in survival rates for some childhood cancers. In children younger than 15 years of age who are

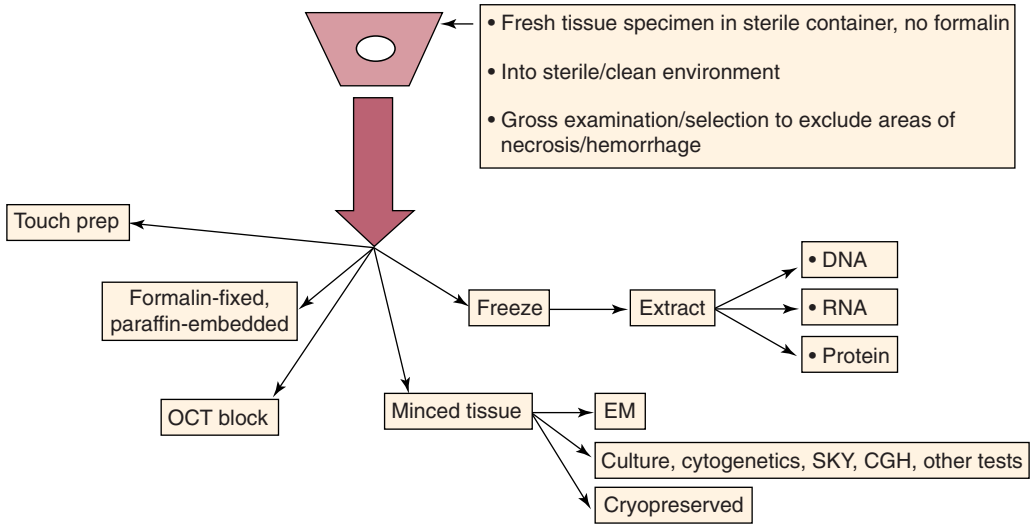

Figure 200-1. Tissue-handling algorithm for histopathologic workup. CGH, comparative genomic hybridization; EM, electron microscopy; FISH, fluorescence in situ hybridization; SKY, spectral karyotyping.

diagnosed with solid tumors, the survival rate has more than doubled—from 28% in 1960 to a more than 75% 5-year survival rate in 1993 and an 80% 3-year survival rate in 1995.[6] Particularly impressive survival gains have been achieved with Wilms' tumor and Hodgkin's lymphoma, both of which now have cure rates exceeding 90%.[2] Outcome data during this 30-year period show that the slopes of curves describing survival over time have remained fairly constant for all types of tumors. Advances in treatment and gains in survival have been achieved in a slow, incremental manner based on results of multicenter clinical trials. In spite of these advances, approximately 25% of children diagnosed with cancer will die of their disease.

The progress in survival rates for childhood cancer largely reflects the impact of clinical trials. Initiated first in 1948 to enable Farber and colleagues[7] to document the efficacy of methotrexate in inducing remission in some children with acute lymphocytic leukemia, most clinical trials today are conducted by the Children's Cancer Group or the Pediatric Oncology Group. In these trials, standard therapy is compared with a modification of that therapy, and if the modified protocol is superior, it then becomes the new standard. Progress is tedious, but from the perspective of time, it has been tremendously rewarding.

The possibility of more rapid advances in diagnosis and management is becoming increasingly real as studies of the molecular biology of childhood malignancies elucidate several requisite steps for tumorigenesis. Two important cytogenetic events, translocation and amplification, are important in tumor development and can act synergistically to generate potent oncogenic activity.[8] Nonrandom chromosomal translocations typically activate oncogenes by one of two mechanisms.[9] The first mechanism, frequently found in lymphoid malignancies, places the coding sequence of one gene under the regulatory control of a second gene. This juxtaposition results in increased or inappropriate expression of the first gene. The second mechanism generates a new gene, which is a chimera of two other genes that is formed by joining their coding regions. For amplification events, additional copies of a cellular gene are generated in the form of double-minute chromosomes or homogeneously staining regions.[10]

The pathologic evaluation of childhood tumors is very different from that of adult tumors. Because of the large numbers of mesenchymal tumors that can look very primitive and similar on light microscopy—small round blue cell (SRBC) tumors—use of newer techniques such as immunochemical, molecular, or ultrastructural analysis is necessary for accurate diagnosis. Proper diagnosis is crucial to developing a treatment plan and for prediction of clinical behavior. Every child with suspected leukemia-lymphoma or neuroblastoma should have a workup to evaluate gene translocations, antigen expression, and gene amplification. Critical to this pathologic workup is the delivery of fresh tissue to the pathologist for proper handling. Figure 200-1 shows proper tissue handling to ensure the availability of tissue for all types of analysis. Fresh tissue has the messenger ribonucleic acid (mRNA) necessary to carry out cell cultures for molecular genetic analysis and for growth of a permanent cell line. Because tissue often is not handled properly and is fixed in formalin before arriving at the pathologist's laboratory, techniques have been developed to obtain molecular genetic information from fixed or frozen tissue by such means as reverse transcriptase–polymerase chain reaction (RT-PCR) analysis, flow cytometry, fluorescence-activated cell sorting (FACS), and fluorescence in situ hybridization (FISH). However, RT-PCR analysis requires intact RNA, which can be obtained only by snap-frozen tissue stored at −70° C from viable tumor areas without tumor necrosis. Some success has been achieved with use of fixed, paraffin-embedded tissue for RT-PCR assays, but further work is needed in this effort.

Because resources are limited, a practical way to handle biopsy tissue must be adopted (see Fig. 200-1). After delivery of fresh tissue to the pathologist, the tissue is examined by routine hematoxylin and eosin (H&E) stains. If the diagnosis is not clear, additional methods are brought into play to establish a diagnosis such as immunohistochemistry, molecular genetic analysis, electron microscopy, cytogenetic studies, and deoxyribonucleic acid (DNA) sequencing (Table 200-1). These evolving techniques are used judiciously and are rarely all needed. The most common secondary procedure after examination of H&E stains is immunohistochemistry, followed by special stains, electron microscopy, and molecular studies. Immunohistochemistry is used to confirm the histogenesis of a tumor. Approximately 35 antibodies are commonly used in pediatric tumor workups in the categories of general (vimentin), hematopoietic, neural, myogenic, epithelial, and miscellaneous. Immunohistochemistry and electron microscopy have largely replaced the use of special stains, but a few are still useful, such as trichrome, pentachrome, reticulin, myeloperoxidase, and periodic acid–Schiff (PAS) stains. Electron microscopy is used primarily to clarify conflicting results from other studies such as immunohistochemistry. Molecular genetic techniques include five major methods: polymerase chain reaction (PCR) analysis, cytogenetic studies, FISH, spectral karyotyping (SKY), and comparative genomic hybridization (CGH). These techniques are used to detect genomic alterations (translocations, amplifications, or deletions) from chromosomal analysis. Many protocols require the use of special studies for ploidy and molecular genetics to enter a patient into a protocol treatment arm. The availability of molecular genetics has revolutionized childhood cancer diagnosis, providing accurate diagnoses that help guide therapy and predict clinical aggressiveness. Molecular genetic analysis of childhood tumors should not be taken with blind faith because two problems can

be encountered: certain tumor-specific translocations only occur in a percentage of tumors, and in some cases, the same translocation can occur in a phenotypically different tumor. Still, molecular genetics has enormous value in the diagnostic workup of the difficult, primitive pediatric tumors.

Head and neck tumors of childhood are reviewed in this chapter. This subset of malignancies accounts for approximately 12% of all childhood cancers and, in order of relative prevalence, includes lymphomas (27%: Hodgkin's lymphoma 17%, non-Hodgkin's lymphoma 10%), neural tumors (23%: retinoblastoma and neuroblastoma), thyroid malignancies (21%, with papillary carcinoma the most common pathologic diagnosis), and soft tissue sarcomas (12%: rhabdomyosarcoma; 8%, nonrhabdomyosarcoma soft tissue sarcomas [NRSTSs]).[5] Age has a marked effect on tumor type and modifies this order of prevalence considerably. The age factor is obviously pertinent to a directed evaluation and diagnostic workup (Table 200-2).

Discussion in this chapter is limited to lymphomas, rhabdomyosarcomas, neuroblastomas, NRSTSs, salivary gland malignancies, thyroglossal duct carcinomas, post-transplantation lymphoproliferative disorders, malignant teratomas, and the histiocytoses. Thyroid and nasopharyngeal carcinomas are adequately covered elsewhere in this book.

Table 200-1

Diagnostic Methods for Tumor Diagnosis

Method	Comment
Light microscopy	Used in all cases
Immunohistochemistry	Widely used ancillary diagnostic
Molecular genetic: reverse transcriptase–polymerase chain reaction (RT-PCR)	Common molecular diagnostic method
Molecular genetic: FISH	Replacing cytogenetics in many cases
Molecular genetic: in situ hybridization	Specialized use
Special stains	Still useful in some cases, inexpensive
Electron microscopy	Used to augment light microscopy
Cytogenetics	Used when no suitable FISH probes available
Molecular genetic: SKY, CGH	Newer diagnostic methods
Molecular genetic: DNA sequencing	For rare cases

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; SKY, spectral karyotyping.

Lymphomas

Non-Hodgkin's Lymphomas

Acute lymphoblastic leukemia, defined as leukemic involvement of greater than 25% of the bone marrow, is the most common pediatric malignancy. *Lymphomas*, defined as leukemic tumor cells extending beyond bone marrow sites and involving less than 25% of the bone marrow, are the third most common cancers in children in the United States,[11] and non-Hodgkin's lymphomas represent 60% of these diagnoses. The annual incidence in children younger than 15 years of age is 7 to 8 per 1 million, with peak ages between 7 and 11 years. Boys are preferentially affected in a 3:1 ratio,[12,13] and the disease is twice as common in whites as in blacks.[14] Although adult lymphomas are primarily nodal, childhood lymphomas are predominantly extranodal. Since 1973, the annual incidence of non-Hodgkin's lymphoma has risen by approximately 30%. Although the reasons for this increase remain unclear, specific populations of children who are at greater risk for non-Hodgkin's lymphoma have been identified. These groups include children with congenital immunodeficiency syndrome (Wiskott-Aldrich syndrome, ataxia-telangiectasia, and X-linked lymphoproliferative disease), children with acquired immunodeficiency syndrome (AIDS), and children who have received immunosuppressive therapy for organ or bone marrow transplantation. Patients treated for Hodgkin's lymphoma and solid tumors with chemotherapy are at an increased risk for non-Hodgkin's lymphoma as well. Common to all these patients is deficient or impaired T-cell function.

Geographic differences in the incidence rates and subtypes of non-Hodgkin's lymphoma are striking. For example, non-Hodgkin's lymphoma is rare in Japan, whereas in equatorial Africa and northeastern Brazil, Burkitt's lymphoma is endemic and accounts for approximately 50% of all cancers.[11] An association with Epstein-Barr virus (EBV) and BL has been demonstrated in these areas.[15] Even in cases of sporadic Burkitt's lymphoma in the United States for which standard screening yields a negative result,[16] EBV genomic DNA can be detected with molecular biology.

Presentation and Evaluation

Characterized by an acute onset with rapid progression, prompt diagnosis and initiation of therapy are important to reduce morbidity and ensure long-term survival.[17] In 23% to 46% of affected children, primary disease occurs within the abdominal cavity and involves, in decreasing order of frequency, the distal ileum, cecum, and appendix.[18,19] Mediastinal primary tumors are slightly less common and are

Table 200-2

Age-Incidence Ranking for Head and Neck Tumors in Children

Ranking of Tumors by Age (years)			
0-1	**1-5**	**6-10**	**11-20**
Neuroblastoma	Rhabdomyosarcoma	Lymphoma	Lymphoma
Rhabdomyosarcoma	Lymphoma	Rhabdomyosarcoma	Thyroid malignancies
Lymphoma	Neuroblastoma	Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS)	Nasopharyngeal malignancies
NRSTS	NRSTS	Thyroid malignancies	Salivary gland neoplasms

Table 200-3

Diagnostic and Staging Evaluation for Non-Hodgkin's Lymphoma

Essential	Useful	Occasionally Indicated
History	Intravenous urography	Contrast studies of the gastrointestinal tract
Physical examination	Special radiologic views (airway)	CT, MRI of the brain
Specimens for histology, cytology, immunophenotyping, genotyping	CT, MRI of primary site	CT, MRI of spinal cord
Complete blood count		Creatinine clearance
Serum chemistries (electrolytes, liver, renal serum chemistries, LDH, uric acid)	Epstein-Barr virus studies	Urinary uric acid Serum lactic acid
Bone marrow aspiration and biopsy	Protein electrophoresis	
Cerebrospinal fluid analysis	Acid-base studies	Liver biopsy
Urinalysis		Bone scan
Chest radiography		
Gallium-67 scanning		
Abdominal imaging		

CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.

diagnosed in 15% to 45% of cases.[20] Primary head and neck involvement occurs in 5% to 10% of children and originates in the salivary glands, larynx, paranasal sinuses, orbit, scalp, and Waldeyer's ring.[19] Proximity to the CNS makes direct extension possible.

The rapid progression of disease mandates prompt referral to a specialized management center before biopsy so that a pediatric oncologist can expedite the diagnostic and staging evaluation (Table 200-3) and determine the site and procedure to obtain tissue for histologic, cytologic, immunophenotyping, and genotyping analyses, with consultation from the surgeon and pathologist if necessary. Definitive diagnosis requires biopsy, sometimes by excision of a cervical node. Mediastinal involvement should be assessed by neck and chest CT before any procedure under general anesthesia. Disseminated disease is the rule, however, and often adequate numbers of malignant cells are found in the bone marrow, spinal fluid, or pleural or ascites fluid, obviating surgical intervention entirely. The presence of pancytopenia suggests bone marrow involvement, and when more than 25% of the marrow is replaced with tumor, children are assigned a diagnosis of acute lymphoblastic leukemia.

Management

Dramatic improvement in overall cure rates among children with non-Hodgkin's lymphoma reflects the incremental development of effective multimodal chemotherapeutic regimens through well-planned clinical trials. Systemic therapy is imperative because occult micrometastases affect more than 80% of children with non-Hodgkin's lymphoma and cure rates are less than 20% when only local therapy is used.[17] Management protocols are based on the extent of disease as determined by the staging workup and the histologic subtype.

The most widely used staging classification is the St. Jude Children's Research Hospital classification, based on the Ann Arbor staging system for Hodgkin's lymphoma, modified for non-Hodgkin's lymphoma (Table 200-4). Chemotherapy with combination drug therapy is the backbone of management, traditionally with agents used for acute lymphoblastic leukemia (i.e., cyclophosphamide, doxorubicin, vincristine, and prednisone, and for extensive or recurrent disease, methotrexate, Ara-C, etoposide, and ifosfamide). Overall cure rates are in the range of 70% to 90%, depending on tumor subtype. Radiotherapy has no routine role in the treatment of non-Hodgkin's lymphoma. Its use is reserved for massive disease, and surgery is used only occasionally in children with life-threatening tracheal compression. Response to therapy is assessed by monitoring tumor size and activity using a variety of imaging modalities or invasive techniques.

Histopathology and Molecular Biology

The histopathology of non-Hodgkin's lymphoma is extremely variable and has been categorized in various ways. The traditional and widely adopted Rappaport classification uses histologic pattern, cell type, and degree of differentiation to categorize tumors. In children, the categories seen with the most frequency are B-cell phenotype (Burkitt's lymphoma, Burkitt's-like lymphoma, large B-cell lymphoma), pre-T-cell origin (lymphoblastic lymphoma), and T-cell origin (anaplastic large-cell lymphomas and peripheral T-cell lymphomas). The diffuse histologic pattern is almost universal within these categories.[17]

The development of immunologic markers has added refinement to categorization and contributed to the identification of molecular mechanisms in pathogenesis. Best studied are the small, noncleaved-cell lymphomas, particularly Burkitt's lymphoma (Fig. 200-2). In Burkitt's lymphoma, EBV, a B-cell mitogen, probably fosters the establishment of a premalignant state by expanding the pool of lymphocytes in which chromosomal transformations can occur. Classic to Burkitt's lymphoma is the translocation of the *myc* gene from chromosome 8 to a position juxtaposed to an immunoglobulin receptor subunit gene on chromosomes 14 (80%), and less commonly to chromosomes 2 or 22 [t(8;14), t(8;2), t(8;22), respectively].[21,22] Unregulated expression of the *myc* gene disrupts regulation of the expression of target genes that are required for the normal progression of the cell cycle.[23-25]

Approximately 80% of large-cell lymphomas have a t(2;5) chromosomal rearrangement.[26] The precursor RNA can be detected by a RT-PCR assay, which has become an important diagnostic tool.[27] Although the impact of molecular biology has yet to revolutionize clinical practice, it will inevitably refine our diagnostic capabilities and permit the development of target tumor–specific therapy.

Hodgkin's Lymphoma

In 1832, Thomas Hodgkin described the disease that now bears his name. Although characterized by the presence of mononuclear cells (Hodgkin's cells) and binucleated or multinucleated tumor cells (Reed-

Table 200-4

Staging Systems for Non-Hodgkin's Lymphoma

	Staging System	
Stage	**Ann Arbor**	**St. Jude Children's Research Hospital**
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)	Single tumor (extranodal) or single anatomic area (nodal) excluding the mediastinum or abdomen
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)	Single extranodal site with regional lymph node involvement; two or more nodal areas on the same side of the diaphragm; two single extranodal tumors ± regional node disease on the same side of the diaphragm; primary gastrointestinal tract tumor, usually in the ileocecal area ± involvement of associated mesenteric nodes
III	Involvement of lymph node regions on both sides of the diaphragm (III) ± extranodal involvement (IIIE) ± splenic involvement (IIIS), or both (IIISE)	Two single extranodal tumors ± regional node disease on opposite sides of the diaphragm; two or more nodal areas on opposite sides of the diaphragm; all extensive primary intra-abdominal disease; unresectable; all primary intrathoracic tumors (mediastinal, pleural, thymic); all primary paraspinal or epidural tumors regardless of other sites
IV	Diffuse involvement of one or more extralymphatic organs; organs or tissues ± associated lymph node enlargement	Any of the above + initial CNS or bone marrow involvement (<25%)

CNS, central nervous system.

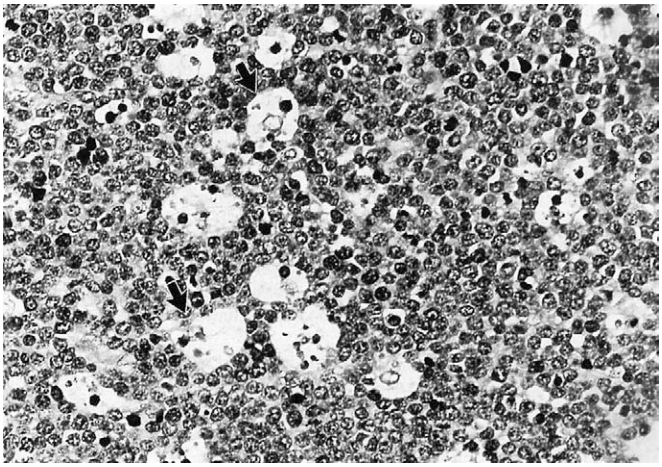

Figure 200-2. Non-Hodgkin's lymphoma categorized as malignant lymphoma with diffuse, small, noncleaved cells (Burkitt's lymphoma EBL7). Small non-cleaved lymphocytes diffusely replace this lymph node. The size is monotonous, differentiating it from non—Burkitt's lymphoma BL, which exhibits more variation in nuclei size and shape. Histiocytes *(arrows)* with their abundant pale cytoplasm and engulfed cellular material are scattered among the malignant lymphocytes, giving a "starry-sky" appearance. (Original magnification, 400×.)

Sternberg cells) in a background of variable and often abundant reactive cells, a single unifying principle of the biologic nature of Hodgkin's lymphoma and of the origin of the Reed-Sternberg cell has remained elusive.[28] Current data suggest that Hodgkin's lymphoma represents a group of diseases with an uncertain relationship to each other.[29] Age at diagnosis follows a bimodal distribution, with the first peak occurring between 15 and 40 years of age and the second peak occurring after age 50. Approximately 4% of cases occur in children younger than 10 years of age, and 11% are found in children between 10 and 16 years of age.[30]

Presentation and Evaluation

In more than 90% of childhood and adult cases, Hodgkin's lymphoma arises in the lymph nodes, typically causing an asymmetrical adenopathy that is firm, rubbery, and nontender. Particularly common is the combination of mediastinal and right supraclavicular nodal disease. The spleen is the most common extranodal site of involvement. Constitutional symptoms (B symptoms) may be present and include fever of 38° C or higher, drenching night sweats, or unexplained loss of 10% or more of body weight. Diagnosis is made by lymph node biopsy, and the disease is then staged using the classification developed in 1971 by the Ann Arbor workshop[31] and modified 18 years later to incorporate newer procedures such as CT (see Table 200-4, Ann Arbor staging system).[32] Substage classifications include A for asymptomatic disease, B for B symptoms (as described earlier in the chapter), and E for extension to an adjacent extranodal site. The staging system is based on the premise that Hodgkin's lymphoma spreads through the lymphatics to contiguous nodal groups and through the circulation to extranodal sites, although these modes of spreading have not been clearly established and multifocal involvement may represent multicentric disease.[29]

Clinical staging procedures include history, physical examination with measurement of lymph nodes, chest radiograph, CT scan of neck and chest, CT or MRI of abdomen, and laboratory tests (complete blood count with differential, erythrocyte sedimentation rate determination, renal and hepatic function tests, alkaline phosphatase assay). CT has limited sensitivity for detection of abdominal adenopathy in children because of their lack of retroperitoneal fat.[33] Therefore, abdominal MRI may be a better study for determining extent of abdominal and pelvic disease. Pathologic staging includes excisional lymph node biopsy. Bone marrow aspiration and biopsy is reserved for patients with stage III or IV disease or B symptoms. Routine use of surgical staging with splenectomy and lymph node sampling is no longer in use because of improved imaging techniques, routine use of systemic therapy, and the knowledge that splenectomy is associated with increased infectious and neoplastic complications. Stage at presentation is similar among children and adults, with approximately 60% of patients presenting with stage I or II disease and 40% of those presenting with stage II or IV disease, regardless of age.[30] In children younger than 10 years of age, however, stage I disease is more common (18%) and stage IV disease is less common (3%) than in adolescents

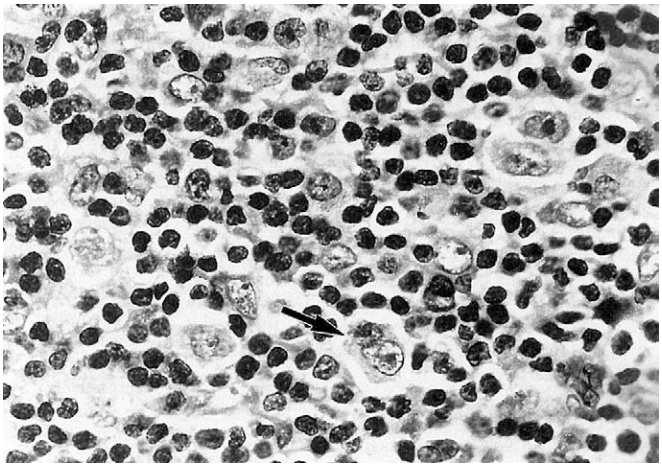

Figure 200-3. Hodgkin's lymphoma of the nodular sclerosing subtype. A mixed population of lymphocytes, histiocytes, and plasma cells along with binucleated Reed-Sternberg cells *(arrow)* are present. (Original magnification, 480×.)

(8% and 15%, respectively) and adults (11% and 11%, respectively). Systemic B symptoms also are less likely in younger patients (19%) than in adolescents (30%) and adults (32%).

Management

Management of Hodgkin's lymphoma varies according to stage. In most centers, radiation therapy is recommended for stage IA and stage IIA disease. Because of the high relapse rate among children with stage IIA disease of the mediastinum, chemotherapy also may be given.[34] For more advanced disease, chemotherapy either alone or as part of a combined regimen including radiotherapy is used.[35]

Long-term results for pediatric patients with early-stage Hodgkin's lymphoma suggest a prognosis similar to that in adults, with cure rates of approximately 90%.[36] With use of combined-modality therapy for stage IV disease, overall survival rates are slightly lower (approximately 80%).[35] When patients who have received only chemotherapy demonstrate relapse at nodal sites, salvage radiotherapy should be considered.[37]

Histopathology and Molecular Biology

The major histologic types of Hodgkin's lymphoma recognized by the Lukes, Butler, and Rye classifications include lymphocytic predominance, mixed cellularity, nodular sclerosis, and lymphocytic depletion (Fig. 200-3).[29] Further subclassification probably is unncessary, because current management protocols have eliminated differences in survival rates between the most common types (mixed cellularity and nodular sclerosis).

Micromanipulation of histologic sections to isolate and analyze individual Hodgkin's and Reed-Sternberg cells has verified an origin from B-lineage cells at various stages of development.[38] Ig heavy chain rearrangements have also been detected by PCR amplification in approximately 25% of cases.[39] These studies suggest that Hodgkin's lymphoma represents a clonal lymphocyte population and that different chromosomal rearrangements may be associated with different subclasses of disease.

Post-Transplantation Lymphoproliferative Disorder

As solid organ transplantation success rates have improved, diseases related to chronic immunosuppression have increased in prevalence. Post-transplantation lymphoproliferative disorder (PTLD) is the term for all abnormal proliferations of lymphoid tissue in the transplant recipient, ranging from lymphoid hyperplasia to malignant non-Hodgkin's lymphoma. Risk factors for the development of PTLD are the degree of immunosuppression, use of potent immunosuppressive agents such as tacrolimus, EBV seronegative status at time of transplantation, young age, donor-recipient mismatch, severe graft-versus-host disease (GVHD), T-cell depletion of donor marrow, use of anti–T-cell monoclonal antibodies, and high-dose antithymocyte globulin for GVHD prophylaxis. The rate of PTLD ranges from 8% to 28%,[40] depending on the immunosuppressive agents used. The rate of PTLD is higher in liver, heart, and heart-lung transplant recipients. The rate of PTLD is lower for renal transplant recipients, probably because of the higher level of immunosuppression needed in the former group.[41] Most PTLDs are of B-cell origin, but early PTLD can manifest as plasmacytic hyperplasia or as a polymorphic lymphoid process.[42] When PTLD affects the tonsils and adenoids, it often is of the plasmacytic hyperplasia type. When PTLD is seen in the lymph nodes, it is often a polymorphic lymphoid lesion. Treatment of PTLD includes decreasing the immunosuppression, to which most patients respond. When a transplant recipient presents with enlargement of the tonsils and adenoids, removal of the affected tissue (i.e., by tonsillectomy and adenoidectomy) is indicated to evaluate the tissue for PTLD. Removal of the affected tissue often is curative. Other therapies for PTLD include intravenous immunoglobulin, interferon alfa, antiviral therapy (with acyclovir or ganciclovir), and immunotherapy with donor T-lymphocyte infusion.

A correlation between EBV infection and PTLD is well documented.[43] In immunosuppressed patients, the T-lymphocyte response to the EBV infection is suppressed and the B-cell proliferation turned on by the virus infecting the B-lymphocytes is allowed to proceed unchecked. Thus, EBV seronegativity at the time of transplantation is a risk factor for the development of PTLD, because active EBV infection after transplantation can initiate this polyclonal response from the B lymphocytes infected with the Epstein-Barr virus.

Sarcomas

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, representing 13% of all pediatric malignancies. Rhabdomyosarcoma is the third most common neoplasm in childhood after neuroblastoma and Wilms' tumor. The annual incidence of this tumor in children younger than 20 years of age is 4.3 cases per 1 million children, affecting approximately 350 children in the United States each year.[44] Approximately 35% of these children present with disease in the head and neck. Sites of involvement include the orbit, nose and paranasal sinuses, oropharynx, soft tissues, nasopharynx, and external ear or mastoid. Because of the high possibility of contiguous spread to the CNS, the paranasal sinuses, infratemporal fossa, middle ear, and nasopharynx are classified as parameningeal sites.

In the 1960s, fewer than one third of children with rhabdomyosarcoma survived, but cure rates now approximate 70%, largely reflecting advances made by the Intergroup Rhabdomyosarcoma Study Committee (IRSC).[45,46] Before the formation of the IRSC in 1972, the relatively small numbers of patients, short follow-up times, and the confounding effects of varied treatments limited univariate and multivariate analyses, especially for small subgroups of patients. However, when three pediatric centers agreed to pool patients and investigate resources, it became possible to identify prognostic variables of crucial importance for stratifying patients in clinical trials. Valid comparisons of alternative therapies were developed, and therapies were tailored according to the risk of relapse. The data obtained through the collaborative, multimodality therapeutic protocols developed and studied by the IRSC have allowed a steady improvement in the curability of rhabdomyosarcoma, especially the locally extensive tumors.

Presentation and Evaluation

A majority of affected children are younger than 6 years of age when the diagnosis of rhabdomyosarcoma is made.[47] The spectrum of presenting signs and symptoms varies greatly depending on the site of the primary tumor, the age of the child, and the presence or absence of metastatic disease. Presentation in the head and neck most frequently is heralded by a local swelling. Fewer than one half of these children have pain. Nasal discharge or obstruction, signs of cranial nerve

involvement, otorrhea, hearing loss, fetor, and proptosis are even less frequent.[48]

The orbit is involved in nearly one third of rhabdomyosarcomas of the head and neck,[48] with the typical presentation being that of a rapidly developing, unexplained proptosis. In decreasing order of frequency, rhabdomyosarcoma also affects the oral cavity and pharynx (29%), the face and neck region (24%), and the ears and sinuses (9%). Nasopharyngeal and paranasal sinus involvement can cause nasal obstruction or epistaxis, and otitis media, facial nerve palsy, or tumor filling the ear canal is often the presenting symptom of temporal bone disease.[49]

The diagnostic workup of children with suspected rhabdomyosarcoma must address two complementary issues: the nature and extent of the primary disease and the presence or absence of locoregional or metastatic disease. To assess the former, CT and MRI are essential. To assess the latter, common sites for metastases must be evaluated, including the lungs, bone, and bone marrow. A minimal test battery consists of complete blood count, serum electrolyte panel, liver and renal function tests, baseline coagulation studies, CT scan of the chest, a ^{99m}Tc-diphosphonate bone scan, and bilateral aspiration and biopsy of iliac bone marrow.

Surgery is a necessary part of the diagnostic and staging evaluation and is an essential component in the Intergroup Rhabdomyosarcoma Study Clinical Grouping Classification (IRSCGC) (Table 200-5). Although this staging system is widely used, it was revised in 1991 and the primary tumor, regional lymph nodes, and distant metastasis (TNM) classification is now used for Intergroup Rhabdomyosarcoma Study (IRS) patients in IRS groups IV and beyond. For instance, patients in IRSCGC group III represent a heterogeneous collection of patients who have resectable and unresectable tumors, depending on the experience of the institution. As surgery techniques have advanced, especially in the skull base, and reconstructive techniques such as microvascular reconstruction are more widely available, complete extirpation often is feasible for rhabdomyosarcoma in the head and neck.[48] In some centers, however, surgery may be limited to partial removal or excisional biopsy to establish the diagnosis. Additional important variables that were not considered in the IRSCGC were the degree of local extension and the status of the primary echelon nodes. To address these shortcomings, the IRSC now uses the TNM classification, similar to that used to characterize disease extent in adults with solid tumors (Table 200-6).

Table 200-5

Intergroup Rhabdomyosarcoma Study Clinical Grouping Classification*

Group	Definition
I	Localized disease, completely resected
II	Compromised or regional resections with microscopic residual disease
III	Incomplete resection or biopsy with gross residual disease
IV	Distant metastatic disease present at onset

*Used in Intergroup Rhabdomyosarcoma Studies I through III.

Management

Multimodal, multiagent therapy is the mainstay of management of rhabdomyosarcoma, along with surgical removal or biopsy and radiotherapy for local control. Several different chemotherapeutic agents are used, with appropriate selections based on the initial extent of disease and its site of origin. During the 1980s and 1990s, cisplatin, etoposide, and dacarbazine have been used in combination for rhabdomyosarcoma. Other agents used include ifosfamide and either etoposide or doxorubicin for new and recurrent rhabdomyosarcoma. IRS IV looked at combinations of these drugs; for metastatic rhabdomyosarcoma, it found that the combination of ifosfamide and doxorubicin improved outcome.[50] Some children, such as those with orbital rhabdomyosarcoma, require less intensive, two- or three-drug therapy and do well. By contrast, children with metastatic disease require extremely intensive therapy and still do poorly. Although they respond to initial chemotherapy, 75% relapse within 18 to 24 months.[51] To improve this outcome, efforts are ongoing to develop new active chemotherapeutic agents and to use dose-intensifying regimens with hematopoietic growth factors or autologous hematopoietic progenitor cells.

Radiotherapy is required to eradicate residual tumor cells at the primary site or to treat gross persistent disease. Guidelines for dosage and radiation fields evolved during the IRS I, II, and III. Local control is achieved in 80% to 90% of children using 4000 to 4500 cGy for microscopic residual disease and 4500 to 5000 cGy for tumors larger than 5 cm.[52] Prophylactic irradiation of clinically uninvolved regional nodes is unnecessary. With parameningeal tumors, 4500 to 5500 cGy is required. With overt parenchymal, meningeal, or cerebrospinal fluid involvement, whole-brain irradiation and intrathecal chemotherapy are indicated.[53,52] Hyperfractionation was evaluated in IRS IV as an approach to maintain local control rates and to reduce late side effects. Hyperfractionation did not result in significant improvement in local disease control over conventional radiation therapy.[54] Radiation therapy guidelines in IRS V have been simplified, with the basic emphasis placed on reducing the dose of radiation for most patients. This is being

Table 200-6

TNM Pretreatment Staging Classification for IRS Study IV

Stage	Sites	T*	Size	Nodes†	Metastases‡
1	Orbit, head and neck (excluding parameningeal), genitourinary (excluding bladder/prostate)	T1 or T2	A or B	N0, N1, or Nx	M0
2	Bladder/prostate, extremity, cranial parameningeal sites, other (includes trunk, retroperitoneum)	T1 or T2	A	N0 or Nx	M0
3	Bladder/prostate, extremity, cranial parameningeal	T1 or T2	B	N0, N1, or Nx	M0
4	All	T1 or T2	A or B	N0 or Nx	M1

*Tumor: T1, confined to anatomic site of origin; T2, extension or infiltration into surrounding tissue (A ≤5 cm in diameter; B >5 cm in diameter).
†Nodes: N0, no distant metastases; Nx, clinical status unknown; N1, clinically involved.
‡Metastases: M0, no distant metastases; M1, distant metastases present.
IRS, Intergroup Rhabdomyosarcoma Study; TNM, tumor-node-metastases.

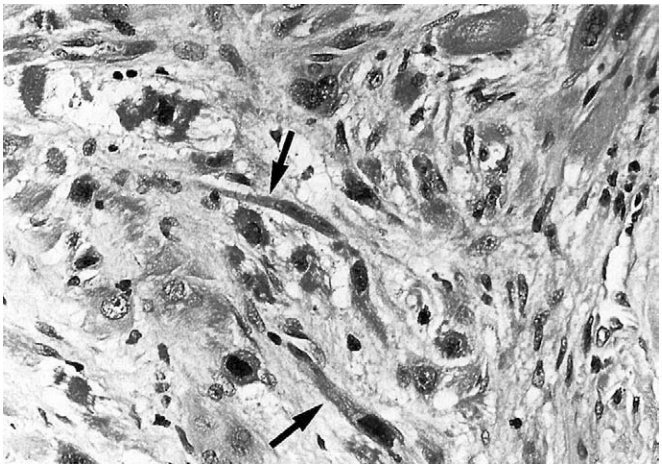

Figure 200-4. Embryonal rhabdomyosarcoma. The cells show a mixture of shapes but a spindled or elongated morphology is evident overall. Strap cells *(arrows)*, which resemble primitive muscle cells and are classically described in rhabdomyosarcomas, are easily seen in this example but may be difficult to identify in some cases. Immunohistochemical staining for muscle-specific markers can be useful in these instances. (Original magnification, 350×.)

accomplished in conjunction with delayed surgical resection of alveolar type tumors or initially unresectable tumors in anatomically unfavorable sites. With the refinement of aggressive craniofacial and intracranial surgical techniques that minimize postoperative morbidity, surgery is playing a more important role in selected patients with head and neck rhabdomyosarcoma. Specifically, if the tumor can be completely resected, the patient can avoid radiotherapy and its long-term complications, with no compromise in survival. Patients who are able to have complete removal of their tumors fare much better than those in whom gross residual tumor is left behind. Complete resection of skull base–parameningeal rhabdomyosarcoma is now more often a reality with advances of skull base surgery techniques and use of free-tissue transfer techniques for reconstruction.[55] In addition, salvage surgery after cytoreductive combination chemotherapy and radiotherapy can be offered to convert a partial response (PR) or stable disease (SD) to a complete response (CR).[56] For most children in group III, intensification of therapy using a risk-based study design has significantly improved management outcome. The largest gains have been realized in children with gross residual tumor after biopsy. In selected patient subsets, it also has been possible to decrease therapy.[57]

Histopathology and Molecular Biology

The histologic classification of rhabdomyosarcoma is based on the resemblance of these tumors to normal fetal skeletal muscle before innervation. The first formal classification was proposed by Horn and Enterline[58] in 1958 and subsequently was adopted by the IRSC and the World Health Organization. Subtypes include embryonal, botryoid (a subtype of embryonal), alveolar, and pleomorphic. Embryonal rhabdomyosarcoma of the botryoid subtype is the most common variant, accounting for 60% of tumors. It is characterized by variable amounts of spindle and primitive cells that are either tightly packed or loosely dispersed in a myxoid background. Rhabdomyoblasts are present in a variety of shapes, leading to unusual designations like tadpole, racquet, or strap cells (Fig. 200-4). The botryoid subtype accounts for 5% of cases and tends to arise in the mucosa-lined organs of the nasopharynx, external auditory canal, and genitourinary tracts. It is characterized grossly by the presence of polypoid masses and microscopically by the presence of subepithelial aggregates of tumor cells known as the cambium layer. Metastases are rare and the prognosis is excellent. Alveolar rhabdomyosarcomas are diagnosed in 20% of affected children and are characterized by the presence of fibrovascular septa that form alveolus-like spaces that contain freely floating monomorphous round malignant cells with abundant eosinophilic cytoplasm. Pleomorphic rhabdomyosarcomas show features of both embryonal and alveolar subtypes but are uncommon in children.[46] Cytogenetic studies of alveolar rhabdomyosarcoma have identified frequent chromosomal rearrangements and amplification. The most commonly recognized translocation events, t(2;13) and t(1;13), are found in 64% and 18% of cases, respectively.[59] The result is fusion of the *PAX3* gene on chromosome 2 or the *PAX7* gene on chromosome 1 with the *FKHR* gene on chromosome 13. In the case of *PAX3*, the new chimeric transcription factor excessively activates transcription from binding targets of wild-type *PAX3*. Molecular assays for *PAX3-PAX7* fusion genes have identified additional cases that do not have cytogenetically detectable rearrangements. On the basis of these more sensitive studies, the overall frequency of *PAX3-PAX7-FKHR* chimera appears to be higher than 90%.[8] Also, the presence of the *PAX3-FKHR* and *PAX7-FKHR* gene fusions correlate with poor clinical outcome. The prevalence and presumed importance of these fusion genes in tumorigenesis suggest that drugs designed to block their intracellular activity may be effective chemotherapeutic agents.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

NRSTSs of childhood have a combined annual incidence of approximately 2 to 3 cases per 1 million and comprise a large number of uncommon tumors, including fibrosarcoma, dermatofibrosarcoma protuberans (DFSP), epithelioid sarcoma, synovial sarcoma, malignant fibrous histiocytoma, hemangiopericytoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, liposarcoma, and soft tissue clear cell sarcoma.[47] Although rhabdomyosarcoma accounts for 60% of soft tissue sarcomas in children younger than 5 years of age, NRSTSs account for approximately 75% of all soft tissue sarcomas in teenaged patients (15 to 19 years of age).[44] The diagnostic evaluation for a child with a suspected NRSTS is identical to that for a child with rhabdomyosarcoma because tumor distinction is impossible on clinical grounds alone. This limitation makes it imperative to obtain enough tissue to establish a diagnosis without compromising the possibility of future surgical extirpation.

The rarity of these tumors has made the IRSCGC the most commonly used staging system (see Table 200-6), although the TNM system for soft tissue sarcomas in adults also has been applied by modifying the histologic grading classification.[60,61] The pathologic evaluation of these tumors typically takes into consideration factors such as necrosis, mitotic activity, cellularity, matrix formation, and pleomorphism. Because specific chromosome translocations define many of the soft tissue sarcomas, measures of ploidy and the demonstration of certain molecular genetic abnormalities will undoubtedly prove valuable in guiding prognostically based management protocols in the future.

Currently, the most important factors determining the likelihood of cure are histologic grade and tumor resectability.[62] The latter is particularly important for high-grade malignancies. Unfortunately, tumor size and invasiveness preclude complete resection in 30% to 50% of cases, and long-term locoregional control with adjuvant chemoradiotherapy usually is unsuccessful in the presence of either gross residual or metastatic disease (1 of 26 survivors with gross residual or metastatic disease versus 29 of 36 survivors with completely resected tumors or microscopic residual disease). Although the roles of radiotherapy and chemotherapy have not yet been standardized, data from the NCI Pediatric Branch indicate that a substantial number of children may benefit from appropriate intense multimodality therapy. Management of these children should be based on selected clinical protocols designed to assess responsiveness and long-term outcome.

Fibrosarcoma

Fibrosarcoma is a rare malignancy of the head and neck, with only 7 of 53 cases (13%) reported by the Armed Forces Institute of Pathology and 22 of 110 cases (20%) reported by Soule and Pritchard.[63] Neck disease occurs most commonly, followed in descending order of frequency by involvement of the oral cavity, scalp, auriculoparotid region, and face.[64] Hematogenous and lymphatic spread are extremely rare.[65]

Children of all ages are affected and typically present with an asymptomatic, slowly enlarging mass.[66] In infants, a unique form of

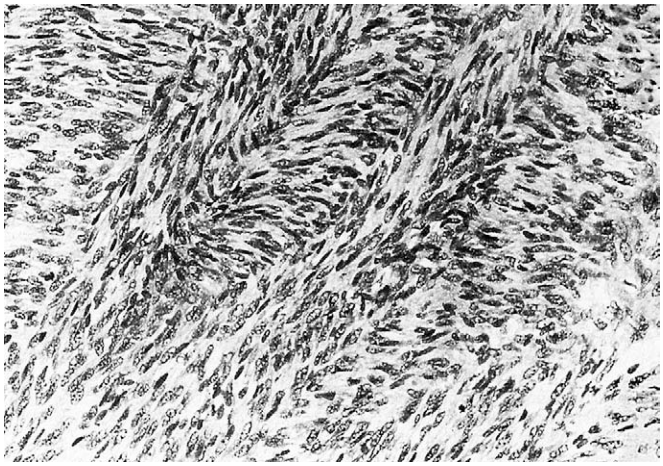

Figure 200-5. Fibrosarcoma. Discrete fascicles of spindle cells form intersecting patterns, sometimes producing a herringbone effect. (Original magnification, 200×.)

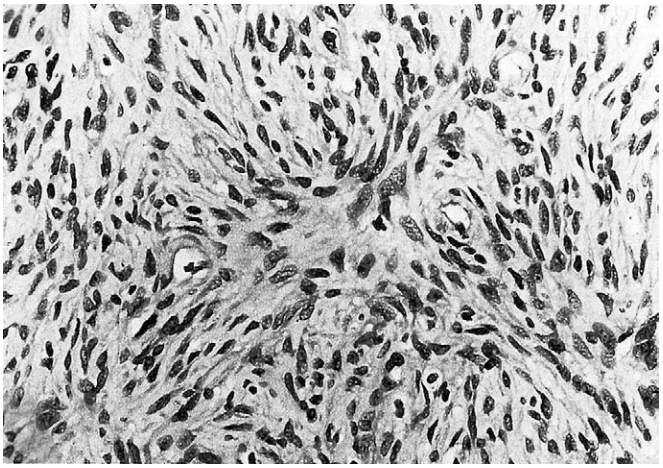

Figure 200-6. Dermatofibrosarcoma protuberans. This intermediate-grade malignancy is in the group of fibrohistiocytic tumors. Many of the tumors in this group have plump spindle cells arranged in patterns frequently described as cartwheel, whorling, or storiform (from the Latin *storea*—a rush mat) because of its woven appearance. (Original magnification, 275×.)

congenital fibrosarcoma occurs that is considered a histologically low-grade fibrosarcoma.[67] Although these tumors can be large, the long-term outlook is quite good, perhaps reflecting an enhanced sensitivity to chemotherapeutic agents. Some unresectable congenital fibrosarcomas respond to preoperative chemotherapy, permitting a later, less mutilating surgical procedure with clear margins.[68,69] By contrast, fibrosarcoma is more aggressive in older children, survival rate is lower, and the impact of multimodal therapy is not obvious. Management requires wide local excision to optimize the chances of survival. The absence of a true capsule makes intraoperative assessment of the degree of tumor spread difficult.

The excised mass typically is gray-tan with hemorrhagic and necrotic areas.[70] Composed mostly of spindle-shaped fibroblasts or myofibroblasts with scanty cytoplasm, histologic grading is possible and is based on degree of cellularity, cellular maturity, and amount of collagen production (Fig. 200-5). Cytogenetic studies have shown an association with trisomies of chromosomes 8, 11, 17, and 20.[71,72] Karyotyping studies show a recurring t(12;15) translocation.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a nodular cutaneous tumor with a high propensity for local recurrence after simple excision. It usually appears as a firm, solitary, flesh-colored nodule, although multiple masses or an area of induration can occur. The trunk is the favored site of involvement, followed by the extremities and the head and neck, especially the scalp and supraclavicular fossa.[73]

Approximately 12% of affected persons are older children,[73] but dermatofibrosarcoma protuberans has been diagnosed in patients younger than 10 years of age. Time to diagnosis may exceed 2 years, with size at diagnosis up to 2 cm. Management requires wide excision for a successful long-term outcome, reflecting the "pseudocapsule" and finger-like extensions of this tumor. With surgical margins less than 2 cm, recurrence rates approximate 40%; with margins wider than 2 cm, recurrence rates drop to 25%; and with margins wider than 3 cm, few recurrences are reported.[74,75] However, given the regional anatomy of the head and neck, achieving a 2.5- to 3-cm margin can be difficult. Even with Mohs' technique, extensive surgery may be required.[76] Although local recurrence rates of 50% to 70% are reported, with repeated procedures, 90% of affected patients can be rendered free of disease.[77] Consensus is lacking regarding the cell of origin of dermatofibrosarcoma protuberans. The primary mass usually is grossly encapsulated and well circumscribed, although it can send multiple pseudopod-like projections laterally and deeply (3 cm or more).[78] These extensions are easily missed on histologic sectioning. Histologic examination shows elongated cells with a storiform organization (Fig. 200-6).

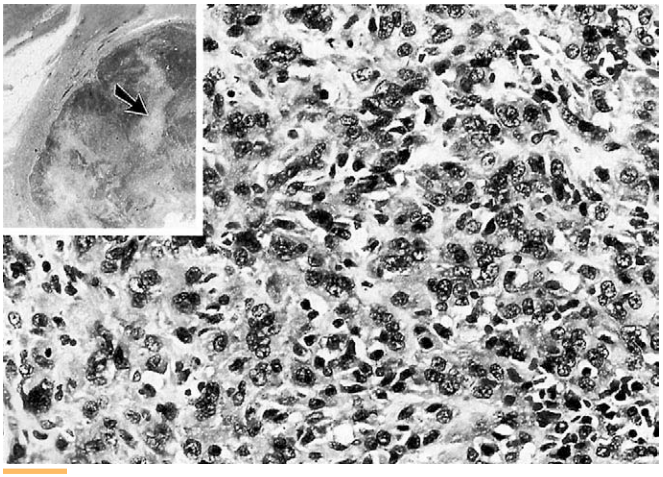

Figure 200-7. Epithelioid sarcoma. This unusual tumor is composed of epithelial-like cells that have polygonal-shaped cytoplasm. The lower-power view *(inset)* reveals a distinct nodular appearance. Necrosis *(arrow)* in the center of the nodules is characteristic. (Original magnification, 400×; low-power inset: original magnification, 5×.)

Epithelioid Sarcoma

Epithelioid sarcoma can easily be confused with a variety of benign and malignant conditions such as necrobiotic granuloma, rhabdoid tumor, rhabdomyosarcoma, and Ki-1 lymphoma.[79-82] It occurs throughout infancy and early childhood, although most individuals are not diagnosed until the second to fourth decades of life.[83] Approximately 10% of cases involve the head and neck, produce nontender, nonulcerated swelling, and follow a protracted course of repeated local recurrences with eventual distant metastases. More aggressive tumors that metastasize early are uncommon. Once the diagnosis has been made, complete surgical resection should always be attempted because the role and efficacy of chemotherapy and radiotherapy have not been clearly established.

The characteristic histologic pattern is one of nodules separated by fibrous septa (Fig. 200-7). The cells inside the nodules are polygonal, are variable in size, and may cluster, suggesting squamous differentiation. Areas of necrosis and an inflammatory infiltrate are common. The molecular biology of epithelioid sarcoma has shown multiple structural changes, most frequently the deletion of 1p21-22.[83]

Neuroectodermal Tumors

Neuroblastomas

Neuroblastomas are the most common extracerebral solid tumors of infancy and childhood.[84] Their annual incidences in white and nonwhite children under 15 years of age are 10.4 and 8.3 per 1 million, respectively.[85] Arising from primitive neuroectodermal cells of neural crest origin as embryonal tumors of the sympathetic nervous system, neuroblastomas can develop wherever sympathetic nervous tissue is found. Primary tumors occur paravertebrally along the sympathetic chain from the neck to the pelvis and from paraganglia from the adrenal medulla, the organ of Zuckerkändl, or the retroperitoneal, inguinal, paratesticular, testicular, oviductal, or ovarian paraganglia. The most unusual aspect of this tumor is the frequent occurrence of spontaneous regression, typically in infants with a small primary tumor, liver involvement, subcutaneous nodules, and patchy bone marrow infiltration without major replacement of hematopoietic cells.[86]

Presentation and Evaluation

Primarily a tumor of infancy and early childhood, as many as 50% of cases are diagnosed in infants younger than 1 year of age and 80% are detected in children younger than 5 years of age.[87] Presenting signs and symptoms depend on the site of the primary lesion, the presence and site of metastases, and the secretion of hormones and vasoactive substances. The most common site of origin is the adrenal medulla or adjacent retroperitoneum, but 2% to 5% of neuroblastomas develop in the head and neck region.

Primary cervical tumors generally are detected at an earlier age and at a lower stage than tumors detected elsewhere, reflecting the greater facility with which abnormalities in the neck are recognized. Laryngotracheal or pharyngeal compression can lead to airway obstruction, dysphagia, or aspiration. Ipsilateral ptosis occurs if the superior cervical ganglion is involved. Primary neuroblastoma of the orbit may cause proptosis, periorbital ecchymoses (panda eyes), and ocular muscle paresis. However, more subtle findings such as edema of the conjunctivae or eyelids, papilledema, and retinal hemorrhage may be noted. Because the sympathetic nervous system is intimately associated with the development and maintenance of eye color, heterochromia irides is possible.[88] Another finding peculiar to the head and neck is the cardiofacial syndrome, or "asymmetrical crying face." This type of congenital facial weakness becomes most apparent with crying and reflects disease involvement of the motor cortex, the nucleus or peripheral root of cranial nerve VII, or the muscles of facial expression.[89]

Paraspinal neuroblastoma may extend through adjacent intervertebral foramina into the spinal cord (*en sablier* tumors) to produce paraplegia. Although this finding is most commonly associated with mediastinal and retroperitoneal tumors, it can occur with cervical disease.[90,91] Neuroblastoma also is a noteworthy cause of congenital paraparesis; clinical features of neurologic dysfunction in neonates are difficult to recognize, however, and diagnosis may be delayed.

The diagnostic and metastatic evaluation of children with neuroblastoma of the head and neck requires multiple imaging studies, immunocytochemistry studies, routine histologic examination, and cytogenetic analysis. For suspected cervical disease, CT and MRI to evaluate the neck should be complemented by abdominal CT and MRI, chest radiograph, bone scans, and bone marrow aspirates and biopsies to appropriately stage the tumor. The International Neuroblastoma Staging System (INSS) was developed in 1991 to help stage patients uniformly for clinical trials and biologic studies. The staging system is based on clinical experience with neuroblastoma, reflecting the degree of tumor burden, surgical resectability, and the pattern of metastatic spread (Table 200-7).

Several genetic markers have been identified in neuroblastoma tumors correlating with clinical course, but determination of the best predictors awaits further study in large numbers of patients. These markers include tumor cell DNA index, *MYCN* gene copy number, allelic loss of 1p, and unbalanced gain of 17q. *MYCN* amplification occurs in approximately 25% of primary neuroblastomas and amplification is associated with advanced stage and poor prognosis. Tumor markers such as catecholamine metabolites, ferritin, neuron-specific enolase, lactate dehydrogenase, and the disialoganglioside G_{D2} are helpful in diagnosis and disease monitoring but have largely been replaced by genetic markers (e.g., *MYCN* amplification) for risk stratification.[86] The frequency of abnormal elevations depends on disease burden and therefore hampers detection of neuroblastoma at an early stage. Catecholamines and their metabolites (vanillylmandelic acid, homovanillic acid, and dopamine) are elevated in 90% to 95% of children with neuroblastoma and have been very successfully developed by the Japanese for use in urine screening programs despite high false-negative rates.[92] Tests on 115,000 infants suggest that a majority of neuroblastomas can be discovered before the age of 1 year, when prognosis is most favorable.[92]

Table 200-7

International Neuroblastoma Staging System

Stage	Description
1	Localized tumor with complete gross resection, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor (enlarged contralateral lymph nodes must be negative microscopically)
3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stages 1, 2A, or 2B), with dissemination limited to skin, liver, or bone marrow (limited to infants younger than 1 year of age)

Management

Management of neuroblastoma is determined by the stage of disease and sites of involvement. Patients are stratified into low-, intermediate-, and high-risk groups based on the various prognostic variables available (age at diagnosis, INSS stage, tumor histopathology, DNA content of the tumor, and *MYCN* amplification). Treatment of stage I neuroblastomas consists of surgical removal. Chemotherapy is the main modality of treatment in intermediate- and high-risk patients. Radiation therapy is also used, but by itself is not curative due to the high rate of metastatic disease. In the head and neck, surgical intervention most commonly implies excisional biopsy for stages II, III, and IV. A cervical sympathetic ganglion is usually involved and is resected. Adjacent, enlarged nodes should also be removed, although a formal radical neck dissection is not required.[93] In cases in which complete resection would cause unacceptable morbidity, a second surgical procedure can be planned

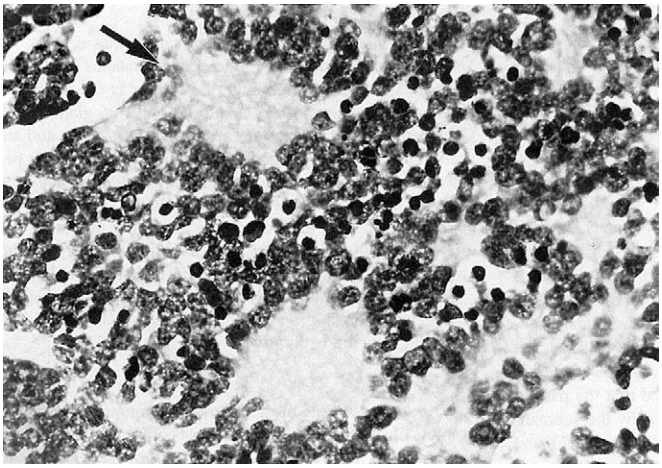

Figure 200-8. Neuroblastoma. Small blue cells characterize this neoplasm. The differential diagnosis of "small blue cell" tumors in children also includes lymphoma and peripheral neuroectodermal tumor/Ewing's sarcoma. Other tumors can also be considered in this group. Neuroblastoma can be differentiated by its relatively uniform cell appearance and neurofibrillary material between the cells. Pseudorosettes (Homer-Wright rosettes) are illustrated *(arrow)* but often are not seen. Immunohistochemical marking and electron microscopy can be useful to demonstrate neural-associated proteins or neural-associated structures (e.g., neurosecretory granules). (Original magnification, 425×.)

12 to 24 weeks after completion of chemotherapy.[94] Unfortunately, despite the large number of chemotherapeutic agents that are active in newly diagnosed patients, long-term remission remains elusive for children older than 1 year of age with INSS stage IV disease (approximately 45% of all children with neuroblastoma).

Histopathology and Molecular Biology

Grossly, neuroblastoma is a discrete solid mass with well-circumscribed contours. Coagulative necrosis may develop in nonviable areas, sometimes with dystrophic calcification. Microscopically, the tumor represents one of the "small blue cell" neoplasms of childhood that is exquisitely susceptible to smear or crush artifact. Iatrogenic damage may obscure cytologic details, making it difficult to make an unequivocal histologic diagnosis.[95] The prototype neuroblastoma is composed of small uniform cells that are 7 to 10 mm in diameter and have dense hyperchromatic nuclei with minimal perinuclear cytoplasm (Fig. 200-8). Immunohistochemistry has revolutionized diagnostic histopathology, and a battery of selected antibodies is used to evaluate specific cellular and subcellular aspects of these neoplasms.

Elucidation of molecular biology also has affected diagnosis and management protocols. Deletions in the short arm of chromosome 1 (1p36) are the most common structural aberration and identify children with a poor prognosis.[84] A less frequent abnormality is amplification of the N-*myc* oncogene.[96,97] This event is associated with advanced stages of disease and rapid tumor progression, perhaps because amplification usually accompanies 1p deletions.

The clinical implication of these studies is that infants with 1p deletions, N-*myc* amplification, and diploidy or tetraploidy are at high risk for recurrence and require aggressive therapy at diagnosis. Management failures appear to be a result of the development of multidrug resistance associated with overexpression of multidrug resistance–associated protein, even when a diverse range of structurally and functionally unrelated chemotherapeutic agents is used.[98]

Based on advances in the molecular biology of neuroblastoma, priorities for future trials will include defining subsets of children who do not require therapy, improving durability of remissions for disseminated disease by exploiting cytokines for dose intensification, defining the place of autologous bone marrow transplantation, exploring means for reversing drug resistance, evaluating tumor-targeted radiotherapy, and identifying new active chemotherapeutic agents.

Ewing's Sarcoma Family of Tumors

Ewing's Sarcoma and Peripheral Primitive Neuroectodermal Tumor

Ewing's sarcoma (ES) and peripheral primitive neuroectodermal tumor (PPNET) are now considered to be in the same spectrum of malignancy—the Ewing's sarcoma family of tumors (ESFTs). Based on molecular genetic and cytogenetic information, both of these tumors are now known to be of neural crest origin. The chromosomal translocation [t(11;22)(q24;q12)] is present in 85% of ESFTs.[99] This reciprocal translocation results in the formation of an *ews*-fli1 fusion gene. ES is a neuroectodermal tumor primarily affecting the long bones and pelvis. Extraosseous ES can occur in soft tissue. A more differentiated form of ES, PPNET (or neuroepithelioma) also can occur in bone or soft tissue. Both ES and PPNET appear similar on histochemical staining and share a unique nonrandom translocation. ESFTs occur primarily in the second decade of life and are seen in whites but rarely in blacks in the United States and in Africa. Although these tumors are primarily found in the extremities, pelvis, chest wall, and spine-paravertebral region, they can manifest in the head and neck as a primary or metastatic tumor. Cure can be expected in up to two thirds of patients with localized disease.

Evaluation of patients with ESFT should include plain films and MRI studies of the primary site, CT scan of the chest, bone scans, bone marrow aspiration and biopsy, complete blood count, baseline blood chemistry studies, and serum lactate dehydrogenase determination. Surgery, radiation therapy, and chemotherapy all are important modalities in treatment. Virtually all patients will have metastases or microscopic metastatic disease at presentation; therefore, chemotherapy is always needed.

Salivary Gland Malignancies

Childhood malignancies of the salivary glands are rare. In a review of 2135 children under 16 years of age who developed salivary gland tumors, only 17 (0.79%) malignancies were recorded (15 [0.7%] mucoepidermoid and 2 [0.09%] acinar cell carcinomas).[100] Most of these malignancies involved the parotid gland. Other authors have confirmed this bias, and from an overview of nine different studies, Rasp and Permanetter[101] concluded that the parotid gland is the favored site (88.5%), followed by the submandibular gland (7.7%), the minor salivary glands (3.3%), and the sublingual gland (0.5%). A unique feature of these tumors is that most appear to be induced by radiation.[102]

Presentation and Evaluation

Children with salivary gland malignancies usually are in their second decade of life at diagnosis. The majority also are survivors of another malignancy, most frequently acute lymphoblastic leukemia diagnosed 10 years earlier for which cranial radiotherapy was required.[103] Chemotherapy, age at the time of therapy, and genetic susceptibility are additional risk factors that may contribute to the development of secondary salivary gland malignancies.[102]

Regardless of location, the most common presentation is as an asymptomatic mass, although facial nerve involvement occasionally accompanies parotid gland disease.[103] The presence of cervical adenopathy does not imply metastatic disease. It more likely reflects common childhood reactive hyperplasia seen as a sequela of repeated upper respiratory infections. Evaluation by CT and MRI is helpful to delineate tumor boundaries and for planning surgical resection.

Management

Salivary gland malignancies in children should be excised. Although the primary principle of surgical excision is accepted, the extent of the procedure and the value of multimodal therapy are not as clearly defined. For parotid gland disease, superficial or total parotidectomy is required, and unless tumor invasion dictates otherwise, the facial nerve should be spared. Complete excision should also be the goal for tumors

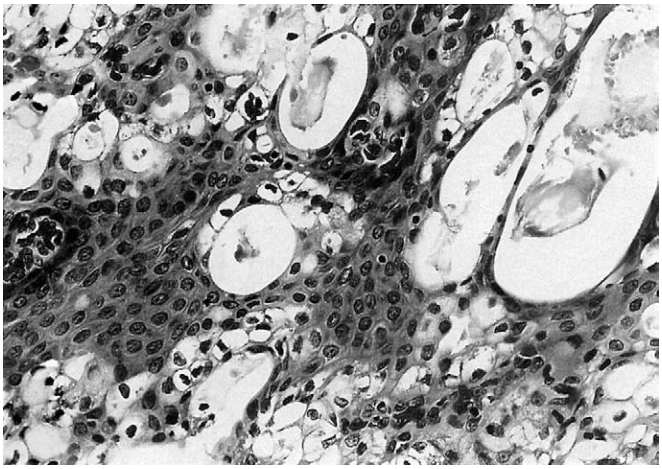

Figure 200-9. Mucoepidermoid carcinoma. Mucus-producing and squamous tumor cells are the prime histologic components of mucoepidermoid carcinomas. Mucous cells containing rounded intracytoplasmic mucous droplets are evident along with pavement-like squamous cells with distinct cellular boundaries. Larger cysts containing mucus also are present. (Original magnification, 320×.)

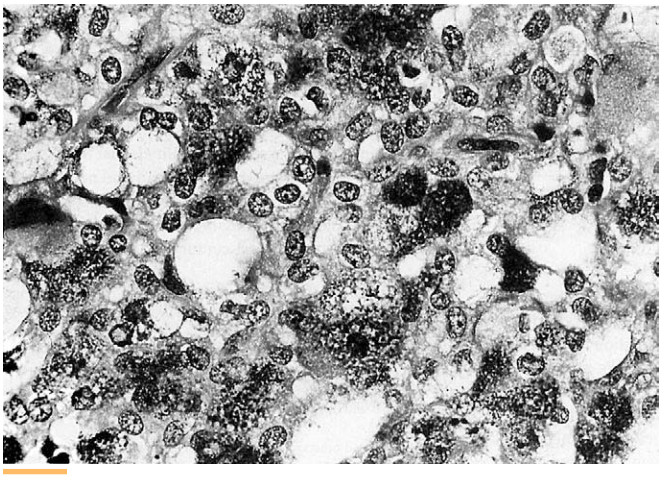

Figure 200-10. Acinic cell carcinoma. Tumor cells appear similar histologically to normal acinar unit cells, but their lack of arrangement of organization into functional units helps in differentiation. These cells have a granular appearance, and some show large basophilic granules. Microcystic changes are seen in this case. (Original magnification, 420×.)

of the submandibular, sublingual, and minor salivary glands. Radiotherapy is reserved for children with high- or intermediate-grade malignancies of the major salivary glands and high-grade malignancies of the minor salivary glands. The value of radiotherapy as adjuvant therapy in intermediate-grade tumors of the soft palate is debatable. Routine use of elective neck dissection for patients with clinically negative necks is not recommended or beneficial for children with malignant salivary gland disease. Chemotherapy with cisplatin-based drugs is reserved for palliation or metastatic disease.

Histopathology and Molecular Biology

Mucoepidermoid and acinic cell carcinomas account for 60% of childhood salivary gland malignancies (45% and 15%, respectively),[104] although the former is the only type that has been diagnosed in the intraoral salivary glands.[105,106] Mucoepidermoid carcinomas are usually low grade and are seldom fatal (Fig. 200-9), whereas acinic cell carcinomas behave like their adult counterparts (Fig. 200-10). Probably the only epithelial salivary gland tumor unique to children is the embryoma, or sialoblastoma.[107] Recognized only in newborns or during the first year of life, this malignancy is morphologically similar to stages in the development of the embryonic anlage of salivary gland tissue. Fewer than one quarter of such tumors show either biologic or histologic signs of malignancy, and complete surgical excision is curative.[107]

Table 200-8

Teratoma Types

Type*	Distribution of Cases (%)	Frquency of Hydramnios (%)	Mortality Rate (%)
I	12.4	56	100
II	45.6	23	43.4
III	17.1	8.1	2.7
IV	14.3		3.2
V	10.6		43.5

*I, moribund neonate or stillborn infant; II, neonate with respiratory distress; III, neonate without respiratory distress; IV, child 1 month to 18 years of age; V, adult.

Teratomas

Teratomas are the most common extragonadal germ cell tumors of childhood. They arise most commonly in a midline or paraxial location from the brain to the sacral area and involve the head and neck in 1 of every 40,000 births.[108] In this region, sites of involvement include the soft tissues of the neck (cervical teratomas), superficial facial structures in and about the temporal fossa and zygomatic area, oral cavity, oronasopharynx, and orbit.[109]

Presentation and Evaluation

More than 75% of cervical teratomas are diagnosed in neonates, two thirds of whom have respiratory distress significant enough to cause stridor.[62] Hydramnios, stillbirth, and premature labor are other frequent accompaniments.[109] This information, in addition to age at diagnosis and respiratory ability, was used by Jordan and Gauderer[110] to define five different disease types (Table 200-8). The high mortality rate in the adult group (type V) reflects the correspondingly high rate of malignant transformation. By contrast, death in neonates usually results from respiratory obstruction as a result of lesion bulk and location. Malignant degeneration is much less common, although it does occur.

Rothschild and associates[111] described seven neonates with teratomas that metastasized to the cervical nodes, lungs, and liver. The metastatic deposits were composed of either mature glial tissue or a mixture of mature and immature elements. Differentiation suggests that the presence of metastases does not necessarily portend a bleak prognosis.[112] This impression was supported by the findings of Rothschild's group,[111]: Death was secondary to metastatic disease in only one patient with metastases. Benign teratomas arising in the paranasal sinuses are extremely rare, and all of the malignant lesions of the sinonasal tract have occurred in adults.[109]

Management

The recommended treatment for head and neck teratomas is surgical excision. When a neonate is experiencing respiratory difficulty, the first priority should be stabilization of the airway. In utero diagnosis of a large cervicofacial teratoma will allow time for perinatal planning of the ex utero intrapartum treatment (EXIT procedure), to secure the infant's airway before the maternal-fetal circulation is divided.[113]

Histopathology and Molecular Biology

Teratomas in neonates and infants contain tridermic tissue elements: ectoderm, endoderm, and mesoderm. Although the preponderant tissue is most often neuroepithelium, other tissues that can be involved include fetal cartilage, myogenic tissue, and epithelium (squamous, ciliated, columnar, enteric, and endocrine). In type II and type III teratomas, malignancy is not equated with the degree of immaturity of the tissue elements and instead reflects immaturity of the host (Fig. 200-11).[109]

Thyroglossal Duct Carcinomas

Thyroglossal duct carcinoma may arise in a thyroglossal duct cyst, although this is a rare occurrence. It may be an incidental finding on removal of the benign-appearing cyst or may manifest as a midline enlarging mass with features suggestive of malignancy, especially if the cyst has a largely solid character. Treatment consists of complete removal along with the midline portion of the hyoid bone, as is done in the Sistrunk procedure. Close follow-up is necessary along with thyroid suppression.[114] Prophylactic total thyroidectomy is necessary if metastasis to the thyroid gland is detected. Incidence of papillary carcinoma in the remaining thyroid gland is 25%. Therefore, some workers recommend prophylactic total thyroid gland removal.[115]

Figure 200-11. Teratoma. Multiple cell types in a haphazard arrangement are evident in this low-power view showing squamous cells *(open arrow)*, mucus-containing goblet cells *(curved arrow)* lining a cyst, and smooth muscle cells *(solid straight arrow)*. (Original magnification, 50×.)

Histiocytoses

The histiocytoses are a family of disorders of histiocytes that can range in clinical importance from focal and easily controlled to fatal. The histiocytoses are diseases of histiocytes. Accordingly, infiltration or accumulation of cells of the monocyte-macrophage series is seen in the involved tissues. A majority of the histiocytoses are not malignant but proliferative lesions, possibly disorders of immunoregulation. It is thought that perhaps the initiating event for the histiocytoses is immunologic stimulation of a Langerhans cell, an antigen-presenting cell, which then continues proliferating in an uncontrolled manner. The International Histiocyte Society has proposed the classification system shown in Table 200-9.[116] Class I histiocytosis, formerly known as histiocytosis X, is now known as *Langerhans cell histiocytosis*, which includes the diseases formerly classified under the histiocytosis X label: eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease.

Pathology

Grossly, the lesions of Langerhans cell histiocytosis are granulomatous. By light microscopy, Langerhans cells are seen. By electron microscopy, Birbeck granules are seen. The lesions may be purely histiocytic or may be a mixture of histiocytes and eosinophils.

Clinical Presentation and Evaluation

The clinical presentation varies from an asymptomatic lytic bone lesion, found incidentally on radiographs, to generalized manifestations such as diabetes insipidus, fever, or weight loss. The first step in the evaluation and management of a patient with such a lesion must include a biopsy of the involved tissue. Care must be taken with the biopsy, because Langerhans cells with Birbeck granules can be found in normal skin. Pathologically, the diagnosis can be confirmed by Birbeck granules on electron microscopy, or by CD1a-positive staining in lesional cells. S100 immunostaining also is present in Langerhans cell histiocytosis cells and not on normal histiocytes. Once the lesion is identified

Table 200-9

Classification of Childhood Histiocytoses

Class I	Class II	Class III
Dieases included: Langerhans cell histiocytosis	IAHS; FEL; grouped together as the hemophagocytic lymphohistiocytoses (HLH)	Malignant histiocytosis; acute monocytic leukemia; true histiocytic lymphoma
Cellular characteristics of the lesions: Langerhans cells with cleaved nuclei and Birbeck granules seen on electron microscopy; cell surface antigens include S100 and CD1a; cells mixed with varying proportions of eosinophils; multinucleated giant cells sometimes seen	Morphologically normal, reactive macrophages with prominent erythrophagocytosis; process involves entire reticuloendothelial system	Neoplastic cellular proliferation of cells exhibiting characteristics of macrophages or dendritic cells or their precursors; localized or systemic
Proposed pathophysiologic mechanisms of the histiocytoses: Immunologic stimulation of a normal antigen-presenting cell—the Langerhans cell—in an uncontrolled manner	Histiocytic reaction secondary to an unknown antigenic stimulation (FEL) or to an infectious agent (IAHS), with erythrophagocytosis possibly reflecting foreign antigens adsorbed on erythrocytes or activation of macrophages by excess lymphokine production because of abnormal immunoregulation	Neoplasm; clonal autonomous uncontrolled proliferative process

FEL, familial erythrophagocytic lymphohistiocytosis; IAHS, infection-associated hemophagocytic syndrome.

as being in the histiocytosis family, the workup should include a complete blood count, skeletal survey, a CT scan of the head, liver function tests, coagulation studies, and determination of urine osmolality after water deprivation. Monostotic bone disease (formerly known as eosinophilic granuloma) clearly carries a better prognosis than polyostotic bone disease (formerly known as Hand-Schüller-Christian disease). The fulminant presentation, formerly known as Letterer-Siwe disease, is most commonly seen in infants younger than 2 years of age.

Treatment

Class I histiocytoses can be treated with curettage, excision, intralesional steroids, systemic steroids, or low-dose radiotherapy. Curiously, single monostotic lesions often regress spontaneously after biopsy, curettage, or steroid injection. If a single lesion is not resolving and is threatening a vital structure, low-dose radiotherapy, in the range of 500 to 800 cGy, can be curative,. The role of chemotherapy is reserved for multisystem involvement and widespread disease. The agents used are vinblastine and etoposide, with or without steroids. In general, the poor-prognosis groups are those comprising children younger than 2 years of age and children with organ dysfunction (liver, bone marrow, lungs). Unfortunately, little gain has been obtained in the treatment of the 15% of cases of Langerhans cell histiocytosis that are resistant to treatment or progress in a fulminant fashion. In an effort to optimize therapy for disseminated Langerhans cell histiocytosis, the Histiocyte Society opened a prospective, randomized treatment study in 1991, LCH-1. LCH-1 showed that vinblastine and etoposide are equivalent drugs in terms of response, toxicity, survival probability, probability of disease reactivation, and sequelae.[117] LCH-1 also identified lack of rapid response to treatment (less than 6 weeks) as another poor prognostic indicator. Other experimental treatment approaches include bone marrow transplantation, and 2-chlorodeoxyadenosine (an antimetabolite) for severe cases.

Class II histiocytoses, infection-associated hemophagocytic syndrome and familial erythrophagocytic lymphohistiocytosis (FEL), are diseases of the mononuclear phagocytic cell series, excluding Langerhans cells (see Table 200-9). The histiocytic reaction in these disorders is presumed to be from an underlying pathogenic process. FEL is usually rapidly fulminant and fatal, despite chemotherapy. Because the cells causing this disease are benign, it is not surprising that chemotherapy is usually not successful. Bone marrow transplantation is currently being studied in a controlled study and the initial results have been encouraging.

Class III histiocytoses are the only malignant histiocytoses (see Table 200-9). Three types are recognized: acute monocytic leukemia, malignant histiocytosis, and true histiocytic sarcoma. These diseases are treated with systemic chemotherapy.

Sequelae of Management

More than 12,000 children and adolescents under 20 years of age are diagnosed with cancer each year in the United States.[118] The overall survival rate is nearly 80%. A growing population of survivors requires long-term follow-up. The morbidity of managing head and neck cancers in children must be measured not during a 5- to 10-year interval but throughout a lifetime of more than 70 years. As cure rates improve, therapy must be refined to optimize growth potential and fertility and minimize the risk of second malignancies without sacrificing the primary goal of tumor eradication. The immediate sequelae of radiotherapy to the head and neck are similar in both children and adults. Acutely, mucositis, otitis externa, and alopecia are common. Subacutely, somnolence develops in approximately one third of children who receive whole-brain irradiation. Transient demyelination also can occur, leading to a sensation of electrical shocks at various levels below the neck elicited by flexion of the head or torso (Lhermitte's syndrome). Late effects include problems with transverse myelopathy, sensorineural hearing loss, endocrinopathies, and abnormal development of irradiated structures.[119]

Most disheartening of all is the possibility of a second malignancy. This risk is not insubstantial: Children who have survived one malignancy are three to six times more likely to develop another cancer than is the general population.[120] Thus, the risk of a second malignancy in long-term survivors (5 years) of all forms of childhood cancer appears to be 2% to 3%.[121] Contributing factors include radiotherapy, chemotherapy, age at treatment, and genetic susceptibility. Especially vulnerable are children previously treated for retinoblastoma and survivors of Hodgkin's lymphoma who receive mantle irradiation. Reported tumors include acute leukemias; bone and soft tissue sarcomas; and carcinomas of the skin, breast, thyroid, and salivary glands.[102]

Because children can tolerate greater doses or greater dose intensities of irradiation than adults, they also are at higher risk for delayed or chronic toxicities that become evident years after treatment. Growth retardation is found in approximately one third of pediatric brain tumor survivors, and in approximately 10% of pediatric leukemia survivors. Children treated at an age younger than 5 years with irradiation for brain tumors are especially susceptible to the linear growth retardation. Musculoskeletal problems such as scoliosis, avascular necrosis of bone, and osteoporosis are seen in approximately one third of pediatric cancer survivors, secondary to irradiation or steroid use, especially dexamethasone. Dental problems such as arrested tooth development or malocclusion and caries are common with radiotherapy to the facial or pharyngeal areas. Learning problems and neuropsychological problems are seen with cranial irradiation, especially in children younger than 36 months of age. Radiation to the neck also can cause thyroid dysfunction as a late effect.

Most radiation-induced second neoplasms occur more than 15 years after treatment of the first. Unfortunately, as duration of follow-up increases, so does risk.[122] Among chemotherapeutic agents, cyclophosphamide has been implicated in the development of solid tumors. Etoposide, an epipodophyllotoxin that acts by inhibiting the enzyme topoisomerase II, has been implicated in the development of second leukemias. The sobering reality is that the treatment of primary malignancies of the head and neck in children is extremely toxic, and the burden of a successful outcome can be immense. Addressing these issues remains a challenge for the 21st century.

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CHAPTER TWO HUNDRED AND ONE

Salivary Gland Disease in Children

Gresham T. Richter

David L. Walner

Charles M. Myer, III

Key Points

- A good history and physical examination is the best tool in diagnosing salivary gland problems in children.
- Ultrasound with or without fine-needle aspiration is useful for diagnosis of most parotid and submandibular gland diseases in children who are tolerant of the procedure.
- For complete evaluation of the nature and extent of salivary gland masses, cross-sectional imaging with CT or MRI with contrast is necessary.
- Inflammatory conditions are the most frequently encountered salivary entities in young children.
- Salivary neoplasms are uncommon in children, mostly occur in the second decade, and are malignant in more than 50% of cases.
- The incidence of mumps virus parotitis is waning since the advent of the mumps vaccine. Beyond mumps, common viral etiologies of parotitis include Epstein-Barr virus, parainfluenza viruses, and adenovirus.
- A solid, firm, and fixed salivary mass that persists for greater than 6 weeks is an appropriate candidate for open surgical biopsy.
- Hemangiomas are the most frequently encountered benign tumors of the parotid gland. Pleomorphic adenomas are the most common benign epithelial tumors.
- Mucoepidermoid carcinoma is the most common malignancy of the parotid and most common tumor secondary to radiation exposure.
- Persistent sialorrhea beyond 4 years of age is considered abnormal and should be investigated for treatment including medical (glycopyrrolate) and surgical (submandibular gland excision and parotid duct ligation) options.

Salivary gland disease is an uncommon but manageable condition in the pediatric population. Inflammatory conditions of the salivary glands are more frequently encountered because salivary tumors account for only 1% of all childhood neoplasms. Infections can be either acute (bacterial and viral) or chronic (ductal obstruction, mycobacterial, and granulomatous disease) with the parotid being the most frequently affected gland. When a persistent salivary gland mass is present, possible neoplastic and congenital processes should be explored with an understanding that the risk of malignancy for salivary tumors is greater in young children. A complete differential diagnosis includes inflammatory, neoplastic, vascular, congenital, traumatic, and a myriad of less common diseases (Table 201-1). Clues gleaned from a thorough history and physical examination can help identify the disease in each pediatric patient. Ultrasound, computed tomography, magnetic resonance imaging, and fine-needle aspiration (FNA) have proven to be safe and valuable diagnostic tools for delineating inflammatory from benign and malignant salivary gland conditions (Figs. 201-1 to 201-3). Chronic sialorrhea (drooling) is a frequent and chronic problem, especially in neurologically impaired children, that can be addressed with both medical and surgical therapy.

Anatomy

The salivary system consists of the major paired parotid, submandibular, and sublingual glands and the minor salivary glands. All salivary glands are derivatives of ectoderm. During their development, they pierce the surrounding mesenchyme and arborize before terminating into multiple acini. The parotid gland lies between the external auditory canal, mandibular ramus, and mastoid tip. It is separated, by the stylomandibular ligament, from the submandibular gland, which rests between the anterior and posterior digastric tendons just below the body of the mandible. Both glands are covered by the superficial portion of the deep cervical fascia that either envelops (parotid) or separates (submandibular) the gland from adjacent lymph nodes. The largest salivary gland is the parotid, which is located in the parotid space harboring the facial nerve, external carotid artery, and retromandibular vein. It is artificially divided into two lobes, the deep and superficial, by the facial nerve. Accessory parotid glands with a connection to the parotid duct can be identified along the masseteric muscle in 20% of people. Although rare, agenesis of the parotid gland has also been reported.

An arborized draining system leads to a single and final secretory duct for both the parotid and submandibular glands known as Stensen's

Table 201-1

Differential Diagnosis of Pediatric Salivary Gland Disease

Inflammatory		Congenital	Neoplastic				
Acute	**Chronic**	**Cysts**	**Benign**	**Malignant**	**Traumatic**	**Autoimmune**	**Other**
Bacterial	*Obstructive*	Dermoid	*Vascular Anomaly*	*Epithelial*	Penetrating cheek	Benign lymphoepithelial	Allergy
Suppurative	Sialectasis	Branchial cleft	Hemangioma	Mucoepidermoid	Blunt gland trauma	disease	Medication induced
Lymphadenitis	Sialolithiasis	Branchial pouch	Lymphatic malformation	carcinoma	Radiation injury	Sjögren's syndrome	Chronic sialorrhea
Viral	Mucocele	Congenital ductal	Arteriovenous malformation	Acinic cell carcinoma			Systemic conditions
Mumps	cyst		Venous malformation	Adenocarcinoma			Obesity
EBV	*Granulomatous*		*Epithelial*	Adenocystic carcinoma			Prader-Willi
Parainfluenza	Mycobacterial		Pleomorphic adenoma	*Nonepithelial*			Cystic fibrosis
HIV	Actinomycosis		Cystadenoma	Rhabdomyosarcoma			
	Sarcoid		lymphomatosum	Lymphoma			
			Monomorphic adenomas				

EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

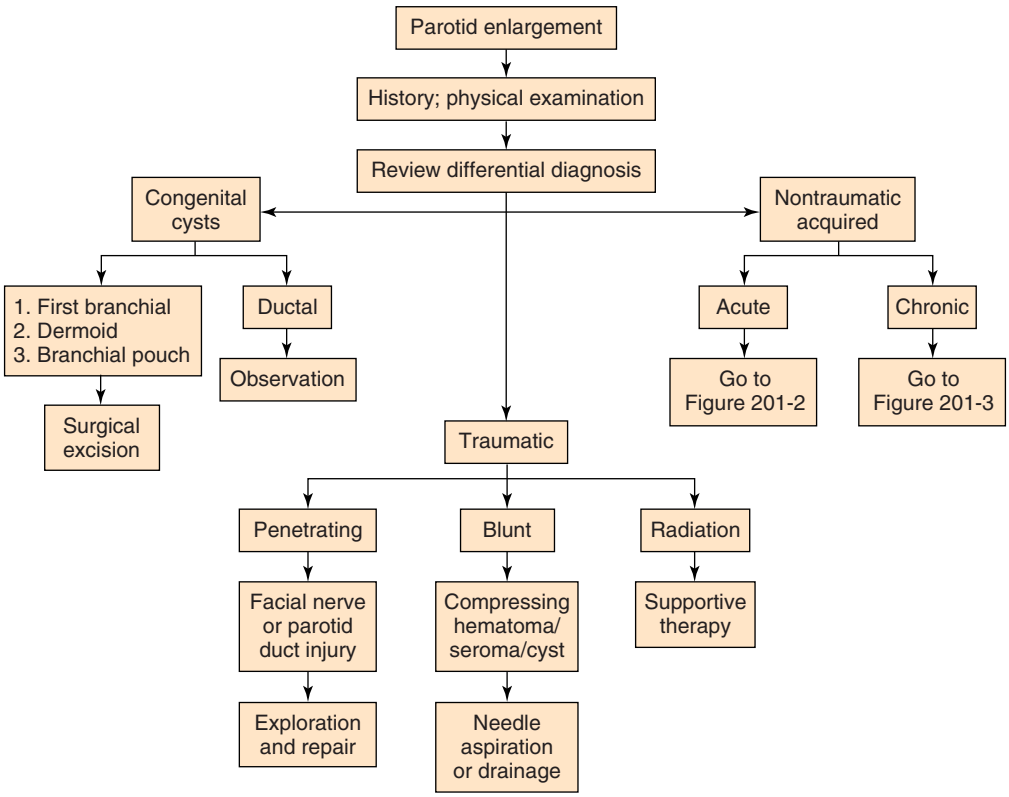

Figure 201-1. Parotid enlargement.

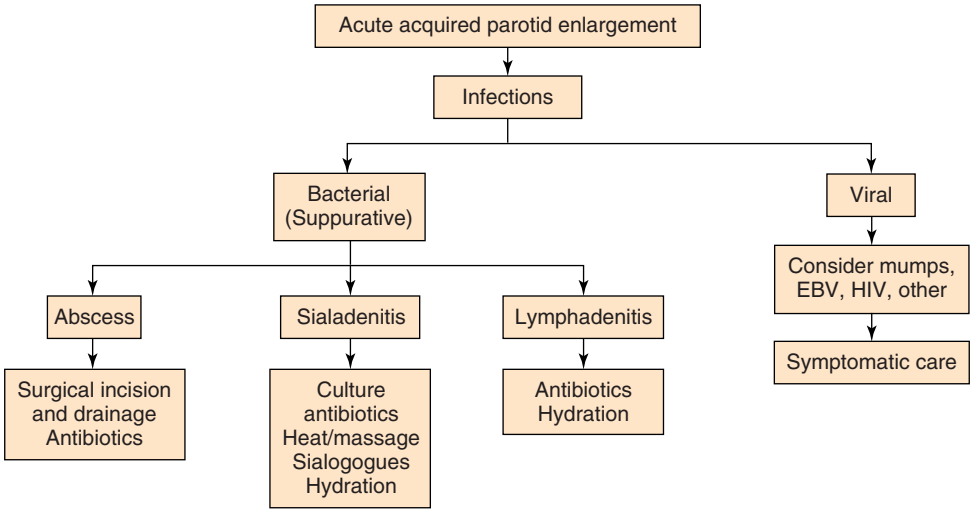

Figure 201-2. Acute acquired parotid enlargement. EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

and Wharton's ducts, respectively. The sublingual glands are located in the floor of the mouth immediately below the mucosa and drain at its medial surface via 10 to 12 small ducts (ducts of Rivinus). They are the source of mucoid cysts, otherwise known as *ranulas,* which are frequently discovered in young children. The remaining upper aerodigestive tract is lined by literally hundreds of minor salivary glands that lie just deep to the mucosa. The highest concentration of minor glands are in the buccal, lingual, labial, and palatal regions. Each minor gland uses only one draining duct. Occlusion of these ducts can lead to small mucoceles. Frequently found along the lower lip of young children, treatment involves excision or marsupialization.

A few salient differences exist in the anatomy of the salivary system and its adjoining structures in children and adults. In infants the parotid gland is lighter and rounder. It lies wedged between the masseter muscle and the ear and gradually grows during childhood over the surface of the parotid duct. The facial nerve exits the skull base just deep to the subcutaneous tissue to enter the parotid gland in children younger than 2 years of age, making it particularly prone to traumatic injury. Thereafter, formation of the tympanic ring and mastoid tip allows the facial nerve to take a deeper and more protected position behind the mastoid bone and tragal cartilage. Similarly, after exiting the stylomastoid foramen, the nerve takes a more abrupt and lateral course in children than in adults, with the marginal mandibular nerve often riding in a superficial course over the mandible. These variations in facial nerve anatomy contribute to parotid and mastoid surgery as common iatrogenic causes of facial paralysis in children. Familiarity

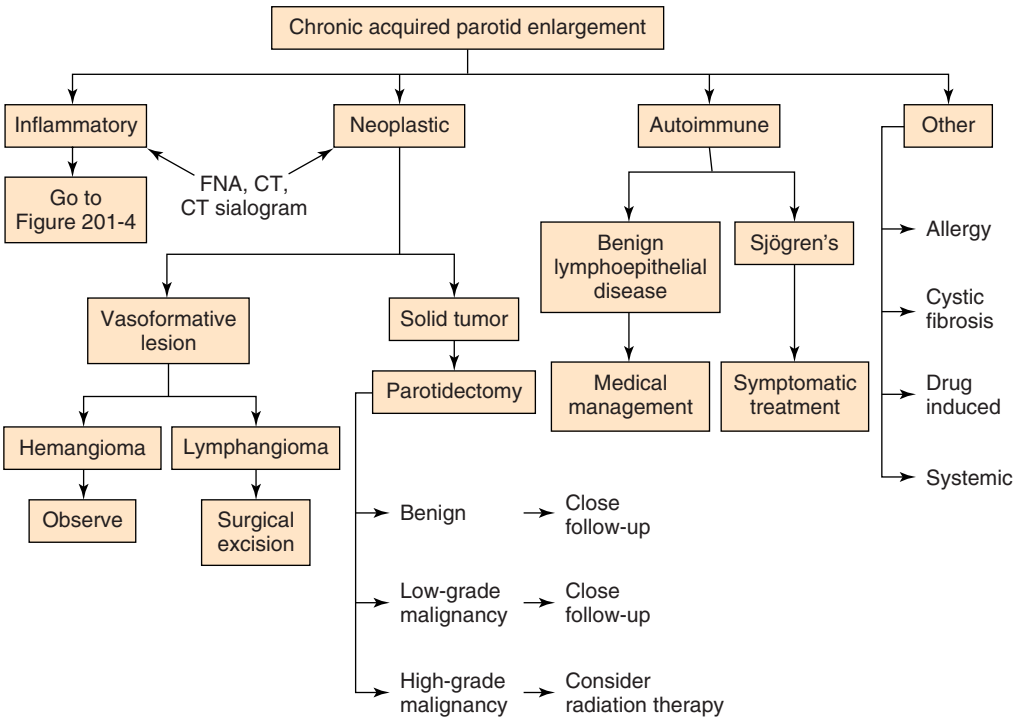

Figure 201-3. Chronic acquired parotid enlargement. CT, computed tomography; FNA, fine-needle aspiration.

with pediatric anatomy is thereby recommended before operating in a young patient.

In addition, the submandibular and sublingual glands are small in infants. Rapid growth of up to five times their initial size occurs during the first 2 years of life. Surgeons should be aware that, in very young children, the sublingual and submandibular glands are often anatomically contiguous.

Physiology of the salivary glands is thoroughly addressed in Chapter 84. Briefly, salivary flow is controlled by the superior salivatory nuclei (submandibular and sublingual glands) and inferior salivatory nuclei (parotid gland) via the autonomic nervous system. Only a small amount of saliva is secreted during the night because resting salivary flow increases during the day and peaks in the late afternoon. Resting salivary secretions are produced predominantly by the submandibular (60%) and sublingual (10%) glands with the submandibular glands creating the bulk of the fluid. The production of parotid secretions, which are serous in nature, is increased during eating. Saliva produced from all glands is critical for deglutition and acts as an infectious barrier for the mucosa and dentition by creating a surface coat of mucoid secretions, enzymes (e.g.. lysosyme), and immunoglobulins (IgA). In select children, excessive saliva and drooling (sialorrhea) can lead to aspiration, pulmonary compromise, mouth and skin maceration, and social isolation.[1] These patients often require medical or surgical therapy, or both, to reduce salivary flow from the major glands.

History and Physical Examination

A thorough history is the most important tool in diagnosing salivary gland problems in children. The onset, duration, and severity of symptoms provide valuable clues to the pathologic nature of the problem and allow the practitioner to quickly delineate among neoplastic, congenital, and inflammatory processes. Congenital disorders such as hemangiomas and cysts will often become evident shortly after birth. Neoplastic processes are more frequently seen in children older than 10 years.[2-4] In contrast, an inflammatory condition is the most common salivary pathology in toddlers and is marked by acute onset, brief duration, and painful swelling. Chronic conditions may be more difficult to differentiate by history alone, but gradual and painless growth at or near salivary tissue is suspicious for neoplasm until proven otherwise. Intermittent swelling associated with eating will signify salivary duct obstruction by stones or strictures, whereas recurrent and diffuse bilateral cheek swelling may indicate recurrent parotitis or chronic sialectasis.

The location and number of glands involved should be elicited in the history. Diffuse edema of the involved gland suggests inflammatory disease while focal and palpable lesions are the hallmark of neoplasm (Fig. 201-4). Bilateral involvement suggests systemic conditions. The character, quality, and quantity of the salivary secretions are also important. Serous secretions suggest a viral etiology, whereas malodorous purulent material indicates bacterial disease. The presence of fever, chills, or a recent upper respiratory infection should also be ascertained. An immunization history for mumps vaccine should be obtained. Questioning should elicit any history of trauma including injury from blunt or sharp objects, animal scratches, or recent dental procedures. The presence of congenital anomalies or cysts should be identified. Awareness of any underlying systemic diseases, which may include immune deficiency, allergy, or autoimmune disease, can be helpful.

The physical examination should include bimanual palpation of all major salivary glands. This consists of simultaneous palpation of the salivary gland structures in both intraoral and extraoral manners. This will also help distinguish salivary gland enlargement from cervical lymphadenopathy. It is important to identify whether the mass is cystic or solid, tender or nontender, and mobile or fixed. Facial movement (CN VII) should be assessed for subtle asymmetry or weakness. Symmetry and mobility of the tongue (CN XII) and sensation of the tongue (CN V) should be checked. Fixed nodules, cervical lymphadenopathy, and facial nerve involvement suggest malignant disease. Floor-of-mouth masses with enlarged perifacial lymph nodes need to be assessed for submandibular malignancy. Careful inspection of the salivary gland orifices should be performed with attention focused on the quantity (minimal, adequate, or excessive) and consistency (serous or suppurative) of the salivary content during palpation or "milking" the gland. Repeat examination may be helpful and necessary to follow the natural history of the disease.

Laboratory Studies

Laboratory studies are helpful in diagnosing and following salivary gland disease in children. If an infectious etiology is present, the leukocyte count will assist in determining whether adequate therapy is

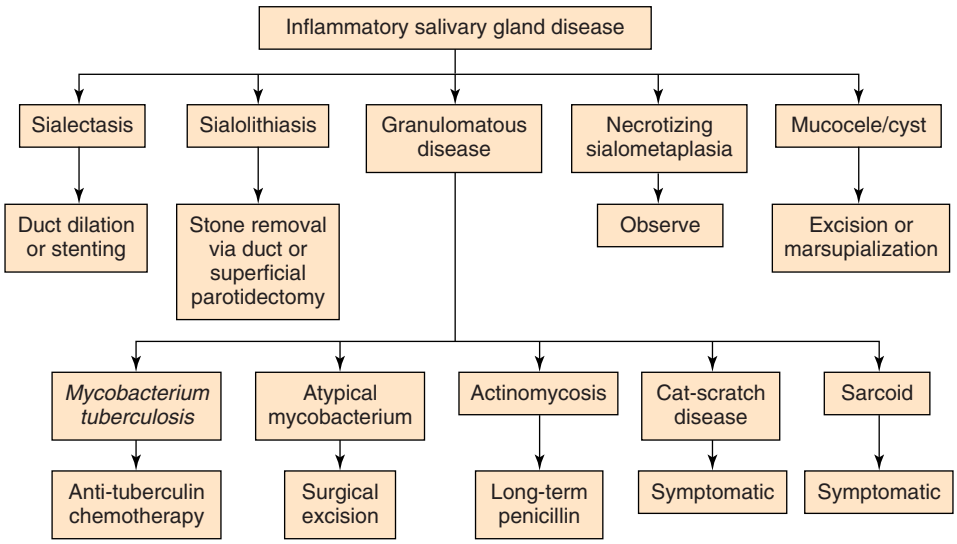

Figure 201-4. Inflammatory salivary gland disease.

being used. C-reactive protein is another nonspecific marker for bacterial infections and can be followed for treatment progress. Patients with risk factors or suspicion for human immunodeficiency virus (HIV) must be tested appropriately. A purified protein derivative (PPD) skin test and chest radiograph are employed in the pediatric population with salivary disease when mycobacterial infections (tuberculosis and atypical) are considered. Aerobic and anaerobic cultures of purulent material draining from duct orifices may help direct antibiotic coverage.

FNA is an easy and relatively safe technique for the diagnosis of palpable or deep-lying salivary masses. This can often be employed as an adjunct to diagnostic ultrasonography during the evaluation of pediatric salivary masses. With a well-trained cytopathologist, FNA can be an effective tool in diagnosing difficult lesions. In adults, up to 93% of benign and malignant lesions of the salivary glands can be differentiated.[5] Unfortunately, FNA is not commonly employed in the pediatric population because sedation or general anesthesia is often required. Moreover, pediatric pathologists are not universally versed in identification of salivary tumors due to the rarity of neoplasms in this population. Nonetheless, the unique architecture of pleomorphic adenoma and Warthin's tumor often makes it easy to diagnose them by FNA. Cytologic evaluation of sialadenitis shows polymorphonuclear leukocytes in a background of necrotic cellular debris. Cultures may also be obtained from aspirated contents at the time of FNA. Cystic lesions and poorly differentiated carcinomas are more difficult to assess by FNA and should undergo excisional biopsy for definitive answers.

In general, unusual and longstanding salivary masses should undergo FNA in tolerant pediatric patients before a surgical plan is developed. Surgical resection of discovered malignancies by FNA can be designed more appropriately. Misdiagnoses and nondiagnostic results are rare in FNA of pediatric head and neck masses. Regardless, most fine-needle aspirates lead to the diagnosis of a chronic inflammatory condition and can offset the use of open procedures in pediatric patients.[6,7]

Radiology

Radiographic imaging has played an increasing role in the diagnosis and perioperative decision making for salivary gland lesions. Improved radiographic instruments have allowed practitioners to delineate inflammatory and benign disease from malignant processes. Commonly employed techniques include plain film radiography, ultrasonography, sialography, radionucleotide scanning, computed tomography (CT), and magnetic resonance imaging (MRI). New MR technologies such as dynamic contrast-enhanced MRI, diffusion-weighted MRI, and MR spectrscopy have proven helpful in better differentiating benign from malignant salivary gland tumors.[8]

In children, ultrasonography is the most useful tool in evaluating salivary gland pathology and can be employed as a primary radiographic modality in nearly all cases. Ultrasound is an expedient, safe, and relatively painless technique that is ideal for examining pediatric patients. Ultrasonography can identify and assess adjacent vascular structures, distinguish focal from diffuse disease, clarify cystic from solid masses, and guide FNA. Lesions can be measured and easily followed with repeat examinations. The location of obstructing calculi within salivary ducts, despite their radiolucency, can be identified clearly with ultrasound. Nearly all sialoliths greater than 2 mm in size can be detected. Additional advantages to ultrasonography include low cost, avoidance of radiation, and avoidance of anesthesia.

Simple plain film radiography has become a less frequently used imaging tool for pediatric salivary masses as imaging speed and quality has improved in more informative radiographic tools such as CT and MRI. However, plain films remain easy to perform and detect the presence of radiopaque ductal stones within the major salivary glands. Unfortunately, up to 20% of submandibular calculi and 80% of parotid calculi are radiolucent and not well visualized with this technique.

Sialography involves the injection of contrast medium into the salivary duct during radiographic imaging in order to outline the salivary ductal system. Similar to plain film radiographs, this technique is gradually being replaced by CT sialography, MRI, and salivary duct endoscopy.[9,10] CT sialography can be valuable for detecting sialolithiasis, ductal dilatation, and strictures of the major salivary glands and has been used to evaluate obstructive disease, inflammatory lesions, penetrating trauma, and mass lesions. A filling defect and dilation of the main duct or intraglandular ducts will be seen when calculi are present. Chronic sialadenitis may show sialectasis or ductal ectasia. Salivary fistula or sialoceles can be picked up using this technique following trauma to a salivary gland.[11] Regardless, in the face of acute sialadenitis, sialography should not be performed because this can exacerbate disease and injure the involved gland.

For complete evaluation of the nature and extent of salivary gland masses, cross-sectional imaging with CT or MRI is necessary. Contrast-enhanced CT is best fitted for evaluating inflammatory conditions such as abscesses, obstructing sialoadenitis, cystic disease, sialolithiasis, and acute inflammation. Imaging should be performed both before and after administration of intravenous contrast. CT is an excellent tool to study both intrinsic and extrinsic masses of the parotid gland, and the relationship of the mass to critical anatomic structures such as the facial nerve are well illustrated with coronal and sagittal reconstructions.[8] The main benefits of CT scans in children are its speed and quietness relative to the slow, claustrophobic, and loud nature of MRI machines.

Bony architecture is better defined by CT and can provide information on the integrity of adjacent bone in malignant processes.

However, in patients with suspected neoplastic disease, MRI provides the best information on the exact location and degree of disease penetration.[11] In malignant processes, tumor infiltration of adjacent structures, soft tissue destruction, perineural spread, and meningeal penetration is best detected by MRI. This provides more information for operative planning. Standard axial T1- and T2-weighted MRI illustrate tumor margins and growth patterns. Coronal images, fat suppression, and gadolinium enhancement help identify perineural spread. Moreover, newer MR techniques have the ability to delineate benign from malignant processes with reported sensitivities and specificities above 90% using dynamic contrast or diffusion weighted methodology.[8] The drawback of MRI is that it can be difficult for children to tolerate and thereby be subject to the risks of sedation or general anesthesia required to perform the procedure.

Sialendoscopy

Sialendoscopy is a novel technique that has gained acceptance as a tool for diagnosing and treating a variety of salivary gland lesions in adults.[12] Since its development in the early 1990s, improvements in instruments and technique have allowed its application in the pediatric population. Semirigid sialendoscopes with external diameters between 1.1 mm and 1.6 mm are now available and can accommodate the pediatric salivary duct orifices. The endoscope includes two channels, one for irrigation and the other for instrumentation. Following routine dilation of the salivary duct, sialendoscopy is performed with continuous irrigation to maintain patency during exploration. This tool is best designed, and has proven applicable, to diagnose and treat obstructive pathology of pediatric unilateral salivary diseases. Diagnosis of salivary duct stenosis can be achieved with this technique, while wire baskets, lithotripsy, and YAG lasers can be simultaneously deployed to address small obstructing sialoliths.[13]

Biopsy

When diagnosis of a salivary mass has proven difficult with other modalities, open surgical biopsy is the next best approach. A solid, firm mass that persists for more than 6 weeks is a good candidate for open surgical biopsy. An incisional biopsy is inappropriate unless lymphoma is present; the cell type must be determined to direct management. An excisional biopsy should be performed following nondiagnostic FNA in a mass with a high index of suspicion for malignancy. Also, when confidence in cytopathology is low or an FNA cannot be performed, excisional biopsy is warranted. For masses within the superficial lobe of the parotid gland, an excisional biopsy will include the whole lobe with identification and preservation of the facial nerve. Occasionally, an isolated parotid tail lesion can be excised without the need for a superficial parotidectomy or facial nerve dissection. Tumors of the submandibular gland require complete excision of the gland and removal of adjacent lymph nodes (perifacial) for appropriate oncologic workup. Local excision with wide margins should be performed with minor salivary gland lesions. Examination of the draining lymphatic beds should be performed both prior and during excisional biopsies. Radiographic imaging with CT or MRI will help assess the extent of deep tissue penetration before elective biopsy.

Inflammatory Diseases of the Salivary Glands

Inflammatory conditions of the salivary glands are rare in children. Acute processes occur in the majority of cases that involve either viral or bacterial disease. The peak incidence is during puberty with most cases occurring between 12 and 18 years of age (>40%).[14] Submandibular disease is most commonly associated with proximal sialolithiasis and should be investigated appropriately. Granulomatous disease is a cause for a significant bulk of cases (primarily in toddlers) due to inflamed periglandular lymph nodes. Similar to adults, immunocompromised children are particularly prone to salivary gland infections and ductal stasis and obstruction and should be monitored closely. The most common clinical manifestation of salivary gland involvement is xerostomia and bilateral painless enlargement of the parotid glands.[15] Autoimmune disorders in children are rare but often manifest as inflammation of the major salivary glands.

Viral

Once the most common cause of viral sialadenitis, the mumps virus has virtually been eliminated as a cause of parotitis in the United States since the institution of the mumps vaccine in 1982. However, a few cases emerge annually in local and migrating patients who are without prior vaccination. The reader is directed to review the current guidelines and contraindications for mumps vaccination, which is beyond the scope of this chapter. However, other viruses can mimic mumps sialadenitis and should be included in the differential of vaccinated children with diffuse bilateral salivary gland disease. Beyond mumps, the most common viral sources of childhood sialadenitis are Epstein-Barr virus (EBV, incidence = 14%), parainfluenza viruses (4%, types 1, 2 and 3), adenovirus, (3%), HHV-6, human immunodeficiency virus, coxsackievirus, and influenza.[16] Most cases of viral sialadenitis are self-limited with conservative management of warm compresses, sialogogues, analgesics, anti-inflammatories, and hydration as the mainstay of therapy. The disease course of a few viral processes deserves special mention.

Mumps

Mumps parotitis is characterized by self-limiting bilateral diffuse parotid and submandibular gland enlargement. The gonads, meninges, and pancreas can also be involved and should be examined in these patients. The disease more frequently occurs during the winter and spring months, with 85% of cases occurring in the pediatric age group. The incubation period is 14 to 21 days, but the contagious period lasts from 2 to 3 days before the development of swelling and lasts until the swelling remits. During the incubation period, the patient develops a prodrome of symptoms including malaise, loss of appetite, chills, fever, and sore throat. The major salivary glands become tender and swollen, and the patient reports trismus and difficulty chewing. Although the duct orifice may be swollen, the saliva is clear. The temperature is elevated to 100° F to 103° F, and the leukocyte count is normal or slightly elevated with lymphocytosis. Although the diagnosis is clinical, amylase levels, complement fixation, and hemagglutination tests can be used for confirmation. Histologic examination reveals extensive cytoplasmic vacuolization of acinar cells. Management is symptomatic, and the swelling usually resolves over several weeks. Complications include sialectasis, exacerbation of diabetes, orchitis, meningoencephalitis, and sensorineural hearing loss (especially unilateral).

Epstein-Barr Virus

EBV is the cause of heterophil-positive infectious mononucleosis and has been implicated as a major cause of acute inflammation of the salivary glands in pubescent children.[16] Disease symptoms range from an asymptomatic infection to fulminant lymphoproliferative disease. EBV is emitted in the saliva and has been colloquially termed the "kissing" disease due to its oral transmission. In fact, 10% to 20% of healthy seropositive persons can shed EBV into their oropharynx.

The long incubation period of EBV ranges from 30 to 50 days. A triad of fever, sore throat, and posterior cervical adenopathy occurs in more than 80% of patients. Lethargy can persist for months in infected patients. The cervical adenopathy can involve the periparotid or perifacial (submandibular) lymph nodes with subsequent involvement of adjacent glands. Again, there is no specific therapy for EBV infection, but improvements in serologic detection have helped practitioners identify disease early and accurately. Children often need weeks of isolation and rest before returning to normal daily activity. Corticosteroids can be used for life-threatening complications but are unlikely necessary in isolated salivary gland cases. Recently, nearly 50% of salivary gland tumors and oral malignancies of nonodontogenic origin have been associated with EBV. Thus in children with rare oropharyngeal or salivary malignancies, isolation of EBV genome by polymerase chain reaction may help families come to terms with the source of such rare tumors.[17]

Human Immunodeficiency Virus

Salivary gland disease is a common manifestation of HIV in infected children. More than 50% of cases of pediatric HIV present with head and neck masses with the majority of patients having major salivary gland enlargement.[18] The enlargement can be lymphoproliferative, cystic, or both, with the parotid glands being the most frequently affected salivary entity. Parotid swelling of various degrees has been found in more than 10% of HIV-positive children.[19] The submandibular and sublingual glands can be involved as well. The incidence of ranula has been shown to be increased in HIV pediatric patients.[20] The high rate of salivary gland involvement is probably related to the presence of HIV within the saliva. Quantitative changes to the saliva can contribute to glandular hypertrophy, reduced salivary flow, stasis of secretions, and xerostomia.[21] Slow continuous enlargement is the hallmark disease in pediatric AIDS patients. The pathophysiology remains elusive. However, in children, bilateral lymphoepithelial cystic enlargement or intraglandular lymph node enlargement of the parotid glands is common. Cystic disease can often be seen in combination with lymphocytic interstitial pneumonitis.[22] Latent manifestation of EBV and cytomegalovirus in these patients may also contribute to salivary gland pathology.

Management of an HIV salivary lesion is generally conservative. Acute symptoms should be managed similarly to other salivary gland disease in healthy pediatric patients with techniques such as sialogogues and warm compresses. Imaging (CT or MRI) will help identify occult pathology. Antibiotic coverage for potential bacterial processes and fluoride treatment to prevent dental caries from xerostomia should also be employed. Consultation with an infectious diseases specialist is appropriate in these complex patients. Needle aspiration is indicated if a salivary lesion in an HIV-positive child grows to an uncomfortable or deforming size. Patients with HIV are particularly susceptible to lymphoma and Kaposi's sarcoma and can present with isolated salivary gland masses. Open biopsy is indicated only for lesions suspected of malignancy (lymphoma, Kaposi's sarcoma) that cannot be identified by FNA.

Bacterial

Primary bacterial salivary gland infections are rare in the pediatric population. Dental infections, periglandular lymphadenitis, and floor of mouth and submandibular triangle processes need to be considered in the differential of acute bacterial sialadenitis because these may be the source of inflamed salivary tissues. When suppurative sialadenitis does present, it most commonly occurs acutely and within the parotid gland. The normally serous saliva of these glands contains limited bacteriostatic activity (lysozymes) compared with the mucinous secretions of the submandibular and sublingual glands and likely contributes to the predominance of bacterial disease occurring in the parotid. Submandibular gland infections are associated with proximal sialolithiasis more than 40% of the time.[14] This is rare for the parotid gland.[23] The primary cause of submandibular infections appears to be salivary stasis of dependent and viscous mucous secretions of the submandibular duct. Predisposing factors include congential Wharton's duct stricture, ductal trauma, dehydration, autoimmune disorders, and congenital sialectasis. Similarly, recurrent sialadenitis has been associated with traumatic injury to the ductal orifices by repetitive biting of the buccal mucosa, dental appliances, and tooth eruption.[24] Retrograde oral bacteria transmission via the salivary ducts is thought be a culprit in disease.

Signs and symptoms of acute bacterial sialadenitis include rapid onset of focal pain, edema, and erythema of the soft tissues overlying the affected gland. Disease is predominantly unilateral. Spiking fevers are often present with symptoms worsening during deglutition. Purulent discharge found draining from the involved gland's duct is pathognomonic for disease. Most children remain nontoxic during acute episodes but, as the acute phase passes, residual induration and enlargement of the gland may persist for several months. Facial nerve paresis is extremely rare. The most common pathogens associated with bacterial sialadenitis are coagulase-positive *Staphylococcus aureus, Streptococcus viridans,* and *Haemophilus influenzae.* Less frequently identified bacteria include *Streptococcus pneumoniae, Escherichia coli, Bacteroides melaninogenicus,* and *Streptococcus micros* (Table 201-2).[25,26] Cultures of aspirated material or swabs of the purulent ductal secretions will help guide antibiotic coverage.

Table 201-2

Acute Suppurative Sialadenitis

Most common	*Staphylococcus aureus* (coagulase-positive) *Streptococcus viridans* *Haemophilus influenzae* *Peptostreptococcus* spp.
Less common	*Streptococcus pneumoniae* *Escherichia coli* *Bacteroides melaninogenicus*

Management includes the use of systemic antibiotics, local heat and massage, fluids, and sialogogues (lemon juice, sour candy). Penicillinase-resistant antistaphylococcal antibiotics are recommended to cover gram-positive and anaerobic organisms until culture results return. Rarely, patients not responding to initial therapy may require intravenous antibiotics and hospitalization. Screening for immunocompromised states is thereby recommended. Bacterial disease not responding to standard therapy should also be evaluated for underlying granulomatous or neoplastic processes including mycobacterial infections, cat-scratch disease, and lymphoma.

Abscess

Persistent inflammation, hyperpyrexia, and progressive edema overlying the parotid gland suggest the possibility of an abscess. The gland will not be fluctuant until late in abscess formation because of the numerous fascial investments within the gland. Ultrasonography can help diagnose and potentially guide FNA of a parotid abscess, so it should be employed initially in these cases. Significant involvement of adjacent structures or evidence of deep soft tissue disease warrants a CT examination of the head and neck. If an abscess is identified, surgical incision and drainage is appropriate. Drainage is accomplished through a standard parotid incision along the preauricular crease, raising a skin flap, and then opening the superficial glandular fascia parallel to the branches of the facial nerve. Drains should be placed, and the wound closed loosely to heal by secondary intention. One must observe for spread of disease into the contiguous fascial spaces of the neck and mediastinum.

Submandibular abscesses are frequently associated with proximal ductal sialolithiasis. Rapid enlargement of the submandibular triangle suggests diffuse disease within this confined space. Patients will complain of submandibular and floor-of-mouth pain shortly after a meal. Extension beyond the submandibular space can lead to Ludwig's angina and airway obstruction and should be treated urgently. Removal of the involved gland is recommended therapy with drainage of the overlying abscess within the submandibular and sublingual fascial compartments. Airway status and the need for temporary tracheotomy should be evaluated when managing patients with Ludwig's angina.

Recurrent Sialadenitis

Repeated infections of the salivary glands have been shown to cause ductal metaplasia, parenchymal restructuring, and an increase in mucin production and quantity of viscous secretions that can lead to recurrent salivary stasis. Patients with recurrent disease present with low-grade edema and tenderness of the gland with slightly purulent secretions. Unfortunately, once the glandular architecture is altered, opportunistic oral flora are more likely to cause recurrent disease. These patients are frequently chronically infected with various organisms, and immunologic dysfunction such as IgA deficiency appears to play a role in its development.[27,28] Broad-spectrum antibiotics should be used and measures to increase salivary flow and reduce viscosity need to be instituted. Ductal dilatation may improve cases of recalcitrant disease. Gland excision remains the last resort for treatment. Although the most effective

and reliable mode of therapy is parotidectomy, many surgeons delay definitive surgery for fear of injuring the facial nerve during surgical dissection. A total parotidectomy with facial nerve preservation is appropriate for recurrent parotitis because superficial parotidectomy alone is thought to increase the risk of recurrent disease.

Neonatal Sialadenitis

Neonatal sialadenitis is more common in the parotid gland than in the submandibular gland. Possible causes of neonatal sialadenitis are anatomic deformities of the oral cavity, dehydration, sialolithiasis, and prematurity. Approximately 40% of neonates with parotitis are premature. The most common organism in neonatal sialadenitis is *S. aureus.* Other organisms identified are *E. coli, Pseudomonas aeruginosa, Moraxella catarrhalis,* and various streptococci. The salivary secretions should be cultured and a Gram stain obtained. The disease is usually limited to a single gland and signs and symptoms of systemic disease may not be seen. Diagnosis is confirmed by physical examination when a warm, tender, erythematous mass is palpated and pus is expressed from the accompanying salivary duct. Appropriate antimicrobial therapy and adequate hydration result in resolution of the disease in less than 1 week. Recurrence is uncommon.[29] Lymphadenitis of nodes surrounding the parotid or submandibular gland, or both, can mimic sialadenitis. This may be difficult to determine on physical examination. Ultrasonography is helpful in cases not responding to conservative medical management (hydration, antibiotics). Infections involving the scalp, face, or nasopharynx need to be considered.

Viral sialadenitis is seen infrequently during the perinatal period but may occur when there is maternal transmission of virus. This is influenced by the onset of maternal disease, the mode of transmission (transplacental or at delivery), the type of virus, and the host's defenses. A mumps infection in the newborn can range from mild to severe and careful observation is necessary. Cytomegalovirus is another potential viral source of sialadenitis in newborns. Diagnosis can be determined by urine examination. However, its course may be devastating and should be considered early in infants with salivary inflammation. Clearly, infants with suspected viral sialadenitis should be isolated from other newborns.

Necrotizing Sialometaplasia

Necrotizing sialometaplasia is a benign, self-healing (reactive) inflammatory process of salivary gland tissue that clinically and histologically mimics a malignant neoplasm. It most commonly affects adults but has been reported in adolescents. It arises in mucus-secreting cells and can be found in the parotid gland, sublingual gland, hard and soft palates, and lower lip. Its clinical appearance ranges from minor submucosal edema with overlying erythema to an erosive ulcer. It usually presents as a painless ulcerated lesion or a nodular swelling. Most cases involving the extrapalatal minor salivary glands and major salivary glands are iatrogenically induced after surgery, trauma, or radiotherapy, with a mean duration of 18 days from the insult to the development of the lesion. In the major salivary glands, necrotizing sialometaplasia occurs secondary to focal lobular sialadenitis and prior surgical manipulation.[25,30] Typically, the process appears as a 1- to 3-cm crater-like ulcerative lesion. Histologically, lobular necrosis is present with pools of mucin that elicit a granulation tissue reaction with associated acute and chronic inflammation. In addition, extensive squamous cell metaplasia is present. The lesion heals spontaneously in 6 to 12 weeks. Although total excision of the lesion may be carried out as definitive therapy, it is not necessary or indicated.[30]

Granulomatous Disease

Granulomatous diseases are characterized by intense inflammatory reactions, sponsored by the host, around a central pathogen or antigen within one or more organ systems. Granulomatous processes, despite the etiology, rarely involve the salivary system. However, several pathogens causing granulomatous inflammation of the major salivary glands have been identified. In particular, actinomycosis, tuberculosis, atypical mycobacterial infections, and sarcoidosis have all been implicated. Their incidence in children remains unknown, but they are considered unusual. In these conditions, salivary gland involvement is often the result of inflamed periglandular lymph nodes. Regardless, granulomatous diseases should be included in the differential of pediatric patients with atypical and chronic salivary gland inflammation.

Mycobacterial

Nontuberculous mycobacterial infections of the salivary glands are most frequently seen in children. The average age at presentation is 16 to 36 months. Cervicofacial lymphadenitis is the most common manifestation. *Mycobacterium avium-intracellulare* accounts for 70% to 90% of cases. Involvement caused by *Mycobacterium bovis* has become less common since the widespread pasteurization of milk. Infection may occur by *Mycobacterium kansasii* and *Mycobacterium scrofulaceum.*[31] Periparotid and submandibular lymph nodes are frequently involved with the formation of cutaneous sinus tracts (Fig. 201-5). The Mantoux test will likely be weakly positive, whereas chest radiography is generally normal. Diagnosis is based on clinical judgment and exclusion of other diseases. FNA may help to rule out an abscess; however, culture results can take 6 weeks until an organism is seen. Management of nontuberculous mycobacterial infections may be conservative but usually requires surgical removal of the disease process. If the parotid gland is affected,

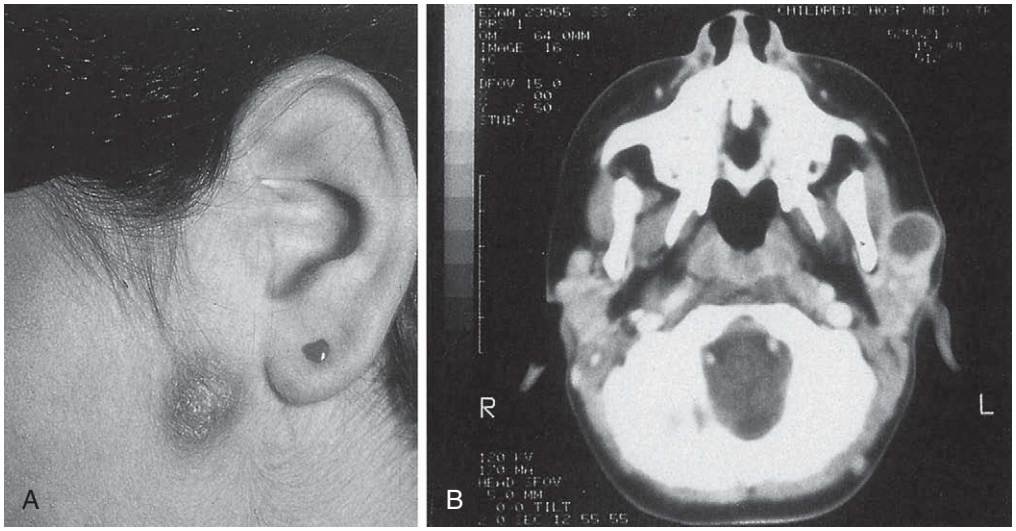

Figure 201-5. **A,** Patient with an atypical mycobacterial infection involving the parotid gland. **B,** Computed tomography with contrast of the same patient. Notice the rim-enhancing parotid lesion.

a superficial parotidectomy with facial nerve preservation is necessary. Removal of involved skin is often necessary during excision. Antituberculous drugs have not been effective in managing this condition. Use of a macrolide (e.g., clarithromycin) as an adjunct to surgery, especially in cases of incomplete excision, appears to be effective in some cases.

Primary tuberculosis of the salivary system is uncommon. No more than 100 cases affecting the salivary glands have been reported, but this disease entity should always be considered in patients with a slow-growing firm to hard nodular mass.[32] The parotid gland is most frequently involved and the disease generally stays unilateral. Primary tuberculosis parotitis is thought to develop from disease spreading via fascial communication with infected tonsils or teeth. Diagnosis may occur by FNA with aspirated material of the involved gland revealing *Mycobacterium tuberculosis* var. *hominis*. Polymerase chain reaction (PCR) testing of FNA contents has proven useful in difficult-to-diagnose cases. Treatment usually involves typical systemic antituberculosis drugs, but excision is frequently curative.

Actinomycosis

Actinomycosis is an infectious disease caused by a gram-positive anaerobic organism. Occurrence is usually in the cervicofacial region and frequently involves the salivary glands. Infections often follow dental extraction or oral trauma. The precipitating event allows mucosal invasion of the organism and a slowly progressive inflammatory reaction. Typically, patients have a painless, indurated enlargement of the gland that mimics a neoplasm. Lymph node necrosis characteristically leads to multiple draining cutaneous fistulae. FNA or fistulous tract drainage culture will reveal characteristic sulfur granules and gram-positive rods. Biopsy specimens are often multiloculated abscesses with whitish-yellow pus. Anaerobic cultures are positive. Management is with penicillin and consists of a 6-week parenteral course followed by 6 months of oral administration.[33] Cure rates approach 90%.

Sarcoid

Sarcoidosis is an idiopathic granulomatous disease. Sarcoidosis is less common in children but, when present, occurs in the second decade of life. It presents with bilateral diffuse enlargement of the parotid glands. Uveoparotid fever (Heerfordt's syndrome) is a form of sarcoidosis characterized by uveitis, parotid enlargement, and facial paralysis. Symptoms may include fever, malaise, weakness, nausea, and night sweats. Chest radiography looking for hilar adenopathy and an acetylcholinesterase level will assist with the diagnosis. A biopsy from the lip or tail of the parotid will confirm the diagnosis. The disease is self-limited, so no specific management is necessary with regard to salivary gland disease. Systemic involvement or complications may necessitate corticosteroid use.

Autoimmune Disease

Benign Lymphoepithelial Disease

Benign lymphoepithelial disease is typically seen in children older than 5 years of age. Although the cause is unknown, an autoimmune mechanism is suspected. It is characterized by unilateral or bilateral enlargement of the major or minor salivary glands or lacrimal glands.[34] Salivary gland enlargement in children with benign lymphoepithelial disease is usually sudden and is characterized by a tender gland accompanied by a fever. It persists for a variable length of time. In some cases, episodes of swelling are recurrent and the gland can remain enlarged. The condition usually resolves spontaneously during adolescence.

Benign lymphoepithelial disease is managed in an identical fashion to acute sialadenitis when purulent secretions are present. With recurrent disease, sialectasis and, rarely, cavitary changes can be shown on CT sialography or MRI. Medical therapy is appropriate unless cavitary changes occur, whereby the gland should then be removed. If an affected gland develops nodularity, distinction from a neoplasm is necessary. If FNA cannot differentiate the two, surgical excision is required.

Sjögren's Syndrome

Primary Sjögren's syndrome in children is uncommon. Sjögren's syndrome is characterized by lymphocyte-mediated destruction of the exocrine glands leading to xerostomia and keratoconjunctivitis sicca. Symptoms include burning oral discomfort and a sandy sensation in the eye. Patients with Sjögren's syndrome have a greater incidence of recurrent parotitis. If a child has recurrent parotitis and a history of dry eyes or xerostomia, further evaluation is indicated. Immunologic tests for antinuclear antibodies and antibodies to Sjögren's syndrome antigens A and B (SS-A and SS-B) are present in 50% to 80% of infected individuals. The sialographic abnormalities show varying degrees of sialectasis. This entity involves the minor salivary glands in 70% of patients and a diagnosis can be obtained with a labial, palatal, or tail of parotid biopsy. Management is symptomatic. In adults, this lesion is associated with an increased incidence of lymphoma.

Chronic Sialadenitis

Chronic inflammatory disease of the salivary glands, also known as *sialectasis,* is associated with repeated episodes of acute sialadenitis and subsequent obstruction of the glandular drainage pathway. The primary causative event is considered to be lowered secretion rate and salivary stasis. Chronic obstructive sialadenitis is associated frequently with salivary duct strictures or sialolithiasis. The strictures may have several causes including recurrent infection, trauma, neoplasms, or congenital abnormalities. Regardless of the cause, progressive dilation and sacculation of the salivary ductal system can lead to chronic uniglandular enlargement. This condition can lead to permanent damage to the gland with ductal ectasia, progressive acinar destruction, and lymphocytic infiltrate.[35]

A child with chronic sialadenitis usually presents with diffuse enlargement of a salivary gland. Massage of the gland will usually produce only small amounts of saliva at the duct orifice. Recurrent swelling will occur during eating, which is followed by gradual relief as emptying of the gland occurs over a 2-hour period. Over time, xerostomia becomes a complaint in up to 80% of patients. A stricture may sometimes be identified by sialography showing ductal dilation proximal to the stricture and delayed emptying of the ducts. Simple dilation or incision may correct the stricture. Repair of the parotid duct requires more elaborate surgery with a higher risk of failure. If a stricture is not found, chronic conservative therapy (sialogogues, massage, and antibiotics) will frequently control disease and prevent progression. When conservative measures fail, excision of the submandibular or parotid gland with facial nerve preservation is occasionally required. Chronic recurrent parotitis may lead to development of a benign lymphoepithelial lesion that may need removal for cosmetic reasons.

Juvenile Recurrent Parotitis

Although rare, juvenile recurrent parotitis (JRP) is the second most common inflammatory condition of the parotid gland next to mumps. It is marked by recurrent pain and swelling of one (60%) or both (40%) parotid glands that can have associated systemic features of fever and malaise. Xerostomia may be present as well. Nonpurulent secretions can be elicited from the parotid duct and set this disease apart from recurrent bacterial parotitis. The age of onset appears bimodal, with peak incidence around 3 to 6 and 10 years of age.[36] A decrease in the frequency of infections is observed during adolescent years.

Thought to be associated with nonobstructive sialectasis within the gland, JRP should be managed nonsurgically with conservative therapy such as analgesics, sialogogues, oral rinses, warm compresses, parotid massage, and antibiotics directed toward oral flora. JRP is an international phenomenon, but no consensus of etiology has been established. Causative factors may be congenital aberrations of the ductal architecture, autoimmune disease, genetic predisposition, allergy, or occult viral and bacterial infections. Regardless, ultrasound and sialography have been shown to help delineate JRP from other parotid entities. The heterogeneous echoes of JRP identified by ultrasound differ from the homogeneous echogenicity of parotid glands infected by mumps. Sialectasis identified by sialography or MRI supports the diagnosis.

Sialolithiasis

Salivary gland ductal calculi are unusual in children but should be considered in patients with chronic or recurrent salivary gland inflam-

mation. Retrospective reviews suggest that only 3% to 13% of cases of sialolithiasis occur in the pediatric population. The average age of onset in this group is 12 years, with only rare presentations in children younger than 10 years old. As in adults, more than 90% of cases involve Wharton's duct of the submandibular glands, whereas calculi within Stensen's duct or the parotid gland are extremely unusual.[37] Salivary gland calculi form by deposition of calcium salts, predominantly calcium phosphate, around a central organic nidus (e.g., desquamated epithelial cells, bacteria, foreign body). Bacterial infection may initiate the process due to changes in pH, fluid composition, and ductal morphology. The submandibular glands release alkaline and viscous secretions that must traverse a long, tortuous, and narrow duct against gravity before entering the oral cavity. This leads to increased fluid stasis and susceptibility to calculi formation in contrast to the parotid gland, which expels serous material from a relatively short, broad, and dependent cannula.

Signs and symptoms of sialolithiasis in children are of shorter duration but more common than that seen in adults. Glandular pain and postprandial swelling are significant indicators of disease. In contrast to bacterial sialadenitis, purulent discharge is uncommon (2% to 12% of cases). Ductal obstruction leads to tenderness and inflammation of the involved gland. Symptoms increase with enlargement of the stone, ultimately requiring medical attention. Fevers may be present, too. In children younger than 10 years of age, tenderness is more often intraoral. A single calculus less than 1 cm in diameter within the distal aspect of the involved duct is generally the rule in children.[37] Often this can be palpated by bimanual examination and makes extraction easier. If necessary, dental occlusal radiographs and ultrasonography allow visualization and confirm the presence of calculi along the submandibular duct or parenchyma.

Management of a calculus near the orifice of the submandibular duct can be performed by probing the duct or through a small intraoral incision. If the calculus is positioned in the parenchyma of the submandibular gland, gland removal is required. During excision, the duct should be ligated as close to the mouth as possible to prevent infection of the ductal remnant. Parotid calculi near the orifice of the duct can be removed intraorally, but the duct should be repaired and stented to prevent postoperative stricture. If a calculus within the parenchyma of the parotid gland causes persistent symptoms, a parotidectomy, with facial nerve preservation, may be required.

Sialendoscopy is a novel option in addressing pediatric salivary gland stones. Endoscopes approaching 1.1 mm in size are now available. The endoscope constitutes two channels, one for the irrigation and the other for endoscopy. Continuous irrigation during endoscopy is required to maintain duct patency following standard dilatation. Wire baskets, YAG laser, and lithotripsy have proven effective in treating small obstructing stones from the salivary duct orifice of adult patients.[12] Some evidence suggest the applicability of sialendoscopy in children.[13,38]

Cysts and Mucoceles

Acquired

Acquired salivary cysts may be associated with neoplasms, benign lymphoepithelial lesions, trauma, parotitis, calculi, duct obstruction, or mucus extravasation. Mucous retention cysts usually involve the minor salivary glands and are commonly seen on the lips, buccal mucosa, and tongue. These true cysts with an epithelial lining result from duct obstruction. A ranula is a mucous retention cyst of the sublingual gland and is described as plunging when it extends from the floor of the mouth through the mylohyoid musculature into the neck. Mucoceles, in contrast, are not true cysts and do not contain an epithelial lining. Mucoceles represent mucous extravasation into the surrounding soft tissue. If necessary, management of mucous retention cysts and mucoceles is by excision or marsupialization.

Congenital

Congenital salivary gland cysts can be classified into dermoid cysts, congenital ductal cysts, and branchial cleft anomalies. Dermoid cysts characteristically contain white keratinizing squamous epithelium that is apparent on excision. These cysts are composed of elements from all three germinal layers. Dermoid cysts usually appear as isolated masses within the substance of the parotid gland. Total removal is necessary to prevent recurrence. This is best accomplished by a subtotal parotidectomy with facial nerve preservation. Congenital ductal cysts most commonly occur within the parotid gland and are rare at other salivary locations. In contrast to dermoids, congenital ductal cysts generally manifest in infancy as enlargement of the parotid gland. The diagnosis can be confirmed with sialography and observation is advised unless recurrent infections occur.

Derivatives of embryologic branchial clefts can also emerge within or adjacent to major salivary glands. The parotid gland is often involved when a first branchial cleft anomaly is present. These can be either type 1 or type 2 first branchial cleft anomalies, which are defined by their location and presence of ectoderm, with or without mesoderm, within the cyst parenchyma (see Fig. 201-8). Type 2 anomalies are more frequently associated with the parotid gland as they course anterior and inferior to the auricle into the gland parenchyma along their path toward the neck. The tract always passes close to the facial nerve and often ends inferior to the angle of the mandible. Infections or drainage of these anomalies often lead to their diagnosis. Safe removal of these anomalies requires preoperative CT or MR imaging and intraoperative facial nerve dissection.

Type 1 branchial defects are duplication anomalies of the membranous external auditory canal. These defects are composed only of ectoderm. Located within the periauricular soft tissues and the parotid gland, they commonly present as sinus tracts or areas of localized swelling near the postauricular sulcus, concha, or anterior tragus. The tympanic membrane and middle ear space are rarely involved. Complete surgical removal is curative. Histologic examination reveals a squamous epithelial lining without skin appendages. When the lesion extends into the parotid gland, the facial nerve should be identified and preserved.

Vascular Anomalies

Vascular anomalies of the head and neck commonly involve one or more salivary entities. On the basis of the histologic classification derived by Mulliken and Glowacki,[39] and agreed on by the International Society for the Study of Vascular Anomalies in 1996, vascular anomalies are classified as either vascular tumors or vascular malformations. Hemangiomas are the most frequently encountered representative of the former. They are composed of aberrant and rapidly proliferating endothelial cells often confined within the substance of the cutaneous and subcutaneous tissue. Extension into deeper structures may occur as seen in the parotid gland. Most will present within the first 6 weeks of life and, unlike other tumors, will characteristically involute over time. This has led to a benign neglect approach to hemangiomas because most will resolve without sequelae. Other vascular tumors include Kaposi-like infantile hemangioendotheliomas and glomus tumors that develop from aberrant proliferation of vascular cells but do not follow the natural course of hemangiomas. In contrast, vascular malformations consist of ectatic development of vascular channels of one or more elements of the normal circulatory system. On the basis of their source vessels, they are subclassified into venous, lymphatic, arterial-venous, and lymphatic-venous malformations. They grow by expansion and vascular recruitment and, without intervention, can eventually invade normal structural architecture including muscle and bone. Although rare, vascular malformations can be notoriously difficult to cure because recurrence is common depending on their type.

Hemangiomas

Hemangiomas are the most common benign tumor of the parotid gland. Of salivary gland hemangiomas, 80% occur in the parotid gland, 18% in the submandibular gland, and 2% in the minor salivary glands. This parotid tumor is generally contained within the subcutaneous and intracapsular portion of the gland with rare extension into the submucosa, mucosa, or dermis (Fig. 201-6). They are usually discovered shortly after birth (3 to 6 weeks). After it appears, the hemangioma grows rapidly over months and plateaus for a period of time before its slow but progressive involution. Of affected children, 50% have com-

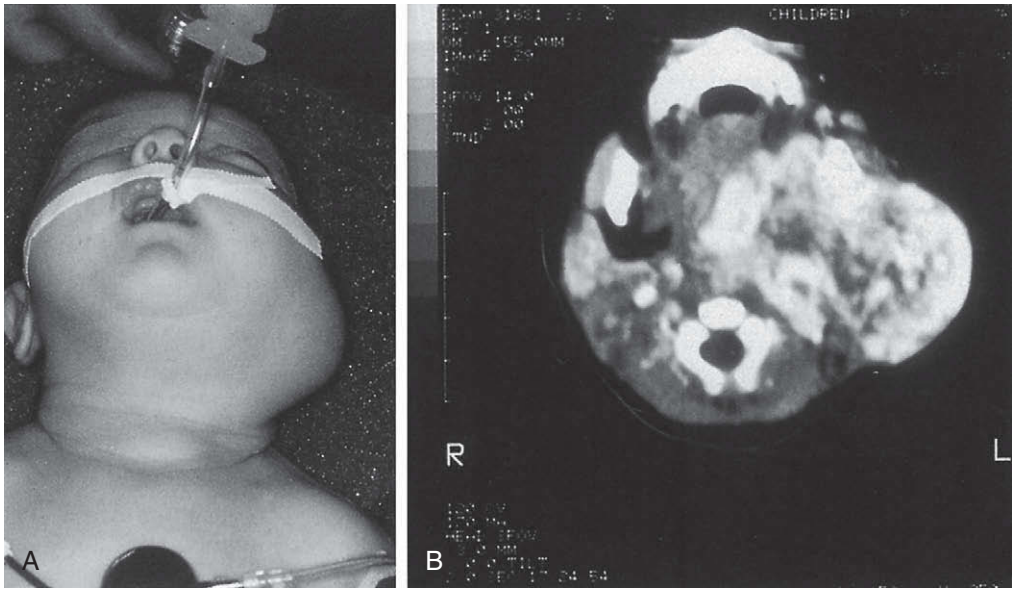

Figure 201-6. **A,** Patient with a hemangioma of the parotid gland. **B,** Computed tomography with contrast shows a parotid gland mass consistent with a hemangioma and extension into the retropharyngeal space.

plete involution of the lesion by age 5 years, 70% have involution by 7 years of age, and 90% by 9 years of age.[40]

Infants with parotid hemangiomas typically present with asymptomatic facial asymmetry and a fluctuant cheek mass that is soft to rubbery on palpation. Vascular staining may indicate disease. Bright red macules or bluish discoloration will indicate either superficial or deep (subcutaneous) disease, respectively. Parotid hemangiomas can be either segmental or focal with the former often engaged in other locations of the face either in a random or more frequently encountered "beard" distribution with involvement of both parotid glands. Hemangiomas can cause the parotid gland to increase up to five times its normal size. Focal disease frequently undergoes a defined proliferative phase up to 1 year of life that is followed by gradual involution. The proliferative phase of segmental disease is less clear because these lesions generally grow larger, take longer to involute, and are more difficult to eradicate than their focal counterparts. Regardless, the general lobular architecture of the native gland is typically preserved with limited or no impact on the acini and ductal structures.

Diagnosis is usually by history and physical examination. If necessary, ultrasound, CT, or MRI will confirm the diagnosis. Biopsy is unnecessary; however, if the mass is firm, painful, or rapidly grows, histologic sampling may be necessary to rule out a malignancy. Most of these tumors undergo spontaneous involution, which requires the use of observation to follow up most of these lesions. Potential complications of hemangiomas may include a localized consumptive coagulopathy known as the *Kasabach-Merritt syndrome.*

Excision of a salivary gland hemangioma is indicated when there is excessively rapid growth of the mass, severe facial deformity, functional impairment, infection, hemorrhage, or ulceration. Laser therapy has not proven completely effective over natural involution to reduce vascular staining or speed involution of these tumors.[41] However, use of the flash pump dye laser is appropriate for ulcerative and bleeding lesions because this can lead to rapid epithelialization and repair of these sites.[42] If necessary, subtotal parotidectomy, with facial nerve preservation, or total submandibular gland excision can be performed and only after the end of the proliferative phase of these lesions. Bipolar cautery is recommended because it eases dissection of these highly vascular tumors. Segmental disease is likely better managed with either systemic or intralesional injections (triamcinolone acetonide/betamethasone [Kenalog/Celestone] mixture) of corticosteroids because resection of these multiple lesions and sites can be difficult. Steroids should be instituted only during the proliferative phase. Although controversial, recent investigation into these treatment modalities has illustrated improved functional and cosmetic results.[43,44] Nonetheless, the risk of systemic side effects of corticosteroids including hypertension, irritability, Cushing's syndrome, and adrenal insufficiency should be respected and frequently monitored during their use. Tapering systemic doses to therapeutic response is advocated.[44] Interferon is no longer recommended for fear of spastic diplegia and has been circumvented by the use of vincristine for complicated disease. Of final note, patients with segmental facial hemangiomas involving the parotid should be screened for associated anomalies of PHACES syndrome including Posterior fossa abnormalities, Arterial anomalies, Cardiac anomalies, Eye abnormalities, and Sternal defects, with MRI, echocardiogram and ophthalmologic referral.

Lymphatic Malformations

Of the vascular malformations, lymphatic malformations are those that most commonly affect the salivary structures, making them the second most common vascular anomaly found in the salivary glands. Before the recent classification of vascular anomalies, these lesions have been previously named cystic hygromas and lymphangiomas. A venous component to these lesions is also common (lymphatic-venous malformations) and should be considered at initial evaluation and when surgical resection is considered.

Lymphatic malformations are soft, painless, and compressible benign masses that represent areas of regional lymphatic dilation. Lymphatic malformations have been divided into two categories on the basis of the size of their lymphatic channel aberrations. Lesions consisting predominantly of small lymphatic spaces, less than 2 cm in diameter, are considered microcystic. Those with spaces greater than 2 cm are known as *macrocystic lymphatic malformations* and have been known as cystic hygromas in the past. Mixed lesions of these two types are also common.

Lymphatic malformations involve the head and neck in more than 50% of cases. Infiltration of the salivary glands is common but not frequently the source of disease.[45] These malformations can involve any of the major salivary glands and usually present as an asymptomatic fluctuant mass (Fig. 201-7). They are present at birth and grow at unpredictable rates. However, rapid growth and ectasia can occur with upper respiratory tract infections. Approximately 50% to 60% of patients present with these tumors before age 1 and about 90% of the tumors occur before the end of the second year of life. The diagnosis can be confirmed when cystic areas, septations, and air fluid levels are found on imaging with ultrasound, CT, or MRI. Gadolinium-enhanced MRI will provide clarity of all soft tissues involved and is recommended

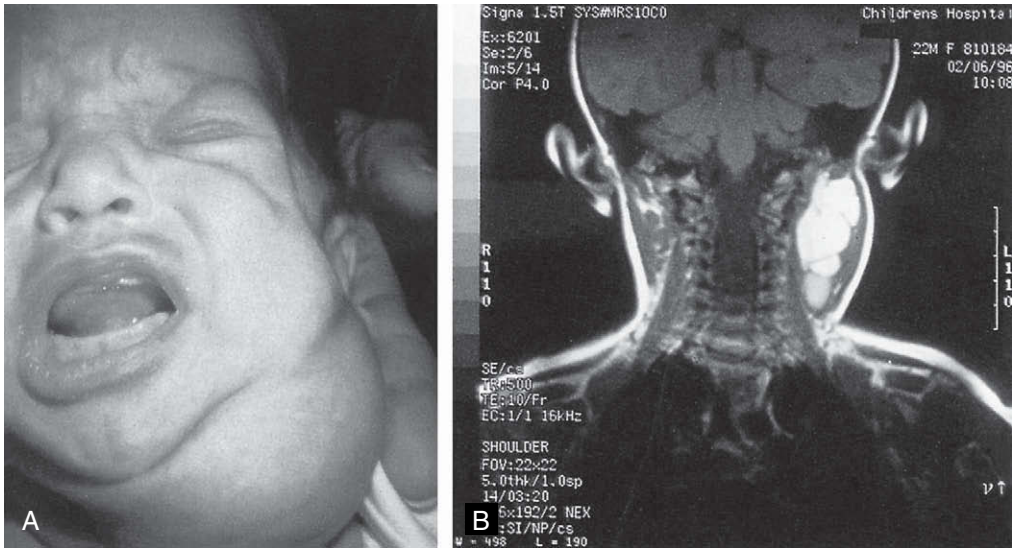

Figure 201-7. **A,** Lymphangioma with involvement of the submandibular and parotid glands. **B,** Magnetic resonance imaging (T1-weighted) shows multiple loculated spaces consistent with a lymphangioma.

as a primary imaging modality. Examination of the chest, mediastinum, and airway is recommended in larger lesions that are seen in approximately the lower third of the neck.

Unlike hemangiomas, lymphatic malformations rarely undergo spontaneous resolution. Although it has been reported in small lesions, resolution is thought to occur as a result of autosclerosis of the cystic space. More frequently, infiltration of local tissue, especially with microcystic disease, can lead to destruction and deformation of normal bone and muscle leading to significant functional and cosmetic consequences. Macrocystic disease (cystic hygroma) can be approached with either sclerotherapy or surgical resection. Sclerotherapy is recommended for deep lesions not surrounding prominent vascular or nervous structures because various agents (e.g., ethanol, bleomycin) have a small risk of associated nerve and vessel injury. Sclerosis of superficial lesions can also lead to skin ulceration. Consultation with the interventional radiologist is paramount for these vascular malformations.

Surgical removal of macrocystic disease is often curative. OK-432 (Picibanil) sclerotherapy, although not currently FDA approved, has been reported as a successful treatment of these lesions.[46] Definitive therapy potentially can be delayed until the child is several years old to make surgical dissection less difficult. Prompt removal of lymphatic malformations is necessary when the potential for airway obstruction exists. This potential is highest in tumors of the sublingual glands, submandibular glands, or minor salivary glands. A tracheotomy may be necessary if the malformation cannot be removed completely. Recurrence of macrocystic lymphatic malformation is uncommon when all evidence of gross tumor is removed. If residual disease remains, recurrence is estimated to occur in up to 35% of cases.[47] Microcystic disease is difficult to erradicate and often requires staged surgical resections with bony recontouring. Infiltration of muscle and nerve is common. Perioperative systemic steroids reduced postoperative edema often encountered following partial resection of these lesions. Use of systemic steroids is also recommended during upper respiratory infection in children with lymphatic malformations to prevent lymphatic edema and growth.

Neoplasms

Salivary gland neoplasms in children are uncommon, with an annual incidence of 1 to 2 cases per 100,000 juveniles. Salivary gland tumors account for 8% of all pediatric head and neck tumors with less than 5% of these occurring in patients 16 years of age or younger.[47] Pediatric salivary gland neoplasms are classified into three histologic groups: benign, low-grade malignant, and high-grade malignant. Sometimes intermediate-grade classification is also used. Management choices inherently depend on histologic type because more aggressive therapy (resection with radiation) is advocated for high-grade lesions.

As mentioned previously, the majority of benign salivary lesions are of vascular origin. The second most common are epithelial tumors. These are predominantly benign and occur most frequently in children in the second decade of life.[2,4,48] Overall, the most common epithelial tumor in children is the pleomorphic adenoma (Table 201-3). Others include Warthin's tumor, oncocytoma, and various adenomas. In contrast to adults, the incidence of malignant tumors is inversely proportional to the age of the patient. Several reports suggest that 23% to 50% of all salivary gland tumors in children are malignant.[3] Fortunately, most of these are of low-grade histology. The most common are mucoepidermoid and acinic cell carcinomas, which account for 60% of the malignant epithelial salivary neoplasms in children.[4] Rare but most frequently encountered nonepithelial malignancies are rhabdomyosarcoma and lymphoma.[2]

The parotid gland is the primary location for salivary gland neoplasms (85% to 90%).[4] These frequently present as a slow-growing mass with average time of onset to ultimate diagnosis approximating 1 to 2 years.[48] Thus it is safe practice to consider all deep, painless, and noninflammatory parotid masses as neoplasms until proven otherwise. Submandibular gland lesions also present as painless swellings but are harbored within the submandibular triangle. A rare minor salivary gland lesion will tend to occur as an oral mass or ulceration. In general, submandibular and minor salivary gland neoplasms have a higher rate of malignancy. Perineural involvement with symptomatic paresthesias (lingual nerve) or weakness (facial nerve or hypoglossal nerve) is suggestive of high-grade processes. Fixation and pain are also indicative of aggressive malignant disease. Pain (30%) and facial paralysis (15%) often accompany malignant parotid tumors.

Benign

Pleomorphic Adenoma (Benign Mixed Tumor)

The most common nonvascular or epithelial salivary gland tumor in children is the pleomorphic adenoma.[49] The highest incidence of pleomorphic adenoma in children is in the pubertal and prepubescent child.[3] These adenomas consist of both mesenchymal and epithelial cell lines derived from the intercalated duct reserve cell. The tumor most often presents as a slow-growing, firm, discrete nodule that is freely mobile and about 1 cm in diameter. Facial paralysis is atypical and should alert the physician that a malignant process is present. Although pleomorphic adenomas appear encapsulated, they have a highly lobular

Table 201-3

Salivary Gland Neoplasms in Children

Benign*		Malignant†	
Hemangioma	111	Mucoepidermoid carcinoma	122
Mixed tumor (pleomorphic adenoma)	94	Acinic cell carcinoma	30
Vascular proliferative tumor	40	Undifferentiated carcinoma	22
Lymphangioma	18	Adenocarcinoma	19
Lymphoepithelial tumor	3	Adenoid cystic carcinoma	16
Cystadenoma	3	Malignant mixed tumor	10
Warthin's tumor	3	Rhabdomyosarcoma	6
Plexiform neurofibroma	2	Undifferentiated sarcoma	5
Xanthoma	2	Mesenchymal sarcoma	5
Neurolemmoma	1	Unclassified carcinoma	4
Adenoma	1	Squamous cell carcinoma	3
Lipoma	1	Lymphoma	3
TOTAL	279	Ganglioneuroblastoma	1
		TOTAL	246

*Adapted from Schuller DE, McCabe BF. Salivary gland neoplasms in children. *Otolaryngol Clin North Am.* 1977;10:399.
†Adapted from Shikhani AH, Johns ME. Tumors of the major salivary glands in children. *Head Neck Surg.* 1988;10:257.

architecture with microscopic pseudopod extensions that prohibit enucleation as a therapeutic alternative. Recurrence rates approach 40% with this surgical technique. Multiglandular involvement in children is unusual. Most of these tumors are 1 to 3 cm in size and located within the superficial lobe or tail of the parotid gland.

The diagnosis of a pleomorphic adenoma, as is the case for most salivary neoplasms, is best confirmed by FNA with ultrasound guidance as needed. Incisional biopsies are contraindicated. MRI will provide better clarity of soft tissue extension in unusual cases. If FNA is inadequate or unavailable, excisional biopsy consisting of a lateral (superficial) parotid lobectomy with facial nerve preservation is appropriate. Total excision of the submandibular gland is necessary when pleomorphic adenomas are found in this gland. Rarely, a mixed tumor abutting the parotid gland, but not infiltrating it, can be removed with a completely intact capsule-sparing parotid tissue and facial nerve dissection. Recurrence after superficial parotidectomy for pleomorphic adenoma in the pediatric population is reported by Shikhani and Johns[50] to be as high as 19.5%, which is considerably greater than that seen in adults (1%). The reasons for this remain unclear but may be related to the misdiagnosis and drainage of previously presumed lymph node infections.

Other Benign

Several rare benign neoplasms have been described in the pediatric population. These include plexiform neurofibroma, Warthin's tumor (papillary cystadenolymphomatosum), embryoma, monomorphic adenoma (basal cell, clear cell, glycogen-rich adenoma), lipoma, and teratoma in descending frequency.[51]

Warthin's tumors theoretically arise from trapped ductal epithelium (striated ducts) within intraparotid lymph nodes and are histologically characterized by oncocytes lying among dense stoma of lymphatic origin. These are typically well-circumscribed lesions that are rare in children and occur in less than 2% of all benign epithelial salivary gland tumors. CT, MRI, and FNA will help diagnose these solid tumors that are often nestled within the tail of the parotid gland. Surgical excision with superficial parotidectomy is often curative, although small secondary lesions may arise later in the same gland. The remaining benign processes are managed similarly to Warthin's tumor both diagnostically and surgically with imaging and resection of the tumor with a wide cuff of adjacent normal gland. The exception is the plexiform neurofibroma that may involve numerous head and neck sites beyond the primary gland. Controversy on treatment, timing, and extent of resection is prevalent in the literature and beyond the scope of this chapter.

Malignant

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignant epithelial salivary gland neoplasm in children, accounting for approximately 50% of salivary gland malignancies. Most are low-grade lesions that tend to have a good prognosis.[2,49,52] These are also the most frequently encountered radiation-induced salivary gland tumors in children.[53,54] Mucoepidermoid carcinomas are composed of cells with squamous differentiation and cells with mucinous differentiation. Lower-grade neoplasms are commonly cystic, showing predominant mucinous differentiation. Higher-grade neoplasms show greater squamous differentiation and resemble squamous cell carcinoma. Again, histologic grade correlates well with prognosis.

Management is essentially the same in children and adults. Low-grade malignancies of the parotid gland are managed by an appropriate parotidectomy sufficient to remove the tumor with a generous cuff of normal parotid and preserving the facial nerve. The lymph nodes around the digastric triangle should be evaluated at the time of surgery and, if involved, a neck dissection should be done. High-grade malignancies are managed with total parotidectomy. Recurrence rates for superficial versus total parotidectomy for mucoepidermoid carcinoma of the parotid are 30.7% and 0%, respectively.[55] This underscores the

implementation of more extensive resection for this disease. This is offset by the risks to the facial nerve. Temporary facial nerve paralysis has been reported to occur in 25% and 16% of total and superficial parotidectomies, respectively, after removal of parotid lesions and facial nerve preservation in children. Permanent loss is rare but more common in malignant tumors.

The facial nerve is preserved in all cases unless gross tumor invasion into the nerve is present. Radical surgery with nerve sacrifice should not be performed on the basis of the results of frozen section alone. However, once confirmed by permanent histologic evaluation, invasion of the nerve should be managed with resection until final sections reveal no further disease. Surgeons need to be prepared for mastoidectomy and temporal bone dissection in suspected cases. In this scenario, immediate facial nerve grafting is performed. Postoperative radiotherapy often is given to patients with high-grade malignancies.[52]

Submandibular gland malignancies are managed with submandibular gland excision and submandibular triangle nodal dissection. High-grade tumors often are given postoperative radiotherapy. Ten-year survival rates for low-grade mucoepidermoid carcinoma have approached 95%.[4]

Acinic Cell Carcinoma

Acinic cell carcinoma is the second most common malignancy and accounts for approximately 12% of the total number of epithelial malignancies of the salivary gland in children.[38] Most acinic cell carcinomas are low-grade malignancies and are diagnosed in pubescent adolescents. They are characterized by cells with bland nuclei and an abundant basophilic cytoplasm. The behavior of acinic cell neoplasms is similar to mucoepidermoid carcinoma because patients present with a slow-growing solitary mass with or without associated pain. Management is the same as low-grade mucoepidermoid carcinoma: an appropriate parotidectomy sufficient to remove the tumor with a generous cuff of normal parotid tissue, preserving the facial nerve.

Other Malignant

Adenocarcinoma and undifferentiated carcinoma, adenoid cystic carcinoma, and malignant mixed tumors are rare but can occur in the pediatric population. Primary sarcomas of the salivary glands in children are also uncommon. When present, rhabdomyosarcoma is the most common. All of these malignancies demonstrate high recurrence rates and poor prognosis. Undifferentiated carcinomas tend to occur in children younger than 10 years of age.[48] Epithelial salivary gland tumors identified in the first month of life are termed *embryomas* or *sialoblastomas* and are malignant in 25% of cases.

Surgery remains the mainstay for the more aggressive lesions with the goal of complete removal. Total parotidectomy is advocated because it may affect local control. Lymph node disease in the neck is estimated to occur in less than 15% of cases, oncologically warranting cervical lymphadenectomy in cases of gross nodal involvement or poorly differentiated lesions. In particular, elective neck dissection without clear involvement should be done only for high-grade malignancies where occult disease is estimated to be greater than 15% (high-grade mucoepidermoid, rhabdomyosarcoma, undifferentiated, and rare squamous cell carcinoma).

Minor salivary gland neoplasms are rare in the pediatric population. Most are pleomorphic adenomas or low-grade mucoepidermoid carcinomas. Regardless of etiology, wide local excision with a cuff of normal adjacent tissue is recommended for both diagnosis and therapy. This is usually curative for these and other malignant neoplasms of these glands.

Role of Irradiation

Irradiation of the major and minor salivary glands in children is generally reserved for high-grade lesions in which significant risk of recurrence and mortality is evident. Other indications include those seen in adults and include remaining gross or microscopic disease, inadequate margins, nodal involvement, perineural spread, and adjacent soft tissue extension. The risk of postradiation sequelae is high in young patients and includes limitations in facial growth, development of secondary tumors, dental caries and trismus.[56]

Trauma

Most salivary gland injuries are seen in association with penetrating wounds of the cheek. Few cause serious injury to the facial nerve or salivary duct system. Any penetrating wound deep to the parotideomasseteric fascia can injure these structures. If the laceration extends anterior to a line dropped from the lateral canthus of the eye, the facial nerve does not need to be explored. Satisfactory reinnervation will occur through peripheral nerve branches. When a laceration is posterior to this line and the facial nerve is paralyzed, exploration of the wound and reapproximation of the proximal and distal segments of the nerve are obligatory.

Exploration of the facial nerve should occur within 72 hours of the injury so that electrical stimulation of the distal segment is possible. Epineural repair of the severed branches can be accomplished with the aid of an operating microscope. A 6-0 to 8-0 nylon suture is ideal for this purpose. If tension exists on the suture line, a cable graft is preferable. The best results are obtained when the anastomosis is accomplished with fresh, sharp nerve ends. Recovery of facial nerve function after transection and repair requires 6 to 12 months.

The parotid duct (Stensen's duct) is located on a line drawn from the tragus to the midpoint between the upper lip margin and the columella. The parotid duct is likely to be injured if a laceration courses through the masseter muscle. Pooling of saliva in the wound is a frequent finding. Lacerations involving Stensen's duct should be repaired when they are detected because the resultant inflammatory response leads to a high probability of a salivary fistula, sinus tract, or an obstructive cyst. This repair should occur as early as the patient is medically stable and staff are available. The preferable method is to perform the ductal repair using 6-0 or 7-0 nylon suture over a small stent (polyethylene tubing). The tubing remains in place approximately 10 days. When the orifice of Stensen's or Wharton's duct has undergone significant injury, surgical rerouting of the remaining duct through the buccal mucosa may be necessary. If this is not possible, ligation at this site is also a reasonable option.

Blunt trauma to the salivary glands may cause less obvious injury than penetrating trauma. Injury to the parotid duct can result in a salivary pseudocyst with associated swelling and recurrence after FNA. Repeat aspiration and a pressure dressing may be necessary. Children who require dental appliances can develop chronic irritation of the salivary ducts resulting in stasis. Salivary gland swelling has been described in neonates resulting from a compression-type birth injury from a forceps delivery.

Sialorrhea

Sialorrhea (drooling) is defined by the unintentional loss of saliva beyond the lip margin. This usually results from an inability to coordinate oral control and swallowing and is a natural phenomenon in infants as they gradually gain function of their oral-motor skills. Drooling normally subsides in these children during neuromuscular maturity and should resolve around 18 months of age. Persistent sialorrhea beyond 4 years of age is thereby considered abnormal and should be investigated for treatment options. This most frequently occurs in neurologically impaired children with the highest incidence in patients diagnosed with cerebral palsy (10% to 25%). Specific delay in oral motor function in these patients can last up to 6 years of age and should be kept in mind when considering sialorrhea therapy.

The submandibular and sublingual glands produce the most saliva (70%) during the normal, unstimulated basal state. The role of saliva is to maintain oral homeostasis with respect to pH, dental health, control of bacterial growth, lubrication, and digestion of food (amylase). On sympathetic stimulation (eating and preparation to eat) the parotid gland produces the preponderance of saliva with dramatic increase in flow.[57] Excessive production or ineffective dissolution (voluntary swallowing) can lead to persistent drooling and its consequences including maceration of the lips and chin, chapping, dehydration, infection, foul odor, and aspiration. This can lead to significant hygienic issues, costs, and social isolation as patients continuously soil their clothes, furniture, and caregivers. Assessment of sialorrhea is often determined by subjective scales answered by the patient's caregivers with specific rating of

the severity and frequency of drooling. The results thereby help guide management.

Medical Management

A multidisciplinary approach is appropriate for these patients because management decisions often include otolaryngologists, speech therapists, physical therapists, social workers, and pediatric dentists.[1] In otherwise healthy children with sialorrhea, nasal obstruction and dental disease are common sources and should be assessed carefully because management may be directed at this problem. Adenoidectomy, turbinectomy, allergic desensitization, and management of dental hygiene can be performed. In neurologically impaired children the approach is not as simple. In such patients with associated malocclusion, macroglossia, and orthodontic problems, surgical correction of these deformities or the application of orthodontic appliances can improve mild cases of sialorrhea.

However, neurologic dysfunction is the primary culprit for disease in sialorrhea patients. An initial attempt at speech therapy or physical therapy is appropriate before beginning extensive medical or surgical management. This method provides a physiologic approach to the problem using oral-motor and behavior modification. Conservative management includes correcting posture to more upright positions and techniques to improve oral competence (closing mouth) and reducing tongue thrust. Biofeedback has been used in higher-functioning patients and shown to be effective in mild to moderate cases of sialorrhea. This is aimed to elicit a swallow or mouth wiping by the patient on hearing a repeated tone. Unfortunately, habituation to the stimulus occurs in most patients over time.[58] Indications for delay in therapy include normally developing children up to 6 years of age with a sole complaint of sialorrhea, cerebral palsy patients with mild to moderate sialorrhea before 6 years of age, and sialorrhea following acute neurologic deficits (wait 6 to 12 months).[1]

Medical regimens have involved the use of oral (glycopyrrolate) and topical (scopolamine) anticholinergics. Unfortunately, these have generally been unsuccessful due to the broad side-effect profile, making their use unattractive. Even more selective agents with limited blood-brain barrier penetration such as glycopyrrolate have nearly 60% of patients experiencing various side effects such as hyperactivity, irritability, xerostomia, constipation, and urinary retention. Regardless, in patients without side effects, glycopyrrolate at dose 0.10 mg/kg has proven effective in maintaining reduction of sialorrhea. This is thereby often used before contemplating surgical intervention. Botulinum injection is also used in some cases and has been successful in temporarily reducing sialorrhea.

Surgical Management

Surgical management of sialorrhea is generally reserved for patients in whom nonsurgical measures have not been effective, those with moderate to profuse sialorrhea and older than 6 years of age, dramatically developmentally delayed children with moderate to profuse drooling, sialorrhea with more than one documented episode of aspiration pneumonia annually, and patients requiring chronic and frequent maintenance of secretions by their caregivers. Although less clear, patients who require several bib or clothing changes daily or hourly suctioning are considered appropriate candidates. Botox injections of the major salivary glands have proven effective in reducing sialorrhea and seems appropriate in patients with poor neurologic prognosis, surgical risk factors, and determining those in whom surgery may be effective.[1] However, repeated injections will be necessary, thus limiting its use in the general population of sialorrhea patients.

Bilateral submandibular gland excision with parotid duct ligation has most consistently controlled drooling. It has supplanted other surgical options including submandibular duct rerouting, submandibular duct rerouting with bilateral tympanic neurectomies and chorda tympani nerve sections, and tympanic neurectomies with chorda tympani nerve sections alone. This procedure is safe and reliable and results in few complications.[59] Another less invasive option is that of four-duct ligation, which includes ligation of both parotid ducts and both submandibular ducts all via transoral approach. No conclusive studies have determined the overall benefit from this less invasive procedure.

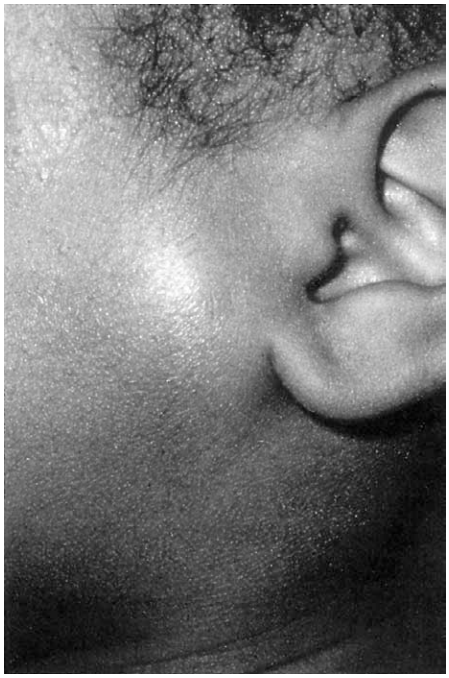

Figure 201-8. A first branchial cleft anomaly that has become an infected cyst.

Rare Disorders

Allergy

Allergic reactions can cause bilateral parotid enlargement. The enlargement is usually of rapid onset and transient nature. Resolution is usually spontaneous when the offending allergen is eliminated. Certain foods (seafood, strawberries) may precipitate this reaction. Investigation of the saliva or leukocyte differential may reveal a relative eosinophilia.

Cystic Fibrosis

Patients with cystic fibrosis can develop salivary gland enlargement. The submandibular gland is involved more frequently than the parotid gland. When a child younger than 2 years of age presents with diffuse parotid enlargement without an associated infection, a sweat chloride test should be performed to rule out cystic fibrosis. The mechanism of the swelling is unknown, but increased concentrations of calcium and phosphorus are found in the saliva.

Aberrant Salivary Glands

Heterotopic salivary gland tissue is defined as the existence of salivary tissue in locations external to the major and minor salivary glands. This is a rare entity and when present usually presents as a sinus tract in the right side of the lower neck along the anterior border of the sternocleidomastoid muscle with close proximity to the sternoclavicular joint. Most are noticed at birth or shortly thereafter. The tracts may drain saliva-like fluid related to meals. Excision is the treatment of choice. The sinus tracts are generally short in comparison with that of branchial cleft fistulas.[39]

Agenesis of the major salivary glands can occur. Diagnosis can be confirmed with pertechnetate nuclear medicine imaging. The scan may be diagnostic in a child with idiopathic xerostomia. Early identification is important so that proper oral hygiene can be started. The oral sequelae include dental carries and candidiasis.

Systemic Conditions and Medications

Systemic conditions in which bilateral diffuse salivary enlargement can occur include obesity, alcoholism, portal cirrhosis, malnutrition (kwashiorkor, hypovitaminosis A), gastrointestinal absorption disease (celiac disease, Chagas' disease), chronic pancreatitis, uremia, thyroid

disease (hypothyroidism), diabetes, bulimia, and abnormalities of the pituitary-adrenal axis. Salivary gland enlargement has been associated with several drugs including phenytoin, thiourea, isoproterenol, methimazole, phenothiazine, thiocyanate, iodine compounds, and heavy metals.

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CHAPTER TWO HUNDRED AND TWO

Congenital Disorders of the Larynx

Anna H. Messner

Key Points

- The most common cause of stridor in infants is laryngomalacia—but not all stridor can be assumed to be due to laryngomalacia.
- Laryngomalacia is most likely due to altered laryngeal tone and sensorimotor integrative function, which improves with increasing age.
- Infants with laryngomalacia are likely to have gastropharyngeal reflux requiring evaluation and treatment.
- Supraglottoplasty is a highly successful treatment for severe laryngomalacia with a low complication rate.
- Noniatrogenic neonatal unilateral and bilateral vocal cord paralysis will resolve spontaneously in greater than 50% of patients.
- Posterior glottic stenosis and arytenoid fixation can mimic neurologic vocal cord paralysis.
- All children with anterior laryngeal webs should undergo genetic testing for abnormalities of chromosome 22q11.
- Patients with subglottic hemangiomas often present with a history of "recurrent croup" because the lesion mimics the subglottic swelling of croup, and the symptoms improve with steroid treatment.
- Laryngeal cysts, including vallecular thyroglossal duct cysts, saccular cysts, and subglottic cysts, are a source of potentially severe airway obstruction.
- In the patient with feeding problems, recurrent aspiration, and stridor, the otolaryngologist must maintain a high index of suspicion that a laryngeal cleft may be present, as well as a low threshold to perform direct laryngoscopy in the operating room to rule out potential clefts.

Stridor is the hallmark of any laryngeal obstruction. Much can be learned about the nature of the laryngeal problem by closely observing the infant and listening to the noise produced as air passes through the obstruction. Stridor resulting from supraglottic or glottic obstruction is typically present on inspiration, whereas biphasic stridor originates from obstruction at or below the level of the glottis in the upper trachea. Expiratory stridor is the result of lesions in the distal trachea or mainstem bronchi.

Dynamic evaluation of the larynx by flexible laryngoscopy is best performed in the patient who is awake. Although at least a 2.5-mm diameter fiberoptic laryngoscope is recommended for optimal viewing, fiberoptic laryngoscopes with diameters as small as 1.9 mm allow the neonatal larynx to be viewed with a minimum of trauma to the young patient. Direct laryngoscopy of the neonatal larynx with a telescope or microscope provides the best optics (Fig. 202-1). To fully evaluate the larynx, the endoscopist should note findings in the vallecula, piriform fossae, postcricoid region, arytenoids, interarytenoid area, aryepiglottic folds, epiglottis, false vocal cords, ventricles, true vocal cords, and the subglottis.

Laryngomalacia

Without question, the most common cause of stridor in infants is laryngomalacia, a disease more commonly found in term infants, and in males more than females.[1] The newborn with laryngomalacia typically develops intermittent, inspiratory stridor within the first 2 weeks of life, which resolves slowly over several months. Many authors describe the stridor as high-pitched, but compared to the stridor of vocal cord paralysis it is relatively low-pitched and does not have a musical quality. The stridor nearly always worsens with feeding, and often the baby will need to take breaks while feeding in order to breathe. The stridor of mild laryngomalacia often improves with crying as tone in the pharynx is increased. Conversely, in moderate-to-severe laryngomalacia, the stridor typically will worsen with crying because of the increased airflow through the severely collapsed larynx. Laryngomalacia may be an isolated finding in the otherwise healthy infant or may be associated with other neurologic disorders such as cerebral palsy.

The median time to spontaneous resolution of stridor is 9 months of age, and 75% will have no stridor by 18 months of age.[2] Infrequently, the laryngomalacia is severe, resulting in feeding difficulties, failure to thrive, apnea, pectus excavatum, or cyanosis. In these cases, surgical intervention is recommended to prevent worsening failure to thrive, cor pulmonale, and cardiac failure.[1-3]

The inspiratory stridor of laryngomalacia results from collapse of the supraglotttic larynx, creating a narrow airway and turbulent airflow (Fig. 202-2). The etiology of this collapse has been elusive but it appears to be related to neuromuscular hypotonia. Sensorimotor integration of peripheral sensory afferent reflexes, brainstem function, and the motor efferent response are responsible for laryngeal function and tone.[1] The laryngeal adductor reflex (LAR) is a vagal nerve-mediated reflex activated by sensory stimulation of the mechanoreceptors and chemoreceptors of the superior laryngeal nerve located in the region of the aryepiglottic fold. Dysfunction anywhere along the afferent, brainstem,

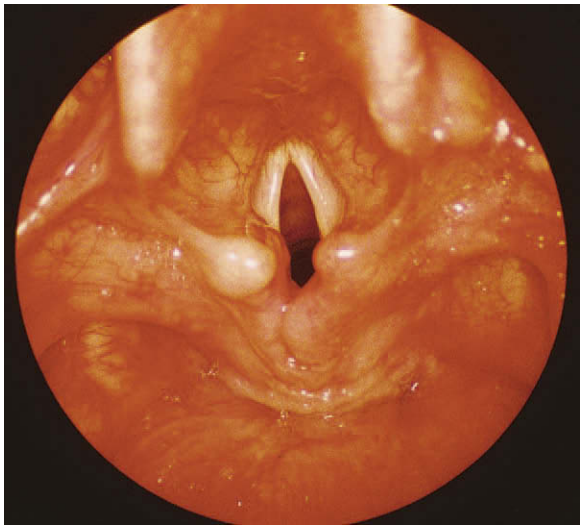

Figure 202-1. Normal infant larynx. Anatomic areas to be examined include epiglottis, vallecula, piriform sinuses, arytenoid cartilages, interarytenoid area, aryepiglottic folds, false vocal cords, ventricles, true vocal cords, anterior commissure, and subglottis. *(From Benjamin B. The pediatric airway, slide #2, Slide Lecture Series. American Academy of Otolaryngology–Head and Neck Surgery, 1992.)*

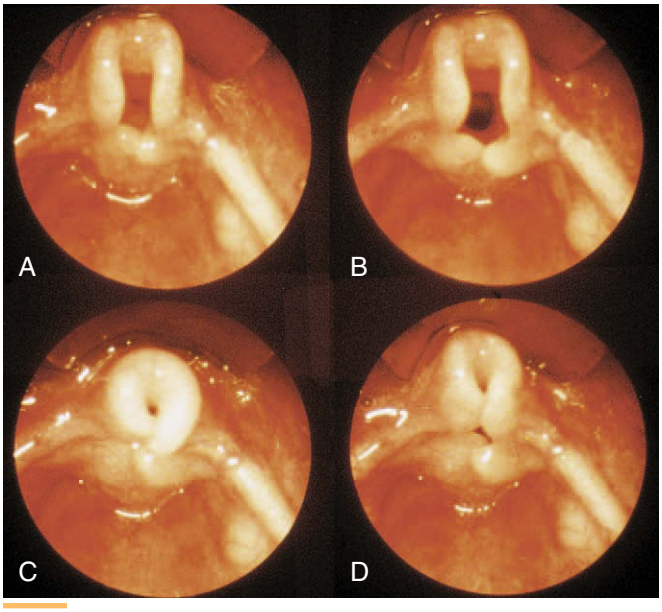

Figure 202-2. Laryngomalacia. Progressive airway obstruction on inspiration. Note omega-shaped epiglottis. *(From Benjamin B. The pediatric airway, slide #2, Slide Lecture Series. American Academy of Otolaryngology–Head and Neck Surgery, 1992.)*

or efferent pathway of the LAR can result in altered laryngeal tone and function. Infants with laryngomalacia have been found to have elevated laryngopharyngeal sensory testing thresholds, showing that the sensorimotor integrative function of the larynx is altered, likely leading to the weak laryngeal tone seen in infants with laryngomalacia.[1]

In several series, a high prevalence of gastroesophageal reflux disease (GERD) has been reported in patients with laryngomalacia (50% to 100%).[1,4-6] When present, GERD can cause airway edema and thus contribute to the airway compromise. Children with laryngomalacia should be evaluated for GERD and if airway surgery is needed, care should be taken to control GERD before surgery to avoid GERD-induced delayed healing.[6] Mild GERD may improve with the treatment of laryngomalacia when the negative intrathoracic intraesophageal pressures decrease. Conversely, treatment of GERD may improve laryngomalacia as acid ceases to irritate the larynx and edema resolves.[5] In the child with GERD related to airway obstruction, the GERD can be expected to improve significantly after aryepiglottoplasty.[7]

The diagnosis of laryngomalacia requires an endoscopic examination; however, the optimal type of endoscopic examination is somewhat controversial. If the patient is sedated and undergoes fiberoptic flexible laryngoscopy (FFL), the topical lidocaine typically used can cause increased collapse of the arytenoids and folding of the epiglottis during inspiration—possibly leading to overestimation of the severity of laryngomalacia.[8] These findings suggest that the optimal way to diagnose laryngomalacia is with FFL in the awake patient. Conversely, the awake technique has been found to miss mild laryngomalacia or lead to overdiagnosis in the patient with a normal airway.[9] The advantages of awake FFL compared to FFL under general anesthesia include the ability to perform the examination expediently in the clinic setting with the parents present, without the need for sedation, leading to less medical expense. The primary disadvantage of the awake FFL is that in nearly all cases the infant is crying during the examination, which can alter the appearance of the supraglottic structures. An omega-shaped epiglottis is often associated with laryngomalacia but can also be found in otherwise normal infants with no airway obstruction. If fluoroscopy is performed, downward anterior displacement and bowing of the aryepiglottic folds, horizontal infolding of the epiglottis, and in some cases, narrowing of the trachea are seen on inspiration, all of which reverse on expiration.[10]

Approximately 17% of infants with laryngomalacia have a second synchronous lesion that may lead to airway difficulties.[11] The decision to perform a bronchoscopy in patients who present with typical laryngomalacia is also controversial. Some contend that bronchoscopy need be done only in select infants with laryngomalacia who present with "apnea, failure to thrive, or features inconsistent with isolated laryngomalacia."[2,12] Others strongly recommend a complete evaluation of the tracheobronchial tree in all symptomatic infants to avoid missing life-threatening lesions.[13]

The anatomic abnormality causing the supraglotttic obstruction of laryngomalacia varies among infants. Most have anterior prolapse of the mucosa overlying the arytenoid cartilages (57%); others have short aryepiglottic folds that tether the epiglottis posteriorly (15%), posterior collapse of the epiglottis (12%), or some combination of these findings (15%).[2] Several classification systems have been proposed with none being predominant at this time.[2,14,15]

Approximately 10% to 31% of infants seen by a pediatric otolaryngologist require surgical intervention for their laryngomalacia.[1] Surgery is indicated if there is feeding difficulty with failure to thrive, cyanosis, apnea, respiratory distress, or hypoxia. The current standard treatment is supraglottoplasty (aryepiglottoplasty) (Fig. 202-3). The surgical resection can be performed using the carbon dioxide (CO_2) laser, laryngeal microscissors, or microdébrider.[1-3,5,16] Various types of supraglottoplasty have been described based on what portion of the prolapsing supraglottis is removed: the tissue overlying the arytenoids (with care taken to preserve the interarytenoid mucosa), the aryepiglottic folds, or the posterior portion of the epiglottis.[5] Unilateral supraglottoplasty has been advocated by some authors to relieve the airway obstruction while reducing the risk of postoperative supraglottic stenosis.[17,18]

Short aryepiglottic folds that tether the supraglotttic structures in close anterior and posterior approximation can be divided or excised.[19] If the epiglottis is displaced posteriorly, an epiglottopexy can be performed.[20] In this procedure the mucosa of the lingual surface of the epiglottis and the corresponding mucosa of the base of the tongue are removed with the CO_2 laser, then the epiglottis is sutured to the tongue base. These procedures are well tolerated by the infants, typically requiring only a short 1- to 3-day hospital stay. The success of the various forms of supraglottoplasty-epiglottopexy are high, with the vast majority of children obtaining relief from their obstruction.[3,16,19-23] Those children who do not improve with supraglottoplasty usually have underlying neurologic or syndromal abnormalities or associated tracheomalacia and may require a tracheotomy.[22,23] Complications are

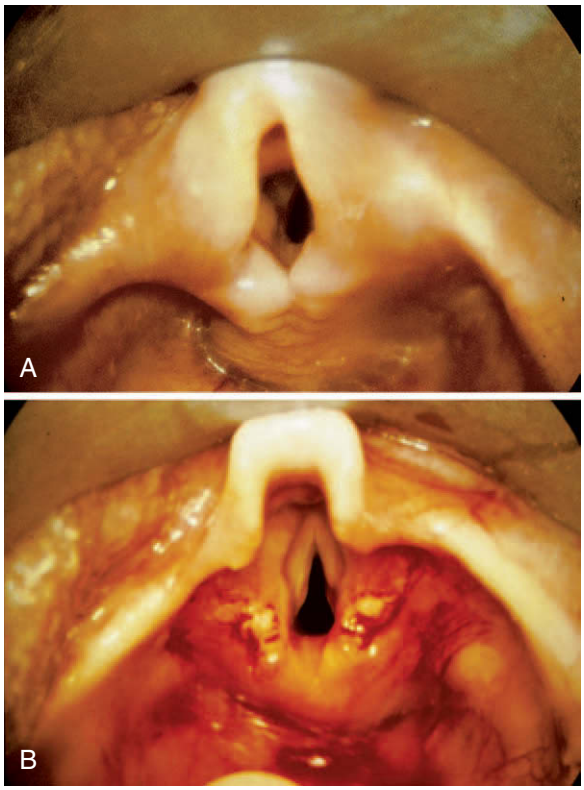

Figure 202-3. Laryngomalacia. Infant larynx before and after supraglottoplasty.

rare, with the most feared being supraglottic stenosis, which may occur in up to 4% of cases.[22] More frequently, transient dysphagia and aspiration can occur in approximately 10% to 15% of patients.[1]

Although laryngomalacia is typically thought of as occurring only in infants, it is occasionally observed in older children and adults. Neurologically impaired children (i.e., those with cerebral palsy) with poor pharyngeal control can develop laryngomalacia. Exercise-induced laryngomalacia results when enough inspiratory force occurs during exercise to draw the aryepiglottic folds into the larynx, partially obstructing the glottis.[24,25] In severe cases with redundant aryepiglottic folds, supraglottoplasty can be beneficial. Similarly, if the epiglottis is elongated and flaccid, a partial epiglottidectomy can be effective.[26]

Vocal Fold Paralysis

Vocal fold paralysis (VFP) is another common cause of neonatal stridor. The stridor is inspiratory or biphasic, with a high-pitched musical quality. VFP in a newborn may be idiopathic or can result from birth trauma, central or peripheral neurologic diseases, or thoracic diseases or procedures.[27,28] The diagnosis is best made by FFL in the awake patient so that the effect of anesthesia on vocal fold function is minimized.

Iatrogenic left VFP may be present following thoracic surgery, particularly patent ductus arteriosus (PDA) ligation or repair of an interrupted aortic arch. In these infants, the left recurrent laryngeal nerve is damaged at the point that it passes around the ductus arteriosus (unless a right aortic arch is present). The incidence of recurrent laryngeal nerve injury is estimated at 1% to 7.4% of PDA ligation cases.[29,30] Most infants with a unilateral VFP are brought to the attention of the otolaryngologist for evaluation of a weak cry or stridor or for inability to wean the infant off ventilatory support if thoracic surgery was performed.[30,31] Of those children evaluated by a pediatric otolaryngologist with a unilateral vocal fold paralysis after cardiac surgery approximately 35% will recover vocal fold function.[31] At least half of these patients will have swallowing dysfunction, usually aspiration or laryngeal penetration with modified barium swallow.[31,32] Although many of the patients with a unilateral vocal fold paralysis will be able to feed orally, many will initially require a gastrostomy tube.[31,32]

The more difficult problem is bilateral VFP. The degree of airway obstruction is often severe, requiring a tracheotomy in up to 73% of children.[33-35] The diagnosis of vocal fold paralysis can be made on FFL, but differentiation between bilateral vocal fold fixation and neurogenic VFP cannot be made unless direct laryngoscopy is performed and the glottis palpated. Laryngeal electromyography in the pediatric patient under a light plane of anesthesia can also be helpful to differentiate fixation vs paralysis and assist with prognosis.[36,37]

Workup of patients with idiopathic VFP should include a magnetic resonance imaging (MRI) scan of the brain to rule out an Arnold-Chiari malformation or other intracranial cause of brainstem compression.[38-40] If such a malformation is identified, then early decompression is recommended to obtain a better outcome.[40] If idiopathic congenital bilateral VFP is present, a genetics consultation is recommended to evaluate the patient for chromosome abnormalities.[41]

Approximately 70% of noniatrogenic unilateral vocal fold paralyses will resolve spontaneously, most within the first 6 months of life.[27] The patient with unilateral VFP is often able to compensate for purposes of feeding without medical intervention. Sometimes an infant will require nasogastric feeds on a short-term basis or a gastrostomy tube. An occupational or speech pathology feeding consult is helpful with these infants to rule out aspiration (as seen on modified barium swallow) and to counsel the parents on how to feed the patient. Most often, these infants should start with a slow-flow nipple, then work up to a regular nipple. The voice of most infants with a unilateral VFP is quiet but audible and gains strength with time.

Occasionally, the child with unilateral VFP has problems with severe aspiration and dysphonia. In these children, injection of the vocal fold can be helpful. Most commonly, injection materials used include cadaveric dermis (Cymetra), calcium hydroxyapatite (Radiesse or Radiesse Voice Gel), hydrated porcine gelatin powder (Surgifoam), or absorbable gelatin sponge (Gelfoam), or autologous fat.[42,43] Alternatively, in the older child a medialization laryngoplasty (thyroplasty) can be performed.[42-45] The retrospective review by Link and others of 12 type I thyroplasty procedures in eight pediatric patients ages 2 to 17 years demonstrated that the anatomically lower position of the vocal fold (compared with that in adults) must be taken into consideration if optimum outcomes are to be obtained in children.[45]

The vocal folds spontaneously become mobile in up to 65% of patients with bilateral VFP.[27,46] Prognosis is better if there are no associated anomalies.[33] Most recovery of vocal fold function occurs within 24 to 36 months, although it has been reported in patients up to 11 years of age.[33,34] If recovery occurs after 2 to 3 years, it is often incomplete because of laryngeal muscle atrophy, cricoarytenoid fixation, and synkinesis.[33] The timing of possible surgical intervention is debated. Some authors recommend intervention at a young age. Others suggest waiting until adolescence when the patient is able to decide.[33,34,47]

Many surgical options are possible to improve the airway of a patient with bilateral vocal cord paralysis.[48] The plethora of surgical options indicates that none is uniformly successful—particularly in the young patient. Endoscopically, a lateral cordotomy can be performed to increase the glottic area.[49,50] An arytenoidectomy can be performed via an endoscopic or external cervical approach or using the Woodman approach.[33,51] Alternatively, an arytenoidopexy can be performed using a laterocervical approach.[27,52,47] Triglia and colleagues performed an arytenoidopexy on 34 children with bilateral vocal cord paralysis who had a mean age of 20 months.[47] Of the 15 children who had a tracheotomy or endotracheal tube (ETT) before the procedure, 14 were successfully decannulated postoperatively. Another option is to expand the cricoid cartilage by placing a costal cartilage graft posteriorly, thereby separating the arytenoids and increasing the area between the vocal folds. This procedure can be performed with a laryngofissure or endoscopic approach.[53,54] Finally, lateralization of the paralyzed cord has been described as a potentially reversible approach to vocal cord paralysis.[55]

Hartnick and colleagues described 52 children who underwent surgery for bilateral VFP.[56] The procedures most successful in realizing tracheotomy decannulation were those that included vocal cord

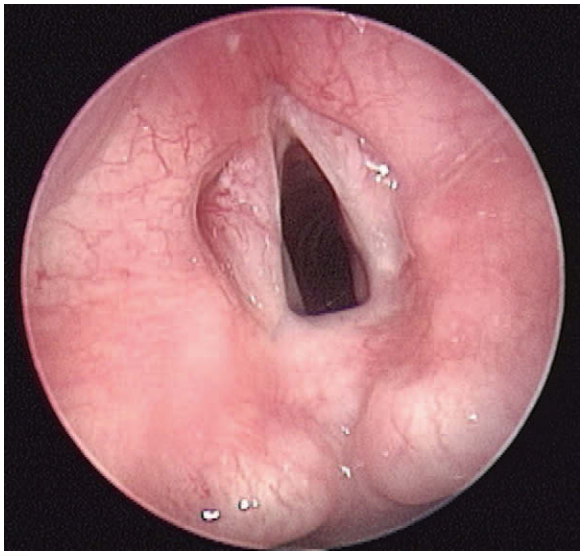

Figure 202-4. Interarytenoid web. *(Copyright Peter Koltai, MD.)*

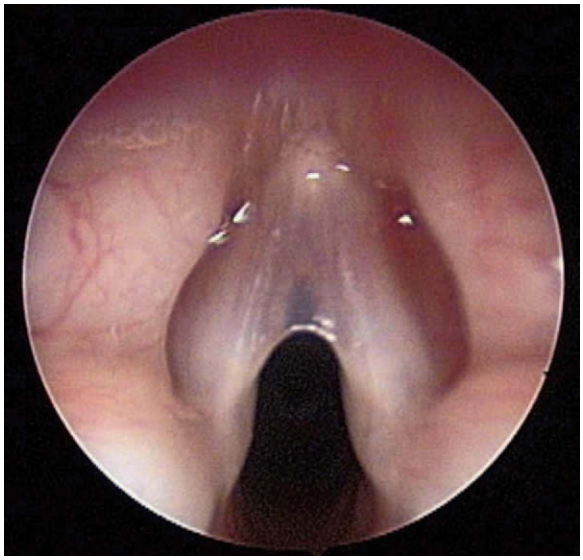

Figure 202-5. Anterior glottic web. Patient presented with chronic hoarseness and mild stridor. *(Copyright Peter Koltai, MD.)*

lateralization procedures combined with a partial arytenoidectomy (71% decannulation rate). These procedures were more successful than CO_2 laser cordotomy or arytenoidectomy procedures (29% decannulation), for isolated arytenoidopexy procedures (25% decannulation) or for posterior costal cartilage graft procedures (60% decannulation). No prospective randomized studies have been performed to evaluate the outcomes of these different surgical options, although meta-analysis has suggested that external arytenoidopexy and external arytenoidectomy are more effective than carbon dioxide ablation procedures.[57]

Laryngeal Web/Atresia

Posterior Webs

Apparent bilateral vocal cord paralysis may occur if an interarytenoid web is present in the posterior larynx causing limited vocal fold abduction (Fig. 202-4). This type of congenital web is rare and often necessitates a tracheotomy in the early years of life.[58] Stridor is the major presenting clinical feature, but patients can also present with obstructive cyanosis at birth or with episodes of apnea.

Diagnosis is made at the time of microscopic laryngoscopy with palpation of the interarytenoid area. Posterior webs may be associated with subglottic stenosis, and bulky arytenoids and abnormal laryngeal position are often present. Management options include long-term tracheotomy with probable decannulation after 3 to 5 years, division of the web (frequently unsuccessful), arytenoidectomy, or open airway reconstruction with a posterior cartilage graft.[58]

Anterior Webs

Anterior congenital laryngeal webs are also rare anomalies typically diagnosed in the neonatal period after an investigation for the source of aphonia and stridor (Fig. 202-5). Occasionally a minor web will not be diagnosed until the child is older and undergoes an evaluation for chronic hoarseness. Most commonly, a web will cause partial obstruction of the anterior glottis and will extend into the subglottic area, causing congenital subglottic stenosis.[59]

The most severe form of a laryngeal web is total atresia of the larynx (Fig. 202-6). A fetus with laryngeal atresia or a web obstructing nearly all of the larynx will develop congenital high airway obstruction syndrome (CHAOS). Magnetic resonance imaging of the affected fetus will show enlarged echogenic lungs, inverted diaphragms, massive ascites, and dilated airways (Fig. 202-7).[60,61] Death results in these infants unless a tracheotomy is performed at the time of birth, therefore delivery by ex utero intrapartum treatment (EXIT procedure) is recommended. The EXIT procedure establishes an airway before completion of birth, while the neonate remains on placental support.

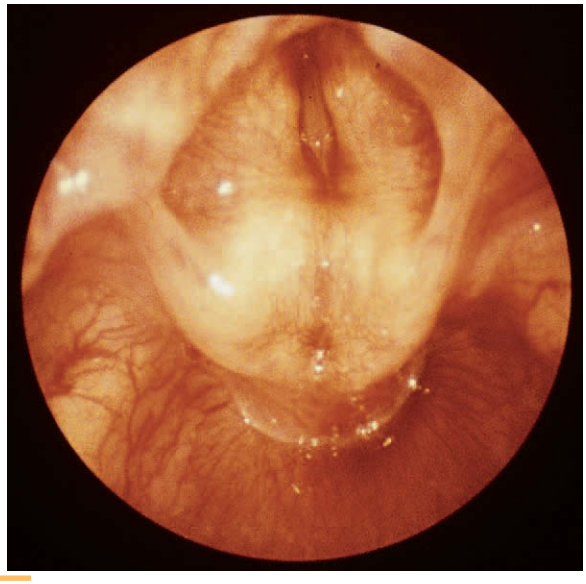

Figure 202-6. Laryngeal atresia. *(From Benjamin B. The pediatric airway, slide #33, Slide Lecture Series. American Academy of Otolaryngology–Head and Neck Surgery, 1992.)*

Many anterior laryngeal webs are associated with deletions of chromosome 22q11.[63] In a review of 17 patients with anterior glottic webs, 11 (65%) were found to be positive for chromosome 22q11.2 deletion.[63] These same microscopic and submicroscopic deletions cause a wide range of phenotypes including DiGeorge's syndrome, velocardiofacial (Shprintzen) syndrome, conotruncal anomaly face syndrome, and sporadic or familial heart defects (Table 202-1). The acronym CATCH 22 (cardiac defect, abnormal facies, thymus hypoplasia, cleft palate, hypocalcemia, and chromosome 22 deletion) has been used to describe the various phenotypes. For this reason, all patients with a diagnosis of laryngeal web should undergo genetic screening and a thorough cardiovascular evaluation, with particular attention being paid to the aortic arch. Delayed diagnosis of a vascular ring can occur in the patient with a laryngeal web whose stridor and dysphagia are attributed only to the presence of the web.[62]

Successful treatment of an anterior laryngeal web most often demands that an open approach be used so that the subglottic narrow-

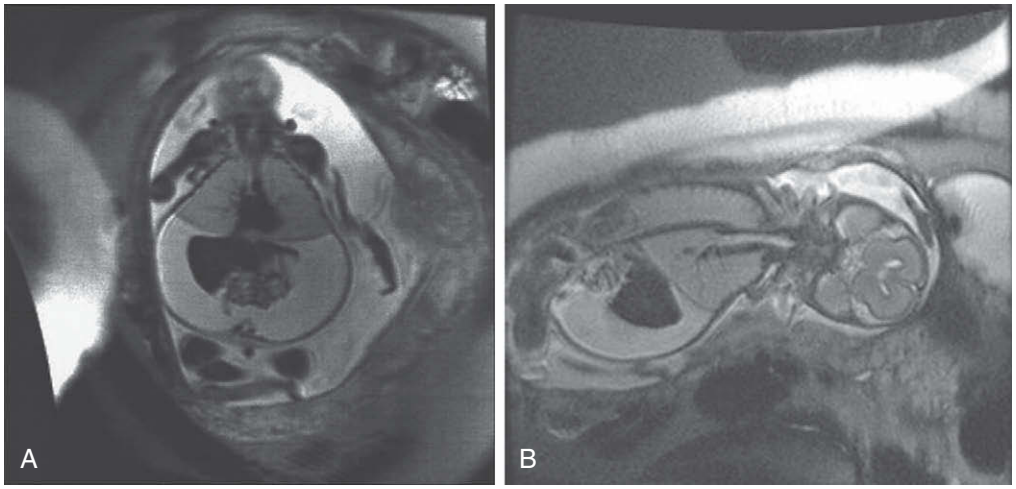

Figure 202-7. **A,** Fetus with congenital high airway obstruction syndrome due to laryngeal atresia. Magnetic resonance imaging (MRI) scan of the fetus in utero shows abnormally large, echogenic lungs and massively enlarged fluid-filled fetal lungs with associated chest deformation and fetal heart compression by the enlarged lungs. **B,** MRI shows an abrupt, V-shaped termination of the trachea with the apex pointing superiorly. *(From Erickson V, Messner A. Radiology quiz case 2. Congenital high airway obstruction syndrome (CHAOS).* Arch Otolaryngol Head Neck Surg. *2007;133:299-301.)*

Table 202-1

Syndromes Associated with Congenital Laryngeal Anomalies

Laryngeal Anomaly	Chromosome Affected	Associated Syndromes	Other Associated Anomalies
Laryngeal web	22q11	Velocardiofacial DiGeorge Conotruncal face	Cardiac anomalies Cleft palate–velopharyngeal insufficiency Hypocalcemia Abnormal facies
Laryngotracheal cleft or bifid epiglottis	GLI3	Pallister-Hall (congenital hypothalamic hamartoblastoma)	Polydactyly Pituitary dysfunction Imperforate anus Hamartoblastomas
Laryngotracheal cleft or hypoplastic epiglottis		Opitz-Frias	Hypertelorism Cleft palate–cleft lip Intracranial anomalies Hypospadias Bifid scrotum, uvula, tongue

ing can be corrected.[64,65] Laryngotracheal reconstruction or laryngofissure and silastic keel are used to correct the defect. If laryngotracheal reconstruction is performed, the approach can sometimes be single-staged. In rare cases in which the web is limited, endoscopic treatment may be successful.

Congenital Subglottic Stenosis

Subglottic stenosis in a term newborn is defined as a cricoid diameter of less than 3.5 mm.[66] Congenital, as opposed to acquired, stenosis is typically the result of malformation of the cricoid cartilage. Normally, at the inferior margin of the cricoid cartilage the transverse and anteroposterior diameters of the normal infant larynx are equal, resulting in a ring configuration. In some infants with congenital subglottic stenosis, an elliptical cricoid is present with a transverse diameter that is significantly smaller than the anteroposterior diameter, which may cause respiratory distress and predispose the larynx to injury from endotracheal tube intubation.[66,67] The elliptical cricoid may be found in association with a laryngeal cleft. An "occult" or submucous posterior laryngeal cleft may be associated with subglottic stenosis. This type of cleft is difficult to identify, however, because the soft tissue overlying the posterior cricoid appears normal.

In comparison with the elliptical cricoid, the transverse diameter may be greater than the anteroposterior diameter, causing a flattened cricoid, which again may lead to respiratory distress and intubation trauma. The flattened cricoid may be associated with a trapped first tracheal ring, where the first tracheal ring is inside the cricoid cartilage, thereby reducing the size of the lumen. A narrowed subglottic space can also be caused by a generalized thickening of the cricoid.

The stridor of subglottic stenosis may be inspiratory or biphasic and worsens with patient agitation (increased airflow). A mild stenosis may be asymptomatic until an upper respiratory tract infection causes subglottic edema and the child presents to medical personnel with symptoms consistent with croup. Prolonged or recurrent croup may be caused by mild subglottic stenosis.

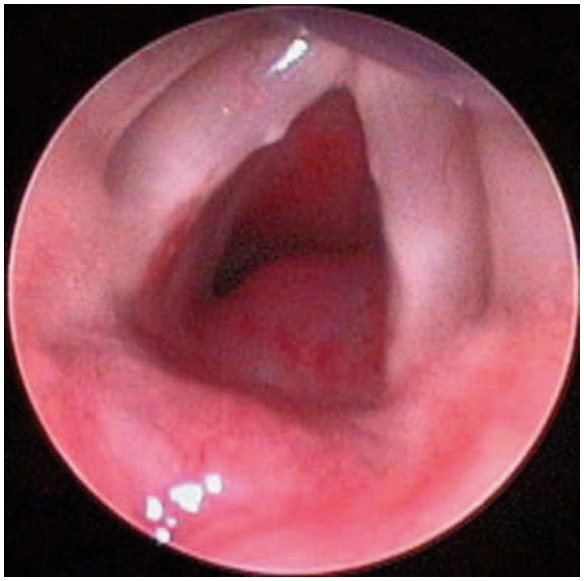

Figure 202-8. Right posterior subglottic hemangioma.

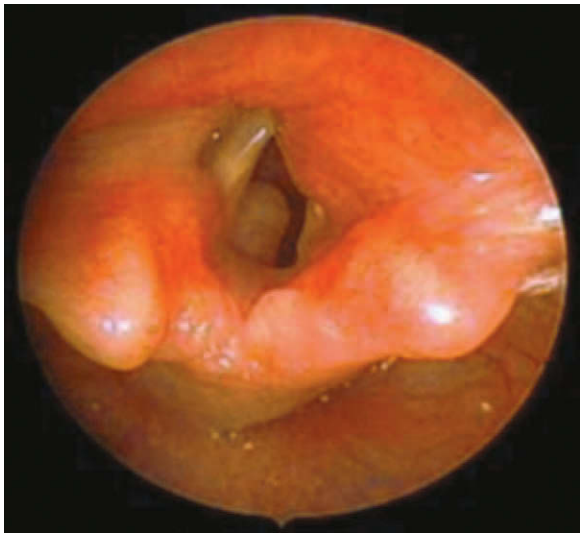

Figure 202-9. Left subglottic cyst.

Direct laryngoscopy and bronchoscopy are needed to fully evaluate subglottic narrowing. Objective measurement at the time of laryngoscopy by sequential gentle placement of endotracheal tubes of various sizes is recommended.[68] The stenosis is then graded: grade I, less than 50% obstruction; grade II, 52% to 70% obstruction; grade III, 71% to 99% obstruction; grade IV, no detectable lumen.[68]

In patients with grade I stenosis, a watchful waiting approach can be taken and the child will likely grow out of the problem as the cricoid cartilage grows. In the child with a more significant stenosis, surgical intervention is usually needed. Because it is primarily a cartilaginous problem, congenital subglottic stenosis does not typically respond to dilation or laser treatment, which is sometimes effective in soft tissue acquired stenoses. If the stenosis is grade II or III, a tracheotomy will likely be needed until the cricoid grows to a sufficient size to allow decannulation, or a laryngotracheal reconstruction performed to expand the cricoid ring. For further details of surgical management, see Chapters 71 and 206 on subglottic stenosis.

Hemangiomas and Subglottic Cysts

Mass lesions in the subglottic area can mimic the symptoms of subglottic stenosis. Subglottic hemangiomas are benign vascular malformations characterized by endothelial hyperplasia. They are twice as common in females as in males, and the patients typically present to medical caregivers in the first 6 months of life with inspiratory or biphasic stridor.[69,70] Often these patients are thought to have nonresolving croup, because they have a barking cough that responds temporarily to oral steroids. Hemangiomas grow rapidly in the first 6 months of life, stabilize for approximately a year, then slowly involute until they are gone, usually by the age of 3 years. To avoid total airway obstruction, medical or surgical intervention is usually needed.

Diagnosis is made at the time of direct laryngoscopy, with viewing of the subglottic area via telescope or microscope (Fig. 202-8). Narrowing of the subglottis can sometimes be seen on x-ray examination of the neck, and computed tomography (CT) or MRI scan can assist in the diagnosis.

The traditional medical treatment used for management of the patient with a subglottic hemangioma is systemic steroids. In most children, systemic steroids result in at least partial regression of the hemangiomas. Steroid therapy alone has been advocated as the primary method of management.[71] Long-term therapy lasting several months is needed if the hemangioma is to be controlled, leading to possible severe side effects such as Cushing's syndrome, hypertension, diabetes, and growth retardation. Intralesional steroids and short-term intubation also have been recommended as a method to control the subglottic hemangioma. Using a protocol of steroid injection followed by 1 week of intubation has resulted in patent airways at a mean of 9.5 months of age in 82% of the 15 patients treated at one institution.[72] Propanolol, a beta-blocking agent, has been used successfully to treat infantile hemangiomas. The conditions under which it will be most successful have not yet been identified.

The traditional surgical option to relieve the airway obstruction associated with subglottic hemangioma is a tracheotomy. The tracheotomy tube bypasses the lesion. Once the lesion involutes, the patient can be decannulated, on average 27 months after the tracheotomy was placed.[69] Accidental decannulation and tracheostomy tube obstruction are the major drawbacks of this approach. The mortality rate of a tracheostomy in an infant is generally accepted to be between 1% and 2%.[73] In addition, the care required to keep an infant with a tracheostomy tube safe is tremendous, causing a severe strain on the patient's family.

The carbon dioxide and potassium titanyl phosphate (KTP) lasers have been used to control hemangiomas.[69,74] Using a CO_2 laser has been reported to be successful,[70,75] but others have reported that the laser did not result in earlier tracheotomy decannulation.[69] It has been proposed that the KTP laser may be the superior instrument for treatment of the hemangiomas because the KTP beam is preferentially absorbed by hemoglobin, making it more applicable to the treatment of vascular lesions.[74] The most significant complication associated with the laser is subglottic stenosis, which has been reported in up to 18% of cases.[75,76] At least one report did not find any advantage of the tracheostomy and laser compared with the tracheostomy alone.[69]

Open surgical resection via a laryngofissure has been reported to be successful in several cases.[69,77,78] This approach seems to be particularly useful in the patients with circumferential or bilateral subglottic hemangiomas.

Another lesion that can mimic the symptoms of a subglottic hemangioma is the subglottic cyst (Fig. 202-9). In one review, 55 patients with subglottic cysts were identified.[79] All had been intubated in the neonatal period and 94% were born prematurely at 24 to 31 weeks of gestation. Intubation trauma is believed to be the cause of these lesions.[80] The cysts can be unroofed with either a laser or microlaryngeal instruments, but recurrence is common.[81,82]

Thyroglossal Duct Cyst

Cysts at the base of tongue in the vallecula are a rare but potentially lethal source of airway obstruction in a neonate (Fig. 202-10). Cases of acute airway obstruction with sudden death have been reported.[83-85] The obstructing cysts are of thyroglossal duct origin and have pseudostratified ciliated or squamous epithelium, with mucous glands and thyroid follicles in the subjacent stroma.[86] If thyroid follicles are not

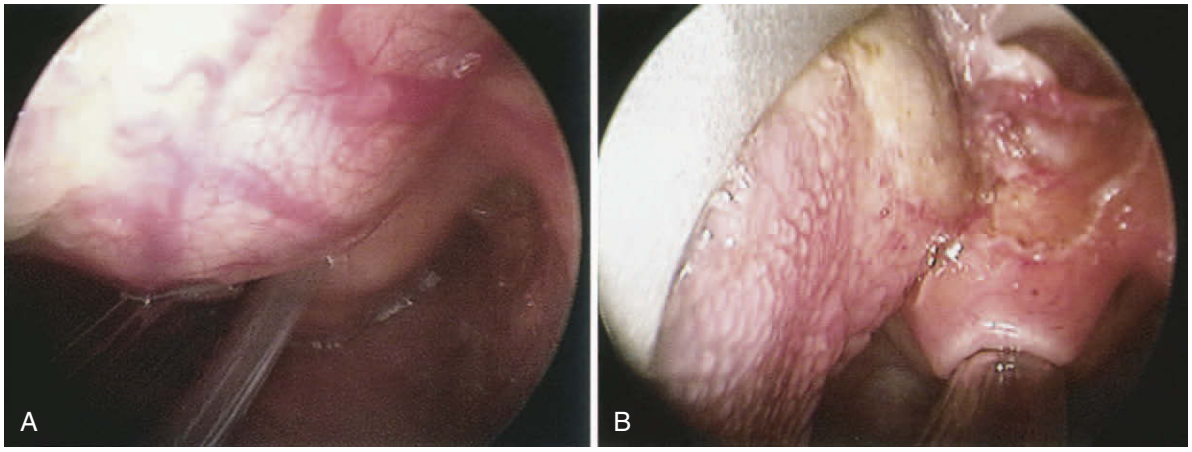

Figure 202-10. Vallecular thyroglossal duct cyst before and after marsupialization.

seen, the pathologist sometimes will call it a vallecular cyst instead of a thyroglossal duct cyst, but the origin is the same. In addition, cysts that occur on the epiglottis or in the vallecula and originate from obstruction of the submucosal glands are sometimes are called "ductal cysts."[87] Infants with thyroglossal duct cysts at the foramen cecum typically develop symptoms within the first few weeks of life. Most commonly the baby will present with stridor but feeding difficulties, coughing, cyanotic episodes, failure to thrive, and breath-holding spells may be present.[87-90] The voice may be normal or may have a muffled quality.

Diagnosis is made at the time of flexible or direct laryngoscopy. A lateral neck x-ray film, CT scan, or MRI scan may be helpful in the diagnosis, but endoscopy is the major diagnostic tool. Definitive treatment should not be delayed for these other investigations in the infant with airway obstruction.[88] The differential diagnosis of a vallecular mass in children also includes a dermoid, teratoma, lingual thyroid, lymphatic malformation, or hemangioma.[85] If a thyroglossal duct cyst or lingual thyroid is identified, then a thyroid scan or ultrasound should be performed to identify other functioning thyroid tissue.

Treatment of all types of vallecular cysts is by endoscopic surgical removal or marsupialization. Aspiration of the cysts for definitive treatment is not advocated because they will recur. In an emergency situation with a tenuous airway, the cyst can be aspirated, with definitive surgical treatment following.

Laryngeal Cysts

Saccular cysts and laryngoceles are unusual causes of respiratory obstruction in children. The anterior-superior portion of the laryngeal ventricle leads to a pouch of mucous membrane called the saccule. The saccule rises superiorly between the false vocal fold, the base of the epiglottis, and the inner surface of the thyroid cartilage. Scant muscle surrounds the saccule, compressing it to express its secretions on the vocal folds. Laryngoceles (abnormal dilation or herniation of the saccule) can be internal, confined to the interior of the larynx and extending posterosuperiorly into the area of the false vocal fold and aryepiglottic fold, or laryngoceles can be external, passing through the thyrohyoid membrane and presenting as a mass in the neck. If both an internal and external component are present, the laryngocele is termed a *combined laryngocele.* The radiographic finding of an air-containing rounded mass in the neck or supraglottic region, sometimes with air-fluid levels, confirms the presence of a laryngocele.[10]

Saccular cysts result from the obstruction of the laryngeal saccule orifice, or the collecting ducts of the submucosal glands located around the ventricle produce the saccular cysts. Saccular cysts may be anterior, protruding between the anterior and posterior vocal cords, or lateral, extending into the false vocal cord and aryepiglottic fold (Figs. 202-11 and 202-12). Laryngoceles produce intermittent upper airway obstruction and hoarseness because of episodic filling with air, whereas saccular cysts produce constant symptoms because of mucoid fluid within the cyst. Diagnosis is made at the time of flexible or direct laryngoscopy.

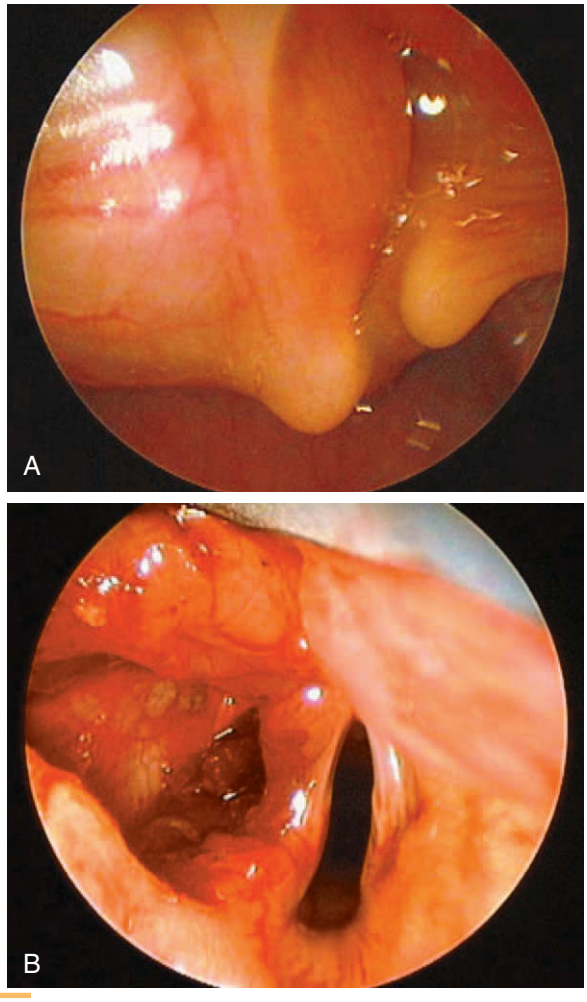

Figure 202-11. **A,** Left lateral saccular cyst. The 17-month-old female presented with a muffled cry and history of stridor when younger. **B,** Area of saccular cyst following endoscopic resection.

Other laryngeal lesions, such as hemangiomas, laryngeal duplication cysts, hamartomas, choristomas, and teratomas, can present with similar symptoms and appearance.[91-94]

Typically, treatment of the cysts involves endoscopic marsupialization of the cyst, most commonly with the CO_2 laser so that the back wall of the cyst can be ablated.[95] Recurrence after marsupialization of a posterior saccular cyst is common, often necessitating several

Figure 202-12. Computed tomography scan of child with a lateral saccular cyst.

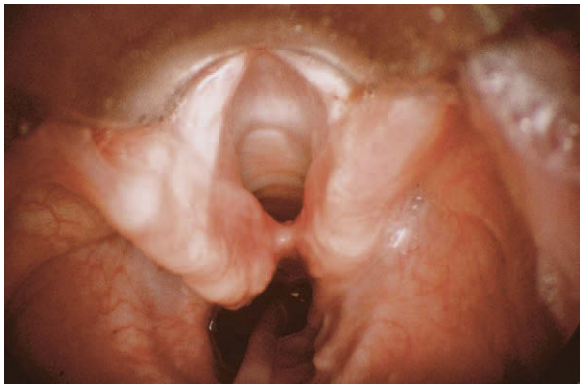

Figure 202-13. Laryngotracheal cleft—Benjamin-Inglis type 3. *(From Benjamin B: The pediatric airway, slide #34, Slide Lecture Series. American Academy of Otolaryngology–Head and Neck Surgery, 1992).*

endoscopic procedures.[96] Tracheotomy may be required and subglottic stenosis is a potential complication of the treatment. Alternatively, removal of the cyst can be achieved via a lateral cervical approach through the thyrohyoid membrane.[97]

Laryngeal-Laryngotracheoesophageal Cleft

Laryngeal cleft (LC) and laryngotracheoesophageal clefts (LTECs) are rare congenital anomalies caused by failure of the posterior cricoid lamina to fuse and incomplete development of the tracheoesophageal septum (Fig. 202-13). This developmental failure leads to an abnormal communication between the posterior portion of the larynx and esophagus.

Presenting symptoms depend on the extent of the cleft. Small clefts involving only the interarytenoid musculature (type 1) are difficult to diagnose and the need for a high index of suspicion cannot be overemphasized. There are wide variations in the reported incidence of presenting symptoms suggesting that the diagnosis of mild LCs is an inexact science. Feeding difficulties and aspiration have been reported to occur in 40% to 90% of patients, and stridor in 15% to 94% of patients.[98-100] Recurrent pneumonia and chronic cough are also commonly seen with this diagnosis. The severity of symptoms typically increases with the extent of the cleft. Patients with LTECs that extend into the trachea present with signs and symptoms of severe aspiration, respiratory distress, and cyanosis.[101]

Most patients with LC and LTECs have other congenital abnormalities, most commonly including tracheoesophageal fistula (TEF), esophageal atresia, congenital heart disease, cleft lip and palate, micrognathia, glossoptosis, laryngomalacia, and Opitz-Frias syndrome (see Table 202-1).[102] A tracheoesophageal fistula is present in approximately 25% of patients with an LC or LTEC and is an important prognostic indicator of possible failure of the surgical repair.[100-104]

Diagnosis is made at the time of microdirect laryngoscopy where the interarytenoid mucosa is spread laterally to reveal the cleft larynx. Care must be taken to look at and palpate the interarytenoid area, because the cleft may be missed if only a flexible bronchoscopy or direct laryngoscopy without palpation is performed. In a group of 20 children, the average interarytenoid notch height relative to the vocal folds has been found to be approximately 3 mm.[105] In this study, a low interarytenoid notch height was found to be significantly correlated with laryngeal incompetence and aspiration. In the patient with a laryngeal cleft, bronchoscopy and esophagoscopy should also be performed and a biopsy of the esophagus considered if there is any evidence of gastroesophageal reflux. Other diagnostic tests often performed include barium swallow, functional endoscopic evaluation of swallow (FEES), and chest x-ray study to evaluate the extent of aspiration.[98] Barium swallow shows spillover of barium from the esophagus into the trachea. High small clefts may be difficult to differentiate from high H-type tracheoesophageal fistulas.[10]

Multiple classification schemes have been described, all based on the vertical length of the cleft (Table 202-2), with the Benjamin-Inglis system being used most commonly (Fig. 202-14).[103,106-109] In addition, submucous "occult" laryngeal clefts have been described.[66,110,111] The submucous laryngeal cleft consists of a posterior midline cartilage defect, with intact soft tissue including mucosa and interarytenoid muscle. It is associated with subglottic stenosis and typically is not identified unless a postmortem examination is performed.

Early repair of LCs and LTECs are recommended to avoid irreversible pulmonary damage from continued aspiration.[108] The method of surgical repair for LCs and LTECs depends on the type of cleft present. For clefts that extend only through the interarytenoid musculature, antireflux therapy may be enough to control symptoms. At some centers, conservative treatment with temporary nasogastric tube feedings is recommended.[99] If a Benjamin-Inglis type I or II cleft is symptomatic, endoscopic or open surgical repair is possible.[100] If the significance of the cleft for a particular patient is unknown, Gelfoam can be injected into the interarytenoid area to determine whether symptoms are alleviated and to provide clarification of the contribution of the posterior laryngeal cleft to the clinical status of the patient.[112]

For some clefts that extend into the cricoid and all clefts that extend below the cricoid (Benjamin-Inglis type II-IV), an open procedure is required. These clefts are best repaired using an anterior laryngofissure to avoid injury to the vascular and neural structures.[113,114] If the cleft extends to the carina (type IV), an anterior laryngofissure and median sternotomy are recommended.[115] Most patients require a tracheotomy in at least the perioperative period. If the median sternotomy approach is used, then the intrathoracic part of the repair is performed with the patient on cardiopulmonary bypass or extracorporeal membrane oxygenation.[102,115] The prognosis is grim for patients with a type IV LTEC that extends all the way to the carina.[115]

Most commonly, a two-layer closure of the cleft is performed with absorbable sutures. If possible, the two layers should not directly oppose each other to minimize the chance for breakdown and recurrent clefting. Tracheoesophagoplasty with two overlapping flaps via an anterior approach has also been used with good results.[113] An interposition graft may be placed between the two suture lines. Possible grafts include a sternocleidomastoid or strap muscle flap (inferiorly based), tibial periosteum, auricular cartilage, or temporalis fascia.[101,104,114,115]

Outcomes of surgical repair vary.[101,113,114] A higher rate of suture line breakdown occurs in the more extensive clefts and after surgical repair of an LC or an LTEC in any child who also has a tracheoesopha-

Table 202-2

Laryngeal and Laryngotracheoesophageal Cleft Classification

Cleft Location	Petterson	Armitage	Evans	Benjamin/Inglis*	Myer/Cotton*
Laryngeal					
Interarytenoid	Type I	Type IA	Type I	Type I	LI
Partial cricoid	Type I	Type IB	Type II	Type II	LII
Complete cricoid	Type I	Type IC	Type II	Type II	LIII
Laryngotracheoesophageal					
Into cervical trachea	Type II	Type II	Type II	Type III	LTEI
To intrathoracic trachea/carina	Type III	Type III	Type III	Type IV	LTEII

*Most useful classification systems.

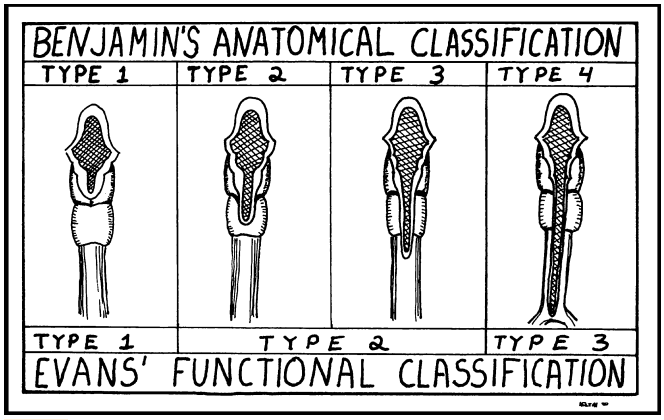

Figure 202-14. Benjamin-Inglis classification system for laryngeal clefts. *(Copyright Peter Koltai, MD.)*

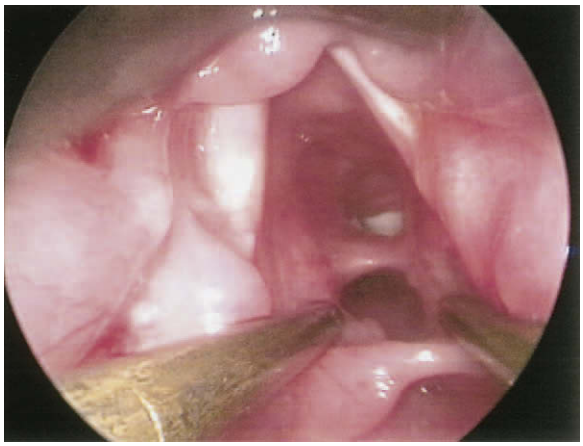

Figure 202-15. Benjamin/Inglis stage 3, Myer/Cotton Stage LTEI recurrent laryngotracheal cleft after two open attempts at repair. Note small mucosal bridge at proximal end of cleft and tracheotomy tube within the trachea.

geal fistula (see Fig. 202-14). In a retrospective review of 25 children who underwent a Myer-Cotton classification type LII, LIII, or LTEI cleft repair, 12 of 14 (86%) who had a previously repaired TEF subsequently developed a recurrent LC or LTEC (Fig. 202-15).[104] Of the remaining 11 patients who did not have a TEF, only one experienced a suture line breakdown. Gastroesophageal reflux and eosinophil gastroenteritis can also negatively affect the surgical repair and thus should be treated aggressively.[116-118]

Bifid Epiglottis

A bifid epiglottis is a rare anomaly defined as a cleft of the epiglottis encompassing at least two thirds of its length.[119] The infants typically present with stridor or aspiration, although they also can be asymptomatic. The diagnosis is made on laryngoscopy, and if the epiglottis is lax, prolapsing into the laryngeal inlet, supraglottoplasty can be performed.

Associated congenital anomalies are common and tend to be midline.[120] In the head and neck these anomalies include cleft palate, cleft uvula, micrognathia, and microglossia (see Table 202-1). Polydactyly has been reported in approximately 75% of patients with a bifid epiglottis.[121] The hypothalamic-pituitary axis is often disrupted in children with a bifid epiglottis. Congenital hamartomas or the absence of the pituitary gland can lead to growth hormone insufficiency with resultant growth retardation, secondary hypothyroidism with resultant cretinism, or secondary hypoadrenalism resulting in salt wasting and hypoglycemia.

Pallister-Hall syndrome (PHS), or congenital hypothalamic hamartoblastoma syndrome, is commonly associated with a bifid epiglottis.[122] Laryngoscopic examination of 26 subjects with PHS showed that 15 had a bifid or cleft epiglottis (58%). Other associated features of the syndrome include polydactyly, pituitary dysfunction, imperforate anus, and laryngotracheal cleft. It has an autosomal dominant inheritance pattern, with variable expressivity and is caused by a mutation in the GLI3 gene.[122] Because of the high incidence of hypothalamic-pituitary problems, all infants with a congenitally bifid epiglottis should undergo an MRI of the brain, an endocrine evaluation, and a genetics consultation.

Summary

Congenital laryngeal anomalies cause a spectrum of airway difficulties. In laryngomalacia, the stridor is transient and in most cases resolves spontaneously without intervention. Conversely, laryngeal atresia or obstructing vallecular cysts can lead to neonatal death. Although nearly all anomalies present with stridor, they can cause a host of other problems for the young child, including dysphagia, aspiration, failure to thrive, and dysphonia. Laryngoscopy, either direct or flexible, is the procedure most likely to diagnose the problem, although complete laryngotracheobronchial endoscopy may be needed to rule out a laryngeal cleft or other synchronous airway lesions.

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CHAPTER TWO HUNDRED AND THREE

Voice Disorders

Sukgi S. Choi

George H. Zalzal

Key Points

- Evaluation and management of voice disorders in children can be more challenging because of their inability to cooperate, lack of awareness of the problem, and lack of motivation to change.
- Otolaryngologic evaluation of a child with voice disorder begins with detailed history, physical examination, flexible laryngoscopy, and videostroboscopy.
- Voice evaluation by a speech pathologist should include perceptual, acoustic, and aerodynamic analyses.
- Voice therapy plays an essential role in management of pediatric voice disorders and should be used liberally both preoperatively and postoperatively.
- Voice disorders can be due to functional and organic etiologies. Organic voice disorders requiring primarily surgical management include vocal fold paralysis, laryngeal web, posterior glottic stenosis, recurrent respiratory papillomatosis (RRP), and malignant tumors. Vocal fold granulomas typically require medical management. Vocal nodules, cysts, polyps, and sulcus are initially managed with voice therapy but may require surgery.
- Surgery, especially in very young children, should be undertaken with caution.

Voice production starts with the expiration phase of respiration, which provides the air pressure to vibrate the vocal folds. The lowest periodic component of vocal fold vibration is termed *fundamental frequency* and is perceived as pitch.[1] Harmonics are integer multiples of fundamental frequency in voiced sounds. The energy or intensity in the harmonic components decreases as frequency increases.

Sound waves generated by vocal fold vibration are modified by the size, shape, and tenseness of the resonating chamber, which consists of the oropharynx, the nasopharynx, and the nasal cavities. The resonance of the vocal tract is termed *formant*.[1] Although an infinite number of formants exist, only the first four formants (F1, F2, F3, and F4) are of clinical interest; the lowest frequency formant is F1. Each formant is characterized by its center frequency and bandwidth. Constriction of the vocal tract near a volume velocity maximum or minimum can respectively lower or raise the formant frequency. The resulting sound wave is further modified by the articulators (lips, teeth, tongue), resulting in voice and speech production. A normal voice should be pleasing in quality and have appropriate balance of oral and nasal resonance, intensity, fundamental frequency level, and prosody. Voice disorder can result in a voice that is unpleasant for the listener or can interfere with effective communication.

The underlying cause of a voice disorder can be organic or functional. Organic voice disorders result from congenital or acquired anatomic abnormalities. Functional disorders are caused by emotional or psychological problems but can lead to anatomic alterations. However, even when a voice disorder results primarily from an organic cause, there is often a psychological overlay.[2]

Although the reported incidence of voice disorders in children varies greatly, most voice surveys of children show a 6% to 9% incidence of voice disorders.[3] Voice disorders are categorized depending on the area of problem: voice quality, resonance, loudness, and pitch. This classification is arbitrary, and a voice disorder often has several problem areas. Any anatomic abnormality involving the free edge of the vocal fold can affect voice quality and result in harshness, breathiness, or hoarseness. Disturbances in resonance can be caused by hypernasality or hyponasality. Loudness or intensity problems occur when a child speaks too loudly or too softly. Deviations in pitch occur with inappropriate speaking fundamental frequency, narrow pitch range, or excessive pitch breaks. An algorithm for the evaluation and management of voice disorders is outlined in Fig. 203-1.

Evaluation

The evaluation of a voice disorder in a child requires a systematic approach. Additional evaluation by specialists from a variety of disciplines including a pediatrician, pulmonologist, gastroenterologist, psychologist, and social worker may be necessary. A detailed history, including medical, birth, growth and development, and speech and language history is obtained, followed by detailed voice history to determine the cause of the voice disorder and its contributing factors, potentially including any pulmonary disease. Typically, voice history should include a description of the disorder, time of onset, any known causes, severity of the disorder, exacerbating or alleviating factors, voice use history, and any previous history of voice or speech therapy.

Social and functional impact of voice impairment can be evaluated using rating scales such as Pediatric Voice Outcomes survey (PVOS), Pediatric Voice-Related Quality-of-Life Survey (PVRQOL), and Pediatric Voice Handicap Index (pVHI).[4-6] These rating scales are designed to provide physicians with the parents' perception of the severity of the child's voice disorder and its impact on the child's daily life; they are used to follow the child's progress before and after therapy and surgical intervention.

Physical examination should concentrate on the head and neck areas. The ears are examined for evidence of previous and current ear disease. A nasal examination should reveal any deviation of the septum

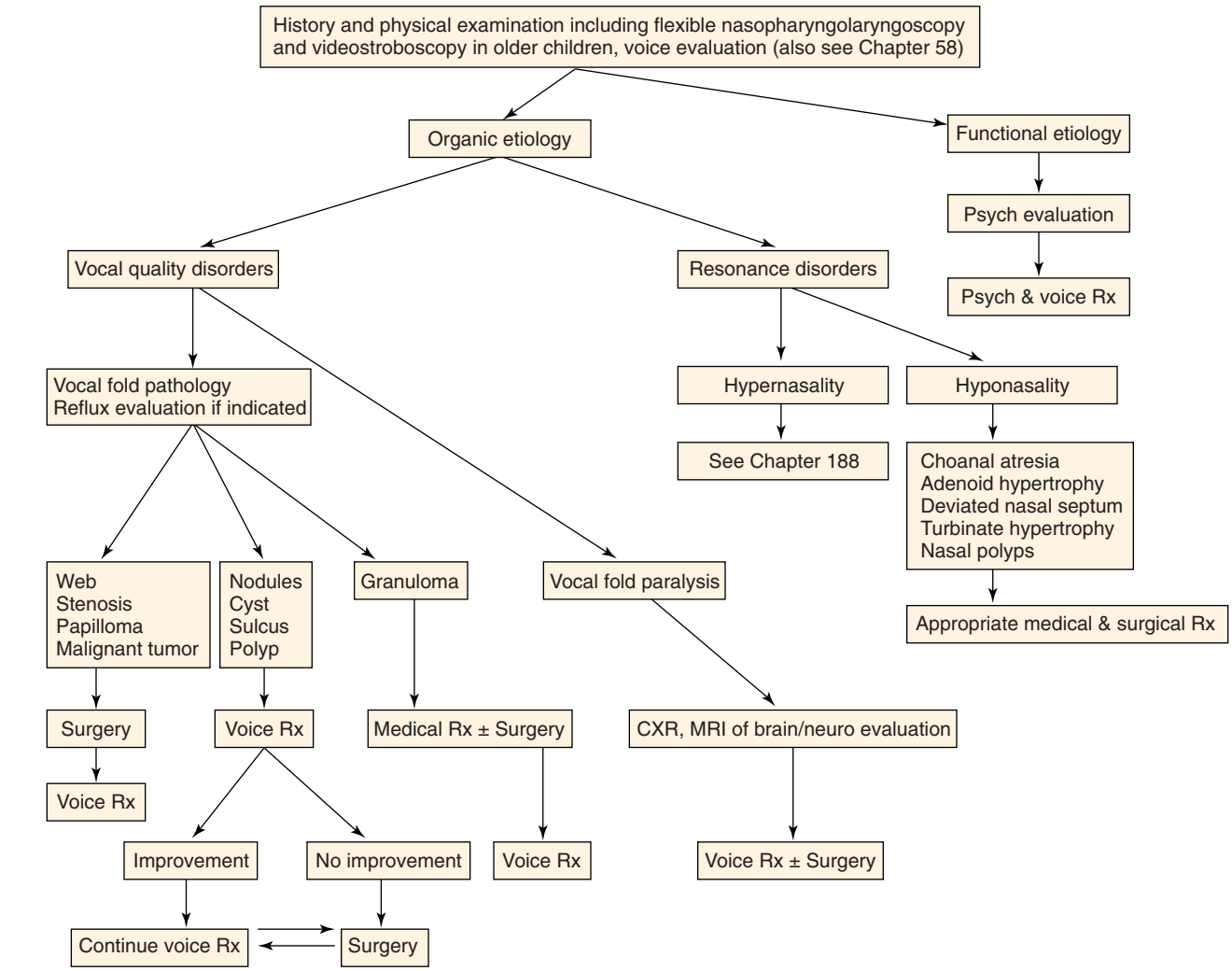

Figure 203-1. Evaluation and management of voice disorders in children.

and turbinate abnormalities. An oropharyngeal examination should focus on the structural integrity and mobility of the soft palate and is followed by flexible fiberoptic nasopharyngolaryngoscopy. Flexible fiberoptic scopes determine the size of the adenoid, velopharyngeal function, and any pathology in the supraglottic and glottic areas.

Stroboscopic examination, which uses a short burst of light in synchrony with vocal fold motion, can seemingly slow down the movement of the vocal folds and allow more careful examination of the vocal folds and their motion.[7] It is particularly useful in differentiating superficial from deep lesions. Laryngeal stroboscopy can delineate vocal fold symmetry, periodicity, vibratory amplitude, mucosal wave, glottal closure, and rigidity,[7] but it is not possible in many children. Bouchayer and Cornut[8] found that stroboscopic examination in children often had to be quick; therefore their results tended to be inconclusive. Hirschberg and colleagues[9] found that stroboscopy was possible only in children older than 6 or 7 years. McAllister and others[10] completed stroboscopic examination in only half of 60 patients age 10 years and older. The newer digital flexible endoscopes may allow stroboscopic examination in younger children.[11] In our voice clinic, digital flexible stroboscopy has been used successfully in children as young as age 3 years. Although stroboscopic examination can be instrumental in accurate diagnosis of a voice disorder, rigid endoscopy under anesthesia may be necessary in some children to establish diagnosis and for therapeutic intervention.

The child's voice is evaluated by a speech-language pathologist, usually in a voice laboratory. A typical voice evaluation consists of perceptual, acoustic, and aerodynamic analyses carried out as the child performs several speaking tasks. There are no universally accepted standards for speech and voice evaluation, and the speaking tasks, the speech parameters measured, and the method of measurement vary greatly.

There are several commonly used speaking tasks.[3] The first is oral reading, which is possible only in older children. Children who can read at third grade level or better are given a specific passage to read; younger children are allowed to select the reading material. The second task is conversational speech or connected speech at least 1 minute long. The child is asked to tell a story about a picture or talk about a specific topic (e.g., pets, a vacation, a hobby). Based on these two tasks, the speech-language pathologist can perceptually and acoustically analyze the child's speech for most voice parameters, including prosody.

The remaining speaking tasks are designed to evaluate more isolated aspects of the child's voice. The third task consists of counting from 1 to 10, 60 to 70, and 90 to 100.[3] The counting is done carefully, once slowly and then as rapidly as possible. This is repeated for three levels of loudness (soft, average, loud) and pitch (low, modal, high). This task reveals any problems with laryngeal tone, resonance, pitch, and loudness.

The fourth speaking task is the production of isolated speech sounds. This consists of sustaining certain vowel sounds (e.g., /a/, /i/) for at least 5 seconds and repeating them three times to determine laryngeal tone, resonance, and fundamental frequency. The child should then sustain /a/ at a comfortable pitch and loudness for as long as possible after a deep inspiration and repeat this three times with a break in between each attempt to determine the maximal phonation time and whether the child had adequate respiratory drive to maintain

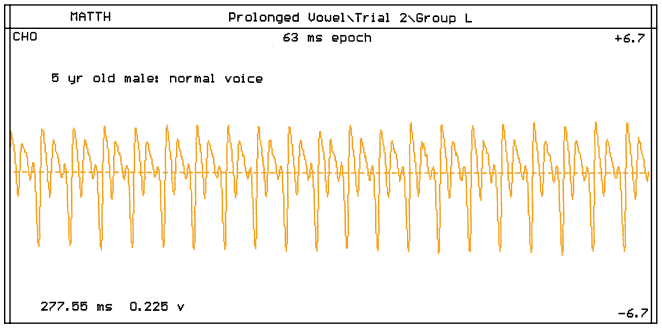

Figure 203-2. Voice tracing of a normal voice sustaining a prolonged vowel: mean fundamental frequency, 332.53 Hz; jitter, 0.36%; shimmer, 1.9%; harmonic/noise ratio, 12.37 dB.

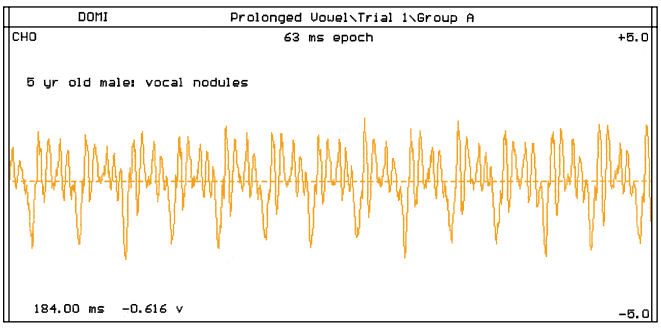

Figure 203-3. Voice tracing of a hoarse voice (caused by vocal nodules) sustaining a prolonged vowel: mean fundamental frequency, 220.60 Hz; jitter, 2.26%; shimmer, 4.34%; harmonic/noise ratio, 7.84 dB.

continuous voice.[3] This same procedure is repeated with /s/ and /z/. In a normally functioning larynx, the s:z ratio should be close to 1. However, a lesion in the vocal fold margins (e.g., vocal fold nodules) increases the amount of airflow and decreases the time on /z/, resulting in a ratio of 1.4 or greater 95% of the time.[12]

Finally, the examiner should instruct the child to repeat certain consonants, words, and short sentences to assess the child's articulation abilities and speech intelligibility. The words and sentences are typically chosen to bring out specific problems such as velopharyngeal insufficiency.

The speech samples are analyzed, and a voice profile can be then developed using scales such as the Buffalo III voice profile.[3] This voice profile classifies voice abnormalities as follows: 1, normal; 2, mild; 3, moderate; 4, severe; or 5, very severe. It evaluates laryngeal tone, pitch, loudness, nasal resonance, oral resonance, breath supply, muscles, voice abuse, rate, speech anxiety, speech intelligibility, and overall voice rating. Other perceptual scales such as GRBAS and Consensus Auditory-Perceptual Evaluation-Voice (CAPE-V) are also used in the evaluation of pediatric voice.[13,14]

Aerodynamic analysis provides objective measures of the velopharyngeal and vocal fold functions. The oral-nasal acoustic ratio and palatal efficiency rating computed instantaneously have been used to evaluate velopharyngeal function.[15,16] Laryngeal airway resistance can be measured to assess the effective closure of the vocal folds to airflow. This is measured noninvasively using an anesthesia mask, a pressure-sensing catheter, and a flow-sensing pneumotachometer. Values less than 30 cm H_2O/L/sec indicate inadequate closure, whereas values greater than 60 cm H_2O/L/sec are associated with hyperkinetic voice disorders.[17] Normative aerodynamic measures for children age 6 to 10 are available.[18] These techniques of aerodynamic analysis are being replaced by computer-assisted voice analysis programs.

Computer-assisted analysis of voice disorder was introduced in 1990 and is being used with increasing frequency.[19] This technology presents the opportunity to supplement perceptual evaluation of voice disorders and has replaced many traditional methods of evaluation. Evaluation of naturalness and intelligibility of speech still requires the human ear.

Computer-assisted voice analysis can provide the mean fundamental frequency, intensity, and amplitude of voice based on a small voice sample (0.5 second) for comparison with existing normative values for age and sex (Figs. 203-2 and 203-3).[19] Until recently, no normative data for children in these analyses was available and normative data from adult studies in the literature were used[20]; however, in 2002, Campisi and colleagues[21] published a pediatric normative database for computer-assisted voice analysis.

Other information provided by computerized voice analysis includes harmonics-noise ratio, amplitude perturbation (shimmer), frequency perturbation (jitter), and electroglottography. Aerodynamic measures can be obtained in less than 60 seconds using the pneumotachographic mask. Parameters that can be measured include subglottal pressure; transglottal airflow; oral pressure; nasal flow; airflow; resistance and efficiency; inspiratory, expiratory, and pause aerodynamics; and nasal and velopharyngeal resistance. Voice analysis is also discussed in Chapter 58.

Voice Therapy

There are important differences between voice therapy in children and in adults. Children often do not have the insight that their voice needs to be modified and they lack the motivation to change. Therefore, the therapist must work to increase the child's awareness of his or her vocal behaviors and awareness of behaviors that require change.

Voice therapy entails two stages.[22] The first stage consists of 10 exploratory sessions, each lasting 35 to 40 minutes. This stage helps determine the goals and specific procedures to be used in stage 2, which consists of regular voice therapy sessions for 2 to 5 months. The frequency of therapy is determined by the severity of the dysphonia. Therapy should be supplemented by practice at home to hasten resolution of dysphonia. The total therapy duration is approximately 4 to 5 months; improvement or resolution of dysphonia should be significant.

During the initial phase of voice therapy, the mechanisms of voice production and voice problems are explained to the child in simple terms, and a list of rules regarding good and bad voice are provided.[3,22] A main goal of therapy is to eliminate vocal abuse by decreasing the total amount of talking; however, even in highly motivated children, total voice rest may not be feasible. Listening training and auditory feedback are essential in voice therapy because, to correct a voice disorder, the patient should learn to differentiate normal and abnormal voices for comparison with his or her own voice.[3]

Problematic muscular tonus, loudness, pitch, and rate require therapy. These areas are often closely interrelated and should be managed simultaneously. The child is taught the following steps to correct a problematic voice parameter[3]: correct rules of specific voice parameters; identification of incorrect and correct voice habits in others; recognition of personal use of incorrect voice and modification of this habit; recognition of personal use of correct voice; recognition of situations that cause personal use of poor voice habits and good voice habits; and an increase in the amount of time that correct habits are used. These steps can be applied to any problematic voice parameter.

Voice production depends on well-coordinated movement of muscles involved in phonation. Hyperfunction or excessive muscular tonus frequently occurs in children with benign laryngeal pathology, whereas hypofunction with flaccid muscular tonus occurs in those with functional dysphonia. For both problems, control of muscular tonus and proper positioning of the laryngeal, pharyngeal, and oral structure should be taught. To correct hyperfunctional states, posture instruction, breathing exercises, relaxation procedures, muscle tension reduction technique, chewing method, muscle stretching exercises, and biofeedback can be used.[23-25] Wilson[3] found that the chewing method and progressive relaxation are particularly useful in reducing muscular tension. For hypofunctional states, the pushing method increases muscular tension.[26]

Excessive loudness of voice is accompanied by high pitch, rapid rate of speaking, and hyperfunctional state. Therefore it is often neces-

sary to manage these problems simultaneously. Eliminating loud speaking is particularly important in children with vocal nodules. Correct training for loudness, pitch, and rate involves teaching the child to listen and to monitor various voice parameters. Often, modifying loudness lowers pitch, and attention to loudness and pitch normalize the rate of speaking.

Functional Etiology

Functional voice disorder is diagnosed when no anatomic or organic cause can be found. Functional dysphonia is categorized as disturbed mutation, psychological dysphonia, imitation, and faulty learning.[3] Mutation is the change of voice that occurs during puberty. Pitch lowers in males and, to a lesser extent, in females. Mutation can be delayed, prolonged, or incomplete. High pitch, hoarseness, and voice breaks are characteristic. Mutational voice disorder can result from endocrine pathology.[3]

Functional dysphonia resulting from psychological causes seldom occurs in children; only isolated case reports can be found in the literature.[27] The underlying psychological problems are related to or are part of tensional symptoms, adjustment, anxiety, or personality disorders.[28] Functional dysphonia may be a form of conversion hysteria. The disorder may be complete aphonia or partial loss of voice. The dysphonia is often variable, with effortful voice production and easy fatigue. Laryngeal examination may show ventricular band approximation, bowed vocal folds, or hypoadducted vocal folds (hysterical aphonia). Vocal fold movement is normal with inhalation and cough.

Faulty learning[29] occurs when a child imitates cleft palate or hearing-impaired speech or learns to talk louder than normal because of the presence of hearing-impaired persons in the household.

In adults, several approaches have been used to manage functional dysphonia, including behavior therapy, hypnosis, speech therapy, psychotherapy, and a combination of speech therapy and psychotherapy. In children, the optimal management is unknown but psychotherapy or psychological counseling is often carried out in conjunction with voice therapy.

Organic Etiology

Resonance Disorders

Resonance disorders include hypernasality and hyponasality. Hypernasality is usually caused by velopharyngeal insufficiency from underlying palatal abnormalities. Hyponasality can result from any underlying condition that causes nasal or nasopharyngeal obstruction. The underlying pathology may be choanal atresia, deviated nasal septum, turbinate hypertrophy, nasal polyps, or, most frequently, adenoid hypertrophy. In performing adenoidectomy, particular attention should be paid to the structural integrity of the palate to decrease the incidence of postoperative velopharyngeal incompetence. Accurate diagnosis and appropriate medical and surgical management of these underlying conditions are further discussed in Chapter 188.

Vocal Quality Disorders: Surgical Management

Vocal Fold Paralysis

Vocal fold paralysis in children results from birth trauma and congenital anomalies of the central nervous system and the heart and great vessels. Any infant or child with vocal fold paralysis should be evaluated with chest radiograph and imaging of the central nervous system.[30-33] Vocal fold paralysis is the second most common cause of congenital stridor in children and represents 10% of congenital anomalies of the larynx.[34] Prognosis for spontaneous recovery is better for acquired, right-sided, and unilateral paralysis.[35-37]

More than 50% of vocal fold paralysis in children is bilateral.[32,38] Because arytenoid fixation can be mistaken for bilateral vocal fold paralysis, the cricoarytenoid joint should be palpated at rigid endoscopy. Laryngeal electromyography may be the most specific and sensitive test to determine the presence of vocal fold paralysis. More than 50% of the time, bilateral vocal fold paralysis requires tracheotomy for the establishment of an airway; however, the voice is often normal. Although spontaneous recovery of vocal fold function is possible after 2 to 3 years, late recovery is often incomplete because of laryngeal muscle atrophy, synkinesis, and cricoid fixation.[39] If vocal fold function does not return spontaneously after 10 to 12 months, surgery to decannulate the child should be considered.[31,40]

Surgical options to correct bilateral vocal fold paralysis consist of reinnervation with a nerve-muscle flap, cordotomy, lateralization procedures (e.g., arytenoidopexy), arytenoidectomy through a posterolateral external approach, arytenoidectomy through laryngofissure, or endoscopic arytenoidectomy.[31,40-44] Reinnervation of the posterior cricoarytenoid muscle is not universally successful,[38] although Tucker[45] reported it to be the management of choice in children. Because of the small size of the laryngeal structure, endoscopic techniques can be more difficult and less successful in children.[31,46] Cordotomy, a procedure in which the membranous vocal fold is sectioned from the vocal process of arytenoid, has limited use in children and may be useful as an adjunct to other procedures.[41,47] Narcy and colleagues[40] found Woodman's procedure to have a higher failure rate and recommended arytenoidopexy by an external posterolateral approach. However, Bower and colleagues[31] recommended arytenoidectomy through a laryngofissure because it provided better exposure, better control over the final fold position, and a high rate of success (84%). Although most patients have adequate voice postoperatively, breathiness, hoarseness, and pitch change are seen, and patients may require voice therapy. The resulting voice disorder is inversely proportional to the adequacy of the airway.

Unilateral vocal fold paralysis rarely requires airway intervention and often goes unrecognized until the child is older. The voice in unilateral vocal fold paralysis is hoarse, weak, and breathy. It usually improves spontaneously over 6 to 12 months by contralateral vocal fold compensation; recovery may be hastened by the use of voice therapy. However, in a few patients, persistent problems with dysphonia or aspiration require surgical intervention.[48] Surgical options include vocal fold injection, surgical medialization, and reinnervation. Surgical interventions should be done in conjunction with preoperative and postoperative voice therapy.

Polytef injection immediately improves voice; however, it is irreversible and changes vocal fold vibratory characteristics and thus results in poor vocal quality. Furthermore, in children, determining the amount of polytef to inject is difficult because general anesthesia is often necessary and airway obstruction is possible because of the small size of the larynx.[45] Levine and colleagues[48] recommended injection of an absorbable gelatin sponge, which is similar to polytef injection except that its effects are temporary. Fat injection appears to be well tolerated by the body, does not cause the vocal fold to become stiff, and is not absorbed extensively.[49] Recently, other injection materials such as AlloDerm and calcium hydroxyapatite have become available[50] but they have not yet been widely used in children.

Several surgical techniques are available for medialization of the vocal fold.[45,51-53] Isshiki type I thyroplasty is theoretically reversible and does not change the vibratory characteristics of the vocal fold; however, it does not restore tensioning capability of the vocal folds and requires external incision and a temporary tracheotomy in most cases. In children, this procedure is technically more difficult and may cause airway compromise. Experience with thyroplasty in children has been limited because of a lack of knowledge about the effect of this technique on thyroid cartilage growth.[48] Gray and colleagues[47] recommended thyroplastic operations only in patients with mature larynx because they believed that the operation may fix the distance between the arytenoid and thyroid cartilage. Link and others[54] have reported their experience with thyroplasty in children ages 2 to 17 years and have recommended modified surgical approach in children to compensate for their lower position of vocal folds. Although voice quality improves using objective measurement, the resulting voice is not ideal.[55]

Selective reinnervation of the adductors of the larynx does not compromise potential spontaneous recovery, necessitate tracheotomy, or preclude eventual use of other techniques; it restores tensioning capability, thereby providing better pitch control. However, it is an open procedure, and motion may not be observed for up to 6 months.[45]

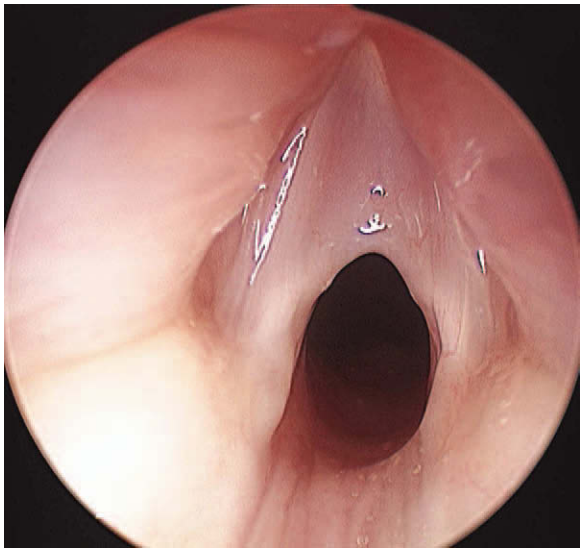

Figure 203-4. Type 2 laryngeal web.

Excellent results have been reported by Crumley[56] and Tucker.[45] Tucker advocated it to be the procedure of choice in children.[45]

Laryngeal Web

Smith and Caitlin[57] reported that glottic web and atresia account for 5% of congenital anomalies; however, some consider the true incidence of congenital web of larynx to be more common, whereas others consider it more rare. Web occurs because of failure of the epithelium, which temporarily obliterates the developing laryngotracheal lumen, to reabsorb during the eighth week of embryogenesis. Glottic web is classified depending on its severity.[58] Type 1 is an anterior web involving 35% or less of the glottis. True folds are visible within the web, and there is little or no subglottic extension. Although there is usually no airway obstruction, voice dysfunction is common. Type 2 is an anterior web involving up to 50% of the glottis (Fig. 203-4). True folds are usually visible within the web, and subglottic involvement is minimal. Voice disorder is the common presenting symptom. However, airway compromise can be seen with upper respiratory tract infections. Type 3 involves up to 75% of the glottis, and the anterior portion of the web is solid and extends into the subglottis. Most of the true folds are visible within the web. Airway obstruction and voice disorder are moderately severe. Type 4 involves up to 90% of the glottis, and the web is uniformly thick and extends into the subglottic area with resulting subglottic stenosis. Infants with this type of web are aphonic with severe airway compromise.

In 1985, Cohen and others[58] reviewed 51 cases of children with laryngeal web and recommended that surgery be tailored according to web severity. A type 2 web was divided with a knife, microsurgical scissors, or laser followed by dilations. Types 3 and 4 were managed by tracheotomy and insertion of a laryngeal keel through a laryngofissure. The anterior commissure is not adequately reconstructed by any surgical procedure, and the resulting voice continues to be abnormal and requires vocal rehabilitation.

Recommended management of a thin laryngeal web involves endolaryngeal division of the web with a knife or CO_2 laser with temporary placement of a keel to prevent readhesion. Thick glottic webs are approached through precise midline thyrotomy, a laryngofissure with removal of excess tissue under direct vision using a fiberoptic laryngoscope, and placement of a mucosal graft fixated with fibrin glue or stenting.[59] The use of CO_2 laser in cases of thick web is not recommended. The resulting voice is reportedly satisfactory, but objective postoperative analysis of voice is unavailable.

Posterior Glottic Stenosis and Cricoarytenoid Joint Fixation

Posterior glottic stenosis in children can be congenital (e.g., caused by interarytenoid web or cricoarytenoid fixation). More commonly, posterior glottic stenosis results from airway trauma from intubation. Bogdasarian and Olson[60] classified posterior glottic stenosis into four types. This classification was later modified for the pediatric population by Irving and associates.[61] Type I is vocal process adhesion, type II is posterior commissure or interarytenoid scar, type III is congenital or acquired unilateral cricoarytenoid fixation with or without interarytenoid scar, and type IV is congenital or acquired bilateral cricoarytenoid fixation with or without interarytenoid scar.

With interarytenoid web and scarring, there is bilaterally impaired abduction but normal adduction; these patients tend to have a normal voice.[62] The main presenting symptom in these cases is airway compromise. In cricoarytenoid joint fixation, adduction and abduction of the vocal fold are limited, which may also cause dysphonia. To distinguish cricoarytenoid joint fixation from vocal fold paralysis, palpation of the cricoarytenoid joint at rigid endoscopy is necessary. Laryngeal electromyography may be necessary for definitive diagnosis.

Benjamin and Mair[62] noted that interarytenoid webs are often associated with other airway abnormalities. They recommend that interarytenoid web be managed by long-term watchful waiting or by tracheotomy if associated abnormalities of the airway exist. In the case of pediatric posterior glottic stenosis, arytenoidectomy should be avoided to prevent the possibility of aspiration, deterioration of voice, and difficulty with future airway repair.[63] Although many techniques have been tried, anterior and posterior cricoidotomy with posterior graft appears to give the most consistent results and is considered the procedure of choice in children.[61,63] Improved vocal fold mobility has been observed postoperatively with this technique.[63,64]

The postoperative voice is considered to be functional in most children; a voice disorder consisting of hoarseness and breathiness often persists.[63] Bogdasarian and Olson[60] noted in adult patients that final voice results depended on the severity of stenosis; the same applies to children.

Recurrent Respiratory Papillomatosis

RRP is the most common benign neoplasm of the larynx. Papilloma patients present with hoarseness or airway obstruction. Papillomas have a predilection for anatomic sites where ciliated and squamous epithelia are juxtaposed. Common sites in the larynx are the mid zone of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricles, and the undersurface of the vocal folds.[65] Recurrent respiratory papillomatosis is often diagnosed in patients between the ages of 2 and 3 years. Juvenile and adult-onset forms of the disease are possible; the juvenile form has a more aggressive clinical course. The need for tracheotomy in juvenile RRP is reportedly 14% to 21%.[66,67]

An association between cervical human papillomavirus (HPV) types 6 and 11 in the mother and RRP in the child has been established.[68-70] HPV is found in the genital tract of approximately 25% of women of child-bearing age and is clinically apparent in 2% to 5%. Shah and others[71] estimate the risk of HPV transmission to be 1 in 400 vaginal births in mothers with active condylomata.

Surgery is the management of choice, although it is only palliative because the natural history of RRP is one of recurrence. The goal of surgery is to establish a stable airway and a serviceable voice. Surgical options are CO_2 laser ablation and microlaryngoscopy with forceps removal; CO_2 laser ablation is generally accepted as the procedure of choice.[67] More recent reports indicate that removal of papillomas with microdébrider can be more efficient and atraumatic.[72] Papillomas are removed to the level of the mucosa or submucosa, avoiding the deeper muscular and ligamentous levels. Caution should be exercised in removing papillomas from the anterior and posterior commissure areas because irreversible scarring can result. Although removal of RRP temporarily improves the voice, the increasing number of required procedures results in scarring of the vocal folds and deterioration of the voice.

Leventhal and others[73] recommended the use of interferon in any patient requiring surgery every 2 to 3 months. The duration of management should be 6 months. If there is neither a response nor a complete response, management should be discontinued, but if there is a partial response management should be continued. However, the results of

interferon management of RRP have been disappointing. After the cessation of interferon therapy, there is a rebound effect and papillomas recur at an increased rate.[74] Intralesional administration of cidofovir, an acyclic nucleoside phosphate, has shown promise in treating severe cases of RRP in pediatric patients.[75] Other adjuvant therapies (e.g., photodynamic therapy, acyclovir, ribavirin, isotretinoin, indole 3-carbinol) are infrequently used.[67]

Malignant Tumors

Malignant tumors of the pediatric larynx are rare. Isolated case reports are seen in the literature, but more extensive experience is lacking. A 15-year review of malignant laryngeal tumors at a tertiary pediatric referral center revealed only four cases.[76] These laryngeal tumors are usually in the sarcoma group, most commonly rhabdomyosarcoma. Other malignancies include squamous cell carcinoma, lymphoma, mucoepidermoid carcinoma, neuroectodermal tumor, and metastatic carcinoma.[77-80] Spontaneous malignant degeneration of longstanding RRP has an incidence of 2% to 3%.[81] In addition, squamous cell carcinoma may be seen in patients who have RRP and a history of radiotherapy.

Patients with laryngeal tumors present with voice change (often hoarseness), stridor, and progressive airway obstruction. Delay in diagnosis is common because of a low suspicion for malignancy. Any child with persistent hoarseness should thus be fully evaluated. Management goals are patient survival and preservation of laryngeal function, when possible. Management depends on the tumor histology and consists of combination surgery, radiotherapy, and chemotherapy.

Radiotherapy of a prepubescent larynx can result in a fibrotic infantile larynx with no useful voice, airway, or swallowing function.[76] This should be considered when deciding on a management protocol. Ohlms and associates[76] provide an example of a prepubescent child with a laryngeal rhabdomyosarcoma. Although radiotherapy may have provided adequate local control, total laryngectomy was chosen to improve local control. Total laryngectomy was justified because it provided a better chance of cure, whereas the larynx may have been useless after undergoing radiotherapy.

Vocal Quality Disorders: Medical Management

Granuloma

Patients with vocal fold granuloma commonly exhibit hoarseness. Granuloma often results from intubation trauma. Habitual throat clearing, excessive glottal attacks, and reflux esophagitis are also important causal factors.[82] Inflammation over the vocal process of arytenoid progresses to infection involving the perichondrium and formation of granuloma. Histologically, the granulomas are nonspecific reparative granulation tissue covered by hyperplastic squamous epithelium.[83]

Children with vocal fold granuloma should be evaluated for gastroesophageal reflux disease (GERD). The most reliable means of diagnosing GERD is prolonged (24 hours) pH manometry study.[84] A reflux event is defined as a drop in the pH to less than 4. Normally, the time that pH is less than 4 is approximately 6.3% upright, 1.2% supine, and 4.2% total.[85] Other less specific and less sensitive methods are barium esophagography, radionuclide scanning, and lipid-laden macrophage testing for aspiration.

The primary management of vocal fold granuloma is management of the underlying GERD. Most granulomas resolve with medical management. Management of GERD involves[86] (1) dietary and lifestyle modifications and the use of antacids; (2) H_2 blockers (cimetidine, ranitidine, famotidine), prokinetic agents (bethanechol, metoclopramide, cisapride), and mucosal cytoprotectants (sucralfate) in combination; and (3) proton pump inhibitors (omeprazole, lansoprazole) combined with surgical repair of hiatal hernia and the reestablishment of lower esophageal sphincter function.

Surgical removal (CO_2 laser or sharp incision with microlaryngeal instruments) of the vocal fold granuloma is reserved for lesions causing airway obstruction (Fig. 203-5).[83,84] Regardless of the surgical technique used, recurrence is frequent. Although voice therapy has been recommended, it does not appear to be an effective primary management modality for vocal fold granulomas.

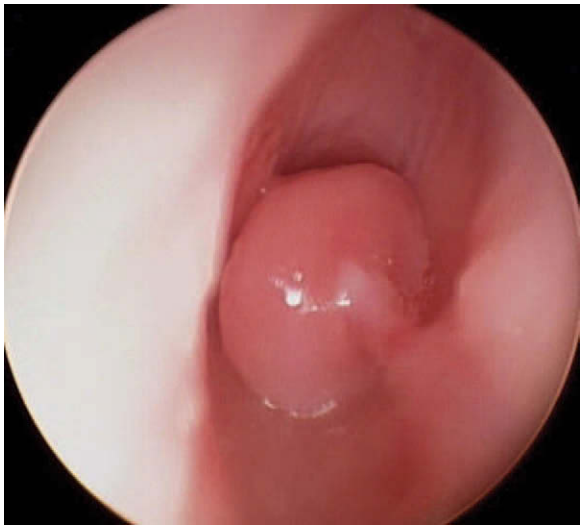

Figure 203-5. Large granuloma with laryngeal obstruction requiring surgery.

Vocal Quality Disorders: Voice Therapy with or without Surgery

Opinions about the management of cysts, polyps, sulcus vocalis, and nodules differ widely. Traditionally, surgery was discouraged in children because of the small size of the larynx, difficulty in reinforcing voice rest postoperatively, and high recurrence when underlying vocal behavior is not modified. Surgery was recommended for only the most recalcitrant and severe dysphonia. However, some surgeons have reported that surgery of the pediatric larynx is safe and technically feasible with good results, as seen in a series by Bouchayer and Cornut[8] of 191 children who underwent microsurgery. Advocates of surgery recommend waiting until the child is 8 to 9 years old.[8,87] This recommendation is in agreement with the recent report describing the development of the three-layered vocal fold in children approximating that of adult vocal folds by age 7.[88] In addition to the age, a highly motivated patient and involved parents are prerequisites to surgery.

Preoperative and postoperative voice therapy is essential. Surgical intervention is most often performed by microsurgical technique, although CO_2 laser is infrequently used. The principles of surgery are to remove the pathology with maximal preservation of normal mucosa and to avoid injury to the anterior commissure and vocal ligament.

Nodules

Most voice disorders in children result from vocal nodules. Vocal nodules occur frequently, often as a result of misuse or overuse of the larynx (hyperfunctional state). Other conditions that can lead to predisposition for vocal nodules include gastroesophageal reflux and velopharyngeal insufficiency.[47] The incidence of hoarseness, a symptom of dysphonia, in schoolchildren is estimated to be approximately 5%.[89] Of children evaluated by an otolaryngologist for chronic hoarseness, 38% to 78% have vocal nodules. Thus more than 1 million children in the United States have vocal nodules. Vocal nodules are most often seen as a child enters a group activity. They occur more commonly in boys. Patients with vocal nodules exhibit hoarseness and breathiness. A stroboscopic examination shows decreased mucosal waves and incomplete approximation of the free edges.[89]

Vocal nodules result from mechanical trauma and occur at the free edge of the anterior and middle third of the vocal fold (Fig. 203-6). Often, vocal nodules are bilateral, although unilateral nodules can occur. Vocal nodules develop in three stages[90]: (1) an inflammatory phase with increased vascularity and protein accumulation; (2) localized

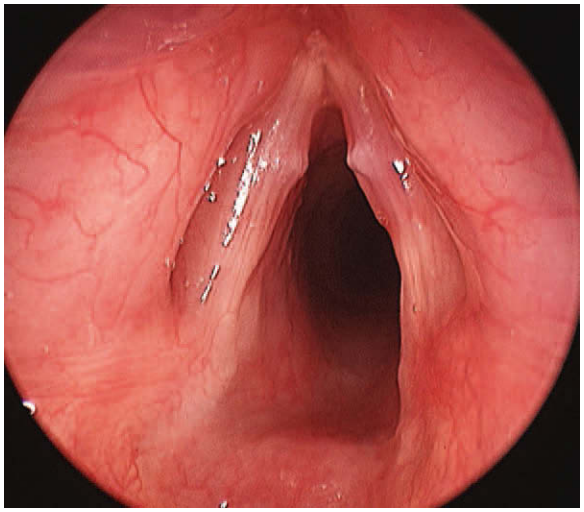

Figure 203-6. Vocal nodules.

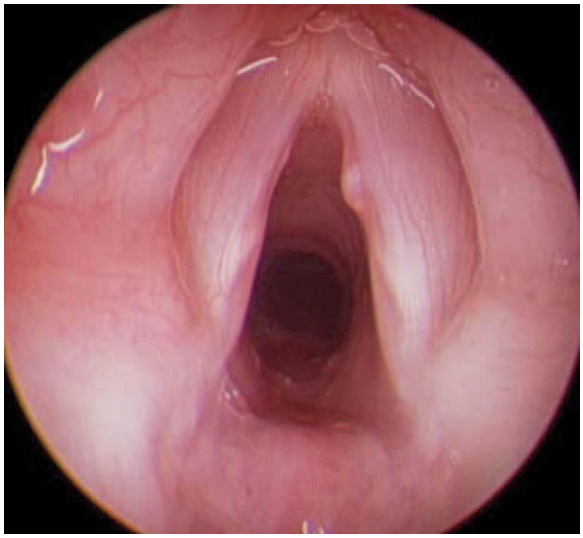

Figure 203-7. Right vocal fold cyst.

swelling on the edge of the vocal fold that appears as grayish, translucent thickening (nodules are reversible within 24 to 48 hours if trauma is eliminated); and (3) replacement of thickening by fibrotic tissue that appears gray or white. Histologically, circumscribed hyperplasia or hyperkeratinization and secondary hyaline degeneration in the lamina propria are seen.[91]

Management options include voice therapy, surgery, voice therapy plus surgery, and no intervention.[8,87,89,92-94] It is difficult to determine the success of differing modes of management because follow-up of control groups (no management) is rare. Because of the benign nature of nodules, patients who undergo medical or surgical management are often lost to follow-up evaluation. The fact that vocal nodules in children often resolve spontaneously by puberty may also influence management. The most widely accepted management option for vocal fold nodules in children is voice therapy. According to von Leden,[89] most nodules resolve or show significant improvement within 3 to 6 months of initiating voice therapy. Surgery is considered in children who fail to show improvement with voice therapy and in whom severe hoarseness interferes with daily functioning.[87,89]

The surgical management of choice is microsurgical excision, although CO_2 laser has been used. The nodule is stretched medially and removed at its base with microscissors without excessive mucosal removal. Bilateral nodules can usually be removed in one sitting; however, care should be taken to avoid injuring the anterior commissure. Some surgeons recommend removing bilateral nodules in stages that are 4 weeks apart.[87] Voice rest is recommended for 7 to 10 days. Long-term results depend on the quality of voice therapy, but they are generally good. Recurrences are frequent without voice therapy.

Cysts and Sulcus Vocalis

It is unclear whether epidermoid cysts and sulcus of the vocal folds are congenital or acquired lesions. Some authors[95,96] support the view that these lesions are acquired, whereas Bouchayer and colleagues[97] theorize that they are congenital. In a series of 2334 patients, Bouchayer and Cornut[8] found that congenital lesions of the vocal folds were the most frequently seen benign lesions requiring surgical intervention; they believe these congenital lesions are often overlooked or misdiagnosed.

Patients with either lesion often present with hoarseness, voice breaks, and vocal fatigue. With epidermoid cysts, unilateral submucosal swelling of the superior mid-third surface often occurs with associated edema of the contralateral vocal fold (Fig. 203-7). Reduced mucosal waves are seen on stroboscopy. Epidermoid cysts are lined with stratified keratinizing squamous epithelium and contain keratin debris. With sulcus vocalis, the surface epithelium invaginates into Reinke's space and adheres to the vocal ligament, resulting in a longitudinal furrow parallel to the edge of the vocal fold and an oval glottic chink. Stroboscopy shows incomplete closure of the free edges of the vocal folds.

Cysts and sulcus vocalis usually do not resolve spontaneously although voice can improve with therapy.[8,98] Epidermoid cysts are often mistaken for vocal nodules, and patients are thus referred for voice therapy. Referral to an otolaryngologist occurs when the voice disorder does not resolve after several months of voice therapy. Sulcus vocalis is often difficult to diagnose in children because careful examination of the larynx with a stroboscope is often impossible. These children are referred for voice abnormality that fails to improve with voice therapy.

Epidermoid cyst and sulcus vocalis are managed by microsurgery. For cysts, a mucosal incision is made on the superior surface of the vocal fold, parallel to the free edge, and the cyst is dissected. Bouchayer and Cornut[8] recommend intrafoldal injection of the surgical site with corticosteroid to decrease the inflammation. Woo and colleagues[99] reported improved laryngeal microsurgery results using 6-0 chronic Endoknot sutures to close the microflaps of the vocal fold. Sulci are resected by making incisions in the superior and inferior edges of the pocket and dissecting the pocket from the vocal ligament. A slicing mucosa surgical technique that detaches the mucosa of the sulcus and interrupts the longitudinal fibrotic tension line has been used with good results.[100] Although the resulting voice is improved compared with the preoperative state, it is not perfect. Postoperative voice therapy is important and has significant effect on voice results. Therapy is recommended for at least 3 to 6 months.

Polyps

Vocal fold polyps occur infrequently in children and adolescents.[101,102] They arise from chronic abuse of the larynx or from a single traumatic episode. Hoarseness is the most common presenting symptom. The polyps occur at the junction of the anterior and middle third of the vocal fold and may be fusiform, pedunculated, or generalized.[103] A recent study showed that polyps are caused by circulation impediment, thrombosis, exudation, and edema of the lamina propria. Inflammation and secondary atrophy of the vocal fold epithelium occur.[91]

Vocal fold polyps can improve with voice therapy but may require surgical removal.[8,90,98,103] Pedunculated polyps are removed at the base using CO_2 laser or microscissors. For generalized polyps, an incision is made over the superior surface of the vocal fold, and the fibrous exudate is suctioned out or vaporized.[8] The resulting voice quality depends on the degree of irreversible damage to the superficial layer of the lamina propria by fibrous or hyaline infiltration. Voice therapy is recommended before and after surgery to prevent recurrences.[8,22]

Summary

Voice disorders are commonly seen in children. Evaluation and treatment of voice disorders are more complicated in children than in adults because of their inability to cooperate, lack of awareness of the problem,

and lack of motivation for change. There have been significant recent advances in technology and establishment of normative data for pediatric voice parameters. Surgery should be undertaken cautiously, especially in very young children because the larynx is not mature and surgery is more difficult. Voice therapy should be used extensively both preoperatively and postoperatively.

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CHAPTER TWO HUNDRED AND FOUR

Recurrent Respiratory Papillomatosis

Craig S. Derkay

Russell A. Faust

Key Points

- Recurrent respiratory papillomatosis (RRP) is a devastating, rare disease in which papillomas of the airway cause hoarseness and airway obstruction.
- The disease is caused by human papillomavirus (HPV) 6 or 11, the same subtypes responsible for the development of genital warts and low-risk cervical intraepithelial neoplasias of the genitourinary tract.
- The age of disease onset and clinical course are highly variable.
- Surgical therapy for RRP requires a team approach with otolaryngologists, anesthesia providers, and operating room personnel working together in a facility properly equipped to manage difficult airways.
- In addition to surgical débridement accomplished with the use of microdébriders, pulsed dye and carbon dioxide (CO_2) lasers and microlaryngoscopy "cold-steel" techniques, multiple medical modalities have been used without consistently effective results.
- Parental support and education are invaluable adjuncts to the safe care of children with RRP.
- The recent introduction of a quadrivalent HPV vaccine offers hope for prevention of transmission of the virus to neonates and may significantly reduce the future incidence of RRP and oropharyngeal cancers.

Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx in children. Despite its benign histology, RRP has potentially fatal consequences and is often difficult to treat because of its tendency to recur and spread throughout the respiratory tract. Long neglected from an epidemiologic standpoint, initiatives to better understand this disease process have been launched in the United States through coordination between the Centers for Disease Control and Prevention (CDC) and the American Society of Pediatric Otolaryngology (ASPO) and internationally through the British Association of Paediatric Otolaryngology (BAPO) and by Canadian Paediatric Otolaryngology physicians.

This chapter discusses the etiology, immunology, epidemiology, and transmission of RRP. Clinical features including pertinent aspects of the history, physical examination, airway endoscopy, and other considerations are highlighted. Management principles for performing surgical and nonsurgical treatments, the indications and results for employing adjuvant therapies, and their results are discussed. Ongoing research initiatives, promising strategies, the potential for a quadrivalent human papilloma vaccine (HPV) to reduce its incidence and the RRP Task Force's contributions to understanding this frustrating disease are also reviewed.

Epidemiology

Recurrent respiratory papillomatosis is a disease of viral etiology, caused by human papillomavirus (HPV) types 6 and 11, and is characterized by the proliferation of benign squamous papillomas within the aerodigestive tract.[1-3] Although it is a benign disease, RRP has potentially fatal consequences because of its involvement of the airway and because of the risk, albeit low, of malignant conversion.[4] In addition to the emotional burden to the patients and their families associated with the need for repeated surgery,[5] the economic cost of this relatively rare chronic disease is high, having been estimated at $150 million annually.[6]

RRP is both the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness.[7] The disease is often difficult to treat because of its tendency to recur and spread throughout the aerodigestive tract. Although it most often involves the larynx, RRP may involve the entire aerodigestive tract. The course of the disease is variable, with some patients experiencing spontaneous remission, whereas others may suffer from aggressive papillomatous growth and respiratory compromise, requiring multiple surgical procedures through many years.

RRP may have its clinical onset during either childhood or adulthood. It may affect people of any age, with the youngest patient identified at 1 day of life and the oldest at 84 years.[6] Two distinct forms of RRP are generally recognized: a juvenile or aggressive form and an adult or less aggressive form. The aggressive form, although most prevalent in children, can also occur in adults. Children whose RRP was diagnosed at younger ages (younger than 3 years) have been found to be 3.6 times more likely to have more than four surgical procedures per year and almost two times more likely to have two or more anatomic sites affected than children whose RRP was diagnosed at older ages (older than 3 years).[6] Similarly, children with disease progression are generally diagnosed at younger ages than those who remain stable or become disease-free.[8-10] In most pediatric series, the delay in diagnosis

from the time of onset of symptoms averages about 1 year.[6,11] In 75% of children with RRP, diagnosis was made before the fifth birthday.[12]

The true incidence and prevalence of RRP are uncertain. It is estimated that between 80 and 1500 new cases of childhood-onset RRP occur in the United States each year.[6,13] While the incidence among children in the United States is estimated at 4.3 per 100,000 children, the incidence among adults is 1.8 per 100,000.[6,14] These figures are comparable with those found in a Danish survey. In a subpopulation incorporating 50% of the population of that country, the rate among children was 3.62 per 100,000, whereas adult-onset cases occurred at a rate of 3.94 per 100,000.[15] The National Registry of children with RRP, composed of the clinical practices at 22 pediatric otolaryngology sites, calculates a mean number of procedures at 19.7 per child with an average of 4.4 procedures per year.[6,14] Based on the incidence data, this translates into more than 10,000 surgical procedures annually for children with RRP in the United States.

Virology of Human Papillomavirus

HPV, belonging to the Papovaviridae family, is a small deoxyribonucleic acid (DNA)-containing, nonenveloped, icosahedral (20-sided), capsid virus with a double-stranded circular DNA of 7900 base-pairs long. HPV is epitheliotropic (infects epithelial cells). The HPVs have been grouped on the basis of shared genetic code homology, with viruses that share less than 90% identity in specific regions of the virus being defined as separate types. On this basis, the HPVs are numbered to distinguish them. Nearly 100 different HPV types have been identified. Grouping HPV types based on their DNA homology has allowed us to identify closely related types. Functionally, these groupings correlate with their tissue preference as well as similar pathophysiology.[16] The HPVs are members of a large family of papillomaviruses that infect vertebrates ranging from birds to humans, causing epithelial neoplasms that can be benign or malignant. These viruses are designated by their natural host species (e.g., bovine papillomavirus, murine papillomavirus, and human papillomavirus). Each papillomavirus is specific for its host species, and this specificity is thought to be absolute. Within each species, similar types of papillomavirus exhibit specificity for epithelial tissues of different sites (e.g., oral mucosa, genital mucosa, or skin). In humans, this tissue specificity is less absolute, and some HPV types exhibit more of a preference for certain tissues.

Until the 1990s, HPV had been suspected but not confirmed as the causative agent in RRP. This uncertainty resulted from an inability to culture the virus in vitro and from the failure to demonstrate viral particles consistently in papilloma lesions using electron microscopy or HPV antibodies. With the advent of molecular probes, HPV DNA has been identified in virtually every papilloma lesion studied. The most common types identified in the airway are HPV 6 and HPV 11—the same types responsible for more than 90% of genital condylomata. Specific viral subtypes may be correlated with disease severity and clinical course. Children infected with HPV 11 appear to have a more obstructive airway course early in the disease and a greater likelihood of undergoing tracheotomy to maintain a safe airway.[10,17]

In addition to the HPV group that includes HPV 6 and 11, two other major groups of HPV are associated with mucosal lesions in the aerodigestive and genital tracts. HPV 6 and 11, responsible for the majority of RRP, are members of a group believed to have a low malignant potential compared with some other groups. In contrast, the group that contains HPV 16 and HPV 18 is associated with malignancies in the genital and aerodigestive tracts.[16] The group that contains HPV 31 and HPV 33 exhibits malignant potential that lies somewhere in between.

HPV is thought to infect stem cells within the basal layer of mucosa.[18,19] After infection of the stem cells, the viral DNA can either be actively expressed or it can exist as a latent infection in mucosa that remains clinically and histologically normal. To produce viral proteins or to replicate the virus, the viral DNA must somehow reactivate the host replication genes. The viral genome consists of three regions: an upstream regulatory region and the two regions named according to the phase of infection in which they are expressed—early (E) and late (L) regions. The E-region genes are involved in the replication of the viral genome, interaction with the host cell intermediate filaments, and transforming activities, and are potential oncogenes, depending on the HPV type. The L-region genes encode the viral structural proteins.[20-22]

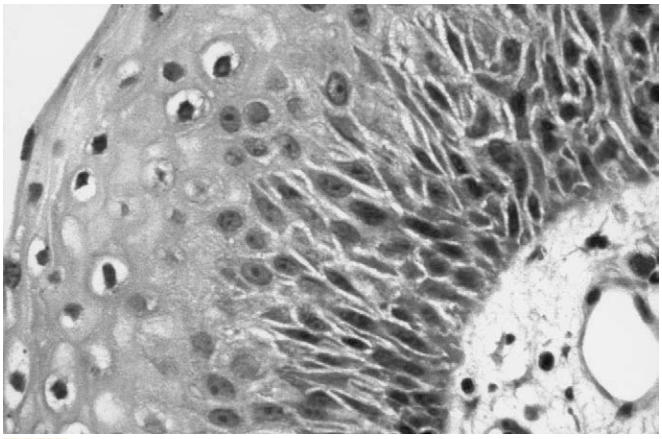

Figure 204-1. Histopathology of human recurrent respiratory papillomatosis. Micrograph of laryngeal mucosa infected with human papillomavirus.

Figure 204-2. Gross appearance of respiratory papillomas during laryngoscopy. Appearance of massive, exophytic papillomatosis of the larynx.

The induction of cellular proliferation is a fundamental property of HPV, although the mechanism of action remains unclear. We are slowly gathering information regarding the interaction of viral gene products with cellular proteins. For example, several of the viral E-region gene products have been shown to bind and inactivate certain cellular tumor-suppressor proteins.[21,23] Conversely, HPV has been shown to activate the epidermal growth factor (EGF) receptor pathway, known to be associated with proliferation of epithelial cells.[3] Thus there are likely several mechanisms by which HPV induces cellular proliferation in the aerodigestive mucosa.

Histologically, this mucosal proliferation results in multiple "fronds" or finger-like projections with a central fibrovascular core, covered by stratified squamous epithelium (Fig. 204-1).[18] When papillomas are microscopic, they may assume a superficial-spreading configuration, with a velvety appearance (Fig. 204-2). When they exhibit a more macroscopic or exophytic growth pattern, they appear grossly

as "cauliflower" projections (see Fig. 204-2). Papilloma lesions may be sessile or pedunculated and often occur in irregular exophytic clusters. Typically, the lesions are pinkish to white in coloration. Iatrogenic implantation of papilloma may be preventable by avoiding injury to nondiseased squamous or ciliated epithelium adjacent to areas of frank papilloma. Ciliated epithelium undergoes squamous metaplasia when exposed to repeated trauma and is replaced with nonciliated epithelium that creates an iatrogenic squamocellularly junction. This may also explain the observation that RRP flourishes in the presence of uncontrolled gastroesophageal reflux. Most RRPs do not exhibit dysplasia, abnormal mitoses, or hyperkeratosis.[18] Without exception, RRP exhibits delayed maturation of the epithelium, resulting in significantly thickened basal cell layer and nucleated cells in the superficial layers.[24] This is thought to be in part because of the interaction of HPV gene products with the EGF receptor pathway.[3] The sum result of these cellular effects is that, although HPV-infected cells do not rapidly divide, there is a disproportionate increase in the number of dividing basal cells. Thus expansion of the RRP tissue mass may occur very rapidly, because of the large number of dividing cells.[19]

During viral latency there is very little viral RNA expressed. Even so, HPV DNA can be detected in normal-appearing mucosa in RRP patients who have been in remission for years, and unknown stimuli can result in reactivation and clinical recurrence following years of remission.[25,26] Thus activation of viral expression can occur any time after the establishment of latent infection. Gene products of early region gene E6, E7, and possibly E5 are required for papilloma induction, but the details of the mechanism of HPV activation are unknown. To "cure" RRP, it is necessary to modulate the host response to the virus and, ideally, eliminate latent infection.

It is likely that the host immune system plays an important role in the pathogenesis of HPV-induced lesions. Both the humoral and the cellular immune responses may be compromised in children with RRP, and the patient's immunocompetence may be associated with the clinical course of the disease. The role of cytokines, such as interleukin-2, interleukin-4, and interleukin-10, and expression of the major histocompatibility complex (MHC) antigens in the dysfunction of the cell-mediated immune response in children with RRP has been demonstrated.[27,28]

Transmission

An association between cervical HPV infection in the mother and the incidence of RRP has been well established. However, the precise mode of transmission is still not clear.[18] The universality of HPV in the lower genital tract rivals that of any other sexually transmitted disease in humans. It is estimated that at least one million cases of genital papillomas occur per year in the United States.[29] These are most commonly manifested as condylomata acuminata involving the cervix, vulva, or other anogenital sites in women or the penis of male sexual partners of affected women. Colposcopic (subclinical) changes are seen in about 4% of women, whereas DNA positive biopsies without a visible lesion are seen in 10% of women. HPV antibody positivity (without DNA or a clinical lesion) is estimated in 60% of women (81 million). HPV has been estimated to be present in the genital tract of as many as 25% of all women of child-bearing age worldwide. One study reported that the incidence of HPV infections in sexually active young college women is highest, with a cumulative incidence of 43% during a 36-month period.[30] Clinically apparent HPV infection has been noted in 1.5% to 5% of pregnant women in the United States.[31] More than 30% of American women are currently infected with HPV with 7.5 million 14- to 24-year-olds currently infected and one fourth of women younger than 60 years of age infected at any given time.[32] Up to 90% of lesions are undetectable clinically at 2 years. The highest prevalence is in women 20 to 24 years of age. More than 50% of women will initially acquire HPV within 4 years of their first sexual intercourse. As in RRP, HPV 6 and HPV 11 are the most common subtypes identified in cervical condylomata.

Vertical transmission occurring during delivery through an infected birth canal is presumed to be the major mode of transmitting the infection in children whereas in utero and transplacental transfer of HPV, sexual abuse, and direct contact are thought to play a minor role. The support for vertical transmission lies in the fact that overt maternal condyloma are seen in more than 50% of mothers who give birth to children with RRP.[33] The same subtypes (HPV 6 and 11) are involved, and cesarean delivery of children seems to be preventive to some extent.[34]

Patients with childhood-onset RRP are more likely to be first born and vaginally delivered than are control patients of similar age.[35,36] Kashima and others hypothesized that primigravid mothers are more likely to have a long second stage of labor and that the prolonged exposure to the virus leads to a higher risk of infection in the first-born child. They also suggested that newly acquired genital HPV lesions are more likely to shed virus than longstanding lesions, accounting for the higher incidence of papilloma disease observed among the offspring of young mothers of low socioeconomic status—the same group that is most likely to acquire sexually transmitted diseases such as HPV.[35,36]

Despite the close association between maternal condylomata and the development of RRP, only a small portion of children exposed to genital condylomata at birth actually go on to development of clinical RRP.[37] Although HPV could be recovered from the nasopharyngeal secretions of 30% of infants exposed to HPV in the birth canal, the number of infants expected to manifest evidence of RRP is only a small fraction of this population.[37] Clearly, other factors (patient immunity, timing, length and volume of virus exposure, local trauma) must be important determinants in the development of RRP. Even though cesarean section delivery would seem to reduce the risk of transmission of the disease, this procedure is associated with a higher morbidity and mortality for the mother and a much higher economic cost than elective vaginal delivery. Furthermore, reports of neonatal papillomatosis suggest that, in at least some cases, transmission may occur in utero.[1] However, with such a high rate of subclinical maternal HPV infection and such a low rate of actual new cases of childhood RRP, elective cesarean delivery as a means of preventing RRP is currently not practical or recommended.[1] The risk of a child contracting the disease from a mother who has an active genital condyloma lesion during vaginal delivery is only approximately 1 in 231 to 400.[22,34,36] The characteristics that distinguish this one child from the other 230 to 399 remain elusive. In summary, a better understanding of the risk factors associated with RRP is needed before the efficacy of cesarean delivery or other preventive measures can be fully assessed.

Prevention

The new quadrivalent HPV vaccine (Gardasil, Merck and Co., Inc.), is licensed and indicated for the prevention of cervical cancer, adenocarcinoma in situ, and intraepithelial neoplasia grades 1-3; vulvar and vaginal intraepithelial neoplasias grades 2-3; and genital warts associated with HPV 6, 11, 16, and 18. The CDC Advisory Committee on Immunization Practices (ACIP)[32] has recommended vaccination for all girls ages 11 to 12, girls and women ages 13 to 26 who have not yet been vaccinated, and girls as young as age 9, in whom the physician believes it would be appropriate. Based upon the pivotal clinical studies, the vaccine is predicted to reduce the incidence, morbidity, and mortality of cervicovaginal HPV disease. An added and often overlooked benefit may be a concomitant decrease in the incidence of RRP and HPV-associated head and neck cancers.

The ability of the quadrivalent vaccine to prevent HPV 6/11/16/18-associated cervical and genital disease was established in the phase 3 FUTURE I and II trials, and their immunogenicity in the target group of vaccinees was established in immunogenicity bridging trials.[38] In FUTURE I, the quadrivalent vaccine was 100% effective in preventing cervical intraepithelial neoplasia (CIN) or worse, genital warts, and vulvovaginal neoplasia. In FUTURE II, the vaccine was 100% effective in preventing HPV 16/18-associated CIN. Both Future I and II were conducted in women in the age range at highest risk for HPV acquisition.[38,39] However, it appears that the vaccine will be most effective if administered to individuals who have not yet become sexually active. Immunogenicity bridging studies were conducted to assess the immunogenicity of the vaccine in this population, and established that immunogenicity among younger girls was equal to if not superior to the response among 16- to 23-year-old women, suggesting that the quadrivalent HPV vaccine is immunogenic in this population and thus likely to be effective in preventing disease.[40] A separate study in 9- to

15-year-olds established that in this younger population immunogenicity lasts at least 18 months.[41]

There is also a bivalent HPV vaccine currently in phase 3 trials. This vaccine provides protection against HPV 16 and 18, but not 6 and 11.[38] Early phase 2 data for this vaccine suggest that it is 100% effective in preventing incident and persistent cervical HPV 16 and 18 infections in the according-to-protocol (ATP) sample, and 93% effective in preventing HPV 16- or 18-related disease in the intention-to-treat analysis; efficacy against disease was not presented for the ATP cohort. This vaccine's efficacy against HPV 16 and 18 suggests that, like the quadrivalent vaccine, it may reduce the incidence of HPV-associated head and neck cancers. However, because the bivalent vaccine does not protect against HPV 6 and 11, it will not likely affect the vertical transmission of HPV 6 or 11 from mother to child.

Widespread use of the quadrivalent HPV vaccine promises to dramatically reduce the morbidity and mortality of cervical cancer and drastically reduce the incidence of genital warts. If the vaccine is as effective in preventing HPV infection of the oral cavity as of the cervix and genital tract, then, vaccination could be expected to reduce the incidence of HPV-associated oropharyngeal cancers by as much as 30%. In addition, a near-universal vaccination program providing the quadrivalent vaccine should all but eradicate RRP in future generations. Thus vaccination against HPV offers additional benefits above and beyond prevention of cervical cancers, some of which are unique to the quadrivalent vaccine.

Clinical Features

Inasmuch as the vocal fold is usually the first and predominant site of papilloma lesions, hoarseness is the principal presenting symptom in RRP.[42] The child's voice may be described as hoarse or weak from the time of birth. Particularly in very young children, changes in voice may go unnoticed. Stridor is often the second clinical symptom to develop, beginning as an inspiratory noise and becoming biphasic with progression of the disease. Less commonly, chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute life-threatening events may be the presenting symptoms. The duration of symptoms before diagnosis varies. Not uncommonly, a mistaken diagnosis of asthma, croup, allergies, vocal nodules, or bronchitis is entertained before a definitive diagnosis is made. However, the initial presentation in infants, whose airway dimensions are small, may be with acute respiratory distress during an otherwise routine upper respiratory tract infection. The natural history of RRP is highly variable. After presentation, the disease may undergo spontaneous remission or persist in a stable state requiring only periodic surgical treatment. At the other extreme, RRP may become extremely aggressive, requiring frequent surgical treatment (every few days to weeks), prompting early institution of medical adjuvant therapy. A waxing-waning clinical course of remissions and exacerbations is common for RRP.

Because of the rarity of RRP and the slowly progressive nature of the disease, some cases may go unrecognized until respiratory distress results from papillomas obstructing the airway. The result is a relatively high need for tracheotomy to be performed in these children. Shapiro and others noted that RRP tracheotomy patients presented at a younger age and with more widespread disease, often involving the distal airway before tracheotomy.[43] In their experience with 13 patients, they did not believe that the tracheotomy itself led to spread of disease outside the larynx. In the CDC National RRP Registry, children with tracheotomy were initially diagnosed with RRP at a younger age (2.7 years) than those without a tracheotomy (3.9 years).[14] Others have suggested that tracheotomy may activate or contribute to the spread of disease lower in the respiratory tract.[44] Cole and colleagues reported that tracheal papillomas developed in half of their tracheotomy patients and that, despite attempts to avoid this procedure, 21% of their patients still required a long-term tracheotomy.[45] Prolonged tracheotomy and the presence of subglottic papillomata at the time of tracheotomy have been associated with an increased risk of distal tracheal spread. Most authors agree that tracheotomy is a procedure to be avoided unless absolutely necessary. Interestingly, Boston and colleagues from Cincinnati noted successful laryngotracheal reconstruction in a series of children with subglottic stenosis and RRP.[46] When a tracheotomy is unavoidable, decannulation should be considered as soon as the disease is managed effectively with endoscopic techniques. Children with bronchopulmonary dysplasia who require prolonged endotracheal intubation may also be at increased risk for development of RRP.[47] Through interruption of the continuous respiratory mucosal surface, an endotracheal tube may have the same role in the mechanical dissemination-implantation of RRP as tracheotomy, as a risk for distal spread of disease. Several authors have noted an association between RRP caused by HPV 11 (as opposed to HPV 6) and distal spread of papilloma.[10]

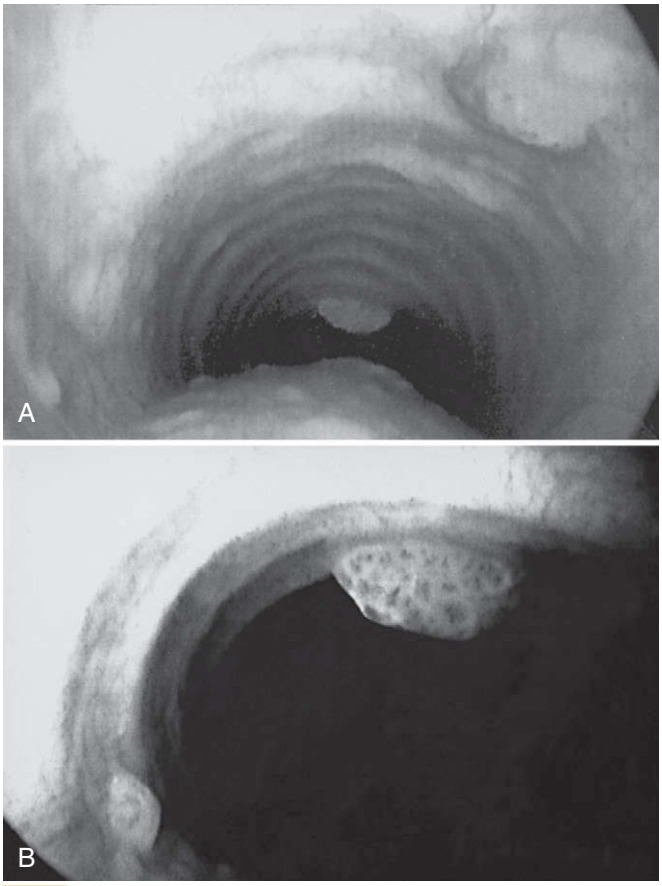

Figure 204-3. Tracheal spread of recurrent respiratory papillomatosis. Note nodular, exophytic lesions in distal trachea.

Extralaryngeal spread of respiratory papillomata has been identified in approximately 30% of children and in 16% of adults with RRP.[6] The most frequent sites of extralaryngeal spread were, in decreasing order of frequency, the oral cavity, trachea, and bronchi (Fig. 204-3).[6,42] Pulmonary papilloma lesions begin as asymptomatic noncalcified peripheral nodules.[48] These lesions eventually enlarge to undergo central cavitation and central liquefactive necrosis with air-fluid levels on a computed tomography scan (Fig. 204-4). These patients present clinically with recurrent bronchiectasis, pneumonia, and declining pulmonary status. The clinical course of the pulmonary spread of RRP is insidious and may progress through the years, but eventually manifests in respiratory failure because of destruction of lung parenchyma. For this reason, the finding of pulmonary lesions in a patient with RRP is a grave development with no currently available treatment modality that has shown more than anecdotal promise. Furthermore, pulmonary dissemination is anecdotally associated with a higher risk of malignant transformation of RRP.

Malignant transformation of RRP into squamous cell carcinoma has been documented in several case reports. A total of 26 patients was identified as having progressed to squamous cell carcinoma in the task force survey.[6] Dedo and Yu reported malignant transformation in 4 of 244 (1.6%) RRP patients treated during 2 decades.[49] When death occurs in a patient with RRP, it is usually as a complication of frequent

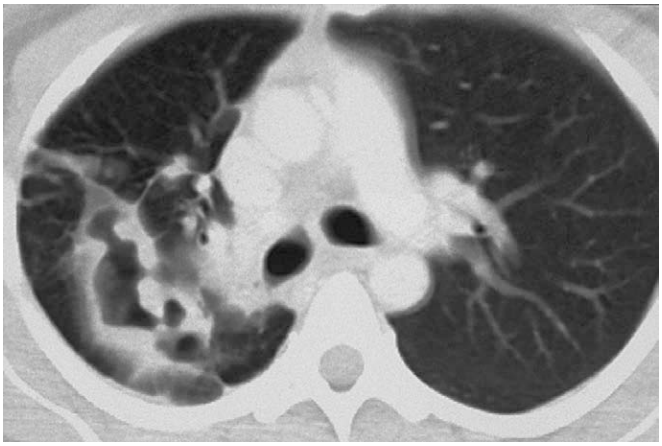

Figure 204-4. Pulmonary spread of recurrent respiratory papillomatosis. Note lytic, cavitary lesions on computed tomography.

surgical procedures or caused by respiratory failure because of distal disease progression. RRP presenting in the neonatal period is thought to be a negative prognostic factor, with a greater likelihood for mortality and need for tracheotomy.[8,9]

Patient Assessment

History

Persistent or progressive stridor and dysphonia, with the possible development of respiratory distress, are the most consistent signs and symptoms of RRP in children (see the Practice Pathway Flow Chart, Fig. 204-5). In the absence of severe respiratory distress, a careful history should be obtained. Information regarding the time of onset of symptoms, possible airway trauma including a history of previous intubation, and characteristics of the cry are obviously important. Hoarseness, although a common and often benign clinical complaint in young children, always indicates some abnormality of structure or function. Because of the precision of laryngeal mechanics, hoarseness may result from a remarkably small lesion and thus be an early sign in the course of a disease process. On the other hand, if the lesion's origin is remote from the vocal cords, hoarseness may present as a late sign. Although histologically the same lesion, a papilloma that produces hoarseness in one patient may produce stridor and obstruction in another, depending on the size and location of the lesion. The quality of the voice change may give only limited clues to its etiology, whereas other characteristics such as age of onset, rate of progression, associated infection, history of trauma or surgery, and the presence of respiratory or cardiac distress may be of much greater significance. A low-pitched, coarse, fluttering voice suggests a subglottic lesion, whereas a high-pitched, cracking voice; aphonia; or breathy voice suggests a glottic lesion. Associated high-pitched stridor also suggests a glottic or subglottic lesion. Although stridor that has been present since birth is more often associated with laryngomalacia, subglottic stenosis, vocal cord paralysis, or a vascular ring, it should be realized that neonates can also present with papillomatosis. Associated symptoms such as feeding difficulties, allergic symptoms, vocal abuse, and the presence of hereditary congenital anomalies may help distinguish RRP from alternative diagnoses, including vocal fold nodules, vocal fold paralysis, subglottic cysts, subglottic hemangioma, and subglottic stenosis. In the absence of any history suggesting these lesions, review of the perinatal period may reveal a history of maternal or paternal condylomata. If the onset of stridor and dysphonia is gradual and progressive through weeks or months, then neoplastic growth compromising the airway must be considered and investigated.

Certainly not every child with a hoarse voice or cry merits investigation beyond an assessment of symptoms. However, in the presence of hoarseness with respiratory distress, tachypnea, decreased air entry, tachycardia, cyanosis, dysphagia, chronic cough, failure to thrive, recurrent pneumonia, or dysphagia, the larynx must be visualized and a firm diagnosis of the cause of hoarseness must be made. Any child with slowly progressive hoarseness merits investigation and the clinician should not wait until total aphonia or airway problems occur.[50]

Physical Examination

Children presenting with symptoms consistent with RRP must undergo a thorough and organized physical examination. The child's respiratory rate and degree of distress must first be assessed. The physician should observe the child for tachypnea or the onset of fatigue that may indicate impending respiratory collapse. The child should be observed for flaring of the nasal ala and the use of accessory neck or chest muscles. Increasing cyanosis and air hunger may cause the child to sit with the neck hyperextended in an attempt to improve airflow. If a child is gravely ill, additional examination should not be undertaken outside the operating room (OR), the emergency department, or the intensive care unit, where resuscitation equipment for intubation of the airway, endoscopic evaluation, and possible tracheotomy are readily available. In the stable, well-oxygenated child, additional examination can proceed. The most important part of the examination is auscultation with the aid of a stethoscope. The physician should listen over the nose, open mouth, neck, and chest to help localize the probable site of the respiratory obstruction. The authors prefer to pull the bell off the stethoscope and listen over these areas with the open tube. The respiratory cycle, which is normally composed of a shorter inspiratory phase and a longer expiratory phase, should then be observed. Stridor of a laryngeal origin is most often musical and may begin as inspiratory, but will progress to biphasic as airway obstruction worsens. Infants with stridor should be placed in various positions to elicit any changes in the stridor. A child with RRP would not be expected to demonstrate much change in the stridor with position change in contrast to infants with laryngomalacia, a vascular ring, or a mediastinal mass. Pulse oximetry can add objective information on the child's respiratory status. In the stable patient in whom asthma is a likely diagnosis, pulmonary function testing may also be helpful.

Airway Endoscopy

The preoperative diagnosis of RRP is best made with a flexible fiberoptic nasopharyngoscope. Careful, sequential inspection of the pharynx, hypopharynx, larynx, and subglottis provides the critical information necessary to make the diagnosis of RRP and allows estimation of lumen size, vocal cord mobility, and the urgency of operative intervention. Advances in instrumentation of flexible nasopharyngoscopes have resulted in instruments as small as 1.8 mm in diameter, which when combined with the newest low-light, three-chip endoscopic cameras, allow passage in even the smallest newborns. Even the smallest diameter scopes provide excellent images that can be viewed on a video monitor and recorded for later review. Topical decongestant and local anesthesia can be applied by spray, dropper, or pledget. Oxymetazoline is the decongestant of choice because of its lack of cardiac side effects. Topical Pontocaine may be used to enhance patient cooperation, but the dosage must be critically monitored in the small infant to avoid cardiotoxicity.

Most clinicians find that visualization with the flexible nasopharyngoscope is far superior to that obtained with indirect mirror laryngoscopy in young children. Patient cooperation, however, is required even with good topical anesthesia. In infants, this is not a large issue because they can easily be restrained in an upright, sitting position in the parent's or nurse's lap for evaluation. Likewise, most children older than 6 or 7 years of age can be "talked into" cooperating for the examination. It is the intermediate age group, between 1 and 6 years of age, who may be the most difficult to examine, taxing the patience and skill of even the most experienced clinicians. Although dynamic evaluation can be appreciated when children are spontaneously breathing, endoscopy in the OR under anesthesia is warranted in any child suspected to have RRP who cannot be fully examined in the outpatient setting.[50]

Surgical Management

Classic Management

At present, there is no "cure" for RRP, and no single modality has consistently been shown to be effective in eradication of RRP. The

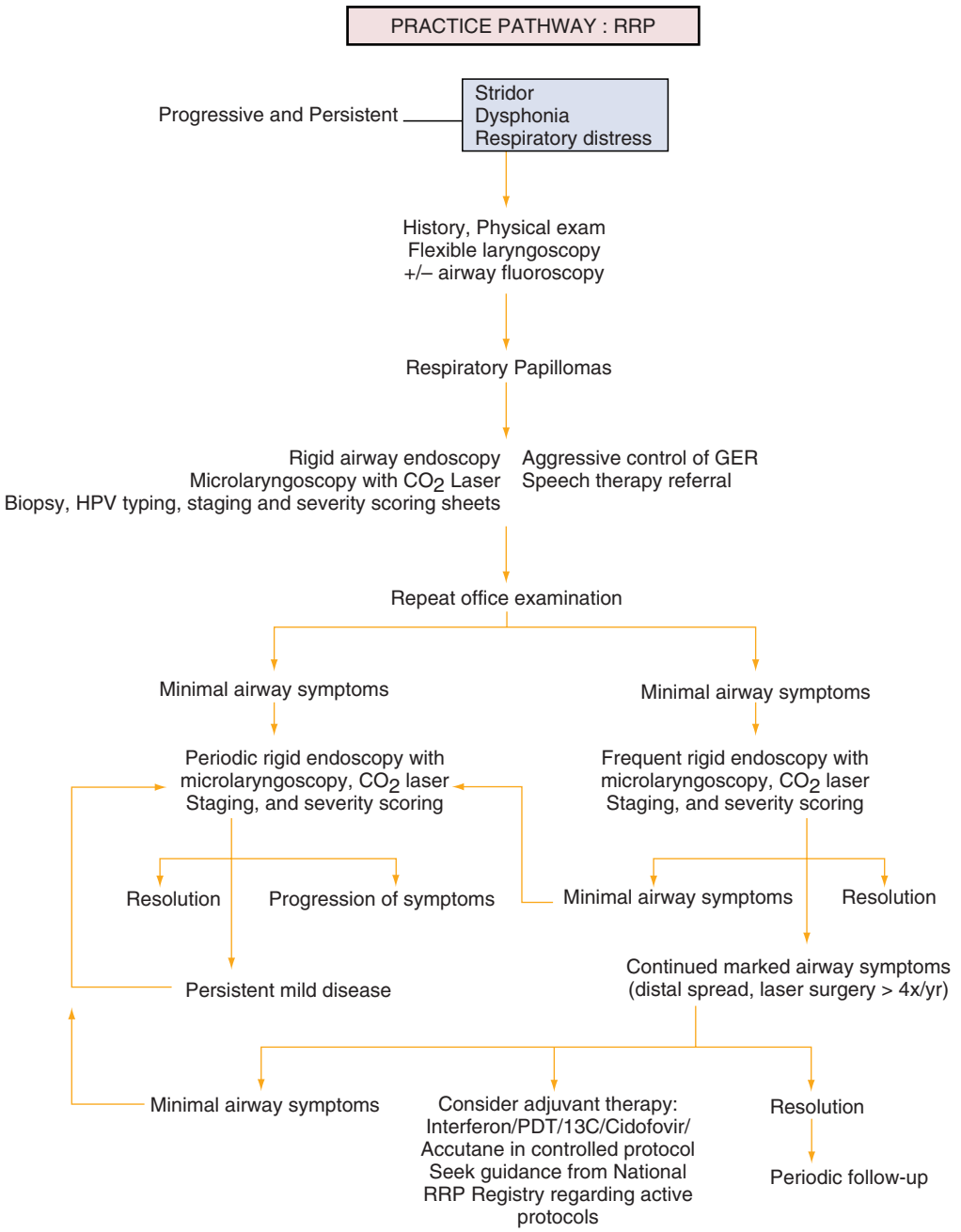

Figure 204-5. Practice pathway for recurrent respiratory papillomatosis. GER, gastroesophageal reflux; HPV, human papillomavirus; PDT, photodynamic therapy; RRP, recurrent respiratory papillomatosis.

current standard of care is surgical therapy with a goal of complete removal of papillomas and preservation of normal structures. In patients in whom anterior or posterior commissure disease or highly aggressive papillomas are present, the goal may be subtotal removal with clearing of the airway. It is advisable to debulk as much disease as possible while preserving normal morphology and anatomy and preventing the complications of subglottic and glottic stenosis, web formation, and resulting airway stenosis. Table 204-1 lists treatment options for RRP.

Until recently, the CO_2 laser has been favored over cold instruments in the treatment of RRP involving the larynx, pharynx, upper trachea, and nasal and oral cavities.[6] When coupled to an operating microscope, the laser vaporizes the lesions with precision, causing minimal bleeding. When used with a no-touch technique, it minimizes damage to the vocal cords and limits scarring. Dedo reported on a series of 244 patients with RRP treated with the CO_2 laser used every 2 months and achieved "remission" in 37%, "clearance" in 6%, and "cure" in 17%.[49] The CO_2 laser has an emission wave length of 10,600 nm and converts light to thermal energy. The CO_2 laser delivers energy that is absorbed by intracellular water, effectively vaporizing the cells.[51] It provides a controlled destruction of tissues with vaporization of water, and it cauterizes tissue surfaces. The smoke plume contains water vapor and destroyed tissue material. Its drawbacks relate to safety of the operating room personnel, patient, and surgeon. The laser may glance off metal used in the suspension of the larynx and injure eyes or skin that it hits. A misfire may also hit areas on the patient that are not protected by a wet towel to absorb the laser energy. In addition, the laser smoke or "plume" has been found to contain active viral DNA, a potential source of infection.[52-54] Smoke evacuators are necessary for safety of exposed individuals. Most importantly, since the laser generates heat, ignition of the endotracheal tube may occur with an inadvertent laser strike. In the oxygen-rich environment provided by anesthetic gases, this can lead to explosion or fire in the airway. The surgeon who

Table 204-1

Treatment Options in RRP

Treatment	Number of Patients Reported
Laser therapy The standard for papilloma removal.	**Hundreds**
Microdébrider removal An evolving standard for papilloma removal.	**Hundreds**
Acyclovir Inhibits thymidine kinase, an enzyme not encoded by HPV. 4 patients treated with postoperative acyclovir, with "no recurrence in 3 cases"[105] 4 patients treated with acyclovir as adjuvant therapy to routine surgical/laser treatment. One of the 4 patients exhibited "less aggressive disease during the treatment period." The authors conclude that acyclovir "is not recommended in the treatment of juvenile respiratory papillomatosis."[106]	**8**
Cidofovir First member of group of antiviral agents known as acyclic phosphonate nucleotide analogs; they inhibit viral DNA polymerase. Cidofovir is directly injected into laryngeal sites of RRP. Large-scale trials are ongoing. 14 of 17 patients with "severe" RRP who underwent cidofovir injections experienced a "complete response."[71] 10 of 10 children with RRP who underwent cidofovir injections showed a response with short-term follow-up.[72] 14 of 14 adults with RRP exhibited disease remission after 1 to 6 injections of cidofovir.[107] Similarly, percutaneous injections of cidofovir resulted in clinical improvement in 5 of 5 adults and 5 of 5 children undergoing intralesional injections.[108,109] A larger study of 26 adults and children receiving intralesional injections found that one third exhibited complete remission; two thirds of the patients exhibited reduction in disease; none exhibited worsening of disease.[75,76] A report of a single patient with pulmonary spread of RRP suggests that systemic cidofovir may be effective in some instances. A patient had documented regression of lung RRP lesions in response to systemic cidofovir.[78]	**>50**
Indole-3-carbinol (I-3-C) I-3-C affects the ratio of estradiol hydroxylation. 18 patients, Phase I trial: one third (6 patients) exhibited "cessation of their papilloma growth"; one third exhibited "reduced papilloma growth rate"; one third exhibited "no clinical response."[84]	**18**
Interferon-alpha This most widely used adjuvant therapy appears to modulate host immune response to virus. Most common adverse side effects include flulike symptoms, but can include severe central nervous system effects such as coma.[67,68]	**>100**
Mumps vaccine 11 children with RRP were treated with regular laser excision; 9 of 11 patients (82%) had "remission induced by 1 to 10 injections, with follow-up at 5 to 19 months." In subsequent series, remission was induced in 29 of 38 patients (76%) by 4 to 26 injections, with follow-up at 2 to 5 years.[95]	**49**
Retinoids ANY in RRP trials?	**?**
Photodynamic therapy (PDT-DHE)	**>100**
Photodynamic therapy (PDT-Foscan)	**Ongoing Clinical Trials**
Vaccines A fusion protein composed of heat shock protein and the E7 gene product of human papillomavirus (HSP-E7) has been used successfully as a novel vaccine in patients with anogenital warts, where 13 of 14 adult patients had resolution of warts at week 24.[110] This novel approach had been in clinical trials as potential therapy for RRP; however, the pharmaceutical company responsible was financially insolvent and clinical trials have been halted. The quadrivalent HPV vaccine indicated for the prevention of cervical cancer[32] promises to dramatically reduce the morbidity and mortality of cervical cancer, but also has the potential to reduce aerodigestive squamous cell carcinoma as well as to eradicate RRP in future generations.[32]	**Ongoing Clinical Trials**

is not aware of injury to deeper tissue layers with injudicious laser usage may cause unacceptable scarring and subsequent abnormal vocal fold function. Inappropriate and aggressive use of the laser may also cause injury to tissues that are not affected and create an environment suitable for implantation of viral particles. Use of the CO_2 laser can also result in delayed local tissue damage, which may be related to the total number of laser surgeries and the severity of RRP disease.

Although the CO_2 laser allows for precision of surgery and excellent hemostasis, multiple procedures are often necessary. Frequent interval laser laryngoscopies are recommended in an attempt to avoid

tracheotomy and permit the child to develop good phonation with preservation of normal vocal cord anatomy. The latest generation of laser microspot micromanipulator enables the surgeon to use a spot size of 250 mm at 400-mm focal length and 160 mm at 250-mm focal length.

Although the CO_2 laser is the most commonly used laser for RRP in the larynx, the potassium titanium phosphate (KTP), 585-nm flash dye, and argon laser could also be used. Papillomata that have extended down the tracheobronchial tree often require use of the KTP or pulse dye laser coupled with a ventilating bronchoscope for removal. Occasionally, the ventilating resectoscope can also be used in these circumstances.

Emerging Technologies

The use of the CO_2 laser on the true vocal folds must be judicious given the potential for significant postoperative scar tissue formation from unrecognized heat transfer. To minimize the risk of scar formation in the true vocal folds, cold steel excision can be used successfully following the principles of phono-microsurgery, submucosal dissection, and microinstrumentation. This approach may have treatment advantages over CO_2 laser surgery, especially in the adult RRP patient.[55-57] In their initial series, Zeitels and Sataloff report recurrence of papilloma in none of the six adults at 2 years follow-up after resection for primary disease. Of those who presented with recurrent papillomatosis, 6 of 16 (38%) continued to recur after their microflap procedure.[57]

Publications have highlighted the potential benefits of other surgical technologies in managing RRP. Bower and others evaluated the feasibility and safety of the flash pump dye laser in nine children and found good early results.[58] McMillan and others published preliminary results regarding their positive experience with the 585-nm pulsed dye laser in three patients.[59] Zeitels reported on office-based use of the 532-nm pulsed KTP laser for treatment of recurrent glottal papillomatosis and dysplasias, noting at least 75% regression of disease in two thirds of patients who could tolerate the procedure.[60] Rees and Koufman also demonstrated tolerance for in-office pulsed dye laser treatments involving 328 procedures in 131 adult patients, with patients overwhelmingly preferring the in-office pulsed dye laser over surgeries under general anesthesia.[61] Zeitels and others currently favor use of a solid-state fiber-based thulium laser that functions similarly to a CO_2 laser with the benefit of being delivered through a small glass fiber.[62]

A number of investigators are now replacing their use of the CO_2 laser with the endoscopic microdébrider as a means of quickly debulking laryngeal disease. In a small, randomized study, Pasquale and others observed improved voice quality, less OR time, less mucosal injury, and a cost benefit in direct comparison of the microdébrider and the CO_2 laser.[63] El-Bitar and Zalzal, and Patel and others, have observed similar improved outcomes with the use of the endoscopic microdébrider.[64,65] A web-based survey of members of the American Society of Pediatric Otolaryngologists (ASPO) found the majority of respondents now favoring the use of "shaver" technology.[4]

Because no therapeutic regimen reliably eradicates the HPV, when there is a question about whether papilloma in an area needs to be removed, it is prudent to accept some residual papilloma rather than risk damage to normal tissue and produce excessive scarring. Even with the removal of all clinically evident papilloma, latent virus remains in adjacent tissue. Therefore the aim of therapy in extensive disease should be to reduce the tumor burden, decrease the spread of disease, create a safe and patent airway, optimize voice quality, and increase the time interval between surgical procedures. Staged papilloma removal for disease in the anterior commissure is appropriate to prevent the apposition of two raw mucosal surfaces.

Anesthetic Techniques

Several different anesthetic techniques have been advocated in endoscopic procedures to remove papillomas in children. With all methods, the airway must be handled with the utmost delicacy to minimize iatrogenic microtrauma to the mucosa.

Spontaneous Ventilation

In spontaneous ventilation, intravenous agents such as propofol are used along with oxygen and anesthetic gases such as sevoflurane that are entrained through a side port of the laryngoscope or through an endotracheal tube or nasal trumpet placed in the pharynx. The patient's own efforts are responsible for maintenance of anesthesia. Advantages are the unobstructed surgical field, but the technique is hard to master and requires an anesthesiologist who is well attuned to his or her patient. Laryngospasm, awakening, and other movement can take place with disastrous results.

Intermittent Apnea-Reintubation

Intermittent apnea-reintubation allows for the widest range of anesthetic types and provides for an unobstructed surgical view. The patient is anesthetized, intubated, suspended, and examined. The microscope is used to visualize the larynx and the tube is withdrawn while the laser or microdébrider is used. The tube is then replaced under direct visualization if the patient's oxygenation diminishes and/or the carbon dioxide level rises. Although the time for operative intervention is limited, this method is simple and effective. It does have the drawback of potentially spreading the virus through the repeated placement of the tube, however.

Wrapped or "Laser-Safe" Endotracheal Tube

Use of a wrapped or "laser-safe" endotracheal tube to protect the tube from accidental ignition by the laser can be effective and permits no significant alteration in anesthetic or surgical management. The tube remains in the surgical field, potentially obscuring the posterior glottis and subglottis. A wrapped tube must be protected (usually with electromagnetic tape or foil) to reduce risk of airway fire. There are commercially available "laser safe" tubes. Cuffs must also be protected with moist surgical cottonoids to prevent their rupture.

Jet Ventilation

Another anesthetic alternative is the use of jet ventilation for microsurgery of the larynx. Jet ventilation eliminates the potential fire hazard inherent in the use of the endotracheal tube when used with the CO_2 laser and allows good visualization of the vocal cords. A limitation of this technique is the possibility of transmission of HPV particles into the distal airway. The jet cannula can be placed either above or below the vocal cords and each approach has its own particular benefit. It is preferable to place the cannula proximal to the end of the laryngoscope to decrease the risk of possible pneumothorax or pneumomediastinum. With large laryngeal lesions, narrowed airways, and ball-valve lesions, there may develop a high degree of outflow obstruction that could lead to increased intrathoracic pressure and a subsequent pneumothorax. This may also result if there is inadequate muscle relaxation. Jet ventilation also requires constant communication between the operating surgeon and the anesthesiologist. Excessive mucosal drying and damage can occur, as can insufflation of air into the stomach with gastric distention. As mentioned earlier in this chapter, there is also the potential risk of disseminating papilloma or blood into the tracheobronchial tree.

Although not appropriate for most children with RRP, office endoscopy using light or topical anesthesia can be used along with the pulsed dye laser in selected adults.

Adjuvant Treatment Modalities

Although surgical management remains the mainstay therapy for RRP, ultimately as many as 20% of patients with the disease will require some form of adjuvant therapy. The most widely adopted criteria for initiating adjuvant therapy are a requirement for more than four surgical procedures per year, rapid regrowth of papilloma disease with airway compromise, or distal multisite spread of disease. Some of these adjuvant treatment options are summarized in Table 204-1.

Antiviral Modalities

Interferon

The first widely employed adjuvant therapy was alpha-interferon.[6,66,67] The exact mechanism by which interferon elicits its response is unknown. It appears to modulate host immune response by increasing production of a protein kinase and endonuclease, which inhibits viral protein synthesis.[68] Interferons are a class of proteins that are manufac-

tured by cells in response to a variety of stimuli including viral infection. The enzymes that are produced block the viral replication of RNA and DNA and alter cell membranes to make them less susceptible to viral penetration.

Common interferon side effects fall into two categories: acute reactions (fever and generalized flulike symptoms, chills, headache, myalgias, and nausea that seem to decrease with prolonged therapy) and chronic reactions (decrease in the growth rate of the child, elevation of liver transaminase levels, leukopenia spastic diplegia, and febrile seizures). Thrombocytopenia has been reported, as have rashes, dry skin, alopecia, generalized pruritus, and fatigue. Acetaminophen has been found to effectively relieve fever, and interferon injections are best tolerated at bedtime. Interferon produced by recombinant DNA techniques appears to have fewer side effects and better efficacy than blood bank-harvested interferon. If the side effects can be tolerated then therapy is initiated at 5 million units/m^2 body surface area administered by subcutaneous injection on a daily basis for 28 days, then 3 days per week for at least a 6-month trial. After 6 months in children with excellent responses and no severe side effects, the dosage can be decreased to 3 million units/m^2 for 3 days a week with further slow weaning as tolerated.

Ribavirin

Ribavirin is an antiviral drug used to treat respiratory syncytial virus pneumonia in infants that has also shown some promise in the treatment of aggressive laryngeal papillomatosis. Ostrow and others at the University of Minnesota have completed a small trial in eight patients using ribavirin in an oral form at 23 mg/kg/day divided four times daily after an initial intravenous loading dose, showing an increase in surgical interval in those treated.[69]

Acyclovir

Another antiviral treatment that has been advocated in the treatment of RRP is acyclovir. Although the activity of acyclovir is dependent on the presence of virally encoded thymidine kinase, an enzyme that is not known to be encoded by papillomavirus, conflicting clinical results have been obtained in several small series. Theoretically, it would not be expected to have a positive effect. However, it has been postulated that perhaps acyclovir is most effective when there are simultaneous disease factors such as infection with herpes simplex virus. Such viral co-infections with herpes simplex virus 1, cytomegalovirus, and Epstein-Barr virus (HSV-1, CMV, and EBV) have been demonstrated in RRP patients, and these patients with viral co-infections appear to have a more aggressive clinical course.[70]

Cidofovir

Recent reports have stimulated interest in the intralesional injection of cidofovir (Vistide)—(S)-1-[3-hydroxy-2-(phosphonylmethoxyethyl)-propyl]-cytosine (HPMPC)—a drug approved by the U.S. Food and Drug Administration for use in human immunodeficiency virus (HIV) patients with cytomegalovirus under expedited, fast-track guidelines. Despite a lack of controlled, randomized, blinded clinical trials in children with RRP, cidofovir is currently the most frequently used adjuvant drug.[4] Snoeck and others reported a series of 17 patients with severe RRP treated with cidofovir at 2.5 mg/mL injected directly into the papilloma bed after laser surgery experienced a complete response in 14 days.[71] Pranksy and coworkets have used this therapy in 10 children with severe RRP with short-term follow-up showing a response in all 10 patients,[72] and long-term follow-up has been encouraging.[73,74] Similarly encouraging results have been reported by Naiman and others in a small cohort of adults and children treated with a protocol-driven approach using a high dose of cidofovir at 2-week intervals.[75,76] Co and Woo have also demonstrated efficacy in a small cohort of adults with RRP treated with serial office-based intralesional injections of cidofovir.[77] Finally, there has been one encouraging successful treatment of pulmonary multicystic papillomatosis using systemic cidofovir.[78]

Based on animal studies that demonstrated a high level of carcinogenicity, and on case reports of progressive dysplasia in patients with RRP,[79] the RRP Task Force has published guidelines for clinicians interested in using cidofovir in their RRP patients.[80] Despite the anecdotal nature of most of the cidofovir studies and reports, the preliminary results are encouraging enough to consider this a treatment option in severely affected RRP patients.

Photodynamic Therapy

Photodynamic therapy (PDT) applied to the treatment of RRP has been studied extensively at Long Island Jewish Hospital by Shikowitz and associates.[81] PDT is based on the transfer of energy to a photosensitive drug. The original drug used was dihematoporphyrin ether (DHE), which has a tendency to concentrate within papillomas more so than in surrounding normal tissue. Patients are typically treated intravenously with 4.25 mg/kg of DHE before photoactivation with an argon pump dye laser. A small but statistically significant decrease in RRP growth, especially in patients whose disease was worse, was seen with the use of PDT and DHE. The drawback of this therapy is that patients become markedly photosensitive for periods lasting 2 to 8 weeks. A new drug, m-tetra(hydroxyphenyl)chlorine (Foscan), has shown efficacy in HPV-induced tumors in rabbits with minimal tissue damage and less photosensitivity. A clinical trial using this drug in a parallel-arm, randomized trial of 23 severely affected patients ages 4 to 60 resulted in improvement in laryngeal disease; however, remissions failed to be maintained over 3 to 5 years and the therapy was poorly tolerated by a quarter of the patients.[82]

Indole-3-Carbinol

There has been recent interest in the dietary supplement, indole-3-carbinol, a compound that is found in high concentration in cruciferous vegetables such as cabbage, cauliflower, and broccoli. Results in an open label, multicenter study coordinated by Rosen of treating RRP with indole-3-carbinol were encouraging. During the short follow-up of the study (a minimum of 8 months), one third of the patients had a cessation of their papilloma growth and did not require further surgery, one third of the patients exhibited reduced papilloma growth rate, and one third did not show a clinical response.[83,84] The role of estrogens on the growth of RRP has been conjectured since the discovery that RRP exhibits increased binding of estrogen.[85] Subsequent to that report, inhibition of estrogen metabolism using indole-3-carbinol has been shown to reduce the formation of HPV-induced papilloma tumors in immunocompromised mice by nearly 75%.[86] Most recently, the clinical response to indole-3-carbinol in children with RRP was closely correlated with the ratio of hydroxylated estradiol in urine.[84] Longer follow-up of a larger, blinded, controlled trial seems warranted before universally recommending this therapy.

Celecoxib

Celecoxib (Celebrex) is a selective inhibitor of the enzyme COX-2, which is overexpressed in RRPs and stimulates their growth.[87] Preliminary encouraging results in a small cohort of adults with Celebrex has led to an NIH-funded multicenter trial led by investigators at Long Island Jewish Hospital that is currently active (no longer enrolling) for adults with RRP.

Retinoids

Retinoids, which are metabolites and analogues of vitamin A, are known modulators of cellular proliferation and differentiation of diverse histologic cell types. In the aerodigestive tract, excess vitamin A has been found to suppress squamous differentiation, and may result in mucous metaplasia.[88] In contrast, vitamin A deficiency may result in hyperkeratinization and squamous metaplasia.[89] However, there are a variety of retinoids with opposing effects on epithelial cell metabolism.[90-93] Thus to state that retinoids as a class of agents have a beneficial or deleterious effect on mucosal differentiation would be an oversimplification. With this caveat, 13-cis-retinoic acid (Accutane) has gained some popularity as a systemic treatment for RRP.[94] The dosage for retinoic acid is 1 to 2 mg/kg/day. This therapy is maintained for 6 months or until the patient develops side effects he cannot tolerate. Care has to be taken in sexually active patients because Accutane has well-known teratogenic effects.

Mumps Vaccine

Intralesional injection of mumps vaccine and MMR vaccine has been investigated in an open-label single-center trial with moderate success.[95]

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS : ___ DATE OF SURGERY:___ SURGEON:___
PATIENT ID #: ___ INSTITUTION:___

1. How long since the last papilloma surgery? ___days, ___weeks,___months,___years,
___ don't know, ___1st surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months?___
3. Describe the patient's voice today: ___aphonic, ___abnormal, ___normal,___other
4. Describe the patient's stridor today: ___absent, ___present with activity, ___present at rest,
___ don't know
5. Describe the urgency of today's intervention: ___scheduled, ___urgent, ___ emergent

FOR EACH SITE, SCORE AS: 0 = NONE, 1 = SURFACE LESION, 2 = RAISED LESION, 3 = BULKY LESION

LARYNX
Epiglottis
Lingual surface _____ Laryngeal surface ____
Aryepiglottic folds: Right___ Left___
False vocal cords: Right___ Left___
True vocal cords: Right___ Left___
Arytenoids: Right___ Left___
Anterior commissure_____ Posterior commissure_____
Subglottis_____

TRACHEA:
Upper one-third _____
Middle one-third_____
Lower one-third_____
Bronchi: Right_____ Left_____
Tracheotomy stoma_____

OTHER:
Nose_____
Palate_____
Pharynx_____
Esophagus_____
Lungs_____
Other_____

TOTAL SCORE ALL SITES: _____

Figure 204-6. Staging assessment sheet for recurrent respiratory papillomatosis. *(From Derkay CS, Malis DJ, Zalzal G, et al. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis.* Laryngoscope. *1998;108:935-937.)*

These positive results, however, have not been reproduced by other investigators.[96]

Antireflux Therapy

The role of gastroesophageal reflux in exacerbation of RRP deserves special mention. Recent case reports have shown that the rate of recurrence of respiratory papillomatosis in children may decrease significantly after antireflux therapy.[97,98] The H_2-antihistamine Cimetidine (ranitidine) has been shown to have immunomodulatory effects.[99,100] This has resulted in several reports of its use against various virally based diseases, including RRP.[98,101] A recent small case series from Buffalo demonstrated efficacy in previously resistant children with RRP.[102] It is for these reasons that optimal control of extraesophageal reflux disease has been advocated as a means of improving outcomes, along with surgical therapy. The authors routinely place their RRP patients on an antireflux regimen.

Staging Severity

It is helpful when tracking the progression of a child's disease, communicating with other surgeons, and treating patients in a protocol format to have a surgical scoring system to assess severity and clinical course of RRP disease. Although several scoring and staging systems have been proposed, clinicians and researchers have not yet adopted a uniformly acceptable nomenclature for describing RRP lesions that is simple yet comprehensive. This has created confusion in the RRP literature and in physician-to-physician communications regarding patients' response to therapies. In addition, the absence of a universally accepted staging system has hampered our abilities to accurately report the results of adjuvant therapies or document the natural course of the disease. We have introduced a severity-staging system for RRP in a format that incorporates the best qualities of the existing systems by numerically grading the extent of papillomatosis at defined aerodigestive subsites, assessing functional parameters, diagrammatically catalogs subsite involvement, and assigning a final numeric score to the patient's current extent of disease (Figs. 204-5 through 204-7).[47,103,104] Using software designed at the University of Washington (Seattle) and licensed to the ASPO, this staging system is now computerized and available to pediatric otolaryngologists and bronchoesophagologists to allow them to objectively and subjectively measure an individual patient's clinical course and response to therapy through time. Health Insurance Portability and Accountability Act–compliant encryption technology with this software offers promise to allow clinicians from

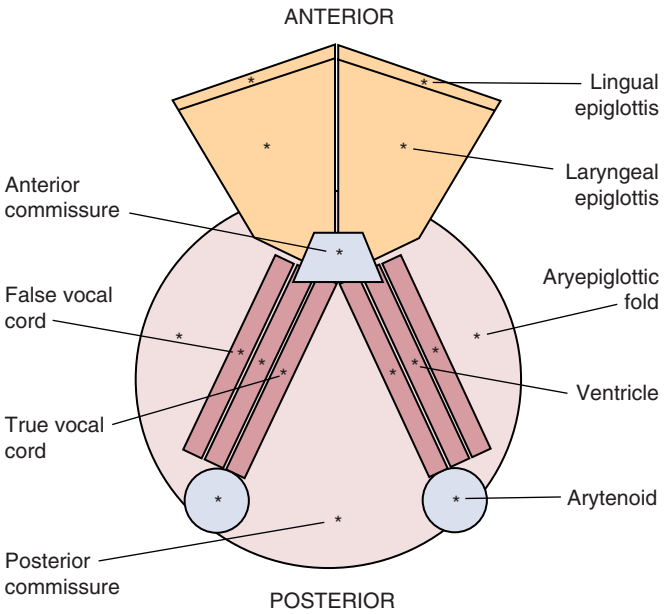

Figure 204-7. Diagram of laryngeal sites that may be scored. *(From Hester RP, Derkay CS, Burke BL, Lawson ML. Reliability of a staging assessment system for recurrent respiratory papillomatosis.* Int J Pediatr Otorhinolaryngol. *2003;67:505-509.)*

around the world to anonymously share some of their patient data to enhance our knowledge of this disease and promote multi-institutional investigations.

Registry and Task Force Initiatives

It should be stressed that participation in national and regional protocols of adjuvant treatment modalities is essential for the scientific community to learn more about RRP. A national registry of patients with RRP has been formed through the cooperation of the ASPO and the CDC.[14] The registry tracked nearly 600 children at 22 sites with data on more than 11,000 surgical procedures. Data from the national registry aided in the identification of patients suitable for enrollment in multi-institutional studies of adjuvant therapies and better defined the risk factors for transmission of HPV and the cofactors that may determine the aggressiveness of RRP. An RRP task force, made up of the principal investigators at each of the registry sites as well as representatives from the adult RRP research community and patient/parent advocacy groups, meets twice yearly to facilitate research initiatives. The RRP task force has completed a set of Practice Guidelines (RRP Task Force, 2000) to help guide the clinician in the diagnosis and management of children with RRP, and has authored public health guidelines regarding RRP and statements on the use of cidofovir. The Task Force is engaged in providing a statement on the value of viral typing and is facilitating an investigation of the genes responsible for aggressive RRP. They have also facilitated the development of similar groups of RRP investigators in Canada and Europe and are currently working with their colleagues outside of the United States to study the benefits of the quadrivalent HPV vaccine for treatment and prevention of RRP.

Other Considerations

Children with newly diagnosed RRP warrant a substantial time commitment on the part of the otolaryngologist to engage the family in a frank and open discussion of the disease and its management. Support groups such as the Recurrent Respiratory Papilloma Foundation (www.rrpf.org) and the International (www.rrpwebsite.org) can be a vital resource for information and support. RRP patients require frequent office visits and endoscopic procedures at the outset to establish the aggressiveness of their disease. The patients are encouraged to return to the office or call as often as necessary while family members and the health care team become familiar with the child's symptoms and level of distress. While infant home intercom-type monitors are often recommended, apnea-bradycardia monitors and pulse oximetry are generally not necessary. Repeat flexible fiberoptic laryngoscopy may be used in the office, and speech and language therapy is offered early in the course of the disease. Control of other medical factors such as reflux and asthma is also aggressively pursued.

Summary

RRP is a frustrating, capricious disease with the potential for morbid consequences because of its involvement of the airway and the risk of malignant degeneration. The goals of surgical therapy are to maintain a safe airway with a serviceable voice while avoiding excessive scarring. No single modality of therapy has been consistently shown effective in eradicating RRP. When children require surgical therapy more frequently than four times in 12 months or have evidence of distal spread of RRP outside of the larynx, adjuvant medical therapy should be considered. Many adjuvant therapies have been investigated to supplement surgical therapy. These range from dietary supplements and control of extraesophageal reflux disease to potent antiviral and chemotherapeutic agents and photodynamic therapies. Although several of these modalities have shown promise, no adjuvant therapy to date has "cured" RRP.

Strides are being made in learning more about the natural history of the disease. A registry of RRP patients, and software to help clinicians share information on and accurately follow their RRP patients, has been developed. Future research is needed regarding prevention of transmission of HPV from mother to child. Specifically, the roles of cesarean section and gynecologic surgery during pregnancy need to be elucidated. Universal or near-universal use of an HPV vaccine that provides protection against HPV 6 and 11 may do for RRP what the Hib vaccine has done for *H. influenzae* type B epiglottitis—virtually eliminating new cases in less than a decade. Further refinements in surgical techniques, including the use of new office-based lasers to minimize laryngeal scarring, also need to be studied. Surgical therapy for RRP requires a skilled team consisting of otolaryngologists, anesthesia providers, and operating room personnel working together in a facility properly equipped to manage difficult pediatric airways. Because of the recurrent nature of RRP and the potential for airway obstruction, parental support and education can be invaluable to the safety of the child with RRP.

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CHAPTER TWO HUNDRED AND FIVE

Evaluation and Management of the Stridulous Child

David Albert

Simone Boardman

Marlene Soma

Key Points

- The quality of stridor may be *characteristic* of a particular pathology but is never *diagnostic*; the diagnosis can only be confirmed with certainty after endoscopy.
- Improvement in stridor can paradoxically be due to worsening airway obstruction and reduced airflow.
- Laryngotracheobronchoscopy is the gold standard in the assessment of the stridulous child. It is now a highly technical procedure and the whole team (surgeon, anesthetist, and nursing assistant) needs to work closely together to perform the examination safely and to optimize the assessment.
- Children with croup who demonstrate increased work of breathing in the clinics or emergency departments should be treated with glucocorticoids.
- The risk with low tracheobronchial obstruction is that neither intubation nor tracheostomy will relieve the obstruction, although positive pressure will tend to improve malacia and to a lesser extent stenosis.
- A difficult and potentially dangerous situation occurs if a tracheotomy is attempted for tapering long segment tracheal stenosis. Not only is it not possible to insert a normal neonatal size tracheotomy tube but the tracheotomy itself severely limits the therapeutic options for surgical reconstruction of the stenosis.
- Medical therapy with steroids, antireflux treatment, nebulized adrenaline (epinephrine), heliox, and antibiotics in some cases may avert the need for more invasive measures such as tracheotomy.
- Therapeutic surgical options to manage the stridulous child include tracheotomy, endoscopic and open laryngeal surgery. Treatment is individualized depending on the underlying pathology, associated comorbidity, and social circumstances.

A stridulous child with airway obstruction demands prompt attention from parents and clinicians alike. There are many good reasons to treat pediatric patients with great respect; they have less respiratory reserve and their smaller airways are more easily compromised. In the acute situation, the infant airway can deteriorate rapidly and provide significant clinical challenges. The history and examination are rarely sufficient for a firm diagnosis; however, deciding which patients require further investigation may be difficult. Even after appropriate noninvasive investigations (e.g., imaging), there may still be a number of possible diagnoses. Flexible endoscopy in the office is useful but gives limited information beyond the glottis. The definitive diagnostic tool of laryngotracheobronchoscopy requires highly specialized equipment and an experienced surgical, anesthetic, and nursing team.

Advances in medical technology impact the likely underlying diagnoses of modern-day stridor and its management.[1] Developments in neonatal intensive care have seen improved neonatal survival and the associated challenges of the airway pathology seen in these children. Routine childhood immunization with the *Haemophilus influenzae* type B (HiB) vaccine has led to a precipitous decline in epiglottitis, making it a rarity. Improvements in endoscopic equipment have revolutionized the quality of optical images obtainable and captured for digital recording. It has also allowed for the development of endoscopic interventions in the compromised pediatric airway, many of which may now be used in combination to avoid tracheotomy or open airway surgery.

This chapter describes a current and safe approach to assessing and treating the airway of the stridulous child. The diagnostic workup is reviewed in detail and the medical and surgical management of acute and chronic airway obstruction is reviewed, with special attention given to the situations of postextubation stridor and postpartum neonatal airway obstruction. The principles of tracheotomy, endoscopic, and open laryngeal surgery are discussed.

Definition and Physical Principles

Stridor is an audible respiratory noise derived from turbulent airflow due to narrowing or obstruction of the upper airway. Stridor may be inspiratory, biphasic, or expiratory in nature. It is classically a harsh sound, which can vary in quality from a squeak to a whistling noise. Stertor describes the snoring-like noise, which typically originates from nasopharyngeal or oropharyngeal obstruction. Clinically, however, the supraglottic larynx can occasionally produce this quality of noise.

Table 205-1

Differential Diagnosis of Airway Obstruction

	Supralaryngeal	Laryngeal	Tracheobronchial
Congenital	Choanal atresia	Laryngomalacia	Tracheomalacia/bronchomalacia
	Choanal/midnasal/piriform aperture stenosis	Vocal cord palsy	Tracheal stenosis
	Benign tumor	Laryngeal atresia	Extrinsic compression
	Nasal glioma	Laryngotracheal stenosis	Vascular compression (e.g., aberrant brachiocephalic, double aortic arch, vascular ring, pulmonary artery sling)
	Encephalocele	Laryngeal web	Mediastinal tumor
	Meningocele	Posterior laryngeal cleft	Tracheal atresia
	Nasopharyngeal mass (e.g., hairy polyp, teratoma)	Cysts	Complete tracheal rings
	Structural	Vallecular cyst	Tracheal cysts
	Midface hypoplasia (e.g., Apert's, Crouzon's, Down syndrome)	Laryngeal cyst	
	Micrognathia (e.g., Pierre Robin, Treacher Collins)		
	Macroglossia (e.g., Down syndrome, cystic hygroma, lingual thyroid)		
	Cysts		
	Dermoid		
	Thyroglossal duct cyst		
	Neurological dysfunction		
Acquired	Adenotonsillar hypertrophy	Trauma	Postintubation/instrumentation
	Infection	Intubation trauma (e.g., subglottic stenosis)	Tracheal stenosis
	Tonsillitis	Cricoarytenoid joint fixation	Foreign body
	Adenoiditis	Surgical trauma (e.g., laser)	Reflux
	Infectious mononucleosis	Thermal and caustic burns	Infection
	Retropharyngeal abscess	Infection	Croup
	Ludwig's angina	Croup	Bacterial tracheitis
	Rhinitis	Epiglottitis	Postsurgical malacia (e.g., tracheostomy, tracheoesophageal fistula repair)
	Foreign body	Reflux laryngitis	Extrinsic compression
	Thermal and caustic burns	Benign tumor	Mediastinal tumor (e.g., hemangioma, cystic hygroma, lymphadenopathy, thyroid mass)
		Papillomatosis	
		Hemangioma	
		Cystic hygroma	
		Malignant tumor (e.g., rhabdomyosarcoma)	
		Foreign body	

Obstruction from all levels of the airway should thus be considered when approaching the differential diagnoses of airway obstruction (Table 205-1).

It is helpful to review the physical principles of tubular flow according to Poiseuille's law, which states that $Q = [\pi r^4(P_1\text{-}P_2)]/8\eta L$; where Q is flow, r is radius, P is pressure, η is viscosity, and L is length of tube. From this law, resistance is inversely proportional to the radius to the fourth power. From a practical viewpoint, this explains why minor narrowing in a child's airway is of much greater consequence than in an adult. For example, 1 mm of edema in a 4-mm diameter pediatric airway will reduce the cross-sectional area by 75% (16-fold increase in resistance), whereas in a 12-mm adult airway, the same 1 mm of edema reduces the airway area by just 30% (twofold increase in resistance) as demonstrated in Fig. 205-1.[2]

Assessment

It is important to perform a rapid initial evaluation of the stridulous child to assess their degree of respiratory distress and thus the urgency of their clinical presentation. If the patient has acute airway obstruction with significant respiratory distress, particularly if the patient is tiring, then the history, examination, and initial resuscitation must take place simultaneously. A comprehensive history and exhaustive examination can be completed once the situation is controlled. If the child's condition is stable, then a thorough assessment can be conducted.

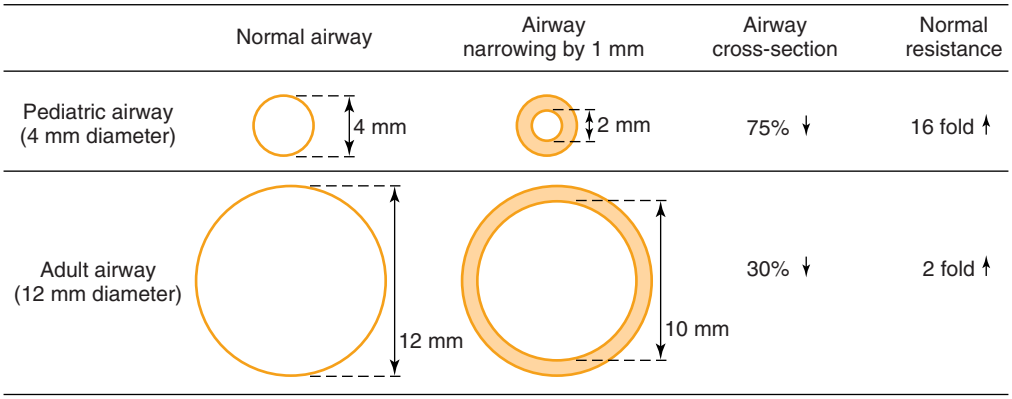

Figure 205-1. Effect of airway narrowing upon airway cross-section and resistance in the pediatric and adult airway.[2]

Stridor may be *characteristic* of a particular pathology but is never *diagnostic*. The diagnosis can be confirmed with certainty only after endoscopy. However, the combination of a thorough history, examination, and investigation can in some conditions (e.g., mild laryngomalacia) provide sufficient diagnostic probability to avoid initial rigid endoscopy. Seventeen percent of infants with laryngomalacia have a synchronous lesion that may be contributing to their airway compromise.[3] This may be missed without assessment via rigid endoscopy.

History

In an acutely stridulous child, even a brief history may aid in determining the source of the airway obstruction. Particular note should be taken of any possible foreign body ingestion or concurrent illness. A careful and thorough history will aid in formulating the differential diagnosis as long as the child has a stable airway.

Features of the stridor, including the timing of onset, progression, variability, and presence of exacerbating or relieving factors should be carefully established. Stridor present from birth suggests an underlying anatomic cause. This generally denotes a fixed congenital narrowing such as a laryngeal web, subglottic stenosis, or tracheal narrowing.[4] Dynamic conditions such as laryngomalacia typically become evident in the first few weeks of life, while congenital vocal cord palsy is also a common cause of neonatal stridor. A gradual increase in severity of stridor or airway compromise implies progressive obstruction. The obstruction may be luminal (as in a subglottic hemangioma) or extrinsic (as with a mediastinal mass or vascular anomaly). Alternatively over a longer period of time, increasing stridor may coincide with increased respiratory demands as the child becomes more active. Typically, laryngomalacia improves during rest or sleep but is worsened by crying, feeding, or physical activity. Airway obstruction associated with supine positioning may occur with supralaryngeal obstruction, such as micrognathia wherein there is associated airway obstruction by the tongue base. More rarely a pedunculated laryngeal mass, for example, a vallecular cyst, can give positional variation in the stridor as it is displaced in and out of the airway (Fig. 205-2). Improved airway obstruction with crying may occur in gross nasal obstruction such as bilateral choanal atresia.

Airway obstruction produces a number of associated symptoms (Table 205-2) that may be useful in formulating a differential diagnosis. Parents have often observed signs of increased respiratory work, including tracheal tug, subcostal recession, and suprasternal or sternal indrawing. Apneas with cyanosis may occur and parents often attempt resuscitation if these are severe. These episodes are typical of severe tracheobronchomalacia and are sometimes termed *dying spells*. The differential diagnosis includes underlying congenital cardiac disease, hence these episodes should be investigated further. Cough is typical of tracheoesophageal fistula and tracheomalacia, and raises the possibility of aspiration. Hoarseness suggests laryngeal pathology such as laryngeal papillomatosis (Fig. 205-3), whereas supralaryngeal pathology may give a muffled voice. Voice change may also occur in vocal cord palsy, although these children can also present with airway compromise and a normal voice.[5,6] Tachypnea and dyspnea are not limited to upper airway obstruction, but a clear description of exertional dyspnea in an older child may provide a useful functional assessment of severity.

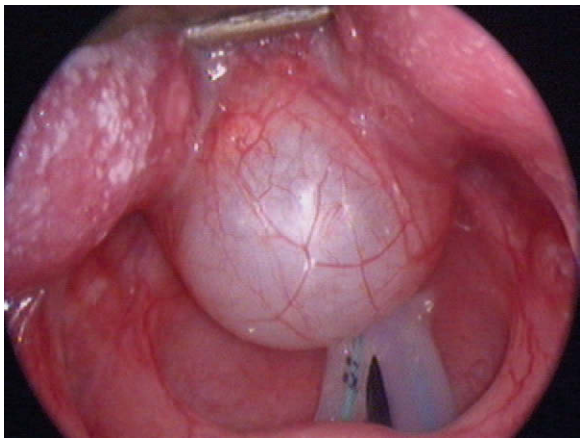

Figure 205-2. Endoscopic view of supraglottic larynx demonstrating a vallecular cyst.

The baby may feed slowly due to airway obstruction and "run out of breath" or "come up for air" during feeds. Bottle-fed babies may require thickened feeds or a "slow teat" (i.e., one with small holes). Uncomplicated slow feeding, although often a source of significant maternal anxiety, is not necessarily of concern in isolation. However, if there is failure to thrive and documented poor weight gain on the centile growth chart, further investigation and possible intervention should be considered. Laryngomalacia commonly gives rise to feeding difficulties but it is important to consider other causes. Choking episodes, documented aspiration, or recurrent chest infections may occur with vocal cord palsy, tracheoesophageal fistula, or rarely a laryngeal cleft (see Fig. 205-21). Gastroesophageal reflux is also common in infants with stridor and may exacerbate airway obstruction via edema.

The possibility of foreign body aspiration should always be raised with the parents although it is an unusual cause of isolated stridor. The clinician must however maintain a high index of suspicion to avoid missing this diagnosis, particularly if there is a history of a choking episode. The parent or caregiver may not necessarily witness events of foreign body aspiration and so the likelihood of this should be assessed. Caustic ingestion or thermal injury to the hypopharynx or supraglottis sustained by the infant drinking from microwave-heated bottles can also cause upper airway obstruction.

The clinician should determine whether the child has been systemically unwell, possibly with high temperatures. Acute episodes of airway infection will cause acute inflammation and obstruction. Viral laryngotracheitis (croup) classically has a barking cough with low-grade

Table 205-2

Features of History and Examination in the Stridulous Child

Symptoms	Signs
Stridor	Characteristics of stridor
Timing of onset	Quality, duration, timing
Progression	General appearance/syndromic features
Variability	Work of respiration:
Exacerbating/relieving factors	Respiratory rate, distress, fatigue, accessory muscle use, recession, nasal flaring, tracheal tug
Features of systemic infection	Positioning for optimal airway
Apneas/cyanosis (dying spells)	Drooling
Parental observation of recession	Quality of cry
Shortness of breath, respiratory rate	Observation chart: temperature, pulse rate
Cough	Nasal patency
Feeding difficulties	Oropharynx—mandible, tongue, tonsils
Aspiration/reflux	Neck—fullness/masses, torticollis
Cry/hoarseness	Auscultation of upper airway and chest
Specific questioning regarding foreign body aspiration	Remainder of earn, nose, throat assessment (e.g., ears)
Past history:	
Perinatal	
Intubation history	
Recurrent/persisting croup or bronchiolitis	
Comorbidities (e.g., neurologic—Arnold-Chiari, vascular malformation, cardiac disease/surgery, "birth marks"	

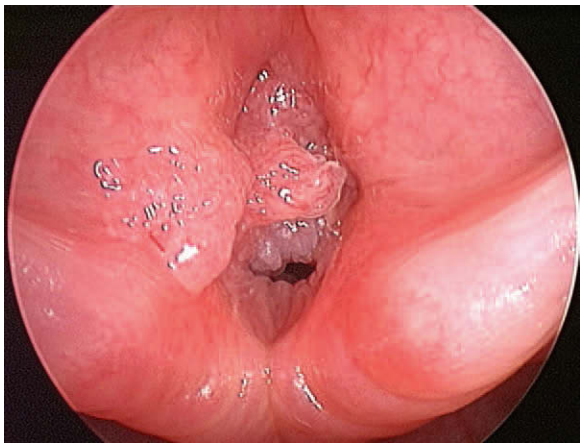

Figure 205-3. Laryngeal papillomata involving the vocal cords and extending onto the right false cord with significant airway obstruction and dysphonia.

fever and a preceding prodromal upper respiratory tract infection. Epiglottitis typically produces rapidly progressive upper airway obstruction in association with drooling, marked odynophagia, and a "muffled" voice. It is now very rare due to a dramatic reduction in incidence since implementation of Hib immunizations. Bacterial tracheitis has a variable onset with a toxic appearance, high fevers, cough, and stridor.

The obstetric and perinatal histories are often relevant, especially if the child was born prematurely and required ventilation. Parents

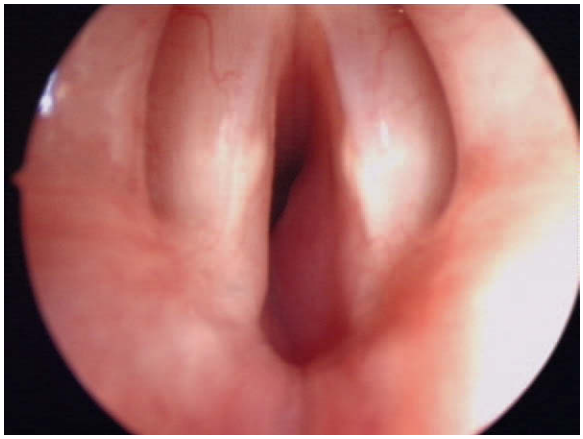

Figure 205-4. Endoscopic view of subglottic hemangioma presenting with increasing stridor.

should be specifically asked about neonatal intubation. This history must be taken carefully because the passage of nasogastric tubes for feeding or nasal/oral mucous suctioning may be mistaken for intubation. Previous intubation places the child at an increased risk of acquired subglottic stenosis (see Fig. 205-13). If the child was recently intubated or is being assessed due to failed extubation, it is worthwhile to obtain details, including size of the endotracheal tube used in comparison to the predicted age-appropriate tube, presence of a leak during intubation, use of steroids at the time of extubation, and any previous history of failed extubations.

Other comorbidities may predispose to airway obstruction, for example, vocal cord palsy in Arnold-Chiari malformation or birth injury, neurologic disease giving rise to hypotonia, or iatrogenic injury following cardiac surgery. A previously diagnosed syndrome may alert the clinician to potential pathology that is recognized as a component of the syndrome, for example, laryngeal webs in velocardiofacial syndrome. Vascular malformations, congenital cardiac disease, or vascular anomalies may give extrinsic compression of the airway and subsequent tracheomalacia. Parents should be asked about the presence of any "birthmarks," in that 50% of children with a subglottic hemangioma have a cutaneous lesion at the time of diagnosis (Fig. 205-4).[7] There is a markedly increased risk for children with cutaneous hemangiomas in a "beard" distribution, with 63% having significant airway involvement (Fig. 205-5).[8] The clinician should be particularly vigilant in assessing children with a history of recurrent episodes of laryngotracheitis or bronchiolitis that has been slow to settle. These children ought to be thoroughly assessed for an underlying source of airway obstruction that is being exacerbated by superimposed upper respiratory tract infection (Fig. 205-6).

Examination

An overall assessment of the degree of respiratory distress and airway compromise should be expedited in the acute situation and a full examination completed if the child's condition is stable (see Table 205-2). Observation of the child at rest in the parent's arms provides an initial assessment of the degree of respiratory distress, the characteristics of any stridor, and whether the child appears systemically unwell. It also allows time to gain the child's confidence before any further examination. A careful general examination is necessary to avoid missing subtle features of related syndromes or of other general pediatric disease. Syndromic features, if present, may suggest likely sources of airway obstruction associated with the particular syndrome, for example, micrognathia in Pierre Robin sequence, macroglossia in Beckwith-Wiedemann syndrome, or anterior glottic webs in velocardiofacial syndrome (Fig. 205-7).

Simple inspection of the child reveals valuable information regarding the work of breathing and degree of obstruction. Potential findings of increased respiratory work include suprasternal or sternal recession, subcostal indrawing, "see-saw" or paradoxical abdominal movement

Figure 205-5. Extensive cutaneous cervicofacial hemangioma in a "beard" distribution in an infant with transglottic, tracheal, and mediastinal hemangioma.

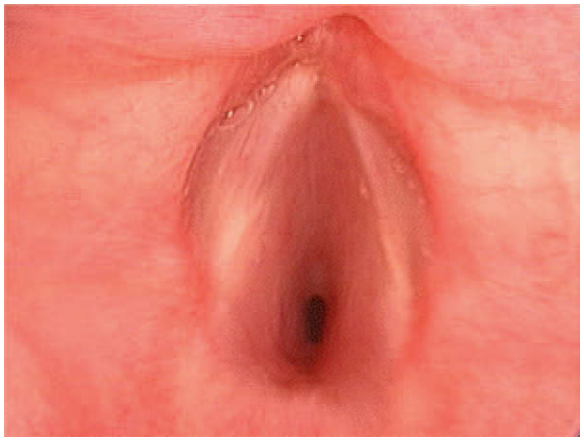

Figure 205-6. Severe congenital (grade III) subglottic stenosis presenting for rigid laryngobronchoscopy on a background of recurrent episodes of croup.

during respiration, nasal flaring, tracheal tug, anxiety, irritability, or evidence of fatigue. The amount of recession is a better indicator of the severity of airway compromise than the degree of stridor. Stridor can paradoxically become quieter and less apparent as the obstruction worsens due to the diminishing airflow and may be a sign of impending respiratory arrest. Pallor and subsequent cyanosis are late events in pediatric patients and no comfort should be taken from the fact that a child still appears pink. Children may position themselves to optimize their own airway as is classically described in epiglottitis, where children prefer to sit upright with their head in a "sniffing" position. Pectus excavatum may be seen in children with chronic airway obstruction due to negative intrathoracic pressure in their highly compliant rib cage.[2]

The observation chart should be checked for elevated temperatures, tachycardia, or tachypnea. Drooling may occur in epiglottitis, severe oropharyngeal inflammation, or deep neck space infection. Any cough or change in voice or cry should be noted. The clinician should listen carefully to the audible respiratory noise to differentiate between inspiratory stridor, biphasic stridor, expiratory stridor or wheeze, and stertor. This can be useful in determining the likely anatomic site of the pathology, although this is not absolute and is only useful as a guide.

Inspiratory stridor typically occurs due to obstruction at the level of the supraglottis or glottis. Obstruction arising in the bronchi or lower trachea classically produces an expiratory stridor or prolongation of the

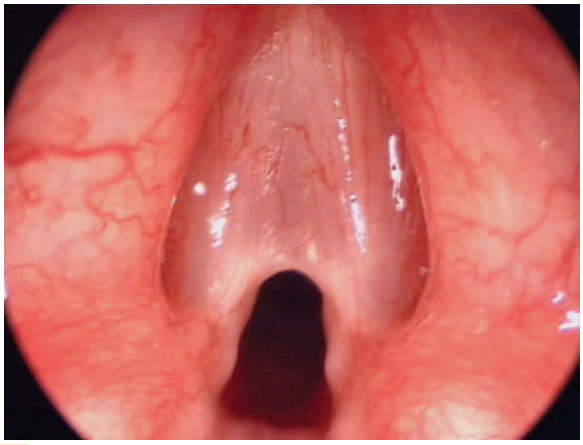

Figure 205-7. Anterior glottic web presenting with stridor in a child with velocardiofacial syndrome.

expiratory phase. Biphasic stridor can occur with obstruction anywhere in the laryngotracheobronchial tree but is classically associated with either upper tracheal or subglottic pathology where it is attributed to the fixed luminal diameter of the cricoid. The characteristic sound of stridor, even in a common condition such as laryngomalacia,[9] is so variable as to be of little diagnostic use in isolation. Laryngomalacia has been traditionally described as having stridor that is of a musical quality, while stridor in vocal cord palsy has a breathy quality, viral laryngotracheitis has a barking cough and tracheomalacia has a brassy cough. It is important to recognize that these descriptions are highly subjective and their assessment is not reliably reproducible.

Nasal patency is assessed via fogging of a mirror or metal tongue depressor. Nasal airflow may also be detected via a wisp of cotton wool or using the bell end of a stethoscope. This is particularly relevant if supralaryngeal obstruction is suspected. The clinician should also make a conscious assessment of jaw and tongue size. Stridor and recession vary as the child rests, cries, and sleeps. It can be useful to observe the child while the child feeds, particularly if poor feeding or aspiration has been reported. Auscultation may be used to aid in localizing the site of maximal obstruction but the transmission of sound through the thorax is variable, often making this technique difficult. Auscultation is useful to detect heart murmurs and wheeze.

The nose, throat, neck, and ears should also be examined. The oropharynx is examined to assess the size and appearance of tonsils and palate, and to check for oropharyngeal swelling or fullness. The neck is also inspected and palpated to identify swelling or masses. The usual caution should be used in examining a child with possible epiglottitis wherein sudden airway obstruction may be precipitated. In this situation, equipment for immediate intubation must be present if examination is to be attempted. It is also acceptable to make a provisional diagnosis of epiglottitis based on history and appearance of the child, with formal examination performed in the safety of the operating room under endoscopic control.

Nonendoscopic Investigations

Investigations should not be routinely conducted but judicious use may be helpful. Selection of investigations should be tailored to the clinical presentation on the basis of the history and examination findings and are not necessary in every patient.

O_2 Saturation Monitoring

O_2 saturation monitoring is noninvasive and readily accessible, although considerable airway obstruction may occur without desaturation, as long as the child is not tiring and continues to have the energy to overcome the obstruction. Care should be taken in administering supplemental oxygen because this can maintain O_2 saturations while masking raised levels of CO_2. Arterial blood gases are useful in this situation. From a clinical viewpoint, cyanosis occurs very late in pediatric respiratory distress.

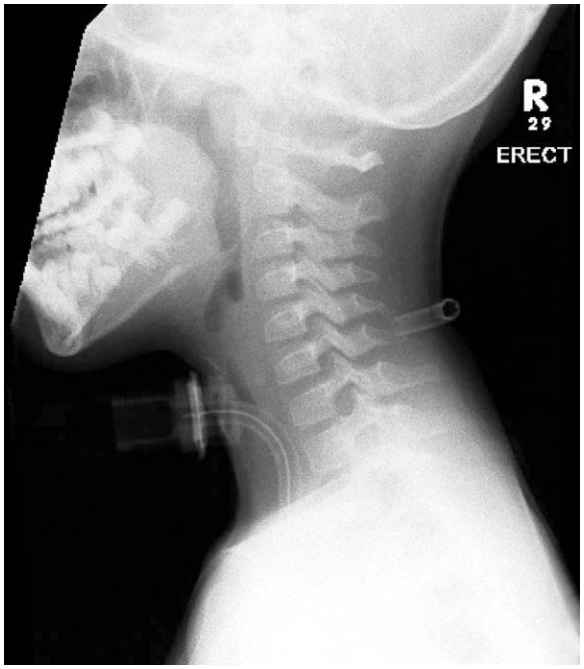

Figure 205-8. Lateral neck x-ray study with enhancement of the tracheal air column demonstrating a stenotic segment with obliteration of the airway for 7 mm craniocaudally from the glottic level.

Figure 205-9. Magnetic resonance imaging study of head and neck demonstrating cystic hygroma in the left cervical region with airway compression, tracheal displacement to the right, and mediastinal extension.

Radiology

Soft tissue lateral neck x-ray examination demonstrates the airway outline from the nasopharynx to the subglottis. Posterior-anterior chest x-ray study shows the lung fields and mediastinum. Persistent air trapping may be demonstrated on the side of a bronchial foreign body in inspiratory/expiratory views. A decubitus view may be useful in young children, where normally the dependent lung deflates.[10] A Cincinnati (high-kilovoltage filter) view enhances the tracheal air column while de-emphasizing bony cervical spine to demonstrate the major airways. These x-ray techniques may be useful as screening investigations (Fig. 205-8).[11,12] Careful consideration of the stability of the child's airway is mandatory and radiology should not be undertaken if there is any potential for acute airway deterioration. Policy for suspected epiglottitis differs between centers; however, the result of the x-ray study may not influence management[13] and may be associated with significant risk to the child. Further imaging should be performed according to the endoscopy findings.

Videofluoroscopy is an excellent way of demonstrating tracheomalacia and can be combined with a contrast swallow to exclude vascular compression,[14,15] tracheoesophageal fistula, or aspiration. It may demonstrate diaphragmatic immobility on the side of a foreign body airway obstruction. Bronchograms using safe nonionic contrast media are useful for outlining the luminal surface of the lower airway, demonstrating tracheobronchial stenosis and malacia. Opening pressures of the collapsed bronchi and lower trachea can also be measured to determine the level of airway support needed. Computed tomography (CT) and magnetic resonance imaging (MRI)[12,16,17] continue to lack sensitivity in assessing airway stenoses and cannot replace endoscopic assessment. They are useful in demonstrating vascular anomalies and extrinsic compression of the airway (Fig. 205-9). Virtual endoscopy uses radiologic data to create computer simulations that may be viewed as one would conventional endoscopy. Helical CT with multiplanar reconstruction provides three-dimensional images, which are used in real time to simulate endoscopy views. It is noninvasive and allows retrograde luminal airway views. Although it demonstrates some fixed airway stenoses, it is not helpful in detecting obstruction during dynamic movement as occurs in tracheomalacia or vocal cord palsy. There is also a lack of detail, with airway pathology such as glottic webs being poorly demonstrated.[18]

Other Investigations

Vocal cord ultrasound can be used, with experience, to demonstrate vocal cord palsy to complement the endoscopic findings.[19] The role of *laryngeal EMG* in the management of vocal cord immobility is yet to be fully defined.[20] Airway obstruction that worsens during sleep is usually a feature of pharyngeal obstruction, such as adenotonsillar obstruction or craniofacial anomaly. Laryngotracheal pathology at any level including laryngomalacia may, however, occasionally worsen during sleep, thus requiring *sleep study* investigation.[21] *Pediatric lung function tests* are seldom used because of compliance and cooperation issues. Flow volume loops[22] may help localize the site of obstruction and other tests such as peak flows or ventilation-perfusion scans may be used upon the advice of a pulmonologist. Gastroesophageal reflux[23-26] is not discussed in detail in this chapter but can be investigated via double probe pH studies, contrast studies, milk scan, or esophagoscopy with lower esophageal biopsy. Echocardiography detects congenital heart disease but does not demonstrate all abnormal vasculature, thus it cannot be used to exclude vascular anomalies.

Endoscopy

Pediatric airway endoscopy requires a full range of specialized pediatric endoscopy equipment and an experienced team. An inadequate evaluation needs to be repeated, and referral to an experienced center should be made as required to ensure a single comprehensive and definitive evaluation. A systematic approach provides a diagnosis in most cases.[27]

Flexible Endoscopy in the Office or Ward

The introduction of ultrathin endoscopes[28] in a range of diameters with good optics has allowed even neonates to undergo endoscopy without the need for a general anesthetic. This is usually considered a screening procedure, in that the view of the larynx may be suboptimal. Rigid endoscopy of the airway is superior in examining the airway for structural abnormalities. Flexible endoscopy is useful in assessing the dynamic airway for vocal cord movement or features of laryngomalacia. A systematic approach must be adopted, observing first the nasal cavity followed by the postnasal space, oropharynx, supraglottis, and glottis

during dynamic respiration and phonation. It is difficult to obtain good views of the subglottis. This is purely a diagnostic procedure, with no opportunity for therapeutic procedures, in contrast to a rigid laryngotracheobronchoscopy. Flexible endoscopy under sedation in an endoscopy suite is widely practiced by pediatricians and pulmonologists[29-31] and is used by otolaryngologists as an adjunct to rigid endoscopy.[32] Rigid endoscopy is helpful if the diagnosis remains unclear despite flexible endoscopy, if there is clinical suspicion of a second airway lesion, or if subglottic/tracheal or bronchial pathology is suspected.

Laryngotracheobronchoscopy

Laryngotracheobronchoscopy[33] is the gold standard in the evaluation of the stridulous child. It enables a thorough assessment to be performed while the airway is maintained and allows findings to be visually recorded for future reference. The airway may be formally sized to grade any narrowing. It also may incorporate therapeutic procedures, including foreign body removal or the endoscopic management of airway pathology. It requires an experienced team skilled in airway assessment, including the surgeon, anesthetist, and nursing assistant, who work closely to ensure an optimal and safe examination. The use of a video is essential to facilitate training and allows the anesthetist and nurse to follow the procedure and status of the airway on the monitor.

It is vital that accurate records are kept in a standardized form within a department.[34] Digital prints provide a valid record of static conditions while video clips record dynamic findings. Digital images and video recordings should be saved and archived. This provides an invaluable source of information for sequential clinical comparisons, teaching, and medicolegal purposes.

Anesthetic Considerations

This procedure requires a cooperative approach to airway management with both the anesthetic team and surgeon sharing the control of the airway. The use of atropine premedication provides a dry surgical field and improves the efficacy of topical anesthesia. It is most effective via intramuscular injection. Anesthesia is often induced using slow masked inhalational anaesthesia. Halothane is a volatile agent that has been traditionally used and is nonirritating to the airway, allowing for smooth maintenance of anesthesia during instrumentation of the airway. Halothane is now difficult to obtain and other inhalational agents such as isoflurane, sevoflurane, and intravenous agents are being used. Sevoflurane[35] is also nonirritating, rapid in onset, and allows rapid delivery of high concentrations. Topical lidocaine is applied to the airway to minimize airway stimulation during the procedure and helps avoid laryngospasm. Lidocaine dose needs to be carefully measured to avoid overdosage.[36,37]

Anesthetic practice varies between centers but most units use spontaneous respiration for pediatric patients rather than paralysis and jet ventilation simulating normal respiration. Jet ventilation prevents coughing or gagging[38-40] but requires pressures above physiologic levels[38,41] with an associated risk of pneumothorax in neonates and smaller children. Dynamic conditions such as malacia and cord palsy cannot be identified. Apneic endoscopy is also possible after initial hyperventilation with 100% oxygen, although progressive hypoxemia and hypercarbia limit the operating time and condition of the patient.[42]

After induction, the child is ventilated down to a level of anesthesia that allows the rigid endoscope to be passed without gagging but maintains spontaneous respiration. The child may be intubated before the endoscopy or alternatively the airway may be controlled via a mask. Ideally the endoscopist has a view of an airway that is not altered by the passage of an endotracheal tube and, if the child is intubated, the tube is withdrawn during the procedure. A transnasal endotracheal tube may be positioned with the tip in the hypopharynx to optimize delivery of anesthetic gases and oxygen without obstructing the view of the airway. Airway control can be regained at any stage via intubation or through the use of a bronchoscope.

A laryngeal mask[43] may be useful for fiberoptic bronchoscopy particularly if the patient is difficult to intubate due to mandibular hypoplasia.

Figure 205-10. Rigid laryngobronchoscopy using a zero degree telescope demonstrating optimal positioning of the child and operating room set-up to allow accurate airway assessment.

Operative Technique

A suspension laryngoscope and microscope are traditionally used to examine the larynx, with a ventilating bronchoscope to examine the tracheobronchial tree (Fig. 205-10). Rigid telescopes provide excellent images and many centers now perform the assessment using a telescope, with digital images recorded at each anatomic level. High-quality images may be captured via the use of a wide Storz photographic telescope. A 4-mm rigid telescope should provide adequate images for data records, provided there is careful focusing and appropriate camera settings to ensure optimal captured images. For routine examination, the telescope and camera can be held in the left hand with a probe used in the right while the laryngoscope is in suspension. The microscope is used if there is to be manipulation of the airway requiring both hands of the operating surgeon. Differing techniques are adopted, according to individual departmental preferences. The procedure may be combined with rigid esophagoscopy, according to departmental protocols.

Preparation and Positioning

It is essential to anticipate equipment requirements so all equipment can be checked and prepared before commencement. A range of Hopkins rod telescopes should be available, which includes all lengths and diameters that may be required, so the endoscopist is fully prepared for all eventualities. Charts that predict age-appropriate sizes of bronchoscopes should be consulted and be readily available in the operating room.[44] The appropriate bronchoscope needs to be checked and assembled and at least one size smaller must be on hand. A 30-degree telescope may be used to enable assessment of the supraglottis without splinting. It may also assist assessment of an anteriorly placed larynx. A microscope should be available with the 400-mm lens to be used with standard laryngeal instruments. A 350-mm lens may be useful in small neonates by "bringing the patient closer" to allow easier manipulation of larynx.

A small sandbag is placed under the shoulders, with supporting lateral sandbags placed for children with long thin heads, as is typically seen in ex-premature neonates. A Mayo table supports the laryngostat clear of the chest.

Microlaryngoscopy Technique

A suspension straight-blade laryngoscope is gently inserted while assessing the overall appearance of the laryngopharynx, taking care to protect the teeth, lips, and oral mucosa while keeping the tongue midline to provide a well-centered view. The laryngoscope is placed in the vallecula and the epiglottis is carefully lifted forward. An overall assessment of the larynx can be made while an endotracheal tube is in situ and while providing a degree of stability, particularly in a compromised pediatric airway. Removal of the endotracheal tube allows a superior view and a probe may be used to independently palpate the arytenoids

Figure 205-11. Ventilating bronchoscope.

to assess the mobility of the cricoarytenoid joints and any limitation in joint movement. Absence of independent arytenoid movement on palpation is indicative of interarytenoid scarring. A posterior laryngeal cleft should be excluded by passing the probe between the arytenoids to allow comparison of the inferior limit of the interarytenoid groove with the posterior commissure. The subglottis should also be inspected from above. Topical decongestion and vasoconstriction of the airway may be helpful, particularly in the presence of low-grade inflammation or edema. Any airway narrowing should be formally sized. The largest endotracheal tube that permits a leak at less than 30 cm H_2O of pressure provides a measure of the airway diameter. Subglottic stenosis may then be graded using the Cotton-Myer grading system,[45] thus allowing reproducible assessment of the stenosis and aiding in treatment selection. If there is airway compromise or instability, assessment time may be limited. It is thus essential to be prepared to move ahead with bronchoscopy at any stage.

Bronchoscopy Technique

Traditionally, a ventilating bronchoscope (Fig. 205-11) has been used to assess the distal airway, which provides a means of actively ventilating the patient during the procedure, if required. An age-appropriate sized bronchoscope is used unless stenosis is suspected. A smaller-diameter rigid Hopkins rod telescope can be used as an alternative to examine the airway in a spontaneously breathing child, particularly if there is significant subglottic stenosis. The rigid telescope may reduce local airway trauma and lessen airway splinting, while allowing the distal airway to be visualized.

An anesthetic laryngoscope is placed in the vallecula while passing the bevel of the bronchoscope through the vocal cords under vision or via the monitor. The subglottis, trachea, carina, and main bronchi are systematically examined and findings recorded via digital images and/or videos. Evidence of tracheomalacia should be sought in the absence of positive airway pressure to avoid splinting of the airway and using a small bronchoscope withdrawn from the area being assessed. The ratio of cartilage to trachealis is significant in recording the type of malacia. The presence of complete tracheal rings is of importance when considering slide tracheoplasty for the treatment of long segment tracheal stenosis.[46] Extrinsic compression and prominent transmitted pulsation may be evident where there is an underlying vascular anomaly, which can be confirmed with imaging.

Dynamic Airway Assessment

A dynamic assessment of the larynx may be performed as the child lightens and is observed while the child recovers from the anesthesia. Dynamic views can be achieved by withdrawing the bronchoscope so that it is positioned just posterior to the tip of the epiglottis. This allows a good view of the vocal cords to exclude vocal cord immobility. It is useful if the anesthetist calls the phase of respiration, thus allowing the endoscopist to check for paradoxical cord movement. The arytenoids and adjacent mucosa can also be visualized to check for evidence of laryngomalacia. Anterior collapse of the epiglottis may be masked, however. A 30- or 70-degree telescope may offer improved views for dynamic assessment.

An excellent technique for dynamic assessment of vocal cord movement utilizes a laryngeal mask with a fiberoptic bronchoscope passed through to visualize the airway. The flexible endoscope is positioned just proximal to the laryngeal inlet to observe airway dynamics.[47]

Complications

Complications are unusual in rigid laryngobronchoscopy with a reported overall complication rate of 1.9%.[48] Possible complications include oral injury, subglottic injury, pneumothorax, cardiac complications, loss of control of the airway, and bleeding. Blood in the airway impairs oxygenation and ventilation, rather than giving rise to difficulties due to volume of blood loss.[42] Risks associated with procedural complication include cardiac anomalies, airway foreign body, tracheal stenosis, and biopsy or abscess drainage,[48] and particular care should be taken in these cases.

Postoperative Care and Planning

Airway obstruction may increase following the procedure due to underlying pathology, edema, blood, secretions, or postintubation croup. Edema is usually maximal within 4 hours and settles by 24 hours. Humidified oxygen by mask is initially tried. Nebulized epinephrine (1:1000) may be tried but the child must be kept under observation and reviewed within an hour for recurrence due to its limited duration of action.[42] The patient may be given intraoperative dexamethasone if there is a potential for edema from instrumentation of the airway. Steroids may be continued in the postoperative period depending on the endoscopy findings and underlying airway pathology. The patient must be recovered by nursing staff experienced in the care of pediatric airways and remain as an inpatient for close observation until the airway is adequately stable for discharge.

The operative record should clearly record the endoscopy findings, ideally with a photographic record of the findings. Using the endoscopic assessment, a plan of management can then be decided upon and discussed with the parents postoperatively.

Treatment of Acute Airway Obstruction

Medical Treatment

The child who arrives in the emergency department with acute airway obstruction should undergo rapid evaluation. Assessment, history, and active resuscitation should proceed while measures are taken to stabilize the airway. The physician should determine the degree of airway obstruction by observing the child for recession and work of respiration while taking a brief history from the accompanying adult. Details will be obtained regarding the length of history, recent systemic illness, and possibility of foreign body inhalation. The nursing staff should check the oxygen saturation and set up humidified oxygen. Another team member should contact the operating room and anesthesiologist to advise that the child may require intubation. The otolaryngologist may also be contacted and asked to attend the intubation,[49] depending on the unit's protocol. This situation clearly benefits from careful planning, with most units having a protocol for how to deal with the stridulous child.

Supplemental oxygen reduces the ventilatory requirement to maintain adequate oxygen saturation in cases of airway obstruction with normal alveolar function. The potential for CO_2 retention should be kept in mind. Heliox (helium-oxygen gas mixture) may be used to relieve respiratory distress, decrease the work of breathing, and improve gas exchange.[50] It does this due to its low density, which results in a lower resistance to gas flow.[51,52] It has no direct effect on the underlying pathology and thus must be viewed only as a "therapeutic bridge," allowing time for definitive treatment to be commenced.[50] Steroids and nebulized epinephrine may also be used to help optimize the airway in the acute situation.

Laryngotracheitis (viral croup) can be treated with intravenous, oral, or nebulized steroids. There is no objective evidence that raising the humidity of the inspired air is beneficial.[53] Nebulized budesonide[54] is used in the home environment for children with recurrent croup. Corticosteroids are beneficial and are routinely recommended for the treatment of croup.[55] Klassen[56] recommends that children with croup symptoms and increased work of breathing should be treated with either nebulized budesonide (2 mg) or oral/intramuscular dexamethasone (0.15 to 0.6 mg/kg). Oral dexamethasone is easily administered, widely available, and low in cost. L-epinephrine (5 mL of 1 : 1000) or racemic epinephrine (0.5 mL) should be considered if there is moderate or severe distress because it has been found to give clinical improvement and reduce the need for intubation.[57]

Other infective causes of airway obstruction respond promptly to antibiotic therapy. This includes bacterial tracheitis or epiglottitis, which is rare, although vaccine failure[58,59] has been documented. Appropriate intravenous antibiotic therapy should be commenced while the airway is stabilized via short-term intubation if required.

Therapeutic Intubation

Intubation is increasingly used as an alternative to tracheotomy in acute airway obstruction. Pediatric tracheotomy is avoided if possible due to the potential for morbidity, even with short-term usage. Intubation may not be possible, for example, in severe subglottic stenosis, impacted foreign bodies, or advanced epiglottitis. As this situation may be unexpectedly encountered even by skilled, experienced pediatric anesthesiologists, most hospitals require an otolaryngologist to be informed if a child with airway obstruction is to be intubated. It may be necessary to have an emergency tracheotomy set open with the correct size tube already selected.

The child is "gassed down" slowly and the larynx is inspected to exclude epiglottitis. The child may then be manageable on a nasal pharyngeal airway with continuous positive airway pressure (CPAP). If intubation is required, it is important to minimize any damage to the inflamed subglottic mucosa. This is achieved by gentle intubation with a small, soft tube that is adequate for ventilation and suction of secretions. A nasotracheal tube is preferable to an oral intubation to help minimize tube movement. The secure nasotracheal tube ought to be placed and assessed by suctioning the secretions and testing for a leak. Any persisting element of airway obstruction or tenacious secretions should be further investigated by passing a ventilating bronchoscope. This helps exclude bacterial tracheitis[60,61] or a foreign body. Endoscopic suctioning and clearance of debris from the airway may be performed and is particularly beneficial in bacterial tracheitis. Significant tracheobronchomalacia may also give persisting obstruction after intubation and will usually respond to CPAP.

Emergency Tracheotomy

Emergency tracheotomy is a rare occurrence in departments with experienced pediatric anesthesiologists.[49,62] Otolaryngologists are often asked to attend a potentially difficult intubation but are rarely needed. If emergent tracheotomy is required, however, the surgical set and appropriate tube must be immediately available. The neonate needs to be in a straight supine position with the neck extended over a roll. A long, vertical, strictly midline incision is made through skin and down to the trachea, guided by palpation of the trachea. The main danger lies in drifting off the midline and a finger on either side of the larynx is helpful. If a pediatric tracheotomy tube is not available, a pediatric endotracheal tube can be used, ensuring it remains above the carina.

Endoscopic Removal of Foreign Bodies

Foreign body removal has been greatly facilitated by the introduction of foreign body optical extraction forceps that have a central channel for an extra-long Hopkins rod telescope. Different forceps are available for the removal of various types of foreign bodies. The foreign body and adjacent airway can be carefully examined while the removal is planned using a fine suction catheter in the bronchoscope alongside the rigid telescope. The use of topical adrenaline before any attempt at removal optimizes local conditions by vasoconstricting the mucosa and reducing bleeding.[63]

Table 205-3

Management Options for the Difficult to Extubate Neonate

Treat reflux
Leave tube in place for at least 1 week between trials of extubation
Steroids to cover extubation
Nasal prong ± CPAP postextubation to support airway
Endoscopic optimization of airway—removal of small granulations, cysts
Cricoid split
Single-stage laryngeal reconstruction
Tracheotomy ± stent to maintain airway

Approach to Postextubation Stridor

Extubation should not be attempted until the child has an optimal chance of success. Failed extubation requiring subsequent reintubation predisposes to further deterioration of the airway with additional edema, ulceration, and perichondritis. There should be no active respiratory infection, minimal pressure support, and a normal oxygen requirement at the time of extubation. Reflux should be adequately treated and steroids commenced if indicated. Extubation should proceed once sedation has worn off and the child is awake to maximize the likelihood of success. If postextubation stridor and obstruction occur, the airway can be further optimized with nebulized epinephrine,[64] intravenous dexamethasone[65] before and after extubation, and continuous positive airway pressure via nasal cannula. Therapeutic reintubation for laryngeal rest has been demonstrated to be beneficial,[66-68] allowing any reversible component of the airway inflammation to settle.

If extubation fails, despite appropriate medical measures and laryngeal rest, endoscopic procedures are being increasingly used to optimize the airway (Table 205-3). Alternatively, a cricoid split may be performed. Single-stage laryngotracheal reconstruction can be used in patients who fail cricoid split or who have a mature stenosis. Tracheotomy is reserved for those who are not suitable for an alternative approach. These surgical options are discussed later.

Expected Airway Obstruction in the Postpartum Neonate

Antenatal diagnosis of airway obstruction enables a definitive plan of management to be formulated before delivery. Routine prenatal ultrasonography may diagnose large masses, including cervical teratoma,[69,70] cystic hygroma,[71] or rhabdomyosarcoma[72] with associated airway obstruction. Further details of the anatomy can then be defined using MRI.[73,74] Airway obstruction may be detected on ultrasound, even in the absence of a mass. Antenatally diagnosed congenital high airway obstruction syndrome (CHAOS) exhibits features including tracheal dilation and lung hypertrophy, as seen in laryngeal atresia.[75] Polyhydramnios may also occur if an obstructing lesion is compressing the esophagus and impairing fetal swallowing.[76] Other ultrasound features may include diaphragmatic eversion, ascites, and ultimately fetal hydrops.[77] Holinger and others first described the successful airway management of an antenatally diagnosed cervical teratoma in 1985.[70] The technique of securing the neonatal airway while the uteroplacental blood flow was maintained was subsequently described in the early 1990s.[73,78] This procedure has become known as the ex utero intrapartum treatment (EXIT)[79,80] or OOPS (operation on placental support)[71] and should be considered when perinatal airway obstruction is anticipated. The multidisciplinary team usually includes pediatricians, obstetricians, anesthetists, and ENT surgeons. Other specialties may be involved, depending on the underlying pathology. At planned cesarean section, adequate uteroplacental flow is maintained while the airway is established. The placenta allows continued gas exchange while the airway is stabilized. Direct laryngoscopy and intubation is then

Figure 205-12. Computed tomography scan (axial view) demonstrating bilateral choanal atresia.

performed. Rigid laryngobronchoscopy may be used to define the anatomy and possibly place a guidewire for intubation guidance if there is marked distortion or poor visualization of the airway. If intubation is not possible, the trachea is exposed and a tracheotomy performed. The surgeon should be mindful that a large neck mass will hyperextend the neck and anteriorly displace the trachea. This may mean that the tracheotomy is placed more distally than planned. Once the airway is secured the umbilical cord is clamped and the delivery is completed.[76] Extracorporeal membranous oxygenation can be used particularly in the presence of severe congenital cardiac disease.[81] Resection of an obstructing mass is usually delayed until the child's condition is stabilized.[81]

Unexpected Airway Obstruction in the Postpartum Neonate

Airway obstruction may not always be antenatally diagnosed. The delivery team may be presented with a neonate with unexpected airway obstruction. An anatomic approach to the differential diagnoses and management of these infants is helpful.

Supralaryngeal

Nasal or nasopharyngeal obstruction can be highly significant in the newborn who is an obligate nasal breather. Nasal suction removes secretions and allows assessment of the patency of the nasal airway. Choanal atresia is the most common diagnosis in complete nasal obstruction and can be investigated via CT scan (Fig. 205-12). It may be difficult to pass a nasal suction catheter in a neonate with prominent turbinates or, less commonly, piriform aperture stenosis, midnasal stenosis, or choanal stenosis. Nasopharyngeal masses such as teratomas may also obstruct the airway. Nasal or nasopharyngeal airway obstruction is relieved by an oral airway. Oropharyngeal sources of obstruction (such as micrognathia with a retroposed tongue) may also be improved by positioning and oral airway placement.

Laryngeal

Laryngeal obstruction shows no improvement with an oral airway but is relieved by intubation. Airway obstruction associated with severe laryngomalacia, vocal cord palsy, laryngeal cysts, or polyps will improve with intubation. A small-shouldered tube may be temporarily positioned through a laryngeal stenosis to secure the airway. Some units now advocate using a laryngeal mask for neonatal resuscitation[82] to avoid exacerbation of the stenosis by attempts at intubation. It may be possible to ventilate a neonate with laryngeal atresia and a low tracheoesophageal fistula although this is rare. In these cases, there will be none of the characteristic findings of congenital upper airway obstruction on antenatal ultrasound. On closer examination in this instance, the tube is found in the esophagus with ventilation occurring via the fistula.[83]

If intubation is not possible and there is inadequate ventilation via a laryngeal mask or very fine endotracheal tube, the trachea must be opened to ventilate the neonate. In the emergency situation, needle puncture of the cricothyroid membrane or trachea is possible but not easy, while emergency open tracheotomy is also difficult unless the surgeon has current experience of neonatal tracheotomy. It may be difficult to palpate the laryngeal cartilage in a neonate. It is of greater importance to remain in the midline when locating the airway, rather than focusing on the level of entry. The principles of emergency tracheotomy are discussed earlier. In tracheal puncture, the first and second fingers of the left hand are placed either side of the trachea and the needle inserted vertically, strictly in the midline until air can be aspirated. Larger needles can be inserted above or below the first if necessary. A tracheotomy will bypass laryngeal lesions such as congenital webs or subglottic stenosis.

Tracheobronchial

Obstruction due to distal tracheal or bronchial pathology, including tracheobronchomalacia, may not improve with either intubation or tracheotomy. Positive pressure will aid in splinting the airway and improve malacia. It is less helpful for distal airway stenosis. Use of an extended (long) tracheotomy tube will physically support tracheomalacia but will not assist in carinal malacia or bronchomalacia. A tapering long-segment tracheal stenosis presents a difficult clinical situation, because it is often possible to insert only a very small tracheotomy tube. In addition the tracheotomy severely limits the therapeutic options for surgical reconstruction of the stenosis. The patient with a long-segment tracheal stenosis requires referral for consideration of slide tracheoplasty, which is recognized as the best treatment for this condition in the current era.[46]

Treatment of Chronic Airway Obstruction

The evaluation of a child with chronic airway obstruction is not dissimilar to the acute situation; however, one has the luxury of time to perform a thorough clinical assessment and systematic investigations as required. The management options are more complex as the emphasis shifts from acute resuscitation and relieving the obstruction to addressing the underlying condition and preventing complications. The choice of treatment is influenced by the severity of the symptoms and signs, coexisting morbidity, the patient's social situation, surgeon's preference, availability of equipment, and other pediatric services, particularly intensive care.

Conservative options include watchful waiting and the use of medical treatments to address general and specific conditions. Tracheotomy may be chosen to "buy time" until the child grows and the condition resolves, or in some situations it may be definitive. Other surgical treatments include a vast spectrum of endoscopic techniques available to open laryngeal framework surgery.

Medical Management

There are several conditions presenting with chronic airway compromise that may be managed expectantly with regular clinical review and supportive therapy only (e.g., mild to moderate laryngomalacia, unilateral vocal cord palsy, grade I subglottic stenosis). The input of allied health departments such as speech and language therapy and dietetics is beneficial with regard to concurrent feeding, swallowing, and aspiration issues. Respiratory review to manage underlying lung disease and the consideration of CPAP may be appropriate in some situations. The use of a nasopharyngeal airway to bypass supralaryngeal airway obstruction is highly effective and relatively noninvasive.[84] It may be used to avoid surgery in certain cases of midface hypoplasia, neuromuscular disorders, glossoptosis, and micrognathia/retrognathia. It is also a valuable postoperative adjunct following adenotonsillectomy in the child with severe obstructive sleep apnea.

Gastroesophageal reflux is thought to aggravate airway conditions and possibly contribute to apnea, recurrent upper respiratory tract infections, laryngomalacia, and subglottic stenosis, although consistent

Table 205-4

Indications for Pediatric Tracheotomy

- Upper airway obstruction
  - Anatomic, e.g., craniofacial abnormality, laryngeal pathology
  - Functional, e.g., vocal cord palsy
- Prolonged ventilatory support
- Neurologic dysfunction
- Facilitation of major head and neck surgery
- Management of secretions

evidence to support the hypothesis is limited.[85,86] Adjuvant antireflux treatment is generally well tolerated and effective in the pediatric population. Its use, although empirical at times, may improve airway symptoms, circumvent the need for surgery, and enhance surgical outcomes.

Systemic steroids are often used intermittently to treat acute deterioration in the setting of chronic airway obstruction. Long-term doses require careful monitoring for side effects but have been successfully used as an adjuvant treatment for conditions such as subglottic hemangioma in many series.[87-89] Airway edema from croup responds well to steroids and some children with this condition benefit from having dexamethasone available for recurrent attacks at home.[57]

Antibiotics are useful to treat acute infective exacerbations in the setting of chronic airway obstruction. The prophylactic use of antibiotics is also recommended in the setting of open laryngeal surgery to reduce the chance of postoperative wound infection from direct exposure to the respiratory tract.

Tracheotomy

The indications for insertion of a pediatric tracheotomy have changed over the past decades.[90] Tracheotomy is more commonly requested to bypass chronic airway obstruction from craniofacial or upper airway abnormalities, or to support prolonged ventilation than for acute infective conditions such as laryngotracheobronchitis and epiglottitis (Table 205-4). Tracheotomy may be a temporary treatment while waiting for the child to outgrow the underlying condition (e.g., subglottic hemangioma or severe laryngomalacia), or until the child is old enough to undergo other definitive procedures. Its insertion may be permanent but is generally not undertaken without consideration of care requirements and the potential morbidity associated with it. The overall complication rate is up to 44% and tracheotomy-related death as high as 3.6% in some series.[91,92]

Techniques to avoid tracheotomy include the use of maximal medical treatments to reduce edema and inflammation while surgical alternatives are directed toward addressing the site of obstruction and minimizing resistance to airflow. For example, in developing subglottic stenosis, the options of laryngeal rest,[67] cricoid split,[93-95] endoscopic balloon dilatation with mitomycin C,[96] and single-stage laryngotracheal reconstruction[97,98] may avoid the need for tracheotomy. A case of early subglottic stenosis and its response to balloon dilatation is shown in Figs. 205-13 and 205-14.

Once the decision has been made to proceed with a pediatric tracheotomy, a comprehensive discussion should take place with the primary care clinicians before surgery. Informed consent encompasses not only details of the operative procedure and possible complications, but also a full brief on the long-term implications of caring for a child with a tracheotomy, preferably meeting another family of a child with a tracheotomy. The family circumstances need to be assessed, home suctioning equipment arranged, basic life support training given, and other support offered if needed.

Surgical Procedure

The operation is usually conducted under general anesthesia with the child intubated or a laryngeal mask in place. The position is supine with a small shoulder roll to provide slight neck extension. An adhesive tape under the chin retracts any dewlap and anchors the head (Fig. 205-15). Skin marking of the cricoid and sternal notch is useful although may be difficult to palpate in a small infant. Either a horizontal or short vertical skin incision can be used. In children, removal of a subcutaneous fat plug is helpful and the thyroid isthmus can be simply divided using bipolar diathermy. It is crucial to stay midline in a pediatric tracheotomy and one should frequently pause to check the dissection plane. A vertical incision is made through the third and fourth tracheal rings without removal of cartilage and nonabsorbable stay sutures placed on either side of the incision (Fig. 205-16). These sutures assist in replacement of a tube ,which is dislodged before the tract is established. The sutures are removed with the first tube change at 1 week. If a future laryngotracheal reconstruction (LTR) or open laryngeal cleft repair is planned, the tracheal opening may be placed lower, being mindful of the innominate (brachiocephalic) vessels and lung apices. Occasionally, a high innominate vein needs to be protected from the tracheotomy tube by a small inferiorly based flap instead of the vertical incision. Vicryl maturation sutures from the tracheal opening to the skin reduce the chance of false passage creation and assist in establishment of the stomal tract. They have not been shown to increase the rate of tracheocutaeous fistula.[99,100]

Local policy will dictate tracheotomy tube type but beware inserting one that is too long, particularly in neonates, for whom special short tubes are available. Consideration of the underlying condition, patient anatomy, and frequency for tube change influences the choice of tracheotomy tube.[101] An extended length tube may be required if the neck and chest wall are bulky, or length may be required internally to

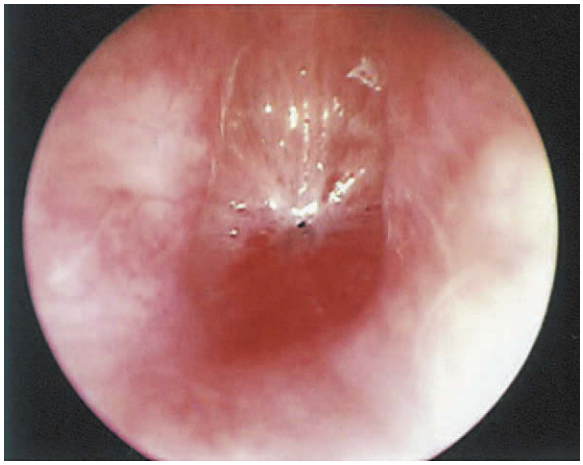

Figure 205-13. Balloon dilatation of early subglottic stenosis—before dilatation.

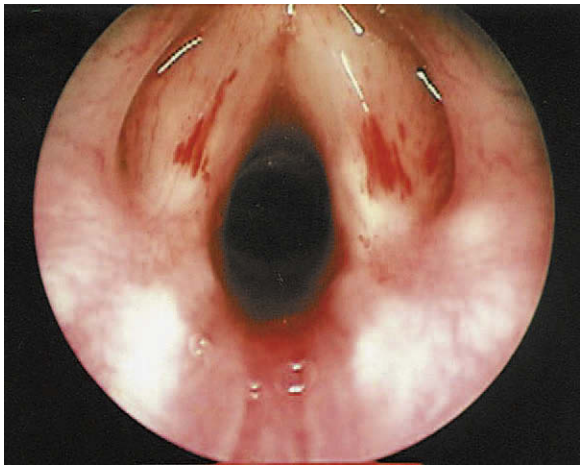

Figure 205-14. Balloon dilatation of early subglottic stenosis—after dilatation.

Figure 205-15. Ideal positioning for pediatric airway surgery using shoulder roll, head ring, and chin strap to stabilize the head.

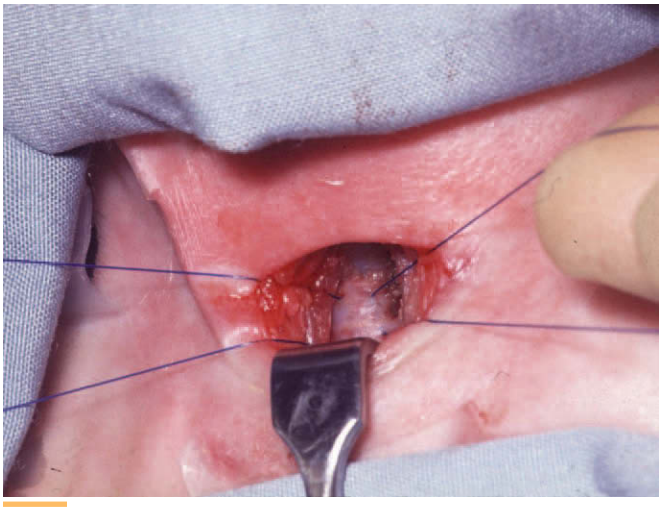

Figure 205-16. Nonabsorbable stay sutures placed on either side of the tracheotomy opening as a safety measure to assist in replacement of a dislodged tube.

support tracheomalacia or a tracheal stenosis. Cuffed tracheotomy tubes are placed infrequently in the pediatric population except to protect the airway in the presence of aspiration. The use of a cuffed tube is usually unnecessary and avoided if possible in that the pediatric airway is particularly sensitive to ischemic insult and prone to ulceration, granulation, and ultimately stenosis.[102] Lateral skin sutures to close the tracheotomy neck wound should not be applied tightly because this predisposes to surgical emphysema.

The percutaneous technique of tracheotomy is not suitable for children because the landmarks may be hard to distinguish, the trachea is soft, pliable, and mobile, the lumen is small, and one may easily drift from the midline.

Tracheotomy Complications

Early complications such as accidental tube dislodgment may be a life-threatening emergency in a small child. This can be prevented by adjusting the tapes carefully to only allow one fingerbreadth between the skin and the tapes, and by providing stay sutures through the trachea on either side of the incision (see Fig. 205-16). These sutures are pulled apart in the event of tube dislodgment to open the incision, bring the trachea to the surface, and guide tube reinsertion into the tracheal lumen. Conventional adult tracheal dilators are usually too large, but a small, curved artery clamp may help. The technique of using a cut suction catheter through the lumen of an appropriate sized tracheotomy tube to guide its insertion has the advantage of confirming tracheal position by successful suctioning of secretions and the opportunity for jet ventilation to maintain oxygenation if required.[103] An emergency box should always be at the child's bedside containing two spare tracheotomy tubes (one a size smaller), suction catheters, lubricant, scissors, and spare tapes. Tube blockage is avoided by humidification, frequent suctioning, and an awareness of the problem.

Postoperatively, a chest x-ray study is imperative to check the tube length and exclude a rare pneumothorax, which can occur from puncturing the lung apex or from positive-pressure ventilation. Hemorrhage is rarely a complication in children if the thyroid isthmus has been divided with electrocautery rather than ligated after division between clamps. Subcutaneous emphysema may be prevented by having a snug fit of the tube in the trachea and avoiding tight wound closure and excessively high-pressure ventilation. Tube dislodgment and blockage remain the most important late complications and are responsible for tracheotomy-related mortality. Stomal and tracheal granulations are the result of physical factors such as movement and plasticizers in the tube, combined with infective factors from the skin and airway. The use of antibiotic ointment around the tube may improve but never remove the granulations. Longstanding suprastomal granulations within the tracheal lumen are associated with the development of suprastomal collapse, which is commonly responsible for difficult decannulation that requires further surgery. Tracheal erosion may occur because of a poor-fitting tracheotomy tube, particularly if metal. Erosion can involve the mediastinum, esophagus, or major vessel. An acquired tracheoesophageal fistula requires closure with an open operation and interposition of muscle. Small bleeds around or from the tracheotomy tube may herald the dramatic erosion of a major vessel.[104] Although suprastomal and tracheal granulations can give rise to small hemorrhages, any tracheotomy bleeding should be taken seriously and investigated radiologically or endoscopically. In very longstanding tracheotomy, the tube may migrate and require surgical repositioning.

Tracheotomy Decannulation

Adults and children with a short-duration tracheotomy (less than 1 month) can be decannulated after appropriate assessment by simply having the tube removed and the stoma covered with an occlusive dressing.[105] Most children, however, are more difficult to decannulate because of multiple factors including suprastomal collapse and granulation, the relatively small size of the airway, and, possibly, psychological dependence or attachment to their tracheotomy tube. A more controlled process for decannulation is used in these children. A recent formal endoscopic examination of the airway, ideally within 1 month, is required before any attempt is made to try decannulation.[106] The most common causes of failed decannulation are significant suprastomal collapse and granulation, and this should be addressed at the time of surgery.

The child is admitted to hospital for a supervised trial of "ward decannulation." The tracheotomy tube is downsized in a stepwise manner, usually one to two sizes smaller each day until the smallest tube has been tolerated. The tracheotomy tube is then blocked for 24 hours and the child is kept on the ward for careful observation at night. If the trial of capping is uneventful, the tube is completely removed and the stoma covered with an occlusive dressing. A further 48-hour period of observation is recommended in that failure may occur at any stage. In the case of failed decannulation, the smallest tube is simply reinserted in the stoma and gradually upsized. Time may be required to allow the airway to grow; however, a repeat endoscopy should be performed before any further trials of decannulation to exclude concurrent pathology such as cord fixation or palsy, suprastomal granuloma or collapse, and tracheomalacia.[107]

Surgical Decannulation

If significant suprastomal collapse is identified that is not responsive to endoscopic measures, a "surgical decannulation" will be required. In principle, the stoma is formally closed, sometimes with additional support from a cartilage graft and period of intubation. At the begin-

ning of the operation, the child is intubated nasally with an age-appropriate tube. The tracheocutaneous fistula is excised, preserving the tracheal wall, unless a cartilage graft is required. If cartilage is not required (mild to moderate collapse only), the stoma is closed primarily and sutures are taken laterally to the sternomastoid to prevent collapse of the repair. If cartilage is required, it is harvested from a rib and carved to a boat shape as for laryngotracheal reconstruction (see open surgical techniques section). The malacic wall is excised until firmer cartilage is exposed. The cartilage graft is sutured to strengthen the anterior tracheal wall with minimal or no air leak. If the trachea is very malacic, an oversize graft can be supported on the sternomastoids, lifting the graft and anterior tracheal wall forward. Postoperatively, the patient remains nasally intubated for 5 to 7 days with the endotracheal tube acting as a stent for the reconstruction.

Endoscopic Treatment of the Larynx and Tracheobronchial Tree

The microsurgical techniques and equipment that are needed in pediatric laryngology are much closer to those of adult phonosurgery than general adult laryngology. Skill, patience and special instrumentation are required. Any damage to the delicate vocal fold may produce lifelong dysphonia that could prove difficult to correct. Optimal anesthetic conditions with the child breathing spontaneously without laryngeal intubation are crucial in this setting. Endoscopic treatment provides the opportunity for therapeutic intervention at the time of a diagnostic procedure, thus avoiding further general anesthesia and open surgery. Many techniques are minimally invasive with reduced trauma and risk to adjacent tissues than in open techniques. The opportunity for photo and video documentation is also extremely useful. Pledgets soaked in 1:10,000 adrenaline (epinephrine) help prepare the operative site before any procedure. Suspension laryngoscopy allows two-handed surgery; however, some may prefer the magnification, distal access, and range of movement afforded by newer generation telescopes and cameras. The surgeon's armamentarium includes the use of "cold steel" microinstrumentation, lasers (CO_2, KTP, thulium), balloons, microdébriders, indwelling stents, grafts, and sutures. Topical medical treatments such as steroids, cidofovir, and mitomycin C can also be administered endoscopically.

Microinstrumentation

Sharp dissection using cupped forceps and microscissors is precise and causes minimal damage to surrounding structures, and the mucosal injury is generally quick to heal. Cystic lesions and nodules may be successfully marsupialized or resected with less trauma than with a laser. Indeed, in inexperienced hands the laser probably has greater potential for damage. Aryepiglottic trimming for laryngomalacia[108] was originally described using sharp dissection. The aryepiglottic folds may simply be released or a small wedge of bulky arytenoid mucosa removed to prevent the forward prolapse of the posterior larynx and arytenoids, which is typical of the condition. Microinstrumentation with the sickle knife and sharp blades can be used to perform other procedures such as an endoscopic cricoid split (Fig. 205-17). In these cases, decompression of the cricoid ring followed by short-term stenting with an endotracheal tube may allow sufficient expansion of the subglottis to enable extubation and avert the need for a tracheostomy in early subglottic stenosis.[109]

Laser

The CO_2 laser for the larynx, and more recently the KTP laser for the trachea and bronchi, have been considered an essential part of the equipment needed to manage the pediatric airway. Other lasers such as the Nd:YAG and thulium laser have also been used in the respiratory tract. Newer techniques and instrumentation, however, may supersede use of the laser due to the delicate nature of the pediatric airway and its sensitivity to thermal injury. A number of improvements, including super pulsing, have reduced the collateral damage that occurs around the intended area of vaporization, making the laser relatively safe and effective in experienced hands. One should always err on the side of conservatism when using the laser in the pediatric airway (Fig. 205-18). Great care must be taken not to damage normal tissues and produce a

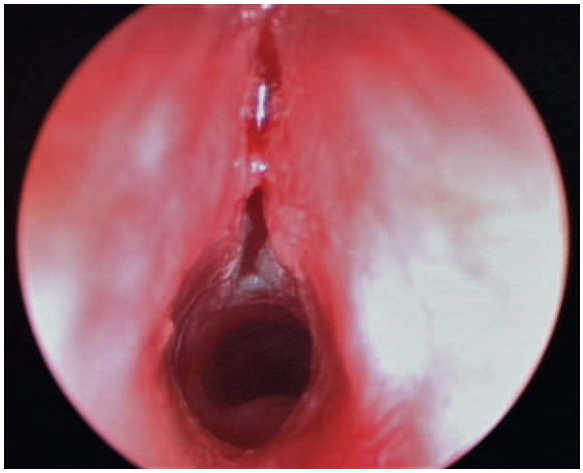

Figure 205-17. Endoscopic cricoid split performed in anterior midline using a sickle knife followed by balloon dilatation for subglottic stenosis.

Figure 205-18. Acquired complete glottic stenosis following excessive laser treatment for subglottic hemangioma.

secondary stenosis. A laser-safe tube must be used to provide anesthesia in all these cases; it is withdrawn into the pharynx and the inspired oxygen concentration is reduced to allow safe lasering of an unobstructed field.

The radiant energy produced by the CO_2 laser with a wavelength of 10.2 μm is strongly absorbed by tissues with a high water content with minimal penetration of surrounding tissues. It is useful for supraglottic and laryngeal pathology when attached to the operating microscope. CO_2 laser bronchoscopes have been developed, however, the optics are vastly inferior to normal telescopes, the technique is different, and its use is limited.

The KTP laser emits light at 532 nm (similar to the argon laser) that is preferentially absorbed by hemoglobin and has a greater penetration depth. It may be delivered via fiberoptic fibers to the lower airway, allowing precise access to distal lesions that cannot easily be reached with the CO_2 laser. The KTP laser fibers are sufficiently thin to be passed alongside a suction catheter of a conventional ventilating bronchoscope, providing an excellent view, hemostasis, and controlled vaporization.

The thulium laser is a continuous wave laser with a wavelength of 2013 nm. It has the advantage of being deliverable down a glass fiber with precise cutting and coagulation characteristics, and limited deep tissue penetration. Its use in the pediatric airway for laryngomalacia, laryngeal cysts, vocal cord palsy, tracheal hemangioma, and papillomatosis has recently been described.[110]

Techniques employed with the laser include excision of a wide variety of lesions,[111] vaporization of tissue, the encouragement of controlled scarring, and its use as a precise dissection tool. Postintubation granulomas can be accurately excised or vaporized, and cystic lesions marsupialized or debulked with good hemostasis and minimal postoperative edema. Subglottic hemangioma can be controlled with regular treatments, although the time to resolution is unchanged and there is a potential risk of subglottic scarring and stenosis especially with the CO_2 laser.[87-89] Propanolol is a recent therapy that can cause hemangiomas to regress.

Laser arytenoidectomy may be used for vocal cord palsy to remove the arytenoid and posterior vocal cord. This provides a posterior airway while preserving the function of the anterior vocal cord for phonation. Laryngeal papillomatosis responds well to vaporization with the laser, with potential reduction of viable viral particles that may seed down the trachea. Laser epiglottoplasty and supraglottoplasty for laryngomalacia is quick and bloodless,[112] and when used in the vallecula, scarring is promoted with elevation of a prolapsing epiglottis. Similarly, KTP laser to suprastomal granulomas secondary to tracheostomy tube placement may improve the airway lumen and stiffen up the anterior tracheal wall, facilitating subsequent decannulation.[113,114] Attempts to use the laser to divide anterior webs or subglottic stenosis, however, have generally been unsuccessful due to the tendency for recurrent and sometimes more severe stenoses.

Balloons

Endoscopic treatment of the pediatric airway using vascular-type balloons has become more popular in the last decade. They may be positioned under direct vision using the Hopkins rod or operating microscope and gradually inflated until the desired diameter and pressure are reached. The radial force generated is gentle and there is little mucosal injury. When using a spontaneous inhalational anesthetic technique, the anesthetist must be prepared for a period of total airway occlusion and apnea. One should avoid exceeding the burst pressure of the balloon or overstretching the airway, which potentially risks the development of cartilaginous injury and malacia. There are several situations in which endoscopic balloon dilatation is used for the stridulous child: in the case of early evolving stenosis following airway surgery or intubation, after division of posterior glottic scar bands, with endoscopic cricoid split, and to assist or maintain expansion of tracheal and bronchial stents.[96,115-117]

Microdébrider

The powered microdébrider was initially introduced to otolaryngologists as an additional tool in the treatment of nasal polyps and endoscopic sinus surgery. The development of longer blades with smaller angled cutting surfaces has seen its use migrate to the airway, including the pediatric airway. The concurrent suction attached to the handpiece allows abnormal tissue to be drawn into the blade and precise excision follows. This has been particularly suitable for cases of recurrent respiratory papillomatosis in which preservation of the submucosal tissues is crucial to avoid damage to the vocal ligament and scarring. In fact, a recent survey of members of the American Society of Pediatric Otolaryngology has noted that the microdébrider is now favored for the treatment of laryngeal papillomatosis over the CO_2 laser.[118] The technique is relatively fast, safe, and well tolerated. It has also been shown to cause equivalent immediate postoperative pain, greater improvement in voice quality and the overall procedure cost is lower in some centers.[119-121] The blade may be passed into the subglottis and upper trachea but access may be limited distally. The microdébrider has also been used to remove granulations and even subglottic hemangioma in some centers.[88,122]

Stents, Keels, and Grafts

Maintenance of the pediatric airway occasionally requires techniques of anatomic augmentation or the use of foreign materials to prevent collapse and to discourage stenosis. Many of these procedures can be performed endoscopically, thus avoiding an open operation and related potential morbidity. Glottic and subglottic stents may be positioned, secured, and later removed endoscopically. Expandable metallic stents used for tracheal and bronchial pathology can be placed endoscopically under radiologic guidance. Silastic sheeting used as a keel at the anterior commissure in cases of anterior webbing may be temporarily sutured into place through the neck. The use of the Montgomery T-tube in specialized circumstances of laryngotracheal disease can be inserted endoscopically using a heavy Prolene suture to guide the proximal limb toward the larynx. Recent reports of insertion of cartilage expansion grafts into the posterior larynx following endoscopic posterior cricoid split are also promising.[123]

Endoscopic Sutures

The development of endoscopic instrumentation such as the Lichtenberger needle holder has expanded the options available to the endoscopic airway surgeon. Type I and II laryngotracheoesophageal clefts may be sutured closed after endoscopic trimming of the common mucosal cleft wall. Interrupted sutures are used to close the defect on the tracheal and esophageal aspects with particular attention given to repairing the distal-most point where a fistula may persist. Two-layered repairs of type III laryngeal clefts have also been described, although the technique remains challenging.[124] In cases of vocal cord paralysis, endoscopic arytenoidopexy using a lateralizing suture has been performed with some success.[125,126] This may be temporizing or permanent.

Endoscopic Administration of Topical Treatments

Certain topical treatments can be applied endoscopically to the pediatric airway to assist in the management of the chronically stridulous child. Direct intralesional injection of papillomas with the antiviral cidofovir after debulking of the lesions is effective in reducing recurrence in approximately 60% of severe cases.[127] Its mechanism of action is via inhibition of the HPV viral DNA polymerization process; however, its use is reserved for those patients with aggressively progressing disease as the long-term side effects and potential for malignant transformation have yet to be documented.[128] Corticosteroids may be injected into evolving stenoses and into subglottic hemangiomas followed by a short period of postoperative intubation. The results have been encouraging so far.[87] Mitomycin C is an antineoplastic agent that has been used against solid tumors in the breast, lung, pancreas, and bladder. It was first used in the airway in 1998[129] and has since been applied topically to inhibit fibroblast growth, granulation tissue formation, and cicatricial scarring in many sites including the airway. The optimal dosage has yet to be agreed upon, although most centers tend to prefer 0.2 to 0.4 mg/mL applied on cotton pledgets for up to 5 minutes.[130]

Principles of Open Laryngeal Surgery

Open laryngeal framework surgery allows access to the upper respiratory tract from the supraglottis to the cervical trachea. These procedures are generally performed in the elective setting with careful consideration of the nature of the airway problem and its etiology, the patient's comorbidity and healing tendencies. As for tracheotomy, a meticulous dissection technique is essential, with attention paid to midline anatomic landmarks. The oblique fibers of the cricothyroid muscles are a useful guide to the cricoid cartilage. Anesthesia and ventilation may be maintained via endotracheal intubation or a temporary tracheotomy distal to the operative site depending on the circumstances. If a full laryngofissure is required, the position of the anterior commissure at the vertical midpoint of the thyroid cartilage is marked to allow accurate apposition on closure. Failure to do this may result in suboptimal voice outcomes. Placement of a surgical drain is strongly advised when postoperative air leak is likely to occur to reduce the chance of wound infection and surgical emphysema.

Open procedures may definitively address anatomic narrowing by allowing removal of tissue (stenoses, granulomas and other pathology), decompression of the lumen (cricoid split; Fig. 205-19), or expansion and augmentation with cartilage grafting (laryngotracheal reconstruction (Fig. 205-20), surgical decannulation and stomal reconstruction). Complete resection of a severe stenosis with end-to-end anastomosis is appropriate in some settings (cricotracheal resection). Subglottic hemangiomata may be definitively excised with a single stage open

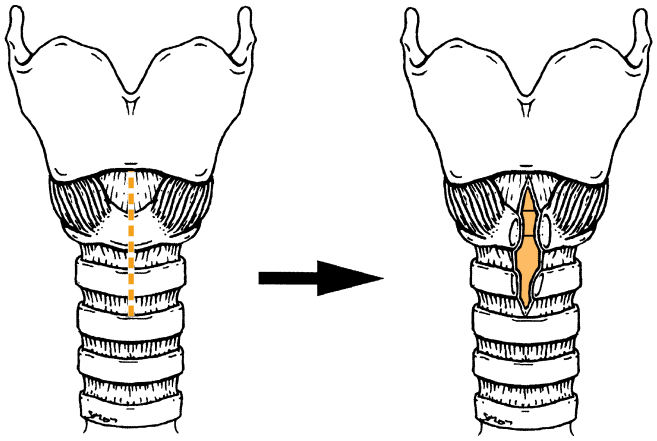

Figure 205-19. Principles of the anterior cricoid split operation: the cricoid and upper tracheal ring are opened in the midline to decompress the airway.

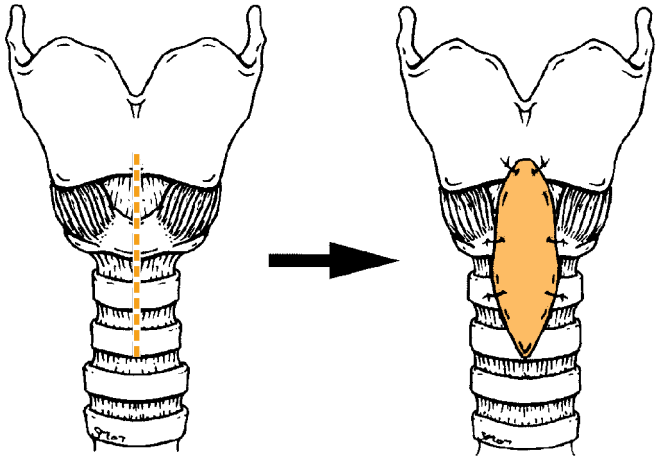

Figure 205-20. Principles of laryngotracheal reconstruction: an anterior cartilage graft is used to augment the subglottic lumen; this may be combined with a posterior cricoid split with or without posterior cartilage graft.

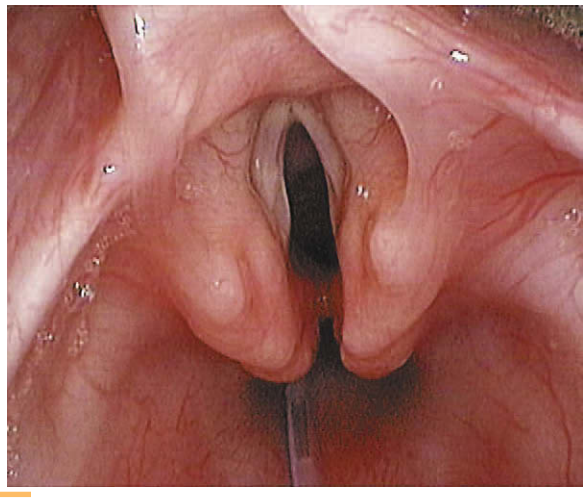

Figure 205-21. Endoscopic view of type 3 laryngeal cleft[131] (total cricoid cleft extending completely through the cricoid cartilage).

resection incorporating the techniques of cartilage augmentation into the repair. Laryngotracheoesophageal clefts can be repaired in two layers using a temporalis fascia or tibial periosteum graft as a reinforcing layer (Fig. 205-21). Maximal supportive medical therapy in the perioperative period with nutritional support, steroids, antibiotics, and antireflux treatment are important adjuncts to open surgery. Endoscopic follow-up is essential to monitor outcomes, granulations, and tendency to restenosis. This may need to be frequent in the early postoperative stages. (See Chapters 202 and 206 for further coverage of laryngeal surgery.)

The Future

The evaluation and management of the stridulous child can be a challenge for the general and pediatric otolaryngologist. Improved neonatal care and a greater understanding of the effects of intubation has led to a decline in iatrogenic airway disease in the last few decades. A systematic approach is essential with direct rigid endoscopic assessment remaining the gold standard investigation over other modalities. Medical management of the compromised airway is preferable if it can be achieved without jeopardizing patient safety. Minimally invasive therapeutic endoscopic measures are gaining popularity and may avert the need for a tracheotomy or open surgery in certain circumstances. The provision of optimal anesthetic conditions is pivotal to success of many pediatric airway procedures. Reconstructive airway techniques continue to be applied to a range of conditions with great success.

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CHAPTER TWO HUNDRED AND SIX

Glottic and Subglottic Stenosis

George H. Zalzal

Robin T. Cotton

Key Points

Majority are caused by trauma:

- Iatrogenic
    - Prolonged intubation
    - Laryngeal surgery
- External neck trauma to a lesser extent
- Congenital (usually less severe and less frequent) even more infrequently
- Burns, ingestions
- Infection
- Inflammation (gastroesophageal reflux or Wegener's)
- Types:
- Anterior, posterior, circumferential, complete: all may be associated with movement disorders
- Prevention:
    - Repair of laryngeal fractures and lacerations
    - Proper tracheotomy techniques
    - Appropriate endolaryngeal surgery
    - Avoidance of intubation trauma
- Diagnosis:
- History and Physical
- Radiology
    - Soft tissue AP and lateral
    - CT
    - MRI
- Endoscopy (flexible and rigid)
- Others
- Pulmonary functions, voice assessment, pH probe, FEES, PFTs
- Management is through (1) expansion or (2) resection. Specifically:
- Endoscopic
- Anterior cricoid split
- Expansion surgery
    - Grafting and stenting
    - Single stage laryngotracheoplasty
- Resection
- Cricotracheal

Chronic laryngeal stenosis is a partial or complete cicatricial narrowing of the endolarynx and may be congenital or acquired. The condition is rare and presents multiple problems affecting soft tissue and cartilage. Iatrogenic injuries and external neck trauma account for most cases. Chronic laryngeal stenosis in pediatric patients may be managed differently from that in adult patients, but the principles of expansion versus resection surgery remain the same. Of all laryngeal stenoses, chronic subglottic stenosis is the most common and presents significant challenges in management (Fig. 206-1).

Etiology and Pathophysiology

Congenital Laryngeal Stenosis

Congenital stenosis is secondary to inadequate recanalization of the laryngeal lumen after completion of normal epithelial fusion at the end of the third month of gestation.[1] The final pathologic findings depend on the degree of recanalization. Thus if the laryngeal lumen is not recanalized and remains completely obliterated, it will result in complete laryngeal atresia; if it is partially recanalized, incomplete atresia,

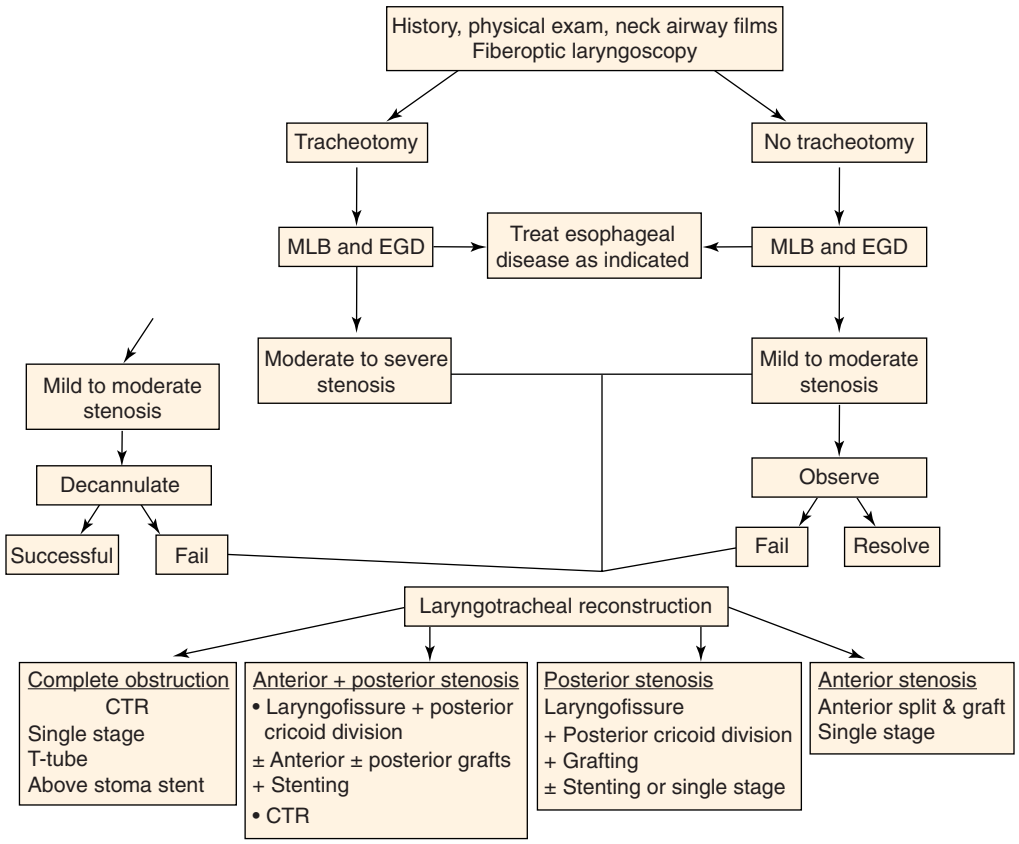

Figure 206-1. Algorithm for management of laryngeal stenosis.

stenosis, or webbing will occur. The cricoid cartilage is usually abnormally developed.

Congenital Laryngeal Atresia and Web

Laryngeal atresia can occur at any laryngeal level or combination of levels. The clinical picture depends on the severity of the lesion. In complete atresia, the glottis is closed at or above the vocal cords by a firm fibrous membrane. The neonate is aphonic, tries vigorously to breathe, undergoes rapid deterioration, becomes cyanotic despite continued respiratory efforts, and soon dies of asphyxia unless immediate tracheotomy is performed.[2,3] The condition is incompatible with life unless an emergency tracheotomy is performed or there is an associated tracheoesophageal or bronchoesophageal fistula. The most severe type of congenital laryngeal atresia presents as stillbirth and may not be recognized.

Congenital laryngeal webs account for about 5% of congenital anomalies of the larynx.[4] About 75% occur at the glottic level, and the rest are supraglottic or subglottic.[5] An association between anterior glottic web, the chromosome 22q11.2 deletion, and velocardiofacial syndrome has been established.[6-8] All patients with anterior glottic web should have their chromosome 22q11.2 deletion status determined by standard fluorescent in situ hybridization (FISH) analysis. Most webs present at birth or in the first few months of life. The severity of the web varies. Only a few are severe enough to require airway support by intubation or tracheotomy. A laryngeal web is often an abnormality of the glottis and the subglottic cricoid region (Fig. 206-2). The differential diagnosis includes bilateral vocal cord paralysis and congenital interarytenoid joint fixation. It is important to detect associated anomalies of the larynx, the respiratory tract, and other organ systems.

Treatment of congenital laryngeal atresia and web is presented later in this chapter under treatment of specific disorders.

Congenital Subglottic Stenosis

The normal subglottic lumen diameter in the full-term neonate is 4.5 to 5.5 mm and in premature babies is about 3.5 mm. A subglottic

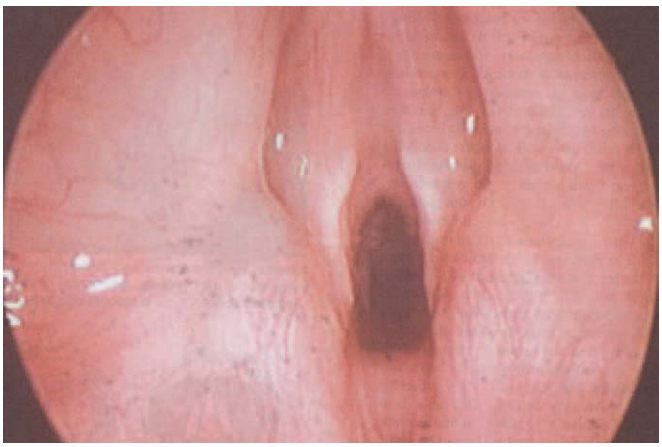

Figure 206-2. Endoscopic view of a congenital glottic web with subglottic extension.

diameter of 4 mm or less in a full-term neonate is considered to be narrowed.

Congenital subglottic stenosis (SGS) is considered to be congenital in the absence of a history of endotracheal intubation or other apparent acquired causes of stenosis. The diagnosis may be difficult to confirm, and it is unknown how many intubated premature infants who fail extubation have underlying congenital stenosis. Thus, by best approximation, congenital subglottic stenosis is the third most common congenital disorder of the larynx after laryngomalacia and recurrent laryngeal nerve paralysis. Acquired subglottic stenosis is more common than congenital stenosis because of the use of prolonged endotracheal intubation for respiratory support.

Congenital SGS is a clinical endoscopic diagnosis describing various histopathologic conditions that produce narrowing of the sub-

glottic airway. Congenital SGS can be divided into membranous and cartilaginous types.[9-11] The membranous type is a fibrous soft tissue thickening of the subglottic area caused by increased fibrous connective tissue or hyperplastic dilated mucous glands with no inflammatory reaction. It is usually circumferential, with the narrowest area 2 to 3 mm below the true vocal cords, sometimes extending upward to include the true vocal cords.[12]

The cartilaginous types are more variable, but the most common type is a thickening or deformity of the cricoid cartilage causing a shelf-like plate of cartilage, partially filling the concave inner surface of the cricoid ring and extending posteriorly as a solid rigid sheet, leaving only a small posterior opening.[13]

Symptoms depend on the degree of subglottic narrowing. In severe cases, respiratory distress and stridor are present at birth; in milder cases, the symptoms become evident during the first few weeks or months of life, presenting as prolonged or recurrent croup. Differential diagnosis includes subglottic hemangioma and subglottic cysts. Infants usually become symptomatic within 3 months of birth because of increased activity and increased ventilation requirements.[2,9]

Minimal laryngeal swelling secondary to infection or endoscopy may precipitate airway obstruction because the cricoid cartilage limits the swelling of tissue in any direction except toward the laryngeal lumen at the expense of the airway. Therefore great care is needed when endoscopy is performed on these children to prevent trauma to the subglottic mucosa.

Endoscopic diagnosis is essentially by means of flexible fiberoptic endoscopy to assess vocal cord function and rigid endoscopy to assess the degree of anatomic obstruction. Postendoscopic edema is avoided by operating on a quiet, relaxed infant who is well-oxygenated. Cooperation between the endoscopist and anesthesiologist is essential, as is gentle instrumentation, preferably with the rigid rod lens system telescope alone without the sheath. If postoperative edema occurs, aggressive management should be started with cool mist racemic epinephrine by aerosol or intermittent positive-pressure breathing, and a short course of high-dose intravenous corticosteroids.

Congenital subglottic stenosis is most often less severe than acquired stenosis and may therefore be managed more conservatively. Some patients outgrow the condition.[12-14] Management depends on the degree and severity of stenosis, shape (whether the cricoid cartilage is normal or abnormal), and whether there are associated congenital anomalies.

Mild cases of stenosis are managed conservatively by watchful waiting and regular follow-up because many children outgrow the problem. During observation, vigorous medical management of viral infection is recommended. More severe cases requiring airway support may be managed by tracheotomy and reconstructive repair, or by single-stage laryngotracheal reconstruction using costal cartilage grafting for expansion of the subglottic airway.

Acquired Laryngeal Stenosis

Trauma is the most common cause of acquired laryngeal stenosis in children and adults and may be external or internal.

External Laryngeal Trauma

Blunt trauma to the neck sustained during motor vehicle accidents injures the larynx when the anterior surface of the extended neck strikes the dashboard or steering wheel, causing a laryngeal framework fracture. This is more common in adults than in children, in whom the prominent mandible and relatively high position of the larynx protect the latter from injury. Fractures of the larynx occur secondary to in-home accidents when the neck is injured by striking furniture such as a coffee table. Chronic acquired laryngeal stenosis is a sequela of severe laryngeal trauma with fracture of the cricoid and thyroid cartilages with or without displacement, or of inadequately managed early stages of laryngeal trauma.

Another mechanism of blunt laryngeal trauma, the so-called clothesline injury, occurs when a person riding a bicycle hits the anterior neck on a branch or clothesline, sustaining laryngeal fracture, and thyrotracheal or cricotracheal separation. A patient may have a separation of the cricoid and trachea and still survive the injury. Penetrating wounds of the larynx are usually less common than blunt trauma and are more common in adults than in children.

Internal Laryngeal Trauma

Most cases of internal laryngeal injury are iatrogenic, secondary to prolonged endotracheal intubation, which is the most common cause of chronic laryngeal stenosis. Approximately 90% of cases of acquired chronic subglottic stenosis in infants and children occur secondary to endotracheal intubation.[12,14] The reported incidence of stenosis after intubation ranges from less than 1% to 8.3%.[15-19] This rate is much lower than the 12% to 20% reported in the late 1960s and early 1970s because of recognition of the problem and institution of preventive methods. Despite improvement in neonatal care, the incidence has stabilized at around 1% over the past 10 years.[19,20] These figures may underestimate the true incidence of the disease in the pediatric population because many infants who are intubated do not survive the primary illness. In addition, some acquired subglottic stenosis may not be recognized unless an infection of the upper respiratory tract develops or the patient requires reintubation later in life. The areas most commonly injured are the subglottic region in children and the posterior endolarynx in adults.[21]

In children, the subglottic region is especially prone to injury from endotracheal tube intubation for various reasons. First, the cricoid cartilage is the only area in the upper airway that has a complete circular cartilaginous ring, preventing the outward extension of traumatic edema. Second, the pseudostratified, ciliated, columnar respiratory epithelium lining this region is delicate and tends to deteriorate under the stress of an indwelling tube. Third, the subglottic submucosa is made up of loose areolar tissue that allows edema to develop easily and quickly. Fourth, the subglottic region is the narrowest portion of the pediatric airway.[12]

The pathophysiology of acquired subglottic stenosis is well described in the literature.[3,22-24] The endotracheal tube causes pressure necrosis at the point of interface with tissue, leading to mucosal edema and ulceration. As ulceration deepens, normal ciliary flow is interrupted, with mucociliary stasis leading to secondary infection and perichondritis. With further infection, chondritis and cartilaginous necrosis occur, especially with collapse of the airway during inspiration. Healing occurs by secondary intention with granulation tissue proliferation in the areas of ulceration and deposition of fibrous tissue in the submucosa. Primary healing of the laryngeal injury is hindered by the presence of loose and mobile subglottic mucosa, poor blood supply to the cartilage, and constant motion of the larynx associated with swallowing and head movement.[23,25] Study of intubated larynges from infants of 22 to 40 weeks' gestation who survived a few hours to 300 days showed acute injury was almost invariable and up to 100% of the subglottic epithelium was lost within a few hours of intubation, but progression of injury was relatively short lived. Ulcer healing started after a few days, rapidly progressed from day 10, and, in most cases, was complete after 30 days. This study suggests that longstanding acute injury of the subglottis is the exception rather than the rule, even with the endotracheal tube remaining in place.[23]

Duration of intubation and the size of the endotracheal tube are the most important factors in the development of laryngeal stenosis. No definite safe time limit for endotracheal intubation has been established. Severe injury has been reported after 17 hours of intubation in adults[22] and 1 week after intubation in neonates.[26] Several studies in adults have shown that a 7- to 10-day period is acceptable, after which prolongation of intubation is accompanied by an increased incidence of laryngotracheal complications.[21] Premature infants tolerate more prolonged intubation (weeks rather than days). Explanations include relative immaturity of the laryngeal cartilage in the neonates (more hypercellular with scant gel-like matrix) rendering it more pliable, thus yielding to pressure,[27] and the high location of the neonatal larynx in the neck with its posterior tilt and funnel shape.[25]

Insertion of an oversized endotracheal tube increases the risk of laryngeal injury. In children, the tube size should allow an air leak at 20 cm H_2O pressure if possible. Polymeric silicone and polyvinyl chloride are considered the safest materials for prolonged intubation.

Shearing motion of the tube causes abrasive traumatic action on the mucosa, especially in patients who are restless, those on respirators, and those with orotracheal intubation. Superimposed bacterial infec-

Figure 206-3. **A,** Endoscopic view of interarytenoid adhesion shows a posterior fistular tract resulting from a scar tissue band between the vocal process of the arytenoids cartilages. **B,** Endoscopic view of posterior glottic stenosis with vocal cord fixation. **C,** Same lesion as in **B,** after repair with posterior cartilage grafting and stenting, achieving full vocal cord mobility.

tion compounds the mechanical mucosal trauma by increasing the inflammatory response and scar tissue formation. Repeated intubations cause increased trauma and increase the risk of sequelae. Nasogastric tubes can cause pressure necrosis and cricoid chondritis if placed in the midline. Coexistence of endotracheal and nasogastric tubes may increase laryngeal complications.

When inexperienced personnel care for intubated patients, intubation complications may increase. Education of physician and nursing personnel caring for intubated patients markedly increases the expertise of that care. Systemic factors including chronic illness, general disability, immunosuppression, anemia, neutropenia, toxicity, dehydration, hypoxemia, poor perfusion, radiotherapy, and the presence of gastric acid reflux encourage the vulnerability of laryngeal mucosa to injury by decreasing tissue resistance and increasing infection rate.

Other Causes of Laryngeal Stenosis

Laryngeal stenosis may occur secondary to laryngeal injury resulting from laryngeal surgery. Emergency cricothyroidotomy through the cricothyroid membrane[28] and high tracheotomy can produce severe stenosis, particularly in children. Supraglottic stenosis and collapse may be related to prior laryngeal or tracheal injury. Acquired anterior glottic web can occur after excision of a laryngeal polyp or papilloma in the anterior commissure area if the anterior portions of both vocal cords are denuded simultaneously.[29] Laryngeal stenosis also is described after endoscopic microsurgery with modalities such as electrocautery or laser.[30]

Chondroradionecrosis can lead to scarring and stenosis shortly after radiotherapy or as long as 20 years later.[31] Intralaryngeal burns from fumes, smoke inhalation, or caustic lye ingestion can give rise to chronic laryngeal stenosis.[32]

Chronic Infection

Laryngeal stenosis secondary to chronic infection is rare except in isolated endemic geographic areas. It has been described in tuberculosis, syphilis, leprosy, glanders, typhoid fever, scarlet fever, diphtheria, mycosis, and laryngeal scleroma.

Chronic Inflammatory Disease

Laryngeal stenosis has been described secondary to sarcoidosis, lupus erythematosus, Behçet's syndrome, Wegener's granulomatosis, relapsing polychondritis, pemphigoid, epidermolysis bullosa, amyloidosis, and major aphthous ulceration. Management of laryngotracheal stenosis in Wegener's granulomatosis is complex, requiring individualized and often multimodality interventions to achieve satisfactory results.

Chronic inflammation secondary to gastroesophageal reflux (GER) may cause laryngeal stenosis. GER in children can be classified as physiologic, functional, pathologic, or secondary.[33] Many airway manifestations have been attributed to GER including stridor, recurrent croup, exacerbation of subglottic stenosis, and chronic cough. Diagnosis is difficult unless the index of suspicion is high.[34] The role of GER on the outcome of pediatric laryngotracheal reconstruction remains unknown.[35] Until this is clear, the authors recommend that GER is investigated and treated in patients undergoing laryngeal reconstruction during the perioperative period.

Laryngeal Neoplasm

Chondroma, fibroma, hemangioma, and carcinoma can cause laryngeal stenosis because of tumor infiltration or secondary to infective perichondritis, postradiation perichondritis, or postsurgical scarring and stenosis.

Types of Stenosis

Acquired glottic stenosis may be anterior, posterior, circumferential, or complete. Anterior glottic stenosis can be a thin glottic web, which is a bridge of scar tissue covered by epithelium located between the vocal cords involving the anterior commissure. This usually results from enthusiastic endoscopic surgery involving both true cords simultaneously. Thick, anterior glottic scarring is usually more extensive and results in true vocal cords, false cords, and laryngeal ventricles adhering to one another without any intervening web. The cause is often unmanaged severe external laryngeal trauma. Posterior glottic stenosis usually results from prolonged endotracheal tube intubation.

Pressure necrosis of the mucosa overlying the vocal process of the arytenoid occurs, followed by ulceration and granulation tissue formation on the medial surface of the body of the arytenoid cartilage. A similar process occurs to a variable degree in the interarytenoid area with involvement of the interarytenoid muscle, causing fibrous ankylosis of one or both cricoarytenoid joints.[36] Posterior glottic scar frequently extends downward to the subglottic region. It is important to differentiate between a complete posterior glottic stenosis, in which the scar is located in the interarytenoid space and posterior commissure, and an interarytenoid adhesion, in which the scar is between the vocal processes of the arytenoids with a small posterior, mucosally lined sinus tract in the posterior commissure area (Figs. 206-3 and 206-4A). The scarring of the posterior commissure may be confined to the submucosa (see Fig. 206-4B) or extend into one (see Fig. 206-4C) or both (see Fig. 206-4D) cricoarytenoid joints.

The voice is generally good because of the adducted position of the vocal cords. The major symptoms are referable to the airway. In mild or moderate cases, the patient may be able to ventilate without a tracheotomy and may experience only exercise intolerance. Patients who have a more severe stenosis may need a tracheotomy for adequate respiratory exchange. Diagnosis by indirect laryngoscopy is difficult and may be confused with bilateral vocal cord paralysis.[37] Diagnosis at direct laryngoscopy is made by careful observation of the posterior commissure. The true vocal cords are closely approximated because the vocal processes, and occasionally the arytenoid bodies, are tethered together by heavy scar. A posterior sinus tract should be carefully sought and is particularly difficult to see in the pediatric larynx. Unlike vocal cord paralysis, in posterior glottic stenosis the cricoarytenoid joints are partially or completely immobile on a passive motion test. Palpation of the arytenoids shows that they may be rocked in an anteroposterior direction but will not slide from side to side. Complete total glottic stenosis rarely occurs in isolation and is usually accompanied by supraglottic or subglottic stenosis. In children, it is a sequela of endotracheal intubation, lye ingestion, and thermal burn.

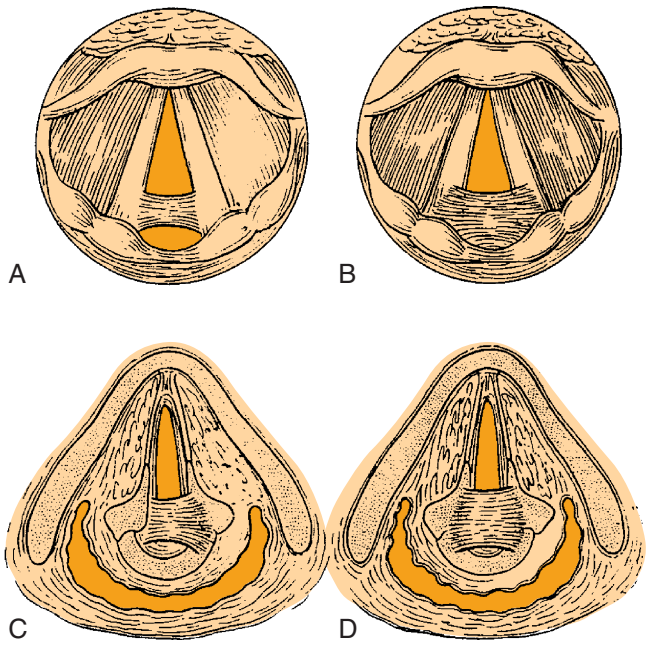

Figure 206-4. Posterior subglottic stenosis. **A,** Interarytenoid adhesion with a mucosally lined tract posteriorly. **B,** Posterior commissure and interarytenoid scar without a mucosally lined tract posteriorly. **C,** Posterior commissure scar extending into the right cricoarytenoid joint. **D,** Posterior commissure scar extending into both cricoarytenoid joints.

Prevention

Factors important in reducing the incidence of laryngotracheal stenosis include:

1. Early exploration of laryngeal fractures to minimize serious sequelae.

2. High tracheotomy and cricothyroidotomy should be avoided except in extreme emergencies. If it is suspected that a high tracheotomy or cricothyroidotomy has been performed, endoscopy is indicated. If the suspicion is confirmed, the neck should be explored, and the tracheotomy site should be relocated to a lower position to prevent chronic subglottic stenosis. However, if the repair of a cricotracheal resection is planned, a high tracheotomy rather than a lower one is advantageous because it reduces the length of the resection.

3. When performing a tracheotomy, the surgeon should avoid extensive resection of the tracheal wall and use the smallest size tracheotomy tube compatible with ventilation and suctioning.

4. Aggressive endoscopy for benign laryngeal lesions should be avoided, especially for those in the anterior commissure area, to prevent formation of an anterior glottic web. The procedures should be staged 2 weeks apart for each side. Different principles may be appropriate for malignant lesions.

5. Intubation and endoscopy should be performed gently on relaxed patients.

6. Circumstances contributing to laryngeal trauma secondary to prolonged intubation should be recognized and avoided whenever possible.

Diagnosis of Congenital and Acquired Laryngeal Stenosis

Laryngeal stenosis is diagnosed by a thorough history and physical examination, radiologic evaluation, and endoscopic examination of the airway and esophagus.[38] Other investigations such as pulmonary function tests also may be helpful.

History and Physical Examination

Mild to moderate laryngeal stenosis is usually asymptomatic until an infection of the upper respiratory tract causes additional narrowing of the airway, resulting in respiratory distress. These patients usually have a tendency toward prolonged courses of upper respiratory tract infections.

In acquired stenosis, there is a history of laryngeal insult. Symptoms usually occur 2 to 4 weeks after the original insult, although the latent period can occasionally be longer. In congenital stenosis, symptoms usually appear at or shortly after birth, suggesting the possibility of a laryngeal anomaly.

The main symptoms of laryngeal stenosis relate to airway, voice, and feeding. Progressive respiratory difficulty is the prime symptom of airway obstruction with biphasic stridor, dyspnea, air hunger, and vigorous efforts of breathing with suprasternal, intercostal, and diaphragmatic retraction. Abnormal cry, aphonia, or hoarseness occurs when the vocal cords are affected. Dysphagia and feeding abnormality with recurrent aspiration and pneumonia can occur.

Complete physical examination of the upper aerodigestive tract should be performed to rule out associated congenital anomalies or acquired injuries.

Radiologic Evaluation

Radiologic evaluation is performed after stabilization of the airway. Radiography helps assess the exact site and length of the stenotic segment, especially for totally obliterated airways. The soft tissue radiograph is the single most important view in children. The anteroposterior high-kilovoltage technique increases visibility of the upper airway by enhancing the tracheal air column while deemphasizing the bony cervical spine. In acquired stenosis, small areas of calcification may be seen, denoting the site of previous injury. Fluoroscopy is helpful in studying tracheal dynamics.

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful. High-speed CT has reduced imaging time and is becoming more popular in the assessment of airway lesions. MRI still requires a significant amount of time, necessitating sedation in younger patients.

Evaluation of swallowing is important before airway reconstruction because dysfunctional feeding may complicate airway reconstruction by increasing the risk of aspiration postoperatively. Patients undergoing surgical correction of airway anomalies should have a historical screen for feeding problems. Patients with marginal feeding skills may be unable to compensate for the altered anatomy created by the reconstruction.

Videofluoroscopic swallowing studies (VSS) provide radiographic reviews of the bolus during swallowing. The presence of laryngeal penetration and aspiration can be documented and assessment of the ability of the child to protect the airway can be made. Many children with congenital anomalies of the airway, however, cannot tolerate the volume of contrast necessary to visualize the swallowing mechanism, and have significant oral aversion behaviors that preclude the introduction of any material into the mouth because of lack of exposure to nutritional stimuli at developmentally sensitive periods of their development. This makes the assessment of swallowing safety impossible by this method and an endoscopic evaluation of swallowing should be performed.

Endoscopic Examination

Indirect laryngoscopy alone is inadequate for diagnosis. Direct endoscopic visualization of the larynx is essential to study the stenosis carefully. Flexible fiberoptic endoscopy assesses the dynamics of vocal cord function and the upper airway, including the trachea.[39] In patients with severe burns with neck contractures, flexible endoscopy may be the only method to visualize the larynx. Flexible retrograde tracheoscopy through the tracheotomy site may provide useful information in some cases.

Rigid and flexible endoscopy of the airway and esophagus should be performed in the operating room with the patient under general

anesthesia. The rigid telescope is especially important in the examination of children because it better visualizes the small larynx. However, it is important to recognize that the airway lumen should be measured by passing bronchoscopes or endotracheal tubes of known sizes and cannot be gauged by the use of telescopes alone.[40]

Flexible endoscopy and spiral CT with mutiplanar resolutions have to be considered complementary techniques to rigid endoscopy in the preoperative evaluation and follow-up of children with laryngotracheal stenosis.[41]

Evaluation of Gastroesophageal and Gastrolaryngopharyngeal Reflux

GER is a common occurrence in children and adults. Many infants have no pathologic symptoms related to GER (the happy spitters). The current prevailing, although not universal, opinion is that GER and gastrolaryngopharyngeal reflux (GLPR) are likely to play a role in the development and exacerbation of SGS and may affect adversely the successful outcome of laryngotracheal reconstruction (LTR). GER and GLPR are defined as involuntary passage of gastric contents into the esophagus and pharynx, and are commonly occurring physiologic phenomena. It is not the presence of reflux that determines gastroesophageal reflux disease (GERD) or gastrolaryngopharyngeal reflux disease (GLPRD), but rather the frequency, intensity, and associated symptoms of reflux that distinguishes GERD and GLPRD from GER and LPR. Unfortunately, there is no gold standard for recognizing or excluding GERD and GLPRD, and differentiation between physiologic and pathologic reflux can be difficult. All diagnostic tests available for GER and GLPR have significant limitations. Generally, they tend to have high specificity but low sensitivity. Of the tests available today, 24-hour esophageal pH probe using a dual probe technique is believed to be the most reliable. This test, when used in conjunction with history, esophagoscopy, and esophageal biopsy, yields the best information in determining the likelihood of GERD and GLPRD.

Esophagogastroduodenoscopy with Biopsy

Esophagogastroduodenoscopy (EGD) allows direct visualization of the esophageal, gastric, and duodenal mucosa, as well as facilitating biopsy of any suspicious lesions. Any esophageal mucosal irritation, erosion, ulceration, epithelial metaplasia as in Barrett's esophagitis, or stricture should be noted and biopsied. Histologic findings of esophagitis are confirmed. EGD is a surgical procedure, with its own potential risks of bleeding, infection, intestinal perforation, mediastinitis, or peritonitis. This test is recommended when esophagitis is suspected, but not required for every patient undergoing reflux evaluation. When esophagitis is detected, EGD with biopsy may be repeated to determine treatment efficacy.

It is important to recognize eosinophilic esophagitis as a separate entity from GER. Control of this is important prior to surgical reconstruction of the airway.

Treatment of GER and GLPR starts with dietary and lifestyle modifications and can be supplemented by pharmacologic agents. If control of GER and GLPR is not achieved with maximum medical therapy, a surgical consultation should be obtained. Proper communication between the otolaryngologist, the gastroenterologist, and the surgeon based on the previous investigations leads to instituting the most appropriate therapeutic program for the individual patient.

Functional Endoscopic Evaluation of Swallowing

The functional endoscopic evaluation of the swallow (FEES) study requires the passage of a flexible endoscope transnasally into the hypopharynx. The hypopharynx can be visualized and parameters similar to those rated in VSS related to airway protection can be determined. In addition, secretions spilling from the oral cavity that pool in the hypopharynx may be visualized and their aspiration risk assessed. An assessment of hypopharyngeal sensation also can be made by demonstrating the laryngeal closure response elicited from a calibrated air stimulus to the larynx. Decreased sensation is correlated with an increased aspiration potential. If VSS is precluded because of oral aversion, then a FEES study is performed.

Table 206-1

Grading of Laryngeal Stenosis

Grade	Percentage of Laryngeal Lumen Obstruction
I	Less than 70%
II	70% to 90%
III	More than 90%; identifiable lumen is present (no matter how narrow)
IV	Complete obstruction; no lumen

Voice Assessment

Psychoacoustic evaluation and acoustic analysis of the voice may be used to establish the degree of vocal abnormality before surgery and compare it with voice analysis after surgery.[42,43]

Although assessment of pre- and postoperative vocal quality in young children may be frustrating, improvement in technology has made the task easier and several reports have been published regarding specific voice issues. In general, the voice results are unsatisfactory, with the vocal parameters suggesting a pattern of lower than optimum pitch and a restricted pitch range. Vocal quality appears to be disturbed in most patients; however, laryngeal reconstruction makes oral communication possible.[43-46]

Pulmonary Function Test

Pulmonary function tests with the spirometric maximum inspiration and expiration flow rates, flow volume loops, or pressure flow loops show characteristic changes in upper airway stenosis and can be used to compare the postoperative results with preoperative values.[47]

Management

Management should be individualized according to pathologic findings, patient age, degree and consistency of stenosis (hard or soft and percentage of stenosis), and general condition of the patient. Management of adults differs from that of children, and some operations useful in children are not applicable to adults.

All cases of moderate or severe laryngeal stenosis require a tracheotomy at or below the third tracheal ring to establish a safe airway. Stenosis that does not require a tracheotomy constitutes a mild case. A four-stage grading system has been widely adopted (Table 206-1).[40,48]

The first thing to do is to secure the airway if immediate repair cannot be performed. Severe cases of congenital subglottic stenosis or marked cartilaginous cricoid deformity need a tracheotomy to maintain an adequate airway. When a tracheotomy is performed, the smallest tube that permits adequate ventilation should be used. The tube should allow air leakage to occur to avoid injury to the tracheal mucosa and simultaneously preserve phonatory potential.

Tracheotomy was required in congenital subglottic stenosis in less than half of a large series of patients.[12] Once the airway is secured, two basic management modalities are considered: endoscopic or external. Endoscopic methods include traditional dilation including balloon dilation and techniques that use laser excision of stenotic areas. Open surgical methods include expansion and resection surgery. The morbidity of open reconstruction is higher, but this is balanced against the multiplicity and futility of endoscopic procedures when inappropriately used. In general, less severe cases respond to endoscopic methods, and more severe cases require external reconstruction. If the cartilaginous framework of the larynx is significantly deficient, endoscopy is unlikely to be successful.

The best chance for the patient lies in the first operation.[49] Endoscopic techniques for isolated subglottic stenosis may be successful in grade I and occasionally grade II subglottic stenosis. Expansion laryngotracheal surgery is very successful in grades II, III, and some grade IV. Partial cricotracheal resection is successful in some grade III and

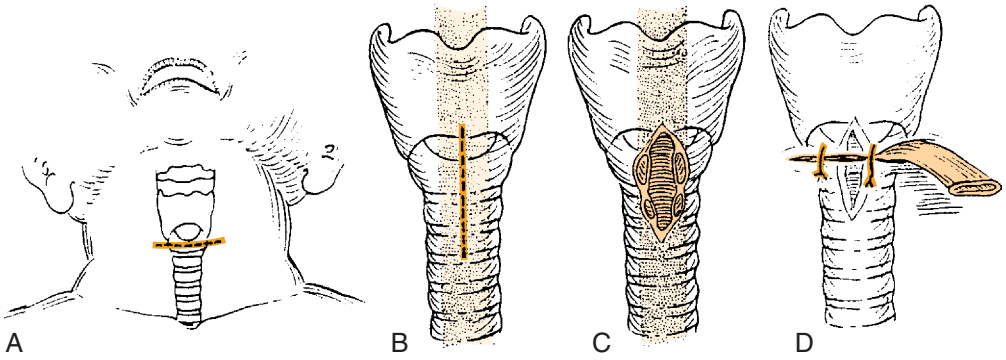

Figure 206-5. Anterior cricoid split. **A,** Skin incision. **B,** Midline laryngeal incision through cartilage and mucosa. **C,** With the cricoid cartilage decompressed, the endotracheal tube is ghosted in **B** and **C. D,** Loose skin closure with a drain inserted.

IV stenosis where there is a clear margin between the stenosis and the vocal cords.

Endoscopic Management

Dilation is sometimes useful early in the development of stenosis. It is not recommended for mature, firm stenosis or cartilaginous stenosis. Dilation is usually performed alone or supplemented with local or systemic corticosteroids or intralaryngeal stenting. The use of corticosteroids in all stages of acquired SGS is controversial. Corticosteroids tend to decrease scar formation by their anti-inflammatory action of delaying synthesis of collagen in early stages of wound healing and increasing collagen lysis in the later phases. Corticosteroids also delay wound healing by delaying the epithelial migration necessary to resurface the denuded area, thus increasing scar formation and predisposing to infection. Corticosteroids may be used systemically or locally. Local injection into subglottic scar is technically difficult and may be ineffective if a pressure injection system is not used. Resorption of cartilage secondary to the presence of local corticosteroids is a serious complication. Inhalation corticosteroids are believed to reduce granulation tissue formation after stent removal or early after endotracheal tube injury.

Mitomycin C is an antineoplastic antibiotic that acts as an alkylating agent by inhibiting deoxyribonucleic acid and protein synthesis. Experimental animal studies[50] and postendoscopic application[51,52] seem promising; however, there seems to be no advantage to its use after open surgical repair.[53] There is a risk of acute airway obstruction from excessive accumulation of fibrinous debris at the operative site in humans and animals after applying mitomycin to sites treated with CO_2 laser and dilatation.[54,55]

Endoscopic scar excision using the carbon dioxide (CO_2) laser is popular because it allows the surgeon to vaporize scar tissue with precision, producing minimal damage to healthy areas. Tissue destruction is directly related to the amount of energy delivered by the laser and the duration of exposure. If minimal energy of short duration is delivered, damage to the underlying and normal surrounding structures is minimal. However, if the laser is used at high energy levels for long times, it acts similar to any other uncontrolled method of tissue excision. The laser is useful for managing early stenosis with granulation tissue and may improve the airway without causing significant bleeding or edema, thus avoiding the need for a tracheotomy. Many authors have reported adequate results in managing early or mild SGS using the CO_2 laser,[56,57] generally with multiple procedures. CO_2 laser treatment was found to be effective in 92% of grade I subglottic stenosis but declined to 46% in grade II and to 13% in grade III. In order to avoid worsening of the airway it is recommended that CO_2 laser treatment be used only once if the airway lumen does not improve.[58] Endoscopic management has not been successful in the presence of the following conditions:

1. Circumferential cicatricial scarring
2. Abundant scar tissue greater than 1 cm in vertical dimension
3. Fibrotic scar tissue in the interarytenoid area of the posterior commissure
4. Severe bacterial infection of the trachea after tracheotomy
5. Exposure of perichondrium or cartilage during CO_2 excision, predisposing to perichondritis and chondritis
6. Combined laryngotracheal stenosis
7. Failure of previous endoscopic procedures
8. Significant loss of cartilaginous framework

Anterior Cricoid Split Operation

The anterior cricoid split operation (Fig. 206-5) was described in 1980 as an alternative to tracheotomy in the management of acquired SGS in premature infants.[59] The procedure has subsequently been used in the management of congenital SGS.[60] The concept is to split the cricoid and upper first and second tracheal rings in the midline anteriorly, thus allowing expansion of the cricoid ring. It is indicated in cases of congenital SGS caused by a small cricoid ring (i.e., not otherwise seriously deformed) or extensive submucosal fibrosis with healthy cricoid cartilage. It should be used only in patients whose condition is severe enough to require airway support and in whom lung function is adequate to permit decannulation. Use of auricular,[61] thyroid alar cartilage,[62] and hyoid[63] grafts has been reported to improve the success rate of the cricoid split operation. There are many factors that determine the success of the cricoid split procedure and hence the variability of its success from a low of 35% to a high of 88%.[64,65] Performing a cricoid split on a healthy infant with isolated subglottic stenosis yields the best results. Poor results occur when patients are generally sick and the airway lesion is not restricted to the subglottis.

With the patient under general endotracheal anesthesia, a horizontal skin incision is made over the cricoid to expose the cricoid and upper two tracheal rings. A single vertical incision is made through the anterior cartilaginous ring of the cricoid and through the mucosa to expose the endotracheal tube. The incision is extended inferiorly to divide the upper two tracheal rings in the midline. When the incision is made through the cricoid, the cricoid springs open, and the endotracheal tube is readily visible in the lumen. The incision in the larynx is extended superiorly in the midline to include the lower third of the thyroid cartilage to a level just inferior to the anterior commissure, but it can be extended to within 2 mm of the thyroid notch (Fig. 206-6).[66] Stay sutures of 3-0 Prolene are placed on each side of the incised cricoid. These can be used as retractors in the postoperative period if the endotracheal tube becomes dislodged and cannot be reinserted. The skin is loosely approximated around an elastic band drain. The endotracheal tube is left in place for about 7 days and acts as a stent while the mucosal swelling subsides and the split cricoid and tracheal rings heal.

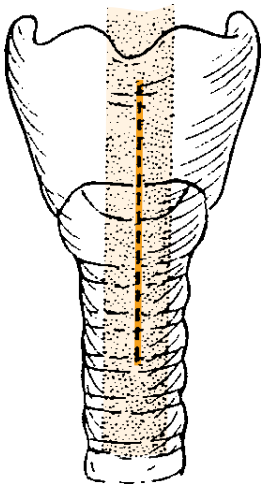

Figure 206-6. Incision for an anterior cricoid split in the management of SGS in infants (compare with Fig. 206-7.)

Endoscopy is not performed at extubation. Corticosteroids are administered before extubation and continued for 5 days.

External Expansion Surgery

Surgical reconstruction is recommended when conservative efforts to establish a satisfactory airway are inappropriate or have failed. In weighing the advantages of open reconstruction versus endoscopic management, the surgeon should consider his or her personal expertise and the severity of the lesion. In general, SGS grades III and IV lesions require external methods. Grade II may be amenable to either method. Occasionally, open surgery is required when the stenosis is of such a degree that tracheotomy has not been required.

Before surgery is performed, vocal cord paralysis should be ruled out. There should be no reason for the patient to continue to be tracheotomy-dependent despite adequate patency of the airway (e.g., presence of neurologic deficit or chronic pulmonary disease). The goal and rationale of open reconstructive surgery are to achieve early decannulation with minimal detrimental effect on the voice.

External surgical repair should be directed at the site and severity. Each case should be individualized. The two main methods of repair are resection and expansion surgery.[67-71] Expansion surgery is a collection of techniques that aim to widen the glottic and subglottic lumen. These techniques combine the use of laryngeal and cricoid splits, cartilage grafts, and stenting with success rates of higher than 90%.[72-75] Many techniques for correction of stenosis are available, but choosing the most appropriate procedure and achieving a successful outcome are problematic. Surgical repair at the youngest age possible is important for a child's speech and language development, as well as for eliminating the morbidity and mortality associated with a tracheotomy.

Combined Laryngofissure and Posterior Cricoid Division

Division of the posterior cricoid lamina through a partial laryngofissure is the method of choice for combined posterior glottic and SGS for grade II and moderate grade III. The operation is effective in patients of all ages. Cartilage grafts can augment the lumen. Scar removal is unnecessary in this procedure.

With the patient under general anesthesia administered via the tracheotomy, a horizontal skin incision is made incorporating the upper portion of the stoma (Fig. 206-7). Subplatysmal flaps are elevated superiorly and inferiorly, and the strap muscles are retracted laterally, exposing the thyroid, cricoid, and upper tracheal rings. A midline anterior incision is made in the larynx and upper trachea, extending from the superior thyroid notch to the tracheotomy site. After injection of 1% lidocaine with epinephrine 1 : 100,000 into the posterior larynx, the posterior scar and full length of the posterior lamina of the cricoid are divided, taking care to cut strictly in the midline, down to the level of the hypopharyngeal mucosa. The laryngeal scar should not be

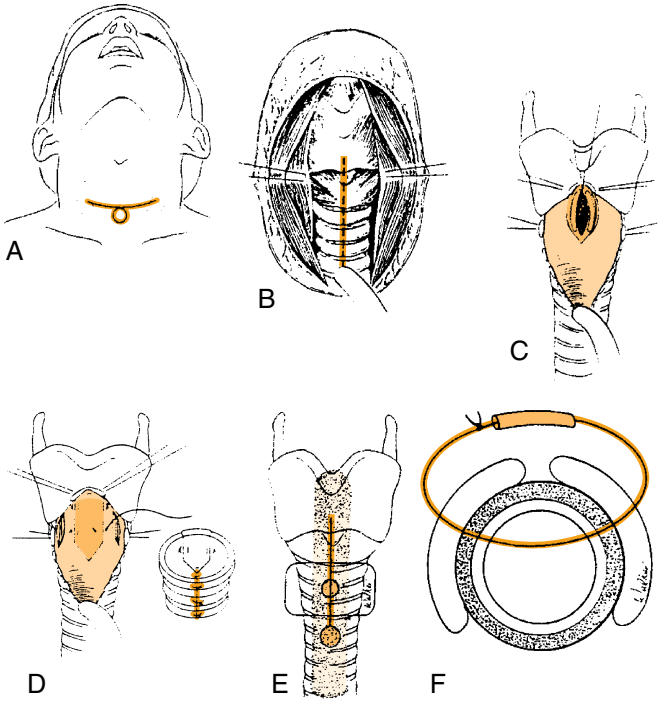

Figure 206-7. Anterior laryngofissure with division of the posterior and lateral lamina of cricoid, together with posterior cricoid cartilage graft insertion. **A,** Horizontal skin incision incorporates the superior aspect of tracheotomy. **B,** Skin flap elevated in the neck and laryngofissure. **C,** Division of the posterior lamina of the cricoid. **D,** Autogenous cartilage graft interposed posteriorly between divided ends of the cricoid lamina and sutured in place. **E,** Laryngofissure closed anteriorly with a suprastomal stent in place. **F,** Anchoring suture through suprastomal stent.

excised. The incision is carried superiorly into the interarytenoid area through the interarytenoid muscle (when fibrosed) and inferiorly for about 1 cm into the membranous tracheoesophageal septum. The divided halves of the posterior cricoid lamina are distracted laterally and an autogenous costal cartilage (see Fig. 206-7) is used to maintain separation of the divided halves of the cricoid lamina. A stent is inserted suprastomally for 2 to 6 weeks. A variety of stents is advocated and each has its own specific application. The use of stents is being replaced more and more by the use of single stage laryngoplasty. It is also advisable to avoid a complete laryngofissure so as not to disrupt the anterior commissure, which could lead to deleterious voice results.

Grafts

In children, autogenous costal cartilage is the graft material of choice, especially when there is little identifiable cricoid cartilage remaining anteriorly.[12,76,77] Because of the abundance of available costal cartilage, any length of cartilage can be obtained to graft the subglottis and trachea. Ear cartilage[75] and free thyroid cartilage graft are alternatives in special circumstances. The use of vascularized hyoid interposition techniques should be discouraged in children because the hyoid is too small to augment effectively the subglottic lumen, the bone is too hard to sculpture, and the muscle pedicle tends to ossify, causing secondary compression of the larynx. Cartilage graft survival has been proven experimentally and clinically in children and adults.[78]

Thyroid alar cartilage is excellent for use in the anterior subglottic region but is limited to grade II and few grade III lesions[79] because of its limited thickness compared to costal cartilage and inability to use it in the posterior cricoid area. Removal of the alar cartilage does not seem to cause a laryngeal deformity but no long-term follow-up is available.[80,81]

Autogenous Costal Cartilage Reconstruction

The patient is positioned in an extended neck position. The tracheotomy tube is replaced with an endotracheal tube to allow easy access to

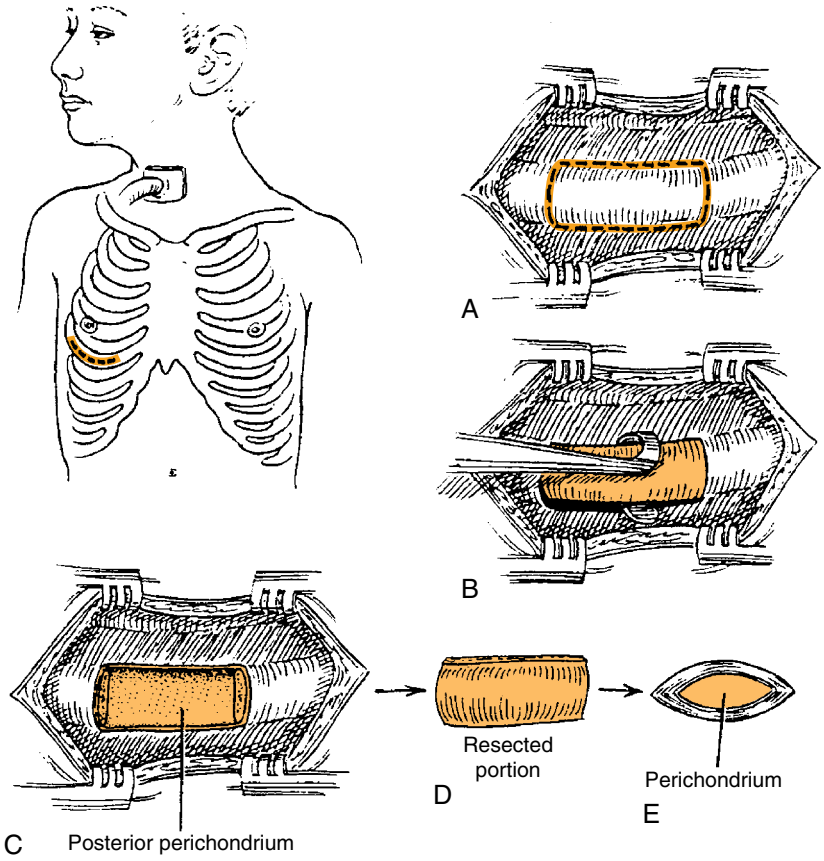

Figure 206-8. Donor site of a costal cartilage graft used for anterior augmentation of stenotic cricotracheal area. **A,** Incision over the fifth costal cartilage to obtain a costal cartilage graft. **B,** Perichondrial incisions are made along the inferior and superior borders of the rib, with care taken not to injure underlying cartilage. **C,** Dissection in the subperichondrial plane is accomplished so that the pericardium on the posterior part of the rib remains in situ on the chest wall of the patient. **D,** A 4-cm length of costal cartilage is removed and placed in physiologic saline solution. Lining perichondrium remains only on the anterior aspect of the graft. **E,** Costal cartilage graft is shaped into an ellipse and beveled to prevent the graft from settling into the lumen.

the neck and adequate anesthesia. The lower face, neck, and chest are scrubbed and draped. A 3-cm horizontal skin incision is made just inferior to the right mammary gland and is deepened to include the subcutaneous tissue and muscle. Costal cartilage is identified (Fig. 206-8), and the longest straight segment is removed with overlying lateral perichondrium, leaving the medial perichondrium in situ. The cartilage is fashioned to fit the intended site of transplantation. If the stenosis is anterior, cartilage is trimmed to a modified boat shape (see Fig. 206-8).[82] Flanges at the edges of the cartilage graft prevent prolapse into the lumen and allow maximum use of the width of the graft for distraction of the cricoid and upper trachea (Fig. 206-9). The regular boat-shaped graft is used for distraction of posteriorly cut cricoid segments in the management of posterior glottic and subglottic stenosis.[83] Indications for use of a cartilage graft in the posterior glottis and subglottis are: (1) posterior glottic or subglottic stenosis; (2) isolated subglottic shelves; and (3) circumferential SGS, when the posterior cricoid lamina has been divided. Despite suturing, creation of flanges, or both, the graft is not stable enough to remain in place and stenting is needed for several days.

A large series of posterior cartilage grafting with animal study documentation of survival of posteriorly placed cartilage grafts has been reported.[84] In cases of severe SGS, anterior and posterior grafts have yielded success rates greater than 90% after a single procedure within a short time after removal of the stent.[85,86]

Stents

Stents are used to counteract scar contractures and promote a scaffold for epithelium to cover the lumen of the airway. Stents also hold the reconstructed area in place and prevent mechanical disruption secondary to movement of the laryngotracheal complex during breathing, swallowing, and attempts at phonation. Stenting is necessary when using grafts to expand stenosed areas of the airway. Grafts provide rigidity and support and fill gaps in the incised and distracted segments to avoid the formation of fibrous tissue with subsequent contraction. If the grafts are dislodged, failure to correct the stenosis will follow.

When choosing stents, the physician should focus on the material, size, location, and duration of stenting. Many types of stents have been used and each has its own application. T-tubes continue to be used successfully in children and adults, special care is needed to avoid tube blockage.[87] Repair of laryngotracheal stenosis in almost all cases, except the anterior subglottis, requires brief stenting to keep the grafts in place and lend support to reconstructed areas. Long-term stenting is occasionally indicated.

Single-Stage Laryngotracheal Reconstruction

Single-stage laryngotracheal reconstruction (SSLTR) implies the use of cartilage grafts to obtain stability of the reconstructed airway and compress the prolonged stenting period of traditional LTR methods into a briefer period of endotracheal intubation. SSLTR may include an anterior cartilage graft, a posterior cartilage graft, or both, and often includes a cartilage graft of the former stoma site. The grafts are supported temporarily by a full-length endotracheal tube fixed in position through the nasal route. The optimal time for intubation has not been established definitively. In general, approximately 2 to 4 days of intubation are necessary for anterior cartilage grafts alone, and about 7 days are recommended if a posterior graft is used as well. A tendency exists to decrease the time of intubation with increasing age through childhood. SSLTR demands comprehensive knowledge of the principles of LTR

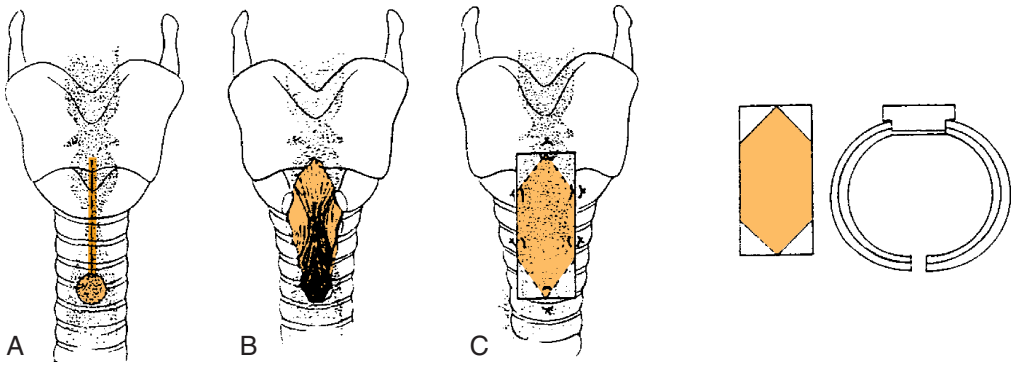

Figure 206-9. Anterior cartilage graft. **A,** Vertical incision is made into the thyroid cartilage from a point immediately below the anterior commissure through the upper tracheal rings, with care taken to remain in the midline. **B,** Intraluminal scar and lining mucosa are incised along the length of the stenotic segment. **C,** Costal cartilage is shaped into a modified boat (*inset*) and placed in position with the lining of the perichondrium facing internally.

and significant experience in the techniques. In addition, the otolaryngologist must have complete confidence in the nursing, anesthesia, and intensive care resources available at his or her institution.

SSLTR is indicated primarily in SGS without significant obstructions in the trachea or significant tracheomalacia. SSLTR may include all variations of the cricoid cartilage division and, in most cases, these divisions are stabilized by the use of a cartilage graft.

The concept of SSLTR is appealing because of the advantage of immediate decannulation or even the avoidance of tracheotomy altogether in a child who does not have a tracheotomy in place. Long-term stenting with its potential complications is also unnecessary. These advantages must be weighed against the potential for airway complications in the perioperative period, possible replacement of the tracheotomy, and complications that may arise during the intensive care required by these patients intubated for a prolonged period of time.

Certainly one requirement of SSLTR is meticulous management of the patient's condition in the ICU postoperatively. The nasotracheal airway must be maintained securely during the time of stenting without accidental extubation. Toddlers are prone to self-extubation unless carefully managed and sedated as appropriate. Older children and adults often can tolerate endotracheal intubation without any sedation.[88] Some centers use titration sedation to prevent agitation and accidental self-extubation, avoiding pharmacologic paralysis. One argument for using paralysis is that even if the patient is not accidentally extubated, motion of a nasotracheal tube in a surgical site results in poor healing. Although many variables determine success in the expansion of SGS, including preoperative grade, PR, underlying medical conditions, airway, and surgical technique, it has not been possible to quantify this particular effect. Further argument against the use of heavy sedation is the withdrawal symptoms that many children experience after cessation of the sedation drugs. The argument against pharmacologic paralysis is the necessity for immediate reintubation, should accidental extubation occur, and that postoperative pulmonary morbidity is high. These children develop migratory atelectasis, often with exacerbation of reactive airway disease or pulmonary infiltrates despite intensive pulmonary toilet, bronchodilator therapy, broad-spectrum antibiotics, and chest physiotherapy. The success of SSLTR is dependent on not only the surgical technique but also on intensive careful postoperative management.

Most surgeons exclude patients with notable craniofacial or vertebral anomalies from SSLTR to avoid a potentially difficult emergent reintubation.

SSLTR remains an excellent treatment modality for the repair of SGS in infants. It is reported that infants weighing more than 4 kg and those with a gestational age greater than 30 weeks have a greater chance for successful extubation and eventual airway patency. It appears that infants weighing fewer than 4 kg have more complications surrounding extubation. This may be because of the other underlying disease states often present in these neonates.

Cricoid Resection with Thyrotracheal Anastomosis

Surgical resection of the anterior arch of the cricoid cartilage, together with a portion of the posterior cricoid lamina below the cricothyroid articulation with thyrotracheal anastomosis, was first suggested in 1953[89] and resurgence of this procedure in adults[90-93] encouraged use in children. Several authors report good results.[60,88,109] In children with isolated tracheal stenosis, repair with resection and end-to-end anastomosis yields excellent results.[94] When the stenosis involves the subglottis, the resection becomes technically difficult, but excellent results have been reported by several authors.[67,95-100] The procedure is applicable to the few patients in grades III and IV SGS. Arytenoid prolapse has been described as a complication in children[101] but not in adults.[102] Several reports favor CTR over LTR for grade 4 stenosis.[68,69] The current recommended strategy is to perform partial cricotracheal resection (PCTR) as a primary or salvage procedure in patients with grades III and grade IV stenosis.[102] Risk factors for failure are presence of unilateral or bilateral vocal cord paralysis.[103] Cricotracheal resection has been reported in children weighing less than 10 kg with excellent results.[104] No deleterious effects on laryngeal growth or function have been observed in humans.[105] In cases where the margins for resection are close to the vocal cords especially posteriorly, PCTR with grafting is indicated. It is very important not to resect a significant portion of the posterior cricoid plate, since animal studies have shown airway impairment in such cases. Vertical posterior cricoid laminotomy is safe.[106] The partial cricotracheal resection procedure has eliminated the need for four-quadrant cricoid division which still is an excellent procedure with good results in some cases.[107]

With the patient under general anesthesia through the tracheotomy, the larynx and upper airway are dissected and identified. The dissection is performed on the cricoid in a subperichondrial plane to avoid injury to the recurrent laryngeal nerve. The superior resection line starts at the inferior border of the thyroid cartilage and passes obliquely posteroinferiorly to cross the lower margin of the cricoid plate below the level of the cricothyroid joints (Fig. 206-10). The distal resection line is made immediately below the inferior border of the stenosis. To compensate for the disparity in the diameters between the tracheal and subglottic lumen, the superior cut of the tracheal lumen is beveled, and the membranous trachea may need to be plicated. Primary thyrotracheal anastomosis is accomplished by advancement of the distal segment superanteriorly to the residual posterior shell of the cricoid cartilage and suturing a tongue of mucosa from the posterior trachea to the remaining laryngeal mucosa. Cartilage sutures are then placed at the anastomosis, which should be kept free of tension. This is best accomplished by suprahyoid laryngeal mobilization and tension-relieving sutures in the cartilage. After surgery, extension of the neck is to be avoided for 10 days by placing three sutures from the chin to the upper chest area. Stenting is generally used either with an endotracheal tube (single-stage technique), a T-tube, or a suprastomal stent.

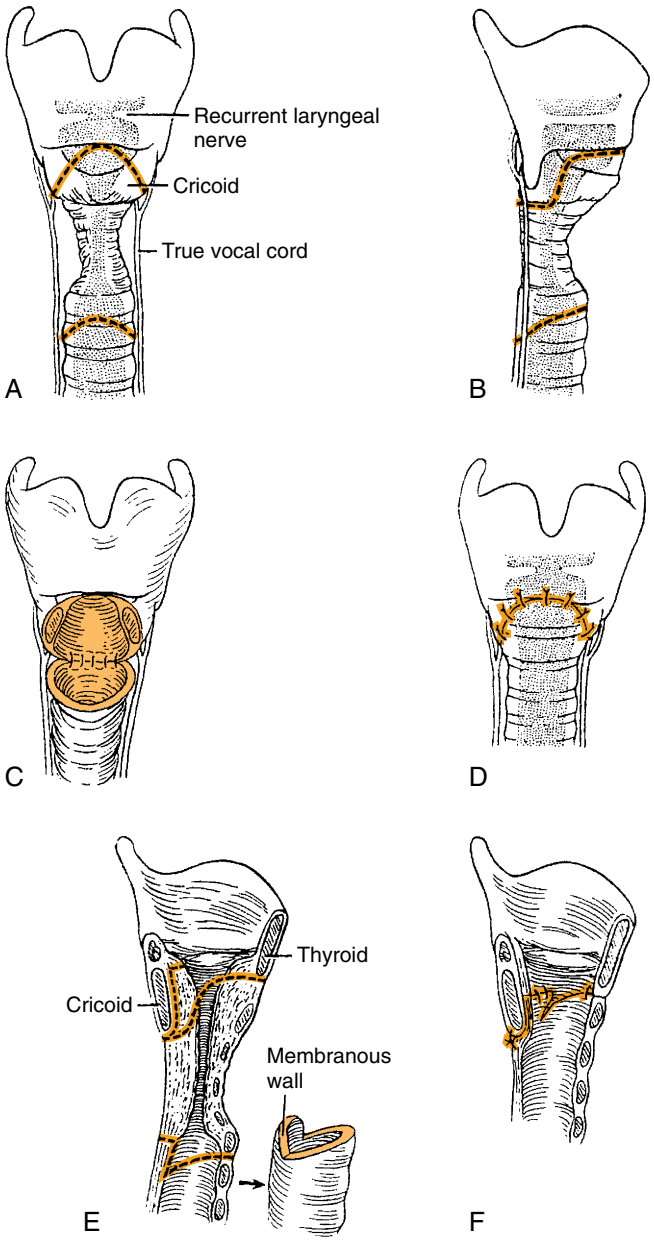

Figure 206-10. Partial cricoid resection with thyrotracheal anastomosis. **A,** Anterior view of the stenotic area to be resected, including the anterior cricoid lamina. **B,** Lateral view of the same area. Note the preservation of the posterior cricoid lamina and the location of the recurrent laryngeal nerve. **C,** After resection. The trachea is beveled and approximated to the subglottis. **D,** Suturing is completed (3-0 polyglactin 910). **E,** If a posterior subglottic thick scar is present, it is resected with preservation of the posterior cricoid cartilage, and a mucosal flap is developed from the posterior tracheal wall. **F,** Suturing of the mucosal flap is performed, and coverage of raw areas is achieved.

Management of Specific Disorders

Congenital

Atresia and Webs

The immediate management of laryngeal atresia is by establishing an airway at birth through an emergency tracheotomy. Rarely, it may be possible to pass a small bronchoscope through an incomplete atresia into the trachea, followed by a tracheotomy. It is extremely difficult to insert a large-bore needle into the highly mobile trachea of infants, and a neck incision with tracheotomy is the preferable method of establishing an emergency airway. Occasionally, tracheal agenesis coexists. After adequate airway is maintained, the elective surgical correction of laryngeal atresia generally restores respiratory function, but the phonatory and protective functions may remain significantly impaired after surgery.

Treatment of laryngeal webs depends on the thickness of the web.[3] A thin web may be broken down by passage of the bronchoscope or incised with a surgical knife, scissors, or the CO_2 laser. An attempt should be made to incise the web along one vocal cord, followed 2 weeks later by incision along the opposite side (to prevent further web formation). However, the smaller the larynx, the more difficult this is to achieve.

The less common thick glottic webs are more difficult to manage, and may be difficult or impossible to incise or dilate because of the associated subglottic-cricoid abnormality.

Tracheotomy may be required to establish the airway. Surgical excision of the glottic web and cartilaginous abnormality via a laryngofissure approach, followed by stenting and placement of an anterior autogenous costal cartilage graft, can be performed in a single or double stage.[108,109] The optimum age for surgery is unknown, and the possibility of aggravating the situation with an ill-judged operation should be considered. However, infants with severe obstruction above the tracheotomy are at greater risk of dying of cannula obstruction because of their decreased reserve airway above the tracheotomy. In such cases, earlier reconstruction should be considered. Endoscopic placement of a keel in children is difficult, and the external approach is recommended for best results.

Anterior Glottic Stenosis

Small anterior webs less than 2- to 3-mm wide produce minimal or no symptoms, and surgery is usually unnecessary. Thin anterior webs can be managed by microendoscopic incision of the web with a microsurgical knife or CO_2 laser. A keel may be placed endoscopically[110]; however, if this technique fails or if longer, thick anterior glottic scars are present, an external approach is needed. Tracheotomy is performed, followed by laryngofissure and incision of the stenotic area or web with the surgical knife. Resection of scar tissue should be minimized because this creates further mucosal loss. The umbrella keel gives reliable results and should be inserted for 2 weeks. The keel prevents restenosis in the anterior commissure during reepithelialization. If the keel is used for 2 weeks or fewer, granulation tissue formation is minimal. The design of the keel is such that contact with the posterior glottis is avoided, thus minimizing scarring secondary to the keel itself.

Stenosis and Vocal Cord Paralysis

Vocal cord paralysis can accompany anterior, posterior, or complete glottic stenosis. Bilateral vocal cord paralysis, associated with acquired glottic stenosis, needs a partial arytenoidectomy with lateralization of the true cord in addition to the operation discussed earlier in this chapter for correction of glottic stenosis. This is generally required unilaterally and occasionally bilaterally. Arytenoidectomy is reliably performed through the anterior thyrotomy approach. If done as a separate and later operation, an endoscopic laser arytenoidectomy is a valid alternative.[111] Arytenoid separation has been reported to be helpful.[112]

Posterior Glottic Stenosis

Management of posterior glottic stenosis varies with the degree of pathologic findings.[113] A simple interarytenoid adhesion requires a different approach from scarring involving both cricoarytenoid joints (see Fig. 206-4). It is a major challenge because the voice is generally excellent. Children with Down syndrome have a higher rate of posterior glottic stenosis than the general population.[114] Endoscopic division of the adhesion is sufficient if a mucosally lined sinus tract is present posteriorly. This is easily accomplished with a microsurgical knife while the posterior surface of the mucosally lined sinus is protected by insert-

ing a microsuction tip. In the absence of a mucosally lined sinus tract, simple endoscopic incision of the scar results in restenosis. Partial laryngofissure, however, is the most common approach for such cases and is required for more advanced cases with cricoarytenoid joint fixation. Endoscopic posterior cricoid split with grafting is another approach for repair.[115]

In children with severe posterior glottic scarring with cricoarytenoid joint fixation or subglottic extension, a division of the posterior cricoid lamina in the midline with insertion of a free autogenous costal cartilage graft (see Fig. 206-7) is recommended.[83,116] Complete glottic stenosis is difficult to manage, and voice results are usually poor because of severe scarring involving the vocal cords. Also, it may be associated with a decrease in the anteroposterior diameter of the larynx secondary to external trauma. Management involves incising the scar in an anteroposterior manner, posterior cartilage grafting, and placing a stent. Cartilage grafts should not be used in the anterior commissure area.

Anterior Subglottic Stenosis

Anterior subglottic stenosis is managed by incising the scar anteriorly and placing a modified boat-shaped cartilage graft[82] (see Fig. 206-9) to keep the segments of the cricoid distracted. The perichondrium of the graft should be at the level of the mucosa. At the end of the procedure, endoscopic examination of the subglottic airway is recommended to check for possible poor placement or partial collapse of the graft. The cartilage graft can usually be extended inferiorly to cover the tracheostomy if a single stage is planned.

Endotracheal intubation after a single-stage laryngotracheoplasty can range from 2 days for simple anterior cartilage[117] grafting to 2 weeks for moderately severe stenosis repaired with anterior and posterior grafts.[118]

Postoperative Management

Postoperative management[119] is affected by whether a stent was used. In patients in whom stents were not used, antibiotics for 2 weeks after the surgery are recommended and endoscopy is indicated once the patient is ready for decannulation. When stenting has been used, long-term, low-dose antibiotics are recommended for the duration of stenting to prevent infection. Appropriate tracheotomy care is extremely important. The caregiver should be proficient and knowledgeable about routine and emergency care because the control of GER is important.

Decannulation

The tracheotomy tube is gradually downsized and eventually plugged. Children should always be under adult supervision.[120] Once a child is ready for decannulation, endoscopy should be performed to ensure the airway is clear and the factors that influence successful decannulation after surgery have been well described. Occasionally suprastomal granulomas are seen. If the child is being considered for decannulation, these granulomas should be removed; however, if the child is not ready for decannulation, removal of suprastomal granulomas is not indicated unless they are completely obstructing the airway.[121]

The presence of suprastomal collapse can prevent decannulation, and further management may be needed.[122] When the child can tolerate the tracheotomy plugging for as long as he or she is awake, the decision for decannulation is made and the child is admitted to the hospital where the tracheotomy is plugged overnight with continuous monitoring. If there is no oxygen desaturation or apnea, the tracheotomy tube is removed the following morning, the stoma is covered with an occlusive dressing, and the child is kept for an additional night, again with continuous monitoring. Tracheotomy tube fenestration is not performed. A residual tracheocutaneous fistula may need to be surgically closed.

Summary

Glottic and subglottic stenosis, although rare, are difficult to manage. Surgical goals are to produce as early as possible[123] an adequate airway, an acceptable voice, and a competent larynx to avoid aspiration. The keys to successful outcome depend on (1) accurate preoperative and intraoperative assessment; (2) correct choice of surgical procedure; (3) meticulous surgery directed at the site of the lesion; and (4) close postoperative care and monitoring.

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CHAPTER TWO HUNDRED AND SEVEN

Diagnosis and Management of Tracheal Anomalies and Tracheal Stenosis

Greg R. Licameli

Mark A. Richardson

Key Points

- The management and diagnosis of tracheomalacia and tracheal stenosis is complex and has evolved over the last two decades as experience grows with this condition.
- This chapter addresses tracheomalacia, congenital tracheal stenosis, and the management of tracheal stenosis with various surgical techniques.

The diagnosis and surgical management of tracheal stenosis, whether acquired or congenital, remains a challenge. In infants and children, tracheal stenosis has a high morbidity and mortality, particularly for those with severe disease, and is often associated with other congenital anomalies that require concomitant repair. Over the past 2 decades, certain principles of management have been developed that have improved patient outcomes. The evaluation and development of a logical management plan for these complex cases often requires the involvement of multiple medical specialties.

Embryology

The trachea develops as an evagination of foregut mesenchyme in the fourth week of gestation. This gradually expands caudally to form the developing lungs and joins together posteriorly to form the common membranous wall of the esophagus and trachea. Initially, this evagination has an extensive communication with the ventrocaudal part of the pharynx. From this primordial outgrowth, the trachea extends caudad ventral to and roughly parallel with the esophagus. Only the epithelial lining and the glands of the trachea are derived from the original entodermal outgrowth from the pharynx. The cartilage, connective tissue, and muscle of its wall are formed by mesenchymal cells that migrate to become massed around the growing entodermal tube. Usually by the ninth week, developing cartilaginous rings can be identified.

Tracheomalacia

Tracheomalacia, which is the absence or deformity of the tracheal cartilage, can present with inspiratory and expiratory stridor, wheezing (which may be mistaken for asthma), chronic cough, and recurrent respiratory infections. It may be subdivided into two categories: primary tracheomalacia, which is an intrinsic deformity of the tracheal cartilage in the absence of any other pathology, and secondary tracheomalacia, which is due to extrinsic compression, most commonly related to cardiac or vascular anomalies, as well as tracheoesophageal fistula.[1,2]

The symptoms of primary tracheomalacia tend to improve as the child's tracheobronchial tree grows in caliber, and surgical intervention is often not required. This condition occurs in both premature and mature infants. In contrast, the causes of secondary tracheomalacia usually require surgical correction to remove the cause of the compression and subsequently to assess the residual tracheal wall integrity.

Vascular Anomalies—Vascular Rings

Vascular rings are the result of abnormal development of the aortic arch complex. The most common complete vascular ring is a double aortic arch, in which the ascending aorta bifurcates to encase both the trachea and esophagus as it joins the descending aorta. Symptoms begin early in childhood and are related to both respiration and feeding. A barium swallow study shows a posterior compression of the esophagus.

A second but less common vascular ring arises from the persistence of the right aortic arch, with a left ligamentum arteriosum usually associated with a retroesophageal left subclavian artery, or less commonly, mirror branching of the right and left subclavian and common carotid arteries, and may present with similar symptoms as a double aortic arch.[3]

Surgical division of the ring immediately improves symptoms related to swallowing; however, symptoms related to the associated tracheal deformity may take some time to resolve as the patient grows.

Vascular Anomalies—Arterial Compression

The most common cause of vascular compression of the trachea is from an anomalous innominate artery compression. A more distal origin of the innominate artery from the aorta causes compression of the right anterior trachea that endoscopically demonstrates a triangular-shaped

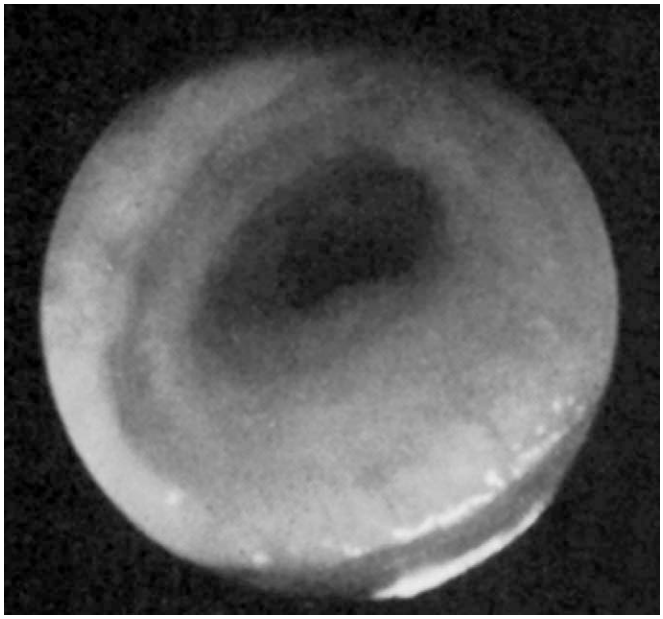

Figure 207-1. Long-segment tracheal stenosis (complete rings).

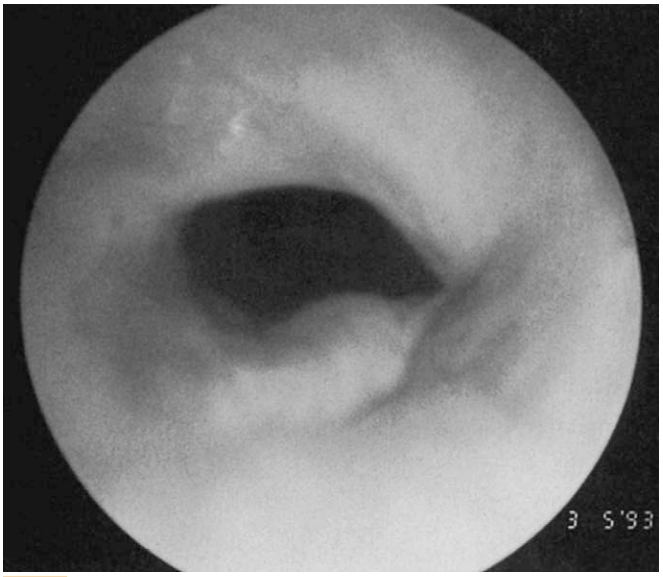

Figure 207-2. Short-segment tracheal stenosis.

deformity. Lifting the tip of the bronchoscope against the artery diminishes the right brachial pulse. Chest radiographs show anterior tracheal compression but no esophageal deformity.[3] Often these patients present with inspiratory or biphasic stridor, cough, recurrent respiratory infections and reflex apnea, with the latter often referred to as "dying spells."[4]

Pulmonary artery anomalies can also cause tracheal compression. In this situation, the aberrant left pulmonary artery arises on the right and passes between the esophagus and trachea, causing compression of the trachea and right bronchus, which is seen on endoscopy. Division of the artery with reanastomosis improves symptoms of stridor and wheezing.[5]

Other tracheal pathologies (e.g., congenital tracheal enlargement, cysts, abnormal tracheal bifurcation) are also in the differential diagnosis for congenital anomalies of the tracheobronchial tree.

Tracheoesophageal Fistula

Tracheoesophageal fistula is a common congenital abnormality, presenting at birth with respiratory distress, excessive mucus, feeding difficulties, and aspiration. It is often associated with tracheomalacia.[6] Five types have been described, with the most common abnormality occurring with the proximal esophagus ending in a blind pouch and the lower esophagus connected to the trachea via a fistula. The majority of cases are diagnosed by the inability to pass a catheter orally into the stomach.[7] Severe aspiration can occur with the use of radiologic contrast studies; therefore its use is controversial. Endoscopic examination is critical in the evaluation and planning of surgical intervention.[8] One half of all patients have congenital anomalies of other organ systems, including cardiac, genitourinary, and gastrointestinal abnormalities. A small percentage of patients have an intact esophageal lumen with a small connection to the trachea, known as an *H-type fistula*. These patients are usually less dramatically affected and diagnosis may be defied for months. Careful investigation with both contrast radiography and endoscopy is required to identify the small connection from the upper posterior trachea to the esophagus.[9]

Diagnosis

The severity of tracheal stenosis usually determines the age of presentation, which can be quite variable, ranging from days to weeks or even months. A long-segment stenosis with a markedly limited tracheal diameter would ordinarily present in early infancy with evidence of respiratory obstruction, especially when the airway may be compromised by secretions or infection, which produce additional incremental difficulties in adequate respiration (Fig. 207-1). Shorter segments, with a more moderate degree of obstruction in terms of tracheal diameter, may appear later in infancy or early childhood when the increasing respiratory demands of growing infants outstrip the capacity of the narrow airway to provide adequate levels of air and gas exchange (Fig. 207-2).

Any child who is being considered for bronchoscopy and who has atypical asthma, inspiratory and expiratory stridor, and recurrent respiratory disease should also have a potential diagnosis of tracheal stenosis. Poor weight gain and sometimes poor feeding are also associated with tracheal stenosis. Chest radiography may be helpful but is often nondiagnostic due to the dynamic aspects of the pediatric trachea. In some cases, however, a suggestion of the stenosis can be evident on close examination of the radiograph. A minority of patients with congenital tracheal stenosis present without any associated malformations and a careful assessment of particularly the cardiac vasculature is required.[10]

Endoscopy

Endoscopic evaluation with a rigid bronchoscope is clearly the most accurate means of diagnosing tracheal stenosis and assessing its length, degree, and character. Due to the limited diameter of the trachea, however, endoscopy must be approached expertly and with full availability of the smallest equipment possible. In some cases, placement of an endotracheal tube through the larynx to the level of the stenosis may cause a loss of ventilatory capability as a result of obstruction of the tube at the site of the stenosis. Additionally, even the smallest bronchoscope (4-mm outer diameter) might not pass through the stenosis and, in some cases, placement of a rigid bronchoscope for ventilation and the use of the longer rigid telescope (2.5-mm outer diameter) or ultra-thin flexible bronchoscope (2-mm outer diameter) might be the only means of visualization of the length of the stenosis and identification of any distal abnormalities in the tracheobronchial tree.

Endoscopic evaluation of the airway performed with rigid instrumentation and with the patient under general anesthesia is, however, accompanied by the greatest risk and requires skill in performing anesthesia, expert endoscopic skills, and a full complement of pediatric endoscopic instruments and photographic documentation capability. Minor trauma to the mucosa could precipitate an obstructive event. Once the patient has been given general anesthesia, additional anesthesia can be administered by applying lidocaine topically to the tracheal mucosa. Ideally the patient can maintain spontaneous ventilation, so that the adequacy of neuromuscular movement in the larynx can be assessed. It is generally wise to use the telescope as an initial form of evaluation without the accompanying bronchoscope for tracheoscopy to determine whether there is a significant stenosis and to identify its

approximate location and the nature of the tracheal rings (i.e., whether they are complete or incomplete). In some cases, even the smallest 2.5-mm pediatric bronchoscope (4-mm outer diameter) will not pass through the stricture, and again, the bronchoscopic telescope might be the only instrument able to pass through the stenosis to visualize the carina and distal bronchi. The patient must be hyperventilated for such an examination to be possible, but in so doing the length of the trachea affected can be gauged and a potential surgical procedure designed.

The length of the stenotic segment should always be estimated during the course of endoscopy as well as the degree of involvement of the trachea and the main bronchi, and is frequently underestimated. The determination whether a tracheal stenosis is congenital or acquired is an important one. Commonly, the congenital stenotic tracheal segment is associated with a somewhat longer trachea than the native and normal trachea of newborns. Congenital problems are often associated with other abnormalities of vascular structure and genetic defects. Acquired stenoses are accompanied by irregular scarring, perichondritis, and loss of cartilaginous support, which complicate surgical resection and reanastomosis.

Radiology

Computed tomography (CT) and magnetic resonance imaging (MRI) provide accurate evaluations of the airway, with MR images having a slight edge in depicting finer detail and the actual nature of the stenosis. There is an inherent risk for infants and children, who may require sedation or general anesthesia before examination.

Because some cases of congenital tracheal stenosis are often associated with a vascular ring or pulmonary artery sling, some means of determining whether there are abnormalities in the great vessels of the heart should be performed. Echocardiography or MRI might be satisfactory in some cases, although arteriography or heart catheterization may be necessary to fully identify or rule out the possibility of aberrant vasculature.

If additional information must be obtained, contrast bronchography can be performed with a thin solution of contrast material to outline the tracheal dimensions and bronchial branchings. This contrast material must be thinned because the secretions themselves and inflammation—which is sometimes stimulated by the contrast—can cause significant problems in ventilation for the patient. Despite the inherent danger in contrast bronchography, it does provide a measurable evaluation of long-segment tracheal stenosis and any accompanying bronchial abnormalities, which are often seen in congenital stenoses. There is increasing evidence that bronchography and angiography is being supplanted by spiral CT with multiplanar reconstruction and MRI.[11]

Advances in CT/MRI have allowed for fine detail three-dimensional reconstructions to provide a virtual endoscopy of the airway. It is limited by not being able to provide a dynamic assessment of either tracheomalacia or bronchomalacia, may not provide enough resolution to define subtle anatomic abnormalities, and can underestimate the degree and extent of the narrowing.[12] It has the advantages of being able to evaluate the airway distal to a stenosis that cannot be traversed by bronchoscopy and can be used in the measurement of the airway caliber over time. It should be considered as a complementary technique to formal rigid or flexible endoscopy in selected patients.[13]

Associated Anomalies

Congenital tracheal stenosis is often associated with other developmental anomalies. Cardiovascular anomalies are the most common, occurring in up to one half of cases, and include patent ductus arteriosus, ventricular septal defects, left pulmonary artery sling, aberrant subclavian artery, and double aortic arch.[10] Anomalies of the bronchopulmonary, gastrointestinal, renal, or skeletal systems should also be sought. Several authors believe that the simultaneous repair of both tracheal and cardiac defects provides better postoperative management and long-term outcomes.[14,15]

Louksnov and colleagues thought that a key element to achieving a 97% survival rate in 37 patients who underwent surgical repair was the use of cardiopulmonary bypass, which allowed them extensive mobilization of the tracheobronchial tree and a tension-free anastomosis,[14] as well as better exposure of the operative field.[16]

Table 207-1

Cantrell and Guild Structural Classification

Type 1	Generalized hypoplasia of the entire trachea
Type 2	Funnel stenosis—normal proximal trachea with distal narrowing to carina
Type 3	Segmental stenosis with up to three rings involved

Data from Cantrell JR, Guild H. Congenital stenosis of the trachea. *Am J Surg.* 1964;108:297-305.

Table 207-2

Anton-Pacheco Functional Classification

Type: Mild	None or occasional symptoms
Type: Moderate	Respiratory symptoms without respiratory compromise
Type: Severe	Respiratory compromise
Subtype A	No other associated malformations
Subtype B	Associated malformations

Data from Anton-Pacheco J, et al. Patterns of management of congenital tracheal stenosis. *J Pediatr Surg.* 2003;38:1452-1458.

Classification

Congenital tracheal stenosis was originally classified based on anatomic morphologies as described by Cantrell and Guild,[17] and was augmented by the development of a clinical symptom classification by Anton-Pacheco.[11] These complementary approaches allow better correlation of anatomic findings with patient symptoms, important for surgical planning and outcome (Tables 207-1 and 207-2).

Surgery

Surgery for tracheal stenosis can be categorized generally in the following ways: (1) conservative management; (2) endoscopic, using laser or dilation; (3) resection and reanastomosis, including slide tracheoplasty; or (4) augmentative procedures using cartilage, perichondrium, or vascularized tissue.

Conservative Management

The role of conservative or nonsurgical management of congenital tracheal stenosis has recently been better defined. Historically, patients were treated conservatively because of poor surgical outcomes. There is increasing evidence that a carefully selected group of patients with congenital tracheal stenosis will resolve their difficulties with growth of the airway. This is largely due to the fact that tracheal airflow is proportional to the fourth power of the radius of the trachea. Patients with mild stenosis and occasional symptoms can be managed with respiratory physiotherapy, antibiotics in case of infection, supplemental oxygen, and close observation.[11,18] Rutter and colleagues described seven patients with complete tracheal rings who did not require surgical intervention.[19]

Cheng and colleagues reported their experience with 22 consecutive patients, 11 who underwent surgery and 11 who were followed nonsurgically. Initial diagnosis was made with bronchoscopy and supported by radiologic and clinical findings. The patients who were observed later (1.5 vs 0.4 years), were less symptomatic, had less severe tracheal narrowing (58% vs 30% of normal tracheal diameter), and had a lower mortality than the surgical group. Six of the 11 patients in the

observation group underwent serial CT measurements of the tracheal diameter. These data showed that five of six patients experienced an increased rate of tracheal growth compared with normal pediatric tracheal growth until approximately 7.5 years of age, when it then grew at a normal rate. The researchers suggested conservative management if the stenosis was not long segment and if the most stenotic segment was less than 60% of the normal trachea.[18]

Surgical management broadly involves two modalities: endoscopic tracheoplasty and open tracheal reconstruction. Endoscopic options include tracheal dilation, intraluminal stent placement, and laser ablation. Biopsies can be performed if there is suspicion of systemic disease such as amyloidosis or sarcoidosis. Open tracheal reconstruction can include the use of autologous, homologous, or inert stenting material to enlarge the airway diameter or to remove stenotic segments. The morbidity of an endoscopic approach is less than that of an open procedure but often involves repeated surgery. Selection of a therapeutic approach depends on the type of airway anomaly and can involve a variety of endoscopic modalities either alone or combined with an open approach to the trachea.

Dilation

Dilation of strictures has traditionally been performed with Jackson or Maloney rigid dilators. This method involves serial dilation with progressively larger-diameter bougies but has a tendency to shear tissue, which may create more scarring and further stricture formation.[20] In comparison, balloon tracheoplasty imparts only radial forces to the lesion and is less traumatic to the surrounding tissues. Balloon devices range from catheters developed for percutaneous transluminal angioplasty to specially designed balloons that fit over the tip of a rigid bronchoscope. Balloon-tipped catheters are connected to an inline pressure gauge and a water-filled syringe that delivers a steady, constant dilation. Serial dilation is performed with increasingly larger balloons. Balloon-tipped catheters can also be placed under radiologic guidance to confirm placement (Fig. 207-3).[21]

A 15-year experience of balloon tracheoplasty in 37 patients was reported by Hebra and associates.[20] Short-term improvement for both congenital and acquired lesions was seen in 90% of patients, with long-term improvement in 54%. Complications were infrequent and included tracheitis, atelectasis, and pneumomediastinum. This method appears to be most useful in the management of soft granulation tissue or to aid in delaying open reconstruction in premature or medically unstable infants.

Messino and colleagues[22] and Bag and associates[23] have described aggressive balloon dilation of complete tracheal rings with endotracheal stenting in children younger than 2 years of age. The posterior wall of a complete ring is the weakest point, as demonstrated by their postmortem studies, and allows disruption of the trachea with subsequent fibrotic healing. This method should be reserved for critically ill patients because complications can be life threatening.

Laser Therapy

Laser therapy is often combined with dilation procedures in the endoscopic management of tracheal strictures or obstructing masses. Use of the laser allows precise tissue ablation with less trauma to the surrounding tissue compared with cryosurgery and electrocautery.[24] Early reports described the use of the carbon dioxide laser with a bronchoscopic coupler and a rigid bronchoscope to manage tracheal lesions.[25] With the development of improved optics and laser micromanipulators mounted directly to the microscope, visualization and precision have improved. Lesions most amenable to this technique are soft granulation and short segments of mature fibrosis. Simpson and others[24] and Ossoff and associates[26,27] listed the following factors as contributing to laser therapy failure: circumferential scarring, fibrosis greater than 1 cm in vertical length, tracheomalacia, and severe bacterial infection in the presence of a tracheostomy.

A method using radial incisions and dilation with a rigid bronchoscope for moderate to severe subglottic and tracheal stenosis was described by Shapshay and coworkers.[28] Success was attributed to the preservation of islands of epithelium between the radial incisions. Results were good at 1-year follow-up (Fig. 207-4). Mucosal preservation was also advocated by Dedo and Sooy,[29] who described the use of the carbon dioxide laser in the elevation of mucosal flaps. An incision is made into the superior surface of the scar, creating a trapdoor flap, and the underlying fibrous tissue is ablated with the laser with replacement of the mucosal flap (Fig. 207-5). Success with these techniques appears to be dependent on reepithelialization before scar formation, avoidance of extensive tissue damage, preservation of mucosa, and careful patient selection.

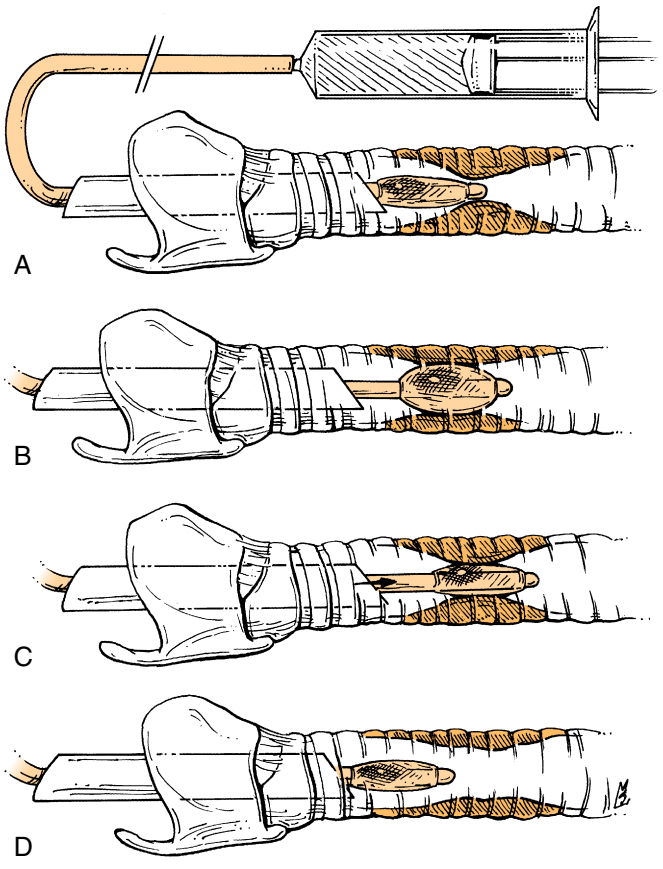

Figure 207-3. Pneumatic dilation of short-segment, acquired stenosis. Balloon insertion **(A)** and inflation **(B)**, reduction of stenosis **(C)**, and balloon deflation and removal **(D)**.

Intralesional and systemic corticosteroids have been suggested by some authors to aid in the prevention of scar formation and stenosis at the site of mucosal injury. However, corticosteroids may reduce epithelial migration, increase scar formation, or weaken existing cartilaginous support.[30] Other adjunctive measures include the use of antibiotics and antireflux medications. Mitomycin C is an antitumor antibiotic that inhibits fibroblastic proliferation and has been used in airway reconstruction to help prevent scar formation, with varied success.[31-33]

The combination of endoscopic laser division of tracheal stenosis or complete tracheal rings with balloon dilatation has been successfully reported.[34-36] Advantages purported by Andrew and associates include the ability to perform this technique with spontaneous respiration in a patient with a suboptimal airway, and the avoidance of endotracheal intubation after the procedure, which could incite further stenosis.[36]

Stents

Stents are important in the management of tracheal stenosis and can be used in either endoscopic or open approaches. Montgomery[37] first described the use of a polymeric silicone (Silastic T tube; Boston Medical Products) in 1965. This type of stent allows ventilation, support for soft tissue grafts and cartilage, and tracheal lumen suctioning. This tube is used in conjunction with a tracheostomy and is placed under endoscopic guidance. Maniglia[38] reported on the use of the T-tube stent in 53 adult patients with tracheal stenosis, subglottic stenosis, or both, with good results in 85%. Problems associated with

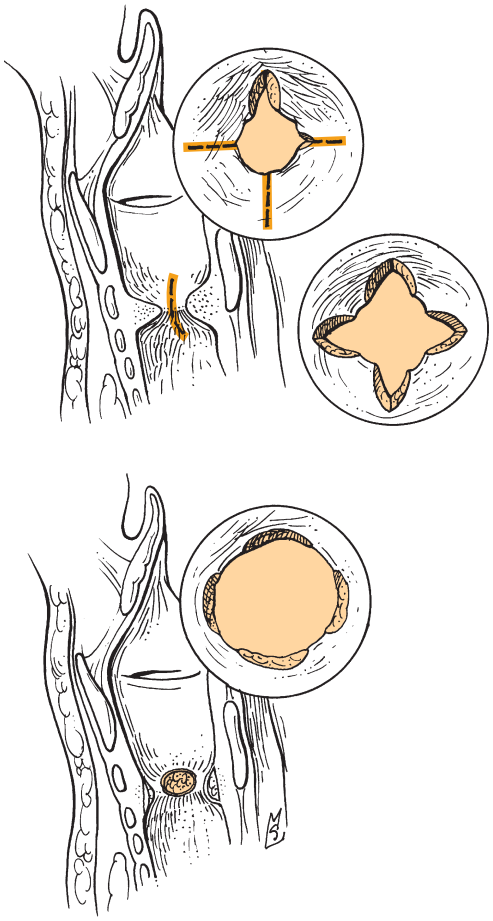

Figure 207-4. Star-shaped laser incision and dilation (Shapshay).

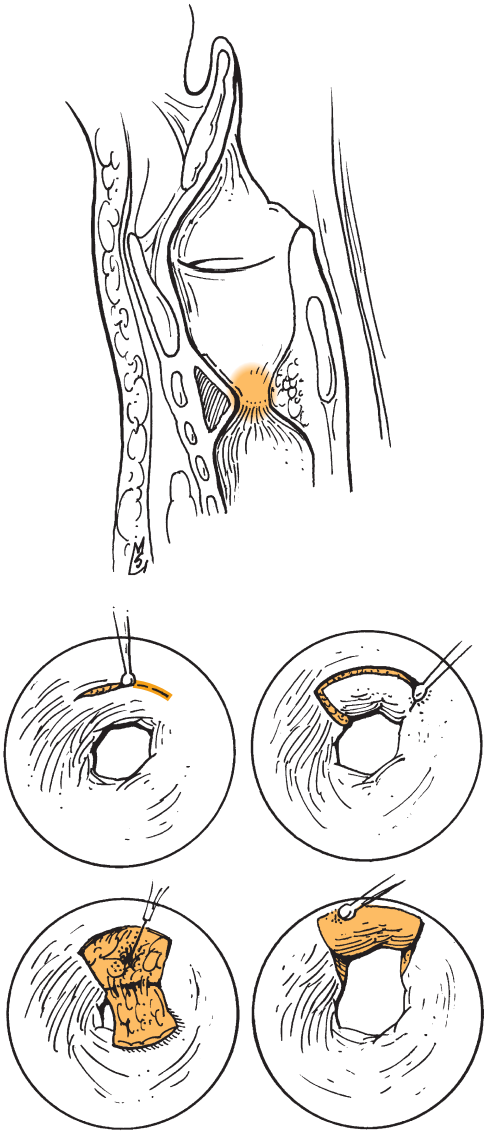

Figure 207-5. Laser trapdoor flap.

stents include obstruction, granulation tissue formation, infection, and malposition. Phillips reported use of this tube in 10 children with complex airway stenosis, the majority requiring stenting due to difficulties with severe granulation and stenosis of the subglottis after laryngotracheal reconstruction. This author and others emphasized the need for meticulous postoperative care to prevent luminal obstruction with secretions.[39]

The use of solid stents in children is limited. One version is the Dumon stent, modified from the Montgomery T-tube stent. It is a cylindrical solid silicone stent with external studs to hold it in place. Its main advantage is ease of removal, but its use in children has been limited because wall thickness itself can cause luminal obstruction in relatively small-caliber airways. Migration and occlusion from secretions, due to impairment of mucociliary clearance, are more problematic than expandable stents.

Experience with indwelling expandable stents in children has been limited, and initially these devices were used primarily in adults with advanced tracheobronchial malignancies.[40] Materials currently in use include self-expanding woven polymers and stainless steel wire, which are placed bronchoscopically. Mair and colleagues[41] demonstrated faster mucosalization and improved tracheal patency with polymer stents versus stainless steel stents both in a piglet model and in children. Bugmann and associates[42] reported on the successful use of an expandable Z-shaped wire stent in a 6-month-old patient with severe tracheomalacia. No complications were reported at 2-year follow-up. In adults, Nashef and colleagues,[43] among others,[23] found that the most common complication of stent placement was the formation of granulation tissue. Concerns raised by the authors regarding their use in children include the uncertainty of long-term tolerance of these stents, mucosal hypersecretion, and the risk of perforation and migration (Fig. 207-6).

Over the past decade, experience with expandable metal stents has increased. Filler and colleagues[44] reported on 16 children who required 30 balloon expandable metallic stents (Palmaz) over a 5-year period. All patients had improvement of their respiratory status, and three died of underlying cardiac disease. Obstruction in these patients was due to tracheomalacia, bronchomalacia, prior surgery, or vascular compression. Vinograd outlined his experience with metallic stents in 32 pediatric patients retrospectively reviewed. Initial stent insertion was uncomplicated, but the degree to which the stent needed to be expanded within the airway was much more difficult to gauge. Underexpansion could potentially cause stent displacement and overexpansion could cause mucosal injury and excessive granulation tissue formation. Although most patients had immediate relief of their airway obstruction, repeated endoscopies for removal of granulation tissue was required in 20 patients, and excessive granulation tissue occurred in another six patients who subsequently required stent removal. The authors also raised the question of the optimal period of time to leave the stent in place. Periodic expansion of the stent with patient growth needs to be balanced with the unknown effects on tracheal growth. In addition, stent removal was considered difficult with the potential development of life-threatening airway obstruction during extraction.[45]

A potential advantage to this type of stent is the ability to reexpand the stent as the child grows to accommodate a larger airway caliber.

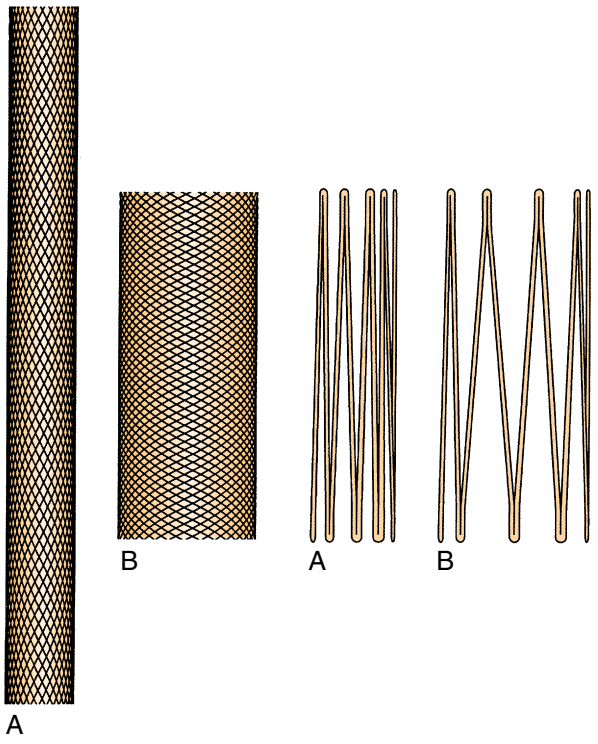

Figure 207-6. Polymer and wire stents in unexpanded **(A)** and expanded **(B)** forms.

Another advantage is that the stent is balloon expandable and can be removed more easily than a self-expanding stent such as the Gianturco stent, which is primarily used in adults. Furthermore, the wire mesh design preserves mucociliary clearance and hinders migration of the stent, unlike solid silicone stents.

The most common complication with the Palmaz stent was development of obstructing granulation tissue that necessitated early removal of the stent in three patients in the Filler[22] series. Because of the inability to remove the stent in a patient who underwent laser resection of stent granulation tissue, the authors advocate balloon compression or endoscopic scraping to address this problem. Furman and colleagues[46] reported on six patients requiring 12 Palmaz stents over a 3-year period with similar results and believed that stenting should be used in patients for whom conventional therapy had failed.

In a group of five infants ranging in age from 7 days to 12 months, Maeda and colleagues[47] reported on their success in treating congenital tracheal stenosis with stenting over a 3-year period. At follow-up bronchoscopy, the stents were found to be covered with respiratory mucosa. Granulation tissue developed at the site of the stent in all children, and one child died of intractable pneumonia related to recurrent granulation tissue.

A multicenter review by Jacobs and colleagues discussed the use of stenting in 33 children and highlighted the need to adapt the various stents available to the patient and their particular pathology, as evidenced by their use of custom carinal stents fashioned from cardiopulmonary bypass venous cannulas. They emphasized the need for accurate diagnosis before the surgical treatment of any extrinsic and intrinsic airway obstruction. In this series, stents were used as a primary modality to stabilize the airway or to support reconstruction after a variety of reconstructive procedures, with complications similar to earlier published reports.[48]

Experience with Nitinol stents in two children with tracheal stenosis was favorable.[49] Nitinol stents are formed from the metal alloy of nickel and titanium and are less reactive in the airway than stainless steel stents, potentially avoiding difficulties with granulation tissue formation. Another property of this alloy is its ability to reduce in size with temperature cooling, potentially facilitating its removal from the airway. Another promising area is the use of extraluminal microplates to support tracheal expansion[50] and the use of stainless steel wire to act as a scaffolding for pericardial patch tracheoplasty.[51]

In summary, stents can be useful as a primary modality for treatment, allowing time for very small children or children in unstable condition to grow and tolerate more complex open repairs if necessary. They can also be used in the postoperative period to support the repair or to salvage the airway in the case of stenosis. Experience in this area continues to grow in this small group of complex patients.

Open Repair

Acquired stenoses are often further complicated by scarring, poor vascular supply, and chronic infection. Tracheal resection and reanastomosis have been widely used in hundreds of adult patients for tracheal stenosis since the 1960s; however, Halsband[52] found only 26 reports of these procedures in children between 1969 and 1984. In general, surgical therapy should be pursued when conservative or nonsurgical therapy fails or is deemed inappropriate. A variety of techniques are available for the surgical management of tracheal stenosis, including tracheoplasty with autologous material, wedge resection, slide tracheoplasty, total resection with end-to-end anastomosis, tracheal homograft reconstruction, and stenting with bioinert materials. Often, multiple techniques must be used.

Tracheoplasty can be performed with rib cartilage as described by Kimura and others.[53] Cartilage is a rigid autologous tissue that derives its nutritional support through diffusion and can survive without a direct vascular supply. Because of this, cartilage has been widely used as a tracheal graft material. The surgical technique involves securing the airway either by a previously placed tracheostomy or by endotracheal intubation, which is performed orally and then converted to a transtracheal site once the trachea is exposed. The area of stenosis is exposed anteriorly and the extent of the stenosis is outlined bronchoscopically, either by palpation with the bronchoscope or using the light of the telescope. The external appearance of the trachea can underestimate the extent of the stenosis.[54] Intraluminal granulation tissue is removed and the scar is incised. A rib graft is harvested (usually a fifth or sixth rib on the right is used) and fashioned as described previously. Perichondrium is preserved on the anterior surface of the rib graft and becomes the luminal surface of the airway. The graft is held in place by interrupted suture material and, depending on the extent of the stenosis, is supported with an endotracheal tube for 5 to 7 days (Fig. 207-7). For longer-term stenting, an Aboulker or T-tube stent can be used. The decision of whether to use cardiopulmonary bypass, extracorporeal membrane oxygenation, or distal tracheal intubation during the procedure is controversial and depends on the site of the lesion and the surgeon's personal preference. Pericardium is the most commonly used alternative to rib augmentation and also has good long-term survival rates (Fig. 207-8).[55-58] Other autologous materials that can be used include periosteum,[59] pedicled muscle flaps,[60,61] composite grafts,[62] the esophagus,[63,64] omentum,[65] and solvent-preserved dura.[66]

Kimura and others[53] were the first to report successful repair of a 1-year-old with complete stenosis of the trachea using costal cartilage. Their experience was updated with an additional four patients in 1988.[67] Long-term survival was 80%, with one death due to respiratory distress 10 months after repair. Complications related to this procedure include anastomotic breakdown, stenosis, and granulation tissue formation at the suture line. Jaquiss and colleagues,[54] among others,[68] described six patients who underwent rib tracheoplasty (mean age, 14 weeks) with an average stenosis of 70% of the total length of the trachea. All patients had survived at a follow-up of 6 months to 7.6 years. Bronchoscopy was performed three times or fewer postoperatively in all but one patient. These authors advocated cardiopulmonary bypass to obtain an unobstructed view of the airway during repair. Lobe and others[66] reported on seven infants with congenital tracheal stenosis, four of whom underwent repair with costal cartilage.[69] One death caused by pneumonia occurred 5 weeks postoperatively.

The experience with costal cartilage tracheoplasty continues to grow. Forsen and colleagues[70] reported on 10 patients with congenital long-segment tracheal stenosis repaired at an average age of 18 weeks with costal cartilage tracheoplasty. They were followed up for an

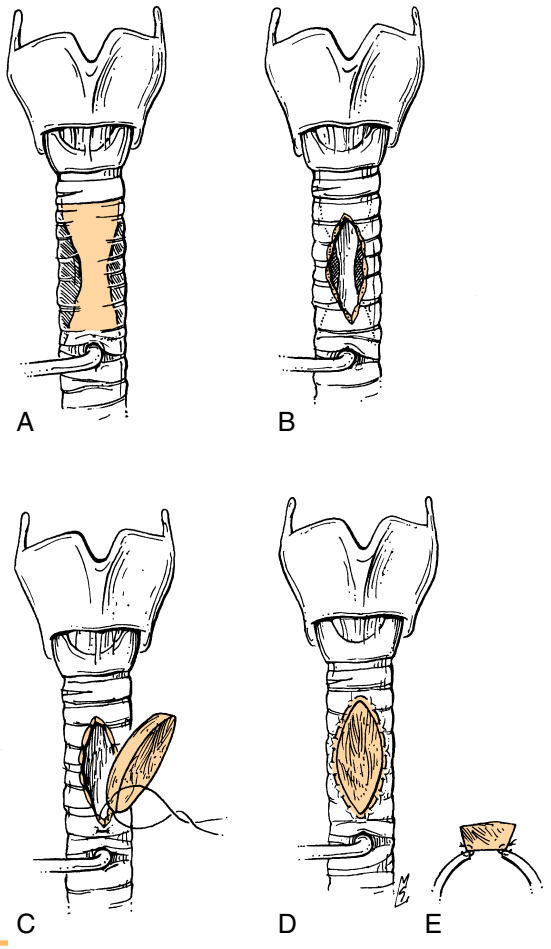

Figure 207-7. Cartilage graft placement for augmentation of tracheal stenosis. **A**, Area of stenosis. **B**, Stenosis excised. **C** and **D**, Placement of graft. **E**, Surgical result. Note the graft placement in lumen **E**.

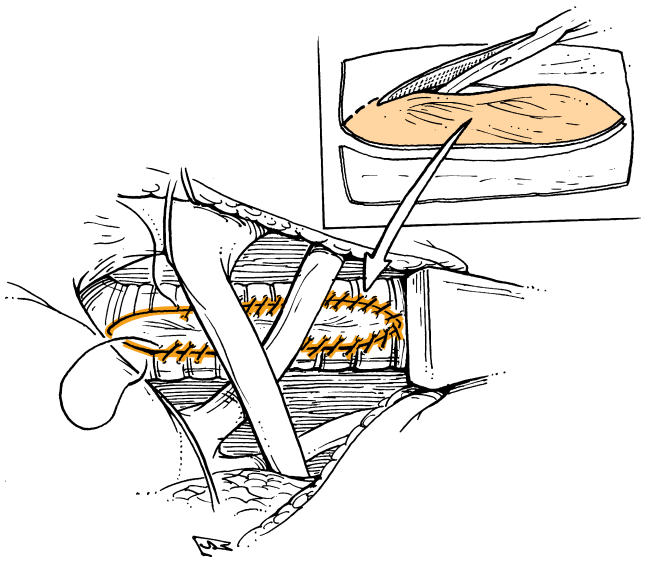

Figure 207-8. Pericardial patch sewn in position.

average of 8 years, and 70% of patients were active without tracheostomy. Kamata and colleagues[71] detailed their experience with 11 infants who underwent tracheobronchial reconstruction with costal cartilage grafts. Similar to other studies, frequent postoperative bronchoscopies were needed, and the use of extracorporeal membrane oxygenation

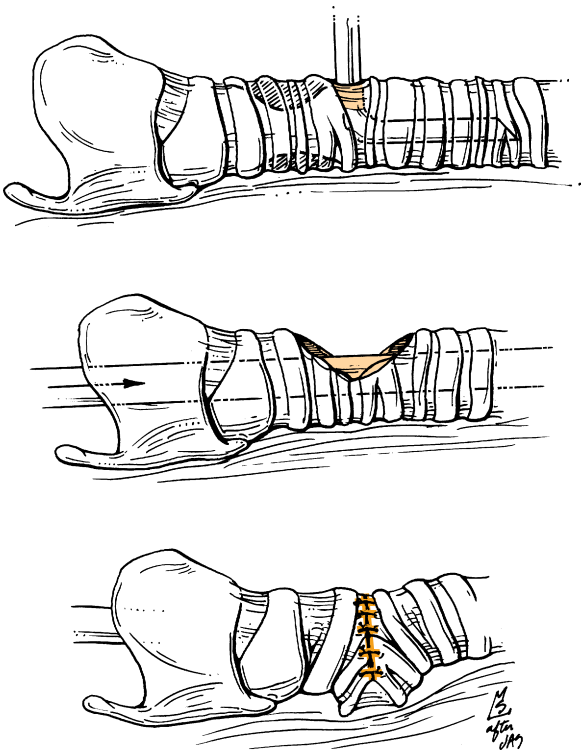

Figure 207-9. Wedge section and closure.

(ECMO) facilitated repair. A common finding in all these series was a high incidence of associated cardiovascular and pulmonary anomalies.

Troublesome to repair is the formation of granulation tissue at the graft site. One advantage of rib graft in contrast to pericardial grafts is that the endotracheal tube does not need to be beyond the proximal edge of the graft for stenting purposes and subsequently decreases granulation tissue formation.[54] DeLorimier and others[72] have suggested that the formation of granulation tissue is more likely if the graft involves 30% or more of the luminal surface. Epithelialization of costal cartilage grafts in the trachea has been demonstrated in both animals and humans.[73] Grillo and colleagues[74] have stated that the use of absorbable (polyglycolic acid polymer) versus nonabsorbable suture material reduces the amount of granulation seen at the anastomotic site.

The technique of wedge resection is most useful for a localized stenosis involving one or two tracheal rings. This method may be useful in small infants in whom the recurrent laryngeal nerve can be difficult to identify. After oral intubation, the lesion is defined and an anterior wedge of trachea is removed. The defect is closed primarily with interrupted sutures. Weber and colleagues[75] used this procedure successfully in four patients with localized stenosis (Fig. 207-9).

Segmental resection is successful for repair of long-segment tracheal stenosis comprising less than 50% of the tracheal length. In children, this operation uses the principles of tracheal repair that were developed for adults.[76] Following endoscopy to outline the extent of the lesion, the stenotic segment is excised. Dissection beyond the stenosis is kept to a minimum to preserve the vascular supply to the trachea. Sutures are placed submucosally and tied extraluminally. Important to the success of the repair is the ability to achieve a tension-free anastomotic suture line. Various techniques can be applied, including suprahyoid release, infrahyoid release, peritracheal mobilization, intercartilaginous incisions, perihilar release, dissection of the pulmonary vasculature, transplantation of the left mainstem bronchus, and neck flexion with chin-to-chest suturing (Fig. 207-10).[77-79]

The results of several authors have been encouraging.[75,78,80,81] Nakayama and others[82] reported on 10 patients, four of whom underwent tracheal resection. They emphasized the association of multiple tracheobronchial and vascular anomalies in these patients and the need for a detailed preoperative evaluation. Healy[69] reported on three chil-

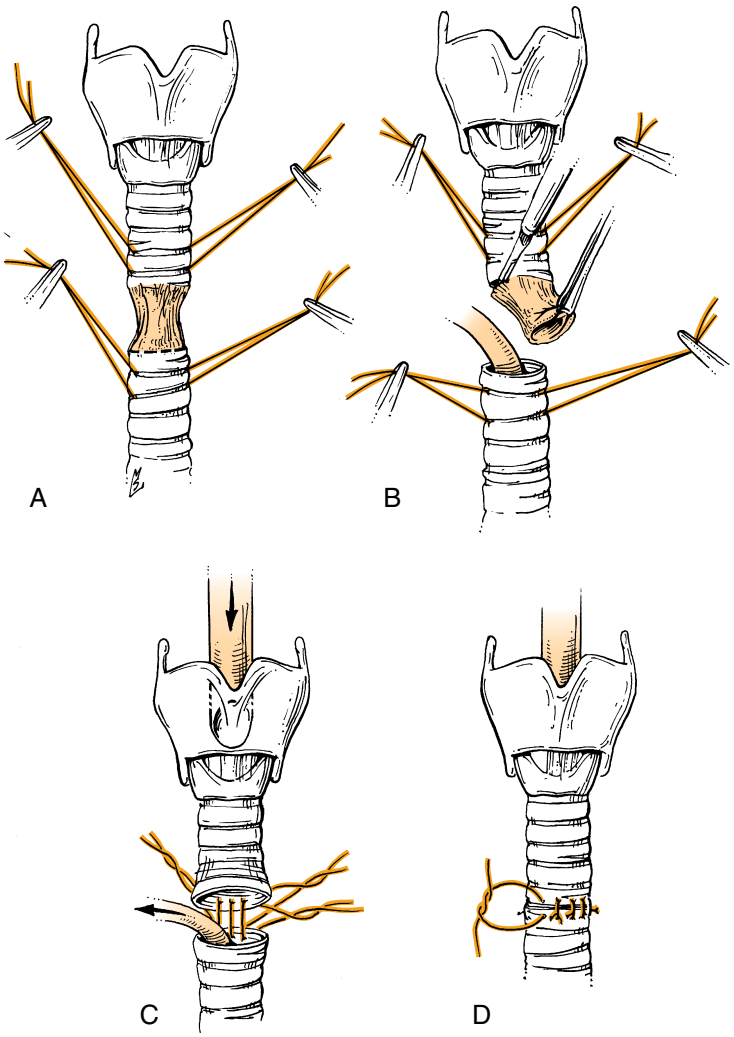

Figure 207-10. **A**, Area of stenosis. **B**, Resection of stenosis with intubation of trachea distally. **C**, Interrupted absorbable sutures placed circumferentially and reintubated from above **(D)**.

dren, ages 4 weeks to 3 years, who were successfully resected. The author thought that three to five tracheal rings could be resected in children without a laryngeal release. He also commented that postoperative endotracheal intubation can often be avoided in adults, but in children the cartilage is still very pliable and may not offer sufficient resistance to tracheal collapse at the anastomotic site. Two patients who required postoperative nasotracheal intubation were not mechanically ventilated but were allowed to breathe spontaneously in an intensive care unit setting and were successfully extubated several days later. DeLorimier and others[72] detailed their experience with 45 patients with tracheobronchial stenoses. Seventeen patients underwent segmental resection, with three anastomotic strictures developing postoperatively. These strictures were resected with success in two patients. In their series of 52 patients ranging in age from 7 weeks to 15 years, Grillo and Zannini[83] undertook segmental resection in 20. Good results were obtained in 17 patients. The remaining 32 patients were treated conservatively, with 24 requiring either a T tube or tracheotomy. In their series of 21 patients with congenital tracheal stenosis, Benjamin and colleagues[84] also treated 12 patients without surgery. This experience lends support to the individualized treatment options and the nonsurgical management of selected patients.

Segmental resection is often not possible due to the length of trachea to be resected. First described by Tsang and others,[85] slide tracheoplasty involves dividing the stenosis transversely in the midportion and then incising the upper segment vertically posteriorly and the lower segment vertically anteriorly. The two ends are then placed over each other, effectively halving the stenotic segment while doubling the circumference. The distance that the tracheal ends need to move is half that of a resection and primary reanastomosis. This fact aids in reducing tension along the suture line, which may be more critical in children than in adults.[51] Grillo[86] described two children (ages 3 months and 3 years) and two young adults, all of whom had complete cartilaginous rings. The stenotic areas were 36% and 50% of the total tracheal length for each group, respectively. Short-term results were deemed good. An advantage to this technique is decreased granulation tissue that is often seen at the site of the cartilage graft reconstruction. Other advantages to this procedure are the avoidance of graft materials, decreased tracheal mobilization, and a good success rate (Fig. 207-11).

Cotter and colleagues[87] reported on 17 patients with congenital tracheal stenosis who underwent tracheoplasty over a 10-year period; 11 underwent augmentation with pericardial grafts or costal cartilage. Five of six patients who had resection and reanastomosis did well for 2 to 9 years after surgery, seven of eight patients with tracheoplasty did well for 2 to 4 years after surgery. This study found that the former group had fewer postoperative bronchoscopies and fewer difficulties with the development of granulation tissue at the suture line. Important in the management of these patients was frequent postoperative bronchoscopy, and the use of cardiopulmonary bypass for some made the operation technically easier. No complications were related to the use of cardiopulmonary bypass. The authors advised segmental resection, when possible, with early extubation to reduce mucosal injury.

Recent reports favor the use of slide tracheoplasty over augmentation with cartilage or pericardial patch grafts for long-segment tracheal

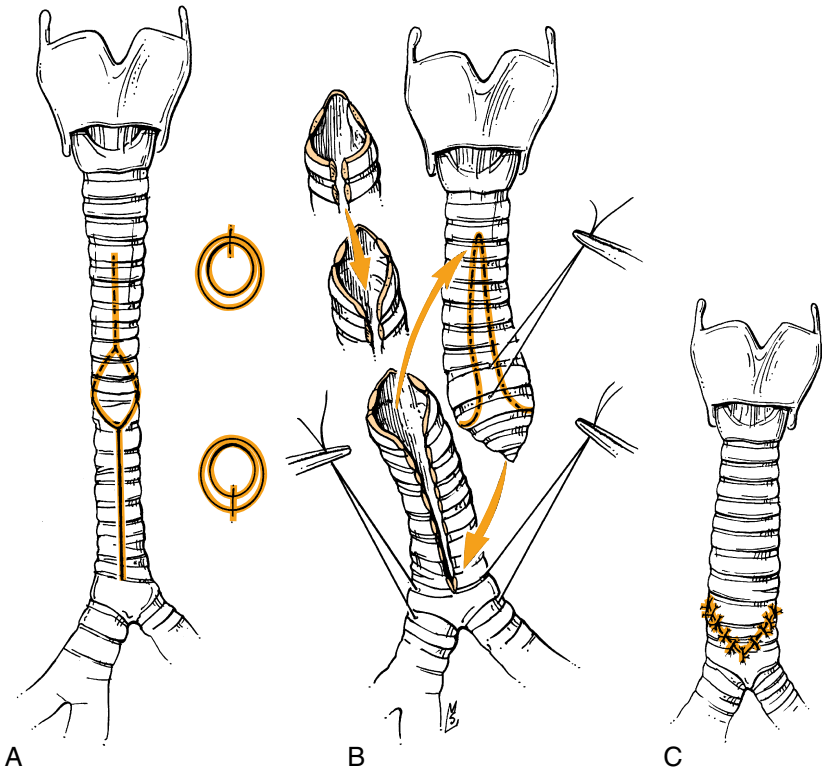

Figure 207-11. Slide tracheoplasty. **A**, Area of stenosis. **B**, The trachea is divided on an angle and then vertically anteriorly and posteriorly. **C**, Surgical result.

stenosis. According to Grillo and colleagues,[88] "Patch tracheoplasty met a previously urgent need but should perhaps be largely reserved for unusual problems." In all juvenile patients, the repaired tracheal segment continues to grow, with complications related to suture line granulomas (two of seven slide tracheoplasty patients) that resolve with a single bronchoscopy without recurrence. Others have reported similar experience with long-term growth of the reconstructed airway and few complications.[88-92]

In the series by Acosta,[93] six patients were treated with resection and reanastomosis and three with slide tracheoplasty. The latter group had favorable outcomes with regard to anastomosis complications such as leaks, mediastinitis, fibrosis, or stenosis. Kim compared eight patients between 12 days and 6 months with congenital tracheal stenosis, four who underwent slide tracheoplasty, three had pericardial patch, and one had resection and end-to-end reanastomosis. Bothersome granulation tissue formation was seen in the pericardial patch subset. Tsugawa compared 17 pediatric patients who underwent slide tracheoplasty with 12 pediatric patients who underwent costal cartilage tracheoplasty and concluded that slide tracheoplasty was the preferred method[94] with similar findings in a group of 10 patients described by Matute.[95] These findings have prompted these authors to recommend slide tracheoplasty as the procedure of choice.

Tracheal homograft transplantation with cadaveric human tracheal homograft is an exciting new modality for the repair of severe long-segment tracheal stenosis in children. Initially described in 1980 in adult patients,[96] 24 children were recently reported by Jacobs and others.[97] An 83% survival rate was achieved, with follow-up ranging from 5 months to 10 years. Tracheal homograft banks exist in Europe, and specimens are fixed in formalin, washed in thimerosal (sodium ethylmercurithiosalicylate), and stored in acetone. The trachea is exposed through a neck incision, a median sternotomy, or both. Cardiopulmonary bypass is used to facilitate the operative field. The anterior part of the trachea is removed, leaving only a posterior tracheal wall intact. Dumon stents are then sutured into the native trachea to provide support for the homograft for 10 to 12 weeks until the graft hardens and reepithelialization occurs. The endotracheal tube is positioned to lie within the lumen of the Dumon stent. The homograft is fashioned to the defect and sutured in place with interrupted sutures (Fig. 207-12).

Postoperative care includes 2 weeks of intravenous antibiotics followed by 4 weeks of oral trimethoprim as well as inhaled albuterol and corticosteroids. No immunosuppression is needed because the thimerosal used in the preparation of the homograft destroys antigenicity. Frequent bronchoscopy is required to remove granulation tissue at the site of the stents.

Advantages to the tracheal homograft include an adequate supply of tissue, which can be placed without suture-line tension, and the presence of a carina, which is needed for distal reconstruction. Ciliated columnar epithelium has been shown to coat the homograft. Tracheal homograft reconstruction is an exciting new approach to severe or recurrent tracheal stenosis.

In 1999, Jacobs and colleagues[98] updated the worldwide experience with tracheal autografts in 31 children. Twenty-one of these patients underwent previous surgical attempts at airway reconstruction, and results were encouraging for both the short and medium terms. Mortality overall was 16%; however, three of the five patients who died had functional airways. Twenty-six patients survived, with 22 patients deemed asymptomatic on follow-up bronchoscopy that showed epithelialization of the grafts. Continued follow-up of these patients is planned in an established database.

Backer and colleagues[99] described six patients with tracheal stenosis resulting from complete tracheal rings that were constructed with partial tracheal resection, posterior end-to-end anastomosis, and anterior repair with the patients' own resected trachea. In four patients, the anterior repair was augmented with pericardial patch. The use of a free tracheal autograft was based on the senior author's observation that the trachea in children with complete tracheal rings was usually longer than average. This technique is more appealing than performing tracheal homografts because the autograft is lined with respiratory epithelium, will not reject from its donor, and has the potential to grow. Intermediate-term results were reported with an additional four patients added to the study in 2000.[100] Nine of ten children were reported on 2 to 44 months postoperatively. One child had dehiscence of the autograft requiring repair within the aortic homograft, and two patients were

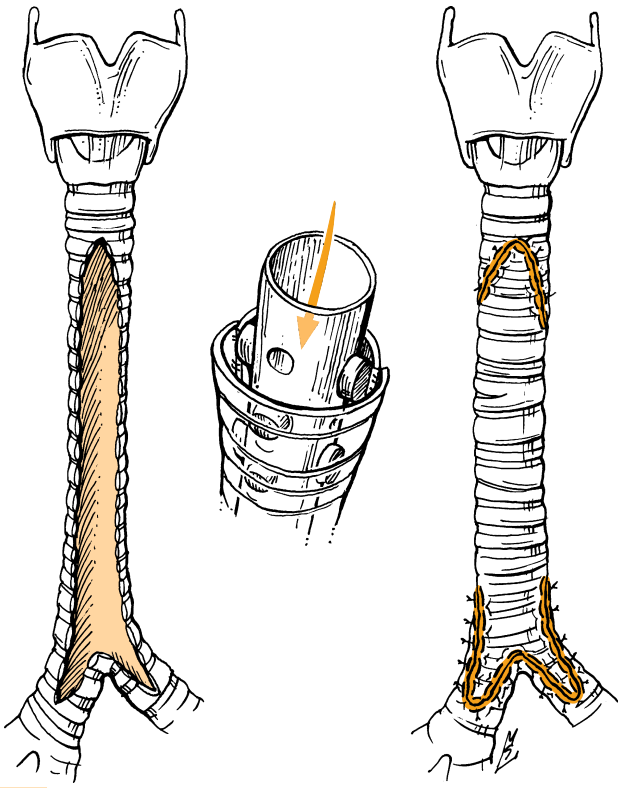

Figure 207-12. Homograft transplant with a Dumon stent.

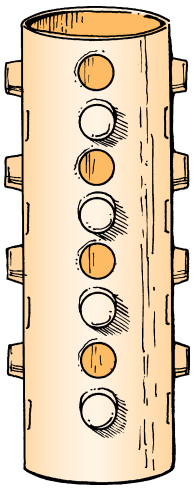

Figure 207-13. Silastic Dumon stent.

trachea dependent. One child died of sepsis and multisystem organ failure, and subsequent autopsy showed that the autograft was well healed. Autografts on serial bronchoscopy appeared to grow with the patient and are difficult to distinguish from the surrounding trachea.

Synthetic tracheal prostheses have not enjoyed the same success as prosthetic devices used elsewhere in the head and neck because the trachea is much more susceptible to infection. Synthetic devices that have been used include ceramic rings, Marlex mesh, and silicone stents.[101] These are complicated by dense granulation tissue reaction, migration of the prosthesis, recurrent stenosis, and the risk of vascular erosion (Fig. 207-13).

Fortunately, over the last few years, several papers have been published looking at these multiple surgical techniques. In a study by Anton-Pacheco and colleagues involving 19 patients from 3 days to 7 years, 14 underwent surgery over a 13-year period. For symptomatic cases with short segment stenosis, defined as less than 30% of total tracheal length, tracheal resection with anastomosis was preferred, and in long-segment stenosis (greater than 70%), slide tracheoplasty was recommended.[102] Backer reviewed a single institution's experience with four surgical techniques over 18 years involving 50 patients. Current management included resection/anastomosis for short stenosis (up to eight rings), and for long-segment stenosis, a tracheal autograft technique later supplanted by the pericardial tracheoplasty procedure in use until 1996.[103] Chui performed a retrospective analysis of 68 patients treated at six centers to determine prognostic factors that influence mortality after repair with either cartilage patch or slide tracheoplasty. No difference was seen between the two techniques, but a higher mortality was seen in two groups of patients: those younger than 1 month of age and those with intracardiac anomalies.[104] These findings were also corroborated by Herrera in 2007 in an excellent review of the literature. In reviewing the literature over a 42-year period, the researcher concluded that short segment stenosis was best treated with resection and long-segment stenosis was best treated with tracheoplasty, with cardiopulmonary bypass as part of the standard of care for these operations.[105]

Complications related to open surgical resection have been addressed by several authors.[52,67,74,106] The most common complication of tracheal reconstruction is the formation of granulation tissue at the anastomotic site or around the stent. This problem is usually managed with bronchoscopic-guided laser removal and with intravenous or intralesional injection of corticosteroid. Anastomotic leak or separation is often caused by excessive tension at the site of resection. Several techniques have been described to lessen the tension, including the supralaryngeal-, tracheal-, and hilar-releasing maneuvers mentioned earlier. Recurrent laryngeal nerve injury is rare and is usually managed conservatively if it is unilateral. Aspiration can also complicate recurrent laryngeal nerve injury and may be seen after thyrohyoid or suprahyoid release.

Complications can be avoided by ensuring several factors before surgery.[107] Ideally, the surgical resection candidate should not be mechanically ventilated, should not be taking steroids, and should not have prior radiotherapy to the area. Muscle flaps between the esophagus and trachea can reduce the incidence of fistula formation. Glottic competence should be evaluated, especially in neurologically compromised patients.

Conclusion

Evaluation and management of tracheal stenosis is a complex undertaking, as evidenced by the numerous methods available for reconstruction. In general, limited tracheal stenoses can be managed endoscopically, whereas longer stenoses are better corrected through an open approach. The trend over the last decade is for segmental resection and reanastomosis for short-segment stenosis and use of slide tracheoplasty or augmentation of long-segment stenosis. The experience with both tracheal homografts and autografts continues to grow. No one surgical method is appropriate for every setting, and often the surgeon must use several therapeutic options. Furthermore, the surgeon must recognize the limitations and complications of each of the various management options to ensure a successful outcome.

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For complete list of references log onto www.expertconsult.com.

CHAPTER TWO HUNDRED AND EIGHT

Foreign Bodies of the Airway and Esophagus

Lauren D. Holinger

Sheri A. Poznanovic

Key Points

- The highest incidence occurs in children 1 to 3 years old.
- Most airway foreign bodies are located in the bronchi.
- Most esophageal foreign body impactions occur in the cervical esophagus, just below the cricopharyngeus muscle.
- An aerodigestive tract foreign body frequently mimics other conditions and is often the result of an unwitnessed episode; the diagnosis must be considered in any patient with prolonged or unusual pulmonary symptoms.
- Complete airway obstruction resulting from a foreign body and esophageal impaction with a battery are emergencies. Delayed diagnosis may lead to complications.
- Esophageal foreign body impaction is frequently associated with vomiting and dysphagia, but may also manifest with respiratory distress.
- There is a high rate of spontaneous passage of esophageal coins into the stomach.
- Negative radiographic findings do not rule out the presence of a foreign body. Generally, chest radiography is an adjunctive procedure to a thorough history and physical examination.
- Communication with the anesthesiologist regarding the anesthetic and endoscopy plan is essential before any surgical intervention.
- Endoscopic instrumentation revolutionized the field of bronchoesophagography, and reduced the mortality associated with aerodigestive tract foreign bodies.
- Careful endoscopic removal of foreign objects under direct vision is the safest management for patients with foreign bodies of the airway and esophagus.
- Stricter industry standards for toy part sizes and increased public awareness have helped to decrease fatalities from choking.

Foreign bodies in the airway, pharynx, and esophagus continue to be a diagnostic and therapeutic challenge for practicing otolaryngologists. Despite improvement in public awareness and emergency care, foreign bodies result in approximately 150 deaths per year in children secondary to asphyxiation.[1] Most deaths occur before hospital intervention.

Although the role of the otolaryngologist begins after the child is evaluated initially by emergency department or primary care physicians, otolaryngologists and primary care physicians should have a high index of suspicion for foreign body aspiration or ingestion. Because a foreign body can mimic other conditions, particularly without a witnessed event, there can be a delay in management that may lead to complications.

Before the 20th century, bronchotomy was the method of choice for airway foreign body removal. Most patients with foreign body aspiration died from the initial event, the attempt at removal, or complications thereof. Although intubation of the airway was suggested at the time of Hippocrates, Killian in 1895 was the first to use a hollow tube to evaluate the tracheobronchial airway.[2] He used this technique to remove a bone from the right main bronchus in 1897, becoming the first to perform endoscopic removal of an airway foreign body.

Endoscopic illumination was initially used in esophagoscopy and was incorporated into a bronchoscope by Jackson,[2] who revolutionized the field of bronchoesophagography with the development of instruments and techniques for foreign body removal. The principles he and his son developed[3] were paramount in reducing the mortality associated with airway foreign bodies and are still the basis of foreign body removal today.

The introduction of the rod-lens telescope in the 1970s greatly improved the visualization of bronchoscopic removal of foreign bodies. Foreign body removal has been performed with topical anesthesia and sedation. With new, safer anesthetic agents and improved anesthesia techniques and monitoring, however, general anesthesia is now routine.

Children frequently swallow objects that pass through the gastrointestinal tract without problems. This also may occur in adults. Foreign bodies occasionally become lodged in the esophagus because of the object's size or shape, narrowing of the esophageal lumen, extrinsic compression, or anatomic abnormalities.

Before the mid-1850s, the most common management for suspected esophageal foreign body impaction was to attempt to push the object into the stomach. Various instruments, including curved hooks, forceps, and even a walking cane, were used. Dupuytren was reported to pinch the neck of patients vigorously to crush a food impaction in the cervical esophagus, allowing it to pass to the stomach.[2] The first esophagoscope used in 1890 by Mackenzie was later improved by Jackson, Ingals, and Mosher. The earliest rigid esophagoscopies for foreign body extraction by Jackson and Ingals were performed on awake patients in a sitting position. Because anesthesia risks have decreased, and instrumentation for endoscopic removal of esophageal foreign bodies has improved, these procedures are now performed with the patient supine and under general endotracheal anesthesia.

Epidemiology

The incidence of airway and esophageal foreign bodies has not changed significantly, but the safety in removal has increased dramatically. Most aerodigestive foreign bodies are esophageal—85% as reported by Hsu and colleagues.[4] Most airway foreign body aspirations occur in patients younger than 15 years old. In this age group, choking-related episodes treated in the emergency department number approximately 29.9 per 100,000 population.[1] The highest incidence occurs between 1 and 3 years of age; 25% of patients are younger than 1 year.[5-9] The reasons toddlers are most susceptible are (1) they lack molars necessary for proper grinding of food; (2) they have less-controlled coordination of swallowing, and immaturity in laryngeal elevation and glottic closure; (3) there is an age-related tendency to explore the environment by placing objects in the mouth; and (4) they are often running or playing at the time of ingestion.[10] Older children and adolescents may have an anatomic abnormality[11] or a neurologic impairment.[12] Accidental aspiration or ingestion of objects tends to be twice as common in boys. Vegetable matter is seen in approximately 70% to 80% of airway foreign body ingestions; the most common are peanuts in the United States, watermelon seeds in Egypt,[13] and pumpkin seeds in Greece.[14] The percentage of aspirated and ingested metallic foreign bodies, especially safety pins, has decreased, primarily because of the widespread use of disposable diapers. Plastic pieces constitute approximately 5% to 15% of airway foreign bodies; plastic pieces tend to remain longer because they are inert and radiolucent.

The most common esophageal foreign bodies are coins (75% of cases).[5-9] Meat and vegetable matter impactions are less common in children. Round objects, trinkets, disk batteries, and sharp objects constitute less than 20% of impacted esophageal foreign bodies. The duration of impaction before endoscopic removal is less than 24 hours in most patients, more than 1 week in 6%, and of unknown duration in 10%.[6,7]

Of patients with multiple esophageal foreign body impactions, 80% have an esophageal anomaly on further evaluation.[6] Of patients with recurrent esophageal foreign bodies, 19% have esophageal anomalies that previously required surgical repair.

Location

Most airway foreign bodies become lodged in the bronchi because their size and configuration allow passage through the larynx and trachea (Fig. 208-1). Larger objects become impacted in the larynx or trachea, sometimes causing complete obstruction, which is an acute emergency. Bronchial foreign bodies are more common in the right main bronchus in adults, which is thought to be caused by the position of the carina to the left of the midline and its lesser angle of divergence from the tracheal axis.[15] Several authors report airway foreign bodies in children with equal frequency in the right and left main bronchi, with no clear explanation for this occurrence.[2,16,17]

Most esophageal foreign body impactions occur in the cervical esophagus just below the cricopharyngeus muscle (Fig. 208-2).[5,6,8] Another 4% to 5% of esophageal foreign bodies become lodged at the midesophagus or distal esophagus, often caused by extraluminal compression by the aortic arch or left main bronchus (Fig. 208-3). Esophageal foreign body impactions also can occur above an esophageal stricture.[6]

Acute Airway Obstruction

Complete airway obstruction resulting from a foreign body is an absolute emergency. Food (e.g., hot dogs, candies) and nonfood objects (e.g., toys, balloons) commonly become lodged in the larynx and trachea. Increased public awareness, availability of emergency personnel, and the widespread use of the Heimlich maneuver have greatly reduced the mortality of acute obstruction.[18] The most important factor in reducing mortality is recognition of the person in acute airway distress. Coughing and gagging indicate partial obstruction. Older children and adults may signal choking by grasping the neck.

The Committee on Accident and Poison Prevention of the American Academy of Pediatrics developed guidelines in accord with the American Red Cross and the American Heart Association for manage-

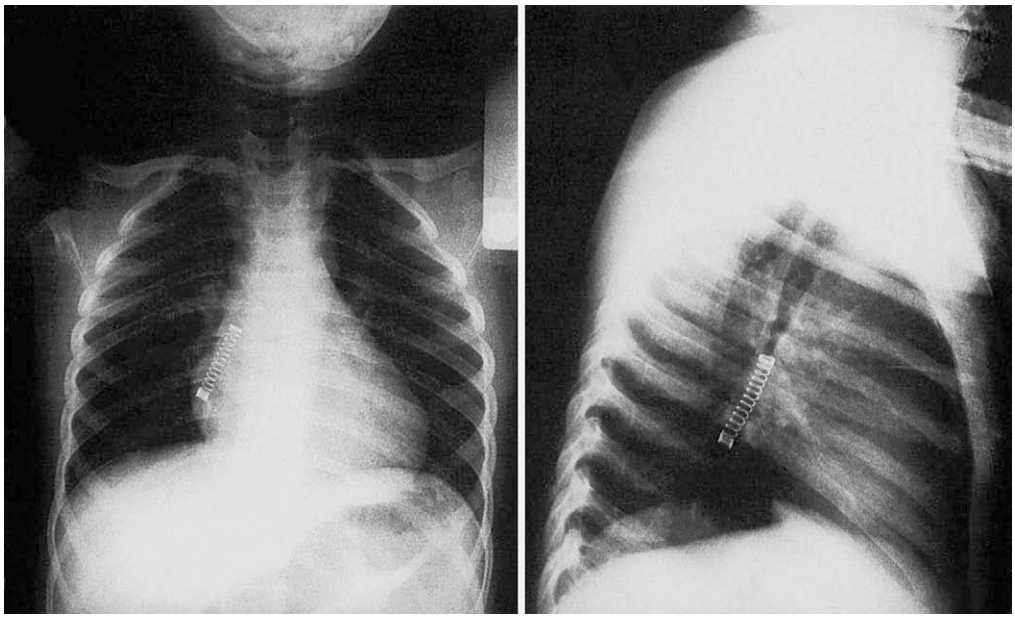

Figure 208-1. Posteroanterior and lateral views of a pen spring in right main bronchus.

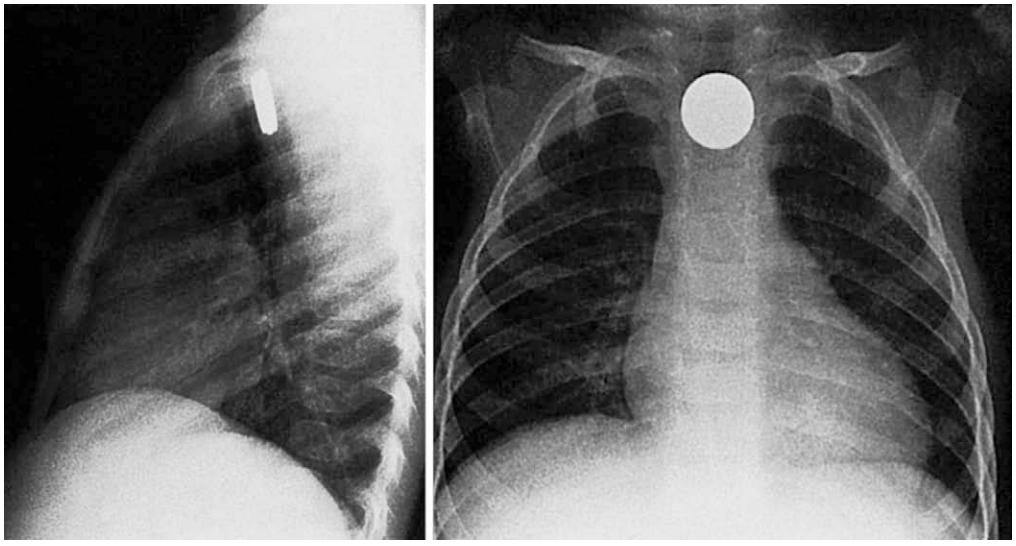

Figure 208-2. Posteroanterior and lateral films of two pennies and a nickel in a typical esophageal location immediately below the cricopharyngeus.

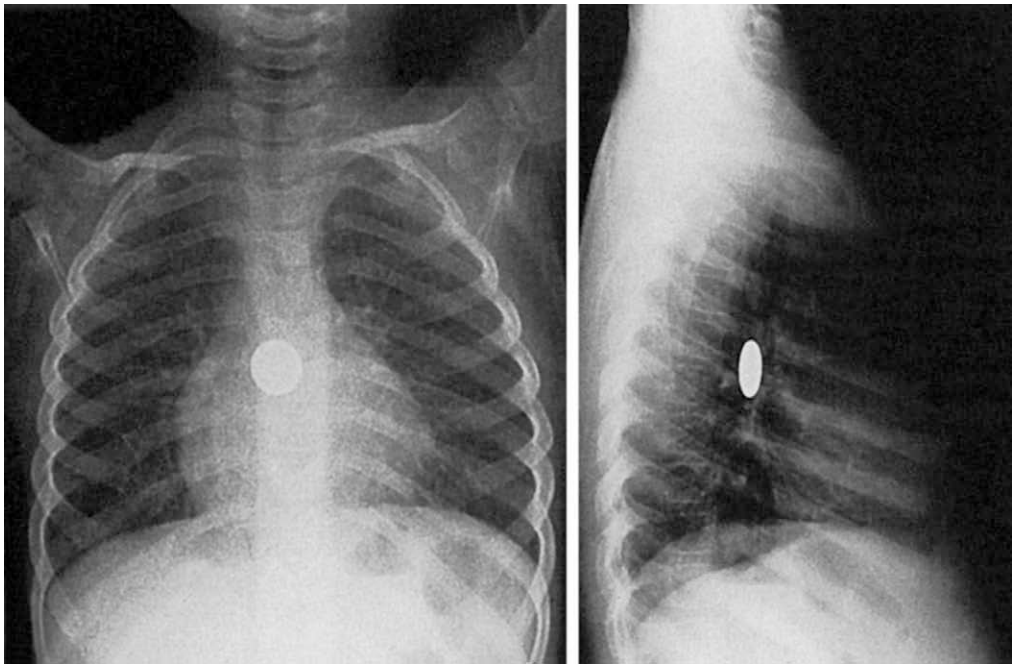

Figure 208-3. Posteroanterior and lateral chest films of a coin in the midesophagus.

ment of choking victims.[19] For infants, rescue breaths and chest compressions are recommended. Children older than 1 year require gentle abdominal thrusts while supine. Older children and adults are positioned standing, sitting, or recumbent for the Heimlich maneuver. Back blows or abdominal thrusts in individuals with only partial obstructions could lead to complete obstruction and are not recommended.

Symptoms

Foreign body aspiration is suspected when a victim has acute choking or severe coughing with respiratory distress. The diagnosis sometimes is obscured if the event is unwitnessed in a young child. Some children do not admit to aspiration because of fear of punishment. Symptoms of foreign body aspiration can mimic conditions such as asthma, croup, and pneumonia. Onset of wheezing in an otherwise healthy child should prompt suspicion of foreign body aspiration.

There are three clinical phases of foreign body aspiration.[15] The initial phase consists of choking, gagging, and paroxysms of coughing or airway obstruction that occur at the moment of aspiration. The choking, gagging, and coughing subside during the asymptomatic phase when the foreign body becomes lodged, and the reflexes fatigue. The asymptomatic phase can last hours to weeks. Complications occur in the third phase, when obstruction, erosion, or infection causes hemoptysis, pneumonia, atelectasis, abscess, or fever.

A careful history and physical examination are most important in diagnosing foreign body aspiration. Determining the site of the obstruction is important in the management of the problem.

Laryngeal Foreign Bodies

A foreign body in the larynx may constitute an airway emergency that requires lifesaving first aid before transport to the hospital. Irregular foreign bodies or orientation in the sagittal plane may produce only

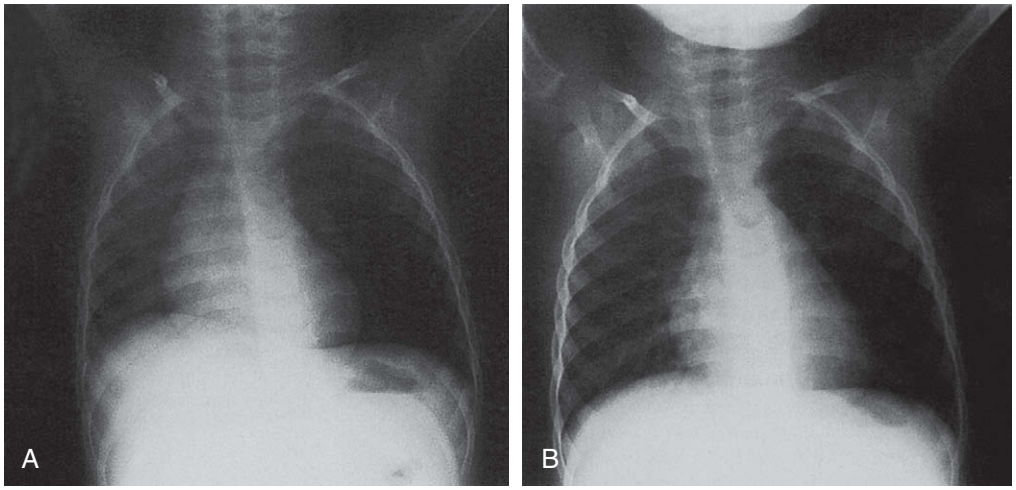

Figure 208-4. **A** and **B,** Expiratory **(A)** and inspiratory **(B)** chest films show hyperinflation on side of left bronchial foreign body (a peanut fragment). This is a typical early finding.

partial obstruction, allowing adequate air movement around the obstruction. Resulting laryngeal edema can lead to complete obstruction. Typically, these patients have symptoms of obstruction and hoarseness. Some symptoms can mimic croup.[3] Delayed diagnosis may lead to complications.

Tracheal Foreign Bodies

Patients with tracheal foreign bodies are seen in similar fashion, but typically do not have hoarseness. Jackson and Jackson[3] described three signs associated with tracheal foreign bodies: the "asthmatoid wheeze," the "audible slap" produced from foreign body contact with the trachea, and the "palpable thud" over the trachea. As with laryngeal foreign bodies, edema can progress to complete obstruction.

Bronchial Foreign Bodies

Of airway foreign bodies, 80% to 90% are found in the bronchi.[20] These patients typically have a triad of cough, wheezing, and decreased breath sounds. One large series reported that 65% have the classic triad,[17] but 95% have at least one finding.[16]

The asymptomatic phase may give a false sense of security that the problem has resolved and lead to a delay in diagnosis. Chest auscultation may reveal decreased breath sounds or wheezing. Sudden onset of wheezing is particularly suggestive of a bronchial foreign body, especially if unilateral, but may be a subtle finding.[21] Occasionally, bronchial foreign bodies can cause respiratory compromise as a result of swelling of dried vegetable matter (e.g., dried beans and peas) or edema around the object, producing complete obstruction and lobar collapse. Movement of the foreign body from one main bronchus to the other produces respiratory distress, resulting from obstruction of the previously normally ventilating lung.

Esophageal foreign body impaction is most frequently associated with vomiting, odynophagia, dysphagia, and ptyalism.[5-8] If the ingestion is witnessed, gagging or choking may be reported. A large foreign body may cause symptoms of airway obstruction and cough caused by compression or irritation of the upper airway. In long-standing esophageal foreign body impaction, fever and other symptoms of respiratory infection may be present.[6]

A careful history and physical examination are the first steps necessary to diagnose esophageal foreign body impaction. Appropriate radiographic evaluation further aids diagnosis and management.

Radiographic Evaluation

Laryngotracheal Foreign Bodies

Airway films—high-kilovolt posteroanterior and lateral soft tissue radiographs of the neck—are the radiographic examination of choice to identify laryngeal and tracheal foreign bodies. Chest radiographs are ordered before intervention. Neck films may show subglottic narrowing. Esclamado and Richardson[20] reported that 92% of patients with tracheal foreign bodies had abnormal neck radiographs, whereas 50% had normal chest films. When such children do not respond rapidly to medical management, foreign body aspiration must be ruled out.

Bronchial Foreign Bodies

Children with bronchial foreign bodies can be radiographically normal or may show obstructive emphysema (air trapping or hyperinflation—an early finding) and atelectasis or consolidation (late findings). Even if the diagnosis is strongly suspected by history and physical examination, posteroanterior and lateral chest radiographs are performed. Chest radiography generally is an adjunctive procedure because the history and physical examination are sufficient to suspect a bronchial foreign body.

During normal respiration, the airway dilates with inspiration and contracts on expiration. This respiratory cycle can be altered by the presence of bronchial foreign bodies.[22] Small objects may cause no radiographic abnormalities. Foreign bodies that obstruct mainly on expiration generate a check-valve effect, resulting in hyperinflation of the affected side and mediastinal shift to the opposite side (Fig. 208-4). This is a typical early finding. A ball-valve effect is produced later when foreign bodies obstruct on inspiration and open on expiration, producing atelectasis on the affected side and a mediastinal shift toward the affected side (Fig. 208-5). When the object completely obstructs the bronchus, a stop-valve effect occurs, leading to consolidation of the lobe involved.

Inspiratory and expiratory chest films can aid in the diagnosis, showing hyperinflation on expiratory films or atelectasis on inspiratory films. In younger children who cannot cooperate, lateral decubitus films may help. The dependent lung should collapse normally, but remains inflated in bronchial obstruction. Fluoroscopic evaluation is of little benefit; decreased diaphragmatic movement on the side of the obstruction is helpful in only 50% of cases.[16] Simultaneous biplane fluoroscopy is used for extraction of radiopaque foreign bodies in the lung periphery.

Radiographic findings often suggest but do not diagnose foreign body aspiration. Asthma and mucous plugging can simulate foreign body aspiration. Mu and associates[23] reported that 35% of patients having normal radiographic studies were later found to have bronchial foreign bodies. Other studies show the lack of sensitivity or specificity of radiographs in diagnosing airway foreign bodies.[24,25] In cases of suspected foreign bodies, endoscopic evaluation is important because negative radiographs are not enough to rule out the presence of a foreign body.[24]

Esophageal Foreign Bodies

When an esophageal foreign body is suspected by history and physical examination, a radiologic evaluation is performed to assess its location and size, and to anticipate the possibility of multiple foreign bodies. Posteroanterior and lateral airway films and posteroanterior and lateral chest films, including the abdomen, are performed. Foreign bodies rotate to the greatest diameter of the lumen; flat objects in the esophagus usually are oriented in the coronal plane.[26] It is imperative to obtain a lateral airway and chest film to evaluate for possible battery ingestion because a battery can easily mimic a coin on posteroanterior view.

There is a high rate of spontaneous passage of esophageal coins into the stomach.[27] Predictors for a high rate of spontaneous passage include location in the distal esophagus, male gender, and age older than 5 years.[28] An observation period of 8 to 16 hours is considered appropriate management in otherwise healthy children with asymptomatic esophageal coins.[29] A repeat radiograph is warranted before attempted removal to confirm the location of the coin. A handheld metal detector may improve the timing and ease of confirming the location of blunt metallic foreign objects within the esophagus just before administration of general anesthesia.[30]

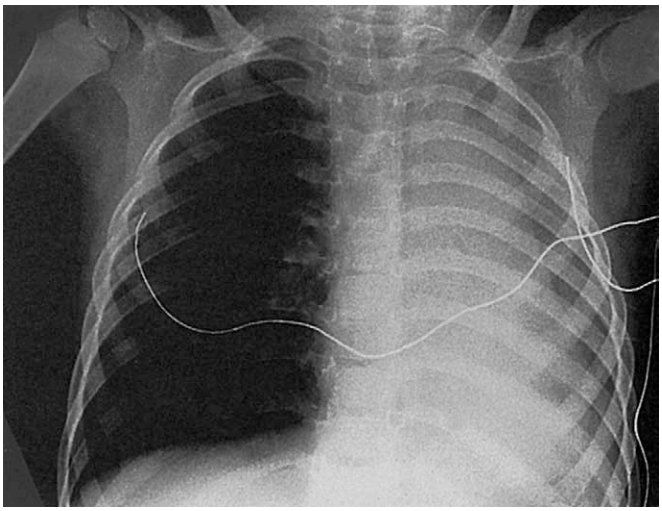

Figure 208-5. Anteroposterior chest film of left lobar collapse secondary to candy corn in the left main bronchus.

In rare cases in which an esophageal foreign body was not found on initial endoscopy and migrated extraluminally, fluoroscopy with contrast material may aid in preoperative location of the object. Open surgical exploration is rarely required to retrieve a foreign body.[26]

Management

Most patients who arrive at the hospital with airway foreign bodies have passed the acute phase and are no longer in respiratory distress. Patients in respiratory distress are given support until the endoscopy team can safely attempt removal. This support may include oxygen, heliox,[31] or intubation. With rare exceptions, esophageal foreign body impactions are not dire emergencies. There is time to obtain a history regarding the ingestion and a pertinent medical history. An inadequate diagnostic workup and hasty preparation of the operating suite likely lead to a poor outcome. Other associated conditions, such as tetanus immunization status or blood lead levels,[32] should be appropriately ascertained and treated.

The standard radiographic posteroanterior and lateral airway and chest films may give adequate information for foreign body removal. If the foreign body is sharp or irregularly shaped, a radiograph in the plane of the greatest dimension of the foreign body may help plan removal. If a suspected esophageal foreign body is radiolucent, a barium contrast study should be avoided because it would delay endoscopy in that the patient can no longer take anything by mouth, and the foreign object may be obscured by the material swallowed. Generally, the patient should take nothing by mouth for 6 hours, and then be adequately hydrated.

The basic principles of endoscopic foreign body removal have not changed since Jackson's time.[3,8] The type and size of endoscope depend on the age of the patient and the location of the object. Foreign body forceps are selected on the basis of practice with a similar object, preferably a duplicate brought in by the patient's family. It is important that the operating room personnel be familiar with the planned procedure, and that communication with the anesthesiologist regarding the anesthetic and endoscopy plan has occurred.

Equipment

Age-appropriate equipment for endoscopic foreign body removal is carefully selected before the patient is brought to the operating room (Table 208-1). Equipment should be in good working order and checked before the procedure. All members of the endoscopy team should be familiar with the location, setup, and use of the instrumentation. If there is inadequate equipment or a lack of trained personnel, transfer of the patient to an adequately equipped center with an experienced endoscopy team should be considered.

Table 208-1

Guidelines for Selection of Bronchoscope, Esophagoscope, and Laryngoscope for Diagnostic Endoscopy by Age

Mean Age (Range)	Bronchoscope Size*	mm*	Laryngoscope Size*	Esophagoscope Size*
Premature infant	2.5	3.7	8	4
Term newborn (newborn to 3 mo)	3	5.8	8	4-5
6 mo (3-18 mo)	3.5	5.7	9	5-6
18 mo (1-3 yr)	3.7	6.3	10.5	6
3 yr (2-6 yr)	4	6.7	10.5-12	6-7
7 yr (5-10 yr)	5	7.8	12	7
10 yr (>10 yr to adolescent)	6	8.2	16	8

*Outside diameter given in millimeters.

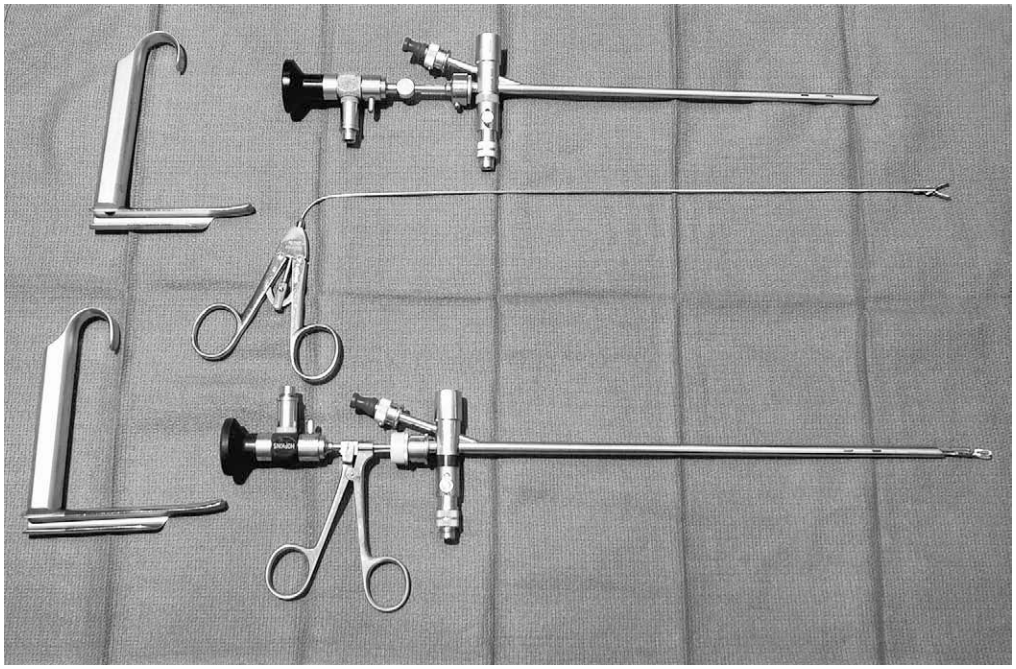

Figure 208-6. Instruments for endoscopic removal of an airway foreign body.

Laryngoscopy visualizes laryngeal foreign bodies and facilitates passage of a bronchoscope. Preferred bronchoscopes with a rod-lens telescope are the Doesel-Huzly bronchoscopes (Karl Storz) (Fig. 208-6). Age-appropriate sizes minimize laryngeal edema. For airway foreign bodies, two bronchoscopes are prepared so that if one fails, another is immediately available. For esophageal foreign bodies, an esophageal speculum and appropriate-sized esophagoscope for the patient's age and size are chosen. Suctions and forceps should be checked to ensure they are of adequate length to be used with the endoscopy equipment. Active or passive action forceps may be used; in most situations, the improved visualization achieved with optical forceps is preferable. Because of their size, optical forceps may impair the ability to ventilate a patient adequately through the bronchoscope; alternate forceps should be readily available.[3,7,8] With all endoscopic foreign body procedures, safety glasses should be worn by the endoscopy team, and a dental guard should be placed before introduction of the endoscope.

Anesthesia

Unless the patient is in extremis, foreign body removal is performed under general anesthesia to provide optimal airway control and patient comfort. The plan for induction and maintenance of anesthesia, and the method of evaluation and removal of the foreign body should be communicated preoperatively between the anesthesiologist and endoscopist. Patients are given nothing by mouth for an adequate time to reduce the risk of aspiration. Patients are placed supine for mask induction using volatile inhalational agents for children. Eye protection prevents corneal abrasions. Spontaneous respiration is maintained. The larynx is topically anesthetized with 1% to 4% lidocaine to inhibit laryngeal reflexes and to reduce the incidence of laryngospasm.

For a suspected laryngeal foreign body, patients are preoxygenated. After mask induction, anesthesia is maintained with an insufflation catheter through the nares into the hypopharynx. For tracheobronchial foreign body removal, the laryngoscope tip is placed in the vallecula to expose the larynx for passage of the bronchoscope. The patient breathes through the bronchoscope until the conclusion of the procedure. For esophageal foreign bodies, the patient undergoes endotracheal intubation. The endotracheal tube prevents inadvertent aspiration of the foreign body into the airway during attempted removal, and minimizes any tracheal compression caused by a rigid esophagoscope.

Technique

For bronchial foreign bodies, the healthy bronchus is examined first. The bronchoscope is positioned above the foreign body, and secretions are gently suctioned to expose the object fully. Before and during the attempt at removal, 100% oxygen is given. The forceps are placed through the bronchoscope, and the foreign body is engaged. The bronchoscope, forceps, and foreign body are removed as a unit, and the bronchoscope is returned immediately to the airway for ventilation and assessment for other foreign bodies. As previously mentioned, simultaneous biplane fluoroscopy can be used for extraction of radiopaque foreign bodies in the lung periphery.[33]

Occasionally, attempts at endoscopic retrieval fail, and thoracotomy is required. If the foreign body is too large to be extracted through the larynx, the foreign body may be broken into small fragments and removed through the bronchoscope. Alternatively, a tracheotomy is performed, and the foreign body is removed through the neck, maintaining the airway and delivering the object with bronchoscopic guidance.[34,35]

For esophageal foreign body removal, an esophageal speculum or esophagoscope is passed through the right side of the mouth and directed toward the pyriform sinus. The scope is angled toward the sternal notch. The esophageal lumen is kept in view at all times while the esophagoscope is gently advanced until the foreign body is visualized. The foreign body is engaged with the forceps; the esophagoscope is advanced toward the object; and the foreign body, forceps, and esophagoscope are removed as a single unit. If multiple foreign bodies are suspected, the esophagoscope is reinserted to assess the condition of the esophageal mucosa, and to identify additional foreign bodies below the primary one. Multiple foreign bodies are found in 5% of patients (Fig. 208-7).[6]

Removal of Sharp Objects

Extraction of sharp, pointed, or unusually shaped objects can be extremely challenging.[7,36] Locating the point is crucial. Usually, the tip of a pointed object engages the mucosa, causing the object to tumble and proceed with the point trailing. Pointed objects may be bendable or breakable; analysis of a duplicate may aid in this determination. The endoscope is aligned parallel to the long axis of the airway or esophagus to minimize the likelihood of damage to the surrounding mucosa. During the extraction, the object first is moved distally to disengage the point.

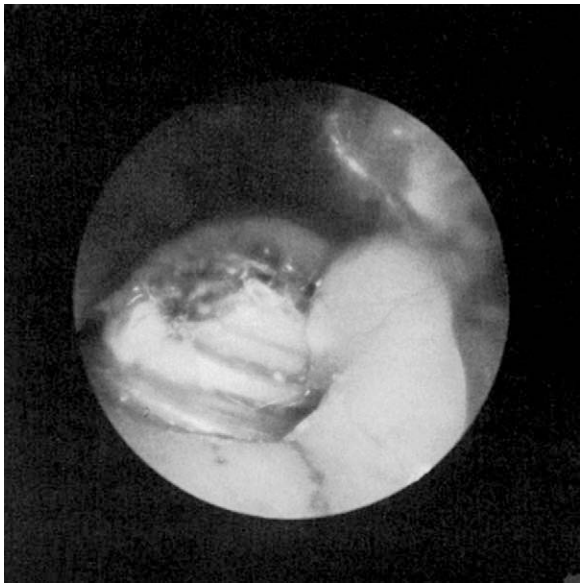

Figure 208-7. Multiple coins in the esophagus of a patient with a history of tracheoesophageal fistula.

Pin-bending forceps may be used for bendable objects; this reconfigures the object's point to trail on removal. Safety pins are uniquely challenging; pins that become lodged are invariably open. The incidence of safety pins as foreign bodies has decreased with the introduction of disposable diapers. Two methods of removal are suggested: (1) sheathing the point within the endoscope while locking the forceps closed to hold the keeper against the outside of the tube particularly during extraction through the larynx, and (2) gastric version (under fluoroscopic guidance) of esophageal safety pins, using rotation forceps to flip the safety pin point down within the stomach. The Clerf-Arrowsmith pin-closing forceps risk entanglement with the safety pin, which becomes virtually impossible to remove. This dangerous tool is not recommended. If a sharp object is severely impacted or embedded, an open surgical approach may be the safest method of foreign body removal.[5,7]

Long or large objects in children younger than 2 years may not pass through the duodenum. It is preferable to remove these objects from the stomach endoscopically before they migrate further or perforate a bowel wall. If a disk battery traverses beyond the esophagus, and the patient remains asymptomatic, parents are advised to check the patient's stools for passage and to return immediately to the hospital if fever or abdominal pain occurs.[7,37] An abdominal film should be obtained for delayed passage. Children younger than 6 years who have swallowed a battery 15 mm in diameter or larger that has not passed out of the stomach within 48 hours should undergo endoscopic removal. Many batteries 15 mm or greater do not pass out of the stomach and cause corrosive injury in an acidic environment.

Disk Battery Ingestions

Disk batteries are commonly used in hearing aids, calculators, watches, and other portable electronic devices. The peak incidence of ingestion occurs at age 1 to 2 years. In 33% of cases, the ingested battery is from the child's hearing aid.[38] A patient with a history of ingestion and esophageal lodging of disk batteries (also known as button batteries) requires immediate action.[7,37,38] In 1 hour, the esophageal mucosa may be damaged; in 4 hours, leakage of caustic battery contents may cause erosion through the muscular wall of the esophagus; and within 6 or more hours, an esophageal perforation leading to mediastinitis, tracheoesophageal fistula, or death may occur.[7,37,38] If esophageal lodging of a disk battery is suspected, radiography localizes the battery. An immediate esophagoscopy is performed to remove the battery and assess the patient's esophageal mucosa. Most batteries of this type are of a smaller diameter (<15 mm) and usually traverse the gastrointestinal tract with only minor injury. Larger button batteries (≥15 mm in diameter) are more likely to lodge in the esophagus or stomach, causing serious corrosive injury. Mercuric oxide–containing batteries can cause systemic mercury poisoning if they open in the gastrointestinal tract. The imprint code of a duplicate battery should be conveyed to a Poison Control Center or Button Battery Ingestion Hotline for specific information.[38]

Pill Ingestions

Medications in pill form may lodge within the esophagus because of delayed esophageal transit, dry swallow (i.e., swallowing without liquids), adherent tablets, or a supine swallow. The pill may cause caustic injury through various mechanisms because of prolonged contact with the esophageal mucosa.[39] More than 70 different medications in pill form have been reported to cause caustic injury. Antibiotics and antivirals account for 60% of cases. Most heal without significant injury. Anti-inflammatory medications have been reported in fewer cases, but a third of these patients have had significant hemorrhage or had strictures develop.[39]

Most injured patients have no predisposing factor other than improper swallowing of pills; however, any functional or anatomic abnormality of the esophagus may give rise to this condition. Patients usually are seen with sudden onset of retrosternal pain, dysphagia, and odynophagia.[39] Fever, hematemesis, and dehydration are less common presenting symptoms. Often, patients recall the sensation of a pill sticking in the esophagus before the onset of symptoms, or have swallowed a pill without water or at bedtime.[39] Most symptoms resolve over days to weeks.

Endoscopy should be considered if the symptoms are severe, persistent, or atypical, or if hematemesis or a stricture is suspected.[39] Esophagoscopy can differentiate other potential causes, such as infection, malignancy, or gastroesophageal reflux disease. In addition, any pill remnants may be removed, and an accurate assessment may be made of the degree of mucosal injury. The most common findings on esophagoscopy are small, shallow, discrete ulcers that may be single or multiple. Large, circumferential lesions several centimeters in length have been reported.[39] Most shallow ulcers heal spontaneously. Deep injuries may lead to stricture formation and perforation. Education of the public and health care personnel in methods of proper pill swallowing is important to prevent pill-induced esophageal injuries.

Esophageal Perforation

Perforation of the esophagus in a patient with an impacted esophageal foreign body may be caused by the object itself, by the length of time that the object has been lodged, or by attempts to retrieve the object.[8,26,38,40-42] If perforation is suspected preoperatively, esophageal perforation may be diagnosed on preoperative radiographic evaluation. Cervical subcutaneous emphysema, retroesophageal abscess, or an obvious extraluminal portion of the esophageal foreign body may be apparent.[5] Fever with tachycardia, tachypnea, and increased pain all may be early signs of a perforation.[5,43] With early recognition and management, the mortality rate for esophageal perforation has decreased from 60% to 9%.[42] After esophagography has been performed to locate and evaluate the extent of the injury, early institution of nothing by mouth and broad-spectrum antibiotics may be all that is necessary in pharyngoesophageal perforations,[41,43] the most common area injured in endoscopic removal of esophageal foreign bodies. In more severe injuries, drainage, closure, or more complex surgical repairs may be necessary.

Postoperative Management

After esophagoscopy for foreign body extraction, children are observed and given nothing by mouth for 4 hours. Patients are monitored for fever, tachycardia, and tachypnea, all signs of possible perforation. Antibiotics are not routinely given unless significant esophageal injury is evident.

When appropriate-sized bronchoscopes are used for brief procedures, racemic epinephrine or corticosteroids are not given. Chest physiotherapy may help to clear inspissated secretions. A routine postoperative radiograph is unnecessary unless the patient's symptoms

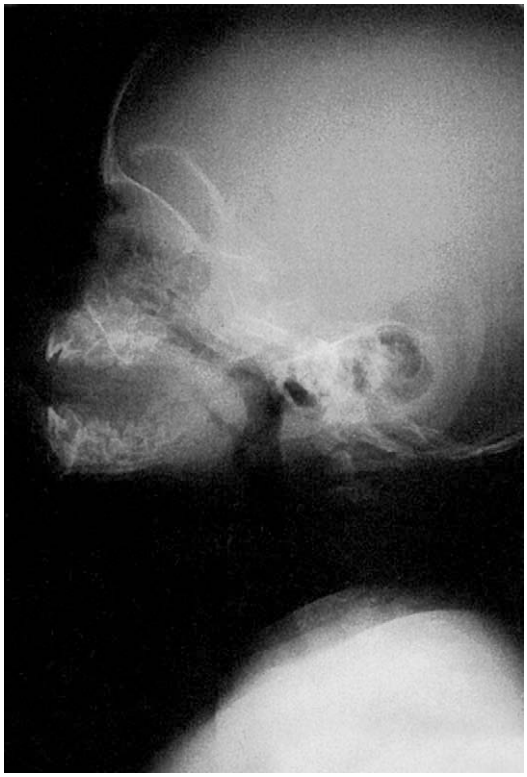

Figure 208-8. Lateral neck film reveals retroesophageal abscess.

persist or progress. When extraction attempts fail or are incomplete, patients are rested for several days, and then returned to the operating room for repeat endoscopy. One more recent study examined factors associated with increased pulmonary recovery time after foreign body removal. A recovery time of more than 1 week was associated with preoperative inflammatory findings by radiologic study, procedure time greater than 50 minutes, and worsening postoperative radiologic findings.[44]

Complications

Before the 20th century, the mortality rate caused by foreign body aspiration was high, with most patients dying of complications. In 1882, Weiss reported 937 cases for which bronchotomy was performed, with a 27% mortality rate; however, 23% died without management.[2] Jackson's techniques reduced the mortality rate to about 2%.[22] The present rate is 2% or less.[4,11,16,17,45,46]

Most complications are the result of delayed diagnosis and treatment.[17,21,47,48] Earlier diagnosis correlates with fewer complications.[48] Of laryngotracheal foreign bodies, 45% were associated with major complications, and 67% were associated with major complications when the delay was longer than 24 hours.[20] The introduction of rod-lens telescopes has reduced the incidence of missed or incomplete removal of foreign bodies, reducing complications further.

Pneumonia and atelectasis are the most common complications after bronchial foreign body removal. Patients usually respond to intravenous antibiotics and chest physiotherapy. Bleeding can occur because of granulation tissue or erosion into a major vessel. Pneumothorax and pneumomediastinum can result from an airway tear. Small perforations typically heal spontaneously, and do not require specific management. Impaction of the foreign body can cause airway obstruction, converting a controlled situation into an emergency. Laryngeal inflammation and edema have decreased significantly with the use of appropriate-sized endoscopic equipment.

Long-term complications (e.g., granulation tissue, stricture formation) can occur at the site where the foreign body is lodged. Certain foreign bodies are more likely to cause more complications.[48] The oils of nuts may contribute to edema and granulation tissue.[3]

The most frequent complications of endoscopic esophageal foreign body removal are categorized as those occurring before endoscopy, during endoscopy, and after endoscopy.[39] Vomiting and respiratory distress are most common preoperatively. During esophagoscopy, the endotracheal tube may be dislodged, and the patient may have cricopharyngeal spasm, esophageal mucosal injury, or perforation. After esophagoscopy, vomiting, aspiration, a second missed foreign body, and fever are the most common complications. Esophageal perforation, retroesophageal abscess, mediastinitis, and death are rare (Fig. 208-8). In several large series of endoscopic esophageal foreign body removal, there were no life-threatening complications.[5,6,41,42]

Controversies in Management

Nonendoscopic means of foreign body extraction have been suggested. These methods have been detrimental in some cases, causing emergent situations and even death. Although chest physiotherapy and bronchodilators have been suggested as a management for airway foreign bodies, this proposal has been retracted.[49]

Flexible bronchoscopic removal of airway foreign bodies seems attractive, with more recent literature advocating its use in adults and increasing experience in pediatrics as a diagnostic tool.[9] Unless the endoscopist also is skilled at rigid bronchoscopy, flexible bronchoscopic foreign body removal in children is not recommended,[25] especially in small children. The main problems are poor control of the airway and of the foreign body itself.[9,25]

For impacted esophageal foreign bodies, bougienage with esophageal dilators or a nasogastric tube has been proposed to push foreign bodies into the stomach.[2,49] This blind technique may cause esophageal injury and is not universally accepted. Foley catheter removal with fluoroscopic control of blunt radiopaque esophageal foreign bodies has been recommended for a single object lodged below the cricopharyngeus for a short duration.[23,42,50] Advantages include reduced cost and avoidance of general anesthesia. Few serious complications have been reported when this technique was used in healthy children. Other authors[6,26,49] point out that the risks of general anesthesia in these patients are small. This technique does not allow a postretrieval assessment of the esophageal mucosa or identification of a nonradiopaque second foreign body. Because the coin is not grasped using this technique, loss of control of the coin at the level of the posterior pharynx can result in an airway emergency. In addition, there is a risk of vomiting and aspiration with an unprotected airway, and young patients who have this procedure while awake and restrained in a steep head-down position may experience emotional trauma.

Use of various pharmacologic agents in the management of esophageal foreign bodies has also been proposed. Papain (meat tenderizer) has been used in patients with impacted esophageal meat boluses.[49] Papain was given as a 5% solution to adult patients, with the meat passing in most instances. However, there were at least two cases of mediastinitis and death in these patients caused by necrosis of the esophagus and perforation. Glucagon produces relaxation of the smooth muscle of the esophagus, promoting passage into the stomach. One open-label study in pediatric patients failed to show a higher incidence of passage in patients who received glucagon versus placebo.[51] Sumatriptan prolongs fundic relaxation and delays gastric emptying. Studies conducted so far have revealed an increase in the rate of gastroesophageal reflux and the number of esophageal mother waves.[52,53]

Flexible esophagoscopy has been used for removal of blunt objects or meat impaction. Sharp objects pose a greater risk, however, because of the inability to sheath the object as with a rigid esophagoscope.[36]

Careful endoscopic removal of foreign objects under direct vision is the safest management for patients with foreign bodies of the airway and esophagus. Prevention is ideal, with increased education of the public, especially individuals who supervise children—parents, teachers, and other care providers—on age-appropriate foods and household objects. Stricter government and industry standards for toy part sizes and appropriately sized containers have helped to decrease fatalities from choking, but have come about only through the cooperation of physicians, consumer advocacy groups, and governmental public health agencies.[54,55]

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CHAPTER TWO HUNDRED AND NINE

Gastroesophageal Reflux and Laryngeal Disease

Philippe Contencin

Thierry Van den Abbeele

Natacha Teissier

Key Points

- Other than gastroesophageal reflux (GER) disease, with its digestive and general signs and symptoms and valid tests, the definition of GER-related laryngeal disorders remains unclear.
- No true specific features of GER-related laryngeal disorders have been found, and the role of refluxed acid (or nonacid) gastric content in their occurrence is still unknown.
- Only a statistical correlation between GER and some inflammatory processes of the pediatric larynx has been found.
- Several possible mechanisms have been described, including direct epithelial injury, and indirect harm via vague mediated reflexes with or without vocal misuse.
- In addition to classic signs and symptoms of GER, the diagnosis is based on therapeutic trials, esophageal pH, and, for the future, impedance monitoring.
- Although most controlled studies (in adults) show no efficacy, anti-GER treatment or proton pump inhibitors or both are advised in selected cases of apnea with laryngospasm, associations with regional neuromuscular disorders (including laryngomalacia), recurrent croup, and laryngeal surgery.

First reported in the 19th century for bronchitis, the involvement of gastroesophageal reflux (GER) in the respiratory tract is still a controversial topic. Most pulmonologists consider GER as a possible aggravating factor for asthma. The involved mechanism of it is unknown, however.

The pediatric larynx is a sensitive organ subject to spasm and edema in case of minor harm. Evidence of the association of GER and laryngeal disorders in newborns to adults has been found. Data suggesting a cause-and-effect relationship are still missing, however.

History

Internists and otolaryngologists have reported possible airway involvement in adult patients with upper digestive disorders. By the end of the 19th century, Osler mentioned the occurrence of dyspnea in the postprandial period when the gastric cavity is full. From the early 1970s, with the description of "hiatal hernia" in adults, to more recent pediatric studies, it has become obvious that some laryngeal inflammatory processes develop in conjunction with upper digestive malfunctions, including GER.

The first modern clinical demonstration of GER-related laryngeal harm was made by Ward and colleagues[1] in glottic granulomas and contact ulcers in adults, and by Little and colleagues[2] in subglottic stenosis in an animal model. In infants and children, GER was initially shown through barium studies to be responsible for recurrent croup.[3] Similarly, apnea in premature newborns and various forms of laryngitis were linked to GER by means of esophageal and pharyngeal pH monitoring.[4,5] Finding decreases in pharyngeal pH to 2 at the laryngeal inlet or above in cases of pediatric chronic rhinitis/laryngitis raises a high index of suspicion of the role of acid reflux in these disorders of the airway. There was a statistically significant difference in upper and lower pH monitoring data between these patients and controls.[6] Some control patients and even gastroenterology patients might have pH variations that were close to each other, however, without any rhinolaryngologic symptoms. Since those studies were performed, control infants and children could not ethically be tested. Many studies focused on in vitro tests and on the efficacy of anti-GER treatments in patients.

Definition

GER is an abnormal and repeated ascent of gastric content into the esophagus (and possibly above it). There is a physiologic GER that occurs mainly in the postprandial period. Small amounts of refluxed material may cause burping at any age and a small degree of emesis in the infant. Sometimes it is also called "functional" GER because esophageal pH monitoring may show a few acid periods (<5% of recorded time at pH less than 4 on a 20-hour basis) that are considered unharmful to the esophagus. In this case, no other digestive symptom is noted, and upper digestive endoscopy is normal.

GER disease (GERD) is believed to have gastrointestinal or extragastrointestinal signs. Gastrointestinal signs include emesis, dysphagia,

choking, gagging, and failure to thrive in children. Extragastrointestinal signs include chronic coughing, wheezing, hoarseness, sore throat, stridor, recurrent croup, and obstructive apnea. Heartburn is extremely rare.

GERD was defined using gastrointestinal criteria; normal values for GER tests were established according to this definition. These criteria are not entirely appropriate in cases of a laryngeal disorder (also improperly called "laryngopharyngeal reflux" in adults). An extensive assessment for GER with "normal" results may be associated with chronic laryngeal inflammation; however, abnormal results indicating GERD may be found in cases of asymptomatic and endoscopically normal larynges. Many authors emphasized the particular pH profile of "airway-linked" GER. In a cohort of 90 children with pH monitoring, Zalesska-Krecicka and coworkers[7] found a high prevalence of daytime refluxes when patients with laryngeal disorders were in the upright position.

Physiopathology

The anatomic proximity and the neurofunctional collusion of the human larynx to the hypopharynx and upper esophagus lead to its unique vulnerability.[8] In no other mammal species is the larynx so caudal compared with the digestive tract organs. This positioning can explain the diffusion of the gastric juice up to the laryngeal mucosa.[9] Although many patients have GER, why do so few have true laryngeal disorders? It seems that a mechanism peculiar to the larynx is involved, and this can be due to direct contact with the gastric juice or to a vague mediated reflex.

Studies by Willging and Thompson[10] emphasized the role of laryngeal sensitivity in the development of pediatric anomalies such as laryngomalacia and GER-induced laryngeal reflexes. Paradoxical vocal cord motion, laryngospasm, and saliva and food aspiration are associated with abnormal thresholds of local chemoreceptors and mechanoreceptors. It has been shown that premature infants develop progressive swallowing ability and control of the lower esophageal sphincter postnatally, depending on the status of their respiratory and neurologic systems. GER and laryngeal sensitivity are intimately related and involved in cases of prematurity.[11]

Lipan and associates[9] discussed possible mechanisms of potential harm of the larynx by GER. They stated that, compared with classic intraesophageal reflux, cranial involvement by GER may be the result of four failing "barriers" including upper esophageal sphincter and pharyngolaryngeal mucosal resistance. These two domains warrant specialized interest and involvement of gastroenterologists, pathologists, and immunologists to know what exactly differentiates patients with gastrointestinal symptoms from patients with head and neck symptoms affected by GER. In 1998, an experimental rabbit model–based study emphasized the role of hydrogen chloride and pepsin inducing a chemical trauma and the individual laryngeal chemosensitivity.[12] In 2003, Altman and colleagues[13] found expression of a proton pump in the laryngeal mucosa. These mechanisms are held responsible for inflammatory laryngeal pediatric processes and for adult laryngeal carcinomas.[14] Eventually, in an "in vitro" model of laryngeal cultures, Ylitalo and Thibeault[15] showed more changes in gene expression of postcricoidal fibroblasts after 60 seconds of exposure to pepsin at low pH. Some authors denied the role of acid secretions in this domain, however, considering the inefficacy of gastric acid suppressors (i.e., proton pump inhibitors) in healing chronic laryngitis in adults.[16]

Diagnosis

A patient history of combined digestive and respiratory symptoms may help suggest the diagnosis of GERD. In infants, feeding difficulties with tears, apparent life-threatening events with hypotonia, and rise of refluxed food while supine are useful signs that may lead to empirical treatment. Radiographic studies with barium swallow, a search for lipid-laden macrophages at bronchial lavage, and a thoracic scintiscan with ingestion of nuclide elements are not routinely performed. Esophagoscopy with a flexible fiberscope may show esophagitis and large hiatal hernia. These abnormalities are rare, however, in cases with no gastrointestinal symptoms. It is unclear whether laryngoscopy and bronchoscopy can point to marks of GER because no specific features are described other than cobblestoning of the posterior supraglottic or subglottic area.[17,18]

Esophageal pH monitoring is considered by gastroenterologists to be the gold standard for diagnosing GER. Acid periods recorded over 18 to 24 hours can be correlated with airway manifestations (e.g., cough, stridor). An abnormal percentage of the recorded time at a pH less than 4 allows the physician to manage the GER. The question is what percentage should be considered abnormal in the absence of gastrointestinal signs and symptoms. It is unknown whether nonacid or weakly acid reflux may also play a role in the pathogenesis of GER-related laryngeal disorders.[19,20] A negative test does not rule out GER without esophageal lesion, however. Combined pharyngeal and esophageal pH records showed that brief refluxes can reach the laryngeal inlet and cause problems, whereas classic standards for this pH test are considered normal with a poor total acid time. Pharyngeal pH recordings are subject to drifts by dryness, however, and are not used routinely. Many studies have shown that brief diurnal refluxes are usual features of airway-disordered GER. Brief, pharyngeal and nonacid refluxes may be diagnosed easily by a promising test: esophageal impedance recording. This technique, which includes pH monitoring, allows recording of any refluxate, and is expected to enter routine practice.[21]

In adults with laryngeal symptoms and suspicion of GER, a therapeutic trial with a proton pump inhibitor is sometimes recommended, although more recent studies denied any efficacy of these treatments compared with placebo.[16,22] A therapeutic trial with a proton pump inhibitor would not be recommended as a diagnostic test in infants and children.

McMurray and coworkers[23] summarized the optimal assessment in cases of suspected esophagopharyngolaryngeal reflux: endoscopy with mucosal biopsy and dual probe pH monitoring are advocated.[23] This assessment underlies the principle of a mandatory abnormal GER (under gastrointestinal specifications) to start a specific treatment that is still subject of doubt.[9,24]

Disorders

The most frequent GER-related disorders in the airway of children of any age are classically the laryngeal diseases listed in Box 209-1. In older children and adults, dysphonia is the most frequently reported pathologic sign, along with pharyngeal symptoms (e.g., pain, globus sensation). Recurrent subglottic laryngitis with dyspnea (croup) is the most common consequence of GER on the airway in children. A statistically significant correlation with GER was found in patients with recurrent croup using two-channel pH monitoring.[5] Successful anti-GER therapeutic trials and recurrences after stopping management also were noted in patients with recurrent croup.[25]

GER has been shown to have an important role in the development of subglottic stenosis. Long-term endotracheal intubation leads to increased acid pharyngeal reflux. Animal studies have shown that acid placed on the subglottic mucosa after local trauma leads to granulation tissue and fibrous scarring with subsequent stenosis.[2] Some authors believe that successful surgical management of subglottic stenoses in children depends on the control of GER.[26]

Box 209-1

Gastroesophageal Reflux–Related Laryngeal Disorders in Infants and Children

Apnea, laryngospasm
Paradoxical vocal cord motion
Laryngomalacia
Recurrent croup
Laryngeal granulations
Acquired glottic web
Hoarseness, chronic cough
Aspiration
Subglottic stenosis (and laryngeal surgery)

The most important GER-associated laryngeal phenomena in infants are motor disorders. GER is found in more than 90% of cases of laryngomalacia.[27] GER may cause edema at the laryngeal inlet. GER also may be induced by the negative endothoracic pressure resulting from the airway obstruction. GER is probably associated only with pharyngoesophageal motor anomalies that are caused by the neurologic dysfunction that determines laryngomalacia.[27] Glottic and pharyngoesophageal dysfunctions that occur simultaneously with GER lead to aspiration. In return, laryngeal adductor responses seem to coincide with reflux in premature newborns, with subsequent obstructive reflex apnea.[4]

Apnea in neonates and obstructive sleep apnea in adults have been reported as linked to GER. The concomitant time with GER episodes has been shown in premature infants by Orenstein and colleagues.[4] Senior and associates[28] described a decline of obstructive sleep apnea scores at polysomnography with anti-GER treatment. Dyce and coworkers[29] stated that GER is associated with many congenital disorders, including Pierre Robin sequence and 22q11 deletion syndrome.

Hoarseness and vocal fold nodules are sometimes described as a result of GER. Mandell and colleagues[30] compared the results of esophageal biopsy with endoscopic findings and bronchioalveolar lavage in a series of 127 hoarse children including 104 with nodules. There was no correlation between biopsy and bronchioalveolar lavage results, and endoscopy was more contributory than any other test. In a study of 254 pediatric patients, Shah and associates[31] found only one quarter of GER-positive cases. It seems that the incidence of GER in hoarse children may vary depending on the criteria used and the type of assessment made. Vocal cord dysfunction or laryngeal dyskinesia are strongly associated with psychiatric illness and GER.[32]

A link between GER and recurrent respiratory papillomatosis has been suggested by McKenna and Brodsky[33] from a series of four children whose noncompliance with anti-GER treatment determined occurrence of laryngeal symptoms and reappearance of papillomas at endoscopy. All these studies widely favor the close relationship between GER and inflammatory features of the larynx. They do not carry any direct evidence of the role of GER, however, owing to nonspecific aspects of the described features (except for contact ulcers, which are very rare in children).

Possible Role of Gastroesophageal Reflux

Because no direct role of GER has been shown by GER tests, endoscopy, and biopsy, therapeutic trials were used to search for indirect evidence. Besides acid and pepsin, many other components of refluxed material may be harmful, according to experimental animal or in vitro studies. Even powerful antagonists of gastric H^+ ion secretion may be useless in cases of documented GER with laryngeal involvement without esophagitis.

A retrospective study examined the impact of anti-GER treatments on the development of subglottic stenosis after surgery, and found there were fewer tracheostomies remaining in the treated group.[34] This study's method may be biased, however, and the same suspicion arose in other small series.[26,35] Of five published randomized controlled trials on the efficacy of GER treatments versus placebo in adult laryngeal disorders, four were negative, and the positive trial was considered weak because it included only 11 patients in each group.[16]

The implication of GER in laryngeal pathologies remains a controversial topic. It is still unclear how refluxed material ascending from the stomach may be harmful to the laryngeal mucosa, and which mechanisms, common muscular or immune or both, lead to GER and laryngeal inflammation. In the first hypothesis, we may wonder why many patients with GERD have no laryngeal disorder (even while vomiting and aspirating). In the latter, is the common digestive mechanism the cause or the consequence of laryngeal diseases? If it is not the consequence, further studies are necessary to find out if different types of reflux exist, or, more likely, if different types of laryngeal sensitivity could explain the controversial results in the described series. This laryngeal sensitivity may be related to other particular laryngeal descriptions, such as apnea encountered in preterm infants,[36] and laryngeal dysfunctions such as laryngomalacia[10,37] and paradoxical vocal fold motion.[38]

Management

The first step in antireflux management is to ensure that the patient has an age-appropriate diet and lifestyle. Foods that relax the lower esophageal sphincter should be avoided. Small meals at regular times and avoidance of any food or drink 1 hour before bedtime are common recommendations. Infants should be given milk thickened with rice, and fruit juice should be avoided. The posture of the patient at rest also is extremely important. Gravity reduces the frequency and strength of reflux episodes. Raising the head of the bed by 10 to 15 degrees is recommended for children, whereas infants who weigh up to 10 kg can be placed on a special mattress with a 30- to 45-degree slope. Pillows should be avoided. When not in bed, infants should be as upright as possible, even when physiotherapy is applied.

Recommended antireflux drugs (prokinetics) stimulate esophageal and gastric motility, while reinforcing the tonicity of the lower esophageal sphincter. Domperidone and metoclopramide can be prescribed despite their risk of adverse side effects (extrapyramidal syndrome with high dosage). Alginates coat the gastric contents and prevent its reascension. H_2 blockers inhibit gastric acid secretion and have been successfully used in some difficult cases, but some pediatric patients are nonresponders. Proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole) are now widely used in adult and pediatric patients. They prevent the release of hydrogen ions and are useful in severe forms resistant to other management. Management usually continues for years. Drugs can be limited to 2- to 3-month cycles, however, because the spontaneous course of the disease is typically episodic except in infants, in whom management may be continued for longer periods. Surgery (mainly Nissen fundoplication) is appropriate in cases in which severe disorders recur as soon as drugs are withdrawn, or in which medical control is impossible to achieve.

Conclusion

GER is strongly associated with many laryngeal disorders in infants and children, although evidence of a causal relationship is still lacking. This phenomenon is probably explained by different local sensitivities among subjects. The significant association is a strong argument, however, in favor of an anti-GER treatment in the absence of another obvious cause, or when critical surgery involving the airway is planned. Based on their experience, most laryngologists recommend that GER should be sought and managed in cases of recurrent laryngitis and of surgery for subglottic stenosis and other laryngeal abnormalities, such as nodules, cysts, and posterior cleft.[39] Whether prokinetic or anti-H^+ agents are most efficacious is still unknown.

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CHAPTER TWO HUNDRED AND TEN

Aspiration and Swallowing Disorders

David J. Brown

Maureen A. Lefton-Greif

Stacey L. Ishman

Key Points

- In evaluating children with aerodigestive disorders, the first priority is securing a safe airway.
- The coordination of breathing and swallowing is crucial to survival because both functions share the pharynx as a common conduit.
- The four phases of swallowing are the oral preparatory, oral, pharyngeal, and esophageal phases.
- The characteristics of dysphagia are defined by the anatomic site of impairment: nose and nasopharynx, oral cavity and oral pharynx, hypopharynx and larynx, and trachea and esophagus.
- Swallowing must provide sufficient nutrition and fluid for optimal growth and development.
- Videofluoroscopic swallow studies and flexible endoscopic evaluation of swallowing are commonly used evaluation tools to assess the pharyngeal phase of swallowing deficits.
- Dysphagia management may include feeding modifications, supplemental nutrition, oral motor and swallowing therapies, and alternative feeding routes.

Swallowing involves multiple, highly integrated, and partially overlapping actions; however, for discussion purposes, it is frequently separated into three phases—*oral, pharyngeal,* and *esophageal*. During the *oral phase,* food is processed into a "swallow-ready ball" (bolus), and then transported to the back of the mouth. This phase is limited to sucking fluid from a nipple during infancy. After approximately 6 months of age, this phase is sometimes subdivided to include the *oral preparatory phase,* which conditions solid foods requiring chewing. The *pharyngeal phase* comprises a series of complex and interrelated events that direct and propel boluses through the pharynx into the esophagus while the airway is protected. During this phase of swallowing, the velum rises and approximates the pharyngeal walls, breathing stops, the larynx rises, the vocal folds adduct, and the base of tongue and pharyngeal muscles propel the bolus through a relaxed upper esophageal sphincter. The act of swallowing results in mechanical closure of the airway and cessation of breathing. The *esophageal phase* begins when the bolus enters the esophagus and ends when it passes into the stomach.

Typical swallowing maturation involves transformation from the primitive sucking and swallowing reflexes used during infancy into the mature and volitional functions of biting, chewing, and bolus formation necessary for the safe and adequate delivery of nutrients in older children and adults. Appropriate adjustments to growth and developmental changes of the aerodigestive system and changes in airway protective responses are essential to competent postnatal maturation processes. Changes in the anatomic relationships of the oral cavity, pharynx, and larynx occur throughout the first few years of life and are well described. In addition, neurodevelopmental, cognitive, and sensory inputs modulate deglutitive function, and consequently may influence the maturation process.

Competent deglutition (the act of swallowing) is crucial to survival. Two primary functions of swallowing are to direct oral secretions, liquids, and food from the mouth to the stomach while protecting the airway, and to provide sufficient amounts of nutrients and fluids for children to grow and develop optimally. Appropriate adjustments to growth and increases in nutritional needs are crucial to successful postnatal deglutition. Because breathing and swallowing share common conduits, such as the oral cavity and pharynx, their functions are intertwined.

Dysphagia (swallowing dysfunction) may be caused by any condition that interferes with structural integrity of the structures comprising the aerodigestive tract or their coordination. Congenital or acquired structural or anatomic anomalies may cause airway and swallowing defects. This chapter focuses on the evaluation of infants and children with suspected dysphagia and the associated primary aerodigestive tract anomalies. Management approaches to swallowing and airway-related problems are reviewed.

Evaluation of Infants and Young Children with Suspected Dysphagia

Clinical or Bedside Evaluation

Evaluation of all children with feeding and swallowing difficulties begins with taking a thorough history and performing a physical exam-

ination. Children with anatomic anomalies are at increased risk for dysphagia when the underlying conditions interfere with the structural integrity of the oropharynx or the complex coordination of neuromuscular and airway processes involved in deglutition; consequently, the focus of the clinical evaluation is the identification of diagnostic tests that determine the nature and extent of the swallowing impairments, and assist with management decisions. Children who present with structural anomalies as one component of a complex medical history or syndrome (e.g., bronchopulmonary dysplasia or Smith-Lemli-Opitz syndrome) may require other specialized evaluations (e.g., direct laryngoscopy and bronchoscopy) to determine the impact of the associated comorbidities on swallowing.

Instrumental Evaluation

When the clinical evaluation identifies problems that may be caused by or reflect problems that are invisible, an instrumental evaluation is typically recommended. Common examinations that allow for direct visualization of the structures involved in swallowing include radiologic (e.g., upper gastrointestinal series [UGI] and videofluoroscopic swallow studies [VFSS]) and endoscopic (e.g., flexible endoscopic evaluation of swallowing [FEES]) procedures. Clinicians need to be cautious about the interpretation of negative findings of aspiration during UGI, VFSS, and FEES. Each of these evaluations may establish a diagnosis of dysphagia by identifying specific aspects of the pathophysiology of the dysfunction; however, they may fail to detect aspiration even in children who aspirate, particularly when aspiration is episodic.

Upper Gastrointestinal Series

UGI may provide important information for children with anatomic anomalies, particularly when the anomaly is distal to the oropharynx. UGI provides information that allows for assessment of the anatomy and physiology of the esophagus, stomach, and duodenum; defines gastrointestinal obstructions; and identifies malrotation. In addition, it serves as a screen of the oropharyngeal structures and their functions. Decisions about whether liquid barium should be administered orally or by nasogastric tube are determined by the specific diagnostic questions, and whether children are at risk for aspiration secondary to swallowing dysfunction.

Videofluoroscopic Swallow Study

VFSS, sometimes referred to as a modified barium swallow study, may be useful in children suspected to have oropharyngeal dysphagia because it images the structures of the oral cavity, pharynx, and cervical esophagus during deglutition.[1] VFSS may screen gastrointestinal structures distal to the cervical esophagus. The goals of VFSS are to provide information that helps determine whether anatomic or structural abnormalities are present; ascertain if coordination of the structures and functions of the upper aerodigestive tract supports safe and efficient bolus passage; and identify strategies that enhance the safety and efficiency of feeding, while minimizing the dysphagic problems. During VFSS, children ingest liquids or foods or both impregnated with barium contrast material to simulate functional feeding as closely as possible. Consequently, children must be ready, willing, and able to cooperate with VFSS.[2,3]

Flexible Endoscopic Evaluation of Swallowing

FEES is an extension of the routine flexible fiberoptic nasopharyngolaryngoscopy examination, and may be used to evaluate the structures and functions of the nasopharynx, oropharynx, and larynx during phonation, spontaneous swallows, and swallows of liquids and foods.[4,5] FEES may be particularly useful in children who are nonoral feeders, who are unable to cooperate with VFSS, who have vocal fold dysfunction, or in whom their ability to handle their secretions is questionable.

FEES may provide sensory information when the endoscope touches adjacent mucosa or structures. To standardize evaluations of responses to sensory input, calibrated air pulses have been administered endoscopically.[6] The utility of FEES plus sensory air pulse testing (FEES-ST) has been shown during the evaluation and treatment of children with specific diagnostic conditions (e.g., type I laryngeal clefts) and during preoperative evaluations for pediatric airway reconstruction.[7,8] Elevated laryngopharyngeal sensory thresholds have been documented in children with clinical diagnoses of recurrent pneumonia, neurologic disorders, and gastroesophageal reflux disease (GERD).[6] Table 210-1 outlines the utility of using VFSS and FEES based on the anatomic or structural condition.

Other Diagnostic Evaluations

Other diagnostic tests may be needed to determine the cause of the swallowing dysfunction. Imaging of the brainstem may be needed to diagnose abnormalities of the skull base or spine as potential underlying conditions. Specialized evaluations may be needed for children with refractory respiratory conditions. Chest radiographs, pulmonary function tests, high-resolution computed tomography (CT), and bronchoscopy provide information regarding the extent of lung injury. Endoscopy of the gastrointestinal tract may be beneficial for patients with histories or presentations suggestive of gastrointestinal conditions.

Four Anatomic Sites of Dysphagia

The four primary anatomic sites with anomalies of the aerodigestive tract that may adversely affect swallowing and contribute to dysphagia are the nose and nasopharynx, oral cavity and oral pharynx, hypopharynx and larynx, and trachea and esophagus (Fig. 210-1).

Nose and Nasopharynx

Anomalies of the nose and nasopharynx affect the oral and pharyngeal phases of swallowing. Dysphagia from anomalies of the nose and nasopharynx is secondary to upper airway obstruction and the caliber of the upper airway and the child's ability to compensate while swallowing (Fig. 210-2). Bilateral disease has a more significant impact on airway patency and swallowing than unilateral disease.

Any cause of nasal airway obstruction can lead to feeding difficulties, particularly during infancy when nasal airflow is an important component of breathing and feeding. Nasal obstruction can result from myriad conditions, including midface hypoplasia, congenital nasal pyriform aperture stenosis, septal deviation or hematoma, chronic or acute rhinitis, congenital midline nasal masses (including dermoids, encephaloceles, and gliomas), nasal or nasopharyngeal tumors, choanal atresia, and adenoidal hypertrophy. These children frequently have difficulty coordinating feeding and breathing, and may have failure to thrive or recurrent aspiration.[9]

Unilateral nasal disease may not be detected for years and is often associated with unilateral nasal congestion or rhinorrhea. Bilateral disease has a more significant impact on airway patency and swallowing than unilateral disease and is usually recognized soon after birth because the child commonly has severe respiratory difficulties with cyclical cyanosis relieved by crying.[10] These children are also unable to feed effectively, and may have coughing and choking with cyanotic spells when attempting to eat. Diagnostic evaluation often starts with attempted passage of a 6F feeding tube through the nares. A thorough evaluation with flexible fiberoptic endoscopy and imaging should be carried out if nasal obstruction is suspected. Figure 210-2 outlines the evaluation for children with dysphagia that is suspected to originate from the nose and nasopharynx.

Oral Cavity and Oral Pharynx

Anomalies of the oral cavity and oral pharynx may affect the oral and pharyngeal phases of swallowing, and many have the potential for upper airway obstruction. The respiratory issues should be evaluated and stabilized before initiating the feeding efforts or evaluations for suspected dysphagia (Fig. 210-3).

Functional swallowing depends on efficient bolus formation and movement of the bolus from the mouth to the stomach, and coordination of breathing with bolus passage to protect the airway. Successful bottle-feeding and breastfeeding requires compression of the nipple and the generation of sufficient negative intraoral pressure for suction. Anatomic abnormalities that compromise either the compression or the suction actions of nipple feeding may create feeding difficulties by decreasing the efficiency of feeding. Although abnormalities of the oral

Table 210-1

Anatomic Locations, Conditions, Phases of Swallowing Dysfunction, and Utility of Videofluoroscopic Swallow Studies and Flexible Endoscopic Evaluation of Swallowing

Anatomic Location	Anatomic or Structural Condition	Potential Phase of Swallowing Impairment			Indication for VFSS	Indication for FEES
		Oral	Pharyngeal	Esophageal		
Nose and nasopharynx	Midface hypoplasia	+	+		Sometimes	Sometimes
	Pyriform aperture stenosis	+	+		Sometimes	Sometimes
	Deviated septum	+	+		No	No
	Encephalocele	+	+		No	No
	Tumor	+	+		No	No
	Choanal atresia	+	+		No	No
	Adenoid hypertrophy	+	+		No	No
Oral cavity and oropharynx	Cleft lip/palate	+			No	No
	Micrognathia or retrognathia	+	+		Sometimes	Sometimes
	Macroglossia	+	+		Sometimes	Sometimes
	Tumor	+	+		Sometimes	Sometimes
Hypopharynx and larynx	Vallecular cyst		+		No	No
	Laryngomalacia		+		Sometimes	Sometimes
	Vocal fold paralysis/paresis		+		Yes	Yes
	Laryngeal web		+		Sometimes	Sometimes
	Posterior laryngeal cleft		+	+	Yes	Yes
	Subglottic stenosis		+	±	Sometimes	Sometimes
	Subglottic hemangioma		+	±	Sometimes	Sometimes
Trachea and esophagus	GERD		±	+	Sometimes	No
	Eosinophilic esophagitis		±	+	Sometimes	No
	Vascular ring			+	Sometimes	No
	Tracheal stenosis			+	Sometimes	No
	Tracheomalacia			+	Sometimes	No
	Tracheoesophageal fistula			+	Sometimes	No

+, yes; ±, sometimes; FEES, flexible endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease; VFSS, videofluoroscopic swallow studies.

cavity and oropharynx may occur in isolation, they frequently co-occur with defects in other portions of the aerodigestive tract, and may also compromise airway function. As always, airway concerns are the first priority and are addressed before attention is focused on feeding and swallowing. This section reviews common conditions affecting the oral cavity and oropharynx, including cleft lip and palate, micrognathia or retrognathia, and macroglossia.

Cleft lip may affect infant feeding by interfering with the lips and tongue creating a seal around the nipple. This interference may compromise the compression phase of sucking and cause excessive fluid loss. Palatal clefts may compromise the suction phase of nipple feeding by interfering with the generation of the negative intraoral pressure needed to extrude fluid from the nipple. The extent of the impact of any anatomic defect depends on multiple factors (e.g., location and extent of impairment, the presence of other anomalies or comorbidities). Some children with isolated small cleft lips or submucous clefts feed without problems or have mild problems that are amenable to feeding routine adaptations.[11] Special feeders, such as the Haberman feeder or Mead-Johnson nurser, allow infants to compensate when there are problems with the compression phase of nipple feeding. Caregivers squeeze the bottles to deliver fluids. Additionally, a cross-cut nipple can be used to facilitate fluid flow. These adaptations are often used before surgical repair of the cleft lip or palate. Clinicians must be cautious about airway protective mechanisms (i.e., aspiration potential) before recommending any feeding routine adaptation that increases the rate of fluid flow.

Common craniofacial syndromes associated with cleft lip and palate are Apert's, Stickler's, and Treacher Collins syndromes; Pierre Robin sequence; CHARGE (coloboma, heart disease, atresia choanae, retardation, genital hypoplasia, and ear anomalies) association; and 22q11 deletion syndromes including velocardiofacial syndrome and DiGeorge syndrome.[12] These conditions may interfere with aspects of feeding and swallowing beyond those localized to the oral cavity or oropharyngeal structures.

Micrognathia and retrognathia can occur in isolation; however, they also occur in association with Pierre Robin sequence and genetic syndromes such as Goldenhar's, Treacher Collins, Smith-Lemli-Opitz, and cri du chat syndromes. Retrognathia and micrognathia may compromise airway patency and feeding secondary to retrodisplacement of the tongue. In Pierre Robin sequence, airway obstructive patterns are caused by pharyngeal collapse and velum elongation leading to palatal and base of tongue obstruction.[13] In addition to the interference with the compression and suction phases of nipple feeding, the combination of a relatively small oropharynx and nasopharyngeal reflux secondary to a cleft palate may compromise breathing and swallowing coordination. The diagnosis is made by clinical evaluation and confirmed by instrumental assessment, if warranted. The prognosis for successful oral feeding depends on the degree of respiratory distress and the presence

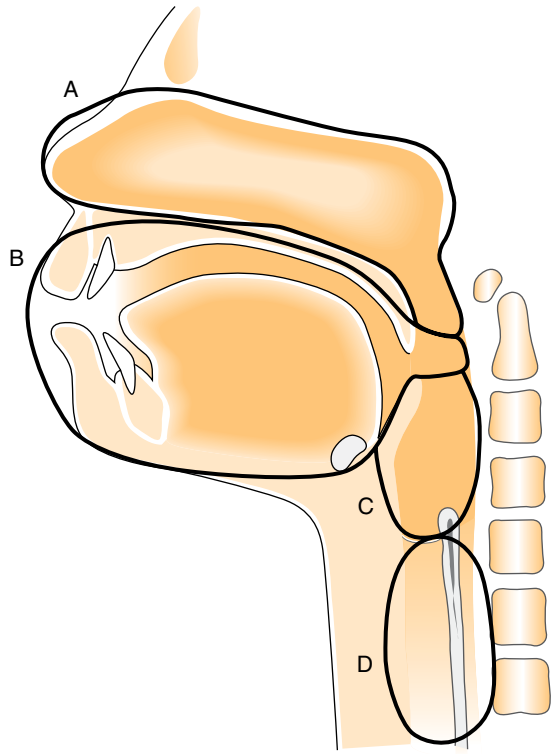

Figure 210-1. Four anatomic sites of dysphagia. **A,** Nose and nasopharynx. **B,** Oral cavity and oral pharynx. **C,** Hypopharynx and larynx. **D,** Trachea and esophagus. *(© 2008 by Johns Hopkins University, Art as*

of associated issues or diagnoses. Patients with Pierre Robin sequence–associated syndromes generally require gastrostomy tube placement despite successful airway intervention.[14]

Macroglossia often leads to feeding difficulty because tongue enlargement may interfere with the creation and maintenance of an adequate lip-tongue and nipple seal. Additionally, tongue movement may be restricted, leading to difficulty controlling food in the oral cavity. Macroglossia is associated with Down syndrome and Beckwith-Wiedemann syndrome. Feeding problems are reported in 50% to 80% of children with Down syndrome; specific dysphagia characteristics include delayed and aberrant oral-motor function, abnormal tongue and mandibular function, and delayed initiation with difficulty of the oral phase of swallowing.[15,16] Hypotonia may also compound feeding and swallowing problems in children with Down syndrome.

Pharyngeal diverticula or tumors are less commonly seen in children. The effects of these conditions depend on the size and location of the defect, and there may be no impact on feeding unless these are significantly enlarged.

Hypopharynx and Larynx

Anomalies of the hypopharynx and larynx may affect the pharyngeal and esophageal phases of swallowing. Initial evaluation usually involves performing a flexible fiberoptic laryngoscopy (Fig. 210-4).

Vallecular cysts are rare mucous retention cysts that manifest with stridor, respiratory distress, dysphagia, and failure to thrive. These cysts sit in the vallecular space and can cause significant retroflexion of the epiglottis, which leads to respiratory distress and dysphagia. Dysphagia can result from interference with base of tongue and epiglottic movement and from obstruction of the natural lateral flow of food around the epiglottis during swallowing. Vallecular cysts can be diagnosed by flexible fiberoptic laryngoscopy, direct laryngoscopy, or a swallow study. They can be seen on CT and magnetic resonance imaging (MRI), but are difficult to see on plain films of the neck.

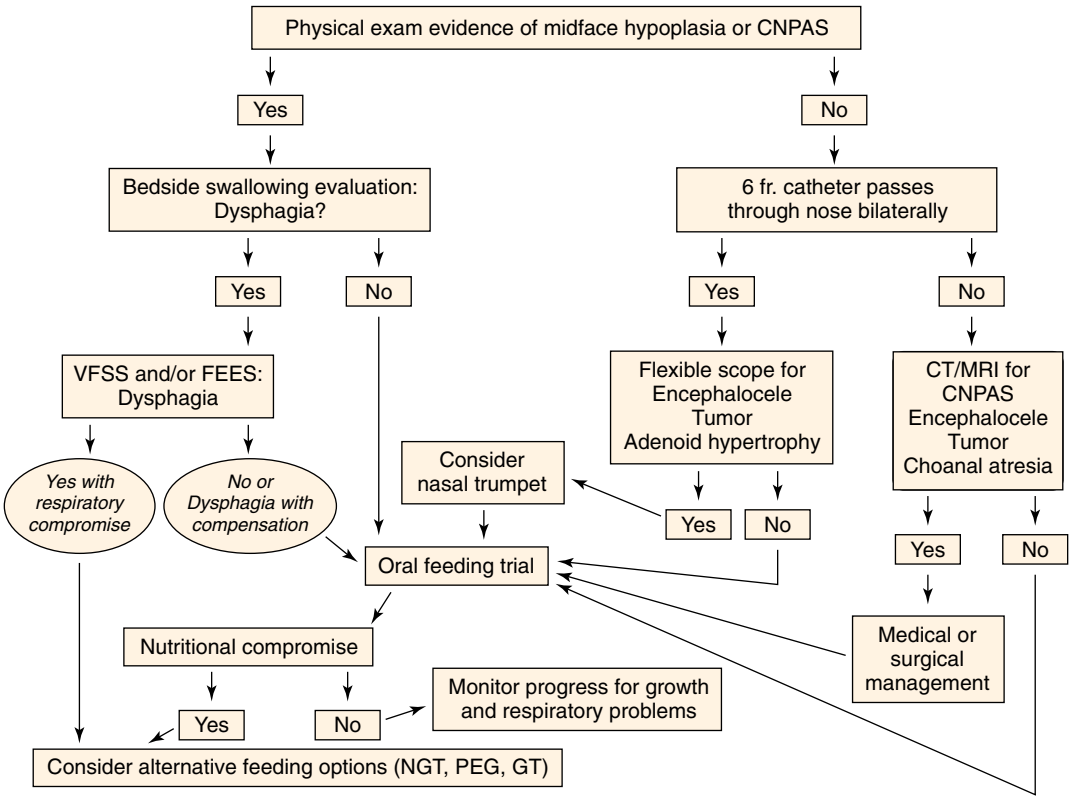

Figure 210-2. Evaluation and management of dysphagia with suspected nose and nasopharynx anomaly. CNPAS, congenital nasal pyriform aperture stenosis; FEES, flexible endoscopic evaluation of swallowing; GT, gastrostomy tube; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; VFSS, videofluoroscopic swallow studies.

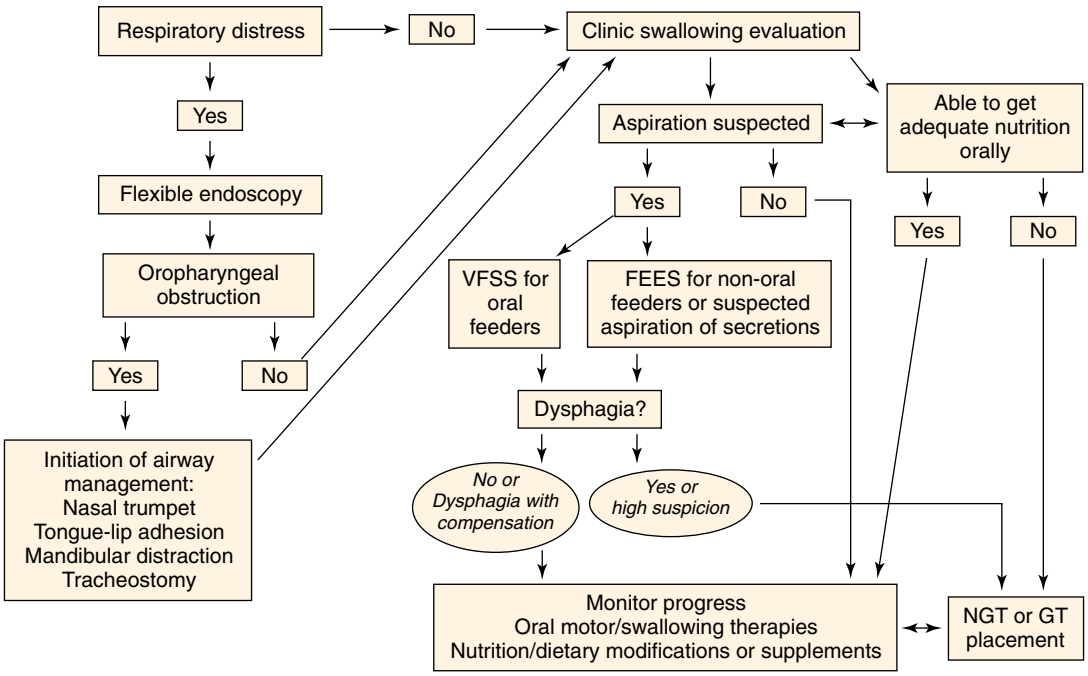

Figure 210-3. Evaluation and management of dysphagia with suspected oral cavity and oropharynx anomaly. FEES, flexible endoscopic evaluation of swallowing; GT, gastrostomy tube; NGT, nasogastric tube; VFSS, videofluoroscopic swallow studies.

Surgical management of vallecular cysts is recommended by marsupialization of the cyst and removal of the mucosal lining, which can be performed with a carbon-dioxide laser, cold knife, or a microdébrider. Yao and colleagues[17] described an 11-week-old infant with a vallecular cyst, choking with feeds, failure to thrive, stridor, laryngomalacia, and gastroesophageal reflux.[17] After surgical removal of the cyst, the aerodigestive symptoms resolved within days, as is often the case. This patient showed improvement in weight percentiles from less than 10th percentile at the time of surgery to the 50th percentile 12 weeks later.

Laryngomalacia is the most common cause of stridor in infants, representing more than 70% of cases. These children present with inspiratory stridor secondary to collapse of the epiglottis or arytenoids or both during inspiration. Many studies have found that laryngomalacia is associated with gastroesophageal reflux and underlying neurologic conditions.[18-20] Respiratory distress can be seen in more severe cases with cyanosis, obstructive sleep apnea, supraclavicular retractions, and subcostal retractions. Severe laryngomalacia can also contribute to feeding difficulties heralded by choking while feeding, failure to thrive, and emesis.

Laryngomalacia is diagnosed by flexible fiberoptic laryngoscopy with the infant awake and upright. Infants with presentations suggestive of dysphagia should have a swallowing evaluation. More than 90% of patients with laryngomalacia are treated nonsurgically with close clinical follow-up. Matthews and coworkers[21] found that of 24 infants diagnosed with laryngomalacia who had 24-hour double-probe pH monitoring, all had at least one episode of pharyngeal refluxate, and greater than 90% had three episodes. Because GERD and laryngomalacia seem to coexist, many clinicians manage laryngomalacia patients with antacids or proton pump inhibitors. For patients with respiratory distress or failure to thrive, a supraglottoplasty is recommended. Lee and associates[22] showed that carbon-dioxide laser supraglottoplasty can improve substernal and suprasternal retractions, but that many patients continued to have choking and feeding problems postoperatively. This condition warrants a postoperative swallowing evaluation and close clinical follow-up.

Vocal fold paralysis represents 10% of congenital laryngeal anomalies. Infants may have unilateral or bilateral vocal fold paralysis, and can present with stridor, recurrent aspiration, and dysphagia from the inability to protect the airway. The diagnosis is best made by flexible fiberoptic laryngoscopy in an awake patient. Management of vocal fold paralysis in children should focus first on establishing a safe airway. After the airway is stable, the nutritional needs should be assessed.

Swallowing difficulties can be evaluated by VFSS or FEES or both. These evaluations can identify penetration, aspiration, the patient's ability to protect the airway adequately, and the effect of changes in feeding utensils (e.g., fast vs. slow flow nipples) or different liquid viscosities (e.g., thin vs. thick liquids). Some infants benefit from a slower swallowing transit time, which can be accomplished by decreasing the flow from the bottle's nipple or by thickening the formula or breast milk. Other infants require a feeding tube to obtain adequate nutrition and hydration.

Laryngeal webs can be congenital, secondary to incomplete resorption of the laryngeal lumen epithelium during embryologic development, or acquired from vocal fold trauma secondary to laryngeal surgery or endotracheal intubation. Infants may present with stridor, a weak cry, hoarseness, respiratory distress, and aphonia, and some may have dysphagia. Laryngeal webs are associated with cardiac and 22q11 anomalies. The diagnosis is made by flexible fiberoptic laryngoscopy or direct laryngoscopy. Thin webs can be managed by endoscopic lysis, whereas thicker webs require an open laryngeal fissure and placement of a laryngeal keel or stent. For patients with preoperative dysphagia, a follow-up swallowing evaluation should be performed postoperatively.

Posterior laryngeal clefts are uncommon congenital anomalies caused by incomplete formation of the septum between the esophagus and the airway. This laryngeal anomaly is associated with tracheoesophageal fistulas in one third of cases. The Benjamin-Inglis classification system describes four types of posterior laryngeal clefts: Type 1 clefts are interarytenoid and lie above the level of the true vocal folds, type 2 clefts extend below the true vocal folds and partially through the cricoid cartilage, type 3 clefts extend into the extrathoracic trachea, and type 4 clefts extend into the intrathoracic trachea.[23] Common presentations are stridor, choking, aspiration, chronic cough, and failure to thrive. Direct laryngoscopy and bronchoscopy should be performed with bimanual palpation and probing of the interarytenoid area to confirm the diagnosis. Microaspiration and penetration can be seen on FEES or VFSS.

The management of posterior laryngeal clefts depends on the extent of the cleft. Chien and colleagues[7] found type 1 posterior

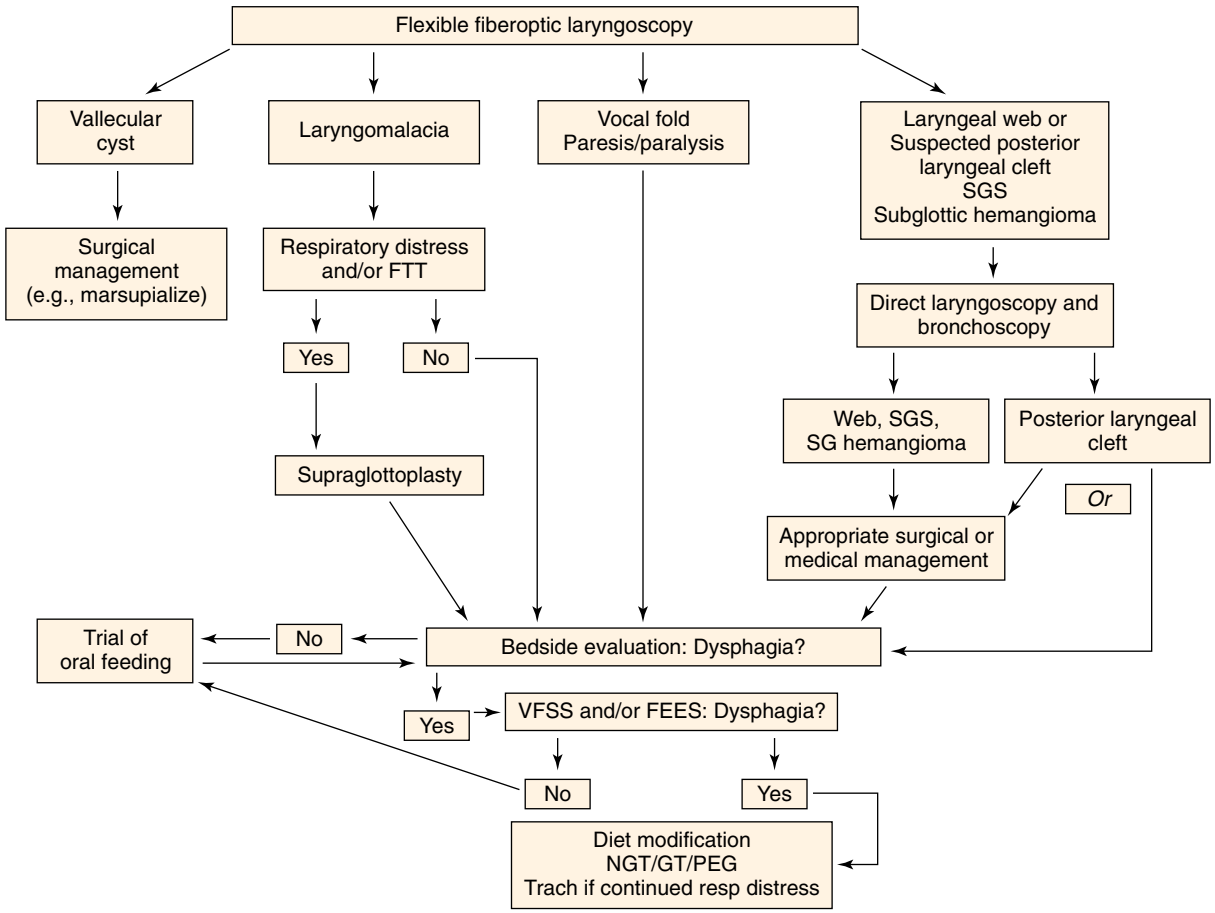

Figure 210-4. Evaluation and management of dysphagia with suspected hypopharynx and larynx anomaly. FEES, flexible endoscopic evaluation of swallowing; FTT, failure to thrive; GT, gastrostomy tube; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; SG, subglottic; SGS, subglottic stenosis; VFSS, videofluoroscopic swallow studies.

laryngeal clefts in 1 of 13 patients presenting to their institution with symptoms of chronic cough or aspiration over a 3-year period. They recommend that type 1 clefts have a trial of nonsurgical management first with a proton pump inhibitor to treat GERD, upright feedings, and thickened feedings. Children who fail conservative treatment should have surgical repair. Types 1 and 2 posterior laryngeal clefts can be repaired endoscopically, whereas type 3 and 4 clefts require an open surgical repair. A postoperative swallowing study should be performed.

Subglottic pathologies such as stenosis and hemangiomas affect swallowing in similar ways. Subglottic anomalies manifest with inspiratory or biphasic stridor, and the best evaluation method is by direct laryngoscopy and bronchoscopy. MRI or three-dimensional CT may be useful in delineating the extent of subglottic narrowing. The increased work of breathing can lead to increased laryngeal refluxate, penetration, and aspiration. The acidic refluxate into the subglottis can lead to further airway edema and narrowing. The first priority for these patients is to ensure a stable airway. When that has been achieved, swallowing function can be assessed by a bedside swallowing evaluation, and VFSS or FEES if indicated.

Trachea and Esophagus

Dysphagia of the trachea and esophagus may affect the pharyngeal and esophageal phases of swallowing. In addition to structural anomalies, inflammatory conditions such as GERD and eosinophilic esophagitis can affect these areas. The initial evaluation depends on the specific condition suspected. Figure 210-5 outlines a working algorithm for evaluating these patients.

GERD symptoms such as regurgitation and emesis occur in 50% to 67% of normal children, with most having symptom resolution by 1 to 2 years of age.[24,25] Children younger than 2 years old present with airway symptoms (stertor, stridor, or cyanosis) and feeding abnormalities (vomiting, dysphagia, and failure to thrive).[26] GERD can affect all of the major aerodigestive anatomic areas (see Fig. 210-1), and has been implicated in stertor, lingual tonsil hypertrophy, arytenoid edema, vocal fold edema, subglottic edema, cobblestoning of the trachea, and blunting of the carina.[27,28]

GERD is also associated with other known conditions that affect the aerodigestive tract. Giannoni and colleagues[20] prospectively evaluated 33 consecutive infants diagnosed with laryngomalacia and noted that 64% had GERD. Additionally, GERD was associated with more severe cases of laryngomalacia and cases with complicated clinical courses. Animal studies have linked gastric acid and pepsin to subglottic stenosis and vocal fold granulomas.[29,30]

When GERD affects the upper aerodigestive tract, it is referred to as *laryngopharyngeal reflux*. The diagnostic workup for LPR in infants lacks consensus and includes symptom assessment questionnaires, flexible fiberoptic laryngopharyngoscopy, single-lumen or double-lumen pH probe, barium esophagogram, scintigraphy, impedance, and laryngeal biopsy. Often a trial of antireflux medication is given to see if symptoms resolve.

GERD can affect the sensation of the larynx and blunt protective reflex mechanisms. Suskind and coworkers[31] retrospectively reviewed 28 infants with GERD and found altered laryngeal sensation by FEES and FEES-ST and dysphagia by VFSS and FEES. GERD was managed medically or surgically, and repeat VFSS and FEES-ST testing showed improved laryngeal sensation and swallowing function. These authors hypothesize that the refluxate causes laryngeal edema and decreased sensation, which alters the laryngeal adductor reflex, and then disrupts the suck-swallow-breathe sequence and causes dysphagia.

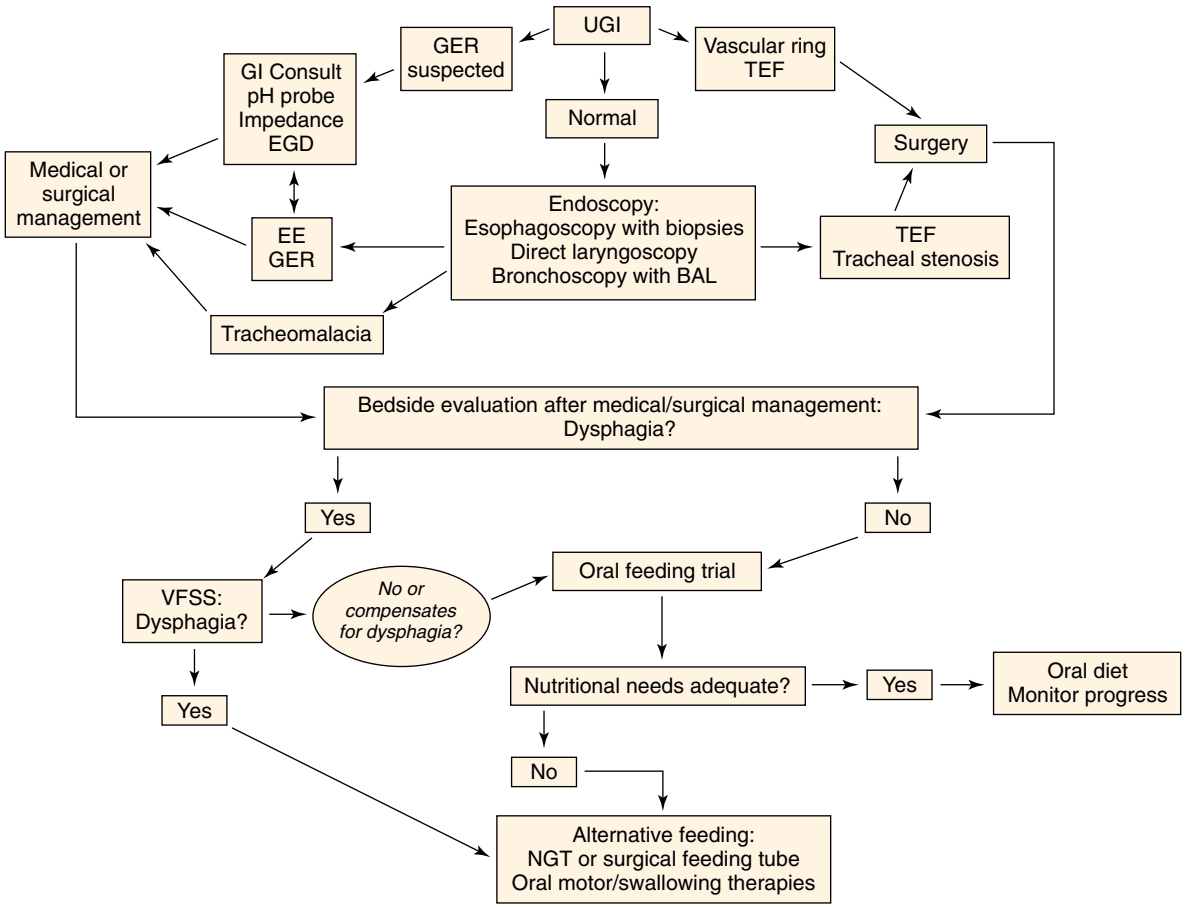

Figure 210-5. Evaluation and management of dysphagia with suspected trachea and esophagus anomaly. BAL, bronchoalveolar lavage; EE, eosinophilic esophagitis; EGD, esophagogastroduodenoscopy; GER, gastroesophageal reflux; GI, gastrointestinal; NGT, nasogastric tube; TEF, tracheoesophageal fistula; UGI, upper gastrointestinal series; VFSS, videofluoroscopic swallow studies.

Eosinophilic esophagitis is an inflammatory process of the mucosal and submucosal layers of the esophagus.[32] Symptoms often mimic the symptoms of GERD with feeding difficulties predominating in infants and toddlers; vomiting and abdominal pain are common in school-age children, and dysphagia is evident in preadolescents.[33] Food impaction may occur in older children and adults. Diagnosis of eosinophilic esophagitis is made by a combination of the clinical symptoms listed previously and histologic confirmation of 15 eosinophils or more per high-powered field along with normal gastric and duodenal biopsy specimens. In addition, biopsies must be performed after 6 to 8 weeks of regular proton pump inhibitor therapy or have a documented negative pH probe study.[34,35] Eosinophilic esophagitis may be patchy, and the diagnosis requires multiple biopsies; often four or five are recommended.

In contrast to GERD, treatment with acid-blocking therapies is ineffective in alleviating symptoms. Dietary changes, such as implementation of an elemental diet, suggest that food allergies play an important part in the pathogenesis of this disease.[36] Elemental diets have been shown to be effective greater than 95% of the time; other approaches include directed elimination diets (>75% effective) and empirical elimination diets (>70% effective).[37] Systemic steroids have also been advocated. Histologic remission has been documented after 4 weeks of corticosteroid use, although recurrence is common within 6 months of the cessation of treatment.[38] Topical corticosteroids, swallowed instead of inhaled, have also been advocated to treat acute eosinophilic esophagitis, and are known to reverse the associated clinical symptoms and histologic changes.[37]

Congenital tracheal stenosis is a rare congenital anomaly consisting of complete, circular tracheal rings. More than one third are associated with pulmonary slings or other cardiovascular anomalies. The dysphagia can be secondary to increased work of breathing or the associated vascular anomalies. CT, three-dimensional CT, and MRI are useful in determining the stenotic length and the presence of associated vascular anomalies. Bronchoscopy confirms the presence of complete tracheal rings and the length of the stenosis. Although many of these children require surgical correction, Rutter and associates[39] estimated 10% can be managed without surgery. Adequate nutrition and growth are crucial for these children. Oral feeders should have evaluation by FEES or VFSS or both because aspiration can result in significant respiratory compromise in these children with small airway caliber.

Tracheomalacia is anterior-to-posterior collapse of the trachea. Children with tracheomalacia present with expiratory stridor, wheezing, coughing, and sometimes dysphagia. Conditions that affect the structural integrity of the trachea such as tracheoesophageal fistulas, esophageal anomalies, vascular rings and slings, and innominate artery anomalies can cause tracheomalacia. The dysphagia can be a result of increased work of breathing, from the associated esophageal anomaly, or from vascular anomalies compressing the esophagus.

The diagnosis can be made by either airway fluoroscopy or bronchoscopy. Esophagograms are useful to identify esophageal anomalies and vascular anomalies compressing the esophagus. MRI can evaluate the extent of vascular anomalies further.

Tracheomalacia related to weak tracheal cartilage often resolves spontaneously in 2 to 3 years, as the child and the tracheal airway grow. Infants who are symptomatic with respiratory distress may require continuous positive airway pressure. Infants with tracheal collapse from esophageal or vascular anomalies benefit from surgical correction of the offending anomaly. Assessment of swallowing function may include VFSS and UGI after surgical correction.

Conclusion

Functional swallowing involves a complex orchestration of events throughout the aerodigestive tract. We have outlined four anatomic areas of the aerodigestive tract that contribute to dysphagia if anomalies are present: nose and nasopharynx, oral cavity and oral pharynx, hypopharynx and larynx, and trachea and esophagus. These four anatomic areas provide a framework for the evaluation and management of dysphagia. When managing children with dysphagia, the first priority is to provide a safe airway for breathing. After the airway is stabilized, swallowing function should be assessed and managed with the ultimate goal of providing sufficient nutrition and fluid for optimal growth and development. The care for children with dysphagia is complex, and a team approach including members from speech-language pathology, nutrition, gastroenterology, and otolaryngology is ideal.

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CHAPTER TWO HUNDRED AND ELEVEN

Caustic Ingestion

Glenn B. Williams

Rose Mary S. Stocks

J. Dale Browne

James N. Thompson

Key Points

- Injuries from caustic ingestion are rare in the United States; 5000 to 15,000 occur per year.
- The current strict public policy on solution labeling and concentration was spearheaded by Jackson in the early 20th century.
- In developing nations without such policies, caustic injuries are more common.
- Acid ingestion leads to coagulative necrosis; alkali ingestion leads to liquefactive necrosis.
- The antrum of the stomach is the most vulnerable to acid ingestion; areas of anatomic narrowing are at greatest risk after alkali ingestion.
- Because of their resemblance to disk-shaped batteries, all coin-shaped foreign bodies should be removed expeditiously.
- Endoscopy is the most useful tool in assessing injury to the upper gastrointestinal tract.
- Typically, infant and toddler caustic ingestions are accidental, whereas adolescent and adult ingestions are suicide attempts.

"Those who cannot remember the past are condemned to repeat it."

—George Santayana

The preceding quote comes to mind when reviewing more recent caustic ingestion literature, most of which is from developing countries. Over the last decade, numerous articles have been published from various institutions in the developing world.[1-10] The fundamental problem is "uncontrolled and cheaper domestic cleaners have been introduced through common informal or open markets."[6] More recent reports estimate the incidence of caustic injuries in the United States to be 5000 to 15,000 per year; this low incidence has not always been the case.[5] During the early 1900s, in concert with the ready availability of cleaning solutions composed of strong alkalis or acids, reports of caustic ingestions filled the medical literature. These early cleaning solutions were packaged in inconspicuous containers that concealed the potential danger of the content. This public health issue was highlighted in a landmark article in 1921 by Jackson,[10] developer of the first distal lighted esophagoscope. Supported by extensive lobbying efforts by Jackson, the U.S. Congress passed legislation that controlled the sale of these potential toxins in 1927. Legislation led to the 1953 creation of the first National Poison Control Center in Chicago. In 1971, the U.S. Federal Hazardous Substance and Poison Prevention Packaging Act passed, mandating childproof container caps and banning excessively hazardous products and concentrations.

Despite these measures, extensive medical literature, and a century's experience, serious injuries secondary to caustic ingestion persist in the United States and abroad. Pediatric caustic ingestions are typically accidental and involve common household items. In adolescents and adults, ingestions are more likely intentional and represent suicide attempts.

Pathophysiology

Acid and alkali solutions are the two main categories of caustic products. Commonly ingested substances include cleaning agents, bleach, concentrated laundry detergent, concentrated ammonia, dishwashing detergent, alkali hair straighteners, nail-decorating liquids, sodium hydroxide–containing glucose testing tablets, and disk batteries.[11-15] Extensive local damage can occur after ingestion of sodium hydroxide–containing glucose test tablets and disk-shaped batteries if they lodge in the esophagus. Disk-shaped batteries are easily swallowed, and if they become lodged cause injury by several mechanisms: leakage of alkali causing direct caustic injury; absorption of toxic substances; pressure necrosis; and electrical discharge, which can cause mucosal burns.[16] Subsequently, the following types of esophageal injuries may occur: esophageal burn with or without perforation, tracheoesophageal fistula, and aortoesophageal fistula. Caustic substances present in farming homes used as disinfectants, pipeline clearance, and cattle horn removal are not subject to U.S. protective packaging legislation.[17]

Acid ingestion leads to coagulative necrosis with eschar formation that subsequently prevents further tissue penetration. Esophageal damage secondary to acid ingestion is less likely because of the protection afforded by the slightly alkaline pH of the esophagus, and because of the resistance of the squamous epithelium to acids. The antrum of the stomach is the most vulnerable region of the upper digestive tract to acidic substances owing to pooling and prolonged contact with the compound.[18]

Alkalis are responsible for more severe caustic ingestion sequelae; multiple factors contribute to the extensive damage. Direct contact with cell membranes leads to their disruption secondary to saponification and proteinate formation as the alkali reacts with membrane components. Solubility of alkalis allows for deeper penetration of the caustic agents typically in areas of anatomic narrowing (e.g., cricopharyngeus,

Box 211-1

Signs and Symptoms of Caustic Ingestion

Oral mucosal erythema, ulceration
Drooling
Tongue edema
Stridor
Hoarseness
Dysphagia
Odynophagia
Chest or back pain
Epigastric pain or tenderness
Vomiting
Hematemesis

aortic arch, left main stem bronchus, and diaphragmatic hiatus).[18] Damage ceases only when the alkali is neutralized by its reaction with tissue. The histopathologic events that occur after a 10% sodium hydroxide burn of esophageal mucosa include edema of the submucosa, inflammation of the submucosa with thrombosis, sloughing of the superficial layers, necrosis of the muscular layer, fibrosis of the deep layers, and delayed re-epithelialization.[19]

Initial Assessment and Diagnosis

Patients with caustic ingestion present with many symptoms, ranging from asymptomatic to overt stridor with severe dysphagia secondary to laryngeal edema and hypopharyngeal or esophageal injury (Box 211-1). As with all injured patients, the primary survey focuses on airway, breathing, and circulation (ABCs). A rapid assessment of the patient's airway and determination of the need for intervention is of primary importance. Simultaneously, patients suspected to have a severe injury should have large-bore intravenous catheters for early fluid resuscitation and medication. Patients with significant oral mucosal burns, tongue edema, hoarseness, stridor, and dyspnea should be monitored closely for possible airway obstruction.

Fiberoptic laryngoscopy is an invaluable tool in the assessment of hypopharyngeal damage and the risk of airway compromise. In a patient with an injured but stable airway, dexamethasone (20 to 30 mg intravenous bolus in adults; 0.5 to 1 mg/kg in children) can help prevent further deterioration. Direct visualization of the larynx is necessary for a successful and safe intubation; blind nasotracheal intubation should be avoided for fear of destabilizing a tenuous airway. If orotracheal intubation cannot be performed safely because of edema or exudate or both, a surgical airway (cricothyrotomy or tracheotomy) is the safer choice. Dyspnea associated with rales and rhonchi may indicate aspiration of caustic material or pulmonary edema. Chest and abdominal radiography should be obtained to rule out pulmonary infiltrates or free air. Patient complaints of epigastric pain and examination findings of peritonitis (e.g., abdominal wall rigidity, tenderness) are highly correlated with gastric injury.[20]

Vital information necessary for appropriate care of a patient with a caustic ingestion includes identification of the ingested agent and its characteristics (pH, concentration, physical form [i.e., granular, liquid]), time and setting of ingestion, and volume swallowed. The social setting of the ingestion may provide clues to the amount of caustic involved in the injury and should be explored in the history. Children ingest caustic substances accidentally while exploring their surroundings or because of lack of parental education or parental neglect.[9,21] Adult ingestions are generally suicide attempts, and large volumes are ingested. In the laboratory, the amount of titratable base is a more accurate predictor of a strong alkaline substance.[22] Vancura and colleagues[23] showed esophageal ulceration at a pH 12.5 or greater and significant mucosal damage with sodium hydroxide concentrations of 0.4% in mongrel cats. pH is clinically a more practical, rapid method of estimating the risk of mucosal injury.

Large volumes of strong acids are generally required to create esophageal injury, whereas a few milliliters of strong alkali can cause extensive damage instantaneously. Injury to the upper gastrointestinal mucosa after acid ingestion is more prolonged and is aided by reflex pylorospasm. Entry of acid into the stomach and contact with the pylorus results in a reflex spasm, leading to increased length of exposure and a predominance of gastric mucosal injuries in these patients. Measures such as emetics or buffering attempts are not recommended because they do not lessen the injury, and they increase the risk of aspiration. Conservative measures are encouraged, such as cleaning oral mucosa burns with water to dilute any remaining caustic, and manually removing any visible lye granules to lessen continuing injury.

Although the acute crises of esophageal perforation and upper airway obstruction are more dramatic, the most common complications from strong alkaline burns result from the more protracted courses of fibrosis and delayed epithelialization. Superficial burns generally heal without sequelae; however, deeper injuries involving the muscular layer and submucosa are associated with a more extensive loss of mucosa with subsequent fibrosis. A characteristic esophageal stricture develops in four stages: (1) An intense inflammatory response with associated dysmotility occurs in the area of the burned mucosa and deeper layers. (2) Granulation tissue with fibroblasts brings a matrix of collagen fibers to the newly formed connective tissue. (3) These collagen fibers begin to contract 3 or 4 weeks after the initial injury, with irregular formation of this collagen matrix, which enables the formation of adhesive bands. (4) Pseudodiverticula form between these adhesions as the contracting process continues until a dense inflexible fibrous scar replaces the destroyed submucosa and muscular layers. Circumferential burns are much more likely to lead to a symptomatic stricture than are noncircumferential injuries.[24]

Endoscopy

The clinician's principal diagnostic challenge lies in accurately predicting which ingestion injuries are prone to rapid, inconsequential healing, and which are prone to stricture formation or perforation. Endoscopy is the most useful method of assessing whether esophageal injury has occurred. Traditional adjunctive studies, such as barium esophagogram, are inadequate because of the reliance on motility disturbance and mucosal irregularities to detect injury[25] and significant false-negative rates (30% to 60%).[26,27] The usefulness of technetium 99m–labeled sucralfate has been shown; it has high sensitivity and specificity in determining the presence of an esophageal injury after pediatric caustic ingestion.[28] The high sensitivity and specificity allow this nuclear medicine study to serve as a screen for injury; however, it does not determine severity of injury or enable intervention. Depending on radiography alone for guidance may lead the clinician to underestimate the degree of injury in some patients.

The timing and necessity of endoscopy remains a topic of debate. Proponents of endoscopy within 24 hours in all cases of caustic ingestions are supported by retrospective reviews detailing instances of significant esophageal injury despite the absence of symptoms or signs of mucosal burns.[3,4,6,29-32] In citing the poor correlation of signs, symptoms, and esophageal injury, such studies frequently do not differentiate the form of the ingested substance (liquid vs. granular), and whether the asymptomatic burns were from more potent liquid alkalis. This association may lead to the conclusion that any form of an ingested caustic may cause significant distal injury even in the absence of signs or symptoms of mucosal burns. Although conservative and cautious, this approach may subject patients (and parents) occasionally to unneeded procedures, worry, and expense. In a retrospective study of 41 ingestions that noted the type of lye ingested, the granular form did not cause significant mucosal injury, whereas all strictures resulted from liquid alkalis.[30]

An alternative view of when to perform endoscopy considers several factors, including form and strength of the caustic, presence or absence of multiple signs and symptoms, and age of the patient. Most adult patients ingest caustic agents as a suicide attempt—this is a more straightforward diagnostic assessment. The volume of agent swallowed is usually great, commonly causing dysphagia, stridor, or oropharyngeal burns. Suicidal adults may be unreliable historians, which forces the

clinician to rely on physical findings to direct therapy, especially because oral mucosal injury may be absent when a strong alkali is quickly swallowed. Consequently, endoscopy is advisable for any adult having ingested a strong alkali or acid (e.g., sodium hydroxide, potassium hydroxide, hydrochloric acid, sulfuric acid), regardless of the lack of presenting symptoms or signs. In suicidal ingestions, the physician should examine the stomach for necrosis with endoscopy, laparoscopy, or laparotomy because a large volume of caustic may have been swallowed.

In contrast, toxic agents are accidentally swallowed in children as a result of innocent curiosity and confusion with food and drink. Just as children do not swallow a great deal of any distasteful food or medicine, they would not swallow any noxious, bitter acid or unpalatable granular lye. These compounds are rarely associated with significant esophageal burns because the volume ingested is generally very small.[30,33,34] Exceptions have been reported, but these cases are associated with presenting combinations of oral burns, drooling, and dysphagia that easily raise suspicion that a significant amount of the compound has been swallowed. In cases of pediatric ingestion of acids or granular lye, endoscopy can be reserved for children with significant oral burns, dysphagia, or stridor. A glucose test tablet or disk-shaped watch battery needs to be endoscopically removed as quickly as possible because these items cause localized transmural necrosis and esophageal perforation. This recommendation can be extended to any coin-shaped object lodged in a child's esophagus because some disk batteries may resemble a coin on chest radiographs (Fig. 211-1).

Most severe pediatric esophageal injuries are the result of just a few milliliters of a strong liquid alkali, usually sodium hydroxide. Some investigators have found that the presence of two or more signs and symptoms (e.g., oral burns, drooling, dysphagia, vomiting, stridor) reliably indicates esophageal injury significant enough to lead to stricture formation or perforation, requiring endoscopy.[33-35] Based on evidence from a retrospective study, one series concluded that unless a pediatric patient is symptomatic (e.g., vomiting, drooling, oral lesions, respiratory distress, hemostasis), endoscopy is unnecessary because asymptomatic children were not found to develop sequelae. The authors of the series confined this recommendation to developed countries with a more controlled, lower concentration of alkalis and acids.[36]

Although such criteria can be helpful in evaluating a child with a questionable history of liquid alkali ingestion, prudent evaluation of a pediatric patient with known ingestion of a strong liquid alkali should consider reported cases of an otherwise silent, significant injury appreciated only through endoscopy. In cases of known pediatric liquid alkali ingestion, endoscopy offers a direct assessment with low morbidity for the presence or absence of significant injury. In borderline patients, a technetium 99m–labeled sucralfate study can be useful. In children without a strong history and with only one presenting sign or symptom, the risk of significant injury is low, and endoscopy can be deferred or held, pending the results of a nuclear medicine study. Otherwise, it is safer to perform endoscopy in all children with known ingestion of a strong liquid alkali or who have positive findings on a technetium 99m–labeled sucralfate study.

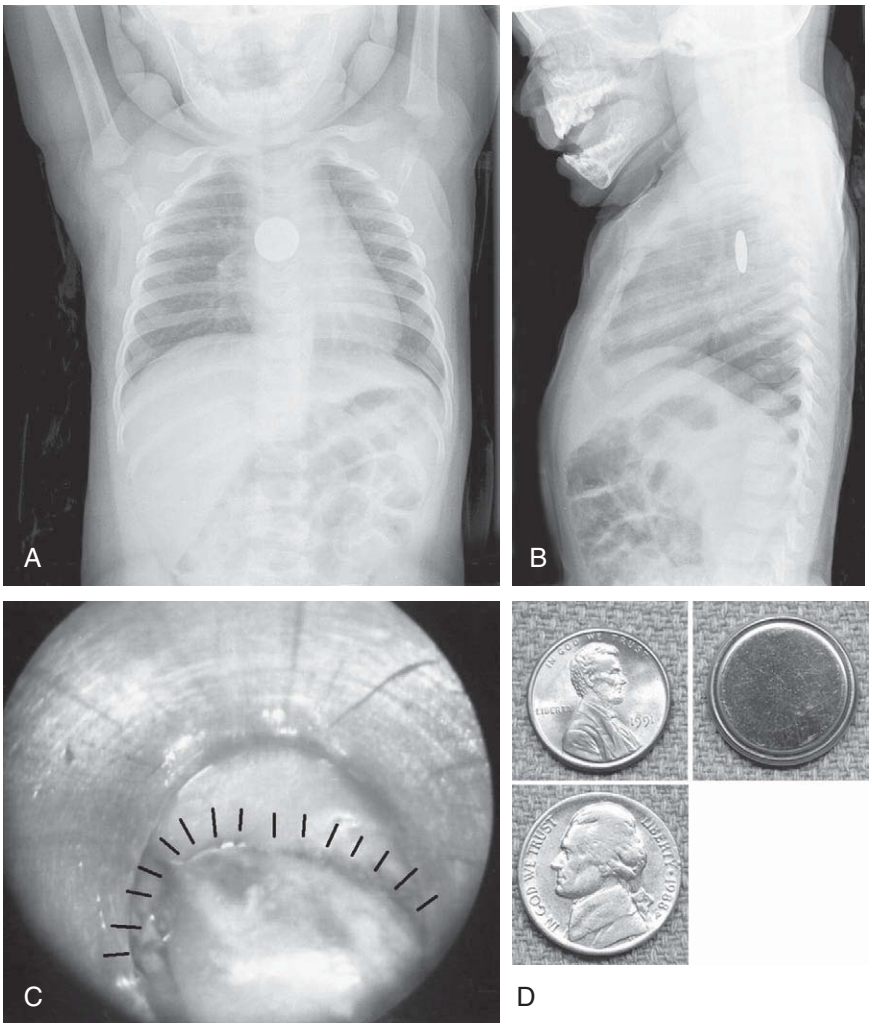

Figure 211-1. **A,** Anterior view of a chest radiograph of a child who has ingested a coin-shaped battery. Note its resemblance to a coin. **B,** Lateral view of battery within the chest. **C,** Endoscopic view of mucosal injury caused by the battery; lines mark circular burn at battery edge. **D,** Visual size comparison of a similar battery, a penny, and a nickel.

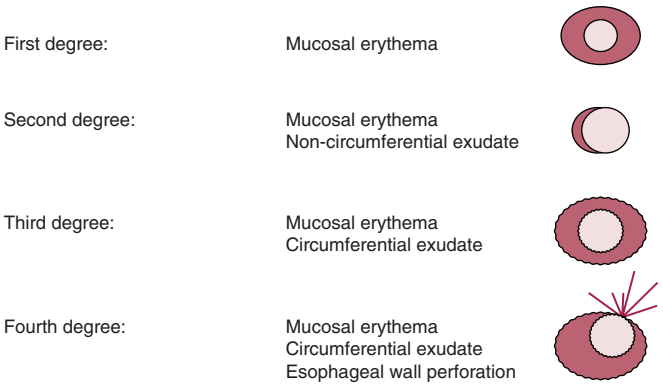

Figure 211-2. Four stages of esophageal burns.

Although any portion of the esophageal wall may be involved with the burn, the areas with the greatest extrinsic compression are most prone to injury. These are the cricopharyngeus, the aortic arch and left main stem bronchus compression sites, and the distal esophagus at the esophagogastric junction. As for other foreign bodies, this site is where solid caustics or batteries may lodge, causing severe localized injuries. When evaluating a significant burn of the esophagus, the endoscopist should be aware of the potential for a tracheoesophageal fistula resulting from the injury, especially at the upper esophageal and midesophageal narrowings. Tracheoscopy should be included when extensive burns are seen in these areas to examine the posterior tracheal wall for injury.

Staging

Methods of endoscopically staging and reporting esophageal burns vary. Historically, a classification borrowed from thermal burns has been used with references to first-degree, second-degree, and third-degree injuries that range from mild mucosal edema, to partial-thickness necrosis, to transmural necrosis.[37] Variations on this method have noted whether the lesion was circumferential. Recurrent difficulties in accurately and consistently applying this method include a failure to appreciate the true burn depth through the endoscope because of a necrotic exudate. Further contributing to endoscopic inaccuracy is difficulty in assessing the true amount of surface area burned because of mucosal edema. Such edema can prevent a complete, circumferential examination and obscure the sometimes subtle changes of an evolving submucosal necrosis, leading to an underestimation of injury in marginally burned areas.

Using modified classifications, four stages can provide the endoscopist with a consistent format for describing caustic injury to the esophageal lumen: first degree, mucosal erythema; second degree, erythema plus noncircumferential exudate; third degree, circumferential exudate; and fourth degree, circumferential exudate with esophageal wall perforation (Fig. 211-2).[38] Additional references to the site and length of the burn can be documented. In this staging system, only first-degree burns consistently heal uneventfully. Second-degree injuries occasionally form strictures, and all third-degree burns generally form strictures. Fourth-degree burns carry the additional risk of sepsis and mediastinitis. Because it is difficult to predict the true depth accurately, there is the potential for a third-degree burn eventually to extend into a fourth-degree burn—hence the need for close follow-up.

Several days after a caustic esophageal injury, any necrotic mucosa, submucosa, and muscular layer will have sloughed. At this point, the esophageal wall is at its weakest and may be prone to perforation, either spontaneously or secondary to an endoscope or nasogastric tube. The same is true for a transmural injury to the gastric wall. Close observation in all patients with third-degree esophageal burns is mandatory in a hospital for several days. Although antibiotics have not been shown to prevent strictures, broad-spectrum antibiotics are prudent in extensive third-degree burns that may lead to perforation.[30]

Additionally, endoscopy in the first 24 hours is safer to minimize the risk of perforation and for early identification of patients at risk for a fourth-degree injury. Although traditionally endoscopy has been aborted at the first significant burn,[10,17] the value and safety of full-length, careful esophagoscopy has been shown, especially in identifying patients with significant distal injury extending into the stomach.[30,37,39-42] With this in mind, endoscopy should be aborted when there is no definable lumen, rather than ceasing at the first severe burn. Although rigid and flexible endoscopes have been used to examine the full length of the esophagus successfully, the flexible model is necessary for adequate visualization of the stomach. If necrosis is identified extending into the gastric mucosa, direct visualization of the outer gastric wall should be strongly considered to rule out a transmural necrosis. Visualization may be by laparoscopy or laparotomy, depending on the surgeon's preference.

Therapy

When esophagogastric mucosal injury is diagnosed, the choice of therapy depends on the degree of injury. Injuries limited to first-degree burns of the esophageal mucosa require no further therapy. Blunt esophagectomy after identification of fourth-degree and selected extensive third-degree esophageal burns reduces the expected mortality from leaving a necrotic esophagus in place.[39,43] Identifying a perforation makes the decision for esophagectomy straightforward. For extensive third-degree burns, a thoracotomy or thoracoscopy for direct examination of the esophageal wall may be indicated to assess for transmural necrosis. Such decisions may be difficult, and may require the judgment and experience of the endoscopist. Débridement at the time of laparotomy or laparoscopy is dictated by the injury. In cases of gastric perforation, débridement of omentum, small bowel, and other intra-abdominal structures may be necessary.

The major controversy in therapeutic choices involves intermediate esophageal burns (i.e., second-degree and localized third-degree injuries). The goals of therapy are to maintain the esophageal lumen by the pharmacologic reduction or prevention of stricture formation and to maintain a conduit from the hypopharynx to the stomach by esophageal dilation, stenting, or reconstruction.

Pharmacologic Therapy

In 1950, Howes[44] and Spain[45] documented the retarding effect of corticosteroids on wound healing in separate laboratory studies. The following year, Rosenberg and coworkers[27] noted decreased stricture formation with corticosteroid therapy after alkali burns of rabbit esophageal mucosa. Although infection led to a high mortality rate, the supposed benefit from corticosteroids seemed clear. The addition of antibiotics reduced mortality, and the subsequent regimen of corticosteroids and antibiotics reduced esophageal strictures in the laboratory setting.[46-48] These findings led to the empirical therapeutic combination of corticosteroids and broad-spectrum antibiotics for significant second-degree and third-degree esophageal injuries. Retrospective analyses produce conflicting results. Some studies have shown benefit in reducing strictures, whereas others have not.[49,50]

In an attempt to resolve this controversy, Anderson and associates[51] reported on a prospective analysis through 18 years of 60 children with esophageal burns secondary to strong caustics (80% alkali). Patients were randomly assigned to receive 21 days of corticosteroids or no therapy, with the degrees of injury stratified equally in both groups. Of 21 patients identified as having circumferential burns, 20 developed strictures. Only 1 of 20 patients with a noncircumferential burn developed a stricture. Corticosteroids had no effect in the patients with circumferential burns. Ironically, the only stricture in the noncircumferential injury occurred in a child who received corticosteroids.

Lathyrogenic drugs that reduce collagen cross bonding have been used in attempts to decrease stricture formation.[52] Compounds such as β-aminopropionitrile, *N*-acetylcysteine, and penicillamine decrease stricture formation in laboratory settings, but their benefit in humans is unproven. Of these medications, penicillamine is the least toxic, and potentially may play a limited role.

Contact with acid and pepsin retards the healing of lye-induced esophageal burns in rabbits.[53] Clinically, the increase of gastroesophageal reflux has been documented in pediatric caustic strictures and subsequent loss of lower esophageal sphincter integrity.[54] With this

information, it follows that efforts to decrease the effects of stomach acid on injured esophageal mucosa may be useful clinically. Sucralfate therapy for caustic esophageal burns has shown promise in the healing of ulcers without stricture formation.[55,56] Although unproven clinically in prospective caustic injury series, the low toxicity of pharmacologically reducing gastroesophageal reflux provides an attractive adjunctive measure in controlling strictures that is worthy of such a study.

Experience has been positive in the use of topical mitomycin in the management of pediatric tracheoesophageal strictures.[57-59] Mitomycin is an antibiotic used as an antineoplastic agent. Its usefulness stems from its behavior as an alkylating agent that inhibits deoxyribonucleic acid and protein synthesis, and fibroblast formation. Although experience in the use of this medication in caustic esophageal injuries is minimal, the successful use of this agent in selected aerodigestive tract lesions may herald some usefulness in caustic injuries.

Mechanical Therapy

The simplest mechanical method for maintaining a lumen in a third-degree esophageal burn is to place a nasogastric tube at the time of initial endoscopy. The true benefit of nasogastric tube stenting varies, with results ranging from spectacular to no benefit.[60,61] In a patient with a third-degree burn and dysphagia, a nasogastric tube provides a convenient stent and a means of nutritional support. Other types of stents have used polymeric silicone tubes in the esophagus with mixed success. Any clear benefit over serial dilations has not been shown.[62] Ideally, if this philosophy is used in guiding therapy, stents should remain in place long enough to allow re-epithelialization (2 to 3 weeks) with some reporting use for 9 to 14 months.[2]

Mild strictures can be serially dilated in a prograde fashion through an esophagoscope with filiform dilators. Cooperative patients (generally adults) may tolerate the periodic swallowing of weighted dilators in the office. Fluoroscopic guided balloon catheter dilation for acquired strictures has shown little success.[63] When identified, multiple strictures are managed most safely with retrograde dilators, popularized by Tucker[64] in the 1920s. A gastrostomy is necessary for the passage of an endless loop of silk exiting the mouth to allow slow, serial increases in caliber, while maintaining a secure position within the narrowed lumen and minimizing the risks of perforation (Fig. 211-3). If a significant, lengthy third-degree burn is identified at initial endoscopy, strong consideration should be given to the placement of a gastrostomy tube and

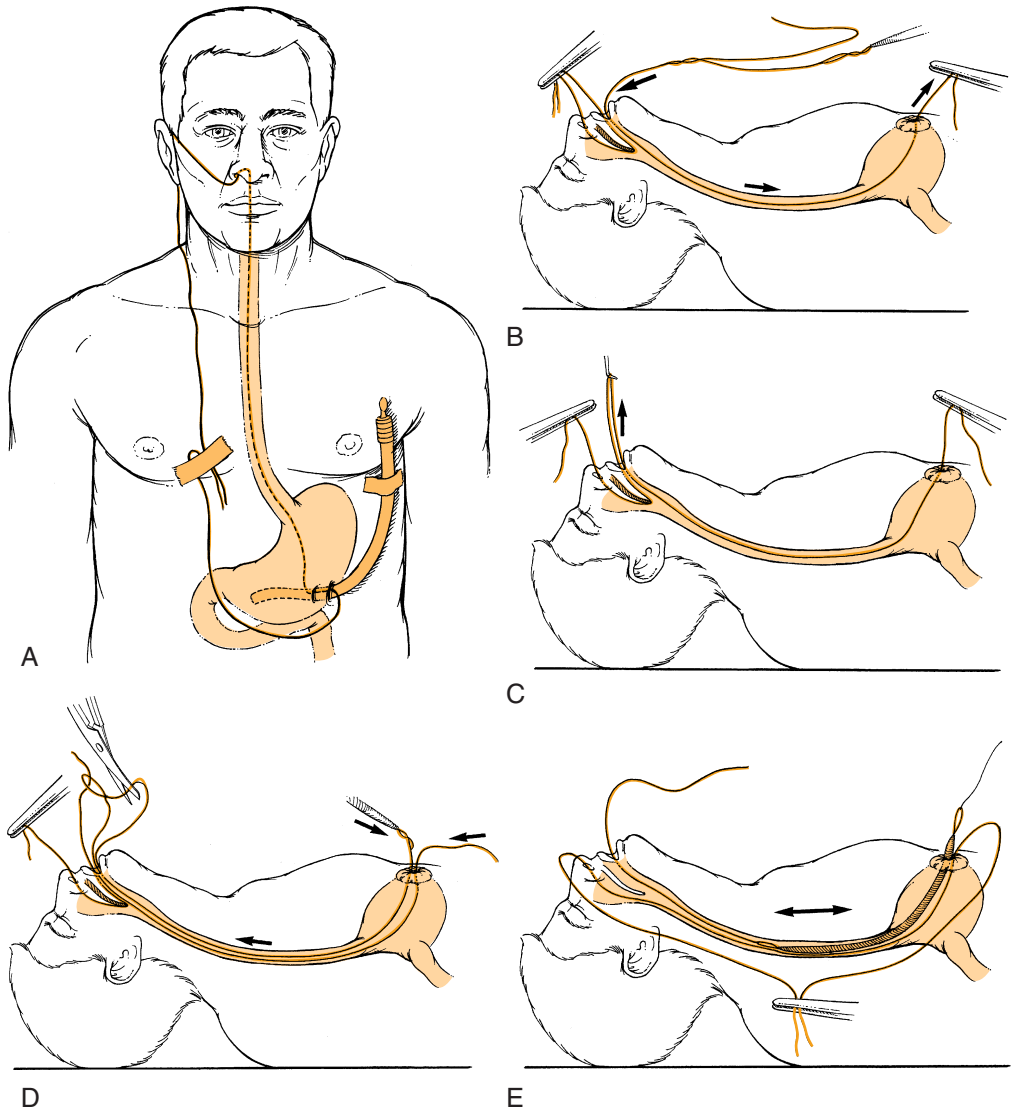

Figure 211-3. **A,** Appearance of a typical patient undergoing chronic retrograde dilations via gastrostomy. A guide string enters the nasal cavity, loops behind the ear, and enters alongside the gastrostomy tube. **B,** String (heavy silk) is retrieved from the posterior pharynx. **C,** A dilator is secured to silk exiting the mouth for gentle progressive prograde dilation. Care is taken to clamp the loop exiting the mouth and nose. **D,** A dilator is secured to silk exiting the gastrostomy tube for gentle progressive retrograde dilations. **E,** When dilator is within the lumen of the strictures, a gentle to-and-fro prograde or retrograde dilation may be accomplished. For security, a second heavy silk loop can be passed before any dilation in case the dilator string breaks.[64]

retrograde silk during the same anesthesia or before discharge to avoid a delay in safe dilation in the outpatient setting.

The timing of stricture dilation depends on the severity of the injury. In second-degree injuries, prophylactic dilation is not recommended, although periodic follow-up is important. Stricture formation may occur 6 weeks from the time of injury, and may become evident only when obstructed with food. Generally, a barium swallow at 3 weeks serves as a baseline in asymptomatic patients and as an initial study before prophylactic dilations in patients with lengthy third-degree injuries that are at high risk for stricture development. Routine barium esophagography is useful for 1 year to monitor progress of a managed stricture, and to rule out the development of an occult stricture. For symptomatic patients, the frequency of dilations depends on patient response. Weekly dilations may be necessary to maintain a viable lumen in severe injuries (Fig. 211-4).

When repetitive dilations fail to relieve symptoms, or when severe esophageal strictures render dilation impossible or fruitless, more aggressive techniques are indicated to reconstruct the conduit from hypopharynx to stomach. Esophageal replacement with gastric tubes, right colon, transverse colon, or descending colon has been described. The right colon has been reported to be the most useful conduit (Fig. 211-5).[65,66] When possible, blunt esophagectomy is preferable to thoracotomy. For isolated strictures, local resection with end-to-end reanastomosis, colon patch esophagoplasty, and esophageal stricture bypass with a colonic conduit have been reported in successful attempts to preserve an injured esophagus.[67-69]

Gastric outlet obstruction as a complication of acid ingestion is well known but uncommon, with an incidence 3.8% to 8.2% in pediatric series.[7,70] Less common is outlet obstruction secondary to alkali ingestion, with 5.3% (9 of 168) of patients developing gastric outlet obstruction in addition to esophageal strictures in the series reported by Ciftci and colleagues.[70] Presenting symptoms include frequent nonbilious emesis and secondary marked weight loss.[7] Treatment is surgical and includes gastrojejunostomy[7] or Billroth I[70] for complete obstruction and the Finney or Heineke-Mikulicz pyloroplasty for patients with partial obstruction.[70]

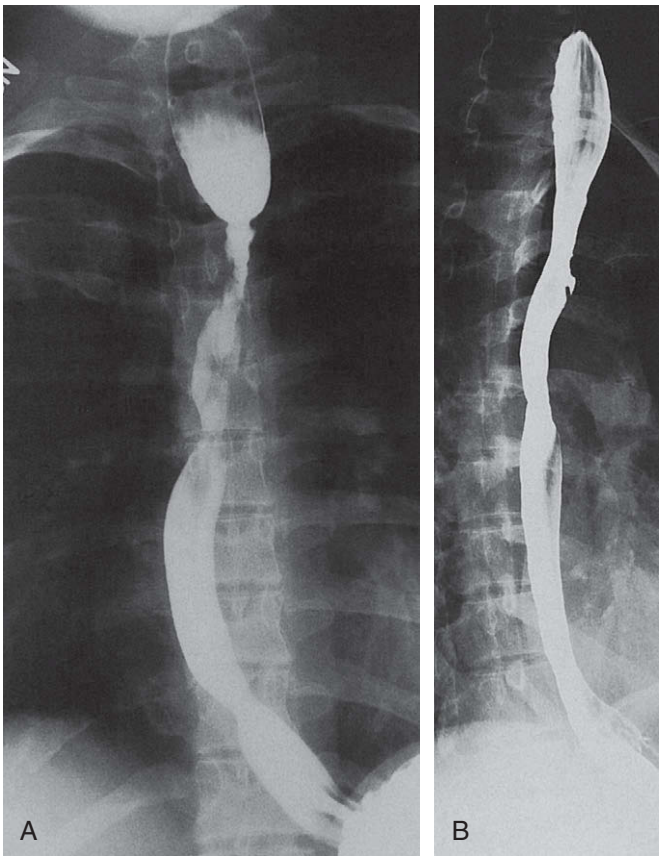

Figure 211-4. **A,** Barium swallow shows midesophageal stricture after lye ingestion in an adolescent 4 weeks after ingestion and at the beginning of retrograde dilations. **B,** Same patient 5 years later, after 4 years of repetitive dilations; the patient has a stable stricture and is generally nonsymptomatic.

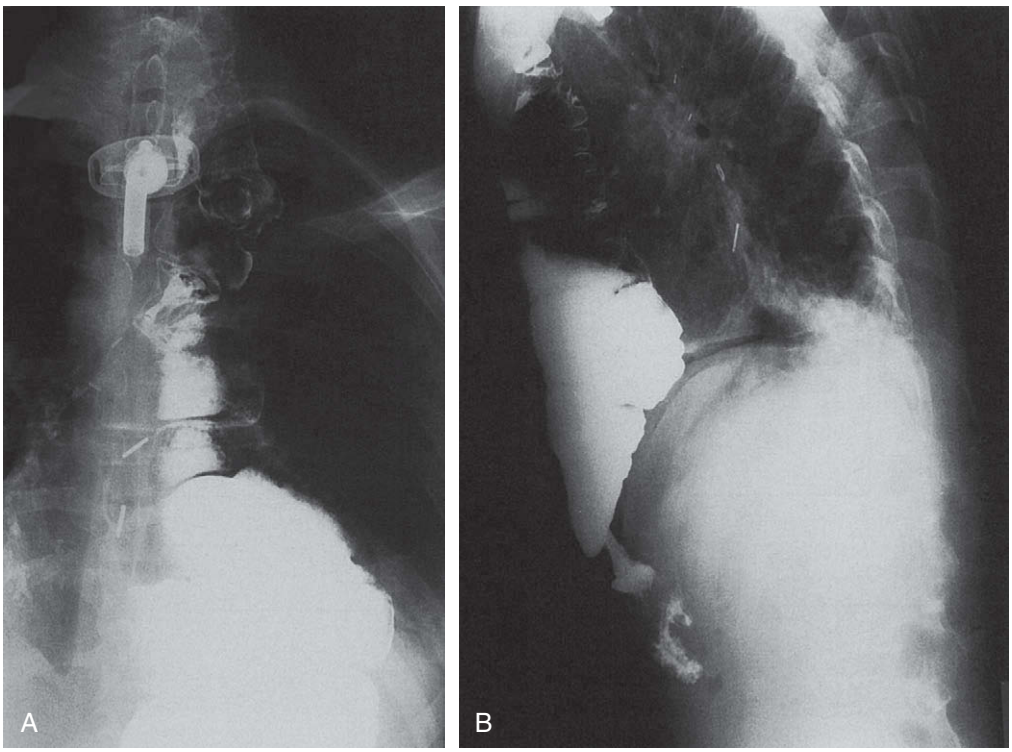

Figure 211-5. **A,** Anterior view of a barium swallow of a patient with a fourth-degree burn necessitating a total blunt esophagectomy with subsequent reconstruction using the right descending colon. The tracheotomy was originally placed emergently because of laryngeal obstruction secondary to supraglottic necrosis or edema. **B,** Lateral view of the same patient. Note the position of colon transfer in the anterior mediastinum.

The benefits from esophagectomy are not limited to the reconstruction of a swallowing conduit. In large series of esophageal carcinomas, a 1% to 4% incidence of caustic ingestion is typical. Although the true increased risk of carcinoma is unknown, it has been estimated at 1000-fold. The tendency for local extension of these malignancies is lower than expected with a higher potential rate of cure because they develop in the fibrotic, stenotic scar.[71] With this in mind, long-term follow-up is essential in any patient with a caustic esophageal stricture. The redevelopment of dysphagia after years of minimal difficulties should prompt an investigation with at least barium esophagography and, if abnormal, esophagoscopy with appropriate biopsy specimens.

In selected patients with a severely strictured esophagus requiring a lifetime of repetitive dilations necessary to maintain any useful lumen, elective esophagectomy with subsequent reconstruction may be reasonable. Additionally, a hiatal hernia, esophagitis, and peptic stricture may develop decades after a severe caustic injury, with resultant progressive fibrosis and dysfunction of the gastroesophageal sphincter. In this setting, the use of traditional dilation techniques as primary long-term therapy actually worsens the situation and the reflux.[72] Aggressive prophylactic antireflux measures with proton pump inhibitors may improve the outlook for these patients by increasing the long-term success of dilation, avoiding the need for aggressive surgery.

Conclusion

Caustic ingestion is an uncommon injury in the United States that varies widely in severity, ranging from minimal mucosal erythema to frank transmural necrosis of the esophagus and stomach with viscous perforation (Fig. 211-6). After appropriate identification of concentra-

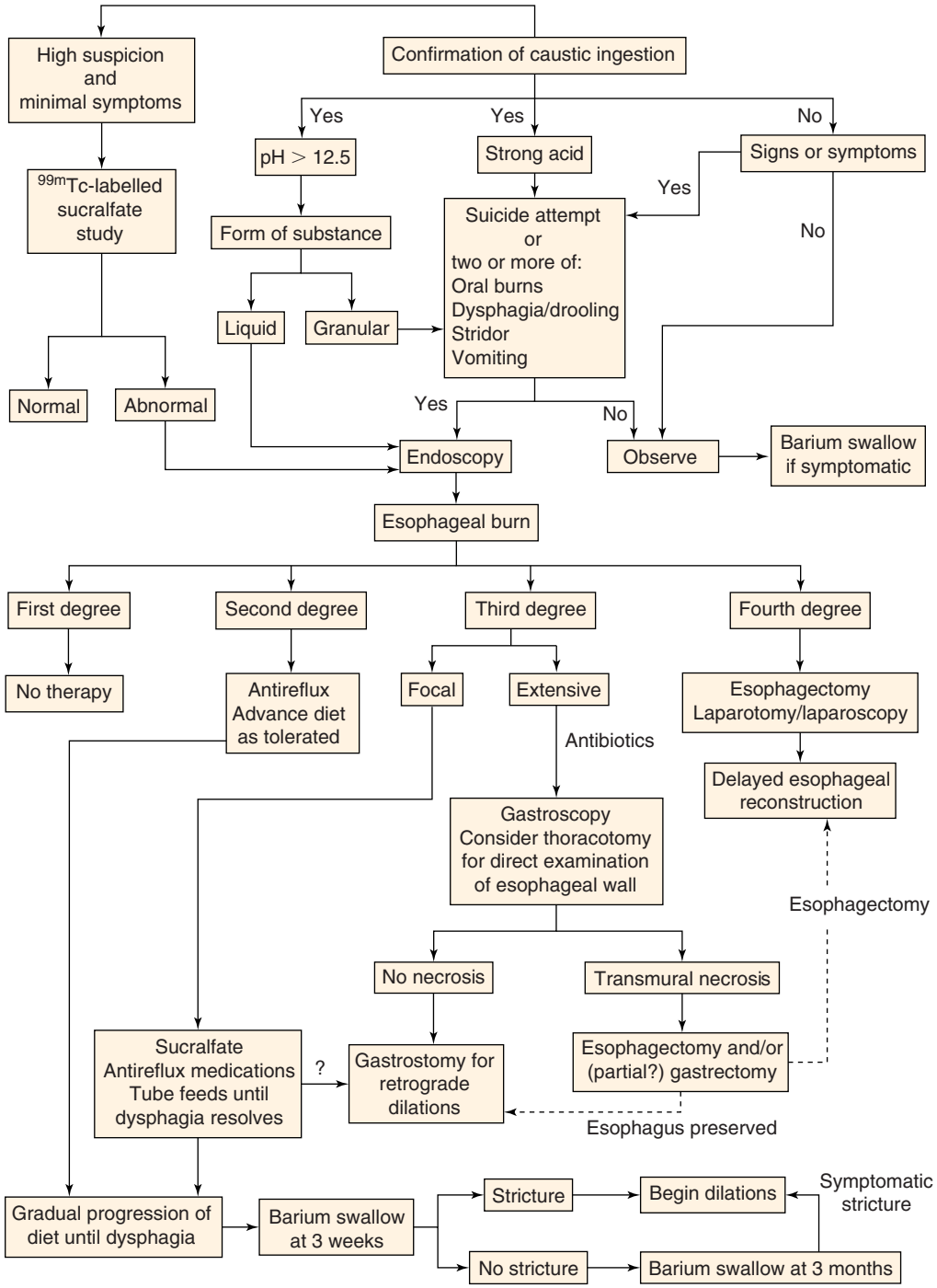

Figure 211-6. Evaluation and treatment of caustic ingestion.

tion, pH, and form of the ingested substance, the clinician should decide whether to evaluate the upper aerodigestive tract further. Full-length esophageal endoscopy is the most accurate initial method of examination, and is indicated after any ingestion of a strong liquid alkali. The need for endoscopy in other settings depends on the strength, volume, and form of the ingested caustic and associated signs and symptoms. Esophageal stricture formation is the chief long-term complication with a potential devastating impact on quality of life. Although repetitive stricture dilations are the mainstay of management, prevention or reduction in the severity of this complication is promising. Extensive necrotic esophageal injuries are doomed to fibrosis, but protocols emphasizing mucosal protectants with aggressive antireflux management may provide a means to minimize stricture formation in second-degree and localized third-degree injuries.

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Index

Note: Page numbers followed by b, f, or t indicate boxes, figures, or tables, respectively.

A

A ring, 967
A trains, in electromyography, 2547
AABR (automated auditory brainstem response), 2721
AAMC (Association of American Medical Colleges), 84t-87t
AAV (adeno-associated virus) vectors, for gene therapy, 18, 18t
  of inner ear, 2191t, 2192
Abbé flap, 352
  in cleft-lip nose repair, 563f-564f
Abbreviated Profile of Hearing Aid Benefit (APHAB), 57
Abducens nerve
  intraoperative monitoring of, 2549-2550, 2550f
  in surgical anatomy of anterior cranial base, 2474
  in surgical anatomy of lateral skull base, 2439f
Abductor spasmodic dysphonia, botulinum toxin therapy for, 839, 841f
ABI. *See* Auditory brainstem implant (ABI).
Ablative vestibular surgery
  labyrinthectomy as, 2366-2368, 2367f
  patient selection for, 2364-2366
    clinical history in, 2364-2365
    consideration of other potential treatments in, 2366
    identification of intracranial pathology in, 2366
    identification of offending labyrinth in, 2365-2366
    poor compensation *vs.* unstable labyrinthine disease in, 2364, 2365t
    residual hearing and selection of procedure in, 2366
    therapeutic trial of vestibular rehabilitation in, 2365
    vestibular testing in, 2365, 2365b
  vestibular compensation after, 2370
  vestibular nerve section as, 2368-2370, 2368f-2369f
ABMS (American Board of Medical Specialties), 80, 84t-87t
  core competencies of, 80, 80b
ABOto (American Board of Otolaryngology), 80b, 84t-87t
ABR. *See* Auditory brainstem response (ABR).
Abrasions, 306
Abrasive surgery, for skin lesions, 294
ABRS (acute bacterial rhinosinusitis), 703-705, 704f
Abscess
  Bezold, 1985-1986, 1986f-1987f
    due to temporal bone infection, 1980t
  brain, 1994
    due to cranial base surgery, 2468
    epidemiology of, 1980t-1981t, 1994
    imaging of, 1994f-1995f
    otitis media and, 2777
    pathogenesis of, 1994
    symptoms of, 1994
    treatment of, 1994
  dentoalveolar, 1252
  epidural, 1995-1996
    epidemiology of, 1980t-1981t
  of infrahyoid prevertebral space, 162f
  of masticator space, 151-152, 152f
  of neck, imaging of, 1407, 1407f
  odontogenic (*See* Odontogenic infections)
  of oral cavity, 156f
  of parapharyngeal space, in children, 2788-2789
  parotid gland, 1152f-1153f
Abscess *(Continued)*
  peritonsillar, 1407, 1407f
    in children, 2788, 2789f
  postauricular, 1985, 1985f-1986f
  retropharyngeal, 1407, 1465-1466
    in children, 2789-2790, 2789f, 2810-2811
      anatomy of, 2810
      clinical features of, 2810
      complications of, 2811
      diagnosis of, 2810-2811, 2810f-2811f
      differential diagnosis of, 2806t
      epidemiology of, 2810
      historical background of, 2810
      imaging of, 2810-2811, 2810f-2811f
      management of, 2811
    imaging of, 1465-1466, 1466f
    infrahyoid, 134
    suprahyoid, 153, 155f
  of salivary gland, in children, 2856
  septal, 2627, 2627f
  subdural, otitis media and, 2777
  of sublingual space, 156, 157f
  temporal root, 1986
  tonsillar, 148, 148f
Absolute alcohol, for embolization, 1933
Absolute ethanol, for embolization, 1933
Absorption
  of laser energy, 28-29, 29f
  of photon, 26, 26f
Abutments, in prosthetic maxillary obturation, 1338-1339
AC (atypical carcinoid), of larynx, 1507
Acantholytic squamous cell carcinoma (ASCC), of larynx, 1506
ACC. *See* Adenoid cystic carcinoma (ACC).
Accelerated fractionation, 1040
Accessible population, 68, 68t
Accessory cartilages, of nose, 496-497, 497f
Accessory nerve. *See* Spinal accessory nerve (SAN).
Accreditation Council for Continuing Medical Education (ACCME), 79, 84t-87t
Accreditation Council for Graduate Medical Education (ACGME), 84t-87t
  core competencies of, 80, 80b
Accuracy, 65
Accutane (13-*cis* retinoic acid)
  for cancer chemoprevention, 1018, 1061-1062
    laryngeal, 1491
ACE (Advanced Combination Encoder), for cochlear implants, 2230, 2231f
ACE-27 (Adult Comorbidity Evaluation 27), 53
Acetaminophen, in children, for pain, 2572
  postoperative, 2594
Acetazolamide (Diamox)
  for Meniere's disease, 2337
  for migraine, 2350
Acetic acid, for cerumen removal, 1958t
Acetic acid with aluminum acetate (Domeboro Otic), 1959t-1960t
  for ear hygiene or chronic ear drainage, 1958
  for otitis externa
    bacterial, 1946, 1953
    fungal, 1954
Acetyl-L-carnitine, for noise-induced hearing loss, 2145
Achalasia, 963-965
  cricopharyngeal, 1398-1399, 1400f
  defined, 963
  differential diagnosis of, 1400
Achalasia *(Continued)*
  endoscopy of, 964, 964f
  esophageal manometry for, 964, 964f
  etiology and pathogenesis of, 963
  imaging of, 1399-1400, 1400f-1401f
    esophogram for, 963-964, 963f-964f
  management of, 964-965
  manometric findings with, 959t
  symptoms of, 963
  vigorous, 1399-1400, 1401f
Achondroplasia, craniofacial abnormalities in, 2633, 2634f
Acid(s), caustic ingestion of, 2956-2957
Acid reflux. *See* Gastroesophageal reflux disease (GERD).
Acid reflux laryngopharyngitis, 863, 863f
Acid taste, transduction of, 1209
Acidifying agents, ototopical, 1959t-1960t
  for ear hygiene or chronic ear drainage, 1958
  for otitis externa
    acute bacterial, 1953
    fungal, 1954
Acid-sensing channels, in sour taste, 1209
Acinic cell carcinoma, of salivary glands, 1185-1186, 1187f
  in children, 2820, 2846, 2846f, 2863
Acinic cell tumor, of parotid gland, 151f
Acinus(i), of salivary gland
  anatomy of, 1133-1134, 1134f, 1162, 1163f
  classification of, 1134, 1134t
  in secretory process, 1134-1135
Acne, after dermabrasion, 399
Acoustic analysis, for voice evaluation, 829t, 834-835
  cepstral peak prominence in, 829t, 830
  combined frequency and intensity in, 829, 829f, 829t
  Fast Fourier Transform in, 829t, 830, 830f
  frequency in, 829, 829t
  intensity (sound pressure level) in, 829, 829t
  linear predictive coding in, 829t, 830, 830f
  long-term average spectrum in, 829t, 830
  nasalance in, 829t, 830
  phonetogram (voice range profile) in, 829, 829f, 829t
  of professional voice, 849
  spectral displays in, 829t, 830, 830f
    with professional voice, 849
  variability in, 829-830, 829t
  of velopharyngeal function, 829t, 830
Acoustic changes, in geriatric patients, 236
Acoustic coupling, 1839-1840, 2000
  with hearing aids, 2205f
Acoustic desensitization protocol, for tinnitus, 2135
Acoustic feedback, with traditional hearing aid, 2204
Acoustic immittance testing, 1890-1891, 1890f, 2020
Acoustic impedance, 1839, 2000, 2017-2018
Acoustic meatus
  anatomy of, 1824f
  external, 320f, 2010f
Acoustic neuroma(s), 2514-2517
  of cerebellopontine angle, 1929t, 2514-2517
    diagnostic studies of, 2516-2517
    imaging of, 2517, 2517t-2518t
    natural history of, 2515, 2515f-2516f
    signs and symptoms of, 2515-2516
  cystic, stereotactic radiation therapy for, 2563
  defined, 2514-2515

Acoustic neuroma(s) *(Continued)*
diagnosis of, 2516-2517
audiometry for, 1897, 1898f, 2516
auditory brainstem response in, 1896-1899, 1898f-1899f, 1911, 2517
errors in, 1901, 1902f
imaging in, 2517, 2517t-2518t
vestibular tests in, 2517
facial nerve involvement in, 2413-2414
vs. facial nerve neuroma, 2414, 2519-2522
imaging of, 173, 175f, 2517, 2517t-2518t
of internal auditory canal, 173, 1928, 1928f
intraoperative monitoring for
of auditory brainstem response, 2553, 2553f
of cranial nerve function, 2543-2545, 2543f-2544f
of direct cochlear nerve action potentials, 2554f
intravestibular, 1921, 1924f
malignant, 2515
natural history of, 2515, 2515f-2516f
in neurofibromatosis type 1, 2515
in neurofibromatosis type 2, 2515
pathogenesis of, 2514-2515
sensorineural hearing loss due to, 2124-2125, 2125f, 2515-2516
sudden, 2128
signs and symptoms of, 2515-2516
stereotactic radiation therapy for, 2558, 2560f
cystic, 2563
fractionation *vs.* nonfractionation of, 2558-2559, 2561t
gamma knife–based, 2559t
hydrocephalus due to, 2563
LINAC-based, 2560t
neurofibromatosis 2–related, 2563
outcome assessment with, 2559-2563
facial nerve outcomes with, 2563
hearing outcomes with, 2562-2563, 2562t
trigeminal nerve outcomes in, 2563
tumor control in, 2562
quality of life with, 2564-2565
radiation dose plan for, 2560f
treatment of failures of, 2564
tumor control with, 2562
unilateral and nonhereditary, 2515
vertigo due to, 2353
Acoustic reflex decay, 1891
Acoustic reflex evoked potentials, to assess facial nerve function, 2388
Acoustic reflex testing
for conductive hearing loss, 2020
for otosclerosis, 2030, 2030f
for sensorineural hearing loss, 2117
Acoustic reflex threshold test, 1891
Acoustic rhinometry, 486-487, 644-645
in allergic rhinitis, 651
to assess effect of treatment, 651-652
equipment for, 486-487, 486f, 644
interpretation of results of, 645
intranasal sites assessed by, 644
reporting results of, 645
rhinogram generated by, 486-487, 487f, 645
vs. rhinomanometry, 644
for snoring and sleep apnea, 651
sources of variability in, 651
technical concerns and testing pitfalls with, 645
technique of, 644-645
Acoustic schwannoma. *See* Acoustic neuroma(s).
Acoustic trauma, 2121-2122, 2121f-2122f, 2141
Acoustic-based treatment strategies
for hyperacusis, 2139
for tinnitus, 2133
acoustic desensitization protocol as, 2135
ambient stimulation as, 2133-2134
combined with education and counseling, 2134-2135
Acoustic-based treatment strategies *(Continued)*
personal listening devices as, 2134
total masking therapy as, 2134
Acousticofacial ganglion, 1851-1852, 1851f
Acquired immunodeficiency syndrome (AIDS), 2114-2115. *See also* Human immunodeficiency virus (HIV)/HIV infection.
nasal manifestations of, 660
otologic manifestations of, 2114-2115
sensorineural hearing loss due to, 2124, 2161-2162
sudden, 2128
Acquired immunodeficiency syndrome (AIDS)-defining conditions, 210-211, 211t
Acquired immunodeficiency syndrome (AIDS) dementia complex, 223
Acquired immunodeficiency syndrome (AIDS)-related parotid cysts, imaging of, 1146, 1146f
Acrivastine (Semprex D), for nonallergic rhinitis, 701t
Acrobot, 39
Acrocephaly, synostotic, 2645, 2645f
Acrochordon, 291
Acromegaly, oral manifestations of, 1251
Acrylic mandibular splint, for pediatric facial fractures, 2701, 2701f
ACS (American College of Surgeons), 84t-87t
Actin filaments, in stereocilia, 2074, 2075f-2076f
Actin γ1 *(ACTG1)* gene, in deafness, 2051t-2058t, 2074-2075
Actinic cheilitis, 283
Actinic keratoses, 283, 284f
Actinic lentigo, 288
Actinomyces israelii, otitis externa due to, 2194-2195
Actinomycosis
deep neck space infections due to, 201
laryngeal and tracheal manifestations of, 893
of salivary glands, 1159
in children, 2858
Action potential (AP), in electrocochleography, 1892-1894, 1907
in Meniere's disease, 2337
Active head movement analysis techniques, 2323-2324, 2324f
Actors, voice disorders in. *See* Professional voice disorders.
Acute bacterial rhinosinusitis (ABRS), 703-705, 704f
Acute chemical labyrinthine upset, due to intratympanic gentamicin, 2189
Acute exacerbation of chronic rhinosinusitis (AECRS), 705, 707, 707f
surgical management of, 741
Acute lymphocytic leukemia, otologic manifestations of, 2108f
Acute myelogenous leukemia, otologic manifestations of, 2108f
otorrhea as, 2197
Acute otitis media (AOM), 1979-1981
in children, 2761-2777
complications and sequelae of, 2776-2777
intracranial, 2776-2777
intratemporal, 2776
diagnosis of, 2761-2762
audiometry in, 2762
immittance testing (tympanometry) in, 2762
physical examination in, 2761-2762
symptoms and signs in, 2761
epidemiology of, 2765-2768
incidence and prevalence of, 2765-2766, 2765f
risk factors in, 2766-2768
trend over time in, 2765-2766
pathophysiology and pathogenesis of, 2762-2765, 2762f
Acute otitis media (AOM) *(Continued)*
allergy and immunology in, 2764-2765
eustachian tube function in, 2762-2763, 2763f
gastroesophageal reflux in, 2765
infection in, 2763-2764, 2764f
prevention of, 2768-2769
antibiotic prophylaxis for, 2771
management of environmental factors in, 2768
vaccines in, 2768-2769
quality of life assessment for, 2773
recurrent, 2771
treatment of, 2770-2771
medical, 2770-2771
observation in, 2770
for recurrent disease, 2771
surgical, 2771, 2773-2776
clinical features of, 1980
complications and sequelae of, 1963, 1979-1981 (*See also* Temporal bone infections, complications of)
in children, 2776-2777
intracranial, 2776-2777
intratemporal, 2776
otitis media with effusion as, 1963
tympanosclerosis as, 1974
diagnosis of, 2761-2762
audiometry in, 2762
immittance testing (tympanometry) in, 2762
physical examination in, 2761-2762
symptoms and signs in, 2761
epidemiology of, 1979-1980
in children, 2765-2768
incidence and prevalence of, 2765-2766, 2765f
risk factors in, 2766-2768
trend over time in, 2765-2766
immunosuppression and, 222-223
pathophysiology and pathogenesis of, 1980-1981, 2762-2765, 2762f
allergy and immunology in, 2764-2765
eustachian tube function in, 2762-2763, 2763f
gastroesophageal reflux in, 2765
infection in, 2763-2764, 2764f
prevention of, 2768-2769
antibiotic prophylaxis for, 2771
management of environmental factors in, 2768
vaccines in, 2768-2769
recurrent, 2771
treatment of, 1980-1981, 2770-2771
medical, 2770-2771
observation in, 2770
for recurrent disease, 2771
surgical, 2771, 2773-2776
Acute retroviral syndrome (ARS), 197
Acute rhinosinusitis (AR, ARS)
bacterial, 703-705, 704f, 732
endoscopic sinus surgery for, 761
frontal, 775
pathogenesis of, 703-705, 704f
radiologic appearance of, 672-673, 673f
recurrent, 705
surgical management of, 741
Acute vestibular deafferentation syndrome, due to intratympanic gentamicin, 2189
Acyclovir (Zovirax)
with chemical peels, 397
for herpes zoster, 2396
for recurrent respiratory papillomatosis, 2890t, 2892
AD (auditory dyssynchrony)
cochlear implant for, 2220, 2240
neurodiagnostic studies with, 1899-1901, 1900f
otoacoustic emissions as, 1907

Ad (adenoviral) vectors
  conditionally replicating, 22
  for gene therapy, 17-18, 17f, 18t
    of inner ear, 2191t, 2192
Ad5CMV-p53 vector, in gene therapy, 21-22
Adams suspension wiring, 335-336
Adaptation
  and olfactory testing, 633
  in vestibular compensation, 2374-2375
Adaptation exercises, in vestibular rehabilitation, 2372-2373, 2375f, 2378
Adaptive immune system, 209, 599-605
  B cells in, 603
    development of, 603
    responses by, 603
  basophils and mast cells in, 605
  eosinophils in, 604
  innate *vs.,* 597-598
  monocytes and macrophages in, 604
  natural killer cells in, 603-604
  neutrophils in, 604
  overview of, 597-598
  platelets and erythrocytes in, 605
  stem cells in, 599-600, 600f
  T cells in, 600-603
    development of, 600-601
    effector, 601-603
    priming of, 601
  Toll-like receptors and, 598
ADCC (antibody-dependent cellular cytotoxicity), 603-604, 606
Addax (ethylene oxide polyoxypropylene glycol), for cerumen removal, 1958t
Addison's disease
  oral manifestations of, 1251
  preoperative evaluation of, 105
Additive effect, of chemoradiation, 1041
Adductor breathing dystonia, 839
Adductor spasmodic dysphonia, botulinum toxin therapy for, 839, 840f
A-delta fibers, in dental pain, 1202-1203
Adeno-associated virus (AAV) vectors, for gene therapy, 18, 18t
  of inner ear, 2191t, 2192
Adenocarcinoma(s)
  breast
    metastatic to ear, 2108f
    skull base metastases of, 173f
  esophageal, 973, 974f
    cervical, 1425
    GERD and, 899
  of hypopharynx, 1425
  of paranasal sinuses, 1131
  of salivary glands
    basal cell, 1191
    NOS, 1191
    polymorphous low-grade, 1184-1185, 1186f
Adenoid(s)
  anatomy of, 2784
    radiographic, 1399f, 1462-1463
  bacteriology of, 2785-2788
  diagnostic assessment of, 2793-2794, 2793f
  hypertrophic, and otitis media, 1872, 1873f
  in immune system, 605, 2784-2785
Adenoid cystic carcinoma (ACC)
  of larynx, 1507
  of masticator space, 155f
  of nasopharynx, 1351
  of oral cavity, 1299
  of paranasal sinuses, 1131
  of salivary glands
    histopathology of, 1183-1184, 1185f
    imaging of, 1146-1147, 1146f-1147f, 1180f
    minor, 1362-1363
  of trachea, 1614, 1614f
"Adenoid facies," 618, 2628, 2629f, 2639
Adenoid hypertrophy, rhinitis due to, 619b
Adenoid pads, 1869, 1869f
  enlarged, and pediatric chronic sinusitis, 2779-2780, 2780f
Adenoid squamous cell carcinoma, of larynx, 1506
Adenoid tissue, 101
Adenoidectomy, 2795-2796
  for chronic sinusitis in children, 2779-2780, 2780f
  immunologic consequences of, 2785
  indications for, 2795-2796, 2795b
  Microdebrider for, 2797-2798
  for obstructive sleep apnea, 2608-2609
  for otitis media, 2796
    acute, 2771
    with effusion, 2772-2773, 2776
  procedure for, 2776, 2798
  rationale for, 2776
  in vocal professional, 858
Adenolymphoma, of salivary glands, 1170-1171
  imaging of, 1146, 1146f
Adenoma(s)
  parathyroid (*See* Parathyroid adenoma)
  pleomorphic (*See* Pleomorphic adenoma(s))
  sebaceum, 292
  thyroid, 1758-1759
    autonomously functioning, 1759
    in children, 2819
    clinical presentation of, 1758
    management and prognosis for, 1759
    pathology of, 1758-1759
    sestamibi–technetium 99m scintigraphy of, 1785f
    toxic, 1744
Adenomatoid odontogenic tumor, 1277
  microscopic features of, 1277
  radiographic features of, 1277
  treatment of, 1277
Adenopathy, physical examination of, 95-96
Adenosine triphosphatase (ATPase)-driven sodium-potassium (Na^+,K^+) pump, in salivary gland secretion, 1135
Adenosine triphosphate (ATP)–magnesium chloride complex, and skin flap viability, 1074
Adenosquamous carcinoma (ASC)
  of hypopharynx and cervical esophagus, 1425
  of larynx, 1506
Adenotonsillar disease, in children, 2782-2802
  adenoidectomy for, 2795-2796
    indications for, 2795-2796
    and otitis media, 2796
  adenotonsillectomy for (*See* Adenotonsillectomy)
  anatomy of, 2783-2784
  due to bacterial infections, 2785-2788
  due to candidiasis, 2786
  chronic adenotonsillar hypertrophy as, 2790-2793
    airway obstruction due to, 2789f-2790f, 2790-2793, 2795
    algorithm for evaluation of, 2783f-2784f
    with attention deficit–hyperactivity disorder, 2791
    cardiopulmonary complications of, 2792, 2792f
    craniofacial growth and, 2792-2793
    diagnostic assessment of, 2793-2794, 2793f
    and enuresis, 2792
    etiology of, 2789f-2790f, 2790
    and growth problems, 2792
    and neurocognitive development, 2791-2792
    and obstructive sleep apnea, 2790-2793
  complications of, 2788-2790
    nonsuppurative, 2788
    parapharyngeal space abscess as, 2788-2789
    peritonsillar infections as, 2788, 2789f
    retropharyngeal space infections as, 2789-2790, 2789f
    suppurative, 2788-2790
  due to *Corynebacterium diphtheriae,* 2786-2787
  diagnostic assessment for, 2793-2794, 2793f
Adenotonsillar disease, in children *(Continued)*
  history of, 2782
  imaging of, 2793-2794, 2793f
  immunology of, 2784-2785
  due to infections of Waldeyer's ring, 2785
  management algorithms for, 2782, 2783f-2784f
  microbiology of, 2785-2788
  due to *Neisseria gonorrhoeae,* 2786
  preoperative assessment for, 2794
  due to streptococcal infection, 2787
  due to syphilis, 2786
  due to tonsillar concretions/tonsilloliths, 2787-2788, 2788f
  due to Vincent's angina, 2786
  due to viral infections, 2785-2786, 2786f
    with Epstein-Barr virus, 2785-2786, 2786f
Adenotonsillar hypertrophy
  chronic, in children, 2790-2793
    with ADHD, 2791
    airway obstruction due to, 2789f-2790f, 2790-2793, 2795
    algorithm for evaluation of, 2783f-2784f
    cardiopulmonary complications of, 2792, 2792f
    craniofacial growth and, 2792-2793
    diagnostic assessment of, 2793-2794, 2793f
    and enuresis, 2792
    etiology of, 2789f-2790f, 2790
    and growth problems, 2792
    and neurocognitive development, 2791-2792
    and obstructive sleep apnea, 2790-2793
  obstructive sleep apnea due to, 252
    in children, 2604-2606, 2790-2793
Adenotonsillectomy, 2796-2801
  anesthesia for, 2598-2599, 2599b, 2797
  antibiotic prophylaxis with, 2797
  complication(s) of, 2799-2801
    airway obstruction and pulmonary edema as, 2800
    atlantoaxial subluxation (Grisel's syndrome) as, 2801
    nasopharyngeal stenosis as, 2800-2801, 2801f
    postoperative hemorrhage as, 2799-2800, 2800f
    velopharyngeal insufficiency as, 2800
  historical background of, 2794-2795
  indications for, 2794b-2795b, 2795
    chronic infections as, 2794b-2795b, 2795
    upper airway obstruction as, 2794b-2795b, 2795
  inpatient *vs.* outpatient, 2799
  intravenous corticosteroids during, 2797-2798
  for obstructive sleep apnea, 2608-2609
  patient discharge after, 2798
  patient preparation for, 2797-2798
  preoperative assessment for, 2794
  preoperative sedation for, 2797
  surgical technique for, 2796-2799, 2798f
    adenoidectomy in, 2798
    Coblator in, 2796
    electrocautery tonsillectomy in, 2797-2799
    Harmonic Scalpel in, 2796-2797
    hemostasis in, 2798-2799
    instrumentation in, 2797, 2797f
    Microdebrider in, 2797
    options for, 2796
    patient positioning in, 2798, 2798f
    subtotal tonsillectomy in, 2797
Adenoviral (Ad) vectors
  conditionally replicating, 22
  for gene therapy, 17-18, 17f, 18t
    of inner ear, 2191t, 2192
Adenovirus, pharyngitis due to, 198
Adenylate cyclase system, in salivary gland secretion, 1137
ADHD (attention deficit–hyperactivity disorder), sleep-disordered breathing and, 2791
Adhesion molecules, in allergic rhinitis, 616, 617f
Adipocyte hyperplasia, 452

Adipose origin, neoplasms of, of larynx, 881
Aditus ad antrum
  anatomy of, 1827, 1829, 1852
  vulnerability to injury of, 1829
Adjuvant analgesics, 243-244
  anticonvulsant agents as, 243-244, 244t
  antidepressants as, 244-245, 245t
Adjuvant radiation therapy, for salivary gland neoplasms, 1197-1198, 1198t
Adjuvant therapy, concomitant chemoradiation as, 1056
Adoptive T-cell immunotherapy, for head and neck squamous cell carcinoma, 1024
Adrenal diseases, oral manifestations of, 1251
Adrenal gland, preoperative evaluation of, 104-105
Adrenal insufficiency, idiopathic primary, preoperative evaluation of, 105
Adrenergic receptors, in salivary gland secretion, 1136, 1137t
ADSNHL (autosomal dominant sensorineural hearing loss)
  genetic testing for, 2098
  nonsyndromic, 2090-2093, 2092t
  syndromic, 2093-2096, 2094t
Adult Comorbidity Evaluation 27 (ACE-27), 53
Adult Emergency Airway Cart, 116
Advanced Combination Encoder (ACE), for cochlear implants, 2230, 2231f
Advanced sleep phase disorder, 264
Advancement flaps, 345-346
  bilateral, 345, 346f
  for cheek defects, 358
    V-Y, 358, 361f
  for cleft lip repair, 2668, 2668f
  for forehead repair, 360-363, 362f
  island, 345
  for lip defects, 352-353
  for nasal defects, 347-348, 347f, 349f
  unipedicle, 345, 345f
  V-Y, 345-346, 346f-347f
    for cheek defects, 358, 361f
  Y-V, 346
Advancement rotation flaps, for forehead repair, 360-362, 362f
Adynamic segments, laryngeal videostroboscopy of, 820
AECRS (acute exacerbation of chronic rhinosinusitis), 705, 707, 707f
  surgical management of, 741
AERD (aspirin-exacerbated respiratory disease), 731-732, 732f
Aerodynamic assessment, in voice evaluation, 828-829, 828t, 835
  of airflow, 828, 828t
  of children, 2878
  of laryngeal airway resistance, 828-829, 828t
  of maximum phonation time, 828
  of phonation threshold pressure, 828, 828t
  of professional voice, 849
  of subglottic air pressure, 828, 828t
  of velopharyngeal function, 828t, 829
AESOP (automated endoscopic system for optimal positioning), 39, 40f
Aesthetic facial analysis. *See* Facial analysis.
Aesthetic units, in facial analysis, 269-270, 274f
African-American nose. *See* Noncaucasian rhinoplasty.
AFRS. *See* Allergic fungal rhinosinusitis (AFRS).
Afterhyperpolarizations (AHPs), in vestibular afferent nerve fibers, 2284-2285, 2284f
AGA (androgenetic alopecia), 374-376, 375f
Agency for Healthcare Research and Quality (AHRQ), 52, 82, 84t-87t
Age-related hearing loss (AHL), 2125-2126, 2126f
  genetic basis for, 2074
  with tinnitus, 2132
Age-related plasticity, 1877, 1879, 1882f
AGES classification, of thyroid cancer, 1754, 1756t
Agger nasi, surgical anatomy of, 740
Agger nasi cells
  in endoscopic dacryocystorhinostomy, 799-800, 800f
  in frontal sinusitis, 776
  normal anatomy of, 665-666, 665f-666f
Aging patients. *See* Geriatric patients.
Aging skin, 390-404
  appearance of, 440f
  classification of, 391, 391t
  esthetician's role in management of, 402
  evaluation of, 391
  and facial expression, 439, 440f
  facial resurfacing for
    chemical peels for, 391-397
      agents for, 392-394
      complications of, 396-397
      contraindications to, 391, 392t
      in dark-skinned individuals, 392
      deep, 394-395
      equipment tray for, 393f
      histologic changes with, 390-391
      indications for, 391, 392t
      medium-depth, 393-394, 393f-394f
      patient selection and education for, 391-392
      and phenol toxicity, 395
      postoperative care after, 396, 396f
      prepeel preparations for, 392
      superficial, 392-393, 403
    contraindications to, 391, 392t
    dermabrasion for, 397-399
      complications of, 399
      equipment for, 398, 398f
      micro-, 402-403
      patient selection and consultation for, 397-398
      postoperative care after, 399, 399f
      technique of, 398-399, 398f-399f
    indications for, 391, 392t
    laser, 399-402
      CO_2, 400, 400f
      Er:YAG, 400
      nonablative, 402, 403t
      postoperative care after, 401-402, 401f
    nonablative, 402, 403t
      laser, 402, 403t
      microdermabrasion for, 402-403
      superficial chemical peels for, 403
  histologic changes of, 390-391
  intrinsic and extrinsic factors in, 439
  medical skin care regimens for, 403-404
  melolabial fold in, 406, 406f
  of midface, 444, 444f
Agranulocytosis, oral manifestations of, 1256
AHI (apnea-hypopnea index), 251, 251b
AHIP (America's Health Insurance Plans), 84t-87t
AHL (age-related hearing loss), 2125-2126, 2126f
  genetic basis for, 2074
  with tinnitus, 2132
AHPs (afterhyperpolarizations), in vestibular afferent nerve fibers, 2284-2285, 2284f
AHRQ (Agency for Healthcare Research and Quality), 52, 82, 84t-87t
AI (apnea index), 251b, 252
AICA. *See* Anterior inferior cerebellar artery (AICA).
AIDS. *See* Acquired immunodeficiency syndrome (AIDS).
AIED. *See* Autoimmune inner ear disease (AIED).
Air leaks, due to neck dissection, 1722-1723
Air pollution, and rhinosinusitis, 731
Air pressure, subglottic
  in professional voice production, 846
  in voice evaluation, 828, 828t
Air stream, through nose, tests that assess, 643
Air-bone gap, 1888, 1888f
  with conductive hearing loss, 2020, 2020f
Air-conduction testing, in pure-tone audiometry, 1888
  masking for, 1889-1890
    errors in, 1901-1902
Air-contrast pharyngogram, 1394, 1395f
Airflow
  in olfaction, 624-625, 625f
  and stridor, 2897, 2898f
  in voice evaluation, 828, 828t, 849
Airflow measurement, for velopharyngeal dysfunction, 2679
Airflow rhinometry, 487
Airway
  anatomy of, and tracheobronchial endoscopy, 998-999, 999f
  difficult (*See* Difficult airway)
  fire in, 119
  foreign bodies in, 975-976, 2935-2943
    acute obstruction due to, 2936-2937
    complications of, 2942
    epidemiology of, 2936
    imaging of, 1411, 1412f, 2938-2939
      vs. tonsillar calcifications, 1411, 1412f
    location of, 2936, 2936f
    management of, 2939-2941
      anesthesia for, 2940
      controversies in, 2942
      equipment for, 2939-2940, 2939t, 2940f
      history of, 2935
      postoperative, 2941-2942
      for sharp objects, 2940-2941
      technique for, 2940, 2941f
    symptoms of, 2937-2938
"Airway Alert," identification of, 115
Airway establishment, for odontogenic infections, 188
Airway hemangioma
  assessment and treatment of, 2828-2829, 2829f
  complications of, 2825, 2826f
Airway infection(s), in children, 2803-2811
  bacterial tracheitis (exudative tracheitis) as, 2809-2810
    clinical features of, 2809
    complications of, 2810
    diagnosis of, 2809, 2809f
    differential diagnosis of, 2806t
    endoscopy of, 2809, 2809f
    epidemiology of, 2809
    imaging of, 2809, 2809f
    management of, 2809-2810, 2809f
    pathogenesis of, 2809
    terminology for, 2809
  croup (laryngotracheitis) as, 2803-2806
    clinical features of, 2803-2804
    defined, 2803
    diagnosis of, 2804
    differential diagnosis of, 2804-2805, 2806t
    epidemiology of, 2803
    etiology of, 2803
    imaging of, 2804, 2804f-2805f
    laryngoscopy of, 2804, 2805f
    management of, 2805-2806
    pathogenesis of, 2803-2804
    spasmodic, 2805
    terminology for, 2803
  retropharyngeal abscess as, 2810-2811
    anatomy of, 2810
    clinical features of, 2810
    complications of, 2811
    diagnosis of, 2810-2811, 2810f-2811f
    differential diagnosis of, 2806t
    epidemiology of, 2810
    historical background of, 2810
    imaging of, 2810-2811, 2810f-2811f
    management of, 2811

Airway infection(s), in children *(Continued)*
supraglottitis (epiglottitis) as, 2806-2809
clinical features of, 2807
complications of, 2808-2809
diagnosis of, 2807-2808, 2807f-2808f
differential diagnosis of, 2806t
endoscopy of, 2808, 2808f
epidemiology of, 2806-2807
etiology of, 2807
histology of, 2807, 2807f
historical background of, 2806-2807
imaging of, 2807f, 2808
management of, 2808
Airway management
for deep neck space infections, 205
for laryngeal trauma, 936
with tracheal neoplasms, 1617
for tracheobronchial endoscopy, 1000
Airway obstruction
after adenotonsillectomy, 2800
in children (*See* Stridulous child)
due to chronic adenotonsillar hypertrophy, 2789f-2790f, 2790-2793, 2795
decongestion for, 655
due to foreign body, 2936-2937
in neonate
expected, 2904-2905
unexpected, 2905
laryngeal, 2905
supralaryngeal, 2905, 2905f
tracheobronchial, 2905
posterior to valve area, 655-656
in Robin sequence, 2673
sleep-related, 2607
valve area stenting for, 655
Airway pressure, subglottic
in professional voice production, 846
in voice evaluation, 828, 828t
Airway protection, during pharyngeal swallow, 1216-1217
Airway resistance, laryngeal, in voice evaluation, 828-829, 828t
Airway restriction
identification of side of nose with greater, 655
threshold level at which patient feels, 655
Airway Service, 116-117
Airway Service resources, 116
Airway stenosis, 943-952
classification of, 944, 944t
local application of mitomycin C for, 946
pathophysiology of, 943-944, 944b
surgical management of, 943-952
for chronic disease, 947-952
anterior glottic, 948
due to anterior wall collapse, 951
cervical tracheal, 951, 951b, 951f
cicatricial membranous, 951
complete glottic, 949-950
complete tracheal, 951-952, 952f
laryngeal release procedures in, 952
posterior glottic, 948-949, 949f
subglottic, 945f, 950-951
supraglottic, 947-948
endoscopic *vs.* open, 945
goals and assessment in, 944, 945f
microsurgical débridement in, 946, 946b, 946f
planning for, 946-947
skin and mucosal grafts in, 946-947
stent placement in, 947, 947f
timing of, 945
Akt receptor, in oral cancer, 1295
Ala
lateral angle of, 509f
medial angle of, 509f
5-ALA (5-aminolevulinic acid)-induced fluorescence, for premalignant lesions of larynx, 1488-1489
Alar base, overly narrowed, revision rhinoplasty for, 593-594, 594f
Alar base modification, in noncaucasian patients, 577-578, 578f
Alar batten grafts, 550, 551f
in revision rhinoplasty, 586-587, 587f
Alar cartilage, 496-497, 497f
lateral crus (crura) of, 496-497, 497f, 509f
in cleft-lip nose repair, 562f
transposition of, 551
medial crus (crura) of, 496-497, 497f, 509f
in cleft-lip nose repair, 561f-562f
Alar defects
extending into facial sulcus, 348
cheek advancement flap for, 348, 349f
cheek pedicle transposition flap for, 348, 349f
full-thickness, 347
bipedicle mucosal advancement flap for, 347, 347f
free cartilage grafts for, 348
melolabial interpolated flap for, 348
due to septoplasty, 491, 491f
Alar layer, 202
Alar margin implant, retrograde, 548, 550f
Alar pinching, revision rhinoplasty for, 587, 587f-589f
Alar reduction, for noncaucasian nose
alar soft tissue sculpting in, 557, 561f
nasal base sculpting in, 556-557, 559f-560f
Alar retraction, 548, 549f
revision rhinoplasty for, 587, 587f-589f
Alar rim grafts, in revision rhinoplasty, 587, 588f-589f
Alar soft tissue sculpting, for noncaucasian nose, 557, 561f
Alar-columellar complex, aesthetic analysis of, 270f-271f, 274
Alar-facial junction, 509f
Alaryngeal voice and speech, 1459, 1594-1610
electrolarynx, 1596, 1596f
esophageal, 1596, 1596f
history of, 1594-1595, 1595f
after laryngopharyngectomy, 1458-1459
physiology of, 1595-1597, 1596f
after total laryngectomy, 1572
after total laryngopharyngectomy, 1575
tracheoesophageal, 1597, 1597f
voice prosthesis(es) for, 1597, 1597f
indwelling *vs.* nonindwelling, 1597-1598, 1598f
postoperative management of, 1600
alimentary care in, 1600
pulmonary care in, 1600, 1602f
and radiotherapy, 1600, 1602b
replacement of, 1601
indications for, 1601
nonindwelling, 1602
for valve discrepancy (periprosthetic leakage), 1602
for valve incompetence (transprosthetic leakage), 1601-1602
secondary, 1600
surgical aspects of, 1598-1600, 1599f-1600f
creation of optimally contoured stoma as, 1599-1600, 1600f
pharyngeal mucosa closure as, 1599-1600, 1601f
prevention of excessively deep stoma as, 1599-1600, 1600f
prevention of hypertonicity of PE segment as, 1599-1600, 1599f
timing of insertion of, 1597-1599
troubleshooting with, 1603-1605
types of, 1597-1598, 1598f
Albers-Schönberg disease, 2112
Albright's disease, oral manifestations of, 1257
Albright's syndrome, fibrous dysplasia in, 2110-2111
Albumin, in saliva, 1139
Alcohol
absolute, for embolization, 1933
dizziness due to, 2310t
for ear hygiene or chronic ear drainage, 1958
Alcohol block, for neuropathic pain, 245-246
Alcohol consumption, and squamous cell carcinoma
of head and neck, 1016
of larynx, 1491, 1512-1513
of oral cavity, 1293, 1365
Alcoholism, oral manifestations of, 1255
Alcohol-vinegar solution, for otitis externa, 1953, 1959t-1960t
ALD(s) (assistive listening devices), 2270-2271
Aldara (imiquimod), for aural papillomatosis, 1957
Aldosteronism, primary, preoperative evaluation of, 104-105
Alendronate, for hyperparathyroidism, 1804
Alexander's law, 2297, 2299f, 2312, 2312f
Alfentanil, for pediatric anesthesia, 2592
Alginic acid, for GERD, 970
Alkali(s), caustic ingestion of, 2956-2958
Alkaptonuria, 2114
Allegra (fexofenadine), for nonallergic rhinitis, 701t
Alleles, 2088
Allergic component, in nonallergic rhinitis, 696
Allergic fungal rhinosinusitis (AFRS), 707, 712-715
in children, 2778, 2780, 2781f
chronic, 707, 733
classification of, 709
diagnosis of, 707, 712-713
epidemiology of, 713-714
imaging of, 706f, 713, 714f
immunochemical staining for, 731, 731f
pathogenesis of, 712-714, 714b
prognosis for, 713
therapy for, 713-715, 715b
Allergic granulomatous angiitis, nasal manifestations of, 659
Allergic nasal mucin, 733
Allergic otitis externa, 1945-1946
Allergic reactions, 608-612
parotid enlargement due to, 2864
Allergic rhinitis (AR), 612-614
burden of disease for, 614
classification of, 617-618
epidemiology of, 612-613
episodic, 617-618
evaluation and diagnosis of, 617-619
acoustic rhinometry in, 651
diagnostic tests in, 619
differential diagnosis in, 618, 619b
history in, 617-618, 619b
physical examination in, 618-619
rhinomanometry in, 651
hygiene hypothesis of, 613-614
intermittent, 618
mild, 618
moderate to severe, 618
pathophysiology of, 614-617, 618f
adhesion molecules and cellular recruitment in, 616, 617f
cellular events in, 615-616
early response to antigen in, 614
hyperresponsiveness in, 616-617
nonspecific, 617
specific, 616-617
late response to antigen in, 615
neuronal contribution to, 614-615
sensitization and immunoglobulin E production in, 614
and pediatric chronic sinusitis, 2778
perennial, 617-618
and pediatric chronic sinusitis, 2778
persistent, 618
seasonal, 617-618
and pediatric chronic sinusitis, 2778

Allergic rhinitis (AR) *(Continued)*
severity of, 618
symptoms of, 617
treatment of, 619-622
anticholinergics in, 620
antihistamines in, 620
anti-IgE in, 622
avoidance in, 619-620
combination, 622
cromolyn sodium in, 620
decongestants in, 620
for eye symptoms, 622
general planning for, 622-623
immunotherapy in, 621-622
novel extracts in, 622
subcutaneous, 621
sublingual, 621-622
intranasal steroids in, 621
leukotriene modifiers in, 620-621
systemic glucocorticosteroids in, 621
Allergic rhinoconjunctivitis, 622
Allergic rhinosinusitis, imaging of, 675
"Allergic salute," 618
Allergy
and otitis media, 2764-2766
preoperative evaluation of, 102
and rhinosinusitis, 731
chronic, 706-707, 706f
pediatric, 2778
Allocation bias, *vs.* efficacy of treatment, 62t
AlloDerm Regenerative Tissue Matrix (Cymetra)
for nasal reconstruction, 368
for tympanoplasty, 2000
for vocal fold medialization
history of, 905
by injection, 905-906
complications of, 907
laryngoscopic, 906-907
percutaneous, 906
Allograft(s)
for craniofacial defect repair, 2657
for ossiculoplasty, 2006
Allograft transplantation, 1098
Alloplastic grafting materials, for nasal skeletal reconstruction, 368
Alloplastic implants, in noncaucasian rhinoplasty, 569-570, 570f
complications of, 578, 578f-579f
Allopurinol, and skin flap viability, 1074
Almond oil, for cerumen removal, 1958t
Alopecia. *See also* Hair loss.
androgenetic, 374-376, 375f
areata, 376
scarring, 375-376
Alpha error, 65, 66t
Alpha particles, 1031-1032
5-Alpha reductase, in hair loss, 375, 375f
5-Alpha reductase inhibitor, for hair loss, 377-378
α- and β-blocker, intraoperative, 112
α-adrenergic blocking agents, and skin flap viability, 1073
α-amylase, in saliva, 1139-1141
α-defensins, 599
α/β ratio, for radiation therapy, 1038-1039
Alpha-hydroxy acids, for aging skin, 404
Alport syndrome (AS), sensorineural hearing loss in, 2051t-2058t, 2094t, 2096-2097
adult-onset, 2118
ALS (amyotrophic lateral sclerosis), laryngeal hypofunction due to, 842
Alternaria spp, rhinosinusitis due to, 705, 732-733
Alternate cover test, 2312-2313
Alternative medicine, for rhinosinusitis, 731, 735t
Alternobaric vertigo, 2343
Aluminum acetate otic drops (Burow's solution), 1959t-1960t
for fungal otitis externa, 1954
Alveolar canal, of mandible, 1319-1320
Alveolar cyst of newborn, 1266, 1266f
microscopic features of, 1266
treatment of, 1266
Alveolar hypoventilation, central, 262t
Alveolar process, of mandible, 1319, 1320f
Alveolar ridge
anatomy of, 1297-1298
squamous cell carcinoma of, 1304-1305
clinical presentation of, 1304, 1304f
epidemiology of, 1304
mandibulectomy for, 1304, 1304f-1305f, 1307f
maxillary, 1304
neck dissection for, 1304
survival with, 1304-1305
Alveolar soft part sarcoma, of neck, 1668
Alveolar ventilation, in newborns, 2570
Alveolus, 998
Alzheimer's disease
olfactory dysfunction in, 635
oral manifestations of, 1254-1255
AMA(s) (antimicrosomal antibodies), 1740-1741
AMA (American Medical Association), 84t-87t
Amalgam tattoo, 1243
clinical features of, 1243, 1243f
defined, 1243
differential diagnosis of, 1243
etiology of, 1243
histopathologic features of, 1243, 1243f
treatment of, 1243
Ambient stimulation, for tinnitus, 2133-2134
Ambulatory Care Quality Alliance (AQA), 84t-87t, 87-88
Ameloblastic carcinoma, 1274
Ameloblastic fibroma, 1274-1275
microscopic findings in, 1274-1275, 1275f
radiographic features of, 1274
treatment of, 1275
Ameloblastic fibro-odontoma, 1275
microscopic findings in, 1275, 1275f
radiographic findings in, 1275
treatment of, 1275
Ameloblastoma
intraosseous type, 1273-1274
defined, 1273
mandibular, 1274
maxillary, 1274
microscopic features of, 1273, 1273f
natural history and treatment of, 1273-1274
radiographic findings in, 1273, 1273f
malignant, 1274-1275
odonto-, 1278
of oral cavity, 1291, 1291f
peripheral (extraosseous), 1274
unicystic, 1271-1272
definitions, clarifications, and treatment for, 1272, 1272f
microscopic features of, 1271, 1271f
vs. multicystic or multilocular, 1272
radiographic features of, 1271
"simple," 1272
American Board of Medical Specialties (ABMS), 80, 84t-87t
core competencies of, 80, 80b
American Board of Otolaryngology (ABOto), 80b, 84t-87t
American College of Surgeons (ACS), 84t-87t
American Medical Association (AMA), 84t-87t
America's Health Insurance Plans (AHIP), 84t-87t
AMES classification, of thyroid cancer, 1754, 1756t
Ames waltzer mouse, deafness in, 2074
AMI (auditory midbrain implant), penetrating, 2262-2263, 2263f
Amifostine, for xerostomia, 1103
Amino acid taste, transduction of, 1209
Aminoglycoside ototoxicity, 1953-1954, 2169
clinical manifestations of, 2170
delayed, 2170
histopathology of, 2170
mechanisms of, 2170-2171
monitoring for, 2170
in noise-induced hearing loss, 2147
pharmacokinetics of, 2169-2170
risk factors for, 2170
sensorineural hearing loss due to, 2119-2120, 2170
with topical preparations, 2119-2120
susceptibility to, 2097, 2170
vertigo due to, 2201, 2310t
vestibular, 2170
5-Aminolevulinic acid (5-ALA)-induced fluorescence, for premalignant lesions of larynx, 1488-1489
Amiodarone (Cordarone)
dizziness due to, 2310t
thyrotoxicosis due to, 1744
Amitriptyline, for neuropathic pain, 244, 245t
Amoxicillin
for endocarditis prophylaxis, 1249t
for otitis media with effusion, 2771-2772
for pediatric surgery prophylaxis, 2597t
Amoxicillin-clavulanate
for acute otitis media, 2770
for pediatric chronic sinusitis, 2779
for rhinosinusitis, 734t
AMP(s). *See* Antimicrobial peptides (AMPs).
Amphotericin B, for rhinosinusitis, 735-736, 735t
fungal, 712, 713t
nonallergic eosinophilic, 714t
Ampicillin
for adenotonsillectomy, 2797
for endocarditis prophylaxis, 1249t
for pediatric surgery prophylaxis, 2597t
Amplitude
of sound waves, 1838-1839, 1839f
of vibration, laryngeal videostroboscopy of, 820, 821f, 848, 848t
Ampullae, of semicircular ducts
anatomy of, 1851f, 1853f, 1854
embryogenesis of, 1852
in vestibular sensation, 2277
Ampullofugal rotation, of endolymph, 2289
Ampullopetal rotation, of endolymph, 2289
Amputation neuromas, due to neck surgery, 1731-1732
Amylase, in saliva, 1139-1141
Amyloidosis
esophageal manifestations of, 979
laryngeal and tracheal manifestations of, 891, 891f
of oral cavity, 1289-1290, 1290f
Amyotrophic lateral sclerosis (ALS), laryngeal hypofunction due to, 842
AN. *See* Auditory neuropathy (AN).
Anagen phase, 374, 374f
Analgesia
patient-controlled, 240, 241t
preemptive, 241
Analgesic ladder, 242-243
Analgesics
adjuvant, 243-244
anticonvulsant agents as, 243-244, 244t
antidepressants as, 244-245, 245t
for cancer pain, 1103
oral sequelae of, 1247t-1248t
ototoxicity of, 2175-2176
hydrocodone as, 2175
salicylates as, 2175-2176
Analog hearing aids, 2267
Analog stimulation, for cochlear implants, 2230, 2230f

Analysis of variance (ANOVA), 71
Anaphylactic reaction, tension pneumothorax *vs.*, 119
Anaphylaxis, preoperative evaluation of, 102
Anaplastic thyroid carcinoma, 1764
  clinical presentation of, 1764
  management and prognosis for, 1764
  pathology of, 1764
Anatomic landmarks and reference points, in facial analysis, 269
  cephalometric, 270b, 272f
  Frankfort horizontal plane as, 269, 272f
  soft tissue, 270b, 271f
ANCAs (antineutrophil cytoplasmic antibodies), in Wegener's granulomatosis, 658, 2103
Androgen metabolic pathway, within skin, 375, 375f
Androgenetic alopecia (AGA), 374-376, 375f
Androgenic factors, in hair loss, 375, 375f
Anechoic tissue, 1643
Anemia
  Fanconi's, tumor suppressor gene in, 1020
  oral manifestations of, 1256
  and radiotherapy, 1041
Anesthesia
  adjuncts to
    antihypertensives as, 112
    paralytic agents as, 111-112
  for anterior and middle cranial base surgery, 2447-2448
  for arytenoid adduction, 914-915
  in children, 2575, 2587-2601
    for adenotonsillectomy, 2598-2599, 2599b
    for airway and esophageal foreign body removal, 2940
    emergence from, 2592-2593
    induction of, 2589-2591
      inhalation, 2590
      intramuscular, 2591
      intravenous, 2590
      parental presence during, 2590
      rapid-sequence, 2590
    intraoperative monitoring standards for, 2588, 2588b
    for laryngeal surgery, 2599-2600
    maintenance of, 2591-2592
      inhalational agents for, 2591
      intravenous agents for, 2591, 2593t
    medical condition(s) affecting, 2594-2597
      asthma as, 2595
      congenital heart disease as, 2596-2597, 2596t-2597t
      cystic fibrosis as, 2595
      diabetes mellitus as, 2596
      prematurity as, 2595
      upper respiratory infection as, 2594-2595
    outside of operating room, 2594
    postoperative management of, 2593-2594
      for nausea and vomiting, 2593
      for pain, 2594
      for postintubation croup, 2593
    preoperative assessment for, 2588
    preparation for, 2588-2589
      behavioral, 2588-2589, 2589t
      nothing-by-mouth orders in, 2589, 2590t
      premedication in, 2589
    for rigid bronchoscopy, 2597-2598, 2597t
    risks of, 2587-2588
  and cranial nerve monitoring, 2544
  for endoscopic sinus surgery, 744-745
    general, 745
    local, 744-745
  for facial trauma, 304
  fasting prior to, 112
  induction of
    agents for, 111
    in children, 2589-2591
Anesthesia *(Continued)*
    inhalation, 2590
    intramuscular, 2591
    intravenous, 2590
    parental presence during, 2590
    rapid-sequence, 2590
  sedatives and opioid as adjuncts to, 111
  standard *vs.* rapid-sequence, 112-113, 113f
  for laryngotracheobronchoscopy, 2902
  for laser surgery, 36-37
  local, 112
    oral sequelae of, 1247t-1248t
  for parathyroidectomy, 1790
  perioperative regional, for postoperative pain control, 241-242
  with recurrent respiratory papillomatosis, 2891
    intermittent apnea-reintubation, 2891
    jet ventilation, 2891
    spontaneous ventilation, 2891
    wrapped or "laser-safe" endotracheal tube, 2891
  for rhinoplasty, 515-519, 518f
    and surgical planes, 516-517, 516f-517f
  routine, 110-111
  for small fenestra stapedotomy, 2030
  topical
    for awake fiberoptic nasotracheal intubation, 124
    for tracheobronchial endoscopy, 1000
  with tracheal neoplasms, 1617
  for tympanoplasty, 2001
  volatile agents for, 111
Anesthesia Fiberoptic Cart, 116
Anesthetics
  local, 112
    oral sequelae of, 1247t-1248t
  topical
    for awake fiberoptic nasotracheal intubation, 124
    for tracheobronchial endoscopy, 1000
Aneuploidy(ies), 4-5
  in thyroid carcinoma, 1752
Aneurysm(s), carotid artery
  of petrous apex, 2525, 2527f
  upper cervical and petrous, 2504, 2504f-2505f
"Angel's kiss," 290-291
Angiitis, allergic granulomatous, nasal manifestations of, 659
Angina
  Ludwig's
    airway establishment for, 188
    due to mandibular space infections, 184, 185f
  Vincent's, 2786
Angiofibroma, 292
  epistaxis due to, 686f
  juvenile
    endovascular treatment of, 1937-1938, 1943f
    nasopharyngeal, 152, 154f, 1349-1351
      clinical features of, 1349
      diagnosis of, 1349-1350, 1350f
      growth patterns of, 1349
      management of, 1350-1351
      pathologic features of, 1349
      recurrence of, 1351
      staging of, 1350, 1350t
    sinonasal, 721-722
      classification systems for, 722
      endoscopic appearance of, 721, 721f
      imaging of, 721
      natural history of, 721
      origin of, 721, 721f
      postoperative surveillance for, 722
      preoperative embolization for, 721-722
      surgical approach for, 718t, 722, 722f-723f, 763
      transnasal endoscopic-assisted surgery for, 2483, 2483f
Angiogenesis
  in acutely raised skin flaps, 1069, 1069f
  in formation of granulation tissue, 1077-1078
Angiography
  prior to anterior and middle cranial base surgery, 2444-2445
  of anterior skull base, 2475
  catheters for, 1932-1933
  computed tomography
    of anterior skull base, 2475, 2475f
    of neck masses, 1637, 1637t
  equipment for, 1932
  of glomus jugulare/vagale tumor, 1935f
  magnetic resonance, 137
    of anterior skull base, 2475
    of neck masses, 1637, 1637t
    of petrous apicitis, 1989f
  of multiple chemodectomas, 1935f
  of neck masses, 1637, 1637t
  of paranasal sinus tumors, 1124
  for penetrating neck trauma, 1630-1632, 1631t, 1632f-1633f
Angiokeratoma corporis diffusum universale, oral manifestations of, 1257
Angioma(s)
  cherry (senile), 290-291
  spider, 291
  strawberry, 290
  tufted, 2824-2825
    Kasabach-Merritt phenomenon with, 2825
Angiopathy, diabetic, presbycusis due to, 232
Angiosarcoma, of neck, 1668
Angiosomes, 1064
  in acutely raised skin flaps, 1069, 1069f
Angular cheilitis, 1230, 1230f
  in HIV, 225, 226f
Angular gyrus, in central auditory pathway, 1837
Angular vestibuloocular reflex (aVOR), 2306, 2307f
  after labyrinthectomy, 2291-2292, 2291f-2293f
Ankle strategy, 2308
Ankylosis, of temporomandibular joint, 1281t, 1282
Ann Arbor staging system, for lymphoma, 1676, 1677t
Annular ligament, of stylomastoid foramen, 1826f
Annulus of Zinn, 440
Anosmia, 633
  congenital, 636
  specific, 636
Anotia, 2742
ANOVA (analysis of variance), 71
Ansa cervicalis
  anatomy of, 2579f-2580f, 2581
  characteristics of, 918-919
  in neuromuscular pedicle procedure, 920, 921f
Ansa cervicalis–recurrent laryngeal nerve anastomosis, for laryngeal reinnervation, 922-923
  advantages of, 922
  clinical results of, 923
  disadvantage of, 922
  history of, 917-918
  surgical indications and contraindications for, 922
  surgical technique for, 922-923, 923f
Ansa hypoglossi nerve, for facial nerve paralysis, 2426-2427
Antacids
  for extraesophageal reflux, 901
  for GERD, 970
Anterior ampullary nerve, 1854f, 2278f
Anterior cerebral artery, 2351f
Anterior cervical lymph nodes, 2582
Anterior cervical space, imaging of, 158, 160f, 162f
Anterior cervical trauma, laryngeal injury due to, 933-934, 934f

Anterior clinoid process
  in surgical anatomy of anterior cranial base, 2442-2443, 2443f, 2472f
  in surgical anatomy of lateral skull base, 2435f
Anterior commissure
  anatomy of, 1486
  laryngeal carcinoma of, 1486
    anatomic basis for, 1486
    imaging of, 161, 1474, 1474f
    treatment of, 1496-1497, 1523
      transoral laser microsurgery for, 1531
Anterior commissure tendon, surgical anatomy of, 1541-1542
Anterior communicating artery, 2351f
Anterior compartment lymph nodes, in neck dissection, 1704, 1704f, 1706t
Anterior cranial base
  anatomy of, 1697
  boundaries of, 2442, 2443f
    anterior, 2442, 2443f
    superior, 2442-2443, 2443f
  surgical anatomy of, 741, 2442-2444
    craniofacial junction in, 2442, 2443f
    extracranial structures related to, 2443, 2444f
    and surgical landmarks of orbital skeleton, 2443-2444, 2444f
    for transnasal endoscopic-assisted surgery, 2471-2475
      anterior cranial fossa in, 2471, 2472f
      clivus in, 2474, 2474f
      nasal cavity in, 2471-2473, 2472f-2473f
      nasopharynx in, 2474
      paranasal sinuses in, 2473-2474, 2473f
      retroclival region in, 2474-2475, 2474f-2475f
Anterior cranial base irradiation, 1697-1699
Anterior cranial base surgery
  anesthesia for, 2447-2448
  bicoronal incision in, 2450-2451, 2450f
  complications of, 2468-2469, 2469t
  electrophysiologic monitoring during, 2450
  flap elevation in, 2450-2451, 2451f
  goals of, 2448, 2448b
  intraoperative imaging during, 2449
  operative approaches for, 2450-2454
    anterior craniofacial resection as, 2451-2453, 2452f-2453f
    basal subfrontal, 2453-2454, 2454f
    endoscopic, 2448-2450
    functional and aesthetic considerations in choice of, 2450
    general considerations with, 2448-2450
    image-guided computer-assisted, 2448-2449, 2449f
    overview of, 2448
    planning of, 2448-2450
    robotic, 2450
    subcranial, 2454, 2454f
  outcomes of, 2469-2470
  pathology and management planning for, 2446-2447, 2447b
  postoperative care after, 2468
  preoperative embolization for, 2446
  preoperative evaluation for, 2444-2448
    angiography in, 2444-2445
    of cerebral blood flow, 2445-2446, 2446f
    other evaluations in, 2446-2447
  reconstruction after, 2467-2468
  transnasal endoscopic-assisted, 2471-2486
    anesthesia for, 2476
    combined approaches for, 2484
    complications of, 2485
    craniocervical junction–odontoid approach for, 2483-2484, 2484f
    instrumentation for, 2476
    patient preparation for, 2475-2476
    pedicled septal flap in, 2476-2477
    postoperative care after, 2484-2485
Anterior cranial base surgery *(Continued)*
    preoperative assessment for, 2475, 2475f
    reconstruction after, 2484
    surgical anatomy for, 2471-2475
      anterior cranial fossa in, 2471, 2472f
      clivus in, 2474, 2474f
      nasal cavity in, 2471-2473, 2472f-2473f
      nasopharynx in, 2474
      paranasal sinuses in, 2473-2474, 2473f
      retroclival region in, 2474-2475, 2474f-2475f
    surgical team setup for, 2476f
    transcribriform approach for, 2482
      with bilateral access, 2482, 2482f
      with unilateral access, 2482
    transmaxillary-transpterygoidal-infratemporal approach for, 2482-2483, 2483f
    transsellar and parasellar approaches for, 2479, 2480f
    transsphenoidal approach for, 2477-2481
      with direct transnasal access, 2477, 2477f
      with petrous apex access, 2481
      with transclival approach, 2479-2481, 2480f-2481f
      with transethmoidal access, 2478-2479, 2479f-2480f
      with transseptal access, 2477-2478, 2477f-2478f
      with transseptal-transnasal access, 2478, 2479f
    transtuberculum-transplanum approach for, 2482
Anterior cranial base tumors
  benign, 2446, 2447b
  fibrous dysplasia as, 2647f
  malignant, 1697-1699, 2446, 2447b
    esthesioneuroblastoma as, 1697-1698, 1698f, 1698t
    sinonasal undifferentiated carcinoma as, 1698-1699
  preoperative planning for, 2446-2447
Anterior cranial fossa
  in surgical anatomy of anterior skull base, 2471, 2472f
  in surgical anatomy of lateral skull base, 2435f
Anterior cranial fossa floor, in surgical anatomy of anterior cranial base, 2442-2443, 2443f-2444f
Anterior craniofacial resection, 2451-2453, 2452f-2453f
Anterior cricoid split operation, 2910f, 2918-2919, 2918f-2919f
Anterior cutaneous nerve, anatomy of, 2578, 2580f
Anterior disk displacement, of temporomandibular joint
  with reduction, 1280, 1282f
  without reduction, 1279-1280, 1282f
Anterior ethmoidal air cells, in frontal sinusitis, 776
Anterior ethmoidal artery
  anatomy of, 682, 684f, 1124f
  bleeding from, 690-691, 691f-692f
  prior to endoscopic sinus surgery, 764, 765f
  septal branch of, 483f
  in surgical anatomy of anterior cranial base, 2471-2473, 2472f
Anterior ethmoidal foramen, 322f, 439
Anterior ethmoidal nerve, 483f
  external branch of, 497, 497f
Anterior ethmoidectomy, in endoscopic sinus surgery, 747, 748f
Anterior fontanelle, 2618f
Anterior glottic gap, laryngeal videostroboscopy of, 819, 820f
Anterior glottic web, 2869, 2869f
  stridor due to, 2899, 2900f
  and velocardiofacial syndrome, 2899, 2900f, 2913
Anterior inferior cerebellar artery (AICA)
  anatomy of, 1856f, 2351f
    surgical, 2403-2404, 2404f
  in posterior fossa surgery, 2540
  in surgical anatomy of anterior skull base, 2481f
  in surgical anatomy of lateral skull base, 2437f, 2439f
Anterior inferior cerebellar artery (AICA) occlusion, sensorineural hearing loss due to, 2123
Anterior lacrimal crest, 439
Anterior lamella, of eyelid, 442-443, 443f
Anterior laryngeal wall stenosis, 951
Anterior laryngofissure, with posterior cricoid division, for laryngeal stenosis, 2919, 2919f
Anterior mallear fold, anatomy of, 1825f
Anterior malleolar fold, anatomy of, 1827f
Anterior malleolar ligament, anatomy of, 1827f
Anterior meningoencephaloceles, surgical management of, 742
Anterior nasal aperture, 320f
Anterior nasal depth, 2617t
Anterior nasal spine, 320f, 509f
Anterior neck dissection, 1719
  defined, 1719, 1719f
  technique for, 1719, 1720f
Anterior neuropore, congenital malformations of nose due to developmental errors of, 2686-2690, 2687f
Anterior ostiomeatal channels, 666f
Anterior ostiomeatal unit, 664, 665f
Anterior palatal artery, 483f
Anterior partial laryngectomy, for glottic cancer, 1517t
Anterior petrous apex (APA), 1975-1976, 1976f
  pneumatic, 1976, 1977f
Anterior rhinoscopy, 100, 484
Anterior scalene muscle, anatomy of, 2579f
Anterior scalp flap, 2450-2451
Anterior semicircular duct, anatomy of, 1851f
Anterior septal angle, 509f
Anterior skull base. *See* Anterior cranial base.
Anterior spinal artery, 2351f
Anterior spiral vein, 1856f
Anterior tonsillar pillar, 1297-1298
Anterior tracheal wall stenosis, 951
Anterior transhyoid pharyngotomy, for hypopharyngeal cancer, 1427-1429, 1428f
Anterior triangle, of neck, 96, 96f, 2578f, 2579-2581
  ansa cervicalis in, 2580f, 2581
  carotid triangle in, 2578f, 2579-2580, 2580f
Anterior triangle dissection, 1709-1710
Anterior tympanic artery, 1828f
Anterior vestibular artery, 1854, 1856f
Anterior visceral space, anatomy of, 203
Anterolateral fontanelle, 2618f
Anterolateral thigh flap, 1082t, 1083
  for hypopharyngeal and esophageal reconstruction, 1455
  for oropharyngeal reconstruction, 1379
    of tongue base, 1390-1391
    of tonsils and pharyngeal wall, 1386
Anthropometry, 269
Antiaging products, 403
Antiangiogenesis, in gene therapy, 22
Antiangiogenic compounds, for head and neck squamous cell carcinoma, 1060
Antiarrhythmics, oral sequelae of, 1247t-1248t
Antiarthritics, oral sequelae of, 1247t-1248t
Antibacterial activity, of saliva, 1141
Antibiotic(s)
  for deep neck space infections, 205-206, 206t
  for odontogenic infections, 178, 188
  oral sequelae of, 1247t-1248t
  for otitis media
    acute, 2770
    with effusion, 2771-2772

Antibiotic(s) *(Continued)*
ototopical, 1959t-1960t
for acute bacterial otitis externa, 1951-1953
evidence-based data on, 1952
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1953-1954
resistance to, 1953
for pediatric chronic sinusitis, 2779
for rhinosinusitis, 733-735
intravenous, 733-734, 735t
issues with, 736
long-term macrolide, 733, 734t
oral, 733
short-term, 734t
topical, 734-735, 735t
for stridulous child, 2906
for vocal professionals, 855
Antibiotic prophylaxis
for acute otitis media, 2771
for burns, 315
for orthopedic joint patients, 1253, 1253t
for sinus surgery, 743, 773
for temporal bone fractures, 2044-2045
Antibody-dependent cellular cytotoxicity (ADCC), 603-604, 606
Antibody-mediated hypersensitivity reactions, 608-612
Anticholinergics
for allergic rhinitis, 620
for nonallergic rhinitis, 701
Anticoagulants
dizziness due to, 2310t
oral sequelae of, 1247t-1248t, 1248, 1250
preoperative evaluation of, 105
Anticonvulsants
for chronic pain, 243-244, 244t
dizziness due to, 2310t
oral sequelae of, 1247t-1248t
Antidepressants
for chronic pain, 244-245, 245t
for migraine, 2350
in palliative care, 1104
for tinnitus, 2137
Antidiarrheal agents, oral sequelae of, 1247t-1248t
Antidromic potentials, to assess facial nerve function, 2388
Antiemetics, for postoperative nausea and vomiting, in children, 2593
Antiepileptics
for chronic pain, 243-244, 244t
dizziness due to, 2310t
oral sequelae of, 1247t-1248t
Antifungal agents
for rhinosinusitis
nonallergic eosinophilic fungal, 715-716
systemic, 735, 735t
topical, 735-736, 735t
topical, 1959t-1960t
for fungal otitis externa, 1954-1955
ototoxicity of, 1955
for rhinosinusitis, 735-736, 735t
Antigen presentation, 602f, 606, 606f
Antigen-presenting cells (APCs), 602f, 606, 606f
Antihelix, of ear, 476-477, 476f, 1824f, 2742f
Antihistamines
oral sequelae of, 1247t-1248t
for otitis media
acute, 2770
with effusion, 2771
for rhinitis
allergic, 620
nonallergic, 700-701, 701t
for rhinosinusitis, 734t, 737
for vocal professionals, 854
Antihypertensives
dizziness due to, 2310t
intraoperative, 112
oral sequelae of, 1247t-1248t, 1248
Anti–immunoglobulin E (anti-IgE)
for allergic rhinitis, 622
for rhinosinusitis, 735t, 737
Anti-inflammatory medications
oral sequelae of, 1247t-1248t
ototopical
classes of, 1956, 1956t
for eczematoid otitis externa, 1956-1957
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1956
Antilipidemics, oral sequelae of, 1247t-1248t
Antimalarials, sensorineural hearing loss due to, 2120
Antimicrobial peptides (AMPs), 598-599
cathelicidins as, 599
defensins as, 599
tissue distribution of, 599
Antimicrobial substances, in saliva, 1140
Antimicrosomal antibodies (AMAs), 1740-1741
Antimycotics, oral sequelae of, 1247t-1248t
Antineoplastic agent(s)
oral sequelae of, 1247t-1248t
ototoxicity of, 2171-2174
carboplatin as, 2173-2174
cisplatin as, 2171-2173
clinical studies on, 2171-2172
delayed, 2171-2172
experimental studies on, 2172
genetic predisposition to, 2172
histopathology of, 2172
mechanics of, 2172-2173
pharmacokinetics of, 2171
risk factors for, 2172
vestibular, 2172
difluoromethylornithine as, 2174
animal studies on, 2174
clinical studies on, 2174
conclusions on, 2174
Antineutrophil cytoplasmic antibodies (ANCAs), in Wegener's granulomatosis, 658, 2103
Antioxidants
for cisplatin ototoxicity, 2173
for noise-induced hearing loss, 2145
oral sequelae of, 1247t-1248t
Anti-Parkinsonian medications, oral sequelae of, 1247t-1248t
Antiphospholipid antibody syndrome, inner ear disease in, 2166
Antiproliferatives, oral sequelae of, 1247t-1248t
Antipyretics, oral sequelae of, 1247t-1248t
Antireflux agents
for extraesophageal reflux in children, 2946
oral sequelae of, 1247t-1248t
for recurrent respiratory papillomatosis, 2893
for rhinosinusitis, 735t, 737
Antireflux surgery, for GERD, 970
Antiretroviral therapy, highly active, 211
Antiseptics, ototopical, 1959t-1960t
for fungal otitis externa, 1955
Antithyroglobulin antibodies (ATAs), 1740
Antithyroid agents, 1739, 1739t
adverse reactions to, 1742
for Graves' disease, 1742
for Graves' ophthalmopathy, 1810
oral sequelae of, 1247t-1248t
for thyroid storm, 1745
Antithyroid antibodies, 1740-1741
Anti-thyroperoxidase (anti-TPO), 1740
Antitragus, 476-477, 476f, 1824f, 2742f
Antitumoral immune response, direct in vivo stimulation of, 21
Antiviral agents
for Bell's palsy, 2395
for rhinosinusitis, 731, 734t
Antrostomy, in endoscopic sinus surgery, 747, 747f
failure of, 764-766, 766f
Antrum, in mastoidectomy, 2011-2012
Anxiety
palliative care for, 1103-1104
professional voice disorders due to, 853
Anxiolytics, oral sequelae of, 1247t-1248t
AOM. *See* Acute otitis media (AOM).
AP (action potential), in electrocochleography, 1892-1894, 1907
in Meniere's disease, 2337
APA (anterior petrous apex), 1975-1976, 1976f
pneumatic, 1976, 1977f
APCs (antigen-presenting cells), 602f, 606, 606f
Apert's syndrome, craniofacial anomalies in, 2641t, 2645-2646
APHAB (Abbreviated Profile of Hearing Aid Benefit), 57
Aphthous stomatitis, 1289, 1289f
in HIV, 227, 227f
recurrent, 1236-1239
clinical features of, 1237-1238
defined, 1236-1237
differential diagnosis of, 1238, 1238t
etiology and pathogenesis of, 1237, 1237t
herpetiform-type, 1238, 1238f
histopathologic features of, 1239
major, 1237-1238, 1238f
minor, 1237, 1238f
treatment of, 1239
Apnea
defined, 251b
obstructive
in children, 2607
sleep (*See* Obstructive sleep apnea (OSA))
Apnea index (AI), 251b, 252
Apnea technique, for pediatric anesthesia, 2600
Apnea-hypopnea index (AHI), 251, 251b
Apoptosis, in ototoxicity, 2171
prevention of, 2189-2190
Appearance
physical examination of, 95
in voice evaluation, 827
Appendix, laryngeal, 876
Apple green birefringence, with amyloidosis, 1289-1290
Apron incision, for neck dissection
radical, 1709, 1710f
selective
of oral cavity, 1714, 1716f
of oropharynx, hypopharynx, and larynx, 1717-1718, 1717f
AQA (Ambulatory Care Quality Alliance), 84t-87t, 87-88
AR. *See* Acute rhinosinusitis (AR, ARS).
AR (allergic rhinitis). *See* Allergic rhinitis (AR).
Ar (argon) laser, 30, 31t
Ar (argon) plasma coagulation, interventional bronchoscopy with, 1010t
Ar (argon) tunable dye laser, 30, 31t
Arachidonic acid metabolism, in rhinosinusitis, 731-732, 732f
Arachis oil
almond oil, rectified camphor oil (Otocerol, Earex), for cerumen removal, 1958t
chlorbutol, paradicholorobenzene, oil of turpentine (Cerumol), for cerumen removal, 1958t
Arachnoid cysts, of cerebellopontine angle, 2523-2524
vs. cholesteatoma, 2519, 2521f
imaging of, 1928, 1929t
Arcanobacterium haemolyticum, pharyngitis due to, 193

Arch bars, in maxillofacial fracture repair, 333, 333f, 337
Arch of Corti, 1840
ARCON treatment, with radiotherapy, 1041
Arcuate eminence
  anatomy of, 1822, 1822f
  in surgical anatomy of lateral skull base, 2436f, 2437
Arcuate fasciculus, in central auditory pathway, 1837
Area ratio, in auditory physiology, 1839-1840, 1840f, 2018-2019
L-Arginine, and skin flap viability, 1074
Argon (Ar) laser, 30, 31t
Argon (Ar) plasma coagulation, interventional bronchoscopy with, 1010t
Argon (Ar) tunable dye laser, 30, 31t
Arhinia, 2690, 2691f
Aromatase, in hair loss, 375, 375f
ARS (acute retroviral syndrome), 197
ARS (acute rhinosinusitis). *See* Acute rhinosinusitis (AR, ARS).
Arterial compression, of trachea, 2925-2926
Arterial cutaneous flaps, 1067, 1067f
Arterial embolization
  for epistaxis, 690, 691f
  for vascular repair, 1633
Arterial oxygen tension (Pao_2), in children, 2570, 2571t
Arteriography
  cross-compression carotid, for cerebral blood flow evaluation, 2490
  four-vessel, prior to lateral cranial base surgery, 2489-2490, 2491f
  of neck masses, 1637, 1637t
  parathyroid, 1788
  for penetrating neck trauma, 1630-1632, 1631t, 1632f-1633f
Arteriovenous fistulas, embolization of
  dural, 1940-1942, 1940f
  facial, 1940, 1940f
Arteriovenous malformation (AVM), 2832, 2833f
  embolization for, 1942, 1942f
  of neck, 1662-1663
  of salivary glands, 1172
Arthritis
  infectious, of temporomandibular joint, 1281-1282, 1281t
  osteo- (degenerative)
    oral manifestations of, 1253
    of temporomandibular joint, 1281-1282, 1281t
  rheumatoid
    laryngeal and tracheal manifestations of, 891, 891f
    oral manifestations of, 1253, 1253t
    of temporomandibular joint, 1281t, 1282
Arthrocentesis, of temporomandibular joint, 1283
Arthroscopy, of temporomandibular joint, 1283
Arthrotomy, of temporomandibular joint, 1283
Articular disk, of temporomandibular joint, 1279-1280
Articular tubercle, 2010f
Articulation
  in speech, 810-812, 833
  speech therapy for, with velopharyngeal dysfunction, 2681
Artifacts
  in auditory brainstem response recording, 2552-2553
  in electromyography, 2547-2548, 2548f
  on MRI, 133-134, 134f
Artificial larynx. *See* Voice prosthesis(es).
Aryepiglottic folds
  anatomy of, 1422
    radiographic, 1398f-1399f, 1463f, 1471, 1471f
  carcinoma of
    imaging of, 1475, 1478f
    supraglottic laryngectomy for, 1554-1555
Aryepiglottic muscle, 1542f-1543f
Aryepiglottoplasty, for laryngomalacia, 2867, 2868f
Arytenoid abduction, for bilateral paralysis, 916
Arytenoid adduction, 912-916
  anesthesia for, 914-915
  cricoarytenoid joint in, 913
  cricoarytenoid muscle in, 913, 914f
  future directions in, 916
  for long-standing laryngeal paralysis, 914
  membranous vocal fold in, 914
  overview of, 912, 913f
  postoperative care after, 916
  surgical procedure for, 915-916, 915f-916f
  vs. thyroplasty, 912-913
  vs. vocal fold injection, 912-913
  vocal process in, 913-914, 913f-914f
Arytenoid cartilage
  anatomy of, 805-806, 1422f
    radiographic, 1399f, 1471, 1473f
    surgical, 1541, 1542f
  laryngeal carcinoma of, 1541
  movement of, 805, 806f
  videoendoscopy of, 816
Arytenoid involvement, supraglottic laryngectomy with, 1554-1555
Arytenoid muscle, 1543f
Arytenoidectomy
  laser, 2909
  for posterior glottic stenosis, 949, 949f
AS (Alport syndrome), sensorineural hearing loss in, 2051t-2058t, 2094t, 2096-2097
  adult-onset, 2118
ASC (adenosquamous carcinoma)
  of hypopharynx and cervical esophagus, 1425
  of larynx, 1506
A-scale, 2140
ASCC (acantholytic squamous cell carcinoma), of larynx, 1506
Ascending cervical artery, in root of neck, 2581-2582, 2581f
Ascending pharyngeal artery, 2580f
Ascending "w," in nasal breathing assessment, 644
Ascertainment bias, *vs.* efficacy of treatment, 62t
Asian nose. *See* Noncaucasian rhinoplasty.
ASIMO, 38, 39f
Asimov, Isaac, 38
Aspergillus fumigatus
  otitis externa and otitis media due to, immunosuppression and, 222-223
  rhinosinusitis due to, 220-221, 220f
Aspergillus niger, otitis externa due to, 2195
Aspergillus spp
  otitis externa due to, 1944-1945, 1945f
  rhinosinusitis due to, 705, 710-711, 712f
    chronic, 732-733
    in immunocompromised host, 220-221, 220f
Aspiration
  due to abnormal swallow, 1217 (*See also* Dysphagia)
  chronic, 925-3
    defined, 925
    etiology of, 925, 926b
    evaluation of, 926
    nonsurgical management of, 926-927
    surgical management of, 927-932
      endolaryngeal stents for, 928, 930f
      epiglottic flap closure of larynx for, 928, 930f
      glottic closure for, 929-931, 931f
      "ideal" procedure for, 927, 927b
      laryngectomy for, 927, 928f
      laryngotracheal separation for, 931-932, 931f
      partial cricoidectomy for, 928
      subperichondrial cricoidectomy for, 927-928, 929f
      tracheoesophageal diversion for, 931-932, 931f-932f
      vertical laryngoplasty for, 928-929, 930f
Aspiration *(Continued)*
    symptoms of, 925-926
    tracheotomy for, 927
    vocal cord medialization for, 927
  foreign body, 975-976, 2935-2943
    acute obstruction due to, 2936-2937
    complications of, 2942
    epidemiology of, 2936
    imaging of, 1411, 1412f, 2938-2939
      vs. tonsillar calcifications, 1411, 1412f
    interventional bronchoscopy for, 1008
    location of, 2936, 2936f
    management of, 2939-2941
      anesthesia for, 2940
      controversies in, 2942
      equipment for, 2939-2940, 2939t, 2940f
      history of, 2935
      postoperative, 2941-2942
      for sharp objects, 2940-2941
      technique for, 2940, 2941f
    stridor due to, 2898
    symptoms of, 2937-2938
Aspiration pneumonia, 1250
Aspirin
  for chemoprevention of oral cancer, 1315
  after free tissue transfer, 1096
  for head and neck squamous cell carcinoma, 1018
  preoperative use of, 105
  sensorineural hearing loss due to, 2120
  for vocal professionals, 855
Aspirin desensitization therapy, for rhinosinusitis, 734t, 737
Aspirin sensitivity, in rhinosinusitis, 731-732, 732f
Aspirin-exacerbated respiratory disease (AERD), 731-732, 732f
Assistive listening devices (ALDs), 2270-2271
Association auditory cortex, 1847
Association of American Medical Colleges (AAMC), 84t-87t
ASSR (auditory steady-state response), 1911-1912
  clinical applications of, 1910f, 1912
  for cochlear implants in children, 2234-2235
Astelin (azelastine)
  for allergic rhinitis, 620
  for nonallergic rhinitis, 701t
  for rhinosinusitis, 734t, 737
Asterion, 320f
Asthenia, in voice evaluation, 827t
Asthma
  exercise-induced, in professional singers, 853
  and GERD, 971
  oral manifestations of, 1250
  pediatric anesthesia with, 2595
ASV (automatic speaking valve), 1599-1600
A-T procedure, for forehead repair, 362, 363f
ATA(s) (antithyroglobulin antibodies), 1740
Ataxia
  cerebellar, 2356-2357
  familial episodic, 2357
  Friedreich's, 2357
ATB. *See* Audiologic test battery (ATB).
Atelectasis, middle ear, 1964, 1964f-1965f
  tympanoplasty with, 2003-2004
Athletes, rhinosinusitis in, 737
Atlantoaxial dislocation, 2355-2356
Atlantoaxial instability, 2355-2356
Atlantoaxial subluxation, due to adenotonsillectomy, 2801
Atlas, assimilation (occipitalization) of, 2355
Atmospheric barotrauma, 2343
Atoh1
  in hair cell regeneration and repair, 2144
  in murine deafness, 2058t-2060t
ATP (adenosine triphosphate)–magnesium chloride complex, and skin flap viability, 1074
ATP2B2, in deafness, 2051t-2058t, 2080
ATP6B1, in deafness, 2051t-2058t

ATPase-driven sodium-potassium (Na^+,K^+) pump, in salivary gland secretion, 1135
Atracurium, for pediatric anesthesia, 2593t
Atresiaplasty, 2754-2757
  alternatives to, 2759
  avoidance of complications of, 2758-2759
  candidacy for, 2753, 2753t
  contraindications to, 2754
  creation of split-thickness skin graft in, 2756, 2756f
  dissection of ossicular mass in, 2755-2756, 2756f
  drilling for new ear canal in, 2755-2756
  ear wick packing in, 2756-2757
  facial nerve in, 2754, 2755f, 2759
  harvesting of temporalis fascia in, 2755, 2755f
  meatoplasty in, 2756-2757
  outcomes of, 2754
  placement of split-thickness skin graft in, 2756, 2757f-2758f
  postauricular incision in, 2755, 2755f
  postoperative care after, 2757-2758
  preoperative evaluation and patient counseling for, 2754, 2754f-2755f
  reconstruction of ossicular chain in, 2756
  removal of atretic plate in, 2755-2756, 2755f
  Silastic strips in, 2756-2757, 2758f
  suturing in, 2756-2757, 2758f
  temporal fascia graft in, 2755f, 2756, 2757f
  timing of, 2754
Atrophic rhinitis, 696-697
Atropine, for premedication in children, 2589
Attention deficit–hyperactivity disorder (ADHD), sleep-disordered breathing and, 2791
Attenuation, 1032-1033
Atticotomy, in ossiculoplasty, 2007-2008
Atypical carcinoid (AC), of larynx, 1507
Atypical mole syndrome, 1107
Atypical neuralgia, *vs.* myofascial pain dysfunction syndrome, 1284t
Audax (choline salicylate and glycerol), for cerumen removal, 1958t
Audibility, threshold of, 1888
Audimax Theraband, for tinnitus, 2136-2137
Audiogram, 1888
  with acoustic neuroma, 1897, 1898f
  of cochlear implant map, 2255
  for dizziness, 2326
  of hearing loss
    conductive, 1888f
    mixed, 1889f
    sensorineural, 1906f
      high-frequency, 1889f, 1907f
  in Meniere's disease, 1894, 1895f
  for nasopharyngeal carcinoma, 1354
  with normal hearing, 1906f-1907f
  and otoacoustic emissions
    distortion product, 1905, 1907f
    transient evoked, 1905, 1906f
Audiologic test battery (ATB), 1887-1903
  for cochlear implantation
    in adults, 2223
    in children, 2225
  to evaluate functional hearing loss, 1901
  to evaluate middle ear function, 1890-1891, 1890f
  historical background of, 1887-1890
  masking in, 1889-1890
  neurodiagnostic studies for auditory neuropathy or dyssynchrony in, 1899-1901, 1900f
  objective tests for differential diagnosis in, 1891-1892
    auditory brainstem response as, 1896, 1896f
      neurodiagnosis with, 1896-1899, 1898f-1899f
    electrocochleography as, 1892-1896, 1894f-1895f
    otoacoustic emissions as, 1891-1892, 1892f-1893f
Audiologic test battery (ATB) *(Continued)*
  sources of error in, 1901-1902
    in clinical judgment, 1901, 1902f
    technical, 1901-1902
  speech testing in, 1888-1889
  test for hearing sensitivity or acuity in, 1888, 1888f
    pure-tone air-conduction testing as, 1888
      masking for, 1889-1890
    pure-tone bone-conduction testing as, 1888, 1888f-1889f
Audiology
  in children, 2574
  effects of radiotherapy on, 2626t
  in infants, 2722
Audiometric correlates
  of ossicular discontinuity, 2005-2006
  of ossicular fixation, 2006
Audiometric thresholds, 1888
  based on auditory brainstem responses
    click-evoked, 1909
    using more frequency-specific stimuli, 1909-1910, 1910f
  based on auditory steady-state response, 1912
Audiometry, 2087
  with acoustic neuroma, 1897, 1898f, 2516
  for otitis media, 2762
  for otosclerosis, 2030, 2030f
  pure-tone (*See* Pure-tone audiometry)
  for sensorineural hearing loss, 2117
  visual reinforcement
    in infants, 2722
    for otitis media, 2762
Auditory brainstem, 1845-1846
Auditory brainstem implant (ABI), 2258-2264
  alternative strategies to, 2263
  anatomy and surgical approaches for, 2260, 2261f
  auditory performance with, 2262
  biocompatibility of, 2259
  with cochlear nerve aplasia, 2263-2264
  complications of, 2260-2261
  history of clinical approaches to, 2259-2260, 2259f
  indications for, 2260
  intraoperative monitoring of, 2260, 2261f
  in patients without neurofibromatosis type 2, 2262
  penetrating, 2262, 2262f
Auditory brainstem response (ABR), 1896, 1908-1911, 2087
  with acoustic neuroma, 1896, 1898f-1899f, 1910-1911, 2517
  advantage of, 1908
  artifacts with, 2552-2553
  audiometric thresholds based on
    click-evoked, 1909
    using more frequency-specific stimuli, 1909-1910, 1910f
  with auditory neuropathy or dyssynchrony, 1899-1901, 1900f
  automated, 2721
  in Bell's palsy, 2393-2394
  with central neural auditory prosthesis, 2260, 2262f
  click-evoked, 1909
  clinical applications of, 1896, 1908-1911
    to assess hearing sensitivity, 1909-1910, 1910f
    in CHAMP procedure, 1911
    for differential diagnosis, 1910-1911
    for intraoperative monitoring, 1899f, 1911
    for neurodiagnosis, 1896-1899, 1898f-1899f
    otoneurologic, 1910-1911
  for cochlear implant, 1913f
    in children, 2225, 2234-2235
  defined, 1896, 1908
  effect of intensity on, 1908, 1909f
  electrically evoked, 1912-1913, 1913f
Auditory brainstem response (ABR) *(Continued)*
  electrocochleography and, 1908
  in infants, 2719-2721
  instrumentation for, 2543
  interpretation of, 1896
  intraoperative monitoring of, 2552-2554
    interpretation of, 2553-2554, 2553f
    and postoperative auditory function, 2553-2554
    reducing electrical and acoustic interference in, 2552-2553
    stimulus and recording parameters, electrodes, and placement in, 2552
  maturational changes in, 1908
  with normal hearing, 1896, 1896f, 1908, 1909f, 1913f
  for otitis media, 2762
  and otoacoustic emissions, 1891-1892, 1893f
  procedure for, 1896, 1908
  for sensorineural hearing loss, 2117
  speech-evoked, 1911
  stacked, 1911
  tone burst–evoked, 1909-1910
Auditory cortex, in central auditory pathway, 1835f-1836f, 1836-1837, 1847
Auditory distortion, with migraine, 2349
Auditory dyssynchrony (AD)
  cochlear implant for, 2220, 2240
  neurodiagnostic studies with, 1899-1901, 1900f
  otoacoustic emissions as, 1907
Auditory evoked potentials, middle and long latency, 1912, 1913f
Auditory meatus
  anatomy of, 1824f
  external, 320f
Auditory midbrain, 1845-1846
Auditory midbrain implant (AMI), penetrating, 2262-2263, 2263f
Auditory nerve
  anatomy of, 1825f, 1834
  in auditory physiology, 1844-1845, 1845f
  in central auditory pathway, 1835f
Auditory neural plasticity. *See* Neural plasticity, in otology.
Auditory neuropathy (AN)
  cochlear implant for, 2220, 2240
  genetic basis of, 2081
  neurodiagnostic studies with, 1899-1901, 1900f
  otoacoustic emissions as, 1907
Auditory pathway(s)
  afferent, 1834, 1834f
  central, 1834-1837, 1835f
    auditory cortex in, 1835f-1836f, 1836-1837
    cochlear nerve in, 1834-1835
    cochlear nucleus in, 1835, 1835f
    inferior colliculus in, 1835f, 1836
    lateral lemniscus in, 1835-1836, 1835f
    medial geniculate body in, 1835f, 1836
    superior olivary complex in, 1835, 1835f
  efferent, 1834, 1834f, 1847-1849
    middle ear muscle reflex pathways as, 1847, 1848f
    olivocochlear reflex pathways as, 1848-1849, 1848f
  neural plasticity in (*See* Neural plasticity, in otology)
Auditory perceptual assessment, of voice, 826-831
  CAPE-V for, 826
  GRBAS for, 826, 827t
  other aspects of, 826-827
  for professional voice, 850
Auditory performance, with cochlear implants
  in adults, 2244-2245
  bilateral, 2247-2251
  in children, 2246
    early studies of, 2246
    measurement of, 2246
    more recent studies of, 2246-2247, 2247f

Auditory performance, with cochlear implants *(Continued)*
factors related to measurement of, 2244-2247
with hearing preservation, 2245-2246
in infants, 2247
predictors of, 2245, 2245f
tests of, 2244
Auditory physiology, 1838-1849
auditory cortex in, 1847
auditory nerve in, 1844-1845, 1845f
cochlear nucleus in, 1845-1846, 1846f
efferent auditory system in, 1847-1849
middle ear muscle reflex pathways in, 1847, 1848f
olivocochlear reflex pathways in, 1848-1849, 1848f
external ear in, 1839
impedance in, 1839
inferior colliculus in, 1846
inner ear in, 1840-1844
basilar membrane of, 1840-1842, 1841f-1842f
cochlea of, 1840, 1841f-1842f
cochlear partition of, 1840-1842, 1842f
endocochlear potential in, 1840, 1841f-1842f
endolymph of, 1841f-1842f
hair cells of
inner, 1841f, 1842, 1844f
outer, 1841f, 1844, 1844f
stereocilia of, 1841f, 1842, 1843f
tip links of, 1841f, 1842, 1843f
tonotopic tuning of, 1844, 1844f
organ of Corti of, 1841f
perilymph of, 1841f-1842f
Reissner's membrane of, 1841f
scala media of, 1840, 1841f-1842f
scala tympani of, 1841f-1842f
scala vestibuli of, 1841f-1842f
spiral ligament of, 1841f
spiral limbus of, 1841f
stapes footplate of, 1840, 1842f
stria vascularis of, 1840, 1841f
tectorial membrane of, 1841f
"third window" of, 1842, 1843f
lateral lemniscus in, 1846
medial geniculate body in, 1846-1847
middle ear in, 1839-1840, 1840f
sound and its measurement in, 1838-1839, 1839f
superior olivary complex in, 1846
Auditory potentials, electrically evoked, 1912-1914
auditory brainstem response as, 1912-1913, 1913f
clinical applications of, 1914
compound action potential as, 1912-1913
with cochlear implants, 1913f, 1914
middle and long latency response as, 1912-1914, 1913f
Auditory rehabilitation, after cochlear implantation, 2253-2257
in adults, 2254-2255
in children, 2254-2255
efficacy of, 2253-2254
Auditory signal, mechanoelectrical transduction of, 1840, 1841f
Auditory steady-state response (ASSR), 1911-1912
clinical applications of, 1910f, 1912
for cochlear implants in children, 2234-2235
Auditory symptoms, of migraine, 2348-2349
distortion as, 2349
hearing loss as, 2348-2349
phonophobia as, 2349
tinnitus as, 2349
Auditory training, after cochlear implantation, 2253-2257
in adults, 2254-2255
in children, 2254-2255
efficacy of, 2253-2254
Auditory tube. *See* Eustachian tube.
Auerbach's plexus, 953, 954f
Aura
migraine with, 247, 2347, 2347b
migraine without, 2347b
Aural atresia, congenital. *See* Congenital aural atresia (CAA).
Aural cholesteatoma. *See* Cholesteatoma.
Aural fullness, 2198
Aural papillomatosis, 1957, 1957f
management options for, 1957
Aural polyp, 1965
Auricle(s), 476-477, 476f
anatomy of, 1823, 1824f, 1944, 2742
physical examination of, 97
Auricular branch block, 242
Auricular cartilage, 476-477
burns of, 316
Auricular defects, prosthetic management of, 1345-1346, 1345t, 1346f
Auricular hematomas, 97, 310, 2038
Auricular muscle group, 442f
Auricular nerve injury, due to otoplasty, 479
Auricular prosthesis, 1345-1346, 1345t, 1346f
Auricular reconstruction. *See* Atresiaplasty.
Auriculocephalic angle, 477
Autofluorescence
in early glottic carcinoma, 1516
in premalignant lesions of larynx, 1488-1489
Autofluorescence bronchoscopy, 1009
Autogenous cartilage grafts
for nasal reconstruction, 368-369, 369f-370f
in noncaucasian rhinoplasty, 569, 570f
complications of, 578, 579f
Autogenous cartilage struts, for nasal tip projection, 535-536, 536f
Autogenous costal cartilage grafts, for laryngeal stenosis, 2919-2920, 2920f
Autogenous costochondral reconstruction, for microtia, 2744, 2744t
Autografts
for craniofacial defect repair, 2657
for ossiculoplasty, 2006, 2025
Autoimmune disorders
laryngeal involvement in, 887, 887f
otologic manifestations of, 2114
of salivary glands, 2858-2863
sensorineural hearing loss due to, 2123-2124
sudden, 2128
Autoimmune inner ear disease (AIED), 2164-2168
clinical presentation of, 2165-2166
cochlear implant for, 2221
defined, 2164
diagnosis of, 2166, 2167t
differential diagnosis of, 2166
epidemiology of, 2165
future directions for, 2167-2168
pathology and pathogenesis of, 2165
animal studies of, 2165
human temporal bone studies of, 2165
sensorineural hearing loss due to, 2124, 2165
fluctuating, 2199
rapidly progressive, 2199-2200
treatment of, 2166-2167
Autoimmune thyroiditis, 1747
oral manifestations of, 1251
ultrasound of, 1644
Autoinflation, for otitis media with effusion, 2772
Autologous fat, for vocal fold medialization, 905-906
Autologous temporalis fascia grafts, for medialization thyroplasty, 910
Autologous whole-cell vaccine, for head and neck squamous cell carcinoma, 1024
Automated auditory brainstem response (AABR), 2721
Automated endoscopic system for optimal positioning (AESOP), 39, 40f
Automatic speaking valve (ASV), 1599-1600
Autonomic control, in salivary gland secretion, 1136
Autonomic dysfunction, preoperative evaluation of, 106
Autonomic reflexes, of oral cavity, 1205-1206
Autoregulation, of capillary blood flow, 1066
Autosomal dominant disorder, 6, 6f, 2088, 2088f
Autosomal dominant sensorineural hearing loss (ADSNHL)
genetic testing for, 2098
nonsyndromic, 2090-2093, 2092t
syndromic, 2093-2096, 2094t
Autosomal recessive inheritance, 2088-2089, 2089f
Autosomal recessive sensorineural hearing loss
nonsyndromic, 2089-2090, 2090f, 2091t
syndromic, 2094t, 2096
Avita (tretinoin)
for aging skin, 403-404
with chemical peels, 392-393
for chemoprevention of oral cancer, 1315
Avitene (microfibrillar collagen), for embolization, 1933
AVM. *See* Arteriovenous malformation (AVM).
Avoidance
for allergic rhinitis, 619-620
for nonallergic rhinitis, 699-700
aVOR (angular vestibulo-ocular reflex), 2306, 2307f
after labyrinthectomy, 2291-2292, 2291f-2293f
Avulsions, soft tissue, 307, 308f
Awake fiberoptic nasotracheal intubation, 122-123
advantages of, 123
avoiding failure in, 125, 126b
bronchoscopy cart for, 123, 123f
conscious sedation for, 124
fiberoptic bronchoscope in, 123-125, 125f
historical perspective on, 122-123
indications for, 123, 123b
keys to successful, 124b
monitoring during, 124
nasal trumpet placement for, 124, 125f
optimal setup for, 125f
patient preparation for, 123-124
technique of, 124-125
topical anesthesia for, 124
Axial pattern flaps, 1067, 1067f
Axonotmesis, 2384-2385
of facial nerve, 2040
Azelastine (Astelin)
for allergic rhinitis, 620
for nonallergic rhinitis, 701t
for rhinosinusitis, 734t, 737
Azithromycin
for endocarditis prophylaxis, 1249t
ototoxicity of, 2176
for pediatric surgery prophylaxis, 2597t

B

B cells, 602f, 603
development of, 603
responses by, 603
T cell–dependent and T cell–independent, 606
B ring, 966f, 967, 968f
B trains, in electromyography, 2547
Bacterial biofilms
on adenoid pads, and pediatric chronic sinusitis, 2779-2780
for chemoprevention of oral cancer, 1315
in chronic rhinosinusitis, 706, 732
disruption of, 735
in chronic suppurative otitis media, 2221
in otitis media and cholesteatoma, 1974, 2764
Bacterial infections
oral manifestations of, 1252
otitis media due to, 2763, 2764f
pediatric chronic sinusitis due to, 2779
of salivary glands, 1151-1153
in children, 2851t, 2856-2857

Bacterial labyrinthitis, 2160
Bacterial laryngitis
  acute, 884
  chronic, 885
Bacterial laryngotracheobronchitis. *See* Bacterial tracheitis.
Bacterial lymphadenopathy, in children, 2818, 2818f-2819f
Bacterial meningitis, hearing loss due to, 2160-2161
Bacterial otitis externa, 1944
  ear wick for, 1945-1946, 1951, 1951f
  otorrhea due to, 2194-2195
  systemic antibiotics for, 1953
  topical therapies for, 1951-1953
    acidifying agents for, 1953
    failure to respond to, 1953, 1953t
    options for, 1951-1953, 1951f
    ototopic antibiotics for, 1951-1953
Bacterial pharyngitis, 191-196
  due to *Arcanobacterium haemolyticum*, 193
  due to *Chlamydia pneumoniae,* 194
  due to *Corynebacterium diphtheriae,* 195-196
    in children, 2786-2787
  due to *Francisella tularensis,* 195
  due to group A beta hemolytic *Streptococcus pyogenes,* 191-193
    in children, 2787
  due to *Mycobacterium tuberculosis,* 195
  due to *Mycoplasma pneumoniae,* 194-195
  due to *Neisseria gonorrhoeae,* 193-194, 194f
  due to *Neisseria gonorrhoeae* (gonococcal), in children, 2786
  due to non–group A beta hemolytic streptococcal infections, 193
    in children, 2787
    complications of, 2788
  due to *Treponema pallidum*, 194
    in children, 2786
  due to *Yersinia enterocolitica*, 196
Bacterial rhinosinusitis
  acute, 703-705, 704f, 732
  chronic, 732, 733f
Bacterial tracheitis, 2809-2810
  clinical features of, 2809
  complications of, 2810
  diagnosis of, 2809, 2809f
  differential diagnosis of, 2806t
  endoscopy of, 2809, 2809f
  epidemiology of, 2809
  imaging of, 2809, 2809f
  management of, 2809-2810, 2809f
  pathogenesis of, 2809
  terminology for, 2809
Bacterial vaccines, to prevent otitis media, 2768-2769
BAFF (B-lymphocyte–activating factor belonging to the TNF family), 609t-610t
BAHA. *See* Bone-anchored hearing aid (BAHA).
Baker's solution, for deep chemical peels, 394-395
BAL (bronchoalveolar lavage), flexible fiberoptic bronchoscopy for, 1003-1004
Balance exercises, in vestibular rehabilitation, 2372-2373, 2378-2379
Balance function studies, in assessment of vestibular compensation, 2376-2377
Balance problems, due to otitis media, 2776
Balance rehabilitation. *See* Vestibular and balance rehabilitation therapy (VBRT).
Balanced carrier, 5
Balanced chromosome complement, 5
Balanced orbital decompression, for Graves' ophthalmopathy, 1814
Baldness. *See also* Hair loss.
  male-pattern, 374-376, 375f
Ballenger swivel knife, for septoplasty, 489-490
Balloon(s), for embolization, 1933
Balloon bronchoplasty, interventional bronchoscopy for, 1009
Balloon catheter sinusotomy, 752-753, 753f
  frontal, 782-783
Balloon dilatation
  of esophageal strictures, 966
    transnasal esophagoscopy in, 984, 984f
  for stridulous child, 2906, 2906f, 2909
  for subglottic stenosis, 2906, 2906f
  for tracheal stenosis, 2928, 2928f
Balloon occlusion test (BOT), for embolization, 1934, 1934f
Balloon test occlusion (BTO), for cerebral blood flow evaluation, 2491
Balloon tracheoplasty, for tracheal stenosis, 2928, 2928f
Bamford-Koval-Bench (BKB) Sentences, for cochlear implants, 2223
Bandeau, in fronto-orbital advancement
  removal of, 2651-2652, 2652f
  reshaping of, 2652, 2652f-2653f
  splitting of, 2652, 2653f
Bannwarth's syndrome. *See* Lyme disease.
BAPTA, and interstereociliary linkages, 2077
Barium swallow
  for hypopharyngeal and cervical esophageal cancer, 1423-1424
  modified, 1394, 1396
    for swallowing disorders, 1217-1218, 1219f
      in children, 2949, 2950t
  for penetrating neck trauma, 1631t, 1633
Baroreflex failure syndrome, due to carotid paraganglioma surgery, 1661
Barotrauma
  atmospheric, 2343
  eustachian tube dysfunction due to, 1872
  facial paralysis with, 2400
  peripheral vestibular disorders due to, 2343
  sensorineural hearing loss due to, 2122, 2199
Barrett's esophagus
  endoscopic appearance of, 967f, 972, 972f
  gastroesophageal junction in, 957f
  GERD and, 972-973
  grading of dysplasia in, 973, 973t
  histologic appearance of, 972, 972f-973f
  imaging of, 1403-1404, 1404f
  long-segment, 972f
  short-segment, 972f
  surveillance for, 972-973, 973t
  transnasal esophagoscopy in, 983, 983f
Bartonella henselae
  deep neck space infections due to, 201
  salivary gland infection due to, 1159
Bartter syndrome, deafness in, 2051t-2058t, 2083
Barttin, in deafness, 2051t-2058t
Basal cell(s)
  of olfactory epithelium, 626f, 627
  of taste buds, 1208
Basal cell adenocarcinoma, of salivary glands, 1191
Basal cell adenomas, of salivary glands, 1170
Basal cell carcinoma (BCC), 283-285
  diagnosis of, 284-285
  epidemiology of, 283
  immunosuppression and, 213t, 215, 284
  morpheaform, 284, 284f
  nodular, 284f
  noduloulcerative, 284f
  pigmented, 284, 284f
  recurrent, 284, 285f
  risk factors for, 283-284
Basal cell hyperplasia theory, of cholesteatoma formation, 1966-1967, 1967f
Basal cell nevus syndrome, 1268
  treatment of, 1268
Basal encephaloceles, of nose, 2687-2688, 2687t, 2688f
Basal lamella, 665f, 667f
Basal subfrontal approach, for anterior cranial base surgery, 2453-2454, 2454f
Basaloid carcinoma, of oral cavity, 1299
Basaloid squamous cell carcinoma (BSCC)
  of hypopharynx and cervical esophagus, 1425
  of larynx, 1506
Base(s)
  cranial (*See* Cranial base)
  nucleotide, 4
  of tongue (*See* Tongue base)
Base view, of facial bones and sinuses, 130
Baseline, assessment of, 53
Basicranium, growth and development of, 2617-2619, 2617t, 2619f-2620f
Basilar artery, 2351f
  in surgical anatomy of anterior cranial base, 2474-2475, 2474f-2475f, 2481f
Basilar impression, 2355
Basilar membrane (BM)
  anatomy of, 1831-1832, 1832f, 1840
  in auditory physiology, 1840-1842, 1841f-1842f
  in cochlear transduction, 2061f-2062f, 2065f
  physical dimensions of, 2060, 2063f
  radial displacement patterns of, 2067, 2069f
  radial shearing forces and displacement of, 2065-2067, 2069f
  in traveling wave, 2061-2062, 2064f
  tuning curves of, 1844, 1844f
Basilar migraine, 2349
Basilar sinus, in surgical anatomy of anterior cranial base, 2474
Basilar venous plexus, in surgical anatomy of anterior cranial base, 2474
Basion, growth and development of, 2617t
Basophil(s)
  in adaptive immune system, 605
  in allergic rhinitis, 616
Bassoon *(Bsn)* gene, in murine deafness, 2058t-2060t, 2080
Battery(ies)
  for external speech processors, 2233
  ingestion of, 2941, 2958, 2958f
Battle's sign, 97
BCC. *See* Basal cell carcinoma (BCC).
B-cell lymphoma, diffuse large. *See* Diffuse large B-cell lymphoma (DLBCL).
BDNF (brain-derived neurotrophic factor)
  for facial nerve paralysis, 2427
  in gene therapy, 2192
  for prevention of ototoxicity, 2189-2191
B2E (Bridges to Excellence), 84t-87t
Beam pattern, of surgical laser, 27
Beam waist, of surgical laser, 27-28, 28f
Beamlets, in intensity-modulated radiation therapy, 1696-1697
Beare-Stevenson cutis gyrata syndrome, craniofacial anomalies in, 2641t
Beclomethasone, for otitis media with effusion, 2772
Beclomethasone nasal (Vancenase, Beconase), for nonallergic rhinitis, 700t
Becquerel, 1031-1032
Becquerel, Antoine, 1031
Becquerel, Henri, 1031
Bed rest, fluid utilization during, for children, 2572t
Behavior problems, obstructive sleep apnea and, 2603-2604
Behavioral audiometry, for otitis media, 2762
Behavioral modification, for extraesophageal reflux, 900-901
Behçet's disease
  esophageal manifestations of, 979
    imaging of, 1405
  nasal manifestations of, 660-661
  oral manifestations of, 1254
Behind-the-ear (BTE) external speech processors, 2229, 2232, 2232f

Behind-the-ear (BTE) hearing aids, 2269-2270, 2270f
in children, 2274
comparison of features of, 2206t
in infants, 2723-2724
selection of, 2266-2267, 2270
Bell stage, of enamel organ development, 1259
Bell's palsy, 2391
auditory symptoms of, 2393-2394
in children, 2397
CNS changes in, 2393-2394
corticosteroids for, 2409-2410, 2410t
defined, 2391
and diabetes, 2401
differential diagnosis of, 2391, 2392t
electromagnetic stimulation in, 2394-2395
electrophysiology and testing for, 2394
electromyography in, 2394
electroneurography in, 2394
interpretation of electrical tests in, 2394
maximal stimulation test in, 2394
nerve conduction velocity in, 2394
nerve excitability threshold in, 2394
etiology of, 2391-2393
facial nerve imaging in, 1924, 1927f, 2395
familial, 2397
histopathology of, 2393
incidence of, 2391-2396
management of, 2395-2396
middle cranial fossa decompression for, 2409-2410, 2409t
oral manifestations of, 1255
polyneuropathy in, 2391, 2398f
prognosis and statistics for, 2395
recurrent, 2397
Bell's phenomenon, 445-446
Benadryl (diphenhydramine)
for allergic rhinitis, 620
for nonallergic rhinitis, 701t
Benign intracranial hypertension (BIH)
CSF rhinorrhea due to, 787
facial paralysis due to, 2400-2401
sensorineural hearing loss due to, 2123
Benign lymphoepithelial cyst (BLEC), in HIV, 217-218, 218f
Benign lymphoepithelial disease, of salivary glands, 1154
in children, 2858
Benign mesenchymal neoplasms, of larynx, 878-882
chondroma as, 881-882
granular cell, 882
lipoma as, 881
mixed, 881
neurilemmoma as, 882
neurofibroma as, 882
oncocytic, 881
recurrent respiratory papillomatosis as, 868f-869f, 878-880
adult-onset, 879
epidemiology of, 878
etiology of, 878-879
juvenile form of, 879
treatment of, 879, 880f
rhabdomyoma as, 881
vascular, 880-881
laryngeal hemangiomas as, 880-881
polypoid granulation tissue as, 880
Benign mixed tumors. *See* Pleomorphic adenoma(s).
Benign paroxysmal positional vertigo (BPPV), 2330-2332
diagnosis of, 2330-2331
findings on examination in, 2330-2331, 2331f
history in, 2330
test results in, 2331
etiology of, 2330
Benign paroxysmal positional vertigo (BPPV) *(Continued)*
historical background of, 2329-2330
horizontal (lateral) canal
positional testing for, 2315-2316, 2331
repositioning maneuver for, 2332
incidence of, 2330
mechanism of, 2330-2332
and migraine, 2350
posterior canal
anatomic and physiologic basis for, 2288-2289, 2288f
conversion of, 2332
positional testing for, 2315, 2315f, 2331, 2331f
repositioning maneuver for, 2331-2332, 2332f
surgical treatment of, 2332
superior canal
positional testing for, 2331
repositioning maneuver for, 2332
treatment of
with repositioning, 2331-2332, 2332f
surgical, 2332, 2360-2361
posterior semicircular canal occlusion as, 2360-2361, 2361f
singular neurectomy as, 2360, 2360f
vestibular rehabilitation for, 2376, 2378t
Benign paroxysmal vertigo, of childhood, and migraine, 2350-2351
Benign vocal fold mucosal disorder(s), 859-882
anatomy and physiology relevant to, 860, 860f-861f
bilateral diffuse polyposis as, 872-873, 872f
diagnosis of, 872
history in, 872
laryngeal examination in, 872
vocal capability battery in, 872
epidemiology of, 872
management of, 872-873
behavioral, 872
medical, 872
surgical, 872-873, 873f
pathophysiology and pathology of, 872
capillary ectasia as, 866-867
diagnosis of, 866-867
history in, 866
laryngeal examination in, 866-867
vocal capability battery in, 866
epidemiology of, 866
epidermoid inclusion cyst with, 868f
hemorrhagic polyp with, 868f
management of, 867
behavioral, 867
medical, 867
surgical, 867
pathophysiology and pathology of, 866
vocal nodules with, 867f
contact ulcer or granuloma as, 874-875, 874f
diagnosis of, 875
history in, 875
laryngeal examination in, 875, 875f
vocal capability battery in, 875
epidemiology of, 874
due to extraesophageal reflux, 902, 902f-903f
management of, 875
pathophysiology and pathology of, 874
epidemiology of, 859
etiology of, 859
patient beliefs about, 861
systemic medications that may affect larynx in, 863
evaluation of, 860-862
direct laryngoscopy and biopsy in, 862
history in, 860-861
common symptom complexes in, 861
onset in, 860-861
other risk factors in, 861
patient beliefs about causes in, 861
Benign vocal fold mucosal disorder(s) *(Continued)*
patient perception of severity and vocal aspirations and consequent motivation for rehabilitation in, 861
talkativeness profile in, 861
vocal commitments in, 861
objective measures of vocal output in, 862
office examination of larynx in, 862, 862f
vocal capability battery in, 861-862
general management options for, 862-863
for acute mucosal swelling of overuse, 863
hydration as, 862
laryngeal instillations for mucosal inflammation as, 863
management of acid reflux laryngopharyngitis as, 863, 863f
sinonasal management as, 862-863
glottic sulcus as, 870-872, 871f
diagnosis of, 870-871
history in, 870
laryngeal examination in, 870-871
vocal capability battery in, 870
epidemiology of, 870
management of, 871-872
behavioral, 871
medical, 871
surgical, 871-872, 872f
mucosal bridge due to, 870, 871f
pathophysiology and pathology of, 869-870
with polypoid nodule, 871f
intracordal cysts as, 869-870
diagnosis of, 869
history in, 869
laryngeal examination in, 869
vocal capability battery in, 869
epidemiology of, 869
epidermoid inclusion, 868f-869f, 869
mucus retention (ductal), 869, 869f-870f
open, 869, 870f
pathophysiology and pathology of, 869
treatment of, 869-870
behavioral, 869-870
medical, 869
surgical, 870, 870f
intubation granuloma as, 875-876, 875f
diagnosis of, 875-876
history in, 875
vocal capability battery in, 875-876
epidemiology of, 875
management of, 876
pathophysiology and pathology of, 875
postoperative dysphonia as, 873-874, 873f
diagnosis of, 873-874
history in, 873
laryngeal examination in, 874
vocal capability battery in, 873-874
epidemiology of, 873
management of, 874
behavioral, 874
medical, 874
pathophysiology and pathology of, 873, 874f
surgery for, 863-865, 864f
symptoms of
in nonsingers, 859, 861
in singers, 859, 861
vocal fold hemorrhage and unilateral (hemorrhagic) vocal fold polyp as, 867-869
with capillary ectasia, 868f
diagnosis of, 868
history in, 868
laryngeal examination in, 868
vocal capability battery in, 868
epidemiology of, 867
pathophysiology and pathology of, 867-868

Benign vocal fold mucosal disorder(s) *(Continued)*
treatment of, 868-869
behavioral, 868
medical, 868
surgical, 868-869
vocal nodules as, 865-866
with capillary ectasia, 867f
defined, 865
diagnosis of, 865
history in, 865
laryngeal examination in, 865
vocal capability battery in, 865
epidemiology of, 865
management of, 865-866
behavioral, 865
medical, 865
surgical, 865-866, 866f, 867t
pathophysiology and pathology of, 865
voice therapy for, 863, 864f
Benzodiazepines, as adjuncts to induction of anesthesia, 111
Benzydamine hydrochloride, for mucositis, 1102
Bernoulli effect, in voice production, 846
Bernstein test, 962-963
Berry's ligament, anatomy of, 1751
Beta decay, 1032
Beta defensins, in middle ear protection, 1871
Beta error, 65, 66t
Beta particles, 1031-1032
Beta-adrenergic agents, for migraine, 2350
β_2-transferrin test, for CSF rhinorrhea, 789, 2044
β-all-*trans* retinoic acid, for cancer chemoprevention, 1061
β-blockers
for Graves' disease, 1743
intraoperative, 112
β-carotene
for cancer chemoprevention, 1061-1062
for chemoprevention of oral cancer, 1315
β-defensins, 599
β-lactamase inhibitors, for streptococcal pharyngitis, 2787
Betadine (povidone-iodine), for embolization, 1933
Betahistine, for Meniere's disease, 2337-2338
Beta-hydroxy acids, for aging skin, 404
Betamethasone valerate cream, for eczematoid otitis externa, 1955-1956
Beta-trace protein (βTP), in CSF rhinorrhea, 790
Betel nuts, and oral cancer, 1294, 1365
Bethanechol, for extraesophageal reflux, 901
Bevacizumab, for nasopharyngeal carcinoma, 1700
Bezold abscess, 1985-1986, 1986f-1987f
due to temporal bone infection, 1980t
BFU-E (burst-forming units–erythroid), 605
BFU-MEG (burst-forming units–megakaryocytes), 605
Bias, 53
allocation, 62t
ascertainment, 62t
detection, 62t
vs. efficacy of treatment, 62t
in outcomes research, 53
selection, 53, 68t
susceptibility, 62t
treatment, 53
Bias velocity, in rotatory chair testing, 2322
Bicarbonate (HCO_3)
in saliva, 1139
in salivary gland secretion, 1135
Bicellular reserve cell theory, of salivary gland tumorigenesis, 1163
Bicklemann, A. G., 251
Bicoronal incision, 2450-2451, 2450f
for nasal fracture repair, 505, 505f
for pediatric facial fracture, 2701-2702, 2703f
Bidirectional sensitivity, of vestibular system, 2278-2279
BIH (benign intracranial hypertension)
CSF rhinorrhea due to, 787
facial paralysis due to, 2400-2401
sensorineural hearing loss due to, 2123
Bilateral advancement flap, 345, 346f
Bilateral cochlear implantation, 2241
for adults, 2224
for children, 2226
results of, 2247-2251
Bilateral hockey stick incision, for neck dissection
radical, 1709, 1710f
selective, 1717-1718, 1717f
Bile, in reflux laryngitis, 886
Bile monitoring, ambulatory 24-hour, 960-961, 961f
Bilevel positive airway pressure (BiPAP), for obstructive sleep apnea
in children, 2610-2611
Bilitec 2000, 960-961, 961f
Bill's bar
anatomy of, 1822, 1823f
in surgical anatomy of lateral skull base, 2437-2439
Bilobed flap
for cheek defects, 357, 359f
for nasal defects, 365-366, 365f
Binaural cochlear implantation, 2241
for adults, 2224
for children, 2226
results of, 2247-2251
Binaural processing, 2248
Binaural squelch, 1846, 2248
Bing-Siebenmann dysplasia, 2727
Binostril approach, for transnasal endoscopic-assisted anterior skull base surgery, 2478, 2479f
Biochemical defects, in recessive disorders, 7
Biocompatibility, in skeletal or cartilaginous defect repair, 2657
Biofilms
on adenoid pads, and pediatric chronic sinusitis, 2779-2780
for chemoprevention of oral cancer, 1315
in chronic rhinosinusitis, 706, 732
disruption of, 735
in chronic suppurative otitis media, 2221
in otitis media and cholesteatoma, 1974, 2764
Bioinformatics, in head and neck squamous cell carcinoma, 1028-1029
Biologic agents, with radiotherapy, 1054, 1055f
Biomarkers
for head and neck squamous cell carcinoma, 1026-1027
epidermal growth factor receptor as, 1026
human papillomavirus as, 1026
loss of heterozygosity as, 1026
margin analysis for, 1027
in oral rinses and saliva, 1026
other, 1026-1027
polymorphisms in DNA repair enzymes as, 1027
serum analysis for, 1026-1027
for laryngeal squamous cell carcinoma, 1493, 1505
for oral cancer, 1295
for salivary gland neoplasms, 1163, 1194
Biomaterials, in skeletal or cartilaginous defect repair, 2657-2658
Biomimetic materials, for craniofacial defect repair, 2658
Bionx plating system, for pediatric facial fractures, 2701t
Biopsy
endobronchial and transbronchial, flexible fiberoptic bronchoscopy for, 1004-1005, 1004f-1005f
fine-needle aspiration
in children, 2574
of salivary glands, 2854
of lymphoma, 1675-1676
of neck masses, 1638
of oropharyngeal cancer, 1366
of salivary glands, 1149, 1149f, 1165-1166, 1180-1181
in children, 2854
of thyroid nodule, 1756-1758
repeat, 1759
ultrasound-guided, 1655f
ultrasound-guided, 1653-1654, 1655f
of glottic cancer, 1518
laryngeal, for benign vocal fold mucosal disorders, 862
of lymphoma
core-needle, 1676
corticosteroids prior to, 1676
fine-needle aspiration, 1675-1676
open, 1676
of melanoma, 1109
of neck masses, 1638
in children, 2814
of oropharyngeal cancer, 1366
fine-needle aspiration, 1366
of paranasal sinus tumors, 1124
of salivary glands, 1149, 1149f, 1165-1166, 1180-1181
in children, 2854-2855
sentinel lymph node (*See* Sentinel lymph node biopsy (SLNB))
of thyroid nodule, 1756-1758
repeat, 1759
ultrasound-guided, 1655f
Biotinidase deficiency, sensorineural hearing loss in, 2094t, 2096
BiPAP (bilevel positive airway pressure), for obstructive sleep apnea
in children, 2610-2611
Bipedicle flap, for nasal reconstruction, 371
Bipedicle mucosal advancement flap, for nasal defects, 347, 347f
Bipolaris, rhinosinusitis due to, 732-733
Birdshots, 1626, 1628t
Birth order, and otitis media, 2767
Bisphosphonates, for hyperparathyroidism, 1804
Bitter taste
individual differences in, 1211-1212
peripheral sensitivity to, 1211
transduction of, 1209
Bizygomatic width, 2617t
BK channel defects, and hearing, 2079
B-K mole syndrome, 288, 288f, 1107
BKB (Bamford-Koval-Bench) Sentences, for cochlear implants, 2223
Blair incision, modified, for parotidectomy, 1172, 1173f, 1195, 1195f
Blast trauma, peripheral vestibular disorders due to, 2343
Blastomycosis, laryngeal and tracheal manifestations of, 885, 892
BLEC (benign lymphoepithelial cyst), in HIV infection, 217-218, 218f
Bleeding
due to neck dissection, 1723
due to thyroid surgery, 1770
Bleeding disorders, oral manifestations of, 1256
Bleomycin, for induction chemotherapy, 1056-1057

Blepharoplasty, 439-451
adjunctive procedure(s) to, 451
Botox for, 451
injectable filler for, 451
skin resurfacing as, 451
aesthetic considerations and ideals and, 444-447
for brow position, 445, 445f
for eyelids, 445-447, 446f
and upper eyelid ptosis, 446-447, 447f
for midface, 447
complications of, 449-451
for facial paralysis, 2430
preoperative planning for, 447
surgical techniques for, 447-451
lid shortening procedure as, 449
of lower eyelid, 448-449
subciliary approach to, 449, 450f-451f
transconjunctival approach to, 448-449, 450f
with ptosis repair, 447-448
of upper eyelid, 447-448, 447f-449f
Blepharospasm, 2401
Blind nasal technique, for difficult airway, 114t
Blindness, due to neck dissection, 1723
Blink reflex, to assess facial nerve function, 2388
intraoperatively, 2555, 2555f
Blom-Singer duckbill prosthesis, 1598f
Blood clot, in wound healing, 1076
Blood dyscrasias, sensorineural hearing loss due to, 2123
Blood supply, to brain, 2351, 2351f
Blood viscosity, decreased, and skin flap viability, 1073-1074
Blood volume, in children, 2571
Blowout fracture, 170f, 321
Blue nevus, 286-287, 287f
Blunt neck trauma, 1634-1635
B-lymphocyte–activating factor belonging to the TNF family (BAFF), 609t-610t
BM. *See* Basilar membrane (BM).
B-mode sonography, 1643
BMPs (bone morphogenetic proteins), in mandibular reconstruction, 1327-1328, 1328f
Board certification, 79-80, 80b
Bode plot, in vestibular tests, 2302, 2303f
Body-cover concept, of phonation, 811
Body-worn (BW) external speech processors, 2229, 2232, 2232f
Boilermaker's deafness, 2121
Bolus fabrication, by maxillofacial prosthodontist, 1331, 1332f
Bone, primary *vs.* secondary, 2614
Bone conduction process, and orbital wall fractures, 2712
Bone disease
due to hyperparathyroidism, 1781
otologic manifestations of, 2108-2112
in fibrous dysplasia, 2110-2111, 2111f
in osteitis fibrosa cystica, 2112
in osteogenesis imperfecta, 2109-2110, 2110f
in osteopetroses, 2111-2112, 2112f-2113f
in Paget's disease, 2108-2109, 2109f
sensorineural hearing loss due to, 2124
Bone erosion
in cholesteatoma and chronic otitis media, 1971-1974, 1972f-1973f
of paranasal sinus walls, 672
Bone formation, 2614
endochondral, 2614, 2615f
intramembranous, 2614
Bone grafts
in cleft-lip nose repair, 559, 564f
for nasal fractures, 505, 505f
for nasal reconstruction, 369, 370f
Bone growth
osteogenesis in, 2614
endochondral, 2614, 2615f
intramembranous, 2614
Bone growth *(Continued)*
remodeling and displacement in, 2614-2615, 2639
of mandible, 2639f
of nasomaxillary complex, 2619, 2621f
Bone healing, 330-331
Bone morphogenetic proteins (BMPs), in mandibular reconstruction, 1327-1328, 1328f
Bone remodeling, 2614-2615, 2639
of mandible, 2639f
of nasomaxillary complex, 2619, 2621f
Bone resorption
in cholesteatoma and chronic otitis media, 1971-1974, 1972f-1973f
with vascular tumors, 2826
Bone sarcomas, of neck, 1666, 1667t
Bone scans, for nasopharyngeal carcinoma, 1354
Bone Source (hydroxyapatite), for chin implants, 465t
Bone-anchored hearing aid (BAHA), 2212-2216
background of, 2213
biology and histology of, 2213
biophysical principles of, 2213
comparison of features of, 2206t
complications of, 2215
components of, 2213f
for conductive hearing loss, 2027
for congenital aural atresia, 2759
design of, 2213
indications and contraindications for, 2212-2213, 2216t
location of, 2204f
materials for, 2213
operative technique for, 2213-2215, 2214f
radiologic implications of, 2213
results of, 2215-2216
sound transduction and coupling to auditory system with, 2205f
for unilateral sensorineural hearing loss, 2216
in young children, 2215
Bone-conduction implantable hearing aids, 2212-2216
background of, 2213
biology and histology of, 2213
biophysical principles of, 2213
comparison of features of, 2206t
complications of, 2215
components of, 2213f
design of, 2213
indications for and contraindications to, 2212-2213, 2216t
in infants, 2723-2724
location of, 2204f
materials for, 2213
operative technique for, 2213-2215, 2214f
radiologic implications of, 2213
results of, 2215-2216, 2216t
sound transduction and coupling to auditory system with, 2205f
for unilateral sensorineural hearing loss, 2216
in young children, 2215
Bone-conduction testing, in pure-tone audiometry, 1888, 1888f-1889f
Bony labyrinth
anatomy of, 1831, 1852, 1853f
embryogenesis of, 1852
Bony vault, rhinoplasty of, 540-542
for bony profile reduction, 540-541, 540f
for narrowing of nose, 541-542
double osteotomies in, 542, 542f-543f
lateral osteotomies in, 541, 542f
medial-oblique osteotomies in, 541, 541f
Boomerang incision, for neck dissection
radical, 1709, 1710f
selective, 1713-1714
BOR (branchio-oto-renal) syndrome
deafness in, 2051t-2058t, 2093-2095, 2094t
inheritance pattern of, 6, 2093-2095
inner ear anomalies in, 2735
Border cells of Held, 1832f
Bordetella pertussis, laryngeal and tracheal manifestations of, 892
Boric acid solution, for fungal otitis externa, 1954
Borrelia burgdorferi. See Lyme disease.
Borrelia vincentii, Vincent's angina due to, 2786
Boston-type craniosynostosis, 2641t
BOT (balloon occlusion test), for embolization, 1934, 1934f
Botryoid odontogenic cyst, 1265-1266
radiographic features of, 1266
treatment of, 1266
Bottle feeding, and otitis media, 2767
Bottom-up approach, for pediatric facial fracture repair, 2706f
Botulinum toxin (Botox)
for achalasia, 965
for alaryngeal speech, 1459
with blepharoplasty, 451
for depressor muscles, 432, 433f
for laryngeal hyperfunction, 839, 840f-841f
for synkinesis, 2432
Bouton vestibular afferent nerve fibers, 2283, 2283f
Bowen's disease, 286
Bowman-Bird protease inhibitor, for chemoprevention of oral cancer, 1315
Boyce's sign, 986-987
BPPV. *See* Benign paroxysmal positional vertigo (BPPV).
Brachiocephalic trunk, in root of neck, 2581f
Brachycephaly
in Down syndrome, 2632
synostotic, 2643f, 2644, 2645f
fronto-orbital advancement for, 2652-2653
Brachytherapy, 1036, 1047
interventional bronchoscopy with endobronchial, 1010t
maxillofacial prosthodontics in, 1332, 1335f
for oral cancer, 1314, 1314f
for unresectable tracheal tumor, 1621
Bradykinin, in skin blood flow, 1066
BRAF gene, in thyroid carcinoma, 1753
Bragg peak, 1034
Brain
blood supply to, 2351, 2351f
effects of radiotherapy on, 2626t
Brain abscess, 1994
due to cranial base surgery, 2468
epidemiology of, 1980t-1981t, 1994
imaging of, 1994f-1995f
otitis media and, 2777
pathogenesis of, 1994
symptoms of, 1994
treatment of, 1994
Brain fungus, due to otitis media, 1992-1993, 1993f
Brain growth, postnatal, 2617t
Brain hernia, due to otitis media, 1992-1993, 1993f
Brain injury, due to cranial base surgery, 2468
Brain size, 2617t
Brain weight, 2617t
Brain-derived neurotrophic factor (BDNF)
for facial nerve paralysis, 2427
in gene therapy, 2192
for prevention of ototoxicity, 2189-2191
Brain-evoked potentials, for olfaction, 632
Brainstem
efferent pathways from vestibular nuclei to, 1865
in surgical anatomy of anterior cranial base, 2475f, 2481f
in surgical anatomy of lateral skull base, 2439f
in vestibular function, 2308

Brainstem *(Continued)*
vestibular nerve terminations in, 1858f, 1859-1860
in vestibulo-ocular reflex, 2296-2297
anatomic and physiologic basis for, 2296
velocity storage in, 2296
velocity-to-position integration in, 2296, 2297f-2298f
clinical implications of, 2296-2297
for Alexander's law, 2297, 2299f
for head-shake nystagmus, 2296-2297
for interpreting rotary chair tests, 2297-2299
for pre- and post-rotatory nystagmus, 2296, 2298f
Brainstem gliomas, intra-axial, 2528
Brainstem lesions, laryngologic manifestations of, 837-838, 838t
Brainstem neoplasms, vestibular symptoms of, 2353-2354
Branchial arches, embryology of, 2583-2584, 2583f
craniofacial syndromes related to, 2585
innervation of, 2584
muscular derivatives of, 2584
skeletal derivatives of, 2583-2584, 2583f
Branchial cleft anomalies
embryology of, 2583
first, 2585
imaging of, 1410, 1410f
neck masses due to, 1639
second through fourth, 2585
Branchial cleft cyst, 2814-2817
in children, 2859
clinical presentation of, 2814, 2814f
embryology of, 2585, 2585f, 2814
imaging of, 131, 158f, 1410, 2814, 2815f
management of, 2814
otorrhea due to infection of, 2195
squamous cell carcinoma arising in, 1671
Branchial cleft fistula, 2585
imaging of, 1410, 1410f
Branchial cleft remnants, 2585
Branchial cleft sinus, 2585
imaging of, 1410
Branchio-otic syndrome, deafness in, 2051t-2058t
Branchio-oto-renal (BOR) syndrome
deafness in, 2051t-2058t, 2093-2095, 2094t
inheritance pattern of, 6, 2093-2095
inner ear anomalies in, 2735
Bravo wireless pH capsule, 961, 961f
Breast adenocarcinoma
metastatic to ear, 2108f
skull base metastases of, 173f
Breastfeeding, and otitis media, 2767
Breathiness, in voice evaluation, 827t
Breathing
laryngeal function in, 807-809, 808f-810f
oral (mouth), 809
pharyngeal function in, 809-810, 810f
in voice evaluation, 827
Bregma, 320f
Bremsstrahlung, 1032
Breslow microstaging, for melanoma, 1113f
Bridges to Excellence (B2E, BTE), 84t-87t
Brn3c, in deafness, 2051t-2058t
Brn4.0, in deafness, 2051t-2058t
Broca's area, in central auditory pathway, 1837
Bronchial foreign bodies
complications of, 2942
imaging of, 2938, 2938f-2939f
location of, 2936, 2936f
management of
anesthesia for, 2940
controversies in, 2942
technique for, 2940
symptoms of, 2938
Bronchial wash, flexible fiberoptic bronchoscopy for, 1003
Bronchioles, anatomy of, 998-999, 999f
Bronchitis, oral manifestations of, 1250
Bronchoalveolar lavage (BAL), flexible fiberoptic bronchoscopy for, 1003-1004
Bronchogenic duplication cyst, compression of pharynx and esophagus due to, 1409f
Bronchoplasty, balloon, interventional bronchoscopy for, 1009
Bronchoscope
fiberoptic, for awake fiberoptic nasotracheal intubation, 123-125, 125f
ventilating, 2903, 2903f
Bronchoscopic brush, flexible fiberoptic bronchoscopy for, 1007
Bronchoscopic lung volume reduction, 1011
Bronchoscopy
airway anatomy and nomenclature for, 998-999, 999f
autofluorescence, 1009
in children
anesthesia for, 2597-2598, 2597t
for foreign body removal, 2939t, 2940
for difficult airway
fiberoptic, 114t
rigid, 113f, 114t
flexible fiberoptic, 1001-1007
care of bronchoscopes for, 1001-1002
diagnostic, 999b, 1003-1007
for bronchial wash, 1003
for bronchoalveolar lavage, 1003-1004
for bronchoscopic brush sampling, 1007
for endobronchial and transbronchial biopsy, 1004-1005, 1004f-1005f
general approaches to, 1003
for transbronchial needle aspiration, 1005-1007, 1005f-1006f
for visual examination, 1003
range and special features of bronchoscopes for, 1001, 1002t, 1003f
imaging prior to, 999-1000
indications for, 999, 999b
innovations and future developments in, 1009-1011
autofluorescence bronchoscopy as, 1009
endobronchial ultrasonography as, 1011
endoscopic/bronchoscopic lung volume reduction as, 1011
interventional, 999b, 1007-1009
for balloon bronchoplasty, 1009
for endobronchial stent placement, 1009
for foreign body removal, 1008
in children, 2939t, 2940
general principles of, 1007-1008
patient preparation and instrument selection for, 1008
for tissue débridement, 1008-1009, 1010t
for laryngomalacia, 2867
patient discussion and informed consent for, 1000
patient positioning and route of entry for, 1000
for penetrating neck trauma, 1631t, 1634
rigid, 1000-1001
sedation and airway management for, 1000
for tracheal neoplasms
diagnostic, 1616-1617
therapeutic, 1619-1622
Bronchoscopy cart, for awake fiberoptic nasotracheal intubation, 123, 123f
Bronchospasm, during anesthesia, in children, 2595
Bronchus(i), anatomy and terminology for, 998-999, 999f
Brooke-Spiegler syndrome, 292
Brow
aesthetic proportions of, 428, 429f, 445, 445f
aging, 428-432, 429f, 445, 445f
Brow depressor muscles
botulinum toxin for, 432, 433f
release of, 434, 434f
Brow lift, 2430
direct, 430, 431t
endoscopic, 431, 431t
midforehead, 430, 431t
Brow muscles, 431, 433f
Brow position, ideal, 445, 445f
Brow ptosis, 445, 445f, 2430
Brow rejuvenation, 428-438
aesthetic proportions for, 428, 429f
brow muscles in, 431, 433f
and characteristics of aging brow, 428-432, 429f
patient selection for, 428-430
anatomic considerations in, 429-430
psychological considerations in, 428
postoperative care after, 434
results of, 434-438, 436f-438f
surgical goals of, 430
surgical technique for, 432-434
brow elevation and fixation in, 434, 435f
frontal and parietal bone dissection in, 432-433
incisions in, 432, 433f
local anesthesia in, 432
release of brow depressor muscles in, 434, 434f
temporal dissection in, 433-434, 433f-434f
technique(s) for, 430-432, 431t
browpexy for, 430, 431t, 432f
coronal forehead lift for, 430, 431t
direct brow lift for, 430, 431t
endoscopic brow lift for, 431, 431t
midforehead brow lift for, 430, 431t
midforehead lift for, 430, 431t
pretrichial forehead lift for, 430, 431t
temporal lift for, 431-432, 431t
treatment of depressor muscles with botulinum toxin for, 432, 433f
Brown-Guss provocation maneuvers, 500
Browpexy, 430, 431t, 432f
Brute force sample, 68, 69t
Bruxism, 262t
BSCC (basaloid squamous cell carcinoma)
of hypopharynx and cervical esophagus, 1425
of larynx, 1506
Bsn (bassoon) gene, in murine deafness, 2058t-2060t, 2080
BSND, in deafness, 2051t-2058t
BTE (Bridges to Excellence), 84t-87t
BTE (behind-the-ear). *See* Behind-the-ear (BTE).
BTO (balloon test occlusion), for cerebral blood flow evaluation, 2491
βTP (beta-trace protein), in CSF rhinorrhea, 790
Buccal bifurcation cysts, infected, 1264-1265
Buccal branch, of facial nerve, 1194f, 2418-2419, 2419f
Buccal carcinoma, 1308-1309
clinical appearance of, 1308f
epidemiology of, 1308
radiation and chemoradiation for, 1309
reconstruction for, 1308-1309, 1309f
squamous cell, 1308, 1308f
surgical treatment of, 1308-1309, 1309f
survival with, 1309
verrucous, 1308
Buccal fatpad, 321f
Buccal lymph nodes, 2582
Buccal membranes, physical examination of, 99
Buccal mucosa, 1295f, 1298
Buccal nerve, 321f
Buccal space involvement, in odontogenic infections, 181, 181f
Buccinator lymph nodes, 1360f
Buccinator musculomucosal flap, for soft palate reconstruction, 1381-1382, 1381f
Buckshots, 1626-1627, 1628t

Bud stage, of enamel organ development, 1259
Budesonide, for eczematoid otitis externa, 1955
Budesonide nasal spray (Rhinocort)
  for nonallergic rhinitis, 700t
  for rhinosinusitis, 734t, 736
Buffalo III voice profile, 2878
Buffering, saliva in, 1141
Buflomedil, and skin flap viability, 1073
Buildup region, in radiation, 1033
Bulb insufflator, for ear hygiene or chronic ear drainage, 1958, 1961f
Bulbar conjunctiva, 444
Bulbopontine sulcus, in surgical anatomy of lateral skull base, 2439f
Bulk flow, across interstitial space, 1066
Bulla frontalis, in frontal sinusitis, 776
Bullet(s)
  expanding, 1626, 1627f
  fragmenting, 1627f
  high-velocity, 1626, 1626f
  low-velocity, 1625
  self-exploding, 1627f
  tumbling, 1625-1626, 1627f
  yaw of, 1625
Bullet injuries, of neck
  due to handgun, 1625
  due to rifle, 1626, 1626f-1627f
  due to shotguns, 1626-1627, 1628t
Bullous myringitis, 1948, 1948f
Bullous oral mucosal lesions, 1231-1240
  erythema multiforme as, 1239-1240, 1254
    clinical features of, 1239, 1239f-1240f
    defined, 1239
    differential diagnosis of, 1239
    etiology and pathogenesis of, 1239
    histopathologic features of, 1239-1240
    treatment of, 1240
  herpes simplex infection as
    primary, 1235, 1252
      clinical features of, 1235, 1235f
      defined, 1235
      diagnosis of, 1235
      differential diagnosis of, 1235
      etiology and pathogenesis of, 1235
      treatment of, 1235, 1252
    recurrent, 1235-1236, 1252
      clinical features of, 1236, 1236f
      defined, 1235
      differential diagnosis of, 1236
      etiology and pathogenesis of, 1235-1236
      histopathology of, 1236, 1237f
      vs. recurrent aphthous stomatitis, 1238, 1238t
      treatment of, 1236
  mucous membrane (cicatricial) pemphigoid as, 1233-1235, 1254
    clinical differential diagnosis of, 1234, 1234t
    clinical features of, 1233-1234, 1233f-1234f
    defined, 1233
    etiology and pathogenesis of, 1233
    histopathologic features of, 1234-1235, 1234f
    treatment of, 1235
  pemphigus vulgaris as, 1231-1233, 1254
    clinical differential diagnosis of, 1232
    clinical presentation of, 1232, 1232f
    defined, 1231-1232
    etiology/pathogenesis of, 1232
    histopathologic features of, 1232-1233, 1232f-1233f
    treatment of, 1233
  recurrent aphthous stomatitis as, 1236-1239
    clinical features of, 1237-1238
    defined, 1236-1237
    differential diagnosis of, 1238, 1238t
    etiology and pathogenesis of, 1237, 1237t
    herpetiform-type, 1238, 1238f
    histopathologic features of, 1239
    major, 1237-1238, 1238f
Bullous oral mucosal lesions *(Continued)*
    minor, 1237, 1238f
    treatment of, 1239
  traumatic (eosinophilic) granuloma as, 1240
    clinical features of, 1240, 1240f
    defined, 1240
    differential diagnosis of, 1240
    etiology of, 1240
    histopathologic features of, 1240, 1240f
    treatment of, 1240
Bullous pemphigoid, esophageal manifestations of, 980
Bumetanide, sensorineural hearing loss due to, 2120, 2175
Bupivacaine, intraoperative, 112
Bupivacaine block, for neuropathic pain, 245
Bupropion, for neuropathic pain, 245, 245t
Burden, in psychometric validation, 55
Burkitt's lymphoma, 1679
  in children, 2838, 2839f
  clinical presentation of, 1674
  treatment and prognosis for, 1679
Burns, 314-316
  assessment and treatment of, 315-316
  classification of, 314-315, 315f
  of eyelids, 316
  of lips and oral commissure, 316
  of nasal and utricular cartilage, 316
Burow's solution (aluminum acetate otic drops), 1959t-1960t
  for fungal otitis externa, 1954
Burow's triangles, with advancement flaps, 345, 346f
"Burst" activity, in facial nerve monitoring, 2387, 2547, 2547f
Burst-forming units–erythroid (BFU-E), 605
Burst-forming units–megakaryocytes (BFU-MEG), 605
Burstone analysis, for mentoplasty, 463, 463f
Burwell, C. S., 251
Bushy cells, in cochlear nucleus, 1835, 1845
Buttress(es), of facial skeleton, 331, 331f
  repair of, 336
Buttress graft
  in nasal tip refinement, 576
  in revision rhinoplasty, 589
BW (body-worn) external speech processors, 2229, 2232, 2232f

C

C chemokines, 611t-612t
C fibers
  in dental pain, 1202
  in nonallergic rhinitis, 695
C trains, in electromyography, 2547
Ca^{++}. *See* Calcium (Ca^{++}).
CA (cochlear aqueduct). *See* Cochlear aqueduct (CA).
CA (compressed analog), for cochlear implants, 2230
CAA. *See* Congenital aural atresia (CAA).
Cachexia, palliative care for, 1104
Cacna1D, in murine deafness, 2058t-2060t, 2080
Cadherin 23 (CDH23), in tip links, 2074
Cadherin 23 *(CDH23)* gene, in deafness, 2051t-2058t, 2074
Cadherin expression, in oral cancer, 1301
CAHPS (Consumer Assessment of Health Providers and Services), 82, 84t-87t
Calcifications, tonsillar, 1411, 1412f
Calcifying epithelial odontogenic tumor, 1276
  microscopic findings in, 1276
  radiographic findings in, 1276, 1276f
Calcifying odontogenic cyst (COC), 1268-1269
  microscopic features of, 1269, 1269f
  radiographic features of, 1269
  treatment of, 1269
Calcimimetic agents, for hyperparathyroidism, 1804
Calcitonin
  in calcium homeostasis, 1775
  serum levels of, with thyroid nodule, 1756
Calcitonin gene–related peptide (CGRP)
  in salivary gland secretion, 1137
  and skin flap viability, 1073
Calcitriol, in parathyroid hormone regulation, 1776
Calcium (Ca^{++})
  in saliva, 1139
  serum, 1782
Calcium (Ca^{++})-activated chloride (Cl^{-}) channels, in salivary gland secretion, 1135
Calcium (Ca^{++})-activated potassium (K^{+}) channels, in salivary gland secretion, 1135
Calcium channel blockers
  for achalasia, 965
  for migraine, 2350
Calcium channel defects, and hearing, 2080
Calcium deficiency, oral manifestations of, 1254
Calcium homeostasis, 1775-1777
Calcium hydroxyapatite (Radiesse dermal filler), for vocal fold medialization, 906
Calcium (Ca^{2+})-mediated adaptation, of mechanoelectrical transduction currents, 2078-2079, 2079f
Calcium phosphate cement, for nasal reconstruction, 368
Calcium (Ca^{2+})-transporting plasma membrane 2, in deafness, 2051t-2058t
Calcium–adenosine triphosphatase 2 (Ca^{2+}-ATPase 2), in deafness, 2051t-2058t, 2080
Calcium-sending receptor gene, in parathyroid neoplasm(s), 1775
Calculi, of parotid gland, 150
Calculous lesions, of salivary glands, 1647
Caldwell, George, 756
Caldwell view, 662, 663f
  of facial bones and sinuses, 130
Caldwell-Luc procedure, 756, 756f
Calgary Sleep Apnea Quality of Life Index (SAQLI), 57
Caliber, of handgun, 1625
Caloric testing, 2319-2320
  anatomic and physiologic basis for nystagmus during, 2290
  convective component of, 2319, 2320f-2321f
  nonconvective component of, 2319-2320
  normative values for, 2320
  protocol for, 2320
  recording of eye movements in, 2320, 2321f
Calvaria, growth and development of, 2615-2617, 2617t, 2618f
Calyceal vestibular afferent nerve fibers, 2283, 2283f
Calyx ending, of hair cells, 1857, 1859f
CAMP (Clinical Assessment of Musical Perception), 57
cAMP (cyclic adenosine monophosphate)
  in olfactory transduction, 629
  in salivary gland secretion, 1137
Camper's fascia, 2577
Canal wall down mastoidectomy, 2010-2011
  for chronic otitis media with cholesteatoma, 1969, 1970t
  intact canal wall *vs.,* 2014
    indications for, 2014-2015, 2015f
  operative procedure for, 2013-2014, 2014f
Canal wall up mastoidectomy, 2010
  vs. canal wall down procedure, 2014
  for chronic otitis media with cholesteatoma, 1969, 1970t
  indications for, 2014-2015
Canalicular cell adenomas, of salivary glands, 1170
Canalith repositioning, for benign paroxysmal positional vertigo, 2331-2332, 2332f

Canalithiasis, 2329-2330
  of lateral semicircular canal, 2331
  of posterior semicircular canal, 2331
Canalplasty, in tympanoplasty, 2002
  with lateral graft technique, 2002-2003, 2002f
c-ANCAs (cytoplasmic antineutrophil cytoplasmic antibodies), in Wegener's granulomatosis, 658, 2103
Cancer, gene therapy for, 20-22, 21f
  antiangiogenesis in, 22
  conditionally replicating adenovirus therapy in, 22
  cytotoxic or suicide gene strategies in, 21
  direct in vivo stimulation of antitumor immune response in, 21
  genetic modification of tumor-infiltrating lymphocytes in, 20-21
  modifying oncogenes and tumor suppressor genes in, 21-22
Cancer pain, palliative care for, 1103
Cancer stem cell hypothesis, in head and neck squamous cell carcinoma, 1028
Candida albicans, otitis externa due to, 2195
Candida esophagitis, 976, 976f
  imaging of, 1404, 1405f
Candida spp
  otitis external due to, 1944-1945
  pharyngitis due to, 199-200
Candida superinfections, in chronic suppurative otitis media, 2221
Candidal leukoplakia, 1231, 1231f
Candidiasis
  laryngeal and tracheal, 884-885, 884f, 893
  oropharyngeal, 199-200, 1229-1231, 1252
    acute, 1230, 1230f, 1230t
    angular cheilitis due to, 1230, 1230f
    in children, 2786
    chronic, 1230, 1230t
    clinical features of, 1230-1231
    defined, 1229
    differential diagnosis of, 1231
    erythematous, 1230, 1230f
    etiology and pathogenesis of, 1229-1230
    histopathologic/diagnostic features of, 1231, 1231f
    in HIV, 225, 226f
    hyperplastic, 1231, 1231f
    pseudomembranous, 1230, 1230f
    risk factors for, 1229, 1230t
    treatment of, 1231
Canine smile, 2417-2418
Canine space involvement, in odontogenic infections, 180-181, 180f
Caninus, 321f
Cannulas, for liposuction, 453, 455f
Canthoplasty, 2420-2421
Cantilever bone graft, for nasal fractures, 505, 505f
CAP (compound action potential)
  in Bell's palsy, 2394
  electrically evoked, 1912-1913
    with cochlear implants, 1913f, 1914
Cap graft
  for nasal tip enhancement, 576, 577f
  in revision rhinoplasty, 589
Cap stage, of enamel organ development, 1259
Capek, Joseph, 38
Capek, Karel, 38
CAPE-V (Consensus Auditory Perceptual Evaluation for Voice), 819, 826
Caphosol, for mucositis, 1102
Capillary ectasia, of larynx, 817, 866-867
  diagnosis of, 866-867
    history in, 866
    laryngeal examination in, 866-867
    vocal capability battery in, 866
  epidemiology of, 866
  epidermoid inclusion cyst with, 868f
Capillary ectasia, of larynx *(Continued)*
  hemorrhagic polyp with, 868f
  management of, 867
    behavioral, 867
    medical, 867
    surgical, 867
  pathophysiology and pathology of, 866
  vocal nodules with, 867f
Capillary hemangioma, sinonasal lobular, 718t, 725, 725f
Capillary lake, 866-867
Capillary malformations, 2832-2833, 2834f
Capillary obstruction, in acutely raised skin flaps, 1070-1071
Capillary system, and skin flaps, 1065-1066, 1065f
  acutely raised, 1068-1069
Capsaicin provocation test, in nonallergic rhinitis, 696
Capsid, in Epstein-Barr virus, 1352
Capsulopalpebral fascia, 444
Carbamathione, for noise-induced hearing loss, 2145
Carbamazepine, for neuropathic pain, 243, 244t
Carbamide peroxide (Debrox, Murine removal kit), for cerumen removal, 1958t
Carbogen, with radiotherapy, 1041
Carbon dioxide (CO_2) laser, 31t, 32-33
  for airway stenosis, 945, 2918
  for benign vocal fold mucosal disorders, 864
  for glottic cancer, 1517t, 1519t
  for laryngeal hemangiomas, 881
  optical resonating chamber of, 26, 27f
  for premalignant lesions of larynx, 1490
  for recurrent respiratory papillomatosis, 879, 2889-2891
  for stridulous child, 2908
  for transoral laser microsurgery, 1528
Carbon dioxide (CO_2) laser endoscopic resection, for hypopharyngeal cancer, 1429-1430, 1442
  outcomes of, 1436-1438
Carbon dioxide (CO_2) laser resurfacing
  complications of, 402
  equipment for, 400, 400f
  postoperative care after, 401-402
  results of, 401f-402f
  technique of, 400, 400f
Carbon ion therapy, 1046
Carbon monoxide, in noise-induced hearing loss, 2147-2148
Carbonated apatite (Norian CRS), for chin implants, 465t
Carbonic anhydrase inhibitors, for Meniere's disease, 2337
Carboplatin
  in combination chemotherapy, 1059-1060
  ototoxicity of, 2173-2174
  sensorineural hearing loss due to, 2120, 2173-2174
Carcinoembryonic antigen (CEA)-targeted vaccine, for head and neck squamous cell carcinoma, 1024
Carcinoid tumors
  of larynx
    atypical, 1507
    typical, 1507
  of trachea, 1615, 1615f
Carcinoma ex pleomorphic adenoma, of salivary glands, 1187-1189, 1188f
Carcinoma in situ (CIS)
  of larynx, 1486-1491, 1489f-1490f, 1515
    treatment of, 1489-1490, 1520-1521
  oropharyngeal, 1361
Carcinosarcoma
  of larynx, 1506
  of salivary glands, 1187, 1188f
Cardiac bulge, 2661f, 2691f
Cardiac disease, oral manifestations of, 1246-1249, 1249t
Cardiac output, of newborn, 2571
Cardiac transplantation, oral sequelae of, 1248
Cardiopulmonary bypass, sensorineural hearing loss due to, 2120
Cardiopulmonary complications
  of obstructive sleep apnea, in children, 2604, 2604f
  of sleep-disordered breathing, in children, 2792, 2792f
Cardiovascular disease, oral manifestations of, 1246-1249, 1249t
Cardiovascular manifestations, of hyperparathyroidism, 1781
Cardiovascular system
  in children, 2571-2572
    and blood volume, 2571
    and newborn heart and cardiac output, 2571, 2571t
    and oxygen transport, 2571-2572
    and response to hypoxia, 2571
  preoperative evaluation of, 102
Caregiver Impact Questionnaire, 57
Carina fully implantable hearing system, 2210-2211
  clinical results with, 2210-2211
  components of, 2210, 2210f
  history of, 2210
  placement of, 2210, 2211f
Carinal resections, 1619, 1621f-1622f
  reconstruction after, 1619, 1623f
Caroticotympanic arteries, 1870
Caroticotympanic canaliculus, 1824f
Carotid arteriography, cross-compression, for cerebral blood flow evaluation, 2490
Carotid artery
  in surgical anatomy of lateral skull base, 2436f, 2438
    preoperative management of, 2489
      algorithm for, 2490f, 2491-2492
      cerebral blood flow assessment in, 2490-2491, 2490f
      four-vessel arteriography in, 2489-2490, 2491f
  tinnitus-producing fibromuscular dysplasia of, endovascular treatment for, 1943
Carotid artery aneurysms
  of petrous apex, 2525, 2527f
  upper cervical and petrous, 2504, 2504f-2505f
Carotid artery canal
  anatomy of, 1824f
  inferior foramen of, 1822-1823
  in surgical anatomy of lateral skull base, 2435f-2436f, 2438
  in surgical anatomy of middle cranial base, 2445f
Carotid artery hemorrhage, due to neck surgery, 1728
Carotid artery injury, due to temporal bone trauma, 2039, 2040f, 2047
Carotid artery invasion, imaging of, 166-167
Carotid artery pseudoaneurysm, due to deep neck space infections, 207
Carotid artery rupture, 1479
  due to cranial base surgery, 2468-2469
  due to deep neck space infections, 207
  due to neck dissection, 1723-1724
  due to neck surgery, 1728
  due to radiotherapy, 1048
Carotid artery stenosis, due to neck irradiation, 1695
Carotid blowout syndrome, 1479
  due to neck surgery, 1728
  due to radiotherapy, 1048
Carotid body, 1658-1659
Carotid body tumors, 1657-1658, 1934-1935, 1935f
  endovascular treatment of, 1937, 1937f

Carotid cavernous fistula, due to temporal bone trauma, 2047
Carotid gland, 1657-1658
Carotid groove
  in surgical anatomy of anterior cranial base, 2443f
  in surgical anatomy of middle cranial base, 2445f
Carotid ligation, in extended neck dissection, 1719-1721, 1720f
Carotid paragangliomas, 1657-1658, 2506f
  anatomy and physiology of, 1658-1659
  classification of, 1660
  clinical presentation and diagnosis of, 1659-1660
  etiology of, 1659, 1659t
  history of, 1657-1658
  imaging of, 1658f, 1660-1661
  malignancy of, 1660
  multicentricity of, 1660-1661
  observation for, 1661-1662
  radiation therapy for, 1661
  surgical management of, 1660-1661
Carotid prominence, in surgical anatomy of anterior cranial base, 2473
Carotid sheath, anatomy of, 202
  in children, 2578-2579, 2578f
Carotid sinus syndrome syncope, due to carotid paraganglioma, 1659
Carotid space (CS)
  anatomy of, 203
  imaging of, 150-151, 151f-152f
  schwannoma of, 1663f
Carotid stump pressure, for cerebral blood flow evaluation, 2490
Carotid triangle, 96, 96f, 2578f, 2579-2580
  arterial branches of, 2579-2580, 2580f
Carpenter's syndrome, craniofacial anomalies in, 2646
Cartilage grafts
  for nasal reconstruction, 368-369, 369f-370f
  for nasal tip projection, 535-536, 537f, 549-550, 550f-551f
  for revision rhinoplasty, 583, 584f
  for saddle nose deformity, 555, 556f
Cartilage plumping grafts, for nasal tip projection, 535-536, 536f
Cartilage struts, autogenous, for nasal tip projection, 535-536, 536f
Cartilage tympanoplasty, 2004-2005
Cartilage-mediated growth, in craniofacial growth and development, 2614
Cartilage-splitting approaches, for nasal tip refinement, 522, 523f-526f
Cartilaginous defect repair, biomaterials in, 2657-2658
Cartilaginous glottis, 849
Cartilaginous neoplasms, of larynx, 881-882
Cartilaginous vault rhinoplasty, 536-540
  access to nasal skeleton in, 537-539, 539f
  aesthetic improvement after, 537, 538f
  factors to consider in, 537
  incremental cartilaginous profile alignment in, 539
  mucoperichondrium in, 539-540
  pollybeak deformity due to, 512, 512f, 539, 539f
  for reduction of overlong caudal quadrangular cartilage, 513f
  with traumatic or iatrogenic avulsion of upper lateral cartilage, 539-540, 540f
Carved polymeric silicone (Silastic) implants, for medialization thyroplasty, 908-910, 910f
Carving template, in microtia reconstruction, 2744-2745, 2745f
Case series, 54-55, 54t
  data interpretation with, 59-61
Case-control study, 54, 54t
Caspases, in cisplatin ototoxicity, 2173
Casts, for prosthetic maxillary obturation, 1338-1339, 1338f
Cat scratch disease (CSD)
  in children, 2818
  deep neck space infections due to, 201
  salivary gland involvement in, 1159
Catagen phase, 374, 374f
CATCH-22, 2869
Catenary lever, 2018
Cathelicidins, 599
Catheters, angiographic, 1932-1933
Cauda-conchal sutures, 476f
Caudal extension graft
  in noncaucasian rhinoplasty, 576, 576f
  in revision rhinoplasty, 593
Caudal helix, 476f
Caudal septal deviation, revision rhinoplasty for persistence of, 593
Caudal septal excision, excessive, revision rhinoplasty for, 591f, 593
Caudal septum
  repositioning of, 547, 547f
  in septoplasty, 491-492, 491f-492f
    overaggressive resection of, 492, 492f
  shortening of, 547-548, 547f-548f
"Cauliflower deformity," 310
Caustic esophageal injury, 942, 977-978
  in children, 2956-2964
    algorithm for, 2962f
    endoscopy for, 2957-2959, 2958f
    epidemiology of, 2956
    initial assessment and diagnosis of, 2957
    pathophysiology of, 2956-2957
    signs and symptoms of, 2957b
    staging of, 2959, 2959f
    therapy for, 2959
      mechanical, 2960-2962, 2960f-2961f
      pharmacologic, 2959-2960
  clinical features of, 977
  etiology of, 977
  grading of, 977, 978t
  imaging of, 1404-1405, 1405f
  prognosis for, 977-978
  squamous cell carcinoma due to, 978
  strictures due to, 977-978, 978f-979f
    imaging of, 1405, 1405f
Caustic laryngeal trauma, 939-941
  etiology of, 940-941
  incidence of, 939-940
  management of, 941
Cautery, for epistaxis, 687-688, 687f
$Ca_v1.3$, in murine deafness, 2058t-2060t, 2080
$Ca_v1.3$ channels, 2080-2081
Caval mucosa, in sensation of nasal obstruction, 641-642
Cavernous hemangioma, 290
  epistaxis due to, 684f
Cavernous sinus meningiomas, embolization of, 1938
Cavernous sinus thrombosis
  due to deep neck space infections, 207
  due to odontogenic infections, 181, 182f
  preseptal orbital, 676
Cavernous sinus tumors, surgical approach for, 2509-2510
Cavernous venous sinus, 1699
Cavity dumped lasers, 34
Cavum conchae, 476-477, 1824f
CBF evaluation. *See* Cerebral blood flow (CBF) evaluation.
CBT (cognitive-behavioral therapy), for tinnitus, 2135
CC chemokines, 611t-612t
CCDC50 (coiled-coil domain–containing protein 50/Ymer) gene, in deafness, 2051t-2058t
CCL chemokines, 611t-612t
CCR (cervicocollic reflex), 2307-2308
$CD4^+$ cells, 601
$CD8^+$ cells, 601
CDH23 (cadherin 23), in tip links, 2074
CDH23 (cadherin 23) gene, in deafness, 2051t-2058t, 2074
Cdkn2d (cyclin-dependent kinase inhibitor 2D) gene, in murine deafness, 2058t-2060t
CDP. *See* Computerized dynamic posturography (CDP).
CEA (carcinoembryonic antigen)-targeted vaccine, for head and neck squamous cell carcinoma, 1024
CECT. *See* Contrast-enhanced computed tomography (CECT).
Cefazolin
  for endocarditis prophylaxis, 1249t
  for pediatric surgery prophylaxis, 2597t
Ceftazidime, for rhinosinusitis, 734
Ceftriaxone
  for endocarditis prophylaxis, 1249t
  for pediatric surgery prophylaxis, 2597t
Cefuroxime, for rhinosinusitis, 734t-735t
Celecoxib (Celebrex), for recurrent respiratory papillomatosis, 2892
Celiac disease, oral manifestations of, 1254
Cell cycle, 12, 13f
Cell cycle arrest, due to radiation, 1037, 1037f
Cell division, 12, 13f
Cell membrane, 1066-1067
Cell surface receptors, in salivary gland secretion, 1136-1137, 1136f, 1137t
Cell survival curve, with radiation therapy, 1037-1039, 1038f
Cell-mediated immune response, 602f
Cellular immunodeficiency disorders, 2114
  otologic manifestations of, 2114
Cellular recruitment, in allergic rhinitis, 616, 617f
Cellular systems, and skin flaps, 1065-1067, 1065f
Cellulitis
  of external ear, 1946, 1948
  orbital, due to odontogenic infections, 181, 182f
  retropharyngeal, 2810-2811, 2810f
  of sublingual space, 156, 157f
Censored data, 63t, 64
Center of gravity, in vestibular function, 2308
Centers for Medicare and Medicaid Services (CMS), 84t-87t, 87
Centor scoring system, for GABHS pharyngitis, 193
Central adaptation, and olfactory testing, 633
Central alveolar hypoventilation, 262t
Central apnea index, 251b
Central compartment dissection, 1719
  defined, 1719, 1719f
  technique for, 1719, 1720f
"Central face," concept of, 322
Central facial paralysis, 2401
Central gustatory pathways, 1212-1213, 1212f
Central midface, congenital malformations of nose due to developmental errors of, 2690-2693, 2691f
Central nervous system (CNS) changes, in Bell's palsy, 2393-2394
Central nervous system (CNS) infections, due to cranial base surgery, 2468
Central neural auditory prosthesis, 2258-2264
  alternative strategies to, 2263
  anatomy and surgical approaches for, 2260, 2261f
  auditory performance with, 2262
  biocompatibility of, 2259
  in children with cochlear nerve aplasia, 2263-2264
  complications of, 2260-2261
  history of clinical approaches to, 2259-2260, 2259f
  indications for, 2260

Central neural auditory prosthesis *(Continued)*
intraoperative monitoring of, 2260, 2261f
in patients without neurofibromatosis type 2, 2262
penetrating
brainstem, 2262, 2262f
midbrain, 2262-2263, 2263f
"Central sensitization," 1203
Central sleep apnea, 251b, 256f, 263, 263b
Central tendency, 64t, 66t
Central vestibular disorder(s), 2346-3
cerebellar ataxia syndromes as, 2356-2357
cervical vertigo as, 2354
of craniovertebral junction, 2354-2356
assimilation of atlas as, 2355
atlantoaxial dissociation as, 2355-2356
basilar impression as, 2355
Chiari malformation as, 2356, 2356f
classification of, 2355-2356
pathophysiology of, 2355
focal seizure disorders as, 2357
intracranial complications of otitic infections as, 2347
migraine as, 2347-2350
auditory symptoms of, 2348-2349
distortion as, 2349
hearing loss as, 2348-2349
phonophobia as, 2349
tinnitus as, 2349
without aura, 2347b
aura with, 2347, 2347b
basilar, 2349
diagnosis and classification of, 2347, 2347b
epidemiology of, 2347
etiology of, 2349
without headache, 2349
management of, 2349-2350, 2350f
with neurotologic symptoms, 2349
vestibular disorders associated with, 2350
benign paroxysmal positional vertigo as, 2350
Meniere's disease as, 2350
vestibular disorders related to, 2350-2351
benign paroxysmal vertigo of childhood as, 2350-2351
paroxysmal torticollis as, 2351
vestibular symptoms of, 2347-2348
motion sickness as, 2348
nonspecific dizziness as, 2347
vertigo as, 2347-2348, 2348f
multiple sclerosis as, 2356, 2356f
neoplastic, 2353-2354
of brainstem, 2353-2354
cerebellar, 2354
vestibular schwannomas as, 2353
normal pressure hydrocephalus as, 2357
peripheral *vs.*, 2346, 2347t
physiologic dizziness as, 2357
in mal de débarquement syndrome, 2357
in motion sickness, 2357
vascular, 2351-2353, 2351f
cerebellar hemorrhage as, 2354f
cerebellar infarction as, 2353f
evaluation and management of, 2354f-2355f
lateral medullary syndrome as, 2352f, 2354f
lateral pontomedullary syndrome as, 2353f
vertebrobasilar insufficiency as, 2355f
Centric fusion translocation, 5
Cephalexin
for endocarditis prophylaxis, 1249t
for pediatric surgery prophylaxis, 2597t
Cephalic phase insulin release (CPIR), 1206
Cephalic phase responses, 1206
Cephalic rotation, in nasal tip refinement, 519, 536, 549-550, 551f
Cephalocele, 670, 671f
of petrous apex, 2508
Cephalometric radiography
lateral, for mentoplasty, 463, 463f
of obstructive sleep apnea, 255, 255f
Cephalometric reference points, in facial analysis, 270b, 272f
Cephalosporins
for acute otitis media, 2770
adverse reactions to, 102
Cepstral peak prominence (CPP), in acoustic analysis, for voice evaluation, 829t, 830
Ceramic allografts, for ossiculoplasty, 2006
Ceramics, for craniofacial defect repair, 2657-2658
Cerebellar ataxia syndromes, 2356-2357
Cerebellar atrophy, 2357
Cerebellar degeneration, paraneoplastic, 2357
Cerebellar floccules, in surgical anatomy of lateral skull base, 2439f
Cerebellar hemispheres, in surgical anatomy of lateral skull base, 2439f
Cerebellar hemorrhage, 2354f
Cerebellar horizontal fissure, in surgical anatomy of lateral skull base, 2439f
Cerebellar infarction, 2353f
Cerebellar lesions, laryngologic manifestations of, 837-838, 838t
Cerebellar neoplasm, vestibular symptoms of, 2354
Cerebellar olive, in surgical anatomy of lateral skull base, 2439f
Cerebellopontine angle (CPA)
imaging of, 1926-1928, 1929t
with acoustic schwannoma, 1929t
with arachnoid cyst, 1928, 1929t
with epidermoid tumor, 1928, 1928f, 1929t
with lipoma, 1928, 1929t
with meningioma, 1928, 1928f, 1929t
in surgical anatomy of lateral skull base, 2438
Cerebellopontine angle (CPA) neoplasm(s)
acoustic neuroma as, 2514-2517
diagnostic studies of, 2516-2517
imaging of, 2517, 2517t-2518t
natural history of, 2515, 2515f-2516f
signs and symptoms of, 2515-2516
arachnoid cysts as, 2523-2524
vs. cholesteatoma (epidermoid), 2519, 2521f
imaging of, 1928, 1929t
chondrosarcomas as, 2527, 2528f-2529f
chordomas as, 2526-2527, 2527f-2528f
choroid plexus papilloma as, 2528-2529, 2530f
common, 2514-2524, 2515b
dermoid tumors as, 2527
differential diagnosis of, 2517t-2518t
ependymoma as, 2528-2529, 2531f
facial nerve neuroma as, 2519-2522
diagnostic studies of, 2519-2522
imaging of, 2519-2522, 2521f
signs and symptoms of, 2519
glomus tumors as, 2522-2523, 2523f-2524f
hemangiomas as, 2524, 2525f
intraoperative cranial nerve monitoring with, 2545
lipoma as, 2527, 2529f-2530f
imaging of, 1928, 1929t
meningiomas as, 2517-2518
diagnostic studies of, 2518
imaging of, 1928, 1928f, 2518, 2519f
in differential diagnosis, 1929t, 2518t
with intracanalicular extension, 2520f
sensorineural hearing loss due to, 2125, 2125f
signs and symptoms of, 2518
metastatic, 2526
other cranial nerve neuromas as, 2522, 2522f
primary cholesteatomas (epidermoids) as, 2518-2519
diagnostic studies of, 2519
differential diagnosis of, 2518t, 2524t
imaging of, 2519, 2520f-2521f
signs and symptoms of, 2518-2519
Cerebellopontine angle (CPA) neoplasm(s) *(Continued)*
retrocochlear
hearing loss due to, 2199
vertigo due to, 2202
teratomas as, 2527
uncommon, 2515b, 2526-2527
Cerebellopontine cistern, congenital epidermoid cyst of, 2509f
Cerebellum
afferent pathways to vestibular nuclei from, 1864
efferent pathways from vestibular nuclei to, 1864-1865
in vestibular function, 2308
vestibular nerve projections to, 1860
Cerebral blood flow (CBF) evaluation
prior to anterior and middle cranial base surgery, 2445-2446, 2446f
prior to lateral cranial base surgery, 2490-2491, 2490f
qualitative, 2490-2491
quantitative, 2491
"Cerebral congestion," 2329
Cerebral edema
after lateral skull base surgery, 2513
due to neck dissection, 1723
Cerebral palsy, and obstructive sleep apnea, 2605
Cerebritis, due to temporal bone infection, 1980t
Cerebrospinal fluid (CSF)
in Bell's palsy, 2394
with enlarged cochlear aqueduct, 2734
with enlarged vestibular aqueduct, 2733-2734
physiology of, 786
volume of, 786
Cerebrospinal fluid (CSF) drainage, posturography and, 2326
Cerebrospinal fluid (CSF) fistula(s)
bacterial meningitis due to, 794
due to cranial base surgery, 2468
CT cisternogram of, 2477f
traumatic, 2044-2046
antibiotic prophylaxis for, 2044-2045
closure of, 2045-2046, 2045f
diagnosis of, 2044
infecting organisms with, 2045
meningitis due to, 2044-2045
pathogenesis of, 2044
signs and symptoms of, 2044
treatment algorithm for, 2045-2046, 2045f
Cerebrospinal fluid (CSF) gusher
with wide internal auditory canal, 2735, 2735f
X-linked syndrome of stapes, 2737
Cerebrospinal fluid (CSF) leakage
due to inner ear anomalies, 2735-2737, 2736f
treatment of, 2737, 2739
due to otitis media, 1992-1993, 1993f
due to posterior fossa surgery, 2540
temporal bone, 2509
diagnostic evaluation of, 2509
surgical approach to, 2509
traumatic, 2044
Cerebrospinal fluid (CSF) otorrhea, 788, 2197
Cerebrospinal fluid (CSF) pressure, 786
Cerebrospinal fluid (CSF) rhinorrhea, 785-2
classification of, 786, 786b
complications of, 785
diagnosis of, 788
chemical markers in, 789-791
CSF tracers in, 790-791, 790f
CT cisternography in, 790, 790f
CT in, 791, 791f-792f
diagnostic testing in, 789-791
differential, 788-789
localization studies in, 791, 791f-792f
MR cisternography in, 790-791, 790f
MRI in, 791, 791f
nasal endoscopy in, 791

Cerebrospinal fluid (CSF) rhinorrhea *(Continued)*
patient history in, 789
physical examination in, 789
radionuclide cisternography in, 790
epidemiology of, 786
etiology of, 786, 786b
due to intraoperative injury, with immediate recognition or onset, 795
nontraumatic, 786b, 795
traumatic, 786b, 794-795
after functional endoscopic sinus surgery, 679-680, 680f
historical perspective on, 786
and intracranial pressure, 786-787, 786b
management of, 791-795
comprehensive strategy for, 794-795
conservative, 791-792, 792b
extracranial techniques for, 792-794, 793f-794f
precautions in, 794
transcranial techniques for, 792
maxillofacial trauma with, 326, 334-339
due to nasal fracture, 507
pathophysiology of, 786-788, 787f-788f
patient education on, 794
surgical management of, 742
Cerebrospinal fluid (CSF) tracers, for CSF rhinorrhea, 790-791, 790f-793f
Cerebrovascular accident (CVA)
chronic aspiration due to, 926b
due to lateral skull base surgery, 2512
oral manifestations of, 1250
Cerebrovascular complications
of cranial base surgery, 2468-2469
of lateral skull base surgery, 2512-2513
Cerebrovascular diseases, oral manifestations of, 1250
Certification, 79-80, 80b
maintenance of, 80, 81b
Cerumen impaction, 1957
therapy options for, 1957, 1958t, 2021
Cerumenex (docusate sodium), for cerumen removal, 1958t
Cerumenex (trolamine polypeptide oleate-condensate), for cerumen removal, 1958t
Ceruminolytics, 1957, 1958t
Cerumol (arachis oil, chlorbutol, paradicholorobenzene, oil of turpentine), for cerumen removal, 1958t
Cervical adenopathy. *See* Cervical lymphadenopathy.
Cervical branch, of facial nerve, 1194f
Cervical dissection, in postauricular approach to infratemporal fossa, 2495, 2498f
Cervical epidural anesthesia, 242
Cervical esophageal cancer
advanced, 1439
chemotherapy for, 1439
quality of life with, 1439
approach to management of, 1426
chemoradiotherapy for, 1434
chemotherapy for, 1433-1434
clinical evaluation of, 1423
physical findings in, 1423
presenting symptoms in, 1423, 1423t
fasciocutaneous free flaps for, 1433
gastric pull-up for, 1432, 1432f
imaging of, 1423-1424
barium swallow for, 1423-1424
CT for, 1424, 1424f
MRI for, 1424
PET/CT for, 1424, 1424f
incidence of, 1423
lymph node metastasis of, 1434-1439
pathology of, 1424-1425
radiation therapy for, 1436
therapeutic outcome of, 1436
Cervical esophageal cancer *(Continued)*
reconstruction for
with circumferential defects, 1431-1432
fasciocutaneous free flaps for, 1433
gastric pull-up in, 1432, 1432f
jejunal free flap for, 1432-1433, 1433f
staging of, 1426-1434, 1426t-1427t
therapeutic outcomes for, 1435-1436
total pharyngo-laryngo-esophagectomy for, 1430-1431
Cervical esophagus, 1421-1422
Cervical exploration, for parathyroid adenoma, 1792-1793
Cervical fascia, 2577
deep, 202, 2577-2578, 2578f-2579f
superficial, 202, 2577
surgical anatomy of, 1543f
Cervical lymph node(s)
anatomy of, 1683, 1683f, 1684t
classification of, 1683, 1683f, 1684t, 2582-2583
deep, 2582
superficial, 2582
Cervical lymph node groups, in neck dissection, 1703-1705
levels of, 1703-1705, 1704f, 1706t
radiologic anatomic markers in, 1705, 1707t-1708t
sublevels of, 1704-1705, 1705f, 1706t
Cervical lymph node metastasis(es), 1682-1695
anatomic basis for, 1683, 1683f, 1684t
of cervical esophageal cancer, 1434-1439
chemoradiation therapy for
postoperative, 1693-1694, 1694t
primary, 1693, 1693t
classification of, 1684t
in contralateral neck, 1688, 1690
of hypopharyngeal cancer, 1434-1439
incidence and distribution of, 1686f, 1688t
radiation therapy for, 1689t
imaging of
contrast-enhanced CT for, 164-165, 167f
of laryngeal carcinoma, 1476, 1479f
MRI for, 165-166, 168f
incidence and distribution of, 1684-1688
from clinical and radiologic assessment, 1684-1687, 1685f-1686f
in contralateral neck, 1688
from hypopharyngeal tumors, 1686f, 1688t
from nasopharyngeal tumors, 1687f
from oral cavity tumors, 1685f, 1688t
from oropharyngeal tumors, 1685f, 1688t
pathologic, 1687, 1688t
from supraglottic laryngeal tumors, 1686f, 1688t
of laryngeal carcinoma, 1493-1494, 1493f
embryology and, 1482-1483
glottic, 1497-1498
imaging of, 1476, 1479f
radiation therapy for, 1690t
subglottic, 1501, 1501f
supraglottic, 1500-1501
incidence and distribution of, 1686f, 1688t
of nasopharyngeal carcinoma, 1352-1353, 1353f
incidence and distribution of, 1687f
radiation therapy for, 1690, 1690t
neck control for
with N0 status, 1688, 1690, 1692, 1692t
with N1-N3 status, 1692-1695
postoperative irradiation or chemo-irradiation for, 1693-1694, 1694t
after primary radiotherapy, 1692-1693, 1693t
neck dissection for (*See* Neck dissection)
of oral cavity tumors
incidence and distribution of, 1685f, 1688t
radiation therapy for, 1689t
Cervical lymph node metastasis(es) *(Continued)*
of oropharyngeal cancer, 1360f, 1361t
incidence and distribution of, 1685f, 1688t
radiation therapy for, 1689t
of paranasal sinus tumors, 1130
radiation therapy for
indications for neck node dissection after, 1694
late complications of, 1694-1695
with N0 status, 1688, 1690, 1692, 1692t
with N1-N3 status, 1692-1695
neck control after, 1692-1693, 1693t
postoperative, 1693-1694, 1694t
of retropharyngeal nodes, 1688
target volumes for, 1688-1690
delineation of, 1690-1691, 1691f
for hypopharyngeal tumors, 1689t
for laryngeal tumors, 1690t
for nasopharyngeal tumors, 1690, 1690t
for oral cavity tumors, 1689t
for oropharyngeal tumors, 1689t
techniques for, 1691, 1692f
recurrent, 1695
postoperative, 1693-1694, 1694t
after primary radiation therapy, 1695
retropharyngeal, 1687-1688
of salivary gland tumors, 1196-1197
staging of, 1683-1684, 1684t
of thyroid cancer, 1766
Cervical lymphadenectomy. *See* Neck dissection.
Cervical lymphadenopathy
in children
bacterial, 2818, 2818f-2819f
drug-induced, 2819
fungal, 2818-2819
reactive, 2818
suppurative, 2818, 2818f
viral, 2817-2818
imaging of, 1414-1415, 1415f
CT of, 139
with extracapsular spread, 164-166, 167f
inflammatory (reactive), 164
with invasion of carotid artery, 166-167
metastatic
contrast-enhanced CT of, 164-165, 167f
MRI of, 165-166, 168f
MRI of, 142
with non-Hodgkin's lymphoma, 165-166, 167f
ultrasound of, 143
in immunosuppressed patients, 218-219, 219t
neck masses due to, 1638
in children
bacterial, 2818, 2818f-2819f
fungal, 2818-2819
viral, 2817-2818
Cervical lymphatics, 1312-1313, 1313f
Cervical plexus, 2581
ansa cervicalis of (*See* Ansa cervicalis)
anterior division of, 2579f
cutaneous branches of, 2578, 2580f
for facial nerve grafting, 2422
Cervical plexus block, superficial, 242
Cervical sensory nerve injuries, due to neck surgery, 1731-1732
Cervical skin flaps, for hypopharyngeal and esophageal reconstruction, 1450-1451
Cervical space infections. *See* Deep neck space infections.
Cervical vertigo, 2354
Cervicocollic reflex (CCR), 2307-2308
Cervicofacial advancement flap, for buccal carcinoma, 1309f
Cervital, for ossiculoplasty, 2026t
Cetirizine (Zyrtec)
for nonallergic rhinitis, 701t
for rhinosinusitis, 734t

Cetuximab (Erbitux)
for metastatic squamous cell carcinoma, 1061
with radiotherapy, 1052, 1054
for laryngeal cancer, 1585
CF. *See* Cystic fibrosis (CF).
CFD (computational fluid dynamics), CT with, 643
CFU. *See* Colony-forming unit (CFU).
CGH (comparative genomic hybridization), for head and neck squamous cell carcinoma, 1019
CGRP (calcitonin gene–related peptide)
in salivary gland secretion, 1137
and skin flap viability, 1073
Chalasia, cricopharyngeal, 1399
CHAMP procedure, auditory brainstem response in, 1911
Chance, *vs.* efficacy of treatment, 62t
CHAOS (congenital high airway obstruction syndrome), 2869, 2870f, 2904-2905
Characteristic frequency, 1844-1845, 1845f
Charcot-Leyden crystal (CLC) protein, 604
Charcot-Marie-Tooth syndrome, deafness in, 2051t-2058t
CHARGE association
facial paralysis in, 2397
inner ear anomalies in, 2735
Charged particle beams, in radiotherapy, 1034-1035
Check ligament, 321f
Cheek advancement flap, for nasal defects, 348, 349f
Cheek defects, 355-359
advancement flaps for, 358
V-Y, 358, 361f
rotation flaps for, 357-358, 359f
sub-superficial musculoaponeurotic system dissection for, 357-358, 360f
transposition flaps for, 358-359, 361f
bilobed, 357, 359f
rhombus shaped, 355
Cheek pedicle transposition flap, for nasal defects, 348, 349f
Cheilitis
angular, 1230, 1230f
in HIV, 225, 226f
solar (actinic), 283
Cheiloplasty, 2431, 2431f
Chelating agents, oral sequelae of, 1247t-1248t
Chemesthesis, of oral cavity, 1202
Chemical labyrinthectomy, for Meniere's disease, 2185-2189, 2338-2339, 2338f
Chemical markers, for CSF rhinorrhea, 789-790
Chemical peels, 391-397
agents for, 392-394
complications of, 396-397
contraindications to, 391, 392t
in dark-skinned individuals, 392
deep, 394-395
equipment tray for, 393f
histologic changes with, 390-391
indications for, 391, 392t
medium-depth, 393-394, 393f-394f
patient selection and education for, 391-392
and phenol toxicity, 395
postoperative care after, 396, 396f
prepeel preparations for, 392
superficial, 392-393, 403
Chemical shift artifact, on MRI, 134
Chemical shift selective presaturation, for MRI, 135-136, 136f
Chemical surgery, for skin lesions, 294
Chemodectomas, 1657. *See also* Paragangliomas (PGLs).
multiple, 1934-1935, 1935f
Chemokine(s)
in humoral immune response, 608, 611t-612t
in wound healing, 1076
Chemokine connective tissue–activating peptide-III (CTAP-III), in wound healing, 1076
Chemokine receptor 2 (CXCR2), in wound healing, 1076
Chemokine receptor 4 (CXCR4), in head and neck squamous cell carcinoma, 1060
Chemoprevention
of head and neck squamous cell carcinoma, 1018, 1061-1062
clinical implications of, 1018
of laryngeal cancer, 1491
of oral cancer, 1315
Chemoradiation therapy (CRT), 1041-1043, 1052-1058
for cervical lymph node metastasis
postoperative, 1693-1694, 1694t
primary, 1693, 1693t
concomitant, 1052-1056, 1053t-1054t
as adjuvant therapy, 1056
induction chemotherapy with, 1041-1042, 1052-1053
with adjuvant therapy, 1056
for esophageal carcinoma
definitive, 1445-1447, 1446t-1447t
preoperative, 1444-1445, 1445t
for hypopharyngeal cancer, 1434, 1439, 1442-1444
RADPLAT technique for, 1592
for laryngeal carcinoma, 1501-1503, 1502f
glottic
in advanced stage, 1584-1585, 1584t
with nodal metastases, 1498
optimal dose-fractionation scheme for, 1585-1586
outcomes and prognostic factors with, 1586-1587, 1587t
RADPLAT technique for, 1592
supraglottic, in advanced stage, 1500, 1589
for maxillary sinus tumor, 1130
for nasopharyngeal carcinoma, 1355, 1699f
neck dissection after, 1724
for oral cancer, 1314-1315
RADPLAT technique for, 1054
for laryngeal and hypopharyngeal cancer, 1592
swallowing disorders due to, 1219
for thyroid cancer, 1772
Chemosomatosensory-evoked potentials, 632
Chemotherapy, 1015
adjuvant, for oral cancer, 1314-1315
combination, 1059-1060
for esophageal carcinoma
localized, 1444
metastatic, 1447
historical background of, 1051-1052
for hypopharyngeal cancer, 1433-1434, 1442
advanced, 1439
induction, 1443
for larynx preservation, 1443-1444
induction, 1056-1058, 1058f, 1058t-1059t
clinical trials of, 1056-1058
in concomitant chemoradiation, 1041-1042, 1052-1053
with adjuvant therapy, 1056
defined, 1056
for hypopharyngeal cancer, 1443
for laryngeal carcinoma, 1501-1503, 1502f
for oral cancer, 1314-1315
intra-arterial, 1939
for laryngeal carcinoma
early glottic, 1520
neoadjuvant, 1501-1503, 1502f
for melanoma, 1118
neoadjuvant, for laryngeal carcinoma, 1501-1503, 1502f
for oral cancer, 1314-1315
with radiation therapy (*See* Chemoradiation therapy (CRT))
Chemotherapy *(Continued)*
radiosensitizing, 1040-1043
for recurrent or metastatic disease, 1058-1061
combination, 1059-1060
prognostic factors with, 1058-1059
single agent, 1059
for rhabdomyosarcoma, 2841
for salivary gland neoplasms, 1199
single agent, 1059
for thyroid cancer, 1772
Chemotherapy resistance, gene therapy for, 24
CHEP. *See* Cricohyoidoepiglottopexy (CHEP).
Cherry angiomas, 290
Chest pain, due to esophageal disease states, 956, 971
Chest voice, 846-847, 851
Chest wall displacement, in voice evaluation, 828
Chest x-ray (CXR)
of early glottic carcinoma, 1516
for imaging of pharynx and esophagus, 1393
for neck masses, 1637
Chiari malformation, 2356, 2356f
Chiasmatic sulcus, in surgical anatomy of anterior cranial base, 2472f
Chief cell(s), 1778
Chief cell hyperplasia, of parathyroid glands, 1779
Chief complaint, 94, 94b
Child Health and Illness Profile–Child Edition (CHIP-CE), 57
Child Health Questionnaire (CHQ), 57
Childhood, benign paroxysmal vertigo of, and migraine, 2350-2351
Children
acute otitis media and otitis media with effusion in, 2761-2777
complications and sequelae of, 2776-2777
intracranial, 2776-2777
intratemporal, 2776
diagnosis of, 2761-2762
audiometry in, 2762
immittance testing (tympanometry) in, 2762
physical examination in, 2761-2762
symptoms and signs in, 2761
epidemiology of, 2765-2768
incidence and prevalence of, 2765-2766, 2765f
risk factors in, 2766-2768
trend over time in, 2765-2766
guidelines for, 2773
pathophysiology and pathogenesis of, 2762-2765, 2762f
allergy and immunology in, 2764-2765
eustachian tube function in, 2762-2763, 2763f
gastroesophageal reflux in, 2765
infection in, 2763-2764, 2764f
prevention of, 2768-2769
antibiotic prophylaxis for, 2771
management of environmental factors in, 2768
vaccines in, 2768-2769
quality of life assessment for, 2773
recurrent, 2771
treatment of, 2770-2773
medical, 2770-2772
observation in, 2770-2771
for recurrent disease, 2771
surgical, 2771-2776
adenotonsillar disease in, 2782-2802
adenoidectomy for, 2795-2796
indications for, 2795-2796
and otitis media, 2796
adenotonsillectomy for (*See* Adenotonsillectomy)
anatomy of, 2783-2784
due to bacterial infections, 2785-2788
due to candidiasis, 2786

Children *(Continued)*
chronic adenotonsillar hypertrophy as, 2790-2793
airway obstruction due to, 2789f-2790f, 2790-2793, 2795
algorithm for evaluation of, 2783f-2784f
with attention deficit–hyperactivity disorder, 2791
cardiopulmonary complications of, 2792, 2792f
craniofacial growth and, 2792-2793
diagnostic assessment of, 2793-2794, 2793f
and enuresis, 2792
etiology of, 2789f-2790f, 2790
and growth problems, 2792
and neurocognitive development, 2791-2792
and obstructive sleep apnea, 2790-2793
complications of, 2788-2790
nonsuppurative, 2788
parapharyngeal space abscess as, 2788-2789
peritonsillar infections as, 2788, 2789f
retropharyngeal space infections as, 2789-2790, 2789f
suppurative, 2788-2790
due to *Corynebacterium diphtheriae*, 2786-2787
diagnostic assessment for, 2793-2794, 2793f
history of, 2782
imaging of, 2793-2794, 2793f
immunology of, 2784-2785
due to infections of Waldeyer's ring, 2785
management algorithms for, 2782, 2783f-2784f
microbiology of, 2785-2788
due to *Neisseria gonorrhoeae*, 2786
preoperative assessment for, 2794
due to streptococcal infection, 2787
due to syphilis, 2786
due to tonsillar concretions/tonsilloliths, 2787-2788, 2788f
due to Vincent's angina, 2786
due to viral infections, 2785-2786, 2786f
with Epstein-Barr virus, 2785-2786, 2786f
airway infection(s) in, 2803-2811
bacterial tracheitis (exudative tracheitis) as, 2809-2810
clinical features of, 2809
complications of, 2810
diagnosis of, 2809, 2809f
differential diagnosis of, 2806t
endoscopy of, 2809, 2809f
epidemiology of, 2809
imaging of, 2809, 2809f
management of, 2809-2810, 2809f
pathogenesis of, 2809
terminology for, 2809
croup (laryngotracheitis) as, 2803-2806
clinical features of, 2803-2804
defined, 2803
diagnosis of, 2804
differential diagnosis of, 2804-2805, 2806t
epidemiology of, 2803
etiology of, 2803
imaging of, 2804, 2804f-2805f
laryngoscopy of, 2804, 2805f
management of, 2805-2806
pathogenesis of, 2803-2804
spasmodic, 2805
terminology for, 2803
retropharyngeal abscess as, 2810-2811
anatomy of, 2810
clinical features of, 2810
complications of, 2811
diagnosis of, 2810-2811, 2810f-2811f
differential diagnosis of, 2806t
epidemiology of, 2810
historical background of, 2810
imaging of, 2810-2811, 2810f-2811f
management of, 2811
supraglottitis (epiglottitis) as, 2806-2809
clinical features of, 2807
complications of, 2808-2809
diagnosis of, 2807-2808, 2807f-2808f
differential diagnosis of, 2806t
endoscopy of, 2808, 2808f
epidemiology of, 2806-2807
etiology of, 2807
histology of, 2807, 2807f
historical background of, 2806-2807
imaging of, 2807f, 2808
management of, 2808
anesthesia in, 2575, 2587-2601
for adenotonsillectomy, 2598-2599, 2599b
emergence from, 2592-2593
induction of, 2589-2591
inhalation, 2590
intramuscular, 2591
intravenous, 2590
parental presence during, 2590
rapid-sequence, 2590
intraoperative monitoring standards for, 2588, 2588b
for laryngeal surgery, 2599-2600
maintenance of, 2591-2592
inhalational agents for, 2591
intravenous agents for, 2591, 2593t
medical condition(s) affecting, 2594-2597
asthma as, 2595
congenital heart disease as, 2596-2597, 2596t-2597t
cystic fibrosis as, 2595
diabetes mellitus as, 2596
prematurity as, 2595
upper respiratory infection as, 2594-2595
outside of operating room, 2594
postoperative management of, 2593-2594
for nausea and vomiting, 2593
for pain, 2594
for postintubation croup, 2593
preoperative assessment for, 2588
preparation for, 2588-2589
behavioral, 2588-2589, 2589t
nothing-by-mouth orders in, 2589, 2590t
premedication in, 2589
for rigid bronchoscopy, 2597-2598, 2597t
risks of, 2587-2588
audiology in, 2574
Bell's palsy in, 2397
cardiovascular system in, 2571-2572
and blood volume, 2571
and newborn heart and cardiac output, 2571, 2571t
and oxygen transport, 2571-2572
and response to hypoxia, 2571
caustic ingestion in, 2956-2964
algorithm for, 2962f
endoscopy for, 2957-2959, 2958f
epidemiology of, 2956
initial assessment and diagnosis of, 2957
pathophysiology of, 2956-2957
signs and symptoms of, 2957b
staging of, 2959, 2959f
therapy for, 2959
mechanical, 2960-2962, 2960f-2961f
pharmacologic, 2959-2960
chronic sinusitis in, 2778-2781
cultures for, 2779
etiology of, 2778-2779
imaging of, 2779
irrigation for, 2779
medical management of, 2779
surgical management of, 2779-2781, 2780f-2781f
cochlear implants in, 2224-2226, 2239-2240
audiologic protocol for, 2225, 2234-2235
auditory rehabilitation with, 2254-2255
current trends that affect, 2226
ear selection in, 2226
factors that affect performance in, 2226
and language development, 2239-2240
other evaluations for, 2225
outcome expectations for, 2225-2226
recommendations for referral for, 2226
residual hearing and, 2240
results of, 2246
auditory performance assessments for, 2246
early studies of speech reception in, 2246
for educational placement and support, 2251-2253, 2251f, 2255-2256
for language acquisition, 2249-2251, 2250f
more recent studies of speech reception in, 2246-2247, 2247f
quality-of-life studies for, 2252-2253, 2253f
selection criteria for, 2225-2226
surgical techniques for, 2240
conductive hearing loss in, 2026-2027
with congenital anomalies, 2573
dysphagia in, 2948-2955
anatomic site(s) of, 2949-2954, 2951f
hypopharynx and larynx as, 2950t, 2951-2953, 2953f
nose and nasopharynx as, 2949, 2950t, 2951f
oral cavity and oral pharynx as, 2949-2951, 2950t, 2952f
trachea and esophagus as, 2950t, 2953-2954, 2954f
evaluation of, 2948-2949
clinical or bedside, 2948-2949
instrumental, 2949, 2950t
other diagnostic tests in, 2949
epistaxis in, 686
facial fractures in, 2647, 2697-2717
anesthesia for, 304
associated injuries with, 2698
clinical and physical evaluation of, 2699
complex, 2698
dentoalveolar, 2706-2707, 2710f
emergency management of, 2698-2699
epidemiology of, 2697-2698
etiology of, 2698
facial growth and, 2698-2699
front sinus, 2711, 2712f
mandibular, 2704-2706
arch and body, 2706, 2709f
complications of, 2704
condylar and subcondylar, 2704, 2706f-2708f
epidemiology of, 2698
symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
mandibular immobilization for, 2701, 2701f
maxillomandibular fixation for, 2701
midface, 2707, 2710f
nasal, 2708-2711, 2711f-2712f
naso-orbitoethmoid, 2714
classification of, 2714, 2716f
evaluation of, 2714, 2716f
repair of, 2714, 2716f
open reduction with internal fixation for, 2701-2702
orbital, 2711-2714
evaluation of, 2712, 2713f
of lateral/medial orbital wall, 2712, 2714, 2716f
of orbital apex, 2712, 2713f
of orbital floor, 2712-2713, 2714f-2715f
of orbital roof, 2712-2713, 2716f
patterns of, 2711-2712
permanent *vs.* resorbable plating systems for, 2700-2701, 2700t-2701t

Children *(Continued)*
radiologic examination of, 2699
rigid fixation for, 2699-2700
sequencing of procedures for, 2702, 2704, 2706f
surgical approaches for, 2701-2704
bicoronal incision in, 2701-2702, 2703f
lateral cantholysis in, 2704f
maxillary gingivolabial sulcus approach in, 2701-2702, 2703f
midfacial degloving incision in, 2701-2702
subciliary incision in, 2705f
surgical approaches for, 2701-2704
transcaruncular approach in, 2701-2702, 2705f
surgical management of, 2648, 2649f, 2657
surgical reconstruction for, 2704-2714
zygomaticomalar complex, 2707-2708, 2710f
flexible endoscopy in, 2574
fluids and fluid management in, 2572
and expected fluid losses, 2572t
and fluid utilization during bed rest, 2572t
and ideal electrolyte composition for infants, 2572t
foreign bodies of airway and esophagus in, 2935-2943
acute airway obstruction due to, 2936-2937
complications of, 2942, 2942f
epidemiology of, 2936
esophageal perforation due to, 2941
imaging of, 2938-2939, 2938f-2939f
location of, 2936, 2936f-2937f
management of, 2939-2941
anesthesia for, 2940
controversies in, 2942
for disk batteries, 2941
equipment for, 2939-2940, 2939t, 2940f
historical background of, 2935-2936
for pills, 2941
postoperative, 2941-2942
for sharp objects, 2940-2941
technique for, 2940, 2941f
symptoms of, 2937-2938
general considerations with, 2569-2576
GERD-related laryngeal disease in, 2944-2947
diagnosis of, 2945
disorders due to, 2945-2946, 2945b
evidence of, 2946
history of, 2944
management of, 2946
physiopathology of, 2945
head and neck malignancies in, 2835-2849
vs. adults, 2835
age and, 2837, 2837t
clinical trials for, 2836
epidemiology of, 2835
histiocytoses as, 2847-2848, 2847t
lymphoma as
Hodgkin's, 2838-2840, 2840f
non-Hodgkin's, 2837, 2838t-2839t, 2839f
neuroectodermal, 2844-2845
neuroblastomas as, 2844-2845, 2844t, 2845f
peripheral primitive, 2845
pathologic evaluation of, 2836-2837, 2836f, 2837t
post-transplantation lymphoproliferative disorder as, 2840
risk factors for, 2835
salivary gland, 2845-2846, 2846f
sarcoma as, 2840-2843
dermatofibrosarcoma protuberans as, 2843, 2843f
epithelioid, 2843, 2843f
Ewing's, 2845
fibro-, 2842-2843, 2843f
nonrhabdomyosarcoma soft tissue, 2842
rhabdomyo-, 2840-2842, 2841t, 2842f
Children *(Continued)*
sequelae of management of, 2848
survival with, 2835-2836
teratomas as, 2846-2847
epidemiology of, 2846
histopathology and molecular biology of, 2847, 2847f
management of, 2846
presentation and evaluation of, 2846, 2846t
thyroglossal duct carcinomas as, 2847
tumorigenesis of, 2836
hearing aids in, 2274
bone-anchored, 2215
history taking with, 2573
hospital for, 2575
laryngeal stenosis in, 2912-2924
anterior glottic, 2922
anterior subglottic, 2923
due to atresia and webs, 2922
diagnosis of, 2916-2917
endoscopic examination in, 2916-2917
esophagogastroduodenoscopy and biopsy in, 2917
evaluation of GERD and GLPRD in, 2917
functional endoscopic evaluation of swallowing in, 2917
history and physical examination in, 2916
pulmonary function tests in, 2917
radiologic evaluation in, 2916
voice assessment in, 2917
etiology and pathophysiology of, 2912-2916
acquired, 2914-2915
congenital, 2912-2913, 2913f
grading of, 2917, 2917t
management of, 2917-2921
algorithm for, 2913f
anterior cricoid split operation for, 2918-2919, 2918f-2919f
autogenous costal cartilage reconstruction in, 2919-2920, 2920f-2921f
combined laryngofissure and posterior cricoid division for, 2919, 2919f
cricoid resection with thyrotracheal anastomosis for, 2921, 2922f
decannulation after, 2923
endoscopic, 2918
external expansion surgery for, 2919-2921
grafts in, 2919
postoperative, 2923
single-stage laryngotracheal reconstruction for, 2920-2921
stents in, 2920
posterior glottic, 2922-2923
prevention of, 2916
types of, 2915, 2915f-2916f
with vocal cord paralysis, 2922
laryngeal trauma in, 938
microscopic examination of ear in, 2574
nasal fractures in, 506-507
neck mass(es) in, 2812-2821
acquired, 2817-2819
bacterial lymphadenopathy as, 2818, 2818f-2819f
benign neoplasms as, 2819
drug-induced lymphadenopathy as, 2819
due to fungal infections, 2818-2819
in Kawasaki disease, 2819
malignant neoplasms as, 2819-2820, 2820f
in sarcoidosis, 2819
sialadenitis as, 2819
in sinus histiocytosis, 2819
viral lymphadenopathy as, 2817-2818
algorithm for differential diagnosis of, 2813f
biopsy of, 2814
congenital, 2814-2817
branchial cleft cysts as, 2814, 2814f-2815f
dermoid cysts as, 2816, 2816f-2817f
Children *(Continued)*
hemangiomas as, 2816, 2816f
laryngoceles as, 2816-2817
lymphatic malformations (lymphangiomas) as, 2815, 2817f
sternocleidomastoid tumors of infancy as, 2817, 2817f
teratomas as, 2816, 2816f
thymic cysts as, 2817
thyroglossal duct cysts as, 2814-2815, 2815f
vascular malformations as, 2817
history of, 2812
imaging of, 2813-2814
laboratory studies for, 2814
physical examination of, 2812-2813
needle biopsy in, 2574
obstructive sleep apnea in, 2602-2612
acute-onset or rapidly progressive, 2606
vs. adults, 2603, 2603t
anesthesia with, 2598, 2599b
complications of, 2603-2604
behavior and learning problems as, 2603-2604
cardiopulmonary, 2604, 2604f
growth impairment as, 2603
diagnosis of, 2606-2608
history in, 2606
other studies in, 2607-2608
physical examination in, 2606
polysomnography in, 2606-2607, 2607f, 2607t
epidemiology of, 2603
nonsurgical management of, 2610-2611
pathophysiology of, 2604-2605
polysomnography in, 2606-2607, 2607f, 2607t
indications for, 2608
risk factors for, 2605-2606, 2605t
craniofacial abnormalities as, 2605
mucopolysaccharidoses as, 2606
neuromuscular disease as, 2605-2606
obesity as, 2605
surgical management of, 2608-2610
craniofacial surgery in, 2610, 2610f
other pharyngeal surgery in, 2609-2610
other types of, 2610
tonsillectomy or adenoidectomy in, 2608-2609
tracheotomy in, 2610
olfactory testing in, 632-633
outcome scales for, 56t, 57
pain management in, 2572
paranasal sinus neoplasms in, 1132
parents of, 2573
as patients, 2573
pharyngitis in, 2782, 2783f-2784f
physical examination of, 2574
postoperative management of, 2575
preparation for hospitalization and surgery of, 2574-2575
primary snoring in, 2602-2603
referral sources for, 2572-2573
respiratory system of, 2569-2570
and control of ventilation, 2569-2570
and laryngospasm, 2570
and lung volumes, 2570
and respiratory rate, 2570
and ventilation-perfusion relationships, 2570, 2571t
rhinomanometry for, 645
rhinosinusitis in, 737
salivary gland disease in, 2850-2865
aberrant salivary glands as, 2864, 2864f
due to allergic reactions, 2864
anatomy and, 2850-2853
autoimmune, 2858-2863

Children *(Continued)*
benign lymphoepithelial, 2858
biopsy for, 2855
congenital, differential diagnosis of, 2851t
in cystic fibrosis, 2864
cysts and mucoceles as, 2859
acquired, 2859
congenital, 2859
differential diagnosis of, 2850, 2851t, 2852f-2853f
history and physical examination for, 2853
imaging of, 2854-2855
inflammatory, 2855-2858
abscess as, 2856
due to actinomycosis, 2858
bacterial, 2856-2857, 2856t
diagnostic algorithm for, 2853, 2854f
differential diagnosis of, 2851t
due to Epstein-Barr virus, 2855
granulomatous, 2857-2858, 2857f
due to HIV, 2856
due to mumps, 2855
mycobacterial, 2857-2858, 2857f
sarcoidosis as, 2858
viral, 2855
laboratory studies for, 2853-2854
due to medications, 2864-2865
necrotizing sialometaplasia as, 2857
neoplastic, 1192, 2861-2862, 2862t
benign, 2861-2862
differential diagnosis of, 2851t
malignant, 2862-2863
parotitis as, juvenile recurrent, 2858
sialadenitis as, 2819
acute suppurative, 2856, 2856t
bacterial, 2856-2857, 2856t
chronic, 2858
neonatal, 2857
recurrent, 2856-2857
viral, 2855
sialadenoscopy for, 2855
sialolithiasis as, 2858-2859
sialorrhea as, 2863-2864
in Sjögren's syndrome, 2858
in systemic conditions, 2864-2865
traumatic, 2863-2865
vascular anomalies as, 2859
hemangiomas as, 2859-2860, 2860f
lymphatic malformations as, 2860-2861, 2861f
sedation of, 2572, 2594
sleep-disordered breathing in, 2602-2612
and ADHD, 2791
cardiopulmonary complications of, 2792
classification of, 2602
and enuresis, 2792
and growth problems, 2792
and neurocognitive development, 2791-2792
primary snoring as, 2602-2603
upper airway resistance syndrome as, 2602-2603
stridulous (*See* Stridulous child)
thyroid neoplasms in, 1769-1770
tracheal stenosis in, 2925-2934
anomalies associated with, 2927
due to arterial compression, 2925-2926
classification of, 2927, 2927t
conservative management of, 2927-2928
diagnosis of, 2926-2927
dilation for, 2928, 2928f
embryology of, 2925-2926
endoscopic evaluation of, 2926-2927
imaging of, 2927
laser therapy for, 2928, 2929f
long-segment, 2926, 2926f
treatment of, 2934

Children *(Continued)*
open repair for, 2930-2934
complications of, 2934
costal cartilage tracheoplasty as, 2930-2931, 2931f
granulation at graft site with, 2931
long-segment, 2934
partial tracheal resection, posterior end-to-end anastomosis, and anterior repair with resected trachea in, 2933-2934
pericardial patch in, 2930, 2931f
segmental resection in, 2931-2932, 2932f
short-segment, 2934
slide tracheoplasty in, 2932-2933, 2933f
synthetic tracheal prostheses in, 2934, 2934f
tracheal homograft transplantation in, 2933, 2934f
wedge resection in, 2931, 2931f
short-segment, 2926, 2926f
treatment of, 2934
stents for, 2928-2930, 2930f
due to vascular rings, 2925
tympanoplasty in, 2005
upper airway resistance syndrome in, 2602-2603
voice disorder(s) in, 2876-2883
evaluation of, 2876-2878
aerodynamic analysis in, 2878
algorithm for, 2877f
computer-assisted voice analysis for, 2878, 2878f
history in, 2876
physical examination in, 2876-2877
for social and functional impact, 2876
speaking tasks in, 2877-2878
stroboscopic examination in, 2877
voice profile in, 2878
functional, 2876, 2879
incidence of, 2876
organic, 2876, 2879
of resonance, 2879
of vocal quality
due to cricoarytenoid joint fixation, 2880
due to epidermoid cysts, 2882, 2882f
due to granuloma, 2881, 2881f
due to laryngeal web, 2880, 2880f
due to malignant tumors, 2881
medical management of, 2881
due to posterior glottic stenosis, 2880
due to recurrent respiratory papillomatosis, 2880-2881
due to sulcus vocalis, 2882
surgical management of, 2879-2881
due to vocal fold paralysis, 2879-2880
due to vocal fold polyps, 2882
due to vocal nodules, 2881-2882, 2882f
voice therapy for, 2881-2882
voice therapy for, 2878-2879, 2881-2882
Chin
aesthetic analysis of, 275, 278f
double, liposuction for (*See* Liposuction)
senile ptosis of, 465, 466f
witch's, 465, 466f
Chin deformities
mentoplasty for (*See* Mentoplasty)
senile, 465, 466f
types of, 465, 466f
Chin implants, 465-467
anesthesia for, 465
clinical example of, 470, 471f
complications after, 470
dissection planes for, 465-467, 467f
incision and approach for, 465-467, 467f
intraoral approach for, 467
subperiosteal *vs.* supraperiosteal placement of, 465-467, 467f
surgical procedure for, 465-467
types of, 465, 465t, 467

CHIP-CE (Child Health and Illness Profile–Child Edition), 57
Chlamydia pneumoniae, pharyngitis due to, 194
Chlorbutol, for cerumen removal, 1958t
Chloride (Cl^-), in saliva, 1139
Chloride/bicarbonate (Cl^-/HCO_3^-) exchanger, in salivary gland secretion, 1135
Chloroma, 2107
Chloroquine
ototoxicity of, 2176
sensorineural hearing loss due to, 2120
Chlorpheniramine (Chlor-Trimeton), for nonallergic rhinitis, 701t
Choanal atresia, 2694-2695
bilateral, 2694-2695, 2694f-2695f
clinical presentation of, 2694
endoscopic evaluation of, 2694, 2695f
epidemiology of, 2694
imaging of, 2694, 2694f, 2905f
rhinitis due to, 619b
sinus surgery for, 742
treatment of, 2694-2695, 2695f, 2905
unilateral, 2694-2695, 2694f
Choanal stenosis, rhinitis due to, 619b
Choking, due to abnormal swallow, 1217
Cholesteatoma, 97
acquired, 1964-1965
diagnosis of, 1965, 1965f-1966f
otorrhea due to, 2196
pathogenesis of, 1966
anterior epitympanic, 1968, 1969f
of cerebellopontine angle, 2518-2519
diagnostic studies of, 2519
differential diagnosis of, 1929t, 2518t, 2519, 2524t
imaging of, 2519, 2520f-2521f
signs and symptoms of, 2518-2519
chronic otitis media with, 1964-1969
acquired, 1964-1966, 1965f-1966f
anterior epitympanic, 1968, 1969f
bone erosion in, 1971-1974, 1972f-1973f
complications of, 1968, 1969b
congenital, 1964-1966, 1966f
diagnosis of, 1965, 1965f-1966f
epidemiology of, 1965
management of, 1968-1969, 1969t, 1970b
pathogenesis of, 1965-1968, 1967f
posterior mesotympanic, 1968, 1968f
sensorineural hearing loss due to, 1974
chronic otitis media without, 1969-1971
diagnosis of, 1969, 1970f
management of, 1971
pathogenesis of, 1970-1971, 1971f, 1971t
congenital, 1964-1965
and congenital aural atresia, 2754
diagnosis of, 1965, 1966f
pathogenesis of, 1965-1966
of temporal bone, 2508-2509
diagnostic evaluation of, 2508, 2509f-2510f
surgical approach to, 2508-2509
defined, 1964-1965
diagnosis of, 1965, 1965f-1966f
of external auditory canal, 1949
imaging of, 1917, 1918f
labyrinthine fistula due to, 1989-1990, 1990f
mastoidectomy for, 1969, 1970t, 2014-2015
of middle ear, imaging of
acquired, 1919, 1920f
congenital, 1918-1919, 1919f-1920f
with CT, 174f, 1919f-1920f
with MRI, 1919, 1920f-1921f
pathogenesis of, 1965-1968, 1967f
acquired, 1966
basal cell hyperplasia theory of, 1966-1967, 1967f
congenital, 1965-1966
epithelial invasion theory of, 1967f, 1968

Cholesteatoma *(Continued)*
invagination theory of, 1966, 1967f
squamous metaplasia theory of, 1967f, 1968
of petrous apex, 1924t
drainage of, 2508
posterior mesotympanic, 1968, 1968f
properties of, 1968
retraction pocket, 1965-1966, 1965f, 1967f
of temporal bone
congenital, 2508-2509
diagnostic evaluation of, 2508, 2509f-2510f
surgical approach to, 2508-2509
traumatic, 2038, 2047
with tympanostomy tubes, 2775
Cholesterol, serum
and presbycusis, 232
subclinical hypothyroidism and, 1747
Cholesterol cysts, 2508, 2510f
Cholesterol granuloma
vs. cholesteatoma, 2508, 2510f
of petrous apex, 2524-2525
differential diagnosis of, 1924t, 2515, 2524t
imaging of, 1923, 1925f-1926f, 2477f, 2526f
of skull base, 171, 172f
transmastoid infralabyrinthine drainage of, 2540f
Cholestyramine
for Graves' disease, 1742-1743
for hyperthyroidism, 1739t
Choline salicylate and glycerol (Earex Plus, Audax), for cerumen removal, 1958t
Cholinergic receptors, in salivary gland secretion, 1136-1137
Chondritis, of external ear, 1946, 1948
Chondrocranium-basicranium, 2619
Chondrodermatitis nodularis helicis, 285, 285f
Chondroma
of larynx, 881-882
of trachea, 1612-1613
Chondrosarcoma(s)
of cerebellopontine angle, 2527, 2528f-2529f
of larynx, 1508
of neck, 1669-1670
of paranasal sinuses, 1131
of petrous apex, 2528f
of skull base, 1699, 1923-1924, 1926f, 2529f
Chorda tympani nerve
anatomy of, 1296f, 1297
in surgical anatomy of lateral skull base, 2436f, 2439f, 2441
in taste, 1208, 1211
Chorda tympani nerve damage, due to small fenestra stapedotomy, 2034
Chordoma(s)
of cerebellopontine angle, 2526-2527, 2527f-2528f
of clivus, 2481f, 2510, 2511f
cranial, 2510, 2511f
of nasopharynx, 1351
of petrous apex, 2511f
of skull base, 1699
Choristoma, salivary gland, of middle ear, 2200-2201
Choroid plexus, 2404f
in surgical anatomy of lateral skull base, 2439f
Choroid plexus papillomas, 2528-2529, 2530f
CHP. *See* Cricohyoidopexy (CHP).
CHQ (Child Health Questionnaire), 57
Chromosomal disorders, 4-5
aneuploidies as, 5
rearrangements as, 4-5
Chromosomal rearrangements, 4-5
Chromosome(s), 3
number of, 2088
segregation of, 2088
Chronic adenotonsillar hypertrophy, in children, 2790-2793
with ADHD, 2791
airway obstruction due to, 2789f-2790f, 2790-2793, 2795
algorithm for evaluation of, 2783f-2784f
cardiopulmonary complications of, 2792, 2792f
craniofacial growth and, 2792-2793
diagnostic assessment of, 2793-2794, 2793f
and enuresis, 2792
etiology of, 2789f-2790f, 2790
and growth problems, 2792
and neurocognitive development, 2791-2792
and obstructive sleep apnea, 2790-2793
Chronic obstructive pulmonary disease (COPD), oral manifestations of, 1250
Chronic otitis media (COM), 1981
bacteriology of, 1981
with cholesteatoma, 1964-1969
acquired, 1964-1966, 1965f-1966f
anterior epitympanic, 1968, 1969f
bone erosion in, 1971-1974, 1972f-1973f
complications of, 1968, 1969b
congenital, 1964-1966, 1966f
diagnosis of, 1965, 1965f-1966f
epidemiology of, 1965
management of, 1968-1969, 1969t, 1970b
pathogenesis of, 1965-1968, 1967f
posterior mesotympanic, 1968, 1968f
sensorineural hearing loss due to, 1974
without cholesteatoma, 1969-1971
diagnosis of, 1969, 1970f
management of, 1971
pathogenesis of, 1970-1971, 1971f, 1971t
complications of, 1981 (*See also* Temporal bone infections, complications of)
defined, 1981
perilymph fistula due to, 2342-2343
suppurative, cochlear implant for, 2221
with tympanostomy tubes, 1970-1971, 1981
Chronic rhinosinusitis (CRS)
acute exacerbation of, 705, 707, 707f
surgical management of, 741
bacterial, 732, 733f
defined, 705, 728-729
frontal, 775-783
fungal, 732-733
allergic, 707
invasive, 711
nonallergic, 715-716, 716t
pathogenesis of, 705-707, 706b, 706f, 742-743
radiologic appearance of, 673-674, 674f-675f, 743, 744t
surgical management of, 741, 760-761
Chronic Sinusitis Survey (CSS), 57
Chronic sniffer, 483-484
Chronic suppurative otitis media (CSOM), cochlear implant for, 2221
Churg-Strauss syndrome (CSS)
nasal manifestations of, 659
otorrhea due to, 2196
Chylothorax, due to neck surgery, 1733
Chylous fistula
due to neck dissection, 1723
due to neck surgery, 1732-1733, 1732f
CI(s). *See* Cochlear implant(s) (CIs).
CI (confidence interval), 65, 66t, 67
Ci (curie), 1031-1032
CIC hearing aid. *See* Completely-in-the-canal (CIC) hearing aid.
Cicatricial membranous stenosis, 951
Cicatricial pemphigoid
esophageal manifestations of, 980
nasal manifestations of, 660
ocular scarring (symblepharon) due to, 1233-1234, 1234f
oral, 1233-1235, 1254
Cicatricial pemphigoid *(Continued)*
clinical differential diagnosis of, 1234, 1234t
clinical features of, 1233-1234, 1233f-1234f
defined, 1233
etiology and pathogenesis of, 1233
histopathologic features of, 1234-1235, 1234f
treatment of, 1235
Ciclopirox olamine antifungal cream or solution (Loprox), for fungal otitis externa, 1954-1955, 1959t-1960t
Cidofovir, for recurrent respiratory papillomatosis, 879
intralesional, 879-880, 2890t, 2892
Cigarette smoking
exposure to, and otitis media, 2767
and Graves' ophthalmopathy, 1807
and skin flap survival, 1075
and squamous cell carcinoma
of head and neck, 1016
of larynx, 1491, 1512-1513
of oral cavity, 1293-1294, 1365
Ciliary dyskinesia, primary, nasal manifestations of, 661
Cimetidine (ranitidine), for recurrent respiratory papillomatosis, 2893
Cinchonism, 2176
Cineradiography
in neurologic evaluation, 835-836
of pharynx and esophagus, 1393
Ciprofloxacin, for rhinosinusitis, 734
Ciprofloxacin with dexamethasone (Ciprodex), for otitis externa, 1946, 1952, 1959t-1960t
Ciprofloxacin with hydrocortisone (Cipro HC Otic), for otitis externa, 1946, 1952, 1959t-1960t
Circadian rhythm sleep disorders, 263-264, 264b
Circulatory disorders, presbycusis due to, 232
Circulatory reflexes, larynx in, 809, 810f
Circumvallate papillae
anatomy of, 1295f, 1359f
taste buds in, 1208
Cirrhosis, oral manifestations of, 1255
CIS (carcinoma in situ)
of larynx, 1486-1491, 1489f-1490f, 1515
treatment of, 1489-1490, 1520-1521
oropharyngeal, 1361
CIS (continuous interleaved sampling), for cochlear implants, 2229-2230
13-*cis* retinoic acid (13-cRA, Accutane)
for cancer chemoprevention, 1018, 1061-1062
laryngeal, 1491
cis-acting elements, 4
Cisapride, for GERD, 970
Cisatracurium, for pediatric anesthesia maintenance, 2593t
Cisplatin
in combination chemotherapy, 1059-1060
for induction chemotherapy, 1052-1053, 1056-1058, 1058f
ototoxicity of, 2171-2173
clinical studies on, 2171-2172
delayed, 2171-2172
experimental studies on, 2172
genetic predisposition to, 2172
histopathology of, 2172
mechanics of, 2172-2173
pharmacokinetics of, 2171
risk factors for, 2172
vestibular, 2172
with radiotherapy, 1041-1042, 1053-1054
in RADPLAT regimen, 1054
for recurrent or metastatic disease, 1059
sensorineural hearing loss due to, 2120
Cisternography, for CSF rhinorrhea
computed tomography, 790, 790f
magnetic resonance, 790-791, 790f
overpressure radionuclide, 790

Citalopram, for neuropathic pain, 245
Civatte bodies, in lichen planus, 1228
CK (CyberKnife) stereotactic radiotherapy
  for laryngeal and hypopharyngeal cancer, 1592
  for malignant skull base tumors, 1696
c-Kit, in salivary gland neoplasms, 1199
Cl^- (chloride), in saliva, 1139
Clarin-1 *(CLRN1)* gene, in deafness, 2051t-2058t, 2077-2078
Clarinex (desloratadine), for nonallergic rhinitis, 701t
Clarithromycin
  for endocarditis prophylaxis, 1249t
  for pediatric surgery prophylaxis, 2597t
  for rhinosinusitis, 733, 734t
Claritin (loratadine)
  for allergic rhinitis, 620
  for nonallergic rhinitis, 701t
  for rhinosinusitis, 734t
Clark scale, for melanoma, 1111, 1113f
Classic scattering, 1032
Claudin-11 (Cldn11), in perilymphatic-endolymphatic barrier, 2081, 2082f
Claudin-11 *(Cldn11)* gene, in murine deafness, 2058t-2060t
Claudin-14 (Cldn14), in perilymphatic-endolymphatic barrier, 2081, 2082f
Claudin-14 *(CLDN14)* gene, in deafness, 2051t-2058t, 2081
Claudius' cells, 1832, 1832f
CLC (Charcot-Leyden crystal) protein, 604
CLCN7 gene, in osteopetrosis, 2112
Cleaning, for facial trauma, 304-305
Clearance, saliva for, 1141
Cleft lip, 2659-2675
  anatomy of, 2665-2666
    mucocutaneous junction in, 2665
    muscle abnormalities in
      bilateral, 2666, 2666f
      unilateral, 2665-2666, 2665f-2666f
    nasal deformities in
      bilateral, 2666
      unilateral, 2666, 2666f
    premaxillary bone deformity in, 2666, 2666f
  classification of, 2659, 2660f
  complete, 2659, 2660f
  dysphagia due to, 2950
  embryology of, 2659-2661, 2661f-2662f, 2661t
  epidemiology of, 2664
  incomplete, 2659, 2660f
  molecular genetics of, 2662-2664
  multidisciplinary team for, 2664, 2664b
  nursing care for, 2664-2665, 2665f
  prenatal diagnosis of, 2661-2662, 2663f
  protocol for care of, 2664, 2664t
  repair of, 2667-2668
    bilateral, 2668, 2669f
    definitive unilateral, 2667-2668, 2667f
      advancement flap in, 2668, 2668f
      closure in, 2668, 2668f
      rotation flap in, 2667-2668, 2668f
    primary rhinoplasty for, 2668
    timing of, 2667
  Simonart's band in, 2659, 2660f
Cleft lip nasal deformity, 2692
  anatomy of
    bilateral, 2666
    unilateral, 2666, 2666f
  pathogenesis of, 2690
  rhinoplasty for, 557-559, 561f, 2692
    Abbé flap in, 563f-564f
    with bilateral deformity, 557, 559, 561f, 563f-564f
    columellar lengthening in, 559, 566f
    external approach to, 559, 561f
    lateral ala thinning and placement of maxillary implants in, 562f
Cleft lip nasal deformity *(Continued)*
    Le Fort I maxillary osteotomies in, 559, 564f-565f
    with nasal stenosis, 559, 566f
    open approach to, 559, 562f
    repositioning and suturing of lower lateral cartilage in, 562f
    with severe deformity, 559, 564f-565f
    suturing together of medial crura in, 561f-562f
    with unilateral deformity, 557, 559, 561f-562f
Cleft palate, 2659-2675
  anatomy of, 2666-2667, 2667f
  classification of, 2659, 2660f-2661f
  complete, 2659, 2660f
  embryology of, 2659-2661, 2661t, 2662f-2663f
  epidemiology of, 2664
  incomplete, 2659, 2661f
  molecular genetics of, 2662-2664
  multidisciplinary team for, 2664, 2664b
  nursing care for, 2664-2665, 2665f
  and otitis media, 1872-1873, 1873f, 2674-2675, 2766
  palatoplasty for, 2668-2673
    basic principles of, 2670
    complications of, 2672-2673
    and facial growth, 2669
    Furlow (double-opposing Z-plasty), 2670
      surgical technique for, 2671-2672, 2672f
    goals of, 2668
    techniques of, 2669-2670
    timing of, 2668-2669
    two-flap, 2669-2670, 2670f
      surgical technique for, 2670-2671, 2670f-2671f
  prenatal diagnosis of, 2661-2662
  protocol for care of, 2664, 2664t
  in Robin sequence, 2673
  submucous, 2659, 2661f, 2674
    bifid uvula with, 2793, 2793f
  in velocardiofacial syndrome, 2673-2674, 2674f
Cleft palate feeders, 2665, 2665f
Cleft rhinoplasty, 2668
Cleidocranial dysplasia, 2641t
  parietal foramina with, 2641t
Clemastine (Tavist), for nonallergic rhinitis, 701t
Cl^-/HCO_3^- (chloride/bicarbonate) exchanger, in salivary gland secretion, 1135
Clic5, in stereocilia, 2076f
Clic5 (chloride intracellular channel 5) gene, in murine deafness, 2058t-2060t
Clicks, in auditory brainstem response testing, 1896-1897
  condensation and rarefaction, 1899-1901, 1900f
Clindamycin
  for endocarditis prophylaxis, 1249t
  for pediatric surgery prophylaxis, 2597t
  for rhinosinusitis, 734
Clinical Assessment of Musical Perception (CAMP), 57
Clinical importance, *vs.* statistical significance, 66-67
Clinical outcomes, measurement of, 55-56
Clinical practice guidelines, 70
Clinical target volume (CTV), for radiotherapy, 1044
Clinical Test of Sensory Integration and Balance (CTSIB), 2317
Clinical tumor volume (CTV), for radiotherapy, 1036
Clival tumors
  chordoma as, 2481f, 2510, 2511f
  surgical approaches for, 2509
Clivus
  anatomy of, 1823f
  approaches to, 2509
  radiographic anatomy of, 1399f
Clivus *(Continued)*
  in surgical anatomy of anterior skull base, 2474, 2474f
  in surgical anatomy of lateral skull base, 2435f
  transnasal endoscopic-assisted surgery of, 2479-2481, 2480f-2481f
Closed captioning, 2271
Closure pattern, laryngeal videostroboscopy of, 819, 820f, 848t, 849
Clothesline injury, laryngeal trauma due to, 2914
Clotrimazole (Lotrimin, Mycelex) cream, for fungal otitis externa, 1954-1955, 1959t-1960t
Clouston syndrome, deafness in, 2051t-2058t
Cloverleaf skull, due to craniosynostosis, 2645, 2645f
CLRN1 (clarin-1) gene, in deafness, 2051t-2058t, 2077-2078
Cluster headache, 247-248
CM(s) (cochlear microphonics)
  in electrocochleography, 1907-1908
  with neural hearing loss, 1899-1901, 1900f
CMAP (compound muscle action potential)
  for facial nerve injury, 2041, 2386
  for facial nerve monitoring, 2387
    after tumor removal, 2545
CME (continuing medical education), and performance measurement, 79, 79t
CMN (congenital melanocytic nevi), and melanoma, 1107-1108
CMS (Centers for Medicare and Medicaid Services), 84t-87t, 87
CMT, in deafness, 2051t-2058t
CMV. *See* Cytomegalovirus (CMV).
CNC (Consonant-Nucleus-Consonant) Monosyllable Word Test, for cochlear implants, 2223, 2244
CNPAS. *See* Congenital nasal pyriform aperture stenosis (CNPAS).
CNS (central nervous system) changes, in Bell's palsy, 2393-2394
CNS (central nervous system) infections, due to cranial base surgery, 2468
CNV (contingent negative variation), 632
CO_2. *See* Carbon dioxide (CO_2).
Coagulation disorders
  oral manifestations of, 1256
  oral treatment considerations for, 1246t
Coagulation factor C homology *(COCH)* gene, in deafness, 2051t-2058t
Coagulation screening, for adenotonsillectomy, 2794
Coal tar, for eczematoid otitis externa, 1956-1957
Coblation tonsillectomy, 2796
Cobra deformity, after rhytidectomy, 427
COC. *See* Calcifying odontogenic cyst (COC).
Cocaine, as adjunct to induction of anesthesia, 112
Coccidioidomycosis, laryngeal and tracheal manifestations of, 885, 893
COCH (coagulation factor C homology) gene, in deafness, 2051t-2058t
Cochlea
  anatomy of, 1825f, 1831-1834, 1840, 1841f, 2050, 2061f
    hair cells in, 1832-1834, 1833f
    innervation in, 1834, 1834f
    membranous labyrinth and inner ear fluids in, 1831-1832, 1832f
    osteology in, 1831, 1832f
  anomalies of (*See* Cochlear anomaly(ies))
  in auditory physiology, 1840, 1841f-1842f, 2050-2060
  electrochemical environment of, 1840, 1842f
  embryogenesis of, 1852
  imaging of, 1920-1921, 1922f
  incomplete partition of, 2730-2731
    embryogenesis of, 2728f-2729f, 2729t, 2730-2731

Cochlea *(Continued)*
histology of, 2730-2731, 2731f
imaging of, 2730-2731, 2731f
relative incidence of, 2729t
subtypes of, 2730-2731, 2731f
intratympanic delivery of medications to (*See* Intratympanic delivery)
ion transport within, 2081-2082, 2084f
otosclerosis of, 2029, 2030f
physical dimensions of, 2060, 2063f
sound propagation in, 1840-1842, 1842f
in surgical anatomy of lateral skull base, 2437f, 2438
"third window" of, 1842, 1843f
tonotopic map changes after long-term local excitation of, 1880-1881, 1883f
Cochlear agenesis, 2729f
Cochlear anomaly(ies), 2729-2732
cochlear agenesis as, 2729f
cochlear aplasia as, 2728f, 2729-2730, 2729t
cochlear hyperplasia as, 2732
cochlear hypoplasia as, 2730
embryogenesis of, 2728f-2729f, 2730
imaging of, 2730, 2730f
relative incidence of, 2729t
cochlear implantation for, 2739
in combination with other anomalies, 2728, 2738, 2739f
common cavity as, 2728f-2729f, 2729t, 2731-2732
in congenital aural atresia, 2738
embryogenesis of, 2728-2735, 2728f-2729f
incomplete partition as, 2730-2731
embryogenesis of, 2728f-2729f, 2729t, 2730-2731
histology of, 2730-2731, 2731f
imaging of, 2730-2731, 2731f
relative incidence of, 2729t
subtypes of, 2730-2731, 2731f
relative incidence of, 2729t
Cochlear apex, in cochlear transduction, 2061-2062, 2062f
Cochlear aplasia, 2728f, 2729-2730, 2729t
Cochlear aqueduct (CA)
anatomy of, 1822-1823, 1823f
enlargement of, 2734, 2734f
and CSF leakage, 2736
foramen of, 1824f
in surgical anatomy of lateral skull base, 2435f
Cochlear basal turn dysplasia, 2728
Cochlear canaliculus, 2010f
Cochlear conductive presbycusis, 232, 2126
Cochlear damage, in noise-induced hearing loss, 2141-2143, 2143f
Cochlear duct, anatomy of, 1851f, 1853f, 2061f
Cochlear dysplasia, 2235f
Cochlear echoes, 1891
Cochlear efferent system conditioning, for protection from noise-induced hearing loss, 2144
Cochlear hyperplasia, 2732
Cochlear hypoplasia, 2730
and CSF leakage, 2736f
embryogenesis of, 2728f-2729f, 2730
imaging of, 2730, 2730f
relative incidence of, 2729t
Cochlear implant(s) (CIs), 2204f
in adults, 2222-2224
audiologic protocol for, 2223
auditory rehabilitation with, 2254-2255
current trends that affect, 2224, 2224f
outcome expectations for, 2223
recommendations for referral for, 2224
results of, 2244-2245
with hearing preservation, 2245-2246
predictors of, 2245, 2245f
Cochlear implant(s) (CIs) *(Continued)*
quality-of-life studies for, 2251-2252, 2252f, 2252t
selection criteria for, 2222-2223
for asymmetric hearing loss, 2224
auditory evoked potentials with, 1912-1914, 1913f
for auditory neuropathy or dyssynchrony, 2220, 2240
auditory performance with
in adults, 2244-2245
with bilateral implantation, 2247-2251
in children, 2246
early studies of, 2246
measurement of, 2246
more recent studies of, 2246-2247, 2247f
factors related to measurement of, 2244-2247
with hearing preservation, 2245-2246
in infants, 2247
predictors of, 2245, 2245f
tests of, 2244
auditory rehabilitation after, 2253-2257
in adults, 2254-2255
in children, 2254-2255
efficacy of, 2253-2254
binaural (bilateral), 2241
for adults, 2224
for children, 2226
results of, 2247-2251
in children, 2224-2226, 2239-2240
audiologic protocol for, 2225, 2234-2235
auditory performance with, 2246
early studies of, 2246
measurement of, 2246
more recent studies of, 2246-2247, 2247f
auditory rehabilitation with, 2254-2255
binaural (bilateral), 2226
current trends that affect, 2226
ear selection for, 2226
education with, 2251-2253, 2251f, 2255-2257
factors that affect performance of, 2226
and language development, 2239-2240
other evaluations for, 2225
outcome expectations for, 2225-2226
recommendations for referral for, 2226
residual hearing and, 2240
results of, 2246
auditory performance assessments for, 2246
early studies of speech reception in, 2246
for educational placement and support, 2251-2253, 2251f, 2255-2256
for language acquisition, 2249-2251, 2250f
more recent studies of speech reception in, 2246-2247, 2247f
quality-of-life studies for, 2252-2253, 2253f
selection criteria for, 2225-2226, 2235b
surgical techniques for, 2240
with cochlear ossification, 2235f, 2240
with combined electrical and acoustic stimulation, 2224, 2224f
complications of, 2241
with compromised healing, 2241
for congenital inner ear anomalies, 2739
cost effectiveness of, 2251
defined, 2219-2220
device(s) for, 2227-2233
external speech processors for, 2229
size, weight, and aesthetics of, 2232, 2232f
factors that affect choice of, 2231-2233
batteries as, 2233
external speech processor size, weight, and aesthetics as, 2232, 2232f
MRI compatibility as, 2231-2232
need for special electrode arrays as, 2231
technology differences in speech coding strategy and electrode configuration as, 2231
Cochlear implant(s) (CIs) *(Continued)*
internal receiver stimulators and electrode designs in, 2227-2229
HiRes 90K receiver/stimulator as, 2227-2228, 2228f
Med-El PulsarCI100 and SonataTI100 as, 2228-2229, 2228f-2230f
Nucleus Freedom device with Contour Advance electrode as, 2227, 2227f-2228f
maintenance of, 2255
programming of, 2255
signal processing strategies in, 2229-2231
Advanced Combination Encoder for, 2230, 2231f
analog stimulation as, 2230, 2230f
continuous interleaved sampling as, 2229-2230
fine structure, 2230-2231, 2231f-2232f
spectral emphasis, 2230
spectral peak extraction as, 2230, 2230f
temporal, 2229-2230, 2230f
ear selection for, 2235-2236
algorithm for, 2236f
physical characteristics in, 2235-2236
residual hearing level in, 2236
and speech recognition, 2245, 2245f
general background of, 2219-2220
in infants, 2247, 2724
infectious complications of, 2161
for labyrinthine dysplasia, 2240-2241
and language development, 2239-2240, 2249-2251, 2250f
map for, 2255
meningitis vaccination with, 2236-2237, 2237b
for meningitis-induced deafness, 2240
for neural hearing loss, 1899-1901
and neural plasticity
in animal models of deafness, 1881
in infants with hearing loss, 1885, 1885f
in older adults, 233, 2234-2235
and quality of life, 2251-2252, 2252f, 2252t
with otitis media, 2240
patient evaluation for, 2220-2222, 2234-2235
with acquired deafness, 2220-2221
with auditory neuropathy/auditory dyssynchrony, 2220
with chronic suppurative otitis media, 2221
diagnostic therapy in, 2235
with genetic hearing loss, 2220
genetic testing in, 2235
hearing tests in, 2234-2235
imaging in, 2221-2222, 2222f, 2235, 2235f, 2236b
otologic/medical evaluation in, 2220-2222
physical examination in, 2221, 2234
and quality of life, 2251
in adults and elderly, 2251-2252, 2252f, 2252t
in children, 2252-2253, 2253f
with residual hearing
in adults, 2245-2246
in children, 2240
ear selection for, 2236
results of, 2244-2251
in adults, 2244-2245
with hearing preservation, 2245-2246
predictors of, 2245, 2245f
quality-of-life studies for, 2251-2252, 2252f, 2252t
bilateral, 2247-2251
in children, 2246
auditory performance assessments for, 2246
early studies of speech reception in, 2246
for educational placement and support, 2251-2253, 2251f, 2255-2256
for language acquisition, 2249-2251, 2250f

Cochlear implant(s) (CIs) *(Continued)*
more recent studies of speech reception in, 2246-2247, 2247f
quality-of-life studies for, 2252-2253, 2253f
factors related to measurement of, 2244-2247
in infants, 2247
tests for, 2244
revision, 2241
speech perception with, 2244-2245
predictors of, 2245, 2245f
surgical technique for, 2237-2241
bony seat in, 2238, 2239f
in children, 2240
cochleostomy in, 2239
electrode insertion in, 2239
incisions and flap design for, 2237-2238, 2237f-2238f
mastoidectomy in, 2238-2239
preparation and draping in, 2237
receiver stimulator in, 2239
skin flap in, 2238
for tinnitus, 2137
Cochlear lesions, reorganization of central tonotopic maps after, 1877-1878, 1878f-1879f
in adult subjects, 1878-1879, 1881f
in developmental model, 1878, 1880f
Cochlear malformations. *See* Cochlear anomaly(ies).
Cochlear mechanics
active, 2062-2069, 2064f-2065f
conversion of basilar membrane displacement to radial shearing forces in, 2065-2067, 2069f
outer hair cells in, 2063-2064, 2066f-2067f
prestin (SLC26A5) in, 2064-2065, 2068f
radial displacement patterns of basilar membrane in, 2067, 2069f
tectorial membrane pathophysiology and, 2067-2069
passive, 2050-2062, 2061f-2062f
physical dimensions in, 2060, 2063f
traveling wave in, 2060-2069, 2062f-2064f
Cochlear microphonics (CMs)
in electrocochleography, 1907-1908
with neural hearing loss, 1899-1901, 1900f
Cochlear modiolus, in surgical anatomy of lateral skull base, 2439
Cochlear nerve
anatomy of, 1832f, 1854f, 2278f
anomalies of, 2735
in central auditory pathway, 1834-1835
imaging of, 1928-1929, 1929f
intraoperative monitoring of, 2552
direct action potentials for, 2554, 2554f
and outcome, 2554-2555
in surgical anatomy of lateral skull base, 2437f, 2439
Cochlear nerve aplasia, auditory brainstem implants for, 2263-2264
Cochlear nucleus
in auditory physiology, 1845-1846, 1846f
in central auditory pathway, 1835, 1835f
Cochlear ossification, cochlear implant with, 2235f, 2240
Cochlear otosclerosis, imaging of, 1921-1922, 1925f
Cochlear partition
anatomy of, 1840, 2050, 2061f
in auditory physiology, 1840-1842, 1842f
Cochlear promontory, 1825-1826
Cochlear ramus, 1854, 1856f
Cochlear transduction, 2049-2085
active, 2062-2069, 2064f-2065f
conversion of basilar membrane displacement to radial shearing forces in, 2065-2067, 2069f
outer hair cells in, 2063-2064, 2066f-2067f
prestin (SLC26A5) in, 2064-2065, 2068f
Cochlear transduction *(Continued)*
radial displacement patterns of basilar membrane in, 2067, 2069f
tectorial membrane pathophysiology and, 2067-2069
traveling wave in, 2062-2069, 2064f
endolymph homeostasis in, 2081-2083, 2083f-2084f
genetic basis for, 2050, 2051t-2058t
in murine models, 2050, 2058t-2060t
hair cell transduction in, 2070-2081, 2070f
adaptation of mechanoelectrical transduction currents in, 2078-2079, 2079f
and auditory neuropathy, 2081
and defects in cytoskeletal proteins leading to deafness, 2074-2076, 2076f
defects in hair cell–afferent dendrite synapses and, 2080-2081, 2080f
defects of other hair cell channels and, 2079-2080
hair bundle deflections and receptor potentials in, 2069f, 2071, 2072f
myosin VI in, 2078
stereocilia in, 2070-2071
anatomy of, 2070-2071, 2070f, 2072f
composition of, 2074, 2075f-2076f
cross-linkages between, 2076f, 2077-2078
dynamic regulation of length of, 2076-2077
transduction channels in, 2071-2073
effects of deficiencies of, 2079-2080
gating of, 2073-2074
ion selectivity of, 2073, 2073f
structure of, 2076f
passive, 2050-2062, 2061f-2062f
physical dimensions in, 2060, 2063f
traveling wave in, 2060-2062, 2062f-2063f
perilymphatic-endolymphatic barrier in, 2081, 2082f
Cochleariform process, 1826f, 1827
Cochleosaccular dysplasia, 2727-2728
Cochleosacculotomy, for Meniere's disease, 2126, 2362-2363, 2363f
Cochleostomy, for cochlear implant, 2239
Cochleotopic map reorganization. *See* Tonotopic map reorganization.
Cochleovestibular nerve, 1834-1835
Cochleovestibular nerve injury, in lateral skull base surgery, 2512
Cochlin, in deafness, 2051t-2058t
Codeine, for postoperative pain, 241t
in children, 2594
Coding strand, 4
Codman, Ernest, 52
Codons, 4
Coefficient of determination, 64, 72
Cogan's syndrome, 2341
clinical manifestations of, 2341
etiology and pathogenesis of, 2341
historical background of, 2341
inner ear disease in, 2165
sensorineural hearing loss due to, 2123-2124, 2341
serologic tests for, 2327
treatment of, 2341
typical *vs.* atypical, 2341
Cognitive development, sleep-disordered breathing and, 2791-2792
Cognitive expertise, 79t
Cognitive impairment
obstructive sleep apnea and, 2603-2604
pain with, 240
Cognitive-behavioral therapy (CBT), for tinnitus, 2135
Coherent scattering, 1032
Cohort study, 54, 54t
Coiled terminations, 1201
Coiled-coil domain-containing protein 50/Ymer *(CCDC50)* gene, in deafness, 2051t-2058t
COL1A1
in deafness, 2051t-2058t
in osteogenesis imperfecta, 2109
COL1A2, in osteogenesis imperfecta, 2109
COL2A1, in deafness, 2051t-2058t, 2095
COL4A3, in deafness, 2051t-2058t
COL4A4, in deafness, 2051t-2058t
COL4A5, in deafness, 2051t-2058t, 2097
COL9A1, in deafness, 2051t-2058t, 2069
COL11A1, in deafness, 2051t-2058t, 2095
COL11A2, in deafness, 2051t-2058t, 2069, 2092, 2095
Cold
common, pharyngitis due to, 196
dry air provocation test, in nonallergic rhinitis, 696
Cold air–induced rhinitis, 619b
Cold receptors, in nasal obstruction, 641
Cold steel débridement, interventional bronchoscopy for, 1010t
Colectins, in middle ear protection, 1871
Colestipol, for hyperthyroidism, 1739t
Colitis, ulcerative, oral manifestations of, 1254
Collagen
in skin flaps, 1071
for vocal fold medialization, 905-906
Collagen vascular disease
oral manifestations of, 1251-1252
otologic manifestations of, 2114
vertigo due to, 2201
Collagenase, in bone resorption, 1972-1973
Collagenase-I, in wound healing, 1077
Collecting duct, of salivary gland, 1133-1134
Collision kerma, 1033
Colloid bodies, in lichen planus, 1228
Colloid thyroid nodules, ultrasound of, 1644, 1647f
Colonic transposition, for hypopharyngeal and esophageal reconstruction, 1453, 1454f
Colony-forming unit–basophil mast cell (CFU-BM), 605
Colony-forming unit–eosinophil (CFU-Eo), 604
Colony-forming unit–erythroid (CFU-E), 605
Colony-forming unit–granulocyte-macrophage (CFU-GM), 604
Colony-forming units–megakaryocytes (CFU-MEG), 605
Color Doppler sonography, 1644
of salivary glands, 1167-1168
Columella
anatomy of, 509f
surface defects of, 348
hinge flap for, 348, 350f
paramedian forehead flaps for, 348
Columella retraction, correction of, 547-548, 548f
Columellar lengthening, in cleft-lip nose repair, 559, 566f
Columellar strut
for noncaucasian nose, 560f
in revision rhinoplasty, 593, 593f
COM. *See* Chronic otitis media (COM).
Coma, myxedema, 1749
Combination chemotherapy, for recurrent or metastatic disease, 1059-1060
Combined-modality therapy, for head and neck squamous cell carcinoma, 1052-1058
with biologic agents plus radiotherapy, 1054, 1058f
concomitant chemoradiation as, 1052-1056, 1053t-1054t
as adjuvant therapy, 1056
induction chemotherapy in, 1041-1042, 1052-1053
induction chemotherapy in, 1056-1058, 1058f, 1058t-1059t
in concomitant chemoradiation, 1041-1042, 1052-1053
RADPLAT technique for, 1054

Combitube, 109-110, 110f, 114t
Comet-tail artifact, with colloid thyroid nodule, 1644, 1647f
Common canaliculus
  anatomy of, 798f
  in endoscopic dacryocystorhinostomy, 800-801, 801f
Common carotid artery
  anatomy of, 2579, 2579f-2580f
  in extended neck dissection, 1719-1720
Common carotid artery injury, due to penetrating neck trauma
  imaging of, 1632f
  management of, 1632
Common cavity, of inner ear, 2728f-2729f, 2729t, 2731-2732
Common chemical sense
  in olfactory stimulation, 628-629
  of oral cavity, 1202
Common cochlear artery, anatomy of, 1854, 1856f
Common cold, pharyngitis due to, 196
Comorbidity, 53
Comparative genomic hybridization (CGH), for head and neck squamous cell carcinoma, 1019
Complement system, in humoral immune response, 607-608, 608f
Complement system defects, 2114
  otologic manifestations of, 2114
Complementary DNA, 11-12, 12f
Complete strip technique, for nasal tip refinement, 522, 527f-530f
Complete transfixion incisions, for nasal tip projection, 535-536, 536f
Completely-in-the-canal (CIC) hearing aid, 2270, 2270f
  comparison of features of, 2206t
  evolution of, 2267
  in infants, 2723-2724
Complex calyx endings, of hair cells, 1857, 1859f
Complex traits, 8
Complex-motion tomography, of pharynx and esophagus, 1393
Composite grafts, for nasal reconstruction, 368-369, 369f
Composite turnout flap, for nasal defects, 348, 351f
Compound action potential (CAP)
  in Bell's palsy, 2394
  electrically evoked, 1912-1913
    with cochlear implants, 1913f, 1914
Compound melanocytoma, 287
Compound muscle action potential (CMAP)
  for facial nerve injury, 2041, 2386
  for facial nerve monitoring, 2387
    after tumor removal, 2545
Compound nevus, 286
Compound solution of iodine, for hyperthyroidism, 1739t
Compressed analog (CA), for cochlear implants, 2230
Compression, of dynamic range, with traditional hearing aid, 2205-2207
Compression circuitry, for hearing aids, 2268
Compton scattering, 1032f, 1033
Computational fluid dynamics (CFD), CT with, 643
Computed radiography, of pharynx and esophagus, 1393
Computed tomography (CT), 131
  of acoustic neuroma, 2517
  algorithms for, 131, 131f
  applications of, 139-142
  of cervical lymphadenopathy, 139
  combined with PET, 138
  with computational fluid dynamics, 643
Computed tomography (CT) *(Continued)*
  contrast-enhanced, 132, 132f-133f, 139
    of cervical lymphadenopathy, 164
      with extracapsular spread, 164-166, 167f
      inflammatory (reactive), 164
      with invasion of carotid artery, 166-167
      metastatic, 164-165, 167f
      with non-Hodgkin's lymphoma, 165-166, 167f
    of salivary glands
      with AIDS-related parotid cysts, 1146f
      with pleomorphic adenoma, 1144f
      with sialolithiasis, 1148f
  for CSF rhinorrhea, 791, 792f
  of deep neck space infections, 204, 204f-205f
  of facial trauma, 142
  of Graves' ophthalmopathy, 1809, 1811f
  helical
    of laryngeal carcinoma, 1470
    of pharynx and esophagus, 1396
  high-resolution
    for cochlear implant, 2222, 2222f
      with otosclerosis, 2222, 2222f
      in preoperative evaluation, 2235, 2235f, 2236b
    for CSF rhinorrhea, 791, 791f, 2044
    for dizziness, 2326-2327
    for malignant otitis externa, 1947
    of superior canal dehiscence syndrome, 2340-2341, 2340f
    for temporal bone fracture, 2039, 2040f
  for hyperparathyroidism, 1786-1787
  for hypopharyngeal and cervical esophageal cancer, 1424, 1424f
  image display for, 131-132
  with intensity-modulated radiotherapy, 1044
  of laryngeal carcinoma, 1468-1479, 1494
    early glottic, 1516-1517
  of laryngeal trauma, 935-936, 936f
  of larynx and infrahyoid neck, 132f, 140
  of lateral skull base lesions, 2489
  of maxillofacial trauma, 325-326
    of lower third, 325-326
    of middle third, 325, 326f
    of upper third, 325, 325f
  multidetector, 131, 139
  of nasopharyngeal carcinoma, 1354
  of neck masses, 1637, 1637t
  of neck neoplasms, 1656
  of obstructive sleep apnea, 255, 255f
  of oral cancer, 1300
  of oropharyngeal cancer, 1366
  of paranasal sinus tumors, 1124
  of paranasal sinuses, 140-142, 141f, 662-663
    radiation exposure with, 663
    with rhinosinusitis
      diagnostic, 140-142, 141f
      intraoperative, 744, 772
      preoperative, 743, 744t, 763-764, 764f-765f, 764t
      and surgical outcome, 729
    technique for, 662-663, 664f
  patient cooperation for, 132, 132f
  of petrous apicitis, 1986-1987, 1988f
  of pharynx and esophagus, 1396
  radiation exposure from, 132-133, 133t
  of salivary glands, 139, 1148, 1166, 1180
    with AIDS-related parotid cysts, 1146f
    with parotid lipoma, 1166, 1167f
    with pleomorphic adenoma, 1144f, 1148
    with sialadenitis, 1148
    for sialography, 139-140, 1145f
    with sialolithiasis, 1144f, 1148, 1148f
    with Sjögren's syndrome, 1148
    with Warthin's tumor, 1146f
  spiral (helical), of laryngeal carcinoma, 1470
  of suprahyoid neck, 139, 141f
Computed tomography (CT) *(Continued)*
  of temporal bone and skull base, 142
  3D, of laryngeal carcinoma, 1470
  three-dimensional reconstruction from, 138, 140f
  of thyroid and parathyroid glands, 140
  windows for, 131-132, 131f
  xenon blood flow mapping with, 2491
Computed tomography angiography (CTA)
  of anterior skull base, 2475, 2475f
  of neck masses, 1637, 1637t
Computed tomography (CT) cisternography, for CSF rhinorrhea, 790, 790f
Computed tomography–sestamibi (CT-MIBI) fusion, for hyperparathyroidism, 1785-1786, 1786f
  to localize ectopic glands, 1785-1786, 1787f-1788f
  in re-exploration, 1785-1786, 1788f
  to refine minimally invasive approach, 1785-1786, 1786f
Computer imaging
  in facial analysis, 277-280, 279f-280f
  for revision rhinoplasty, 581-582
  prior to rhinoplasty, 514
Computer-aided modeling, in mandibular reconstruction, 1326-1327, 1327f
Computer-assisted navigation, in endoscopic sinus surgery, 772
Computer-assisted voice analysis, for children, 2878, 2878f
Computerized dynamic posturography (CDP), 2324, 2325f
  motor control test in, 2324-2325
  sensory organization test in, 2325-2326, 2325f-2326f
  use of, 2326-2327
Concha, 477
  bullosa, 741
    endoscopic sinus surgery with, 751, 752f
    imaging of, 668, 669f
  cavum, 2742f
  cymba, 2742f
Conchal cartilage grafts, in noncaucasian rhinoplasty, 569
Conchal hypertrophy, 478-479
Conchal-mastoid sutures, 476f, 477-478
Concomitant chemoradiation, 1052-1056, 1053t-1054t
  as adjuvant therapy, 1056
  induction chemotherapy with, 1041-1042, 1052-1053
    with adjuvant therapy, 1056
Condensation and rarefaction clicks, in auditory brainstem response testing, 1899-1901, 1900f
Conditioning activities, in vestibular rehabilitation, 2372-2373, 2379
Conductive hearing loss, 2017-2027
  audiogram of, 1888, 1888f
  in children, 2026-2027, 2200-2201
  diagnostic evaluation of, 2019-2021
    acoustic immittance testing in, 2020
    acoustic reflex testing in, 2020
    history and physical examination in, 2022b
    pure-tone audiometry and speech testing in, 2020, 2020f
    Rinne test in, 2020, 2020t
    tympanometry for, 2020
    Weber test in, 2020
  due to external auditory canal conditions, 2021-2022, 2023f-2024f
  implantable devices for, 2027
  due to measles, 2158
  due to middle ear conditions, 2023-2026
  pathologic conditions leading to, 2018b
  specific lesions of conductive hearing pathway and, 2019, 2019t

Conductive hearing loss *(Continued)*
in superior semicircular canal syndrome, 2020-2021, 2021f
due to temporal bone trauma, 2046
treatment of, 2021-2026
for conditions of external auditory canal, 2021-2022, 2023f-2024f
for conditions of middle ear (*See* Ossiculoplasty)
for conditions of tympanic membrane, 2022-2023
due to tympanic membrane conditions, 2022-2023
Conductive hearing pathway
mechanical properties of, 2017-2019
specific lesions of, 2019, 2019t
Conductive presbycusis, 232, 2126
Condylar agenesis, 1280, 1281t
Condylar fractures, 1280, 1281t
pediatric, 2704, 2706f-2708f
Condylar hyperplasia, 1280, 1281t
Condylar hypoplasia, 1280, 1281t
Condylar process, of mandible, 1319, 1320f
Condylomata acuminata, maternal, and recurrent respiratory papillomatosis, 2886
Confidence interval (CI), 65, 66t, 67
Confounding, 53
vs. efficacy of treatment, 62t
Confusional arousals, 262t, 264
Congenital anomaly(ies)
children with, 2573
of inner ear, 2726-2740
classification of, 2726-2727, 2727b
cochlear, 2729-2732
cochlear agenesis as, 2729f
cochlear aplasia as, 2728f, 2729-2730, 2729t
cochlear aqueduct enlargement as, 2734, 2734f
cochlear hyperplasia as, 2732
cochlear hypoplasia as, 2728f-2730f, 2729t, 2730
cochlear implantation for, 2739
in combination with other anomalies, 2728, 2738, 2739f
common cavity as, 2728f-2729f, 2729t, 2731-2732
embryogenesis of, 2728-2735, 2728f-2729f
incomplete partition as, 2728f-2729f, 2729t, 2730-2731, 2731f
relative incidence of, 2729t
in congenital aural atresia, 2738
CSF leakage and meningitis due to, 2735-2737, 2736f
of eighth nerve, 2735
evaluation and management of, 2738-2739, 2739f
imaging of, 172-173, 174f, 1920-1921, 1923f, 2738
incidence of, 2727
of internal auditory canal, 2735
narrow, 2735, 2735f
wide, 2735, 2735f
labyrinthine, 2732-2733
in combination with other anomalies, 2728, 2738, 2739f
incidence of, 2727
limited to membranous labyrinth, 2727-2728, 2727b
of membranous and osseous labyrinth, 2727b, 2728-2735
semicircular canal aplasia as, 2732-2733, 2732f
semicircular canal dysplasia as, 2732, 2732f-2733f
membranous labyrinthine dysplasia as
complete, 2727
limited, 2727-2728
Congenital anomaly(ies) *(Continued)*
pathogenesis of, 2726
perilymphatic fistula as, 2737-2738, 2737f
syndrome correlations and familial patterns of, 2735
vestibular aqueduct enlargement as, 2727, 2733-2734, 2733f
X-linked stapes gusher syndrome as, 2737
of larynx, 2866-2875
bifid epiglottis as, 2870t, 2874, 2874f
hemangiomas and subglottic cysts as, 2871, 2871f
hypoplastic epiglottis as, 2870t
laryngeal cysts as, 2872-2873, 2872f-2873f
laryngeal webs/atresia as, 2869-2871
anterior, 2869-2870, 2869f-2870f
posterior, 2869, 2869f
subglottic stenosis as, 2870-2871
syndromes associated with, 2870t
laryngeal-laryngotracheoesophageal cleft as, 2873-2874, 2873f
classification of, 2873, 2874f, 2874t
syndromes associated with, 2870t
laryngomalacia as, 2866-2868, 2867f-2868f
syndromes associated with, 2870t
thyroglossal duct cyst as, 2871-2872, 2872f
vocal fold paralysis as, 2868-2869
of nose, 2686-2696
choanal atresia as, 2694-2695
bilateral, 2694-2695, 2694f-2695f
clinical presentation of, 2694
endoscopic evaluation of, 2694, 2695f
epidemiology of, 2694
imaging of, 2694, 2694f
treatment of, 2694-2695, 2695f
unilateral, 2694-2695, 2694f
cleft lip nasal deformity as, 2690, 2692
complete agenesis of nose (arhinia) as, 2690, 2691f
congenital nasal pyriform aperture stenosis as, 2692-2693
clinical presentation of, 2692-2693
diagnosis of, 2693, 2693f
operative management of, 2693, 2693f
pathogenesis of, 2690, 2692
craniofacial clefts as, 2690, 2692
dermal fistula as, 2687f
dermoids as
clinical presentation of, 2689, 2689f
defined, 2687f, 2688-2689
epidemiology of, 2688-2689
histology of, 2689
imaging of, 2689, 2689f
management of, 2689-2690
due to developmental errors of anterior neuropore, 2686-2690, 2687f
due to developmental errors of central midface, 2690-2693, 2691f
due to developmental errors of nasobuccal membrane, 2693-2695
encephaloceles as, 2687-2688
basal, 2687-2688, 2687t, 2688f
classification of, 2687-2688, 2687t
defined, 2687, 2687f
epidemiology of, 2687
vs. gliomas, 2688
histopathology of, 2688
imaging of, 2688, 2688f
management of, 2688
nasoethmoidal, 2687-2688, 2687t
nasofrontal, 2687-2688, 2687t
naso-orbital, 2687-2688, 2687t
sincipital, 2687-2688, 2687f, 2687t
sphenoethmoidal, 2687t
spheno-orbital, 2687t
terminology for, 2687
Congenital anomaly(ies) *(Continued)*
transethmoidal, 2687t
transsphenoidal, 2687t
gliomas as, 2687f, 2688
vs. encephaloceles, 2688
epidemiology of, 2688
extranasal, 2688
histology of, 2688
imaging of, 2688
intranasal, 2688
management of, 2688
intranasal hemangiomas as, 2695
maxillary mega-incisor with, 2690, 2691f
nasolacrimal duct cysts as, 2693, 2694f
nasopharyngeal teratomas as, 2695, 2696f
other mesodermal and germline malformations as, 2695
overview of, 2686
polyrhinia and supernumerary nostril as, 2690-2692
proboscis lateralis as, 2690, 2692, 2692f
of oral cavity, 1287-1288
developmental cysts as, 1287-1288
dermoid, 1287-1288
duplication, 1287-1288, 1288f
nasoalveolar, 1288, 1288f
lingual thyroid as, 1287
torus as, 1287, 1288f
oral manifestations of, 1257
of temporomandibular joint, 1280, 1281t
Congenital aural atresia (CAA), 2752-2760
bone-anchored hearing aid for, 2759
with cholesteatoma, 2754
classification of, 2753-2754, 2753b, 2753t
embryology of, 2753
epidemiology of, 2752-2753
imaging of, 1917, 1917f, 2754, 2754f
initial evaluation of, 2754
inner ear malformations in, 2738
with microtia, 2743
with poor pneumatization, 2754
reconstructive surgery for, 2754-2757
alternatives to, 2759
avoidance of complications of, 2758-2759
candidacy for, 2753, 2753t
contraindications to, 2754
creation of split-thickness skin graft in, 2756, 2756f
dissection of ossicular mass in, 2755-2756, 2756f
drilling for new ear canal in, 2755-2756
ear wick packing in, 2756-2757
facial nerve in, 2754, 2755f, 2759
harvesting of temporalis fascia in, 2755, 2755f
meatoplasty in, 2756-2757
outcomes of, 2754
placement of split-thickness skin graft in, 2756, 2757f-2758f
postauricular incision in, 2755, 2755f
postoperative care after, 2757-2758
preoperative evaluation and patient counseling for, 2754, 2754f-2755f
reconstruction of ossicular chain in, 2756
removal of atretic plate in, 2755-2756, 2755f
Silastic strips in, 2756-2757, 2758f
suturing in, 2756-2757, 2758f
temporal fascia graft in, 2755f, 2756, 2757f
timing of, 2754
Congenital craniofacial anomaly(ies)
in achondroplasia, 2633, 2634f
clinical manifestations of, 2642-2647
acrocephaly as, 2645, 2645f
brachycephaly as, 2644, 2645f
craniosynostosis as, 2642-2645, 2643f
encephalocele as, 2645, 2646f
facial clefts as, 2645
kleeblattschädel as, 2645, 2645f

Congenital craniofacial anomaly(ies) *(Continued)*
plagiocephaly as, 2643-2644, 2644f
scaphocephaly as, 2642, 2643f
syndromic, 2645-2647
trigonocephaly as, 2642-2643, 2643f, 2648f
in Down syndrome (trisomy 21), 2631-2633, 2631f, 2632b
due to abnormal and poor growth, 2633
of ears, 2632
of eyes, 2632-2633
mandibular and oral manifestations of, 2632
of midface, 2632
of skull, 2632
pathophysiology of, 2640-2642
intrauterine causes in, 2640
metabolic disorders in, 2640
molecular genetics in, 2640, 2641t, 2642f
in Robin sequence (Pierre Robin syndrome), 2630-2631, 2630f
surgical management of, 2649-2657
coronal incision in, 2650, 2650f
distraction osteogenesis in, 2654-2657, 2656f
fronto-orbital advancement in, 2650-2653, 2651f-2654f
monobloc advancement in, 2653-2654, 2655f-2656f
for orbital hypertelorism and dystopia, 2654
for sagittal synostosis, 2650, 2650f-2651f
syndromic, 2645-2647
in Apert's syndrome, 2645-2646
in Carpenter's syndrome, 2646
in Crouzon's syndrome, 2641t, 2645
in facio-oculo-auriculo-vertebral spectrum, 2646-2647
in Jackson-Weiss syndrome, 2646
in mandibulofacial dysostosis (Treacher Collins syndrome, Franceschetti syndrome), 2633-2635, 2633b, 2635f, 2646
in Pfeiffer's syndrome, 2641t, 2646
in Saethre-Chotzen syndrome, 2641t, 2646
in Stickler's syndrome, 2646
in velocardiofacial syndrome, 2646
Congenital epulis, of oral cavity, 1290, 1290f
Congenital hearing loss
epidemiology of, 2086
etiology of, 2200, 2200b
evaluation of, 2097-2099
genetic basis for, 2050, 2051t-2058t
in murine model, 2050, 2058t-2060t
due to labyrinthine infections, 2154-2157
with cytomegalovirus, 2154-2156, 2155f
with rubella, 2154, 2156-2157, 2157f
with syphilis, 2161
Congenital heart disease, pediatric anesthesia with, 2596-2597, 2596t-2597t
Congenital hemangioma, 2824, 2825f
Congenital high airway obstruction syndrome (CHAOS), 2869, 2870f, 2904-2905
Congenital hypomyelinating neuropathy, deafness in, 2051t-2058t
Congenital hypothalamic hamartoblastoma syndrome, 2874
Congenital immunodeficiencies, 209-210, 210t
Congenital labyrinthine abnormalities, CSF otorrhea due to, 2197
Congenital laryngeal cysts, 1468, 2872-2873, 2872f-2873f
Congenital laryngeal stenosis
diagnosis of, 2916-2917
etiology and pathophysiology of, 2912-2913, 2913f
management of, 2922
Congenital lesions
of external auditory canal, imaging of, 1917, 1917f
of oral cavity, 154-156
of sublingual space, 156
of submandibular space, 156-157, 158f
Congenital melanocytic nevi (CMN), and melanoma, 1107-1108
Congenital nasal pyriform aperture stenosis (CNPAS), 2692-2693
clinical presentation of, 2692-2693
diagnosis of, 2693, 2693f
operative management of, 2693, 2693f
pathogenesis of, 2690, 2692
Congenital neck mass(es), 1638-1640, 2814-2817
branchial cleft anomalies as, 1639, 2814, 2814f-2815f
dermoid cysts as, 1639, 2816, 2816f-2817f
hemangiomas as, 1640, 2816, 2816f
laryngoceles as, 2816-2817
lymphangiomas as, 1640, 2815, 2815f
sternocleidomastoid tumors of infancy as, 2817, 2817f
teratomas as, 1639-1640, 2816, 2816f
thymic cysts as, 2817
thyroglossal duct cysts as, 1639, 2814-2815, 2815f
vascular malformations as, 2817
Congenital nevi, 287-288
melanocytic, and melanoma, 1107-1108
Congenital salivary gland cysts, 2859
Congenital torticollis, 2817, 2817f
Congenital vascular lesions, of salivary glands, 1172
arteriovenous malformations as, 1172
hemangiomas as, 1172
lymphatic malformations as, 1172
venous malformations as, 1172
Congestion factor, 645
Conjoint tendon, in brow or forehead rejuvenation, 433-434
Conjunctiva, 443f, 444
Conjunctival fornix, 444
Connective tissue diseases, esophageal manifestations of, 978-979, 979f
imaging of, 1400-1401, 1401f
Connective tissue growth factor (CTGF), in formation of granulation tissue, 1077
Connexin(s) (Cx), in endolymph homeostasis, 2083, 2083f
Connexin 26 *(Cx26)* gene
in deafness, 2051t-2058t, 2083
infant screening for, 2723
Connexin 30 *(Cx30)* gene, in deafness, 2051t-2058t, 2083
Connexin 31 *(Cx31),* in deafness, 2051t-2058t
Connexin 32 *(Cx32)* gene, in deafness, 2051t-2058t
Conn's syndrome, preoperative evaluation of, 104-105
Consanguinity, 6
Conscious sedation
for awake fiberoptic nasotracheal intubation, 124
for tracheobronchial endoscopy, 1000
Consecutive sample, 68, 69t
Consensus Auditory Perceptual Evaluation for Voice (CAPE-V), 819, 826
Consent, informed, 102
Conservation laryngeal surgery, 1539-1562
anatomy and physiology and, 1541-1544
anterior commissure tendon in, 1541-1542
cartilage in, 1541
connective tissue barriers in, 1542-1543, 1544f
conus elasticus in, 1541-1542, 1542f
cricothyroid ligament in, 1541-1542
epiglottis in, 1541
hyoid bone in, 1541
hypoepiglottic ligament in, 1541-1542
paraglottic space in, 1542, 1543f
preepiglottic space in, 1542, 1543f
quadrangular membrane in, 1541-1542, 1542f
skeletal structure in, 1541, 1541f
thyrohyoid membrane in, 1541-1542, 1542f
vocal tendon in, 1541-1542
Conservation laryngeal surgery *(Continued)*
current paradigm for, 1558-1559
current state of, 1540-1541
future developments in, 1560-1561
for glottic tumors, 1496, 1547-1549
epiglottic laryngoplasty as, 1549
complications of, 1549
extended procedures for, 1549
functional outcome of, 1549
key surgical points for, 1549
oncologic results of, 1549
surgical technique for, 1549, 1549f
horizontal partial laryngectomies as, 1549
spectrum of, 1557-1560
supracricoid partial laryngectomy with cricohyoidoepiglottopexy, 1549-1550
complications of, 1551
extended procedures for, 1551
functional outcome of, 1551, 1551t-1552t
key surgical points for, 1550-1551
oncologic results of, 1549-1550
surgical technique for, 1550, 1550f-1551f
vertical hemilaryngectomy as, 1547-1549
complications of, 1549
extended, 1548
frontolateral, 1548
functional outcome of, 1548
with imbrication laryngoplasty, 1548, 1548f
key surgical points for, 1549
oncologic results of, 1547-1548, 1547t-1548t
posterolateral, 1548
surgical technique for, 1548
vertical partial laryngectomies for, 1547
history of, 1540
indications for and contraindications to, 1546-1547
intraoperative conversion to total laryngectomy from, 1557-1558
postoperative management issues with, 1560
preoperative evaluation for, 1544-1546
clinical evaluation of primary site in, 1544-1545, 1545f
overall clinical assessment in, 1546
radiologic evaluation of primary site in, 1545-1546
T stage in, 1546
principles of, 1544
and radiotherapy, 1559-1560
spectrum of, 1557-1560, 1558f-1559f
for supraglottic tumors, 1551-1552, 1552t
horizontal partial laryngectomies as, 1553-1554
spectrum of, 1557-1560
supracricoid laryngectomy with cricohyoidopexy as, 1555-1557
complications of, 1557
functional outcome of, 1556-1557, 1557t
key surgical points for, 1556
oncologic results of, 1555
surgical technique for, 1555-1556, 1556f
supraglottic laryngectomy as, 1553-1554
with arytenoid, aryepiglottic fold, or superior medial pyriform involvement, 1554-1555
with base of tongue extension, 1555
complications of, 1555
extended procedures for, 1554
functional outcome of, 1555
key surgical points for, 1554-1555, 1554f
oncologic results of, 1553, 1553t
surgical technique for, 1553-1554, 1554f
Conservative management
of CSF rhinorrhea, 791-792, 792b
of facial nerve injury, 2040, 2042
of laryngeal trauma, 936
of tracheal stenosis, 2927-2928
Consonant-Nucleus-Consonant (CNC) Monosyllable Word Test, for cochlear implants, 2223, 2244

Consumer Assessment of Health Providers and Services (CAHPS), 82, 84t-87t
Contact dermatitis, otitis externa due to, 1945-1946
Contact guidance, in cholesteatoma formation, 1968
Contact inhibition, in cholesteatoma formation, 1968
Contact ulcer or granuloma, of vocal folds, 874-875, 874f
  diagnosis of, 875
    history in, 875
    laryngeal examination in, 875, 875f
    vocal capability battery in, 875
  epidemiology of, 874
  due to extraesophageal reflux, 902, 902f-903f
  management of, 875
  pathophysiology and pathology of, 874
Contingency tables, 71-72
Contingent negative variation (CNV), 632
Continuing medical education (CME), and performance measurement, 79, 79t
Continuous interleaved sampling (CIS), for cochlear implants, 2229-2230
Continuous positive airway pressure (CPAP), for obstructive sleep apnea, 256-257
  in children, 2610-2611
Continuous wave lasers, 33
Contour Advance electrode, 2227, 2227f-2228f
Contour Emboli (polyvinyl alcohol), for embolization, 1933
Contour irregularities
  after liposuction, 459
  after rhytidectomy, 427
Contrast enhancement, for MRI, 134-135, 135f-136f
Contrast-enhanced computed tomography (CECT), 132, 132f-133f, 139
  of cervical lymphadenopathy, 164
    with extracapsular spread, 164-166, 167f
    inflammatory (reactive), 164
    with invasion of carotid artery, 166-167
    metastatic, 164-165, 167f
    with non-Hodgkin's lymphoma, 165-166, 167f
  of salivary glands
    with AIDS-related parotid cysts, 1146f
    with pleomorphic adenoma, 1144f
    with sialolithiasis, 1148f
Control groups, 53
  and data interpretation, 59-61, 60t
Conus elasticus
  in mucosal wave propagation, 848-849
  surgical anatomy of, 1541-1542, 1542f-1544f
Convective flow, across interstitial space, 1066
Convenience sample, 68, 69t
Conventional radiography (CR), 130-131
  of deep neck space infections, 204-205
  of facial bones, 130
  of neck, 131
  of neck masses, 1637, 1637t
  of paranasal sinuses, 130, 662
    Caldwell view in, 662, 663f
    with rhinosinusitis, 729, 729f
    Waters view in, 662, 663f
  of pharynx and esophagus, 1393, 1394f
  radiation exposure from, 132-133, 133t
  for sialography, 139-140, 1149-1150, 1149f, 1155-1156, 1156f
  of temporal bone, 131
Convergence spasm, 2314
COPD (chronic obstructive pulmonary disease), oral manifestations of, 1250
Cor pulmonale
  due to obstructive sleep apnea, 2604, 2604f
  sleep-disordered breathing and, 2792, 2792f
Cordarone (amiodarone)
  dizziness due to, 2310t
  thyrotoxicosis due to, 1744
Cordectomy, for glottic cancer, 1496, 1517t, 1519t
Core competencies, 80, 80b
Core-needle biopsy, of lymphoma, 1676
Coring out, of tracheal tumor, 1619-1621
"Corkscrew" esophagus, 965, 966f
Cornea, in Graves' ophthalmopathy, 1808, 1809t
Corneal protection, for eyelid trauma, 303, 303f, 308
Corniculate cartilage, 1542f
Corniculate tubercle, 1422f, 1543f
Coronal forehead lift, 430, 431t
Coronal incision
  for craniofacial anomalies, 2650, 2650f
  for pediatric facial fracture, 2701-2702, 2703f
Coronal synostosis
  bilateral, 2644, 2645f
  front-orbital advancement for, 2652-2653, 2653f-2654f
  unilateral, 2643-2644, 2644f, 2648f
Coronavirus, pharyngitis due to, 196
Coronoid process, 1319, 1320f
  osteochondroma of, *vs.* myofascial pain dysfunction syndrome, 1285t
Corpuscular radiation, 1031
Correlation coefficient, 64, 64t, 67
Corrugated esophagitis, 967-968, 969f
Corrugator supercilii muscle
  anatomy of, 321f, 441-442, 442f
  contraction of, 442, 442f
Cortical lesions, laryngologic manifestations of, 837-838, 838t
Cortical tonotopic map reorganization
  age-related, 1877, 1879, 1882f
  experimental studies of
    after cochlear lesions, 1877-1878, 1878f-1879f
      in adult subjects, 1878-1879, 1881f
      in developmental model, 1878, 1880f
    after long-term local excitation of cochlea, 1880-1881, 1883f
  mechanisms of
    at cellular level, 1884
      Hebb's postulate for, 1884, 1884f
      long-term potentiation as, 1884
    at systems level
      in adult subjects, 1883-1884
      in developing subject, 1883
  practical issues relating to, 1884-1886
    for hearing loss in infants, 1885, 1885f
    for other hearing disorders, 1885-1886
  time course of, 1877
Corticosporin Otic Solution (polymyxin, neomycin, and hydrocortisone), for otitis externa, 1946, 1952, 1959t-1960t
Corticosteroids
  for acute otitis media, 2770-2771
  for autoimmune inner ear disease, 2166-2167
  for Bell's palsy, 2395, 2409-2410, 2410t
  prior to biopsy of lymphoma, 1676
  for caustic ingestion, 2959
  for croup, 2805-2806
  for facial nerve injury, 2042
  for Graves' ophthalmopathy, 1811
  for hemangioma of infancy, 2826-2828
  for herpes zoster, 2396
  intralesional, for tracheal stenosis, 2928
  intranasal
    for allergic rhinitis, 621
    for nonallergic rhinitis, 700, 700t
    for sinus surgery, 773
  intratympanic, 2183-2185
    dosing of, 2185
    indications for, 2183
    mechanism of action of, 2183
    for Meniere's disease, 2184
Corticosteroids *(Continued)*
    pharmacokinetics of, 2183-2184
    side effects of, 2185
    for sudden sensorineural hearing loss, 2184-2185
  for laryngeal stenosis, 2918
  for obstructive sleep apnea, 2611
  oral sequelae of, 1247t-1248t
  oral treatment considerations with, 1246t
  for otitis media with effusion, 2772
  ototopical
    classes of, 1956, 1956t
    for eczematoid otitis externa, 1955-1956
    hypersensitivity reaction to, 1954
    mechanism of action of, 1951
    ototoxicity of, 1956
  for professional voice disorders, 854, 854b
  for rhinosinusitis
    systemic, 734t, 736
    topical nasal, 734t, 736
  for sarcoidosis, 659
  for scar revision, 299-300, 301f
  for stridulous child, 2906
  for sudden sensorineural hearing loss, 2157
  systemic
    for allergic rhinitis, 621
    for inner ear disorders, 2184
  for tracheal stenosis, 2928
Corynebacterium diphtheriae, pharyngitis due to, 195-196
  in children, 2786-2787
Cosmetic effects, of radiotherapy, 2626t
Cosmetics, for scar camouflage, 301
Cost effectiveness, of cochlear implants, 2251
Costal cartilage grafts
  for laryngeal stenosis, 2919-2920, 2920f
  for noncaucasian rhinoplasty, 569, 570f
    harvesting of, 570, 571f
    results of, 568
  for revision rhinoplasty, 583, 584f
Costal cartilage tracheoplasty, 2930-2931, 2931f
Costocervical trunk, 2581-2582, 2581f
Cost-utility ratio, of cochlear implants, 2251, 2252t
Cottle elevator, for septoplasty, 488-490, 489f
Cottle maneuver, 484, 484f
Cotton-Myers classification, of airway stenosis, 944, 944t
Cough
  due to abnormal swallow, 1217
  due to GERD, 971
  larynx in, 808
  whooping, laryngeal and tracheal manifestations of, 892
Cover-body theory, of vocal fold vibration, 845, 845f
Cowden's disease, oral manifestations of, 1257
COX. *See* Cyclooxygenase (COX).
Coxsackievirus, herpangina due to, 2785, 2786f
CPA. *See* Cerebellopontine angle (CPA).
CPAP (continuous positive airway pressure), for obstructive sleep apnea, 256-257
  in children, 2610-2611
CpG island hypermethylation, in head and neck squamous cell carcinoma, 1020, 1021f
CPIR (cephalic phase insulin release), 1206
CPP (cepstral peak prominence), in acoustic analysis, for voice evaluation, 829t, 830
CR. *See* Conventional radiography (CR).
13-cRA (13-*cis* retinoic acid)
  for cancer chemoprevention, 1018, 1061-1062
    laryngeal, 1491
Cranial base
  anatomy of, 171
  anterior (*See* Anterior cranial base)
  classification of lesions of, 171
  growth and development of, 2617-2619, 2617t, 2619f-2620f

Cranial base *(Continued)*
imaging of, 171, 1929-1930
with benign lesions, 171, 172f
CT for, 142, 171
prior to endoscopic sinus surgery, 764t
with fractures, 171
with inflammatory lesions, 171
with intracerebral neoplastic processes, 171, 174f
with meningiomas, 1929-1930, 1930f
with metastases, 171, 173f
MRI for, 143, 171
normal anatomy in, 171
with paragangliomas, 171, 174f, 1929, 1930f
lateral (*See* Lateral cranial base)
middle (*See* Middle cranial base)
Cranial base defects
endoscopic endonasal techniques for, 763
localization of, for CSF rhinorrhea, 791, 791f
Cranial base disruption, 334-339
Cranial base irradiation, for malignant tumors, 1695-1700
anterior, 1697-1699
with chemotherapy, 1700
chordoma/chondrosarcoma as, 1699
complications after, 1700
CyberKnife, 1696
esthesioneuroblastoma as, 1697-1698, 1698f, 1698t
intensity-modulated, 1696-1697
middle, 1699-1700
nasopharyngeal carcinoma as, 1699-1700, 1699f, 1700t
proton beam, 1696
sinonasal undifferentiated carcinoma as, 1698-1699
stereotactic, 1696, 1700
Cranial base surgery, robotic, 42, 43f-44f
Cranial base tumor(s)
benign, 2446, 2447b
in children, 2647, 2647f
surgical management of, 2657
malignant, 1697-1700
anterior, 1697-1699, 2446, 2447b
esthesioneuroblastoma as, 1697-1698, 1698f, 1698t
sinonasal undifferentiated carcinoma as, 1698-1699
chondrosarcoma as, 1923-1924, 1926f, 2540f
esthesioneuroblastoma as, 1697-1698, 1698f, 1698t
middle, 1699-1700
chordoma/chondrosarcoma as, 1699
nasopharyngeal carcinoma as, 1699-1700, 1699f, 1700t
sinonasal undifferentiated carcinoma as, 1698-1699
preoperative planning for, 2446-2447
Cranial chordomas, 2510, 2511f
Cranial length, 2617t
Cranial nerve I. *See* Olfactory nerve.
Cranial nerve II. *See* Optic nerve.
Cranial nerve III. *See* Oculomotor nerve.
Cranial nerve IV. *See* Trochlear nerve.
Cranial nerve V. *See* Trigeminal nerve.
Cranial nerve VI. *See* Abducens nerve.
Cranial nerve VII. *See* Facial nerve.
Cranial nerve VIII. *See* Cochlear nerve; Vestibular nerve; Vestibulocochlear nerve.
Cranial nerve IX. *See* Glossopharyngeal nerve.
Cranial nerve X. *See* Vagus nerve.
Cranial nerve XI. *See* Spinal accessory nerve.
Cranial nerve XII. *See* Hypoglossal nerve.
Cranial nerve deficits
due to carotid paraganglioma surgery, 1660-1661
due to cranial base surgery, 2469
HIV-associated, 223
Cranial nerve deficits *(Continued)*
after lateral skull base surgery, 2512
due to nasopharyngeal carcinoma, 1353
due to paranasal sinus tumor, 1123-1124
due to penetrating neck trauma, 1629
due to sphenoidotomy, 768t
Cranial nerve monitoring, 2542-2556
anesthesia and, 2544
auditory brainstem response recording for, 2552-2554
interpretation of, 2553-2554, 2553f
and postoperative auditory function, 2553-2554
reducing electrical and acoustic interference in, 2552-2553
stimulus and recording parameters, electrodes, and placement in, 2552
of cochlear nerve, 2552
direct eighth nerve action potentials for, 2554
detection and interpretation of changes in, 2554
placement of electrodes in, 2554
stimulus and recording parameters in, 2554
of facial nerve, 2545-2549
with acoustic neuroma and other cerebellopontine angle tumors, 2545
activity evoked by electrical stimulation in, 2545-2546
for assessment of functional status after tumor removal, 2545-2546
electromyography for, 2545-2548
for intraoperative identification of nervus intermedius, 2546, 2546f
limitations of, 2547-2548, 2548f
during microvascular decompression, 2548-2549, 2549f
during other otologic surgery, 2549
during parotid surgery, 2549
spontaneous and mechanically evoked activity in, 2546-2548, 2547f
future directions in, 2555-2556, 2555f
instrumentation for, 2543
ninth, tenth, eleventh, and twelfth, 2550-2552, 2551f-2552f
and outcome, 2554-2555
for cochlear nerve preservation, 2554-2555
for facial and other motor cranial nerve preservation, 2554
personnel for, 2542-2543
recording electrodes for, 2543-2544, 2543f
stimulating electrodes for, 2544, 2544f
stimulation criteria for, 2544
third, fourth, and sixth, 2549-2550, 2550f
of trigeminal motor branch, 2550
Cranial width, 2617t
Cranialization, of frontal sinus, 782, 783f
Craniocervical junction, osteoma of, 2484f
Craniocervical junction–odontoid approach, for transnasal endoscopic-assisted anterior skull base surgery, 2483-2484, 2484f
Craniofacial anomaly(ies), 2630-2636, 2638-2658
acquired
due to neoplasm, 2647, 2647f
surgical management of, 2657
due to postnatal conditions, 2640-2642
due to trauma, 2647
surgical management of, 2648, 2649f, 2657
classification of, 2638
clinical manifestations of, 2642-2647
congenital, 2642-2647
acrocephaly as, 2645, 2645f
brachycephaly as, 2643f, 2644, 2645f
craniosynostosis as, 2642-2645, 2643f
encephalocele as, 2645, 2646f
facial clefts as, 2645
kleeblattschädel as, 2645, 2645f
plagiocephaly as, 2643-2644, 2643f-2644f
Craniofacial anomaly(ies) *(Continued)*
scaphocephaly as, 2642, 2643f
syndromic, 2645-2647
trigonocephaly as, 2642-2643, 2643f, 2648f
due to neoplasms, 2647, 2647f
due to trauma, 2647
congenital
in achondroplasia, 2633, 2634f
clinical manifestations of, 2642-2647
acrocephaly as, 2645, 2645f
brachycephaly as, 2644, 2645f
craniosynostosis as, 2642-2645, 2643f
encephalocele as, 2645, 2646f
facial clefts as, 2645
kleeblattschädel as, 2645, 2645f
plagiocephaly as, 2643-2644, 2644f
scaphocephaly as, 2642, 2643f
syndromic, 2645-2647
trigonocephaly as, 2642-2643, 2643f, 2648f
in Down syndrome (trisomy 21), 2631-2633, 2631f, 2632b
due to abnormal and poor growth, 2633
of ears, 2632
of eyes, 2632-2633
mandibular and oral manifestations of, 2632
of midface, 2632
of skull, 2632
pathophysiology of, 2640-2642
intrauterine causes in, 2640
metabolic disorders in, 2640
molecular genetics in, 2640, 2641t, 2642f
in Robin sequence (Pierre Robin syndrome), 2630-2631, 2630f
surgical management of, 2649-2657
coronal incision in, 2650, 2650f
distraction osteogenesis in, 2654-2657, 2656f
fronto-orbital advancement in, 2650-2653, 2651f-2654f
monobloc advancement in, 2653-2654, 2655f-2656f
for orbital hypertelorism and dystopia, 2654
for sagittal synostosis, 2650, 2650f-2651f
syndromic, 2645-2647
in Apert's syndrome, 2641t, 2645-2646
in Carpenter's syndrome, 2646
in Crouzon's syndrome, 2641t, 2645
in facio-oculo-auriculo-vertebral spectrum, 2646-2647
in Jackson-Weiss syndrome, 2646
in mandibulofacial dysostosis (Treacher Collins syndrome, Franceschetti syndrome), 2633-2635, 2633b, 2635f, 2646
in Pfeiffer's syndrome, 2641t, 2646
related to branchial arch structures, 2585
in Saethre-Chotzen syndrome, 2641t, 2646
in Stickler's syndrome, 2646
in velocardiofacial syndrome, 2646
defined, 2638
epidemiology of, 2638-2639
mechanisms of postnatal facial growth and, 2639, 2639f
and obstructive sleep apnea, 2605
in other conditions and syndromes, 2635-2636
and otitis media, 2766
pathophysiology of, 2640-2642
acquired, 2640-2642
intrauterine causes in, 2640
metabolic disorders in, 2640
molecular genetics in, 2640, 2641t, 2642f
patient evaluation for, 2647-2649
craniofacial team in, 2647
history and physical examination in, 2647-2648
imaging in, 2648, 2648f-2649f
indications and timing of intervention in, 2648-2649

Craniofacial anomaly(ies) *(Continued)*
surgical management of, 2649-2658
acquired
due to neoplasm, 2657
due to trauma, 2648, 2649f, 2657
biomaterials in skeletal or cartilaginous defect repair in, 2657-2658
congenital, 2649-2657
coronal incision in, 2650, 2650f
distraction osteogenesis in, 2654-2657, 2656f
fronto-orbital advancement in, 2650-2653, 2651f-2654f
monobloc advancement in, 2653-2654, 2655f-2656f
for orbital hypertelorism and dystopia, 2654
for sagittal synostosis, 2650, 2650f-2651f
indications and timing of, 2648-2649
Craniofacial clefts, 2690, 2692
Craniofacial complex, growth and development of. *See* Craniofacial growth and development.
Craniofacial disassembly, 2448
Craniofacial frontoethmoidectomy, 1126, 1126f
Craniofacial growth and development, 2613-2637
abnormal, 2621-2630
functional endoscopic sinus surgery and, 2623-2625
internal fixation and, 2625-2626
nasal obstruction and dentofacial growth in, 2628-2630, 2629f
open mouth posture with, 2628-2629
review of literature on, 2629-2630
due to nasoseptal trauma and surgery, 2626-2628
animal studies on, 2626-2627
human studies on, 2627-2628, 2627f
surgical timing and approach and, 2628
due to radiotherapy, 2622-2623, 2626t
and adenotonsillar hypertrophy, 2792-2793
bone growth concepts in, 2614
osteogenesis as, 2614
endochondral, 2614, 2615f
intramembranous, 2614
remodeling and displacement as, 2614-2615
general facial changes in, 2615, 2615f-2616f
normal, 2615-2621, 2617t
and pediatric facial fractures, 2698-2699
postnatal, 2639, 2639f
regions in, 2615-2621, 2617t
mandible as, 2620-2621, 2623f-2625f
nasomaxillary complex as, 2619-2620, 2621f-2622f
sinuses in, 2619-2620, 2623f
neurocranium as, 2615-2619, 2617t
basicranium of, 2617-2619, 2617t, 2619f-2620f
calvaria of, 2615-2617, 2617t, 2618f
theories of, 2613-2614
cartilage-mediated, 2614
functional matrix, 2614
genetically preprogrammed, 2614
Craniofacial resection
for ethmoid sinus tumors, 1130
extended, 1126-1127, 1127f
supplemental management in, 1126-1127
for maxillary sinus tumor, 1128
Craniofacial surgery, for obstructive sleep apnea, 2610, 2610f
Craniofacial synostosis, 2639
Craniofacial team, 2647
Craniofrontal syndrome, 2641t
Craniolacuna, 2641t
Craniomaxillofacial resorbable plating systems, for pediatric facial fractures, 2700-2701, 2700t-2701t
Craniomaxillofacial trauma. *See* Maxillofacial trauma.
Craniopharyngioma, of nasopharynx, 1349
Craniosynostosis, 2642-2645, 2643f
acrocephaly due to, 2645, 2645f
Boston-type, 2641t
brachycephaly due to, 2643f, 2644, 2645f
front-orbital advancement for, 2652-2653
with deafness, 2051t-2058t
kleeblattschädel as, 2645, 2645f
Muenke-type, 2641t
plagiocephaly due to, 2643-2644, 2643f-2644f
front-orbital advancement for, 2652-2653, 2653f
scaphocephaly due to
clinical manifestations of, 2642, 2643f
surgical management of, 2650f-2651f
trigonocephaly due to, 2642-2643, 2643f, 2648f
front-orbital advancement for, 2645, 2654f
Craniovertebral junction disorder(s), 2354-2356
assimilation of atlas as, 2355
atlantoaxial dissociation as, 2355-2356
basilar impression as, 2355
Chiari malformation as, 2356, 2356f
classification of, 2355-2356
pathophysiology of, 2355
Cranium, size ratio to face of, 2616f, 2617t
Creep, in skin flaps, 1071
Cresylate otic drops, for fungal otitis externa, 1955, 1959t-1960t
Cribriform area
anatomy of, 1822f
in surgical anatomy of anterior cranial base, 2443, 2444f
Cribriform plate
invasive small cell carcinoma of, 170f
lateral lamella of, and CSF rhinorrhea, 787, 787f
surgical anatomy of, 741
in anterior cranial base, 2442-2443, 2443f, 2471, 2472f
in lateral skull base, 2435
Cricoarytenoid joint
in arytenoid adduction, 913
laryngeal carcinoma of, 1545, 1545f
Cricoarytenoid joint fixation, vocal quality disorder due to, 2880
Cricoarytenoid muscle
in arytenoid adduction, 913, 914f
surgical anatomy of, 1543f
Cricoarytenoid unit, in organ-preservation surgery, 1544
Cricohyoidoepiglottopexy (CHEP)
for glottic cancer, 1517t
supracricoid partial laryngectomy with, 1549-1550
complications of, 1551
extended procedures for, 1551
functional outcome of, 1551, 1551t-1552t
key surgical points for, 1550-1551
oncologic results of, 1549-1550
surgical technique for, 1550, 1550f-1551f
vs. total laryngectomy, 1564
Cricohyoidopexy (CHP)
for advanced supraglottic cancer, 1500
supracricoid laryngectomy with, 1555-1557
complications of, 1557
functional outcome of, 1556-1557, 1557t
key surgical points for, 1556
oncologic results of, 1555
partial, 1564
surgical technique for, 1555-1556, 1556f
Cricoid arch
repair of, 939f
surgical anatomy of, 1543f
Cricoid cartilage
anatomy of, 805-806, 1359f, 1422f
radiographic, 1471, 1473f
surgical, 1541, 1542f-1544f
laryngeal carcinoma of, 1541
physical examination of, 95, 96f
Cricoid lamina, surgical anatomy of, 1543f
Cricoid resection with thyrotracheal anastomosis, for laryngeal stenosis, 2921, 2922f
Cricoid ring, radiographic anatomy of, 1473, 1473f
Cricoid split operation, 2908f, 2910f, 2918-2919, 2918f-2919f
Cricoidectomy, for chronic aspiration
partial, 928
subperichondrial, 927-928, 929f
Cricopharyngeal achalasia, 1398-1399, 1400f
Cricopharyngeal chalasia, 1399
Cricopharyngeal dysfunction, 1398-1399, 1400f
Cricopharyngeal muscle
anatomy of, 1422
in arytenoid adduction, 915
delayed opening of, 1399
during swallow, 833
pharyngeal, 1216-1217, 1216f
in Zenker's diverticulum, 987
Cricothyroid (CT) joint
in arytenoid adduction, 915
surgical anatomy of, 1542f
Cricothyroid (CT) ligament, surgical anatomy of, 1541-1542, 1542f-1543f
Cricothyroid membrane (CTM)
anatomy of, 126
dilation of, 127, 128f
palpation and location of, 127, 127f
relocation of, 127, 127f
transverse incision in, 127, 127f
Cricothyroid (CT) muscle
anatomy of
applied, 807, 807f
surgical, 1543f
characteristics of, 918
in professional voice production, 846-847
Cricothyrotomy, 114t, 126-128
anatomic considerations for, 126
complications after, 128, 128f
contraindications for, 126-127
defined, 126
equipment for, 126b
historical perspectives on, 126
indications for, 126-127
percutaneous, 114t, 128
procedure for, 127
cricoid hook in, 127, 128f
dilation of cricothyroid membrane in, 127, 128f
palpation and location of cricothyroid membrane in, 127, 127f
relocation of cricothyroid membrane in, 127, 127f
tracheostomy tube insertion in, 127, 128f
transverse incision in cricothyroid membrane in, 127, 127f
vertical incision over cricoid cartilage in, 127, 127f
rapid five-step technique for, 128
Cricotracheal resection (CTR), for laryngeal stenosis, 2921, 2922f
Cricotracheal separation, management of, 937
Crile clamp, in repair of medial canthal ligaments, 337f
Crile, George, 1702-1703, 1726
Crista ampullaris
anatomy of, 1854, 1856f-1857f
embryogenesis of, 1852
Crista galli, 1124f
aerated, 670
bifid, with nasal dermoid, 2689, 2689f
in surgical anatomy of anterior cranial base, 2442-2443, 2443f, 2471, 2472f
Critical closing pressure, in skin flaps, 1068
Crohn's disease
esophagitis due to, 1405
oral manifestations of, 1254

Cromolyn sodium, for allergic rhinitis, 620
Cronin technique, in cleft-lip nose repair, 559, 566f
Crookes, William, 1031
Cross-face nerve grafting, 2419, 2424-2425
Crossing over, 3
Crossover, in audiologic testing, 1889
Cross-priming, 1024
Croton oil, for deep chemical peel, 394
Croup, 1465, 1465f, 2803-2806
  clinical features of, 2803-2804
  defined, 2803
  diagnosis of, 2804
  differential diagnosis of, 2804-2805, 2806t
  epidemiology of, 2803
  etiology of, 2803
  imaging of, 2804, 2804f-2805f
  laryngoscopy of, 2804, 2805f
  management of, 2805-2806, 2904
  membranous (bacterial), 1465, 1465f
  pathogenesis of, 2803-2804
  postintubation, 2593
  pseudo-membranous (*See* Bacterial tracheitis)
  spasmodic, 2805
  terminology for, 2803
  viral, 2803
Crouzonodermoskeletal syndrome, craniofacial anomalies in, 2641t
Crouzon's syndrome, craniofacial anomalies in, 2641t, 2645
Crow's feet, 428
CRS. *See* Chronic rhinosinusitis (CRS).
CRT. *See* Chemoradiation therapy (CRT).
"Crumple zones," of face, 322, 322t
Crus commune, 1851f, 1853f
Crus helicis, 1824f
CRYM, in deafness, 2051t-2058t
Cryoglobulinemia, sensorineural hearing loss due to, 2120
Cryotherapy
  interventional bronchoscopy with, 1010t
  for skin lesions, 294
  for unresectable tracheal tumor, 1621
Cryptococcal meningitis, in HIV, 223-224
Cryptococcosis, laryngeal and tracheal manifestations of, 892-893
μ-Crystallin, in deafness, 2051t-2058t
CS (carotid space)
  anatomy of, 203
  imaging of, 150-151, 151f-152f
  schwannoma of, 1663f
CSD (cat scratch disease)
  in children, 2818
  deep neck space infections due to, 201
  salivary gland involvement in, 1159
CSF. *See* Cerebrospinal fluid (CSF).
CSOM (chronic suppurative otitis media), cochlear implant for, 2221
CSP (cysteine-string protein), 2081
CSS (Chronic Sinusitis Survey), 57
CSS (Churg-Strauss syndrome)
  nasal manifestations of, 659
  otorrhea due to, 2196
CT. *See* Computed tomography (CT); Cricothyroid (CT).
CTA (computed tomography angiography)
  of anterior skull base, 2475, 2475f
  of neck masses, 1637, 1637t
CTAP-III (chemokine connective tissue–activating peptide-III), in wound healing, 1076
CTGF (connective tissue growth factor), in formation of granulation tissue, 1077
CTL(s) (cytotoxic T lymphocytes), 601, 602f
CTL2, in autoimmune inner ear disease, 2165
CTM. *See* Cricothyroid membrane (CTM).
CTR (cricotracheal resection), for laryngeal stenosis, 2921, 2922f
CTSIB (Clinical Test of Sensory Integration and Balance), 2317
CTV (clinical target volume), for radiotherapy, 1044
CTV (clinical tumor volume), for radiotherapy, 1036
Cuneiform cartilage, 1542f
Cuneiform tubercle, 1422f, 1543f
Cupula
  anatomy of, 1855, 1857f
  in vestibular system, 2278f, 2279-2283
    torsional pendulum model of, 2279-2283, 2282f
Cupulolithiasis, 2329-2330
  of lateral semicircular canal, 2331
Curets, for treatment and biopsy of skin lesions, 293
Curie (Ci), 1031-1032
Curie, Marie, 1031-1032
Curie, Pierre, 1031
Current steering, for cochlear implants, 2231, 2231f
Cushing's disease, oral manifestations of, 1251
Cutaneous branches, of cervical plexus, 2578, 2580f
Cutaneous diseases
  esophageal manifestations of, 979-980
  nasal manifestations of, 660-661
    in Behçet's disease, 660-661
    in pemphigoid, 660
    in pemphigus vulgaris, 660
    in scleroderma, 660
  oral manifestations of, 1253-1254
Cutaneous flaps. *See* Skin flap(s).
Cutaneous hemangiomas, and airway involvement, 2899, 2900f
Cutaneous neoplasms
  immunosuppression and, 213t, 215
  neck dissection for, 1718-1719
    definition and rationale for, 1718, 1718f
    technique for, 1718-1719
Cuticular plate, 1832-1833, 1833f, 1841f, 1857
CVA (cerebrovascular accident)
  chronic aspiration due to, 926b
  due to lateral skull base surgery, 2512
  oral manifestations of, 1250
Cx. *See* Connexin(s) (Cx).
CXC chemokines, 609t-612t
CXC3C chemokine, 611t-612t
CXCL-14, for head and neck squamous cell carcinoma, 1024
CXCR2 (chemokine receptor 2), in wound healing, 1076
CXCR4 (chemokine receptor 4), in head and neck squamous cell carcinoma, 1060
CXR (chest x-ray)
  of early glottic carcinoma, 1516
  for imaging of pharynx and esophagus, 1393
  for neck masses, 1637
Cyanoacrylates, for embolization, 1933
Cyanotic heart disease, anesthesia with, 2597
CyberKnife (CK) stereotactic radiotherapy
  for laryngeal and hypopharyngeal cancer, 1592
  for malignant skull base tumors, 1696
Cyclic adenosine monophosphate (cAMP)
  in olfactory transduction, 629
  in salivary gland secretion, 1137
Cyclin D1, in laryngeal carcinoma, 1505
Cyclin D3, in laryngeal carcinoma, 1505
Cyclin-dependent kinase inhibitor 2D *(Cdkn2d)* gene, in murine deafness, 2058t-2060t
Cyclooxygenase (COX) inhibitors, and skin flap viability, 1074
Cyclooxygenase-1 (COX-1) inhibitors, for head and neck squamous cell carcinoma, 1018
Cyclooxygenase-2 (COX-2), in laryngeal carcinoma, 1505
Cyclooxygenase-2 (COX-2) inhibitors
  for chemoprevention of oral cancer, 1315
  for head and neck squamous cell carcinoma, 1018
Cyclophosphamide
  for autoimmune inner ear disease, 2167
  for Wegener's granulomatosis, 658
Cyclosporine, for Graves' ophthalmopathy, 1811
Cylindroma, 288f, 292
Cymba conchae, 476-477, 476f, 1824f
Cymetra. *See* AlloDerm Regenerative Tissue Matrix (Cymetra).
Cyst(s), 289
  arachnoid, of cerebellopontine angle, 2523-2524
    vs. cholesteatoma (epidermoid), 2519, 2521f
    imaging of, 1928, 1929t
  benign lymphoepithelial, in HIV, 217-218, 218f
  branchial cleft, 2814
    in children, 2859
    clinical presentation of, 2814, 2814f
    embryology of, 2585, 2585f, 2814
    imaging of, 131, 158f, 1410, 2814, 2814f
    management of, 2814
    otorrhea due to infection of, 2195
    squamous cell carcinoma arising in, 1671
  buccal bifurcation, infected, 1264-1265
  of cerebellopontine angle
    arachnoid, 2523-2524
      vs. cholesteatoma (epidermoid), 2519, 2521f
      imaging of, 1928, 1929t
    dermoid, 2527
    epidermoid, 2518-2519
      diagnostic studies of, 2519
      differential diagnosis of, 1929t, 2518t, 2519, 2524t
      imaging of, 1928, 1928f, 2519, 2520f
      signs and symptoms of, 2518-2519
  cholesterol, 2508, 2510f
  defined, 1260-1262
  dermoid, 289
    of cerebellopontine angle, 2527
    in children, 2859
    nasal
      clinical presentation of, 2689, 2689f
      defined, 2687f, 2688-2689
      epidemiology of, 2688-2689
      histology of, 2689
      imaging of, 2689, 2689f
      management of, 2689-2690
    of neck, 1639, 2816
      clinical appearance of, 2816, 2816f
      embryology of, 2586
      imaging of, 2816, 2817f
    of oral cavity, 1287-1288
  developmental, of oral cavity, 1287-1288
    dermoid, 1287-1288
    duplication, 1287-1288, 1288f
    nasoalveolar, 1288, 1288f
  dorsal, due to injectable silicone, 578, 579f
  ductal
    congenital, 2859
    of larynx, 869, 869f-870f
  duplication
    foregut, compression of pharynx and esophagus due to, 1408-1409, 1409f
    of oral cavity, 1287-1288, 1288f
  epidermoid, 289
    of cerebellopontine angle, 2518-2519
      diagnostic studies of, 2519
      differential diagnosis of, 1929t, 2518t, 2519, 2524t
      imaging of, 1928, 1928f, 2519, 2520f
      signs and symptoms of, 2518-2519
    of cerebellopontine cistern, 2509f
    of larynx, 868f-869f, 869
    of vocal folds, 2882, 2882f

Cyst(s) *(Continued)*
esophageal
imaging of, 1416, 1416f
retention, 1415-1416, 1415f
intracordal, 869-870
diagnosis of, 869
history in, 869
laryngeal examination in, 869
vocal capability battery in, 869
epidemiology of, 869
epidermoid inclusion, 868f-869f, 869
mucous retention (ductal), 869, 869f-870f
open, 869, 870f
pathophysiology and pathology of, 869
treatment of, 869-870
behavioral, 869-870
medical, 869
surgical, 870, 870f
laryngeal
congenital, 1468, 2872-2873, 2872f-2873f
ductal, 869, 869f-870f
epidermoid inclusion, 868f-869f, 869
mucous retention, 869, 869f-870f
saccular, 2872-2873, 2872f-2873f
milia as, 289
mucous, 289
mucous retention, 289
in children, 2859
imaging of, 676, 677f
of larynx, 869, 869f-870f
of petrous apex, 2525, 2526f
nasal, dermoid
clinical presentation of, 2689, 2689f
defined, 2687f, 2688-2689
epidemiology of, 2688-2689
histology of, 2689
imaging of, 2689, 2689f
management of, 2689-2690
nasoalveolar, of oral cavity, 1288, 1288f
nasolacrimal duct, 2693, 2694f
of neck, dermoid, 1639, 2816
clinical appearance of, 2816, 2816f
embryology of, 2586
imaging of, 2816, 2817f
odontogenic (*See* Odontogenic cysts)
of oral cavity
dermoid, 1287-1288
developmental, 1287-1288
dermoid, 1287-1288
duplication, 1287-1288, 1288f
nasoalveolar, 1288, 1288f
duplication, 1287-1288, 1288f
nasoalveolar, 1288, 1288f
parotid, AIDS-related, 1146, 1146f
of petrous apex, mucous retention, 2525, 2526f
pilar (trichilemmal), 289
saccular, 876-878
anterior, 876f-877f, 877
classification of, 877f
clinical scenario with, 877
defined, 877
diagnosis of, 877
etiology of, 876
of larynx, 2872-2873, 2872f-2873f
lateral, 876f, 877, 878f
treatment of, 877-878
salivary gland, 2859
acquired, 2859
congenital, 2859
in steatocystoma multiplex, 289
subglottic, 2871, 2871f
thymic, 2817
thymopharyngeal, 2585
thyroglossal duct, 2814-2815, 2871-2872
clinical presentation of, 2814-2815, 2815f
vs. ectopic thyroid, 2815
embryology of, 2586, 2814
Cyst(s) *(Continued)*
imaging of, 161-162, 165f
infected, needle aspiration of, 206, 206f
neck masses due to, 1639
Sistrunk operation for, 2815
squamous cell carcinoma arising in, 1671
vallecular, 2871-2872, 2872f
thyroid, 1759-1760
clinical presentation of, 1759-1760
management and prognosis for, 1760
pathology of, 1760
Tornwaldt, 1348-1349
imaging of, 148, 1416, 1416f
vallecular, 1416f
dysphagia due to, 2951-2952
stridor due to, 2898, 2898f
vocal fold, 856, 857f
in children, 2882, 2882f
Cystadenoma, papillary, of salivary glands
lymphomatosum, 1146, 1146f, 1170-1171
oncocytic, 1171
Cysteine-string protein (CSP), 2081
Cystic fibrosis (CF)
gene therapy for, 20
nasal manifestations of, 661
pediatric anesthesia with, 2595
salivary gland enlargement due to, 2864
Cystic hygroma, 156-157, 2815, 2901f
Cystic salivary gland disease, 1647
Cystic thyroid nodules, 1644, 1645f
Cytochrome P-450, in head and neck squamous cell carcinoma, 1016
Cytogenetics, of head and neck squamous cell carcinoma, 1019
Cytokines
in allergic rhinitis, 615
in cisplatin ototoxicity, 2173
in humoral immune response, 608, 609t-610t
in otitis media and cholesteatoma, 1973
in rhinosinusitis, 731
Cytomegalic inclusion disease, 2154-2156, 2155f
Cytomegalovirus (CMV)
labyrinthine infections with
clinical features of, 2154-2155
congenital hearing loss due to, 2154-2156, 2155f
diagnosis of, 2154-2155
experimental, 2156
management and prevention of, 2156
temporal bone pathology due to, 2155-2156, 2155f
Meniere's disease due to, 2163
sensorineural hearing loss due to, 2119
in infants, 2723
Cytomegalovirus (CMV) esophagitis, 976, 977f
Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCAs), in Wegener's granulomatosis, 658, 2103
Cytoskeletal protein defects, deafness due to, 2074-2076, 2076f
Cytotoxic gene therapy strategies, 16, 21
Cytotoxic hypersensitivity reactions, 608-612
Cytotoxic T lymphocytes (CTLs), 601, 602f

D

da Vinci, Leonardo, 269, 270f
da Vinci Robotic Surgical System, 39-40, 41f
for laryngeal cancer, 1560-1561
Dacryocystoceles, 2693, 2694f
Dacryocystogram (DCG), 798, 798f-799f
Dacryocystorhinostomy (DCR), endoscopic, 763, 797-802
complications of, 801
evaluation for, 797-798
dacryocystogram in, 798, 798f-799f
scintilligraphy in, 798, 799f
nasal preparation for, 798
Dacryocystorhinostomy (DCR), endoscopic *(Continued)*
outcomes of, 801
revision, 801
surgical technique for, 798-801
agger nasi in, 799-800, 800f
bone removal in, 799-800, 800f
common canaliculus in, 800-801, 801f
creation of flap in, 798, 799f
endoscopic septoplasty in, 798, 799f
flap elevation in, 798-799, 800f
flap positioning in, 800, 800f
frontal process and lacrimal bone in, 799-800, 800f
lacrimal probe in, 800
tube stents in, 800-801, 801f
DAG (diacylglycerol), in salivary gland secretion, 1137
DAMES classification, of thyroid cancer, 1754
Danger space No. 4
anatomy of, 202-203
odontogenic infections of, 186, 186f
DART (dynamic adjustable rotational tip) graft, for saddle nose deformity, 555, 559f
Darwinian tubercle, 476-477, 476f, 2742f
excision of, 478f
Data, uncertainty of, 60t, 64-65
Data interpretation, 59-75
censored data in, 63t, 64
coefficient of determination for, 64, 72
common statistical deceptions in, 72-74, 73t
multiple *P* value phenomenon as, 73t, 74
post hoc *P* values as, 73-74, 73t
powerless equalities as, 73t, 74
selective analysis of results as, 73t, 74
small sample whitewash as, 73, 73t
standard error "switcheroo" as, 72, 73t
surgical satisfaction swindle as, 72
confidence intervals in, 65, 66t, 67
correlation coefficient for, 64, 64t, 67
descriptive statistics for, 63, 64t
effect of study design on, 59, 60t
control group in, 59-61
example of, 61-62, 63t
experimental (randomized controlled) *vs.* observational, 59, 61t-62t
prospective *vs.* retrospective, 61
study type and study methodology in, 61, 62t
effect size in, 66-67
explanations other than efficacy in, 61, 61f, 62t
hypothesis testing in, 65, 66t
examples for, 65-66
null hypothesis in, 65, 66t
P value in, 65, 66t
type I and type II errors in, 65, 66t
importance of principles in, 74-75
key habit(s) for, 59-70, 60t
accepting uncertainty of all data as, 60t, 64-65
checking quality before quantity as, 59-62, 60t
describing before analyzing as, 60t, 62-64
measuring error with right statistical test as, 60t, 65-66
putting clinical importance before statistical significance as, 60t, 66-67
seeking sample source as, 60t, 68-69
viewing science as cumulative process as, 60t, 69-70
levels of evidence in, 69-70, 70t
measurement scales for, 63, 63t
meta-analyses in, 70, 71t
odds ratio, relative risk, and rate difference for, 64, 64t
placebo response in, 61
for popular statistical tests, 70-72
analysis of variance (ANOVA) as, 71
contingency tables as, 71-72
multivariate (regression) procedures as, 72

Data interpretation *(Continued)*
nonparametric, 72
survival analysis as, 72
t-test as, 70-71
research integration in, 69-70
sampling methods in, 68-69, 68t-69t
statistical test(s) for
for independent samples, 66, 67t
measuring error with right, 60t, 65-66
for related samples, 66, 67t
survival analysis in, 64
survival curve in, 64
understanding sample size in, 74
validity in, 68, 68t, 69f
Data logging, with hearing aids, 2269
Data-glove, 39, 39f
Daughter cells, 12
Day care, and otitis media, 2767
Daytime somnolence, 263-264
obesity and, 251
dB (decibel), 1839, 2087
dBA (decibel–A) scale, 2140
DCC (deleted in colorectal cancer) gene, in head and neck squamous cell carcinoma, 1020
DCG (dacryocystogram), 798, 798f-799f
DCR. *See* Dacryocystorhinostomy (DCR).
DDP1 (deafness dystonia peptide 1) gene, in deafness, 2051t-2058t
De la Cruz classification, of congenital aural atresia, 2753, 2753b
De Morgan's spots, 290
Deaf culture, 2099
Deafness. *See also* Hearing loss.
autosomal dominant (DFNA), 2050, 2089
autosomal recessive (DFNB), 2050, 2089
X-linked or mitochondrial (DFN), 2050, 2089
Deafness dystonia peptide 1 *(DDP1)* gene, in deafness, 2051t-2058t
Deafwaddler mice, 2080
Débridement
of burns, 315
after endoscopic sinus surgery, 773-774
of tracheal tumor, 1619-1621
Debrox (carbamide peroxide), for cerumen removal, 1958t
Decadron. *See* Dexamethasone (Decadron, Dexacort).
Decannulation, tracheostomy
with laryngeal stenosis, 2923
surgical, 2907-2908
ward, 2907
Decibel(s) (dB), 1839, 2087
Decibel scale, 1839, 2140
Decibel–A (dBA) scale, 2140
Decompression sickness, inner ear, 2343
Decongestant(s)
for otitis media
acute, 2770
with effusion, 2771
for rhinitis
allergic, 620
nonallergic, 700
for rhinosinusitis, 735t, 736
topical
prior to endoscopic sinus surgery, 745
for obstructive sleep apnea, 257
for vocal professionals, 855
Decongestion, for airway obstruction, 655
Deep cervical fascia, 202, 2577-2578, 2578f-2579f
Deep cervical lymph nodes, 2582
Deep jugular nodes, 1298f
Deep lingual artery, 1296f
Deep neck space, anatomy of, 201-202
anterior visceral space in, 203
carotid space in, 203
danger space in, 202-203
Deep neck space, anatomy of *(Continued)*
deep cervical fascia in, 202
masticator space in, 203
parapharyngeal space in, 202
parotid space in, 203
peritonsillar space in, 203
prevertebral space in, 203
retropharyngeal space in, 202
submandibular and sublingual spaces in, 202
superficial cervical fascia in, 202
Deep neck space infections, 201-208
clinical evaluation of, 203
history in, 203
physical examination in, 203
complications of, 207-208
carotid artery pseudoaneurysm or rupture as, 207
cavernous sinus thrombosis as, 207
Lemierre's syndrome as, 207
mediastinitis as, 207-208
necrotizing fasciitis as, 208
etiology of, 201
imaging studies of, 204-205
CT for, 204, 204f-205f
MRI for, 204
plain film radiography for, 204-205
ultrasonography for, 204-205
laboratory evaluation of, 204
microbiology of, 201
of odontogenic origin, 184-187
lateral pharyngeal, 184-185, 186f
prevertebral (danger space No. 4), 186, 186f
retropharyngeal, 185-186, 187f
airway establishment for, 188
normal anatomy and, 186f
surgical drainage and decompression for, 189-190
treatment of, 205-207
airway management in, 205
antibiotic therapy in, 205-206, 206t
fluid resuscitation in, 205
surgical, 206-207
needle aspiration in, 206, 206f
transcervical incision and drainage in, 207
transoral incision and drainage in, 206-207
Deep temporal fascia, 440
Defensins, 599
Deferoxamine
ototoxicity of, 2176-2177
sensorineural hearing loss due to, 2121, 2176-2177
Degenerate code, 4
Degenerative arthritis, of temporomandibular joint, 1281-1282, 1281t
Degenerative neurologic diseases, chronic aspiration due to, 926b
Deglutition, 833, 1215-1221
disorders of (*See* Dysphagia)
inefficient, 1217
physiology of, 954, 955f, 1207
stage(s) of, 1215, 1218f
esophageal, 1217, 2948
oral, 1206f, 1207, 1215, 1216f, 2948
oral preparatory, 1215, 1216f, 2948
pharyngeal, 1216, 2948
airway protection during, 1216-1217
cricopharyngeal (upper esophageal sphincter) opening during, 1217
delayed triggering of, 1215
neuromuscular activities in, 1216, 1216f
pharyngeal pressure generation during, 1217
programmed, 1216-1217
voluntary, 1215
Dehydrating agents, for Meniere's disease, 2337
Deiodinases, 1738
Deiters' cells, 1832, 1832f-1833f
Déjérine-Sottas syndrome, deafness in, 2051t-2058t
Delayed skin flaps, 1072-1073
Delayed sleep phase syndrome, 262t, 263-264
Delayed-type hypersensitivity (DTH) reactions, 601, 608-612
Deleted in colorectal cancer (DCC) gene, in head and neck squamous cell carcinoma, 1020
Deletion, 4-5
Deliverability, of radiotherapy, 1035
Delivery approaches, for nasal tip refinement, 522, 527f
complete strip technique in, 522, 527f-530f
interrupted strip technique in, 522, 532f-533f
suturing in, 522, 530f-531f, 550-551
DeltaSystem, for pediatric facial fractures, 2701t
Deltopectoral flap, for hypopharyngeal and esophageal reconstruction, 1451-1452, 1452f
Dementia
hearing and, 233
HIV-associated, 223
oral manifestations of, 1254-1255
Demineralization, of teeth, 1141
Demyelinating disorders, vertigo due to, 2202
Denaturing high performance liquid chromatography (DHPLC), 9, 10f
Dendritic cell(s), 604
Dendritic cell–based vaccines, for head and neck squamous cell carcinoma, 1024
Dental artifacts
on CT, 139, 141f
on MRI, 134, 134f
Dental care
after radiation therapy, 1333-1337
with conventional 3D conformal radiation therapy, 1333-1335, 1336f
with intensity-modulated radiation therapy, 1335-1337, 1336f-1337f
ipsilateral *vs.* contralateral, 1335
during radiation therapy, 1333
prior to radiation therapy, 1330-1331, 1330b, 1331f
Dental caries, 1252
Dental changes, in geriatric patients, 236
Dental disease
heart disease and, 1248
and stroke, 1250
Dental erosions, due to GERD, 971-972
Dental extractions, prior to radiation therapy, 1330-1331, 1330b, 1579
Dental infection, 1252
Dental lamina, 1259
Dental lamina cyst, 1266, 1266f
microscopic features of, 1266
treatment of, 1266
Dental pain, 1202-1203
Dental papillae, 1276
Dental procedures
cardiac conditions and, 1248-1249, 1249t
with joint replacement, 1253, 1253t
Dental prostheses, and radiation therapy, 1331
Dental rehabilitation, after resection for malignancy, 1087, 1089f
Dental sac, 1276
Dentigerous cyst, 1263-1264
microscopic features of, 1264
neoplastic potential of, 1264
radiographic features of, 1264, 1264f
treatment of, 1264, 1264f
Dentin sialophosphoprotein *(DSPP)* gene, in deafness, 2051t-2058t
Dentinogenesis imperfecta, 1257
Dentinogenic ghost cell tumor, 1275-1276
Dentition, inherited and congenital disorders affecting, 1257
Dentition eruption, 2617t
Dentoalveolar abscess, 1252

Dentoalveolar evaluation, prior to radiation therapy, 1330-1331, 1330b, 1331f
Dentoalveolar fractures, pediatric, 2706-2707, 2710f
Dentofacial growth, nasal obstruction and, 2628-2630, 2629f
  open mouth posture in, 2628-2629
  review of literature on, 2629-2630
Denture sore mouth, 1230, 1230f
Denude method, for tonsillar and pharyngeal wall reconstruction, 1386, 1387f
Deoxyribonucleic acid (DNA), 3
  structure of, 4, 11
Deoxyribonucleic acid (DNA) chips, 9
Deoxyribonucleic acid (DNA) damage, by radiation, 1036-1043, 1037f
Deoxyribonucleic acid (DNA)-mediated transfer, of therapeutic genes, 15-16, 15f
Deoxyribonucleic acid (DNA) methyltransferases (DNMTs), in head and neck squamous cell carcinoma, 1020
Deoxyribonucleic acid (DNA) repair enzyme polymorphisms, in head and neck squamous cell carcinoma, 1027
Deoxyribonucleic acid (DNA) sequencing, 3, 9
Deoxyribonucleic acid (DNA) testing, 8-9
  DNA chips for, 9
  mutation testing as, 9, 10f
  nucleic acid hybridization and Southern blotting for, 9
  polymerase chain reaction for, 8-9
Deoxyribonucleic acid (DNA) vectors, 15-16, 15f
Depakote (divalproex), for migraine, 2350
Department of Defense (DoD), 84t-87t, 87
Department of Veterans Affairs (VA), 84t-87t, 87
Deposition of dose, in radiation, 1033
Deposition of energy, in radiation, 1033
Depression
  palliative care for, 1103-1104
  after rhytidectomy, 427
  subclinical hypothyroidism and, 1748
Depressor anguli oris, 321f
Depressor dysfunction, digastric transposition for, 2431-2432
Depressor labii, 442f
Depressor supercilii muscle, 433f
Depth of focus, of surgical laser, 27-28, 28f
Dermabrasion, 397-399
  complications of, 399
  contraindications to, 397-398
  defined, 397
  equipment for, 398, 398f
  historical background of, 397
  micro-, 402-403
  patient selection and consultation for, 397-398
  postoperative care after, 399, 399f
  for scar revision, 298-299, 300f
  technique of, 398-399, 398f-399f
Dermal matrix, in formation of granulation tissue, 1077
Dermatitis
  contact, otitis externa due to, 1945-1946
  otorrhea due to, 2194
  due to radiotherapy, 1047
Dermatocartilaginous ligament, 496-497
Dermatofibroma, 288f
Dermatofibrosarcoma protuberans (DFSP), 291-292
  in children, 2843, 2843f
Dermatologic diseases
  esophageal manifestations of, 979-980
  nasal manifestations of, 660-661
    in Behçet's disease, 660-661
    in pemphigoid, 660
    in pemphigus vulgaris, 660
    in scleroderma, 660
  oral manifestations of, 1253-1254
Dermatomyositis
  laryngeal hypofunction due to, 842
  oral manifestations of, 1252
Dermatosis papulosa nigra, 282
Dermis, 1065
Dermoid(s). *See* Dermoid cysts.
Dermoid cysts, 289
  of cerebellopontine angle, 2527
  in children, 2859
  nasal
    clinical presentation of, 2689, 2689f
    defined, 2687f, 2688-2689
    epidemiology of, 2688-2689
    histology of, 2689
    imaging of, 2689, 2689f
    management of, 2689-2690
  of neck, 1639, 2816
    clinical appearance of, 2816, 2816f
    embryology of, 2586
    imaging of, 2816, 2817f
  of oral cavity, 1287-1288
Dermoid tumors. *See* Dermoid cysts.
Dermopathy, thyroid, and Graves' ophthalmopathy, 1808
DermOtic Oil (fluticasone acetonide oil), for eczematoid otitis externa, 1956
Descending vestibular nucleus (DVN), 1861, 1862f
  in velocity storage, 2296
Descending "w," in nasal breathing assessment, 644
Descriptive statistics, 63, 64t
Desflurane, for anesthesia, 111
Desipramine, for neuropathic pain, 244-245
Desired sensation level (DSL) method, for hearing aids, 2271
  in infants, 2724
Desloratadine (Clarinex), for nonallergic rhinitis, 701t
Desmoglein 1 (Dsg1), in pemphigus vulgaris, 1231
Desmoglein 3 (Dsg3), in pemphigus vulgaris, 1231
Desmoplastic melanoma (DM), 1108, 1108f
Desmoplastic-neurotropic melanoma (DNM), 1108
  of oral cavity, 1299
Desoxymethasone cream, for eczematoid otitis externa, 1955-1956
Detection bias, *vs.* efficacy of treatment, 62t
Detection threshold tests, for olfaction, 631
Developmental anomalies. *See also* Congenital anomaly(ies).
  sensorineural hearing loss due to, sudden, 2129
  of temporomandibular joint, 1280, 1281t
Developmental cysts, of oral cavity, 1287-1288
  dermoid, 1287-1288
  duplication, 1287-1288, 1288f
  nasoalveolar, 1288, 1288f
Deviated septum, 483f, 484
  endoscopic sinus surgery with, 751
  imaging of, 668, 669f
  in noncaucasian patient, 573, 576f
  rhinitis due to, 619b
  rhinoplasty with, 513-514, 514f, 546, 546f-547f
  septoplasty for (*See* Septoplasty)
  due to trauma, 482, 484
  with twisted nose, 551-552, 552f
Dexamethasone (Decadron, Dexacort)
  during adenotonsillectomy, 2797-2798
  for caustic ingestion, 2957
  with chemical peel, 396
  for croup, 2806
  for hyperthyroidism, 1739t
  intratympanic delivery of
    for cisplatin ototoxicity, 2173
    dosing for, 2185
    for Meniere's disease, 2184, 2339
    pharmacokinetics of, 2183-2184
    for sudden sensorineural hearing loss, 2184-2185
Dexamethasone (Decadron, Dexacort) *(Continued)*
  for nonallergic rhinitis, 700t
  for postintubation croup, 2593
  for postoperative nausea and vomiting, 2593
  for professional voice disorders, 854
  for thyroid storm, 1745
Dextran, after free tissue transfer, 1096-1097
Dextroscope, 48
DFMO. *See* Difluoromethylornithine (DFMO).
DFN (deafness, X-linked or mitochondrial), 2050, 2089
DFN1, 2093
DFN2, 2093t
DFN3, 2051t-2058t, 2083, 2093, 2093t
  infant screening for, 2723
DFN4, 2093t
DFN5, 2093t
DFN6, 2093t
DFN7, 2093t
DFN8, 2093t
DFNA (deafness, autosomal dominant), 2050, 2089
DFNA1, 2051t-2058t, 2092t
DFNA2, 2051t-2058t, 2079, 2083, 2090-2092, 2092t
DFNA3, 2051t-2058t, 2083, 2092t
DFNA4, 2051t-2058t, 2092t
DFNA5, 2051t-2058t, 2090-2091, 2092t
DFNA6, 2051t-2058t, 2092-2093, 2092t, 2098
DFNA8, 2051t-2058t, 2068, 2092, 2092t, 2098
DFNA9, 2051t-2058t, 2090-2091, 2092t
DFNA10, 2051t-2058t, 2092t
DFNA11, 2051t-2058t, 2092t
DFNA12, 2051t-2058t, 2068, 2092, 2092t, 2098
DFNA13, 2051t-2058t, 2069, 2092, 2092t
DFNA14, 2051t-2058t, 2092-2093, 2092t, 2098
DFNA15, 2051t-2058t, 2090-2091, 2092t
DFNA17, 2051t-2058t, 2092t
DFNA20, 2051t-2058t, 2074-2075, 2092t
DFNA22, 2051t-2058t, 2078, 2092t
DFNA25, 2051t-2058t, 2081
DFNA26, 2051t-2058t, 2074-2075, 2092t
DFNA28, 2051t-2058t, 2092t
DFNA36, 2051t-2058t, 2092t
DFNA38, 2051t-2058t, 2092-2093, 2092t, 2098
DFNA39, 2051t-2058t, 2092t
DFNA44, 2051t-2058t
DFNA48, 2051t-2058t, 2092t
DFNAi, 2051t-2058t
DFNB (deafness, autosomal recessive), 2050, 2089
DFNB1, 2051t-2058t, 2083, 2089-2090, 2090t-2091t, 2098
  infant screening for, 2235
DFNB2, 2091t
DFNB3, 2051t-2058t, 2076, 2091t
DFNB4, 2051t-2058t, 2083, 2091t, 2096, 2098
  infant screening for, 2723
DFNB5, 2091t
DFNB6, 2051t-2058t, 2091t
DFNB7, 2051t-2058t, 2091t
DFNB8, 2051t-2058t
DFNB9, 2051t-2058t, 2080-2081
DFNB10, 2051t-2058t
DFNB11, 2051t-2058t, 2091t
DFNB12, 2051t-2058t, 2074
DFNB16, 2051t-2058t, 2077, 2091t
DFNB18, 2051t-2058t, 2091t
DFNB21, 2051t-2058t, 2068, 2091t, 2092
DFNB22, 2051t-2058t, 2091t
DFNB23, 2051t-2058t, 2074, 2091t
DFNB24, 2051t-2058t, 2075-2076
DFNB28, 2051t-2058t, 2091t
DFNB29, 2051t-2058t, 2081, 2091t
DFNB30, 2051t-2058t, 2091t
DFNB31, 2051t-2058t, 2077, 2091t
DFNB35, 2051t-2058t
DFNB36, 2051t-2058t, 2075, 2091t
DFNB37, 2051t-2058t, 2091t

DFNB49, 2051t-2058t, 2081
DFNB53, 2051t-2058t, 2069
DFNB59, 2051t-2058t
DFNB61, 2051t-2058t
DFNB63, 2051t-2058t
DFNB66, 2051t-2058t
DFNB67, 2051t-2058t, 2091t
DFNBi, 2051t-2058t
DFSP (dermatofibrosarcoma protuberans), 291-292
  in children, 2843, 2843f
DGER (duodenogastroesophageal reflux), ambulatory 24-hour bile monitoring for, 960-961, 961f
DHE (dihematoporphyrin ether), for recurrent respiratory papillomatosis, 2892
DHPLC (denaturing high performance liquid chromatography), 9, 10f
Diabetes mellitus
  and Bell's palsy, 2401
  esophageal manifestations of, 979
  free tissue transfer with, 1091-1092
  oral manifestations of, 1251
  and pediatric anesthesia, 2596
  preoperative evaluation of, 105
  sensorineural hearing loss due to, 2094t, 2097
    sudden, 2129
  and skin flap survival, 1075
Diabetic angiopathy, presbycusis due to, 232
Diacylglycerol (DAG), in salivary gland secretion, 1137
Diagnostic therapy, in voice evaluation, 831
Diagnostic x-rays, energy for, 1034
Dialysis, oral sequelae of, 1255
Diamox (acetazolamide)
  for Meniere's disease, 2337
  for migraine, 2350
Diaphanous homolog 1 *(DIAPH1)* gene, in deafness, 2051t-2058t, 2076
Dicer, 13, 14f
Dichotomous scales, 63, 63t
Dickens, Charles, 251
Dieffenbach, Johann Friedrich, 475
Diet
  for extraesophageal reflux, 900-901
    in children, 2946
  and laryngeal cancer, 1492
  for Meniere's disease, 2337
  for migraine, 2349
  for voice professional, 852-853
Difficult airway, 108-129
  advances in devices and techniques for, 113-115, 114t
  awake fiberoptic nasotracheal intubation for, 122-123
    advantages of, 123
    avoiding failure in, 125, 126b
    bronchoscopy cart for, 123, 123f
    conscious sedation for, 124
    fiberoptic bronchoscope in, 123-125, 125f
    historical perspective on, 122-123
    indications for, 123, 123b
    keys to successful, 124b
    monitoring during, 124
    nasal trumpet placement for, 124, 125f
    optimal setup for, 125f
    patient preparation for, 123-124
    technique of, 124-125
    topical anesthesia for, 124
  blind nasal technique for, 114t
  case presentations of, 119
    with catastrophic events in operating room, 119-120
  classification of, 109, 109f
  Combitube for, 109-110, 110f, 114t
  consequences of, 110
  conventional laryngoscopy for, 114t
  critical failed airway as, 122
Difficult airway *(Continued)*
  due to difficult laryngoscopy, 121
  due to difficult mask ventilation, 121-122
  due to difficult tracheal intubation, 121
  digital technique for, 114t
  education on, 117
    institutional systems approach to, 118
    ongoing, 118
    patient and family, 117-119
    physician, 117-118
  endotracheal tube guides for, 114t
  epidemiology of, 109
  evolution of management of, 122, 122b
  extubation of, 117
  face mask ventilation for, 114t, 115f
  fiberoptic bronchoscopy for, 114t
  Hollinger anterior commissure laryngoscope for, 122, 122f
  Johns Hopkins Airway Management Initiative for, 115-118
    Adult Emergency Airway Cart in, 116
    advanced monitoring in operating room in, 117
    Airway Service resources in, 116
    Anesthesia Fiberoptic Cart in, 116
    conceptual framework of, 115
    education in, 117
      institutional systems approach to, 118
      ongoing, 118
      of patient and family, 117
      of physicians, 117-118
    extubation locations in, 117
    formulation of intraoperative and postoperative plans A, B, and C in, 115-116
    identification of "Airway Alert" in, 115
    in-hospital wristbands and chart labels in, 117
    multispecialty service and joint clinical faculty appointment for, 115
    nursing critical pathway in, 117
    operating room preparation in, 116
    operating room setup in, 117
    postoperative considerations in, 117
    preoperative evaluation in, 115
    staff for, 116-117
    standard anesthesia equipment in, 116
  laryngeal mask airway for, 109-110, 110f, 113, 122, 122b
  legal claims related to, 110
  lighted stylet for, 114t
  medical records of
    electronic, 118-119
    previous, 118
  monitoring of, 111
  as multispecialty problem, 108-111
  operative surgical airway options for, 125-126
    cricothyrotomy as, 114t, 126-128
      anatomic considerations in, 126
      complications after, 128, 128f
      contraindications for, 126-127
      cricoid hook in, 127, 128f
      defined, 126
      dilation of cricothyroid membrane in, 127, 128f
      equipment for, 126b
      historical perspectives on, 126
      indications for, 126-127
      palpation and location of cricothyroid membrane in, 127, 127f
      percutaneous, 114t, 128
      procedure for, 127
      rapid five-step technique for, 128
      relocation of cricothyroid membrane in, 127, 127f
      tracheostomy tube insertion in, 127, 128f
      transverse incision in cricothyroid membrane in, 127, 127f
Difficult airway *(Continued)*
      vertical incision over cricoid cartilage in, 127, 127f
    historical perspectives on, 125-126
  patient identification with, 109-110, 109f-110f
  predictors of, 109
  retrograde intubation for, 114t
  rigid bronchoscopes for, 113f, 114t
  rigid fiberoptic laryngoscope for, 114t
  rigid laryngoscopy for, 114t
  tracheotomy for, 114t
  transtracheal jet ventilation for, 114t
  transtracheal needle ventilation for, 128-129
Difficult laryngoscopy, 121
Difficult mask ventilation (DMV), 121-122
Difficult tracheal intubation, 121
Diffuse esophageal spasm, 965
  esophagogram of, 965, 966f
  imaging of, 1400-1401, 1401f
  manometric findings with, 959t, 965, 965f
Diffuse infiltrative lymphocytosis syndrome (DILS), 1157-1158
  immunosuppression and, 218
Diffuse large B-cell lymphoma (DLBCL), 1677-1678
  clinical presentation of, 1674
  of paranasal sinus and nasal cavity, 1680
    treatment and prognosis for, 1680
  of salivary glands, 1191-1192, 1192f
    treatment and prognosis for, 1680
  of thyroid, 1679
    staging of, 1679
    treatment and prognosis for, 1679
  treatment and prognosis for, 1677-1678
  of Waldeyer's ring, 1680
    treatment and prognosis for, 1680
Diffusion, across interstitial space, 1066
Difluoromethylornithine (DFMO)
  ototoxicity of, 2174
    animal studies on, 2174
    clinical studies on, 2174
    conclusions on, 2174
  sensorineural hearing loss due to, 2120-2121
  and skin flap viability, 1074
Digastric groove
  anatomy of, 1822f, 1824f
  in surgical anatomy of lateral skull base, 2436f
Digastric muscle
  anatomy of, 1296f, 1320, 2578f
  posterior belly of, 1826f
Digastric ridge, 1826f
Digastric sulcus, in surgical anatomy of lateral skull base, 2435-2436, 2435f
Digastric transposition, for depressor dysfunction, 2431-2432
Digenic effect, 8
DiGeorge syndrome, deafness in, 2051t-2058t
Digestion, saliva in, 1141
Digestive enzymes, reflex release of, 1206
Digestive tract evaluation, for penetrating neck trauma, 1633-1634, 1634f-1635f
Digital photography, in facial analysis, 277-280, 279f-280f
Digital radiography, of pharynx and esophagus, 1393
Digital sound processing (DSP), for hearing aids, 2267
Digital technique, for difficult airway, 114t
Dihematoporphyrin ether (DHE), for recurrent respiratory papillomatosis, 2892
1,25-Dihydroxyvitamin D_3, in parathyroid hormone regulation, 1776
Di-iodotyrosine (DIT)
  in thyroid hormone release, 1738
  in thyroid hormone synthesis, 1738

Dilation
for esophageal strictures, due to caustic ingestion, 2960-2962, 2960f-2961f
for tracheal stenosis, 2928, 2928f
Dilator tubae (DT) muscle
anatomy of, 1869f
development of, 1866-1867
in pressure equalization, 1870
DILS (diffuse infiltrative lymphocytosis syndrome), 1157-1158
immunosuppression and, 218
Diltiazem, for hyperthyroidism, 1739t
Dimorphic vestibular afferent nerve fibers, 2283, 2283f
Diode laser, for facial resurfacing, 403t
Diphenhydramine (Benadryl)
for allergic rhinitis, 620
for nonallergic rhinitis, 701t
Diphtheria, pharyngitis due to, 195-196
in children, 2786-2787
Diplopia, due to paranasal sinus tumor, 1123
Dipyridamole, for rhinosinusitis, 734t
Direct audio input, for hearing aid, 2267
Direct brow lift, 430, 431t
Direct cutaneous arteries, 1065, 1065f
Direct nerve implant, for laryngeal reinnervation, 923-924, 924f
Directional microphones, for hearing aids, 2269
Discontinuity defects, maxillofacial prosthodontics for, 1340-1342, 1342f-1343f
Disease
definition of, 53
severity of, 53
Disease-specific scales, as outcome measures, 55-58, 56t
for head and neck cancer, 56-57, 56t
otologic, 56t, 57
pediatric, 56t, 57
rhinologic, 56t, 57
sleep, 56t, 57
symptom, 56t, 57-58
voice, 56t, 57
Disequilibrium, of aging, 233-234
defined, 233
diagnostic methods for, 233
treatment of, 234
vestibular pathology of, 233
Disk battery, ingestion of, 2941, 2958, 2958f
Dislocation, of temporomandibular joint, 1280
Dispersion, descriptive statistics for, 64t
Distal esophageal pressure, 958f
Distal sensory polyneuropathy (DSP), HIV-associated, 223
Distortion product otoacoustic emissions (DPOAEs), 1891, 1905
and audiometric tests, 1905, 1907f
clinical applications of, 1905-1907
defined, 1891, 1905
distortion product in, 1905
frequencies used in, 1905
with high-frequency hearing loss, 1905, 1907f
in infants, 2720-2721
in noise-induced hearing loss, 2146-2147, 2147f-2150f
with normal hearing, 1892f, 1905, 1907f
procedure for, 1891
Distraction osteogenesis
for craniofacial anomalies, 2654-2657, 2656f
for obstructive sleep apnea, 2610
for Robin sequence, 2673
Distress, palliative care for, 1103-1104
DIT (di-iodotyrosine)
in thyroid hormone release, 1738
in thyroid hormone synthesis, 1738
Diuretics
dizziness due to, 2310t
loop
in noise-induced hearing loss, 2147
ototoxicity of, 2174-2175
sensorineural hearing loss due to, 2120
for Meniere's disease, 2126, 2337
Divalproex (Depakote), for migraine, 2350
Divergence paralysis, 2314
Diverticulectomy, transcervical, 991f
Diverticulopexy technique, 992f
Diverticulostomy
endoscopic diathermic, 993f
endoscopic staple, 992-995
complications of, 995
electrocautery technique for, 993f
instruments for, 994f
laser technique for, 993f
limitations of, 994
positioning for, 993f
recurrence after, 995-997
results of, 994-995
technique of, 995f-996f
Diverticulum(a)
esophageal, 974-975, 974f-975f
classification of, 986
double, 986, 989f
mid-, 1402, 1403f
pseudo-, 975, 975f
imaging of, 1406, 1407f
pulsion, 986
traction, 986
types and sites of, 986, 987f-989f
pharyngeal, 1401-1402, 1402f
dysphagia due to, 2951
Zenker's. *See* Zenker's diverticulum (a).
Dix-Hallpike maneuver, 2315-2316, 2315f, 2330-2331, 2331f
Dizziness. *See also* Vertigo.
classification of, 2346
drug-induced, 2310t
evaluation of, 2305-2327
adaptive capabilities of vestibular system in, 2327
algorithm for differential diagnosis in, 2308, 2309f
audiogram for, 2326
background of, 2305
bedside exam for, 2310-2317
dynamic visual acuity in, 2316
eye movements evoked by sound or changes in middle ear pressure in, 2316, 2316f
eye-head coordination in, 2314
head impulse test in, 2314-2315, 2315f
head-shaking nystagmus in, 2314
hyperventilation in, 2316
low-frequency vestibulo-ocular reflex in, 2314
nystagmus in, 2310-2312, 2310t-2311t, 2312f
optokinetic nystagmus in, 2314
positional testing in, 2315-2316, 2315f
saccades in, 2313, 2313f
sensory integration in, 2317
skew deviation and ocular tilt reaction in, 2312-2313, 2312f
smooth pursuit in, 2313-2314
vergence in, 2314
vestibulo-ocular reflex cancellation in, 2314
vestibulospinal function in, 2316-2317
vibration-induced nystagmus in, 2314
high-resolution temporal bone computed tomography for, 2326-2327
history in, 2308-2310, 2309f, 2310t
MRI for, 2327
quantitative testing for, 2317-2324
active head movement analysis techniques for, 2323-2324, 2324f
Dizziness *(Continued)*
caloric, 2319-2320, 2320f-2321f
electrocochleography in, 2323, 2323f
head impulse, 2323
methods of eye movement recordings for, 2317, 2317f
motor control, 2324-2325
for nystagmus, 2317
optokinetic, 2318-2319
posturography in, 2324, 2325f, 2326-2327
rotatory chair, 2320-2323, 2322f-2323f
for saccades, 2317-2318, 2318f
sensory organization, 2325-2326, 2325f-2326f
for smooth pursuit, 2318, 2319f
subjective visual vertical in, 2323
vestibular evoked myogenic potentials in, 2324, 2325f
serologic tests for, 2327
vestibular function in, 2305-2308
brainstem and cerebellum in, 2308
eye movements in, 2305-2307, 2306f-2307f, 2307t, 2309f
head movements in, 2307-2308
peripheral anatomy and physiology in, 2305
due to migraine, 2347
physiologic, 2357
psychophysiologic, 2346
DLBCL. *See* Diffuse large B-cell lymphoma (DLBCL).
DM (desmoplastic melanoma), 1108, 1108f
DMPO (dorsomedial periolivary nucleus), in auditory pathway, 1834f
DMV (difficult mask ventilation), 121-122
DNA. *See* Deoxyribonucleic acid (DNA).
DNM (desmoplastic-neurotropic melanoma), 1108
of oral cavity, 1299
DNMTs (DNA methyltransferases), in head and neck squamous cell carcinoma, 1020
Docetaxel
with chemoradiation, 1041-1042
for induction chemotherapy, 1057-1058
Doctor's Office Quality–Information Technology (DOQ-IT), 84t-87t
Docusate sodium (Cerumenex), for cerumen removal, 1958t
DoD (Department of Defense), 84t-87t, 87
Dohlman, Gosta, 993f
Domeboro Otic. *See* Acetic acid with aluminum acetate (Domeboro Otic).
Dominant disorders, 6, 6f
Dominant-negative effect, 6, 13
Doppler shift, 1643
Doppler ultrasonography, 137
color, 1644
of salivary glands, 1167-1168
of oropharyngeal cancer, 1366
DOQ-IR (Doctor's Office Quality–Information Technology), 84t-87t
Dorello's canal, 1976
Dorsal acoustic stria, 1835, 1835f
Dorsal augmentation, for noncaucasian nose, 556, 569-570
choice of material for, 569, 570f
concept of, 569
results of, 572f-573f
technical considerations for, 569-570, 571f
Dorsal cochlear nucleus, 1835
Dorsal cyst, due to injectable silicone, 578, 579f
Dorsal deformities, revision rhinoplasty for, 584, 585f
Dorsal draw suture, in septal modification, 548, 549f
Dorsal implant, for saddle nose deformity, 555, 556f-558f
Dorsal lingual artery, 1296f
Dorsal stria, in auditory pathway, 1846

Dorsomedial periolivary nucleus (DMPO), in auditory pathway, 1834f
Dorsonasal flap, for nasal defects, 365-366
Dorsum, low, revision rhinoplasty for, 584, 585f
Dorsum sellae, in surgical anatomy of anterior cranial base, 2472f
Dose deposition, in radiation, 1033
Dose-response curves, with radiation therapy, 1038, 1038f
Dose-volume histograms (DVHs), for radiotherapy, 1043
Double chin, liposuction for. *See* Liposuction.
Double-opposing Z-plasty, 2670
  surgical technique for, 2671-2672, 2672f
  for velopharyngeal dysfunction, 2682-2683
Double-strand breaks, by radiation, 1036, 1038
Down syndrome
  craniofacial abnormalities in, 2631-2633, 2631f, 2632b
    due to abnormal and poor growth, 2633
    of ears, 2632
    of eyes, 2632-2633
    mandibular and oral manifestations of, 2632
    of midface, 2632
    of skull, 2632
  inner ear anomalies in, 2735
  and obstructive sleep apnea, 2605-2606
  oral manifestations of, 1257
Doxycycline, for embolization, 1933
DPOAEs. *See* Distortion product otoacoustic emissions (DPOAEs).
Dressing, after liposuction, 459, 459f
Drooling, 2863-2864
  defined, 2863
  epidemiology of, 2863
  medical management of, 2864
  pathogenesis of, 2863-2864
  surgical management of, 2864
Drop attack, 2300
Droperidol, for postoperative nausea and vomiting, 2593
Drug allergies, 94
Drug toxicity, sensorineural hearing loss due to, 2119-2121
  sudden, 2128
Drug-induced epistaxis, 687
Drug-induced esophagitis, 1406, 1406f
Drug-induced hypercalcemia, 1783-1784, 1783t
Drug-induced hypersensitivity, to ototopical antibiotics, 1954
Drug-induced lymphadenopathy, 2819
Drug-induced olfactory dysfunction, 637, 637t
Drug-induced rhinitis, 619b, 696, 697b
Drug-induced sleep videoendoscopy, of obstructive sleep apnea, 253-255
Dry eyes, 446-447, 447f
Dsg1 (desmoglein 1), in pemphigus vulgaris, 1231
Dsg3 (desmoglein 3), in pemphigus vulgaris, 1231
DSL (desired sensation level) method, for hearing aids, 2271
  in infants, 2724
DSP (digital sound processing), for hearing aids, 2267
DSP (distal sensory polyneuropathy), HIV-associated, 223
DSPP (dentin sialophosphoprotein) gene, in deafness, 2051t-2058t
DT (dilator tubae) muscle
  anatomy of, 1869f
  development of, 1866-1867
  in pressure equalization, 1870
DTH (delayed-type hypersensitivity) reactions, 601, 608-612
Ductal cysts
  congenital, 2859
  of larynx, 869, 869f-870f
Ductal secretion, by salivary glands, 1136
Duct(s) of Rivinus, 2850-2852
Ductus reuniens
  anatomy of, 1851f, 1853f-1854f, 2278f
  embryogenesis of, 1852
Duloxetine, for neuropathic pain, 244-245, 245t
Dumbbell tumor, of salivary glands, 1164-1165, 1165f, 1167f-1168f
Dumon stent, for tracheal stenosis, 2929, 2934f
Duodenogastroesophageal reflux (DGER), ambulatory 24-hour bile monitoring for, 960-961, 961f
Duplication, 4-5
Duplication cysts
  foregut, compression of pharynx and esophagus due to, 1408-1409, 1409f
  of oral cavity, 1287-1288, 1288f
Dura, of semicircular canals, 1853f
DuraGen Dermal Graft Matrix, for CSF rhinorrhea, 792-793
Dura-Guard Dural Repair Patch, for CSF rhinorrhea, 792-793
Dural arteriovenous fistulas, embolization of, 1940-1942, 1940f
Dural defect, after transnasal endoscopic-assisted anterior skull base surgery, 2484
Dural septum, in surgical anatomy of lateral skull base, 2437f
Dural tear, due to mastoidectomy, 2015
Durepair Dural Regeneration Matrix, for CSF rhinorrhea, 792-793
DVA (dynamic visual acuity), 2316
DVA (Dynamic Visual Acuity) testing, 2378
DVHs (dose-volume histograms), for radiotherapy, 1043
DVN (descending vestibular nucleus), 1861, 1862f
  in velocity storage, 2296
Dx-pH Measurement System, 962, 962f
Dying spells, in stridulous child, 2898
Dynamic adjustable rotational tip (DART) graft, for saddle nose deformity, 555, 559f
Dynamic airway assessment, for stridor, 2903
Dynamic compensation, for peripheral vestibular lesions, 2373-2376
Dynamic posturography
  for ablative vestibular surgery, 2365
  for vestibular rehabilitation, 2376-2377
Dynamic range
  of auditory neurons, 1844-1845, 1845f
  with hearing aids, 2268
    compression of, 2205-2207
Dynamic visual acuity (DVA), 2316
Dynamic Visual Acuity (DVA) testing, 2378
Dynamic-range compression, for hearing aids, 2268
Dysgeusia, palliative care for, 1103
Dysphagia, 963-968
  algorithm for evaluation of, 954-955, 955f
  due to chemoradiation, 1219
  in children, 2948-2955
    anatomic site(s) of, 2949-2954, 2951f
      hypopharynx and larynx as, 2950t, 2951-2953, 2953f
      nose and nasopharynx as, 2949, 2950t, 2951f
      oral cavity and oral pharynx as, 2949-2951, 2950t, 2952f
      trachea and esophagus as, 2950t, 2953-2954, 2954f
    evaluation of, 2948-2949
      clinical or bedside, 2948-2949
      instrumental, 2949, 2950t
      other diagnostic tests in, 2949
  defined, 954-955
  differential diagnosis of, 990t
  due to eosinophilic esophagitis, 967-968, 969f
  esophageal, 954-956
    vs. oropharyngeal, 956
  due to esophageal motility abnormalities, 963-965, 963b
Dysphagia *(Continued)*
    achalasia as, 963-965
      defined, 963
      endoscopy of, 964, 964f
      esophageal manometry for, 964, 964f
      esophogram of, 963-964, 963f-964f
      etiology and pathogenesis of, 963
      management of, 964-965
      manometric findings with, 959t
      symptoms of, 963
    nonachalasia, 965, 965f-966f
  evaluation for, 1217-1219
    bedside, 1217
    endoscopic, 1218
      for chronic aspiration, 926
    manometry in, 1219
    ultrasonography in, 1219
    videofluoroscopy in, 1217-1218, 1219f
  in geriatric patients, 237
    diagnostic testing for, 237
    treatment of, 237
  due to hypothyroidism, 979
  imaging of, 1398
    ultrasonography for, 1219
    videofluoroscopy for, 1217-1218, 1219f
  due to laryngeal paralysis, 914
  liquid, 954-955
  vs. odynophagia, 956
  oropharyngeal (transfer), 954-955
    vs. esophageal, 956
    evaluation of, 956
  outcome scales for, 57-58
  palliative care for, 1104
  due to post-treatment complications, 1220
  due to radiotherapy, 1219
  due to rings or webs, 966-967, 967f-968f
  screening for, 1217
  signs and symptoms of, 1217
    aspiration (coughing, choking) as, 1217
  solid food, 954-955
  due to strictures, 965-966
    defined, 965-966
    endoscopy of, 965-966, 967f
    esophagram of, 965-966, 966f
    etiology of, 965-966, 966b
    extrinsic, 965-966, 966b
    intrinsic, 965-966, 966b
    refractory, 966
    treatment of, 966
  due to surgical treatment, 1219
    of larynx, 1220
    of pharynx, 1220
    of posterior oral cavity, 1219-1220
    of tongue, 1219
  due to thyroid disease, 1737
  after total laryngopharyngectomy, 1575
  transnasal esophagoscopy in, 983-984, 984f
Dysphonia
  functional, 851
    in children, 2879
  in geriatric patients, 236
  hyperfunctional, 834
  muscle tension, 842, 853
  postoperative, 873-874, 873f
    diagnosis of, 873-874
      history in, 873
      laryngeal examination in, 874
      vocal capability battery in, 873-874
    epidemiology of, 873
    management of, 874
      behavioral, 874
      medical, 874
    pathophysiology and pathology of, 873, 874f
  in professional voice (*See* Professional voice disorders)
  spasmodic, 839
    botulinum toxin therapy for, 839, 840f-841f
    voice breaks in, 834-835

Dysplasia
of larynx, 1486-1491
of oral cavity, 1299
oropharyngeal, 1360
mild, 1360
moderate, 1360
severe, 1360-1361
Dysplastic nevus, 288, 288f
Dyspnea, due to thyroid disease, 1737
Dystonia
adductor breathing, 839
classification of, 838, 838b
diagnosis of, 838
distribution of, 838, 838b
epidemiology of, 838
family history of, 838-839
focal, 838, 838b
generalized, 838
hemi-, 838
laryngeal, 838-839
primary *vs.* secondary, 838
segmental, 838
spread of, 838
Dystrophic epidermolysis bullosa, esophageal manifestations of, 979

E

Ea (early antigen), of Epstein-Barr virus, 1352, 1354
EABR (electrically evoked auditory brainstem response), 1912-1913, 1913f
EABR (evoked auditory brainstem response). *See* Auditory brainstem response (ABR).
EAC. *See* External auditory canal (EAC).
Eagle's syndrome, *vs.* myofascial pain dysfunction syndrome, 1284t
Ear(s)
aesthetic analysis of, 275, 279f
aging of, 231-234
anatomic landmarks of, 2742f
anatomy of, 476-477, 476f, 2742, 2742f
burns of, 316
in Down syndrome, 2632
embryology of, 476-477, 2741, 2742f, 2753
external (*See* External ear)
growth of, 2742
height of, 2742
inner (*See* Inner ear)
melanoma of, 1114
microscopic examination of, 2574
middle (*See* Middle ear)
physical examination of, 97-98
auricles in, 97
external auditory canal in, 97
hearing assessment in, 97-98, 98t
tympanic membrane in, 97, 98f
physiology of (*See* Auditory physiology)
prosthetic, 1345-1346, 1345t, 1346f
protruding, 2742
embryology of, 476-477
etiology of, 476
incidence of, 476
otoplasty for (*See* Otoplasty)
surfer's, 1918, 1918f
swimmer's, 97
telephone, 479
trauma to, 308f, 310, 310f
width of, 2742
Ear canal volumes, 1890-1891
Ear cartilage grafts, for revision rhinoplasty, 583
Ear disorders, in geriatric patients, 231-234
presbycusis as, 232
etiologies of, 232
treatment of, 233
types of, 232
Ear disorders, in geriatric patients *(Continued)*
presbystasis as, 233-234
diagnostic methods for, 233
treatment of, 234
vestibular pathology of, 233
Ear drainage, chronic, topical therapies for, 1957-1958, 1961f
Ear hygiene, topical therapies for, 1957-1958, 1961f
EAR (Effectiveness of Auditory Rehabilitation) scale, 57
Ear wick, for otitis externa, 1945-1946, 1951, 1951f
Ear wick packing, in atresiaplasty, 2756-2757
Earex (arachis oil, almond oil, rectified camphor oil), for cerumen removal, 1958t
Earex Plus (choline salicylate and glycerol), for cerumen removal, 1958t
Early antigen (Ea), of Epstein-Barr virus, 1352, 1354
Early deblocking, 2385
Early Hearing Detection and Intervention (EHDI) program, 2098-2099
Early interventions, for infant hearing loss, 2724
Early Speech Perception (ESP), for cochlear implant, 2225-2226
Earmuffs, for prevention of noise-induced hearing loss, 2151
EAS (electrical and acoustic stimulation), cochlear implants with, 2224, 2224f
EATT1 (excitatory amino acid transporter 1), 2081
EBERs (Epstein-Barr encoded ribonucleic acids), 1352
EBM (evidence-based medicine) recommendations, grading of, 55, 55t, 69-70, 70t
EBRT. *See* External-beam radiation therapy (EBRT).
EBUS (endobronchial ultrasonography), 1011
EBV. *See* Epstein-Barr virus (EBV).
E-cad, in oral cancer, 1301
ECAP (electrically evoked compound action potential), 1912-1913
with cochlear implants, 1913f, 1914
Ecchymosis, postauricular, 97
Echinacea, for rhinosinusitis, 735t
Echogenicity, in ultrasound, 1643
Echography, orbital, of Graves' ophthalmopathy, 1810
ECHOS1, in deafness, 2051t-2058t
Echosonography, transesophageal, 1396
ECoG. *See* Electrocochleography (ECoG).
ECP (eosinophil cationic protein), 604
in otitis media, 2764
Ectropion, 445-446, 2420-2421, 2421f
after blepharoplasty, 450
Eczema, otorrhea due to, 2194
Eczematoid otitis externa, topical therapies for, 1955-1957
anti-inflammatory and immunosuppressive agents as, 1956-1957
options for, 1955
steroids as, 1955-1956
Edema
cerebral
after lateral skull base surgery, 2513
due to neck dissection, 1723
facial, due to neck dissection, 1723, 1729f
laryngeal, in vocal professional, 854
preseptal orbital, due to rhinosinusitis, 676
pulmonary
after adenotonsillectomy, 2800
postobstructive, 119
EDN (eosinophil-derived neurotoxin), 604
EDN3 (endothelin 3) gene, in deafness, 2051t-2058t, 2095
EDNRB (endothelin receptor type B) gene, in deafness, 2051t-2058t, 2095
Edrophonium test, 963
in neurologic evaluation, 835
Education, with cochlear implant, 2251-2253, 2251f, 2255-2257
Educational Resource Matrix (ERM), with cochlear implants, 2251f, 2253
EEMG (evoked encephalomyography), for facial nerve injury, 2041
EER. *See* Extraesophageal reflux (EER).
Effect size, 66-67
Effective dose equivalent, 133
Effective masking, in audiologic testing, 1889
Effectiveness, 52, 54
Effectiveness of Auditory Rehabilitation (EAR) scale, 57
Efferent auditory system, 1847-1849
middle ear muscle reflex pathways in, 1847, 1848f
olivocochlear reflex pathways in, 1848-1849, 1848f
Efficacy, 53-54
explanations other than, 61, 61f, 62t
Eflornithine, sensorineural hearing loss due to, 2120-2121
EGD (esophagogastroduodenoscopy)
for extraesophageal reflux, 899
for laryngeal stenosis, 2917
EGF (epidermal growth factor)
in saliva, 1140
in wound healing, 1076
EGFR. *See* Epidermal growth factor receptor (EGFR).
EGG (electroglottography)
for measurement of vocal fold vibration, 830, 835
for professional voice, 849
EGM (electrogustometry), 2383-2384
EHDI (Early Hearing Detection and Intervention) program, 2098-2099
EHLL (epithelial hyperplastic laryngeal lesions), 1525
EHR (electronic health record), 84t-87t
EI(s) (entry inhibitors), 211
Eicosanoids, in rhinosinusitis, 731-732, 732f
Einstein, Albert, 1032-1033
Elastin, in skin flaps, 1071
Elderly. *See* Geriatric patients.
Elective lymph node dissection (ELND), for melanoma, 1114-1115
Electric acoustic reflex thresholds, for cochlear implants, 2255
Electric stimulation, for tinnitus, 2136-2137
via cochlear implants, 2137
transcutaneous, 2136-2137
Electrical and acoustic stimulation (EAS), cochlear implants with, 2224, 2224f
Electrically evoked auditory brainstem response (EABR), 1912-1913, 1913f
Electrically evoked auditory potentials, 1912-1914
auditory brainstem response as, 1912-1913, 1913f
clinical applications of, 1914
compound action potential as, 1912-1913
with cochlear implants, 1913f, 1914
middle and long latency response as, 1912-1914, 1913f
Electrically evoked compound action potential (ECAP), 1912-1913
with cochlear implants, 1913f, 1914
Electrically evoked long latency responses (ELLRs), 1913-1914
Electrically evoked middle latency responses (EMLRs), 1912-1914
Electroacoustic characteristics, of hearing aid, 2267-2268, 2268f
Electroacoustic stimulation, cochlear implants with, 2224, 2224f
hearing preservation and, 2245-2246

Electrocautery
  interventional bronchoscopy with, 1010t
  in otoplasty, 478
Electrocautery tonsillectomy, 2797-2799
Electrocochleography (ECoG), 1892-1896, 1907-1908
  and auditory brainstem responses, 1908
  clinical applications of, 1908
  with cochlear implant, 1913f
  cochlear microphonic in, 1907-1908
  defined, 1892-1894, 1907
  for dizziness, 2323, 2323f
  for Meniere's disease, 1892-1896, 1895f, 1908, 2337
  with normal hearing, 1894f, 1913f
  procedure for, 1894, 1908
  for sensorineural hearing loss, in adults, 2117
  SP/AP ratio in, 1892-1894
  summating potential in, 1892-1894, 1907
  whole-nerve action potential in, 1892-1894, 1907
Electrodes, for intraoperative cranial nerve monitoring
  recording, 2543-2544, 2543f
  stimulating, 2544, 2544f
Electrodiagnostic testing, of facial nerve function, 2385-2387
  electromyography in, 2386-2387
  electroneuronography in, 2041, 2386, 2387t
  maximal stimulation test in, 2040-2041, 2385-2386, 2387t
  nerve excitability test in, 2040-2041, 2385, 2387t
Electrodogram, 2230, 2230f
Electroglottography (EGG)
  for measurement of vocal fold vibration, 830, 835
  for professional voice, 849
Electrogustometry (EGM), 2383-2384
Electrolarynx voice and speech, physiology of, 1596, 1596f
Electrolyte composition, ideal, for infants, 2572t
Electromagnetic (EM) middle ear implantable hearing aids, 2208-2211
  Carina as, 2210-2211
    clinical results with, 2210-2211
    components of, 2210, 2210f
    history of, 2210
    placement of, 2210, 2211f
  Middle Ear Transducer (MET) as, 2027, 2210-2211
    clinical results with, 2210-2211
    comparison of features of, 2206t
    components of, 2210
    history of, 2210
    indications for, 2210, 2211f
    placement of, 2210, 2211f
  ossicular coupling in, 2207-2208
  sound transduction and coupling to auditory system with, 2205f
  transducer design for, 2207
  Vibrant Soundbridge as, 2208-2210
    clinical data on, 2209
    comparison of features of, 2206t
    components of, 2208-2209, 2208f
    for conductive and mixed hearing loss, 2210
    history of, 2208, 2210
    implantation of, 2209
    indications for, 2209, 2209f
Electromagnetic (EM) radiation, 1031, 1031f
Electromagnetic (EM) stimulation, to assess facial nerve function, 2388-2389
  in Bell's palsy, 2394-2395
Electro-mechanical voice devices, after total laryngectomy, 1572
Electromyography (EMG)
  artifacts in, 2547-2548, 2548f
  for Bell's palsy, 2394
Electromyography (EMG) *(Continued)*
  for cranial nerve monitoring
    anesthesia and, 2544
    of cochlear nerve, 2552
      and outcome, 2554-2555
    electrodes for
      recording, 2543-2544, 2543f
      stimulating, 2544, 2544f
    of facial nerve, 2387-2388, 2545-2548
      for acoustic neuroma and other cerebellopontine angle tumors, 2545
      activity evoked by electrical stimulation in, 2545-2546
      to assess functional status of nerves after tumor removal, 2545-2546
      to identify and map nerves in relation to tumor, 2545
      for intraoperative identification of nervus intermedius, 2546, 2546f
      limitations of, 2547-2548, 2548f
      during microvascular decompression, 2548-2549, 2549f
      during other otologic surgery, 2549
      and outcome, 2554
      during parotid surgery, 2549
      spontaneous and mechanically evoked activity in, 2546-2548, 2547f
    instrumentation for, 2543
    of ninth, tenth, eleventh, and twelfth cranial nerves, 2550-2552, 2551f-2552f
    stimulation criteria for, 2544
    of third, fourth, and sixth cranial nerves, 2549-2552, 2550f
    of trigeminal motor branch, 2550
  for facial nerve injury, 2041, 2386-2387
    evoked, 2386
  laryngeal, 835, 905
    for stridor, 2901
Electron beams, in radiotherapy, 1034, 1035f
Electroneuronography/electroneurography (ENoG)
  for Bell's palsy, 2394
  for facial nerve injury, 2041, 2386, 2387t
  for facial nerve neuroma, 2519
Electronic health record (EHR), 84t-87t
Electronic medical record (EMR), 84t-87t
"Electronic nose," for CSF rhinorrhea, 790
Electronic patient record (EPR), of difficult airway, 118-119
Electronic portal imaging devices (EPIDs), with radiotherapy, 1046
Electronystagmography (ENG), 2317
  of Meniere's disease, 2337
  of saccades, 2318f
  of smooth pursuit, 2319f
Electro-oculography (EOG), 2317, 2317f
Electro-olfactogram (EOG), 632
Electrophysiologic hearing assessment, 1904-1915
  auditory brainstem response for, 1896, 1908-1911
    with acoustic neuroma, 1896, 1898f-1899f, 1911
    advantage of, 1908
    audiometric thresholds based on
      click-evoked, 1909
      using more frequency-specific stimuli, 1909-1910, 1910f
    with auditory neuropathy or dyssynchrony, 1899-1901, 1900f
    click-evoked, 1909
    clinical applications of, 1896, 1908-1911
      to assess hearing sensitivity, 1909-1910, 1910f
      in CHAMP procedure, 1911
      for differential diagnosis, 1910-1911
      for intraoperative monitoring, 1899f, 1911
Electrophysiologic hearing assessment *(Continued)*
      for neurodiagnosis, 1896-1899, 1898f-1899f
      otoneurologic, 1910-1911
    with cochlear implant, 1913f
    defined, 1896, 1908
    effect of intensity on, 1908, 1909f
    electrically evoked, 1912-1913, 1913f
    electrocochleography and, 1908
    interpretation of, 1896
    maturational changes in, 1908
    with normal hearing, 1896, 1896f, 1908, 1909f, 1913f
    and otoacoustic emissions, 1891-1892, 1893f
    procedure for, 1896, 1908
    speech-evoked, 1911
    stacked, 1911
    tone burst–evoked, 1909-1910
  auditory steady-state response for, 1911-1912
    clinical applications of, 1910f, 1912
  electrically evoked auditory potentials for, 1912-1914
    auditory brainstem response as, 1912-1913, 1913f
    clinical applications of, 1914
    compound action potential as, 1912-1913
      with cochlear implants, 1913f, 1914
    middle and long latency response as, 1912-1914, 1913f
  electrocochleography for, 1892-1896, 1907-1908
    auditory brainstem response and, 1908
    clinical applications of, 1908
    with cochlear implant, 1913f
    cochlear microphonic in, 1907-1908
    defined, 1892-1894, 1907
    for Meniere's disease, 1892-1896, 1895f, 1908
    with normal hearing, 1894f, 1913f
    procedure for, 1894, 1908
    SP/AP ratio in, 1892-1894
    summating potential in, 1892-1894, 1907
    whole-nerve action potential in, 1892-1894, 1907
  middle and long latency evoked potentials for, 1912, 1913f
    electronically evoked, 1912-1914
  otoacoustic emissions for, 1891-1892, 1904-1907
    with acoustic neuroma, 1891-1892, 1893f, 1897
    advantages of, 1906
    and audiograms, 1905, 1906f
    and auditory neuropathy or dyssynchrony, 1907
    clinical applications of, 1905-1907
    cochlear echoes in, 1891
    distortion-product, 1891, 1905
      and audiometric tests, 1905, 1907f
      clinical applications of, 1905-1907
      defined, 1891, 1905
      distortion products in, 1905
      frequencies used in, 1905
      with high-frequency hearing loss, 1905, 1907f
      with normal hearing, 1892f, 1905, 1907f
      procedure for, 1891
    with neural hearing loss, 1899-1901
    with normal hearing, 1905, 1906f
    procedure for, 1891
    with sensorineural hearing loss, 1905, 1906f
    spontaneous, 1905
    stimulus-frequency, 1891
    transient evoked, 1891, 1905
      with acoustic neuroma, 1891-1892, 1893f
      advantages of, 1891
      analysis of, 1905
      clinical applications of, 1905-1907
      defined, 1891, 1905
      with normal hearing, 1892f
    types of evoked, 1891, 1905
Electrophysiologic monitoring, during anterior and middle cranial base surgery, 2450

Electrophysiologic testing, of olfactory ability, 632
Electrosurgery, for skin lesions, 294
ELLRs (electrically evoked long latency responses), 1913-1914
ELLRs (evoked long latency responses)
  auditory, 1912, 1913f
  electrically, 1913-1914
ELND (elective lymph node dissection), for melanoma, 1114-1115
EM. *See* Electromagnetic (EM); Erythema multiforme (EM).
Embolic agents, 1933-1934
Embolization
  angiographic catheters for, 1932-1933
  angiographic equipment for, 1932
  embolic agents for, 1933-1934
  for epistaxis, 690, 691f
  of juvenile angiofibroma, 1937-1938, 1938f
    nasopharyngeal, 1351
  of meningiomas, 1938, 1939f
  of paragangliomas, 1934-1937, 1935f
    carotid body tumor as, 1937, 1937f
    glomus jugulare tumor as, 1935-1936, 1936f
    glomus tympanicum tumor as, 1935
    glomus vagale tumor as, 1936-1937, 1936f
  provocative testing to ensure safety of, 1934, 1934f
  of thyroid neoplasms, 1938-1939
  of vascular lesions, 1939-1943
    dural arteriovenous fistulas as, 1940-1942, 1941f
    epistaxis as, 1939-1940, 1940f
    facial arteriovenous fistulas as, 1940, 1940f
    facial vascular malformations as, 1942, 1942f
    hemangiomas of face and neck as, 1942
    pseudoaneurysms as, 1942, 1943f
    tinnitus-producing fibromuscular dysplasia of carotid artery as, 1943
Embosphere Clear, for embolization, 1933
Embryology, of head and neck, 2583-2585, 2583f
  branchial arches in, 2583-2584, 2583f
    craniofacial syndromes related to, 2585
    innervation of, 2584
    muscular derivatives of, 2584
    skeletal derivatives of, 2583-2584, 2583f
  pharyngeal pouch(es) in, 2583-2585, 2583f-2584f
    first, 2584, 2584f-2585f
    fourth through sixth, 2584f-2585f, 2585
    second, 2584, 2584f-2585f
    third, 2584f-2585f, 2585
EMG. *See* Electromyography (EMG).
Emissary vein, in surgical anatomy of lateral skull base, 2436f
EMLA (eutectic mixture of local anesthetics), for premedication of children, 2589
EMLRs (electrically evoked middle latency responses), 1912-1914
EMLRs (evoked middle latency responses)
  auditory, 1912, 1913f
  electrically, 1912-1914
EMP (extramedullary plasmacytoma), of larynx, 1509
Emphysema
  oral manifestations of, 1250
  subcutaneous
    of infrahyoid retropharyngeal space, 161f
    of neck, 1410, 1410f
Empirical Sleepiness and Fatigue Scales, 57
Empty sella syndrome (ESS), CSF rhinorrhea due to, 787
Empyema, subdural, 1994-1995
  epidemiology of, 1980t-1981t, 1994-1995
  imaging of, 1995
  in neonates, 1995
  otitis media and, 2777
  symptoms of, 1995
  treatment of, 1995
EMR (electronic medical record), 84t-87t
ENaCs (epithelial Na^+ channels), in taste, 1208
Enamel organ, development of, 1259
ENB. *See* Esthesioneuroblastoma (ENB).
Encephalocele(s), 2645, 2646f
  classification of, 2645
  defined, 2645
  imaging of, 670, 671f, 765t
  nasal, 2687-2688
    basal, 2687-2688, 2687t, 2688f
    classification of, 2687-2688, 2687t
    defined, 2687, 2687f
    epidemiology of, 2687
    vs. gliomas, 2688
    histopathology of, 2688
    imaging of, 2688, 2688f
    management of, 2688
    nasoethmoidal, 2687-2688, 2687t
    nasofrontal, 2687-2688, 2687t
    naso-orbital, 2687-2688, 2687t
    sincipital, 2687-2688, 2687f, 2687t
    sphenoethmoidal, 2687t
    spheno-orbital, 2687t
    terminology for, 2687
    transethmoidal, 2687t
    transsphenoidal, 2687t
  due to otitis media, 1992-1993, 1993f
  temporal bone, 2509
    diagnostic evaluation of, 2509
    surgical approach to, 2509
Encephalofacial angiomatosis, 1257
Encephalomyography, evoked, for facial nerve injury, 2041
Enchondral bone formation, 2614, 2615f
End of life care, 1104. *See also* Palliative care.
  for geriatric patients, 231
Endaural approach, in tympanoplasty, 2001-2002, 2001f
End-bulbs of Held, 1845
Endobronchial biopsy, flexible fiberoptic bronchoscopy for, 1004-1005, 1004f
Endobronchial brachytherapy, interventional bronchoscopy with, 1010t
Endobronchial stent placement, interventional bronchoscopy for, 1009
Endobronchial ultrasonography (EBUS), 1011
Endocarditis prophylaxis, 102, 1248, 1249t
  for pediatric surgery, 2596, 2596t-2597t
Endocochlear potential, 1840, 1841f-1842f
Endocrine disorders
  oral manifestations of, 1251
  preoperative evaluation of, 104-105
    of adrenal gland, 104-105
    diabetes mellitus as, 105
    of parathyroid, 104
    of thyroid, 104
  sensorineural hearing loss due to, 2125
Endocrine evaluation, prior to anterior and middle cranial base surgery, 2446
Endolaryngeal stents
  for airway stenosis, 947, 947f
  for chronic aspiration, 928, 930f
  for laryngeal trauma, 937, 939f-940f
Endoluminal stents, for unresectable tracheal tumor, 1621-1622
Endolymph, 1832
  in auditory physiology, 1841f-1842f
  in vestibular system, 1855, 2277, 2278f
Endolymph homeostasis, 2081-2083, 2083f-2084f
Endolymph rotation, ampullopetal and ampullofugal, 2289
Endolymphatic diverticulum, 1852
Endolymphatic duct
  anatomy of, 1832, 1851f, 1853f-1854f, 2278f
  operculum of, 1822, 1823f
Endolymphatic fluid, 1832
Endolymphatic hydrops
  audiogram in, 1895f
  electrocochleography in, 1892-1896, 1895f, 1908
  idiopathic (*See* Meniere's disease)
  otosclerosis with, 2035
  sensorineural hearing loss due to, 2126-2127, 2199
  stacked auditory brainstem response in, 1911
  vertigo due to, 2202
Endolymphatic sac, 1825f, 1832, 1851f, 1853f
Endolymphatic sac surgery
  for congenital inner ear anomalies, 2739
  for Meniere's disease, 2126, 2339, 2363-2364, 2363f
Endolymphatic sac tumor, fluctuating hearing loss due to, 2199
Endolymphatic-perilymphatic barrier, 2081, 2082f
Endoscopes, for visualization of larynx, 813-814
  flexible, 814
  rigid, 813-814
Endoscopic brow lift, 431, 431t
Endoscopic CO_2 laser resection, for hypopharyngeal cancer, 1429-1430, 1442
  outcomes of, 1436-1438
Endoscopic dacryocystorhinostomy, 763, 797-802
  complications of, 801
  evaluation for, 797-798
    dacryocystogram in, 798, 798f-799f
    scintilligraphy in, 798, 799f
  nasal preparation for, 798
  outcomes of, 801
  revision, 801
  surgical technique for, 798-801
    agger nasi in, 799-800, 800f
    bone removal in, 799-800, 800f
    common canaliculus in, 800-801, 801f
    creation of flap in, 798, 799f
    endoscopic septoplasty in, 798, 799f
    flap elevation in, 798-799, 800f
    flap positioning in, 800, 800f
    frontal process and lacrimal bone in, 799-800, 800f
    lacrimal probe in, 800
    tube stents in, 800-801, 801f
Endoscopic diathermic diverticulostomy, 993f
Endoscopic esophagodiverticulostomy, 992
Endoscopic excision, of glottic cancer, 1518, 1520f
Endoscopic frontal sinusotomy, 776-778
  accessing frontal recess in, 777, 777f-778f
  confirming location of instrument in, 777-778, 778f
  contrainidications to, 781, 781f
Endoscopic imaging, of early glottic carcinoma, 1515-1516, 1516f
Endoscopic lung volume reduction, 1011
Endoscopic orbital decompression, for Graves' ophthalmopathy, 1814, 1815f-1816f
  combined with open approach, 1814
  combined with optic nerve decompression, 1815
Endoscopic orbital surgery, 763
Endoscopic parathyroid exploration, 1793-1794
Endoscopic repair, for CSF rhinorrhea, 792-794, 793f-794f
Endoscopic sinus surgery (ESS), 739-758, 759-1
  advances in instrumentation for, 762-763
  complications of, 754-755, 754b
    CSF rhinorrhea as, 787, 788f
    hemorrhage as, 754
    intracranial, 755, 755f
    ophthalmic, 754-755
  failure of, 756
  follow-up after revision, 774
  functional
    abnormal facial growth and development due to, 2623-2625
    extent of, 759-760
    ostiomeatal complex in, 760, 760f

Endoscopic sinus surgery (ESS) *(Continued)*
for pediatric chronic sinusitis, 2779-2781, 2780f-2781f
principles of, 743, 759
radiologic evaluation after, 677-680
expected findings in, 677-679, 679f
operative complications in, 679-680, 680f
historical background of, 739
indications for, 741-742, 741b, 760-761
anterior meningoencephaloceles as, 742
choanal atresia as, 742
CSF rhinorrhea as, 742
expanded utilization of transnasal endoscopic sinus approach as, 742
headache and facial pain as, 742
intractable epistaxis as, 742
mucoceles as, 742, 760f, 761, 762f
removal of foreign body as, 742
rhinosinusitis as
with acute complications, 741, 761
allergic fungal, 761, 762f
chronic, 741, 761
invasive fungal, 742, 761
noninvasive fungal, 742, 761
recurrent acute, 741
sinonasal polyposis as, 741
tumors as, 742, 762-763
medical treatment prior to, 763
results of, 755-756
for rhinosinusitis, 742-756, 759-1
with acute complications, 741, 761
anesthesia for, 744-745
general, 745
local, 744-745
anterior ethmoidectomy in, 747, 748f
antibiotics prior to, 743
chronic, 741-743, 761
complete ethmoidectomy in, 748-749, 749f-750f
complications of, 754-755, 754b
hemorrhage as, 754
intracranial, 755, 755f
ophthalmic, 754-755
computer-assisted navigation in, 772
with concha bullosa, 751, 752f
conclusion of procedure for, 751
failure of, 756
frontal sinusotomy in, 750-751, 768-771
agger nasi cell in, 769, 771f-772f
and causes of frontal sinus disease, 769
challenges of, 768
external approaches as adjunct to, 771, 773f
frontal bullar cell in, 772f
frontal recess dissection in, 769, 770b, 770t, 771f
frontal sinus cells in, 769-770, 772f
image-guided navigation system in, 771f
interfrontal sinus septal cell in, 771, 772f
preoperative evaluation for, 768-769
recessus terminalis in, 771
suprabullar cell in, 772f
supraorbital ethmoid cell in, 770-771, 772f
fungal, 742, 761, 762f
image-guided navigation systems in, 743-744, 745f
intraoperative CT scans during, 744, 772
limited *vs.* extended approaches for, 752-753
maxillary antrostomy in, 747, 747f
failure of, 764-766, 766f
Messerklinger technique for, 746
middle turbinate in, 751, 751f, 771
minimally invasive sinus technique in, 743, 752, 760
with mucoceles, 751
nasal endoscopy in, 746, 763
with nasal septal deviation, 751
Endoscopic sinus surgery (ESS) *(Continued)*
patient preparation and positioning for, 745-746
with polyps, 751-752
posterior ethmoidectomy in, 747-748, 749f
postoperative care after, 753-754, 773-774
preoperative assessment for, 743, 763-764
CT in, 743, 744t, 763-764, 764f-765f, 764t
examination in, 743
history in, 743
MRI in, 764, 765t
nasal endoscopy in, 763
recurrent acute, 741
resection of uncinate process in, 746, 746f
results of, 755-756
sinus balloon catheterization in, 752-753, 753f
sphenoid sinusotomy in, 748, 749f
sphenoidotomy in, 748, 749f
complications of, 767, 768t
for fungus ball, 768f-769f
with image-guided navigation system, 770f
Wigand technique for, 746
simulation of, 46-49
Dextroscope for, 48
ES3 for, 46-48, 46f
curriculum development for, 48
validation studies of, 47-48, 47f, 48t
Nasal Endoscopy Simulator for, 49
Paranasal Sinuses Simulator for, 49
rationale for, 46-49
VR-FESS for, 48
surgical anatomy for, 739-741
anatomic variations in, 741
anterior skull base in, 741
ethmoid complex in, 740
frontal sinus in, 740-741
maxillary sinus in, 740
middle turbinate in, 739-740
ostiomeatal complex in, 739, 740f
sphenoid sinus in, 740, 740f
Endoscopic sinus surgery simulator (ES3), 46-48, 46f
curriculum development for, 48
validation studies of
for discriminant and concurrent validity, 47, 47f
vs. performance on other tests of innate ability, 48, 48t
for predictive validity, 48
Endoscopic sphenopalatine artery ligation (ESPAL), for epistaxis, 689-690, 689f-690f
Endoscopic staple diverticulostomy (ESD), 992-995
complications of, 995
electrocautery technique for, 993f
instruments for, 994f
laser technique for, 993f
limitations of, 994
positioning for, 993f
recurrence after, 995-997
results of, 994-995
technique of, 995f-996f
Endoscopic surgery
of anterior and middle cranial base, 2448-2450
in central compartment, 2457-2458, 2457f
for juvenile nasopharyngeal angiofibroma, 1350-1351
for nasopharyngeal carcinoma, 1355, 1355f
Endoscopic transnasal-transsphenoidal resection, 2457-2458, 2457f
Endoscopic treatment
for GERD, 970
of laryngeal stenosis, 2918
of stridulous child, 2908-2909
balloons in, 2906, 2906f, 2909
endoscopic sutures in, 2909
laser in, 2908-2909, 2908f
Endoscopic treatment *(Continued)*
microdebrider in, 2909
microinstrumentation for, 2908, 2908f
stents, keels, and grafts in, 2909
for topical drug administration, 2909
Endoscopic-assisted anterior skull base surgery, transnasal, 2471-2486
anesthesia for, 2476
combined approaches for, 2484
complications of, 2485
craniocervical junction–odontoid approach for, 2483-2484, 2484f
instrumentation for, 2476
patient preparation for, 2475-2476
pedicled septal flap in, 2476-2477
postoperative care after, 2484-2485
preoperative assessment for, 2475, 2475f
reconstruction after, 2484
surgical anatomy for, 2471-2475
anterior cranial fossa in, 2471, 2472f
clivus in, 2474, 2474f
nasal cavity in, 2471-2473, 2472f-2473f
nasopharynx in, 2474
paranasal sinuses in, 2473-2474, 2473f
retroclival region in, 2474-2475, 2474f-2475f
surgical team setup for, 2476f
transcribriform approach for, 2482
with bilateral access, 2482, 2482f
with unilateral access, 2482
transmaxillary-transpterygoidal-infratemporal approach for, 2482-2483, 2483f
transsellar and parasellar approaches for, 2479, 2480f
transsphenoidal approach for, 2477-2481
with direct transnasal access, 2477, 2477f
with petrous apex access, 2481
with transclival approach, 2479-2481, 2480f-2481f
with transethmoidal access, 2478-2479, 2479f-2480f
with transseptal access, 2477-2478, 2477f-2478f
with transseptal-transnasal access, 2478, 2479f
transtuberculum-transplanum approach for, 2482
Endoscopy
for airway stenosis, 944-945, 945f
for caustic ingestion, 2957-2959, 2958f
for foreign body removal, 2939-2940, 2939t, 2940f
gastroesophageal, 956-957
equipment for, 956
of esophageal varices, 958f
for extraesophageal reflux, 899
of gastroesophageal junction
with Mallory-Weiss tear, 957f
normal, 956-957, 957f
with severe esophagitis, 957f
of squamocolumnar junction, 956-957, 956f-957f
technique of, 956-957
for laryngeal trauma, 936
of larynx (*See* Laryngeal videoendoscopy)
in nasal examination, 642
for oral cancer, 1300
of oropharyngeal cancer, 1366, 1366f
for swallowing disorders, 1218
with chronic aspiration, 926
of tracheal stenosis, 2926-2927
virtual, 138, 140f
ENDOSTITCH autosuture device, 993, 994f-996f
Endothelin 3 *(EDN3)* gene, in deafness, 2051t-2058t, 2095
Endothelin receptor type B *(EDNRB)* gene, in deafness, 2051t-2058t, 2095

Endotracheal intubation (ETT)
for croup, 2806
of difficult airway, Hollinger anterior commissure laryngoscope for, 122, 122f
laryngeal trauma due to, 939
etiology of, 939, 941f
incidence of, 939
with intubation granulomas, 939, 941f
with laryngeal stenosis, 939, 940f, 943
in children, 2914-2915
management of, 939
for supraglottitis, 2808
Endotracheal tube(s) (ETT), for laser surgery, 36-37
Endotracheal tube (ETT) guides, for difficult airway, 114t
Endovascular interventional procedures, 1932-1943
for lesions of vascular etiology, 1939-1943
dural arteriovenous fistulas as, 1940-1942, 1941f
epistaxis as, 1939-1940, 1940f
facial arteriovenous fistulas as, 1940, 1940f
facial vascular malformations as, 1942, 1942f
hemangiomas of face and neck as, 1942
pseudoaneurysms as, 1942, 1943f
tinnitus-producing fibromuscular dysplasia of carotid artery as, 1943
materials and techniques for, 1932-1934
angiographic catheters as, 1932-1933
angiographic equipment as, 1932
embolic agents as, 1933-1934
provocative testing to ensure safety of embolization as, 1934, 1934f
for neoplasms, 1934-1939
inter-arterial chemotherapy as, 1939
juvenile angiofibroma as, 1937-1938, 1938f
meningiomas as, 1938, 1939f
paragangliomas as, 1934-1937, 1935f
carotid body tumor as, 1937, 1937f
glomus jugulare tumor as, 1935-1936, 1935f-1936f
glomus tympanicum tumor as, 1935
glomus vagale tumor as, 1936-1937, 1936f
thyroid, 1938-1939
Energy deposition, in radiation, 1033
ENG. *See* Electronystagmography (ENG).
Enhancers, of gene expression, 19
ENoG (electroneuronography)
for Bell's palsy, 2394
for facial nerve injury, 2041, 2386, 2387t
for facial nerve neuroma, 2519
Enteric transplantation, for hypopharyngeal and esophageal reconstruction, 1455-1457
gastro-omental donor site for, 1457-1458, 1457f
jejunal donor site for, 1455-1457, 1456f
Entropion, 445-446
after blepharoplasty, 450
Entry inhibitors (EIs), 211
Enuresis, 262t
with obstructive sleep apnea, 2603
sleep-disordered breathing and, 2792
Environmental factors
in head and neck squamous cell carcinoma, 1016-1018
and nasopharyngeal carcinoma, 1352
in noise-induced hearing loss, 2147-2148
in otitis media, 2767-2768
in rhinosinusitis, 731
Environmental sleep disorder, 262t
Environmental sound enrichment, for tinnitus, 2133-2134
Environmental tobacco smoke (ETS), and chronic rhinosinusitis, 707
Envoy device, 2206t, 2211-2212, 2212f
EOAEs (evoked otoacoustic emissions), in infants, 2720-2721
EOG (electro-oculography), 2317, 2317f
EOG (electro-olfactogram), 632
EORTC-HN35 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire), 56
Eosinophil(s)
in adaptive immune system, 604
in allergic rhinitis, 616
Eosinophil cationic protein (ECP), 604
in otitis media, 2764
Eosinophil peroxidase (EPO), 604
Eosinophil-derived neurotoxin (EDN), 604
Eosinophilia
nonallergic rhinitis with, 619b, 696
in rhinosinusitis, 731
Eosinophilic esophagitis, 967-968, 969f
dysphagia due to, 2954
Eosinophilic granuloma, 2100
of oral cavity, 1240, 1257
clinical features of, 1240, 1240f
defined, 1240
differential diagnosis of, 1240
etiology of, 1240
histopathologic features of, 1240, 1240f
treatment of, 1240
otologic manifestations of, 2101f-2102f
otorrhea as, 2196
Eosinophilic inflammation, in chronic rhinosinusitis, 707
Ependymoma, of cerebellopontine angle, 2528-2529, 2531f
EPID(s) (electronic portal imaging devices), with radiotherapy, 1046
Epidemic vertigo, 2332-2333
Epidermal grafts, for airway stenosis, 947
Epidermal growth factor (EGF)
in saliva, 1140
in wound healing, 1076
Epidermal growth factor receptor (EGFR)
in head and neck squamous cell carcinoma, 1022-1023
biology of, 1022, 1025f
as biomarker, 1026
clinical implications of, 1023
oncogene for, 1019
and targeted therapy, 1060-1061
in laryngeal carcinoma, 1505
in salivary gland neoplasms, 1199
Epidermal growth factor receptor (EGFR) inhibitors, for head and neck squamous cell carcinoma, 1018
Epidermal growth factor receptor tyrosine kinase (EGFR-TK), in non–small cell lung cancer, 1023
Epidermal neoplasm(s), 281-286
actinic keratoses as, 283, 284f
basal cell carcinoma as, 283-285, 284f-285f
chondrodermatitis nodularis helicis as, 285, 285f
dermatosis papulosa nigra as, 282
keratoacanthoma as, 284f, 286
seborrheic keratoses as, 281-282, 282f
squamous cell carcinoma as, 285-286, 285f
warts (verruca vulgaris) as, 282-283
filiform, 282, 282f
flat, 282, 283f
due to molluscum contagiosum, 282-283, 283f
Epidermis, 1065
Epidermoid(s). *See* Epidermoid cyst(s).
Epidermoid cyst(s), 289
of cerebellopontine angle, 2518-2519
diagnostic studies of, 2519
imaging of, 1928, 1928f, 2519, 2520f
in differential diagnosis, 1929t, 2518t, 2519, 2524t
signs and symptoms of, 2518-2519
of cerebellopontine cistern, 2509f
of larynx, 868f-869f, 869
of vocal folds, 2882, 2882f
Epidermoid tumor(s). *See* Epidermoid cyst(s).
Epidermolysis bullosa, esophageal manifestations of, 979
imaging of, 1406, 1406f
Epidural abscess, 1995-1996
epidemiology of, 1980t-1981t
Epigenetic profile, in head and neck squamous cell carcinoma, 1022
Epigenetics, of head and neck squamous cell carcinoma, 1020-1022, 1021f-1022f
Epiglottic cartilage, anatomy of
applied, 806
radiographic, 1471
surgical, 1542f-1543f
Epiglottic flap closure, for chronic aspiration, 928, 930f
Epiglottic laryngoplasty, 1549
complications of, 1549
extended procedures for, 1549
functional outcome of, 1549
key surgical points for, 1549
oncologic results of, 1549
surgical technique for, 1549, 1549f
Epiglottis
anatomy of, 1359f
radiographic, 1397, 1399f, 1463f, 1471f, 1473f
surgical, 1541, 1542f-1543f
bifid, 2870t, 2874, 2874f
carcinoma of
anatomic basis for, 1541
imaging of, 1475, 1477f
pre-glottic space extension of, 1485f
hypoplastic, 2870t
omega, 1464
physical examination of, 100
sarcoidosis of, 1465f
during swallowing, 833
Epiglottitis, 883, 1464
in children, 2806-2809
clinical features of, 2807
complications of, 2808-2809
diagnosis of, 2807-2808, 2807f-2808f
differential diagnosis of, 2806t
endoscopy of, 2808, 2808f
epidemiology of, 2806-2807
etiology of, 2807
histology of, 2807, 2807f
historical background of, 2806-2807
imaging of, 2807f, 2808
management of, 2808
clinical presentation of, 2807
defined, 1464
differential diagnosis of, 1464, 1465f, 2806t
imaging of, 159-161, 1406-1407, 1464
in children, 2807f, 2808
CT for, 1406
plain film, 163f, 1406, 1407f, 1464, 1464f
pseudo-, postlaryngectomy, 1416, 1417f
Epiglottopexy, for laryngomalacia, 2867-2868
Epiglottoplasty, for glottic cancer, 1517t
Epilepsy
olfactory auras in, 636
preoperative evaluation of, 106
Epinephrine, racemic, for croup, 2806
postintubation, 2593
Epiphora, 303
after blepharoplasty, 450-451
due to nasal fracture, 498
due to paranasal sinus tumor, 1123
Epiphrenic diverticula, 974-975, 975f
Episodic rhinitis, 617-618
Epistaxis, 682-693
in adults, 686-687, 687f
due to angiofibroma, 686f
anterior *vs.* posterior, 683-684
due to bleeding from anterior ethmoidal artery, 690-691, 691f-692f

Epistaxis *(Continued)*
cautery for, 687-688, 687f
due to cavernous hemangioma, 684f
in children, 686
drug-induced, 687
embolization for, 690, 691f, 1939-1940, 1940f
emergency department "fast tracking" of, 684, 685b
after endoscopic dacryocystorhinostomy, 801
endoscopic sphenopalatine artery ligation for, 689-690, 689f-690f
epidemiology of, 682
etiology of, 684, 685b
external carotid artery ligation for, 689
first aid measures for, 684
headlamp examination of, 686
due to hereditary hemorrhagic telangiectasia, 691-692, 692f
hot water irrigation for, 691
hypertension and, 686-687
initial assessment of, 684
management protocol for, 692, 693f
maxillary artery ligation for, 688
nasal packing for, 688, 688f
due to nasal trauma, 500
postoperative, 685f
due to pyogenic granuloma, 685f
due to septal perforation, 686f
due to squamous cell carcinoma, 686f
surgical management of, 741
topical treatment of, 687
vascular anatomy and, 682-684
anastomoses in, 682-683, 683f
anterior ethmoid artery in, 682, 684f
facial artery in, 682
greater palatine artery in, 682
internal maxillary artery in, 682
posterior ethmoidal artery in, 682-683
sphenopalatine artery in, 682
vidian artery in, 682, 683f
in Wegener's granulomatosis, 685f
Epithelial grafts, for airway stenosis, 947
Epithelial hyperplastic laryngeal lesions (EHLL), 1525
Epithelial invasion theory, of cholesteatoma formation, 1967f, 1968
Epithelial malignancy
of larynx, 878-880
of paranasal sinuses
staging of, 1128f, 1129, 1129b
Epithelial Na^+ channels (ENaCs), in taste, 1208
Epithelial odontogenic ghost cell tumor, 1275-1276
Epithelial precursor lesions, for oropharyngeal cancer, 1360-1361, 1362f
Epithelial resistance factors, in GERD, 895
Epithelial-myoepithelial carcinoma, of salivary glands, 1191
Epithelioid hemangioendothelioma, of neck, 1668-1669
Epithelioid sarcoma, in children, 2843, 2843f
Epitympanum
anatomy of, 1825-1827, 1827f
in mastoidectomy, 2012-2013, 2013f
in surgical anatomy of lateral skull base, 2438
Epley maneuver, for benign paroxysmal positional vertigo, 2331, 2332f
EPO (eosinophil peroxidase), 604
EPR (electronic patient record), of difficult airway, 118-119
EPSPs (excitatory postsynaptic potentials), in vestibular afferent nerve fibers, 2284-2285, 2284f
Epstein-Barr encoded ribonucleic acids (EBERs), 1352
Epstein-Barr virus (EBV), 1352
and lymphoma
Hodgkin's, 217
nasal T-cell, 660
non-Hodgkin's, 216
and nasopharyngeal carcinoma, 1352, 1354
oral hairy leukoplakia due to, 225-226, 1226
pharyngitis due to, 198-199, 198f
in children, 2785-2786, 2786f
salivary gland inflammation due to, 2855
and salivary gland neoplasms, 1163
vestibular neuritis due to, 2162
ePTFE (expanded polytetrafluoroethylene)
for craniofacial defect repair, 2657
for nasal reconstruction, 368
in noncaucasian rhinoplasty, 569, 570f
Epulis
congenital, of oral cavity, 1290, 1290f
gravidarum, 1256
Epworth Sleepiness Scale (ESS), 57, 253, 253f
Equal-energy principle, 2149-2150
Equitest system, 2324, 2325f
Equivalence studies, 73t, 74
ErbB1, in salivary gland neoplasms, 1199
ErbB2, in salivary gland neoplasms, 1194, 1199
Erbitux (cetuximab)
for metastatic squamous cell carcinoma, 1061
with radiotherapy, 1052, 1054
for laryngeal cancer, 1585
Erbium:yttrium-aluminum-garnet (Er:YAG) laser, 33
Erbium:yttrium-aluminum-garnet (Er:YAG) laser resurfacing, 400
Erb's point, in modified radical neck dissection, 1711
Erector spinae muscle, 2579f
Erlotinib, for cancer chemoprevention, 1062
ERN (Educational Resource Matrix), with cochlear implants, 2251f, 2253
Erosive esophagitis, Los Angeles classification of, 969, 969f
Eruption cyst, 1264, 1264f
treatment of, 1264
Er:YAG (erbium:yttrium-aluminum-garnet) laser, 33
Er:YAG (erbium:yttrium-aluminum-garnet) laser resurfacing, 400
Erysipelas, of external ear, 1948, 1949f
Erythema multiforme (EM), of oral cavity, 1239-1240, 1254
clinical features of, 1239, 1239f-1240f
defined, 1239
differential diagnosis of, 1239
etiology and pathogenesis of, 1239
histopathologic features of, 1239-1240
treatment of, 1240
Erythematous candidiasis, 1230, 1230f
in HIV, 225
Erythrocyte(s), in adaptive immune system, 605
Erythrocyte sludging, in skin flaps, 1068-1069
Erythrokeratoderma variabilis, deafness in, 2051t-2058t
Erythromycin
ototoxicity of, 2176
for pediatric chronic sinusitis, 2779
for rhinosinusitis, 733, 734t
sensorineural hearing loss due to, 2120, 2176
Erythroplakia, of oral cavity, 1298, 1360
ES (Ewing's sarcoma)
in children, 2845
malignant, 1671
oral manifestations of, 1253
ES3 (endoscopic sinus surgery simulator), 46-48, 46f
Eschar excision, for burns, 315
ESD. *See* Endoscopic staple diverticulostomy (ESD).
ESFTs (Ewing's sarcoma family of tumors), in children, 2845
Esmolol, intraoperative, 112
Esophageal acid clearance, in GERD, 895
Esophageal adenocarcinoma, 973, 974f
cervical, 1425
GERD and, 899
Esophageal body
manometry of, 958
physiology of, 954, 955f
Esophageal cancer, 973-974
adenocarcinoma as, 973, 974f
cervical, 1425
GERD and, 899
cervical
adenocarcinoma as, 1425
advanced, 1439
chemotherapy for, 1439
quality of life with, 1439
approach to management of, 1426
chemoradiotherapy for, 1434
chemotherapy for, 1433-1434
clinical evaluation of, 1423
physical findings in, 1423
presenting symptoms in, 1423, 1423t
fasciocutaneous free flaps for, 1433
gastric pull-up for, 1432, 1432f
imaging of, 1423-1424
barium swallow for, 1423-1424
CT for, 1424, 1424f
MRI for, 1424
PET/CT for, 1424, 1424f
incidence of, 1423
lymph node metastasis of, 1434-1439
pathology of, 1424-1425
radiation therapy for, 1436
therapeutic outcome of, 1436
staging of, 1426-1434, 1426t-1427t
therapeutic outcomes for, 1435-1436
total pharyngo-laryngo-esophagectomy for, 1430-1431
esophageal strictures due to, 1408, 1408f
imaging of, 1412-1415, 1414f
reconstruction for (*See* Esophageal reconstruction)
squamous cell carcinoma as, 973
due to caustic injury, 978
localized, 1444-1447
definitive chemoradiation for, 1445-1447, 1446t-1447t
postoperative therapy for, 1444-1447
preoperative therapy for, 1444-1445, 1445t
metastatic, 1447
staging of, 973-974, 974b
tracheal invasion by, 1615
varicoid, 1414f
Esophageal defects, classification of, 1450
Esophageal dilation, for strictures, 966
transnasal esophagoscopy in, 984, 984f
Esophageal disease state(s)
causing dysphagia, 963-968
eosinophilic esophagitis as, 967-968, 969f
esophageal motility abnormalities as, 963-965, 963b
achalasia as, 963-965, 963f-964f
nonachalasia, 965, 965f-966f
rings or webs as, 966-967, 967f-968f
strictures as, 965-966
defined, 965-966
endoscopy of, 965-966, 967f
esophagram of, 965-966, 966f
etiology of, 965-966, 966b
extrinsic, 965-966, 966b
intrinsic, 965-966, 966b
refractory, 966
treatment of, 966
due to caustic injury, 977-978, 978f-979f, 978t
chronic aspiration due to, 926b

Esophageal disease state(s) *(Continued)*
due to foreign body (*See* Esophagus, foreign bodies in)
gastroesophageal reflux disease as, 968-973
Barrett's esophagus due to, 972-973, 972f-973f, 973t
defined, 968
diagnosis of, 968-969, 969f
extraesophageal, 970-973, 970f
asthma due to, 971
chest pain due to, 971
chronic cough due to, 971
dental erosions due to, 971-972
laryngitis due to, 970-971
nonerosive, 968
pathogenesis of, 968
reflux esophagitis in, 968
symptoms of, 968
treatment for, 969-970
infectious esophagitis as, 976-977, 976f-978f
neoplastic (*See* Esophageal cancer; Esophageal neoplasm(s))
due to pill-induced injury, 976, 976b
Esophageal diverticulum(a), 974-975, 974f-975f
classification of, 986
double, 986, 989f
mid-, 1402, 1403f
pseudo-, 975, 975f
imaging of, 1406, 1407f
pulsion, 986
traction, 986
types and sites of, 986, 987f-989f
Esophageal duplication, communicating, 1408-1409, 1409f
Esophageal endoscopy, 956-957
equipment for, 956
of esophageal varices, 958f
for extraesophageal reflux, 899
of gastroesophageal junction
with Mallory-Weiss tear, 957f
normal, 956-957, 957f
with severe esophagitis, 957f
of squamocolumnar junction, 956-957, 956f-957f
technique of, 956-957
Esophageal hematoma, 1416
Esophageal imaging, 1393-1420
of benign neoplasms, 1415-1416
of diverticula, 1402, 1403f
of esophageal narrowing, 1407-1409
due to extrinsic compression, 1408-1409
by foregut duplication cysts, 1408-1409, 1409f
by thyroid goiter, 1409, 1409f
by vertebral osteophytes, 1408, 1409f
due to strictures, 1407-1408, 1408f
due to webs, 1407, 1408f
of fistulas, 1409-1411
due to branchial cleft anomaly, 1410, 1410f
congenital, 1409-1410
due to perforation, 1410-1411, 1410f
postoperative, 1411
tracheoesophageal, 1409-1410
of foreign body, 1411, 1412f
of infection/inflammation, 1403-1407
due to alcohol-induced esophagitis, 1406
due to caustic esophagitis, 1404-1405, 1405f
due to drug-induced esophagitis, 1406, 1406f
due to eosinophilic esophagitis, 1406
due to epidermolysis bullosa, 1406, 1406f
due to graft-versus-host disease, 1406
due to granulomatous esophagitides, 1405
due to infectious esophagitis, 1404, 1405f
due to intramural pseudodiverticulosis, 1406, 1407f
due to pemphigoid, 1406
due to peptic esophagitis, 1406
due to radiation esophagitis, 1406
Esophageal imaging *(Continued)*
due to reflux esophagitis, 1403-1404, 1403f-1404f
of malignant neoplasms, 1413-1414, 1414f
with lymphadenopathy, 1414-1415, 1415f
of motility disorder(s), 1399-1401
due to connective tissue diseases, 1400-1401, 1401f
diminished peristalsis as, 1399-1400, 1400f-1401f
esophageal spasm as, 1400-1401, 1401f
post-treatment, 1416-1418
for monitoring and surveillance, 1418
after radiotherapy, 1418, 1418f
radiographic anatomy in, 1397-1398, 1400f
technique(s) for, 1393-1397
conventional radiography as, 1393, 1394f
CT as, 1396
fluoroscopy as, 1393-1394
modified barium swallow as, 1396
MRI as, 1396
oral contrast agents in, 1396
other nuclear medicine as, 1397
PET-CT as, 1396-1397, 1397f
pharyngoesophagram as, 1394, 1394f-1395f
ultrasound as, 1396
of varices, 1411, 1411f
Esophageal leiomyoma, 1415-1416, 1415f
Esophageal manifestations, of systemic disease, 978-980, 979f
cutaneous, 979-980
Esophageal manometry, 957-958, 958f-959f, 959t
for extraesophageal reflux, 899-900
for swallowing disorders, 1219
Esophageal motility, ineffective, 959t, 965
Esophageal motility abnormalities, 963-965, 963b, 1399-1401
achalasia as, 963-965
defined, 963
endoscopy of, 964, 964f
esophageal manometry for, 964, 964f
esophogram of, 963-964, 963f-964f
etiology and pathogenesis of, 963
management of, 964-965
manometric findings with, 959t
symptoms of, 963
due to connective tissue diseases, 1400-1401, 1401f
diminished peristalsis as, 1399-1400, 1400f-1401f
esophageal spasm as, 1400-1401, 1401f
nonachalasia, 965, 965f-966f
Esophageal narrowing, 1407-1409
due to extrinsic compression, 1408-1409
by foregut duplication cysts, 1408-1409, 1409f
by thyroid goiter, 1409, 1409f
by vertebral osteophytes, 1408, 1409f
due to strictures, 1407-1408, 1408f
due to webs, 1407, 1408f
Esophageal neoplasm(s), 973-974
benign
hematoma as, 1416
imaging of, 1415-1416
leiomyoma as, 1415-1416, 1415f
retention cyst as, 1416, 1416f
Tornwaldt cyst as, 1416, 1416f
vs. tortuous internal carotid artery, 1416, 1416f
malignant (*See* Esophageal cancer)
Esophageal perforation
due to foreign body ingestion, 2941
due to penetrating neck trauma, 1633-1634, 1634f
Esophageal peristalsis, 954, 955f
diminished, 1399-1400, 1400f-1401f
Esophageal pH monitoring
ambulatory 24-hour, 958-960, 959f-960f
Bravo wireless pH capsule for, 961, 961f
for GERD-related laryngeal disease in children, 2945
multichannel intraluminal impedance for, 962
Restech Dx-pH Measurement System for, 962, 962f
Esophageal pseudodiverticula, 975, 975f
Esophageal reconstruction, 1448-1461
with circumferential defects, 1431-1432
classification of defects for, 1450
decision making on, 1450, 1451f
free tissue transfer for, 1454, 1454f
enteric, 1455-1457
gastro-omental donor site for, 1457-1458, 1457f
jejunal donor site for, 1455-1457, 1456f
jejunal free flap for, 1432-1433, 1433f
fasciocutaneous, 1433, 1455
antero-lateral thigh donor site for, 1455
other donor sites for, 1455
radial forearm donor site for, 1455
goals and principles of, 1450
local and regional flaps for, 1450-1452, 1452f
myocutaneous flaps for, 1452-1453
patient population for, 1448
perioperative counseling for, 1448-1449
postsurgical complications of, 1458, 1459f
posttreatment speech and swallowing outcomes of, 1459-1460
preoperative evaluation for, 1449-1450
visceral transposition for, 1453
colonic, 1453, 1454f
gastric, 1432, 1432f, 1453
voice rehabilitation after, 1458-1459
Esophageal retention cysts, 1416, 1416f
Esophageal rings, 966-967, 966f, 968f
transnasal esophagoscopy of, 983-984, 984f
Esophageal spasm, diffuse, 965
esophagogram of, 965, 966f
imaging of, 1400-1401, 1401f
manometric findings with, 959t, 965, 965f
Esophageal speech, 1459
physiology of, 1596, 1596f
after total laryngectomy, 1572
Esophageal squamous cell carcinoma, 973
due to caustic injury, 978
Esophageal stage, of deglutition, 1217, 2948
Esophageal stenosis, after hypopharyngeal reconstruction, 1458
Esophageal strictures, 965-966
due to caustic injury, 977-978, 978f-979f
in children, 2960-2962, 2960f-2961f
imaging of, 1405, 1405f
defined, 965-966
dilation of, 966
transnasal esophagoscopy in, 984, 984f
endoscopy of, 965-966, 967f
due to esophageal carcinoma, 1408, 1408f
etiology of, 965-966, 966b
extrinsic, 965-966, 966b
imaging of, 1407-1408
due to caustic injury, 1405, 1405f
due to esophageal carcinoma, 1408, 1408f
esophagram for, 965-966, 966f
inflammatory, 1403, 1404f
inflammatory, 1403, 1404f
intrinsic, 965-966, 966b
postlaryngectomy, 1416
refractory, 966
after total laryngopharyngectomy, 1575
treatment of, 966
mechanical therapy for, 2960-2962, 2960f-2961f
transnasal esophagoscopy in, 984, 984f
Esophageal symptoms, assessment of, 954-956

Esophageal tears, due to penetrating neck trauma, 1633-1634, 1634f
Esophageal testing, 956-963
  ambulatory 24-hour bile monitoring for, 960-961, 961f
  endoscopy for, 956-957
    equipment for, 956
    of esophageal varices, 958f
    for extraesophageal reflux, 899
    of gastroesophageal junction
      with Mallory-Weiss tear, 957f
      normal, 956-957, 957f
      with severe esophagitis, 957f
    of squamocolumnar junction, 956-957, 956f-957f
    technique of, 956-957
  esophageal manometry for, 957-958, 958f-959f, 959t
  esophageal pH monitoring for
    ambulatory 24-hour, 958-960, 959f-960f
    Bravo wireless pH capsule for, 961, 961f
    multichannel intraluminal impedance for, 962
    Restech Dx-pH Measurement System for, 962, 962f
  provocative, 962-963
Esophageal trauma, 941-942
  caustic, 942, 977-978
    clinical features of, 977
    etiology of, 977
    grading of, 977, 978t
    prognosis for, 977-978
    squamous cell carcinoma due to, 978
    strictures due to, 977-978, 978f-979f
  external, 941-942
  mechanisms of injury in, 933, 934f
  pill-induced, 976, 976b
Esophageal varices, 958f
  imaging of, 1411, 1411f
Esophageal webs, 966-967, 967f
  imaging of, 1407, 1408f
Esophageal-bronchial fistulas, 1009
Esophageal-tracheal fistulas, 1009
Esophagectomy, for caustic ingestion, 2961-2962, 2962f
Esophagitis
  caustic, 942, 977-978
    clinical features of, 977
    etiology of, 977
    grading of, 977, 978t
    imaging of, 1404-1405, 1405f
    prognosis for, 977-978
    squamous cell carcinoma due to, 978
    strictures due to, 977-978, 978f-979f
      imaging of, 1405, 1405f
  drug-induced, 1406, 1406f
  eosinophilic ("ringed," "feline," corrugated), 967-968, 969f
    dysphagia due to, 2954
  erosive, Los Angeles classification of, 969, 969f
  gastroesophageal junction in, 957f
  granulomatous, 1405
  infectious, 976-977
    due to *Candida albicans*, 976, 976f
      imaging of, 1404, 1405f
    due to cytomegalovirus, 976, 977f
    due to herpes simplex virus, 976-977, 977f-978f
      imaging of, 1404, 1405f
    imaging of, 1404, 1405f
  peptic, 1406
  radiation, 1406
  reflux, 968-969, 969f
    imaging of, 1403-1404, 1403f-1404f
  tuberculous, 1405
Esophagodiverticulostomy, endoscopic, 992
Esophagogastroduodenoscopy (EGD)
  for extraesophageal reflux, 899
  for laryngeal stenosis, 2917
Esophagogram, 1394, 1395f
  for extraesophageal reflux, 898
  mucosal-relief, 1394, 1395f
Esophagoscopy
  for foreign body removal, 2939t, 2940
  for penetrating neck trauma, 1631t, 1633-1634, 1634f
  transnasal (*See* Transnasal esophagoscopy (TNE))
Esophagus
  abdominal, 954f
  Barrett's
    endoscopic appearance of, 967f, 972, 972f
    gastroesophageal junction in, 957f
    GERD and, 972-973
    grading of dysplasia in, 973, 973t
    histologic appearance of, 972, 972f-973f
    imaging of, 1403-1404, 1404f
    long-segment, 972f
    short-segment, 972f
    surveillance for, 972-973, 973t
    transnasal esophagoscopy in, 983, 983f
  cancer of (*See* Esophageal cancer)
  cervical, 954f
    anatomy of, 1421-1422
    cancer of (*See* Esophageal cancer, cervical)
  congenital anomalies of, dysphagia due to, 2950t, 2953-2954, 2954f
  "corkscrew," 965, 966f
  defined, 953
  food impactions in, 975
  foreign bodies in, 975-976, 2935-2943
    airway obstruction due to, 1481, 1481f
    classification of, 975
    complications of, 2942, 2942f
    epidemiology of, 2936
    due to food impaction, 975
    imaging of, 1411, 1412f, 2939
    location of, 2936, 2937f
    management of, 2939-2941
      anesthesia for, 2940
      controversies in, 2942
      for disk batteries, 2941
      equipment for, 2939-2940, 2939t
      history of, 2935-2936
      for pills, 2941
      postoperative, 2941-2942
      for sharp objects, 2940-2941
      technique for, 2940
    perforation due to, 2941
    symptoms of, 2938
  normal anatomy and physiology of, 953-954, 954f-955f
  nutcracker, 959t, 965
    imaging of, 1401
  presby-, 1400
  radiographic anatomy of, 1397-1398, 1398f, 1400f
  thoracic, 954f
ESP (Early Speech Perception), for cochlear implant, 2225-2226
ESPAL (endoscopic sphenopalatine artery ligation), for epistaxis, 689-690, 689f-690f
Espin, in stereocilia, 2075, 2076f
Espin *(ESPN)* gene, in deafness, 2051t-2058t
ESRRB (estrogen-related receptor β) gene, in deafness, 2051t-2058t
ESS (Epworth Sleepiness Scale), 57, 253, 253f
ESS (empty sella syndrome), CSF rhinorrhea due to, 787
ESS (endoscopic sinus surgery). *See* Endoscopic sinus surgery (ESS).
Essential tremor, laryngeal hyperfunction due to, 840-841
Esteem-Hearing Implant, 2211-2212, 2212f
Esthesioneuroblastoma (ENB), 1697-1698
  epidemiology of, 1697
  pathogenesis of, 1697
  prognostic factors for, 1697
  treatment for
    approaches to, 1697-1698
    radiation therapy for, 1698, 1698f
    results of, 1697, 1698t
Esthetician, for aging skin, 402
Estlander flap, 352, 356f
Estrogen(s), for hyperparathyroidism, 1804
Estrogen-related receptor β *(ESRRB)* gene, in deafness, 2051t-2058t
Etanercept, for autoimmune inner ear disease, 2167
Ethacrynic acid, sensorineural hearing loss due to, 2120, 2175
Ethanol
  absolute, for embolization, 1933
  percutaneous administration of, for toxic thyroid adenoma, 1744
Ethical issues, with genetics, 9-10
Ethmoid bone, in surgical anatomy of anterior cranial base, 2442-2443, 2443f
Ethmoid bulla
  in endoscopic sinus surgery, 747, 748f
  normal anatomy of, 666-667, 667f
  surgical anatomy of, 740
Ethmoid complex, 740
Ethmoid foramina, in surgical anatomy of anterior cranial base, 2443-2444, 2444f
Ethmoid fractures, naso-orbital, 322
  classification of, 326-327, 327f
  physical examination of, 324, 324f
  repair of, 336-337, 337f
Ethmoid region, in surgical anatomy of anterior cranial base, 2444f
Ethmoid roof
  after functional endoscopic sinus surgery, 672f, 679
  in surgical anatomy of anterior cranial base, 2443
Ethmoid roof height, asymmetry in, 670-671
Ethmoid sinus(es)
  anatomy and physiology of, 320f, 664, 667
  growth and development of, 2619-2620
  roof of, 1124f
  in surgical anatomy of anterior cranial base, 2443, 2472f-2473f, 2473
Ethmoid sinus tumors, 1123, 1130
  external ethmoidectomy for, 1124-1125, 1125f
  staging of, 1129b
Ethmoid vessels, prior to endoscopic sinus surgery, 764, 764t, 765f
Ethmoidal labyrinth, 1124f
Ethmoidectomy
  endoscopic
    anterior, 747-748, 748f
    complete, 748-749, 749f-750f
    failure of, 766-767, 767f
    posterior, 747-748, 749f
  external, 757, 757f, 1124-1125, 1125f
    Lynch-Howarth, 778-779, 779f
  intranasal, 756-757
Ethnic differences, in otitis media, 2766
Ethnic noses, rhinoplasty for. *See* Noncaucasian rhinoplasty.
Ethylene oxide polyoxypropylene glycol (Addax), for cerumen removal, 1958t
Etomidate, for induction of anesthesia, 111
ETS (environmental tobacco smoke), and chronic rhinosinusitis, 707
ETT. *See* Endotracheal intubation (ETT).
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-HN35), 56

Eustachian tube, 1866-1875
  anatomy of, 1825, 1867-1870, 1867f
    anterior pad in, 1869, 1869f
    anterior view of, 1868f
    arterial supply in, 1870
    cartilaginous portion in, 1868-1869, 1869f
    dilatory muscles in, 1869-1870, 1869f
    histology of lumen of, 1870
    junctional portion of, 1868, 1868f
    lateral view of, 1868f
    in middle cranial base, 1699
    mucosa-associated lymphoid tissue in, 1870
    in oropharynx, 1360f
    osseous portion in, 1867, 1867f
    superior view of, 1867f
    tubal lumen in, 1867f, 1870
  embryology and postnatal development of, 1866-1867
  length of, 1866
  location of, 1867
  in otitis media, 2762-2763, 2763f
  patulous, 1872
  pharyngeal opening of, in surgical anatomy of anterior cranial base, 2472f, 2474
  physiology of, 1870-1872
    middle ear protection in, 1871-1872
    mucociliary clearance and drainage in, 1871
    pressure equalization in, 1870-1871
  shape of, 1867
  in surgical anatomy of lateral skull base, 2436f-2437f, 2438
Eustachian tube dysfunction, 1872-1874
  with abnormalities in lateral wall movement, 1872
  aging and, 1872
  classic theory of, 1870-1871
  with cleft palate, 1872-1873, 1873f
  ear pressure and, 1872
  with extraesophageal reflux, 1873
  hereditary component to, 1873-1874
  hypertrophic adenoids and, 1872, 1873f
  mucociliary clearance and, 1871
  nasal allergy and, 1872
  with nasopharyngeal neoplasms, 1873, 1873f
  pathophysiology of, 1872
  with pressure changes, 1872
  respiratory viruses and, 1871
  treatment of, 1874
Eustachian tube function, 1867
Eustachian tube function tests, 1874
Eustachian tube opening, in surgical anatomy of lateral skull base, 2436f
Eutectic mixture of local anesthetics (EMLA), for premedication of children, 2589
Euthyrox (levothyroxine, oral synthetic), for hypothyroidism, 1748-1749
Eversion, in wound repair, 306, 306f
Evidence, levels of, 69, 70t
  and grade of recommendation, 55, 55t, 69-70, 70t
Evidence-based medicine (EBM) recommendations, grading of, 55, 55t, 69-70, 70t
Evidence-based performance measurement, 76-90
  aggregate demand for, 77
  anatomy of performance measures in, 82, 83f
  definition of quality for, 76-77
  engaging in development of, 77-78
  implementation of
    barriers to, 89
    pathway for, 88f
    standardization and, 87-89
  medical professionalism and, 78-82
    board certification and maintenance of certification in, 79-80, 80b-81b
    Institute of Medicine in, 81-82
    physician education in, 79, 79t
Evidence-based performance measurement *(Continued)*
    state medical boards and maintenance of licensure in, 80-81
  motivation for, 76
  process of building a coherent system of, 77-78
  quality-based or value-based purchasing in, 78
  stakeholder groups in, 79-89, 84t-87t
  surgeon's role in, 89
  unifying response to demand for, 77-78
Evoked auditory brainstem response (EABR). *See* Auditory brainstem response (ABR).
Evoked electromyography, 2386
Evoked encephalomyography (EEMG), for facial nerve injury, 2041
Evoked long latency responses (ELLRs)
  auditory, 1912, 1913f
  electrically, 1913-1914
Evoked middle latency responses (EMLRs)
  auditory, 1912, 1913f
  electrically, 1912-1914
Evoked otoacoustic emissions (EOAEs), in infants, 2720-2721
Ewald's First Law, 2288
Ewald's Second Law, 2290-2291
Ewing's sarcoma (ES)
  in children, 2845
  malignant, 1671
  oral manifestations of, 1253
Ewing's sarcoma family of tumors (ESFTs), in children, 2845
Ex utero intrapartum treatment (EXIT procedure)
  for congenital high airway obstruction syndrome, 2869, 2870f, 2904-2905
  for laryngeal atresia, 2869
Ex vivo gene therapy, 18, 19f
Excisional surgery
  for scar revision, 295, 297f
    expansion with, 296-298
      serial, 296
      tissue, 296-298, 297f
  for skin lesions, 293
Excitation-inhibition asymmetry, of semicircular canals, 2290-2291, 2291f
Excitatory amino acid transporter 1 (EATT1), 2081
Excitatory postsynaptic potentials (EPSPs), in vestibular afferent nerve fibers, 2284-2285, 2284f
Excited state, of atom, 1032
Exclusion criteria, 68
Excretory duct, of salivary gland, 1162, 1163f
Exercise, nasal airflow during, 641
Exercise-induced asthma, in professional singers, 853
EXIT procedure (ex utero intrapartum treatment)
  for congenital high airway obstruction syndrome, 2869, 2870f, 2904-2905
  for laryngeal atresia, 2869
Exocrine disorders, oral manifestations of, 1251
Exogen phase, 374
Exons, 4, 5f
Exostoses, of external auditory canal
  imaging of, 1918, 1918f
  management of, 2022, 2024f
Expanded polytetrafluoroethylene (ePTFE)
  for craniofacial defect repair, 2657
  for nasal reconstruction, 368
  in noncaucasian rhinoplasty, 569, 570f
Expansion with excision, for scar revision, 296-298
  serial, 296
  tissue, 296-298, 297f
Experimental studies, data quality of, 59, 60t-62t
Expert opinion, 52, 54-55, 54t
Expiratory force, in phonation, 811-812
Expiratory resistance, in rhinomanometry, 650-651
Exposure keratitis, after facial nerve injury, 2420, 2420f
Exposure time, of surgical laser, 28
Expression microarrays, in head and neck squamous cell carcinoma, 1025
Expressivity, 7, 7f
Extended craniofacial resection, 1126-1127, 1127f
  supplemental management in, 1126-1127
Extended head posture, 2629
Extended maxillotomy, for middle cranial base surgery, 2455t, 2458, 2462f
Extended middle fossa approach, for posterior fossa neoplasms, 2532t, 2538
  advantages and disadvantages of, 2532t, 2538
  basic features of, 2538
  indications for, 2532t, 2538
  surgical exposure in, 2538f
  technique of, 2538
Extended neck dissection, 1703t, 1719-1721, 1720f
Extended vertical hemilaryngectomy, 1548
External acoustic meatus, 320f, 2010f
External auditory canal (EAC)
  anatomy of, 1822f, 1823, 1824f-1825f, 1829
  atresia of, 1917, 1917f
  benign neoplasms of, 1918, 1918f-1919f
  carcinoma of, 2502-2504
    imaging of, 1918, 1919f
    management of, 2502-2504, 2503f
    pertinent anatomy for, 2502
    staging of, 2502, 2502f, 2503b
    symptoms and signs of, 2502
  cholesteatoma of, 1949
    imaging of, 1917, 1918f
  closure of, in postauricular approach to infratemporal fossa, 2495, 2497f
  congenital malformations of (*See* Congenital aural atresia (CAA))
  embryogenesis of, 1824
  exostoses of
    imaging of, 1918, 1918f
    management of, 2022, 2024f
  foreign bodies in, 2021
  imaging of, 172, 1917-1918
    with benign neoplasms, 1918, 1918f-1919f
    with cholesteatoma, 1917, 1918f
    with congenital lesions, 1917, 1917f
    with keratosis obturans, 1917, 1918f
    with malignant neoplasms, 1918, 1919f
    with posinflammatory medial canal fibrosis, 1917-1918, 1918f
    with severe infections, 1917, 1917f
  keratosis obturans of, 1949
    imaging of, 1917, 1918f
    management of, 2021
  narrowing of, 2021
  osteomas of
    imaging of, 1918, 1919f
    management of, 2022
  physical examination of, 97
  posinflammatory medial canal fibrosis of, 1917-1918, 1918f
  severe infections of, 1917, 1917f
  sleeve resection of, 2492
  soft tissue stenosis of, 2021-2022, 2023f
  in surgical anatomy of lateral skull base, 2435, 2435f
  in surgical anatomy of middle cranial base, 2445f
External auditory canal (EAC) stenosis, due to temporal bone trauma, 2038, 2047
External auditory meatus, 320f
  embryology of, 2585f, 2753
External carotid artery
  anatomy of, 1296f, 1359f, 2579, 2580f
    radiographic, 1471f, 1473-1474
  injury of, 1632
  in parotidectomy, 1195-1196
  in surgical anatomy of lateral skull base, 2440f
External carotid artery ligation, for epistaxis, 689

External compression plating, for nasal fractures, 506
External ear
  anatomy of, 1823-1825, 1824f-1825f
    applied, 1944
    tympanic membrane in, 1824-1825, 1825f
  in auditory physiology, 1839
  embryogenesis of, 1824
  imaging of, 172
External ear canal, anatomy of, 1944
External ear disorder(s), topical therapies for, 1950-1962
  acidifying agents as
    for acute bacterial otitis externa, 1953
    for fungal otitis externa, 1954
  for acute bacterial otitis externa, 1951-1953
    acidifying agents as, 1953
    options for, 1951-1953, 1951f
    ototopic antibiotics as, 1951-1953
  antibiotics as, 1959t-1960t
    for acute bacterial otitis externa, 1951-1953
    evidence-based data on, 1952
    hypersensitivity reaction to, 1954
    mechanism of action of, 1951
    ototoxicity of, 1953-1954
    resistance to, 1951-1953
  antifungals as, 1959t-1960t
    for fungal otitis externa, 1954-1955
    ototoxicity of, 1955
  anti-inflammatories as
    for eczematoid otitis externa, 1956-1957
    mechanism of action of, 1951
  antiseptics as, 1955
    for fungal otitis externa, 1955
  for cerumen impaction, 1957
    options for, 1957, 1958t
  for ear hygiene and chronic draining ear, 1957-1958, 1961f
  for eczematoid otitis externa, 1955-1957
    anti-inflammatory and immunosuppressive agents as, 1956-1957
    options for, 1955
    steroids as, 1955-1956
  for fungal otitis externa, 1954-1955
    acidifying agents as, 1954
    antifungals as, 1954-1955
    antiseptics as, 1955
    options for, 1954
  history of, 1950
  immunosuppressive agents as, for eczematoid otitis externa, 1956-1957
  mechanism of action of, 1950-1951
    for antibiotics, 1951
    for anti-inflammatories, 1951
  for myringitis, 1955
  steroids as
    classes of, 1956, 1956t
    for eczematoid otitis externa, 1955-1956
    hypersensitivity reaction to, 1954
    mechanism of action of, 1951
    ototoxicity of, 1956
  summary of available, 1959t-1960t
  for viral infections, 1957, 1957f
    options for, 1957
External ear infection(s), 1944-1949
  bullous myringitis as, 1948, 1948f
  cellulitis as, 1948
    due to otitis externa, 1946
  erysipelas as, 1948, 1949f
  external auditory canal cholesteatoma as, 1949
  furunculosis as, 1949, 1949f, 2021
  keratosis obturans as, 1949
  medial canthal fibrosis due to, 1946-1947, 1946f
  otitis externa as, 1944-1947
    allergic, 1945-1946
    bacterial, 1944
    chronic, 1945, 1946f
External ear infection(s) *(Continued)*
    clinical manifestations of, 1945
    complications of, 1946-1947, 1946f
    defined, 1944
    fungal, 1944-1946, 1945f
    granular, 1945
    incidence and epidemiology of, 1944
    investigations of, 1945
    malignant, 1947-1948
      clinical manifestations of, 1947, 1947f
      defined, 1947
      immunosuppression and, 221-222, 1947
      incidence and epidemiology of, 1947
      investigations of, 1947
      microbiology of, 1947
      treatment of, 1947-1948
    microbiology of, 1945, 1945t
    pathogenesis of, 1944-1945, 1945f
    treatment of, 1945-1946
  perichondritis and chondritis as, 1948
    due to otitis externa, 1946
  viral
    aural papillomatosis as, 1957, 1957f
      management options for, 1957
    herpes zoster oticus as, 1948, 1948f
External ethmoidectomy, 1124-1125, 1125f
External expansion surgery, for laryngeal stenosis, 2919-2921
External fixation, of mandibular fracture, 338
External jugular lymph nodes, 1360f
External jugular vein, 1360f
  anomalies of, 2817
External nasal nerve, 483f
External nasal splinting, 504
External occipital protuberance, 320f
External otitis. *See* Otitis externa (OE).
External plexiform layer, of olfactory bulb, 628f
External speech processors, 2229
  size, weight, and aesthetics of, 2232, 2232f
External validity, 68-69, 68t, 69f
External valve collapse, 493
  revision rhinoplasty for, 586-587, 587f
External-beam radiation therapy (EBRT), 1033. *See also* Radiation therapy (RT).
  for oral cancer, 1314
  for thyroid cancer, 1772
  treatment aspects of, 1035-1036
Extracapsular spread, imaging of, 164-166, 167f
Extracorporeal circulation, for flap salvage, 1075
Extracorporeal shock wave lithotripsy, for sialolithiasis, 1156
Extracranial repair, for CSF rhinorrhea, 792-794, 793f-794f
Extraesophageal reflux (EER), 894-903, 970-973
  asthma due to, 971
  Barrett's esophagus due to, 972-973
    grading of dysplasia in, 973, 973t
    histologic appearance of, 972, 972f-973f
    long-segment, 972f
    short-segment, 972f
    surveillance for, 972-973, 973t
  chest pain due to, 971
  in children, 2944-2947
    diagnosis of, 2945
    disorders due to, 2945-2946, 2945b
    evidence of, 2946
    history of, 2944
    management of, 2946
    physiopathology of, 2945
  chronic cough due to, 971
  contact ulcer due to, 902
  defined, 894
  dental erosions due to, 971-972
  diagnostic evaluation of, 896-900
    esophageal endoscopy in, 899
    esophagogram in, 898
    history in, 896, 896b-897b
Extraesophageal reflux (EER) *(Continued)*
    impedance testing in, 900
    laryngeal sensory testing in, 898-899
    manometry in, 899-900
    pH probe monitoring in, 900
    physical examination and laryngeal endoscopy in, 896-897, 897t, 898b
    voice analysis in, 898
  epidemiology of, 894
  and head and neck cancer, 902-903
  laryngeal granuloma due to, 902, 902f-903f
  laryngitis due to, 886, 886f, 901-902, 970-971
  and otitis media, 1873
  otolaryngologic disorders associated with, 901-903
  pathophysiology of, 894-896
    epithelial resistance factors in, 895-896
    esophageal acid clearance in, 895
    lower esophageal sphincter in, 895, 895b
    mechanisms of symptoms in, 896
    upper esophageal sphincter in, 894-895
  professional voice disorders due to, 852
  symptoms of, 970
  treatment of, 900-901
    algorithm for, 970, 970f
    behavioral modification for, 900-901
    bethanechol for, 901
    H_2 blockers for, 901
    over-the-counter antacids for, 901
    promotility agents for, 901
    proton pump inhibitors for, 901
    sucralfate for, 901
    surgical, 901
Extraglandular parotid lymph node, 1360f
Extramedullary plasmacytoma (EMP), of larynx, 1509
Extranodal marginal cell lymphoma, of thyroid, 1679
Extraocular muscle(s)
  in Graves' ophthalmopathy, 1808, 1809t
  intraoperative monitoring of, 2549-2550, 2550f
  semicircular canal planes and, 2285-2288, 2286f-2288f
Extraocular muscle surgery, for Graves' ophthalmopathy, 1816-1817
Extrapyramidal reaction, *vs.* myofascial pain dysfunction syndrome, 1285t
Extrapyramidal system defects, laryngologic manifestations of, 837-838, 838t
Extrinsic strap muscles, radiographic anatomy of, 1473f
Extubation
  of difficult airway, 117
  stridor after, 2904, 2904t
Exudative tracheitis, 2809-2810
  clinical features of, 2809
  complications of, 2810
  diagnosis of, 2809, 2809f
  differential diagnosis of, 2806t
  endoscopy of, 2809, 2809f
  epidemiology of, 2809
  imaging of, 2809, 2809f
  management of, 2809-2810, 2809f
  pathogenesis of, 2809
  terminology for, 2809
EYA1 gene, in branchio-oto-renal syndrome, 2095
EYA1 (eyes-absent 1 homolog) gene, in deafness, 2051t-2058t
EYA4 (eyes-absent 4 homolog) gene, in deafness, 2051t-2058t
Eye(s)
  aesthetic analysis of, 271
  in Down syndrome, 2632-2633
  effects of radiotherapy on, 2626t
  prosthetic, 1345t, 1346-1347, 1347f
  trauma to, 303
Eye evaluation, for Graves' ophthalmopathy, 1809

Eye movement(s)
  evoked by sound or changes in middle ear pressure, 2316, 2316f
  in superior canal dehiscence syndrome, 2339-2340, 2340f
  methods of recording, 2317, 2317f
  in plane of stimulated semicircular canal, 2285-2289
  anatomic and physiologic basis for, 2285-2288, 2286f-2288f
  clinical importance of, 2288-2289, 2288f
  semicircular canals and, 2306, 2307f
  in vestibular function, 2305-2307, 2306f-2307f, 2307t
Eye protection
  for facial nerve injury, 2420, 2420f
  in laser surgery, 34-35, 35f-36f
Eyebrow(s)
  aesthetic proportions of, 428, 429f
  anatomy of, 440-442
    in Asians *vs.* Occidentals, 442
    blood supply in, 442
    fascial layers of forehead and temporal region in, 440-441, 441f
    motor innervation in, 440, 441f
    musculature in, 441-442, 442f
    sensory innervation in, 440, 441f
Eyebrow position, aesthetic analysis of, 271, 275f, 445, 445f
Eyebrow shape, aesthetic analysis of, 271, 445, 445f
Eyebrow transplantation, 384, 384f
Eye-head coordination, evaluation of, 2314
Eye-head movements, in vestibular function, 2308
Eyelash transplantation, 384
Eyelid(s)
  aesthetic analysis of, 271, 445-447
    lower, 445-446, 446f
    upper, 445, 446f
  anatomy of, 442-444, 443f
    anterior lamella in, 442-443, 443f
    in Asians *vs.* Caucasians, 443
    conjunctiva in, 443f, 444
    lower eyelid retractors in, 444
    orbital fat pads in, 443-444, 444f
    orbital septum in, 443, 443f
    posterior lamella in, 442
    surface, 442, 443f
    tarsus in, 443f, 444
    upper eyelid retractors in, 444
  biomechanics of, 332
  burns of, 316
  in Graves' ophthalmopathy, 1808, 1809t
  paralysis of
    lower, 2420-2421, 2421f
    upper, 2421
  trauma to, 303, 303f, 307-309, 308f
  upper
    aesthetic analysis of, 445, 446f
    ptosis of
      evaluation of, 446-447, 447f
      repair of, 447-448, 447f-449f
Eyelid retractors
  lower, 444
  upper, 444
Eyelid surgery, for Graves' ophthalmopathy, 1817
Eyes-absent 1 homolog *(EYA1)* gene, in deafness, 2051t-2058t
Eyes-absent 4 homolog *(EYA4)* gene, in deafness, 2051t-2058t

F

Fabry's disease, oral manifestations of, 1257
Face
  embryology of, 2659-2661, 2661t
  postoperative imaging of, 173-174
  size ratio of cranium to, 2616f, 2617t
Face, Legs, Activity, Cry, Consolability (FLACC) tool, 240
Face mask ventilation, for difficult airway, 114t, 115f
"Facelift" incision, modified, for parotidectomy, 1172, 1173f
Facelifting. *See* Rhytidectomy.
Faces Pain Scale Revised (FPS-R), 240
Facial analysis, 269-280
  aesthetic units in, 269-270, 274f
  anatomic landmarks and reference points in, 269
    cephalometric, 270b, 272f
    Frankfort horizontal plane as, 269, 272f
    soft tissue, 270b, 271f
  computer imaging and digital photography in, 277-280, 279f-280f
  facial proportions in, 269
    facial height in, 269, 273f
      middle and lower, 269, 273f
    facial symmetry through midsagittal plane in, 269, 272f
    facial width in, 269, 272f
  historical background of, 269
    anthropometry in, 269
    in antiquity, 269
    Renaissance artists in, 269, 270f
  relaxed skin tension lines in, 269-270, 274f
  for rhinoplasty, 514, 514f
  subunit analysis in, 269-275
    of chin, 275, 278f
    of ears, 275, 279f
    of eyes, 271
    of forehead, 270-271
      eyebrow position in, 271, 275f
      eyebrow shape in, 271
      nasofrontal angle in, 270, 274f
    of lips, 274-275, 278f
    of neck, 275, 279f
    of nose, 271-272, 275f
      alar-columellar complex in, 270f-271f, 274
      nasal rotation and projection in, 273-274, 277f
      nasofacial angle in, 272-274, 276f
      nasofacial relationships in, 272-274
      nasofrontal angle in, 270, 272-273, 274f
      nasolabial angle in, 272-273, 276f
      nasomental angle in, 272-273, 276f
    of skin and rhytids, 275, 276b, 279f
Facial anomaly(ies). *See* Craniofacial anomaly(ies).
Facial arteriovenous fistulas, embolization of, 1940, 1940f
Facial artery, 682, 1296, 2579-2580, 2580f
Facial asymmetry, 2621
Facial bipartition, for craniofacial anomalies, 2654, 2656f
Facial bones
  conventional radiography of, 130
  effects of radiotherapy on, 2626t
Facial changes, during normal growth and development, 2615, 2615f-2616f
Facial clefts, 2645. *See also* Cleft lip; Cleft palate.
  molecular genetics of, 2662-2664
Facial defect(s), prosthetic management of, 1344-1345, 1345t
  auricular, 1345-1346, 1345t, 1346f
  nasal, 1345, 1345t, 1346f
  orbital/ocular, 1345t, 1346-1347, 1347f
Facial defect reconstruction, 342-363
  algorithm for, 342, 343f
  of cheek, 355-359
    advancement flaps in, 358
      V-Y, 358, 361f
    rotation flaps for, 357-358, 359f
    sub-superficial musculoaponeurotic system dissection in, 357-358, 360f
Facial defect reconstruction *(Continued)*
    transposition flaps for, 358-359, 361f
      bilobed, 357, 359f
      rhombus shaped, 355
  of forehead, 359-363
    aesthetic considerations in, 359
    central third, 359-360, 362f
    goals of, 359
    lateral, 360-362
      advancement flap for, 360-363, 362f
      advancement rotation flap for, 360-362, 362f
      O-T or A-T procedure for, 362, 363f
      primary wound closure for, 360-362
      rotation flaps for, 362
    primary wound repair for, 359
    tissue expansion in, 363
  of lip, 350-353
    classification of, 351
    greater than two-thirds width, 352
    with lateral defect, 352
    less than one-half width, 351
      primary wound closure in, 351
      V-Y musculocutaneous island pedicle flap in, 356f
    lower
      algorithm for, 351, 355f
      midline, 352-353
    massive or near-total, 352-353, 357f-358f
      melolabial transposition flap for, 353
      temporal forehead flap for, 353
    from one half to two thirds, 351
      Abbé flap for, 352
      Estlander flap for, 352, 356f
      Karapendzic flap for, 351
      lip switch flap for, 351
      local *vs.* regional flaps for, 352
    upper
      algorithm for, 351, 355f
      with large defect, 352
    V-Y advancement flap in, 347f
  local flaps for
    advancement, 345-346
      bilateral, 345, 346f
      island, 345
      unipedicle, 345, 345f
      V-Y, 345-346, 346f-347f
      Y-V, 346
    classification of, 342-343, 343b
    hinge, 346
    pivotal, 343-345
      effective length of, 343, 343f
      interpolated, 344-345, 344f
      rotation, 343-344, 343f
      transposition, 344, 344f
  of nose, 346-350
    aesthetic units in, 346-347, 347f
    approach to, 346-347
    for defects extending into alar facial sulcus, 348
      cheek advancement flap in, 348, 349f
      cheek pedicle transposition flap in, 348, 349f
    for full-thickness central defects of tip or dorsum, 348
      composite turnout flap for, 348, 351f
      paramedian forehead flaps for, 348-350, 352f-354f
    for full-thickness defects of ala, 347
      bipedicle mucosal advancement flap in, 347, 347f
      free cartilage grafts in, 348
      melolabial interpolated flap in, 348
    for surface defects of nasal tip, columella, sidewalls, and dorsum, 348
      hinge flap in, 348, 350f
      paramedian forehead flaps in, 348
    V-Y advancement flap in, 345-346, 346f
Facial dimension, 2617t

Facial edema, due to neck dissection, 1723, 1729f
Facial expression, aging skin and, 439, 440f
Facial fracture(s), 318-341
  anatomy, physiology, and pathophysiology of, 319-323, 320f
    general, 319
    of lower third, 322-323, 323f
    of middle third, 319-322
      areas of protection in, 322, 322t
      infraorbital nerve in, 320, 321f
      maxillae in, 320, 321f
      nasal bones in, 320
      orbits in, 320-321, 322f
      zygoma in, 319, 320f-321f
    of upper third, 319, 319f
  biomechanics of facial skeleton and, 331-333, 331f
    in lower third, 332-333, 332f
    in middle third, 331-332, 331f
    in upper third, 331
  bone healing after, 330-331
  classification of, 326-327
    of lower third, 327
    of middle third, 326-327, 327f
    of upper third, 326
  complications of, 339-340
  defined, 318
  evaluation and diagnosis of, 323-326
    imaging in, 325-326
      of lower third, 325-326
      of middle third, 325, 326f
      of upper third, 325, 325f
    physical examination in, 323-325
      of lower third, 325
      of middle third, 324-325, 324f
      of upper third, 324
  future directions and new horizons for, 340
  historical perspective on, 318-319
  management of, 327-330
    general, 327-328
    surgical access in, 328-330
      to lower third, 329-330, 330f
      to middle third, 328-329, 329f
      to upper third, 328, 328f-329f
  pediatric, 2647, 2697-2717
    associated injuries with, 2698
    clinical and physical evaluation of, 2699
    complex, 2698
    dentoalveolar, 2706-2707, 2710f
    emergency management of, 2698-2699
    epidemiology of, 2697-2698
    etiology of, 2698
    facial growth and, 2698-2699
    front sinus, 2711, 2712f
    mandibular, 2704-2706
      arch and body, 2706, 2709f
      complications of, 2704
      condylar, 2704, 2706f-2708f
      epidemiology of, 2698
      symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
    mandibular immobilization for, 2701, 2701f
    maxillomandibular fixation for, 2701
    midface, 2707, 2710f
    nasal, 2708-2711, 2711f-2712f
    naso-orbitoethmoid, 2714
      classification of, 2714, 2716f
      evaluation of, 2714, 2716f
      repair of, 2714, 2716f
    open reduction with internal fixation for, 2701-2702
    orbital, 2711-2714
      evaluation of, 2712, 2713f
      of lateral/medial orbital wall, 2712, 2714, 2716f
      of orbital apex, 2712, 2713f
      of orbital floor, 2712-2713, 2714f-2715f
Facial fracture(s) *(Continued)*
      of orbital roof, 2712-2713, 2716f
      patterns of, 2711-2712
    permanent *vs.* resorbable plating systems for, 2700-2701, 2700t-2701t
    radiologic examination of, 2699
    rigid fixation for, 2699-2700
    sequencing of procedures for, 2702, 2704, 2706f
    surgical approaches for, 2701-2704
      bicoronal incision in, 2701-2702, 2703f
      lateral cantholysis in, 2704f
      maxillary gingivolabial sulcus approach in, 2701-2702, 2703f
      midfacial degloving incision in, 2701-2702
      subciliary incision in, 2705f
      surgical approaches for, 2701-2704
      transcaruncular approach in, 2701-2702, 2705f
    surgical management of, 2648, 2649f, 2657
    surgical reconstruction for, 2704-2714
    zygomaticomalar complex, 2707-2708, 2710f
  repair of, 333-334
    in lower third, 337-339, 338f
      with edentulous mandible, 339
    in middle third, 334-337
      of buttresses, 336
      canthal ligament in, 337, 337f
      maxillary, 335-336, 335f-336f
      naso-orbital ethmoid, 336-337, 337f
      orbital, 336
      palatal, 335, 335f
      of tooth-bearing segments, 334-335, 334f
      zygomatic, 336
    and occlusion, 330-331, 333-334, 333f
    panfacial, 339
    secondary, revision, or delayed, 340
    in upper third, 333-334, 334f
      with CSF rhinorrhea, 334-339
      with skull base disruption, 334-339
Facial growth and development. *See* Craniofacial growth and development.
Facial height, 269, 273f, 2617t
  middle and lower, 269, 273f
Facial hiatus, 1828
  in surgical anatomy of lateral skull base, 2436f, 2437
  in surgical anatomy of middle cranial base, 2445f
Facial lipoatrophy, HIV-associated, 227-228, 228f
Facial moulage recording, by maxillofacial prosthodontist, 1331, 1332f
Facial nerve
  anatomy of, 1359f, 1827-1829, 2278f
    surgical, 2403-2404, 2404f
  in congenital aural atresia, 2754, 2755f, 2759
  electromagnetic stimulation of, 2394-2395
  first genu of, 1826f, 1827-1828
  general visceral efferent fibers of, 1827-1828
  imaging of, 173, 175f, 1924-1926
    to assess function, 2384
    with Bell's palsy, 1924, 1927f, 2395
    with hemangioma, 1924-1926, 1927f
    with meningioma, 175f
    with neuroma, 1928
    with schwannoma, 1924-1926, 1927f
  infratemporal portion of, 1826f, 1828
  labyrinthine segment of, 2404, 2404f
  mastoid (vertical) segment of, 2404, 2404f
  in mastoidectomy, 2012, 2012f
  in parotidectomy
    anatomy of, 1194, 1194f
    involvement of, 1196
    main trunk of, 1195, 1195f
    marginal mandibular branch of, 1195, 1195f
  physical examination of, 95, 95t
  rerouting of, 2412, 2412f-2413f
    partial, 2412-2413
Facial nerve *(Continued)*
  second genu of, 1826f, 1827-1829
  small fenestra stapedotomy with exposed or overhanging, 2033
  somatic sensory fibers of, 1827-1828
  special sensory fibers of, 1827-1828
  special visceral efferent fibers of, 1827-1828
  in subtotal or total temporal bone resection, 2494-2495
  in surgical anatomy
    of infratemporal fossa, 2440f
    of internal auditory canal, 2437f, 2439
    of jugular foramen, 2439f-2440f
    of lateral skull base, 2436f
    of middle cranial fossa, 2437f, 2438
    of posterior cranial fossa, 2438, 2439f
  trauma to, 309
  tympanic segment of, 1827, 2404, 2404f
  in vestibular system, 1852, 1854f
  visceral afferent fibers of, 1827-1828
  vulnerability to injury of, 1827-1829
Facial nerve decompression, 2041, 2042t
  indications for, 2041
  middle fossa craniotomy as, 2042-2043
  outcome of, 2041, 2042t
  supralabyrinthine approach for, 2041-2042, 2043f
  timing of, 2041-2042
  translabyrinthine approach for, 2041-2042
  transmastoid approach for, 2041-2042
Facial nerve disorder(s), 2391-2402
  hyperkinetic, 2401
    management of, 2432
  paralysis as (*See* Facial nerve paralysis)
Facial nerve dissection, in postauricular approach to infratemporal fossa, 2495-2496
Facial nerve function
  assessment of, 2381-2390
    electrodiagnostic testing in, 2385-2387
      electromyography in, 2386-2387
      electroneuronography in, 2041, 2386, 2387t
      maximal stimulation test in, 2040-2041, 2385-2386, 2387t
      nerve excitability test in, 2040-2041, 2385, 2387t
    facial nerve monitoring for, 2387-2388
    histopathologic classification in, 2384-2385, 2384f
    House-Brackmann grading system in, 2381-2382, 2382t, 2383f, 2417-2418, 2417t
    imaging in, 2384
    physical examination in, 2381-2382
    topognostic tests in, 2382-2384
      of lacrimal function, 2383
      of salivary flow, 2384
      of salivary pH, 2384
      of stapedius reflex, 2383
      of taste, 2383-2384
    unconventional tests for, 2388-2389
      acoustic reflex evoked potentials as, 2388
      antidromic potentials as, 2388
      blink reflex as, 2388
      magnetic stimulation as, 2388-2389
      optical stimulation as, 2389
      transcranial electrical stimulation–induced facial motor evoked potentials as, 2389
  after stereotactic irradiation, 2563
Facial nerve grafting, 2421-2425
  cross-face, 2419, 2424-2425
  selection of donor nerve for, 2422
  surgical planning for, 2421-2424, 2423f
  surgical technique for, 2422-2424, 2424f-2425f
Facial nerve hemangiomas
  vs. facial nerve schwannomas, 2507
  imaging of, 1924-1926, 1927f

Facial nerve injury
  early care of, 2420-2421
  eye protection for, 2420, 2420f
  histopathologic classification of, 2384-2385, 2384f
  iatrogenic, 2399
  in lateral skull base surgery, 2512
  due to mastoidectomy, 2015-2016
  of neck surgery, 1729-1730
  due to posterior fossa surgery, 2541
  due to rhytidectomy, 422-425, 426f
  traumatic, 2039-2044, 2042t, 2398-2399
    assessing degree of, 2040
      compound muscle action potential in, 2041
      electromyography for, 2041
      electroneuronography for, 2041
      evoked encephalomyography for, 2041
      maximal stimulation test for, 2040-2041
      nerve excitability test for, 2040-2041
    classification of, 2040
    conservative treatment of, 2040, 2042
    corticosteroids for, 2042
    delayed onset of paralysis due to, 2040
    epidemiology of, 2039-2040
    imaging of, 2398f
    observation and symptomatic care for, 2398
    outcome of, 2041, 2042t
    pathogenesis of, 2398
    penetrating, 2399
    surgical interventions for, 2041, 2042t, 2398-2399, 2413-2414
      indications for, 2041
      middle fossa craniotomy as, 2042-2043
      outcome of, 2041, 2042t
      supralabyrinthine approach for, 2041-2042, 2043f
      timing of, 2041-2042
      translabyrinthine approach for, 2041-2042
      transmastoid approach for, 2041-2042
    treatment algorithm for, 2042-2044, 2043f
Facial nerve monitoring, 2387-2388, 2545-2549
  for acoustic neuroma and other cerebellopontine angle tumors, 2545
  active, 2387
  advantages of, 2387
  anesthesia and, 2544
  electrodes for
    recording, 2543-2544, 2543f
    stimulating, 2544, 2544f
  electromyography for, 2545-2548
    activity evoked by electrical stimulation in, 2387, 2545-2546
      to assess functional status of nerves after tumor removal, 2545-2546
      to identify and map nerves in relation to tumor, 2387, 2545
      to identify nerve intermedius, 2546, 2546f
    limitations of, 2547-2548, 2548f
    spontaneous and mechanically evoked activity in, 2546-2548
    patterns of, 2387, 2547, 2547f
  in four-channel montage, 2550f
  future directions in, 2555-2556, 2555f
  instrumentation for, 2405, 2405f, 2543
  during microvascular decompression, 2548-2549, 2549f
  during other otologic surgery, 2549
  and outcome, 2387, 2554
  during parotid surgery, 2549
  passive, 2387
  personnel for, 2542-2543
  stimulation criteria for, 2544
Facial nerve neuroma, 2414, 2506-2508
  vs. acoustic neuroma, 2414, 2519-2522
  of cerebellopontine angle, 2519-2522
Facial nerve neuroma *(Continued)*
  diagnostic evaluation of, 2519-2522
  imaging of, 2519-2522, 2521f
  signs and symptoms of, 2519
  diagnostic evaluation of, 2507
  imaging of, 1924-1926, 1927f
  management and surgical approach for, 2414, 2507-2508
  of posterior fossa, 1928
Facial nerve paralysis
  assessment of, 2416-2420, 2417b
  due to barotrauma, 2400
  due to benign intracranial hypertension, 2400-2401
  bilateral, 2397-2398
  central, 2401
  congenital, 2396-2397, 2396b
    rehabilitation of, 2420
  corticosteroids for, 2409-2410, 2410t
  differential diagnosis of, 2392t
  familial, 2397
  herpes zoster, 2393, 2396
  with HIV infection, 2399
  iatrogenic, 2399
  in Kawasaki disease, 2400
  long-standing, 2399
  due to Lyme disease, 2106, 2400
  management algorithm for, 2392f
  due to mastoidectomy, 2015-2016
  in Melkersson-Rosenthal syndrome, 2399
  due to metabolic disorders, 2401
  due to otitis media, 1991, 2400
    epidemiology of, 1980t
    imaging of, 1991f
    treatment for, 1991
  due to parotidectomy, 1176-1177
  in pregnancy, 2399
  progressive, 2398, 2398f
    due to tumor, 2413
  in Ramsay Hunt syndrome, 2393, 2396
  recurrent, 2397
  rehabilitation of, 2416-2433
    adjunctive procedures in, 2417
      for lower third of face, 2431-2432, 2431f
      for middle third of face, 2430-2431, 2431f
      for upper third of face, 2430
    with eyelid dysfunction, 2420-2421
      eye protection for, 2420, 2420f
      lower (ectropion), 2420-2421, 2421f
      upper (lagophthalmos), 2421
    facial nerve grafting for, 2421-2425
      cross-face, 2419, 2424-2425
      selection of donor nerve for, 2422
      surgical planning for, 2421-2424, 2423f
      surgical technique for, 2422-2424, 2424f-2425f
    muscle transfers in, 2427-2430
      masseter, 2427, 2428f
      microneurovascular, 2429-2430
      temporalis, 2427-2429, 2429f
    nerve transposition for, 2425-2427
      of hypoglossal nerve, 2419, 2424f-2426f, 2425-2426
      neurotropic factors in, 2427
      of other nerves, 2426-2427
    patient assessment for, 2416-2420, 2417b
      age in, 2419
      with congenital paralysis, 2420
      considerations in, 2418-2420
      donor consequences in, 2419
      health status in, 2419-2420
      House-Brackmann grading system in, 2417-2418, 2417t
      presence of partial regeneration in, 2418
      prior radiotherapy in, 2420
      smile pattern in, 2417-2418
      status of donor nerves in, 2419
Facial nerve neuroma *(Continued)*
      status of proximal and distal facial nerve in, 2418-2419, 2419f
      time since transection in, 2418
      viability of facial muscles in, 2419
    static procedures for, 2430
      facial sling as, 2430
    with synkinesis, 2432
      botulinum A toxin for, 2432
      selective myectomy for, 2432
  in sarcoidosis, 2400
  due to small fenestra stapedotomy, 2030, 2034
  spontaneous idiopathic, 2391
    auditory symptoms of, 2393-2394
    in children, 2397
    CNS changes in, 2393-2394
    defined, 2391
    and diabetes, 2401
    differential diagnosis of, 2391, 2392t
    electromagnetic stimulation in, 2394-2395
    electrophysiology and testing for, 2394
      electromyography in, 2394
      electroneurography in, 2394
      interpretation of electrical tests in, 2394
      maximal stimulation test in, 2394
      nerve conduction velocity in, 2394
      nerve excitability threshold in, 2394
    etiology of, 2391-2393
    familial, 2397
    histopathology of, 2393
    imaging in, 1924, 1927f, 2395
    incidence of, 2391-2396
    management of, 2395-2396
    middle cranial fossa decompression for, 2409-2410, 2409t
    polyneuropathy in, 2391, 2398f
    prognosis and statistics for, 2395
    recurrent, 2397
  stapedius reflex in, 1891
  traumatic, 2398-2399, 2398f
Facial nerve regeneration, partial, 2418
Facial nerve rehabilitation, 2416-2433
  adjunctive procedures for, 2417
    for lower third of face, 2431-2432, 2431f
    for middle third of face, 2430-2431, 2431f
    for upper third of face, 2430
  with eyelid dysfunction, 2420-2421
    eye protection for, 2420, 2420f
    lower (ectropion), 2420-2421, 2421f
    upper (lagophthalmos), 2421
  facial nerve grafting for, 2421-2425
    cross-face, 2419, 2424-2425
    selection of donor nerve for, 2422
    surgical planning for, 2421-2424, 2423f
    surgical technique for, 2422-2424, 2424f-2425f
  muscle transfers for, 2427-2430
    masseter, 2427, 2428f
    microneurovascular, 2429-2430
    temporalis, 2427-2429, 2429f
  nerve transposition for, 2425-2427
    of hypoglossal nerve, 2419, 2424f-2426f, 2425-2426
    neurotropic factors in, 2427
    of other nerves, 2426-2427
  patient assessment for, 2416-2420, 2417b
    age in, 2419
    with congenital paralysis, 2420
    considerations in, 2418-2420
    donor consequences in, 2419
    health status in, 2419-2420
    House-Brackmann grading system in, 2417-2418, 2417t
    presence of partial regeneration in, 2418
    prior radiotherapy in, 2420
    smile pattern in, 2417-2418
    status of donor nerves in, 2419

Facial nerve rehabilitation *(Continued)*
status of proximal and distal facial nerve in, 2418-2419, 2419f
time since transection in, 2418
viability of facial muscles in, 2419
static procedures for, 2430
facial sling as, 2430
with synkinesis, 2432
botulinum A toxin for, 2432
selective myectomy for, 2432
Facial nerve repair, 2041, 2042t, 2398-2399, 2413-2414
indications for, 2041
middle fossa craniotomy for, 2042-2043
outcome of, 2041, 2042t
supralabyrinthine approach for, 2041-2042, 2043f
timing of, 2041-2042
translabyrinthine approach for, 2041-2042
transmastoid approach for, 2041-2042
Facial nerve schwannomas. *See* Facial nerve neuroma.
Facial nerve surgery, intratemporal, 2403-2415
combination approaches for, 2411-2412
draping for, 2404-2405, 2405f
for facial nerve tumors, 2413-2414, 2414t
general surgical techniques for, 2404-2405
instrumentation for, 2405
intraoperative monitoring for, 2405, 2405f
middle cranial fossa (transtemporal) approach for, 2407-2409
advantages and uses of, 2408-2409
for Bell's palsy, 2409-2410, 2409t-2410t
limitations and potential complications of, 2409
technique of, 2407-2408, 2408f-2409f
nerve repair in, 2413-2414
rerouting in, 2412, 2412f-2413f
partial, 2412-2413
retrolabyrinthine approach for, 2405-2406, 2405f-2406f
retrosigmoid approach for, 2406-2407
advantages and uses of, 2406-2407
limitations and potential complications of, 2407
technique of, 2406, 2407f
surgical anatomy for, 2403-2404, 2404f
translabyrinthine approach for, 2411
advantages and uses of, 2411
limitations and complications of, 2411
technique of, 2411, 2411f-2412f
transmastoid approach for, 2410-2411
advantages and uses of, 2411
limitations and complications of, 2411
technique of, 2410, 2410f
Facial nerve transposition, in postauricular approach to infratemporal fossa, 2497-2498, 2498f
Facial nerve trunk, insults to, 2384-2385
Facial nerve tumors, 2413-2414, 2414t
Facial neuromas. *See* Facial nerve neuroma.
Facial numbness, due to paranasal sinus tumor, 1123
Facial pain, sinus surgery for, 742
Facial palsy. *See* Facial nerve paralysis.
Facial paralysis. *See* Facial nerve paralysis.
Facial processes, fusion of, during embryogenesis, 2639
Facial proportions, 269
facial height in, 269, 273f
middle and lower, 269, 273f
facial symmetry through midsagittal plane in, 269, 272f
facial width in, 269, 272f
Facial recess
in mastoidectomy, 2012, 2012f-2013f
in surgical anatomy of lateral skull base, 2436f
Facial resurfacing
chemical peels for, 391-397
agents for, 392-394
complications of, 396-397
Facial resurfacing *(Continued)*
contraindications to, 391, 392t
in dark-skinned individuals, 392
deep, 394-395
equipment tray for, 393f
histologic changes with, 390-391
indications for, 391, 392t
medium-depth, 393-394, 393f-394f
patient selection and education for, 391-392
and phenol toxicity, 395
postoperative care after, 396, 396f
prepeel preparations for, 392
superficial, 392-393, 403
contraindications to, 391, 392t
dermabrasion for, 397-399
complications of, 399
equipment for, 398, 398f
micro-, 402-403
patient selection and consultation for, 397-398
postoperative care after, 399, 399f
technique of, 398-399, 398f-399f
indications for, 391, 392t
laser, 399-402
CO_2, 400, 400f
Er:YAG, 400
nonablative, 402, 403t
postoperative care after, 401-402, 401f
nonablative, 402, 403t
laser, 402, 403t
microdermabrasion for, 402-403
superficial chemical peels for, 403
Facial schwannomas. *See* Facial nerve neuroma.
Facial skeletal growth, 2615f, 2617t
Facial skeleton
anatomy, physiology, and pathophysiology of, 319-323, 320f
general, 319
of lower third, 322-323, 323f
of middle third, 319-322
areas of protection in, 322, 322t
infraorbital nerve in, 320, 321f
maxillae in, 320, 321f
nasal bones in, 320
orbits in, 320-321, 322f
zygoma in, 319, 320f-321f
of upper third, 319, 319f
biomechanics of, 331-333, 331f
in lower third, 332-333, 332f
in middle third, 331-332, 331f
in upper third, 331
physical examination of, 95
Facial swelling, due to paranasal sinus tumor, 1123
Facial symmetry, through midsagittal plane, 269, 272f
Facial translocation approach, for middle cranial base surgery, 2455t, 2464-2466, 2467f
Facial trauma
due to burns, 314-316
assessment and treatment of, 315-316
classification of, 314-315, 315f
of eyelids, 316
of lips and oral commissure, 316
of nasal and a utricular cartilage, 316
fracture as (*See* Facial fracture(s))
due to frostbite, 316
in geriatric patients, 237
imaging of, 170-171, 170f-171f
CT for, 142
soft tissue, 302-317
approach to, 302-306
anesthesia in, 304
cleaning in, 304-305, 305f
history taking in, 302-303
infection control in, 305
physical examination in, 303-304, 303f
repair in, 305-306, 306f
tetanus prophylaxis for, 303
Facial trauma *(Continued)*
to ears, 308f, 310, 310f
etiology of, 302
to eye, 303
to eyelids, 303, 303f, 307-309, 308f
to facial nerve, 309
to lacrimal apparatus, 307-309, 308f
with large-segment, composite avulsions or amputations, 312, 312f
to lips, 309-310, 309f
to nose, 310-312, 311f
to parotid duct, 312-313, 314f
to salivary glands, 312, 313f
sialocele and salivary fistula due to, 313-314
types of injuries in, 306-307
abrasion as, 306
avulsions as, 307, 308f
laceration as, 307
Facial venous malformations, embolization for, 1942, 1942f
Facial width, 269, 272f
Facies, physical examination of, 95, 95t
Facioauriculovertebral syndrome, 2741
Facio-oculo-auriculo-vertebral spectrum (FOAVS), craniofacial anomalies in, 2646-2647
FACT-HN (Functional Assessment of Cancer Therapy Head and Neck module), 56
Falciform crest
anatomy of, 1822, 1823f
in surgical anatomy of lateral skull base, 2437f, 2439
Fall(s), in elderly, 233
Fallopian canal
anatomy of, 1827-1828
vulnerability to injury of, 1829
False vocal cords, radiographic anatomy of, 1472-1473, 1472f
Falsetto, 811-812, 851
Familial atypical multiple mole-melanoma (FAMMM) syndrome, 1107
Familial episodic ataxia, 2357
Familial facial paralysis, 2397
Familial hemiplegic migraine (FHM), 2349
Familial hyperparathyroidism, 1795-1797
in MEN-I, 1775, 1776f, 1795-1796
in MEN-IIA, 1796
neonatal, 1797
non-MEN, 1796-1797
Familial hypocalciuric hypercalcemia, 1783
Familial hypothyroidism, 1747
Familial vestibulopathy, 2343-2344
FAMMM (familial atypical multiple mole-melanoma) syndrome, 1107
Fanconi's anemia, tumor suppressor gene in, 1020
Farkas, Leslie, 269
Fas, in adaptive immune system, 601
Fascia, of neck, 2577
deep, 2577-2578, 2578f-2579f
superficial, 2577
Fascial layers, of forehead and temporal region, 440-441, 441f
Fascial space involvement, in odontogenic infections, 180-187
cervical (deep neck), 184-187
lateral pharyngeal, 184-185, 186f
prevertebral (danger space No. 4), 186, 186f
retropharyngeal, 185-186, 186f-187f
surgical drainage and decompression for, 189-190
mandibular, 181-184
Ludwig's angina due to, 184, 185f
masseteric, 184, 185f
masticator, 184, 186f
pterygomandibular (medial pterygoid), 184, 185f
secondary, 184
sub-, 183-184, 183f-184f

Fascial space involvement, in odontogenic infections *(Continued)*
sublingual, 183, 183f
submental, 181-183, 183f
temporal, 184, 185f
maxillary, 180-181
buccal, 181, 181f
canine, 180-181, 180f
cavernous sinus thrombosis due to, 181, 182f
orbital cellulitis due to, 181, 182f
natural history of, 179-180
Fasciitis, necrotizing, due to deep neck space infections, 208
Fasciocutaneous free flaps, 1067, 1067f, 1082t, 1083
anterolateral thigh, 1082t, 1083
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379
for hypopharyngeal and esophageal reconstruction, 1433, 1455
anterolateral thigh, 1455
lateral arm, 1455
lateral thigh, 1455
radial forearm, 1455
scapular-parascapular, 1455
lateral arm, 1082t, 1083
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379-1380
lateral thigh, 1082t
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379
for oropharyngeal reconstruction, 1379-1381, 1379f
anterolateral thigh, 1379
lateral arm, 1379-1380
lateral thigh, 1379
radial forearm, 1379, 1379f
radial forearm, 1082t, 1083, 1083f
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379, 1379f
tubed, 1087, 1091f
scapular-parascapular, 1082t
for hypopharyngeal and esophageal reconstruction, 1455
for tongue base reconstruction, 1390-1391
ulnar forearm, 1082t
Fast Fourier Transform (FFT), in acoustic analysis, for voice evaluation, 829t, 830, 830f
Fast neutron, 1034
Fast spin-echo (FSE) imaging, 134
Fasting, prior to anesthesia, 112
in children, 2589, 2590t
Fat(s), dietary, taste of, 1213
Fat saturation, for MRI, 135-136, 136f
Fat suppression methods, for MRI, 135-136, 136f
of laryngeal carcinoma, 1470
FBA. *See* Foreign body aspiration (FBA).
FDG-PET. *See* Fluorodeoxyglucose–positron emission tomography (FDG-PET).
Federation of State Medical Boards (FSMB), 80-81, 84t-87t
Feedback, with traditional hearing aid, 2204
Feedback suppression circuitry, for hearing aids, 2269
FEES (flexible endoscopic evaluation of swallowing), for dysphagia in children, 2949, 2950t
FEES (functional endoscopic evaluation of swallowing)
for chronic aspiration, 926
for laryngeal stenosis, 2917
"Feline" esophagitis, 967-968, 969f
Fenestra, creation of, in small fenestra stapedotomy, 2031-2032, 2032f
Fenestral otosclerosis, 1921-1922, 1925f
Fenretinide, for cancer chemoprevention, 1018, 1061-1062
Fentanyl
as adjunct to induction of anesthesia, 111
for anesthesia maintenance in children, 2591
for postoperative pain, 241t
Fentanyl sublingual spray, for mucositis, 1102
FESS. *See* Functional endoscopic sinus surgery (FESS).
Fever, pharyngoconjunctival, 198
"Fever blisters," in HIV, 226
Fexofenadine (Allegra), for nonallergic rhinitis, 701t
FFB. *See* Flexible fiberoptic bronchoscopy (FFB).
FFL (flexible fiberoptic laryngoscopy), for laryngomalacia, 2867
FFT (Fast Fourier Transform), in acoustic analysis, for voice evaluation, 829t, 830, 830f
FGF(s) (fibroblast growth factors), in wound healing, 1077-1078
FGFR(s) (fibroblast growth factor receptors), in craniofacial anomalies, 2640, 2642f
FGFR3 (fibroblast growth factor receptor 3) gene
in achondroplasia, 2633
in deafness, 2051t-2058t
FHM (familial hemiplegic migraine), 2349
Fiberoptic bronchoscope (FOB)
for awake fiberoptic nasotracheal intubation, 123-125, 125f
for difficult airway, 114t
Fiberoptic intubation (FOI), awake nasotracheal, 122-123
advantages of, 123
avoiding failure in, 125, 126b
bronchoscopy cart for, 123, 123f
conscious sedation for, 124
fiberoptic bronchoscope in, 123-125, 125f
historical perspective on, 122-123
indications for, 123, 123b
keys to successful, 124b
monitoring during, 124
nasal trumpet placement for, 124, 125f
optimal setup for, 125f
patient preparation for, 123-124
technique of, 124-125
topical anesthesia for, 124
Fiberoptic laryngoscope, rigid, for difficult airway, 114t
Fiberoptic nasopharyngoscopy, 101
of obstructive sleep apnea, 253, 254f
Fibrillated ePTFE (Gore-Tex), for chin implants, 465t
Fibrin glue, in intratympanic delivery, 2182
Fibrin sealants, for rhytidectomy, 416-420
Fibroadnexal tumor(s), 291-293
acrochordon as, 291
angiofibroma as, 292
atypical fibroxanthoma as, 292
cylindroma as, 288f, 292
dermatofibroma as, 288f
dermatofibrosarcoma protuberans as, 291-292
fibrous papule as, 288f, 292
hidrocystoma as, 292
keloids and hypertrophic scars as, 291
lipoma as, 293
neurofibromas as, 292
sebaceous hyperplasia as, 288f, 293
syringoma as, 292-293
trichoepithelioma as, 292
xanthelasma as, 293
Fibroblast(s), in formation of granulation tissue, 1077
Fibroblast growth factor(s) (FGFs), in wound healing, 1077-1078
Fibroblast growth factor receptor(s) (FGFRs), in craniofacial anomalies, 2640, 2642f
Fibroblast growth factor receptor 3 *(FGFR3)* gene
in achondroplasia, 2633
in deafness, 2051t-2058t
Fibroepithelial papilloma, 291
Fibroma
ameloblastic, 1274-1275
microscopic findings in, 1274-1275, 1275f
radiographic features of, 1274
treatment of, 1275
irritation, of oral cavity, 1288-1289, 1289f
ossifying, sinonasal, 725-726
subcutaneous, due to neck irradiation, 1695
Fibronectin, in wound contraction, 1078
Fibro-odontoma, ameloblastic, 1275
microscopic findings in, 1275, 1275f
radiographic findings in, 1275
treatment of, 1275
Fibrosarcoma
in children, 2842-2843, 2843f
of larynx, 1508
of neck, 1668
of paranasal sinuses, 1131
Fibrosis, due to radiotherapy, 1048
Fibrous dysplasia, 2110-2111
of anterior skull base, 2647f
cellular and molecular basis of, 2111
clinical manifestations of, 2111
histopathology of, 2111, 2111f
laboratory findings in, 2111
management of, 2111
otologic manifestations of, 2111
radiographic findings in, 2111, 2111f
of sinonasal tract, 718t, 725-726, 726f
Fibrous nonunion, 331, 339-340
Fibrous papule, 288f, 292
Fibrous tumor, solitary, of neck, 1671
Fibrous union, 331, 339-340
Fibroxanthoma, atypical, 292
Fibula flap, for free tissue transfer, 1082t, 1084-1085, 1085f
Fibula osteocutaneous free flap reconstruction
for mandibular defects, 1324-1325, 1325t
for oral cancer, 1316, 1316f
Field cancerization, in head and neck squamous cell carcinoma, 1016, 1061
Filter, in acoustic analysis, for voice evaluation, 830
Finasteride (Propecia), for hair loss, 377-378
Fine structure signal processing, for cochlear implants, 2230-2231, 2231f-2232f
Fine-needle aspiration biopsy (FNAB)
in children, 2574
of salivary glands, 2854
of lymphoma, 1675-1676
of neck masses, 1638
of oropharyngeal cancer, 1366
of salivary glands, 1149, 1149f, 1165-1166, 1180-1181
in children, 2854
of thyroid nodule, 1756-1758
repeat, 1759
ultrasound-guided, 1655f
ultrasound-guided, 1653-1654, 1655f
of parathyroid tumor, 1789
Fine-needle aspiration cytology (FNAC). *See* Fine-needle aspiration biopsy (FNAB).
Fire, in airway, 119
First aid measures, for epistaxis, 684
First bite syndrome
due to carotid paraganglioma surgery, 1660-1661
due to neck surgery, 1732
First branchial cleft cyst, otorrhea due to infection of, 2195
First genu, of facial nerve, 1826f, 1827-1828
FISH (fluorescence in situ hybridization), for head and neck squamous cell carcinoma, 1018-1019

Fissures of Santorini, 1823, 1944
Fistula(s)
  arteriovenous, embolization of
    dural, 1940-1942, 1940f
    facial, 1940, 1940f
  branchial cleft, 2585
    imaging of, 1410, 1410f
  carotid cavernous, due to temporal bone trauma, 2047
  cerebrospinal fluid
    bacterial meningitis due to, 794
    due to cranial base surgery, 2468
    CT cisternogram of, 2477f
    traumatic, 2044-2046
      antibiotic prophylaxis for, 2044-2045
      closure of, 2045-2046, 2045f
      diagnosis of, 2044
      infecting organisms with, 2045
      meningitis due to, 2044-2045
      pathogenesis of, 2044
      signs and symptoms of, 2044
      treatment algorithm for, 2045-2046, 2045f
  chylous
    due to neck dissection, 1723
    due to neck surgery, 1732-1733, 1732f
  horizontal semicircular canal, due to mastoidectomy, 2015
  H-type, 2926
  labyrinthine, 1989-1990, 1990f
  orocutaneous, 179, 180f
  oronasal, after palatoplasty, 2673
  perilymph, 2342-2343
    categories of, 2342
    due to chronic otitis media, 2342-2343
    clinical presentation of, 2342
    congenital, 2737-2738, 2737f
    imaging of, 2342, 2342f
    repair of, 2361-2362
    sensorineural hearing loss due to, 2122, 2199
      fluctuating, 2199
      sudden, 2128
    due to small fenestra stapedotomy, 2034
    due to temporal bone fracture, 2039
    due to trauma, 2342
  pharyngocutaneous
    after hypopharyngeal reconstruction, 1458
    due to neck surgery, 1727-1728, 1728f
    after total laryngectomy, 1571
    after total laryngopharyngectomy, 1575
  of pharynx and esophagus
    branchial cleft anomaly as, 1410, 1410f
    due to perforation, 1410-1411, 1410f
    postoperative, 1411, 1411f
    tracheoesophageal, 1409-1410
  postparotidectomy, 1728
  salivary, due to neck surgery, 1727-1728, 1728f
  due to sphenoidotomy, 768t
  tracheal–innominate artery, 1623
  tracheal–pulmonary artery, 1623
  tracheoesophageal, 2926
    imaging of, 1409-1410
Fistula test
  for labyrinthine fistula, 1990
  for temporal bone fractures, 2039
Fitting range, of hearing aid, 2271, 2272f
Fitzpatrick sun-reactive skin types, 391, 391t
585-nm pulsed dye laser (PDL), 31t, 33
Fixation eye movements, 2305-2306, 2306f, 2307t
FK-506 (tacrolimus), for eczematoid otitis externa, 1956
FKH10, in deafness, 2051t-2058t
FL (follicular lymphoma), 1678
  clinical presentation of, 1674
  treatment and prognosis for, 1678
FLACC (Face, Legs, Activity, Cry, Consolability) tool, 240
Flageolet, 851
FLAIR (fluid-attenuated inversion recovery) imaging, of middle ear cholesteatoma, 1919, 1921f
Flap(s), skin. *See* Skin flap(s).
Flash lamp pulsed lasers, 33-34
Flash lamp pumped dye laser, 31t, 33
Flexible endoscopic evaluation of swallowing (FEES), for dysphagia in children, 2949, 2950t
Flexible endoscopy
  in children, 2574
  for stridor, 2901-2902
Flexible fiberoptic bronchoscopy (FFB), 1001-1007
  bronchoscopes for
    care of, 1001-1002
    range and special features of, 1001, 1002t, 1003f
    "therapeutic," 1001, 1003f
    ultrathin, 1001, 1003f
  diagnostic, 999b, 1003-1007
    for bronchial wash, 1003
    for bronchoalveolar lavage, 1003-1004
    for bronchoscopic brush sampling, 1007
    for endobronchial and transbronchial biopsy, 1004-1005, 1004f-1005f
    general approaches to, 1003
    for transbronchial needle aspiration, 1005-1007, 1005f-1006f
    for visual examination, 1003
  imaging prior to, 999-1000
  indications for, 999, 999b
  patient discussion and informed consent for, 1000
  patient positioning and route of entry for, 1000
  sedation and airway management for, 1000
Flexible fiberoptic laryngoscopy (FFL), for laryngomalacia, 2867
Flexible fiberoptic nasopharyngoscopy, for recurrent respiratory papillomatosis, 2888
Flexible laryngeal mask airway, for children, 2599
Flexible laryngoscopy, 100, 814
  advantages of, 814
  disadvantages of, 814
  in neurologic evaluation, 834
  for professional voice disorders, 851-852, 852t
  protocols for, 816b, 818b
  technique of, 814
  troubleshooting for, 814
Floccular lesions, and vestibular function, 2308
Floccular peduncle, 1861
Flocculus, 2404f
Flonase (fluticasone propionate), for nonallergic rhinitis, 700t
Floor of mouth
  anatomy of, 1297-1298
  carcinoma of, 1307-1308
    cervical metastases of, 1308
    clinical presentation of, 1294f, 1307
    composite resection for, 1307-1308, 1308f, 1315f
    coronal partial mandibulectomy for, 1307-1308, 1308f
    imaging of, 1307
    invasive, 1307
    reconstruction for, 1307, 1315f
    segmental mandibulectomy for, 1307-1308, 1308f
    survival with, 1308
    transoral resection for, 1307
  vasculature of, 1296
Flow-volume loop, for airway stenosis, 945f
Floxin (ofloxacin) otic solution, for otitis externa, 1946, 1952, 1959t-1960t
Fluence, of surgical laser, 28
Fluid losses, expected, in children, 2572t
Fluid resuscitation
  for burns, 315
  for deep neck space infections, 205
Fluid secretion, by salivary glands, 1135, 1135f
Fluid utilization, during bed rest, for children, 2572t
Fluid-attenuated inversion recovery (FLAIR) imaging, of middle ear cholesteatoma, 1919, 1921f
Fluids and fluid management, in children, 2572
  and expected fluid losses, 2572t
  and fluid utilization during bed rest, 2572t
  and ideal electrolyte composition for infants, 2572t
Flumazenil, for premedication in children, 2589
Flunisolide (Nasalide, Nasarel)
  for nonallergic rhinitis, 700t
  for rhinosinusitis, 734t, 736
Fluorescein, intrathecal, for CSF rhinorrhea, 790, 2044
Fluorescence in situ hybridization (FISH), for head and neck squamous cell carcinoma, 1018-1019
Fluorescent tumor markers, for early glottic carcinoma, 1516
Fluoride, in saliva, 1139
Fluoride gel, for dental care during radiation therapy, 1331, 1331f
Fluoride therapy, for otosclerosis, 2034-2035
Fluorodeoxyglucose–positron emission tomography (FDG-PET), 137-138
  applications of, 144, 145f
  with intensity-modulated radiotherapy, 1044
  of laryngeal carcinoma, 1494-1495
    early glottic, 1517
  of oral cancer, 1300
  of salivary glands, 1150, 1168
Fluoroquinolones, for pediatric chronic sinusitis, 2779
Fluoroscopy
  of obstructive sleep apnea, 255
  of pharynx and esophagus, 1393-1394
5-Fluorouracil (5-FU)
  for chemical peels, 392-393
  in combination chemotherapy, 1059-1060
  for induction chemotherapy, 1056-1058, 1058f
  with radiotherapy, 1041-1042, 1052-1054
Fluosol-DA, and skin flap viability, 1073-1074
Fluticasone
  for obstructive sleep apnea, 257
  for rhinosinusitis, 734t
Fluticasone acetonide oil (DermOtic Oil), for eczematoid otitis externa, 1956
Fluticasone furoate (Veramyst), for nonallergic rhinitis, 700t
Fluticasone propionate (Flonase), for nonallergic rhinitis, 700t
Fluticasone propionate cream, for eczematoid otitis externa, 1955-1956
FM (frequency-modulated) receiver, for hearing aid, 2267
FM (frequency-modulated) system, personal, 2271
fMRI (functional magnetic resonance imaging)
  for cerebral blood flow evaluation, 2491
  of olfaction, 632
FNAB. *See* Fine-needle aspiration biopsy (FNAB).
FNAC (fine-needle aspiration cytology). *See* Fine-needle aspiration biopsy (FNAB).
F_0. *See* Frequency (F_0).
FOAVS (facio-oculo-auriculo-vertebral spectrum), craniofacial anomalies in, 2646-2647
FOB (fiberoptic bronchoscope)
  for awake fiberoptic nasotracheal intubation, 123-125, 125f
  for difficult airway, 114t
Focal length, of lens of laser, 28
Focal plane, of surgical laser, 28, 28f
FOI. *See* Fiberoptic intubation (FOI).

Folate deficiency, oral manifestations of, 1254
Foliate papillae, taste buds in, 1208
Follicular cyst, 1263-1264
  microscopic features of, 1264
  neoplastic potential of, 1264
  radiographic features of, 1264, 1264f
  treatment of, 1264, 1264f
Follicular lymphoma (FL), 1678
  clinical presentation of, 1674
  treatment and prognosis for, 1678
Follicular thyroid carcinoma, 1761-1762
  clinical presentation of, 1761-1762
  management and prognosis for, 1762
  pathology of, 1762
Follicular unit extraction (FUE), 384
Follicular-unit hair transplantation, 378, 378f-381f
  completion of procedure for, 383-384
  complications of, 384
  dissection of donor strip in, 382, 382f
  doll's hair appearance with, 378, 378f
  follicular unit extraction for, 384
  graft placement in, 383, 383f
  location of hairline in, 378-379, 381f, 383, 383f
  marking off donor strip of scalp for, 381-382, 382f
  marking out recipient regions for, 379-381, 382f
  micrografts in, 378, 379f-381f
  operative procedure for, 382-384
  postoperative care after, 384
  preoperative evaluation for, 378-382, 381f
  slivers of follicular units in, 382, 383f
  surrounding natural hair growth in, 382-383
Fontaine sign, positive, with carotid paragangliomas, 1659
Fontanelle(s)
  closure of, 2617t
  in newborn, 2615, 2618f
Food impactions, in esophagus, 975
Food sensitivity, and migraines, 2349
Foramen cecum, in surgical anatomy of anterior cranial base, 2442-2443, 2443f, 2471, 2472f
Foramen jugulare, in surgical anatomy of middle cranial base, 2445f
Foramen lacerum
  in surgical anatomy of anterior cranial base, 2472f
  in surgical anatomy of lateral skull base, 2435f, 2436-2437
  in surgical anatomy of middle cranial base, 2444, 2445f
Foramen magnum
  growth and development of, 2617t
  in surgical anatomy of lateral skull base, 2435f
Foramen of Huschke, 1823
Foramen ovale
  anatomy of, 1699
  in surgical anatomy of lateral skull base, 2435f, 2436-2438, 2437f, 2472f
  in surgical anatomy of middle cranial base, 2444, 2445f
Foramen rotundum
  in surgical anatomy of lateral skull base, 2435f, 2438
  in surgical anatomy of middle cranial base, 2444, 2445f
Foramen spinosum
  in surgical anatomy of lateral skull base, 2434, 2435f, 2437-2438, 2441
  in surgical anatomy of middle cranial base, 2444, 2445f
Forced opening test, of eustachian tube function, 1874
Forced oscillation rhinomanometry, 643-644
Fordyce spots, 99
Foregut duplication cysts, compression of pharynx and esophagus due to, 1408-1409, 1409f
Forehead
  aesthetic analysis of, 270-271
    for defect repair, 359
    eyebrow position in, 271, 275f
    eyebrow shape in, 271
    nasofrontal angle in, 270, 274f
  aesthetic proportions of, 428, 429f
  aging, 428-432, 429f
  fascial layers of, 440-441, 441f
Forehead defects, 359-363
  aesthetic considerations with, 359
  central third, 359-360, 362f
  goals of, 359
  lateral, 360-362
    advancement flap for, 360-363, 362f
    advancement rotation flap for, 360-362, 362f
    O-T or A-T procedure for, 362, 363f
    primary wound closure for, 360-362
    rotation flaps for, 362
  primary wound repair for, 359
  tissue expansion for, 363
Forehead feminization, 385, 385f
Forehead flaps, for nasal defects, 366-367, 368f
  paramedian, 348-350, 352f-353f
Forehead lift
  coronal, 430, 431t
  mid-, 430, 431t
  pretrichial, 430, 431t
Forehead rejuvenation, 428-438
  aesthetic proportions for, 428, 429f
  brow muscles in, 431, 433f
  and characteristics of aging brow, 428-432, 429f
  patient selection for, 428-430
    anatomic considerations in, 429-430
    psychological considerations in, 428
  postoperative care after, 434
  results of, 434-438, 436f-438f
  surgical goals of, 430
  surgical technique for, 432-434
    brow elevation and fixation in, 434, 435f
    frontal and parietal bone dissection in, 432-433
    incisions in, 432, 433f
    local anesthesia in, 432
    release of brow depressor muscles in, 434, 434f
    temporal dissection in, 433-434, 433f-434f
  technique(s) for, 430-432, 431t
    browpexy for, 430, 431t, 432f
    coronal forehead lift for, 430, 431t
    direct brow lift for, 430, 431t
    endoscopic brow lift for, 431, 431t
    midforehead brow lift for, 430, 431t
    midforehead lift for, 430, 431t
    pretrichial forehead lift for, 430, 431t
    temporal lift for, 431-432, 431t
  treatment of depressor muscles with botulinum toxin for, 432, 433f
Foreign body(ies)
  in airway, 975-976, 2935-2943
    acute obstruction due to, 2936-2937
    complications of, 2942
    epidemiology of, 2936
    imaging of, 1411, 1412f, 2938-2939
      vs. tonsillar calcifications, 1411, 1412f
    location of, 2936, 2936f
    management of, 2939-2941
      anesthesia for, 2940
      controversies in, 2942
      equipment for, 2939-2940, 2939t, 2940f
      history of, 2935
      postoperative, 2941-2942
      for sharp objects, 2940-2941
      technique for, 2940, 2941f
    symptoms of, 2937-2938
  bronchial
    complications of, 2942
    imaging of, 2938, 2938f-2939f
    location of, 2936, 2936f
Foreign body(ies) *(Continued)*
    management of
      anesthesia for, 2940
      controversies in, 2942
      technique for, 2940
    symptoms of, 2938
  in esophagus, 975-976, 2935-2943
    airway obstruction due to, 1481, 1481f
    classification of, 975
    complications of, 2942, 2942f
    epidemiology of, 2936
    due to food impaction, 975
    imaging of, 1411, 1412f, 2939
    location of, 2936, 2937f
    management of, 2939-2941
      anesthesia for, 2940
      controversies in, 2942
      for disk batteries, 2941
      equipment for, 2939-2940, 2939t
      history of, 2935-2936
      for pills, 2941
      postoperative, 2941-2942
      for sharp objects, 2940-2941
      technique for, 2940
    perforation due to, 2941
    symptoms of, 2938
  in external auditory canal, 2021
  in larynx
    endoscopic removal of, 2904
      anesthesia for, 2940
    imaging of, 1480-1481, 1480f, 2938
    vs. ossification of stylohyoid ligament, 1480, 1481f
    symptoms of, 2937-2938
  rhinitis due to, 619b
  sinonasal, 742
  tracheal
    anesthesia for removal of, 2940
    imaging of, 2938
    symptoms of, 2938
Foreign body aspiration (FBA), 975-976, 2935-2943
  acute obstruction due to, 2936-2937
  complications of, 2942
  epidemiology of, 2936
  imaging of, 1411, 1412f, 2938-2939
    vs. tonsillar calcifications, 1411, 1412f
  interventional bronchoscopy for, 1008
  location of, 2936, 2936f
  management of, 2939-2941
    anesthesia for, 2940
    controversies in, 2942
    equipment for, 2939-2940, 2939t, 2940f
    history of, 2935
    postoperative, 2941-2942
    for sharp objects, 2940-2941
    technique for, 2940, 2941f
  stridor due to, 2898
  symptoms of, 2937-2938
Forked-flap technique, in cleft-lip nose repair, 559, 566f
Forkhead box I1 *(FOXI1)* gene, in deafness, 2051t-2058t, 2096, 2098
Formant(s), 2876
  in acoustic analysis for voice evaluation, 830
  singer's, 847
  in speech, 812
Formant regions, 847
Forward-planning intensity-modulated radiation therapy (FP-IMRT), 1696-1697
Foscan [m-tetra(hydroxyphenyl)chlorin], for recurrent respiratory papillomatosis, 2892
FOSQ (Functional Outcomes of Sleep Questionnaire), 57
Fossa of Rosenmüller, in surgical anatomy of anterior cranial base, 2474
Fossa triangularis, 476-477, 476f, 1824f

Fossa triangularis–temporalis fascia sutures, 476f
Founder effect, 7
Fourth ventricle tumors, 2528-2529, 2530f-2531f
  vestibular symptoms of, 2353-2354
Four-vessel arteriography, prior to lateral cranial base surgery, 2489-2490, 2491f
Fovea ethmoidalis, 741, 2472f
FOXI1 (forkhead box I1) gene, in deafness, 2051t-2058t, 2096, 2098
FP-IMRT (forward-planning intensity-modulated radiation therapy), 1696-1697
FPS-R (Faces Pain Scale Revised), 240
Fractional photolysis, for facial resurfacing, 403t
Fracture(s)
  condylar and subcondylar, 322-323, 1280, 1281t
    pediatric, 2704, 2706f-2708f
  dentoalveolar, 2706-2707, 2710f
  of frontal bone, 319, 319f
  frontal sinus
    classification of, 326
    imaging of, 325, 325f
    management of, 784
    pediatric, 2711, 2712f
    repair of, 333-334
  mandibular, 323
    classification of, 327
    imaging of, 325-326
    pediatric, 2704-2706
      arch and body, 2706, 2709f
      complications of, 2704
      condylar and subcondylar, 2704, 2706f-2708f
      epidemiology of, 2698
      symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
    physical examination of, 325
    repair of, 337-339, 338f
    surgical access to, 329-330, 330f
    teeth in line of, 339
  maxillary
    classification of, 326, 327f
    imaging of, 325
    physical examination of, 324-325
    repair of, 334-337, 334f-336f
  nasal (*See* Nasal fracture(s))
  naso-orbitoethmoid, 322
    classification of, 326-327, 327f
    pediatric, 2714
      classification of, 2714, 2716f
      evaluation of, 2714, 2716f
      repair of, 2714, 2716f
    physical examination of, 324, 324f
    repair of, 336-337, 337f
  orbital
    blowout, 170f, 321, 325, 326f
      pediatric, 325, 326f
    imaging of, 325, 326f
    pediatric, 2711-2714
      evaluation of, 2712, 2713f
      of lateral/medial orbital wall, 2712, 2714, 2716f
      of orbital apex, 2712, 2713f
      of orbital floor, 2712-2713, 2714f-2715f
      of orbital roof, 2712-2713, 2716f
      patterns of, 2711-2712
    physical examination of, 324
    repair of, 336
    surgical access to, 328-329, 329f
  pediatric
    condylar and subcondylar, 2704, 2706f-2708f
    dentoalveolar, 2706-2707, 2710f
    of frontal sinus, 2711, 2712f
    mandibular, 2704-2706
      arch and body, 2706, 2709f
      complications of, 2704
      condylar and subcondylar, 2704, 2706f-2708f
      epidemiology of, 2698
      symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
    naso-orbitoethmoid, 2714
      classification of, 2714, 2716f
      evaluation of, 2714, 2716f
      repair of, 2714, 2716f
    orbital, 2711-2714
      evaluation of, 2712, 2713f
      of lateral/medial orbital wall, 2712, 2714, 2716f
      of orbital apex, 2712, 2713f
      of orbital floor, 2712-2713, 2714f-2715f
      of orbital roof, 2712-2713, 2716f
      patterns of, 2711-2712
    pterygoid plate, 171f
    skull base, 171
    temporal bone (*See* Temporal bone fractures)
    transverse petrous, 174f
Fracture hematoma, 330
Franceschetti syndrome, craniofacial abnormalities in, 2633-2635, 2633b, 2635f
Francisella tularensis, pharyngitis due to, 195
Frankfort horizontal plane, in facial analysis, 269, 272f
  for mentoplasty, 463, 464f
Frechet triple flap repair, for vertical slot defect, 385, 386f
Free cartilage grafts, for nasal defects, 348
Free flap reconstruction, for oral cancer, 1316, 1316f
Free microvascular flaps, 1067
  primary ischemia in, 1075
  reperfusion period for, 1075
  salvage of, 1075
  secondary ischemia in, 1068, 1075
  vascularity of recipient bed with, 1075
Free radical(s)
  in acutely raised skin flaps, 1070-1071, 1071f
  in ototoxicity, 2190
  in radiation damage, 1036
  and skin flap viability, 1074
Free radical scavengers, and skin flap viability, 1074
Free T_3 level, 1740
Free T_4 index, 1740
Free T_4 level, 1740
Free tissue transfer, 1080-1099
  advantages of, 1080-1081, 1081b
  contraindications to, 1091
  costs and outcomes of, 1098
  defined, 1080
  for dental rehabilitation, 1087, 1089f
  with diabetes, 1091-1092
  disadvantages of, 1081-1082, 1081b
  donor site options for, 1082-1083, 1082t, 1083b
  fasciocutaneous (soft tissue) flaps for, 1082t, 1083
    anterolateral thigh, 1082t, 1083
      for hypopharyngeal and esophageal reconstruction, 1455
      for oropharyngeal reconstruction, 1379
    for hypopharyngeal and esophageal reconstruction, 1433, 1455
      anterolateral thigh, 1455
      lateral arm, 1455
      lateral thigh, 1455
      radial forearm, 1455
    lateral arm, 1082t, 1083
      for hypopharyngeal and esophageal reconstruction, 1455
      for oropharyngeal reconstruction, 1379-1380
    lateral thigh, 1082t
      for hypopharyngeal and esophageal reconstruction, 1455
      for oropharyngeal reconstruction, 1379
    for oropharyngeal reconstruction, 1379-1381, 1379f
      anterolateral thigh, 1379
      lateral arm, 1379-1380
      lateral thigh, 1379
      radial forearm, 1379, 1379f
    radial forearm, 1082t, 1083, 1083f
      for hypopharyngeal and esophageal reconstruction, 1455
      for oropharyngeal reconstruction, 1379, 1379f
      tubed, 1087, 1091f
    scapular-parascapular, 1082t
    ulnar forearm, 1082t
  future directions in, 1098
  historical perspectives on, 1081
  for hypopharyngeal and esophageal reconstruction, 1454, 1454f
    enteric, 1455-1457
      gastro-omental donor site for, 1457-1458, 1457f
      jejunal donor site for, 1455-1457, 1456f
    fasciocutaneous, 1433, 1455
      antero-lateral thigh donor site for, 1455
      other donor sites for, 1455
      radial forearm donor site for, 1455
  indications for, 1081-1087, 1081b-1082b
  intraoperative management of, 1092-1093
  muscle and myocutaneous flaps for, 1082t, 1083-1084
    latissimus dorsi, 1082t, 1083-1084, 1084f
      for oropharyngeal reconstruction, 1380
    for oropharyngeal reconstruction, 1380
    rectus abdominis, 1082t, 1083
      for oropharyngeal reconstruction, 1380
  for oropharyngeal reconstruction, 1379-1381
    fasciocutaneous, 1379-1380
      anterolateral thigh, 1379
      lateral arm, 1379-1380
      lateral thigh, 1379
      radial forearm, 1379, 1379f
    musculocutaneous, 1380
      latissimus dorsi myocutaneous, 1380
      rectus abdominis, 1380
    osteocutaneous, 1380-1381
    of soft palate, 1382
      Gehanno method for, 1382
      Lacombe and Blackwell's method for, 1382-1383
      other groups' experience with, 1383
      radial forearm, 1382, 1383f
    of tongue base, 1389
      lateral arm, 1389
      radial forearm, 1389
    of tonsils and pharyngeal wall, 1386
      with combined lateral and superior defects, 1386, 1387f
      lateral arm and thigh, 1386-1387
      radial forearm, 1386
    visceral, 1380, 1380f
  osteocutaneous (vascularized bone) flaps for, 1082t, 1084-1087
    fibula, 1082t, 1084-1085, 1085f
    iliac crest, 1082t, 1087
    for oropharyngeal reconstruction, 1380-1381
    radial forearm, 1082t, 1085-1086, 1086f-1087f
    scapula, 1082t, 1086-1087, 1088f
  other flaps for, 1082t, 1087
    jejunum, 1082t, 1087, 1090f
    omentum, 1082t
    temporal-parietal, 1082t
  patient evaluation and preparation for, 1087-1092
    history and current illness in, 1087-1088
    laboratory and radiologic studies in, 1092
    past medical history in, 1091-1092
    physical examination in, 1088-1091
    surgical treatment planning in, 1092

Free tissue transfer *(Continued)*
postoperative management of, 1096-1098
complications and salvage in, 1097-1098
free flap monitoring in, 1097
pharmacologic, 1096-1097
aspirin in, 1096
dextran in, 1096-1097
heparin in, 1096
surgical techniques for, 1093-1096
drain placement and wound closure in, 1096
free flap harvest in, 1094
free flap inset and microvascular anastomosis in, 1094-1096, 1095f
neck recipient site surgery in, 1094
primary recipient site surgery in, 1093-1094
surgical incisions in, 1093
visceral, for oropharyngeal reconstruction, 1380, 1380f
Freer elevator, for septoplasty, 488, 489f
Frequency (F_0)
in acoustic analysis for voice evaluation, 829, 829t
characteristic, 1844-1845, 1845f
of sound waves, 1838-1839, 1839f
of ultrasound waves, 1643
Frequency distribution, 63, 66
Frequency gain response, for hearing aids, 2267-2268
Frequency response, in vestibular tests, 2302, 2303f
Frequency selective presaturation, for MRI, 135-136, 136f
Frequency-modulated (FM) receiver, for hearing aid, 2267
Frequency-modulated (FM) system, personal, 2271
Frey's syndrome, 2197
after parotidectomy, 1177
Friedreich's ataxia, 2357
Frontal bone
anatomy and physiology of, 319, 319f-320f
fracture of, 319, 319f
imaging of, 325, 325f
repair of, 333-334
surgical access to, 328, 328f-329f
osteomyelitis of, 777f
Paget's disease of, 779-780, 780f
in surgical anatomy of anterior cranial base, 2442-2443
Frontal branch, of facial nerve, 440, 441f
in anterior cranial base surgery, 2451, 2451f
Frontal mucocele, 783
Frontal nerve, 440
Frontal process, in endoscopic dacryocystorhinostomy, 799-800, 800f
Frontal recess
in endoscopic sinus surgery, 750
prior to endoscopic sinus surgery, 764, 764t
after functional endoscopic sinus surgery, 677
normal anatomy of, 665, 665f-667f
reconstruction of lateral wall of, 778-779, 779f
surgical anatomy of, 740-741
Frontal sinus(es)
anatomy of, 319, 319f, 665, 665f
surgical, 740-741
in anterior cranial base, 2442, 2443f, 2473, 2474f
biomechanics of, 331
cranialization of, 782, 783f
prior to endoscopic sinus surgery, 764t
external approaches to, 757
growth and development of, 2619-2620
obliteration of, 779-781
closure in, 780
complications after, 780-781
estimating limit of frontal sinus in, 780, 781f
incision for, 779-780, 780f
materials used for, 780
with Paget's disease, 779-780, 780f
postoperative monitoring after, 780-781
Frontal sinus(es) *(Continued)*
removal of all mucosa in, 780
template for, 779-780
osteoma of, 783-784, 784f
physiology of, 664
pneumosinus dilatans of, 783, 784f
Frontal sinus drainage procedure, median, 779, 779f
Frontal sinus fractures
classification of, 326
imaging of, 325, 325f
management of, 784
pediatric, 2711, 2712f
repair of, 333-334
Frontal sinus surgery
balloon catheter sinusotomy as, 782-783
cranialization of frontal sinus as, 782, 783f
endoscopic frontal sinusotomy as, 776-778
accessing frontal recess in, 777, 777f-778f
confirming location of instrument in, 777-778, 778f
contrainidications to, 781, 781f
history of, 775-776
indications for, 776-783
Lynch-Howarth external ethmoidectomy as, 778-779, 779f
median frontal sinus drainage procedure as, 779, 779f
obliteration of frontal sinuses as, 779-781
closure in, 780
complications after, 780-781
estimating limit of frontal sinus in, 780, 781f
incision for, 779-780, 780f
materials used for, 780
with Paget's disease, 779-780, 780f
postoperative monitoring after, 780-781
removal of all mucosa in, 780
template for, 779-780
Riedel's procedure as, 781-782
indications for, 781-782
postoperative appearance after, 781, 782f
for recurrent infection, 781
Frontal sinus tumors, 1123, 1130
Frontal sinusitis
acute, 775
anatomic variations and, 776
chronic, 775-783
Frontal sinusotomy
balloon catheter, 782-783
in endoscopic sinus surgery, 750-751, 768-771, 776-778
accessing frontal recess in, 777, 777f-778f
agger nasi cell in, 769, 771f-772f
and causes of frontal sinus disease, 769
challenges of, 768
confirming location of instrument in, 777-778, 778f
contrainidications to, 781, 781f
external approaches as adjunct to, 771, 773f
frontal bullar cell in, 772f
frontal recess dissection in, 769, 770b, 770t, 771f
frontal sinus cells in, 769-770, 772f
image-guided navigation system in, 771f
interfrontal sinus septal cell in, 771, 772f
preoperative evaluation for, 768-769
recessus terminalis in, 771
suprabullar cell in, 772f
supraorbital ethmoid cell in, 770-771, 772f
Frontalis muscle, 321f, 433f, 441-442, 444f
Frontobasal meningiomas, embolization of, 1938
Frontoethmoid mucocele, 776f-777f, 783
Frontoethmoid osteoma, 783-784, 784f
Frontoethmoid suture line, in surgical anatomy of anterior cranial base, 2443-2444
Frontoethmoidectomy, craniofacial, 1126, 1126f
Frontofacial monobloc advancement, for craniofacial anomalies, 2653-2654, 2655f-2656f
Frontolateral partial laryngectomy, for glottic cancer, 1517t
Frontolateral vertical hemilaryngectomy, 1548
Frontonasal prominences, in embryology
of lip, 2659-2660, 2661f, 2661t
of nose, 2691f
Fronto-orbital advancement, 2650-2653
bifrontal craniotomy in, 2651-2652, 2651f
for brachycephaly, 2652-2653
closure in, 2653
extent of, 2652-2653, 2653f-2654f
for lambdoid synostosis, 2653
for plagiocephaly, 2652-2653, 2653f
removal of bandeau in, 2651-2652, 2652f
repair of bony defects in, 2653, 2654f
reshaping of bandeau in, 2652, 2652f-2653f
resorbable plates in, 2653
splitting of bandeau in, 2652, 2653f
for trigonocephaly, 2652-2653, 2654f
Frost stitch, 328-329, 329f
Frostbite, 316
Frozen sections, of oropharyngeal cancer, 1366
FSE (fast spin-echo) imaging, 134
FSMB (Federation of State Medical Boards), 80-81, 84t-87t
5-FU. *See* 5-Fluorouracil (5-FU).
FUE (follicular unit extraction), 384
Fugimycin (tacrolimus), for eczematoid otitis externa, 1956
Full denture smile, 2417-2418
Full-thickness skin grafts (FTSGs), for nasal reconstruction, 365
Fully implantable middle ear system, 2027
Function, as outcome measure, 55
Functional Assessment of Cancer Therapy Head and Neck module (FACT-HN), 56
Functional dysphonia, 851
in children, 2879
Functional endoscopic evaluation of swallowing (FEES)
for chronic aspiration, 926
for laryngeal stenosis, 2917
Functional endoscopic sinus surgery (FESS)
abnormal facial growth and development due to, 2623-2625
extent of, 759-760
ostiomeatal complex in, 760, 760f
for pediatric chronic sinusitis, 2779-2781, 2780f-2781f
principles of, 743, 759
radiologic evaluation after, 677-680
expected findings in, 677-679, 679f
operative complications in, 679-680, 680f
Functional hearing loss, evaluation of, 1901
Functional magnetic resonance imaging (fMRI)
for cerebral blood flow evaluation, 2491
of olfaction, 632
Functional matrix hypothesis, of craniofacial growth and development, 2614
Functional Outcomes of Sleep Questionnaire (FOSQ), 57
Functional redundancy, in salivary proteins, 1139
Functional residual capacity, in infants, 2570
Fundamental frequency, 847, 2876
Fundoplication, for extraesophageal reflux, 901
Fungal diseases, 2106
oral manifestations of, 1252
otologic manifestations of, 2106, 2106f
Fungal labyrinthitis, 2160
Fungal laryngitis
acute, 884-885, 884f
chronic, 885
due to blastomycosis, 885
due to coccidioidomycosis, 885

Fungal laryngitis *(Continued)*
due to histoplasmosis, 885
due to paracoccidioidomycosis, 885
Fungal lymphadenopathy, in children, 2818-2819
Fungal otitis externa, 1944-1946, 1945f
otorrhea due to, 2195
topical therapies for, 1954-1955
acidifying agents in, 1954
antifungals in, 1954-1955
ototoxicity of, 1955
antiseptics in, 1955
options for, 1954
Fungal overgrowth, in chronic suppurative otitis media, 2221
Fungal pharyngitis, 199-200
Fungal rhinosinusitis, 709-2
allergic, 707, 712-715
in children, 2778, 2780, 2781f
chronic, 707, 733
classification of, 709
diagnosis of, 707, 712-713
endoscopic sinus surgery for, 761, 762f
epidemiology of, 713-714
imaging of, 706f, 713, 714f
immunochemical staining for, 731, 731f
pathogenesis of, 712-714, 714b
prognosis for, 713
therapy for, 713-715, 715b
chronic, 732-733
allergic, 707
invasive, 711
nonallergic, 715-716, 716t
classification of, 709
fungus balls in, 712, 712f, 714t
in immunocompromised host, 660, 710t
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 220
treatment of, 221
invasive, 705, 709-712
due to *Aspergillus*, 705, 710-711, 712f
in immunocompromised host, 220-221, 220f
due to *Candida*, 711
chronic or indolent, 711
diagnosis of, 711, 711f-712f
due to mucormycosis, 705, 710, 711f
rapidly (fulminant), 709-710, 710f
surgical management of, 742, 761
therapy for, 711-712, 713t
nonallergic eosinophilic, 709, 715-716, 716t
noninvasive, 709
surgical management of, 742, 761
radiologic appearance of, 674-675, 676f
saprophytic, 712
Fungiform papillae, in taste, 1208, 1210, 1212
Fungus balls, of paranasal sinuses, 712, 712f, 714t, 765t
sphenoid, 767, 770f
*N*6-Furfuryladenine (Kinerase), for aging skin, 404
Furlow palatoplasty, 2670
surgical technique for, 2671-2672, 2672f
for velopharyngeal dysfunction, 2682-2683
Furnas suture technique, for otoplasty, 476-477
Furosemide, sensorineural hearing loss due to, 2120, 2175
Furunculosis, of external ear, 1949, 1949f, 2021
Fusiform incisions, for scar revision, 295, 297f
Fusobacterium spp, acute exacerbation of chronic rhinosinusitis due to, 707
F-wave, 2388

G

G protein(s), in salivary gland secretion, 1137
G protein mutations, in thyroid carcinoma, 1752-1753
G protein–coupled receptors
in gustatory transduction, 1208-1209
in olfactory transduction, 629
G1 phase, of cell cycle, 12, 13f
G2 phase, of cell cycle, 12, 13f
GA (genioglossal advancement), for obstructive sleep apnea, 259, 260f
Gabapentin (Neurontin)
for migraine, 2350
for neuropathic pain, 243, 244t
for tinnitus, 2137
GABHS (group A beta hemolytic *Streptococcus pyogenes*), pharyngitis due to, 191-193
in children, 2787
complications of, 2788
Gadolinium enhancement, for MRI, 134-135, 135f-136f
of laryngeal carcinoma, 1470
Gagner, Michel, 39
Gahne, Albert, 1774
Gain
with hearing aids, 2203-2204, 2267-2268
with linear amplification, 2268, 2268f
with nonlinear amplification, 2268, 2268f
target, 2271
vestibuloocular reflex, 2301-2304, 2301f, 2303f
Gait exercises, in vestibular rehabilitation, 2372-2373, 2378-2379
Galanin (GAL), in salivary gland secretion, 1137
Galea aponeurosis, 440
Galectin, in thyroid carcinoma, 1753
Galectin-3, in laryngeal carcinoma, 1505
Gallium-67 citrate scan, for malignant otitis externa, 1947
Gamma Knife radiotherapy, for skull base tumors
benign, 2557, 2558f, 2559t
malignant, 1696
Gamma radiation detection device, for hyperparathyroidism, 1802, 1803f
Gamma rays, 1031-1032
GAN. *See* Greater auricular nerve (GAN).
Ganglioneuroma, 151f
Gap junction(s), 2090f
in endolymph homeostasis, 2081-2083, 2083f-2084f
Gap junction membrane channel protein β1 *(GJB1)* gene, in deafness, 2051t-2058t
Gap junction membrane channel protein β2 *(GJB2)* gene
in deafness, 2051t-2058t, 2083, 2089-2090, 2097
genetic testing for, 2097-2098, 2235
of infants, 2723
Gap junction membrane channel protein β3 *(GJB3)* gene, in deafness, 2051t-2058t, 2083
Gap junction membrane channel protein β6 *(GJB6)* gene
in deafness, 2051t-2058t, 2083
genetic testing for, 2235
Garamycin Ophthalmic (gentamicin), for otitis externa, 1952, 1959t-1960t
Gardasil (human papillomavirus vaccine), 2886-2887, 2890t
Gardner-Robertson scale, for hearing outcomes, after stereotactic irradiation of vestibular schwannoma, 2562, 2562t
Gasserian ganglion, in surgical anatomy of lateral skull base, 2437f, 2438, 2440f
Gastric outlet obstruction, due to caustic ingestion, 2961
Gastric pull-up, for hypopharyngeal and esophageal reconstruction, 1432, 1432f, 1453
Gastric transposition, for hypopharyngeal and esophageal reconstruction, 1432, 1432f, 1453
Gastroesophageal endoscopy, 956-957
equipment for, 956
of esophageal varices, 958f
for extraesophageal reflux, 899
of gastroesophageal junction
Gastroesophageal endoscopy *(Continued)*
with Mallory-Weiss tear, 957f
normal, 956-957, 957f
with severe esophagitis, 957f
of squamocolumnar junction, 956-957, 956f-957f
technique of, 956-957
Gastroesophageal junction (GEJ)
with Barrett's esophagus, 957f
with hiatal hernia, 957f
with Mallory-Weiss tear, 957f
normal anatomy of, 956-957, 957f
with severe esophagitis, 957f
Gastroesophageal reflux (GER)
defined, 2944-2945
physiologic or "functional," 2944
Gastroesophageal reflux disease (GERD), 894-903, 968-973
and airway obstruction, 2905-2906
classification of erosive esophagitis in, 969, 969f
defined, 894, 968, 2944-2945
diagnostic evaluation of, 896-900, 968-969
esophageal endoscopy in, 899, 969, 969f
esophagogram in, 898
history in, 896, 896b-897b
impedance testing in, 900
laryngeal sensory testing in, 898-899
manometry in, 899-900
pH probe monitoring in, 900
physical examination and laryngeal endoscopy in, 896-897, 897t, 898b
voice analysis in, 898
dysphagia due to, 2953
epidemiology of, 894
and esophageal adenocarcinoma, 899
esophageal pH monitoring for
ambulatory 24-hour, 958-960, 959f-960f
Bravo wireless pH capsule for, 961, 961f
multichannel intraluminal impedance for, 962
Restech Dx-pH Measurement System for, 962, 962f
extraesophageal (*See* Extraesophageal reflux (EER))
and head and neck cancer, 902-903
laryngeal stenosis due to, 2915, 2917
and laryngomalacia, 2867
nonerosive, 968
and obstructive sleep apnea, 253
oral manifestations of, 1254
otitis media in, 2765
otolaryngologic disorders associated with, 901-903
chronic laryngitis as, 901-902
contact ulcer and laryngeal granuloma as, 902, 902f-903f
pathophysiology of, 894-896, 968
epithelial resistance factors in, 895-896
esophageal acid clearance in, 895
lower esophageal sphincter in, 895, 895b
mechanisms of symptoms in, 896
upper esophageal sphincter in, 894-895
and pediatric chronic sinusitis, 2778-2779
professional voice disorders due to, 852
reflux esophagitis in, 968
and squamous cell carcinoma of larynx, 1491-1492, 1513
symptoms of, 968
treatment of, 900-901, 969-970
behavioral modification for, 900-901
bethanechol for, 901
H_2 blockers for, 901
over-the-counter antacids for, 901
promotility agents for, 901
proton pump inhibitors for, 901
sucralfate for, 901
surgical, 901
and vocal fold granuloma, 2881

Gastroesophageal reflux disease (GERD)-related laryngeal disease, in children, 2944-2947
diagnosis of, 2945
disorders due to, 2945-2946, 2945b
evidence of, 2946
history of, 2944
management of, 2946
physiopathology of, 2945
Gastrografin swallow, for penetrating neck trauma, 1633
Gastrointestinal disorders
in hyperparathyroidism, 1781
oral manifestations of, 1254
Gastrolaryngopharyngeal reflux (GLPR), and laryngeal stenosis, 2917
Gastro-omental flap, for hypopharyngeal and esophageal reconstruction, 1457-1458, 1457f
GATA3, in deafness, 2051t-2058t
Gaucher's disease, oral manifestations of, 1257
Gaze shift, cancellation of vestibulo-ocular reflex in, 2300-2301
Gaze stabilization
medial vestibulospinal tract in, 1865
vestibular system in maintaining, 2276-2277
anatomic and physiologic basis for, 2276-2277
clinical importance of, 2277
GBI (Glasgow Benefit Inventory), after stereotactic irradiation of vestibular schwannoma, 2564
GBLC (geometric broken line closure), for scar revision, 298, 299f-300f
G-CSF (granulocyte colony-stimulating factor), 604, 609t-610t
GCT (giant cell tumor)
of larynx, 1510
malignant, of neck, 1671
of petrous apex, 2526
GDNF (glial cell–derived neurotrophic factor)
for facial nerve paralysis, 2427
in gene therapy of inner ear, 2192
for prevention of ototoxicity, 2189-2191
GDTF (Guidelines Development Task Force), 89
Gehanno method
for palatal reconstruction, 1382
for tonsillar and pharyngeal wall reconstruction, 1386, 1387f
GEJ. *See* Gastroesophageal junction (GEJ).
Gelclair, for mucositis, 1102
Gelfilm, for tympanoplasty, 2000-2001, 2003
Gelfoam
for embolization, 1933
in intratympanic delivery, 2182
for tympanoplasty, 2000-2001, 2003, 2004f
Gender
and olfactory testing, 633
and otitis media, 2766
Gene(s), 3
defined, 4
liability, 8
replacing defective, 13
structure of, 4, 5f
suicide, 16, 21
Gene expression, 4, 5f, 11-12, 12f
enhancing, 13
site-specific, 20
suppressing, 13, 14f
therapeutic levels of, 19-20
"Gene gun," 15
Gene mapping, 3
Gene silencing
direct delivery of RNA for, 16
RNA interference for, 13, 14f
therapeutic, 23-24
Gene therapy, 12-15
advantages of, 20
applications of, 20-24
Gene therapy *(Continued)*
for head and neck oncology, 20-22, 21f
antiangiogenesis in, 22
conditionally replicating adenovirus therapy in, 22
cytotoxic or suicide gene therapy strategies in, 21
direct in vivo stimulation of antitumor immune response in, 21
genetic modification of tumor-infiltrating lymphocytes in, 20-21
modifying oncogenes and tumor suppressor genes in, 21-22
for inherited disease, 20
for laryngology, 23
for otology/neurotology, 23
for plastic and reconstructive surgery, 22-23
with reconstructive tissue flaps and wound healing, 22-23
with skin grafting, 23
for repair and regeneration of irradiated tissue, 23
basic principle of, 12-13
enhancing gene expression in, 13
future of, 23-24
of inner ear, 2191-2192
delivery of, 2191
preclinical applications of, 2192
safety concerns with, 2192
vectors for, 2191, 2191t
methods of delivering, 15-20, 19f
direct injection of genetic material as, 15-16, 19f
direct delivery of RNA for gene silencing in, 16
DNA-mediated transfer of therapeutic genes in, 15-16, 15f
viral-mediated gene transfer as, 16-18, 18t, 19f
via adeno-associated virus, 18, 18t
via adenoviruses, 17-18, 17f, 18t
via retroviruses, 16, 17f, 18t
permanent *vs.* temporary, 14-15
replacing defective genes in, 13
somatic *vs.* germ cell, 14, 15f
strategies for administering, 18-19, 19f
ex vivo, 18, 19f
in vivo, 18-19, 19f
suppressing gene expression in, 13, 14f
therapeutic gene silencing in, 23-24
therapeutic levels of gene expression in, 19-20
Gene transfer
DNA-mediated, 15-16, 15f
viral-mediated, 16-18, 18t, 19f
via adeno-associated virus, 18, 18t
via adenoviruses, 17-18, 17f, 18t
via retroviruses, 16, 17f, 18t
General appearance
physical examination of, 95
in voice evaluation, 827
Generalizability, 68-69, 68t, 69f
Generic scales, as outcome measures, 55-56, 56t
Genetic alterations, in head and neck squamous cell carcinoma, 1019-1020
cytogenetic, 1019
microsatellites as, 1019
in oncogenes, 1016, 1019-1020
single nucleotide polymorphisms as, 1019
in tumor suppressor genes, 1016, 1020
and Fanconi's anemia, 1020
Genetic code, 4
Genetic disorders, 4
chromosomal, 4-5
aneuploidies as, 4-5
rearrangements as, 4-5
oligogenic, 4, 8
with complex traits, 8
genetic heterogeneity and, 8
Genetic disorders *(Continued)*
mitochondrial, 8, 9f
sporadic cases of, 8
with X-linkage, 8, 8f
single-gene, 4, 6
dominant, 6, 6f
penetrance and expressivity of, 7, 7f
recessive, 6-7, 7f
Genetic distance, 3
Genetic factors
in nasopharyngeal carcinoma, 1352
presbycusis due to, 233
in salivary gland neoplasms, 1164
Genetic heterogeneity, 8
Genetic predisposition, to otitis media, 2766-2767
Genetic preprogrammed theory, of craniofacial growth and development, 2614
Genetic progression model, of head and neck squamous cell carcinoma, 1016
Genetic susceptibility, to laryngeal cancer, 1492, 1513
Genetic testing
for cochlear implants, 2235
for sensorineural hearing loss, 2098
in infants, 2722-2723
Genetically determined disease, otologic manifestations of, 2115
Genetics, 3-10
chromosomal disorders in, 4-5
aneuploidies as, 4-5
rearrangements as, 4-5
DNA structure and genetic code in, 4
ethical issues in, 9-10
fundamentals of, 2088
gene structure and expression in, 4, 5f
genome in, 9
historical background of, 2088
inheritance patterns in, 2088-2089, 2088f
autosomal dominant, 2088, 2088f
autosomal recessive, 2088-2089
mitochondrial, 2089
molecular basis of, 4
Punnett squares for, 2088, 2089f
X-linked, 2089
oligogenic disorders in, 4, 8
with complex traits, 8
genetic heterogeneity and, 8
mitochondrial, 8, 9f
sporadic cases of, 8
with X-linkage, 8, 8f
single-gene disorders in, 4, 6
dominant, 6, 6f
penetrance and expressivity of, 7, 7f
recessive, 6-7, 7f
testing human DNA in, 8-9
DNA chips for, 9
mutation testing for, 9, 10f
nucleic acid hybridization and Southern blotting for, 9
polymerase chain reaction for, 8-9
utility in otolaryngology of molecular, 10
Geniculate fossa, 1826f, 1828
Geniculate ganglion
anatomy of, 1826f, 1827-1828
surgical, 2404f
surgical, in lateral skull base, 2436f-2437f, 2438
vulnerability to injury of, 1829
Genioglossal advancement (GA), for obstructive sleep apnea, 259, 260f
Genioglossus (GG) muscle
anatomy of, 1296f, 1297
in breathing, 810, 810f
Geniohyoid muscle, anatomy of, 1296f, 1320
Genioplasty, osseous, 465, 467-470
anesthesia for, 467
clinical examples of, 470, 472f-473f
complications after, 470

Genioplasty, osseous *(Continued)*
fixation in, 468-470, 470f
gingivolabial incision for, 467, 468f
inscription of bony midline in, 467-468, 469f
lateral extent of, 468, 469f
measurement of osteotomy site in, 467-468, 469f
subperiosteal dissection in, 467, 468f
three-dimensional movement of chin in, 468
vertical lengthening in, 468-470, 469f
vertical shortening in, 468-470, 470f
wound closure in, 470
Genome, 3-4
Gentamicin
intratympanic, 2185-2189
clinical protocols for, 2187-2188
complications of, 2188-2189
concentration of, 2188
dose of, 2188
indications and contraindications for, 2189
injection interval for, 2188
mechanism of action of, 2185-2186
for Meniere's disease, 2185-2189, 2338-2339, 2338f
number of injections of, 2188
pharmacokinetics of, 2186-2187, 2186f-2187f
practical considerations with, 2188
for rhinosinusitis, 734
vestibulotoxicity of, 2344
Gentamicin ophthalmic (Garamycin Ophthalmic), for otitis externa, 1952, 1959t-1960t
Gentian violet, for fungal otitis externa, 1955, 1959t-1960t
Geometric broken line closure (GBLC), for scar revision, 298, 299f-300f
GER (gastroesophageal reflux)
defined, 2944-2945
physiologic or "functional," 2944
GERD. *See* Gastroesophageal reflux disease (GERD).
Geriatric patients, 230-238
access to medical care by, 231
aging skin in (*See* Aging skin)
basic principles of care for, 230-231
cochlear implants in, 233, 2241
and quality of life, 2251-2252, 2252f, 2252t
demographics of, 230
diagnostic testing for, 231
ear disorders in, 231-234
presbycusis as, 232
etiologies of, 232
treatment of, 233
types of, 232
presbystasis as, 233-234
diagnostic methods for, 233
treatment of, 234
vestibular pathology of, 233
end-of-life care for, 231
facial trauma in, 237
falls in, 233
head and neck oncology in, 237
etiology of, 237
treatment of, 237-238
hearing aids in, 2274
nose in, 234
changes in appearance of, 234
common symptoms of disorders of, 234
intranasal examination of, 234
mucoepithelial changes of, 234
olfactory changes of, 234
treatment of disorders of, 234
olfactory loss in, 635, 635f
olfactory testing in, 632-633
otitis media in, 1872
postoperative pain in, 240-241
preoperative evaluation of, 106-107
Geriatric patients *(Continued)*
presbyphagia in, 237
diagnostic testing for, 237
treatment of, 237
presbyphonia in, 234-237
acoustic changes in, 236
dental/mandibular changes in, 236
factors affecting vocal quality in, 234, 235t
glandular changes in, 236
histologic changes in, 234-235, 235f
laryngoscopic appearance in, 235-236
mucosal changes in, 236
respiratory changes in, 236
and sense of taste, 236
treatment of, 236-237
rhinosinusitis in, 737
salivary gland dysfunction in, 1141-1142, 1141f
treatment of, 231
medical, 231
surgical, 231
Germ cell gene therapy, 14, 15f
Gfi1 (growth factor–independent 1) gene, in murine deafness, 2058t-2060t
GG (genioglossus) muscle
anatomy of, 1296f, 1297
in breathing, 810, 810f
Ghost cell(s), in calcifying odontogenic cyst, 1269, 1269f
Ghost cell tumor, epithelial odontogenic (dentinogenic), 1275-1276
Giant cell tumor (GCT)
of larynx, 1510
malignant, of neck, 1671
of petrous apex, 2526
Gianturco-Z stents, 1009
Gingiva, anatomy of, 1295f
Gingival cyst
of adult, 1266
clinical features of, 1266
radiographic features of, 1266
of newborn, 1266, 1266f
microscopic features of, 1266
treatment of, 1266
Gingival melanoma, 1242f
Gingivitis
in HIV, 227
pregnancy, 1256
Gingivolabial sulcus approach, for pediatric facial fracture, 2701-2702, 2703f
Gingivostomatitis, herpetic, 1235, 1235f
GJB1 (gap junction membrane channel protein β1) gene, in deafness, 2051t-2058t
GJB2 (gap junction membrane channel protein β2) gene
in deafness, 2051t-2058t, 2083, 2089-2090, 2097
genetic testing for, 2097-2098, 2235
of infants, 2723
GJB3 (gap junction membrane channel protein β3) gene, in deafness, 2051t-2058t, 2083
GJB6 (gap junction membrane channel protein β6) gene
in deafness, 2051t-2058t, 2083
genetic testing for, 2235
Glabella, 319, 320f, 509f
Glabellar flaps, for nasal defects, 365-366
Glandular odontogenic cyst, 1267
clinical features of, 1267
microscopic features of, 1267, 1267f
radiographic features of, 1267
treatment of, 1267
Glasgow Benefit Inventory (GBI), after stereotactic irradiation of vestibular schwannoma, 2564
Glasgow Children's Benefit Inventory, 57
GLAST (glutamate-aspartate transporter), 2081
Glenoid fossa
anatomy of, 1822f, 1824f
in surgical anatomy of lateral skull base, 2435f
Glial cell–derived neurotrophic factor (GDNF)
for facial nerve paralysis, 2427
in gene therapy of inner ear, 2192
for prevention of ototoxicity, 2189-2191
Glioma(s)
brainstem
intra-axial, 2528
vestibular symptoms of, 2353
of cerebellum, vestibular symptoms of, 2354
nasal, 2688
vs. encephaloceles, 2688
epidemiology of, 2688
extranasal, 2688
histology of, 2688
imaging of, 2688
intranasal, 2688
management of, 2688
sinonasal, 718t
Glissades, 2308, 2313
Globe, anatomy and physiology of, 319, 321f
Globus, 956
Glogau classification, of photoaging skin, 391, 391t
Glomerulonephritis, poststreptococcal, 2788
Glomus jugulare, 1657
Glomus jugulare tumors, 1934-1935, 1935f
of cerebellopontine angle, 2523f-2524f
endovascular treatment of, 1935-1936, 1936f
paragangliomas as, 2505, 2506f
surgical approach to, 2506, 2507f
stereotactic radiation therapy for, 2565, 2565t
Glomus tumor(s), 1657. *See also* Paragangliomas (PGLs).
of cerebellopontine angle, 2522-2523, 2523f-2524f
of skull base, 171, 174f
Glomus tympanicum, 1657
imaging of, 1919-1920, 1921f
Glomus tympanicum tumors, 1934-1935
endovascular treatment of, 1935
paraganglioma as, 2505-2506
Glomus vagale, 151, 152f
Glomus vagale tumors, 1934-1935, 1935f
endovascular treatment of, 1935f-1936f, 1936-1937
paragangliomas as, 2506f
Glossectomy
laser midline, for obstructive sleep apnea, 259
total or subtotal, tongue base reconstruction after, 1389-1390
innervated free latissimus dorsi musculocutaneous flap for, 1389-1390, 1390f
microvascular reconstruction as, 1390
money pouch–like method for, 1390, 1390f
sensate fasciocutaneous flaps for, 1390-1391
Glossopharyngeal nerve
intraoperative monitoring of, 2550-2552, 2551f
in surgical anatomy
of internal auditory canal, 2437f
of jugular foramen, 2440, 2440f
of lateral skull base, 2436f, 2438
of posterior fossa, 2439f
Glossopharyngeal nerve block, for neuropathic pain, 246t
Glossopharyngeal schwannoma, 2507f
Glossoptosis, in Robin sequence, 2673
Glossotomy, median labiomandibular, for hypopharyngeal cancer, 1429
Glottal closure, laryngeal videostroboscopy of, 819, 820f, 848t, 849
Glottal flow, 818
Glottic cancer
advanced-stage, radiation therapy for, 1497, 1583-1588
balancing cure, organ preservation, and quality of life with, 1583-1584
with chemotherapy, 1584-1586, 1584t

Glottic cancer *(Continued)*
complications of, 1587-1588
dose-fractionation schemes for, 1586, 1586t
general principles of, 1585-1586
mini-mantle field technique for, 1586
outcomes and prognostic factors for, 1586-1587, 1587t
patient setup for, 1586
postoperative (adjuvant), 1584-1585, 1584t
shrinking-field technique for, 1586, 1587f
with targeted biologic agents, 1585
anatomic basis for, 1483-1484, 1483f, 1483t, 1543-1544
cervical metastases of, 1494
chemoradiation for
in advanced stage, 1584-1586, 1584t
with nodal metastases, 1498
optimal dose-fractionation scheme for, 1585-1586
outcomes and prognostic factors with, 1586-1587, 1587t
clinical evaluation of, 1545
clinical presentation of, 1493, 1579
conservation laryngeal surgery for, 1496, 1547-1549
epiglottic laryngoplasty as, 1549
complications of, 1549
extended procedures for, 1549
functional outcome of, 1549
key surgical points for, 1549
oncologic results of, 1549
surgical technique for, 1549, 1549f
horizontal partial laryngectomies as, 1549
spectrum of, 1557-1560
supracricoid partial laryngectomy with cricohyoido-epiglottopexy as, 1549-1550
complications of, 1551
extended procedures for, 1551
functional outcome of, 1551, 1551t-1552t
key surgical points for, 1550-1551
oncologic results of, 1549-1550
surgical technique for, 1550, 1550f-1551f
vertical hemilaryngectomy as, 1547-1549
complications of, 1549
extended, 1548
frontolateral, 1548
functional outcome of, 1548
with imbrication laryngoplasty, 1548, 1548f
key surgical points for, 1549
oncologic results of, 1547-1548, 1547t-1548t
posterolateral, 1548
surgical technique for, 1548
vertical partial laryngectomy as, 1547
early-stage, 1512-1524
biopsy of, 1518
chest x-ray of, 1516
defined, 1515
diagnosis of, 1515-1517, 1516f
endoscopic imaging of, 1515-1516, 1516f
MRI and CT of, 1516-1517
PET of, 1517
radiation therapy for, 1519-1520, 1581
complications of, 1583
local control with, 1519, 1522f
outcome and prognostic factors for, 1581-1583, 1582t-1583t
recurrence after, 1520, 1522t
results of, 1519, 1521t
techniques and dose-fractionation schemes for, 1580-1590, 1581f-1582f
epidemiology of, 1512, 1513f
imaging of, 1474-1475, 1474f, 1691f
with impaired vocal cord mobility, 1496
neck dissection for, 1497-1498
radiation therapy for

Glottic cancer *(Continued)*
with advanced-stage disease, 1497, 1583-1588
balancing cure, organ preservation, and quality of life with, 1583-1584
with chemotherapy, 1584-1586, 1584t
complications of, 1587-1588
dose-fractionation schemes for, 1586, 1586t
general principles of, 1585-1586
mini-mantle field technique for, 1586
outcomes and prognostic factors for, 1586-1587, 1587t
patient setup for, 1586
postoperative (adjuvant), 1584-1585, 1584t
shrinking-field technique for, 1586, 1587f
with targeted biologic agents, 1585
with early-stage disease, 1519-1520, 1581
complications of, 1583
effectiveness of, 1496
local control with, 1519, 1522f
outcome and prognostic factors for, 1581-1583, 1582t-1583t
recurrence after, 1520, 1522t
results of, 1519, 1521t
techniques and dose-fractionation schemes for, 1580-1590, 1581f-1582f
recurrence of, 1521t-1522t, 1522-1523
staging of, 1513-1515
direct laryngoscopy for, 1579-1580, 1580f
stage grouping in, 1515, 1515t
T staging in, 1486, 1488t, 1515t
survival with, 1512, 1514f, 1523
treatment of, 1496-1498, 1517-1520
in advanced stage, 1497
algorithm for, 1588f
with anterior commissure involvement, 1496-1497
for carcinoma in situ, 1520-1521
chemotherapy for, 1520
choice of, 1521-1524
in early stage, 1496
endoscopic excision as, 1518, 1520f
for invasive carcinoma, 1521-1524, 1523t
with nodal metastases, 1497-1498
surgical, 1517-1518, 1517t, 1518f, 1519t
transoral laser microsurgery for, 1531
voice considerations in, 1518-1519
Glottic closure, for chronic aspiration, 929-931, 931f
Glottic lacerations, 1634
Glottic stenosis. *See also* Laryngeal stenosis.
anterior, 948
in children, 2915, 2922
management of, 2922
complete, 949-950
posterior, 948-949, 949f
in children, 2915, 2915f, 2922-2923
management of, 2922-2923
vocal quality with, 2880, 2915
Glottic sulcus, 870-872, 871f
diagnosis of, 870-871
history in, 870
laryngeal examination in, 870-871
vocal capability battery in, 870
epidemiology of, 870
management of, 871-872
behavioral, 871
medical, 871
surgical, 871-872, 872f
mucosal bridge due to, 870, 871f
pathophysiology and pathology of, 869-870
with polypoid nodule, 871f
Glottis, 99, 99f
anatomy of, 1483-1484, 1483f, 1483t, 1578
cartilaginous, 849
embryology of, 1482-1483
physical examination of, 100
during swallowing, 833

Glottis respiratoria, 1464
Glottis vocalis, 1464
Glottography, for voice evaluation, 830, 835
GLPR (gastrolaryngopharyngeal reflux), and laryngeal stenosis, 2917
Glucocorticoids
for allergic rhinitis, 621
for croup, 2805-2806
for otitis media with effusion, 2772
for rhinosinusitis
oral, 734t
topical, 734t, 736
for thyroid storm, 1745
for Wegener's granulomatosis, 658
Glucose, in CSF rhinorrhea, 789, 2044
Glutamate-aspartate transporter (GLAST), 2081
Glutathione *S*-transferase (GST)
in head and neck squamous cell carcinoma, 1016-1017
in oral cancer, 1295
Gluten-sensitive enteropathy, oral manifestations of, 1254
Glycolic acid, for chemical peels, 393
Glycoproteins, in saliva, 1140
Glycopyrrolate, for pediatric premedication, 2589
GM-CSF (granulocyte-macrophage colony-stimulating factor), 604, 609t-610t
Goiter(s)
compression of pharynx and esophagus due to, 1409, 1409f
endemic, 1747
intrathoracic, 1766
tobacco smoke and, 1807
toxic
multinodular, 1744-1745
uninodular, 1744
Gold dust, for ear hygiene or chronic ear drainage, 1958
Gold weights, for lagophthalmos, 2421
Gomphosis joint, 1260
Gonococcal pharyngitis, 193-194
in children, 2786
Gonorrhea, oral manifestations of, 1252
Gonzalez-Ulloa and Stevens analysis, for mentoplasty, 464f
Gore-Tex (fibrillated ePTFE), for chin implants, 465t
Gore-Tex (polytetrafluoroethylene) implant, for saddle nose deformity, 555, 558f
Gore-Tex (polytetrafluoroethylene) strip, for medialization thyroplasty, 908, 910, 911f
Gorlin cyst, 1268-1269
microscopic features of, 1269, 1269f
radiographic features of, 1269
treatment of, 1269
Gorlin syndrome, 1268
treatment of, 1268
Gorlin-Goltz syndrome, 1268
treatment of, 1268
Gout, 2113-2114
otologic manifestations of, 2113-2114
GPR98, in deafness, 2051t-2058t
Grab sample, 68, 69t
Grade(s)
of recommendation, 69-70, 70t
in voice evaluation, 827t
Gradenigo's syndrome, 1829, 1975, 1987
Gradient echo techniques, for MRI, 136-137, 137f
Graft(s)
for airway stenosis
epidermal, 947
epithelial, 947
skin, 946-947
alar batten, 550, 551f
in revision rhinoplasty, 586-587, 587f

Graft(s) *(Continued)*
allo-
for craniofacial defect repair, 2657
for ossiculoplasty, 2006
auto-
for craniofacial defect repair, 2657
for ossiculoplasty, 2006, 2025
autogenous cartilage
for laryngeal stenosis, 2919-2920, 2920f
for nasal reconstruction, 368-369, 369f-370f
in noncaucasian rhinoplasty, 569, 570f
complications of, 578, 579f
bone
in cleft-lip nose repair, 559, 564f
for nasal fractures, 505, 505f
for nasal reconstruction, 369, 370f
buttress
in nasal tip refinement, 576
in revision rhinoplasty, 589
cap
for nasal tip enhancement, 576, 577f
in revision rhinoplasty, 589
cartilage
for nasal reconstruction, 368-369, 369f-370f
for nasal tip projection, 535-536, 537f, 549-550, 550f-551f
for revision rhinoplasty, 583, 584f
for saddle nose deformity, 555, 556f
cartilage plumping, for nasal tip projection, 535-536, 536f
caudal extension
in noncaucasian rhinoplasty, 576, 576f
in revision rhinoplasty, 593
costal cartilage
for laryngeal stenosis, 2919-2920, 2920f
for noncaucasian rhinoplasty, 569, 570f
harvesting of, 570, 571f
results of, 568
for revision rhinoplasty, 583, 584f
for CSF rhinorrhea, 792-794, 793f
in endoscopic treatment of stridulous child, 2909
facial nerve, 2421-2425
cross-face, 2419, 2424-2425
selection of donor nerve for, 2422
surgical planning for, 2421-2424
surgical technique for, 2422-2424, 2424f-2425f
in follicular-unit hair transplantation, 383, 383f
micro-, 378, 379f-381f
free cartilage
for full-thickness alar defects, 348
for nasal defects, 348
full-thickness skin, for nasal reconstruction, 365
homo-
for craniofacial defect repair, 2657
for nasal reconstruction, 368
for ossiculoplasty, 2006, 2025, 2026t
jejunal interposition, after laryngopharyngectomy, 1418, 1418f
for laryngeal stenosis
in children, 2919
skin and mucosal, 946-947
in noncaucasian rhinoplasty
autogenous cartilage, 569, 570f
complications of, 578, 579f
caudal extension, 576, 576f
conchal cartilage, 569, 570f
harvesting of, 570, 571f
results of, 568
septal cartilage, 569
in revision rhinoplasty
alar batten, 586-587, 587f
alar rim, 587, 588f-589f
buttress, 589
cap, 589
ear cartilage, 583
lateral crural, 589-590, 590f
Graft(s) *(Continued)*
septal cartilage, 583
shield, 589, 590f
septal cartilage
in noncaucasian rhinoplasty, 569
for revision rhinoplasty, 583
shield
for nasal tip enhancement, 576, 577f
in revision rhinoplasty, 589, 590f
skin
for airway stenosis, 946-947
for burns, 315
gene therapy with, 23
for nasal reconstruction, 365
for oropharyngeal reconstruction, 1376
of tongue base, 1388
of tonsil and pharyngeal wall, 1384
for pharyngeal wall reconstruction, 1384
in prosthetic maxillary obturation, 1338-1339
for tongue base reconstruction, 1388
for tonsillar reconstruction, 1384
skin and mucosal
for airway stenosis, 946-947
for laryngotracheal stenosis, 946-947
split-thickness skin, in atresiaplasty
creation of, 2756, 2756f
placement of, 2756, 2757f-2758f
suturing of, 2756-2757, 2758f
spreader
for middle vault deformities, 585-586
for saddle nose deformity, 555, 559f
for septal and alar asymmetries, 550, 551f
in septoplasty, 490-491, 491f
for twisted nose, 554, 555f
synthetic hair, 387-388
temporalis fascia
in atresiaplasty, 2755f, 2756, 2757f
for medialization thyroplasty, 910
for saddle nose deformity, 555, 557f
for tympanoplasty, 2000
thyroid alar cartilage, for laryngeal stenosis, 2919, 2921f
in tympanoplasty
lateral, 2002-2003, 2002f
medial, 2003, 2004f
xeno-, for craniofacial defect repair, 2657
Grafting materials, for nasal skeletal reconstruction
alloplastic, 368
autogenous cartilage as, 368-369, 369f-370f
bone as, 369, 370f
homograft tissues as, 368
selection of, 367-368
Graft-versus-host disease (GVHD), chronic, and xerostomia, 218
Grainyhead-like 2 *(GRHL2)* gene, in deafness, 2051t-2058t
Granular cell(s), of olfactory bulb, 628f
Granular cell tumor
of larynx, 882
of oral cavity, 1290, 1290f
of trachea, 1612
Granular myringitis, 1955
otorrhea due to, 2196
Granular otitis externa, 1945
Granulation tissue, formation of, 1077-1078
angiogenesis in, 1077-1078
dermal matrix in, 1077
Granulocyte colony-stimulating factor (G-CSF), 604, 609t-610t
Granulocyte-macrophage colony-stimulating factor (GM-CSF), 604, 609t-610t
Granulocytic sarcoma, 2107
Granuloma(s)
cholesterol
vs. cholesteatoma, 2508, 2510f
of petrous apex, 2524-2525
Granuloma(s) *(Continued)*
differential diagnosis of, 1924t, 2515, 2524t
imaging of, 1923, 1925f-1926f, 2477f, 2526f
of skull base, 171, 172f
transmastoid infralabyrinthine drainage of, 2540f
contact, of vocal folds, 874-875, 874f
diagnosis of, 875
epidemiology of, 874
due to extraesophageal reflux, 902, 902f-903f
management of, 875
pathophysiology and pathology of, 874
eosinophilic, 2100
of oral cavity, 1240, 1257
clinical features of, 1240, 1240f
defined, 1240
differential diagnosis of, 1240
etiology of, 1240
histopathologic features of, 1240, 1240f
traumatic, 1240
treatment of, 1240
otologic manifestations of, 2101f-2102f
otorrhea as, 2196
postintubation, 939, 941f
of vocal folds, 875-876, 875f
diagnosis of, 875-876
epidemiology of, 875
management of, 876
pathophysiology and pathology of, 875
postoperative reparative, after small fenestra stapedotomy, 2034
pyogenic, 290
of oral cavity, 1256, 1289, 1289f
of pregnancy, 1256
on septum, 685f
vocal fold, 2881, 2881f
Granulomatosis, Wegener's. *See* Wegener's granulomatosis (WG).
Granulomatous disease
nasal manifestations of, 657-659
in Churg-Strauss syndrome, 659
in sarcoidosis, 658-659
in Wegener's granulomatosis, 658
neck masses due to, 1638
oral manifestations of, 1251-1252
otologic manifestations of, 2100-2106
in Langerhans' cell histiocytosis, 2100-2101, 2101f-2102f
otorrhea as, 2196
in sarcoidosis, 2104-2105, 2104f
in tuberculosis, 2101-2103, 2102f-2103f
in Wegener's granulomatosis, 2103-2104, 2103f-2104f
of salivary gland, in children, mycobacterial, 2857-2858, 2857f
of salivary glands, 1158-1159
due to actinomycosis, 1159
in children, 2858
due to cat scratch disease, 1159
in children, 2857-2858
due to actinomycosis, 2858
due to sarcoidosis, 2858
mycobacterial
in children, 2857-2858, 2857f
nontuberculous, 1158-1159, 1158f
tuberculous, 1158
due to toxoplasmosis, 1159-1160
Granulomatous esophagitis, 1405
Granulomatous rhinitis, 619b
Granulomatous rhinosinusitis, 675
Graves' disease, 1742-1743
clinical manifestations of, 1742
epidemiology of, 1742
historical background of, 1806
natural history of, 1742
oral manifestations of, 1251
pathology of, 1742

Graves' disease *(Continued)*
pathophysiology of, 1806
and thyroid cancer, 1742
thyroid-stimulating antibody in, 1741
treatment of
pharmacologic
β-blockers for, 1743
cholestyramine for, 1742-1743
inorganic iodine for, 1742-1743
lithium carbonate for, 1742-1743
methimazole for, 1742
propylthiouracil for, 1742
radioactive iodine for, 1743
surgical
indications for, 1743
near-total thyroidectomy for, 1743
postoperative problems after, 1743
preoperative preparation for, 1743
subtotal thyroidectomy for, 1743
Graves' ophthalmopathy, 1806-1818
ancillary procedure(s) for, 1816-1817
extraocular muscle surgery as, 1816-1817
eyelid surgery as, 1817
classification of, 1808, 1808t-1809t
clinical evaluation of, 1809-1810
eye evaluation in, 1809
imaging studies in, 1809-1810, 1811f
thyroid function in, 1809
clinical features of, 1808-1817
differential diagnosis of, 1809-1810, 1810t
epidemiology and etiology of, 1807
eye findings in, 1808-1809, 1809t
genetic predisposition to, 1807
medical therapy for, 1810-1811
local therapy in, 1810
steroid therapy in, 1811
thyroid therapy in, 1810
natural history of, 1807
orbital decompression for, 1811-1816
approaches to, 1811, 1812f
balanced, 1814
without bone removal, 1816
combined endoscopic and open approach to, 1814
combined endoscopic orbital and optic nerve, 1815
endoscopic, 1814, 1815f-1816f
goal of, 1811
indications for, 1811
results of, 1811-1812
three-wall, 1815-1816
transantral, 1812-1814
complications of, 1814
modifications of, 1814
outcome of, 1812-1814, 1813f-1814f
technique for, 1812, 1812f-1813f
two-wall, 1816
pathophysiology of, 1806-1807
pretibial myxedema and, 1808
radiotherapy for, 1811
risk factor(s) for
gender as, 1807
thyroid status as, 1807
tobacco as, 1807
team approach to management of, 1810-1817
thyroid disease and, 1807
Gray (Gy), 132-133, 1033
GRBAS scale, for voice assessment, 826, 827t
Great auricular nerve (GAN)
anatomy of, 2578, 2580f
for facial nerve grafting, 2422
in parotidectomy, 1177, 1195
Great auricular nerve (GAN) injury, due to neck surgery, 1731
Greater palatal nerve, 483f
Greater palatine artery, 682, 1295-1296
Greater palatine foramen, 1297f
Greater palatine nerve, 1297f
Greater superficial petrosal nerve (GSPN)
groove for, 1822f
surgical anatomy of, 2404f
in lateral skull base, 2437f, 2438
in middle cranial base, 2444
vulnerability to injury of, 1829
Greater wing of sphenoid bone
in surgical anatomy of lateral skull base, 2434, 2435f
in surgical anatomy of middle cranial base, 2444, 2445f
Greater zygomatic muscle, reinnervation of, 2423f
GRHL2 (grainyhead-like 2) gene, in deafness, 2051t-2058t
Grieg's cephalopolysyndactyly, craniofacial anomalies in, 2641t
Grisel's syndrome, due to adenotonsillectomy, 2801
GRO-α (growth-related oncogene-α), in wound healing, 1076
Groningen prosthesis, 1598f
Gross tumor volume (GTV), for radiotherapy, 1036, 1044
Group A beta hemolytic *Streptococcus pyogenes* (GABHS), pharyngitis due to, 191-193
in children, 2787
complications of, 2788
Group C streptococci, pharyngitis due to, 193
Group G streptococci, pharyngitis due to, 193
Growth and development, craniofacial. *See* Craniofacial growth and development.
Growth factor–independent 1 *(Gfi1)* gene, in murine deafness, 2058t-2060t
Growth impairment, obstructive sleep apnea and, 2603
Growth problems, sleep-disordered breathing and, 2792
Growth sites, in craniofacial growth and development, 2614
Growth-related oncogene-α (GRO-α), in wound healing, 1076
GSPN. *See* Greater superficial petrosal nerve (GSPN).
GST (glutathione *S*-transferase)
in head and neck squamous cell carcinoma, 1016-1017
in oral cancer, 1295
GTV (gross tumor volume), for radiotherapy, 1036, 1044
Guaifenesin
for rhinosinusitis, 735t, 736
for vocal professionals, 855
Guardian stitch, after tracheal resection, 1618, 1620f
Guidelines Development Task Force (GDTF), 89
Guillain-Barré syndrome, facial paralysis in, 2397
Gull-wing incision
for external ethmoidectomy, 757, 757f
for rhinoplasty, 545-546, 546f
"Gum boil," 179
Gumma, of ear canal or middle ear, 2105
Gunshot injuries, of neck
due to handgun, 1625
due to rifle, 1626, 1626f-1627f
due to shotguns, 1626-1627, 1628t
Gustatory cortex
primary, 1212, 1212f
secondary, 1212, 1212f
Gustatory neurons, 1208
Gustatory otorrhea, 2197
Gustatory pathways, central, 1212-1213, 1212f
Gustatory physiology, 1208
central gustatory pathways and function in, 1212-1213, 1212f
gustatory transduction in, 1208-1210, 1210f
interaction with saliva in, 1141, 1213-1214
peripheral sensitivity in, 1210-1212
Gustatory receptors
individual differences in, 1211-1212
regional differences in, 1210-1211
Gustatory rhinitis, 698
Gustatory sensitivity, 1207-1208
Gustatory structures, 1208
Gustatory sweating, after parotidectomy, 1177
Gustatory thalamus, 1212
Gustatory transduction, 1208-1210, 1210f
Gustducin, 1209-1210
GVHD (graft-versus-host disease), chronic, and xerostomia, 218
Gy (gray), 132-133, 1033

H

"H" angle, in chin analysis, 463, 464f
H_1 blockers (histamine$_1$ receptor antagonists), for allergic rhinitis, 620
H_2 blockers (histamine$_2$ receptor antagonists)
for extraesophageal reflux, 901
for GERD, 970
HAART (highly active antiretroviral therapy), 211
Habenula perforata, anatomy of, 1832f, 1834
Haberman feeder, 2665, 2665f
Habituation
and olfactory testing, 633
in vestibular compensation, 2375
Habituation exercises, in vestibular rehabilitation, 2372-2373, 2378
HAD (HIV-associated dementia), 223
Haemophilus influenzae
with CSF fistula, 2045
otitis media due to, 2763
rhinosinusitis due to
acute, 704, 704f, 732
chronic, 706
acute exacerbation of, 707
Haemophilus influenzae type B (HIB), supraglottitis due to, 2807
Haemophilus influenzae type B (HIB) vaccine
to prevent hearing loss, 2161
to prevent otitis media, 2769
Hair bundle(s), 2070-2071, 2072f
directional sensitivity of, 2072f
Hair bundle deflections
and adaptation of mechanoelectrical transduction currents, 2078, 2079f
in cochlear transduction, 2069f, 2071
Hair cell(s)
auditory
anatomy of, 1832-1834, 1833f
in organ of Corti, 1832, 1832f
arrangement of, 2071, 2072f
in cochlear transduction, 2061f-2062f, 2063-2064, 2064f
defects in afferent dendrite synapses with, 2080-2081, 2080f
innervation of, 1834, 1834f
length of, 2070, 2070f
number and density of, 2070
physiology of
inner, 1841f, 1842, 1844f
outer, 1841f, 1844, 1844f
stereocilia of, 1841f, 1842, 1843f
tip links of, 1841f, 1842, 1843f
tonotopic tuning of, 1844, 1844f
receptor potentials for, 2071, 2072f
scanning electron micrograph of, 1833f
vestibular
anatomy of, 1857, 1858f
arrangement of stereocilia and kinocilium in, 1854-1855, 1856f
embryogenesis of, 1852
morphologic polarization of, 1855, 1856f, 2277-2278, 2279f
on otoconial membrane, 1858f

Hair cell(s) *(Continued)*
sensory transduction by, 2277-2278, 2279f
synaptic morphology and function of, 1857-1859, 1859f-1860f
Hair cell channel deficiencies, effects on hearing of, 2079-2080
Hair cell regeneration and repair, and noise-induced hearing loss, 2144
Hair cell transduction, 2070-2081, 2070f
adaptation of mechanoelectrical transduction currents in, 2078-2079, 2079f
and auditory neuropathy, 2081
and defects in cytoskeletal proteins leading to deafness, 2074-2076, 2076f
defects in hair cell–afferent dendrite synapses and, 2080-2081, 2080f
defects of other hair cell channels and, 2079-2080
hair bundle deflections and receptor potentials in, 2069f, 2071, 2072f
myosin VI in, 2078
stereocilia in, 2070-2071
anatomy of, 2070-2071, 2070f, 2072f
composition of, 2074, 2075f-2076f
cross-linkages between, 2076f, 2077-2078
dynamic regulation of length of, 2076-2077
transduction channels in, 2071-2073
effects of deficiencies of, 2079-2080
gating of, 2073-2074
ion selectivity of, 2073, 2073f
structure of, 2076f
Hair cycle, 374, 374f
Hair follicle(s)
anatomy of, 373-374, 374f
miniaturization of, 375, 375f
regeneration of, 388
Hair grafts. *See* Hair also transplantation.
synthetic, 387-388
Hair loss, 373-389
alternatives and future treatment options for, 387-388
classification of, 376, 377f
counseling on, 376, 378f
epidemiology of, 374
etiology of
alopecia areata as, 376
androgenetic alopecia (male pattern baldness) as, 374-376, 375f
infectious, 376
scarring as, 375-376
telogen effluvium as, 376
evaluation of, 376
in females, 376, 377f
medical management of, 376-378
finasteride for, 377-378
minoxidil for, 376-377
nonsurgical hair restoration for, 387
pathophysiology of, 373-376, 374f
anatomy of hair follicle in, 373-374, 374f
androgenic factors in, 375, 375f
miniaturization of hair follicle in, 375, 375f
phases of hair cycle in, 374, 374f
due to rhytidectomy, 426, 427f
surgical management of
eyebrow, eyelash, and mustache transplantation for, 384, 384f
flap procedures for, 385-387, 387f
complications of, 386-387
follicular-unit hair transplantation for, 378, 378f-381f
completion of procedure for, 383-384
complications of, 384
dissection of donor strip in, 382, 382f
doll's hair appearance with, 378, 378f
follicular unit extraction for, 384
graft placement in, 383, 383f
location of hairline in, 378-379, 381f, 383, 383f
Hair loss *(Continued)*
marking off donor strip of scalp for, 381-382, 382f
marking out recipient regions for, 379-381, 382f
micrografts in, 378, 379f-381f
operative procedure for, 382-384
postoperative care after, 384
preoperative evaluation for, 378-382, 381f
slivers of follicular units in, 382, 383f
surrounding natural hair growth in, 382-383
with reconstructive procedures, 387, 388f
scalp reductions for, 384-385, 385f
complications of, 385, 386f
Hair shaft, 373-374
Hair systems, nonsurgical, 387
Hair transplantation
eyebrow, eyelash, and mustache, 384, 384f
follicular-unit, 378, 378f-381f
completion of procedure for, 383-384
complications of, 384
dissection of donor strip in, 382, 382f
doll's hair appearance with, 378, 378f
follicular unit extraction for, 384
graft placement in, 383, 383f
location of hairline in, 378-379, 381f, 383, 383f
marking off donor strip of scalp for, 381-382, 382f
marking out recipient regions for, 379-381, 382f
micrografts in, 378, 379f-381f
operative procedure for, 382-384
postoperative care after, 384
preoperative evaluation for, 378-382, 381f
slivers of follicular units in, 382, 383f
surrounding natural hair growth in, 382-383
Hair weaves, 387
Hairline lowering, 385, 385f
Hairpieces, 387
Hairstyling, for scar camouflage, 301
Hairy leukoplakia, oral, in HIV, 225-226, 226f
Half-gain rule, for hearing aids, 2271
Haller cells, 668-669, 670f
surgical anatomy of, 740
Hallucinations, olfactory, 636
Halo effect, *vs.* efficacy of treatment, 62t
Halo nevus, 287, 287f
Halo sign, in CSF rhinorrhea, 789
Halothane
for anesthesia, 111
in children, 2590
for premedication in children, 2589
Hamartoma
sinonasal, 718t
tracheal, 1617f
Handgun, neck trauma due to, 1625
Hand-Schüller-Christian disease
oral manifestations of, 1257
otologic manifestations of, 2100-2101
otorrhea as, 2196
Haploinsufficiency, 6
Haptic mentoring, 49, 49f
Haptics. *See* Simulation.
Hard palate
anatomy of, 1295f, 1297f, 1298, 1359f
cancer of, 1309-1310
cervical metastases of, 1310
clinical appearance of, 1310f
epidemiology of, 1309-1310
Kaposi's sarcoma as, 1309-1310
melanoma as, 1242f, 1309-1310
reconstruction for, 1310, 1311f
resection of, 1310, 1310f-1311f
squamous cell carcinoma as, 1310, 1310f
survival with, 1310
Hard palate *(Continued)*
minor salivary gland tumors of, 1310
necrotizing sialometaplasia of, 1309-1310
physical examination of, 99
primary and secondary portions of, 1297f
vasculature of, 1295-1296
Harmonic frequencies, 847, 2876
Harmonic Scalpel, for adenotonsillectomy, 2796-2797
Harmonics, in acoustic analysis for voice evaluation, 830, 834-835
Harmonin
in deafness, 2077-2078
in stereocilia, 2076f
Harmony ear-level speech processor, 2232f
Hartley, Gordon, 2728-2729
Harvard staging system, 53
Hashimoto's thyroiditis, 1747
oral manifestations of, 1251
ultrasound of, 1644
Hasner's valve, 798f
Hawthorne effect, *vs.* efficacy of treatment, 62t
HBO therapy. *See* Hyperbaric oxygen (HBO) therapy.
HC-BPPV (horizontal canal benign paroxysmal positional vertigo)
positional testing for, 2315-2316, 2331
repositioning maneuver for, 2332
HCO_3 (bicarbonate)
in saliva, 1139
in salivary gland secretion, 1135
HDIA1, in deafness, 2051t-2058t
HDR (hypoparathyroidism, sensorineural deafness, and renal dysplasia) syndrome, 2051t-2058t
HDR (high-dose-rate) radiotherapy, 1047
Head & Neck Survey (H&NS), 56
Head and neck cancer (HNC)
outcome scales for, 56-57, 56t
pediatric, 2835-2849
vs. adult, 2835
age and, 2837, 2837t
clinical trials for, 2836
epidemiology of, 2835
histiocytoses as, 2847-2848, 2847t
lymphoma as
Hodgkin's, 2838-2840, 2840f
non-Hodgkin's, 2837, 2838t-2839t, 2839f
neuroectodermal, 2844-2845
neuroblastomas as, 2844-2845, 2844t, 2845f
peripheral primitive, 2845
pathologic evaluation of, 2836-2837, 2836f, 2837t
post-transplantation lymphoprolilferative disorder as, 2840
risk factors for, 2835
salivary gland, 2845-2846, 2846f
sarcoma as, 2840-2843
dermatofibrosarcoma protuberans as, 2843, 2843f
epithelioid, 2843, 2843f
Ewing's, 2845
fibro-, 2842-2843, 2843f
nonrhabdomyosarcoma soft tissue, 2842
rhabdomyo-, 2840-2842, 2841t, 2842f
sequelae of management of, 2848
survival with, 2835-2836
teratomas as, 2846-2847
epidemiology of, 2846
histopathology and molecular biology of, 2847, 2847f
management of, 2846
presentation and evaluation of, 2846, 2846t
thyroglossal duct carcinomas as, 2847
tumorigenesis of, 2836
pre-malignant lesions for, 1061
radiotherapy for (*See* Radiation therapy (RT))

Head and neck cancer (HNC) *(Continued)*
squamous cell carcinoma as (*See* Head and neck squamous cell carcinoma (HNSCC))
transnasal esophagoscopy for, 983
ultrasonography in, 1647-1653
Head and Neck Distress Scale (HNDS), 56
Head and Neck Quality of Life (HNQOL), 56
Head and neck squamous cell carcinoma (HNSCC)
biology of, 1015-9
background of, 1015-1016
chemoprevention of, 1018, 1061-1062
clinical implications of, 1018
chemoradiation for, 1052-1058
concomitant, 1052-1056, 1053t-1054t
as adjuvant therapy, 1056
induction chemotherapy with, 1052-1053
in RADPLAT technique, 1054
chemotherapy for, 1015-9
historical background of, 1051-1052
induction, 1056-1058, 1058f, 1058t-1059t
in comcomitant chemoradiation, 1052-1053
for recurrent or metastatic disease, 1058-1061
combination, 1059-1060
prognostic factors with, 1058-1059
single agents in, 1059
environmental exposures and risk factors for, 1016-1018
alcohol as, 1016
cytochrome P-450 as, 1016
glutathione *S*-transferase as, 1016-1017
human papillomavirus as, 1017-1018
other enzymatic systems as, 1017
tobacco as, 1016
epidermal growth factor receptor in, 1022-1023
biology of, 1022, 1025f
as biomarker, 1026
clinical implications of, 1023
oncogene for, 1019
epigenetics of, 1020-1022, 1021f-1022f
expression microarrays and integrative genomics in, 1025
field cancerization in, 1016
genetic alterations in, 1019-1020
cytogenetic, 1019
microsatellites as, 1019
in oncogenes, 1016, 1019-1020
single nucleotide polymorphisms as, 1019
in tumor suppressor genes, 1016, 1020
and Fanconi's anemia, 1020
genetic progression model of, 1016
human papillomavirus in
as biomarker, 1026
as risk factor, 1017-1018
immunotherapy for, 1023-1024
loss of heterozygosity in, 1019-1020, 1026
metastatic progression of, 1060, 1060f
microRNAs in, 1021, 1022f, 1027-1028
mitochondrial mutations in, 1024-1025, 1028f
molecular biomarkers for, 1026-1027
epidermal growth factor receptor as, 1026
human papillomavirus as, 1026
loss of heterozygosity as, 1026
margin analysis for, 1027
in oral rinses and saliva, 1026
other, 1026-1027
polymorphisms in DNA repair enzymes as, 1027
serum analysis for, 1026-1027
novel fields of research on, 1027-1029
bioinformatics as, 1028-1029
cancer stem cell hypothesis as, 1028
microRNAs as, 1027-1028
proteomics as, 1029
targeted therapy for, 1054, 1055f, 1060-1061, 1060f
Head circumference, in Down syndrome, 2632
Head impulse testing, 2314-2315, 2315f
quantitative, 2323
Head injury. *See* Head trauma.
Head movement(s), in vestibular function, 2307-2308
Head movement analysis techniques, active, 2323-2324, 2324f
Head muscles, effects of radiotherapy on, 2626t
Head rotation
encoding of, 2277-2285
by afferents, 2283-2285, 2283f-2284f
cupula in, 2282f
otoconial membrane in, 2283
sensory transduction in, 2277-2279
anatomy of vestibular end organs in, 2277, 2278f
bidirectional sensitivity in, 2278-2279
cupula in, 2277, 2278f
firing rate in, 2278-2279, 2281f
hair cells in, 2277
otolith organs in, 2278, 2281f
stereocilia in, 2277-2278, 2279f
excitatory and inhibitory responses of semicircular canals to
high-acceleration, 2290-2292
anatomic and physiologic basis for, 2290-2291, 2291f
clinical importance of, 2291-2292, 2291f-2293f
in its plane, 2289
anatomic and physiologic basis for, 2282f, 2289
clinical importance of, 2289
graphical representation of, 2293, 2294f
"Head shadow" effect, 1839, 2248
Head thrust test (HTT), 2291-2292, 2292f, 2346
for Meniere's disease, 2337
with superior semicircular canal dehiscence, 2293f
after unilateral labyrinthectomy, 2291f
Head tilt
encoding of, 2277-2285
by afferents, 2283-2285, 2283f-2284f
cupula in, 2282f
with loss of unilateral utricular function, 2299-2300
anatomic and physiologic basis for, 2299-2300
clinical importance of, 2300, 2300f
otoconial membrane in, 2283
sensory transduction in, 2277-2279
anatomy of vestibular end organs in, 2277, 2278f
bidirectional sensitivity in, 2278-2279
cupula in, 2277, 2278f
firing rate in, 2278-2279, 2281f
hair cells in, 2277
otolith organs in, 2278, 2281f
stereocilia in, 2277-2278, 2279f
vs. translation, 2307, 2307f
with unilateral loss of function of, 2299-2300
anatomic and physiologic basis for, 2299-2300
clinical importance of, 2300, 2300f
Head trauma
CSF otorrhea due to, 2197
hearing loss due to, 2199
olfactory loss after, 634-635
sensorineural hearing loss due to, 2121
sudden, 2128
Head velocity, semicircular canal transfer function relative to, 2303, 2303f
Head voice, 846-847, 851
Headache, 246-248
cluster, 247-248
due to CSF rhinorrhea, 789
diagnosis of, 246, 247f
epidemiology of, 246
Headache *(Continued)*
in hemicrania continua, 248
initial evaluation of, 246
medication overuse (rebound), 248
migraine (*See* Migraine)
primary, 246
secondary, 246
sinus surgery for, 742
tension-type, 247
thunderclap, 248
in trigeminal neuralgia, 248
Healing
cochlear implant with compromised, 2241
of maxillofacial fractures, 330-331
by second intention
for nasal defects, 365
for oropharyngeal defects, 1376
of tongue base, 1387-1388
of tonsil and pharyngeal wall, 1383
for oropharyngeal reconstruction, 1376
for surface defects of nasal tip, columella, sidewalls, and dorsum, 365
Health information technology (HIT), 84t-87t
Health Plan Employer Data and Information Set (HEDIS) measures, 82
Health status, as outcome measure, 55
Health Utilities Index (HUI), 56
Health-related quality of life (HRQOL), as outcome measure, 55
Hearing. *See also* Auditory physiology.
and dementias, 233
in vocal professional, 858
Hearing acuity test(s), 1888, 1888f. *See also* Audiologic test battery (ATB).
auditory brainstem response as, 1909-1910
pure-tone air-conduction testing as, 1888
masking for, 1889-1890
pure-tone bone-conduction testing as, 1888, 1888f-1889f
Hearing aids, 2265-2275
age distribution of, 2265-2266, 2266f
in aging patients, 2274
binaural, 2271
bone-anchored (*See* Bone-anchored hearing aid (BAHA))
conventional (traditional)
vs. implantable, 2204f-2205f, 2206t
implantable adjuncts to, 2204f, 2206t, 2217, 2217f
limitation(s) of, 2203-2207, 2204b
acoustic feedback as, 2204
disorder perception of pitch and sound localization, 2207
distortion of spectral shape and phase shifts as, 2204
human factors as, 2205-2207
insufficient gain as, 2203-2204
nonlinear distortion as, 2204
occlusion effects as, 2204
physical factors as, 2203-2205
poor appearance as, 2204
poor transduction efficiency as, 2204-2205
recruitment and compression of dynamic ranges as, 2205-2207
implantable (*See* Implantable hearing aids)
indications for, 2265-2267
communication disorder and motivation as, 2266
hearing loss considerations in, 2265-2266, 2266f
otologic and other factors in, 2266-2267
in infants and children, 2274, 2723-2724
insertion loss with, 2270
monaural, 2271-2272
occlusion effect with, 2270
for otosclerosis, 2034
outcome measurement for, 2274

Hearing aids *(Continued)*
programmable, 2267, 2269
programming of, 2273
rules of thumb for, 2274-2275
selection and fitting of, 2271-2274
ear considerations in, 2271-2272
fitting process in, 2272-2273
fitting range in, 2271, 2272f
orientation, counseling, and follow-up after, 2273-2274
other considerations in, 2265-2267
target gain in, 2271
verification process in, 2273
sound transduction and coupling to auditory system with, 2205f
styles of, 2269-2270
behind-the-ear, 2269-2270, 2270f
completely-in-the-canal, 2270, 2270f
considerations for, 2270
in-the-canal, 2270, 2270f
in-the-ear, 2270, 2270f
receiver-in-the-canal, 2270
technology of, 2267-2271
amplifier in, 2267, 2267f
analog, 2267
automatic control in, 2269
components in, 2267, 2267f
compression circuitry in, 2268
data logging in, 2269
different acoustic responses or programs in, 2269
digital sound processing in, 2267
directional microphones in, 2269
electroacoustic characteristics in, 2267-2268, 2268f
evolution of, 2267
feedback suppression circuitry in, 2269
input transducer in, 2267, 2267f
direct audio input for, 2267
frequency-modulated (FM) receiver as, 2267
microphone as, 2267
telecoil (t-coil) as, 2267
linear amplification in, 2268, 2268f
noise reduction circuitry in, 2269
nonlinear amplification in, 2268, 2268f
open-fit or open-canal, 2270
other features in, 2269
output transducer in, 2267, 2267f
peak clipping in, 2268
programmability in, 2267, 2269
vent in, 2270
wireless connectivity in, 2267
for tinnitus, 2134
Hearing assessment, 97-98, 98t. *See also* Audiologic test battery (ATB); Electrophysiologic hearing assessment.
with temporal bone fracture, 2039
Hearing assistive technologies, 2270-2271
Hearing conservation program, for noise-induced hearing loss, 2150
Hearing Handicap Inventory in the Elderly (HHIE), 57
Hearing impairment. *See also* Hearing loss.
defined, 2151
Hearing in Noise Test (HINT), for cochlear implants, 2223, 2244
Hearing level (HL), 1839
Hearing loss, 2198-2201, 2198b
acquired, 2097-2098
cochlear implant for, 2220-2221
acute, 2198b, 2199
age-related, 2125-2126, 2126f
genetic basis for, 2074
with tinnitus, 2132
animal models of, and effects of cochlear implant electrical stimulation, 1881
audiograms of, 1888, 1888f-1889f
Hearing loss *(Continued)*
categories of, 1888, 1888f
classification of, 2086-2087, 2087t
conductive, 2017-2027
audiogram of, 1888, 1888f
in children, 2026-2027
diagnostic evaluation of, 2019-2021
acoustic immittance testing in, 2020
acoustic reflex testing in, 2020
history and physical examination in, 2022b
pure-tone audiometry and speech testing in, 2020, 2020f
Rinne test in, 2020, 2020t
Weber test in, 2020
due to external auditory canal conditions, 2021-2022, 2023f-2024f
implantable devices for, 2027
due to measles, 2158
due to middle ear conditions, 2023-2026
pathologic conditions leading to, 2018b
pediatric, 2200-2201
specific lesions of conductive hearing pathway and, 2019, 2019t
in superior semicircular canal syndrome, 2020-2021, 2021f
due to temporal bone trauma, 2046
treatment of, 2021-2026
for conditions of external auditory canal, 2021-2022, 2023f-2024f
for conditions of middle ear (*See* Ossiculoplasty)
for conditions of tympanic membrane, 2022-2023
due to tympanic membrane conditions, 2022-2023
congenital
cochlear implants for, 2220
epidemiology of, 2086
etiology of, 2200, 2200b
evaluation of, 2097-2099
genetic basis for, 2050, 2051t-2058t
in murine model, 2050, 2058t-2060t
due to labyrinthine infections, 2154-2157
with cytomegalovirus, 2154-2156, 2155f
with rubella, 2154, 2156-2157, 2157f
with syphilis, 2161
due to defects in cytoskeletal proteins, 2074-2076, 2076f
due to defects in hair cell–afferent dendrite synapses, 2080-2081, 2080f
diagnosis of, 2087, 2087t
epidemiology of, 2050, 2087
evaluation of, 2198-2199
fluctuating, 2198b, 2199
functional, 1901
genetic basis for, 2050, 2051t-2058t
cochlear implants with, 2220
in murine models, 2050, 2058t-2060t
in geriatric patients, 232
etiologies of, 232
treatment of, 233
types of, 232
gradual, 2198b, 2199
in HIV-positive patients, 223-225, 2161-2162
approach to, 224, 225t
due to cryptococcal meningitis, 223-224
due to otosyphilis, 224
due to hypothyroidism, 1746
in immunocompromised patients, 2161-2162
in infants, 2718-2725
ancillary testing for, 2722-2723
genetic testing in, 2722-2723
laboratory testing in, 2722
screening for connexin 26 mutation in, 2723
screening for maternally transmitted infection in, 2723
Hearing loss *(Continued)*
temporal bone imaging in, 2723
testing for Pendred's syndrome in, 2723
assessment of, 2719-2721
auditory brainstem responses in, 2719-2720
comparison of otoacoustic emissions and auditory brainstem responses in, 2721
evoked otoacoustic emissions in, 2720-2721
testing protocols for, 2719, 2720f
delay in identification of, 2719
diagnosis of, 2721-2722
audiology in, 2722
history in, 2721
middle ear effusions in, 2722
otomicroscopy in, 2722
physical examination in, 2721-2722
vestibular function assessment in, 2722
visual reinforcement audiometry in, 2722
history of screening for, 2718-2719
intervention strategies for, 2723-2724
amplification devices as, 2723-2724
bone conduction amplification as, 2723
cochlear implantation as, 2724
early, 2724
surgical therapy as, 2723
and neural plasticity, 1885, 1885f
prevalence of, 2719
due to intratympanic gentamicin, 2188-2189
due to jugular foramen syndromes, 2199, 2199t
mixed, 1888, 1889f
neural, 1899-1901, 1900f
noise-induced, 2121-2122, 2140-2152
vs. acoustic trauma, 2145-2146
anatomic mechanisms underlying, 2143-2144
clinical course of, 2121, 2121f-2122f, 2141, 2142f
cochlear damage in, 2141-2143, 2143f
diagnosis of, 2199
early detection of, 2146-2147, 2147f-2150f
hair cell regeneration and repair and, 2144
interactive effects in, 2147-2148
irreversible, 2141
legal issues with, 2149-2151
nature of, 2121-2122, 2141
new knowledge about cellular and molecular mechanisms of, 2144-2146
permanent threshold shift in, 2141, 2148
prevention of, 2151
protection from
by conditioning of cochlear efferent system, 2144
pharmacologic, 2144-2145
research on, 2143
resistance to, 2144-2145, 2146f
role of otolaryngologist in, 2150-2151
susceptibility to, 2145-2146, 2146f
temporary threshold shift in, 2141, 2148
with tinnitus, 2131-2132
vestibular disorders in, 2148
vibration and, 2148-2149
due to otitis media, 2776
outcome scales for, 57
due to paranasal sinus tumor, 1123
pediatric
conductive, 2200-2201
sensorineural, 2200, 2200b
quantification of, 2087, 2087t
rapidly progressive, 2198b, 2199-2200
sensorineural (*See* Sensorineural hearing loss (SNHL))
sudden, 2127-2130
clinical features of, 2157
etiology of, 2127-2129, 2195b, 2198-2201
due to labyrinthine infections, 2154, 2154b, 2157
prevalence, natural history, and prognosis for, 2127

Hearing loss *(Continued)*
temporal bone pathology in, 2157
treatment of, 2129-2130, 2157
intratympanic steroids for, 2184-2185
systemic steroids for, 2184
due to temporal bone trauma, 2046-2047, 2046f
in transplant recipients, 224-225
vaccines to prevent, 2161
Hearing preservation, cochlear implants with
in adults, 2245-2246
in children, 2240
ear selection for, 2236
Hearing protection, for prevention of noise-induced hearing loss, 2151
Hearing Satisfaction Scale (HHS), 57
Hearing sensitivity test(s), 1888, 1888f. *See also* Audiologic test battery (ATB).
auditory brainstem response as, 1909-1910
pure-tone air-conduction testing as, 1888
masking for, 1889-1890
pure-tone bone-conduction testing as, 1888, 1888f-1889f
Heart, of newborn, 2571
Heart disease, oral manifestations of, 1246-1249, 1249t
Heart murmur, oral treatment considerations with, 1246t
Heart rate, in children, 2571, 2571t
Heart transplantation, oral sequelae of, 1248
Heartburn, 954
Heat and moisture exchanger (HME), 1599-1600, 1602f
Heat shock protein 27 (HSP-27), in oral cancer, 1295
Hebb's postulate, and neural plasticity, 1882-1884, 1884f
HEDIS (Health Plan Employer Data and Information Set) measures, 82
Heerfordt's disease, facial paralysis in, 2400
Helical crus, 476-477
Helical CT
of laryngeal carcinoma, 1470
of pharynx and esophagus, 1396
Helicobacter pylori, in extraesophageal reflux, 899
Helicotrema
anatomy of, 1831, 1832f, 1840, 1841f, 1853f
in cochlear transduction, 2061-2062, 2062f
Heliox
for croup, 2806
for stridor, 2903
Helix, of ear, 476-477, 476f, 1824f, 2742f
Helix electrode system, 2227-2228, 2228f
Helper T cells, 601-602, 602f
Hemangioblastomas, intra-axial, 2528
Hemangioendothelioma
kaposiform, 2824-2825, 2826f
bone resorption with, 2826
Kasabach-Merritt phenomenon with, 2825
of neck
epithelioid, 1668-1669
spindle cell, 1668-1669
Hemangioma(s)
of airway
assessment and treatment of, 2828-2829, 2829f
complications of, 2825, 2826f
capillary
of cerebellopontine angle, 2524, 2525f
sinonasal, 718t, 725, 725f
cavernous, 290
of cerebellopontine angle, 2524
epistaxis due to, 684f
of cerebellopontine angle, 2524, 2525f
cavernous, 2524
congenital, 2824, 2825f
cutaneous, and airway involvement, 2899, 2900f
Hemangioma(s) *(Continued)*
facial
embolization of, 1942
laser therapy for, 2827f-2828f, 2828
medical therapy for, 2826-2828
principles for management of, 2826-2828
surgical therapy for, 2827f-2828f, 2828
facial nerve
vs. facial nerve schwannomas, 2507
imaging of, 1924-1926, 1927f
intranasal, 2695
laryngeal, 874, 2871, 2871f
of masticator space, 152
neck masses due to, 1640, 2816, 2816f
of oral cavity, 1291
of salivary glands, 1172, 2859-2860, 2860f
spindle cell, 1668-1669
subglottic, 1468, 1468f, 2871, 2871f
dysphagia due to, 2953
stridor due to, 2899, 2900f
of trachea, 1613
Hemangioma of infancy (HOI), 290, 2823-2824
of airway
assessment and treatment of, 2828-2829, 2829f
complications of, 2825, 2826f
clinical presentation of, 2823, 2825f
complications of, 2825, 2826f-2827f
diagnosis of, 2823
focal, 2823, 2825f
imaging of, 2823, 2824f
laser therapy for, 2827f-2828f, 2828
medical therapy for, 2826-2828
natural history of, 2823, 2824f
obstruction of visual axis by, 2825, 2826f
persistent tissue changes due to, 2826, 2827f
in PHACES syndrome, 2824, 2825f
principles for management of, 2826-2828
segmental, 2823, 2824f-2825f
surgical therapy for, 2827f-2828f, 2828
ulceration of, 2825, 2827f
Hemangiopericytoma (HPC), of neck, 1670
Hematocrit, in children, 2571-2572
Hematogenous total joint infection, patients at potential increased risk of, 1253, 1253t
Hematologic disorders
oral manifestations of, 1256
preoperative evaluation of, 105-106
due to anticoagulants, 105
congenital, 105
hemoglobinopathies as, 106
due to liver failure, 105-106
thrombocytopenia as, 106
Hematolymphoid neoplasms
of larynx, 1509
extramedullary plasmacytoma as, 1509
lymphoma as, 1509
mucosal malignant melanoma as, 1509
of oropharynx, 1364, 1364f
Hematoma(s)
auricular, 97, 310, 2038
esophageal, 1416
fracture, 330
after liposuction, 459
due to neck surgery, 1729
after otoplasty, 478-479
due to rhytidectomy, 420-421, 425f
septal, 494
due to nasal fracture, 507
pediatric, 2708-2709, 2712f
due to sphenoidotomy, 768t
after total laryngectomy, 1571
Hematopoietic growth factors, 609t-610t
Hematopoietic tumors, of paranasal sinuses, 1131
Hemicrania continua, 248
Hemidystonia, 838
Hemifacial microsomia, 2585
Hemifacial spasm, 2401
facial nerve monitoring with microvascular decompression for, 2548-2549, 2549f
Hemiglossectomy, for tongue carcinoma, 1305-1306, 1305f
Hemilaryngectomy
for glottic cancer, 1517t, 1519t
extended, 1517t
vertical, 1496, 1518f, 1519t, 1547-1549
with anterior commissure involvement, 1497
swallowing disorders due to, 1220
vertical, 1547-1549
complications of, 1549
extended, 1548
frontolateral, 1548
functional outcome of, 1548
for glottic cancer, 1496, 1518f, 1519t, 1547-1549
with anterior commissure involvement, 1497
historical background of, 1540
with imbrication laryngoplasty, 1548, 1548f
key surgical points for, 1549
oncologic results of, 1547-1548, 1547t-1548t
posterolateral, 1548
radiographic appearance after, 1476, 1479f
surgical technique for, 1548
Hemilaryngopharyngectomy, supracricoid, for hypopharyngeal cancer, 1429, 1436
Hemimandibulectomy
for buccal carcinoma, 1309f
for tongue carcinoma, 1306f
Hemitransfixion incision, for septoplasty, 488, 489f
Hemochromatosis, oral manifestations of, 1257
Hemodialysis, oral sequelae of, 1255
Hemodilution, and skin flap viability, 1073
Hemoglobin level, in children, 2571-2572
Hemoglobinopathies
oral manifestations of, 1256
preoperative evaluation of, 106
Hemophilia, preoperative evaluation of, 105
Hemophilia A, oral manifestations of, 1256
Hemorrhage
after adenotonsillectomy, 2783f-2784f, 2794, 2799-2800, 2800f
cerebellar, 2354f
due to endoscopic sinus surgery, 754
functional, 679
due to neck surgery, 1723
of carotid artery, 1728
of internal jugular vein, 1729, 1729f
due to sphenoidotomy, 768t
due to thyroid surgery, 1770
vocal fold, 867-869
with capillary ectasia, 868f
diagnosis of, 868
history in, 868
laryngeal examination in, 868
vocal capability battery in, 868
epidemiology of, 867
pathophysiology and pathology of, 867-868
treatment of, 868-869
behavioral, 868
medical, 868
surgical, 868-869
Hemotympanum, due to temporal bone fracture, 2038, 2039f, 2046
Hennebert's sign, 2105, 2316, 2329-2330
in otosyphilis, 2341
with perilymph fistula, 2342
Hensen's cells, anatomy of, 1832, 1832f-1833f
Heparin
after free tissue transfer, 1096
preoperative use of, 105
Hepatic disease
oral manifestations of, 1255
preoperative evaluation of, 103-104
Hepatitis, oral manifestations of, 1252

HER1, in head and neck squamous cell carcinoma, 1060
HER2, in head and neck squamous cell carcinoma, 1060
Her2/neu
  in oral cancer, 1295
  in salivary gland neoplasms, 1199
Hereditary disorders, sensorineural hearing loss due to, in adults, 2117-2118
Hereditary hemorrhagic telangiectasia (HHT), 291
  epistaxis in, 691-692, 692f
  oral manifestations of, 1257
Hernia, hiatal, gastroesophageal junction in, 957f
Herpangina, 2785, 2786f
Herpes labialis, 1236, 1236f
Herpes simplex virus (HSV)
  and Bell's palsy, 2391-2393
  and chemical peels, 391-392, 397
  deafness due to, 2159-2160
    in infants, 2723
  esophagitis due to, 976-977, 977f-978f
    imaging of, 1404, 1405f
  Meniere's disease due to, 2163
  oral
    in HIV, 226
    primary infection with, 1235, 1252
      clinical features of, 1235, 1235f, 1252
      defined, 1235
      diagnosis of, 1235
      differential diagnosis of, 1235
      etiology and pathogenesis of, 1235
      treatment of, 1235, 1252
    recurrent infection with, 1235-1236, 1252
      clinical features of, 1236, 1236f
      defined, 1235
      differential diagnosis of, 1236
      etiology and pathogenesis of, 1235-1236
      histopathology of, 1236, 1237f
      vs. recurrent aphthous stomatitis, 1238, 1238t
      treatment of, 1236
  pharyngitis due to, 199, 199f
  vestibular neuritis due to, 2162-2163
Herpes simplex virus-1 (HSV-1) vector, for gene therapy of inner ear, 2191t, 2192
Herpes zoster facial paralysis, 2393, 2396
Herpes zoster ophthalmicus, 2396
Herpes zoster oticus, 1948, 1948f
  clinical features of, 2159, 2159f
  diagnosis of, 2159
  management of, 2159
  otorrhea due to, 2195
  sensorineural hearing loss due to, 2119, 2159
    sudden, 2127
  temporal bone pathology in, 2159
Herpesvirus vectors, for gene therapy, 18t
  of inner ear, 2191t, 2192
Herpetic gingivostomatitis, 1235, 1235f
Herpetic palsy, imaging of facial nerve in, 1924, 1927f
Herpetiform-type aphthous ulcerations, 1238, 1238f
Hertwig's epithelial root sheath, 1259
Hertz (Hz), 1838-1839, 1839f
Heschl's gyrus, 1847
Heteroduplex testing, 9
Heterogeneity, genetic, 8
Heteroplasmy, 8, 2089
Heterozygosity, 6, 2088
Hexachlorophene and alcohol (Septisol), for deep chemical peel, 394-395
HHIE (Hearing Handicap Inventory in the Elderly), 57
HHT (hereditary hemorrhagic telangiectasia), 291
  epistaxis in, 691-692, 692f
  oral manifestations of, 1257
HHV. *See* Human herpesvirus (HHV).
Hiatal hernia, gastroesophageal junction in, 957f
Hiatus secondarius, 740
Hiatus semilunaris
  normal anatomy of, 667, 667f
  surgical anatomy of, 740
HIB (*Haemophilus influenzae* type B), supraglottitis due to, 2807
HIB (*Haemophilus influenzae* type B) vaccine
  to prevent hearing loss, 2161
  to prevent otitis media, 2769
Hidrocystoma, 292
HIF (hypoxia inducible factor), in Warburg effect, 1028f
HiFocus 1j electrode system, 2227-2228, 2228f
High-density polyethylene (MEDPOR)
  for auricular reconstruction, 2744t
  for chin implants, 465t
High-dose-rate (HDR) radiotherapy, 1047
Highly active antiretroviral therapy (HAART), 211
High-resolution computed tomography (HRCT)
  for cochlear implant, 2222, 2222f
    with otosclerosis, 2222, 2222f
    in preoperative evaluation, 2235, 2235f, 2236b
  for CSF rhinorrhea, 791, 791f, 2044
  for dizziness, 2326-2327
  for malignant otitis externa, 1947
  of superior canal dehiscence syndrome, 2340-2341, 2340f
  for temporal bone fracture, 2039, 2040f
High-Risk Registry (HRR), for infant hearing loss, 2718-2719
High-speed digital imaging (HSDI), of larynx, 821-823
  applications of, 823
  assessment using, 822-823
  defined, 813
  equipment for, 821
  kymography in, 134f, 154, 822f
  limitations of, 823
Hilger facial nerve stimulator, for facial nerve injury, 2040-2041
Hillocks of His, embryogenesis of, 1824, 2741, 2742f
Hinge flaps, 346
  for nasal defects, 348, 350f, 371-372, 372f
HINT (Hearing in Noise Test), for cochlear implants, 2223, 2244
Hip strategy, 2308
HiRes 90K Bionic Ear device, 2227-2228, 2228f
Histamine provocation test, in nonallergic rhinitis, 695-696
Histamine$_1$ receptor antagonists (H_1 blockers), for allergic rhinitis, 620
Histamine$_2$ receptor antagonists (H_2 blockers)
  for extraesophageal reflux, 901
  for GERD, 970
Histiocytoma, malignant fibrous
  of larynx, 1508
  of neck, 1667
Histiocytosis(es)
  in children, 2847-2848
    classification of, 2847, 2847t
    clinical presentation and evaluation of, 2847-2848
    neck masses due to, 2819
    pathology of, 2847
    treatment of, 2848
  Langerhans' cell (*See* Langerhans' cell histiocytosis (LCH))
  X (*See* Langerhans' cell histiocytosis (LCH))
Histones, 11
  in head and neck squamous cell carcinoma, 1020-1021
Histoplasmosis
  laryngeal and tracheal manifestations of, 885, 892
  oral, in HIV, 226-227
History, 94, 94b
  in assessment of nasal breathing function, 642
  for children, 2573
  of chronic rhinosinusitis, 743
  of facial trauma, 302-303
  of nonallergic rhinitis, 699, 699b
  of present illness, for disorders of professional voice, 850-851
HIT (health information technology), 84t-87t
HIV. *See* Human immunodeficiency virus (HIV)/HIV infection.
HL. *See* Hodgkin's lymphoma (HL).
HL (hearing level), 1839
HLA (human leukocyte antigen) system, 599
HLA-B7 (human leukocyte antigen-B7), in gene therapy, 21
HM (hyoid myotomy), for obstructive sleep apnea, 259, 261f
HME (heat and moisture exchanger), 1599-1600, 1602f
HNC. *See* Head and neck cancer (HNC).
HNDS (Head and Neck Distress Scale), 56
HNQOL (Head and Neck Quality of Life), 56
H&NS (Head & Neck Survey), 56
HNSCC. *See* Head and neck squamous cell carcinoma (HNSCC).
Hoarseness
  gastroesophageal reflux and, 2946
  due to hypothyroidism, 1747
  due to thyroid disease, 1736-1737
Hockey stick incision, for neck dissection
  radical, 1709, 1710f
  selective, 1717-1718, 1717f
Hodgkin, Thomas, 2838-2839
Hodgkin's lymphoma (HL), 1676-1677
  in children, 2819, 2838-2840
    clinical presentation of, 2819, 2839-2840
    histopathology and molecular biology of, 2819, 2840, 2840f
    imaging of, 2820f
    management of, 2840
    staging of, 2839-2840
  clinical presentation of, 1674, 1674f
  complications of, 1677
  epidemiology of, 1673-1674
  imaging of, 1674, 1674f
  immunosuppression and, 213t, 217
  staging of, 1676, 1677t
  treatment and prognosis for, 1676-1677
HOI. *See* Hemangioma of infancy (HOI).
Holdaway analysis, for mentoplasty, 463, 464f
Hollinger anterior commissure laryngoscope, for difficult airway, 122, 122f
Holmium:YAG (Ho:YAG) laser, 33
Holoprosencephaly, 2690
Homograft(s)
  for craniofacial defect repair, 2657
  for nasal reconstruction, 368
  for ossiculoplasty, 2006, 2025, 2026t
Homoplasmy, 2089
Homozygosity, 6, 2088
Horizontal buttresses, 331-332
Horizontal canal benign paroxysmal positional vertigo (HC-BPPV)
  positional testing for, 2315-2316, 2331
  repositioning maneuver for, 2332
Horizontal palpebral fissure, 442
Horizontal partial laryngectomy, 1540, 1549
Horizontal phase, of vocal fold vibration, 849
Horizontal semicircular canal (HSCC) fistula, due to mastoidectomy, 2015
Horizontal semicircular duct, 1851f
Hormonal effects, of radiotherapy, 2626t
Horner's syndrome
  due to neck surgery, 1732, 1732f
  due to thyroid disease, 1736
Hospital Quality Alliance (HQA), 84t-87t, 87

Hospitalization, of children
in dedicated children's hospital, 2575
preparation for, 2574-2575
Hot water irrigation, for epistaxis, 691
Hounsfield units (HU), 131
Hourglass closure, laryngeal videostroboscopy of, 819, 820f
House, William, 2437-2438
House-Brackmann grading system, for facial nerve function, 2381-2382, 2382t, 2383f, 2417-2418, 2417t
Ho:YAG (holmium:YAG) laser, 33
HPC (hemangiopericytoma), of neck, 1670
Hpn, in murine deafness, 2058t-2060t
HPV. *See* Human papillomavirus (HPV).
HQA (Hospital Quality Alliance), 84t-87t, 87
H-ras, in oral cancer, 1294
HRCT. *See* High-resolution computed tomography (HRCT).
HRQOL (health-related quality of life), as outcome measure, 55
HRR (High-Risk Registry), for infant hearing loss, 2718-2719
Hsal1, in deafness, 2051t-2058t
HSCC (horizontal semicircular canal) fistula, due to mastoidectomy, 2015
HSDI. *See* High-speed digital imaging (HSDI).
HSP-27 (heat shock protein 27), in oral cancer, 1295
HSS (Hearing Satisfaction Scale), 57
HSV. *See* Herpes simplex virus (HSV).
HTT. *See* Head thrust test (HTT).
H-type fistula, 2926
HU (Hounsfield units), 131
HUI (Health Utilities Index), 56
Human Genome Project, 2088
Human herpesvirus 1 (HHV-1)
and erythema multiforme, 1239
oral infection with
primary, 1235, 1252
recurrent, 1235-1236, 1252
vs. recurrent aphthous stomatitis, 1238, 1238t
Human herpesvirus 8 (HHV-8), 213
Human immunodeficiency virus (HIV)/HIV infection, 210-212. *See also* Acquired immunodeficiency syndrome (AIDS).
AIDS-defining conditions in, 210-211, 211t
biology and immunology of, 210
diagnosis and classification of, 210-212, 211t
and facial lipoatrophy, 227-228, 228f
facial palsy due to, 2399
and hearing loss, 223-225, 2161-2162
approach to, 224, 225t
due to cryptococcal meningitis, 223-224
due to otosyphilis, 224
highly active antiretroviral therapy for, 211
immune restoration disease in, 211-212
lymphadenopathy due to, in children, 2818
and malignancy, 212-217, 213t
cutaneous neoplasms as, 213t, 215
Hodgkin's lymphoma as, 213t, 217
Kaposi's sarcoma as, 212-215, 213t
epidemiology and pathogenesis of, 212-213
presentation and diagnosis of, 213-214, 214f
treatment of, 214-215
non-Hodgkin's lymphoma as, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
squamous cell carcinoma as, 213t, 215
and malignant otitis externa, 1947
and neuropathies, 223-225
occupational exposure to, 212, 212t
olfactory loss due to, 636
and oral lesions, 225-227, 1252
aphthous ulcers as, 227, 227f
candidiasis as, 225, 226f
Human immunodeficiency virus (HIV)/HIV infection *(Continued)*
differential diagnosis of, 225t
fungal, 227
gingivitis and periodontal disease as, 227
hairy leukoplakia as, 225-226, 226f
due to herpes simplex virus, 226
histoplasmosis as, 226-227
due to human papillomavirus, 227
otologic and neurotologic manifestations of, 221-223
malignant otitis externa as, 221-222
in middle ear, 222-223
due to *P. jiroveci* and *A. fumigatus*, 222-223
pharyngitis due to, 197
postexposure prophylaxis for, 212, 212t
and salivary gland disease, 217-218
in children, 2856
diffuse infiltrative lymphocytosis syndrome as, 218
parotid lesions as, 217-218, 218f
xerostomia as, 218
and sinonasal infection, 219-221
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
transmission of, 210
Human immunodeficiency virus (HIV)-associated dementia (HAD), 223
Human immunodeficiency virus (HIV) wasting syndrome, 210-211
Human immunodeficiency virus–associated salivary gland disease (HIV-SGD), 1157-1158, 1157f
Human leukocyte antigen (HLA) system, 599
Human leukocyte antigen-B7 (HLA-B7), in gene therapy, 21
Human papillomavirus (HPV)
external ear infection with, 1957, 1957f
management options for, 1957
and oral cancer, 1294, 1365
recurrent respiratory papillomatosis due to, 878, 2884-2886
and squamous cell carcinoma, 215
of head and neck
as biomarker, 1026
as risk factor, 1017-1018
of larynx, 1492, 1513
verrucous, 1505
warts due to, 282
oral, in HIV, 227
Human papillomavirus (HPV) vaccine (Gardasil), 2886-2887, 2890t
Humidified air, for croup, 2806
Humoral immune response, 606-608
antibody-dependent cellular cytotoxicity in, 606
B cells in, 603
T cell–dependent and T cell–independent, 606
chemokines in, 608, 611t-612t
complement system in, 607-608, 608f
cytokines in, 608, 609t-610t
immunoglobulins in, 606-607, 607f
Humoral immunodeficiency disorders, 2114
otologic manifestations of, 2114
Hump reduction, in noncaucasian rhinoplasty, 570-573
concept of, 570-571
results of, 574f-575f
technique for, 571-573, 575f
Hunter's syndrome, 2113
and obstructive sleep apnea in children, 2606
otologic manifestations of, 2113, 2113f
Huntington's disease, saccades in, 2313
Hurler's syndrome, 2113
and obstructive sleep apnea in children, 2606
otologic manifestations of, 2113
Hürthle cell tumor, 1762-1763
clinical presentation of, 1762
management and prognosis for, 1762-1763
pathology of, 1762
Hutchinson's triad, 2341
Hydration
for benign vocal fold mucosal disorders, 862
for voice professional, 852-853
Hydraulic lever, 2018-2019
Hydraulic process, and orbital wall fractures, 2712
Hydrocephalus
normal pressure, vestibular symptoms of, 2357
otitic, 1997
after stereotactic radiation therapy, 2563
Hydrocodone
ototoxicity of, 2175
for postoperative pain, 241t
Hydrocortisone
intratympanic delivery of, 2183
for thyroid storm, 1745
Hydrocortisone butyrate cream, for eczematoid otitis externa, 1955-1956
Hydrocortisone cream (Hytone cream)
after chemical peel, 396
for eczematoid otitis externa, 1955-1956
Hydrocortisone/propylene glycol/acetic acid otic solution (VoSol HC), for otitis externa
bacterial, 1953, 1959t-1960t
fungal, 1954, 1959t-1960t
Hydrodynamic delivery, of siRNA, 16
"Hydrodynamic" theory, of dental pain, 1202-1203
Hydrogen cyanide, in noise-induced hearing loss, 2147-2148
Hydrogen peroxide, for cerumen removal, 1958t
Hydromorphone
as adjunct to induction of anesthesia, 111
for anesthesia maintenance in children, 2592
Hydrops, endolymphatic
audiogram in, 1895f
electrocochleography in, 1892-1896, 1895f, 1908
idiopathic (*See* Meniere's disease)
otosclerosis with, 2035
sensorineural hearing loss due to, 2126-2127, 2199
stacked auditory brainstem response in, 1911
vertigo due to, 2202
Hydrops ex-vacuo model, of eustachian tube dysfunction, 1870
Hydroxyapatite (Bone Source), for chin implants, 465t
Hydroxyapatite cap, for ossiculoplasty, 2026t
Hydroxyapatite (VoCoM) implants, for medialization thyroplasty, 908-910, 908f, 910f
Hydroxychloroquine (Plaquenil)
ototoxicity of, 2176
sensorineural hearing loss due to, 2120
5-Hydroxytryptamine$_3$-receptor antagonists, for postoperative nausea and vomiting in children, 2593
Hydroxyurea, with radiotherapy, 1041
Hygiene hypothesis, of allergic rhinitis, 613-614
Hygroma, cystic, 156-157, 2815, 2901f
Hylan B gel (Hylaform), for vocal fold medialization, 905-906
Hyoepiglottic ligament, 1541-1542, 1542f-1543f
Hyoglossus muscle, 1296f, 1297-1298, 1298f
Hyoid bone
anatomy of, 805-806, 1296f, 1359f
radiographic, 1463f, 1471, 1471f, 1473f
surgical, 1541, 1542f-1543f
in breathing, 810
embryology of, 2583-2584
laryngeal carcinoma of, 1541
palpation of, in voice evaluation, 827, 828f
physical examination of, 95, 96f
Hyoid myotomy (HM), for obstructive sleep apnea, 259, 261f

Hyperacusis, 2138-2139
in Bell's palsy, 2393
defined, 2138
epidemiology of, 2138
evaluation of, 2138-2139
impact of, 2139
vs. recruitment, 2138
treatment of, 2139
Hyperacusis Questionnaire, 2138-2139
Hyperadrenalism, oral manifestations of, 1251
Hyperbaric oxygen (HBO) therapy
for osteoradionecrosis, 1048
with radiotherapy, 1041
for skin flap salvage, 1075
and skin flap viability, 1074
for soft tissue avulsions, 307
Hypercalcemia
due to benign tumors, 1783-1784, 1783t
definition of, 1782
differential diagnosis of, 1782, 1782t-1783t
drug-induced, 1783-1784, 1783t
due to endocrine disease, 1783-1784, 1783t
epidemiology of, 1782
familial hypocalciuric, 1783
due to granulomatous disorders, 1783-1784, 1783t
in hyperparathyroidism
differential diagnosis of, 1782, 1782t
evaluation of, 1782-1784
historical background of, 1774
pathogenesis of, 1781
of malignancy, 1783, 1783t
medical management of, 1804
non–PTH-mediated, nonmalignant, 1783-1784, 1783t
preoperative evaluation of, 104
Hypercalcemic crisis, 1781
Hypercalcemic syndrome, 1781
Hyperdynamic facial lines, 275, 279f
Hyperechoic tissue, 1643
Hyperfractionation, 1040
Hyperfunctional disorders, of larynx, 838-842
botulinum toxin therapy for, 839, 840f-841f
due to dystonia, 838-839, 838b
essential tremor as, 840-841
due to myoclonus, 840
due to pseudobulbar palsy, 839-840
stuttering as, 841-842
Hyperfunctional dysphonia, 834
Hyperkeratosis
of larynx, 1486
leukoplakic-type, 1231, 1231f
Hyperkinetic disorders, of facial nerve, 2401
management of, 2432
Hypermethylation, in head and neck squamous cell carcinoma, 1020-1022, 1021f
Hypernasality
after adenotonsillectomy, 2800
assessment of, 2678-2679, 2679t
in children, 2879
Hyperparathyroidism
asymptomatic, 1781
clinical course of untreated, 1782
clinical manifestations of, 1780-1781
cardiovascular, 1781
gastrointestinal, 1781
hypercalcemic abnormalities as, 1781
neurologic, 1781
neuromuscular, 1781
renal and urinary tract, 1781
skeletal, 1781
diagnosis of, 1784
etiology and pathogenesis of, 1774-1775, 1775f-1776f
familial, 1795-1797
in MEN-I, 1775, 1776f, 1795-1796
in MEN-IIA, 1796
Hyperparathyroidism *(Continued)*
neonatal, 1797
non-MEN (isolated), 1796-1797
historical background of, 1774
hypercalcemia in
evaluation of, 1782-1784, 1782t-1783t
historical background of, 1774
pathogenesis of, 1781
incidence of, 1780
localization study(ies) in, 1784-1789, 1784t
gamma radiation detection device for, 1802, 1803f
intraoperative, 1784t, 1789
invasive preoperative, 1784t, 1788-1789
parathyroid arteriography as, 1788
selective venous sampling for PTH as, 1788-1789
ultrasound-guided fine-needle aspiration as, 1789
mediastinal exploration as, 1801-1802, 1802f
noninvasive preoperative, 1784-1788, 1784t
computed tomography as, 1786-1787
computed tomography–sestamibi fusion as, 1785-1786, 1786f-1788f
magnetic resonance imaging as, 1787-1788, 1789f
pertechnetate (technetium 99m) thallous chloride (thallium 201) imaging as, 1784-1785
sestamibi–technetium 99m scintigraphy as, 1785, 1785f, 1788f, 1794f
technetium 99m sestamibi with single photon emission computed tomography as, 1785
ultrasonography as, 1786, 1788f-1789f
unsuccessful, 1801, 1801f-1802f
medical management of, 1804
oral manifestations of, 1251
due to parathyroid adenoma, 1774-1775, 1778-1779
due to parathyroid carcinoma, 1802-1804, 1803f
during pregnancy, 1804
preoperative evaluation of, 104
re-exploration for recalcitrant, 1798-1800
causes of failed exploration with, 1798
operative risk in, 1798-1799
operative strategy for, 1799-1800, 1799f-1800f
preoperative assessment for, 1798
renal failure–induced, 1797-1798
secondary, 1782-1783
recurrent, 1798
surgical management of, 1789-1804
gamma radiation detection device in, 1802, 1803f
indications for, 1789-1790
intraoperative PTH levels with, 1800-1801
for multiple-gland disease, 1794-1795
due to sporadic hyperplasia, 1794-1795, 1794f
due to true double adenoma, 1794, 1794f
parathyroidectomy as, 1790-1792
anesthesia and preparation for, 1790
closure of incision in, 1792
exploration of neck in, 1790-1792, 1791f
postoperative care after, 1792
for single-gland disease, 1792-1794
directed unilateral cervical exploration as, 1792-1793
endoscopic parathyroid exploration in, 1793-1794
minimally invasive techniques for, 1793
strategy and approach to, 1792
tertiary, 1783
and thyroid disease, 1801, 1801f-1802f
Hyperpigmentation
after chemical peel, 396-397
after rhytidectomy, 427
Hyperplasia
of larynx, 1486-1491
oropharyngeal, 1360
Hyperplastic candidiasis, 1231, 1231f
in HIV, 225
Hyperresponsiveness, in allergic rhinitis, 616-617
nonspecific, 617
specific, 616-617
Hypersensitivity, delayed-type, 601
Hypersensitivity reaction(s), 608-612
to ototopical antibiotics, 1954
Hypersomnia(s)
of central origin, 263-264, 264b
idiopathic, 262t, 264
Hypertension
benign (idiopathic) intracranial
CSF rhinorrhea due to, 787
facial paralysis due to, 2400-2401
sensorineural hearing loss due to, 2123
and epistaxis, 686-687
due to hyperparathyroidism, 1781
malignant, 119
pulmonary, due to obstructive sleep apnea, 2604
Hyperthyroidism. *See also* Graves' disease; Thyrotoxicosis.
antithyroid agents for, 1739t
oral manifestations of, 1251
preoperative evaluation of, 104
with thyroid nodule, 1756
Hypertrophic adenoids, and otitis media, 1872, 1873f
Hypertrophic scars, 291
after otoplasty, 479
due to rhytidectomy, 425-426
Hyperventilation, dizziness due to, 2316
Hypervitaminosis D, hypercalcemia due to, 1784
Hypnotic dependent sleep disorder, 262t
Hypoadrenalism, oral manifestations of, 1251
Hypocalcemia
after hypopharyngeal reconstruction, 1458
after thyroid surgery, 1771
Hypoechoic tissue, 1643
Hypoepiglottic ligament, in laryngeal cancer, 1484, 1484f
Hypofunctional disorders, of larynx, 842-843
due to central causes of vocal fold paresis, 842
due to medullary disorders, 842
due to multiple sclerosis, 843
due to myopathies, 842
due to neuromuscular junction disorders, 842
due to Parkinson's disease, 842-843
due to poliomyelitis, 842
psychogenic, malingering, and mixed causes of, 843
vocal fold paresis as, 843
Hypoglossal canal
anatomy of, 1823f
in surgical anatomy of lateral skull base, 2435f
in surgical anatomy of middle cranial base, 2445f
Hypoglossal nerve
anatomy of, 1295, 1296f, 1297-1298
distribution of, 2580f, 2581
intraoperative monitoring of, 2550-2552, 2552f
in surgical anatomy of lateral skull base, 2439f-2440f
Hypoglossal nerve injury
in lateral skull base surgery, 2512
due to neck surgery, 1730-1731
Hypoglossal nerve transposition, for facial nerve paralysis, 2419, 2424f-2426f, 2425-2426
Hypoglycemic agents, oral sequelae of, 1247t-1248t
Hypomethylation, in head and neck squamous cell carcinoma, 1021-1022
Hyponasality
assessment of, 2678, 2678f, 2678t
in children, 2879

Hypoparathyroidism
oral manifestations of, 1251
preoperative evaluation of, 104
sensorineural deafness, and renal dysplasia (HDR) syndrome, 2051t-2058t
Hypopharnygeal stenosis, 947-948
Hypopharyngeal cancer, 1421-1440
advanced-stage, 1438-1439
chemotherapy for, 1439
conventional treatment modalities for, 1442
quality of life with, 1439
radiation therapy for, 1591-1592
complications of, 1591
CyberKnife stereotactic approach for, 1592
future strategies and directions for, 1592
outcome and prognostic factors for, 1591
RADPLAT approach for, 1592
techniques and dose-fractionation schemes for, 1591
anatomy and, 1421-1422, 1422f
approach to management of, 1426
cervical lymph node metastasis of, 1422, 1422f, 1434-1439
incidence and distribution of, 1686f, 1688t
management of, 1434-1439
radiation therapy for, 1689t
chemoradiotherapy for, 1434, 1442
for advanced disease, 1439
after total laryngectomy, 1442-1443
chemotherapy for, 1433-1434, 1442
for advanced disease, 1439
induction, 1443
for larynx preservation, 1443-1444
clinical evaluation of, 1423
physical findings in, 1423
presenting symptoms in, 1423, 1423t
clinical presentation of, 1579
conventional treatment modalities for, 1441-1442
for advanced disease, 1442
for early disease, 1442
diagnostic evaluation/workup for, 1579
early-stage, radiation therapy for, 1590-1591
complications of, 1591
outcome and prognostic factors for, 1591, 1591t
techniques and dose-fractionation schemes for, 1590-1591
epidemiology of, 1441
etiology and biology of, 1425-1426
imaging of, 1413, 1413f-1414f, 1423-1424, 1579
barium swallow for, 1423-1424
CT for, 1424, 1424f
MRI for, 1424
PET/CT for, 1424, 1424f
incidence of, 1422-1423
location and patterns of spread of, 1425
neck dissection for, 1434-1439, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
neck management for, 1580
new treatment modalities for, 1442, 1448, 1449f
overall management of, 1580, 1590
pathology of, 1424-1425
radiation therapy for, 1433, 1443, 1589-1592
with advanced-stage disease, 1591-1592
complications of, 1591
CyberKnife stereotactic approach for, 1592
future strategies and directions for, 1592
outcome and prognostic factors for, 1591
RADPLAT approach for, 1592
techniques and dose-fractionation schemes for, 1591
anatomic considerations in, 1578-1579, 1579f
with early-stage disease, 1590-1591
complications of, 1591
outcome and prognostic factors for, 1591, 1591t
Hypopharyngeal cancer *(Continued)*
techniques and dose-fractionation schemes for, 1590-1591
lymphatic drainage and, 1578-1579, 1579f
overview of, 1578
with recurrent disease, 1591-1592
therapeutic outcomes with, 1436
reconstruction for (*See* Hypopharyngeal reconstruction)
recurrent, radiation therapy for, 1591-1592
squamous cell carcinoma as, intensity-modulated radiotherapy of, 1046
staging of, 1367t, 1426-1434, 1426t-1427t, 1579-1580, 1580f
surgical management of, 1426-1431
endoscopic CO_2 laser resection for, 1429-1430, 1442
outcomes of, 1436-1438
history of, 1426
options for, 1426, 1427t
partial laryngopharyngectomy for, 1429, 1430f
partial pharyngectomy for, 1426-1429
via anterior transhyoid pharyngotomy, 1427-1429, 1428f
via lateral pharyngotomy, 1426-1427
via lateral transthyroid pharyngotomy, 1427, 1428f
via median labiomandibular glossotomy, 1429
supracricoid hemilaryngopharyngectomy for, 1429, 1436
therapeutic outcomes with, 1436-1439, 1437t
total laryngectomy with partial/total pharyngectomy for, 1430, 1431f
total pharyngo-laryngo-esophagectomy for, 1430-1431
therapeutic outcomes of, 1435-1436
with primary radiation therapy, 1436
with primary surgical therapy, 1436-1439, 1437t
Hypopharyngeal lipoma, 1425f
Hypopharyngeal mucosal space, imaging of, 158-159
with lesions, 159, 162f
normal anatomy in, 158-159, 159f-160f
Hypopharyngeal procedures, for obstructive sleep apnea, 258b, 259-260, 260f-261f
Hypopharyngeal reconstruction, 1431-1433, 1448-1461
with circumferential defects, 1431-1432
classification of defects for, 1450
decision making on, 1450, 1451f
free tissue transfer for, 1454, 1454f
enteric, 1455-1457
gastro-omental donor site for, 1457-1458, 1457f
jejunal donor site for, 1455-1457, 1456f
fasciocutaneous, 1433, 1455
antero-lateral thigh donor site for, 1455
other donor sites for, 1455
radial forearm donor site for, 1455
goals and principles of, 1450
jejunal free flap in, 1432-1433, 1433f
local and regional flaps for, 1450-1452, 1452f
myocutaneous flap(s) in, 1452-1453
pectoralis, 1431, 1431f
patient population for, 1448
perioperative counseling for, 1448-1449
postsurgical complications of, 1458, 1459f
posttreatment speech and swallowing outcomes of, 1459-1460
preoperative evaluation for, 1449-1450
visceral transposition for, 1453
colonic, 1453, 1454f
gastric, 1432, 1432f, 1453
voice rehabilitation after, 1458-1459
Hypopharynx
anatomy of, 1359f, 1421-1422, 1422f, 1578
radiographic, 1398f-1399f
dysphagia due to congenital conditions of, 2950t, 2951-2953, 2953f
lymphatic drainage of, 1422, 1422f, 2582
physical examination of, 99-100
Hypopigmentation
after chemical peel, 397
after rhytidectomy, 427
Hypopnea, 251b, 256f
obstructive, in children, 2607
Hypopnea index, 251b
Hypothalamic hypothyroidism, 1747
Hypothesis testing, 65, 66t
examples for, 65-66
null hypothesis in, 65, 66t
P value in, 65, 66t
type I and type II errors in, 65, 66t
Hypothyroidism, 1745-1749
clinical features of, 1745-1746, 1746b
due to endemic goiter, 1747
esophageal manifestations of, 979
etiology of, 1745, 1746b
due to excessive iodine intake, 1747
familial, 1747
goitrous, 1747
hearing loss due to, 1746
hoarseness due to, 1747
hypothalamic, 1747
laboratory diagnosis of, 1748, 1748t
after laryngectomy, 1747
due to lingual thyroid, 1287
management of, 1748-1749
myxedema coma due to, 1749
due to neck irradiation, 1695
nongoitrous, 1747
oral manifestations of, 1251
pituitary, 1747
during pregnancy, 1749
preoperative evaluation of, 104
prevalence of, 1745
after radiation therapy, 1747
due to radiation therapy, 1048
risk factors for, 1745-1746, 1746b
subclinical, 1747-1748
diagnosis of, 1747
effects on lipid, hypothyroid symptoms, and mood of, 1747-1748
natural history of, 1747
prevalence of, 1747
treatment of, 1748
surgery with, 1749
with thyroid nodule, 1756
after total laryngectomy, 1571
transient, 1747
vertigo due to, 1747
Hypotympanum, 1825-1826
Hypoventilation
central alveolar, 262t
obstructive, in children, 2607, 2607f
Hypoventilation syndromes, sleep-related, 263, 263b
Hypovolemic shock, due to pediatric facial fracture, 2699
Hypoxemia
newborn response to, 2571
during sleep in children, 2607
Hypoxemic syndromes, sleep-related, 263, 263b
Hypoxia
newborn response to, 2571
in noise-induced hearing loss, 2144-2145
and radiotherapy, 1041
Hypoxia inducible factor (HIF), in Warburg effect, 1028f
Hypoxic sensitizers, with radiotherapy, 1041
Hyrtl's fissure, 2736

Hysteria, *vs.* myofascial pain dysfunction syndrome, 1285t
Hytone cream (hydrocortisone cream)
after chemical peel, 396
for eczematoid otitis externa, 1955-1956
Hz (hertz), 1838-1839, 1839f

I

^{131}I. *See* Radioactive iodine (^{131}I).
IAC. *See* Internal auditory canal (IAC).
IAR (intermittent allergic rhinitis), 618
IBCA (isobutyl-2-cyanoacrylate), for embolization, 1933
Ibuprofen, and skin flap viability, 1074
I-3-C (indole-3-carbinol), for recurrent respiratory papillomatosis, 879, 2890t, 2892
ICA. *See* Internal carotid artery (ICA).
ICERE-1 protein, in deafness, 2051t-2058t
ICF (International Classification of Functioning), 56
ICP (intracranial pressure), and CSF rhinorrhea, 786-787, 786b
IDEA (Individuals with Disabilities Education Act), 2724
Identification tests, for olfaction, 631
IDL (indirect laryngoscopy), for laryngeal carcinoma, 1494
IFNs. *See* Interferon(s) (IFNs).
IFRS. *See* Invasive fungal rhinosinusitis (IFRS).
Ig(s). *See* Immunoglobulin(s) (Igs).
IGF-I (insulin-like growth factor-I), in wound healing, 1076
IHCs. *See* Inner hair cells (IHCs).
IHI (Institute for Healthcare Improvement), 84t-87t
IJV. *See* Internal jugular vein (IJV).
IL(s). *See* Interleukin(s) (ILs).
Iliac crest flap
for free tissue transfer, 1082t, 1087
for mandibular defects, 1324-1325, 1325t
IM. *See* Infectious mononucleosis (IM).
Image-guided computer-assisted surgery, of anterior and middle cranial base, 2448-2449, 2449f
Image-guided radiotherapy, 1043, 1046-1047
Image-guided surgery (IGS), of paranasal sinuses, 680-681, 743-744, 745f
registration in, 680-681
tracking systems in, 681
Imaging, 130-176
available modalities for, 130-138
computed tomography as, 131, 131f
contrast enhancement for, 132, 133f
image display for, 131-132
patient cooperation for, 132, 132f
radiation exposure from, 132-133, 133t
three-dimensional reconstruction techniques in, 138, 139f
conventional radiography as, 130-131
of facial bones and sinuses, 130
of neck, 131
radiation exposure from, 132-133, 133t
of temporal bone, 131
magnetic resonance angiography as, 137
magnetic resonance imaging as, 133-137
artifacts on, 133-134, 134f
disadvantages of, 137
fat suppression methods for, 135-136, 136f
with frequency (chemical shift) selective presaturation (fat saturation), 135-136, 136f
gadolinium enhancement for, 134-135, 135f-136f
with gradient echo techniques, 136-137, 137f
pulse sequences for, 134-137, 135f-136f
with short T1 inversion recovery (STIR), 135-136, 136f
Imaging *(Continued)*
with spectral presaturation inversion recovery (SPIR), 135-136
T1-weighted, 134, 135f-136f
T2-weighted, 134, 135f-136f
three-dimensional reconstruction techniques in, 138, 139f
in nuclear medicine, 137-138
positron emission tomography as, 137-138
radionuclide imaging as, 138, 139f
ultrasound as, 137
of cochlear implants, 2221-2222, 2222f
of deep neck space infections, 204-205
CT for, 204, 204f-205f
MRI for, 204
plain film radiography for, 204-205
ultrasonography for, 204-205
in differential diagnosis, 144
of Graves' ophthalmopathy, 1809-1810, 1811f
of head and neck, 138-144
computed tomography for, 139-142
with cervical lymphadenopathy, 139
with facial trauma, 142
of larynx and infrahyoid neck, 132f, 140
of paranasal sinuses, 140-142, 141f
of salivary glands, 139
in sialography, 139-140, 1145f, 1150, 1150f
of suprahyoid neck, 139, 141f
of temporal bone and skull base, 142
of thyroid and parathyroid glands, 140
conventional radiography for, in sialography, 139-140, 1149-1150, 1149f
FDG-PET for, 144, 145f
magnetic resonance imaging for, 142-143
of larynx and infrahyoid neck, 142-143
of lymphadenopathy, 142
of paranasal sinuses, 143
of salivary glands, 142
of skull base, 143
of suprahyoid neck, 142
of temporal bone, 143
of thyroid and parathyroid glands, 143
ultrasound for, 143-144
of infrahyoid neck, 143-144
with metastatic lymphadenopathy, 143
of salivary glands, 143
of hypopharyngeal and cervical esophageal cancer, 1413, 1413f-1414f, 1423-1424
barium swallow for, 1423-1424
CT for, 1424, 1424f
MRI for, 1424
PET/CT for, 1424, 1424f
of infrahyoid neck, 157-159
anterior and posterior cervical (lateral cervical) spaces in, 158, 159f-160f, 162f
CT for, 140
hypopharyngeal mucosal space in, 158-159
with lesions, 159, 162f
normal anatomy in, 158-159, 159f-160f
normal anatomy in, 157-159, 159f-160f
prevertebral space in, 158, 159f-160f, 162f
retropharyngeal space in, 158
with lesions, 158, 161f
normal anatomy in, 158, 159f-160f
of larynx, 159-161, 813-824, 1462-1481
with benign mass(es), 1468
congenital cysts as, 1468
laryngocele as, 159-161, 163f, 1468, 1469f
squamous papillomas as, 1468, 1468f
subglottic hemangioma as, 1468, 1468f
with carcinoma, 1494-1495
of anterior commissure, 1474, 1474f
of aryepiglottic fold, 1475, 1478f
with cartilaginous invasion, 1474-1475, 1476f
for conservation laryngeal surgery, 1545-1546
of epiglottis, 1475, 1477f
glottic, 1474-1475, 1474f
Imaging *(Continued)*
with lymph node metastases, 1476, 1479f
normal anatomy and, 1470-1474
paraglottic, 1474
post-therapy, 1476-1479, 1479f
of pyriform sinus, 1475-1476, 1478f
subglottic, 1474, 1475f
supraglottic, 1475-1476
technique for, 1470, 1470f
transglottic, 161, 164f, 1475f, 1476, 1478f
CT for, 132f, 140
flexible endoscopy for, 814
advantages of, 814
disadvantages of, 814
for professional voice disorders, 851-852, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
with foreign bodies, 1480-1481, 1480f-1481f
high-speed digital, 821-823
applications of, 823
assessment using, 822-823
defined, 813
equipment for, 821
kymography in, 134f, 154, 822f
limitations of, 823
with inflammatory disease, 1464-1466
croup as, 1465, 1465f
epiglottitis as, 159-161, 163f, 1406-1407, 1407f, 1464, 1464f-1465f
retropharyngeal abscess as, 1465-1466, 1466f
with laryngomalacia, 1466
MRI for, 142-143
with normal airway, 1462-1464
anatomy of, 1462-1464, 1463f-1464f
technique for, 1462
rigid endoscopy for, 813-814
advantages of, 813
disadvantages of, 813-814
for professional voice disorders, 851, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
stroboscopy for, 818-821
of adynamic segments, 820
of amplitude of vibration, 820, 821f, 848, 848t
of closure pattern, 819, 820f, 848t, 849
common problems and solutions for, 815t-816t
defined, 813
flexible endoscopes in, 814
interpretation of, 848t
interval examination in, 847
of mucosal wave, 820, 848-849, 848t
in neurologic examination, 834
of periodicity, 821, 848, 848t
of phase closure, 819-820
for professional voice, 847-849, 848f, 848t
protocol for, 818-819, 818b
of regularity, 821
rigid endoscopes in, 813-814
of symmetry, 820, 847-848, 848t
of vertical closure level, 821
for vocal fold impairment, 905
with trauma, 159, 162f, 1479-1480, 1480f
videoendoscopy for, 814-818
of arytenoid and vocal fold motion, 816
common problems and solutions for, 815t-816t
defined, 813
flexible endoscopes for, 814
of laryngeal structure, 816
of mucous, 816-817
in neurologic examination, 834
protocol for, 814, 816b

Imaging *(Continued)*
rigid endoscopes for, 813-814
of supraglottic activity, 817, 817f
of vascularity, 817
of vocal fold edges, 818
with vocal cord paralysis, 1466-1467, 1467f
of lymph nodes, 164-167
anatomy and classification of, 163-164
with extracapsular spread, 164-166, 167f
inflammatory (reactive), 164
with invasion of carotid artery, 166-167
metastatic
contrast-enhanced CT of, 164-165, 167f
MRI of, 165-166, 168f
with non-Hodgkin's lymphoma, 165-166, 167f
normal anatomy in, 166f
of maxillofacial trauma, 325-326
of lower third, 325-326
of middle third, 325, 326f
of upper third, 325, 325f
of nasal fractures, 500
of nasopharyngeal carcinoma, 148, 149f
for staging, 1354
of neck masses, 1636-1637, 1637t
of neck neoplasms, 1656-1657
of nose, 167-171
with anatomic variations and congenital abnormalities, 167
for facial trauma, 170-171, 170f-171f
MRI for, 143
nasal cavity in, 169, 170f
ostiomeatal complex in, 168f-169f, 169
of oral cancer, 1300
of oropharyngeal cancer, 1366
of paranasal sinus tumors, 1124
of paranasal sinuses, 167-169, 662-2
with anatomic variations and congenital abnormalities, 668-670
aerated crista galli as, 670
asymmetry in ethmoid roof height as, 670
cephalocele as, 670, 671f
of concha bullosa, 668, 669f
extensive pneumatization of sphenoid sinus as, 669, 671f
giant ethmoid bullosa as, 669
Haller or infraorbital cells as, 668-669, 670f
medial deviation or dehiscence of lamina papyracea as, 669
nasal septal deviation as, 668, 669f
Onodi or sphenoethmoidal cells as, 669
paradoxic middle turbinate as, 668, 669f
of uncinate process, 668, 670f
with complications of inflammatory disease, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
conventional radiography of, 130, 662
Caldwell view in, 662, 663f
Waters view in, 662, 663f
CT for, 140-142, 141f, 662-663
radiation exposure with, 663
technique of, 662-663, 664f
after functional endoscopic sinus surgery, 677-680
expected findings in, 677-679, 679f
operative complications in, 679-680, 680f
for image-guided surgery, 680-681, 743-744, 745f
registration in, 680-681
tracking systems in, 681
interpretation of, 670-672
evaluation of bony outlines in, 672, 672f
evaluation of critical relationships for surgical planning in, 671-672, 672f
Imaging *(Continued)*
identification and description of important structures in, 671
MRI for, 664, 664f
nasal cycle in, 664, 664f
with normal anatomy, 664-668, 665f
agger nasi cell in, 665-666, 665f-666f
anterior ostiomeatal channels in, 666f
anterior ostiomeatal unit in, 664, 665f
basal lamella and sinus lateralis in, 665f, 667f
frontal recess in, 665, 665f-667f
frontal sinuses in, 664-665, 665f
hiatus semilunaris in, 667, 667f
inferior meatus in, 664
inferior turbinate in, 665f
infundibulum in, 665f, 666-667
maxillary sinuses in, 664, 665f
middle meatus in, 664-665, 665f-667f
middle turbinate in, 667
ostiomeatal channels in, 664
posterior ethmoid sinus in, 667
posterior ostiomeatal unit in, 664
primary ostium in, 665, 665f
retrobullar (suprabullar) recess in, 667
sphenoethmoidal recess in, 667, 668f
sphenoid sinus in, 664, 665f, 667-668, 668f
superior meatus in, 664-665
uncinate process in, 666-667, 666f-667f
ostiomeatal unit in, 664-670
with rhinosinusitis, 167-168, 168f, 672-675
acute, 672-673, 673f
allergic, 675
chronic, 673-674, 674f-675f, 743, 744t
fungal, 674-675, 676f
granulomatous, 675
with sinonasal small cell tumor *vs.* sphenoid pyomucocele, 168-169, 169f
of parathyroid glands, 162-163, 165f
CT for, 140
MRI for, 143
ultrasonography for, 1644-1645, 1650f-1652f
of pharynx and esophagus, 1393-1420
with benign neoplasms, 1415-1416
esophageal hematoma as, 1416
esophageal leiomyoma as, 1415-1416, 1415f
retention cyst as, 1416, 1416f
Tornwaldt cyst as, 1416, 1416f
vs. tortuous internal carotid artery, 1416, 1416f
with diverticula, 1401-1402
laryngoceles as, 1402, 1402f
midesophageal, 1402, 1403f
pharyngeal pouches as, 1401-1402, 1402f
Zenker's, 1401, 1402f
with esophageal narrowing, 1407-1409
due to extrinsic compression, 1408-1409, 1409f
due to strictures, 1407-1408, 1408f
due to webs, 1407, 1408f
with fistulas, 1409-1411
due to branchial cleft anomaly, 1410, 1410f
congenital, 1409-1410
due to perforation, 1410-1411, 1410f
postoperative, 1411, 1411f
tracheoesophageal, 1409-1410
with foreign body, 1411, 1412f
with infection/inflammation, 1403-1407
due to abscess, 1407, 1407f
due to alcohol-induced esophagitis, 1406
due to caustic esophagitis, 1404-1405, 1405f
due to drug-induced esophagitis, 1406, 1406f
due to eosinophilic esophagitis, 1406
due to epidermolysis bullosa, 1406, 1406f
due to graft-versus-host disease, 1406
due to granulomatous esophagitides, 1405
due to infectious esophagitis, 1404, 1405f
Imaging *(Continued)*
due to intramural pseudodiverticulosis, 1406, 1407f
due to pemphigoid, 1406
due to peptic esophagitis, 1406
due to radiation esophagitis, 1406
due to reflux esophagitis, 1403-1404, 1403f-1404f
with malignant neoplasms, 1412-1415
of esophagus, 1413-1414, 1414f
of hypopharynx, 1413, 1413f-1414f
with lymphadenopathy, 1414-1415, 1415f
of nasopharynx, 1412-1413, 1413f
of oropharynx, 1413, 1413f
with motility disorder(s), 1398-1401
abnormal deglutition as, 1398
due to connective tissue diseases, 1400-1401, 1401f
cricopharyngeal dysfunction as, 1398-1399, 1400f
diminished peristalsis as, 1399-1400, 1400f-1401f
esophageal spasm as, 1400-1401, 1401f
of esophagus, 1399-1401
of pharynx, 1398-1399
post-treatment, 1416-1418
after laryngectomy, 1416, 1417f
after laryngopharyngectomy, 1416-1418, 1418f
for monitoring and surveillance, 1418, 1419f-1420f
after radiotherapy, 1418, 1418f
radiographic anatomy in, 1397-1398
of esophagus, 1397-1398, 1400f
of pharynx, 1397, 1398f-1399f
technique(s) for, 1393-1397
computed tomography as, 1396
conventional radiography as, 1393, 1394f
fluoroscopy as, 1393-1394
magnetic resonance imaging as, 1396
modified barium swallow as, 1396
oral contrast agents in, 1396
other nuclear medicine as, 1397
PET-CT as, 1396-1397, 1397f
pharyngoesophagram as, 1394, 1394f-1395f
ultrasound as, 1396
with varices, 1411, 1411f
of postoperative neck and face, 173-174, 175f-176f
principle of interpretation of, 144
of salivary glands, 1143-1150, 1166-1168, 1180
with adenoid cystic carcinoma, 1146-1147, 1146f-1147f, 1180f
with AIDS-related parotid cysts, 1146, 1146f
in children, 2854-2855
CT for, 139, 1148, 1166, 1180
of AIDS-related parotid cysts, 1146f
of parotid lipoma, 1166, 1167f
of pleomorphic adenoma, 1144f, 1148
of sialadenitis, 1148
of sialolithiasis, 1144f, 1148, 1148f
of Sjögren's syndrome, 1148
of Warthin's tumor, 1146f
FDG-PET for, 1150, 1168
minor, 1145
MRI for, 142, 1145-1147, 1166, 1180
of adenoid cystic carcinoma, 1146-1147, 1146f-1147f, 1180f
of glomus tumor, 1169f
of mucoepidermoid carcinoma, 1146, 1147f, 1168f
of pleomorphic adenoma, 1148f, 1167f-1168f, 1180f
of ranula, 1146, 1147f
with mucoepidermoid carcinoma, 1146, 1147f
parotid, 1143-1144, 1145f
with pleomorphic adenomas, 1143

Imaging *(Continued)*
CT for, 1144f, 1148
MRI for, 1148f, 1167f-1168f, 1180f
ultrasound for, 1149, 1149f
with ranula, 1146, 1147f
scintigraphy for, 138, 1150
with sialadenitis, 1148
sialography for, 1149-1150
conventional, 139-140, 1149-1150, 1149f
CT, 139-140, 1145f, 1150, 1150f
MR, 1147
for salivary gland injury, 312
with sialolithiasis, 1143, 1144f, 1148, 1148f
sublingual, 1144-1145
submandibular, 1144
ultrasound for, 143, 1148-1149, 1149f, 1167
color Doppler, 1167-1168
with Warthin's tumor, 1146, 1146f
for sensorineural hearing loss, in adults, 2117
of site-specific lesions, 146-167
of skull base, 171, 1929-1930
with benign lesions, 171, 172f
CT for, 142, 171
prior to endoscopic sinus surgery, 764t
with fractures, 171
with inflammatory lesions, 171
with intracerebral neoplastic processes, 171, 174f
with meningiomas, 1929-1930, 1930f
with metastases, 171, 173f
MRI for, 143, 171
normal anatomy in, 171
with paragangliomas, 171, 174f, 1929, 1930f
of suprahyoid neck, 146-157
carotid space in, 150-151, 151f-152f
CT for, 139, 141f
masticator space in, 151-152
with adenoid cystic carcinoma, 155f
with angiofibroma, 152, 154f
with hemangioma and lymphangioma, 152, 153f
with infection, 151-152, 152f
normal anatomy on, 146f, 151-152
with pseudotumors, 152
with squamous cell carcinoma, 152, 154f
MRI for, 142
normal anatomy in, 146-157, 146f-147f
oral cavity in, 153-156
with abscess, 156f
with congenital lesions, 154-156
with non-Hodgkin's lymphoma, 157f
normal anatomy on, 146f, 153-156
with squamous cell carcinoma, 154, 156f
parapharyngeal space in, 131, 146f
parotid space in, 149-150, 150f-151f
pharyngeal mucosal space in, 148-149
with inflammatory lesions, 148, 148f
with non-Hodgkin's lymphoma, 148-149, 149f
normal anatomy on, 146f, 148-149
with squamous cell carcinoma, 148, 149f
with Thornwaldt cyst, 148
prevertebral space in, 146f, 153
retropharyngeal space in, 146f, 152f, 153, 155f
sublingual space in, 156
with abscess and cellulitis, 156, 157f
with congenital lesions, 156
normal anatomy in, 146f, 154, 156
with ranula, 156, 157f
with squamous cell carcinoma, 156
submandibular space in, 146f, 156-157, 158f
of temporal bone, 171-173, 1916
cerebellopontine angle in, 1926-1928, 1929t
with acoustic schwannoma, 1929t
with arachnoid cyst, 1928, 1929t
with epidermoid tumor, 1928, 1928f, 1929t
Imaging *(Continued)*
with lipoma, 1928, 1929t
with meningioma, 1928, 1928f, 1929t
cochlear nerve in, 1928-1929, 1929f
conventional radiography for, 131
CT for, 142
external auditory canal in, 172, 1917-1918
with benign neoplasms, 1918, 1918f-1919f
with cholesteatoma, 1917, 1918f
with congenital lesions, 1917, 1917f
with keratosis obturans, 1917, 1918f
with malignant neoplasms, 1918, 1919f
with postinflammatory medial canal fibrosis, 1917-1918, 1918f
with severe infections, 1917, 1917f
external ear in, 172
facial nerve in, 173, 1924-1926
with Bell's palsy, 1924, 1927f
with hemangioma, 1924-1926, 1927f
with meningioma, 175f
with neuroma, 1928
with schwannoma, 1924-1926, 1927f
inner ear in, 172-173, 1920-1922
with congenital anomalies, 172-173, 174f, 1920-1921, 1923f
with enlarged vestibular aqueduct, 1921, 1923f
with fenestral and cochlear otosclerosis (otospongiosis), 1921-1922, 1925f
with intravestibular schwannoma, 1921, 1924f
with labyrinthitis ossificans, 1921, 1925f
normal appearance of, 1920-1921, 1922f
with superior semicircular canal dehiscence, 1920-1921, 1922f
internal auditory canal in, 173, 1926-1928
with meningioma, 175f
with vestibular schwannoma, 173, 1928, 1928f
mastoid in, 1918-1920
middle ear in, 172, 1918-1920
with aberrant internal carotid artery, 1919-1920, 1921f-1922f
with cholesteatoma, 174f, 1918-1919
with glomus tympanicum, 1919-1920, 1921f
with transverse petrous fracture with osseous dislocation, 174f
MRI for, 143
petrous apex in, 1922-1924, 1924t
with asymmetric pneumatization, 1922-1923, 1924t, 1925f
with cholesteatoma, 1924t
with cholesterol granuloma, 1923, 1924t, 1925f-1926f
with malignant lesions, 1923-1924, 1926f
with mucocele, 1924t
with retained secretions, 1923, 1924t, 1925f
of thyroid gland, 161-162, 1757
CT for, 140
with follicular carcinoma, 161-162, 165f
lingual, 161-162, 165f
MRI for, 143
normal anatomy in, 161
scintigraphy for, 138, 1757-1758
with thyroglossal duct cyst, 161-162, 165f
ultrasonography for, 1644, 1645f-1647f, 1646b
of tracheal tumors, 1616, 1616f-1617f
of visceral space, 159-163
parathyroid glands in, 162-163, 165f
thyroid gland in, 161-162
CT for, 140
with follicular carcinoma, 161-162, 165f
lingual, 161-162, 165f
MRI for, 143
normal anatomy in, 161
scintigraphy for, 138
with thyroglossal duct cyst, 161-162, 165f
Imbalance, 2308-2310
Imbrication laryngoplasty, 1548, 1548f
IMF (intermaxillary fixation) screws, 330-331, 333f
Imipramine, for neuropathic pain, 245t
Imiquimod (Aldara), for aural papillomatosis, 1957
Imitrex (sumatriptan), for migraine, 2349
Immittance audiometry battery, for otosclerosis, 2030
Immittance testing
of eustachian tube function, 1874
for otitis media, 2762
Immune complex–mediated hypersensitivity reactions, 608-612
Immune reconstitution syndrome, 211-212
Immune response
cell-mediated, 602f
direct in vivo stimulation of antitumoral, 21
Immune restoration disease (IRD), 211-212
cryptococcal meningitis in, 224
Immune system, 597-623
adaptive, 209, 599-605
B cells in, 603
development of, 603
responses by, 603
basophils and mast cells in, 605
eosinophils in, 604
innate *vs.,* 597-598
monocytes and macrophages in, 604
natural killer cells in, 603-604
neutrophils in, 604
overview of, 597-598
platelets and erythrocytes in, 605
stem cells in, 599-600, 600f
T cells in, 600-603
development of, 600-601
effector, 601-603
priming of, 601
toll-like receptors and, 598
antigen presentation in, 606, 606f
humoral, 606-608
antibody-dependent cellular cytotoxicity in, 603-604, 606
B cell responses in, 603
T cell–dependent and T cell–independent, 606
chemokines in, 608, 611t-612t
complement system in, 607-608, 608f
cytokines in, 608, 609t-610t
immunoglobulins in, 606-607, 607f
innate, 209, 598-599
adaptive *vs.,* 597-598
antimicrobial peptides in, 598-599
cathelicidins as, 599
defensins as, 599
tissue distribution of, 599
overview of, 597-598
self and nonself in, 599
Toll-like receptors in, 598
activators of, 598
and adaptive immune response, 598
expression and distribution of, 598
and host, 598
lymphoid organs in, 605
lymph nodes as, 605
mucosal, 605
Peyer's patches and lymphoid follicles in, 605
tonsils in, 605
Immune tolerance, 1023
Immunocompromised patients. *See* Immunosuppression.
Immunodeficiency disorder(s)
acquired, 210, 210t
congenital, 209-210, 210t
nasal manifestations of, 660
otitis media in, 2764-2766

Immunodeficiency disorder(s) *(Continued)*
otologic manifestations of, 2114-2115
in AIDS, 2114-2115
primary of congenital, 2114
sensorineural hearing loss due to, 2123-2124
severe combined, 209-210
Immunoglobulin(s) (Igs)
in humoral immune response, 606-607
structure of, 606, 607f
Immunoglobulin A (IgA)
in humoral immune response, 607
in saliva, 1140
Immunoglobulin D (IgD), in humoral immune response, 607
Immunoglobulin E (IgE)
in allergic rhinitis, 614, 619
in humoral immune response, 607
in nonallergic rhinitis, 696
Immunoglobulin G (IgG), in humoral immune response, 607
Immunoglobulin M (IgM), in humoral immune response, 607
Immunoglobulin M (IgM) testing, for infant hearing impairment, 2723
Immunologic disorders, sudden sensorineural hearing loss due to, 2128
Immunology, and otitis media, 2764-2766
Immunopathology, 608-612
Immunosuppressants
oral sequelae of, 1247t-1248t, 1248
sensorineural hearing loss due to, 2124
topical, for eczematoid otitis externa, 1956-1957
Immunosuppression, 209-229
causes of, 209-210, 210t
and cervical lymphadenopathy, 218-219, 219t
and fungal rhinosinusitis, 660, 710t
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 220
treatment of, 221
for Graves' ophthalmopathy, 1811
and hearing loss, 2161-2162
in HIV-positive patients, 223-225
approach to, 224, 225t
due to cryptococcal meningitis, 223-224
due to otosyphilis, 224
in transplant recipients, 224-225
due to HIV/AIDS, 210-212
biology and immunology of, 210
and cutaneous neoplasms, 213t, 215
diagnosis and classification of, 210-212, 211t
and facial lipoatrophy, 227-228, 228f
and hearing loss, 223-225
approach to, 224, 225t
due to cryptococcal meningitis, 223-224
due to otosyphilis, 224
highly active antiretroviral therapy for, 211
and Hodgkin's lymphoma, 213t, 217
immune restoration disease in, 211-212
and Kaposi's sarcoma, 212-215, 213t
epidemiology and pathogenesis of, 212-213
presentation and diagnosis of, 213-214, 214f
treatment of, 214-215
and malignancy, 212-217, 213t
and neuropathies, 223-225
and non-Hodgkin's lymphoma, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
occupational exposure to, 212, 212t
and oral lesions, 225-227
aphthous ulcers as, 227, 227f
candidiasis as, 225, 226f
differential diagnosis of, 225t
fungal, 227
gingivitis and periodontal disease as, 227
hairy leukoplakia as, 225-226, 226f
due to herpes simplex virus, 226
Immunosuppression *(Continued)*
histoplasmosis as, 226-227
due to human papillomavirus, 227
otologic and neurotologic manifestations of, 221-223
malignant otitis externa as, 221-222
in middle ear, 222-223
due to *P. jiroveci* and *A. fumigatus,* 222-223
and salivary gland disease, 217-218
diffuse infiltrative lymphocytosis syndrome as, 218
parotid lesions as, 217-218, 218f
xerostomia as, 218
and sinonasal infection, 219-221
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
and squamous cell carcinoma, 213t, 215
and malignancy, 212-217, 213t
basal cell carcinoma as, 213t, 215, 284
cutaneous neoplasms as, 213t, 215
Hodgkin's lymphoma as, 213t, 217
Kaposi's sarcoma as, 212-215, 213t
epidemiology and pathogenesis of, 212-213
presentation and diagnosis of, 213-214, 214f
treatment of, 214-215
non-Hodgkin's lymphoma as, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
in posttransplantation lymphoproliferative disorder, 213t, 215, 217
squamous cell carcinoma as, 213t, 215
and malignant otitis externa, 221-222, 1947
and neuropathies, 223-225
and oral lesions, 225-227, 1252
aphthous ulcers as, 227, 227f
candidiasis as, 225, 226f
differential diagnosis of, 225t
fungal, 227
gingivitis and periodontal disease as, 227
hairy leukoplakia as, 225-226, 226f
due to herpes simplex virus, 226
histoplasmosis as, 226-227
due to human papillomavirus, 227
oral treatment considerations with, 1246t
otologic and neurotologic manifestations of, 221-223
malignant otitis externa as, 221-222
in middle ear, 222-223
due to *P. jiroveci* and *A. fumigatus,* 222-223
and salivary gland disease, 217-218
diffuse infiltrative lymphocytosis syndrome as, 218
parotid lesions as, 217-218, 218f
xerostomia as, 218
and sinonasal infection, 219-221, 660
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
and sinusitis, 660
spectrum of, 209-210, 210t
Immunotherapy
for allergic fungal rhinosinusitis, 714-715
for allergic rhinitis, 621-622
novel extracts in, 622
subcutaneous, 621
sublingual, 621-622
for head and neck squamous cell carcinoma, 1023-1024
for melanoma, 1118-1119
future investigations on, 1119
interferon in, 1118-1119
interleukin-2 and other cytokines in, 1119
Impact noise, 2121, 2140
Impedance, acoustic, 1839, 2000, 2017-2018
Impedance matching, 1839-1840, 2018
Impedance testing, for extraesophageal reflux, 900
Implant(s)
chin, 465-467
anesthesia for, 465
clinical example of, 470, 471f
complications after, 470
dissection planes for, 465-467, 467f
incision and approach for, 465-467, 467f
intraoral approach for, 467
subperiosteal *vs.* supraperiosteal placement of, 465-467, 467f
surgical procedure for, 465-467
types of, 465, 465t, 467
maxillary, in cleft-lip nose repair, 562f
nasal, for saddle nose deformity, 555, 556f-557f
Implantable adjuncts, to conventional hearing aids, 2204f, 2206t, 2217, 2217f
Implantable hearing aids, 2203-2218
as adjuncts to conventional hearing aids, 2204f, 2206t, 2217, 2217f
bone-conduction (osseointegrated), 2212-2216
background of, 2213
biology and histology of, 2213
biophysical principles of, 2213
comparison of features of, 2206t
complications of, 2215
components of, 2213f
design of, 2213
indications and contraindications for, 2212-2213, 2216t
in infants, 2723-2724
location of, 2204f
materials for, 2213
operative technique for, 2213-2215, 2214f
radiologic implications of, 2213
results of, 2215-2216, 2216t
sound transduction and coupling to auditory system with, 2205f
for unilateral sensorineural hearing loss, 2216
in young children, 2215
conventional (traditional) *vs.,* 2203-2207, 2204b, 2204f-2205f, 2206t
middle ear, 2207-2212
basic design features of, 2207-2208
ossicular coupling as, 2207-2208
transducer design as, 2207
electromagnetic, 2208-2211
Carina as, 2210-2211, 2210f-2211f
Middle Ear Transducer (MET) as, 2206t, 2210-2211, 2211f
sound transduction and coupling to auditory system with, 2205f
Vibrant Soundbridge as, 2206t, 2208-2210, 2208f-2209f
location of, 2204f
piezoelectric, 2211-2212
Esteem-Hearing Implant as, 2211-2212, 2212f
sound transduction and coupling to auditory system with, 2205f
total *vs.* partially, 2208
promise of, 2207
Implantable micropump system, for intratympanic delivery, 2183
Impressions, for prosthetic maxillary obturation, 1338-1339, 1338f
IMPT (intensity-modulated proton therapy), 1046
Impulsive noise, 2121, 2140
IMRT. *See* Intensity-modulated radiation therapy (IMRT).
IMT (inflammatory myofibroblastic tumor), of larynx, 1509-1510
In vivo gene therapy, 18-19, 19f
Incidence, 61
Incision planning, for neck surgery, 1726-1727
Incisive artery, 483

Incisive foramen
anatomy of, 1297f
and palate, 2659, 2660f
Incisura anterior, 1824f
Incisura tensoris, 1827f
Inclusion criteria, 68
Incomplete closure, laryngeal videostroboscopy of, 819
Incomplete partition, of cochlea, 2730-2731
embryogenesis of, 2728f-2729f, 2729t, 2730-2731
histology of, 2730-2731, 2731f
imaging of, 2730-2731, 2731f
relative incidence of, 2729t
subtypes of, 2730-2731, 2731f
Incudal artery, 1828f
Incudostapedial articulation, 1826
Incus
anatomy of, 1826
in auditory physiology, 1839-1840, 1840f
in cochlear transduction, 2062f
embryology of, 2583-2584
ossiculoplasty for absent lenticular process of, 2024, 2024f-2025f
in surgical anatomy of lateral skull base, 2436f
Incus bridge, with cochlear implant, 2238-2239, 2238f
Incus interposition, in ossiculoplasty, 2024-2025, 2024f
Incus-malleus articulation, in surgical anatomy of lateral skull base, 2436f, 2438
Incus-stapes articulation, in surgical anatomy of lateral skull base, 2436f
Independent samples, statistical tests for, 66, 67t
Inderal (propranolol)
for hyperthyroidism, 1739t
for migraine, 2349
for thyroid storm, 1745
Indirect laryngoscopy (IDL), for laryngeal carcinoma, 1494
Indium-111–labeled leukocyte scans, for malignant otitis externa, 1947
Individuals with Disabilities Education Act (IDEA), 2724
Indole-3-carbinol (I-3-C), for recurrent respiratory papillomatosis, 879, 2890t, 2892
Indomethacin
for hemicrania continua, 248
and skin flap viability, 1074
Induction chemotherapy, 1056-1058
clinical trials of, 1056-1058, 1058f, 1058t-1059t
in concomitant chemoradiation, 1041-1042, 1052-1053
with adjuvant therapy, 1056
defined, 1056
for hypopharyngeal cancer, 1443
for laryngeal carcinoma, 1501-1503, 1502f
Infancy
hemangioma of (*See* Hemangioma of infancy (HOI))
sternocleidomastoid tumors of, 2817, 2817f
Infant(s)
cochlear implants in, 2247, 2724
hearing aids in, 2274, 2723-2724
hearing loss in, 2718-2725
ancillary testing for, 2722-2723
genetic testing in, 2722-2723
laboratory testing in, 2722
screening for connexin 26 mutation in, 2723
screening for maternallyl transmitted infection in, 2723
temporal bone imaging in, 2723
testing for Pendred's syndrome in, 2723
assessment of, 2719-2721
auditory brainstem responses in, 2719-2720
comparison of otoacoustic emissions and auditory brainstem responses in, 2721
Infant(s) *(Continued)*
evoked otoacoustic emissions in, 2720-2721
testing protocols for, 2719, 2720f
delay in identification of, 2719
diagnosis of, 2721-2722
audiology in, 2722
history in, 2721
middle ear effusions in, 2722
otomicroscopy in, 2722
physical examination in, 2721-2722
vestibular function assessment in, 2722
visual reinforcement audiometry in, 2722
history of screening for, 2718-2719
intervention strategies for, 2723-2724
amplification devices as, 2274, 2723-2724
bone conduction amplification as, 2723
cochlear implantation as, 2247, 2724
early, 2724
surgical therapy as, 2723
and neural plasticity, 1885, 1885f
prevalence of, 2719
ideal electrolyte composition for, 2572t
laryngoscopy in, 2866, 2867f
lung volumes in, 2570
Infantile acute febrile mucocutaneous lymph node syndrome, facial paralysis in, 2400
Infected buccal bifurcation cysts, 1264-1265
Infection(s)
acute otitis media and otitis media with effusion due to, 2763-2764
bacterial
oral manifestations of, 1252
otitis media due to, 2763, 2764f
pediatric chronic sinusitis due to, 2779
of salivary glands, 1151-1153
ín children, 2851t, 2856-2857
after chemical peel, 397
deep neck space (*See* Deep neck space infections)
of external ear (*See* External ear infection(s))
hair loss due to, 376
of masticator space, 151-152, 152f
odontogenic (*See* Odontogenic infections)
after otoplasty, 479
of retropharyngeal space, 153, 155f
of salivary glands, 1151-1161
acute suppurative sialadenitis as, 1151-1153
clinical manifestations of, 1152, 1152f
complications of, 1153, 1154f
differential diagnosis of, 1152
epidemiology of, 1151
laboratory evaluation of, 1152
pathogenesis of, 1151-1152, 1152f
treatment of, 1152-1153, 1153f
bacterial, 1151-1153
chronic sialadenitis as, 1154, 1155f
granulomatous, 1158-1159
due to actinomycosis, 1159
due to cat scratch disease, 1159
nontuberculous mycobacterial, 1158-1159, 1158f
due to toxoplasmosis, 1159-1160
tuberculous mycobacterial, 1158
neonatal suppurative parotitis as, 1153
recurrent parotitis of childhood as, 1153-1154
sialolithiasis as, 1155-1156, 1155f-1156f
Sjögren's syndrome as, 1160-1161
ultrasound of, 1647
viral, 1156-1158
due to HIV, 1157-1158, 1157f
due to mumps, 1156-1157
after total laryngectomy, 1571
viral
of external ear, 1957, 1957f
topical therapies for, 1957, 1957f
of labyrinth
cytomegalovirus as, 2154-2156, 2155f
herpes simplex virus as, 2159-2160
Infection(s) *(Continued)*
Lassa fever as, 2158-2159
measles as, 2158
mumps as, 2157-2158, 2158f
rubella as, 2156-2157, 2157f
varicella-zoster virus as, 2159, 2159f
oral manifestations of, 1252
otitis media due to, 2764
and pediatric chronic sinusitis, 2778
and rhinosinusitis, 730-731
of salivary glands, 1156-1158
due to HIV, 1157-1158, 1157f
due to mumps, 1156-1157
sensorineural hearing loss due to, 2119, 2199
sudden, 2127
wound, after neck surgery, 1727
Infection control, for facial trauma, 305
Infectious arthritis, of temporomandibular joint, 1281-1282, 1281t
Infectious disease(s)
oral manifestations of, 1252
otologic manifestations of, 2100-2106
in Lyme disease, 2105-2106
in mycotic diseases, 2106, 2106f
otorrhea as, 2196
in syphilis, 2105, 2105f
in tuberculosis, 2101-2103, 2102f-2103f
sensorineural hearing loss due to, 2118-2119
sudden, 2127-2128
Infectious esophagitis, 976-977
due to *Candida albicans,* 976, 976f
imaging of, 1404, 1405f
due to cytomegalovirus, 976, 977f
due to herpes simplex virus, 976-977, 977f-978f
imaging of, 1404, 1405f
imaging of, 1404, 1405f
Infectious mononucleosis (IM)
adenotonsillar disease in, 2785-2786, 2786f
pharyngitis due to, 198-199, 198f
sudden sensorineural hearing loss due to, 2127
vestibular neuritis due to, 2162
Infectious rhinitis, 619b
Inference, 65
Inferior alveolar artery, 1296, 1359f
Inferior alveolar nerve, 1359f
Inferior alveolar vein, 1359f
Inferior anastomotic vein, 2489
Inferior anulus, of tympanic membrane, 1825-1826
Inferior arcuate line, of vocal folds, in mucosal wave propagation, 848-849
Inferior canaliculus, of lacrimal apparatus, 798f
Inferior cervical sympathetic ganglion, in root of neck, 2582
Inferior colliculus
in central auditory pathway, 1835f, 1836, 1846
tonotopic map reorganization in, 1878, 1879f, 1880
Inferior concha, 1359f
Inferior crus, of ear, 476f, 2742f
Inferior deep jugular lymph nodes, 1360f
Inferior hypophyseal arteries, in surgical anatomy of anterior cranial base, 2473f
Inferior incisive muscle, 321f
Inferior medial maxillectomy, 1125, 1125f
Inferior nasal meatus
normal anatomy of, 664
in surgical anatomy of anterior cranial base, 2472, 2472f
Inferior oblique muscles, 443f
in lower eyelid blepharoplasty, 448-449, 450f
semicircular canal planes and, 2287, 2288f
in surgical anatomy of lateral skull base, 2439f
Inferior orbital fissure, 322f
in surgical anatomy of anterior cranial base, 2443-2444, 2444f
in surgical anatomy of lateral skull base, 2441
in surgical anatomy of middle cranial base, 2445f

Inferior orbital rims, 319
Inferior petrosal sinus, in surgical anatomy of lateral skull base, 2489
Inferior punctum, of lacrimal apparatus, 798f
Inferior rectus muscles, 443f
  semicircular canal planes and, 2287, 2288f
Inferior tarsal muscle, 444
Inferior thyroid artery
  anatomy of, 1751, 1752f
  and parathyroid glands, 1778
  in root of neck, 2581-2582, 2581f
Inferior turbinate
  normal anatomy of, 665f, 1124f
  in surgical anatomy of anterior cranial base, 2472, 2472f-2473f
Inferior tympanic artery, 1828f
Inferior vestibular ganglion, 1854f, 2278f
Inferior vestibular nerve, in surgical anatomy of lateral skull base, 2437f, 2439
Inferior vestibular nucleus, 1861, 1862f
Inflammation
  in acutely raised skin flaps, 1070
  and rhinosinusitis, 731, 731f
  and skin flap viability, 1074
Inflammatory bowel disease, oral manifestations of, 1254
Inflammatory collateral cyst, 1263, 1263f
Inflammatory condition(s)
  of esophagus (*See* Esophagitis)
  of larynx, 1464-1466
    croup as, 1465, 1465f
    epiglottitis as, 159-161, 163f, 1464, 1464f-1465f
    laryngeal stenosis due to, 2915
    retropharyngeal abscess as, 1465-1466, 1466f
  of oral cavity, 1288-1290
    amyloidosis as, 1289-1290, 1290f
    fibroma as, 1288-1289, 1289f
    mucosal ulcerations as, 1289, 1289f
    necrotizing sialometaplasia as, 1289, 1299
    pyogenic granuloma as, 1289, 1289f
  of salivary glands, 1151-1161
    acute suppurative sialadenitis as, 1151-1153
      in children, 2856, 2856t
      clinical manifestations of, 1152, 1152f
      complications of, 1153, 1154f
      differential diagnosis of, 1152
      epidemiology of, 1151
      laboratory evaluation of, 1152
      pathogenesis of, 1151-1152, 1152f
      treatment of, 1152-1153, 1153f
    bacterial infections as, 1151-1153
      in children, 2856-2857, 2856t
    in children, 2855-2858
      abscess as, 2856
      due to actinomycosis, 2858
      acute suppurative sialadenitis as, 2856, 2856t
      bacterial, 2856-2857, 2856t
      chronic sialadenitis as, 2858
      diagnostic algorithm for, 2853, 2854f
      differential diagnosis of, 2851t
      due to Epstein-Barr virus, 2855
      granulomatous, 2857-2858, 2857f
      due to HIV, 2856
      due to mumps, 2855
      mycobacterial, 2857-2858, 2857f
      neonatal, 2857
      recurrent, 2856-2857
      sarcoidosis as, 2858
      viral, 2855
    chronic sialadenitis as, 1154, 1155f
      in children, 2858
    granulomatous infections as, 1158-1159
      due to actinomycosis, 1159
      due to cat scratch disease, 1159
      in children, 2857-2858, 2857f
Inflammatory condition(s) *(Continued)*
      due to nontuberculous mycobacterial disease, 1158-1159, 1158f
      due to toxoplasmosis, 1159-1160
      due to tuberculous mycobacterial disease, 1158
    neonatal suppurative parotitis as, 1153
    noninfectious, 1160-1161
    recurrent parotitis of childhood as, 1153-1154
    sialolithiasis as, 1155-1156, 1155f-1156f
    viral infections as, 1156-1158
      in children, 2855
      due to Epstein-Barr virus, 2855
      due to HIV, 1157-1158, 1157f, 2856
      due to mumps, 1156-1157, 2855
Inflammatory lymph nodes, 164
Inflammatory myofibroblastic tumor (IMT), of larynx, 1509-1510
Inflammatory neck masses, 1638
  due to granulomatous diseases, 1638
  due to lymphadenopathy/lymphadenitis, 1638
  due to sialadenitis/sialolithiasis, 1638
Inflammatory phase, of wound healing, 1076
Influenza vaccine, 197
  to prevent otitis media, 2769
Influenzavirus, pharyngitis due to, 196-197
Informed consent, 102
Infracochlear approach, for skull base lesions requiring drainage, 2539, 2540f
Infra-frequency sounds, adverse effects of, 2149
Infrahyoid muscles, characteristics of, 918-919
Infrahyoid neck, imaging of, 157-159
  anterior and posterior cervical (lateral cervical) spaces in, 158, 159f-160f, 162f
  CT for, 140
  hypopharyngeal mucosal space in, 158-159
    with lesions, 159, 162f
    normal anatomy in, 158-159, 159f-160f
  MRI for, 142-143
  normal anatomy in, 157-159, 159f-160f
  prevertebral space in, 158, 159f-160f, 162f
  retropharyngeal space in, 158
    with lesions, 158, 161f
    normal anatomy in, 158, 159f-160f
  ultrasound for, 143-144
Infrahyoid prevertebral space, imaging of, 158, 159f-160f, 162f
Infrahyoid retropharyngeal space, imaging of, 158, 159f-161f
Infralabyrinthine approach, for skull base lesions requiring drainage, 2539, 2540f
Infraorbital cells, 668-669, 670f
Infraorbital fissure, 1124f
Infraorbital foramen, 439-440, 1124f
Infraorbital groove, 322f
Infraorbital lymph node, 1360f
Infraorbital nerve, 320, 321f, 497, 497f
Infraorbital nerve block, 242
Infraorbital neurovascular bundle, 439-440
Infraorbital rims, surgical access to, 329
Infraparotid node, 1297f
Infrared video, for recording eye movements, 2317
Infratemporal access, for transnasal endoscopic-assisted anterior skull base surgery, 2483
Infratemporal fossa
  in surgical anatomy of lateral skull base, 2440-2441, 2440f
  in surgical anatomy of middle cranial base, 2444
Infratemporal fossa approaches, 2495-2501
  for middle skull base surgery, 2461-2464, 2464f
  postauricular, 2495-2500
    cervical dissection in, 2495, 2498f
    closure of external auditory canal in, 2495, 2497f
    extratemporal facial nerve dissection in, 2495-2496
    incisions and skins flaps in, 2495, 2497f
Infratemporal fossa approaches *(Continued)*
    radical mastoidectomy in, 2496, 2498f
    removal of external auditory canal wall skin and tympanic membrane in, 2495, 2497f
    type A, 2497-2499
      closure of wound in, 2499, 2499f
      exposure of jugular bulb and internal carotid artery in, 2498, 2498f-2499f
      facial nerve transposition in, 2497-2498, 2498f
      occlusion of sigmoid sinus in, 2498, 2498f
      tumor removal in, 2498-2499, 2499f
    type B, 2499-2500, 2500f
    type C, 2500, 2501f
  preauricular, 2500-2501, 2501f
Infratemporal fossa dissection, in subtotal or total temporal bone resection, 2494
Infratip lobule, 509f
Infratrochlear nerve, 321f, 497, 497f
Infundibular cells, 740
Infundibulum, 665f, 666-667
Ingals, E. F., 488
Ingestive sequence, 1206, 1206f
Inhalational agents, in children
  for anesthesia induction, 2590
  for anesthesia maintenance, 2591
Inheritance, 4
Inheritance patterns, 2088-2089, 2088f
  autosomal dominant, 2088, 2088f
  autosomal recessive, 2088-2089
  mitochondrial, 2089
  molecular basis of, 4
  Punnett squares for, 2088, 2089f
  X-linked, 2089
Inherited disorders
  gene therapy for, 20
  oral manifestations of, 1257
Inhibitory cutoff, of vestibular hair cells, 2290-2291
Inion, 320f
Injectable filler, with blepharoplasty, 451
Ink4D, in murine deafness, 2058t-2060t
Innate immune system, 209, 598-599
  adaptive *vs.,* 597-598
  antimicrobial peptides in, 598-599
    cathelicidins as, 599
    defensins as, 599
    tissue distribution of, 599
  overview of, 597-598
  self and nonself in, 599
  toll-like receptors in, 598
    activators of, 598
    and adaptive immune response, 598
    expression and distribution of, 598
    and host, 598
Inner border cells, 1833f
Inner ear
  anatomy of, 1825f, 1831-1834
    hair cells in, 1832-1834, 1833f
    innervation in, 1834, 1834f
    membranous labyrinth and inner ear fluids in, 1831-1832, 1832f
    osteology in, 1831, 1832f
  in auditory physiology, 1840-1844
    basilar membrane in, 1840-1842, 1841f-1842f
    cochlea in, 1841f-1842f
    cochlear partition in, 1840-1842, 1842f
    endocochlear potential in, 1840, 1841f-1842f
    endolymph in, 1841f-1842f
    hair cells in
      inner, 1841f, 1842, 1844f
      outer, 1841f, 1844, 1844f
      stereocilia of, 1841f, 1842, 1843f
      tip links of, 1841f, 1842, 1843f
      tonotopic tuning of, 1844, 1844f
    organ of Corti in, 1841f
    perilymph in, 1841f-1842f
    Reissner's membrane in, 1841f

Inner ear *(Continued)*
scala media in, 1840, 1841f-1842f
scala tympani in, 1841f-1842f
scala vestibuli in, 1841f-1842f
spiral ligament in, 1841f
spiral limbus in, 1841f
stapes footplate in, 1840, 1842f
stria vascularis in, 1840, 1841f
tectorial membrane in, 1841f
"third window" in, 1842, 1843f
congenital malformations of, 2726-2740
classification of, 2726-2727, 2727b
cochlear, 2729-2732
cochlear agenesis as, 2729f
cochlear aplasia as, 2728f, 2729-2730, 2729t
cochlear aqueduct enlargement as, 2734, 2734f
cochlear hyperplasia as, 2732
cochlear hypoplasia as, 2728f-2730f, 2729t, 2730
cochlear implantation for, 2739
in combination with other anomalies, 2728, 2738, 2739f
common cavity as, 2728f-2729f, 2729t, 2731-2732
embryogenesis of, 2728-2735, 2728f-2729f
incomplete partition as, 2728f-2729f, 2729t, 2730-2731, 2731f
relative incidence of, 2729t
complete labyrinthine aplasia as, 2729, 2729f-2730f, 2729t
in congenital aural atresia, 2738
CSF leakage and meningitis due to, 2735-2737, 2736f
of eighth nerve, 2735
evaluation and management of, 2738-2739, 2739f
imaging of, 172-173, 174f, 1920-1921, 1923f, 2738
incidence of, 2727
of internal auditory canal, 2735
narrow, 2735, 2735f
wide, 2735, 2735f
labyrinthine, 2732-2733
in combination with other anomalies, 2728, 2738, 2739f
incidence of, 2727
limited to membranous labyrinth, 2727-2728, 2727b
of membranous and osseous labyrinth, 2727b, 2728-2735
membranous labyrinthine dysplasia as, 2727-2728
semicircular canal aplasia as, 2732-2733, 2732f
semicircular canal dysplasia as, 2732, 2732f-2733f
pathogenesis of, 2726
perilymphatic fistula as, 2737-2738, 2737f
sensorineural hearing loss due to, 2200
syndrome correlations and familial patterns of, 2735
vestibular aqueduct enlargement as, 2727, 2733-2734, 2733f
X-linked stapes gusher syndrome as, 2737
growth and development of, 2617t, 2726
imaging of, 172-173, 1920-1922
with congenital anomalies, 172-173, 174f, 1920-1921, 1923f
with enlarged vestibular aqueduct, 1921, 1923f
with fenestral and cochlear otosclerosis (otospongiosis), 1921-1922, 1925f
with intravestibular schwannoma, 1921, 1924f
with labyrinthitis ossificans, 1921, 1925f
normal appearance of, 1920-1921, 1922f
with superior semicircular canal dehiscence, 1920-1921, 1922f
Inner ear conductive presbycusis, 232
Inner ear decompression sickness (IEDS), 2343
Inner ear disease
autoimmune, 2164-2168
clinical presentation of, 2165-2166
defined, 2164
diagnosis of, 2166, 2167t
differential diagnosis of, 2166
epidemiology of, 2165
future directions for, 2167-2168
pathology and pathogenesis of, 2165
animal studies of, 2165
human temporal bone studies of, 2165
sensorineural hearing loss due to, 2124, 2165
treatment of, 2166-2167
gene therapy for, 2191-2192
delivery of, 2191
preclinical applications of, 2192
safety concerns with, 2192
vectors for, 2191, 2191t
intratympanic delivery of medications for (*See* Intratympanic delivery)
systemic steroids for, 2184
Inner ear fluids, 1831-1832, 1832f
Inner hair cells (IHCs)
anatomy of, 1832-1834, 1833f
in organ of Corti, 1832, 1832f, 1840
arrangement of, 2071, 2072f
in auditory physiology, 1841f, 1842, 1844f
in cochlear transduction, 2061f-2062f, 2066-2067
length of, 2070, 2070f
number and density of, 2070
receptor potentials for, 2071, 2072f
scanning electron micrograph of, 1833f
stereocilia on, 2070f, 2071, 2072f
transduction channels in, 2073f
Inner pillar head plate, 1833f
Inner spiral sulcus, 1832, 1832f
Innominate artery compression, of trachea, 2925-2926
Inorganic iodine
for Graves' disease, 1742-1743
for thyroid storm, 1745
Inosculation, in acutely raised skin flaps, 1069, 1069f
Inositol triphosphate (IP_3)
in olfactory transduction, 629
in salivary gland secretion, 1137-1138
"I-notch," in nasal breathing assessment, 644
INS(s) (intranasal steroids), for allergic rhinitis, 621
Insertion loss, with hearing aids, 2270
Inside-out approach, for pediatric facial fracture repair, 2706f
Insomnia, 262-263, 263b
in children, 263
paradoxical, 263
primary (idiopathic), 262t, 263
psychophysiological, 262t, 263
tinnitus and, 2138
Inspiratory resistance, in rhinomanometry, 650-651
Institute for Healthcare Improvement (IHI), 84t-87t
Institute of Medicine (IOM), 81-82, 84t-87t
Insular thyroid carcinoma, 1764
Insular-opercular region, in gustatory pathway, 1212-1213
Insulin growth factors I and II, for facial nerve paralysis, 2427
Insulin release, cephalic phase, 1206
Insulin-like growth factor-I (IGF-I), in wound healing, 1076
Integrase inhibitors, 211
Integrative genomics, in head and neck squamous cell carcinoma, 1025
Integrin(s), in wound healing, 1077
Integrin α8β1 *(Itga8)* gene, in murine deafness, 2058t-2060t
Intense pulse light laser, for facial resurfacing, 403t
Intensity
in acoustic analysis for voice evaluation, 829, 829t
of sound, 1839
Intensity-modulated proton therapy (IMPT), 1046
Intensity-modulated radiation therapy (IMRT), 1043-1046, 1044f
advantages of, 1043
for cervical metastases, 1691-1692, 1692f
clinical results of, 1045-1046, 1045f
complications of, 1700
defining target in, 1044
dental management after, 1335-1337, 1336f-1337f
forward-planning, 1696-1697
for glottic cancer, 1585-1586
inverse-planning, 1043, 1696-1697
for nasopharyngeal carcinoma, 1045, 1699-1700, 1699f, 1700t
number and directions of beams in, 1045
selection and outlining of targets in, 1044-1045, 1045f
for skull base tumors, 1696-1697
and xerostomia, 1103
Interarytenoid adhesion, 2915, 2915f-2916f
Interarytenoid muscle
applied anatomy of, 806
in professional voice production, 846-847
Interarytenoid web, 2869, 2869f
Interaural attenuation, in audiologic testing, 1889
Intercalated duct, of salivary gland, 1134, 1134f, 1162, 1163f
Intercanthal distances
in aesthetic analysis, 271
in evaluation of maxillofacial trauma, 324, 324f
with nasal fracture, 498
normal, 442
Intercanthal line, 496, 497f
Intercellular secretory canaliculi, of salivary gland, 1134f
Interdental discrimination, 1207
Interdomal ligament, 496-497
Interfascicular nerve repair, 2422-2424
Interferon(s) (IFNs), 609t-610t
for hemangioma of infancy, 2826-2828
for recurrent respiratory papillomatosis, 879, 2890t, 2891-2892
for rhinosinusitis, 734t
Interferon-α (IFN-α), 609t-610t
for recurrent respiratory papillomatosis, 879, 2890t, 2891-2892
thyrotoxicosis due to, 1744
Interferon-α-2b (IFN-α-2β), for melanoma, 1118-1119
Interferon-β (IFN-β), 609t-610t
Interferon-γ (IFN-γ), 609t-610t
Intergroup Rhabdomyosarcoma Study Clinical Grouping Classification (IRSCGC), 2841, 2841t
Interior carotid artery, 2351f
Interleukin(s) (ILs), 609t-610t
in allergic rhinitis, 615
Interleukin-1α (IL-1α), 609t-610t
Interleukin-1β (IL-1β), 609t-610t
Interleukin-2 (IL-2), 609t-610t
in gene therapy, 20-21
for head and neck squamous cell carcinoma, 1023-1024
for melanoma, 1119
Interleukin-3 (IL-3), 609t-610t
Interleukin-4 (IL-4), 609t-610t
Interleukin-5 (IL-5), 609t-610t
Interleukin-6 (IL-6), 609t-610t
Interleukin-7 (IL-7), 609t-610t

Interleukin-8 (IL-8), 609t-610t
in wound healing, 1076
Interleukin-9 (IL-9), 609t-610t
Interleukin-10 (IL-10), 609t-610t
Interleukin-11 (IL-11), 609t-610t
Interleukin-12 (IL-12), 609t-610t
for head and neck squamous cell carcinoma, 1023-1024
Interleukin-13 (IL-13), 609t-610t
Interleukin-14 (IL-14), 609t-610t
Interleukin-15 (IL-15), 609t-610t
Interleukin-16 (IL-16), 609t-610t
Interleukin-17 (IL-17), 609t-610t
Interleukin-18 (IL-18), 609t-610t
Interleukin-19 (IL-19), 609t-610t
Interleukin-20 (IL-20), 609t-610t
Interleukin-21 (IL-21), 609t-610t
Interleukin-22 (IL-22), 609t-610t
Interleukin-23 (IL-23), 609t-610t
Interleukin-24 (IL-24), 609t-610t
Interleukin-25 (IL-25), 609t-610t
Interleukin-26 (IL-26), 609t-610t
Interleukin-27 (IL-27), 609t-610t
Interleukin-28 (IL-28), 609t-610t
Interleukin-29 (IL-29), 609t-610t
Intermaxillary fixation (IMF) screws, 330-331, 333f
Intermaxillary segment, in embryology of palate, 2660-2661, 2662f
Intermaxillary suture, 320f
Intermediate acoustic stria
anatomy of, 1835, 1835f
in auditory pathway, 1846
Intermediate crus, of nose, 496-497, 497f
Intermittent allergic rhinitis (IAR), 618
Intermittent apnea-reintubation anesthesia, with recurrent respiratory papillomatosis, 2891
Internal acoustic meatus, 2010f
Internal acoustic pore, in surgical anatomy of lateral skull base, 2437-2438
Internal auditory artery
anatomy of, 1826f, 1854, 2351f
in surgical anatomy of lateral skull base, 2437f, 2439f
Internal auditory canal (IAC)
anatomy of, 1823f
developmental anomalies of, 2735
and CSF leakage, 2735-2736, 2736f
narrow, 2735, 2735f
wide, 2735, 2735f
imaging of, 173, 1926-1928
with meningioma, 175f
with vestibular schwannoma, 173, 1928, 1928f
lipoma of, 2527, 2529f
narrow, 2735, 2735f
in surgical anatomy of lateral skull base, 2435f-2437f, 2438-2439
wide, 2735, 2735f
Internal auditory meatus, in surgical anatomy of middle cranial base, 2445f
Internal carotid artery (ICA)
aberrant, 1919-1920, 1921f-1922f
anatomy of, 1359f, 2579, 2580f
radiographic, 1471f, 1473-1474
aneurysms of upper cervical and petrous, 2504, 2504f-2505f
in extended neck dissection, 1719-1721, 1720f
injury to, 1632, 1633f
due to carotid paraganglioma surgery, 1661
paranasal sinuses and, 671-672
in postauricular approach to infratemporal fossa, 2498, 2498f-2499f
preoperative embolization of, 2446
preoperative management of, 2445-2446, 2446f, 2489
Internal carotid artery (ICA) *(Continued)*
algorithm for, 2490f, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
four-vessel arteriography in, 2489-2490, 2491f
in surgical anatomy of anterior cranial base, 2442-2443, 2472f-2473f, 2474, 2475f
in surgical anatomy of lateral skull base, 2436f-2437f, 2439f-2440f, 2489
in surgical anatomy of middle cranial base, 2444
tortuous, 1416, 1416f
Internal consistency, 55
Internal fixation, and facial growth, 2625-2626
Internal jugular vein (IJV)
anatomy of, 1359f, 2579f
radiographic, 1471f
in modified radical neck dissection, 1713f-1714f
in neck surgery, 1728-1729, 1729f
Internal jugular vein (IJV) hemorrhage, due to neck surgery, 1729, 1729f
Internal jugular vein (IJV) thrombosis, due to neck surgery, 1728-1729
Internal maxillary artery
anatomy of, 682
in surgical anatomy of lateral skull base, 2440f
Internal plexiform layer, of olfactory bulb, 628f
Internal pterygoid muscle, 1359f
Internal receiver stimulators and electrode designs, for cochlear implants, 2227-2229
HiRes 90K receiver/stimulator as, 2227-2228, 2228f
Med-El PulsarCI100 and SonataTI100 as, 2228-2229, 2228f-2230f
ear-level speech processors for, 2232f
Nucleus Freedom device with Contour Advance electrode as, 2227, 2227f-2228f
external speech processors for, 2232f
Internal thoracic artery, in root of neck, 2581-2582
Internal validity, 68-69, 68t, 69f
Internal valve compromise, nasal obstruction due to, 492, 493f
Internasal suture, 320f
International Classification of Functioning (ICF), 56
International Prognostic Index (IPI), for non-Hodgkin's lymphoma, 216
Interneurons, in neural plasticity, 1884
Interobserver reliability, 55
Interosseous fold, 1827f
Interpeak latencies, in auditory brainstem response, 1897
Interpolated flaps, 344-345, 344f
for nasal defects, 347-348
Interpupillary distances, in evaluation of maxillofacial trauma, 324, 324f
Interquartile range, 64t
Interrupted strip technique, for nasal tip refinement, 522, 532f-533f
Intersphenoid synchondrosis, 2619f
Interstereociliary linkages, 2076f, 2077-2078
Interstitial pressure, of skin flaps, 1068, 1069f
Interstitial system, and skin flaps, 1065-1066, 1065f
Intertragal incisure, 477
Intertragal notch, 2742f
Interval examination, in laryngeal stroboscopy, 847
Interventional neuroradiology, 1932-1943
for lesions of vascular etiology, 1939-1943
dural arteriovenous fistulas as, 1940-1942, 1941f
epistaxis as, 1939-1940, 1940f
facial arteriovenous fistulas as, 1940, 1940f
facial vascular malformations as, 1942, 1942f
hemangiomas of face and neck as, 1942
pseudoaneurysms as, 1942, 1943f
tinnitus-producing fibromuscular dysplasia of carotid artery as, 1943
Interventional neuroradiology *(Continued)*
materials and techniques for, 1932-1934
angiographic catheters as, 1932-1933
angiographic equipment as, 1932
embolic agents as, 1933-1934
provocative testing to ensure safety of embolization as, 1934, 1934f
for neoplasms, 1934-1939
inter-arterial chemotherapy as, 1939
juvenile angiofibroma as, 1937-1938, 1938f
meningiomas as, 1938, 1939f
paragangliomas as, 1934-1937, 1935f
carotid body tumor as, 1937, 1937f
glomus jugulare tumor as, 1935-1936, 1935f-1936f
glomus tympanicum tumor as, 1935
glomus vagale tumor as, 1936-1937, 1936f
thyroid, 1938-1939
Interventional techniques, for chronic pain, 245-246, 246t
In-the-canal (ITC) hearing aid, 2270, 2270f
In-the-ear (ITE) hearing aids, 2270, 2270f
in infants, 2723-2724
selection of, 2266-2267, 2270
Intra-arterial chemotherapy, 1939
Intra-articular disk, anterior displacement of
with reduction, 1280, 1282f
without reduction, 1279-1280, 1282f
Intra-axial tumor(s), 2528-2529
brainstem gliomas as, 2528
hemangioblastomas as, 2528
malignant choroid plexus papillomas and ependymomas of fourth ventricle as, 2528-2529, 2530f-2531f
medulloblastomas as, 2528
Intracapsular disorders, of temporomandibular joint, 1280-1282, 1281t
ankylosis as, 1281t, 1282
anterior disk displacement as
with reduction, 1280, 1282f
without reduction, 1279-1280, 1282f
degenerative joint disease as, 1281-1282, 1281t
Intracapsular subtotal tonsillectomy, for obstructive sleep apnea, 2609
Intracellular pH, in sour taste, 1209
Intracellular space, 1066-1067
Intracerebral injury, due to sphenoidotomy, 768t
Intracochlear membrane rupture, sudden sensorineural hearing loss due to, 2128
Intracordal cysts, 869-870
diagnosis of, 869
history in, 869
laryngeal examination in, 869
vocal capability battery in, 869
epidemiology of, 869
epidermoid inclusion, 868f-869f, 869
mucus retention (ductal), 869, 869f-870f
open, 869, 870f
pathophysiology and pathology of, 869
treatment of, 869-870
behavioral, 869-870
medical, 869
surgical, 870, 870f
Intracordal injection, for vocal fold paralysis, 907, 907f
Intracranial approach, for middle cranial base surgery, 2467
Intracranial complications
of endoscopic sinus surgery, 755, 755f
of otitic infections, 2347
Intracranial hypertension, benign (idiopathic)
CSF rhinorrhea due to, 787
facial paralysis due to, 2400-2401
sensorineural hearing loss due to, 2123
Intracranial paraganglioma, 2499f
Intracranial pressure (ICP), and CSF rhinorrhea, 786-787, 786b

Intracranial sources, of otorrhea, 2195b, 2197
Intradermal nevus, 286, 287f
IntraEar Microcatheter, 2182-2183, 2183f
Intraepithelial lymphocytes, in immune system, 605
Intraglandular parotid lymph node, 1360f
Intralabyrinthine shunt, for Meniere's disease, 2126
Intralesional corticosteroids, for scar revision, 299-300, 301f
Intralymphatic metastasis, of melanoma, 1112
Intramembranous bone formation, 2614
Intramuscular induction, of pediatric anesthesia, 2591
Intranasal dimensions, tests that assess, 643, 643f
Intranasal ethmoidectomy, 756-757
Intranasal hemangiomas, 2695
Intranasal steroids (INSs), for allergic rhinitis, 621
In-transit metastasis (ITM), of melanoma, 1110, 1117
Intraocular pressure, increased, in Graves' ophthalmopathy, 1808
Intraoperative cranial nerve monitoring, 2542-2556
  anesthesia and, 2544
  auditory brainstem response recording for, 2552-2554
    interpretation of, 2553-2554, 2553f
    and postoperative auditory function, 2553-2554
    reducing electrical and acoustic interference in, 2552-2553
    stimulus and recording parameters, electrodes, and placement in, 2552
  of cochlear nerve, 2552
    direct eighth nerve action potentials for, 2554
      detection and interpretation of changes in, 2554
      placement of electrodes in, 2554
      stimulus and recording parameters in, 2554
  electrodes for
    recording, 2543-2544, 2543f
    stimulating, 2544, 2544f
  of facial nerve, 2545-2549
    with acoustic neuroma and other cerebellopontine angle tumors, 2545
    activity evoked by electrical stimulation in, 2545-2546
    for assessment of functional status after tumor removal, 2545-2546
    electromyography for, 2545-2548
    for intraoperative identification of nervus intermedius, 2546, 2546f
    limitations of, 2547-2548, 2548f
    during microvascular decompression, 2548-2549, 2549f
    during other otologic surgery, 2549
    during parotid surgery, 2549
    spontaneous and mechanically evoked activity in, 2546-2548, 2547f
  future directions in, 2555-2556, 2555f
  instrumentation for, 2543
  ninth, tenth, eleventh, and twelfth, 2550-2552, 2551f-2552f
  and outcome, 2554-2555
    for cochlear nerve preservation, 2554-2555
    for facial and other motor cranial nerve preservation, 2554
  personnel for, 2542-2543
  stimulation criteria for, 2544
  third, fourth, and sixth, 2549-2550, 2550f
  of trigeminal motor branch, 2550
Intraoral positioning devices, for radiation therapy, 1331, 1333f
Intratemporal facial nerve surgery, 2403-2415
  combination approaches for, 2411-2412
  draping for, 2404-2405, 2405f
  for facial nerve tumors, 2413-2414, 2414t
  general surgical techniques for, 2404-2405
  instrumentation for, 2405
  intraoperative monitoring for, 2405, 2405f
Intratemporal facial nerve surgery *(Continued)*
  middle cranial fossa (transtemporal) approach for, 2407-2409
    advantages and uses of, 2408-2409
    for Bell's palsy, 2409-2410, 2409t-2410t
    limitations and potential complications of, 2409
    technique of, 2407-2408, 2408f-2409f
  nerve repair in, 2413-2414
  rerouting in, 2412, 2412f-2413f
    partial, 2412-2413
  retrolabyrinthine approach for, 2405-2406, 2405f-2406f
  retrosigmoid approach for, 2406-2407
    advantages and uses of, 2406-2407
    limitations and potential complications of, 2407
    technique of, 2406, 2407f
  surgical anatomy for, 2403-2404, 2404f
  translabyrinthine approach for, 2411
    advantages and uses of, 2411
    limitations and complications of, 2411
    technique of, 2411, 2411f-2412f
  transmastoid approach for, 2410-2411
    advantages and uses of, 2411
    limitations and complications of, 2411
    technique of, 2410, 2410f
Intratemporal fossa approaches, for middle cranial base surgery, 2455t
Intrathecal fluorescein, for CSF rhinorrhea, 790, 2044
Intratympanic delivery
  of gentamicin, 2185-2189
    clinical protocols for, 2187-2188
    complications of, 2188-2189
    concentration of, 2188
    dose of, 2188
    indications and contraindications for, 2189
    injection interval for, 2188
    mechanism of action of, 2185-2186
    for Meniere's disease, 2185-2189, 2338-2339, 2338f
    number of injections of, 2188
    pharmacokinetics of, 2186-2187, 2186f-2187f
    practical considerations with, 2188
  kinetics of, 2181, 2181f
  method of, 2182-2183, 2182f-2183f
    via implantable micropump system, 2183
    via sustained-release devices, 2182-2183, 2182f-2183f
  round window membrane in, 2179-2183
    anatomy of, 2179-2180, 2180f
    kinetics of, 2181, 2181f
    method of, 2182-2183, 2182f-2183f
    obstructive adhesions and, 2181-2182
    permeability of, 2180-2181
    physiology of, 2180, 2181f
  of steroids, 2183-2185
    dosing of, 2185
    indications for, 2183
    mechanism of action of, 2183
    for Meniere's disease, 2184, 2339
    pharmacokinetics of, 2183-2184
    side effects of, 2185
    for sudden sensorineural hearing loss, 2184-2185
Intrauterine causes, of craniofacial anomalies, 2640
Intrauterine infection, infant hearing impairment due to, 2723
Intravenous agents, for pediatric anesthesia
  induction of, 2590
  maintenance of, 2591-2592, 2593t
Intravenous immune globulin (IVIG)
  for pediatric chronic sinusitis, 2779
  for rhinosinusitis, 735t, 737
Intravenous smell testing, 632
Intravestibular schwannoma, imaging of, 1921, 1924f
Intrinsic laryngeal muscles, 806-807, 806f-807f
Introns, 4, 5f
Intubation granuloma(s), 939, 941f
  of vocal folds, 875-876, 875f
    diagnosis of, 875-876
      history in, 875
      vocal capability battery in, 875-876
    epidemiology of, 875
    management of, 876
    pathophysiology and pathology of, 875
Invagination theory, of cholesteatoma formation, 1966, 1967f
Invasive fungal rhinosinusitis (IFRS), 705
  due to *Aspergillus,* 705, 710-711, 712f
    in immunocompromised host, 220-221, 220f
  due to *Candida,* 711
  chronic or indolent, 711
  diagnosis of, 711, 711f-712f
  immunosuppression and
    diagnosis of, 220-221, 220f
    presentation and pathogenesis of, 220
    treatment of, 221
  due to mucormycosis, 705, 710, 711f
  rapidly invasive (fulminant), 709-710, 710f
  surgical management of, 742
  therapy for, 711-712, 713t
Inverse filtered flow, for measurement of vocal fold vibration, 830-831
Inverse-planning intensity-modulated radiation therapy (IP-IMRT), 1043, 1696-1697
Inversion, 4-5
Inversion technique, for Zenker's diverticulum, 992f
Inverted papilloma
  ductal, of salivary glands, 1171-1172
  of nasopharynx, 1349
  sinonasal, 718-720, 1127
    endoscopic appearance of, 718-719, 719f
    epidemiology of, 718
    with frontal sinus involvement, 720, 720f
    histologic appearance of, 718
    human papillomavirus and, 718
    imaging of, 719, 719f
    postoperative surveillance for, 720
    recurrence of, 720
    sites for, 718
    and squamous cell carcinoma, 718
    surgical approach for, 718t, 719-720, 720f, 763, 1127
Inverted V sign, after rhinoplasty, 492, 493f
Investing fascia, 202
  of neck, 2577, 2578f
Iodide, in control of thyroid function, 1739
Iodide transport, in thyroid hormone synthesis, 1737, 1737f
Iodination, in thyroid hormone synthesis, 1737f, 1738
Iodine
  compound solution of, for hyperthyroidism, 1739t
  in control of thyroid function, 1739
  daily intake of, 1737
  excessive intake of, hypothyroidism due to, 1747
  inorganic
    for Graves' disease, 1742-1743
    for thyroid storm, 1745
  radioactive
    for Graves' disease, 1743
    for Graves' ophthalmopathy, 1810
    stunning with, 1771
    after thyroid surgery, 1771-1772
    for toxic multinodular goiter, 1745
    for toxic thyroid adenoma, 1744
  in radioactive iodine uptake test, 1741
  in saliva, 1139
Iodine-induced thyrotoxicosis, 1744
Iodothyronine deiodinases, 1738
IOM (Institute of Medicine), 81-82, 84t-87t

Ionic contrast agents, for imaging of pharynx and esophagus, 1396
Ionizing radiation, 1032, 1036
  and parathyroid neoplasm(s), 1775
  and thyroid carcinoma, 1753
Iowa Pain Thermometer (IPT), 240
IP_3 (inositol triphosphate)
  in olfactory transduction, 629
  in salivary gland secretion, 1137-1138
IPI (International Prognostic Index), for non-Hodgkin's lymphoma, 216
IP-IMRT (inverse-planning intensity-modulated radiation therapy), 1043, 1696-1697
Ipodate, for hyperthyroidism, 1739t
Ipratropium bromide
  for allergic rhinitis, 620
  for nonallergic rhinitis, 701
IPT (Iowa Pain Thermometer), 240
IRD (immune restoration disease), 211-212
  cryptococcal meningitis in, 224
Iron deficiency, oral manifestations of, 1254
Iron-dependent pathway, in cisplatin ototoxicity, 2172-2173
Irradiance, of surgical laser, 27
Irradiated tissue, gene therapy for repair and regeneration of, 23
Irradiation. *See* Radiation exposure.
Irregular closure, laryngeal videostroboscopy of, 819
Irregularization, for scar revision, 298
  geometric broken line closure in, 298, 299f-300f
  W-plasty in, 298, 299f
  Z-plasty in, 298, 298f-299f
Irrigation, for pediatric chronic sinusitis, 2779
Irritant rhinitis, 697-698
Irritation fibroma, of oral cavity, 1288-1289, 1289f
IRSCGC (Intergroup Rhabdomyosarcoma Study Clinical Grouping Classification), 2841, 2841t
IRX-2, for head and neck squamous cell carcinoma, 1024
Ischemia-reperfusion injury, in acutely raised skin flaps, 1070, 1074
IsK, in deafness, 2051t-2058t
Island advancement flap, 345
  for lip defects, 356f
Isobutyl-2-cyanoacrylate (IBCA), for embolization, 1933
Isoechoic object, 1643
Isoeffect measurements, in radiotherapy, 1039-1040
Isoflurane
  for anesthesia, 111
  and skin flap viability, 1073
Isotretinoin
  for chemoprevention of oral cancer, 1315
  for head and neck squamous cell carcinoma, 1018
  microtia due to, 2741
Isoxsuprine, and skin flap viability, 1073
Isthmus nasi, in nasal breathing assessment, 644
Isthmus tympani anticus, 1827f
Isthmus tympani oticus, 1827f
ITC (in-the-canal) hearing aid, 2270, 2270f
ITE (in-the-ear) hearing aids, 2270, 2270f
  in infants, 2723-2724
  selection of, 2266-2267, 2270
Item response theory (IRT), 55
Itga8 (integrin $\alpha 8\beta 1$) gene, in murine deafness, 2058t-2060t
ITM (in-transit metastasis), of melanoma, 1110, 1117
Itraconazole, for fungal rhinosinusitis, 713t
IVIG (intravenous immune globulin)
  for pediatric chronic sinusitis, 2779
  for rhinosinusitis, 735t, 737

J

Jackson-Weiss syndrome, craniofacial anomalies in, 2646
Jacobson's organ, 627-628
Jahrsdoerfer grading system, for congenital aural atresia, 2753, 2753t
Jaw, osteoradionecrosis of, 1048
Jaw-closer muscles, 1204
Jaw-closing reflex, 1204, 1204f, 1207
"Jaw-jerk" reflex, 1204
Jaw-opener muscles, 1204
Jaw-opening reflex, 1205, 1205f, 1207
Jaw-tongue reflexes, 1205
JCAHO (Joint Commission on Accreditation of Healthcare Organizations), 82-83, 84t-87t
JCIH (Joint Committee on Infant Hearing), 2718-2719
Jejunal free flap, 1082t, 1087, 1090f
  for hypopharyngeal and esophageal reconstruction, 1432-1433, 1433f, 1455-1457, 1456f
  for oropharyngeal reconstruction, 1380, 1380f
Jejunal interposition graft, after laryngopharyngectomy, 1418, 1418f
Jensen syndrome, deafness in, 2051t-2058t
Jerker mutation, 2075
Jervell and Lange-Nielsen syndrome (JLNS)
  cochlear implant for, 2220
  deafness in, 2051t-2058t, 2083, 2094t, 2096
Jessner's solution, for chemical peels, 392-393
Jet lag, 264
Jet ventilation anesthesia, with recurrent respiratory papillomatosis, 2891-2893
Jitter, in acoustic analysis for voice evaluation, 829-830, 834-835
Jitterbug mice, deafness in, 2058t-2060t, 2075-2076
JLNS (Jervell and Lange-Nielsen syndrome)
  cochlear implant for, 2220
  deafness in, 2051t-2058t, 2083, 2094t, 2096
JNA. *See* Juvenile nasopharyngeal angiofibroma (JNA).
Joint Commission on Accreditation of Healthcare Organizations (JCAHO), 82-83, 84t-87t
Joint Committee on Infant Hearing (JCIH), 2718-2719
Joint replacement, oral treatment considerations with, 1246t
JRP (juvenile recurrent parotitis), 2858
Jugular bulb
  anatomy of, 1822-1823
  paraganglioma of, 2499f
  in postauricular approach to infratemporal fossa, 2498, 2498f-2499f
  in subtotal temporal bone resection, 2494-2495
  in surgical anatomy of lateral skull base, 2436f-2437f, 2489
Jugular bulb injury, due to mastoidectomy, 2016
Jugular chain lymph nodes, 1578-1579
Jugular foramen
  anatomy of, 1822-1823, 1823f
  surgical anatomy of, 2439-2440, 2439f-2440f
    in lateral skull base, 2435f, 2438
    in middle cranial base, 2445f
    with temporal bone, 2436f
Jugular foramen meningiomas, imaging of, 1929-1930, 1930f
Jugular foramen schwannomas
  imaging of, 1929-1930, 1930f, 2522f
  lateral cranial base surgery for, 2504-2505, 2505f
  stereotactic radiation therapy for, 2565
Jugular foramen syndromes, hearing loss due to, 2199, 2199t
Jugular foramen tumors, lateral cranial base surgery for, 2504
Jugular fossa, 1824f
Jugular lymph nodes
  boundaries and landmarks of, 1705, 1707t-1708t
  description of, 1706t
  location of, 1704f-1705f
Jugular lymph nodes *(Continued)*
    lower, 1704, 1704f-1705f
    middle, 1704, 1704f-1705f
    upper, 1704, 1704f-1705f
Jugular paragangliomas, 1662f, 2499f
Jugular process
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Jugular spine, 1822-1823, 1824f
Jugular tuberculum
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Jugular vein(s)
  radiographic anatomy of, 1471f, 1473-1474
  in surgical anatomy of lateral skull base, 2436f, 2439f-2440f
Jugulocarotid node, 1298f
Jugulodigastric nodes, 1298f, 2582
Juguloomohyoid nodes, 1298f, 2582
Jump method, for tonsillar and pharyngeal wall reconstruction, 1386, 1387f
Junctional nevus, 286, 287f
Juri flap, for hair loss, 385-387, 387f
  complications of, 386-387
Juvenile angiofibroma
  endovascular treatment of, 1937-1938, 1943f
  sinonasal, 721-722
    classification systems for, 722
    endoscopic appearance of, 721, 721f
    imaging of, 721
    natural history of, 721
    origin of, 721, 721f
    postoperative surveillance for, 722
    preoperative embolization for, 721-722
    surgical approach for, 718t, 722, 722f-723f, 763
    transnasal endoscopic-assisted surgery for, 2483, 2483f
Juvenile melanoma, 287
Juvenile nasopharyngeal angiofibroma (JNA), 152, 154f, 1349-1351
  clinical features of, 1349
  diagnosis of, 1349-1350, 1350f
  growth patterns of, 1349
  management of, 1350-1351
  pathologic features of, 1349
  recurrence of, 1351
  staging of, 1350, 1350t
Juvenile recurrent parotitis (JRP), 2858

K

K^+. *See* Potassium (K^+).
Kallikreins, in saliva, 1140
Kallmann's syndrome, anosmia in, 636
Kaposiform hemangioendothelioma (KHE), 2824-2825, 2826f
  bone resorption with, 2826
  Kasabach-Merritt phenomenon with, 2825
Kaposi's sarcoma (KS)
  of hard palate, 1309-1310
  immunosuppression and, 212-215, 213t
    epidemiology and pathogenesis of, 212-213
    presentation and diagnosis of, 213-214, 214f
    treatment of, 214-215
  of larynx, 1508-1509
  of oral cavity, 1299
  of oropharynx, 1363-1364, 1364f
Kaposi's sarcoma–associated herpesvirus (KSHV), 213
Karapendzic flap, 351
Karyotype analysis, for head and neck squamous cell carcinoma, 1019
Kasabach-Merritt phenomenon, with vascular tumors, 2825
  of salivary glands, 2860

Kawasaki disease
in children, 2819
facial paralysis in, 2400
KayPENTAX HSDI system, 821
Kcc3
in endolymph homeostasis, 2081-2082
in murine deafness, 2058t-2060t
Kcc4
in endolymph homeostasis, 2081-2082
in murine deafness, 2058t-2060t
KCNE1, in deafness, 2051t-2058t, 2083, 2096
Kcnj10, in murine deafness, 2058t-2060t, 2083
KCNQ1, in deafness, 2051t-2058t, 2083
KCNQ4, in deafness, 2051t-2058t, 2079, 2090-2092
Kearns-Sayre (KS) syndrome, deafness in, 2097
Keisselbach's plexus, 483f
Keloid(s), 291
after neck surgery, 1728
after otoplasty, 479
Keratinizing odontogenic cyst, 1266-1267
microscopic features of, 1267
radiographic features of, 1267, 1267f
Keratinocyte migration, in wound healing, 1076-1077
Keratinocyte proliferation, in wound healing, 1077
Keratitis, exposure, after facial nerve injury, 2420, 2420f
Keratitis-ichthyosis-deafness syndrome, 2051t-2058t
Keratoacanthoma, 284f, 286
Keratocystic odontogenic tumor, 1262, 1267-1268
microscopic features of, 1268
radiographic features of, 1267-1268, 1268f
treatment of, 1268
Keratosis(es)
actinic (solar), 283, 284f
obturans, of external auditory canal, 1949
imaging of, 1917, 1918f
management of, 2021
seborrheic, 281-282, 282f
Kerma, 1033
Ketamine
for anesthesia induction, 111
in children, 2591
for premedication in children, 2589
with congenital heart disease, 2596
for prevention of bronchospasm during anesthesia in children, 2595
Ketoconazole, for fungal rhinosinusitis, 713t
Ketoconazole cream (Nizoral, Xolegel), for fungal otitis externa, 1954-1955, 1959t-1960t
Ketorolac, for postoperative pain in children, 2594
Keystone area, of nose, 496, 497f
KHE (kaposiform hemangioendothelioma), 2824-2825, 2826f
bone resorption with, 2826
Kasabach-Merritt phenomenon with, 2825
KHRI-3, in autoimmune inner ear disease, 2165
Ki-67, in salivary gland neoplasms, 1194
Kidney disease
oral manifestations of, 1255
preoperative evaluation of, 103
sensorineural hearing loss with, 2121
Kidney failure, oral manifestations of, 1255
Kidney failure–induced hyperparathyroidism, 1797-1798
Kidney transplantation, oral sequelae of, 1255
Kiesselbach's plexus, 682
in epistaxis, 686-687
Killian incision, for septoplasty, 488, 489f
Killian-Jamieson's triangle, esophageal diverticulum in, 986, 987f
Killian's triangle
anatomy of, 1422
esophageal diverticulum in, 986, 987f
Kilovoltage (kV) x-rays, 1033
Kinerase (*N*6-furfuryladenine), for aging skin, 404
Kinocilium
anatomy of, 1858f
arrangement of, 1854-1855, 1856f
in hair cell transduction, 2070-2071, 2070f
morphologic polarization of, 1855, 1856f, 2279f
Kir4.1, in murine deafness, 2058t-2060t, 2083
Kit, in deafness, 2051t-2058t
Klebsiella rhinoscleromatis, laryngitis due to, 884
Kleeblattschädel, due to craniosynostosis, 2645, 2645f
Klein-Waardenburg syndrome, 2095
Klinefelter's syndrome, 5
Klippel-Trenaunay-Parkes-Weber syndrome, 291
Knife injuries, neck trauma due to, 1627
Körner's septum, 1829
in mastoidectomy, 2012
Krause end bulbs, 1201
KS (Kaposi's sarcoma). *See* Kaposi's sarcoma (KS).
KS (Kearns-Sayre) syndrome, deafness in, 2097
KSHV (Kaposi's sarcoma–associated herpesvirus), 213
KTP (potassium-titanyl-phosphate) laser, 31t, 33
for facial resurfacing, 403t
for recurrent respiratory papillomatosis, 880, 880f, 2891
for stridulous child, 2908
Kupffer cells, 604
Kuttner's tumor, 1154
kV (kilovoltage) x-rays, 1033
KvLQT1, in deafness, 2051t-2058t, 2083, 2096
Kymography, of larynx, 134f, 154, 822f

L

Labetalol, intraoperative, 112
Labial arteries, 1296
Labyrinth, intratympanic gentamicin for chemical ablation of, 2185-2189
clinical protocols for, 2187-2188
complications of, 2188-2189
concentration of, 2188
dose of, 2188
indications and contraindications for, 2189
injection interval for, 2188
mechanism of action of, 2185-2186
number of injections of, 2188
pharmacokinetics of, 2186-2187, 2186f-2187f
practical considerations with, 2188
Labyrinthectomy, 2366-2368
adaptation of vestibular reflexes after, 2300-2302
anatomic and physiologic basis for, 2300-2302, 2301f
clinical implications of, 2302
disadvantages of, 2367-2368
for Meniere's disease, 2339, 2362
chemical, 2185-2189, 2338-2339, 2338f
patient selection for, 2364-2366, 2365b, 2365t
procedure for, 2366-2368, 2367f
transcanal (oval window), 2366, 2367f
transmastoid, 2366-2367, 2367f
Labyrinthine anomalies, 2732-2733
in combination with other anomalies, 2728, 2738, 2739f
CSF otorrhea due to, 2197
incidence of, 2727
semicircular canal aplasia as, 2732-2733, 2732f
semicircular canal dysplasia as, 2732, 2732f-2733f
Labyrinthine aplasia, complete, 2729
imaging of, 2729f-2730f
inherited, 2735
relative incidence of, 2729t
Labyrinthine concussion, 2343
Labyrinthine disease, poor compensation *vs.* unstable, 2364, 2365t
Labyrinthine dysplasia
cochlear implant with, 2240-2241
membranous
complete, 2727
limited, 2727-2728
Labyrinthine fistula, 1989-1990, 1990f
Labyrinthine infections, 2153-2163
acquired sensorineural hearing loss due to, 2157-2161
with herpes simplex virus, 2159-2160
with Lassa fever, 2158-2159
with measles, 2158
with meningitis, 2160-2161
with mumps, 2157-2158, 2158f
sudden, 2154, 2154b, 2157
with varicella-zoster virus, 2159, 2159f
bacterial and fungal, 2160
with cochlear implant, 2161
congenital hearing loss due to, 2154-2157
with cytomegalovirus, 2154-2156, 2155f
with rubella, 2156-2157, 2157f
with syphilis, 2161
with cytomegalovirus
clinical features of, 2154-2155
congenital hearing loss due to, 2154-2156, 2155f
diagnosis of, 2154-2155
experimental, 2156
management and prevention of, 2156
temporal bone pathology due to, 2155-2156, 2155f
diagnosis of, 2153-2154, 2154b
with herpes simplex virus, 2159-2160
in immunocompromised patients, 2161-2162
with Lassa fever, 2158
with measles, 2158
Meniere's disease due to, 2163
with mumps, 2119, 2157-2158, 2158f
clinical features of, 2157
diagnosis of, 2157
experimental, 2158
sudden, 2127
temporal bone pathology in, 2158, 2158f
with rubella, 2156-2157, 2157f
syphilitic, 2161
vaccines to prevent hearing loss due to, 2161
with varicella-zoster virus, 2159, 2159f
vestibular neuritis due to, 2162-2163, 2162f
viral
cytomegalovirus as, 2154-2156, 2155f
herpes simplex virus as, 2159-2160
Lassa fever as, 2158-2159
measles as, 2158
mumps as, 2157-2158, 2158f
rubella as, 2156-2157, 2157f
varicella-zoster virus as, 2159, 2159f
Labyrinthine segment
anatomy of, 1826f, 1828
surgical, 2404, 2404f
vulnerability to injury of, 1829
Labyrinthine upset, acute chemical, due to intratympanic gentamicin, 2189
Labyrinthine vertigo, 2201-2202
Labyrinthitis
acute (*See* Vestibular neuritis)
suppurative, 1991-1992, 2118
diagnosis of, 1991-1992
epidemiology of, 1980t
etiology of, 1991
imaging of, 1991f-1992f
bacterial and fungal, 2160
diagnosis of, 2118
ossificans, imaging of, 1921, 1925f
in evaluation for cochlear implant, 2222
sensorineural hearing loss due to, 2118
serous, 2118
after small fenestra stapedotomy, 2034
viral, vertigo due to, 2201

Lacerations, 307
Lacrimal apparatus
  anatomy of, 798f
  obstruction of, 797
    anatomic *vs.* functional, 797-798, 798f-799f
  trauma to, 307-309, 308f
Lacrimal bone
  anatomy and physiology of, 320-321, 320f, 798f
  in endoscopic dacryocystorhinostomy, 799-800, 800f
Lacrimal crest, 320-321, 322f
Lacrimal duct, 798f
Lacrimal foramen, 322f
Lacrimal fossa, 439, 1124f
  anatomy and physiology of, 320-321, 322f
  in surgical anatomy of anterior cranial base, 2444f
Lacrimal function, assessment of, 2383
Lacrimal gland, 321f
  pleomorphic adenoma of, 1169, 1170f
  in upper eyelid blepharoplasty, 448
Lacrimal nerve, 321f, 440
Lacrimal obstruction
  anatomic *vs.* functional, 797-798, 798f-799f
  endoscopic dacryocystorhinostomy for (*See* Endoscopic dacryocystorhinostomy)
  pathophysiology of, 797, 798f
Lacrimal puncta, in endoscopic dacryocystorhinostomy, 800
Lacrimal sac, 439, 798f
Lactate dehydrogenase (LDH), with melanoma, 1109-1110, 1113
Lactobacillus spp, dental caries due to, 1252
Lactoferrin
  in middle ear protection, 1871
  in saliva, 1140-1141
LactoSorb plating system, for pediatric facial fractures, 2700, 2701t
Lag screw fixation, of mandibular fracture, 338, 338f
Lagophthalmos, 446, 2421
  after blepharoplasty, 449-450
Laimer's triangle, esophageal diverticulum in, 986, 987f
LAIV (live-attenuated influenza vaccine), to prevent otitis media, 2769
Lambda, 320f
Lambdoid synostosis, 2643-2644
  front-orbital advancement for, 2653
Lamina papyracea
  in endoscopic sinus surgery, 748-749, 750f
  after functional endoscopic sinus surgery, 679, 679f-680f
  medial deviation or dehiscence of, 669, 671-672
Lamina propria, in immune system, 605
Lamotrigine, for neuropathic pain, 243, 244t
Langerhans cell(s), 604, 2100
  in allergic rhinitis, 616
Langerhans' cell eosinophilic granuloma, oral manifestations of, 1257
Langerhans' cell histiocytosis (LCH), 2100-2101
  oral manifestations of, 1257
  otologic manifestations of, 2101
    eosinophilic granulomas as
      of external ear, 2102f
      multiple, 2101f
      unifocal, 2102f
    in Letterer-Siwe disease, 2102f
    otorrhea as, 2196
Language, defined, 2248
Language development, 2248-2249, 2248f-2249f
  cochlear implants and, 2239-2240, 2249-2251, 2250f
  otitis media and, 2776
Lano classification, of airway stenosis, 944t
Laplace transform, 2303
LAR (laryngeal adductor reflex), in laryngomalacia, 2866-2867
Large clear cell adenoma, of parathyroid gland, 1778
Large granular lymphocytes, in adaptive immune system, 603-604
Large vestibular aqueduct syndrome, sensorineural hearing loss in, 2118, 2118f
  sudden, 2129
LARP (left anterior–right posterior) semicircular canal plane, 2285, 2286f, 2287, 2288f
Laryngeal adductor muscles, during breathing, 809, 809f
Laryngeal adductor reflex (LAR), in laryngomalacia, 2866-2867
Laryngeal aditus, 1359f
Laryngeal airway resistance (R_{law}), in voice evaluation, 828-829, 828t
Laryngeal appendix, 876
Laryngeal atresia, 2869, 2869f-2870f, 2913
  management of, 2922
Laryngeal biopsy, for benign vocal fold mucosal disorders, 862
Laryngeal cancer, 1482-1511
  adenoid cystic carcinoma as, 1507
  adenosquamous carcinoma as, 1506
  advanced, 1526
    new treatment protocols for, 1448, 1449f
    transoral laser microsurgery for, 1531-1532, 1532f-1533f
  anatomy and, 1483-1486, 1483f, 1483t
    anterior commissure in, 1486
    glottis in, 1483-1484, 1483f, 1483t
    mucosal lining in, 1484
    paraglottic space in, 1484-1485, 1484f-1485f
    pre-epiglottic space in, 1484, 1484f
    subglottis in, 1483-1484, 1483f, 1483t
    supraglottis in, 1483-1484, 1483f, 1483t
  of anterior commissure, 1486
    anatomic basis for, 1486
    imaging of, 161, 1474, 1474f
    treatment of, 1496-1497
      transoral laser microsurgery for, 1531
  of aryepiglottic fold, 1475, 1478f
  carcinoma in situ as, 1486-1491, 1489f-1490f, 1515
    treatment of, 1489-1490, 1520-1521
  carcinosarcoma as, 1506
  cartilaginous invasion by, 161, 1474
    CT of, 1474, 1476f, 1495
      contrast-enhanced, 161, 164f
    MRI of, 161, 1474-1475, 1476f, 1495
  chemoprevention of, 1491
  in children, 2881
  classification of, 1487t, 1525-1526
  clinical presentation of, 1579
  concomitant chemoradiation for, 1052-1056, 1053t
  conservation laryngeal surgery for (*See* Conservation laryngeal surgery)
  diagnostic evaluation/workup for, 1579
  early, 1526
    transoral laser microsurgery for, 1530-1531
  embryology and, 1482-1483
  of epiglottis, 1475, 1477f
  glottic (*See* Glottic cancer)
  hematolymphoid, 1509
    extramedullary plasmacytoma as, 1509
    lymphoma as, 1509
    mucosal malignant melanoma as, 1509
  histopathology of, 1512, 1514f
  imaging of, 161, 1494-1495, 1579
    of anterior commissure, 161, 1474, 1474f
    of aryepiglottic fold, 1475, 1478f
    with cartilaginous invasion, 161, 1474
      contrast-enhanced CT for, 161, 164f
      CT for, 1474, 1476f, 1495
      MRI for, 161, 1474-1475, 1476f, 1495
Laryngeal cancer *(Continued)*
    for conservation laryngeal surgery, 1545-1546
    CT for, 1468-1479
      with cartilaginous invasion, 1474, 1476f, 1495
      contrast-enhanced, 161, 164f
    of epiglottis, 1475, 1477f
    glottic, 1474-1475, 1474f
    with lymph node metastases, 1476, 1479f
    MRI for, 1468-1479
      with cartilaginous invasion, 161, 1474-1475, 1476f, 1495
    normal anatomy and, 1470-1474
    of paraglottic space, 1474
    PET/CT for, 1470, 1470f
    post-therapy, 1476-1479, 1479f
    of pyriform sinus, 1475-1476, 1478f
    subglottic, 1474, 1475f
    supraglottic, 1475-1476
    technique for, 1470, 1470f
    transglottic, 161, 164f, 1475f, 1476, 1478f
  intermediate, 1526
    transoral laser microsurgery for, 1531
  mucoepidermoid carcinoma as, 1506-1507
  neck dissection for, 1716-1718
    definition and rationale for, 1716-1717, 1717f
    glottic, 1497-1498
    after nonsurgical organ preservation treatment, 1502-1503
    supraglottic, 1500-1501
    technique for, 1717-1718, 1717f
    with transoral laser microsurgery, 1532
  neck management for, 1580
  neuroendocrine, 1507-1508
    carcinoid as
      atypical, 1507
      typical, 1507
    paraganglioma as, 1508
    small cell carcinoma as, 1507-1508
  nodal metastases of, 1493-1494, 1493f
    embryology and, 1482-1483
    glottic, 1497-1498
    imaging of, 1476, 1479f
    radiation therapy for, 1690t
    subglottic, 1501, 1501f
    supraglottic, 1500-1501
      incidence and distribution of, 1686f, 1688t
  organ preservation treatment for, 1501-1503, 1502f (*See also* Conservation laryngeal surgery)
    current paradigm for, 1558-1559
    glottic, 1497
      chemoradiation as, 1584-1585
      targeted biologic agents with radiation therapy as, 1585
    management of neck after, 1502-1503
    recurrence after, 1503-1504
    supraglottic, 1500
  overall management of, 1580
  of paraglottic space, 1484-1485, 1484f-1485f
    anatomic basis for, 1484-1485, 1484f-1485f
    imaging of, 1474
  of preepiglottic space, 1484, 1485f
    anatomic basis for, 1484, 1484f
    imaging of, 1495
  premalignant lesions for, 1486-1491, 1489f-1490f
  of pyriform sinus, 1475-1476, 1478f
  radiation therapy for, 1577-1593
    advanced glottic, 1497, 1583-1588
      balancing cure, organ preservation, and quality of life with, 1583-1584
      with chemotherapy, 1584-1586, 1584t
      complications of, 1587-1588
      dose-fractionation schemes for, 1586, 1586t
      general principles of, 1585-1586
      mini-mantle field technique for, 1586

Laryngeal cancer *(Continued)*
outcomes and prognostic factors for, 1586-1587, 1587t
patient setup for, 1586
postoperative (adjuvant), 1584-1585, 1584t
shrinking-field technique for, 1586, 1587f
with targeted biologic agents, 1585
advanced supraglottic, 1589
outcomes and prognostic factors for, 1589, 1590t
techniques and dose-fractionation schemes for, 1589
anatomic considerations with, 1578-1579, 1578f
with anterior commissure involvement, 1496-1497
CyberKnife stereotactic approach for, 1592
early glottic, 1519-1520, 1581
complications of, 1583
effectiveness of, 1496
local control with, 1519, 1522f
outcome and prognostic factors for, 1581-1583, 1582t-1583t
recurrence after, 1522t
results of, 1519, 1521t
techniques and dose-fractionation schemes for, 1580-1590, 1581f-1582f
early supraglottic, 1496, 1588-1589
complications of, 1589
outcomes and prognostic factors for, 1589, 1589t
techniques and dose-fractionation schemes for, 1588-1589
future strategies and directions for, 1592
lymphatic drainage and, 1578-1579, 1579f
with nodal metastases, 1498
overview of, 1578
RADPLAT approach for, 1592
recurrence after, 1476-1479, 1522, 1522t
with recurrent disease, 1591-1592
subglottic, 1589-1590
with transoral laser microsurgery, 1532-1533
recurrence of, 1476-1479
after radiation therapy, 1476-1479, 1522, 1522t
radiation therapy for, 1591-1592
salivary gland type, 1506-1508
sarcoma as, 1508-1509
chondro-, 1508
fibro-, 1508
Kaposi, 1508-1509
lipo-, 1508
malignant fibrous histiocytoma as, 1508
pseudo-, 1506
sarcomatoid carcinoma as, 1506
second primary tumors in, 1492, 1510
spindle cell carcinoma as, 1506
squamous cell carcinoma as, 1491
acantholytic, 1506
adenoid, 1506
basaloid, 1506
cervical nodal metastases of, 1493-1494, 1493f
embryology and, 1482-1483
glottic, 1497-1498
imaging of, 1476, 1479f
subglottic, 1501, 1501f
supraglottic, 1500-1501
chemoprevention of, 1491
clinical presentation of, 1493-1494
diagnosis and evaluation of, 1494-1495
differential diagnosis of, 1495
history and physical examination in, 1494
imaging in, 1494-1495
operative endoscopic examination in, 1495
distant metastases of, 1494-1495
epidemiology of, 1491-1492, 1512, 1513f
etiology of, 1512-1513
Laryngeal cancer *(Continued)*
follow-up for, 1505
grading of, 1492-1493
human papillomavirus and, 1492, 2887-2888
imaging of, 161, 164f
in situ, 1493
microinvasive, 1493
molecular biology of, 1492
papillary, 1506
pathology of, 1492-1493
prognosis and prognostic predictors for, 1504-1505
clinical features as, 1504
disease factors as, 1504-1505
histopathologic characteristics as, 1504-1505
molecular markers as, 1493, 1505
patient factors as, 1505
radiologic characteristics as, 1504
recurrence of, 1503-1504
stomal, 1504, 1504f
recurrent respiratory papillomatosis and, 2887-2888
risk factor(s) for, 1491-1492, 1512-1513
diet as, 1492
exposure to toxins as, 1492, 1513
genetic susceptibility as, 1492, 1513
human papillomavirus as, 1492, 1513
laryngopharyngeal reflux as, 1491-1492, 1513
second primary tumors as, 1492
tobacco and alcohol as, 1491, 1512-1513
staging of, 1486, 1488t-1489t
radiology in, 1495
transition zones of, 1489, 1490f
treatment of, 1495
acronyms for, 1526-1527
background of, 1512-1515, 1513f-1514f
CO_2 laser for, 33
goals of, 1495
intensity-modulated radiotherapy for, 1046
intensity-modulated radiotherapy of, 1046
nonsurgical organ preservation, 1501-1503, 1502f
options for, 1495, 1496t
prognostic factors in, 1495, 1496t
for recurrence, 1503-1504, 1504f
for subglottic tumors, 1501-1503, 1501f
for supraglottic tumors, 1498-1501, 1498f
therapeutic decision making for, 1495
variants of, 1505-1506
acantholytic, 1506
adenosquamous, 1506
basaloid, 1506
papillary, 1506
spindle cell, 1506
verrucous, 1505-1506, 1505f
staging of, 1486, 1488t-1489t, 1579-1580
laryngoscopy in, 1579-1580, 1580f
radiology in, 1495
and transoral laser microsurgery, 1526
subglottic
anatomic basis for, 1483-1484, 1483f, 1483t
cervical metastases of, 1494
clinical presentation of, 1493, 1579
imaging of, 1474, 1475f
staging of, 1488t, 1580f
treatment of, 1501-1503, 1501f
supraglottic, 1484, 1484f-1485f
anatomic basis for, 1483-1484, 1483f, 1483t
cervical metastases of, 1493-1494
clinical presentation of, 1493, 1579
imaging of, 1475-1476
neck dissection for, 1500-1501
staging of, 1488t, 1580f
treatment of, 1498-1501
in advanced stage, 1500
in early stage, 1498-1500, 1498f
Laryngeal cancer *(Continued)*
with nodal metastases, 1500-1501
transoral laser microsurgery for, 1531
transglottic, 1486
imaging of, 161, 164f, 1475f, 1476, 1478f
transoral laser microsurgery for, 1525-1538
with advanced tumors, 1531-1532, 1532f-1533f
with anterior commissure involvement, 1497
complications of, 1533-1534, 1534f
conclusions on, 1536-1537
contraindications to, 1534
with early tumors, 1496, 1498-1500, 1530-1531
with glottic tumors, 1496
historical background of, 1527
instruments for, 1528-1529
with intermediate tumors, 1531
and neck dissection, 1532
vs. open conservation surgery, 1528
pathology issues with, 1530
and radiotherapy, 1532-1533
results of, 1534-1536
with supraglottic tumors, 1498-1500
techniques for, 1529-1530
theoretical basis of, 1527-1528
with very advanced tumors, 1532
with very early tumors, 1530
due to tumors from continuous sites, 1510
types of local, 1526
verrucous carcinoma as, 1505-1506, 1505f
very advanced, 1526
transoral laser microsurgery for, 1532
very early, 1526
transoral laser microsurgery for, 1530
Laryngeal cartilage
calcification of, in geriatric patients, 235, 235f
invasive carcinoma of, 161, 1474
CT of, 1474, 1476f, 1495
contrast-enhanced, 161, 164f
MRI of, 161, 1474-1475, 1476f, 1495
repair of, 939f
Laryngeal chemoreflex (LCR), 2570
Laryngeal cleft (LC), 2873-2874, 2873f, 2910f
classification of, 2873, 2874f, 2874t
dysphagia due to, 2952-2953
syndromes associated with, 2870t
Laryngeal cysts, congenital, 1468, 2872-2873, 2872f-2873f
Laryngeal denervation
effects of, 919
reinnervation for (*See* Laryngeal reinnervation)
Laryngeal diadochokinesis, 814
Laryngeal edema, in vocal professional, 854
Laryngeal electromyography, 835, 905
for stridor, 2901
Laryngeal examination
for benign vocal fold mucosal disorders, 862, 862f
bilateral diffuse polyposis as, 872
capillary ectasia as, 866-867
contact ulcer or granuloma as, 875
glottic sulcus as, 870-871
intracordal cysts as, 869
postoperative dysphonia as, 874
tools for, 862, 862f
vocal fold hemorrhage and unilateral (hemorrhagic) vocal fold polyp as, 868
vocal nodules as, 865
for disorders of professional voice, 851-852, 852t
Laryngeal hemangiomas, 874, 2871, 2871f
Laryngeal hygiene, in voice professional, 852-853
Laryngeal image biofeedback, for benign vocal fold mucosal disorders, 863, 864f
Laryngeal inlet obliteration, due to trauma, 940f
Laryngeal instillations, for mucosal inflammation, 863

Laryngeal invasion, by tumors from contiguous sites, 1510
Laryngeal lesions, epithelial hyperplastic, 1525
Laryngeal mask airway (LMA), 110f
  for difficult airway, 109-110, 113, 114t, 122, 122b
  flexible, for children, 2599
Laryngeal mass, differential diagnosis of, 1487t
Laryngeal motion, 805-807, 806f-807f
Laryngeal mucosal lacerations, 1634
Laryngeal muscles, characteristics of, 918
Laryngeal musculoskeletal tension, in voice evaluation, 827-831, 828f
Laryngeal nerve, recurrent. *See* Recurrent laryngeal nerve (RLN).
Laryngeal obstruction, in neonate, 2905
Laryngeal open repair, for laryngeal trauma, 936-937, 939f
Laryngeal papillomatosis, stridor due to, 2898, 2899f
Laryngeal paralysis
  arytenoid adduction for (*See* Arytenoid adduction)
  clinical impact of, 912
  dysphagia due to, 914
  pathophysiology of, 912-913
  "posterior gap" in, 912, 913f
  variation in symptoms of, 912
  vocal fold positions in, 912-913
  vocal process in, 913-914
Laryngeal preservation surgery, 1501-1503, 1502f
  for glottic tumors, 1497
  management of neck after, 1502-1503
  recurrence after, 1503-1504
  for supraglottic tumors, 1500
Laryngeal reinnervation, 917-924
  ansa cervicalis–recurrent laryngeal nerve anastomosis for, 922-923
    advantages of, 922
    clinical results of, 923
    disadvantage of, 922
    history of, 917-918
    surgical indications and contraindications for, 922
    surgical technique for, 922-923, 923f
  direct nerve implant for, 923-924, 924f
  effects of denervation and, 919
  history of, 917
  neuromuscular pedicle for, 919-922
    for bilateral paralysis, 920
    complications of, 922
    future of, 922
    history of, 917
    indications for, 920
    laboratory investigations of, 919-920
    rationale for, 919
    reported results of, 920-921
    technique for, 920, 921f
    for unilateral paralysis, 920
  physiologic and anatomic issues in, 918-919
    infrahyoid muscles as, 918-919
    laryngeal muscles as, 918
    muscle fibers in general as, 918
    nerve characteristics as, 918
  principles of, 919-924
Laryngeal release procedures, for laryngotracheal stenosis, 952
Laryngeal sensory testing, for extraesophageal reflux, 898-899
Laryngeal skeleton, anatomy of
  radiographic, 1471
  surgical, 1541, 1541f
Laryngeal stenosis, 943-952
  in children, 2912-2924
    anterior glottic, 2922
    anterior subglottic, 2923
    due to atresia and webs, 2922
    diagnosis of, 2916-2917
Laryngeal stenosis *(Continued)*
    endoscopic examination in, 2916-2917
    esophagogastroduodenoscopy and biopsy in, 2917
    evaluation of GERD and GLPRD in, 2917
    functional endoscopic evaluation of swallowing in, 2917
    history and physical examination in, 2916
    pulmonary function tests in, 2917
    radiologic evaluation in, 2916
    voice assessment in, 2917
  etiology and pathophysiology of, 2912-2916
    acquired, 2914-2915
    congenital, 2912-2913, 2913f
  grading of, 2917, 2917t
  management of, 2917-2921
    algorithm for, 2913f
    anterior cricoid split operation for, 2918-2919, 2918f-2919f
    autogenous costal cartilage reconstruction in, 2919-2920, 2920f-2921f
    combined laryngofissure and posterior cricoid division for, 2919, 2919f
    cricoid resection with thyrotracheal anastomosis for, 2921, 2922f
    decannulation after, 2923
    endoscopic, 2918
    external expansion surgery for, 2919-2921
    grafts in, 2919
    postoperative, 2923
    single-stage laryngotracheal reconstruction for, 2920-2921
    stents in, 2920
  posterior glottic, 2922-2923
  prevention of, 2916
  types of, 2915, 2915f-2916f
  with vocal cord paralysis, 2922
due to chronic infection, 2915
due to chronic inflammatory disease, 2915
classification of, 944, 944t
CO_2 laser for, 32
congenital
  diagnosis of, 2916-2917
  etiology and pathophysiology of, 2912-2913, 2913f
  management of, 2922
due to GERD, 2915, 2917
local application of mitomycin C for, 946
pathophysiology of, 943-944, 944b
surgical management of, 943-952
  for chronic disease, 947-952
    anterior glottic, 948
    due to anterior wall collapse, 951
    complete glottic, 949-950
    laryngeal release procedures in, 952
    posterior glottic, 948-949, 949f
    subglottic, 945f, 950-951
    supraglottic, 947-948
  endoscopic *vs.* open, 945
  goals and assessment in, 944, 945f
  microsurgical débridement in, 946, 946b, 946f
  planning for, 946-947
  skin and mucosal grafts in, 946-947
  stent placement in, 947, 947f
due to trauma, 937-939, 939f-940f, 943
  in children
    external, 2914
    internal, 2914-2915
Laryngeal stroboscopy, 818-821
  of adynamic segments, 820
  of amplitude of vibration, 820, 821f, 848, 848t
  in children, 2877
  of closure pattern, 819, 820f, 848t, 849
  common problems and solutions for, 815t-816t
  defined, 813
  of early glottic carcinoma, 1515-1516
Laryngeal stroboscopy *(Continued)*
  flexible endoscope for, 814
    advantages of, 814
    disadvantages of, 814
    protocol for, 818b
    technique of, 814
    troubleshooting for, 814
  interpretation of, 848t
  interval examination in, 847
  of mucosal wave, 820, 848-849, 848t
  in neurologic examination, 834
  of periodicity, 821, 848, 848t
  of phase closure, 819-820
  of professional voice, 847-849, 848f, 848t
  protocol for, 818-819, 818b
  of regularity, 821
  rigid endoscopes for, 813-814
    advantages of, 813
    disadvantages of, 813-814
    protocol for, 818b
    technique of, 814
    troubleshooting for, 814
  of symmetry, 820, 847-848, 848t
  of vertical closure level, 821
  for vocal fold impairment, 905
Laryngeal structure, videoendoscopy of, 816
Laryngeal surgery
  anesthesia for, in children, 2599-2600
  conservation (*See* Conservation laryngeal surgery)
  swallowing disorders due to, 1220
  in vocal professional, 855-857
Laryngeal trauma, 933-941, 1479-1480
  caustic or thermal, 939-941
    etiology of, 940-941
    incidence of, 939-940
    management of, 941
  external, 933-938
    anterior cervical, 933-934, 934f
    blunt *vs.* penetrating, 933-934, 934f
    in children, 938
    classification of, 936, 936t-937t
    cricotracheal separation due to, 937
    diagnosis of, 934-935
    etiology of, 933-934, 934f
    examination and initial management of, 935, 935t
    incidence of, 933
    laryngeal inlet obliteration due to, 940f
    laryngeal stenosis due to, 937-939, 939f-940f, 943
      in children, 2914
    management of, 936-937
      airway management in, 936
      choice of therapy for, 936
      conservative, 936
      for cricotracheal separation, 937
      diagnostic or therapeutic endoscopy in, 936
      endolaryngeal stenting for, 937, 939f-940f
      open laryngeal repair in, 936-937, 939f
      partial or total laryngectomy for, 937, 940f
      postoperative care in, 937
      protocol for, 938f
      surgical, 936-937
      for vocal cord immobility, 937
    mechanism of injury in, 934-935
    outcome of, 938, 941f, 941t
    sequelae of, 937-938, 940f
    symptoms of, 934-935, 935t
    vocal cord immobility due to, 937-938
  iatrogenic, 939
    etiology of, 939, 941f
    incidence of, 939
    with intubation granulomas, 939, 941f
    with laryngeal stenosis, 939, 940f, 943
      in children, 2914-2915
      management of, 939

Laryngeal trauma *(Continued)*
imaging of, 159, 162f, 1479-1480
CT for, 935-936, 936f, 1480f
NEXUS criteria for, 935-936, 935b
internal, laryngeal stenosis due to, 2914
mechanisms of injury in, 933, 934f
Laryngeal ventricle, radiographic anatomy of, 1463f, 1472-1473
Laryngeal videoendoscopy, 814-818
of arytenoid and vocal fold motion, 816
common problems and solutions for, 815t-816t
defined, 813
flexible endoscope for, 814
advantages of, 814
disadvantages of, 814
protocol for, 816b
technique of, 814
troubleshooting for, 814
of laryngeal structure, 816
of mucous, 816-817
in neurologic examination, 834
protocol for, 814, 816b
rigid endoscopes for, 813-814
advantages of, 813
disadvantages of, 813-814
protocol for, 816b
technique of, 814
troubleshooting for, 814
of supraglottic activity, 817, 817f
of vascularity, 817
of vocal fold edges, 818
Laryngeal videoendoscopy and stroboscopy (LVES). *See* Laryngeal stroboscopy; Laryngeal videoendoscopy.
Laryngeal webs, 2869-2871, 2913
anterior, 2869-2870, 2869f
in congenital high airway obstruction syndrome, 2869, 2870f
dysphagia due to, 2952
epidemiology of, 2913
etiology and pathophysiology of, 2913
in laryngeal atresia, 2869, 2869f-2870f
posterior, 2869, 2869f
stridor due to, 2899, 2900f
syndromes associated with, 2869, 2870t
treatment of, 2922
vocal quality disorder due to, 2880, 2880f
Laryngectomy
for chronic aspiration, 927, 928f
for glottic cancer
in advanced stage
near-total, 1497
partial, 1497
total, 1497
anterior partial, 1517t
frontolateral partial, 1517t
partial, 1496
subtotal, 1517t
horizontal partial, 1540, 1549
hypothyroidism after, 1747
for laryngeal trauma, 937, 940f
near-total, 1564
olfactory dysfunction after, 637
supracricoid
with cricohyoidopexy, 1555-1557
complications of, 1557
functional outcome of, 1556-1557, 1557t
key surgical points for, 1556
oncologic results of, 1555
surgical technique for, 1555-1556, 1556f
historical background of, 1540
supracricoid partial
with cricohyoido-epiglottopexy, 1549-1550
complications of, 1551
extended procedures for, 1551
functional outcome of, 1551, 1551t-1552t
key surgical points for, 1550-1551
Laryngectomy *(Continued)*
oncologic results of, 1549-1550
surgical technique for, 1550, 1550f-1551f
for laryngeal cancer
with anterior commissure involvement, 1497
historical background of, 1540
intermediate, 1531
supraglottic, 1500
supraglottic, 1553-1554
with arytenoid, aryepiglottic fold, or superior medial pyriform involvement, 1554-1555
with base of tongue extension, 1555
complications of, 1555
extended procedures for, 1554
functional outcome of, 1555
historical background of, 1540
key surgical points for, 1554-1555, 1554f
oncologic results of, 1553, 1553t
surgical technique for, 1553-1554, 1554f
for supraglottic cancer, in early stage
open supraglottic, 1498-1500, 1498f
supraglottic partial, 1498-1500, 1498f
supraglottic subtotal, recurrence after, 1476
swallowing disorders due to, 1220
total, 1563-1572
chemotherapy after, 1442-1443
complication(s) of, 1570-1571
drain failure as, 1571
early, 1571
hematoma as, 1571
hypothyroidism as, 1571
infection as, 1571
late, 1571
pharyngocutaneous fistula as, 1571
stomal stenosis as, 1571
wound dehiscence as, 1571
historical development of, 1563-1564
indications for, 1564-1565
intraoperative conversion from conservation laryngeal surgery to, 1557-1558
vs. organ preservation surgery, 1564
with partial/total pharyngectomy, for hypopharyngeal cancer, 1430, 1431f
patient selection and workup for, 1565
pharyngeal reconstruction after, 1569-1570, 1570f
postoperative management of, 1570-1571
radiographic appearance after, 1416, 1417f-1418f
recurrence after, 1476
rehabilitation after, 1572
of swallowing, 1572
of voice (*See* Voice rehabilitation)
repair and reconstruction after, 1569-1570
for subglottic cancer, 1501
for supraglottic cancer, in advanced stage, 1500
technique for, 1565-1569
access to larynx in, 1566
airway management in, 1565-1566, 1565f
entry into larynx in, 1566, 1568f
entry into trachea in, 1566
incision in, 1565-1566, 1565f
inspection of specimen in, 1566-1568, 1569f
patient positioning in, 1565-1566
skeletonization of larynx in, 1566, 1567f
thyroid gland in, 1566
tracheoesophageal puncture in, 1568-1569, 1569f
tracheotomy in, 1566-1568
wound closure in, 1568-1569, 1569f
tracheal stoma after, 1570, 1571f
tumor recurrence after, 1416, 1417f
vertical partial, 1540, 1547
voice rehabilitation after (*See* Voice rehabilitation)
wide-field, 1568-1569, 1570f
Laryngitis, 883-888
acute, 883-885
bacterial, 884
fungal, 884-885, 884f
due to phonotrauma, 883-884, 884f
viral, 884
chronic, 885-886
due to autoimmune disorders, 887, 887f
bacterial, 885
due to extraesophageal reflux, 901-902
fungal, 885
due to blastomycosis, 885
due to coccidioidomycosis, 885
due to histoplasmosis, 885
due to paracoccidioidomycosis, 885
mycobacterial, 885-886, 886f
noninfectious, 886
and malignant transformation, 883
reflux, 886, 886f, 901-902, 970-971
in voice professional, 852
significance of, 883
in vocal professional, 853-854
due to reflux, 852
Laryngocele, 876-878, 1402, 2816-2817, 2872-2873
classification of, 877, 1402, 1468
clinical scenario with, 877, 2816-2817
defined, 877, 1468, 2816
diagnosis of, 877
etiology of, 159-161, 876
external, 159-161, 1468, 2816
imaging of, 159-161, 1402, 1468
CT for, 163f, 1402f, 1468, 1469f
plain films for, 1468, 1469f
internal, 159-161, 163f, 1402f, 1468, 1469f, 2816
mixed, 159-161, 1468, 1469f
treatment of, 877-878
types of, 876f
Laryngofissure, with posterior cricoid division, for laryngeal stenosis, 2919, 2919f
Laryngofissure approach, for glottic cancer, 1517t, 1519t
Laryngologic manifestations, of neurologic diseases, 837-838, 838t
Laryngology, gene therapy in, 23
Laryngomalacia, 1466, 2866-2868
bronchoscopy for, 2867
classification of, 2867
clinical presentation of, 2866
dysphagia due to, 2952
flexible fiberoptic laryngoscopy for, 2867
gastroesophageal reflux and, 2946
GERD with, 2867
in older children and adults, 2868
pathophysiology of, 2866-2867, 2867f
stridor due to, 2866
surgical intervention for, 2867-2868, 2868f
Laryngopathia praemenstrualis, 850
Laryngopharyngeal cancer, advanced, 1438-1439
chemotherapy for, 1439
quality of life with, 1439
Laryngopharyngeal reflux (LPR), 886, 886f, 901-902, 970-971
defined, 894
diagnostic evaluation of, 896-900
esophageal endoscopy in, 899
esophagogram in, 898
history in, 896, 896b-897b
impedance testing in, 900
laryngeal sensory testing in, 898-899
manometry in, 899-900
pH probe monitoring in, 900
physical examination and laryngeal endoscopy in, 896-897, 897t, 898b
voice analysis in, 898

Laryngopharyngeal reflux (LPR) *(Continued)*
dysphagia due to, 2953
epidemiology of, 894
and head and neck cancer, 902-903
laryngitis due to, 886, 886f
otolaryngologic disorders associated with, 901-903
chronic laryngitis as, 901-902
contact ulcer and laryngeal granuloma as, 902, 902f-903f
pathophysiology of, 894-896
epithelial resistance factors in, 895-896
esophageal acid clearance in, 895
lower esophageal sphincter in, 895, 895b
mechanisms of symptoms in, 896
upper esophageal sphincter in, 894-895
professional voice disorders due to, 852
and rhinosinusitis, 732
and squamous cell carcinoma of larynx, 1491-1492, 1513
treatment of, 900-901, 971
behavioral modification for, 900-901
bethanechol for, 901
H_2 blockers for, 901
over-the-counter antacids for, 901
promotility agents for, 901
proton pump inhibitors for, 901, 971
sucralfate for, 901
surgical, 901
Laryngopharyngeal Reflux Disease Index, 897, 898b
Laryngopharyngectomy
jejunal interposition graft after, 1418, 1418f
partial, for hypopharyngeal cancer, 1429, 1430f
radiographic appearance after, 1416-1418, 1418f
total, 1572-1575
complication(s) of
early, 1575
functional swallowing problems as, 1575
late, 1575
stricture as, 1575
defined, 1572
historical development of, 1572
incision for, 1565f
indications for, 1573
patient selection and workup for, 1573
postoperative management of, 1574-1575
reconstruction after, 1574, 1574f-1575f
rehabilitation after, 1575
technique for, 1573-1574, 1573f
entry into pharynx in, 1573-1574
initial steps in, 1573-1574
neck dissection in, 1573
patient positioning and anesthetic considerations in, 1573
with superior mediastinal adenopathy, 1574, 1574f
thyroid gland in, 1574
voice after, 1575
voice rehabilitation after, 1458-1459
Laryngopharyngitis, acid reflux, 863, 863f
Laryngopharyngoesophagectomy, total, 1574, 1574f
for cervical esophageal cancer, 1430-1431
Laryngoplasty
epiglottic, 1549
complications of, 1549
extended procedures for, 1549
functional outcome of, 1549
key surgical points for, 1549
oncologic results of, 1549
surgical technique for, 1549, 1549f
imbrication, 1548, 1548f
vertical, for chronic aspiration, 928-929, 930f
Laryngopyocele, 877
Laryngoscope(s), 864, 864f
Hollinger anterior commissure, for difficult airway, 122, 122f
for transoral laser microsurgery, 1529
Laryngoscopic appearance, in geriatric patients, 235-236
Laryngoscopic injection, for vocal fold medialization, 906-907, 907f
Laryngoscopy, 100
for airway stenosis, 944
for benign vocal fold mucosal disorders, 862
for difficult airway, 121
conventional, 114t
rigid, 114t
fiberoptic, 114t
direct
for laryngeal carcinoma, 1495
microscopic, for glottic cancer, 1519t
for penetrating neck trauma, 1631t, 1634
equipment for, 864, 864f
for extraesophageal reflux, 896-897, 897t, 898b
transnasal fiberoptic, 898
fiberoptic flexible, for laryngomalacia, 2867
flexible, 100, 814
advantages of, 814
disadvantages of, 814
in neurologic evaluation, 834
for professional voice disorders, 851-852, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
for foreign body removal, 2939t, 2940
indirect, for laryngeal carcinoma, 1494
in infants, 2866, 2867f
for laryngeal carcinoma
direct, 1495
indirect, 1494
rigid, 813-814
advantages of, 813
disadvantages of, 813-814
for professional voice disorders, 851, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
virtual, 138, 140f, 1464, 1464f
Laryngospasm
in children, 2570
recurrent paroxysmal, 808
Laryngotracheal cleft, 2873-2874, 2873f
classification of, 2873, 2874f, 2874t
syndromes associated with, 2870t
Laryngotracheal injury, due to penetrating neck trauma, 1634
Laryngotracheal reconstruction, single-stage, for laryngeal stenosis, 2920-2921
Laryngotracheal separation, for chronic aspiration, 931-932, 931f
Laryngotracheal stenosis, 943-952
classification of, 944, 944t
CO_2 laser for, 32
local application of mitomycin C for, 946
pathophysiology of, 943-944, 944b
surgical management of, 943-952
for chronic disease, 947-952
anterior glottic, 948
due to anterior wall collapse, 951
cervical tracheal, 951, 951b, 951f
cicatricial membranous, 951
complete glottic, 949-950
complete tracheal, 951-952, 952f
laryngeal release procedures in, 952
posterior glottic, 948-949, 949f
subglottic, 945f, 950-951
supraglottic, 947-948
endoscopic *vs.* open, 945
goals and assessment in, 944, 945f
microsurgical débridement in, 946, 946b, 946f
planning for, 946-947
skin and mucosal grafts in, 946-947
Laryngotracheal stenosis *(Continued)*
stent placement in, 947, 947f
timing of, 945
due to trauma, 937-939, 939f-940f, 943
Laryngotracheitis, 1465, 1465f, 2803-2806
clinical features of, 2803-2804
defined, 2803
diagnosis of, 2804
differential diagnosis of, 2804-2805, 2806t
epidemiology of, 2803
etiology of, 2803
imaging of, 2804, 2804f-2805f
laryngoscopy of, 2804, 2805f
management of, 2805-2806, 2904
membranous (bacterial), 1465, 1465f
pathogenesis of, 2803-2804
postintubation, 2593
spasmodic, 2805
terminology for, 2803
Laryngotracheobronchitis. *See* Laryngotracheitis.
bacterial (membranous) (*See* Bacterial tracheitis)
Laryngotracheobronchoscopy, for stridor, 2902
anesthetic considerations for, 2902
bronchoscopy technique for, 2903, 2903f
complications of, 2903
dynamic airway assessment during, 2903
equipment for, 2902-2903, 2902f
microlaryngoscopy technique for, 2902-2903
postoperative car after, 2903
preparation and positioning for, 2902
Laryngotracheoesophageal clefts (LTECs), 2873-2874, 2873f
classification of, 2873, 2874f, 2874t
syndromes associated with, 2870t
Laryngovideostroboscopy. *See* Laryngeal stroboscopy.
Larynx
anatomy of, 1578
applied, 805, 806f-807f
cartilage in, 805-806, 806f
mucosa in, 807
musculature in, 806-807, 806f-807f
nerve supply in, 807
post-therapy, 1476-1479, 1479f
radiographic, 1462-1464, 1578f
aryepiglottic folds in, 1471, 1471f
arytenoid cartilage in, 1471, 1473f
coronal plane in, 1473f
cricoid cartilage in, 1471, 1473f
cricoid ring in, 1473, 1473f
epiglottic cartilage in, 1471
epiglottis in, 1471f, 1473f
external carotid artery in, 1471f, 1473-1474
extrinsic strap muscles in, 1473f
false vocal cords in, 1472-1473, 1472f
hyoid bone in, 1471, 1471f, 1473f
internal carotid artery in, 1471f, 1473-1474
jugular veins in, 1471f, 1473-1474
laryngeal skeleton in, 1471
laryngeal ventricle in, 1472-1473
median glossoepiglottic fold in, 1471f
midsagittal plane in, 1473f
paralaryngeal (paraglottic) space in, 1471f, 1473
preepiglottic space in, 1471f, 1473, 1473f
pyriform sinuses in, 1471f, 1472
soft tissue structures in, 1471
sternocleidomastoid muscle in, 1471f
subglottic, 1473f
superior thyroid notch in, 1472f
supraglottic, 1471f
thyroid cartilage in, 1471, 1473f
true vocal cords in, 1472, 1472f-1473f
valleculae in, 1471f
surgical, 1541-1544
anterior commissure tendon in, 1541-1542
cartilage in, 1541

Larynx *(Continued)*
connective tissue barriers in, 1542-1543, 1544f
conus elasticus in, 1541-1542, 1542f
cricothyroid ligament in, 1541-1542
epiglottis in, 1541
hyoid bone in, 1541
hypoepiglottic ligament in, 1541-1542
paraglottic space in, 1542, 1543f
preepiglottic space in, 1542, 1543f
quadrangular membrane in, 1541-1542, 1542f
skeletal structure in, 1541, 1541f
thyrohyoid membrane in, 1541-1542, 1542f
vocal tendon in, 1541-1542
artificial (*See* Voice prosthesis(es))
benign mass(es) of, 1468
congenital cysts as, 1468
laryngocele as, 159-161, 163f, 1468, 1469f
squamous papillomas as, 1468, 1468f
subglottic hemangioma as, 1468, 1468f
benign mesenchymal neoplasms of, 878-882
chondroma as, 881-882
granular cell, 882
lipoma as, 881
mixed, 881
neurilemmoma as, 882
neurofibroma as, 882
oncocytic, 881
recurrent respiratory papillomatosis as, 868f-869f, 878-880
adult-onset, 879
epidemiology of, 878
etiology of, 878-879
juvenile form of, 879
treatment of, 879, 880f
rhabdomyoma as, 881
vascular, 880-881
laryngeal hemangiomas as, 880-881
polypoid granulation tissue as, 880
benign vocal fold mucosal disorders of (*See* Benign vocal fold mucosal disorder(s))
congenital disorder(s) of, 2866-2875
bifid epiglottis as, 2870t, 2874, 2874f
dysphagia due to, 2950t, 2951-2953, 2953f
hemangiomas and subglottic cysts as, 2871, 2871f
hypoplastic epiglottis as, 2870t
laryngeal cysts as, 2872-2873, 2872f-2873f
laryngeal webs/atresia as, 2869-2871
anterior, 2869-2870, 2869f-2870f
posterior, 2869, 2869f
subglottic stenosis as, 2870-2871
syndromes associated with, 2870t
laryngeal-laryngotracheoesophageal cleft as, 2873-2874, 2873f
classification of, 2873, 2874f, 2874t
syndromes associated with, 2870t
laryngomalacia as, 2866-2868, 2867f-2868f
syndromes associated with, 2870t
thyroglossal duct cyst as, 2871-2872, 2872f
vocal fold paralysis as, 2868-2869
connective tissue barriers within, 1542-1543, 1544f
electrical artificial, 1459
embryology of, 1482-1483
epiglottic flap closure of, for chronic aspiration, 928, 930f
foreign bodies in
endoscopic removal of, 2904
anesthesia for, 2940
imaging of, 1480-1481, 1480f-1481f
vs. ossification of stylohyoid ligament, 1480, 1481f
symptoms of, 2937-2938

Larynx *(Continued)*
functions of, 807-809, 833
in circulatory reflexes, 809, 810f
in control of ventilation, 808-809, 808f-809f
in cough, 808
as immune organ, 886-887, 887f
in protection, 808, 833
sensory receptors in, 809
in speech, 810-812, 811b, 811f, 833
GERD-related disease of, in children, 2944-2947
diagnosis of, 2945
disorders due to, 2945-2946, 2945b
evidence of, 2946
history of, 2944
management of, 2946
pathophysiology of, 2945
in geriatric patients, 234-237
acoustic changes in, 236
dental/mandibular changes in, 236
factors affecting vocal quality in, 234, 235t
glandular changes in, 236
histologic changes in, 234-235, 235f
laryngoscopic appearance in, 235-236
mucosal changes in, 236
respiratory changes in, 236
and sense of taste, 236
treatment of, 236-237
giant cell tumor of, 1510
imaging of, 159-161, 813-824, 1462-1481
with benign mass(es), 1468
congenital cysts as, 1468
laryngocele as, 159-161, 163f, 1468, 1469f
squamous papillomas as, 1468, 1468f
subglottic hemangioma as, 1468, 1468f
with carcinoma, 161, 164f
of anterior commissure, 1474, 1474f
of aryepiglottic fold, 1475, 1478f
with cartilaginous invasion, 1474-1475, 1476f
of epiglottis, 1475, 1477f
glottic, 1474-1475, 1474f
with lymph node metastases, 1476, 1479f
normal anatomy and, 1470-1474
paraglottic, 1474
post-therapy, 1476-1479, 1479f
of pyriform sinus, 1475-1476, 1478f
subglottic, 1474, 1475f
supraglottic, 1475-1476
technique for, 1470, 1470f
transglottic, 161, 164f, 1475f, 1476, 1478f
CT for, 132f, 140
flexible endoscopy for, 814
advantages of, 814
disadvantages of, 814
for professional voice disorders, 851-852, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
with foreign bodies, 1480-1481, 1480f-1481f
high-speed digital, 821-823
applications of, 823
assessment using, 822-823
defined, 813
equipment for, 821
kymography in, 134f, 154, 822f
limitations of, 823
with inflammatory disease, 1464-1466
croup as, 1465, 1465f
epiglottitis as, 159-161, 163f, 1406-1407, 1407f, 1464, 1464f-1465f
retropharyngeal abscess as, 1465-1466, 1466f
with laryngomalacia, 1466
MRI for, 142-143
narrow-band, 813, 823-824, 823f-824f
with normal airway, 1462-1464
anatomy of, 1462-1464, 1463f-1464f
technique for, 1462

Larynx *(Continued)*
rigid endoscopy for, 813-814
advantages of, 813
disadvantages of, 813-814
for professional voice disorders, 851, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
stroboscopy for, 818-821
of adynamic segments, 820
of amplitude of vibration, 820, 821f, 848, 848t
of closure pattern, 819, 820f, 848t, 849
common problems and solutions for, 815t-816t
defined, 813
flexible endoscopes in, 814
interpretation of, 848t
interval examination in, 847
of mucosal wave, 820, 848-849, 848t
in neurologic examination, 834
of periodicity, 821, 848, 848t
of phase closure, 819-820
for professional voice, 847-849, 848f, 848t
protocol for, 818-819, 818b
of regularity, 821
rigid endoscopes in, 813-814
of symmetry, 820, 847-848, 848t
of vertical closure level, 821
for vocal fold impairment, 905
with trauma, 159, 162f, 1479-1480, 1480f
videoendoscopy for, 814-818
of arytenoid and vocal fold motion, 816
common problems and solutions for, 815t-816t
defined, 813
flexible endoscopes for, 814
of laryngeal structure, 816
of mucous, 816-817
in neurologic examination, 834
protocol for, 814, 816b
rigid endoscopes for, 813-814
of supraglottic activity, 817, 817f
of vascularity, 817
of vocal fold edges, 818
with vocal cord paralysis, 1466-1467, 1467f
inflammatory disease of, 1464-1466
croup as, 1465, 1465f
epiglottitis as, 159-161, 163f, 1406-1407, 1407f, 1464, 1464f-1465f
retropharyngeal abscess as, 1465-1466, 1466f
inflammatory myofibroblastic tumor of, 1509-1510
lymphatic drainage of, 1578-1579, 1579f, 2582
metastases to, 1510
mucosal lining of, 1484
mucous in, videoendoscopy of, 816-817
necrotizing sialometaplasia of, 1493
neoplasms of uncertain behavior of, 1509-1510
neurologic disorders of, 837-843
hyperfunctional, 838-842
botulinum toxin therapy for, 839, 840f-841f
due to dystonia, 838-839, 838b
essential tremor as, 840-841
due to myoclonus, 840
due to pseudobulbar palsy, 839-840
stuttering as, 841-842
hypofunctional, 842-843
due to central causes of vocal fold paresis, 842
due to medullary disorders, 842
due to multiple sclerosis, 843
due to myopathies, 842
due to neuromuscular junction disorders, 842
due to Parkinson's disease, 842-843
due to poliomyelitis, 842

Larynx *(Continued)*
psychogenic, malingering, and mixed causes of, 843
vocal fold paresis as, 843
laryngologic manifestations of neurologic diseases as, 837-838, 838t
neurologic evaluation of, 832-836
acoustic analysis in, 834-835
aerodynamic assessment in, 835
cineradiography in, 835-836
edrophonium test in, 835
electromyography in, 835, 905
flexible laryngoscopy in, 834
glottography in, 835
indications for, 832-833, 833b
normal function and, 833
performance measures in, 835-836
rating scales in, 834
sensory assessment in, 836
during pharyngeal swallow, 1216-1217, 1216f
physical examination of, 99-100, 99f-100f
flexible endoscopy in, 100
postnasal descent of, 805, 806f
premalignant lesions and carcinoma in situ of, 1486-1491, 1489f-1490f, 1515
treatment of, 1489-1490, 1490t
in-office, 1490-1491
pseudoepitheliomatous hyperplasia of, 1493
pseudoretropharyngeal mass of, 1462, 1463f
saccular disorders of, 876-878
classification of, 876f, 877
clinical scenario with, 877
diagnosis of, 877
etiology of, 876
laryngocele as, 876f, 877
laryngopyocele as, 877
saccular cysts as, 877, 877f
anterior, 876f-877f, 877
lateral, 876f, 877, 878f
treatment of, 877-878
sensory receptors in, 807, 809
during swallowing, 833
systemic medicines that may affect, 863
taste buds in, 1208
vascularity of, videoendoscopy of, 817
Laser(s)
argon (Ar), 30, 31t
argon tunable (pumped) dye, 30, 31t
beam pattern of, 27
beam waist of, 27-28, 28f
carbon dioxide, 31t, 32-33
cavity dumped, 34
continuous wave, 33
control of, 26-28
exposure time in, 28
power in, 27, 29f
spot size in, 27-28, 28f-29f
defined, 26
depth of focus of, 27-28, 28f
erbium:YAG, 33
flash lamp pulsed, 33-34
flash lamp pumped dye, 31t, 33
fluence of, 28
focal length of lens of, 28
focal plane of, 28, 28f
history of, 25-26
holmium:YAG, 33
irradiance of, 27
KTP, 31t, 33
mode-locked, 34
neodymium:YAG, 31t, 32
pulse structure of, 33-34
pulsed, 30
pulsed dye, 31t, 33
Q-switched, 34
quantum physics of, 26, 26f
safety considerations with, 34-37
Laser(s) *(Continued)*
anesthesia and risk of intraoperative fire as, 36-37
education on, 34
eye protection as, 34-35, 35f-36f
protocol for, 34
effectiveness of, 37
skin protection as, 35
smoke evacuation as, 35
tissue effects of, 28-30, 30f
types and applications of, 30-33, 31t
wound created by, 29-30, 30f
Laser ablation, 30
interventional bronchoscopy with, 1010t
Laser device, 26, 27f
Laser Doppler velocimetry, for assessment of nasal airway, 643-644
Laser midline glossectomy (LMG), for obstructive sleep apnea, 259
Laser resurfacing, 399-402
CO_2, 400, 400f
complications of, 402
Er:YAG, 400
nonablative, 402, 403t
postoperative care after, 401-402, 401f
results of, 401f-402f
Laser surgery, 25-37
endotracheal tubes for, 36-37
for hemangioma of infancy, 2827f-2828f, 2828
history of, 25-26
for laryngeal stenosis, 2918
for recurrent respiratory papillomatosis
with carbon dioxide laser, 879, 2889-2891
pulsed dye laser for, 880, 880f, 2891
for skin lesions, 294
for stridulous child, 2908-2909, 2908f
for tracheal stenosis, 2928, 2929f
Laser vaporization, for unresectable tracheal tumor, 1619-1621
Laser-assisted uvulopalatoplasty, in vocal professional, 858
"Laser-safe" endotracheal tube, with recurrent respiratory papillomatosis, 2891
Lassa fever, sensorineural hearing loss due to, 2158-2159
sudden, 2127
LAT (lidocaine-adrenaline-tetracaine) anesthesia, for facial trauma, 304
Lateral ala, thinning of, in cleft-lip nose repair, 562f
Lateral alar angle, 509f
Lateral ampullary nerve, 1854f, 2278f
Lateral arm flap, 1082t, 1083
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379-1380
of tongue base, 1389
of tonsils and pharyngeal wall, 1386-1387
Lateral arteriorrhaphy, for vascular repair, 1632-1633, 1634f
Lateral canal benign paroxysmal positional vertigo
positional testing for, 2315-2316, 2331
repositioning maneuver for, 2332
Lateral canthal angle, 442
Lateral canthal tendon, 439
Lateral cantholysis, for pediatric facial fracture, 2704f
Lateral canthoplasty, 2420-2421
Lateral canthus, in brow or forehead rejuvenation, 434, 434f
Lateral cephalometric radiograph, for mentoplasty, 463, 463f
Lateral cervical space, 158, 162f
Lateral cranial base, surgical anatomy of, 2434-2438, 2442, 2443f, 2488-2489
abducens nerve in, 2439f
anterior clinoid process in, 2435f
anterior cranial fossa in, 2435f
Lateral cranial base, surgical anatomy of *(Continued)*
anterior division in, 2442-2444
anterior boundaries of, 2442, 2443f
boundaries in, 2442, 2443f
craniofacial junction in, 2442, 2443f
extracranial structures related to, 2443, 2444f
superior boundaries of, 2442-2443, 2443f
and surgical landmarks of orbital skeleton, 2443-2444, 2444f
anterior inferior cerebellar artery in, 2437f, 2439f
arcuate eminence in, 2436f, 2437
Bill's bar (vertical crest) in, 2437-2439
brainstem in, 2439f
bulbopontine sulcus in, 2439f
carotid artery canal in, 2435f-2436f, 2438
carotid artery in, 2436f, 2438
cerebellar floccules in, 2439f
cerebellar hemispheres in, 2439f
cerebellar horizontal fissure in, 2439f
cerebellar olive in, 2439f
cerebellopontine angle in, 2438
chorda tympani nerve in, 2436f, 2439f, 2441
choroid plexus in, 2439f
clivus in, 2435f
cochlea in, 2437f, 2438
cochlear aqueduct in, 2435f
cochlear modiolus in, 2439
cochlear nerve in, 2437f, 2439
craniofacial junction in, 2442, 2443f
cribriform plate in, 2435
digastric groove in, 2436f
digastric sulcus in, 2435-2436, 2435f
dural septum in, 2437f
emissary vein in, 2436f
epitympanum in, 2438
eustachian tube in, 2436f-2437f, 2438
eustachian tube opening in, 2436f
external auditory canal in, 2435, 2435f
external carotid artery in, 2440f
facial hiatus in, 2436f, 2437
facial nerve in, 2436f-2437f, 2438-2439, 2439f-2440f
facial recess in, 2436f
foramen lacerum in, 2435f, 2436-2437
foramen magnum in, 2435f
foramen ovale in, 2435f, 2436-2438, 2437f
foramen rotundum in, 2435f, 2438
foramen spinosum in, 2434, 2435f, 2437-2438, 2441
gasserian ganglion in, 2437f, 2438, 2440f
geniculate ganglion in, 2436f-2437f, 2438
glenoid fossa in, 2435f
glossopharyngeal nerve in, 2436f-2437f, 2438, 2439f-2440f, 2440
greater superficial petrosal nerve in, 2437f, 2438
greater wing of sphenoid bone in, 2434, 2435f
hypoglossal nerve canal in, 2435f
hypoglossal nerve in, 2439f-2440f
incus in, 2436f
incus-malleus articulation in, 2436f, 2438
incus-stapes articulation in, 2436f
inferior oblique muscle in, 2439f
inferior orbital fissure in, 2441
inferior vestibular nerve in, 2437f, 2439
infratemporal cranial fossa in, 2440-2441, 2440f
internal acoustic pore (porus acusticus) in, 2437-2438
internal auditory artery in, 2437f, 2439f
internal auditory canal in, 2435f-2437f, 2438-2439
internal carotid artery in, 2436f-2437f, 2439f-2440f
internal maxillary artery in, 2440f
jugular bulb in, 2436f-2437f
jugular foramen in, 2435f-2436f, 2438-2440, 2439f-2440f
jugular process in, 2435f

Lateral cranial base, surgical anatomy of *(Continued)*
jugular tuberculum in, 2435f
jugular vein in, 2436f, 2439f-2440f
lateral pterygoid muscle in, 2441
lateral pterygoid process in, 2435f
lateral semicircular canal in, 2436f, 2439f
mandible in, 2440f
mandibular division of trigeminal nerve in, 2437f, 2438, 2440f, 2441
masseter muscle in, 2440f
mastoid antrum in, 2438
mastoid bone in, 2435, 2435f
mastoid process in, 2435
mastoid tegmen in, 2435f
mastoid tip in, 2435f
maxillary artery in, 2441
maxillary division of trigeminal nerve in, 2437f, 2438, 2440f
medial pterygoid muscle in, 2441
medial pterygoid process in, 2435f
middle cranial fossa in, 2434, 2435f-2437f, 2438
middle division in, 2444
boundaries in, 2442, 2443f
craniofacial junction in, 2442, 2443f
extracranial view of, 2444, 2445f
foramina along floor of, 2444, 2445f
intracranial view of, 2444, 2445f
lateral pterygoid plate in, 2444, 2445f
lateral view of, 2444, 2445f
sphenoid spine in, 2444
superomedial boundary of, 2444
middle meningeal artery in, 2437f, 2438, 2440f
middle meningeal artery sulcus in, 2436f
nervus intermedius (of Wrisberg) in, 2437f
occipital bone in, 2435f
occipitomastoid suture in, 2435, 2435f
oculomotor nerve in, 2439f
ophthalmic division of trigeminal nerve in, 2437f, 2438
ossicular chain in, 2436f
parietal bone in, 2434
parietomastoid suture in, 2435, 2435f
parotid gland in, 2439f-2440f
petroclival sutures in, 2436
petro-occipital sulcus in, 2435f, 2438
petro-occipital suture in, 2438
petrosphenoid suture in, 2435f
petrosquamous suture in, 2434, 2436f
petrotympanic suture in, 2435
petrous apex in, 2435f, 2436
petrous bone in, 2436, 2437f
petrous bone projection in, 2435f
pons in, 2439f
pontine-mesencephalic sulcus in, 2439f
posterior clinoid process in, 2435f
posterior cranial fossa in, 2435f, 2438-2440, 2439f
posterior division in, 2442, 2443f
posterior semicircular canal in, 2436f, 2439f
pteroygoid venous plexus in, 2441
pteroygomaxillary fissure in, 2441
pteroygomaxillary fossa in, 2435f
pyramidal eminence in, 2436f
quadrangular cerebellar lobule in, 2439f
rectus capitis major muscle in, 2439f
rectus lateralis muscle in, 2439f
round window niche in, 2436f
sella in, 2435f
semicanal of tensor tympani muscle in, 2436f
sigmoid sinus impression in, 2435f
sigmoid sinus in, 2436f, 2439f-2440f
sphenoid bone in, 2435f
sphenopalatine foramen in, 2435f
spinal accessory nerve in, 2436f, 2438, 2439f-2440f, 2440
squamosa in, 2434, 2435f-2436f
stapes in, 2436f

Lateral cranial base, surgical anatomy of *(Continued)*
stapes tendon in, 2436f
styloid process in, 2435, 2435f
stylomastoid foramen in, 2435
subarcuate artery in, 2439f
subarcuate fossa in, 2435f, 2438
superior laryngeal nerve in, 2440f
superior oblique muscle in, 2439f
superior orbital fissure in, 2435f, 2438
superior petrosal sinus impression in, 2435f
superior petrosal (petrous) sinus in, 2436f, 2438
superior petrosal vein in, 2439f
superior semicircular canal in, 2436f-2437f, 2439f
superior vestibular nerve in, 2437f, 2438-2439
suprameatal spine in, 2435f
tegmen mastoideum in, 2438
tegmen tympani in, 2438
temporal bone in, 2434, 2436f
temporis muscle in, 2440f
tensor tympani muscle in, 2437f, 2438
transverse (falciform) crest in, 2437f, 2439
transverse sinus in, 2436f, 2439f
Trautmann's triangle in, 2436f
trigeminal depression (Meckel's cave) in, 2435f, 2436-2437
trigeminal impression in, 2435f
trigeminal nerve in, 2439f
trochlear nerve in, 2439f
tympanic bone in, 2434-2435, 2435f, 2439f
tympanic membrane in, 2436f
tympanic sulcus in, 2435
tympanomastoid suture in, 2434-2435, 2435f
tympanosquamous suture in, 2434, 2435f
vagus nerve in, 2436f-2437f, 2438, 2439f-2440f, 2440
vertebral artery in, 2439f
vestibular aqueduct in, 2435f
vestibulocochlear nerve in, 2438, 2439f
zygoma in, 2435f-2436f
Lateral cranial base lesion(s)
aneurysms of upper cervical and petrous internal carotid artery as, 2504, 2504f-2505f
evaluation of, 2489-2492
carotid management algorithms in, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
qualitative, 2490-2491
quantitative, 2491
CT and MRI for, 2489
four-vessel arteriography in, 2489-2490, 2491f
preoperative carotid artery management in, 2489
algorithm for, 2490f, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
four-vessel arteriography in, 2489-2490, 2491f
postsurgical and postinfectious encephalocele and CSF leaks as, 2509
Lateral cranial base neoplasm(s)
carcinoma as, 2502-2504
management of, 2502-2504, 2503f
pertinent anatomy for, 2502
staging of, 2502, 2502f, 2503b
symptoms and signs of, 2502
of cavernous sinus, 2509-2510
choice of surgical approach for, 2492-2501
chordoma as, 2510, 2511f
of clivus, 2509
evaluation of, 2489-2492
carotid management algorithms in, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
qualitative, 2490-2491
quantitative, 2491
CT and MRI for, 2489

Lateral cranial base neoplasm(s) *(Continued)*
four-vessel arteriography in, 2489-2490, 2491f
preoperative carotid artery assessment in, 2489, 2490f
facial nerve schwannomas as, 2506-2508
diagnostic evaluation of, 2507
management and surgical approach to, 2507-2508
of jugular foramen, 2504
schwannomas as, 2504-2505, 2505f
paragangliomas as, 2505-2506
diagnostic evaluation of, 2505, 2506f-2507f
preoperative evaluation of, 2491f
radiotherapy for, 2506
surgical approach to, 2505-2506, 2507f
symptoms of, 2505
of parapharyngeal space, 2510, 2512f
of petrous apex, 2508, 2508f
sleeve resection of external auditory canal for, 2492
Lateral cranial base surgery, 2487-2513
choice of approach for, 2492-2501
complications of, 2511-2513
intraoperative, 2511
postoperative, 2512-2513
cerebrovascular, 2512-2513
cranial nerve deficits as, 2512
encephalocele and CSF leaks as, 2509
infratemporal fossa approaches for, 2495-2501
postauricular, 2495-2500
cervical dissection in, 2495, 2498f
closure of external auditory canal in, 2495, 2497f
closure of wound in, 2499, 2499f
exposure of jugular bulb and internal carotid artery in, 2498, 2498f-2499f
extratemporal facial nerve dissection in, 2495-2496
facial nerve transposition in, 2497-2498, 2498f
incisions and skins flaps in, 2495, 2497f
occlusion of sigmoid sinus in, 2498, 2498f
radical mastoidectomy in, 2496, 2498f
removal of external auditory canal wall skin and tympanic membrane in, 2495, 2497f
tumor removal in, 2498-2499, 2499f
type A, 2497-2499, 2498f-2499f
type B, 2499-2500, 2500f
type C, 2500, 2501f
preauricular, 2500-2501, 2501f
for nasopharyngeal tumors, 2510-2511
postsurgical encephalocele and CSF leaks with
diagnostic evaluation of, 2509
surgical approach to, 2509
Lateral cricoarytenoid (LCA) muscle
applied anatomy of, 806
characteristics of, 918
in professional voice production, 846-847
Lateral cricothyroid muscle, applied anatomy of, 806
Lateral crural grafts, in revision rhinoplasty, 589-590, 590f
Lateral crus(crura), of alar cartilage, 496-497, 497f, 509f
in cleft-lip nose repair, 562f
transposition of, 551
Lateral facial approach, for middle cranial base surgery, 2462, 2465f
Lateral lamella of cribriform plate (LLCP), and CSF rhinorrhea, 787, 787f
Lateral lemniscal nuclei, in central auditory pathway, 1835-1836, 1835f
Lateral lemniscus, in central auditory pathway, 1835-1836, 1835f, 1846
Lateral medullary syndrome, 2313, 2352f, 2354f

Lateral nasal prominences, in embryology
of lip, 2660, 2661f-2662f, 2661t
of nose, 2691f
Lateral nasal wall, in surgical anatomy of anterior cranial base, 2472, 2472f-2473f
Lateral nasal wall deformities, revision rhinoplasty for, 586
Lateral neck dissection, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
Lateral olfactory tract, 628f
Lateral olivocochlear (LOC) reflex pathways, in efferent auditory system, 1848-1849
Lateral orbital rim, surgical access to, 328-329, 329f
Lateral orbital tubercle, 439
Lateral orbital wall, 439
Lateral orbital wall fractures, pediatric, 2712, 2714
Lateral periapical cyst, 1263
Lateral periodontal cyst, 1265-1266
microscopic features of, 1265-1266, 1265f
radiographic features of, 1265
treatment of, 1266
Lateral pharyngeal node, 1298f
Lateral pharyngeal space
anatomy of, 202
odontogenic infections of, 184-185, 186f
Lateral pharyngotomy approach
for hypopharyngeal cancer, 1426-1427
for oropharyngeal cancer, 1371, 1371f
Lateral pontomedullary syndrome, 2353f
Lateral process, 1824, 1825f, 1826-1827
Lateral pterygoid muscle
anatomy of, 1320
in surgical anatomy of lateral skull base, 2441
Lateral pterygoid plate, in surgical anatomy of middle cranial base, 2444, 2445f
Lateral pterygoid process, in surgical anatomy of lateral skull base, 2435f
Lateral radicular cyst, 1263
Lateral rectus muscle(s)
semicircular canal planes and, 2285-2287, 2286f-2287f
in surgical anatomy of anterior cranial base, 2472f
Lateral retropharyngeal nodes, 1422
Lateral rhinotomy
for middle cranial base surgery, 2455t, 2458, 2458f
for nasopharyngeal carcinoma, 1355-1356, 1355f
Lateral semicircular canal (LSSC)
anatomy of, 1826f, 1827, 1851f, 1854f, 2278f
dysplasia of, 2732, 2732f-2733f
imaging of, 1922f
in surgical anatomy of lateral skull base, 2436f, 2439f
Lateral sinus thrombosis
epidemiology of, 1980t-1981t
imaging of, 1996f-1997f, 1997
otitis media and, 2777
pathogenesis of, 1996
signs and symptoms of, 1996-1997
treatment of, 1997
Lateral skull base. *See* Lateral cranial base.
Lateral superior olive (LSO), in auditory pathway, 1834-1835, 1834f, 1846
Lateral thigh flap(s), 1082t
for hypopharyngeal and esophageal reconstruction, 1455
for oropharyngeal reconstruction, 1379
of tongue base, 1390-1391
of tonsils and pharyngeal wall, 1386-1387
Lateral transtemporal sphenoid approach, for middle cranial base surgery, 2462, 2465f
Lateral transthyroid pharyngotomy, for hypopharyngeal cancer, 1427, 1428f
Lateral vertical buttress, 319, 331, 331f
Lateral vestibular nucleus (of Dieters), 1860-1861, 1862f
Lateral vestibulospinal tract, in postural balance, 1865
Lateral view, of facial bones and sinuses, 130
Lateralized radicular cyst, 1263
Latex, adverse reactions to, 102
Lathyrogenic drugs, for caustic ingestion, 2959
Latissimus dorsi musculocutaneous flap, for oropharyngeal reconstruction, 1378, 1378f
of tongue base, 1389
Latissimus dorsi myocutaneous free flap, 1082t, 1083-1084, 1084f
for hypopharyngeal and esophageal reconstruction, 1452
for oropharyngeal reconstruction, 1380
of tongue base, 1389-1390, 1390f
LATS (long-acting thyroid stimulator), 1741
LC. *See* Laryngeal cleft (LC).
LCA (lateral cricoarytenoid) muscle
applied anatomy of, 806
characteristics of, 918
in professional voice production, 846-847
LCH. *See* Langerhans' cell histiocytosis (LCH).
LCR (laryngeal chemoreflex), 2570
LDH (lactate dehydrogenase), with melanoma, 1109-1110, 1113
LDL (low-density lipoprotein) cholesterol, subclinical hypothyroidism and, 1747
Leapfrog Group, 84t-87t, 87
Learning problems, obstructive sleep apnea and, 2603-2604
Leeches, medicinal, for flap salvage, 1075, 1098
LeFort I fractures, 326, 327f
pediatric, 2707
repair of, 334-335, 334f
LeFort I osteotomy(ies)
in cleft-lip nose repair, 559, 564f-565f
for juvenile nasopharyngeal angiofibroma, 1350-1351
for middle cranial base surgery, 2455t, 2458, 2460f
LeFort II fractures, 326, 327f
pediatric, 2707
repair of, 335-336, 335f-336f
LeFort III fractures, 326, 327f
pediatric, 2707
Left anterior–right posterior (LARP) semicircular canal plane, 2285, 2286f, 2287, 2288f
Legal issues
with difficult airway, 110
with noise-induced hearing loss, 2149-2151
Leiomyoma
esophageal, 1415-1416, 1415f
of trachea, 1613
Leiomyosarcoma, of neck, 1670
Leksell, Lars, 1696
Lemierre's syndrome, due to deep neck space infections, 207
Length-to-width ratio, of skin flaps, 1068, 1068f
Lentigo, solar (actinic, senilis), 288
Lentigo maligna (LM), 1108
surgical excision of, 1114
Lentigo maligna melanoma (LMM), 287f, 1108
surgical excision of, 1114
Lentiviral vectors, for gene transfer, 16, 18t
Leprosy, laryngitis due to, 885
Leptomeningeal nevus flammeus, 291
LES. *See* Lower esophageal sphincter (LES).
Leser-Trélat sign, 282
Lesser occipital nerve, 2578, 2580f
Lesser palatine nerve, 1297f
Lesser wing of sphenoid bone, in surgical anatomy of middle cranial base, 2444, 2445f
Lesser zygomatic muscle, reinnervation of, 2423f
Letterer-Siwe disease, 2100-2101
oral manifestations of, 1257
otologic manifestations of, 2102f
otorrhea as, 2196
Leucine-rich transmembrane *O*-methyltransferase *(LRTOMT)* gene, in deafness, 2051t-2058t
Leucovorin, for induction chemotherapy, 1056
Leukemia
oral manifestations of, 1256
otologic manifestations of, 2107, 2108f
otorrhea as, 2197
sensorineural hearing loss due to, 2123
Leukocytosis, in deep neck infections, 204
Leukoedema, oral, 1222-1223
clinical features of, 1222, 1223f
defined, 1222
etiology and pathogenesis of, 1222
histopathologic features of, 1222, 1223f
management of, 1223
Leukoencephalopathy, progressive multifocal, HIV-associated, 223
Leukoplakia
candidal, 1231, 1231f
oral, 1223-1225
chemoprevention of, 1225
clinical features of, 1224-1225, 1224f
defined, 1223
etiology of, 1223-1224, 1223f-1224f
hairy, 1226, 1226f
in HIV, 225-226, 226f
histopathologic features of, 1225, 1226f
malignant transformation of, 1223, 1298
proliferative verrucous, 1225, 1225f
thin, 1224f, 1225
of tongue, 1362f
treatment of, 1225
Leukoplakic-type hyperkeratosis, 1231, 1231f
Leukotriene modifiers
for allergic rhinitis, 620-621
for rhinosinusitis, 735t, 736
Levator anguli oris, 321f
Levator aponeurosis, 443f, 444
in upper eyelid blepharoplasty, 448
Levator labii, 442f
Levator labii superioris, reinnervation of, 2423f
Levator nasi, 442f
Levator palpebrae, 321f
Levator palpebrae superioris, 444
Levator repositioning, for velopharyngeal dysfunction, 2682
Levator scapulae muscle, 2579f
Levator veli palatini (LVP) muscle
anatomy of, 1360f, 1868f, 1870
in cleft palate, 2666-2667
development of, 1866
in pressure equalization, 1870
in velopharyngeal function, 2676, 2677t
Levels of evidence, 69-70, 70t
Lever ratio, in auditory physiology, 1840, 1840f
Levetiracetam, for neuropathic pain, 244t
Levocetirizine (Xyzal), for nonallergic rhinitis, 701t
Levothyroxine, oral synthetic (Euthyrox, Levothroid, Levoxyl, Synthroid, Unithroid), for hypothyroidism, 1748-1749
Lexical Neighborhood Test (LNT), for cochlear implant, 2225-2226
Lhermitte's sign, due to radiotherapy, 1049
LHFPL5 (lipoma HMGIC fusion partner-like 5) gene, in deafness, 2051t-2058t
Liability genes, 8
Licensure, maintenance of, 80-81
Lichen planus
esophageal manifestations of, 980
oral, 1226-1229, 1253-1254
atrophic or erythematous, 1227, 1227f
bullous variant of, 1227-1228
clinical differential diagnosis of, 1228
clinical features of, 1227-1228
erosive, 1227, 1228f
etiology and pathogenesis of, 1227
histopathologic features of, 1228, 1228f

Lichen planus *(Continued)*
and oral carcinoma, 1229, 1298-1299
plaque form of, 1227
reticular-type, 1227, 1227f
systemic diseases and, 1228
treatment of, 1228
Lichenoid dysplasia, 1229
Lichenoid lesion, oral, 1229
Lid crease, 442, 443f
Lid lag, in Graves' ophthalmopathy, 1808
Lid shortening procedure, 449
Lidocaine (Xylocaine)
with anesthesia induction, 111-112
in children, 2590
for facial trauma, 304
for prevention of bronchospasm during anesthesia, in children, 2595
and skin flap viability, 1073
Lidocaine (Xylocaine) block, for neuropathic pain, 245
Lidocaine (Xylocaine) provocation test, for embolization, 1934
Lidocaine-adrenaline-tetracaine (LAT) anesthesia, for facial trauma, 304
LIFE (lung imaging fluorescence endoscope) system, for early glottic carcinoma, 1516
Lifelong learning, 79t
Lifestyle modifications, for GERD, 969-970
Lighted stylet, for difficult airway, 114t
Lightheadedness, 2308-2310
Limbus, 1832f
Limen nasi, 641
Limen vestibuli, 641
LINACs. *See* Linear accelerator(s) (LINACs).
Lindbergh Operation, 39
Linear acceleration, encoding of, 2277-2285
by afferents in, 2283-2285, 2283f-2284f
cupula in, 2282f
otoconial membrane in, 2283
sensory transduction in, 2277-2279
anatomy of vestibular end organs in, 2277, 2278f
bidirectional sensitivity in, 2278-2279
cupula in, 2277, 2278f
firing rate in, 2278-2279, 2281f
hair cells in, 2277
otolith organs in, 2278, 2281f
stereocilia in, 2277-2278, 2279f
Linear accelerator(s) (LINACs), 1034
block diagram of, 1034f
megavoltage x-rays produced by, 1034
orthovoltage x-rays produced by, 1034
photograph of, 1035f
radiation production from, 1032-1033
in stereotactic radiation therapy, 2557-2558, 2560t
Linear accelerator (LINAC)-based stereotactic irradiation, for malignant skull base tumors, 1696
Linear amplification, for hearing aids, 2268, 2268f
Linear jerk, 2284
Linear predictive coding (LPC) spectrum, in acoustic analysis for voice evaluation, 829t, 830, 830f
Linear tomography, of pharynx and esophagus, 1393
Lingual artery, 1295, 1296f, 2579-2580, 2580f
Lingual frenulum, 1297-1298
Lingual muscles, 1205
Lingual nerve, 1296f, 1297-1298
Lingual nerve injury, due to neck surgery, 1731
Lingual reflexes, 1205
Lingual thyroid gland, 161-162, 165f, 1287, 1736
Lingual tonsil(s), in immune system, 605
Lingual tonsillectomy, for obstructive sleep apnea, 259
Lingual veins, 1295
Lingualplasty, for obstructive sleep apnea, 259
Lip(s)
aesthetic analysis of, 274-275, 278f
anatomy of, 1296-1297
burns of, 316
cancer of, 1302
lymphatic drainage of, 1296-1297, 1297f
neurologic examination of, 833-834
physical examination of, 98
squamous cell carcinoma of, 1302-1304
clinical findings in, 1294f, 1302, 1302f
epidemiology of, 1302
neck metastases of, 1303-1304
prognostic features of, 1303
resection and reconstruction of, 1303-1304, 1303f
Abbe-Estlander flap in, 1303-1304, 1303f
Karapandzic fan flap in, 1303-1304, 1303f
survival with, 1304
trauma to, 309-310, 309f
Lip defects, 350-353
classification of, 351
greater than two-thirds width, 352
lateral, 352
less than one-half width, 351
primary wound closure for, 351
V-Y musculocutaneous island pedicle flap for, 356f
lower
algorithm for, 351, 355f
midline, 352-353
massive or near-total, 352-353, 357f-358f
melolabial transposition flap for, 353
temporal forehead flap for, 353
from one half to two thirds, 351
Abbé flap for, 352
Estlander flap for, 352, 356f
Karapendzic flap for, 351
lip switch flap for, 351
local *vs.* regional flaps for, 352
upper
algorithm for, 351, 355f
large, 352
V-Y advancement flap for, 347f
Lip switch flap, 351
Lip wedge excision, 2431, 2431f
Lipectomy
submental, 456
suction, 452, 456
Lipid(s), subclinical hypothyroidism and, 1747
Lipid-lowering drugs, sensorineural hearing loss due to, 2121
Lipoadenoma, of parathyroid gland, 1778
Lipoatrophy, facial, HIV-associated, 227-228, 228f
Lipocontouring. *See* Liposuction.
Lipofection, 15
Lipoma(s), 293
of cerebellopontine angle, 2527, 2529f-2530f
imaging of, 1928, 1929t
in children, 2819
hypopharyngeal, 1425f
of internal auditory canal, 2527, 2529f
of larynx, 881
of neck, 1663
atypical, 1670
neck masses due to, 1641
in children, 2819
of oral cavity, 1291
parotid, 1166, 1167f
Lipoma HMGIC fusion partner-like 5 *(LHFPL5)* gene, in deafness, 2051t-2058t
Lipopeptides, and toll-like receptors, 598
Lipopolysaccharides (LPSs), and Toll-like receptors, 598
Lipoproteins
subclinical hypothyroidism and, 1747
and Toll-like receptors, 598
Liposarcoma, of neck, 1670
Liposarcoma of the larynx (LSL), 1508
Liposhaving, 452, 456, 458f
Liposome vector, for gene therapy, 16, 19f
of inner ear, 2191t
Liposuction, 452-460
adipocyte hyperplasia and, 452
anesthesia for, 456
common pitfalls in, 453, 455f
complications of, 459
defined, 452
instrumentation for, 453, 455f
integration into facial plastic and reconstructive surgery of, 452, 453f
patient preparation for, 455, 455f
patient selection for, 452-453, 454f
postsurgical dressing after, 459, 459f
recovery phase after, 459
results of, 459, 460f
surgical technique for, 456-459
determining depth of dissection in, 456, 457f
developing subcutaneous tunnels in, 456, 456f
distal feathering in, 456, 457f
identification of plane of dissection in, 456, 456f
incisions in, 456
liposhaving in, 456, 458f
multiple distal tunneling in, 456, 457f
open, 456-459
with other cosmetic procedures, 456-459
sites that can be approached in, 456, 458f
submental lipectomy in, 456
suction lipectomy in, 456
ultrasonic, 452
Lithium, for hyperthyroidism, 1739t
Lithium carbonate, for Graves' disease, 1742-1743
Lithium compounds, hypercalcemia due to, 1784
Little's area, 682
in epistaxis, 686-687
Live-attenuated influenza vaccine (LAIV), to prevent otitis media, 2769
Liver disease, oral manifestations of, 1255
Liver failure, preoperative evaluation of, 103-106
LL. *See* Lymphoblastic lymphoma (LL).
LL-37, 599
LLCP (lateral lamella of cribriform plate), and CSF rhinorrhea, 787, 787f
LLR (long latency response)
auditory evoked, 1912, 1913f
electrically evoked, 1913-1914, 1913f
LM (lentigo maligna), 1108
surgical excision of, 1114
LMG (laser midline glossectomy), for obstructive sleep apnea, 259
LMM (lentigo maligna melanoma), 287f, 1108
surgical excision of, 1114
LNT (Lexical Neighborhood Test), for cochlear implant, 2225-2226
Lobes, of lung, 998
Lobular capillary hemangioma, sinonasal, 718t, 725, 725f
Lobule(s)
of ear, 476-477, 476f, 1824f, 2742f
reduction of, 478f
of lung, 998
Lobule transfer, in microtia reconstruction, 2746, 2747f
LOC (lateral olivocochlear) reflex pathways, in efferent auditory system, 1848-1849
Local anesthetic(s), 112
oral sequelae of, 1247t-1248t
Local anesthetic blocks, for neuropathic pain, 245
Local flap(s)
advancement, 345-346
bilateral, 345, 346f
island, 345
unipedicle, 345, 345f

Local flap(s) *(Continued)*
V-Y, 345-346, 346f-347f
Y-V, 346
classification of, 342-343, 343b
complications of, 366
hinge, 346
for hypopharyngeal and esophageal reconstruction, 1450-1452
for oropharyngeal reconstruction, 1376-1377
palatal island, 1376-1377, 1376f
of soft palate, 1381
buccinator musculomucosal, 1381-1382, 1381f
palatal island mucosal, 1382
Superior Constrictor Rotation-Advancement Flap (SCARF) as, 1382, 1382f
uvulopalatal, 1377f, 1381
tongue, 1376
of tonsils and pharyngeal wall, 1384-1385
uvulopalatal, 1377, 1377f
pivotal, 343-345
effective length of, 343, 343f
interpolated, 344-345, 344f
rotation, 343-344, 343f
transposition, 344, 344f
Local overpressure therapy, for Meniere's disease, 2338
Localization study(ies), for hyperparathyroidism, 1784-1789, 1784t
gamma radiation detection device for, 1802, 1803f
intraoperative, 1784t, 1789
invasive preoperative, 1784t, 1788-1789
parathyroid arteriography as, 1788
selective venous sampling for PTH as, 1788-1789
ultrasound-guided fine-needle aspiration as, 1789
mediastinal exploration as, 1801-1802, 1802f
noninvasive preoperative, 1784-1788, 1784t
computed tomography as, 1786-1787
computed tomography–sestamibi fusion as, 1785-1786, 1786f-1788f
magnetic resonance imaging as, 1787-1788, 1789f
pertechnetate (technetium 99m) thallous chloride (thallium 201) imaging as, 1784-1785
sestamibi–technetium 99m scintigraphy as, 1785, 1785f, 1788f, 1794f
technetium 99m sestamibi with single photon emission computed tomography as, 1785
ultrasonography as, 1786, 1789f
unsuccessful, 1801, 1801f-1802f
Lockwood's ligament, 439
LOH (loss of heterozygosity), in head and neck squamous cell carcinoma, 1019-1020, 1026
Long latency response (LLR)
auditory evoked, 1912, 1913f
electrically evoked, 1913-1914, 1913f
Long process incus, anatomy of, 1825f
Long-acting thyroid stimulator (LATS), 1741
Long-term average spectra (LTAS), in acoustic analysis for voice evaluation, 829t, 830
Long-term potentiation (LTP), in neural plasticity, 1882-1884
Longus capitis muscle, 2579f
Longus colli muscle, 2579f
Longus colli muscle flap, for lateral pharyngeal wall defects, 1384-1385
Loop diuretics
in noise-induced hearing loss, 2147
ototoxicity of, 2174-2175
sensorineural hearing loss due to, 2120
Loprox (ciclopirox olamine antifungal cream or solution), for fungal otitis externa, 1954-1955, 1959t-1960t
Loratadine (Claritin)
for allergic rhinitis, 620
for nonallergic rhinitis, 701t
for rhinosinusitis, 734t
Los Angeles classification, of erosive esophagitis, 969, 969f
Loss of heterozygosity (LOH), in head and neck squamous cell carcinoma, 1019-1020, 1026
Lotrimin (clotrimazole) cream, for fungal otitis externa, 1954-1955, 1959t-1960t
Lou Gehrig's disease, laryngeal hypofunction due to, 842
Low-density lipoprotein (LDL) cholesterol, subclinical hypothyroidism and, 1747
Lower esophageal sphincter (LES)
anatomy of, 953, 954f
in GERD, 895, 895b
impairment of, 1400
manometry of, 958, 958f
physiology of, 954, 955f
Lower esophageal sphincter (LES) pressure, 958f
Lower esophageal sphincter (LES) relaxation, transient, 954, 968
Lower eyelid
aesthetic analysis of, 445-446, 446f
paralysis of, 2420-2421, 2421f
Lower eyelid blepharoplasty, 448-449
subciliary approach to, 449, 450f-451f
transconjunctival approach to, 448-449, 450f
Lower eyelid retractors, 444
Lower jugular lymph nodes, in neck dissection, 1704, 1704f, 1706t
Lower lateral cartilage, of nose, 497f
in cleft-lip nose repair, 562f-564f
reshaping of, 577
Lower lip, of vocal folds, in mucosal wave propagation, 848-849
Lower lip defects
algorithm for, 351, 355f
midline, 352-353
LPC (linear predictive coding) spectrum, in acoustic analysis for voice evaluation, 829t, 830, 830f
LPR. *See* Laryngopharyngeal reflux (LPR).
LPSs (lipopolysaccharides), and toll-like receptors, 598
LRTOMT (leucine-rich transmembrane *O*-methyltransferase) gene, in deafness, 2051t-2058t
LSL (liposarcoma of the larynx), 1508
LSO (lateral superior olive), in auditory pathway, 1834-1835, 1834f, 1846
LSSC. *See* Lateral semicircular canal (LSSC).
L-strut, in septoplasty, 489-490, 490f
LTα (lymphotoxin α), 609t-610t
LTαβ (lymphotoxin αβ), 609t-610t
LTAS (long-term average spectra), in acoustic analysis for voice evaluation, 829t, 830
LTECs (laryngotracheoesophageal clefts), 2873-2874, 2873f
classification of, 2873, 2874f, 2874t
syndromes associated with, 2870t
LTP (long-term potentiation), in neural plasticity, 1882-1884
Lubrication, saliva in, 1140-1141
Ludwig classification, of hair loss, 376, 377f
Ludwig's angina
airway establishment for, 188
due to mandibular space infections, 184, 185f
Lugol's solution
for Graves' disease, 1742-1743
for hyperthyroidism, 1739t
Lumbar drains, for CSF rhinorrhea, 792
Lumbar puncture, for meningitis due to temporal bone infection, 1982
Lund-MacKay scoring system, 53
for chronic sinusitis, 674
Lung, anatomy of, 998-999
Lung carcinoma, tracheal invasion by, 1615
Lung function tests, for stridor, 2901
Lung imaging fluorescence endoscope (LIFE) system, for early glottic carcinoma, 1516
Lung volume(s), in children, 2570
Lung volume reduction, endoscopic/bronchoscopic, 1011
LVES (laryngeal videoendoscopy and stroboscopy). *See* Laryngeal stroboscopy; Laryngeal videoendoscopy.
LVP muscle. *See* Levator veli palatini (LVP) muscle.
Lyme disease, 2105-2106, 2400
diagnosis of, 2400
facial paralysis in, 2106, 2400
head and neck symptoms of, 2400
otologic manifestations of, 2106
sensorineural hearing loss due to, 2119
sudden, 2128
stages of, 2400
treatment of, 2400
Lymph node(s)
anatomy and classification in, 163-164
imaging of, 164-167
with extracapsular spread, 164-166, 167f
inflammatory (reactive), 164
with invasion of carotid artery, 166-167
metastatic
contrast-enhanced CT of, 164-165, 167f
MRI of, 165-166, 168f
with non-Hodgkin's lymphoma, 165-166, 167f
normal anatomy in, 166f
in immune system, 605
number of positive, in melanoma, 1111
Lymph node biopsy, sentinel. *See* Sentinel lymph node biopsy (SLNB).
Lymph node dissection
for melanoma
elective, 1114-1115
therapeutic, 1114, 1116
for salivary gland tumors, 1196-1197
Lymph node metastasis(es). *See* Cervical lymph node metastasis(es).
Lymph node regions, physical examination of, 96-97, 96f
Lymphadenitis, neck masses due to, 1638
Lymphadenopathy
in children
bacterial, 2818, 2818f-2819f
drug-induced, 2819
fungal, 2818-2819
reactive, 2818
suppurative, 2818, 2818f
viral, 2817-2818
imaging of, 164-167
CT of, 139
with extracapsular spread, 164-166, 167f
inflammatory (reactive), 164
with invasion of carotid artery, 166-167
metastatic
contrast-enhanced CT of, 164-165, 167f
MRI of, 165-166, 168f
MRI of, 142
with non-Hodgkin's lymphoma, 165-166, 167f
ultrasound imaging of, 143
in immunosuppressed patients, 218-219, 219t
neck masses due to, 1638
in children
bacterial, 2818, 2818f-2819f
fungal, 2818-2819
viral, 2817-2818
Lymphangiomas
of masticator space, 152, 153f
neck masses due to, 1640, 2815, 2815f
of posterior cervical space, 158, 162f
with salivary gland involvement, 2861f
Lymphatic clinical target volumes, selection and delineation of, 1044

Lymphatic drainage
of larynx and hypopharynx, 1578-1579, 1579f, 2582
of skin flaps, 1068
Lymphatic malformations, 2829-2830
associated conditions with, 2829-2830, 2831f
clinical assessment and behavior of, 2829, 2830f
diagnostic evaluation of, 2829
imaging of, 2824f, 2829
macrocystic, 2860-2861
mandibular overgrowth with, 2823f
of neck, 1640, 2815, 2815f
of salivary glands, 1172, 2860-2861, 2861f
sclerotherapy for, 2830-2831
spontaneous resolution of, 2830, 2831f
surgery for, 2831, 2832f
Lymphatic system
of neck, 1683, 1683f, 2582-2583
classification of cervical lymphatics in, 2582-2583
deep cervical lymph nodes in, 2582
for pharynx and larynx, 2582
superficial lymph nodes in, 2582
of oropharynx, 1359-1360, 1360f-1361f, 1361t
Lymphoblastic lymphoma (LL), 1679
clinical presentation of, 1674
fine-needle aspiration of, 1675
treatment and prognosis for, 1679
Lymphocytes
in allergic rhinitis, 616
B, 602f, 603
development of, 603
responses by, 603
T cell–dependent and T cell–independent, 606
in Graves' ophthalmopathy, 1807
intraepithelial, 605
large granular, 603-604
T, 600-603
cytotoxic, 601, 602f
development of, 600-601
effector, 601-603
helper, 601-602, 602f
priming of, 601
regulatory, 602-603
in wound healing, 1076
Lymphocytoma, due to Lyme disease, 2106
Lymphoepithelial carcinoma, of oropharynx, 1362
Lymphoepithelial cyst, benign, in HIV, 217-218, 218f
Lymphoepitheliomas, of hypopharynx and cervical esophagus, 1425
Lymphoid follicles, in immune system, 605
Lymphoid organs, 605
lymph nodes as, 605
Lymphoid stem cells, 599-600, 600f
Lymphoid tumors, of paranasal sinuses, 1131
Lymphoma(s)
biopsy of
core-needle, 1676
corticosteroids prior to, 1676
fine-needle aspiration, 1675-1676
open, 1676
Burkitt's, 1679
in children, 2838, 2839f
clinical presentation of, 1674
treatment and prognosis for, 1679
in children, 2819-2820, 2837
Burkitt's, 2838, 2839f
Hodgkin's, 2819, 2838-2840
clinical presentation of, 2819, 2839-2840
histopathology and molecular biology of, 2819, 2840, 2840f
imaging of, 2820f
management of, 2840
staging of, 2839-2840
neck masses due to, 2819-2820, 2820f
Lymphoma(s) *(Continued)*
non-Hodgkin's, 2819-2820, 2837
epidemiology of, 2837
histopathology and molecular biology of, 2838, 2839f
management of, 2838
presentation and evaluation of, 2837-2838, 2838t
staging of, 2838, 2839t
diffuse large B-cell, 1677-1678
clinical presentation of, 1674
of paranasal sinus and nasal cavity, 1680
treatment and prognosis for, 1680
of salivary glands, 1191-1192, 1192f
treatment and prognosis for, 1680
of thyroid, 1679
staging of, 1679
treatment and prognosis for, 1679
treatment and prognosis for, 1677-1678
of Waldeyer's ring, 1680
treatment and prognosis for, 1680
follicular, 1678
clinical presentation of, 1674
treatment and prognosis for, 1678
of head and neck, 1673-1681
biopsy of, 1674-1676
core-needle, 1676
corticosteroids prior to, 1676
fine-needle aspiration, 1675-1676
open, 1676
classification of, 1675, 1675t
clinical presentation of, 1674, 1674f
epidemiology of, 1673-1674
Hodgkin's, 1676-1677
clinical presentation of, 1674, 1674f
complications of, 1677
epidemiology of, 1673-1674
treatment and prognosis for, 1676-1677
nodal, 1676-1679
non-Hodgkin's
Burkitt's, 1674
clinical presentation of, 1674, 1674f
diffuse large B-cell, 1677-1678
epidemiology of, 1673
follicular, 1674, 1678
highly aggressive, 1674, 1679
indolent, 1674, 1678
lymphoblastic, 1674-1675
MALT, 1674, 1679-1680
mantle cell, 1678-1679
paranasal sinus and nasal cavity, 1680
salivary gland, 1679-1680
small lymphocytic, 1674, 1674f, 1678
thyroid, 1679
highly aggressive, 1679
clinical presentation of, 1674
treatment and prognosis for, 1679
Hodgkin's, 1676-1677
in children, 2819, 2838-2840, 2840f
clinical presentation of, 2819, 2839-2840
histopathology and molecular biology of, 2819, 2840, 2840f
imaging of, 2820f
management of, 2840
staging of, 2839-2840
clinical presentation of, 1674, 1674f
complications of, 1677
epidemiology of, 1673-1674
imaging of, 1674, 1674f
immunosuppression and, 213t, 217
staging of, 1676, 1677t
treatment and prognosis for, 1676-1677
of hypopharynx and cervical esophagus, 1424-1425
indolent, 1678
clinical presentation of, 1674
treatment and prognosis for, 1678
Lymphoma(s) *(Continued)*
lymphoblastic, 1679
clinical presentation of, 1674
fine-needle aspiration of, 1675
treatment and prognosis for, 1679
MALT, 1679-1680
clinical presentation of, 1674
of salivary glands, 1191-1192, 1192f, 1679-1680
treatment and prognosis for, 1680
of thyroid, 1679
staging of, 1679
treatment and prognosis for, 1679
mantle cell, 1678-1679
treatment and prognosis for, 1678-1679
mediastinal mass ratio for, 1676
of nasal cavity, 1680
therapy and prognosis for, 1680
of neck, 1671
neck masses due to, 1640
in children, 2819-2820, 2820f
NK/T, of nasal cavity, 1680
therapy and prognosis for, 1680
non-Hodgkin's
Burkitt's, 1674
in children, 2819-2820, 2837
epidemiology of, 2837
histopathology and molecular biology of, 2838, 2839f
management of, 2838
presentation and evaluation of, 2837-2838, 2838t
staging of, 2838, 2839t
clinical presentation of, 1674, 1674f
diffuse large B-cell, 1677-1678
epidemiology of, 1673
follicular, 1674, 1678
highly aggressive, 1674, 1679
imaging of, 148-149, 149f
immunosuppression and, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
indolent, 1674, 1678
of larynx, 1509
lymphoblastic, 1674-1675
MALT, 1674, 1679-1680
mantle cell, 1678-1679
nodal involvement by, 165-166, 167f
of oral cavity, 157f
of oropharynx, 1364, 1364f
paranasal sinus and nasal cavity, 1680
of salivary glands, 1191-1192, 1192f, 1679-1680
small lymphocytic, 1674, 1674f, 1678
staging of, 1676, 1677t
thyroid, 1679
of paranasal sinuses, 1131, 1680
therapy and prognosis for, 1680
plasmablastic, 216
salivary gland, 1191-1192, 1192f, 1679-1680
treatment and prognosis for, 1680
sensorineural hearing loss due to, 2123
small lymphocytic, 1678
clinical presentation of, 1674
imaging of, 1674, 1674f
treatment and prognosis for, 1678
staging of, 1676, 1677t
T-cell, nasal manifestations of, 659-660
thyroid, 1679, 1764
diffuse large B-cell, 1679
staging of, 1679
treatment and prognosis for, 1679
extranodal marginal cell, 1679
MALT, 1679
staging of, 1679
treatment and prognosis for, 1679

Lymphoma(s) *(Continued)*
marginal zone, 1679
non-Hodgkin's, 1679
staging of, 1679
treatment and prognosis for, 1679
Waldeyer's ring, 1680
treatment and prognosis for, 1680
Lymphoproliferative disorder, posttransplantation, 213t, 215, 217
in children, 2818, 2840
Lymphoscintigraphy
for oral cancer, 1313
with sentinel lymph node biopsy, 1115-1117, 1116f
Lymphoscintigraphy-directed neck dissection, 1721-1722
Lymphotoxin α (LTα), 609t-610t
Lymphotoxin αβ (LTαβ), 609t-610t
Lynch-Howarth external ethmoidectomy, 778-779, 779f
Lyre's sign, for paraganglioma, 1641
Lysozyme, 598
in middle ear protection, 1871
in saliva, 1140
Lytic antigens, of Epstein-Barr virus, 1352

M

M (metastatic) classification, for melanoma, 1111t, 1113
M phase, of cell cycle, 12, 13f
MAC (membrane attack complex), 608
Macewen's triangle, 1822f
MACIS classification, of thyroid cancer, 1754, 1756t
Macrocirculatory system, and skin flaps, 1064-1066, 1065f
Macrogenia, 463
Macroglobulinemia, Waldenström's, sensorineural hearing loss due to, 2123
Macroglossia, dysphagia due to, 2951
Macrolide antibiotics
for acute otitis media, 2770
long-term, for rhinosinusitis, 733, 734t
ototoxicity of, 2176
Macromolecule secretion, by salivary glands, 1135-1136
Macrophage(s)
in adaptive immune system, 604
in wound healing, 1076
Macrophage colony-stimulating factor (M-CSF), 604, 609t-610t
Macropore plating system, for pediatric facial fractures, 2701t
Macula sacculi, 2278
arrangement of otoliths in, 1855, 1858f, 2278, 2280f
embryogenesis of, 1852
morphologic polarization of, 1855, 1856f, 2278, 2280f
orientation of, 1855, 1857f
Macula utriculi, 2278
arrangement of otoliths in, 1855, 1858f, 2278, 2280f
embryogenesis of, 1852
morphologic polarization of, 1855, 1856f, 2278, 2280f
orientation of, 1855, 1857f
MAGE (melanoma antigen E) tumor–associated antigen, in head and neck squamous cell carcinoma, 1024
Magnesium, for migraine, 2349
Magnetic resonance angiography (MRA), 137
of anterior skull base, 2475
of neck masses, 1637, 1637t
of petrous apicitis, 1989f
Magnetic resonance (MR) cisternography, for CSF rhinorrhea, 790-791, 790f
Magnetic resonance imaging (MRI), 133-137
of acoustic neuroma, 2517
applications of, 142-143
artifacts on, 133-134, 134f
and cochlear implants, 2231-2232, 2236b
for CSF rhinorrhea, 791, 791f
of deep neck space infections, 204
disadvantages of, 137
for dizziness, 2327
effect on hearing of, 2149
of facial nerve, 2384
fast spin-echo, 134
fat suppression methods for, 135-136, 136f
with frequency (chemical shift) selective presaturation (fat saturation), 135-136, 136f
functional
for cerebral blood flow evaluation, 2491
of olfaction, 632
gadolinium enhancement for, 134-135, 135f-136f
with gradient echo techniques, 136-137, 137f
of Graves' ophthalmopathy, 1810
for hyperparathyroidism, 1787-1788, 1789f
for hypopharyngeal and cervical esophageal cancer, 1424
with intensity-modulated radiotherapy, 1044
of laryngeal carcinoma, 1468-1479, 1494
early glottic, 1516-1517
of larynx and infrahyoid neck, 142-143
of lymphadenopathy, 142
metastatic, 165-166, 168f
magnetic field strengths of, 133
of malignant otitis externa, 1947
of nasopharyngeal carcinoma, 1354
of neck masses, 1637, 1637t
of neck neoplasms, 1656-1657
of obstructive sleep apnea, 255
of oral cancer, 1300
of oropharyngeal cancer, 1366
of paranasal sinus tumors, 1124
of paranasal sinuses, 143, 664, 664f
prior to endoscopic sinus surgery, 764, 765t
permanent *vs.* superconducting magnets in, 133
of petrous apicitis, 1986-1987, 1988f-1989f
of pharynx and esophagus, 1396
pulse sequences for, 133-137, 135f-136f
of salivary glands, 142, 1145-1147, 1166, 1180
with adenoid cystic carcinoma, 1146-1147, 1146f-1147f
with glomus tumor, 1169f
with mucoepidermoid carcinoma, 1146, 1147f, 1168f
with pleomorphic adenoma, 1148f, 1167f-1168f, 1180f
with ranula, 1146, 1147f
for sensorineural hearing loss in adults, 2117
with short T1 inversion recovery (STIR), 135-136, 136f
of skull base, 143
anterior, 2475
lateral, 2489
slice thickness in, 133
with spectral presaturation inversion recovery (SPIR), 135-136
spin density–weighted, 134, 136f
for stereotactic radiation therapy, 2558
of suprahyoid neck, 142
surface coils in, 133
T1-weighted, 134, 135f-136f
T2-weighted, 134, 135f-136f
of temporal bone, 143
three-dimensional reconstruction from, 138, 140f
of thyroid and parathyroid glands, 143
Magnetic resonance (MR) sialography, 1147
Magnetic resonance (MR) spectroscopy, of laryngeal carcinoma, 1470
Magnetic search coil technique, for recording eye movements, 2317
Magnetic stimulation, to assess facial nerve function, 2388-2389
in Bell's palsy, 2394-2395
Maintenance activities, in vestibular rehabilitation, 2372-2373, 2379
Maintenance of certification (MOC), 80, 81b
MAIS (Meaningful Auditory Integration Scale), for cochlear implant, 2225
Major basic protein (MBP), 604
in allergic rhinitis, 616
Major histocompatibility complex (MHC) molecules, 599
Major histocompatibility complex (MHC)-restricted cytotoxicity, 603-604
Major histocompatibility complex (MHC) restriction, 603-604
Mal de débarquement (MDD) syndrome, 2357
Malabsorption diseases, oral manifestations of, 1254
Malar eminence
anatomy and physiology of, 319
biomechanics of, 332
Malar prominences, with aging, 444
MALDI-TOF (matrix-assisted laser desorption-ionization–time-of-flight), in head and neck squamous cell carcinoma, 1029
Male-pattern baldness, 374-376, 375f
Malignancy(ies)
in geriatric patients, 237-238
etiology of, 237
treatment of, 237-238
hypercalcemia of, 1783, 1783t
immunosuppression and, 212-217, 213t
cutaneous neoplasms in, 213t, 215
Hodgkin's lymphoma in, 213t, 217
Kaposi's sarcoma in, 212-215, 213t
epidemiology and pathogenesis of, 212-213
presentation and diagnosis of, 213-214, 214f
treatment of, 214-215
non-Hodgkin's lymphoma in, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
in posttransplantation lymphoproliferative disorder, 213t, 215, 217
squamous cell carcinoma in, 213t, 215
Malignant fibrous histiocytoma (MFH)
of larynx, 1508
of neck, 1667
Malignant giant cell tumor (MGCT), 1671
Malignant hypertension (MH), 119
Malignant melanoma (MM). *See* Melanoma.
Malignant mixed tumors, of salivary glands, 1186-1189
carcinoma ex pleomorphic adenoma as, 1187-1189, 1188f
metastasizing, 1189
true (carcinosarcoma), 1187, 1188f
Malignant otitis externa (MOE), 1947-1948
clinical manifestations of, 1947, 1947f
conductive hearing loss due to, 2021, 2023f
defined, 1947
immunosuppression and, 221-222, 1947
incidence and epidemiology of, 1947
investigations of, 1947
microbiology of, 1947
otorrhea due to, 2195
treatment of, 1947-1948
Malignant peripheral nerve sheath tumor (MPNST), 1670-1671
Mallear stria, 1824, 1825f
Malleolar artery, 1828f
Malleus, 97, 98f
anatomy of, 1826
in auditory physiology, 1839-1840, 1840f, 2018
in cochlear transduction, 2062f

Malleus fixation, 2024-2025
  small fenestra stapedotomy with, 2033
Mallory-Weiss syndrome, 1410-1411
Mallory-Weiss tear, gastroesophageal junction in, 957f
Malnutrition, palliative care for, 1104
Malocclusion
  after maxillofacial trauma, 339
  due to paranasal sinus tumor, 1123
Maloney bougies, for esophageal strictures, 966
MALT. *See* Mucosa-associated lymphoid tissue (MALT).
Malunion, after maxillofacial trauma, 339
Mammillary bodies, in surgical anatomy of anterior cranial base, 2481f
Mandible
  anatomy of, 320f, 322-323, 1319, 1320f
    alveolar canal in, 1319-1320
    alveolar process in, 1319, 1320f
    body of mandible in, 1319, 1320f
    coronoid and condylar processes in, 1319, 1320f
    dentulous *vs.* edentulous, 1319, 1320f
    mandibular notch in, 1319, 1320f
    mental foramen in, 1319, 1320f
    rami in, 1319, 1320f
  biomechanics of, 332-333, 332f
  body of, 1319, 1320f
  dentulous, *vs.* edentulous, 1319, 1320f
  in Down syndrome, 2632
  edentulous
    vs. dentulous, 1319, 1320f
    repair of, 339
  growth and development of, 2620-2621
    downward translation in, 2621, 2624f
    mandibular arch in, 2621, 2624f
    Meckel's cartilage in, 2620-2621, 2623f
    rotational changes in, 2621, 2625f
    size in, 2621, 2624f
    surface remodeling in, 2621, 2623f
  odontogenic tumors of, 1270-1271, 1271f
  osteoradionecrosis of, 1048
  physiology of, 320f, 322-323
  reconstruction of (*See* Mandibular reconstruction)
  in surgical anatomy of lateral skull base, 2440f
  surgical treatment of, 1310-1312
    with oral cancer
      for access, 1311
      mandible-sparing procedures in, 1311
      marginal mandibulectomy for, 1311, 1312f
      paramedian mandibulotomy in, 1311
      pull-through technique for, 1311, 1312f-1313f
      segmental mandibulectomy for, 1311-1312, 1312t
  tension and compression areas in, 331-332, 331f-332f
  vasculature of, 1296
Mandible-sparing procedures, 1311
Mandibular advancement, for obstructive sleep apnea, 257f
  in children, 2610
Mandibular ameloblastomas, 1274
Mandibular arch, in embryology of nose, 2691f
Mandibular branch, of facial nerve, 1194f
Mandibular changes, in geriatric patients, 236
Mandibular condylar fossa, in surgical anatomy of middle cranial base, 2444, 2445f
Mandibular discontinuity defects, maxillofacial prosthodontics for, 1340-1342, 1342f-1343f
Mandibular distraction, 2656, 2656f
  for obstructive sleep apnea in children, 2610, 2610f
  for Robin sequence, 2673
Mandibular division, of trigeminal nerve, in surgical anatomy of lateral skull base, 2437f, 2438, 2440f, 2441
Mandibular fix-bridge system, with free tissue transfer, 1093-1094
Mandibular fossa, 2011f
Mandibular fractures, 323
  classification of, 327
  imaging of, 325-326
  pediatric, 2704-2706
    arch and body, 2706, 2709f
    complications of, 2704
    condylar and subcondylar, 2704, 2706f-2708f
    epidemiology of, 2698
    symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
  physical examination of, 325
  repair of, 337-339, 338f
  surgical access to, 329-330, 330f
  teeth in line of, 339
Mandibular hypoplasia, obstructive sleep apnea due to, 2610, 2610f
Mandibular movement, nonarticular conditions producing limitation of, 1285t
Mandibular nerve block
  for neuropathic pain, 246t
  for postoperative pain, 242
Mandibular notch, 1319, 1320f
Mandibular overgrowth, with lymphatic malformation, 2823f
Mandibular prominences, in embryology
  of lip, 2661f-2662f, 2661t
  of nose, 2691f
Mandibular prosthesis, 1340, 1341f-1342f
  with discontinuity defects, 1340-1342, 1342f-1343f
Mandibular reconstruction, 1315-1316, 1319-1328
  anatomy of mandible and, 1319, 1320f
    alveolar canal in, 1319-1320
    alveolar process in, 1319, 1320f
    body of mandible in, 1319, 1320f
    coronoid and condylar processes in, 1319, 1320f
    dentulous *vs.* edentulous, 1319, 1320f
    mandibular notch in, 1319, 1320f
    mental foramen in, 1319, 1320f
    rami in, 1319, 1320f
  background and history of, 1319, 1320f, 1322-1324
  classification of defects for, 1321-1322, 1323f
  computer-assisted modeling for, 1326-1327, 1327f
  current method(s) of, 1324-1326
  fibular free flap, 1316, 1316f
  future approaches to, 1327-1328, 1328f
  goals of, 1320, 1322
  location of defect and, 1316
  after mandibulectomy
    with anterior defect, 1321, 1321f
    with lateral defect, 1321, 1322f
    marginal, 1320
    segmental, 1321
  movement of mandible and, 1320
  outcomes of, 1326
  reconstruction plate alone for, 1324
  reconstruction plate with osseous free tissue transfer for, 1324
    advantages and disadvantages of, 1324
    flap inset in, 1324f, 1325
    flap options for, 1324, 1325t
    planning and harvesting of flaps in, 1324-1325, 1324f
  reconstruction plate with soft tissue flap for, 1325
    advantages and disadvantages of, 1325
    plate extrusion with, 1325, 1326f
    plate fracture with, 1325-1326, 1326f
    volume-based, 1325, 1326f
Mandibular reconstruction plate (MRP), 337-338, 1324
  with osseous free tissue transfer, 1324
    advantages and disadvantages of, 1324
    flap inset in, 1324f, 1325
    flap options for, 1324, 1325t
    planning and harvesting of flaps in, 1324-1325, 1324f
  with soft tissue flap, 1325
    advantages and disadvantages of, 1325
    plate extrusion with, 1325, 1326f
    plate fracture with, 1325-1326, 1326f
    volume-based, 1325, 1326f
Mandibular resection prosthesis, 1340, 1341f-1342f
Mandibular space involvement, in odontogenic infections, 181-184
  Ludwig's angina due to, 184, 185f
  masseteric, 184, 185f
  masticator, 184, 186f
  pterygomandibular (medial pterygoid), 184, 185f
  secondary, 184
  sub-, 183-184, 183f-184f
  sublingual, 183, 183f
  submental, 181-183, 183f
  temporal, 184, 185f
Mandibular splint, acrylic, for pediatric facial fractures, 2701, 2701f
Mandibular swing approach, for oropharyngeal cancer, 1371-1372, 1372f
Mandibulectomy
  for alveolar ridge carcinoma, 1304, 1304f-1305f, 1307f
  for excision of tumors in parapharyngeal space, 1176, 1176f
  mandibular resection prosthesis with, 1340, 1341f-1342f
  marginal, 1311, 1312f
    defect from, 1320, 1321f
  for retromolar trigone carcinoma, 1307, 1307f
  segmental, 1311-1312, 1312t
    defect from, 1321, 1321f
    free tissue transfer after, 1093-1094
Mandibulofacial dysostosis (MFD), 2585
  craniofacial abnormalities in, 2633-2635, 2633b, 2635f, 2646
Mandibulotomy
  for middle cranial base surgery, 2455t, 2458, 2460f
  paramedian, 1311
Mannequins, for difficult airway management, 118
Manometric rhinometry, 643-644
Manometry, esophageal, 957-958, 958f-959f, 959t
  for extraesophageal reflux, 899-900
  for swallowing disorders, 1219
Mantle cell lymphoma (MCL), 1678-1679
  treatment and prognosis for, 1678-1679
MAPK (mitogen-activated protein kinase) pathway, in thyroid carcinoma, 1753
Marble bone disease, 2112
Marcel Proust syndrome, 636
Marescaux, Jacques, 39
Marfanoid syndrome, craniofacial anomalies in, 2641t
Marfan's syndrome, oral manifestations of, 1257
Margin analysis, for biomarkers, in head and neck squamous cell carcinoma, 1027
Marginal cells, of taste buds, 1208
Marginal mandibular branch, of facial nerve, 2418-2419
"Marginal mandibular lip," 2431
Marginal zone lymphoma, of thyroid, 1679
Margin-reflex-distance (MRD), 446
Market accountability, 82
Marshall syndrome, deafness in, 2051t-2058t
Martell, Charles, 1774
MARVELD2, in deafness, 2051t-2058t

Marx hyperbaric oxygen regimen, after radiation therapy, 1333
Maser, 25
MASH (Multiple-Activity Scale for Hyperacusis), 2138-2139
Mask ventilation, difficult, 121-122
Masking, in audiologic testing, 1889-1890
  effective, 1889
  errors in, 1901-1902
Masking dilemma, 1890
Masking therapy, for tinnitus, 2134
MASS1, in deafness, 2051t-2058t
Masseter muscle
  anatomy of, 321f, 1320, 1359f, 1821
  in surgical anatomy of lateral skull base, 2440f
Masseter transfer, for facial nerve paralysis, 2427, 2428f
Masseteric space involvement, in odontogenic infections, 184, 185f
Mast cell(s)
  in adaptive immune system, 605
  in allergic rhinitis, 616
  in wound healing, 1078
Mast cell–mediated hypersensitivity reactions, 608-612
Mastication, 1206-1207, 1206f
  muscles and reflex control of, 1204-1205, 1204f-1205f
Masticator space (MS)
  anatomy of, 203
  imaging of, 151-152
    with adenoid cystic carcinoma, 155f
    with angiofibroma, 152, 154f
    with hemangioma and lymphangioma, 152, 153f
    with infection, 151-152, 152f
    normal anatomy on, 146f, 151-152
    with pseudotumors, 152
    with squamous cell carcinoma, 152, 154f
  odontogenic infections of, 184, 186f
Masticatory rhythm, 1206-1207
Mastoid abscess, due to temporal bone infection, 1980t
Mastoid air cell system, in pressure equalization, 1870-1871
Mastoid antrum, in surgical anatomy of lateral skull base, 2438
Mastoid bone
  anatomy of, 1823f
  imaging of, 1918-1920
  in surgical anatomy of lateral skull base, 2435, 2435f
Mastoid emissary vein, foramen for, 1822f
Mastoid foramen, 2010f
Mastoid obliteration, 2011
Mastoid part, of temporal bone, 1821-1822, 1822f, 1829
  anatomy of, 2009-2010, 2010f
Mastoid pneumatization, otitis media with effusion and, 1963-1964
Mastoid powder, for ear hygiene or chronic ear drainage, 1958
Mastoid process
  anatomy of, 2010f
  in craniofacial skeleton, 320f
  in osteology of temporal bone, 1821-1822, 1822f, 1824f
  in surgical anatomy of lateral skull base, 2435
  in surgical anatomy of middle cranial base, 2445f
Mastoid segment
  anatomy of, 1826f
    surgical, 2404, 2404f
  vulnerability to injury of, 1826f
Mastoid sources, of otorrhea, 2195-2196, 2195b
Mastoid tegmen, in surgical anatomy of lateral skull base, 2435f
Mastoid tip
  anatomy of, 1821-1822, 1822f
    in infants, 2010
  in surgical anatomy of lateral skull base, 2435f
Mastoidectomy, 2009-2016
  anatomic basis for, 2009-2010, 2010f
  canal wall down, 2010-2011
    for chronic otitis media with cholesteatoma, 1969, 1970t
    intact canal wall *vs.,* 2014
      indications for, 2014-2015, 2015f
    operative procedure for, 2013-2014, 2014f
  canal wall up (intact canal wall), 2010
    vs. canal wall down procedure, 2014
    for chronic otitis media with cholesteatoma, 1969, 1970t
    indications for, 2014-2015
  for cholesteatoma, 1969, 1970t, 2014-2015
  for cochlear implant, 2238-2239
  complication(s) of, 2015-2016
    dural tear as, 2015
    facial nerve injury as, 2015-2016
    horizontal semicircular fistula as, 2015
    sigmoid sinus and jugular bulb injury as, 2016
  history of, 2009
  nomenclature for, 2010-2011, 2010b
  operative procedure for, 2011-2014
    bur selection for, 2011
    facial nerve in, 2012, 2012f
    incision in, 2011, 2011f
    initial bur cuts in, 2011, 2011f
    irrigation in, 2011
    Körner's septum in, 2012
    location of antrum in, 2011-2012
    opening of epitympanum in, 2012-2013, 2013f
    opening of facial recess in, 2012, 2012f-2013f
    saucerization in, 2011-2012
    surgical site preparation in, 2011
    tegmen plate in, 2011-2012
    thinning of posterior wall in, 2011-2012
  radical, 2011
    modified, 2011
    in postauricular approach to infratemporal fossa, 2496, 2498f
  simple, 2010
Mastoiditis
  acute, 1983, 1983f
    otorrhea due to, 2196
  chronic, 1984-1985, 1985f
    otorrhea due to, 2196
  coalescent, 1983-1984
    diagnosis of, 1984, 1984f
    etiology of, 1983
    otorrhea due to, 2196
    pathology of, 1983-1984
    pathophysiology of, 1984
    treatment of, 1984
  masked, 1985
  mycobacterial, 2196
  otitis media and, 2776
Matas test, for cerebral blood flow evaluation, 2490
Matched samples, statistical tests for, 66, 67t
Math1
  in hair cell regeneration and repair, 2144
  in murine deafness, 2058t-2060t
Matrix metalloproteinase(s) (MMPs)
  in bone resorption, 1972
  in head and neck squamous cell carcinoma, 1019-1020
Matrix metalloproteinase-1 (MMP-1), in head and neck squamous cell carcinoma, 1077
Matrix-assisted laser desorption-ionization–time-of-flight (MALDI-TOF), in head and neck squamous cell carcinoma, 1029
Maxilla(e)
  anatomy and physiology of, 320, 320f-321f
  biomechanics of, 332
  frontal process of, 509f
  growth and development of, 2619-2620, 2621f-2622f
  odontogenic tumors of, 1270-1271
Maxillary ameloblastomas, 1274
Maxillary antrostomy, in endoscopic sinus surgery, 747, 747f
  failure of, 764-766, 766f
Maxillary antrum
  height of, 2617t
  malignant neoplasms of, 1122-1123
Maxillary artery
  anatomy of, 2580f
  in surgical anatomy of lateral skull base, 2441
Maxillary artery ligation, for epistaxis, 688
Maxillary crest, in septoplasty, 490, 490f
Maxillary division, of trigeminal nerve, in surgical anatomy of lateral skull base, 2437f, 2438, 2440f
Maxillary fractures
  classification of, 326, 327f
  imaging of, 325
  physical examination of, 324-325
  repair of, 334-337, 334f-336f
Maxillary gingivolabial sulcus approach, for pediatric facial fracture, 2701-2702, 2703f
Maxillary implants, in cleft-lip nose repair, 562f
Maxillary incisors, in chin analysis, 464, 464f
Maxillary lymph node, 1360f
Maxillary mega-incisor, 2690, 2691f
Maxillary nerve block
  for neuropathic pain, 246t
  for postoperative pain, 242
Maxillary obturation, prosthetic, 1338
  definitive, 1339-1340
    for dentate patients, 1339-1340, 1340f
    for edentulous patients, 1340, 1340f-1341f
  interim, 1339, 1339f
  surgical, 1338-1339
    abutments in, 1338-1339
    impressions for diagnostic casts in, 1338-1339, 1338f
    postoperative radiograph of, 1338, 1338f
    preoperative assessment for, 1338, 1338f
    preservation of support structures in, 1338
    removal of packing material and prosthesis in, 1339, 1339f
    securing of prosthesis in, 1338-1339, 1339f
    skin graft in, 1338-1339
Maxillary osteotomies, in cleft-lip nose repair, 559, 564f-565f
Maxillary process, in embryology of palate, 2662f
Maxillary prominences, in embryology
  of lip, 2659-2660, 2661f-2662f, 2661t
  of nose, 2691f
  of palate, 2660-2661
Maxillary prosthesis, 1338
  definitive, 1339-1340
    for dentate patients, 1339-1340, 1340f
    for edentulous patients, 1340, 1340f-1341f
  interim, 1339, 1339f
  surgical, 1338-1339
    abutments in, 1338-1339
    impressions for diagnostic casts in, 1338-1339, 1338f
    postoperative radiograph of, 1338, 1338f
    preoperative assessment for, 1338, 1338f
    preservation of support structures in, 1338
    removal of packing material and prosthesis in, 1339, 1339f
    securing of prosthesis in, 1338-1339, 1339f
    skin graft in, 1338-1339

Maxillary sinus(es)
anatomy and physiology of, 319f, 320, 664, 665f
growth and development of, 2619-2620, 2623f
medial wall of, prior to endoscopic sinus surgery, 764t
pneumatization of, prior to endoscopic sinus surgery, 764
surgical anatomy of, 740
in anterior cranial base, 2474
Maxillary sinus defect, reconstruction of, 1128
Maxillary sinus tumors, 1128-1130
chemoradiotherapy for, 1130
combined irradiation and surgery for, 1128
inoperable, 1130
radiotherapy for, 1128-1130
staging of, 1129b
surgery alone for, 1128
Maxillary space involvement, in odontogenic infections, 180-181
buccal, 181, 181f
canine, 180-181, 180f
cavernous sinus thrombosis due to, 181, 182f
orbital cellulitis due to, 181, 182f
Maxillary swing, for nasopharyngeal carcinoma, 1356, 1356f
Maxillectomy
alone, 1128
for hard palate malignancy, 1310, 1310f
medial, 1125, 1125f
inferior, 1125, 1125f
for nasopharyngeal carcinoma, 1355-1356, 1355f
with orbital exenteration, 1125-1126
partial, for buccal carcinoma, 1309f
prosthetic maxillary obturation with (*See* Maxillary obturation, prosthetic)
radical, 1125-1126, 1125f
with radiotherapy, 1128
Maxillofacial prosthodontics, 1329-1347
for acquired facial defects, 1344-1345, 1345t
auricular, 1345-1346, 1345t, 1346f
nasal, 1345, 1345t, 1346f
orbital/ocular, 1345t, 1346-1347, 1347f
prosthetic maxillary obturation in, 1338
definitive, 1339-1340
for dentate patients, 1339-1340, 1340f
for edentulous patients, 1340, 1340f-1341f
interim, 1339, 1339f
surgical, 1338-1339
abutments in, 1338-1339
impressions for diagnostic casts in, 1338-1339, 1338f
postoperative radiograph of, 1338, 1338f
preoperative assessment for, 1338, 1338f
preservation of support structures in, 1338
removal of packing material and prosthesis in, 1339, 1339f
securing of prosthesis in, 1338-1339, 1339f
skin graft in, 1338-1339
and radiation therapy, 1330
dental diagnoses and oral surgical management prior to, 1330-1331, 1330b, 1331f
dental management after, 1333-1337
with conventional 3D conformal radiation therapy, 1333-1335, 1336f
with intensity-modulated radiation therapy, 1335-1337, 1336f-1337f
ipsilateral *vs.* contralateral, 1335
dental management during, 1333
overview of interactions of, 1337-1344
prosthodontic support of radiation oncologist in, 1331-1332
with brachytherapy, 1332, 1335f
for facial moulage recording and bolus fabrication, 1331, 1332f
intraoral positioning devices in, 1331, 1333f
Maxillofacial prosthodontics *(Continued)*
for portals and shielding devices, 1331-1332, 1334f
shelf for tissue-equivalent material in, 1332, 1335f
for tumor-ablative surgical defects, 1337-1338
of mandible, 1340, 1341f-1342f
discontinuity, 1340-1342, 1342f-1343f
of maxilla, 1338
of soft palate, 1343-1344, 1344f
of tongue, 1342-1343, 1344f
Maxillofacial trauma, 318-341
anatomy, physiology, and pathophysiology of, 319-323, 320f
general, 319
of lower third, 322-323, 323f
of middle third, 319-322
areas of protection in, 322, 322t
infraorbital nerve in, 320, 321f
maxillae in, 320, 321f
nasal bones in, 320
orbits in, 320-321, 322f
zygoma in, 319, 320f-321f
of upper third, 319, 319f
biomechanics of facial skeleton and, 331-333, 331f
in lower third, 332-333, 332f
in middle third, 331-332, 331f
in upper third, 331
bone healing after, 330-331
classification of, 326-327
of lower third, 327
of middle third, 326-327, 327f
of upper third, 326
complications of, 339-340
defined, 318
evaluation and diagnosis of, 323-326
imaging in, 325-326
of lower third, 325-326
of middle third, 325, 326f
of upper third, 325, 325f
physical examination in, 323-325
of lower third, 325
of middle third, 324-325, 324f
of upper third, 324
fracture repair for, 333-334
in lower third, 337-339, 338f
with edentulous mandible, 339
in middle third, 334-337
of buttresses, 336
canthal ligament in, 337, 337f
maxillary, 335-336, 335f-336f
naso-orbital ethmoid, 336-337, 337f
orbital, 336
palatal, 335, 335f
of tooth-bearing segments, 334-335, 334f
zygomatic, 336
and occlusion, 330-331, 333-334, 333f
panfacial, 339
secondary, revision, or delayed, 340
in upper third, 333-334, 334f
with CSF rhinorrhea, 334-339
with skull base disruption, 334-339
future directions and new horizons for, 340
historical perspective on, 318-319
management of, 327-330
general, 327-328
surgical access in, 328-330
to lower third, 329-330, 330f
to middle third, 328-329, 329f
to upper third, 328, 328f-329f
pediatric, 2647, 2697-2717
associated injuries with, 2698
clinical and physical evaluation of, 2699
complex, 2698
dentoalveolar fracture due to, 2706-2707, 2710f
Maxillofacial trauma *(Continued)*
emergency management of, 2698-2699
epidemiology of, 2697-2698
etiology of, 2698
facial growth and, 2698-2699
front sinus fracture due to, 2711, 2712f
mandibular fracture due to, 2704-2706
arch and body, 2706, 2709f
complications of, 2704
condylar and subcondylar, 2704, 2706f-2708f
epidemiology of, 2698
symphyseal and parasymphyseal, 2704-2706, 2708f-2709f
mandibular immobilization for, 2701, 2701f
maxillomandibular fixation for, 2701
midface fracture due to, 2707, 2710f
nasal fractures due to, 2708-2711, 2711f-2712f
naso-orbitoethmoid, 2714
classification of, 2714, 2716f
evaluation of, 2714, 2716f
repair of, 2714, 2716f
open reduction with internal fixation for, 2701-2702
orbital fracture due to, 2711-2714
evaluation of, 2712, 2713f
of lateral/medial orbital wall, 2712, 2714, 2716f
of orbital apex, 2712, 2713f
of orbital floor, 2712-2713, 2714f-2715f
of orbital roof, 2712-2713, 2716f
patterns of, 2711-2712
permanent *vs.* resorbable plating systems for, 2700-2701, 2700t-2701t
radiologic examination of, 2699
rigid fixation for, 2699-2700
sequencing of procedures for, 2702, 2704, 2706f
surgical approaches for, 2701-2704
bicoronal incision in, 2701-2702, 2703f
lateral cantholysis in, 2704f
maxillary gingivolabial sulcus approach in, 2701-2702, 2703f
midfacial degloving incision in, 2701-2702
subciliary incision in, 2705f
transcaruncular approach in, 2701-2702, 2705f
surgical management of, 2648, 2649f, 2657
surgical reconstruction for, 2704-2714
zygomaticomalar complex fractures due to, 2707-2708, 2710f
Maxillomandibular advancement (MMA), for obstructive sleep apnea, 260, 261f
Maxillomandibular fixation (MMF), 335-336, 335f-336f
avoiding need for, 328, 330-331
biomechanics with, 332
with free tissue transfer, 1093-1094
and occlusion, 333, 335-336
pediatric, 2701
for subcondylar fractures, 338-339
Maxillotomy, extended, for middle cranial base surgery, 2455t, 2458, 2462f
Maximal stimulation test (MST)
for Bell's palsy, 2394
for facial nerve injury, 2040-2041, 2382t, 2385-2386
Maximum interincisal opening (MIO), 1280
Maximum phonation time (MPT)
in tracheoesophageal speech, 1597
in voice evaluation, 828, 849
Maximum phonational frequency range (MPFR), 829
Maximum resistance, in rhinomanometry, 650
MBP (major basic protein), 604
in allergic rhinitis, 616

MBS (modified barium swallow), 1394, 1396
for swallowing disorders, 1217-1218, 1219f
in children, 2949, 2950t
MCA (minimal cross-sectional area), in rhinomanometry and acoustic rhinometry, 643f, 644
anatomic, 644
physiologic, 644
McCaffrey classification, of airway stenosis, 944, 944t
McFee incision, for radical neck dissection, 1709, 1710f
mCi (millicurie), 1031-1032
MCL (mantle cell lymphoma), 1678-1679
treatment and prognosis for, 1678-1679
Mcoln3, in murine deafness, 2058t-2060t
MCP-1 (monocyte chemoattractant protein-1), in wound healing, 1076
M-CSF (macrophage colony-stimulating factor), 604, 609t-610t
M.D. Anderson Dysphagia Inventory (MDADI), 57-58
M.D. Anderson Symptom Inventory, Head and Neck Module, 56
MDD (mal de débarquement) syndrome, 2357
Mead-Johnson feeder, 2665, 2665f
Mean, 63-64, 64t
regression to, *vs.* efficacy of treatment, 62t
Mean airflow rate, in voice evaluation, 849
Meaningful Auditory Integration Scale (MAIS), for cochlear implant, 2225
Measles
conductive hearing loss due to, 2158
diagnosis of, 2158
sensorineural hearing loss due to, 2119, 2158
sudden, 2127
Measurement scales, for describing and analyzing data, 63, 63t
Meatal foramen
anatomy of, 1826f
surgical, 2403-2404, 2404f
in Bell's palsy, 2393
vulnerability to injury of, 1829
Meatoplasty, in atresiaplasty, 2756-2757
MEC. *See* Mucoepidermoid carcinoma (MEC).
Mechanical débridement, of tracheal tumor, 1619-1621
Mechanical presbycusis, 232, 2126
Mechanoelectrical transduction (MET) channel, in hair cell transduction, 2072f
Mechanoelectrical transduction (MET) currents, adaptation of, in hair cell transduction, 2078-2079, 2079f
Mechanoreceptors, of oral cavity, 1201-1202, 1201f
Meckel's cartilage, 2583, 2583f, 2620-2621, 2623f
Meckel's cave, in surgical anatomy of lateral skull base, 2435f, 2436-2437
Med-El PulsarCI100, 2228-2229, 2228f-2230f
ear-level speech processors for, 2232f
Med-El Sonata TI100, 2228-2229, 2228f-2230f
ear-level speech processors for, 2232f
Medial antebrachial cutaneous nerve, for facial nerve grafting, 2422
Medial canal fibrosis
due to otitis externa, 1946-1947, 1946f
postinflammatory, 1917-1918, 1918f
Medial canthal ligaments
anatomy and physiology of, 320-321, 322f
of lacrimal apparatus, 798f
repair of, 336-337, 337f
Medial canthal relationships, in evaluation of maxillofacial trauma, 324, 324f
Medial crural footplate, 509f
Medial crus(crura), of alar cartilage, 496-497, 497f, 509f
in cleft-lip nose repair, 561f-562f
Medial geniculate body
in central auditory pathway, 1835f, 1836, 1846-1847
tonotopic map reorganization in, 1879-1880
Medial incudal fold, 1827f
Medial maxillectomy, 1125, 1125f
for nasopharyngeal carcinoma, 1355-1356, 1355f
Medial nasal prominences, in embryology
of lip, 2660, 2661f-2662f, 2661t
of nose, 2691f
of palate, 2660-2661
Medial nucleus of trapezoid body (MNTB), in auditory pathway, 1834f
Medial olfactory tract, 628f
Medial olivocochlear (MOC) reflex pathways, in efferent auditory system, 1848-1849, 1848f
Medial olivocochlear (MOC) "unmasking," 1849
Medial orbital wall, 439
prior to endoscopic sinus surgery, 764, 764f, 764t
Medial orbital wall fractures, pediatric, 2712, 2714, 2716f
Medial pterygoid involvement, in odontogenic infections, 184, 185f
Medial pterygoid muscle, in surgical anatomy of lateral skull base, 2441
Medial pterygoid process, in surgical anatomy of lateral skull base, 2435f
Medial rectus muscle(s)
semicircular canal planes and, 2285-2287, 2286f-2287f
in surgical anatomy of anterior cranial base, 2472f
Medial superior olive (MSO), in auditory pathway, 1834-1835, 1834f, 1846
Medial vertical buttress, 331, 331f
Medial vestibular nucleus (MVN) (of Schwalbe), 1861, 1862f
in velocity storage, 2296
Medial vestibulospinal tract, in gaze stabilization, 1865
Medialization thyroplasty, 904-911
advantages of, 908
arytenoid adduction *vs.*, 912-913
autologous temporalis fascia grafts for, 910
complications of, 911
disadvantages of, 908
factors affecting outcome of, 908
with Gore-Tex strip, 908, 910, 911f
historical aspects of, 904-905
implant placement in, 909-910, 910f
indications for, 905, 908
limitations of, 910
outcome measures for, 910
patient evaluation and selection for, 905
prefabricated implants for, 908, 908f, 910
prosthesis templates in, 909-910, 910f
technique for, 908-911, 909f
Median, 63-64, 64t
Median frontal sinus drainage procedure, 779, 779f
Median glossoepiglottic fold, radiographic anatomy of, 1471f
Median hyoepiglottic ligament, 1359f
Median labiomandibular glossotomy, for hypopharyngeal cancer, 1429
Mediastinal exploration, for hyperparathyroidism, 1801-1802, 1802f
Mediastinal mass ratio (MMR), for lymphomas, 1676
Mediastinitis, due to deep neck space infections, 207-208
Medical history, 94, 94b
for disorders of professional voice, 850
Medical Outcomes Study Short Form-36 (SF-36), 56, 642
Medical professionalism, 78-82
board certification and maintenance of certification in, 79-80, 80b-81b
Institute of Medicine in, 81-82
Medical professionalism *(Continued)*
physician education in, 79, 79t
state medical boards and maintenance of licensure in, 80-81
Medical records, of difficult airway
electronic, 118-119
previous, 118
Medication(s), for systemic diseases, oral sequelae of, 1246, 1247t-1248t
Medication history, 94
Medication overuse headache, 248
MEDPOR (high-density polyethylene)
for auricular reconstruction, 2744t
for chin implants, 465t
Medulla, in surgical anatomy of anterior cranial base, 2474f
Medullary disorders, laryngeal hypofunction due to, 842
Medullary thyroid carcinoma (MTC), 1763-1764
clinical presentation of, 1763
management and prognosis for, 1763-1764
nodal metastasis of, 1766
pathology of, 1763
Medulloblastomas
intra-axial, 2528
vestibular symptoms of, 2353-2354
MEE (middle ear effusion)
collection vehicle for aspiration of, 2773-2774, 2774f
and hearing loss in infants, 2722
otitis media with (*See* Otitis media with effusion (OME))
Megaelectron volts (MeV), 1033
Mega-incisor, maxillary, 2690, 2691f
Megalin, and cisplatin ototoxicity, 2172
Megavoltage (MV) electrons, 1033
Megavoltage (MV) x-rays, 1033-1034
Meissner corpuscles, 1201
Meissner's plexus, 953, 954f
Melanocytic neoplasm(s), 286-289
blue nevus as, 286-287, 287f
compound nevus as, 286
congenital nevi as, 287-288
dysplastic nevus as, 288, 288f
halo nevus as, 287, 287f
intradermal nevus as, 286, 287f
junctional nevus as, 286, 287f
lentigo maligna melanoma as, 287f
nevocellular nevus as, 286
nevus sebaceus as, 287f, 289
solar (actinic) lentigo as, 288
Spitz nevus as, 287
superficial spreading melanoma as, 285f
Melanocytic nevus(i)
blue, 286-287, 287f
compound, 286
congenital, 287-288
and melanoma, 1107-1108
dysplastic, 288, 288f
halo, 287, 287f
intradermal, 286, 287f
junctional, 286, 287f
nevocellular, 286
of oral mucosa
clinical features of, 1241
histopathologic features of, 1242
treatment of, 1243
sebaceus, 287f, 289
Spitz, 287
Melanocytoma, compound, 287
Melanoma, 1106-1120
ABCD checklist for, 1109
chemotherapy for, 1118
classification of, 1108-1109
congenital melanocytic nevi and, 1107-1108
desmoplastic, 1108, 1108f

Melanoma *(Continued)*
desmoplastic-neurotropic, 1108
of oral cavity, 1299
diagnostic workup for, 1109-1110
biopsy in, 1109
history in, 1109
metastatic workup in, 1109-1110, 1110b, 1110t
physical examination in, 1109
differential diagnosis for, 1109
of ear, 1114
epidemiology of, 1107
etiology of, 1107-1108
follow-up and surveillance for, 1119
genetics of, 1107, 1107b
of hard palate, 1242f, 1309-1310
immunotherapy for, 1118-1119
future investigations on, 1119
interferon in, 1118-1119
interleukin-2 and other cytokines in, 1119
in-transit metastasis with, 1110, 1117
juvenile, 287
lentigo maligna, 287f, 1108
surgical excision of, 1114
mucosal, 1108-1109
of larynx, 1509
of oral cavity, 1242-1243
clinical features of, 1242, 1242f
differential diagnosis of, 1242
etiology and pathogenesis of, 1241, 1241t
histopathologic features of, 1242-1243, 1242f-1243f
treatment of, 1243
of oropharynx, 1364-1365, 1364f-1365f
of neck, 1671
nodular, 1108
of paranasal sinuses, 1131-1132
prognostic factors for, 1110-1113
anatomic site as, 1113
intralymphatic metastasis as, 1112
lactate dehydrogenase as, 1109-1110, 1113
number of positive lymph nodes as, 1111
and predictors of survival, 1112b
tumor burden as, 1111-1112
tumor ulceration as, 1111-1112
radiation therapy for, 1118
risk factors for, 1107, 1107b
signs and symptoms of, 1109
staging of, 1110-1113
Breslow microstaging in, 1113f
Clark scale in, 1111, 1113f
clinical and pathologic groupings in, 1112t
molecular, 1118
summary of revisions in, 1111, 1112b
TNM classification for, 1111, 1111t
metastatic (M) classification (distant metastases) in, 1111t, 1113
nodal (N) classification (regional disease) in, 1111-1113, 1111t
tumor (T) classification (localized disease) in, 1111, 1111t, 1113f
superficial spreading, 285f, 1108
surgical management of distant metastases of, 1118
surgical management of primary tumor in, 1113-1114
closure and reconstruction in, 1114
of ear, 1114
wide local excision and surgical margins in, 1113-1114, 1114t
surgical management of regional lymph nodes in, 1114-1118
elective lymph node dissection in, 1114-1115
sentinel lymph node biopsy in, 1115-1118
complexity in head and neck region of, 1117
excision of primary tumor prior to, 1115, 1116f
Melanoma *(Continued)*
future investigations on, 1117-1118
histologic evaluation of, 1116
indications for, 1115, 1115b
inflammation and fibrosis due to, 1117
injury to facial nerve due to, 1117
intraoperative lymphatic mapping for, 1115, 1116f
learning curve for, 1116
lymphoscintigraphy with, 1115-1117, 1116f
and overall survival, 1117
potential therapeutic benefits of, 1117
as prognostic factor, 1117
risk of in-transit metastasis with, 1117
technique for, 1115-1116
therapeutic lymph node dissection after, 1116
therapeutic lymph node dissection in, 1114, 1116
of unknown primary, 1109
Melanoma antigen E (MAGE) tumor–associated antigen, in head and neck squamous cell carcinoma, 1024
Melanosis, focal ("smoker's"), of oral mucosa, 1241f
Melanotic macules, of oral mucosa, 1241
clinical features of, 1241, 1241f
defined, 1241
differential diagnosis of, 1242
etiology and pathogenesis of, 1241, 1241t
histopathologic features of, 1242, 1242f
treatment of, 1243
MELAS (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes) syndrome, sensorineural hearing loss in, 2094t, 2097
Melkersson-Rosenthal syndrome, 2399
facial paralysis in, 2399
oral manifestations of, 1257
Melolabial flap
for lip defects, 353
for nasal defects, 366, 367f, 371f
Melolabial fold, in aging, 406, 406f
Melolabial interpolated flap, for nasal defects, 348
Membrane attack complex (MAC), 608
Membranous labyrinth
anatomy of, 1831-1832, 1832f, 1852, 1853f
embryogenesis of, 1852
malformations limited to, 2727-2728, 2727b
malformations of osseous and, 2727b, 2728-2735
ruptures in, in Meniere's disease, 2334
Membranous labyrinthine dysplasia
complete, 2727
limited, 2727-2728
Membranous laryngotracheobronchitis. *See* Bacterial tracheitis.
MEN. *See* Multiple endocrine neoplasia (MEN).
MEN-1 tumor suppressor gene, in parathyroid neoplasm(s), 1775, 1776f
Meniere, Prosper, 2329, 2333
Meniere's disease, 2333-2339
atypical, 2335
bilateral, 2333
clinical course of, 2335
clinical features of, 2333, 2335, 2335t
sensorineural hearing loss as, 2126-2127, 2335t
fluctuating, 2199
history of, 2337
sudden, 2129
severity of, 2335, 2336t
tinnitus as, 2335t, 2337
vertigo as, 2202, 2335t
cochlear, 2335
diagnosis of, 2335-2337
AAO-HNS criteria for, 2335, 2335t
audiogram in, 1895f
clinical presentation in, 2335, 2335t
defined, 2333
dehydrating agents in, 2337
Meniere's disease *(Continued)*
electrocochleography in, 1892-1896, 1895f, 1908, 2337
electronystagmography in, 2337
hearing loss and tinnitus in, 2337
heat thrust testing in, 2337
history in, 2335-2337
imaging studies in, 2333-2334, 2334f
stacked auditory brainstem response in, 1911
vestibular evoked myopotentials in, 2337
endolymphatic hydrops in, 2333-2334, 2334f
etiology of, 2334-2335
infectious, 2163, 2335
familial, 2333
historical background of, 2329, 2333
imaging studies in, 2333-2334, 2334f
incidence of, 2333
and migraine, 2350
otosclerosis with, 2035
pathogenesis of, 2333-2334, 2334f
ruptures in membranous labyrinth in, 2334
severity of, 2335, 2336t
treatment of, 2126, 2337-2339
dietary modification and diuretics in, 2337
historical background of, 2329
intratympanic gentamicin for, 2185-2189, 2338-2339, 2338f
clinical protocols for, 2187-2188
complications of, 2188-2189
concentration of, 2188
dose of, 2188
indications and contraindications for, 2189
injection interval for, 2188
mechanism of action of, 2185-2186
number of injections of, 2188
pharmacokinetics of, 2186-2187, 2186f-2187f
practical considerations with, 2188
intratympanic steroids for, 2184, 2339
local overpressure therapy for, 2338
surgical, 2362-2364
cochleosacculotomy for, 2126, 2362-2363, 2363f
endolymphatic sac surgery for, 2126, 2339, 2363-2364, 2364f
labyrinthectomy for, 2339, 2362
vestibular nerve section for, 2339, 2362
symptomatic, 2338
vasodilators in, 2337-2338
vestibular, 2335
Meniett device, 2338
Meningioma(s)
of cerebellopontine angle, 2517-2518
diagnostic studies of, 2518
imaging of, 1928, 1928f, 2518, 2519f
in differential diagnosis, 1929t, 2518t
with intracanalicular extension, 2520f
sensorineural hearing loss due to, 2125, 2125f
signs and symptoms of, 2518
endovascular treatment of, 1938, 1938f
of internal auditory canal, 175f
jugular foramen, 1929-1930, 1930f
of posterior fossa
embolization of, 1938
with petrous apex involvement, 2508f
Meningitis
bacterial, hearing loss due to, 2160-2161
due to cranial base surgery, 2468
cryptococcal, in HIV, 223-224
due to CSF fistulas, 794, 2044
delayed, due to temporal bone fracture, 2037-2038, 2038f
hearing loss due to
cochlear implants for, 2240
sudden, 2127
due to inner ear anomalies, 2736f, 2737, 2739
due to otitis media, 1993-1994, 2777

Meningitis *(Continued)*
diagnosis of, 1993
imaging in, 1993-1994, 1994f
lumbar puncture for, 1982
epidemiology of, 1980t-1981t, 1993
pathogenesis of, 1993
pathology of, 1993
symptoms of, 1993
treatment of, 1993-1994
due to posterior fossa surgery, 2541
Meningitis vaccination, with cochlear implants, 2236-2237, 2237b
Meningocele
with CSF rhinorrhea, 787
defined, 2645, 2687
imaging of, 765t
Meningoencephalocele
anterior, surgical management of, 742
with CSF rhinorrhea, 787, 791f-792f
defined, 2645, 2687
endoscopic view of, 2646f
due to otitis media, 1992-1993, 1993f
Meningoencephalocystocele, defined, 2645
Menopause, oral health during and after, 1256-1257
Menstrual cycle
oral changes during, 1256
and professional voice, 850
Menstrual cycle synchrony, olfaction in, 630
Mental foramen, of mandible, 1319, 1320f
Mental nerve, in osseous genioplasty, 467, 470
Mental protuberance, 320f
Mental tubercle, 320f
Mentalis muscle, 442f
Mentalis strain, 461, 462f
Menthol, for vocal professionals, 855
Menthol-sensitive receptors, in nasal mucosa, 641-642
Mentocervical angle, in aesthetic analysis, 275, 279f
Mentoplasty, 461-474
chin implants in, 465-467
anesthesia for, 465
clinical example of, 470, 471f
complications after, 470
dissection planes for, 465-467, 467f
incision and approach for, 465-467, 467f
intraoral approach for, 467
subperiosteal *vs.* supraperiosteal placement of, 465-467, 467f
surgical procedure for, 465-467
types of, 465, 465t, 467
clinical examples of, 470, 471f-473f
complications after, 470
correction of soft tissue ptosis in, 465
osseous genioplasty in, 465, 467-470
anesthesia for, 467
clinical examples of, 470, 473f
complications after, 470
fixation in, 468-470, 470f
gingivolabial incision for, 467, 468f
inscription of bony midline in, 467-468, 469f
lateral extent of, 468, 469f
measurement of osteotomy site in, 467-468, 469f
subperiosteal dissection in, 467, 468f
three-dimensional movement of chin in, 468
vertical lengthening in, 468-470, 469f
vertical shortening in, 468-470, 470f
wound closure in, 470
patient evaluation for, 461-465
Burstone analysis in, 463, 463f
Gonzalez-Ulloa and Stevens analysis in, 464f
history in, 461
Holdaway "H" angle in, 463, 464f
horizontal relationships in, 463, 464f
lateral cephalometric radiograph in, 463, 463f
Mentoplasty *(Continued)*
panoramic radiograph (Panorex) in, 462-463, 462f
photography in, 461-462, 462f
physical examination in, 461, 462f
Ricketts analysis in, 463, 463f
Steiner analysis in, 463, 463f
symmetry in sagittal plane in, 464-465
vertical relationships in, 463-464, 464f
procedure selection for, 461, 462t, 465
MEP(s) (motor evoked potentials), transcranial electrical stimulation–induced, to assess facial nerve function, 2389
Meperidine
for pediatric anesthesia, 2592
for postoperative pain, 241t
Merbromin (Mercurochrome), for fungal otitis externa, 1955
Merkel cells, 1201
Merocel wicks, in atresiaplasty, 2756-2757
MERRF (myoclonic epilepsy and red ragged fibers) syndrome, sensorineural hearing loss in, 2094t, 2097
Mesotympanum, 1825-1826, 1827f
Messenger RNA, 11-12, 12f
Messerklinger technique, for endoscopic sinus surgery, 746
MET (D-methionine), for noise-induced hearing loss, 2145
MET (Middle Ear Transducer). *See* Middle Ear Transducer (MET).
MET (mechanoelectrical transduction) channel, in hair cell transduction, 2072f
MET (mechanoelectrical transduction) currents, adaptation of, in hair cell transduction, 2078-2079, 2079f
Meta-analyses, 70, 71t
Metabolic disorders
craniofacial anomalies due to, 2640
facial paralysis due to, 2401
otologic manifestations of, 2112-2114
in gout, 2113-2114
in mucopolysaccharidoses, 2112-2113, 2113f
in ochronosis, 2114
presbycusis due to, 232
sensorineural hearing loss due to, 2125
vertigo due to, 2201
Metabolic manipulation, and skin flap viability, 1074-1075
Metabolic myopathies, laryngeal hypofunction due to, 842
Metabolic presbycusis, 232
Metachronous lesion, in oral cancer, 1301-1302
Metallic artifacts
on CT, 139, 141f
on MRI, 134, 134f
Metallic coils, for embolization, 1933
Metastasis(es)
cervical lymph node (*See* Cervical lymph node metastasis(es))
to larynx, 1510
rapidly progressive hearing loss due to, 2200
to salivary glands, 1191
to skull base, 171, 173f
to trachea, 1615-1616
Metastasizing mixed tumor, of salivary glands, 1189
Metastatic (M) classification, for melanoma, 1111t, 1113
Metastatic disease, systemic chemotherapy for, 1058-1061
combination, 1059-1060
prognostic factors with, 1058-1059
single agent, 1059
Metastatic lesions
of cerebellopontine angle, 2526
of ear, 2107-2108, 2108f
otorrhea due to, 2196-2197
Metastatic lesions *(Continued)*
of neck, 1664
from distant tumor, 1664-1666
from regional tumor, 1664
from unknown primary, 1664, 1665f
Metastatic lymphadenopathy
CT of, 139
MRI of, 142
ultrasound of, 143
Metastatic workup, for melanoma, 1109-1110, 1110b, 1110t
Methacholine challenge test, in nonallergic rhinitis, 695
Methacrylates, for craniofacial defect repair, 2657
Methadone, for postoperative pain, 241t
Methicillin-resistant *Streptococcus aureus* (MRSA), rhinosinusitis due to
acute, 704, 732
chronic, 732, 733f
Methimazole
adverse reactions to, 1742
for Graves' disease, 1742
for hyperthyroidism, 1739t
D-Methionine (MET), for noise-induced hearing loss, 2145
Methotrexate (Rheumatrex)
for autoimmune inner ear disease, 2167
in combination chemotherapy, 1059-1060
dizziness due to, 2310t
for induction chemotherapy, 1056-1057
for recurrent or metastatic disease, 1059
for recurrent respiratory papillomatosis, 879
for sarcoidosis, 659
for Wegener's granulomatosis, 658
Methoxyisobutyl isonitrile (MIBI). *See* Sestamibi.
Methylation, in head and neck squamous cell carcinoma, 1020-1022, 1021f
Methylprednisolone
with chemical peel, 396
intratympanic delivery of
dosing for, 2185
pharmacokinetics of, 2183-2184
for sudden sensorineural hearing loss, 2184-2185
for vestibular neuritis, 2162
Methylprednisone, for rhinosinusitis, 734t
Metoclopramide
for extraesophageal reflux, 901
for GERD, 970
Metopic suture, 320f
Metopic synostosis, 2642-2643, 2643f
Metoprolol, intraoperative, 112
Metrizamide powder (Nycomed), for embolization, 1933
MeV (megaelectron volts), 1033
MFD (mandibulofacial dysostosis), 2585
craniofacial abnormalities in, 2633-2635, 2633b, 2635f, 2646
MFH (malignant fibrous histiocytoma)
of larynx, 1508
of neck, 1667
MGCT (malignant giant cell tumor), 1671
MH (malignant hypertension), 119
MHC (myosin heavy chain) isoforms
in lingual muscles, 1205
in muscles of mastication, 1204
MHC (major histocompatibility complex) molecules, 599
MHC (major histocompatibility complex)-restricted cytotoxicity, 603-604
MHC (major histocompatibility complex) restriction, 603-604
MIBI (methoxyisobutyl isonitrile). *See* Sestamibi.
MIBI-SPECT (technetium-99m sestamibi scintigraphy with single photon emission computed tomography), for hyperparathyroidism, 1785

Michel's aplasia, 2200, 2729
  imaging of, 2729f-2730f
  inherited, 2735
  relative incidence of, 2729t
Miconazole cream (Micatin, Monistat), for fungal otitis externa, 1954-1955, 1959t-1960t
Micro Retin A (tretinoin)
  for aging skin, 403-404
  with chemical peels, 392-393
  for chemoprevention of oral cancer, 1315
Microcirculatory changes, in acutely raised skin flaps, 1068-1069
Microcirculatory impairment, of skin flaps, 1071f
Microdebrider
  for adenoidectomy, 2797-2798
  for recurrent respiratory papillomatosis, 2891
  for stridulous child, 2909
Microdeletion chromosome 22 syndrome, cleft lip and palate in, 2673-2674, 2674f
Microdermabrasion, 402-403
Microfibrillar collagen (Avitene), for embolization, 1933
Microgenia, 463
Microglial cells, 604
Micrognathia
  dysphagia due to, 2950-2951
  and obstructive sleep apnea, 2610
Microlaryngoscopy, 864, 864f
Microlaryngoscopy partial cordectomy, for glottic cancer, 1517t
Microneurovascular muscle transfer, for facial nerve paralysis, 2429-2430
Microphone, for hearing aid, 2267
  directional, 2269
Microphthalmia transcription factor *(MITF)* gene, in deafness, 2051t-2058t, 2095
MicroRNAs (miRNAs, miRs), in head and neck squamous cell carcinoma, 1021, 1022f, 1027-1028
Microsatellite repeats, in head and neck squamous cell carcinoma, 1019
Microscopic direct laryngoscopy, for glottic cancer, 1519t
Microscopic examination, of ear, in children, 2574
Microsurgical débridement, for airway stenosis, 946, 946b, 946f
Microtia, 2741-2751
  atypical, 2742, 2743f
    reconstruction for, 2747-2748, 2749f-2750f
  classic, 2742, 2743f
  classification of, 2742
  ear anatomy and, 2742, 2742f
  embryology of, 2741, 2742f
  epidemiology of, 2741
  evaluation of, 2742-2743
  reconstruction for
    advantages and disadvantages of, 2744t
    atypical, 2747-2748, 2749f-2750f
    autogenous costochondral, 2744, 2744t
    classic, 2744-2747
      cartilage implantation in, 2744-2746
      carving of framework and helix in, 2746, 2746f
      construction of implant in, 2746, 2746f
      creation of postauricular sulcus in, 2746, 2748f
      donor site in, 2745, 2745f
      incision in, 2745-2746
      lobule transfer in, 2746, 2747f
      placement of implant in, 2746, 2747f
      templates in, 2744-2745, 2745f
      tragus reconstruction in, 2747, 2748f
    complications of, 2748-2751
    planning for, 2743-2744, 2744t
  treatment options for, 2744t
  type I, 2742, 2742f
Microtia *(Continued)*
  type II, 2742, 2743f
  type III, 2742, 2743f
Microvarices, of larynx, 817
Microvascular decompression, facial nerve monitoring with, 2548-2549, 2549f
Microvascular reconstruction, total glossectomy with, 1390
Microvillar cells, of olfactory epithelium, 626, 627f
Microwaves, effect on hearing of, 2149
Midazolam
  for adenotonsillectomy, 2797
  as adjunct to induction of anesthesia, 111
  for premedication in children, 2589
    with congenital heart disease, 2596
Middle cerebral artery, 2351f
Middle cervical sympathetic ganglion, in root of neck, 2582
Middle constrictor muscle, 1296f
Middle cranial base
  anatomy of, 1699
  central and lateral compartments of, 2454-2455, 2455f
  surgical anatomy of, 2444
    boundaries in, 2442, 2443f
    craniofacial junction in, 2442, 2443f
    extracranial view of, 2444, 2445f
    foramina along floor of, 2444, 2445f
    intracranial view of, 2444, 2445f
    lateral pterygoid plate in, 2444, 2445f
    lateral view of, 2444, 2445f
    sphenoid spine in, 2444
    superomedial boundary of, 2444
Middle cranial base irradiation, 1699-1700
Middle cranial base surgery
  anesthesia for, 2447-2448
  complications of, 2468-2469, 2469t
  electrophysiologic monitoring during, 2450
  goals of, 2448, 2448b
  intraoperative imaging during, 2449
  operative approaches for, 2454-2467
    for central compartment, 2455-2461, 2455t
      endoscopic, 2457-2458, 2457f
      extended maxillotomy, 2455t, 2458, 2462f
      facial translocation, 2455t, 2464-2466, 2467f
      intratemporal fossa, 2455t
      lateral rhinotomy, 2455t, 2458, 2458f
      Le Fort I osteotomy as, 2455t, 2458, 2460f
      mandibulotomy, 2455t, 2458, 2460f
      midfacial degloving, 2455t, 2458, 2459f
      midfacial split, 2455t, 2458-2461, 2463f
      transantral, 2455t, 2458, 2459f
      transethmoidal sphenoidotomy, 2455-2457, 2455t, 2456f
      transoral, 2455t, 2458, 2461f
      transpalatal, 2455t, 2458, 2461f
      transseptal sphenoidotomy, 2455-2457, 2455t, 2456f
    division into central and lateral compartments in, 2454-2455, 2455f
    endoscopic, 2449-2450
      for central compartment, 2457-2458, 2457f
    functional and aesthetic considerations in choice of, 2450
    general considerations with, 2448-2450
    image-guided computer-assisted, 2448-2449, 2449f
    for lateral compartment, 2461-2467
      infratemporal, 2461-2464, 2464f
      intracranial, 2467
      lateral facial, 2462, 2465f
      lateral transtemporal sphenoid, 2462, 2465f
      subtemporal-preauricular infratemporal approach, 2462, 2466f
      transfacial, 2464-2467, 2467f
      transtemporal, 2461
Middle cranial base surgery *(Continued)*
    overview of, 2448
    planning of, 2448-2450
    robotic, 2450
  outcomes of, 2469-2470
  pathology and management planning for, 2446-2447, 2447b
  postoperative care after, 2468
  preoperative embolization for, 2446
  preoperative evaluation for, 2444-2448
    angiography in, 2444-2445
    of cerebral blood flow, 2445-2446, 2446f
    other evaluations in, 2446-2447
  reconstruction after, 2467-2468
Middle cranial base tumors, malignant, 1699-1700
  chordoma/chondrosarcoma as, 1699
  nasopharyngeal carcinoma as, 1699-1700, 1699f, 1700t
Middle cranial fossa, in surgical anatomy of lateral skull base, 2434, 2435f-2437f, 2438
Middle cranial fossa approach
  for intratemporal facial nerve surgery, 2407-2409
    advantages and uses of, 2408-2409
    for Bell's palsy, 2409-2410, 2409t-2410t
    limitations and potential complications of, 2409
    technique of, 2407-2408, 2408f-2409f
  for skull base lesions requiring drainage, 2539
Middle ear
  anatomy of, 1825-1827, 1825f-1827f
  in auditory physiology, 1839-1840, 1840f
  bidirectional gas exchange in, 1870-1871
  effects of radiotherapy on, 2626t
  embryogenesis of, 1825
  imaging of, 172, 1918-1920
    with aberrant internal carotid artery, 1919-1920, 1921f-1922f
    with cholesteatoma
      acquired, 1919, 1920f
      congenital, 1918-1919, 1919f-1920f
      with CT, 174f, 1919f-1920f
      with MRI, 1919, 1920f-1921f
    with glomus tympanicum, 1919-1920, 1921f
    with transverse petrous fracture with osseous dislocation, 174f
  infection of (*See* Otitis media (OM))
  mucociliary clearance and drainage of, 1871
  protection of, 1871-1872
  salivary gland choristoma of, 2200-2201
  sound transfer in, 2017-2019
Middle ear aeration, in sound transmission, 2000
Middle ear atelectasis, 1964, 1964f-1965f
  tympanoplasty with, 2003-2004
Middle ear cavity, 1825-1826
Middle ear effusion (MEE)
  collection vehicle for aspiration of, 2773-2774, 2774f
  and hearing loss in infants, 2722
  otitis media with (*See* Otitis media with effusion (OME))
Middle ear function, tests to evaluate, 1890-1891, 1890f
Middle ear implants, 2207-2212
  basic design features of, 2207-2208
    ossicular coupling as, 2207-2208
    transducer design as, 2207
  electromagnetic, 2208-2211
    Carina as, 2210-2211
      clinical results with, 2210-2211
      components of, 2210, 2210f
      history of, 2210
      placement of, 2210, 2211f
    Middle Ear Transducer (MET) as, 2027, 2210-2211
      clinical results with, 2210-2211
      comparison of features of, 2206t
      components of, 2210
      history of, 2210

Middle ear implants *(Continued)*
indications for, 2210, 2211f
placement of, 2210, 2211f
ossicular coupling in, 2207-2208
sound transduction and coupling to auditory system with, 2205f
transducer design for, 2207
Vibrant Soundbridge as, 2208-2210
clinical data on, 2209
comparison of features of, 2206t
components of, 2208-2209, 2208f
for conductive and mixed hearing loss, 2210
history of, 2208, 2210
implantation of, 2209
indications for, 2209, 2209f
location of, 2204f
piezoelectric, 2211-2212
Esteem-Hearing Implant as, 2211-2212, 2212f
ossicular coupling in, 2207-2208
sound transduction and coupling to auditory system with, 2205f
transducer design for, 2207
total *vs.* partial, 2208
Middle ear muscle reflex pathways, in efferent auditory system, 1847, 1848f
Middle ear pressure changes, eye movements evoked by, 2316, 2316f
Middle ear sources, of otorrhea, 2195-2196, 2195b
Middle Ear Transducer (MET), 2027, 2210-2211
clinical results with, 2210-2211
comparison of features of, 2206t
components of, 2210
history of, 2210
indications for, 2210, 2211f
placement of, 2210, 2211f
Middle Eastern patient, hump reduction in, 570-573
concept of, 570-571
results of, 574f-575f
technique for, 571-573, 575f
Middle fossa approach
for middle cranial base surgery, 2467
for posterior fossa neoplasms, 2532t, 2534-2536
advantages and disadvantages of, 2532t, 2536
basic features of, 2534
extended, 2532t, 2538
advantages and disadvantages of, 2532t, 2538
basic features of, 2538
indications for, 2532t, 2538
surgical exposure in, 2538f
technique of, 2538
indications for, 2532t, 2534-2535
surgical exposure in, 2535f
technique of, 2535-2536, 2535f
Middle fossa craniotomy, for facial nerve decompression, 2042-2043
Middle jugular lymph nodes, in neck dissection, 1704, 1704f, 1706t-1708t
Middle latency response (MLR)
auditory evoked, 1912, 1913f
electrically evoked, 1912-1914
Middle meningeal artery
groove for, 1822f
in surgical anatomy of lateral skull base, 2437f, 2438, 2440f
Middle meningeal artery sulcus, in surgical anatomy of lateral skull base, 2436f
Middle nasal meatus
normal anatomy of, 664-665, 665f-667f
in surgical anatomy of anterior cranial base, 2472, 2472f
Middle skull base. *See* Middle cranial base.
Middle temporal artery, sulcus for, 2010f
Middle turbinate
in endoscopic sinus surgery, 751, 751f, 771
normal anatomy of, 667
paradoxic, 668, 669f
surgical anatomy of, 739-740
in anterior cranial base, 2472, 2472f-2473f
Middle vault deformities, revision rhinoplasty for, 585-586, 586f
Midesophageal diverticula, 974, 974f
imaging of, 1402, 1403f
Midface
aesthetic ideals for, 447
aging of, 444, 444f
congenital malformations of nose due to developmental errors of, 2690-2693, 2691f
in Down syndrome, 2632
Midface fractures, pediatric, 2707, 2710f
Midface lift, 2431
Midface soft tissue laxity and sagging, after facial paralysis, 2431
Midfacial clefting, 2690, 2692
Midfacial degloving approach
for middle cranial base surgery, 2455t, 2458, 2459f
for pediatric facial fracture, 2701-2702
Midfacial split approach, for middle cranial base surgery, 2455t, 2458-2461, 2463f
Midforehead brow lift, 430, 431t
Midforehead flap, 344-345
Midforehead lift, 430, 431t
Midline cleft, 2586
Midline lesions, of neck, 2586
Midline malignant reticulosis, 659-660
Migraine, 246-247, 2347-2350
auditory symptoms of, 2348-2349
distortion as, 2349
hearing loss as, 2123, 2348-2349
phonophobia as, 2349
tinnitus as, 2349
without aura, 2347b
aura with, 2347, 2347b
basilar, 2349
diagnosis and classification of, 2347, 2347b
epidemiology of, 2347
etiology of, 2349
familial hemiplegic, 2349
familial vestibulopathy with, 2344
family history of, 2349
without headache, 2349
management of, 2349-2350, 2350f
with neurotologic symptoms, 2349
vestibular disorders associated with, 2350
benign paroxysmal positional vertigo as, 2350
Meniere's disease as, 2350
vestibular disorders related to, 2350-2351
benign paroxysmal vertigo of childhood as, 2350-2351
paroxysmal torticollis as, 2351
vestibular symptoms of, 2347-2348
motion sickness as, 2348
nonspecific dizziness as, 2347
vertigo as, 2202, 2347-2348, 2348f
Migraine accompaniments, 2349
Migraine equivalent, 2349
MII (multichannel intraluminal impedance), 962
Milia, 289
after skin resurfacing, 451
Millard forked-flap technique, in cleft-lip nose repair, 559, 566f
Millard rotation advancement closure, for cleft lip, 2667-2668, 2667f
advancement flap in, 2668, 2668f
closure in, 2668, 2668f
rotation flap in, 2667-2668, 2668f
Millicurie (mCi), 1031-1032
Mineral oil, for cerumen removal, 1958t
Mini Rhinoconjunctivitis QoL Questionnaire, 57
Minimal cross-sectional area (MCA), in rhinomanometry and acoustic rhinometry, 643f, 644
anatomic, 644
physiologic, 644
Minimally invasive sinus technique (MIST), 743, 752, 760
Minimally invasive techniques, for parathyroid surgery, 1793
Minimally invasive thyroidectomy, 1769, 1769f
Mini-mantle field technique, for glottic cancer, 1586
Minimum Speech Test Battery for Adult Cochlear Implant Users (MSTB), 2223, 2244
Miniplate, for mandibular fracture, 338
MinK, in deafness, 2051t-2058t
Minoxidil, for hair loss, 376-377
MIO (maximum interincisal opening), 1280
miR(s) (microRNAs), in head and neck squamous cell carcinoma, 1021, 1022f, 1027-1028
miRNAs (microRNAs), in head and neck squamous cell carcinoma, 1021, 1022f, 1027-1028
MirrorSuite, 279-280
MIST (minimally invasive sinus technique), 743, 752, 760
MIT (monoiodotyrosine)
in thyroid hormone release, 1738
in thyroid hormone synthesis, 1738
MITF (microphthalmia transcription factor) gene, in deafness, 2051t-2058t, 2095
Mitochondrial disorders, 8, 8f, 2088f, 2089
Mitochondrial DNA (mtDNA), 2089
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome, sensorineural hearing loss in, 2094t, 2097
Mitochondrial mutations, in head and neck squamous cell carcinoma, 1024-1025, 1028f
Mitochondrial sensorineural hearing loss
nonsyndromic, 2093, 2093t
screening for, 2090t
syndromic, 2094t, 2097
Mitogen-activated protein kinase (MAPK) pathway, in thyroid carcinoma, 1753
Mitomycin C
for airway stenosis, 946, 2918
for caustic ingestion, 2960
with radiotherapy, 1041
Mitotic death, due to radiation, 1037
Mitral cell, of olfactory bulb, 628f
Mivacurium, for pediatric anesthesia, 2593t
Mixed acinus, 1134, 1134t
Mixed apnea index, 251b
Mixed sleep apnea, 251b
MLC (multileaf collimator), in radiotherapy, 1035-1036
MLR (middle latency response)
auditory evoked, 1912, 1913f
electrically evoked, 1912-1914
MM (malignant melanoma). *See* Melanoma.
MMA (maxillomandibular advancement), for obstructive sleep apnea, 260, 261f
MMF. *See* Maxillomandibular fixation (MMF).
MMP. *See* Mucous membrane pemphigoid (MMP).
MMP(s) (matrix metalloproteinases)
in bone resorption, 1972
in head and neck squamous cell carcinoma, 1019-1020
MMP-1 (matrix metalloproteinase-1), in head and neck squamous cell carcinoma, 1077
MMR (mediastinal mass ratio), for lymphomas, 1676
MNTB (medial nucleus of trapezoid body), in auditory pathway, 1834f
Möbius syndrome, facial paralysis in, 2397
MOC (maintenance of certification), 80, 81b
MOC (medial olivocochlear) reflex pathways, in efferent auditory system, 1848-1849, 1848f

MOC (medial olivocochlear) "unmasking," 1849
Modafinil, for obstructive sleep apnea, 257
Modal register, of voice production, 850-851
Mode, 64t
Mode-locked lasers, 34
Modified barium swallow (MBS), 1394, 1396
  for swallowing disorders, 1217-1218, 1219f
    in children, 2949, 2950t
Modified radical neck dissection (MRND), 1711-1712
  definition of, 1703t, 1711, 1712f
  historical perspective on, 1703
  indications for, 1711
  for oral cancer, 1313
  results of, 1721
  technique for, 1711-1712, 1713f-1714f
Modified Schobinger incision, for radical neck dissection, 1709, 1710f
Modified voice use, for vocal abuse, 853
Modiolus, anatomy of, 1831, 1832f, 1834, 1840, 1841f, 2049-2050
MOE. *See* Malignant otitis externa (MOE).
Mohr-Tranebjaerg syndrome, deafness in, 2051t-2058t, 2094t, 2097
Mole(s), 286
  atypical, 1107
Molecular biology, 11-12
  cell division in, 12, 13f
  gene expression in, 11-12, 12f
  of laryngeal cancer, 1492
Molecular biomarkers
  for head and neck squamous cell carcinoma, 1026-1027
    epidermal growth factor receptor as, 1026
    human papillomavirus as, 1026
    loss of heterozygosity as, 1026
    margin analysis for, 1027
    in oral rinses and saliva, 1026
    other, 1026-1027
    polymorphisms in DNA repair enzymes as, 1027
    serum analysis for, 1026-1027
  for laryngeal squamous cell carcinoma, 1493, 1505
  for salivary gland neoplasms, 1194
Molecular genetics, of orofacial clefts, 2662-2664
Molecular staging, of melanoma, 1118
Molluscum contagiosum, 282-283, 283f
Mometasone, for otitis media with effusion, 2772
Mometasone furoate nasal spray (Nasonex)
  for nonallergic rhinitis, 700t
  for rhinosinusitis, 734t, 736
"Mona Lisa" smile, 2417-2418
Mondini, Carlo, 2728-2729
Mondini malformation, 172-173, 174f
  congenital hearing loss due to, 2200
  CSF otorrhea due to, 2197
Mondini's dysplasia, 2730-2731
  embryogenesis of, 2728f-2729f, 2729t, 2730-2731
  familial, 2735
  histology of, 2730-2731, 2731f
  historical background of, 2728-2729
  imaging of, 2730-2731, 2731f
  relative incidence of, 2729t
  subtypes of, 2730-2731, 2731f
Monistat (miconazole cream), for fungal otitis externa, 1954-1955, 1959t-1960t
Monobloc advancement, for craniofacial anomalies, 2653-2654, 2655f-2656f
Monocyte(s)
  in adaptive immune system, 604
  in allergic rhinitis, 616
  in wound healing, 1076
Monocyte chemoattractant protein-1 (MCP-1), in wound healing, 1076
Monoiodotyrosine (MIT)
  in thyroid hormone release, 1738
  in thyroid hormone synthesis, 1738
Mononucleosis, infectious
  adenotonsillar disease in, 2785-2786, 2786f
  pharyngitis due to, 198-199, 198f
  sudden sensorineural hearing loss due to, 2127
  vestibular neuritis due to, 2162
Monosodium glutamate (MSG), taste of, 1213
Monostotic fibrous dysplasia, of paranasal sinuses, 1132
Montelukast
  for allergic rhinitis, 620-621
  for rhinosinusitis, 735t, 736
Montgomery T-tube, 1009
Moraxella catarrhalis
  otitis media due to, 2763
  rhinosinusitis due to
    acute, 704, 704f, 732
    acute exacerbation of chronic, 707
Moraxella catarrhalis vaccine, to prevent otitis media, 2769
Morphine
  as adjunct to induction of anesthesia, 111
  for pediatric anesthesia maintenance, 2591-2592
  for postoperative pain, 241t
  topical, for mucositis, 1102
Morquio's syndrome, 2113
Morsicatio, 1223
Mosaicism, 5
Motion artifacts, on MRI, 133-134, 134f
Motion sickness, 2357
  and migraine, 2348
Motor control test, 2324-2325
Motor evoked potentials (MEPs), transcranial electrical stimulation–induced, to assess facial nerve function, 2389
Motor function, oral, 1203-1207
  autonomic reflexes in, 1205-1206
  jaw-tongue reflexes in, 1205
  lingual muscles and reflexes in, 1205
  mastication as, 1206-1207, 1206f
  muscles of mastication and reflex control in, 1204-1205, 1204f-1205f
  oral phase of deglutition as, 1206f, 1207
Motor nerve complications, of neck surgery, 1729-1731
  facial, 1729-1730
  hypoglossal, 1730-1731
  phrenic, 1731, 1731f
  spinal accessory, 1730, 1731f
  vagus, 1730
Motor vehicle collisions
  laryngeal trauma due to, 2914
  pediatric facial fractures due to, 2698
Mouth. *See* Oral cavity.
Mouth breathing, 809, 2628-2629
  and craniofacial growth, 2792-2793
Movement disorders, sleep-related, 265, 265b
MPD syndrome. *See* Myofascial pain dysfunction (MPD) syndrome.
MPFR (maximum phonational frequency range), 829
M-plasty, for forehead defects, 359-360, 362f
MPNST (malignant peripheral nerve sheath tumor), of neck, 1670-1671
MPS. *See* Mucopolysaccharidoses (MPS).
MPT (maximum phonation time)
  in tracheoesophageal speech, 1597
  in voice evaluation, 828, 849
MPZ (myelin protein zero) gene, in deafness, 2051t-2058t, 2081
MR (magnetic resonance) cisternography, for CSF rhinorrhea, 790-791, 790f
MR (magnetic resonance) sialography, 1147
MR (magnetic resonance) spectroscopy, of laryngeal carcinoma, 1470
MRA. *See* Magnetic resonance angiography (MRA).
MRD (margin-reflex-distance), 446
MRI. *See* Magnetic resonance imaging (MRI).
MRND. *See* Modified radical neck dissection (MRND).
MRP. *See* Mandibular reconstruction plate (MRP).
MRSA (methicillin-resistant *Streptococcus aureus*), rhinosinusitis due to
  acute, 704, 732
  chronic, 732, 733f
MS. *See* Masticator space (MS); Multiple sclerosis (MS).
MSG (monosodium glutamate), taste of, 1213
MSLT (multiple sleep latency test), 263-264
MSO (medial superior olive), in auditory pathway, 1834-1835, 1834f, 1846
MST (maximal stimulation test)
  for Bell's palsy, 2394
  for facial nerve injury, 2040-2041, 2382t, 2385-2386
MSTB (Minimum Speech Test Battery for Adult Cochlear Implant Users), 2223, 2244
M&T (myringotomy with tympanostomy tube insertion)
  for acute otitis media, 2771
  for otitis media with effusion, 2772
MTC. *See* Medullary thyroid carcinoma (MTC).
mtDNA (mitochondrial DNA), 2089
m-tetra(hydroxyphenyl)chlorin (Foscan), for recurrent respiratory papillomatosis, 2892
MTRNR1, 2093t
MTTS1, 2093t
MUC5AC gene, in otitis media, 1871
Mucins, in saliva, 1140-1141
Mucoceles, 289
  in children, 2859
  endoscopic sinus surgery for, 742, 760f, 761, 762f
  frontoethmoid, 776f-777f, 783
  imaging of, 169, 169f, 676, 678f, 765t
  of petrous apex, 2524t, 2525, 2527f
  surgical management of, 742
Mucociliary diseases, nasal manifestations of, 661
  in cystic fibrosis, 661
  in primary ciliary dyskinesia, 661
Mucocutaneous end organs, 1201
Mucocutaneous junction, in cleft lip, 2665
Mucocutaneous lymph node syndrome, in children, 2819
Mucoepidermoid carcinoma (MEC)
  of larynx, 1506-1507
  of salivary glands
    in children, 2820, 2846, 2846f, 2862-2863
    differential diagnosis of, 1183
    grading of, 1183, 1184t
    histopathology of, 1182-1183, 1183f
    imaging of, 1146, 1147f, 1168f
    minor, 1363
  of trachea, 1615
Mucoepithelial changes, with aging, 234
Mucolytic agents
  for rhinosinusitis, 735t, 736
  for vocal professionals, 855
Mucoperichondrium, in rhinoplasty, 539-540, 546
Mucopolysaccharidoses (MPS), 2112-2113
  craniofacial anomalies due to, 2640
  and obstructive sleep apnea, 2606
  otologic manifestations of, 2113, 2113f
Mucormycosis
  otologic manifestation of, 2106f
  rhinosinusitis due to, 705, 710, 711f
Mucosa, effects of radiotherapy on, 2626t
Mucosa-associated lymphoid tissue (MALT)
  in eustachian tube, 1870
  in middle ear protection, 1871

Mucosa-associated lymphoid tissue (MALT) lymphoma, 1679-1680
clinical presentation of, 1674
of salivary glands, 1191-1192, 1192f, 1679-1680
treatment and prognosis for, 1680
of thyroid, 1679
staging of, 1679
treatment and prognosis for, 1679
Mucosal changes, in geriatric patients, 236
Mucosal edema, olfactory dysfunction due to, 625, 635f
Mucosal grafts, for airway stenosis, 946-947
Mucosal immune system, 605
Peyer's patches and lymphoid follicles in, 605
tonsils in, 605
Mucosal lesions, oral. *See* Oral mucosal lesions.
Mucosal melanocytic nevi, of oral cavity
clinical features of, 1241
histopathologic features of, 1242
treatment of, 1243
Mucosal melanoma, 1108-1109
of larynx, 1509
of oropharynx, 1364-1365, 1364f-1365f
Mucosal ulcerations, of oral cavity, 1289, 1289f
Mucosal wave, laryngeal videostroboscopy of, 820, 848-849, 848t
Mucosal-relief esophagogram, 1394, 1395f
Mucositis
palliative care for, 1101-1102
due to radiotherapy, 1047, 1047f, 1102
Mucotrol, for mucositis, 1102
Mucous acinus, 1134, 1134f, 1134t
Mucous cysts, 289
Mucous membrane pemphigoid (MMP)
esophageal manifestations of, 980
nasal manifestations of, 660
ocular scarring (symblepharon) due to, 1233-1234, 1234f
oral, 1233-1235, 1254
clinical differential diagnosis of, 1234, 1234t
clinical features of, 1233-1234, 1233f-1234f
defined, 1233
etiology and pathogenesis of, 1233
histopathologic features of, 1234-1235, 1234f
treatment of, 1235
Mucous retention cysts, 289
in children, 2859
imaging of, 676, 677f
of larynx, 869, 869f-870f
of petrous apex, 2525, 2526f
Muenke syndrome, deafness in, 2051t-2058t
Muenke-type craniosynostosis, 2641t
Müller maneuver, in obstructive sleep apnea, 253, 254f
Müller's muscle
anatomy of, 443f, 444
in upper eyelid blepharoplasty, 448, 449f
Multicellular theory, of salivary gland tumorigenesis, 1163
Multichannel intraluminal impedance (MII), 962
Multifactorial traits, 8
MULTIFIRE ENDO GIA 30 stapler, 993-994
Multileaf collimator (MLC), in radiotherapy, 1035-1036
Multinodular thyroid gland, ultrasound imaging of, 1644
Multiple endocrine adenomatosis type 3, oral manifestations of, 1257
Multiple endocrine neoplasia type I (MEN-I)
defined, 1795
epidemiology of, 1795
familial hyperparathyroidism in, 1795-1796
genetic basis for, 1775, 1776f, 1795
Multiple endocrine neoplasia type IIA (MEN-IIA)
defined, 1773
familial hyperparathyroidism in, 1796
genetic basis for, 1796
and medullary thyroid carcinoma, 1763-1764
Multiple endocrine neoplasia type IIB (MEN-IIB), and medullary thyroid carcinoma, 1763-1764
Multiple myeloma, 2106-2107
otologic manifestations of, 2107, 2107f
Multiple sclerosis (MS)
laryngeal hypofunction due to, 843
oral manifestations of, 1255
preoperative evaluation of, 106
sensorineural hearing loss due to, 2122-2123
sudden, 2129
vertigo due to, 2202
vestibular symptoms of, 2356, 2356f
Multiple sleep latency test (MSLT), 263-264
Multiple system atrophy, laryngeal hypofunction due to, 843
Multiple-Activity Scale for Hyperacusis (MASH), 2138-2139
Multivariate analysis, 72
Mumps
salivary gland involvement in, 1156-1157
in children, 2855
sensorineural hearing loss due to, 2119, 2157-2158, 2158f
clinical features of, 2157
diagnosis of, 2157
experimental, 2158
sudden, 2127
temporal bone pathology in, 2158, 2158f
vestibular neuritis due to, 2162
Mumps vaccine, for recurrent respiratory papillomatosis, 2890t, 2892-2893
Mupirocin, for rhinosinusitis, 734, 735t
Murine removal kit (carbamide peroxide), for cerumen removal, 1958t
Muscarinic receptors, in salivary gland secretion, 1136-1137
Muscle fibers, characteristics of, 918
Muscle flaps, for free tissue transfer, 1082t, 1083-1084
latissimus, 1082t, 1083-1084, 1084f
rectus abdominis, 1082t, 1083
Muscle neoplasms, of larynx, 881
Muscle relaxants
oral sequelae of, 1247t-1248t
for pediatric anesthesia, 2592, 2593t
Muscle tension dysphonia, 842, 853
Muscle transfers, for facial nerve paralysis, 2427-2430
masseter, 2427, 2428f
microneurovascular, 2429-2430
temporalis, 2427-2429, 2429f
Muscle weakness, due to hyperparathyroidism, 1781
Muscular disorders, chronic aspiration due to, 926b
Muscular dystrophy(ies)
laryngeal hypofunction due to, 842
myotonic, oral manifestations of, 1255
Muscular tension dysphonia, 842, 853
Muscular triangle, of neck, 96, 96f, 2578f
Muscularis uvulae
in cleft palate, 2666-2667
in velopharyngeal function, 2676, 2677t
Musculocutaneous arteries, 1065, 1065f
Musculocutaneous flaps, 1067, 1067f
for free tissue transfer, 1082t, 1083-1084
latissimus, 1082t, 1083-1084, 1084f
for oropharyngeal reconstruction, 1380
for oropharyngeal reconstruction, 1380
rectus abdominis, 1082t, 1083
for oropharyngeal reconstruction, 1380
Musculoskeletal tension, in voice evaluation, 827-831, 828f
Mustache transplantation, 384
Mustarde suture technique, for otoplasty, 475-478, 476f-477f
Mutation testing, 9, 9f-10f
MV (megavoltage) electrons, 1033
MV (megavoltage) x-rays, 1033-1034
MVN (medial vestibular nucleus), 1861, 1862f
in velocity storage, 2296
M-wave, 2388
MX350-1, for head and neck squamous cell carcinoma, 1018
Myasthenia gravis
abnormal pharyngeal motility due to, 1398
edrophonium test for, 835
laryngeal hypofunction due to, 842
oral manifestations of, 1255
Mycelex (clotrimazole) cream, for fungal otitis externa, 1954-1955, 1959t-1960t
Mycobacterial infection
lymphadenopathy due to, 2818, 2819f
of salivary glands
in children, 2857-2858, 2857f
nontuberculous, 1158-1159, 1158f
tuberculous, 1158
Mycobacterial laryngitis, 885-886, 886f
Mycobacterial mastoiditis, 2196
Mycobacterium tuberculosis. *See* Tuberculosis (TB).
Mycophenolate mofetil, microtia due to, 2741
Mycoplasma pneumoniae, pharyngitis due to, 194-195
Mycoplasma spp, bullous myringitis due to, 1948
Mycostatin (nystatin cream), for fungal otitis externa, 1954-1955, 1959t-1960t
Mycotic diseases. *See* Fungal diseases.
Myectomy, selective, for synkinesis, 2432
Myelin protein zero *(MPZ)* gene, in deafness, 2051t-2058t, 2081
Myeloid stem cells, 600, 600f
Myeloma, multiple, 2106-2107
otologic manifestations of, 2107, 2107f
Myelopathy, due to radiotherapy, 1049
Myenteric plexus, 953, 954f
Myers-Cotton classification, of airway stenosis, 944, 944t
MYH9 (myosin heavy chain IX) gene, in deafness, 2051t-2058t
MYH14 (myosin heavy chain XIV) gene, in deafness, 2051t-2058t
Mylohyoid muscle, anatomy of, 1296f-1297f, 1297-1298, 1320, 2578f
MYO. *See* Myosin.
Myocardium, of newborn, 2571
Myoclonic epilepsy and red ragged fibers (MERRF) syndrome, sensorineural hearing loss in, 2094t, 2097
Myoclonus, oculopalatolaryngopharyngeal, 840
Myocutaneous flaps, 1067, 1067f
for free tissue transfer, 1082t, 1083-1084
latissimus, 1082t, 1083-1084, 1084f
for oropharyngeal reconstruction, 1380
for oropharyngeal reconstruction, 1380
rectus abdominis, 1082t, 1083
for oropharyngeal reconstruction, 1380
for hypopharyngeal and esophageal reconstruction, 1452-1453
Myoepithelial carcinoma, of salivary glands, 1191
Myoepithelial cells, of salivary glands, 1134, 1134f, 1163f
Myoepithelioma, of salivary glands, 1171
Myofascial pain dysfunction (MPD) syndrome, of temporomandibular joint, 1283-1285
clinical features of, 1283-1284
defined, 1283
differential diagnosis of, 1284t-1285t
epidemiology of, 1283
etiology of, 1283, 1283f
treatment of, 1284-1285, 1286f
Myopathies, laryngeal hypofunction due to, 842
Myosin(s), in stereocilia, 2076f
Myosin 1A *(MYO1A)* gene, in deafness, 2051t-2058t
Myosin 1c, in adaptation of mechanoelectrical transduction currents, 2079, 2079f

Myosin heavy chain (MHC) isoforms
in lingual muscles, 1205
in muscles of mastication, 1204
Myosin heavy chain IX *(MYH9)* gene, in deafness, 2051t-2058t
Myosin heavy chain XIV *(MYH14)* gene, in deafness, 2051t-2058t
Myosin IIIA, in stereocilia, 2077
Myosin IIIA *(MYO3A)* gene, in deafness, 2051t-2058t
Myosin VI, in stereocilia, 2078
Myosin VI *(MYO6)* gene, in deafness, 2051t-2058t, 2078
Myosin VIIA *(MYO7A)* gene, in deafness, 2051t-2058t, 2077-2078, 2096
Myosin XVA, in hair bundle development, 2077
Myosin XVA *(MYO15A)* gene, in deafness, 2051t-2058t, 2076
Myositis, *vs.* myofascial pain dysfunction syndrome, 1285t
Myositis ossificans, *vs.* myofascial pain dysfunction syndrome, 1285t
Myotomy, surgical, for achalasia, 964-965
Myotonic muscular dystrophy, oral manifestations of, 1255
Myringitis
bullous, 1948, 1948f
defined, 1955
granular, 1955
otorrhea due to, 2196
topical therapies for, 1955
Myringotomy
for acute otitis media, 2771
with tympanostomy tube insertion, 2771
for eustachian tube dysfunction, 1874
for otitis media with effusion, 2772
with tympanostomy tube insertion, 2772
Myringotomy with tympanostomy tube insertion (M&T)
for acute otitis media, 2771
for otitis media with effusion, 2772
Myxedema, pretibial, and Graves' ophthalmopathy, 1808
Myxedema coma, 1749
Myxoma, odontogenic, 1276-1277, 1276f
microscopic findings in, 1276
radiographic findings in, 1276
treatment and prognosis for, 1276-1277, 1277f

N

N (nodal) classification, for melanoma, 1111-1113, 1111t
*N*6-furfuryladenine (Kinerase), for aging skin, 404
Na^+. *See* Sodium (Na^+).
NaCl (sodium chloride), gustatory response to, 1208-1209
NADP-regulated thyroid hormone–binding protein, in deafness, 2051t-2058t
NA-EFRS (nonallergic eosinophilic fungal rhinosinusitis), 709, 715-716, 716t
Na^+,K^+ (sodium-potassium) pump, ATPase-driven, in salivary gland secretion, 1135
NAP-2 (neutrophil-activating peptide-2), in wound healing, 1076
Napoleon I, 251
NAR. *See* Nonallergic rhinitis (NAR).
Narcolepsy, 262t, 264
Narcotic analgesics. *See* Opioids.
NARES (nonallergic rhinitis with eosinophilia syndrome), 619b, 696
Narrow-band imaging (NBI), of larynx, 813, 823-824, 823f-824f
Nasacort (triamcinolone), for nonallergic rhinitis, 700t
Nasal airflow, 485-487
during exercise, 641
peak, 643
physical factors affecting, 643
in rhinomanometry
measurement of, 647
and transnasal pressure, 643
with rhinosinusitis, 730
and transnasal pressure, 643
Nasal allergy, and otitis media, 1872
Nasal base sculpting, for noncaucasian nose, 556-557, 559f-560f
Nasal block, 501-502
Nasal bones, anatomy and physiology of, 320
Nasal breathing function, 640-642
anatomy of, 641-642
septum and turbinates in, 641
nasal valve in, 641, 641f
site of sensation of obstruction in, 641-642
assessment of, 642-644
acoustic rhinometry for, 643-645
in allergic rhinitis, 651
to assess effect of treatment, 651-652
equipment for, 486-487, 486f, 644
interpretation of results of, 645
intranasal dimensions and cross-sectional area in, 643, 643f
intranasal sites assessed by, 644
reporting results of, 645
rhinogram generated by, 486-487, 487f, 645
vs. rhinomanometry, 644
for snoring and sleep apnea, 651
sources of variability in, 651
technical concerns and testing pitfalls with, 645
technique of, 644-645
nasal examination in, 642
objective testing of nasal airway in, 642-644
air stream through nose in, 643
to assess effects of treatment, 651-652
for challenge testing in allergic rhinitis, 651
in clinical evaluation of patient with nasal obstruction, 652-656
complementary information in, 656
correlation between results and symptoms with, 654
criteria for, 642
history of, 642
in identifying site of pathology affecting airflow, 655-656
intranasal dimensions and cross-sectional area in, 643, 643f
laser Doppler velocimetry for, 643-644
for normal nasal airway, 652t-653t, 654f
other methods of, 643-644
role of, 651-652
for snoring and sleep apnea, 651
sources of variability in, 651
and threshold level at which patient feels airway restriction, 655
when results do not match physical findings or symptoms, 653-654
when symptoms are not due to airway restriction, 653
patient history in, 642
rhinomanometry for, 643-651
vs. acoustic rhinometry, 644
active *vs.* passive, 647-648
in allergic rhinitis, 651
anterior *vs.* posterior, 645-647, 648f-649f
to assess effect of treatment, 651-652
for children, 645
defined, 642
equipment for, 645
examining pressure-flow curve in, 648-649, 649f-650f
inspiratory or expiratory values in, 650-651
Nasal breathing function *(Continued)*
intranasal sites assessed by, 644
maximum (vertex) resistance in, 650
measurement of nasal airflow in, 647
measurement of transnasal pressure in, 645-647, 648f
nasal airflow and transnasal pressure in, 643
nasal resistance in, 649-650, 650f
parameters in, 649-651, 650f
reporting results of, 648-651
sources of variability in, 651
technical concerns and testing pitfalls with, 645-648
technique of, 645, 645f-648f
unilateral *vs.* bilateral measurements in, 648, 649f
pathologic conditions affecting, 642
physiologic factors affecting, 640-641
Nasal bridge length, 2617t
Nasal cartilage, burns of, 316
Nasal cavity
bony outlines of, 672, 672f
imaging of, 169, 170f
lymphoma of, 1680
therapy and prognosis for, 1680
in surgical anatomy of anterior cranial base, 2443, 2471-2473, 2472f-2473f
Nasal challenge testing, objective measurement methods in, 651
Nasal clefts, 2690, 2692
Nasal cycle, 486, 641
MRI of, 664, 664f
Nasal defects, 346-350, 364-372
aesthetic units and, 346-347, 347f, 364
approach to, 346-347
extending into alar facial sulcus, 348
cheek advancement flap for, 348, 349f
cheek pedicle transposition flap for, 348, 349f
full-thickness alar, 347, 371-372
bipedicle mucosal advancement flap for, 347, 347f
free cartilage grafts for, 348
melolabial interpolated flap for, 348
full-thickness central defects of tip or dorsum as, 348
composite turnout flap for, 348, 351f
paramedian forehead flaps for, 348-350, 352f-354f
involving skeletal supporting structures, 367-371
grafting material for
alloplastic, 368
autogenous cartilage as, 368-369, 369f-370f
bone as, 369, 370f
homograft tissues as, 368
selection of, 367-368
prosthetic management of, 1345, 1345t, 1346f
reconstruction of, 364-372
external covering layer in, 364-367
framework in, 367-371
internal lining in, 371-372
surface defects of nasal tip, columella, sidewalls, and dorsum as, 348, 364-367
bilobed flaps for, 365-366, 365f
complications of local flaps for, 366
dorsonasal (Rieger) flap for, 365-366
forehead flap for, 366-367, 368f
full-thickness skin grafts for, 365
glabellar flaps for, 365-366
healing by second intention for, 365
hinge flap for, 348, 350f
melolabial flap for, 366, 367f
paramedian forehead flaps for, 348
primary closure for, 365, 365f
retroauricular flap for, 365-366
transposition flaps for, 365-366, 366f
vestibular lining reconstruction for, 371-372, 371f-372f
V-Y advancement flap for, 345-346, 346f

Nasal depth, anterior and posterior, 2617t
Nasal dilator strips, for obstructive sleep apnea, 257
Nasal dorsum
  cartilaginous, 509f
  full-thickness central defects of, 348
    composite turnout flap for, 348, 351f
    paramedian forehead flaps for, 348-350, 352f-354f
  growth and development of, 2617t
  reconstruction of, 371
  surface defects of, 348
    hinge flap for, 348, 350f
    paramedian forehead flaps for, 348
Nasal endoscopy, 100
  for CSF rhinorrhea, 791
  in endoscopic sinus surgery, 746, 763
Nasal Endoscopy Simulator, 49
Nasal examination
  in assessment of nasal breathing function, 642
  for professional voice disorders, 851
Nasal fracture(s), 496-507
  acute intervention for, 500
  algorithm for management of, 501, 502f
  cantilever bone graft for, 505, 505f
  classification of, 498-499, 498f-499f
  complications of, 507
  diagnostic assessment of, 499-500
    history in, 499
    physical examination in, 499-500
    radiography in, 325, 500
  external compression plating for, 506
  external nasal splinting for, 504
  injuries associated with, 498
  mucoperiosteal tunnel dissection and wire for, 506, 506f
  nasal anatomy and, 496-497, 497f
  "open-book", 2708, 2711f
  pathophysiology of, 497-498
  pediatric, 506-507, 2708-2711, 2711f-2712f
  percutaneous Kirschner wire for, 506, 506f
  reduction of
    alternative methods for, 506, 506f
    in children, 2628
    closed
      anesthesia for, 501-502
      care after, 504
      equipment and medications for, 503, 503f
      vs. open, 500-501, 501f
      technique for, 502-504, 503f-504f
    open
      vs. closed, 500-501, 501f
      failed, 503-504
      technique for, 504-506, 505f
    timing of, 500
  septal splints for, 504
Nasal function, and nonallergic rhinitis, 695
Nasal height, 2617t
Nasal implant, for saddle nose deformity, 555, 556f-558f
Nasal innervation, and nonallergic rhinitis, 695
Nasal lymphoma, 1680
  therapy and prognosis for, 1680
Nasal manifestations, of systemic diseases, 657-661
  cutaneous, 660-661
    Behçet's disease as, 660-661
    pemphigoid as, 660
    pemphigus vulgaris as, 660
    scleroderma as, 660
  granulomatous, 657-659
    Churg-Strauss syndrome as, 659
    in sarcoidosis, 658-659
    Wegener's granulomatosis as, 658
  immunodeficiency, 660
    AIDS as, 660
    sinusitis in immunocompromised patient as, 660
Nasal manifestations, of systemic diseases *(Continued)*
  mucociliary, 661
    cystic fibrosis as, 661
    primary ciliary dyskinesia as, 661
  neoplastic, 659-660
    T-cell lymphoma as, 659-660
Nasal meatuses
  normal anatomy of, 664-665
  in surgical anatomy of anterior cranial base, 2472, 2472f
"Nasal neurotic," 483-484
Nasal obstruction
  and dentofacial growth, 2628-2630, 2629f
    open mouth posture in, 2628-2629
    review of literature on, 2629-2630
  evaluation of, 483-485, 642-644
    acoustic rhinometry for, 643-645
      in allergic rhinitis, 651
      to assess effect of treatment, 651-652
      equipment for, 486-487, 486f, 644
      interpretation of results of, 645
      intranasal dimensions and cross-sectional area in, 643, 643f
      intranasal sites assessed by, 644
      reporting results of, 645
      rhinogram generated by, 486-487, 487f, 645
      vs. rhinomanometry, 644
      for snoring and sleep apnea, 651
      sources of variability in, 651
      technical concerns and testing pitfalls with, 645
      technique of, 644-645
    anterior rhinoscopy for, 484
    Cottle maneuver in, 484, 484f
    with deviated nasal septum, 483f, 484
    during forced inspiration, 483-484, 484f
    nasal airflow and nasal resistance in, 485-487
    nasal examination in, 642
    nasal valve angle and nasal valve area in, 485, 485f
    objective testing of nasal airway in, 642-644
      air stream through nose in, 643
      to assess effects of treatment, 651-652
      for challenge testing in allergic rhinitis, 651
      in clinical evaluation, 652-656
      complementary information in, 656
      correlation between results and symptoms with, 654
      criteria for, 642
      history of, 642
      in identifying site of pathology affecting airflow, 655-656
      intranasal dimensions and cross-sectional area in, 643, 643f
      laser Doppler velocimetry for, 643-644
      for normal nasal airway, 651-653, 652t-653t, 654f
      other methods of, 643-644
      role of, 651-652
      for snoring and sleep apnea, 651
      sources of variability in, 651
      and threshold level at which patient feels airway restriction, 655
      when results do not match physical findings or symptoms, 653-654
      when symptoms are not due to airway restriction, 653
    patient history in, 642
    rhinomanometry for, 643-651
      vs. acoustic rhinometry, 644
      active *vs.* passive, 647-648
      in allergic rhinitis, 651
      anterior *vs.* posterior, 645-647, 648f-649f
      to assess effect of treatment, 651-652
      for children, 645
Nasal obstruction *(Continued)*
      defined, 642
      equipment for, 645
      examining pressure-flow curve in, 648-649, 649f-650f
      inspiratory or expiratory values in, 650-651
      intranasal sites assessed by, 644
      maximum (vertex) resistance in, 650
      measurement of nasal airflow in, 647
      measurement of transnasal pressure in, 645-647, 648f
      nasal airflow and transnasal pressure in, 643
      nasal resistance in, 649-650, 650f
      parameters in, 649-651, 650f
      reporting results of, 648-651
      sources of variability in, 651
      technical concerns and testing pitfalls with, 645-648
      technique of, 645, 645f-648f
      unilateral *vs.* bilateral measurements in, 648, 649f
    with tip ptosis, 484, 485f
  due to external valve collapse, 493
  after facial paralysis, 2430-2431
  due to internal valve compromise, 492, 493f
  measurement of, 486-487, 486f-487f
  olfactory dysfunction due to, 633, 634f-635f
  paradoxic, 484, 486
  septal
    evaluation of, 483f, 484
    vs. turbinate, 486
  sites of sensation of, 641-642
  symptoms of, with open airway, 653
Nasal Obstruction Symptom Evaluation (NOSE), 57
Nasal ocular reflex, in allergic rhinitis, 614-615
Nasal packing, for epistaxis, 688, 688f
Nasal passageways, in olfactory stimulation, 624-625, 625f
Nasal peak inspiratory flowmeter, 643
Nasal pits, 482, 2660, 2661f, 2691f
Nasal placodes, 482, 2659-2660, 2661f, 2691f
Nasal polyp(s)
  endoscopic sinus surgery for, 751-752
  olfactory dysfunction due to, 625, 634f
  surgical management of, 741
Nasal polyposis
  in aspirin-exacerbated respiratory disease, 732f
  with methicillin-resistant *Staphylococcus aureus* infection, 733f
  surgical management of, 741
Nasal pressure-flow curves
  normal range for, 652, 654f
  in rhinomanometry, 648-649, 649f-650f
Nasal projection, in aesthetic analysis, 273-274, 277f
Nasal prosthesis, 1345, 1345t, 1346f
Nasal provocation testing
  in nonallergic rhinitis, 695-696
  objective measurement methods in, 651
Nasal reconstruction, 364-372. *See also* Nasal defects.
  of external covering layer, 364-367
    aesthetic units in, 364
    full-thickness skin grafts for, 365
    healing by secondary intention in, 365
    local flaps in, 365-366, 365f
      advantages of, 365-366
      bilobed, 365-366, 365f
      complications of, 366
      dorsonasal (Rieger), 365-366
      forehead, 366-367, 368f
      glabellar, 365-366
      melolabial, 366, 367f
      retroauricular, 365-366
      transposition, 365-366, 366f

Nasal reconstruction *(Continued)*
primary closure in, 365, 365f
skin texture and thickness in, 364-365
of framework, 367-371
grafting material for
alloplastic, 368
autogenous cartilage as, 368-369, 369f-370f
bone as, 369, 370f
homograft tissues as, 368
selection of, 367-368
of internal lining, 371-372, 371f-372f
Nasal reflex arc, 695
Nasal resistance, 485-487
in normal individuals *vs.* those with nasal obstruction, 653, 654f
in rhinomanometry, 649-650, 650f
total normal, 652, 653t
unilateral normal mean and median, 652, 652t
Nasal rotation, in aesthetic analysis, 273-274, 277f
Nasal saline lavage, for rhinosinusitis, 734t, 736
Nasal septal mucosal flap, 2478, 2479f
Nasal septum, 481-495
anatomy and embryology of, 482-483, 482f, 497, 1359f
blood supply and innervation of, 483, 483f
caudal
repositioning of, 547, 547f
in septoplasty, 491-492, 491f-492f
overaggressive resection of, 492, 492f
shortening of, 547-548, 547f-548f
deviated, 483f, 484
endoscopic sinus surgery with, 751
imaging of, 668, 669f
in noncaucasian patient, 573, 576f
rhinitis due to, 619b
rhinoplasty with, 513-514, 514f, 546, 546f-547f
due to trauma, 482, 484
with twisted nose, 551-552, 552f
examination of, 483-485
fracture of, 498, 501, 501f
closed reduction of, 503, 503f
open reduction of, 505-506
functions of, 482
growth centers of, 2627, 2627f
and nasal breathing function, 641
perforation of, epistaxis due to, 686f
pyogenic granuloma on, 685f
radiographic anatomy of, 1398f
surgery on (*See* Septoplasty)
in surgical anatomy of anterior cranial base, 2471-2472, 2472f
tension, 492, 493f
variations in, 482, 482f
Nasal sidewalls, surface defects of, 348
hinge flap for, 348, 350f
paramedian forehead flaps for, 348
Nasal skeletal reconstruction, 367-371
grafting material for
alloplastic, 368
autogenous cartilage as, 368-369, 369f-370f
bone as, 369, 370f
homograft tissues as, 368
selection of, 367-368
Nasal skin, texture and thickness of, 364-365
Nasal splints, after septoplasty, 494
Nasal stenosis, in cleft-lip nose repair, 559, 566f
Nasal surgery, for obstructive sleep apnea, 258, 258b
Nasal tip
anatomy of, 509f
asymmetrical, in newborn, 2709-2711
overrotation of, revision rhinoplasty for, 590, 590f-591f
persistently wide or bulbous, revision rhinoplasty for, 589-590, 590f
pinched, revision rhinoplasty for, 590, 591f-592f
Nasal tip *(Continued)*
ptosis of, 484, 485f
caudal extension graft for, 576, 576f
due to overaggressive resection of caudal septum, 492, 492f
revision rhinoplasty for, 590-593, 593f
after rhinoplasty, 519, 520f
Nasal tip bossae, revision rhinoplasty for, 588-589, 590f
Nasal tip defects
full-thickness central, 348
composite turnout flap for, 348, 351f
paramedian forehead flaps for, 348-350, 352f-354f
surface, 348
hinge flap for, 348, 350f
paramedian forehead flaps for, 348
primary closure of, 365, 365f
Nasal tip deformities, revision rhinoplasty for, 588
irregularities and bossae as, 588-589, 590f
overrotation (short nose) as, 590, 590f-591f
persistently wide or bulbous tip as, 589-590, 590f
pinched tip as, 590, 591f-592f
ptotic tip as, 590-593, 593f
Nasal tip projection, 520, 535-536, 549-551
autogenous cartilage struts for, 535-536, 536f
cephalic rotation for, 519, 536, 549-550, 551f
onlay tip cartilage grafts for, 535-536, 537f, 549-550, 550f-551f
partial-transfixion *vs.* complete-transfixion incisions for, 535-536, 536f
plumping grafts for, 535-536, 536f
transdomal sutures for, 536
Nasal tip protrusion, 2617t
Nasal tip refinement, 519-536
considerations in, 520, 522f
delivery approaches for, 522, 527f
complete strip technique in, 522, 527f-530f
interrupted strip technique in, 522, 532f-533f
suturing in, 522, 530f-531f, 550-551
incisions, approaches, and techniques for, 520, 521f, 521t
in noncaucasian patients, 573-577
cap graft in, 576, 577f
caudal extension graft in, 576, 576f
concept of, 573-576
reshaping of lower lateral cartilage in, 577
shield graft in, 576, 577f
technique for, 576-577
thinning of subcutaneous tissue in, 577, 577f
nondelivery (cartilage-splitting, retrograde-eversion) approaches for, 522, 523f-526f
objective of, 519
open approach for, 522-535, 534f-535f
indications for, 521b
preservation of lateral crus and strip of alar cartilage in, 520-522, 522f
tip projection in, 520, 535-536, 549-551
autogenous cartilage struts for, 535-536, 536f
cephalic rotation for, 519, 536, 549-550, 551f
onlay tip cartilage grafts for, 535-536, 537f, 549-550, 550f-551f
partial-transfixion *vs.* complete-transfixion incisions for, 535-536, 536f
plumping grafts for, 535-536, 536f
transdomal sutures for, 536
tip ptosis after, 519, 520f
tip support mechanisms and, 519, 520f
Nasal tip support mechanisms, 519, 520f
Nasal trumpet, for awake fiberoptic nasotracheal intubation, 124, 125f
Nasal turbinates
anatomy and embryology of, 482-483
hypertrophy of, 486
and nasal breathing function, 641
in surgical anatomy of anterior cranial base, 2472, 2472f
Nasal valve
defined, 641
external, collapse of, 493
internal, compromise of, 492, 493f
and nasal breathing function, 641, 641f
vs. nasal valve area, 641
septoplasty with correction of, 493
Nasal valve angle, 485, 485f
Nasal valve area, 485, 485f
defined, 641
description of, 641, 641f
Nasalance, in acoustic analysis, for voice evaluation, 829t, 830
Nasalide (flunisolide)
for nonallergic rhinitis, 700t
for rhinosinusitis, 734t, 736
Nasarel (flunisolide)
for nonallergic rhinitis, 700t
for rhinosinusitis, 734t, 736
Nascher, I. L., 230
Nasion, 320f, 509f
growth and development of, 2617t
Nasoalveolar cysts, of oral cavity, 1288, 1288f
Nasobuccal membrane, 482
congenital malformations of nose due to developmental errors of, 2693-2695
Nasoethmoid complex (NEC) fractures, 322
classification of, 326-327, 327f
physical examination of, 324, 324f
repair of, 336-337, 337f
Nasoethmoidal encephalocele, 2687-2688, 2687t
Nasofacial angle, in aesthetic analysis, 272-274, 276f
Nasofacial relationships, in aesthetic analysis, 272-274
nasofacial angle in, 272-274, 276f
nasofrontal angle in, 270, 272-273, 274f
nasolabial angle in, 272-273, 276f
nasomental angle in, 272-273, 276f
Nasofrontal angle
in aesthetic analysis, 270, 272-273, 274f
in rhinoplasty, 514
Nasofrontal angle modifications, rhinoplasty for, 548-549, 550f
Nasofrontal encephalocele, 2687-2688, 2687t
Nasofrontal suture, 497f
Nasogastric tube, for caustic ingestion, 2960
Nasolabial angle
in aesthetic analysis, 272-273, 276f
anatomy of, 509f
in rhinoplasty, 514
with tip ptosis, 485f
Nasolacrimal duct cysts, 2693, 2694f
Nasolacrimal duct injury, in functional endoscopic sinus surgery, 679
Nasolacrimal groove
in embryology of lip, 2661f-2662f
in embryology of nose, 2691f
Nasolaryngoscopy, flexible fiberoptic, for recurrent respiratory papillomatosis, 2888
Nasomaxillary complex, growth and development of, 2619-2620, 2621f-2622f
sinuses in, 2619-2620, 2623f
Nasomental angle, in aesthetic analysis, 272-273, 276f
Nasometry, for velopharyngeal dysfunction, 2679, 2679f
Nasonex (mometasone furoate nasal spray)
for nonallergic rhinitis, 700t
for rhinosinusitis, 734t, 736
Naso-orbital encephalocele, 2687-2688, 2687t
Naso-orbitoethmoid (NOE) fractures, 322
classification of, 326-327, 327f
pediatric, 2714, 2716f

Naso-orbitoethmoid (NOE) fractures *(Continued)*
pediatric, 2714
classification of, 2714, 2716f
evaluation of, 2714, 2716f
repair of, 2714, 2716f
physical examination of, 324, 324f
repair of, 336-337, 337f
pediatric, 2714, 2716f
Nasopalatine nerve, 483f, 1297f
Nasopharyngeal biopsy, 1353
Nasopharyngeal carcinoma (NPC), 1351-1357, 1699-1700
audiogram and tympanogram for, 1354
cervical lymph node metastasis of, 1352-1353, 1353f
incidence and distribution of, 1687f
radiation therapy for, 1690, 1690t
in children, 2820
classification of, 1353-1354, 1354t
clinical presentation of, 1352-1353, 1353f
endoscopic appearance in, 1353, 1354f
nodal metastases in, 1352-1353, 1353f
diagnosis of, 1353-1354
epidemiology of, 1350-1351, 1699
Epstein-Barr virus and, 1352, 1354
etiology of, 1352
environmental factors in, 1352
Epstein-Barr virus in, 1352, 1354
genetic factors in, 1352
imaging of, 148, 149f, 1412-1413, 1413f
for staging, 1354
vs. myofascial pain dysfunction syndrome, 1284t
prognosis for, 1356-1357
recurrences of
local, 1355
regional, 1356, 1357f
staging of, 1354
imaging in, 1354
treatment of, 1354-1355
approach to, 1354-1355, 1699
chemoradiation for, 1355
pretreatment planning for, 1354
radiation therapy for, 1354-1355
intensity-modulated, 1045, 1699-1700, 1699f, 1700t
surgical, 1355
endoscopic approach for, 1355, 1355f
lateral rhinotomy and medial maxillectomy approach for, 1355-1356, 1356f
for local recurrences, 1355
maxillary swing for, 1356, 1356f
other approaches to, 1356
of regional recurrences, 1356, 1357f
VEGF in, 1700
Nasopharyngeal lymphoma, 149f
Nasopharyngeal stenosis, after adenotonsillectomy, 2800-2801, 2801f
Nasopharyngeal teratomas, 2695, 2696f
Nasopharyngeal tumor(s), 1348-1357
adenoid cystic carcinoma as, 1351
angiofibroma as, 152, 154f, 1349-1351
clinical features of, 1349
diagnosis of, 1349-1350, 1350f
growth patterns of, 1349
management of, 1350-1351
pathologic features of, 1349
recurrence of, 1351
staging of, 1350, 1350t
chordoma as, 1351
classification of, 1349t
craniopharyngioma as, 1349
diagnostic approach for, 1348-1349
lateral skull base approach for, 2510-2511
nasopharyngeal carcinoma as (*See* Nasopharyngeal carcinoma (NPC))
and otitis media, 1873, 1873f
squamous papilloma as, 1349
Tornwaldt cyst/bursa as, 1348-1349
Nasopharyngoscopy
in children, 2574
fiberoptic, 101
of obstructive sleep apnea, 253, 254f
Nasopharynx
anatomy of, 1359f
radiographic, 1398f-1399f
dysphagia due to congenital anomalies of, 2949, 2950t, 2951f
physical examination of, 100-101
in surgical anatomy of anterior skull base, 2474
Nasoseptal surgery, effects on craniofacial growth and development of, 2627-2628
Nasoseptal trauma, abnormal facial growth and development due to, 2626-2628
animal studies on, 2626-2627
human studies on, 2627-2628, 2627f
surgical timing and approach and, 2628
Nasotracheal intubation
awake fiberoptic, 122-123
advantages of, 123
avoiding failure in, 125, 126b
bronchoscopy cart for, 123, 123f
conscious sedation for, 124
fiberoptic bronchoscope in, 123-125, 125f
historical perspective on, 122-123
indications for, 123, 123b
keys to successful, 124b
monitoring during, 124
nasal trumpet placement for, 124, 125f
optimal setup for, 125f
patient preparation for, 123-124
technique of, 124-125
topical anesthesia for, 124
for stridor, 2904
National Business Group on Health (NBGH), 84t-87t, 87
National Committee for Quality Assurance (NCQA), 82, 84t-87t
National Emergency X-Radiography Utilization Study (NEXUS) criteria, for laryngeal trauma, 935-936, 935b
National Guidelines Clearinghouse (NGC), 84t-87t
National Quality Forum (NQF), 84t-87t, 87
National Quality Measures Clearinghouse (NQMC), 84t-87t
National Surgical Quality Improvement Program (NSQIP), 84t-87t
Natural history, *vs.* efficacy of treatment, 62t
Natural killer (NK) cells, in adaptive immune system, 603-604
Nausea, postoperative, in children, 2593
Nbc3, in murine deafness, 2058t-2060t
NBGH (National Business Group on Health), 84t-87t, 87
NBI (narrow-band imaging), of larynx, 813, 823-824, 823f-824f
N-butyl-2-cyanoacrylate (NBCA), for embolization, 1933
NCQA (National Committee for Quality Assurance), 82, 84t-87t
ND (Norrie disease) gene, in deafness, 2051t-2058t
Nd:YAG (neodymium:yttrium-aluminum-garnet) laser, 31t, 32
for facial resurfacing, 403t
Near-total laryngectomy (NTL), 1564
for advanced glottic cancer, 1497
Near-total thyroidectomy, for Graves' disease, 1743
NEC fractures. *See* Nasoethmoid complex (NEC) fractures.
Neck
aesthetic analysis of, 275, 279f
anatomy of, 2577-2586
anterior triangle of, 2578f, 2579-2581
ansa cervicalis in, 2580f, 2581
carotid triangle in, 2578f, 2579-2580, 2580f
Neck *(Continued)*
conventional radiography of, 131
embryology of, 2583-2585, 2583f
branchial arches in, 2583-2584, 2583f
craniofacial syndromes related to, 2585
innervation of, 2584
muscular derivatives of, 2584
skeletal derivatives of, 2583-2584, 2583f
pharyngeal pouch(es) in, 2583-2585, 2583f-2584f
first, 2584, 2584f-2585f
fourth through sixth, 2584f-2585f, 2585
second, 2584, 2584f-2585f
third, 2584f-2585f, 2585
lymphatic system of, 1683, 1683f, 2582-2583
classification of cervical lymphatics in, 2582-2583
deep cervical lymph nodes in, 2582
for pharynx and larynx, 2582
superficial lymph nodes in, 2582
midline lesions of, 2586
physical examination of, 95, 96f
adenopathy in, 95-96
lymph node regions in, 96-97, 96f
thyroid gland in, 95
triangles of, 96-97, 96f
posterior triangle of, 2577-2579, 2578f-2579f
accessory nerve in, 2578-2579, 2580f
arterial branches in, 2579
cutaneous branches of cervical plexus in, 2578, 2580f
fascia in, 2577
deep, 2577-2578, 2578f-2579f
superficial, 2577
postoperative changes in, 173-174, 175f
postradiation changes in, 1476-1479
radiation changes in, 173-174, 176f
root of, 2581-2582, 2581f
subcutaneous emphysema of, 1410, 1410f
Neck abscess, 1407, 1407f
Neck control
with N0 status, 1688, 1690, 1692, 1692t
with N1-N3 status, 1692-1695
postoperative irradiation or chemo-irradiation for, 1693-1694, 1694t
after primary radiotherapy, 1692-1693, 1693t
Neck dissection, 1702-1725
algorithm for, 1724, 1724f
anterior, 1703
central compartment, 1719
defined, 1719, 1719f
technique for, 1719, 1720f
for cancer of midline structures of anterior lower neck, 1719
definition and rationale for, 1719, 1719f
technique for, 1719, 1720f
for cervical esophageal cancer, 1434-1439
cervical lymph node groups in, 1703-1705
levels of, 1703-1705, 1704f, 1706t
radiologic anatomic markers for, 1705, 1707t-1708t
sublevels of, 1704-1705, 1705f, 1706t
after chemoradiation, 1724
classification of, 1705-1721
complication(s) of, 1722-1724
air leaks as, 1722-1723
bleeding as, 1723
blindness as, 1723
carotid artery rupture as, 1723-1724
chylous fistula as, 1723
facial/cerebral edema as, 1723
for cutaneous malignancies, 1718-1719
definition and rationale for, 1718, 1718f
technique for, 1718-1719
defined, 1702
elective, 1702
extended, 1703t, 1719-1721, 1720f

Neck dissection *(Continued)*
historical perspective on, 1702-1703
for hypopharyngeal cancer, 1434-1439, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
for laryngeal cancer, 1716-1718
definition and rationale for, 1716-1717, 1717f
glottic, 1497-1498
after nonsurgical organ preservation treatment, 1502-1503
supraglottic, 1500-1501
technique for, 1717-1718, 1717f
with trasoral laser microsurgery, 1532
lateral, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
lymphoscintigraphy-directed, 1721-1722
with N0 status, 1692
for nasopharyngeal carcinoma, 1356
for oral cavity cancer, 1312-1314, 1313f, 1713-1716
definition and rationale for, 1713, 1714f
technique for, 1713-1716, 1715f-1716f
for oropharyngeal cancer, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
posterolateral, 1718-1719
after radiation therapy, 1694, 1721
radical, 1705-1709
anterior triangle dissection in, 1709-1710
defined, 1703t, 1705, 1709f
dissection of upper neck compartments in, 1710-1711
flap elevation in, 1709, 1711f
historical perspective on, 1702-1703
incision planning for, 1709, 1710f
indications for, 1705
modified, 1711-1712
definition of, 1703t, 1711, 1712f
historical perspective on, 1703
indications for, 1711
results of, 1721
technique for, 1711-1712, 1713f-1714f
nodular masses at site of, 1476
for oral cancer, 1313
positioning for, 1709
posterior triangle dissection in, 1709
results of, 1721
results of, 1721-1722
for salivary gland tumors, 1196-1197
selective, 1712-1713
for cancer of midline structures of anterior lower neck, 1719
definition and rationale for, 1719, 1719f
technique for, 1719, 1720f
for cutaneous malignancies, 1718-1719
definition and rationale for, 1718, 1718f
technique for, 1718-1719
definition of, 1703t, 1712
historical perspective on, 1703
for oral cavity cancer, 1313, 1713-1716
definition and rationale for, 1713, 1714f
technique for, 1713-1716, 1715f-1716f
for oropharyngeal, hypopharyngeal, and laryngeal cancer, 1716-1718
definition and rationale for, 1716-1717, 1717f
technique for, 1717-1718, 1717f
rationale for, 1712-1713
results of, 1721
for thyroid cancer, 1719, 1719f-1720f
sequelae of, 1722
supraomohyoid, 1313-1314, 1703
for oral cancer, 1313-1314, 1713
definition and rationale for, 1713, 1714f
technique for, 1713-1716, 1715f-1716f
Neck dissection *(Continued)*
terminology of, 1703, 1703t
therapeutic, 1702
Neck injury. *See* Neck trauma.
Neck irradiation
indications for neck node dissection after, 1694
late complications after, 1694-1695
with N0 status, 1688, 1690, 1692, 1692t
with N1-N3 status, 1692-1695
neck control after, 1692-1693, 1693t
postoperative, 1693-1694, 1694t
of retropharyngeal nodes, 1688
for salivary gland neoplasms, 1198
target volumes for, 1688-1690
delineation of, 1690-1691, 1691f
for hypopharyngeal tumors, 1689t
for laryngeal tumors, 1690t
for nasopharyngeal tumors, 1690, 1690t
for oral cavity tumors, 1689t
for oropharyngeal tumors, 1689t
techniques for, 1691, 1692f
Neck lump, in nasopharyngeal carcinoma, 1352-1353, 1353f
Neck management, for laryngeal and hypopharyngeal cancer, 1580
Neck mass(es)
in children, 2812-2821
acquired, 2817-2819
bacterial lymphadenopathy as, 2818, 2818f-2819f
benign neoplasms as, 2819
drug-induced lymphadenopathy as, 2819
due to fungal infections, 2818-2819
in Kawasaki disease, 2819
malignant neoplasms as, 2819-2820, 2820f
in sarcoidosis, 2819
sialadenitis as, 2819
in sinus histiocytosis, 2819
viral lymphadenopathy as, 2817-2818
algorithm for differential diagnosis of, 2813f
biopsy of, 2814
congenital, 2814-2817
branchial cleft cysts as, 2814, 2814f-2815f
dermoid cysts as, 2816, 2816f-2817f
hemangiomas as, 2816, 2816f
laryngoceles as, 2816-2817
lymphatic malformations (lymphangiomas) as, 2815, 2817f
sternocleidomastoid tumors of infancy as, 2817, 2817f
teratomas as, 2816, 2816f
thymic cysts as, 2817
thyroglossal duct cysts as, 2814-2815, 2815f
vascular malformations as, 2817
history of, 2812
imaging of, 2813-2814
laboratory studies for, 2814
physical examination of, 2812-2813
congenital, 1638-1640, 2814-2817
branchial cleft anomalies as, 1639, 2814, 2814f-2815f
dermoid cysts as, 1639, 2816, 2816f-2817f
hemangiomas as, 1640, 2816, 2816f
laryngoceles as, 2816-2817
lymphangiomas as, 1640, 2815, 2815f
sternocleidomastoid tumors of infancy as, 2817, 2817f
teratomas as, 1639-1640, 2816, 2816f
thymic cysts as, 2817
thyroglossal duct cysts as, 1639, 2814-2815, 2815f
vascular malformations as, 2817
diagnostic imaging of, 1636-1637, 1637t
epidemiology of, 1636, 1637f
history and physical examination for, 1636, 1637f
Neck mass(es) *(Continued)*
inflammatory, 1638
due to granulomatous diseases, 1638
due to lymphadenopathy/lymphadenitis, 1638
due to sialadenitis/sialolithiasis, 1638
due to paranasal sinus tumor, 1123
due to primary neoplasms, 1640-1641
lipomas as, 1641
lymphoma as, 1640
neurogenic, 1640-1641
paragangliomas as, 1641
of salivary glands, 1640
thyroid, 1640
unknown
differential diagnosis of, 1638-1640
initial workup of, 1637-1638, 1638f
unknown primary squamous cell carcinoma as, 1641-1642, 1641t
Neck muscles, effects of radiotherapy on, 2626t
Neck neoplasm(s), 1656-1672
benign, 1657-1664
in children, 2819
lipomas as, 2819
neurofibromas as, 2819
pleomorphic adenomas as, 2819
thyroid adenomas as, 2819
lipomas as, 1663
in children, 2819
neurofibromas as, 1663, 1664f
in children, 2819
of parapharyngeal space, 1663-1664, 1665f
of peripheral nerves, 1663
neurofibromas as, 1663, 1664f
schwannomas as, 1663, 1663f
pleomorphic adenomas as, 2819
thyroid adenomas as, 2819
vascular, 1657
arteriovenous malformations as, 1662-1663
carotid paragangliomas as, 1657-1658, 1658f, 1659t
epidemiology of, 1657-1659
jugular paragangliomas as, 1662f
nomenclature for, 1657
pathology of, 1657, 1658f
vagal paragangliomas as, 1661-1662
in children
benign, 2819
lipomas as, 2819
neurofibromas as, 2819
pleomorphic adenomas as, 2819
thyroid adenomas as, 2819
malignant, 2819-2820
lymphomas as, 2819-2820, 2820f
nasopharyngeal carcinoma as, 2820
neuroblastomas as, 2820, 2844-2845, 2844t, 2845f
rhabdomyosarcomas as, 2820
of salivary gland, 2820, 2845-2846, 2846f
thyroid carcinoma as, 2820
diagnostic evaluation of, 1656
malignant, 1664-1671
carcinoma arising within thyroglossal duct cyst as, 1671
in children, 2819-2820
lymphomas as, 2819-2820, 2820f
nasopharyngeal carcinoma as, 2820
neuroblastomas as, 2820, 2844-2845, 2844t, 2845f
rhabdomyosarcomas as, 2820
of salivary gland, 2820, 2845-2846, 2846f
thyroid carcinoma as, 2820
lymphoma as, 1671
in children, 2819-2820, 2820f
melanoma as, 1671
metastatic, 1664

Neck neoplasm(s) *(Continued)*
from distant tumor, 1664-1666
from regional tumor, 1664
from unknown primary, 1664, 1665f
nasopharyngeal carcinoma as, in children, 2820
neuroblastomas as, in children, 2820, 2844-2845, 2844t, 2845f
of parapharyngeal space, 1666
primary, 1664-1666
of salivary gland, in children, 2820, 2845-2846, 2846f
sarcomas as, 1666
alveolar soft part, 1668
angio-, 1668
bone, 1666, 1667t
chondro-, 1669-1670
classification and staging of, 1666, 1666t-1667t
epithelioid hemangioendothelioma as, 1668-1669
Ewing's, 1671
fibro-, 1668
hemangiopericytoma as, 1670
leiomyo-, 1670
lipo-, 1670
malignant fibrous histiocytoma as, 1667
malignant giant cell tumor as, 1671
malignant peripheral nerve sheath tumor as, 1670-1671
osteo-, 1668
rhabdomyo-, 1667-1668, 1668f, 1669t, 2820
soft tissue, 1666, 1666t
synovial, 1670
solitary fibrous tumor as, 1671
squamous cell carcinoma arising in branchial cleft cyst as, 1671
thyroid carcinoma as, in children, 2820
radiologic studies of, 1656-1657
Neck node metastasis. *See* Cervical lymph node metastasis(es).
Neck spaces, 202-203
anterior visceral, 203
carotid, 203
danger, 202-203
masticator, 203
parapharyngeal, 202
parotid, 203
peritonsillar, 203
prevertebral, 203
retropharyngeal, 202
submandibular and sublingual, 202
Neck surgery, complication(s) of, 1726-1734
chyle/chest, 1732-1733
chylothorax as, 1733
chylous fistula as, 1732-1733, 1732f
pneumothorax as, 1733
nerve, 1729-1732
cervical sensory, 1731-1732
facial, 1729-1730
greater auricular, 1731
hypoglossal, 1730-1731
lingual, 1731
motor, 1729-1731
phrenic, 1731, 1731f
sensory, 1731-1732
spinal accessory, 1730, 1731f
sympathetic, 1732, 1732f
vagus, 1730
vascular, 1728-1729
carotid artery hemorrhage as, 1728
hematoma as, 1729
of internal jugular vein, 1728-1729, 1729f
wound, 1726-1728
incision planning and, 1726-1727
infection as, 1727
salivary fistula as, 1727-1728, 1728f
scar formation as, 1728, 1729f
Neck surgery, complication(s) of *(Continued)*
seroma as, 1727, 1727f
wound dehiscence and flap necrosis as, 1727
Neck trauma, 1625-1635
blunt, 1634-1635
penetrating
airway management for, 1629
algorithmic approach to, 1631f
angiography for, 1630-1632, 1631t, 1632f-1633f
barium swallow for, 1631t, 1633
classification of, 1628-1629, 1630f
cranial nerve injury due to, 1629
diagnostic evaluation of, 1630
digestive tract evaluation for, 1633-1634, 1634f-1635f
direct laryngoscopy and bronchoscopy for, 1631t, 1634
esophagoscopy for, 1631t, 1633-1634, 1634f
imaging of, 1629-1630
initial management of, 1629
management of laryngotracheal injury due to, 1634
mandatory *vs.* selective exploration of, 1627-1630, 1629t, 1630f, 1631t
mortality from, 1627-1628, 1629t
physical properties of objects causing, 1625-1627
due to handgun, 1625
due to knife and stab injuries, 1627
due to rifle, 1626, 1626f-1627f
due to shotguns, 1626-1627, 1628t
signs and symptoms of, 1626b
vascular injury due to
imaging of, 1630-1632, 1631t, 1632f-1633f
management of, 1632-1633, 1633f-1634f
Necrotizing fasciitis, due to deep neck space infections, 208
Necrotizing otitis externa. *See* Malignant otitis externa (MOE).
Necrotizing sialometaplasia
in children, 2857
of hard palate, 1309-1310
of larynx, 1493
of oral cavity, 1289, 1299
Needle aspiration, for deep neck space infections, 206, 206f
Needle biopsy, in children, 2574
Negative plasticity, 1881
Negatron, 1031-1032
Neisseria gonorrhoeae
oral manifestations of, 1252
pharyngitis due to, 193-194, 194f
in children, 2786
Neoadjuvant chemotherapy, for laryngeal carcinoma, 1501-1503, 1502f
Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, 31t, 32
for facial resurfacing, 403t
Neonatal familial hyperparathyroidism, 1797
Neonatal sialadenitis, 2857
Neonatal suppurative parotitis (NSP), 1153
Neonate(s). *See* Newborn(s).
Neopharynx, postlaryngectomy, 1415f, 1416
Neoplastic disease
nasal manifestations of, 659-660
in T-cell lymphoma, 659-660
olfactory loss due to, 636
otologic manifestations of, 2106-2108
in leukemia, 2107, 2108f
metastatic, 2107-2108, 2108f
in multiple myeloma, 2106-2107, 2107f
otorrhea as, 2196-2197
sensorineural hearing loss due to, 2124-2125, 2125f
sudden, 2128
Neoplastic rhinitis, 619b
Neovascularization
in acutely raised skin flaps, 1069, 1069f
and skin flap viability, 1073
Nerve blocks
for neuropathic pain, 245-246, 246t
for postoperative pain control, 241-242
Nerve complication(s), of neck surgery, 1729-1732
motor, 1729-1731
facial, 1729-1730
hypoglossal, 1730-1731
phrenic, 1731, 1731f
spinal accessory, 1730, 1731f
vagus, 1730
sensory, 1731-1732
cervical, 1731-1732
greater auricular, 1731
lingual, 1731
sympathetic, 1732, 1732f
Nerve conduction velocity, in Bell's palsy, 2394
Nerve excitability test (NET)
for Bell's palsy, 2394
for facial nerve injury, 2040-2041, 2385, 2387t
Nerve growth factor (NGF)
for facial nerve paralysis, 2427
for prevention of ototoxicity, 2189-2190
in submandibular gland, 1140
Nerve injury, due to rhytidectomy, 422-425, 426f
Nerve regeneration, 919-924
Nerve section, in acutely raised skin flaps, 1069-1070
Nerve sheath neoplasms, of facial nerve, 2414
Nerve transection, complete, 2384-2385
Nervus intermedius (of Wrisberg), 2403-2404
intraoperative identification of, 2546, 2546f
in surgical anatomy of lateral skull base, 2437f
NET (nerve excitability test)
for Bell's palsy, 2394
for facial nerve injury, 2040-2041, 2385, 2387t
Neural hearing loss, neurodiagnostic studies with, 1899-1901, 1900f
Neural integrator, in vestibular function, 2308
Neural origin, laryngeal neoplasms of, 882
Neural plasticity, in otology, 1876-1886
age-related, 1877, 1879, 1882f
basic mechanisms of, 1881-1884
for cortical map plasticity in adult subjects, 1883-1884
at systems physiology level, 1882-1883
for tonotopic map reorganization in developing subject, 1883
cellular level mechanisms of, 1884
Hebb's postulate for, 1884, 1884f
long-term potentiation in, 1884
definition of, 1876-1877
experiments showing, 1877-1881
on adult *vs.* developmental plasticity of sensory systems, 1879, 1882f
on animal models of deafness and effects of cochlear implant electrical stimulation, 1881
on conditions for plasticity in adult cortex, 1881
on cortical frequency map reorganization in adult subjects, 1878-1879, 1881f
developmental *vs.* adult, 1879, 1882f
historical background of, 1877
on reorganization of central tonotopic maps after cochlear lesions, 1877-1878, 1878f-1879f
on tonotopic map changes after long-term local excitation of cochlea, 1880-1881, 1883f
on tonotopic map reorganization at subcortical levels, 1879-1880
on tonotopic reorganization in a developmental model, 1878, 1880f
negative, 1881

Neural plasticity, in otology *(Continued)*
practical issues relating to, 1884-1886
for hearing loss in infants, 1885, 1885f
for other hearing disorders, 1885-1886
for tinnitus, 1886
time course of, 1877
and tinnitus treatment strategies, 2133
Neural presbycusis, 232, 2126
Neural Response Imaging (NRI), 2255
Neural Response Telemetry (NRT), 2255
Neurapraxia, 2384-2385
Neurilemmomas. *See* Schwannoma(s).
Neuroblastoma(s)
in children, 2844-2845
epidemiology of, 2844
histopathology and molecular biology of, 2845, 2845f
management of, 2844-2845
neck masses due to, 2820
presentation and evaluation of, 2844, 2844t
neck masses due to, 1640
in children, 2820
Neurocognitive development, sleep-disordered breathing and, 2791-2792
Neurocranium, 2443f
growth and development of, 2615-2619, 2617t
basicranium in, 2617-2619, 2617t, 2619f-2620f
calvaria in, 2615-2617, 2617t, 2618f
size ratio to face of, 2616f, 2617t
Neurodiagnosis
with auditory brainstem response, 1896-1899, 1898f-1899f
with auditory neuropathy or dyssynchrony, 1899-1901, 1900f
Neuroectodermal tumors, in children, 2844-2845
neuroblastomas as, 2844-2845
epidemiology of, 2844
histopathology and molecular biology of, 2845, 2845f
management of, 2844-2845
neck masses due to, 2820
presentation and evaluation of, 2844, 2844t
peripheral primitive, 2845
Neuroendocrine carcinoma, high-grade, of salivary glands, 1190-1191, 1190f
Neuroendocrine tumor of the larynx (NTL), 1507-1508
carcinoid as
atypical, 1507
typical, 1507
paraganglioma as, 1508
small cell carcinoma as, 1507-1508
Neurofibroma(s), 292
of carotid space, 150-151
in children, 2819
of infrahyoid prevertebral space, 162f
of larynx, 882
of neck, 1663, 1664f
neck masses due to, 1640
in children, 2819
of oral cavity, 1290-1291
Neurofibromatosis type 1 (NF1), acoustic neuromas in, 2515
Neurofibromatosis type 2 (NF2)
acoustic neuromas in, 2515
stereotactic radiation therapy for, 2563
central neural auditory prosthesis for (*See* Central neural auditory prosthesis)
cochlear implant for, 2220
sensorineural hearing loss in, 2094t, 2095
Neurogenic neoplasms, neck masses due to, 1640-1641
Neurologic complications, of radiotherapy, 1049
Neurologic disorders
in HIV, 223-225
of larynx, 837-843
hyperfunctional, 838-842
botulinum toxin therapy for, 839, 840f-841f
due to dystonia, 838-839, 838b
essential tremor as, 840-841
due to myoclonus, 840
due to pseudobulbar palsy, 839-840
stuttering as, 841-842
hypofunctional, 842-843
due to central causes of vocal fold paresis, 842
due to medullary disorders, 842
due to multiple sclerosis, 843
due to myopathies, 842
due to neuromuscular junction disorders, 842
due to Parkinson's disease, 842-843
due to poliomyelitis, 842
psychogenic, malingering, and mixed causes of, 843
vocal fold paresis as, 843
laryngologic manifestations of neurologic diseases as, 837-838, 838t
oral manifestations of, 1254-1255
preoperative evaluation of, 106
sensorineural hearing loss due to, 2122-2123
Neurologic dysfunction, in voice evaluation, 827
Neurologic evaluation, 101, 101t
of larynx and pharynx, 832-836
acoustic analysis in, 834-835
aerodynamic assessment in, 835
cineradiography in, 835-836
edrophonium test in, 835
electromyography in, 835, 905
flexible laryngoscopy in, 834
glottography in, 835
indications for, 832-833, 833b
normal function and, 833
performance measures in, 835-836
rating scales in, 834
sensory assessment in, 836
of mouth, larynx, and pharynx, 833-834
for pediatric facial fracture, 2699
Neurologic impairment, of upper airway, diagnosis of, 832-833, 833b
Neurologic manifestations, of hyperparathyroidism, 1781
Neurolytic blocks, for neuropathic pain, 245-246
Neuroma(s)
acoustic (*See* Acoustic neuroma(s))
amputation, due to neck surgery, 1731-1732
facial nerve (*See* Facial nerve neuroma)
neck masses due to, 1640
Neuromuscular blockers (NMBs), intraoperative, 111-112
Neuromuscular disorders
chronic aspiration due to, 926b
and obstructive sleep apnea in children, 2605-2606
Neuromuscular junction disorders, laryngeal hypofunction due to, 842
Neuromuscular pedicle (NMP)
for facial nerve paralysis, 2426-2427
for laryngeal reinnervation, 919-922
for bilateral paralysis, 920
complications of, 922
future of, 922
history of, 917
indications for, 920
laboratory investigations of, 919-920
rationale for, 919
reported results of, 920-921
technique for, 920, 921f
for unilateral paralysis, 920
Neuromuscular symptoms, of hyperparathyroidism, 1781
Neuronal control, of salivary gland secretion, 1136
neurotransmitters and receptors in, 1136-1137, 1136f, 1137t
signal transduction in, 1137-1138
adenylate cyclase system in, 1137
G proteins in, 1137
phospholipase C system in, 1137-1138
Neurontin (gabapentin)
for migraine, 2350
for neuropathic pain, 243, 244t
for tinnitus, 2137
Neuropathic pain
anticonvulsant agents for, 243-244, 244t
antidepressants for, 244-245, 245t
interventional techniques for, 245-246, 246t
palliative care for, 1103
Neuropathies, in HIV, 223-225
Neuropeptide(s), in allergic rhinitis, 615
Neuropeptide Y (NPY), in salivary gland secretion, 1137
Neuropraxia, of facial nerve, 2040
Neurotmesis, 2384-2385
of facial nerve, 2040
Neurotologic examination, for temporal bone fracture, 2038-2039
Neurotologic manifestations, of immunosuppression, 221-223
malignant otitis externa as, 221-222
in middle ear, 222-223
due to *P. jiroveci* and *A. fumigatus,* 222-223
Neurotologic surgery, cranial nerve monitoring in, 2542-2556
anesthesia and, 2544
auditory brainstem response recording for, 2552-2554
interpretation of, 2553-2554, 2553f
and postoperative auditory function, 2553-2554
reducing electrical and acoustic interference in, 2552-2553
stimulus and recording parameters, electrodes, and placement in, 2552
of cochlear nerve, 2552
direct eighth nerve action potentials for, 2554
detection and interpretation of changes in, 2554
placement of electrodes in, 2554
stimulus and recording parameters in, 2554
of facial nerve, 2545-2549
with acoustic neuroma and other cerebellopontine angle tumors, 2545
activity evoked by electrical stimulation in, 2545-2546
for assessment of functional status after tumor removal, 2545-2546
electromyography for, 2545-2548
for intraoperative identification of nervus intermedius, 2546, 2546f
limitations of, 2547-2548, 2548f
during microvascular decompression, 2548-2549, 2549f
during other otologic surgery, 2549
during parotid surgery, 2549
spontaneous and mechanically evoked activity in, 2546-2548, 2547f
future directions in, 2555-2556, 2555f
instrumentation for, 2543
ninth, tenth, eleventh, and twelfth, 2550-2552, 2551f-2552f
and outcome, 2554-2555
for cochlear nerve preservation, 2554-2555
for facial and other motor cranial nerve preservation, 2554
personnel for, 2542-2543
recording electrodes for, 2543-2544, 2543f
stimulating electrodes for, 2544, 2544f
stimulation criteria for, 2544
third, fourth, and sixth, 2549-2550, 2550f
of trigeminal motor branch, 2550

Neurotologic symptoms, migraine with, 2349
Neurotology, gene therapy in, 23
Neurotransmitters, in salivary gland secretion, 1136-1137, 1136f, 1137t
Neurotrophic factors, for facial nerve paralysis, 2427
Neurotrophic tyrosine receptor kinase type 1, in thyroid carcinoma, 1753
Neurotrophin(s) (NTs)
  in gene therapy of inner ear, 2192
  for prevention of ototoxicity, 2189-2191
Neurotrophin-3 (NT-3)
  in gene therapy of inner ear, 2192
  for prevention of ototoxicity, 2190
Neutron, fast, 1034
Neutron beam radiotherapy, for salivary gland neoplasms, 1198-1199
Neutron therapy, 1046
Neutrophil(s)
  in adaptive immune system, 604
  in wound healing, 1076
Neutrophil-activating peptide-2 (NAP-2), in wound healing, 1076
Nevocellular nevus, 286
Nevoid basal cell carcinoma syndrome, 1268
  treatment of, 1268
Nevus(i)
  araneus, 291
  blue, 286-287, 287f
  compound, 286
  congenital, 287-288
    melanocytic, and melanoma, 1107-1108
  dysplastic, 288, 288f
  flammeus, 291
  halo, 287, 287f
  intradermal, 286, 287f
  junctional, 286, 287f
  melanocytic
    congenital, and melanoma, 1107-1108
    of oral mucosa
      clinical features of, 1241
      histopathologic features of, 1242
      treatment of, 1243
  nevocellular, 286
  salmon patch, 290-291
  sebaceus of Jadassohn, 287f, 289
  Spitz, 287
Newborn(s)
  airway obstruction in
    expected, 2904-2905
    unexpected, 2905
      laryngeal, 2905
      supralaryngeal, 2905, 2905f
      tracheobronchial, 2905
  asymmetrical nasal tip deformities in, 2709-2711
  blood volume of, 2571
  control of ventilation in, 2569-2570
  gingival (dental lamina, alveolar) cyst of, 1266, 1266f
    microscopic features of, 1266
    treatment of, 1266
  hearing loss in, 2718-2725
    ancillary testing for, 2722-2723
      genetic testing in, 2722-2723
      laboratory testing in, 2722
      screening for connexin 26 mutation in, 2723
      screening for maternally transmitted infection in, 2723
      temporal bone imaging in, 2723
      testing for Pendred's syndrome in, 2723
    assessment of, 2719-2721
      auditory brainstem responses in, 2719-2720
      comparison of otoacoustic emissions and auditory brainstem responses in, 2721
      evoked otoacoustic emissions in, 2720-2721
      testing protocols for, 2719, 2720f
Newborn(s) *(Continued)*
    diagnosis of, 2721-2722
      audiology in, 2722
      history in, 2721
      middle ear effusions in, 2722
      otomicroscopy in, 2722
      physical examination in, 2721-2722
      vestibular function assessment in, 2722
      visual reinforcement audiometry in, 2722
    history of screening for, 2718-2719
    intervention strategies for, 2723-2724
      amplification devices as, 2274, 2723-2724
      bone conduction amplification as, 2723
      cochlear implantation as, 2247, 2724
      early, 2724
      surgical therapy as, 2723
  heart and cardiac output of, 2571, 2571t
  oxygen transport in, 2571-2572
  respiratory rate in, 2570
  response to hypoxia in, 2571
  subdural empyema in, 1995
  ventilation-perfusion relationships in, 2570, 2571t
NEXUS (National Emergency X-Radiography Utilization Study) criteria, for laryngeal trauma, 935-936, 935b
NF. *See* Neurofibromatosis (NF).
NGC (National Guidelines Clearinghouse), 84t-87t
NGF (nerve growth factor)
  for facial nerve paralysis, 2427
  for prevention of ototoxicity, 2189-2190
  in submandibular gland, 1140
NHL. *See* Non-Hodgkin's lymphoma (NHL).
Niacin deficiency, oral manifestations of, 1254
NICH (non-involuting congenital hemangioma), 2824, 2825f
Nicotinamide, with radiotherapy, 1041
NIDDM (non–insulin-dependent diabetes mellitus), sensorineural hearing loss in, 2094t, 2097
Nifedipine, and skin flap viability, 1073
Nightmares, 262t, 264-265
NIHL. *See* Noise-induced hearing loss (NIHL).
Nijmegen Cochlear Implant Questionnaire, 57
Nine-step inflation-deflation tympanometric test, 1874
NIS (sodium/iodide symporter), in thyroid hormone synthesis, 1737
Nissen fundoplication, for extraesophageal reflux, 901
Nitinol stent, for tracheal stenosis, 2930
Nitrates, for achalasia, 965
Nitric oxide (NO)
  and rhinosinusitis, 732
  and skin flap viability, 1074
  in wound healing, 1076-1077
Nitric oxide synthases (NOSs), in wound healing, 1076-1077
Nitrogen mustards, sensorineural hearing loss due to, 2120
Nitroglycerin, and skin flap viability, 1073
Nitrous oxide, for pediatric anesthesia, 2590
Nizoral (ketoconazole cream), for fungal otitis externa, 1954-1955, 1959t-1960t
NK (natural killer) cells, in adaptive immune system, 603-604
Nkcc1, in murine deafness, 2058t-2060t, 2083
NKCC2 protein, in deafness, 2051t-2058t
NK/T lymphoma, of nasal cavity, 1680
  therapy and prognosis for, 1680
NMBs (neuromuscular blockers), intraoperative, 111-112
N-methyl-D-aspartate (NMDA) glutamate receptors, in central sensitization, 1203
N-methyl-D-aspartate (NMDA) receptor, in neural plasticity, 1884
NMP. *See* Neuromuscular pedicle (NMP).
NMSC (nonmelanoma skin cancer), immunosuppression and, 213t, 215
NNRTs (non-nucleoside reverse transcriptase inhibitors), 211
NO (nitric oxide)
  and rhinosinusitis, 732
  and skin flap viability, 1074
  in wound healing, 1076-1077
Nocturnal oxygen supplementation, for obstructive sleep apnea in children, 2611
Nocturnal polysomnography, of obstructive sleep apnea, 255, 255b, 256f
Nocturnal Rhinoconjunctivitis Questionnaire, 57
Nodal (N) classification, for melanoma, 1111-1113, 1111t
Nodal involvement, of salivary gland tumors, 1196-1197
Nodal metastasis(es). *See* Cervical lymph node metastasis(es).
Nodes of Rouvière, 1422
Nodular melanoma, 1108
NOE fractures. *See* Naso-orbitoethmoid (NOE) fractures.
Noise, 1838-1839
  continuous or steady-state, 2140
  defined, 2121, 2140
  fluctuating, 2140
  impulsive or impact, 2121, 2140
  intermittent, 2140
  measurement of, 2140-2141
  other adverse effects caused by, 2148-2149
  presbycusis due to, 232-233
Noise dosimeter, personal, 2140-2141
Noise reduction circuitry, for hearing aids, 2269
Noise-induced hearing loss (NIHL), 2121-2122, 2140-2152
  vs. acoustic trauma, 2141, 2145-2146
  anatomic mechanisms underlying, 2143-2144
  clinical course of, 2121, 2121f-2122f
  cochlear damage in, 2141-2143, 2143f
  diagnosis of, 2199
  early detection of, 2146-2147, 2147f-2150f
  hair cell regeneration and repair and, 2144
  interactive effects in, 2147-2148
  irreversible, 2141
  legal issues with, 2149-2151
  nature of, 2121-2122, 2141
  new knowledge about cellular and molecular mechanisms of, 2144-2146
  pattern of, 2141, 2142f
  permanent threshold shift in, 2141, 2148
  prevention of, 2151
  protection from
    by conditioning of cochlear efferent system, 2144
    pharmacologic, 2144-2145
  research on, 2143
  resistance to, 2144-2145, 2146f
  role of otolaryngologist in, 2150-2151
  susceptibility to, 2145-2146, 2146f
  temporary threshold shift in, 2141, 2148
  with tinnitus, 2131-2132
  vestibular disorders in, 2148
  vibration and, 2148-2149
Nominal scales, 63, 63t
Nonadrenergic, noncholinergic secretory response, in salivary glands, 1137
Nonallergic eosinophilic fungal rhinosinusitis (NA-EFRS), 709, 715-716, 716t
Nonallergic rhinitis (NAR), 619b, 694-2
  atrophic, 696-697
  classification of, 696-699, 697b
  defined, 695
  diagnosis of, 699
    diagnostic testing for, 699
    history of, 699, 699b
    physical examination for, 699

Nonallergic rhinitis (NAR) *(Continued)*
economic impact of, 695
epidemiology of, 695
gustatory, 698
hormonal, 696
idiopathic, 619b, 695, 698
irritant, 697-698
local factors associated with, 698-699, 698b
medication-induced, 619b, 696, 697b
occupational, 698
pathophysiology of, 695-696
allergic component in, 696
nasal function and innervation in, 695
perennial, 695
during pregnancy, 696, 702
problems resulting from, 695
provocation testing in, 695-696
systemic conditions associated with, 698-699, 698b
terminology for, 695
treatment of, 699-702
anticholinergics for, 701
antihistamines for, 700-701, 701t
avoidance for, 699-700
general considerations in, 702
surgical, 701-702
topical nasal corticosteroids for, 700, 700t
vasomotor, 619b, 695, 698
Nonallergic rhinitis with eosinophilia syndrome (NARES), 619b, 696
Noncaucasian rhinoplasty, 556-557, 568-579
aesthetic considerations in, 569
alar base modification in, 577-578, 578f
alar soft tissue sculpting in, 557, 561f
anatomic considerations in, 568-569, 569f, 569t
complications of, 578, 578f-579f
for correction of deviated nose, 573, 576f
dorsal augmentation in, 556, 569-570
choice of material for, 569, 570f
concept of, 569
results of, 572f-573f
technical considerations for, 569-570, 571f
hump reduction in, 570-573
concept of, 570-571
results of, 574f-575f
technique for, 571-573, 575f
nasal base sculpting in, 556-557, 559f-560f
objective of, 568
tip surgery in, 573-577
cap graft in, 576, 577f
caudal extension graft in, 576, 576f
concept of, 573-576
reshaping of lower lateral cartilage in, 577
shield graft in, 576, 577f
technique for, 576-577
thinning of subcutaneous tissue in, 577, 577f
Nonchromaffin tumors, 1657
Nonconductive hearing loss, neurodiagnostic studies with, 1899-1901, 1900f
Nondelivery approaches, for nasal tip refinement, 522, 523f-526f
Nonerosive reflux disease, 968
Non–group A beta hemolytic streptococcal infections, pharyngitis due to, 193
Non-Hodgkin's lymphoma (NHL)
Burkitt's, 1674
in children, 2819-2820, 2837
epidemiology of, 2837
histopathology and molecular biology of, 2838, 2839f
management of, 2838
presentation and evaluation of, 2837-2838, 2838t
staging of, 2838, 2839t
clinical presentation of, 1674, 1674f
diffuse large B-cell, 1677-1678
epidemiology of, 1673
Non-Hodgkin's lymphoma (NHL) *(Continued)*
follicular, 1674, 1678
highly aggressive, 1674, 1679
imaging of, 148-149, 149f
immunosuppression and, 213t, 215-216
diagnosis of, 216
epidemiology and presentation of, 216
prognosis and treatment for, 216-217
indolent, 1674, 1678
of larynx, 1509
lymphoblastic, 1674-1675
MALT, 1674, 1679-1680
mantle cell, 1678-1679
nodal involvement by, 165-166, 167f
of oral cavity, 157f
of oropharynx, 1364, 1364f
paranasal sinus and nasal cavity, 1680
of salivary glands, 1191-1192, 1192f, 1679-1680
small lymphocytic, 1674, 1674f, 1678
staging of, 1676, 1677t
thyroid, 1679
Noninferiority studies, 73t, 74
Non–insulin-dependent diabetes mellitus (NIDDM), sensorineural hearing loss in, 2094t, 2097
Non-involuting congenital hemangioma (NICH), 2824, 2825f
Nonlinear amplification, for hearing aids, 2268, 2268f
Nonlinear distortion, with traditional hearing aid, 2204
Nonmelanoma skin cancer (NMSC), immunosuppression and, 213t, 215
Non-nucleoside reverse transcriptase inhibitors (NNRTs), 211
Nonodontogenic infection, *vs.* myofascial pain dysfunction syndrome, 1285t
Nonparametric tests, 72
Nonpenetrance, 7, 7f
Nonpolarizing muscle relaxants, for pediatric anesthesia, 2592, 2593t
Non–rapid eye movement (NREM) sleep, 261-262
Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS), 2842
Nonself, *vs.* self, in immune system, 599
Non–small cell lung cancer (NSCLC), epidermal growth factor receptor tyrosine kinase in, 1023
Nonsteroidal anti-inflammatory drugs (NSAIDs)
for postoperative pain, 241
sensorineural hearing loss due to, 2120
Nonsurgical organ preservation treatment, for laryngeal carcinoma, 1501-1503, 1502f
glottic, 1497
management of neck after, 1502-1503
recurrence after, 1503-1504
supraglottic, 1500
Nontuberculous mycobacteria (NTM), salivary gland infection with, 1158-1159, 1158f
in children, 2857-2858, 2857f
Nonunion, 331, 339-340
No-reflow phenomenon, in acutely raised skin flaps, 1070-1071
Norian CRS (carbonated apatite), for chin implants, 465t
Normal flora, of mouth, 177, 179f
Normal standard dose (NSD), in radiotherapy, 1039-1040
Norrie disease, sensorineural hearing loss in, 2094t
Norrie disease *(ND)* gene, in deafness, 2051t-2058t
Norrin, in deafness, 2051t-2058t
Nortriptyline, for neuropathic pain, 244-245, 245t
Norwood classification, of hair loss, 376, 377f
NOS(s) (nitric oxide synthases), in wound healing, 1076-1077
Nose
aesthetic analysis of, 271-272, 275f
alar-columellar complex in, 270f-271f, 274
for defect repair, 346-347, 347f, 364
nasal rotation and projection in, 273-274, 277f
nasofacial relationships in, 272-274
nasofacial angle in, 272-274, 276f
nasofrontal angle in, 270, 272-273, 274f
nasolabial angle in, 272-273, 276f
nasomental angle in, 272-273, 276f
air stream through, tests that assess, 643
anatomy of, 167-171, 322, 482-483
and nasal fractures, 496-497, 497f
surgical, 509f
vascular, 497, 682-684
anastomoses in, 682-683, 683f
anterior ethmoid artery in, 682, 684f
facial artery in, 682
greater palatine artery in, 682
internal maxillary artery in, 682
posterior ethmoidal artery in, 682-683
sphenopalatine artery in, 682
vidian artery in, 682, 683f
bridge of, 509f
burns of, 316
congenital malformations of, 2686-2696
choanal atresia as, 2694-2695
bilateral, 2694-2695, 2694f-2695f
clinical presentation of, 2694
endoscopic evaluation of, 2694, 2695f
epidemiology of, 2694
imaging of, 2694, 2694f
treatment of, 2694-2695, 2695f
unilateral, 2694-2695, 2694f
cleft lip nasal deformity as, 2690, 2692
complete agenesis of nose (arhinia) as, 2690, 2691f
congenital nasal pyriform aperture stenosis as, 2692-2693
clinical presentation of, 2692-2693
diagnosis of, 2693, 2693f
operative management of, 2693, 2693f
pathogenesis of, 2690, 2692
craniofacial clefts as, 2690, 2692
dermal fistula as, 2687f
dermoids as
clinical presentation of, 2689, 2689f
defined, 2687f, 2688-2689
epidemiology of, 2688-2689
histology of, 2689
imaging of, 2689, 2689f
management of, 2689-2690
due to developmental errors of anterior neuropore, 2686-2690, 2687f
due to developmental errors of central midface, 2690-2693, 2691f
due to developmental errors of nasobuccal membrane, 2693-2695
dysphagia due to, 2949, 2950t, 2951f
encephaloceles as, 2687-2688
basal, 2687-2688, 2687t, 2688f
classification of, 2687-2688, 2687t
defined, 2687, 2687f
epidemiology of, 2687
vs. gliomas, 2688
histopathology of, 2688
imaging of, 2688, 2688f
management of, 2688
nasoethmoidal, 2687-2688, 2687t
nasofrontal, 2687-2688, 2687t
naso-orbital, 2687-2688, 2687t
sincipital, 2687-2688, 2687f, 2687t
sphenoethmoidal, 2687t
spheno-orbital, 2687t
terminology for, 2687
transethmoidal, 2687t
transsphenoidal, 2687t

Nose *(Continued)*
gliomas as, 2687f, 2688
vs. encephaloceles, 2688
epidemiology of, 2688
extranasal, 2688
histology of, 2688
imaging of, 2688
intranasal, 2688
management of, 2688
intranasal hemangiomas as, 2695
maxillary mega-incisor with, 2690, 2691f
nasolacrimal duct cysts as, 2693, 2694f
nasopharyngeal teratomas as, 2695, 2696f
other mesodermal and germline malformations as, 2695
overview of, 2686
polyrhinia and supernumerary nostril as, 2690-2692
proboscis lateralis as, 2690, 2692, 2692f
cross-sectional area of, tests that assess, 643, 643f
double, 2690-2692
embryology of, 482-483, 496, 2660, 2690, 2691f
in geriatric patients, 234
changes in appearance of, 234
common symptoms of disorders of, 234
intranasal examination of, 234
mucoepithelial changes of, 234
olfactory changes of, 234
treatment of disorders of, 234
imaging of, 167-171
for facial trauma, 170-171, 170f-171f
nasal cavity in, 169, 170f
ostiomeatal complex in, 168f-169f, 169
paranasal sinuses in, 167-169, 168f-169f
keystone area of, 496, 497f
physical examination of, 100
physiology of, 322, 485-487
prosthetic, 1345, 1345t, 1346f
root of, 509f
sensory innervation of, 497, 497f
trauma to, 310-312, 311f
twisted
rhinoplasty for, 551-554
in noncaucasian patient, 573, 576f
osteotomies in, 551-554, 552f-554f
preoperative examination of, 551, 552f
results of, 511f-512f, 553f-554f
septal reconstruction in, 551
spreader grafts in, 554, 555f
varieties of, 552f
NOSE (Nasal Obstruction Symptom Evaluation), 57
Nostril
supernumerary (accessory), 2690-2692
in surgical anatomy of anterior cranial base, 2472f
Nostril sill excision, 577-578, 578f
Notch of Rivinus, 1826-1827
Nothing-by-mouth orders, for pediatric anesthesia, 2589, 2590t
NOX-3, in cisplatin ototoxicity, 2172
NPC. *See* Nasopharyngeal carcinoma (NPC).
NPY (neuropeptide Y), in salivary gland secretion, 1137
NQF (National Quality Forum), 84t-87t, 87
NQMC (National Quality Measures Clearinghouse), 84t-87t
NR3B2, in deafness, 2051t-2058t
NREM (non–rapid eye movement) sleep, 261-262
NRI (Neural Response Imaging), 2255
NRS (Numeric Rating Scale), 240
NRSTS (nonrhabdomyosarcoma soft tissue sarcoma), 2842
NRT (Neural Response Telemetry), 2255
NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors), 211
NSAIDs (nonsteroidal anti-inflammatory drugs)
for postoperative pain, 241
sensorineural hearing loss due to, 2120
NSCLC (non–small cell lung cancer), epidermal growth factor receptor tyrosine kinase in, 1023
NSD (normal standard dose), in radiotherapy, 1039-1040
NSP (neonatal suppurative parotitis), 1153
NSQIP (National Surgical Quality Improvement Program), 84t-87t
NST (nucleus of the solitary tract), in gustatory pathway, 1212-1213
NT(s). *See* Neurotrophin(s) (NTs).
NTL. *See* Neuroendocrine tumor of the larynx (NTL).
NTL (near-total laryngectomy), 1564
for advanced glottic cancer, 1497
NTM (nontuberculous mycobacteria), salivary gland infection with, 1158-1159, 1158f
in children, 2857-2858, 2857f
Nuclear antigens, of Epstein-Barr virus, 1352
Nuclear imaging, 137-138
of pharynx and esophagus, 1397
positron emission tomography as, 137-138
applications of, 144, 145f
radionuclide, 138, 139f
of salivary glands, 138, 1150
Nucleic acid hybridization, 9
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), 211
Nucleotide(s), 4
wobble, 4
Nucleus basalis, in neural plasticity, 1881
Nucleus Contour Advance electrode, 2227, 2227f-2228f
Nucleus Freedom device, 2227, 2227f-2228f
external speech processors for, 2232f
Nucleus Hybrid device, 2224, 2224f
Nucleus of the solitary tract (NST), in gustatory pathway, 1212-1213
Nuel's spaces, 1832, 1832f
Null hypothesis, 65, 66t
Numeric Rating Scale (NRS), 240
Numerical scales, 63, 63t
Nutcracker esophagus, 959t, 965
imaging of, 1401
Nutrition
and migraine, 2349
in palliative care, 1104
Nutritional support, vascular supply of skin in, 1064
Nycomed (metrizamide powder), for embolization, 1933
Nystagmus, 2310-2312
anatomic and physiologic basis for, 2289
Bruns', 2312
during caloric testing, 2290
"centripetal," 2310t-2311t
"convergence-retraction," 2310t-2311t
defined, 2289, 2307t
"dissociated," 2310t-2311t
downbeat, 2310t-2311t
evaluation of
in bedside exam, 2310-2312
recording methods for, 2317
gaze-evoked, 2310t-2311t
head-shaking, 2296-2297, 2314
hyperventilation-induced, 2316
"infantile" or "congenital," 2310t-2311t
irritative, 2294
jerk, 2310-2312
optokinetic, 2277, 2314
"pendular," 2310t-2311t
"perverted," 2310t-2311t
positional and positioning, 2315-2316, 2315f
pre- and post-rotatory, 2296, 2298f, 2329
purely torsional, 2310t-2311t
Nystagmus *(Continued)*
quick phases of, 2289
"seesaw," 2310t-2311t
sensitivity axes of semicircular canals and, 2294-2295, 2295f
slow phases of, 2289
spontaneous, of vestibular origin, 2312
in superior canal dehiscence syndrome, 2339-2340, 2340f
due to temporal bone fracture, 2039
types of, 2310t-2311t
upbeat, 2310t-2311t
vibration-induced, 2314
Nystatin cream (Mycostatin), for fungal otitis externa, 1954-1955, 1959t-1960t

O

O_2. *See* Oxygen.
O_2^- (superoxide anion radical), in acutely raised skin flaps, 1070-1071, 1071f
OA (osteoarthritis)
oral manifestations of, 1253
of temporomandibular joint, 1281t, 1282
OAEs. *See* Otoacoustic emissions (OAEs).
Obesity
and gustatory physiology, 1213
and obstructive sleep apnea, 251-253
in children, 2605
and otitis media, 2768
Oblique arytenoid muscle, surgical anatomy of, 1542f
Oblique rectus muscle, in surgical anatomy of anterior cranial base, 2472f
Obliteration, of frontal sinuses, 779-781
closure in, 780
complications after, 780-781
estimating limit of frontal sinus in, 780, 781f
incision for, 779-780, 780f
materials used for, 780
with Paget's disease, 779-780, 780f
postoperative monitoring after, 780-781
removal of all mucosa in, 780
template for, 779-780
Observation
for acute otitis media, 2770
for carotid paragangliomas, 1661-1662
for otitis media with effusion, 2771
Observational studies, 54, 54t
data quality of, 59, 60t-62t
Obstructive apnea, in children, 2607
Obstructive hypopnea, in children, 2607
Obstructive hypoventilation, in children, 2607, 2607f
Obstructive sleep apnea (OSA), 250-266
in children, 2602-2612
acute-onset or rapidly progressive, 2606
vs. adults, 2603, 2603t
anesthesia with, 2598, 2599b
complications of, 2603-2604
behavior and learning problems as, 2603-2604
cardiopulmonary, 2604, 2604f
growth impairment as, 2603
diagnosis of, 2606-2608
history in, 2606
other studies in, 2607-2608
physical examination in, 2606
polysomnography in, 2606-2607, 2607f, 2607t
epidemiology of, 2603
nonsurgical management of, 2610-2611
pathophysiology of, 2604-2605
polysomnography in, 2606-2607, 2607f, 2607t
indications for, 2608
risk factors for, 2605-2606, 2605t
adenotonsillar hypertrophy as, 2604-2606, 2790-2793

Obstructive sleep apnea (OSA) *(Continued)*
craniofacial abnormalities as, 2605
mucopolysaccharidoses as, 2606
neuromuscular disease as, 2605-2606
obesity as, 2605
surgical management of, 2608-2610
craniofacial surgery in, 2610, 2610f
other pharyngeal surgery in, 2609-2610
other types of, 2610
tonsillectomy or adenoidectomy in, 2608-2609
tracheotomy in, 2610
symptoms and signs of, 2603, 2603t
concomitant sleep disorders with, 261, 262t
consequences of untreated, 252-253
defined, 251b, 252
diagnosis of, 253-255
cephalometric radiography in, 255, 255f
with comorbid conditions, 253
computed tomography in, 255, 255f
differential, 253, 253b
drug-induced sleep videoendoscopy in, 253-255
Epworth Sleepiness Scale in, 253, 253f
fiberoptic nasopharyngoscopy in, 253, 254f
fluoroscopy in, 255
MRI in, 255
Müller maneuver in, 253, 254f
nocturnal polysomnography in, 255, 255b, 256f
physical examination in, 253, 254b
in women, 253
gastroesophageal reflux and, 253, 2946
historical perspectives on, 251
obesity and, 251-253
in children, 2605
outcome scales for, 56t, 57
parasomnias associated with, 265, 265b
pathophysiology of, 252
symptoms of, 252, 252b
treatment of, 255-261
medical, 256-257
CPAP for, 256-257
nasal dilator strips for, 257
oral appliances for, 257, 257f
pharmacologic, 257
weight loss for, 256
surgical, 257-261
endoscopic studies prior to, 258
hypopharyngeal procedures for, 258b, 259-260, 260f-261f
indications for, 257, 257b
nasal procedures for, 258, 258b
palatal procedures for, 251t, 258-259, 258b, 258f, 260f
postoperative management after, 261
preoperative planning for, 257
stepwise protocol for, 257-258, 258b
tongue base procedures for, 259
tracheotomy for, 260-261
Obstructive sleep apnea syndrome (OSAS). *See* Obstructive sleep apnea (OSA).
Obstructive sleep-related breathing disorders, classification of, 251-252, 251b
Obturatoria stapedis, 1827f
Occipital artery, 2580, 2580f
sulcus for, 1824f
Occipital bone, in surgical anatomy of lateral skull base, 2435f
Occipital lymph node, 1360f, 2582
Occipital triangle, of neck, 96, 96f, 2578f
Occipitalization, of atlas, 2355
Occipitofrontalis muscle, 442f
Occipitomastoid suture, in surgical anatomy of lateral skull base, 2435, 2435f
Occlusion
anatomy and physiology of, 323
after maxillofacial trauma, 330-331, 333-334, 333f
Occlusion effects, with hearing aids, 2204, 2270
Occlusive bubble, for facial nerve injury, 2420, 2420f
Occult metastases, of salivary gland tumors, 1196-1197
Occupational exposure
to HIV infection, 212, 212t
to noise, sensorineural hearing loss due to (*See* Noise-induced hearing loss (NIHL))
to toxins, and laryngeal squamous cell carcinoma, 1492, 1513
Occupational rhinitis, 698
Ochronosis, 2114
otologic manifestations of, 2114
OCT (optical coherence tomography), for premalignant lesions of larynx, 1489, 1490f
Octopus cells, in cochlear nucleus, 1835, 1845
Octreotide, for hyperthyroidism, 1739t
Octyl-2-cyanoacrylate, in otoplasty, 478
Ocular defects, prosthetic management of, 1345t, 1346-1347, 1347f
Ocular flutter, 2313
Ocular hypotelorism, in Down syndrome, 2632-2633
Ocular motor apraxia, 2314
Ocular motor nerve injury, in lateral skull base surgery, 2512
Ocular scarring, due to cicatricial pemphigoid, 1233-1234, 1234f
Ocular tilt reaction, 2300, 2300f, 2312-2313, 2312f
Oculofacial prosthesis, 1345t, 1346-1347, 1347f
Oculomotor nerve, 2351f
intraoperative monitoring of, 2549-2550, 2550f
in surgical anatomy of anterior skull base, 2481f
in surgical anatomy of lateral skull base, 2439f
Oculopalatolaryngopharyngeal myoclonus, 840
Odds ratio, 64, 64t
Odontoameloblastoma, 1278
Odontogenesis, 1259-1260
enamel organ in, 1259
root development in, 1260
stages of, 1260
Odontogenic cysts, 1260-1269
in basal cell nevus syndrome, 1268
treatment of, 1268
botryoid, 1265-1266
radiographic features of, 1266
treatment of, 1266
calcifying (Gorlin), 1268-1269
microscopic features of, 1269, 1269f
radiographic features of, 1269
treatment of, 1269
classification of, 1260-1262, 1261b
common, 1262, 1265
defined, 1260-1262
dentigerous (follicular), 1263-1264
microscopic features of, 1264
neoplastic potential of, 1264
radiographic features of, 1264, 1264f
treatment of, 1264, 1264f
eruption, 1264, 1264f
treatment of, 1264
gingival
of adult, 1266
clinical features of, 1266
radiographic features of, 1266
of newborn (dental lamina, alveolar), 1266, 1266f
microscopic features of, 1266
treatment of, 1266
Odontogenic cysts *(Continued)*
glandular (sialo-), 1267
clinical features of, 1267
microscopic features of, 1267, 1267f
radiographic features of, 1267
treatment of, 1267
infected buccal bifurcation, 1264-1265
inflammatory collateral, 1263, 1263f
keratinizing (orthokeratinizing), 1266-1267
microscopic features of, 1267
radiographic features of, 1267, 1267f
kerato- (parakeratinizing, keratocystic), 1262, 1267-1268
in basal cell nevus syndrome, 1268
microscopic features of, 1268
radiographic features of, 1267-1268, 1268f
treatment of, 1268
lateral periodontal, 1265-1266
microscopic features of, 1265-1266, 1265f
radiographic features of, 1265
treatment of, 1266
lateralized radicular (lateral radicular, lateral periapical), 1263
malignancies arising in, 1269, 1270b
paradental, 1264-1265
radiographic features of, 1265
pathogenesis of, 1262
periapical (radicular, periradicular), 1262-1263
microscopic features of, 1262-1263, 1262f
radiographic features of, 1262, 1262f
treatment of, 1263, 1263f
primordial, 1265
residual, 1263
of undetermined origin, 1265
defined, 1265, 1265f
Odontogenic ghost cell tumor, 1275-1276
Odontogenic infections, 177-190
direction of spread of, 179-180, 179f-180f
fascial space involvement in, 180-187
cervical (deep neck), 184-187
lateral pharyngeal, 184-185, 186f
prevertebral (danger space No. 4), 186, 186f
retropharyngeal, 185-186, 186f-187f
surgical drainage and decompression for, 189-190
mandibular, 181-184
Ludwig's angina due to, 184, 185f
masseteric, 184, 185f
masticator, 184, 186f
pterygomandibular (medial pterygoid), 184, 185f
secondary, 184
sub-, 183-184, 183f-184f
sublingual, 183, 183f
submental, 181-183, 183f
temporal, 184, 185f
maxillary, 180-181
buccal, 181, 181f
canine, 180-181, 180f
cavernous sinus thrombosis due to, 181, 182f
orbital cellulitis due to, 181, 182f
natural history of, 179-180
management of, 180, 187-190
airway establishment in, 188
assessment and support of hose defenses in, 188
choice of antibiotic in, 178, 188
history and physical examination in, 187-188
identification of bacteria in, 188
surgical drainage and decompression in, 188-190
for deep neck space infections, 189-190
for jaw space infections, 189, 189f
for vestibular infections, 188-189
microbiology of, 177-178, 178t, 188
and implications for antibiotics, 178
vs. myofascial pain dysfunction syndrome, 1285t
natural history of, 178

Odontogenic keratocyst (OKC), 1262, 1267-1268
in basal cell nevus syndrome, 1268
microscopic features of, 1268
orthokeratinizing, 1266-1267
microscopic features of, 1267
radiographic features of, 1267, 1267f
parakeratinizing, 1262, 1267-1268
in basal cell nevus syndrome, 1268
microscopic features of, 1268
radiographic features of, 1267-1268, 1268f
treatment of, 1268
radiographic features of, 1267-1268, 1268f
treatment of, 1268
Odontogenic myxoma, 1276-1277, 1276f
microscopic findings in, 1276
radiographic findings in, 1276
treatment and prognosis for, 1276-1277, 1277f
Odontogenic tumors, 1270-1274
adenomatoid, 1277
microscopic features of, 1277
radiographic features of, 1277
treatment of, 1277
ameloblastic carcinoma as, 1274
ameloblastic fibroma as, 1274-1275
microscopic findings in, 1274-1275, 1275f
radiographic features of, 1274
treatment of, 1275
ameloblastic fibro-odontoma, 1275
microscopic findings in, 1275, 1275f
radiographic findings in, 1275
treatment of, 1275
ameloblastoma as
intraosseous type, 1273-1274
defined, 1273
mandibular, 1274
maxillary, 1274
microscopic features of, 1273, 1273f
natural history and treatment of, 1273-1274
radiographic findings in, 1273, 1273f
malignant, 1274-1275
odonto-, 1278
peripheral (extraosseous), 1274
unicystic, 1271-1272
definitions, clarifications, and treatment for, 1272, 1272f
microscopic features of, 1271, 1271f
vs. multicystic or multilocular, 1272
radiographic features of, 1271
"simple," 1272
calcifying epithelial (Pindborg) as, 1276
microscopic findings in, 1276
radiographic findings in, 1276, 1276f
classification of, 1270, 1270b
epithelial (dentinogenic) ghost cell, 1275-1276
malignant, 1269, 1270b
in mandible, 1270-1271, 1271f
in maxilla, 1270-1271
odontogenic myxoma as, 1276-1277, 1276f
microscopic findings in, 1276
radiographic findings in, 1276
treatment and prognosis for, 1276-1277, 1277f
odontomas as, 1277
microscopic findings in, 1277
radiographic findings in, 1277
treatment of, 1277
squamous, 1278
treatment of, 1276
Odontomas, 1277
microscopic findings in, 1277
radiographic findings in, 1277
treatment of, 1277
Odor aversion, 630
Odor memory, 630-631, 631b
Odorant-binding proteins, 629
Odynophagia, 956
OE. *See* Otitis externa (OE).
Office of the National Coordinator for Health Information Technology (ONC-HIT), 84t-87t, 89
Ofloxacin (Floxin) otic solution, for otitis externa, 1946, 1952, 1959t-1960t
OHCs. *See* Outer hair cell(s) (OHCs).
Ohngren's line, 1127, 1128f
OI. *See* Osteogenesis imperfecta (OI).
OKAN (optokinetic afternystagmus), 2319
OKC. *See* Odontogenic keratocyst (OKC).
OKN (optokinetic nystagmus), 2277, 2314
Old age dependency ratio, 230
Older patients. *See* Geriatric patients.
Olfaction, 624-639
with rhinosinusitis, 730
stimulation and measurement of, 631-632
Olfactometer, 631
Olfactory auras, in epilepsy, 636
Olfactory bulb, in olfactory stimulation, 628, 628f
Olfactory changes, with aging, 234
Olfactory coding, 629-630, 629f
Olfactory cognition, 630-631, 631b
Olfactory connections, in brain, 628
Olfactory cross-adaptation, and olfactory testing, 633
Olfactory dysfunction(s), 633-639
congenital, 636
decreased olfaction as, 633
diagnostic assessment of, 637-638
distorted olfaction (parosmia and phantosmia) as, 633, 636, 639
epidemiology of, 633, 634t
etiology of
aging as, 635, 635f
epilepsy as, 636
head trauma as, 634-635
HIV infection as, 636
medications as, 637, 637t
neoplasms as, 636
obstructive nasal and sinus disease as, 633, 634f-635f
psychiatric disorders as, 636
surgery as, 637
toxic exposure as, 636
upper respiratory infection as, 633-637
idiopathic, 637
management of, 638-639, 638f
Olfactory ensheathing cells, 626
Olfactory epithelium
cell types in, 626, 626f
basal cells as, 626f, 627
microvillar cells as, 626, 627f
olfactory ensheathing cells as, 626
olfactory receptor neuron as, 626, 626f-627f
supporting or sustentacular cells as, 626-627, 626f
and lamina propria, 626, 626f
in olfactory stimulation, 625-627
and respiratory epithelium, 625, 625f
Olfactory glomeruli, 628, 628f
Olfactory hallucinations, 636
Olfactory knob, 626, 627f
Olfactory map, 628, 630
Olfactory mucus, in olfactory stimulation, 625
Olfactory receptor neuron, 626, 626f-627f
Olfactory reference syndrome, 636
Olfactory stimulation, 624-629
common chemical sense in, 628-629
nasal passageways in, 624-625, 625f
olfactory bulb in, 628, 628f
olfactory connection to brain in, 628
olfactory epithelium in, 625-627
cell types of, 626, 626f
basal cells as, 626f, 627
microvillar cells as, 626, 627f
olfactory ensheathing cells as, 626
olfactory receptor neuron as, 626, 626f-627f
Olfactory stimulation *(Continued)*
supporting or sustentacular cells as, 626-627, 626f
and lamina propria, 626, 626f
and respiratory epithelium, 625, 625f
olfactory mucus in, 625
orthonasal, 631
retronasal, 631
vomeronasal organ in, 627-628, 627f
Olfactory testing, 631-632
factors affecting, 632-633
adaptation and habituation as, 633
age as, 632-633
gender as, 633
Olfactory transduction, 629-630, 629f
Olfactory-evoked potentials, 632
Oligogenic disorders, 4, 8
with complex traits, 8
genetic heterogeneity and, 8
mitochondrial, 8, 9f
sporadic cases of, 8
with X-linkage, 8, 8f
Oligonucleotides, 9
Olive oil, for cerumen removal, 1958t
Olivocochlear bundle, in auditory pathway, 1834-1835, 1834f
Olivocochlear reflex pathways, in efferent auditory system, 1848-1849, 1848f
Olopatadine hydrochloride
for allergic rhinitis, 620
for rhinosinusitis, 734t, 737
OM. *See* Otitis media (OM).
OM-6 scale, 57
Omalizumab, for rhinosinusitis, 735t, 737
allergic fungal, 715
OMC (ostiomeatal complex)
in functional endoscopic sinus surgery, 760, 760f
imaging of, 168f-169f, 169
surgical anatomy of, 739, 740f
OME. *See* Otitis media with effusion (OME).
Omega epiglottis, 1464
Omentum flaps, for free tissue transfer, 1082t
Omeprazole, for extraesophageal reflux, 901
Omohyoid muscle
anatomy of, 2578f
in neuromuscular pedicle procedure, 920, 921f
OMU (ostiomeatal unit)
in chronic sinusitis, 674, 674f
after functional endoscopic sinus surgery, 677-679
and sinus physiology, 664-670
ONC-HIT (Office of the National Coordinator for Health Information Technology), 84t-87t, 89
Oncocytic adenoma, of parathyroid gland, 1778
Oncocytic neoplasms, of larynx, 881
Oncocytic papillary cystadenoma, of salivary glands, 1171
Oncocytoma, of salivary glands, 1171
Oncogenes, 12
in head and neck squamous cell carcinoma, 1016, 1019-1020
modification of, 21-22
in thyroid carcinoma, 1752-1753
Ondansetron, for postoperative nausea and vomiting in children, 2593
Onlay tip cartilage grafts, for nasal tip projection, 535-536, 537f, 549-550, 550f-551f
Onodi cells, 669, 740, 749f
in surgical anatomy of anterior cranial base, 2473
Onyx, for embolization, 1933
Onyx-015 vector, in gene therapy, 22
OOPS (operation on placental support), for congenital high airway obstruction syndrome, 2904-2905
OPC. *See* Oropharyngeal candidiasis (OPC).

Open approach, for nasal tip refinement, 522-535, 534f-535f
  indications for, 521b
Open bite deformities, 461, 462f
Open laryngeal surgery
  for laryngeal trauma, 936-937, 939f
  for stridulous child, 2909-2910, 2910f
Open mouth posture (OMP), 2628-2630, 2629f
Open quotient, in measurement of vocal fold vibration, 830-831
Open reduction, for subcondylar fractures, 338-339
Open reduction with internal fixation (ORIF), for pediatric facial fractures, 2701-2702
Open sky incision, for nasal fracture repair, 505, 505f
Open supraglottic laryngectomy (OSGL), for early supraglottic cancer, 1498-1500, 1498f
"Open-book" fracture, of nose, 2708, 2711f
Open-canal fittings, for hearing aids, 2270
Open-fit technology, for hearing aids, 2270
Operation on placental support (OOPS), for congenital high airway obstruction syndrome, 2904-2905
OPGL (osteoprotegerin ligand), 609t-610t
Ophthalmic artery(ies), in surgical anatomy of anterior cranial base, 2472f-2473f
Ophthalmic complications, of endoscopic sinus surgery, 754-755
Ophthalmic division, of trigeminal nerve, 440
  in surgical anatomy of lateral skull base, 2437f, 2438
Ophthalmic division block, 242
Ophthalmologic considerations, with posterior fossa surgery, 2541
Ophthalmopathy, Graves'. *See* Graves' ophthalmopathy.
Opioids
  addiction *vs.* tolerance to, 240, 242
  as adjuncts to induction of anesthesia, 111
  in children
    for anesthesia maintenance, 2591-2592
    for pain, 2572
      postoperative, 2594
  chronic use of, and postoperative pain control, 241
  for noncancer chronic pain, 243
  via patient-controlled analgesia, 240, 241t
Opsoclonus, 2313
Optic canal(s), 322f, 335f
  fracture of, 2479, 2479f
  in surgical anatomy of anterior cranial base, 2442-2444, 2443f, 2472f, 2473-2474
  in surgical anatomy of middle cranial base, 2444, 2445f
Optic chiasm, in surgical anatomy of anterior cranial base, 2475f
Optic foramen, 320-321, 440, 1124f
  in surgical anatomy of anterior cranial base, 2444f
Optic nerve(s)
  paranasal sinuses and, 672, 672f
  in surgical anatomy of anterior cranial base, 2473f-2475f
Optic nerve decompression, combined endoscopic orbital and, for Graves' ophthalmopathy, 1815
Optic nerve injury, in functional endoscopic sinus surgery, 679, 680f
Optic nerve involvement, in Graves' ophthalmopathy, 1808-1809, 1809t
Optical coherence tomography (OCT), for premalignant lesions of larynx, 1489, 1490f
Optical resonating chamber, of carbon dioxide laser, 26, 27f
Optical stimulation, to assess facial nerve function, 2389
Opticocarotid recess, in surgical anatomy of anterior cranial base, 2473-2474
Optokinetic afternystagmus (OKAN), 2319
Optokinetic nystagmus (OKN), 2277, 2314
Optokinetic testing, 2318-2319
Optokinetic tracking, 2306f, 2307t, 2318-2319
Oral appliances, for obstructive sleep apnea, 257, 257f
Oral breathing, 809
Oral cancer, 1249-1250, 1293-1318
  adenoid cystic carcinoma as, 1299
  adjunctive chemotherapy for, 1314-1315
  of alveolar ridge, 1304-1305
    clinical presentation of, 1304, 1304f
    epidemiology of, 1304
    mandibulectomy for, 1304, 1304f-1305f, 1307f
    maxillary, 1304
    neck dissection for, 1304
    survival with, 1304-1305
  anatomic basis for, 1295-1298, 1295f
    alveolar ridge in, 1297-1298
    arteriovenous, 1295-1296, 1296f-1297f
    buccal mucosa in, 1295f, 1298
    floor of mouth in, 1297-1298
    hard palate in, 1295f, 1298
    lips in, 1296-1297, 1297f
    retromolar trigone in, 1295f, 1297, 1298f
    tongue in, 1297, 1298f
  of buccal mucosa, 1308-1309
    clinical appearance of, 1308f
    epidemiology of, 1308
    radiation and chemoradiation for, 1309
    reconstruction for, 1308-1309, 1309f
    squamous cell, 1308, 1308f
    surgical treatment of, 1308-1309, 1309f
    survival with, 1309
    verrucous, 1308
  cervical lymph node metastasis of
    incidence and distribution of, 1685f, 1688t
    radiation therapy for, 1689t
  chemoprevention of, 1315
  desmoplastic-neurotropic melanoma as, 1299
  diagnostic evaluation of, 1299-1300
    endoscopy for, 1300
    history and physical examination in, 1299-1300, 1300f
  epidemiology of, 1295
  etiology of, 1293-1295, 1294f
  of floor of mouth, 1307-1308
    cervical metastases of, 1308
    clinical presentation of, 1294f, 1307
    composite resection for, 1307-1308, 1308f, 1315f
    coronal partial mandibulectomy for, 1307-1308, 1308f
    imaging of, 1307
    invasive, 1307
    reconstruction for, 1307, 1315f
    segmental mandibulectomy for, 1307-1308, 1308f
    survival with, 1308
    transoral resection for, 1307
  of hard palate, 1309-1310
    cervical metastases of, 1310
    clinical appearance of, 1310f
    epidemiology of, 1309-1310
    Kaposi's sarcoma of, 1309-1310
    melanoma of, 1242f, 1309-1310
    reconstruction for, 1310, 1311f
    resection of, 1310, 1310f-1311f
    squamous cell carcinoma as, 1310, 1310f
    survival with, 1310
  imaging of, 1300
  of lip, 1302-1304
    clinical findings in, 1294f, 1302, 1302f
    epidemiology of, 1302
    neck metastases of, 1303-1304
    prognostic features of, 1303
    resection and reconstruction of, 1303-1304, 1303f
Oral cancer *(Continued)*
      Abbe-Estlander flap in, 1303-1304, 1303f
      Karapandzic fan flap in, 1303-1304, 1303f
    survival with, 1304
  long-term management and rehabilitation for, 1316-1317
    follow-up in, 1317, 1317t
    pain management in, 1316
    palliative care in, 1316
    for speech and swallowing, 1316
  molecular biology of, 1294-1295
  neck dissection for, 1312-1314, 1313f, 1713-1716
    definition and rationale for, 1713, 1714f
    technique for, 1713-1716, 1715f-1716f
  organ preservation protocols for, 1315
  pathology of, 1298-1299
  photodynamic therapy for, 1315
  premalignant lesions and, 1298-1299
  preoperative assessment of, 1300
  preoperative interventions for, 1300
  prognosis for, 1300-1302, 1301t
  radiation therapy for, 1314
    brachytherapy as, 1314, 1314f
    external beam, 1314
    package time for, 1314
  of retromolar trigone, 1306-1307
    clinical presentation of, 1306
    resection for, 1307, 1307f
    survival with, 1307
  sarcomas as, 1299, 1299f
  second primary tumors with, 1301-1302
  squamous cell carcinoma as, 1299
    of alveolar ridge–retromolar trigone, 1307f
    basaloid, 1299
    of buccal mucosa, 1308f
    epidemiology of, 1295
    etiology of, 1293-1295, 1294f
    of floor of mouth, 1294f, 1315f
    of hard palate, 1310f
    of lip, 1294f, 1302f-1303f
    sarcomatoid, 1299
    of tongue, 1306f
    verrucous, 1299
  staging of, 1300, 1301t
  surgical treatment of, 1302-1315
    of alveolar ridge, 1304-1305, 1304f-1305f
    approaches for, 1302
    of buccal mucosa, 1308-1309, 1308f-1309f
    complications of, 1317
    of floor of mouth, 1307-1308, 1308f
    of hard palate, 1309-1310, 1310f-1311f
    of lip, 1302-1304, 1302f-1303f
    of mandible, 1310-1312, 1312f-1313f, 1312t
    of neck, 1312-1314, 1313f
    perioperative antibiotics with, 1302
    preoperative assessment for, 1300
    reconstruction after, 1315-1316, 1315f-1316f
    of retromolar trigone, 1306-1307, 1307f
    of tongue, 1305-1306, 1305f-1306f
  of tongue, 1305-1306
    advanced-stage, 1306
    cervical lymph node metastases of, 1306
    clinical presentation of, 1305
    composite resection of, 1305, 1305f-1306f
    differential diagnosis of, 1305
    epidemiology of, 1295, 1305
    etiology of, 1305
    gross pathology of, 1305f
    hemiglossectomy for, 1305-1306, 1305f
    hemimandibulectomy for, 1306f
    local invasion by, 1305, 1305f-1306f
    reconstruction for, 1305-1306
    survival with, 1306
    wide local excision for, 1305
  treatment considerations for, 1302

Oral candidiasis, 199-200, 1229-1231, 1252
  acute, 1230, 1230f, 1230t
  angular cheilitis due to, 1230, 1230f
  chronic, 1230, 1230t
  clinical features of, 1230-1231
  defined, 1229
  differential diagnosis of, 1231
  erythematous, 1230, 1230f
  etiology and pathogenesis of, 1229-1230
  histopathologic/diagnostic features of, 1231, 1231f
  in HIV, 225, 226f
  hyperplastic, 1231, 1231f
  pseudomembranous, 1230, 1230f
  risk factors for, 1229, 1230t
  treatment of, 1231
Oral cavity
  anatomy of, 1295-1298, 1295f, 1359f
    alveolar ridge in, 1297-1298
    arteriovenous, 1295-1296, 1296f-1297f
    buccal mucosa in, 1295f, 1298
    floor of mouth in, 1297-1298
    hard palate in, 1295f, 1298
    lips in, 1296-1297, 1297f
    retromolar trigone in, 1295f, 1297, 1298f
    tongue in, 1297, 1298f
  benign neoplasm(s) of, 1290-1292
    ameloblastoma as, 1291, 1291f
    congenital epulis as, 1290, 1290f
    granular cell tumor as, 1290, 1290f
    hemangioma as, 1291
    lipoma as, 1291
    neurofibroma as, 1290-1291
    papilloma as, 1290, 1290f
    pleomorphic adenoma as, 1291-1292, 1292f
  congenital condition(s) of, 1287-1288
    developmental cysts as, 1287-1288
      dermoid, 1287-1288
      duplication, 1287-1288, 1288f
      nasoalveolar, 1288, 1288f
    dysphagia due to, 2949-2951, 2950t, 2952f
    lingual thyroid as, 1287
    torus as, 1287, 1288f
  dysplasia of, 1299
  erythroplakia of, 1298
  imaging of, 153-156
    with abscess, 156f
    with congenital lesions, 154-156
    with non-Hodgkin's lymphoma, 157f
    normal anatomy on, 146f, 153-156
    with squamous cell carcinoma, 154, 156f
  inflammatory/traumatic condition(s) of, 1288-1290
    amyloidosis as, 1289-1290, 1290f
    fibroma as, 1288-1289, 1289f
    mucosal ulcerations as, 1289, 1289f
    necrotizing sialometaplasia as, 1289, 1299
    pyogenic granuloma as, 1289, 1289f
  malignant neoplasms of (*See* Oral cancer)
  neurologic examination of, 833-834
  normal flora of, 177, 179f
  physical examination of, 98-99
  physiology of, 1200-1214
    motor function in, 1203-1207
      autonomic reflexes in, 1205-1206
      jaw-tongue reflexes in, 1205
      lingual muscles and reflexes in, 1205
      mastication as, 1206-1207, 1206f
      muscles of mastication and reflex control in, 1204-1205, 1204f-1205f
      oral phase of deglutition as, 1206f, 1207
    sensory function in, 1201-1203
      central projections of trigeminal system in, 1203
      common chemical sense in, 1202
      dental pain in, 1202-1203
      oral somesthesia in, 1201-1202, 1201f-1202f
Oral cavity *(Continued)*
    specialized sensory system of taste in, 1207-1214
      central gustatory pathways and function in, 1212-1213, 1212f
      gustatory physiology in, 1208
      gustatory sensitivity in, 1207-1208
      gustatory structures in, 1208
      gustatory transduction in, 1208-1210, 1210f
      interaction between saliva and taste in, 1213-1214
      peripheral sensitivity in, 1210-1212
  posterior, swallowing disorders due to surgery of, 1219-1220
  premalignant lesions of, 1298-1299
  somatosensory innervation of, 1201
  sublingual space of (*See* Sublingual space (SLS))
  submandibular space of (*See* Submandibular space (SMS))
  tuberculosis of, 1250-1251
  verrucous hyperplasia of, 1299
Oral commissure, burns of, 316
Oral contrast agents, for imaging of pharynx and esophagus, 1396
Oral hairy leukoplakia, 1226, 1226f
  in HIV infection, 225-226, 226f
Oral health, women's, 1256-1257
  during and after menopause, 1256-1257
  during menses, 1256
  during pregnancy, 1256
  during puberty, 1256
Oral histoplasmosis, in HIV infection, 226-227
Oral hygiene, in palliative care, 1101
Oral lesions, in HIV infection, 225-227, 1252
  aphthous ulcers as, 227, 227f
  candidiasis as, 225, 226f
  differential diagnosis of, 225t
  fungal, 227
  gingivitis and periodontal disease as, 227
  hairy leukoplakia as, 225-226, 226f
  due to herpes simplex virus, 226
  histoplasmosis as, 226-227
  due to human papillomavirus, 227
Oral leukoplakia, 1223-1225
  chemoprevention of, 1225
  clinical features of, 1224-1225, 1224f
  defined, 1223
  etiology of, 1223-1224, 1223f-1224f
  hairy, 1226, 1226f
    in HIV infection, 225-226, 226f
  histopathologic features of, 1225, 1226f
  malignant transformation of, 1223, 1298
  proliferative verrucous, 1225, 1225f
  thin, 1224f, 1225
  treatment of, 1225
Oral lichen planus, 1226-1229, 1253-1254
  atrophic or erythematous, 1227, 1227f
  bullous variant of, 1227-1228
  clinical differential diagnosis of, 1228
  clinical features of, 1227-1228
  erosive, 1227, 1228f
  etiology and pathogenesis of, 1227
  histopathologic features of, 1228, 1228f
  and oral carcinoma, 1229, 1298-1299
  plaque form of, 1227
  reticular-type, 1227, 1227f
  systemic diseases and, 1228
  treatment of, 1228
Oral lichenoid lesion, 1229
Oral manifestations
  of Down syndrome, 2632
  of systemic diseases, 1245-1258
    arthritides and bone disorders as, 1253
      Ewing's sarcoma as, 1253
      osteoarthritis as, 1253
      Paget's disease as, 1253
Oral manifestations *(Continued)*
      Reiter's syndrome as, 1253
      rheumatoid arthritis as, 1253, 1253t
    cerebrovascular, 1250
    collagen-vascular and granulomatous, 1251-1252
      dermatomyositis-polymyositis as, 1252
      sarcoidosis as, 1252
      scleroderma as, 1252
      Sjögren's syndrome as, 1251
      systemic lupus erythematosus as, 1251-1252
      Wegener's granulomatosis as, 1252
    dermatologic, 1253-1254
      erythema multiforme as, 1254
      lichen planus as, 1253-1254
      mucous membrane pemphigoid as, 1254
      pemphigus vulgaris as, 1254
    endocrine and exocrine, 1251
      adrenal, 1251
      diabetes mellitus as, 1251
      parathyroid, 1251
      pituitary, 1251
      thyroid, 1251
    gastrointestinal, 1254
      Behçet's syndrome as, 1254
      Crohn's disease and ulcerative colitis as, 1254
      gastroesophageal reflux disease as, 1254
      malabsorption diseases as, 1254
    of heart, 1246-1249, 1249t
    hematologic, 1256
      bleeding disorders as, 1256
      hemoglobin problems as, 1256
      white blood cell disorders as, 1256
    infectious, 1252
      bacterial, 1252
      fungal, 1252
      viral, 1252
    inherited and congenital, 1257
    of liver, 1255
    malignant neoplasms as, 1249-1250
    neurologic, 1254-1255
      Bell's palsy as, 1255
      dementias (including Alzheimer's disease) as, 1254-1255
      multiple sclerosis as, 1255
      myasthenia gravis as, 1255
      myotonic muscular dystrophy as, 1255
      Parkinson's disease as, 1255
    pulmonary, 1250-1251
    renal, 1255
Oral motor function, 1203-1207
  autonomic reflexes in, 1205-1206
  jaw-tongue reflexes in, 1205
  lingual muscles and reflexes in, 1205
  mastication as, 1206-1207, 1206f
  muscles of mastication and reflex control in, 1204-1205, 1204f-1205f
  oral phase of deglutition as, 1206f, 1207
Oral mucosal lesions, 1222-1244
  pigmented, 1241-1243
    amalgam tattoo as, 1243
      clinical features of, 1243, 1243f
      defined, 1243
      differential diagnosis of, 1243
      etiology of, 1243
      histopathologic features of, 1243, 1243f
      treatment of, 1243
    melanoma as, 1242-1243
      clinical features of, 1242, 1242f
      differential diagnosis of, 1242
      etiology and pathogenesis of, 1241, 1241t
      histopathologic features of, 1242-1243, 1242f-1243f
      treatment of, 1243
    melanotic macules as, 1241
      clinical features of, 1241, 1241f
      defined, 1241

Oral mucosal lesions *(Continued)*
differential diagnosis of, 1242
etiology and pathogenesis of, 1241, 1241t
histopathologic features of, 1242, 1242f
treatment of, 1243
mucosal melanocytic nevi as
clinical features of, 1241
histopathologic features of, 1242
treatment of, 1243
red/white, 1222-1231
candidiasis as, 199-200, 1229-1231, 1252
acute, 1230, 1230f, 1230t
angular cheilitis due to, 1230, 1230f
chronic, 1230, 1230t
clinical features of, 1230-1231
defined, 1229
differential diagnosis of, 1231
erythematous, 1230, 1230f
etiology and pathogenesis of, 1229-1230
histopathologic/diagnostic features of, 1231, 1231f
hyperplastic, 1231, 1231f
pseudomembranous, 1230, 1230f
risk factors for, 1229, 1230t
treatment of, 1231
leukoedema as, 1222-1223
clinical features of, 1222, 1223f
defined, 1222
etiology and pathogenesis of, 1222
histopathologic features of, 1222, 1223f
management of, 1223
leukoplakia as, 1223-1225
chemoprevention of, 1225
clinical features of, 1224-1225, 1224f
defined, 1223
etiology of, 1223-1224, 1223f-1224f
hairy, 1226, 1226f
histopathologic features of, 1225, 1226f
malignant transformation of, 1223, 1298
proliferative verrucous, 1225, 1225f
thin, 1224f, 1225
treatment of, 1225
lichen planus as, 1226-1229, 1253-1254
atrophic or erythematous, 1227, 1227f
bullous variant of, 1227-1228
clinical differential diagnosis of, 1228
clinical features of, 1227-1228
erosive, 1227, 1228f
etiology and pathogenesis of, 1227
histopathologic features of, 1228, 1228f
and oral carcinoma, 1229, 1298-1299
plaque form of, 1227
reticular-type, 1227, 1227f
systemic diseases and, 1228
treatment of, 1228
submucous fibrosis as, 1229, 1295
clinical features of, 1229
defined, 1229
etiology and pathogenesis of, 1229
histologic/diagnostic features of, 1229
treatment of, 1229
verruciform xanthoma as, 1229
clinical features of, 1229
defined, 1229
etiology and pathogenesis of, 1229
histopathologic/diagnostic features of, 1229
treatment of, 1229
vesiculobullous/ulcerative, 1231-1240
erythema multiforme as, 1239-1240, 1254
clinical features of, 1239, 1239f-1240f
defined, 1239
differential diagnosis of, 1239
etiology and pathogenesis of, 1239
histopathologic features of, 1239-1240
treatment of, 1240

Oral mucosal lesions *(Continued)*
mucous membrane (cicatricial) pemphigoid as, 1233-1235, 1254
clinical differential diagnosis of, 1234, 1234t
clinical features of, 1233-1234, 1233f-1234f
defined, 1233
etiology and pathogenesis of, 1233
histopathologic features of, 1234-1235, 1234f
treatment of, 1235
pemphigus vulgaris as, 1231-1233, 1254
clinical differential diagnosis of, 1232
clinical presentation of, 1232, 1232f
defined, 1231-1232
etiology/pathogenesis of, 1232
histopathologic features of, 1232-1233, 1232f-1233f
treatment of, 1233
primary herpes simplex infection as, 1235, 1252
clinical features of, 1235, 1235f, 1252
defined, 1235
diagnosis of, 1235
differential diagnosis of, 1235
etiology and pathogenesis of, 1235
treatment of, 1235, 1252
recurrent aphthous stomatitis as, 1236-1239
clinical features of, 1237-1238
defined, 1236-1237
differential diagnosis of, 1238, 1238t
etiology and pathogenesis of, 1237, 1237t
herpetiform-type, 1238, 1238f
histopathologic features of, 1239
major, 1237-1238, 1238f
minor, 1237, 1238f
treatment of, 1239
recurrent herpes simplex infection as, 1235-1236, 1252
clinical features of, 1236, 1236f
defined, 1235
differential diagnosis of, 1236
etiology and pathogenesis of, 1235-1236
histopathology of, 1236, 1237f
vs. recurrent aphthous stomatitis, 1238, 1238t
treatment of, 1236
traumatic (eosinophilic) granuloma as, 1240
clinical features of, 1240, 1240f
defined, 1240
differential diagnosis of, 1240
etiology of, 1240
histopathologic features of, 1240, 1240f
treatment of, 1240
Oral mucosal pigmentation, inherited and congenital disorders affecting, 1257
Oral phosphate salts, for hyperparathyroidism, 1804
Oral preparatory stage, of deglutition, 1215, 1216f, 2948
Oral preservation treatment, *vs.* total laryngectomy, 1564
Oral rinses, biomarkers in, for head and neck squamous cell carcinoma, 1026
Oral sequelae, of medications for systemic diseases, 1246, 1247t-1248t
Oral somesthesia, 1201-1202, 1201f-1202f
Oral stage, of deglutition, 1206f, 1207, 1215, 1216f, 2948
Oral treatment considerations, due to systemic conditions, 1246, 1246t
Oral warts, in HIV, 227
Oral-facial-digital syndrome, 1257
Orbicularis muscle, in aging, 406, 406f
Orbicularis oculi muscle
with aging, 444
anatomy of, 433f, 441-443, 442f-443f
botulinum toxin for, 432, 433f
in lower eyelid blepharoplasty, 448-449, 450f
origin of, 443
paralysis of, 2420, 2420f, 2423f

Orbicularis oculi muscle *(Continued)*
sphincter mechanism of, 443, 443f
in upper eyelid blepharoplasty, 448
Orbicularis oris muscle, 442f
in cleft lip, 2665-2666, 2665f-2666f
Orbit(s)
anatomy and physiology of, 320-321, 322f, 439-444
biomechanics of, 332
effects of radiotherapy on, 2626t
endoscopic surgery of, 763
growth and development of, 2617t
invasive small cell carcinoma of, 170f
in surgical anatomy of anterior cranial base, 2443-2444, 2444f
Orbital apex, 320-321
Orbital apex fractures, pediatric, 2712, 2713f
Orbital blowout fractures, 170f, 321, 325, 326f
pediatric, 325, 326f
Orbital cellulitis, due to odontogenic infections, 181, 182f
Orbital complications
of functional endoscopic sinus surgery, 679, 680f
of rhinosinusitis, 676-677
Orbital decompression, for Graves' ophthalmopathy, 1811-1816
approaches to, 1811, 1812f
balanced, 1814
without bone removal, 1816
combined endoscopic and open approach to, 1814
combined endoscopic orbital and optic nerve, 1815
endoscopic, 1814, 1815f-1816f
goal of, 1811
indications for, 1811
results of, 1811-1812
three-wall, 1815-1816
transantral, 1812-1814
complications of, 1814
modifications of, 1814
outcome of, 1812-1814, 1813f-1814f
technique for, 1812, 1812f-1813f
two-wall, 1816
Orbital defects, prosthetic management of, 1345t, 1346-1347, 1347f
Orbital dystopia, surgical correction of, 2654
Orbital echography, of Graves' ophthalmopathy, 1810
Orbital edema, preseptal, due to rhinosinusitis, 676
Orbital enucleation, prosthesis for, 1346
Orbital evisceration, prosthesis for, 1346
Orbital exenteration
prosthesis for, 1346-1347
radial maxillectomy with, 1125-1126
Orbital fat pads, 443-444, 444f
Orbital floor, 439-440
surgical access to, 328-329
Orbital floor fractures, pediatric, 2712-2713, 2714f-2715f
Orbital fractures
blowout, 170f, 321, 325, 326f
pediatric, 325, 326f
imaging of, 325, 326f
pediatric, 2711-2714
evaluation of, 2712, 2713f
of lateral/medial orbital wall, 2712, 2714, 2716f
of orbital apex, 2712, 2713f
of orbital floor, 2712-2713, 2714f-2715f
of orbital roof, 2712-2713, 2716f
patterns of, 2711-2712
physical examination of, 324
repair of, 336
surgical access to, 328-329, 329f
Orbital hemorrhage, after blepharoplasty, 449
Orbital hypertelorism, surgical correction of, 2654

Orbital periosteum, 439
Orbital rim, lateral, surgical access to, 328-329, 329f
Orbital roof, in surgical anatomy of anterior cranial base, 2443
Orbital roof fractures, pediatric, 2712-2713, 2716f
Orbital septum
  anatomy of, 443, 443f
  in lower eyelid blepharoplasty
    with subciliary approach, 449, 450f
    transconjunctival, 448-449, 450f
  in upper eyelid blepharoplasty, 448, 449f
Orbital wall(s), 439
Orbital wall fractures, pediatric, 2712, 2714, 2716f
Ordinal scales, 63, 63t
ORFFF (osteocutaneous radial forearm free flap), 1082t, 1085-1086, 1086f-1087f
Organ of Corti
  anatomy of, 1832, 1832f, 1840, 1841f
  in auditory physiology, 1841f
  in cochlear transduction, 2061f, 2067f, 2069f
  embryogenesis of, 1852
  in noise-induced hearing loss, 2142-2143, 2142f
Organ preservation treatment
  for laryngeal carcinoma, 1501-1503, 1502f (*See also* Conservation laryngeal surgery)
    current paradigm for, 1558-1559
    glottic, 1497
      chemoradiation as, 1584-1585
      targeted biologic agents with radiation therapy as, 1585
    management of neck after, 1502-1503
    recurrence after, 1503-1504
    supraglottic, 1500
  for oral cancer, 1315
  principles of, 1544
Orientation, hearing aid, 2273-2274
ORIF (open reduction with internal fixation), for pediatric facial fractures, 2701-2702
ORN (osteoradionecrosis), 1048, 1314, 1317, 1478-1479
ORNC (overpressure radionuclide cisternography), for CSF rhinorrhea, 790
Orocutaneous fistula, 179, 180f
Orodigitofacial dysostosis, 1257
Orofacial clefts. *See also* Cleft lip; Cleft palate.
  molecular genetics of, 2662-2664
Oromotor reflexes
  autonomic, 1205-1206
  jaw-tongue, 1205
  lingual, 1205
  of muscles of mastication, 1204-1205, 1204f-1205f
Oronasal fistula, after palatoplasty, 2673
Oropharyngeal cancer, 1249-1250, 1358-1374
  anatomy of oropharynx and, 1358-1360, 1359f
    base of tongue in, 1359, 1359f
    lymphatics in, 1359-1360, 1360f-1361f, 1361t
    oropharyngeal wall in, 1359, 1360f
    soft palate in, 1359
    tonsillar fossae in, 1359
  of base of tongue, 1369-1370
  carcinoma in-situ as, 1361
  cervical lymph node metastasis of, 1360f, 1361t
    incidence and distribution of, 1685f, 1688t
    radiation therapy for, 1689t
  classification of, 1360-1365, 1362t
  complications of, 1372-1373
  diagnostic evaluation of, 1365-1372
    anamnesis in, 1365-1366
    endoscopy, biopsy, and frozen section in, 1366, 1366f
    imaging in, 1366
    physical examination in, 1366
  epithelial precursor lesions for, 1360-1361, 1362f
  follow-up for, 1372, 1373f
  hematolymphoid, 1364, 1364f
Oropharyngeal cancer *(Continued)*
  imaging of, 1366, 1413, 1413f
  intensity-modulated radiotherapy for, 1046
  Kaposi's sarcoma as, 1363-1364, 1364f
  lymphatic spread of, 1359-1360, 1360f-1361f, 1361t
  lymphoepithelial, 1362
  management algorithm for, 1368, 1368f
  mucosal malignant melanoma as, 1364-1365, 1364f-1365f
  neck dissection for, 1716-1718
    definition and rationale for, 1716-1717, 1717f
    technique for, 1717-1718, 1717f
  of oropharyngeal wall, 1370
  prognostic factors for, 1373
  quality of life with, 1373
  reconstruction for (*See* Oropharyngeal reconstruction)
  salivary gland tumors as, 1362-1363
  of soft palate, 1368-1369, 1368f
  soft tissue tumors as, 1363-1364, 1364f
  special treatment considerations for, 1372
  squamous cell carcinoma as, 1361-1362, 1365
    clinical presentation of, 1361, 1362f, 1365
    etiology of, 1365
    grading of, 1361-1362, 1363t
    imaging of, 149f
    pathology of, 1361
  staging of, 1366-1367, 1367t
  surgical approach(es) for, 1370
    lateral and transhyoid pharyngotomy as, 1371, 1371f-1372f
    mandibular swing, 1371-1372, 1372f
    transoral, 1370-1371, 1370f-1371f
  of tonsillar fossae, 1369, 1369f
Oropharyngeal candidiasis (OPC), 199-200, 1229-1231, 1252
  acute, 1230, 1230f, 1230t
  angular cheilitis due to, 1230, 1230f
  chronic, 1230, 1230t
  clinical features of, 1230-1231
  defined, 1229
  differential diagnosis of, 1231
  erythematous, 1230, 1230f
  etiology and pathogenesis of, 1229-1230
  histopathologic/diagnostic features of, 1231, 1231f
  in HIV, 225, 226f
  hyperplastic, 1231, 1231f
  pseudomembranous, 1230, 1230f
  risk factors for, 1229, 1230t
  treatment of, 1231
Oropharyngeal reconstruction, 1375-1392
  considerations for, 1375
  cost of, 1375-1376
  historical background of, 1375
  option(s) for, 1376-1379, 1376f
    free tissue transfer as, 1379-1381
      anterolateral thigh, 1379
      fasciocutaneous, 1379-1380, 1379f
      lateral arm, 1379-1380
      lateral thigh, 1379
      latissimus dorsi myocutaneous, 1380
      musculocutaneous, 1380
      osteocutaneous, 1380-1381
      radial forearm, 1379, 1379f
      rectus abdominis, 1380
      visceral, 1380, 1380f
    healing by second intention as, 1376
    local flap(s) as, 1376-1377
      palatal island, 1376-1377, 1376f
      tongue, 1376
      uvulopalatal, 1377, 1377f
    primary closure as, 1376
    regional flaps as, 1377-1379
      latissimus dorsi musculocutaneous, 1378, 1378f
Oropharyngeal reconstruction *(Continued)*
      pectoralis major, 1377, 1377f
      platysmal myocutaneous, 1377, 1378f
      temporalis, 1377-1378
      temporoparietal fascial, 1377-1378, 1378f
      trapezius musculocutaneous, 1378-1379
    skin grafts as, 1376
  preoperative evaluation for, 1375
  of soft palate, 1381-1383
    algorithm for, 1384f
    free flaps for, 1382
      Gehanno method for, 1382
      Lacombe and Blackwell's method for, 1382-1383
      other groups' experience with, 1383
      radial forearm, 1382, 1383f
    local flaps for, 1381
      buccinator musculomucosal, 1381-1382, 1381f
      palatal island mucosal, 1382
      Superior Constrictor Rotation-Advancement Flap (SCARF) as, 1382, 1382f
      uvulopalatal, 1377f, 1381
    prosthetic obturation for, 1381
    speech function after, 1383
  of tongue base, 1387-1391
    algorithm for, 1391f
    free flaps for, 1389
      lateral arm, 1389
      radial forearm, 1389
    goals of, 1387
    healing by second intention for, 1387-1388
    local flaps for, 1388
    primary closure for, 1387-1388
    regional flaps for
      latissimus dorsi, 1389
      pectoralis major myocutaneous, 1388-1389
      platysmal myocutaneous, 1389
    skin grafting for, 1388
    after total or subtotal glossectomy, 1389-1390
      innervated free latissimus dorsi musculocutaneous flap for, 1389-1390, 1390f
      microvascular reconstruction as, 1390
      money pouch–like method for, 1390, 1390f
      sensate fasciocutaneous flaps for, 1390-1391
  of tonsil and pharyngeal wall, 1383-1387
    algorithm for, 1388f
    free flaps for, 1386
      with combined lateral and superior defects, 1386, 1387f
      lateral arm and thigh, 1386-1387
      radial forearm, 1386
    healing by second intention for, 1383
    local flaps for, 1384-1385
    primary closure for, 1383-1384
    regional flaps for
      pectoralis major, 1385, 1385f
      platysmal myocutaneous, 1385
      sternocleidomastoid myocutaneous, 1385-1386
      temporalis, 1386
      temporoparietal fascia, 1386
    skin grafting for, 1384
Oropharyngeal surgery, robotic, 42-43
Oropharyngeal wall
  anatomy of, 1359, 1360f
  cancer of
    cervical lymph node metastasis of, 1361t
    clinical presentation of, 1365
    management of, 1370
Oropharyngeal wall reconstruction, 1383-1387
  algorithm for, 1388f
  free flaps for, 1386
    with combined lateral and superior defects, 1386, 1387f

Oropharyngeal wall reconstruction *(Continued)*
lateral arm and thigh, 1386-1387
radial forearm, 1386
healing by second intention for, 1383
local flaps for, 1384-1385
primary closure for, 1383-1384
regional flaps for
pectoralis major, 1385, 1385f
platysmal myocutaneous, 1385
sternocleidomastoid myocutaneous, 1385-1386
temporalis, 1386
temporoparietal fascia, 1386
skin grafting for, 1384
Oropharyngocutaneous fistula, due to radiotherapy, 1048
Oropharynx
anatomy of, 1358-1360, 1359f
base of tongue in, 1359, 1359f
lymphatics in, 1359-1360, 1360f-1361f, 1361t
oropharyngeal wall in, 1359, 1360f
radiographic, 1398f
soft palate in, 1359
tonsillar fossae in, 1359
dysphagia due to congenital conditions of, 2949-2951, 2950t, 2952f
lymphatics of, 1359-1360, 1360f-1361f, 1361t
physical examination of, 99, 99f
Orotracheal intubation, with pediatric facial fractures, 2698-2699
Orthodontic devices, for obstructive sleep apnea in children, 2611
Orthokeratinizing odontogenic cyst, 1266-1267
microscopic features of, 1267
radiographic features of, 1267, 1267f
Orthokeratinizing odontogenic keratocyst, 1266-1267
microscopic features of, 1267
radiographic features of, 1267, 1267f
Orthonasal stimulation, 631
Orthopedic joint patients, antibiotic prophylaxis for, 1253, 1253t
Orthovoltage x-rays, 1034
OSA. *See* Obstructive sleep apnea (OSA).
OSA-18 scale, 57
OSAS (obstructive sleep apnea syndrome). *See* Obstructive sleep apnea (OSA).
Oscillopsia, 2277, 2309, 2344
OSD-6 scale, 57
OSGL (open supraglottic laryngectomy), for early supraglottic cancer, 1498-1500, 1498f
OSMED (otospondylomegaepiphyseal dysplasia) syndrome, deafness in, 2051t-2058t
Osseointegrated implantable hearing aids, 2212-2216
background of, 2213
biology and histology of, 2213
biophysical principles of, 2213
comparison of features of, 2206t
complications of, 2215
components of, 2213f
design of, 2213
indications and contraindications for, 2212-2213, 2216t
in infants, 2723-2724
location of, 2204f
materials for, 2213
operative technique for, 2213-2215, 2214f
radiologic implications of, 2213
results of, 2215-2216, 2216t
sound transduction and coupling to auditory system with, 2205f
for unilateral sensorineural hearing loss, 2216
in young children, 2215
Osseous free tissue transfer, mandibular reconstruction plate with, 1324
advantages and disadvantages of, 1324
flap inset in, 1324f, 1325
flap options for, 1324, 1325t
planning and harvesting of flaps in, 1324-1325, 1324f
Osseous genioplasty, 465, 467-470
anesthesia for, 467
clinical examples of, 470, 472f-473f
complications after, 470
fixation in, 468-470, 470f
gingivolabial incision for, 467, 468f
inscription of bony midline in, 467-468, 469f
lateral extent of, 468, 469f
measurement of osteotomy site in, 467-468, 469f
subperiosteal dissection in, 467, 468f
three-dimensional movement of chin in, 468
vertical lengthening in, 468-470, 469f
vertical shortening in, 468-470, 470f
wound closure in, 470
Osseous labyrinth
anatomy of, 1831, 1852, 1853f
embryogenesis of, 1852
malformations of membranous and, 2727b, 2728-2735
Osseous spiral lamina, 1831, 1832f, 1834
Ossicles
anatomy of, 1826
blood supply of, 1828f
in cochlear transduction, 2050-2060, 2062f
hearing loss due to total loss of, 2019, 2019t
Ossicular branch, 1828f
Ossicular chain
anatomy of, 1825f, 1826, 1827f
in auditory physiology, 1839, 1840f, 2017-2019
blood supply of, 1828f
in cochlear transduction, 2050-2060, 2062f
reconstruction of (*See* Ossiculoplasty)
in surgical anatomy of lateral skull base, 2436f
Ossicular coupling, 1839, 2000
in middle ear implants, 2207-2208
Ossicular discontinuity
audiometric correlates of, 2005-2006
ossiculoplasty for, 2008
pathophysiology of, 2005
Ossicular dislocation, 174f
Ossicular disruption, hearing loss due to
with closure of oval window, 2019, 2019t
with intact tympanic membrane, 2019, 2019t
with tympanic membrane perforation, 2019, 2019t
Ossicular fixation
audiometric correlates of, 2005-2006
ossiculoplasty with, 2007-2008, 2024-2025
pathophysiology of, 2005
Ossicular lever, 2018
Ossicular prosthesis(es), 2006
causes of failure of, 2008
hydroxyapatite cap for, 2026t
length of, 2025
materials for, 2006
Cervital as, 2026t
choice of, 2007, 2007f
comparison of, 2026, 2026t
Plastipore as, 2026t
titanium as, 2006, 2025-2026, 2026t
for otosclerosis
measurement of, 2031, 2031f-2032f
placement of, 2031-2032, 2032f
partial, 2006
with absent lenticular process of incus, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
Ossicular prosthesis(es) *(Continued)*
total, 2006
with absent stapes superstructure, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
Ossicular reconstruction. *See* Ossiculoplasty.
Ossiculoplasty, 2005-2008, 2023-2026
for absent lenticular process of incus, 2024, 2024f-2025f
for absent stapes superstructure, 2024, 2025f
autografts for, 2006, 2025
causes of failure of, 2008
factors affecting surgical decisions in, 2006-2007, 2007f
goal of, 2006-2007
homografts for, 2006, 2025, 2026t
length of prosthesis in, 2025
materials for, 2006
choice of, 2007, 2007f
comparison of, 2026, 2026t
with ossicular fixation, 2007-2008, 2024-2025
partial ossicular replacement prosthesis (PORP) for, 2006
with absent lenticular process of incus, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
pathophysiology and, 2005
audiometric correlates of, 2005-2006
ossicular discontinuity in, 2005
ossicular fixation in, 2005
patient selection for, 2023, 2024b
surgical techniques for, 2007-2008
with ossicular discontinuity, 2008
with ossicular fixation, 2007-2008
for temporal bone trauma, 2046-2047
timing of, 2007
titanium prostheses for, 2006, 2025-2026, 2026t
total ossicular replacement prosthesis (TORP) for, 2006
with absent stapes superstructure, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
with tympanosclerosis, 2007-2008, 2024-2025
Ossifying fibroma, sinonasal, 725-726
Osteitis
deformans (*See* Paget's disease)
fibrosa cystica, 1774, 1782
with laryngeal involvement, 882
oral manifestations of, 1257
otologic manifestations of, 2112
of paranasal sinus walls, 672, 672f
of skull base, 171
Osteoarthritis (OA)
oral manifestations of, 1253
of temporomandibular joint, 1281t, 1282
Osteochondroma, of coronoid process, *vs.* myofascial pain dysfunction syndrome, 1285t
Osteocutaneous flaps, for free tissue transfer, 1082t, 1084-1087
fibula, 1082t, 1084-1085, 1085f
iliac crest, 1082t, 1087
for oropharyngeal reconstruction, 1380-1381
radial forearm, 1082t, 1085-1086, 1086f-1087f
scapula, 1082t, 1086-1087, 1088f
Osteocutaneous radial forearm free flap (ORFFF), 1082t, 1085-1086, 1086f-1087f
Osteogenesis, 2614
distraction
for craniofacial anomalies, 2654-2657, 2656f
for obstructive sleep apnea, 2610
for Robin sequence, 2673
endochondral, 2614, 2615f
intramembranous, 2614

Osteogenesis imperfecta (OI), 2109-2110
  clinical features of, 2109-2110
  deafness in, 2051t-2058t, 2109-2110
  genetic basis for, 2109-2110
  management of, 2110
  oral manifestations of, 1257
  otologic manifestations of, 2110, 2110f
  radiographic imaging of, 2109-2110, 2110f
Osteogenic sarcomas, of paranasal sinuses, 1131
Osteohypertrophic nevus flammeus, 291
Osteoma(s)
  of craniocervical junction, 2484f
  of external auditory canal
    imaging of, 1918, 1919f
    management of, 2022
  sinonasal, 723-725
    classification of, 723
    endoscopic appearance of, 723
    epidemiology of, 723
    ethmoid, 724f
    frontal, 724-725, 724f
    frontoethmoid, 783-784, 784f
    imaging of, 723-725, 723f-724f
    ivory ("eburnated"), 723, 723f-724f
    mature (spongiosum), 723
    microscopic appearance of, 723
    mixed, 723, 724f
    pathogenesis of, 723
    postoperative surveillance for, 725
    spongiosum variant of, 724f
    surgical approach for, 718t, 724-725
    symptoms of, 723
Osteomyelitis
  of frontal bone, 777f
  of skull base, 171
Osteopetrosis(es), 2111-2112
  autosomal dominant
    type I, 2112
    type II, 2112
      otologic manifestations of, 2112, 2113f
  autosomal recessive, 2112
    otologic manifestations of, 2112, 2112f
  malignant, 2112
  oral manifestations of, 1257
  otologic manifestations of, 2112, 2112f-2113f
Osteophytes, vertebral, compression of pharynx and esophagus due to, 1408, 1409f
Osteoprotegerin ligand (OPGL), 609t-610t
Osteoradionecrosis (ORN), 1048, 1314, 1317, 1478-1479
Osteosarcoma
  of neck, 1668
  of oral cavity, 1299f
Osteotomy(ies)
  maxillary, in cleft-lip nose repair, 559, 564f-565f
  for narrowing of nose, 541-542
    double, 542, 542f-543f
    lateral, 541, 542f
    medial-oblique, 541, 541f
  for twisted nose, 551-554
    intermediate, 553, 554f
    lateral, 552-554, 553f
    medial, 552-553, 552f-553f
Ostiomeatal channels, 664
Ostiomeatal complex (OMC)
  in functional endoscopic sinus surgery, 760, 760f
  imaging of, 168f-169f, 169
  surgical anatomy of, 739, 740f
Ostiomeatal unit (OMU)
  in chronic sinusitis, 674, 674f
  after functional endoscopic sinus surgery, 677-679
  and sinus physiology, 664-670
Ostmann's fatty tissue
  anatomy of, 1869, 1869f
  in pressure equalization, 1870
O-T procedure, for forehead repair, 362, 363f
Otalgia, 2197-2198
  with bloody or serous otorrhea, 2195-2196
  primary, 2197
  referred, 2197-2198
Otic capsule, 1840
Otic pit, 1851-1852
Otic placode, 477, 1851-1852
Otic vesicle, 1851-1852
Otitic hydrocephalus, 1997
Otitic infections, intracranial complications of, 2347
Otitis externa (OE), 97, 1944-1947
  allergic, 1945-1946
  bacterial, 1944
    ear wick for, 1945-1946, 1951, 1951f
    otorrhea due to, 2194-2195
    systemic antibiotics for, 1953
    topical therapies for, 1951-1953
      acidifying agents as, 1953
      failure to respond to, 1953, 1953t
      options for, 1951-1953, 1951f
      ototopic antibiotics as, 1951-1953
  chronic, 1945, 1946f, 1953
  clinical manifestations of, 1945
  complications of, 1946-1947, 1946f
  conductive hearing loss due to, 2021, 2023f
  defined, 1944
  eczematoid, topical therapies for, 1955-1957
    anti-inflammatory and immunosuppressive agents as, 1956-1957
    options for, 1955
    steroids as, 1955-1956
  fungal, 1944-1946, 1945f
    otorrhea due to, 2195
    topical therapies for, 1954-1955
      acidifying agents as, 1954
      antifungals as, 1954-1955
      antiseptics as, 1955
      options for, 1954
      ototoxicity of, 1955
  granular, 1945
  immunosuppression and, 221-223
  incidence and epidemiology of, 1944
  investigations of, 1945
  malignant or necrotizing, 1947-1948
    clinical manifestations of, 1947, 1947f
    conductive hearing loss due to, 2021, 2023f
    defined, 1947
    imaging of, 1917, 1917f
    immunosuppression and, 221-222, 1947
    incidence and epidemiology of, 1947
    investigations of, 1947
    microbiology of, 1947
    otorrhea due to, 2195
    treatment of, 1947-1948
  microbiology of, 1945, 1945t
  otorrhea due to, 2194-2195
  pathogenesis of, 1944-1945, 1945f
  treatment of, 1945-1946
Otitis media (OM), 1963-1978
  acute, 1979-1981
    in children, 2761-2777
      complications and sequelae of, 2776-2777
      diagnosis of, 2761-2762
      epidemiology of, 2765-2768
      pathophysiology and pathogenesis of, 2762-2765, 2762f
      prevention of, 2768-2769
      recurrent, 2771
      treatment of, 2770-2771
    clinical features of, 1980
    complication(s) of, 1963, 1979-1981 (*See also* Temporal bone infections, complications of)
    otitis media with effusion as, 1963
    tympanosclerosis as, 1974
Otitis media (OM) *(Continued)*
    epidemiology of, 1979-1980
    immunosuppression and, 222-223
    otorrhea due to, 2196
    pathogenesis of, 1980-1981
    treatment of, 1980-1981
  adenoidectomy for, 2796
  adhesive, 1964, 1965f
  chronic, 1981
    bacteriology of, 1981
    with cholesteatoma, 1964-1969
      acquired, 1964-1966, 1965f-1966f
      anterior epitympanic, 1968, 1969f
      bone erosion in, 1971-1974, 1972f-1973f
      complications of, 1968, 1969b
      congenital, 1964-1966, 1966f
      diagnosis of, 1965, 1965f-1966f
      epidemiology of, 1965
      management of, 1968-1969, 1969t, 1970b
      pathogenesis of, 1965-1968, 1967f
      posterior mesotympanic, 1968, 1968f
      sensorineural hearing loss due to, 1974
    without cholesteatoma, 1969-1971
      diagnosis of, 1969, 1970f
      management of, 1971
      pathogenesis of, 1970-1971, 1971f, 1971t
    complications of, 1981 (*See also* Temporal bone infections, complications of)
    defined, 1981
    otorrhea due to, 2195-2196
    perilymph fistula due to, 2342-2343
    suppurative, cochlear implant for, 2221
    with tympanostomy tubes, 1970-1971, 1981
  and cleft palate, 1872-1873, 1873f, 2674-2675
  and cochlear implants, 2240
  with effusion (*See* Otitis media with effusion (OME))
  eustachian tube dysfunction and
    aging and, 1872
    with cleft palate, 1872-1873, 1873f
    ear pressure and, 1872
    with extraesophageal reflux, 1873
    hereditary component to, 1873-1874
    hypertrophic adenoids and, 1872, 1873f
    mucociliary clearance and, 1871
    nasal allergy and, 1872
    with nasopharyngeal neoplasms, 1873, 1873f
    pathophysiology of, 1872
    respiratory viruses and, 1871
  facial nerve paralysis due to, 1991, 2400
    epidemiology of, 1980t
    imaging of, 1991f
    treatment for, 1991
  immunosuppression and, 222-223
  middle ear atelectasis due to, 1964, 1964f-1965f
  mucociliary clearance and, 1871
  vs. myofascial pain dysfunction syndrome, 1284t
  petrositis due to, 1975-1977
    anatomic basis for, 1975-1976, 1976f-1977f
    diagnostic tests for, 1977, 1977f
    historical notes on, 1975
    management of, 1977
    symptoms of, 1976-1977, 1976t
  respiratory viruses and, 1871
  sensorineural hearing loss due to, 2118-2119
  serous, immunosuppression and, 222-223
  tuberculous, 2101-2103, 2102f-2103f
  tympanosclerosis due to, 1974-1975
    diagnosis of, 1974, 1974f
    epidemiology of, 1974
    management of, 1975, 1975f
    pathogenesis of, 1974-1975, 1975f
Otitis media with effusion (OME)
  in children, 2761-2777
    complications and sequelae of, 2776-2777
      intracranial, 2776-2777
      intratemporal, 2776

Otitis media with effusion (OME) *(Continued)*
diagnosis of, 2761-2762
audiometry in, 2762
immittance testing (tympanometry) in, 2762
physical examination in, 2761-2762
symptoms and signs in, 2761
epidemiology of, 2765-2768
incidence and prevalence of, 2765
risk factors in, 2766-2768
trend over time in, 2765-2766
guidelines for, 2773
pathophysiology and pathogenesis of, 2762-2765, 2762f
allergy and immunology in, 2764-2765
eustachian tube function in, 2762-2763, 2763f
gastroesophageal reflux in, 2765
infection in, 2763-2764, 2764f
prevention of, 2768-2769
antibiotic prophylaxis for, 2771
management of environmental factors in, 2768
vaccines in, 2768-2769
quality of life assessment for, 2773
recurrent, 2771
treatment of, 2771-2773
medical, 2771-2772
observation in, 2771
for recurrent disease, 2771
surgical, 2772-2776
clinical course of, 1963
etiology of, 1963
and mastoid pneumatization, 1963-1964
middle ear atelectasis due to, 1964, 1964f-1965f
sensorineural hearing loss due to, 1974
tympanosclerosis due to, 1974
OTOA (otoancorin) gene, in deafness, 2051t-2058t
Otoacoustic emissions (OAEs), 1891-1892, 1904-1907
with acoustic neuroma, 1891-1892, 1893f, 1897
advantages of, 1906
and audiograms, 1905, 1906f
and auditory neuropathy or dyssynchrony, 1907
clinical applications of, 1905-1907
cochlear echoes in, 1891
distortion product, 1891, 1905
and audiometric tests, 1905, 1907f
clinical applications of, 1905-1907
defined, 1891, 1905
distortion products in, 1905
frequencies used in, 1905
with high-frequency hearing loss, 1905, 1907f
in infants, 2720-2721
with normal hearing, 1892f, 1905, 1907f
procedure for, 1891
evoked
in infants, 2720-2721
types of, 1891, 1905
with neural hearing loss, 1899-1901
for noise-induced hearing loss
early detection of, 2146-2147, 2147f-2150f
susceptibility to, 2144
with normal hearing, 1905, 1906f
with otitis media, 2762
procedure for, 1891
with sensorineural hearing loss, 1905, 1906f, 2117
spontaneous, 1905
stimulus-frequency, 1891
transient evoked, 1891, 1905
with acoustic neuroma, 1891-1892, 1893f
advantages of, 1891
analysis of, 1905
clinical applications of, 1905-1907
defined, 1891, 1905
in infants, 2720-2721
with normal hearing, 1892f
Otoancorin *(OTOA)* gene, in deafness, 2051t-2058t
Otocadherin, in deafness, 2051t-2058t
Otocerol (arachis oil, almond oil, rectified camphor oil), for cerumen removal, 1958t
Otoconia. *See* Otolith(s).
Otoconial membrane
response to head acceleration by, 2283
in vestibular system, 1855, 1858f
Otocyst, 1851-1852, 1851f
Otoferlin *(OTOF)* gene, in deafness, 2051t-2058t, 2080-2081
Otogelin, 2067
Otogelin *(Otog)* gene, in murine deafness, 2058t-2060t, 2067-2069
Otolith(s), in vestibular system, 1855, 1858f
anatomy of, 2277, 2278f
arrangement of, 2278, 2280f
estimated patterns of excitation and inhibition for, 2278, 2281f
morphologic polarizations of stereociliary bundles in, 2278, 2280f
Otolith membrane
response to head acceleration by, 2283
in vestibular system, 1855, 1858f
Otolithic crisis of Tumarkin, 2300
Otologic disease, outcome scales for, 56t, 57
Otologic manifestations
of immunosuppression, 221-223
malignant otitis externa as, 221-222
in middle ear, 222-223
due to *P. jiroveci* and *A. fumigatus,* 222-223
of systemic diseases, 2100-2115, 2101t
of bone, 2108-2112
in fibrous dysplasia, 2110-2111, 2111f
in osteitis fibrosa cystica, 2112
in osteogenesis imperfecta, 2109-2110, 2110f
in osteopetroses, 2111-2112, 2112f-2113f
in Paget's disease, 2108-2109, 2109f
collagen vascular and autoimmune, 2114
genetically determined, 2115
granulomatous and infectious, 2100-2106
in Langerhans' cell histiocytosis, 2100-2101, 2101f-2102f
in Lyme disease, 2105-2106
in mycotic diseases, 2106, 2106f
in sarcoidosis, 2104-2105, 2104f
in syphilis, 2105, 2105f
in tuberculosis, 2101-2103, 2102f-2103f
in Wegener's granulomatosis, 2103-2104, 2103f-2104f
immunodeficiency, 2114-2115
in AIDS, 2114-2115
primary or congenital, 2114
neoplastic, 2106-2108
in leukemia, 2107, 2108f
metastatic, 2107-2108, 2108f
in multiple myeloma, 2106-2107, 2107f
storage and metabolic, 2112-2114
in gout, 2113-2114
in mucopolysaccharidoses, 2112-2113, 2113f
in ochronosis, 2114
Otologic symptoms and syndromes, 2194-2202
aural fullness as, 2198
hearing loss as, 2198-2201, 2198b
acute, 2198b, 2199
fluctuating, 2198b, 2199
gradual, 2198b, 2199
due to jugular foramen syndromes, 2199, 2199t
pediatric
conductive, 2200-2201
sensorineural, 2200, 2200b
rapidly progressive, 2198b, 2199-2200
otalgia as, 2197-2198
primary, 2197
referred, 2197-2198
Otologic symptoms and syndromes *(Continued)*
otorrhea as, 2194-2197, 2195b
external ear sources of, 2194-2197, 2195b
intracranial sources of, 2195b, 2197
neoplastic disease causing, 2196-2197
systemic disease associated with, 2196
infectious, 2196
noninfectious, 2196
tympanic membrane, middle ear, and mastoid sources of, 2195-2196, 2195b
vertigo as, 2201-2202
labyrinthine, 2201-2202
retrocochlear, 2202
time course of, 2201, 2201b
Otologics fully implantable middle ear system, 2027
Otology, gene therapy in, 23
Otomastoiditis, immunosuppression and, 222
Otomicroscopy
in children, 2574
in infants, 2722
Otomycosis, 1944-1945, 1945f
otorrhea due to, 2195
Otoplasty, 475-480
cartilage-cutting *vs.* cartilage-sparing techniques of, 477, 477f
complications of, 478-479
electrocautery in, 478
graduated-approach, 477-478, 478f
history of, 475-476, 476f
incisionless, 478
octyl-2-cyanoacrylate in, 478
other techniques of, 478
results of, 479-480, 479f-480f
suture techniques in, 477-478, 477f
complications of, 479
history of, 475-476, 476f
Mustarde, 475-476, 476f
Otoprotective agents, 2189-2191
Otorrhea, 97, 2194-2197
bloody or serous, otalgia with, 2195-2196
CSF, 788, 2197
gustatory, 2197
purulent
due to chronic dermatitis or eczema, 2194
due to infection of first branchial cleft cyst, 2195
due to otitis externa, 2194
sources of, 2194-2197, 2195b
external ear, 2194-2197, 2195b
intracranial, 2195b, 2197
neoplastic, 2196-2197
systemic, 2196
infectious, 2196
noninfectious, 2196
tympanic membrane, middle ear, and mastoid, 2195-2196, 2195b
topical therapies for, 1957-1958
with tympanostomy tubes, 1971, 2774-2775
Otos (otospiralin) gene, in murine deafness, 2058t-2060t
Otosclerosis, 2028-2035
alternative treatment of, 2034-2035
fluoride therapy as, 2034-2035
hearing aids as, 2034
clinical course of, 2028-2029
clinical presentation of, 2028
defined, 2028
evaluation of, 2029-2030
audiometry in, 2030, 2030f
history in, 2029-2030
physical examination in, 2030
far-advanced, 2035
fenestral and cochlear, imaging of, 1921-1922, 1925f
histopathology of, 2028-2029, 2029f-2030f
inheritance of, 2028-2030

Otosclerosis *(Continued)*
with Meniere's disease, 2035
prevalence of, 2028, 2029t
sensorineural hearing loss due to, 2124
small fenestra stapedotomy for, 2030-2032
with laser minus prosthesis, 2033
laser *vs.* microdrill in, 2033
postoperative care after, 2032-2033
postoperative complication(s) of, 2030, 2034
facial paralysis as, 2030, 2034
perilymph fistula as, 2034
reparative granuloma as, 2034
sensorineural hearing loss as, 2030, 2034
serous labyrinthitis as, 2034
taste disturbance as, 2034
tinnitus as, 2034
tympanic membrane perforation as, 2034
vertigo as, 2030, 2034
procedure for, 2030-2032
anesthesia for, 2030
creation of fenestra in, 2031-2032, 2032f
flap elevation in, 2031, 2031f
incisions for, 2031
measurement of distance from incus to footplate in, 2031, 2031f-2032f
placement of prosthesis in, 2031-2032, 2032f
positioning for, 2031, 2031f
removal of posterior superior bony wall in, 2031, 2031f
stapedectomy *vs.,* 2030
surgical problems in, 2033-2034
chorda tympani nerve damage as, 2034
exposed, overhanging facial nerve as, 2033
fixed malleus as, 2033
floating footplate as, 2033
intraoperative vertigo as, 2034
perilymph gusher as, 2034
solid or obliterated footplate as, 2033
tympanic membrane perforation as, 2034
stapedectomy for
in children, 2035
revision, 2035
vs. stapedotomy, 2030
Otoscopy
in children, 2574
pneumatic, for otitis media, 2761-2762
for temporal bone fractures, 2038f-2039f
Otospiralin *(Otos)* gene, in murine deafness, 2058t-2060t
Otospondylomegaepiphyseal dysplasia (OSMED) syndrome, deafness in, 2051t-2058t
Otospongiosis, 2028
imaging of, 1921-1922, 1925f
Otosyphilis, 2105, 2105f, 2341-2342
early *vs.* late, 2341
in HIV, 224
treatment for, 2341-2342
Ototopical agents
acidifying, 1959t-1960t
for acute bacterial otitis externa, 1953
for fungal otitis externa, 1954
for acute bacterial otitis externa, 1951-1953
acidifying agents as, 1953
antibiotics as, 1951-1953
failure to respond to, 1953, 1953t
options for, 1951-1953, 1951f
antibiotics as, 1959t-1960t
for acute bacterial otitis externa, 1951-1953
evidence-based data on, 1952
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1953-1954
resistance to, 1953
antifungals as, 1959t-1960t
for fungal otitis externa, 1954-1955
ototoxicity of, 1955
Ototopical agents *(Continued)*
anti-inflammatories as
for eczematoid otitis externa, 1956-1957
mechanism of action of, 1951
antiseptics as, 1955
for fungal otitis externa, 1955
for cerumen impaction, 1957
options for, 1957, 1958t
for ear hygiene and chronic draining ear, 1957-1958, 1961f
for eczematoid otitis externa, 1955-1957
anti-inflammatory and immunosuppressive agents as, 1956-1957
options for, 1955
steroids as, 1955-1956
for fungal otitis externa, 1954-1955
acidifying agents as, 1954
antifungals as, 1954-1955
antiseptics as, 1955
options for, 1954
history of, 1950
immunosuppressive, for eczematoid otitis externa, 1956-1957
mechanism of action of, 1950-1951
for antibiotics, 1951
for anti-inflammatories, 1951
for myringitis, 1955
defined, 1955
options for, 1955
sensorineural hearing loss due to, 2119-2120
steroids as
classes of, 1956, 1956t
for eczematoid otitis externa, 1955-1956
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1956
summary of available, 1959t-1960t
for viral infections, 1957, 1957f
options for, 1957
Ototoxicity, 2169-2178
of aminoglycoside antibiotics, 1953-1954, 2169
clinical manifestations of, 2170
delayed, 2170
histopathology of, 2170
mechanisms of, 2170-2171
monitoring for, 2170
in noise-induced hearing loss, 2147
pharmacokinetics of, 2169-2170
risk factors for, 2170
sensorineural hearing loss due to, 2119-2120, 2170
with topical preparations, 2119-2120
susceptibility to, 2097, 2170
vertigo due to, 2201
vestibular, 2170
of analgesics, 2175-2176
hydrocodone as, 2175
salicylates as, 2175-2176
of antineoplastic agent(s), 2171-2174
carboplatin as, 2173-2174
cisplatin as, 2171-2173
clinical studies on, 2171-2172
delayed, 2171-2172
experimental studies on, 2172
genetic predisposition to, 2172
histopathology of, 2172
mechanics of, 2172-2173
pharmacokinetics of, 2171
risk factors for, 2172
vestibular, 2172
difluoromethylornithine as, 2174
animal studies on, 2174
clinical studies on, 2174
conclusions on, 2174
of deferoxamine, 2176-2177
of erythromycin and related macrolide antibiotics, 2176
Ototoxicity *(Continued)*
of loop diuretics, 2174-2175
monitoring for, 2177
in noise-induced hearing loss, 2147
of quinine and related drugs, 2176
sensorineural hearing loss due to, 2119-2121
sudden, 2128
of topical antibiotics, 1953-1954
of topical antifungals, 1955
of topical steroids, 1956
of vancomycin, 2177
Outcome(s)
assessment of, 53-54
categories of, 55-56
descriptive statistics for, 64t
Outcome measures, with rhinosinusitis, 730, 730t
Outcomes research, 52-58
defined, 52
future directions for, 58
history of, 52-53
key terms and concepts in, 53-54
assessment of baseline as, 53
comorbidity in, 53
definition of disease in, 53
disease severity in, 53
assessment of outcomes as, 53-54
effectiveness in, 52, 54
efficacy in, 53-54
assessment of treatment as, 53
control groups in, 53
biasing and confounding in, 53
measurement of clinical outcomes in, 55-56
categories of outcomes for, 55-56
psychometric validation for, 55
outcome measures in, 56, 56t
disease-specific scales as, 55-58, 56t
for head and neck cancer, 56-57, 56t
otologic, 56t, 57
pediatric, 56t, 57
rhinologic, 56t, 57
sleep, 56t, 57
symptom, 56t, 57-58
voice, 56t, 57
generic scales as, 55-56, 56t
study design for, 54-55, 54t
case series as, 54-55, 54t
case-control, 54, 54t
expert opinion as, 52, 54-55, 54t
grading of evidence-based medicine recommendations as, 55, 55t
observational (cohort), 54, 54t
other types of, 55
randomized trial as, 52, 54, 54t
Outer hair cell(s) (OHCs)
anatomy of, 1832-1834, 1832f-1833f, 1840
arrangement of, 2071, 2072f
in auditory physiology, 1841f, 1844, 1844f
in cochlear transduction
active, 2063-2064, 2064f, 2066f-2067f
passive, 2061f-2062f
length of, 2070, 2070f
in noise-induced hearing loss, 2141-2142, 2142f
number and density of, 2070
and otoacoustic emissions, 1904-1906
receptor potentials for, 2071, 2072f
stereocilia on, 2070f, 2071, 2072f
transduction channels in, 2073f
Outer hair cell (OHC) motility, prestin (SLC26A5) and, 2064-2065, 2068f
Oval window
anatomy of, 1831, 1840, 1853f
atresia of, 1917, 1917f
in cochlear transduction, 2062f
hearing loss due to ossicular disruption with closure of, 2019, 2019t
in sound transmission, 2019

Overbite, 323, 323f
Overjet, 323, 323f
Overpressure radionuclide cisternography (ORNC), for CSF rhinorrhea, 790
Overpressure therapy, local, 2338
Overrotation, of nasal tip, revision rhinoplasty for, 590, 590f-591f
Oxcarbazepine, for neuropathic pain, 243, 244t
Oxidative stress, in noise-induced hearing loss, 2144-2145
Oxycephaly, synostotic, 2645, 2645f
Oxycodone, for postoperative pain, 241t
Oxygen free radicals, in acutely raised skin flaps, 1070-1071, 1071f
Oxygen saturation monitoring, for stridor, 2900
Oxygen supplementation
  nocturnal, for obstructive sleep apnea in children, 2611
  for stridor, 2903
Oxygen transport, in children, 2571-2572
Oxymetazoline
  for obstructive sleep apnea, 257
  for rhinosinusitis, 735t, 736
Oxyphil cells, 1778

P

P values, 65, 66t
  multiple, 73t, 74
  post hoc, 73-74, 73t
P_0, in deafness, 2051t-2058t
p16, in head and neck squamous cell carcinoma, 1020-1021
p53
  in head and neck squamous cell carcinoma, 1020, 1024
  in laryngeal carcinoma, 1505
  in oral cancer, 1295
  in thyroid carcinoma, 1753
Pa (pascal), 1839
PABI (penetrating auditory brainstem implant), 2262, 2262f
Pacemaker, pediatric anesthesia with, 2587
Pacific Business Group on Health (PBGH), 84t-87t, 87
Pacifier use, and otitis media, 2767
Package time, for oral cancer, 1314
Paclitaxel
  in combination chemotherapy, 1060
  with radiotherapy, 1041-1042
PACS (picture archival and communication systems), 138
Paget, James, 1223
Paget's disease, 2108-2109
  clinical manifestations of, 2108
  epidemiology of, 2108
  etiology of, 2108
  of frontal bone, 779-780, 780f
  genetic basis for, 2108
  oral manifestations of, 1253
  otologic manifestations of, 2109, 2109f
  radiographic findings in, 2108, 2109f
  sensorineural hearing loss due to, 2124
Pain, 239-249
  acute postoperative, 240-242
    defined, 239
    epidemiology of, 240
    management of
      with chronic opioid therapy, 241
      NSAIDs for, 241
      in older adults, 240-241
      opioid addiction *vs.* tolerance in, 240
      patient satisfaction with, 240
      patient-controlled analgesia for, 240, 241t
      preemptive analgesia for, 241
      regional anesthesia for, 241-242
Pain *(Continued)*
  chronic, 242-246
    adjuvant analgesics for, 243-244
      anticonvulsant agents as, 243-244, 244t
      antidepressants as, 244-245, 245t
    analgesic ladder for, 242-243
    ceiling of efficacy and/or safety with, 243
    defined, 239, 242-243
    first-line agents for, 243
    guidelines for opioid use for, 243
    interventional techniques for, 245-246, 246t
    types of, 242-243
  with cognitive impairment, 240
  defined, 239
  due to headache, 246-248
    cluster, 247-248
    diagnosis of, 246, 247f
    epidemiology of, 246
    in hemicrania continua, 248
    initial evaluation of, 246
    medication overuse (rebound), 248
    migraine, 246-247
    primary, 246
    secondary, 246
    tension-type, 247
    thunderclap, 248
    in trigeminal neuralgia, 248
  measurement of, 239-240
  neuropathic
    anticonvulsant agents for, 243-244, 244t
    antidepressants for, 244-245, 245t
    interventional techniques for, 245-246, 246t
    palliative care for, 1103
  palliative care for, 1103
Pain management
  in children, 2572
    postoperative, 2594
  postoperative
    in children, 2594
    after surgical resection of oral cancer, 1316
Pair production, 1032f, 1033
Paired box gene 2 *(PAX2),* in deafness, 2051t-2058t
Paired box gene 3 *(PAX3),* in deafness, 2051t-2058t, 2095
Paired samples, statistical tests for, 66, 67t
Palatal augmentation prosthesis, 1342-1343, 1344f
Palatal bulb obturator, for velopharyngeal dysfunction, 2681, 2682f
Palatal fracture, repair of, 335, 335f
Palatal implant, for obstructive sleep apnea, 258-259
Palatal island mucosal flap, for oropharyngeal reconstruction, 1376-1377, 1376f
  of soft palate, 1382
  of tonsils and pharyngeal wall, 1385
Palatal lift, for velopharyngeal dysfunction, 2681, 2681f
Palatal lift prosthesis, 1343-1344
Palatal reconstruction, 1381-1383
  algorithm for, 1384f
  free flaps for, 1382
    Gehanno method for, 1382
    Lacombe and Blackwell's method for, 1382-1383
    other groups' experience with, 1383
    radial forearm, 1382, 1383f
  jejunal flaps for, 1380, 1380f
  local flaps for, 1381
    buccinator musculomucosal, 1381-1382, 1381f
    palatal island mucosal, 1382
    Superior Constrictor Rotation-Advancement Flap (SCARF) as, 1382, 1382f
    uvulopalatal, 1377f, 1381
  prosthetic obturation for, 1381
  speech function after, 1383
Palatal surgery, for obstructive sleep apnea, 251t, 258-259, 258b, 258f, 260f
Palate
  inherited and congenital disorders affecting, 1257
  non-Hodgkin's lymphoma of, 1364f
  pleomorphic adenoma of, 1169, 1169f
  primary *vs.* secondary, 2659, 2660f
Palatine shelves, 2661, 2662f-2663f
Palatine tonsil(s)
  anatomy of, 1359f, 2783-2784
    radiographic, 1463f-1464f
  embryology of, 2585f
  in immune system, 605
Palatoglossal arch, 1359f
Palatoglossus muscle
  anatomy of, 1297, 1359f-1360f
  in velopharyngeal function, 2676, 2677t
Palatopharyngeal arch, 1359f
Palatopharyngeus muscle
  anatomy of, 1360f
  in velopharyngeal function, 2676, 2677t
Palatoplasty, 2668-2673
  basic principles of, 2670
  complications of, 2672-2673
  and facial growth, 2669
  Furlow (double-opposing Z-plasty), 2670
    surgical technique for, 2671-2672, 2672f
    for velopharyngeal dysfunction, 2682-2683
  goals of, 2668
  techniques of, 2669-2670
  timing of, 2668-2669
  two-flap, 2669-2670, 2670f
    surgical technique for, 2670-2671, 2670f-2671f
Palifermin, for mucositis, 1102
Palindromic sequence, 9
Palliative care, 1100-1105
  for dysphagia and speech dysfunction, 1104
  for end of life, 1104
  for mucositis, 1101-1102
  for nutrition, 1104
  for oral cancer, 1316
  oral hygiene in, 1101
  for pain, 1103
  pretreatment management in, 1101
  for psychological distress, 1103-1104
  for taste dysfunction, 1103
  for xerostomia, 1102-1103
Palliative treatment, for tracheal tumors, 1619-1624
Pallister-Hall syndrome (PHS), 2874
Palmaz stent, for tracheal stenosis, 2929-2930
Palmoplantar hyperkeratosis, deafness in, 2051t-2058t
Palmoplantar keratoderma, deafness in, 2051t-2058t
Palpebral conjunctiva, 444
Palpebral fissure, 442, 445
Palpebral opening, in aesthetic analysis, 271
Palpebral springs, for lagophthalmos, 2421
Pancuronium, for pediatric anesthesia, 2593t
Panfacial fractures, 339
Panje prosthesis, 1598f
Panoramic radiograph (Panorex), for mentoplasty, 462-463, 462f
Pansynostosis, 2641t
PaO_2 (arterial oxygen tension), in children, 2570, 2571t
Papillary cystadenoma, of salivary glands
  lymphomatosum, 1170-1171
    imaging of, 1146, 1146f
  oncocytic, 1171
Papillary dermis, 1065
Papillary squamous cell carcinoma (PSCC), of larynx, 1506
Papillary thyroid carcinoma, 1760-1761
  clinical presentation of, 1760
  management and prognosis for, 1760-1761
  pathology of, 1760
  ultrasound of, 1646f
    metastatic, 1648f-1649f

Papilloma(s)
choroid plexus, 2528-2529, 2530f
fibroepithelial, 291
inverted (Schneiderian, inverted type)
ductal, of salivary glands, 1171-1172
of nasopharynx, 1349
sinonasal, 718-720, 1127
endoscopic appearance of, 718-719, 719f
epidemiology of, 718
with frontal sinus involvement, 720, 720f
histologic appearance of, 718
human papillomavirus and, 718
imaging of, 719, 719f
postoperative surveillance for, 720
recurrence of, 720
sites for, 718
and squamous cell carcinoma, 718
surgical approach for, 718t, 719-720, 720f, 763, 1127
of oral cavity, 1290, 1290f
squamous
of larynx, 1468, 1468f
of nasopharynx, 1349
of oral cavity, 1290, 1290f
of trachea, 1612
Papillomatosis
aural, 1957, 1957f
management options for, 1957
laryngeal, stridor due to, 2898, 2899f
recurrent respiratory (*See* Recurrent respiratory papillomatosis (RRP))
PAR (perennial allergic rhinitis), 617-618
and pediatric chronic sinusitis, 2778
Parabrachial nucleus, in gustatory pathway, 1212-1213
Paracoccidioidomycosis, laryngitis due to, 885
Paradental cyst, 1264-1265
radiographic features of, 1265
Paradoxic nasal obstruction, 484, 486
Paragangliomas (PGLs), 1657
carotid, 1657-1658, 2506f
anatomy and physiology of, 1658-1659
classification of, 1660
clinical presentation and diagnosis of, 1659-1660
endovascular treatment of, 1937, 1937f
etiology of, 1659, 1659t
history of, 1657-1658
imaging of, 1658f, 1660-1661
malignancy of, 1660
multicentricity of, 1660-1661
observation for, 1661-1662
radiation therapy for, 1661
surgical management of, 1660-1661
of cerebellopontine angle, 2522-2523, 2523f-2524f
endovascular treatment of, 1934-1937, 1935f
for carotid body tumor, 1937, 1937f
for glomus jugulare tumor, 1935-1936, 1935f-1936f
for glomus tympanicum tumor, 1935
for glomus vagale tumor, 1936-1937, 1936f
epidemiology of, 1657-1659
familial syndromes of, 1659, 1659t, 2506f
glomus jugulare, 2505, 2506f
endovascular treatment of, 1935-1936, 1935f-1936f
surgical approach to, 2506, 2507f
glomus tympanicum, 2505-2506
endovascular treatment of, 1935
glomus vagale, 2506f
endovascular treatment of, 1936-1937, 1936f
imaging of, 151, 152f
intracranial, 2499f
jugular, 1662f, 2499f
of larynx, 1508
neck masses due to, 1641
Paragangliomas (PGLs) *(Continued)*
nomenclature for, 1657
pathology of, 1657, 1658f
of skull base, 171, 174f, 1929, 1930f
stereotactic radiation therapy for, 2565, 2565t
of temporal bone, 2505-2506
diagnostic evaluation of, 2505, 2506f-2507f
preoperative evaluation of, 2491f
radiotherapy for, 2506
surgical approach to, 2505-2506, 2507f
symptoms of, 2505
vagal, 1661-1662
clinical presentation and diagnosis of, 1662
management of, 1662-1663
Paraglottic space (PGS)
anatomy of, 1484-1485, 1484f-1485f
radiographic, 1471f, 1473
surgical, 1542, 1543f-1544f
laryngeal cancer of
anatomic basis for, 1484-1485, 1484f-1485f
imaging of, 1474
Parainfluenza virus, pharyngitis due to, 196
Parakeratinizing odontogenic keratocyst, 1262, 1267-1268
in basal cell nevus syndrome, 1268
microscopic features of, 1268
radiographic features of, 1267-1268, 1268f
treatment of, 1268
Parakeratosis, of larynx, 1486
Palaryngeal space, radiographic anatomy of, 1471f, 1473
Paralytic agents, intraoperative, 111-112
Paramedian forehead flaps, for nasal defects, 348, 352f-353f
Paramedian mandibulotomy, 1311
Paramedian pontine reticular formation (PPRF), in velocity-to-position integration, 2296, 2297f
Paranasal sinus(es)
anatomy of
normal, 167, 664-668, 665f
agger nasi cell in, 665-666, 665f-666f
anterior ostiomeatal channels in, 666f
anterior ostiomeatal unit in, 664, 665f
basal lamella and sinus lateralis in, 665f, 667f
ethmoid bulla in, 666-667, 667f
ethmoid sinuses in, 664, 667
frontal recess in, 665, 665f-667f
frontal sinuses in, 664-665, 665f
hiatus semilunaris in, 667, 667f
inferior meatus in, 664
inferior turbinate in, 665f
infundibulum in, 665f, 666-667
maxillary sinuses in, 664, 665f
middle meatus in, 664-665, 665f-667f
middle turbinate in, 667
ostiomeatal channels in, 664
ostiomeatal unit in, 664-670
posterior ostiomeatal unit in, 664
primary ostium in, 665, 665f
retrobullar (suprabullar) recess in, 667
sphenoethmoidal recess in, 667, 668f
sphenoid sinus in, 664, 665f, 667-668, 668f
superior meatus in, 664-665
uncinate process in, 666-667, 666f-667f
variations in, 741
surgical, 739-741, 1124f
anatomic variations in, 741
anterior skull base in, 741
ethmoid complex in, 740
frontal sinus in, 740-741
maxillary sinus in, 740
middle turbinate in, 739-740
ostiomeatal complex in, 739, 740f
sphenoid sinus in, 740, 740f
in transnasal endoscopic-assisted anterior skull base surgery, 2473-2474, 2473f
Paranasal sinus(es) *(Continued)*
bony outlines of, 672, 672f
effects of radiotherapy on, 2626t
growth and development of, 2619-2620, 2623f
imaging of, 167-169, 662-2
with anatomic variations and congenital abnormalities, 668-670
aerated crista galli as, 670
asymmetry in ethmoid roof height as, 670
cephalocele as, 670, 671f
of concha bullosa, 668, 669f
extensive pneumatization of sphenoid sinus as, 669, 671f
giant ethmoid bullosa as, 669
Haller or infraorbital cells as, 668-669, 670f
medial deviation or dehiscence of lamina papyracea as, 669
nasal septal deviation as, 668, 669f
Onodi or sphenoethmoidal cells as, 669
paradoxic middle turbinate as, 668, 669f
of uncinate process, 668, 670f
with complications of inflammatory disease, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
with congenital and developmental anomalies, 167
conventional radiography for, 130, 662
Caldwell view in, 662, 663f
Waters view in, 662, 663f
CT for, 140-142, 141f, 662-663
radiation exposure with, 663
technique of, 662-663, 664f
after functional endoscopic sinus surgery, 677-680
expected findings in, 677-679, 679f
operative complications in, 679-680, 680f
for image-guided surgery, 680-681, 743-744, 745f
registration in, 680-681
tracking systems in, 681
with inflammatory disease, 167-168, 168f, 672-675
acute rhinosinusitis as, 672-673, 673f
allergic rhinosinusitis as, 675
chronic rhinosinusitis as, 673-674, 674f-675f
fungal rhinosinusitis as, 674-675, 676f
granulomatous rhinosinusitis as, 675
interpretation of, 670-672
evaluation of bony outlines in, 672, 672f
evaluation of critical relationships for surgical planning in, 671-672, 672f
identification and description of important structures in, 671
MRI for, 143, 664, 664f
nasal cycle in, 664, 664f
with normal anatomy, 664-668, 665f
agger nasi cell in, 665-666, 665f-666f
anterior ostiomeatal channels in, 666f
anterior ostiomeatal unit in, 664, 665f
basal lamella and sinus lateralis in, 665f, 667f
ethmoid bulla in, 666-667, 667f
ethmoid sinuses in, 664, 667
frontal recess in, 665, 665f-667f
frontal sinuses in, 664-665, 665f
hiatus semilunaris in, 667, 667f
inferior meatus in, 664
inferior turbinate in, 665f
infundibulum in, 665f, 666-667
maxillary sinuses in, 664, 665f
middle meatus in, 664-665, 665f-667f
middle turbinate in, 667
ostiomeatal channels in, 664
posterior ostiomeatal unit in, 664

Paranasal sinus(es) *(Continued)*
primary ostium in, 665, 665f
retrobullar (suprabullar) recess in, 667
sphenoethmoidal recess in, 667, 668f
sphenoid sinus in, 664, 665f, 667-668, 668f
superior meatus in, 664-665
uncinate process in, 666-667, 666f-667f
with sinonasal small cell tumor *vs.* sphenoid pyomucocele, 168-169, 169f
intensity-modulated radiotherapy of, 1045-1046, 1045f
and optic nerve, 672, 672f
physiology of, 664-670
Paranasal sinus tumor(s), 1121-1132
anatomic basis of, 1122-1123
ethmoid sinus in, 1123
frontal sinus in, 1123
lymphatics in, 1123
maxillary antrum in, 1122-1123
sphenoid sinus in, 1123
benign, 717-727, 718t
diagnosis of, 717-718
fibrous dysplasia as, 718t, 725-726, 726f
glioma as, 718t
hamartoma as, 718t
inverted papilloma (Schneiderian papilloma, inverted type) as, 718-720
endoscopic appearance of, 718-719, 719f
epidemiology of, 718
with frontal sinus involvement, 720, 720f
histologic appearance of, 718
human papillomavirus and, 718
imaging of, 719, 719f
postoperative surveillance for, 720
recurrence of, 720
sites for, 718
and squamous cell carcinoma, 718
surgical approach for, 718t, 719-720, 720f, 763
juvenile angiofibroma as, 721-722
classification systems for, 722
endoscopic appearance of, 721, 721f
imaging of, 721
natural history of, 721
origin of, 721, 721f
postoperative surveillance for, 722
preoperative embolization for, 721-722
surgical approach for, 718t, 722, 722f-723f, 763
lobular capillary hemangioma as, 718t, 725, 725f
ossifying fibroma as, 725-726
osteoma as, 723-725
classification of, 723
endoscopic appearance of, 723
epidemiology of, 723
ethmoid, 724f
frontal, 724-725, 724f
imaging of, 723-725, 723f-724f
ivory ("eburnated"), 723, 723f-724f
mature (spongiosum), 723
microscopic appearance of, 723
mixed, 723, 724f
pathogenesis of, 723
postoperative surveillance for, 725
spongiosum variant of, 724f
surgical approach for, 718t, 724-725
symptoms of, 723
pleomorphic adenoma as, 718t
schwannoma as, 726-727, 726f
surgical approach for, 718, 718t, 763
cervical lymph node metastasis of, 1130
in children, 1132
complications of, 1131
diagnostic assessment of, 1124
biopsy in, 1124
imaging studies for, 1124
Paranasal sinus tumor(s) *(Continued)*
angiography, 1124
CT, 1124
MRI, 1124
PET, 1124
intermediate, 1127
inverted papillomas as, 1127
malignant, 1127-1128
adenocarcinoma as, 1131
adenoid cystic carcinoma as, 1131
algorithm for evaluation and management of, 1122f
epidemiology and survival with, 1121-1122, 1123t
epithelial
staging of, 1127-1128, 1128f, 1129b
ethmoid, sphenoid, and frontal, 1130
staging of, 1129b
hematopoietic and lymphoid, 1131
involvement of cervical lymph nodes in, 1130
lymphoma as, 1131, 1680
therapy and prognosis for, 1680
maxillary, 1128-1130
chemoradiotherapy for, 1130
combined irradiation and surgery for, 1128
inoperable, 1130
radiotherapy for, 1128-1130
staging of, 1129b
surgery alone for, 1128
melanoma as, 1131-1132
sarcomas as, 1131
staging of, 1127-1128, 1128f, 1129b
therapeutic decision-making for, 1131
physical findings with, 1123-1124
surgical options for, 1124-1127
anatomic reference for, 1124f
classical "open" procedures as, 1124-1127
craniofacial frontoethmoidectomy as, 1126, 1126f
extended craniofacial resection as, 1126-1127, 1127f
external ethmoidectomy as, 1124-1125, 1125f
inferior medial maxillectomy as, 1125, 1125f
medial maxillectomy as, 1125, 1125f
radical maxillectomy as, 1125-1126, 1125f
minimally invasive approaches as, 1127
symptoms of, 1123
Paranasal sinus walls, evaluation of, 672, 672f
Paranasal Sinuses Simulator, 49
Paraneoplastic cerebellar degeneration (PCD), 2357
Paraneoplastic pemphigus, 1231-1232
Paraneoplastic syndromes
sensorineural hearing loss due to, 2124
vertigo due to, 2202
Parapharyngeal space (PPS)
anatomy of, 202
lymph nodes in, 1422f
imaging of, 131, 146f
Parapharyngeal space (PPS) abscess, in children, 2788-2789
Parapharyngeal space (PPS) tumor(s), 2510, 2512f
benign, 1663-1664, 1665f
of salivary glands, 1174-1176
mandibulectomy approach for, 1176, 1176f
transcervical approach for, 1174-1176, 1175f
malignant, 1664-1666
of salivary glands, 1195-1196, 1196f
of salivary glands
benign, 1174-1176
mandibulectomy approach for, 1176, 1176f
transcervical approach for, 1174-1176, 1175f
malignant, 1195-1196, 1196f
Parasellar approach, for transnasal endoscopic-assisted anterior skull base surgery, 2479, 2480f
Parasomnias, 264-265, 265b
Parasympathetic control, of salivary gland secretion, 1136
Parathyroid adenoma, 1774-1775, 1778-1779
atypical, 1778-1779
double, 1785f, 1794, 1794f, 1798
ectopic
within carotid sheath, 1800f
intrathymic, 1800f
intrathyroidal, 1789f
mediastinal, 1787f, 1802f
missed, 1798
re-exploration for, 1799-1800, 1800f
superior, 1786f, 1800f
imaging of, 162-163, 165f
CT for, 1786-1787
CT-MIBI fusion, 1785-1786, 1786f-1788f
MRI for, 1787-1788, 1789f, 1802f
scintigraphy for, 138, 139f
sestamibi–technetium 99m scintigraphy for, 1785, 1785f, 1802f
technetium 99m sestamibi with SPECT for, 1785
technetium 99m thallium 201, 162-163, 165f
ultrasonography for, 1644-1645, 1650f-1652f, 1786, 1789f
inferior, 1802f
intraoperative photograph of, 1788f
large clear cell, 1778
lipoadenoma as, 1778
localization of
cervical exploration for, 1792-1793
CT for, 1786-1787
CT-MIBI fusion imaging of, 1785-1786, 1786f-1788f
endoscopic exploration for, 1793-1794
gamma radiation detection device for, 1802, 1803f
intraoperative, 1789
mediastinal exploration for, 1801-1802, 1802f
minimally invasive techniques for, 1793
missed, 1798
MRI for, 1787-1788, 1789f, 1802f
with multiple-gland disease, 1794-1795
parathyroid arteriography for, 1788
re-exploration for, 1799-1800, 1800f
scintigraphy for, 138, 139f
selective venous sampling for PTH for, 1788-1789
sestamibi–technetium 99m scintigraphy for, 1785, 1785f, 1802f
with sporadic hyperplasia, 1794-1795, 1794f
technetium 99m sestamibi with SPECT for, 1785
technetium 99m thallium 201 imaging for, 1784-1785
ultrasonography for, 1644-1645, 1650f-1652f, 1786, 1789f
ultrasound-guided fine needle aspiration for, 1789
unsuccessful, 1801, 1801f-1802f
oncocytic, 1778
superior
ectopic, 1786f
pseudo-intrathyroidal, 1800f
undescended, 1789f
water clear cell, 1778
Parathyroid adenomatosis 1 oncogene *(PRAD1),* in hyperparathyroidism, 1774-1775, 1775f
Parathyroid arteriography, 1788
Parathyroid carcinoma, 1779, 1802-1804, 1803f
Parathyroid disorder(s), 1773-1805
historical background of, 1774
hyperparathyroidism as (*See* Hyperparathyroidism)
oral manifestations of, 1251

Parathyroid exploration
causes of failed, 1798
endoscopic, 1793-1794
indications for, 1789-1790
minimally invasive techniques for, 1793
for multiple-gland disease, 1794-1795
repeat, 1798-1800
causes of failed exploration with, 1798
operative risk in, 1798-1799
operative strategy for, 1799-1800, 1799f-1800f
preoperative assessment for, 1798
for single-gland disease, 1792-1794
surgical strategy and approach to, 1792
technique for, 1790-1792, 1791f
Parathyroid gland(s)
anatomy of, normal, 1777
vascular, 1778
ectopic
CT-MIBI fusion imaging of, 1786f-1787f
intraoperative photograph of, 1788f
intrathyroidal, 1777, 1788f
mediastinal, 1802, 1803f
technetium-99 sestamibi imaging of, 1774
ultrasound of, 1645
embryology of, 1780, 1780f, 2585f
enlargement of
multiple glandular, 1779
single glandular, 1778-1779
histopathology of, 1778
imaging of, 162-163, 165f
CT for, 140
MRI for, 143
ultrasound imaging for, 1644-1645, 1650f-1652f
inferior, 1777
location of, 1777
morphologic characteristics of, 1777-1778
preoperative evaluation of, 104
superior, 1777
supernumerary, 1777
CT-MIBI fusion imaging of, 1787f
mediastinal, 1802, 1803f
in MEN-I, 1795-1796
during thyroid surgery, 1752, 1765f, 1766
Parathyroid gland hyperplasia, 1779
chief cell, 1779
sporadic, 1794-1795, 1794f
ultrasound of, 1645
water clear cell, 1779
Parathyroid hormone (PTH)
in calcium homeostasis, 1775-1777
functions of, 1775
historical background of, 1774
immunometric "sandwich" assays of, 1776-1777
intraoperative levels of, 1792-1793, 1800-1801
metabolism of, 1776
secretion and regulation of, 1775-1777
selective venous sampling for, 1788-1789
Parathyroid hormone (*PTH*) gene, in hyperparathyroidism, 1774-1775, 1775f
Parathyroid hyperplasia, 1779
chief cell, 1779
sporadic, 1794-1795, 1794f
ultrasound of, 1645
water clear cell, 1779
Parathyroid neoplasm(s), etiology and pathogenesis of, 1775, 1776f
Parathyroid surgery, 1789-1804
gamma radiation detection device in, 1802, 1803f
indications for, 1789-1790
intraoperative PTH levels with, 1792-1793, 1800-1801
for multiple-gland disease, 1794-1795
due to sporadic hyperplasia, 1794-1795, 1794f
due to true double adenoma, 1794, 1794f
parathyroidectomy as, 1790-1792
anesthesia and preparation for, 1790
closure of incision in, 1792
Parathyroid surgery *(Continued)*
exploration of neck in, 1790-1792, 1791f
postoperative care after, 1792
for single-gland disease, 1792-1794
directed unilateral cervical exploration as, 1792-1793
endoscopic parathyroid exploration in, 1793-1794
minimally invasive techniques for, 1793
strategy and approach to, 1792
Parathyroidectomy, 1790-1792
anesthesia and preparation for, 1790
with autotransplantation
for MEN-I, 1795
for renal failure–induced hyperparathyroidism, 1797-1798
closure of incision in, 1792
exploration of neck in, 1790-1792, 1791f
postoperative care after, 1792
radiation-guided, 1793
subtotal, for renal failure–induced hyperparathyroidism, 1797-1798
Parent(s), of child as patient, 2573
Parental presence, during anesthesia induction, in children, 2590
Parietal bone, 320f
in surgical anatomy of lateral skull base, 2434
Parietal foramina, 2641t
with cleidocranial dysplasia, 2641t
Parietal incisura, 2010f
Parietomastoid suture, in surgical anatomy of lateral skull base, 2435, 2435f
Parkinsonism, preoperative evaluation of, 106
Parkinson's disease
laryngeal hypofunction due to, 842-843
olfactory dysfunction in, 635
oral manifestations of, 1255
Parkinson's-plus syndromes, laryngeal hypofunction due to, 843
Parosmia, 633, 636
Parotid cysts, AIDS-related, 1146, 1146f
Parotid duct, trauma to, 312-313, 314f
Parotid gland(s)
accessory, 2850
anatomy of, 1133-1134, 1359f
in children, 2850-2853
radiographic, 1143-1144, 1144f
contributions to saliva of, 1134t
hemangioma of, 2859-2860, 2860f
neuronal control of, 1136
physical examination of, 95
salivary flow rate and composition of saliva in, 1138t
sialolithiasis of, 1155-1156
in surgical anatomy of lateral skull base, 2439f-2440f
trauma to, 312, 313f
in children, 2863
Parotid gland abscess, 1152f-1153f
Parotid gland neoplasm(s)
acinic cell tumor as, 151f
benign
basal cell adenomas as, 1170
clinical features of, 1164-1165, 1165f-1166f
oncocytic papillary cystadenoma as, 1171
oncocytoma as, 1171
pleomorphic adenoma as, 1169
imaging of, 150, 150f
malignant, physical examination of, 1179
Parotid injury, due to rhytidectomy, 426-427
Parotid lesions, in HIV, 217-218, 218f
Parotid lipoma, 1166, 1167f
Parotid lymph node(s), 2582
extraglandular, 1360f
Parotid mass, ultrasonography of, 1654f
Parotid space (PS)
anatomy of, 203
imaging of, 149-150, 150f-151f
Parotid surgery, facial nerve monitoring during, 2549
Parotidectomy
for benign neoplasms, 1172-1174, 1173f
complication(s) of, 1176-1177
facial nerve paresis or paralysis as, 1176-1177
gustatory sweating ("Frey's syndrome") as, 1177
salivary fistula as, 1177
sensory abnormalities as, 1177
facial nerve monitoring during, 2549
fistula after, 1728
for malignant neoplasms, 1194-1196
elevation of skin flap in, 1195
external carotid artery in, 1195-1196
facial nerve in
anatomy of, 1194, 1194f
involvement of, 1196
main trunk of, 1195, 1195f
marginal mandibular branch of, 1195, 1195f
greater auricular nerve in, 1195
modified Blair incision for, 1195, 1195f
partial deep, 1194-1196, 1196f
retromandibular (posterior facial) vein in, 1195-1196, 1195f
superficial, 1194-1195
total, 1194-1196
Parotitis
chronic, 1154, 1155f
vs. myofascial pain dysfunction syndrome, 1284t
recurrent
of childhood, 1153-1154
juvenile, 2858
suppurative
acute, 1151-1153
clinical manifestations of, 1152, 1152f
complications of, 1153, 1154f
defined, 1151
differential diagnosis of, 1152
epidemiology of, 1151
laboratory evaluation of, 1152
pathogenesis of, 1151-1152, 1152f
sialolithiasis and, 1151-1152, 1155, 1155f
treatment of, 1152-1153, 1153f
neonatal, 1153
viral, 1156-1158
in children
due to Epstein-Barr virus, 2855
due to HIV, 2856
due to mumps, 2855
HIV-associated, 1157-1158, 1157f
in children, 2856
due to mumps, 1156-1157
in children, 2855
Paroxetine, for neuropathic pain, 245
Paroxysmal torticollis, and migraine, 2351
Pars flaccida
anatomy of, 1824, 1825f
of tympanic membrane, 97, 98f
Pars flaccida cholesteatoma, 174f
Pars tensa, 1825f
Partial cricoidectomy, for chronic aspiration, 928
Partial dynamic-range compression, for hearing aids, 2268
Partial laryngectomy, for glottic cancer, 1496
in advanced stage, 1497
Partial ossicular replacement prosthesis (PORP), 2006
with absent lenticular process of incus, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
Partial-transfixion incisions, for nasal tip projection, 535-536, 536f

Particle beams, in radiotherapy, 1034-1035, 1035f
Particulate radiation, 1031
Parulis, 179
Pascal (Pa), 1839
Passagio, 851
Passavant's ridge, 2676
Past pointing, 2316-2317
Patch method, for tonsillar and pharyngeal wall reconstruction, 1386, 1387f
Paterson-Brown-Kelly syndrome, and postcricoid carcinoma, 1425-1426
Paterson-Kelly syndrome, 967
Patient education
  on difficult airway, 117-119
  for nonallergic rhinitis, 699-700
Patient history, 94, 94b
Patient Outcomes of Surgery–Head/Neck (POS-Head/Neck), 57
Patient Questionnaire of Vocal Performance (VPQ), 826, 826t
Patient scales, for voice evaluation, 825-826, 826t, 834
  Patient Questionnaire of Vocal Performance as, 826, 826t
  Reflux Symptom Index as, 826, 826t
  Voice Activity and Participation Profile as, 826, 826t
  Voice Handicap Index as, 826, 826t, 834
  Voice Outcome Survey as, 826, 826t
  Voice Symptom Scale as, 826, 826t
  Voice-Related Quality of Life scale as, 826, 826t, 834
Patient verification, for radiotherapy, 1035
Patient-controlled analgesia (PCA), 240, 241t
  for oral cancer, 1316
  for postoperative pain in children, 2594
PAX2 (paired box gene 2), in deafness, 2051t-2058t
PAX3 (paired box gene 3), in deafness, 2051t-2058t, 2095
PAX8/PPARγγ1 rearrangement, in thyroid carcinoma, 1753
"Pay for performance," 78
PBGH (Pacific Business Group on Health), 84t-87t, 87
PBK (Phonetically Balanced Kindergarten) Test, for cochlear implant, 2225
PBL (plasmablastic lymphoma), 216
PBP (progressive bulbar palsy), laryngeal disorders due to, 839-840, 842
PBP (pseudobulbar palsy), laryngeal disorders due to, 839-840, 842
PC (posterior cervical) space, 158, 159f-160f, 162f
PCA. *See* Posterior cricoarytenoid (PCA).
PCA (patient-controlled analgesia), 240, 241t
  for oral cancer, 1316
  for postoperative pain in children, 2594
P-cad, in oral cancer, 1301
PC-BPPV. *See* Posterior canal benign paroxysmal positional vertigo (PC-BPPV).
PCD (paraneoplastic cerebellar degeneration), 2357
PCDH15 (protocadherin-15), in tip links, 2074
PCDH15 (protocadherin-15) gene, in deafness, 2051t-2058t, 2074
PCNA (proliferating cell nuclear antigen), in salivary gland neoplasms, 1194
PCPI (Physician Consortium for Performance Improvement), 82-87, 84t-87t
PCR (polymerase chain reaction), 8-9
PCV7 (pneumococcal conjugate vaccine)
  with cochlear implants, 2237, 2237b
  to prevent otitis media, 2763, 2768
    maternal immunization with, 2768-2769
PDGF (platelet-derived growth factor), in wound healing, 1076
PDL (periodontal ligament)
  in interdental discrimination, 1207
  tactile sensitivity of, 1201-1202, 1202f
PDL (pulsed dye laser). *See* Pulsed dye laser (PDL).
PDLA (poly D-lactic acid), in resorbable plating system, for pediatric facial fractures, 2700, 2700t
PDS (polydioxanone), in resorbable plating system, for pediatric facial fractures, 2700, 2700t
PDS (pendrin) gene, in deafness, 2051t-2058t, 2083
PDT. *See* Photodynamic therapy (PDT).
PE (pharyngoesophageal) segment, in alaryngeal speech
  physiology of, 1596
  prevention of hypertonicity of, 1599-1600, 1599f
Peak clipping, with hearing aids, 2268
Peak inspiratory flowmeter, nasal, 643
Pectoralis major flap
  for buccal carcinoma, 1309f
  for hypopharyngeal and esophageal reconstruction, 1452
  for hypopharyngeal cancer, 1431, 1431f
  for oral cancer, 1316
  for oropharyngeal reconstruction, 1377, 1377f
    of tongue base, 1388-1389
    of tonsils and pharyngeal wall, 1385, 1385f
Pediatric diseases, outcome scales for, 56t, 57
Pediatric patients. *See* Children.
Pediatric Quality of Life Inventory (PedQL), 57
Pediatric Voice Handicap Index (pVHI), 2876
Pediatric Voice Outcomes Survey (PVOS), 57, 2876
Pediatric Voice-Related Quality-of-Life survey (PVQOL), 57, 2876
Pedicle flaps. *See also* Free tissue transfer.
  salvage of, 1075
Pedigree(s), 2088, 2088f
  of dominantly inherited trait, 6, 6f, 2088f
  of mitochondrial disorder, 8, 8f, 2086
  of recessively inherited trait, 2086
  variable expression and nonpenetrance in, 7, 7f
  of X-linked recessive disorder, 7, 7f, 2086
PedQL (Pediatric Quality of Life Inventory), 57
PEH (pseudoepitheliomatous hyperplasia), of larynx, 1493
Pejvakin *(PJVK)* gene, in deafness, 2051t-2058t
Pellagra, oral manifestations of, 1254
Pellets, shotgun, 1626, 1628t
Pemberton's sign, in thyroid disease, 1736, 1754-1756
Pemphigoid
  bullous, esophageal manifestations of, 980
  esophageal manifestations of, 980
    imaging of, 1406
  laryngeal involvement in, 887
  mucous membrane (cicatricial)
    esophageal manifestations of, 980
    nasal manifestations of, 660
    ocular scarring (symblepharon) due to, 1233-1234, 1234f
    oral, 1233-1235, 1254
      clinical differential diagnosis of, 1234, 1234t
      clinical features of, 1233-1234, 1233f-1234f
      defined, 1233
      etiology and pathogenesis of, 1233
      histopathologic features of, 1234-1235, 1234f
      treatment of, 1235
  nasal manifestations of, 660
Pemphigus
  paraneoplastic, 1231-1232
  vulgaris
    esophageal manifestations of, 980
    laryngeal and tracheal manifestations of, 887, 887f, 891-892, 892f
    nasal manifestations of, 660
    oral, 1231-1233, 1254
      clinical differential diagnosis of, 1232
      clinical presentation of, 1232, 1232f
      defined, 1231-1232
Pemphigus *(Continued)*
      etiology/pathogenesis of, 1232
      histopathologic features of, 1232-1233, 1232f-1233f
      treatment of, 1233
Pendred syndrome (PS)
  cochlear implant for, 2220
  deafness in, 2051t-2058t, 2083, 2094t, 2096
  genetic testing for, 2098
    in infants, 2723
  inner ear anomalies in, 2735
Pendrin, in thyroid hormone synthesis, 1737
Pendrin *(PDS)* gene, in deafness, 2051t-2058t, 2083
Penetrance, 7, 7f
Penetrating auditory brainstem implant (PABI), 2262, 2262f
Penetrating auditory midbrain implant, 2262-2263, 2263f
Penetrating facial nerve injuries, 2399
Penetrating neck trauma
  airway management for, 1629
  algorithmic approach to, 1631f
  angiography for, 1630-1632, 1631t, 1632f-1633f
  barium swallow for, 1631t, 1633
  classification of, 1628-1629, 1630f
  cranial nerve injury due to, 1629
  diagnostic evaluation of, 1630
  digestive tract evaluation for, 1633-1634, 1634f-1635f
  direct laryngoscopy and bronchoscopy for, 1631t, 1634
  esophagoscopy for, 1631t, 1633-1634, 1634f
  imaging of, 1629-1630
  initial management of, 1629
  management of laryngotracheal injury due to, 1634
  mandatory *vs.* selective exploration of, 1627-1630, 1629t, 1630f, 1631t
  mortality from, 1627-1628, 1629t
  physical properties of objects causing, 1625-1627
    with handgun, 1625
    for knife and stab injuries, 1627
    with rifle, 1626, 1626f-1627f
    with shotguns, 1626-1627, 1628t
  signs and symptoms of, 1626b
  vascular injury due to, 1630-1632, 1631t, 1632f-1633f
    management of, 1632-1633, 1633f-1634f
Penicillin
  adverse reactions to, 102
  for otosyphilis, 2341-2342
  for streptococcal pharyngitis, 2787
Pentoxifylline, and skin flap viability, 1073-1074
PEP (postexposure prophylaxis), for HIV infection, 212, 212t
Pepsin
  in GERD, 896
  in reflux laryngitis, 886, 886f
Peptic esophagitis, 1406
Peptic strictures, 1403, 1404f
Peptostreptococcus spp, acute exacerbation of chronic rhinosinusitis due to, 707
PER (persistent allergic rhinitis), 618
Percentile, 64t
Perceptual evaluation, of voice, 826-831
  auditory, 826-831
    CAPE-V for, 826
    GRBAS for, 826, 827t
    other aspects of, 826-827
    for professional voice, 850
  tactile, 827-831, 828f
  visual, 827
Perchlorate, for hyperthyroidism, 1739t
Percutaneous cricothyrotomy, 114t, 128
Percutaneous injection, for vocal fold medialization, 906, 906f-907f

Perennial allergic rhinitis (PAR), 617-618
and pediatric chronic sinusitis, 2778
Perennial nonallergic rhinitis, 695
Perennial rhinitis, 619b, 695
nonallergic, noninfectious, 695
Performance cancellation, professional voice disorders requiring, 854, 854b
Performance measurement, 76-90
aggregate demand for, 77
anatomy of performance measures in, 82, 83f
definition of quality for, 76-77
engaging in development of, 77-78
implementation of
barriers to, 89
pathway for, 88f
standardization and, 87-89
medical professionalism and, 78-82
board certification and maintenance of certification in, 79-80, 80b-81b
Institute of Medicine in, 81-82
physician education in, 79, 79t
state medical boards and maintenance of licensure in, 80-81
motivation for, 76
process of building coherent system of, 77-78
quality-based or value-based purchasing in, 78
stakeholders in, 79-89, 84t-87t
surgeon's role in, 89
unifying response to demand for, 77-78
Performance Status Scale, 56
Performers, voice disorders in. *See* Professional voice disorders.
Perfusion washout, for flap salvage, 1075
Perfusion zones, 1064-1065, 1065f
Periapical cyst, 1262-1263
lateral, 1263
microscopic features of, 1262-1263, 1262f
radiographic features of, 1262, 1262f
treatment of, 1263, 1263f
Pericardial patch, for tracheal stenosis, 2930, 2931f
Perichondritis
of external ear, 1946, 1948
after otoplasty, 479
Perichondrium, anatomy of, 1944
Pericoronitis, *vs.* myofascial pain dysfunction syndrome, 1284t
Pericranial flap, for cochlear implant, 2238
Periesophageal nodes, anatomy of, 1422f
Perigeniculate region, vulnerability to injury of, 1826f
Perilymph, 1832, 1840
in auditory physiology, 1841f-1842f
Perilymph fistula, 2342-2343
categories of, 2342
due to chronic otitis media, 2342-2343
clinical presentation of, 2342
congenital, 2737-2738, 2737f
imaging of, 2342, 2342f
repair of, 2361-2362
sensorineural hearing loss due to, 2122, 2199
fluctuating, 2199
sudden, 2128
due to small fenestra stapedotomy, 2034
due to temporal bone fracture, 2039
due to trauma, 2342
Perilymph gusher
in evaluation for cochlear implant, 2221-2222
during small fenestra stapedotomy, 2034
Perilymphatic duct, 1853f
Perilymphatic fistula. *See* Perilymph fistula.
Perilymphatic fluid, 1832
Perilymphatic-endolymphatic barrier, 2081, 2082f
Perineurial disruption, 2384-2385
Period, of sound waves, 1838-1839, 1839f
Periodic limb movement disorder (PLMD), 262t, 265
Periodicity, laryngeal videostroboscopy of, 821, 848, 848t
Periodontal cyst, lateral, 1265-1266
microscopic features of, 1265-1266, 1265f
radiographic features of, 1265
treatment of, 1266
Periodontal disease
alcoholism and, 1255
bacterial infections and, 1252
diabetes mellitus and, 1251
heart disease and, 1248
in HIV, 227
during pregnancy, 1256
and stroke, 1250
Periodontal ligament (PDL)
in interdental discrimination, 1207
tactile sensitivity of, 1201-1202, 1202f
Periorbita, 439
Periorbital area, aesthetic considerations and ideals in, 444-447
for brow position, 445, 445f
for eyelids, 445-447, 446f
and upper eyelid ptosis, 446-447, 447f
for midface, 447
Periotic tissue, 1852
Periparotid node, 1298f
Peripheral myelin protein 22 *(PMP22)* gene, in deafness, 2051t-2058t, 2081
Peripheral nerve disorders, chronic aspiration due to, 926b
Peripheral nerve injury, histopathologic classification of, 2384-2385, 2384f
Peripheral nerve sheath tumor, malignant, of neck, 1670-1671
Peripheral nerves neoplasms, of neck, 1663
neurofibromas as, 1663, 1664f
schwannomas as, 1663, 1663f
Peripheral neuropathy, HIV-associated, 223
Peripheral primitive neuroectodermal tumor (PPNET), 2845
Peripheral sensitivity, in gustatory physiology, 1210-1212
Peripheral vestibular apparatus
autonomic supply of, 1854
efferent innervation of, 1854, 1855f
Peripheral vestibular disorder(s), 2328-2345
benign paroxysmal positional vertigo as, 2330-2332
diagnosis of, 2330-2331
findings on examination in, 2330-2331, 2331f
history in, 2330
test results in, 2331
etiology of, 2330
incidence of, 2330
mechanism of, 2330-2332
treatment of
with repositioning, 2331-2332, 2332f
surgical, 2332, 2360-2361, 2360f-2361f
bilateral vestibular hypofunction as, 2344
central *vs.,* 2346, 2347t
clinical relevance of, 2329
Cogan's syndrome as, 2341
compensation for, 2373-2374
dynamic, 2373-2376
static, 2373-2374
enlarged vestibular aqueduct as, 2344, 2344f
epidemiology of, 2329
familial vestibulopathy as, 2343-2344
historical background of, 2329-2330
Meniere's disease as, 2333-2339
diagnosis of, 2335-2337
AAO-HNS criteria for, 2335, 2335t
clinical presentation in, 2335, 2336t
dehydrating agents in, 2337
electrocochleography in, 2337
electronystagmography in, 2337
Peripheral vestibular disorder(s) *(Continued)*
hearing loss and tinnitus in, 2337
heat thrust testing in, 2337
history in, 2335-2337
vestibular evoked myopotentials in, 2337
etiology of, 2334-2335
historical background of, 2333
incidence of, 2333
pathogenesis of, 2333-2334, 2334f
severity of, 2335, 2336t
treatment of, 2337-2339
dietary modification and diuretics in, 2337
endolymphatic sac surgery for, 2126, 2339, 2363-2364, 2364f
intratympanic injection for, 2338-2339, 2338f
labyrinthectomy for, 2339
local overpressure therapy for, 2338
nerve section for, 2339
symptomatic, 2338
vasodilators in, 2337-2338
otosyphilis as, 2341-2342
perilymph fistulas as, 2342-2343, 2342f
superior canal dehiscence syndrome as, 2339-2341, 2339f-2340f
due to trauma, 2343
baro-, 2343
nonpenetrating, 2343
blast, 2343
labyrinthine concussion as, 2343
penetrating, 2343
vestibular neuritis as, 2332-2333
Peripheral vestibular physiology, 2328-2329
Periradicular cyst, 1262-1263
microscopic features of, 1262-1263, 1262f
radiographic features of, 1262, 1262f
treatment of, 1263, 1263f
Peristalsis
esophageal, 954, 955f
diminished, 1399-1400, 1400f-1401f
during pharyngeal swallow, 1216f
Peritoneal dialysis, oral sequelae of, 1255
Peritonsillar abscess, 1407, 1407f
in children, 2788, 2789f
Peritonsillar infections, in children, 2788, 2789f
Peritonsillar space
anatomy of, 203
infections of, 206-207
Permanent threshold shift (PTS), 2121, 2141
Peroxisome proliferator-activated receptor (PPAR), for chemoprevention of oral cancer, 1315
Persistent allergic rhinitis (PER), 618
Personal FM system, 2271
Personal listening devices
in noise-induced hearing loss, 2150-2151
for tinnitus, 2134
Personal noise dosimeter, 2140-2141
Pertechnetate scanning. *See* Technetium-99m (^{99m}Tc) scanning.
PES. *See* Preepiglottic space (PES).
Pes anserinus, 2418-2419, 2419f
PET. *See* Positron emission tomography (PET).
Petroclival fissure, in surgical anatomy of anterior cranial base, 2474
Petroclival sutures, in surgical anatomy of lateral skull base, 2436
Petro-occipital sulcus
anatomy of, 1823f
in surgical anatomy of lateral skull base, 2435f, 2438
Petro-occipital suture, in surgical anatomy of lateral skull base, 2438
Petrosal approach, for posterior fossa neoplasms, 2532t, 2539
advantages and disadvantages of, 2532t, 2539
basic features of, 2539
indications for, 2532t, 2539
technique of, 2539, 2539f

Petrositis, 1975-1977, 1986-1989
anatomic basis for, 1975-1976, 1976f-1977f, 1986-1989
defined, 1986
diagnostic tests for, 1977, 1977f
epidemiology of, 1980t
historical note on, 1975
imaging of, 1986-1987
CT for, 1986-1987, 1988f
MR angiography for, 1989f
MRI for, 1986-1987, 1988f-1989f
management of, 1977
pathogenesis of, 1986
pathology of, 1986-1987
symptoms of, 1976-1977, 1976t, 1987
treatment of, 1987-1989
Petrosphenoid suture, in surgical anatomy of lateral skull base, 2435f
Petrosquamous suture, in surgical anatomy of lateral skull base, 2434, 2436f
Petrotympanic fissure, 1828f, 2010f
Petrotympanic suture, in surgical anatomy of lateral skull base, 2435
Petrotympanic suture line, 1823
Petrous apex
anatomy of, 1822f, 1831, 1975-1976
anterior, 1975-1976, 1976f
carotid artery aneurysms of, 2525, 2527f
and foramen magnum, 1976f
imaging of, 1922-1924, 1924t
with asymmetric pneumatization, 1922-1923, 1924t, 1925f
with cholesteatoma, 1924t
with cholesterol granuloma, 1923, 1924t, 1925f-1926f
with malignant lesions, 1923-1924, 1926f
with mucocele, 1924t
with retained secretions, 1923, 1924t, 1925f
pneumatic, 1976, 1977f
pneumatization of, 1867, 1986
asymmetric, 1922-1923, 1924t, 1925f
vs. neoplasms, 2525, 2526f
via infralabyrinthine cell tract, 1988f
via retrolabyrinthine cell tract, 1988f
via supralabyrinthine cell tract, 1987f
posterior, 1975-1976, 1976f
retained secretions in, 1923, 1924t, 1925f
in surgical anatomy of lateral skull base, 2435f, 2436
transcochlear approach to, 2499-2500, 2500f
Petrous apex access
for lateral cranial base neoplasms, 2508, 2508f
for transnasal endoscopic-assisted anterior skull base surgery, 2481
Petrous apex effusion, 2525
Petrous apex tumor(s), 2524-2526
cephalocele as, 2508
cholesteatoma as, 1924t
drainage of, 2508
cholesterol granuloma as, 2524-2525
differential diagnosis of, 1924t, 2515, 2524t
imaging of, 1923, 1925f-1926f, 2477f, 2526f
chondrosarcoma as, 2528f
chordoma as, 2511f
giant cell tumors as, 2526
malignant, 1923-1924, 1926f
mucocele, mucous retention cysts, and petrous apex effusion as, 1924t, 2524t, 2525, 2526f-2527f
surgical access for
for lateral cranial base neoplasms, 2508, 2508f
for transnasal endoscopic-assisted anterior skull base surgery, 2481
Petrous apicitis, 1975-1977, 1986-1989
anatomic basis for, 1975-1976, 1976f-1977f, 1986-1989
defined, 1986
diagnostic tests for, 1977, 1977f
epidemiology of, 1980t
history of, 1975
imaging of, 1986-1987
CT for, 1986-1987, 1988f
MR angiography for, 1989f
MRI for, 1986-1987, 1988f-1989f
management of, 1977
pathogenesis of, 1986
pathology of, 1986-1987
symptoms of, 1976-1977, 1976t, 1987
treatment of, 1987-1989
Petrous bone, in surgical anatomy of lateral skull base, 2436, 2437f
Petrous bone projection, in surgical anatomy of lateral skull base, 2435f
Petrous fracture, transverse, 174f
Petrous part, of temporal bone, 2010f
anterior surface of, 1822, 1822f
inferior surface of, 1822-1823, 1824f
posterior surface of, 1822, 1823f
Peutz-Jeghers syndrome, oral manifestations of, 1257
PEX7 gene, in Refsum disease, 2096
Peyer's patches, in immune system, 605
Pfeiffer's syndrome, craniofacial anomalies in, 2641t, 2646
PG(s) (prostaglandins)
in acutely raised skin flaps, 1070, 1070f
in bone remodeling, 1973
and skin flap viability, 1073
PGA (polyglycolic acid), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
PGLs. *See* Paragangliomas (PGLs).
PGS. *See* Paraglottic space (PGS).
pH
intracellular, in sour taste, 1209
salivary, 2384
pH monitoring, esophageal
ambulatory 24-hour, 958-960, 959f-960f
Bravo wireless pH capsule for, 961, 961f
for GERD-related laryngeal disease in children, 2945
multichannel intraluminal impedance for, 962
Restech Dx-pH Measurement System for, 962, 962f
pH probe monitoring, for extraesophageal reflux, 900
PHACES syndrome, 290
hemangioma of infancy in, 2824, 2825f
Phagocyte function disorders, 2114
otologic manifestations of, 2114
Phagocytosis
by monocytes and macrophages, 604
by neutrophils, 604
Phalangeal cells, 1832
Phalangeal processes, 1832, 1832f-1833f
Phantosmia, 633, 636, 639
Pharmacologic toxicity, sensorineural hearing loss due to, 2119-2121
sudden, 2128
Pharyngeal arches, 2659-2660, 2661f
in embryology of nose, 2691f
Pharyngeal cancer, 1412-1415
carcinoma as, 1412-1415
of hypopharynx, 1413, 1413f-1414f
with lymphadenopathy, 1414-1415, 1415f
of nasopharynx, 1412-1413, 1413f
of oropharynx, 1413, 1413f
Pharyngeal constrictors, in breathing, 809
Pharyngeal contraction, during pharyngeal swallow, 1217
Pharyngeal defects, classification of, 1450
Pharyngeal dilators, in breathing, 810, 810f
Pharyngeal disorders, chronic aspiration due to, 926b
Pharyngeal diverticula, 1401-1402, 1402f
dysphagia due to, 2951
Pharyngeal flap, for velopharyngeal dysfunction, 2683
Pharyngeal flap surgery, for obstructive sleep apnea, 2609-2610
Pharyngeal fossa, 1359f
Pharyngeal function, in breathing, 809-810, 810f
Pharyngeal imaging, 1393-1420
with benign neoplasms, 1415-1416
retention cyst as, 1416, 1416f
Tornwaldt cyst as, 1416, 1416f
vs. tortuous internal carotid artery, 1416, 1416f
with diverticula, 1401-1402
laryngoceles as, 1402, 1402f
pharyngeal pouches as, 1401-1402, 1402f
Zenker's, 1401, 1402f
with fistulas, 1409-1411
due to perforation, 1410-1411, 1410f
postoperative, 1411, 1411f
with foreign body, 1411, 1412f
with infection/inflammation, 1403-1407
due to abscess, 1407, 1407f
due to epiglottitis, 1406-1407, 1407f
with malignant neoplasms, 1412-1415
carcinoma as, 1412-1415
of hypopharynx, 1413, 1413f-1414f
with lymphadenopathy, 1414-1415, 1415f
of nasopharynx, 1412-1413, 1413f
of oropharynx, 1413, 1413f
with motility disorder(s), 1398-1399
abnormal deglutition as, 1398
cricopharyngeal dysfunction as, 1398-1399, 1400f
post-treatment, 1416-1418
after laryngectomy, 1416, 1417f
after laryngopharyngectomy, 1416-1418, 1418f
for monitoring and surveillance, 1418, 1419f-1420f
after radiotherapy, 1418, 1418f
radiographic anatomy in, 1397, 1398f-1399f
technique(s) for, 1393-1397
conventional radiography as, 1393, 1394f
CT as, 1396
fluoroscopy as, 1393-1394
modified barium swallow as, 1396
MRI as, 1396
oral contrast agents in, 1396
other nuclear medicine as, 1397
PET-CT as, 1396-1397, 1397f
pharyngoesophagram as, 1394, 1394f-1395f
ultrasound as, 1396
Pharyngeal leak, postoperative, 1411, 1411f
Pharyngeal mucosal space (PMS), imaging of, 148-149
with inflammatory lesions, 148, 148f
with non-Hodgkin's lymphoma, 148-149, 149f
normal anatomy on, 146f, 148-149
with squamous cell carcinoma, 148, 149f
with Tornwaldt cyst, 148
Pharyngeal neoplasm(s)
benign, 1415-1416
esophageal hematoma as, 1416
esophageal leiomyoma as, 1415-1416, 1415f
retention cyst as, 1416, 1416f
Tornwaldt cyst as, 1416, 1416f
vs. tortuous internal carotid artery, 1416, 1416f
malignant, 1412-1415
carcinoma as, 1412-1415
of hypopharynx, 1413, 1413f-1414f
with lymphadenopathy, 1414-1415, 1415f
of nasopharynx, 1412-1413, 1413f
of oropharynx, 1413, 1413f

Pharyngeal nerve, 1297f
Pharyngeal obturator prosthesis, 1343, 1344f
Pharyngeal palsy, unilateral, 1398
Pharyngeal pouch(es)
  embryology of, 2583-2585, 2583f-2584f
    first, 2584, 2584f-2585f
    fourth through sixth, 2584f-2585f, 2585
    second, 2584, 2584f-2585f
    third, 2584f-2585f, 2585
  imaging of, 1401-1402, 1402f
Pharyngeal pressure generation, during pharyngeal swallow, 1217
Pharyngeal recess, in surgical anatomy of anterior cranial base, 2474
Pharyngeal reconstruction, after total laryngectomy, 1569-1570, 1570f
Pharyngeal swallow, 1216, 2948
  airway protection during, 1216-1217
  cricopharyngeal (upper esophageal sphincter) opening during, 1217
  delayed triggering of, 1215
  neuromuscular activities in, 1216, 1216f
  pharyngeal pressure generation during, 1217
Pharyngeal tonsils, 1359f, 2784
Pharyngeal tubercle, in surgical anatomy of anterior cranial base, 2474
Pharyngeal wall
  anatomy of, 1359, 1360f
  cancer of
    cervical lymph node metastasis of, 1361t
    clinical presentation of, 1365
    management of, 1370
Pharyngeal wall reconstruction, 1383-1387
  algorithm for, 1388f
  free flaps for, 1386
    with combined lateral and superior defects, 1386, 1387f
    lateral arm and thigh, 1386-1387
    radial forearm, 1386
  healing by second intention for, 1383
  local flaps for, 1384-1385
  primary closure for, 1383-1384
  regional flaps for
    pectoralis major, 1385, 1385f
    platysmal myocutaneous, 1385
    sternocleidomastoid myocutaneous, 1385-1386
    temporalis, 1386
    temporoparietal fascia, 1386
  skin grafting for, 1384
Pharyngectomy, for hypopharyngeal cancer
  partial, 1426-1429
    via anterior transhyoid pharyngotomy, 1427-1429, 1428f
    via lateral pharyngotomy, 1426-1427
    via lateral transthyroid pharyngotomy, 1427, 1428f
    via median labiomandibular glossotomy, 1429
    with total laryngectomy, 1430, 1431f
  total, 1430, 1431f
Pharyngitis, 191-200
  bacterial, 191-196
    due to *Arcanobacterium haemolyticum,* 193
    due to *Chlamydia pneumoniae,* 194
    due to *Corynebacterium diphtheriae,* 195-196
      in children, 2786-2787
    due to *Francisella tularensis,* 195
    due to group A beta hemolytic *Streptococcus pyogenes,* 191-193
      in children, 2787
    due to *Mycobacterium tuberculosis,* 195
    due to *Mycoplasma pneumoniae,* 194-195
    due to *Neisseria gonorrhoeae* (gonococcal), 193-194, 194f
      in children, 2786
    due to non–group A beta hemolytic streptococcal infections, 193
Pharyngitis *(Continued)*
      in children, 2787
      complications of, 2788
    due to *Treponema pallidum,* 194
      in children, 2786
    due to *Yersinia enterocolitica,* 196
  in children, 2782, 2783f-2784f
    due to *Corynebacterium diphtheriae,* 2786-2787
    due to *Neisseria gonorrhoeae,* 2786
    streptococcal, 2787
    due to syphilis, 2786
    due to Vincent's angina, 2786
    viral, 2785-2786
  defined, 191
  differential diagnosis of, 191
  epidemiology of, 191
  etiologies for, 191, 192t
  fungal, 199-200
    due to *Candida* spp, 199-200
      in children, 2786
  traumatic, 194, 194f
  viral, 196-199
    due to adenovirus, 198
    in children, 2785-2786
    due to common cold (rhinovirus, coronavirus, parainfluenza virus), 196
    due to Epstein-Barr virus, 198-199, 198f
    due to herpes simplex virus, 199, 199f
    due to HIV, 197
    due to influenzavirus, 196-197
Pharyngobasilar fascia retropharyngeal, 1359f
Pharyngocele, lateral, 986, 987f-988f
Pharyngoconjunctival fever, 198
Pharyngocutaneous fistula
  after hypopharyngeal reconstruction, 1458
  due to neck surgery, 1727-1728, 1728f
  after total laryngectomy, 1571
  after total laryngopharyngectomy, 1575
Pharyngoesophageal defects, classification of, 1450
Pharyngoesophageal (PE) segment, in alaryngeal speech
  physiology of, 1596
  prevention of hypertonicity of, 1599-1600, 1599f
Pharyngoesophageal webs, 966-967, 967f
  imaging of, 1407, 1408f
Pharyngoesophagography, postlaryngectomy, 1416, 1417f-1418f
Pharyngoesophagram, 1394, 1394f-1395f
Pharyngogram, 1394, 1394f
  air-contrast, 1394, 1395f
Pharyngo-laryngo-esophagectomy, total, 1574, 1574f
  for cervical esophageal cancer, 1430-1431
Pharyngomaxillary space, anatomy of, 202
Pharyngoplasty
  transpalatal advancement, for obstructive sleep apnea, 258, 260f
  for velopharyngeal dysfunction, 2683
Pharyngostomy, after hypopharyngeal reconstruction, 1458, 1459f
Pharyngotomy
  for hypopharyngeal cancer
    anterior transhyoid, 1427-1429, 1428f
    lateral, 1426-1427
    lateral transthyroid, 1427, 1428f
  for oropharyngeal cancer
    lateral, 1371, 1371f
    transhyoid, 1371, 1372f
Pharyngotympanic tube, 2585f. *See also* Eustachian tube.
Pharynx
  bacteriology of, 2785-2788
  lymphatic drainage of, 2582
  motility disorder(s) of, 1398-1399
    abnormal deglutition as, 1398
    cricopharyngeal dysfunction as, 1398-1399, 1400f
Pharynx *(Continued)*
  neurologic evaluation of, 832-836
  radiographic anatomy of, 1397, 1398f-1399f
  in swallowing, 833
  swallowing disorders due to surgery of, 1220
  taste buds in, 1208
Phase closure, laryngeal videostroboscopy of, 819-820
Phase shifts, with traditional hearing aid, 2204
Phelps, Peter, 2728-2729
Phenol
  structure and function of, 394-395
  toxicity of, 395
Phenol block, for neuropathic pain, 245-246
Phenol chemical peels, 394-395
  agent for, 394-395
  complications of, 396-397
  occluded *vs.* nonoccluded, 395
  patient preparation and education for, 395
  patient selection for, 395
  postoperative care after, 396
  results of, 396f
  technique of, 395
  toxicity of, 395
Phenotype, 2088
Phenoxybenzamine, and skin flap viability, 1073
Phentolamine, and skin flap viability, 1073
Phenylephrine
  for allergic rhinitis, 620
  for rhinosinusitis, 736
Phenylpropanolamine, for rhinosinusitis, 735t, 736
Phenylthiocarbamide (PTC), taste sensitivity to, 1211-1212
Phenytoin, for neuropathic pain, 243
Pheochromocytoma, 120, 1657
  preoperative evaluation of, 105
Pheromones, 624, 627-628, 630, 631b
Philtrum, embryology of, 2660, 2662f
Phonation
  defined, 833
  in geriatric patients, 234-237
    acoustic changes in, 236
    dental/mandibular changes in, 236
    factors affecting vocal quality in, 234, 235t
    glandular changes in, 236
    histologic changes in, 234-235, 235f
    laryngoscopic appearance in, 235-236
    mucosal changes in, 236
    respiratory changes in, 236
    and sense of taste, 236
    treatment of, 236-237
  process of, 833
  in speech, 810-811, 811b, 811f
Phonation threshold pressure, in voice evaluation, 828, 828t
Phoneme-specific velopharyngeal dysfunction, 2679
Phonetically Balanced Kindergarten (PBK) Test, for cochlear implant, 2225
Phonetogram, in acoustic analysis for voice evaluation, 829, 829f, 829t
Phonophobia, with migraine, 2349
Phonotrauma, laryngitis due to, 883-884, 884f
Phosphatase and tensin homolog (PTEN) gene, in thyroid carcinoma, 1753
Phosphate, in saliva, 1139
Phosphate salts, oral, for hyperparathyroidism, 1804
Phospholipase C system, in salivary gland secretion, 1137-1138
Photoaging skin types, 275, 276b, 391, 391t
Photodisintegration, 1033
Photodynamic therapy (PDT)
  interventional bronchoscopy with, 1010t
  for oral cancer, 1315
  for premalignant lesions of larynx, 1491
  for recurrent respiratory papillomatosis, 2890t, 2892
  for unresectable tracheal tumor, 1621

Photoelectric effect, 1032-1033, 1032f
Photoglottography, for voice evaluation, 835
Photography, prior to rhinoplasty, 514, 515f
Photolysis, fractional, for facial resurfacing, 403t
Photon, 1031
  absorption of, 26, 26f
  spontaneous emission of, 26, 26f
  stimulated emission of, 26, 26f
Photon beams, in radiotherapy, 1033-1034, 1035f
Phrenic ampulla, 1397-1398, 1400f
Phrenic nerve, 2579f
Phrenic nerve injury, 1731, 1731f
Phrenic nerve paralysis, due to neck surgery, 1731
Phrenic nerve paresis, due to neck surgery, 1731, 1731f
Phrenic nerve reinnervation, 917
PHS (Pallister-Hall syndrome), 2874
PHYH gene, in Refsum disease, 2096
Physical examination, 94-101
  of children, 2574
  for chronic rhinosinusitis, 743
  for disorders of professional voice, 851-852, 852t
  of ears, 97-98
    auricles in, 97
    external auditory canal in, 97
    hearing assessment in, 97-98, 98t
    tympanic membrane in, 97, 98f
  of facial skeleton, 95
  of facial trauma, 303-304, 303f
  of facies, 95, 95t
  of general appearance, 95
  of larynx and hypopharynx, 99-100, 99f-100f
    flexible endoscopy in, 100
  of maxillofacial trauma, 323-325
    of lower third, 325
    of middle third, 324-325, 324f
    of upper third, 324
  of nasopharynx, 100-101
  of neck, 95, 96f
    adenopathy in, 95-96
    lymph node regions in, 96-97, 96f
    thyroid gland in, 95
    triangles of, 96-97, 96f
  for nonallergic rhinitis, 699
  of nose, 100
  of oral cavity, 98-99
  of oropharynx, 99, 99f
  of parotid gland, 95
  of skin, 95
Physician Consortium for Performance Improvement (PCPI), 82-87, 84t-87t
Physician education, and performance measurement, 79, 79t
Physician-patient relationship, 78-82
PI(s) (protease inhibitors), 211
Pickwickian syndrome, 251
Picture archival and communication systems (PACS), 138
Piebald syndrome, deafness in, 2051t-2058t
Pierre Robin syndrome, craniofacial abnormalities in, 2630-2631, 2630f
Piezoelectric middle ear implantable hearing aids, 2211-2212
  Esteem-Hearing Implant as, 2211-2212, 2212f
  ossicular coupling in, 2207-2208
  sound transduction and coupling to auditory system with, 2205f
  transducer design for, 2207
Pigeon feeder, 2665, 2665f
Pigmentation changes
  after blepharoplasty, 451
  after chemical peel, 396-397
  after liposuction, 459
  after rhytidectomy, 427
  after skin resurfacing, 451
Pigmented oral mucosal lesions, 1241-1243
  amalgam tattoo as, 1243
    clinical features of, 1243, 1243f
    defined, 1243
    differential diagnosis of, 1243
    etiology of, 1243
    histopathologic features of, 1243, 1243f
    treatment of, 1243
  melanoma as, 1242-1243
    clinical features of, 1242, 1242f
    differential diagnosis of, 1242
    etiology and pathogenesis of, 1241, 1241t
    histopathologic features of, 1242-1243, 1242f-1243f
    treatment of, 1243
  melanotic macules as, 1241
    clinical features of, 1241, 1241f
    defined, 1241
    differential diagnosis of, 1242
    etiology and pathogenesis of, 1241, 1241t
    histopathologic features of, 1242, 1242f
    treatment of, 1243
  mucosal melanocytic nevi as
    clinical features of, 1241
    histopathologic features of, 1242
    treatment of, 1243
Pilar cysts, 289
Pillars
  of Corti, 1832, 1832f
  of facial skeleton, 331, 331f
Pill-induced esophageal injury, 976, 976b, 2941
Pilocarpine, for xerostomia due to radiotherapy, 1048
Pimecrolimus cream, for eczematoid otitis externa, 1956
Pinch test, 445, 446f, 447-448, 448f
Pinched nasal tip, revision rhinoplasty for, 590, 591f-592f
Pincushioning, with local flaps, 366
Pindborg tumor, 1276
  microscopic findings in, 1276
  radiographic findings in, 1276, 1276f
Pinna(e)
  anatomy of, 476-477, 476f
  in sound transmission, 2019
Piriform sinus. *See* Pyriform sinus(es).
Pistol, neck trauma due to, 1625
Piston prosthesis, for otosclerosis
  measurement of, 2031, 2031f-2032f
  placement of, 2031-2032, 2032f
Pitch
  in computed tomography, 131
  disordered perception of, with traditional hearing aid, 2207
Pitch control, 812
Pituitary diseases, oral manifestations of, 1251
Pituitary fossa
  in surgical anatomy of anterior cranial base, 2443f
  in surgical anatomy of middle cranial base, 2445f
Pituitary gland, in surgical anatomy of anterior cranial base, 2473f-2475f
Pituitary hypothyroidism, 1747
Pituitary stalk, in surgical anatomy of anterior cranial base, 2474-2475, 2475f
Pivotal flaps, 343-345
  effective length of, 343, 343f
  interpolated, 344-345, 344f
  rotation, 343-344, 343f
  transposition, 344, 344f
PJVK (pejvakin) gene, in deafness, 2051t-2058t
PLA (polylactic acid), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
Placebo effect, 61, 62t
Plagiocephaly, synostotic, 2643-2644, 2643f-2644f
  anterior, 2643f
  deformational, 2643f-2644f, 2644
  front-orbital advancement for, 2652-2653, 2653f
  posterior, 2643f
Plain film radiography. *See* Conventional radiography (CR).
Planning tumor volume (PTV), for radiotherapy, 1036, 1044-1045, 1045f
Planum sphenoidale, in surgical anatomy of anterior cranial base, 2442-2443, 2443f, 2471, 2472f
Plaquenil (hydroxychloroquine)
  ototoxicity of, 2176
  sensorineural hearing loss due to, 2120
Plasmablastic lymphoma (PBL), 216
Plasmacytoma
  extramedullary, 2107
    of larynx, 1509
  solitary bone, 2107
Plasmid(s), 15-16, 15f
Plasmid vector, for gene therapy of inner ear, 2191t
Plasmin, in wound healing, 1077
Plasminogen activator, in bone resorption, 1972-1973
Plastic surgery, gene therapy for, 22-23
  with reconstructive tissue flaps and wound healing, 22-23
  with skin grafting, 23
Plasticity, neural. *See* Neural plasticity.
Plastipore, for ossiculoplasty, 2026t
Platelet(s), in adaptive immune system, 605
Platelet count, preoperative evaluation of, 106
Platelet disorders, oral manifestations of, 1256
Platelet glycoprotein IIb/IIIa inhibitor, and skin flap viability, 1074
Platelet-derived growth factor (PDGF), in wound healing, 1076
Plating systems, permanent *vs.* resorbable, for pediatric facial fractures, 2700-2701, 2700t-2701t
Platinum derivatives, in noise-induced hearing loss, 2147
Platybasia, 2355
Platysma, 321f, 442f
Platysmal myocutaneous flap, for oropharyngeal reconstruction, 1377, 1378f
  of tongue base, 1389
  of tonsils and pharyngeal wall, 1385
Play audiometry, for otitis media, 2762
Pleconaril, for rhinosinusitis, 734t
Pleiotropism, 7
Pleomorphic adenoma(s)
  in children, 2819
  of larynx, 881
  of oral cavity, 1291-1292, 1292f
  of parapharyngeal space, 1663-1664, 1665f
  of salivary gland, 1168-1169
    carcinoma ex, 1187-1189, 1188f
    in children, 2861-2862
    clinical features of, 1166f, 1169
    histopathology of, 1169
    imaging of, 1143
      CT for, 1144f, 1148
      MRI for, 1148f, 1167f-1168f, 1180f
      parotid, 150, 150f
      ultrasound imaging, 1149, 1149f
    of lacrimal gland, 1169, 1170f
    malignant transformation of, 1169
    metastasizing, 1189
    of palate, 1169, 1169f
    pathogenesis of, 1168-1169
    recurrent, 1169, 1170f
    sites of, 1169, 1169f-1170f
    submandibular, 1653f
  sinonasal, 718t
PLGA (polymorphous low-grade adenocarcinoma), of salivary glands, 1184-1185, 1186f

Plica aryepiglottica, 1543f
Plica interarytaenoidea, 1543f
Plica stapedis, 1827f
Plica ventricularis, 815t-816t, 853
  surgical anatomy of, 1543f
Plica vocalis, 1543f
PLLA (poly L-lactic acid), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
PLMD (periodic limb movement disorder), 262t, 265
Plummer-Vinson syndrome, 967
  and postcricoid carcinoma, 1425-1426
Plumping grafts, for nasal tip projection, 535-536, 536f
Pluripotent stem cells, in adaptive immune system, 599-600, 600f
PMCA2, in deafness, 2051t-2058t, 2080
PML (progressive multifocal leukoencephalopathy), HIV-associated, 223
PMMML (primary mucosal malignant melanoma of the larynx), 1509
PMP22 (peripheral myelin protein 22) gene, in deafness, 2051t-2058t, 2081
PMS. *See* Pharyngeal mucosal space (PMS).
Pneumatic dilation
  for achalasia, 964-965
  for tracheal stenosis, 2928, 2928f
Pneumatic otoscopy, for acute otitis media, 2761-2762
Pneumatization
  of petrous apex, 1867, 1986
    asymmetric, 1922-1923, 1924t, 1925f
      vs. neoplasms, 2525, 2526f
    via infralabyrinthine cell tract, 1988f
    via retrolabyrinthine cell tract, 1988f
    via supralabyrinthine cell tract, 1987f
  of sphenoid sinus, 669, 670f
Pneumocephalus, due to cranial base surgery, 2468
Pneumococcal capsular polysaccharide vaccine (PPV23, Pneumovax), with cochlear implants, 2236-2237, 2237b
Pneumococcal conjugate vaccine (PCV7, Prevnar)
  with cochlear implants, 2237, 2237b
  to prevent otitis media, 2763, 2768
    maternal immunization with, 2768-2769
Pneumococcal polysaccharide–meningococcal outer membrane protein complex conjugate (PncOMPC) vaccine, to prevent otitis media, 2768
Pneumococcal vaccine
  to prevent hearing loss, 2161
  to prevent otitis media, 2768
    maternal immunization with, 2768-2769
Pneumocystis jiroveci
  otologic manifestations of, 2114-2115
  otomastoiditis due to, immunosuppression and, 222
Pneumolabyrinth, 2737, 2737f
Pneumomediastinum, 1410, 1410f
Pneumonia, aspiration, 1250
Pneumosinus dilatans, 783, 784f
Pneumothorax
  due to neck surgery, 1733
  tension, *vs.* anaphylactic reaction, 119
Pneumovax (pneumococcal capsular polysaccharide vaccine), with cochlear implants, 2236-2237, 2237b
PNH (polymyxin, neomycin, and hydrocortisone), for otitis externa, 1946, 1952, 1959t-1960t
PnoOMPC (pneumococcal polysaccharide–meningococcal outer membrane protein complex conjugate) vaccine, to prevent otitis media, 2768
Pogonion, in chin analysis, 463, 463f-464f
Point estimate, 65
Point of equilibrium, in radiation, 1033
Poiseuille's equation, 1073, 2897
Poliomyelitis, laryngeal hypofunction due to, 842
Politzer test, of eustachian tube function, 1874
Politzerization, 1870
Pollybeak deformity, 512, 512f, 539, 539f
  revision rhinoplasty for, 584-585, 586f
Poly D-lactic acid (PDLA), in resorbable plating system, for pediatric facial fractures, 2700, 2700t
Poly L-lactic acid (PLLA), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
Polyamide mesh, for nasal reconstruction, 368
Polyarteritis nodosa, sensorineural hearing loss due to, 2124, 2166
Polychondritis, relapsing
  laryngeal and tracheal manifestations of, 890
  sensorineural hearing loss due to, 2124
Polyclitus, 269
Polydimethylsiloxane. *See* Silicone (polydimethylsiloxane, Silastic).
Polydioxanone (PDS), in resorbable plating system, for pediatric facial fractures, 2700, 2700t
Polyethylene, high-density
  for auricular reconstruction, 2744t
  for chin implants, 465t
Polyethylene implant, for nasal reconstruction, 368
Polygenic traits, 8
Polyglycolic acid (PGA), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
Polylactic acid (PLA), in resorbable plating system, for pediatric facial fractures, 2700, 2700t-2701t
Polymer(s), for craniofacial defect repair, 2657
Polymer allografts, for ossiculoplasty, 2006
Polymerase chain reaction (PCR), 8-9
Polymorphic reticulosis, 659-660
Polymorphisms, in DNA repair enzymes, in head and neck squamous cell carcinoma, 1027
Polymorphous low-grade adenocarcinoma (PLGA), of salivary glands, 1184-1185, 1186f
Polymyositis, oral manifestations of, 1252
Polymyxin, neomycin, and hydrocortisone (PNH, Cortisporin Otic Solution), for otitis externa, 1946, 1952, 1959t-1960t
Polyneuropathy, in Bell's palsy, 2391, 2392t
Polyostotic fibrous dysplasia, oral manifestations of, 1257
Polyp(s)
  aural, 1965
  nasal
    endoscopic sinus surgery for, 751-752
    olfactory dysfunction due to, 625, 634f
    surgical management of, 741
  in paranasal sinuses, 676, 678f
  vocal fold, 867-869
    with capillary ectasia, 868f
    in children, 2882
    diagnosis of, 868
      history in, 868
      laryngeal examination in, 868
      vocal capability battery in, 868
    epidemiology of, 867
    pathophysiology and pathology of, 867-868
    treatment of, 868-869
      behavioral, 868
      medical, 868
      surgical, 868-869
    in vocal professional, 846
Polypeptides, in saliva, 1140
Polypoid granulation tissue, of larynx, 880
Polyposis
  sinonasal
    in aspirin-exacerbated respiratory disease, 732f
    endoscopic sinus surgery for, 751-752
Polyposis *(Continued)*
    with methicillin-resistant *Staphylococcus aureus* infection, 733f
    surgical management of, 741
  vocal fold, 872-873, 872f
    diagnosis of, 872
      history in, 872
      laryngeal examination in, 872
      vocal capability battery in, 872
    epidemiology of, 872
    management of, 872-873
      behavioral, 872
      medical, 872
      surgical, 872-873, 873f
    pathophysiology and pathology of, 872
Polyrhinia, 2690-2692
Polysomnography (PSG), for obstructive sleep apnea, 255, 255b, 256f
  in children, 2606-2607, 2607f, 2607t, 2794
    indications for, 2608
Polytef injection, for vocal fold paralysis in children, 2879
Polytetrafluoroethylene (Teflon), for vocal fold medialization
  history of, 905
  by injection, 905-906
    complications of, 907, 908f
Polytetrafluoroethylene carbon, for nasal reconstruction, 368
Polytetrafluoroethylene (Gore-Tex) implant, for saddle nose deformity, 555, 558f
Polytetrafluoroethylene (Gore-Tex) strip, for medialization thyroplasty, 908, 910, 911f
Polyvinyl alcohol (PVA, PVA Foam, Trufill, Contour Emboli), for embolization, 1933
Pons
  in surgical anatomy of anterior cranial base, 2474f
  in surgical anatomy of lateral skull base, 2439f
Pontine arteries, 2351f
Pontine-mesencephalic sulcus, in surgical anatomy of lateral skull base, 2439f
PONV (postoperative nausea and vomiting), in children, 2593
Popcorn activity, in facial nerve monitoring, 2547f
Population
  accessible, 68, 68t
  target, 68, 68t
Porous high-density polyethylene implant, for nasal reconstruction, 368
PORP. *See* Partial ossicular replacement prosthesis (PORP).
Porphyromonas gingivalis, 1252
PORT (postoperative radiation therapy), 1042-1043
Port wine stain, 291, 2832-2833
Porus acusticus
  anatomy of, 1822
  in surgical anatomy of lateral skull base, 2437-2438
Posaconazole, for fungal rhinosinusitis, 712, 713t
POS-Head/Neck (Patient Outcomes of Surgery–Head/Neck), 57
Positional testing, 2315-2316, 2315f
  after vestibular rehabilitation, 2373f-2374f
Positioning template, in microtia reconstruction, 2744-2745, 2745f
Positron, 1031-1032
Positron emission tomography (PET), 137-138
  applications of, 144, 145f
  for cerebral blood flow evaluation, 2491
  with intensity-modulated radiotherapy, 1044
  of laryngeal carcinoma, 1494-1495
    early glottic, 1517
  of nasopharyngeal carcinoma, 1354
  of neck masses, 1637, 1637t
  of neck neoplasms, 1656-1657
  of olfaction, 632

Positron emission tomography (PET) *(Continued)*
of oral cancer, 1300
of oropharyngeal cancer, 1366
of paranasal sinus tumors, 1124
of salivary glands, 1150, 1168
Positron emission tomography/computed tomography (PET/CT), 138
for hypopharyngeal and cervical esophageal cancer, 1424, 1424f
of laryngeal carcinoma, 1470, 1470f, 1494-1495
of neck neoplasms, 1656-1657
of pharynx and esophagus, 1396-1397, 1397f
for tumor recurrence, 1418, 1419f-1420f
Postauricular abscess, 1985, 1985f-1986f
Postauricular approach(es)
to infratemporal fossa, 2495-2500
cervical dissection in, 2495, 2498f
closure of external auditory canal in, 2495, 2497f
extratemporal facial nerve dissection in, 2495-2496
incisions and skin flaps in, 2495, 2497f
radical mastoidectomy in, 2496, 2498f
removal of external auditory canal wall skin and tympanic membrane in, 2495, 2497f
type A, 2497-2499
closure of wound in, 2499, 2499f
exposure of jugular bulb and internal carotid artery in, 2498, 2498f-2499f
facial nerve transposition in, 2497-2498, 2498f
occlusion of sigmoid sinus in, 2498, 2498f
tumor removal in, 2498-2499, 2499f
type B, 2499-2500, 2500f
type C, 2500, 2501f
for mastoidectomy, 2011, 2011f
for tympanoplasty, 2001-2002
Postauricular ecchymosis, 97
Postauricular lymph node, 1360f
Postauricular sulcus, in microtia reconstruction, 2746, 2748f
Postcricoid carcinoma
Plummer-Vinson syndrome and, 1425-1426
total laryngopharyngectomy for, 1573
Postcricoid region, 1421
Posterior ampullary nerve, 1854f, 2278f
Posterior auricular artery, 2580, 2580f
Posterior canal benign paroxysmal positional vertigo (PC-BPPV)
anatomic and physiologic basis for, 2288-2289, 2288f
conversion of, 2332
positional testing for, 2315, 2315f, 2331, 2331f
repositioning maneuver for, 2331-2332, 2332f
surgical treatment of, 2332
Posterior cerebral artery(ies), 2351f
in surgical anatomy of anterior skull base, 2481f
Posterior cervical (PC) space, 158, 159f-160f, 162f
Posterior clinoid process, in surgical anatomy of lateral skull base, 2435f
Posterior commissure scar, 2915, 2916f
Posterior commissure stenosis, 948
Posterior communicating artery, 2351f
Posterior cranial fossa. *See* Posterior fossa.
Posterior cricoarytenoid (PCA) ligament, 1542f
Posterior cricoarytenoid (PCA) muscle
anatomy of
applied, 806, 806f
surgical, 1542f
botulinum toxic injection of, for spasmodic dysphonia, 841f
in breathing, 808-809, 808f
characteristics of, 918
compartmentalization of, 806-807, 807f
reinnervation of, 917-918
Posterior cricoid division, laryngofissure with, for laryngeal stenosis, 2919, 2919f
Posterior ethmoid, prior to endoscopic sinus surgery, 764t
Posterior ethmoid air cells, and internal carotid artery, 671-672
Posterior ethmoid branch, 483f
Posterior ethmoidal artery
anatomy of, 682-683, 1124f
in surgical anatomy of anterior cranial base, 2471-2473, 2472f
Posterior ethmoidal foramen, 322f, 439
Posterior ethmoidectomy, in endoscopic sinus surgery, 747-748, 749f
Posterior facial vein
anatomy of, 1359f
in parotidectomy, 1195-1196, 1195f
Posterior fontanelle, 2618f
Posterior fossa
in surgical anatomy of anterior cranial base, 2475f
in surgical anatomy of lateral skull base, 2435f, 2438-2440, 2439f
Posterior fossa neoplasm(s), 2514-2541
of cerebellopontine angle
acoustic neuroma as, 2514-2517
diagnostic studies of, 2516-2517
imaging of, 2517, 2517t-2518t
natural history of, 2515, 2515f-2516f
signs and symptoms of, 2515-2516
arachnoid cysts as, 2523-2524
chondrosarcomas as, 2527, 2528f-2529f
chordomas as, 2526-2527, 2527f-2528f
common, 2514-2524, 2515b
dermoid tumors as, 2527
differential diagnosis of, 2517t-2518t
facial nerve neuroma as, 2519-2522
diagnostic studies of, 2519-2522
imaging of, 2519-2522, 2521f
signs and symptoms of, 2519
glomus tumors as, 2522-2523, 2523f-2524f
hemangiomas as, 2524, 2525f
lipomas as, 2527, 2529f-2530f
meningiomas as, 2517-2518
diagnostic studies of, 2518
imaging of, 1928, 1928f, 1929t, 2518, 2518t, 2519f-2520f
signs and symptoms of, 2518
metastatic, 2526
other cranial nerve neuromas as, 2522, 2522f
primary cholesteatomas as, 2518-2519
diagnostic studies of, 2519
imaging of, 2519, 2520f-2521f
signs and symptoms of, 2518-2519
teratomas as, 2527
uncommon, 2515b, 2526-2527
differential diagnosis of, 2514, 2515b
intra-axial, 2528-2529
brainstem gliomas as, 2528
hemangioblastomas as, 2528
malignant choroid plexus papillomas and ependymomas of fourth ventricle as, 2528-2529, 2530f-2531f
medulloblastomas as, 2528
meningiomas as
embolization of, 1938
with petrous apex involvement, 2508f
of petrous apex, 2524-2526
vs. asymmetrical pneumatization, 2525, 2526f
vs. carotid artery aneurysms, 2525, 2527f
cholesterol granulomas as, 2524-2525, 2524t, 2526f
giant cell tumors as, 2526
mucocele, mucus retention cysts, and petrous apex effusion as, 2524t, 2525, 2526f-2527f
requiring drainage, surgical approaches for, 2539
infralabyrinthine, 2539, 2540f
middle cranial fossa, 2539
Posterior fossa neoplasm(s) *(Continued)*
transcanal intracochlear, 2539, 2540f
translabyrinthine, 2539
surgical approaches for, 2529-2539, 2532t
combined (petrosal), 2532t, 2539
advantages and disadvantages of, 2532t, 2539
basic features of, 2539
indications for, 2532t, 2539
technique of, 2539, 2539f
complications of, 2540-2541
CSF leaks as, 2540
facial nerve injury as, 2541
involving anteroinferior cerebellar artery, 2540
meningitis as, 2541
ophthalmologic, 2541
with drainage, 2539
infralabyrinthine, 2539, 2540f
middle cranial fossa, 2539
transcanal intracochlear, 2539, 2540f
translabyrinthine, 2539
experimental, 2539
extended middle fossa, 2532t, 2538
advantages and disadvantages of, 2532t, 2538
basic features of, 2538
indications for, 2532t, 2538
surgical exposure in, 2538f
technique of, 2538
middle fossa, 2532t, 2534-2536
advantages and disadvantages of, 2532t, 2536
basic features of, 2534
indications for, 2532t, 2534-2535
surgical exposure in, 2535f
technique of, 2535-2536, 2535f
patient management with, 2540-2541
intraoperative, 2540
postoperative, 2540
preoperative, 2540
retrolabyrinthine, 2532t, 2536
advantages and disadvantages of, 2532t, 2536
basic features of, 2536
indications for, 2532t, 2536
surgical exposure in, 2536f
technique of, 2536, 2536f
retrosigmoid (suboccipital), 2532t, 2533-2534
advantages and disadvantages of, 2532t, 2534
basic features of, 2533
indications for, 2532t, 2533
surgical exposure in, 2533f
technique of, 2534, 2534f
selection of, 2539-2540
transcochlear, 2532t, 2537
advantages and disadvantages of, 2532t, 2537
basic features of, 2537
indications for, 2532t, 2537
surgical exposure in, 2537f
technique of, 2537, 2537f
translabyrinthine, 2530-2533, 2532t
advantages and disadvantages of, 2532t, 2533
basic features of, 2530
indications for, 2530, 2532t
requiring drainage, 2539
surgical exposure in, 2531f
technique of, 2530-2532, 2533f
tumor removal in, 2532-2533
transotic, 2532t, 2537-2538
advantages and disadvantages of, 2532t, 2538
basic features of, 2537
indications for, 2532t, 2537-2538
technique for, 2538, 2538f
vestibular symptoms of, 2354
Posterior glottic gap, laryngeal videostroboscopy of, 819, 820f
Posterior hypopharyngeal wall, 1421
Posterior hypopharyngeal wall carcinoma, total laryngopharyngectomy for, 1573

Posterior incudal ligament, anatomy of, 1827f
Posterior inferior cerebellar artery, 2351f
Posterior lamella, of eyelid, 442
Posterior laryngeal clefts, dysphagia due to, 2952-2953
Posterior lateral nasal artery, in surgical anatomy of anterior cranial base, 2473f
Posterior mallear fold, 1825f
Posterior medial scalene muscle, 2579f
Posterior nasal depth, 2617t
Posterior ostiomeatal unit, 664
Posterior petrous apex (PPA), 1975-1976, 1976f
  pneumatic, 1976, 1977f
Posterior pole, 320f
Posterior semicircular canal
  anatomy of, 2278f
  in surgical anatomy of lateral skull base, 2436f, 2439f
Posterior semicircular canal occlusion, 2360-2361, 2361f
Posterior semicircular duct, 1851f, 1854f
Posterior spiral vein, 1856f
Posterior suspensory ligament, 1751
Posterior triangle, of neck, 2577-2579, 2578f-2579f
  accessory nerve in, 2578-2579, 2580f
  arterial branches in, 2579
  cutaneous branches of cervical plexus in, 2578, 2580f
  fascia in, 2577
    deep, 2577-2578, 2578f-2579f
    superficial, 2577
Posterior triangle dissection, 96, 96f, 1709
Posterior triangle lymph nodes, 1704, 1704f, 1706t-1708t
Posterior vestibular artery, 1854, 1856f
Posterior vestibular vein, 1856f
Posterior wall augmentation, for velopharyngeal dysfunction, 2683-2684
Posterolateral fontanelle, 2618f
Posterolateral neck dissection, 1718-1719
Posterolateral vertical hemilaryngectomy, 1548
Postexposure prophylaxis (PEP), for HIV infection, 212, 212t
Postintubation croup, in children, 2593
Postintubation granuloma(s), 939, 941f
  of vocal folds, 875-876, 875f
    diagnosis of, 875-876
      history in, 875
      vocal capability battery in, 875-876
    epidemiology of, 875
    management of, 876
    pathophysiology and pathology of, 875
Postobstructive pulmonary edema, 119
Postoperative dysphonia, 873-874, 873f
  diagnosis of, 873-874
    history in, 873
    laryngeal examination in, 874
    vocal capability battery in, 873-874
  epidemiology of, 873
  management of, 874
    behavioral, 874
    medical, 874
  pathophysiology and pathology of, 873, 874f
Postoperative epistaxis, 685f
Postoperative management, for children, 2575
Postoperative nausea and vomiting (PONV), in children, 2593
Postoperative neck and face, imaging of, 173-174, 175f-176f
Postoperative radiation therapy (PORT), 1042-1043
Postparotidectomy fistula, 1728
Postpolio syndrome, laryngeal hypofunction due to, 842
Postsaccadic drift, 2308, 2313
Poststreptococcal glomerulonephritis, 2788
Post-styloid compartment, 202
Poststyloid space, 1699
Post-tetanic potentiation, 1884
Posttransplantation lymphoproliferative disorder (PTLD), 213t, 215, 217
  in children, 2818, 2840
Postural balance, lateral vestibulospinal tract in, 1865
Postural control exercises, in vestibular rehabilitation, 2372-2373, 2378-2379
Postural rehabilitation, posturography in, 2326
Postural tone, sudden changes in saccular activity and changes in, 2300
  anatomic and physiologic basis for, 2300
  clinical importance of, 2300
Posture
  in vestibular function, 2308
  vestibular system in maintaining stability of, 2276-2277
    anatomic and physiologic basis for, 2276-2277
    clinical importance of, 2277
  in voice evaluation, 827
Posturography, 2324, 2325f
  dynamic
    for ablative vestibular surgery, 2365
    for vestibular rehabilitation, 2376-2377
  motor control test in, 2324-2325
  sensory organization test in, 2325-2326, 2325f-2326f
  use of, 2326-2327
Potassium (K^+)
  in endolymph homeostasis, 2081-2082, 2084f
  in saliva, 1139
Potassium (K^+) channels, in hair cell transduction, 2073, 2073f
  effects of deficiencies of, 2079-2080
Potassium iodide, saturated solution of
  for Graves' disease, 1742-1743
  for hyperthyroidism, 1739t
Potassium-titanyl-phosphate (KTP) laser, 31t, 33
  for facial resurfacing, 403t
  for recurrent respiratory papillomatosis, 880, 880f, 2891
  for stridulous child, 2908
POU3F4, in deafness, 2051t-2058t, 2083
POU4F3, in deafness, 2051t-2058t
Povidone-iodine (Betadine), for embolization, 1933
Powder insufflator, for ear hygiene or chronic ear drainage, 1958, 1961f
Power
  of statistical test, 65, 66t
  of surgical laser, 27, 29f
Powered microsurgical debrider, interventional bronchoscopy with, 1010t
PPA (posterior petrous apex), 1975-1976, 1976f
  pneumatic, 1976, 1977f
PPAR (peroxisome proliferator-activated receptor), for chemoprevention of oral cancer, 1315
PPIs. *See* Proton pump inhibitors (PPIs).
PPNET (peripheral primitive neuroectodermal tumor), 2845
PPRF (paramedian pontine reticular formation), in velocity-to-position integration, 2296, 2297f
PPS. *See* Parapharyngeal space (PPS).
PPV23 (pneumococcal capsular polysaccharide vaccine), with cochlear implants, 2236-2237, 2237b
Practice performance assessment, 79t
PRAD1 (parathyroid adenomatosis 1 oncogene), in hyperparathyroidism, 1774-1775, 1775f
Pramoxine hydrochloride and hydrocortisone (Pramosone steroid cream), after chemical peel, 396
Preauricular infratemporal approach, 2500-2501, 2501f
Preauricular node, 1297f
Precapillary sphincter, 1066
Precision, 65
Prednisolone, for hemangioma of infancy, 2826-2828
Prednisone
  for autoimmune inner ear disease, 2166
  for Graves' ophthalmopathy, 1811
  for herpes zoster oticus, 1948
  for hyperthyroidism, 1739t
  for otosyphilis, 2341-2342
  for rhinosinusitis, 734t
  for sarcoidosis, 659
  for Wegener's granulomatosis, 658
Preeclampsia, and facial palsy, 2399
Preemptive analgesia, 241
Preepiglottic space (PES)
  anatomy of, 1484, 1484f
    radiographic, 1471f, 1473, 1473f
    surgical, 1542, 1543f
  laryngeal cancer of
    anatomic basis for, 1484, 1484f
    imaging of, 1495
Pregabalin (isobutyl-GABA), for neuropathic pain, 243, 244t
Preglandular node, 1298f
Pregnancy
  facial paralysis in, 2399
  hyperparathyroidism during, 1804
  hypothyroidism during, 1749
  oral health during, 1256
  rhinitis during, 696, 702
  rhinosinusitis during, 737
  thyroid neoplasms during, 1770
Pregnancy gingivitis, 1256
Pregnancy granuloma, 1256
Pregnancy tumor, 1256
Premalignant lesions
  for head and neck cancer, 1061
  of larynx, 1486-1491, 1489f-1490f
    treatment of, 1489-1490, 1490t
      in-office, 1490-1491
  of oral cavity, 1298-1299
Premature infants, anesthesia for, 2595
Prematurity, and otitis media, 2766
Premaxillary bone deformity, in cleft lip, 2666, 2666f
Premedication, for anesthesia in children, 2589
  with congenital heart disease, 2596
Prenatal diagnosis, of cleft lip and palate, 2661-2662, 2663f
Prenatal testing, for sensorineural hearing loss, 2098
Preoperative embolization, for juvenile nasopharyngeal angiofibroma, 1351
Preoperative evaluation, 101-107
  of allergy, 102
  of cardiovascular system, 102
  consent in, 102
  of endocrine disorders, 104-105
    of adrenal gland, 104-105
    diabetes mellitus as, 105
    of parathyroid, 104
    of thyroid, 104
  of hematologic disorders, 105-106
    due to anticoagulants, 105
    congenital, 105
    hemoglobinopathies as, 106
    due to liver failure, 105-106
    thrombocytopenia as, 106
  of hepatic disorders, 103-104
  of neurologic disorders, 106
  of older patients, 106-107
  of renal system, 103
  of respiratory system, 102-103
  routine screening tests in, 101
PRES, in deafness, 2051t-2058t

Presbycusis, 232
defined, 232
etiologies of, 232
inner ear conductive (mechanical), 232, 2126
neural, 232, 2126
sensorineural hearing loss due to, 2125-2126, 2126f
sensory, 232, 2126
strial (metabolic), 232, 2126
with tinnitus, 2132
treatment of, 233
types of, 232
Presbyesophagus, 1400
Presbyphagia, 237
diagnostic testing for, 237
treatment of, 237
Presbyphonia, 234-237
acoustic changes in, 236
dental/mandibular changes in, 236
factors affecting vocal quality in, 234, 235t
glandular changes in, 236
histologic changes in, 234-235, 235f
laryngoscopic appearance in, 235-236
mucosal changes in, 236
respiratory changes in, 236
and sense of taste, 236
treatment of, 236-237
Presbystasis, 233-234
defined, 233
diagnostic methods for, 233
treatment of, 234
vestibular pathology of, 233
Preseptal orbital edema, due to rhinosinusitis, 676
Preshunt sphincters, 1066
Pressure changes, and eustachian tube dysfunction, 1872
Pressure flow measurement, for velopharyngeal dysfunction, 2679
Prestin
in hair cells, 1844
and outer hair cell motility, 2064-2065, 2068f
Prestyloid compartment, 202
Presyncope, 2346
Pretibial myxedema, and Graves' ophthalmopathy, 1808
Pretrichial forehead lift, 430, 431t
Prevalence, 61
Prevascular node, 1298f
Prevertebral fascia, 202, 2577-2578, 2578f, 2580f
Prevertebral layer, 202
Prevertebral space (PVS)
anatomy of, 203
infrahyoid, 158, 159f-160f, 162f
odontogenic infections of, 186, 186f
suprahyoid, 146f, 153
Prevnar (pneumococcal conjugate vaccine)
with cochlear implants, 2237, 2237b
to prevent otitis media, 2763, 2768
maternal immunization with, 2768-2769
Primary auditory cortex, 1847
Primary autoimmune inner ear disease, sensorineural hearing loss due to, 2124
Primary ciliary dyskinesia, nasal manifestations of, 661
Primary closure
of forehead defects, 359-362
of lip defects, 351
of nasal defects, 365, 365f
for oropharyngeal reconstruction, 1376
of tongue base, 1387-1388
of tonsil and pharyngeal wall, 1383-1384
Primary mucosal malignant melanoma of the larynx (PMMML), 1509
Primary ostium, of maxilla, 665, 665f
Primo passagio, 851
Primordial cyst, 1265
Probe therapy, in voice evaluation, 831
Proboscis lateralis, 2690, 2692, 2692f
Procerus muscle, 321f, 433f, 441-442, 442f
Processus vocalis, 1543f
Professional accountability, 82
Professional standing, 79t
Professional voice disorders, 844-858
anatomic considerations with, 845-846
basement membrane and lamina propria in, 846, 846f
blood vessels in, 845-846
cover-body theory of vocal fold vibration in, 845, 845f
causes of, 852-854
anxiety as, 853
extraesosphageal reflux as, 852
laryngeal hygiene as, 852-853
laryngitis as, 853
pulmonary disease as, 853
vocal abuse and misuse as, 853
vocal fold varices as, 853-854
evaluation of, 850-852
history of present illness in, 850-851
medical history in, 850
physical examination in, 851-852, 852t
laryngeal stroboscopy for, 847-849, 848f, 848t
management of, 854-857
medical therapy for, 854-855, 854b
speech language pathologist and vocal pedagogue in, 852, 855
surgical therapy for, 855-857, 856f-857f
postoperative care after, 856-857, 858t
performance cancellation due to, 854, 854b
types of
cysts as, 856, 857f
superficial vocal cord lesions as, 855-856, 856f
vocal fold varices as, 846-847, 856, 857f
voice analysis for, 849-850
acoustic measures in, 849
aerodynamic measures in, 849
electroglottography in, 849
perceptual analysis in, 850
spectrometry in, 849
voice outcomes in, 850
voice production and, 846-847
Professional voice patients, related surgical procedures in, 857-858
Professional voice production, 846-847
Programmable hearing aids, 2267, 2269
programming of, 2273
Progressive bulbar palsy (PBP), laryngeal disorders due to, 839-840, 842
Progressive multifocal leukoencephalopathy (PML), HIV-associated, 223
Progressive spinal muscular atrophy (PSMA), laryngeal hypofunction due to, 842
Progressive supranuclear palsy (PSP), laryngeal hypofunction due to, 843
Progressive systemic sclerosis (PSS), esophageal manifestations of, 979, 979f
Prokinetic agents
for extraesophageal reflux in children, 2946
for GERD, 970
Proliferating cell nuclear antigen (PCNA), in salivary gland neoplasms, 1194
Proliferation phase, of wound healing, 1076-1078
formation of granulation tissue in, 1077-1078
angiogenesis in, 1077-1078
dermal matrix in, 1077
reepithelialization in, 1076-1077
keratinocyte migration in, 1076-1077
keratinocyte proliferation in, 1077
wound contraction in, 1078
Proliferative verrucous leukoplakia, 1225, 1225f
Promoter(s), of gene expression, 19
Promoter hypermethylation, in head and neck squamous cell carcinoma, 1021
Promotility agents, for extraesophageal reflux, 901
PROP (propylthiouracil), taste sensitivity to, 1211-1212
Propecia (finasteride), for hair loss, 377-378
Proper cochlear artery, 1854, 1856f
Prophylaxis
antibiotic
for acute otitis media, 2771
for burns, 315
for orthopedic joint patients, 1253, 1253t
for sinus surgery, 743, 773
for temporal bone fractures, 2044-2045
for cluster headaches, 248
for CSF fistulas, 794
for migraines, 247
postexposure, for HIV infection, 212, 212t
subacute bacterial endocarditis, for pediatric surgery, 2596, 2596t-2597t
for trigeminal neuralgia, 248
Propofol, for anesthesia induction, 111
in children, 2590
Propoxyphene, for postoperative pain, 241t
Propranolol (Inderal)
for hyperthyroidism, 1739t
for migraine, 2349
for thyroid storm, 1745
Proptosis
in Graves' ophthalmopathy, 1808, 1809t
due to paranasal sinus tumor, 1123-1124
Propylene glycol, for cerumen removal, 1958t
Propylene glycol and acetic acid otic solution (VoSol), for otitis externa, 1946, 1953, 1959t-1960t
Propylthiouracil (PROP), taste sensitivity to, 1211-1212
Propylthiouracil (PTU)
adverse reactions to, 1742
for Graves' disease, 1742
for hyperthyroidism, 1739t
Prosody, in voice evaluation, 826-827
Prospective studies, 61
Prostaglandins (PGs)
in acutely raised skin flaps, 1070, 1070f
in bone remodeling, 1973
and skin flap viability, 1073
Prostate carcinoma, skull base metastases of, 173f
Prosthesis(es)
ossicular (*See* Ossicular prosthesis(es))
for velopharyngeal dysfunction, 2681-2682, 2681f-2682f
voice (*See* Voice prosthesis(es))
Prosthetic ear, 1345-1346, 1345t, 1346f
Prosthetic eye, 1345t, 1346-1347, 1347f
Prosthetic management
of acquired facial defects, 1344-1345, 1345t
auricular, 1345-1346, 1345t, 1346f
nasal, 1345, 1345t, 1346f
orbital/ocular, 1345t, 1346-1347, 1347f
of head and neck defects (*See* Maxillofacial prosthodontics)
of tumor-ablative surgical defects, 1337-1338
of mandible, 1340, 1341f-1342f
discontinuity, 1340-1342, 1342f-1343f
of maxilla, 1338
of soft palate, 1343-1344, 1344f
of tongue, 1342-1343, 1344f
Prosthetic maxillary obturation, 1338
definitive, 1339-1340
for dentate patients, 1339-1340, 1340f
for edentulous patients, 1340, 1340f-1341f
interim, 1339, 1339f
surgical, 1338-1339
abutments in, 1338-1339
impressions for diagnostic casts in, 1338-1339, 1338f
postoperative radiograph of, 1338, 1338f
preoperative assessment for, 1338, 1338f
preservation of support structures in, 1338

Prosthetic maxillary obturation *(Continued)*
removal of packing material and prosthesis in, 1339, 1339f
securing of prosthesis in, 1338-1339, 1339f
skin graft in, 1338-1339
Prosthetic nose, 1345, 1345t, 1346f
Prosthetic obturation
maxillary (*See* Prosthetic maxillary obturation)
for soft palate reconstruction, 1381
Protease inhibitors (PIs), 211
Protection, saliva in, 1140-1141
Protein(s)
formation of, 4, 5f, 11-12, 12f
salivary, 1139-1140, 1139t-1140t
Protein tyrosine phosphatase receptor Q (Ptprq)
and interstereociliary linkages, 2077
in stereocilia, 2076f
Protein tyrosine phosphatase receptor Q *(Ptprq)* gene, in murine deafness, 2058t-2060t
Proteomics, in head and neck squamous cell carcinoma, 1029
Protocadherin-15 (PCDH15), in tip links, 2074
Protocadherin-15 *(PCDH15)* gene, in deafness, 2051t-2058t, 2074
Proton beam radiotherapy, for malignant skull base tumors, 1696
Proton pump inhibitors (PPIs)
for extraesophageal reflux, 901
in children, 2946
for GERD, 970
for laryngoesophageal reflux, 901, 971
for rhinosinusitis, 735t
Proton therapy, 1046
Proto-oncogenes, in head and neck squamous cell carcinoma, 1016, 1019-1020
Protopic (tacrolimus), for eczematoid otitis externa, 1956
Provocation testing
in nonallergic rhinitis, 695-696
objective measurement methods in, 651
Provocative testing, of esophagus, 962-963
Provox 2 anterograde replacement system, 1598f
Provox voice rehabilitation system, 1598f
Proximal esophageal pressure, 958f
Prussak's space, anatomy of, 1826-1827
PS (Pendred syndrome). *See* Pendred syndrome (PS).
PS (parotid space)
anatomy of, 203
imaging of, 149-150, 150f-151f
P_s (subglottic air pressure)
in professional voice production, 846
in voice evaluation, 828, 828t, 849
PSCC (papillary squamous cell carcinoma), of larynx, 1506
Pseudallescheria boydii, invasive fungal rhinosinusitis due to, 705
Pseudoaneurysms
embolization of, 1942, 1943f
due to radiotherapy, 1049
Pseudoarthrosis, 331, 339-340
Pseudobulbar palsy (PBP), laryngeal disorders due to, 839-840, 842
Pseudodiverticula, esophageal, 975, 975f
imaging of, 1406, 1407f
Pseudoephedrine, for rhinosinusitis, 736
Pseudoepiglottitis, postlaryngectomy, 1416, 1417f
Pseudoepitheliomatous hyperplasia (PEH), of larynx, 1493
Pseudohypoacusis
evaluation of, 1901
sensorineural hearing loss due to, 2125
Pseudohypoparathyroidism, oral manifestations of, 1251
Pseudomembranous candidiasis, 1230, 1230f
in HIV, 225, 226f
Pseudo-membranous croup. *See* Bacterial tracheitis.
Pseudomonas aeruginosa, otitis externa due to, 1945, 2194-2195
malignant, 1947
Pseudoretropharyngeal mass, 1462, 1463f
Pseudosarcoma, of larynx, 1506
Pseudosulcus, due to extraesophageal reflux, 897
Pseudotumor(s)
cerebri, CSF rhinorrhea due to, 787
of masticator space, 152
Pseudovallecula, prevention of formation of, 1599-1600, 1601f
PSG (polysomnography), for obstructive sleep apnea, 255, 255b, 256f
in children, 2606-2607, 2607f, 2607t, 2794
indications for, 2608
PSMA (progressive spinal muscular atrophy), laryngeal hypofunction due to, 842
PSP (progressive supranuclear palsy), laryngeal hypofunction due to, 843
PSS (progressive systemic sclerosis), esophageal manifestations of, 979, 979f
Psychiatric disorders, olfactory dysfunctions in, 636
Psychogenic disorders, sensorineural hearing loss due to, 2129
Psychological distress, palliative care for, 1103-1104
Psychological effects, of radiotherapy, 2626t
Psychometric validation, 55
Psychotherapeutic agents, oral sequelae of, 1247t-1248t
Psychotropic medications, in palliative care, 1104
PTA (pure-tone average), 1888-1889
PTC (phenylthiocarbamide), taste sensitivity to, 1211-1212
PTEN (phosphatase and tensin homolog) gene, in thyroid carcinoma, 1753
Pterygoid hamulus, 1297f, 1360f
Pterygoid muscle, 1320
Pterygoid plate, 1124f
Pterygoid plate fractures, 171f
Pterygoid process, 2445f
Pterygoid venous plexus, 2441
Pterygomandibular involvement, in odontogenic infections, 184, 185f
Pterygomaxillary fissure, 2441
Pterygomaxillary fossa, 2435f
Pterygopalatine fossa
anatomy of, 1699
in surgical anatomy of anterior cranial base, 2473
Pterygopalatine ganglion
anatomy of, 1297f
in surgical anatomy of anterior cranial base, 2473
PTH. *See* Parathyroid hormone (PTH).
PTLD (posttransplantation lymphoproliferative disorder), 213t, 215, 217
in children, 2818, 2840
Ptosis
brow, 445, 445f
of chin, 465, 466f
of nasal tip, 484, 485f
caudal extension graft for, 576, 576f
due to overaggressive resection of caudal septum, 492, 492f
revision rhinoplasty for, 590-593, 593f
after rhinoplasty, 519, 520f
of upper eyelid
evaluation of, 446-447, 447f
repair of, 447-448, 447f-449f
Ptprq (protein tyrosine phosphatase receptor Q)
and interstereociliary linkages, 2077
in stereocilia, 2076f
Ptprq (protein tyrosine phosphatase receptor Q) gene, in murine deafness, 2058t-2060t
PTS (permanent threshold shift), 2121, 2141
PTU (propylthiouracil)
adverse reactions to, 1742
for Graves' disease, 1742
for hyperthyroidism, 1739t
PTV (planning tumor volume), for radiotherapy, 1036, 1044-1045, 1045f
Puberty, oral health during, 1256
Pull-through technique, as mandible-sparing procedure, 1311, 1312f-1313f
Pulmonary artery anomalies, tracheal compression due to, 2926
Pulmonary diseases
oral manifestations of, 1250-1251
professional voice disorders due to, 853
Pulmonary edema
after adenotonsillectomy, 2800
postobstructive, 119
Pulmonary function, in geriatric patients, 236
Pulmonary function testing
for airway stenosis, 944, 945f
in children, 2917
preoperative, 103
for tracheal neoplasms, 1616
Pulmonary hypertension, due to obstructive sleep apnea, in children, 2604
Pulmonary vascular resistance, factors influencing, 2597, 2597t
Pulpitis, *vs.* myofascial pain dysfunction syndrome, 1284t
Pulse sequences, for MRI, 133-137, 135f-136f
Pulsed dye laser (PDL), 30
585-nm, 31t, 33
for facial resurfacing, 403t
for premalignant lesions of larynx, 1490-1491
for recurrent respiratory papillomatosis, 880, 880f, 2891
for stridulous child, 2908
Pulsion diverticula, 986
Punch biopsy, for skin lesions, 293
Punnett squares, 2088, 2089f
Pure tone, 1838-1839
Pure-tone audiometry, 1888, 1888f
air-conduction testing in, 1888
masking for, 1889-1890
errors in, 1901-1902
bone-conduction testing in, 1888, 1888f-1889f
for conductive hearing loss, 2020, 2020f
for sensorineural hearing loss, in adults, 2117
Pure-tone average (PTA), 1888-1889
Pure-tone Stenger test, 1901
Purkinje cells, in modification of vestibuloocular reflex, 2301, 2301f
Purkinje, Jan E., 2329
PVA (polyvinyl alcohol), for embolization, 1933
PVA Foam (polyvinyl alcohol), for embolization, 1933
pVHI (Pediatric Voice Handicap Index), 2876
PVOS (Pediatric Voice Outcomes Survey), 57, 2876
PVQOL (Pediatric Voice-Related Quality-of-Life survey), 57, 2876
PVS. *See* Prevertebral space (PVS).
Pyogenic granuloma, 290
of oral cavity, 1256, 1289, 1289f
on septum, 685f
Pyramidal eminence
anatomy of, 1825-1829, 1827f
in surgical anatomy of lateral skull base, 2436f
Pyramidal lobe, of thyroid gland, 1751, 1751f
Pyriform aperture, 641f
edge of, 509f
Pyriform aperture stenosis, congenital nasal, 2692-2693
clinical presentation of, 2692-2693
diagnosis of, 2693, 2693f
operative management of, 2693, 2693f
pathogenesis of, 2690, 2692
Pyriform sinus(es)
anatomy of, 1421, 1422f
radiographic, 1397, 1463f, 1471f, 1472
lymphatic drainage from, 1422, 1422f

Pyriform sinus carcinoma, 162f
advanced, 1438-1439
chemotherapy for, 1439
quality of life with, 1439
imaging of, 1413f, 1423-1424, 1424f, 1475-1476, 1478f
surgical management of
endoscopic CO_2 laser resection for, 1429-1430, 1442
outcomes of, 1436-1438
partial laryngopharyngectomy for, 1429, 1430f
partial pharyngectomy for, 1426-1429
via anterior transhyoid pharyngotomy, 1427-1429, 1428f
via lateral pharyngotomy, 1426-1427
via lateral transthyroid pharyngotomy, 1427, 1428f
via median labiomandibular glossotomy, 1429
supracricoid hemilaryngopharyngectomy for, 1429, 1436
total laryngectomy with partial/total pharyngectomy for, 1430, 1431f
total laryngopharyngectomy for, 1573-1574
Pyriform sinus mucosa, in arytenoid adduction, 915
Pyrosis, 954

Q

Q (quality factor), of radiation, 133
QALY (quality-adjusted life-year), costs per, for cochlear implants
in adults, 2251, 2252t
in children, 2252-2253, 2253f
QASC (Quality Alliance Steering Committee), 84t-87t
QIOs (quality improvement organizations), 84t-87t
QOL. *See* Quality of life (QOL).
QOLRAD (Quality of Life in Reflux and Dyspepsia), 57-58
QSQ (Quebec Sleep Questionnaire), 57
Q-switched laser, 34
Q-switched Nd:YAG laser, for facial resurfacing, 403t
Quadrangular cartilage, of nose, 496
reduction of overlong caudal, 513f
Quadrangular cerebellar lobule, in surgical anatomy of lateral skull base, 2439f
Quadrangular membrane, surgical anatomy of, 1541-1542, 1542f-1544f
Quadratus, 321f
Quadrilateral cartilage, 482
in septoplasty, 490
Quality, definition of, 76-77
Quality Alliance Steering Committee (QASC), 84t-87t
Quality factor (Q), of radiation, 133
Quality improvement. *See* Performance measurement.
Quality improvement organizations (QIOs), 84t-87t
Quality of life (QOL)
cochlear implants and, 2251
in adults and elderly, 2251-2252, 2252f, 2252t
in children, 2252-2253, 2253f
with hypopharyngeal or cervical esophageal cancer, 1439
with otitis media, 2773
as outcome measure, 55
with rhinosinusitis, 730, 730t
after stereotactic irradiation of vestibular schwannoma, 2564-2565
Quality of Life in Reflux and Dyspepsia (QOLRAD), 57-58
Quality of Well Being (QWB), 56
Quality-adjusted life-year (QALY), costs per, for cochlear implants
in adults, 2251, 2252t
in children, 2252-2253, 2253f
Quality-based purchasing, 78
Quebec Sleep Questionnaire (QSQ), 57
Quid, and oral cancer, 1294, 1365
Quinine
ototoxicity of, 2176
sensorineural hearing loss due to, 2120, 2176
Quinolones, for rhinosinusitis, 734t, 736
Quivering mutation, 2081
QWB (Quality of Well Being), 56

R

RA (rheumatoid arthritis)
laryngeal and tracheal manifestations of, 891, 891f
oral manifestations of, 1253, 1253t
of temporomandibular joint, 1281t, 1282
Racemic epinephrine, for croup, 2806
postintubation, 2593
Racial differences, in otitis media, 2766
Rad, 132-133, 1031, 1033
Radial forearm free flap (RFFF)
fasciocutaneous, 1082t, 1083, 1083f
for hypopharyngeal and esophageal reconstruction, 1433, 1455
for oropharyngeal reconstruction, 1379, 1379f
tubed, 1087, 1091f
for oral cancer, 1316
for oropharyngeal reconstruction, 1379, 1379f
of soft palate, 1382, 1383f
of tongue base, 1389
of tonsils and pharyngeal wall, 1386
osteocutaneous, 1082t, 1085-1086, 1086f-1087f
for mandibular defects, 1324-1325, 1325t
after total laryngopharyngectomy, 1574, 1574f-1575f
Radiation
characteristics of, 1031, 1031f-1032f
defined, 1031
electromagnetic, 1031, 1031f
ionizing, 1032, 1036
particulate (corpuscular), 1031
spontaneous emission of, 26, 26f
stimulated emission of, 26, 26f
Radiation absorbed dose, 132-133
Radiation damage
gene therapy for, 23
mechanisms of, 1036-1043, 1037f
Radiation dose, 1033
Radiation dose equivalent, 133
Radiation esophagitis, 1406
Radiation exposure, 132-133, 133t
and parathyroid neoplasms, 1775
and salivary gland neoplasms, 1163
sensorineural hearing loss due to, 2122
and skin flap survival, 1075
and thyroid carcinoma, 1753
Radiation fractionation, 1040
Radiation physics, 1031-1033
characteristics of radiation in, 1031, 1031f
deposition of dose in, 1033
deposition of energy in, 1033
interactions of x-rays with matter in, 1032-1033, 1032f
coherent scattering as, 1032
Compton scattering as, 1032f, 1033
pair production as, 1032f, 1033
photodisintegration as, 1033
photoelectric effect as, 1032-1033, 1032f
radiation production in
from linear accelerators, 1032-1033
by radioactive decay, 1031-1032
Radiation production
from linear accelerators, 1032-1033
by radioactive decay, 1031-1032
Radiation therapy (RT), 1030-1050
abnormal facial growth and development due to, 2622-2623, 2626t
adjuvant
for advanced-stage glottic cancer, 1584-1585, 1584t
for salivary gland neoplasms, 1197-1198, 1198t
advanced technologies in, 1043-1047
brachytherapy as, 1047
imaging-guided, 1043, 1046-1047
intensity-modulated, 1043-1046, 1044f
advantages of, 1043
clinical results of, 1045-1046, 1045f
defining target in, 1044
inverse planning in, 1043
number and directions of beams in, 1045
selection and outlining of targets in, 1044-1045, 1045f
neutron and carbon ion therapy as, 1046
proton therapy as, 1046
basic physics of, 1031-1033
characteristics of radiation in, 1031, 1031f
deposition of dose in, 1033
deposition of energy in, 1033
interactions of x-rays with matter in, 1032-1033, 1032f
coherent scattering as, 1032
Compton scattering as, 1032f, 1033
pair production as, 1032f, 1033
photodisintegration as, 1033
photoelectric effect as, 1032-1033, 1032f
radiation production in
from linear accelerators, 1032-1033
by radioactive decay, 1031-1032
brachytherapy for, 1036, 1047
interventional bronchoscopy with endobronchial, 1010t
maxillofacial prosthodontics in, 1332, 1335f
for oral cancer, 1314, 1314f
for unresectable tracheal tumor, 1621
for carotid paragangliomas, 1661
for cervical lymph node metastases
of hypopharyngeal tumors, 1689t
indications for neck node dissection after, 1694
of laryngeal tumors, 1690t
late complications of, 1694-1695
with N0 status, 1688, 1690, 1692, 1692t
with N1-N3 status, 1692-1695
of nasopharyngeal tumors, 1690, 1690t
neck control after, 1692-1693, 1693t
of oral cavity tumors, 1689t
of oropharyngeal tumors, 1689t
postoperative, 1693-1694, 1694t
retropharyngeal, 1688
target volumes for, 1688-1690
delineation of, 1690-1691, 1691f
for hypopharyngeal tumors, 1689t
for laryngeal tumors, 1690t
for nasopharyngeal tumors, 1690, 1690t
for oral cavity tumors, 1689t
for oropharyngeal tumors, 1689t
techniques for, 1691, 1692f
with chemotherapy (*See* Chemoradiation therapy (CRT))
conservation laryngeal surgery and, 1559-1560
in conventional medicine, 1033-1036
brachytherapy for, 1036
energy of x-rays used in, 1033-1036
external beam radiation for, 1033
treatment aspects of, 1035-1036
linear accelerators in, 1034
block diagram of, 1034f
megavoltage x-rays produced by, 1034
orthovoltage x-rays produced by, 1034
photograph of, 1035f
particle beams in, 1034-1035, 1035f
treatment planning for, 1036

Radiation therapy (RT) *(Continued)*
for cranial base tumors, 1695-1700
anterior, 1697-1699
benign, 2557-2566
cystic schwannomas as, 2563
dose selection for, 2558
facial nerve outcomes with, 2563
fractionation *vs.* nonfractionation of, 2558-2559, 2561t
gamma knife–based, 2559t
hearing outcomes with, 2562-2563, 2562t
hydrocephalus due to, 2563
imaging for, 2558
jugular foramen schwannomas as, 2565
LINAC-based, 2560t
neurofibromatosis 2–related vestibular schwannoma as, 2563
outcome assessment with, 2559-2563
paraganglioma as, 2565, 2565t
principles of, 2557-2558, 2558f
quality of life with, 2564-2565
radiobiology of, 2558
treatment of failures of, 2564
trigeminal nerve outcomes with, 2563
tumor control with, 2562
vestibular schwannomas as, 2558, 2560f
with chemotherapy, 1700
complications after, 1700
malignant, 1695-1700
anterior, 1697-1699
with chemotherapy, 1700
chordoma/chondrosarcoma as, 1699
complications after, 1700
CyberKnife, 1696
esthesioneuroblastoma as, 1697-1698, 1698f, 1698t
intensity-modulated, 1696-1697
middle, 1699-1700
nasopharyngeal carcinoma as, 1699-1700, 1699f, 1700t
proton beam, 1696
sinonasal undifferentiated carcinoma as, 1698-1699
stereotactic, 1696, 1700
middle, 1699-1700
dental management after, 1333-1337
with conventional 3D conformal radiation therapy, 1333-1335, 1336f
with intensity-modulated radiation therapy, 1335-1337, 1336f-1337f
ipsilateral *vs.* contralateral, 1335
dental management during, 1333
dental management prior to, 1330-1331, 1330b, 1331f, 1579
for esophageal carcinoma, preoperative, 1444
facial moulage recording and bolus fabrication for, 1331, 1332f
and facial nerve rehabilitation, 2420
four Rs of, 1039-1040, 1039f
for Graves' ophthalmopathy, 1811
for hard palate malignancy, 1310
high-dose-rate, 1047
historical background of, 1031
for hypopharyngeal cancer, 1433, 1443, 1589-1592
advanced-stage, 1591-1592
complications of, 1591
CyberKnife stereotactic approach for, 1592
future strategies and directions for, 1592
outcome and prognostic factors for, 1591
RADPLAT approach for, 1592
techniques and dose-fractionation schemes for, 1591
anatomic considerations in, 1578-1579, 1579f

Radiation therapy (RT) *(Continued)*
early-stage, 1590-1591
complications of, 1591
outcome and prognostic factors for, 1591, 1591t
techniques and dose-fractionation schemes for, 1590-1591
lymphatic drainage and, 1578-1579, 1579f
overview of, 1578
recurrent, 1591-1592
therapeutic outcome of, 1436
hypothyroidism after, 1747
imaging-guided, 1043, 1046-1047
intensity-modulated, 1043-1046, 1044f
advantages of, 1043
for cervical metastases, 1691-1692, 1692f
clinical results of, 1045-1046, 1045f
complications of, 1700
defining target in, 1044
dental management after, 1335-1337, 1336f-1337f
forward-planning, 1696-1697
for glottic cancer, 1585-1586
inverse-planning, 1043, 1696-1697
for malignant skull base tumors, 1696-1697
for nasopharyngeal carcinoma, 1045, 1699-1700, 1699f, 1700t
number and directions of beams in, 1045
selection and outlining of targets in, 1044-1045, 1045f
and xerostomia, 1103
intraoral positioning devices for, 1331, 1333f
for laryngeal cancer, 1577-1593
advanced glottic, 1497, 1583-1588
balancing cure, organ preservation, and quality of life with, 1583-1584
with chemotherapy, 1584-1586, 1584t
complications of, 1587-1588
dose-fractionation schemes for, 1586, 1586t
general principles of, 1585-1586
mini-mantle field technique for, 1586
outcomes and prognostic factors for, 1586-1587, 1587t
patient setup for, 1586
postoperative (adjuvant), 1584-1585, 1584t
shrinking-field technique for, 1586, 1587f
with targeted biologic agents, 1585
advanced supraglottic, 1589
outcomes and prognostic factors for, 1589, 1590t
techniques and dose-fractionation schemes for, 1589
anatomic considerations with, 1578-1579, 1578f
with anterior commissure involvement, 1496-1497
CyberKnife stereotactic approach for, 1592
early glottic, 1519-1520, 1581
complications of, 1583
effectiveness of, 1496
local control with, 1519, 1522f
outcome and prognostic factors for, 1581-1583, 1582t-1583t
recurrence after, 1522t
results of, 1519, 1521t
techniques and dose-fractionation schemes for, 1580-1590, 1581f-1582f
early supraglottic, 1496, 1588-1589
complications of, 1589
outcomes and prognostic factors for, 1589, 1589t
techniques and dose-fractionation schemes for, 1588-1589
future strategies and directions for, 1592
lymphatic drainage and, 1578-1579, 1579f
with nodal metastases, 1498
overview of, 1578

Radiation therapy (RT) *(Continued)*
RADPLAT approach for, 1592
recurrence after, 1476-1479, 1522, 1522t
recurrent, 1591-1592
subglottic, 1589-1590
with trasoral laser microsurgery, 1532-1533
laryngeal stenosis due to, 2915
Marx hyperbaric oxygen regimen after, 1333
for maxillary sinus tumor, 1128-1130
with maxillectomy, 1128
maxillofacial prosthetics and, 1330
dental diagnoses and oral surgical management prior to, 1330-1331, 1330b, 1331f
dental management after, 1333-1337
with conventional 3D conformal radiation therapy, 1333-1335, 1336f
with intensity-modulated radiation therapy, 1335-1337, 1336f-1337f
ipsilateral *vs.* contralateral, 1335
dental management during, 1333
overview of interactions of, 1337-1344
prosthodontic support of radiation oncologist in, 1331-1332
with brachytherapy, 1332, 1335f
for facial moulage recording and bolus fabrication, 1331, 1332f
intraoral positioning devices in, 1331, 1333f
for portals and shielding devices, 1331-1332, 1334f
shelf for tissue-equivalent material in, 1332, 1335f
for melanoma, 1118
for nasopharyngeal carcinoma, 1354-1355
intensity-modulated, 1045, 1699-1700, 1699f, 1700t
of neck
radiographic appearance after, 1476-1479
for salivary gland neoplasms, 1198
neck after, 173-174, 176f
neck dissection after, 1694, 1721
neutron beam, for salivary gland neoplasms, 1198-1199
for oral cancer, 1314
brachytherapy as, 1314, 1314f
external beam, 1314
package time for, 1314
oral treatment considerations with, 1246t
postoperative, 1042-1043
for premalignant lesions of larynx, 1490
prosthetic voice rehabilitation and, 1600, 1602b
proton beam, for malignant skull base tumors, 1696
radiobiology in, 1036-1043, 1037f
cell cycle arrest in, 1037, 1037f
cell survival in, 1037-1039, 1038f
clinical applications of, 1040-1043
with concomitant chemotherapy, 1041-1043
hypoxia in, 1041
radiation fractionation as, 1040
radiosensitizers as, 1040-1043
mitotic death in, 1037
radiosensitivity in, 1037
tissue-radiation characterizations in, 1039-1040, 1039f
radiographic appearance of pharynx and esophagus after, 1418, 1418f
for rhabdomyosarcoma, 2841-2842
and salivary gland neoplasms, 1163
for salivary gland neoplasms, 1197-1199
adjuvant, 1197-1198, 1198t
in children, 2863
of neck, 1198
neutron beam, 1198-1199
shelf for tissue-equivalent material in, 1332, 1335f
shielding devices for, 1331-1332, 1334f
side effects of, 1047-1049

Radiation therapy (RT) *(Continued)*
acute, 1047
dermatitis as, 1047
mucositis as, 1047, 1047f
xerostomia as, 1047
late toxicities as, 1048-1049
fibrosis as, 1048
neurologic complications as, 1049
osteoradionecrosis as, 1048
thyroid dysfunction as, 1048
vascular complications as, 1048-1049
xerostomia as, 1048
and skin flap survival, 1075
stereotactic
for benign skull base tumors, 2557-2566
cystic schwannomas as, 2563
dose selection for, 2558
facial nerve outcomes with, 2563
fractionation *vs.* nonfractionation of, 2558-2559, 2561t
gamma knife–based, 2559t
hearing outcomes with, 2562-2563, 2562t
hydrocephalus due to, 2563
imaging for, 2558
jugular foramen schwannomas as, 2565
LINAC-based, 2560t
neurofibromatosis 2–related vestibular schwannoma as, 2563
outcome assessment with, 2559-2563
paraganglioma as, 2565, 2565t
principles of, 2557-2558, 2558f
quality of life with, 2564-2565
radiobiology of, 2558
treatment of failures of, 2564
trigeminal nerve outcomes with, 2563
tumor control with, 2562
vestibular schwannomas as, 2558, 2560f
CyberKnife
for laryngeal and hypopharyngeal cancer, 1592
for malignant skull base tumors, 1696
defined, 1696, 2557
dose selection for, 2558
history of, 1696
imaging for, 2558
for malignant skull base tumors, 1696, 1700
principles of, 2557-2558, 2558f
radiobiology of, 2558
swallowing disorders due to, 1219
with targeted biologic agents, 1054, 1055f
for laryngeal cancer, 1585
and taste, 1214
three-dimensional conformal, 1043
for cervical metastases, 1691-1692
for glottic cancer
advanced-stage, 1585-1586
early-stage, 1581, 1581f-1582f
for thyroid cancer, 1772
Radiation-guided parathyroidectomy, 1793
Radiation-induced fibrosis (RIF), 1048
Radiation-induced thyroid follicular necrosis, 1744
Radical maxillectomy, 1125-1126, 1125f
Radical neck dissection (RND), 1705-1709
anterior triangle dissection in, 1709-1710
defined, 1703t, 1705, 1709f
dissection of upper neck compartments in, 1710-1711
flap elevation in, 1709, 1711f
historical perspective on, 1702-1703
incision planning for, 1709, 1710f
indications for, 1705
modified, 1711-1712
definition of, 1703t, 1711, 1712f
historical perspective on, 1703
indications for, 1711
for oral cancer, 1313
Radical neck dissection (RND) *(Continued)*
results of, 1721
technique for, 1711-1712, 1713f-1714f
nodular masses at site of, 1476
for oral cancer, 1313
positioning for, 1709
posterior triangle dissection in, 1709
results of, 1721
Radicular cyst, 1262-1263
lateralized (lateral), 1263
microscopic features of, 1262-1263, 1262f
radiographic features of, 1262, 1262f
treatment of, 1263, 1263f
Radiesse dermal filler (calcium hydroxyapatite), for vocal fold medialization, 906
Radioactive decay, radiation production by, 1031-1032
Radioactive iodine (^{131}I)
for Graves' disease, 1743
for Graves' ophthalmopathy, 1810
stunning with, 1771
after thyroid surgery, 1771-1772
for toxic multinodular goiter, 1745
for toxic thyroid adenoma, 1744
Radioactive iodine uptake test, 1741
Radioactivity, 1031-1032
Radiobiology, 1036-1043, 1037f
cell cycle arrest in, 1037, 1037f
cell survival in, 1037-1039, 1038f
clinical applications of, 1040-1043
with concomitant chemotherapy, 1041-1043
hypoxia in, 1041
radiation fractionation as, 1040
radiosensitizers as, 1040-1043
defined, 1036
mechanisms of damage in, 1036-1043, 1037f
mitotic death in, 1037
radiosensitivity in, 1037
of stereotactic radiation therapy, 2558
tissue-radiation characterizations in, 1039-1040, 1039f
Radiofrequency neurotomy, for neuropathic pain, 246
Radiofrequency tongue base ablation (RFA), for obstructive sleep apnea, 259
Radiofrequency tonsil reduction, for obstructive sleep apnea, 2609
Radionuclide scintigraphy, 138, 139f
for CSF rhinorrhea, 790
of neck masses, 1637, 1637t
of salivary glands, 138, 1150
of thyroid nodule, 1757-1758
Radiosensitivity, 1037
Radiosensitizers, 1040-1043
Radiotherapy. *See* Radiation therapy (RT).
Radix graft, improperly placed, revision rhinoplasty for, 584
Radixin, in stereocilia, 2075-2076, 2076f
Radixin *(RDX)* gene, in deafness, 2051t-2058t, 2075-2076
RADPLAT regimen, 1054
for laryngeal and hypopharyngeal cancer, 1592
RALP (right anterior–left posterior) semicircular canal plane, 2285, 2286f, 2287
Ramsay Hunt syndrome, 1948. *See also* Herpes zoster oticus.
facial nerve paralysis in, 2393, 2396
Ramus(i), 320f
of mandible, anatomy of, 1319, 1320f, 1359f
Random cutaneous flaps, 1067, 1067f
Random sample, 68, 69t
Randomized clinical trials (RCTs), 52, 54, 54t
data quality of, 59, 60t-62t
Range, 64t
Ranitidine (Cimetidine), for recurrent respiratory papillomatosis, 2893
RANKL (receptor activator of NF-κB ligand), in bone resorption, 1972
RANTES, in otitis media, 2764
Ranula(s)
in children, 2850-2852, 2859
imaging of, 1146, 1147f
of sublingual space, 156, 157f
of submandibular space, 157
Rapid eye movement (REM) sleep, 261-262
Rapid eye movement (REM) sleep behavior disorder (RBD), 264-265
Rapid maxillary expansion (RME)
for nasal obstruction, 2630
for obstructive sleep apnea in children, 2611
Rapidly involuting congenital hemangioma (RICH), 2824
Rapid-sequence induction (RSI), 112-113
in children, 2590
RARS (recurrent acute rhinosinusitis), 705
RAS. *See* Recurrent aphthous stomatitis (RAS).
Rate difference, 64, 64t
RB tumor suppressor gene, in parathyroid neoplasm(s), 1776f
RBD (REM sleep behavior disorder), 264-265
RCTs (randomized clinical trials), 52, 54, 54t
data quality of, 59, 60t-62t
RDX (radixin) gene, in deafness, 2051t-2058t, 2075-2076
Reactive lymph nodes, 164
Reactive lymphadenopathy, 2818
Reactive oxygen species (ROS), in ototoxicity
of aminoglycosides, 2171
of carboplatin, 2173-2174
of cisplatin, 2172
Real-ear aided response or gain (REAR/G), 2273
Real-ear insertion gain (REIG), 2273
Real-ear unaided response or gain (REUR/G), 2273
Real-ear-to-coupler difference (RECD), in infants, 2724
Rearrangements, chromosomal, 4-5
Rebound headache, 248
Receiver-in-the-canal (RIC) fitting, for hearing aids, 2270
Receptor activator of NF-κB ligand (RANKL), in bone resorption, 1972
Receptor potentials, in hair cell transduction, 2071, 2072f
Recessive disorders, 6-7, 7f
Recommendation, grades of, 69-70, 70t
Reconstruction
for congenital aural atresia, 2754-2757
alternatives to, 2759
avoidance of complications of, 2758-2759
candidacy for, 2753, 2753t
contraindications to, 2754
creation of split-thickness skin graft in, 2756, 2756f
dissection of ossicular mass in, 2755-2756, 2756f
drilling for new ear canal in, 2755-2756
ear wick packing in, 2756-2757
facial nerve in, 2754, 2755f, 2759
harvesting of temporalis fascia in, 2755, 2755f
meatoplasty in, 2756-2757
outcomes of, 2754
placement of split-thickness skin graft in, 2756, 2757f-2758f
postauricular incision in, 2755, 2755f
postoperative care after, 2757-2758
preoperative evaluation and patient counseling for, 2754, 2754f-2755f
reconstruction of ossicular chain in, 2756
removal of atretic plate in, 2755-2756, 2755f
Silastic strips in, 2756-2757, 2758f
suturing in, 2756-2757, 2758f
temporal fascia graft in, 2755f, 2756, 2757f
timing of, 2754

Reconstruction *(Continued)*
for hypopharyngeal cancer, 1431-1433
with circumferential defects, 1431-1432
fasciocutaneous free flaps in, 1433
gastric pull-up in, 1432, 1432f
jejunal free flap in, 1432-1433, 1433f
pectoralis myocutaneous flap in, 1431, 1431f
mandibular (*See* Mandibular reconstruction)
for microtia
advantages and disadvantages of, 2744t
atypical, 2747-2748, 2749f-2750f
autogenous costochondral, 2744, 2744t
classic, 2744-2747
cartilage implantation in, 2744-2746
carving of framework and helix in, 2746, 2746f
construction of implant in, 2746, 2746f
creation of postauricular sulcus in, 2746, 2748f
donor site in, 2745, 2745f
incision in, 2745-2746
lobule transfer in, 2746, 2747f
placement of implant in, 2746, 2747f
templates in, 2744-2745, 2745f
tragus reconstruction in, 2747, 2748f
complications of, 2748-2751
planning for, 2743-2744, 2744t
for oral cancer, 1315-1316
of alveolar ridge, 1304
of buccal mucosa, 1308-1309, 1309f
of floor of mouth, 1307, 1315f
free flap, 1316, 1316f
of hard palate, 1310, 1311f
of lip, 1303-1304, 1303f
of tongue, 1305-1306
oropharyngeal (*See* Oropharyngeal reconstruction)
for skull base defects, 2467-2468
after subtotal or total temporal bone resection, 2495
after total laryngopharyngectomy, 1574, 1574f-1575f
after transnasal endoscopic-assisted anterior skull base surgery, 2484
Reconstructive procedures, hair loss with, 387, 388f
Reconstructive surgery, gene therapy for, 22-23
with reconstructive tissue flaps and wound healing, 22-23
with skin grafting, 23
Recording electrodes, for intraoperative cranial nerve monitoring, 2543-2544, 2543f
Recruitment
vs. hyperacusis, 2138
with traditional hearing aid, 2205-2207
Rectus abdominis free flap, 1082t, 1083
for oropharyngeal reconstruction, 1082t, 1083
of tongue base, 1390, 1390f
of tonsils and pharyngeal wall, 1386
Rectus capitis major muscle, 2439f
Rectus lateralis muscle, 2439f
Recurrent acute rhinosinusitis (RARS), 705
Recurrent aphthous stomatitis (RAS), 1236-1239
clinical features of, 1237-1238
defined, 1236-1237
differential diagnosis of, 1238, 1238t
etiology and pathogenesis of, 1237, 1237t
herpetiform-type, 1238, 1238f
histopathologic features of, 1239
major, 1237-1238, 1238f
minor, 1237, 1238f
treatment of, 1239
Recurrent laryngeal nerve (RLN)
applied anatomy of, 807
characteristics of, 918
denervation of
effects of, 919
reinnervation for (*See* Laryngeal reinnervation)
in root of neck, 2582
Recurrent laryngeal nerve (RLN) *(Continued)*
and thyroid gland, 1752, 1752f
in thyroid surgery
identification of, 1765, 1765f
injury of, 1770-1771
invasive carcinoma of, 1766
reoperative, 1767
Recurrent laryngeal nerve (RLN) injury
electromyography of, 835
due to thyroid surgery, 1770-1771
Recurrent parotitis of childhood (RPC), 1153-1154
Recurrent paroxysmal laryngospasm, 808
Recurrent respiratory papillomatosis (RRP), 878-880, 2884-2895
adult-onset, 879
clinical features of, 2887-2888, 2887f-2888f
CO_2 laser for, 32
epidemiology of, 878, 2884-2885
etiology of, 878-879, 2885-2886
extralaryngeal spread of, 2887, 2887f-2888f
gastroesophageal reflux and, 2946
gross appearance of, 868f-869f, 2885f
histopathology of, 2885-2886, 2885f
juvenile form of, 879
malignant transformation of, 2887-2888
other considerations with, 2894
patient assessment for, 2888, 2889f
airway endoscopy in, 2888
history in, 2888
physical examination in, 2888
practice pathway for, 2889f
prevention of, 2886-2887, 2890t
registry and task force initiatives for, 2894
staging severity of, 2893-2894, 2893f-2894f
support groups for, 2894
tracheostomy and, 2887
transmission of, 2886
treatment of, 2890t
adjuvant modality(ies) for, 2891-2893
acyclovir as, 2890t, 2892
antireflux therapy as, 2893
celecoxib as, 2892
cidofovir as, 879-880, 2890t
indole-3-carbinol as, 879, 2890t, 2892
interferon as, 879, 2890t., 2891-2892
methotrexate as, 879
mumps vaccine as, 2890t, 2892-2893
photodynamic therapy as, 2890t, 2892
retinoids as, 2890t, 2892
ribavirin as, 2892
vaccines for, 2890t
surgical, 2888-2891
anesthetic techniques for, 2891
carbon dioxide laser for, 879, 2889-2891
emerging technologies for, 2891
microdebrider for, 2891
pulsed dye laser for, 880, 880f, 2891
virology of, 2885-2886
vocal quality disorder due to, 2880-2881
Recurrent Respiratory Papillomatosis Foundation, 2894
Redistribution, in radiotherapy, 1039, 1039f
Reduced penetrance, 7
Reed-Sternberg cells, 2838-2839
Reepithelialization, 1076-1077
keratinocyte migration in, 1076-1077
keratinocyte proliferation in, 1077
Reexcision, for scar revision, 295, 297f
Referral sources, for children, 2572-2573
Referred pain, trigeminal system in, 1203
Refixation saccade, 2292
Reflection, of laser energy, 28-29, 29f
Reflux. *See also* Gastroesophageal reflux disease (GERD).
outcome scales for, 57-58
Reflux esophagitis, 968-969, 969f, 1403-1404, 1403f-1404f
Reflux Finding Score (RFS), 897, 897t
Reflux laryngitis, 886, 886f
in voice professional, 852
Reflux laryngopharyngitis, 863, 863f
Reflux Symptom Index (RSI), 826, 826t, 896, 897b
Refsum disease
biochemical defect in, 7
sensorineural hearing loss in, 2094t, 2096
Region of transient electronic equilibrium, in radiation, 1033
Regional anesthesia, for postoperative pain control, 241-242
Regional flaps
for hypopharyngeal and esophageal reconstruction, 1450-1452
for oropharyngeal reconstruction, 1377-1379
latissimus dorsi musculocutaneous, 1378, 1378f
pectoralis major, 1377, 1377f
platysmal myocutaneous, 1377, 1378f
temporalis, 1377-1378
temporoparietal fascial, 1377-1378, 1378f
of tongue base
latissimus dorsi, 1389
pectoralis major myocutaneous, 1388-1389
platysmal myocutaneous, 1389
of tonsils and pharyngeal wall
pectoralis major, 1385, 1385f
platysmal myocutaneous, 1385
sternocleidomastoid myocutaneous, 1385-1386
temporalis, 1386
temporoparietal fascia, 1386
trapezius musculocutaneous, 1378-1379
Register shifts, 851
Registration, for image-guided sinus surgery, 680-681
Regression procedures, 72
Regression to the mean, *vs.* efficacy of treatment, 62t
Regularity, laryngeal videostroboscopy of, 821
Regulatory accountability, 82
Regulatory T cells (Tregs), 602-603
Regurgitation, 956
Rehabilitation
after cochlear implantation, 2253-2257
in adults, 2254-2255
in children, 2254-2255
efficacy of, 2253-2254
facial nerve (*See* Facial nerve rehabilitation)
after total laryngectomy, 1572
for swallowing, 1572
for voice, 1572
after total laryngopharyngectomy, 1575
vestibular (*See* Vestibular and balance rehabilitation therapy (VBRT))
voice (*See* Voice rehabilitation)
Reicher's cartilage, 2583-2584
Reinke's space, 812, 845
surgical anatomy of, 1544f
Reissner's membrane
anatomy of, 1831-1832, 1832f, 2050, 2061f
in auditory physiology, 1841f
Reiter's syndrome, oral manifestations of, 1253
Relapsing polychondritis
laryngeal and tracheal manifestations of, 890
sensorineural hearing loss due to, 2124
Related samples, statistical tests for, 66, 67t
Relative risk, 64, 64t
Relaxed skin tension lines (RSTLs), 269-270, 274f
and scars, 295, 296f
Release maneuvers, with tracheal resection, 1618-1619, 1620f
Reliability, in psychometric validation, 55
rem (Roentgen equivalent for man), 133
REM (rapid eye movement) sleep, 261-262
REM (rapid eye movement) sleep behavior disorder (RBD), 264-265

Remifentanil
for anesthesia induction, 111
for anesthesia maintenance in children, 2592
Remineralization, of teeth, 1141
Remodeling phase, of wound healing, 1078
Renal disease
oral manifestations of, 1255
preoperative evaluation of, 103
sensorineural hearing loss with, 2121
Renal failure, oral manifestations of, 1255
Renal failure–induced hyperparathyroidism, 1797-1798
Renal symptoms, of hyperparathyroidism, 1781-1782
Renal transplantation, oral sequelae of, 1255
Renal-coloboma syndrome, deafness in, 2051t-2058t
Rendu-Osler-Weber syndrome, 291
oral manifestations of, 1257
Renin, in saliva, 1140
Renova (tretinoin)
for aging skin, 403-404
with chemical peels, 392-393
for chemoprevention of oral cancer, 1315
Reoxygenation, in radiotherapy, 1039, 1039f
Repair, in radiotherapy, 1039
Repaired Facial Nerve Recovery Scale (RFNRS), 2414, 2414t
Repeated samples, statistical tests for, 66, 67t
Reperfusion injury, in acutely raised skin flaps, 1070, 1074
Repopulation, in radiotherapy, 1039
Repose tongue suspension procedure, for obstructive sleep apnea, 259-260
Repositioning maneuvers, for benign paroxysmal positional vertigo, 2331-2332, 2332f
RERA (respiratory effort–related arousals), 251-252, 251b
RERA (respiratory effort–related arousal) index, 251b
Rerouting, of facial nerve, 2412, 2412f-2413f
partial, 2412-2413
Research integration, 69-70
Residual cyst, 1263
Residual hearing
cochlear implants with
in adults, 2245-2246
in children, 2240
ear selection for, 2236
in patient selection for ablative vestibular surgery, 2366
Reskeletonization, in septoplasty, 491
Resonance
in speech, 810-812, 833
speech therapy for, with velopharyngeal dysfunction, 2681
in voice evaluation, 826-827
Resonance disorders, in children, 2879
Resorbable Fixation System, for pediatric facial fractures, 2701t
Resorbable plating systems, for pediatric facial fractures, 2700-2701, 2700t-2701t
Respiratory changes, in geriatric patients, 236
Respiratory disturbance index, 251b
Respiratory effort–related arousal(s) (RERA), 251-252, 251b
Respiratory effort–related arousal (RERA) index, 251b
Respiratory epithelium, in olfactory area, 625, 625f
Respiratory rate, in children, 2570
Respiratory syncytial virus (RSV) vaccine, to prevent otitis media, 2769
Respiratory system
of children, 2569-2570
and control of ventilation, 2569-2570
and laryngospasm, 2570
and lung volumes, 2570
Respiratory system *(Continued)*
and respiratory rate, 2570
and ventilation-perfusion relationships, 2570, 2571t
preoperative evaluation of, 102-103
Respiratory viruses, and otitis media, 1871
Responsiveness, in psychometric validation, 55
Restech Dx-pH Measurement System, 962, 962f
Restless leg syndrome (RLS), 265
Restriction enzymes, 9
Restriction sites, 9
Rests of Malassez, 1259
Resurfacing, facial. *See* Facial resurfacing.
RET oncogene
suppression of expression of, 13
in thyroid carcinoma, 1753
Retention cysts, esophageal, 1415-1416, 1415f
Reticular dermis, 1065
Reticular lamina
anatomy of, 1832-1833, 1832f
in cochlear transduction, 2065-2066, 2069f
scanning electron micrograph of, 1833, 1833f
Reticulosis, midline malignant (polymorphic), 659-660
Retin A (tretinoin)
for aging skin, 403-404
with chemical peels, 392-393
for chemoprevention of oral cancer, 1315
Retinal slip velocity, 2277
Retinoic acid (Retin A)
after chemical peel, 396
for head and neck squamous cell carcinoma, 1018
Retinoids
for cancer chemoprevention, 1018, 1061-1062
for recurrent respiratory papillomatosis, 2890t, 2892
Retinol, for cancer chemoprevention, 1018, 1061-1062
Retinyl palmitate, for cancer chemoprevention, 1061-1062
Retroauricular flap, for nasal defects, 365-366, 371f
Retroauricular lymph nodes
anatomy of, 1718f, 2582
dissection of, 1718-1719
Retrobulbar fibroblast, in Graves' ophthalmopathy, 1807
Retrobulbar recess
normal anatomy of, 667
surgical anatomy of, 740
Retroclival region
in surgical anatomy of anterior skull base, 2474-2475, 2474f-2475f
transnasal endoscopic-assisted surgery of, 2479-2481, 2480f-2481f
Retrocochlear neoplasm, in cerebellopontine angle, hearing loss due to, 2199
Retrocochlear vertigo, 2202
Retrognathia, dysphagia due to, 2950-2951
Retrograde dilators, for esophageal strictures, due to caustic ingestion, 2960-2962, 2960f-2961f
Retrograde intubation, for difficult airway, 114t
Retrograde-eversion approaches, for nasal tip refinement, 522, 523f-526f
Retrolabyrinthine approach
for intratemporal facial nerve surgery, 2405-2406, 2405f-2406f
for posterior fossa neoplasms, 2532t, 2536
advantages and disadvantages of, 2532t, 2536
basic features of, 2536
indications for, 2532t, 2536
surgical exposure in, 2536f
technique of, 2536, 2536f
Retromandibular vein, in parotidectomy, 1195-1196, 1195f
Retromolar trigone
anatomy of, 1295f, 1297, 1298f
carcinoma of, 1306-1307
clinical presentation of, 1306
resection for, 1307, 1307f
survival with, 1307
lymphatic drainage of, 1297, 1298f
melanoma of, 1364f
vasculature of, 1296
Retronasal stimulation, 631
Retropharyngeal abscess, 1407, 1465-1466
in children, 2789-2790, 2789f, 2810-2811
anatomy of, 2810
clinical features of, 2810
complications of, 2811
diagnosis of, 2810-2811, 2810f-2811f
differential diagnosis of, 2806t
epidemiology of, 2810
historical background of, 2810
imaging of, 2810-2811, 2810f-2811f
management of, 2811
imaging of, 1465-1466, 1466f
infrahyoid, 134
suprahyoid, 153, 155f
Retropharyngeal cellulitis, 2810-2811, 2810f
Retropharyngeal lymph node(s), in hypopharyngeal and cervical esophageal cancer, 1434-1435
Retropharyngeal lymph node metastasis, 1687-1688
Retropharyngeal lymphadenopathy, 1414, 1415f
Retropharyngeal space (RPS)
anatomy of, 202
infections of, 207
in children, 2789-2790, 2789f
odontogenic, 185-186, 187f
airway establishment for, 188
normal anatomy and, 186f
of infrahyoid neck, imaging of, 158
with lesions, 158, 161f
normal anatomy in, 158, 159f-160f
of suprahyoid neck, imaging of, 146f, 152f, 153, 155f
Retrosigmoid approach
for intratemporal facial nerve surgery, 2406-2407
advantages and uses of, 2406-2407
limitations and potential complications of, 2407
technique of, 2406, 2407f
for posterior fossa neoplasms, 2532t, 2533-2534
advantages and disadvantages of, 2532t, 2534
basic features of, 2533
indications for, 2532t, 2533
surgical exposure in, 2533f
technique of, 2534, 2534f
Retrospective studies, 61
Retrovascular node, 1298f
Retroviral vectors
for gene therapy of inner ear, 2191t
for gene transfer, 16, 17f, 18t
RetroX, 2204f, 2206t, 2217, 2217f
REUR/G (real-ear unaided response or gain), 2273
Revascularization, of acutely raised skin flaps, 1069, 1069f
Review of systems, 94, 94b
Revision rhinoplasty, 580-594
for alar pinching and retraction, 587, 587f-589f
for caudal septal deviation, 593
for caudal septal excision (short nose), 593
computer imaging for, 581-582
for dorsal irregularity, 584
due to errors of omission, 582, 582t
due to excessive excision, 582, 582t, 583f
due to failure to restabilize, 582, 582t
general considerations with, 582-583, 582t, 583f
grafting material for, 583, 584f
due to gross errors of judgment, 582-583, 582t, 583f
for improperly placed radix graft, 584
for lateral nasal wall deformities, 586

Revision rhinoplasty *(Continued)*
for low dorsum/saddle deformity, 584, 585f
for middle vault deformities, 585-586, 586f
due to minor errors of technique, 582, 582t
for nasal tip deformities, 588
irregularities and bossae as, 588-589, 590f
overrotation (short nose) as, 590, 590f-591f
persistently wide or bulbous tip as, 589-590, 590f
pinched tip as, 590, 591f-592f
ptotic tip as, 590-593, 593f
for overly narrowed alar base, 593-594, 594f
patient interview for, 580-581
photography for, 581
physical examination for, 581
for pollybeak deformity, 584-585, 586f
of skin–soft tissue envelope, 581, 594
for supra-alar and external valve collapse, 586-587, 587f
Reynell Developmental Language Scale, 2249-2250
RFA (radiofrequency tongue base ablation), for obstructive sleep apnea, 259
RFFF. *See* Radial forearm free flap (RFFF).
RFNRS (Repaired Facial Nerve Recovery Scale), 2414, 2414t
RFS (Reflux Finding Score), 897, 897t
Rhabdomyoma, of larynx, 881
Rhabdomyosarcoma (RMS)
in children, 2820, 2840-2842
epidemiology of, 2820, 2840
histopathology and molecular biology of, 2842, 2842f
management of, 2820, 2841-2842
presentation and evaluation of, 2840-2841, 2841t
sites of, 2820
survival with, 2840
of middle ear or mastoid, 2501-2502
of neck, 1667-1668, 1668f, 1669t
of paranasal sinuses, 1132
Rheologic disorders, sensorineural hearing loss due to, 2123
Rheology, and skin flap viability, 1073-1074
Rheumatic fever, acute, 2788
Rheumatoid arthritis (RA)
laryngeal and tracheal manifestations of, 891, 891f
oral manifestations of, 1253, 1253t
of temporomandibular joint, 1281t, 1282
Rheumatrex. *See* Methotrexate (Rheumatrex).
Rhinion, 496, 497f
Rhinitis
allergic (*See* Allergic rhinitis (AR))
atrophic, 696-697
chronic (*See* Nonallergic rhinitis (NAR))
cold air–induced, 619b
drug-induced, 619b, 696, 697b
granulomatous, 619b
gustatory, 698
idiopathic, 695
in immunocompromised patient, 660
infectious, 619b
irritant, 697-698
due to mechanical obstruction, 619b
medicamentosa, 862-863
neoplastic, 619b
nonallergic (*See* Nonallergic rhinitis (NAR))
occupational, 698
perennial, 619b, 695
nonallergic, noninfectious, 695
during pregnancy, 696, 702
vasomotor, 619b, 695, 698
Rhinitis Outcome Questionnaire, 57
Rhinitis Quality of Life Questionnaire (RQLQ), 642
Rhinoconjunctivitis, allergic, 622
Rhinocort (budesonide nasal spray)
for nonallergic rhinitis, 700t
for rhinosinusitis, 734t, 736
Rhinohygrometry, 642
Rhinologic disease, outcome scales for, 56t, 57
Rhinomanometry, 643-651
vs. acoustic rhinometry, 644
active *vs.* passive, 647-648
in allergic rhinitis, 651
anterior
placement of pressure tubing for, 645-646, 648f
vs. posterior, 645-647
technique of, 645
baseline collection in, 645f
dilating devices in, 648f
for left nasal airway, 647f-648f
positioning in, 645f
for right nasal airway, 646f-647f
to assess effect of treatment, 651-652
for children, 645
defined, 642
equipment for, 645
examining pressure-flow curve in, 648-649, 649f-650f
forced oscillation, 643-644
inspiratory or expiratory values in, 650-651
intranasal sites assessed by, 644
maximum (vertex) resistance in, 650
nasal airflow in
measurement of, 647
and transnasal pressure, 643
nasal resistance in, 649-650, 650f
parameters in, 649-651, 650f
posterior (peroral)
vs. anterior, 645-647
placement of pressure tubing for, 645-646, 649f
postnasal (pernasal), placement of pressure tubing for, 645-646, 649f
reporting results of, 648-651
sources of variability in, 651
technical concerns and testing pitfalls with, 645-648
technique of, 645
baseline collection in, 645f
dilating devices in, 648f
for left nasal airway, 647f-648f
positioning in, 645f
for right nasal airway, 646f-647f
transnasal pressure in
measurement of, 645-647, 648f
nasal airflow and, 643
unilateral *vs.* bilateral measurements in, 648, 649f
Rhinometry
acoustic, 486-487, 643-645
in allergic rhinitis, 651
to assess effect of treatment, 651-652
equipment for, 486-487, 486f, 644
interpretation of results of, 645
intranasal sites assessed by, 644
reporting results of, 645
rhinogram generated by, 486-487, 487f, 645
vs. rhinomanometry, 644
for snoring and sleep apnea, 651
sources of variability in, 651
technical concerns and testing pitfalls with, 645
technique of, 644-645
airflow, 487
manometric, 643-644
Rhinoplasty, 508-544
anesthesia for, 515-519, 518f
and surgical planes, 516-517, 516f-517f
anosmia after, 637
of bony vault, 540-542
for bony profile reduction, 540-541, 540f
for narrowing of nose, 541-542
double osteotomies in, 542, 542f-543f
lateral osteotomies in, 541, 542f
medial-oblique osteotomies in, 541, 541f
Rhinoplasty *(Continued)*
of cartilaginous vault, 536-540
access to nasal skeleton in, 537-539, 539f
aesthetic improvement after, 537, 538f
factors to consider in, 537
incremental cartilaginous profile alignment in, 539
mucoperichondrium in, 539-540
pollybeak deformity due to, 512, 512f, 539, 539f
for reduction of overlong caudal quadrangular cartilage, 513f
with traumatic or iatrogenic avulsion of upper lateral cartilage, 539-540, 540f
for cleft-lip nose, 557-559, 561f
Abbé flap in, 563f-564f
with bilateral deformity, 557, 559, 561f, 563f-564f
columellar lengthening in, 559, 566f
external approach to, 559, 561f
lateral ala thinning and placement of maxillary implants in, 562f
Le Fort I maxillary osteotomies in, 559, 564f-565f
with nasal stenosis, 559, 566f
open approach to, 559, 562f
repositioning and suturing lower lateral cartilage in, 562f
with severe deformity, 559, 564f-565f
suturing together medial crura in, 561f-562f
with unilateral deformity, 557, 559, 561f-562f
complications of
noncaucasian, 578, 578f-579f
revision rhinoplasty for (*See* Rhinoplasty, revision)
components of successful, 516f
inverted V sign after, 492, 493f
of nasal tip, 519-536
considerations in, 520, 522f
delivery approaches to, 522, 527f
complete strip technique in, 522, 527f-530f
interrupted strip technique in, 522, 532f-533f
suturing in, 522, 530f-531f, 550-551
incisions, approaches, and techniques for, 520, 521f, 521t
in noncaucasian patients, 573-577
cap graft in, 576, 577f
caudal extension graft in, 576, 576f
concept of, 573-576
reshaping of lower lateral cartilage in, 577
shield graft in, 576, 577f
technique for, 576-577
thinning of subcutaneous tissue in, 577, 577f
nondelivery (cartilage-splitting, retrograde-eversion) approaches to, 522, 523f-526f
objective of, 519
open approach to, 522-535, 534f-535f
indications for, 521b
preservation of lateral crus and strip of alar cartilage in, 520-522, 522f
tip projection in, 520, 535-536, 549-551
autogenous cartilage struts for, 535-536, 536f
cephalic rotation for, 519, 536, 549-550, 551f
onlay tip cartilage grafts for, 535-536, 537f, 549-550, 550f-551f
partial-transfixion *vs.* complete-transfixion incisions for, 535-536, 536f
plumping grafts for, 535-536, 536f
transdomal sutures for, 536
tip ptosis after, 519, 520f
tip support mechanisms and, 519, 520f
for nasofrontal angle modifications, 548-549, 550f
noncaucasian, 556-557, 568-579
aesthetic considerations in, 569
alar base modification in, 577-578, 578f

Rhinoplasty *(Continued)*
alar soft tissue sculpting in, 557, 561f
anatomic considerations in, 568-569, 569f, 569t
complications of, 578, 578f-579f
for correction of deviated nose, 573, 576f
dorsal augmentation in, 556, 569-570
choice of material for, 569, 570f
concept of, 569
results of, 572f-573f
technical considerations for, 569-570, 571f
hump reduction in, 570-573
concept of, 570-571
results of, 574f-575f
technique for, 571-573, 575f
nasal base sculpting in, 556-557, 559f-560f
objective of, 568
tip surgery in, 573-577
cap graft in, 576, 577f
caudal extension graft in, 576, 576f
concept of, 573-576
reshaping of lower lateral cartilage in, 577
shield graft in, 576, 577f
technique for, 576-577
thinning of subcutaneous tissue in, 577, 577f
postsurgical considerations after, 542-543
preoperative patient assessment for, 508-519
anatomic evaluation in, 508-514
aesthetic analysis in, 514, 514f
with major deformities, 508-512, 511f-512f
with minimal deformities, 508-512, 509f-510f
normal nasal surgical anatomy and, 509f
palpation of internal vestibules in, 513, 513f
rhinoscopy in, 513-514, 514f
skin quality in, 512-513, 512f
tip recoil in, 513, 513f
laboratory evaluation in, 514-515
photography and imaging in, 514, 515f
revision, 580-594
for alar pinching and retraction, 587, 587f-589f
for caudal septal deviation, 593
for caudal septal excision (short nose), 593
computer imaging for, 581-582
for dorsal irregularity, 584
due to errors of omission, 582, 582t
due to excessive excision, 582, 582t, 583f
due to failure to restabilize, 582, 582t
general considerations with, 582-583, 582t, 583f
grafting material for, 583, 584f
due to gross errors of judgment, 582-583, 582t, 583f
for improperly placed radix graft, 584
for lateral nasal wall deformities, 586
for low dorsum/saddle deformity, 584, 585f
for middle vault deformities, 585-586, 586f
due to minor errors of technique, 582, 582t
for nasal tip deformities, 588
irregularities and bossae as, 588-589, 590f
overrotation (short nose) as, 590, 590f-591f
persistently wide or bulbous tip as, 589-590, 590f
pinched tip as, 590, 591f-592f
ptotic tip as, 590-593, 593f
for overly narrowed alar base, 593-594, 594f
patient interview for, 580-581
photography for, 581
physical examination for, 581
for pollybeak deformity, 584-585, 586f
of skin–soft tissue envelope, 581, 594
for supra-alar and external valve collapse, 586-587, 587f
for saddle nose deformity, 554-555
dynamic adjustable rotational tip graft in, 555, 559f
implant material in, 555, 556f-557f
indications for, 555, 558f

Rhinoplasty *(Continued)*
for septal and columella modifications, 546-548, 546f-547f
caudal repositioning in, 547, 547f
dorsal draw suture in, 548, 549f
making final septal assessment in, 548, 549f
septocolumellar complex in, 548, 549f-550f
shortening of caudal septum in, 547-548, 547f-548f
with septal deviation, 513-514, 514f, 546, 546f-547f
special techniques in, 545-567
for cleft-lip nose, 557-559, 561f
Abbé flap in, 563f-564f
with bilateral deformity, 559, 561f, 563f-564f, 566
columellar lengthening in, 559, 566f
external approach to, 559, 561f
lateral ala thinning and placement of maxillary implants in, 562f
Le Fort I maxillary osteotomies in, 559, 564f-565f
with nasal stenosis, 559, 566f
open approach to, 559, 562f
repositioning and suturing lower lateral cartilage in, 562f
with severe deformity, 559, 564f-565f
suturing together medial crura in, 561f-562f
with unilateral deformity, 557, 559, 561f-562f
external approach for, 545-546, 546f
incisions and soft tissue elevation for, 545-546, 546f
for nasofrontal angle modifications, 548-549, 550f
for noncaucasian nose (*See* Rhinoplasty, noncaucasian)
open approach for, 545-546
preoperative analysis for, 545-546
for saddle nose deformity, 554-555
dynamic adjustable rotational tip graft in, 555, 559f
implant material in, 555, 556f-557f
indications for, 555, 558f
for septal and columella modifications, 546-548, 546f-547f
caudal repositioning in, 547, 547f
dorsal draw suture in, 548, 549f
making final septal assessment in, 548, 549f
septocolumellar complex in, 548, 549f-550f
shortening of caudal septum in, 547-548, 547f-548f
for tip and alar asymmetries, 549-551
alar batten grafts in, 550, 551f
suture techniques in, 550-551
tip grafts in, 549-550, 550f-551f
transposition techniques in, 551
for twisted nose, 551-554, 552f
osteotomies in, 551-554, 552f-554f
septal reconstruction in, 551
spreader grafts in, 554, 555f
surgical landmarks in, 519, 519f
surgical philosophy of, 508
for tip and alar asymmetries, 549-551
alar batten grafts in, 550, 551f
suture techniques in, 550-551
tip grafts in, 549-550, 550f-551f
transposition techniques in, 551
for twisted nose, 551-554
in noncaucasian patient, 573, 576f
osteotomies in, 551-554
intermediate, 553, 554f
lateral, 552-554, 553f
medial, 552-553, 552f-553f
preoperative examination of, 551, 552f
results of, 511f-512f, 553f-554f

Rhinoplasty *(Continued)*
septal reconstruction in, 551
spreader grafts in, 554, 555f
RhinoQOL (Rhinosinusitis Quality of Life survey), 57
Rhinorrhea, cerebrospinal fluid. *See* Cerebrospinal fluid (CSF) rhinorrhea.
Rhinoscleroma, laryngitis due to, 884
Rhinoscopy
anterior, 100, 484
prior to rhinoplasty, 513-514, 514f
of rhinosinusitis, 730
Rhinosinusitis
abbreviations used in, 729t
acute
bacterial, 703-705, 704f, 732
endoscopic sinus surgery for, 761
frontal, 775
pathogenesis of, 704-705, 704f
radiologic appearance of, 672-673, 673f
recurrent, 705
surgical management of, 741
allergic
fungal, 712-715
in children, 2778, 2780, 2781f
chronic, 707, 733
classification of, 709
diagnosis of, 707, 712-713
epidemiology of, 713-714
imaging of, 706f, 713, 714f
immunochemical staining for, 731, 731f
pathogenesis of, 712-714, 714b
prognosis for, 713
therapy for, 713-715, 715b
radiologic appearance of, 675
in athletes, 737
bacterial
acute, 703-705, 704f, 732
chronic, 732, 733f
in children, 737
chronic
acute exacerbation of, 705, 707, 707f
surgical management of, 741
bacterial, 732, 733f
defined, 705, 728-729
frontal, 775-783
fungal, 732-733
allergic, 707, 733
invasive, 711
nonallergic, 715-716, 716t
pathogenesis of, 705-707, 706b, 706f, 742-743
radiologic appearance of, 673-674, 674f-675f
surgical management of, 741, 760-761
classification of, 703-704
complications of, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
defined, 703-704
diagnosis of, 728-730
imaging in, 729, 729f
rhinoscopy in, 730
smell and nasal airflow in, 730
in elderly, 737
endoscopic sinus surgery for, 742-756
with acute complications, 741
anesthesia for, 744-745
general, 745
local, 744-745
antibiotics prior to, 743
chronic, 741-743
complications of, 754-755, 754b
hemorrhage as, 754
intracranial, 755, 755f
ophthalmic, 754-755

Rhinosinusitis *(Continued)*
computer-assisted navigation in, 772
with concha bullosa, 751, 752f
conclusion of procedure for, 751
ethmoidectomy in
anterior, 747, 748f
complete, 748-749, 749f-750f
failure of, 766-767, 767f
posterior, 747-748, 749f
failure of, 756
frontal sinusotomy in, 750-751, 768-771
agger nasi cell in, 769, 771f-772f
and causes of frontal sinus disease, 769
challenges of, 768
external approaches as adjunct to, 771, 773f
frontal bullar cell in, 772f
frontal recess dissection in, 769, 770b, 770t, 771f
frontal sinus cells in, 769-770, 772f
image-guided navigation system in, 771f
interfrontal sinus septal cell in, 771, 772f
preoperative evaluation for, 768-769
recessus terminalis in, 771
suprabullar cell in, 772f
supraorbital ethmoid cell in, 770-771, 772f
fungal
invasive, 742
noninvasive, 742
image-guided navigation systems in, 743-744, 745f
intraoperative CT scans during, 744, 772
limited *vs.* extended approaches for, 752-753
maxillary antrostomy in, 747, 747f
failure of, 764-766, 766f
Messerklinger technique for, 746
minimally invasive sinus technique in, 743, 752, 760
with mucoceles, 751
nasal endoscopy in, 746, 763
with nasal septal deviation, 751
patient preparation and positioning for, 745-746
with polyps, 751-752
postoperative care after, 753-754, 773-774
preoperative assessment for, 743
examination in, 743
history in, 743
imaging in, 743, 744t
recurrent acute, 741
resection of uncinate process in, 746, 746f
results of, 755-756
sinus balloon catheterization in, 752-753, 753f
sphenoid sinusotomy in, 748, 749f
sphenoidotomy in, 748, 749f
complications of, 767, 768t
for fungus ball, 768f-769f
with image-guided navigation system, 770f
treatment of middle turbinate in, 751, 751f, 771
Wigand technique for, 746
epidemiology of, 728
frontal
acute, 775
anatomic variations and, 776
chronic, 775-783
fungal, 709-2
allergic, 712-715
chronic, 707
classification of, 709
diagnosis of, 707, 712-713
endoscopic sinus surgery for, 761, 762f
epidemiology of, 713-714
imaging of, 706f, 713, 714f
immunochemical staining for, 731, 731f
pathogenesis of, 712-714, 714b
prognosis for, 713
therapy for, 713-715, 715b

Rhinosinusitis *(Continued)*
chronic, 732-733
allergic, 707
invasive, 711
nonallergic, 715-716, 716t
classification of, 709
endoscopic sinus surgery for, 761, 762f
fungus balls in, 712, 712f, 714t
in immunocompromised host, 660, 710t
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 220
treatment of, 221
invasive, 705, 709-712
due to *Aspergillus,* 220-221, 220f, 705, 710-711, 712f
due to *Candida,* 711
chronic or indolent, 711
diagnosis of, 711, 711f-712f
due to mucormycosis, 705, 710, 711f
rapidly (fulminant), 709-710, 710f
surgical management of, 742, 761
therapy for, 711-712, 713t
nonallergic eosinophilic, 709, 715-716, 716t
noninvasive, 709
surgical management of, 742, 761
radiologic appearance of, 674-675, 676f
saprophytic, 712
granulomatous, 675
immunosuppression and, 219-221, 660
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
medical treatment of, 733-737
alternative, 731, 735t
antibiotics for, 733-735
intravenous, 733-734, 735t
long-term macrolide, 733, 734t
oral, 733
short-term, 734t
topical, 734-735, 735t
antifungals for
systemic, 735, 735t
topical, 735-736, 735t
antihistamines for, 734t, 737
anti-IgE (omalizumab) for, 735t, 737
anti-reflux therapy for, 735t, 737
antivirals for, 731, 734t
aspirin desensitization therapy for, 734t, 737
in athletes, 737
in children, 737
decongestants for, 735t, 736
in elderly, 737
intravenous immune globulin for, 735t, 737
issues with antimicrobials for, 736
leukotriene modifiers for, 735t, 736
mucolytics for, 735t, 736
nasal saline lavage for, 734t, 736
during pregnancy, 737
with proven benefit in comparative trials, 734t
without proven benefit in comparative trials, 735t
steroids for
systemic, 734t, 736
topical nasal, 734t, 736
outcome measures and quality of life with, 730, 730t
pathogenesis of, 703-708
predisposing factor(s) for, 730-733
allergy as, 731
bacteria as, 732
eicosanoids and aspirin sensitivity triad as, 731-732, 732f
environmental irritants as, 731
fungi as, 732-733
inflammation as, 731, 731f
laryngopharyngeal reflux as, 732
nitric oxide as, 732

Rhinosinusitis *(Continued)*
superantigens as, 706, 732
viral illness as, 730-731
during pregnancy, 737
radiologic appearances of, 167-168, 672-675, 729
acute, 672-673, 673f
allergic, 675
chronic, 673-674, 674f-675f
with complications, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
on CT, 140-142, 141f, 729
granulomatous, 675
on plain radiographs, 729, 729f
recurrent, 728
signs and symptoms of, 703, 704b
Rhinosinusitis Disability Index (RSDI), 642
Rhinosinusitis Outcome Measure, 57
Rhinosinusitis Quality of Life survey (RhinoQOL), 57
Rhinostereometry, 643
Rhinotomy, lateral
for middle cranial base surgery, 2455t, 2458, 2458f
for nasopharyngeal carcinoma, 1355-1356, 1355f
Rhinovirus, pharyngitis due to, 196
Rhizopus oryzae, rhinosinusitis due to, 710
Rhytid(s), 275, 279f
Rhytidectomy, 405-427
complication(s) of, 420-427
contour deformities as, 427
depression as, 427
hair loss as, 426, 427f
hematoma as, 420-421, 425f
nerve injury as, 422-425, 426f
parotid injury as, 426-427
pigmentary changes as, 427
scars as, 425-426, 425f, 427f
skin flap necrosis as, 421-422, 425f-426f
composite, 406
deep-plane, 406, 407f, 409
hair restoration after, 387, 388f
historical perspective on, 405-408
melolabial fold in, 406, 406f
orbicularis muscle in, 406, 406f
postoperative care after, 420
results of, 414f-415f, 417f-418f, 423f-424f
SMAS-, 409
extended, 409
SMAS flap for, 405-406, 409
SMAS in, 405, 406f
strip SMAS-ectomy for, 409
subcutaneous, 408-409
subperiosteal, 410
advantages and disadvantages of, 407-408, 408t
defined, 410
historical perspective on, 407
surgical approaches for, 408, 410
combined, 408, 410
transoral, 408, 410
transorbital, 408, 410, 410f
transtemporal, 407f, 408, 410
sub-SMAS, 406
supra-SMAS, 409-410
advantages and disadvantages of, 408, 408t
defined, 409
extended, 406, 408-410
historical perspective on, 406
surgical approaches to, 408-410, 409t
surgical technique for, 410-420
drain insertion and wound closure in, 420
fibrin sealants in, 416-420
incisions in, 410-411

Rhytidectomy *(Continued)*
for men, 411, 412f
for women, 410-411, 411f
mid-facelift in, 413
procedure for, 413, 415f-416f
results of, 413, 417f-418f
skin flap elevation in, 413-416
extent of skin undermining in, 413, 418f
over parotid gland in preauricular area, 413-416, 419f
posterior neck dissection in, 413-416
subplatysmal dissection in, 413-416, 420f
superior musculoaponeurotic system in, 413-416, 419f
suturing in, 413-416, 421f
in temple, 413
trimming of cervical skin flap in, 413-416, 421f
skin trimming in, 416-420, 422f-423f
submentoplasty in, 411-413
aesthetic considerations for, 411, 412f
procedure for, 411-413, 413f
results of, 414f-415f
Rib cartilage, for auricular reconstruction, 2744, 2744t
Ribavirin, for recurrent respiratory papillomatosis, 2892
Ribbon synapse, with hair cells, 2080, 2080f
Riboflavin, for migraine, 2349
Riboflavin deficiency, oral manifestations of, 1254
Ribonucleic acid (RNA), direct delivery of, for gene silencing, 16
Ribonucleic acid (RNA)-induced silencing complex (RISC), 13, 14f
Ribonucleic acid interference (RNAi), 13, 14f
therapeutic applications of, 23-24
RIC (receiver-in-the-canal) fitting, for hearing aids, 2270
RICH (rapidly involuting congenital hemangioma), 2824
Ricketts analysis, for mentoplasty, 463, 463f
Rickettsia rickettsii, sensorineural hearing loss due to, 2119
Riedel's procedure, 781-782
indications for, 781-782
postoperative appearance after, 781, 782f
for recurrent infection, 781
Rieger flap, for nasal defects, 365-366
RIF (radiation-induced fibrosis), 1048
Rifle, neck trauma due to, 1626, 1626f-1627f
Right anterior–left posterior (RALP) semicircular canal plane, 2285, 2286f, 2287
Right hilar release, with tracheal resection, 1618-1619, 1620f
Right-hand rule, for head rotation, 2293, 2294f
Rigid bronchoscopy, 1000-1001
for difficult airway, 113f, 114t
pediatric anesthesia for, 2597-2598, 2597t
Rigid fixation, for pediatric facial fracture, 2699-2700
Rigid laryngoscopy, 813-814
advantages of, 813
disadvantages of, 813-814
for professional voice disorders, 851, 852t
protocols for, 816b, 818b
technique of, 814
troubleshooting for, 814
Rima glottidis, 1464
surgical anatomy of, 1543f
Rima vestibuli, 1543f
Ring-down artifact, with colloid thyroid nodule, 1644
"Ringed" esophagitis, 967-968, 969f
Rinne test, 98, 98t, 2020, 2020t
for otosclerosis, 2030
RISC (RNA-induced silencing complex), 13, 14f
Rising "w," in nasal breathing assessment, 644
Risk factors, in medical history, 94, 94b
R_{law} (laryngeal airway resistance), in voice evaluation, 828-829, 828t
RLN. *See* Recurrent laryngeal nerve (RLN).
RLS (restless legs syndrome), 265
RME (rapid maxillary expansion)
for nasal obstruction, 2630
for obstructive sleep apnea in children, 2611
RMS. *See* Rhabdomyosarcoma (RMS).
RNA (ribonucleic acid), direct delivery of, for gene silencing, 16
RNA (ribonucleic acid)-induced silencing complex (RISC), 13, 14f
RNAi (ribonucleic acid interference), 13, 14f
therapeutic applications of, 23-24
RND. *See* Radical neck dissection (RND).
Robbins classification, of cervical lymph nodes, 1683, 1683f, 1684t
Robert's syndrome, 2690
Robin, Pierre, 2673
Robin sequence
cleft lip and palate in, 2673
craniofacial abnormalities in, 2630-2631, 2630f
Robodoc, 39
Robotic surgery
of anterior and middle cranial base, 2450
defined, 38-39
history of, 39, 39f-40f
instruments for, 40, 42f
for laryngeal cancer, 1560-1561
in otolaryngology, 39-43
clinical applications of, 41
for oropharyngeal surgery, 42-43
for skull base surgery, 42, 43f-44f
for thyroidectomy, 41-42
experimental origins of, 40-41
articulated instruments in, 40, 42f
in cadaver, 40-41, 43f
da Vinci surgical system in, 40, 41f
in mannequin, 41
operating room orientation in, 41, 43f
in porcine model, 40, 41f
for submandibular gland resection, 40-41, 42f-43f
future directions for, 43-44
procedural times for, 40, 42f
Robotics, 38-44
active, 38-39
definitions for, 38-39
history of, 38, 39f
passive, 38-39
semiactive, 38-39
Rocky Mountain spotted fever, sensorineural hearing loss in, 2119
Rocuronium
in children
for anesthesia maintenance, 2593t
for rapid-sequence anesthesia induction, 2590
intraoperative, 112
Roentgen, 1031
Roentgen equivalent for man (rem), 133
Roentgen, Wilhelm, 1031
Romano-Ward syndrome, deafness in, 2096
Romberg test, 2316-2317
ROS (reactive oxygen species), in ototoxicity
of aminoglycosides, 2171
of carboplatin, 2173-2174
of cisplatin, 2172
Rosai-Dorfman disease, 2819
Rosenmüller's fossa, anatomy of, 1359f
radiographic, 1398f-1399f
Rosenthal's canal, 1832f, 1834
Rose's position, for adenotonsillectomy, 2798, 2798f
Rotation advancement closure, for cleft lip, 2667-2668, 2667f
advancement flap in, 2668, 2668f
closure in, 2668, 2668f
rotation flap in, 2667-2668, 2668f
Rotation flaps, 343-344, 343f
for cheek defects, 357-358, 359f
in cleft lip repair, 2667-2668, 2668f
for forehead repair, 362
advancement, 360-362, 362f
Rotatory chair testing, 2320-2323
bias velocity in, 2322
with cerebellar abnormalities, 2322
directionally dependent asymmetries in, 2322
interpretation of, 2297-2299
protocol for, 2320-2322
step changes in head velocity in, 2322-2323, 2323f
with unilateral vestibular loss, 2322, 2322f
for vestibular rehabilitation, 2377
Roughness, in voice evaluation, 827t
Round window
anatomy of, 1826f, 1831, 1840
in cochlear transduction, 2062f
Round window membrane (RWM), 2179-2183
with aging, 2180
anatomy of, 2179-2180, 2180f
delivery of therapeutic agents across
kinetics of, 2181, 2181f
method of, 2182-2183, 2182f-2183f
"false," 2180
obstructive adhesions of, 2181-2182
permeability of, 2180-2181
physiology of, 2180, 2181f
Round window niche, in surgical anatomy of lateral skull base, 2436f
Rowe midfacial disimpacters, 335-336
Roxithromycin, for rhinosinusitis, 733, 734t
RPC (recurrent parotitis of childhood), 1153-1154
RPS. *See* Retropharyngeal space (RPS).
RQLQ (Rhinitis Quality of Life Questionnaire), 642
RRP. *See* Recurrent respiratory papillomatosis (RRP).
RSDI (Rhinosinusitis Disability Index), 642
RSI (Reflux Symptom Index), 826, 826t, 896, 897b
RSI (rapid-sequence induction), 112-113
in children, 2590
RSTLs (relaxed skin tension lines), 269-270, 274f
and scars, 295, 296f
RSV (respiratory syncytial virus) vaccine, to prevent otitis media, 2769
RT. *See* Radiation therapy (RT).
Rubella, congenital deafness due to, 2154, 2156-2157, 2157f, 2723
Rubeola. *See* Measles.
Rubin osteotome, for rhinoplasty, 540, 540f
with hump reduction, 573
Ruffini's endings, 1202
RWM. *See* Round window membrane (RWM).

S

S phase, of cell cycle, 12, 13f
Saccade(s), 2305-2306, 2306f, 2307t, 2313
anticipatory or corrective, in vestibular compensation, 2375
evaluation of
in bedside exam, 2313
testing for, 2317-2318, 2318f
main sequence of, 2313
neural signal for, 2313, 2313f
normal latency of, 2313
refixation, 2292
Saccular activity, changes in postural tone due to sudden changes in, 2300
anatomic and physiologic basis for, 2300
clinical importance of, 2300

Saccular cysts, 876-878
  anterior, 876f-877f, 877
  classification of, 877f
  clinical scenario with, 877
  defined, 877
  diagnosis of, 877
  etiology of, 876
  of larynx, 2872-2873, 2872f-2873f
  lateral, 876f, 877, 878f
  treatment of, 877-878
Saccular disorders, of larynx, 876-878
  classification of, 876f, 877
  clinical scenario with, 877
  diagnosis of, 877
  etiology of, 876
  laryngocele as, 876f, 877
  laryngopyocele as, 877
  saccular cysts as, 877, 877f
    anterior, 876f-877f, 877
    lateral, 876f, 877, 878f
  treatment of, 877-878
Saccular macula. *See* Macula sacculi.
Saccular nerve, 1854f, 2278f
Saccule
  anatomy of, 1851f, 1853f-1854f, 2278f
  embryogenesis of, 1852
  of larynx, 876
  in vestibular system
    arrangement of, 2278, 2280f
    estimated patterns of excitation and inhibition for, 2278, 2281f
    morphologic polarizations of stereociliary bundles in, 2278, 2280f
Sacculus. *See* Saccule.
Saddle nose deformity, rhinoplasty for, 554-555
  dynamic adjustable rotational tip graft in, 555, 559f
  implant material in, 555, 556f-557f
  indications for, 555, 558f
  revision, 584, 585f
Saethre-Chotzen syndrome, craniofacial anomalies in, 2641t, 2646
Safety considerations, with lasers, 34-37
  anesthesia and risk of intraoperative fire as, 36-37
  education on, 34
  eye protection as, 34-35, 35f-36f
  protocol for, 34
    effectiveness of, 37
  skin protection as, 35
  smoke evacuation as, 35
Safety pins, in airway or esophagus, 2941
Sagittal synostosis, 2642, 2643f
  surgical management of, 2650, 2650f-2651f
Salicylates
  in noise-induced hearing loss, 2147
  ototoxicity of, 2175-2176
  sensorineural hearing loss due to, 2120, 2176
Salicylic acid
  for chemical peels, 392-393
  after free tissue transfer, 1096
Saline, for cerumen removal, 1958t
Saline spray, after endoscopic sinus surgery, 773
Saliva
  biomarkers in, for head and neck squamous cell carcinoma, 1026
  composition of, 1138-1139, 1138t
    inorganic component in, 1138t, 1139
    organic components in, 1138t-1140t, 1139-1140
    variability in, 1138-1139
  contribution by salivary glands to, 1134t
  flow rate of, 1133, 1138, 1138t
    control of, 1138
    factors influencing, 1138
    intraoral variations in, 1138
Saliva *(Continued)*
  functions of, 1133, 1140-1141
    antibacterial activity as, 1141
    buffering and clearance as, 1141
    lubrication and protection as, 1140-1141
    maintenance of tooth integrity as, 1141
    taste and digestion as, 1141, 1213-1214
  osmolarity of, 1138-1139
  pH of, 1138-1139
  reflex release of, 1205-1206
  relative viscosities of, 1134t
Salivary duct carcinoma (SDC), 1189-1190, 1189f
Salivary fistula
  due to neck surgery, 1727-1728, 1728f
  after parotidectomy, 1177
  posttraumatic, 313-314
Salivary flow test, 2384
Salivary gland(s)
  aberrant, 2864, 2864f
  anatomy of, 1162, 1163f
    in children, 2850-2853
  contribution to saliva by, 1134t
  embryology of, 1162
  fine-needle aspiration biopsy of, 1149, 1149f, 1165-1166, 1180-1181
    in children, 2854
  in geriatric patients, 236
  histology of, 1179, 1182f
  imaging of, 1143-1150
    with adenoid cystic carcinoma, 1146-1147, 1146f-1147f, 1180f
    with AIDS-related parotid cysts, 1146, 1146f
    anatomic basis for, 1143-1145
    in children, 2854-2855
    CT for, 139, 1148, 1166, 1180
      of AIDS-related parotid cysts, 1146f
      of parotid lipoma, 1166, 1167f
      of pleomorphic adenoma, 1144f, 1148
      of sialadenitis, 1148
      of sialolithiasis, 1144f, 1148, 1148f
      of Sjögren's syndrome, 1148
      of Warthin's tumor, 1146f
    FDG-PET for, 1150, 1168
    with malignant neoplasms, 1180
    minor, 1145
    MRI for, 142, 1145-1147, 1166, 1180
      of adenoid cystic carcinoma, 1146-1147, 1146f-1147f, 1180f
      of glomus tumor, 1169f
      of mucoepidermoid carcinoma, 1146, 1147f, 1168f
      of pleomorphic adenoma, 1148f, 1167f-1168f, 1180f
      of ranula, 1146, 1147f
    with mucoepidermoid carcinoma, 1146, 1147f, 1168f
    parotid, 1143-1144, 1145f
    with pleomorphic adenomas, 1143
      CT for, 1144f, 1148
      MRI for, 1148f, 1167f-1168f, 1188f
      ultrasound for, 1149, 1149f
    with ranula, 1146, 1147f
    scintigraphy for, 138, 1150
    with sialadenitis, 1148
    sialography for, 1149-1150
      conventional, 139-140, 1149-1150, 1149f, 1155-1156, 1156f
      CT, 139-140, 1145f, 1150, 1150f
      MR, 1147, 1155-1156
      for salivary gland injury, 312
    with sialolithiasis, 1143, 1144f, 1148, 1148f
    sublingual, 1144-1145
    submandibular, 1144
    ultrasound for, 143, 1148-1149, 1149f, 1167, 1645-1647
Salivary gland(s) *(Continued)*
    with acute infections, 1647
    with calculous lesions, 1647
    color Doppler, 1167-1168
    with cystic salivary gland disease, 1647
    with parotid mass, 1654f
    with Sjögren's syndrome, 1647
    with submandibular pleomorphic adenoma, 1653f
  with Warthin's tumor, 1146, 1146f
  major, 1133
  minor, 1133
    anatomy of, 1133-1134
      in children, 2850-2852
    benign neoplasms of, 1165
      basal cell adenomas as, 1170
      canalicular cell adenomas as, 1170
      oncocytomas as, 1171
      pleomorphic adenoma as, 1169, 1170f
    contributions to saliva of, 1134t
    imaging of, 1145
    malignant neoplasms of
      adenoid cystic carcinoma as, 1362-1363
      excision of, 1196
      of hard palate, 1310
      of larynx, 1506-1508
      mucoepidermoid carcinoma as, 1363
      physical examination of, 1179
  physiology of, 1133-1142
    in children, 2853
  secretory unit of, 1133-1134, 1134f
Salivary gland calculi. *See* Sialolithiasis.
Salivary gland choristoma, of middle ear, 2200-2201
Salivary gland cysts, 2859
  acquired, 2859
  congenital, 2859
Salivary gland disease
  benign lymphoepithelial, 1154
    in children, 2858
  in children, 2850-2865
    aberrant salivary glands as, 2864, 2864f
    due to allergic reactions, 2864
    anatomy and, 2850-2853
    autoimmune, 2858-2863
    benign lymphoepithelial, 2858
    biopsy for, 2855
    congenital, differential diagnosis of, 2851t
    in cystic fibrosis, 2864
    cysts and mucoceles as, 2859
      acquired, 2859
      congenital, 2859
    differential diagnosis of, 2850, 2851t, 2852f-2853f
    history and physical examination for, 2853
    imaging of, 2854-2855
    inflammatory, 2855-2858
      abscess as, 2856
      due to actinomycosis, 2858
      bacterial, 2856-2857, 2856t
      diagnostic algorithm for, 2853, 2854f
      differential diagnosis of, 2851t
      due to Epstein-Barr virus, 2855
      granulomatous, 2857-2858, 2857f
      due to HIV, 2856
      due to mumps, 2855
      mycobacterial, 2857-2858, 2857f
      sarcoidosis as, 2858
      viral, 2855
    juvenile recurrent parotitis as, 2858
    laboratory studies for, 2853-2854
    due to medications, 2864-2865
    necrotizing sialometaplasia as, 2857
    neoplastic, 1192, 2861-2862, 2862t
      benign, 2861-2862
      differential diagnosis of, 2851t
      malignant, 2862-2863

Salivary gland disease *(Continued)*
sialadenitis as, 2819
acute suppurative, 2856, 2856t
bacterial, 2856-2857, 2856t
chronic, 2858
neonatal, 2857
recurrent, 2856-2857
viral, 2855
sialadenoscopy for, 2855
sialolithiasis as, 2858-2859
sialorrhea as, 2863-2864
in systemic conditions, 2864-2865
traumatic, 2863-2865
vascular anomalies as, 2859
hemangiomas as, 2859-2860, 2860f
lymphatic malformations as, 2860-2861, 2861f
cysts and mucoceles as, 2859
acquired, 2859
congenital, 2859
ultrasound imaging of, 1647
HIV-associated, 1157-1158, 1157f
immunosuppression and, 217-218
diffuse infiltratrive lymphocytosis syndrome as, 218
parotid lesions as, 217-218, 218f
xerostomia as, 218
inflammatory, 1151-1161
bacterial infections as, 1151-1153
in children, 2856-2857, 2856t
in children, 2855-2858
abscess as, 2856
due to actinomycosis, 2858
bacterial, 2856-2857, 2856t
diagnostic algorithm for, 2853, 2854f
differential diagnosis of, 2851t
due to Epstein-Barr virus, 2855
granulomatous, 2857-2858, 2857f
due to HIV, 2856
due to mumps, 2855
mycobacterial, 2857-2858, 2857f
sarcoidosis as, 2858
viral, 2855
chronic sialadenitis as, 1154, 1155f
granulomatous infections as, 1158-1159
due to actinomycosis, 1159
due to cat scratch disease, 1159
in children, 2857-2858, 2857f
due to nontuberculous mycobacterial disease, 1158-1159, 1158f
due to toxoplasmosis, 1159-1160
due to tuberculous mycobacterial disease, 1158
neonatal suppurative parotitis as, 1153
noninfectious, 1160-1161
recurrent parotitis of childhood as, 1153-1154
sialolithiasis as, 1155-1156, 1155f-1156f
viral infections as, 1156-1158
in children, 2855
due to Epstein-Barr virus, 2855
due to HIV, 1157-1158, 1157f, 2856
due to mumps, 1156-1157, 2855
necrotizing sialometaplasia as, 2857
neoplastic (*See* Salivary gland neoplasm(s))
sialadenitis as
acute suppurative, 1151-1153
in children, 2856, 2856t
clinical manifestations of, 1152, 1152f
complications of, 1153, 1154f
differential diagnosis of, 1152
epidemiology of, 1151
laboratory evaluation of, 1152
pathogenesis of, 1151-1152, 1152f
treatment of, 1152-1153, 1153f
in children
acute suppurative, 2856, 2856t
bacterial, 2856-2857, 2856t
chronic, 2858
neonatal, 2857
recurrent, 2856-2857
viral, 2855
chronic, 1154, 1155f
in children, 2858
sialolithiasis as
in children, 2858-2859
ultrasound of, 1647
in Sjögren's syndrome, 1160-1161
in children, 2858
traumatic, 312, 313f
in children, 2863-2865
sialocele and salivary fistula due to, 313-314
vascular anomalies as, 2859
hemangiomas as, 2859-2860, 2860f
lymphatic malformations as, 1172, 2860-2861, 2861f
Salivary gland dysfunction, aging and, 1141-1142, 1141f
Salivary gland hypofunction, 1138
Salivary gland neoplasm(s)
benign, 1162-1177
basal cell adenomas as, 1170
canalicular adenomas as, 1170
in children, 2861-2862
complications of, 1176-1177
facial nerve paresis or paralysis as, 1176-1177
gustatory sweating ("Frey's syndrome") as, 1177
salivary fistula as, 1177
sensory abnormalities as, 1177
congenital vascular, 1172
arteriovenous malformations as, 1172
hemangiomas as, 1172
lymphatic malformations as, 1172
venous malformations as, 1172
dumbbell, 1164-1165, 1165f, 1167f-1168f
glomus tumors as, 1169f
incidence of, 1164
by histologic type, 1164, 1164t
by site of origin, 1164, 1164f
inverted ductal papilloma as, 1171-1172
management of, 1172-1176
excision of parapharyngeal salivary gland tumors in, 1174-1176, 1176f
parotidectomy for, 1172-1174, 1173f
submandibular gland excision for, 1174, 1174f
myoepithelioma as, 1171
oncocytoma as, 1171
papillary cystadenoma as
lymphomatosum (Warthin's tumors), 1170-1171
oncocytic, 1171
parapharyngeal, excision of, 1174-1176, 1175f
parotid lipoma as, 1166, 1167f
patient evaluation for, 1164-1168
clinical features in, 1164-1165, 1165f-1166f
fine-needle aspiration biopsy in, 1165-1166
imaging in, 1166-1168, 1167f-1169f
pleomorphic adenoma as, 1168-1169
carcinoma ex, 1187-1189, 1188f
in children, 2861-2862
clinical features of, 1166f, 1169
histopathology of, 1169
imaging of, 1167f-1168f
of lacrimal gland, 1169, 1170f
malignant transformation of, 1169
metastasizing, 1189
of palate, 1169, 1169f
pathogenesis of, 1168-1169
recurrent, 1169, 1170f
sites of, 1169, 1169f-1170f
sialadenoma papilliferum as, 1171
Warthin's tumor as, 2862
Salivary gland neoplasm(s) *(Continued)*
biomarkers for, 1163
in children, 1192, 2861-2862, 2862t
benign, 2861-2862
differential diagnosis of, 2851t
malignant, 2845-2846, 2862-2863
epidemiology of, 2845
histopathology and molecular biology of, 2846, 2846f
management of, 2845-2846
neck mass due to, 2820
presentation and evaluation of, 2845
embryology of, 1162, 1163f
Epstein-Barr virus and, 1163
etiology of, 1163-1164
genetic factors in, 1164
other factors in, 1163-1164
radiation in, 1163
viral, 1163
fine-needle aspiration biopsy of, 1149, 1149f, 1165-1166, 1180-1181
histogenesis of, 1163
malignant, 1178-1199
acinic cell carcinoma as, 1185-1186, 1187f
in children, 2820, 2846, 2846f, 2863
adenocarcinoma as
basal cell, 1191
NOS, 1191
polymorphous low-grade, 1184-1185, 1186f
adenoid cystic carcinoma as
histopathology of, 1183-1184, 1185f
imaging of, 1146-1147, 1146f-1147f, 1180f
cervical lymph node metastasis of, 1196-1197
chemotherapy for, 1199
in children, 1192, 2845-2846, 2862-2863
epidemiology of, 2845
histopathology and molecular biology of, 2846, 2846f
management of, 2845-2846
neck mass due to, 2820
presentation and evaluation of, 2845
epidemiology of, 1143, 1178
by histologic type, 1178, 1179t
by site, 1178, 1179t
epithelial-myoepithelial carcinomas as, 1191
histopathology of, 1181-1192, 1182f, 1182t
lymphoma as, 1191-1192, 1192f, 1679-1680
treatment and prognosis for, 1680
metastatic, 1191
minor salivary gland excision for, 1196
mixed, 1186-1189
carcinoma ex pleomorphic adenoma as, 1187-1189, 1188f
metastasizing, 1189
true (carcinosarcoma), 1187, 1188f
molecular markers for, 1194
mucoepidermoid carcinoma as
in children, 2820, 2846, 2846f, 2862-2863
differential diagnosis of, 1183
grading of, 1183, 1184t
histopathology of, 1182-1183, 1183f
imaging of, 1146, 1147f, 1168f
with N+ neck, 1197
with N0 neck, 1196-1197
of oropharynx, 1362-1363
other, 1191
parotidectomy for, 1194-1196
branches of facial nerve in, 1194, 1194f
elevation of skin flap in, 1195
external carotid artery in, 1195-1196
with facial nerve involvement, 1196
greater auricular nerve in, 1195
main trunk of facial nerve in, 1195, 1195f
marginal mandibular branch of facial nerve in, 1195, 1195f
modified Blair incision for, 1195, 1195f
partial deep, 1194-1196, 1196f

Salivary gland neoplasm(s) *(Continued)*
retromandibular (posterior facial) vein in, 1195-1196, 1195f
superficial, 1194-1195
total, 1194-1196
patient evaluation for, 1178-1181
biopsy in, 1180-1181
physical examination in, 1178-1179
radiologic studies in, 1180, 1180f
staging in, 1181, 1181t
prognostic variables for, 1192-1194, 1193t
clinical, 1192-1193
histologic, 1193-1194
molecular markers as, 1194
radiation therapy for, 1197-1199
adjuvant, 1197-1198, 1198t
in children, 2863
of neck, 1198
neutron beam, 1198-1199
salivary duct carcinoma as, 1189-1190, 1189f
small cell carcinoma as, 1190-1191, 1190f
squamous cell carcinoma as, 1190
sublingual gland excision for, 1196
submandibular gland excision for, 1196
surgical treatment of, 1194-1197
neck masses due to, 1640
radiation and, 1163
ultrasonography of, 1645-1647, 1653f-1654f
Salivary gland secretion, 1133-1136
anatomy of secretory unit in, 1133-1134, 1134f
neuronal control of, 1136
neurotransmitters and receptors in, 1136-1137, 1136f, 1137t
signal transduction in, 1137-1138
adenylate cyclase system in, 1137
G proteins in, 1137
phospholipase C system in, 1137-1138
process of, 1134-1136
ductal, 1136
fluid, 1135, 1135f
macromolecule, 1135-1136
Salivary gland unit, 1162, 1163f
Salivary pH, 2384
Salivation, reflex, 1205-1206
Sal-like 1 *(SALL1)* gene, in deafness, 2051t-2058t
Salmon patch, 290-291
Salpingopharyngeal fold, 1359f
Salpingopharyngeus muscle
anatomy of, 1870
development of, 1866
Salt restriction, for Meniere's disease, 2337
Salty taste
individual differences in, 1211-1212
peripheral sensitivity to, 1211
transduction of, 1208-1209
Sample size
calculation of, 74
determination of, 68t
small, 73, 73t
Sampling methods, 68-69, 68t-69t
SAN. *See* Spinal accessory nerve (SAN).
Sanguinaria, oral leukoplakia due to, 1223-1224, 1224f
SANS, in deafness, 2051t-2058t, 2077-2078
Saphenous vein repair, for aneurysms of upper cervical and petrous internal carotid artery, 2504, 2505f
Saprophytic fungal rhinosinusitis, 712
SAQLI (Sleep Apnea Quality of Life Index), 57
SAR (seasonal allergic rhinitis), 617-618
and pediatric chronic sinusitis, 2778
Sarcoidosis, 2104-2105
in children, 2819
salivary gland involvement in, 2858
clinical course of, 659
clinical presentation of, 2104
diagnosis of, 659
Sarcoidosis *(Continued)*
epidemiology of, 658-659, 2104
of epiglottis, 1465f
etiology of, 658
facial paralysis in, 2400
laboratory findings in, 2104, 2104f
laryngeal and tracheal manifestations of, 890-891, 890f
nasal manifestations of, 658-659
oral manifestations of, 1252
otologic manifestations of, 2105
pathology of, 659, 2104f
sudden sensorineural hearing loss due to, 2129
treatment of, 659, 2104
Sarcoma(s)
alveolar soft part, 1668
angio-, 1668
bone, 1666, 1667t
in children, 2840-2843
dermatofibrosarcoma protuberans as, 2843, 2843f
epithelioid, 2843, 2843f
Ewing's, 2845
fibro-, 2842-2843, 2843f
nonrhabdomyosarcoma soft tissue, 2842
rhabdomyo-, 2820, 2840-2842
epidemiology of, 2820, 2840
histopathology and molecular biology of, 2842, 2842f
management of, 2820, 2841-2842
presentation and evaluation of, 2840-2841, 2841t
sites of, 2820
survival with, 2840
chondro-
of cerebellopontine angle, 2527, 2528f-2529f
of larynx, 1508
of neck, 1669-1670
of paranasal sinuses, 1131
of petrous apex, 2528f
of skull base, 1699, 1923-1924, 1926f, 2529f
dermatofibrosarcoma protuberans as, 2843, 2843f
epithelioid
in children, 2843, 2843f
of neck, 1668-1669
Ewing's
in children, 2845
of neck, 1671
of oral cavity, 1253
fibro-
in children, 2842-2843, 2843f
of larynx, 1508
of neck, 1668
of paranasal sinuses, 1131
granulocytic, 2107
hemangiopericytoma as, 1670
Kaposi's
of hard palate, 1309-1310
immunosuppression and, 212-215, 213t
epidemiology and pathogenesis of, 212-213
presentation and diagnosis of, 213-214, 214f
treatment of, 214-215
of larynx, 1508-1509
of oral cavity, 1299
of oropharynx, 1363-1364, 1364f
of larynx, 1508-1509
chondro-, 1508
fibro-, 1508
Kaposi, 1508-1509
lipo-, 1508
malignant fibrous histiocytoma as, 1508
pseudo-, 1506
leiomyo-, 1670
lipo-
of larynx, 1508
of neck, 1670
Sarcoma(s) *(Continued)*
malignant fibrous histiocytoma as
of larynx, 1508
of neck, 1667
malignant giant cell tumor as, 1671
malignant peripheral nerve sheath tumor as, 1670-1671
of neck, 1666
alveolar soft part, 1668
angio-, 1668
bone, 1666, 1667t
chondro-, 1669-1670
classification and staging of, 1666, 1666t-1667t
epithelioid hemangioendothelioma as, 1668-1669
Ewing's, 1671
fibro-, 1668
hemangiopericytoma as, 1670
leiomyo-, 1670
lipo-, 1670
malignant fibrous histiocytoma as, 1667
malignant giant cell tumor as, 1671
malignant peripheral nerve sheath tumor as, 1670-1671
osteo-, 1668
rhabdomyo-, 1667-1668, 1668f, 1669t
soft tissue, 1666, 1666t
synovial, 1670
nonrhabdomyosarcoma soft tissue, 2842
of oral cavity, 1299, 1299f
osteo-
of neck, 1668
of oral cavity, 1299f
of paranasal sinuses, 1131
postradiation, 1479
pseudo-, of larynx, 1506
rhabdomyo-
in children, 2820, 2840-2842
epidemiology of, 2820, 2840
histopathology and molecular biology of, 2842, 2842f
management of, 2820, 2841-2842
presentation and evaluation of, 2840-2841, 2841t
sites of, 2820
survival with, 2840
of middle ear or mastoid, 2501-2502
of neck, 1667-1668, 1668f, 1669t
of paranasal sinuses, 1132
soft tissue, 1666, 1666t
synovial, 1670
Sarcomatoid carcinoma, of larynx, 1506
Sarcomatoid squamous cell carcinoma, of oral cavity, 1299
SAS (Simultaneous Analog Stimulation), for cochlear implants, 2230, 2230f
Satisfaction surveys, 72
Saturated solution of potassium iodide (SSKI)
for Graves' disease, 1742-1743
for hyperthyroidism, 1739t
Saturation, of auditory neurons, 1844-1845, 1845f
Saucer fracture, of orbital floor, pediatric, 2712-2713, 2715f
Savage, Terry, 2086
Savary-Guillard dilator, for esophageal strictures, 966
SBE (subacute bacterial endocarditis) prophylaxis, for pediatric surgery, 2596, 2596t-2597t
Scala media
anatomy of, 1831-1832, 1832f, 1840, 1841f
in auditory physiology, 1840, 1841f-1842f
in cochlear transduction, 2050, 2061f-2062f
Scala tympani
anatomy of, 1831, 1832f, 1840, 1841f, 1853f
in auditory physiology, 1841f-1842f
in cochlear transduction, 2050, 2061f-2062f

Scala vestibuli
  anatomy of, 1831, 1832f, 1840, 1841f, 1853f
  in auditory physiology, 1841f-1842f
  in cochlear transduction, 2050, 2061f-2062f
Scales, for psychometric validation, 55
Scalp, 440, 441f
Scalp extenders, for hair loss, 384, 385f
Scalp reductions, for hair loss, 384-385, 385f
  complications of, 385, 386f
Scanning speech, 837-838
Scapha, 476-477, 476f, 1824f
Scapha-conchal sutures, 476f-477f
Scaphal reduction, 478f
Scaphocephaly, synostotic
  clinical manifestations of, 2642, 2643f, 2650f
  surgical management of, 2650f-2651f
Scaphoid fossa, 2742f
Scapula composite flap, for oral cancer, 1316
Scapula free flap, 1082t, 1086-1087, 1088f
Scapular flap, for hypopharyngeal and esophageal reconstruction, 1455
Scapular osteocutaneous free flap, for mandibular defects, 1324-1325, 1324f, 1325t
Scapular-parascapular flaps, for free tissue transfer, 1082t
Scar(s)
  hypertrophic, 291
    after neck surgery, 1728, 1729f
    after otoplasty, 479
    due to rhytidectomy, 425-426
  after neck surgery, 1728, 1729f
  and relaxed skin tension lines, 295, 296f
  due to rhytidectomy, 425-426, 425f, 427f
Scar revision and camouflage, 295-301
  cosmetics and hairstyling for, 301
  dermabrasion for, 298-299, 300f
  excision for, 295, 297f
  expansion with excision for, 296-298
    serial, 296
    tissue, 296-298, 297f
  indications for, 295
  irregularization for, 298
    geometric broken line closure in, 298, 299f-300f
    W-plasty in, 298, 299f
    Z-plasty in, 298, 298f-299f
  silicone sheeting for, 300-301
  steroids for, 299-300, 301f
  techniques for, 295
SCARF (Superior Constrictor Rotation-Advancement Flap), for reconstruction of soft palate, 1382, 1382f
Scarlet fever, 2788
Scarpa's fascia, 2577
Scarpa's ganglion, 1851f, 1852-1854
Scarring alopecia, 375-376
Scattering, of laser energy, 28-29, 29f
SCC. *See* Squamous cell carcinoma (SCC).
SCC(s) (semicircular canals). *See* Semicircular canal(s) (SCCs).
SCCHN (squamous cell carcinoma of the head and neck). *See* Head and neck squamous cell carcinoma (HNSCC).
SCCNET (small cell carcinoma, neuroendocrine type), of larynx, 1507-1508
SCDS (superior canal dehiscence syndrome). *See* Superior semicircular canal dehiscence (SSCD) syndrome.
SCF (stem cell factor), 609t-610t
Schaefer-Fuhrman classification, of laryngeal trauma, 936, 936t
Schatzki's ring, 966f, 967, 968f
  transnasal esophagoscopy of, 984f
Scheibe aplasia, 2200
Scheibe dysplasia, 2727-2728
Schirmer test, 446-447, 447f, 2383
SCHLP (supracricoid hemilaryngopharyngectomy), for hypopharyngeal cancer, 1429, 1436
Schneiderian papilloma, inverted type
  of nasopharynx, 1349
  sinonasal, 718-720
    endoscopic appearance of, 718-719, 719f
    epidemiology of, 718
    with frontal sinus involvement, 720, 720f
    histologic appearance of, 718
    human papillomavirus and, 718
    imaging of, 719, 719f
    postoperative surveillance for, 720
    recurrence of, 720
    sites for, 718
    and squamous cell carcinoma, 718
    surgical approach for, 718t, 719-720, 720f, 763
Schobinger incision, modified, for radical neck dissection, 1709, 1710f
Schüller projection, of temporal bone, 131
Schwabach test, 98
Schwannoma(s)
  acoustic (*See* Acoustic neuroma(s))
  of ethmoid region, 2479, 2480f
  facial nerve (*See* Facial nerve neuroma)
  glossopharyngeal, 2507f
  imaging of, 150-151
  of jugular foramen
    imaging of, 1929-1930, 1930f, 2522f
    lateral cranial base surgery for, 2504-2505, 2505f
    stereotactic radiation therapy for, 2565
  of larynx, 882
  of neck, 1663, 1663f
  neck masses due to, 1640
  sinonasal, 726-727, 726f
  trigeminal, 2512f
  vestibular (*See* Acoustic neuroma(s))
Schwartze sign, 2030
SCID (severe combined immunodeficiency), 209-210
Scintigraphy, 138, 139f
  for CSF rhinorrhea, 790
  of neck masses, 1637, 1637t
  of salivary glands, 138, 1150
  of thyroid nodule, 1757-1758
Scintillations, in migraine, 247
Scintilligraphy, of lacrimal obstruction, 798, 799f
Scissors excision, for skin lesions, 293
SCIT (subcutaneous immunotherapy), for allergic rhinitis, 621
SCJ. *See* Squamocolumnar junction (SCJ).
Scleroderma
  esophageal manifestations of, 979, 979f
    imaging of, 1400, 1401f
  vs. myofascial pain dysfunction syndrome, 1285t
  nasal manifestations of, 660
  oral manifestations of, 1252
Sclerotherapy, for lymphatic malformations, 2830-2831
Scoring systems, 53
Scotoma, in migraine, 247
SCPL. *See* Supracricoid partial laryngectomy (SCPL).
Screening, for infant hearing loss, 2718-2719
Scrofula, imaging of, 166f
Scurvy, oral manifestations of, 1254
SD (standard deviation), 63, 64t
  vs. standard error, 73, 73t
SDB. *See* Sleep-disordered breathing (SDB).
SDC (salivary duct carcinoma), 1189-1190, 1189f
SDF-1 (stromal cell–derived factor), in head and neck squamous cell carcinoma, 1060
SDH (succinate-dehydrogenase), in familial paraganglioma syndromes, 1659, 1659t
SDT (speech detection threshold), 1888-1889
SE (standard error), *vs.* standard deviation, 73, 73t
Seasonal allergic rhinitis (SAR), 617-618
  and pediatric chronic sinusitis, 2778
Seasonality, of otitis media, 2767
Sebaceous hyperplasia, 288f, 293
Seborrheic keratoses, 281-282, 282f
Second genu, of facial nerve, 1826f, 1827-1829
Second intention healing
  of oropharyngeal defects, 1376
    of tongue base, 1387-1388
    of tonsil and pharyngeal wall, 1383
  of surface defects of nasal tip, columella, sidewalls, and dorsum as, 365
  with trasoral laser microsurgery, 1533
Second malignancy
  with pediatric head and neck malignancies, 2848
  radiation therapy and, 2626t
Second primary tumors (SPTs)
  of larynx, 1492, 1510
  in oral cancer, 1301-1302
Secretory duct, of salivary gland, 1133-1135
Secretory endpiece, of salivary gland, 1133-1134
Secretory proteins, in salivary gland secretion, 1135-1136
Secretory unit, of salivary gland, 1134-1135
Secundum passagio, 851
Sedation
  of children, 2572, 2594
  for tracheobronchial endoscopy, 1000
Sedatives, as adjuncts to induction of anesthesia, 111
Segmental resection, for tracheal stenosis, 2931-2932, 2932f
Segregation, of chromosomes, 2088
Seizures
  focal, vestibular symptoms of, 2357
  preoperative evaluation of, 106
SELDI-TOF (surface-enhanced laser desorption-ionization–time-of-flight), in head and neck squamous cell carcinoma, 1029
Selection bias, 53, 68t
Selection criteria, 68
Selective neck dissection (SND), 1712-1713
  for cancer of midline structures of anterior lower neck, 1719
    definition and rationale for, 1719, 1719f
    technique for, 1719, 1720f
  for cutaneous malignancies, 1718-1719
    definition and rationale for, 1718, 1718f
    technique for, 1718-1719
  definition of, 1703t, 1712
  historical perspective on, 1703
  for oral cancer, 1313, 1713-1716
    definition and rationale for, 1713, 1714f
    technique for, 1713-1716, 1715f-1716f
  for oropharyngeal, hypopharyngeal, and laryngeal cancer, 1716-1718
    definition and rationale for, 1716-1717, 1717f
    technique for, 1717-1718, 1717f
  rationale for, 1712-1713
  results of, 1721
  for thyroid cancer, 1719, 1719f-1720f
Selective serotonin reuptake inhibitors (SSRIs)
  for migraine, 2350
  for tinnitus, 2137
Self, *vs.* nonself, in immune system, 599
Self-assessment, 79t
Sella
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Sella turcica, 1699
Sellick maneuver, during rapid-sequence anesthesia induction, in children, 2590
Semicanal, of tensor tympani muscle, 2436f
Semicircular canal(s) (SCCs)
  anatomy of, 1825f, 1831, 1850-1851, 1851f, 1853f, 2278f
  in cochlear transduction, 2062f

Semicircular canal(s) (SCCs) *(Continued)*
congenital anomalies of, 2732-2733
in combination with other anomalies, 2728, 2738, 2739f
in congenital aural atresia, 2738
incidence of, 2727
semicircular canal aplasia as, 2732-2733, 2732f
semicircular canal dysplasia as, 2732, 2732f-2733f
embryogenesis of, 1851-1852, 1851f
encoding of head rotation, linear acceleration, and tilt by, 2277-2285
afferents in, 2283-2285, 2283f-2284f
cupula in, 2282f
otoconial membrane in, 2283
sensory transduction in, 2277-2279
anatomy of vestibular end organs in, 2277, 2278f
bidirectional sensitivity in, 2278-2279
cupula in, 2277, 2278f
firing rate in, 2278-2279, 2281f
hair cells in, 2277
otolith organs in, 2278, 2281f
stereocilia in, 2277-2278, 2279f
excitation-inhibition asymmetry of, 2290-2291, 2291f
excitatory and inhibitory responses to head rotation by
high-acceleration, 2290-2292
anatomic and physiologic basis for, 2290-2291, 2291f
clinical importance of, 2291-2292, 2291f-2293f
in its plane, 2289
anatomic and physiologic basis for, 2282f, 2289
clinical importance of, 2289
and eye movements, 2306, 2307f
imaging of, 1920-1921, 1922f
interpretation of any stimulus that excites afferents as excitatory rotation in plane of, 2289
anatomic and physiologic basis for, 2289
clinical importance of, 2289-2290
for nystagmus during caloric testing, 2290
in posterior canal benign paroxysmal positional vertigo, 2289-2290
in superior canal dehiscence syndrome, 2290, 2290f
orientation of, 1852, 1852f
and stimulation of eye movements, 2285-2289
anatomic and physiologic basis for, 2285-2288, 2286f-2288f
clinical importance of, 2288-2289, 2288f
response to simultaneous stimuli of, 2292-2294
anatomic and physiologic basis for, 2292-2294, 2294f-2295f
clinical implications of, 2294
sensitivity axis(es) of, 2293-2294, 2294f
and nystagmus, 2294-2295, 2295f
stimulation of, eyes movements in plane of canal produced by, 2285-2289
anatomic and physiologic basis for, 2285-2288, 2286f-2288f
clinical importance of, 2288-2289, 2288f
transfer function relative to head velocity for, 2303, 2303f
Semicircular canal (SCC) aplasia, 2732-2733, 2732f
Semicircular canal (SCC) dysplasia, 2732, 2732f-2733f
Semont maneuver, for benign paroxysmal positional vertigo, 2331
Semprex D (acrivastine), for nonallergic rhinitis, 701t
Senile angiomas, 290-291
Senile sebaceous hyperplasia, 293
Sensitivity axis(es), of semicircular canals, 2293-2294, 2294f
and nystagmus, 2294-2295, 2295f
Sensitization, in allergic rhinitis, 614
Sensorineural hearing loss (SNHL)
due to acoustic neuroma, 2124-2125, 2125f, 2515-2516
sudden, 2128
in adults, 2116-2130
clinical evaluation of, 2116-2117
audiometric testing in, 2117
history in, 2116
laboratory testing in, 2117
physical examination in, 2116
radiographic testing in, 2117
vestibular testing in, 2117
cochlear *vs.* retrocochlear, 2117
etiology of, 2117-2127
bone disorders as, 2124
endocrine and metabolic, 2125
hereditary disorders as, 2117-2118, 2118f
immune, 2123-2124
infectious, 2118-2119
inner ear anomalies as, 2118, 2118f
neoplastic, 2124-2125, 2125f
neurologic, 2122-2123
paraneoplastic, 2124
pharmacologic toxicity as, 2119-2121
pseudohypacusis as, 2125
renal, 2121
traumatic, 2121-2122, 2121f-2122f
unknown, 2125-2127, 2126f
vascular and hematologic, 2123
sudden, 2127-2130
etiology of, 2127-2129
prevalence, natural history, and prognosis of, 2127
treatment of, 2129-2130
audiogram of, 1888, 1889f, 1906f-1907f
in children, 2200, 2200b
prevalence of, 2719
due to cholesteatoma, 1974
congenital
due to congenital anomalies of inner ear, 2727
due to labyrinthine infections, 2154-2157
with cytomegalovirus, 2154-2156, 2155f
with rubella, 2154, 2156-2157, 2157f
with syphilis, 2161
epidemiology of, 2087
genetic, 2086-2099, 2200
autosomal dominant
nonsyndromic, 2090-2093, 2092t
syndromic, 2093-2096, 2094t
autosomal recessive
nonsyndromic, 2089-2090, 2090f, 2091t
syndromic, 2094t, 2096
background of, 2086-2089
cultural considerations with, 2099
diagnosis of, 2097-2098
epidemiology of, 2089t
genetic testing for, 2098
mitochondrial
nonsyndromic, 2093, 2093t
screening for, 2090t
syndromic, 2094t, 2097
nonsyndromic, 2089-2093
adult-onset, 2117
autosomal dominant, 2090-2093, 2092t
autosomal recessive, 2089-2090, 2090f, 2091t
epidemiology of, 2089, 2089t
high-frequency, 2090-2092
low-frequency, 2092-2093
midfrequency, 2092
mitochondrial, 2093, 2093t
screening for, 2090t
X-linked, 2093, 2093t
Sensorineural hearing loss (SNHL) *(Continued)*
patient management with, 2097-2099
prenatal testing for, 2098
prevention of, 2099
syndromic, 2093-2097, 2094t, 2200, 2200b
in Alport syndrome, 2094t, 2096-2097
autosomal dominant, 2093-2096, 2094t
autosomal recessive, 2094t, 2096
in biotinidase deficiency, 2094t, 2096
in branchio-oto-renal syndrome, 2093-2095, 2094t
epidemiology of, 2089t
in Jervell and Lange-Nielsen syndrome, 2094t, 2096
in MELAS, 2094t, 2097
in MERRF, 2094t, 2097
mitochondrial, 2094t, 2097
in Mohr-Tranebjaerg syndrome, 2094t, 2097
in neurofibromatosis type 2, 2094t, 2095
in non–insulin-dependent diabetes mellitus, 2094t, 2097
in Norrie's disease, 2094t
in Pendred syndrome, 2094t, 2096
in Refsum disease, 2094t, 2096
screening for, 2090t
in Stickler syndrome, 2094t, 2095
in Treacher Collins syndrome, 2094t, 2096
in Usher syndrome, 2094t, 2096
in Waardenburg syndrome, 2094t, 2095-2096
X-linked, 2094t, 2096-2097
treatment of, 2098-2099
X-linked
nonsyndromic, 2093, 2093t
syndromic, 2094t, 2096-2097
in HIV-positive patients, 223-225
approach to, 224, 225t
due to cryptococcal meningitis, 223-224
due to otosyphilis, 224
in infants, 2718-2725
ancillary testing for, 2722-2723
genetic testing in, 2722-2723
laboratory testing in, 2722
screening for connexin 26 mutation in, 2723
screening for maternally transmitted infection in, 2723
temporal bone imaging in, 2723
testing for Pendred's syndrome in, 2723
assessment of, 2719-2721
auditory brainstem responses in, 2719-2720
comparison of otoacoustic emissions and auditory brainstem responses in, 2721
evoked otoacoustic emissions in, 2720-2721
testing protocols for, 2719, 2720f
delay in identification of, 2719
diagnosis of, 2721-2722
audiology in, 2722
history in, 2721
middle ear effusions in, 2722
otomicroscopy in, 2722
physical examination in, 2721-2722
vestibular function assessment in, 2722
visual reinforcement audiometry in, 2722
history of screening for, 2718-2719
intervention strategies for, 2723-2724
amplification devices as, 2723-2724
bone conduction amplification as, 2723
cochlear implantation as, 2724
early, 2724
surgical therapy as, 2723
due to labyrinthine infections, 2118-2119, 2153-2163
acquired, 2157-2161
with herpes simplex virus, 2159-2160
with Lassa fever, 2158-2159
with measles, 2158
with meningitis, 2160-2161

Sensorineural hearing loss (SNHL) *(Continued)*
with mumps, 2157-2158, 2158f
sudden, 2154, 2154b, 2157
with varicella-zoster virus, 2159, 2159f
bacterial and fungal, 2160
with cochlear implant, 2161
congenital, 2154-2157
with cytomegalovirus, 2154-2156, 2155f
with rubella, 2156-2157, 2157f
in immunocompromised patients, 2161-2162
syphilitic, 2161
vaccines to prevent hearing loss due to, 2161
vestibular neuritis due to, 2162-2163, 2162f
due to Lassa fever, 2158-2159
sudden, 2127
in Meniere's disease, 2126-2127, 2335t
fluctuating, 2199
history of, 2337
sudden, 2129
with migraine, 2123, 2348-2349
noise-induced, 2121-2122, 2121f-2122f
otoacoustic emissions with
distortion product, 1905, 1907f
transient evoked, 1905, 1906f
due to small fenestra stapedotomy, 2030, 2034
sudden, 2127-2130
due to acoustic neuroma, 2128
clinical features of, 2157
etiology of, 2127-2129, 2195b, 2198-2201
due to labyrinthine infections, 2154, 2154b, 2157
prevalence, natural history, and prognosis of, 2127
temporal bone pathology in, 2157
treatment of, 2129-2130, 2157
intratympanic steroids for, 2184-2185
systemic steroids for, 2184
due to temporal bone trauma, 2047
in transplant recipients, 224-225
unilateral, bone-anchored hearing aid for, 2216
Sensory abnormalities, after parotidectomy, 1177
Sensory assessment, laryngopharyngeal, 836
Sensory integration, evaluation of, 2317
Sensory nerve complications, of neck surgery, 1731-1732
cervical, 1731-1732
greater auricular, 1731
lingual, 1731
Sensory organization test (SOT), 2325-2326, 2325f-2326f
Sensory presbycusis, 232, 2126
Sensory substitution, in vestibular compensation, 2375
Sensory substitution exercises, in vestibular rehabilitation, 2372-2373, 2378
"Sensory-specific" satiety, 1212-1213
Sentences-in-noise (SIN), for cochlear implants, 2223
Sentinel lymph node biopsy (SLNB)
for melanoma, 1115-1118
complexity in head and neck region of, 1117
excision of primary tumor prior to, 1115, 1116f
future investigations on, 1117-1118
histologic evaluation of, 1116
indications for, 1115, 1115b
inflammation and fibrosis due to, 1117
injury to facial nerve due to, 1117
intraoperative lymphatic mapping for, 1115, 1116f
learning curve for, 1116
lymphoscintigraphy with, 1115-1117, 1116f
and overall survival, 1117
potential therapeutic benefits of, 1117
as prognostic factor, 1117
risk of in-transit metastasis with, 1117
technique of, 1115-1116
therapeutic lymph node dissection after, 1116
for oral cancer, 1313-1314
Sentinel lymph node mapping, 1115, 1116f
Sentinel vein, in brow or forehead rejuvenation, 433-434, 433f
Septal abscess, 2627, 2627f
Septal artery, in surgical anatomy of anterior cranial base, 2473, 2473f
Septal branch
of anterior ethmoid artery, 483f
of sphenopalatal artery, 483f
Septal cartilage grafts
in noncaucasian rhinoplasty, 569
in revision rhinoplasty, 583
Septal deviation, 483f, 484
endoscopic sinus surgery with, 751
imaging of, 668, 669f
in noncaucasian patient, 573, 576f
rhinitis due to, 619b
rhinoplasty with, 513-514, 514f, 546, 546f-547f
septoplasty for (*See* Septoplasty)
due to trauma, 482, 484
with twisted nose, 551-552, 552f
Septal fracture, 498, 501, 501f
closed reduction of, 503, 503f
open reduction of, 505-506
Septal hematoma, 494
due to nasal fracture, 507
pediatric, 2708-2709, 2712f
Septal modifications, rhinoplasty for, 546-548, 546f-547f
caudal repositioning in, 547, 547f
dorsal draw suture in, 548, 549f
making final septal assessment in, 548, 549f
septocolumellar complex in, 548, 549f-550f
shortening of caudal septum in, 547-548, 547f-548f
Septal mucoperichondrial flap, for nasal reconstruction, 371-372, 372f
Septal nerve, 483f
Septal perforation, 493-494, 493f
epistaxis due to, 686f
Septal splints, after nasal fractures, 504
Septal spur, 482, 482f, 489, 494, 669f
Septisol (hexachlorophene and alcohol), for deep chemical peel, 394-395
Septocolumellar complex, in rhinoplasty, 548, 549f-550f
Septocutaneous arteries, 1065, 1065f
Septolabial angle, correction of acute, 547-548, 548f
Septomaxillary ligament, in craniofacial growth and development, 2614
Septoplasty, 488-494
adjuncts to, 494
alar deformity due to, 491, 491f
anesthesia and analgesia for, 488
bony deflection or spur in, 482, 482f, 489, 494
with caudal absence and tip collapse, 492, 492f
caudal septum in, 491-492, 491f-492f
complications of, 494
Cottle and Freer elevators in, 488, 489f
with crooked nose, 494
defined, 488
effects on craniofacial growth and development of, 2627-2628
elevation of mucoperiosteum in, 488-489
endoscopic, with endoscopic dacryocystorhinostomy, 798, 799f
evolution of technique for, 487-488
incisions and planes of dissection for, 488, 489f
L-strut in, 489-490, 490f
maxillary crest in, 490, 490f
with nasal valve correction, 493
postoperative care after, 494, 494f
of previously fractured nose, 483-484
reoperation after, 492-493, 493f
reskeletonization in, 491
with septal perforation repair, 493-494, 493f
Septoplasty *(Continued)*
spreader graft placement in, 490-491, 491f
suturing in, 491, 491f
in vocal professional, 858
wedge excision in, 490-491, 490f
Septum, nasal. *See* Nasal septum.
Sequencing, 3, 9
Serial excision, for scar revision, 296
Serologic tests, for dizziness, 2327
Seroma
after liposuction, 459
after neck surgery, 1727, 1727f
Serotonin (5-hydroxytryptamine$_3$)-receptor antagonists, for postoperative nausea and vomiting in children, 2593
Serotonin-norepinephrine reuptake inhibitors, for neuropathic pain, 244
Serous acinus, 1134, 1134f, 1134t
Serous demilune, 1134, 1134f
Serous labyrinthitis, after small fenestra stapedotomy, 2034
Serous otitis media (SOM), immunosuppression and, 222-223
Sertraline, for tinnitus, 2137
Serum analysis, for biomarkers, for head and neck squamous cell carcinoma, 1026-1027
Sesamoid cartilages, 497f
Sestamibi–technetium 99m scintigraphy, for hyperparathyroidism, 1785
due to double parathyroid adenoma, 1785, 1785f
due to mediastinal supernumerary thyroid gland, 1802, 1803f
and multinodular thyroid disease, 1801, 1801f
due to multiple-gland hyperplasia, 1794, 1794f
due to parathyroid carcinoma, 1803, 1803f
Severe combined immunodeficiency (SCID), 209-210
Severity, of disease, 53
Sevoflurane, for anesthesia, 111
in children, 2590
Sexually transmitted diseases, oral manifestations of, 1252
SF-36 (Medical Outcomes Study Short Form-36), 56, 642
SGL (supraglottic partial laryngectomy), for early-stage supraglottic cancer, 1498-1500, 1498f
SGNs (spiral ganglion neurons), salvage of, 2189-2191
SGS. *See* Subglottic stenosis (SGS).
Shaker 2 mutant mouse, 2076
Shave biopsy, for skin lesions, 293
Shield graft
for nasal tip enhancement, 576, 577f
in revision rhinoplasty, 589, 590f
Shielding devices, for radiation therapy, 1331-1332, 1334f
Shift worker disorder, 262t, 264
Shimmer, in acoustic analysis for voice evaluation, 829-830, 834-835
Short nose, revision rhinoplasty for
due to excessive caudal septal excision, 591f, 593
due to overrotation, 590, 590f-591f
Short T1 inversion recovery (STIR), MRI with, 135-136, 136f
Short-hairpin RNA (shRNA), 14f, 16
Short-interfering RNA (siRNA)
direct delivery of, 16
in RNA interference, 13, 14f
Shotgun(s), neck trauma due to, 1626-1627, 1628t
Shotgun shells, 1626, 1628t
Shoulder dysfunction, after neck dissection, 1722
Shoulder region, of cell survival curve, 1037-1038, 1038f

Shprintzen-Goldberg syndrome, craniofacial anomalies in, 2641t
Shrapnell's membrane, 1824, 1825f
Shrinking field technique, for radiation therapy for glottic cancer, 1586, 1587f
shRNA (short-hairpin RNA), 14f, 16
Shy-Drager syndrome, laryngeal hypofunction due to, 843
Sialadenitis
  acute suppurative, 1151-1153
    in children, 2856, 2856t
    clinical manifestations of, 1152, 1152f
    complications of, 1153, 1154f
    defined, 1151
    differential diagnosis of, 1152
    epidemiology of, 1151
    laboratory evaluation of, 1152
    pathogenesis of, 1151-1152, 1152f
    sialolithiasis and, 1151-1152, 1155, 1155f
    treatment of, 1152-1153, 1153f
  in children, 2819
    acute suppurative, 2856, 2856t
    bacterial, 2856-2857, 2856t
    chronic, 2858
    neonatal, 2857
    recurrent, 2856-2857
    viral, 2855
  chronic, 1154, 1155f
    in children, 2858
  neck masses due to, 1638
    in children, 2819
  of parotid gland, 150
Sialadenoma papilliferum, 1171
Sialadenoscopy, in children, 2855
Sialectasis, in children, 2858
Sialocele, posttraumatic, 313-314
Sialoendoscopy, for sialolithiasis, 1156
Sialogogues, for xerostomia due to radiotherapy, 1048
Sialography, 1149-1150
  in children, 2854
  conventional, 139-140, 1149-1150, 1149f, 1155-1156, 1156f
  CT, 139-140, 1145f, 1150, 1150f
  MR, 1147
  for salivary gland injury, 312
Sialolithiasis, 1155-1156, 1156f
  and acute suppurative sialadenitis, 1151-1152, 1155, 1155f
  in children, 2858-2859
  clinical manifestations of, 1155
  defined, 1155
  epidemiology of, 1155
  etiology of, 1155
  imaging of, 1143, 1155-1156
    conventional sialography for, 1155-1156, 1156f
    CT for, 1143, 1148, 1148f
    MR sialography for, 1155-1156
    of submandibular gland, 1144f, 1154, 1157f
  management of
    extracorporeal shock wave lithotripsy for, 1156
    nonsurgical, 1156
    of parotid gland, 1156
    sialendoscopy for, 1156
    surgical, 1156, 1156f
  neck masses due to, 1638
  of parotid gland, 1155-1156
  stone composition in, 1155
  of submandibular gland, 1155
    imaging of, 1144f, 1154, 1157f
    surgical management of, 1156, 1156f
  ultrasound imaging of, 1647
Sialometaplasia, necrotizing
  in children, 2857
  of hard palate, 1309-1310
  of larynx, 1493
  of oral cavity, 1289, 1299
Sialo-odontogenic cyst, 1267
  clinical features of, 1267
  microscopic features of, 1267, 1267f
  radiographic features of, 1267
  treatment of, 1267
Sialoperoxidase, in saliva, 1140
Sialorrhea, 2863-2864
  defined, 2863
  epidemiology of, 2863
  medical management of, 2864
  pathogenesis of, 2863-2864
  surgical management of, 2864
Sick euthyroid syndrome, 1748
Sickle cell anemia, preoperative evaluation of, 106
Sickle cell disease, sensorineural hearing loss due to, 2120
Sickness Impact Profile, 56
SIDS (sudden infant death syndrome), 2570
Sievert (Sv), 133
Sigmoid sinus
  in subtotal temporal bone resection, 2494-2495
  in surgical anatomy of lateral skull base, 2436f, 2439f-2440f
Sigmoid sinus impression
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Sigmoid sinus injury, due to mastoidectomy, 2016
Sigmoid sinus occlusion, in postauricular approach to infratemporal fossa, 2498, 2498f
Sigmoid sulcus, 1823f, 2010f
Signal processing strategies, for cochlear implants, 2229-2231
  Advanced Combination Encoder as, 2230, 2231f
  analog stimulation as, 2230, 2230f
  continuous interleaved sampling as, 2229-2230
  fine structure, 2230-2231, 2231f-2232f
  spectral emphasis, 2230
  spectral peak extraction as, 2230, 2230f
  temporal, 2229-2230, 2230f
Signal transduction, in salivary gland secretion, 1137-1138
  adenylate cyclase system in, 1137
  G proteins in, 1137
  phospholipase C system in, 1137-1138
Silastic. *See* Silicone (polydimethylsiloxane, Silastic).
Silicone (polydimethylsiloxane, Silastic)
  for chin implants, 465t
  injectable, dorsal cyst due to, 578, 579f
  for medialization thyroplasty, 908-910, 910f
  in noncaucasian rhinoplasty, 569, 570f
Silicone (polydimethylsiloxane, Silastic) rubber, for nasal reconstruction, 368
Silicone (polydimethylsiloxane, Silastic) sheeting, for scar revision, 300-301
Silicone (polydimethylsiloxane, Silastic) slings, for lagophthalmos, 2421
Silicone (polydimethylsiloxane, Silastic) strips, in atresiaplasty, 2756-2757, 2758f
Silver nitrate gel, for fungal otitis externa, 1955
Silverstein MicroWick, 2182, 2182f
Simonart's band, 2659, 2660f
Simple calyx endings, of hair cells, 1857, 1859f
Simple harmonic motion, 1838-1839, 1839f
Simulation, 45-51
  advantages of, 45
  for difficult airway management, 118
  of endoscopic sinus surgery, 46-49
    Dextroscope for, 48
    ES3 for, 46-48, 46f
      curriculum development for, 48
      validation studies of, 47-48, 47f, 48t
    Nasal Endoscopy Simulator for, 49
    Paranasal Sinuses Simulator for, 49
    rationale for, 46-49
    VR-FESS for, 48
  of temporal bone surgery, 49-50, 49f-50f
  virtual reality, 45-46
Simultaneous Analog Stimulation (SAS), for cochlear implants, 2230, 2230f
SIN (sentences-in-noise), for cochlear implants, 2223
Sincipital encephaloceles, of nose, 2687-2688, 2687f, 2687t
Singers, voice disorders in. *See* Professional voice disorders.
Singer's formant, 847
Singing Voice Handicap Index, 57
Single nucleotide polymorphisms (SNPs), 9
  in head and neck squamous cell carcinoma, 1019
Single photon emission computed tomography (SPECT)
  of Graves' ophthalmopathy, 1810
  of malignant otitis externa, 1947
  of oral cancer, 1300
  technetium 99m scintigraphy with, for hyperparathyroidism, 1785
Single strand conformation polymorphism (SSCP), 9
Single-gene disorders, 4, 6
  dominant, 6, 6f
  penetrance and expressivity of, 7, 7f
  recessive, 6-7, 7f
Single-stage laryngotracheal reconstruction (SSLTR), for laryngeal stenosis, 2920-2921
Single-strand breaks, by radiation, 1036
Singular neurectomy, 2360, 2360f
Sinonasal infection, immunosuppression and, 219-221
  diagnosis of, 220-221, 220f
  presentation and pathogenesis of, 219-220
  treatment of, 221
Sinonasal management, for benign vocal fold mucosal disorders, 862-863
Sinonasal neoplasm(s)
  benign, 717-727, 718t
    diagnosis of, 717-718
    fibrous dysplasia as, 718t, 725-726, 726f
    glioma as, 718t
    hamartoma as, 718t
    inverted papilloma (Schneiderian papilloma, inverted type) as, 718-720
      endoscopic appearance of, 718-719, 719f
      epidemiology of, 718
      with frontal sinus involvement, 720, 720f
      histologic appearance of, 718
      human papillomavirus and, 718
      imaging of, 719, 719f
      postoperative surveillance for, 720
      recurrence of, 720
      sites for, 718
      and squamous cell carcinoma, 718
      surgical approach for, 718t, 719-720, 720f, 763
    juvenile angiofibroma as, 721-722
      classification systems for, 722
      endoscopic appearance of, 721, 721f
      imaging of, 721
      natural history of, 721
      origin of, 721, 721f
      postoperative surveillance for, 722
      preoperative embolization for, 721-722
      surgical approach for, 718t, 722, 722f-723f, 763
    lobular capillary hemangioma as, 718t, 725, 725f
    ossifying fibroma as, 725-726
    osteoma as, 723-725
      classification of, 723
      endoscopic appearance of, 723
      epidemiology of, 723
      ethmoid, 724f
      frontal, 724-725, 724f
      imaging of, 723-725, 723f-724f
      ivory ("eburnated"), 723, 723f-724f

Sinonasal neoplasm(s) *(Continued)*
mature (spongiosum), 723
microscopic appearance of, 723
mixed, 723, 724f
pathogenesis of, 723
postoperative surveillance for, 725
spongiosum variant of, 724f
surgical approach for, 718t, 724-725
symptoms of, 723
pleomorphic adenoma as, 718t
schwannoma as, 726-727, 726f
surgical approach for, 718, 718t, 763
malignant, 1127-1128
adenocarcinoma as, 1131
adenoid cystic carcinoma as, 1131
algorithm for evaluation and management of, 1122f
epidemiology and survival with, 1121-1122, 1123t
epithelial
management of
staging of, 1127-1128, 1128f, 1129b
ethmoid, sphenoid, and frontal, 1130
staging of, 1129b
hematopoietic and lymphoid, 1131
involvement of cervical lymph nodes in, 1130
lymphoma as, 1131, 1680
therapy and prognosis for, 1680
maxillary, 1128-1130
chemoradiotherapy for, 1130
combined irradiation and surgery for, 1128
inoperable, 1130
radiotherapy for, 1128-1130
staging of, 1129b
surgery alone for, 1128
melanoma as, 1131-1132
sarcomas as, 1131
staging of, 1127-1128, 1128f, 1129b
therapeutic decision-making for, 1131
Sinonasal Outcome Test (SNOT-20), 57, 642, 730
Sinonasal polyp(s), endoscopic sinus surgery for, 751-752
Sinonasal polyposis
in aspirin-exacerbated respiratory disease, 732f
with methicillin-resistant *Staphylococcus aureus* infection, 733f
surgical management of, 741
Sinonasal undifferentiated carcinoma (SNUC), 1698-1699
Sinus(es). *See* Paranasal sinus(es).
Sinus balloon catheterization, 752-753, 753f
Sinus disease, olfactory dysfunction due to, 633
Sinus histiocytosis, in children, 2819
Sinus lateralis, 665f, 667f
Sinus mucocele, 676, 678f
Sinus surgery, 739-758
endoscopic (*See* Endoscopic sinus surgery (ESS))
external procedures for, 756-757
Caldwell-Luc procedure as, 756, 756f
external ethmoidectomy as, 757, 757f
for frontal sinus, 757
intranasal ethmoidectomy as, 756-757
for sphenoid sinus, 757
historical background of, 739
indications for, 741-742, 741b
anterior meningoencephaloceles as, 742
choanal atresia as, 742
CSF rhinorrhea as, 742
endoscopic transnasal approach as, 742
headache and facial pain as, 742
intractable epistaxis as, 742
mucoceles as, 742
removal of foreign body as, 742
rhinosinusitis as
with acute complications, 741
chronic, 741
invasive fungal, 742
Sinus surgery *(Continued)*
noninvasive fungal, 742
recurrent acute, 741
sinonasal polyposis as, 741
tumors as, 742
minimally invasive, 743, 752, 760
surgical anatomy for, 739-741
anatomic variations in, 741
anterior skull base in, 741
ethmoid complex in, 740
frontal sinus in, 740-741
maxillary sinus in, 740
middle turbinate in, 739-740
ostiomeatal complex in, 739, 740f
sphenoid sinus in, 740, 740f
in vocal professional, 858
Sinus tympani
anatomy of, 1825-1826
in mastoidectomy, 2015, 2015f
Sinusitis. *See also* Rhinosinusitis.
acute
frontal, 775
radiologic appearance of, 672-673, 673f
allergic, 675
chronic
frontal, 775-783
pediatric, 2778-2781
cultures for, 2779
etiology of, 2778-2779
imaging of, 2779
irrigation for, 2779
medical management of, 2779
surgical management of, 2779-2781, 2780f-2781f
radiologic appearance of, 673-674, 674f-675f
complications of, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
frontal
acute, 775
anatomic variations and, 776
chronic, 775-783
granulomatous, 675
immunosuppression and, 219-221, 660
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
vs. myofascial pain dysfunction syndrome, 1284t
radiologic appearance of, 167-168, 168f, 672-675
acute, 672-673, 673f
allergic, 675
chronic, 673-674, 674f-675f
with complications, 676-677
inflammatory polyps as, 676, 678f
mucocele as, 676, 678f
mucous retention cyst as, 676, 677f
orbital, 676-677
on CT, 140-142, 141f
granulomatous, 675
rhino- (*See* Rhinosinusitis)
use of term, 729
siRNA (short-interfering RNA)
direct delivery of, 16
in RNA interference, 13, 14f
Sistrunk operation, for thyroglossal duct cyst, 2815
SIX1 gene
in branchio-oto-renal syndrome, 2095
in deafness, 2051t-2058t
SIX5 gene
in branchio-oto-renal syndrome, 2095
in deafness, 2051t-2058t
Sizing template, in microtia reconstruction, 2744-2745, 2745f
Sjögren's syndrome (SS)
autoantibodies in, 1160
clinical presentation of, 1160
defined, 1160
diagnostic criteria for, 1160
differential diagnosis of, 1160
etiology of, 1160
and malignant lymphoproliferative disorders, 1160
ocular findings in, 1160
oral manifestations of, 1251
physical examination for, 1160
primary, 1160
salivary gland involvement in, 1160-1161
in children, 2858
imaging of, 1148, 1647
secondary, 1160
systemic manifestations of, 1160
treatment of, 1160-1161
SJS (Stevens-Johnson syndrome), 1239
SK2 channel defects, and hearing, 2079-2080
Skeletal abnormalities, due to hyperparathyroidism, 1781
Skeletal defect repair, biomaterials in, 2657-2658
Skeletal dysplasias, and obstructive sleep apnea, 2605
Skew deviation, 2312-2313
Skewing quotient, in measurement of vocal fold vibration, 830-831
Skin
aesthetic analysis of, 275, 276b, 279f
aging (*See* Aging skin)
anatomy and physiology of, 1065-1067
angiosomes in, 1064
capillary system in, 1066
cellular systems in, 1066-1067
interstitial system in, 1066
macrocirculatory system in, 1065-1066, 1065f
zones of perfusion in, 1064-1065, 1065f
effects of radiotherapy on, 2626t
physical examination of, 95
vascular supply to, 1064
Skin cancer, immunosuppression and, 213t, 215
Skin Cancer Index, 57
Skin diseases
esophageal manifestations of, 979-980
nasal manifestations of, 660-661
in Behçet's disease, 660-661
in pemphigoid, 660
in pemphigus vulgaris, 660
in scleroderma, 660
oral manifestations of, 1253-1254
Skin erythema dose, 1031
Skin flap(s), 1064-1079
acutely raised, 1067-1071
capillary obstruction (no-reflow phenomenon) in, 1070-1071
critical closing pressure in, 1068
free radical formation in, 1070-1071, 1071f
impairment of vascular supply in, 1067-1068
increased interstitial pressure in, 1068, 1069f
inflammation and prostaglandins in, 1070, 1070f
length-to-width ratio in, 1068, 1068f
microcirculatory changes in, 1068-1069
neovascularization in, 1069, 1069f
nerve section in, 1069-1070
reperfusion injury in, 1070
vascular territories in, 1067, 1068f
advancement, 345-346
bilateral, 345, 346f
island, 345
unipedicle, 345, 345f
V-Y, 345-346, 346f-347f
Y-V, 346

Skin flap(s) *(Continued)*
anatomy and physiology of skin and, 1065-1067
angiosomes in, 1064
capillary system in, 1065-1066, 1065f
cellular systems in, 1065-1067, 1065f
interstitial system in, 1065-1066, 1065f
macrocirculatory system in, 1064-1066, 1065f
zones of perfusion in, 1064-1065, 1065f
arterial (axial pattern), 1067, 1067f
attempts to alter viability of, 1072-1074
delay as, 1072-1073
with increased blood supply, 1072, 1072f, 1072t
inflammation as, 1074
neovascularization as, 1073
rheology as, 1073-1074
tissue expansion as, 1074
vasodilators in, 1073
direct, 1073
indirect, 1073
biomechanics of, 1071-1072, 1071f
classification of, 342-343, 343b, 1067, 1067f
complications of, 366
delayed, 1072-1073
free microvascular, 1067
primary ischemia in, 1075
reperfusion period for, 1075
salvage of, 1075
secondary ischemia in, 1068, 1075
vascularity of recipient bed with, 1075
for hair loss, 385-387, 387f
complications of, 386-387
hinge, 346
impaired, 1075
salvage of, 1075
myocutaneous and fasciocutaneous, 1067, 1067f
necrosis of, 1068
after neck surgery, 1727
with rhytidectomy, 421-422, 425f-426f
pedicled, salvage of, 1075
pivotal, 343-345
effective length of, 343, 343f
interpolated, 344-345, 344f
rotation, 343-344, 343f
transposition, 344, 344f
prolonged viability of, 1074-1075
hyperbaric oxygen and, 1074
metabolic manipulation and, 1074-1075
protection against harmful agents and, 1074
random, 1067, 1067f
cutaneous, 1067, 1067f
stresses due to, 1064
undermining of, 1071-1072
Skin grafting
for airway stenosis, 946-947
for burns, 315
gene therapy for, 23
for nasal reconstruction, 365
for oropharyngeal reconstruction, 1376
of tongue base, 1388
of tonsil and pharyngeal wall, 1384
Skin lesion(s), 281-294
cysts as, 289
dermoid, 289
epidermoid, 289
milia as, 289
mucous, 289
pilar, 289
in steatocystoma multiplex, 289
epidermal, 281-286
actinic keratoses as, 283, 284f
basal cell carcinoma as, 283-285, 284f-285f
chondrodermatitis nodularis helicis as, 285, 285f
dermatosis papulosa nigra as, 282
keratoacanthoma as, 284f, 286
seborrheic keratoses as, 281-282, 282f
Skin lesion(s) *(Continued)*
squamous cell carcinoma as, 285-286, 285f
warts (verruca vulgaris) as, 282-283
filiform, 282, 282f
flat, 282, 283f
due to molluscum contagiosum, 282-283, 283f
fibroadnexal, 291-293
acrochordon as, 291
angiofibroma as, 292
atypical fibroxanthoma as, 292
cylindroma as, 288f, 292
dermatofibroma as, 288f
dermatofibrosarcoma protuberans as, 291-292
fibrous papule as, 288f, 292
hidrocystoma as, 292
keloids and hypertrophic scars as, 291
lipoma as, 293
neurofibromas as, 292
sebaceous hyperplasia as, 288f, 293
syringoma as, 292-293
trichoepithelioma as, 292
xanthelasma as, 293
melanocytic, 286-289
blue nevus as, 286-287, 287f
compound nevus as, 286
congenital nevi as, 287-288
dysplastic nevus as, 288, 288f
halo nevus as, 287, 287f
intradermal nevus as, 286, 287f
junctional nevus as, 286, 287f
lentigo maligna melanoma as, 287f
nevocellular nevus as, 286
nevus sebaceus as, 287f, 289
solar (actinic) lentigo as, 288
Spitz nevus as, 287
superficial spreading melanoma as, 285f
telangiectasia as, 291
hereditary hemorrhagic, 291
spider angioma as, 291
venous lakes as, 288f, 291
treatment methods and biopsy techniques for, 293-294
chemical or abrasive surgery as, 294
cryosurgery as, 294
electrosurgery as, 294
excisional surgery as, 293
laser surgery as, 294
vascular, 290-291
cherry angiomas as, 290
infantile hemangiomas as, 290
port wine stain as, 291
pyogenic granuloma as, 290
salmon patch as, 290-291
Skin protection, in laser surgery, 35
Skin quality, in rhinoplasty, 512-513, 512f
Skin resurfacing, with blepharoplasty, 451
Skin sparing, in radiotherapy, 1033-1034
Skin tag, 291
Skin tension lines, relaxed, 269-270, 274f
Skin testing, for allergic rhinitis, 619
Skin types, sun-reactive (photoaging), 275, 276b
Skin–soft tissue envelope (SSTE), revision rhinoplasty of, 581, 594
Skipped generation, 2089
Skull
cloverleaf, due to craniosynostosis, 2645, 2645f
in Down syndrome, 2632
Skull base. *See* Cranial base.
SKY (spectral karyotyping), for head and neck squamous cell carcinoma, 1019
Slc. See Solute carrier family *entries.*
SLE (systemic lupus erythematosus), oral manifestations of, 1251-1252
Sleep apnea
acoustic rhinometry for, 651
central, 251b, 256f, 263, 263b
mixed, 251b
obstructive (*See* Obstructive sleep apnea (OSA))
Sleep Apnea Quality of Life Index (SAQLI), 57
Sleep disorder(s), 261-266
circadian rhythm, 264, 264b
classification of, 261-266, 262b
hypersomnias of central origin as, 263-264, 264b
insomnia as, 262-263, 263b
isolated symptoms, apparently normal variants, and unresolved issues with, 265-266, 265b
with obstructive sleep apnea, 261, 262t
obstructive sleep apnea as (*See* Obstructive sleep apnea (OSA))
outcome scales for, 56t, 57
parasomnias as, 264-265, 265b
sleep-related breathing disorders as, 263, 263b
sleep-related movement disorders, 265, 265b
Sleep hygiene, inadequate, 262t, 263
Sleep onset REM periods (SOREMPs), 263-264
Sleep paralysis, 264-265
Sleep stages, 261-262
Sleep study, for stridor, 2901
Sleep talking, 262t
Sleep terrors, 262t, 264
Sleep videoendoscopy, drug-induced, of obstructive sleep apnea, 253-255
Sleep-disordered breathing (SDB), 263, 263b
in children, 2602-2612
and ADHD, 2791
cardiopulmonary complications of, 2792
classification of, 2602
and enuresis, 2792
and growth problems, 2792
and neurocognitive development, 2791-2792
obstructive sleep apnea as (*See* Obstructive sleep apnea (OSA))
primary snoring as, 2602-2603
upper airway resistance syndrome as, 2602-2603
classification of, 251-252, 251b
indices of, 251b
symptoms of, 252b
Sleepiness, daytime, 263-264
obesity and, 251
Sleep-related breathing disorders, 263, 263b
classification of, 251-252, 251b
indices of, 251b
symptoms of, 252b
Sleep-related hypoventilation/hypoxemic syndromes, 263, 263b
Sleep-related movement disorders (SRMDs), 265, 265b
Sleep-related upper airway obstruction, 2607
Sleepwalking, 262t, 264
Slide tracheoplasty, 2932-2933, 2933f
SLIT (sublingual immunotherapy), for allergic rhinitis, 621-622
SLL. *See* Small lymphocytic lymphoma (SLL).
SLN. *See* Superior laryngeal nerve (SLN).
SLNB. *See* Sentinel lymph node biopsy (SLNB).
Slow-wave sleep, 261-262
SLS. *See* Sublingual space (SLS).
SLUG, in deafness, 2051t-2058t
Small cell carcinoma
invasive, of cribriform plate and orbits, 170f
neuroendocrine type (SCCNET), of larynx, 1507-1508
of salivary glands, 1190-1191, 1190f
Small fenestra stapedotomy, 2030-2032
with laser minus prosthesis, 2033
laser *vs.* microdrill in, 2033
postoperative care after, 2032-2033
postoperative complication(s) of, 2030, 2034

Small fenestra stapedotomy *(Continued)*
facial paralysis as, 2030, 2034
perilymph fistula as, 2034
reparative granuloma as, 2034
sensorineural hearing loss as, 2030, 2034
serous labyrinthitis as, 2034
taste disturbance as, 2034
tinnitus as, 2034
tympanic membrane perforation as, 2034
vertigo as, 2030, 2034
procedure for, 2030-2032
anesthesia for, 2030
creation of fenestra in, 2031-2032, 2032f
flap elevation in, 2031, 2031f
incisions for, 2031
measurement of distance from incus to footplate in, 2031, 2031f-2032f
placement of prosthesis in, 2031-2032, 2032f
positioning for, 2031, 2031f
removal of posterior superior bony wall in, 2031, 2031f
stapedectomy *vs.,* 2030
surgical problems in, 2033-2034
chorda tympani nerve damage as, 2034
exposed, overhanging facial nerve as, 2033
fixed malleus as, 2033
floating footplate as, 2033
intraoperative vertigo as, 2034
perilymph gusher as, 2034
solid or obliterated footplate as, 2033
tympanic membrane perforation as, 2034
Small lymphocytic lymphoma (SLL), 1678
clinical presentation of, 1674
imaging of, 1674, 1674f
treatment and prognosis for, 1678
Small round blue cell (SRBC) tumors, 2836
SMAS. *See* Superficial musculoaponeurotic system (SMAS).
SMCP (submucous cleft palate), 2659, 2661f, 2674
bifid uvula with, 2793, 2793f
Smell. *See* Olfaction.
Smell Identification Test, 637-638
Smile pattern, in facial nerve assessment, 2417-2418
Smith, Will, 38
Smith-Magenis syndrome, deafness in, 2051t-2058t
Smoke evacuation, in laser surgery, 35
"Smoker's melanosis," 1241f
Smoking
exposure to, and otitis media, 2767
and Graves' ophthalmopathy, 1807
and skin flap survival, 1075
and squamous cell carcinoma
of head and neck, 1016
of larynx, 1491, 1512-1513
of oral cavity, 1293-1294, 1365
Smooth pursuit, 2277, 2306f, 2307t
evaluation of
in bedside exam, 2313-2314
testing for, 2318, 2319f
Smooth pursuit tracking system, in vestibular compensation, 2375
SMS (submandibular space)
anatomy of, 202
imaging of, 146f, 156-157, 158f
odontogenic infections of, 183-184, 183f-184f
SMV (submentovertex) view, of facial bones and sinuses, 130
SNAI2, in deafness, 2051t-2058t, 2095
Snap test, 445, 446f
SND. *See* Selective neck dissection (SND).
Snell's waltzer mice, 2078
SNHL. *See* Sensorineural hearing loss (SNHL).
Sniffer, chronic, 483-484
Sniffin' Sticks, 631
Sniffing, in olfaction, 625
SNORE-25 (Symptoms of Nocturnal Obstruction and Respiratory Events), 57
Snoring, 251, 266
acoustic rhinometry for, 651
in children
due to obstructive sleep apnea. *See* Obstructive sleep apnea (OSA).
primary, 2602-2603
due to upper airway resistance syndrome, 2602-2603
SNOT-20 (Sinonasal Outcome Test), 57, 642, 730
SNPs (single nucleotide polymorphisms), 9
in head and neck squamous cell carcinoma, 1019
SNUC (sinonasal undifferentiated carcinoma), 1698-1699
SOC (superior olivary complex), in central auditory pathway, 1835, 1835f, 1846
Social history, 94
Socioeconomic status, and otitis media, 2767
SOD (superoxide dismutase), and skin flap viability, 1074
Sodium (Na^+)
in saliva, 1139
in taste, 1208
Sodium bicarbonate, for cerumen removal, 1958t
Sodium channels, in taste, 1208
Sodium chloride (NaCl), gustatory response to, 1208-1209
Sodium restriction, for Meniere's disease, 2126
Sodium salts, gustatory response to, 1208-1209
Sodium tetradecyl sulfate (Sotradecol), for embolization, 1933
Sodium/hydrogen (Na^+,H^+) exchanger, in salivary gland secretion, 1135
Sodium/iodide symporter (NIS), in thyroid hormone synthesis, 1737
Sodium-potassium (Na^+,K^+) pump, ATPase-driven, in salivary gland secretion, 1135
Sodium-potassium-chloride (Na^+,K^+-$2Cl^-$) cotransporter, in salivary gland secretion, 1135
Soft palate
anatomy of, 1295f, 1359f, 1366
cancers of
cervical lymph node metastasis of, 1361t
clinical presentation of, 1365
management of, 1368-1369, 1368f
neurologic evaluation of, 834
during pharyngeal swallow, 1216, 1216f
taste buds on, 1208, 1211
Soft palate reconstruction, 1381-1383
algorithm for, 1384f
free flaps for, 1382
Gehanno method for, 1382
Lacombe and Blackwell's method for, 1382-1383
other groups' experience with, 1383
radial forearm, 1382, 1383f
local flaps for, 1381
buccinator musculomucosal, 1381-1382, 1381f
palatal island mucosal, 1382
Superior Constrictor Rotation-Advancement Flap (SCARF) as, 1382, 1382f
uvulopalatal, 1377f, 1381
prosthetic obturation for, 1381
speech function after, 1383
Soft palate resection, prostheses for, 1343-1344, 1344f
Soft tissue(s), effects of radiotherapy on, 2626t
Soft tissue avulsions, 307, 308f
Soft tissue flap(s)
for free tissue transfer, 1082t, 1083
anterolateral thigh, 1082t, 1083
lateral arm, 1082t, 1083
lateral thigh, 1082t
radial forearm, 1082t, 1083, 1083f
tubed, 1087, 1091f
scapular-parascapular, 1082t
ulnar forearm, 1082t
Soft tissue flap(s) *(Continued)*
mandibular reconstruction plate with, 1325
advantages and disadvantages of, 1325
plate extrusion with, 1325, 1326f
plate fracture with, 1325-1326, 1326f
volume-based, 1325, 1326f
Soft tissue landmarks and reference points, in facial analysis, 270b, 271f
Soft tissue sarcomas, 1666, 1666t
Soft tissue stenosis, of external auditory canal, 2021-2022, 2023f
Soft tissue trauma, 302-317
approach to, 302-306
anesthesia in, 304
cleaning in, 304-305, 305f
history taking in, 302-303
infection control in, 305
physical examination in, 303-304, 303f
repair in, 305-306, 306f
tetanus prophylaxis for, 303
to ears, 308f, 310, 310f
etiology of, 302
to eye, 303
to eyelids, 303, 303f, 307-309, 308f
to facial nerve, 309
to lacrimal apparatus, 307-309, 308f
with large-segment, composite avulsions or amputations, 312, 312f
to lips, 309-310, 309f
to nose, 310-312, 311f
to parotid duct, 312-313, 314f
to salivary glands, 312, 313f
sialocele and salivary fistula due to, 313-314
types of injuries in, 306-307
abrasion as, 306
avulsions as, 307, 308f
laceration as, 307
Soft tissue tumors, of oropharynx, 1363-1364, 1364f
SOHND. *See* Supraomohyoid neck dissection (SOHND).
Solar cheilitis, 283
Solar keratoses, 283, 284f
Solar (actinic) lentigo, 288
Solitary fibrous tumor, 1671
Solute carrier family 4 member 7 *(Slc4a7)* gene, in murine deafness, 2058t-2060t
Solute carrier family 12 member 2 *(Slc12a2)* gene, in murine deafness, 2058t-2060t
Solute carrier family 12 member 6 *(Slc12a6)* gene, in murine deafness, 2058t-2060t
Solute carrier family 12 member 7 *(Slc12a7)* gene, in murine deafness, 2058t-2060t
Solute carrier family 17 member 8 *(SLC17A8)* gene, in deafness, 2051t-2058t, 2081
Solute carrier family 19 member 2 *(SLC19A2)* gene, in deafness, 2051t-2058t
Solute carrier family 26 member 4 *(SLC26A4)* gene, in deafness, 2051t-2058t, 2096, 2098
Solute carrier family 26 member 5 (SLC26A5), and outer hair cell motility, 2064-2065, 2068f
Solute carrier family 26 member 5 *(SLC26A5)* gene, in deafness, 2051t-2058t
SOM (serous otitis media), immunosuppression and, 222-223
Somatic gene therapy, 14, 15f
Somatic tinnitus, 2132-2133, 2132t
Somesthesia, oral, 1201-1202, 1201f-1202f
Somnolence, daytime, 263-264
obesity and, 251
Sonotubometry, for eustachian tube assessment, 1874
SOOF (suborbicularis oculi fat), 444, 447
after facial paralysis, 2431
Sore throat. *See* Pharyngitis.
SOREMPs (sleep onset REM periods), 263-264

SOT (sensory organization test), 2325-2326, 2325f-2326f
Sotradecol (sodium tetradecyl sulfate), for embolization, 1933
Sound, 1838-1839, 1839f
  defined, 2017
  eye movements evoked by, 2316, 2339-2340, 2340f
Sound enrichment, for tinnitus, 2133-2134
Sound localization
  in binaural processing, 2248
  external ear in, 1839
  with traditional hearing aid, 2207
Sound pressure, 1839
Sound pressure level (SPL), 1839, 2140
  in acoustic analysis for voice evaluation, 829, 829t
Sound protection, eustachian tube in, 1871-1872
Sound stimulation, for tinnitus, 2133-2134
Sound transduction, with hearing aids, 2205f
Sound transfer, in middle ear, 2017-2019
Sound transmission, 2000, 2017-2019, 2050-2060, 2062f
Sour taste
  peripheral sensitivity to, 1211
  transduction of, 1209
Source-filter hypothesis, of speech, 812
Southern blotting, 9
SOX2, in deafness, 2051t-2058t
SOX10, in Waardenburg syndrome, 2095
SP (substance P), in salivary gland secretion, 1137
SP (summating potential), in electrocochleography, 1892-1894, 1907
  in Meniere's disease, 2337
Space-frequency map, 2060-2061, 2063f
SP/AP (summating potential/action potential) ratio, 1892-1894
  in Meniere's disease, 2337
Spasmodic dysphonia, 839
  botulinum toxin therapy for, 839, 840f-841f
  voice breaks in, 834-835
Spatial coherence, 26, 27f
SPCC (spindle cell carcinoma), of larynx, 1506
SPEAK (spectral peak extraction), for cochlear implants, 2230, 2230f
Speaking tasks, in pediatric voice evaluation, 2877-2878
SPECT. *See* Single photon emission computed tomography (SPECT).
Spectral displays, in acoustic analysis for voice evaluation, 829t, 830, 830f
  of professional voice, 849
Spectral emphasis strategies, for cochlear implants, 2230
  Advanced Combination Encoder as, 2230, 2231f
  spectral peak extraction as, 2230, 2230f
Spectral karyotyping (SKY), for head and neck squamous cell carcinoma, 1019
Spectral peak extraction (SPEAK), for cochlear implants, 2230, 2230f
Spectral presaturation inversion recovery (SPIR), MRI with, 135-136
Spectral shape, distortion of, with traditional hearing aid, 2204
Spectral tilt, in acoustic analysis for voice evaluation, 830
β-Spectrin 4 *(Spnb4)* gene, in murine deafness, 2058t-2060t, 2081
Spectrogram, in acoustic analysis for voice evaluation, 830, 830f
Spectrometry, for voice analysis of professional voice, 849
Speech
  alaryngeal (*See* Alaryngeal voice and speech)
  defined, 833
  effects of radiotherapy on, 2626t
Speech *(Continued)*
  esophageal, 1459
    physiology of, 1596, 1596f
    after total laryngectomy, 1572
  after hypopharyngeal and esophageal reconstruction, 1459-1460
  laryngeal function in, 810-812, 811b, 811f, 833
  scanning, 837-838
  after surgical resection of oral cancer, 1316
  tracheoesophageal
    physiology of, 1597, 1597f
    after total laryngectomy, 1572
Speech aid, for soft palate resection, 1343, 1344f
Speech analysis, for velopharyngeal dysfunction, 2678-2679, 2678f, 2678t-2679t
Speech bulb prosthesis, for velopharyngeal dysfunction, 2681, 2682f
Speech control, sensory input to, 812
Speech detection threshold (SDT), 1888-1889
Speech discrimination testing, 1889
  for sensorineural hearing loss in adults, 2117
Speech dysfunction, palliative care for, 1104
Speech endoscopy, for velopharyngeal dysfunction, 2680, 2680f
Speech language pathologist, for professional voice disorders, 855
Speech mapping, with hearing aid, 2273
Speech pathologist, for benign vocal fold mucosal disorders, 863, 864f
Speech perception, with cochlear implants
  in adults, 2244-2245
    predictors of, 2245, 2245f
  in children
    early studies of, 2246
    more recent studies of, 2246-2247, 2247f
    tests for, 2246
Speech reception, with cochlear implants
  in adults, 2244-2245
    predictors of, 2245, 2245f
  in children
    early studies of, 2246
    more recent studies of, 2246-2247, 2247f
    tests for, 2246
Speech reception threshold (SRT), 1888-1889
  masking for, 1889
Speech recognition, with cochlear implants
  in adults, 2244-2245
    predictors of, 2245, 2245f
  in children
    early studies of, 2246
    more recent studies of, 2246-2247, 2247f
    tests for, 2246
Speech recognition tests, for cochlear implants, 2223
Speech rehabilitation, after laryngectomy. *See* Voice rehabilitation.
Speech testing, in audiologic test battery, 1888-1889
Speech therapy, for velopharyngeal dysfunction, 2680-2681
  articulation in, 2681
  compensatory strategies in, 2681
  resonance in, 2681
Speech videofluoroscopy, for velopharyngeal dysfunction, 2679-2680
Speech-language development, otitis media and, 2776
Sphenoethmoid synchondrosis, 2619f
Sphenoethmoidal cells, 669, 740, 749f
  in surgical anatomy of anterior cranial base, 2473
Sphenoethmoidal encephalocele, 2687t
Sphenoethmoidal recess(es)
  normal anatomy of, 667, 668f
  in surgical anatomy of anterior cranial base, 2472
Sphenoid bone, 320f
  lesser and greater wings of, 322f, 335f
  in surgical anatomy of anterior cranial base, 2442-2443, 2443f
  in surgical anatomy of lateral skull base, 2435f
Sphenoid ostium(ia), 740, 741f, 2472, 2473f
Sphenoid sinus(es)
  anatomy of
    normal, 664, 665f, 667-668, 668f
    surgical, 740, 741f
      in anterior cranial base, 2443, 2472f-2474f, 2473
  prior to endoscopic sinus surgery, 764, 764t
  extensive pneumatization of, 669, 670f
  external approaches to, 757
  after functional endoscopic sinus surgery, 679
  growth and development of, 2619-2620
  and internal carotid artery, 671-672
  and optic nerve, 672, 672f
Sphenoid sinus tumors, 1123, 1130
Sphenoid spine, in surgical anatomy of middle cranial base, 2444, 2445f
Sphenoidotomy
  in endoscopic sinus surgery, 748, 749f
    complications of, 767, 768t
    for fungus ball, 768f-769f
    with image-guided navigation system, 770f
  in middle cranial base surgery
    transethmoidal, 2455-2457, 2455t, 2456f
    transseptal, 2455-2457, 2455t, 2456f
Spheno-occipital synchondrosis, 2617-2619, 2619f-2620f
Spheno-orbital encephalocele, 2687t
Sphenopalatine artery
  anatomy of, 682
  septal branch of, 483f
Sphenopalatine artery ligation, endoscopic, for epistaxis, 689-690, 689f-690f
Sphenopalatine foramen
  in surgical anatomy of anterior cranial base, 2473f
  in surgical anatomy of lateral skull base, 2435f
Sphenopalatine ganglion, 497
Sphincter pharyngoplasty, for velopharyngeal dysfunction, 2683
Spider angioma, 291
Spin density–weighted image, 134, 135f-136f
Spinal accessory lymph nodes
  anatomy of, 1360f
  in neck dissection, 1705f
Spinal accessory nerve (SAN)
  intraoperative monitoring of, 2550-2552, 2550f
  in modified radical neck dissection, 1712, 1713f-1714f, 1730
  in neck dissection, 1722
  in posterior triangle, 2578-2579, 2579f-2580f
  in surgical anatomy of lateral skull base, 2436f, 2438, 2439f-2440f, 2440
Spinal accessory nerve (SAN) injury
  in lateral skull base surgery, 2512
  due to neck surgery, 1730, 1731f
Spinal accessory nerve (SAN) transposition, for facial nerve paralysis, 2426
Spinal cord input, to vestibular nuclei, 1864
Spinal nerve, posterior ramus of, 2579f
Spindle cell carcinoma (SPCC), of larynx, 1506
Spindle cell hemangioendothelioma, 1668-1669
Spindle cell hemangioma, 1668-1669
Spindle-shaped gap, laryngeal videostroboscopy of, 819, 820f
Spine of Henle, anatomy of, 1822f, 2009-2010
Spinocerebellar atrophy, 2357
SPIR (spectral presaturation inversion recovery), MRI with, 135-136
Spiral CT, of laryngeal carcinoma, 1470
Spiral ganglion, anatomy of, 1832f, 1834, 1854f, 2278f

Spiral ganglion cells, in auditory physiology, 1844, 1845f
Spiral ganglion neurons (SGNs), salvage of, 2189-2191
Spiral lamina, 1831, 1832f, 1834
Spiral ligament
  anatomy of, 1832f
  in auditory physiology, 1841f
  in cochlear transduction, 2061f
Spiral limbus
  anatomy of, 1832
  in auditory physiology, 1841f
Spiral modiolar artery, 1854, 1856f
Spirochaeta denticulata, Vincent's angina due to, 2786
Spitz nevus, 287
SPL (sound pressure level), 1839, 2140
  in acoustic analysis for voice evaluation, 829, 829t
Spleen, in immune system, 605
Splenius muscle, 2579f
Splice sites, 4, 5f
Split bridge, for cochlear implant, 2238-2239, 2238f
Split-thickness skin graft (STSG), in atresiaplasty
  creation of, 2756, 2757f
  placement of, 2756, 2757f-2758f
  suturing of, 2756-2757, 2758f
Spnb4 (β-spectrin 4) gene, in murine deafness, 2058t-2060t, 2081
Spontaneous emission, of radiation, 26, 26f
Spontaneous ventilation anesthesia
  in children, 2599-2600
  with recurrent respiratory papillomatosis, 2891
Spot size, of surgical laser, 27-28, 28f-29f
Spreader grafts
  in revision rhinoplasty for middle vault deformities, 585-586
  for saddle nose deformity, 555, 559f
  for septal and alar asymmetries, 550, 551f
  in septoplasty, 490-491, 491f
  for twisted nose, 554, 555f
SPTs (second primary tumors)
  of larynx, 1492, 1510
  in oral cancer, 1301-1302
Spurring, nasal septal deviation with, 482, 482f, 489, 494, 669f
SQA (Surgical Quality Alliance), 84t-87t, 88
Squamocolumnar junction (SCJ), of esophagus
  with Barrett's esophagus, 957f, 972
  with hiatal hernia, 957f
  normal anatomy of, 956-957, 956f-957f
  in transnasal esophagoscopy, 982-983, 983f
Squamosa, in surgical anatomy of lateral skull base, 2434, 2435f-2436f
Squamous cell carcinoma (SCC), 285-286
  basaloid
    of hypopharynx and cervical esophagus, 1425
    of larynx, 1506
  cervical lymph node metastasis of (*See* Cervical lymph node metastasis(es))
  clinical presentation of, 285f, 286
  cutaneous, immunosuppression and, 213t, 215
  defined, 1361
  epidemiology of, 285
  epistaxis due to, 686f
  esophageal, 973
    due to caustic injury, 978
    cervical, 1425
      imaging of, 1414f, 1424f
    imaging of, 1412-1415
    localized, 1444-1447
      definitive chemoradiation for, 1445-1447, 1446t-1447t
      postoperative therapy for, 1444-1447
      preoperative therapy for, 1444-1445, 1445t
    metastatic, 1447
Squamous cell carcinoma (SCC) *(Continued)*
  of external auditory canal and temporal bone
    computed tomography of, 2502f
    imaging of, 1918, 1919f
    symptoms and signs of, 2502
  extraesophageal reflux and, 902-903
  head and neck (*See* Head and neck squamous cell carcinoma (HNSCC))
  of hypopharynx, 1425
    chemoradiation for, 1442-1444
    chemotherapy for, 1442
      induction, 1443
      after total laryngectomy, 1442-1443
    conventional treatment modalities for, 1441-1442
      for advanced disease, 1442
      for early disease, 1442
    epidemiology of, 1441
    imaging of, 1414f, 1424f
    new treatment modalities for, 1442
    radiation therapy for, 1443
      intensity-modulated, 1046
  laryngeal, 1491
    acantholytic, 1506
    adenoid, 1506
    basaloid, 1506
    cervical nodal metastases of, 1493-1494, 1493f
      embryology and, 1482-1483
      glottic, 1497-1498
      imaging of, 1476, 1479f
      subglottic, 1501, 1501f
      supraglottic, 1500-1501
    chemoprevention of, 1491
    clinical presentation of, 1493-1494
    diagnosis and evaluation of, 1494-1495
      differential diagnosis in, 1495
      history and physical examination in, 1494
      imaging in, 1494-1495
      operative endoscopic examination in, 1495
    distant metastases of, 1494
    epidemiology of, 1491-1492, 1512, 1513f
    etiology of, 1512-1513
    follow-up for, 1505
    grading of, 1492-1493
    human papillomavirus and, 1492, 2887-2888
    imaging of, 161, 164f
    in situ, 1493
    microinvasive, 1493
    molecular biology of, 1492
    papillary, 1506
    pathology of, 1492-1493
    prognosis and prognostic predictors for, 1504-1505
      clinical features as, 1504
      disease factors as, 1504-1505
      histopathologic characteristics as, 1504-1505
      molecular markers as, 1493, 1505
      patient factors as, 1505
      radiologic characteristics as, 1504
    recurrence of, 1503-1504
      stomal, 1504, 1504f
    recurrent respiratory papillomatosis and, 2887-2888
    risk factor(s) for, 1491-1492, 1512-1513
      diet as, 1492
      exposure to toxins as, 1492, 1513
      genetic susceptibility as, 1492, 1513
      human papillomavirus as, 1492, 1513
      laryngeal reflux as, 1491-1492, 1513
      second primary tumors as, 1492
      tobacco and alcohol as, 1491, 1512-1513
    staging of, 1486, 1488t-1489t
      radiology in, 1495
    transition zones of, 1489, 1490f
    treatment of, 1495
      background of, 1512-1515, 1513f-1514f
      CO_2 laser for, 33
Squamous cell carcinoma (SCC) *(Continued)*
      goals of, 1495
      intensity-modulated radiotherapy for, 1046
      nonsurgical organ preservation, 1501-1503, 1502f
      options for, 1495, 1496t
      prognostic factors in, 1495, 1496t
      for recurrence, 1503-1504, 1504f
      for subglottic tumors, 1501-1503, 1501f
      for supraglottic tumors, 1498-1501, 1498f
      therapeutic decision making for, 1495
    variants of, 1505-1506
      acantholytic, 1506
      adenosquamous, 1506
      basaloid, 1506
      papillary, 1506
      spindle cell, 1506
      verrucous, 1505-1506, 1505f
  of masticator space, 152, 154f
  of neck
    arising in branchial cleft cyst, 1671
    arising in thyroglossal duct cyst, 1671
    with unknown primary, 1641-1642, 1641t, 1664, 1665f
  noncutaneous, immunosuppression and, 213t, 215
  of oral cavity, 154, 156f, 1299
    of alveolar ridge–retromolar trigone, 1307f
    basaloid, 1299
    of buccal mucosa, 1308f
    epidemiology of, 1295
    etiology of, 1293-1295, 1294f
    of floor of mouth, 1294f, 1315f
    of hard palate, 1310, 1310f
    lichen planus and, 1229
    of lip, 1302-1304
      clinical findings in, 1294f, 1302, 1302f
      epidemiology of, 1302
      neck metastases of, 1303-1304
      prognostic features of, 1303
      reconstruction for, 1303-1304, 1303f
      resection of, 1303, 1303f
      survival with, 1304
    sarcomatoid, 1299
    of tongue, 1306f
    verrucous, 1299
  oropharyngeal, 1361-1362, 1365
    clinical presentation of, 1361, 1362f, 1365
    etiology of, 1365
    grading of, 1361-1362, 1363t
    imaging of, 149f, 1413f
    pathology of, 1361
    of tonsil, 1362f, 1369f
    transnasal esophagoscopy in, 983
    of uvula, 1368f
  pharyngeal, imaging of, 1412-1415
  of pharyngeal mucosal space, 148, 149f
  pigmented, 285f, 286
  of pyriform sinus, 162f, 1424f
  recurrence or metastasis of, 285-286
  risk factors for, 285
  of salivary glands, 1190
  of sublingual space, 156
  of thyroid gland, 1764
  of trachea, 1613-1614, 1614f
Squamous cell carcinoma of the head and neck (SCCHN). *See* Head and neck squamous cell carcinoma (HNSCC).
Squamous cell dysplasia, of larynx, 1486
Squamous metaplasia theory, of cholesteatoma formation, 1967f, 1968
Squamous odontogenic tumor, 1278
Squamous papilloma(s)
  of larynx, 1468, 1468f
  of nasopharynx, 1349
  of oral cavity, 1290, 1290f
  of trachea, 1612

Squamous part, of temporal bone, 1821, 1822f
Square-wave jerks, 2313
Squelch, in binaural processing, 1846, 2248
SRBC (small round blue cell) tumors, 2836
SRMDs (sleep-related movement disorders), 265, 265b
SRT. *See* Stereotactic radiation therapy (SRT).
SRT (speech reception threshold), 1888-1889
  masking for, 1889
SS (Sjögren's syndrome). *See* Sjögren's syndrome (SS).
SS (Stickler syndrome)
  craniofacial anomalies in, 2646
  deafness in, 2051t-2058t, 2094t, 2095
SS (synovial sarcoma), 1670
SSCD syndrome. *See* Superior semicircular canal dehiscence (SSCD) syndrome.
SSCP (single strand conformation polymorphism), 9
SSKI (saturated solution of potassium iodide)
  for Graves' disease, 1742-1743
  for hyperthyroidism, 1739t
SSLTR (single-stage laryngotracheal reconstruction), for laryngeal stenosis, 2920-2921
SSRIs (selective serotonin reuptake inhibitors)
  for migraine, 2350
  for tinnitus, 2137
SSTE (skin–soft tissue envelope), revision rhinoplasty of, 581, 594
Stabbing, neck trauma due to, 1627
Staging, FDG-PET for, 144
Staging systems, 53
Stakeholders, in performance measurement, 79-89, 84t-87t
Standard deviation (SD), 63, 64t
  vs. standard error, 73, 73t
Standard error (SE), *vs.* standard deviation, 73, 73t
Standardization, 87-89
Stapedectomy
  in children, 2035
  for far-advanced otosclerosis, 2035
  for Meniere's disease, 2035
  in ossiculoplasty, 2007, 2024-2025
  revision, 2035
  vs. stapedotomy, 2030
Stapedial fixation
  acoustic reflex testing for, 2030, 2030f
  due to otosclerosis, 2028-2029, 2029f
Stapedial reflex measures, 1890-1891
Stapedius reflex, assessment of, 2383
Stapedius reflex pathways, in efferent auditory system, 1847, 1848f
Stapedotomy
  in ossiculoplasty, 2024-2025
  small fenestra (*See* Small fenestra stapedotomy)
Stapes
  absent superstructure of, ossiculoplasty for, 2024, 2025f
  anatomy of, 1853f
  in auditory physiology, 1839, 1840f
  in cochlear transduction, 2050-2060, 2062f
  embryology of, 2583-2584, 2583f
  in surgical anatomy of lateral skull base, 2436f
Stapes footplate
  in auditory physiology, 1839-1840, 1840f, 1842f, 2018-2019
  embryology of, 2583-2584
  floating, small fenestra stapedotomy with, 2033
  solid or obliterated, small fenestra stapedotomy with, 2033
Stapes footplate fixation, 2024-2025
Stapes gusher syndrome, X-linked, 2737
Stapes tendon, in surgical anatomy of lateral skull base, 2436f
Staphylococcus aureus
  furunculosis of external ear due to, 1949
  laryngitis due to, 885
  otitis externa due to, 2194-2195
    malignant, 1947
  rhinosinusitis due to
    acute, 704, 704f, 732
    chronic, 706, 732
  salivary gland infections due to, 1252
Staphylococcus spp, otitis externa due to, 1945
Stare, in Graves' ophthalmopathy, 1808
Starling equation, 1066
STAT1 activation, in oral cancer, 1301
State medical boards, 80-81
State migration, 53
Statherin, in saliva, 1140
Static compensation, for peripheral vestibular lesions, 2373-2374
Static facial sling, for facial nerve paralysis, 2430
Statistical significance, 66-67
  based on subgroup comparisons, 73t, 74
Statistical tests, 65-66, 66t
  for independent samples, 66, 67t
  for related samples, 66, 67t
  used by otolaryngologists, 70-72
    analysis of variance (ANOVA) as, 71
    contingency tables as, 71-72
    multivariate (regression) procedures as, 72
    nonparametric, 72
    survival analysis as, 72
    t-test as, 70-71
Statoacoustic receptor cell potentials, in hair cell transduction, 2071, 2072f
Steatocystoma multiplex, 289
Steiner analysis, for mentoplasty, 463, 463f
Stellate lacerations, 307
Stellate neurons, in cochlear nucleus, 1835
Stem cell(s), in adaptive immune system, 599-600, 600f
Stem cell factor (SCF), 609t-610t
Stenbeck, Thor, 1031
Stenger test, pure-tone, 1901
Stenosis.
  laryngeal. *See* Laryngeal stenosis.
  subglottic. *See* Subglottic stenosis.
  supraglottic, 947-948
  upper airway. *See* Upper airway stenosis.
Stensen's duct
  anatomy of, 2850-2852
  sialography of, 1150
  trauma to, in children, 2863
Stents
  for caustic ingestion, 2960
  endolaryngeal
    for airway stenosis, 947, 947f
    for chronic aspiration, 928, 930f
    for laryngeal trauma, 937, 939f-940f
  for laryngeal stenosis, 2920
  for tracheal stenosis, 2928-2930, 2930f
Stenvers projection, of temporal bone, 131
Stepping test, 2316-2317
Stereocilia
  in auditory system
    anatomy of, 1832-1833, 1833f, 1840, 1841f
    arrangement of, 2071, 2072f
    in auditory physiology, 1841f, 1842, 1843f
    in cochlear transduction, 2061f, 2065-2067, 2069f
    composition of, 2074, 2075f-2076f
    cross-linkages between, 2076f, 2077-2078
    in hair cell transduction, 2070-2071
      anatomy of, 2070-2071, 2070f, 2072f
      composition of, 2074, 2075f-2076f
      cross-linkages between, 2076f, 2077-2078
      dynamic regulation of length of, 2076-2077
    lengths of, 2070f, 2071
      dynamic regulation of, 2076-2077
Stereocilia *(Continued)*
    number of, 2071
    in waltzer mice, 2074
  in vestibular system
    anatomy of, 1857, 1858f
    arrangement of, 1854-1855, 1856f
    morphologic polarization of, 1855, 1856f, 2279f
    sensory transduction by, 2277-2278, 2279f
Stereociliary bundles, in vestibular system, morphologic polarizations of, 2278, 2280f
Stereocilin (STRC), and interstereociliary linkages, 2077
Stereocilin *(STRC)* gene, in deafness, 2051t-2058t
Stereolithographic modeling, in mandibular reconstruction, 1326-1327, 1327f
Stereotactic computer-assisted surgery, of anterior and middle cranial base, 2448-2449, 2449f
Stereotactic radiation therapy (SRT)
  for benign skull base tumors, 2557-2566
    dose selection for, 2558
    gamma knife–based, 2559t
    imaging for, 2558
    jugular foramen schwannomas as, 2565
    LINAC-based, 2560t
    paraganglioma as, 2565, 2565t
    principles of, 2557-2558, 2558f
    radiobiology of, 2558
    vestibular schwannomas as, 2558, 2560f
      cystic, 2563
      facial nerve outcomes with, 2563
      fractionation *vs.* nonfractionation of, 2558-2559, 2561t
      hearing outcomes with, 2562-2563, 2562t
      hydrocephalus due to, 2563
      neurofibromatosis 2–related, 2563
      outcome assessment with, 2559-2563
      quality of life with, 2564-2565
      treatment of failures of, 2564
      trigeminal nerve outcomes with, 2563
      tumor control with, 2562
  CyberKnife
    for laryngeal and hypopharyngeal cancer, 1592
    for malignant skull base tumors, 1696
  defined, 1696, 2557
  dose selection for, 2558
  Gamma Knife, 2557, 2558f, 2559t
  history of, 1696
  imaging for, 2558
  linear accelerator (LINAC)-based, 2557-2558, 2560t
  for malignant skull base tumors, 1696, 1700
  principles of, 2557-2558, 2558f
  radiobiology of, 2558
Sternocleidomastoid muscle
  anatomy of, 1359f, 1821-1822, 2578f
    radiographic, 1471f
  in modified radical neck dissection, 1712, 1713f
Sternocleidomastoid myocutaneous flap, for reconstruction of tonsils and pharyngeal wall, 1385-1386
Sternocleidomastoid tumors, of infancy, 2817, 2817f
Sternohyoid muscle, 2578f
Sternomastoid muscle, 2579f
Sternothyroid muscle
  characteristics of, 918-919
  surgical anatomy of, 1543f
Steroids. *See* Corticosteroids.
Stertor, defined, 2896-2897
Stevens-Johnson syndrome (SJS), 1239
Stickler syndrome (SS)
  craniofacial anomalies in, 2646
  deafness in, 2051t-2058t, 2094t, 2095
Stimulated emission, of radiation, 26, 26f
Stimulating electrodes, for intraoperative cranial nerve monitoring, 2544, 2544f
Stimulus-frequency otoacoustic emissions, 1891

STIR (short T1 inversion recovery), MRI with, 135-136, 136f
Stoma, for voice prosthesis, 1597, 1597f
  creation of optimally contoured, 1599-1600, 1600f
  postoperative care for, 1600, 1602f
  prevention of excessively deep, 1599-1600, 1600f
Stomal recurrences, of laryngeal carcinoma, 1504, 1504f
Stomal stenosis, after total laryngectomy, 1571
Stomatitis
  aphthous, 1289, 1289f
    in HIV, 227, 227f
    recurrent, 1236-1239
      clinical features of, 1237-1238
      defined, 1236-1237
      differential diagnosis of, 1238, 1238t
      etiology and pathogenesis of, 1237, 1237t
      herpetiform-type, 1238, 1238f
      histopathologic features of, 1239
      major, 1237-1238, 1238f
      minor, 1237, 1238f
      treatment of, 1239
  uremic, 1255
Stomodeum, 2661f, 2691f
Stop codons, 4
Storage diseases, otologic manifestations of, 2112-2114
  in gout, 2113-2114
  in mucopolysaccharidoses, 2112-2113, 2113f
  in ochronosis, 2114
"Stork bite," 290-291
Strain, in voice evaluation, 827t
Strangulation injuries, 934-935
Stratum intermedium, in tooth development, 1259
Strawberry angioma, 290
STRC (stereocilin), and interstereociliary linkages, 2077
STRC (stereocilin) gene, in deafness, 2051t-2058t
Streptococcal tonsillitis-pharyngitis, 193
  in children, 2787
  complications of, 2788
Streptococcus mutans, dental caries due to, 1252
Streptococcus pneumonia, otitis media due to, 2763
Streptococcus pneumoniae
  with CSF fistula, 2045
  rhinosinusitis due to
    acute, 704-705, 704f, 732
    chronic, 706, 732
      acute exacerbation of, 707
Streptococcus pneumoniae vaccine
  to prevent hearing loss, 2161
  to prevent otitis media, 2763, 2768
    maternal immunization with, 2768-2769
Streptococcus pyogenes
  group A beta hemolytic, pharyngitis due to, 191-193
    in children, 2787
    complications of, 2788
  otitis media due to, 2763
Streptococcus viridans, salivary gland infections due to, 1252
Streptokinase, for free flap salvage, 1098
Stress relaxation, in skin flaps, 1071
Stress-strain curve, for skin flaps, 1071
Stria of Held, in auditory pathway, 1846
Stria of Monaco, in auditory pathway, 1846
Stria vascularis
  anatomy of, 1831-1832, 1832f
  in auditory physiology, 1840, 1841f
  in cochlear transduction, 2061f
Strial presbycusis, 232, 2126
Striated duct, of salivary gland, 1134, 1134f, 1162, 1163f
Strictures, esophageal. *See* Esophageal strictures.
Stridor
  biphasic, 2900
  in child (*See* Stridulous child)
  defined, 2896-2897
  expiratory, 2900
  inspiratory, 2900
  postextubation, 2904, 2904t
Stridulous child, 2896-2911
  with acute airway obstruction, 2903-2905
    emergency tracheotomy for, 2904
    endoscopic removal of foreign bodies for, 2904
    medical management for, 2903-2904
    therapeutic intubation for, 2904
  due to airway hemangiomas, 2899, 2899f-2900f
  due to anterior glottic web, 2899, 2900f
  assessment of, 2897-2901
    examination in, 2899-2900, 2899t
    flexible endoscopy in, 2901-2902
    history in, 2897t, 2898-2899
    imaging in, 2901, 2901f
    laryngotracheobronchoscopy in, 2902
      anesthetic considerations for, 2902
      bronchoscopy technique for, 2903, 2903f
      complications of, 2903
      dynamic airway assessment during, 2903
      equipment for, 2902-2903, 2902f
      microlaryngoscopy technique for, 2902-2903
      postoperative car after, 2903
      preparation and positioning for, 2902
    other investigations in, 2901
    oxygen saturation monitoring in, 2900
  with chronic airway obstruction, 2905-2910
    endoscopic treatment of, 2908-2909
      balloons in, 2906, 2906f, 2909
      endoscopic sutures in, 2909
      laser in, 2908-2909, 2908f
      microdébrider in, 2909
      microinstrumentation for, 2908, 2908f
      stents, keels, and grafts in, 2909
      for topical drug administration, 2909
    medical management for, 2905-2906
    open laryngeal surgery for, 2909-2910, 2910f
    tracheotomy for, 2906
      complications of, 2907
      indications for, 2906, 2906t
      patient positioning for, 2906, 2907f
      preoperative planning for, 2906
      surgical decannulation of, 2907-2908
      surgical procedure for, 2906-2908, 2907f
      techniques to avoid, 2906, 2906f
      ward decannulation of, 2907
  definition of, 2896-2897
  differential diagnosis of, 2897t
  future developments for, 2910
  due to laryngeal papillomatosis, 2898, 2899f
  due to laryngomalacia, 2866
  physical principles of airway narrowing in, 2897, 2898f
  postextubation, 2904, 2904t
  postpartum
    expected airway obstruction in, 2904-2905
    unexpected airway obstruction in, 2905
      laryngeal, 2905
      supralaryngeal, 2905, 2905f
      tracheobronchial, 2905
  due to subglottic stenosis, 2900f
  due to vallecular cyst, 2898, 2898f
  due to vocal fold paralysis, 2868
Striola, in vestibular system, 1855, 1858f, 2278, 2280f
Stroboscope, defined, 818
Stroboscopy, laryngeal, 818-821
  of adynamic segments, 820
  of amplitude of vibration, 820, 821f, 848, 848t
  of closure pattern, 819, 820f, 848t, 849
  common problems and solutions for, 815t-816t
  defined, 813
Stroboscopy, laryngeal *(Continued)*
  of early glottic carcinoma, 1515-1516
  flexible endoscope for, 814
    advantages of, 814
    disadvantages of, 814
    protocol for, 818b
    technique of, 814
    troubleshooting for, 814
  interpretation of, 848t
  interval examination in, 847
  of mucosal wave, 820, 848-849, 848t
  in neurologic examination, 834
  of periodicity, 821, 848, 848t
  of phase closure, 819-820
  for professional voice, 847-849, 848f, 848t
  protocol for, 818-819, 818b
  of regularity, 821
  rigid endoscopes for, 813-814
    advantages of, 813
    disadvantages of, 813-814
    protocol for, 818b
    technique of, 814
    troubleshooting for, 814
  of symmetry, 820, 847-848, 848t
  of vertical closure level, 821
  for vocal fold impairment, 905
Stroke
  due to lateral skull base surgery, 2512
  oral manifestations of, 1250
Stromal cell–derived factor (SDF-1), in head and neck squamous cell carcinoma, 1060
STSG (split-thickness skin graft), in atresiaplasty
  creation of, 2756, 2757f
  placement of, 2756, 2757f-2758f
  suturing of, 2756-2757, 2758f
Student's *t*-test, 70-71
Study design, 54-55, 54t
  case series as, 54-55, 54t
  case-control, 54, 54t
  and data interpretation, 59-61, 60t-61t
  and data quality, 59, 60t
  expert opinion as, 52, 54-55, 54t
  grading of evidence-based medicine recommendations as, 55, 55t
  observational (cohort), 54, 54t
  other types of, 55
  randomized trial as, 52, 54, 54t
Study sample, 68t
Stunning, with radioactive iodine, 1771
Sturge-Weber syndrome, 291
  oral manifestations of, 1257
Stuttering, 841-842
Styloglossus muscle, 1296f, 1297, 1359f
Stylohyoid ligament
  embryology of, 2583-2584
  ossification of, 1480, 1481f
Stylohyoid muscle, 1296f, 1359f
Styloid foramen, 2404f
Styloid ligament, 2583f
Styloid process
  anatomy of, 320f, 1296f, 1822-1823, 1822f, 1824f, 1826f, 2010f
    radiographic, 1398f
  elongated, *vs.* myofascial pain dysfunction syndrome, 1284t
  embryology of, 2583-2584, 2583f
  in surgical anatomy of lateral skull base, 2435, 2435f
  in surgical anatomy of middle cranial base, 2445f
Stylomastoid artery, 1826f
Stylomastoid foramen
  anatomy of, 1822-1823, 1824f
  annular ligament of, 1826f
  in surgical anatomy of lateral skull base, 2435
  in surgical anatomy of middle cranial base, 2445f
Stylopharyngeus muscle, 1296f, 1359f

Subacute bacterial endocarditis (SBE) prophylaxis, for pediatric surgery, 2596, 2596t-2597t
Subarcuate artery, in surgical anatomy of lateral skull base, 2439f
Subarcuate fossa
  anatomy of, 1823f, 2010f
  in surgical anatomy of lateral skull base, 2435f, 2438
Subciliary approach
  for lower eyelid blepharoplasty, 449, 450f-451f
  for pediatric facial fracture, 2705f
Subclavian artery, root of neck and, 2581-2582, 2581f
Subclavian steal syndrome, 2351
Subclavian triangle, of neck, 2578f
Subcondylar fractures, 322-323, 1280, 1281t
  pediatric, 2704, 2706f-2708f
  physical examination of, 325
  repair of, 338-339
Subcranial approach, for anterior cranial base surgery, 2454, 2454f
Subcutaneous emphysema
  of infrahyoid retropharyngeal space, 161f
  of neck, 1410, 1410f
Subcutaneous fibroma, due to neck irradiation, 1695
Subcutaneous immunotherapy (SCIT), for allergic rhinitis, 621
Subcutaneous layer, 1065
Subcutaneous tissue, thinning of, in nasal tip refinement, 577, 577f
Subcutaneous tunnels, in liposuction, 456, 456f
Subdural abscess, otitis media and, 2777
Subdural empyema, 1994-1995
  epidemiology of, 1980t-1981t, 1994-1995
  imaging of, 1995
  in neonates, 1995
  otitis media and, 2777
  symptoms of, 1995
  treatment of, 1995
Subglottal resections, for tracheal tumors, 1619, 1620f
Subglottic air pressure (P_s)
  in professional voice production, 846
  in voice evaluation, 828, 828t, 849
Subglottic airway, radiographic anatomy of, 1463f
Subglottic cancer
  anatomic basis for, 1483-1484, 1483f, 1483t
  cervical metastases of, 1494
  clinical presentation of, 1493, 1579
  imaging of, 1474, 1475f
  staging of, 1488t, 1580f
  treatment of, 1501-1503, 1501f
    radiation therapy for, 1589-1590
Subglottic cyst, 2871, 2871f
Subglottic hemangioma, 1468, 1468f, 2871, 2871f
  dysphagia due to, 2953
  stridor due to, 2899, 2900f
Subglottic stenosis (SGS), 945f, 950-951. *See also* Laryngeal stenosis.
  anterior, in children, 2923
  balloon dilatation for, 2906, 2906f
  congenital, 2870-2871, 2913-2914
  dysphagia due to, 2953
  gastroesophageal reflux and, 2945
  due to internal laryngeal trauma, 2914-2915
  stridor due to, 2899, 2900f
Subglottis, 99, 99f
  anatomy of, 1483-1484, 1483f, 1483t, 1578
    surgical, 1544f
  embryology of, 1482
  physical examination of, 100
Subharmonic frequencies, 847
Subjective visual horizontal (SVH), perceptual test of, 2300
Subjective visual vertical (SVV), perceptual test of, 2300, 2323
Sublingual artery, 1296f
Sublingual gland(s)
  anatomy of, 1133-1134
    in children, 2850-2853
    radiographic, 1144-1145
  contributions to saliva of, 1134t
  malignant neoplasms of
    excision of, 1196
    physical examination of, 1179
Sublingual immunotherapy (SLIT), for allergic rhinitis, 621-622
Sublingual lymph nodes, 2582
Sublingual space (SLS)
  anatomy of, 202
  imaging of, 156
    with abscess and cellulitis, 156, 157f
    with congenital lesions, 156
    normal anatomy in, 146f, 154, 156
    with ranula, 156, 157f
    with squamous cell carcinoma, 156
  odontogenic infections of, 183, 183f
Submandibular fossa, 1296f
Submandibular gland(s)
  anatomy of, 1133-1134, 1296f
    in children, 2850-2853
    radiographic, 1144, 1399f
  contributions to saliva of, 1134t
  CT of, 139
  neuronal control of, 1136
  physical examination of, 96f
  pleomorphic adenoma of, 1653f
  salivary flow rate and composition of saliva in, 1138t
  sialolithiasis of, 1155
    imaging of, 1144f, 1154, 1157f
    surgical management of, 1156, 1156f
  sialolithiasis promoting factors in, 1140
  trauma to, 312
Submandibular gland neoplasm(s)
  benign
    clinical features of, 1165
    excision of, 1174, 1174f
  malignant
    excision of, 1196
    physical examination of, 1179
Submandibular gland resection, robotic surgery for, 40-41, 42f-43f
Submandibular lymph nodes
  anatomy of, 1297f-1298f, 1360f, 2582
  in neck dissection, 1704-1705, 1704f-1705f, 1706t-1708t
Submandibular region, musculature of, 1296f
Submandibular space (SMS)
  anatomy of, 202
  imaging of, 146f, 156-157, 158f
  odontogenic infections of, 183-184, 183f-184f
Submandibular triangle, of neck, 96, 96f, 2578f
Submental lipectomy, 456
Submental lymph nodes
  anatomy of, 1297f-1298f, 1360f
  in neck dissection, 1704, 1704f-1705f, 1706t-1708t
Submental space involvement, in odontogenic infections, 181-183, 183f
Submental triangle, 2578f
Submentoplasty, 411-413
  aesthetic considerations for, 411, 412f
  procedure for, 411-413, 413f
  results of, 414f-415f
Submentovertex (SMV) view, of facial bones and sinuses, 130
Submucous cleft palate (SMCP), 2659, 2661f, 2674
  bifid uvula with, 2793, 2793f
Submucous fibrosis, oral, 1229, 1298
  clinical features of, 1229
  defined, 1229
  etiology and pathogenesis of, 1229
Submucous fibrosis, oral *(Continued)*
  histologic/diagnostic features of, 1229
  treatment of, 1229
Submuscular recess lymph nodes, in neck dissection, 1707t-1708t
Suboccipital approach, for posterior fossa neoplasms, 2532t, 2533-2534
  advantages and disadvantages of, 2532t, 2534
  basic features of, 2533
  indications for, 2532t, 2533
  surgical exposure in, 2533f
  technique of, 2534, 2534f
Suboccipital lymph nodes
  anatomy of, 1718f
  dissection of, 1718-1719
Suborbicularis oculi fat (SOOF), 444, 447
  after facial paralysis, 2431
Subparotid node, 1298f
Subperichondrial cricoidectomy, for chronic aspiration, 927-928, 929f
Substance P (SP), in salivary gland secretion, 1137
Substitution, in vestibular compensation, 2375
Substitution exercises, in vestibular rehabilitation, 2372-2373, 2378
Sub-superficial musculoaponeurotic system dissection, for cheek defects, 357-358, 360f
Subtemporal craniectomy, for middle cranial base surgery, 2465f, 2467, 2467f
Subtemporal-preauricular infratemporal approach, for middle cranial base surgery, 2462, 2466f
Subtilisin, and interstereociliary linkages, 2077
Subtotal laryngectomy, for glottic cancer, 1517t
Subtotal thyroidectomy, for Graves' disease, 1743
Succinate-dehydrogenase (SDH), in familial paraganglioma syndromes, 1659, 1659t
Succinylcholine
  in children
    for anesthesia maintenance, 2592
    for rapid-sequence anesthesia induction, 2590
  intraoperative, 111-112
Sucralfate
  for caustic ingestion, 2959-2960
  for extraesophageal reflux, 901
  for GERD, 970
Suction lipectomy, 452, 456
Sudden infant death syndrome (SIDS), 2570
Sufentanil, as adjunct to induction of anesthesia, 111
Suicide genes, 16, 21
Sulcus vocalis, 2882
Sulindac, for head and neck squamous cell carcinoma, 1018
Sullivan, Colin, 251
Sumatriptan (Imitrex), for migraine, 2349
Summating potential (SP), in electrocochleography, 1892-1894, 1907
  in Meniere's disease, 2337
Summating potential/action potential (SP/AP) ratio, 1892-1894
  in Meniere's disease, 2337
Summation, in auditory processing, 1846, 2248
Sun-reactive skin types, 275, 276b, 391, 391t
Superantigens, in chronic rhinosinusitis, 706, 732
Superficial cervical fascia, 202, 2577
Superficial cervical lymph nodes, 2582
Superficial cervical plexus block, 242
Superficial musculoaponeurotic system (SMAS), 405, 406f
  in deep-plane rhytidectomy, 406, 407f
  and temporoparietal fascia, 440-441, 441f
Superficial musculoaponeurotic system (SMAS) flap, 405-406, 409
Superficial petrosal artery, 1826f, 1828f
Superficial petrosal nerve, 1826f
Superficial spreading carcinoma, 285f
Superficial spreading melanoma, 285f, 1108
Superficial temporal artery, 2580f

Superficial vocal fold lesions, in vocal professional, 855-856, 856f
Superficial x-rays, energy for, 1034
Superior alveolar arteries, 1295-1296
Superior ampullary nerve, 1854f, 2278f
Superior canal benign paroxysmal positional vertigo
  positional testing for, 2331
  repositioning maneuver for, 2332
Superior canal dehiscence syndrome (SCDS). *See* Superior semicircular canal dehiscence (SSCD) syndrome.
Superior canaliculus, of lacrimal apparatus, 798f
Superior cerebellar artery, 2351f
  in surgical anatomy of anterior skull base, 2481f
Superior cervical sympathetic ganglion, in root of neck, 2582
Superior constrictor muscle
  anatomy of, 1359f
  in velopharyngeal function, 2676, 2677t
Superior Constrictor Rotation-Advancement Flap (SCARF), for reconstruction of soft palate, 1382, 1382f
Superior crus, of ear, 476f, 2742f
Superior deep jugular lymph nodes, 1360f
Superior incudal fold, 1827f
Superior laryngeal nerve, in surgical anatomy of lateral skull base, 2440f
Superior laryngeal nerve (SLN)
  anatomy of, 807, 1422
  injury during thyroid surgery of, 1770
  in taste, 1211
  and thyroid gland, 1751-1752
Superior malleolar fold, 1827f
Superior malleolar ligament, 1827f
Superior medial pyriform involvement, supraglottic laryngectomy for laryngeal cancer with, 1554-1555
Superior mediastinal adenopathy, total laryngopharyngectomy with, 1574, 1574f
Superior mediastinal lymph nodes, in neck dissection, 1704, 1704f, 1706t-1708t
Superior nasal meatus
  normal anatomy of, 664-665
  in surgical anatomy of anterior cranial base, 2472, 2472f
Superior oblique muscles
  semicircular canal planes and, 2287, 2288f
  in surgical anatomy of lateral skull base, 2439f
Superior olivary complex (SOC), in central auditory pathway, 1835, 1835f, 1846
Superior ophthalmic vein thrombosis, due to rhinosinusitis, 676
Superior orbital fissure, anatomy of, 322f, 440, 1823f
  surgical
    in anterior cranial base, 2443-2444, 2444f
    in lateral skull base, 2435f, 2438
    in middle cranial base, 2444, 2445f
Superior orbital fissure syndrome, 320-321
Superior petrosal sinus, in surgical anatomy of lateral skull base, 2436f, 2438, 2489
Superior petrosal sinus impression
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Superior petrosal sulcus, 1823f
Superior petrosal vein, in surgical anatomy of lateral skull base, 2439f
Superior pharyngeal constrictor muscle, 1360f
Superior punctum, of lacrimal apparatus, 798f
Superior rectus muscle(s), 443f
  semicircular canal planes and, 2287, 2288f
  in surgical anatomy of anterior cranial base, 2472f
Superior saccular nerve, 1854f, 2278f
Superior semicircular canal
  anatomy of, 1827, 1854f, 2278f
  in surgical anatomy of lateral skull base, 2436f-2437f, 2439f
Superior semicircular canal dehiscence (SSCD) syndrome, 1842, 1843f, 2339-2341
  anatomic and physiologic basis for, 2290, 2290f
  auditory manifestations of, 2341
  clinical features of, 2339
  eye movements evoked by pressure changes in, 2316f
  hearing loss due to, 2020-2021, 2021f
  imaging of, 1920-1921, 1922f
    high-resolution CT for, 2340-2341, 2340f, 2362f
  ocular responses to sound in, 2339-2340, 2340f
  pathophysiology of, 2339-2340, 2339f-2340f
  severity of, 2340
  treatment of, 2341
    surgical, 2361
  vestibular evoked myogenic potentials in, 2341
Superior semicircular duct, 1851f
Superior tarsal muscle, 443f, 444
Superior tarsal plate, 321f
Superior thyroid artery
  anatomy of, 1751-1752, 2579-2580, 2580f
  and parathyroid glands, 1778
Superior thyroid notch, radiographic anatomy of, 1472f
Superior turbinate, in surgical anatomy of anterior cranial base, 2472, 2472f
Superior tympanic artery, 1828f
Superior vestibular ganglion, 1854f, 2278f
Superior vestibular nerve, 2404f
  in surgical anatomy of lateral skull base, 2437f, 2438-2439
Superior vestibular nucleus (of Bechterew), 1860, 1862f
Supernumerary nostril, 2690-2692
Superoxide anion radical (O_2^-), in acutely raised skin flaps, 1070-1071, 1071f
Superoxide dismutase (SOD), and skin flap viability, 1074
Supervoltage x-rays, 1034
Supporting cells
  of olfactory epithelium, 626-627, 626f
  in vestibular system, 1854-1855, 1858f
Suppurative lymphadenopathy, in children, 2818, 2818f
Supra-alar collapse, revision rhinoplasty for, 586-587, 587f
Supra-alar pinching, revision rhinoplasty for, 585-586, 586f
Suprabullar cells, in endoscopic sinus surgery, 749, 750f
Suprabullar recess
  normal anatomy of, 667
  surgical anatomy of, 740
Supraclavicular lymph nodes, in neck dissection, 1705f
Supraclavicular nerve, 2578, 2580f
Supraclavicular triangle, of neck, 96, 96f
Supracricoid hemilaryngopharyngectomy (SCHLP), for hypopharyngeal cancer, 1429, 1436
Supracricoid laryngectomy
  with cricohyoidopexy, 1555-1557
    complications of, 1557
    functional outcome of, 1556-1557, 1557t
    key surgical points for, 1556
    oncologic results of, 1555
    surgical technique for, 1555-1556, 1556f
  historical background of, 1540
Supracricoid partial laryngectomy (SCPL)
  with anterior commissure involvement, 1497
  historical background of, 1540
  intermediate, 1531
  supraglottic, in advanced stage, 1500
Supracricoid partial laryngectomy with cricohyoidoepiglottopexy (SCPL-CHEP), 1549-1550
  complications of, 1551
  extended procedures for, 1551
  functional outcome of, 1551, 1551t-1552t
  key surgical points for, 1550-1551
  oncologic results of, 1549-1550
  surgical technique for, 1550, 1550f-1551f
  vs. total laryngectomy, 1564
Supracricoid partial laryngectomy with cricohyoidopexy (SCPL-CHP), 1564
Supraglottic activity, videoendoscopy of, 817, 817f
Supraglottic cancer
  advanced-stage
    chemoradiation for, 1500, 1589
    radiation therapy for, 1589
      outcomes and prognostic factors for, 1589, 1590t
      techniques and dose-fractionation schemes for, 1589
  anatomic basis for, 1483-1484, 1483f, 1483t, 1542-1543
  cervical metastases of, 1493-1494
  chemoradiation for, 1500, 1589
  clinical evaluation of, 1545
  clinical presentation of, 1493, 1579
  conservation laryngeal surgery for, 1551-1552, 1552t
    horizontal partial laryngectomies as, 1553-1554
    spectrum of, 1557-1560
    supracricoid laryngectomy with cricohyoidopexy as, 1555-1557
      complications of, 1557
      functional outcome of, 1556-1557, 1557t
      key surgical points for, 1556
      oncologic results of, 1555
      surgical technique for, 1555-1556, 1556f
    supraglottic laryngectomy as, 1553-1554
      with arytenoid, aryepiglottic fold, or superior medial pyriform involvement, 1554-1555
      with base of tongue extension, 1555
      complications of, 1555
      extended procedures for, 1554
      functional outcome of, 1555
      key surgical points for, 1554-1555, 1554f
      oncologic results of, 1553, 1553t
      surgical technique for, 1553-1554, 1554f
  early-stage, radiation therapy for, 1496, 1588-1589
    complications of, 1589
    outcomes and prognostic factors for, 1589, 1589t
    techniques and dose-fractionation schemes for, 1588-1589
  imaging of, 1475-1476
    of aryepiglottic folds, 1475, 1478f
    of epiglottis, 1475, 1477f
    of pyriform sinuses, 1475-1476, 1478f
  neck dissection for, 1500-1501
  radiation therapy for
    with advanced-stage disease, 1589
      outcomes and prognostic factors for, 1589, 1590t
      techniques and dose-fractionation schemes for, 1589
    with early-stage disease, 1496, 1588-1589
      complications of, 1589
      outcomes and prognostic factors for, 1589, 1589t
      techniques and dose-fractionation schemes for, 1588-1589
  staging of, 1488t, 1580f
  treatment of, 1498-1501
    in advanced stage, 1500
    in early stage, 1498-1500, 1498f

Supraglottic cancer *(Continued)*
with nodal metastases, 1500-1501
transoral laser microsurgery for, 1531
Supraglottic jet ventilation, for pediatric anesthesia, 2600
Supraglottic lacerations, 1634
Supraglottic laryngectomy, 1553-1554
with arytenoid, aryepiglottic fold, or superior medial pyriform involvement, 1554-1555
with base of tongue extension, 1555
complications of, 1555
extended procedures for, 1554
functional outcome of, 1555
historical background of, 1540
key surgical points for, 1554-1555, 1554f
oncologic results of, 1553, 1553t
surgical technique for, 1553-1554, 1554f
swallowing disorders due to, 1220
Supraglottic partial laryngectomy (SGL), for early-stage supraglottic cancer, 1498-1500, 1498f
Supraglottic stenosis, 947-948
Supraglottic subtotal laryngectomy, recurrence after, 1476
Supraglottis, 99, 99f
anatomy of, 1483-1484, 1483f, 1483t, 1578
surgical, 1542-1543, 1544f
embryology of, 1482
innervation of, 1544
Supraglottitis, 883, 1464
in children, 2806-2809
clinical features of, 2807
complications of, 2808-2809
diagnosis of, 2807-2808, 2807f-2808f
differential diagnosis of, 2806t
endoscopy of, 2808, 2808f
epidemiology of, 2806-2807
etiology of, 2807
histology of, 2807, 2807f
historical background of, 2806-2807
imaging of, 2807f, 2808
management of, 2808
clinical presentation of, 2807
defined, 1464
differential diagnosis of, 1464, 1465f, 2806t
imaging of, 159-161, 1406-1407, 1464
in children, 2807f, 2808
CT for, 1406
plain film, 163f, 1406, 1407f, 1464, 1464f
pseudo-, postlaryngectomy, 1416, 1417f
Supraglottoplasty, for laryngomalacia, 2867, 2868f
Suprahyoid musculature, palpation of, in voice evaluation, 827, 828f
Suprahyoid neck, imaging of, 146-157
carotid space in, 150-151, 151f-152f
CT for, 139, 141f
masticator space in, 151-152
with adenoid cystic carcinoma, 155f
with angiofibroma, 152, 154f
with hemangioma and lymphangioma, 152, 153f
with infection, 151-152, 152f
normal anatomy on, 146f, 151-152
with pseudotumors, 152
with squamous cell carcinoma, 152, 154f
MRI for, 142
normal anatomy in, 146-157, 146f-147f
oral cavity in, 153-156
with abscess, 156f
with congenital lesions, 154-156
with non-Hodgkin's lymphoma, 157f
normal anatomy on, 146f, 153-156
with squamous cell carcinoma, 154, 156f
parapharyngeal space in, 131, 146f
parotid space in, 149-150, 150f-151f
Suprahyoid neck, imaging of *(Continued)*
pharyngeal mucosal space in, 148-149
with inflammatory lesions, 148, 148f
with non-Hodgkin's lymphoma, 148-149, 149f
normal anatomy on, 146f, 148-149
with squamous cell carcinoma, 148, 149f
with Tornwaldt cyst, 148
prevertebral space in, 146f, 153
retropharyngeal space in, 146f, 152f, 153, 155f
sublingual space in, 156
with abscess and cellulitis, 156, 157f
with congenital lesions, 156
normal anatomy in, 146f, 154, 156
with ranula, 156, 157f
with squamous cell carcinoma, 156
submandibular space in, 146f, 156-157, 158f
Suprainfundibular cell, surgical anatomy of, 740
Supralabyrinthine approach, for facial nerve decompression, 2041-2042, 2043f
Supralaryngeal obstruction, in neonate, 2905, 2905f
Supramandibular lymph node, 1360f
Supramarginal gyrus, in central auditory pathway, 1837
Suprameatal spine, 2010f
in surgical anatomy of lateral skull base, 2435f
Supraomohyoid neck dissection (SOHND), 1703
for oral cancer, 1313-1314, 1713-1716
definition and rationale for, 1713, 1714f
technique for, 1713-1716, 1715f-1716f
Supraorbital artery, 439
Supraorbital bandeau, in fronto-orbital advancement
removal of, 2651-2652, 2652f
reshaping of, 2652, 2652f-2653f
splitting of, 2652, 2653f
Supraorbital cells, in frontal sinusitis, 776
Supraorbital ethmoid cells, surgical anatomy of, 741
Supraorbital foramina, in surgical anatomy of anterior cranial base, 2442, 2443f
Supraorbital nerve, 321f, 439-440, 441f
Supraorbital neurovascular pedicle, technique for preserving, 2451, 2451f
Supraorbital notch, 322f
in surgical anatomy of anterior cranial base, 2442, 2443f
Supraorbital rims, 319
Suprascapular artery
anatomy of, 2579
in root of neck, 2581-2582, 2581f
Suprascapular vein, 2579
Supratrochlear nerve, 321f, 440, 441f, 497, 497f
Supratubal recess
anatomy of, 1826f, 1827
in mastoidectomy, 2012-2013, 2013f
Sural nerve, for facial nerve grafting, 2422
Surface-enhanced laser desorption-ionization–time-of-flight (SELDI-TOF), in head and neck squamous cell carcinoma, 1029
Surfactant, in middle ear protection, 1871
Surfer's ear, imaging of, 1918, 1918f
Surgical decompression, for Bell's palsy, 2395
Surgical drainage and decompression, of odontogenic infections, 188-190
of deep neck space, 189-190
of jaw space, 189, 189f
vestibular, 188-189
Surgical history, 94
Surgical margins, with melanoma, 1113-1114, 1114t
Surgical myotomy, for achalasia, 964-965
Surgical Quality Alliance (SQA), 84t-87t, 88
Surrogate endpoints, biomarkers as, 1026
Surveillance, after surgical resection of oral cancer, 1317, 1317t
Survival analysis, 64, 72
Survival curve, 64
Survival rate, 64t
Susceptibility bias, *vs.* efficacy of treatment, 62t
Sushruta, 475
Sustained-release devices, for intratympanic delivery, 2182-2183, 2182f-2183f
Sustentacular cells, of olfactory epithelium, 626-627, 626f
Sutton's disease, in HIV, 227, 227f
Suturing
for facial trauma, 305-306, 306f
for nasal tip refinement, 522, 530f-531f, 550-551
for otoplasty, 477-478, 477f
complications of, 479
history of, 475-476, 476f
Mustarde technique for, 475-478, 476f-477f
for septoplasty, 491, 491f
Sv (sievert), 133
SVH (subjective visual horizontal), perceptual test of, 2300
SVV (subjective visual vertical), perceptual test of, 2300, 2323
Swallowing, 833, 1215-1221
functional endoscopic evaluation
for chronic aspiration, 926
for laryngeal stenosis, 2917
functions of, 2948
after hypopharyngeal and esophageal reconstruction, 1459-1460
inefficient, 1217
maturation of, 2948
physiology of, 954, 955f, 1207
stage(s) of, 1215, 1218f, 2948
esophageal, 1217, 2948
oral, 1206f, 1207, 1215, 1216f, 2948
oral preparatory, 1215, 1216f, 2948
pharyngeal, 1216, 2948
airway protection during, 1216-1217
cricopharyngeal (upper esophageal sphincter) opening during, 1217
delayed triggering of, 1215
neuromuscular activities in, 1216, 1216f
pharyngeal pressure generation during, 1217
programmed, 1216-1217
voluntary, 1215
after surgical resection of oral cancer, 1316
after total laryngectomy, 1572
Swallowing disorder(s). *See* Dysphagia.
Sweet taste
individual differences in, 1211-1212
peripheral sensitivity to, 1211
transduction of, 1209
Swimmer's ear, 97
Symblepharon, due to cicatricial pemphigoid, 1233-1234, 1234f
Symmetry, laryngeal videostroboscopy of, 820, 847-848, 848t
Sympathetic control, of salivary gland secretion, 1136
Sympathetic nerve injury, due to neck surgery, 1732, 1732f
Sympathetic trunk, in root of neck, 2582
Sympathomimetics, oral sequelae of, 1247t-1248t
Symphyseal region, anatomy and physiology of, 322-323
Symphysis
anatomy and physiology of, 322-323
menti, 320f
Symptoms, outcome scales for, 56t, 57-58
Symptoms of Nocturnal Obstruction and Respiratory Events (SNORE-25), 57
Synaptic bars, of hair cells, 1833-1834, 1833f, 1857, 1859f
Synaptic plasticity, 1884, 1884f
Synaptic ribbons, of hair cells, 1833-1834, 1833f, 1857, 1859f
Synaptic strengthening, Hebb's postulate for, 1884, 1884f
Synaptobrevin, 2080-2081

Synchondroses, in craniofacial growth and development, 2617-2619, 2619f-2620f
Synchronous lesion, in oral cancer, 1301-1302
Synergistic effect, of chemoradiation, 1041
Synkinesis, 904, 2384-2385
  with Bell's palsy, 2396
  management of, 2432
    botulinum A toxin for, 2432
    selective myectomy for, 2432
Synostosis
  coronal
    bilateral, 2644, 2645f
    fronto-orbital advancement for, 2652-2653, 2653f-2654f
    unilateral, 2643-2644, 2644f, 2648f
  craniofacial, 2639
  imaging of, 2648, 2648f
  lambdoid, 2643-2644
    fronto-orbital advancement for, 2653
  metopic, 2642-2643, 2643f
  pan-, 2641t
  sagittal, 2642, 2643f
    surgical management of, 2650, 2650f-2651f
Synovial sarcoma (SS), 1670
Synthetic biomimetic materials, for craniofacial defect repair, 2658
Synthroid (levothyroxine, oral synthetic), for hypothyroidism, 1748-1749
Syphilis
  diagnosis of, 2341
  HIV and, 224
  oral manifestations of, 1252, 1257
  otologic manifestations of, 2105, 2105f, 2341-2342
    early *vs.* late, 2341
    treatment for, 2341-2342
  pharyngitis due to, 194
    in children, 2786
  sensorineural hearing loss due to, 2119, 2161
    fluctuating, 2199
    in infants, 2723
    sudden, 2127-2128
Syringoma, 292-293
Systematic sample, 68, 69t
Systemic disease(s)
  laryngeal and tracheal manifestations of, 889-893
    in actinomycosis, 893
    in amyloidosis, 891, 891f
    in blastomycosis, 885, 892
    in candidiasis, 884-885, 884f, 893
    in coccidioidomycosis, 885, 893
    in cryptococcosis, 892-893
    in histoplasmosis, 885, 892
    in pemphigus, 887, 887f, 891-892, 892f
    in relapsing polychondritis, 890
    in rheumatoid arthritis, 891, 891f
    in sarcoidosis, 890-891, 890f
    in tuberculosis, 885-886, 886f, 892
    in Wegener's granulomatosis, 889-890, 890f
    in whooping cough, 892
  nasal manifestations of, 657-1
    cutaneous, 660-661
      in Behçet's disease, 660-661
      in pemphigoid, 660
      in pemphigus vulgaris, 660
      in scleroderma, 660
    granulomatous, 657-659
      in Churg-Strauss syndrome, 659
      in sarcoidosis, 658-659
      in Wegener's granulomatosis, 658
    immunodeficiency, 660
      in AIDS, 660
      sinusitis in immunocompromised patient as, 660
    mucociliary, 661
      in cystic fibrosis, 661
      in primary ciliary dyskinesia, 661
Systemic disease(s) *(Continued)*
    neoplastic, 659-660
      in T-cell lymphoma, 659-660
  oral manifestations of, 1245-1258
    arthritides and bone disorders as, 1253
      Ewing's sarcoma as, 1253
      osteoarthritis as, 1253
      Paget's disease as, 1253
      Reiter's syndrome as, 1253
      rheumatoid arthritis as, 1253, 1253t
    cerebrovascular, 1250
    collagen-vascular and granulomatous, 1251-1252
      dermatomyositis-polymyositis as, 1252
      sarcoidosis as, 1252
      scleroderma as, 1252
      Sjögren's syndrome as, 1251
      systemic lupus erythematosus as, 1251-1252
      Wegener's granulomatosis as, 1252
    dermatologic, 1253-1254
      erythema multiforme as, 1254
      lichen planus as, 1253-1254
      mucous membrane pemphigoid as, 1254
      pemphigus vulgaris as, 1254
    endocrine and exocrine, 1251
      adrenal, 1251
      diabetes mellitus as, 1251
      parathyroid, 1251
      pituitary, 1251
      thyroid, 1251
    gastrointestinal, 1254
      Behçet's syndrome as, 1254
      Crohn's disease and ulcerative colitis as, 1254
      gastroesophageal reflux disease as, 1254
      malabsorption diseases as, 1254
    of heart, 1246-1249, 1249t
    hematologic, 1256
      bleeding disorders as, 1256
      hemoglobin problems as, 1256
      white blood cell disorders as, 1256
    infectious, 1252
      bacterial, 1252
      fungal, 1252
      viral, 1252
    inherited and congenital, 1257
    of liver, 1255
    malignant neoplasms as, 1249-1250
    neurologic, 1254-1255
      Bell's palsy as, 1255
      dementias (including Alzheimer's disease) as, 1254-1255
      multiple sclerosis as, 1255
      myasthenia gravis as, 1255
      myotonic muscular dystrophy as, 1255
      Parkinson's disease as, 1255
    pulmonary, 1250-1251
    renal, 1255
  oral sequelae of medications for, 1246, 1247t-1248t
  oral treatment considerations due to, 1246, 1246t
  otologic manifestations of, 2100-2115, 2101t
    of bone, 2108-2112
      in fibrous dysplasia, 2110-2111, 2111f
      in osteitis fibrosa cystica, 2112
      in osteogenesis imperfecta, 2109-2110, 2110f
      in osteopetroses, 2111-2112, 2112f-2113f
      in Paget's disease, 2108-2109, 2109f
    collagen vascular and autoimmune, 2114
    genetically determined, 2115
    granulomatous and infectious, 2100-2106
      in Langerhans' cell histiocytosis, 2100-2101, 2101f-2102f
      in Lyme disease, 2105-2106
      in mycotic diseases, 2106, 2106f
      otorrhea as, 2196
      in sarcoidosis, 2104-2105, 2104f
      in syphilis, 2105, 2105f
Systemic disease(s) *(Continued)*
      in tuberculosis, 2101-2103, 2102f-2103f
      in Wegener's granulomatosis, 2103-2104, 2103f-2104f
    immunodeficiency, 2114-2115
      in AIDS, 2114-2115
      primary of congenital, 2114
    neoplastic, 2106-2108
      in leukemia, 2107, 2108f
      metastatic, 2107-2108, 2108f
      in multiple myeloma, 2106-2107, 2107f
    otorrhea as, 2196
    storage and metabolic, 2112-2114
      in gout, 2113-2114
      in mucopolysaccharidoses, 2112-2113, 2113f
      in ochronosis, 2114
  with rhinitis, 698-699, 698b
Systemic lupus erythematosus (SLE), oral manifestations of, 1251-1252
Systemic vascular resistance, factors influencing, 2597, 2597t

T

T & T olfactometer, 631
T cell(s), 600-603
  cytotoxic, 601, 602f
  development of, 600-601
  effector, 601-603
  in head and neck squamous cell carcinoma, 1023-1024
  helper, 601-602, 602f
  priming of, 601
  regulatory, 602-603
T cell–dependent (TD) B cell responses, 606
T cell–independent B cell responses, 606
T cell–mediated hypersensitivity reactions, 601, 608-612
T (tumor) classification, for melanoma, 1111, 1111t, 1113f
T1 receptors (T1Rs), in gustatory transduction, 1209, 1210f
T1-weighted images (T1WI), 134, 135f-136f
T2 receptors (T2Rs), in gustatory transduction, 1209, 1210f
T2-weighted images (T2WI), 134, 135f-136f
T_3. *See* 3,5,3′-Triiodothyronine (T_3).
T_4. *See* Thyroxine (T_4).
TA (tufted angioma), 2824-2825
  Kasabach-Merritt phenomenon with, 2825
TA muscle. *See* Thyroarytenoid (TA) muscle.
TAARs (trace amine–associated receptors), 630-631
TAC (tetracaine-adrenaline-cocaine) anesthesia, for facial trauma, 304
Tacrolimus (FK-506, Fugimycin, Protopic), for eczematoid otitis externa, 1956
Tactile perceptual evaluation, in voice assessment, 827-831, 828f
Tactile sensitivity, of oral cavity, 1201-1202, 1201f-1202f
Taft, William Howard, 251
Tailchaser mice, 2078
Talbot's law, 818, 847
Talkativeness profile, 861
Tandem walking, 2316-2317
Tangier disease, oral manifestations of, 1257
TARA, in deafness, 2051t-2058t
Target population, 68, 68t
Targeted therapy
  historical background of, 1052
  with radiotherapy, 1054, 1055f
    for laryngeal cancer, 1585
  for salivary gland neoplasms, 1199
Tarsal plates, 444
Tarsorrhaphy, 2420, 2421f
Tarsus
  anatomy of, 443f, 444
  in lower eyelid blepharoplasty, 448-449, 450f

Taste, 1207-1214
  assessment of, 2383-2384
  categories of, 1207
  of dietary fats, 1213
  in geriatric patients, 236
  gustatory sensitivity in, 1207-1208
  gustatory structures in, 1208
  hedonic attribute of, 1207-1208
  individual differences in, 1211-1212
  physiology of, 1208
    central gustatory pathways and function in, 1212-1213, 1212f
    gustatory transduction in, 1208-1210, 1210f
    interaction with saliva in, 1141, 1213-1214
    with obesity, 1213
    peripheral sensitivity in, 1210-1212
    "sensory-specific" satiety in, 1212-1213
  radiation therapy and, 1214
  of umami, 1207, 1209, 1213
Taste buds, 1208
Taste disturbance, due to small fenestra stapedotomy, 2034
Taste dysfunction, palliative care for, 1103
Taste-odor tests, 632
Tattoos
  amalgam (*See* Amalgam tattoo)
  traumatic, 305, 305f
Tavist (clemastine), for nonallergic rhinitis, 701t
Tazarotene cream, for aging skin, 403-404
TB. *See* Tuberculosis (TB).
TBBX (transbronchial biopsy), flexible fiberoptic bronchoscopy for, 1004-1005, 1004f-1005f
TBG (thyroxine-binding globulin), 1738
TBII (thyroid binding inhibitory immunoglobulins), 1741
TBNA (transbronchial needle aspiration), flexible fiberoptic bronchoscopy for, 1005-1007, 1005f-1006f
T-box 1 *(TBX1)* gene, in deafness, 2051t-2058t
T-box transcription factor 18 *(Tbx18)* gene, in murine deafness, 2058t-2060t
TBP (thyroxine-binding protein), 1738
^{99m}Tc. *See* Technetium-99m (^{99m}Tc).
TC (typical carcinoid), of larynx, 1507
TCA(s) (tricyclic antidepressants)
  for migraine, 2350
  for neuropathic pain, 244-245
TCA (trichloroacetic acid). *See* Trichloroacetic acid (TCA).
T-cell lymphoma, nasal manifestations of, 659-660
tcMEP (transcranial motor evoked potential), for intraoperative monitoring, 2555, 2555f
TCOF1
  in deafness, 2051t-2058t
  in mandibulofacial dysostosis, 2633
T-coil (telecoil), for hearing aid, 2267
$TcPCO_2$ (transcutaneous carbon dioxide pressure), in skin flaps, 1068
$TcPO_2$ (transcutaneous oxygen pressure), in skin flaps, 1068
TD (T cell–dependent) B cell responses, 606
TE. *See* Tracheoesophageal (TE).
Technetium-99m (^{99m}Tc) scanning, 138, 139f
  for malignant otitis externa, 1947
  for thyroid nodule, 1757-1758
Technetium-99m (^{99m}Tc) sestamibi scintigraphy, for hyperparathyroidism, 1785
  due to double parathyroid adenoma, 1785, 1785f
  due to mediastinal supernumerary thyroid gland, 1802, 1803f
  and multinodular thyroid disease, 1801, 1801f
  due to multiple-gland hyperplasia, 1794, 1794f
  due to parathyroid carcinoma, 1803, 1803f
Technetium-99m (^{99m}Tc) sestamibi scintigraphy with single photon emission computed tomography (MIBI-SPECT), for hyperparathyroidism, 1785
Technetium-99m (^{99m}Tc) thallous chloride imaging, for hyperparathyroidism, 1784-1785
TECTA (α-tectorin) gene
  in deafness, 2051t-2058t, 2067-2068, 2092
  genetic testing for, 2098
Tectb (β-tectorin) gene, in murine deafness, 2058t-2060t, 2067-2069.
Tectorial membrane
  anatomy of, 1832, 1832f, 2067
  in auditory physiology, 1841f
  in cochlear transduction, 2050, 2061f, 2065-2066, 2069f
  mass and stiffness of, 2067
  pathophysiology of, 2067-2069
  in surgical anatomy of anterior cranial base, 2474
α-Tectorin, 2067
α-Tectorin *(TECTA)* gene
  in deafness, 2051t-2058t, 2067-2068, 2092
  genetic testing for, 2098
β-Tectorin, 2067
β-Tectorin *(Tectb)* gene, in murine deafness, 2058t-2060t, 2067-2069.
Teeth
  anatomy and physiology of, 323
  development of, 1259-1260
    enamel organ in, 1259
    root development in, 1260
    stages of, 1260
  effects of radiotherapy on, 2626t
  eruption of, 2617t
  extraction of, prior to radiation therapy, 1330-1331, 1330b
  in geriatric patients, 236
  infections of (*See* Odontogenic infections)
  maintaining integrity of, saliva in, 1141
  physical examination of, 98
  tactile sensitivity of, 1201-1202
TEF (tracheoesophageal fistula), 2926
  imaging of, 1409-1410
Teflon (polytetrafluoroethylene), for vocal fold medialization
  history of, 905
  by injection, 905-906
    complications of, 907, 908f
Tegmen mastoideum, in surgical anatomy of lateral skull base, 2438
Tegmen plate, in mastoidectomy, 2011-2012
Tegmen tympani
  anatomy of, 1827
  in surgical anatomy of lateral skull base, 2438
Telangiectasia, 291
  hereditary hemorrhagic, 291
    epistaxis in, 691-692, 692f
    oral manifestations of, 1257
  spider angioma as, 291
  venous lakes as, 288f, 291
Telecanthus, in evaluation of maxillofacial trauma, 324, 324f
Telecoil (t-coil), for hearing aid, 2267
Telementoring, 38-39
Telephone ear deformity, 479
Telepresence, 38-39
Telerobotic surgery, 38-39
  transatlantic, 39
Telogen effluvium, 376, 382, 426
Telogen phase, 374, 374f
TEM (transverse electromagnetic mode), 27, 28f
Template(s), in microtia) reconstruction, 2744-2745, 2745f
Template strand, 4
Temporal arteritis, *vs.* myofascial pain dysfunction syndrome, 1284t
Temporal bone, 320f
  anatomy of, 2009-2010, 2010f
    in infants, 2010
  in autoimmune inner ear disease, 2165
  in bacterial labyrinthitis, 2160
Temporal bone *(Continued)*
  congenital rubella infection of, 2156-2157, 2157f
  cytomegalic inclusion disease of, 2155-2156, 2155f
  in herpes zoster oticus, 2159
  imaging of, 171-173, 1916
    cerebellopontine angle in, 1926-1928, 1929t
      with acoustic schwannoma, 1929t
      with arachnoid cyst, 1928, 1929t
      with epidermoid tumor, 1928, 1928f, 1929t
      with lipoma, 1928, 1929t
      with meningioma, 1928, 1928f, 1929t
    cochlear nerve in, 1928-1929, 1929f
    conventional radiography for, 131
    CT for, 142
    external auditory canal in, 172, 1917-1918
      with benign neoplasms, 1918, 1918f-1919f
      with cholesteatoma, 1917, 1918f
      with congenital lesions, 1917, 1917f
      with keratosis obturans, 1917, 1918f
      with malignant neoplasms, 1918, 1919f
      with postinflammatory medial canal fibrosis, 1917-1918, 1918f
      with severe infections, 1917, 1917f
    external ear in, 172
    facial nerve in, 173, 1924-1926
      with Bell's palsy, 1924, 1927f
      with hemangioma, 1924-1926, 1927f
      with meningioma, 175f
      with neuroma, 1928
      with schwannoma, 1924-1926, 1927f
    for infant hearing impairment, 2723
    inner ear in, 172-173, 1920-1922
      with congenital anomalies, 172-173, 174f, 1920-1921, 1923f
      with enlarged vestibular aqueduct, 1921, 1923f
      with fenestral and cochlear otosclerosis (otospongiosis), 1921-1922, 1925f
      with intravestibular schwannoma, 1921, 1924f
      with labyrinthitis ossificans, 1921, 1925f
      normal appearance of, 1920-1921, 1922f
      with superior semicircular canal dehiscence, 1920-1921, 1922f
    internal auditory canal in, 173, 1926-1928
      with meningioma, 175f
      with vestibular schwannoma, 173, 1928, 1928f
    mastoid in, 1918-1920
    middle ear in, 172, 1918-1920
      with aberrant internal carotid artery, 1919-1920, 1921f-1922f
      with cholesteatoma, 174f, 1918-1919
      with glomus tympanicum, 1919-1920, 1921f
      with transverse petrous fracture with osseous dislocation, 174f
    MRI for, 143
    petrous apex in, 1922-1924, 1924t
      with asymmetric pneumatization, 1922-1923, 1924t, 1925f
      with cholesteatoma, 1924t
      with cholesterol granuloma, 1923, 1924t, 1925f-1926f
      with malignant lesions, 1923-1924, 1926f
      with mucocele, 1924t
      with retained secretions, 1923, 1924t, 1925f
  in measles, 2158
  multiple myeloma of, 2107, 2107f
  in mumps, 2158, 2158f
  osteology of, 1821-1823
    lateral view of, 1822f
    mastoid part in, 1821-1822, 1822f, 1829
      anatomy of, 2009-2010, 2010f

Temporal bone *(Continued)*
petrous part in, 2010f
anterior surface of, 1822, 1822f
inferior surface of, 1822-1823, 1824f
posterior surface of, 1822, 1823f
squamous part in, 1821, 1822f
superior view of, 1822f
tympanic part in, 320f, 1822f, 1823, 2010f
pneumatization of, 1829
secondary mycosis of, 2195
in sudden sensorineural hearing loss, 2157
in surgical anatomy of lateral skull base, 2434, 2436f
in surgical anatomy of middle cranial base, 2445f
syphilis of, 2161
in vestibular neuritis, 2162, 2162f
Temporal bone fractures, 2036-2048
bilateral, 2036
classification of, 2036-2038
longitudinally oriented, 2036-2037, 2037f
mixed-oriented, 2037f
otic capsule–disrupting, 2037-2038
otic capsule–sparing, 2037-2038
transverse-oriented, 2036-2037, 2037f
cochlear implant for, 2221
complications of, 2039-2047
carotid artery injury as, 2039, 2040f, 2047
cholesteatoma as, 2038, 2047
CSF fistulas as, 2044-2046
closure of, 2045-2046, 2045f
treatment algorithm for, 2045-2046, 2045f
delayed meningitis as, 2037-2038, 2038f
external auditory canal stenosis as, 2038, 2047
facial nerve injury as, 2039-2044, 2042t, 2398-2399
assessing degree of, 2040
classification of, 2040
compound muscle action potential in, 2041
conservative treatment of, 2040, 2042
corticosteroids for, 2042
delayed onset of paralysis due to, 2040
electromyography for, 2041
electroneuronography for, 2041
epidemiology of, 2039-2040
evoked encephalomyography for, 2041
imaging of, 2398f
maximal stimulation test for, 2040-2041
middle fossa craniotomy for, 2042-2043
nerve excitability test for, 2040-2041
observation and symptomatic care for, 2398
outcome of, 2041, 2042t
pathogenesis of, 2398
supralabyrinthine approach for, 2042, 2043f
surgical interventions for, 2041, 2042t, 2398-2399
translabyrinthine approach for, 2041-2042
transmastoid approach for, 2042
treatment algorithm for, 2042-2044, 2043f
hearing loss as, 2046-2047, 2046f
hemotympanum as, 2038, 2039f, 2046
nystagmus as, 2039
perilymph fistula as, 2039
profuse hemorrhage as, 2038
vertigo as, 2039, 2201
epidemiology of, 2036, 2037f
evaluation of, 2038-2039
fistula test in, 2039
hearing assessment in, 2039
imaging in, 2039, 2040f
neurotologic examination in, 2038-2039
otoscopy in, 2038f-2039f
physical examination in, 2038
tympanic membrane in, 2038
open, 2036
pathophysiology of, 2036
severe, 2038-2039
Temporal bone infections, complications of, 1979-1998
diagnosis of, 1981-1982
history in, 1981-1982
imaging in, 1982
lumbar puncture in, 1982
physical examination in, 1982
epidemiology of, 1979-1981
age distribution in, 1979, 1980t
extracranial, 1979, 1980t
intracranial, 1979, 1980t-1981t
extracranial (intratemporal), 1983-1993
acute mastoiditis as, 1983, 1983f
acute suppurative labyrinthitis as, 1991-1992, 1991f-1992f
age distribution of, 1979, 1980t
Bezold abscess as, 1985-1986, 1986f-1987f
chronic mastoiditis as, 1984-1985, 1985f
coalescent mastoiditis as, 1983-1984, 1984f
encephalocele and CSF leakage as, 1992-1993, 1993f
facial nerve paralysis as, 1991, 1991f
labyrinthine fistula as, 1989-1990, 1990f
masked mastoiditis as, 1985
petrous apicitis as, 1986-1989, 1988f-1989f
postauricular abscess as, 1985, 1985f-1986f
temporal root abscess as, 1986
general considerations for, 1979
intracranial, 1993-1997
age distribution in, 1979, 1980t
brain abscess as, 1994, 1994f-1995f
epidemiology of, 1979, 1980t
epidural abscess as, 1995-1996
interrelationship of, 1979, 1981t
lateral sinus thrombosis as, 1996-1997, 1996f-1997f
meningitis as, 1993-1994, 1994f
otitic hydrocephalus as, 1997
subdural empyema as, 1994-1995
otitis media and
acute, 1979-1981
chronic, 1981
pathophysiology of, 1981
treatment of, 1982-1983
Temporal bone neoplasm(s), 2488b
carcinoma as, 2502-2504
management of, 2502-2504, 2503f
pertinent anatomy for, 2502
staging of, 2502, 2502f, 2503b
symptoms and signs of, 2502
choice of surgical approach for, 2492-2501
complications of, 2511-2513
intraoperative, 2511
postoperative, 2512-2513
cerebrovascular, 2512-2513
cranial nerve deficits as, 2512
congenital cholesteatoma as, 2508-2509
diagnostic evaluation of, 2508, 2509f-2510f
surgical approach to, 2508-2509
evaluation of, 2489-2492
carotid management algorithms in, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
qualitative, 2490-2491
quantitative, 2491
CT and MRI for, 2489
four-vessel arteriography in, 2489-2490, 2491f
preoperative carotid artery management in, 2489
algorithm for, 2490f, 2491-2492
cerebral blood flow assessment in, 2490-2491, 2490f
four-vessel arteriography in, 2489-2490, 2491f
facial nerve schwannomas as, 2506-2508
diagnostic evaluation of, 2507
management and surgical approach to, 2507-2508
Temporal bone neoplasm(s) *(Continued)*
infratemporal fossa approaches for, 2495-2501
postauricular, 2495-2500
cervical dissection in, 2495, 2498f
closure of external auditory canal in, 2495, 2497f
closure of wound in, 2499, 2499f
exposure of jugular bulb and internal carotid artery in, 2498, 2498f-2499f
extratemporal facial nerve dissection in, 2495-2496
facial nerve transposition in, 2497-2498, 2498f
incisions and skins flaps in, 2495, 2497f
occlusion of sigmoid sinus in, 2498, 2498f
radical mastoidectomy in, 2496, 2498f
removal of external auditory canal wall skin and tympanic membrane in, 2495, 2497f
tumor removal in, 2498-2499, 2499f
type A, 2497-2499, 2498f-2499f
type B, 2499-2500, 2500f
type C, 2500, 2501f
preauricular, 2500-2501, 2501f
lateral (partial) temporal bone resection for, 2492-2493
for carcinoma, 2503-2504
closure in, 2493, 2493f
incisions for, 2492-2493, 2493f
margins of resection for, 2492f
mastoidectomy and facial recess approach in, 2493, 2493f
removal of specimen in, 2493, 2493f
paragangliomas as, 2505-2506
diagnostic evaluation of, 2505, 2506f-2507f
preoperative evaluation of, 2491f
radiotherapy for, 2506
surgical approach to, 2505-2506, 2507f
symptoms of, 2505
postsurgical encephalocele and CSF leaks with
diagnostic evaluation of, 2509
surgical approach to, 2509
rhabdomyosarcoma as, 2501-2502
subtotal temporal bone resection for, 2494
for carcinoma, 2503-2504
defined, 2493
delineation of sigmoid sinus and jugular bulb in, 2494-2495
facial nerve management in, 2494-2495
incision for, 2494, 2494f
indications for, 2493
infratemporal fossa dissection in, 2494
margins of resection for, 2492f
neck dissection in, 2494
osteotomy in, 2495
proximal vascular control in, 2494
reconstruction after, 2495
temporal craniotomy in, 2494, 2494f
total temporal bone resection for, 2495
for carcinoma, 2504
defined, 2493-2494
facial nerve management in, 2494
incision for, 2494
indications for, 2493-2494
infratemporal fossa dissection in, 2494
margins of resection for, 2492f
neck dissection in, 2494
proximal vascular control in, 2494
reconstruction after, 2495
temporal craniotomy in, 2494
Temporal bone resection
lateral (partial), 2492-2493
for carcinoma, 2503-2504
closure in, 2493, 2493f
incisions for, 2492-2493, 2493f
margins of resection for, 2492f

Temporal bone resection *(Continued)*
mastoidectomy and facial recess approach in, 2493, 2493f
removal of specimen in, 2493, 2493f
subtotal, 2494
for carcinoma, 2503-2504
defined, 2493
delineation of sigmoid sinus and jugular bulb in, 2494-2495
facial nerve management in, 2494-2495
incision for, 2494, 2494f
indications for, 2493
infratemporal fossa dissection in, 2494
margins of resection for, 2492f
neck dissection in, 2494
osteotomy in, 2495
proximal vascular control in, 2494
reconstruction after, 2495
temporal craniotomy in, 2494, 2494f
total, 2495
for carcinoma, 2504
defined, 2493-2494
facial nerve management in, 2494
incision for, 2494
indications for, 2493-2494
infratemporal fossa dissection in, 2494
margins of resection for, 2492f
neck dissection in, 2494
proximal vascular control in, 2494
reconstruction after, 2495
temporal craniotomy in, 2494
Temporal bone surgery
CSF otorrhea due to, 2197
simulation of, 49-50, 49f-50f
surgical anatomy for, 2488-2489
Temporal branch, of facial nerve, 440, 441f, 1194f
Temporal coherence, 26, 27f
Temporal craniotomy
for middle cranial base surgery, 2467
in subtotal or total temporal bone resection, 2494, 2494f
Temporal fascia, 440
in brow or forehead rejuvenation, 433-434, 433f
Temporal fat pad, 440
Temporal forehead flap, for lip defects, 353
Temporal fossa, 320f
Temporal lift, 431-432, 431t
Temporal line, 320f, 1821, 1822f, 2009, 2010f
Temporal region, fascial layers of, 440-441, 441f
Temporal root abscess, 1986
Temporal signal processing strategies, for cochlear implants, 2229-2230, 2230f
analog stimulation as, 2230, 2230f
continuous interleaved sampling as, 2229-2230
Temporal space involvement, in odontogenic infections, 184, 185f
Temporal squama, 1822f-1823f, 2010f
Temporalis fascia graft
in atresiaplasty, 2755f, 2756, 2757f
for medialization thyroplasty, 910
for saddle nose deformity, 555, 557f
for tympanoplasty, 2000
Temporalis flap, for oropharyngeal reconstruction, 1377-1378
of tonsils and pharyngeal wall, 1386
Temporalis muscle
anatomy of, 1320, 1821
in surgical anatomy of lateral skull base, 2440f
Temporalis transfer, for facial nerve paralysis, 2427-2429, 2429f
Temporary threshold shift (TTS), 2121, 2141
Temporomandibular disorders (TMDs), 1279-1286
agenesis as, 1281t
ankylosis as, 1281t, 1282
anterior disk displacement as, 1281t
with reduction, 1280, 1282f
without reduction, 1280-1281, 1282f
Temporomandibular disorders (TMDs) *(Continued)*
arthritis as, 1281-1282
degenerative, 1281, 1281t
infectious, 1281-1282, 1281t
rheumatoid, 1253, 1281t, 1282
traumatic, 1281, 1281t
clinical presentation of, 1279
condylar and subcondylar fractures as, 1280
condylar hyperplasia as, 1281t
condylar hypoplasia as, 1281t
congenital and developmental, 1280
defined, 1279
differential diagnosis of, 1281t
dislocation as, 1280
intracapsular, 1280-1282
myofascial pain dysfunction syndrome as, 1283-1285
clinical features of, 1283-1284
defined, 1283
differential diagnosis of, 1284t-1285t
epidemiology of, 1283
etiology of, 1283, 1283f
treatment of, 1284-1285, 1286f
neoplasms as, 1280, 1281t
vs. myofascial pain dysfunction syndrome, 1285t
Temporomandibular joint (TMJ)
anatomy and physiology of, 322-323, 1279-1280
in geriatric patients, 236
in interdental discrimination, 1207
physical examination of, 95
Temporomandibular joint (TMJ) dysfunction, tinnitus with, 2132-2133
Temporomandibular joint (TMJ) surgery, 1282-1283
arthrocentesis as, 1283
arthroscopy as, 1283
arthrotomy as, 1283
Temporoparietal fascia, 440
Temporoparietal fascial flap, for oropharyngeal reconstruction, 1377-1378, 1378f
of tonsils and pharyngeal wall, 1386
Temporoparietal flaps, for free tissue transfer, 1082t
Temporoparietal-occipital (TPO) pedicle flaps, for hair loss, 385-387, 387f
complications of, 386-387
TEN (toxic epidermal necrolysis), 1239
Tension pneumothorax, *vs.* anaphylactic reaction, 119
Tension septum, 492, 493f
Tension-type headache (TTH), 247
Tensor fold, anatomy of, 1827f
Tensor tympani (TT) muscle
anatomy of
in eustachian tube, 1867, 1867f-1868f
in middle ear, 1825-1826
tensor veli palatini and, 1869-1870
in efferent auditory system, 1847
in pressure equalization, 1870
in surgical anatomy of lateral skull base, 2437f, 2438
Tensor tympani (TT) tendon, anatomy of, 1827f
Tensor veli palatini (TVP) muscle
anatomy of
in eustachian tube, 1869-1870, 1869f
in middle ear, 1825
in oral cavity, 1297f
in oropharynx, 1360f
in cleft palate, 2666-2667
development of, 1866
in pressure equalization, 1870
in velopharyngeal function, 2677t
TEOAEs. *See* Transient evoked otoacoustic emissions (TEOAEs).
TEP. *See* Tracheoesophageal puncture (TEP).
Teratomas
of cerebellopontine angle, 2527
in children, 2846-2847
epidemiology of, 2846
histopathology and molecular biology of, 2847, 2847f
management of, 2846
presentation and evaluation of, 2846, 2846t
nasopharyngeal, 2695, 2696f
neck masses due to, 1639-1640, 2816, 2816f
Terbinafine, for rhinosinusitis, 713t, 735t
Terminal cell, surgical anatomy of, 740
Tessier, Paul, 318
Test-retest reliability, 55
Tetanus prophylaxis, for facial trauma, 303
Tetracaine-adrenaline-cocaine (TAC) anesthesia, for facial trauma, 304
Tetracycline, for embolization, 1933
3,5,3′,5′-Tetraiodothyronine (T_4), 1737. *See also* Thyroid hormone(s).
oral synthetic, for hypothyroidism, 1748-1749
serum free, 1740
in thyrotoxicosis, 1742
Tetraspan membrane protein of hair cell stereocilia *(TMHS)* gene, in deafness, 2051t-2058t
TFCP2L3 (transcription factor cellular promotor 2-like 3) gene, in deafness, 2051t-2058t
TG. *See* Thyroglobulin (TG).
TGF (transforming growth factor), 609t-610t
TGF-α (transforming growth factor α), in wound healing, 1076
TGF-β (transforming growth factor β), 609t-610t
in wound healing, 1076
TH1 cells, 601
in otitis media, 2764
TH2 cells, 601
in otitis media, 2764
TH17 cells, 601-602
Thalamus, in auditory pathway, 1846-1847
Thalassemia
oral manifestations of, 1256
preoperative evaluation of, 106
Thalidomide, microtia due to, 2741
Thallium 201 (Tl 201) imaging, for hyperparathyroidism, 1784-1785
Thallous chloride imaging, for hyperparathyroidism, 1784-1785
Thanatophoric dysplasia, craniofacial anomalies in, 2641t
Therapeutic lymph node dissection (TLND), for melanoma, 1114, 1116
Thermal ablation, interventional bronchoscopy with, 1010t
Thermal laryngeal trauma, 939-941
etiology of, 940-941
incidence of, 939-940
management of, 941
Thermal sensitivity, of oral cavity, 1201
Thermoregulation, vascular supply of skin in, 1064
θ-defensins, 599
THI (Tinnitus Handicap Inventory), 2135, 2138
Thiamine-responsive megaloblastic anemia syndrome, deafness in, 2051t-2058t
Thiazide diuretics, hypercalcemia due to, 1784
Thiopental, for anesthesia induction, 111
in children, 2590
Third "mobile window," in superior canal dehiscence syndrome, 2339-2340
Third-gain rule, for hearing aids, 2271
Thoracic duct, anatomy of, 2582
Thornwaldt cyst. *See* Tornwaldt cyst.
THRB (thyroid hormone receptor β) gene, in deafness, 2051t-2058t

Three-dimensional conformal radiotherapy (3DCRT), 1043
  for cervical metastases, 1691-1692
  for glottic cancer
    advanced-stage, 1585-1586
    early-stage, 1581, 1581f-1582f
Three-dimensional (3D) CT, of laryngeal carcinoma, 1470
Three-dimensional reconstruction, from CT or MRI, 138, 140f
Three-field technique, for radiation therapy, for glottic cancer, 1586, 1587f
Three-wall orbital decompression, for Graves' ophthalmopathy, 1815-1816
Threshold, of auditory neurons, 1839-1840, 1844-1845, 1845f
Throat, sore. *See* Pharyngitis.
Throat cultures, 2787
Thrombocytopenia
  oral manifestations of, 1256
  preoperative evaluation of, 106
Thromboxane synthetase, in acutely raised skin flaps, 1070, 1070f
"Through-and-through" resection, for buccal carcinoma, 1308-1309, 1309f
Through-the-scope (TTS) balloons, for esophageal strictures, 966
Thrush, 1230, 1230f
  in HIV, 225, 226f
Thulium laser, for stridulous child, 2908
Thunderclap headache, 248
Thymic cysts, 2817
Thymopharyngeal cysts, 2585
Thyroarytenoid (TA) muscle
  anatomy of
    applied, 806-807, 807f
    surgical, 1543f
  botulinum toxin injection of, for spasmodic dysphonia, 840f
  in breathing, 810f
  characteristics of, 918
  in pitch control, 812
  in professional voice production, 846-847
Thyrocervical trunk, in root of neck, 2581-2582
Thyroepiglottic ligament, surgical anatomy of, 1542f-1543f
Thyroglobulin (TG)
  serum measurement of, 1740
    with thyroid nodule, 1756
  in thyroid hormone storage and release, 1737f, 1738
  in thyroid hormone synthesis
    iodination of, 1737f, 1738
    synthesis of, 1737-1738, 1737f
Thyroglossal duct carcinomas, 2847
Thyroglossal duct cyst(s), 2814-2815, 2871-2872
  clinical presentation of, 2814-2815, 2815f
  vs. ectopic thyroid, 2815
  embryology of, 2586, 2814
  imaging of, 161-162, 165f
  infected, needle aspiration of, 206, 206f
  neck masses due to, 1639
  Sistrunk operation for, 2815
  squamous cell carcinoma arising in, 1671
  vallecular, 2871-2872, 2872f
Thyrohyoid ligament, surgical anatomy of, 1542f
Thyrohyoid membrane, surgical anatomy of, 1541-1542, 1542f-1543f
Thyrohyoid muscle, characteristics of, 918-919
Thyrohyoid space, palpation of, in voice evaluation, 827, 828f
Thyroid adenoma, 1758-1759
  autonomously functioning, 1759
  in children, 2819
  clinical presentation of, 1758
Thyroid adenoma *(Continued)*
  management and prognosis for, 1759
  pathology of, 1758-1759
  sestamibi–technetium 99m scintigraphy of, 1785f
  toxic, 1744
Thyroid alar cartilage graft, for laryngeal stenosis, 2919, 2921f
Thyroid antibody status, 1740-1741
Thyroid binding inhibitory immunoglobulins (TBII), 1741
Thyroid cancer
  anaplastic, 1764
    clinical presentation of, 1764
    management and prognosis for, 1764
    pathology of, 1764
  in children, 1769-1770, 2820
  clinical presentation of, 1751
  epidemiology of, 1751
  etiology of, 1753
  follicular, 1761-1762
    clinical presentation of, 1761-1762
    imaging of, 161-162, 165f
    management and prognosis for, 1762
    pathology of, 1762
  follow-up for, 1772
  in geriatric patients, 238
  Graves' disease and, 1742
  Hürthle cell, 1762-1763
    clinical presentation of, 1762
    management and prognosis for, 1762-1763
    pathology of, 1762
  insular, 1764
  with laryngeal invasion, 1510
  lymphoma as, 1764
  medullary, 1763-1764
    clinical presentation of, 1763
    management and prognosis for, 1763-1764
    nodal metastasis of, 1766
    pathology of, 1763
  metastatic, 1764
    ultrasound imaging of, 1644, 1648f-1649f
  molecular basis for, 1752-1753
  papillary, 1760-1761
    clinical presentation of, 1760
    management and prognosis for, 1760-1761
    pathology of, 1760
  during pregnancy, 1770
  risk factors for, 1753
    with aggressive behavior, 1756, 1756t
  selective neck dissection for, 1719, 1719f-1720f
  squamous cell, 1764
  staging and classification of, 1753-1754
    AGES and MACIS, 1754
    AMES, 1754, 1756t
    TNM, 1754, 1755t
  surgical management of (*See* Thyroid surgery)
  tracheal invasion by, 1615
  ultrasound of, 1644, 1646b, 1646f
    metastatic, 1644, 1648f-1649f
Thyroid capsule, anatomy of, 1751
Thyroid cartilage
  anatomy of, 805-806, 1359f
    radiographic, 1471, 1473f
    surgical, 1541, 1542f-1544f
  laryngeal carcinoma of, 1541
    imaging of, 1474-1475, 1476f
  palpation of, in voice evaluation, 827, 828f
  physical examination of, 95, 96f
  repair of, 936-937
Thyroid cyst, 1759-1760
  clinical presentation of, 1759-1760
  management and prognosis for, 1760
  pathology of, 1760
Thyroid dermopathy, and Graves' ophthalmopathy, 1808
Thyroid disorder(s), 1735-1749
  history and review of symptoms for, 1736
  hyperparathyroidism and, 1801, 1801f-1802f
  hypothyroidism as, 1745-1749
    clinical features of, 1745-1746, 1746b
    due to endemic goiter, 1747
    etiology of, 1745, 1746b
    due to excessive iodine intake, 1747
    familial, 1747
    goitrous, 1747
    hearing loss due to, 1746
    hoarseness due to, 1747
    hypothalamic, 1747
    laboratory diagnosis of, 1748, 1748t
    after laryngectomy, 1747
    management of, 1748-1749
    myxedema coma due to, 1749
    nongoitrous, 1747
    pituitary, 1747
    prevalence of, 1745
    after radiation therapy, 1747
    risk factors for, 1745-1746, 1746b
    subclinical, 1747-1748
      diagnosis of, 1747
      effects on lipid, hypothyroid symptoms, and mood of, 1747-1748
      natural history of, 1747
      prevalence of, 1747
      treatment of, 1748
    surgery with, 1749
    transient, 1747
    vertigo due to, 1747
  oral manifestations of, 1251
  physical examination for, 1736-1737
  due to radiotherapy, 1048
  thyrotoxicosis as, 1741-1745
    defined, 1741
    ectopic, 1745
    epidemiology of, 1741
    etiology of, 1742, 1742t
    exogenous, 1744
    due to Graves' disease, 1742-1743
    overt, 1741
    pathophysiology of, 1742
    subclinical, 1741, 1745
    thyroid storm in, 1745
    due to thyroiditis, 1744
    due to toxic multinodular goiter, 1744-1745
    due to toxic thyroid adenoma, 1744
Thyroid eye disease. *See* Graves' ophthalmopathy.
Thyroid follicular necrosis, radiation-induced, 1744
Thyroid function
  control of, 1738-1739
  in Graves' ophthalmopathy, 1809
Thyroid function study(ies), 1739-1741
  circulating thyroid hormone measurement as, 1739-1740
  in hypothyroidism, 1748, 1748t
  radioactive iodine uptake test as, 1741
  serum thyroglobulin measurement as, 1740
  serum thyrotropin measurement as, 1740, 1741f
  thyroid antibody status as, 1740-1741
  thyroid-stimulating antibody measurement as, 1741
Thyroid gland, 1735-1749
  anatomy of, 1359f, 1736
    surgical, 1751-1752, 1751f-1752f
  blood supply to and from, 1751-1752, 1752f
  ectopic
    lingual, 161-162, 165f, 1287, 1736
    median, 1639
    vs. thyroglossal duct cyst, 2815
  embryology of, 1751
  imaging of, 161-162
    CT for, 140
    with follicular carcinoma, 161-162, 165f
    lingual, 161-162, 165f

Thyroid gland *(Continued)*
MRI for, 143
normal anatomy in, 161
scintigraphy for, 138
with thyroglossal duct cyst, 161-162, 165f
ultrasonography for, 1644, 1645f-1647f, 1646b
multinodular, ultrasound imaging of, 1644
physical examination of, 95, 1736-1737
physiology of, 1737-1739, 1737f
control of function in, 1738-1739
iodide transport in, 1737, 1737f
iodination and thyroperoxidase in, 1737f, 1738
thyroglobulin in, 1737-1738, 1737f
thyroid hormones in, 1737
and antithyroid agents, 1739, 1739t
circulating, 1737f, 1738-1740
mechanism of action of, 1739
metabolism of, 1737f, 1738
storage and release of, 1737f, 1738
synthesis of, 1737f, 1738
during pregnancy, 1770
preoperative evaluation of, 104
Thyroid goiter
compression of pharynx and esophagus due to, 1409, 1409f
endemic, 1747
intrathoracic, 1766
tobacco smoke and, 1807
toxic
multinodular, 1744-1745
uninodular, 1744
Thyroid hormonal status, and Graves' ophthalmopathy, 1807
Thyroid hormone(s), 1737
and antithyroid agents, 1739, 1739t
circulating, 1737f, 1738
measurement of, 1739-1740
free *vs.* bound, 1738
mechanism of action of, 1739
metabolism of, 1737f, 1738
storage and release of, 1737f, 1738
synthesis of, 1737f, 1738
iodide transport in, 1737, 1737f
iodination and thyroperoxidase in, 1737f, 1738
thyroglobulin in, 1737-1738, 1737f
in thyrotoxicosis, 1742
thyrotoxicosis due to, 1744
Thyroid hormone receptor β *(THRB)* gene, in deafness, 2051t-2058t
Thyroid hormone replacement, after thyroid surgery, 1771
Thyroid hormone resistance, and deafness, 2051t-2058t
Thyroid isotope scanning, 1757-1758
Thyroid lobe(s), 1751, 1751f
Thyroid lobectomy, for thyroid adenoma, 1759
Thyroid lymphomas, 1679
staging of, 1679
treatment and prognosis for, 1679
Thyroid neoplasm(s), 1750-1772
in children, 1769-1770
classification of, 1759t
embolization of, 1938-1939
epidemiology of, 1750
Hürthle cell tumor as, 1762-1763
clinical presentation of, 1762
management and prognosis for, 1762-1763
pathology of, 1762
malignant (*See* Thyroid cancer)
molecular basis for, 1752-1753
neck masses due to, 1640
during pregnancy, 1770
surgical management of (*See* Thyroid surgery)
thyroid adenoma as, 1758-1759
autonomously functioning, 1759
in children, 2819
Thyroid neoplasm(s) *(Continued)*
clinical presentation of, 1758
management and prognosis for, 1759
pathology of, 1758-1759
sestamibi–technetium 99m scintigraphy of, 1785f
toxic, 1744
thyroid cyst as, 1759-1760
clinical presentation of, 1759-1760
management and prognosis for, 1760
pathology of, 1760
Thyroid nodule(s)
algorithm for management of, 1758, 1758f
in children, 1769-1770
"cold," 1758
colloid, 1644, 1647f
cystic, 1644, 1645f
epidemiology of, 1750-1751
evaluation of, 1754-1758
fine-needle aspiration cytology for, 1756-1758
history and physical examination for, 1754-1756
imaging for, 1757
laboratory studies for, 1756
thyroid isotope scanning for, 1757-1758
fine-needle aspiration biopsy of, 1756-1758
repeat, 1759
ultrasound-guided, 1655f
"hot," 1758
imaging of, 1757
CT and MRI for, 1757
thyroid isotope scanning for, 1757-1758
ultrasound for, 1644, 1757
colloid, 1644, 1647f
cystic, 1644, 1645f
malignant, 1644, 1646b, 1646f
with multiple nodules, 1644
solid hyperfunctioning, 1644
malignant, 1644, 1646b, 1646f
multiple, 1644
neck masses due to, 1640
during pregnancy, 1770
solid hyperfunctioning, 1644
Thyroid storm, 104, 1745
Thyroid surgery, 1764-1771
approach to, 1764-1766
exposure of thyroid gland in, 1765
incision for, 1764-1765
parathyroid glands in, 1752, 1765f, 1766
positioning for, 1764-1765
recurrent laryngeal nerve in, 1765, 1765f
strap muscles in, 1765
thyroid dissection in, 1765, 1765f
transection of isthmus in, 1766
in children, 1769-1770
complication(s) of, 1770-1771
bleeding as, 1770
hypocalcemia as, 1771
recurrent laryngeal nerve injury as, 1770-1771
superior laryngeal nerve injury as, 1770
extended, 1766, 1767f-1768f
extent of, 1768-1769
follow-up after, 1772
with intrathoracic goiter, 1766
management of regional lymphatics in, 1766
minimally invasive, 1769, 1769f
parathyroid glands during, 1752
postoperative management after, 1771-1772
external-beam radiotherapy and chemotherapy in, 1772
radioactive iodine treatment in, 1771-1772
thyroid hormone replacement in, 1771
during pregnancy, 1770
with recurrent laryngeal nerve invasion, 1766
reoperative, 1767-1768
Thyroidectomy
for Graves' disease
near-total, 1743
subtotal, 1743
minimally invasive, 1769, 1769f
robotic, 41-42
with total laryngectomy, 1566
with total laryngopharyngectomy, 1574
Thyroiditis, 1744
acute suppurative, 1744
Hashimoto's (autoimmune), 1747
oral manifestations of, 1251
ultrasound imaging of, 1644
painless or silent, 1744
subacute, 1743-1744
lymphocytic, 1744
Thyroid-stimulating antibody, 1741
Thyroid-stimulating hormone (TSH). *See* Thyrotropin (TSH).
Thyrometabolic status, measurement of, 1739-1740
Thyroperoxidase (TPO), in thyroid hormone synthesis, 1737f, 1738
Thyropharyngeal muscle, surgical anatomy of, 1543f
Thyroplasty, medialization, 904-911
advantages of, 908
arytenoid adduction *vs.,* 912-913
autologous temporalis fascia grafts for, 910
complications of, 911
disadvantages of, 908
factors affecting outcome of, 908
with Gore-Tex strip, 908, 910, 911f
historical aspects of, 904-905
implant placement in, 909-910, 910f
indications for, 905, 908
limitations of, 910
outcome measures for, 910
patient evaluation and selection for, 905
prefabricated implants for, 908, 908f, 910
prosthesis templates in, 909-910, 910f
technique for, 908-911, 909f
Thyrotoxicosis, 1741-1745
defined, 1741
ectopic, 1745
epidemiology of, 1741
etiology of, 1742, 1742t
exogenous, 1744
due to Graves' disease, 1742-1743
with Graves' ophthalmopathy, 1810
oral manifestations of, 1251
overt, 1741
pathophysiology of, 1742
subclinical, 1741, 1745
thyroid storm in, 1745
due to thyroiditis, 1744
due to toxic multinodular goiter, 1744-1745
due to toxic thyroid adenoma, 1744
Thyrotracheal anastomosis, cricoid resection with, for laryngeal stenosis, 2921, 2922f
Thyrotropin (TSH)
in control of thyroid function, 1738-1739
elevation of, due to nonthyroidal illness, 1748
and Graves' ophthalmopathy, 1807, 1809
serum measurement of, 1740, 1741f
for thyroid nodule, 1758
Thyrotropin (TSH) receptor, in thyroid carcinoma, 1752-1753
Thyrotropin-releasing hormone (TRH), in control of thyroid function, 1739
Thyroxine (T_4), 1737. *See also* Thyroid hormone(s).
oral synthetic, for hypothyroidism, 1748-1749
serum free, 1740
in thyrotoxicosis, 1742
Thyroxine-binding globulin (TBG), 1738
Thyroxine-binding protein (TBP), 1738
Tic douloureux, 248

Tidal volume, in infants, 2570
Tietz syndrome, deafness in, 2051t-2058t
Tight junctions, in perilymphatic-endolymphatic barrier, 2081, 2082f
TIL (tumor-infiltrating lymphocytes), genetic modification of, 13, 20-21
Times 1 adaptation exercise, 2375f, 2378
Times 2 adaptation exercise, 2375f, 2378
TIMM8A (translocase of mitochondrial inner membrane 8A) gene
  in deafness, 2051t-2058t
  in Mohr-Tranebjaerg syndrome, 2097
Tinactin (tolnaftate), for fungal otitis externa, 1954-1955, 1959t-1960t
Tinnitus, 2131-2138
  clinical evaluation of, 2137-2138
  comorbidities with, 2138
  deafferentation–loss-of-inhibition hypothesis of, 2133
  defined, 2131
  due to erythromycin, 2176
  and insomnia, 2138
  in Meniere's disease, 2335t, 2337
  with migraine, 2349
  neural plasticity and, 1886
  objective, 2131, 2132t
    pulsatile, 2131, 2132t
  due to quinine, 2176
  due to salicylates, 2175-2176
  due to small fenestra stapedotomy, 2034
  standardized outcome measures for, 2138
  subjective, 2132t
    defined, 2131
    epidemiology of, 2131
    idiopathic, 2131-2133
    patterns of hearing loss in, 2131-2132, 2132t
    somatic, 2132-2133, 2132t
    typewriter, 2133
  treatment strategies for, 2133-2137
    acoustic-based, 2133
      acoustic desensitization protocol as, 2135
      ambient stimulation as, 2133-2134
      combined with education and counseling, 2134-2135
      personal listening devices as, 2134
      total masking therapy as, 2134
    cognitive-behavioral, 2135
    electric stimulation as, 2136-2137
      via cochlear implants, 2137
      transcutaneous, 2136-2137
    pharmacologic, 2137
    transcranial magnetic stimulation as, 2135-2136
Tinnitus Handicap Inventory (THI), 2135, 2138
Tinnitus retraining therapy (TRT), 2134-2135
  for hyperacusis, 2139
Tinnitus-producing fibromuscular dysplasia, of carotid artery, endovascular treatment for, 1943
Tip links
  in auditory physiology, 1841f, 1842, 1843f
  composition of, 2072f, 2074
  in hair cell transduction, 2072f, 2073-2074
  in vestibular physiology, 2277-2278, 2279f
Tip projection, 520, 535-536
  in aesthetic analysis, 273-274, 277f
  autogenous cartilage struts for, 535-536, 536f
  cephalic rotation for, 519, 536, 549-550, 551f
  onlay tip cartilage grafts for, 535-536, 537f, 549-550, 550f-551f
  partial-transfixion *vs.* complete-transfixion incisions for, 535-536, 536f
  plumping grafts for, 535-536, 536f
  transdomal sutures for, 536
Tip ptosis, 484, 485f
  caudal extension graft for, 576, 576f
  due to overaggressive resection of caudal septum, 492, 492f
  revision rhinoplasty for, 590-593, 593f
  after rhinoplasty, 519, 520f
Tip recoil, 513, 513f
Tip rotation, in aesthetic analysis, 273-274, 277f
Tip support mechanisms, 519, 520f
Tirapazamine, with radiotherapy, 1041
Tissue adhesives, for facial trauma, 306
Tissue débridement, interventional bronchoscopy for, 1008-1009, 1010t
Tissue effects, of surgical laser, 28-30, 30f
Tissue engineering, in mandibular reconstruction, 1327-1328, 1328f
Tissue expansion
  for forehead repair, 363
  for hair loss, 384, 385f
  for scar revision, 296-298, 297f
  and skin flap viability, 1074
Tissue flaps, gene therapy for, 22-23
Tissue-radiation characterizations, 1039-1040, 1039f
Titanium, for craniofacial defect repair, 2657
Titanium chain link implants, for lagophthalmos, 2421
Titanium prostheses, for ossiculoplasty, 2006, 2025-2026, 2026t
TIV (trivalent inactivated influenza vaccine), to prevent otitis media, 2769
TIVA (total intravenous anesthesia), in children, 2592
Tl 201 (thallium 201) imaging, for hyperparathyroidism, 1784-1785
TLESR (transient lower esophageal sphincter relaxation), 954, 968
TLM. *See* Transoral laser microsurgery (TLM).
TLND (therapeutic lymph node dissection), for melanoma, 1114, 1116
TLRs. *See* Toll-like receptors (TLRs).
TM. *See* Tympanic membrane (TM).
TMC1 (transmembrane channel-like gene 1), in deafness, 2051t-2058t
TMDs. *See* Temporomandibular disorders (TMDs).
TMHS (tetraspan membrane protein of hair cell stereocilia) gene, in deafness, 2051t-2058t
TMIE (transmembrane inner ear expressed gene), in deafness, 2051t-2058t
TMJ. *See* Temporomandibular joint (TMJ).
Tmprss1 (transmembrane protease serine 1) gene, in murine deafness, 2058t-2060t
TMPRSS3 (transmembrane protease serine 3) gene, in deafness, 2051t-2058t
TMS (transcranial magnetic stimulation), for tinnitus, 2135-2136
TNE. *See* Transnasal esophagoscopy (TNE).
TNF (transnasal fiberoptic laryngoscopy), for extraesophageal reflux, 898
TNF (tumor necrosis factor), 609t-610t
TNF-α (tumor necrosis factor α), in gene therapy, 21
TNF-β (tumor necrosis factor β), 609t-610t
TNFerade, in gene therapy, 21
TNM classification. *See* Tumor-node-metastasis (TNM) classification.
TOAE (transitory otoacoustic emission), for otitis media, 2762
Tobacco
  and Graves' ophthalmopathy, 1807
  and skin flap survival, 1075
  and squamous cell carcinoma
    of head and neck, 1016
    of larynx, 1491, 1512-1513
    of oral cavity, 1293-1294, 1365
Tobacco smoke exposure, and otitis media, 2767
Tobramycin, for rhinosinusitis, 734-735, 735t
Tobramycin with dexamethasone (Tobradex), for otitis externa, 1952, 1959t-1960t
Tolerance, immune, 1023
Toll-like receptors (TLRs), 598
  activators of, 598
  and adaptive immune response, 598
  expression and distribution of, 598
  and host, 598
Tolnaftate (Tinactin), for fungal otitis externa, 1954-1955, 1959t-1960t
Tone(s), 1838-1839
Tone-pips, in auditory brainstem response testing, 1896-1897
Tongue
  anatomy of, 1297
  fungiform papillae on, 1208
  leukoplakia of, 1362f
  lymphatic drainage of, 1297, 1298f
  muscles and reflexes of, 1205
  neurologic examination of, 833
  physical examination of, 98
  in swallowing
    in oral preparatory stage, 1215, 1216f
    in oral stage, 1215, 1216f
  tactile sensitivity of, 1201, 1201f
  taste buds on, 1208
Tongue base
  anatomy of, 1359, 1359f
    radiographic, 1399f
  lymphatics of, 1361f
Tongue base cancer
  cervical lymph node metastasis of, 1361t
  clinical presentation of, 1365
  management of, 1369-1370
Tongue base extension, laryngeal cancer with, supraglottic laryngectomy for, 1555
Tongue base procedures, for obstructive sleep apnea, 259
Tongue base reconstruction, 1387-1391
  algorithm for, 1391f
  free flaps for, 1389
    lateral arm, 1389
    radial forearm, 1389
  goals of, 1387
  healing by second intention for, 1387-1388
  local flaps for, 1388
  primary closure for, 1387-1388
  regional flaps for
    latissimus dorsi, 1389
    pectoralis major myocutaneous, 1388-1389
    platysmal myocutaneous, 1389
  skin grafting for, 1388
  after total or subtotal glossectomy, 1389-1390
    innervated free latissimus dorsi musculocutaneous flap for, 1389-1390, 1390f
    microvascular reconstruction as, 1390
    money pouch–like method for, 1390, 1390f
    sensate fasciocutaneous flaps for, 1390-1391
Tongue base retraction, during pharyngeal swallow, 1217
Tongue carcinoma, 1305-1306
  advanced-stage, 1306
  cervical lymph node metastases of, 1306
  clinical presentation of, 1305
  composite resection of, 1305, 1305f-1306f
  differential diagnosis of, 1305
  epidemiology of, 1295, 1305
  etiology of, 1305
  gross pathology of, 1305f
  hemiglossectomy for, 1305-1306, 1305f
  hemimandibulectomy for, 1306f
  local invasion by, 1305, 1305f-1306f
  palatal augmentation prosthesis for, 1342-1343, 1344f

Tongue carcinoma *(Continued)*
reconstruction for, 1305-1306
survival with, 1306
wide local excision for, 1305
Tongue flaps, for oropharyngeal reconstruction, 1376
Tongue prosthesis, 1342-1343, 1344f
Tongue reduction surgery, for obstructive sleep apnea in children, 2609
Tongue resection, palatal augmentation prosthesis for, 1342-1343, 1344f
Tongue surgery, swallowing disorders due to, 1219
Tongue suspension, for obstructive sleep apnea in children, 2610
Tonic activity, in facial nerve monitoring, 2387, 2547, 2547f
Tonotopic map, 2060-2061, 2063f
Tonotopic map reorganization
age-related, 1877, 1879, 1882f
experimental studies of
after cochlear lesions, 1877-1878, 1878f-1879f
in adult subjects, 1878-1879, 1881f
in developmental model, 1878, 1880f
after long-term local excitation of cochlea, 1880-1881, 1883f
at subcortical levels, 1879-1880
mechanisms of
at cellular level, 1884
Hebb's postulate for, 1884, 1884f
long-term potentiation as, 1884
at systems level of
in adult subjects, 1883-1884
in developing subject, 1883
practical issues relating to, 1884-1886
for hearing loss in infants, 1885, 1885f
for other hearing disorders, 1885-1886
time course of, 1877
Tonotopic tuning
of afferent auditory neurons, 1845
of basilar membrane, 1840-1842, 1844f
of hair cells, 1844, 1844f
Tonsil(s)
anatomy of, 2783-2784
bacteriology of, 2785-2788
diagnostic assessment of, 2793-2794
in immune system, 605
immunology of, 2784-2785
lymphoma of, 1364f
physical examination of, 99
radiographic anatomy of, 1462-1463, 1464f
squamous cell carcinoma of, 1362f, 1369f
Tonsillar abscess, imaging of, 148, 148f
Tonsillar calcifications, 1411, 1412f
Tonsillar capsule, 2783
Tonsillar concretions, 2787-2788, 2788f
Tonsillar crypts, 2783-2784
Tonsillar fossae
anatomy of, 1359, 2784
cancer of
cervical lymph node metastasis of, 1361t
clinical presentation of, 1365
management of, 1369, 1369f
melanoma as, 1365f
Tonsillar hypertrophy, due to Epstein-Barr virus, 2786f
Tonsillar pillars, radiographic anatomy of, 1398f
Tonsillar reconstruction, 1383-1387
algorithm for, 1388f
free flaps for, 1386
with combined lateral and superior defects, 1386, 1387f
lateral arm and thigh, 1386-1387
radial forearm, 1386
healing by second intention for, 1383
local flaps for, 1384-1385
primary closure for, 1383-1384
pectoralis major, 1385, 1385f
platysmal myocutaneous, 1385
Tonsillar reconstruction *(Continued)*
regional flaps for
sternocleidomastoid myocutaneous, 1385-1386
temporalis, 1386
temporoparietal fascia, 1386
skin grafting for, 1384
Tonsillectomy
for acute otitis media, 2771
Coblation, 2796
electrocautery, 2797-2799
hemorrhage after, 2783f-2784f, 2794, 2799-2800, 2800f
hemostasis after, 2798-2799
history of, 2782
immunologic consequences of, 2785
indications for, 2794b, 2795
for obstructive sleep apnea
in children, 2608-2609
lingual, 259
subtotal, 2797
in vocal professional, 857
Tonsillitis, 1464f
chronic recurrent, 2795
complication(s) of, 2788-2790
nonsuppurative, 2788
parapharyngeal space abscess as, 2788-2789
peritonsillar infections as, 2788, 2789f
retropharyngeal space infections as, 2789-2790, 2789f
suppurative, 2788-2790
streptococcal, 2787
Tonsilloliths, 99, 2787-2788, 2788f
Tonsillopharyngitis, due to group A beta hemolytic *Streptococcus pyogenes,* 192
Tooth buds, 1259
Tooth development, 1259-1260
enamel organ in, 1259
root development in, 1260
stages of, 1260
Tooth eruption, 2617t
Tooth extractions, prior to radiation therapy, 1330-1331, 1330b
Tooth infections. *See* Odontogenic infections.
Tooth integrity, maintenance of, saliva in, 1141
Tooth pain, 1202-1203
Tooth root, development of, 1260
"Toothy" smile, 2417-2418
Topical anesthesia
for awake fiberoptic nasotracheal intubation, 124
for tracheobronchial endoscopy, 1000
for vocal professionals, 855
Topical decongestants, for obstructive sleep apnea, 257
Topical nasal corticosteroids, for nonallergic rhinitis, 700, 700t
Topical therapies, for external ear disorders, 1950-1962
acidifying agents as, 1959t-1960t
for acute bacterial otitis externa, 1953
for fungal otitis externa, 1954
for acute bacterial otitis externa, 1951-1953
acidifying agents as, 1953
antibiotics as, 1951-1953
failure to respond to, 1953, 1953t
options for, 1951-1953, 1951f
antibiotics as, 1959t-1960t
for acute bacterial otitis externa, 1951-1953
evidence-based data on, 1952
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1953-1954
resistance to, 1953
antifungals as, 1959t-1960t
for fungal otitis externa, 1954-1955
ototoxicity of, 1955
Topical therapies, for external ear disorders *(Continued)*
anti-inflammatories as
for eczematoid otitis externa, 1956-1957
mechanism of action of, 1951
antiseptics as, 1955
for fungal otitis externa, 1955
for cerumen impaction, 1957
options for, 1957, 1958t
for ear hygiene and chronic draining ear, 1957-1958, 1961f
for eczematoid otitis externa, 1955-1957
anti-inflammatory and immunosuppressive agents as, 1956-1957
options for, 1955
steroids as, 1955-1956
for fungal otitis externa, 1954-1955
acidifying agents as, 1954
antifungals as, 1954-1955
antiseptics as, 1955
options for, 1954
history of, 1950
immunosuppressive agents as, for eczematoid otitis externa, 1956-1957
mechanism of action of, 1950-1951
for antibiotics, 1951
for anti-inflammatories, 1951
for myringitis, 1955
steroids as
classes of, 1956, 1956t
for eczematoid otitis externa, 1955-1956
hypersensitivity reaction to, 1954
mechanism of action of, 1951
ototoxicity of, 1956
summary of available, 1959t-1960t
for viral infections, 1957, 1957f
options for, 1957
Topiramate, for neuropathic pain, 244t
Topognostic tests, for assessment of facial nerve function, 2382-2384
of lacrimal function, 2383
of salivary flow, 2384
of salivary pH, 2384
of stapedius reflex, 2383
of taste, 2383-2384
Torcular Herophili, 2489
Tornwaldt cyst, 1348-1349
imaging of, 148, 1416, 1416f
TORP. *See* Total ossicular replacement prosthesis (TORP).
TORS (transoral robotic surgery), for laryngeal cancer, 1560-1561
Torsemide, ototoxicity of, 2175
Torsional pendulum model, of cupular displacement, 2279-2283, 2282f
Torticollis
congenital, 2817, 2817f
paroxysmal, and migraine, 2351
Torus
of oral cavity, 1287, 1288f
mandibularis, 1287
palatinus, 99, 1287, 1288f
tubarius
of eustachian tube, 1869, 1869f
anatomy of, 1825
of oropharynx
anatomy of, 1359f
radiographic anatomy of, 1398f-1399f
of tube, 1359f
Total intravenous anesthesia (TIVA), in children, 2592
Total laryngectomy, 1563-1572
for advanced glottic cancer, 1497
for advanced supraglottic cancer, 1500
complication(s) of, 1570-1571
drain failure as, 1571
early, 1571

Total laryngectomy *(Continued)*
hematoma as, 1571
hypothyroidism as, 1571
infection as, 1571
late, 1571
pharyngocutaneous fistula as, 1571
stomal stenosis as, 1571
wound dehiscence as, 1571
historical development of, 1563-1564
indications for, 1564-1565
intraoperative conversion from conservation laryngeal surgery to, 1557-1558
vs. organ preservation surgery, 1564
with partial/total pharyngectomy, for hypopharyngeal cancer, 1430, 1431f
patient selection and workup for, 1565
pharyngeal reconstruction after, 1569-1570, 1570f
postoperative management of, 1570-1571
recurrence after, 1476
rehabilitation after, 1572
of swallowing, 1572
of voice (*See* Voice rehabilitation)
for subglottic cancer, 1501
technique for, 1565-1569
access to larynx in, 1566
airway management in, 1565-1566, 1565f
entry into larynx in, 1566, 1568f
entry into trachea in, 1566
incision in, 1565-1566, 1565f
inspection of specimen in, 1566-1568, 1569f
patient positioning in, 1565-1566
skeletonization of larynx in, 1566, 1567f
thyroid gland in, 1566
tracheoesophageal puncture in, 1568-1569, 1569f
tracheotomy in, 1566-1568
wound closure in, 1568-1569, 1569f
tracheal stoma after, 1570, 1571f
Total laryngopharyngectomy, 1572-1575
complication(s) of
early, 1575
functional swallowing problems as, 1575
late, 1575
stricture as, 1575
defined, 1572
historical development of, 1572
incision for, 1565f
indications for, 1573
patient selection and workup for, 1573
postoperative management of, 1574-1575
reconstruction after, 1574, 1574f-1575f
rehabilitation after, 1575
technique for, 1573-1574, 1573f
entry into pharynx in, 1573-1574
initial steps in, 1573-1574
neck dissection in, 1573
patient positioning and anesthetic considerations in, 1573
with superior mediastinal adenopathy, 1574, 1574f
thyroid gland in, 1574
voice after, 1575
Total laryngopharyngoesophagectomy, 1574, 1574f
for cervical esophageal cancer, 1430-1431
Total masking therapy, for tinnitus, 2134
Total ossicular replacement prosthesis (TORP), 2006
with absent stapes superstructure, 2024, 2025f
factors affecting success of, 2023
with ossicular discontinuity, 2008
results with, 2006
Total pharyngo-laryngo-esophagectomy, 1574, 1574f
for cervical esophageal cancer, 1430-1431
Townes-Brocks syndrome, deafness in, 2051t-2058t
Toxic epidermal necrolysis (TEN), 1239
Toxic exposure, olfactory loss due to, 636
Toxic multinodular goiter, 1744-1745
Toxic thyroid adenoma, 1744
Toxin dependent sleep disorder, 262t
Toxoplasma gondii infection
of brain, 223
of salivary glands, 1159-1160
Toxoplasmosis
lymphadenopathy due to, in children, 2818
salivary gland involvement in, 1159-1160
Toynbee maneuver, 1870
Toynbee test, of eustachian tube function, 1874
TPO (thyroperoxidase), in thyroid hormone synthesis, 1737f, 1738
TPO (temporoparietal-occipital) pedicle flaps, for hair loss, 385-387, 387f
complications of, 386-387
T1R(s) (T1 receptors), in gustatory transduction, 1209, 1210f
T2R(s) (T2 receptors), in gustatory transduction, 1209, 1210f
Trace amine–associated receptors (TAARs), 630-631
Trachea
anatomy of, 998-999, 999f
embryology of, 2925-2926
vascular compression of, 2925-2926
Tracheal anomaly(ies)
arterial compression as, 2925-2926
dysphagia due to, 2950t, 2953-2954, 2954f
tracheoesophageal fistula as, 2926
tracheomalacia as, 2925
vascular rings as, 2925
Tracheal foreign bodies
anesthesia for removal of, 2940
imaging of, 2938
symptoms of, 2938
Tracheal homograft transplantation, 2933, 2934f
Tracheal intubation, difficult, 121
Tracheal lacerations, 1634
Tracheal neoplasm(s), 1611-1624
anesthetic management with, 1617
classification of, 1611, 1612t-1613t
diagnosis of, 1616-1617
bronchoscopy in, 1616-1617
pulmonary function testing in, 1616
radiographic evaluation in, 1616, 1616f-1617f
symptoms, signs, and physical examination in, 1616
historical review of, 1611-1612
overview of, 1611
primary, 1611-1612
benign, 1612-1613, 1612t-1613t
chondroma as, 1612-1613
granular cell tumor as, 1612
hamartoma as, 1617f
hemangioma as, 1613
leiomyoma as, 1613
miscellaneous, 1613
squamous papilloma as, 1612
treatment of, 1619
classification of, 1612, 1612t
epidemiology of, 1612, 1613t
malignant, 1612t-1613t, 1613-1615
adenoid cystic carcinoma as, 1614, 1614f
carcinoid tumors as, 1615, 1615f
carinal resections for, 1619, 1621f-1623f
mucoepidermoid carcinoma as, 1615
other, 1614-1615
palliative treatment for, 1619-1624
release maneuvers for, 1618-1619, 1620f
squamous cell carcinoma as, 1613-1614, 1614f
subglottal resections for, 1619, 1620f
therapeutic bronchoscopy for, 1619-1622
tracheal resection and primary reconstruction for, 1617-1618, 1618f-1620f
Tracheal neoplasm(s) *(Continued)*
treatment of, 1617
unresectable, 1619-1624
staging of, 1612
secondary, 1611, 1612t, 1615-1616
treatment of, 1617-1619
for benign tumors, 1619
complications of, 1623-1624
for primary malignant tumors, 1617
anesthetic management in, 1617
carinal resections in, 1619, 1621f-1623f
release maneuvers in, 1618-1619, 1620f
subglottal resections in, 1619, 1620f
tracheal resection and primary reconstruction in, 1617-1618, 1618f-1620f
results of, 1622
for unresectable tumors, 1619-1624
therapeutic bronchoscopy in, 1619-1622
Tracheal prostheses, synthetic, for tracheal stenosis, 2934, 2934f
Tracheal resection, 1617-1618, 1618f-1620f
release maneuvers with, 1618-1619, 1620f
Tracheal stenosis, 943-952
due to anterior wall collapse, 951
cervical, 951, 951b, 951f
in children, 2925-2934
anomalies associated with, 2927
due to arterial compression, 2925-2926
classification of, 2927, 2927t
conservative management of, 2927-2928
diagnosis of, 2926-2927
dilation for, 2928, 2928f
embryology of, 2925-2926
endoscopic evaluation of, 2926-2927
imaging of, 2927
laser therapy for, 2928, 2929f
long-segment, 2926, 2926f
treatment of, 2934
open repair for, 2930-2934
complications of, 2934
costal cartilage tracheoplasty in, 2930-2931, 2931f
granulation at graft site with, 2931
long-segment, 2934
partial tracheal resection, posterior end-to-end anastomosis, and anterior repair with resected trachea in, 2933-2934
pericardial patch in, 2930, 2931f
segmental resection in, 2931-2932, 2932f
short-segment, 2934
slide tracheoplasty in, 2932-2933, 2933f
synthetic tracheal prostheses in, 2934, 2934f
tracheal homograft transplantation in, 2933, 2934f
wedge resection in, 2931, 2931f
short-segment, 2926, 2926f
treatment of, 2934
stents for, 2928-2930, 2930f
due to vascular rings, 2925
cicatricial membranous, 951
classification of, 944, 944t
complete, 951-952, 952f
diagnosis of, 2926-2927
dysphagia due to, 2954
local application of mitomycin C for, 946
long-segment, 2926, 2926f
pathophysiology of, 943-944, 944b
short-segment, 2926, 2926f
surgical management of, 943-952
for chronic disease, 947-952
endoscopic *vs.* open, 945
goals and assessment in, 944, 945f
planning for, 946-947
skin and mucosal grafts in, 946-947
timing of, 945
Tracheal stoma, after total laryngectomy, 1570, 1571f

Tracheal–innominate artery fistula, 1623
Tracheal–pulmonary artery fistula, 1623
Tracheitis, bacterial (exudative), 2809-2810
  clinical features of, 2809
  complications of, 2810
  diagnosis of, 2809, 2809f
  differential diagnosis of, 2806t
  endoscopy of, 2809, 2809f
  epidemiology of, 2809
  imaging of, 2809, 2809f
  management of, 2809-2810, 2809f
  pathogenesis of, 2809
  terminology for, 2809
Tracheobronchial endoscopy, 998-1012
  airway anatomy and nomenclature for, 998-999, 999f
  flexible fiberoptic, 1001-1007
    care of bronchoscopes for, 1001-1002
    diagnostic, 999b, 1003-1007
      for bronchial wash, 1003
      for bronchoalveolar lavage, 1003-1004
      for bronchoscopic brush sampling, 1007
      for endobronchial and transbronchial biopsy, 1004-1005, 1004f-1005f
      general approaches to, 1003
      for transbronchial needle aspiration, 1005-1007, 1005f-1006f
      for visual examination, 1003
    range and special features of bronchoscopes for, 1001, 1002t, 1003f
  imaging prior to, 999-1000
  indications for, 999, 999b
  innovations and future developments in, 1009-1011
    autofluorescence bronchoscopy as, 1009
    endobronchial ultrasonography as, 1011
    endoscopic/bronchoscopic lung volume reduction as, 1011
  interventional, 999b, 1007-1009
    for balloon bronchoplasty, 1009
    for endobronchial stent placement, 1009
    for foreign body removal, 1008
    general principles of, 1007-1008
    patient preparation and instrument selection for, 1008
    for tissue débridement, 1008-1009, 1010t
  patient discussion and informed consent for, 1000
  patient positioning and route of entry for, 1000
  rigid, 1000-1001
  sedation and airway management for, 1000
Tracheobronchial obstruction, in neonate, 2905
Tracheobronchoscopy. *See* Tracheobronchial endoscopy.
Tracheoesophageal diversion, for chronic aspiration, 931-932, 931f-932f
Tracheoesophageal fistula (TEF), 2926
  imaging of, 1409-1410
Tracheoesophageal puncture (TEP)
  in total laryngectomy, 1568-1569, 1569f, 1572
  transnasal esophagoscopy in, 984
  for voice prosthesis, 1459, 1599
    and radiation therapy, 1600, 1602b
    secondary, 1600
Tracheoesophageal (TE) speech
  physiology of, 1597, 1597f
  after total laryngectomy, 1572
Tracheoesophageal voice prosthesis, 1459
Tracheomalacia, 2925
  dysphagia due to, 2954
Tracheoplasty, 2930-2934
  balloon, 2928, 2928f
  complications of, 2934
  costal cartilage, 2930-2931, 2931f
  granulation at graft site with, 2931
  long-segment, 2934
Tracheoplasty *(Continued)*
  partial tracheal resection, posterior end-to-end anastomosis, and anterior repair with resected trachea in, 2933-2934
  pericardial patch in, 2930, 2931f
  segmental resection in, 2931-2932, 2932f
  short-segment, 2934
  slide, 2932-2933, 2933f
  synthetic tracheal prostheses in, 2934, 2934f
  tracheal homograft transplantation in, 2933, 2934f
  wedge resection in, 2931, 2931f
Tracheostoma, after total laryngectomy, 1570, 1571f
Tracheostomy, 125-126
  for deep neck space infections, 205
  and recurrent respiratory papillomatosis, 2887
  for Robin sequence, 2673
Tracheostomy tube, for children, 2906-2907
Tracheostomy tube insertion, in cricothyrotomy, 127, 128f
Tracheotomy
  for chronic aspiration, 927
  for difficult airway, 114t
  for obstructive sleep apnea, 260-261
    in children, 2610
  for stridulous child, 2906
    complications of, 2907
    emergency, 2904
    indications for, 2906, 2906t
    patient positioning for, 2906, 2907f
    preoperative planning for, 2906
    surgical decannulation of, 2907-2908
    surgical procedure for, 2906-2908, 2907f
    techniques to avoid, 2906, 2906f
    ward decannulation of, 2907
Tracking systems, for image-guided sinus surgery, 681
Traction diverticula, 986
Tragus, 476-477, 476f
  anatomy of, 1824f, 2742f
Tragus reconstruction, in microtia reconstruction, 2747, 2748f
"Train" activity, in facial nerve monitoring, 2387, 2547, 2547f
Tranquilizers, dizziness due to, 2310t
trans elements, 5f
Transantral approach, for middle cranial base surgery, 2455t, 2458, 2459f
Transantral orbital decompression, for Graves' ophthalmopathy, 1812-1814
  complications of, 1814
  modifications of, 1814
  outcome of, 1812-1814, 1813f-1814f
  technique for, 1812
    ethmoidectomy in, 1812, 1812f
    incisions into periorbital fascia in, 1812, 1813f
    removal of orbital floor in, 1812, 1813f
    sublabial buccogingival incision in, 1812, 1812f
Transantrosphenoidal approach, for middle cranial base surgery, 2455t, 2458, 2459f
Transbasal approach, for anterior cranial base surgery, 2453-2454, 2454f
Transbronchial biopsy (TBBX), flexible fiberoptic bronchoscopy for, 1004-1005, 1004f-1005f
Transbronchial needle aspiration (TBNA), flexible fiberoptic bronchoscopy for, 1005-1007, 1005f-1006f
Transcanal approach, for tympanoplasty, 2001, 2001f
Transcanal infracochlear approach, for skull base lesions requiring drainage, 2539, 2540f
Transcartilaginous approaches, for nasal tip refinement, 522, 523f-526f
Transcaruncular approach, for pediatric facial fracture, 2701-2702, 2705f
Transcervical approach, for excision of tumors in parapharyngeal space, 1174-1176, 1175f
Transcervical diverticulectomy, 991f
Transcervical incision and drainage, for deep neck space infections, 207
Transclival approach, for transnasal endoscopic-assisted anterior skull base surgery, 2479-2481, 2480f-2481f
Transcochlear approach
  to petrous apex, 2499-2500, 2500f
  for posterior fossa neoplasms, 2532t, 2537
    advantages and disadvantages of, 2532t, 2537
    basic features of, 2537
    indications for, 2532t, 2537
    surgical exposure in, 2537f
    technique of, 2537, 2537f
Transconjunctival blepharoplasty, 448-449, 450f
Transcranial electrical stimulation–induced facial motor evoked potentials, to assess facial nerve function, 2389
Transcranial magnetic stimulation (TMS), for tinnitus, 2135-2136
Transcranial motor evoked potential (tcMEP), for intraoperative monitoring, 2555, 2555f
Transcranial repair, for CSF rhinorrhea, 792
Transcribriform approach, for transnasal endoscopic-assisted anterior skull base surgery, 2482
  with bilateral access, 2482, 2482f
  with unilateral access, 2482
Transcription, of genes, 4, 5f, 11-12, 12f
Transcription factor cellular promotor 2-like 3 *(TFCP2L3)* gene, in deafness, 2051t-2058t
Transcutaneous carbon dioxide pressure ($TcPCO_2$), in skin flaps, 1068
Transcutaneous electric stimulation, for tinnitus, 2136-2137
Transcutaneous oxygen pressure ($TcPO_2$), in skin flaps, 1068
Transdomal suturing
  for nasal tip projection, 536
  for nasal tip refinement, 522, 530f-531f
Transduction channels, in hair cell transduction, 2071-2073
  effects of deficiencies of, 2079-2080
  gating of, 2073-2074
  ion selectivity of, 2073, 2073f
  structure of, 2076f
Transduction efficiency, with traditional hearing aid, 2204-2205
Transesophageal echosonography, 1396
Transethmoidal access, for transnasal endoscopic-assisted anterior skull base surgery, 2478-2479, 2479f-2480f
Transethmoidal encephalocele, 2687t
Transethmoidal sphenoidotomy, for middle cranial base surgery, 2455-2457, 2455t, 2456f
Transfacial approach, for middle cranial base surgery, 2464-2467, 2467f
Transfection, 15-16, 15f
Transfixion incision, for septoplasty, 488, 489f
Transforming growth factor (TGF), 609t-610t
Transforming growth factor α (TGF-α), in wound healing, 1076
Transforming growth factor β (TGF-β), 609t-610t
  in wound healing, 1076
Transglottic cancer
  anatomic basis for, 1486
  imaging of, 161, 164f, 1475f, 1476, 1478f
Transhyoid pharyngotomy approach, for oropharyngeal cancer, 1371, 1372f
Transient evoked otoacoustic emissions (TEOAEs), 1891, 1905
  with acoustic neuroma, 1891-1892, 1893f
  advantages of, 1891
  analysis of, 1905
  clinical applications of, 1905-1907

Transient evoked otoacoustic emissions (TEOAEs) *(Continued)*
defined, 1891, 1905
in infants, 2720-2721
in noise-induced hearing loss, 2146-2147, 2147f-2150f
with normal hearing, 1892f
Transient lower esophageal sphincter relaxation (TLESR), 954, 968
Transient receptor potential (TRP) channel, in gustatory transduction, 1209-1210
Transition register, 851
Transition voice, 851
Transition zones, of laryngeal carcinoma, 1489, 1490f
Transitory otoacoustic emission (TOAE), for otitis media, 2762
Translabyrinthine approach
for facial nerve decompression, 2041-2042
for intratemporal facial nerve surgery, 2411
advantages and uses of, 2411
limitations and complications of, 2411
technique of, 2411, 2411f-2412f
for posterior fossa neoplasms, 2530-2533, 2532t
advantages and disadvantages of, 2532t, 2533
basic features of, 2530
indications for, 2530, 2532t
requiring drainage, 2539
surgical exposure in, 2531f
technique of, 2530-2532, 2533f
tumor removal in, 2532-2533
Translation
of DNA, 4, 11-12, 12f
vs. head tilt, 2307, 2307f
with unilateral loss of function of, 2299-2300
anatomic and physiologic basis for, 2299-2300
clinical importance of, 2300, 2300f
Translational vestibulo-ocular reflexes, 2306-2307, 2309f
Translocase of mitochondrial inner membrane 8A *(TIMM8A)* gene
in deafness, 2051t-2058t
in Mohr-Tranebjaerg syndrome, 2097
Translocation, 4-5
Transmandibular approach, for middle cranial base surgery, 2455t, 2458, 2460f
Transmastoid approach
for facial nerve decompression, 2041-2042, 2411
for intratemporal facial nerve surgery, 2410-2411
advantages and uses of, 2411
limitations and complications of, 2411
technique of, 2410, 2410f
Transmastoid labyrinthine drainage, of cholesterol granuloma, 2540f
Transmaxillary approach, for transnasal endoscopic-assisted anterior skull base surgery, 2482-2483, 2483f
Transmembrane channel-like gene 1 *(TMC1),* in deafness, 2051t-2058t
Transmembrane inner ear expressed gene *(TMIE),* in deafness, 2051t-2058t
Transmembrane protease serine 1 *(Tmprss1)* gene, in murine deafness, 2058t-2060t
Transmembrane protease serine 3 *(TMPRSS3)* gene, in deafness, 2051t-2058t
Transmission, of laser energy, 28-29, 29f
Transnasal access, direct, for transnasal endoscopic-assisted anterior skull base surgery, 2477, 2477f
Transnasal endoscopic sinus approach, 742
Transnasal endoscopic-assisted anterior skull base surgery, 2471-2486
anesthesia for, 2476
combined approaches for, 2484
complications of, 2485
Transnasal endoscopic-assisted anterior skull base surgery *(Continued)*
craniocervical junction–odontoid approach for, 2483-2484, 2484f
instrumentation for, 2476
patient preparation for, 2475-2476
pedicled septal flap in, 2476-2477
postoperative care after, 2484-2485
preoperative assessment for, 2475, 2475f
reconstruction after, 2484
surgical anatomy for, 2471-2475
anterior cranial fossa in, 2471, 2472f
clivus in, 2474, 2474f
nasal cavity in, 2471-2473, 2472f-2473f
nasopharynx in, 2474
paranasal sinuses in, 2473-2474, 2473f
retroclival region in, 2474-2475, 2474f-2475f
surgical team setup for, 2476f
transcribriform approach for, 2482
with bilateral access, 2482, 2482f
with unilateral access, 2482
transmaxillary-transpterygoidal-infratemporal approach for, 2482-2483, 2483f
transsellar and parasellar approaches for, 2479, 2480f
transsphenoidal approach for, 2477-2481
with direct transnasal access, 2477, 2477f
with petrous apex access, 2481
with transclival access, 2479-2481, 2480f-2481f
with transethmoidal access, 2478-2479, 2479f-2480f
with transseptal access, 2477-2478, 2477f-2478f
with transseptal-transnasal access, 2478, 2479f
transtuberculum-transplanum approach for, 2482
Transnasal esophagoscopy (TNE), 981-985
accuracy of, 982
in Barrett's esophagitis, 983, 983f
complications of, 984
in dysphagia, 983-984, 984f
of early glottic carcinoma, 1516, 1516f
equipment for, 981, 982f
for extraesophageal reflux, 899
in head and neck oncology, 983
history of, 981
indications for, 983-984
normal findings in, 982-983, 983f
in stricture dilation, 984, 984f
technique for, 982, 982f
therapeutic applications of, 984
tolerance of unsedated examination in, 981-982
in transesophageal puncture, 984
Transnasal fiberoptic laryngoscopy (TFL), for extraesophageal reflux, 898
Transnasal pressure, in rhinomanometry
measurement of, 645-647, 648f
nasal airflow and, 643
Transoral approach
for middle cranial base surgery, 2455t, 2458, 2461f
for oropharyngeal cancer, 1370-1371, 1370f-1371f
Transoral esophagoscopy, for extraesophageal reflux, 899
Transoral incision and drainage, for deep neck space infections, 206-207
Transoral injection, for vocal fold medialization, 906
Transoral laser microsurgery (TLM)
for hypopharyngeal cancer, 1429-1430, 1442
outcomes of, 1436-1438
for laryngeal cancer, 1525-1538
advanced, 1531-1532, 1532f-1533f
complications of, 1533-1534, 1534f
conclusions on, 1536-1537
contraindications to, 1534
costs of, 1534
Transoral laser microsurgery (TLM) *(Continued)*
early, 1530-1531
glottic, 1496
supraglottic, 1498-1500
glottic
with anterior commissure involvement, 1497
in early stage, 1496
historical background of, 1527
instruments for, 1528-1529
intermediate, 1531
and neck dissection, 1532
vs. open conservation surgery, 1528
pathology issues with, 1530
and radiotherapy, 1532-1533
results of, 1534-1535
Gottingen Group, 1535-1536
supraglottic, in early stage, 1498-1500
techniques for, 1529-1530
theoretical basis of, 1527-1528
very advanced, 1532
very early, 1530
terms and definitions for, 1525-1526
Transoral robotic surgery (TORS), for laryngeal cancer, 1560-1561
Transorbital projection, of temporal bone, 131
Transotic approach, for posterior fossa neoplasms, 2532t, 2537-2538
advantages and disadvantages of, 2532t, 2538
basic features of, 2537
indications for, 2532t, 2537-2538
technique for, 2538, 2538f
Transpalatal advancement pharyngoplasty, for obstructive sleep apnea, 258, 260f
Transpalatal approach, for middle cranial base surgery, 2455t, 2458, 2461f
Transplantation
and cervical lymphadenopathy, 219
and hearing loss, 224-225
and non-Hodgkin's lymphoma, 213t, 215-216
posttransplantation lymphoproliferative disorder after, 213t, 215, 217
and sinonasal infection, 219-221
diagnosis of, 220-221, 220f
presentation and pathogenesis of, 219-220
treatment of, 221
and squamous cell carcinoma, 215
and xerostomia, 218
Transposition flaps, 344, 344f
for cheek defects, 358-359, 361f
bilobed, 357, 359f
rhombus shaped, 355
for lip defects, 353
for nasal defects, 348, 349f, 365-366, 366f
Transpterygoid approach, for transnasal endoscopic-assisted anterior skull base surgery, 2483
Transsellar approach, for transnasal endoscopic-assisted anterior skull base surgery, 2479, 2480f
Transseptal access, for transnasal endoscopic-assisted anterior skull base surgery, 2477-2478, 2477f-2478f
Transseptal coaptation sutures, 546-547, 547f
Transseptal sphenoidotomy, for middle cranial base surgery, 2455-2457, 2455t, 2456f
Transseptal-transnasal access, for transnasal endoscopic-assisted anterior skull base surgery, 2478, 2479f
Transsphenoidal approach, for transnasal endoscopic-assisted anterior skull base surgery, 2477-2481
with direct transnasal access, 2477, 2477f
with petrous apex access, 2481
with transclival access, 2479-2481, 2480f-2481f
with transethmoidal access, 2478-2479, 2479f-2480f
with transseptal access, 2477-2478, 2477f-2478f
with transseptal-transnasal access, 2478, 2479f

Transsphenoidal encephalocele, 2687t
Transsphenoidal-transclival approach, for transnasal endoscopic-assisted anterior skull base surgery, 2479-2481, 2480f-2481f
Transtemporal approach
  for intratemporal facial nerve surgery, 2407-2409
    advantages and uses of, 2408-2409
    for Bell's palsy, 2409-2410, 2409t-2410t
    limitations and potential complications of, 2409
    technique of, 2407-2408, 2408f-2409f
  for middle cranial base surgery, 2461
Transtracheal jet ventilation, for difficult airway, 114t
Transtracheal needle ventilation, 128-129
Transtuberculum-transplanum approach, for transnasal endoscopic-assisted anterior skull base surgery, 2482
Transverse arytenoid cartilage, 1542f
Transverse arytenoid muscle, 1359f
Transverse cervical artery
  anatomy of, 2579
  in root of neck, 2581-2582, 2581f
Transverse cervical lymph nodes
  anatomy of, 1360f
  in neck dissection, 1705f
Transverse cervical vein, 2579
Transverse crest, in surgical anatomy of lateral skull base, 2437f, 2439
Transverse electromagnetic mode (TEM), 27, 28f
Transverse sinus, in surgical anatomy of lateral skull base, 2436f, 2439f
Trapdoor flaps, 346
  for tracheal stenosis, 2928, 2929f
Trapdoor fracture, of orbital floor, pediatric, 2712, 2714f
Trapezius muscle, anatomy of, 2578f-2579f
Trapezius musculocutaneous flap, for oropharyngeal reconstruction, 1378-1379
Trapezoid body, in auditory pathway, 1846
Trauma
  acoustic, 2121-2122, 2121f-2122f, 2141
  chronic aspiration due to, 926b
  CSF rhinorrhea due to, 786b, 794-795
  esophageal, 941-942
    caustic, 942, 977-978
      clinical features of, 977
      etiology of, 977
      grading of, 977, 978t
      prognosis for, 977-978
      squamous cell carcinoma due to, 978
      strictures due to, 977-978, 978f-979f
    external, 941-942
    mechanisms of injury in, 933, 934f
  facial (*See* Facial trauma)
  laryngeal (*See* Laryngeal trauma)
  neck (*See* Neck trauma)
  peripheral vestibular disorders due to, 2343
    baro-, 2343
    nonpenetrating, 2343
      blast, 2343
      labyrinthine concussion as, 2343
    penetrating, 2343
  to salivary glands, 312, 313f
    in children, 2863-2865
    sialocele and salivary fistula due to, 313-314
  sensorineural hearing loss due to, 2121-2122, 2121f-2122f
    sudden, 2128
  soft tissue, 302-317
    approach to, 302-306
      anesthesia in, 304
      cleaning in, 304-305, 305f
      history taking in, 302-303
      infection control in, 305
      physical examination in, 303-304, 303f
      repair in, 305-306, 306f
      tetanus prophylaxis for, 303
Trauma *(Continued)*
    to ears, 308f, 310, 310f
    etiology of, 302
    to eye, 303
    to eyelids, 303, 303f, 307-309, 308f
    to facial nerve, 309
    to lacrimal apparatus, 307-309, 308f
    with large-segment, composite avulsions or amputations, 312, 312f
    to lips, 309-310, 309f
    to nose, 310-312, 311f
    to parotid duct, 312-313, 314f
    to salivary glands, 312, 313f
      sialocele and salivary fistula due to, 313-314
    types of injuries in, 306-307
      abrasion as, 306
      avulsions as, 307, 308f
      laceration as, 307
  temporal bone (*See* Temporal bone fractures)
  vertigo due to, 2039, 2201
Traumatic condition(s), of oral cavity, 1288-1290
  amyloidosis as, 1289-1290, 1290f
  fibroma as, 1288-1289, 1289f
  mucosal ulcerations as, 1289, 1289f
  necrotizing sialometaplasia as, 1289, 1299
  pyogenic granuloma as, 1289, 1289f
Traumatic facial paralysis, 2398-2399, 2398f
Traumatic granuloma, of oral cavity, 1240
  clinical features of, 1240, 1240f
  defined, 1240
  differential diagnosis of, 1240
  etiology of, 1240
  histopathologic features of, 1240, 1240f
  treatment of, 1240
Traumatic pharyngitis, 194, 194f
Traumatic tattoos, 305, 305f
Trautmann's triangle, in surgical anatomy of lateral skull base, 2436f
Traveling wave, in cochlear transduction
  active, 2062-2069, 2064f
  passive, 2060-2062, 2062f-2063f
Treacher Collins syndrome
  branchial arch structures in, 2585
  craniofacial abnormalities in, 2633-2635, 2633b, 2635f, 2646
  deafness in, 2051t-2058t, 2094t, 2096
TREACLE gene, in mandibulofacial dysostosis, 2633
Treacle protein, in deafness, 2051t-2058t
Treatment, assessment of, 53
Treatment bias, 53
Tregs (regulatory T cells), 602-603
Tremor
  defined, 840
  essential, laryngeal hyperfunction due to, 840-841
  voice (vocal), 840-841
Treponema denticola, 1252
Treponema pallidum
  oral manifestations of, 1252
  pharyngitis due to, 194
    in children, 2786
Treponema vincentii, Vincent's angina due to, 2786
Tretinoin (Retin A, Renova, Micro Retin A, Avita)
  for aging skin, 403-404
  with chemical peels, 392-393
  for chemoprevention of oral cancer, 1315
TRH (thyrotropin-releasing hormone), in control of thyroid function, 1739
Triamcinolone (Nasacort), for nonallergic rhinitis, 700t
Triangular fossa, of ear, 2742f
Triangularis muscle, 321f
Tricellulin *(TRIC)* gene, in deafness, 2051t-2058t, 2081
Trichilemmal cysts, 289
Trichion, 378-379
Trichloroacetic acid (TCA)
  for chemical peels, 392-393
    history of, 391, 393
    Jessner's solution before, 393
    postoperative care after, 394
    results of, 394f
    technique of, 393-394, 393f-394f
  for ear hygiene or chronic ear drainage, 1958
Trichoepithelioma, 292
Tricyclic antidepressants (TCAs)
  for migraine, 2350
  for neuropathic pain, 244-245
Trigeminal depression
  anatomy of, 1822, 1822f
  in surgical anatomy of lateral skull base, 2435f, 2436-2437
Trigeminal gasserian ganglion block, for neuropathic pain, 246t
Trigeminal impression
  anatomy of, 1823f
  in surgical anatomy of lateral skull base, 2435f
Trigeminal nerve
  intraoperative monitoring of, 2550, 2550f
  in olfactory stimulation, 628-629
  in surgical anatomy of anterior cranial base, 2473f
  in surgical anatomy of lateral skull base, 2439f
Trigeminal nerve block, 242
Trigeminal nerve toxicity, due to stereotactic irradiation, 2563
Trigeminal nerve transposition, for facial nerve paralysis, 2419
Trigeminal neuralgia, 248
  microvascular decompression for, facial nerve monitoring with, 2548-2549
  vs. myofascial pain dysfunction syndrome, 1284t
Trigeminal neuromas, 2522, 2522f
Trigeminal pain, 1203
Trigeminal schwannoma, 2512f
Trigeminal system, central projections of, 1203
Trigonocephaly, synostotic, 2642-2643, 2643f, 2648f
  front-orbital advancement for, 2645, 2654f
3,5,3′-Triiodothyronine (T_3), 1737. *See also* Thyroid hormone(s).
  serum free, 1740
  in thyrotoxicosis, 1742
TRIOBP, in deafness, 2051t-2058t, 2076
Trismus
  due to deep neck space infection, 185-186
  due to masticator space infection, 184, 186f
  due to paranasal sinus tumor, 1123
Trisomies, 5
Trisomy 21. *See* Down syndrome.
Trisomy E, inner ear anomalies in, 2735
Triticeal cartilage, 1542f
Trivalent inactivated influenza vaccine (TIV), to prevent otitis media, 2769
Trochlear nerve
  intraoperative monitoring of, 2549-2550, 2550f
  in surgical anatomy of lateral skull base, 2439f
Trochlear notch, 322f
Trolamine polypeptide oleate-condensate (Cerumenex), for cerumen removal, 1958t
Tropomycin–receptor kinase A, in thyroid carcinoma, 1753
Trotter's syndrome, *vs.* myofascial pain dysfunction syndrome, 1284t
TRP (transient receptor potential) channel, in gustatory transduction, 1209-1210
Trpm13, in murine deafness, 2058t-2060t
TRT (tinnitus retraining therapy), 2134-2135
  for hyperacusis, 2139
True vocal folds
  anatomy of, 1359f
    radiographic, 1472, 1472f-1473f
  carcinoma of, imaging of, 1474-1475, 1474f
  physical examination of, 100

Trufill (polyvinyl alcohol), for embolization, 1933
Tryptans, for migraines, 247
TSGs. *See* Tumor suppressor genes (TSGs).
TSH. *See* Thyrotropin (TSH).
TT. *See* Tensor tympani (TT).
t-test, 70-71
TTH (tension-type headache), 247
TTS (temporary threshold shift), 2121, 2141
TTS (through-the-scope) balloons, for esophageal strictures, 966
Tubal artery, 1870
Tubal lumen, of eustachian tube, 1867f, 1870
Tuberculosis (TB)
  cervical lymphadenopathy due to
    in children, 2818, 2819f
    in HIV-positive patients, 219
  deep neck space infections due to, 201
  laryngeal and tracheal manifestations of, 885-886, 886f, 892
  of oral cavity, 1250-1251
  otologic manifestations of, 2101-2103, 2102f-2103f
    otorrhea as, 2196
  pharyngitis due to, 195
  of salivary glands, 1158
    in children, 2858
Tuberculous esophagitis, 1405
Tuberculous nodal mass, 166f
Tuberculous otitis media, 2101-2103, 2102f-2103f
Tuberculous salivary gland infection, 1158
Tuberous sclerosis, oral manifestations of, 1257
Tubulotympanic recess, 1866
Tufted angioma (TA), 2824-2825
  Kasabach-Merritt phenomenon with, 2825
Tufted cell, of olfactory bulb, 628f
Tularemia, pharyngitis due to, 195
Tullio phenomenon, 2316
  due to acquired cholesteatoma, 2196
  with labyrinthine fistula, 1989
  in superior canal dehiscence syndrome, 2290, 2329-2330, 2339
Tumarkin attacks, due to intratympanic gentamicin, 2189
Tumor burden, in melanoma, 1111-1112
Tumor (T) classification, for melanoma, 1111, 1111t, 1113f
Tumor necrosis factor (TNF), 609t-610t
Tumor necrosis factor α (TNF-α), in gene therapy, 21
Tumor necrosis factor β (TNF-β), 609t-610t
Tumor suppressor genes (TSGs), 12
  in Fanconi's anemia, 1020
  in head and neck squamous cell carcinoma, 1016, 1020
  modification of, 21-22
Tumor ulceration, with melanoma, 1111-1112
Tumor vaccines, for head and neck squamous cell carcinoma, 1023-1024
Tumor-infiltrating lymphocytes (TIL), genetic modification of, 13, 20-21
Tumor-node-metastasis (TNM) classification
  for melanoma, 1111, 1111t
    metastatic (M) classification (distant metastases) in, 1111t, 1113
    nodal (N) classification (regional disease) in, 1111-1113, 1111t
    tumor (T) classification (localized disease) in, 1111, 1111t, 1113f
  for thyroid cancer, 1754, 1755t-1756t
Tuning, tonotopic
  of afferent auditory neurons, 1845
  of basilar membrane, 1840-1842, 1844f
  of hair cells, 1844, 1844f
Tuning curves, of basilar membrane, 1844, 1844f
Tuning fork testing, 97-98, 98t
Tunnel of Corti, 1832, 1832f
Turbinates
  anatomy and embryology of, 482-483
  hypertrophy of, 486
  and nasal breathing function, 641
  in surgical anatomy of anterior cranial base, 2472, 2472f
Turbinectomy, in vocal professional, 858
Turn-down flaps, 346
Turner's syndrome, 5
  oral manifestations of, 1257
Turn-in flaps, 346
Turricephaly, synostotic, 2645, 2645f
TVP muscle. *See* Tensor veli palatini (TVP) muscle.
TW (tympanometric width), with otitis media, 2762
T1WI (T1-weighted images), 134, 135f-136f
T2WI (T2-weighted images), 134, 135f-136f
Twisted nose
  rhinoplasty for, 551-554
    in noncaucasian patient, 573, 576f
    osteotomies in, 551-554
      intermediate, 553, 554f
      lateral, 552-554, 553f
      medial, 552-553, 552f-553f
    preoperative examination of, 551, 552f
    results of, 511f-512f, 553f-554f
    septal reconstruction in, 551
    spreader grafts in, 554, 555f
  varieties of, 552f
Two-flap palatoplasty, 2669-2670, 2670f
  surgical technique for, 2670-2671, 2670f-2671f
Two-hit effect, 6
Two-mass model, of phonation, 811
Two-thirds tumor, 1277
Two-wall decompression, of superior-lateral orbit, for Graves' ophthalmopathy, 1816
Tympanic anulus, 1825-1826, 1825f
Tympanic bone, 2434-2435, 2435f, 2439f
Tympanic canaliculus, 1822-1823
Tympanic cavity, 2585f
Tympanic cover layer, 2050
Tympanic membrane (TM)
  anatomy of, 1824-1825, 1825f
  in auditory physiology, 1839-1840, 1840f, 2018-2019
  in cochlear transduction, 2050-2060, 2062f
  hearing loss due to total loss of, 2019, 2019t
  in otitis media, 2761-2762
  physical examination of, 97, 98f
  in surgical anatomy of lateral skull base, 2436f
  tympanoplasty with atrophic and atelectatic, 2003-2004
Tympanic membrane perforation, 1969-1971
  diagnosis of, 1969, 1970f
  hearing loss due to, 2000, 2019, 2019t
    management of, 2022-2023
  management of, 1971
  with ossicular disruption, hearing loss due to, 2019, 2019t
  due to otitis externa, 1947
  pathogenesis of, 1970-1971, 1971f, 1971t
  repair of (*See* Tympanoplasty)
  due to small fenestra stapedotomy, 2034
  traumatic, 2038
Tympanic membrane sources, of otorrhea, 2195-2196, 2195b
Tympanic membrane surface electrode, electrocochleography with, 1894, 1894f
Tympanic part, of temporal bone, 320f, 1822f, 1823, 2010f
Tympanic segment
  anatomy of, 1826f
    surgical, 2404, 2404f
  vulnerability to injury of, 1826f, 1829
Tympanic sulcus, 2435
Tympanocentesis, for acute otitis media, 2771
Tympanogram, for nasopharyngeal carcinoma, 1354
Tympanomastoid fissure, 2010f
Tympanomastoid suture, 2434-2435, 2435f
Tympanomastoid suture line, 1822f, 1823
Tympanomeatal flap, in tympanoplasty, 2001, 2001f
  with lateral graft technique, 2002
  with medial graft technique, 2003, 2004f
Tympanomeningeal fissure, 2736
Tympanometric test, nine-step inflation-deflation, 1874
Tympanometric width (TW), with otitis media, 2762
Tympanometry, 1890-1891, 1890f
  for conductive hearing loss, 2020
  for eustachian tube assessment, 1874
  for otitis media, 2762
  for sensorineural hearing loss, 2117
Tympanoplasty, 1999-2005
  with atrophic and atelectatic tympanic membrane, 2003-2004
  cartilage, 2004-2005
  classification of, 1999
  defined, 1999
  formal procedure for, 2001
    anesthesia in, 2001
    approaches and incisions in, 2001-2002, 2001f
    graft placement in, 2002
      lateral graft (overlay) technique for, 2002-2003, 2002f
      medial graft technique for, 2003, 2004f
  functional considerations with, 1999-2000
  graft materials for, 2000
  minimalist techniques for, 2000-2002
  pediatric, 2005
  preoperative evaluation for, 2000
  with tympanosclerosis, 2003
Tympanosclerosis, 1974-1975
  audiometric correlates of, 2005-2006
  diagnosis of, 1974, 1974f
  epidemiology of, 1974
  management of, 1975, 1975f
  ossiculoplasty for, 2007-2008, 2024-2025
  pathogenesis of, 1974-1975, 1975f
  pathophysiology of, 2005
  tympanoplasty with, 2003
  with tympanostomy tubes, 2775
Tympanosquamous suture, 2434, 2435f
Tympanosquamous suture line, 1822f, 1823, 1824f
Tympanostomy tubes, 2773-2776
  blockage of, 2775
  chronic otitis media with, 1970-1971, 1981
  complications and sequelae of, 2774-2776
    cholesteatoma as, 2775
    displacement into middle ear as, 2775
    early extrusion as, 2775
    otorrhea as, 1971, 2774-2775
    persistent perforation as, 2775
    retained tubes as, 2775
    tube blockage as, 2775
    tube displacement into middle ear as, 2775
    tympanosclerosis, atrophy, and retraction pockets as, 2775
  indications for, 2774
  for otitis media
    acute, 2771
    with effusion, 2772
  placement of, 2773-2774
    aspiration of effusions during, 2773-2774, 2774f
    perioperative and postoperative ototopical drops for, 2774
    postsurgical follow-up after, 2774
  rationale for, 2773
  selection of, 2774
  water precautions with, 2775-2776
Tympanum, congenital malformations of. *See* Congenital aural atresia (CAA).

Type I error, 65, 66t
Type II error, 65, 66t
Typewriter tinnitus, 2133
Typical carcinoid (TC), of larynx, 1507

U

UARS (upper airway resistance syndrome), 251-252
  in children, 2602-2603
UDPGT (uridine diphosphate-glucuronosyl transferase), in head and neck squamous cell carcinoma, 1017
UES. *See* Upper esophageal sphincter (UES).
UGI (upper gastrointestinal) series, for dysphagia in children, 2949
ULC (upper lateral cartilage), of nose, 496, 497f, 509f
  revision rhinoplasty for collapse of, 585-586, 586f
Ulcer(s), contact, of vocal folds, 874-875, 874f
  diagnosis of, 875
  epidemiology of, 874
  due to extraesophageal reflux, 902, 902f-903f
  management of, 875
  pathophysiology and pathology of, 874
Ulceration(s)
  aphthous, 1289, 1289f
    in HIV, 227, 227f
    recurrent, 1236-1239
      clinical features of, 1237-1238
      defined, 1236-1237
      differential diagnosis of, 1238, 1238t
      etiology and pathogenesis of, 1237, 1237t
      herpetiform-type, 1238, 1238f
      histopathologic features of, 1239
      major, 1237-1238, 1238f
      minor, 1237, 1238f
      treatment of, 1239
  of melanoma, 1111-1112
Ulcerative colitis, oral manifestations of, 1254
Ulcerative oral mucosal lesions, 1231-1240
  erythema multiforme as, 1239-1240, 1254
    clinical features of, 1239, 1239f-1240f
    defined, 1239
    differential diagnosis of, 1239
    etiology and pathogenesis of, 1239
    histopathologic features of, 1239-1240
    treatment of, 1240
  herpes simplex infection as
    primary, 1235, 1252
      clinical features of, 1235, 1235f, 1252
      defined, 1235
      diagnosis of, 1235
      differential diagnosis of, 1235
      etiology and pathogenesis of, 1235
      treatment of, 1235, 1252
    recurrent, 1235-1236, 1252
      clinical features of, 1236, 1236f
      defined, 1235
      differential diagnosis of, 1236
      etiology and pathogenesis of, 1235-1236
      histopathology of, 1236, 1237f
      vs. recurrent aphthous stomatitis, 1238, 1238t
      treatment of, 1236
  mucous membrane (cicatricial) pemphigoid as, 1233-1235, 1254
    clinical differential diagnosis of, 1234, 1234t
    clinical features of, 1233-1234, 1233f-1234f
    defined, 1233
    etiology and pathogenesis of, 1233
    histopathologic features of, 1234-1235, 1234f
    treatment of, 1235
  pemphigus vulgaris as, 1231-1233, 1254
    clinical differential diagnosis of, 1232
    clinical presentation of, 1232, 1232f
    defined, 1231-1232
    etiology/pathogenesis of, 1232
Ulcerative oral mucosal lesions *(Continued)*
    histopathologic features of, 1232-1233, 1232f-1233f
    treatment of, 1233
  recurrent aphthous stomatitis as, 1236-1239
    clinical features of, 1237-1238
    defined, 1236-1237
    differential diagnosis of, 1238, 1238t
    etiology and pathogenesis of, 1237, 1237t
    herpetiform-type, 1238, 1238f
    histopathologic features of, 1239
    major, 1237-1238, 1238f
    minor, 1237, 1238f
    treatment of, 1239
  traumatic (eosinophilic) granuloma as, 1240
    clinical features of, 1240, 1240f
    defined, 1240
    differential diagnosis of, 1240
    etiology of, 1240
    histopathologic features of, 1240, 1240f
    treatment of, 1240
Ulnar forearm flap, for free tissue transfer, 1082t
Ultimobranchial body, 2584f-2585f
Ultra-frequency sounds, adverse effects of, 2149
Ultrasonic liposuction, 452
Ultrasonography (US), 137
  applications of, 143-144
  basics of, 1643-1644
  B-mode, 1643
  of deep neck space infections, 204-205
  Doppler, 137
    color, 1644
      of salivary glands, 1167-1168
    of oropharyngeal cancer, 1366
  endobronchial, 1011
  for fine-needle aspiration biopsy, 1653-1654, 1655f
    of parathyroid tumor, 1789
  of Graves' ophthalmopathy, 1810
  of head and neck cancer, 1647-1653
  for hyperparathyroidism, 1786, 1789f
  of infrahyoid neck, 143-144
  of metastatic lymphadenopathy, 143
  of neck masses, 1636-1637, 1637t
  of neck neoplasms, 1657
  parathyroid, 1644-1645, 1650f-1652f
  of pharynx and esophagus, 1396
  of salivary glands, 143, 1148-1149, 1149f, 1167, 1645-1647
    with acute infections, 1647
    with calculous lesions, 1647
    color Doppler, 1167-1168
    with cystic disease, 1647
    with parotid mass, 1654f
    in Sjögren's syndrome, 1647
    with submandibular pleomorphic adenoma, 1653f
  for swallowing disorders, 1219
  technique of, 1643-1644, 1645f
  terminology for, 1643
  of thyroid gland, 1644, 1757
    with colloid nodule with comet-tail or ring-down artifact, 1644, 1647f
    with cystic nodule, 1644, 1645f
    with lymph node metastases, 1644, 1648f-1649f
    with malignant tumor, 1644, 1646b, 1646f
    multinodular, 1644
    with recurrent thyroid carcinoma, 1644
    with solid hyperfunctioning nodule, 1644
    with solitary nodule, 1644
  utility and limitations of, 1644
  vocal cord, for stridor, 2901
Ultraviolet light exposure, and oral cancer, 1294, 1294f
Ultravoice, after total laryngectomy, 1572
Umami, 1207, 1209, 1213
Umbo, of tympanic membrane, 97, 98f, 1824, 1825f
Uncertainty, of all data, 60t, 64-65
Uncinate process
  anatomy of
    normal, 666-667, 666f-667f
    surgical, 739, 740f
  atelectatic, 668, 670f
  in endoscopic sinus surgery, 746, 746f, 750-751
  variations in, 668, 670f
Unimate, 38
Unipedicle advancement flaps, 345, 345f
Unithroid (levothyroxine, oral synthetic), for hypothyroidism, 1748-1749
Universal Newborn Hearing Screening (UNHS), 2719
University of Washington Quality of Life scale (UW-QOL), 56
Unknown primary
  melanoma of, 1109
  squamous cell carcinoma metastatic to neck from, 1641-1642, 1641t, 1664, 1665f
Unloading reflex, 1204, 1204f
Unrestricted toxicity, 603-604
Upper aerodigestive tract, in geriatric patients
  presbyphagia of, 237
    diagnostic testing for, 237
    treatment of, 237
  presbyphonia of, 234-237
    acoustic changes in, 236
    dental/mandibular changes in, 236
    factors affecting vocal quality in, 234, 235t
    glandular changes in, 236
    histologic changes in, 234-235, 235f
    laryngoscopic appearance in, 235-236
    mucosal changes in, 236
    respiratory changes in, 236
    and sense of taste, 236
    treatment of, 236-237
Upper airway obstruction
  after adenotonsillectomy, 2800
  in children (*See* Stridulous child)
  due to chronic adenotonsillar hypertrophy, 2789f-2790f, 2790-2793, 2795
  decongestion for, 655
  due to foreign body, 2936-2937
  in neonate
    expected, 2904-2905
    unexpected, 2905
      laryngeal, 2905
      supralaryngeal, 2905, 2905f
      tracheobronchial, 2905
  posterior to valve area, 655-656
  in Robin sequence, 2673
  sleep-related, 2607
  valve area stenting for, 655
Upper airway resistance syndrome (UARS), 251-252
  in children, 2602-2603
Upper airway stenosis, 943-952
  classification of, 944, 944t
  local application of mitomycin C for, 946
  pathophysiology of, 943-944, 944b
  surgical management of, 943-952
    for chronic disease, 947-952
      anterior glottic, 948
      due to anterior wall collapse, 951
      cervical tracheal, 951, 951b, 951f
      cicatricial membranous, 951
      complete glottic, 949-950
      complete tracheal, 951-952, 952f
      laryngeal release procedures in, 952
      posterior glottic, 948-949, 949f
      subglottic, 945f, 950-951
      supraglottic, 947-948
    endoscopic *vs.* open, 945
    goals and assessment in, 944, 945f

Upper airway stenosis *(Continued)*
microsurgical débridement in, 946, 946b, 946f
planning for, 946-947
skin and mucosal grafts in, 946-947
stent placement in, 947, 947f
timing of, 945
Upper deep cervical node, 1297f
Upper esophageal sphincter (UES)
anatomy of, 953, 954f
in GERD, 894-895
incompetence of, 1399
manometry of, 958, 959f
during pharyngeal swallow, 1216-1217, 1216f
physiology of, 954, 955f
Upper eyelid
aesthetic analysis of, 445, 446f
paralysis of, 2421
Upper eyelid blepharoplasty, 447-448, 447f-449f
Upper eyelid blepharoplasty incision, 328-329, 329f
Upper eyelid crease, 442, 443f
Upper eyelid ptosis
evaluation of, 446-447, 447f
repair of, 447-448, 447f-449f
Upper eyelid retractors, 444
Upper gastrointestinal (UGI) series, for dysphagia in children, 2949
Upper jugular lymph nodes, in neck dissection, 1704, 1704f-1705f, 1706t
Upper lateral cartilage (ULC), of nose, 496, 497f, 509f
revision rhinoplasty for collapse of, 585-586, 586f
Upper lip, of vocal folds, in mucosal wave propagation, 848-849
Upper lip defects
algorithm for, 351, 355f
large, 352
Upper motor neuron diseases, preoperative evaluation of, 106
Upper respiratory infection (URI)
olfactory loss after, 633-637
and otitis media, 2767
pediatric anesthesia with, 2594-2595
UPPP (uvulopalatopharyngoplasty), for obstructive sleep apnea, 251, 258, 258f, 259t
in children, 2609
Uremic stomatitis, 1255
Uridine diphosphate-glucuronosyl transferase (UDPGT), in head and neck squamous cell carcinoma, 1017
Urinary tract symptoms, of hyperparathyroidism, 1781
Urokinase, for flap salvage, 1075
US. *See* Ultrasonography (US).
USH1C, in deafness, 2051t-2058t
USH2A, in deafness, 2051t-2058t
USH3A, in deafness, 2051t-2058t
Usher syndrome (US)
clinical variants of, 2096
cochlear implant for, 2220
epidemiology of, 2096
genetic basis for, 2051t-2058t, 2074, 2077-2078, 2094t, 2096
genetic testing for, 2098
inheritance pattern of, 6, 8
inner ear anomalies in, 2735
interstereociliary linkages in, 2077
sensorineural hearing loss in, 2077-2078, 2096
adult-onset, 2118
Usherin
and deafness, 2051t-2058t, 2077
in stereocilia, 2076f
Utricle
anatomy of, 1851f, 1853f-1854f, 2278f
embryogenesis of, 1852
Utricle *(Continued)*
sensing of head tilt and translation with unilateral loss of function of, 2299-2300
anatomic and physiologic basis for, 2299-2300
clinical importance of, 2300, 2300f
in vestibular system
arrangement of, 2278, 2280f
estimated patterns of excitation and inhibition for, 2278, 2281f
morphologic polarizations of stereociliary bundles in, 2278, 2280f
Utricular macula. *See* Macula utriculi.
Utriculosaccular chamber, 1852
Utriculus. *See* Utricle.
Uveoparotid fever, facial paralysis in, 2400
Uvula
bifid, 2793, 2793f
physical examination of, 99
radiographic anatomy of, 1398f
squamous cell carcinoma of, 1368f
Uvulopalatal flap, for oropharyngeal reconstruction, 1377, 1377f
of soft palate, 1377f, 1381
Uvulopalatopharyngoplasty (UPPP), for obstructive sleep apnea, 251, 258, 258f, 259t
in children, 2609
Uvuolpalatoplasty, laser-assisted, in vocal professional, 858
UW-QOL (University of Washington Quality of Life scale), 56

V

VA. *See* Vestibular aqueduct (VA).
Vaccine(s)
for head and neck squamous cell carcinoma, 1023-1024
human papillomavirus, 1023-1024
to prevent hearing loss, 2161
to prevent otitis media, 2768-2769
for recurrent respiratory papillomatosis, 2890t
Vacuum-assisted closure (VAC) device, 307
and skin flap viability, 1074-1075
Vagal paragangliomas, 1661-1662
clinical presentation and diagnosis of, 1662
management of, 1662-1663
Vagus nerve
in deep cervical fascia, 2579f
intraoperative monitoring of, 2550-2552, 2551f
in root of neck, 2581f, 2582
surgical anatomy of
auricular branch in, 2440
in brainstem and cerebellum, 2439f
in infratemporal region, 2440f
in internal auditory canal, 2437f
in jugular foramen, 2438, 2439f-2440f
in posterior fossa, 2439f
in temporal bone, 2436f
Vagus nerve injury
in lateral skull base surgery, 2512
due to neck surgery, 1730
Valacyclovir (Valtrex)
with chemical peels, 392, 397
for herpes zoster oticus, 1948
Validation, psychometric, 55
Validation studies, for endoscopic sinus surgery simulator
for discriminant and concurrent validity, 47, 47f
vs. performance on other tests of innate ability, 48, 48t
for predictive validity, 48
Validity
external, 68-69, 68t, 69f
internal, 68-69, 68t, 69f
in psychometric validation, 55
Vallecula(e)
anatomy of
radiographic, 1397, 1463f, 1471f
surgical, 1543f
pseudo-, prevention of formation of, 1599-1600, 1601f
Vallecular cyst(s)
dysphagia due to, 2951-2952
imaging of, 1416f
stridor due to, 2898, 2898f
Valproic acid derivatives, for migraine, 2350
Valsalva maneuver, eye movements evoked by, 2316, 2316f
Valsalva test, of eustachian tube function, 1874
Value-based purchasing, 78
Valve area stenting, for airway obstruction, 655
Valvular damage, oral treatment considerations with, 1246t
Valvular disease, antibiotic prophylaxis with, 1248, 1249t
VAMP (vesicle-associated membrane protein), 2080-2081
van der Hoeve–de Kleyn syndrome. *See* Osteogenesis imperfecta (OI).
Vancenase (beclomethasone nasal), for nonallergic rhinitis, 700t
Vancomycin
ototoxicity of, 2177
sensorineural hearing loss due to, 2120
VAPP (Voice Activity and Participation Profile), 826, 826t
Variability measures, in acoustic analysis for voice evaluation, 829-830, 829t
Variable closure, laryngeal videostroboscopy of, 819
Variable expressivity, 7, 7f, 2088
Variance, analysis of, 71
Varicella vaccine (Zostavax), 2159
Varicella-zoster oticus, 1948, 1948f
clinical features of, 2159, 2159f
diagnosis of, 2159
management of, 2159
sensorineural hearing loss due to, 2119, 2159
sudden, 2127
temporal bone pathology in, 2159
vestibular neuritis due to, 2162
Varicella-zoster virus (VZV)
and Bell's palsy, 2391-2393
deafness and vertigo due to, 2159, 2159f
Meniere's disease due to, 2163
oral manifestations of, 1252
Ramsay Hunt syndrome due to, 2396
Vascular anatomy, of nose, 497, 682-684
anastomoses in, 682-683, 683f
anterior ethmoid artery in, 682, 684f
facial artery in, 682
greater palatine artery in, 682
internal maxillary artery in, 682
posterior ethmoidal artery in, 682-683
sphenopalatine artery in, 682
vidian artery in, 682, 683f
Vascular anomaly(ies), 2822-2834
arteriovenous malformations as, 2832, 2833f
capillary malformations as, 2832-2833, 2834f
classification of, 2823t
lymphatic malformations as, 2829-2830
associated conditions with, 2829-2830, 2831f
clinical assessment and behavior of, 2829, 2830f
diagnostic evaluation of, 2829
imaging of, 2824f, 2829
mandibular overgrowth with, 2823f
of salivary glands, 2861f
sclerotherapy for, 2830-2831
spontaneous resolution of, 2830, 2831f
surgery for, 2831, 2832f

Vascular anomaly(ies) *(Continued)*
neoplastic (*See* Vascular neoplasm(s))
of salivary glands, 2858
hemangiomas as, 2859-2860, 2860f
lymphatic malformations as, 2861f
venous malformations as, 2832
clinical presentation of, 2832, 2833f
imaging of, 2824f
treatment of, 2832, 2833f
Vascular complication(s)
of deep neck space infections, 207-208
of neck surgery, 1728-1729
carotid artery hemorrhage as, 1728
hematoma as, 1729
of internal jugular vein, 1728-1729, 1729f
of radiotherapy, 1048-1049
Vascular compression, of trachea, 2925-2926
Vascular disorder(s)
presbycusis due to, 232
sensorineural hearing loss due to, 2123, 2166
sudden, 2128-2129, 2199
vertigo due to, 2201-2202
with vestibular symptoms, 2351-2353, 2351f
cerebellar hemorrhage as, 2354f
cerebellar infarction as, 2353f
evaluation and management of, 2354f-2355f
lateral medullary syndrome as, 2352f, 2354f
lateral pontomedullary syndrome as, 2353f
vertebrobasilar insufficiency as, 2355f
Vascular endothelial growth factor(s) (VEGFs)
in head and neck squamous cell carcinoma, 1060
in laryngeal carcinoma, 1505
in nasopharyngeal carcinoma, 1700
and skin flap viability, 1073
in wound healing, 1077-1078
Vascular endothelial growth factor (VEGF) inhibitors, for head and neck squamous cell carcinoma, 1060
Vascular injury, due to penetrating neck trauma, 1630-1632, 1631t, 1632f-1633f
management of, 1632-1633, 1633f-1634f
Vascular lesions, endovascular therapy for, 1939-1943
dural arteriovenous fistulas as, 1940-1942, 1941f
epistaxis as, 1939-1940, 1940f
facial arteriovenous fistulas as, 1940, 1940f
facial vascular malformations as, 1942, 1942f
hemangiomas of face and neck as, 1942
pseudoaneurysms as, 1942, 1943f
tinnitus-producing fibromuscular dysplasia of carotid artery as, 1943
Vascular loops, sensorineural hearing loss due to, 2120
Vascular malformations. *See* Vascular anomaly(ies).
Vascular neoplasm(s), 290-291, 2823-2826
and bone resorption, 2826
cherry angiomas as, 290
complications of, 2825, 2826f-2827f
facial nerve involvement in, 2414
hemangioma as (*See* Hemangioma(s))
of salivary glands, 2859-2860, 2860f
kaposiform hemangioendothelioma as, 2824-2825, 2826f
and Kasabach-Merritt phenomenon, 2825
of larynx, 880-881
of neck, 1657
arteriovenous malformations as, 1662-1663
carotid paragangliomas as, 1657-1658
anatomy and physiology of, 1658-1659
classification of, 1660
clinical presentation and diagnosis of, 1659-1660
etiology of, 1659, 1659t
history of, 1657-1658
imaging of, 1658f, 1660-1661
malignancy of, 1660
multicentricity of, 1660-1661
Vascular neoplasm(s) *(Continued)*
observation for, 1661-1662
radiation therapy for, 1661
surgical management of, 1660-1661
epidemiology of, 1657-1659
jugular paragangliomas as, 1662f
nomenclature for, 1657
pathology of, 1657, 1658f
vagal paragangliomas as, 1661-1662
neck mass due to, 2817
port wine stain as, 291
pyogenic granuloma as, 290
salmon patch as, 290-291
tufted angioma as, 2824-2825
Vascular neuralgia, *vs.* myofascial pain dysfunction syndrome, 1284t
Vascular rings, 2925
Vascular supply
impairment of, in acutely raised skin flaps, 1067-1068, 1068f-1069f
to skin, purposes of, 1064
Vascular territories, in skin flaps, 1067-1068, 1068f
Vascularized bone flaps, for free tissue transfer, 1082t, 1084-1087
fibula, 1082t, 1084-1085, 1085f
iliac crest, 1082t, 1087
radial forearm, 1082t, 1085-1086, 1086f-1087f
scapula, 1082t, 1086-1087, 1088f
Vasoactive intestinal peptide (VIP), in salivary gland secretion, 1137
Vasodilation, in salivary glands, 1137
Vasodilators
for Meniere's disease, 2337-2338
oral sequelae of, 1247t-1248t
and skin flap viability, 1073
Vasomotor rhinitis, 619b, 695, 698
VBRT. *See* Vestibular and balance rehabilitation therapy (VBRT).
VC (verrucous carcinoma)
of larynx, 1505-1506, 1505f
of oral cavity, 1299
VCA (viral capsid antigen), of Epstein-Barr virus, 1352, 1354
VCFS (velocardiofacial syndrome)
anterior glottic web in, 2899, 2900f, 2913
cleft lip and palate in, 2673-2674, 2674f
craniofacial anomalies in, 2646
VCR (vestibulocollic reflex), 1851, 2276, 2307-2308
VDS (Verbal Descriptor Scale), 240
Vectors
DNA, 15-16, 15f
nonviral, 16, 19f
viral, 16-18, 18t, 19f
adeno-associated virus as, 18, 18t
adenoviruses as, 17-18, 17f, 18t
retroviruses as, 16, 17f, 18t
Vecuronium, for pediatric anesthesia maintenance, 2593t
VEGFs. *See* Vascular endothelial growth factor(s) (VEGFs).
Vein of cochlear aqueduct, 1856f
Vein of Labbé, 2489
Vein of round window, 1856f
Vein of vestibular aqueduct, 1856f
Velar port, 2676
Velocardiofacial syndrome (VCFS)
anterior glottic web in, 2899, 2900f, 2913
cleft lip and palate in, 2673-2674, 2674f
craniofacial anomalies in, 2646
Velocity storage, brainstem in, 2296, 2308
Velocity-to-position integration, brainstem in, 2296, 2297f-2298f
Velopharyngeal closure, during pharyngeal swallow, 1216
Velopharyngeal closure pattern, 2680, 2680f
Velopharyngeal dysfunction (VPD), 2676-2685
approaches to diagnosis and management of, 2678
assessment of, 2678-2680
general speech analysis in, 2678-2679, 2678f, 2678t-2679t
imaging studies in, 2679
nasometry in, 2679, 2679f
pressure flow in, 2679
speech endoscopy in, 2680, 2680f
speech videofluoroscopy in, 2679-2680
causes of, 2678
defined, 2678
phoneme-specific, 2679
treatment of, 2680-2684
prosthetics for, 2681-2682, 2681f-2682f
speech therapy for, 2680-2681
articulation in, 2681
compensatory strategies in, 2681
resonance in, 2681
surgical intervention(s) for, 2682-2684
choice of, 2684
double-opposing Z-plasty palatoplasty as, 2682-2683
levator repositioning as, 2682
pharyngeal flap as, 2683
pharyngoplasty as, 2683
posterior wall augmentation as, 2683-2684
Velopharyngeal function, 2676
acoustic assessment of, 830
aerodynamic assessment of, 828t, 829
anatomic basis for, 2676, 2677t
Velopharyngeal inadequacy, defined, 2678
Velopharyngeal insufficiency
after adenotonsillectomy, 2800
defined, 2678
impact of, 2679
after palatoplasty, 2673
Velopharyngeal mislearning, 2678-2679
Velopharyngeal port, 2676
Velopharyngeal sphincter, in cleft palate, 2666-2667
Velopharynx
functional anatomy of, 2676, 2677t
muscles of, 2676, 2677t
VEMPs (vestibular evoked myogenic potentials), 2300, 2324, 2325f
in Meniere's disease, 2337
in superior canal dehiscence syndrome, 2341
Venlafaxine, for neuropathic pain, 244-245, 245t
Venous lakes, 288f, 291
Venous malformations, 2832
clinical presentation of, 2832, 2833f
imaging of, 2824f
of neck, 2817
of salivary glands, 1172
treatment of, 2832, 2833f
embolization for, 1942, 1942f
Venous outflow, of skin flaps, 1068
Venous stroke, due to lateral skull base surgery, 2513
Vent, for hearing aids, 2270
Ventilating bronchoscope, 2903, 2903f
Ventilation
control of, in children, 2569-2570
difficult (*See* Difficult airway)
larynx in, 808-809, 808f-809f
Ventilation tubes, for otitis media, with cleft palate, 2675
Ventilation-perfusion relationships, in children, 2570, 2571t
Ventral acoustic stria, 1835, 1835f
Ventral cochlear nucleus, 1835, 1845
Ventral nucleus of trapezoid body (VNTB), in auditory pathway, 1834f
Ventral stria, in auditory pathway, 1846
Ventricular ligament, surgical anatomy of, 1544f

Veramyst (fluticasone furoate), for nonallergic rhinitis, 700t
Verapamil, and skin flap viability, 1073
Verbal Descriptor Scale (VDS), 240
Vergence eye movements, 2305-2306, 2306f, 2307t
  evaluation of, 2314
Verification, of hearing aids, 2273
Vermilion border, 1295f, 1296-1297
Verocay bodies, in schwannomas, 1663
Verruca vulgaris, 282-283
  filiform, 282, 282f
  flat, 282, 283f
  due to molluscum contagiosum, 282-283, 283f
Verruciform xanthoma, oral, 1229
  clinical features of, 1229
  defined, 1229
  etiology and pathogenesis of, 1229
  histopathologic/diagnostic features of, 1229
  treatment of, 1229
Verrucous carcinoma (VC)
  of larynx, 1505-1506, 1505f
  of oral cavity, 1299
Verrucous hyperplasia, of oral cavity, 1299
Verrucous leukoplakia, proliferative, 1225, 1225f
Vertebral artery, 2351f
  in root of neck, 2581-2582, 2581f
  in surgical anatomy of anterior skull base, 2481f
  in surgical anatomy of lateral skull base, 2439f
Vertebral osteophytes, compression of pharynx and esophagus due to, 1408, 1409f
Vertebrobasilar arterial occlusion, sensorineural hearing loss due to, 2123
Vertebrobasilar insufficiency, 2355f
Vertex resistance, in rhinomanometry, 650
Vertical buttresses, 331, 331f
Vertical closure level, laryngeal videostroboscopy of, 821
Vertical crest, in surgical anatomy of lateral skull base, 2437-2439
Vertical hemilaryngectomy, 1547-1549
  complications of, 1549
  extended, 1548
  frontolateral, 1548
  functional outcome of, 1548
  with imbrication laryngoplasty, 1548, 1548f
  key surgical points for, 1549
  oncologic results of, 1547-1548, 1547t-1548t
  posterolateral, 1548
  surgical technique for, 1548
Vertical hemilaryngectomy (VHL)
  for glottic cancer, 1496, 1518f, 1519t, 1547-1549
    with anterior commissure involvement, 1497
  historical background of, 1540
  radiographic appearance after, 1476, 1479f
Vertical laryngoplasty, for chronic aspiration, 928-929, 930f
Vertical partial laryngectomy, 1540, 1547
Vertical phase, of vocal fold vibration, 848-849
Vertical ramus, biomechanics of, 333
Vertical slot defect, after scalp reductions, 385, 386f
  Frechet triple flap repair for, 385, 386f
Vertical transmission, 2088
Vertico-ocular reflex, in vestibular compensation, 2375
Vertigo, 2201-2202. *See also* Dizziness.
  ablative surgery for
    labyrinthectomy as, 2366-2368, 2367f
    patient selection for, 2364-2366
      clinical history in, 2364-2365
      consideration of other potential treatments in, 2366
      identification of intracranial pathology in, 2366
      identification of offending labyrinth in, 2365-2366
      poor compensation *vs.* unstable labyrinthine disease in, 2364, 2365t
Vertigo *(Continued)*
    residual hearing and selection of procedure in, 2366
    therapeutic trial of vestibular rehabilitation in, 2365
    vestibular testing in, 2365, 2365b
  vestibular compensation after, 2370
  vestibular nerve section as, 2368-2370, 2368f-2369f
  acute vestibular, systemic steroids for, 2184
  alternobaric, 2343
  anatomic and physiologic basis for, 2289
  benign paroxysmal of childhood, and migraine, 2350-2351
  benign paroxysmal positional, 2330-2332
    diagnosis of, 2330-2331
      findings on examination in, 2330-2331, 2331f
      history in, 2330
      test results in, 2331
    etiology of, 2330
    historical background of, 2329-2330
    horizontal canal
      positional testing for, 2315-2316, 2331
      repositioning maneuver for, 2332
    incidence of, 2330
    mechanism of, 2330-2332
    and migraine, 2350
    posterior canal
      anatomic and physiologic basis for, 2288-2289, 2288f
      conversion of, 2332
      positional testing for, 2315, 2315f, 2331, 2331f
      repositioning maneuver for, 2331-2332, 2332f
      surgical treatment of, 2332
    superior canal
      positional testing for, 2331
      repositioning maneuver for, 2332
    treatment of
      with repositioning, 2331-2332, 2332f
      surgical, 2332, 2360-2361, 2360f-2361f
      vestibular rehabilitation for, 2376, 2378t
  central (*See* Central vestibular disorder(s))
  cervical, 2354
  defined, 2308-2310, 2329, 2346
  duration of, 2329
  epidemic, 2332-2333 (*See also* Vestibular neuritis)
  etiology of, 2201-2202, 2201b
  history of, 2329
  due to hypothyroidism, 1747
  intractable, intratympanic gentamicin for, 2185-2189
    clinical protocols for, 2187-2188
    complications of, 2188-2189
    concentration of, 2188
    dose of, 2188
    indications and contraindications for, 2189
    injection interval for, 2188
    mechanism of action of, 2185-2186
    number of injections of, 2188
    pharmacokinetics of, 2186-2187, 2186f-2187f
    practical considerations with, 2188
  labyrinthine, 2201-2202
  in Meniere's disease, 2202, 2335t
  migrainous, 2202, 2347-2348, 2348f
  peripheral (*See* Peripheral vestibular disorder(s))
  retrocochlear, 2202
  due to small fenestra stapedotomy
    intraoperative, 2034
    postoperative, 2030, 2034
  due to temporal bone fracture, 2039
  time course of, 2201, 2201b
  due to varicella-zoster virus, 2159, 2159f
Very large G-protein–coupled receptor 1 *(VLGR1)* gene, in deafness, 2051t-2058t, 2077
Vesicle-associated membrane protein (VAMP), 2080-2081
Vesicular glutamate transporter-1 *(VGLUT1)* gene, in deafness, 2081
Vesicular glutamate transporter-3 *(VGLUT3)* gene, in deafness, 2051t-2058t, 2081
Vesiculobullous oral mucosal lesions, 1231-1240
  erythema multiforme as, 1239-1240, 1254
    clinical features of, 1239, 1239f-1240f
    defined, 1239
    differential diagnosis of, 1239
    etiology and pathogenesis of, 1239
    histopathologic features of, 1239-1240
    treatment of, 1240
  herpes simplex infection as
    primary, 1235, 1252
      clinical features of, 1235, 1235f, 1252
      defined, 1235
      diagnosis of, 1235
      differential diagnosis of, 1235
      etiology and pathogenesis of, 1235
      treatment of, 1235, 1252
    recurrent, 1235-1236, 1252
      clinical features of, 1236, 1236f
      defined, 1235
      differential diagnosis of, 1236
      etiology and pathogenesis of, 1235-1236
      histopathology of, 1236, 1237f
      vs. recurrent aphthous stomatitis, 1238, 1238t
      treatment of, 1236
  mucous membrane (cicatricial) pemphigoid as, 1233-1235, 1254
    clinical differential diagnosis of, 1234, 1234t
    clinical features of, 1233-1234, 1233f-1234f
    defined, 1233
    etiology and pathogenesis of, 1233
    histopathologic features of, 1234-1235, 1234f
    treatment of, 1235
  pemphigus vulgaris as, 1231-1233, 1254
    clinical differential diagnosis of, 1232
    clinical presentation of, 1232, 1232f
    defined, 1231-1232
    etiology/pathogenesis of, 1232
    histopathologic features of, 1232-1233, 1232f-1233f
    treatment of, 1233
  recurrent aphthous stomatitis as, 1236-1239
    clinical features of, 1237-1238
    defined, 1236-1237
    differential diagnosis of, 1238, 1238t
    etiology and pathogenesis of, 1237, 1237t
    herpetiform-type, 1238, 1238f
    histopathologic features of, 1239
    major, 1237-1238, 1238f
    minor, 1237, 1238f
    treatment of, 1239
  traumatic (eosinophilic) granuloma as, 1240
    clinical features of, 1240, 1240f
    defined, 1240
    differential diagnosis of, 1240
    etiology of, 1240
    histopathologic features of, 1240, 1240f
    treatment of, 1240
Vestibular ablation
  intratympanic gentamicin for, 2185-2189
    clinical protocols for, 2187-2188
    complications of, 2188-2189
    concentration of, 2188
    dose of, 2188
    indications and contraindications for, 2189
    injection interval for, 2188
    mechanism of action of, 2185-2186
    number of injections of, 2188
    pharmacokinetics of, 2186-2187, 2186f-2187f
    practical considerations with, 2188
  labyrinthectomy for, 2366-2368, 2367f
  patient selection for, 2364-2366

Vestibular ablation *(Continued)*
clinical history in, 2364-2365
consideration of other potential treatments in, 2366
identification of intracranial pathology in, 2366
identification of offending labyrinth in, 2365-2366
poor compensation *vs.* unstable labyrinthine disease in, 2364, 2365t
residual hearing and selection of procedure in, 2366
therapeutic trial of vestibular rehabilitation in, 2365
vestibular testing in, 2365, 2365b
vestibular compensation after, 2370
vestibular nerve section for, 2368-2370, 2368f-2369f
Vestibular afferent nerve fibers
encoding by, 2283-2285, 2284f
firing rate of, 2278-2279, 2281f
interpretation of excitation of, 2289
anatomic and physiologic basis for, 2289
clinical importance of, 2289-2290
for nystagmus during caloric testing, 2290
in posterior canal benign paroxysmal positional vertigo, 2289-2290
in superior canal dehiscence syndrome, 2290, 2290f
irregular, 2284-2285, 2284f
morphology of, 2283, 2283f
regular, 2283-2285, 2284f
synaptic morphology and function of, 1857-1859, 1859f-1860f
Vestibular and balance rehabilitation therapy (VBRT), 2372-2
adaptive capabilities and, 2327
as adjunctive modality, 2377
assessment for, 2376
clinical history in, 2376
vestibular testing in, 2376
basis of, 2302
expected results of, 2379
goals of, 2372, 2373f-2374f
history of, 2372
patient education on, 2379
patient selection criteria for, 2376-2377
as adjunctive modality, 2377
balance function studies in, 2376-2377
inappropriate candidates in, 2377
as primary treatment modality, 2376-2377
as therapeutic trial, 2377
physiologic rationale for, 2373-2376
dynamic compensation in, 2374-2376
static compensation in, 2374
positional testing after, 2373f-2374f
posturography in, 2326
as primary treatment modality, 2376-2377
techniques for, 2372-2373, 2378-2379, 2378t
adaptation exercises as, 2372-2373, 2375f, 2378
balance and postural control exercises as, 2372-2373, 2378-2379
conditioning activities as, 2372-2373, 2379
gait exercises as, 2372-2373, 2378-2379
habituation exercises as, 2372-2373, 2378
maintenance activities as, 2372-2373, 2379
sensory substitution exercises as, 2372-2373, 2378
therapeutic trial of, 2365, 2377
for uncompensated vestibular neuritis, 2365t
videonystagmography after, 2373f-2374f
Vestibular apparatus
embryology of, 1851-1852, 1851f
peripheral
autonomic supply of, 1854
efferent innervation of, 1854, 1855f
Vestibular aqueduct (VA)
anatomy of, 1823f, 1832, 2010f
enlarged, 2733-2734
in adults, 2344, 2344f
clinical manifestations of, 2734
in combination with other anomalies, 2728, 2738, 2739f
and CSF leakage, 2735-2736, 2736f
embryology of, 2733-2734
imaging of, 1921, 2733
CT for, 1921, 1923f, 2733, 2733f
MRI for, 1921, 1923f, 2733, 2733f
incidence of, 2727, 2733
treatment of, 2734, 2739
in surgical anatomy of lateral skull base, 2435f
Vestibular Autorotation Test, 2323-2324, 2324f
Vestibular cecum, 1853f
Vestibular commissural system, 1863, 1863f
Vestibular compensation, 2300-2302
anatomic and physiologic basis for, 2300-2302, 2301f
assessment of, 2376
clinical history in, 2376
vestibular testing in, 2376
clinical implications of, 2302
defined, 2373-2374
dynamic, 2373-2376
effect of suppressive drugs on, 2302
postoperative, 2370
static, 2373-2374
with static *vs.* fluctuating loss of vestibular function, 2302
and vestibular rehabilitation, 2302
Vestibular deafferentation syndrome, acute, due to intratympanic gentamicin, 2189
Vestibular decompensation, 2370
Vestibular deficits, static *vs.* fluctuating, 2302
Vestibular destructive therapy, for Meniere's disease, 2126
Vestibular disorder(s)
associated with migraine, 2350
benign paroxysmal positional vertigo as, 2350
Meniere's disease as, 2350
central (*See* Central vestibular disorder(s))
due to noise, 2148
peripheral (*See* Peripheral vestibular disorder(s))
related to migraine, 2350-2351
benign paroxysmal vertigo of childhood as, 2350-2351
paroxysmal torticollis as, 2351
Vestibular efferent nerve fibers, 2285
Vestibular end organ(s)
anatomy of, 1853f, 1854-1855, 2277, 2278f
ampulla in, 1851f-1852f, 1854
crista ampullaris in, 1854, 1856f-1857f
cupula in, 1855, 1857f
endolymph in, 1855
hair cells in, 1854-1855, 1856f
kinocilium in, 1854-1855, 1856f
macula sacculi in, 1855, 1856f-1858f
macula utriculi in, 1855, 1856f-1858f
otolith membrane in, 1855, 1858f
otoliths in, 1855, 1858f
stereocilia in, 1854-1855, 1856f
striola in, 1855, 1858f
supporting cells in, 1854-1855
blood supply to, 1854, 1856f
Vestibular evoked myogenic potentials (VEMPs), 2300, 2324, 2325f
in Meniere's disease, 2337
in superior canal dehiscence syndrome, 2341
Vestibular eye movements, 2307t
Vestibular function, 2305-2308
assessment of, in infants, 2722
bilateral loss of, 2344
brainstem and cerebellum in, 2308
Vestibular function *(Continued)*
eye movements in, 2305-2307, 2306f-2307f, 2307t, 2309f
head movements in, 2307-2308
peripheral anatomy and physiology in, 2305
unilateral loss of, adaptation of vestibular reflexes with, 2300-2302
anatomic and physiologic basis for, 2300-2302, 2301f
clinical implications of, 2302
Vestibular ganglion, 1852-1854
Vestibular ganglionitis. *See* Vestibular neuritis.
Vestibular hair cells, excitation-inhibition asymmetry of, 2290-2291, 2291f
Vestibular labyrinth, intratympanic delivery of medications to. *See* Intratympanic delivery.
Vestibular ligament, 1542f
Vestibular nerve
anatomy of
in auditory system, 1832f
in vestibular system, 1851f, 1852-1854, 1854f, 2278f
distribution to end organs of, 1852, 1854f
organization of inputs to vestibular nuclei from, 1861-1863, 1863f
projections to cerebellum from, 1860
terminations in brainstem of, 1858f, 1859-1860
Vestibular nerve section, 2368-2370
for Meniere's disease, 2339, 2362
results of, 2370
selective, 2368
infralabyrinthine approach for, 2370
lateral suboccipital craniotomy approach for, 2370
middle fossa approach for, 2368-2369, 2369f
retrolabyrinthine, 2369-2370, 2369f
retrosigmoid approach for, 2370
transcochlear, 2368, 2368f
translabyrinthine, 2368
transmastoid, 2368f
for uncompensated vestibular neuritis, 2365t
Vestibular neural plasticity. *See* Neural plasticity, in otology.
Vestibular neuritis, 2162-2163, 2332-2333
clinical features of, 2159, 2332-2333
diagnostic testing for, 2333
etiology of, 2333
infectious causes of, 2159
management of, 2159
pathophysiology of, 2294
with sudden sensorineural hearing loss, 2333
temporal bone pathology in, 2159, 2162f, 2333
treatment of, 2333
vestibular nerve section *vs.* vestibular rehabilitation for, 2365t
Vestibular neuropathy. *See* Vestibular neuritis.
Vestibular nuclei
anatomic subdivisions of, 1860-1861, 1862f
efferent projection pathways from, 1864-1865, 1864f
organization of vestibular nerve inputs to, 1861-1863, 1863f
other inputs to, 1863-1864, 1864f
pathways from cerebellum to, 1864
spinal cord afferents to, 1864
terminations of vestibular nerve in, 1859-1860, 1861f
visual inputs to, 1863-1864
Vestibular ototoxicity
of aminoglycoside antibiotics, 2170
of cisplatin, 2172
Vestibular paralysis. *See* Vestibular neuritis.
Vestibular ramus, 1854, 1856f

Vestibular reflexes, adaptation to unilateral loss of vestibular function of, 2300-2302
anatomic and physiologic basis for, 2300-2302, 2301f
clinical implications of, 2302
for effect of suppressive drugs, 2302
with static *vs.* fluctuating loss, 2302
for vestibular rehabilitation, 2302
Vestibular rehabilitation. *See* Vestibular and balance rehabilitation therapy (VBRT).
Vestibular schwannoma. *See* Acoustic neuroma(s).
Vestibular sensory epithelium
cellular morphology of, 1855-1857, 1856f, 1858f
specialized subregions of, 1858-1859, 1859f-1860f
Vestibular skin, in sensation of nasal obstruction, 641-642
Vestibular surgery, 2359-2371
for ablative control of vertigo
labyrinthectomy as, 2366-2368, 2367f
patient selection for, 2364-2366
clinical history in, 2364-2365
consideration of other potential treatments in, 2366
identification of intracranial pathology in, 2366
identification of offending labyrinth in, 2365-2366
poor compensation *vs.* unstable labyrinthine disease in, 2364, 2365t
residual hearing and selection of procedure in, 2366
therapeutic trial of vestibular rehabilitation in, 2365
vestibular testing in, 2365, 2365b
vestibular compensation after, 2370
vestibular nerve section as, 2368-2370, 2368f-2369f
for benign paroxysmal positional vertigo, 2360-2361
posterior semicircular canal occlusion as, 2360-2361, 2361f
singular neurectomy as, 2360, 2360f
for Meniere's disease, 2362-2364
cochleosacculotomy as, 2126, 2362-2363, 2363f
endolymphatic sac surgery as, 2126, 2339, 2363-2364, 2364f
rationale for, 2359-2360
for repair of perilymphatic fistula, 2361-2362
for superior semicircular canal dehiscence, 2361, 2362f
Vestibular symptoms, of migraine, 2347-2348
motion sickness as, 2348
nonspecific dizziness as, 2347
vertigo as, 2202, 2347-2348, 2348f
Vestibular system, 1850-1865
adaptive capabilities of, 2327
age-related degeneration of, 233
bidirectional sensitivity of, 2278-2279
cellular morphology of vestibular sensory epithelium in, 1855-1857, 1858f
central pathways of, 1859-1865
anatomic subdivisions of vestibular nuclei in, 1860-1861, 1862f
efferent projection pathways from vestibular nuclei in, 1864-1865, 1864f
organization of vestibular nerve inputs to vestibular nuclei in, 1861-1863, 1863f
other inputs to vestibular nuclei in, 1863-1864, 1864f
projections of vestibular nerve to cerebellum in, 1860
terminations of vestibular nerve in brainstem in, 1858f, 1859-1860
dynamic disturbance of, 2327
embryology of, 1851-1852, 1851f
Vestibular system *(Continued)*
experimental viral infections of, 2163
in maintaining stable vision and posture, 2276-2277
anatomic and physiologic basis for, 2276-2277
clinical importance of, 2277
overall organization of labyrinth in, 1852-1854
facial nerve in, 1852
membranous labyrinth and bony labyrinth in, 1852, 1853f
orientation of semicircular canals in, 1852, 1852f
vestibular (Scarpa's) ganglion in, 1852-1854
vestibular nerve in, 1852-1854, 1854f
vestibule in, 1852
vestibulocochlear nerve in, 1852, 1853f
peripheral vestibular apparatus in
autonomic supply of, 1854
efferent innervation of, 1854, 1855f
principles of applied physiology of, 2276-2304
static imbalance of, 2327
synaptic morphology and function of vestibular afferents in, 1857-1859, 1859f-1860f
vestibular end organs in
anatomy of, 1853f, 1854-1855
ampulla in, 1851f-1852f, 1854
crista ampullaris in, 1854, 1856f-1857f
cupula in, 1855, 1857f
endolymph in, 1855
hair cells in, 1854-1855, 1856f
kinocilium in, 1854-1855, 1856f
macula sacculi in, 1855, 1856f-1858f
macula utriculi in, 1855, 1856f-1858f
otolith membrane in, 1855, 1858f
otoliths in, 1855, 1858f
stereocilia in, 1854-1855, 1856f
striola in, 1855, 1858f
supporting cells in, 1854-1855
blood supply to, 1854, 1856f
Vestibular testing
for ablative vestibular surgery, 2365, 2365b
with acoustic neuroma, 2517
in assessment of vestibular compensation, 2376
gain, phase, and time constant in, 2302-2304, 2303f
for sensorineural hearing loss, 2117
Vestibule, 1825f, 1831
anatomy of, 1852
imaging of, 1920-1921, 1922f
Vestibulocochlear anastomosis of Oort, 1835
Vestibulocochlear artery, 1854, 1856f
Vestibulocochlear nerve
anatomy of, 1852, 1853f
in surgical anatomy of lateral skull base, 2438, 2439f
Vestibulocollic reflex (VCR), 1851, 2276, 2307-2308
Vestibulo-ocular reflex (VOR), 1851, 2276
active head movement analysis techniques for, 2323-2324, 2324f
adaptation exercises and, 2378
angular, 2306, 2307f
after labyrinthectomy, 2291-2292, 2291f-2293f
brainstem circuitry in, 2296-2297
anatomic and physiologic basis for, 2296
velocity storage in, 2296
velocity-to-position integration in, 2296, 2297f-2298f
clinical implications of, 2296-2297
for Alexander's law, 2297, 2299f
for head-shake nystagmus, 2296-2297
for interpreting rotary chair tests, 2297-2299
for pre- and post-rotatory nystagmus, 2296, 2298f
efferent projection pathways from vestibular nuclei in, 1865
eye movements in, 2306, 2306f
Vestibulo-ocular reflex (VOR) *(Continued)*
head movements in, 2308
after labyrinthectomy, 2291-2292, 2291f-2293f
low-frequency, 2314
orientation of semicircular canals and, 2285-2287, 2286f-2287f
in patient selection for ablative vestibular surgery, 2365
translational, 2306-2307, 2309f
Vestibulo-ocular reflex (VOR) cancellation, 2300-2301, 2306f, 2314
Vestibulo-ocular reflex (VOR) gain, 2301-2304, 2301f, 2303f
Vestibulopathy
familial, 2343-2344
recurrent, 2335
Vestibulospinal reflexes (VSRs), 1851, 2276
evaluation of, 2316-2317
Vestibulothalamic pathways, 1865
Vestibulotoxicity, 2344
Vezatin, in stereocilia, 2078
VFP. *See* Vocal fold paralysis (VFP).
VFSS (videofluoroscopic swallow study), for dysphagia in children, 2949, 2950t
VGLUT1 (vesicular glutamate transporter-1) gene, in deafness, 2081
VGLUT3 (vesicular glutamate transporter-3) gene, in deafness, 2051t-2058t, 2081
VHL. *See* Vertical hemilaryngectomy (VHL).
VHL (von Hippel–Lindau) protein, in Warburg effect, 1028f
Viadent-related leukoplakia, 1223-1224, 1224f
Vibrant Soundbridge semi-implantable hearing aid, 2208-2210
clinical data on, 2209
comparison of features of, 2206t
components of, 2208-2209, 2208f
for conductive and mixed hearing loss, 2210
history of, 2208, 2210
implantation of, 2209
indications for, 2209, 2209f
Vibrating ossicular prosthesis (VORP), 2208, 2208f
Vibration, and noise-induced hearing loss, 2148-2149
Vickers and Gorlin criteria, for unicystic ameloblastoma, 1271
Videoendoscopy
drug-induced, of obstructive sleep apnea, 253-255
of early glottic carcinoma, 1515-1516
laryngeal, 814-818
of arytenoid and vocal fold motion, 816
common problems and solutions for, 815t-816t
defined, 813
endoscopes for, 813-814
of laryngeal structure, 816
of mucus, 816-817
in neurologic examination, 834
protocol for, 814, 816b
of supraglottic activity, 817, 817f
of vascularity, 817
of vocal fold edges, 818
Videofluoroscopic swallow study (VFSS), for dysphagia in children, 2949, 2950t
Videofluoroscopy
speech, for velopharyngeal dysfunction, 2679-2680
for stridor, 2901
for swallowing disorders, 1217-1218, 1219f
Videonystagmography (VNG), and vestibular rehabilitation, 2373f-2374f, 2376-2377
Videostroboscopy, laryngeal, 818-821
of adynamic segments, 820
of amplitude of vibration, 820, 821f, 848, 848t
of closure pattern, 819, 820f, 848t, 849
common problems and solutions for, 815t-816t
defined, 813
of early glottic carcinoma, 1515-1516

Videostroboscopy, laryngeal *(Continued)*
flexible endoscope for, 814
advantages of, 814
disadvantages of, 814
protocol for, 818b
technique of, 814
troubleshooting for, 814
interpretation of, 848t
interval examination in, 847
of mucosal wave, 820, 848-849, 848t
in neurologic examination, 834
of periodicity, 821, 848, 848t
of phase closure, 819-820
for professional voice, 847-849, 848f, 848t
protocol for, 818-819, 818b
of regularity, 821
rigid endoscopes for, 813-814
advantages of, 813
disadvantages of, 813-814
protocol for, 818b
technique of, 814
troubleshooting for, 814
of symmetry, 820, 847-848, 848t
of vertical closure level, 821
for vocal fold impairment, 905
Vidian artery, 682, 683f
Vinblastine
for induction chemotherapy, 1056
sensorineural hearing loss due to, 2120
Vincent's angina, 2786
Vincristine
for hemangioma of infancy, 2826-2828
for induction chemotherapy, 1056-1057
sensorineural hearing loss due to, 2120
VIP (vasoactive intestinal peptide), in salivary gland secretion, 1137
Viral capsid antigen (VCA), of Epstein-Barr virus, 1352, 1354
Viral infection(s)
of external ear, 1957, 1957f
topical therapies for, 1957, 1957f
options for, 1957
of labyrinth
cytomegalovirus as, 2154-2156, 2155f
herpes simplex virus as, 2159-2160
Lassa fever as, 2158-2159
measles as, 2158
mumps as, 2157-2158, 2158f
rubella as, 2156-2157, 2157f
varicella-zoster virus as, 2159, 2159f
oral manifestations of, 1252
otitis media due to, 2764
and pediatric chronic sinusitis, 2778
and rhinosinusitis, 730-731
of salivary glands, 1156-1158
in children, 2855
due to Epstein-Barr virus, 2855
due to HIV, 2856
due to mumps, 2855
due to HIV, 1157-1158, 1157f
in children, 2856
due to mumps, 1156-1157
in children, 2855
sensorineural hearing loss due to, 2119, 2199
sudden, 2127
Viral labyrinthitis, vertigo due to, 2201
Viral laryngitis, 884
Viral lymphadenopathy, in children, 2817-2818
Viral parotitis, 1156-1158
in children, 2855
due to Epstein-Barr virus, 2855
due to HIV, 2856
due to mumps, 2855
due to HIV, 1157-1158, 1157f
in children, 2856
due to mumps, 1156-1157
in children, 2855
Viral pharyngitis, 196-199
due to adenovirus, 198
in children, 2785-2786
due to common cold (rhinovirus, coronavirus, parainfluenza virus), 196
due to Epstein-Barr virus, 198-199, 198f
due to herpes simplex virus, 199, 199f
due to HIV, 197
due to influenza virus, 196-197
Viral vaccines, to prevent otitis media, 2769
Viral vectors, 16-18, 18t, 19f
adeno-associated virus as, 18, 18t
adenoviruses as, 17-18, 17f, 18t
conditionally replicating, 22
retroviruses as, 16, 17f, 18t
Viral-mediated gene transfer, 16-18, 18t, 19f
via adeno-associated virus, 18, 18t
via adenoviruses, 17-18, 17f, 18t
via retroviruses, 16, 17f, 18t
Virtual endoscopy, 138, 140f
Virtual laryngoscopy, 1464, 1464f
Virtual reality (VR) headset, 39, 39f
Virtual reality (VR) simulator, 45-46
Visceral fascia, 202, 2577, 2578f
Visceral space, imaging of, 159-163
with abscess, 161f
larynx in, 159-161
with epiglottitis, 159-161, 163f
with laryngoceles, 159-161, 163f
with squamous cell carcinoma, 161, 164f
with trauma, 159, 162f
parathyroid glands in, 162-163, 165f
thyroid gland in, 161-162
CT for, 140
with follicular carcinoma, 161-162, 165f
lingual, 161-162, 165f
MRI for, 143
normal anatomy in, 161
scintigraphy for, 138
with thyroglossal duct cyst, 161-162, 165f
Visceral tissue free flaps, for oropharyngeal reconstruction, 1380, 1380f
Visceral transposition, for hypopharyngeal and esophageal reconstruction, 1453
colonic, 1453, 1454f
gastric, 1453
Viscerocranium, 2443f
Viscerovertebral angle, 1799, 1799f
Vision, vestibular system in maintaining stability of, 2276-2277
anatomic and physiologic basis for, 2276-2277
clinical importance of, 2277
Vision loss, due to paranasal sinus tumor, 1123
Visual acuity, dynamic, 2316
Visual acuity examination, prior to anterior and middle cranial base surgery, 2446
Visual analog pain scale, 239
Visual fixation, 2305-2306, 2306f, 2307t
Visual input, to vestibular nuclei, 1863-1864
Visual perceptual examination, in voice assessment, 827
Visual reinforcement audiometry (VRA)
in infants, 2722
for otitis media, 2762
Visual vestibular mismatch, due to intratympanic gentamicin, 2189
Vitamin A
for cancer chemoprevention, 1018, 1061-1062
for olfactory dysfunction, 639
Vitamin A deficiency, oral manifestations of, 1254
Vitamin B_2, for migraine, 2349
Vitamin B_2 deficiency, oral manifestations of, 1254
Vitamin B_{12} deficiency, oral manifestations of, 1254
Vitamin C
for aging skin, 404
with chemical peel, 396
for rhinosinusitis, 731, 735t
Vitamin C deficiency, oral manifestations of, 1254
Vitamin D
and allergic rhinitis, 613
in calcium homeostasis, 1775
hypercalcemia due to excessive intake of, 1784
Vitamin D deficiency, oral manifestations of, 1254
Vitamin E, for chemoprevention of oral cancer, 1315
Vitamin K deficiency, oral manifestations of, 1254
Vitruvian man, 269, 270f
VLGR1 (very large G-protein–coupled receptor 1) gene, in deafness, 2051t-2058t, 2077
VNG (videonystagmography), and vestibular rehabilitation, 2373f-2374f, 2376-2377
VNTB (ventral nucleus of trapezoid body), in auditory pathway, 1834f
Vocal abuse
laryngitis due to, 883-884, 884f
by voice professional, 853
Vocal capability battery, for benign vocal fold mucosal disorders, 861-862
bilateral diffuse polyposis as, 872
capillary ectasia as, 866
contact ulcer or granuloma as, 875
glottic sulcus as, 870
intracordal cysts as, 869
intubation granuloma as, 875-876
postoperative dysphonia as, 873-874
vocal fold hemorrhage and unilateral (hemorrhagic) vocal fold polyp as, 868
vocal nodules as, 865
Vocal commitments, assessment of, 861
Vocal cord(s). *See* Vocal fold(s).
Vocal fold(s)
applied anatomy of, 805-806
false, radiographic anatomy of, 1472-1473, 1472f
microarchitecture of, 860, 860f
movement of, 805, 806f
neurologic evaluation of, 834
in phonation, 811, 811f, 833
positioning of, 812
shape of, 812
vibratory capacity of, 812
physiology of, 860, 860f
in pitch control, 812
superficial lesions of, in vocal professional, 855-856, 856f
true
anatomy of, 1359f
radiographic, 1472, 1472f-1473f
carcinoma of, imaging of, 1474-1475, 1474f
physical examination of, 100
vibratory cycle of, 860, 861f
videoendoscopy of, 816, 817f
edges in, 818
Vocal fold angle, in laryngeal paralysis, 912, 913f
Vocal fold atrophy, in geriatric patients, 234-235
Vocal fold cysts, 856, 857f
in children, 2882, 2882f
Vocal fold granuloma, 2881, 2881f
Vocal fold hemorrhage, 854, 867-869
with capillary ectasia, 868f
diagnosis of, 868
history in, 868
laryngeal examination in, 868
vocal capability battery in, 868
epidemiology of, 867
pathophysiology and pathology of, 867-868
treatment of, 868-869
behavioral, 868
medical, 868
surgical, 868-869

Vocal fold immobility, 843
  CO_2 laser for, 33
  due to trauma, 937
Vocal fold injection, 905-907
  vs. arytenoid adduction, 912-913
  complications of, 907, 908f
  laryngoscopic, 906-907, 907f
  materials used in, 905-906
  percutaneous, 906, 906f-907f
  transoral, 906
Vocal fold medialization, 904-911
  in children, 2879
  for chronic aspiration, 927
  historical aspects of, 904-905
  by injection, 905-907
    vs. arytenoid adduction, 912-913
    complications of, 907, 908f
    laryngoscopic, 906-907, 907f
    materials used in, 905-906
    percutaneous, 906, 906f-907f
    transoral, 906
  medialization thyroplasty for, 908-911
    advantages of, 908
    arytenoid adduction *vs.,* 912-913
    disadvantages of, 908
    factors affecting outcome of, 908
    with Gore-Tex strip, 908, 910, 911f
    implant placement in, 909-910, 910f
    indications for, 905, 908
    prefabricated implants for, 908, 908f, 910
    prosthesis templates in, 909-910, 910f
    technique for, 908-911, 909f
  patient evaluation and selection for, 905
Vocal fold mobility
  clinical evaluation of, 1545
  glottic cancer with impaired, 1496
Vocal fold mucosal disorders, benign. *See* Benign vocal fold mucosal disorder(s).
Vocal fold nodules. *See* Vocal nodules.
Vocal fold paralysis (VFP), 843
  in children, 2879-2880
    dysphagia due to, 2952
  chronic aspiration due to, 927
  congenital, 2868-2869
  etiology of, 1466-1467
  iatrogenic left, 2868
  imaging of, 1466-1467, 1467f
  laryngeal reinnervation for (*See* Laryngeal reinnervation)
  laryngeal stenosis and, 2922
  due to laryngeal trauma, 937-938
  due to thyroid disease, 1737
  vocal fold medialization for (*See* Vocal fold medialization)
Vocal fold paresis, 843
  causes of, 843
    central, 842
  clinical presentation of, 843
  diagnosis of, 843
  vocal fold positioning in, 843
Vocal fold polyp(s)
  in children, 2882
  unilateral (hemorrhagic), 867-869
    with capillary ectasia, 868f
    diagnosis of, 868
      history in, 868
      laryngeal examination in, 868
      vocal capability battery in, 868
    epidemiology of, 867
    pathophysiology and pathology of, 867-868
    treatment of, 868-869
      behavioral, 868
      medical, 868
      surgical, 868-869
  in vocal professional, 846
Vocal fold polyposis, bilateral diffuse, 872-873, 872f
  diagnosis of, 872
    history in, 872
    laryngeal examination in, 872
    vocal capability battery in, 872
  epidemiology of, 872
  management of, 872-873
    behavioral, 872
    medical, 872
    surgical, 872-873, 873f
  pathophysiology and pathology of, 872
Vocal fold positions, in laryngeal paralysis, 912-913
Vocal fold reinnervation. *See* Laryngeal reinnervation.
Vocal fold stripping, 872-873, 873f
  for premalignant lesions of larynx, 1490
Vocal fold ultrasound, for stridor, 2901
Vocal fold varix(ices), 846-847, 856, 857f
Vocal fold vibration
  cover-body theory of, 845, 845f
  horizontal phase of, 849
  measures of, 830-831
    electroglottography for, 830, 835
      for professional voice, 849
    inverse filtered flow for, 830-831
    videostroboscopy for, 818-821
      adynamic segments in, 820
      amplitude of vibration in, 820, 821f, 848, 848t
      closure patterns in, 819, 820f, 848t, 849
      interpretation of, 848t
      interval examination in, 847
      mucosal wave in, 820, 848-849, 848t
      of periodicity, 821, 848, 848t
      phase closure in, 819-820
      for professional voice, 847-849, 848f, 848t
      protocol for, 818-819, 818b
      regularity in, 821
      symmetry in, 820, 847-848, 848t
      vertical closure level in, 821
      for vocal fold impairment, 905
  vertical phase of, 848-849
Vocal ligament
  anatomy of, 860, 860f, 1484f
    surgical, 1542f-1544f
  in vocal fold vibration, 845
Vocal misuse
  laryngitis due to, 883-884, 884f
  by voice professional, 853
Vocal muscle, 1543f
Vocal nodules, 865-866
  with capillary ectasia, 867f
  in children, 2881-2882, 2882f
  defined, 865
  diagnosis of, 865
    history in, 865
    laryngeal examination in, 865
    vocal capability battery in, 865
  epidemiology of, 865
  gastroesophageal reflux and, 2946
  management of, 865-866
    behavioral, 865
    medical, 865
    surgical, 865-866, 866f, 867t
  pathophysiology and pathology of, 865
  in vocal professionals, 846, 853, 855
  voice therapy for, 863
Vocal output, objective measures of, for benign vocal fold mucosal disorders, 862
"Vocal overdoer" syndrome, 861
Vocal overuse
  acute mucosal swelling of, 863
  laryngitis due to, 883-884, 884f
Vocal pedagogue, for professional voice disorders, 852, 855
Vocal Performance Questionnaire (VPQ), 57, 826, 826t
Vocal process
  in arytenoid adduction, 913-914, 913f-914f
  in laryngeal paralysis, 913-914
Vocal professionals. *See* Professional voice disorders.
Vocal quality disorders, in children
  due to cricoarytenoid joint fixation, 2880
  due to epidermoid cysts, 2882, 2882f
  due to granuloma, 2881, 2881f
  due to laryngeal web, 2880, 2880f
  due to malignant tumors, 2881
  medical management of, 2881
  due to posterior glottic stenosis, 2880
  due to recurrent respiratory papillomatosis, 2880-2881
  due to sulcus vocalis, 2882
  surgical management of, 2879-2881
  due to vocal fold paralysis, 2879-2880
  due to vocal fold polyps, 2882
  due to vocal nodules, 2881-2882, 2882f
  voice therapy for, 2881-2882
Vocal rehabilitation, after laryngectomy. *See* Voice rehabilitation.
Vocal tendon, 1541-1542
Vocal tremor, 840-841
Vocalization, 846-847
VoCoM (hydroxyapatite) implants, for medialization thyroplasty, 908-910, 908f, 910f
Vogt-Koyanagi-Harada syndrome, inner ear disease in, 2165
Voice
  alaryngeal (*See* Alaryngeal voice and speech)
  chest, 846-847, 851
  head, 846-847, 851
  outcome scales for, 56t, 57
  transition, 851
Voice Activity and Participation Profile (VAPP), 826, 826t
Voice analysis
  computer-assisted, for children, 2878, 2878f
  for extraesophageal reflux, 898
Voice breaks, 846-847
  in professional voice, 851
  in spasmodic dysphonia, 834-835
Voice considerations, with early glottic cancer, 1518-1519
Voice disorder(s)
  in children, 2876-2883
    evaluation of, 2876-2878
      aerodynamic analysis in, 2878
      algorithm for, 2877f
      computer-assisted voice analysis for, 2878, 2878f
      history in, 2876
      physical examination in, 2876-2877
      for social and functional impact, 2876
      speaking tasks in, 2877-2878
      stroboscopic examination in, 2877
      voice profile in, 2878
    functional, 2876, 2879
    incidence of, 2876
    organic, 2876, 2879
    of resonance, 2879
    of vocal quality
      due to cricoarytenoid joint fixation, 2880
      due to epidermoid cysts, 2882, 2882f
      due to granuloma, 2881, 2881f
      due to laryngeal web, 2880, 2880f
      due to malignant tumors, 2881
      medical management of, 2881
      due to posterior glottic stenosis, 2880
      due to recurrent respiratory papillomatosis, 2880-2881
      due to sulcus vocalis, 2882
      surgical management of, 2879-2881
      due to vocal fold paralysis, 2879-2880

Voice disorder(s) *(Continued)*
due to vocal fold polyps, 2882
due to vocal nodules, 2881-2882, 2882f
voice therapy for, 2881-2882
voice therapy for, 2878-2879, 2881-2882
in singers (*See* Professional voice disorders)
Voice evaluation, 825-831
diagnostic (probe) therapy for, 831
for laryngeal stenosis, 2917
measurements in, 827-831
acoustic analysis for, 829t, 834-835
cepstral peak prominence in, 829t, 830
combined frequency and intensity in, 829, 829f, 829t
Fast Fourier Transform in, 829t, 830, 830f
frequency in, 829, 829t
intensity (sound pressure level) in, 829, 829t
linear predictive coding in, 829t, 830, 830f
long-term average spectrum in, 829t, 830
nasalance in, 829t, 830
phonetogram (voice range profile) in, 829, 829f, 829t
for professional voice, 849
spectral displays in, 829t, 830, 830f
variability in, 829-830, 829t
of velopharyngeal function, 829t, 830
aerodynamic, 828-829, 828t, 835
airflow as, 828, 828t
laryngeal airway resistance as, 828-829, 828t
maximum phonation time as, 828
phonation threshold pressure as, 828, 828t
of professional voice, 849
subglottic air pressure as, 828, 828t
of velopharyngeal function, 828t, 829
of chest wall displacement, 828
of vocal fold vibration, 830-831
electroglottography for, 830, 835
inverse filtered flow for, 830-831
patient scales for, 825-826, 826t, 834
Patient Questionnaire of Vocal Performance as, 826, 826t
Reflux Symptom Index as, 826, 826t
Voice Activity and Participation Profile as, 826, 826t
Voice Handicap Index as, 826, 826t, 834
Voice Outcome Survey as, 826, 826t
Voice Symptom Scale as, 826, 826t
Voice-Related Quality of Life scale as, 826, 826t, 834
perceptual, 826-831
auditory, 826-831
CAPE-V for, 826
GRBAS for, 826, 827t
other aspects of, 826-827
for professional voice, 850
tactile, 827-831, 828f
visual, 827
for professional voice, 849-850
Voice Handicap Index, 57, 826, 826t, 834
Voice Outcome Survey (VOS), 826, 826t
Voice production, 846-847, 2876
modal register of, 850-851
Voice profile, for children, 2878
Voice prosthesis(es), 1597, 1597f
history of, 1594-1595, 1595f
indwelling *vs.* nonindwelling, 1597-1598, 1598f
physiology of, 1595-1597, 1596f
postoperative management of, 1600
alimentary care in, 1600
pulmonary care in, 1600, 1602f
and radiotherapy, 1600, 1602b
replacement of, 1601
indications for, 1601
nonindwelling, 1602
for valve discrepancy (periprosthetic leakage), 1602
Voice prosthesis(es) *(Continued)*
for valve incompetence (transprosthetic leakage), 1601-1602
secondary, 1600
surgical aspects of, 1598-1600, 1599f-1600f
creation of optimally contoured stoma as, 1599-1600, 1600f
pharyngeal mucosa closure as, 1599-1600, 1601f
prevention of excessively deep stoma as, 1599-1600, 1600f
prevention of hypertonicity of PE segment as, 1599-1600, 1599f
timing of insertion of, 1597-1599
troubleshooting with, 1603-1605
types of, 1597-1598, 1598f
Voice quality
assessment of, 826-831
CAPE-V for, 826
GRBAS for, 826, 827t
other aspects of, 826-827
in geriatric patients, 234-237
acoustic changes and, 236
dental/mandibular changes and, 236
factors affecting, 234, 235t
glandular changes and, 236
histologic changes and, 234-235, 235f
laryngoscopic appearance and, 235-236
mucosal changes and, 236
respiratory changes and, 236
and sense of taste, 236
treatment of, 236-237
Voice quality disorders, in children
due to cricoarytenoid joint fixation, 2880
due to epidermoid cysts, 2882, 2882f
due to granuloma, 2881, 2881f
due to laryngeal web, 2880, 2880f
due to malignant tumors, 2881
medical management of, 2881
due to posterior glottic stenosis, 2880
due to recurrent respiratory papillomatosis, 2880-2881
due to sulcus vocalis, 2882
surgical management of, 2879-2881
due to vocal fold paralysis, 2879-2880
due to vocal fold polyps, 2882
due to vocal nodules, 2881-2882, 2882f
voice therapy for, 2881-2882
Voice range profile (VRP), in acoustic analysis for voice evaluation, 829, 829f, 829t
Voice rehabilitation, 1594-1610
electrolarynx voice and speech for, 1596, 1596f
esophageal voice and speech for, 1596, 1596f
history of, 1594-1595, 1595f
after laryngopharyngectomy, 1458-1459
physiology of, 1595-1597, 1596f
after total laryngectomy, 1572
after total laryngopharyngectomy, 1575
tracheoesophageal voice and speech for, 1597, 1597f
voice prosthesis(es) for, 1597, 1597f
indwelling *vs.* nonindwelling, 1597-1598, 1598f
postoperative management of, 1600
alimentary care in, 1600
pulmonary care in, 1600, 1602f
and radiotherapy, 1600, 1602b
replacement of, 1601
indications for, 1601
nonindwelling, 1602
for valve discrepancy (periprosthetic leakage), 1602
for valve incompetence (transprosthetic leakage), 1601-1602
secondary, 1600
surgical aspects of, 1598-1600, 1599f-1600f
creation of optimally contoured stoma as, 1599-1600, 1600f
Voice rehabilitation *(Continued)*
pharyngeal mucosa closure as, 1599-1600, 1601f
prevention of excessively deep stoma as, 1599-1600, 1600f
prevention of hypertonicity of PE segment as, 1599-1600, 1599f
timing of insertion of, 1597-1599
troubleshooting with, 1603-1605
types of, 1597-1598, 1598f
Voice Symptoms Scale (VoiSS), 57, 826, 826t
Voice therapy
for benign vocal fold mucosal disorders, 863, 864f
for children, 2878-2879, 2881-2882
for postoperative dysphonia, 874
Voice tremor, 840-841
Voice-Related Quality of Life (V-RQOL) Instrument, 57, 826, 826t
in neurologic evaluation, 834
pediatric, 57
VoiSS (Voice Symptoms Scale), 57, 826, 826t
Voit's anastomosis, 1852-1854
Volatile anesthetic agents, 111
Volume correction, for hyperparathyroidism, 1804
Vomer, 320f
Vomeronasal cartilage, 482
Vomeronasal organ, 482
in olfactory stimulation, 627-628, 627f
Vomiting, pediatric postoperative, 2593
von Békésy, Georg, 2050
von Hippel–Lindau (VHL) protein, in Warburg effect, 1028f
von Recklinghausen's disease, 1774, 1782
acoustic neuromas in, 2515
with laryngeal involvement, 882
oral manifestations of, 1257
otologic manifestations of, 2112
von Willebrand's disease
oral manifestations of, 1256
preoperative evaluation of, 105
VOR. *See* Vestibulo-ocular reflex (VOR).
Voriconazole, for rhinosinusitis, 712, 713t, 735, 735t
VORP (vibrating ossicular prosthesis), 2208, 2208f
VOS (Voice Outcome Survey), 826, 826t
VoSol (propylene glycol and acetic acid otic solution), for otitis externa, 1946, 1953, 1959t-1960t
VoSol HC (hydrocortisone/propylene glycol/acetic acid otic solution), for otitis externa
bacterial, 1953, 1959t-1960t
fungal, 1954, 1959t-1960t
VOXEL-MAN TempoSurg simulator, 50
VPD. *See* Velopharyngeal dysfunction (VPD).
VPQ (Patient Questionnaire of Vocal Performance), 826, 826t
VPQ (Vocal Performance Questionnaire), 57, 826, 826t
VR (virtual reality) headset, 39, 39f
VR (virtual reality) simulator, 45-46
VRA (visual reinforcement audiometry)
in infants, 2722
for otitis media, 2762
VR-FESS, 48
VRP (voice range profile), in acoustic analysis for voice evaluation, 829, 829f, 829t
V-RQOL (Voice-Related Quality of Life) Instrument, 57, 826, 826t
in neurologic evaluation, 834
pediatric, 57
VSRs (vestibulospinal reflexes), 1851, 2276
evaluation of, 2316-2317
V-Y advancement flap, 345-346, 346f-347f
for cheek defects, 358, 361f
for lip defects, 356f
VZV. *See* Varicella-zoster virus (VZV).

W

Waardenburg-Hirschsprung disease, deafness in, 2051t-2058t, 2095
Waardenburg syndrome (WS)
  inner ear anomalies in, 2735
  sensorineural hearing loss in, 2051t-2058t, 2094t, 2095-2096
    adult-onset, 2117-2118, 2118f
  types of, 2095
  variable expression and nonpenetrance in, 7, 7f
Waardenburg-Shah syndrome, 2095
Wagner-Grossman hypothesis, for vocal fold paralysis, 912
Waldenström's macroglobulinemia, sensorineural hearing loss due to, 2123
Waldeyer's ring
  anatomy of, 2783
  infections of, 2785
Waldeyer's ring lymphomas, 1680
  treatment and prognosis for, 1680
Wallenberg's syndrome, 2313, 2352f, 2354f
Wallerian degeneration, 2384-2385
Walsh scoring system, for GABHS pharyngitis, 192-193
Walsh-Ogura operation. *See* Transantral orbital decompression.
Waltzer mouse, deafness in, 2074
Warburg effect, 1024-1025, 1028f
Warfarin
  epistaxis due to, 687
  preoperative use of, 105
Wart(s), 282-283
  filiform, 282, 282f
  flat, 282, 283f
  due to molluscum contagiosum, 282-283, 283f
  oral, in HIV, 227
Warthin, Aldred, 1170-1171
Warthin's tumors, 1170-1171
  in children, 2862
  imaging of, 1146, 1146f
Water brash, 956
Water clear cell adenoma, of parathyroid gland, 1778
Water clear cell hyperplasia, of parathyroid gland, 1779
Water precautions, with tympanostomy tubes, 2775-2776
Waters view, 130, 662, 663f
Watson, Patrick, 1563
Web(s)
  esophageal, 966-967, 967f
    imaging of, 1407, 1408f
  laryngeal, 2869-2871, 2913
    anterior, 2869-2870, 2869f
    in congenital high airway obstruction syndrome, 2869, 2870f
    dysphagia due to, 2952
    epidemiology of, 2913
    etiology and pathophysiology of, 2913
    in laryngeal atresia, 2869, 2869f-2870f
    posterior, 2869, 2869f
    stridor due to, 2899, 2900f
    syndromes associated with, 2869, 2870t
    treatment of, 2922
    vocal quality disorder due to, 2880, 2880f
Web formation, after neck surgery, 1728, 1729f
Weber test, 97-98, 98t, 2020
  for otosclerosis, 2030
Wedge excision biopsy, for skin lesions, 293
Wedge resection, for tracheal stenosis, 2931, 2931f
Wegener, Friedrich, 658
Wegener's granulomatosis (WG), 2103-2104
  clinical presentation of, 2103
  diagnosis of, 658, 2103
  epidemiology of, 658
  epistaxis due to, 685f
  etiology and pathogenesis of, 2103
Wegener's granulomatosis (WG) *(Continued)*
  inner ear disease in, 2165-2166
  laboratory findings in, 2103
  laryngeal and tracheal manifestations of, 889-890, 890f
  nasal manifestations of, 658
  oral manifestations of, 1252
  otologic manifestations of, 2103f, 2104
    otorrhea as, 2196
  pathology of, 658, 2104f
  prognosis for, 2103-2104
  sensorineural hearing loss due to, 2124
  treatment of, 658
  type 1, 658
  type 2, 658
  type 3, 658
Weight loss, for obstructive sleep apnea, 256
Weir procedure, for noncaucasian nose, 556
Wens, 289
Wernicke's area, in central auditory pathway, 1836-1837, 1847
WFS1 (Wolfram syndrome gene 1), in deafness, 2051t-2058t, 2092-2093, 2098
WG. *See* Wegener's granulomatosis (WG).
Wharton's duct
  anatomy of, 2850-2852
  sialography of, 1149-1150
Whirler mice, 2077
Whirlin, in stereocilia, 2076f, 2078
Whirlin *(WHRN)* gene, in deafness, 2051t-2058t, 2077
Whistletone register, 851
White blood cell disorders, oral manifestations of, 1256
Whitnall's ligament, 439, 444
Whitnall's tubercle, 439
Whooping cough, laryngeal and tracheal manifestations of, 892
WHO-QOL (World Health Organization quality of life scale), 56
WHRN (whirlin) gene, in deafness, 2051t-2058t, 2077
Wide dynamic-range compression, for hearing aids, 2268
Wide local excision (WLE), of melanoma, 1113-1114
Wide-field laryngectomy, 1568-1569, 1570f
Wig(s), 387
Wigand technique, for endoscopic sinus surgery, 746
Williams, Frand, 1031
Williams, Robin, 38
Witch's chin, 465, 466f
WLE (wide local excision), of melanoma, 1113-1114
Wobble nucleotide, 4
Wolf High Speed Endocam, 821
Wolff's law, 330, 2613
Wolfram syndrome gene 1 *(WFS1),* in deafness, 2051t-2058t, 2092-2093, 2098
Wolframin, and deafness, 2051t-2058t
Women
  hair loss in, 376, 377f
  oral health of, 1256-1257
    during and after menopause, 1256-1257
    during menses, 1256
    during pregnancy, 1256
    during puberty, 1256
World Health Organization quality of life scale (WHO-QOL), 56
Wormian bone, in osteogenesis imperfecta, 2109-2110, 2110f
Wound, created by laser, 29-30, 30f
Wound closure, for facial trauma, 305-306, 306f
Wound complication(s), of neck surgery, 1726-1728
  incision planning and, 1726-1727
  infection as, 1727
  salivary fistula as, 1727-1728, 1728f
  scar formation as, 1728, 1729f
  seroma as, 1727, 1727f
  wound dehiscence and flap necrosis as, 1727
Wound contraction, 1078
Wound dehiscence
  after neck surgery, 1727
  after total laryngectomy, 1571
Wound healing, 1075-1078
  cell types in, 1076t
  gene therapy for, 22-23
  inflammatory phase of, 1076
  proliferation phase of, 1076-1078
    formation of granulation tissue in, 1077-1078
      angiogenesis in, 1077-1078
      dermal matrix in, 1077
    reepithelialization in, 1076-1077
      keratinocyte migration in, 1076-1077
      keratinocyte proliferation in, 1077
    wound contraction in, 1078
  remodeling phase of, 1078
Wound infection, after neck surgery, 1727
Wound tension, in skin flaps, 1071
W-plasty
  for forehead defects, 359-360, 362f
  for scar revision, 298, 299f
Wrapped endotracheal tube, with recurrent respiratory papillomatosis, 2891
Wrinkle(s), 275, 279f. *See also* Aging skin.
  rhytidectomy for (*See* Rhytidectomy)
Wrinkle cream products, 403
WS. *See* Waardenburg syndrome (WS).

X

X inactivation, 8
X linkage, 8
Xanthelasma, 293
Xanthine oxidase, in acutely raised skin flaps, 1070-1071, 1071f
Xanthine oxidase inhibitor, and skin flap viability, 1074
Xanthoma, oral verruciform, 1229
  clinical features of, 1229
  defined, 1229
  etiology and pathogenesis of, 1229
  histopathologic/diagnostic features of, 1229
  treatment of, 1229
XCL chemokines, 611t-612t
Xenografts, for craniofacial defect repair, 2657
Xenon CT blood flow mapping, for cerebral blood flow evaluation, 2491
Xeroderma pigmentosa, and melanoma, 1107
Xeroradiography, of pharynx and esophagus, 1393
Xerostomia
  with aging, 1141-1142, 1141f
  immunosuppression and, 218
  palliative care for, 1102-1103
  due to radiotherapy, 1047-1048, 1102-1103
X-linked dominant disorder, 6, 2089
X-linked inhibitor of apoptosis (XIAP), in aminoglycoside ototoxicity, 2171
X-linked recessive disorders, 7, 7f, 2088f, 2089
X-linked sensorineural hearing loss
  nonsyndromic, 2093, 2093t
  syndromic, 2094t, 2096-2097
X-linked stapes gusher syndrome, 2737
Xolegel (ketoconazole cream), for fungal otitis externa, 1954-1955, 1959t-1960t
X-rays
  interaction with matter of, 1032-1033, 1032f
  interactions with DNA of, 1036-1043, 1037f
Xylocaine. *See* Lidocaine (Xylocaine).
Xyzal (levocetirizine), for nonallergic rhinitis, 701t

Y

Yersinia enterocolitica, pharyngitis due to, 196
Yodel, 846-847
Y-V advancement flaps, 346

Z

Zafirlukast
  for allergic rhinitis, 620-621
  for rhinosinusitis, 735t, 736
Zellballen, in paragangliomas, 1657, 1658f
Zenker, Friedrich Albert von, 987
Zenker's diverticulum(a), 974, 986-997
  classification of, 987, 991t
  defined, 986
  diagnosis of, 986-987, 989f-990f
  differential diagnosis of, 986-987, 990t
  epidemiology of, 986
  history of, 986-987, 987f
  imaging of, 1401, 1402f
  management of, 987-997
    algorithm for, 997, 997f
    endoscopic techniques for, 992-997
      complications of, 995
      electrocautery technique in, 993f
      equipment for, 994f
      history of, 992, 993f
      laser technique in, 993f
      positioning for, 993f
      procedure for, 992-995, 995f-996f
      results of, 994-995
Zenker's diverticulum(a) *(Continued)*
    external techniques for, 988-992
      complications of, 992
      diverticulopexy technique as, 992f
      history of, 988-990
      inversion technique as, 992f
      procedure for, 990-992
      transcervical diverticulectomy as, 991f
    recurrence after, 995-997
  pathophysiology of, 986-987
  presentation of, 986-987
Zeus telerobotic system, 39, 40f
Zileuton
  for allergic rhinitis, 620-621
  for rhinosinusitis, 735t, 736
Zinc, for olfactory dysfunction, 639
Zinc deficiency, oral manifestations of, 1254
Zinc gluconate, for rhinosinusitis, 731, 735t
Z-line, in transnasal esophagoscopy, 982
Zones of perfusion, 1064-1065, 1065f
Zonisamide, for neuropathic pain, 244t
Zostavax (varicella vaccine), 2159
Zovirax (acyclovir)
  with chemical peels, 397
  for herpes zoster, 2396
  for recurrent respiratory papillomatosis, 2890t, 2892
Z-palatoplasty, for obstructive sleep apnea, 258, 260f
Z-plasty, for scar revision, 298, 298f-299f
Zygoma
  anatomy and physiology of, 319, 320f-321f
  biomechanics of, 332
  in surgical anatomy of lateral skull base, 2435f-2436f
Zygomatic arch(es)
  anatomy and physiology of, 319, 320f
  biomechanics of, 332
  depressed, *vs.* myofascial pain dysfunction syndrome, 1285t
Zygomatic bone, 320f
Zygomatic branch, of facial nerve, 1194f
Zygomatic fractures
  imaging of, 325
  repair of, 336
  surgical access to, 328-329
Zygomatic injury, physical examination of, 324
Zygomatic process
  anatomy of, 1821, 1822f-1823f, 2010f
  articular tubercle of, 1822f
Zygomatic root, 1822f, 1824f
Zygomatic "tripod," biomechanics of, 332
Zygomaticofacial nerve, 321f
Zygomaticomalar complex fractures, pediatric, 2707-2708, 2710f
Zygomaticus major muscle, 321f, 442f, 444
Zygomaticus minor muscle, 442f, 444
Zyrtec (cetirizine)
  for nonallergic rhinitis, 701t
  for rhinosinusitis, 734t